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*

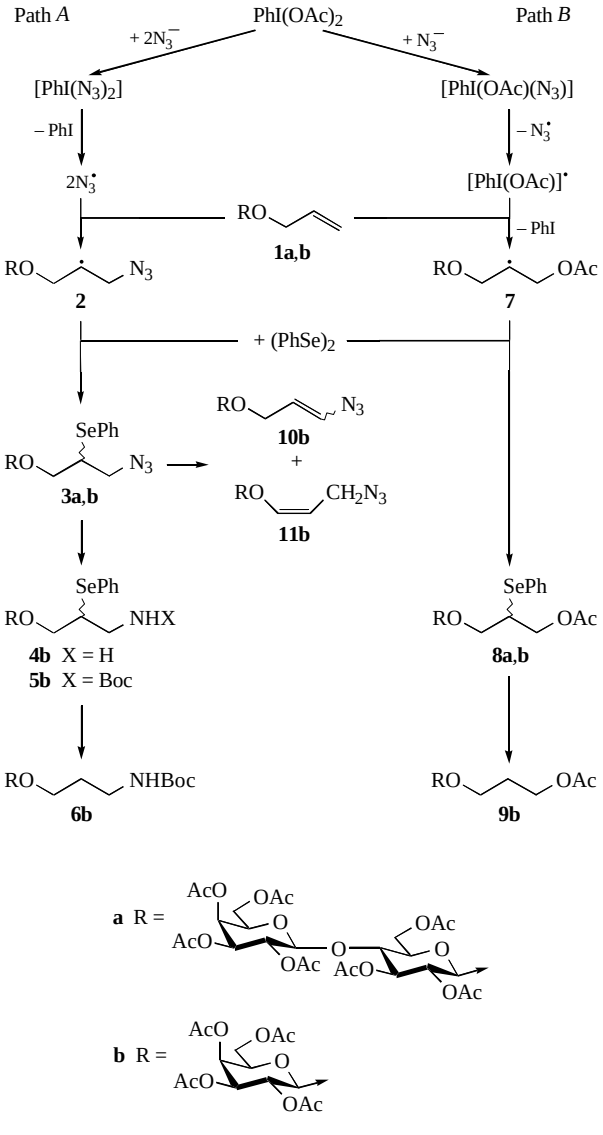
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation.
Fax:+7 095 135 8784; e-mail: nen@ioc.ac.ru

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 glycobiology 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 glycosides[3] 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 azidophenylselenylation[4] of allyl glycosides followed by subsequent reduction of the azido function and removal of the phenylselenyl 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 developed[4] for aliphatic alkenes. Treatment of **1a** (0.05 mmol) with NaN_3 (2.4 equiv.), $(PhSe)_2$ (0.6 equiv.) and $PhI(OAc)_2$ (1.4 equiv.) in CH_2Cl_2 (0.5 ml) at 20 °C (18 h)



Scheme 1

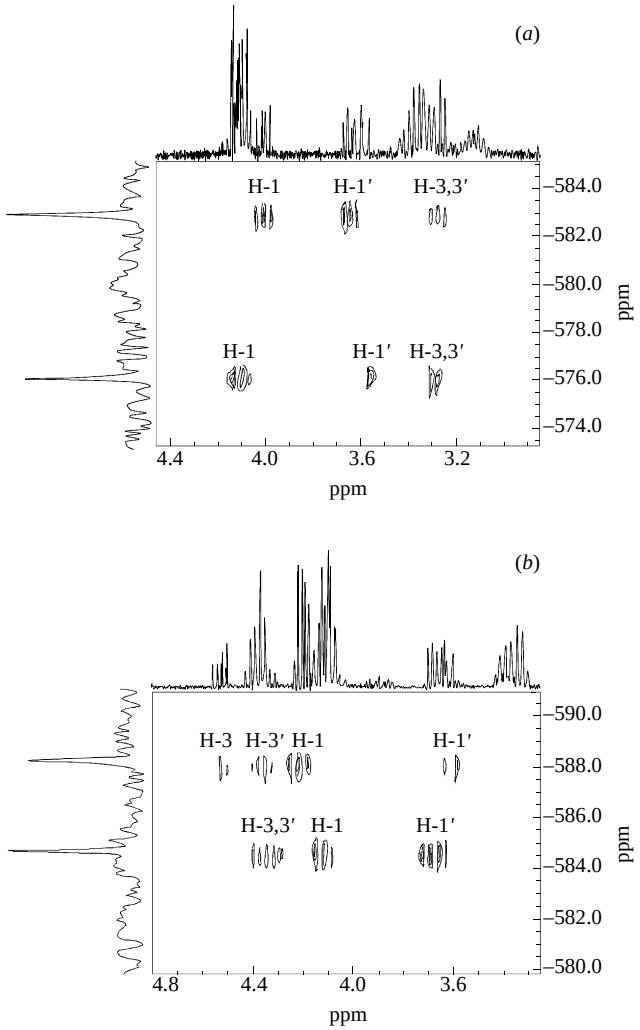


Figure 1 2D ^1H–^{77}Se NMR spectra of compounds **3b** (*a*) and **8b** (*b*) (Bruker AM-300, 303 K, C_6D_6). Numeration of atoms in the aglycon: sugar-1-2-3.

Table 1 ^{1}H, ^{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	*e*
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	*f*
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		*g*
6b	3.58	3.94	1.88	3.19	3.19	67.9	29.8	37.8		*h*
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*
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	*j*
9b	3.56	3.96	1.90	4.12	4.12	70.7	28.8	61.1		*k*
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		

[a]NMR 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 ^{1}H (2.225 ppm) and ^{13}C NMR (31.45 ppm) and $(PhSe)_2$ in ^{77}Se NMR (–460 ppm[11]). 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. [b]Numeration of atoms in the aglycon: sugar-1-2-3. [c] ^{1}H, ^{13}C and ^{77}Se NMR spectra were recorded in C_6D_6. [d] ^{1}H and ^{77}Se NMR spectra were recorded in C_6D_6. [e]C_6H_5Se 6.93–7.47 (5H). [f]C_6H_5Se 7.03–7.62 (5H). [g]C_6H_5Se 7.29–7.61 (5H); $(CH_3)_3C$ 1.41 (9H). [h]$(CH_3)_3C$ 1.43 (9H). [i]C_6H_5Se 6.91–7.53 (5H); CH_3CO 1.52–1.96 (24H). [j]C_6H_5Se 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 (^{1}H 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 ^{1}H, ^{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 ^{1}H 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 unambigously by 2D ^{1}H–^{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 ^{1}H–^{77}Se HMQC experiments[10] were optimized for the observation of couplings with J_{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 $^2J_{H-Se}$ is known[11] to be *ca.* 10 Hz.

The competitive acetoxyphenylselenylation observed can be rationalised as follows. The azidophenylselenylation reaction (Scheme 1, path *A*) is thought[4] to involve oxidation of two azide anions by $PhI(OAc)_2$ into azide radicals followed by their addition to alkene **1** and subsequent trapping of the resulting carbon-centered azido radical **2** with $(PhSe)_2$. Apparently, oxidation of azide anion by $PhI(OAc)_2$ proceeds (Scheme 1, path *A*) *via* an exchange reaction leading to $PhI(N_3)_2$, 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 $PhI(OAc)_2$ may occur (path *B*) leading to the mixed species $PhI(OAc)(N_3)$, which decomposes into azide and $PhI(OAc)^{\bullet}$ 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 $(PhSe)_2$ 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 $PhI(OAc)_2$ (2 equiv. in total) to a solution of **1b** (0.41 mmol), $(PhSe)_2$ (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

H_2O (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 Bu_3SnH (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** {$[\alpha]_D^{29}$ –15° (*c* 0.25, $CHCl_3$)} in 93% yield. Similarly, deselenation (Bu_3SnH–AIBN, toluene) of **8b** afforded 3-acetoxypropyl glycoside **9b** {$[\alpha]_D^{30}$ –5° (*c* 1, $CHCl_3$)} 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 N_3 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.

This work was supported by the President of the Russian Federation (grant no. 96-15-96991) and the Russian Foundation for Basic Research (grant no. 97-03-33037a). The authors are grateful to Yurii V. Mironov (The Higher Chemical College, Moscow) for technical assistance.

References

1 *Methods in Enzymology* (*Neoglycoconjugates, parts A and B*), eds. Y. C. Lee and R. T. Lee, Academic Press, San Diego, California, 1994, vols. 242, 247.
2 G. Magnusson, A. Ya. Chernyak, J. Kihlberg and L. O. Kononov, in *Neoglycoconjugates: Preparation and Application*, eds. Y. C. Lee and R. T. Lee, Academic Press, San Diego, California, 1994, p. 53.
3 N. V. Bovin, E. Yu. Korchagina, T. V. Zemlyanukhina, N. E. Byramova, O. E. Galanina, A. E. Zemlyakov, A. E. Ivanov, V. P. Zubov and L. V. Mochalova, *Glycoconj. J.*, 1993, **10**, 142.
4 M. Tingoli, M. Tiecco, D. Chianelli, R. Balduci and A. Temperini, *J. Org. Chem.*, 1991, **56**, 6809.
5 M. A. Bernstein and L. D. Hall, *Carbohydr. Res.*, 1980, **78**, c1.
6 R. T. Lee and Y. C. Lee, *Carbohydr. Res.*, 1974, **37**, 193.
7 M. A. Nashed, *Carbohydr. Res.*, 1983, **123**, 241.
8 K. Okamoto, T. Kondo and T. Goto, *Tetrahedron*, 1987, **43**, 5919.
9 L. O. Kononov, A. V. Kornilov, A. A. Sherman, E. V. Zyryanov, A. S. Shashkov, G. V. Zatonsky and N. E. Nifant'ev, *Bioorg. Khim.*, 1998, **24**, in press.
10 A. Bax and S. Subramanian, *J. Magn. Reson.*, 1986, **67**, 565.
11 W. McFarlane and R. J. Wood, *J. Chem. Soc., Dalton Trans.*, 1972, 1397.
12 T. Ercegovic and G. Magnusson, *J. Org. Chem.*, 1996, **61**, 179.

Received: Moscow, 15th October 1997
Cambridge, 28th November 1997; Com. 7/07604E