Model synthesis of 2,3:5,6-di-*O*-isopropylidene- *S*-α-D-mannofuranosyl-*N*,*N*-diisopropylphosphoramidofluoridothioate and 2,3:5,6-di-*O*-isopropylidene-Se-α-D-mannofuranosyl-*N*,*N*-di-isopropylphosphoramidofluoridoselenoate *via* P(III)-OAr intermediates and a thiono-thiolo (selenono-selenolo) rearrangement

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Dedicated to Prof. Jan Michalski on his ninetieth birthday

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Abstract

Phosphitylation of the glycosidic center of sugar derivative **2** by phosphoroamidite **1** leads to the intermediate P(III) ester **3**. Conversion of **3** into fluorophosphoroamidite **4** and subsequently oxidation by elemental sulfur or selenium affords the corresponding thiono- and selenono- esters **5** and **6**. The latter compounds are readily rearranged into their thiolo- or selenolo- isomers in the presence of Bu_4NI as catalyst (TBAI). The total yield of **7** and **8** exceeds 90%.

Keywords: Phosphitylation, thiono-thiolo (selenono-selenolo) rearrangement, fluorophosphoramidite, phosphoramidofluoridothioate (selenoate)

Introduction

Thio- and seleno- analogs of glycosyl phosphates are useful intermediates in the synthesis of modified monosaccharides and as glycosyl donors.[1] Michalska and associates have found that this class of compounds can be readily prepared e.g. from glycosyl bromides by condensation with thiophosphate or selenophosphate salts.[2] Glycosyl S- or Se phosphates are major products of these reactions. Another pathway leading to glycosyl thiophosphates is based on the known reaction between P(III) esters and alkyl (aryl) thiocyanates.[3] Alkyl and aryl thiocyanates react with trialkyl phosphite and their structural analogues to give alkyl or aryl cyanates and the corresponding thiolo-esters. This reaction is believed to proceed by a mechanism involving

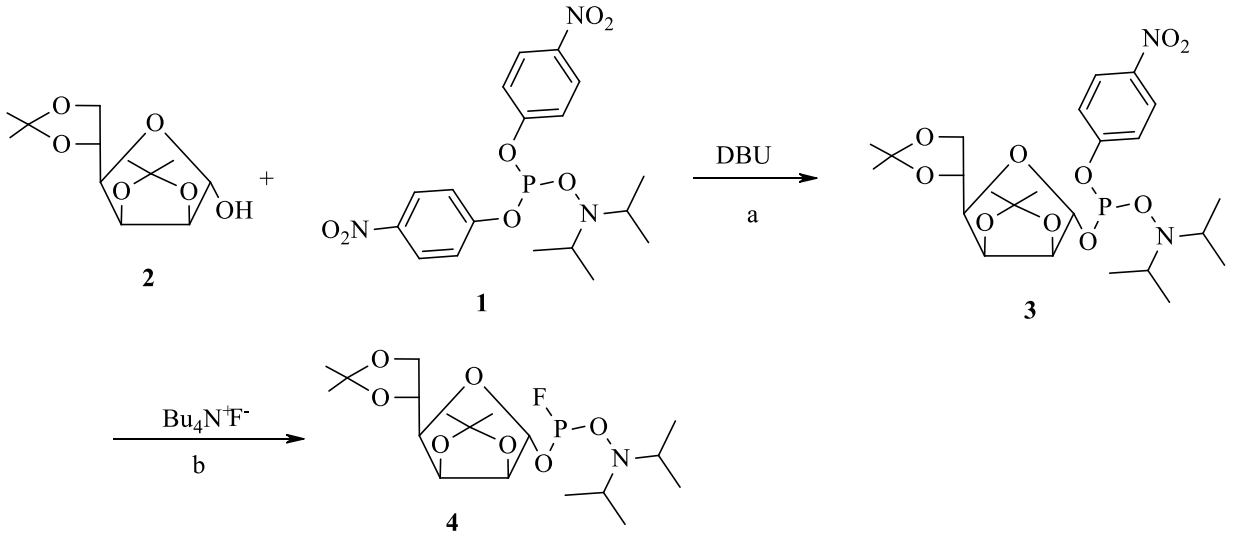
displacement of the CN group by nucleophilic attack of P(III) phosphorus on electrophilic sulfur *via* formation of a phosphonium-type intermediate. The procedure has been recently used to prepare glycosyl thiophosphates as potential glycosyl donors.[4] However, this method is limited to glycosyl thiocyanates that do not rearrange readily into isomeric isothiocyanates. Such isomerization may be slowed down by bulky protecting groups at the sugar moiety. In every described case, however, isomeric products are formed in substantial amounts. Because glycosyl thiophosphates and selenophosphates can be synthesized directly from glycosyl halides, as mentioned above, this approach seems to be of limited use.[2]

Since the seminal work of Letsinger and Caruthers it became obvious that phosphitylation procedures are of special importance in the synthesis of biophosphates and their structural analogs.[5] We have recently become interested in pursuing the use of specially designed phosphitylation reagents in the synthesis of glycosyl thiophosphates and their seleno- analogs as a possible alternative to the methods described above. We anticipated that such an approach could not only be more efficient but also would allow the construction of more complex glycosyl-phosphorus ester structures, such as those derived from thio- and seleno- fluoro-phosphoric acids.

Results and Discussion

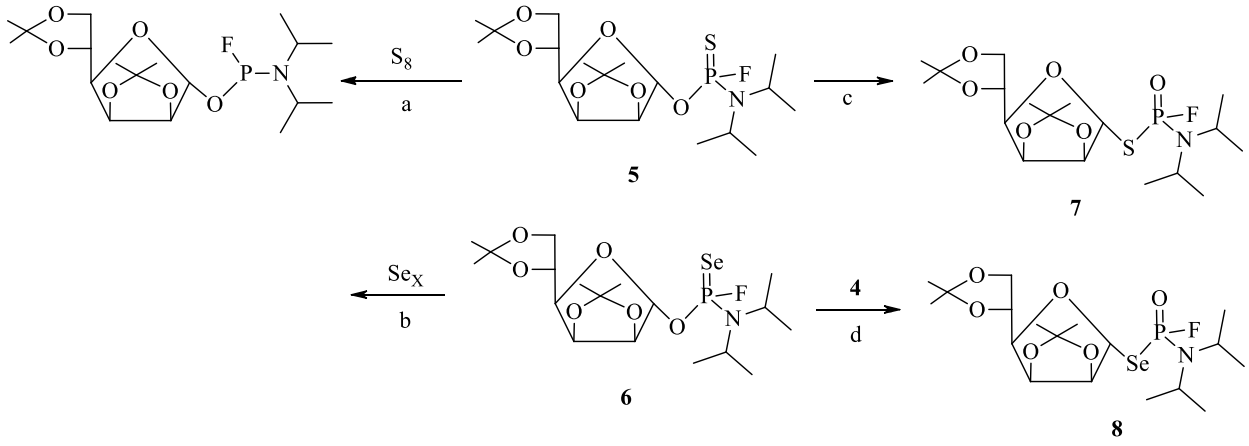
We discuss a model strategy based on *O*,*O*-di-(4-nitrophenyl)-*N*,*N*-diisopropylphosphoro-amidite **1** as a phosphitylation reagent and 2,3,5,6-di-isopropylidene- α-D-mannofuranose **2** as an example sugar. The amidite **1** belongs to a group of ambident reagents containing two different types of leaving group at tricoordinate phosphorus center: 4-nitrophenoxy and di-isopropylamino.[6] The former can be activated by strong bases like DBU, the latter by tetrazole or - more conveniently – by trimethylchlorosilane.[7] It is important to mention that phosphitylation employing an aryloxy leaving group does not interfere with subsequent use of amido group. The opposite is also true.

When α-D-mannofuranose **2** was allowed to react with the phosphitylating reagent **1** in acetonitrile at 20 ºC in the presence of DBU, the α-D-mannofuranosyl-*O*-(4-nitrophenyl) phosphoroamidite **3** was formed within 10 min in over 95% yield after purification by silica gel column chromatography, and was obtained as a mixture of diastereoisomers in a ratio of 1:1. The compound **3** is potentially useful as a phosphitylating reagent by replacement of the di-isopropylamino group and as an intermediate in the synthesis of α-D-mannofuranosyl fluorophosphoroamidite **4** *via* exchange of the 4-nitrophenoxy group. It has been earlier established that an aryloxy group can readily be replaced by a fluoride anion.[8] Indeed, the fluorophosphoroamidite **4** was formed in almost quantitative yield when **3** was kept for 10 min. with tetrabutylammonium fluoride (TBAF) in acetonitrile solution. Both reactions **a** and **b** shown in Scheme 1 can be performed as a one-flask procedure at 20 ºC.



Scheme 1

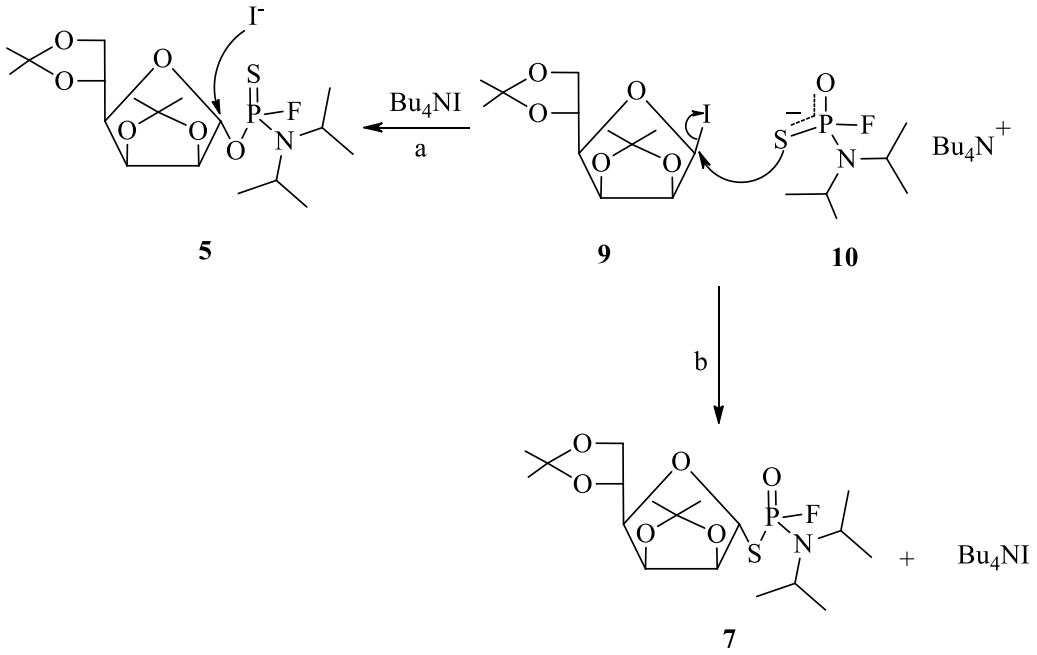
Transformation of **4** into the thionofluorophosphate or selenonofluorophosphate takes place by addition of elemental sulfur or selenium at 20ºC in diisopropylamine. Rates of addition of sulfur and selenium are distinctly different: at 20ºC the sulfurization is complete in 1 h while under the same reaction conditions the selenization reaction requires 10 h.



Scheme 2

Compounds **5** and **6** were formed in almost quantitative yield after purification by silica gel chromatography, and isolated in 95% yield, as a mixture of diastereoisomers in a ratio of 1:1. The thiono- and seleno-esters **5**, **6** were readily rearranged into their thermodynamically more stable thiolo- and selenolo- isomers **7**, **8**. This transformation (Scheme 2, steps **c** and **d**), related to the Emmet-Pishchimuka reaction, requires heating to over 100 ºC but the temperature can be

effectively reduced to below 60 ºC when *tetra*-butylammonium iodide (TBAI) is used as the catalyst.[9] The rearrangement of both compounds **5** and **6** proceeds in acetonitrile solution in almost quantitative yields. A plausible intermediate in this rearrangement is the iodoglycosyl compound **9** which is formed *via* nucleophilic displacement at the sugar glycosylic center by iodide anion derived from the catalyst. This intermediate, formed with inversion of configuration at glycosylic carbon, provides β-D- iodomannofuranose **10** which undergoes a second nucleophilic displacement by the fluoroamidothiophosphorus acid anion. This second displacement proceeds more likely with inversion of configuration at the glycosylic carbon atom. Two inversions result in the final retention (Scheme 3). ^{31}P NMR spectroscopy failed to show formation of the iodide **9** and salts **10.** This can be explained if the reaction b (Scheme 3) is very fast.



Scheme 3

A similar mechanistic picture is likely to be valid in the case of the seleno compound. The α-D-mannofuranosyl structure of compounds **3**-**8** was rigorously confirmed by ^{1}H-, ^{13}C- ^{19}F- and ^{31}P- NMR spectroscopy. They all have the same α-D-configuration at the glycosylic mannose furanose center. In respect to the center of chirality at the phosphorus atom, they are all isolated as 1:1 mixtures of diastereomers.

Conclusions

It has been demonstrated earlier that the thermal >P(S)(OR) → >P(O)(SR) rearrangement may proceed with either retention or inversion of configuration at C or P centers. Our results do not allow us to draw any definite mechanistic conclusion.[10]

In summary, we have shown that even complex P-thiolo compounds can be synthesized readily in excellent yield and under mild conditions from a 1-OH sugar *via* phosphitylating procedures. This methodology is superior to methods employed earlier and in particular to those based on the intermediate formation of glycosylthiocyanate.

Experimental Section

General. The solvents were of reagent grade and were distilled and dried by conventional methods before use. The products were purified by flash chromatography on silica gel 60 (Merck 0.063 mm, 230-400 mesh ASTM). NMR spectra were obtained on a Bruker AC 200 spectrometer. δ-Values are reported in ppm relative to Me_4Si as standard for ^1H NMR (200.13 and 300.13 MHz) and relative to H_3PO_4 as external standard for ^{31}P NMR (80.96 and 121.49 MHz.), and as relative to $CFCl_3$ as external standard for ^{19}F NMR (188.15 MHz). The signals are expressed as s (singlet), d (doublet), t (triplet) or m (multiplet). Coupling constants (*J*) are in Hz

Bis-(*O*-4-nitrophenyl)-*N,N*-diisopropylphosphoramidite (1). (Route a). A solution of *N,N*-di-isopropyldichlorophosphoramidite (10 mmol) in dry THF (10 ml) was added dropwise at room temperature under a nitrogen atmosphere to a solution of sodium 4-nitrophenolate (20 mmol) in dry THF (50 ml) with stirring for 2h. The sodium chloride was removed by filtration. The filtrate evaporated to dryness and the compound **1** purified by column chromatography (Et_2O: n-pentane: triethylamine, 50:30:5 v/v, Rf 0.75) Yield 95%. (Route b) The solution of trimethyl (*p*-nitrophenoxy)silane (20 mmol) in dry THF (20 ml) was added to a solution of *N,N*-di-isopropyldichlorophosphoramidite (10 mmol) in dry THF (20 ml) at RT. The mixture was stirred for 1h, then trimethylchlorosilane and solvent were removed under reduced pressure to give the pure phosphoramidite **1**. Yield 97%. δ_P (80.96 MHz, $CDCl_3$) 144.8; δ_H (200.13 MHz, $CDCl_3$) 1.01 (12H, d, *J* 6.8 $N[CH(C\underline{H}_3)_2]_2$), 3.46-3.65 (2H, m, $N[C\underline{H}(CH_3)_2]_2$), 6.75 (4H, d, *J* 9.13, Ph-H_{ortho}) 7.86 (4H, d, *J* 9.12, Ph-H_{meta}), m.p. 120-122°C; pale yellow crystals, FAB(M+1) Calcd for $C_{18}H_{22}N_3O_6P$: 407.13, Found: 408.50.

***O*-[2,3:5,6–Di-*O,O*-isopropylidene-α-D-mannofuranosyl]-*O*-(4-nitrophenyl)-*N,N*-diisopropylphosphoramidite (3).** To a solution of the α-D-mannofuranose (0.26 g, 1.0 mmol) and DBU (0.167g 1.1 mmol) in dry acetonitrile (5 mL) was added dropwise at RT under a nitrogen atmosphere a solution of *bis*-(*O*-4-nitrophenyl)-*N,N*-di-isopropyl-phosphoramidite **3** (0.167g 1.1 mmol) in dry acetonitrile (15 mL) with stirring for 10 min. The mixture was evaporated to dryness. The residue was purified by column chromatography using CH_2Cl_2: CH_3COCH_3 (10:3 v/v) as eluent to give pure **3** as a mixture of diastereoisomers in a ratio of 1:1. Yield 91%. ^{31}P- NMR ($CDCl_3$) 145.6, 146.6. Anal. Calcd. for $C_{24}H_{37}N_2O_{10}P$: C, 52.94; H, 6.85; P, 5.69. Found C, 53.00; H, 6.75; P, 5.52%.

***O*-[2,3:5,6–Di-*O,O*-isopropylidene-α-D-mannofuranosyl]-*N,N*-diisopropylfluorophosphoramidite (4).** To a solution of aryl phosphoramidite **3** (0.53 g, 1.0 mmol) in dry THF (10 mL) was

added TBAF (1.2 mmol) at RT. After 10 min., *tetra*-n-butylammonium 4-nitrophenolate was removed by filtration. The filtrate was concentrated *in vacuo* and residue was purified by column chromatography using CH_2Cl_2:CH_3COCH_3 as eluent to give a 1:1 mixture of diastereomers of the fluorophosphoramidite **4.** Yield 93%. ^{31}P NMR ($CDCl_3$) 154.5 ppm $J_{P\text{-}F}$ = 1126.9 Hz, 154.3 ppm $J_{P\text{-}F}$ = 1112.3 Hz; ^{19}F- NMR ($CDCl_3$) -78.82ppm $J_{F\text{-}P}$ = 1126.4 Hz, -79.26 ppm, $J_{F\text{-}P}$ 1113.1 Hz. Anal. Calcd. for $C_{18}H_{33}FNO_6P$: C, 52.80; H, 8.12; P 7.56. Found: C, 52.64; H, 8.01; P, 7.52%.

***O*-[2,3:5,6–Di-*O*,*O*-isopropylidene-α-D-mannofuranosyl]-*N*,*N*-diisopropylphosphoramido-fluoridothioate 5.** To a solution of **4** (0.41 g, 1.0 mmol) in dry $(C_3H_7)_2NH$ (5 ml) THF was added sulfur (0.064 g, 2 mmol) with stirring during 1 h at RT. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel chromatography, using $C_2H_4Cl_2$ as eluent, to provide 0.4g. (86%) of the title compound, obtained as a mixture of diastereomers in a ratio of 1:1. ^{31}P- NMR ($CDCl_3$) 69.4, 71.8 ppm; ^{19}F- NMR ($CDCl_3$) 40.1, $J_{F\text{-}P}$ = 1050.0 Hz., 37.0 ppm $J_{F\text{-}P}$ = 1066.67 Hz.; ^{1}H NMR ($CDCl_3$) 1.2 – 1.5 (m, 18H); 3.60 – 3.87 (m, 2H, $J_{H\text{-}H}$ = 6.40 Hz., $J_{H\text{-}P}$ = 1.34 Hz., ^{i}Pr); 3.90 – 4.10 (m, 3H, $J_{H5\text{-}H6(7)}$ = 5.67 Hz., $J_{H6\text{-}H7}$ = 8.73 Hz., $J_{H4\text{-}H5}$ = 4.07 Hz., H_4, H_6, H_7); 4.30 – 4.40 (m, 1H, $J_{H4\text{-}H5}$ = 4.07 Hz., H_5); 4.71, 4.74 (2d, 1H, $J_{H2\text{-}H3}$ = 5.67 Hz., $J_{H2\text{-}H3}$ = 5.64 Hz., H_2); 4.77 – 4.84 (2d, 1H, $J_{1\ H2\text{-}H3}$ = 5.67 Hz., $J_{2\ H2\text{-}H3}$ = 5.64 Hz., $J_{H3\text{-}H4}$ = 3.19 Hz., H_3); 5.90, 5.91 (2d. 1H $J_{1\ H1\text{-}P}$ = 6.98 Hz., $J_{2\ H1\text{-}P}$ = 8.14 Hz., H_1); ^{13}C NMR ($CDCl_3$) 22.13, 22.19, 24.39, 24.54, 25.01, 25.68, 25.74, 26.76, 47.62, 47.72, 47.81 (CH-N), 66.94 (C_3), 82.29 (C_4), 85.57, 85.77, 85.93 (C_2), 104.30, 104.42, 104.49, (C_1), 109.16, 109.30, 113.04, 113.15., MS (LSI Cs^+) *m/z* 442.4 (M+H). Anal. Calcd. for $C_{18}H_{33}FNO_6PS$: C, 48.97; H, 7.53; P, 7.02. Found: C, 47.64; H, 7.11; P, 7.12%

***O*-[2,3:5,6–Di-*O*,*O*-isopropylidine-α-D-mannofuranosyl]-*N*,*N*-diisopropylphosphoramido fluoridoselenoate (6).** Selenium powder (0.158 g, 2 mmol) was added to a solution of **4** (0.41 g, 1.0 mmol) in dry $(C_3H_7)_2NH$ (5 ml), the mixture was stirred for 12 h at RT, and then was concentrated *in vacuo* and purified by column chromatography, using $C_2H_4Cl_2$ as eluent to give **6,** obtained as a mixture of diastereomers in a 1:1 ratio. R_f = 0.5 ($C_2H_4Cl_2$). Yield 92% (0.45 g). ^{31}P- NMR ($CDCl_3$) 73.31, $J_{P\text{-}Se}$ = 1013.27 Hz., 76.21, $J_{P\text{-}Se}$ = 977.08 Hz; ^{19}F NMR ($CDCl_3$) -39.97, $J_{F\text{-}P}$ = 1103.66 Hz., $J_{F\text{-}Se}$ = 114.62Hz.; 28.45, $J_{F\text{-}P}$ = 1122.49 Hz., $J_{F\text{-}Se}$ = 106.39 Hz.; ^{1}H NMR 1.12 – 1.51 (m, 18H), 3.71 – 3.92 (m, 2H, $J_{H\text{-}H}$ = 6.45 Hz., $J_{H\text{-}P}$ = 1.42 Hz., ^{i}Pr), 3.95 - 4.15 (m, 3H, H_4, H_6, H_7), 4.35 – 4.45 (m, 1H, H_5), 4.78 – 5.00 (m, 2H, H_2, H_3), 6.01, 6.03, 6.04 (3s, $J_{1\ H1\text{-}P}$ = 7.26 Hz., $J_{2\ H1\text{-}P}$ = 9.13 Hz., H_1), Ms (LSI Cs^+) *m/z* 489.4 (m+H). Anal. Calcd. for $C_{18}H_{33}FNO_6PSe$: C, 44.27; H, 6.81; P, 6.34. Found: C, 43.96; H, 6.90; P, 6.32%.

***S*-[2,3:5,6–Di-*O*,*O*-isopropylidine-α-D-mannofuranosyl]-*N*,*N*-diisopropylphosphoramido fluoridothioate (7).** To a solution of **5** (0.44g, 1.0 mmol) in dry acetonitrile (5 ml) was added *tetra*-butylammonium iodide (0.04 g 0.1 mmol) and stirring 6 h at RT. The reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography, using 1,2-dichloroethane/ethyl acetate 5:1 as eluent, to provide 0.42g. (95%) of the title compound**,** obtained as a mixture of diastereomers in a ratio of 1:1. R_f = 0.3. ^{31}P- NMR ($CDCl_3$) 27.3, 28.3: ^{19}F- NMR ($CDCl_3$) -35.2, $J_{F\text{-}P}$ = 1037.54 Hz., -34.8 ppm, $J_{F\text{-}P}$ = 1088.24 Hz.; ^{1}H-

NMR ($CDCl_3$) 1.20–1.54 (m, 18H), 3.45–3.65 (m, 2H, J_{H-H} = 6.35 Hz., J_{H-P} = 1.45Hz, ^{i}Pr), 3.90–4.13 (m, 3H, $J_{H5-H6(7)}$ = 6.09 Hz., J_{H6-H7} = 8.70 Hz., J_{H4-H5} = 4.25 Hz., J_{H4-H6} = 2.03 Hz., H_4, H_6, H_7), 4.34-4.48 (m, 1H, J_{H4-H5} = 4.25 Hz., J_{H4-H6} = 2.03 Hz., H_5), 4.75-4.95 (m, 2H, $J_{1\ H2-H3}$ = 5.80 Hz., $J_{2\ H2-H3}$ = 6.38, Hz., J_{H3-H4} = 3.77 Hz., H_3, H_2), 5.86, 6.94 (2d, 1H, $J_{1\ H1-P}$ = 7.54 Hz., $J_{2\ H1-P}$ = 10.17 Hz., $^{4}J_{1\ H1-H4}$ = 0.87 Hz., $^{4}J_{H1-H4}$ = 0.80 Hz., H_1); ^{13}C- NMR ($CDCl_3$) 21.63, 21.77, 22.39, 22,55, 24.40, 24.52, 24.77, 25.61, 26.57, 47.10, 47.20 (CH-N), 66.36, 66.59 (C_6), 72.09, 72.25 (C_5), 79.04, 79.18 (C_3), 81.22, 81.51 (C_4), 86.51, 86.75, 87.30, 87.51 (C_2), 89.70, 90.04 (C_1), 108.87, 109.03, 112.91, 113.00. MS (LSI Cs^+) *m/z* 442.4 (M+H). Anal. Calcd. for $C_{18}H_{33}FNO_6PS$: C, 48.97; H, 7.53; P, 7.02. Found: C, 47.73; H, 7.41; P, 7.02%.

***Se*-[2,3:5,6–di-*O,O* isopropylidine-α-D-mannofuranosyl]-*N,N*-diisopropylphosphoramido fluoridoselenoate (8)**. To a solution of **6** (0.49g, 1.0 mmol) in dry acetonitrile (5 ml) was added tetrabutylammonium iodide (0.04 g, 0.1 mmol) and the mixture stirred 6 h at RT. The mixture was evaporated under reduced pressure. The residue was purified by silica gel chromatography, using 1,2-dichloroethane/ethyl acetate 5:1 as eluent to provide 0.48 g. (98%) of the title compound**,** obtained as a mixture of diastereomers in a ratio of 1:1. R_f = 0.4 (1,2-dichloroethane:ethyl acetate, 5:1). ^{31}P- NMR ($CDCl_3$) 19.5 ppm, J_{P-Se} = 1152.14 Hz., J_{P-Se} = 471.36 Hz.; ^{19}F NMR ($CDCl_3$) -25.8, J_{F-P} = 1152.14 Hz., J_{F-Se} = -49.74 Hz., 20.2ppm J_{F-P} = 1140.59 Hz., J_{F-Se} = 32.00 Hz.; ^{1}H NMR ($CDCl_3$) 1.20 – 1.50 (m, 18H), 3.41 – 3.65 (m, 2H, J_{H-H} = 6.41 Hz., J_{H-P} = 1.47 Hz., ^{i}Pr), 9.94 – 4.12 (m, 3H, $J_{H5-H6(7)}$ = 8.73 Hz., J_{H4-H5} = 3.87 Hz., H_4, H_6, H_7), 4.38 – 4.50 (m, 1H, J_{H4-H5} = 3.87 Hz.), 4.77 – 4.85 (m, 1H, J_{H3-H4} = 3.62 Hz., $J_{1\ H2-H3}$ = 5.92 Hz., $J_{2\ H2-H3}$ = 5.90 Hz., H_3), 4.97, 5.08 (2d, 1H, $J_{1\ H2-H3}$ = 5.92 Hz., $J_{2\ H2-H3}$ = 5.90 Hz., H_2), 6.17, 6.25 (2d, 1H, J_{1H1-P} = 6.92 Hz., $J_{2\ H1-P}$ = 8.95 Hz., $^{4}J_{1\ H1-H4}$ = 1.11Hz., $^{4}J_{2\ H1-H4}$ = 0.96 Hz., $J_{1\ H1-Se}$ = 8.42 Hz., $J_{2\ H1-Se}$ = 6.86 Hz., H_1); ^{13}C- NMR ($CDCl_3$) 21.90, 22.09, 22.73, 22.87, 24.84, 25.09, 25.92, 26.88, 47.11, 47.21 (CH-N), 66.74, 66.88 (C_6), 72.27, 72.40, (C_5), 79.09, 79.23 (C_3), 82.21, 82.51 (C_4), 87.24, 87.96 (C_20, 88.84, 89.13 (C_1), 109.40, 113.25. MS (LSI Cs^+) *m/z* 489.3 (M+H). Anal. Calcd. for $C_{18}H_{33}FNO_6PSe$: C, 44.27; H, 6.81; P, 6.34. Found: C, 44.32; H, 6.88; P, 6.30%.

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10. An alternative explanation can be considered: the α-configuration is forced by a strong anomeric effect at the 1-OH center of D-mannofuranose. Therefore the observed retention in the isomerization (Scheme 3) may be caused by the above effect.