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Fluorinated and Conformationally Fixed Derivatives of L-HomoDMDP: Synthesis and Glycosidase Inhibition

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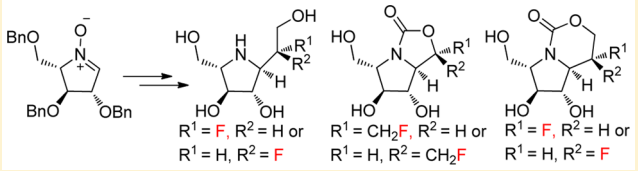
Supporting Information

ABSTRACT: Fluorinated and conformationally fixed derivatives of L-homoDMDP, i.e., 2,5-dideoxy-2,5-imino-DL-*glycero*-L-*manno*-heptitol, have been synthesized from D-xylose-derived cyclic nitrone **10** with oxazolidinone **19** or **28** and oxazinanone **22** or **32** as key intermediates. An evaluation of glycosidase inhibition showed replacement of the C-6 hydroxyl groups with fluoride in L-homoDMDP and its C-6 epimer did not have a significant influence on α-glucosidase inhibition by these iminosugars, while replacement of an amino group with a cyclic carbamate group in most conformationally fixed derivatives led to a sharp decrease in the level of glycosidase inhibition, revealing the importance of the free amino group in interaction of enzymes with these molecules.



INTRODUCTION

2,5-Dideoxy-2,5-imino-D-mannitol (DMDP)[1−5] was first isolated from leaves of *Derris eliptica* (Leguminosae) in 1976[1] and soon recognized as the parent structure for a series of subsequently isolated iminosugars, including 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1),[3,6−8] homoDMDP,[9−11] 7-deoxy-homoDMDP,[5,9] 6-C-alkyl derivatives of DMDP,[5,12] australine,[13] and alexine.[14] DMDP and its derivatives were found to exhibit attractive biological activities,[15−19] such as glycosidase inhibition,[3,9,10,20−27] and as anti-HIV[21,26,28−30] and anticancer agents,[31−34] that thus made them important research targets for the past four decades. Moreover, the synthetic enantiomers of some naturally occurring iminosugars are more potent glycosidase inhibitors than the natural products themselves.[25,35−37] For example, L-DMDP (**1**) exhibited α-glucosidase inhibitory activities more potent and specific than those of the natural product DMDP.[36−38] Similar biological activities were also found for the related L-AB1[20,35] and L-homoDMDP (**3**).[38] Thus, the L-enantiomers are also likely to provide potential new chemotherapeutic agents. Structure−activity relationship studies of these compounds will help in the evaluation of the potential of this type of molecules.

Fluorine is one of the most efficient and useful tools in structure−activity relationship study.[38−43] Introduction of fluorine into a lead compound or veterinary drug will not only help in understanding the docking mode of the molecule and enzyme but also afford derivatives with modified biological activities and selectivities.[44−48] In previous studies,[38] we have set out an initial examination of the structure−activity relationship of L-DMDP and L-homoDMDP (Figure 1) and found the C-3 hydroxyl group of these compounds played an important role in interaction with enzymes, and fluorination of the C-3 hydroxyl led to a sharp decrease in the level of glycosidase inhibition (**2** and **4**). Combining the results of Stütz et al.,[40] we can establish that hydroxyls of the iminosugar core should remain intact to prevent weakening of glycosidase

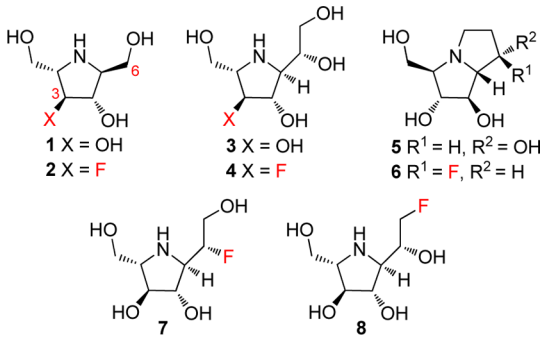


Figure 1. L-DMDP, L-homoDMDP, australine, and their fluorinated analogues.

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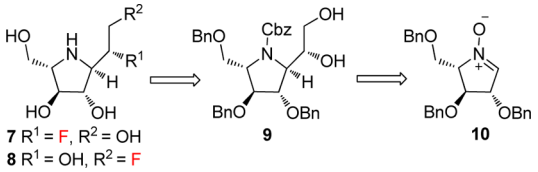
inhibition. In our recent study,[49] C-7 fluorination of australine (**6**) considerably enhanced the potency of its inhibition against α-glucosidase. This enriches the few examples in which the fluorination of a hydroxy group increases rather than greatly decreases the level of inhibition. The results prompted us to study the effects of substitution of the side chain hydroxyl groups in DMDP derivatives with fluoride; this modification should not interfere with interaction of the iminosugar core and its acceptor. It is therefore clear that L-homoDMDP is a good candidate for such studies. Thus, in this work, we report the synthesis of L-homoDMDP derivatives with the C-6 or C-7 hydroxyls substituted with fluoride (**7** and **8**) and examine their glycosidase inhibition.

Retrosynthesis showed that the cyclic nitrone[50,51] **10** derived from D-xylose[52,53] is a good starting material for compounds **7** and **8** (Scheme 1). Because of the steric hindrance of *N*-Cbz, the C-6 and C-7 hydroxyls of intermediate **9** may show different reactivity while reacting with fluorination reagents, thus affording the desired C-6 and C-7 fluorinated derivatives.

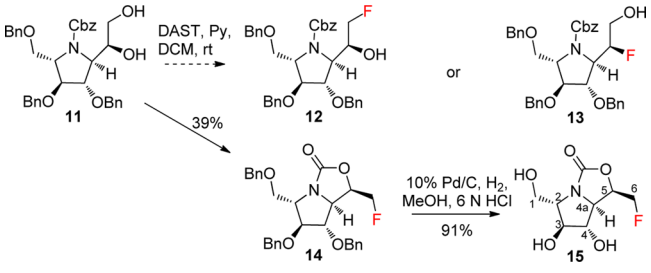
Scheme 1. Retrosynthesis of Fluorinated L-HomoDMDP Analogues from Cyclic Nitrones



RESULTS AND DISCUSSION

Synthesis of C-6 and C-7 Fluorinated Derivatives of L-HomoDMDP. Key intermediate **9** and its C-6 epimer **11** were prepared by previously reported procedures.[38] Reaction of **11** with diethylaminosulfur trifluoride (DAST) in the presence of pyridine was overall slow, and some intermediates clearly involving the Et_2N group were detected by NMR characterization. Continuing stirring of the solution for several days resulted in conversion of the intermediates to fluorinated oxazolidinone **14** in 39% yield finally, together with some unidentified side products. To determine its C-5 configuration, **14** was hydrogenated under routine conditions to afford debenzylated product **15** (Scheme 2). The C-5 configuration of **15** was then determined to be the *R*-configuration through NOESY experiments because a strong interaction of H-4 and H-6 was observed. The result indicated that inversion of the configuration at position C-6 of **11** had occurred during the fluorination procedure.

Scheme 2. Synthesis of Fluorinated and Conformationally Fixed Analogues of L-HomoDMDP



Because the NEt_2 groups were found in the initial reaction intermediates of **11** and DAST, we tentatively assumed that DAST preferentially reacted with the primary hydroxyl group in **11** to furnish intermediate **16** (Scheme 3). On one hand, attack of fluoride at the C-7 leaving group would afford product **12**, which would continue to react with another equivalent of DAST to give intermediate **17**. The carbonyl in the Cbz group then attacked the C-6 leaving group in S_N2 mode, resulting in an inversion of the C-6 configuration from the *S*-configuration in **11** to the *R*-configuration in **14**. On the other hand, the C-6 hydroxyl in **16** could attack the C-7 leaving group, affording epoxide **18**,[54,55] which would form intermediate **12** by attack of fluoride[56] or oxazolidinone **19** via intramolecular 5-*exo*-*tet* opening of the epoxide and give product **14** by reaction with another equivalent of DAST. Notably, cyclic sulfite **20** is also considered to be a possible intermediate in the reaction, though no report of the formation of the cyclic derivative by diols and DAST has been published.

In view of the low yield of the reaction and inability to achieve C-6 fluorinated product **7**, another reaction route must be designed. Bicyclic derivatives such as **19** are no doubt good candidates. Synthetic methods for this type of carbamate have been well-documented in the literature.[57−61] Herein, the synthesis was based on our previously reported procedures;[38,62] treatment of **9** with sodium hydride at room temperature provided oxazolidinone **19** and oxazinanone **22** in 82% total yield (Scheme 4). By the same procedures, bicyclic derivatives **28** and **32** were obtained from **11** in 85% total yield (Scheme 5).

Fluorination of oxazolidinones **19** and **28** afforded compounds **14** and **29**, respectively, both in moderate yields. Low yields of the reaction may be attributed to the formation of side products with an Et_2N group (detected by NMR characterization), which failed to be converted to the target fluorination product **14** or **29** by further reaction. Subsequent hydrogenolysis of the four oxazolidinones resulted in products **21**, **30**, **15**, and **31**, respectively (Schemes 4 and 5). The C-5 configuration of oxazolidinone **31** was confirmed as *S* by a NOESY experiment that showed strong H4 and H5 correlation. While oxazinanones **22** and **32** were reacted with DAST, fluorination gave anticipated products **23** and **33** together with elimination products **24** and **34**, respectively. The C-5 configurations of **23** and **33** were determined via their hydrogenation products **25** and **35**. The C-5 configuration of compound **35** was determined to be *R* through NOESY experiments because a strong interaction of H-4 and H-5 was observed. Accordingly, the C-5 configuration of product **25** was determined to be *S*. Therefore, fluorination of **22** and **32** had been finished in usual S_N2 pattern.

Hydrolysis of oxazinanones **33** and **23** provided amines **36** and **26**, respectively, which were then debenzylated to give the target products, 6-deoxy-6-fluorinated-L-homoDMDP (**7**) and its C-6 epimer **27**. Surprisingly, while the same hydrolysis procedures were applied for fluorinated oxazolidinones **14** and **29**, decomposition of the starting materials was observed. Various bases, including KOH and K_2CO_3, and different reaction temperatures were tried, but no positive result was achieved.

Glycosidase Inhibition. Compounds **7**, **15**, **21**, **25**, **27**, **30**, **31**, and **35** were assayed as potential inhibitors of a range of glycosidases, and the results are summarized in Table 1.

L-HomoDMDP (**3**) and 6-*epi*-L-homoDMDP showed potent and moderate inhibition of rat intestinal sucrase (IC_{50} values of

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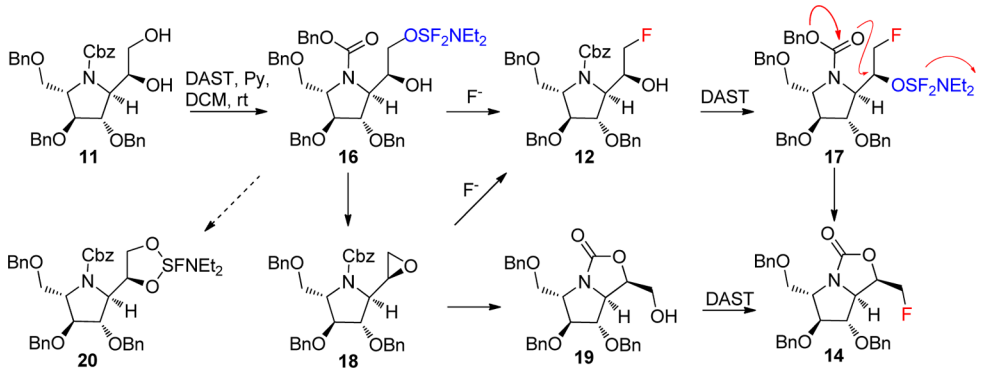
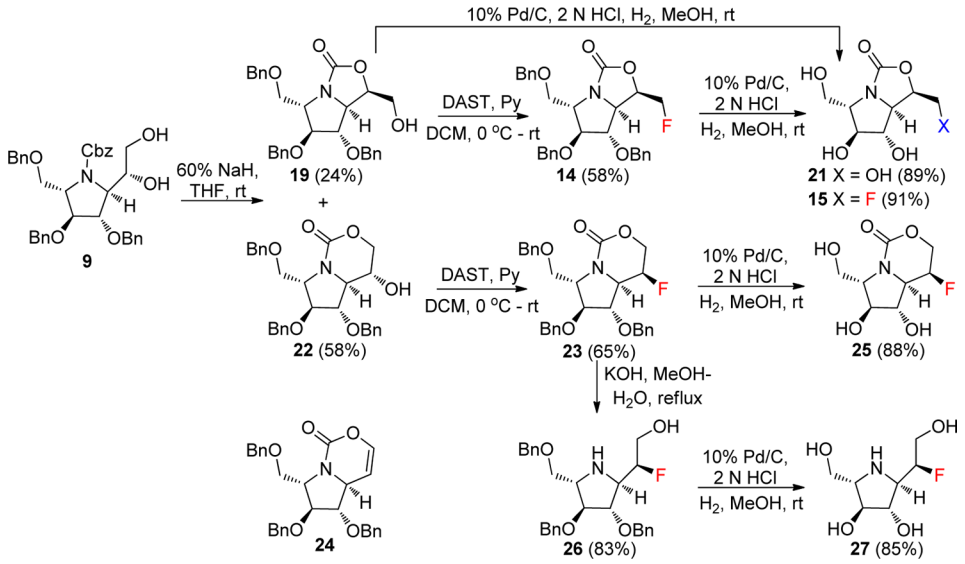
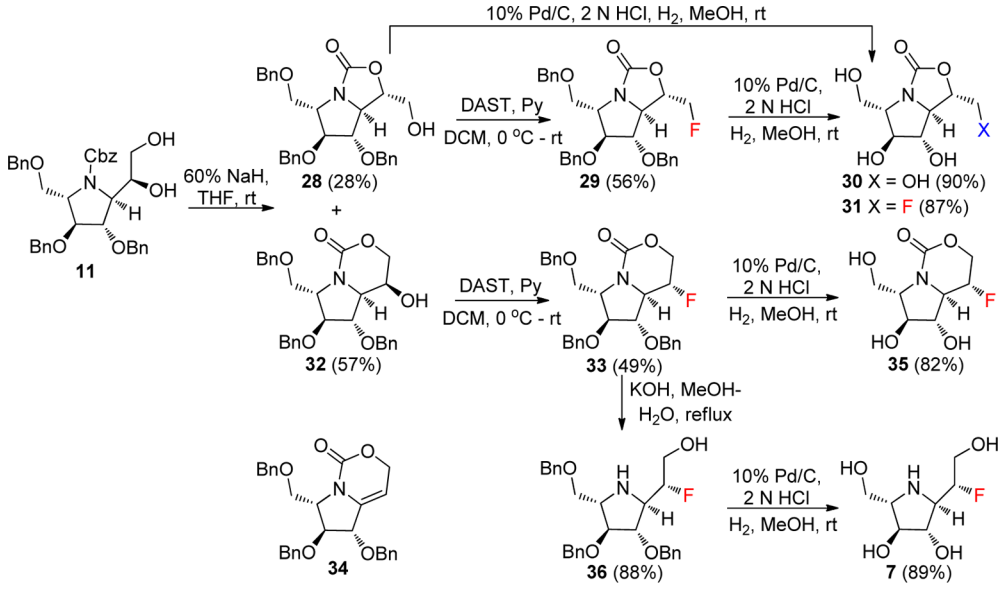
Scheme 3. Possible Mechanism for Formation of Oxazolidinone 14



Scheme 4. Preparation of L-HomoDMDP Derivatives from 9



Scheme 5. Preparation of L-HomoDMDP Derivatives from 11



5.5 and 64 μM, respectively).[38] 6-Deoxy-6-fluorinated-L-homoDMDP (7) showed a slightly decreased level of inhibition of rice α-glucosidase (IC_{50} = 82 μM), while its C-6 epimer **27** had slightly stronger inhibition of the same enzyme (IC_{50} = 59 μM). Conformationally fixed fluorinated L-homoDMDP derivatives showed obvious decreases in inhibitory activity,

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Table 1. Concentrations of Iminosugars Giving 50% Inhibition of Various Glycosidases

	IC_{50} (μM)									
enzyme	**3**[a]	6-*epi*-**3**[a]	**7**	**27**	**25**	**35**	**21**	**30**	**31**	**15**
α-glucosidase										
yeast	NI[b] (8%)[c]	NI (7%)	NI (2%)	NI (6%)	NI (5%)	356	NI (3%)	NI (26%)	NI (48%)	NI (9%)
Aspergillus niger	ND[d]	ND	NI (14%)	NI (0%)	NI (0%)	NI (0%)	ND	ND	ND	NI (32%)
rice	28	328	82	59	NI (39%)	NI (42%)	NI (29%)	NI (44%)	NI (13%)	23
rat intestinal maltase	29	163	162	255	NI (31%)	240	NI (40%)	305	NI (23%)	89
rat intestinal sucrase	5.5	64	ND	ND	ND	ND	ND	ND	ND	ND
β-glucosidase										
almond	NI (14%)	NI (7%)	NI (0%)	NI (9%)	NI (10%)	NI (39%)	NI (17%)	NI (11%)	NI (19%)	533.5
bovine liver	NI (4%)	NI (0%)	NI (17%)	NI (6%)	NI (5%)	NI (42%)	NI (0%)	NI (0%)	NI (12%)	NI (7%)
α-galactosidase										
coffee bean	NI (4%)	NI (4%)	NI (6%)	NI (1%)	NI (1%)	290	NI (0%)	NI (0%)	596	NI (32%)
β-galactosidase										
bovine liver	NI (9%)	NI (3%)	NI (24%)	NI (1%)	NI (5%)	NI (35%)	NI (0%)	NI (6%)	NI (32%)	NI (19%)
α-mannosidase										
jack beans	NI (1%)	NI (4%)	NI (1%)	NI (2%)	NI (4%)	NI (10%)	NI (1%)	NI (0%)	NI (2%)	NI (0%)
β-mannosidase										
snail	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (15%)	NI (0%)	NI (0%)	NI (0%)
α-L-fucosidase										
bovine kidney	NI (1%)	NI (0%)	NI (9%)	NI (4%)	NI (2%)	NI (40%)	NI (12%)	NI (1%)	NI (31%)	NI (0%)
trehalase										
porcine kidney	NI (9%)	NI (12%)	NI (2%)	NI (0%)	NI (3%)	NI (6%)	NI (0%)	NI (2%)	NI (0%)	NI (4%)
amyloglucosidase										
A. niger	NI (1%)	NI (6%)	NI (4%)	NI (1%)	NI (6%)	NI (0%)	NI (2%)	NI (0%)	NI (0%)	NI (6%)
α-L-rhamnosidase										
Pandanus decumbens	NI (7%)	NI (6%)	NI (3%)	NI (14%)	NI (25%)	NI (7%)	NI (25%)	NI (1%)	NI (0%)	NI (12%)

[a]Taken from ref 38. [b]NI, no inhibition (<50% inhibition at 1000 μM). [c]Numbers in parentheses are inhibition percents at 1000 μM. [d]ND, not determined.

compound **15** being an exception. Oxazolidinone **15** exhibited weak inhibition of β-glucosidase and inhibition of rice α-glucosidase (IC_{50} = 23 μM) similar to that of L-homoDMDP (**3**). Compounds **31** and **35** also showed weak inhibition of coffee bean α-galactosidase (IC_{50} values of 596 and 290 μM, respectively).

Therefore, replacement of the C-6 hydroxyl group with fluoride did not cause a significant decrease in the level of glycosidase inhibition, which indicated that the C-6 hydroxyl group played an unimportant role in interaction with enzymes. For most oxazolidinone and oxazinanone derivatives, substitution of the cyclic carbamate group with an amino group sharply decreased the level of glycosidase inhibition of the derivatives, which showed that the free amino group in these molecules may play an important role in interaction with enzymes. This result is consistent with previous reports[59−61,63,64] that *N*-acylated iminosugars are almost always much weaker inhibitors of glycosidases than the parent iminosugars.

CONCLUSIONS

In summary, fluorinated and conformationally fixed derivatives of L-homoDMDP have been prepared from nitrone-derived oxazolidinones and oxazinanones. Glycosidase assays showed that C-6 fluorinated derivatives **7** and **27** exhibited glycosidase inhibition similar to that of L-homoDMDP and its C-6 epimer. Conformationally fixed derivatives **21**, **25**, **30**, **31**, and **35** showed a sharp decrease in the level of or disappearance of glycosidase inhibition, while oxazolidinone derivative **15** was found to have similar glycosidase inhibitory activities with L-homoDMDP. This indicates that the C-6 hydroxyl groups in L-homoDMDP-related molecules do not have an important effect in their interaction with enzymes; the study also confirms that the corresponding carbamates are in general much weaker inhibitors than their amine analogues. The biological studies reported are valuable for the design of DMDP-related lead compounds.

EXPERIMENTAL SECTION

General Methods. All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Tetrahydrofuran was dried over 4 Å molecular sieve. Dichloromethane was distilled from CaH_2 immediately before being used. Analytical TLC was performed with 0.20 mm silica gel 60F plates with a 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, and H_2O] or a 0.5% solution of $KMnO_4$ in acetone. Chromatographic purification of products was conducted by flash column chromatography on silica gel (200−300 mesh). Acidic ion exchange chromatography was performed on Dowex 50WX8-400 resin, H^+ form. Melting points were measured with an electrothermal melting point apparatus and are uncorrected. Polarimetry was determined using a polarimeter with concentrations (c) given in grams per 100 mL. Infrared spectra were obtained from a FT-IR spectrometer. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a magnetic resonance spectrometer (^1H at 300 or 600 MHz, ^{13}C at 75 or 150 MHz, and ^{19}F at 376 or 565 MHz) using $CDCl_3$ (with TMS as an internal standard), MeOD, or D_2O (with H_2O as an internal standard) as a solvent. High-resolution mass spectra (HRMS) were recorded on a LTQ/FT linear ion trap mass spectrometer.

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Material and Methods for the Enzyme Inhibition Assay. With rat intestinal maltase and sucrase as exceptions, other enzymes were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). Brush border membranes prepared from rat small intestine according to the method of Kessler et al.[65] were assayed at pH 6.8 for rat intestinal maltase and sucrase using maltose and sucrose. The released D-glucose was determined colorimetrically using the Glucose CII-test (Wako Pure Chemical Ind., Osaka, Japan). Other glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as a substrate in a buffer solution at the optimal pH value of each enzyme. The reaction was stopped by adding 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

General Procedures for the Synthesis of Oxazolidinone 19 or 28 and Oxazinanone 22 or 32. To a solution of diol **9** or **11** (1 equiv) in THF was added NaH (60%, 6 equiv) and the mixture stirred at room temperature overnight. An aqueous NH_4Cl solution was added, and the solution was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 5:1 petroleum ether/EtOAc) to give anticipated oxazolidinone **19** or **28** and oxazinanone **22** or **32**. Data for **19** (Lit.[62]): light yellow syrup, 0.28 g, 24% yield from **9** (1.40 g, 2.35 mmol); $[\alpha]_D^{20}$ −1.9 (*c* 1.04 in CH_2Cl_2); ν_{max} 3439 m, 3031 w, 2867 m, 1759 vs, 1454 m, 1365 m, 1209 m, 1071 s, 739 s, 699 s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37−7.23 (15H, m, *Ph*CH_2O), 4.73−4.42 (7H, m, PhC*H*$_2$O), 4.26 (1H, t, *J* = 4.2 Hz), 4.21−4.16 (1H, m), 4.13−4.08 (1H, m), 4.01 (1H, t, *J* = 7.8 Hz), 3.79−3.67 (2H, m), 3.57 (2H, d, *J* = 5.7 Hz); δ_C (75 MHz, $CDCl_3$) 160.4, 137.8, 137.4, 137.2, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 127.5, 86.2, 81.9, 76.1, 73.4, 72.4, 72.2, 70.0, 63.4, 62.5, 60.7.

Data for **22** (Lit.[38]): light yellow solid, 0.67 g, 58% yield from **9** (1.40 g, 2.35 mmol); mp 72−74 °C; $[\alpha]_D^{20}$ +19.1 (*c* 3.24 in CH_2Cl_2); ν_{max} 3063 w, 3031 w, 2867 m, 1673 vs, 1457 w, 1454 m, 1434 m, 1363 m, 1260 w, 1089 s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25−7.17 (15H, m, *Ph*CH_2O), 4.65−4.35 (6H, m, PhC*H*$_2$O), 4.23−4.18 (1H, m, H2), 4.10−4.05 (2H, m, H3 and H6), 3.99−3.93 (1H, m, H4), 3.79 (1H, t, *J* = 10.1 Hz, H6), 3.73−3.66 (m, 1H, H5), 3.58 (dd, 1H, *J* = 9.6, 6.9 Hz, H1), 3.51 (dd, 1H, *J* = 9.6, 4.5 Hz, H1), 3.44 (dd, 1H, *J* = 8.4, 5.7 Hz, H4a); δ_C (75 MHz, $CDCl_3$) 152.6, 138.0, 137.9, 137.7, 128.5, 128.0, 127.9, 127.8, 86.9, 82.8, 73.3, 72.1, 71.8, 69.9, 68.2, 65.7, 64.5, 63.0.

Data for **28** (Lit.[62]): light yellow syrup, 0.58 g, 28% yield from **11** (2.50 g, 4.19 mmol); $[\alpha]_D^{20}$ +16.7 (*c* 0.48 in CH_2Cl_2); ν_{max} 3437 w, 3031 w, 2867 m, 1756 s, 1454 m, 1366 m, 1252 m, 1216 m, 1104 s, 1063 s, 739 m, 698 m cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.34−7.23 (15H, m, *Ph*CH_2O), 4.67−4.44 (6H, m, PhC*H*$_2$O), 4.33 (1H, q, *J* = 4.2 Hz), 4.22 (1H, t, *J* = 3.3 Hz), 4.16−4.11 (1H, m), 3.90 (1H, dd, *J* = 6.0, 3.9 Hz), 3.77 (1H, t, *J* = 5.4 Hz), 3.69 (1H, dd, *J* = 12.3, 3.6 Hz), 3.61−3.50 (3H, m); δ_C (75 MHz, $CDCl_3$) 160.4, 137.9, 137.5, 137.3, 128.6, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 87.9, 85.5, 80.2, 73.3, 72.5, 72.0, 69.4, 64.0, 63.4, 62.5.

Data for **32**: white solid, 1.16 g, 57% yield from **11** (2.50 g, 4.19 mmol); mp 136−138 °C; $[\alpha]_D^{20}$ −5.6 (*c* 1.08 in CH_2Cl_2); ν_{max} 3331 m, 2902 m, 2869 m, 1652 s, 1475 m, 1454 m, 1365 m, 1112 s, 1028 m, 735 m, 695 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32−7.22 (15H, m, *Ph*CH_2O), 4.69−4.41 (6H, m, PhC*H*$_2$O), 4.33−4.23 (3H, m), 4.16−4.12 (2H, m), 4.01 (1H, s), 3.79 (1H, dd, *J* = 9.9, 5.1 Hz), 3.68 (1H, dd, *J* = 7.5, 2.7 Hz), 3.54 (1H, dd, *J* = 9.6, 3.0 Hz), 2.88 (1H, d, *J* = 18.3 Hz); δ_C (75 MHz, $CDCl_3$) 151.8, 138.1, 137.9, 137.7, 128.5, 128.4, 128.0, 127.9, 127.7, 82.6, 81.8, 73.3, 72.8, 72.2, 71.1, 68.5, 64.1, 62.3, 60.5; δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.5, 128.4, 128.0, 127.9, 127.7, 82.6, 81.8, 64.1, 62.3, 60.5; negative, 73.3, 72.8, 72.2, 71.1, 68.5; HRMS(ESI) calcd for $C_{29}H_{31}NO_6Na^+$ $[M + Na]^+$ *m*/*z* 512.2044, found *m*/*z* 512.2050.

General Procedures for Hydrogenation of Oxazolidinone 19 or 28. Oxazolidinone **19** or **28** (1 equiv) was dissolved in methanol, followed by 10% Pd/C (20 wt %) and 2 N HCl. The suspension was stirred under a hydrogen atmosphere for 24−48 h when TLC showed completion of the reaction. Hydrogen was then replaced with nitrogen, and the catalyst was removed from the reaction mixture by filtration and then washed three times with MeOH. The filtrate was concentrated in vacuo, affording target compound **21** or **30**. Data for **21**: light yellow syrup, 59.8 mg, 89% yield from **19** (0.15 g, 0.31 mmol); $[\alpha]_D^{20}$ −26.9 (*c* 0.67 in MeOH); ν_{max} 3358 m, 2935 w, 1735 s, 1654 w, 1401 m, 1231 m, 1108 s, 1035 vs cm^{-1}; δ_H (300 MHz, D_2O) 4.93 (1H, td, *J* = 6.9, 3.3 Hz), 4.16 (1H, dd, *J* = 9.0, 7.2 Hz), 4.08 (1H, t, *J* = 6.6 Hz), 4.04 (1H, d, *J* = 8.7 Hz), 4.00 (1H, dd, *J* = 9.3, 3.6 Hz), 3.92 (1H, dd, *J* = 12.6, 9.6 Hz), 3.82 (1H, dd, *J* = 12.0, 3.9 Hz), 3.69 (1H, dd, *J* = 12.0, 5.4 Hz), 3.62−3.57 (1H, m); δ_C (75 MHz, D_2O) 162.0, 78.2, 77.4, 73.6, 63.6, 62.0, 60.7, 59.7; δ_C (Dept-135, 75 MHz, D_2O) positive, 78.2, 77.4, 73.6, 63.6, 62.0; negative, 60.7, 59.7; HRMS(ESI) calcd for $C_8H_{14}NO_6^+$ $[M + H]^+$ *m*/*z* 220.0816, found *m*/*z* 220.0814.

Data for **30**: light yellow syrup, 12.3 mg, 90% yield from **28** (30.4 mg, 0.06 mmol); $[\alpha]_D^{20}$ 0 (*c* 0.18 in MeOH); ν_{max} 3355 m, 2932 w, 1735 s, 1381 m, 1241 m, 1098 s, 1046 vs cm^{-1}; δ_H (300 MHz, D_2O) 4.76 (1H, t, *J* = 4.5 Hz), 4.11 (1H, t, *J* = 6.2 Hz), 3.04 (1H, t, *J* = 7.4 Hz), 3.89 (1H, dd, *J* = 12.9, 3.0 Hz), 3.82−3.75 (2H, m), 3.73−3.69 (2H, m), 3.67−3.61 (1H, m); δ_C (75 MHz, D_2O) 162.5, 80.4, 78.5, 77.8, 64.7, 62.9, 62.2, 60.7; δ_C (Dept-135, 75 MHz, D_2O) positive, 80.4, 78.5, 77.8, 64.7, 62.9; negative, 62.2, 60.7; HRMS(ESI) calcd for $C_8H_{14}NO_6^+$ $[M + H]^+$ *m*/*z* 220.0816, found *m*/*z* 220.0816.

General Fluorination Procedures for the Synthesis of Oxazolidinone 14 or 29 and Oxazinanone 23 or 33. To a solution of DAST (1.2 equiv) and pyridine (6 equiv) in dichloromethane was added the solution of oxazolidinone **19** or **28** and oxazinanone **22** or **32** in dichloromethane at 0 °C. The reaction mixture was stirred overnight at room temperature when TLC showed completion of the reaction. The reaction mixture was quenched with an aqueous $NaHCO_3$ solution and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 5:1 petroleum ether/EtOAc) to give anticipated fluorinated oxazolidinone **14** or **29** and oxazinanone **23** (accompanied by side product **24**) or **33** (accompanied by side product **34**). Data for **14**: yellow syrup, 69.8 mg, 58% yield from **19** (0.12 g, 0.25 mmol); $[\alpha]_D^{20}$ +2.4 (*c* 0.85 in CH_2Cl_2); ν_{max} 3033 w, 2866 m, 1764 vs, 1362 m, 1211 m, 1101 s, 743 m, 702 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34−7.22 (15H, m, *Ph*CH_2O), 4.84−4.72 (1H, m, H5), 4.66−4.32 (8H, m, H6 and PhC*H*$_2$O), 4.24 (1H, t, *J* = 3.5 Hz, H3), 4.14 (1H, dd, *J* = 8.4, 5.4 Hz, H4), 4.08−3.99 (2H, m, H1 and H4a), 3.61−3.56 (2H, m, H1 and H2); δ_C (75 MHz, $CDCl_3$) 159.6 (OC═O), 137.7, 137.3, 137.1, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8 (Ph), 86.1 (C3), 82.0 (C4), 80.5 (d, *J* = 173.3 Hz, C6), 73.8 (d, *J* = 21.4 Hz, C5), 73.4 (C1), 72.4, 72.2, 69.9 (PhCH_2O), 62.9 (d, *J* = 4.8 Hz, C4a), 62.4 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 86.1, 82.0, 73.8, 62.9, 62.4; negative, 80.5, 73.4, 72.4, 72.2, 69.9; HRMS(ESI) calcd for $C_{29}H_{31}FNO_5^+$ $[M + H]^+$ *m*/*z* 492.2181, found *m*/*z* 492.2181.

Data for **29**: light yellow syrup, 0.23 g, 56% yield from **28** (0.41 g, 0.84 mmol); $[\alpha]_D^{20}$ +11.8 (*c* 3.21 in CH_2Cl_2); ν_{max} 3063 w, 3032 w, 2866 w, 1765 m, 1454 m, 1365 m, 1253 m, 1217 m, 1099 s, 1062 s, 1028 m, 739 m, 699 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27−7.12 (15H, m, *Ph*CH_2O), 4.51 (2H, dd, *J* = 12.0, 3.3 Hz, PhC*H*$_2$O), 4.44 (2H, s, PhC*H*$_2$O), 4.36 (3H, dd, *J* = 11.7, 6.6 Hz, PhC*H*$_2$O and H6), 4.31−4.28 (1H, m, H6), 4.26−4.20 (1H, m, H5), 4.17−4.10 (1H, m, H3), 4.08−4.04 (1H, m, H2), 3.81 (1H, dd, *J* = 6.0, 4.2 Hz, H4), 3.67 (1H, dd, *J* = 6.3, 3.9 Hz, H4a), 3.47 (2H, d, *J* = 5.7 Hz, H1); δ_C (75 MHz, $CDCl_3$) 160.0 (OC═O), 137.9, 137.5, 137.4, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7 (Ph), 87.9 (C4), 85.5 (C3), 82.4 (d, *J* = 175.2 Hz, C6), 77.2 (d, *J* = 20.7 Hz, C5), 73.3, 72.6, 72.1 (PhCH_2O), 69.5 (C1), 63.5 (d, *J* = 5.4 Hz, C4a), 62.7 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7, 87.9, 85.5, 77.2, 63.5, 62.7; negative, 82.4, 73.3, 72.6, 72.1, 69.5; HRMS(ESI) calcd for $C_{29}H_{31}FNO_5^+$ $[M + H]^+$ *m*/*z* 492.2181, found *m*/*z* 492.2177.

Data for **23**: light yellow solid, 0.21 g, 65% yield from **22** (0.32 g, 0.65 mmol); mp 75−77 °C; $[\alpha]_D^{20}$ −1.9 (*c* 1.07 in CH_2Cl_2); ν_{max} 3032 w, 2868 m, 1707 vs, 1460 m, 1429 m, 1361 m,1277 m, 1105 vs, 744 m, 700 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24−7.11 (15H, m, *Ph*CH_2O),

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4.71 (1H, d, $J_{H,F}$ = 44.1 Hz, H5), 4.60−4.34 (7H, m, H3 and PhCH_2O), 4.23 (1H, t, J = 5.1 Hz, H4), 4.18−4.14 (1.5H, m, H2 and H6), 4.04−3.94 (1.5H, m, H2 and H6), 3.78 (1H, dd, J = 9.9, 3.9 Hz, H1), 3.63 (1H, dd, J = 28.8, 8.4 Hz, H4a), 3.47 (1H, d, J = 8.1 Hz, H1); δ_C (75 MHz, $CDCl_3$) 150.4 (OC═O), 138.0, 137.8, 137.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8 (Ph), 82.6 (C3), 82.1 (d, J = 5.5 Hz, C4), 80.1 (d, J = 182.3 Hz, C5), 73.4, 73.0, 72.6 (PhCH_2O), 68.9 (C1), 67.9 (d, J = 20.7 Hz, C6), 62.3 (C2), 62.2 (d, J = 19.7 Hz, C4a); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 82.6, 82.1, 80.1, 62.3, 62.2; negative, 73.4, 73.0, 72.6, 68.9, 67.9; HRMS(ESI) calcd for $C_{29}H_{31}FNO_5^+$ $[M + H]^+$ m/z 492.2181, found m/z 492.2179.

Data for side product **24**: yellow syrup, 0.08 g, 26% yield from **22** (0.32 g, 0.65 mmol); $[\alpha]_D^{20}$ −15.3 (c 1.05 in CH_2Cl_2); ν_{max} 3322 w, 3033 m, 2870 m, 1726 vs, 1419 m, 1361 m, 1266 m, 1214 m, 1102 vs, 742 m, 703 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.20−7.06 (15H, m, PhCH_2O), 6.20 (1H, dd, J = 6.3, 2.3 Hz, H6), 5.02 (1H, dd, J = 6.3, 1.7 Hz, H5), 4.58−4.36 (6H, m, PhCH_2O), 4.14−3.99 (3H, m, H2, H3 and H4a), 3.77 (1H, dd, J = 9.0, 2.0 Hz, H4), 3.67 (1H, dd, J = 9.6, 2.0 Hz, H1), 3.51 (1H, dd, J = 9.3, 3.0 Hz, H1); δ_C (75 MHz, $CDCl_3$) 148.4 (OC═O), 139.8 (C6), 138.0, 137.9, 137.8, 137.7, 137.6, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7 (Ph), 102.0 (C5), 88.4 (C4), 83.2 (C3), 73.5, 72.7, 72.4 (PhCH_2O), 69.2 (C1), 62.5 (C4a), 58.6 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 139.8, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 102.0, 88.4, 83.2, 62.5, 58.6; negative, 73.5, 72.7, 72.4, 69.2; HRMS(ESI) calcd for $C_{29}H_{29}NO_5Na^+$ $[M + Na]^+$ m/z 494.1938, found m/z 494.1946.

Data for **33**: yellow syrup, 0.24 g, 49% yield from **32** (0.49 g, 1.00 mmol); $[\alpha]_D^{20}$ +33.3 (c 0.24 in CH_2Cl_2); ν_{max} 3032 w, 2920 m, 1713 vs, 1424 m, 1360 m, 1258 m, 1100 s, 743 m, 700 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30−7.18 (15H, m, PhCH_2O), 4.71 (0.5H, dd, J = 10.5, 6.2 Hz, H5), 4.58−4.37 (6.5H, m, H5 and PhCH_2O), 4.22−4.11 (4H, m, H2, H3 and H6), 3.84 (1H, dd, J = 7.2, 4.1 Hz, H4), 3.77−3.63 (2H, m, H1 and H4a), 3.58−3.54 (1H, m, H1); δ_C (75 MHz, $CDCl_3$) 151.4 (OC═O), 137.8, 137.3, 137.2, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7 (Ph), 85.8 (C4), 84.6 (d, J = 178.5 Hz, C5), 82.8 (C3), 73.4, 72.2, 72.1 (PhCH_2O), 68.5 (C1), 66.4 (d, J = 26.8 Hz, C6), 63.4 (d, J = 27.5 Hz, C4a), 62.7 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 85.8, 84.6, 82.8, 63.4, 62.7; negative, 73.4, 72.2, 72.1, 68.5, 66.4; HRMS(ESI) calcd for $C_{29}H_{31}FNO_5^+$ $[M + H]^+$ m/z 492.2181, found m/z 492.2162.

Data for side product **34**: yellow syrup, 0.15 g, 32% yield from **32** (0.49 g, 1.00 mmol); $[\alpha]_D^{20}$ +6.9 (c 0.29 in CH_2Cl_2); ν_{max} 2924 m, 1715 vs, 1457 m, 1202 m, 1098 vs, 742 m, 701 m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37−7.21 (15H, m, PhCH_2O), 5.06 (1H, s, H5), 4.93−4.80 (2H, m, H6), 4.62−4.37 (8H, m, H2, H3 and PhCH_2O), 4.18 (1H, s, H4), 3.84 (1H, dd, J = 9.3, 4.5 Hz, H1), 3.67−3.61 (1H, m, H1); δ_C (75 MHz, $CDCl_3$) 151.1 (OC═O), 139.4 (C4a), 138.0, 137.2, 137.1, 128.6, 128.5, 128.4, 128.0, 127.7 (Ph), 96.0 (C5), 81.1, 80.3 (C3 and C4), 73.2, 71.4, 71.1 (PhCH_2O), 67.8, 67.3 (C1 and C6), 63.0 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.6, 128.5, 128.4, 128.0, 127.7, 96.0, 81.1, 80.3, 63.0; negative, 73.2, 71.4, 71.1, 67.8, 67.3; HRMS(ESI) calcd for $C_{29}H_{30}NO_5^+$ $[M + H]^+$ m/z 472.2118, found m/z 472.2127.

Synthesis of Fluorinated Oxazolidinone 15 or 31 and Oxazinanone 25 or 35. Hydrogenation of **14**, **29**, and oxazinanone **23** or **33** was performed according to the general hydrogenation procedures to give products **15**, **31**, and oxazinanone **25** or **35**. Data for **15**: yellow syrup, 16.5 mg, 91% yield from **14** (40.5 mg, 0.08 mmol); $[\alpha]_D^{20}$ −12.3 (c 0.82 in MeOH); ν_{max} 3356 s, 2933 m, 1740 vs, 1400 m, 1233 m, 1111 m, 1044 m, 774 m cm^{-1}; δ_H (600 MHz, D_2O) 5.08 (1H, dt, J = 24.0, 3.9 Hz, H5), 4.93 (0.5H, dd, J = 11.4, 2.1 Hz, H6), 4.88−4.84 (1.5H, m, H6), 4.15 (1H, t, J = 8.1 Hz, H3), 4.10−4.07 (2H, m, H4 and H4a), 3.81 (1H, dd, J = 12.0, 3.6 Hz, H1), 3.69 (1H, dd, J = 12.0, 5.4 Hz, H1), 3.59 (1H, dd, J = 9.0, 5.4 Hz, H2); δ_C (75 MHz, D_2O) 161.6 (OC═O), 80.8 (d, J = 168.6 Hz, C6), 78.1 (C3), 75.1 (d, J = 18.6 Hz, C5), 73.7 (d, J = 2.9 Hz, C4), 63.5 (C2), 61.6 (d, J = 4.8 Hz, C4a), 60.6 (C1); δ_C (Dept-135, 75 MHz, D_2O) positive, 78.1, 75.1, 73.7, 63.5, 61.6; negative, 80.8, 60.6; ^{19}F NMR (376 MHz, D_2O) δ −231.0 (dt, J = 71.4, 22.6 Hz, 1F); HRMS(ESI) calcd for $C_8H_{13}FNO_5^+$ $[M + H]^+$ m/z 222.0772, found m/z 222.0773.

Data for **31**: yellow syrup, 11.8 mg, 87% yield from **29** (30.0 mg, 0.06 mmol); $[\alpha]_D^{20}$ 0 (c 0.18 in MeOH); ν_{max} 3355 m, 1753 m, 1736 m, 1410 m, 1243 m, 1092 s, 1045 s cm^{-1}; δ_H (600 MHz, MeOD) 4.77 (1H, ddd, J = 22.8, 7.2, 4.2 Hz, H5), 4.70 (0.5H, dd, J = 10.8, 3.0 Hz, H6), 4.64−4.60 (1H, m, H6), 4.53 (0.5H, dd, J = 10.8, 4.8 Hz, H6), 4.14 (1H, t, J = 5.4 Hz, H3), 3.90 (1H, t, J = 6.3 Hz, H4), 3.76 (1H, dd, J = 11.4, 4.2 Hz, H1), 3.70−3.67 (2H, m, H1 and H4a), 3.62 (1H, dd, J = 9.6, 4.8 Hz, H2); δ_C (75 MHz, D_2O) 162.1 (OC═O), 83.1 (d, J = 169.7 Hz, C6), 78.3 (C3), 78.2 (d, J = 16.2 Hz, C5), 77.8 (C4), 64.7 (C2), 62.1 (d, J = 6.2 Hz, C4a), 60.6 (C1); δ_C (Dept-135, 75 MHz, D_2O) positive, 78.3, 78.2, 77.8, 64.7, 62.0; negative, 83.1, 60.6; ^{19}F NMR (565 MHz, D_2O) δ −232.7 (s, 1F); HRMS(ESI) calcd for $C_8H_{12}FNO_5Na^+$ $[M + Na]^+$ m/z 244.0592, found m/z 244.0590.

Data for **25**: yellow syrup, 32.7 mg, 88% yield from **23** (82.6 mg, 0.17 mmol); $[\alpha]_D^{20}$ −9.8 (c 0.82 in MeOH); ν_{max} 3335 s, 2949 m, 1676 vs, 1471 m, 1439 m, 1335 m, 1300 m, 1224 m, 1065 m cm^{-1}; δ_H (600 MHz, D_2O) 5.28 (1H, d, $J_{H,F}$ = 46.8 Hz, H5), 4.67 (1H, t, J = 11.7 Hz, H6), 4.50 (1H, dd, J = 38.4, 13.2 Hz, H6), 4.21−4.14 (2H, m, H3 and H4), 4.04 (1H, dd, J = 12.0, 3.0 Hz, H1), 3.79−3.75 (2H, m, H1 and H4a), 3.72 (1H, dd, J = 6.6, 3.0 Hz, H2); δ_C (150 MHz, D_2O) 153.5 (OC═O), 79.7 (d, J = 178.2 Hz, C5), 74.4 (C3), 73.0 (d, J = 6.2 Hz, C4), 68.9 (d, J = 20.1 Hz, C6), 63.8 (C2), 62.1(d, J = 19.8 Hz, C4a), 59.0 (C1); δ_C (Dept-135, 75 MHz, D_2O) positive, 79.5, 74.2, 72.8, 63.6, 61.9; negative, 68.7, 58.8; ^{19}F NMR (376 MHz, D_2O) δ −208.1 (dd, J = 75.2 Hz, 37.6 Hz, 1F); HRMS(ESI) calcd for $C_8H_{13}FNO_5^+$ $[M + H]^+$ m/z 222.0772, found m/z 222.0773.

Data for **35**: yellow syrup, 21.0 mg, 82% yield from **33** (57.0 mg, 0.12 mmol); $[\alpha]_D^{20}$ +82.9 (c 0.56 in MeOH); ν_{max} 3342 s, 2937 m, 1685 vs, 1440 m, 1358 m, 1057 m cm^{-1}; δ_H (600 MHz, D_2O) 5.12 (1H, ddd, $J_{H,F}$ = 48.6, 9.0, 4.8 Hz, H5), 4.48−4.40 (2H, m, H6), 4.16 (1H, t, J = 7.2 Hz, H3), 4.02−3.96 (2H, m, H1 and H4), 3.79 (1H, dd, J = 12.6, 3.0 Hz, H1), 3.75−3.69 (2H, m, H2 and H4a); δ_C (150 MHz, D_2O) 154.4 (OC═O), 84.7 (d, J = 173.4 Hz, C5), 77.3 (C4), 75.3 (C3), 66.5 (d, J = 25.2 Hz, C6), 64.2 (C2), 62.8 (d, J = 26.7 Hz, C4a), 59.6 (C1); δ_C (Dept-135, 75 MHz, D_2O) positive, 84.5, 77.1, 75.1, 64.1, 62.6; negative, 66.4, 59.5; ^{19}F NMR (376 MHz, D_2O) δ −194.1 to −194.3 (m, 1F); HRMS(ESI) calcd for $C_8H_{13}FNO_5^+$ $[M + H]^+$ m/z 222.0772, found m/z 222.0773.

General Hydrolysis Procedures for the Synthesis of Amine 26 or 36. To the solution of fluorinated oxazinanone **23** or **33** (1 equiv) in a 2:1 MeOH/H_2O solvent was added KOH (8.8 equiv) and the mixture refluxed overnight. After TLC showed completion of the reaction, water was added, and then the mixture was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 1:1 petroleum ether/EtOAc) to give anticipated hydrolysis product **26** or **36**. Data for **26**: light yellow solid, 0.15 g, 83% yield from **23** (0.19 g, 0.39 mmol); mp 51−53 °C; $[\alpha]_D^{20}$ −22.0 (c 0.55 in CH_2Cl_2); ν_{max} 3336 w, 3031 w, 2865 m, 1496 w, 1454 m, 1363 w, 1098 s, 1028 m, 738 s, 698 s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31−7.19 (15H, m, PhCH_2O), 4.61−4.43 (7H, m, H6 and PhCH_2O), 4.03 (1H, t, J = 2.1 Hz, H3), 3.96 (1H, t, J = 4.4 Hz, H4), 3.82 (1H, t, J = 4.4 Hz, H7), 3.74 (1H, dd, J = 9.6 Hz, H7), 3.53 (2H, s, br, NH and OH), 3.49 (2H, d, J = 5.4 Hz, H1), 3.42−3.32 (2H, m, H2 and H5); δ_C (75 MHz, $CDCl_3$) 138.0, 137.7, 128.6, 128.5, 128.0, 127.9 (Ph), 93.2 (d, $J_{C,F}$ = 174.2 Hz, C6), 85.7 (d, J = 4.7 Hz, C4), 85.2 (C3), 73.3, 72.3, 72.0 (PhCH_2O), 69.6 (C1), 63.2 (d, J = 22.3 Hz, C7), 62.5 (d, J = 19.3 Hz, C5), 61.7 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.6, 128.5, 128.0, 127.9, 93.2, 85.7, 85.2, 62.5, 61.7; negative, 73.3, 72.3, 72.1, 69.6, 63.2; HRMS(ESI) calcd for $C_{28}H_{33}FNO_4^+$ $[M + H]^+$ m/z 466.2388, found m/z 466.2386.

Data for **36**: yellow syrup, 83.5 mg, 88% yield from **33** (0.10 g, 0.20 mmol); $[\alpha]_D^{20}$ −46.2 (c 0.13 in CH_2Cl_2); ν_{max} 3342 w, 3030 w, 2864 m, 1496 w, 1454 m, 1364 w, 1096 s, 1028 m, 737 s, 698 s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34−7.24 (15H, m, PhCH_2O), 4.60−4.41 (7H, m, H6 and PhCH_2O), 4.12 (1H, t, J = 2.7 Hz, H3), 3.97 (1H, dd, J = 5.4, 3.3 Hz, H4), 3.87 (1H, t, J = 4.4 Hz, H7), 3.81 (1H, d, J = 4.8 Hz, H7), 3.51 (2H, d, J = 5.1 Hz, H1), 3.48−3.40 (1H, m, H5), 3.28 (1H,

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dd, J = 9.9, 4.8 Hz, H2), 3.15 (1H, s, br, OH); δ_C (75 MHz, $CDCl_3$) 137.94, 137.92, 137.8, 128.5, 127.93, 127.90, 127.86, 127.84, 127.78 (Ph), 90.9 (d, $J_{C,F}$ = 172.3 Hz, C6), 86.1 (C4), 85.6 (C3), 73.2, 72.1, 71.7 ($PhCH_2O$), 69.0 (C1), 64.3 (d, J = 25.0 Hz, C5), 63.7 (d, J = 24.2 Hz, C7), 62.3 (C2); δ_C (Dept-135, 75 MHz, $CDCl_3$) positive, 128.5 127.94, 127.90, 127.86, 127.84, 127.78, 90.9, 86.1, 85.6, 64.3, 62.3; negative, 73.2, 72.1, 71.7, 68.9, 63.7; HRMS(ESI) calcd for $C_{28}H_{33}FNO_4^+$ $[M + H]^+$ m/z 466.2388, found m/z 466.2392.

6-Deoxy-6-fluorinated-L-homoDMDP (7) and Its C-6 Epimer, 27. Hydrogenation of **36** and **26** was conducted according to the general hydrogenation procedures. The crude products were purified by an acidic ion exchange column (Dowex 5WX8-400, H^+ form, Aldrich, column size of 1.3 cm × 14 cm), eluting with distilled water (100 mL) and then 1 N NH_4OH (50 mL), affording 6-deoxy-6-fluorinated-L-homoDMDP (**7**) and its C-6 epimer, **27**. Data for **27**: yellow syrup, 35.0 mg, 85% yield from **26** (97.7 mg, 0.21 mmol); $[\alpha]_D^{20}$ −22.5 (c 1.51 in MeOH); ν_{max} 3335 vs, 2929 m, 1413 m, 1053 s cm^{-1}; δ_H (300 MHz, D_2O) 4.78 (1H, ddd, $J_{H,F}$ = 49.2 Hz, $J_{H,H}$ = 9.9 Hz, $J_{H,H}$ = 5.1 Hz, H6), 4.05 (1H, t, J = 7.8 Hz, H4), 3.96−3.90 (2H, m, H1 and H3), 3.84 (1H, d, J = 5.1 Hz, H1), 3.82−3.69 (2H, m, H7), 3.22 (1H, ddd, J = 21.9, 8.1, 4.8 Hz, H5), 3.10−3.04 (1H, m, H2); ^{19}F NMR (376 MHz, D_2O) δ −199.3 (dt, J = 75.2, 26.3 Hz, 1F); HRMS(ESI) calcd for $C_7H_{15}FNO_4^+$ $[M + H]^+$ m/z 196.0980, found m/z 196.0980.

Data for **7**: yellow syrup, 29.0 mg, 89% yield from **36** (77.6 mg, 0.17 mmol); $[\alpha]_D^{20}$ −27.5 (c 1.38 in MeOH); ν_{max} 3390 vs, 2928 m, 1726 m, 1568 s, 1421 m, 1096 m cm^{-1}; δ_H (300 MHz, D_2O) 4.63 (1H, ddd, $J_{H,F}$ = 49.8 Hz, $J_{H,H}$ = 9.6 Hz, $J_{H,H}$ = 5.1 Hz, H6), 4.12 (1H, t, J = 7.2 Hz, H4), 3.87−3.82 (2H, m, H1 and H3), 3.76 (1H, d, J = 4.2 Hz, H1), 3.73−3.61 (2H, m, H7), 3.16 (1H, ddd, J = 18.6, 7.2, 5.7 Hz, H5), 3.00−2.94 (1H, m, H2); δ_C (75 MHz, D_2O) 95.2 (d, $J_{C,F}$ = 171.6 Hz, C6), 77.4 (d, J = 8.5 Hz, C4), 77.3 (C3), 61.7 (C2), 61.3 (d, J = 20.2 Hz, C7), 60.9 (C1), 59.6 (d, J = 20.9 Hz, C5); δ_C (Dept-135, 75 MHz, D_2O) positive, 95.2, 77.4, 77.3, 61.7, 59.6; negative, 61.3, 60.9; ^{19}F NMR (376 MHz, D_2O) δ −200.3 (t, J = 69.6 Hz, 1F); HRMS(ESI) calcd for $C_7H_{15}FNO_4^+$ $[M + H]^+$ m/z 196.0980, found m/z 196.0981.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra and infrared spectra of intermediates and products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00571.

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Notes

The authors declare no competing financial interest.

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