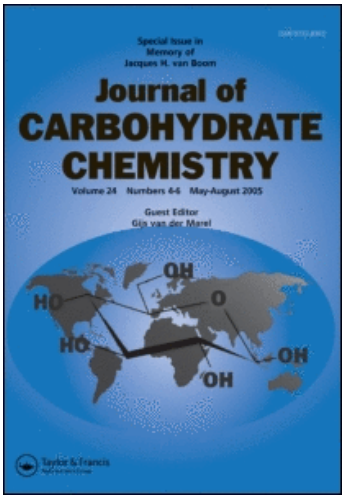

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THE EFFECT OF SUBSTITUENTS ON THE REACTIVITY OF THE DOUBLE BOND OF D-GLYCALS

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ABSTRACT

A study was made concerning the effect of substituents at O-3, O-4 and O-6 of D-galactal and D-glucal (1,5-anhydro-2-deoxy-D-lyxo- and -D-arabino-hex-1-enitol, respectively) on the double bond reactivity in the chloroazide addition reaction. Results from the quantum chemical calculations of the model structures (ab initio) and also of the whole cyclic molecules in the half-chair conformation (MINDO-3) together with the reaction indices of olefin carbon atoms are presented. These studies show that (1) the double bond reactivity and the chloroazide addition mechanism are only affected by the substituent at O-3; (2) the influence of the acyl group is only due to its inductive effect; (3) no interaction between the acyl and the olefin fragments through space was detected. Three O-acetyl-di-O-benzyl-D-galactals were synthesized.

INTRODUCTION

Protecting groups are capable of significantly changing the rates and even pathways of chemical reactions occurring at the adjacent reacting centers. In the development of a method for the production of 2-azido-2-deoxyglycosyl halides, glycosylating

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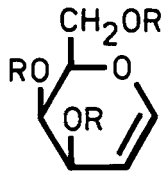
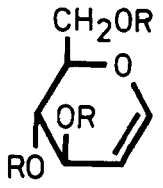
agents for the synthesis of 2-amino-2-deoxy-α-D-glycosides, we have observed the effect of protecting groups on the addition of chloroazide to the double bond of glycals.[1] This work treats in more detail the effect of substituents at O-3, O-4 and O-6 of D-galactal and D-glucal on the double bond reactivity in this reaction.

RESULTS AND DISCUSSION

The Addition of Chloroazide to Acetylated and Benzylated Glycals. The completely acetylated glycals 1 and 5 attach chloroazide in tetrachloromethane both in the dark and under UV irradiation to give a mixture of four substances (out of eight possible) of types A, B, C and D (Scheme 1). The ratio of the products in the





1 R = Ac
2 R = $PhCH_2$
3 R = PhCO
4 R = Me

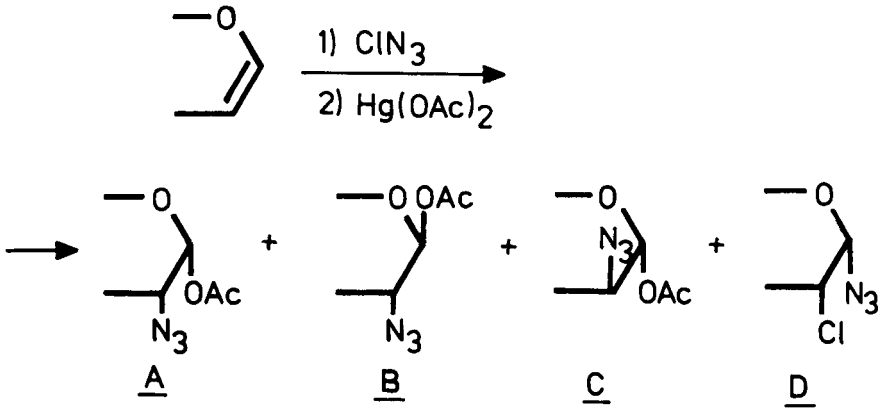
5 R = Ac
6 R = $PhCH_2$

dark and under irradiation conditions is the same, for the galactal 1, (A + B):C:D = 9:1:2, the only difference being that under irradiation conditions the reaction rate increased by ca. two orders of magnitude. This suggests that in the two cases, in the dark and under irradiation, the reaction occurs by the same (radical) mechanism (for more details see Ref. 1).

In contrast, for the benzylated glycals 2 and 6 one observes a sharp difference in the composition of the addition products

obtained in the dark or under irradiation. Thus, in the case of the galactal 2 in the dark the glycosyl azide of type D (in 90% yield) is the only adduct whereas irradiation gives rise to a mixture of A (37%), B (39%) and D (8%). A very plausible explanation for this result is the occurrence of two parallel processes, viz., radical and ionic, the former predominating under the irradiation conditions and the latter in the dark.

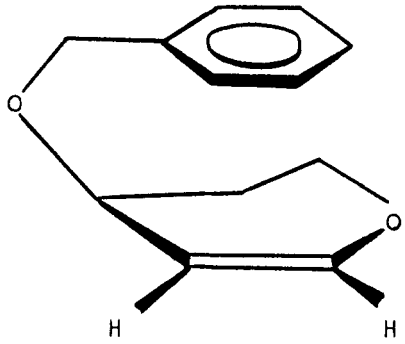
SCHEME 1



The rate of chloroazide addition to the benzylated glycals 2 and 6 in tetrachloromethane shows a very strong difference from that of the acetates 1 and 5. With a twofold excess of chloroazide the former reaction practically immediately after mixing the reagents whereas the latter require much longer reaction times (2 h under irradiation and 200 h in the dark). Thus, the chloroazide addition rate between the benzyl ethers and the acetates differs by at least two orders of magnitude for the radical reaction while the ionic reaction for the acetates (in tetrachloromethane) does not take place at all. In ionic addition of chloroazide to benzylated glycals (carbon tetrachloride in the dark) Ferrier-type products of elimination were not found.

The Type of the Effect of Substituents. To explain the above stated most significant differences one might propose that the

aromatic ring of the benzyl group accelerates the addition reaction due to a polarization interaction through space. Such an interaction would also account for the absence of type C compounds in the reactions of the benzylated glycals. Alternatively, the C=O group of the acetyl substituent decelerates the reaction due to an inductive effect.



In order to determine what influence if any the "through space" and/or "inductive effect" has on the course of the chloroazide addition reaction, two novel glycals (3 and 4) have been synthesized by D-galactal benzoylation and methylation, respectively. The substituents in 3 contain both an aromatic ring and an acyl group whereas 4 contains neither. The benzoylated glycal 3 was found to react just as the acetylated one does (the addition rates and the ratios of the products for 1 and 3 are practically the same), and the methylated glycal 4 just as the benzylated glycal does. This implies that the acyl group is responsible for the differences in the chloroazide addition rates and rules against a glycal-phenyl π-π through space polarization interaction.

The relative addition rates were determined in competitive reactions with a deficient amount of chloroazide (in this and all other cases). The structure of the addition products was confirmed from ^{1}H NMR data.

The nature of the effect thus detected was specified by means of quantum chemical calculations. To study the interaction through space in a pure form, i.e. without superimposition of the inductive effect, a consideration was given to the model systems with no covalent bonds between the functional fragments (Fig. 1).

The ab initio calculations were performed in the minimal and extended bases. The mutual position of the studied fragments in space was widely varied from 2.9 to 5.0 Å. No gain in energy, exceeding 0.9 kcal/mol, was observed, and the reaction indices for the C-1 and C-2 atoms remained unchanged in all cases. On the other hand, the structure 7 - 10 whose interacting fragments are covalently bonded but have maximum spatial separations, the inductive effect was studied in a pure form, as a first approximation, free of any polarization component (MINDO-3). Table 1 lists the results of these calculations which bear out the inductive effect of the acyl group on the double bond reactivity.

7 R = $PhCH_2$
8 R = Me
9 R = CHO
10 R = H

TABLE 1.

Ab initio Calculations of the Reaction Indices for the Structures 7 - 10

Structure	Charge at C-1	Charge at C-2	Free valence index at C-2
7	+0.329	-0.263	0.623
8	+0.330	-0.264	0.623
9	+0.320	-0.087	0.513
10	+0.328	-0.259	0.620

O-Benzyl (7), O-methyl (8) and OH (10) derivatives show almost identical reaction indices, but formate (9) differs from 7, 8 and 10 and carries nearly zero negative charge. Therefore, 3-O-acyl derivatives have low reactivity in ionic and radical processes.

Thus, the reason for the substantial difference in the reactivities of the completely benzylated and completely acetylated glycals lies in the inductive effect of the acyl substituent at O-3 which lowers the double bond reactivity.

Substituents at O-4 and O-6. The individual effects of each of the acetyl groups at O-3, O-4 and O-6 for D-galactal were also determined. To do so, three new substituted D-galactals (11 - 13) were synthesized (Scheme 2).

The glycals 12 and 13 were found to attach chloroazide with the same rate as the glycal 2 does, whereas compound 11 reacted at least one order of magnitude slower. The quantum chemical calculationals (MINDO-3) performed for the structurally related molecules 14 - 17 demonstrate that the effect of the acetyl group takes place at O-3 only. This time, consideration was given not the fragments but rather to the whole cyclic molecules in their half-chair conformation with the geometric parameters being unoptimized.

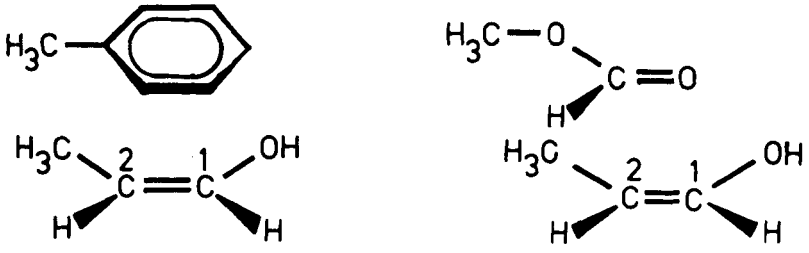
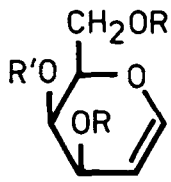
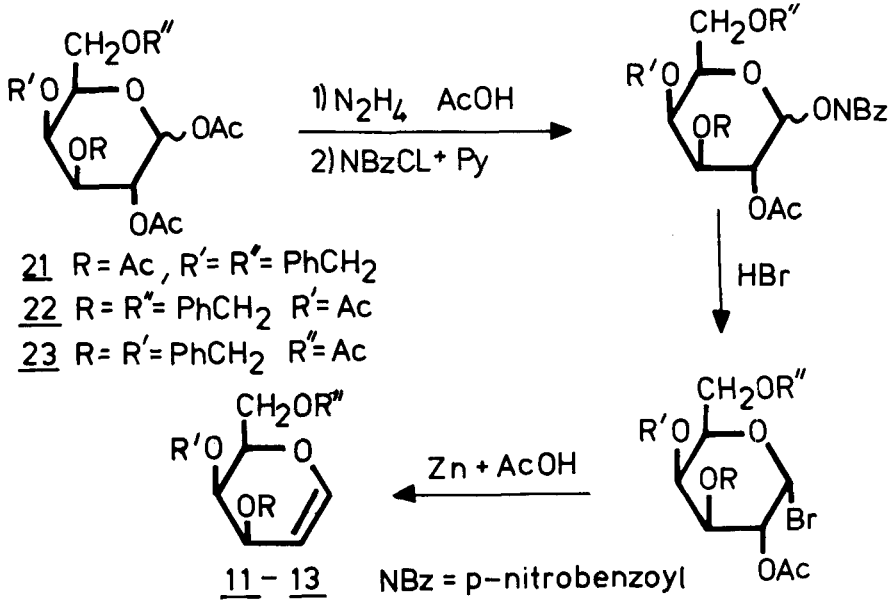


FIG.1



11 R = Ac, R′ = R″ = $PhCH_2$
12 R = R″ = $PhCH_2$, R′ = Ac
13 R = R′ = $PhCH_2$, R″ = Ac
14 R = R′ = R″ = H
15 R = Ac, R′ = R″ = H
16 R = R″ = H, R′ = Ac
17 R = R′ = H, R″ = Ac
18 R = R′ = $PhCH_2$, R″ = H
19 R = R″ = $PhCH_2$, R′ = H
20 R = H, R′ = R″ = $PhCH_2$

The Synthesis of Starting Glycals. The glycals 11 - 13 are synthesized as shown below (Scheme 2). Hydrazine acetate was used to selectively remove the 1-O-acetyl group[2] in compounds 21 - 23, then the resultant reducing derivatives were acylated with p-nitrobenzoyl chloride. After that the p-nitrobenzoates were converted into glycosyl bromides by use of hydrogen bromide. With the aid of



21 R = Ac, R′ = R″ = $PhCH_2$
22 R = R″ = $PhCH_2$ R′ = Ac
23 R = R′ = $PhCH_2$ R″ = Ac

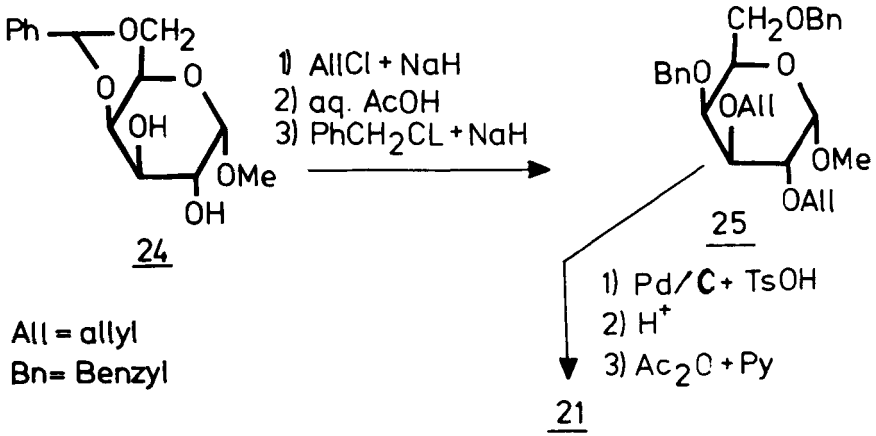
11 – 13 NBz = p-nitrobenzoyl

SCHEME 2

reductive elimination the bromides gave the glycals 11 - 13. The direct synthesis of the bromides from the acetates 21 - 23 by their reaction with hydrogen bromide in dichloromethane or in acetic acid was not successful because of paralleling debenzylation.

All the synthesis stages (from the acetates to the glycals) were carried out with no purification of the intermediates. At the last stage the desired glycals were isolated by column chromatography (substances with the maximum R_f value) in 25-35% yields relative to the starting acetates. An attempt to produce 12 by selective benzylation of D-galactal 14 with benzyl bromide (2 equiv.) showed that instead of the expected galactal 19, a 4,6-derivative 20 was formed (cf. Ref. 3), identical to the deacetylation product of 11.

The starting compound 21 was synthesized from methyl 4,6-O-benzylidene-α-D-galactopyranoside 24 (Scheme 3).

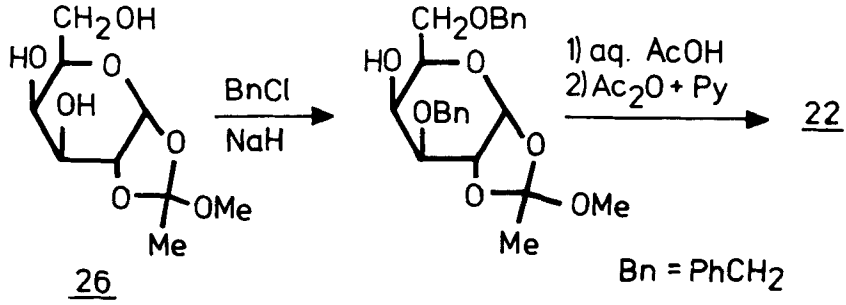


SCHEME 3

The protecting allyl groups in compound 25 were removed with 10% Pd/C in the presence of p-toluenesulfonic acid.[4]

The starting compound 23 (α-anomer) was obtained by selective acetolysis[5] of 1,2-di-O-acetyl-3,4,6-tri-O-benzyl-D-galactopyranose which in turn was synthesized from the orthoester 26, as described for a D-gluco analogue.[5]

The key stage of the synthesis of the acetate 22 consisted in a partial benzylation of the orthoester 26 with two equivalents of benzyl chloride (Scheme 4). The structure of 12 and, hence, of 22 is confirmed by the fact that this glycal differs from 11 and 13 by its ^{1}H NMR spectrum and also by an R_f value. In other words, the orthoester 26, as distinct from the glycal 18, undergoes benzylation, as expected, at O-3 and O-6.



26

SCHEME 4

Conclusions. The experiments described suggest that (1) the reactivity of the glycal double bond is only affected by the substituent at O-3, it being sharply lowered by the acyl groups; (2) the lower reactivity is caused by the inductive effect of these groups.

EXPERIMENTAL

General Methods. Melting points were determined with a Boetius apparatus. Optical rotations were measured with a Perkin Elmer Model 141 polarimeter at 20° in chloroform (c 1.0). ^{1}H NMR spectra were recorded with a Varian XL-100 instrument at 100 MHz with tetramethylsilane as internal standard and IR spectra with a UR-20 spectrophotometer. TLC was performed on 60F-254 silica gel plates (E. Merck, Darmstadt) and column chromatography on silica gel L 40-100 μm (Chemapol, Czechoslovakia). Solvents were evaporated in vacuo at 30-40°. A mercuric UV lamp with a wide spectrum

was used as the irradiation source, reactions were carried out in a quartz vessel at 0 °C.

1,2,3-Tri-O-acetyl-4,6-di-O-benzyl-α-D-galactopyranose (21). Methyl 4,6-O-benzylidene-α-D-galactopyranoside[6] (24, 30 mmol) and sodium hydride (65 mmol) were stirred for 1 h in dimethylformamide (150 mL) and then to the mixture was added allyl chloride (7 mL). After 15 h the mixture was treated with methanol (5 mL), diluted with chloroform, washed with water and evaporated. The residue was heated for 2 h with 80% acetic acid (200 mL) at 100° and evaporated. Then the residue was dissolved in dimethylformamide (150 mL) and treated with benzyl chloride and sodium hydride (65 mmol each). After 15 h the mixture was treated with methanol (5 mL), diluted with chloroform, washed with water and evaporated. Compound 25 was isolated by column chromatography in toluene-acetone (19:1) in 86% yield, $[\alpha]_D$ + 51°; ^{1}H NMR (CCl_4):δ 3.34 (s, 3H, Me), 5.20 (m, 4H, 2 CH_2=), 5.85 (m, 2H, 2 CH=), 7.21 (s, 10H, 2 Ph). A mixture of 25 (20 mmol), 10% Pd/C (10 g) and p-toluensulfonic acid (1 g) was boiled for 72 h with stirring in 90% aqueous dioxane (200 mL). The catalyst was filtered off, washed with methanol and the filtrate was evaporated. The residue was boiled for 6 h in a mixture of acetic acid (130 mL) water (130 mL) and M hydrochloric acid (50 mL) and evaporated. The residue was acetylated with a mixture of acetic anhydride and pyridine in the usual manner, after which α-anomer (21) was isolated by column chromatography in toluene-ether (9:1) in 63% yield; $[\alpha]_D$ + 36°; ^{1}H NMR (CCl_4):δ 1.90, 1.98, 2.11 (each s, each 3 H, 3 Ac), 6.22 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 7.23 (s, 10H, 2 Ph).

Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.19; H, 6.22. Found: C, 64.10; H, 6.31.

1,2,6-Tri-O-acetyl-3,4-di-O-benzyl-α-D-galactopyranose (23). 1,2-Di-O-acetyl-3,4,6-tri-O-benzyl-D-galactopyranose was obtained from orthoester 26 by the method described in the literature[5] and then acetolyzed for 20 h as described in the same work. Reaction progress was monitored by TLC using toluene-acetone (7:1). The

yield of 23 was 81%, syrup; $[\alpha]_D$ + 51°; ^{1}H NMR (CCl_4):δ 1.90, 1.93, 2.04 (each s, each 3H, 3 Ac), 6.24 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 7.26, 7.30 (each s, each 5H, 2 Ph).

Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.19, H, 6.22. Found: C, 64.14; H, 6.27.

3-O-Acetyl-4,6-di-O-benzyl-D-Galactal (11). A mixture of 21 (8 mmol) and hydrazine acetate (9 mmol) in dimethylformamide (40 mL) was stirred for 5 h at 30°, diluted with chloroform, washed with water, dried and evaporated. The residue was dissolved in dichloromethane (50 mL) and then to the solution were added p-nitrobenzoyl chloride (10 mmol) and pyridine (4 mL). After the 15 h the mixture obtained was diluted with chloroform, washed with water, M hydrochloric acid, a sodium hydrogencarbonate solution, dried and evaporated. The residue was dissolved in a solution of hydrogen bromide in dichloromethane (50 mL), saturated at 0-5°. The solution was kept for 30 min at 0°, evaporated at 20° and the residue was treated with acetic acid. p-Nitrobenzoic acid was filtered off and the filtrate was added, with vigorous stirring at 0-5°, to a mixture of zinc dust (20 g), sodium acetate trihydrate (15 g), cupric sulfate pentahydrate (0,5 g) and 60% acetic acid (60 mL). The mixture was stirred for another 1 h and filtered. The filtrate was diluted by half with water and extracted with dichloromethane. The extract was washed with water, a sodium hydrogencarbonate solution, dried and evaporated. The most mobile reaction product (11) was isolated by column chromatography of the residue in toluene-ethyl acetate-hexane (20:2:3) in 25% yield (relative to 21), syrup; $[\alpha]_D$ -34°; ^{1}H NMR (CCl_4); 1.94 (s, 3H, Ac), 6.30 dd, 1H, $J_{1,2}$ 6.4 Hz, $J_{1,3}$ 1.6 Hz, H-1), 7.22 (s, 10H, 2 Ph); IR: 1650, 1749 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.71; H, 6.63.

4-O-Acetyl-3,6-di-O-benzyl-D-galactal (12). To a solution of the orthoester 26 (20 mmol) in dimethylformamide (100 mL) was added benzyl chloride (44 mmol) and then to the mixture obtained was

added sodium hydride (44 mmol) at 20° with vigorous stirring for 3 h. After 15 h the mixture was diluted with chloroform, washed with water, evaporated, treated with 90% acetic acid, evaporated to dryness and acetylated with a mixture of acetic anhydride and pyridine. After the standard treatment the residue was subjected to column chromatography in ether-hexane (3:2) and then in toluene-ethyl acetate (4:1) to give anomeric mixture 22 (in the ^{1}H NMR spectrum the ratio of acetyl to benzyl protons was 3:2) in 56% yield. Then the glycal 12 was obtained from 22, as described for 11, in 29% yield; mp 51° (ether-hexane); $[\alpha]_D$ -19°; ^{1}H NMR (CCl_4):δ 1.98 (s, 3H, Ac), 6.22 d, 1H, $J_{1,2}$ 6.5 Hz, H-1), 7.26 (s, 10H, 2 Ph); IR: 1640, 1735 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.71; H, 6.63.

6-O-Acetyl-3,4-di-O-benzyl-D-galactal (13). The compound was obtained from 23, as described above, in 35% yield; mp 47°; (ether-hexane); $[\alpha]_D$ -71°; ^{1}H NMR (CCl_4):δ 1.97 (s, 3H, Ac), 6.22 (dd, 1H, $J_{1,2}$ 6.1 Hz, $J_{1,3}$ 1.2 Hz, H-1), 7.26 (s, 10H, 2 Ph); IR: 1655, 1735 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.61; H, 6.67.

4,6-Di-O-benzyl-D-galactal (20). The title compound was obtained by deacetylation of 11 by the Zemplén method (in quantitative yield) or by partial benzylation of D-galactal, as described for the benzylation of 26; mp 68° (ether); $[\alpha]_D$ -17°; ^{1}H NMR (DMSO-d_6): δ 3.30 (s, 1H, OH), 6.29 (dd, 1H, $J_{1,2}$ 6.1 Hz, $J_{1,3}$ 1.5 Hz, H-1), 7.31 (s, 10H, 2Ph); IR: 1650, 3300 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.62; H, 6.76.

3,4,6-Tri-O-methyl-D-galactal (4). Tri-O-acetyl-D-galactal (22 mmol) was deacetylated by the Zemplén method, the resulting compound 14 was dissolved in dimethylformamide (80 mL), and to the solution obtained was added sodium hydride (100 mmol) and then in 15 min, dropwise, methyl iodide (100 mmol). The mixture was kept

for 15 h, treated with methanol (10 mL), diluted with chloroform, washed with water and dried. The title compound 4 was isolated by column chromatography in ether in 71% yield, syrup; ^{1}H NMR (CCl_4): 3.45 (9H, 3 Me), 6.17 (d, 1H, $J_{1,2}$ 5.6 Hz, H-1); IR: 1640 cm^{-1}. This compound underwent decomposition during 1-5 days at 0°.

3,4,6-Tri-O-benzoyl-D-galactal (3). Tri-O-acetyl-D-galactal (22 mmol) was deacetylated by the Zemplén method, the resulting compound 14 was dissolved in pyridine (80 mL) and to the solution was added benzoyl chloride (90 mmol) at 20°. After 48 h the mixture was diluted with chloroform, washed with water, M hydrochloric acid, a sodium hydrogencarbonate solution, water, and dried. The chromotographically homogeneous product (3, 98% yield) was obtained after evaporation of the solution; syrup; $[\alpha]_D$ -133°; ^{1}H NMR (CCl_4):δ 6.56 (d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 7.90 (m, 10H, 2Ph); IR: 1645 cm^{-1}.

Anal. Calcd for $C_{27}H_{22}O_7$: C, 80.74; H, 4.84. Found: C, 70.69; H, 4.90.

Comparison of the Reaction Rates of Glycals. The relative rates of the chloroazide addition reactions were determined in a competitive reaction with the glycal 2. To a solution of the compound 2 (4 mmol) and other glycal (4 mmol) in tetrachloromethane at 0° was added chloroazide (2 mmol) in the dark. After 24 h glycosyl azides obtained were isolated by column chromatography. The yields of the azides corresponded to the relative rates of the competitive reactions. A similar method was used to compare the rate of the reaction of tri-O-acetyl-D-galactal with the glycal 3 under irradiation.

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