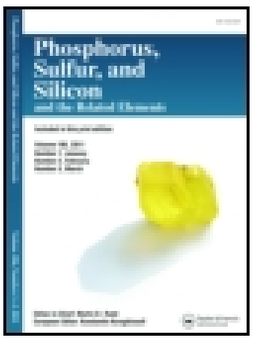

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Reaction of DAST with sugar hydroxyphosphonates

Application of DAST mediated reactions in transformations of *α*-hydroxyphosphonates derived from *O*-isopropylidene-protected carbohydrate derivatives

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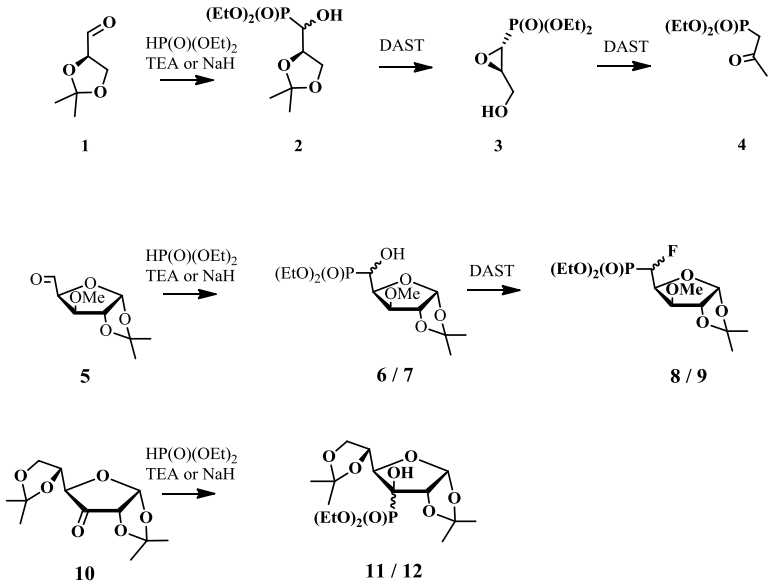
In memoriam to Professor Harry R. Hudson

ABSTRACT

Various *α*-hydroxyphosphonates derived from *O*-isopropylidene glyceraldehyde, hexofuranose and pentofuranose have been prepared to test nucleophilic fluorination reactions. The substrates have been conveniently prepared in Pudovik reactions and the stereoselectivity, as well as the configuration of the obtained carbohydrates have been described. Reactions have been accomplished using DAST as the fluorinating reagent. Treatment of protected glycerol phosphonate with DAST gave unusual conversions leading to fosfomycin analogue possessing an oxirane ring. Subsequent reaction with diethylaminesulfur trifluoride (DAST) yielded *β*-ketophosphonate. By contrast, stereoselective deoxyfluorination of hydroxyphosphonates derived from an *O*-isopropylidenepentofuranose gave the major fluoride possessing D-glu configuration while the reaction with di-*O*-isopropylidene hexofuranose derivative, has not been successful presumably due to stereochemical properties of the substrate.



Keywords

α-Hydroxyphosphonate, Carbohydrate, Fluorinated Phosphonate, Pudovik reaction, Rearrangement, DAST

1. Introduction

Phosphate esters are a group of organic compounds fulfilling important functions in living organisms such as genetic information or energy storage and transfers, as well as in signaling pathways. For this reasons, their analogues are attractive targets in the synthesis of biologically active compounds. One of the possibilities gave the application of phosphonate as surrogates of naturally occurring phosphates. The replacement of the C–O–P bridge in phosphates by the C–CH_2–P in phosphonates make them more hydrolytically stable.[1] The syntheses of phosphonate carbohydrate analogues possessing a phosphorus atom as a part of the furanose or pyranose ring,[2] bearing an exocyclic phosphonate functionality [3] as well as carbohydrate derived polyhydroxyphosphonates [4] have been already reported. On the other hand, an additional introduction of one or two fluorine atoms to alkylphosphonates makes them isosteric or isopolar

phosphate substitutes. Thus, *α*-monofluoroalkylphosphonates and *α*,*α*-difluoroalkylphosphonates are usually more reactive, lipophilic and resistant to hydrolysis in biological environment.[5-7] The fluorinated phosphonosugar derivatives possess attractive biological properties and were applied as inhibitors of enzymes such as glycerol-3-phosphate dehydrogenase,[4g,4h] glucose-6-phosphate dehydrogenase,[3g,8] phosphatidylinositol phospholipase C,[9] transferase,[3h] among others. They were also exploited as ligands binding to lysophosphatidic acid receptors.[4a,4e] One of the common strategy in synthesis of fluorinated phosphonates has involved nucleophilic fluorination of appropriate *α*-hydroxyphosphonates with diethylaminesulfur trifluoride (DAST).[10] However, depending on phosphonate system, besides the fluorination *via* substitution [3g, 4e, 5a,11-13] other reactions such as eliminations [5a] or rearrangement [5a, 12] have been reported.

In our previous work we studied fluorination reaction in tertiary alcohols derived from di-*O*-isopropylidenehexofuranose and 1,2-*O*-isopropylidenepentofuranose.[14] We found that deoxyfluorination with DAST have been affected by the adjacent bottom–face 1,2-*O*-isopropylidene group oxygen atom leading mainly to one diastereoisomer. Moreover, the inversion of configuration and allylic rearrangement have led to two chiral regioisomers in the case of carbohydrate allylic fluorides. This particular stereocontrol prompted us to verify fluorination of chiral hydroxyphosphonates derived from (*R*) -glyceraldehyde and other *O*-isopropylidene protected carbohydrate systems. Herein, we present our results.

2. Results and Discussion

As the convenient starting materials carbohydrates possessing an aldehyde or ketone group have been used. The appropriate *α*-hydroxyphosphonates have been obtained under the conditions of

Pudovik reaction. Thus introducing the phosphonate moiety to 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde **1** gave diethyl (((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hydroxymetyl)phosphonate **2**.[4b] Treatment of diethyl phosphite by bases such as triethylamine TEA or NaHfollowed by addition of **1** gave a mixture of two diastereoisomers of **2** in 71% yield (TEA, THF, RT, 21d;1:0.52 ratio) or in 23% yield (NaH, THF, RT, 4d; 1:0.62 ratio), respectively. The reaction with (*R*)-(+)-*α*-methoxy-*α*- (trifluoromethyl)phenylacetyl chloride [(*R*)-(+)-MTPA-Cl] according to Mosher method has confirmed the configurations of new stereogenic C1 center of *α*-hydroxyphosphonates **2** as 1*S* for the major diastereoisomer.[15] This results are in agreement with an analogous assignment and diastereoselectivity for addition of dimethyl phosphite to 2,3-*O*-isopropylidene (*R*)-glyceraldehyde **1**.[15] On the other hand the (*S*)-Al–Li-bis(binaphthoxide) catalyzed addition of chiral di (1*R*,2*S*,5*R*)-menthyl phosphite to protected (*R*)-glyceraldehyde gave better diastereoselectivity (90% d.e.).[4b]

Next, nucleophilic deoxyfluorination of **2** (1:0.52, *dr*) using diethylaminesulfur trifluoride (DAST) gave compound **3** with 60% yield (Scheme 1).

Formation of one diastereoisomer of **3** has been confirmed by one signal at δ_P: 18.9 in ^{31}P NMR spectrum. However, the lack of the analogous signal in ^{19}F NMR as well as distinctive doublets at δ_H: 3.1 with J_{HP} 30 Hz and δ_C: 47 (J_{CP} 203 Hz) [16] indicated formation of oxirane **3** as a rearrangement product. The stereochemistry ((1*R*,2*R*) of **3** has been determined in comparison of the spectra to the literature data. So, diethyl ((1*S*,2*S*)-3-(hydroxymethyl)-oxiran-2-yl)-phosphonate has been already obtained in few steps synthesis starting from (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonate.[17]

The plausible mechanism of observed, DAST mediated transformation of **2** leading to **3** is presented in Scheme 2.

At the beginning, due to the reaction of (1*S*,2*R*) **2** with DAST, the *α*-hydroxyl moiety was converted into a good leaving group with concomitant HF releasing (stage A). Next, the HF catalyzed removal of 2,3-*O*-isopropylidene protecting group (stages B and C) led to the partially protected vicinal 2,3-diol. Subsequent attack of the electron pair derived from the oxygen atom of 2-hydroxyl group on adjacent DAST-derived leaving group followed by HF elimination and deprotection (stage D) gave analogue of fosfomycin - compound **3**. It is noteworthy, that only one major diastereoisomer of **2** (1*S*,2*R*) underwent that DAST- mediated rearrangement while the second diastereoisomer of **2** stayed intact in the reaction mixture. Moreover, the internal SN_2 type reaction of the last step of proposed transformation has been confirmed by the 1*R*,2*R* configuration of obtained oxiranephosphonate **3**. The participation of oxygen derived from 1,2-*O*-isopropylidene neighboring group during DAST treatment of alcohols origin di-*O*-isopropylidenehexofuranose and 1,2-*O*-isopropylidenepentofuranose has been observed as well, leading to excellent diastereoselectivity of deoxyfluorinations.[14] <AQ>On the other hand, anchimeric assistance throughout nucleophilic fluorination of aminoacids descended *α*-hydroxyphosphonates yielded in formation of both diastereoisomers.[18]<AQ> Subsequent treatment of **3** with DAST gave the non-fluorinated *β*-ketophosphonate **4** [19] in moderate yield 51% after isolation. (Scheme 1). Since in this particular DAST- caused rearrangement, the presence of the protected hydroxyl group in the neighborhood of reaction centre has been necessary, we were looking for similar transformation in other *α*-hydroxyphosphonate carbohydrate derivatives. Thus, Pudovik reaction performed on

1,2-*O*-isopropylidene-3-*O*-methyl-*α*-D-xylo-pentadialdo-1,4-furanose **5** [20] ($HP(O)(OEt)_2$, TEA, 80 C, 52h) gave a mixture of two epimeric carbohydrate 5-C-phosphonates with L-*ido*- **6** or D-*gluco*- **7** configurations (ratio 1:0.52 in crude reaction mixture) [21] with 63% yield and 1:0.25 ratio after isolation (Scheme 3).

The configuration of the new stereogenic C5 center has been confirmed by the reaction of **6/7** with (*R*)-(+)-*α*-methoxy-*α*-(trifluoromethyl)phenylacetyl chloride [(*R*)-(+)-MTPA-Cl] *i.e.* Mosher reagent.[15] The phosphite (Nu) appears to have added preferentially from the less hindered face according to Felkin-Ahn model (along the C4 - C5 bond) to give L-ido isomer **6** (5*S*) as the major compound (Scheme 3). However, the less favored addition from the up-side of the ring, attributed to the steric impact of the bulky 3-*O*-methyl group, has been observed as well, leading to configuration D-gluco in **7** (5*R*). This results are parallel to the studies reported by Kovensky *et al*.[20] Thus, vinyl magnesium bromide attacks aldehyde **5** yielding 6,7-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl- (*α*-D-gluco-hept-6-enofuranose) and (-*β*-L-ido-hept-6-enofuranose) with an excess of last-mentioned carbohydrate (ratio 1:1.2). Then, the reaction of carbohydrate -derived *α*-hydroxyphosphonates (1:0.25) **6**/**7** with DAST has been carried out yielding major **8** and a traces of **9** (ratio 1: 0.03 after isolation)(Scheme 4).

The analysis of ^{31}P NMR spectrum indicated formation of one major product matched with signals at δ_P: 16.7 (d) and at δ_F: -216.0 (ddd) while the minor product's signals were located at δ_P: 14.6 (d) and at δ_F: -215.8 (dddd) possessing geminal values $^2J_{PF}$ 70 Hz and $^2J_{F\text{-}H5}$ 44 Hz confirming the formation of *α*-fluorophosphonate carbohydrate derivatives.[22] The configuration at C5 in carbohydrates **8** and **9** has been verified by comparing coupling constants values observed for fluorine and vicinal hydrogen atom H4 (*gauche*, ^3J 5 Hz for **8** and *anti*, ^3J

14 Hz in case of **9**), as well as bigger coupling constants between hydrogen atoms H5 and H4 (*anti*, ^{3}J 9 Hz in case of **8**). This results have supported the stereochemical assignment at C5 as being 5*R* and D-gluco configuration for major fluoride **8**.[16] On the same time, the carbohydrate **7** has been proved to be less reactive with DAST presumably due to steric hindrance preventing reaction of C5 -OH group with the fluorinating reagent. Attempted prolongation of the reaction time (in DCM) has caused the decomposition of both starting materials. Analogous reactions carried out in others conditions (in various range of temperature or in solvents such as THF or DMF) have not been successful.

<AQ>As others convenient to study *α*-hydroxyphosphonates hexofuranose derivatives have been employed.</AQ> Thus, the TEA-catalyzed addition of diethyl phosphite to 1,2 ;5,6-di-*O*-isopropylidene-*α*-D-ribo-hexofuran-3-ulose **10** [23] (TEA, neat, 45 °C, 19h) as indicated on Felkin-Ahn model (along C3 - C4 bond) has led to C3 epimeric carbohydrates **11**/**12** (1:0.35 ratio after isolation, respectively) in 92% yield (Scheme 5).

The assignment of configuration of the obtained new stereogenic C3 centre of the predominant carbohydrate **11** has been based on vicinal P-H4 couplings constants values (δ_H: 3.97, *trans*, *J* 29 Hz) [3k, 3i] supporting phosphite (Nu) addition from the top *β*-face of the furanose ring. The more favored up-side addition to planar carbonyl bond giving rise to formation of major epimer was frequently observed in case of the addition to C=O bond of **10**.[3k,14,24] Next, reaction of **11/12** with DAST has been performed. However, despite of our efforts (different amount of DAST, various solvents, ranges of temperature) the conversion of **11**/**12** with DAST failed. Apparently, in this case nucleophilic attack or displacement by SN_2 mechanism couldn't occur due to steric impact of the bulky *O*-isopropylidene groups at carbon atoms C1/C2 and C5/C6. On

the other hand, if reaction proceeded *via* SN_1, a carbocation centered on the *α*-carbon would be strongly destabilized by the electron-withdrawing phosphonate group.[25]

3. Experimental

General procedure for the preparation of α-hydroxyphosphonates (Pudovik reaction)

To the mixture of aldehyde or ketone (1 eq.) and diethyl phosphite (1 eq.), triethylamine (TEA, 0.2 eq.) was added and the reaction mixture was stirred at 80 °C (monitored by TLC). Then, the solvent was evaporated and the residue was extracted with DCM and washed with a saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, evaporated and purified by column chromatography (EtOAc) to give products as oils. The Supplemental Materials contains sample ^{1}H, ^{13}C and ^{31}P NMR of the products 2, 3, 4, 6/7, 8/9, and 11/12 (Figures S 1 – S 18).

*Diethyl ((S/R)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)phosphonate **2***

Reaction of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **1** (972 mg, 7.48 mmol, 1 eq.) in THF (30 mL) with $HP(O)(OEt)_2$ (1.033 g, 7.48 mmol, 1 eq.) and TEA (80 mg, 0.75 mmol, 0.1 eq.) in THF (5 mL) was carried out at room temperature for 21 d, followed by extraction and column chromatography (See: *General procedure.*) and gave compound **2** [4b] as two diastereoisomers mixture (1:0.52 ratio) with a yield 71% (1.432 g).

Note: The reaction of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **1** (137 mg, 1.06 mmol, 1 eq.) added to the mixture of $HP(O)(OEt)_2$ (146 mg, 1.06 mmol, 1 eq.) and NaH (42 mg, 1.06 mmol, 1 eq.) in THF (5 mL) at room temperature for 4 d, followed by extraction and column chromatography (See: *General procedure*) and gave compound **2 (**66 mg) with a yield 23% as two diastereoisomers mixture (ratio 1:0.62).

Compound **2** (ratio 1:0.52) had: ^{1}H NMR(300 MHz): δ 4.46 (ddd, *J* = 6.6, 5.2, 3.8 Hz, 1×0.52 H, C*H*P(OH)), 4.40–4.35 (m, 1H, C*H*P(OH)), 4.24–4.04 (m, 6H+6×0.52 H, C*H*, C*H*H, OC*H*$_2$CH$_3$), 3.94 (ddd, *J* = 8.5, 6.8, 0.5 Hz, 1H, C*H*H), 3.85 (dd, *J* = 9.5, 5.3 Hz, 1×0.52 H, CH*H*) , 1.39 (s, 6×0.52 H, *i*–Pr), 1.37(s, 6H, *i*–Pr), 1.36 (t, *J* = 7.1Hz, 6H, OCH$_2$C*H*$_3$), 1.35 (t, *J* = 7.1Hz, 6×0.52 H, OCH$_2$C*H*$_3$); ^{31}P NMR(121 MHz): δ 22.59 (s, 1P), 21.51 (s, 0.52 P).

GC–MS (Calcd for $C_{10}H_{21}O_6P$: 268$[M]^+$) found *m*/*z* = 253 $[M–Me]^+$, R_t 13.56/13.76 min

1.2.2. Diethyl [1,2-O-isopropylidene-3-O-methyl-α-L-ido-pentofuranose] 5-C-phosphonate ***6*** *and diethyl [1,2-O-isopropylidene-3-O-methyl-α-D-gluco-pentofuranose] 5-C-phosphonate* ***7***

The reaction of 1,2-*O*-isopropylidene-3-*O*-methyl-α-*D*-xylo-pentadialdo-1,4-furanose **5** [20] (573 mg, 2.83 mmol), HP(O)(OEt)$_2$ (1.04 eq. 407 mg, 2.95 mmol) and triethylamine (0.21 eq. 102 mg, 0.6 mmol) was stirred for 52 h at 80 °C, after extraction and column chromatography (hexane : AcOEt, 3 :7 → AcOEt →AcOEt:SSE, 1:1, v:v, and gave products **6/7** (606 mg) as a mixture (ratio 1:0.52, respectively) with a yield 63%.

Compound **6** had: ^{1}H NMR δ 5.99 (dd, *J* = 3.9, 1.2 Hz, 1H, H1), 4.58 (d, *J* = 3.9 Hz, 1H, H2), 4.40 – 4.33 (m, 2H, H4, H5), 4.28–4.15 (m, 4H, OC*H*$_2$CH$_3$), 4.12 (d, *J* = 2.7 Hz, 1H, H3), 3.48 (s, 3H, OC*H*$_3$), 1.49 (s, 3H, *i*–Pr), 1.37 (t, *J* = 7.5 Hz, 6H, OCH$_2$C*H*$_3$), 1.33 (s, 3H, *i*–Pr); ^{13}C NMR: δ 111.7(*i*–Pr), 104.6 (d, *J* = 2.2 Hz, C1), 86.0 (C3), 81.3(C2), 76.8 (d, *J* = 13.3 Hz, C4), 67.7 (d, *J* = 161.0 Hz, C5), 63.1 (d, *J* = 7.1 Hz, OCH$_2$CH$_3$), 62.4 (d, *J* = 7.1 Hz, OCH$_2$CH$_3$)), 57.7 (OCH$_3$), 26.6, 26.1 (2×*i*–Pr), 16.4 (d, *J* = 5.6 Hz, 2×OCH$_2$CH$_3$); ^{31}P NMR: δ 21.30 (s); GC–MS (Calcd for $C_{13}H_{25}O_8P$: 340$[M]^+$) found *m*/*z* = 326 $[M–Me+H]^+$, R_t 16.28 min.

Compound **7** had: ^{1}H NMR δ 5.97 (d, *J* = 3.9 Hz, 1H, H1), 4.60 (d, *J* = 3.9 Hz, 1H, H2), 4.50 (td, *J* = 5.8, 3.5 Hz, 1H, H4), 4.40 – 4.33 (m, 1H, H5), 4.28–4.15 (m, 4H, OC*H*$_2$CH$_3$), 3.91 (dd, *J* =

3.5, 0.5 Hz, 1H, H3), 3.43 (s, 3H, OC*H*$_3$), 1.50 (s, 3H, *i*–Pr), 1.37 (t, *J* = 7.4 Hz, 6H, OCH$_2$C*H*$_3$), 1.33 (s, 3H, *i*–Pr); ^{13}C NMR: δ 112.0 (*i*–Pr), 104.8 (d, *J* = 2.5 Hz, C1), 85.6 (d, *J* = 5.5 Hz, C3), 81.6 (C2), 78.2 (d, *J* = 4.5 Hz, C4), 66.7 (d, *J* = 166.6 Hz, C5), 63.1 (d, *J* = 6.3 Hz, O*C*H$_2$CH$_3$), 62.7 (d, *J* = 6.8 Hz, O*C*H$_2$CH$_3$), 57.7 O*C*H$_3$, 26.8, 26.3 (2×*i*–Pr), 16.4 (d, *J* = 6.0 Hz, 2×OCH$_2$*C*H$_3$); ^{31}P NMR: δ 20.71 (s); GC–MS (Calcd for C$_{13}$H$_{25}$O$_8$P: 340[M]$^+$) found *m*/*z* = 326 [M–Me+H]$^+$, R_t 16.54 min.

Diethyl (1,2;5,6-di-O-isopropylidene-a-D-allofuranose) 3-C-phosphonate ***11*** *and diethyl (1,2;5,6-di-O-isopropylidene-a-D-glucofuranose) 3-C-phosphonate* ***12***

To the 1,2 ;5,6-di-*O*-isopropylidene-α-*D*-ribo-hexofuran-3-ulose **10** [23] (590 mg, 2.285 mmol, 1 eq.) HP(O)(OEt)$_2$ (315 mg, 2.285 mmol, 1 eq.) and triethylamine (51 mg, 0.484 mmol, 0.21 eq.) were added and the reaction mixture was stirred for 19 h at 45 °C. Then, the residue was extracted, column chromatographed (CHCl$_3$:MeOH; 100:2; v:v, see: *General procedure 1.2.*) to give products **11/12** (833 mg) as a mixture (1:0.35 ratio, respectively) with a yield 92%.

Compound **11** had: ^{1}H NMR δ 5.79 (d, *J* = 3.7 Hz, 1H, H1), 4.73 (dd, *J* = 8.0, 3.7 Hz, 1H, H2), 4.62 (ddd, *J* = 7.4, 6.3, 5.2 Hz, 1H, H5), 4.26 – 4.19 (m, 4H, OC*H*$_2$CH$_3$), 4.18 – 4.11 (m, 1H, H6), 4.00 (dd, *J* = 8.7, 5.0 Hz, 1H, H6'), 3.97 (dd, *J* = 29.1, 7.7 Hz, 1H, H4), 3.21 (br d, *J* = 12.5 Hz, 1H, OH), 1.60 (s, 3H, *i*–Pr), 1.46 (d, *J* = 0.5 Hz, 3H, *i*–Pr), 1.39 (d, *J* = 0.4 Hz, 3H, *i*–Pr), 1.38 (s, 3H, –Pr), 1.37 (td, *J* = 7.1, 0.6 Hz, 3H, OCH$_2$C*H*$_3$), 1.36 (td, *J* = 7.1, 0.4 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR δ 113.3 (*i*–Pr), 109.6(*i*–Pr), 104.4 (C1), 82.3 (d, *J* = 5.8 Hz, C2), 80.5 (d, *J* = 8.7 Hz, C5), 79.0 (d, *J* = 168.6 Hz, C3), 73.9 (d, *J* = 3.7 Hz, C4), 67.0 (C6), 64.0 (d, *J* = 6.9 Hz, O*C*H$_2$CH$_3$), 62.9 (d, *J* = 7.4 Hz, O*C*H$_2$CH$_3$), 26.7 (*i*–Pr), 26.6 (*i*–Pr), 26.56 (*i*–Pr), 25.1(*i*–

Pr), 16.5 (d, *J* = 5.5 Hz, OCH_2CH_3), 16.3 (d, *J* = 6.1 Hz, OCH_2CH_3); ^{31}P NMR: δ 19.14 (s); GC–MS (Calcd for $C_{16}H_{29}O_9P$: 396 $[M]^+$) found *m*/*z* = 381 $[M–Me]^+$, R_t 16.85 min.

Compound **12** had: ^1H NMR δ 5.86 (d, *J* = 4.0 Hz, 1H, H1), 4.78 (dd, *J* = 10.7, 4.0 Hz, 1H, H2), 4.43 – 4.37 (m, 1H, H5), 4.33 – 4.27 (m, 4H, OCH_2CH_3), 4.18 – 4.11 (m, 2H, H6/6'), 3.90 (dd, *J* = 8.9, 7.0 Hz, 1H, H4), 3.41 (br d, *J* = 13.8 Hz, 1H, OH), 1.63 (s, 3H, *i*–Pr), 1.45 (d, *J* = 0.5 Hz, 3H, *i*–Pr), 1.42 (d, *J* = 0.5 Hz, 3H, *i*–Pr), 1.38 (s, 3H, *i*–Pr), 1.38 (td, *J* = 7.1, 0.5 Hz, 3H, OCH_2CH_3), 1.36 (td, *J* = 7.1, 0.5 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ 114.5 (*i*–Pr), 109.1 (*i*–Pr), 105.3 (d, *J* = 6.0 Hz, C1), 85.0 (d, *J* = 12 Hz, C5), 81.0 (d, *J* = 6.8 Hz, C2), 79.0 (d, *J* = 168.6 Hz, C3), 75.8 (d, *J* = 4.6 Hz, C4), 66.3 (C6), 63.7 (d, *J* = 7.3 Hz, OCH_2CH_3), 63.6 (d, *J* = 6.9 Hz, OCH_2CH_3), 27.0 (2×*i*–Pr), 26.5 (*i*–Pr), 25.3 (*i*–Pr), 16.5 (d, *J* = 5.4 Hz, OCH_2CH_3), 16.3 (d, *J* = 6.1 Hz, OCH_2CH_3); ^{31}P NMR: δ 21.07 (s); GC–MS (Calcd for $C_{16}H_{29}O_9P$: 396 $[M]^+$) found *m*/*z* = 381 $[M–Me]^+$, R_t 16.86 min.

General procedure for the reaction of α-hydroxyphosphonates with (R) -α-methoxy-α-trifluoromethylphenylacetic chloride (MTPA-Cl) - determination of configuration of α-hydroxyl group with Mosher reagent.

To the solution of α-hydroxyphosphonate (1 eq.) in dry pyridine (2 mL), (*R*)-MTPA-Cl (1 eq.) was added and the reaction mixture was stirred for 6 hours at room temperature. Then, solvent was evaporated, the remaining mixture was partitioned (brine//DCM) and the separated inorganic layer was extracted (DCM), dried ($MgSO_4$) and evaporated to give a diastereoisomeric mixture of products as slightly yellow oil.

1.3.1. *(1R,2R) - and (1S,2R) -Diethyl 2,3-dihydroxy-2,3-O-isopropylidene-1-[(S) -2'-methoxy- 2'-(trifluoromethyl)phenylacetoxy]propy lphosphonate (S) -MTPA-**2** (R,R) and (S) - MTPA-**2** (S,R)*

Reaction of **2** (50 mg, 0.186 mmol) with (*R*)-MTPA-Cl (1.1 eq. 52 mg, 0.205 mmol) carried out according to a general procedure (*1.3*) gave a 91 mg of mixture of two diastereoisomers (1:0.52 ratio) indicating as major compound *(S) - MTPA-**2** (S,R)* [^{31}P NMR: δ 15.45 (s)]**,** while minor diastereoisomer *(S) - MTPA-**2** (R,R)* had ^{31}P NMR: δ 16.53 (s).

*Diethyl [1,2-O-isopropylidene-5-O-[-[(S)-2' -methoxy-2'-(trifluoromethyl) phenylacetoxy]3-O-methyl-α-L-ido-pentofuranose] 5-C-phosphonate (S) -MTPA-**6** (5S)*

*and diethyl [1,2-O-isopropylidene-5-O-[-[(S)-2'-methoxy-2'-(trifluoromethyl) phenylacetoxy] -3-O-methyl-α-D-gluco-pentofuranose] 5-C-phosphonate (S)- MTPA-**7** (5R)*

Reaction of **6**/**7** (32 mg, 0.093 mmol) with (*R*)-MTPA-Cl (61 mg, 0.242 mmol, 2.6 eq) carried out according to a general procedure (*1.3*) gave a 55 mg of mixture of two compounds (1:0.52 ratio) indicating as major compound (*S*) - MTPA-**6** (*5S*) [^{31}P NMR: δ 16.29 (s)]**,** while minor diastereoisomer (*S*) - MTPA-**7** (*5R*) had ^{31}P NMR: δ 17.10 (s).

General procedure for the DAST- mediated transformation of α-hydroxyphosphonates

To a mixture of DAST (1.5 eq. or 4 eq.) in dry DCM (6 mL) at -78 ^{o}C, a solution of alcohol (1 eq.) in DCM (2 mL) was added dropwise. The mixture was stirred at -78 °C for 2 h, and then an additional 2 h at room temperature. Then, the reaction mixture was poured into small portions of saturated $NaHCO_{3\ (aq)}$. solution containing ice chips and extracted with DCM. The combined organic layers were washed with small portions of H_2O, dried (Na_2SO_4), filtered and evaporated

under reduced pressure. The product was purified on a silica gel (EtOAc or EtOAc→ EtOAc/SSE, 1:1, v:v or $CHCl_3$→ $CHCl_3$/MeOH 85:15, v:v) to give products.

*Diethyl ((2R,3R)-3-(hydroxymethyl)oxiran-2-yl)phosphonate **3***

Reaction of **2** (241 mg, 0.9 mmol) with DAST (179 µL, 172 mg, 1.34 mmol, 1.5 eq) in dry DCM (6 mL) carried out according to the general procedure gave compound **3** with a yield of 60% (113 mg) and **2** (2*R*,3*R*; 66mg). Compound **3** had ^{1}H NMR (300 MHz): δ 4.23-4.13 (m, 4H, OC*H*$_2$CH$_3$), 3.99 (br d, *J* = 13 Hz, 1H, C*H*HOH), 3.74 (dd, *J* = 13.0, 3.4 Hz, 1H, CH*H*OH), 3.46 (ddt, *J* = 5.1, 3.4, 2.5 Hz, 1H, C*H*O$_{ox}$), 3.14 (dd, *J* = 30.5, 2.6 Hz, 1H, C*H*P), 1.36 (td, *J* = 7.1, 0.5 Hz, 3H, OCH$_2$C*H*$_3$), 1.35 (td, *J* = 7.1, 0.5 Hz, 3H, OCH$_2$C*H*$_3$);^{13}C NMR: δ 63.2 (d, *J* = 6.5 Hz, O*C*H$_2$CH$_3$), 62.9 (d, *J* = 6.5 Hz, O*C*H$_2$CH$_3$), 60.2 (CH$_2$OH), 56.6 (*C*HO$_{ox}$), 47.0 (d, *J* = 203.1 Hz, *C*HP), 16.4 (2d, *J* = 5.7 Hz,2×OCH$_2$*C*H$_3$); ^{31}P NMR(121 MHz): δ 18.88 (s); GC–MS (Calcd for $C_7H_{15}O_5P$: 210[M]$^+$) found *m*/*z* = 211 [M+H]$^+$, R_t 12.98 min.

*2.1.2. Diethyl (2-oxopropyl)phosphonate **4***

Reaction of **3** (106 mg, 0.39 mmol) with DAST (79 µL, 96 mg, 0.59 mmol, 1.5 eq) in dry DCM (6 mL) carried out according to a general procedure (*2.1*) at -84 °C, 2h, next RT 2h, gave compound **4** with a yield 51% (50 mg). Compound **4** had ^{1}H NMR(600 MHz) δ: 4.18-4.08 (m, 4H, OC*H*$_2$CH$_3$), 3.11 (dq, *J* = 22.6, 0.5 Hz, 2H, C*H*$_2$P), 2.33 (t, *J* = 0.5 Hz, 3H, C*H*$_3$), 1.35 (t, *J* = 7.5 Hz, 3H, OCH$_2$C*H*$_3$), 1.34 (t, *J* = 7.5 Hz, 3H, OCH$_2$C*H*$_3$);^{13}C NMR: δ 199.9 (d, *J* = 6.1 Hz, *C*O), 62.7 (d, *J* = 6.4 Hz, 2×O*C*H$_2$CH$_3$), 43.2 (d, *J* = 126.9Hz, *C*H$_2$P), 31.4 (*C*H$_3$),16.3 (d, *J* = 6.2 Hz, 2×OCH$_2$*C*H$_3$); ^{31}P NMR(243 MHz): δ 20.3 (s); GC–MS (Calcd for $C_7H_{15}O_4P$: 194 [M]$^+$) found *m*/*z* 195 [M+H]$^+$, R_t 10.7 min.

Diethyl [5-deoxy-5-fluoro-1,2-O-isopropylidene-3-O-methyl-α-D-gluco-pentofuranose] 5-C-phosphonate ***8*** *and diethyl [5-deoxy-5-fluoro-1,2-O-isopropylidene-3-O-methyl-α-L-ido-pentofuranose] 5-C-phosphonate* ***9***

Reaction of **6/7** (71 mg, 0.21 mmol) with DAST (111 µL, 135 mg, 0.84 mmol, 4 eq.) in dry dry DCM (6 mL) carried out according to the general procedure was stirred at -78 °C for 2 h, and then at 45 °C for 2.5 h, followed by extraction and column chromatography ($CHCl_3$→ $CHCl_3$/MeOH 85:15, v:v) to form compound **8/9** (ratio 1:0.1 in crude reaction mixture) with a yield 26% (18 mg) and ratio 1: 0.03, respectively. Compound **8** had ^{1}H NMR (600 MHz) δ 5.95 (dd, *J* = 3.7, 2.1 Hz, 1H, H1), 4.96 (ddd, *J* = 44.4, 9.5, 0.8 Hz, 1H, H5), 4.60 (dd, *J* = 3.7, 2.1 Hz, 1H, H2), 4.51 (dddd, *J* = 9.4, 8.2, 5.4, 3.1 Hz, 1H, H4), 4.29 – 4.24 (m, 4H, OC*H*$_2$CH$_3$), 3.88 (d, *J* = 3.1 Hz, 1H, H3), 3.47 (s, 3H, OC*H*$_3$), 1.52 (s, 3H, *i*–Pr), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.36 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.35 (s, 3H, *i*–Pr); ^{13}C NMR (151 MHz) δ 112.2 (*i*–Pr), 105.6 (C1), 84.2 (dd, J_{CF} = 177.3, J_{CP} = 169.8 Hz, C5), 83.4 (d, J_{CP} = 9.6 Hz, C3), 81.3 (C2), 77.0 (d, J_{CF} = 29.2 Hz, C4), 63.3 (d, *J* = 6.5 Hz, 2×O*C*H$_2$CH$_3$), 58.3 (O*C*H$_3$), 26.9 (*i*–Pr), 26.3 (*i*–Pr), 16. 5 (d, *J* = 5.9 Hz, OCH$_2$*C*H$_3$), 16.4 (d, *J* = 5.9 Hz, OCH$_2$*C*H$_3$); ^{31}P NMR (243 MHz) δ: 16.72 (d, *J* = 70.2 Hz); ^{19}F NMR (565 MHz) δ: –216.03 (ddd, *J* = 70.1, 44.2, 5.3 Hz).

Diagnostic signals for compound **9**: ^{31}P NMR (243 MHz) δ:14.62 (d, *J* = 69.0 Hz); ^{19}F NMR(565 MHz) δ: –215.80 (dddd, *J* = 69.2, 47.3, 14.5, 3.0 Hz). GC–MS (Calcd for $C_{13}H_{24}FO_7P$: 342 $[M]^+$) found *m*/*z* = 343 $[M+H]^+$, R_t 15.68 min.

Conclusions

In summary, we have prepared the convenient *α*-hydroxyphosphonate derivatives **2, 6/7, 11/12** of *O*-isopropylidene glyceraldehyde **1**, pentofuranose **5** and hexofuranose **10**. The stereoselective

introductions of phosphonate moiety have been accomplished by Pudovik reactions. The determination of resulted configurations have been achieved based on NMR spectroscopy supported by the reactions of *α*-hydroxyphosphonates with Mosher reagent. Next, the nucleophilic fluorinations with DAST have been performed. The ability of DAST to react distinctly depended on the regio-and stereochemical properties of the substrates. Thus, DAST -mediated reaction of *O*-isopropylidene glycerol phosphonate **2** gave unexpected oxirane containing fosfomycin analogue **3**. Subsequent reaction of **3** with DAST has yielded *β*-ketophosphonate **4**. Stereoselective deoxyfluorination of hydroxyphosphonates derived from an *O*-isopropylidenepentofuranose **6/7** led to *α*-fluorophosphonate **8** with D-gluco configuration contaminated by the traces of L-ido fluoride **9**. Attempted fluorination of di-*O*-isopropylidene hexofuranose hydroxyphosphonates **11/12** with DAST has failed, most probably due to sterical hindrance of applied carbohydrate system or electron-withdrawing properties of phosphonate moiety.

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References

[1] Engel, R. *Chem. Rev.* **1977**, 77, 349–367.

[2] a) Dayde, B.; Pierra, C.; Gosselin, G.; Surleraux D.; Ilagouma A. T.; Laborde C.; Volle J.-N.; Virieux, D.; Pirat, J.-L. *Eur. J. Org. Chem.* **2014**, 6, 1333–1337; b) Hernández-Guerra D.; Rodríguez M. S.; Suárez E. *Org. Lett.* **2013**, 15, 250–253; c) Ferry, A.; Guinchard, X.; Retailleau, P.; Crich, D. *J. Am. Chem. Soc*. **2012**, 134, 12289–12301; d) Bosco, M.; Bisseret, P.; Eustache J.; *Tetrahedron Lett.* **2003**, 44, 2347–2350; e) Harvey, T. C.; Simiand, C.; Weiler, L.; Withers, S. G. *J. Org, Chem*. **1997**, 62,6722–6725; f) Wróblewski, A. E. *Tetrahedron* **1986**, 42, 3595–3606;g) Wróblewski, A. E. *Z. Naturforsch*. *B* **1986**, 41, 791–792; h) Wróblewski, A. E. *Carbohydr. Res*. **1984**, 125, C1–C4; i) Thiem, J.; Guenter, M. *Phosphorus Sulfur* **1984**, 20, 67–79; j) Thiem, J.; Guenter, M.; Paulsen, H.; Kopf, *J. Chem. Ber*. **1977**, 110, 3190–3200.

[3] a) Meurillon, M., Marton, Z., Hospital, A., Jordheim, L. P.; Béjaud J.; Lionne, C.; Dumontet, C.; Perigaud, C.; Chaloin, L., Peyrottes, S. *Eur. J. Med. Chem*. **2014**, 77, 18–37; b) Košiová, I.; Šimák, O.; Panova, N.; Buděšínský, M.; Petrová, M.; Rejman, D.; Liboska, R.; Páv, O.; Rosenberg, I. *Eur. J. Med. Chem*. **2014** , 74, 145–168; c) Gabrielli, L., Airoldi, C., Sperandeo, P.; Gianera, S.; Polissi, A.; Nicotra, F.; Cipolla, L. *Eur. J. Org. Chem*. **2013**, 34, 7776–7784; d) Choi, S.-H.; Mansoorabadi, S. O.; Liu, Y.-N.; Chien, T.-C.; Liu, H.-W. *J. Am. Chem. Soc.* **2012**, 134, 13946–13949; e) Nasomjai, P.; O'Hagan, D.; Slawin, A. M. *Beilstein J. Org. Chem.* **2009**, 5, 37–44; f) Kolodiazhnyi, O. I.; Guliaiko, I. V. *J. Gen. Chem.* **2004**,74, 1746–1747; g) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498–4508; h) Kovensky, J.; McNeil, M.; Sinay, P. *J. Org. Chem*. **1999**, 64, 6202–6205; i) Serra, C.;

Dewynter, G.; Montero, J.-L.; Imbach, J.-L. *Tetrahedron* **1994**, 50 ,28, 8427–8444; j) Wroblewski, A. E. *Liebigs Ann. Chem*. **1986**, 11, 1854–1862; k) Evelyn, L.; Hall, L.D.; Steiner, P.R.; Stokes, D.H. *J. Chem. Soc., Chem Commun.***1969**, 576–577.

[4] a) Xu, Y.; Aoki, J.; Shimizu, K.; Umezu-Goto, M.; Hama, K.; Takanezawa, Y.; Yu, S.; Mills, G. B.; Arai, H.; Qian, L.; Prestwich, G.D. *J. Med. Chem.* **2005**, 48, 3319–3327; b) Kolodyazhnaya, A. O.; Kukhar, V. P.; Chernega, A. N.; Kolodyazhnyi, O. I. *Tetrahedron Asymm*. **2004**, 15, 1961–1963; c)Kolodyazhnaya, A. O.; Kukhar, V. P.; Kolodyazhnyi, O. I.; *J. Gen. Chem.* **2004**,74, 2058-2059; d) Kolodyazhnaya, A. O.; Kukhar V. P.; Kolodyazhnyi, O. I. *J. Gen. Chem.* **2004**,74, 1045-1046; e) Xu, Y.; Qian, L.; Prestwich G.D. *J. Org. Chem.* **2003**, 68, 5320–5330; f) Wróblewski, A. E.; Balcerzak, K. B. *Tetrahedron* **1998**, 54, 6833–6840; g) Nieschalk, J.; Batsanov, A.S.; O'Hagan, D.; Howard, J. A. K. *Tetrahedron* **1996,** *52*, 165–176; h) Nieschalk, J.; O'Hagan, D.; *J. Chem. Soc., Chem. Comm*.**1995**, 719-720; i) Paulsen, H.; Kuhne, H. *Chem. Ber*.**1975**, 108, 1239–1245.

[5] a) Blackburn, G. M.; Kent D.E.; *J. Chem. Soc., Perkin Trans. 1*, **1986**, 913-917; b) Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1425–1430; c) Blackburn, G. M.; Rashid A.; *J. Chem. Soc., Chem. Comm. 1*, **1988**, 317–319.

[6] Chambers, R.D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, 45, 5101–5108.

[7] Forget, S. M.; Bhattasali, D.; Hart, V. C.; Cameron, T. S.; Syvitskiad, R. T.; Jakeman, D. L. *Chem. Sci*., **2012**, 3, 1866–1878.

[8] Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, 112, 13–33.

[9] Campbell, A. S.; Thatcher, G. R. J. *Tetrahedron Lett*. **1991,** 32, 2207–2210.

[10] a) Fauq, A.H. N,N-diethylaminosulfur trifluoride, in: L. Paquette (Ed.), *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, New York, 2004; b) Middleton W. J. *J. Org. Chem.* **1975**, 40, 574–578.

[11] Yokomatsu, T.; Yamagishi, T.; Matsumoro, K.; Shibuya, S. *Tetrahedron* **1996,** 52, 11725–11738.

[12] Blackburn, G.M.; Kent, D.E. *J. Chem. Soc. Chem. Comm*. **1981**, 511–513.

[13] Sanders, T.C., Hammond, G.B., *J. Org. Chem*. **1993,** 58, 5598–5599.

[14] Rapp, M., Bilska, M., Koroniak, H. *J. Fluorine Chem.* **2011,** 132, 1232–1240.

[15] Hammerschmidt, F.; Li, Y. F. *Tetrahedron*, **1994,** 50, 10253–10264.

[16] Hesse, M.; Meier, H.; Zeeh, B. *Spectroscopic methods in organic chemistry* Thieme, 1997, New York

[17] Wróblewski, A. E.; Bąk-Sypień, I. I., *Tetrahedron: Asymmetry*, **2007,** 18, 520–526.

[18] Kaźmierczak, M., Koroniak, H. *J. Fluorine Chem.***2012**, 139, 23–27

[19] Dawson, N.D.; Burger, A. *J. Am. Chem. Soc.*,**1952** , 74, 5312-5314.

[20] a) Kovensky, J.; Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Sizun, P.; Hérault, J.-P.; Herbert, J.-M.; Petitou, M.; Sinay, P. *Eur. J. Org. Chem*. **2002**, 3595–3603; b) Tronchet, J. M. J.; Baehler, B.; Eder, H.; Le-Hong, N.; Perret, F.; Poncet, J.; Zumwald, J.-B. *Helv. Chim. Acta* **1973**, 56, 1310–1318.

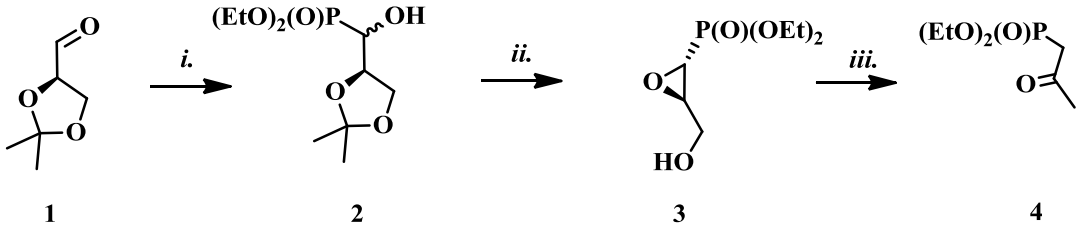
[21] a)Yanovskii, A. I.; Struchkov, Yu. T.; Uzlova, L. A.; Kist'yan, G. K.; Zhdanov, Yu. A. *J. Str. Chem.*,**1989**, 30, 134–140; b) Zhdanov, Yu. A.; Glebova, Z. I.; Kist'yan, G. K.; Polenov, V. A.; Uzlova, L. A. *J. Gen. Chem. USSR* (Engl. Transl.),**1984**, 54, 1660–1663,1478–1481.

[22] W.R, Dolbier Jr; *Guide to fluorine NMR for organic chemists.* Wiley Interscience, 2009

[23] Garegg P.J.; Samuelsson B. *Carbohydr. Res.* **1978,** 67, 267–270.

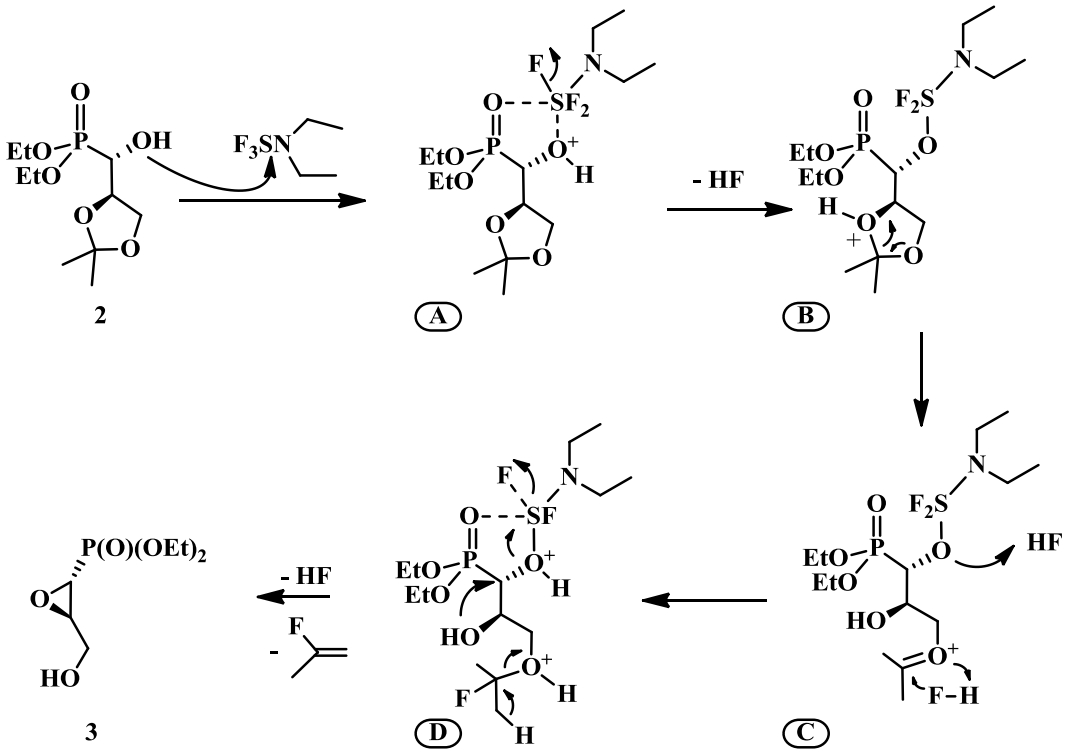
[24] Rapp, M.; Cai, X.; Xu, W.; Dolbier, Jr. W.R; Wnuk, S.F. *J. Fluorine Chem.* **2009**, 130, 321–328.

[25] Creary X.*Chem. Rev*. **1991**, 91, 1625–1678.

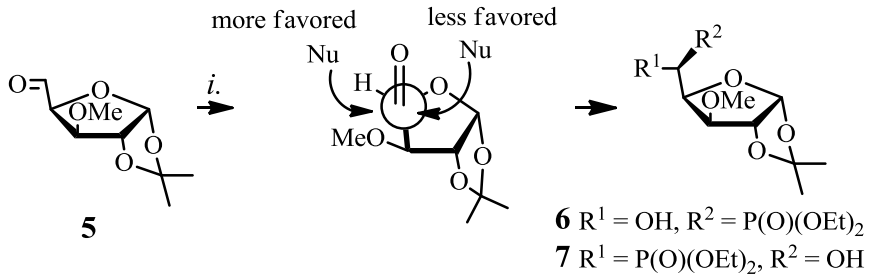


1 2 3 4

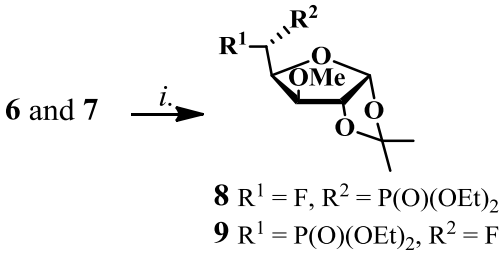
Scheme 1. *i.* $HP(O)(OEt)_2$, TEA, THF (1:0.52 *dr*, 71%) or $HP(O)(OEt)_2$, NaH, THF (1:0.62 *dr*, 23%); *ii.* DAST, -78 °C, 2h, next RT 2 h, work up (60%); *iii.* DAST, -84 °C, 2 h, next RT 2 h, work up (51%).



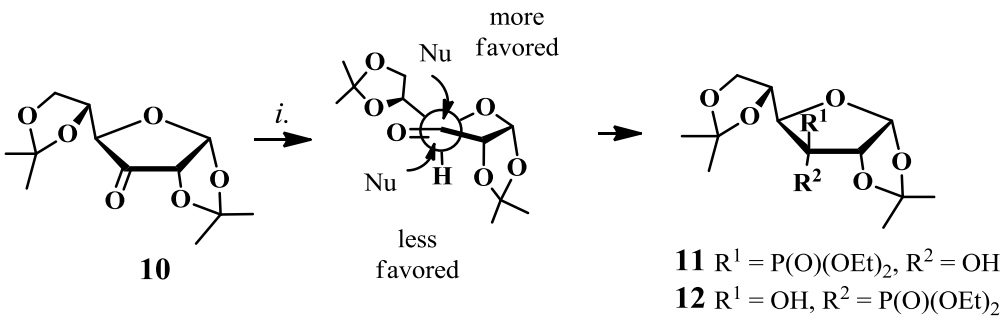
Scheme 2. The mechanism of DAST-mediated transformation of **2** yielding **3**.



Scheme 3. *i.* $HP(O)(OEt)_2$, TEA, 80 °C, 52 h (1:0.25 **6**/**7**, 63%)



Scheme 4. *i.* DAST, DCM, -78 °C, 0.5 h, next 45°C, 2.5 h, work up (1:0.03 **8**/**9**, 26%)



Scheme 5. *i.* $HP(O)(OEt)_2$, TEA, 45 °C, 19 h (1:0.35 *dr*, 92%)