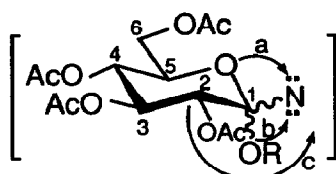


## Photolysis of Methyl 1-Azido Glucosides: unprecedented Expansions of the Pyranose Ring under high Stereocontrol

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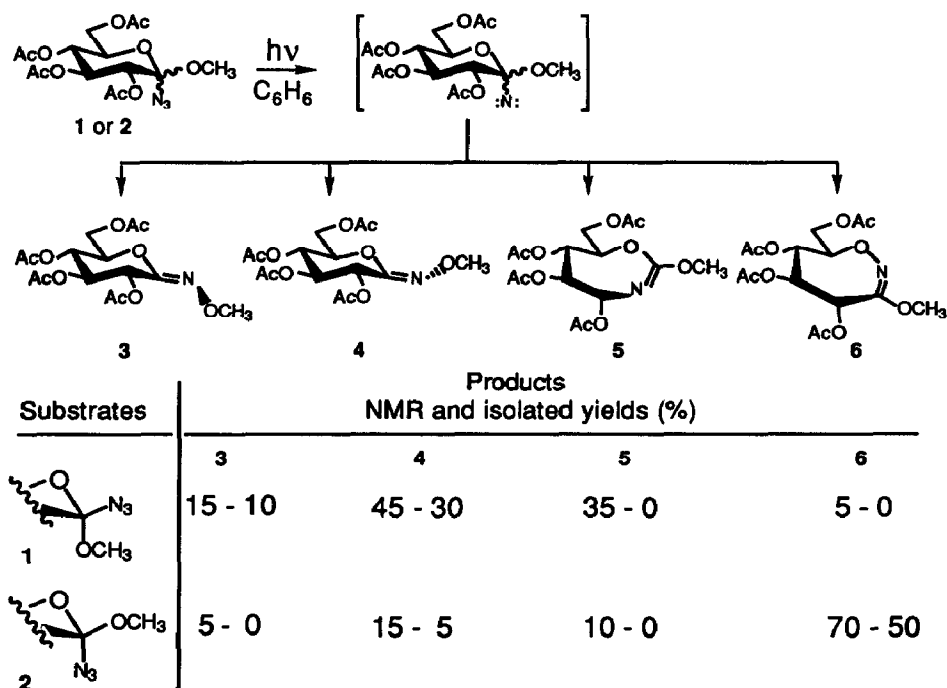
**Abstract:** New structures arising from the photolysis of peracetylated methyl 1-azido-D-glucopyranosides account for the formation of excited intermediates which undergo stereocontrolled migrations of either the O-5 oxygen atom (a) or, competitively, the O-1 oxygen atom (b) or the C-2 carbon atom (c), depending, respectively, on the  $\alpha$  or  $\beta$  orientation of the azido group in the substrate.

Glycosyl azides constitute an accessible class of sugar derivatives<sup>1</sup> which is receiving considerable attention due to the versatile reactivity of the azido group<sup>2</sup>. In particular, as we recently observed, they open a high-yielding route toward unprecedented sugar bromoiminolactones under free-radical condition<sup>3</sup>. In addition, anomeric diazides proved interesting substrates leading to new sugar-derived tetrazoles in good yields<sup>4</sup>. Treatment of peracetylated sugar ortholactones by trimethylsilyl azide in the presence of boron trifluoride etherate appeared deceiving as regard to the diazide preparation, although the exchange of a single alkoxy group occurred readily, leading to peracetylated methyl 1-azido-D-glucopyranosides **1** and **2**<sup>5</sup>. Such azido sugars in which the anomeric hydrogen atom has been replaced by an alkoxy group appeared promising substrates to develop new synthetic transformations at the anomeric centre of sugars. To this end, the photolysis of each anomer **1** or **2** was investigated. It was hoped that the bond reorganization triggered by the generation of a nitrene (or, possibly, an excited azide, not represented in the schemes) attached to C-1 could be easily interpreted since the anomeric centre in **1** or **2** is linked to four different groups, with a known stereochemistry (NMR, X-ray analysis<sup>5</sup>).



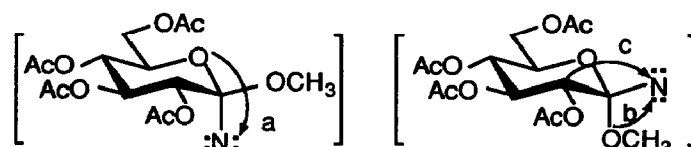
Photolysis of a benzene solution (4 mL) of **1** or **2** (163 mg, 0.4 mmol) was carried out with a medium pressure mercury lamp (Hanovia, 450 W, unfiltered light), using a quartz tube (1cm external diameter) close to the lamp (~1 cm). Irradiation of the solution (~30–40°C) was maintained until TLC showed the disappearance of the starting materials (~5h in both cases). Then, after benzene removal under reduced pressure, the crude reaction mixture dissolved in deuteriochloroform was examined by <sup>1</sup>H and <sup>13</sup>C NMR before purification by column chromatography on silica gel (silica gel 60-Merck) with ethyl acetate-*n*-hexane 1:1 v/v as the solvent. The structures of the outcoming products<sup>6</sup> (**3**, **4**, **6** then **5** on TLC) as well as their estimated proportion (<sup>1</sup>H NMR)<sup>7</sup> and their isolated yields are indicated in the scheme. Except for compound **5** which decomposed<sup>8</sup> on silica gel during the purification step, both figures are in good agreement, indicating a clean reaction (neither trailings nor polar spot on TLC plates).

The structures of the products can be rationalized by invoking intermediates which gave rise to bond reorganization (1,2-shifts)<sup>9,10</sup>. Whereas both 3 and 4 resulted from the migration of the methoxy group, 5 and 6 are explained by the creation of a new bond between the nitrogen atom and, respectively, the C-2 carbon atom or the O-5 oxygen atom. *Quite interestingly, the product distribution clearly shows a striking difference depending on the anomeric configuration of the substrates.* In the case of 1 (equatorial azido group), migration of the OMe group predominated (3 + 4: ~50 %) over that of the C-2 carbon atom (5: ~35 %). However, 2 was selectively transformed in 6 (~60 %) due to the migration of the O-5 oxygen atom. Beside the unexpected creation of a N—O bond<sup>10</sup>, these data show that rearrangements of excited nitrogen-containing intermediates attached to the anomeric center occurred with a high stereocontrol to produce either hydroximolactone derivatives or ring-expanded structures. In order to decide whether these latter compounds resulted from the formers by a photo-Beckmann rearrangement, a benzene solution of 4 was exposed to UV light for 3h<sup>15</sup>. After this treatment, either TLC or <sup>1</sup>H NMR showed the sample to consist essentially of unaltered starting material. This is in keeping with the reluctance of *peracetylated* (*Z*)-hydroximo-aldonolactone derivatives to undergo the Beckmann rearrangement<sup>11</sup>. Finally, although 1,2-shifts are the preferred processes triggered by photodecomposition of alkyl azides<sup>9</sup>, couplings to yield azo derivatives have been observed<sup>12</sup> when triplet nitrenes are involved. Studies delineating the electronic states of the intermediates (discrete nitrene or excited azide, either singlet or triplet<sup>9</sup>) took advantage of this dichotomy. In the present case, photolysis of a benzene solution of 1 and acetophenone ( $5 \times 10^{-3}$  M) as a triplet (azide<sup>12</sup> or nitrene<sup>13</sup>) sensitizer, led to the same transformation, although with a somewhat higher selectivity (<sup>1</sup>H NMR distribution of 3, 4, 5, 6: 3, 45, 45, 7%)<sup>14</sup>.



The purification step did not alter compound **3** since the isolated yield reflect the crude mixture distribution. However, (*E*)-**3** isomerized spontaneously to (*Z*)-**4**, either in the pure state (within a few days) or in solution (~24 h in chloroform), in agreement with the independantly observed greater stability of various (*Z*)-sugar iminolactone derivatives<sup>3,11</sup>. The (*E*) configuration in **3** is supported by the deshielded signals observed for both the H-2 proton and C-1 carbon in the NMR spectra<sup>3,11</sup>. The structure attributed to the labile compound **5** rests on NMR examination of the crude reaction mixtures which contained up to 45 % of this material. In particular, the chemical shift of the C-1<sup>15</sup> signal (155.1 ppm) is close to that reported for a related 7-membered structure (152.8 ppm) obtained from sugar hydroximolactones by the Beckmann rearrangement<sup>11</sup>. The absolute configuration assigned to the C-2 carbon atom in **5** stems from the <sup>3</sup>J<sub>H-2,H-3</sub> value (8.4 Hz)<sup>16</sup> which is similar to that recorded for <sup>3</sup>J<sub>H-2,H-3</sub> in **6** (8.7 Hz). In this latter compound, there is no doubt about the *trans* relationship of the H-2 and H-3 protons. Hence, the configuration of the migrating carbon atom was retained along the process 1→**5**. To our knowledge, **6** represents a new class of sugar-derived cyclic (7-membered) N-alkoxy imidate<sup>17</sup>. The bond reorganization leading to this compound was not anticipated on the ground of literature data<sup>10</sup>. We have shown that the minor tetrazole obtained from a peracetylated anomeric diazide by photolysis also exhibit such a N—O linkage<sup>4</sup>. The ring-expanded structures obtained in both cases are similar in several respects concerning either their reactivity (lower stability of **5** as compared to **6** whose deacetylation led to the corresponding free compound readily identified by NMR<sup>6</sup>, in keeping with the observations concerning the tetrazoles) or their spectroscopic data. In particular, the <sup>2</sup>J<sub>C-1,H-2</sub> and <sup>3</sup>J<sub>C-1,H-3</sub> heteronuclear couplings observed in 2D-NMR spectra of **6** are particularly significant to prove the continuity of the sugar carbon chain in **6**.

In conclusion, photolysis of both anomers of peracetylated methyl 1-azido-D-glucopyranoside gave rise to a bond reorganization in the vicinity of the anomeric carbon, leading either to methoxy iminolactone derivatives or to new ring-expanded structures. These processes showed a high stereocontrol resulting in the preferential migration of either the O-5 ring oxygen atom (a) or, competitively, the O-1 glycosidic atom (b) or the C-2 carbon atom (c), as illustrated<sup>18</sup> below, depending, respectively, on the α or β orientation of the azido group in the initial substrates. Investigations are in progress to extend the scope of this unprecedented approach.



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6. Satisfactory elemental analyses have been obtained for compounds 4 and 6. NMR data for CDCl<sub>3</sub> solutions, unless otherwise indicated, with tetramethylsilane as the internal reference ( $\delta$  ppm, J Hz); <sup>1</sup>H NMR (200.13 MHz): 3: 6.03 (d, 1H, J<sub>2,3</sub> 3.4, H-2), 5.18 to 5.10 (m, 2H, H-3, H-4), 4.44 (m, 1H, H-5), 4.29 (m, 2H, H-6, H-6'), 3.79 (s, 3H, OMe), 2.14, 2.10, 2.10, 2.08 (3H\*4, acetyl); 3 (C<sub>6</sub>D<sub>6</sub>): 6.44 (d, 1H, J<sub>2,3</sub> 3.3, H-2), 5.46 (t, 1H, J<sub>3,4</sub> 4.7, H-3), 5.31 (dd, 1H, J<sub>4,5</sub> 9.2, H-4), 4.35 to 4.05 (m, 3H, H-5, H-6, H-6'), 3.61 (s, 3H, OMe), 1.65, 1.61, 1.60, 1.57 (3H\*4, acetyl); 4: 5.41 (d, 1H, J<sub>2,3</sub> 3.4, H-2), 5.11 to 5.17 (m, 2H, H-3, H-4), 4.55 (dq, 1H, J<sub>4,5</sub> 9.6, J<sub>5,6</sub> 3.9, H-5), 4.38 (dd, 1H, J<sub>5,6'</sub> ~3, H-6), 4.30 (dd, 1H, J<sub>6,6'</sub> ~12, H-6'), 3.86 (s, 3H, OMe), 2.159, 2.112, 2.105, 2.083 (3H\*4, acetyl); 5: 6.11 (d, 1H, J<sub>2,3</sub> 8.4, H-2), 5.10 (t, 1H, J<sub>3,4</sub> 8.1, H-3), 5.33 (dd, 1H, J<sub>4,5</sub> 9.2, H-4), 4.22 to 4.37 (m, 2H, J<sub>5,6</sub> 2, H-5, H-6), 4.18 (dd, 1H, J<sub>6,6'</sub> ~12, H-6') 3.74 (s, 3H, OMe), 2.109, 2.098, 2.043, 2.040 (3H\*4, acetyl); 6: 6.11 (d, 1H, J<sub>2,3</sub> 8.7, H-2), 5.20 to 5.33 (m, 2H, H-3, H-4), 4.28 (dd, 1H, J<sub>6,6'</sub> 12.0, H-6), 4.20 (dd, 1H, J<sub>5,6'</sub> 3.5, H-6'), 3.94 (dq, 1H, J<sub>5,6</sub> 5.5, H-5), 3.81 (s, 3H, OMe), 2.12, 2.11, 2.08, 2.04 (3H\*4, acetyl); 6: (C<sub>6</sub>D<sub>6</sub>): 6.35 (m, 1H, J<sub>2,3</sub> ~8.7, H-2), 5.43 to 5.49 (m, 2H, H-3, H-4), 3.87 (m, 1H, J<sub>4,5</sub> ~7.6, J<sub>5,6</sub> ~5, H-5), 4.31 (dd, 1H, J<sub>5,6'</sub> 3.6, H-6), 4.20 (dd, 1H, J<sub>6,6'</sub> 12.1, H-6'); <sup>13</sup>C NMR (50.32 MHz): 3: 155.4 (C-1), 74.2, 71.3, 62.8, 68.0 (C-2 to C-5), 62.1 (C-6), 62.1 (OMe); 3 (C<sub>6</sub>D<sub>6</sub>): 156.0 (C-1), 74.4, 72.2, 63.4, 68.6 (C-2 to C-5), 61.9 (C-6), 62.4 (OMe), 169.9, 169.6, 168.9, 168.2 (C=OCH<sub>3</sub>), 20.1, 20.0, 19.9 (C=OCH<sub>3</sub>); 4: 146.8 (C-1), 73.8, 72.1, 67.7, 68.9 (C-2 to C-5), 61.5 (C-6), 62.8 (OMe), 170.6, 169.1, 169.1, 168.2 (C=OCH<sub>3</sub>), 20.8, 20.7, 20.6, 20.6 (C=OCH<sub>3</sub>); 5: 155.1 (C-1), 79.1, 77.8, 71.7, 68.9 (C-2 to C-5), 62.2 (C-6), 56.4 (OMe); 6: 172.2 (C-1), 79.2 (C-5), 71.0 (C-4), 67.6 (C-2), 70.4 (C-3), 62.4 (C-6), 56.4 (OMe), 170.7, 169.5, 169.3, 169.1 (C=OCH<sub>3</sub> at C-6, C-3, C-2, C-4, respectively), 20.8, 20.6, 20.5, 20.3 (C=OCH<sub>3</sub> at C-6, C-2, C-3, C-4, respectively). For 6, unambiguous assignments and <sup>1</sup>J<sub>C,H</sub> coupling constants (J<sub>C-2,H-2</sub> ~154 Hz, J<sub>C-3,H-3</sub> to J<sub>C-6,H-6</sub> ~152 Hz) were obtained from 2D NMR spectra (HMQC and HMBC gradients). The recorded correlations showed clearly that long range heteronuclear couplings exist between the C-1 carbon atom and the H-2, H-3 and methoxy protons. Other data: 4: mp 97-98°C (diethyl ether-petroleum ether),  $\nu$  C=N: 1655 cm<sup>-1</sup>, [ $\alpha$ ]<sub>D</sub> +84° (c = 0.3, chloroform); 6:  $\nu$  C=N: 1620 cm<sup>-1</sup>, [ $\alpha$ ]<sub>D</sub> -9° (c = 0.5, chloroform), MS e.i.: m/z 376 [M+1]<sup>+</sup> 0.22 %, c.i. (NH<sub>3</sub>): m/z 376 [M+1]<sup>+</sup> 100 %. The spectroscopic data obtained from 6 upon deacetylation are:  $\nu$  C=N: 1615 cm<sup>-1</sup>, <sup>1</sup>H NMR (D<sub>2</sub>O): 4.84 (d, 1H, J<sub>2,3</sub> 9.8, H-2), 3.47 (t, 1H, J<sub>3,4</sub> 8.4, H-3), 3.63 (t, 1H, J<sub>4,5</sub> 9.9, H-4), 3.49 (dq, 1H, J<sub>5,6</sub> 2.4, H-5), 3.90 (dd, 1H, J<sub>5,6</sub> 6.2, H-6), 3.68 (dd, 1H, J<sub>6,6'</sub> 12.5, H-6'), 3.77 (3H, OMe); <sup>13</sup>C NMR (D<sub>2</sub>O): 178.8 (C-1), 75.7, 69.7, 75.0, 86.8 (C-2 to C-5), 63.7 (C-6), 58.7 (OMe).
7. The product distribution was calculated from the area of the well separated methoxy singlets.
8. The decomposition of 5 during column chromatography can be explained by either an enhanced basicity of the nitrogen atom due to the stabilisation of positive charge at the sp<sup>2</sup>-hybridized carbon atom by the attached heteroatoms or a higher reactivity of the protonated species, as compared to those derived from 3, 4 or 6. As a result, this centre should be prone to nucleophilic attack by water to yield either cyclic or opened non isolated carbamates (see ref. 11).
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14. To avoid oxygen, which is known as a triplet quencher (ref. 13), argon was bubbled for 40 mn into the solution, prior to irradiation (2h30).
15. For the sake of clarity, atom numbering in product 5 follows that of the parent sugar.
16. Literature data show that an opposite configuration at C-2 in 5 should result in a <sup>3</sup>J<sub>H-2,H-3</sub> coupling of about 2 Hz (ref. 11).
17. For a recent although quite different synthesis of related 5-membered ring structures, see: Barrett, A. G. M.; Dhanak, D.; Lebold, S. A.; Russell, M. A. *J. Org. Chem.*, **1991**, *56*, 1894-1901.
18. Concerted migration-nitrogen loss, without the intervention of a discrete nitrene intermediate is not excluded<sup>9</sup>.

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