D-*Gluco*-hept-2-ulose and Novel Deoxyfluoro Derivatives as Seven-Carbon Analogues of F-Deoxy-D-glucose (FDG)

Yevgeniy Leshch, Daniel Waschke, Julian Thimm, Joachim Thiem*

University of Hamburg, Faculty of Science, Department of Chemistry, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
Fax +49(40)428384325; E-mail: thiem@chemie.uni-hamburg.de

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Abstract: Ketoheptoses, seven-carbon sugars, were recognized to display pharmacological properties that are potentially suitable for in vivo diagnostic of diabetes and cancers using ^{19}F-MRI. The present paper describes efficient syntheses towards ketoheptoses and exemplary a series of regioisomeric fluoro derivatives of D-*gluco*-hept-2-ulose.

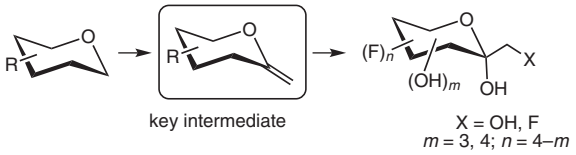
Key words: ketoheptose, fluoro D-glucoheptulose, Petasis reagent, Selectfluor, C1 chain elongation

Understanding the course of diseases is commonly approached by monitoring the progression of changes in the system. Most problematic hereby is the choice of an effective diagnostic marker. Therefore, in vivo diagnostic in humans remains a challenging task that has to be tailored for each disease and in future potentially for every patient.[1,2] A number of invasive (e.g., surgery, biopsy) and noninvasive techniques (PET, MRI, CT) are in clinical use to date. However, access to nontoxic smart markers showing high sensitivity as contrast agents and the ability to specifically target at molecular level are scarce.[3]

Since carbohydrates play an integral role in animals and plants, even slightest dysfunctions in the machinery responsible for sugar transport and metabolism are involved in a number of major diseases such as diabetes and cancer.[4] Others involve the presence or absence of carbohydrates moieties indicating tumor as well as pathogen activity.[5]

Hence it is no surprise that functionalized carbohydrates are used and are promising markers for quantitative and qualitative monitoring of modulated or distorted carbohydrate uptake and metabolism activity. With respect to carbohydrate based contrast agents, tracers like 2-^{18}F-deoxy-D-glucose as well as other ^{18}F-deoxy-D-glucoses are frequently used, and [^{18}F]fluoroazomycin-arabinofuranoside (FAZA) is fairly new in positron emission tomography (PET) scanning.[6] Due to undesired toxicity and short half-life, a shift from ^{18}F-PET to NMR based ^{19}F-MRI or combination techniques are currently under evaluation.[7] Since glucose is ubiquitously present FDG (F-deoxy-D-glucose) application is based on the rationale that, for example, in some cancer types, tumorous cells show a spatially centered relatively higher glucose metabolism in a fasting patient. However, there are a number of false positives due to infection and inflammation or undetected and early stage tumors – not showing a significant higher metabolic rate.[8] Realization of current limitations of contrast agents leads to the search for 'smarter' highly specific, nontoxic MRI contrast agents.

Rare naturally occurring ketoheptoses were isolated from plants early on and their physiological properties studied.[9] In 1970 and 1972, Nelkin showed the potential diabetogenic properties of D-*manno*- or D-*gluco*-hept-2-ulose in rats after injection-induced hyperglycemia.[10] Other groups proposed their use in anticancer treatment.[11] The mechanism is considered to be caused via their uptake by a sugar transporter (GLUT2 receptor) leading to an inhibition of glucose metabolism and insulin secretion, which in turn is likely due to an inhibition of hexokinase isoenzymes. Regioisomeric fluorinated ketoheptoses do not only allow for ^{19}F MRI detection, but the study of mechanistic aspects and metabolic fate in vivo. This approach enables organ and tissue specific contrast agent fine tuning.[10–12] Synthetic access to ketoheptoses and their derivatives has been largely disregarded due to the complexity of a C1 extended anomeric position of hexoses. However, due to their structural resemblance to hexoses the synthesis of heptoses represents a promising target. The present work describes the synthesis of five regioisomeric fluorinated D-*gluco*-hept-2-ulose starting from D-glucose. Key step in the synthesis of ketoheptoses is the C1 chain elongation of hexoses followed by their bishydroxylation. The exocyclic enol ether is a key intermediate for further derivatization controlled by suitable protecting group schemes (Scheme 1).



Scheme 1 Generalized pathway towards ketoheptoses and fluoroketoheptoses via the exocyclic enol ether key intermediate allowing for functionalization

As an example, the synthesis of regioisomer fluoro-D-*gluco*-hept-2-ulose is presented. Using the exocyclic enol ether **1**, our group[13] reported recently on bishydroxylation reaction that leads to D-*gluco*-hept-2-ulose (**2**). For the synthesis of 1-deoxy-1-fluoro-D-*gluco*-hept-2-ulose (**4**),

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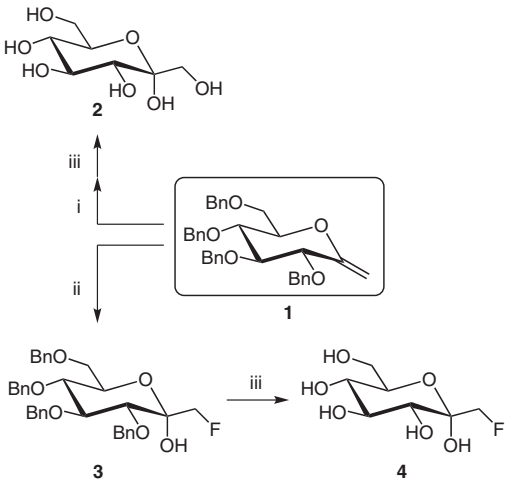
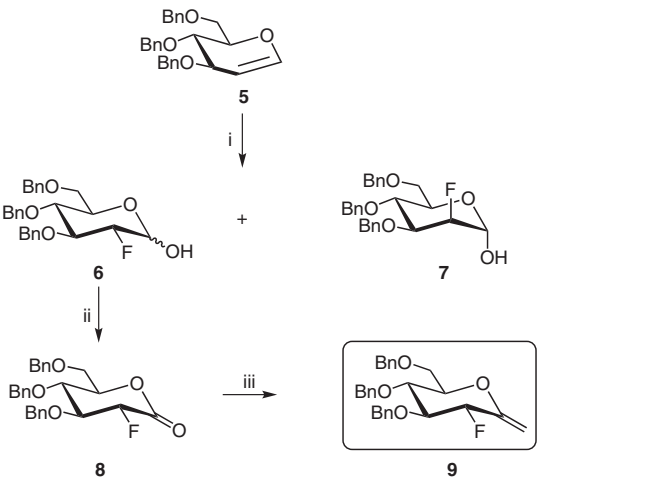
the exocyclic enol ether **1** was first fluorinated using Selectfluor.[13,14] The regioselective introduction of fluorine occurred via electrophilic addition of a cationic fluorine to the double bond of the exocyclic ether **1** and afforded **3** in 65% yield. Exclusively the α-anomer was formed, as confirmed by NOESY experiments. Debenzylation of **3** with palladium(II) hydroxide in MeOH and EtOAc gave 1-deoxy-1-fluoro-α-D-*gluco*-hept-2-ulopyranose (**4**) in quantitative yield (Scheme 2).



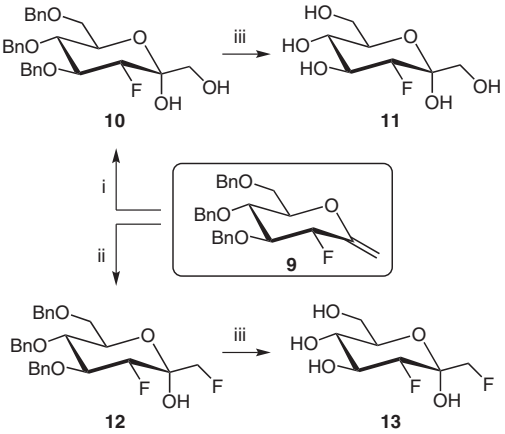
Scheme 2 *Reagents and conditions*: (i) K_2CO_3, $K_3[Fe(CN)_6]$, $K_2OsO_2(OH)_4$, *t*-BuOH, H_2O, r.t., 24 h (ii) Selectfluor, DMF, H_2O, r.t., 12 h, 65%; (iii) H_2, $Pd(OH)_2$/C, MeOH, EtOAc, 24 h, ~100%.

3,4,6-Tri-*O*-benzyl-D-glucal (**5**) was prepared by the well-known five-step procedure from D-glucose and served as precursor for the preparation of 2-deoxysugars.[15] Selectfluor reacted with glucal **5** in the presence of water to give the D-*gluco*-configured compound **6** (44%) as a ~2:1 anomeric mixture (determined by NMR spectroscopy) and the D-*manno*-configured compound **7** (33%), which could be easily separated by column chromatography.[13] Subsequently, **6** was oxidized to the related lactone **8** using DMSO and acetic anhydride at room temperature according to the Albright–Goldman procedure.[16] Petasis reagent (Me_2TiCp_2) was used[17] for methylenation of the lactone **8** and gave the C1 elongated **9** in 70% yield (Scheme 3). In a likewise manner the *manno*-configured precursor **7** leads to the 3-deoxy-3-fluoro-D-*manno*-hept-2-ulose series (not shown).



Scheme 3 *Reagents and conditions*: (i) Selectfluor, DMF, H_2O, r.t., 12 h, **6**: 44%, **7**: 33% (ii) Ac_2O, DMSO, 30 °C, 24 h, 85%; (iii) Petasis reagent, toluene, 75 °C, 24 h, 70%.

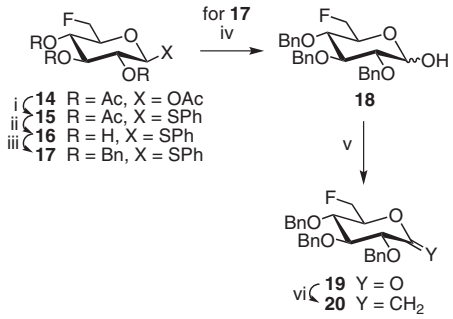
Sharpless dihydroxylation[18] and/or fluorination of **9** gave either the 3-fluoro compound **10** and 1,3-difluoro compound **12** as α-anomers as judged by NOESY experiments. Finally, **10** and **12** were hydrogenated to furnish 3-deoxy-3-fluoro-α-D-*gluco*-hept-2-ulopyranose (**11**) in 92% yield and 1,3-dideoxy-1,3-difluoro-α-D-*gluco*-hept-2-ulopyranose (**13**) in 86% yield (Scheme 4).



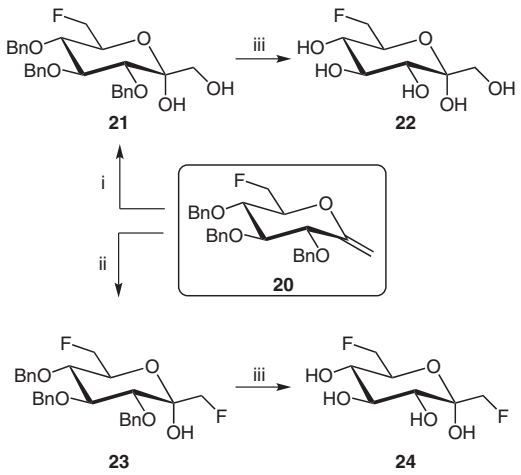
Scheme 4 *Reagents and conditions*: (i) K_2CO_3, $K_3[Fe(CN)_6]$, $K_2OsO_2(OH)_4$, *t*-BuOH, H_2O, r.t., 24 h, 87%; (ii) Selectfluor, DMF, H_2O, r.t., 12 h, 75%; (iii) H_2, $Pd(OH)_2$/C, MeOH, EtOAc, r.t., 24 h, **11**: 92%, **13**: 86%.

Starting from 6-fluoro derivative **14**[19] the corresponding thioglycoside **15** was obtained after glycosylation with thiophenol in 80% yield. Deacetylation under Zemplén conditions[20a,b] provided thiolglycoside **16** in 96% yield. Perbenzylation gave **17** in 91% yield. Finally, hydrolysis of **17** using NBS in acetone and water afforded the desired hemiacetal **18**.[21] Oxidation of **18** to the related lactone **19** using DMSO/acetic anhydride at room temperature was conducted according to the Albright–Goldman procedure.[16] Finally, methylenation of **19** led to 2,6-anhydro-3,4,5-tri-*O*-benzyl-1,7-dideoxy-7-fluoro-D-*gluco*-hept-1-enitol (**20**) (Scheme 5).

By following dihydroxylation and fluorination of **20**, 3,4,5,-tri-*O*-benzyl-7-deoxy-7-fluoro-α-D-*gluco*-hept-2-ulopyranose (**21**) and 3,4,5-tri-*O*-benzyl-1,7-deoxy-1,7-difluoro-α-D-*gluco*-hept-2-ulopyranose (**23**) were obtained as α-anomers in good yield (91% for **21**, 74% for **23**). The configuration of compound **21** and **23** were deduced from NOESY experiments. After hydrogenation of **21** and **23**, 7-deoxy-7-fluoro-α-D-*gluco*-hept-2-ulopyranose (**22**) and 1,7-deoxy-1,7-difluoro-α-D-*gluco*-hept-2-ulopyranose (**24**) were obtained in 94% and 95% yield, respectively (Scheme 6).



Scheme 5 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$, thiophenol, CH_2Cl_2, 0 °C to r.t., 12 h, 80%; (ii) NaOMe, MeOH, r.t., 8 h, 96%; (iii) NaH, Bu_4NI, BnBr, DMF, r.t., 12 h, 91%; (iv) NBS, acetone, H_2O, r.t., 2 h, 83%; (v) Ac_2O, DMSO, 30 °C, 24 h, 86%; (vi) Petasis reagent, toluene, 75 °C, 24 h, 80%.



Scheme 6 *Reagents and conditions*: (i) K_2CO_3, $K_3[Fe(CN)_6]$, $K_2OsO_2(OH)_4$, *t*-BuOH, H_2O, r.t., 24 h, 91%; (ii) Selectfluor, DMF, H_2O, r.t., 12 h, 74%; (iii) H_2, $Pd(OH)_2$/C, MeOH, EtOAc, r.t., 24 h, **22**: 94%, **24**: 95%.

In conclusion, exocyclic enol ethers were obtained from hexoses using a C1 chain elongation by Petasis reagent. These key precursors could be employed for facile synthesis of regioisomerically fluorinated compounds by Selectfluor. Employing methods, which should be as well applicable to other configurations, D-*gluco*-hept-2-ulose and five novel mono- and difluorinated derivatives of D-*gluco*-heptoses were synthesized in good yields. Their ability to be selectively taken up via sugar transporters and their use for ^{19}F-MRI are under current investigation.

Commercially available starting materials were used without further purification. All solvents used for the syntheses were purified according to conventional procedures. Petroleum ether (PE) refers to a hydrocarbon mixture with a boiling range of 50–70 °C. TLC was carried out on aluminum sheets coated with silica gel 60 (Merck). For detection, TLC plates were treated with an alcoholic solution of H_2SO_4, followed by heating. Flash column chromatography was performed on silica gel 60 (40–63 μm; Merck) and silica gel 60 RP-18 (40–63 μm; Merck). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX 400, AC 400, DRX 500 spectrometers and ^{19}F NMR spectra were recorded on a Varian Gemini-2000BB spectrometer with the residual solvent as the internal standard. Melting points were measured on an Apotec capillary melting point apparatus and are uncorrected. Optical rotations were determined at 20 °C using a Kruess P8000 polarimeter (589 nm, Na). HRMS-ESI was performed on Agilent-6224-TOF ESI/MS and a Thermo Finnigan MAT 95 XL.

Fluorination; General Procedure 1 (GP 1)
The enol compound (1 equiv) was dissolved in DMF–H_2O (1:1), Selectfluor (1.5–10 equiv) was added, and the mixture was stirred at r.t. for 12 h. After completion of the reaction, EtOAc (50 mL) was added and the organic layer was washed with H_2O (3 × 50 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The product was isolated by column chromatography under the indicated conditions.

Hydrogenation; General Procedure 2 (GP 2)
The protected monosaccharide (1 equiv) was dissolved in MeOH–EtOAc (1:1), a catalytic amount of 20% $Pd(OH)_2$/C was added, and the reaction mixture was stirred under a H_2 for 24 h. The solution was filtered and the solvent was removed in vacuo. The product was isolated by column chromatography (RP-18, H_2O).

Dihydroxylation; General Procedure 3 (GP 3)
The enol compound (1 equiv) was dissolved in *t*-BuOH-H_2O (1:1), and K_2CO_3 (3 equiv) and $K_3[Fe(CN)_6]$ (3 equiv), and catalytic amount of $K_2OsO_2(OH)_4$ were added. The reaction mixture was stirred at r.t. for 24 h. After completion, EtOAc (30 mL) and H_2O (30 mL) were added, the organic layer washed with H_2O (3 × 30 mL), and dried (Na_2SO_4).The product was isolated by column chromatography (Et_2O).

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-fluoro-α-D-*gluco*-hept-2-ulopyranose (3)
The synthesis was carried out according to GP 1 with **1** (500 mg, 0.93 mmol), DMF–H_2O (15 mL), and Selectfluor (3.36 g, 9.3 mmol). After workup, the crude residue was purified by column chromatography (PE–EtOAc, 2:1) to give **3** as a colorless oil; yield: 343 mg (65%); $[\alpha]_D^{25}$ +29.5 (*c* 0.55, $CHCl_3$); R_f = 0.19 (PE–Et_2O, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42–7.15 (m, 20 H, H-Ar), 6.50 (br s, 1 H, OH), 4.83–4.77 (m, 3 H, CH_2Ph), 4.75 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.59 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.55 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.54 (d, J = 11.0 Hz, 1 H, CH_2Ph), 4.48 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.35 (dd, $J_{1a,1b}$ = 9.5 Hz, $J_{1a,F}$ = 47.5 Hz, 1 H, H-1a), 4.22 (dd, $J_{1b,1a}$ = 9.5 Hz, $J_{1b,F}$ = 47.5 Hz, 1 H, H-1b), 3.95 (dd, $J_{4,3}$ = 9.3 Hz, $J_{4,5}$ = 9.3 Hz, 1 H, H-4), 3.89 (ddd, $J_{6,7b}$ = 2.6 Hz, $J_{6,7a}$ = 4.5 Hz, $J_{6,5}$ = 10.0 Hz, 1 H, H-6), 3.67 (dd, $J_{7a,6}$ = 4.5 Hz, $J_{7a,7b}$ = 10.9 Hz, 1 H, H-7a), 3.58 (dd, $J_{7b,6}$ = 2.6 Hz, $J_{7b,7a}$ = 10.9 Hz, 1 H, H-7b), 3.55–3.46 (m, 2 H, H-3, H-5).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 138.6, 138.3, 138.2 (Cq-Ar), 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4 (CH-Ar), 95.7 ($J_{C,F}$ = 18.5 Hz, C-2), 82.5 ($J_{C,F}$ = 178.3 Hz, C-1), 82.2 (C-4), 78.7 (C-3), 78.2 (C-5), 74.5, 74.4, 73.9, 72.3 (*C*H_2Ph), 70.8 (C-6), 68.7 (C-7).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –226.2 (t, $J_{F,I}$ = 47.5 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{37}FO_6$ + Na: 595.2466; found: 595.2483; [M + K]$^+$ 611.2206; found: 611.2216.

1-Deoxy-1-fluoro-α-D-*gluco*-hept-2-ulopyranose (4)
The synthesis was carried out according to GP 2 with **3** (300 mg, 0.52 mmol), MeOH–EtOAc (10 mL), and a catalytic amount of 20% $Pd(OH)_2$/C. The crude residue was purified by column chromatography to give **4** as a colorless syrup; yield: 110 mg (~100%); $[\alpha]_D^{25}$ +58.9 (*c* 0.50, H_2O).

^{1}H NMR (400 MHz, D_2O): δ = 4.54 (dd, $J_{1a,1b}$ = 9.8 Hz, $J_{1a,F}$ = 46.6 Hz, 1 H, H-1a), 4.40 (dd, $J_{1b,1a}$ = 9.8 Hz, $J_{1b,F}$ = 46.6 Hz, 1 H, H-1b),

3.92–3.83 (m, 2 H, H-6, H-7a), 3.82–3.75 (m, 2 H, H-4, H-7b), 3.54 (d, $J_{3,4}$ = 9.5 Hz, 1 H, H-3), 3.45 (dd, $J_{5,4}$ = 9.6 Hz, $J_{5,6}$ = 9.6 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, D_2O): δ = 96.2 ($J_{C,F}$ = 17.5 Hz, C-2), 83.3 ($J_{C,F}$ = 175.2 Hz, C-1), 73.5 (C-4), 72.7 (C-6), 70.3 (C-3), 69.6 (C-5), 60.7 (C-7).

^{19}F NMR (188 MHz, D_2O): δ = –231.2 (t, $J_{F,1}$ = 46.6 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_7H_{13}FO_6$ + Na: 235.0588; found: 235.0595.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-fluoro-D-glucono-1,5-lactone (8)

To a solution of **6** (1.96 g, 4.33 mmol) in anhyd DMSO (11.0 mL) was added Ac_2O (8.9 mL) at 30 °C. The reaction mixture was stirred for 24 h at 30 °C and then diluted with H_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude residue was isolated by column chromatography (PE–Et_2O, 1:2) to give **8** as a colorless solid; yield: 1.66 g (85%); mp 58–59 °C; $[\alpha]_D^{25}$ +44.5 (*c* 1.02, $CHCl_3$); R_f = 0.53 (PE–Et_2O, 1:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40–7.18 (m, 15 H, H-Ar), 5.38 (dd, $J_{2,3}$ = 8.6 Hz, $J_{2,F}$ = 47.0 Hz, 1 H, H-2), 4.73–4.67 (m, 3 H, CH_2Ph), 4.57–4.50 (m, 3 H, H-5, CH_2Ph), 4.48 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.22 (ddd, $J_{3,4}$ = 7.7 Hz, $J_{3,2}$ = 8.6 Hz, $J_{3,F}$ = 15.3 Hz, 1 H, H-3), 3.96 (dd, $J_{4,5}$ = 7.7 Hz, $J_{4,3}$ = 7.7 Hz, 1 H, H-4), 3.71–3.55 (m, 2 H, H-6a, H-6b).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 ($J_{C,F}$ = 21.8 Hz, C-1), 137.8, 137.7, 137.5 (Cq-Ar), 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 127.6 (CH-Ar), 88.2 ($J_{C,F}$ = 189.5 Hz, C-2), 79.8 ($J_{C,F}$ = 18.3 Hz, C-3), 78.3 (C-5), 74.4 ($J_{C,F}$ = 9.5 Hz, C-4), 73.2, 73.0, 72.3 (*C*H_2Ph), 68.0 (C-6).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –195.2 (dd, $J_{F,3}$ = 15.3 Hz, $J_{F,2}$ = 47.0 Hz).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{27}FO_5$: 451.1915; found: 451.1950; [M + Na]$^+$ 473.1735; found: 473.1770.

2,6-Anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-3-fluoro-D-gluco-hept-1-enitol (9)

The lactone **8** (1.09 g, 2.41 mmol) and Me_2TiCp_2 (1.04 g, 4.86 mmol) were dissolved in anhyd toluene (20 mL) under an argon atmosphere and heated to 75 °C. The reaction mixture was stirred for 48 h at 75 °C and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (PE–Et_2O + 0.5% Et_3N, 5:1) to give **8** as a yellowish solid; yield: 753 mg (70%), mp 49–50 °C; $[\alpha]_D^{25}$ +58.8 (*c* 0.33, $CHCl_3$); R_f = 0.43 (PE–Et_2O, 5:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40–7.13 (m, 15 H, H-Ar), 5.10 (dd, $J_{3,4}$ = 7.0 Hz, $J_{3,F}$ = 49.1 Hz, 1 H, H-3), 4.77 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.71 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.69 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.67 (s, 1 H, H-1a), 4.58 (s, 1 H, H-1b), 4.54 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.50 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.48 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 3.81 (ddd, $J_{4,3}$ = 7.0 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,F}$ = 13.3 Hz, 1 H, H-4), 3.76–3.63 (m, 4 H, H-5, H-6, H-7).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.1 ($J_{C,F}$ = 18.7 Hz, C-2), 138.0, 137.9, 137.8 (Cq-Ar), 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 124.3 (CH-Ar), 94.1 ($J_{C,F}$ = 6.1 Hz, C-1), 89.2 ($J_{C,F}$ = 182.1 Hz, C-3), 81.6 ($J_{C,F}$ = 19.8 Hz, C-4), 77.5 (C-6), 76.1 ($J_{C,F}$ = 6.2 Hz, C-5), 73.3, 72.9, 72.3 (*C*H_2Ph), 68.4 (C-7).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –185.6 (dd, $J_{F,4}$ = 13.3 Hz, $J_{F,3}$ = 49.1 Hz).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{29}FO_4$: 449.2123; found: 449.2152; [M + Na]$^+$ 471.1942; found: 471.1978.

4,5,7-Tri-*O*-benzyl-3-deoxy-3-fluoro-α-D-*gluco*-hept-2-ulopyranose (10)

The synthesis was carried out according to GP 3 with **9** (267 mg, 595 μmol), *t*-BuOH–H_2O (10 mL), K_2CO_3 (247 mg, 1.79 mmol), $K_3[Fe(CN)_6]$ (589 mg, 1.79 mmol), and a catalytic amount of $K_2OsO_2(OH)_4$. The reaction mixture was stirred at r.t. for 24 h. After workup, the crude product was purified by column chromatography to give **10** as a colorless oil; yield: 251 (87%); $[\alpha]_D^{25}$ +42.8 (*c* 0.26, $CHCl_3$); R_f = 0.43 (Et_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42–7.14 (m, 15 H, H-Ar), 6.28 (s, 1 H, OH), 4.99 (dd, $J_{OH,1}$ = 6.0 Hz, $J_{OH,1}$ = 6.2 Hz, 1 H, OH), 4.78 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.75 (d, *J* = 10.8 Hz, 1 H, CH_2Ph), 4.72 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.53 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.52 (d, *J* = 10.8 Hz, 1 H, CH_2Ph), 4.48 (dd, $J_{3,4}$ = 9.7 Hz, $J_{3,F}$ = 50.2 Hz, 1 H, H-3), 4.46 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.03–3.94 (m, 1 H, H-4), 3.90 (ddd, $J_{6,7b}$ = 2.2 Hz, $J_{6,7a}$ = 4.6 Hz, $J_{6,5}$ = 10.0 Hz, 1 H, H-6), 3.65 (dd, $J_{7a,6}$ = 4.6 Hz, $J_{7a,7b}$ = 11.0 Hz, 1 H, H-7a), 3.58 (dd, $J_{7b,6}$ = 2.2 Hz, $J_{7b,7a}$ = 11.0 Hz, 1 H, H-7b), 3.50–3.35 (m, 3 H, H-1, H-5).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 138.6, 138.2, 138.1 (Cq-Ar), 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4 (CH-Ar), 95.7 ($J_{C,F}$ = 18.9 Hz, C-2), 89.8 ($J_{C,F}$ = 188.6 Hz, C-3), 80.7 ($J_{C,F}$ = 16.5 Hz, C-4), 77.5 ($J_{C,F}$ = 7.8 Hz, C-5), 73.9, 73.8, 73.3 (*C*H_2Ph), 70.4 (C-6), 68.8 (C-7), 62.9 (C-1).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –197.4 (dd, $J_{F,4}$ = 12.7 Hz, $J_{F,3}$ = 50.2 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{31}FO_6$ + Na: 505.1997; found: 505.1999.

3-Deoxy-3-fluoro-α-D-*gluco*-hept-2-ulopyranose (11)

The synthesis was carried out according to GP 2 with **10** (238 mg, 493 μmol), MeOH–EtOAc (10 mL), and a catalytic amount of 20% $Pd(OH)_2$/C. The crude residue was purified by column chromatography to give **11** as a colorless syrup; yield: 96 mg (92%); $[\alpha]_D^{25}$ +56.9 (*c* 1.70, H_2O).

^{1}H NMR (400 MHz, D_2O): δ = 4.43 (dd, $J_{3,4}$ = 9.4 Hz, $J_{3,F}$ = 49.7 Hz, 1 H, H-3), 4.02 (ddd, $J_{4,3}$ = 9.4 Hz, $J_{4,5}$ = 9.4 Hz, $J_{4,F}$ = 13.9 Hz, 1 H, H-4), 3.90–3.77 (m, 3 H, H-6, H-7), 3.73 (dd, $J_{1a,F}$ = 1.5 Hz, $J_{1a,1b}$ = 12.0 Hz, 1 H, H-1a), 3.61 (dd, $J_{1b,F}$ = 1.5 Hz, $J_{1b,1a}$ = 12.0 Hz, 1 H, H-1b), 3.51 (dd, $J_{5,4}$ = 9.4 Hz, $J_{5,6}$ = 9.5 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, D_2O): δ = 96.4 ($J_{C,F}$ = 18.9 Hz, C-2), 89.4 ($J_{C,F}$ = 186.8 Hz, C-3), 72.5 (C-6), 71.9 ($J_{C,F}$ = 17.5 Hz, C-4), 66.8 ($J_{C,F}$ = 7.6 Hz, C-1), 63.4 (C-5), 60.7 (C-7).

^{19}F NMR (188 MHz, D_2O): δ = –201.2 (dd, $J_{F,4}$ = 13.9 Hz, $J_{F,3}$ = 49.7 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_7H_{13}FO_6$ + Na: 235.0588; found: 235.0589.

4,5,7-Tri-*O*-benzyl-1,3-dideoxy-1,3-difluoro-α-D-*gluco*-hept-2-ulopyranose (12)

The synthesis was carried out according to GP 1 with **9** (90 mg, 200 μmol), DMF–H_2O (5 mL), and Selectfluor (710 mg, 2.0 mmol). After workup, the crude residue was purified by column chromatography (PE–Et_2O, 2:1) to give **12** as a colorless oil; yield: 73 (75%); $[\alpha]_D^{25}$ +47.9 (*c* 0.21, $CHCl_3$); R_f = 0.34 (PE–Et_2O, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.40–7.23 (m, 13 H, H-Ar), 7.22–7.14 (m, 2 H, H-Ar), 6.98 (br s, 1 H, -OH), 4.82–4.69 (m, 3 H, CH_2Ph), 4.56–4.46 (m, 3 H, CH_2Ph), 4.40 (dd, $J_{3,4}$ = 9.2 Hz, $J_{3,F}$ = 50.6 Hz, 1 H, H-3), 4.38 (dd, $J_{1a,1b}$ = 9.7 Hz, $J_{1a,F}$ = 47.1 Hz, 1 H, H-1a), 4.30 (dd, $J_{1b,1a}$ = 9.7 Hz, $J_{1b,F}$ = 47.1 Hz, 1 H, H-1b), 4.02 (ddd, $J_{4,3}$ = 9.2 Hz, $J_{4,5}$ = 9.4 Hz, $J_{4,F}$ = 12.4 Hz, 1 H, H-4), 3.91 (ddd, $J_{6,7b}$ = 1.1 Hz, $J_{6,7a}$ = 4.4 Hz, $J_{6,5}$ = 9.5 Hz, 1 H, H-6), 3.66 (dd, $J_{7a,6}$ = 4.4 Hz, $J_{7a,7b}$ = 10.9 Hz, 1 H, H-7a), 3.58 (dd, $J_{7b,6}$ = 1.1 Hz,

$J_{7b,7a}$ = 10.9 Hz, 1 H, H-7b), 3.52 (dd, $J_{5,4}$ = 9.4 Hz, $J_{5,6}$ = 9.5 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 138.4, 138.1, 138.0 (Cq-Ar), 128.2, 128.2, 127.9, 127.7, 127.6, 127.6, 127.5 (CH-Ar), 93.9 ($J_{C,F}$ = 18.1, $J_{C,F}$ = 18.4 Hz, C-2), 89.8 ($J_{C,F}$ = 190.7 Hz, C-3), 82.1 ($J_{C,F}$ = 178.6 Hz, C-1), 80.2 ($J_{C,F}$ = 15.8 Hz, C-4), 77.1 ($J_{C,F}$ = 7.7 Hz, C-5), 74.0, 73.9, 72.3 (*C*H$_2$Ph), 70.6 (C-6), 68.4 (C-7).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –197.1 (dd, $J_{F,4}$ = 12.4 Hz, $J_{F,3}$ = 50.6 Hz), –227.8 (t, $J_{F,1}$ = 47.1 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{30}F_2O_5$ + Na: 507.1954; found: 507.1953; [M + K]$^+$ 523.1693; found: 523.1691.

1,3-Dideoxy-1,3-difluoro-α-D-*gluco*-hept-2-ulopyranose (13)

The synthesis was carried out according to GP 2 with **12** (65 mg, 134 μmol), MeOH–EtOAc (3 mL), and a catalytic amount of 20% Pd(OH)$_2$/C. The crude residue was purified by column chromatography to give **13** as a colorless syrup; yield: 24 mg (86%); $[\alpha]_D^{25}$ +48.9 (*c* 1.65, H$_2$O).

^{1}H NMR (500 MHz, D$_2$O): δ = 4.55 (dd, $J_{1a,1b}$ = 10.0 Hz, $J_{1a,F}$ = 47.2 Hz, 1 H, H-1a), 4.45 (dd, $J_{3,4}$ = 9.3 Hz, $J_{3,F}$ = 50.3 Hz, 1 H, H-3), 4.40 (dd, $J_{1b,1a}$ = 10.0 Hz, $J_{1b,F}$ = 47.2 Hz, 1 H, H-1b), 4.12 (ddd, $J_{4,3}$ = 9.3 Hz, $J_{4,5}$ = 9.5 Hz, $J_{4,F}$ = 12.6 Hz, 1 H, H-4), 3.93–3.84 (m, 2 H, H-6, H-7a), 3.68 (dd, $J_{7b,6}$ = 5.3 Hz, $J_{7b,7a}$ = 12.4 Hz, 1 H, H-7b), 3.52 (dd, $J_{5,4}$ = 9.5 Hz, $J_{5,6}$ = 9.7 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, D$_2$O): δ = 89.3 ($J_{C,F}$ = 188.5 Hz, C-3), 82.8 ($J_{C,F}$ = 176.2 Hz, C-1), 72.7 (C-6), 71.7 ($J_{C,F}$ = 17.4 Hz, C-4), 69.0 ($J_{C,F}$ = 7.8 Hz, C-5), 60.3 (C-7).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –201.0 (dd, $J_{F,4}$ = 12.6 Hz, $J_{F,3}$ = 50.3 Hz), –231.6 (t, $J_{F,1}$ = 47.2 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_7H_{12}F_2O_5$ + Na: 237.0545; found: 237.0529.

Phenyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-fluoro-1-thio-β-D-glucopyranoside (15)

Under an argon atmosphere, compound **14**[13b] (1.97 g, 5.63 mmol) was dissolved in anhyd CH_2Cl_2 (20 mL), and thiophenol (1.72 mL, 16.9 mmol) was added. Then $BF_3{\cdot}OEt_2$ (3.56 mL, 28.2 mmol) was added dropwise at 0 °C and he mixture stirred for 1 h. The mixture was warmed up to r.t. and stirred overnight. After completion of the reaction, sat. aq $NaHCO_3$ (20 mL) was added and the organic layer was washed with H_2O (20 mL), sat. aq $NaHCO_3$ (20 mL), and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by column chromatography (PE–EtOAc, 2:1) to give **15** as a colorless solid; yield: 1.8 g (80%); mp 126–127 °C; $[\alpha]_D^{25}$ –10.1 (*c* 0.51, $CHCl_3$); R_f = 0.28 (PE–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 2 H, H-Ar), 7.30–7.23 (m, 3 H, H-Ar), 5.18 (dd, $J_{3,2}$ = 9.3 Hz, $J_{3,4}$ = 9.3 Hz, 1 H, H-3), 4.94 (dd, $J_{4,3}$ = 9.3 Hz, $J_{4,5}$ = 9.9 Hz, 1 H, H-4), 4.89 (dd, $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 10.0 Hz, 1 H, H-2), 4.66 (d, $J_{1,2}$ = 10.0 Hz, 1 H, H-1), 4.50–4.44 (m, 1 H, H-6a, H-6b), 4.38–4.32 (m, 1 H, H-6a, H-6b), 3.68 (dddd, $J_{5,6a}$ = 2.1 Hz, $J_{5,6b}$ = 4.4 Hz, $J_{5,4}$ = 9.9 Hz, $J_{5,F}$ = 24.2 Hz, 1 H, H-5), 2.02 (s, 3 H, OCOCH$_3$), 1.96 (s, 3 H, OCOCH$_3$), 1.92 (s, 3 H, OCOCH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 169.4, 169.2 (C=O), 133.2 (CH-Ar), 131.5 (Cq-Ar), 129.1, 128.5 (CH-Ar), 85.8 (C-1), 81.4 ($J_{C,F}$ = 175.8 Hz, C-6), 75.5 ($J_{C,F}$ = 19.7 Hz, C-5), 73.9 (C-3), 69.9 (C-2), 67.9 ($J_{C,F}$ = 6.9 Hz, C-4), 20.7, 20.6, 20.5 (OCO*C*H$_3$).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –232.1 (td, $J_{F,5}$ = 24.2 Hz, $J_{F,6}$ = 47.2 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}FO_7S$ + Na: 423.0884; found: 423.0883.

Phenyl 6-Deoxy-6-fluoro-1-thio-β-D–glucopyranoside (16)

Compound **15** (1.75 g, 4.37 mmol) was dissolved in anhyd MeOH (20 mL) and a catalytic amount of a 0.5 M NaOMe in MeOH was added. The reaction mixture was stirred at r.t. After completion of the reaction, Amberlite IR-120 H$^+$ was added until the mixture was neutralized. The ion exchange resin was filtered off and the solvent removed in vacuo. The crude product was purified by column chromatography (EtOAc) to give **16** as a colorless solid, yield: 1.15 g (96%); mp 128–129 °C; $[\alpha]_D^{25}$ –47.1 (*c* 0.51, MeOH); R_f = 0.27 (EtOAc).

^{1}H NMR (500 MHz, CD_3OD): δ = 7.60–7.53 (m, 2 H, H-Ar), 7.37–7.25 (m, 3 H, H-Ar), 4.65 (ddd, $J_{6a,5}$ = 1.8 Hz, $J_{6a,6b}$ = 10.3 Hz, $J_{6a,F}$ = 47.6 Hz, 1 H, H-6a), 4.62 (d, $J_{1,2}$ = 9.8 Hz, 1 H, H-1), 4.60 (ddd, $J_{6b,5}$ = 4.7 Hz, $J_{6b,6a}$ = 10.6 Hz, $J_{6b,F}$ = 47.6 Hz, 1 H, H-6b), 3.49 (dddd, $J_{5,6a}$ = 1.8 Hz, $J_{5,6b}$ = 4.7 Hz, $J_{5,4}$ = 9.8 Hz, $J_{5,F}$ = 23.8 Hz, 1 H, H-5), 3.42 (dd, $J_{3,2}$ = 9.3 Hz, $J_{3,4}$ = 9.3 Hz, 1 H, H-3), 3.36–3.32 (m, 1 H, H-4), 3.22 (dd, $J_{2,3}$ = 9.3 Hz, $J_{2,1}$ = 9.8 Hz, 1 H, H-2).

^{13}C NMR (125 MHz, CD_3OD): δ = 134.9 (Cq-Ar), 133.1, 129.9, 128.6 (CH-Ar), 89.3 (C-1), 83.4 ($J_{C,F}$ = 171.9 Hz, C-6), 80.2 ($J_{C,F}$ = 17.9 Hz, C-5), 79.6 (C-3), 73.6 (C-2), 67.9 ($J_{C,F}$ = 7.1 Hz, C-4).

^{19}F NMR (188 MHz, CD_3OD): δ = –236.9 (td, $J_{F,5}$ = 23.8 Hz, $J_{F,6}$ = 47.6 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}FO_4S$ + Na: 297.0567; found: 297.0568.

Phenyl 2,3,4-Tri-*O*-benzyl-6-deoxy-6-fluoro-1-thio-β-D-glucopyranoside (17)

Thioglycoside **16** (1.07 g, 3.90 mmol) was added to a suspension of NaH (0.7 g, 18.3 mmol) in anhyd DMF (25 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 2 h. Then a catalytic amount of Bu_4NI (15 mg, 39 μmol) was added and the mixture was treated dropwise with benzyl bromide (1.6 mL, 13 mmol). The mixture was stirred overnight and the remaining NaH was destroyed with EtOH. The reaction mixture was diluted with H_2O (100 mL) and Et_2O (100 mL) and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude residue was purified by column chromatography (PE–Et_2O, 3:1) to give **17** as a colorless solid; yield: 1.93 (91%); mp 111–112 °C; $[\alpha]_D^{25}$ +2.11(*c* 0.53, $CHCl_3$); R_f = 0.32 (PE–Et_2O, 3:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.50–7.45 (m, 2 H, H-Ar), 7.38–7.22 (m, 18 H, H-Ar), 5.04 (d, $J_{1,2}$ = 9.8 Hz, 1 H, H-1), 4.84–4.77 (m, 3 H, C*H*$_2$Ph), 4.75 (d, *J* = 11.3 Hz, 1 H, C*H*$_2$Ph), 4.69 (d, *J* = 10.7 Hz, 1 H, C*H*$_2$Ph), 4.66–4.62 (m, 1 H, H-6a, H-6b), 4.59 (d, *J* = 11.1 Hz, 1 H, C*H*$_2$Ph), 4.55-4.48 (m, 1 H, H-6a, H-6b), 3.82 (dd, $J_{3,2}$ = 9.4 Hz, $J_{3,4}$ = 9.5 Hz, 1 H, H-3), 3.75 (dddd, $J_{5,6a}$ = 2.2 Hz, $J_{5,6b}$ = 4.7 Hz, $J_{5,4}$ = 9.9 Hz, $J_{5,F}$ = 26.6 Hz, 1 H, H-5), 3.49 (dd, $J_{4,3}$ = 9.5 Hz, $J_{4,5}$ = 9.9 Hz, 1 H, H-4), 3.44 (dd, $J_{2,3}$ = 9.4 Hz, $J_{2,1}$ = 9.8 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 138.4, 138.0, 137.9, 133.9 (Cq-Ar), 130.1, 129.1, 128.2, 128.2, 128.1, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 127.0 (CH-Ar), 85.5 (C-1), 85.2 (C-3), 82.1 ($J_{C,F}$ = 170.2 Hz, C-6), 80.3 (C-2), 76.6 ($J_{C,F}$ = 18.7 Hz, C-5), 76.5 ($J_{C,F}$ = 6.9 Hz, C-4), 74.6, 74.2, 74.0 (*C*H$_2$Ph).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –230.9 (td, $J_{F,5}$ = 26.6 Hz, $J_{F,6}$ = 47.7 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{33}FO_4S$ + Na: 567.1976; found: 567.1989.

2,3,4-Tri-*O*-benzyl-6-deoxy-6-fluoro-D-glucopyranose (18)

Compound **17** (1.39 g, 2.55 mmol) was dissolved in a mixture of acetone–H_2O (9:1, 50 mL) and treated with NBS (1.43 g, 8.03 mmol). The reaction mixture was stirred at r.t. for 2 h. After completion of

the reaction, H_2O (150 mL) was added and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (150 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude residue was purified by column chromatography (PE–Et_2O, 1:1) to give an anomeric mixture (α/β = 1.4:1) **18** as a colorless solid; yield: 0.96 g (83%); R_f = 0.23 (PE–Et_2O, 1:1).

18α

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.40–7.21 (m, 15 H, H-Ar), 6.74 (d, $J_{OH,1}$ = 4.8 Hz, 1 H, OH), 5.24 (dd, $J_{1,2}$ = 3.7 Hz, $J_{1,OH}$ = 4.8 Hz, 1 H, H-1), 4.87 (d, J = 11.2 Hz, 1 H, CH_2Ph), 4.78 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.77–4.72 (m, 1 H, CH_2Ph), 4.69 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.63 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.63–4.60 (m, 1 H, H-6a, H-6b), 4.58 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.54–4.50 (m, 1 H, H-6a, H-6b), 3.89 (dddd, $J_{5,6a}$ = 2.2 Hz, $J_{5,6a}$ = 4.7 Hz, $J_{5,4}$ = 9.9 Hz, $J_{5,F}$ = 26.4 Hz, 1 H, H-5), 3.87 (dd, $J_{3,2}$ = 9.1 Hz, $J_{3,4}$ = 9.2 Hz, 1 H, H-3), 3.46–3.35 (m, 2.7 H, H-2, H-4).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 138.7, 138.6, 138.5 (Cq-Ar), 128.2, 128.2, 128.1, 127.7, 127.7, 127.6, 127.4, 127.3 (CH-Ar), 89.6 (C-1), 82.2 ($J_{C,F}$ = 170.2 Hz, C-6), 80.8 (C-3), 79.9 (C-2), 76.7 ($J_{C,F}$ = 6.9 Hz, C-4), 74.4, 74.0, 73.5 (*C*H_2Ph), 71.6 (*C*H_2Ph), 68.7 ($J_{C,F}$ = 17.9 Hz, C-5).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –231.2 (td, $J_{F,5}$ = 26.4 Hz, $J_{F,6}$ = 47.5 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{29}FO_5$ + Na: 475.1891; found: 475.1899.

2,3,4-Tri-*O*-benzyl-6-deoxy-6-fluoro-D-glucono-1,5-lactone (19)

To a solution of **18** (300 mg, 663 μmoL) in anhyd DMSO (4 mL) was added Ac_2O (1.4 mL) at 30 °C. The reaction mixture was stirred for 24 h at 30 °C and then diluted with H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (PE–Et_2O, 1:1) to give **19** as a colorless solid; yield: 254 mg (86%); mp 71–72 °C; $[\alpha]_D^{25}$ +72.1 (*c* 1.00, $CHCl_3$); R_f = 0.38 (PE–Et_2O, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.42–7.26 (m, 15 H, H-Ar), 4.87 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.75–4.62 (m, 7 H, H-5, H-6, CH_2Ph), 4.59 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.41 (d, $J_{2,3}$ = 5.7 Hz, 1 H, H-2), 4.09 (dd, $J_{3,2}$ = 5.7 Hz, $J_{3,4}$ = 6.3 Hz, 1 H, H-3), 3.86 (dd, $J_{4,3}$ = 6.3 Hz, $J_{4,5}$ = 8.6 Hz, 1 H, H-4).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.6 (C-1), 137.1, 137.5, 137.4 (Cq-Ar), 128.3, 128.3, 127.9, 127.8, 127.8, 127.7 (CH-Ar), 81.4 ($J_{C,F}$ = 171.0 Hz, C-6), 79.3 (C-3), 77.4 (C-2), 76.7 ($J_{C,F}$ = 18.3 Hz, C-5), 76.6 ($J_{C,F}$ = 6.1 Hz, C-4), 72.8, 72.5, 72.4 (*C*H_2Ph).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –230.2 (td, $J_{F,5}$ = 26.4 Hz, $J_{F,6}$ = 47.7 Hz).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{27}FO_5$: 451.1915; found: 451.1928; [M + Na]$^+$ 473.1735; found: 473.1750.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-1,7-dideoxy-7-fluoro-D-gluco-hept-1-enitol (20)

The lactone **19** (214 mg, 472 μmol) and Me_2TiCp_2 (220 mg, 1.06 mmol) were dissolved in anhyd toluene (20 mL) under an argon atmosphere and heated to 75 °C. The reaction mixture was stirred for 24 h at 75 °C and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (PE–Et_2O + 0.5% Et_3N, 5:1) to give **20** as a colorless solid; yield: 169 mg (80%), mp 76–78 °C; $[\alpha]_D^{25}$ +44.07 (*c* 0.26, $CHCl_3$); R_f = 0.36 (PE–Et_2O 5:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.40–7.23 (m, 15 H, H-Ar), 4.73 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.68 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.67 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.67–4.54 (m, 4 H, H-1a, H-7, CH_2Ph), 4.57 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.53 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.47 (s, 1 H, H-1b), 4.11 (d, $J_{3,4}$ = 4.9 Hz, 1 H, H-3), 4.03 (dddd, $J_{6,7a}$ = 2.1 Hz, $J_{6,7b}$ = 4.7 Hz, $J_{6,5}$ = 10.2 Hz, $J_{6,F}$ = 27.4 Hz, 1 H, H-6), 3.78 (dd, $J_{4,3}$ = 4.9 Hz, $J_{4,5}$ = 6.0 Hz, 1 H, H-4), 3.59 (dd, $J_{5,4}$ = 6.0 Hz, $J_{5,6}$ = 10.2 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.5 (C-2), 137.9, 137.8, 137.7 (Cq-Ar), 128.3, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6 (CH-Ar), 93.8 (C-1), 82.0 ($J_{C,F}$ = 170.9 Hz, C-7), 81.9 (C-4), 77.0 (C-3), 76.2 ($J_{C,F}$ = 6.5 Hz, C-5), 75.0 ($J_{C,F}$ = 17.6 Hz, C-6), 72.5, 72.0, 70.8 (*C*H_2Ph).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –232.4 (dd, $J_{F,6}$ = 27.4 Hz, $J_{F,7}$ = 47.9 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{29}FO_4$ + Na: 471.1942; found: 471.1449.

3,4,5-Tri-*O*-benzyl-7-deoxy-7-fluoro-α-D-*gluco*-hept-2-ulopyranose (21)

The synthesis was carried out according to GP 3 with **20** (80 mg, 178 μmol), *t*-BuOH–H_2O (5 mL), K_2CO_3 (80 mg, 579 μmol), $K_3[Fe(CN)_6]$ (180 mg, 546 μmol), and catalytic amount of $K_2OsO_2(OH)_4$. The reaction mixture was stirred at r.t. for 24 h. After workup, the crude product was purified by column chromatography to give **21** as a colorless solid; yield: 78 mg (91%); mp 110–111 °C; $[\alpha]_D^{25}$ –5.2 (*c* 0.25, $CHCl_3$); R_f = 0.48 (Et_2O).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.42–7.22 (m, 15 H, H-Ar), 5.97 (s, 1 H, OH), 4.96 (dd, $J_{OH,1b}$ = 5.3 Hz, $J_{OH,1a}$ = 6.7 Hz, 1 H, OH), 4.83 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.81–4.77 (m, 2 H, CH_2Ph), 4.75 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.68 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.57 (d, J = 11.2 Hz, 1 H, CH_2Ph), 4.60 (ddd, $J_{7a,6}$ = 4.1 Hz, $J_{7a,7b}$ = 10.4 Hz, $J_{7a,F}$ = 47.3 Hz, 1 H, H-7a), 4.51 (ddd, $J_{7b,6}$ = 1.1 Hz, $J_{7b,7a}$ = 10.4 Hz, $J_{7b,F}$ = 47.3 Hz, 1 H, H-7b), 3.93 (dd, $J_{4,5}$ = 9.3 Hz, $J_{4,3}$ = 9.6 Hz, 1 H, H-4), 3.89 (dddd, $J_{6,7b}$ = 1.1 Hz, $J_{6,7a}$ = 4.1 Hz, $J_{6,5}$ = 10.0 Hz, $J_{6,F}$ = 28.7 Hz, 1 H, H-6), 3.59 (d, $J_{3,4}$ = 9.6 Hz, 1 H, H-3), 3.51 (dd, $J_{1a,OH}$ = 6.7 Hz, $J_{1a,1b}$ = 11.3 Hz, 1 H, H-1a), 3.42 (dd, $J_{5,4}$ = 9.3 Hz, $J_{5,6}$ = 10.0 Hz, 1 H, H-5), 3.39 (dd, $J_{1b,OH}$ = 5.3 Hz, $J_{1b,1a}$ = 11.3 Hz, 1 H, H-1b).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 138.1, 138.7, 138.2 (Cq-Ar), 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.4 (CH-Ar), 98.0 (C-2), 82.5 ($J_{C,F}$ = 170.7 Hz, C-7), 82.4 (C-4), 78.7 (C-3), 77.3 ($J_{C,F}$ = 6.4 Hz, C-5), 74.4, 74.2, 73.9 (*C*H_2Ph), 69.9 ($J_{C,F}$ = 17.4 Hz, C-6), 63.4 (C-1).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –230.0 (td, $J_{F,6}$ = 28.7 Hz, $J_{F,7}$ = 47.3 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{31}FO_6$ + Na: 505.1997; found: 505.2009.

7-Deoxy-7-fluoro-α-D-*gluco*-hept-2-ulopyranose (22)

The synthesis was carried out according to GP 2 with **21** (60 mg, 124 μmol), MeOH–EtOAc (4 mL), and a catalytic amount of 20% $Pd(OH)_2$/C. The crude residue was purified by column chromatography to give **22** as a colorless syrup; yield: 24 mg (94%); $[\alpha]_D^{25}$ +39.5 (*c* 0.80, H_2O).

^{1}H NMR (400 MHz, D_2O): δ = 4.75 (ddd, $J_{7a,6}$ = 3.7 Hz, $J_{7a,7b}$ = 10.7 Hz, $J_{7a,F}$ = 47.4 Hz, 1 H, H-7a), 4.68 (ddd, $J_{7b,6}$ = 1.7 Hz, $J_{7b,7a}$ = 10.6 Hz, $J_{7b,F}$ = 47.4 Hz, 1 H, H-7b), 3.93 (dddd, $J_{6,7a}$ = 1.7 Hz, $J_{6,7b}$ = 3.7 Hz, $J_{6,5}$ = 10.0 Hz, $J_{6,F}$ = 28.8 Hz, 1 H, H-6), 3.77 (dd, $J_{4,5}$ = 9.6 Hz, $J_{4,3}$ = 9.6 Hz, 1 H, H-4), 3.72 (d, $J_{1a,1b}$ = 11.8 Hz, 1 H, H-1a), 3.57 (d, $J_{1b,1a}$ = 11.8 Hz, 1 H, H-1b), 3.53 (d, $J_{3,4}$ = 9.6 Hz, 1 H, H-3), 3.52 (dd, $J_{5,4}$ = 9.6 Hz, $J_{5,6}$ = 10.0 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, D_2O): δ = 97.8 (C-2), 82.7 ($J_{C,F}$ = 166.9 Hz, C-7), 73.5 (C-4), 71.3 ($J_{C,F}$ = 17.4 Hz, C-6), 70.6 (C-3), 68.7 ($J_{C,F}$ = 6.9 Hz, C-5), 63.8 (C-1).

^{19}F NMR (188 MHz, D_2O): δ = –234.8 (td, $J_{F,6}$ = 28.8 Hz, $J_{F,7}$ = 47.4 Hz).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_7H_{13}FO_6$ + Na: 235.0588; found: 235.0597.

3,4,5-Tri-*O*-benzyl-1,7-deoxy-1,7-difluoro-α-D-*gluco*-hept-2-ulopyranose (23)

The synthesis was carried out according to GP 1 with **20** (80 mg, 178 μmol), DMF–H_2O (4 mL), and Selectfluor (630 mg, 1.78 μmol). After workup, the crude residue was purified by column chromatography (PE–Et_2O, 1:1) to give **23** as a colorless oil; yield: 64 mg (74%); mp 85–86 °C; $[\alpha]_D^{25}$ +12.7 (*c* 0.36, $CHCl_3$); R_f = 0.29 (PE–Et_2O, 1:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.40–7.23 (m, 15 H, H-Ar), 6.61 (s, 1 H, OH), 4.85–4.76 (m, 4 H, CH_2Ph), 4.61 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.60 (ddd, $J_{7a,6}$ = 3.9 Hz, $J_{7a,7b}$ = 10.5 Hz, $J_{7a,F}$ = 48.2 Hz, 1 H, H-7a), 4.59 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.53 (ddd, $J_{7b,6}$ = 1.1 Hz, $J_{7b,7a}$ = 10.5 Hz, $J_{7b,F}$ = 48.2 Hz, 1 H, H-7b), 4.35 (dd, $J_{1a,1b}$ = 9.5 Hz, $J_{1a,F}$ = 47.7 Hz, 1 H, H-1a), 4.23 (dd, $J_{1b,1a}$ = 9.5 Hz, $J_{1b,F}$ = 47.7 Hz, 1 H, H-1b), 3.98 (dd, $J_{4,5}$ = 9.3 Hz, $J_{4,3}$ = 9.5 Hz, 1 H, H-4), 3.91 (ddd, $J_{6,7a}$ = 3.9 Hz, $J_{6,5}$ = 9.8 Hz, $J_{6,F}$ = 28.8 Hz, 1 H, H-6), 3.50 (d, $J_{3,4}$ = 9.5 Hz, 1 H, H-3), 3.49 (dd, $J_{5,4}$ = 9.3 Hz, $J_{5,6}$ = 9.8 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 138.5, 138.1, 138.0 (Cq-Ar), 128.3, 128.2, 128.2, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4 (CH-Ar), 95.9 ($J_{C,F}$ = 18.4 Hz, C-2), 83.4 ($J_{C,F}$ = 178.2 Hz, C-1), 83.2 ($J_{C,F}$ = 171.2 Hz, C-7), 82.0 (C-4), 78.5 (C-3), 77.1 ($J_{C,F}$ = 6.2 Hz, C-5), 74.5, 74.4, 73.0 (*C*H_2Ph), 70.1 ($J_{C,F}$ = 17.6 Hz, C-6).

^{19}F NMR (188 MHz, DMSO-d_6): δ = –226.6 (t, $J_{F,1}$ = 47.7 Hz), –230.9 (td, $J_{F,6}$ = 28.8 Hz, $J_{F,7}$ = 48.2 Hz).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{28}H_{30}F_2O_5$: 507.1954; found: 507.1954.

1,7-Deoxy-1,7-difluoro-α-D-*gluco*-hept-2-ulopyranose (24)

The synthesis was carried out according to GP 2 with **23** (50 mg, 103 μmol), MeOH–EtOAc (4 mL), and a catalytic amount of 20% $Pd(OH)_2$/C. The crude residue was purified by column chromatography to give **24** as a colorless syrup; yield: 20 mg (95%); $[\alpha]_D^{25}$ +37.5 (*c* 0.55, H_2O).

^{1}H NMR (400 MHz, D_2O): δ = 4.80 (ddd, $J_{7a,6}$ = 3.7 Hz, $J_{7a,7b}$ = 10.9 Hz, $J_{7a,F}$ = 47.4 Hz, 1 H, H-7a), 4.71 (ddd, $J_{7b,6}$ = 1.7 Hz, $J_{7b,7a}$ = 10.9 Hz, $J_{7b,F}$ = 47.4 Hz, 1 H, H-7b), 4.58 (dd, $J_{1a,1b}$ = 9.9 Hz, $J_{1a,F}$ = 46.6 Hz, 1 H, H-1a), 4.42 (dd, $J_{1b,1a}$ = 9.9 Hz, $J_{1b,F}$ = 46.6 Hz, 1 H, H-1b), 4.03 (dddd, $J_{6,7b}$ = 1.7 Hz, $J_{6,7a}$ = 3.7 Hz, $J_{6,5}$ = 10.3 Hz, $J_{6,F}$ = 28.7 Hz, 1 H, H-6), 3.83 (dd, $J_{4,5}$ = 9.4 Hz, $J_{4,3}$ = 9.6 Hz, 1 H, H-4), 3.59 (d, $J_{3,4}$ = 9.6 Hz, 1 H, H-3), 3.58 (dd, $J_{5,4}$ = 9.4 Hz, $J_{5,6}$ = 10.3 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, D_2O): δ = 95.9 ($J_{C,F}$ = 17.6 Hz, C-2), 82.8 ($J_{C,F}$ = 175.75 Hz, C-1), 82.2 ($J_{C,F}$ = 168.0 Hz, C-7), 73.2 (C-4), 71.4 ($J_{C,F}$ = 17.6 Hz, C-6), 70.1 (C-3), 68.4 ($J_{C,F}$ = 7.0 Hz, C-5).

^{19}F NMR (188 MHz, D_2O): δ = –231.6 (t, $J_{F,1}$ = 46.6 Hz), –235.3 (td, $J_{F,6}$ = 28.7 Hz, $J_{F,7}$ = 47.4 Hz).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_7H_{12}F_2O_5$: 215.0726; found: 215.1266.

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