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PHOTOREACTION OF METHYL 4,6-*O*-BENZYLIDENE-2,3-DIDEOXY-3-NITRO-β-D-*erythro*-HEX-2-ENOPYRANOSIDE WITH 1,3-DIOXOLANE AND TETRAHYDROFURAN

TOHRU SAKAKIBARA* AND TOSHIO NAKAGAWA

Department of Chemistry, Yokohama City University, Seto, Kanazawa-ku, Yokohama 236 (Japan)

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ABSTRACT

Irradiation of the title compound in 1,3-dioxolane and in tetrahydrofuran respectively afforded the D-*gluco* and D-*manno* isomers having the 1,3-dioxolan-2-yl and tetrahydrofuran-2-yl group at C-2, besides the glycosid-3-ulose and nitro alcohol; in the later case, the dimer was also isolated.

INTRODUCTION

Photochemical investigation of nitro sugars, where the nitro group is not attached to an aromatic ring, is limited to (*E*)-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enose, in which isomerization of the double bond affords the *Z* isomer, and a rearrangement–fragmentation process yields (*E*)- and (*Z*)-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-5-enos-7-ulose[1]. On the other hand, the *o*-nitrobenzyl group is frequently used as a photochemically labile protecting-group[2].

Studies concerning nucleophilic addition reactions to methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**1**) revealed that most nucleophiles approach exclusively from the equatorial side of the molecule, giving the β-D-glucopyranoside as a kinetically controlled product[3,4]. Such high stereoselectivity may be partially attributable to electrostatic repulsion between an approaching nucleophile and both the ring-oxygen atom[3] and O-1. If this is true, radical addition reactions of **1** are predicted to be less stereoselective than nucleophilic addition reactions.

In order to examine the prediction, we performed photo-addition reactions of **1** in 1,3-dioxolane and in tetrahydrofuran (THF).

RESULTS AND DISCUSSION

A solution of **1** in 1,3-dioxolane was irradiated with a high-pressure mercury

*To whom correspondence should be addressed.

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TABLE I

CHEMICAL SHIFTS (δ) AT 100 MHz OF THE PRODUCTS IN CHLOROFORM-*d* (Me_4Si AS INTERNAL STANDARD)

Product	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6e*	*H-2'*	*PhCH*	*OMe*
2	4.52	2.91	4.94	4.09	3.45	3.80	4.37	5.08	5.52	3.52
5	4.47	2.81	4.86	4.15	3.43	3.83	4.38	~4.0	5.53	3.53
6	4.44	2.60	5.00	4.06	3.49	3.81	4.38	~4.04	5.52	3.55
7	4.66	3.22	4.66	4.91	3.45	a	4.40	5.32	5.71	3.55
9	4.58	2.98	4.52	4.66	3.42	3.91	4.39	4.28	5.70	3.50
10	4.38	2.37	5.15	4.04	3.45	3.82	4.37		5.49	3.57

[a]The signal appeared at δ 4.1–3.7.

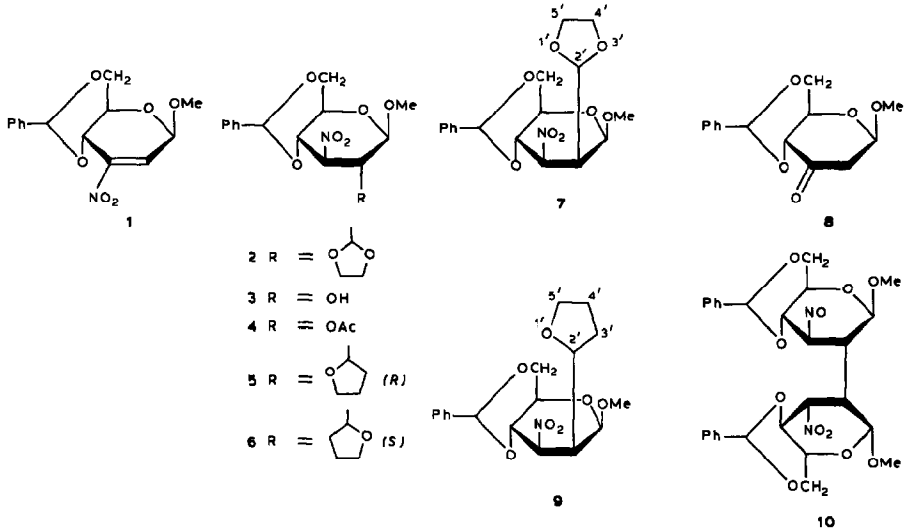
TABLE II

FIRST-ORDER COUPLING-CONSTANTS (Hz) MEASURED AT 100 MHz FOR THE PRODUCTS IN CHLOROFORM-*d*

Product	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$	$J_{2,2'}$
2	8.8	10.6	10.0	10.0	10.3	5.0	10.3	1.6
5	8.3	11.0	9.8	9.8	9.8	4.9	9.8	3.0
6	8.3	10.5	10.5	9.0	9.8	4.9	10.5	4.5
7	2.2	6.0	10.4	8.9	10.4	4.5	10.4	2.2
9	1.2	4.5	10.9	10.3	10.3	4.5	10.3	8.4
10	9.0	11.3	9.8	9.8	10.1	4.8	10.1	

lamp for 10 h, to give a complicated mixture from which methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-(dioxolan-2-yl)-3-nitro-β-D-glucopyranoside (**2**) was precipitated by ethanol. The residue was chromatographed on silica gel with 30:1 (v/v) benzene–ethyl acetate as the eluant to give, successively, additional **2** (total yield 27.3%), the D-mannopyranoside **7** (11%), the glycosid-3-ulose **8**, (ref. 5; 4.9%), and the alcohol **3** (ref. 6); compound **3** was isolated as the acetate **8** (5.2%; ref. 6). Compounds **4** and **8** were identical with the respective authentic samples, as shown by i.r. and ^{1}H-n.m.r. spectroscopy. The D-*gluco* and D-*manno* configurations having the $^4C_1$ conformations for **2** and **7**, respectively, were determined by the coupling constants; $J_{1,2}$ 8.8 and $J_{2,3}$ 10.6, $J_{3,4}$ 10.0 Hz for **2**, and $J_{1,2}$ 2.2, $J_{2,3}$ 6.0, and $J_{3,4}$ 10.4 Hz for **7**.

Similar photoreaction of **1** (5 mmol) in THF (150 mL) for 8 h at ~60° yielded the following (chromatography); the D-mannopyranoside **9** (10.8%), D-glucopyranosides **5** (5.7%) and **6** (2.0%), dimer **10** (4.8%), glycosid-3-ulose **8** (3.0%), and nitro alcohol **3** in turn; the last compound was isolated as the acetate **4** (4.2%). When compound **1** (1.5 mmol) was irradiated in THF (15 mL) for 8 h at ~24°, compounds **9** (40.2%), **5** (7.9%), and **6** (1.5%) were isolated, besides small amounts of **3** and **8**. Most of the proton signals were assigned by decoupling techniques and, in the case



of **9**, by comparison with those of the 3-*C*-deuterated derivative of **9**. Assignment of the D-*manno* configuration to **9** and of the D-*gluco* configuration to **5** and **6** was based on the coupling constants: $J_{1,2}$ 1.2, $J_{2,3}$ 4.5, and $J_{3,4}$ 10.9 Hz for **9**; $J_{1,2}$ 8.3, $J_{2,3}$ 11.0, and $J_{3,4}$ 9.8 Hz for **5**, and $J_{1,2}$ 8.3, $J_{2,3} = J_{3,4} = 10.5$ Hz for **6**.

The structure of the 1,3-dioxolan-2-yl and tetrahydrofuran-2-yl groups of these adducts is noteworthy. For the D-*manno* isomer **7**, the three *gauche* conformers I, II, and III should be taken into consideration (see Fig. 1). All of these conformers have a 1,3-diaxial-like interation, in which the interaction between the methoxyl group and the ring-oxygen atom in the five-membered ring (depicted as O) seems nearly equal to that between O-5 and O. Therefore, conformer III, having additional repulsion between C-4 and O, must be less stable than II. Although the 1,3-diaxial-like interaction involving the nitro group seems to have the most destabilizing effect[7,8], it is quite possible that the interaction between the nitro group and the dioxolanyl ring-oxygen atom is not repulsive but attractive†. If this is the case, conformer II is the most stable, and the $J_{2,2'}$ value of **7** must be large. Compound **7**, however, has a small value, $J_{2,2'}$ 2.2 Hz, suggesting that **7** exists as conformer I, at least, mainly. In spite of the fact that the only difference between **7** and **9** is at the 3′ position of the five-membered ring (an oxygen atom in the former and a methylene group in the latter), the tetrahydrofuran-2-yl derivative **9** has a large $J_{2,2'}$ value (8.4 Hz). This reveals that **9** exists mainly as conformer IV, if the configuration of C-2′ is

†Eliel and co-workers[9] found that the 5-axial isomer of 2-isopropyl-5-nitro-1,3-dioxane preponderates over the corresponding 5-equatorial isomer. They explained this fact by (*a*) attractive electrostatic interaction between the positively polarized nitrogen atom of the nitro group and the negatively polarized ring-oxygen atom, and (**b**) p-π^* overlap of the ring-oxygen unshared electron pairs with the π^* orbitals of the nitro group. A similar result was observed in 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-2-nitro-D-arabinitol and -ribitol[10].

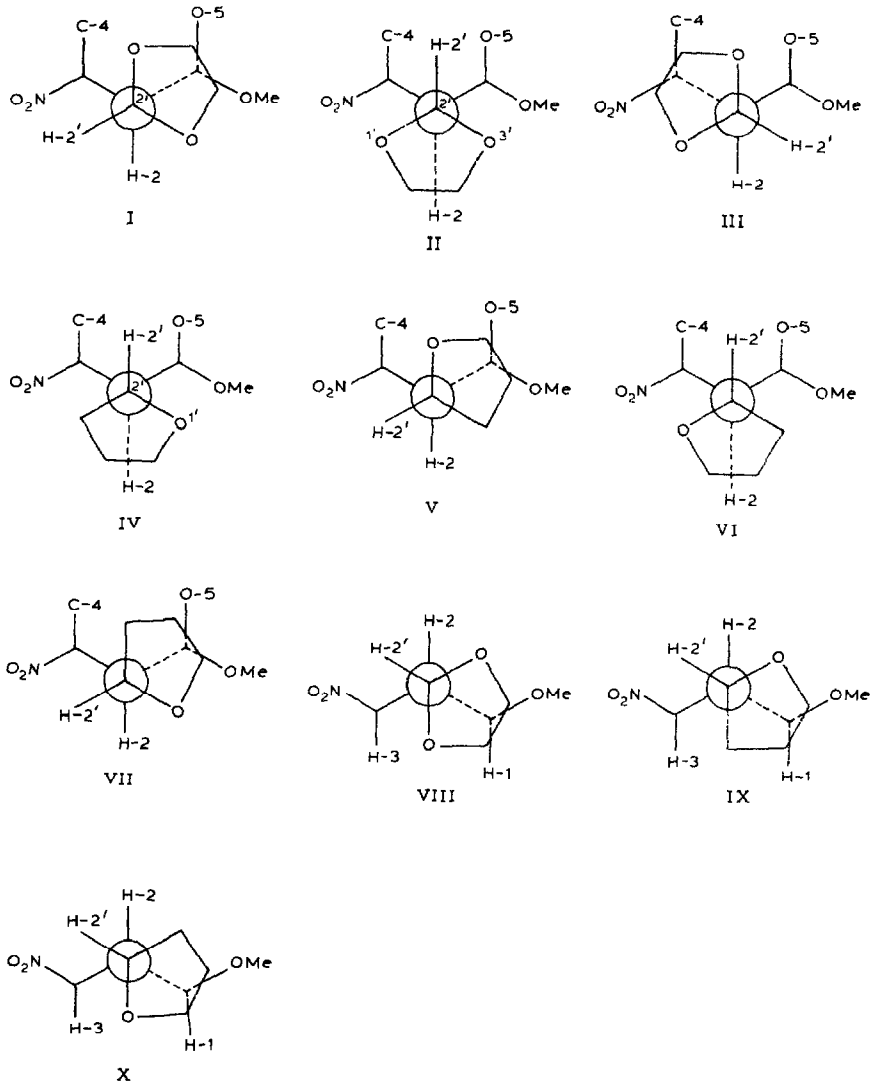


Fig. 1. "Newman" projections of the conformation, showing C-2' to C-2 for the D-*manno* (7) and (9) and D-*gluco isomers* (2), (5), and (6).

R, or as VI, if it is *S*. Because 1,3-diaxial interaction between hydroxyl and methyl groups is comparable to that between two hydroxyl or two acetoxyl groups[11], it is reasonable to assume that the repulsion between the nitro and methylene groups is greater than that between the methoxyl and methylene groups. The conformer V, therefore, might be more stable than IV. On the other hand, it is possible that conformer VI is more stable than VII, because VII is destabilized by steric repulsion due to the orientation of the bulky methylene group, compared with the oxygen

atom, toward the sterically crowded pyranose ring. Although the *S* configuration at C-2′ of **9** is thus plausible, this was not confirmed, because of failure to detect the alternative C-2′ isomer of **9**, required for this purpose.

Similar arguments could be applied to the D-*gluco* isomers. The most stable conformer of **2** should be VIII and, for tetrahydrofuranyl derivatives **5** and **6**, be IX and X, or X and IX, respectively, in which no 1,3-diaxial-like interaction between the nitro group and the methylene group or oxygen atom in the five-membered ring is involved. The chemical-shift difference of H-2 signals for VIII and IX should be smaller than that of those for VIII and X, because of the presence or absence of an oxygen atom near the proton. Similarly, the chemical-shift difference for the H-3 signals for VIII and X should be smaller than that of those for VIII and IX. For compound **2**, the signal of H-2 resonates at δ 2.91 and that of H-3 at δ 4.94, whereas those of **5** and **6** are at δ 2.81 and 4.86 and at δ 2.60 and 5.00, respectively. These results suggest that the configuration of C-2′ of **5** and **6** is respectively *R* and *S*, existing mainly in the conformations IX and X, respectively.

A dimer structure for **10** was suggested on the basis of its elemental analysis and mass spectrum [*m/z* 588 (M^+) and 542 ($M-NO_2$]. On steric grounds the D-*manno* configuration for **10** is not likely, but the D-*gluco* one is. This is supported by the coupling constants: $J_{1,2}$ 9.0, $J_{2,3}$ 11.3, and $J_{3,4} = J_{4,5}$ 9.8 Hz.

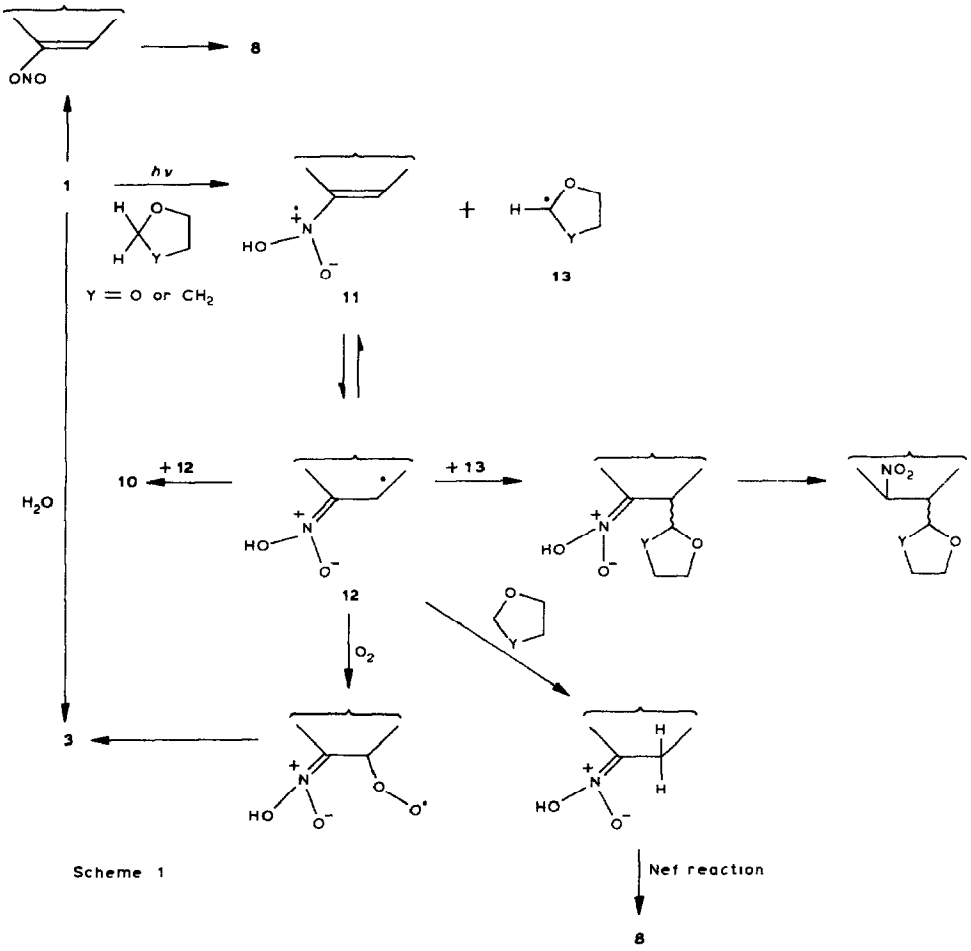
The photochemical reaction of **1** was retarded in commercially available tetrahydrofuran or in the presence of *p*-dinitrobenzene (scavenger), whereas it was not affected by the addition of acetone or benzophenone (added as a sensitizer).

A reasonable reaction mechanism (see Scheme 1) involves an excited nitro group, which abstracts a hydrogen atom from a solvent to provide the radicals **11** and **13**; the former should attain equilibrium with the radical **12**. Radicals **12** and **13** could combine to give the adducts (**2**,**5**-**7**, and **9**), and dimerization of **12** would afford the dimer **10**. Alternatively, the radical **12** reacts with oxygen to provide the alcohol **3** or abstracts a hydrogen atom from the solvent, followed by the Nef reaction, to give the glycosid-3-ulose **8**. It is also possible to form **8** *via* nitro–nitrite rearrangement[12]. The possibility is not excluded that the alcohol **3** is formed directly from the nitro alkene **1** with water contaminating the system.

Although the yields of adducts were not high, the stereoselectivity of radical addition reactions was, as expected, much lower than that of nucleophilic addition reactions.

EXPERIMENTAL

General methods. — Melting points were determined in capillaries and are uncorrected. I.r. spectra were recorded for potassium bromide discs, and n.m.r. spectra were recorded with a JNM-PS 100 (JEOL) spectrometer, for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. Solutions were evaporated under diminished pressure. Column chromatography was conducted on silica gel (C-300, Walkogel, Japan). T.l.c. was performed with silica gel GF 254



Scheme 1

(Merck, Darmstadt) with 10:1 (v/v) benzene–ethyl acetate.

Irradiation of **1** *in 1,3-dioxolane.* — The nitro alkene[6] **1** (2.93 g, 10 mmol) in 150 mL of 1,3-dioxolane (freshly distilled from lithium aluminum hydride before use) was irradiated in a Riko photoreactor with a high-pressure mercury lamp in a water-cooled Pyrex immersion-well for 10 h. After evaporation of the solvent, addition of ethanol caused formation of a precipitate. Recrystallization from ethanol gave 840 mg of D-*gluco* isomer **2**; m.p. 179.5–180.5°, $[\alpha]_D^{22}$ −86° (*c* 1, chloroform); ν_{max} 1560 cm^{-1} (NO_2); R_F 0.71.

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55,58, H, 5.76; N, 3.81. Found: C, 55.75; H, 5.76; N, 3.74.

The ethanolic solutions were combined, and evaporated, and the residue was chromatographed on silica gel with 30:1 (v/v) benzene–ethyl acetate as the eluant. The first fraction was 161 mg (total 27.3%) of additional **2**. The second fraction (510 mg) was a mixture of the D-*manno* isomer **7** and an unidentified product, from

which methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-(dioxolan-2-yl)-3-nitro-β-D-mannopyranoside (**7**) crystallized from ethanol; 404 mg (11%); m.p. 161.5–162°, $[\alpha]_D^{22}$ −26.4° (*c* 1, chloroform); ν_{max} 1565 cm^{-1} (NO_2); R_F 0.61.

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.65; H, 5.78; N, 3.92.

The third fraction (150 mg) consisted mainly of methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*erythro*-hexopyranosid-3-ulose (**8**) which was recrystallized from isopropyl alcohol (yield 130 mg, 4.9%), identical with an authentic sample[5].

The fourth fraction (~360 mg) was a complicated mixture, which was reduced with sodium borohydride (~60 mg) in methanol, and the product acetylated with acetic anhydride (1 mL)–pyridine (0.8 mL) in dichloromethane (5 mL). After 2 h, the mixture was partitioned between dichloromethane and water. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. Addition of ethanol caused precipitation of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**4**) (100 mg, 3.2%), identical with an authentic sample[6].

Irradiation of **1** *in tetrahydrofuran.* — The nitro alkene[6] **1** (1.47 g, 5 mmol) in 150 mL of THF (freshly distilled from lithium aluminum hydride before use) was similarly irradiated for 8 h at 60°. After evaporation of the solvent, the syrup was chromatographed on silica gel with benzene as the eluant. The first fraction (150 mg) was methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-2-*C*-[(*S*)-tetrahydrofuran-2-yl]-β-D-mannopyranoside (**9**), which was recrystallized from ethanol; m.p. 176.5°–177.5°, $[\alpha]_D^{22}$ −61.6° (*c* 1, chloroform); ν_{max} 1550 cm^{-1} (NO_2); R_F 0.62.

Anal. Calc. for $C_{18}H_{23}NO_7$: C, 59,18, H, 6.33; N, 3.83. Found: C, 59.01; H, 6.40; N, 3.81.

The second fraction (135 mg) was a mixture of the D-*manno* (**9**) and D-*gluco* isomers **5** in the ratio of 1:1 as judged from ^{1}H-n.m.r. spectroscopy. Compound **9** was isolated by recrystallization from ethanol as the first crop (total yield 150 mg + 48 mg, 10.8%), and methyl 4,5-*O*-benzylidene-2,3-dideoxy-3-nitro-2-*C*-[(*R*)-tetrahydrofuran-2-yl]-β-D-glucopyranoside (**5**) as the second crop, m.p. 108.5–109.5°, $[\alpha]_D^{22}$ −60.4° (*c* 0.5, chloroform); ν_{max} 1562 cm^{-1} (NO_2); R_F 0.53.

Anal. Calc. for $C_{18}H_{23}NO_7$: C, 59.18; H, 6.33; N, 3.83. Found: C, 59.10; H, 6.25; N, 3.76.

The third fraction (127 mg) was a mixture of **5** and **6** in the ratio of 1.6:1. Recrystallization from ethanol gave **5** as the first crop (total yield, 36.5 mg, 2.0%), and the residue crystallized from isopropyl alcohol, to give methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-2-*C*-[(*S*)-tetrahydrofuran-2-yl]-β-D-glucopyranoside (**6**) (36.5 mg, 2%); m.p. 185–186°, $[\alpha]_D^{22}$ −98.2° (*c* 1, chloroform); ν_{max} 1550 cm^{-1} (NO_2); R_F 0.52.

Anal. Calc. for $C_{18}H_{23}NO_7$: C, 59,18, H, 6.33; N, 3.83. Found: C, 59.04; H, 6.33; N, 3.69.

The fourth fraction (72 mg) consisted of **10**, together with small amounts of **5** and **6**. Recrystallization from acetone–ethanol afforded 61 mg (4.8%) of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-(methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-

β-D-glucopyranosid-2-yl)-3-nitro-β-D-glucopyranoside (**10**); m.p. >290° (dec.), $[\alpha]_D^{22}$ −44.0° (*c* 0.5, chloroform); ν_{max} 1550 cm^{-1} (NO_2); *m/z* 588 (M^+) and 542 ($M - NO_2$); R_F 0.41.

Anal. Calc. for $C_{28}H_{32}N_2O_{12}$: C, 57,14, H, 5.48; N, 4.76. Found: C, 57.24; H, 5.46; N, 4.55.

The fifth fraction (77 mg) was mainly comprised of the glycosid-3-ulose **8**, which was recrystallized from isopropyl alcohol (40 mg, 3.0%), identical with an authentic sample[5].

The sixth fraction (374 mg) consisted of many compounds, as judged from the ^{1}H-n.m.r. and i.r. spectra (the presence of hydroxyl, carbonyl, and nitro groups). This fraction was similarly reduced and the products acetylated. Chromatographic separation with 30:1 benzene–ethyl acetate afforded the acetate **4** (74 mg, 4.2%).

Similar irradiation of **1** (440 mg, 1.5 mmol) in THF (15 mL) for 8 h at room temperature, and chromatographic separation, gave **9** (40.2%), **5** (7.9%), and **6** (1.5%), besides small amounts of **3** and **8**.

The 3-deuterio derivative of **9** was prepared as follows. A solution of **9** (29 mg) and 0.2M sodium hydroxide-*d* in tetrahydrofuran (3 mL) was stirred for 1 h at room temperature, and then partitioned between dilute hydrochloric acid and ethyl acetate. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to a residue whose ^{1}H-n.m.r. spectrum showed that C-3 of **9** was completely monodeuterated.

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