Stereoselective Synthesis of 5,5-Dimethyl-2-oxo-2-(3,4,6-tri-*O*-acetyl-2-deoxy-α-D-hexopyranosylseleno)-1,3,2-dioxaphosphorinane: Novel Observations on the Selenono–Selenolo Isomerization of Phosphoroselenoates

Maria Michalska,* Joanna Borowiecka, Paweł Lipka, and Teresa Rokita-Trygubowicz
Laboratory of Organic Chemistry, Institute of Chemistry, Medical Academy, Muszyńskiego 1, 90-151 Łódź, Poland

The first example of a 1-phosphoroselenoate of a 2-deoxy sugar has been obtained by three independent routes: (A) selenophosphorylation of 3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose (**4**) with selenophosphorochloridate (**5**) followed by selenono–selenolo isomerization; (B) condensation of 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl bromide (**8**) with *O,O*-dialkylphosphoroselenoate (**9**), and (C) addition of *O,O*-dialkylphosphoroselenoic acid (**11**) to 3,4,6-tri-*O*-acetyl-D-glucal (**1**). All these reactions proceed with high yield and full stereoselectivity to afford the α-selenophosphate of 2-deoxy-D-*arabino*-hexopyranose (**7**). It has been shown that the selenono–selenolo isomerization (**6**) ⟶ (**7**) which occurs in route (A) proceeds *via* the intermediate 2-deoxyglycosyl chloride (**12**). This finding confirms the mechanism proposed by Chabrier *et al.* for the selenono–selenolo phosphate isomerization catalyzed by ammonium halides.

This paper is a part of our studies on thio and seleno analogues of sugar phosphates which are both useful as intermediates in the synthesis of modified monosaccharides[1–4] and as glycosyl donors.[5–7]

The glycosyl phosphoroselenoates derived from D-pentoses and D-hexoses were prepared in this laboratory by condensation of the corresponding glycosyl halides with *O,O*-dialkylphosphoroselenoates. This reaction led to a mixture of selenolo and selenono isomers, the former predominanting. The selenono phosphates were also obtained by selenophosphorylation of 1-OH sugars with selenophosphorochloridate. It has been demonstrated that the selenono compounds can be thermally transformed into the selenolo isomers. This isomerization was accompanied by anomerization leading to the thermodynamically more stable α-isomer.[8] The aim of the present work was to achieve a stereoselective synthesis of an *Se*-(2-deoxy-D-*arabino*-hexapyranosyl)phosphoroselenoate, the first example of a 1-phosphoroselenoate of a 2-deoxysugar.

Results and Discussion

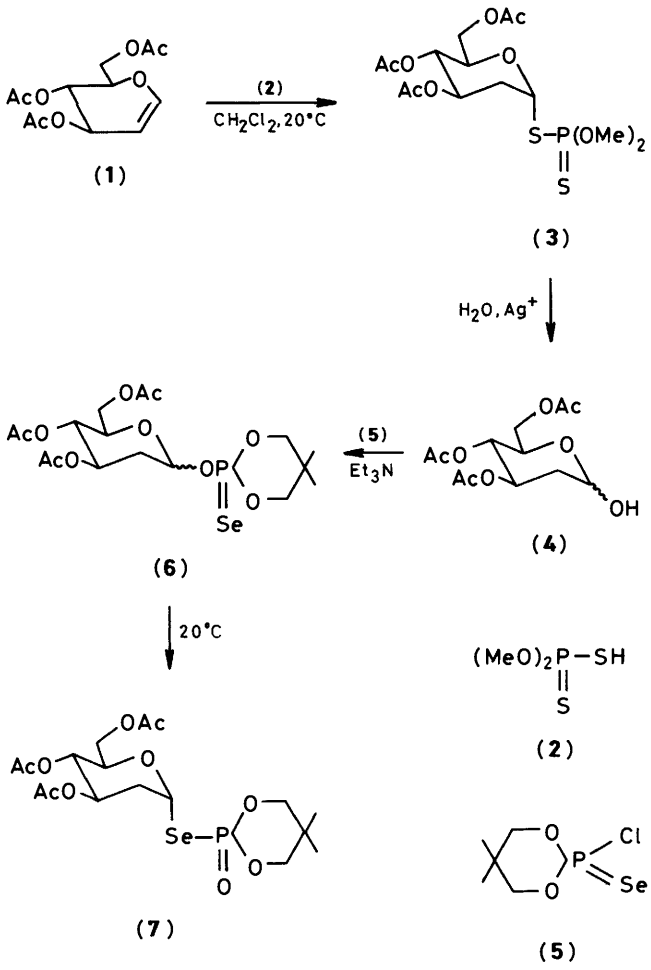
Selenophosphorylation of 3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-D-arabino-*hexopyranose: Route A.*—The starting 3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose (**4**) was prepared by selective hydrolysis of the readily available and anomerically stable *O,O*-dimethyl-*S*-(3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosylthio)phosphorodithioate (**3**).[7] The hydrolysis performed in aqueous acetone in the presence of silver salts afforded (**4**), m.p. 104—105 °C, in almost quantitative yield. Thus (**4**) was readily available in this way.† The reaction of (**4**) with the selenophosphorochloridate (**5**) in the presence of triethylamine, performed in dichloromethane solution, proceeded smoothly at 20 °C to yield, as the only phosphorus-containing product, 5,5-dimethyl-2-oxo-2-(3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosylseleno)-1,3,2-dioxaphosphorinane (**7**) in quantitative yield.

This welcome but somewhat unexpected result demonstrated that under specific reaction conditions the selenono-selenolo isomerization proceeds at room temperature. Monitoring of the reaction course by ^{31}P n.m.r. spectroscopy established the formation of the intermediate selenono phosphate (**6**). Its presence in the reaction mixture was confirmed by the lowfield signal [$\delta(^{31}P)$ 62.1 p.p.m.] characteristic of the P=Se grouping.[11] This signal disappeared when the isomerization process was completed. The structure of the α-selenolophosphate (**7**) was established by ^1H and ^{13}C n.m.r. spectroscopy. The value of the chemical shift and splitting of the anomeric 1-H proton signal (δ 6.38 dd; $J_{1,2a}$ 4.7 Hz; $J_{1,2e} \sim 1$ Hz, and $^2J_{P,1-H}$ 7.2 Hz) as well as the doublet signals for the anomeric and 2-deoxy carbon atoms [δ(C-1) = 80.7 d; $^2J_{P,C-1}$ 3 Hz; δ(C-2) = 37.7 d; $^3J_{P,C-2}$ = 7 Hz] were indicative of the C–Se–P arrangement at C-1 and of α-configuration of the selenophosphoryl substituent. The selenolo structure of (**7**) was further confirmed by ^{31}P n.m.r. results: $\delta(^{31}P) = 9.7$; $J_{P,Se} = 450$ Hz.[8,11] The α-selenolophosphate (**7**) is a crystalline compound, m.p. 114—115 °C, readily soluble in organic solvents. It is worth noting that although the starting 1-OH sugar (**4**) is a 4:1 equilibrium mixture of α and β isomers, the final product consisted exclusively of the α-selenolo isomer, as shown by ^1H, ^{13}C, and ^{31}P n.m.r. spectroscopy. This result indicates that a pronounced anomeric effect is connected with the selenophosphoryl substituent. It is most likely that the β⟶α isomerization occurs at the stage of the selenolo isomer.

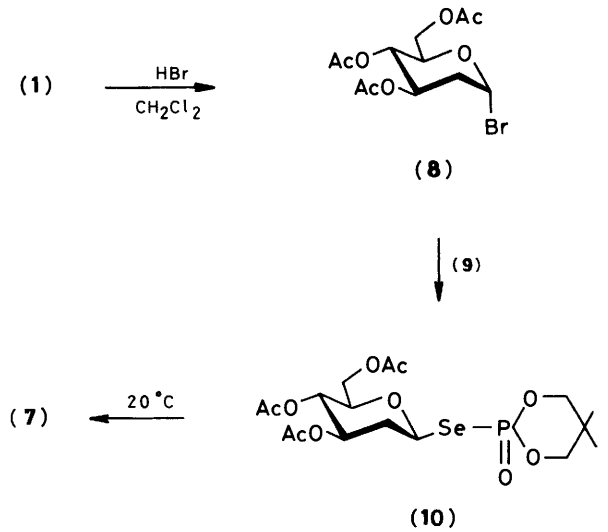
The mechanistic aspect of the selenono-selenolo isomerization involved in route (A) is discussed in a separate section.

Glycosylation of 2-*Seleno*-2-*oxo*-5,5-*dimethyl*-1,3,2-*dioxaphosphorinane Triethylammonium Salt: Route B.*—The second method of synthesis of (**7**) was based on glycosylation of the phosphoroselenoate (**9**) by 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl bromide (**8**).

† Previously (**4**) has been obtained, among other products, in the reaction between 3,4,6-tri-*O*-acetyl-D-glucal and hydrogen bromide[9] or hydrogen chloride[10] and subsequent treatment with aqueous acetone in the presence of silver carbonate. A more practical method for preparation of (**4**) involved the reaction of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose with hydrogen chloride in toluene followed by treatment of the resulting product with water and silver carbonate.[10]



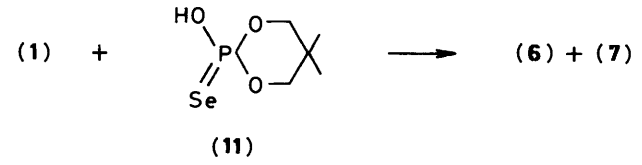
Scheme 1.



Scheme 2.

It was expected that this reaction would proceed with predominant formation of the carbon–selenium bond.[8] The selenono isomer (**6**), if formed (as the minor product), would immediately be converted into the selenolo compound (**7**), as demonstrated in route A. 2-Deoxyglucosyl bromide (**8**) was prepared *in situ* by reaction of hydrogen bromide with 3,4,6-tri-*O*-acetyl-D-glucal in benzene (or dichloromethane) and was immediately allowed to react with the phosphoroselenoate (**9**). The reaction, performed at room temperature, was accomplished within 1 h to afford the selenolophosphate as a 1:1 mixture of β (**10**) and α (**7**) isomers, in quantitative overall yield. Monitoring of the reaction course by a ^{31}P n.m.r. spectroscopic method showed that the β isomer (**10**) was the primary, kinetically controlled product, which slowly underwent anomerization into (**7**). When the reaction mixture was kept for an additional 4 days, full anomerization occurred and the final product was identical with the α selenolophosphate (**7**) obtained by route (A).

Addition of Phosphoroselenoic Acid to 3,4,6-*Tri*-O-*acetyl*-D-*glucal: Route C.*—The third approach to the synthesis of (**7**) was based on addition of the phosphoroselenoic acid (**11**) to 3,4,6-tri-*O*-acetyl-D-glucal (**1**).



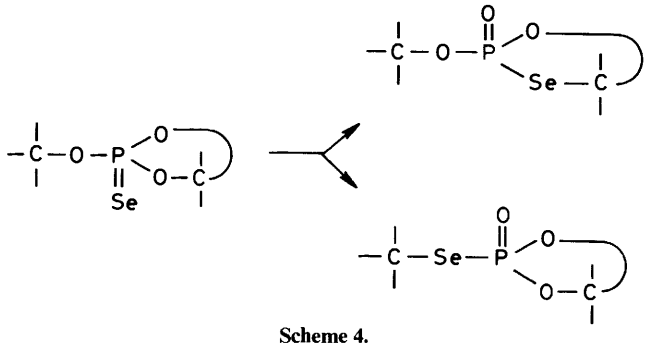
Scheme 3.

We expected the formation of both selenolo and selenono isomers.[12] The addition reaction performed in boiling dichloromethane and completed within 12 h afforded, a mixture of (**7**) and (**6**), in 7:1 ratio, respectively. The pure selenolo isomer (**7**) was easily isolated in 70% yield by crystallization from diethyl ether.

It is of interest to note that under these reaction conditions no selenono–selenolo isomerization was observed. This is apparently contradictory to the observation of the spontaneous selenono–selenolo isomerization occurring in route A, at room temperature. In order to elucidate this problem we undertook complementary spectroscopic studies of the reactions involved in route A.

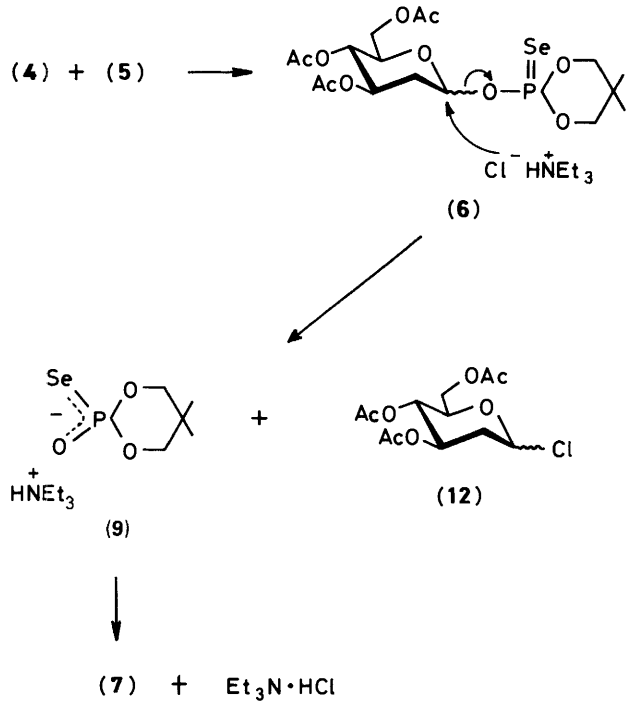
Mechanism of the Selenono–Selenolo Isomerization involved in Route A.—The studies on thiono–thiolo and selenono–selenolo isomerizations in the carbohydrate series were initiated in this laboratory, special emphasis being put on the thio- and seleno-sugar phosphates bearing a phosphorus residue at the anomeric carbon atom.[8–13]

The thiono–thiolo rearrangement P(S)OR ⟶ P(O)SR plays an important role in phosphorus–sulphur chemistry. It is known that in the thiophosphate series the thiolo form is thermodynamically more stable. It has been found that the selenono–selenolo isomerization P(Se)OR ⟶ P(O)SeR proceeds generally at a higher rate.[14] These isomerization processes take place either thermally or under the influence of catalysts.[15] Chabrier and associates used tetraethylammonium iodide as the isomerization catalyst in series of cyclic thiono and selenono phosphates.[14,16] Exocyclic and endocyclic products were



Scheme 4.

observed. The course of this isomerization depends on the electrophilicity of the α-carbon atoms. The authors postulated intermediate formation of *C*-iodides and selenophosphate anions which recombine to give the isomerized products. This work has a direct link with our observations on the selenono–selenolo isomerization occurring in the 2-deoxysugar 1-selenophosphates. The isomerization observed in our case can be explained in a similar manner to that described by the French authors. The triethylammonium chloride formed during the condensation of (**4**) with (**5**) reacts with the 2-deoxyglycosyl selenonophosphate (**6**) to yield the intermediate 1-chloro-2-deoxyglucose (**12**) which condenses with the ambident selenophosphate anion (**9**) to give the isomerized product (**7**).



Scheme 5.

In our case this exocyclic selenolo isomer is exclusively formed due to the pronounced electrophilic character of the anomeric carbon atom. A high concentration of 1-chloro-2-deoxyglucose (**12**) was found by ^{13}C n.m.r. spectroscopy in the early stage of the reaction.* Formation of the 2-deoxyglycosyl chloride (**12**) both parallels formation of the selenoacid anion (**9**),† and corroborates the known ability of sugar 1-thiophosphates to act as glycosyl donors.[5–7,17] Our work provides experimental evidence for the mechanism of selenono–selenolo isomerization, proposed by Chabrier *et al.*[16] Extrapolating our results we believe that a similar mechanism can also be accepted for analogous thiono–thiolo isomerizations. The observed fact that under the conditions employed in synthetic pathway C no selenono–selenolo isomerization takes place, has its rationale in the lack of a suitable catalyst.

* The observed resonance signals were identical with those of the genuine 3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-chloro-D-*arabino*-hexopyranose (δ_C 90.6, C-1), 38.8 (C-2), 61.5 (C-6), and 68.4 and 68.1 p.p.m. (C-3, C-4).

† Compound (**9**) was easily detectable by ^{31}P n.m.r. (δ_P 46.7 p.p.m.) and by ^{13}C n.m.r. [δ_C 75.8 (d, $^2J_{P,C}$ 5.6 Hz, CH_2) and 22.9 (CH_3, dioxaphosphorinane ring)].

Experimental

General Procedures.—M.p.s were determined with a Boetius PHMKO 5 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies of the Polish Academy of Sciences, Łódź. ^{31}P N.m.r. spectra were determined in $CDCl_3$ or CH_2Cl_2 with H_3PO_4 as external standard (JEOL 60 MHz FT machine operating at 24.3 MHz). ^{13}C N.m.r. spectra were determined in $CDCl_3$ (Bruker 100 MHz, Tesla BS 567A, 25.2 MHz). ^1H N.m.r. spectra were determined in $CDCl_3$ or C_6D_6 (with Bruker 400 MHz or Varian 60 MHz spectrophotometers). Specific rotations were determined with a Polamat A polarimeter. T.l.c. was carried out on silica gel plates (Kieselgel 60 F_{254} Merck) with benzene–chloroform–acetone (3:1:1) as the developing solvent. Detection was affected by exposure to iodine vapours and, in parallel, by phosphate reagent.

3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-D-arabino-*hexopyranose* (**4**): *Anomeric Deprotection.*—To the solution of *O,O*-dimethyl-*S*-(3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-phosphorodithioate[7] (**3**) (0.43 g, 1 mmol) in acetone (2 ml), water was added (0.02 ml, 1 mmol) followed by silver carbonate (0.55 g, 2 mmol) and silver perchlorate (0.07 g, 0.3 mmol). The mixture was heated under reflux with continuous stirring for 30 min. The precipitated silver phosphorodithioate δ[(^{31}P) 108 p.p.m.] and the excess of catalyst were filtered off, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The crude, crystalline product (**4**) (0.27 g, quantitative yield) was either recrystallized from diethyl ether (× 2) or precipitated with light petroleum from carbon tetrachloride solution. Analytically pure (**4**) was obtained (75%, 0.2 g) as a 4:1 mixture of α and β isomer; colourless needles, m.p. 104–105 °C; $[\alpha]_D^{19}$ +109 (*c* 1, $CHCl_3$) {lit., m.p. 93—95 °C; $[\alpha]_D^{20}$ +86 (*c* 1, EtOH);[9] m.p. 94—97 °C[10]}; δ(Varian 60 MHz, $CDCl_3$) 1.70—1.86 (m, 2a-H), 2.03 (s), 2.06 (s), and 2.10 (s) (3 × $OCOCH_3$), 2.26—2.46 (m, 2e-H), 3.43 (s, OH), 3.96—4.43 (m, 5,6,6′-H), and 4.73—5.50 (m, 1α-H, 1β-H, 3-H, 4-H); δ_C(Tesla BS 567A, 25.2 MHz) 20.7 and 20.9 ($COCH_3$), 35.2 (C-2α), 37.5 (C-2β), 62.5 (C-6α,β), 67.9 (C-3α), 68.9 (C-4α,β), 69.5 (C-5α), 70.6 (C-3β), 72.0 (C-5β), 91.6 (C-1α), 93.9 (C-1β), 170.0, 170.4, and 171.0 (CH_3C=O) (Found: C, 49.6; H, 6.4. Calc. for $C_{12}H_{18}O_8$: C, 49.66; H, 6.26%).

Synthesis of 5,5-*Dimethyl*-2-*oxo*-2-(3,4,6-*tri*-O-*acetyl*-2-*deoxy*-α-D-*hexopyranosylseleno*)-1,3,2-*dioxaphosphorinane* (**7**).—*Route A.* Anhydrous triethylamine (0.5 g, 5 mmol) was added to a solution of compound (**4**) (1 g, 3.5 mmol) and 2-chloro-5,5-dimethyl-2-seleno-1,3,2-dioxaphosphorinane (**5**) (1 g, 4 mmol) in methylene dichloride (30 ml). The mixture was kept at 20 °C until ^{31}P n.m.r. spectroscopy showed only one signal at δ 9.74 p.p.m. (4 days). The mixture was then diluted with water (25 ml) and aqueous layer extracted with dichloromethane (2 × 2.5 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure and the crystalline residue was dissolved in carbon tetrachloride and the solution diluted with light petroleum until permanent turbidity was achieved. As the solution was cooled (0—5 °C), colourless crystals (needles) were deposited and these were filtered off (1.6 g, 91.5%), m.p. 114—115 °C; $[\alpha]_{578}^{20}$ +214 (*c* 1.6 $CHCl_3$); $\nu_{max.}$ 1 280 cm^{-1} (PO); δ_P 9.7 p.p.m. ($J_{P,Se}$ 450 Hz); δ_C(sugar ring) 80.7 (d, $^2J_{P,C}$ 3 Hz, C-1), 37.7 (d, $^3J_{P,C}$ 7 Hz, C-2), 69.4 (C-3), 68.7 (C-4), 72.3 (C-5), 61.7 (C-6), 170.6, 170.0, and 169.6 (3 × $COCH_3$), 20.7, 20.6, and 20.5 p.p.m. (3 × $COCH_3$); δ_C(phosphorinane ring) 77.9 (d, $^2J_{P,C}$ 7 Hz) and 77.5 (d, $^2J_{P,C}$ 8 Hz, 2 × OCH_2), 32.4 [d, $^3J_{P,C}$ 7 Hz, -$(OCH_2)_2CMe_2$]; 22.0 (*ax*-CH_3, and 20.4 (*eq*-CH_3); δ_H(Bruker 400 MHz, $CDCl_3$), 6.38 (dd, 1-H, $J_{1,2a}$ 4.7 Hz, $^3J_{P,1}$ 7.2 Hz, $J_{1,2e}$ < 1 Hz), 2.47 (dd, 2e-H,

$J_{2e,2a}$ 14 Hz, $J_{2e,3}$ 5 Hz), 2.23—2.33 (m, 13 lines, 2a-H, $J_{1,2a}$, 4.7 Hz, $J_{2a,2e}$ 14 Hz, $J_{2a,3}$ 11.5 Hz, $^4J_{P,2a}$ 2 Hz), 5.14—5.21 (ddd, 3-H, $J_{3,4}$ 9.7 Hz), 5.0 (t, $J_{4,5}$ 9.7 Hz), 4.08—4.12 (m, 8 lines, 5-H, $J_{5,6}$ 4.3 Hz, $J_{5,6'}$ 2.7 Hz), 4.30 (dd, 6-H, $J_{6,6'}$, 12. 5 Hz), 4.01 (dd, 6′-H), 1.97 (s), 2.00 (s), and 2.02 (s) (3 × $OCOCH_3$); δ_H(phosphorinane ring) 0.85 (s) and 1.25 (s) (2 × CH_3), 3.83 (ddd, H_e, $^3J_{P,e}$ 25 Hz, $J_{e,a}$ 11.2 Hz, $^4J_{e,e'}$ 3.2 Hz), 3.86 (ddd, $H_{e'}$, $^3J_{P,e'}$ 25 Hz, $J_{e',a'}$ 11.2 Hz), 4.05 (t, H_a, $J_{a,e}$ 11.2 Hz, $^3J_{P,a}$ 11.2 Hz), and 4.08 (t, $H_{a'}$, $J_{a',e'}$ 11.2 Hz, $^3J_{P,a'}$ 11.2 Hz) (Found: C, 40.65; H, 5.9; P, 6.05. Calc. for $C_{17}H_{27}O_{10}SeP$: C, 40.72; H, 5.42; P, 6.18%).

Route B. A stream of dry hydrogen bromide was passed into a dried solution of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) (5.4 g, 20 mmol) in benzene (20 ml) until it was saturated (15—20 min). The gas stream was then reduced and bubbling continued for *ca.* 60 min.[18] Evaporation of the reaction mixture to dryness at 30 °C afforded a syrup from which the remaining acid was removed by co-distillation with benzene (3 × 30 ml portions). The crude, sirupy 3,4,5-tri-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranosyl bromide (of α-configuration, as evidenced by ^1H and ^{13}C n.m.r. spectroscopy) was dissolved in dry dichloromethane (10 ml) and triethylammonium 5,5-dimethyl-2-oxo-2-seleno-1,3,2-dioxaphosphorinane (**9**) (6.6 g, 20 mmol) in dichloromethane (10 ml) added. After 1 h the precipitate of triethylammonium hydrobromide was filtered off, the filtrate evaporated to dryness, and the residue diluted with diethyl ether to precipitate the residual salt which was then filtered off; its ^{31}P n.m.r. spectrum showed two signals at 9.7 and 9.2 p.p.m. After 4 days the syrupy product solidified and now showed only one signal (δ 9.7 p.p.m.) in its ^{31}P n.m.r. spectrum indicative of the α-anomer. Crystallization of the product from benzene–hexane yielded (**7**) (7.2 g, 73%) as colourless needles, m.p. 114—115 °C; $[\alpha]_{578}^{20}$ +214 (*c* 1.6, $CHCl_3$). N.m.r. results for the α-selenophosphate were identical with those for the compound (**7**) obtained by route A.

Route C. 3,4,5-Tri-*O*-acetyl-D-glucal (**1**) (1.36 g, 5 mmol) and the phosphoroselenoic acid (**11**)[19] (1.11 g, 5 mmol) were dissolved in dichloromethane (20 ml) and refluxed for 12 h [until t.l.c. showed no traces of (**1**)]. The solvent was then removed under reduced pressure and the residue (δ_P 9.58 and 62.34 p.p.m., integrated as 7:1) crystallized from diethyl ether (× 3) to give analytically pure (**7**) as colourless crystals (1.92 g, 70%), m.p. 115—116 °C; the spectroscopic results for (**7**) thus obtained were identical with those for the compound obtained by Route A.

Acknowledgements

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