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Glycosidation of an Ambident Organic Phosphoroselenothioate in the Presence of a Lewis Acid

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ABSTRACT: *An ambident O,O-dialkylphosphoroselenothioate is glycosidated in the presence of boron trifluoride etherate to give both Se- and S-glycosyl-phosphoroselenothioates, the former predominating. The stereochemical course of this reaction depends on the kind of sugar substrates. By selective oxidation of the mixture of products, the Se-glycosyl derivative is isolated.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 259–262, 1999

INTRODUCTION

Glycosidation of phosphorodithioate [1], phosphorothioate, and phosphoroselenoate [2,3] catalyzed by a Lewis acid allows the synthesis of thio- and seleno analogues of sugar phosphates. The present article is a continuation of the study on the synthesis of modified sugar phosphates: It is now extended to the selenothiophosphate anion **1** [4]. Previously, **1** was glycosidated with per-*O*-acetylated glycosyl α-bromides [5], to yield a mixture of isomers, β-*Se*- and β-*S*-glycosylphosphorothioselenoates. The method of choice was the selective oxidation that enabled us to separate the unoxidized selenolo isomer from the oxidation product of the thiolo component.

RESULTS AND DISCUSSION

β-D-Hexopyranoses: peracetylated gluco- **2a** [6], galacto- **2b** [7], 2-deoxy-*arabino*- **2c** [8], and per-*O*-benzylated unprotected 1-OH-gluco- **2d** [9] as glycosyl donors having different modes of activation of the anomeric position and protection of the sugar moiety were applied to the glycosidation of **1** [4], promoted by $BF_3 \cdot Et_2O$, at room temperature, in 1,2-dichloroethane. The reactants were used in equimolar amounts; the amount of $BF_3 \cdot Et_2O$ was 3 molar equivalents. The course of reaction and time necessary to accomplish the reaction was determined by ^{31}P and ^{1}H NMR monitoring. According to the spectral data, two series of products were formed, **3** and **4**, where **3** prevailed in the reaction mixture.

The chemical shifts and $^{1}J_{P\text{-}Se}$ were indicative [4] in distinguishing isomers and establishing of structures of glycosyl selenothiophosphates. The selenolo compounds **3** exhibited $\delta\ ^{31}P \approx 76$ and $^{1}J_{P,Se} = 420$–460 Hz, whereas the thiolo isomer **4** had $\delta\ ^{31}P \approx 85$ and $^{1}J_{P,Se} \approx 970$ Hz.

The products were isolated as mixture of isomers **3** and **4**. The proportions of isomers **3**:**4** determined in the crude reaction mixtures were the same as determined after crystallization (according to ^{31}P NMR data); the yields were quantitative and no-phosphorus-containing products other than **3** and **4** were formed (except in the reaction with **2d**). The structures of mixtures of products were established by the spectroscopic and physical data.

For the separation of the isomers **3** and **4**, the described method [5] of selective oxidation of **4** into **5**, by using *m*-chloroperbenzoic acid, was applied. The oxidation of primary reaction mixture **3** and **4** gave a mixture **3** and **5** that can be separated by frac-

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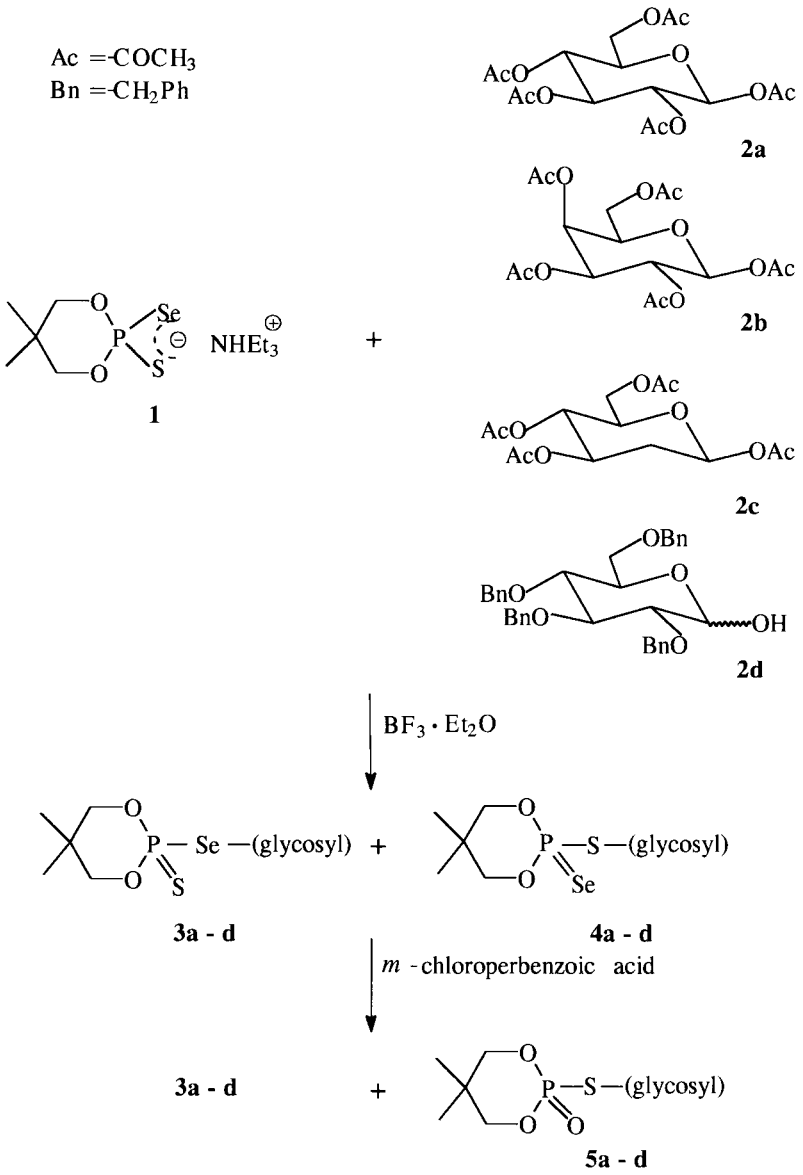
tional crystallization (see Scheme). As ^{31}P NMR data determined, the ratio **3** to **5** after the oxidation had considerably changed in favor of **3**, in comparison to **3** to **4**, prior to oxidation. The isolated isomers **3a–3d** were characterized by spectroscopic and physical data. The reaction rate and stereochemical outcome of heterophosphorylation at the anomeric center depended on the kind of substituent at C-2 of the sugar.

Peracetylated monosaccharides **2a** and **2b** with **1** gave similar proportions of isomers **3** and **4** as obtained previously [5]. This result indicates anchimeric assistance of the C-2 -$OCOCH_3$ group in intermediate formation of acyloxonium ion, resulting in *trans*-glycosidation. The spectral and physical data of isolated **3a,b** were in agreement with the data described [5].

Peracetylated 2-deoxy-*β*-D-*arabino*-hexopyranose **2c** underwent substitution faster than the substrates with an -OAc group at C-2 and resulted in the stereospecific formation of the thermodynamically more stable of the axial anomers **3c** and **4c**. Attempts at isolation of **3c** failed, due to the instability of the product.

The reaction of **2d** was more complex. ^{31}P NMR monitoring of the reaction course indicated that, at the beginning, four products were formed [**3d** (α + β) and **4d** (α + β)]. During the reaction, anomerization $\beta \rightarrow \alpha$ proceeded. Thus after 7 days, the mix-



SCHEME 1

ture of products α-**3d** and α-**4d** was isolated. After selective oxidation, isomer **3d** was isolated and characterized.

In summary, we have demonstrated that both 1-*O*-acyl sugars **2a–c** or 1-*O*-unprotected sugar **2d** can be applied to the glycosidation of the *O*,*O*-dialkylphosphoroselenothioate **1** catalyzed by $BF_3 \cdot Et_2O$. It offers a novel approach to the glycosyl thioselenophosphates.

EXPERIMENTAL

Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. Optical rotations were determined with the Polamat A polarimeter. IR spectra were obtained by using the Infinity MI-60 FT-IR spectrometer. ^1H, ^{13}C, and ^{31}P NMR were measured in $CDCl_3$ solutions, on a Bruker DPX spectrometer operating at 250.13 MHz, 62.9 MHz, and 101.25 MHz, respectively. Elemental analyses were performed by the Microanalytical Laboratory of this Institute on a Perkin Elmer PE 2400 CHNS analyzer.

Solvents were dried and distilled prior to use. 3-Chloroperbenzoic acid (~90%) was purchased from Fluka AG.

General Oxidation Procedure. The crystalline mixture of (**3** and **4**) isomers obtained in glycosylation reactions was dissolved in CH_2Cl_2 (7 mL) and cooled to 0°C. *m*-Chloroperbenzoic acid was suspended in CH_2Cl_2 (8 mL), cooled to 0°C, and added in one portion to the solution of isomers. The separation of elemental Se was observed. After 20 minutes the mixture was washed with satd. Na_2CO_3 aq. and the organic layer dried ($MgSO_4$). After evaporation of solvent in vacuo, the crude syrupy product was analyzed by means of ^{31}P NMR.

Glycosidation of **1** *with* **2a–c** *in the presence of* $BF_3 \cdot Et_2O$

Reaction **1** *with* **2a**. **2a** (1.5 g, 3.83 mmol) and **1** (1.33 g, 3.84 mmol) were dissolved in 1,2-dichloroethane (75 mL), and then $BF_3 \cdot Et_2O$ (1.63 g, 1.45 mL, 11.48 mmol) was added, and the reaction mixture was kept for 30 hours at room temperature. The reaction mixture was washed with satd. $NaHCO_3$ (2 × 85 mL), water (85 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo, the syrupy residue was crystallized twice from CCl_4-heptane to give 1 g (45%) of a crystalline product, as colorless needles, mp. 144–145°C (Ref. [5] mp. 144–146°C). The product was shown to be a mixture of two isomers (^{31}P NMR δ: 85.2 $^1J_{P,Se}$ = 976, (**4a**); 76.18, $J_{P,Se}$ = 424, (**3a**) integration ~1:2.33). $[\alpha]_{578}$ + 19.32° (*c* 1.04, $CHCl_3$) ^{13}C NMR δ (selected): 86.1 (C-1, **4a**); 83.6 (C-1, **3a**).

The mixture of isomers **3a** and **4a** (0.995 g, 1.73 mmol) was reacted with *m*-chloroperbenzoic acid (0.332 g 1.73 mmol). The ^{31}P NMR spectra of the crude reaction mixture showed two signals: ^{31}P NMR δ: 78.18; $^1J_{P,Se}$ = 423 (**3a**) and 16.33 (**5a**) integration 4.7:1. After 4 crystallizations from MeOH, **3a** (0.214 g, 22%) was isolated as colorless needles, mp. 136–138°C (Ref. [5] mp. 140–141°C); $[\alpha]_{578}$ + 15.02° (*c* 1.07, $CHCl_3$) [Ref. [5] $[\alpha]_D$ + 11.6° (*c* 1.7, $CHCl_3$)]; ^{31}P NMR δ: 76.18, $^1J_{P,Se}$ = 423, [Ref. [5] ^{31}P NMR δ: 76, $^1J_{P,Se}$ = 442]; ^{13}C NMR (CD_3COCD_3) δ: 170.6–169.5 (4s, 4 × C=O), 84.3 (d, $^2J_{C,P}$ = 2.9, C-1), 78.2 (d, $^2J_{C,OP}$ = 9.2, OCH_2), 73.6 (C-3), 70.9 (d, $^3J_{C,P}$ = 8.45, C-2), 68.1 (C-4), 61.7 (C-6), 32.5 (d, $^3J_{C,P}$ = 6.96, *C* CH_3), 22.3–20.6 (4 × CH_3 (OAc), $CH_{3\ ax}$, $CH_{3\ eq}$). ^1H NMR and IR spectra for **3a** were identical with those described [5].

Reaction **1** *with* **2b**. **2b** (1.5 g, 3.83 mmol) and **1** (1.33 g, 3.84 mmol) were dissolved in 1,2-dichloroethane (75 mL), then $BF_3 \cdot Et_2O$ (1.63 g, 1.45 mL, 11.48 mmol) was added, and the reaction mixture was kept for 25 hours at room temperature. The reaction mixture was washed with satd. $NaHCO_3$ (2 × 85 mL), water (85 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the syrupy residue was twice crystallized from CCl_4-heptane to give 1.50 g, (68%) of a crystalline product, as colorless needles, mp. 157–160°C (Ref. [5] mp. 167–170°C). The product was shown to be a mixture of two components [^{31}P NMR δ: 85.59, $^1J_{P,Se}$ = 974 (**4b**); 76.47, $^1J_{P,Se}$ = 426 (**3b**), integration ~1:2.44]. $[\alpha]_{578}$ + 27.7° (*c* 1.15, $CHCl_3$); ^{13}C NMR δ (selected): 86.64 (C-1) **4b**, 84.25 (d, $J_{C,P}$ = 3, C-1) **3b**.

The mixture of isomers **3b** and **4b** (1.49 g, 2.59 mmol) was reacted with *m*-chloroperbenzoic acid (0.5 g, 2.6 mmol). The ^{31}P NMR spectra of the crude reaction mixture showed two signals [^{31}P NMR δ: 76.47, $^1J_{P,Se}$ = 426 (**3b**); 16.62 (**5b**) integrated as ~3.35:1]. After 2 crystallizations from MeOH, **3b** (0.389 g, 26%) was isolated as colorless needles, mp. 161–164°C [Ref. [5] mp. 166–168°C]; $[\alpha]_{578}$ + 31.6°C (*c* 1.11, $CHCl_3$), [Ref. [5] $[\alpha]_D$ + 3.2° (*c* 1.4, $CHCl_3$)]; ^{31}P NMR δ: 74.49, $^1J_{P,Se}$ = 426, [Ref. [5] 75, $^1J_{P,Se}$ = 424]; ^{13}C NMR δ: 170.3–169.7 (4s, 4 × *C* = O), 84.4 (d, $^2J_{C,P}$ = 3, C - 1), 78.23 (d, $J_{C,P}$ = 9.2, OCH_2), 76.4 (C - 5), 71.5 (C - 3), 68.2 (d, $^3J_{C,P}$ = 8.5, C-2), 67.3 (C-4); 61.2 (C-6), 32.5 (d, $^3J_{C,P}$ = 6.9, *C* CH_3), 22.3–20.5 [m, 4 × CH_3 (OAc), $CH_{3\ ax}$, $CH_{3\ eq}$].

^1H NMR and IR spectra of **3b** were identical with described values [5].

Reaction **1** *with* **2c**. **2c** (1.3 g, 3.9 mmol) and **1** (1.35 g, 3.9 mmol) were dissolved in 1,2-dichloroethane (80 mL), then $BF_3 \cdot Et_2O$ (1.66 g, 1.47 mL, 11.7 mmol) was added, and the reaction mixture was kept for 6 hours at room temperature. The reaction mixture was washed with satd. $NaHCO_3$ (2 × 85 mL), water (85 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the syrupy residue was twice crystallized from CCl_4-heptane to give 0.955 g (47%) of a crystalline product, as colorless needles, mp. 109–111 °C. The product was shown to be a mixture of two components [^{31}P NMR δ: 84.03, $^1J_{P,Se}$ = 965 (**4c**); 75.20, $^1J_{P,Se}$ = 450 (**3c**), integration ~1:1.65]; $[\alpha]_{578}$ + 200° (*c* 1.02, $CHCl_3$); ^{13}C NMR δ (selected): 85.7 (C-1) **4c**, 84.9 (C-1) **3c**; IR $\nu_{P=S}$ = 674 cm^{-1}, ν_{OAc} = 1744 cm^{-1}. ^{1}H NMR δ (selected): 6.41 [dd, 1H, $J_{1,2}$ = 4.75, $J_{1,P}$ = 9, H-1(α)] **3c**, 6.13 [dd, 1H, $J_{1,2}$ = 4.75, $J_{1,P}$ = 10.75, H-1 (α)] **4c**, 2.55–2.36 [m, H-2 (deoxy), 2.07–2.03 (m, OAc), 1.28–0.93 (4s, 2 × 5,5-dimethyl)]. Anal. $C_{17}H_{27}O_9PSSe$ (517.31) requires: C, 39.47%; H, 5.26%. Found: C, 39.46%; H, 5.14%.

The mixture of isomers **3c** and **4c** (0.96 g, 1.86 mmol) was reacted with *m*-chloroperbenzoic acid (0.357 g, 1.86 mmol). The ^{31}P NMR spectra of the crude reaction mixture showed two signals [^{31}P NMR δ: 75.2, $^1J_{P,Se}$ = 455 (**3c**); 16.7 (**5c**) integration ~3.8:1]. Attempts at separation of **3c** from **5c** were unsuccessful.

Reaction **1** *with* **2d**. **2d** (1.5 g, 2.77 mmol) and **1** (0.96 g, 2.77 mmol) were dissolved in 1,2-dichloroethane (55 mL), then $BF_3 \cdot Et_2O$ (1.05 mL, 1.18 g, 8.31 mmol) was added, and the reaction mixture was left for 7 days at room temperature. The reaction mixture was washed with satd. $NaHCO_3$ (2 × 85 mL) water (85 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the syrupy residue was crystallized twice from CCl_4-heptane to give 0.775 g (36%) of a crystalline product as colorless needles, mp. 135–138°C. The product was shown to be a mixture of two components (^{31}P NMR δ: 87.33 $J_{P,Se}$ = 962 (**4d**) and 77.78, $^1J_{P,Se}$ = 463 (**3d**) integration ~1:1.90). $[\alpha]_{578}$ + 137.1° (*c* 1.05, $CHCl_3$); ^{13}C NMR δ (selected): 90.95 (C-1), **3d**, 89.5 (C-1), **4d**. Anal. $C_{39}H_{45}O_7PSSe$ (767.71) requires: C, 61.02%; H, 5.91%. Found: C, 60.73%; H, 6.10%.

The mixture of isomers **3d** and **4d** (0.759 g, 0.99 mmol) was reacted with *m*-chloroperbenzoic acid (0.190 g, 1.1 mmol). The ^{31}P NMR spectra of the crude reaction mixture showed two signals [^{31}P NMR δ: 77.79, $^1J_{P,Se}$ = 453 (**3d**), 18.89 (**5d**), integration 3.13:1]. After several crystallizations from MeOH, **3d**, 0.167 g (22%), was isolated as colorless needles, mp 132–134°C; $[\alpha]_{578}$ + 152.3° (*c* 0.99, $CHCl_3$); ^{31}P NMR δ: 77.79, $^1J_{P,Se}$ = 455 (**3d**); ^{1}H NMR δ: 7.37–7.13 (m, 4 × Ph), 6.61 [dd, 1H $J_{1,2}$ = 5, $J_{1,P}$ = 9.75, H-1 (α)], 5.03–4.42 (m, 4 × CH_2Ph, 2 × OCH_2), 4.18–3.65 (m, 6H, H-2, 3, 4, 5, 6, 6′), 1.23, 0.82 (2s, 5.5-dimethyl); ^{13}C NMR δ (selected): 138.4–137.1 (4C, ipso Ph), 128.4–127.7 (m, Ph), 91 (C-1), 32.3 [d, $^3J_{C,P}$ = 6.9, *C* (CH_3)], 22.4 ($CH_{3\,ax}$), 20.9 (CH_{3eq}); IR $\nu_{P=S}$ = 674 cm^{-1}. Anal. $C_{39}H_{45}O_7PSSe$ (767.71) requires: C, 61.02%; H, 5.91%. Found: C, 61.20%; H, 5.60%.

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