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PAPER

L-DMDP, L-homoDMDP and their C-3 fluorinated derivatives: synthesis and glycosidase-inhibition†

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L-DMDP and L-homoDMDP, the enantiomers of naturally occurring DMDP and homoDMDP have been synthesized from D-xylose derived cyclic nitrone **9**. Their 3-deoxy-3-fluorinated analogues were also obtained from polyhydroxylated fluorinated cyclic nitrone **10**, which was prepared from fluorinated sugar **12** in seven steps. Bioactivities of these iminosugars against various glycosidases were evaluated. While L-DMDP and L-homoDMDP are potent inhibitors of α-glucosidases, a sharp decrease of inhibition was found when the C-3 hydroxyl group of these compounds was replaced by fluoride, which showed the great importance of the C-3 hydroxyl in their interaction with enzymes.

Introduction

Naturally occuring polyhydroxylated pyrrolidines[1] such as DMDP **1**[2–3] and related homoDMDP **2**[4–6] (Fig. 1) are potent inhibitors of some glycosidases with mild inhibition of others. Interestingly, the synthetic L-enantiomer of DMDP **3** was found to be an even more powerful and specific α-glucosidase inhibitor than the natural product.[7] Similar interesting biological activities were also found with other D- and L- iminosugars, such as the natural DAB and the synthetic enantiomer LAB, the natural (–)-steviamine and its enantiomer (+)-steviamine.[8] Though no substantive explanation was given for the experimental results, it provided a promising new direction for pharmaceutical chemistry. In order to find more selective and better glycosidase inhibitors on the basis of our previous study of L-iminosugars,[7] we have synthesized the enantiomers of DMDP, homoDMDP and their C-3 fluorinated derivatives (**3–6**) and examined their glycosidase inhibition.

While fluoride and hydroxyl groups are chemical isosteres,[9] the incorporation of fluorine or a fluorinated group often furnishes molecules with unique properties that can not be attained by any other elements. Introduction of fluorine into pharmaceutical and veterinary drugs to enhance their pharmacological properties has become almost standard practice. We are interested in a synthesis and biological activity study of fluorinated L-DMDP derivatives with one or more hydroxyl groups replaced by fluoride, thus to further enhance biological performance of this type of molecules and discover relationship between structure and activities as glycosidases inhibitors.

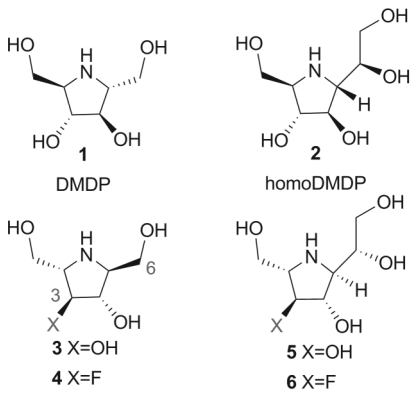

Fig. 1 DMDP, homoDMDP, their enantiomers and 3-deoxy-3-fluorinated analogues.

Since Stütz *et al.*[10] reported the replacement of the C6 hydroxyl group of DMDP by a fluoro atom or methoxyl group led to a 10 or 10^2-fold reduction of inhibition of glycosidases, the C6 hydroxyl group was believed to be important for interactions of DMDP with the enzyme. The results drove us to consider the possibility of pursuing DMDP derivatives in which the hydroxyl group of C-3 or C-4 is substituted by fluoride which will not interfere with the hydrogen-bond interaction of the C6 hydroxyl group and its acceptor. 3-Deoxy-3-fluoro-L-DMDP (**4**) and 3-deoxy-3-fluoro-L- homoDMDP (**6**) are thus synthesized and evaluated

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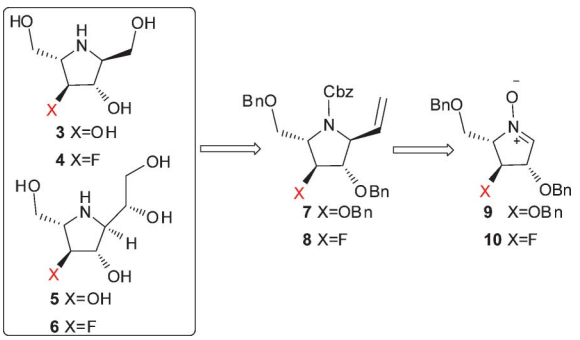
against various glycosidases together with L-DMDP (**3**) and L-homoDMDP (**5**).

Retrosynthesis (Scheme 1) for compounds **3–6** showed that the cyclic nitrone[11] **9** derived from D-xylose is a good starting material for **3** and **5**, while fluorinated analogues **4** and **6** can be synthesized effeciently from fluorinated nitrone **10** with a Grignard addition reaction and dihydroxylation as the key steps. According to the retrosynthetic analysis, we started the synthesis from preparation of the fluorinated nitrone **10**. Nitrone **9** was synthesized in hundreds of grams *via* the reported procedure.[11–12]



Scheme 1 Retrosynthesis of L-DMDP, L-homoDMDP and their 3-deoxy-3-fluorinated analogues from cyclic nitrones.

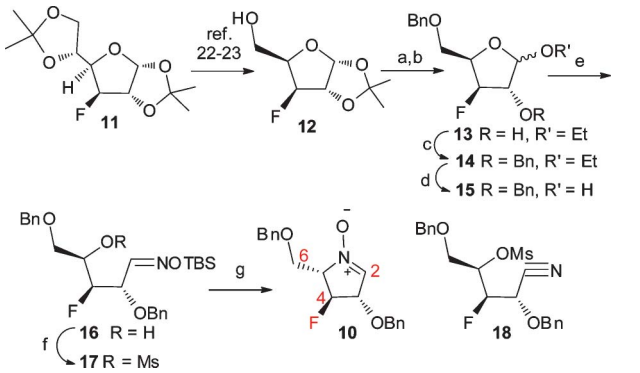
There are generally two strategies to prepare fluorinated iminosuars. That is, introducing fluoride into an existed iminosugar unit[13] or preparing fluorinated iminosugars from a fluoride-containing segment such as fluorinated amino acid or sugar.[14] As a special class of compounds, fluorinated nitrones or *N*-oxides were originally developed in the form of pyridine *N*-oxide,[15] quinoline *N*-oxide, isoquinoline *N*-oxide,[16] pyrroline *N*-oxide,[17] and pyrrolinone *N*-oxide.[18] Though many fluorinated nitrones or *N*-oxides have already been well documented in the literature, no fluorinated polyhydroxylated cyclic nitrone with one or more hydroxyl groups replaced by fluoride has been reported previously.

Results and discussion

Synthesis of fluorinated nitrone (10)

The key intermediate nitrone **10** was synthesized *via* the reported methods[11–12,19] with slight modifications, starting from fluorinated sugar **11** which could be prepared on a large scale from diacetone glucose (Scheme 2).[21]

Selective hydrolysis of the 5,6-acetonide, followed by oxidation and reduction gave compound **12** in 88% yield.[22–23] The alcohol **12** was then treated with benzyl bromide/NaH to furnish the C-5 hydroxyl protected sugar, of which the 1,2-*O*-isopropylidene group was then hydrolyzed with hydrochloric acid in ethanol to directly provide ethyl glycoside **13** as a mixture of α/β isomers (α/β = 56 : 44). **13** was then benzylated to afford the dibenzylated compound **14** as a yellow syrup, which was hydrolyzed in routine acidic conditions[24] to give **15**. The hydrolysis process was slow and incomplete, with some **14** remaining even after refluxing the reaction mixture at 100 °C for 24 h. However, such prolonged heating caused decompostion, so that the reaction was stopped at an appropriate stage and the starting material **14** was recovered.



Scheme 2 Synthesis of fluorinated nitrone **10**. *Reagents and conditions*: a) BnBr, 60% NaH, THF, RT; b) conc. HCl, EtOH, 40 °C, 63% for two steps; c) BnBr, 60% NaH, THF, 40 °C, 85%; d) 1 N HCl, dioxane, 80 °C, 79%; e) NH_2OTBS, PPTs, anhydrous $MgSO_4$, dry toluene, reflux, 98%; f) MsCl, pyridine, DCM, 96%; g) TBAF, THF, 0 °C, 15 min, then $NH_2OH{\cdot}HCl$, $NaHCO_3$, 65 °C, 68%.

Two repetitions of the process provided product **15** in 79% total yield.

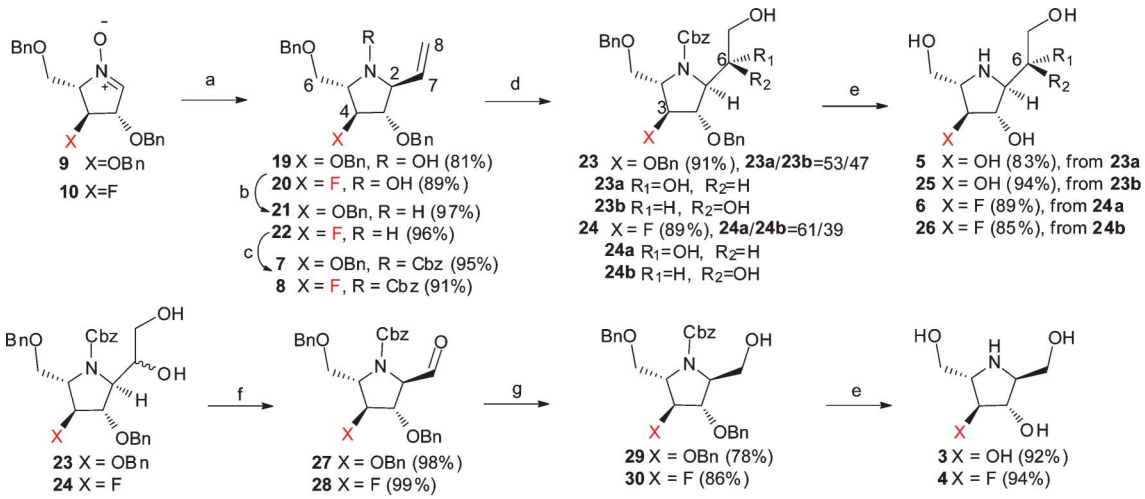
15 was converted to the target cyclic nitrone **10** in three steps. Thus, **15** was refluxed with NH_2OTBS in dry toluene in the presence of anhydrous $MgSO_4$ and catalytic amount of pyridinium *p*-toluenesulfonate (PPTs) to give the ring-opening product **16** in quantitative yield. The free hydroxyl group in **16** was esterified with mesyl chloride with two equivalents of pyridine to afford methanesulfonate **17**; heating or excess base caused elimination to form **18**. Removal of the TBS group of **17** by TBAF at 0 °C gave the unprotected oxime which on further treatment with two equivalents of NH_2OH at 65 °C for 48 h afforded the target cyclic nitrone **10** together with unreacted oxime. Reaction of the recovered oxime with more hydroxylamine gave conversion to nitrone **10** in 68% total yield. Treatment of the silyl ether **17** with TBAF at higher temperature[19,24–25] gave lower yield of **10** (45% optimum yield). The cyclic nitrone **10** was a stable light yellow syrup and could be stored under cold conditions for several months.

Synthesis of L-DMDP (3), L-homoDMDP (5), and their 3-deoxy-3-fluorinated analogues (4 and 6)

The execution of the synthesis of L-DMDP (**3**), L-homoDMDP (**5**), and their 3-deoxy-3-fluorinated analogues (**4** and **6**) is depicted in Scheme 3.

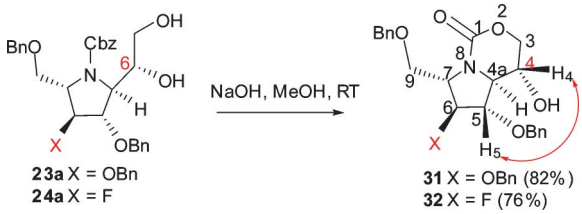
Starting from cyclic nitrone **9** or **10**, the key intermediate compounds **19** or **20** were obtained in excellent yields by nucleophilic addition of vinyl magnesium chloride with nitrone **9** or **10**, respectively, according to the reported method.[19–20] Reduction of hydroxylamine **19** or **20** by Zn–$Cu(OAc)_2$-AcOH[26] or Fe–$Cu(OAc)_2$-AcOH gave the corresponding amine **21** or **22**, respectively, which was treated with CbzCl in weak basic conditions to afford *N*-Cbz derivative **7** or **8**, all in excellent yields. L-DMDP (**3**) and L-homoDMDP (**5**) were then synthesized from **7**, and their 3-deoxy-3-fluorinated analogues (**4** and **6**) from **8**.

To synthesize L-DMDP (**3**) and L-homoDMDP (**5**), dihydroxylation[27] of compound **7** afforded a mixture of two separable epimeric diols **23a** and **23b** in 91% yield with poor diastereoselectivity (**23a** : **23b** = 53 : 47). In order to determine the



Scheme 3 Synthesis of L-DMDP, L-homoDMDP and their 3-deoxy-3-fluorinated analogues. *Reagents and conditions*: a) CH_2=CHMgCl, THF, 0 °C - RT; b) Zn (for **19**) or Fe (for **20**), $Cu(OAc)_2$, AcOH, RT; c) CbzCl, $NaHCO_3$, THF/H_2O, RT; d) OsO_4, NMO, acetone, RT; e) 10% Pd/C, 6 N HCl, H_2, MeOH, RT; f) $NaIO_4$, $EtOH/H_2O$, RT; g) $NaBH_4$, EtOH, RT.

C-6 configuration of the side-chain in **23a** and **23b**, compound **23a** was treated with NaOH-MeOH at room temperature to form its bicyclic derivative **31** in 82% yield (Scheme 4). The C-4 configuration in compound **31** was then determined as *R*-configuration through NOESY experiments since a strong interaction of H-4 and H-5 was observed. Therefore, the C-6 configuration of the side-chain in **23a** was determined as *R*-configuration, and the C-6 configuration of the side-chain in **23b** as *S*-configuration. Subsequent hydrogenolysis of **23a** or **23b** gave L-homoDMDP **5** or its C-6 epimer **25**, respectively, in high yield. The diol side-chain of **23** (mixture of **23a** and **23b**) was oxidized by $NaIO_4$[23] to form aldehyde **27**, which was directly reduced by $NaBH_4$ without further purification to afford **29**. Further hydrogenolysis of **29** led to L-DMDP **3**. ^{1}H NMR and ^{13}C NMR spectra of compounds **3** and **5** are identical to those reported for natural DMDP **1** and homoDMDP **2** with optical rotation [**3**:$[\alpha]_D^{20}$ −51.8 (*c* 0.97 in H_2O); **5**:$[\alpha]_D^{20}$ −40.0 (*c* 0.15 in H_2O)] opposite to those of natural products [**1**: $[\alpha]_D^{20}$ +56.4 (*c* 7 in H_2O);[2] **2**: $[\alpha]_D^{25}$ +31.5 (*c* 0.44 in H_2O)[4]].



Scheme 4 NOESY interaction in **31** and **32**.

The 3-deoxy-3-fluorinated analogues, compounds **4** and **6**, were synthesized through the generally similar procedures to those for the synthesis of **3** and **5**. Thus, dihydroxylation of compound **8** gave a mixture of two separable epimeric diols **24a** and **24b** in 89% isolated yield with poor diastereoselectivity (**24a** : **24b** = 61 : 39). The C-6 configuration of the side-chain in **24a** and **24b** was determined by NOESY experiments of the configuration-retained bicyclic derivative **32** which was made through treatment of **24a** with NaOH-MeOH at room temperature in 76% yield (Scheme 4). The C-6 configuration of the side-chain in **24a** and **24b** were determined as *R*- and *S*-configuration, respectively. Subsequent hydrogenolysis of **24a** or **24b** afforded 3-deoxy-3-fluoro-L-homoDMDP **6** or its C-6 epimer **26**, respectively, in high yield. Oxidation of the diol side-chain of **24** (mixture of **24a** and **24b**) by $NaIO_4$ formed aldehyde **28**, which was directly reduced by $NaBH_4$ without further purification to afford **30**. Further hydrogenolysis of **30** gave 3-deoxy-3-fluoro-L-DMDP **4** in 94% yield.

Evaluation against various glycosidases of L-DMDP (3), L-homoDMDP (5), 6-*epi*-L-homoDMDP (25), and their 3-deoxy-3-fluorinated analogues (4, 6 and 26)

Compounds **3**–**6** together with **25** and **26** were assayed as potential inhibitors of a range of glycosidases, the results are summarized in Table 1.

L-DMDP (**3**)[7] and L-homoDMDP (**5**) showed potent inhibition of α-glucosidase (IC_{50} 0.83 μM and 5.5 μM, respectively, against rat intestinal sucrase) and 6-*epi*-L- homoDMDP (**25**) was a moderate inhibitor of α-glucosidase (IC_{50} 64 μM against rat intestinal sucrase). However, their C-3 fluorinated analogues **4**, **6** and **26** showed virtually no inhibition of the tested enzymes, except compound **4** showed weak inhibition of α-glucosidase (IC_{50} 809 μM against rat intestinal sucrase) and trehalase from porcine kidney (IC_{50} 494 μM). Therefore, the replacement of the C-3 hydroxyl group with a fluoro atom in either **3** or **5** has caused loss of glycosidase inhibitory activity, which indicates the importance of the C-3 hydroxyl group in the interaction between enzymes and these molecules. The biological study results observed herein might be valuable for further structure–activity studies on the DMDP-related iminosugars.

Conclusion

In summary, we have developed a simple and efficient method for the synthesis of L-DMDP and L-homoDMDP *via* the chemistry of sugar-derived cyclic nitrones. L-DMDP (**3**), L-homoDMDP (**5**) and its C-6 epimer **25** have been synthesized smoothly from

Table 1 Concentration of iminosugars giving 50% inhibition of various glycosidases

Enzyme	IC_{50} (μM)					
	3	**4**	**5**	**6**	**25**	**26**
α-Glucosidase						
Yeast	NI[a] (23.3%)[b]	NI (3.7%)	NI (8.2%)	NI (2.8%)	NI (7.3%)	NI (2.4%)
Rice	1.5	NI (20.5%)	28	NI (0.1%)	328	NI (0%)
Rat intestinal maltase	1.8	NI (19.1%)	29	NI (0.1%)	163	NI (1.2%)
Rat intestinal isomaltase	0.76	NI (20.0%)	112	NI (0%)	161	NI (10.1%)
Rat intestinal sucrase	0.83	809	5.5	NI (13.1%)	64	NI (20.4%)
β-Glucosidase						
Almond	NI (10.6%)	NI (7.5%)	NI (14.0%)	NI (1.7%)	NI (7.1%)	NI (5.6%)
C. saccharolyticum	NI (12.4%)	NI (5.1%)	NI (6.7%)	NI (9.5%)	NI (1.5%)	NI (6.7%)
Bovine liver	NI (0.7%)	NI (0.7%)	NI (3.9%)	NI (3.4%)	NI (0.2%)	NI (4.9%)
α-Galactosidase						
Coffee beans	NI (8.7%)	NI (6.8%)	NI (4.4%)	NI (1.1%)	NI (4.1%)	NI (14.2%)
Human lysosome	NI (4.4%)	NI (5.6%)	NI (2.5%)	NI (3.1%)	NI (3.7%)	NI (3.9%)
β-Galactosidase						
Bovine liver	NI (2.8%)	NI (9.8%)	NI (9.1%)	NI (10.7%)	NI (3.0%)	NI (5.6%)
Rat intestinal lactase	NI (19.7%)	NI (12.2%)	NI (42.2%)	NI (0%)	NI (12.0%)	NI (6.8%)
α-Mannosidase						
Jack beans	NI (0.5%)	NI (43.6%)	NI (1.1%)	NI (39.3%)	NI (4.0%)	NI (2.4%)
β-Mannosidase						
Helix pomatia	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)
α-L-Fucosidase						
Bovine kidney	NI (0%)	NI (0%)	NI (1.2%)	NI (0%)	NI (0.3%)	NI (0.3%)
Trehalase						
Porcine kidney	179	494	NI (9.1%)	NI (6.2%)	NI (11.9%)	NI (9.1%)
Amyloglucosidase						
A. niger	NI (0%)	NI (0%)	NI (0.6%)	NI (0%)	NI (5.5%)	NI (0%)
α-L-Rhamnosidase						
P. decumbens	NI (27.2%)	NI (0%)	NI (6.9%)	NI (0.3%)	NI (6.3%)	NI (1.3%)

[a] NI: No inhibition (less than 50% inhibition at 1000 μM). [b] (···): inhibition % at 1000 μM.

the readily available sugar-derived cyclic nitrones **9** in excellent overall yields; while their C-3 fluorinated derivatives, *i.e.*, 3-deoxy-3-fluoro-L-DMDP (**4**), 3-deoxy-3-fluoro-L-homoDMDP (**6**) and its C-6 epimer **26** have been synthesized in excellent overall yields from the fluorinated cyclic nitrone **10** which was prepared from the readily available fluorosugar **11**. Compounds **3–6**, **25** and **26** were assayed against a range of various glycosidases, which showed that L-DMDP (**3**) and L-homoDMDP (**5**) were potent inhibitors of α-glucosidase, while their C-3 fluorinated analogues showed no inhibition of the tested glycosidases. This indicates that the C-3 hydroxyl in DMDP-related molecules may play an important role in their interaction with enzymes. These results might be vaulable for further structure–activity studies of the DMDP-related iminosugars and for design and synthesis of more potent and selective glycosidase inhibitors.

Experimental

Material and methods

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Tetrahydrofuran was distilled from sodium and benzophenone immediately before use. Analytical TLC was performed with 0.20 mm silica gel 60F plates with 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, H_2O) or a 0.5% solution of $KMnO_4$ in acetone. Chromatographic purification of products was carried out by flash column chromatography on silica gel (200–300 mesh). Acidic ion exchange chromatography was performed on Amberlite IR-120 (H^+) or Dowex 50WX8-400, H^+ form. Melting points were determined using an electrothermal melting point apparatus. Melting points are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-480 plus Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or D_2O on a Bruker AV300, AV400 or AV600 magnetic resonance spectrometer (^1H at 300 MHz or 600 MHz, ^{13}C at 75 MHz, ^{19}F at 376 MHz). High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ/FT mass spectrometer or a GCT mass spectrometer mass spectrometer. Polarimetry was carried out using an Optical ActivityAA-10R polarimeter and the measurements were made at the sodium D-line with a 0.5 dm pathlength cell. Concentrations (*c*) are given in gram per 100 mL.

3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-xylofuranose (12)

To a solution of **11** (10.3 g, 39.3 mmol) in THF (50 mL) was added 1 N HCl (5 mL), and stirred at room temperature overnight. Aqueous NaOH was used to neutralize the acid, solvent and water was removed under vacuum. The residue was dissolved in MeOH (50 mL), aqueous $NaIO_4$ (8.4 g, 39.4 mmol/10 mL water) was added at room temperature, many white particles appeared. The solid was filtered 1 h later, washed with EA and MeOH, the filtrate was then concentrated under reduced pressure to give an aldehyde as light yellow syrup. The aldehyde was

dissolved in EtOH (100 mL) again and cooled to 0 °C, $NaBH_4$ (1.5 g, 40.5 mmol) was added in several batches, obvious heat was observed. The suspension was stirred for 0.5 h and quenched by aqueous NH_4Cl, solvent was then removed under vacuum. The residue was washed by EtOAc for several times, the filtrate was concentrated and purified by flash column chromatography (silica gel, petroleum ether/EtOAc 5 : 1) to give **12** (6.6 g, 87%) as a light yellow oil. $[\alpha]_D^{20}$ −17.1 (*c* 1.06 in CH_2Cl_2); ν_{max}/cm^{-1} 3438 m, 2985 w, 1656 w, 1381 m, 1217 m, 164 m, 1079 s, 1021 s; δ_H (300 MHz; $CDCl_3$) 5.91 (1H, d, J = 3.7 Hz, H1), 4.92 (1H, dd, $J_{H,F}$ = 50.2 Hz, $J_{H,H}$ = 1.7 Hz, H3), 4.62 (1H, dd, J = 11.1 Hz, 3.7 Hz, H2), 4.25 (1H, ddd, J = 30.1 Hz, 6.0 Hz, 4.1 Hz, H4), 3.77 (2H, d, J = 6.1 Hz, H5), 3.40 (1H, s, br, OH), 1.42, 1.25 (3H each, s, CMe_2); δ_C (75 MHz; $CDCl_3$) 111.3 (*C*Me_2), 103.8 (C1), 93.0 (d, $J_{C,F}$ = 182.0 Hz, C3), 81.7 (d, J = 32.3 Hz, C2), 79.5 (d, J = 18.8 Hz, C4), 58.2 (d, J = 9.8 Hz, C5), 25.6, 25.2 (CMe_2); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 103.8, 93.0, 81.7, 79.5, 25.6, 25.2; negative, 58.2. [lit.[22] δ_H (250 MHz; $CDCl_3$) 5.91 (1H, d, J = 3.8 Hz, H1), 4.92 (1H, dd, $J_{H,F}$ = 50.4 Hz, $J_{H,H}$ = 2.3 Hz, H3), 4.62 (1H, dd, J = 11.1 Hz, 3.8 Hz, H2), 4.28 (1H, m, H4), 3.82 (2H, m, H5), 1.41, 1.25 (3H each, s, CMe_2)]

3-Deoxy-3-fluoro-1-*O*-ethyl-5-*O*-benzyl-D-xylofuranose (13)

To a suspension of NaH (6.2 g, 60%, 0.16 mol) in THF (100 mL) was added dropwise a solution of **12** (19.8 g, 0.10 mol) in THF (50 mL). BnBr (12.4 mL, 0.10 mol) was added dropwise 10 min later. After TLC showed completion of the reaction, the suspension was poured into iced saturated aqueous NH_4Cl solution carefully, and extracted with EtOAc (2 × 50 mL), EtOAc phases were combined and concentrated. The crude benzylation product was stirred with EtOH (200 mL) and conc. HCl (10 mL) at 40 °C overnight. The solution was concentrated under reduced pressure and neutralized by aqueous $NaHCO_3$, the solution was extracted with EtOAc (3 × 50 mL), dried over Na_2SO_4, concentrated again, and then purified by flash column chromatography (silica gel, petroleum ether/EtOAc 20 : 1 to 5 : 1) to get compound **13** (17.6 g, 63%) as a mixture of α and β isomers (α/β = 56 : 44), yellow oil. **13**: ν_{max}/cm^{-1} 3434 m, 2977 m, 2925 m, 1720 w, 1496 w, 1453 m, 1371 m, 1091 s, 1048 s, 741 m, 699 m; δ_H (300 MHz; $CDCl_3$) 7.34–7.27 (5H, m, *Ph*CH_2O), 5.18–4.74 (2H, m, H1 and H3), 4.64–4.51 (2H, m, PhCH_2O), 4.42–4.21 (2H, m, H2 and H4), 3.77–3.47 (4H, m, H5 and CH_2CH_3), 3.13–3.07 (1H, m, OH), 1.26–1.15 (3H, m, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 137.9, 137.8, 128.6, 128.4, 128.1, 127.9, 127.8, 127.7 (Ph), 108.1, 100.5 (C1), 97.2 (d, $J_{C,F}$ = 183.0 Hz, C3), 95.4 (d, $J_{C,F}$ = 186.8 Hz, C3), 80.1 (d, J = 19.5 Hz, C2), 78.9 (d, J = 26.3 Hz, C2), 77.2 (d, J = 19.5 Hz, C4), 76.4 (d, J = 28.5 Hz, C4), 73.8, 73.6, 73.5 (Ph*C*H_2O), 68.6, 68.5 (C5), 64.6, 63.7 (*C*H_2CH_3), 15.1 (CH_2CH_3); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 108.1, 100.5, 97.2, 95.4, 80.1, 78.9, 77.2, 76.4, 15.1; negative, 73.8, 73.6, 73.5, 68.6, 68.5, 64.6, 63.7; HRMS(ESI) calcd for $C_{14}H_{19}FNO_4Na^+$ $[M+Na]^+$ 293.1160, found 293.1162.

3-Deoxy-3-fluoro-1-*O*-ethyl-2,5-di-*O*-benzyl-D-xylofuranose (14)

Similar benzylation procedures to **12** were performed on **13** (13.1 g, 48.5 mmol) to afford **14** (14.8 g, 85%) as light yellow oil. **14**: ν_{max}/cm^{-1} 3347 m, 3064 m, 3033 m, 2977 s, 2927 s, 1725 m, 1604 w, 1496 m, 1454 s, 1372 s, 1206 m, 1111 vs, 747 s, 699 s; δ_H (300 MHz; $CDCl_3$) 7.33–7.25 (10H, m, *Ph*CH_2O), 5.13–4.88 (2H, m, H1 and H3), 4.67–4.52 (4H, m, PhCH_2O), 4.48–4.38 (1H, m, H4), 4.16–4.05 (1H, m, H2), 3.82–3.44 (4H, m, H5 and CH_2CH_3), 1.25–1.15 (3H, m, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 138.1, 137.4, 137.2, 128.6, 128.5, 128.3, 128.1, 127.8 (Ph), 106.4, 101.1, 99.8 (C1), 96.4 (d, $J_{C,F}$ = 185.3 Hz, C3), 93.7 (d, $J_{C,F}$ = 186.8 Hz, C3), 86.3 (d, J = 26.3 Hz, C2), 83.5 (d, J = 24.0 Hz, C2), 80.0 (d, J = 20.3 Hz, C4), 75.9 (d, J = 20.3 Hz, C4), 73.6, 73.5, 72.7, 72.4 (Ph*C*H_2O), 68.4, 68.0 (C5), 63.9, 63.8 (*C*H_2CH_3), 15.2 (CH_2CH_3); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.5, 128.3, 128.1, 127.8, 106.4, 101.1, 99.8, 96.4, 93.7, 86.3, 83.5, 80.0, 75.9, 15.2; negative, 73.6, 73.5, 72.7, 72.4, 68.4, 68.0, 63.9, 63.8; HRMS(ESI) calcd for $C_{21}H_{25}FO_4Na^+$ $[M+Na]^+$ 383.1629, found 383.1622.

3-Deoxy-3-fluoro-2,5-di-*O*-benzyl-D-xylofuranose (15)

To a solution of **l4** (14.5 g, 40.3 mmol) in dioxane (100 mL) was added 1 N HCl (50 mL), and stirred at 90 °C overnight. The solution was concentrated under reduced pressure and neutralized by aqueous $NaHCO_3$, then extracted with EtOAc (3 × 50 mL), dried over Na_2SO_4, and concentrated again to get a dark brown oil, which was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 20 : 1 to 5 : 1) to furnish 10.3 g light yellow syrup (**15**), and 0.4 g starting material (**14**), 79% yield. **15**: ν_{max}/cm^{-1} 3380 s, 2929 m, 1454 w, 1046 s, 741 m, 698 m; δ_H (300 MHz; $CDCl_3$) 7.29–7.23 (10H, m, *Ph*CH_2O), 5.46 (0.5H, d, J = 3.9 Hz, H1β), 5.30 (0.5H, s, H1α), 5.12–4.91 (1H, m, H3), 4.58–4.33 (5H, m, H4 and PhCH_2O), 4.09–3.99 (1H, m, H2), 3.75–3.62 (2H, m, H5); δ_C (75 MHz; $CDCl_3$) 138.0, 137.7, 137.2, 136.7, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8 (Ph), 101.5 (d, J = 10.8 Hz, C1), 96.1 (d, J = 12.0 Hz, C1), 94.7 (d, $J_{C,F}$ = 185.0 Hz, C3), 94.3 (d, $J_{C,F}$ = 186.3 Hz, C3), 87.0 (d, J = 24.2 Hz, C2), 81.6 (d, J = 26.8 Hz, C2), 79.6 (d, J = 19.9 Hz, C4), 77.6 (d, J = 32.0 Hz, C4), 73.7, 73.6, 73.3, 72.2 (Ph*C*H_2O), 68.1 (d, J = 10.1 Hz, C5), 67.3 (d, J = 11.3 Hz, C5); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 101.5, 96.1, 94.7, 94.3, 87.0, 81.6, 79.6, 77.6; negative, 73.7, 73.6, 73.3, 72.2, 68.1, 67.3; HRMS(ESI) calcd for $C_{19}H_{21}FNO_4Na^+$ $[M+Na]^+$ 355.1316, found 355.1304.

(2*S*,3*S*,4*S*)-2,5-Di-*O*-benzyl-3-fluoro-4-hydroxypentanal *O*-(*tert*-butyldimethylsilyl) oxime (16)

The well-protected 3-deoxy-3-fluoro-D-xylofuranose **15** (0.3 g, 0.9 mmol) was dissolved in toluene (10 mL), NH_2OTBS (0.3 g, 2.0 mmol), anhydrous $MgSO_4$ and catalytic amount of PPTs was followed. The mixture was immediately transferred to a 100 °C oil bath and stirred for 0.5 h. After cooling to room temperature, the solution was washed with water twice and dried over $MgSO_4$, then evaporated to get a red oil, which was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 15 : 1) to give **16** (0.4 g, 98%) as a light yellow oil. It's a mixture with *E*/*Z* ratio as 76 : 24. **16**: ν_{max}/cm^{-1} 3454 m, 3033 m, 2929 s, 2858 s, 1496 m, 1455 m, 1362 m, 1253 s, 1114 s, 1028 m, 931 s, 839 s, 785 m, 735 m, 697 s; δ_H (300 MHz; $CDCl_3$) 7.63 (0.77H, d, J = 7.8 Hz, H1, *E*), 7.36–7.30 (10H, m, *Ph*CH_2O), 7.06 (0.23H, d, J = 6.1 Hz, H1, *Z*), 4.68–4.37 (4H, m, PhCH_2O), 4.67 (1H, dt, $J_{H,F}$ = 46.8 Hz, $J_{H,H}$ = 3.9 Hz, H3), 4.28 (1H, dq, J = 22.8 Hz, 7.8 Hz, H2), 4.13–4.03 (1H, m, H4), 3.58–3.44 (2H, m, H5), 3.15 (0.22H, d, J = 3.3 Hz, OH, *Z*), 2.88 (0.78H, d, J = 3.6 Hz, OH, *E*), 0.99 (6.79H, s, *t*-Bu,

E), 0.94 (2.21H, s, *t*-Bu, *Z*), 0.24 (4.72H, s, CH_3, *E*), 0.21 (1.28H, s, CH_3, *Z*); δ_C (75 MHz; $CDCl_3$) 153.2 (d, J = 5.6 Hz, C1, *Z*), 151.5 (d, J = 6.6 Hz, C1, *E*), 137.8, 137.7, 136.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8 (Ph), 92.7 (d, $J_{C,F}$ = 180.7 Hz, C3, *E*), 91.8 (d, $J_{C,F}$ = 180.8 Hz, C3, *Z*), 75.7 (d, J = 19.7 Hz, C2, *E*), 73.6, 72.4 (Ph*C*H_2O), 71.9 (d, J = 21.0 Hz, C2, *Z*), 71.0 (Ph*C*H_2O), 69.9 (d, J = 19.8 Hz, C4), 69.8 (d, J = 6.0 Hz, C5), 69.5 (d, J = 6.1 Hz, C5), 26.1 (d, J = 8.4 Hz, *t*-Bu, *E*), 18.2 (d, J = 9.8 Hz, *t*-Bu, *Z*), −5.2 (d, J = 6.5 Hz, *C*H_3); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 153.2, 151.5, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 92.7, 91.8, 75.7, 71.9, 69.9, 26.1, 18.2, −5.2; negative, 73.6, 72.4, 71.0, 69.8, 69.5; Found: C, 65.47; H, 7.70; N, 3.12. $C_{25}H_{36}NO_4FSi$ requires C, 65.04; H, 7.86; N, 3.03%.

(2*S*,3*S*,4*S*)-2,5-Di-*O*-benzyl-3-fluoro-4-(methanesulfonate) pentanal *O*-(*tert*-butyldimethylsilyl) oxime (17)

The mixture **16** (0.41 g, 0.9 mmol) was dissolved in DCM (5 mL), with Et_3N (0.24 mL, 1.7 mmol) as base, MsCl (0.07 mL, 0.9 mmol) was added dropwise at 0–5 °C, then stirred overnight at room temperature, TLC showed completion of the reaction. It was washed with 1 N HCl twice and then water for 3 times. DCM phase was concentrated under reduced pressure to get dark red oil. It was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 15 : 1) to give a yellow syrup **17** (0.46 g, 96%) also as a mixture of E/Z isomers. **17**: ν_{max}/cm^{-1} 3032 w, 2955 m, 2930 m, 2858 m, 1497 w, 1472 m, 1455 m, 1362 s, 1254 m, 1178 s, 1120 m, 1027 m, 930 s, 839 s, 788 m, 740 m, 699 m; δ_H (300 MHz; $CDCl_3$) 7.66 (0.79H, d, J = 7.5 Hz, H1, *E*), 7.42–7.28 (10H, m, *Ph*CH_2O), 7.11 (0.21H, d, J = 5.4 Hz, H1, *Z*), 5.12–5.04 (1H, m, H4), 4.88 (0.79H, dd, $J_{H,F}$ = 47.1 Hz, $J_{H,H}$ = 2.4 Hz, H3), 4.86 (0.21H, dd, $J_{H,F}$ = 47.4 Hz, $J_{H,H}$ = 2.4 Hz, H3), 4.63–4.13 (5H, m, PhCH_2O and H2), 3.72–3.67 (1H, m, H5), 3.40 (1H, dd, J = 11.4 Hz, 3.6 Hz, H5), 3.32 (0.51H, s, O*Ms*, *Z*), 3.05 (2.49H, s, O*Ms*, *E*), 1.05 (7.58H, s, *t*-Bu, *E*), 0.99 (2.42H, s, *t*-Bu, *Z*), 0.30 (4.37H, s, CH_3, *E*), 0.26 (1.63H, s, CH_3, *Z*); δ_C (75 MHz; $CDCl_3$) 152.7 (d, J = 5.3 Hz, C1, *Z*), 151.0 (d, J = 6.0 Hz, C1, *E*), 137.1, 136.4, 136.2, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0 (Ph), 93.3 (d, $J_{C,F}$ = 182.3 Hz, C3, *E*), 92.0 (d, $J_{C,F}$ = 179.3 Hz, C3, *Z*), 80.5 (d, J = 21.0 Hz, C4, *Z*), 80.1 (d, J = 20.3 Hz, C4, *E*), 73.6, 73.5 (Ph*C*H_2O), 73.3 (d, J = 17.3 Hz, C2, *E*), 71.9, 70.7 (Ph*C*H_2O), 69.5 (d, J = 18.0 Hz, C2, *Z*), 68.4 (d, J = 7.5 Hz, C5), 38.9 (O*Ms*, *Z*), 38.4 (O*Ms*, *E*), 26.1, 25.8 (*t*-Bu), −5.2, −5.3 (*C*H_3); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 152.7, 151.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 93.3, 92.0, 80.5, 80.1, 73.3, 69.5, 38.9, 38.4, 26.1, 25.8, −5.2, −5.3; negative, 73.6, 73.5, 71.9, 70.7, 68.4.

(2*S*,3*S*,4*S*)-2,5-Di-*O*-benzyl-3-fluoro-4-(methanesulfonate) pentanenitrile (18)

18: yellow oil, side product in synthesis of **17** under excess base or heating. $[\alpha]_D^{20}$ +58.8 (*c* 1.23 in CH_2Cl_2); ν_{max}/cm^{-1} 3033 w, 2875 w, 1495 w, 1455 m, 1362 s, 1178 s, 1124 m, 972 m, 932 m, 810 m, 748 m, 700 m; δ_H (300 MHz; $CDCl_3$) 7.37–7.20 (10H, m, *Ph*CH_2O), 5.04–4.94 (1.5H, m, H4 and H3), 4.83–4.79 (1.5H, m, H3 and H2), 4.45–4.27 (4H, m, PhCH_2O), 3.72–3.48 (2H, m, H5), 3.02 (3H, s, OMs); δ_C (75 MHz; $CDCl_3$) 136.8, 134.5, 129.2, 129.0, 128.7, 128.3, 128.1 (Ph), 114.5 (d, J = 4.5 Hz, *C*N), 89.1 (d, $J_{C,F}$ = 188.3 Hz, C3), 77.6 (d, J = 19.5 Hz, C4), 73.7, 72.9 (Ph*C*H_2O), 67.9 (d, J = 6.8 Hz, C5), 66.0 (d, J = 21.0 Hz, C2), 38.5 (d, J = 2.3 Hz, OMs); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 129.2, 129.0, 128.7, 128.3, 128.1, 89.1, 77.6, 66.0, 38.5; negative, 73.7, 72.9, 67.9; HRMS(ESI) calcd for $C_{20}H_{22}FNO_5SNa^+$ $[M+Na]^+$ 430.1095, found 430.1097.

(3*S*,4*S*,5*R*)-3-(Benzyloxy)-5-((benzyloxy)methyl)-4-fluoro-pyrrole-1-oxide (10)

17 (23.7 g, 44.0 mmol) was dissolved in THF (100 mL) and cooled to 0–5 °C. TBAF (12.3 g, 47.1 mmol) was added in several batches and stirred for 15 min, then poured into water (200 mL). EtOAc (3 × 50 mL) was used to extract the solution, then organic phases were combined and directly concentrated under reduced pressure to give the oxime intermediate. The intermediate was dissolved in EtOH (100 mL) and water (25 mL), NH_2OH·HCl (5.9 g, 85.5 mmol) and $NaHCO_3$ (7.9 g, 94.1 mmol) was followed. The mixture was stirred at 60 °C for 48 h, EtOH was then removed *in vacuo*. The residue was extracted with EtOAc (3 × 50 mL), dried over $MgSO_4$, then purified by flash column chromatography (silica gel, petroleum ether/EtOAc 5 : 1 to 2 : 1) to afford pure **10** as yellow oil and recover part of **17** which was recycled once to get altogether 9.9 g nitrone **10**, 68% yield. **10**: $[\alpha]_D^{20}$ +24 (*c* 0.67 in CH_2Cl_2); ν_{max}/cm^{-1} 3367 m, 3032 w, 2922 m, 2867 m, 1656 w, 1580 m, 1453 m, 1361 m, 1094 s, 1028 s, 740 m, 698 m; δ_H (300 MHz; $CDCl_3$) 7.25–7.16 (10H, m, *Ph*CH_2O), 6.89 (1H, s, H2), 5.22 (1H, d, $J_{H,F}$ = 52.5 Hz, H4), 4.66 (1H, d, J = 21.6 Hz, H3), 4.61–4.42 (4H, m, PhCH_2O), 4.10–4.01 (2H, m, H5 and H6), 3.77–3.73 (1H, m, H6), 2.87 (1H, s, H_2O); δ_C (75 MHz; $CDCl_3$) 137.4, 136.7 (Ph), 133.2 (C2), 128.7, 128.5, 128.3, 128.0, 127.9, 127.6, 127.5, 127.0 (Ph), 93.1 (d, $J_{C,F}$ = 185.3 Hz, C4), 81.7 (d, J = 28.5 Hz, C3), 77.3 (d, J = 26.3 Hz, C5), 73.5, 72.0 (Ph*C*H_2O), 65.0 (d, J = 5.3 Hz, C6); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 133.2, 128.7, 128.5, 128.3, 128.0, 127.9, 127.6, 127.0, 93.1, 81.7, 77.3; negative, 73.5, 72.0, 65.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −182.2 (t, J = 24.4 Hz, 1F); HRMS(ESI) calcd for $C_{19}H_{21}FNO_3^+$ $[M+H]^+$ 330.1500, found 330.1494.

General procedures for synthesis of hydroxylamine 19 and 20

Nitrone **9** or **10** (1 eq) was dissolved in dry THF, purged with argon and cooled to 0 °C, vinyl magnesium chloride (1.6 M, 2.5 eq) was injected by a syringe slowly to maintain the system below 10 °C. The reaction was quenched by aqueous NH_4Cl 5 min later, and extracted with EtOAc twice. The combined EtOAc phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 5 : 1) to give anticipated product **19** or **20**.

19: white solid, 81% yield. mp 74–75 °C; $[\alpha]_D^{20}$ +28.9 (*c* 0.83 in $CHCl_3$); ν_{max}/cm^{-1} 3258 w, 3031 w, 2865 m, 1497 w, 1454 m, 1362 w, 1206 w, 1096 s; δ_H (300 MHz; $CDCl_3$) 7.35–7.25 (15H, m, *Ph*CH_2O), 6.04 (1H, ddd, J = 17.4 Hz, 10.9 Hz, 8.1 Hz), 5.32 (1H, dd, J = 17.4 Hz, 1.8 Hz), 5.27 (1H, dd, J = 11.5 Hz, 1.8 Hz), 4.58–4.44 (6H, m), 3.97 (1H, t, J = 3.4 Hz), 3.91 (1H, dd, J = 5.3 Hz, 3.0 Hz), 3.79 (1H, dd, J = 7.5 Hz, 6.0 Hz), 3.75 (1H, dd, J = 9.6 Hz, 6.0 Hz), 3.64 (1H, dd, J = 9.6 Hz, 8.9 Hz), 3.52 (1H, dd, J = 8.9 Hz, 5.6 Hz); δ_C (75 MHz; $CDCl_3$) 138.1, 138.0, 135.4, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 119.4, 86.0, 83.8, 73.4, 72.9, 71.9, 71.7, 69.7, 67.9 [conforms to NMR of its enantiomer[20]]; HRMS(ESI) calcd for $C_{28}H_{31}NO_4^+$ $[M+H]^+$ 446.2331, found 446.2325.

20: yellow syrup, 89% yield. $[\alpha]_D^{20}$ 0 (*c* 1.06 in CH_2Cl_2); ν_{max}/cm^{-1} 3269 m, 3064 m, 3031 m, 2867 m, 1645 w, 1496 m, 1454 m, 1363 m, 1099 vs, 1028 s, 993 m, 738 s, 698 s; δ_H (300 MHz; $CDCl_3$) 7.31–7.25 (10H, m, *Ph*CH_2O), 7.13 (1H, s, NOH), 5.97 (1H, ddd, *J* = 17.7 Hz, 10.2 Hz, 8.1 Hz, H7), 5.31 (1H, d, *J* = 16.8 Hz, H8), 5.27 (1H, d, *J* = 9.9 Hz, H8), 5.04 (1H, dt, $J_{H,F}$ = 53.7 Hz, $J_{H,H}$ = 2.9 Hz, H4), 4.68–4.48 (4H, m, PhCH_2O), 4.05 (1H, ddd, *J* = 22.5 Hz, 6.6 Hz, 2.4 Hz, H3), 3.79–3.59 (4H, m, H2, H5 and H6); δ_C (75 MHz; $CDCl_3$) 137.9, 137.5 (Ph), 134.9 (C7), 128.7, 128.6, 128.5, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5 (Ph), 119.9 (C8), 97.9 (d, $J_{C,F}$ = 183.8 Hz, C4), 85.1 (d, *J* = 24.0 Hz, C3), 73.4 (Ph*C*H_2O), 72.8 (d, *J* = 5.3 Hz, C2), 72.2 (Ph*C*H_2O), 70.1 (d, *J* = 23.3 Hz, C5), 66.9 (d, *J* = 5.3 Hz, C6); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 134.9, 128.7, 128.6, 128.5, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 97.9, 85.1, 72.8, 70.1; negative, 119.9, 73.3, 72.2, 66.9; Found: C, 70.07; H, 6.74; N, 3.99. $C_{21}H_{24}FNO_3$ requires C, 70.57; H, 6.77; N, 3.92%.

General procedures for synthesis of amine 21 and 22

Copper(II) acetate (0.1 eq) was added to a suspension of activated zinc (10 eq) or iron powder (10 eq, used as received) in acetic acid, and the mixture was stirred at 30 °C for 1 h until copper colour disappeared. A solution of hydroxylamine **19** or **20** (1 eq) in acetic acid was added, and the reaction mixture was stirred at 30 °C overnight. Solvent was removed in vacuum, the residue was neutralized by aqueous $NaHCO_3$ and washed with EtOAc for three times. The resulting filtrate was extracted with EtOAc, then organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Part of the crude product was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 3 : 1) to give the target product (**21** or **22**) for NMR and yield calculation. The remaining product was directly used in the next step.

21: yellow syrup, 97% yield. $[\alpha]_D^{20}$ −13.8 (*c* 0.15 in $CHCl_3$); ν_{max}/cm^{-1} 3324 w, 3030 w, 2861 m, 1497 w, 1454 m, 1363 w, 1095 s; δ_H (300 MHz; $CDCl_3$) 7.38–7.15 (15H, m), 5.84 (1H, ddd, *J* = 17.3 Hz, 10.1 Hz, 7.2 Hz), 5.18 (1H, d, *J* = 17.7 Hz), 5.03 (1H, d, *J* = 10.3 Hz), 4.53–4.41 (6H, m), 3.82–3.76 (2H, m), 3.59 (1H, dd, *J* = 7.0 Hz, 6.4 Hz), 3.45–3.41 (2H, m), 3.34 (1H, dd, *J* = 10.0 Hz, 4.6 Hz), 2.06 (1H, br); δ_C (75 MHz; $CDCl_3$) 137.7, 137.2, 137.1, 127.4, 127.3, 126.8, 126.7, 126.6, 115.1, 88.2, 84.9, 72.2, 71.0, 70.8, 69.8, 63.4, 60.3; HRMS(ESI) calcd for $C_{28}H_{32}NO_3^+$ $[M+H]^+$ 430.2377, found 430.2378.

22: yellow syrup, 96% yield. $[\alpha]_D^{20}$ −11.1 (*c* 0.18 in CH_2Cl_2); ν_{max}/cm^{-1} 3031 w, 2864 m, 1642 w, 1496 w, 1453 m, 1366 m, 1097 vs, 1027 m, 738 s, 698 s; δ_H (300 MHz; $CDCl_3$) 7.33–7.24 (10H, m, *Ph*CH_2O), 5.87 (1H, ddd, *J* = 17.1 Hz, 10.2 Hz, 6.9 Hz, H7), 5.26 (1H, d, *J* = 17.1 Hz, H8), 5.13 (1H, d, *J* = 10.2 Hz, H8), 4.92 (1H, dt, $J_{H,F}$ = 53.7 Hz, $J_{H,H}$ = 3.5 Hz, H4), 4.68–4.55 (4H, m, PhCH_2O), 3.93 (1H, ddd, *J* = 20.1 Hz, 5.7 Hz, 3.6 Hz, H3), 3.69 (1H, t, *J* = 6.3 Hz, H2), 3.58–3.48 (3H, m, H5 and H6); δ_C (75 MHz; $CDCl_3$) 138.0 (C7), 137.9, 137.7, 128.5, 128.4, 127.8, 127.7 (Ph), 116.4 (C8), 99.0 (d, $J_{C,F}$ = 182.3 Hz, C4), 88.0 (d, *J* = 22.5 Hz, C3), 73.3, 72.2 (Ph*C*H_2O), 69.7 (d, *J* = 6.0 Hz, C6), 64.0 (d, *J* = 6.0 Hz, C2), 61.3 (d, *J* = 24.0 Hz, C5); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 138.0, 128.5, 128.4, 127.8, 127.7, 99.0, 88.0, 64.0, 61.3; negative, 116.4, 73.3, 72.2, 69.7; HRMS(ESI) calcd for $C_{21}H_{25}FNO_2^+$ $[M+H]^+$ 342.1864, found 342.1864.

General procedures for synthesis of *N*-Cbz protected acetal 7 and 8

The crude amine **21** or **22** (1 eq) was dissolved in THF, followed by $NaHCO_3$ solid (3 eq) and water, then CbzCl (1.2 eq) was added in one batch and stirred at RT for 1 h. Water was added, the mixture was then extracted with EtOAc twice, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, then purified by flash column chromatography (silica gel, petroleum ether/EtOAc 6 : 1) to give **7** or **8**.

7: colorless syrup, 95% yield. $[\alpha]_D^{20}$ +5.4 (*c* 0.74 in $CHCl_3$); ν_{max}/cm^{-1} 1701 vs; δ_H (300 MHz; $CDCl_3$) 7.27–7.09 (20H, m), 5.79 (1H, m), 5.21–4.92 (4H, m), 4.55 (1H, dd, *J* = 10.7 Hz, 8.6 Hz), 4.46–4.20 (7H, m), 4.15–4.10 (2H, m), 3.95 (0.5H, dd, *J* = 8.5 Hz, 4.3 Hz), 3.77 (1H, d, *J* = 2.5 Hz), 3.66 (0.5H, dd, *J* = 9.6 Hz, 4.3 Hz), 3.43 (1H, t, *J* = 9.6 Hz); δ_C (75 MHz; $CDCl_3$) 155.1, 138.6, 137.8, 136.7, 136.6, 128.6, 128.5, 128.3, 128.1, 127.9, 127.6, 116.4, 86.9, 82.8, 73.1, 71.4, 71.0, 67.9, 67.0, 66.4, 63.2; HRMS(ESI) calcd for $C_{36}H_{38}NO_5^+$ $[M+H]^+$ 564.2744, found 564.2745; $C_{36}H_{37}NNaO_5^+$ $[M+Na]^+$ 586.2564, found 586.2577.

8: light yellow syrup, 91% yield. $[\alpha]_D^{20}$ +12.0 (*c* 1.00 in CH_2Cl_2); ν_{max}/cm^{-1} 3032 w, 2827 w, 1705 s, 1495 w, 1454 m, 1407 s, 1351 s, 1261 w, 1215 m, 1095 s, 1028 m, 925 m, 797 w, 769 w, 738 s, 697 m; δ_H (300 MHz; $CDCl_3$) 7.21–7.15 (15H, m, *Ph*CH_2O and *Ph*CH_2OC═O), 5.64 (1H, t, *J* = 7.8 Hz, H7), 5.18–4.92 (5H, m, H4, H8 and PhCH_2OC═O), 4.55–4.25 (6H, m, PhCH_2O, H5 and H6), 3.96–3.63 (2H, m, H3 and H6), 3.44 (1H, dd, *J* = 18.3 Hz, 9.0 Hz, H2); δ_C (75 MHz; $CDCl_3$) 153.7, 152.9 (*C*═O), 137.1, 136.8, 135.9, 135.3 (Ph), 134.5, 134.0 (C7), 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 126.7, 126.6 (Ph), 116.2, 115.7 (C8), 94.4 (d, $J_{C,F}$ = 180.0 Hz, C4), 93.3 (d, $J_{C,F}$ = 180.8 Hz, C4), 84.7 (d, *J* = 26.3 Hz, C3), 84.0 (d, *J* = 26.3 Hz, C3), 72.1, 70.8 (Ph*C*H_2O), 66.5 (d, *J* = 10.5 Hz, C6), 66.0 (Ph*C*H_2OC═O), 65.7 (d, *J* = 9.8 Hz, C6), 65.4 (d, *J* = 6.8 Hz, C2), 62.5 (d, *J* = 22.5 Hz, C5), 62.0 (d, *J* = 21.8 Hz, C5); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 134.5, 134.0, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 126.6, 94.4, 93.3, 84.7, 84.0, 65.4, 62.5, 62.0; negative, 116.2, 115.7, 72.1, 70.8, 66.5, 66.0, 65.7; Found: C, 72.49; H, 6.46; N, 2.84. $C_{29}H_{30}FNO_4$ requires C, 73.24; H, 6.36; N, 2.95%.

General procedures for synthesis of diol 23 and 24

N-Cbz protected acetal **7** or **8** (1 eq) was dissolved in acetone, followed by 60 v% aqueous NMO (10 eq) and 0.5 wt% aqueous OsO_4 (0.01 eq) solution. *Caution!* The mixture was stirred at RT for four days. Saturated aqueous $NaHSO_3$ was added and stirred for 1 h, then extracted with EtOAc for three times, organic phases were combined, dried over $MgSO_4$ and concentrated in vacuum, then purified by flash column chromatography (silica gel, petroleum ether/EtOAc 1 : 1) to give separable diol **23a** and **23b** (**23a**/**23b** = 53/47, 91% total yield) or **24a** and **24b** (**24a**/**24b** = 61/39, 89% total yield).

23a: colorless syrup, 48% yield. $[\alpha]_D^{20}$ +37.0 (*c* 1.20 in $CHCl_3$); ν_{max}/cm^{-1} 3432 s, 3032 w, 2938 w, 1681 vs, 1497 w, 1454 m, 1415 m, 1213 w, 1073 vs; δ_H (300 MHz; $CDCl_3$) 7.39–7.23 (20H, m), 5.16 (2H, s), 4.56 (2H, d, *J* = 12.1 Hz), 4.48 (2H, d, *J* = 11.8 Hz), 4.42 (2H, d, *J* = 12.1 Hz), 4.30 (1H, s), 4.23 (1H, s), 4.16 (1H, dd, *J* = 10.4 Hz, 3.9 Hz), 4.06 (1H, br, d, *J* = 6.7 Hz), 3.94 (1H, br, s), 3.81 (1H, dd, *J* = 8.8 Hz, 4.1 Hz), 3.59 (1H, m), 3.53 (1H, dd, *J* = 10.4 Hz, 8.9 Hz), 3.56 (1H, br, s); δ_C (75 MHz; $CDCl_3$) 156.2,

138.1, 137.5, 135.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 82.8, 82.6, 73.1, 71.4, 71.3, 71.0, 68.2, 67.7, 66.3, 63.6, 62.8; δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 82.8, 82.5, 71.0, 66.2, 63.6; negative, 73.1, 71.4, 71.3, 68.2, 67.7, 62.8; HRMS(ESI) calcd for $C_{36}H_{40}NO_7^+$ $[M+H]^+$ 598.2799, found 598.2812.

23b: colorless syrup, 43% yield. $[\alpha]_D^{20}$ +35.4 (*c* 0.91 in $CHCl_3$); ν_{max}/cm^{-1} 3125 vs, 1760 m, 1454 w, 1401 vs, 1097 m; HRMS(ESI) calcd for $C_{36}H_{40}NO_7^+$ $[M+H]^+$ 598.2799, found 598.2797.

24a: light yellow syrup, 54% yield. $[\alpha]_D^{20}$ +57.4 (*c* 0.98 in CH_2Cl_2); ν_{max}/cm^{-1} 3429 m, 3032 m, 2939 m, 1701 s, 1496 w, 1454 m, 1415 s, 1350 s, 1211 w, 1093 s, 1029 m, 998 m, 739 m, 698 s; δ_H (300 MHz; $CDCl_3$) 7.21–7.09 (15H, m, *Ph*CH_2O and *Ph*CH_2OC═O), 5.14–4.94 (3H, m, H3 and PhC*H*$_2$OC═O), 4.51–4.03 (7H, m, PhC*H*$_2$O, H4, H5 and H6), 3.89 (1H, s, H2), 3.66 (1H, t, *J* = 4.4 Hz, H7), 3.56 (1H, d, *J* = 11.1 Hz, H1), 3.43 (2H, t, *J* = 9.6 Hz, H1 and H7), 2.96 (1H, s, OH); δ_C (75 MHz; $CDCl_3$) 157.0 (*C*═O), 137.9, 137.2, 135.8, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7 (Ph), 95.1 (d, $J_{C,F}$ = 179.3 Hz, C3), 81.5 (d, *J* = 28.5 Hz, C4), 73.5 (C6), 73.2, 71.7 (Ph*C*H_2O), 68.1 (Ph*C*H_2OC═O), 67.3 (C5), 67.1 (C1), 64.2 (C7), 63.7 (d, *J* = 21.8 Hz, C2); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 95.1, 81.5, 73.4, 67.3, 63.7; negative, 73.2, 71.7, 68.1, 67.1, 64.2; HRMS(ESI) calcd for $C_{29}H_{32}FNO_6Na^+$ $[M+Na]^+$ 532.2106, found 532.2105.

24b: light yellow syrup, 35% yield. $[\alpha]_D^{20}$ +45.1 (*c* 1.02 in CH_2Cl_2); ν_{max}/cm^{-1} 3435 m, 3063 w, 3032 m, 2943 m, 1685 s, 1496 m, 1454 s, 1415 s, 1349 s, 1211 m, 1095 s, 999 m, 913 m, 771 m, 739 m, 698 m; δ_H (300 MHz; $CDCl_3$) 7.19–7.04 (15H, m, *Ph*CH_2O and *Ph*CH_2OC═O), 5.09 (1H, d, $J_{H,F}$ = 49.2 Hz, H3), 4.97 (2H, s, PhC*H*$_2$OC═O), 4.49–4.19 (5H, m, PhC*H*$_2$O and H4), 4.08 (1H, ddd, *J* = 23.4 Hz, 9.9 Hz, 3.6 Hz, H2), 3.93 (1H, d, *J* = 5.7 Hz, H6), 3.84 (1H, s, OH), 3.65 (1H, dt, *J* = 8.4 Hz, 3.9 Hz, H1), 3.51–3.35 (4H, m, H1, H5 and H7); δ_C (75 MHz; $CDCl_3$) 156.3 (*C*═O), 137.9, 137.4, 135.8, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5 (Ph), 95.7 (d, $J_{C,F}$ = 180.0 Hz, C3), 82.8 (d, *J* = 26.3 Hz, C4), 73.2, 71.7 (Ph*C*H_2O), 71.0 (d, *J* = 5.3 Hz, C5), 68.0 (Ph*C*H_2OC═O), 67.2 (d, *J* = 9.8 Hz, C1), 65.3 (C6), 64.0 (d, *J* = 22.5 Hz, C2), 62.6 (C7); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 95.7, 82.8, 71.0, 65.3, 64.0; negative, 73.2, 71.7, 68.0, 67.2, 62.6; Found: C, 67.80; H, 6.38; N, 2.81. $C_{29}H_{32}FNO_6$ requires C, 68.35; H, 6.33; N, 2.75%.

General procedures for synthesis of L-homoDMDP (5), its C-3 fluorinated derivative (6) and their C-6 epimers (25 and 26)

The *N*-Cbz protected diol **23a**, **23b**, **24a** or **24b** (1 eq) was dissolved in methanol, followed by 10% Pd/C (20 wt%) and 6 N HCl. The suspension was stirred under hydrogen atmosphere for 48–60 h, and TLC showed completion of the reaction. Hydrogen was then replaced by nitrogen, catalyst was filtered, and the filtrate was concentrated *in vacuo*. The residue was neutralized with conc. NH_3 and concentrated again. The residue was then purified by an acidic ion exchanger column (Dowex 5W×8-400, H^+ form, Aldrich, column size: 1.3 × 14 cm), eluting with distilled water (100 mL) and then 1 N NH_4OH (50 mL), affording the target compound **5**, **25**, **6** or **26**.

5: light yellow syrup, 83% yield. $[\alpha]_D^{20}$ −40.0 (*c* 0.15 in H_2O) [lit.[4] $[\alpha]_D^{25}$ +31.5 (*c* 0.44 in H_2O) for its enantiomer]; ν_{max}/cm^{-1} 3228 s, 2941 w, 1106 w, 1061 w; δ_H (300 MHz; D_2O) 4.00 (1H, t, *J* = 7.1 Hz), 3.78 (1H, t, *J* = 7.5 Hz), 3.70 (1H, dd, *J* = 6.8 Hz, 3.4 Hz), 3.69–3.61 (2H, m), 3.55 (1H, dd, *J* = 11.7 Hz, 6.0 Hz), 3.52 (1H, dd, 1H, *J* = 11.6 Hz, 6.8 Hz), 2.97–2.95 (1H, m), 2.92 (1H, dd, *J* = 7.2 Hz, 5.5 Hz); δ_C (75 MHz; D_2O) 77.9, 77.8, 72.9, 63.4, 61.8, 61.6, 61.4; δ_C (Dept-135; 75 MHz; D_2O) positive, 77.9, 77.8, 72.8, 61.8, 61.4; negative, 63.3, 61.6; HRMS(ESI) calcd for $C_7H_{16}NO_5^+$ $[M+H]^+$ 194.1023, found 194.1028.

25: light yellow solid, 94% yield. mp 118–120 °C; $[\alpha]_D^{20}$ −35.1 (*c* 0.97 in H_2O); ν_{max}/cm^{-1} 3317 vs, 2918 m, 1412 m, 1046 s; δ_H (300 MHz; D_2O) 3.86 (1H, t, *J* = 7.5 Hz), 3.78–3.66 (2H, m), 3.63–3.46 (4H, m), 2.99 (1H, dd, *J* = 10.5 Hz, 6.6 Hz), 2.89 (1H, t, 1H, *J* = 6.5 Hz) [^{1}H NMR accords with that of its enantiomer[5]]; δ_C (75 MHz; D_2O) 77.5, 77.2, 71.1, 63.3, 61.8, 61.5; δ_C (Dept-135; 75 MHz; D_2O) positive, 77.5, 77.2, 71.1, 61.5; negative, 63.3, 61.8; HRMS(ESI) calcd for $C_7H_{16}NO_5^+$ $[M+H]^+$ 194.1023, found 194.1023.

6: yellow syrup, 89% yield. $[\alpha]_D^{20}$ −35.6 (*c* 1.13 in MeOH); ν_{max}/cm^{-1} 3344 vs, 2934 m, 1409 m, 1040 s; δ_H (300 MHz; D_2O) 4.69 (1H, dt, $J_{H,F}$ = 49.8 Hz, $J_{H,H}$ = 4.8 Hz, H3), 4.12 (1H, ddd, *J* = 21.9 Hz, 7.5 Hz, 5.1 Hz, H4), 3.69–3.63 (1H, m, H6), 3.60–3.41 (4H, m, H1 and H7), 3.24 (1H, ddd, *J* = 19.2 Hz, 11.1 Hz, 5.4 Hz, H2), 2.89 (1H, dd, *J* = 7.2 Hz, 5.7 Hz, H5); δ_C (75 MHz; D_2O) 99.6 (d, $J_{C,F}$ = 180.8 Hz, C3), 76.5 (d, *J* = 24.0 Hz, C4), 71.0 (C6), 63.3 (C7), 62.2 (d, *J* = 6.8 Hz, C5), 61.1 (d, *J* = 4.5 Hz, C1), 60.7 (d, *J* = 22.5 Hz, C2); δ_C (Dept-135; 75 MHz; D_2O) positive, 99.6, 76.5, 71.0, 62.2, 60.7; negative, 63.3, 61.1; HRMS(ESI) calcd for $C_7H_{15}FNO_4^+$ $[M+H]^+$ 196.0980, found 196.0980.

26: yellow syrup, 85% yield. $[\alpha]_D^{20}$ −15.3 (*c* 1.18 in MeOH); ν_{max}/cm^{-1} 3337 vs, 2934 m, 1410 m, 1041 s; δ_H (300 MHz; D_2O) 4.72 (1H, dt, $J_{H,F}$ = 53.1 Hz, $J_{H,H}$ = 4.1 Hz, H3), 4.25 (1H, ddd, *J* = 21.6 Hz, 6.3 Hz, 4.2 Hz, H4), 3.65–3.44 (5H, m, H1, H6 and H7), 3.26 (1H, ddd, *J* = 19.5 Hz, 10.2 Hz, 5.7 Hz, H2), 2.93 (1H, t, *J* = 6.2 Hz, H5); δ_C (75 MHz; D_2O) 100.0 (d, $J_{C,F}$ = 180.0 Hz, C3), 76.5 (d, *J* = 24.8 Hz, C4), 72.1 (C6), 63.3 (C7), 62.7 (d, *J* = 6.0 Hz, C5), 61.5 (d, *J* = 23.3 Hz, C2), 60.6 (d, *J* = 6.0 Hz, C1); δ_C (Dept-135; 75 MHz; D_2O) positive, 100.0, 76.5, 72.1, 62.8, 61.5; negative, 63.3, 60.6; HRMS(ESI) calcd for $C_7H_{15}FNO_4^+$ $[M+H]^+$ 196.0980, found 196.0979.

General procedures for synthesis of aldehyde 27 and 28

The diol mixture of **23** or **24** (1 eq) was dissolved in MeOH, aqueous $NaIO_4$ (1 eq) was added at room temperature, many white particles appeared. TLC showed completion of the reaction 1 h later, particles were filtered, washed with EtOAc and MeOH, the filtrate was then concentrated under reduced pressure to give the aldehyde **27** or **28**.

27: light yellow syrup, 98% yield. $[\alpha]_D^{20}$ +57.0 (*c* 1.20 in $CHCl_3$); ν_{max}/cm^{-1} 3032 w, 2867 w, 1706 vs, 1454 m, 1409 s, 1350 s, 1207 m, 1096 s; δ_H (300 MHz; $CDCl_3$) 9.46 (0.5H, d, *J* = 1.5 Hz, C*H*O), 9.37 (0.5H, d, *J* = 1.8 Hz, C*H*O), 7.38–7.18 (20H, m, *Ph*CH_2O), 5.24–5.06 (2H, m), 4.70–4.30 (8H, m), 4.18 (1H, s), 4.07 (1H, d, *J* = 4.5 Hz), 3.87 (1H, ddd, *J* = 66.6 Hz, 9.0 Hz, 4.5 Hz), 3.65–3.57 (1H, m); δ_C (75 MHz; $CDCl_3$) 200.3, 200.1, 155.5, 155.3, 138.3, 138.1, 137.0, 136.8, 136.1, 135.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 84.6, 83.4, 81.2, 79.8, 73.2, 73.1, 71.8,

71.1, 70.9, 68.2, 67.7, 67.6, 67.5, 63.5, 63.2; HRMS(ESI) calcd for $C_{35}H_{36}NO_6^+$ $[M+H]^+$ 566.2537, found 566.2518.

28: light yellow syrup, 99% yield. $[\alpha]_D^{20}$ +57.1 (*c* 0.49 in CH_2Cl_2); ν_{max}/cm^{-1} 3447 w, 3033 w, 2871 w, 1708 s, 1453 m, 1411 s, 1351 s, 1207 m, 1097 s, 990 m, 741 m, 698 m; δ_H (300 MHz; $CDCl_3$) 9.35 (1H, d, *J* = 27.9 Hz, *H*C═O), 7.26–7.15 (15H, m, *Ph*CH_2O and *Ph*CH_2OC═O), 5.20–4.98 (3H, m, H3 and PhC*H*$_2$OC═O), 4.59–4.23 (6H, m, PhC*H*$_2$O, H1 and H4), 4.07 (1H, d, *J* = 11.1 Hz, H5), 3.98–3.84 (1H, m, H1), 3.70–3.45 (1H, m, H2); δ_C (75 MHz; $CDCl_3$) 198.9 (d, *J* = 8.3 Hz, H*C*═*O*), 155.0, 154.1 (PhCH$_2$O*C*═*O*), 137.9, 137.7, 136.3, 135.8, 135.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7 (Ph), 94.6 (d, *J* = 179.3 Hz, C3), 93.4 (d, *J* = 178.5 Hz, C3), 83.3 (d, *J* = 30.8 Hz, C4), 82.3 (d, *J* = 30.8 Hz, C4), 73.3, 72.2 (Ph*C*H$_2$O), 70.8 (C5), 67.9, 67.8 (Ph*C*H$_2$OC═O), 67.1 (d, *J* = 9.8 Hz, C1), 66.4 (d, *J* = 9.8 Hz, C1), 63.8 (d, *J* = 21.8 Hz, C2), 63.3 (d, *J* = 21.8 Hz, C2); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 198.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 94.6, 93.4, 83.3, 82.3, 70.8, 63.8, 63.3; negative, 73.3, 72.2, 67.9, 67.8, 67.1, 66.4; HRMS(ESI) calcd for $C_{28}H_{28}FNO_5Na^+$ $[M+Na]^+$ 500.1844, found 500.1854.

General procedures for synthesis of alcohol 29 and 30

The solution of aldehyde **27** or **28** (1 eq) in EtOH was cooled by an ice-water bath, and $NaBH_4$ (1.1 eq) was added in several batches, obvious heat can be observed. The suspension was stirred for 1 h and quenched by aqueous NH_4Cl, EtOH and water was removed *in vacuo*, the residue was washed by EtOAc several times and salt was filtered. The filtrate was concentrated *in vacuo* to give alcohol **29** or **30**.

29: light yellow syrup, 78% yield. $[\alpha]_D^{20}$ +24.0 (*c* 0.50 in $CHCl_3$); ν_{max}/cm^{-1} 3445 m, 3031 m, 2923 m, 1760 m, 1698 s, 1496 m, 1454 m, 1410 m, 1349 m, 1209 m, 1094 vs, 736 m, 697 m; δ_H (300 MHz; $CDCl_3$) 7.23–7.10 (20H, m, *Ph*CH_2O), 5.02 (2H, dd, *J* = 36.9 Hz, 12.3 Hz, PhC*H*$_2$OC═O), 4.56–4.24 (6H, m, PhC*H*$_2$O), 4.08 (1H, d, *J* = 14.7 Hz), 4.00 (1H, s), 3.91 (1H, s), 3.80 (3H, s), 3.62 (1H, dd, *J* = 9.0 Hz, 4.2 Hz), 3.43 (1H, t, *J* = 9.3 Hz); δ_C (75 MHz; $CDCl_3$) 155.7, 154.7, 138.4, 138.1, 137.4, 137.3, 137.0, 136.3, 136.2, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 85.3, 84.2, 81.7, 80.6, 73.1, 71.4, 71.3, 68.4, 67.6, 67.5, 67.3, 66.8, 65.4, 63.7, 63.6, 63.4, 62.0; δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 85.3, 84.2, 81.7, 80.6, 66.8, 65.4, 63.4; negative, 73.1, 71.4, 71.3, 68.4, 67.6, 67.5, 67.3, 63.7, 62.0.

30: light yellow syrup, 86% yield. $[\alpha]_D^{20}$ +24.9 (*c* 0.89 in CH_2Cl_2); ν_{max}/cm^{-1} 3447 w, 3032 w, 2937 w, 1764 w, 1703 s, 1497 w, 1454 m, 1413 s, 1350 m, 1096 s, 1028 m, 739 m, 698 m; δ_H (300 MHz; $CDCl_3$) 7.42–7.38 (15H, m, *Ph*CH_2O and *Ph*CH_2OC═O), 5.46–5.14 (3H, m, H3 and PhC*H*$_2$OC═O), 4.76–4.52 (4H, m, PhC*H*$_2$O), 4.48–4.05 (5H, m, H1, H4 and H6), 3.85–3.65 (2H, m, H2 and H5); δ_C (75 MHz; $CDCl_3$) 155.5, 154.5 (PhCH$_2$O*C*═*O*), 138.3, 138.0, 137.5, 137.3, 136.3, 136.1, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7 (Ph), 95.3 (d, $J_{C,F}$ = 179.3 Hz, C3), 94.8 (d, $J_{C,F}$ = 177.8 Hz, C3), 82.9 (d, *J* = 26.3 Hz, C4), 82.7 (d, *J* = 27.0 Hz, C4), 73.3, 71.9 (Ph*C*H$_2$O), 67.7 (Ph*C*H$_2$OC═O), 67.5 (d, *J* = 5.3 Hz, C1), 66.4, 65.1 (C5), 63.6 (d, *J* = 22.5 Hz, C2), 62.3, 60.8 (C6); δ_C (Dept-135; 75 MHz; $CDCl_3$) positive, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 95.3, 94.8, 82.9, 82.7, 66.4, 65.1, 63.6; negative, 73.3, 71.9, 67.7, 67.5, 62.3, 60.8; HRMS(ESI) calcd for $C_{28}H_{31}FNO_5^+$ $[M+H]^+$ 480.2181, found 480.2161.

General procedures for synthesis of L-DMDP (3) and its C-3 fluorinated analogue (4)

The *N*-Cbz protected alcohol **29** or **30** (1 eq) was dissolved in methanol, followed by 10% Pd/C (20 wt%) and 6 N HCl, the suspension was stirred under hydrogen atmosphere for 48–72 h. TLC showed completion of the reaction. Hydrogen was then replaced by nitrogen, catalyst was filtered, and the filtrate was concentrated *in vacuo*. The residue was neutralized with conc. NH_3 and concentrated again. The residue was then purified by an acidic ion exchanger column (Dowex 5W×8-400, H^+ form, Aldrich, column size: 1.3 × 14 cm), eluting with distilled water (100 mL) and then 1 N NH_4OH (50 mL), affording the target compound **3** or **4**.

3: light yellow solid, 92% yield. mp 108–110 °C; $[\alpha]_D^{20}$ −51.8 (*c* 0.97 in H_2O) [lit.[7] mp 116–117 °C (MeOH); $[\alpha]_D^{23}$ −52.7 (*c* 0.28 in H_2O)]; δ_H (300 MHz; D_2O) 3.93 (2H, d, *J* = 6.3 Hz, H3 and H4), 3.76–3.71 (4H, m, H6), 3.42 (2H, s, H2 and H5); δ_C (75 MHz; D_2O) 74.0, 62.2, 57.7; δ_C (Dept-135; 75 MHz; D_2O) positive, 74.1, 62.3; negative, 57.7.

4: yellow syrup, 94% yield. $[\alpha]_D^{20}$ −40.2 (*c* 1.00 in MeOH); ν_{max}/cm^{-1} 3321 s, 2933 m, 1424 m, 1045 s; δ_H (300 MHz; D_2O) 4.72 (1H, dt, $J_{H,F}$ = 54.0 Hz, $J_{H,H}$ = 4.5 Hz, H3), 4.07 (1H, ddd, *J* = 21.0 Hz, 6.6 Hz, 4.5 Hz, H4), 3.64–3.51 (4H, m, H1 and H6), 3.26 (1H, ddd, *J* = 20.7 Hz, 11.1 Hz, 6.0 Hz, H2), 3.01 (1H, dd, *J* = 11.7 Hz, 5.7 Hz, H5); δ_C (75 MHz; D_2O) 100.0 (d, $J_{C,F}$ = 180.8 Hz, C3), 76.5 (d, *J* = 23.2 Hz, C4), 62.4 (d, *J* = 6.0 Hz, C5), 61.4, 61.2 (C1 and C6), 60.8 (C2); δ_C (Dept-135; 75 MHz; D_2O) positive, 100.0, 76.5, 62.4, 60.8; negative, 61.4, 61.2; HRMS(ESI) calcd for $C_6H_{13}FNO_3^+$ $[M+H]^+$ 166.0874, found 166.0873.

General procedures for synthesis of 31 and 32 for NOESY determination of diol 23 and 24

To a solution of diol **23a** or **24a** (1 eq) in MeOH was added NaOH (10 eq) and stirred at room temperature overnight. Water was added and the solution was extracted with EtOAc twice, organic phases were combined and concentrated under reduced pressure, then directly purified by preparative plate to get bicyclic product **31** or **32**.

31: light yellow syrup, 82% yield. $[\alpha]_D^{20}$ +15.4 (*c* 1.02 in $CHCl_3$); ν_{max}/cm^{-1} 3063 w, 3031 w, 2867 m, 1673 vs, 1457 w, 1454 m, 1434 m, 1363 m, 1260 w, 1089 s; δ_H (600 MHz; $CDCl_3$) 7.27–7.17 (15H, m, *Ph*CH_2O), 4.56 (2H, s, PhC*H*$_2$O), 4.48 (1H, d, *J* = 11.9 Hz, PhC*H*$_2$O), 4.44 (1H, d, *J* = 11.6 Hz, PhC*H*$_2$O), 4.42 (1H, d, *J* = 12.0 Hz, PhC*H*$_2$O), 4.38 (1H, d, *J* = 11.6 Hz, PhC*H*$_2$O), 4.16–4.14 (1H, m, H7), 4.12 (1H, dd, *J* = 3.8 Hz, 3.3 Hz, H6), 4.09 (1H, dd, *J* = 10.5 Hz, 4.6 Hz, H3), 3.89 (1H, dd, *J* = 6.7 Hz, 4.4 Hz, H5), 3.82 (1H, t, *J* = 10.2 Hz, H3), 3.74–3.71 (m, 1H, H4), 3.64 (dd, 1H, *J* = 9.5 Hz, 6.4 Hz, H9), 3.53 (dd, 1H, *J* = 9.6 Hz, 3.7 Hz, H9), 3.42 (dd, 1H, *J* = 7.9 Hz, 7.5 Hz, H4a), 2.61 (br s, 1H, OH); δ_C (75 MHz; $CDCl_3$) 150.6, 136.9, 136.5, 127.6, 127.5, 127.4, 127.0, 126.9, 126.7, 86.0, 81.9, 72.3, 71.1, 68.2, 67.5, 64.5, 63.7, 61.7; HRMS(ESI) calcd for $C_{29}H_{32}NO_6^+$ $[M+H]^+$ 490.2224, found 490.2226.

32: light yellow solid, 76% yield. mp 84–86 °C; $[\alpha]_D^{20}$ −31.6 (*c* 0.38 in CH_2Cl_2); ν_{max}/cm^{-1} 3353 m, 3032 w, 2922 m, 1682 s, 1471 m, 1437 m, 1361 w, 1280 m, 1100 s, 1029 m, 998 m, 740 m, 698 m; δ_H (600 MHz; $CDCl_3$) 7.39–7.30 (10H, m, *Ph*CH_2O), 5.31 (1H, dt, $J_{H,F}$ = 55.8 Hz, $J_{H,H}$ = 4.8 Hz, H6), 4.84–4.54 (4H, m, PhCH_2O), 4.42 (1H, ddd, *J* = 21.6 Hz, 9.0 Hz, 5.4 Hz, H5), 4.35 (1H, dd, *J* = 12.0 Hz, 2.4 Hz, H3), 4.23 (1H, d, *J* = 12.0 Hz, H3), 4.18 (1H, dt, *J* = 27.0 Hz, 3.6 Hz, H7), 4.05 (1H, s, H4), 3.92 (1H, dd, *J* = 10.2 Hz, 3.6 Hz, H9), 3.76–3.72 (2H, m, H4a and H9), 2.93 (1H, d, *J* = 7.2 Hz, OH); HRMS(ESI) calcd for $C_{22}H_{24}FNO_5Na^+$ $[M+Na]^+$ 424.1531, found 424.1534.

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