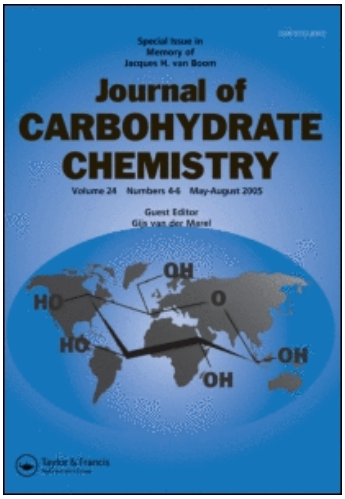

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SYNTHESIS OF GLYCOSYL AZIDES BY THE ADDITION OF PHENYLSELENENYL AZIDE TO GLYCALS

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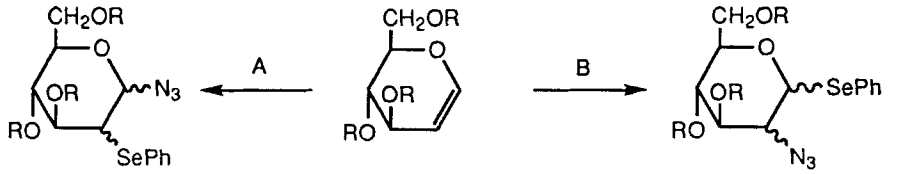
ABSTRACT

The addition of phenylselenenyl azide to glycals is carried out under conditions that give 2-deoxy-2-phenylselenoglycosyl azides. This regiochemistry is opposite to that obtained under free-radical conditions, which are known to produce 2-azido-2-deoxyselenoglycosides. The addition reaction is carried out with phenylselenenyl chloride and sodium azide in dimethylformamide, and is stereoselective for *trans* addition. Tri-*O*-benzyl-D-glucal and di-*O*-benzyl-L-rhamnal each gave two addition products, in which the phenylselenyl and azido groups were either *trans* diaxial or *trans* diequatorial. Tri-*O*-benzyl-D-galactal gave only the *trans* diaxial addition product.

INTRODUCTION

Glycosyl azides are used as intermediates in the synthesis of glycosyl amines, phosphinimines, and carbohydrate triazoles.[1] Several syntheses of asparagine-linked glycoconjugates also utilize glycosyl azides as precursors.[2] Properties of the azido group that are especially useful in carbohydrate chemistry are its compatibility with methods of glycosylation,[3] its stability to conditions used for removing hydroxyl protecting groups (e.g. deacetylation[1] and desilylation[2]), and its facile reduction to an amino group under a wide variety of conditions.[4] The

azido group is most often introduced at the anomeric center by nucleophilic displacement reactions of glycosyl halides with azide anion. An alternate method for introducing azide, which also incorporates the useful phenylselenyl group, is the addition of phenylselenenyl azide to a glycal. This reaction can afford either 2-azido-2-deoxy-1-selenoglycosides or glycosyl azides with a phenylselenyl group at the 2-position, depending on whether the addition takes place by a free-radical (B) or polar addition (A) pathway (Scheme 1).



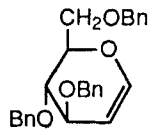
Scheme 1

Two recent publications describe the synthesis of 2-azido-2-deoxy-1-selenoglycosides by the free-radical addition of phenylselenenyl azide to glycals.[5,6] Azide radicals are generated in these procedures by the oxidation of azide ion with (diacetoxyiodo)benzene. Diphenyldiselenide serves as the source of the phenylselenyl group.[7] The free-radical additions of $PhSeN_3$ to glycals were stereoselective, giving either one or two of the four possible diastereomeric products. The addition was regiospecific for anti-Markovnikov products; formation of the regio-isomeric glycosyl azides was not reported.

During the course of our studies of the azidoselenenylation reaction,[8] we wondered if the addition of $PhSeN_3$ to glycals could be carried out under conditions that would favor the formation of glycosyl azides (Markovnikov products), which would presumably result from a polar addition reaction (path A, Scheme 1). In the first report of direct azidoselenenylation,[9] Hassner and Amarasekara reported the addition of phenylselenenyl azide to dihydropyran. The reaction gave only the *trans* Markovnikov isomer, consistent with a mechanism involving an episelenonium ion or a related, bridged intermediate which is captured by azide anion. The Hassner method uses phenylselenenyl chloride and sodium azide in DMSO. We were unable to obtain isolable yields of addition products from tri-*O*-acetyl-D-glucal or its tri-*O*-benzyl analog

when the reaction was carried out in DMSO; however, when DMF was used as the solvent, glycosyl azides were obtained from benzylated glycals[10] **1**, **2**, and **3** in yields of 82, 83, and 67%, respectively. The addition was stereoselective, and gave *trans* addition products. Synthesis of the phenylselenenyl azide-glycal adducts and structure analysis of the products by NMR are described below.

Two stereoisomeric glycosyl azides were obtained in each case from glycals **1** and **2** while a single isomer was detected in the ^1H NMR spectrum of the product of addition to glycal **3**. Markovniknov regiochemistry was evident from the ^1H and ^{13}C chemical shifts in the NMR spectra of the addition products. Chemical shifts for H-1 in the glycosyl azides typically appear upfield of the H-1 resonance for selenoglycosides, for example, the H-1 resonance for glycosyl azide **5**



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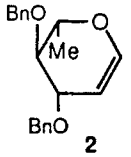

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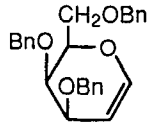

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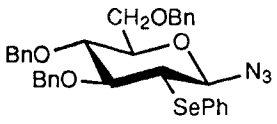

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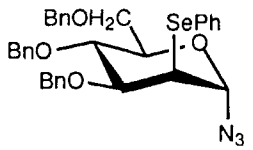

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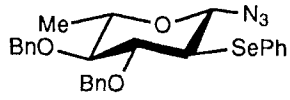

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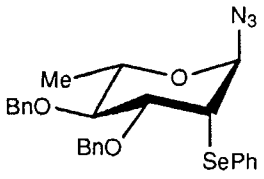

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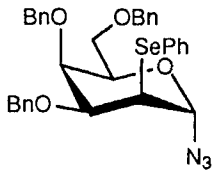

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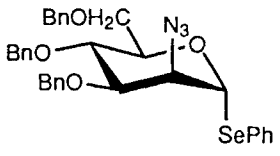

9

appears at 5.54 ppm, compared to 5.78 ppm for the known regioisomeric selenoglycoside **9** of the same (α-D-*manno*) configuration.[5] Chemical shift values for H-2 in the regioisomeric products are also different; H-2

resonances for **5** and **9** are 3.66 and 4.18 ppm, respectively. In the ^{13}C NMR spectra, values of 90.25 and 48.49 ppm are observed for the chemical shifts of C-1 and C-2 in **5**; corresponding values of 83.8 and 63.7 ppm are reported for **9**. The large difference in the ^{13}C NMR chemical shifts between azido- and phenylseleno-substituted carbons was useful in assigning regiochemistry of the addition products. The assignment of product stereochemistry was based on vicinal proton coupling constants (Table 1) and NOE difference spectroscopy. Irradiation of the H-1 resonance in **5** resulted in a 12% enhancement of the H-2 signal and a 6% enhancement of those of the ortho protons of the aromatic ring (PhSe group). No enhancement of the H-3 or H-5 resonances was observed as would be expected if H-1 were axial. Corresponding experiments could not be performed on **4** due to spectral overlap of the H-1 resonance with benzyl group proton resonances. The relationhip between H-1 and H-5 in **4** is analogous in the structure assigned as **6**. Irradiation of the H-1 signal in **6** did result in a 12% enhancement of the H-5 resonance, suggesting a *syn* diaxial relationship for these two protons.

The regiospecific formation of glycosyl azides in the phenylselenenyl azide additions described above is consistent with a polar addition mechanism. The stereoselectivity for *trans* addition implies that an episelenonium ion, or related bridged intermediate, is involved; however, the reaction could also proceed via an "open" oxocarbenium ion. Kinetic studies of the addition of phenylselenenyl chloride to dihydropyran support a mechanism in which an episelenonium ion opens to an oxocarbenium ion that reacts with chloride.[11] Theoretical methods have recently shown that high selectivity for *trans* addition of organosulfur reagents to glycals does not require the formation of intermediate episulfonium ions.[12] Other examples of *trans*-selective additions to glycals involving organoselenium reagents have been reported. Treatment of 3,4,6-tri-*O*-benzyl-D-glucal with phenylselenenyl chloride followed by an alcohol gave the *trans* 2-deoxy-2-selenoglycoside.[13] *Trans* diaxial addition was reported for the addition of a methyl evermicoside derivative to a protected glycal, also carried out in the presence of phenylselenenyl chloride.[14] An application to the synthesis of showdomycin analogs has been reported.[15] In contrast, the addition of phenylselenenyl azide to glycal **3** by the free-radical procedure gave only the *cis* selenoglycoside

Table 1. ^1H NMR Data for 2-Deoxy-2-phenylseleno Glycosyl Azides

	4	5	6	7	8
δ(ppm)					
H-1	4.54 d	5.54 d	4.51 d	5.44 d	5.70 dd
H-2	2.97 dd	3.66 dd	2.99 dd	3.67 dd	3.41 ddd
H-3	3.66 dd	4.07 dd	3.53 dd	4.02 ddd	4.02 ddd
H-4	3.68 dd	3.88 dd	3.22 dd	3.44 dd	3.90 m
H-5	3.44 dt	3.96 ddd	3.39 ddd	3.89 ddd	4.10 m
H-6a	3.73 d	3.81 dd	1.31 d	1.36 d	3.66 dd
H-6b		3.72 dd			
$PhCH_2O$-	5.08 and 4.91 ABq	4.86 and 4.51 ABq	5.07 and 4.90 ABq	4.23 and 4.62 ABq	5.05 and 4.59 ABq
$PhCH_2O$-	4.82 and 4.58 ABq	4.63 and 4.53 ABq	4.81 and 4.65 ABq	4.63 and 4.52 ABq	4.83 and 4.56 ABq
$PhCH_2O$-	4.63 and 4.54 ABq	4.70 and 4.53 ABq	-	-	4.50 and 4.39 ABq
J(Hz)					
$J_{1,2}$	10.0	2.3	10.2	2.0	1.7
$J_{2,3}$	10.3	4.4	11.0	4.6	4.6
$J_{3,4}$	8.1	7.7	8.4	8.7	2.4
$J_{4,5}$	9.7	9.2	9.5	9.3	1.4
$J_{5,6a}$	3.2	4.3	6.1	6.2	6.2
$J_{5,6b}$	-	2.0	-	-	-
$J_{1,5}$	-	-	-	0.7	-
$J_{1,3}$	-	-	-	0.6	0.6
$J_{2,4}$	-	-	-	-	1.1
$J_{4,6}$	-	-	-	-	0.9

with the α-*galacto* configuration.[6] It is interesting to note that mechanistically different addition reactions involving tri-*O*-benzyl-D-galactal proceed with higher selectivity than that observed for other glycals, and that different isomers are favored by the two procedures.

The addition of phenylselenenyl azide to glycals described herein complements the existing free-radical procedure. Glycosyl azides are obtained directly from glycals in good yields, and the reaction is regiospecific. *Trans*-addition products are favored in the cases examined. The variety of transformations that can be carried out on both azido and phenylselenyl groups suggests applications of the products in synthetic carbohydrate chemistry. Both groups can be transformed oxidatively and reductively. The latter would be valuable in the synthesis of 2-deoxy analogs of peptide-linked glycoconjugates.

EXPERIMENTAL

Optical rotations were measured in methanol solution at 18 °C using a Perkin-Elmer 241 polarimeter. IR spectra were recorded with an Analect 6160 FT-IR spectrometer. ^{1}H NMR spectra were recorded at 200.06 MHz and ^{13}C NMR spectra were recorded at 50.3 MHz using a Varian XL 200 MHz spectrometer. All spectra were obtained in $CDCl_3$ solution, which was used as the internal ^{13}C NMR standard (δ = 76.9 ppm). ^{1}H NMR spectra were referenced to tetramethylsilane. Partial relaxation ^{1}H spectroscopy enabled chemical shifts and coupling constants to be assigned in crowded spectra. For example, the highly overlapped anomeric and benzyl methylene protons of compound **4** were assigned using a pulse sequence of the form D1-P1-D2-PW, where D1 was the recycle delay, P1 was a π inversion pulse, D2 was a delay used to tune the appearance of multiplets based on their relaxation times, and PW was an observe pulse. One-dimensional NOE difference spectroscopy was carried out with standard Varian software, including use of DOCYCL excitation cycling of the selected multiplet. Percent enhancements were corrected for the actual excitation level of the selected multiplet. Microanalyses were obtained from Robertson Microlit Laboratories, Inc. Thin-layer chromatography was performed with aluminum-supported plates of silica gel 60 F_{254} (Merck). Plates were developed by dipping in a solution of ceric ammonium molybdate or phosphomolybdic acid and heating. Flash

chromatography[16] was carried out on 40 μm silica gel (Baker). Anhydrous dimethylformamide was purchased in Sure-Seal bottles from Aldrich Chemical Co.

3,4-6-Tri-*O*-benzyl-2-deoxy-2-phenylseleno-β-D-glucopyranosyl azide (4) and 3,4,6-Tri-*O*-benzyl-2-deoxy-2-phenylseleno-α-D-mannopyranosyl azide (5). A mixture of phenylselenenyl chloride (0.575 g, 3.0 mmol), sodium azide (0.392 g, 6.0 mmol), and anhydrous DMF (15 mL) was stirred under nitrogen at room temperature for 20 min. A solution of tri-*O*-benzyl-D-glucal (0.417 g, 1.0 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at room temperature for 3 days. Water (25 mL) was added and the mixture was extracted with diethyl ether (3x30 mL). The organic phase was washed with water (5x20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography using 10% ethyl acetate-petroleum ether as the eluant. Fractions of R_f 0.58 were combined to give **4** (0.12 g, 20%): $[\alpha]_D$ -20.6 (*c* 1.1, CH_3OH); IR (neat) 2112 (N_3) cm^{-1}; ^{13}C NMR δ 90.87 (C-1), 82.79, 79.27, 77.18, 76.00 ($PhCH_2$), 75.24 ($PhCH_2$), 73.74, ($PhCH_2$), 68.52 (C-6), 50.45 (C-2).

Anal. Calcd for $C_{33}H_{33}N_3O_4Se$: C, 64.49; H, 5.41; N, 6.84. Found: C, 64.62; H, 5.60; N, 6.55.

The fractions of R_f 0.73 were combined to give **5** (0.39 g, 62%): $[\alpha]_D$ + 41.95 (*c* 1.0, CH_3OH); IR (neat) 2106 cm^{-1}; ^{13}C NMR δ 90.25 (C-1), 78.17, 74.80, 73.85, 73.65 ($PhCH_2$), 73.37 ($PhCH_2$), 71.54 ($PhCH_2$), 68.64 (C-6), 48.49 (C-2).

Anal. Calcd for $C_{33}H_{33}N_3O_4Se$: C, 64.49; H, 5.41; N, 6.84. Found: C, 64.62; H, 5.67; N, 6.59.

3,4-Di-*O*-benzyl-2,6-dideoxy-2-phenylseleno-β-L-glucopyranosyl azide (6) and 3,4-Di-*O*-benzyl-2,6-dideoxy-2-phenylseleno-α-L-mannopyranosyl azide (7). A mixture of phenylselenenyl chloride (0.203 g, 1.1 mmol) and sodium azide (0.138 g, 2.1 mmol) in anhydrous DMF (10 mL) was stirred at room temperature under nitrogen for 20 min. Di-*O*-benzyl-L-rhamnal (0.109 g, 0.39 mmol) in anhydrous DMF (2 mL) was added and the reaction was stirred for 24 h at room temperature. Processing of the reaction was carried out as described above and the products were separated by flash chromatography using 5% ethyl acetate-petroleum ether as the eluant. Fractions of R_f 0.49 were combined to give **6** (0.079 g, 42%): $[\alpha]_D$ +45.18 (*c* 0.97, CH_3OH); IR

(nujol) 2104 (N_3) cm^{-1}; ^{13}C NMR δ 90.43 (C-1), 84.66, 82.35, 75.79 ($PhCH_2$), 75.33 ($PhCH_2$), 73.79, 50.52 (C-2), 17.66 (C-6).

Anal. Calcd for $C_{26}H_{27}N_3O_3Se$: C, 61.42; H, 5.35; N, 8.26. Found: C, 61.58; H, 5.51; N, 8.04.

The fractions of R_f 0.51 were combined to give **7** (0.079 g, 42%): $[\alpha]_D$ -48.22 (*c* 1.1, CH_3OH); IR (neat) 2104 (N_3) cm^{-1}; ^{13}C NMR δ 90.00 (C-1), 80.43, 78.05, 75.13 ($PhCH_2$), 71.38 ($PhCH_2$), 70.14, 48.77 (C-2), 18.00 (C-6).

Anal. Calcd for $C_{26}H_{27}N_3O_3Se$: C, 61.42; H, 5.35; N, 8.26. Found: C, 61.38; H, 5.40; N, 8.26.

3,4-6-Tri-*O*-benzyl-2-deoxy-2-phenylseleno-α-D-talopyranosyl azide (8). Glycosyl azide **8** was prepared from tri-*O*-benzyl-D-galactal (0.100 g, 0.24 mmol), phenylselenenyl chloride (0.124 g, 0.65 mmol), and sodium azide (0.086 g, 1.32 mmol) in anhydrous DMF (8 mL) by the method described above for compounds **6** and **7**. The crude product was purified by flash chormatography using 7% ethyl acetate-petroleum ether to give **8** (0.98 g, 67%): R_f 0.36; $[\alpha]_D$ +5.54 (*c* 0.98, CH_3OH); IR (neat) 2104 (N_3) cm^{-1}; ^{13}C NMR δ 91.85 (C-1), 74.57 ($PhCH_2$), 74.39, 73.36 ($PhCH_2$), 73.17, 72.36, 70.05 ($PhCH_2$), 68.58 (C-6), 46.90 (C-2).

Anal. Calcd for $C_{33}H_{33}N_3O_4Se$: C, 64.49; H, 5.41; N, 6.84. Found: C, 64.51; H, 5.51; N, 6.78.

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