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Synthesis of monofluorinated isofagomine analogues and evaluation as glycosidase inhibitors

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ABSTRACT

The straightforward synthesis of monofluorinated isofagomine analogues **1**–**3** was described. The synthetic strategy featured that the chiral carbon center bearing fluorine atom was constructed stereoselectively via silicon-induced Reformatskii–Claisen rearrangement of allyl bromofluoroacetate. These compounds were tested for inhibition of five glycosidases. The 3*S*,4*R*,5*R* isomer **3** has been found to be a potent inhibitor against β-glucosidase from almonds with K_i value of 11.9 μM.

1. Introduction

Iminosugars have received increasing attention among synthetic chemists and biochemists in recent years because these compounds and their derivatives have significant therapeutic potential for the treatment of metabolic diseases, inhibition of tumor metastasis and control of infections of fungi and viruses [1]. Two iminosugar-based drugs have successfully completed clinical trials: Glyset™ (N-hydroxyethyl-DNJ) in 1996 for treatment of complications associated with type II diabetes, and Zavesca™ (N-butyl-1-DNJ) in 2003 as the first oral drug for Gaucher disease, a severe lysosomal storage disorder (Fig. 1) [1e]. Isofagomine [2], which mimics the transition state of glycoside cleavage in its protonated form, exhibits potent inhibition to several glycosidases, especially β-glucosidase from sweet almond with K_i value of 0.11 μM, and currently undergoes Phase I and II clinical trials sponsored by Amicus Therapeutics. Moreover, the C-4 epimer of isofagomine, isogalactofagomine, is also a strong glycosidase inhibitor [3].

In spite of the initial potential shown by these molecules, iminosugars as a therapeutic class have not been as promising as expected. The main reason may be that many glycosidase inhibitors are poor in clinical selectivity and cause unacceptable side effects [4]. To overcome this limitation, considerable efforts have been made on structure modification of leading iminosugars. It is well known that the electronegative properties of fluorine make it a near 'isoelectronic' replacement for the hydroxyl group. Furthermore, the strong gauche and antiperiplanar effects of fluorine atom due to its high electronegativity has profound stereoelectronic effect on neighboring groups, thereby the fluorine substituent can lead to a change in the preferred molecular conformation, which could affect protein binding affinity and selectivity at molecular level [5]. Several fluorinated iminosugars have been studied [6]. Among them, the fluorinated analogue at C-2′ of Miglitol shows an inhibitory activity four times higher than the parent compound for the α-galactosidase from green coffee beans and low cytotoxicity against a panel of human cell lines, making it an promising candidate for further investigations [6a]. Recently, *gem*-4,4-difluoromethylated isofagomine analogues have been investigated by our group [2a], and we found that when a hydroxyl group is unessential it could be replaced by *gem*-difluoro with minor change or even increase in the enzyme inhibition. Since fluoromethylene group (CHF) and *gem*-difluoromethylene group (CF_2) have distinct electron-withdrawing ability [7], we suppose that 4-fluoroisofagomine will have an another profile of glycosidases inhibition in comparison with *gem*-4,4-difluoromethylated isofagomine analogues, which could give us a deeper understanding of the fluorine effects on the bioactivity of isofagomine analogues. On the basis of the above consideration and our continuing interest in the fluorinated iminosugars [2a,8], we described herein the synthesis and biological evaluation of monofluorinated isofagomine analogues **1**–**3** (Fig. 2).

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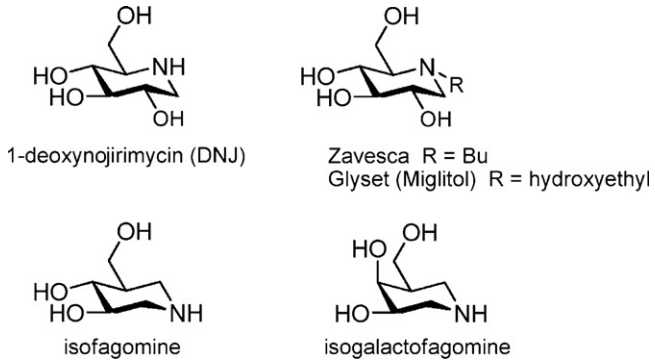


Fig. 1. Selected iminosugars as glycosidase inhibitors.

2. Results and discussion

2.1. Chemistry

Very recently, our group has developed the stereoselective synthesis of monofluorinated synthons **4** and **5** by the Reformatskii–Claisen rearrangement of allyl bromofluoroacetate via α-fluoro silyl ketene acetal (Scheme 1) [9]. Based on our reported synthetic strategy to *gem*-4,4-difluoromethylated isofagomine analogues [2a], we think that synthons **4** and **5** are the suitable precursors for preparation of target molecules **1**–**3**. Accordingly, treatment of compound **4** with $NaBH_4$ in the presence of cerium chloride heptahydrate afforded two separable diastereoisomeric alcohols **6** and **7** in 81% and 11% yield, respectively. Then protection of alcohols **6** and **7** to benzylic ethers **8** and **9**, which are converted to diols **10** and **11** via ozonolysis followed by $NaBH_4$ reduction *in situ*, respectively. Diols **10** and **11** are subjected to methylsulfonyl chloride, followed by cyclization of corresponding mesylates with neat benzylamine to afford piperidines **12** and **13** in 85% and 81% yield, respectively. Selective debenzylation of ethers **12** and **13** was carried out in the presence of BCl_3 in dichloromethane at 0 °C to give triols **14** and **15**, which were transformed to alcohols **16** and **17** through oxidation with $NaIO_4$ and subsequent reduction with $NaBH_4$ in 72% and 73% yield over two steps, respectively. Finally, 4-fluoroisofagomine analogues **1** and **2** were obtained by hydrogenation of **16** and **17** in the presence of 20% $Pd(OH)_2/C$ (Scheme 2).

All the characterization data of compounds **10** and **11** were identical to diols **10′** and **11′**, which were prepared from our reported compounds **18** and **19** [9] via benzylation, ozonolysis and subsequent $NaBH_4$ reduction. Therefore, the absolute configuration of target molecules **1** and **2** at C-3 position generated by Luche reduction could be determined as *S* and *R* according to the configuration of compounds **18** and **19** (Scheme 3).

Diastereoisomer **3** of 4-fluoroisofagomines **1** and **2** was also prepared by a similar procedure from compound **5** (Scheme 4).

The absolute configuration of **3** was determined by the X-ray crystal structure of the *p*-nitrobenzoylated compound **26** (Fig. 3), which was prepared from the reaction of triol **25** with 4-nitrobenzoyl chloride (Scheme 4).

2.2. Enzymology

The synthesized 4-fluoroisofagomine analogues **1**–**3** were evaluated for their inhibitory activities toward five glycosidases namely the β-glucosidase from almonds, α-glucosidase from baker yeast, β-galactosidases from *Aspergillus orizae*, α-galactosidase from Green Coffee beans, α-mannosidases from Jack beans. All assays were performed at 25 °C and pH 6.8 using the corresponding nitrophenyl glycoside substrates. The K_i value obtained are summarized in Table 1.

Compounds **1** and **2** showed no or negligible inhibition toward β-glucosidase from almonds and β-galactosidases from *Aspergillus orizae*, but displayed moderate inhibition of α-glucosidase from baker yeast and α-galactosidase from Green Coffee beans with a K_i

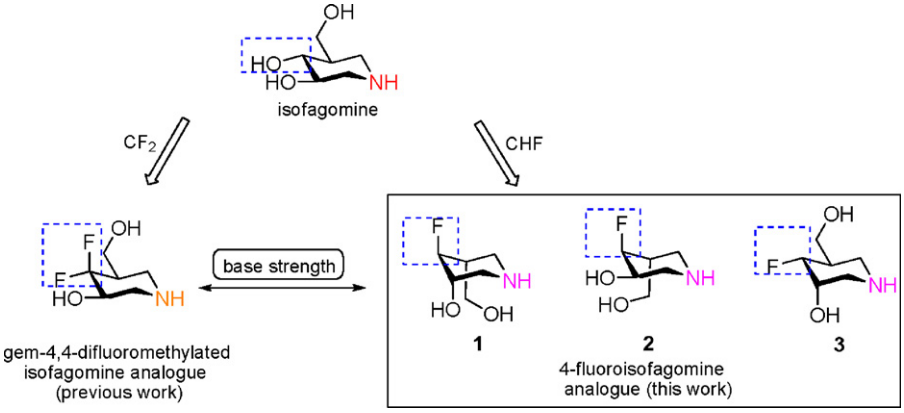
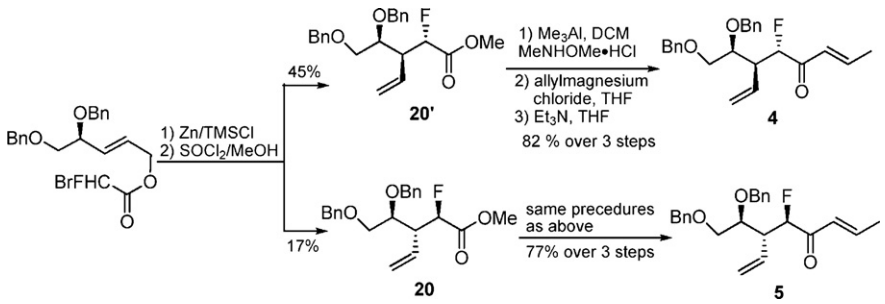
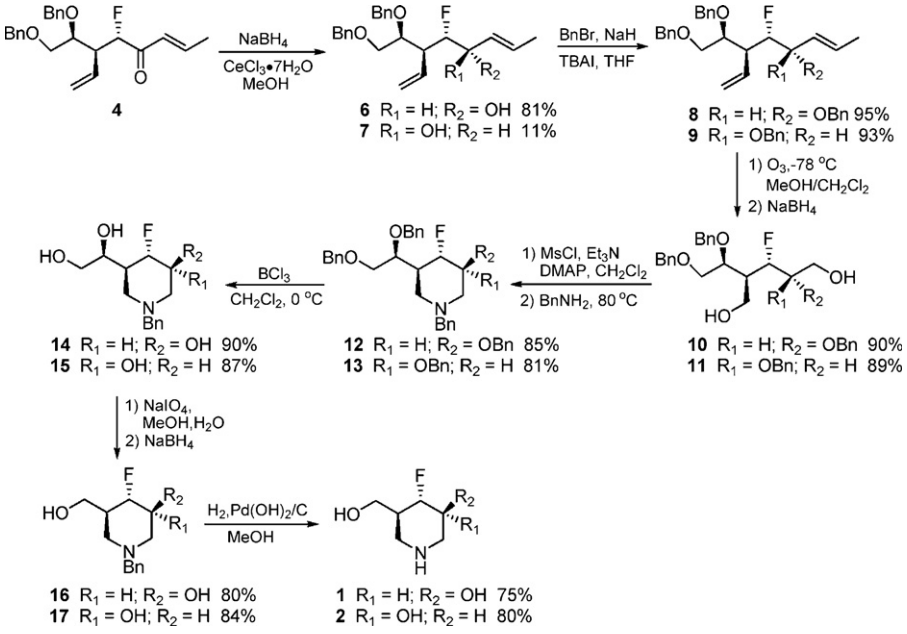


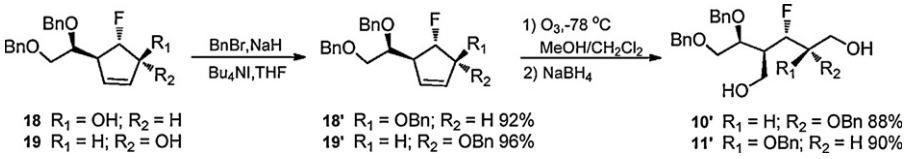
Fig. 2. Rational design of 4-fluoroisofagomine analogues.



Scheme 1. Synthesis of key fluorinated synthons **4** and **5** via Reformatskii–Claisen rearrangement.



Scheme 2. Synthesis of target molecules **1**–**2** from compound **4**.

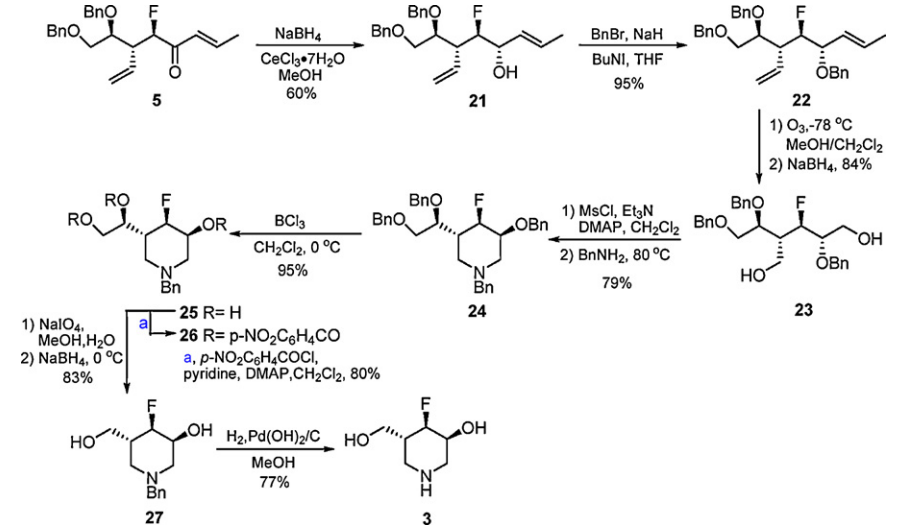


Scheme 3. Assignment of the configuration of compounds **1**–**2**.

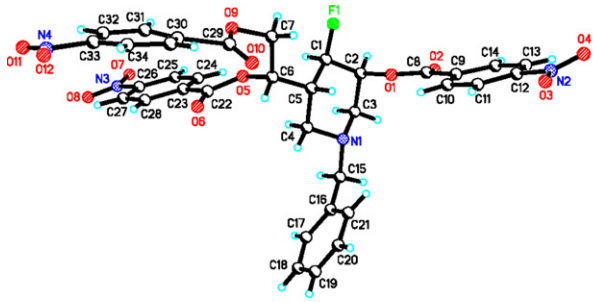
value of 200 μM approximately. Toward α-mannosidases from Jack beans, compound **2** also gave a K_i value of 290 μM. Compound **3** showed moderate inhibition to α-galactosidase from Green Coffee beans and α-mannosidases from Jack beans similar to compound **2**, but inhibited β-glucosidase from almonds potently at 11.9 μM.

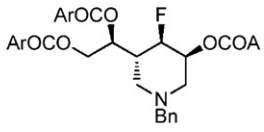
It is known that the stereochemistry of an iminosugar is crucial for its ability to bind the glycosidase, since hydroxyl groups are involved in the binding, and epimerization of a single hydroxyl group may change the inhibition level significantly [10]. Comparison of the K_i value of compounds **1**–**3** versus β-glucosidase from almonds with literature values for isofagomine and its analogues **28**–**30** [2b], and *gem*-4,4-difluoromethylated isofagomine analogues **31**–**33** [2a] (Fig. 4) show that the introduction of fluoromethylene group at C-4 site to compound **30** has a positive influence on inhibition. Although analogues **1** and **2** have an attenuated inhibition in contrast with difluoromethylated analogues **31** and **32**, compound **3** is 100 times more potent than both **30** and difluoromethylated analogue **33**. This is highly remarkable.

The relationship between pH and the inhibition of β-glucosidase from almonds by compound **3** was also established (Chart 1). The data showed that **3** inhibits β-glucosidase from almonds well



Scheme 4. Synthesis of target molecule **3** from compound **5**.





26

Ar = *p*-nitrophenyl

Fig. 3. X-ray crystal structure of compound **26**.

Table 1
Inhibition constants of 4-fluoroisofagomine analogue **1–3** at 25 °C and pH 6.8.

Enzyme	K_i (μM)		
	1	**2**	**3**
β-Glucosidase[a]	>1000	>1000	11.9
α-Glucosidase[b]	194	226	919
β-Galactosidase[c]	>1000	>1000	ND[f]
α-Galactosidase[d]	194	218	183
α-Mannosidase[e]	ND[f]	290	251

[a] From almonds.
[b] From baker yeast.
[c] From *Aspergillus orizae*.
[d] From Green Coffee beans.
[e] From Jack beans.
[f] Not determined.

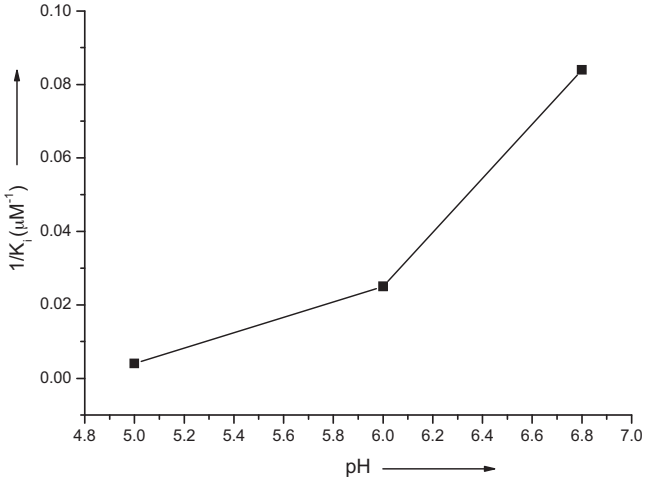


Chart 1. pH versus $1/K_i$ for **3** at 25 °C toward β-glucosidase from almonds.

at neutral condition, but a sharp drop of inhibition takes place when the solution turns to be acidic. This profile is identical to that of *gem*-4,4-difluoromethylated isofagomine analogues [2a]. The pK_a of compound **3** is predicted to 8.8 using an empirical rule [11], while compounds **30** and **33** are 9.2 and 7.6 respectively. The significant variation in K_i value is thus explained by the large difference in stereoelectronic effect between CF_2, CHF, and CH(OH) groups [12]. We speculate that the interactions of iminosugar **3** binding to glycosidases, have benefited from exploiting 'polar hydrophobic' effect [13] of the C–F bond relative to C–OH, so the inhibitory activity is enhanced greatly.

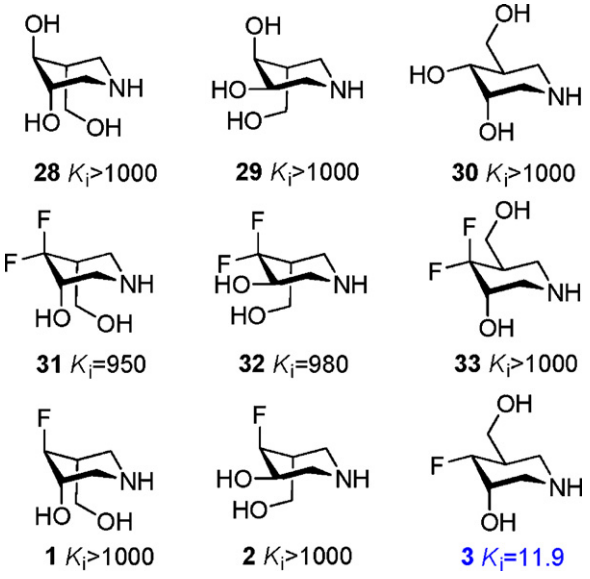


Fig. 4. Comparison of the inhibition constants of 4-fluoroisofagomine analogues with 4-deoxy-4,4-difluoroisofagomine analogues and their parent molecules.

3. Conclusion

In summary, we described herein the design and synthesis of 4-fluoroisofagomine analogues **1–3**. The biological evaluation showed that compound **3**, despite having a wrong stereochemistry at C-3, was a potent inhibitor of β-glucosidase from almonds. This work shows that we can exploit the 'polar hydrophobic' effect of the C–F bond relative to C–OH to modify iminosugar, in which the basicity of the molecule will not be greatly altered.

4. Experimental

4.1. General

4.1.1. Chemistry

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. THF was distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride. Petroleum ether refers to the fraction of light petroleum ether with bp 60–90 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-300, Bruker AM-400 or Varian Mercury-300 spectrometers. ^{19}F NMR was recorded on a Bruker AM-300 spectrometer ($FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are in hertz. Optical rotations were measured using a Perkin-Elmer 241 or 341 polarimeter. Crystallographic data were analyzed with Rigaku FCR Diffractimer.

4.1.2. Enzyme inhibition

Each glycosidase assay was performed by preparing eight 2 mL samples in cuvettes, containing 1 mL sodium phosphate buffer (0.1 M) of right pH along with 0.04–0.80 mL of different substrates.

The concentration of the substrate was in the range of 0.25–5 K_m. The substrates used were 2-nitrophenyl-β-D-galactopyranoside, 4-nitrophenyl-α-D-galactopyranoside, 4-nitrophenyl-β-D-glucopyranoside, 4-nitrophenyl-α-D-glucopyranoside, or 4-nitrophenyl-α-D-mannopyranoside. Also added was 0.02–0.1 mL of a solution of either the inhibitor or water, and finally each cuvette was filled up to a total volume of 1.9 mL with distilled water. Four of the samples contained the inhibitor at a fixed concentration but with varying concentrations of nitrophenyl glycoside. The other four samples contained no inhibitor, but also varying concentrations of nitrophenyl glycoside. Finally the reaction was started by adding 0.1 mL of a diluted solution of enzyme solution. The formation of 4- or 2-nitrophenol was monitored for 2 min at 25 °C by measurement of the absorbance at 400 nm. Initial velocities were calculated from the slopes from each reaction and used to construct two Hanes plots ($[S]/v$ vs $[S]$), one with and one without inhibitor, which also was used to check whether inhibition was competitive. From the two Michaelis–Menten constants, K_m and K_m', thus obtained, the inhibition constant, K_i, was calculated. All assays were performed at 25 °C. The inhibition constants (K_i) were obtained from the formula $K_i = [I]/(K_M'/K_M^{-1})$, where K_M' and K_M are Michaelis–Menten constants with and without inhibitor present.

4.2. General procedure of the preparation of iminosugars 1–3

4.2.1. (4S,5S,6S,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluoroocta-2,7-dien-4-ol (6)

A solution of compound **4** [8] (385 mg, 1.0 mmol) and $CeCl_3{\bullet}7H_2O$ (745 mg, 2.0 mmol) in methanol (10 mL) was cooled to 0 °C, and $NaBH_4$ (77 mg, 2.0 mmol) was added in portions. The solution remained at the temperature for 20 min and quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether: ethyl acetate = 9:1) to give compound **6** (313 mg) and **7** (43 mg) as a clear oil in 81% and 11% yield, respectively. Data for compound **6**: clear oil; $[\alpha]_D^{25} = 20.0°$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.58 (m, 10H), 6.15–5.96 (m, 3H), 5.60 (d, *J* = 6.0 Hz, 1H), 5.18–4.81 (m, 5H), 4.51–4.41 (m, 2H), 3.99–3.81 (m, 2H), 3.28 (dd, *J* = 17.4 Hz, 8.4 Hz, 1H), 2.07 (d, *J* = 6.3 Hz, 1H);^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.9, 138.2, 132.5, 132.4, 130.1, 128.4, 128.3, 128.2, 127.6, 127.4, 120.7, 93.6 (d, *J* = 180.3 Hz), 76.7, 75.9, 75.9, 73.6, 73.3, 72.1, 71.1 (d, *J* = 19.1 Hz), 47.8 (d, *J* = 20.7 Hz), 17.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −205.5 (ddd, *J* = 34.1 Hz, 28.2 Hz, 6.8 Hz, 1F); IR (KBr) υ_{max} 3589, 3449, 3030, 2917, 1496, 1454, 1365, 1090, 736, 697 cm^{-1}; MS (ESI) *m*/*z* 385 $(M+H)^+$, 407 $(M+Na)^+$; HRMS Calcd for $C_{24}H_{29}O_3FNa$: 407.1998; Found: 407.1993.

4.2.2. (4R,5S,6S,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluoroocta-2,7-dien-4-ol (7)

Data for compound **7**: clear oil; $[\alpha]_D^{25}$ = 13.7? (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7. 21 (m, 10H), 5.76–5.52 (m, 3H), 5.17 (d, *J* = 10.8 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 4.87–4.43 (m, 5H), 4.17–4.02 (m, 2H), 3.60–3.41 (m, 2H), 2.54 (dd, *J* = 16.8 Hz, 5.4 Hz, 1H), 1.70 (d, *J* = 15.0 Hz, 3H); ^{13}C NMR(100.7 MHz, $CDCl_3$) δ 138.7, 138.3, 132.3, 132.2, 130.9, 128.4, 128.3, 127.8, 127.6, 127.6, 127.6, 127.0, 126.9, 120.3, 94.0 (d, *J* = 179.4 Hz), 75.8, 73.7, 73.4, 73.3, 73.2, 71.5, 48.6(d, *J* = 19.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −202.4 (ddd, *J* = 34.4 Hz, 26.5 Hz, 8.7 Hz, 1F); IR (KBr) υ_{max} 3585, 3445, 3030, 2918, 2859, 1496, 1454, 1094, 736, 697 cm^{-1}; MS (ESI) *m*/*z* 407 $(M+Na)^+$; HRMS Calcd for $C_{24}H_{29}O_3FNa$: 407.1998; Found: 407.1993.

4.2.3. (4S,5S,6S,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-4-benzyloxy-5-fluoroocta-2,7-diene (8)

To a suspended solution of NaH (60% in oil, 186 mg, 4.46 mmol), Bu_4NI (80 mg, 0.21 mmol), and THF (8 mL) at 0 °C under nitrogen atmosphere, a solution of compound **6** (920 mg, 2.4 mmol) in THF (4 mL) was added dropwise. The mixture was stirred at rt for 30 min. BnBr (700 mg, 4.1 mmol) in THF (4 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 2 h and then quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ether. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether: ethyl acetate = 30:1) to give compound **8** (313 mg) as a light yellow oil in 95% yield. $[\alpha]_D^{25} = 33.8°$ (*c* 3.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 15H), 5.71–5.59 (m, 3H), 5.06 (d, *J* = 9.9 Hz, 1H), 4.96 (d, *J* = 9.9 Hz, 1H), 4.83–4.44 (m, 5H), 3.77 (dd, *J* = 28.8 Hz, 5.4 Hz, 1H), 3.58–3.47 (m, 2H), 3.05–3.02 (m, 1H), 1.77 (d, *J* = 3.9 Hz, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 139.2, 138.5, 138.4, 132.6, 132.5, 130.9, 128.4, 128.3, 128.3, 128.1, 128.1, 127.6, 127.5, 127.4, 120.3, 94.0 (d, *J* = 183.7 Hz), 78.2 (d, *J* = 17.0 Hz), 76.0, 76.0, 73.8, 73.2, 72.7, 70.1, 47.6 (d, *J* = 20.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −202.4 (dd, *J* = 45.7 Hz, 29.0 Hz, 1F); IR (KBr) υ_{max} 3064, 3030, 2918, 2861, 1454, 1097, 735, 696 cm^{-1}; MS (ESI) *m*/*z* 492 $(M+NH_4)^+$; HRMS Calcd for $C_{31}H_{35}O_3FNa$: 497.2468; Found: 497.2462.

4.2.4. (4R,5S,6S,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-4-benzyloxy-5-fluoroocta-2,7-diene (9)

Using the same condition as described for compound **8**, compound **9** (287 mg, 93% yield) was prepared as a light yellow oil from compound **7** (250 mg, 0.65 mmol). $[\alpha]_D^{25} = -6.5°$ (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.28 (m, 15H), 5.74–5.50 (m, 3H), 5.11–4.80 (m, 2H), 4.76–4.31 (m, 7H), 4.06 (t, *J* = 6.0 Hz, 1H), 3.85 (dd, *J* = 33.6 Hz, 8.7 Hz, 1H), 3.57–3.39 (m, 2H), 2.53 (dd, *J* = 18.3 Hz, 9.6 Hz, 1H), 1.79 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.9, 138.4, 138.4, 132.8, 132.6, 132.5, 128.4, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5, 127.5, 125.1, 125.1, 120.1, 92.9 (d, *J* = 181.6 Hz), 80.0 (d, *J* = 18.7 Hz), 75.6 (d, *J* = 5.0 Hz), 73.7, 73.2, 71.7, 69.8, 48.5 (d, *J* = 19.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −200.2 (ddd, *J* = 33.0 Hz, 26.2 Hz, 5.1 Hz, 1F); IR (KBr) υ_{max} 3063, 3029, 2920, 2857, 1738, 1453, 1366, 1217, 1092, 735, 697 cm^{-1}; MS (ESI) *m*/*z* 492 $(M+NH_4)^+$, 497 $(M+Na)^+$; HRMS Calcd for $C_{31}H_{35}O_3FNa$: 497.2468; Found: 497.2462.

4.2.5. (2S,3S,4S)-2-(Benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3-fluoropentane-1,5-diol (10)

A solution of compound **8** (820 mg, 1.73 mmol) in dichloromethane and methanol (20 mL, V/V = 1:1) was cooled to −78 °C and treated with ozone until the solvent appeared blue. Nitrogen was bulbed inside until the bule color disappeared, and $NaBH_4$ (660 mg, 1.74 mmol) was added in portions. The mixture was returned to room temperature and stirred for 3 h, then be quenched with saturated aqueous NH_4Cl solution (30 mL). The mixture was extracted with ethyl acetate, dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) on silica gel to give **10** as a clear oil (712 mg) in 88% yield. $[\alpha]_D^{25} = -7.2°$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 15H), 4.96 (dd, *J* = 46.2 Hz, 9.3 Hz, 1H), 4.83–4.49 (m, 6H), 4.21 (t, *J* = 4.5 Hz, 1H), 3.92–3.60 (m, 6H), 3.45 (d, *J* = 12.0 Hz, 1H), 2.99 (d, *J* = 12.3 Hz, 1H), 2.27 (t, *J* = 9.9 Hz, 2H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.1, 137.9, 128.5, 128.5, 128.5, 128.0, 128.0, 127.9, 127.9, 127.8, 127.6, 91.9 (d, *J* = 174.6 Hz), 73.8, 73.4, 72.6, 71.4, 61.7 (d, *J* = 6.0 Hz), 59.7 (d, *J* = 9.1 Hz), 42.4 (d, *J* = 18.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −206.4 (ddd, *J* = 40.9 Hz, 29.6 Hz, 11.3 Hz, 1F); IR (KBr) υ_{max} 3425, 2872, 1454, 1273, 1067, 1027, 737, 698 cm^{-1}; MS (ESI) *m*/*z* 469

(M+H)$^+$, 491 (M+Na)$^+$; HRMS Calcd for $C_{28}H_{33}O_5FNa$: 491.2201; Found: 491.2204.

4.2.6. (2R,3S,4S)-2-(Benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3-fluoropentane-1,5-diol (11)

Using the same condition as described for compound **10**, compound **11** (790 mg, 89% yield) was prepared as a clear oil from compound **9** (900 mg, 1.90 mmol). $[\alpha]_D^{25} = -19.3^\circ$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 15H), 4.98 (d, *J* = 47.1 Hz, 1H), 4.76–4.53 (m, 6H), 4.16 (m, 1H), 3.92–3.78 (m, 4H), 3.72–3.63 (m, 2H), 3.60 (t, *J* = 5.1 Hz, 1H), 2.84 (s, 1H), 2.10 (s, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 137.8, 137.7, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 91.5 (d, *J* = 174.9 Hz), 78.0 (d, *J* = 17.9 Hz), 77.4 (t, *J* = 3.2 Hz), 77.1, 76.8, 73.6, 72.9, 72.5, 70.7, 61.4 (d, *J* = 7.6 Hz), 59.4 (d, *J* = 7.0 Hz), 43.1 (d, *J* = 30.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −200.9 (ddd, *J* = 38.6 Hz, 27.5 Hz, 6.9 Hz, 1F); IR (KBr) υ_{max} 3432, 2872, 1454, 1278, 1069, 1027, 737 cm^{-1}; MS (ESI) *m*/*z* 469 (M+H)$^+$, 491 (M+Na)$^+$; HRMS Calcd for $C_{28}H_{33}O_5FNa$: 491.2210; Found: 491.2204.

4.2.7. (3S,4S,5S)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4-fluoropiperidine (12)

A solution of compound **10** (203 mg, 0.434 mmol) in dry dichloromethane (3 mL) was cooled to 0 °C. Et_3N (0.31 mL, 2.22 mmol), DMAP (8 mg, 0.07 mmol), and MsCl (0.15 mL, 1.97 mmol) were added. The mixture was stirred at rt for 4 h and then quenched with water. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was dissolved in $BnNH_2$ (1 mL) and heated for 18 h at 80 °C. Then the mixture was directly purified by flash chromatography (petroleum ether: ethyl acetate = 15:1) to give compound **12** (199 mg) as a light yellow oil in 85% yield for two steps. $[\alpha]_D^{25} = -11.6^\circ$ (*c* 3.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 20H), 4.76–4.42 (m, 7H), 4.01 (dd, *J* = 7.8 Hz, 6.0 Hz, 1H), 3.61–3.51 (m, 1H), 3.49–3.43 (m, 4H), 3.05 (t, *J* = 5.1 Hz, 1H), 2.83 (d, *J* = 8.4 Hz, 1H), 2.28–1.94 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8, 138.7, 138.4, 138.3, 129.2, 129.1, 129.1, 128.7, 128.6, 128.6, 128.5, 128.0, 127.9, 127.9, 127.9, 127.9, 127.4, 127.3, 95.2 (d, *J* = 135.4 Hz), 78.0, 77.8, 77.5, 75.0, 74.0, 73.6, 72.9, 71.3, 62.4, 57.3, 55.7 (d, *J* = 7.3 Hz), 51.1 (d, *J* = 6.7 Hz), 43.2 (d, *J* = 12.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −190.0 (d, *J* = 48.5 Hz, 1F); IR (KBr) υ_{max} 3062, 3029, 2911, 1495, 1453, 1241, 1126, 984, 737, 697 cm^{-1}; MS (ESI) *m*/*z* 540 (M+H)$^+$; HRMS Calcd for $C_{35}H_{39}O_3FN$: 540.2914; Found: 540.2909.

4.2.8. (3R,4S,5S)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4-fluoropiperidine (13)

Using the same condition as described for compound **12**, compound **13** (291 mg, 81% yield) was prepared as a clear oil from compound **11** (312 mg, 0.67 mmol). $[\alpha]_D^{25} = -17.8^\circ$ (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.25 (m, 20H), 4.76–4.41 (m, 6H), 3.95 (dd, *J* = 10.2 Hz, 5.1 Hz, 1H), 3.72 (d, *J* = 13.8 Hz, 1H), 3.64–3.33 (m, 5H), 2.77 (d, *J* = 6.0 Hz, 2H), 2.57–2.44 (m, 1H), 2.39 (d, *J* = 9.3 Hz, 1H), 2.16 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.7, 138.5, 138.2, 138.1, 129.1, 128.4, 128.3, 128.2, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.1, 127.0, 90.5 (d, *J* = 192.4 Hz), 75.3, 73.4, 73.3, 71.4, 62.3, 53.3, 50.4, 40.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −196.5 (m, 1F); IR (KBr) υ_{max} 2923, 2853, 1307, 1241, 1130, 984, 746, 698 cm^{-1}; MS (ESI) *m*/*z* 540 (M+H)$^+$; HRMS Calcd for $C_{35}H_{39}O_3FN$: 540.2914; Found: 540.2909.

4.2.9. (S)-1-((3S,4S,5S)-1-Benzyl-4-fluoro-5-hydroxypiperidin-3-yl)ethane-1,2-diol (14)

A solution of compound **12** (200 mg, 0.37 mmol) in dry dichloromethane (3 mL) was cooled to 0 °C under nitrogen atmosphere and BCl_3 (1 M solution in dichloromethane, 3.7 mL, 3.7 mmol) was added dropwise. The reaction mixture remained at this temperature for 3 h and then quenched with methanol (5 mL). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (dichloromethane: methanol = 12:1) to give compound **14** (90 mg) as a foam in 90% yield. $[\alpha]_D^{25} = -24.8^\circ$ (*c* 0.2, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.62–7.50 (m, 5H), 4.54 (dt, *J* = 48.3, 9.0 Hz, 1H), 4.46 (d, *J* = 12.9 Hz, 1H), 4.38 (d, *J* = 12.9 Hz, 1H), 4.10–4.00 (m, 2H), 3.60–3.31 (m, 7H), 3.03 (dt, *J* = 61.5 Hz, 12.6 Hz, 2H), 2.39 (dd, *J* = 21.3 Hz, 10.2 Hz, 1H); ^{13}C NMR(75.5 MHz, CD_3OD) δ 131.1, 130.0, 129.0, 129.0, 67.2, 63.4, 48.5, 48.3, 48.1, 47.9, 47.6; ^{19}F NMR (282 MHz, CD_3OD) δ −195.3 (m, 1F); IR (KBr) υ_{max} 3337, 2926, 1475, 1287, 1217, 1044, 972 cm^{-1}; MS (ESI) *m*/*z* 270 (M+H)$^+$; HRMS Calcd for $C_{14}H_{21}O_3FN$: 270.1506; Found: 270.1500.

4.2.10. (S)-1-((3S,4S,5R)-1-Benzyl-4-fluoro-5-hydroxypiperidin-3-yl)ethane-1,2-diol (15)

Using the same condition as described for compound **14**, compound **15** (78 mg, 87% yield) was prepared as a clear oil from compound **13** (180 mg, 0.33 mmol). $[\alpha]_D^{25} = -35.1^\circ$ (*c* 1.3, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.66–7.60 (m, 5H), 4.58 (d, *J* = 13.2 Hz, 1H), 4.40 (t, *J* = 4.5 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 4.06 (dd, *J* = 6.0 Hz, 3.9 Hz, 1H), 3.74–3.60 (m, 3H), 3.46–3.18 (m, 3H), 2.89 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR(100.7 MHz, CD_3OD) δ 130.9, 129.8, 129.0, 117.0, 63.9, 63.7, 63.4, 59.9, 48.5; ^{19}F NMR (282 MHz, CD_3OD) δ −195.3 (dd, *J* = 46.5 Hz, 20.6 Hz, 1F); IR (KBr) υ_{max} 3348, 1641, 1459, 1236, 1129, 1058, 983, 762, 702 cm^{-1}; MS (ESI) *m*/*z* 270 (M+H)$^+$; HRMS Calcd for $C_{14}H_{21}O_3FN$: 270.1506; Found: 270.1500.

4.2.11. (3S,4S,5S)-1-Benzyl-4-fluoro-5-(hydroxymethyl)piperidin-3-ol (16)

A solution of compound **14** (74 mg, 0.275 mmol) in methanol (2 mL) was added saturated aqueous $NaIO_4$ solution (1.0 mL) dropwise. The mixture was stirred strongly for 15 min at rt and then cooled to 0 °C. $NaBH_4$ (72 mg, 1.9 mmol) was added in portions. The mixture was stirred for 30 min at rt and quenched with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (petroleum ether: ethyl acetate = 2:1) on silica gel to give **16** as a foam (53 mg) in 80% yield. $[\alpha]_D^{25} = -13.7^\circ$ (*c* 0.7, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.35–7.25 (m, 5H), 4.11 (dt, *J* = 52.2 Hz, 8.4 Hz, 1H), 3.84–3.53 (m, 5H), 3.03–2.99 (m, 2H), 2.05–1.88 (m, 3H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 137.2, 129.1, 128.0, 127.1, 95.0 (d, *J* = 179.1 Hz), 69.7 (d, *J* = 17.9 Hz), 61.7, 59.8, 57.3 (d, *J* = 9.1 Hz), 54.0 (d, *J* = 9.0 Hz), 42.6 (d, *J* = 17.3 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −194.3 (d, *J* = 48.5 Hz, 1F); IR (KBr) υ_{max} 3394, 2931, 1453, 1389, 1215, 1023, 920 cm^{-1}; MS (ESI) *m*/*z* 240 (M+H)$^+$; HRMS Calcd for $C_{13}H_{19}O_2FN$: 240.1400; Found: 240.1394.

4.2.12. (3R,4S,5S)-1-Benzyl-4-fluoro-5-(hydroxymethyl)piperidin-3-ol (17)

Using the same condition as described for compound **16**, compound **17** (60 mg, 84% yield) was prepared as a foam from compound **15** (82 mg, 0.30 mmol). $[\alpha]_D^{25} = -25.6^\circ$ (*c* 1.1, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.78–7.66 (m, 5H), 4.86 (dd, *J* = 49.2 Hz, 8.7 Hz, 1H), 4.41 (d, *J* = 12.6 Hz, 1H), 4.12–3.97 (m, 4H), 3.27 (d, *J* = 31.2 Hz, 2H), 2.86–2.65 (m, 3H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 136.1, 129.2, 128.0, 127.3, 90.7 (d, *J* = 179.5 Hz), 65.8 (d, *J* = 17.8 Hz), 61.5, 60.2, 55.6 (d, *J* = 6.2 Hz), 52.6, 38.9 (d, *J* = 19.0 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −198.1 (m, 1F); IR (KBr) υ_{max} 3394, 2925, 2815, 1454, 1034, 761, 700 cm^{-1}; MS (ESI) *m*/*z* 240 (M+H)$^+$; HRMS Calcd for $C_{13}H_{19}O_2FN$: 240.1400; Found: 240.1394.

*4.2.13. (3S,4S,5S)-4-Fluoro-5-(hydroxymethyl)piperidin-3-ol (**1**)*

A solution of compound **16** (40 mg, 0.17 mmol) in methanol (4 mL) was hydrogenated in the presence of 20% $Pd(OH)_2/C$ (4 mg) at atmospheric pressure and at rt. After stirring for 8 h, the reaction mixture was filtrated and concentrated. The residue was purified by flash chromatography (dichloromethane: methanol = 4:1) to give compound **1** (19 mg) as a foam in 75% yield. $[\alpha]_D^{25} = -9.5^\circ$ (*c* 0.4, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.20 (dt, *J* = 52.2 Hz, 9.9 Hz, 1H), 3.77–3.59 (m, 3H), 3.34 (d, *J* = 11.4 Hz, 1H), 3.16–3.10 (m, 2H), 2.52–2.33 (m, 2H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 94.8 (d, *J* = 170.5 Hz), 59.1, 48.3, 48.0, 47.8, 47.4, 46.0; ^{19}F NMR (282 MHz, CD_3OD) δ −198.1 (d, *J* = 64.6 Hz, 1F); IR (KBr) υ_{max} 3394, 2925, 2815, 1454, 1034, 761, 700 cm^{-1}; MS (ESI) *m*/*z* 150 $(M+H)^+$; HRMS Calcd for $C_6H_{13}O_2FN$: 150.0930; Found: 150.0925.

*4.2.14. (3R,4S,5S)-4-Fluoro-5-(hydroxymethyl)piperidin-3-ol (**2**)*

Using the same condition as described for compound **1**, compound **2** (19 mg, 80% yield) was prepared as a foam from compound **17** (38 mg, 0.16 mmol). $[\alpha]_D^{25} = -47.1^\circ$ (*c* 0.7, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.56 (dd, *J* = 34.2 Hz, 9.9 Hz, 1H), 4.04 (d, *J* = 7.2 Hz, 1H), 3.74–3.58 (m, 2H), 3.14–2.51 (m, 3H), 2.39–2.12 (m, 2H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 90.6 (d, *J* = 180.8 Hz), 65.7 (d, *J* = 17.8 Hz), 65.2 (d, *J* = 17.4 Hz), 60.1, 59.5, 58.3, 48.5 (d, *J* = 83.6 Hz), 45.5 (d, *J* = 5.8 Hz), 44.3, 39.0 (d, *J* = 17.9 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −192.5 (m, 1F); IR (KBr) υ_{max} 3394, 2925, 2815, 1454, 1034, 761, 700 cm^{-1}; MS (ESI) *m*/*z* 150 $(M+H)^+$; HRMS Calcd for $C_6H_{13}O_2FN$: 150.0930; Found: 150.0925.

*4.2.15. (5R,6R,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluoroocta-2,7-dien-4-one (**5**)*

Using the same condition as described for compound **4** [8], compound **5** (318 mg, 77% yield) was prepared as yellow oil from compound **20** (400 mg, 1.08 mmol, containing trace amount of other isomers) over three steps. $[\alpha]_D^{25} = 13.5^\circ$ (*c* 4.5, $CHCl_3$); ^1H NMR(300 MHz, $CDCl_3$) δ 7.34–7.04 (m, 10H), 6.98 (dt, *J* = 22.2 Hz, 6.9 Hz, 1H), 6.41 (d, *J* = 15.3 Hz, 1H), 5.81 (dt, *J* = 17.1 Hz, 9.3 Hz, 1H), 5.23–5.06 (m, 3H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.54 (s, 2H), 3.82 (dd, *J* = 9.9 Hz, 5.1 Hz, 1H), 3.65 (d, *J* = 4.8 Hz, 2H), 3.09–2.93 (m, 1H), 1.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 196.3 (d, *J* = 22.0 Hz), 145.6, 145.5, 138.5, 138.2, 131.5, 131.5, 128.4, 128.3, 127.7, 127.7, 127.6, 126.1, 120.5, 94.3 (d, *J* = 187.9 Hz), 78.4, 76.8, 73.4, 72.6, 70.7, 48.8 (d, *J* = 19.1 Hz), 18.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −199.2 (dd, *J* = 49.4 Hz, 28.5 Hz, 1F); IR (KBr) υ_{max} 3064, 3030, 2916, 2863, 1695, 1627, 1496, 1454, 1094, 736, 698 cm^{-1}; MS (ESI) *m*/*z* 383 $(M+H)^+$, 400 $(M+NH_4)^+$, 405 $(M+Na)^+$; HRMS Calcd for $C_{24}H_{27}O_3FNa$: 405.1842; Found: 405.1836.

*4.2.16. (4S,5R,6R,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluoroocta-2,7-dien-4-ol (**21**)*

Using the same condition as described for compound **6**, compound **21** (138 mg, 60% yield, the other isomer can not get purely by flash chromatography) was prepared as a clear oil from compound **5** (230 mg, 0.60 mmol). $[\alpha]_D^{25} = -9.4^\circ$ (*c* 10.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.22 (m, 10H), 5.90–5.68 (m, 2H), 5.38 (dd, *J* = 14.7 Hz, 6.6 Hz, 1H), 5.22 (d, *J* = 9.9 Hz, 1H), 5.10 (d, *J* = 17.4 Hz, 1H), 4.72–4.42 (m, 5H), 4.18–4.08 (m, 1H), 3.76–3.63 (m, 3H), 2.80–2.65 (m, 1H), 1.70 (s, 1H), 1.69 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.5, 138.2, 133.0, 132.9, 130.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 120.0, 95.2 (d, *J* = 176.7 Hz), 79.1, 79.0, 76.8, 73.4, 72.8, 72.6, 70.7, 47.0 (d, *J* = 19.1 Hz), 18.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −205.5 (ddd, *J* = 44.0 Hz, 29.3 Hz, 15.5 Hz, 1F); IR (KBr) υ_{max} 3578, 3442, 3030, 2917, 2860, 1496, 1454, 1098, 736, 698 cm^{-1}; MS (ESI) *m*/*z* 407 $(M+Na)^+$; HRMS Calcd for $C_{24}H_{29}O_3FNa$: 407.1998; Found: 407.1993.

*4.2.17. (4S,5R,6R,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-4-benzyloxy-5-fluoroocta-2,7-dienel (**22**)*

Using the same condition as described for compound **8**, compound **22** (231 mg, 95% yield) was prepared as a clear oil from compound **21** (197 mg, 0.51 mmol). $[\alpha]_D^{25} = -27.9^\circ$ (*c* 2.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (m, 15H), 5.90–5.77 (m, 1H), 5.69–5.57 (m, 1H), 5.34 (dd, *J* = 15.3 Hz, 9.0 Hz, 1H), 5.19 (d, *J* = 10.5 Hz, 1H), 5.08 (d, *J* = 17.7 Hz, 1H), 4.69–4.28 (m, 7H), 3.81–3.70 (m, 1H), 3.62 (s, 2H), 2.84–2.69 (m, 1H), 1.73 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.7, 138.4, 138.3, 133.3, 133.3, 132.1, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 126.7, 126.6, 119.7, 94.1 (d, *J* = 179.5 Hz), 79.6, 79.4, 78.6, 78.5, 73.4, 72.5, 71.2, 70.0, 47.0 (d, *J* = 19.5 Hz), 18.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −202.4 (ddd, *J* = 44.6 Hz, 26.2 Hz, 17.5 Hz, 1F); IR (KBr) υ_{max} 3064, 3030, 2916, 2864, 1496, 1454, 1097, 735, 696 cm^{-1}; MS (ESI) *m*/*z* 492 $(M+NH_4)^+$, 497 $(M+Na)^+$; HRMS Calcd for $C_{31}H_{35}O_3FNa$: 497.2468; Found: 497.2462.

*4.2.18. (2S,3R,4R)-2-(Benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3-fluoropentane-1,5-diol (**23**)*

Using the same condition as described for compound **10**, compound **23** (212 mg, 84% yield) was prepared as a clear oil from compound **22** (256 mg, 0.54 mmol). $[\alpha]_D^{25} = -19.5^\circ$ (*c* 4.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 15H), 4.88 (d, *J* = 46.5 Hz, 1H), 4.67–4.38 (m, 6H), 3.91–3.62 (m, 7H), 3.41 (dt, *J* = 18.6 Hz, 4.5 Hz, 1H), 2.43 (br, 2H), 2.25 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 137.8, 137.8, 137.8, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.7, 92.5 (d, *J* = 175.3 Hz), 78.1, 77.9, 77.4, 73.5, 72.8, 72.5, 70.7, 61.4 (d, *J* = 7.5 Hz), 59.4 (d, *J* = 6.9 Hz), 43.1 (d, *J* = 19.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −204.5 (m, 1F); IR (KBr) υ_{max} 3483, 3031, 2924, 2872, 1454, 1071, 1028, 738, 698 cm^{-1}; MS (ESI) *m*/*z* 469 $(M+H)^+$, 491 $(M+Na)^+$; HRMS Calcd for $C_{28}H_{33}O_5FNa$: 491.2210; Found: 491.2204.

*4.2.19. (3S,4R,5R)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4-fluoropiperidine (**24**)*

Using the same condition as described for compound **12**, compound **24** (125 mg, 79% yield) was prepared as a yellow oil from compound **23** (138 mg, 0.29 mmol). $[\alpha]_D^{25} = -12.5^\circ$ (*c* 7.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (m, 20H), 4.70 (d, *J* = 54.6 Hz, 1H), 4.71–4.42 (m, 6H), 3.75–3.46 (m, 6H), 2.96 (d, *J* = 10.8 Hz, 1H), 2.88 (d, *J* = 12.0 Hz, 1H), 2.61 (d, *J* = 37.5 Hz, 1H), 2.27–2.13 (m, 2H), 2.10–1.86 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.6, 138.4, 138.3, 138.1, 129.3, 129.0, 128.4, 128.3, 128.3, 127.9, 127.6, 127.6, 127.5, 127.1, 87.9 (d, *J* = 174.5 Hz), 77.8, 76.8, 73.4, 73.2, 73.0, 72.4, 71.0, 70.3, 62.9, 51.2, 50.6, 38.8 (d, *J* = 17.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −200.8 (d, *J* = 33.0 Hz, 1F); IR (KBr) υ_{max} 3086, 3062, 3029, 2867, 1495, 1453, 1363, 1098, 735, 698 cm^{-1}; MS (ESI) *m*/*z* 540 $(M+H)^+$; HRMS Calcd for $C_{35}H_{39}O_3FN$: 540.2914; Found: 540.2909.

*4.2.20. (S)-1-((3R,4R,5S)-1-Benzyl-4-fluoro-5-hydroxypiperidin-3-yl)ethane-1,2-diol (**25**)*

Using the same condition as described for compound **14**, compound **25** (71 mg, 86% yield) was prepared as a foam from compound **24** (165 mg, 0.31 mmol). $[\alpha]_D^{25} = 0.2^\circ$ (*c* 5.9, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 7.59–7.51 (m, 5H), 4.72–4.31 (m, 3H), 4.13 (s, 1H), 3.71 (s, 4H), 3.33–3.13 (m, 4H), 2.71 (d, *J* = 33.0 Hz, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 131.2, 130.0, 129.0, 128.6, 86.2 (d, *J* = 176.4 Hz), 69.6, 63.3, 63.2, 63.0, 60.5, 51.8, 50.2, 36.0 (d, *J* = 18.0 Hz), 48.5, 40.1; ^{19}F NMR (282 MHz, CD_3OD) δ −202.6 (dd, *J* = 47.9 Hz, 37.5 Hz, 1F); IR (KBr) υ_{max} 3308, 2941, 1459, 1220, 1106, 1002, 936 cm^{-1}; MS (ESI) *m*/*z* 270 $(M+H)^+$; HRMS Calcd for $C_{14}H_{21}O_3FN$: 270.1506; Found: 270.1500.

4.2.21. (S)-1-((3R,4R,5S)-1-Benzyl-4-fluoro-5-(4-nitrobenzoyloxy)piperidin-3-yl)ethane-1,2-diyl bis(4-nitrobenzoate) (26)

Compound **25** (22 mg, 0.082 mmol), DMAP (3 mg, 0.0246 mmol) was dissolved in dry pyridine (1 mL), cooled to 0 °C, then *p*-$NO_2C_6H_4COCl$ (200 mg, 1.08 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise. The mixture was returned to room temperature and stirred for 12 h, then at 50 °C for another 12 h. The mixture was cooled to room temperature, CH_2Cl_2 (10 mL) was added in. The organic phase was washed with saturated sodium bicarbonate, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether: ethyl acetate = 4:1) on silica gel to give **26** as a light yellow solid (37 mg, 80% yield). m.p. 226 °C; $[\alpha]_D^{25}$ = 6.6° (*c* 2.3, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32–8.02 (m, 12H), 5.75 (s, 1H), 5.40 (s, 1H), 4.96–4.86 (m, 2H), 4.70–4.64 (m, 2H), 3.64 (d, *J* = 13.5 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 2.96–2.56 (m, 5H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 161.5, 160.9, 148.3, 148.1, 134.7, 132.2, 132.0, 128.3, 128.2, 128.1, 126.1, 125.8, 124.8, 121.1, 120.1, 69.2, 59.5, 47.2, 36.4; ^{19}F NMR (282 MHz, CD_3OD) δ −200.0 (m, 1F); IR (KBr) υ_{max} 3003, 1716, 1530, 1359, 1268, 1223, 1102, 721 cm^{-1}; MS (ESI) *m*/*z* 150 $(M+H)^+$; HRMS Calcd for $C_6H_{13}O_2FN$: 150.0930; Found: 150.0925; Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference number: CCDC 815092.

4.2.22. (3S,4R,5R)-1-Benzyl-4-fluoro-5-(hydroxymethyl)piperidin-3-ol (27)

Using the same condition as described for compound **16**, compound **27** (59 mg, 83% yield) was prepared as a foam from compound **25** (80 mg, 0.30 mmol). $[\alpha]_D^{25}$ = −2.3° (*c* 0.6, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.43–7.31 (m, 5H), 4.60 (d, *J* = 46.5 Hz, 1H), 3.92 (s, 1H), 3.82–3.57 (m, 4H), 2.83–2.72 (m, 3H), 2.54–2.34 (m, 2H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 129.4, 128.1, 127.6, 65.2 (d, *J* = 22.5 Hz), 61.5, 59.5, 54.1, 50.5, 38.1; ^{19}F NMR (282 MHz, CD_3OD) δ −202.5 (m, 1F); IR (KBr) υ_{max} 3390, 2929, 1706, 1495, 1455, 1058, 759, 701 cm^{-1}; MS (ESI) *m*/*z* 240 $(M+H)^+$; HRMS Calcd for $C_{13}H_{19}O_2FN$: 240.1340; Found: 240.1394.

4.2.23. (3S,4R,5R)-4-Fluoro-5-(hydroxymethyl)piperidin-3-ol (3)

Using the same condition as described for compound **1**, compound **3** (19 mg, 77% yield) was prepared as a foam from compound **27** (40 mg, 0.17 mmol). $[\alpha]_D^{25}$ = 5.6? (*c* 0.3, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 4.71 (d, *J* = 3.6 Hz, 1H), 4.17 (s, 1H), 3.74–3.55 (m, 2H), 3.46–3.23 (m, 3H), 2.93 (t, *J* = 12.6 Hz, 2H), 2.64–2.42 (m, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 94.8 (d, *J* = 170.5 Hz), 59.1, 48.3, 48.0, 47.8, 47.4, 46.0; ^{19}F NMR (282 MHz, CD_3OD) δ −204.3 (dd, *J* = 47.1 Hz, 34.4 Hz, 1F); IR (KBr) υ_{max} 3351, 2963, 2933, 2793, 1453, 1390, 1050, 917 cm^{-1}; MS(ESI) *m*/*z* 150 $(M+H)^+$; HRMS Calcd for $C_6H_{13}O_2FN$: 150.0930; Found: 150.0925.

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