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# Synthesis of 6-fluoro-D-olivose (2,6-dideoxy-6-fluoro-D-*arabino*-hexopyranose)

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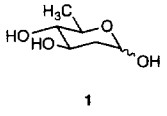
**Abstract**

An efficient synthesis of 6-fluoro-D-olivose **5** (2,6-dideoxy-6-fluoro-D-*arabino*-hexopyranose) starting from D-glucose is reported. Key features of the synthesis involve the early introduction of the fluorine atom at C-6 and the Fischer reductive elimination as a strategy to achieve C-2 deoxygenation. The route, the first to this compound, is efficient providing gramme quantities of **5** for biotransformation studies.


*Keywords:* 6-Fluoro-D-olivose; Fluoro-deoxysugar; Fluorinated antibiotics

## 1. Introduction

6-Deoxysugars such as D-olivose **1** and L-rhodinose **2**, are a ubiquitous moiety in antitumor antibiotics produced by *Streptomyces* bacteria [1,2], and several of these compounds, such as mithramycin **3** [3], are of clinical significance. The elucidation of the biosynthetic pathway to these 6-deoxysugar moieties, both at the biochemical [4,5] and molecular biological level [6], is a current research focus in many laboratories [1,2].



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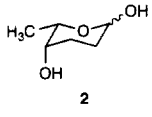

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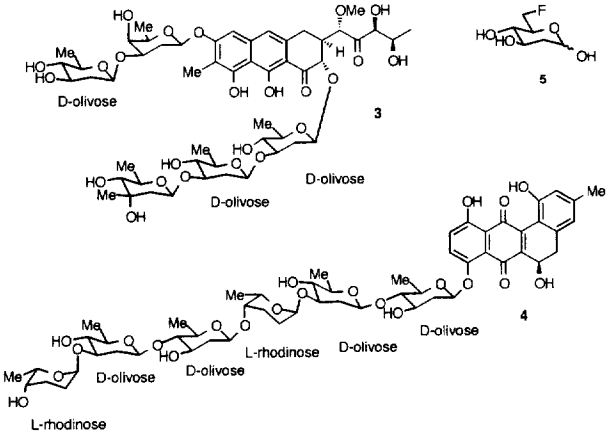
It was recently demonstrated [7] that deuterium labelled L-rhodinose **2** could become incorporated into the oligosaccharide moiety of landomycin A **4** in *S. cyanogenis*, albeit at a low level. This observation contradicted the conventional view that such 6-deoxysugars must derive from nucleoside coupled glucose (e.g., UDP–glucose), *via* a series of obligate sugar–nucleoside intermediates prior to glycosylation. The result suggests a recycling pathway for reactivating any hydrolysed UDP-6-deoxysugars for antibiotic biosynthesis. The operation of such a pathway offers an opportunity to prepare novel antibiotic analogues by the addition of appropriately modified 6-deoxysugars to the producing *Streptomyces* culture. With a view to a semisynthetic approach towards novel fluorinated antitumor antibiotics we have developed a synthesis of 6-fluoro-D-olivose **5**.




This substitution involves the direct replacement of fluorine for a C-6 hydrogen in D-olivose **1**. In general the substitution of a single hydrogen by fluorine does not induce a significant steric perturbation [8,9] and although the electronic influences can be dramatic it is anticipated that the

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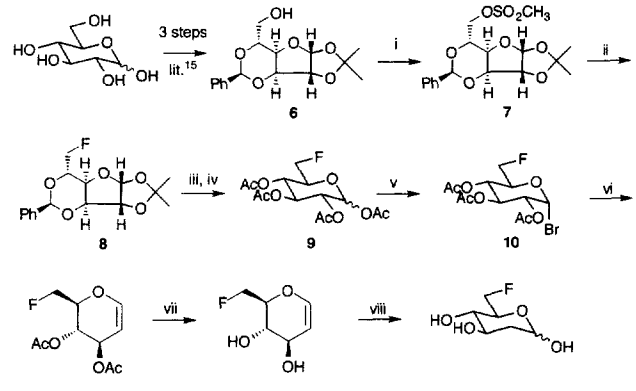
influence of the fluorine atom on glycosidation events operating along the pathway should be kept to a minimum with fluorine at this position. The replacement of a hydrogen rather than an hydroxyl by fluorine is favoured by us as key hydrogen bonding interactions are not removed. In general fluorodeoxysugar analogues are poor substitutes for their parent sugars in biological systems [10,11].

We envisioned that 6-fluoro-D-olivose **5** should be obtainable by following the classic route to 2-deoxysugars *via* glycals [12,13] (enol ethers) and hydration of the resulting enol ether under acidic conditions [14]. Fluorine could be introduced by nucleophilic displacement of a C-6 hydroxyl. Although *N,N*-dimethyamino sulphur trifluoride (DAST) [15] and hydrogen fluoride/triethylamine [16] have been successfully employed in the fluorination of carbohydrates, a two step approach was chosen where a C-6 mesylate was displaced by fluoride ion. This approach is much more favourable for large scale preparations. D-Glucose has the correct absolute configuration to act as a template for the synthesis of **5** and emerged as an attractive starting material as shown in Scheme 1. Fluorination of 3,4-di-*O*-acetyl-D-glucal *via* its C-6 tosylate provides the desired 3,4-di-*O*-acetyl-6-fluoro-D-rhamnal **11** in very low yield [17] due to formation of an 5,6- unsaturated product, thus to avoid these difficulties the fluorine atom was introduced at an earlier stage of the synthesis. A known protocol for the preparation of 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl bromide **10** [18] was followed which introduces fluorine by reaction of 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-methylsulfonyloxy-α-D-glucofuranose **7** with potassium fluoride (Scheme 1). Mesylate **7** is readily obtained in four steps from D-glucose [19–22] however, the reported methods involve heating in ethylene glycol to 200°C [23] or pressurised reaction conditions [18]. A modified method (140°C in diethylene glycol) employing milder conditions gave an excellent yield. Deprotection and acetylation was achieved by acidic hydrolysis in aqueous methanol. This gave 6-deoxy-6-fluoro-D-glucose, which was treated directly with acetic anhydride in pyridine to afford a mixture of α-, and β-anomers of the triacetate of 6-deoxy-6-fluoro-D-glucose **9** [18].

The synthesis now required a C-2 deoxygenation and the method of Fischer proved successful here. This involved treatment of triacetate **9** with hydrobromic acid in acetic acid to yield the α-glycosyl bromide **10** [18]. Reductive elimination with zinc–copper couple in aqueous acetate/acetic acid solution cleanly gave the required 3,4-di-*O*-acetyl-6-fluoro-D-rhamnal **11** as a colourless oil and in good yield. Generally, acetate hydrolysis is carried out before hydration of the enol ether moiety of acetylated glycals. Accordingly the acetates were removed by transesterification of **11** with methanol in the presence of a catalytic amount of sodium methoxide. The resultant 6-fluoro-D-rhamnal **12** was efficiently recovered and was converted to the target 2,6-deoxysugar **5** by treatment with dilute sulphuric acid. 6-Fluoro-D-olivose **5** was recrystallised from ethyl acetate and gave an




Scheme 1. (i) MsCl, pyridine, 0°C, 5 h, 65%; (ii) KF, diethylene glycol, 140°C, 30 min, 87%; (iii) 50% MeOH, $H_2SO_4$, reflux, 1 h; (iv) $Ac_2O$, pyridine, 100°C 1 h, 85%; (v) 30% HBr/HOAc, r.t., 2 h, 95%; (vi) Zn/Cu, 50% HOAc, NaOAc, −10°C to 0°C, 2.5 h, 95%; (vii) MeOH, NaOMe, r.t., 2 h, 76%; (viii) 4% $H_2SO_4$, 4°C, 16 h, 87%.

analytically pure product, which was a 1.2:1 mixture of α- and β-anomers. The $^{13}$C-NMR shown in Fig. 1 illustrates clearly the presence of both anomers as well as the $^{13}$C–$^{19}$F-NMR couplings between the fluorine and the sugar carbons atoms. This synthetic route has allowed us to prepare 750 mg of **5** for biotransformation studies.

## 2. Experimental

IR spectra were recorded on a Perkin–Elmer 257 Spectrometer. NMR spectra were obtained on a Bruker AC-250 or a Varian XL200 instrument in $CDCl_3$ or $D_2O$. Chemical shifts are quoted relative to TMS for $^1$H- and $^{13}$C-NMR spectra and $^{19}$F-NMR chemical shifts are quoted as negative relative to fluorotrichloromethane. Solvents were dried and distilled prior to use. Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. Column chromatography was carried on silica gel (Merck, Kieselgel 60, 230–400 mesh).

### *2.1. 3,5-O-Benzylidene-1,2-O-isopropylidene-6-methylsulfonyloxy-α-D-glucofuranose 7 [22]*

3,5-*O*-Benzylidene-1,2-*O*-isopropylidene-α-D-glucopyranose **6** [19–21] was dissolved in pyridine (30 ml), cooled to 0°C and methanesulfonyl chloride (6.7 g, 58.5 mmol) was added with stirring. After 5 h at the same temperature the mixture was poured into ethyl acetate/iced water, the organic layer separated, washed with dilute HCl until acidic and saturated aqueous sodium hydrogen carbonate and then dried over $MgSO_4$. Evaporation under reduced pressure gave the crude product which was recrystallised from ethanol to give **7** as colourless crystals (14.3 g, 65%).

$^1$H-NMR ($CDCl_3$): 1.36 (s, 3H, $(CH_3)_2C$), 1.52 (s, 3H, $(CH_3)_2C$), 3.04 (s, 3H, $CH_3SO_2O$), 4.13 (br, 1H, H-4), 4.46 (d, $J$=2.2 Hz, 1H, H-3), 4.52 (dd, $J$=3.7 Hz, $J$=10.1

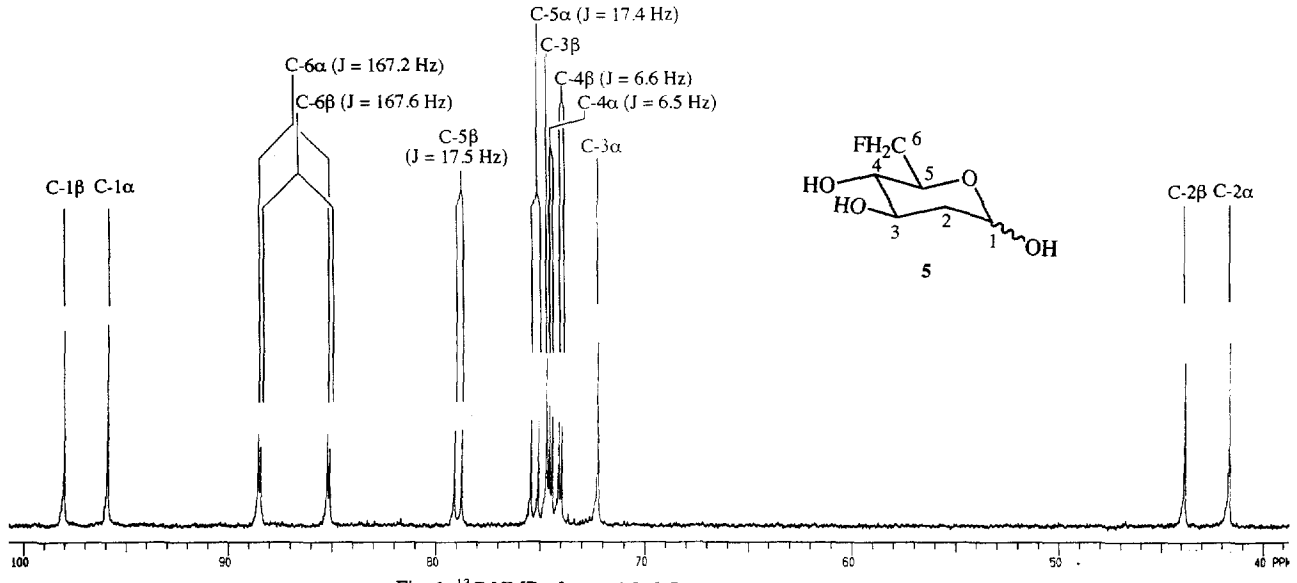



Fig. 1. $^{13}$C-NMR of α- and β-6-fluoro-D-olivose **5** ($J = J_{C,F}$).

Hz, 1H, H-6a), 4.45–4.53 (m, 1H, H-5), 4.67 (d, $J$ = 3.7 Hz, 1H, H-2), 4.68 (dd, $J$ = 6.2 Hz, $J$ = 10.1 Hz, 1H, H-6b), 5.81 (s, 1H, PhC*H*), 6.04 (d, $J$ = 3.7 Hz, 1H, H-1), 7.36–7.38 (m, 3H, Ph), 7.46–7.48 (m, 3H, Ph). $^{13}$C-NMR ($CDCl_3$): 26.1, 26.7 ($CH_3$), 37.9 ($CH_3SO_2O$), 67.8 (C-3), 71.5 (C-5), 72.1 (C-6), 77.8 (C-2), 83.7 (C-4), 94.7 ($Me_2C$), 104.9 (CHPh), 112.1 (C-1), 126.1 (C3′, C-5′), 128.3 (C-2′, C-6′), 129.3 (C-4′), 137.0 (C-1′). IR (KBr): 3068, 3028, 2984, 2937, 2908, 1457, 1357 (S=O), 1176 (S=O), 1090, 1018, 760, 697. M.p. = 136–138°C, lit. [22]: 132–133°C. $[\alpha]_D^{25} = +14.3$ ($c$ = 2.5, pyridine), lit. [22]: +12.8 (pyridine). Anal. calcd. for $C_{17}H_{22}O_8S$: C, 52.84; H, 5.74; S, 8.30. Found: C, 52.63; H, 5.66; S, 8.43%.

### 2.2. 3,5-O-Benzylidene-6-deoxy-6-fluoro-1,2-O-isopropylidene-α-D-glucofuranose 8

Mesylate **7** (10.8 g, 27.95 mmol) was dissolved in dry diethylene glycol and dry KF (10.5 g, 180.7 mmol) added. The mixture was then heated with stirring to 140°C and left at this temperature for 30 min. After cooling to room temperature the reaction mixture was diluted with plenty of water, extracted into diethyl ether and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue recrystallised from 2-propanol. Additional material was recovered after purification of the mother liquors by column chromatography (ethyl acetate/petrol ether 1:4) to afford **8** (7.51g, 87%) as a white crystalline solid.

$^1$H-NMR ($CDCl_3$): 1.35 (s, 3H, $(CH_3)_2C$), 1.55 (s, 3H, $(CH_3)_2C$), 4.29 (br, 1H, H-4), 4.40 (dm, $J$ = 38.6 Hz, 1H, H-5), 4.52 (br, 1H, H-3), 4.68 (d, $J$ = 3.3 Hz, 1H, H-2), 4.73–5.05 (m, 2H, H-6a,b), 5.91 (d, $J$ = 1.8 Hz, 1H, C*H*Ph), 6.05 (d, $J$ = 3.6 Hz, 1H, H-1), 7.36–7.39 (m, 3H, Ph), 7.47–7.49 (m, 2H, Ph). $^{13}$C-NMR ($CDCl_3$); 20.9, 21.5 ($CH_3$), 67.4 (C-3), 67.5 (d, $J$ = 17.4 Hz, C-5), 73.2 (C-2), 78.8 (C-4), 81.0 (d, $J$ = 172.9 Hz, C-6), 90.7 ($Me_2C$), 99.7 (*C*HPh), 106.7 (C-1), 120.9 (C-3′, C-5′), 123.1 (C-2′, C-6′), 124.0 (C-4′), 132.5 (C-1′). $^{19}$F-NMR ($CDCl_3$): −224.6 (dt, $J$ = 38.6 Hz, $J$ = 47.4 Hz). IR (KBr): 3094, 3068, 3040, 2994, 2939, 2915, 2862, 1453, 1380, 1216, 1136, 1086, 1018, 760, 705. M.p. = 103–105°C, lit. [23]: 104–105°C. $[\alpha]_D^{25} = +33.2$ ($c$ = 1, MeOH), lit. [23]: +32.4 ($c$ = 1.9, MeOH). Anal. calcd. for $C_{16}H_{19}FO_5$: C, 61.93; H, 6.17. Found: C, 61.82; H, 6.12%.

### 2.3. 2,3,4-Tri-O-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl bromide 10

1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-fluoro-D-glucopyranose **9** (3.03 g, 8.6 mmol), obtained [18] from 3,5-*O*-Benzylidene-6-deoxy-6-fluoro-1,2-isopropylidene-α-D-glucopyranose **8** in 85% yield, was dissolved in 30% HBr solution in acetic acid (8 ml) at room temperature. After stirring for 1 h dichloromethane (10 ml) was added and the mixture stirred for a further 1 h. The solvents were removed under reduced pressure, the residue redissolved in dichloromethane and again removed under reduced pressure in order to remove remaining HBr. Iced water was added, the aqueous phase extracted into dichloromethane and the organic layer separated and then washed twice with iced water. After drying with $MgSO_4$ the solvent was removed under reduced pressure, the residue taken up in a small amount of dichloromethane and diluted with petroleum ether to give colourless crystals of glycosyl bromide **10** (3.05 g, 95%).

$^1$H-NMR ($CDCl_3$): 2.03 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 4.26 (ddt, $J$ = 2.7 Hz, $J$ = 10.4 Hz, $J$ = 24.9 Hz, 1H, H-5), 4.47 (ddd, $J$ = 3.3 Hz, $J$ = 10.8 Hz, $J$ = 46.8 Hz, 1H, H-6a), 4.53 (ddd, $J$ = 2.4 Hz, $J$ = 10.8 Hz, $J$ = 46.8 Hz, 1H, H-6b), 4.82 (dd, $J$ = 4.0 Hz, $J$ = 9.7 Hz, 1H, H-2), 5.19 (t, $J$ = 10.2 Hz, 1H, H-4), 5.56 (t, $J$ = 9.7 Hz, 1H, H-3), 6.62 (d, $J$ = 4.0 Hz, 1H, H-1). $^{13}$C-NMR ($CDCl_3$): 20.5 ($CH_3$), 20.6 ($CH_3$), 66.7, 70.1, 70.5 (C-2, C-3, C-4),

72.6 (d, $J$=18.8 Hz, C-5), 80.1 (d, $J$=176.0 Hz, C-6), 86.5 (C-1), 169.2 (C=O), 169.7 (C=O), 169.9 (C=O). $^{19}$F-NMR ($CDCl_3$): −234.1 (dt, $J$=24.9 Hz, $J$=46.8 Hz). IR (KBr): 2997, 2962, 2906 (CH), 1752 (C=O), 1422, 1385, 1259, 1222, 1040, 915, 610. M.p. 128–129°C, lit. [18]: 127–128 C°. $[\alpha]_D^{25}$ = +246 ($c$=2.5, $CHCl_3$), lit. [18]: +234 ($CHCl_3$). Anal. calcd. for $C_{12}H_{16}BrFO_7$: C, 38.83; H, 4.35. Found: C, 39.07; H, 4.39%.

### 2.4. 1,2-Dehydro-3,4-di-O-acetyl-2,6-dideoxy-6-fluoro-D-arabino-hexopyranose 11

A solution of sodium acetate trihydrate (5.9 g, 43.4 mmol) in water (8.6 ml) and acetic acid (5.9 ml) was cooled to −10°C by means of an ice–salt mixture. A solution of copper (II) sulphate pentahydrate (325 mg, 1.3 mmol) in water (1.2 ml) was added to produce a dark blue colour. Zinc powder (3.25 g, 49.7 mmol) was then added with vigorous stirring in one portion, which caused disappearance of the colour. Glycosyl bromide **10** (3.05 g, 8.22 mmol) was added over a period of 30 min and the mixture stirred for another 30 min during which the temperature was allowed to rise to −5°C. Stirring was continued at 0°C for 1.5 h, inorganic material filtered off, the residue washed with 50% aqueous acetic acid and the filtrate diluted with ice cold water. The aqueous solution was then extracted five times into dichloromethane, the organic extracts washed with iced water, $Na_2CO_3$ solution, iced water and dried over $MgSO_4$. Care was taken that the temperature remained at about 0°C during work up. After removal of the solvent under reduced pressure di-*O*-acetyl glycal **11** remained as a colourless oil (1.81 g, 95%), which was essentially pure but a small fraction was purified further by column chromatography (ethyl acetate/petroleum ether 1:3) for analysis.

$^1$H-NMR ($CDCl_3$): 2.05 (s, 3H, $CH_3$), 2.10 (s, 3H, $CH_3$), 4.31 (ddt, $J$=3.2 Hz, $J$=6.5 Hz, $J$=20.4 Hz, 1H, H-5), 4.54 (ddd, $J$=3.2 Hz, $J$=10.3 Hz, $J$=46.6 Hz, 1H, H-6a), 4.61 (ddd, $J$=5.8 Hz, $J$=10.3 Hz, $J$=47.5 Hz, 1H, H-6b), 4.86 (dd, $J$=3.5 Hz, $J$=6.1 Hz, 1H, H-2), 5.20 (dd, $J$=5.7 Hz, $J$=6.9 Hz, 1H, H-4), 5.32 (m, 1H, H-3), 6.49 (d, $J$=6.1 Hz, 1H, H-1). $^{13}$C-NMR ($CDCl_3$): 20.7 ($CH_3$), 20.9 ($CH_3$), 66.6, 66.7 (C-3, C-4), 74.4 (d, $J$=20.1 Hz, C-5), 80.5 (d, $J$=172.5 Hz, C-6), 98.7 (C-2), 145.5 (C-1), 169.4 (C=O), 170.2 (C=O). $^{19}$F-NMR ($CDCl_3$): −230.5 (dt, $J$=20.9 Hz, $J$=46.8 Hz). IR (film): 2963, 1741 (C=O), 1649 (C=C), 1373, 1223 (C–O), 1046, 1019. $[\alpha]_D^{25}$ = −70.2 ($c$=3.2, $CHCl_3$), Lit. [17]: ($c$=−71.1, $c$=1, $CHCl_3$). Anal. calcd. for $C_{10}H_{13}FO_5$: C, 51.73; H, 5.64. Found: C, 51.74; H, 5.72%.

### 2.5. 1,2-Dehydro-2,6-dideoxy-6-fluoro-D-arabino-hexopyranose 12

Sodium (16 mg) was added to dry methanol (26 ml) under an atmosphere of nitrogen and di-*O*-acetyl glycal **11** (1.71 g, 7.36 mmol) was then added to the solution. After stirring for 2 h carbon dioxide was flushed through the reaction flask with vigorous stirring until neutral pH was reached. Methanol was distilled off under reduced pressure and the remaining oil crystallised upon standing. Recrystallisation from toluene afforded colourless crystals of **12** (833 mg, 76%).

$^1$H-NMR ($D_2O$): 3.59 (dd, $J$=7.3 Hz, $J$=9.5 Hz, 1H, H-4), 3.91 (dddd, $J$=1.9 Hz, $J$=4.0 Hz, $J$=9.5 Hz, $J$=27.5 Hz, 1H, H-5), 4.11 (d, br, $J$=7.0 Hz, 1H, H-3), 4.57 (partly omitted, ddd, $J$=1.9 Hz, $J$=10.9 Hz, $J$=46.9 Hz, 1H, H-6a), 4.65 (ddd, $J$=4.0 Hz, $J$=10.9 Hz, $J$=46.9 Hz, 1H, H-6b), 4.68 (dd, $J$=2.8 Hz, $J$=5.9 Hz, 1H, H-2), 6.26 (d, $J$=5.9 Hz, 1H, H-1). $^{13}$C-NMR ($CDCl_3$): 68.8, 70.1 (C-3, C-4), 76.7 (d, $J$=17.9 Hz, C-5), 81.6 (d, $J$=172 Hz), 102.8 (C-2), 144.4 (C-1). $^{19}$F-NMR ($D_2O$): −235.1 (dt, $J$=27.5 Hz, $J$=47.3 Hz). IR (film): 3361 (OH), 3013 (CH), 2979, 2931, 2905 (CH), 1651 (C=C), 1413, 1237, 1069, (C–O), 866, 654. M.p. = 56–58°C. $[\alpha]_D^{25}$ = −17.3 ($c$=2.5, $CHCl_3$). Anal. calcd. for $C_6H_9FO_3$: C,48.65; H, 6.12. Found: C, 48.51; H, 6.12%.

### 2.6. 2,6-Dideoxy-6-fluoro-D-arabino-hexopyranose 5

6-Fluoro-D-rhamnal **12** (767 mg, 5.18 mmol) was dissolved in ice cold 5% $H_2SO_4$ (6 ml) and left 16 h at 4°C. To the cold solution was added $BaCO_3$ and stirred at 0°C until slightly alkaline. After dilution with ice cold methanol the slurry was filtered and the filtrate concentrated under reduced pressure. In order to remove water the residue was twice dissolved in ethanol and evaporated under reduced pressure. The crude material was then dissolved in warm ethyl acetate, filtered and crystallisation was induced by seeding. The crystals were filtered off and washed with diethyl ether and dichloromethane to give 6-fluoro-D-olivose **5** (748 mg, 87%) as a mixture of anomers.

$^1$H-NMR ($D_2O$): 1.33 (dt, $J$=10.1 Hz, $J$=12.0 Hz, 1H, H-2aβ), 1.52 (dt, $J$=3.5 Hz, $J$=12.6 Hz, 1H, H-2aα), 1.95 (dd, $J$=4.9 Hz, $J$=13.4 Hz, 1H, H-2eα), 2.08 (ddd, $J$=1.3 Hz, $J$=4.9 Hz, $J$=12.5 Hz, 1H, H-2eβ), 3.19 (t, $J$=10.1 Hz, 1H, H-4), 3.27 (t, $J$=9.5 Hz, 1H, H-4), 3.40 (dt, $J$=2.7 Hz, $J$=9.7 Hz, 1H, H-3β), 3.48–3.62 (m, 1H, H-3α), 3.62–3.85 (m, 1H, H-5), 4.32–4.59 (m, 2H, H-6), 4.78 (dd, $J$=1.1 Hz, $J$=9.6 Hz, 1H, H-1β), 5.20 (d, $J$=2.9 Hz, 1H, H-1α). $^{13}$C-NMR ($D_2O$): α-anomer: 41.6 (C-2), 72.2 (C-3), 74.4 (d, $J$=6.5 Hz, C-4)), 75.2 (d, $J$=17.4 Hz, C-5), 86.8 (d, $J$=167.2 Hz, C-6), 95.9 (C-1). β-anomer: 43.8 (C-2), 74.6 (C-3), 74.0 (d, $J$=6.6 Hz, C-4), 78.9 (d, $J$=17.5 Hz, C-5), 86.7 (d, $J$=167.6 Hz, C-6), 98.0 (C-1). $^{19}$F-NMR ($D_2O$): β-anomer: −235.16 (dt, $J$=26.8 Hz, $J$=47.3 Hz), α-anomer: −236.17 (dt, $J$=29.7 Hz, $J$=47.5 Hz). IR (KBr): 3383 (OH), 2924 (CH), 1636, 1429, 1265, 1115, 1067, 990. M.p. = 102–104°C. $[\alpha]_D^{25}$ = +34.7 ($c$=1.6, water). Anal. calcd. for $C_6H_{11}FO_4$: C, 43.37; H, 6.67. Found: C, 43.38; H, 6.65%.

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