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Synthesis and biological evaluation of potent glycosidase inhibitors: 4-deoxy-4,4-difluoroisofagomine and analogues

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ABSTRACT

A series of 4,4-difluoroisofagomine analogues were synthesized. These compounds were tested for inhibition of eight glycosidases. The 3*R*,5*R* isomer **1** is a new and potent inhibitor against β-glucosidase from almonds with K_i value of 1.2 μM. The influence of the *gem*-difluoromethylene group (CF_2) on binding to glycosidases is discussed. It is concluded that only non-essential hydroxyl groups can be replaced by the *gem*-difluoro group and that in such a case (β-glycosidase) the change in inhibition is, interestingly, a result of the change in base strength.

1. Introduction

Iminosugars and azasugars (polyhydroxypiperidines and pyrrolidines), which frequently are analogues of natural products, have attracted increasing attention for synthetic chemists and biochemists due to their significant biological activities. They often serve as strong inhibitors of glycosidases and glycotransferases[1] and have a tremendous potential as agents to treat a variety of carbohydrate-mediated diseases, such as diabetes, cancer, AIDS, hepatitis, Gaucher's disease, and influenza.[2] Among this group of inhibitors, *N*-butyl-1-DNJ (Zavesca) and *N*-hydroxyethyl-DNJ (Miglitol) have been successfully completed clinical trials for type I Gaucher disease and lysosomal storage disorder.[3] Isofagomine (Fig. 1), which mimic the transition state of glycoside cleavage in its protonated form, shows a broad spectrum of strong inhibition against glycosidases, especially β-glucosidase (sweet almond).[4] Noteworthy, it inhibits β-glucosidase, glucoamylase, and isomaltase more strongly than 1-deoxynojirimycin (DNJ, Fig. 1).[5] Interestingly, isogalactofagomine, a diastereoisomer of isofagomine, also appears to be extremely potent against β-glucosidase.[6]

In spite of considerable efforts have been expended to develop iminosugars as potent glycosidase inhibitors, their lack of selectivity has been shown to cause problems and side effects in therapeutic applications.[1a] Modification of a known iminosugar inhibitor is a promising strategy for obtaining stronger and more selective inhibitors toward a certain glycosidase of therapeutic interest. In recent years, employing this strategy, tremendous efforts have been made.[7] However, rare reports have described the effect of electron-withdrawing groups on the iminosugars bioactivities, especially when electron-withdrawing groups are introduced in the piperidine ring.[8] Recently we designed and synthesized *gem*-4,4-difluoromethylated nojirimycin analogues, and found that the strongly electron-withdrawing *gem*-difluoromethylene group had an important influence on the inhibition of glycosidase.[9] To continue our research on the fluorinated glycosidase inhibitors, herein, we first described the synthesis and biological evaluation of 4-deoxy-4,4-difluoroisofagomine analogues **1**–**14** (Fig. 2).

The design of 4-deoxy-4,4-difluoroisofagomine analogues **1**–**14** was based on the following considerations: Firstly, isofagomine and its stereoisomer isogalactofagomine are very potent inhibitors of β-glycosidase. The configurational difference between these two compounds at C4 is non-essential for the inhibition of almond β-glucosidase. It is indicated that C4 is a good position to modify isofagomine as a result to discover new β-glycosidase inhibitors. Secondly, the strong electron-withdrawing *gem*-difluoromethylene group would greatly affect the pK_a of iminosugars, which could have some interesting consequences, such as increasing iminosugars selectivity toward a certain glycosidase.[9] Consequently, we expected that the presence of a CF_2 group at C4 of isofagomine analogues would change their biological activity and selectivity and led us to further study their structure–activity relationship.

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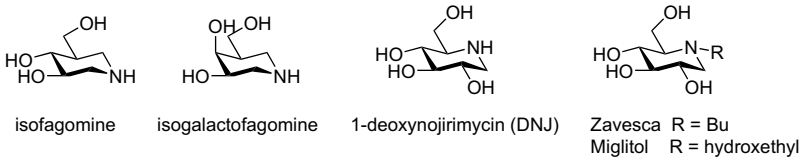
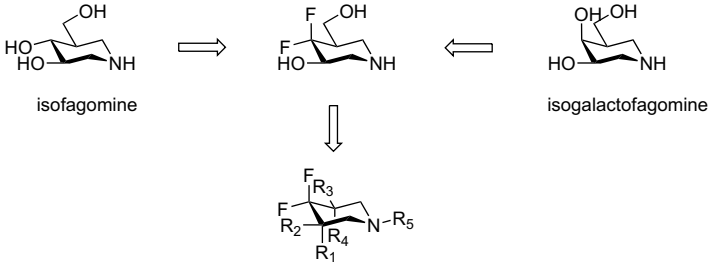


Figure 1. Selected glycosidase inhibitors.



1: R_1=H, R_2=OH, R_3=CH_2OH, R_4=H, R_5=H
2: R_1=OH, R_2=H, R_3=CH_2OH, R_4=H, R_5=H
3: R_1=H, R_2=OH, R_3=H, R_4=CH_2OH, R_5=H
4: R_1=OH, R_2=H, R_3=H, R_4=CH_2OH, R_5=H
5: R_1=H, R_2=OH, R_3=CH_2OH, R_4=H, R_5=Bn
6: R_1=OH, R_2=H, R_3=CH_2OH, R_4=H, R_5=Bn
7: R_1=H, R_2=OH, R_3=H, R_4=CH_2OH, R_5=Bn
8: R_1=OH, R_2=H, R_3=H, R_4=CH_2OH, R_5=Bn
9: R_1=H, R_2=OH, R_3=CH_2OH, R_4=H, R_5=Bu
10: R_1=OH, R_2=H, R_3=CH_2OH, R_4=H, R_5=Bu
11: R_1=H, R_2=OH, R_3=H, R_4=CH_2OH, R_5=Bu
12: R_1=OH, R_2=H, R_3=H, R_4=CH_2OH, R_5=Bu
13: R_1=H, R_2=OH, R_3=H, R_4=CH_2OH, R_5=$(CH_2)_2OH$
14: R_1=OH, R_2=H, R_3=H, R_4=CH_2OH, R_5=$(CH_2)_2OH$

Figure 2. Rational design of 4-deoxy-4,4-difluoroisofagomine analogues **1**–**14**.

2. Results and discussion

2.1. Chemistry

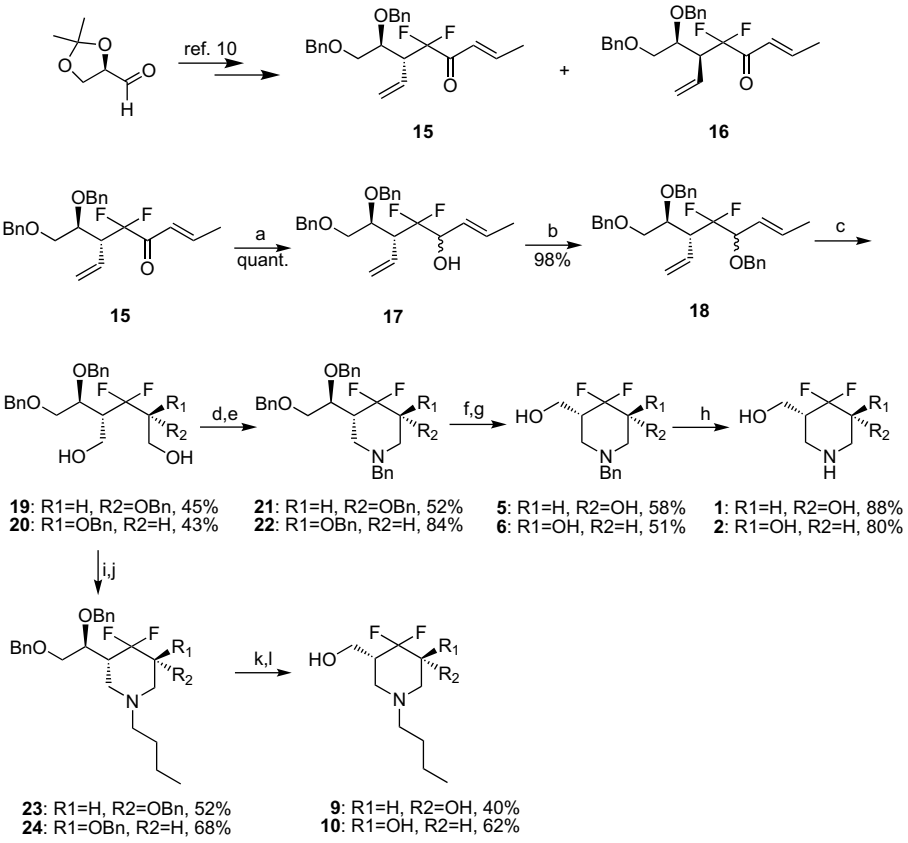
Our strategy to construct 4,4-difluoropiperidine ring was mainly based on difluoromethylated building blocks **15** and **16** developed in our group (Scheme 1).[10] Compounds **15** and **16** were prepared from 1-(*R*)-glyceraldehyde acetonide in 10 steps. Starting from compound **15**, a series of 4-deoxy-4,4-difluoroisofagomine analogues **1**, **2**, **5**, **6**, **9**, and **10** were synthesized. Since any diastereoisomers of 4-deoxy-4,4-difluoroisofagomine is meaningful to evaluate its bioactivity and further investigate the structure–activity relationship, the racemic diastereoisomers of alcohol **17** were obtained in quantitative yield by reduction of compound **15** with $NaBH_4$ in the presence of $CeCl_3\cdot 7H_2O$. Treatment of alcohol **17** with benzyl bromide in the presence of sodium hydride and catalytic tetrabutylammonium iodide gave compound **18** in 98% yield. The conversion of **18** to the key intermediate diols **19** and **20** was achieved by the following two steps: (1) ozonation of alkene in dichloromethane/methanol at −78 °C and (2) reduction of resulting dialdehyde with $NaBH_4$. Gratifyingly, diastereoisomers **19** and **20** could be readily separated by column chromatography in 45% and 43% yields, respectively. Diols **19** and **20** were subjected to methylsulfonyl chloride, respectively, followed by cyclization of corresponding mesylates with neat benzylamine to afford piperidines **21** and **22** in 52% and 84% yields, respectively.[11] However, when compounds **21** and **22** were treated with hydrogen in the presence of 20% $Pd(OH)_2$/C or less active 10% Pd/C in methanol at rt, all of the four benzyl groups were removed. The selective deprotection of three benzylethers was carried out by treatment of piperidines **21** and **22** with BCl_3 in heptane/dichloromethane at 0 °C.[12] Finally, the resulting alcohols were converted to target molecules **5** and **6** in 58% and 51% yields, respectively, over three steps by oxidation with $NaIO_4$ and subsequent reduction with $NaBH_4$. The target molecules 4-deoxy-4,4-difluoroisofagomine analogues, (3*R*,5*R*)-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol **1** and (3*S*,5*R*)-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol **2** were obtained by hydrogenation of **5** and **6** in the presence of 20% $Pd(OH)_2$/C in methanol. The *N*-butyl iminosugars **9** and **10** were obtained from the diols **19** and **20** by cyclization of corresponding mesylates with neat *n*-butylamine in five steps using similar procedure.

Similarly, starting from compound **16**, 4,4-difluroroisofagomine analogues **3**, **4**, **7**, **8**, **11**, and **12** were successfully synthesized (Scheme 2). For the synthesis of *N*-hydroxyethyliminosugars **13** and **14**, the intermediates **33** and **34** were protected with benzoyl chloride, and the resulting benzoylates were converted to compounds **37** and **38** using similar strategy as described for preparation of compound **1**. Finally, treatment of **37** and **38** with NH_3/MeOH afforded the desired iminosugars **13** and **14**.

The absolute configurations of target molecules **3**–**4**, **7**–**8**, and **11**–**14** were assigned by the X-ray crystal structure of compound **8**[13] (Fig. 3) based on the known configuration at C5 that derived from *gem*-difluoromethylated ketones **16**.[10] Since compounds **1**, **2**, **5**, **6**, and **9**, **10** are enantiomers of compounds **3**, **4**, **7**, **8** and **11**, **12**, respectively, we can easily confirm their absolute configurations by comparison of optical rotations.

2.2. Enzymology

The synthesized 4-deoxy-4,4-difluoroisofagomine analogues were evaluated to their inhibition activities toward eight glycosidases namely the β-glucosidase from almonds, α-glucosidase from baker yeast, and *Bacillius stearothermophilus*, β-galactosidases from *Saccharomyces fragilis*, *Aspergillus orizae* and bovine liver, α-galactosidase



Scheme 1. Synthesis of 4-deoxy-4,4-difluroroisofagomine analogues **1**–**14** from compounds **15** and **16**. Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (b) NaH, BnBr, TBAI, THF; (c) O_3, CH_2Cl_2/MeOH (1:1), −78 °C, then $NaBH_4$, −78 °C to rt; (d) MsCl, Et_3N, DMAP, CH_2Cl_2; (e) $BnNH_2$, 80 °C; (f) i. BCl_3 (1 M in heptane), CH_2Cl_2, 0 °C; (g) $NaIO_4$, H_2O, MeOH, then $NaBH_4$; (h) 20% $Pd(OH)_2$/C, H_2, MeOH; (i) MsCl, Et_3N, DMAP, CH_2Cl_2; (j) *n*-$BuNH_2$, reflux; (k) BCl_3 (1 M in heptane), CH_2Cl_2, 0 °C; (l) $NaIO_4$, H_2O, MeOH, then $NaBH_4$.

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 values obtained are summarized in Table 1.

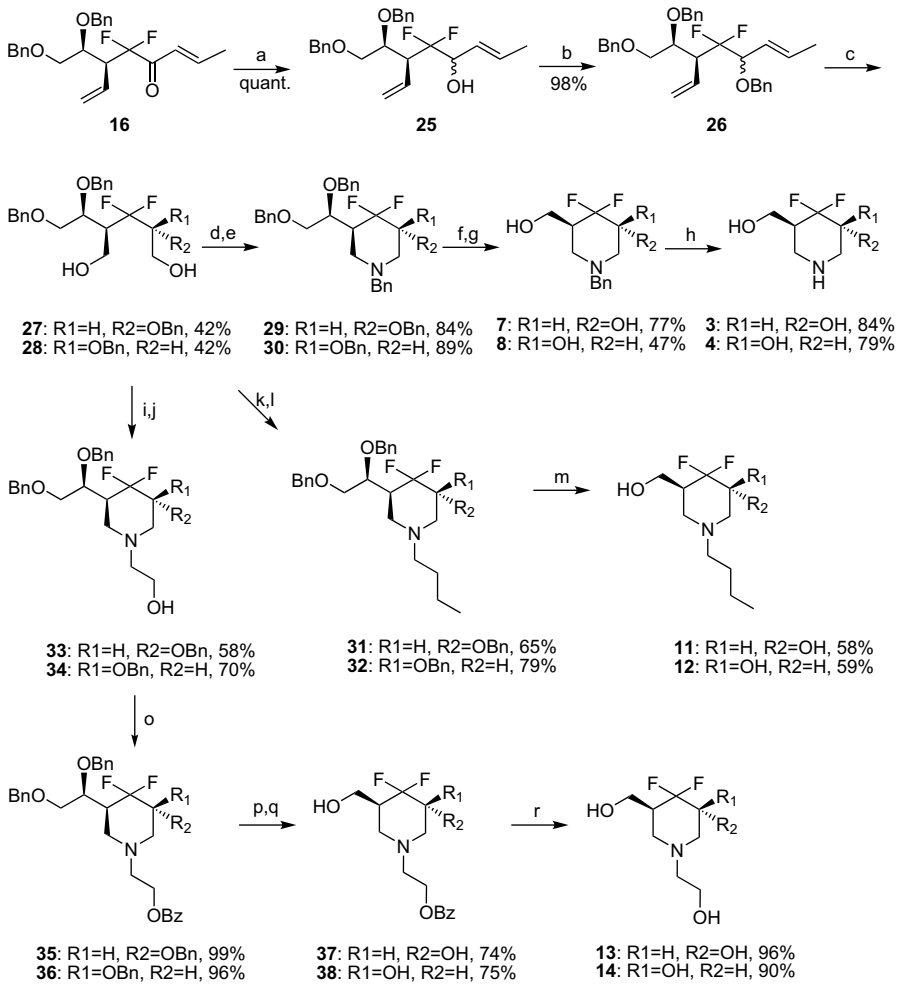
The *N*-substituted compounds **5**–**14** showed insignificant inhibition of all eight enzymes at concentrations of 0.2 or 1 mM depending on the solubility of the compounds, which meant that K_i's were above those values. This is in accordance with previous results that have showed that alkylation of the amine in isofagomine impedes inhibition.[14] Likewise compounds **1**–**4** displayed no or negligible inhibition (K_i>1 mM) against all the enzymes except β-glucosidase from almond and β-galactosidase from bovine liver. However toward those two enzymes the inhibition was competitive and gave the K_i values 1.2, 4270, 980, and 950 μM versus β-glucosidase and 165, 610, 2480 and 250 μM versus β-galactosidase (Table 1).

It is known that the stereochemistry of an azasugar glycosidase inhibitor is crucial for its ability to bind the enzyme, since many hydroxyl groups are involved in the binding, epimerisation of a single hydroxyl group may change the inhibition level significantly.[14] Stereochemical resemblance with the substrate is likewise crucial. Compound **1** resembles, through the stereochemistry at C3 and C5, D-glucose, D-mannose, D-galactose, and D-talose, while compound **2** resembles D-gulose, D-idose, D-altrose or D-allose. Compounds **3** and **4**, being enantiomers of **1** and **2**, respectively, resemble the corresponding L-hexoses. In this light, the inhibition profile of compounds **1**–**4** is understandable: compound **1** is a good inhibitor of β-glucosidase and inhibits β-galactosidase while the other inhibitors are weaker. The absence of a hydroxyl group at C2 is the explanation why mannosidase inhibition is negligible (Table 1).

Comparison of the K_i of compounds **1**–**4** versus β-glucosidase from almonds with literature values for isofagomine and some analogues (**39**–**46**, Fig. 4)[7f,14] shows that the introduction of the *gem*-difluoride at C4 has a minor influence on inhibition (Fig. 4). Compound **1** is 10–15 times weaker than isofagomine **43** and isogalactofagomine **39**, but is two-fold stronger than the 4-deoxyisofagomine **46**. This means there is some positive contribution to binding from a hydroxyl group regardless of configuration that cannot be emulated by the difluoride, but that the difluoride nevertheless does contribute to binding since it is better than deoxy.

It is also seen that compounds **2**–**4** are actually slightly more potent than the hydroxylated analogues **40**–**45**. This can be explained by the wrong configuration of **40**–**45**, which makes the removal of wrongly positioned OH advantageous at least when replaced with difluoride. Obviously the electron-withdrawing effect of *gem*-difluoromethylene group (CF_2) must be crucial for the binding as it decreases the pK_a of the amine in these compounds. By using NMR,[15] we determined the pK_a for **1** and **2** to 6.86 and 7.57, respectively. Comparing these values with the pK_a of hydroxylated isofagomines **39**, **43**, **40**, and **44** that are 8.4, 8.8, 9.2 and 9.4,[16,17] respectively, we see that the difference is 1.5–1.9 pH units, which is substantial. This means that at the test pH of 6.8, compounds **1** and **2** are not fully protonated, while the other inhibitors are. In any case, the data show that when modifying C4 the change in inhibition is not simply a product of changing pK_a: the pK_a values of **1**, **43**, **39**, and **46** are 6.86, 8.8, 8.4, and 9.0 while pK_i values are 5.9, 7.0, 7.0, and 5.6, respectively.

The pH dependency of the inhibition of β-glucosidase by **1** was determined and is shown in Chart 1. The data show a very sharp curve with a maximum of inhibition located at pH 6.8, which is identical to pK_a. In contrast to the *gem*-4,4-difluoromethylated



Scheme 2. Synthesis of 4,4-difluroroisofagomine analogues **3**–**4**, **7**–**8**, and **13**–**14** from compound **16**. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt; (b) NaH, BnBr, TBAI, THF; (c) i. O_3, CH_2Cl_2/MeOH (1:1), −78 °C; ii. $NaBH_4$, −78 °C to rt; (d) i. MsCl, Et_3N, DMAP, CH_2Cl_2; ii. $BnNH_2$, 80 °C; (e) i. BCl_3 (1 M) in heptane, CH_2Cl_2, 0 °C; ii. $NaIO_4$, H_2O, MeOH, rt; iii. $NaBH_4$; (f) 20% Pd(OH)/C, H_2, MeOH, rt; (g) i. MsCl, Et_3N, DMAP, CH_2Cl_2; ii. $H_2NCH_2CH_2OH$, 80 °C; (h) i. MsCl, Et_3N, DMAP, CH_2Cl_2; ii. *n*-$BuNH_2$, reflux; (i) i. 20% Pd(OH)/C, H_2, MeOH; ii. $NaIO_4$, H_2O, MeOH, rt; iii. $NaBH_4$; (j) BzCl, DMAP, Et_3N, CH_2Cl_2; (k) i. 10% Pd/C, H_2, MeOH; ii. $NaIO_4$, H_2O, MeOH, rt; iii. $NaBH_4$; (l) NH_3/MeOH.

nojirimicin derivatives that have the unprotonated form as the most active inhibitor form,[9] no such information can be extracted here. Both unprotonated and protonated forms may be active. The data are consistent either with protonated inhibitor binding to monoprotonated enzyme (the active form) or protonated inhibitor binding to unprotonated (inactive) enzyme.

From the pK_a values the stereochemical substituent constant of an axial fluorine in the γ position of the ring atom can be predicted, which is useful for empirical pK_a predictions.[16,17] From the pK_a of **1** and **2** we can calculate a constant of σ=1.2, which is a difference of 0.2 from the value of a fluorine atom in the equatorial position.[17]

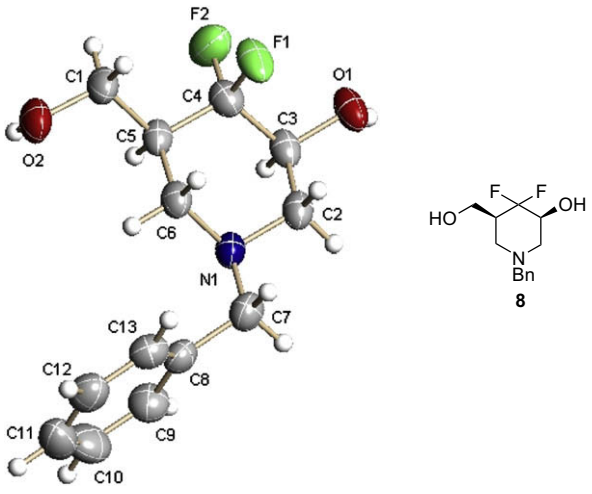


Figure 3. The X-ray crystallographic structure of compound **8**.

3. Conclusion

In summary, 4-deoxy-4,4-difluoroisofagomine analogues **1**–**14** were synthesized. The biological evaluation showed that (3*R*,5*R*)-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol **1** was a good inhibitor of β-glucosidase from almonds, while alkylated or stereoisomeric analogues were significantly weaker. This is however similar to the behavior of isofagomine. The work shows that when a hydroxyl group is unessential it can be replaced by the *gem*-difluoro with minor change or even increase in the inhibition. The pH dependence of enzyme activity and inhibition study shows that the strong electron-withdrawing effect of *gem*-difluoromethylene group indeed decreases the pK_a value of compound **1** significantly. There may be cases where such a modulation will be advantageous.

Table 1
Inhibition constants at 25 °C of 4,4-difluoroisofagomine analogues **1**–**14** at pH 6.8

Enzyme	K_i (μM)													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
β-Glucosidase[a]	1.2	4270	980	950	>200	>200	>200	>200	>1000	>1000	>1000	>1000	>1000	>1000
α-Glucosidase[b]	>1000	>1000	>1000	>1000	>200	>200	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
α-Glucosidase[c]	>1000	>1000	>1000	>1000	>200	>200	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
β-Galactosidase[d]	165	610	2480	250	>200	>200	>200	>200	>1000	>1000	>1000	ND	>1000	>1000
β-Galactosidase[e]	>1000	>1000	>1000	>1000	>200	>200	>200	>200	>1000	>1000	ND[i]	ND	>1000	ND
β-Galactosidase[f]	>1000	>1000	>1000	>1000	>200	>200	>200	>200	>1000	>1000	ND	ND	>1000	ND
α-Galactosidase[g]	>1000	>1000	>1000	>1000	>200	>200	>200	>200	>1000	>1000	ND	ND	>1000	ND
α-Mannosidase[h]	>1000	>1000	>1000	>1000	>200	>200	>200	>200	>1000	>1000	ND	ND	>1000	ND

[a] From almond.
[b] From baker yeast.
[c] From *B. stearothermophilus*.
[d] From bovine liver.
[e] From *S. fragilis*.
[f] From *A. oryzae*.
[g] From coffee beans.
[h] From Jack beans.
[i] Not determined.

4. Experimental section

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. All melting points are uncorrected.

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.

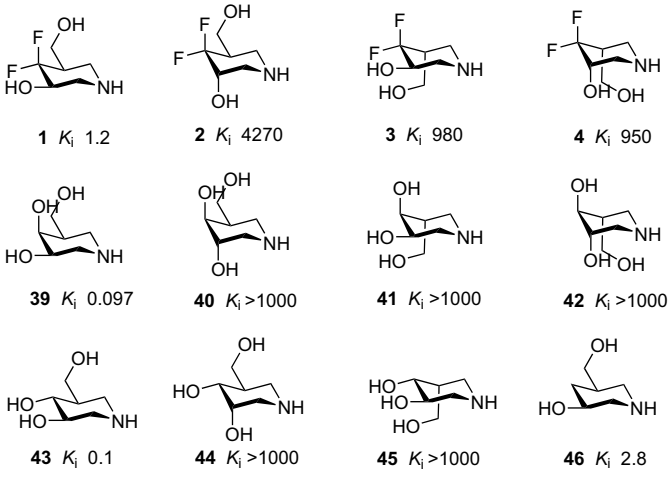


Figure 4. Comparison of the inhibition constants of 4-deoxy-4,4-difluoroisofagomine analogues **1**–**4** with their isofagomine analogues for β-glucosidase from almonds. Data for compounds **39**–**46** are taken from Refs. 7f and 14. K_i in μM.

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, 2, 5, 6, and 9, 10

*4.2.1. (R,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5,5-difluoroocta-2,7-dien-4-ol (**17**)*

A solution of **15** (1.00 g, 2.5 mmol) and $CeCl_3\cdot 7H_2O$ (1.86 g, 5.00 mmol) in methanol (27 mL) was cooled to 0 °C, and $NaBH_4$

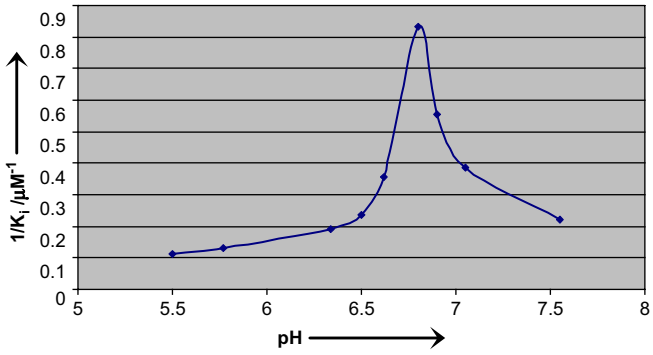


Chart 1. pH versus $1/K_i$ for **1** at 25 °C versus β-glucosidase from almonds.

(0.19 g, 5.00 mmol) was added in portions. The solution remained at the temperature for 10 min and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=15:1) to give compound **17** (1.00 g, 100%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.38 (m, 10H), 5.65–5.85 (m, 2H), 5.50–5.61 (m, 1H), 5.22–5.32 (m, 2H), 4.52–4.82 (m, 4H), 4.18–4.35 (m, 2H), 3.89–4.03 (m, 1H), 3.73–3.78 (m, 1H), 3.54–3.64 (m, 1H), 2.20 (br, 1H), 1.73–1.75 (d, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) −110.54 δ (ddd, J=252.9, 16.9, 10.4 Hz, 0.33F), −113.86 (dt, J=252.4, 17.8, 7.05 Hz, 0.33F), −109.28 (ddd, J=253.2, 20.3, 6.5 Hz, 0.67F), −116.46 (ddd, J=253.8, 16.9, 9.6 Hz, 0.67F); IR (thin film) ν_{max} 3424, 3033, 2867, 1497, 1454, 1092, 737, 698 cm^{-1}; MS (ESI) m/z 425 [$(M+Na)^+$]. Anal. Calcd for $C_{24}H_{28}F_2O_3$: C, 71.62; H, 7.01. Found: C, 71.53; H, 6.91.

4.2.2. ((2S,3R,E)-4,4-Difluoro-3-vinyloct-6-ene-1,2,5-triyl)tris(oxy)tris(methylene)tribenzene (**18**)

To a suspended solution of NaH (60% in oil, 186 mg, 4.47 mmol), Bu_4NI (83 mg, 0.22 mmol), and THF (10 mL) at 0 °C under nitrogen atmosphere, a solution of compound **17** (900 mg, 2.24 mmol) in THF (8 mL) was added dropwise. The mixture was stirred at rt for 30 min. BnBr (768 mg, 4.47 mmol) in THF (2 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 1.5 h and then quenched with saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (15 mL×3). The combined extracts was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate=30:1) to give compound **18** (1.08 g, 98%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (m, 15H), 5.87–5.40 (m, 2H), 5.27–5.08 (m, 1H), 4.72–4.51 (m, 5H), 4.31–4.25 (m, 1H), 4.16–3.88 (m, 2H), 3.77–3.73 (d, J=10.5 Hz, 1H), 3.61–3.53 (m, 1H), 3.42–3.17 (m, 1H), 1.82–1.75 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.94 (dt, J=256.6, 14.1 Hz, 0.57F), −113.03 (ddd, J=255.5, 17.8, 8.5 Hz, 0.57F), −109.80 (ddd, J=255.2, 25.9, 4.2 Hz, 0.44F), −115.77 (ddd, J=255.5, 18.9, 5.6 Hz, 0.44F); IR(thin film) $\nu\nu_{max}$ 3066, 3032, 2865, 1498, 1455, 1207, 1099, 736, 697 cm^{-1}; MS (ESI) m/z 515.3 [$(M+Na)^+$]. Anal. Calcd for $C_{31}H_{34}F_2O_3$: C, 75.59; H, 6.96. Found: C, 75.52; H, 6.94.

4.2.3. (2R,4R)-2-(Benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3,3-difluoropentane-1,5-diol (**19**) and (2S,4R)-2-(benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3,3-difluoropentane-1,5-diol (**20**)

A solution of compound **18** (1.05 g, 2.13 mmol) in methanol/dichloromethane (25 mL, 1:1) was cooled to −78 °C and treated with ozone until the color of solution became blue. The cooling bath was removed and $NaBH_4$ (824 mg, 21.8 mmol) was added in portions. The mixture was stirred for 1 h and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1) to give compounds **19** (445 mg, 43%) and **20** (466 mg, 45%) as clear oil. Data of compound **19**: $[\alpha]_D^{28}$ +3.1 (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.36 (m, 15H), 4.76–4.55 (m, 6H), 4.12–4.08 (m, 1H), 3.99–3.72 (m, 7H), 2.80–2.64 (m, 1H), 2.59 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.78, 137.72, 136.99, 128.53, 128.34, 128.16, 127.85, 127.74, 127.60, 123.76 (t, J=250.3 Hz), 79.80 (t, J=27.1 Hz), 75.86 (d, J=5.4 Hz), 73.93, 73.41, 72.32, 70.37, 60.26, 58.05 (t, J=5.4 Hz), 46.84 (t, J=20.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.52 (ddd, J=264.2, 22.8, 9.0 Hz, 1F), −107.54 (dt, J=264.8, 13.8 Hz, 1F); IR (thin film) ν_{max} 3422, 3032, 2877, 1497, 1455, 1104, 736, 698 cm^{-1}; MS (ESI) m/z 509.3 [$(M+Na)^+$]; HRMS calcd for $C_{28}H_{32}F_2O_5Na$: 509.2118580. Found: 509.2110016. Data of compound **20**: $[\alpha]_D^{28}$ −11.8 (c 1.1, $CHCl_3$); ^1H NMR(300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 15H), 4.72–4.53 (m, 6H), 4.16–4.11 (m, 1H), 4.03–3.69 (m, 6H), 2.87–2.71 (m, 1H), 2.52 (br, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.73, 137.35, 128.41, 128.33, 128.11, 127.96, 127.94, 127.83, 127.74, 127.66, 127.57, 123.92 (t, J=250.1 Hz), 80.26 (t, J=26.9 Hz), 76.20 (t, J=3.7 Hz), 73.97, 73.43 (d, J=6.8 Hz), 72.30, 69.97, 60.21 (t, J=4.2 Hz), 57.91 (t, 5.8 Hz), 46.09 (t, J=20.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.894 (t, J=13.5 Hz, 2F); IR (thin film) ν_{max} 3431, 3032, 2876, 1497, 1455, 1099, 737, 698 cm^{-1}; MS (ESI) m/z 487.3 [$(M+H)^+$], 509.3 [$(M+Na)^+$]; HRMS calcd for $C_{28}H_{32}F_2O_5Na$: 509.2101. Found: 509.21100.

4.2.4. (3R,5R)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)-ethyl)-4,4-difluoropiperidine (**21**)

A solution of compound **19** (400 mg, 0.82 mmol) in dry dichloromethane (12 mL) was cooled to 0 °C. NEt_3 (0.62 mL, 4.44 mmol), DMAP (17 mg, 0.14 mmol), and MsCl (0.3 mL, 3.94 mmol) were added. The reaction 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 $BnNH_2$ (distilled before use, 1.2 mL) and heated for 18 h at 80 °C. Then the mixture was directly purified by silica gel column chromatography (petroleum ether/ethyl acetate=15:1) to give compound **21** (239 mg, 52% from compound **19**) as a clear oil: $[\alpha]_D^{27}$ +34.0 (c 1.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.90–4.51 (m, 6H), 4.15–4.11 (m, 1H), 3.84–3.70 (m, 2H), 3.65–3.53 (m, 3H), 3.03–2.99 (d, J=10.8 Hz, 2H), 2.62–2.48 (m, 1H), 2.32–2.16 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.27, 138.12, 137.60, 137.45, 128.78, 128.71, 128.41, 128.30, 128.27, 128.23, 128.19, 128.12, 127.76, 127.73, 127.48, 127.44, 127.20, 121.88 (t, J=250.7 Hz), 75.83 (t, J=19.5 Hz), 74.72, 73.42 (dd, J=13.2, 11.1 Hz), 73.17, 72.37, 70.75, 61.65, 50.31 (d, J=7.9 Hz), 50.62 (d, J=7.4 Hz), 44.97 (t, J=20.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.83 (d, J=240.8 Hz, 1F), −128.50 (d, J=239.7 Hz, 1F); IR (thin film) ν_{max} 3031, 2871, 1496, 1455, 1105, 1085, 737, 698 cm^{-1}; MS (ESI) m/z 558.4 [$(M+H)^+$], 580.4 [$(M+Na)^+$]; HRMS calcd for $C_{35}H_{38}F_2NO_3$: 558.2811. Found: 558.28143.

4.2.5. (3S,5R)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidine (**22**)

Using the same conditions as described for compound **21**, compound **22** (481 mg, 84% for two steps) was prepared as a clear oil from compound **20** (500 mg, 1.03 mmol): $[\alpha]_D^{27}$ +18.6 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.32 (m, 20H), 4.83–4.65 (m, 4H), 4.61 (s, 2H), 4.16–4.11 (m, 1H), 3.92–3.51 (m, 6H), 3.11–2.94 (m, 3H), 2.42–2.36 (t, J=10.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.34, 138.18, 137.66, 137.46, 128.95, 128.73, 128.22, 128.18, 128.13, 128.11, 128.07, 127.73, 127.58, 127.43, 127.37, 127.35, 127.12, 126.86, 121.95 (t, J=246.9 Hz), 75.51, 75.44 (dd, J=29.9, 21.3 Hz), 73.55, 73.13, 72.36 (d, J=5.2 Hz), 71.15, 61.67, 53.32, 51.03, 41.64 (t, J=19.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.08 (d, J=247.0 Hz, 1F), −113.53 (dd, J=245.3, 25.4 Hz, 1F); IR (thin film) ν_{max} 3031, 2818, 1496, 1454, 1101, 736, 697 cm^{-1}; MS (ESI) m/z 558.4 [$(M+H)^+$]; HRMS calcd for $C_{35}H_{38}F_2NO_3$: 558.2818. Found: 558.28143.

4.2.6. (3R,5R)-1-Benzyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**5**)

A solution of compound **21** (350 mg, 0.63 mmol) in dry dichloromethane (10 mL) was cooled to 0 °C under nitrogen atmosphere and BCl_3 (1 M solution in heptane, 6.3 mL, 6.30 mmol) was added. The reaction mixture remained at the temperature for 3 h and then quenched with methanol (4 mL). The solvent was removed under reduced pressure. The residue (203 mg) was dissolved in methanol (35 mL) and the saturated aqueous $NaIO_4$ (5.25 mL) was added dropwise. The reaction mixture was stirred strongly for 15 min and then cooled to 0 °C. $NaBH_4$ (343 mg, 9.10 mmol) was added in

portions. The mixture was stirred for 30 min at rt and quenched with saturated aqueous NH_4Cl. Methanol was removed under reduced pressure. The resulting mixture was extracted with ethyl acetate. The combined organic phase was dried over $NaSO_4$ and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1) to give compound **5** (93 mg, 58% from compound **21**) as a white solid: mp 123–125 °C; $[\alpha]_D^{26}$ +26.7 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.35–7.22 (m, 5H), 3.96–3.91 (dd, *J*=11.1, 3.6 Hz, 1H), 3.89–3.75 (m, 1H), 3.65–3.49 (m, 3H), 3.11–3.07 (m, 1H), 2.98–2.91 (m, 1H), 2.28–2.05 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.65, 130.35, 129.44, 128.53, 122.54 (t, *J*=246.3 Hz), 70.09 (t, *J*=21.3 Hz), 62.87, 58.29 (d, *J*=2.9 Hz), 57.25 (d, *J*=7.5 Hz), 54.28 (d, *J*=8.1 Hz), 46.17 (t, *J*=20.1 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −117.47 (d, *J*=222.2 Hz, 1F), −137.22 (d, *J*=176.3 Hz, 1F); IR (KBr) ν_{max} 3512, 2898, 1500, 1394, 1228, 1089, 760, 709 cm^{-1}; MS (ESI) *m*/*z* 258.2 [(M+H)$^+$], 280.2 [(M+Na)$^+$]; HRMS calcd for $C_{13}H_{18}F_2NO_2$: 258.13029. Found: 258.13001.

4.2.7. (3S,5R)-1-Benzyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**6**)

Using the same conditions as described for compound **5**, compound **6** (113 mg, 51% for there steps) was prepared as a white solid from compound **22** (480 mg, 0.86 mmol): mp 113 °C; $[\alpha]_D^{27}$ +34.6 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.37–7.22 (m, 5H), 3.88–3.83 (dd, *J*=10.5, 3.6 Hz, 1H), 3.78–3.69 (m, 1H), 3.61–3.54 (m, 3H), 2.93–2.90 (d, *J*=10.2 Hz, 1H), 2.76–2.72 (d, *J*=11.1 Hz, 1H), 2.52–2.38 (m, 2H), 2.31–2.28 (m, 1H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 137.35, 128.92, 127.97, 126.99, 121.38 (t, *J*=247.8 Hz), 67.51 (t, *J*=25.9 Hz), 61.52, 57.76, 55.77, 52.41, 42.21 (t, *J*=19.3 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −119.96 (d, *J*=255.8 Hz, 1F), −123.86 (d, *J*=249.9 Hz, 1F); IR (KBr) ν_{max} 3290, 2839, 1473, 1168, 1085, 760, 703 cm^{-1}; MS (ESI) *m*/*z* 258.2 [(M+H)$^+$]; HRMS calcd for $C_{13}H_{18}F_2NO_2$:258.13059. Found: 258.13001.

4.2.8. (3R,5R)-4,4-Difluoro-5-(hydroxymethyl)piperidin-3-ol (**1**)

A solution of compound **5** (60 mg, 0.23 mmol) in methanol (5.2 mL) was hydrogenated in the presence of 20% $Pd(OH)_2$/C (30 mg) at atmospheric pressure and at rt. After stirring for 3 h, the reaction mixture was filtrated and the solvent was evaporated. The residue was purified by silica gel column chromatography (dichloromethane/methanol=5:1) to give compound **1** (35 mg, 88%) as a white solid: mp 130–132 °C; $[\alpha]_D^{24}$ 30.6 (*c* 0.7, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.94–3.89 (dd, *J*=11.4, 4.2 Hz, 1H), 3.76–3.62 (m, 1H), 3.59–3.53 (dd, *J*=11.4, 8.7 Hz, 1H), 3.20–3.14 (dt, *J*=13.2, 3.6 Hz, 1H), 3.09–3.02 (m, 1H), 2.67–2.52 (m, 2H), 2.14–1.95 (m, 1H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 122.68 (t, *J*=247.3 Hz), 70.56 (t, *J*=21.1 Hz), 58.40 (t, *J*=4.7 Hz), 50.32 (d, *J*=5.6 Hz), 47.74 (t, *J*=19.5 Hz), 46.92 (d, *J*=6.1 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −112.45 (d, *J*=237.2 Hz, 1F), −132.94 (br, 1F); IR (KBr) ν_{max} 3431, 3265, 2941, 1461, 1217, 1107 cm^{-1}; MS (ESI) *m*/*z* 168.1 [(M+H)$^+$]; HRMS calcd for $C_6H_{12}F_2NO_2$: 168.08295. Found: 168.08306.

4.2.9. (3S,5R)-4,4-Difluoro-5-(hydroxymethyl)piperidin-3-ol (**2**)

Using the same conditions as described for compound **1**, compound **2** (40 mg, 80%) was prepared as a white solid from compound **22** (78 mg, 0.3 mmol): mp 120 °C; $[\alpha]_D^{20}$ +65.5 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.93–3.88 (dd, *J*=11.1, 3.9 Hz, 1H), 3.73–3.66 (m, 1H), 3.56–3.49 (dd, *J*=11.4, 8.1 Hz, 1H), 3.22–3.17 (m, 1H), 3.01–2.97 (d, *J*=14.4 Hz, 1H), 2.89–2.83 (dt, *J*=13.8, 1.8 Hz, 1H), 2.58–2.50 (t, *J*=10.8 Hz, 1H), 2.48–2.29 (m, 1H); ^{13}C NMR (75.4 MHz, MeOH-d_4) δ 123.09 (t, *J*=242.9 Hz), 68.09 (dd, *J*=31.6, 21.9 Hz), 58.71 (t, *J*=4.0 Hz), 50.37 (d, *J*=5.2 Hz), 46.70 (d, *J*=6.3 Hz), 43.46 (t, *J*=18.4 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −112.23 (d, *J*=241.4 Hz, 1F), −121.33 (d, *J*=242.8 Hz, 1F); IR (KBr) ν_{max} 3292, 2935, 2745, 1459, 1158, 1076 cm^{-1}; MS (ESI) *m*/*z* 168.1 [(M+H)$^+$]; HRMS calcd for $C_6H_{12}F_2NO_2$: 168.0832. Found: 168.08306.

4.2.10. (3R,5R)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-1-butyl-4,4-difluoropiperidine (**23**)

A solution of compound **19** (200 mg, 0.41 mmol) in dry dichloromethane (6 mL) was cooled to 0 °C. NEt_3 (0.31 mL, 2.22 mmol), DMAP (9 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 residue was dissolved in *n*-$BuNH_2$ (distilled before use, 4 mL) and refluxed for 18 h. Then the mixture was directly purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1) to give compound **23** (111 mg, 52% from compound **19**) as a pale yellow oil: $[\alpha]_D^{27}$ +41.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 15H), 4.89–4.63 (m, 4H), 4.61–4.52 (dd, *J*=15.3, 12.3 Hz, 2H), 4.10–4.06 (m, 1H), 3.82–3.77 (dd, *J*=10.8, 3 Hz, 2H), 3.76–3.63 (m, 1H), 3.59–3.53 (dd, *J*=11.1, 6.9 Hz, 1H), 2.99–2.93 (m, 1H), 2.52–2.31 (m, 3H), 2.21–2.13 (td, *J*=11.1, 1.5 Hz, 1H), 2.10–2.02 (t, *J*=11.4 Hz, 1H), 1.45–1.35 (m, 2H), 1.32–1.23 (m, 2H), 0.93–0.89 (t, *J*=6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.32, 138.22, 137.71, 128.40, 128.30, 128.26, 127.87, 127.55, 127.54, 127.50, 121.95 (t, *J*=250.7 Hz), 75.79 (t, *J*=20.1 Hz), 74.77, 73.59 (d, *J*=2.1 Hz), 73.30, 72.51, 71.03 (d, *J*=3.7 Hz), 57.26, 54.81 (d, *J*=7.9 Hz), 50.65 (d, *J*=7.4 Hz), 44.97 (t, *J*=19.5 Hz), 28.99, 20.50, 13.95; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.75 (d, *J*=238.0 Hz, 1F), −128.43 (d, *J*=232.9 Hz, 1F); IR (thin film) ν_{max} 3065, 3032, 2932, 2870, 1497, 1455, 1095, 735, 697 cm^{-1}; MS (ESI) *m*/*z* 524.5 [(M+H)$^+$], 546.5 [(M+Na)$^+$]; HRMS calcd for $C_{32}H_{39}F_2NO_3Na$: 546.28060. Found: 546.27902.

4.2.11. (3S,5R)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-1-butyl-4,4-difluoropiperidine (**24**)

Using the same conditions as described for compound **23**, compound **24** (164 mg, 68%) was prepared as a clear oil from compound **20** (225 mg, 0.46 mmol): $[\alpha]_D^{24}$ +18.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 15H), 4.90–4.86 (d, *J*=12.9 Hz, 1H), 4.75 (s, 2H), 4.73–4.69 (d, *J*=12.6 Hz, 1H), 4.62 (s, 2H), 4.13–4.09 (dd, *J*=6.9, 3.6 Hz, 1H), 3.88–3.84 (dd, *J*=10.5, 2.4 Hz, 1H), 3.70–3.60 (m, 2H), 3.04–2.92 (m, 3H), 2.51–2.18 (m, 4H), 1.56–1.51 (m, 2H), 1.48–1.31 (m, 2H), 1.01–0.96 (t, *J*=7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.31, 128.19, 137.60, 128.25, 128.15, 128.08, 127.85, 127.75, 127.67, 127.41, 122.05 (dd, *J*=254.4, 247.5 Hz), 75.40, 73.99 (dd, *J*=29.9, 21.9 Hz), 73.17, 72.65, 72.40, 71.26, 57.42, 54.22 (d, *J*=5.7 Hz), 50.96 (d, *J*=5.8 Hz), 41.39 (t, *J*=19.0 Hz), 28.62, 20.53, 13.89; ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.53 (d, *J*=243.1 Hz), −113.42 (dd, *J*=243.9, 27.4 Hz); IR (thin film) ν_{max} 3032, 2932, 2872, 2816, 1497, 1455, 1096, 736, 697 cm^{-1}; MS (ESI) *m*/*z* 524.5 [(M+H)$^+$]; HRMS calcd for $C_{32}H_{40}F_2NO_3$: 524.29703. Found: 524.29708.

4.2.12. (3R,5R)-1-Butyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**9**)

A solution of compound **23** (174 mg, 0.33 mmol) in methanol/ethyl acetate (7:1, 8 mL) was hydrogenated in the presence of 10% Pd/C (116 mg) at atmospheric pressure and at rt. After stirring for 3 days, the reaction mixture was filtrated and concentrated. The residue was dissolved in methanol (19 mL) and the saturated aqueous $NaIO_4$ (2.1 mL) was added dropwise. The reaction mixture was stirred strongly for 15 min. $NaBH_4$ (158 mg, 4.18 mmol) was added in portions. The reaction mixture was stirred for 30 min at rt and then quenched with saturated aqueous NH_4Cl. Methanol was removed as possibly under reduced pressure. The resulting mixture was extracted with ethyl acetate. The combined organic phase was dried over $NaSO_4$ and concentrated. The crude product was purified by silica gel column chromatography to give compound **9** (30 mg, 40% for three steps from compound **23**) as a clear oil: $[\alpha]_D^{25}$ +9.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02–3.82 (m, 3H), 2.79–2.62 (m, 4H), 2.43–2.38 (t,

J=7.2 Hz, 2H), 2.25–2.15 (m, 1H), 1.54–1.43 (m, 2H), 1.39–1.25 (m, 2H), 0.95–0.90 (t, J=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −104.88 (br, 1F), −117.00 (br, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.99 (t, J=244.8 Hz), 68.29 (dd, J=27.6, 20.5 Hz), 60.75, 57.25, 57.12, 54.00, 43.00 (t, J=19.8 Hz), 28.82, 20.41, 13.86; IR (thin film) ν_{max} 3354, 2960, 2874, 1473, 1221, 1100 cm^{-1}; MS (ESI) m/z 224.2 [(M+H)$^+$]; HRMS calcd for $C_{10}H_{20}O_2NF_2$: 224.1473. Found: 224.14566.

4.2.13. (3S,5R)-1-Butyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**10**)

Using the same conditions as described for compound **9**, compound **10** (39 mg, 62% for three steps) was prepared as a pale yellow oil from compound **24** (145 mg, 0.28 mmol): $[\alpha]_D^{25}$ +26.1 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97–3.92 (dd, J=11.1, 3.3 Hz, 2H), 3.75–3.69 (dd, J=10.8, 4.8 Hz, 1H), 3.43 (br, 2H), 2.90–2.88 (d, J=6.0 Hz, 1H), 2.65 (s, 2H), 2.48–2.34 (m, 4H), 1.51–1.41 (m, 2H), 1.36–1.24 (m, 2H), 0.92–0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 121.63 (t, J=248.6 Hz), 67.79 (t, J=25.4 Hz), 59.93, 57.00, 56.21, 53.46, 41.65 (t, J=19.9 Hz), 28.87, 20.45, 13.89; ^{19}F NMR (282 MHz, $CDCl_3$) δ −114.23 (br, 1F), −120.52 (br, 1F); IR (thin film) ν_{max} 3253, 2954, 2899, 1459, 1115, 1080 cm^{-1}; MS (ESI) m/z 224.2 [(M+H)$^+$]; HRMS calcd for $C_{10}H_{20}O_2NF_2$: 224.1473. Found: 224.14566.

4.3. General procedure of the preparation of iminosugars 3, 4, 7, 8, 11, 12, and 13, 14

4.3.1. (S,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5,5-difluoroocta-2,7-dien-4-ol (**25**)

Using the same conditions as described for compound **17**, compound **25** (610 mg, quant.) was prepared as a clear oil from compound **16** (610 mg, 1.52 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.38 (m, 10H), 5.77–6.01 (m, 2H), 5.51–5.68 (m, 1H), 5.11–5.34 (m, 2H), 4.65–4.75 (dd, J=11.4, 21.3 Hz, 2H), 4.45–4.57 (dd, J=12, 20.7 Hz, 2H), 4.11–4.32 (m, 2H), 3.43–3.65 (m, 2H), 2.93–3.20 (m, 1H), 2.24 (br, 1H), 1.74–1.77 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.38 (ddd, J=249.9, 11.8, 16.1 Hz, 0.5F), −113.74 (dt, J=250.4, 14.7 Hz, 0.5F), −111.59 (ddd, J=252.4, 25.1, 2.82 Hz, 0.5F), −117.06 (ddd, J=252.7, 21.2, 7.1 Hz, 0.5F); IR (thin film) ν_{max} 3424, 3033, 2918, 2866, 1498, 1454, 1205, 1093, 736, 698 cm^{-1}; MS (ESI) m/z 420 [(M+NH$_4$)$^+$]. Anal. Calcd for $C_{24}H_{28}F_2O_3$: C, 71.62; H, 7.01. Found: C, 71.74; H, 7.01.

4.3.2. ((2S,3S,E)-4,4-Difluoro-3-vinyloct-6-ene-1,2,5-triyl)tris(oxy)tris(methylene)tribenzene (**26**)

Using the same conditions as described for compound **18**, compound **26** (3.85 g, 98%) was prepared as a clear oil from compound **25** (3.2 g, 1.52 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 15H), 6.00–5.69 (m, 2H), 5.63–5.46 (m, 1H), 5.30–4.28 (m, 6H), 4.26–4.06 (dt, J=46.2, 6.6 Hz, 1H), 4.01–3.88 (m, 1H), 3.59–3.53 (m, 1H), 3.47–3.42 (m, 1H), 3.32–2.95 (m, 1H), 1.86–1.79 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.77 (m, 1F), −112.00 (dd, J=254.9, 28.5 Hz, 0.5F), −115.68 (ddd, J=253.2, 20.6, 2.3 Hz, 0.5F); IR (thin film) ν_{max} 3032, 2867, 1498, 1454, 1207, 1101, 736, 697 cm^{-1}; MS (ESI) m/z 515.3 [(M+Na)$^+$]. Anal. Calcd for $C_{31}H_{34}F_2O_3$: C, 75.59; H, 6.96. Found: C, 75.34; H, 7.14.

4.3.3. (2R,4S)-2-(Benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3,3-difluoropentane-1,5-diol (**27**) and (2S,4S)-2-(benzyloxy)-4-((S)-1,2-bis(benzyloxy)ethyl)-3,3-difluoropentane-1,5-diol (**28**)

Using the same conditions as described for compounds **19** and **20**, compounds **27** (330 mg, 42%) and **28** (315 mg, 40%) were prepared as clear oils from compound **26** (790 mg, 1.6 mmol). Compound **27**: $[\alpha]_D^{27}$ +5.3 (c 0.7, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 15H), 4.78–4.49 (m, 6H), 4.26–4.22 (t, J=5.4 Hz, 1H), 3.99–3.97 (d, 2H), 3.93–3.76 (m, 3H), 3.68–3.59 (dd, J=10.8, 16.2 Hz, 2H), 2.61 (br, 1H), 2.55–2.43 (t, J=17.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.74, 137.61, 137.32, 128.47, 128.39, 128.36, 128.00, 127.97, 127.88, 127.81, 127.75, 127.60, 124.01 (t, J=249.8 Hz), 79.85 (t, J=25.0 Hz), 75.59 (t, J=3.2 Hz), 74.07, 73.27, 73.09, 70.86, 60.47 (t, J=4.5 Hz), 57.86 (t, J=5.2 Hz), 45.68 (t, J=20.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −105.25 (ddd, J=263.4, 18.0, 12.7 Hz, 1F), −108.68 (ddd, J=263.4, 16.1, 9.9 Hz, 1F); IR (thin film) ν_{max} 3425, 3033, 2934, 2873, 1498, 1455, 1115, 1029, 739, 698 cm^{-1}; MS (ESI) m/z 509.3 [(M+Na)$^+$]; HRMS calcd for $C_{28}H_{32}F_2O_5Na$: 509.21315. Found: 509.21100. Compound **28**: $[\alpha]_D^{25}$ −3.6 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.32 (m, 15H), 4.79–4.50 (m, 6H), 4.26–4.22 (td, J=5.4, 1.8 Hz, 1H), 3.99–3.81 (m, 5H), 3.63–3.61 (d, J=6.0 Hz, 2H), 2.56–2.44 (m, 1H), 2.24 (br, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.80, 137.64, 137.08, 128.50, 128.36, 128.35, 128.09, 127.98, 127.84, 127.77, 127.70, 127.55, 123.71 (t, J=250.1 Hz), 79.26 (t, J=27.4 Hz), 75.43 (t, J=2.7 Hz), 73.56, 73.29 (d, J=0.8 Hz), 73.21, 71.11, 60.21 (t, J=4.1 Hz), 58.05 (dd, J=2.7, 7.6 Hz), 45.78 (t, J=21.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −105.97 (ddd, J=263.1, 16.6, 9.0 Hz, 1F), −109.13 (ddd, J=264.5, 26.2, 5.4 Hz, 1F); IR (thin film) ν_{max} 3439, 3033, 2871, 1498, 1455, 1207, 1116, 738, 699 cm^{-1}; MS (ESI) m/z 509.3 [(M+Na)$^+$]; HRMS calcd for $C_{28}H_{32}F_2O_5Na$: 509.2121. Found: 509.21100.

4.3.4. (3R,5S)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidine (**29**)

Using the same conditions as described for compound **21**, compound **29** (481 mg, 84% for two steps) was prepared as a pale yellow oil from compound **27** (500 mg, 1.03 mmol): $[\alpha]_D^{29}$ −17.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 20H), 4.76–4.54 (m, 6H), 4.12–4.07 (dd, J=10.1, 4.5 Hz, 1H), 3.78–3.49 (m, 5H), 3.14–3.10 (d, J=11.4 Hz, 1H), 2.99–2.94 (d, J=12.9 Hz, 1H), 2.90–2.76 (m, 1H), 2.53–2.45 (t, J=10.8 Hz, 1H), 2.36–2.31 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.49, 138.23, 137.79, 129.03, 128.28, 128.20, 127.77, 127.61, 127.54, 127.47, 127.43, 127.17, 121.93 (t, J=247.3 Hz), 74.83, 74.49 (d, J=10.4 Hz), 74.21, 73.25, 72.25, 71.94, 61.74, 53.11, 51.25, 40.83 (t, J=18.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.67 (d, J=244.2 Hz), −115.97 (dd, J=243.4, 24.5 Hz); IR (thin film) ν_{max} 3031, 2919, 2864, 2265, 1687, 1496, 1455, 1103, 736, 697 cm^{-1}; MS (ESI) m/z 558.3 [(M+H)$^+$]; HRMS calcd for $C_{35}H_{38}F_2NO_3$: 558.2815. Found: 558.28143.

4.3.5. (3S,5S)-1-Benzyl-3-(benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidine (**30**)

Using the same conditions as described for compound **21**, compound **30** (50 mg, 89% for two steps) was prepared as a pale yellow oil from compound **28** (50 mg, 0.1 mmol): $[\alpha]_D^{26}$ −25.4 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.37 (m, 20H), 4.96–4.61 (m, 6H), 4.23–4.18 (dd, J=9.6, 4.8 Hz, 1H), 3.91–3.67 (m, 5H), 3.20–3.10 (m, 2H), 2.61–2.39 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.10, 138.12, 137.60, 128.73, 128.67, 128.22, 128.19, 128.12, 128.07, 127.80, 127.66, 127.60, 127.44, 127.08, 126.60, 121.93 (t, J=250.3 Hz), 75.83 (t, J=19.6 Hz), 73.78, 73.24, 73.05, 70.83, 61.69, 56.75, 54.29 (d, J=7.46 Hz), 51.16 (d, J=8.0 Hz), 43.66 (t, J=19.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.96 (d, J=230.4 Hz, 1F), −129.97 (d, J=212.6 Hz, 1F); IR (thin film) ν_{max} 3035, 2926, 2872, 1674, 1498, 1456, 1201, 1136, 738, 699 cm^{-1}; MS (ESI) m/z 558.3 [(M+H)$^+$]; HRMS calcd for $C_{35}H_{38}F_2NO_3$: 558.2815. Found: 558.28143.

4.3.6. (3R,5S)-1-Benzyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**7**)

Using the same conditions as described for compound **5**, compound **7** (78 mg, 77% for three steps) was prepared as a white solid from compound **29** (242 mg, 0.43 mmol): mp 114 °C; $[\alpha]_D^{29}$ −35.2 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.19 (m, 5H), 3.87–3.82 (dd, J=11.4, 3.9 Hz, 2H), 3.69–3.64 (dd, J=11.4, 5.1 Hz, 1H), 3.58–3.46 (dd, J=23.1, 13.2 Hz, 2H), 2.99–2.83 (m, 3H), 2.61 (s, 2H),

2.34 (s, 2H); ^{13}C NMR (75.4 MHz, CDCl3) δ 138.65, 129.01, 128.57, 127.69, 121.52 (t, J=248.7 Hz), 67.73 (t, J=25.4 Hz), 61.70, 59.82, 55.77, 53.07, 41.60 (t, J=18.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −114.30 (br, 1F), −119.27 (br, 1F); IR (KBr) ν_{max} 3286, 2962, 2840, 1499, 1473, 1168, 1085, 760, 703 cm^{-1}; MS (ESI) m/z 258.2 [(M+H)$^+$]; HRMS calcd for $C_{13}H_{18}F_2NO_2$: 258.1301. Found: 258.13001.

4.3.7. (3S,5S)-1-Benzyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**8**)

Using the same conditions as described for compound **5**, compound **8** (97 mg, 47% for three steps) was prepared as a white solid from compound **30** (518 mg, 0.93 mmol): mp 123 °C; $[\alpha]_D^{29}$ −27.1 (c 0.5, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.34–7.23 (m, 5H), 3.95–3.90 (dd, J=11.1, 3.3 Hz, 1H), 3.88–3.74 (m, 1H), 3.65–3.55 (dd, J=16.8, 12.9 Hz, 2H), 3.55–3.48 (dd, J=11.1, 8.4 Hz, 1H), 3.10–3.07 (d, J=7.8 Hz, 1H), 2.96–2.92 (m, 1H), 2.27–2.05 (m, 3H); ^{13}C NMR (75.4 MHz, MeOH-d_4) δ 138.69, 130.33, 129.40, 128.49, 122.50 (t, J=247.5 Hz), 70.11 (t, J=20.7 Hz), 62.88 (d, J=1.1 Hz), 58.27 (d, J=3.5 Hz), 57.28 (d, J=7.5 Hz), 54.28 (d, J=8.1 Hz), 46.21 (t, J=19.6 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −117.78 (d, J=272.4 Hz, 1F), −137.52 (d, J=197.4 Hz, 1F); IR (KBr) ν_{max} 3512, 2929, 2898, 2843, 1500, 1394, 1228, 1201, 760, 709 cm^{-1}; MS (ESI) m/z 258.2 [(M+H)$^+$]; HRMS calcd for $C_{13}H_{18}F_2NO_2$: 258.1301. Found: 258.13001.

4.3.8. (3R,5S)-4,4-Difluoro-5-(hydroxymethyl)piperidin-3-ol (**3**)

Using the same conditions as described for compound **1**, compound **3** (26 mg, 84%) was prepared as a white solid from compound **7** (48 mg, 0.19 mmol): mp 104 °C; $[\alpha]_D^{20}$ −66.4 (c 0.5, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.92–3.87 (dd, J=11.1, 3.9 Hz, 1H), 3.70–3.65 (m, 1H), 3.55–3.49 (dd, J=11.1, 8.4 Hz, 1H), 3.20–3.16 (m, 1H), 2.99–2.81 (dd, J=39.3, 14.4 Hz, 2H), 2.55–2.48 (t, J=10.2 Hz, 1H), 2.45–2.27 (m, 1H); ^{13}C NMR (75.4 MHz, MeOH-d_4) δ 123.07 (dd, J=251.5, 243.5 Hz), 68.15 (dd, J=31.6, 21.3 Hz), 58.72 (t, J=4.6 Hz), 50.42 (d, J=5.1 Hz), 46.76 (d, J=6.3 Hz), 43.60 (t, J=19.5 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −112.79 (d, J=241.4 Hz, 1F), −122.13 (d, J=240.3 Hz, 1F); IR (KBr) ν_{max} 3314, 2941, 1457, 1364, 1157, 1072 cm^{-1}; MS (ESI) m/z 168.1 [(M+H)$^+$]; HRMS calcd for $C_6H_{12}F_2NO_2$: 168.0836. Found: 168.08306.

4.3.9. (3S,5S)-4,4-Difluoro-5-(hydroxymethyl)piperidin-3-ol (**4**)

Using the same conditions as described for compound **1**, compound **4** (36 mg, 79%) was prepared as a white solid from compound **8** (70 mg, 0.27 mmol): mp 138 °C; $[\alpha]_D^{27}$ −29.0 (c 1.0, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.94–3.89 (dd, J=11.1, 3.3 Hz, 1H), 3.75–3.62 (m, 1H), 3.59–3.53 (dd, J=11.4, 8.7 Hz, 1H), 3.20–3.13 (dt, J=13.2, 3.3 Hz, 1H), 3.09–3.02 (dt, J=12.9, 4.2 Hz, 1H), 2.67–2.52 (m, 2H), 2.14–1.95 (m, 1H); ^{13}C NMR (75.4 MHz, MeOH-d_4) δ 122.67 (t, J=246.9 Hz), 70.57 (t, J=21.3 Hz), 58.421 (t, J=4.7 Hz), 50.34 (d, J=5.4 Hz), 47.75 (t, J=19.2 Hz), 46.92 (d, J=6.3 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −113.98 (d, J=244.5 Hz, 1F), −134.58 (br, 1F); IR (KBr) ν_{max} 3435, 3269, 2941, 1462, 1374, 1217 cm^{-1}; MS (ESI) m/z 168.1 [(M+H)$^+$]; HRMS calcd for $C_6H_{12}F_2NO_2$: 168.0838. Found: 168.08306.

4.3.10. (3R,5S)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-1-butyl-4,4-difluoropiperidine (**31**)

Using the same conditions as described for compound **23**, compound **31** (139 mg, 65% for two steps) was prepared as a pale yellow oil from compound **27** (200 mg, 0.41 mmol): $[\alpha]_D^{28}$ −4.8 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.31 (m, 15H), 4.85–4.59 (m, 6H), 4.13–4.08 (dd, J=10.2, 4.5 Hz, 1H), 3.73–3.58 (m, 3H), 3.07–2.95 (q, J=11.7 Hz, 2H), 2.85–2.67 (m, 1H), 2.49–2.27 (m, 4H), 1.54–1.43 (m, 2H), 1.40–1.28 (m, 2H), 0.97–0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.48, 138.16, 137.70, 128.30, 128.24, 128.16, 127.90, 127.76, 127.72, 127.50, 127.43, 127.42, 122.16 (t, J=247.2 Hz), 74.08, 73.96 (dd, J=32.0, 20.4 Hz), 73.23 (2C), 72.56 (d, J=2.2 Hz), 72.03, 57.59, 54.24 (d, J=6.5 Hz), 51.16 (d, J=7.5 Hz), 40.66 (t, J=19.3 Hz), 28.86 (d, J=8.1 Hz), 20.58 (d, J=8.1 Hz), 13.99; ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.58 (d, J=244.5 Hz), −115.41 (dd, J=243.6, 31.6 Hz); IR (thin film) ν_{max} 3032, 2957, 2932, 2867, 1498, 1455, 1117, 736, 697 cm^{-1}; MS (ESI) m/z 524.4 [(M+H)$^+$]; HRMS calcd for $C_{32}H_{40}F_2NO_3$: 524.2976. Found: 524.29708.

4.3.11. (3S,5S)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-1-butyl-4,4-difluoropiperidine (**32**)

Using the same conditions as described for compound **23**, compound **32** (171 mg, 79% for two steps) was prepared as a pale yellow oil from compound **28** (200 mg, 0.41 mmol): $[\alpha]_D^{28}$ −28.5 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 15H), 4.90–4.53 (m, 6H), 4.12–4.07 (dd, J=9.9, 5.4 Hz, 1H), 3.79–3.58 (m, 3H), 3.04–3.01 (m, 2H), 2.41–2.20 (m, 5H), 1.47–1.36 (m, 2H), 1.34–1.24 (m, 2H), 0.95–0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.26, 138.09, 137.73, 128.38, 128.31, 128.25, 127.96, 127.83, 127.57, 127.55, 122.07 (t, J=249.0 Hz), 75.82 (t, J=20.1 Hz), 73.78, 73.52 (d, J=2.1 Hz), 73.29 (d, J=1.6 Hz), 73.23, 71.17, 57.34, 54.87 (d, J=7.9 Hz), 51.11 (d, J=8.4 Hz), 43.67 (t, J=20.1 Hz), 29.09, 20.50, 13.96; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.81 (d, J=237.7 Hz), −130.66 (d, J=223.3 Hz); IR (thin film) ν_{max} 3032, 2957, 2932, 2863, 1497, 1455, 1121, 736, 697 cm^{-1}; MS (ESI) m/z 524.5 [(M+H)$^+$]; HRMS calcd for $C_{32}H_{40}F_2NO_3$: 524.2974. Found: 524.29708.

4.3.12. (3R,5S)-1-Butyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**11**)

Using the similar conditions as described for compound **9**, compound **11** (32 mg, 58% for three steps) was prepared as a clear oil from compound **31** (129 mg, 0.25 mmol): $[\alpha]_D^{27}$ −21.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98–3.93 (dd, J=11.1, 3.6 Hz, 2H), 3.75–3.69 (dd, J=10.8, 4.5 Hz, 1H), 3.18 (br, 3H), 2.90–2.88 (m, 2H), 2.53 (s, 2H), 2.47–2.34 (m, 4H), 1.51–1.41 (m, 2H), 1.36–1.24 (m, 2H), 0.93–0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.57 (t, J=248.6 Hz), 67.71 (t, J=25.3 Hz), 59.89, 56.98, 56.12, 53.40, 41.54 (t, J=20.6 Hz), 28.79, 20.41, 13.87; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.03 (br, 1F), −115.99 (br, 1F); IR (thin film) ν_{max} 3365, 2961, 2875, 1173, 1111, 1081 cm^{-1}; MS (ESI) m/z 224.2 [(M+H)$^+$]; HRMS calcd for $C_{10}H_{20}O_2NF_2$: 224.14533. Found: 224.14566.

4.3.13. (3S,5S)-1-Butyl-4,4-difluoro-5-(hydroxymethyl)piperidin-3-ol (**12**)

Using the similar conditions as described for compound **9**, compound **12** (38 mg, 59% for three steps) was prepared as a pale yellow oil from compound **32** (152 mg, 0.29 mmol): $[\alpha]_D^{25}$ −9.9 (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12–3.80 (m, 5H), 2.82–2.69 (m, 3H), 2.42–2.37 (t, J=7.2 Hz, 2H), 2.26–2.12 (m, 1H), 1.53–1.43 (m, 2H), 1.38–1.24 (m, 2H), 0.94–0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.90 (t, J=249.1 Hz), 68.31 (t, J=20.5 Hz), 60.95, 57.31, 57.17, 54.10, 42.81 (d, J=19.3 Hz), 28.83, 20.42, 13.88; ^{19}F NMR (282 MHz, $CDCl_3$) δ −104.96 (br, 1F), −117.75 (br, 1F); IR (thin film) ν_{max} 3391, 3284, 2961, 2811, 1456, 1100 cm^{-1}; MS (ESI) m/z 224.2 [(M+H)$^+$]; HRMS calcd for $C_{10}H_{20}O_2NF_2$: 224.1473. Found: 224.14566.

4.3.14. 2-((3R,5S)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidin-1-yl)ethanol (**33**)

Using the same conditions as described for compound **21**, compound **33** (159 mg, 58% for two steps) was prepared as a yellow oil from compound **27** (262 mg, 0.54 mmol): $[\alpha]_D^{27}$ −13.5 (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 15H), 4.80–4.53 (m, 6H), 4.09–4.04 (dd, J=10.2, 5.1 Hz, 1H), 3.70–3.61 (m, 3H), 3.59–3.56 (t, J=5.4 Hz, 2H), 3.02–2.95 (m, 2H), 2.82–2.46 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.25, 138.02, 137.57, 128.41, 128.34,

128.25, 127.84, 127.69, 127.58, 121.85 (t, J=253.9 Hz), 74.52 (dd, J=29.7, 20.4 Hz), 73.92, 73.24, 73.21, 72.79, 71.28, 58.01, 57.88, 53.80 (d, J=6.9 Hz), 50.53 (d, J=6.9 Hz), 40.67 (t, J=19.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.03 (d, J=245.3 Hz, 1F), −115.29 (dd, J=244.5, 26.2 Hz, 1F); IR (thin film) ν_{max} 3032, 2868, 1497, 1455, 1102, 739, 698 cm^{-1}; MS (ESI) m/z 512.4 [(M+H)$^+$], 534.4 [(M+Na)$^+$]; HRMS calcd for $C_{30}H_{36}F_2NO_4$: 512.2615. Found: 512.26069.

4.3.15. 2-((3S,5S)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidin-1-yl)ethanol (**34**)

Using the same conditions as described for compound **21**, compound **34** (212 mg, 70% for two steps) was prepared as a yellow oil from compound **28** (290 mg, 0.6 mmol): $[\alpha]_D^{26}$ −36.6 (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.28 (m, 15H), 4.89–4.52 (m, 6H), 4.11–4.06 (dd, J=9.3, 5.1 Hz, 1H), 3.76–3.55 (m, 5H), 3.04–3.01 (m, 2H), 2.57 (t, J=5.7 Hz, 2H), 2.41 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.14, 138.00, 137.58, 128.48, 128.41, 128.32, 127.99, 127.85, 127.69, 127.66, 121.88 (t, J=250.2 Hz), 75.70 (t, J=19.5 Hz), 73.63 (d, J=2.1 Hz), 73.56, 73.27, 73.23 (d, J=1.6 Hz), 70.74 (d, J=2.1 Hz), 58.51 (d, J=1.1 Hz), 58.08, 54.68 (d, J=7.9 Hz), 51.03 (d, J=8.4 Hz), 43.67 (t, J=19.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.89 (d, J=241.1 Hz, 1F), −130.34 (d, J=237.4 Hz, 1F); IR (thin film) ν_{max} 3032, 2931, 2868, 1497, 1455, 1116, 738, 698 cm^{-1}; MS (ESI) m/z 512.4 [(M+H)$^+$], 534.5 [(M+Na)$^+$]; HRMS calcd for $C_{30}H_{36}F_2NO_4$: 512.2585. Found: 512.26069.

4.3.16. 2-((3R,5S)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidin-1-yl)ethyl benzoate (**35**)

DMAP (44 mg, 0.36 mmol), NEt_3 (0.42 mL, 3.00 mmol), and BzCl (distilled before use, 0.07 mL, 0.60 mmol) were added to a solution of compound **33** (154 mg, 0.30 mmol) in dichloromethane (5.2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 3 h at rt and quenched with saturated aqueous NH_4Cl (2 mL). The two layers were separated and the aqueous layers were extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10:1) give compound **35** (184 mg, 99%) as a clear oil: $[\alpha]_D^{26}$ −2.7 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.06 (dd, J=7.2 Hz, 5.4H, 2H), 7.60–7.54 (td, J=8.4, 1.5 Hz, 1H), 7.45–7.29 (m, 17H), 4.86–4.65 (m, 4H), 4.60 (s, 2H), 4.53–4.49 (t, J=6 Hz, 2H), 4.16–4.11 (m, 3H), 3.21–3.09 (m, 2H), 3.00–2.75 (m, 3H), 2.67–2.59 (t, J=11.4 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.18, 138.36, 138.05, 137.52, 132.79, 129.93, 129.41, 128.25, 128.21, 128.17, 128.10, 127.70, 127.64, 127.62, 127.42, 127.38, 127.36, 121.72 (dd, J=246.3, 254.9 Hz), 76.58, 74.06 (dd, J=31.5, 20.3 Hz), 73.83, 73.10 (d, J=5.9 Hz), 72.48, 71.65, 62.45, 55.61, 54.25 (d, J=6.9 Hz), 51.10 (d, J=7.5 Hz), 40.52 (t, J=19.15 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.02 (d, J=245.1 Hz, 1F), −115.18 (dd, J=245.6, 30.7 Hz, 1F); IR (thin film) ν_{max} 3032, 2866, 1719, 1454, 1274, 1115, 738, 713, 698 cm^{-1}; MS (ESI) m/z 616.4 [(M+H)$^+$], 638.4 [(M+Na)$^+$]; HRMS calcd for $C_{37}H_{40}O_5NF_2$: 616.2859. Found: 616.28691.

4.3.17. 2-((3S,5S)-3-(Benzyloxy)-5-((S)-1,2-bis(benzyloxy)ethyl)-4,4-difluoropiperidin-1-yl)ethyl benzoate (**36**)

Using the same conditions as described for compound **35**, compound **36** (295 mg, 96%) was prepared as a pale yellow oil from compound **34** (254 mg, 0.5 mmol): $[\alpha]_D^{26}$ −20.4 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–8.13 (dd, J=8.1, 1.2 Hz, 2H), 7.64–7.59 (t, J=7.8 Hz, 1H), 7.50–7.35 (m, 15H), 4.95–4.90 (d, J=12.3 Hz, 1H), 4.78–4.59 (m, 5H), 4.51–4.47 (t, J=6 Hz, 2H), 4.22–4.17 (q, J=9.9, 4.8 Hz, 1H), 3.84–3.66 (m, 3H), 3.22–3.18 (d, J=10.2 Hz, 2H), 2.90–2.86 (t, J=5.7 Hz, 2H), 2.63–2.38 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.85, 137.92, 137.74, 137.35, 132.55, 129.67, 129.14, 127.99, 127.94, 127.88, 127.49, 127.45, 127.38, 127.18, 127.17, 121.48 (t, J=249.6 Hz), 76.38, 75.44 (t, J=19.8 Hz), 73.29, 73.03, 72.78, 70.56, 61.97, 55.24, 54.42 (d, J=8.0 Hz), 51.13 (d, J=8.6 Hz), 43.42 (t, J=19.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.56 (d, J=228.9 Hz), −130.0 (d, J=227.9 Hz); IR (thin film) ν_{max} 3032, 2863, 1719, 1602, 1497, 1454, 1274, 1114, 739, 713, 698 cm^{-1}; MS (ESI) m/z 616.5 [(M+H)$^+$], 638.4 [(M+Na)$^+$]; HRMS calcd for $C_{37}H_{40}O_5NF_2$: 616.2870. Found: 616.28691.

4.3.18. 2-((3R,5S)-4,4-Difluoro-3-hydroxy-5-(hydroxymethyl)-piperidin-1-yl)ethyl benzoate (**37**)

Pd/C (10%, 140 mg) was added to a solution of compound **35** (184 mg, 0.30 mmol) in methanol (10 mL). The reaction mixture was stirred for 4 days under hydrogen atmosphere and then filtered. The filtrate was concentrated. The residue was dissolved in methanol (18 mL) and saturated aqueous $NaIO_4$ was added dropwise. The reaction mixture was stirred strongly for 5 min at rt and then cooled to 0 °C. $NaBH_4$ (143 mg, 3.78 mmol) was added in portions and the mixture was stirred at the same temperature for 20 min followed by being quenched with saturated aqueous NH_4Cl (6 mL). Methanol was removed under reduced pressure and the resulting mixture was extracted with ethyl acetate. The extracts were combined and dried over Na_2SO_4. The solvent was removed. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to give compound **37** (70 mg, 74% for two steps) as a white solid: mp 119–121 °C; $[\alpha]_D^{25}$ −21.4 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.04–8.02 (d, J=7.5 Hz, 2H), 7.62–7.57 (t, J=7.2 Hz, 1H), 7.49–7.44 (t, J=8.1 Hz, 2H), 4.50–4.41 (m, 2H), 3.89–3.84 (dd, J=11.1 Hz, 3 Hz, 1H), 3.80–3.72 (m, 1H), 3.61–3.55 (dd, J=10.5, 8.4 Hz, 1H), 3.04–3.02 (d, J=6.9 Hz, 1H), 2.93–2.79 (m, 3H), 2.72–2.68 (d, J=12.3 Hz, 1H), 2.54–2.45 (m, 2H); ^{13}C NMR (75.4 MHz, MeOH-d_4) δ 167.99, 134.28, 131.35, 130.57, 129.59, 122.62 (t, J=248.0 Hz), 68.84 (t, J=24.8 Hz), 63.64, 59.06, 57.65, 56.75, 54.18, 43.65 (t, J=20.1 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −116.51 (d, J=243.1 Hz, 1F), −120.28 (d, J=225.0 Hz, 1F); IR (KBr) ν_{max} 3269, 2838, 1716, 1602, 1453, 1279, 1072, 1020, 714 cm^{-1}; MS (ESI) m/z 316.2 [(M+H)$^+$], 338.2 [(M+Na)$^+$]; HRMS calcd for $C_{15}H_{20}O_4NF_2$: 316.1352. Found: 316.13415.

4.3.19. 2-((3S,5S)-4,4-Difluoro-3-hydroxy-5-(hydroxymethyl)-piperidin-1-yl)ethyl benzoate (**38**)

Using the same conditions as described for compound **37**, compound **38** (103 mg, 75% for two steps) was prepared as a white solid from compound **36** (270 mg, 0.44 mmol): mp 77–79 °C; $[\alpha]_D^{25}$ −16.0 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01–7.99 (d, J=7.2 Hz, 2H), 7.56–7.51 (t, J=7.5 Hz, 1H), 7.44–7.38 (t, J=15.3 Hz, 2H), 4.49–4.34 (m, 2H), 3.96–3.90 (dd, J=11.4, 4.2 Hz, 1H), 3.88–3.78 (m, 1H), 3.75–3.69 (dd, J=11.4, 6.3 Hz, 1H), 2.93–2.72 (m, 4H), 2.60 (s, 2H), 2.21–2.15 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.71, 133.15, 129.60, 129.50, 128.38, 120.88 (t, J=249.6 Hz), 68.43 (t, J=21.2 Hz), 61.74, 59.47, 56.99, 55.60, 53.23, 43.69 (t, J=20.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.52 (br, 1F), −128.32 (br, 1F); IR (KBr) ν_{max} 3404, 3210, 2793, 1729, 1605, 1455, 1277, 1101, 708, 693 cm^{-1}; MS (ESI) m/z 316.2 [(M+H)$^+$], 338.2 [(M+Na)$^+$]; HRMS calcd for $C_{15}H_{20}O_4NF_2$: 316.1335. Found: 316.13549.

4.3.20. (3R,5S)-4,4-Difluoro-1-(2-hydroxyethyl)-5-(hydroxymethyl)piperidin-3-ol (**13**)

Compound **37** (89 mg, 0.28 mmol) was dissolved in a saturated solution of ammonia in methanol (30 mL). The reaction solution was stirred 32.5 h at rt and then concentrated. The residue was purified by silica gel column chromatography (dichloromethane/methanol=7:1) to give compound **13** (57 mg, 96%) as a clear oil: $[\alpha]_D^{25}$ −37.9 (c 0.4, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.91–3.86 (dd, J=11.1, 3.9 Hz, 1H), 3.78–3.66 (m, 1H), 3.65–3.61 (t, J=5.1 Hz, 2H), 3.58–3.52 (dd, J=11.1, 9.3 Hz, 1H), 3.05–3.02 (d, J=10.2 Hz, 1H), 2.92–2.88 (d, J=12 Hz, 1H), 2.63–2.38 (m, 4H), 2.24–

2.17 (t, J=10.8 Hz, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 123.01 (t, J=245.7 Hz), 69.24 (t, J=27.8 Hz), 60.63, 60.02, 59.13, 58.02 (t, J=2.8 Hz), 54.49, 43.42 (t, J=17.4 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −116.68 (d, J=242.5 Hz, 1F), −121.60 (d, J=243.9 Hz, 1F); IR (thin film) ν_{max} 3366, 2951, 2831, 1169, 1085, 1029 cm^{-1}; MS (ESI) m/z 212.1 [(M+H)$^+$], 234.1 [(M+Na)$^+$]; HRMS calcd for $C_8H_{15}O_3NF_2Na$: 234.0926. Found: 234.09122.

4.3.21. (3S,5S)-4,4-difluoro-1-(2-hydroxyethyl)-5-(hydroxymethyl)piperidin-3-ol (**14**)

Using the same conditions as described for compound **13**, compound **14** (56 mg, 90%) was prepared as a clear oil from compound **38** (92 mg, 0.29 mmol): $[\alpha]_D^{25}$ −28.4 (c 1.4, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.95–3.77 (m, 2H), 3.69–3.65 (t, J=5.7 Hz, 2H), 3.58–3.51 (dd, J=10.5, 7.8 Hz, 1H), 3.11–2.99 (m, 2H), 2.62–2.59 (t, J=5.4 Hz, 2H), 2.31–2.15 (m, 3H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 122.72 (t, J=245.6 Hz), 70.15 (t, J=21.1 Hz), 60.48, 60.28, 58.60 (d, J=3.9 Hz), 58.08 (d, J=7.1 Hz), 54.91 (d, J=7.4 Hz), 46.34 (t, J=19.6 Hz); ^{19}F NMR (282 MHz, MeOH-d_4) δ −116.53 (d, J=241.7 Hz, 1F), −136.15 (br, 1F); IR (thin film) ν_{max} 3363, 2946, 2836, 1473, 1220, 1096 cm^{-1}; MS (ESI) m/z 212.1 [(M+H)$^+$], 234.1 [(M+Na)$^+$]; HRMS calcd for $C_8H_{15}O_3NF_2Na$: 234.0928. Found: 234.09122.

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