JOC The Journal of Organic Chemistry

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3-Fluoroazetidinecarboxylic Acids and *trans,trans*-3,4-Difluoroproline as Peptide Scaffolds: Inhibition of Pancreatic Cancer Cell Growth by a Fluoroazetidine Iminosugar

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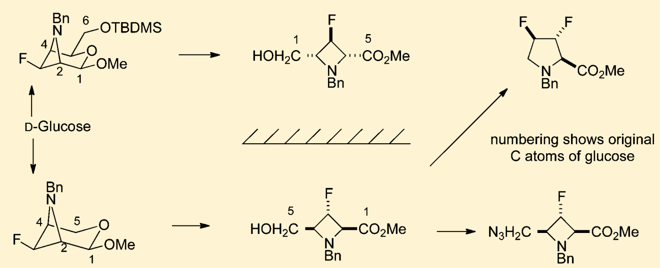
S Supporting Information

ABSTRACT: Reverse aldol opening renders amides of 3-hydroxyazetidinecarboxylic acids (3-OH-Aze) unstable above pH 8. Aze, found in sugar beet, is mis-incorporated for proline in peptides in humans and is associated with multiple sclerosis and teratogenesis. Aze-containing peptides may be oxygenated by prolyl hydroxylases resulting in potential damage of the protein by a reverse aldol of the hydroxyazetidine; this, rather than changes in conformation, may account for the deleterious effects of Aze. This paper describes the synthesis of 3-fluoro-Aze amino acids as hydroxy-Aze analogues which are not susceptible to aldol cleavage. 4-(Azidomethyl)-3-fluoro-Aze and 3,4-difluoroproline are new peptide building blocks. *trans,trans*-2,4-Dihydroxy-3-fluoroazetidine, an iminosugar, inhibits the growth of pancreatic cancer cells to a similar degree as gemcitabine.



■ INTRODUCTION

Organofluorine compounds play a central role in the pharmaceutical industry.[1] There is much current interest in azetidine,[2] including azetidine carboxylic acids,[3] as a pharmacophore in medicinal chemistry;[4] over 180 patents with azetidine in the title have been published since 2013.[5] Azetidinecarboxylic acid (Aze) **1**, a four-membered ring analogue of proline **2** first isolated from *Convallaria majalis* in 1955,[6] occurs in many plants, including sugar beet,[7] and in supplements to many foods.[8] Aze is mis-incorporated into proteins as a substitute for proline **2** in humans and causes numerous toxic effects[9] including teratogenesis and congenital malformations.[10] There is a correlation between areas of high sugar beet consumption and the occurrence of multiple sclerosis; dangers of Aze entering the human food chain[11] are increasingly recognized.[12]

3-OH-Aze **3** has only been prepared by oxidation of Aze **1** by proline hydroxylases.[13] The formation of *trans,trans*-3-hydroxy-4-hydroxymethyl-L-Aze **4** from D-glucose was the first chemical synthesis of an unprotected 3-OH-Aze **3**.[14] Compound **3** is a ring-contracted analogue of the dihydroxyproline **5**.[15] The roles of 2-oxoglutarate (2OG)-dependent prolylhydroxylases in eukaryotes include collagen stabilization, hypoxia sensing, and translational regulation and are of considerable interest from therapeutic perspectives; the RPS23 hydroxylases in *S. cerevisiae* (Tpa1p), *Schizosaccharomyces pombe*, and green algae have been shown to catalyze an unprecedented dihydroxylation modification giving peptides containing **5**.[16] Synthetic peptides containing **5** or its azetidine analogues as constituents may provide interesting probes in biological investigations (Figure 1). However, although the amide **6** is a potent inhibitor of hexosaminidases,[17] **6** is unstable above pH 8 due to a reverse aldol opening of the azetidine ring and thus is not suitable for the preparation of stable peptidomimetics. Microbial 2-oxoglutarate-dependent dioxygenases also cause oxidation of Aze-containing peptides **7** in which oxygen-modified hydroxyl-Aze peptides **8** will be susceptible to aldol ring opening, thus severely damaging the protein structure.[18] Modification of the secondary structure of proteins containing Aze instead of Pro may affect their biological function; however, the damage in protein structure inherent in the introduction of oxygen into C3 of an azetidine amide may be the cause of much of the pathology of the Aze-Pro substitution. Access to stable functionalized Aze analogues may

Received: March 6, 2015
Published: April 10, 2015

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

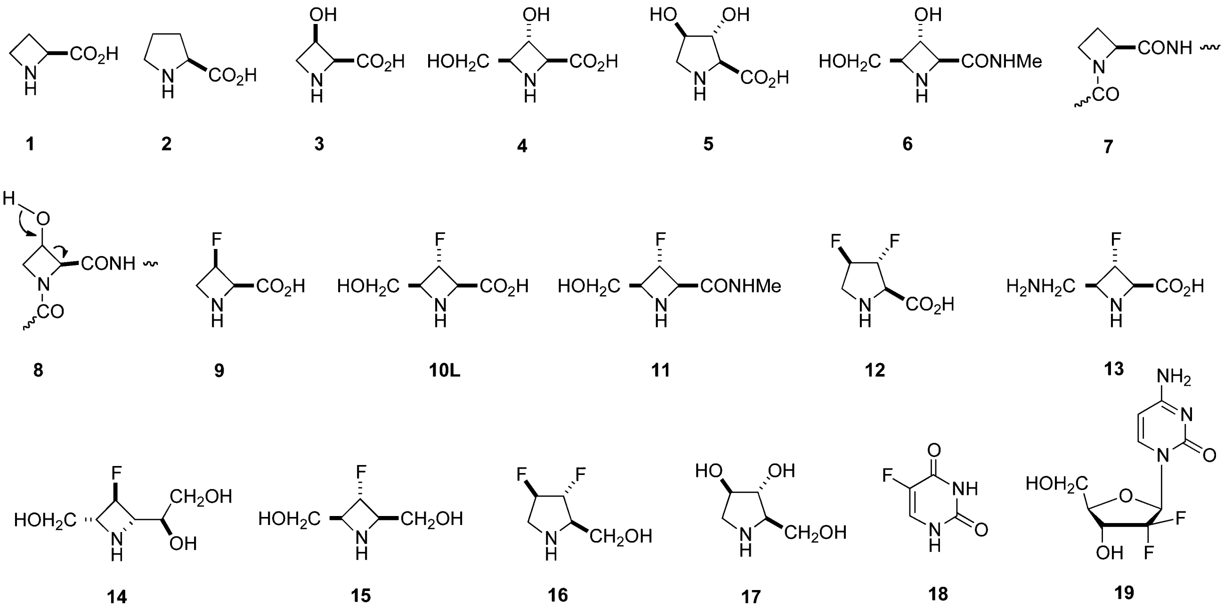


Figure 1. Azetidine and pyrrolidine structures: synthetic targets.

allow investigation of peptides with interesting biological and structural features.

Since unprotected 3-OH-Aze derivatives cannot give stable peptides, 3-fluoro-Aze **9** where fluorine replaces the hydroxyl group may be an alternative peptidomimetic. In 1970, **9** was formed by the direct photofluorination of Aze.[19] In spite of there being considerable interest in 3-fluoroazetidines,[20] there are no reports of the use of **9** or its derivatives as a template for the introduction of 3-fluoro-Aze components into peptides.

This paper describes the synthesis of protected building blocks for the incorporation of the enantiomeric 3-fluoro-Aze **10L** and **10D** into peptides; both the amide **11** and a dimer derived from **10L** were stable, showing 3-fluoro-Aze to be suitable as a peptide mimetic. Building blocks for inclusion of *trans,trans*-difluoroproline **12** and the δ-amino-Aze **13** were also prepared; oligomers of δ-amino-oxetane[21] and -THF[22] analogues of **13** show a predisposition toward adopting a wide range of secondary structures. None of the fluoro iminosugars, including the fluoroazetidines **14** and **15**, and the difluoropyrrolidine analogue **16** of the α-glucosidase inhibitor DAB **17**,[23] showed any inhibition of any glycosidase. The *meso*-fluoroazetidine diol **15** was compared to 5-fluorouracil **18** and gemcitabine **19** and demonstrated significant inhibition of pancreatic cancer cell growth; the anticancer activity of fluoroazetidine **15** provides a further example of biological activity of iminosugars which does *not* depend on glycosidase inhibition.

■ RESULTS AND DISCUSSION

Synthesis. Treatment of 1,3-di-*O*-triflates derived from carbohydrates with benzylamine provides a strategy for the efficient synthesis of many azetidines.[24] In particular, the cyclization of 2,4-triflates of pyranoses, such as **22** and **25**, to form bicyclic azetidines in high yields is reliable *provided all the substituents in the pyranose ring are equatorial* (*trans* to each other).[25] No other stereochemistry allows any cyclization, and it has not been possible to adjust the stereochemistry after the bicyclic azetidine has been formed.[26]

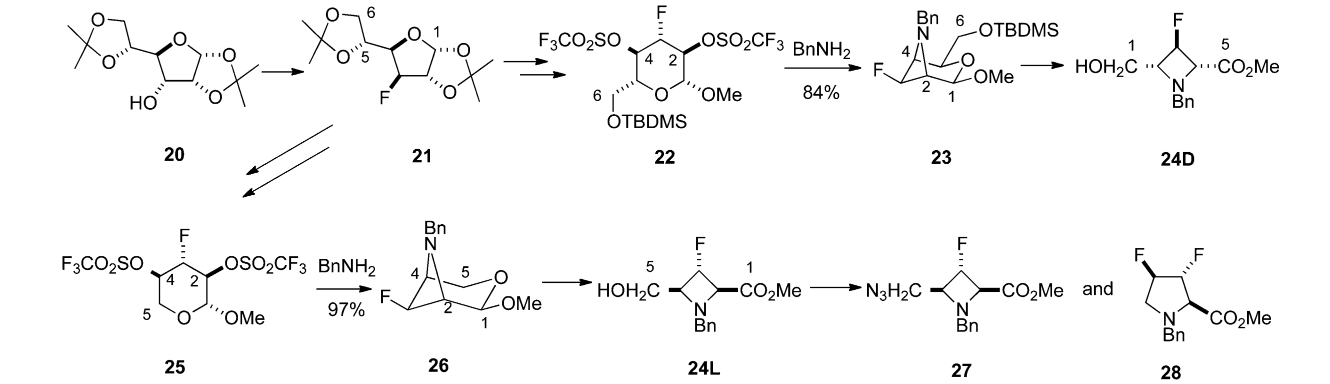
The diacetonide of 3-fluoroglucose **21**, the starting material for all the 3-fluoroazetidines prepared, is formed in 97% yield from diacetone allose **20**[27] by triflation and nucleophilic displacement with cesium fluoride in 2-methyl-2-propanol[28] on a large scale (over 100 g).[29] Compound **21** was transformed by standard carbohydrate manipulations into the pyranose ditriflates **22** and **25** which underwent high-yield reactions with benzylamine to give the bicyclic azetidines **23** and **26**, respectively. Ring opening of **23**, followed by periodate cleavage of the C5−C6 bond of glucose, allowed access to the fluoro-D-Aze **24D**. The bicyclic azetidine **26**, in which the C5−C6 bond of glucose had been cleaved prior to cyclization, led to the L-enantiomer **24L**. Activation of the primary hydroxyl group in **24L** toward nucleophilic substitution can lead to the synthesis of the azidomethyl-Aze **27** or of the ring-expanded difluoroproline **28** as building blocks for the incorporation of novel amino acids into peptides (Scheme 1).

The synthesis of the D-*trans,trans*-Aze ester **24D** from the diacetonide **21** required cleavage of the C5−C6 bond *after* the formation of azetidine ring (Scheme 2). Hydrolysis of the acetonide **21** by Dowex H^+, followed by peracetylation in pyridine, afforded the tetraacetate **29** as a 1:1 anomeric mixture (97%).[30] Treatment of the tetraacetate **29** with HBr in acetic acid gave the anomeric bromide which, with methanol in the presence of silver carbonate, gave the β-methyl pyranoside **30**[31] (87%). Removal of the acetate groups in **30** with sodium methoxide in methanol gave the triol **31** (96%) in which the primary hydroxyl group selectively reacted with *tert*-butyldimethylsilyl (TBDMS) chloride in the presence of imidazole in DMF to give the silyl ether **32** (98%). Esterification of the diol **32** with trifluoromethanesulfonic (triflic) anhydride formed the ditriflate **22**. Treatment of **22** with benzylamine in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in acetonitrile afforded the bicyclic azetidine **23** (84% over two steps); only the β-anomer of the ditriflate **22** allowed cyclization to the azetidine ring.

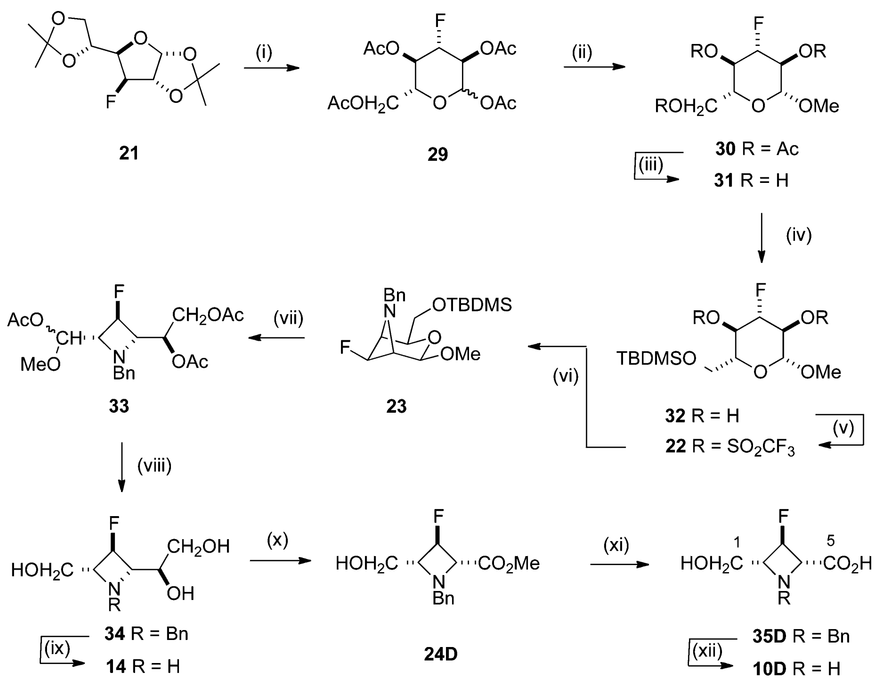
The acid hydrolysis of the bicycle **23** under a wide range of conditions, followed by treatment of the crude product with sodium borohydride, only gave traces of the triol **34**. However, acetolysis of **23** by acetic anhydride in the presence of boron trifluoride etherate gave the mixed acetal **33** in 100% yield. All attempts to directly reduce **33** with sodium borohydride under a variety of conditions afforded only traces of **34**. Accordingly sequential reduction of the triacetate acetal **33** with DIBALH in toluene, followed by sodium borohydride in methanol, formed

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

Scheme 1. Synthetic Strategy and Targets (Numbering Refers to Original C in Glucose)



Scheme 2. Synthesis of D-*trans,trans*-Aze 24D[a]



[a]Reagents and conditions (i) Dowex (50W X8, H^+), then Ac_2O, pyridine, 97% (ii) HBr, AcOH, then $AgCO_3$, MeOH, 87%; (iii) NaOMe, MeOH, 96%; (iv) TBDMSCl, imidazole, 98%; (v) $(CF_3SO_2)_2O$, pyridine; (vi) $BnNH_2$, DIPEA, MeCN, 84%; (vii) $Et_2O{\cdot}BF_3$, Ac_2O, 100%; (viii) DIBALH, toluene, then $NaBH_4$, MeOH, 97%; (ix) Pd/C, H_2, H_2O, dioxane, 88%; (x) $NaIO_4$, H_2O, dioxane, then I_2, K_2CO_3, MeOH, 69%; (xi) K_2CO_3, H_2O, dioxane, 57%; (xii) Pd/C, H_2, H_2O, dioxane, 45% (numbering refers to original C in glucose).

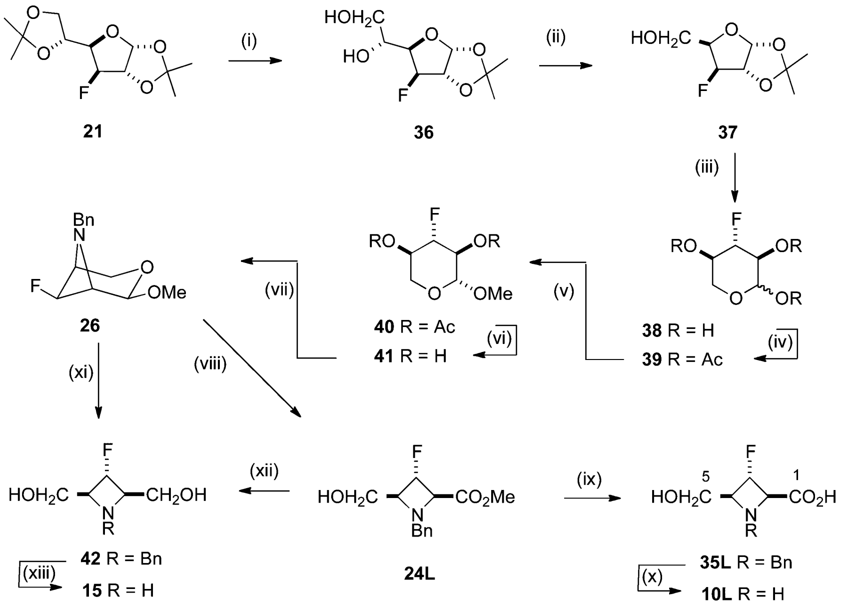
the azetidine iminosugar **34** in 97% yield. These conditions were also required in the hydrolysis of other bicyclic nitrogen heterocycles.[32] Oxidative cleavage of the 1,2-diol moiety in **34** by sodium periodate in aqueous dioxane, followed by further oxidation of the crude aldehyde by iodine in methanol, gave the peptidomimetic building block **24D** in 69% yield (45% overall yield from the diacetone fluoroglucose **21**).

Unprotected azetidine derivatives were prepared from **24D** for assaying their biological properties. Hydrogenolysis of the benzyl group in **34** in the presence of 10% palladium on charcoal in aqueous dioxane gave the azetidine iminosugars **14** (88%). Hydrolysis of the methyl ester **24D** by potassium carbonate in aqueous dioxane gave the *N*-benzyl Aze **35D** (57%) from which the benzyl group was removed by hydrogenolysis in the presence of palladium to give the fluoro D-Aze **10D** (45%).

A similar sequence of reaction with cleavage of the C5−C6 bond *before* the formation of azetidine ring gave the L-*trans,trans*-Aze ester **24L** (Scheme 3). Mild acid hydrolysis of the diacetonide **21** gave the monoacetonide **36** (100%). Oxidation of the diol in **36** by sodium periodate, followed by sodium borohydride reduction of the resulting aldehyde, afforded **37** (92%). Hydrolysis of **37** by Dowex resin in aqueous dioxane gave 3-fluoroxylose **38**[33] (88%) in an α:β ratio of 3:2. Compound **38** with acetic anhydride in pyridine yielded an anomeric mixture of the triacetate **39** (89%). Treatment of **39** with HBr in acetic acid followed by reaction of the resulting bromide with silver carbonate in methanol gave the diacetate **40** (60%); removal of the acetate protecting groups by sodium methoxide in methanol gave the β-methyl xylopyranoside **41** (97%). Esterification of the diol **41** with triflic anhydride in dichloromethane in the presence of pyridine gave the ditriflate **25**; treatment of **25** with benzylamine in acetonitrile in the presence of DIPEA afforded the bicyclic azetidine **26** (97%). Hydrolysis of the acetal in **26** with hydrochloric acid in aqueous dioxane gave the corresponding lactol

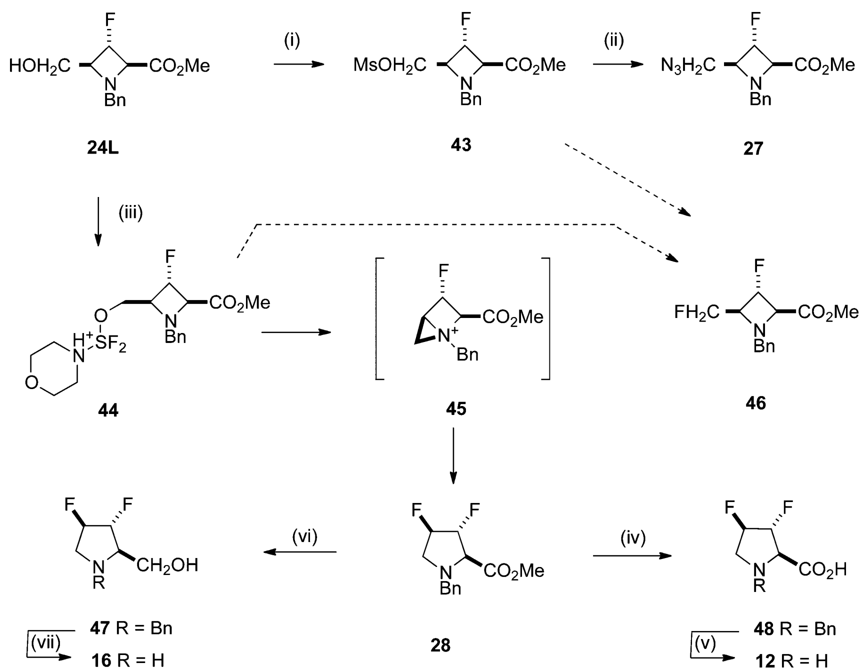
DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

Scheme 3. Synthesis of L-*trans,trans*-Aze 24L[a]



[a]Reagents and conditions (i) MeOH, 1% H_2SO_4, 100%; (ii) $NaIO_4$, H_2O, dioxane, then $NaBH_4$, 92%; (iii) Dowex (50W X8, H^+), H_2O, dioxane, 88%; (iv) Ac_2O, pyridine, 89%; (v) HBr, AcOH; then $AgCO_3$, MeOH, 60%; (vi) MeONa, MeOH, 97%; (vii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; then $BnNH_2$, MeCN, 97%; (viii) HCl, H_2O, dioxane; then I_2, K_2CO_3, MeOH, 74%; (ix) K_2CO_3, H_2O, dioxane, 43%; (x) Pd/C, H_2, H_2O, dioxane, 82%; (xi) HCl, H_2O, dioxane; then $NaBH_4$, MeOH, 40%; (xii) $NaBH_4$, MeOH, 90%; (xiii) Pd/C, H_2, H_2O, dioxane, 100% (numbering refers to original C in glucose).

Scheme 4. Peptide Building Blocks[a]



[a]Reagents and conditions: (i) MsCl, pyridine, 100%; (ii) NaN_3, DMF, 80%; (iii) XtalFluor-M, $Et_3N{\cdot}3HF$, CH_2Cl_2, 84%; (iv) NaOH, H_2O, dioxane, 64%; (v) Pd/C, H_2, H_2O, dioxane, 86%; (vi) $LiAlH_4$, THF, 66%; (vii) Pd/C, H_2, H_2O, dioxane, 82%.

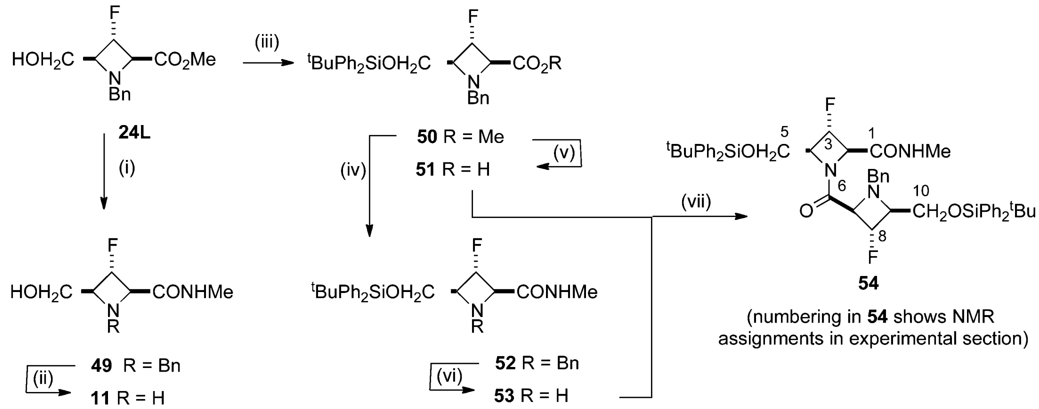
which was oxidized by iodine in methanol to give the L-Aze ester building block **24L** (74%) in an overall yield of 30% from the diacetonide **21**.

Hydrolysis of the methyl ester **24L** by potassium carbonate in aqueous dioxane gave the *N*-benzyl acid **35L** (43%) from which the benzyl group was removed by hydrogenolysis in the presence of palladium on charcoal to produce the azetidine carboxylic acid **10L** (82%). The lactol derived from hydrolysis of **26** was reduced by sodium borohydride in methanol to give the *meso*-diol **42** (40%); alternatively, sodium borohydride reduction of the ester **24L** gave **42** in 90% yield. Hydrogenolysis of the *N*-benzyl group in **42** gave the *meso*-azetidine **15** (100%).

Other peptide building blocks were prepared from the L-ester **24L** (Scheme 4). The mesylate **43**, formed by treatment of **24L**

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

Scheme 5. Amide Formation[a]



[a]Reagents and conditions: (i) $MeNH_2$, $CaCl_2$, MeOH, 74%; (ii) Pd/C, H_2, H_2O, dioxane, 90%; (iii) TBDMSCl, imidazole, DMF, 95%; (iv) $MeNH_2$, $CaCl_2$, MeOH, 100%; (v) K_2CO_3, H_2O, dioxane; (vi) Pd/C, H_2, H_2O, dioxane; (vii) **51**, **53**, HBTU, DMF, 45% from **50**.

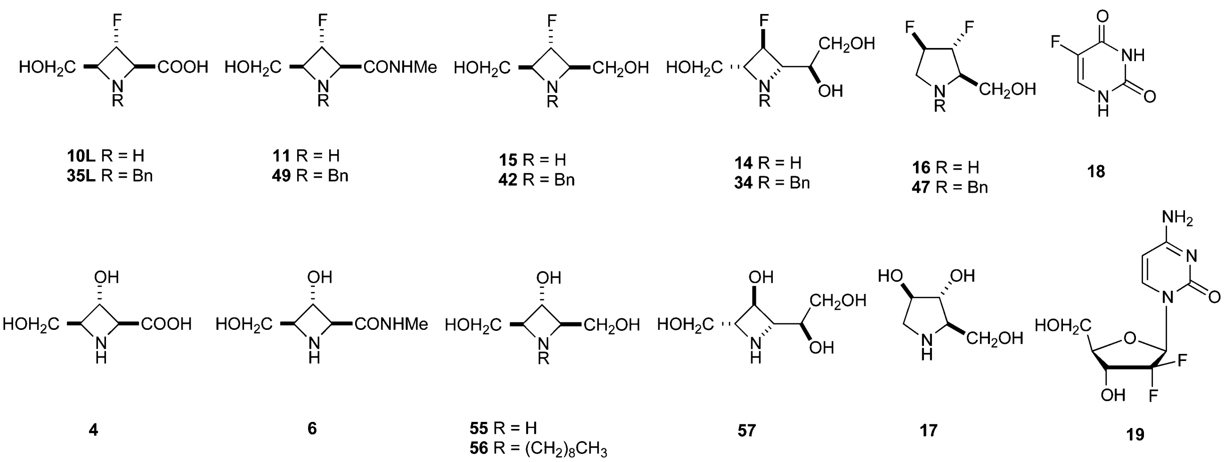


Figure 2. Compounds assayed for inhibition of glycosidases and/or pancreatic cancer cell growth.

with mesyl chloride in pyridine (100%), with sodium azide in DMF gave the azide **27** (80%) as a precursor to δ-amino Aze analogues. A variety of reagents for attempted displacement of the mesylate **43** by fluoride nucleophiles gave complex mixtures, which gave very low yields of the difluoroazetidine **46**. However, reaction of **24L** with XtalFluor-M[34] and triethylamine:HF in dichloromethane afforded the difluoroproline ester **28** (84%). Neighboring group participation by the ring nitrogen on the initial complex **44** with the azetidine nitrogen would give the bicyclic aziridinium ion **45** to afford the ring-expanded proline **28**. Compound **28** would allow fluoro analogues of dihydroxyproline **5** to be incorporated into peptides. Examples of ring expansions of azetidines to pyrrolidines[35] and opening of aziridinium ions by fluoride[36] have been reported.

Hydrolysis of **28** with aqueous sodium hydroxide gave the *N*-benzylproline **48** (64%) from which the benzyl group was removed by palladium-catalyzed hydrogenolysis to give *trans*,-*trans*-3,4-difluoro-L-proline **12** (86%). Reduction of **28** with lithium aluminum hydride in THF gave **47** (66%). Hydrogenolysis of the benzyl group in **47** afforded **16** (82%), the difluoro analogue of DAB **17**, an iminosugar which has been isolated from many plant sources.

The stability of the 3-fluoro Aze motif in peptides was firmly established (Scheme 5). Reaction of the ester **24L** with methylamine in methanol in the presence of calcium chloride formed the methylamide **49** (74%). Palladium-catalyzed hydrogenolysis of **49** in aqueous dioxane formed **11** (90%); unlike the corresponding 3-OH azetidine amide **6**, the 3-fluoro amide **11** was stable to a wide range of pH and vulnerable to neither hydrolysis nor ring fragmentation on treatment with acid or base. A dipeptide **54** was prepared from **24L**. Protection of the primary hydroxyl in **24L** with TBDMS chloride in DMF in the presence of imidazole gave the fully protected silyl ether **50** (95%); hydrolysis of **50** with potassium carbonate in aqueous dioxane afforded the free acid **51**. The ester **50** was converted to the corresponding methylamide **52** on reaction with methylamine in methanol in the presence of calcium chloride (100%); the benzyl group in **52** was removed by hydrogenation in the presence of palladium to give the free amine **53**. The acid **51** and the amine **53** were coupled with *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) in DMF to give the fully protected dipeptide **54** (45% from **50**). The dipeptide was stable and indicated that such Aze analogues could be useful as components for peptides and for study of the predisposition of substituted Aze units to induce secondary structure.

Bioassays. *Glycosidase Inhibition.* The fluoro iminosugars prepared in this paper were compared with the analogous 3-OH azetidines (Figure 2) as inhibitors of the following glycosidases (Table 1, Supporting Information):[37,38] α-glucosidases (EC 3.2.1.20, rice, yeast, *Aspergillus niger*), β-glucosidases (EC 3.2.1.21, almond, bovine liver, *A. niger*), α-galactosidase (EC 3.2.1.22, coffee beans), β-galactosidase (EC 3.2.1.23, bovine liver), α-mannosidase (EC

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

Table 1. Concentration of Fluoroazetidine 15, 5-Fluorouracil 18, and Gemcitabine 19 against Human Cancer Cell Lines

	IC_{50} (μM)			
	PANC-1	Hep G2	SW480	MCF-7
fluoroazetidine **15**	165.3 ± 9.1	80.3 ± 6.2	194.7 ± 1.2	332.4 ± 50.2
5-fluorouracil **18**	33.7 ± 11.6	22.5 ± 8.9	9.4 ± 4.1	3.1 ± 0.4
gemcitabine **19**	122.9 ± 66.4	2.6 ± 0.1	2.8 ± 0.1	3.1 ± 0.2

3.2.1.24, Jack bean), β-mannosidase (EC 3.2.1.25, snail), α-L-rhamnosidase (EC 3.2.1.40, *Penicillium decumbens*), α-L-fucosidase (EC 3.2.1.44, bovine kidney), β-glucuronidases (EC 3.2.1.31, *Escherichia coli*, bovine liver), trehalase (EC 3.2.1.28, porcine kidney), and amyloglucosidases (EC 3.2.1.3, *A. niger*, *Rhizopus* sp.), β-*N*-acetylglucosaminidases (EC 3.2.1.52, human placenta, bovine kidney, Jack bean, HL 60, *Aspergillus oryzae*), α-*N*-acetylgalactosaminidase (EC 3.2.1.49, chicken liver, *Charonia lampas*), and β-*N*-acetylgalactosaminidases, (EC 3.2.1.53, HL 60, *A. oryzae*).

Several azetidine iminosugars show specific inhibition of nonmammalian glycosidases.[24] Although no significant inhibition of any glycosidase is shown either by the free acid **4** or by the iminohexitol **57**, *meso*-azetidine triol **55** is a potent inhibitor of yeast α-glucosidase (IC_{50} 9.5 μM) and a good inhibitor of trehalase (IC_{50} 30 μM) and rice α-glucosidase (IC_{50} 83 μM).[25] Potent inhibition of the yeast enzyme is rare; DAB **17** and DMDP are only natural iminosugars to do so.[39] The *N*-nonyl derivative **56** is an inhibitor of some ceramide-specific glucosyl transferases and glucosidases.[40] The amide **6** is a potent inhibitor of a number of β-hexosaminidases but shows no inhibition of any other glycosidase; however it decomposes rapidly above pH 8.[14] Assays of the fluoro azetidines **10L**, **11**, **14**, and **15** showed there was *no* inhibition of any glycosidase (Table 1, Supporting Information). The fluoro prolinol **16**, the fluorine analogue of DAB **17**, similar showed no inhibition of any glucosidase. The *N*-benzyl analogues **34**, **35L**, **42**, **47**, and **49** also showed no glycosidase inhibition (Table 2, Supporting Information). Replacement of hydroxyl groups in iminosugars by fluorine substituents almost invariably reduces or eliminates glycosidase inhibition;[41] the only exception so far reported is increased glucosidase inhibition in fluorinated australines.[42]

Inhibition of Various Human Cancer Cell Growth. In the first screening, the fluoro compounds (**10L**, **10D**, **11**, **15**, and **14**) and their oxygen equivalents (**4**, **6**, **55**, and **57**) were tested for growth inhibition effects against human pancreatic carcinoma cell line (PANC-1)[43] and were compared with 5-fluorouracil **18** and gemcitabine **19** as positive controls.[44] The PANC-1 cells were incubated in an atmosphere of 5% CO_2 at 37 °C and subcultured every 3 days. In all experiments, cells were grown to 80–90% confluence. The growth inhibition activities were elucidated by MTT assay. PANC-1 (1×10^4 cells/mL) was seeded in each well of 96-well plates. After incubation with 200 μM test compounds for 72 h, the MTT solution (1 mg/mL in PBS: pH 7.4) was added to each well (10 μL/well). The plate was incubated for an additional 4 h at 37 °C, and the resulting MTT-formazan crystals produced were dissolved with 200 μL of DMSO. Absorbance was measured by FLUOstar OPTIMA (BMG LABTECH) at 540 nm. The given values were counted in triplicate. Growth inhibition was estimated as the reduction in values from a DMSO control. Preliminary results indicate that only *meso*-azetidine **15** showed significant inhibition of growth PANC-1 cells; different samples of **15** synthesized by the alternative pathways in Scheme 3 showed the same activity. Of all the fluoroiminosugars tested, only **15** showed activity; the *N*-benzyl derivative **42** gave no inhibition. It is noteworthy that the fluoroazetidine diol **15** did not inhibit any glycosidases; in contrast the *meso*-triol **55** was a good inhibitor of several glucosidases but had no effect on growth of cancer cells.

Thus, we next investigated the effect of the fluoro *meso*-azetidine **15** on growth inhibition effects against various human cancer cells (Table 1). The IC_{50} values of *meso*-azetidine **15**, fluorouracil **18**, and gemcitabine **19** toward PANC-1 were 165.3 ± 9.1, 33.7 ± 11.6, and 122.9 ± 66.4 μM, respectively. It is noteworthy that growth inhibition potency of **15** against PANC-1 was equivalent to gemcitabine **19**. Furthermore, **15** also showed superior inhibition spectrum widely against human liver carcinoma (Hep G2), human colon adenocarcinoma (SW480), and human breast adenocarcinoma cell line (MCF-7), with IC_{50} values of 80.3 ± 6.2, 194.7 ± 1.2, and 332.4 ± 50.2 μM, respectively. The inhibition mechanism of **15** is now under investigation, but the inhibition is similar to that of **18** and **19** as it had the same induction profile of apoptosis for the cancer cells and the effects depended on the incubation time.

■ CONCLUSION

Because of the instability of amides of 3-OH-Aze such as **6**, it is not possible to incorporate such moieties into peptides. Oxygenation of Aze-containing peptides by prolyl hydroxylases may account for the pathologies associated with human consumption of Aze. In contrast, the fluoro analogues are stable, and the enantiomeric fluoro-Aze esters **24D** and **24L** and the difluoroproline ester **28** provide suitable building blocks for modified azetidine and proline peptides. The azidomethyl azetidine **27** is a dipeptide isostere, which may form oligomers with disposition to form novel secondary structures. None of the fluoroazetidines show any significant inhibition of glycosidases. The inhibition of pancreatic cell growth by the *meso*-fluoroazetidine diol **15** is a further example of biological activity of an iminosugar which is *not* due to glycosidase inhibition; other analogues will be studied in the hope of elucidating the mechanism.

■ EXPERIMENTAL SECTION

General Experimental Procedures. All commercial reagents were used as supplied. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with 60 F_{254} silica. Plates were visualized using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2 M aqueous sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations are quoted in 10^3 deg·cm^2·g^{-1} at concentrations (c) in g·100 mL^{-1}. ^{1}H and ^{13}C NMR spectra were assigned by utilizing 2D COSY, HSQC, and HMBC spectra. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in hertz. Residual signals from the solvents were used as an internal reference.[45] For solutions in D_2O acetonitrile was used as an internal reference. HRMS measurements were made using a microTOF mass analyzer.

3-Deoxy-1,2;5,6-di-*O*-isopropylidene-3-fluoro-α-D-glucofuranose, 21. Triflic anhydride (11.0 mL, 38.1 mmol) was added dropwise to a solution of 1,2;5,6-di-*O*-isopropylidene-D-allose (5.30 g, 20.3 mmol) and anhydrous pyridine (10 mL, 76.7 mmol) in dichloromethane

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

(25 mL) at −20 °C. After 1.5 h, TLC (cyclohexane/ethyl acetate, 1:1) indicated the consumption of the starting material (R_f 0.30) and the formation of one major product (R_f 0.64). The reaction mixture was diluted with DCM (40 mL) and washed with HCl (2 M, aq 3 × 40 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude triflate (7.5 g) as yellow crystalline solid.

Cesium fluoride (9.10 g, 60.0 mmol) was added in one portion to a solution of the crude triflate (7.5 g) in 2-methyl-2-propanol (30 mL). The reaction mixture was stirred at 80 °C for 26 h until TLC (cyclohexane/ethyl acetate, 2:1) indicated consumption of the triflate (R_f 0.54) and formation of a new product (R_f 0.61). The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 1:1 $H_2O/NaHCO_3$ (satd aq, 50 mL) and brine (50 mL) sequentially, and the aqueous layer was back-extracted with DCM (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 6:1 → 4:1) to give the title compound **21** as clear oil (4.70 g, 89%): HRMS (ESI +ve) found 285.1110 [M + Na]$^+$, $C_{12}H_{19}FNaO_5^+$ requires 285.1109; $[\alpha]_D^{20}$ −19.7 (*c* 1.06, $CHCl_3$) [lit.[46] $[\alpha]_D^{20}$ −37.0 (*c* 1.00, $CHCl_3$)]; ν_{max} (thin film) fingerprint region only; δ_H ($CDCl_3$, 400 MHz) 1.32 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.50 (3H, s, CH_3), 4.03 (1H, dd, H6, $J_{6,5}$ 4.8, J_{gem} 8.8), 4.10 (1H, ddd, H4, $J_{4,3}$ 2.2, $J_{4,5}$ 8.3, $J_{4,F}$ 29.1), 4.12 (1H, dd, H6′, $J_{6',5}$ 6.1, J_{gem} 8.8), 4.28 (1H, ddd, H5, $J_{5,6}$ 4.9, $J_{5,6'}$ 6.1, $J_{5,4}$ 8.3), 4.69 (1H, dd, H2, $J_{2,1}$ 3.8, $J_{2,F}$ 10.6), 5.01 (1H, dd, H3, $J_{4,3}$ 2.2, $J_{3,F}$ 49.9), 5.95 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz) 25.1 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 67.2 (C6), 72.0 (d, C5, $J_{5,F}$ 7.0), 80.6 (d, C4, $J_{4,F}$ 19.1), 82.5 (d, C2, $J_{2,F}$ 33.4), 93.8 (d, C3, $J_{3,F}$ 184.4), 105.2 (C1), 109.5 ($C(CH_3)_2$), 112.4 ($C(CH_3)_2$); δ_F ($CDCl_3$, 376 MHz) −207.6 (ddd, $J_{F,2}$ 10.8, $J_{F,4}$ 29.2, $J_{F,3}$ 49.8); *m/z* (ESI +ve) 263 ([M + H]$^+$, 100), 285 ([M + Na]$^+$, 72).

3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-*α*-D-glucofuranose, 36. A solution of the diacetonide **21** (4.20 g, 16.0 mmol) in methanol (20 mL) and 1% aqueous sulfuric acid (20 mL) was stirred at rt for 18 h after which TLC (ethyl acetate) indicated the disappearance of starting material (R_f 0.88) and the formation of a product (R_f 0.65). The reaction mixture was neutralized with triethylamine, and the solvent was removed in vacuo to give a residue that was purified by column chromatography (cyclohexane/ethyl acetate, 3:1 → 0:1) to form the monoacetonide **36** (3.55 g, 100%). HRMS *m/z* (ESI +ve) found 245.0794 [M + Na]$^+$, $C_9H_{15}FNaO_5^+$ requires 245.0796; $[\alpha]_D^{20}$ −18.5 (*c* 0.80, $CHCl_3$); ν_{max} (thin film) 3411 (br, m, OH); δ_H ($CDCl_3$, 400 MHz) 1.33 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.68 (2H, s, OH), 3.75 (1H, ddd, H6, *J* 0.5, $J_{6,5}$ 5.1, J_{gem} 11.5), 3.86 (1H, dd, H6′, $J_{6',5}$ 3.2, J_{gem} 11.5) 3.96 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.3, $J_{5,4}$ 8.7), 4.16 (1H, ddd, H4, $J_{4,3}$ 2.2, $J_{4,5}$ 8.8, $J_{4,F}$ 29.3), 4.70 (1H, dd, H2, $J_{2,1}$ 3.9, $J_{2,F}$ 10.8), 5.09 (1H, dd, H3, $J_{3,4}$ 2.2, $J_{3,F}$ 49.9), 5.96 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz) 26.2 (CH_3), 26.6 (CH_3), 64.1 (C6), 68.3 (d, C5, $J_{5,F}$ 6.4), 79.7 (d, C4, $J_{4,F}$ 19.1), 82.4 (d, C2, $J_{2,F}$ 31.8), 94.1 (d, C3, $J_{3,F}$ 182.8), 105.1 (C1), 112.4 ($C(CH_3)_2$); δ_F ($CDCl_3$, 376 MHz) −208.0 (ddd, $J_{F,2}$ 10.8, $J_{F,4}$ 29.2, $J_{F,3}$ 49.8); *m/z* (ESI +ve) 245 ([M + Na]$^+$, 100).

3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-*α*-D-xylofuranose, 37. Sodium periodate (14.5 g, 67.6 mmol) was added in portions to a solution of diol **36** (12.5 g, 56.3 mmol) in 1,4-dioxane/H_2O (2:1, 60 mL). The reaction mixture was stirred at rt for 3 h until TLC (cyclohexane/ethyl acetate, 1:1) showed the consumption of starting material (R_f 0.15) and the formation of a new major product (R_f 0.31) after which time ethanol (50 mL) was added and stirred for a further 20 min. The white solid formed was removed by filtration, and sodium borohydride (2.13 g, 56.3 mmol) was added to the stirred reaction mixture. After 2 h, the formation of the desired product **37** and the consumption of the intermediate aldehyde was confirmed by mass spectrometry (aldehyde: *m/z* 245 [M + MeOH + Na$^+$]). The reaction mixture was adjusted to pH 7 by addition of acetic acid. The mixture was filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography (cyclohexane/ethyl acetate, 6:1 → 1:1) to afford the title compound **37** (9.90 g, 92%): HRMS *m/z* (ESI +ve) found 215.0686 [M + Na]$^+$, $C_8H_{13}FNaO_4^+$ requires 215.0690; $[\alpha]_D^{20}$ −25.1 (*c* 0.95, $CHCl_3$) [lit.[47] $[\alpha]_D^{20}$ −17.1 (*c* 1.06, DCM)]; ν_{max} (thin film) 3437 (br, w, OH); δ_H ($CDCl_3$, 400 MHz) 1.32 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.98 (1H, s, OH), 3.88 (1H, dd, H5, $J_{5,4}$ 5.5, J_{gem} 11.7), 3.93 (1H, ddd, H5′, *J* 1.2, $J_{5',4}$ 6.6, J_{gem} 11.7), 4.35 (1H, dddd, H4, $J_{4,3}$ 2.3, $J_{4,5}$ 5.5, $J_{4,5'}$ 6.6, $J_{4,F}$ 30.2), 4.70 (1H, dd, H2, $J_{2,1}$ 3.9, $J_{2,F}$ 11.2), 4.97 (1H, dd, H3, $J_{3,4}$ 2.4, $J_{3,F}$ 50.4), 5.99 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz) 26.2 (CH_3), 26.6 (CH_3), 59.8 (d, C5, $J_{5,F}$ 9.5), 80.2 (d, C4, $J_{4,F}$ 19.1), 82.8 (d, C2, $J_{2,F}$ 33.4), 94.1 (d, C3, $J_{3,F}$ 184.4), 104.8 (C1), 112.3 ($C(CH_3)_2$); δ_F ($CDCl_3$, 376 MHz) −208.7 (ddd, $J_{F,2}$ 11.4, $J_{F,4}$ 30.2, $J_{F,3}$ 50.4); *m/z* (ESI +ve) 215 ([M + Na]$^+$, 100).

3-Deoxy-3-fluoro-D-xylose, 38. Dowex (50W X8, H$^+$) (2.00 g) was added to a solution of monoacetonide **37** (9.90 g, 51.6 mmol) in 1,4-dioxane/H_2O (1:1, 60 mL). The reaction mixture was stirred at 80 °C for 18 h, after which TLC analysis (ethyl acetate) indicated the disappearance of starting material (R_f 0.74) and the formation of a single product (R_f 0.29). The reaction mixture was filtered and the solvent removed in vacuo to give a residue that was purified by column chromatography (cyclohexane/ethyl acetate, 4:1 → 10% methanol in ethyl acetate) to give the unprotected xylose **38** (6.90 g, 88%) as a white solid in a 3:2, *α*:*β* ratio: HRMS *m/z* (ESI +ve) found 175.0383 [M + Na]$^+$, $C_5H_9FNaO_4^+$ requires 175.0377; mp 106−108 °C (lit.[48] mp 127 °C); ν_{max} (thin film) 3284 (br, s, OH); δ_H (CD_3OD, 400 MHz) 3.20 (1H, ddd, H5*β*, *J* 1.2, *J* 10.8, J_{gem} 11.6), 3.28−3.36 (1H, m, H2*β*), 3.51−3.61 (2H, m, H2*α*, H5*α*), 3.65−3.78 (3H, m, H4*α*, H4*β*, H5′*α*), 3.84 (1H, dt, H5′*β*, $J_{5',4}$ 6.1, J_{gem} 11.5), 4.16 (1H, dt, H3*β*, $J_{3,2} = J_{3,4}$ 8.8, $J_{3,F}$ 53.1), 4.42 (1H, d, H1*β*, $J_{1,2}$ 7.8), 4.44 (1H, dt, H3*α*, $J_{3,2} = J_{3,4}$ 8.4, $J_{3,F}$ 54.4), 5.07 (1H, t, H1*α*, $J_{1,2} = J_{1,F}$ 3.7); δ_C (CD_3OD, 100 MHz) 61.8 (d, C5*α*, $J_{5,F}$ 8.0), 65.7 (d, C5*β*, $J_{5,F}$ 9.5), 69.6 (d, C4*α*, $J_{4,F}$ 19.1), 69.9 (d, C4*β*, $J_{4,F}$ 17.5), 72.2 (d, C2*α*, $J_{2,F}$ 15.9), 74.5 (d, C2*β*, $J_{2,F}$ 17.5), 94.4 (d, C1*α*, $J_{1,F}$ 11.1) 96.5 (d, C3*α*, $J_{3,F}$ 179.6) 98.2 (d, C3*β*, $J_{3,F}$ 182.8) 98.4 (d, C1*β*, $J_{1,F}$ 12.7); δ_F (CD_3OD, 376 MHz) −195.8 (ddt, F*β*, *J* 6.7, $J_{F,2} = J_{F,4}$ 13.6, $J_{F,3}$ 52.8), −201.3 to −201.5 (m, F*α*); *m/z* (ESI +ve) 175 ([M + Na]$^+$, 100).

3-Deoxy-3-fluoro-1,2,4-tri-*O*-acetyl-D-xylopyranose, 39. A solution of fluoroxylose **38** (6.90 g, 45.4 mmol) in acetic anhydride/pyridine (1:1, 60 mL) was stirred at rt for 14 h until TLC (cyclohexane/ethyl acetate, 1:1) indicated the consumption of the starting material (R_f 0.00) and the formation of a single major product (R_f 0.71). The solvent was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (60 mL) and washed sequentially with HCl (2 M, aq, 2 × 60 mL), $NaHCO_3$ (satd aq, 60 mL), and brine (60 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to afford a residue which was purified by column chromatography (cyclohexane/ethyl acetate, 7:1 → 5:1) to give triacetate xylopyranose **39** (11.3 g, 89%) as a white solid in an 8:5, *α*:*β* ratio of anomers: HRMS *m/z* (ESI +ve) found 301.0696 ([M + Na]$^+$), $C_{11}H_{15}FNaO_7^+$ requires 301.0696; mp 44−48 °C; ν_{max} (thin film) 1751 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 2.09 (3H, s, CH_3), 2.11 (12H, s, 4 x CH_3), 2.15 (3H, s, CH_3), 3.46 (1H, dd, H5*β*, $J_{5,4}$ 7.8, J_{gem} 12.2), 3.61 (1H, dd, H5*α*, $J_{5,4}$ 10.8, J_{gem} 11.2), 3.97 (1H, ddd, H5′*α*, *J* 4.6, *J* 6.3, J_{gem} 11.1), 4.18 (1H, dt, H5′*β*, $J_{5',4} = J$ 4.7, J_{gem} 12.2), 4.63 (1H, dt, H3*β*, $J_{3,2} = J_{3,4}$ 7.7, $J_{3,F}$ 49.9), 4.82 (1H, dt, H3*α*, $J_{3,2} = J_{3,4}$ 9.3, $J_{3,F}$ 53.3), 5.02−5.18 (4H, m, H2*α*, H2*β*, H4*α*, H4*β*), 5.69 (1H, d, H1*β*, $J_{1,2}$ 6.6), 6.27 (1H, t, H1*α*, $J_{1,2} = J_{1,F}$ 3.7); δ_C ($CDCl_3$,100 MHz) 20.5, 20.6, 20.7 (×3), 20.8 (CH_3), 60.1 (d, C5*α*, $J_{5,F}$ 6.4), 61.8 (d, C5*β*, $J_{5,F}$ 5.6), 68.2 (d, C4*β*, $J_{4,F}$ 21.5), 68.8 (d, C4*α*, $J_{4,F}$ 17.5), 69.2 (d, C2*β*, $J_{2,F}$ 21.5), 69.6 (d, C2*α*, $J_{2,F}$ 17.5), 88.5 (d, C3*α*, $J_{3,F}$ 190.0), 89.1 (d, C3*β*, $J_{3,F}$ 188.4), 89.6 (d, C1*α*, $J_{1,F}$ 9.5), 91.6 (d, C1*β*, $J_{1,F}$ 8.7), 169.7, 169.1 (×2), 169.6, 169.7 (C═O); δ_F ($CDCl_3$, 376 MHz) −194.9 (ddt, F*β*, $J_{F,5}$ 4.6, $J_{F,2} = J_{F,4}$ 12.6, $J_{F,3}$ 50.4), −199.0 (dddt, F*α*, $J_{F,1}$ 3.4, $J_{F,5}$ 4.6, $J_{F,2} = J_{F,4}$ 12.6, $J_{F,3}$ 53.1); *m/z* (ESI +ve) 301 ([M + Na]$^+$, 100).

Methyl 3-Deoxy-2,4-di-*O*-acetyl-3-fluoro-*β*-D-xylopyranoside, 40. Hydrobromic acid (33% wt in acetic acid, 24.3 mL, 98.9 mmol) was added dropwise to a solution of triacetate **39** (5.50 g, 19.8 mmol) in acetic acid and DCM (7:3, 50 mL), and the reaction was stirred at 5 °C for 5 h until TLC (cyclohexane/ethyl acetate, 1:1) showed the disappearance of starting material (R_f 0.63) and the formation of a major product (R_f 0.77). The reaction mixture was diluted with DCM (20 mL), washed successively with ice−water (50 mL), cold $NaHCO_3$ (satd aq, 50 mL), and ice−water (50 mL). The solvent was concentrated in vacuo to afford the crude bromide as an orange solid.

Silver carbonate (9.30 g, 33.4 mmol) was added to a solution of the crude bromide in methanol (90 mL), and the reaction mixture was

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

stirred in the dark at rt for 15 h until TLC (cyclohexane/ethyl acetate, 1:1) showed the formation of major product (R_f 0.47) and no remaining starting material. After filtration, the solvent was removed in vacuo to afford a residue which was purified by column chromatography (cyclohexane/ethyl acetate, 8:1 → 5:1) to afford the pure methyl diacetate **40** (3.00 g, 60%) as a white solid: HRMS *m/z* (ESI +ve) found 273.0747 [M + Na]$^+$, $C_{10}H_{15}FNaO_6^+$ requires 273.0745; mp 78−80 °C; $[\alpha]_D^{20}$ −71.3 (*c* 0.85, $CHCl_3$) [lit.[49] mp 80−81 °C; $[\alpha]_D^{20}$ −73 (*c* 1.00, $CHCl_3$)]; ν_{max} (thin film) 1749 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 2.10 (3H, s, $COCH_3$), 2.12 (3H, s, $COCH_3$), 3.31 (1H, dd, H5, $J_{5,4}$ 8.3, J_{gem} 12.0), 3.46 (3H, s, OCH_3), 4.15 (1H, dt, H5′, $J_{5',4} = J_{5',F}$ 4.9, J_{gem} 12.0), 4.36 (1H, d, H1, $J_{1,2}$ 6.4), 4.57 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 7.9, $J_{3,F}$ 50.5), 4.99−5.08 (2H, m, H2, H4); δ_C ($CDCl_3$, 100 MHz) 20.7 (×2) ($COCH_3$), 56.5 (OCH_3), 60.8 (d, C5, $J_{5,F}$ 6.4), 68.9 (d, C4, $J_{4,F}$ 20.7), 70.4 (d, C2, $J_{2,F}$ 20.7), 89.7 (d, C3, $J_{3,F}$ 188.4), 101.0 (d, C1, $J_{1,F}$ 8.0), 169.2 (C═O), 169.7 (C═O); δ_F ($CDCl_3$, 376 MHz) −194.7 (ddt, $J_{F,5'}$ 5.0, $J_{F,2} = J_{F,4}$ 12.9, $J_{F,3}$ 50.4); *m/z* (ESI +ve) 273 ([M + Na]$^+$, 100).

Methyl 3-Deoxy-3-fluoro-β-D-xylopyranoside, 41. Sodium methoxide (177 mg, 3.3 mmol) was added to a solution of diacetate **40** (8.20 g, 32.8 mmol) in methanol (100 mL). The reaction mixture was stirred at 40 °C for 15 h when TLC analysis (cyclohexane/ethyl acetate, 1:1) indicated the disappearance of starting material (R_f 0.47) and the formation of a product (R_f 0.19). The solvent was concentrated in vacuo and the residue purified by column chromatography (cyclohexane/ethyl acetate, 1:1 → 0:1) to obtain the title compound **41** (5.27 g, 97%) as a white solid: HRMS *m/z* (ESI +ve) found 189.0527 [M + Na]$^+$, $C_6H_{11}FNaO_4^+$ requires 189.0534; mp 100−102 °C; $[\alpha]_D^{20}$ −61.8 (*c* 0.43, MeOH) [lit.[49] mp 102−104 °C; $[\alpha]_D^{20}$ −56.0 (*c* 1.00, MeOH)]; ν_{max} (thin film) 3395 (br, m, OH), 1749 (s, C═O); δ_H (CD_3CN, 400 MHz) 3.15 (1H, ddd, H5, $J_{5,F}$ 1.2, $J_{5,4}$ 10.2, J_{gem} 11.6), 3.35 (1H, dddd, H2, $J_{2,OH}$ 4.2, $J_{2,1}$ 7.5, $J_{2,3}$ 8.7, $J_{2,F}$ 14.2), 3.43 (3H, s, CH_3), 3.54 (1H, d, OH, *J* 4.8), 3.58 (1H, d, OH, *J* 4.8), 3.72 (1H, ddddd, H4, $J_{4,OH}$ 5.1, $J_{4,5'}$ 5.6, $J_{4,3}$ 8.3, $J_{4,5}$ 10.2, $J_{4,F}$ 13.4), 3.84 (1H, dt, H5′, $J_{5',4} = J_{5',F}$ 5.9, J_{gem} 11.6), 4.11 (1H, dd, H1, *J* 1.0 $J_{1,2}$ 7.6), 4.17 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 8.6, $J_{3,F}$ 52.8); δ_C (CD_3CN, 100 MHz) 57.3 (CH_3), 65.2 (d, C5, $J_{5,F}$ 8.8), 69.0 (d, C4, $J_{4,F}$ 17.5), 72.7 (d, C2, $J_{2,F}$ 18.3), 97.7 (d, C3, $J_{3,F}$ 182.0), 104.9 (d, C1, $J_{1,F}$ 11.1); δ_F (CD_3CN, 376 MHz) −194.8 (ddt, $J_{F,5'}$ 5.7, $J_{F,2} = J_{F,4}$ 13.7, $J_{F,3}$ 52.6); *m/z* (ESI +ve) 189.1 ([M + Na]$^+$, 100).

Methyl *N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-β-L-ribopyranoside, 26. Triflic anhydride (14.0 mL, 125.2 mmol) was added dropwise to a solution of diol **41** (5.20 g, 31.3 mmol) and pyridine (11.0 mL, 187.8 mmol) in DCM (50 mL) at −20 °C. The reaction mixture was stirred between −20 and −10 °C for 2 h, after which TLC (cyclohexane/ethyl acetate, 1:1) showed the consumption of starting material (R_f 0.12) and the formation of one major product (R_f 0.65). The reaction mixture was diluted with DCM (30 mL) and washed with HCl (2 M, aq, 2 × 70 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to afford the crude triflate (13.3 g) as an orange solid.

Benzylamine (13.0 mL, 156.5 mmol) was added to a solution of crude triflate (13.3 g) in acetonitrile (80 mL), and the reaction mixture was stirred at 65−70 °C for 2 h until TLC analysis (cyclohexane/ethyl acetate, 1:1) indicated the consumption of the starting material (R_f 0.65) and the formation of a single product (R_f 0.67). The solvent was concentrated in vacuo and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 7:1 → 2:1) to obtain ribopyranoside **26** (7.20 g, 97%) as a light yellow oil: HRMS *m/z* (ESI +ve) found 238.1239 [M + H]$^+$, $C_{13}H_{17}FNO_2^+$ requires 238.1238; $[\alpha]_D^{20}$ −13.7 (*c* 1.13, $CHCl_3$); ν_{max} (thin film) fingerprint region only; δ_H ($CDCl_3$, 400 MHz) 3.42 (3H, s, OCH_3), 3.64 (1H, ddt, H4, $J_{4,5} = J_{4,5'}$ 1.7, $J_{4,2}$ 4.5, $J_{4,F}$ 11.0), 3.73 (1H, ddd, H2, *J* 1.3, $J_{2,4}$ 4.5, $J_{2,F}$ 11.6), 3.75 (1H, br-d, H5, J_{gem} 11.0), 4.09 (2H, s, H6), 4.33 (1H, ddd, H5′, *J* 1.3, *J* 5.1, J_{gem} 10.9), 4.67 (1H, t, H1, *J* 1.2), 4.93 (1H, d, H3, $J_{3,F}$ 58.9), 7.15−7.37 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 51.3 (C6), 55.9 (OCH_3), 61.5 (d, C5, $J_{5,F}$ 5.6), 64.5 (d, C4, $J_{4,F}$ 18.3), 67.4 (d, C2, $J_{2,F}$ 18.3), 93.3 (d, C3, $J_{3,F}$ 210.6), 100.2 (d, C1, $J_{1,F}$ 8.0), 126.7, 128.2, 128.3 (ArCH), 138.9 (ArC); δ_F ($CDCl_3$, 376 MHz) −206.5 (br-d, $J_{F,3}$ 59.3) *m/z* (ESI +ve) 238.2 ([M + H]$^+$, 100), 260 ([M + Na]$^+$, 2).

Methyl *N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-L-ribonate, 24L. Ribopyranoside **26** (200 mg, 0.84 mmol) was dissolved in 2 M aq HCl/1,4-dioxane (5:1, 2 mL). The reaction mixture was stirred at 40 °C for 21 h. After the consumption of starting material and the formation of aldehyde was confirmed by mass spectrometry (*m/z* (ESI +ve) 278 [M + MeOH + Na]$^+$), the solvent was removed in vacuo to give a black solid. A solution of the black solid and potassium carbonate (349 mg, 2.53 mmol) was stirred at 0 °C under nitrogen atmosphere. Iodine solution (271 mg, 1.09 mmol), which was predissolved in anhydrous methanol (4 mL) by sonication, was added dropwise into the reaction mixture at 0 °C. Then the mixture was stirred under 5 °C for 2 h until the completion of reaction was confirmed by the mass spectrum. Sodium sulfite (satd aq, 5 mL) was poured into the reaction mixture, and distilled water (40 mL) was added to dissolve the precipitate. The aqueous layer was exacted with ethyl acetate (4 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtrated and concentrated in vacuo to afford the crude product which was further purified by column chromatography (cyclohexane/ethyl acetate, 5:1 → 1:1) to yield the title compound **24L** as a brown oil (157 mg, 74%).

Large Scale. Ribopyranoside **26** (1.565 g, 6.6 mmol) was dissolved in 2 M aq HCl/1,4-dioxane (5:1, 120 mL). The reaction mixture was stirred at 40 °C for 21 h. After the consumption of starting material and the formation of aldehyde was confirmed by mass spectrometry (*m/z* (ESI +ve) 278 [M + MeOH + Na]$^+$), solvent was removed in vacuo to give a black solid. A solution of the black solid and potassium carbonate (2.74 g, 19.8 mmol) was stirred at 0 °C under nitrogen atmosphere in MeOH (60 mL). Iodine (2.18g, 8.6 mmol), which was predissolved in anhydrous methanol (60 mL) by sonication, was added dropwise into the reaction mixture at 0 °C. Then the mixture was stirred at 0 °C for 2 h until completion of reaction was confirmed by mass spectrum. Sodium sulfite (satd aq, 30 mL) was poured into the reaction mixture, and distilled water (100 mL) was added to dissolve the precipitate. The aqueous layer was exacted with ethyl acetate (4 × 100 mL), and the combined organic layers were dried ($MgSO_4$), filtrated, and concentrated in vacuo to afford the crude product which was further purified by column chromatography (cyclohexane/ethyl acetate, 5:1 → 1:1) to yield the title compound **24L** as a brown oil (920 mg, 55%): HRMS *m/z* (ESI +ve) found 276.1014 [M + Na]$^+$, $C_{13}H_{16}FNNaO_3^+$ requires 276.1006; $[\alpha]_D^{20}$ −43.8 (*c* 0.54, $CHCl_3$); ν_{max} (thin film) 3439 (br, w, OH), 1740 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 2.35 (1H, s, OH), 3.17 (1H, dd, H5, $J_{5,4}$ 2.7, J_{gem} 12.1), 3.37 (1H, ddddd, H4, *J* 0.6, $J_{4,5'}$ 2.2, $J_{4,5}$ 2.7, $J_{4,3}$ 4.9, $J_{4,F}$ 21.7), 3.44 (1H, dd, H5′, $J_{5',4}$ 2.1, J_{gem} 12.1), 3.70 (3H, s, OCH_3), 3.73 (1H, d, H6, J_{gem} 12.5), 3.78 (1H, ddd, H2, *J* 0.6, $J_{2,3}$ 4.8, $J_{2,F}$ 22.2), 3.99 (1H, d, H6′, J_{gem} 12.5), 5.05 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 4.9, $J_{3,F}$ 55.9), 7.26−7.36 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 52.1 (OCH_3), 60.1 (d, C5, $J_{5,F}$ 4.0), 60.5 (C6), 68.0 (d, C2, $J_{2,F}$ 21.5), 69.7 (d, C4, $J_{4,F}$ 20.7), 84.4 (d, C3, $J_{3,F}$ 213.8), 128.0, 128.6, 129.3 (ArCH), 135.9 (ArC), 170.2 (d, C1, *J* 5.6); δ_F ($CDCl_3$, 376 MHz) −181.5 (dt, $J_{F,2} = J_{F,4}$ 22.0 $J_{F,3}$ 55.7; *m/z* (ESI +ve) 254.2 ([M + H]$^+$, 100), 276.1 ([M + Na]$^+$, 22).

Methyl *N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-L-ribonamide, 49. Methylamine (0.3 mL, 2.6 mmol, in absolute ethanol) was added to a solution of methyl ester **24L** (32 mg, 0.13 mmol) and calcium chloride (14 mg, 0.13 mmol) in anhydrous methanol (1.5 mL). The reaction mixture was stirred at 40 °C for 2 h until the completion of reaction was confirmed by mass spectrometry (*m/z* (ESI +ve) 253 [M + H]$^+$). The reaction mixture was poured onto ethyl acetate (50 mL), dried ($MgSO_4$), and filtered and the solvent removed in vacuo to yield the title compound **49** as a yellow oil which was used without further purification (24 mg, 74%): HRMS *m/z* (ESI +ve) found 275.1166 [M + Na]$^+$, $C_{13}H_{17}FN_2NaO_2^+$ requires 275.1166; $[\alpha]_D^{20}$ −16.5 (*c* 1.22, $CHCl_3$); ν_{max} (thin film) 3337 (br, m, OH, NH), 1654 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 2.62 (3H, dt, H7, *J* 1.2, $J_{7,NH}$ 4.9), 3.36−3.46 (1H, m, H4), 3.40 (1H, dd, H5, $J_{5,4}$ 2.8, J_{gem} 11.9), 3.53 (1H, dd, H5′, $J_{5,4}$ 3.1, J_{gem} 12.1), 3.71 (1H, ddt, H2, *J* 1.6, $J_{2,3}$ 4.9, $J_{2,F}$ 23.2), 3.75 (1H, d, H6, J_{gem} 12.0), 3.80 (1H, d, H6′, J_{gem} 12.2), 4.81 (1H, dt, H3, $J_{3,2} = J_{3,4}$ = 4.6, $J_{3,F}$ 56.2), 6.70 (1H, br-s, NH), 7.26−7.35 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 25.6 (C7), 60.8 (d, C5, $J_{5,F}$ 4.0), 70.3 (d, C4, $J_{2,F}$ 19.1), 61.6 (C6), 70.5 (d, C2, $J_{4,F}$ 19.1), 85.8 (C3, d, $J_{3,F}$ 216.2), 128.2, 128.8, 129.3 (ArCH), 136.2 (ArC), 170.1 (C1); δ_F ($CDCl_3$, 376 MHz) −177.1 (dt, $J_{F,2} = J_{F,4}$ 23.4 $J_{F,3}$ 56.3); *m/z* (ESI +ve) 253 ([M + H]$^+$, 100), 275 ([M + Na]$^+$, 25).

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

Methyl 3-Fluoro-2,4-imino-2,3,4-trideoxy-L-ribonamide, 11. Palladium on charcoal (10% wt, 5 mg) was added to a solution of protected riboamide **49** (24 mg, 0.095 mmol) in 1,4-dioxane/H_2O (1:2, 3 mL). The reaction mixture was flushed with argon and hydrogen gas sequentially. The reaction mixture was stirred vigorously for 3 h at rt under hydrogen until the completion of reaction was confirmed by mass spectrometry (*m/z* (ESI +ve) 163 $[M + H]^+$). After filtration, the solvent was removed in vacuo to afford the title compound **11** as a light yellow oil which was used without further purification (14 mg, 90%): HRMS *m/z* (ESI +ve) found 185.0696 $[M + Na]^+$, $C_6H_{11}FN_2NaO_2^+$ requires 185.0697; $[\alpha]_D^{20}$ −61.5 (*c* 0.69, MeOH); ν_{max} (thin film) 3275 (br, m, OH, NH), 1659 (s, C=O); δ_H (CD_3OD, 400 MHz) 2.81 (3H, s, H6), 3.74 (2H, s, H5), 4.28 (1H, br-d, H4, $J_{4,F}$ 16.8), 4.65 (1H, br-d, H2, $J_{2,F}$ 17.3), 5.10 (1H, br-d, H3, $J_{3,F}$ 55.5); δ_C (CD_3OD, 100 MHz) 26.0 (C6), 63.4 (d, C5, $J_{5,F}$ 4.0), 64.1 (d, C2, $J_{2,F}$ 16.0), 64.3 (d, C4, $J_{4,F}$ 16.0), 90.6 (d, C3, $J_{3,F}$ 214.0), 174.2 (C1); δ_F (CD_3OD, 376 MHz) −177.0 (dt, $J_{F,2} = J_{F,4}$ 19.8 $J_{F,3}$ 54.3); *m/z* (ESI +ve) 163 ($[M + H]^+$, 100), 185 ($[M + Na]^+$, 16).

***N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-L-ribonic Acid, 35L.** Potassium carbonate (29 mg, 0.21 mmol) was added to a solution of methyl ester **24L** (40 mg, 0.16 mmol) in 1,4-dioxane/H_2O (1:2, 3 mL). The reaction mixture was stirred at 40 °C for 18 h until the completion of reaction was confirmed by mass spectrometry. HCl (2 M, aq, 0.4 mL) was added to adjust the mixture to pH 4. The solvent was removed in vacuo to obtain the crude acid, which was then loaded in 1,4-dioxane/H_2O (1:2) onto a short column of Dowex (50W X8, H^+) (prewashed with water, 1,4-dioxane and water sequentially until the eluent was neutral). After washing again with water and 1,4-dioxane and water (1:2), the pure product was released with aqueous ammonia (2 M). Then solvent was removed in vacuo to yield the title compound **35L** as a light yellow glass (22 mg, 43%): HRMS *m/z* (ESI +ve) found 240.1020 $[M + H]^+$, $C_{12}H_{15}FNO_3^+$ requires 240.1030; $[\alpha]_D^{20}$ −13.5 (*c* 1.07, H_2O); ν_{max} (thin film) 3070 (br, s, OH), 1630 (s, C=O); δ_H (Py-d_5, 400 MHz) 3.63 (1H, dq, H4, $J_{4,3} = J_{4,5} = J_{4,5'}$ 4.5, $J_{4,F}$ 22.1), 3.73 (1H, dd, H5, $J_{5,4}$ 4.6, J_{gem} 11.7), 3.77 (1H, dd, H5′, $J_{5',4}$ 4.0, J_{gem} 11.6), 3.95 (1H, d, H6, J_{gem} 13.0), 4.15 (1H, dd, H2, $J_{2,3}$ 5.0, $J_{2,F}$ 23.3), 4.35 (1H, d, H6′, J_{gem} 13.0), 5.62 (1H, dt, H3, $J_{3,2}=J_{3,4}$ 4.9, $J_{3,F}$ 57.0), 7.22−7.64 (5H, m, ArH), 7.87 (2H, br-s, OH); δ_C (Py-d_5, 100 MHz) 61.4 (C6), 62.4 (d, C5, $J_{5,F}$ 3.2), 69.6 (d, C2, $J_{2,F}$ 18.3), 70.7 (d, C4, $J_{4,F}$ 18.3), 88.0 (d, C3, $J_{3,F}$ 210.6), 128.1, 129.0, 130.6 (ArCH), 137.8 (ArC), 174.0 (C1); δ_F (Py-d_5, 376 MHz) −178.5 (dt, $J_{F,2} = J_{F,4}$ 22.8, $J_{F,3}$ 56.8); *m/z* (ESI +ve) 240 ($[M + H]^+$, 100), 262 ($[M + Na]^+$, 25).

3-Fluoro-2,4-imino-2,3,4-trideoxy-L-ribonic Acid [(2*R*,3*S*,4*S*)-3-Fluoro-4-(hydroxymethyl)azetidine-2-carboxylic Acid], 10L. Palladium on charcoal (10% wt, 5 mg) was added to a solution of *N*-benzyl-protected ribonic acid **35L** (21 mg, 0.09 mmol) in 1,4-dioxane/H_2O (2 mL, 1:2). The reaction was flushed with nitrogen, argon, and hydrogen gas sequentially and stirred vigorously for 15 h at rt under hydrogen until mass spectrometry showed the completion of reaction. After filtration, the solvent was removed in vacuo to obtain a residue which was purified on a short column of Dowex (50W X8, H^+) (as illustrated above). The solvent was removed in vacuo to afford the title compound **10L** as a light yellow glass (11 mg, 82%): HRMS *m/z* (ESI −ve) found 148.0409 $[M - H]^-$, $C_5H_7FNO_3^-$ requires 148.0415; $[\alpha]_D^{20}$ −30.6 (*c* 0.50, H_2O); ν_{max} (thin film) 3233 (br, s, OH), 1630 (s, C=O); δ_H (D_2O, 400 MHz) 3.91 (1H, dd, H5, $J_{5,4}$ 3.7, J_{gem} 13.2), 3.97 (1H, dd, H5′, $J_{5',4}$ 3.9, J_{gem} 13.2), 4.66 (1H, dq, H4, $J_{4,3} = J_{4,5} = J_{4,5'}$ 4.2, $J_{4,F}$ 19.3), 4.92 (1H, dd, H2, $J_{2,3}$ 4.8, $J_{2,F}$ 21.3), 5.31 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 4.8, $J_{3,F}$ 56.1); δ_C (D_2O, 100 MHz) 58.0 (d, C5, $J_{5,F}$ 4.0), 63.8 (d, C2, $J_{2,F}$ 24.6), 64.9 (d, C4, $J_{4,F}$ 26.2), 87.9 (d, C3, $J_{3,F}$ 210.6), 170.4 (C1); δ_F (D_2O, 376 MHz) −178.3 (dt, $J_{F,2} = J_{F,4}$ 20.4, $J_{F,3}$ 56.1); *m/z* (ESI −ve): 148 ($[M - H]^+$, 100).

***N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-*meso*-ribitol, 42.** *Method 1.* The bicyclic azetidine **26** (100 mg, 0.42 mmol) was dissolved in 2 M aq HCl/1,4-dioxane (5:1, 1 mL). The reaction mixture was stirred at 40 °C for 23 h after which the consumption of starting material and the formation of aldehyde were confirmed by mass spectrometry (*m/z* (ESI +ve) 278 $[M + MeOH + Na]^+$). The solvent was removed in vacuo to give a black glass.

Sodium borohydride (196 mg, 2.52 mmol) was added to a solution of the black residue in methanol (4 mL). After the solution was stirred at rt for 2 h, mass spectrometry (*m/z* 248) showed the completion of reaction. The solvent was concentrated in vacuo to obtain a residue which was purified on a short column of Dowex (50W X8, H^+) (prewashed with water, 1,4-dioxane, and water sequentially until the eluent was neutral) to yield the desired diol **42** as a brown oil (39 mg, 40% over two steps).

Method 2. Sodium borohydride (15 mg, 0.39 mmol) was added into a solution of methyl ester **24L** (100 mg, 0.39 mmol) in methanol (2 mL) at 0 °C. After the solution was stirred at rt for 3 h, mass spectrometry (*m/z* 248) showed the completion of reaction. The solvent was removed in vacuo to obtain a residue that was purified on a short column of Dowex (50W X8, H^+) (prewashed with water, 1,4-dioxane, and water sequentially until the eluent was neutral) to yield the desired diol **42** as a brown oil (79 mg, 90%): HRMS *m/z* (ESI +ve) found 248.1057 $[M + Na]^+$, $C_{12}H_{16}FNNaO_2^+$ requires 248.1057; $[\alpha]_D^{20}$ 0.0 (*c* 1.0, CH_3OH); ν_{max} (thin film) 3355 (br, s, OH); δ_H ($CDCl_3$, 400 MHz) 2.81 (2H, br-s, OH x 2), 3.25 (2H, ddt, H2(4), $J_{2,1} = J_{2,1'}$ 3.2, $J_{2,3}$ 5.1, $J_{2,F}$ 22.8), 3.36 (2H, dd, H1(5), $J_{1,2}$ 3.2, J_{gem} 11.7), 3.52 (2H, dd, H1′(5′), $J_{1',2}$ 2.8, J_{gem} 11.9), 3.78 (2H, s, H6), 4.93 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 4.7, $J_{3,F}$ 56.8), 7.27−7.36 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 60.8 (d, C1(5), *J* 4.8), 61.2 (C6), 70.3 (d, C2(4), *J* 19.9), 83.9 (d, C3, *J* 207.4), 127.9, 128.6, 129.1 (ArCH), 137.0 (ArC); δ_F ($CDCl_3$, 376 MHz) −184.2 (dt, $J_{F,2} = J_{F,4}$ 22.9, $J_{F,3}$ 56.1); *m/z* (ESI +ve) 248 ($[M + Na]^+$, 100).

3-Fluoro-2,4-imino-2,3,4-trideoxy-*meso*-ribitol, 15. Palladium on charcoal (10% wt, 5 mg) was added to a solution of *N*-benzyl-protected ribonic acid **42** (20 mg, 0.09 mmol) in 1,4-dioxane/H_2O (1:2). The reaction was flushed with nitrogen, argon, and hydrogen gas sequentially and stirred vigorously for 5 h at rt under hydrogen until mass spectrometry showed the completion of the reaction (*m/z* (ESI +ve) 136 $[M + H]^+$). After filtration, the solvent was concentrated in vacuo to obtain a residue which was purified by a short column of Dowex (50W X8, H^+) (as illustrated above). The solvent was concentrated in vacuo to afford the title compound **15** as a light yellow oil (12 mg, 100%): HRMS *m/z* (ESI +ve) found 158.0590 $[M + Na]^+$, $C_5H_{10}FNNaO_2^+$ requires 158.0588; $[\alpha]_D^{20}$ 0.0 (*c* 1.0, CH_3OH); ν_{max} (thin film) 3330 (br, s, OH); δ_H (D_2O, 400 MHz) 3.66 (4H, d, H1(5), $J_{1,2}$ 5.7), 3.90 (2H, dq, H2(4), $J_{2,1} = J_{2,3} = J$ 5.8, $J_{2,F}$ 21.4), 4.80 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 5.7, $J_{3,F}$ 56.0); δ_C (D_2O, 100 MHz) 62.3 (d, C2(4), $J_{2,F}$ 20.0), 62.8 (d, C1(5), $J_{1,F}$ 3.8), 89.3 (d, C3, $J_{3,F}$ 209.8); δ_F (D_2O, 376 MHz) −174.8 (dt, $J_{F,2} = J_{F,4}$ 21.8, $J_{F,3}$ 56.4); *m/z* (ESI +ve) 136 ($[M + H]^+$, 100).

Methyl *N*-Benzyl-3-fluoro-2,4-imino-5-*O*-mesyl-2,3,4-trideoxy-L-ribonate, 43. Methanesulfonyl chloride (0.05 mL, 0.60 mmol) was added to a solution of methyl ester **24L** (100 mg, 0.40 mmol) in pyridine (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h when TLC (cyclohexane/ethyl acetate, 1:1) showed the consumption of starting material (R_f 0.38) and the formation of product (R_f 0.46). The solvent was removed in vacuo, and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate, 5:1 → 2:1) to give the product **43** as a yellow oil (133 g, 100%): HRMS *m/z* (ESI +ve) found 354.0777 $[M + Na]^+$, $C_{14}H_{18}FNNaO_5S^+$ requires 354.0782; $[\alpha]_D^{20}$ −22.1 (*c* 0.57, $CHCl_3$); ν_{max} (thin film) 1744 (s, C=O); δ_H ($CDCl_3$, 400 MHz) 2.97 (3H, s, CH_3), 3.44 (1H, dq, H4, $J_{4,3} = J_{4,5} = J_{4,5'}$ 4.6, $J_{4,F}$ 20.7), 3.66 (3H, s, CH_3), 3.73 (1H, dd, H2, $J_{2,3}$ 5.1, $J_{2,F}$ 21.3), 3.79 (1H, d, H6, J_{gem} 12.7), 3.93 (1H, d, H6′, J_{gem} 12.5), 3.97 (1H, dd, H5, $J_{5,4}$ 4.2, J_{gem} 11.3), 4.10 (1H, dd, H5′, $J_{5',4}$ 4.5, J_{gem} 11.6), 4.95 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 5.0, $J_{3,F}$ 55.3), 7.25−7.36 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 37.6 (SO_2CH_3), 52.1 (OCH_3), 60.5 (C6), 66.4 (d, C4, $J_{4,F}$ 21.5), 67.7 (d, C2, $J_{2,F}$ 21.5), 67.9 (d, C5, $J_{5,F}$ 4.0), 84.5 (d, C3, $J_{3,F}$ 217.0), 128.0, 128.5, 129.6 (ArCH), 135.3 (ArC), 169.8 (C1, d, *J* 4.8); δ_F ($CDCl_3$, 376 MHz) −179.6 (dt, $J_{F,2} = J_{F,4}$ 20.9, $J_{F,3}$ 55.3); *m/z* (ESI +ve) 332 ($[M + H]^+$, 100).

Methyl *N*-Benzyl-5-azido-3-fluoro-2,4-imino-2,3,4,5-tetra-deoxy-L-ribonate, 27. Sodium azide (13 mg, 0.20 mmol) was added to a solution of mesylate **43** (50 mg, 0.15 mmol) in DMF (2 mL), and the reaction mixture was stirred at 60 °C for 26 h. After this time, TLC analysis (cyclohexane/ethyl acetate, 1:1) indicated the disappearance of the starting material (R_f 0.48) and the formation of a single product

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

(R_f 0.78). The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1:1 H_2O/brine (satd aq) (3 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to obtain a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 7:1 → 5:1) to yield the title compound **27** as a light yellow oil (32 mg, 80%): HRMS m/z (ESI +ve) found 301.1072 $[M + Na]^+$, $C_{13}H_{15}FN_4NaO_2^+$ requires 301.1071; $[\alpha]_D^{20}$ −61.7 (c 1.62, $CHCl_3$); ν_{max} (thin film) 2102 (s, N_3), 1743 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 3.05 (1H, dd, H5, $J_{5,4}$ 4.4, J_{gem} 13.2), 3.10 (1H, dd, H5′, $J_{5',4}$ 4.4, J_{gem} 13.2), 3.33 (1H, ddq, H4, J 0.7, $J_{4,3} = J_{4,5} = J_{4,5'}$ 4.7, $J_{4,F}$ 21.2), 3.70 (3H, s, CH_3), 3.70 (1H, ddd, H2, J 0.7, $J_{2,3}$ 5.0, $J_{2,F}$ 21.5), 3.75 (1H, d, H6, J_{gem} 12.5), 4.00 (1H, d, H6′, J_{gem} 12.7), 4.96 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 5.0, $J_{3,F}$ 55.7), 7.30−7.35 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 51.5 (d, C5, $J_{5,F}$ 4.0), 52.1 (CH_3), 60.9 (C6), 67.4 (d, C4, $J_{4,F}$ 20.7), 68.0 (d, C2, $J_{2,F}$ 21.5), 85.3 (d, C3, $J_{3,F}$ 215.4), 127.9, 128.5, 129.7 (ArCH), 135.6 (ArC), 170.0 (d, C1, $J_{1,F}$ 5.6); δ_F ($CDCl_3$, 376 MHz) −179.7 (dt, $J_{F,2} = J_{F,4}$ 21.5, $J_{F,3}$ 55.7); m/z (ESI +ve) 301 ($[M + Na]^+$, 100).

Methyl *N*-Benzyl-5-*O*-(*tert*-butyldimethylsilyl)-3-fluoro-2,4-imino-2,3,4-trideoxy-L-ribonate, 50. *tert*-Butyldimethylsilyl chloride (111 mg, 0.74 mmol) was added to a solution of methyl ester **24L** (157 mg, 0.62 mmol) in DMF (10 mL), and the reaction mixture was stirred at rt for 2 h. After this time, TLC analysis (cyclohexane/ethyl acetate, 1:1) indicated the disappearance of starting material (R_f 0.50) and the formation of a major product (R_f 0.87). The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1:1 H_2O/brine (satd aq) (2 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to yield the title compound **50** as a brown oil (218 mg, 95%): HRMS m/z (ESI +ve) found 390.1878 $[M + Na]^+$, $C_{19}H_{30}FNNaO_3Si^+$ requires 390.1871; $[\alpha]_D^{20}$ −16.4 (c 0.90, $CHCl_3$); ν_{max} (thin film) 1745 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 0.00, 0.01 (2 × 3H, 2s, CH_3), 0.87 (9H, s, $C(CH_3)_3$), 3.27 (1H, dq, H4, $J_{4,3} = J_{4,5} = J_{4,5'}$ 5.4, $J_{4,F}$ 21.5), 3.47 (1H, ddd, H5, J 1.0, $J_{5,4}$ 5.4, J_{gem} 10.8), 3.51 (1H, dd, H5′, $J_{5',4}$ 5.7, J_{gem} 10.8), 3.64 (1H, dd, H2, $J_{2,3}$ 5.1, $J_{2,F}$ 21.5), 3.65 (3H, s, OCH_3), 3.82 (1H, d, H6, J_{gem} 12.9), 3.91 (1H, d, H6′, J_{gem} 12.9), 4.85 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 5.1, $J_{3,F}$ 56.2), 7.25−7.35 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) −5.5, −5.4 (CH_3Si), 18.2 ($C(CH_3)_2$), 25.8 ($C(CH_3)_2$), 51.9 (OCH_3), 60.9 (C6), 63.7 (d, C5, $J_{5,F}$ 4.0), 67.8 (d, C2, $J_{2,F}$ 21.5), 69.3 (d, C4, $J_{4,F}$ 19.1), 86.2 (d, C3, $J_{3,F}$ 214.6), 127.6, 128.3, 129.7 (ArCH), 136.0 (ArC), 170.6 (d, C1, $J_{1,F}$ 4.8); δ_F ($CDCl_3$, 376 MHz) −179.0 (dt, $J_{F,2} = J_{F,4}$ 21.8, $J_{F,3}$ 56.1); m/z (ESI +ve) 368 ($[M + H]^+$, 100), 390 ($[M + Na]^+$, 30).

Methyl *N*-Benzyl-5-*O*-(*tert*-butyldimethylsilyl)-3-fluoro-2,4-imino-2,3,4-trideoxy-L-ribonamide, 52. Methylamine (0.30 mL, 2.6 mmol, in absolute ethanol) was added to a solution of methyl ester **50** (42 mg, 0.11 mmol) and calcium chloride (12.0 mg, 0.11 mmol) in anhydrous methanol (1.0 mL). The reaction mixture was stirred at 45 °C for 2 h when the completion of reaction was confirmed by mass spectrometry (m/z (ESI +ve) 367 $[M + H]^+$). The pH of the reaction mixture was adjusted to pH 5 using NH_4Cl (satd aq)/H_2O (1:3, 2 mL), and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried ($MgSO_4$) and filtered, and solvent was removed in vacuo to yield the amide **52** as a yellow oil (41 mg, 100%): HRMS m/z (ESI +ve) found 389.2037 $[M + Na]^+$, $C_{19}H_{31}FN_2NaO_2Si^+$ requires 389.2031; $[\alpha]_D^{20}$ −4.4 (c 0.82, $CHCl_3$); ν_{max} (thin film) 1681 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 0.01 (6H, s, CH_3), 0.88 (9H, s, $C(CH_3)_3$), 2.62 (3H, d, NCH_3, $J_{CH3,NH}$ 4.9), 3.32−3.42 (1H, m, H4), 3.38 (1H, dd, H5, J 3.3, J_{gem} 11.1), 3.53 (1H, dd, H5′, $J_{5',4}$ 3.5, J_{gem} 10.9), 3.68 (1H, dd, H2, $J_{2,3}$ 4.5, $J_{2,F}$ 24.1), 3.73 (1H, d, H6, J_{gem} 12.5), 3.80 (1H, d, H6′, J_{gem} 12.2), 4.73 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 4.4, $J_{3,F}$ 56.2), 6.88 (1H, q, NH, $J_{NH,CH3}$ 5.0), 7.25−7.35 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) −5.6, −5.5 (CH_3Si), 18.2 ($C(CH_3)_2$), 25.4 (NCH_3), 25.7 ($C(CH_3)_2$), 61.7 (C6), 62.2 (d, C5, $J_{5,F}$ 4.8), 70.4 (d, C4, $J_{4,F}$ 19.9), 70.5 (d, C2, $J_{2,F}$ 20.7), 86.2 (d, C3, $J_{3,F}$ 216.2), 127.9, 128.6, 129.2 (ArCH), 136.6 (ArC), 170.4 (d, C1, $J_{1,F}$ 5.6); δ_F ($CDCl_3$, 376 MHz) −176.3 (dt, $J_{F,2} = J_{F,4}$ 24.3, $J_{F,3}$ 56.4); m/z (ESI +ve) 367 ($[M + H]^+$, 100), 389 ($[M + Na]^+$, 30).

Methyl *N*-(*N*-Benzyl-8-fluoro-7,9-imino-8,7,9-trideoxy-10-*O*-(*tert*-butyldimethylsilyl)-L-ribonamido)-3-fluoro-2,4-imino-2,3,4-trideoxy-5-*O*-(*tert*-butyldimethylsilyl)-L-ribonamide, 54. Potassium carbonate (19 mg, 0.14 mmol) was added to a solution of methyl ester **50** (40 mg, 0.11 mmol) in 1,4-dioxane/H_2O (2 mL, 1:1). The reaction mixture was stirred at 40 °C for 26 h until mass spectrometry indicated completion of the hydrolysis (m/z (ESI −ve): 352 $[M - H]^-$), and the solvent was removed in vacuo.

Palladium on charcoal (10% wt., 5 mg) was added to a solution of **52** (40 mg, 0.11 mmol) in 1,4-dioxane/H_2O (3 mL, 1:2). The reaction was flushed with argon and hydrogen gas sequentially and then stirred vigorously for 5 h at rt under hydrogen until mass spectrometry showed the completion of reaction (m/z (ESI +ve) 277 $[M + H]^+$). After filtration, the solvent was removed in vacuo to afford a residue that was used without further purification.

N,*N*,*N*′,*N*′-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU, 50 mg, 0.13 mmol) was added to a solution of the crude acid (57 mg) and amine (30 mg) in anhydrous DMF (1.5 mL). After the mixture was stirred for 20 min, triethylamine (0.02 mL) was added to the reaction mixture, which was stirred rt for a further 20 h until TLC analysis (cyclohexane/ethyl acetate, 1:1) showed the consumption of the starting materials and formation of one major product (R_f 0.75). The reaction mixture was diluted with ethyl acetate (20 mL) and washed with half saturated brine (20 mL). The organic layer was dried ($MgSO_4$) and filtered and the solvent removed in vacuo to give a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 1:1) to give the pure peptide **54** as a yellow oil (30 mg, 45%): HRMS m/z (ESI +ve) found 634.3288 $[M + Na]^+$, $C_{30}H_{51}F_2N_3NaO_4Si_2^+$ requires 634.3278; $[\alpha]_D^{20}$ −44.0 (c 0.93, $CHCl_3$); ν_{max} (thin film) 1682 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 0.01, 0.03, 0.06, 0.07 (12H, 4s, CH_3), 0.85 (9H, s, $C(CH_3)_3$), 0.88 (9H, s, $C(CH_3)_3$), 2.74 (3H, d, NCH_3, $J_{CH3,NH}$ 4.9), 3.36 (1H, dq, H9, $J_{9,8} = J_{9,10} = J_{9,10'}$ 5.0, $J_{9,F}$ 21.9), 3.56 (1H, dd, H7, $J_{7,8}$ 4.9, $J_{7,F}$ 20.3), 3.50−3.64 (1H, m, H4), 3.57−3.63 (1H, m, H5), 3.70 (2H, br-s, -$\underline{CH_2}$Ar), 3.74 (2H, br-s, H10), 4.19 (1H, d, H5′, J_{gem} 12.2), 4.31 (1H, br-d, H2, $J_{2,F}$ 23.7), 4.79 (1H, dt, H8, $J_{8,7} = J_{8,9}$ 4.8, $J_{8,F}$ 56.1), 5.08 (1H, br-d, H3, $J_{3,F}$ 55.3), 7.26−7.35 (5H, m, ArH), 7.43 (1H, br-s, NH); δ_C ($CDCl_3$, 100 MHz) −5.7, −5.4 (x 2) (CH_3Si), 18.2 ($C(CH_3)_2$), 25.7 ($NHCH_3$), 25.8 ($C(CH_3)_3$), 62.5 (C5, -$\underline{C}H_2$Ar), 64.1 (C10), 66.0 (C7), 67.0 (C2), 68.6 (d, C4, $J_{4,F}$ 25.4), 70.9 (d, C9, $J_{9,F}$ 18.3), 85.5 (d, C3, $J_{3,F}$ 194.7), 86.1 (d, C8, $J_{8,F}$ 218.6), 128.3, 128.6, 128.9 (ArCH), 136.2 (ArC), 167.7, 167.8 (C1, C6); δ_F ($CDCl_3$, 376 MHz) −177.7 (dt, $J_{F,7} = J_{F,9}$ 21.2, $J_{F,8}$ 56.1), −184.4 (dt, $J_{F,2} = J_{F,4}$ 22.9, $J_{F,3}$ 55.3); m/z (ESI +ve) 612 ($[M + H]^+$, 100), 634 ($[M + Na]^+$, 30).

***N*-Benzyl-3*R*,4*R*-difluoro-L-proline Methyl Ester, 28.** A solution of azetidine methyl ester **24L** (289 mg, 0.79 mmol) in DCM (2 mL) was added dropwise to a solution of XtalFluor-M (289 mg, 1.19 mmol) and TEA·3HF (0.26 mL, 1.19 mmol) in DCM (2 mL) at −78 °C. After being stirred for 1 h, the mixture was stirred at rt for 18 h until TLC (cyclohexane/ethyl acetate, 2:1) showed the disappearance of starting material (R_f 0.16) and the formation of major product (R_f 0.56). The mixture was diluted with half saturated $NaHCO_3$ (10 mL) and stirred for a further 20 min before extraction with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to obtain a crude residue which was purified by flash chromatography (cyclohexane/ethyl acetate, 7:1 → 6:1) to yield the desired product **28** as a yellow oil (169 mg, 84%): HRMS m/z (ESI +ve) found 278.0958 $[M + Na]^+$, $C_{13}H_{15}F_2NNaO_2^+$ requires 278.0963; $[\alpha]_D^{20}$ −64.2 (c 0.31, $CHCl_3$); ν_{max} (thin film) 1746 (s, C═O); δ_H ($CDCl_3$, 400 MHz) 2.85 (1H, dddd, H5, $J_{5,3F}$ 2.0, $J_{5,4}$ 5.0, J_{gem} 11.7, $J_{5,4F}$ 31.9), 3.26 (1H, ddt, H5′, $J_{5',3} = J_{5',4}$ 1.4, J_{gem} 11.6, $J_{5',4F}$ 20.9), 3.51 (1H, dd, H2, $J_{2,3}$ 3.7, $J_{2,3F}$ 26.9), 3.66 (1H, d, H6, J_{gem} 13.1), 3.76 (3H, s, OCH_3), 4.05 (1H, d, H6′, J_{gem} 13.2), 5.05 (1H, dddt, H4, $J_{4,3} = J_{4,5'}$ 1.3, $J_{4,5}$ 4.9, $J_{4,3F}$ 14.9, $J_{4,4F}$ 50.7), 5.27 (1H, dddt, H3, $J_{3,4} = J_{3,5'}$ 1.3, $J_{3,2}$ 3.7, $J_{3,4F}$ 16.6, $J_{3,3F}$ 50.1), 7.25−7.36 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 52.4 (OCH_3), 56.2 (dd, C5, $J_{5,3F}$ 2.4, $J_{5,4F}$ 23.1), 57.5 (C6), 69.8 (dd, C2, $J_{2,3F}$ 0.8, $J_{2,4F}$ 26.2), 97.9 (dd, C4, $J_{4,3F}$ 29.0, $J_{4,4F}$ 182.4), 97.9 (dd, C3, $J_{3,4F}$ 32.7, $J_{3,3F}$ 186.4), 127.5, 128.4, 128.9 (ArCH), 136.7 (ArC), 170.4 (d, C1, $J_{1,F}$ 8.8); δ_F ($CDCl_3$, 376 MHz) −184.6 (ddddd, 3F, $J_{3F,5}$ 2.3, $J_{3F,4F}$ 8.0, $J_{3F,4}$ 14.9, $J_{3F,2}$ 26.3, $J_{3F,3}$ 50.4), −186.6 (ddddd, 4F, $J_{4F,3F}$ 7.9, $J_{4F,3}$ 16.4, $J_{4F,5'}$ 20.9, $J_{4F,5}$ 32.0, $J_{4F,4}$ 50.7); m/z (ESI +ve) 256 ($[M + H]^+$, 100%).

***N*-Benzyl-2*R*,3*R*-difluoro-2,4-imino-1,2,3,4-tetradeoxyl-D-arabinofuranose, 47.** Lithium aluminum hydride (1 M in THF) (0.24 mL, 0.24 mmol) was added dropwise to a solution of difluoromethyl

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

ester **28** (30 mg, 0.120 mmol) in anhydrous THF at −78 °C. The reaction mixture was stirred for 1 h until TLC analysis (cyclohexane/ethyl acetate, 2:1) showed the consumption of the starting material (R_f 0.67) and formation of a major product (R_f 0.37). The reaction was quenched with NH_4Cl (satd aq) to pH 6 and extracted with ethyl acetate (2 × 15 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield pure alcohol **47** as a clear oil which was used without further purification (18 mg, 66%): HRMS *m/z* (ESI +ve) found 250.1008 $[M + Na]^+$, $C_{12}H_{15}F_2NNaO^+$ requires 250.1014; $[\alpha]_D^{20}$ −70.6 (*c* 0.90, MeOH); ν_{max} (thin film) 3348 (br, w, OH); δ_H (CD_3OD, 400 MHz) 2.72 (1H, dddd, H1, $J_{1,3F}$ 3.0, $J_{1,2}$ 4.6, J_{gem} 12.1, $J_{1,2F}$ 36.7), 2.74−2.85 (1H, m, H4), 3.09 (1H, ddq, H1′, $J = J = J$ 1.0, J_{gem} 12.1, $J_{1',2F}$ 20.5), 3.48 (1H, d, H6, J_{gem} 13.2), 3.64 (1H, ddt, H5, $J = J$ 0.7, $J_{5,4}$ 6.1, J_{gem} 11.5), 3.67 (1H, ddt, H5′, $J = J$ 1.1, $J_{5',4}$ 4.9, J_{gem} 11.6), 4.05 (1H, d, H6′, J_{gem} 13.1), 4.91−5.11 (2H, m, H3, H2), 7.23−7.36 (5H, m, ArH); δ_C (CD_3OD, 100 MHz) 58.3 (dd, C1, $J_{1,3F}$ 2.4, $J_{1,2F}$ 22.3), 59.5 (C6), 61.6 (d, C5, $J_{5,4F}$ 6.4), 71.3 (dd, C4, J 1.6, $J_{4,3F}$ 22.3), 95.3 (dd, C2, $J_{2,3F}$ 29.4, $J_{2,2F}$ 179.6), 98.6 (dd, C3, $J_{3,2F}$ 28.6, $J_{3,3F}$ 177.2), 128.4, 129.4, 130.1 (ArCH), 139.2 (ArC); δ_F (CD_3OD, 376 MHz) −187.7 (ddddd, 3F, $J_{3F,1}$ 3.4, $J_{3F,2F}$ 6.9, $J_{3F,2}$ 13.7, $J_{3F,4}$ 28.6, $J_{3F,3}$ 50.1), −188.1 (ddddd, 2F, $J_{2F,3F}$ 6.9, $J_{2F,3}$ 17.2, $J_{2F,1'}$ 20.6, $J_{2F,1}$ 36.6, $J_{2F,2}$ 50.4); *m/z* (ESI +ve) 228 ($[M + H]^+$, 100).

2*R*,3*R*-Difluoro-2,4-imino-1,2,3,4-tetradeoxy-D-arabinofuranose, 16. Palladium on charcoal **47** (10% wt., 5 mg) was added to a solution of *N*-benzyl difluoro alcohol (15 mg, 0.066 mmol) in 1,4-dioxane/H_2O (1:1, 2 mL). The reaction was flushed with argon and hydrogen gas sequentially and stirred vigorously for 2 h at rt under hydrogen until mass spectrometry showed the completion of reaction (*m/z* (ESI +ve) 138 $[M + H]^+$). After filtration, the solvent was removed in vacuo to afford the title compound **16** as a clear oil (7 mg, 82%): HRMS *m/z* (ESI +ve) found 138.0725 $[M + H]^+$, $C_5H_{10}F_2NO^+$ requires 138.0725; $[\alpha]_D^{20}$ +4.3 (*c* 0.37, MeOH); ν_{max} (thin film) 3321 (br, m, OH); δ_H (D_2O, 400 MHz) free base: 3.18 (1H, dddd, H1, $J_{1,3F}$ 2.2, $J_{1,2}$ 3.9, J_{gem} 13.9, $J_{1,2F}$ 36.7), 3.24 (1H, dd, H1′, J_{gem} 13.9, $J_{1',2F}$ 23.3), 3.33 (1H, ddt, H4, $J_{4,3}$ 3.5, $J_{4,5} = J_{4,5'}$ 6.5, $J_{4,3F}$ 27.5), 3.69 (1H, dd, H5, $J_{5,4}$ 6.5, J_{gem} 11.6), 3.73 (1H, ddt, H5′, $J_{5',3} = J_{5',F}$ 1.0, $J_{5',4}$ 6.0, J_{gem} 11.7), 5.04 (1H, dddt, H3, $J_{3,2} = J_{3,5'}$ 1.0, $J_{3,4}$ 3.5, $J_{3,2F}$ 16.4, $J_{3,3F}$ 50.1), 5.27 (1H, dddt, H2, $J_{2,1'} = J_{2,3}$ 1.0, $J_{2,1}$ 4.1, $J_{2,3F}$ 12.5, $J_{2,2F}$ 50.0); δ_C (D_2O, 100 MHz) 50.5 (dd, C1, $J_{1,3F}$ 2.4, $J_{1,2F}$ 23.4), 61.3 (d, C5, $J_{5,F}$ 7.6), 64.9 (d, C4, $J_{4,3F}$ 23.8), 96.8 (dd, C2, $J_{2,3F}$ 30.5, $J_{2,2F}$ 174.5), 97.8 (dd, C3, $J_{3,2F}$ 29.5, $J_{3,3F}$ 177.3); δ_F (D_2O, 376 MHz) −188.5 (ddddd, 3F, $J_{3F,1}$ 2.3, $J_{3F,2F}$ 6.9, $J_{3F,2}$ 12.6, $J_{3F,4}$ 27.5, $J_{3F,3}$ 50.3), −188.9 (ddddd, 2F, $J_{3F,2F}$ 6.9, $J_{2F,3}$ 16.0, $J_{2F,1'}$ 22.7, $J_{2F,1}$ 35.2, $J_{2F,2}$ 50.4); *m/z* (ESI +ve) 138 ($[M + H]^+$, 100).

***N*-Benzyl-3*R*,4*R*-difluoro-L-proline, 48.** Sodium hydroxide (1 M, aq, 0.24 mL, 0.24 mmol) was added to a solution of difluoromethyl ester **28** (28 mg, 0.11 mmol) in 1,4-dioxane/H_2O (1:1, 2 mL). After the solution was stirred at 40 °C for 4 h, mass spectrometry showed the formation of product and disappearance of starting of material. Then solvent was removed in vacuo to afford a residue which was loaded onto a Serdolit CG 400 resin column (the resin was prestirred in sodium hydroxide (1 M, aq) for 15 min, and then flushed with H_2O until the eluent was neutral). After washing with 1,4-dioxane and H_2O, acetic acid (2 M, aq) was used to release the product. The solvent was removed in vacuo to give the pure product **48** as a light yellow glass (17 mg, 64%): HRMS *m/z* (ESI +ve) found 264.0805 $[M + Na]^+$, $C_{12}H_{13}F_2NNaO_2^+$ requires 264.0807; $[\alpha]_D^{20}$ −11.7 (*c* 0.16, MeOH), ν_{max} (thin film) 3030 (OH, br), 1677 (C=O, s); δ_H (D_2O, 400 MHz) 3.96 (1H, ddt, H5, $J_{5,4} = J_{5,3F}$ 3.1, J_{gem} 14.0, $J_{5,4F}$ 40.0), 4.21 (1H, dd, H5′, J_{gem} 13.9, $J_{5',4F}$ 17.3), 4.56 (1H, d, H6, J_{gem} 12.9), 4.70 (1H, d, H6′, J_{gem} 12.9), 4.73 (1H, d, H2, $J_{2,F}$ 26.6), 5.48−5.63 (2H, m, H3, H4), 7.49−7.59 (5H, m, ArH); δ_C (D_2O, 100 MHz) 58.3 (d, C5, $J_{5,4F}$ 21.0), 60.7 (C6), 72.0 (d, C2, $J_{2,3F}$ 23.8), 91.8 (dd, C3/C4, J 33.4, J 186.0), 95.0 (dd, C3/C4, J 31.5, J 179.3), 129.4, 129.7 (ArCH), 131.1 (ArC), 131.5 (ArCH), 167.5 (d, C1, $J_{1,F}$ 9.5); δ_F (D_2O, 376 MHz) −182.0 (ddddd, 3F, $J_{3F,5}$ 2.9, $J_{3F,4F}$ 6.3, $J_{3F,4}$ 14.3, $J_{3F,2}$ 26.9, $J_{3F,3}$ 48.2), −193.2 (ddddd, 4F, $J_{4F,3F}$ 8.0, $J_{4F,3}$ 14.9, $J_{4F,5'}$ 17.2, $J_{4F,5}$ 39.7, $J_{4F,4}$ 47.4); *m/z* (ESI +ve) 242 ($[M + H]^+$, 100).

3*R*,4*R*-Difluoro-L-proline, 12. Palladium on charcoal (10% wt, 5 mg) was added to a solution of *N*-benzyldifluoroproline **48** (17 mg, 0.07 mmol) in 1,4-dioxane/H_2O (1:1, 2 mL). The reaction was flushed with argon and hydrogen gas sequentially and stirred vigorously for 4 h at rt under hydrogen until mass spectrometry showed the completion of reaction (*m/z* (ESI −ve) 150 $[M − H]^-$). After filtration, the solvent was removed in vacuo to afford the title compound **12** as a light yellow glass (10 mg, 86%): HRMS *m/z* (ESI −ve) found 150.0367 $[M − H]^-$, $C_5H_6F_2NO_2^-$ requires 150.0372; $[\alpha]_D^{20}$ −4.6 (*c* 0.19, MeOH); ν_{max} (thin film) 3023 (br, s, OH), 1636 (s, C=O); δ_H (D_2O, 400 MHz) 3.82 (1H, ddt, H5, $J_{5,4} = J$ 3.1, J_{gem} 14.5, $J_{5,4F}$ 39.1), 3.96 (1H, dd, H5′, J_{gem} 14.2, $J_{5',4F}$ 21.8), 4.61 (1H, d, H2, $J_{2,F}$ 24.9), 5.42−5.54 (1H, m, H4), 5.58 (1H, dd, H3, $J_{3,4}$ 6.3, $J_{4,F}$ 47.9); δ_C (D_2O, 100 MHz) 50.3 (d, C5, $J_{5,4F}$ 22.9), 66.5 (d, C2, $J_{2,3F}$ 20.0), 92.2 (dd, C4, $J_{4,3F}$ 32.4, $J_{4,4F}$ 177.4), 95.5 (dd, C3, $J_{3,4F}$ 32.9, $J_{3,3F}$ 182.6), 168.7 (d, C1, $J_{1,F}$ 12.4); δ_F (D_2O, 376 MHz, ^1H-decoupled) −185.8 (d, J 15.6), −190.5 (d, J 15.6); *m/z* (ESI −ve) 150 ($[M − H]^-$, 100).

1,2,4,6-Tetra-*O*-acetyl-3-deoxy-3-fluoro-D-glucopyranoside, 29. *Method 1.* A solution of **21** (6.88 g, 26.24 mmol) in 1:1 water/trifluoroacetic acid (20.5 mL) was stirred at rt for 18 h after which TLC analysis (ethyl acetate) showed complete conversion of the starting material (R_f 0.97) to a single major product (R_f 0.06). The mixture was concentrated in vacuo, and the crude 3-deoxy-3-fluoroglucose was used without any further purification.

Acetic acid anhydride (95.9 mL, 931.5 mmol) was added to a solution of the crude glucopyranose in pyridine (95.9 mL), and the reaction mixture was stirred at rt. After 4 h, TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (baseline) to two major products (R_f 0.67 and 0.57) and a minor product (R_f 0.16). The mixture was concentrated in vacuo, and the resulting oil was partitioned between ethyl acetate (130 mL) and 1:1 $NaHCO_3$ (satd aq)/brine (130 mL). The aqueous layer was extracted with ethyl acetate (2 × 130 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 77:23) to give the title compound **29** as a white solid (8.53 g, 93%).

Method 2. A solution of **21** (15.28 g, 58.3 mmol) in a mixture of 1,4-dioxane (75 mL) and water 30 mL was stirred with Dowex (50W X8, H^+) at 65 °C for 18 h after which TLC analysis (ethyl acetate) showed complete conversion of the starting material (R_f 0.93) to a single major product (R_f 0.07). The mixture was concentrated in vacuo, and the crude 3-deoxy-3-fluoroglucose was used without any further purification.

Acetic anhydride (75 mL, 931.5 mmol) was added to a solution of the crude glucopyranose (10.6 g) in pyridine (75 mL), and the reaction mixture was stirred at rt. After 18 h, TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (R_f 0.00) to a single major product (R_f 0.89). The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (10% → 25% ethyl acetate in cyclohexane) to give the title compound **29** as a white solid as a 1:1 mixture of anomers (19.75 g, 97%): HRMS *m/z* (ESI +ve) found 373.0910 $[M + Na]^+$, $C_{14}H_{19}FNaO_9^+$ requires 373.0905; mp 86−88 °C; ν_{max} (thin film) 1744 (s, C=O); δ_H ($CDCl_3$, 400 MHz) 2.05 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.08 (×2) (2 × 3H, 2s, CH_3), 2.09 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.14 (3H, s, CH_3), 3.72 (1H, dddd, H5β, $J_{5,F}$ 1.3, $J_{5,6}$ 2.2, $J_{5,6'}$ 4.5, $J_{5,4}$ 10.1), 3.98−4.04 (1H, m, H5α), 4.08 (1H, dt, H6α, $J_{6,5} = J_{6,F}$ 2.1, J_{gem} 12.5), 4.09 (1H, dt, H6β, $J_{6,5} = J_{6,F}$ 1.9, J_{gem} 12.6), 4.22 (1H, dd, H6′α, $J_{6',5}$ 4.3, J_{gem} 12.6), 4.24 (1H, dd, H6′β, $J_{6',5}$ 4.5, J_{gem} 12.6), 4.59 (1H, dt, H3β, $J_{3,2} = J_{3,4}$ 9.1, $J_{3,F}$ 49.5), 4.80 (1H, dt, H3α, $J_{3,2} = J_{3,4}$ 9.4, $J_{3,F}$ 53.3), 5.14 (1H, ddd, H2α, $J_{2,1}$ 3.8, $J_{2,3}$ 9.7, $J_{2,F}$ 12.1), 5.15−5.18 (3H, m, H2β, H4α, H4β), 5.63 (1H, d, H1β, $J_{1,2}$ 8.3), 6.31 (1H, d, H1α, $J_{1,2}$ 3.8); δ_C ($CDCl_3$, 100 MHz) 20.4 (CH_3), 20.5 (×2) (CH_3), 20.6 (CH_3), 20.7 (CH_3), 61.2 (C6α, C6β), 67.6 (d, C4α/C4β, $J_{4,F}$ 19.0), 67.6 (d, C4α/C4β, $J_{4,F}$ 18.3), 69.5 (d, C2α, $J_{2,F}$ 17.5), 69.6 (d, C5α, $J_{5,F}$ 8.0), 70.2 (d, C2β, $J_{2,F}$ 19.1), 71.8 (d, C5β, $J_{5,F}$ 7.2), 90.4 (d, C1α, $J_{1,F}$ 9.5), 89.5 (d, C3α, $J_{3,F}$ 189.9), 91.1 (d, C1β, $J_{1,F}$ 11.1), 91.5 (d, C3β, $J_{3,F}$ 191.5), 168.5, 168.9 (×2), 169.1, 169.5, 170.5, 170.6 (C=O);); δ_F ($CDCl_3$, 376 MHz) −200.0 (ddt, J 3.4, $J = J$ 12.6, $J_{F,3}$ 52.7), −196.0 (dt, $J_{F,2} = J_{F,4}$ 12.6, $J_{F,3}$ 51.5; *m/z* (ESI +ve) 373 ($[M + Na]^+$, 100). 20:1 ratio: major β-anomer data: δ_H ($CDCl_3$, 400 MHz) 2.08 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.11 (3H, s, CH_3), 3.73 (1H, dddd, H5, $J_{5,6}$ 1.3, J 2.3, $J_{5,6'}$ 4.6, J 10.1), 4.11 (1H, dt, H6, $J_{6,5}$ 1.8, J_{gem} 12.4), 4.26 (1H, dd, H6′, $J_{6',5}$ 4.7, J_{gem} 12.5), 4.59 (1H, dt, H3, J 9.1, $J_{3,F}$ 51.8), 5.20−5.28 (2H, m, H2, H4), 5.64 (1H, d, H1, $J_{1,2}$ 8.3); δ_C ($CDCl_3$, 100 MHz) 20.6 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 61.3 (C6), 67.6 (d, C2, $J_{2,F}$ 19.1), 70.2 (d, C4, $J_{4,F}$ 19.1), 71.8

DOI: 10.1021/acs.joc.5b00463
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(d, C5, $J_{5,F}$ 8.1), 91.1 (d, C1, $J_{1,F}$ 11.1), 91.6 (d, C3, $J_{3,F}$ 191.2), 169.0, 169.0, 169.1, 170.6 (4 × C=O).

Methyl 2,4,6-Tri-*O*-acetyl-3-deoxy-3-fluoro-*β*-D-glucopyranoside, 30. HBr (33% in acetic acid, 38.7 mL, 213.7 mmol) was added dropwise to a solution of **29** (4.86 g, 13.87 mmol) in DCM (0.13 mL) at 0 °C. The solution was stirred for 5 h at 0 °C after which TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (R_f 0.52) to a single major product (R_f 0.77). The reaction mixture was diluted with DCM (90 mL) and poured onto ice−water (90 mL). The organic layer was washed with ice-cold $NaHCO_3$ (satd aq, 90 mL), and the aqueous layer was extracted with DCM (90 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo at 20 °C to give the crude bromide which was used without further purification.

Silver carbonate (6.50 g, 23.59 mmol) was added to a solution of crude bromide in methanol (62.3 mL), and the mixture was stirred at rt in the dark for 18 h after which TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (R_f 0.77) to a single major product (R_f 0.48). The reaction mixture was filtered through Celite and concentrated in vacuo, and the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 77:23) to give the title compound **30** as a white solid (3.91 g, 87%): HRMS *m/z* (ESI +ve) found 345.0967 [M + Na]$^+$, $C_{13}H_{19}FNaO_8^+$ requires 345.0956; mp 87−90 °C; $[\alpha]_D^{20}$ −26.7 (*c* 0.81, $CHCl_3$); ν_{max} (thin film) 1744 (s, C=O); δ_H ($CDCl_3$, 400 MHz) 2.09 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.12 (3H, CH_3), 3.50 (3H, s, OMe), 3.60 (1H, a-ddq, H5, $J_{5,6} = J = J$ 1.3, $J_{5,6'}$ 4.7, $J_{5,4}$ 10.0), 4.16 (1H, ddd, H6, $J_{6,5}$ 1.4, $J_{6,F}$ 2.5, J_{gem} 12.3), 4.26 (1H, dd, H6′, $J_{6',5}$ 4.8, J_{gem} 12.3), 4.35 (1H, dd, H1, J 0.7, $J_{1,2}$ 8.1), 4.54 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 9.1, $J_{3,F}$ 52.2), 5.10 (1H, ddd, H2, $J_{2,1}$ 8.0, $J_{2,3}$ 9.2, $J_{2,F}$ 13.3), 5.21 (1H, ddd, H4, $J_{4,5}$ 9.1, $J_{4,3}$ 10.0, $J_{4,F}$ 12.5); δ_C ($CDCl_3$, 100 MHz) 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 57.0 (OCH_3), 61.7 (C6), 68.3 (d, C4, $J_{4,F}$ 19.1), 70.9 (d, C5, $J_{5,F}$ 8.1), 71.2 (d, C2, $J_{2,F}$ 19.1), 91.7 (d, C3, $J_{3,F}$ 190.3), 101.1 (d, C1, $J_{1,F}$ 11.1), 169.1, 170.7 (3 × C=O); δ_F ($CDCl_3$, 376 MHz) −195.9 (dt, $J_{F,2} = J_{F,4}$ 12.8, $J_{F,3}$ 52.2); *m/z* (ESI +ve) 345 ([M + Na]$^+$, 100).

Methyl 3-Deoxy-3-fluoro-*β*-D-glucopyranoside, 31. Sodium methoxide (0.65 g, 12.0 mmol) was added to a solution of **30** (6.45 g, 20.03 mmol) in methanol (71 mL) at rt. After 5 h, TLC analysis (ethyl acetate) showed complete conversion of the starting material (R_f 0.90) to a single major product (R_f 0.33). The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (ethyl acetate/methanol, 17:3) to give the title compound **31** as a colorless oil (3.77 g, 96%) which crystallized on standing: HRMS *m/z* (ESI +ve) found 219.0632 [M + Na]$^+$, $C_7H_{13}FNaO_5^+$ requires 219.0639; mp 120−124 °C; $[\alpha]_D^{20}$ −34.7 (*c* 0.73, CH_3OH) [lit.[50] mp 129.5−130 °C; $[\alpha]_D$ −33.5 (*c* 1.2, H_2O)]; ν_{max} (thin film) 3361 (br, m, OH); δ_H (CD_3OD, 400 MHz) 3.27 (1H, a-ddq, H5, $J_{5,6'} = J = J$ 1.2, $J_{5,6}$ 5.4, $J_{5,4}$ 9.9), 3.39 (1H, ddd, H2, $J_{2,1}$ 7.8, $J_{2,3}$ 9.1, $J_{2,F}$ 14.2), 3.54 (3H, s, OCH_3), 3.57 (1H, ddd, H4, $J_{4,3}$ 8.7, $J_{4,5}$ 9.9, $J_{4,F}$ 14.2), 3.70 (1H, dd, H6, $J_{6,5}$ 5.4, J_{gem} 12.0), 3.87 (1H, ddd, H6′, $J_{6',5}$ 1.3, $J_{6',F}$ 2.3, J_{gem} 12.0), 4.20 (1H, dd, H1, J 0.7, $J_{1,2}$ 7.8), 4.24 (1H, dt, H3, $J_{3,2} = J_{3,4}$ 8.8, $J_{3,F}$ 52.8); δ_C (CD_3OD, 100 MHz) 57.5 (OMe), 62.2 (C6), 69.7 (d, C4, $J_{4,F}$ 18.1), 73.6 (d, C2, $J_{2,F}$ 18.1), 76.7 (d, C5, $J_{5,F}$ 9.1), 98.5 (d, C3, $J_{3,F}$ 182.2), 104.6 (d, C1 $J_{1,F}$ 12.1); δ_F ($CDCl_3$, 376 MHz) −196.1 (dt, $J_{F,2} = J_{F,4}$ 14.3, $J_{F,3}$ 52.6); *m/z* (ESI +ve) 219 ([M + Na]$^+$, 100).

Methyl 6-*O*-(*tert*-butyldimethysilyl)-3-deoxy-3-fluoro-*β*-D-glucopyranoside, 32. Imidazole (5.42 g, 79.6 mmol) and *tert*-butyldimethylsilyl chloride (5.20 g, 34.5 mmol) were added to a solution of **31** (5.20 g, 26.5 mmol) in anhydrous DMF (10.0 mL) at −20 °C. The reaction mixture was stirred for 2.5 h at −20 °C after which the mixture was allowed to warm to rt. After 3 h, TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (R_f 0.03) to a single major product (R_f 0.58). The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1:1 water/brine (3 × 60 mL). The combined aqueous layers were extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 9:1 → 4:1 → 13:7) to give the title compound **32** as a white solid (7.42 g, 98%): HRMS *m/z* (ESI +ve) found 333.1504 [M + Na]$^+$, $C_{13}H_{27}FNaO_5Si^+$ requires 333.1504; mp 80−84 °C; $[\alpha]_D^{20}$ −40.0 (*c* 1.27, $CHCl_3$); ν_{max} (thin film) 3267 (br, m, OH); δ_H ($CDCl_3$, 400 MHz) 0.10 (6H, 2*s*, CH_3Si), 0.90 (9H, s, $(CH_3)CSi$), 2.66 (1H, br-s, 2-OH), 3.35 (1H, dddd, H5, J 1.0, $J_{5,6'}$ 4.8, $J_{5,6}$ 5.8, J 9.5), 3.39 (1H, br-s, 4-OH), 3.54 (3H, s, OMe), 3.58 (1H, ddd, H2, $J_{2,1}$ 7.8, $J_{2,3}$ 9.1, $J_{2,F}$ 13.6), 3.78−3.86 (1H, m, H4), 3.86 (1H, ddd, H6, J 0.8, $J_{6,5}$ 5.8, J_{gem} 10.6), 3.96 (1H, ddd, H6′, J 0.8, $J_{6',5}$ 4.8, J_{gem} 10.6), 4.21 (1H, dd, H1, J 0.8, $J_{1,2}$ 7.8), 4.42 (1H, dt, H3, $J_{3,4} = J_{3,2}$ 8.8, $J_{3,F}$, 52.8); δ_C ($CDCl_3$, 100 MHz) −5.5 (2 × CH_3Si), 18.2 ($(CH_3)CSi$), 25.8 ($(CH_3)CSi$), 57.3 (OMe), 64.2 (C6), 71.3 (d, C4, $J_{4,F}$ 17.6), 72.3 (d, C2, $J_{2,F}$ 17.6), 73.1 (d, C5, $J_{5,F}$ 8.0), 96.4 (d, C3, $J_{3,F}$ 183.0), 102.8 (d, C1, $J_{1,F}$ 12.0); δ_F ($CDCl_3$, 376 MHz) −196.4 (dt, $J_{F,2} = J_{F,4}$ 13.7, $J_{F,3}$ 52.7); *m/z* (ESI +ve) 310 ([M + Na]$^+$, 100).

Methyl *N*-Benzyl-6-*O*-(*tert*-butyldimethylsilyl)-3-fluoro-2,4-imino-2,3,4-trideoxy-*β*-D-talopyranoside, 23. Triflic anhydride (16.1 mL, 95.7 mmol) was added to a solution of pyridine (15.5 mL, 191 mmol) and diol **32** (7.42 g, 23.9 mmol) in DCM (100 mL) at −30 °C. The reaction mixture was stirred at −30 to −10 °C for 2 h after which time TLC analysis (cyclohexane/ethyl acetate, 3:1) showed almost complete conversion of the starting material (R_f 0.17) to a single major product (R_f 0.67). A further portion of pyridine (3.86 mL, 47.8 mmol) and triflic anhydride (4.0 mL, 23.9 mmol) was added, and the reaction stirred for a further 1 h at −30 °C after which the reaction mixture was diluted with DCM (80 mL) and washed with 2 M HCl (100 mL) and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude ditriflate **22** (13.73 g, quant). [Partial data: δ_H ($CDCl_3$, 400 MHz) 0.10 (6H, 2*s*, CH_3Si), 0.92 (9H, s, $(CH_3)CSi$), 3.55−3.58 (1H, m, H5), 3.59 (3H, s, OMe), 3.89 (1H, dd, H6, $J_{6,5}$ 3.3, J_{gem} 12.1), 3.98 (1H, dd, H6′, $J_{6',5}$ 2.1, J_{gem} 12.0), 4.49 (1H, d, H1, $J_{1,2}$ 8.1), 4.69 (1H, ddd, H2, $J_{2,1}$ 7.8, $J_{2,3}$ 9.1, $J_{2,F}$ 12.9), 4.83 (1H, dt, H3, $J_{3,4} = J_{3,2}$ 8.9, $J_{3,F}$ 51.6), 5.16 (1H, ddd, H4, $J_{4,3}$ 9.0, $J_{4,5}$ 9.6, $J_{4,F}$ 12.1); δ_C ($CDCl_3$, 100 MHz) −5.6 (CH_3Si), −5.5 (CH_3Si), 18.3 ($(CH_3)_3CSi$), 25.7 ($(CH_3)_3CSi$), 57.7 (OMe), 60.3 (C6), 72.7 (d, C5, $J_{5,F}$ 6.0), 78.1 (d, C4, $J_{4,F}$ 18.1), 81.8 (d, C2, $J_{2,F}$ 18.1), 89.6 (d, C3, $J_{3,F}$ 196.2), 99.8 (d, C1, $J_{1,F}$ 9.1).]

Benzylamine (13.0 mL, 120 mmol) and *N*,*N*-diisopropylethylamine (10.2 mL, 59.8 mmol) were added to a solution of the crude ditriflate (13.73 g) in acetonitrile (140 mL), and the solution was heated to 65 °C. After 18 h, TLC analysis (cyclohexane/ethyl acetate, 3:1) showed complete conversion of the starting material (R_f 0.72) to a single major product (R_f 0.80). The reaction mixture was concentrated and the residue was purified by flash chromatography (1% → 5% → 10%, ethyl acetate in cyclohexane) to give the title compound **23** as a light yellow oil (7.6 g, 84%): HRMS *m/z* (ESI +ve) found 404.2019 [M + Na]$^+$, $C_{20}H_{32}FNNaO_3Si^+$ requires 404.2028; $[\alpha]_D^{20}$ −47.1 (*c* 1.15, $CHCl_3$); ν_{max} (thin film) fingerprint region only; δ_H ($CDCl_3$, 400 MHz) −0.05 (3H, s, CH_3Si), −0.01 (3H, s, CH_3Si), 0.82 (9H, s, $(CH_3)_3CSi$), 3.47 (3H, s, OMe), 3.51 (1H, ddd, H2, $J_{2,1}$ 1.3, $J_{2,4}$ 6.0, $J_{2,F}$ 13.2), 3.68 (1H, ddd, H4, $J_{4,5}$ 1.2, $J_{4,2}$ 6.0, $J_{4,F}$ 13.3), 3.78 (1H, ddd, H6, $J_{6,F}$ 1.7, $J_{6,5}$ 5.4, J_{gem} 9.5), 3.84 (1H, dd, H6′, $J_{6',5}$ 8.2, J_{gem} 9.2), 3.94 (1H, ddt, H5, $J_{5,4} = J_{5,F}$ 1.2, $J_{5,6}$ 5.4, $J_{5,6'}$ 8.2), 4.26 (2H, br-s, CH_2Ph), 4.81 (1H, t, H1, $J_{1,2} = J_{1,F}$ 1.2), 5.07 (1H, d, H3, $J_{3,F}$ 58.4), 7.19−7.24 (1H, m, ArH), 7.27−7.32 (2H, m, ArH), 7.39−7.43 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) −5.5 (2 × CH_3Si), 18.2 ($(CH_3)CSi$), 25.8 ($(CH_3)CSi$), 56.0 (CH_2Ph), 56.1 (OMe), 63.1 (C6), 65.1 (d, C4, $J_{4,F}$ 18.3), 67.7 (d, C2, $J_{2,F}$ 18.3), 77.2 (d, C5, $J_{5,F}$ 6.4), 98.3 (d, C3, $J_{3,F}$ 213.0), 100.8 (d, C1, $J_{1,F}$ 11.1), 126.8, 128.2, 128.3 (ArCH), 139.0 (ArC); δ_F ($CDCl_3$, 376 MHz) −197.0 (dt, $J_{F,2} = J_{F,4}$ 13.2, $J_{F,3}$ 58.4); *m/z* (ESI +ve) 382 ([M + H]$^+$, 100).

5,6-Di-*O*-acetyl-*N*-benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-D-talose Acetyl Methyl Acetal, 33. Boron trifluoride diethyl etherate (4.5 mL, 36.7 mmol) was added dropwise to a solution of **23** (3.11 g, 8.2 mmol) in acetic anhydride (30 mL) at −30 °C before warming to rt. After 18 h, mass spectrometry (ESI +ve) showed the formation of the desired product 412 [M + H$^+$] and no remaining starting material. The mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (40 mL) and washed with $NaHCO_3$ (satd aq, 3 × 20 mL). The organic fraction was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% → 30% ethyl acetate in cyclohexane) gave the title mixed acetal **33** (3.37 g, quant) as a pale yellow oil in a 1:1 ratio of

DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258

diastereoisomers: HRMS *m/z* (ESI +ve) found 412.1775 $[M + H]^+$, $C_{20}H_{27}FNO_7^+$ requires 412.1766; ν_{max} (thin film) 1738 (s, C=O); δ_H ($CDCl_3$, 400 MHz) 1.93 (3H, s, CH_3), 1.94 (3H, s, CH_3), 1.97 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.18 (3H, s, CH_3), 3.36 (1H, dt, H2, $J_{2,1}$ = $J_{2,3}$ 5.1, $J_{2,F}$ 22.5), 3.37 (1H, dt, H2, $J_{2,1}$ = $J_{2,3}$ 4.7, $J_{2,F}$ 22.5), 3.39 (3H, s, OCH_3), 3.41−3.52 (2H, m, H4), 3.43 (3H, s, OCH_3), 3.77 (1H, d, CH_2Ph, J_{gem} 13.2), 3.80 (1H, d, CH_2Ph, J_{gem} 13.0), 3.86 (1H, d, CH_2Ph, J_{gem} 13.7), 3.87 (1H, d, CH_2Ph, J_{gem} 13.2), 4.05 (1H, dd, H6, $J_{6,5}$ 6.2, J_{gem} 12.1), 4.11 (1H, dd, H6, $J_{6,5}$ 6.2, J_{gem} 12.1), 4.29 (1H, dd, H6′, $J_{6',5}$ 3.7, J_{gem} 12.0), 4.35 (1H, dd, H6′, $J_{6',5}$ 3.8, J_{gem} 12.1), 4.85 (1H, dt, H3, $J_{3,2}$ = $J_{3,4}$ 4.8, $J_{3,F}$ 55.9), 4.89 (1H, dt, H3, $J_{3,2}$ = $J_{3,4}$ 4.7, $J_{3,F}$ 55.7), 4.89−4.94 (1H, m, H5), 5.00 (1H, ddd, H5, $J_{5,6'}$ 3.8, $J_{5,6}$ 6.0, $J_{5,4}$ 7.2), 5.46 (1H, d, H1, $J_{1,2}$ 4.9), 5.66 (1H, d, H1, $J_{1,2}$ 5.1), 7.25−7.39 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 20.7 (3 × CH_3), 20.8 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 57.2 (OMe), 57.7 (OMe), 60.9 (CH_2Ph), 61.6 (CH_2Ph), 62.2 (2 × C6), 67.7 (d, C4, $J_{4,F}$ 20.7), 68.2 (d, C4, $J_{4,F}$ 20.7), 69.2 (d, C2, $J_{2,F}$ 20.7), 69.9 (d, C2, $J_{2,F}$ 19.9), 71.4 (d, C5, $J_{5,F}$ 25.4), 71.5 (d, C5, $J_{5,F}$ 25.4), 83.5 (d, C3, $J_{3,F}$ 211.6), 83.5 (d, C3, $J_{3,F}$ 211.4), 97.4 (d, C1, $J_{1,F}$ 19.9), 97.5 (d, C1, $J_{1,F}$ 19.9), 127.6, 127.7, 128.5 (x 2), 128.9, 129.3 (ArCH), 136.6, 137.2 (ArC), 170.0, 170.1, 170.5, 170.6 (x 2), 170.7 (C=O); δ_F ($CDCl_3$, 376 MHz) −179.8 (dt, $J_{F,4}$ = $J_{F,5}$ 22.9, $J_{F,3}$ 56.1), −180.0 (dt, $J_{F,4}$ = $J_{F,5}$ 22.9, $J_{F,3}$ 56.1); *m/z* (ESI +ve) 412 ($[M + H]^+$, 100), 434 ($[M + Na]^+$, 40).

***N*-Benzyl-4-fluoro-3,5-imino-3,4,5-trideoxy-D-altritol, 34.** DIBALH (1.5 M in toluene, 6.1 mL, 9.2 mmol) was added dropwise to a solution of **33** (471 mg, 1.1 mmol) in DCM (5 mL) at −78 °C. After 1.5 h, mass spectrometry (ESI +ve) showed the formation of the desired product 254 $[M + H^+]$ or gemdiol 272 $[M + H^+]$ and no remaining starting material. The reaction mixture was diluted with ethyl acetate (20 mL) and stirred with sodium potassium tartrate solution (25 mL, satd aq) until two layers were formed. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo.

Sodium borohydride (48 mg, 1.3 mmol) was added to a solution of the crude in methanol (6 mL), and the reaction mixture was stirred for 30 min. Mass spectrometry showed complete conversion of the starting material and the formation of the triol. The mixture was quenched with a few drops of glacial acetic acid and subsequently concentrated in vacuo. The crude triol was purified by ion exchange chromatography on Dowex (50W X8, H^+) washing with dioxane and water and eluting with 2 M NH_3 and 1:1, 2 M NH_3/dioxane. The ammoniacal fractions were concentrated *in vacuo* to give the triol **34** as a colorless oil (284 mg, 97%).

Large Scale. DIBALH (1.5 M in toluene, 19.7 mL, 29.5 mmol) was added dropwise to a solution of **33** (1.52 g, 3.7 mmol) in DCM (16 mL) at −78 °C. After 1.5 h, mass spectrometry (ESI +ve) showed the formation of the desired product 254 $[M + H^+]$ or gemdiol 272 $[M + H^+]$ and no remaining starting material. The reaction mixture was diluted with ethyl acetate (30 mL) and stirred with sodium potassium tartrate solution (80 mL, satd aq) for 2 h when two layers were formed. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo.

Sodium borohydride (154 mg, 4.1 mmol) was added to a solution of the crude in methanol (20 mL), and the reaction mixture was stirred for 30 min after which mass spectrometry showed complete conversion of the starting material and the formation of the triol. The mixture was quenched with a few drops of glacial acetic acid and subsequently concentrated in vacuo. The crude triol was purified by ion-exchange chromatography on Dowex (50W X8, H^+) washing with dioxane and water and eluting with 2 M NH_3 and 1:1, 2 M NH_3/dioxane. The ammoniacal fractions were concentrated in vacuo to give the triol **34** as a colorless oil (806 mg, 85%): HRMS *m/z* (ESI +ve) found 278.1170 $[M + Na]^+$, $C_{13}H_{18}FNNaO_3^+$ requires 278.1163. Data for HCl salt: $[\alpha]_D^{20}$ −12.0 (*c* 0.85, CH_3OH); ν_{max} (thin film) 3299 (s, OH); δ_H (CD_3OD, 400 MHz) 3.22 (1H, dd, H6, $J_{6,5}$ 3.9, J_{gem} 12.8), 3.64 (1H, dd, H1, $J_{1,2}$ 5.4, J_{gem} 11.5), 3.68 (1H, dd, H1′, $J_{1',2}$ 4.2, J_{gem} 11.6), 3.71 (1H, dd, H6′, $J_{6',5}$ 4.3, J_{gem} 12.8), 4.10−4.15 (1H, m, H2), 4.50 (1H, d, CH_2Ph, J_{gem} 13.0), 4.51−4.61 (2H, m, H3, H5), 4.68 (1H, d, CH_2Ph, J_{gem} 13.0), 5.25 (1H, dt, H4, $J_{4,3}$ = $J_{4,5}$ 5.8, $J_{4,F}$ 56.3), 7.49−7.64 (5H, m, ArH); δ_C (CD_3OD, 100 MHz) 58.2 (d, C6, $J_{6,F}$ 2.4), 59.9 (CH_2Ph), 63.5 (C1), 69.7 (d, C2, $J_{2,F}$ 3.2), 72.5 (d, C5, *J* 25.4), 74.4 (d, C3, *J* 25.4), 83.5 (d, C4, $J_{4,F}$ 209.0), 130.1 (ArC), 130.5, 131.5, 132.7 (ArCH); δ_F (CD_3OD, 376 MHz) −183.9 (dt, $J_{F,5}$ = $J_{F,3}$ 18.9, $J_{F,4}$ 56.1). Data for free base: $[\alpha]_D^{20}$ +36.7 (*c* 0.78, CH_3OH); ν_{max} (thin film) 3366 (s, OH); δ_H (CD_3OD, 400 MHz) 3.12−3.18 (1H, m, H6), 3.15−3.23 (1H, m, H5), 3.22−3.27 (1H, m, H6′), 3.33 (1H, dt, H3, $J_{3,2}$ = $J_{3,4}$ 5.1, $J_{3,F}$ 29.3), 3.50 (1H, dd, H1, $J_{1,2}$ 6.5, J_{gem} 11.3), 3.55 (1H, dd, H1′, $J_{1',2}$ 5.4, J_{gem} 11.3), 3.64 (1H, d, CH_2Ph, J_{gem} 12.4), 3.66 (1H, dt, H2, $J_{2,1'}$ = $J_{2,3}$ 5.3, $J_{2,1}$ 6.5), 4.03 (1H, d, CH_2Ph, J_{gem} 12.5), 4.80 (1H, dt, H4, $J_{4,3}$ = $J_{4,5}$ 4.8, $J_{4,F}$ 57.2), 7.25−7.38 (5H, m, ArH); δ_C (CD_3OD, 100 MHz) 62.4 (d, C6, $J_{6,F}$ 4.0), 63.3 (CH_2Ph), 64.3 (C1), 71.2 (d, C5, $J_{5,F}$ 19.1), 71.7 (d, C3, $J_{3,F}$ 19.9), 73.4 (d, C2, $J_{2,F}$ 4.8), 86.7 (d, C4, $J_{4,F}$ 207.4), 128.6, 129.4, 130.8 (ArH), 138.6 (ArC); δ_F (CD_3OD, 376 MHz) −182.0 (dt, $J_{F,5}$ = $J_{F,3}$ 24.0, $J_{F,4}$ 57.2); *m/z* (ESI +ve) 256 ($[M + H]^+$, 100).

4-Fluoro-3,5-imino-3,4,5-trideoxy-D-altritol, 14. Palladium on charcoal (10% wt., 5 mg) was added to a solution of **34** (23 mg, 0.091 mmol) in 1,4-dioxane/water (1:2, 1.5 mL). The reaction mixture was flushed with argon and subsequently flushed with hydrogen. The mixture was stirred for 18 h after which mass spectrometry showed the formation of the product and no remaining starting material. The reaction mixture was filtered through (GF/B glass microfiber) and concentrated in vacuo. The residue was loaded (1:2 1,4-dioxane/water) on a Dowex (50W X8, H^+) column which was prewashed with water until the pH was neutral. The column was washed with water, 1,4-dioxane, 2 M ammonia, and 1:1 1,4-dioxane/2 M ammonia. The ammoniacal fractions were concentrated in vacuo to give the title compound **14** as a light yellow oil (17 mg, 88%): HRMS *m/z* (ESI +ve) found 188.0693 $[M + Na]^+$, $C_6H_{12}FNNaO_3^+$ requires 188.0693. Data for HCl salt: $[\alpha]_D^{20}$ −35.3 (*c* 0.86, CH_3OH); ν_{max} (thin film) 3334 (s, br, OH, NH); δ_H (CD_3OD, 400 MHz) 3.61 (1H, dd, H_1, $J_{1,2}$ 5.4, J_{gem} 11.2), 3.68 (1H, dd, H1′, $J_{1',2}$ 4.2, J_{gem} 11.2), 3.89 (1H, dd, H6, $J_{6,5}$ 4.4, J_{gem} 12.7), 3.94 (1H, dd, H6′, $J_{6',5}$ 5.1, J_{gem} 12.7), 4.04 (1H, dt, H2, $J_{2,1'}$ 4.1, $J_{2,1}$ = $J_{2,3}$ 5.4), 4.50−4.60 (1H, m, H5), 4.64 (1H, ddd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 5.6, $J_{3,F}$ 18.7), 5.33 (1H, dt, H4, $J_{4,3}$ = $J_{4,5}$ 5.9, $J_{4,F}$ 55.9); δ_C (CD_3OD, 100 MHz) 58.7 (d, C6, $J_{6,F}$ 3.2), 63.9 (C1), 66.3 (d, C5, $J_{5,F}$ 25.5), 67.1 (d, C3, $J_{3,F}$ 25.5), 68.9 (d, C2, $J_{2,F}$ 3.2), 85.6 (d, C4, $J_{4,F}$ 209.0); δ_F (CD_3OD, 376 MHz) −183.5 (dt, $J_{F,5}$ = $J_{F,3}$ 18.3, $J_{F,4}$ 56.1); *m/z* (ESI +ve) 166 ($[M + H]^+$, 100).

Methyl *N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-D-ribonate, 24D. Sodium periodate (928 mg, 4.3 mmol) was added to a solution of **34** (922 mg, 3.6 mmol) in aqueous acetone (2:1, water/acetone, 36 mL) and was stirred at rt for 1 h. TLC analysis (ethyl acetate) showed complete conversion of the starting material (R_f 0.56) to a single major product (R_f 0.74). Ethanol (40 mL) was added to the reaction mixture and stirred for 2 h after which the resultant precipitate was removed via filtration (GF/B glass microfibre). The filtrate was concentrated in vacuo at 20 °C to give the crude aldehyde (803 mg).

Potassium carbonate (1.5 g, 10.8 mmol) was added to a solution of the crude aldehyde (803 mg) in methanol (40 mL). Iodine (1.19 g, 4.7 mmol) was dissolved (sonication) in methanol (40 mL) and was subsequently added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (R_f 0.02) to a single major product (R_f 0.56). The reaction was quenched with Na_2SO_3 (satd aq) until the solution was colorless, the mixture was partitioned between ethyl acetate (100 mL) and water (100 mL), and the aqueous fraction was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (10% → 67%, ethyl acetate in cyclohexane) to give the title compound **24D** as a brown oil (627 mg, 69%): HRMS *m/z* (ESI +ve) found 276.1003 $[M + Na]^+$, $C_{13}H_{16}FNNaO_3^+$ requires 276.1006; $[\alpha]_D^{20}$ +50.0 (*c* 0.5, $CHCl_3$); ν_{max} (thin film) 3450 (w, br, OH), 1740 (s, C=O); δ_H ($CDCl_3$, 400 MHz) 2.44 (1H, br-s, OH), 3.17 (1H, dd, H5, $J_{5,4}$ 2.8, J_{gem} 12.1), 3.37 (1H, ddddd, H4, *J* 0.6, $J_{4,5'}$ 2.1, $J_{4,5}$ 2.8, $J_{4,3}$ 4.9, $J_{4,F}$ 21.5), 3.43 (1H, dd, H5′, $J_{5',4}$ 1.7, J_{gem} 12.2), 3.70 (3H, s, OCH_3), 3.73 (1H, d, CH_2Ph J_{gem} 12.5), 3.78 (1H, dd, H2, $J_{2,3}$ 4.9, $J_{2,F}$ 22.3), 3.98 (1H, d, CH_2Ph, J_{gem} 12.5), 5.05 (1H, dt, H3, $J_{3,4}$ = $J_{3,5}$ 4.9, $J_{3,F}$ 56.0), 7.26−7.36 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 52.1 (OCH_3), 60.1 (d, C5,

DOI: 10.1021/acs.joc.5b00463
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$J_{5,F}$ 4.0), 60.5 (CH_2Ph), 67.9 (d, C2, $J_{2,F}$ 21.5), 69.7 (d, C4, $J_{4,F}$ 20.7), 84.4 (d, C3, $J_{3,F}$ 214.6), 128.0, 128.6, 129.3 (ArCH), 135.9 (ArC), 170.2 (d, C1, $J_{1,F}$ 4.8); δ_F ($CDCl_3$, 376 MHz) −181.5 (dt, $J_{F,2}$ = $J_{F,4}$ 22.3, $J_{F,3}$ 55.7); *m/z* (ESI +ve) 254 ($[M + H]^+$, 100), 276 ($[M + Na]^+$, 50).

***N*-Benzyl-3-fluoro-2,4-imino-2,3,4-trideoxy-D-ribonic Acid, 35D.** Potassium carbonate (16 mg, 0.114 mmol) was added to a solution of **24D** (22 mg, 0.087 mmol) in 1:2 1,4-dioxane/water (1.6 mL). The solution was heated to 40 °C and stirred for 18 h after which TLC analysis (cyclohexane/ethyl acetate, 1:1) showed complete conversion of the starting material (R_f 0.71) to a single major product (R_f 0.0). HCl (2 M, 0.2 mL) was added to the reaction mixture until pH 4, and the solvent was removed in vacuo. The residue was loaded (1:2, 1,4-dioxane/water) onto a Dowex (50W X8, H^+) column, which was prewashed with water, 1,4-dioxane and water sequentially. The column was eluted with water followed by 1,4-dioxane after which the product was released with ammonia (2 M). The ammoniacal fraction was concentrated in vacuo to give the title compound **35D** as a light yellow glass (12 mg, 57%): HRMS *m/z* (ESI +ve) found 262.0853 $[M + Na]^+$, $C_{12}H_{14}FNNaO_3^+$ requires 262.0850; $[\alpha]_D^{20}$ +14.1 (*c* 0.4, H_2O); ν_{max} (thin film) 3227 (w, br, OH), 1631 (s, C=O); δ_H (Py-d_5, 400 MHz) 3.62 (1H, dq, H4, $J_{4,3}$ = $J_{4,5}$ = $J_{4,5'}$ 4.6, $J_{4,F}$ 22.3), 3.73 (1H, dd, H5, $J_{5,4}$ 4.9, J_{gem} 11.7), 3.76 (1H, dd, H5′, $J_{5',4}$ 4.3, J_{gem} 11.5), 3.95 (1H, d, CH_2Ph, J_{gem} 13.0), 4.15 (1H, dd, H2, $J_{2,3}$ 5.0, $J_{2,F}$ 23.4), 4.36 (1H, d, CH_2Ph, J_{gem} 13.0), 5.62 (1H, dt, H3, $J_{3,2}$ = $J_{3,4}$ 5.0, $J_{3,F}$ 57.1), 6.76 (br-s, OH), 7.21−7.60 (5H, m, ArH); δ_C (Py-d_5, 126 MHz) 61.4 (CH_2Ph), 62.5 (C5), 69.4 (d, C2, $J_{2,F}$ 20.0), 70.7 (d, C4, $J_{4,F}$ 19.1), 88.0 (d, C3, $J_{3,F}$ 211.7), 128.2, 129.0, 130.6 (ArCH), 137.8 (ArC), 173.8 (d, C1, $J_{1,F}$ 3.8); δ_F (Py-d_5, 376 MHz) −178.5 (dt, $J_{F,2}$ = $J_{F,4}$ 22.9, $J_{F,3}$ 57.2); *m/z* (ESI +ve) 240 ($[M + H]^+$, 100), 262 ($[M + Na]^+$, 50); *m/z* (ESI −ve) 238 ($[M − H]^+$, 100).

3-Fluoro-2,4-imino-2,3,4-trideoxy-D-ribonic Acid, 10D. Palladium on charcoal (10% wt., 5 mg) was added to a solution of **35D** (24 mg, 0.010 mmol) in 1,4-dioxane/water (1:2, 2 mL). The reaction mixture was flushed with argon and subsequently flushed with hydrogen. The mixture was stirred for 18 h after which mass spectrometry showed the reaction went to completion. The reaction mixture was filtered through (GF/A glass microfiber) and concentrated in vacuo. The residue was loaded (1:2, 1,4-dioxane/water) on a Dowex (50W X8, H^+) column which was prewashed with water until the pH was neutral. The column was washed with water, 1,4-dioxane, 2 M ammonia, and 1:1 1,4-dioxane/2 M ammonia. The ammoniacal fractions were concentrated in vacuo to give the title compound **10D** as a light yellow glass (6.6 mg, 45%): HRMS *m/z* (ESI −ve) found 148.0414 $[M − H]^-$, $C_5H_7FNO_3^-$ requires 148.0415; $[\alpha]_D^{20}$ +23.3 (*c* 0.27, H_2O); ν_{max} (thin film) 3236 (w, br, OH), 1631 (s, C=O); δ_H (D_2O, 400 MHz) 3.91 (1H, dd, H5, $J_{5,4}$ 3.8, J_{gem} 13.2), 3.98 (1H, dd, H5′, $J_{5',4}$ 4.1, J_{gem} 13.2), 4.67 (1H, dq, H4, $J_{4,3}$ = $J_{4,5}$ = $J_{4,5'}$ 4.2, $J_{4,F}$ 19.2), 4.93 (1H, dd, H2, $J_{2,3}$ 4.9, $J_{2,F}$ 21.3), 5.32 (1H, dt, H3, $J_{3,2}$ = $J_{3,4}$ 4.7, $J_{3,F}$ 56.1); δ_C (D_2O,126 MHz) 57.9 (d, C5, $J_{5,F}$ 3.8), 63.8 (d, C2, $J_{2,F}$ 23.8), 65.0 (d, C4, $J_{4,F}$ 26.7), 87.9 (d, C3, $J_{3,F}$ 210.8), 170.3 (d, C1, $J_{1,F}$ 4.8); δ_F (D_2O, 470 MHz) −178.3 (ddd, $J_{F,4}$ 19.3, $J_{F,2}$ 21.3, $J_{F,3}$ 56.0); *m/z* (ESI −ve) 148 ($[M − H]^-$, 100).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra (^1H, ^{13}C and ^{19}F) and inhibition tables. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by the Leverhulme Trust (G.W.J.F.) and a Grant-in-Aid for Scientific Research (C) (No. 26460143) (A.K.) from the Japanese Society for the Promotion of Science (JSPS).

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DOI: 10.1021/acs.joc.5b00463
J. Org. Chem. 2015, 80, 4244−4258