New and Efficient Synthesis of Protected 2-Azido-2-deoxy-glycopyranoses from the Corresponding Glycal

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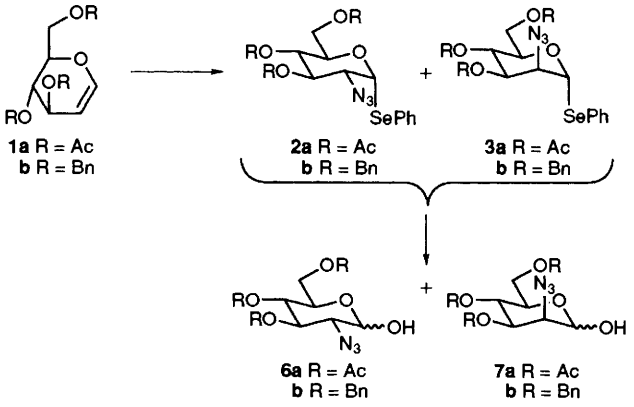
Diversely protected 2-azido-2-deoxy-D-glycopyranoses are prepared by azido phenylselenylation of the corresponding glycal followed by hydrolysis of the resulting selenoglycosides: from protected D-galactal, protected 2-azido-2-deoxy-D-galactopyranose is obtained, as the sole product in 72% overall yield.

Protected 2-azido-2-deoxy derivatives of galactose and glucose are employed for the synthesis of biologically important 2-amino-2-deoxy-galactose (and glucose) containing glycosides.[1] The azidonitration of protected glycals disclosed by Lemieux and Ratcliffe in 1979,[2] is still the best route to these derivatives. The obtained 2-azido-1-nitrate adducts could be transformed into various glycosyl donors by displacement of the anomeric nitrate by halide ions[2] or potassium *O*-ethyl dithio-carbonate.[3] Efficient glycosyl donors such as trichloroacetimidates[4] and fluorides[5] also can be prepared after hydrolysis of the anomeric *O*-nitrate. The problem of the hydrolysis was addressed and several solutions were proposed.[4,6,7]

We report herein a new route to protected 2-azido-2-deoxy glycopyranoses in which a protected glycal is transformed by azido-phenylselenylation into a phenyl 2-azido-2-deoxy selenoglycoside which is readily hydrolysed into the title product.

Azido-phenylselenylation of double bonds is a very versatile reaction because it allows the one-step introduction of two functionalities in a molecule.[8,9] Moreover, with unsymmetrical olefins, the regioselectivity can be controlled: with electrophilic phenylselenium species (*e.g.* PhSeCl) in the presence of azide ion, Markovnikov adducts are prevalent[8] whereas anti-Markovnikov addition products are obtained by treatment of an olefin with sodium azide and diphenyldiselenide in the presence of (diacetoxyiodo)benzene which oxidizes azido ion into azido radical.[9] Giuliano *et al.* reported the formation of mixtures of regioisomers in the azido-phenylselenylation of exocyclic alkenes under a variety of conditions.[10] Although one example of azido-phenylselenylation of cyclic enol ether has been reported,[9] to the best our knowledge protected glycals have not been subjected to these reaction conditions.

The azido radical can be obtained by oxidation of azido ion by many oxidants.[9,11,12] In the presence of an olefin, diazido derivatives were generally obtained, except for the azido-nitration of Lemieux[2] in which an excess of cerium ammonium nitrate is employed. We expected that the radically induced azido-phenylselenylation of protected glycals would afford 2-azido-2-deoxy selenoglycosides which could be hydrolysed into 2-azido-2-deoxy glycosides under mild conditions.



Scheme 1

Commercially available tri-*O*-acetyl-D-glucal **1a** was employed to evaluate several oxidants and solvents in the presence of sodium azide and diphenyldiselenide.

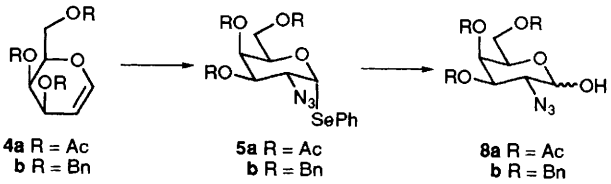
The best results were obtained when **1a** (1 mmol) was reacted with (diacetoxyiodo)benzene (1.4 mmol) and sodium azide (2.4 mmol) in the presence of diphenyldiselenide (0.6 mmol) in CH_2Cl_2 (4 ml) at room temp. (48 h) in agreement with the results of Tingoli *et al.*[9] After classical work-up and flash chromatography with CH_2Cl_2 a mixture of **2a** and **3a** (60:40) was isolated in 91% yield.† The diasteroisomeric products were readily distinguishable by examining the H-1 signals in the ^1H NMR spectrum. Interestingly only the α-anomers were formed, as indicated by the values of the H-1, H-2 coupling constants (H-1 of the *gluco* isomer **2a**, δ 5.95, $J_{1,2}$ 5.3 Hz in $CDCl_3$, H-1 of the *manno* isomer **3a**, δ 5.8, bs, in $CDCl_3$).[13]

When the benzylated D-glucal **1b** was treated under the same conditions, a mixture of **2b** and **3b** was formed in the same proportions but some degradation was observed before the reaction was complete.‡ When **1b** was reacted with azidotrimethylsilane (4 equiv.) tetra-*n*-butylammonium fluoride (0.2 equiv.) and *N*-phenylselenophthalimide (*N*-PSP) (2 equiv.) in methylene chloride as described by Giuliano *et al.*, for exocyclic alkenes,[10] **2b** and **3b** (50:50) were obtained in 60% yield. This result was difficult to rationalize because there is no oxidant to generate the azido radical.

When tri-*O*-acetyl-D-galactal **4a** was treated with (diacetoxyiodo)benzene in the presence of $(PhSe)_2$ as **1a**, the α-*galacto* isomer **5a** was obtained as the sole product in crystalline form† (70%, m.p. 104–105 °C, $[\alpha]_D$ 170 c = 1 in CH_2Cl_2). The *galacto* configuration was unambiguously determined by ^1H NMR (H-1, δ 6.0, $J_{1,2}$ 5.4 Hz in $CDCl_3$). Although the *talo* azido-nitrate is formed (4–8%) during azido-nitration of diversely protected D-galactal derivatives,[2,3] no *talo* isomer could be detected by ^1H NMR spectroscopy in the crude mixture. When **4b** was reacted with *N*-PSP as **1b**, complete stereocontrol was observed and the α-*galacto* selenoglycoside **5b** was obtained as the sole product† (72%, oil, $[\alpha]_D$ 157 c = 1 in CH_2Cl_2, H-1, δ 5.95, $J_{1,2}$ 5.22 Hz in $CDCl_3$).

Our results with the tri-*O*-acetyl-D-glycals are in good agreement with a rapid addition of electrophilic azido radical[11] to C-2 of the electron-rich double bond affording an anomeric radical stabilized in the α configuration by the anomeric effect. Further homolytic reaction with $(PhSe)_2$ affords the α-selenoglycoside.[9] However, further work is necessary to understand the mechanism of the reaction with *N*-PSP.

These easily obtained 2-azido-2-deoxy-selenoglycosides were subjected to hydrolysis to generate the anomeric hydroxy. Owing to the *soft* nature of the selenium atom, *soft* catalysts such as heavy metal salts were evaluated.



Scheme 2

When the mixture of **2b** and **3b**† (1 mmol) was treated with mercury trifluoroacetate (1.5 mmol) in tetrahydrofuran (THF)–H_2O (2 ml, 1:1) at room temp., the reaction was complete within 30 min, and a mixture of *gluco*-**6b** and *manno*-**7b** derivatives was obtained in 93% yield.† Silica gel column chromatography (eluent: ether–petrol ether, 1:2) afforded **6b** in crystalline form (66%, m.p., 97 °C $[\alpha]_D$ 17 $c = 1$ in $CHCl_3$)[14] **7b** as an oil (12%, $[\alpha]_D$ 27.2 $c = 1$ in $CHCl_3$) and a mixture of **6b** and **7b** (15%). Treatment of the *galacto* derivative **5b** under the same conditions afforded **8b** after flash chromatography as an oil (90%, $[\alpha]_D$ 98.2 $c = 1$ in CH_2Cl_2).

Under these conditions, the hydrolysis of the acetylated derivatives **2a**, **3a** and **5a** was very slow, presumably because of the electron-withdrawing effect of acetoxy groups disfavouring the formation of the carbenium ion. When NIS (5 equiv.) was employed instead of mercury trifluoroacetate the reaction was complete in 12 h at room temp. From **2a–3a** an inseparable mixture of **6a** and **7a** was obtained (90%). The *galacto* azido-selenoglycoside **5a** was transformed into **8a** (87%).

The complete stereocontrol obtained in the *galacto* series makes this new procedure very useful. For convenience it has been verified that the two steps can be carried without purification of the intermediate azido-selenoglycosides **5b**. In this case, after azido-selenylation of **4a**, the precipitate is filtered off and the solvent is evaporated. Hydrolysis of the crude **5b**, (mercury trifluoroacetate, THF–H_2O) afforded **8b** after flash chromatography (72% overall yield).

We believe that the efficient procedure described in this paper will be a useful addition to the preparation of 2-azido-2-deoxy-glycosyl donors from glycals.

The study of the scope and limitations of this route is in progress in our laboratory.

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Footnotes

† All new compounds described gave C, H, N analysis and spectroscopic data in agreement with the structure. Selected data are given in the text.

‡ Presumably by oxidative cleavage of the benzyl groups. A mixture of **2b** and **3b** was isolated in 14% yield by working-up the reaction before important degradation.

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