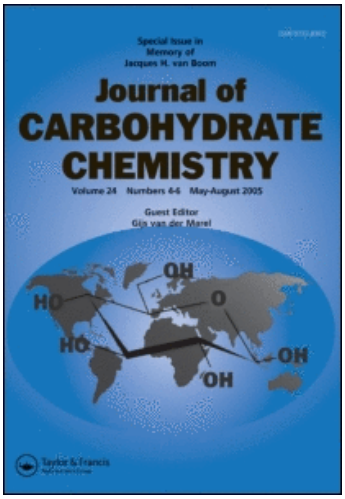

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Synthesis of 3-Fluoro-Oxetane δ-Amino Acids

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Starting from D-xylose, 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonic acid **11** was synthesized over 10 steps including ring contraction, fluorination, and ester hydrolysis. Bromine oxidation of D-xylose followed by benzylidenation in a one-pot procedure led to a ca. 1:1 mixture of lactone **3** and 2,4;3,5-dibenzylidene xylonic acid (**4**) as by-product. For the synthesis of the D-*xylo* derivative **24**, the chosen starting material was 1,2-*O*-isopropylidene-α-D-xylofuranose. A total of 14 steps including epimerization, ring contraction, fluorination, and saponification led to the desired fluoro-oxetane δ-amino acid **24**. Hydrolysis of the 3-fluoro-oxetane δ-amino esters **10** and **23** by means of LiOH was successful in agreement with the results previously reported for similar 3-methoxy oxetanes, whereas chemical hydrolysis was not possible for 3-hydroxy derivatives.

Keywords Carbohydrate amino acids; δ-Amino acids; Oxetanes; Carbohydrate scaffolds

INTRODUCTION

Oxetane δ-amino acids (Fig. 1) are useful chiral scaffolds that can be synthesized from carbohydrates.[1] The four-membered rings present little flexibility and exhibit well-defined exit vectors orienting the substituents in space. Few contributions were made on the synthesis of oxetane amino acids,[1,2] and the Fleet group has also investigated the conformational behavior of oxetane-based oligomers.[3] Carbohydrate amino acids with pyranose and furanose forms have already shown high potential as rigid templates to induce specific

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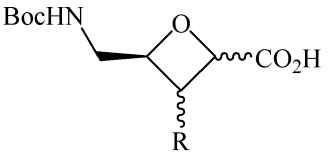

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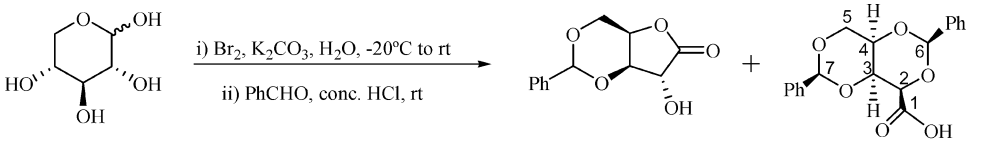
Figure 1: Structure of oxetane δ-amino acids.

conformations in peptide mimetics[4] to construct oligomeric carbohydrate-peptide hybrids[5] and are useful scaffolds for parallel chemistry purposes.[6]

In the present work we report the synthesis of oxetane δ-amino acids **1** with different configurations containing a fluoride substituent at C-3. It has been well recognized that the presence of fluorine can induce favorable properties in bioactive compounds. In medicinal chemistry approaches, fluorine is frequently introduced to improve the metabolic stability by blocking metabolically labile sites. Fluorine can also be used to modulate physicochemical properties such as lipophilicity or basicity. It may exert a substantial effect on the conformation of a molecule and is being used to enhance the binding affinity to target proteins.[7]

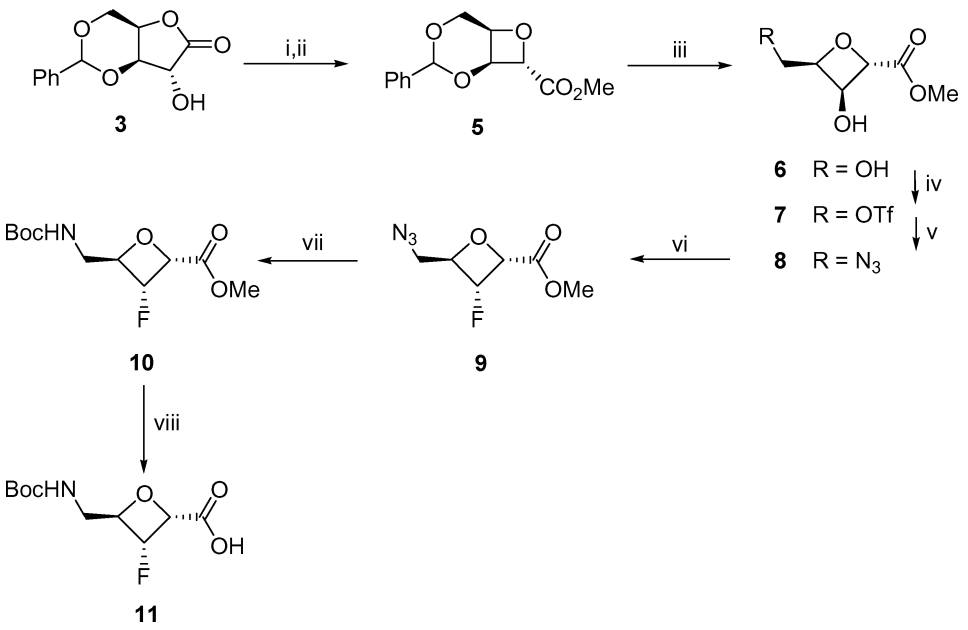
RESULTS AND DISCUSSION

Starting from D-xylose (**2**), we made use of a straightforward anomeric oxidation and benzylidene protection previously reported by Fleet's group[2b] to furnish the 1,4-xylonolactone **3** (Scheme 1). Although the yields were reported to be in the range of 50%, we could only reach 39% but were able to identify a by-product formed in considerable amount (37%). MS, ^{1}H-NMR, and IR spectroscopy allowed us to assign the structure of this compound as that of the known 2,4;3,5-dibenzylidene xylonic acid (**4**).[8] NMR assignments were based on 1D ^{1}H NMR, 2D COSY, 2D HSQC, 2D HMBC, and 2D NOESY experiments. From a 2D NOESY experiment, cross-peaks between H-7/H-3, H-7/H-5a, H-3/H-5a and H-6/H-2, H-6/H-4, H-2/H-4 were observed, which proved the expected conformation of **4** as a *cis*-decalin system.



2 **3** 39% **4** 37%

Scheme 1: One-pot anomeric oxidation of D-xylose and benzylidene protection.



Scheme 2: (i) Tf_2O, DCM, Py, −30°C, 1 h; (ii) K_2CO_3, MeOH, −12°C, 4 h, 65% (2 steps); (iii) H_2, Pd/C, MeOH/dioxane 1:1, rt, 2 h, 87%; (iv) Tf_2O, Et_2O/DCM 5:1, 4 Å molecular sieves, −15°C, 50 min; (v) NaN_3, acetone, rt, 2 h, 72% (2 steps); (vi) DAST, MeCN, −20°C to reflux, 1 h, 75%; (vii) H_2, Pd/C, EtOAc, Boc_2O, rt, 2 h, 85%; (viii) LiOH 1N, HCl 1N, 0–5°C, 1 h, 97%.

The 1,4-lactone **3** was submitted to ring contraction using the methodology described by Witty et al.,[9] and triflation of the starting lactone was followed by treatment with potassium carbonate, leading to the benzylidene-protected oxetane **5**[2b] in 65% yield (Sch. 2). Deprotection was accomplished by catalytic hydrogenation to afford the known diol **6**[1a,2b] in 87% yield. This compound was reacted further to compound **7**[1a] by nonbasic triflation,[10] followed by selective introduction of a primary azide by means of sodium azide to furnish the intermediate **8**.[1a]

The oxetane derivative **8** containing a free hydroxyl group was the key intermediate for the fluorine introduction at C-3. The first attempt to substitute the hydroxyl group by fluoride made use of the standard reaction with diethylaminosulfur trifluoride (DAST) in dichloromethane. However, reaction either at room temperature or under reflux conditions gave the desired fluoro derivative **9** in poor yield. Theoretical studies on fluorination reaction by DAST indicate that the formation of fluoride ions is endoenergetic when the reaction takes place in solvents with low dielectric constants such as dichloromethane.[11] In addition, fluoride ion formation may be facilitated by the presence of pyridine; however, in this case it did not lead to any improvement in the yield of **9**. The reaction was then carried out using acetonitrile as solvent, and the best results were obtained when DAST was added at −20°C

and the mixture was warmed up to reach reflux conditions to afford the desired fluoro derivative **9** in 75% yield.

One-pot reduction of azide **9** in the presence of *tert*-butoxycarbonyl anhydride furnished the protected amine **10** in a good yield. Saponification by means of LiOH was a clean reaction and gave the desired oxetane δ-amino acid **11** in 97% yield. This result is in keeping with the one obtained for the hydrolysis of methyl esters in 3-methoxy oxetane derivatives,[1b] whereas for a 3-hydroxy oxetane derivative this reaction was not successful by chemical approaches.[1a]

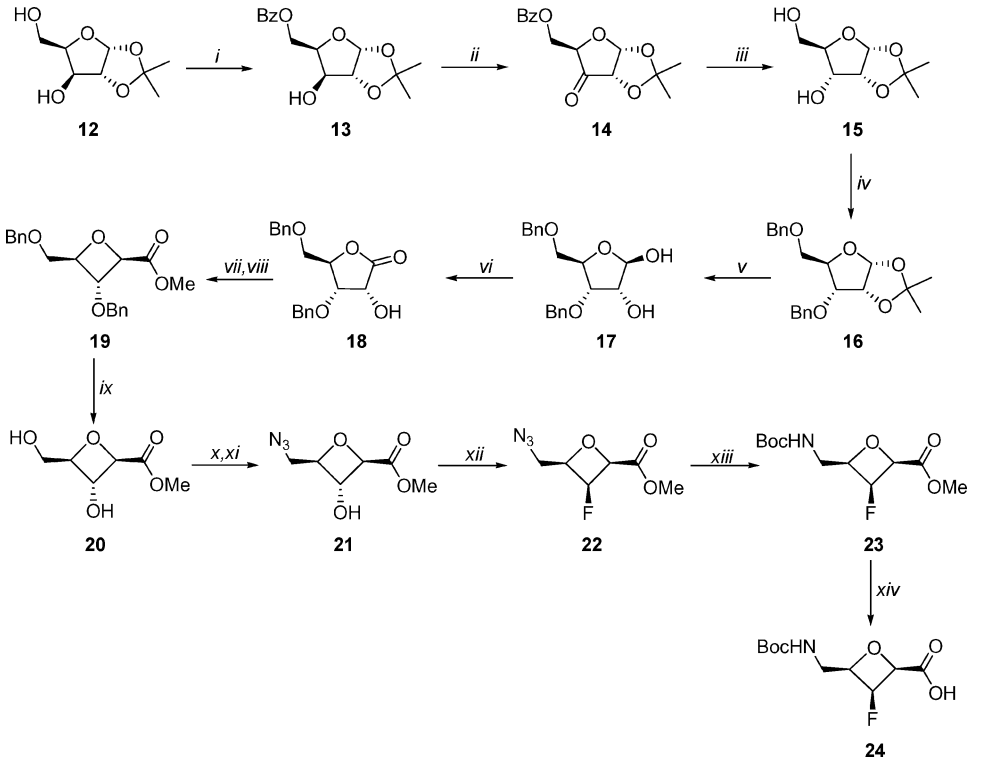
With respect to structural assignments, the characteristic couplings of the fluorine atom with the geminal and vicinal protons were observed; the H-3 signal for **9** is a ddd at δ 5.53 ppm with a characteristic $J_{3,F}$ of 56.1 Hz. The signals for H-2 and H-4 exhibit coupling constants with the fluorine of 15.2 Hz and 19.1 Hz, respectively. The coupling constants of *trans*- and *cis*-oriented vicinal protons in the obtained D-*arabino* configured oxetanes were in agreement with the characteristic range of values observed for similar oxetane systems.[1b]

In view of the synthesis of oxetanes with D-*xylo* configuration we targeted the benzyl protected D-ribono-1,4-lactone **18**[9] (Sch. 3) as an intermediate for the ring contraction step. Selective protection of the primary alcohol of commercial 1,2-*O*-isopropylidene-α-D-xylofuranose (**12**) yielded the benzoate **13**.[14] The well-established PDC oxidation giving **14** was followed by $NaBH_4$ reduction to achieve the required inversion of configuration at C-3 together with benzoyl cleavage and afforded 1,2-*O*-isopropylidene-α-D-ribofuranose (**15**) in good yield. Benzylation of the diol **15** gave **16**, and isopropylidene hydrolysis led, in this case, to the β-anomer **17**, which was further oxidized with bromine to give the desired α-hydroxy lactone **18**[9] in 79% yield.

For the synthesis of the oxetane δ-azido ester **21**, the best yields were obtained when the crude lactone **18** was reacted. Ring contraction was achieved by triflation and treatment with K_2CO_3 in methanol. The resulting crude **19**[9] was hydrogenated to yield the diol **20**. Triflation of this product using the non-basic procedure was not possible due to the low solubility of the diol **20** in CH_2Cl_2. Hence, triflation was performed with triflic anhydride in CH_2Cl_2 and in the presence of pyridine. After reaction with sodium azide in acetone, the desired compound **21** was obtained in a 53% overall yield from the lactone **18**. An alternative synthesis of **20** using a longer synthetic scheme starting from diacetone glucose was previously reported.[12]

In the first attempt to synthesize the fluoro derivative **22**, the azide **21** was reacted with DAST in MeCN at -20°C. After workup and flash chromatography, the MS of the product fractions suggested the presence of the intermediate **25** (Sch. 4) in agreement with Tewson and Welch's[13] proposal for DAST reactions.

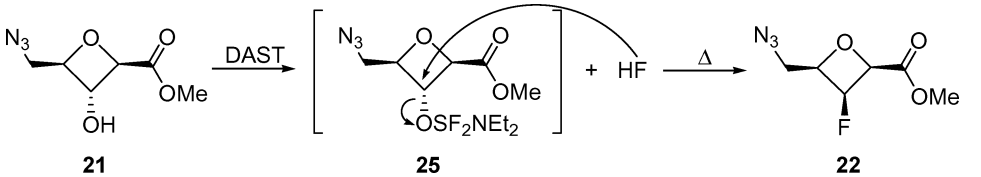
The introduction of the fluorine atom in **22** will encounter some steric hindrance as all substituents are located on the same side of the oxetane ring.



Scheme 3: (*i*) BzCl, Et_3N, DCM, 0–5°C, 1.5 h, 90%; (*ii*) PDC, Ac_2O, DCM, reflux, 2.5 h, 83%; (*iii*) $NaBH_4$, EtOH/H_2O 7:1, rt, overnight, 89%; (*iv*) (a) NaH, DMF, rt, 2 h, (b) BnBr, DMF, rt, 2 h, 90%; (*v*) AcOH (30%, aq.), reflux, 2 h, 91%; (*vi*) Br_2, $BaCO_3$, dioxane/H_2O 1:2, rt, 3 h, 79%; (*vii*) Tf_2O, DCM, py, −30 to −10°C, 15 min; (*viii*) K_2CO_3, MeOH, −12°C, 1 h; (*ix*) H_2, Pd/C 10%, MeOH/dioxane 1:1, rt, 2 h; (*x*) Tf_2O, DCM, py, −30°C; (*xi*) NaN_3, acetone, rt, overnight, 53% from **18**; (*xii*) DAST, Py, MeCN, −20°C, 1.5 h, then 50°C, 3 h; (*xiii*) H_2, Pd/C, EtOAc, Boc_2O, rt, 1.5 h, 52% over 2 steps; (*xiv*) LiOH 1N, HCl 1N, 0–5°C, 30 min, 97%.

The intermediate **25** was therefore heated to 50°C to afford the desired product **22**. In this case it was shown that addition of 1 eq of pyridine improved the reaction rate.

Compound **22** is volatile, and the best results were obtained when no purification was performed, so that after DAST reaction and workup the crude



Scheme 4: Fluorination of **21** by DAST reagent.

22 was further hydrogenated in the presence of *tert*-butoxycarbonyl anhydride to achieve the protected amine **23** (Sch. 3) in 52% yield over the two steps.

In agreement with the results for the saponification of the fluoro derivative **10**, treatment of **23** with 1 N LiOH led to the δ-amino acid **24** in an excellent yield of 97%.

In conclusion, the two diastereomeric fluorinated oxetane δ-amino acids **11** and **24** were synthesized in good overall yield. These scaffolds will be used for the generation of various compound libraries.

EXPERIMENTAL

General Methods

Solvents and reagents were bought from Fluka, Merck, Aldrich, or Acros Organics. The DAST reagent supplied by Acros Organics was used. Solutions were concentrated below 50°C in vacuo on Büchi rotary evaporators. Qualitative TLC was performed on precoated silica gel 60F-254 plates (Merck); compounds were detected by UV light (254 nm) and spraying with a 10% solution of conc. sulfuric acid in methanol or with a cerium sulfate aqueous solution, followed by heating. Column chromatography was carried out on silica gel (63–200, 60) from Chemie Brunschwig or 60G (0.040–0.063 mm) from Merck. Melting points were determined with an Electrothermal 9100 or Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 spectrometer in a 1-dm cell at given temperatures, either at Faculdade de Ciências da Universidade de Lisboa (FCUL) or at F. Hoffmann-La Roche Ltd. NMR spectra were recorded on Bruker spectrometers: Avance 300 (300 MHz for ^{1}H NMR) or AM 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) at F. Hoffmann-La Roche Ltd., and Avance 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) at FCUL. Chemical shifts are given in ppm relative to tetramethylsilane. Mass spectra were recorded on API III Sciex, Perkin Elmer for negative (ISN) and positive (ISP) electrospray ionization. High-resolution mass spectra were recorded on a Finnigan LTQ FT from Thermo for positive (ESI) and negative (NSI) electrospray ionization at F. Hoffmann-La Roche Ltd. Elemental analyses were performed by Solvias AG, Basel, Switzerland. Known compounds have the following CAS registry numbers: **4** [20603-35-4], **5** [131550-06-6], **6** [134651-25-5], 7 [908608-59-3], **8** [807617-89-6], **13** [6022-96-4], **14** [6698-46-0], **15** [37077-81-9], **18** [131139-05-4], **19** [131139], **20** [134651-21-1].

3,5-*O*-Benzylidene-D-xylono-1,4-lactone (3)[2b] and 2,4;3,5-Di-*O*-benzylidene-D-xylonic Acid (4)[8]

A solution of D-xylose (20.0 g, 0.13 mol) in water (54 mL) was cooled in an ice water bath. Potassium carbonate (22.6 g, 0.16 mol) was added in portions

while keeping the temperature below 20°C. The mixture was cooled to 5°C, and bromine (8 mL, 0.15 mol) was added dropwise over 45 min while keeping the temperature below 10°C. The resulting orange solution was stirred at 10°C for 30 min and then at rt overnight, when one major product was observed. The reaction was quenched by careful addition of 88% formic acid (1.66 mL) until the solution became colorless. The solution was concentrated at 50°C, and acetic acid (13.4 mL) was added. The reaction mixture was concentrated at 50°C to remove any residual water. The crude xylono-1,4-lactone was used without purification.

To a solution of the crude lactone (assumed 19.7 g, 0.13 mol) in benzaldehyde (200 mL) was added conc. HCl (15 mL). The reaction was stirred at rt overnight to give two different products identified by TLC (EtOAc/cyclohexane 1:1). The mixture was concentrated under high vacuum to a quarter volume. Diethyl ether (80 mL) was added, and a precipitate formed. The mixture was filtered, and the residue was washed with ether. The filtrate was concentrated and chromatographed (1:3 EtOAc/cyclohexane) to give the desired benzylidene protected lactone **3** as a colorless solid (12.0 g, 51 mmol, 39%). The solid residue of the filtration was then washed with acetone to separate the by-product from the residual salts. The filtrate was concentrated, and the by-product recrystallized from acetone/*n*-hexane to give compound **4** as a colorless solid (16.5 g, 48 mmol, 37%).

Data for **3**: $[\alpha]_D^{20}$ +11.2 (*c* 1.00, CH_2Cl_2). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ 7.46–7.44 (m, 2H, Ph), 7.38–7.36 (m, 3H, Ph) 5.54 (s, 1H, CHPh), 4.59–4.53 (m, 3H, H-2, H-4, H-5a), 4.32 (br s, 1H, H-3), 4.19 (B(ABX), 1H, $J_{4,5b} = 1.8$ Hz, $J_{5a,5b} = 13.5$ Hz, H-5b), 3.41 (br s, 1H, OH).

Data for **4**: $[\alpha]_D^{20}$ −18.6 (*c* 1.00, DMF), lit.[8]: $[\alpha]_D^{20}$ −21.13 (*c* 1.05, DMF). m.p. 202.2–203.0°C, lit.[8]: 198.5–200.0°C. MS(ionspray): 343.1 $[M+H]^+$, 360.4 $[M+NH_4]^+$, 365.1 $[M+Na]^+$. ^{1}H NMR (400 MHz, DMSO; COSY, NOESY): δ 12.90 (s, 1H, COOH), 7.52–7.50 (m, 2H, Ph), 7.44–7.35 (m, 8H, Ph), 5.75 (s, 1H, C*Ha*HbPh), 5.69 (s, 1H, CHa*Hb*Ph), 4.78 (d, 1H, $J_{2,3} = 2.1$ Hz, H-2), 4.37 (br t, 1H, $J_{2,3} \approx J_{3,4} \approx 1.8$ Hz, H-3), 4.21 (A(ABX), 1H, $J_{4,5a} = 1.8$ Hz, $J_{5a,5b} = 12.8$ Hz, H-5a), 4.16 (B(ABX), 1H, $J_{4,5b} = 1.3$ Hz, H-5b), 4.04 (br q, 1H, H-4). ^{13}C NMR (100 MHz, DMSO; HSQC, HMBC): δ 169.28 (COOH), 138.78 (Ph), 138.43 (Ph), 129.37 (Ph), 129.21 (Ph), 128.50 (Ph), 128.47 (Ph), 126.92 (Ph), 126.58 (Ph), 99.5 (*C*HaPh), 99.9 (*C*HbPh), 76.63 (C-2), 70.55 (C-3), 69.87 (C-4), 69.51 (C-5). IR (cm^{-1}): 2580–2620 (COOH), 1738 (C = O(COOH)), 1608 and 1498 (aromatic), 1097 (COC), 763 and 700 (Ph, monosubstituted).

Methyl 2,4-anhydro-3,5-O-benzylidene-D-lyxonate (5)[2b]

To a solution of the starting 3,5-*O*-benzylidene-D-xylono-1,4-lactone **4** (11.9 g, 50.4 mmol) in CH_2Cl_2 (250 mL) and pyridine (7.3 mL, 1.8 eq) was added dropwise at −30°C trifluoromethanesulfonic anhydride (10.2 mL, 1.2 eq).

After 1 h the reaction mixture was diluted with CH_2Cl_2 and washed with saturated solution of $NaHCO_3$ and then with 1N HCl. After drying with $MgSO_4$ and filtration and evaporation of the solvent, the crude 3,5-*O*-benzylidene-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone was immediately used for the next reaction step without further purification. To a solution of triflated lactone in absolute MeOH (420 mL) at -12°C was added potassium carbonate (6.9 g, 1 eq). The resulting suspension was stirred over 4 h, and the reaction mixture was filtered over Celite. The filtrate was concentrated and chromatographed (EtOAc/cyclohexane 1:3) to furnish pure oxetane **5** (8.17 g, 32.7 mmol, 65% yield) as a colorless solid. $[\alpha]_D^{20} = -3.2$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.29 (m, 5H, Ph), 5.42 (s, 1H, C*H*Ph), 4.99 (d, 1H, $J_{2,3} = 2.2$ Hz, H-2), 4.92 (dd, 1H, $J_{3,4} = 5.1$ Hz, H-3), 4.89 (dd, 1H, $J_{4,5a} = 0$ Hz, $J_{4,5b}$ 2.5 Hz, H-4), 4.30 (d, 1H, $J_{5a,5b} = 14.0$ Hz, H-5a), 3.99 (dd, 1H, H-5b), 3.94 (s, 3H, OMe).

Methyl 2,4-Anhydro-5-azido-5-deoxy-3-fluoro-D-arabinonate (9)

To a solution of **8**[1a] (500 mg, 2.7 mmol) in acetonitrile (40 mL) at -20°C was added DAST (1.0 mL, 8.1 mmol), and the mixture was stirred for 20 min. The temperature was then raised to reflux temperature over 1 h. After concentration, the mixture was dissolved in CH_2Cl_2 (50 mL) and washed with a saturated solution of $NaHCO_3$ (30 mL). After drying over $MgSO_4$ and filtration and concentration, the residue obtained was chromatographed (EtOAc/cyclohexane 1:4) to yield the desired fluoro derivative as a colorless oil (383 mg, 2.02 mmol, 75%). $[\alpha]_D^{20}$ +61 (*c* 1.00, CH_2Cl_2). MS: *m*/*z* 190.3 $[M+H]^+$, 212.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.53 (ddd, 1H, $J_{2,3} = 6.7$ Hz, $J_{3,4} = 4.5$ Hz, $J_{3,F} = 56.1$ Hz, H-3), 5.23 (ddd, 1H, $J_{2,4} = 1.1$ Hz, $J_{2,F} = 15.2$ Hz, H-2), 5.14 (dddd, 1H, $J_{4,5a} = 3.4$ Hz, $J_{4,5b} = 3.0$ Hz, $J_{4,F} = 19.1$ Hz, H-4), 3.89 (s, 3H, OMe), 3.72 (A(ABX), 1H, $J_{5a,5b} = 14.2$ Hz, H-5a) 3.48 (B(ABX), 1H, H-5b). Anal. Calcd. for $C_6H_8FN_3O_3$ (189.15): C, 38.10; H, 4.26; N, 22.22. Found: C, 38.38; H, 4.32; N, 21.98.

Methyl 2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonate (10)

To a 0.12 M solution of azide **9** (1.14 g, 6.0 mmol) in EtOAc was added Pd/C (10% m/m), and the suspension was stirred vigorously for 30 min under an atmosphere of hydrogen. A 0.12 M solution of Boc_2O in EtOAc (52.5 mL, 1.05 eq) was then added, and the reaction mixture was stirred at rt under H_2 atmosphere for 2 h. The catalyst was removed by filtration, and the solvent was evaporated. Chromatography (EtOAc/cyclohexane 1:2) of the obtained residue gave the pure product **10** (1.35 g, 5.1 mmol, 85%) as a colorless oil. $[\alpha]_D^{20}$ +42 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (ddd, 1H, $J_{2,3} = 6.8$ Hz,

$J_{3,4}$ = 4.8 Hz, $J_{3,F}$ = 56.0 Hz, H-3), 5.13 (ddd, 1H, $J_{2,F}$ = 14.8 Hz, H-2), 5.03 (dddd, 2H, $J_{4,5a}$ = 3.4 Hz, $J_{4,5b}$ = 3.0 Hz, $J_{4,F}$ = 19.1 Hz, H-4), 4.93 (br s, 1H, NH), 3.86 (s, 3H, OMe), 3.58 (dd, 1H, $J_{4,5a}$ = 4.4 Hz, $J_{5a,5b}$ = 14.8 Hz, $J_{5a,NH}$ = 7.2 Hz, H-5a), 3.41 (ddd, 1H, $J_{5b,NH}$ = 4.7 Hz, $J_{5a,5b}$ = 14.8 Hz, H-5b), 1.46 (s, 9H, Boc). Anal. Calcd. for $C_{11}H_{18}FNO_5$ (263.27): C, 50.19; H, 6.89; N, 5.32. Found: C, 49.96; H, 6.74; N, 5.35.

2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonic Acid (11)

To a 0.06 M solution of ester **10** (1.5 g, 5.7 mmol) in THF was added 1N aqueous LiOH (3 eq) at 0–5°C, and the mixture was stirred for 1 h. Then, maintaining the temperature range, 1N HCl (3 eq) was added, and the mixture was stirred for 30 min. Brine was added, and the product was extracted three times with *tert*-butylmethyl ether. The organic layers were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated to give the product **11** as a colorless hygroscopic foam (1.38 g, 5.54 mmol, 97%). MS (ionspray neg.): m/z 248.3 $[M\text{-}H]^-$. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.41 (ddd, 1H, $J_{2,3}$ = 6.7 Hz, $J_{3,4}$ = 4.7 Hz, $J_{3,F}$ = 55.7 Hz, H-3), 5.18 (dd, 1H, $J_{2,F}$ = 15.3 Hz, H-2), 5.03 (br dq, 1H, $J_{4,5a} \approx J_{4,5b} \approx$ 4.3 Hz, $J_{4,F}$ = 19.5 Hz, H-4), 3.54–3.39 (m, 2H, H-5a, H-5b), 1.47 (s, 9H, Boc). HRMS (pNSI) m/z 272.09052 $[M+Na]^+$, calcd. 272.09047 for $C_{10}H_{16}FNO_5Na$.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (13)[14]

To a solution of commercial 1,2-*O*-isopropylidene-α-D-xylofuranose (50.02 g, 0.26 mol) in CH_2Cl_2 (1 L) in an ice bath was added Et_3N (108 mL, 0.78 mol). Benzoyl chloride (33.2 mL, 0.29 mol) was added dropwise within 30 min. The mixture was stirred for 1.5 h at 0–5°C, and the reaction was quenched by the addition of water (50 mL). The organic phase was washed twice with a saturated solution of $NaHCO_3$ (250 mL), dried with $MgSO_4$, and filtered, and the solvents were evaporated. Column chromatography (EtOAc/cyclohexane 1:3, 2:3, 1:1) of the residue gave the desired product as a colorless solid (68.9g, 0.23 mol, 90%). MS (ionspray): m/z 295.2 $[M+H]^+$, 312.2 $[M+NH_4]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–8.04 (m, 5H, Ph), 5.96 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.81 (A(ABX), 1H, $J_{4,5a}$ = 9.4 Hz, $J_{5a,5b}$ = 12.7 Hz, H-5a), 4.60 (d, 1H, $J_{2,3} \approx$ 0 Hz, H-2), 4.38 (B(ABX), 1H, H-5b), 4.37 (ddd, H, $J_{4,5b}$ = 4.5 Hz, H-4), 4.17 (br dd, 1H, $J_{3,4}$ = 2.2 Hz, H-3), 3.23 (d, 1H, $J_{3,OH}$ = 4.0 Hz, OH), 1.51 (s, 3H, Me(*i*-prop)), 1.33 (s, 3H, Me(*i*-prop)).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-erythro-pent-3-ulofuranose (14)[14,15]

A solution of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (20.03 g, 0.068 mol) in CH_2Cl_2 (200 mL) was treated with pyridinium dichromate (13.08 g, 0,035 mol) and acetic anhydride (19.3 mL, 0.204 mol) over 2.5 h at reflux. The reaction mixture was diluted with ether (50 mL) and filtered through a silica gel column (300g, ether/CH_2Cl_2 1:4, then 2:3). After evaporation of solvents the residue was chromatographed over silica gel (EtOAc/cyclohexane, 1:3, 2:3, 1:1) to afford a colorless solid (16.44 g, 83%). MS (ionspray): m/z 310.1 $[M+NH_4]^+$, 315.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.95 (m, 5H, Ph), 6.14 (d, 1H, $J_{1,2} = 4.4$ Hz, H-1), 4.71 (A(ABX), 1H, $J_{4,5a} = 2.8$ Hz, H-5a), 4.69 (dd≈br s, 1H, H-4), 4.47 (B(ABX), 1H, $J_{4,5b} = 4.7$ Hz, $J_{5a,5b} = 13.4$ Hz, H-5b), 4.44 (d, 1H, H-2), 1.52 (s, 3H, Me(*i*-prop)), 1.44 (s, 3H, Me(*i*-prop)).

1,2-O-Isopropylidene-α-D-ribofuranose (15)[15,16]

To a solution of the keto sugar **14** (15.34 g, 52 mmol) in EtOH/H_2O (7:1, 180 mL) cooled in an ice bath was added sodium borohydride (2.38 g, 63 mmol) under stirring. The reaction mixture was allowed to reach rt, and stirring was continued overnight (16.5 h). The reaction mixture was passed through Amberlite columns (IRC-50, 120 g followed by IRA-400, 120 g, washing with EtOH). After concentration, the residue was chromatographed over silica gel (450 g) with EtOAc/MeOH/H_2O (93:5:2) to give the desired product **15** (8.9 g, 46.8 mmol, 89%). MS (ionspray): m/z 208.1 $[M+NH_4]^+$, 213.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (d, 1H, $J_{1,2} = 3.9$ Hz, H-1), 4.59 (dd≈t, 1H, $J_{2,3} = 5.1$ Hz, H-2), 4.01 (ddd≈dt, 1H, H-3), 3.97 (ddd, 1H, $J_{4,5a} = 2.4$ Hz, H-5a), 3.84 (br ddd, 1H, $J_{3,4} = 9.0$ Hz, $J_{4,5b} = 3.6$ Hz, H-4), 3.76 (ddd, 1H, $J_{5a,5b} = 12.0$ Hz, H-5b), 2.38 (d, 1H, $J_{3,OH\text{-}3} = 10.5$ Hz, OH-3), 2.05 (br s, 1H, OH-5), 1.58 (s, 3H, Me(*i*-prop)), 1.38 (s, 3H, Me(*i*-prop)).

3,5-Di-O-benzyl-1,2-O-isopropylidene-α-D-ribofuranose (16)[9,17]

A 1 M solution of 1,2-isopropylidene-α-D-ribofuranose (**15**, 8.9 g, 46.8 mmol) in absolute DMF was added dropwise at rt to a 1.3 M suspension of sodium hydride (60% in mineral oil, 2.3 eq) in absolute DMF. After stirring the mixture until release of H_2 stopped, it was cooled to 10°C, and benzyl bromide (14 mL, 2.5 eq) was added dropwise. The reaction mixture was allowed to reach rt and was stirred for 2 h, and then the reaction was quenched by careful addition of isopropanol (3% v/v). DMF was evaporated in vacuo. After addition of water and brine (1:1) the product was extracted twice with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue obtained was chromatographed (EtOAc/cyclohexane 1:9, 3:7) to give the desired product as colorless oil (15.6 g, 90%). MS

(ionspray): m/z 371.4 $[M+H]^+$, 388.3 $[M+ NH_4]^+$, 393.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.26 (m, 10H, 2Ph), 5.76 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 5.54 (A(AB), 1H, $J_{a,b} = 11.9$ Hz, OC*Ha*HbPh), 4.73 (B(AB), 1H, OCHa*Hb*Ph), 4.57 (A(AB), 1H, $J_{a',b'} = 12.2$ Hz, OC*Ha*'Hb'Ph), 4.56 (dd≈t, 1H, H-2), 4.49 (B(AB), 1H, OCHa'*Hb*'Ph), 4.18 (ddd, 1H, $J_{4,5a} = 2.2$ Hz, $J_{4,5b} = 3.8$ Hz, H-4), 3.86 (dd, 1H, $J_{2,3} = 4.3$ Hz, $J_{3,4} = 8.9$ Hz, H-3), 3.76 (A(ABX), 1H, $J_{5a,5b} = 11.3$ Hz, H-5a), 3.57 (B(ABX), 1H, H-5b), 1.59 (s, 3H, *i*-prop), 1.36 (s, 3H, *i*-prop).

3,5-Di-*O*-benzyl-β-D-ribofuranose (17)

A solution of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose (89.3 g, 0.24 mol) in aqueous acetic acid (1.8 L, 30%) was stirred under reflux conditions (≈112°C) for 2 h, the reaction mixture was then cooled in an ice bath over 1 h, and precipitation of the product was observed. The colorless solid was filtered and dried to yield the title compound **17** (60.6 g, 0.18 mol, 76%). The filtrates were concentrated, and the residue was chromatographed (EtOAc/cyclohexane 1:1) to obtain more of the desired substance (11.54 g, 0.035 mol, 15%, total yield 72.14 g, 0.22 mol, 91%). MS: m/z 348.3 $[M+ NH_4]^+$, 353.4 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.26 (m, 10H, Ph), 5.23 (d, 1H, $J_{1,2} = 7.4$ Hz, H-1), 4.61 (A(AB), 1H, $J_{a,b} = 8.3$ Hz, OC*Ha*HbPh), 4.56 (B(AB), 1H, OCHa*Hb*Ph), 4.51 (A(AB), 1H, $J_{a',b'} = 5.6$ Hz OC*Ha*'Hb'Ph,), 4.48 (B(AB), 1H, OCHa'*Hb*'Ph), 4.28 (dd, 1H, $J_{3,4} = 5.9$ Hz, H-3), 4.21 (ddd, 1H, $J_{4,5a} = 3.0$ Hz, $J_{4,5b} = 2.9$ Hz, H-4), 4.03 (dd, 1H, $J_{2,3} = 4.7$ Hz, H-2), 3.64 (A(ABX), 1H, $J_{5a,5b} = 10.3$ Hz, H-5a), 3.55 (B(ABX), 1H, H-5b), 3.36 (br s, 1H, OH-1), 2.69 (d, 1H, OH-2). The ^1H NMR of the chromatographed material showed a small amount of the α-anomer (ca. 5%).

3,5-Di-*O*-benzyl-D-ribono-1,4-lactone (18)[9]

To a 0.03 M solution of 3,5-di-*O*-benzyl-β-D-ribofuranose (17.8 g, 53.8 mmol) in dioxane/water (1:2) was added barium carbonate (14.9 g, 1.4 eq). After cooling the solution to 0°C, bromine (11.0 mL, 8 eq) was added dropwise. The reaction mixture was stirred in the dark for 3 h. The reaction mixture was then allowed to warm up to +10°C, and sodium carbonate was added until neutralization. In order to destroy residual bromine, sodium thiosulfate was added until a white precipitate appeared, and the reaction mixture was filtered over Celite. The solvents were evaporated in vacuo, and after the addition of water the product was extracted with EtOAc. The organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was chromatographed over silica gel (EtOAc/cyclohexane 1:2) to give the desired lactone (14.02 g, 42.7 mmol, 79%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.22 (m, 10H, Ph), 4.72–4.64 (AB, 2H, $J_{a,b} = 12.0$ Hz, OCH_2Ph), 4.67 (dd, 1H, $J_{2,3} = 5.9$ Hz, H-2), 4.55–4.23 (AB, 2H, $J_{a',b'} = 11.9$ Hz, OCH_2'Ph),

4.50 (dd≈t, 1H, H-4), 4.19 (d, 1H, $J_{3,4} \approx 0$ Hz, H-3), 3.67 (A(ABX), 1H, $J_{4,5a} = 3.0$ Hz, $J_{5a,5b} = 10.9$ Hz, H-5a), 3.56 (B(ABX), 1H, $J_{4,5b} = 2.5$ Hz, H-5b), 2.82 (d, 1H, $J_{2,OH\text{-}2} = 9.5$ Hz, OH-2).

Methyl 2,4-Anhydro-3,5-di-*O*-benzyl-D-ribonate (19)[9]

To a solution of the lactone **18** (4.3 g, 13.1 mmol) in CH_2Cl_2 (65.5 mL) and pyridine (1.9 mL, 1.8 eq) at −30°C, trifluoromethanesulfonic anhydride (1.2 eq) was added dropwise. After 45 min the reaction mixture was diluted with CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ and then with 1N HCl solution. After drying with $MgSO_4$ and filtration and evaporation of the solvent, the crude 3,5-*O*-benzylidene-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone was immediately used for the next reaction step without further purification. To a 0.12 M solution of triflated lactone in absolute MeOH at −12°C was added potassium carbonate (1.81 g, 1 eq). The resulting suspension was stirred over 3 h, and the reaction mixture was filtered over Celite to give the crude **19.** This was filtrated over a silica gel column (applied with CH_2Cl_2 and eluted with EtOAc) in order to remove salts, and the obtained residue (3.93 g) was used for the following reaction with no further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.28 (m, 10H, 2Ph), 5.01 (d, 1H, $J_{2,3} = 5.2$ Hz, H-2), 4.76 (ddd, 1H, $J_{3,4} \approx 4.9$ Hz, H-4), 4.67–4.60 (AB, 2H, $J_{a,b} = 8.7$ Hz, OCH_2Ph), 4.54–4.48 (AB, 2H, $J_{a',b'} = 5.4$ Hz, OCH_2'Ph), 4.52 (dd≈t, 1H, H-3), 3.61 (A(ABX), 1H, $J_{4,5a} = 3.7$ Hz, $J_{5a,5b} = 11.5$ Hz, H-5a), 3.55 (B(ABX), 1H, $J_{4,5b} = 4.0$ Hz, H-5b), 3.25 (s, 3H, OMe).

Methyl 2,4-Anhydro-D-ribonate (20)[18]

To a 0.07 M solution of methyl 2,4-anhydro-3,5-di-*O*-benzyl-D-ribonate (**19**, 3.93 g, assumed 11.5 mmol) in MeOH/dioxane 1:1 was added Pd/C (10% m/m). The reaction mixture was stirred at rt under hydrogen atmosphere for 3 h. The catalyst was then removed by filtration. The filtrate was concentrated to dryness, and the obtained crude product (colorless oil) was reacted without further purification (1.62 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (d, 1H, $J_{2,3} = 4.9$ Hz, H-2), 4.74 (t, 1H, H-3), 4.71 (ddd, 1H, $J_{3,4} = 5.1$ Hz, H-4), 3.84 (A(ABX), 1H, $J_{4,5a} = 2.5$ Hz, $J_{5a,5b} = 13.4$ Hz, H-5a), 3.80 (s, 3H, OMe), 3.65 (B(ABX), 1H, $J_{4,5b} = 2.0$ Hz, H-5b).

Methyl 2,4-Anhydro-5-azido-5-deoxy-D-ribonate (21)

To a solution of the crude methyl 2,4-anhydro-D-ribonate (1.62 g, assumed 10.0 mmol) in CH_2Cl_2 (50 mL) pyridine (0.76 mL, 1.0 eq) was added dropwise trifluoromethanesulfonic anhydride (2.0 mL, 1.2 eq) cooled below −30°C. After 30 min the reaction mixture was diluted with CH_2Cl_2 and washed with

saturated solution of $NaHCO_3$ and then with 1N HCl solution. The organic phases were dried over $MgSO_4$ and filtered and the solvent was evaporated. To a 0.1 M acetone solution of the crude triflate was added sodium azide (3.9 g, 6 eq). After stirring overnight at rt the reaction mixture was concentrated. Iced water was added, and the product was extracted with *tert*-butylmethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue obtained was chromatographed (EtOAc/cyclohexane 1:4) to furnish compound **21** as a colorless oil (1.29 g, 6.9 mmol, 53% from lactone **18**). $[\alpha]_D^{20}$ −82 (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 4.95 (d, 1H, $J_{2,3} = 4.8$ Hz, H-2), 4.76–4.69 (m, 2H, H-3, H-4), 3.84 (s, 3H, OMe), 3.63 (A(ABX), 1H, $J_{4,5a} = 3.0$ Hz, $J_{5a,5b} = 13.7$ Hz, H-5a), 3.44 (B(ABX), 1H, $J_{4,5b} = 3.3$ Hz, H-5b), 3.26 (br d, 1H, OH).

Methyl 2,4-Anhydro-5-azido-5-deoxy-3-fluoro-D-xylonate (22)

To a solution of azide **21** (263.4 mg, 1.41 mmol) in acetonitrile (10 mL) at −20°C was added DAST (0.36 mL, 2.75 mmol), and the mixture was stirred until conversion into the intermediate (1.5 h, see Sch. 4). The solution was then allowed to reach rt, and pyridine (0.11 mL, 1.4 mmol) was added while the temperature was increased to 50°C. After 3 h complete consumption of the intermediate was observed, and the brown solution was cooled, diluted with diethyl ether, and washed with a saturated solution of $NaHCO_3$. The aqueous layer was washed with diethyl ether and the organic phases were combined, dried, and concentrated. The evaporation of diethyl ether was monitored so that evaporation of the product could be avoided. The crude compound **22** (282.9 mg) was reacted without further purification. H^1 NMR (300 MHz, $CDCl_3$): δ 5.65 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx 5.8$ Hz, $J_{3,F} = 56.2$ Hz, H-3), 5.30 (dd, 1H, $J_{2,F} = 18.4$ Hz, H-2), 5.02–4.91 (m, 1H, $J_{4,F} = 15.5$ Hz, H-4), 3.86 (s, 3H, OMe), 3.80 (A(ABX), 1H, $J_{4,5a} = 1.7$ Hz, H-5a), 3.67 (B(ABX), 1H, $J_{5a,5b} = 13.0$ Hz, H-5b).

Methyl 2,4-Anhydro5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-xylonate (23)

To a 0.12 M solution of the crude azide **22** (considered 1.41 mmol) in EtOAc was added Pd/C (10% m/m), and the suspension was stirred vigorously for 30 min under hydrogen atmosphere. A 0.12 M solution of Boc_2O (0.32 g, 1.05 eq) in EtOAc (12.5 mL) was then added, and the reaction mixture was stirred at rt under H_2 atmosphere for 1.5 h. The catalyst was removed by filtration, and the solvent was evaporated. Chromatography of the obtained residue (EtOAc/heptane 1:4 to 1:1) yielded the pure product **23** as a colorless oil (193 mg, 0.73 mmol, 52%). $[\alpha]_D^{20}$ +41.0 (*c* 0.89, $CHCl_3$). H^1 NMR (300 MHz, $CDCl_3$): δ 5.60 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx 5.6$ Hz, $J_{3,F} = 56.6$ Hz, H-3), 5.28 (dd, 1H, $J_{2,F} = 18.9$ Hz, H-2), 5.04–4.91 (m, 2H, H-4, NH), 3.84 (s, 3H, OMe), 3.69–3.54 (m, 2H,

H-5a, H-5b), 1.44 (s, 9H, Boc). HRMS (pNSI) m/z 264.12418 $[M+H]^+$, calcd. 264.12418 for $C_{11}H_{18}FNO_5$.

2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonic Acid (24)

To a 0.06 M solution of the methyl ester **23** (97.8 mg, 0.38 mmol) in THF was added 1N aqueous LiOH (3 eq) at 0–5°C, and the mixture was stirred for 30 min. Then, maintaining the temperature range, 1N HCl (3 eq) was added, and the mixture was stirred for 30 min. Brine was added, and the product was extracted three times with tert-butylmethyl ether. The organic layers were combined, dried over $MgSO_4$, and filtered and the solvent was evaporated to give the product **24** as colorless hygroscopic foam (91.7 mg, 0.37 mmol, 97%). MS (ionspray neg.): m/z 248.3 $[M-H]^-$. H^1 NMR (300 MHz, $CDCl_3$): δ 5.64 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx 6.0$ Hz, $J_{3,F} = 56.1$ Hz, H-3), 5.29 (dd, 1H, $J_{2,F} = 17.8$ Hz, H-2), 5.01–4.86 (m, 2H, H-4, NH), 4.08–3.95 (m, 1H, H-5a), 3.29–3.19 (m, 1H, H-5b), 1.46 (s, 9H, Boc). HRMS (pNSI) m/z 272.09057 $[M+Na]^+$, calcd. 272.09047 for $C_{10}H_{16}FNO_5Na$.

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