

Synthesis of spacer-armed glycosides using azidophenylselenylation of allyl glycosides

Andrei A. Sherman, Leonid O. Kononov, Alexander S. Shashkov, Georgij V. Zatonsky and Nikolay E. Nifant'ev*

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation.
Fax: +7 095 135 8784; e-mail: nen@ioc.ac.ru*

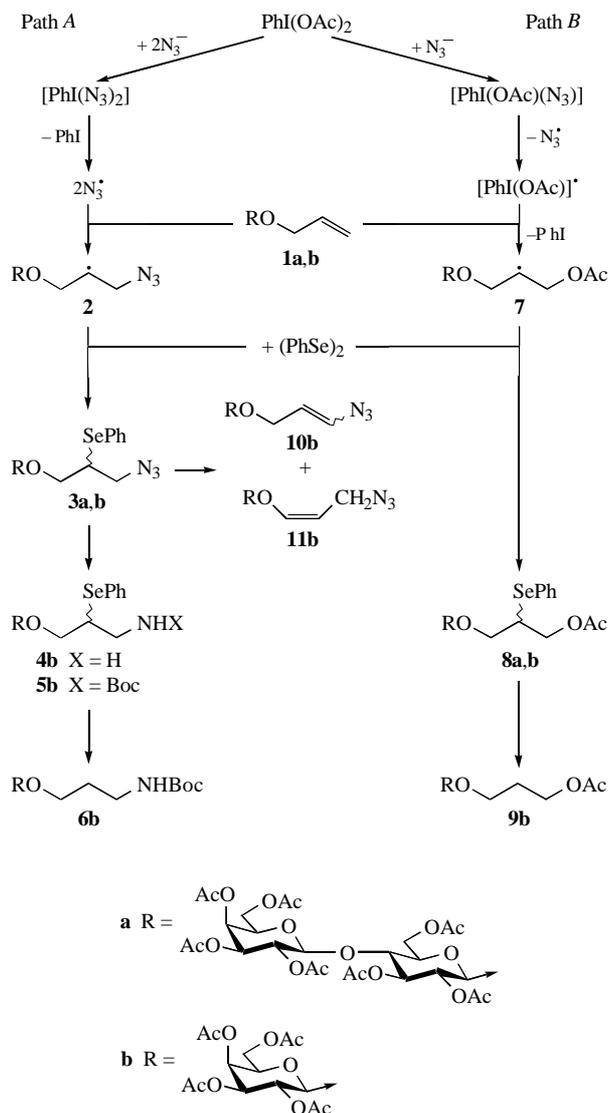
Protected 3-aminopropyl spacer-armed glycosides that can be further used for the preparation of neoglycoconjugates have been prepared from allyl glycosides using azidophenylselenylation of the double bond as a key step.

Neoglycoconjugates are synthetic compounds that emulate the behaviour of the natural glycoconjugates and are useful tools in glyobiology research.^{1,2} A prerequisite for the preparation of neoglycoconjugates is the accessibility of a spacer-armed glycoside, *i.e.* a glycoside with a functional group in the aglycon that can be used for coupling to a carrier. An amino function at the terminal position of an aglycon alkyl chain has been widely used for this purpose.² For example, 3-aminopropyl glycosides³ have already been used for the preparation of various neoglycoconjugates. However, there still exists a need for the development of new approaches to the preparation of such spacer-armed glycosides from simple glycosides (so called pre-spacer glycosides) under mild conditions. Such an

approach would be of special importance for long-chain oligosaccharides.

Retrosynthetic analysis shows that 3-aminopropyl glycosides may be obtained by addition of a synthetic equivalent of the amino group to the double bond of allyl glycosides. We anticipated that azidophenylselenylation⁴ of allyl glycosides followed by subsequent reduction of the azido function and removal of the phenylselenenyl moiety (Scheme 1, path A) could constitute a new approach to the preparation of 3-aminopropyl spacer-armed glycosides from allyl glycosides (for other methods of functionalization of allyl glycosides see refs. 5–7).

Peracetylated allyl lactoside **1a**^{8,9} was chosen as a model substrate for azidophenylselenylation which was performed under the conditions developed⁴ for aliphatic alkenes. Treatment of **1a** (0.05 mmol) with NaN₃ (2.4 equiv.), (PhSe)₂ (0.6 equiv.) and PhI(OAc)₂ (1.4 equiv.) in CH₂Cl₂ (0.5 ml) at 20 °C (18 h)



Scheme 1

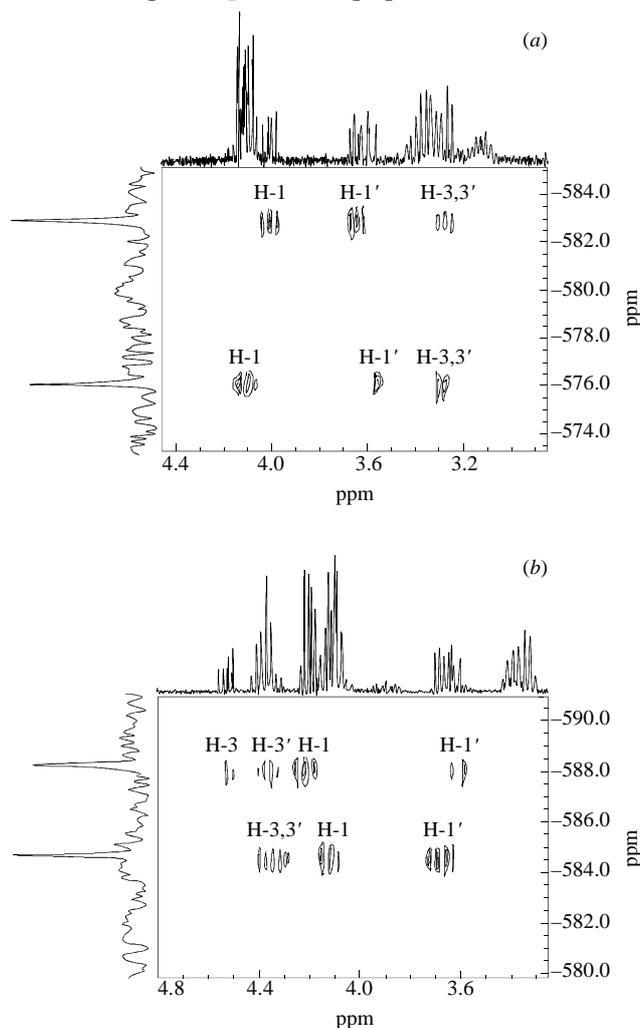


Figure 1 2D ¹H–⁷⁷Se NMR spectra of compounds **3b** (a) and **8b** (b) (Bruker AM-300, 303 K, C₆D₆). Numeration of atoms in the aglycon: sugar-1-2-3.

Table 1 ^1H , ^{13}C and ^{77}Se NMR data (δ/ppm)^{a,b} for aglycons in compounds **3a,b**, **5b**, **6b**, **8a,b**, **9b**, **10b** and **11b**.

Compound	H-1	H-1'	H-2	H-3	H-3'	C-1	C-2	C-3	Se	Other
3a^c	3.63	4.07	3.12	3.27	3.35	70.2	43.3 43.7	52.5	-575 -580	<i>e</i>
3b^d	4.09 4.01	3.60 3.65	3.11 3.14	3.35 3.35	3.29 3.28	69.7 69.9	43.4 42.9	52.4 52.5	-576 -583	<i>f</i>
5b	3.65-3.80	4.11-4.17	3.42-3.47	3.34	3.44	70.7	44.2 44.5	42.4		<i>g</i>
6b	3.58	3.94	1.88	3.19	3.19	67.9	29.8	37.8		<i>h</i>
8a^c	4.39-4.53	4.39-4.53	3.37	3.58-3.70	4.04-4.16	69.5	42.4 42.7	64.3		<i>i</i>
8b^d	4.21 4.12	3.64 3.69	3.40 3.38	4.52 4.37	4.38 4.27	69.4 69.9	41.8 42.3	64.1 64.2	-588 -585	<i>j</i>
9b	3.56	3.96	1.90	4.12	4.12	70.7	28.8	61.1		<i>k</i>
10b (E)	4.15	4.32	5.41	6.15		63.2	131.1	115.2		
10b (Z)	4.17		5.03	6.33		66.7	129.1	114.6		
11b	6.33		5.01	4.17		101.8	129.1	68.1		

^aNMR spectra were recorded with a Bruker AM-300 instrument at 303 K in CDCl_3 unless otherwise stated. Acetone was used as an external standard in ^1H (2.225 ppm) and ^{13}C NMR (31.45 ppm) and $(\text{PhSe})_2$ in ^{77}Se NMR (-4.60 ppm¹¹). In all compounds the chemical shifts of the protons and carbons of the sugar moiety were very close to the published^{6,8,9} ones and thus are not presented. ^bNumeration of atoms in the aglycon: sugar-1-2-3. ^c ^1H , ^{13}C and ^{77}Se NMR spectra were recorded in C_6D_6 . ^d ^1H and ^{77}Se NMR spectra were recorded in C_6D_6 . ^e $\text{C}_6\text{H}_5\text{Se}$ 6.93-7.47 (5H). ^f $\text{C}_6\text{H}_5\text{Se}$ 7.03-7.62 (5H). ^g $\text{C}_6\text{H}_5\text{Se}$ 7.29-7.61 (5H); $(\text{CH}_3)_2\text{C}$ 1.41 (9H). ^h $(\text{CH}_3)_3\text{C}$ 1.43 (9H). ⁱ $\text{C}_6\text{H}_5\text{Se}$ 6.91-7.53 (5H); CH_3CO 1.52-1.96 (24H). ^j $\text{C}_6\text{H}_5\text{Se}$ 7.01-7.55 (5H); CH_3CO 1.62-1.98 (15H). ^k CH_3CO 1.98-2.16 (15H).

unexpectedly afforded two adducts **3a** (31%, 1.2:1 ratio of diastereoisomers) and **8a** (23%, 1.3:1 ratio of diastereoisomers) rather than a single product (*cf.* ref. 4). Unidentified products possessing neither allyl nor aromatic fragments (^1H NMR data) were also isolated in *ca.* 20% yield.

The presence of PhSe groups in both adducts **3a** and **8a**, seven AcO groups in **3a** and eight AcO groups in **8a** was evident from ^1H , ^{13}C and ^{77}Se NMR data (Table 1). Compound **3a** has an absorption band at 2108 cm^{-1} in the IR spectrum which is characteristic of an azido group whereas in **8a** this band was absent. The spectral data obtained allowed us to surmise that **3a** and **8a** were the products of azidophenylselenylation and acetoxyphenylselenylation of **1a**, respectively.

The overlap of signals of five aglycon protons and four H-6 protons of glucose and galactose residues in the ^1H NMR spectra of **3a** and **8a** complicated the determination of the exact substitution pattern of the aglycon. In order to simplify interpretation of the spectra, azidophenylselenylation of allyl galactoside **1b**⁶ was performed under the same conditions. The reaction afforded the desired azido adduct **3b** (23%, 1.1:1 ratio of diastereoisomers) together with the acetoxy derivative **8b** (42%, 1.4:1 ratio of diastereoisomers).

The structures of the adducts **3b** and **8b** were determined similarly by a combination of NMR and IR spectroscopies. However, in this case it was possible to prove unambiguously by 2D ^1H - ^{77}Se NMR spectroscopy the position of the phenylselenyl moiety at C-2 of the aglycon in both **3b** and **8b**. Thus, the spectra (Figure 1) of both compounds **3b** and **8b** contained correlation cross-peaks between the selenium signals and the signals of all methylene protons of the aglycon. This is possible only if the PhSe moiety is attached to the C-2 carbon. 2D ^1H - ^{77}Se HMQC experiments¹⁰ were optimized for the observation of couplings with $J_{\text{H-Se}}$ 5 Hz, hence the spectra do not contain correlation cross-peaks between selenium and the proton at C-2 of the aglycon since the geminal $^2J_{\text{H-Se}}$ is known¹¹ to be *ca.* 10 Hz.

The competitive acetoxyphenylselenylation observed can be rationalised as follows. The azidophenylselenylation reaction (Scheme 1, path A) is thought⁴ to involve oxidation of two azide anions by $\text{PhI}(\text{OAc})_2$ into azide radicals followed by their addition to alkene **1** and subsequent trapping of the resulting carbon-centered azido radical **2** with $(\text{PhSe})_2$. Apparently, oxidation of azide anion by $\text{PhI}(\text{OAc})_2$ proceeds (Scheme 1, path A) via an exchange reaction leading to $\text{PhI}(\text{N}_3)_2$, which decomposes rapidly into two azide radicals and PhI. When the concentration of azide anion is low (due to the poor solubility of NaN_3 in CH_2Cl_2), substitution of only one AcO group in

$\text{PhI}(\text{OAc})_2$ may occur (path B) leading to the mixed species $\text{PhI}(\text{OAc})(\text{N}_3)$, which decomposes into azide and $\text{PhI}(\text{OAc})^\bullet$ radicals. The latter can react with alkene **1** by transfer of an AcO radical and liberation of PhI. Subsequent trapping of the resulting carbon-centered acetoxy radical **3** with $(\text{PhSe})_2$ completes the acetoxyphenylselenylation. Thus, it is likely that the low concentration of azide anion in the reaction medium is responsible for the formation of the acetoxy adducts **8a,b**.

In order to increase the effective concentration of azide anion we performed the reaction in other solvents. In MeCN the ratio of the adducts **3b** and **8b** was similar to that obtained in CH_2Cl_2 , but in pyridine or in tetramethylurea the formation of **3b** prevailed over **8b** (TLC data). Addition of water did not influence the **3b/8b** ratio, but decreased the reaction rate significantly. In *N,N*-dimethylformamide (DMF) the reaction was slow, however, it resulted in the exclusive formation of **3b**. We reasoned that the addition of a crown ether would further increase the effective concentration of azide anion and hence accelerate the reaction. Portion-wise addition of $\text{PhI}(\text{OAc})_2$ (2 equiv. in total) to a solution of **1b** (0.41 mmol), $(\text{PhSe})_2$ (0.6 equiv.) and NaN_3 (3 equiv.) in anhydrous DMF (2 ml) containing 18-crown-6 (1 equiv.) at 20 °C (72 h) yielded 86% of azidophenylselenylation adduct **3b** as the only product. Formation of acetoxyphenylselenylation by-product **8b** was totally suppressed under high effective concentration of azide anion.

Further transformation of the azidophenylselenylation adduct **3b** into the target 3-aminopropyl glycoside required removal of the phenylselenyl residue and reduction of the azido moiety, which could be accomplished either simultaneously or in a step-wise manner (in any order). However, attempted reduction of azide and simultaneous deselenation of **3b** with Bu_3SnH and AIBN in refluxing toluene failed leading to complex mixtures resulting probably from competitive reactions of the amine initially formed from azide (*cf.* ref. 12). Deselenation of **3b** using elimination of PhSeOH from the corresponding selenoxide formed *in situ* by oxidation (H_2O_2) of **3b** afforded nearly quantitatively the corresponding *cis* and *trans* vinyl azides **10b** together with *cis* vinyl ether **11b** in a 2:4:1 ratio. Hydrogenation (H_2 , 10% Pd/C, AcOEt, AcOH, 20 °C) of the mixture of **10b** and **11b** resulted in decomposition.

These results suggested that the phenylselenyl moiety should be cleaved only after reduction of the azide. Thus, **3b** was first converted into **5b** in 62% overall yield in a one-pot reduction/protection sequence: reaction of azide **3b** (0.066 mmol) with Ph_3P (1.5 equiv.) in refluxing THF (3 ml) and hydrolysis of the phosphimine thus formed by addition of

H₂O (1.7 ml) to give free amine **4b** which was transformed into **5b** by treatment with *N*-(*tert*-butyloxycarbonyloxy)succinimide (7 equiv.). Reductive deselenation of **5b** (0.032 mmol) was effected with Bu₃SnH (6 equiv.) and AIBN (0.1 equiv.) in refluxing toluene (1 ml) to give in 15 min the target 3-*N*-(*tert*-butyloxycarbonylamino)propyl glycoside **6b** {[α]_D²⁹ -15° (c 0.25, CHCl₃)} in 93% yield. Similarly, deselenation (Bu₃SnH–AIBN, toluene) of **8b** afforded 3-acetoxypropyl glycoside **9b** {[α]_D³⁰ -5° (c 1, CHCl₃)} in 83% yield.

The terminal position of the NHBoc and AcO groups in the aglycons of **6b** and **9b**, respectively, was evident from their NMR spectra (Table 1). This fact served as unambiguous proof of the terminal position of the N₃ and AcO moieties in the adducts **3b** and **8b**, and hence of the penultimate position of the phenylselenyl group in **3b** and **8b**, thus proving the ascribed regioselectivity of azido- and acetoxy-phenylselenylation.

In conclusion, the described sequence of reactions (azido-phenylselenylation–reduction of azide–deselenation) is a useful approach for the transformation of allyl glycosides into protected 3-aminopropyl glycosides.

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