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Skipped Fluorination Motifs: Synthesis of Building Blocks and Comparison of Lipophilicity Trends with Vicinal and Isolated Fluorination Motifs

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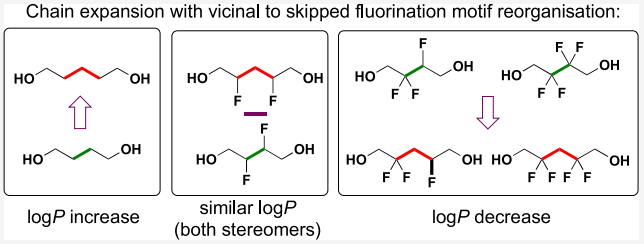
ABSTRACT: Given there is an optimal lipophilicity range for orally bioavailable drugs, structural modifications applied in the drug development process are not only focused on optimizing bioactivity but also on fine-tuning lipophilicity. Fluorine introduction can be used for both purposes. Insights into how fluorine introduction affects lipophilicity are thus of importance, and systematic series of fluorinated compounds with measured octanol−water partition coefficients are a powerful way to enhance our qualitative understanding in this regard and are essential as input for computational log *P* estimation programs. Here, we report a detailed comparison of all possible vicinal and skipped (1,3-substituted) fluorination motifs when embedded in structurally equivalent environments (X−CF_nH_{2-n}−CF_mH_{2-m}−X versus X−CF_nH_{2-n}−CH_2−CF_mH_{2-m}−X, with n,m ≠ 0 and X = CH_2OH) to compounds with isolated fluorination ($n \neq 0$; $m = 0$, and including X−CH_2−CF_nH_{2-n}−CH_2−X, $n = 0-2$). It is shown that skipped fluorination is more powerful for log *P* reduction purposes compared to single or vicinal fluorination. Efficient stereoselective syntheses of the compounds with skipped fluorination motifs are reported, which where relevant can be made enantioselective using known chiral building blocks. These compounds, and some intermediates, will be of interest as advanced fluorinated building blocks.



INTRODUCTION

The realization of the critical importance of simultaneous optimization of physical properties and of bioactivities in the drug development process has been a major recent development in medicinal chemistry.[1−8] Lipophilicity has been recognized as a useful proxy for a range of properties related to absorption, distribution, metabolism, excretion, and toxicity (ADMET) of orally administered bioactive compounds and is therefore an often-used parameter in the optimization process.[3,7,9−11] It is defined as the partition coefficient *P* of a compound between octanol and water, and expressed as its logarithm (log *P*). For ionizable compounds, partitioning is measured at a particular pH and expressed as the logarithm of its distribution coefficient ($\log D_{pH}$). Chromatographic methods have been developed where retention times are related to lipophilicities.[12,13] These methods have gained in popularity due to their simplicity and ability to generate a high-throughput of experimental data, but accuracies are naturally dependent on the quality of the training set used to establish the correlation between log *P* and retention time. The understanding of how lipophilicity is influenced by structural changes is of great importance in drug discovery. Systematic studies exploring structure−lipophilicity relationships, especially when using actual octanol−water partition coefficient values, are thus of great interest. Such studies also have importance for data input in computational log *P* calculation efforts.[14,15] While every structural modification of a compound will affect its log *P* value, fluorine introduction has proven to be particularly useful in this regard, mainly due to a combination of its very strong electronegativity and its small size.[16] Initiated by the seminal work of Müller and colleagues,[17−22] the influence of aliphatic chain fluorination on lipophilicities has been investigated by a number of groups, for example, by investigating new motifs[23−28] and introduction of fluorine on aliphatic systems[29−33] or in amino acid side chains.[34−36]

A subset of these studies involve vicinal fluorination motifs (Figure 1). Müller was the first to discover the lower lipophilicity of the vicinal difluoro motif compared to the geminal analogues[19] and that the relative stereochemistry was not important (compare **A2** with **A3**/**A4** and **B2**-**B4** with **B5**/**B6**). He also showed that a further extension to the trifluorinated motif as in **B7**/**B8** only led to a small additional

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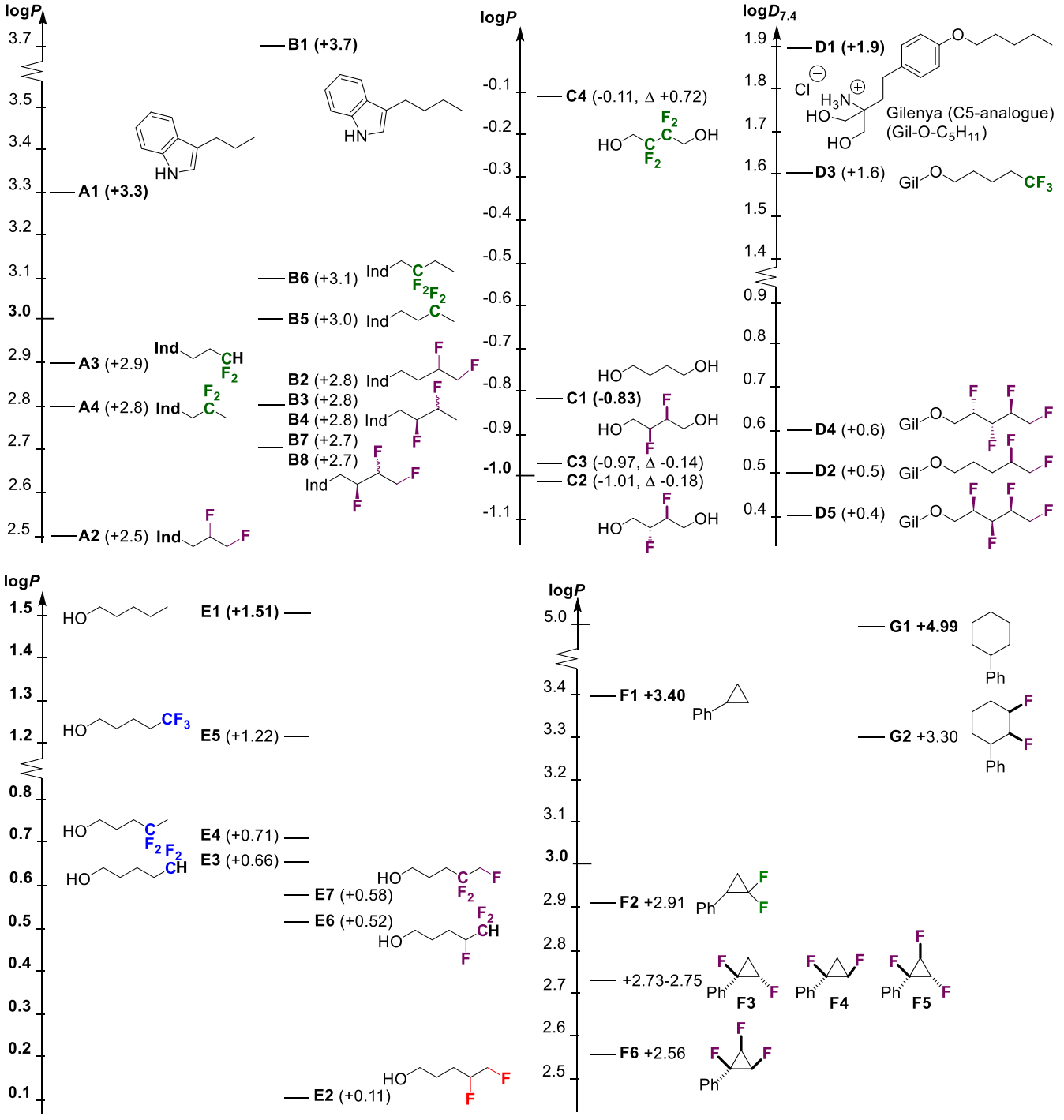

Figure 1. Precedent involving aliphatic vicinal and multivicinal fluorine motifs.

log *P* decrease.[19] However, compared to the nonfluorinated "parents" **A1**/**B1**, a significant decrease in log *P* was obtained. In contrast, our group reported that the two vicinal difluoride compounds **C2** and **C3** only gave modest lipophilicity decreases compared to the nonfluorinated parent **C1**, but confirmed the irrelevance of relative stereochemistry.[27] Hunter also recently reported that diastereoisomers of acyclic vicinal difluorinated compounds gave very similar log *P* values (not shown).[14] Nevertheless, the lipophilicity-decreasing effect of the vicinal difluoride motif introduction was convincingly demonstrated by Gilmour using Gilenya analogues.[37,38] The nonfluorinated parent with a pentoxy chain **D1** is significantly more lipophilic than **D2**, while the trifluoromethylated **D3** only showed a modest decrease. Interestingly, two multivicinal analogues **D4** and **D5** were also synthesized,[38] but showed similar lipophilicities to the vicinal difluorinated **D2**, although the effect of relative stereochemistry is now more pronounced.

Through analysis of all possible fluorination motifs on the pentan-1-ol 4- and 5-positions, we showed that 4,5-difluoropentan-1-ol **E2** displayed the largest lipophilicity decrease of all motifs investigated and that its log *P* value (+0.11) is even lower than that of propan-1-ol (+0.30, not shown), which has two fewer carbon atoms.[23] It can be seen that the log *P* of **E2** is much decreased compared to that of the

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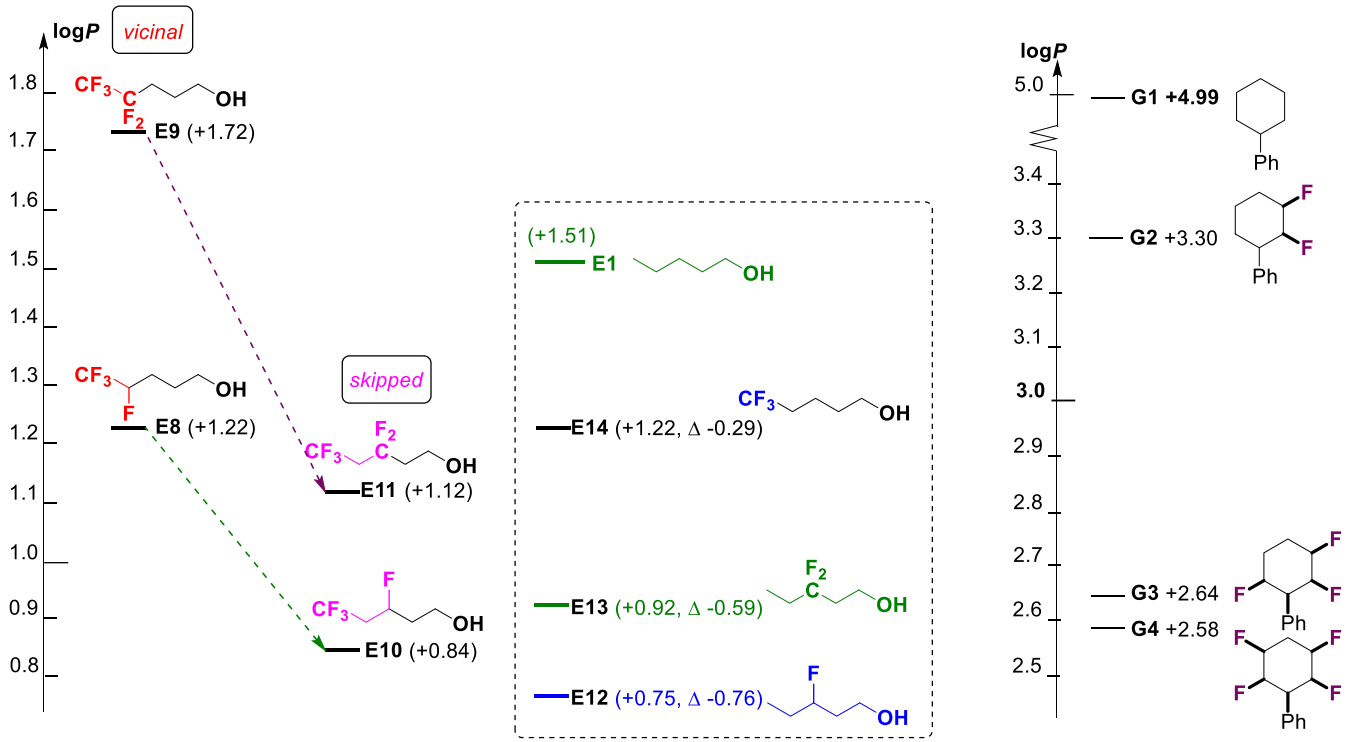


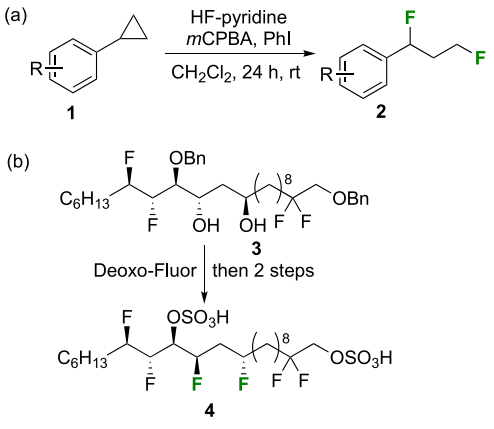
Figure 2. Vicinal and skipped fluorination motif matched pairs.

corresponding geminal analogues **E3**/**E4** and that the decrease is larger compared to that observed in series **A** and **B**. We also showed that the corresponding "motif extension" from a (geminal) trifluoromethyl group (**E5**) to the vicinal trifluorinated motifs as in **E6**/**E7** also leads to significant log *P* decreases. O'Hagan has reported on geminal and vicinal difluorinated phenyl cyclopropanes,[31,32] with the geminal difluorinated **F2** being more lipophilic compared to the vicinal difluorinated compounds **F3** and **F4**. Perhaps surprisingly, there was no measurable difference between the *cis* and *trans*-isomers. The *all-cis* trifluorinated derivative **F6** is the most polar in the series, with its diastereomer **F5** having the same log *P* as the vicinal difluorinated analogues **F3**/**F4**. Finally, O'Hagan also reported on the significant log *P* decrease when introducing *cis*-vicinal difluorination on phenyl cyclohexane (**G1** to **G2**).

In contrast to vicinal fluorination motifs, skipped fluorination motifs are only recently beginning to be investigated for their effect on lipophilicity. Our group showed that compared to vicinal fluorination motifs, the corresponding skipped motifs (Figure 2) had a much lower lipophilicity (compare **E8**/**E9** with **E10**/**E11**).[23] It is interesting to compare the skipped fluorination motif with its individual constituent motifs: the log *P* decrease caused by the skipped tetrafluorination motif in **E10** is in between that of the monofluorinated **E12** and the trifluoromethylated **E14** (likewise for the other motif). Hence, the log *P* decrease caused by a skipped motif is less than the "sum" of the decrease obtained by introducing its constituents. O'Hagan has shown that introducing a skipped fluorine in **G2**, leading to **G3**, causes a large log *P* decrease.[39] Introducing a fourth fluorine (**G4**) did not show much further decrease however.

Compared to vicinal difluorination patterns, there are a number of synthetic methodologies reported for the synthesis of 1,3-skipped fluorination of aliphatic chains in small molecules (Scheme 1). Relevant to the motifs reported herein, the Jacobsen group reported a direct introduction through

Scheme 1. Synthetic Precedence Examples for the Skipped Difluoro Motif



oxidative ring-opening of substituted cyclopropanes with HF-pyridine, illustrated by the conversion of **1** to **2**.[40] The Carreira group reported the synthesis of fluorodanicalipin A **4**,[41] a fluorinated analogue of the chlorosulfolipid danicalipin A, by the simultaneous stereospecific nucleophilic deoxyfluorination of the corresponding 1,3-diol groups in **3**. The repeating skipped monofluoro motif has been reported in fluoropolymers, though this chemistry has not been widely explored on small molecules.[42]

Synthetically useful examples toward a skipped trifluorination motif within acyclic chains have not been reported, although the methodology shown in Scheme 2 could, in principle, be applied. The Studer group reported that treatment of **5**, obtained via 1,2-carboboration of the

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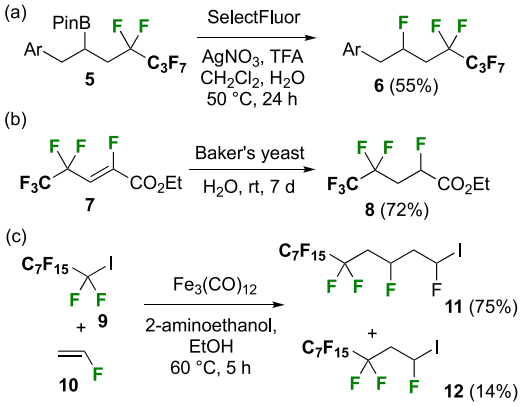
Scheme 2. Synthetic Precedence for the Skipped Trifluoro Motif



corresponding alkene, with SelectFluor and silver nitrate achieved a radical deboronofluorination to provide the skipped fluoro species **6** in a moderate yield.[43] Another interesting approach was taken by Kitazume and Ishikawa, who synthesized the motif via alkene reduction of a fluorinated α,β-unsaturated ester such as **7** with Baker's yeast, although a long reaction time (7 days) was required to obtain **8**.[44] Fuchikami and Ojima inadvertently produced the skipped fluoro pattern while investigating the transition-metal-catalyzed addition of perfluoroalkyl halides to alkenes.[45] The perfluorooctylation of vinyl fluoride **10** with **9** afforded a mixture of the perfluoroalkyl iodides **11** and **12**, which conveniently contained the skipped motif alongside a halide handle for further functionalization at the terminal position.

The skipped tetrafluoro motif has perhaps received the most attention due to its widely reported use in fluorinated polymers and surfactants (Scheme 3).[46−48] In a representative example, the Ameduri group reacted vinylidene fluoride **13** with iodide **14** and obtained telomers of various lengths containing skipped difluoromethylene groups (**15**). In their synthesis of fluorinated palmitic acid derivatives, the O'Hagan group employed sequential deoxyfluorinations in neat diethylaminosulfur trifluoride (DAST) to obtain the skipped tetrafluoro motif in the center of the long aliphatic chain:[49] following the first deoxofluorination of ketone **16**, the pendant alkene in **17** was converted to the epoxide and opened with pentylmagnesium bromide. Oxidation of the resultant alcohol to ketone **18** and treatment with DAST then afforded **19**. Both fluorinations required neat DAST at elevated temperatures. In a related approach, the Chiechi group directly fluorinated β-dithiolane **21**, obtained from the corresponding propargylic ketone **20**, using HF-pyridine, to obtain **22**. This was subsequently converted to the skipped 1,3-tetrafluoro compound **23** with Morph-DAST.[50]

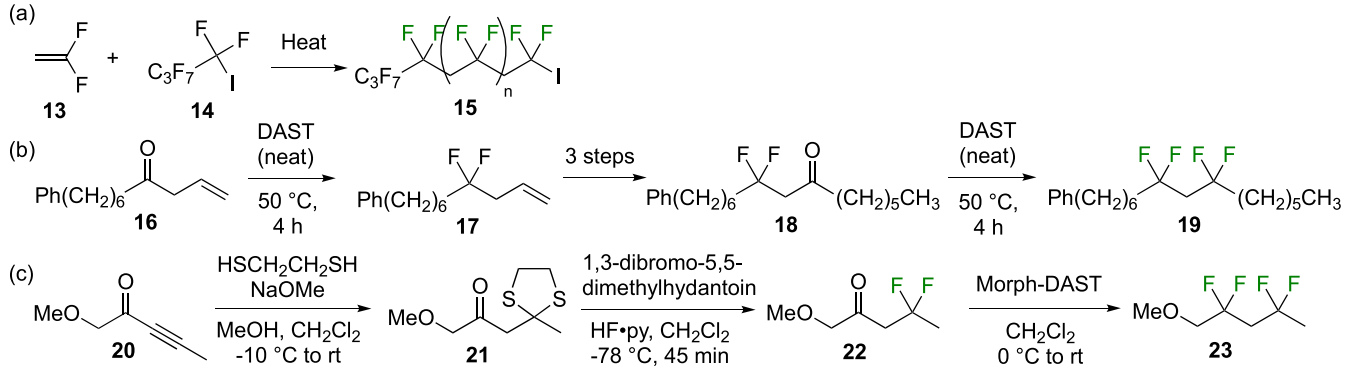
In this contribution, we report on a systematic investigation to compare internal vicinal fluorination motifs with their (internal) skipped counterparts, using the 1,4-butanediol and 1,5-pentanediol scaffolds **C** and **H**, respectively (Figure 3). For this investigation, we opted to have a constant structural feature at the molecule termini, with the structural change focused on the extension of the two-carbon vicinal motif with the three-carbon skipped motif without any additional influence caused by fluorination motifs being at different distances from a polar functional group or aliphatic chain terminus.

The syntheses[51] and lipophilicities[27] of **C2**−**C4** have been reported and are included for discussion purposes, which also will involve comparison with monofluorinated and geminal difluorinated analogues **C6**, **C7**, and **H6**−**H9**, as well as with the hexafluorinated **H10**. The synthesis of **H2**−**H5** employs different strategies compared to the literature precedence, and is, where relevant, fully stereoselective.

RESULTS AND DISCUSSION

Synthesis. *Skipped Target Compounds H2−H5—Retrosynthetic Analysis.* The approach taken for the synthesis of these targets is shown in Scheme 4. While for the purposes of the lipophilicity measurements racemic compounds are adequate, we sought to develop synthetic routes that allowed enantioselective synthesis where applicable. For the *anti*-1,3-difluorinated **H2**, the final fluorine introduction was envisaged by deoxyfluorination of the fluorohydrin **24**, to be accessed by reductive opening of known lactone **25**,[52] whose synthesis from lactone **26** has been reported by the Liotta group using a fully diastereoselective electrophilic fluorination. Lactone **26** is easily procured from glutamic acid,[53,54] conveniently enabling the synthesis of either enantiomer of **H2** depending on the absolute configuration of the amino acid used. It is worth mentioning that direct enantioselective monofluorination of 1,5-pentanedialdehyde, for example, using the MacMillan methodology,[55] which would directly yield **H2** (after aldehyde reduction) was briefly investigated, but no formation of the desired product was ever observed. The synthesis of the *meso*-compound **H3** was envisaged from the 2,4-dideoxy-difluorinated levoglucosan **28**, with the required one-carbon C−C bond cleavage and alcohol reduction being more than offset by

Scheme 3. Synthetic Precedence for the Skipped Tetrafluoro Motif



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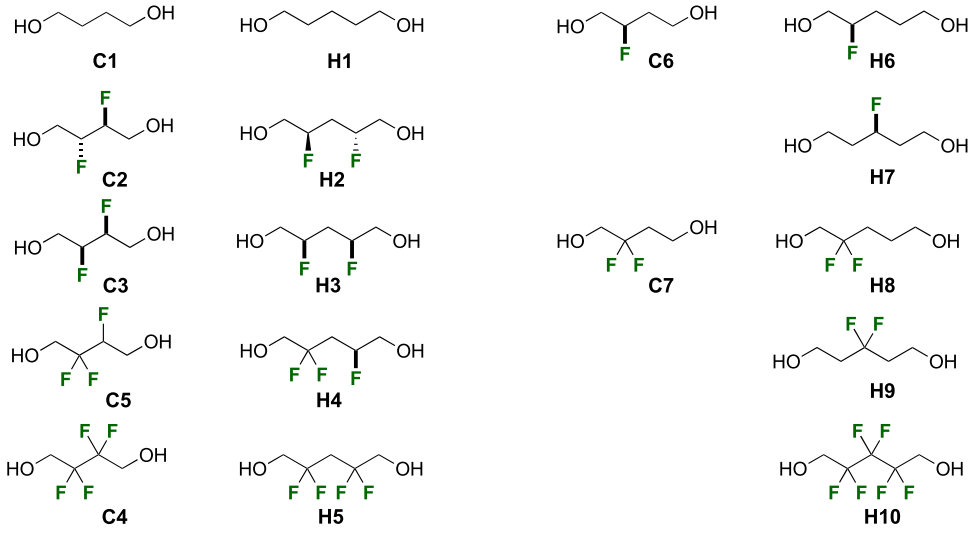
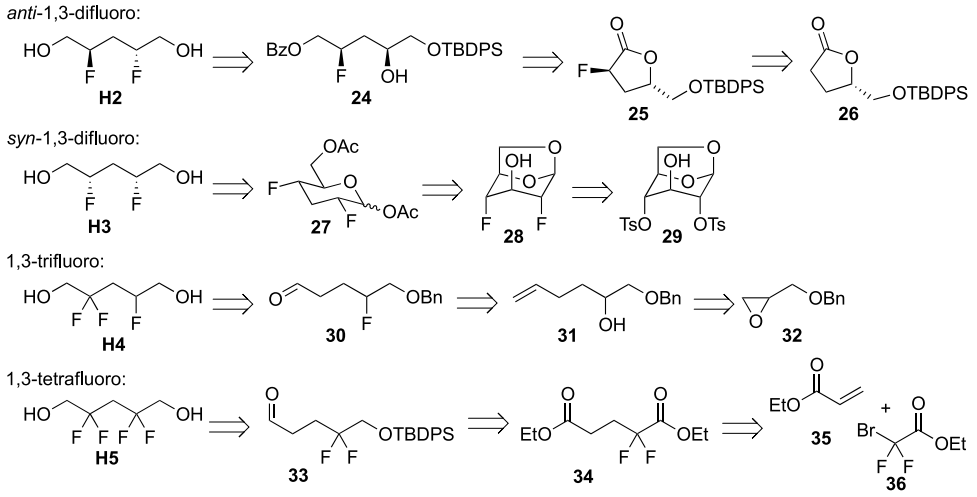
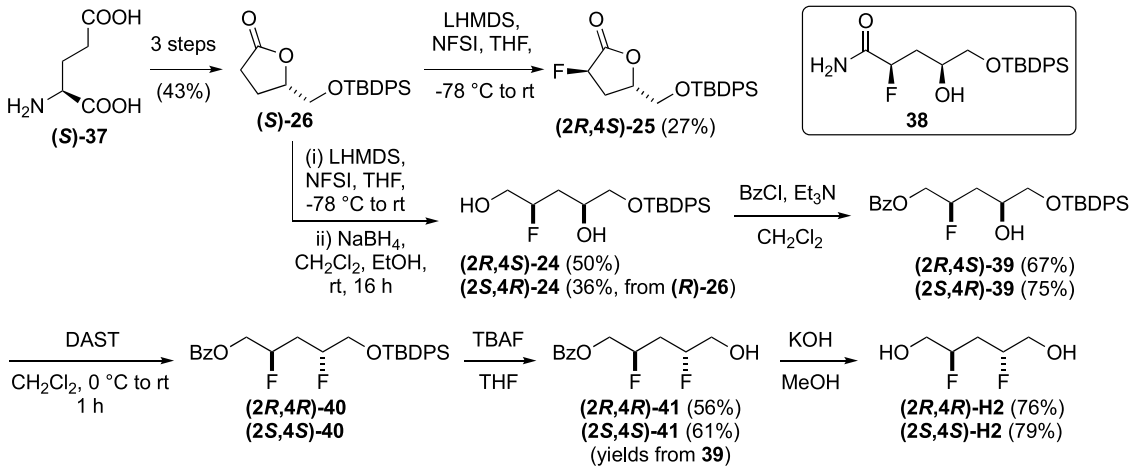


Figure 3. Nonfluorinated parent substrates with the fluorination motif types studied.

Scheme 4. Retrosynthetic Analysis of the Skipped Fluorinated Pentanediols



Scheme 5. Enantioselective Synthesis of Both Enantiomers of the Skipped Difluorinated H2



the ease of the double fluorine introduction: one-pot bis-fluorination of the ditosylate **29** has been optimized on large scale by both the Giguère group and us,[56,57] making this an attractive starting point for **H3**.

For the synthesis of **H4**, an electrophilic α-difluorination/aldehyde reduction sequence as developed by the Lindsley group[58,59] was envisaged, leading to **30** as a precursor. The fluorination in **30** was envisaged to be achieved by

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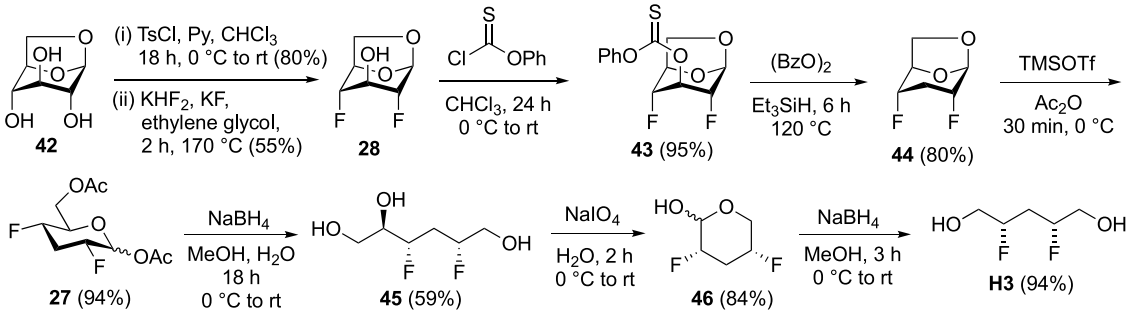
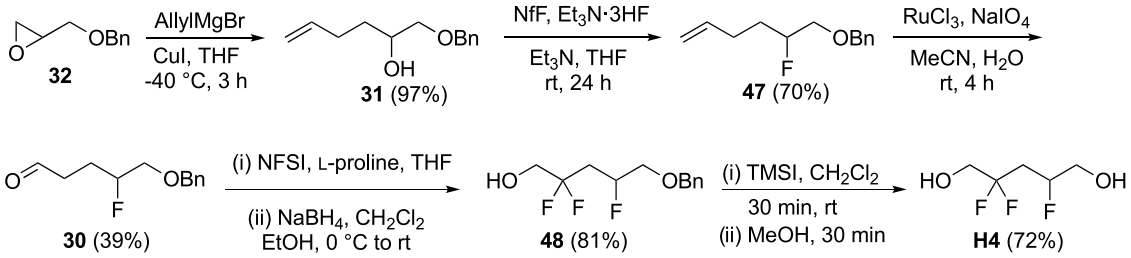
Scheme 6. Synthesis of the *syn*-1,3-Difluorinated Diol H3



Scheme 7. Synthesis of the Skipped Trifluoro Substrate H4



deoxyfluorination of known alcohol **31**, which can be obtained from epoxide opening of the commercially available building block **32**. Both enantiomers of **32** are available, so this route could provide either enantiomer of **H4**, although only the racemic synthesis is reported here. To introduce the skipped tetrafluorination to obtain **H5**, we opted for a different strategy to O'Hagan and Chiechi's nucleophilic fluorination sequences. Instead, aldehyde electrophilic fluorination as also proposed for **H4** was envisaged, with aldehyde **33** to be obtained from known diester **34**,[60] which has been obtained by a fluorinated building block approach involving Michael-type methodology as originally described by the Kumadaki group.[61,62]

Anti-1,3-difluoro Synthesis (H2). Lactone (*S*)-**26** (Scheme 5) was obtained through a well-documented sequence from L-glutamic acid (*S*)-**37**,[53,54] involving diazotization and concomitant intramolecular stereoretentive cyclization to the lactone, reduction of the pendant acid to alcohol, and its protection as a *tert*-butyl diphenyl silyl ether. The electrophilic fluorination of (*S*)-**26** with LiHMDS and NFSI gave (2*R*,4*S*)-**25** with complete diastereoselectivity, as reported by Liotta et al.[52] In our hands, however, the reaction proved capricious, with a low yield (27%) as our best result, compared to the reported 50−70%. In a subsequent attempt, the yield of (2*R*,4*S*)-**25** was reduced to 10%, but the byproduct **38** was isolated in a significant 15% yield. This suggested that ammonia, originating from the ammonium chloride reaction quench, had reacted with the electrophilic lactone ring of (2*R*,4*S*)-**25**. As a result, the quench was altered to a minimum quantity of water and the reaction mixture was carefully concentrated under reduced pressure and telescoped into the subsequent reduction. Treatment of the crude (2*R*,4*S*)-**25** with $NaBH_4$ successfully provided a 50% yield of (2*R*,4*S*)-**24** across two steps.

Repeating this two-step sequence starting from (*R*)-**26** on a 10-fold increase in scale gave a reduced yield of 36%. In both cases, selective protection of the primary alcohol as a benzoyl ester afforded **39** in moderate yields. This compound was then ready for the final key step in the synthesis: stereospecific nucleophilic deoxyfluorination to obtain the *anti*-1,3-difluoro compound **40**. The use of two equivalents of DAST for 1 h at 0 °C is reported to be compatible with a TBDPS group.[63,64] The purity of the isolated material was low; however, treatment of the impure mixture with TBAF enabled isolation of pure **41** in good yields. Finally, treatment with KOH in methanol provided the diol **H2** in a 76−79% yield. The measured optical activity of the **H2** enantiomers confirmed the stereochemical outcome of the nucleophilic fluorination as occurring with inversion (as expected) without any trace of neighboring group participation of the protected alcohol, which is easily determined since the resulting retention would give the optically inactive *meso*-diastereomer **H3**.

Syn-1,3-Difluoro Synthesis (H3). The difluorinated sugar derivative **28** (Scheme 6) was obtained from levoglucosan (**42**), involving tosylation of the alcohols at positions 2 and 4 to obtain ditosylate **29** (not shown) and their stereoretentive displacement with fluoride (45% across the two steps).[56,57] Reduction of the 3-OH group was achieved by the tin hydride-free conditions, as reported by the Roberts group,[65] via the thiocarbonyl derivative **43**.

The 1,6-anhydrobridge was opened using TMSOTf and acetic anhydride, to provide the acetylated pyranose **27** as an inseparable mixture of anomers. Simultaneous reduction of the hemiacetal and both esters gave triol **45** upon which oxidative cleavage of the vicinal diol was achieved to produce the lactol **46**. Finally, reduction of this compound with sodium borohydride provided an excellent yield of **H3**.

Skipped Trifluoro Synthesis (H4). This synthesis commenced with known alcohol **31** (Scheme 7), which is accessible in one step from commercially available benzyl glycidol **32**.[66] Deoxyfluorination using nonafluorobutanesulfonyl fluoride (NfF) and triethylamine-HF to give **47** and oxidative cleavage of the alkene resulted in the required aldehyde **30** to effect the electrophilic difluorination step. This was achieved by sequential fluorination of the L-proline enamine intermediate when excess NFSI is present.[58,59] The resulting 2,2-difluorinated aldehyde was reduced without

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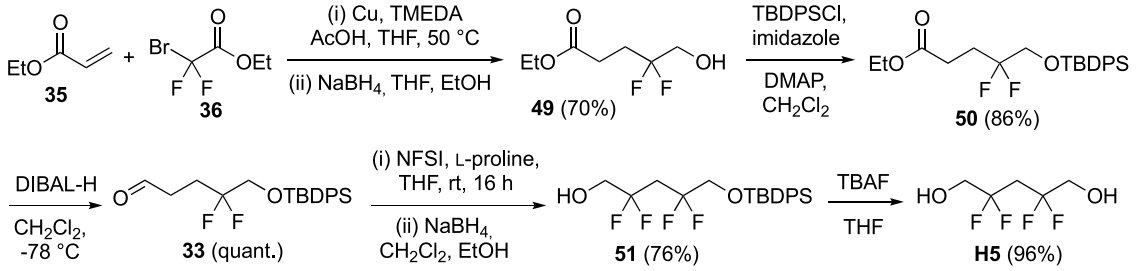
Scheme 8. Synthesis of the Skipped Tetrafluoro Diol H5



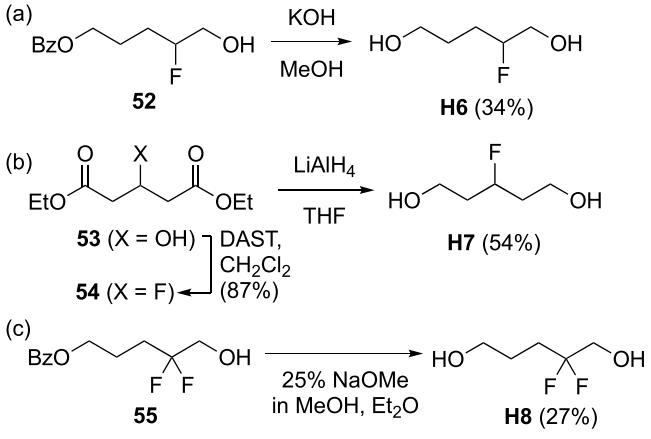
purification to give trifluorinated alcohol **48**, in an overall 81% yield from **30**. Finally, removal of the benzyl protecting group using conditions reported by Jung and Lyster[67] afforded the diol **H4**.

For the purposes of log *P* calculation, the racemic compound was sufficient; however, alcohol **31** is equally accessible in enantiopure form from commercially available enantiopure benzyl glycidol.

*Skipped Tetrafluoro Synthesis (**H5**).* This sequence commenced with the copper-catalyzed conjugate addition[61,62] of ethyl bromodifluoroacetate **36** to ethyl acrylate **35** (Scheme 8). Acetic acid was added as a protic additive, due to the resulting improvement in yield reported by the Shin group.[60] The adduct was directly subjected to $NaBH_4$ treatment, which led to the selective reduction of the more electrophilic ester group to give **49**. Protection of the obtained alcohol as TBDPS ether **50** and partial ester reduction yielded aldehyde **33**. Without further purification, this aldehyde was subjected to the same two-step difluorination/reduction sequence as before, which provided the skipped tetrafluoro compound **51**. Finally, alcohol deprotection afforded an excellent yield of the diol **H5**.

*1,5-Pentanediol Targets (**H6, H7, H8**).* Benzoate cleavage of known **52**[23] gave target **H6** (Scheme 9a). Treatment of

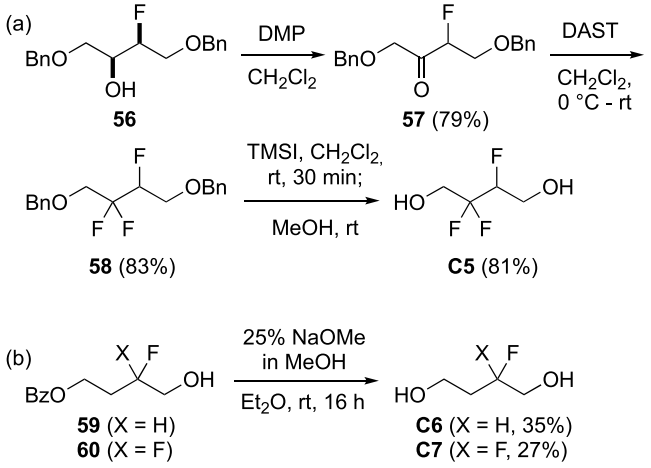
Scheme 9. Synthesis of Mono- and Geminal Difluorinated 1,5-Pentanediol Targets



commercially available **53** with DAST afforded the fluorinated compound **54** in excellent yield, and the subsequent reduction to the diol afforded the diol **H7** (Scheme 9b). Finally, benzoate methanolysis of known **55**[23] led to **H8** (Scheme 9c).

*1,4-Butanediol Targets (**C5, C6, C7**).* Alcohol oxidation of known racemic *syn*-**56**[51] (Scheme 10a) using Dess–Martin periodinane gave ketone **57**, and subsequent treatment with excess DAST efficiently led to the vicinal trifluoro motif in **58**. Simultaneous TMSI-mediated[67] deprotection of the two

Scheme 10. Synthesis of the 1,4-Butanediol Targets



benzyl alcohols afforded the diol **C5**. Finally, benzoate methanolysis of known **59** and **60** (Scheme 10b)[23] led to **C6** and **C7** in modest yield.

Lipophilicity. The lipophilicity data for 1,4-butanediol **C1** and its fluorinated derivatives are shown in Figure 4. Monofluorination (**C6**) leads to a log *P* decrease, while geminal difluorination (**C7**) leads to an almost equal log *P* increase. The contrast with the same types of fluorine introduction on the monohydroxylated analogue, 1-butanol **I1** (inset, Figure 4), is interesting: monofluorination at its 2- or 3-positions, which have the same relative position of the fluorination relative to the OH groups in **C6**, leading to **I2** and **I3**, leads to a much larger decrease in log *P*. The same is true for geminal difluorination at these positions (**I4** and **I5**), albeit much less pronounced for **I4**. This is a typical illustration of the context dependence in log *P* modulation upon introduction of a given motif in similar parents having very different lipophilicities: 1,4-butanediol is much more polar than 1-butanol, hence the fluorine dipole effect will be reduced relative to hydrophobic effects such as introduction of hydrophobic surface and alcohol hydrogen-bond basicity and lone pair polarizability reduction, resulting in a smaller log *P* decrease (for monofluorination, **C6**) or even in a log *P* increase (**C7**).

While the vicinal difluorinated derivatives **C2**/**C3** are less lipophilic compared to **C1** (see Figure 1/4), the vicinal trifluorinated motif in **C5** leads to a higher log *P*, and there is a further increase to the vicinal tetrafluorinated **C4**. The occurrence of antiperiplanar C–F bonds, with their opposing dipole moments, will be an important reason for this. However, while the geminal difluorinated **C7** is more lipophilic than parent **C1**, the corresponding vicinal difluorinated motifs (**C2**, **C3**, same fluorine count) are much more polar, leading to a

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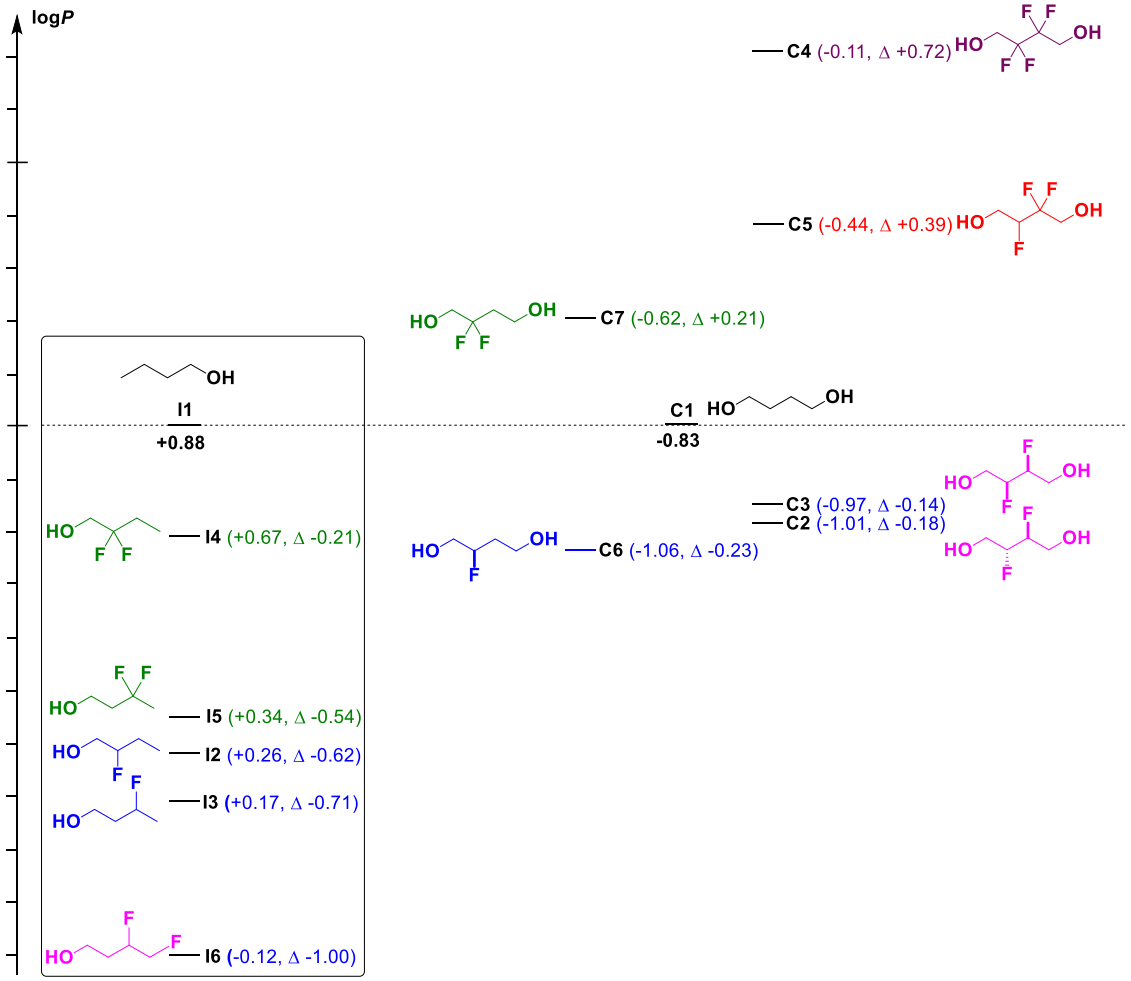

Figure 4. Lipophilicities of fluorinated 1,4-butanediol derivatives, in comparison to relevant fluorinated 1-butanols. Lipophilicity scales for the compound series are normalized to their nonfluorinated parents.

lower log *P* than **C1**. This is consistent with Müller's original observation (see Figure 1).[19]

Extending monofluorination at the butanol 3- or 4-position to 3,4-difluorobutan-1-ol (**I2**/**I3** to **I6**, Figure 4) has been shown to lead to a log *P* decrease.[23] In contrast, application of such a motif extension in the 1,4-butanediol series leads to lipophilicity increases: introducing a fluorine adjacent to the existing C−F group in **C6** leads to **C2**/**C3**, which have slightly higher lipophilicity. This contrasts with the 0.23 log *P* decrease upon monofluorination of **C1** to **C6**. Introducing a fluorine next to the CF_2 group in **C7** to give **C5** leads to a (larger) log *P* increase. Introducing geminal difluorination adjacent to an existing C−F group leads to a significant lipophilicity increase (**C6** to **C5**), and the same observation is made going from **C7** to **C4**. This contrasts with a modest log *P* increase upon geminal difluorination of **C1**. Hence, for the 1,4-butanediol parent, vicinal fluorination serves to increase lipophilicities.

For the 1,5-pentanediol derivatives (Figure 5), C2-monofluorination of **H1** to give **H6** leads again to a log *P* decrease and geminal C2-difluorination (**H8**) leads to a log *P* increase. With 1,5-pentanediol **H1** being less polar than 1,4-butanediol **C1**, the log *P* decrease upon monofluorination of **H1** is larger than that of **C1** (see Figure S2 for a direct comparison). The same context dependence-derived effects apply to the geminal difluorinated derivatives and also explain, as observed for **C1**, why geminal difluorination to **H8** leads to a log *P* increase, while for **E1** this leads to a log *P* decrease.

There is a difference in trend when comparing mono- and difluorination between the 2- and 3-positions of **H1**: the C3-monofluorinated **H7** has a higher log *P* than the C2-monofluorinated **H6**, but the C3-difluorinated **H9** has a lower log *P* compared to the C2-difluorinated **H8**. This can be qualitatively explained, over and above any context dependence issues, by taking into account the relative distance between the fluorination sites and both OH groups and comparing these with the 1-pentanol (**E1**) data (inset, Figure 5): 2,2-difluoropentan-1-ol (**E17**) is much more lipophilic than its geminal fluorination regioisomers **E5** and **E15**, resulting in **H8** to have a higher log *P* than **H9**. Conversely, 4-fluoropentan-1-ol **E3** is much less lipophilic, which must dominate the log *P* of **H6**, leading to its lower value.

Introduction of the skipped difluorination motif leads to a strong log *P* reduction, although the influence of the relative stereochemistry is again minimal. Hence, skipped difluorination is much less lipophilic than geminal difluorination (cf. **H8**/**H9**). Even the skipped trifluoro motif in **H4** leads to a log *P* decrease compared to **H1**; however, the skipped tetrafluorinated **H5** has a higher log *P*.

Also, in contrast to the butanediol scenario, introducing a second fluorine in the skipped position to an existing C−F (**H6** to **H2**/**H3**) or to an existing CF_2 (**H8** to **H4**) leads to a

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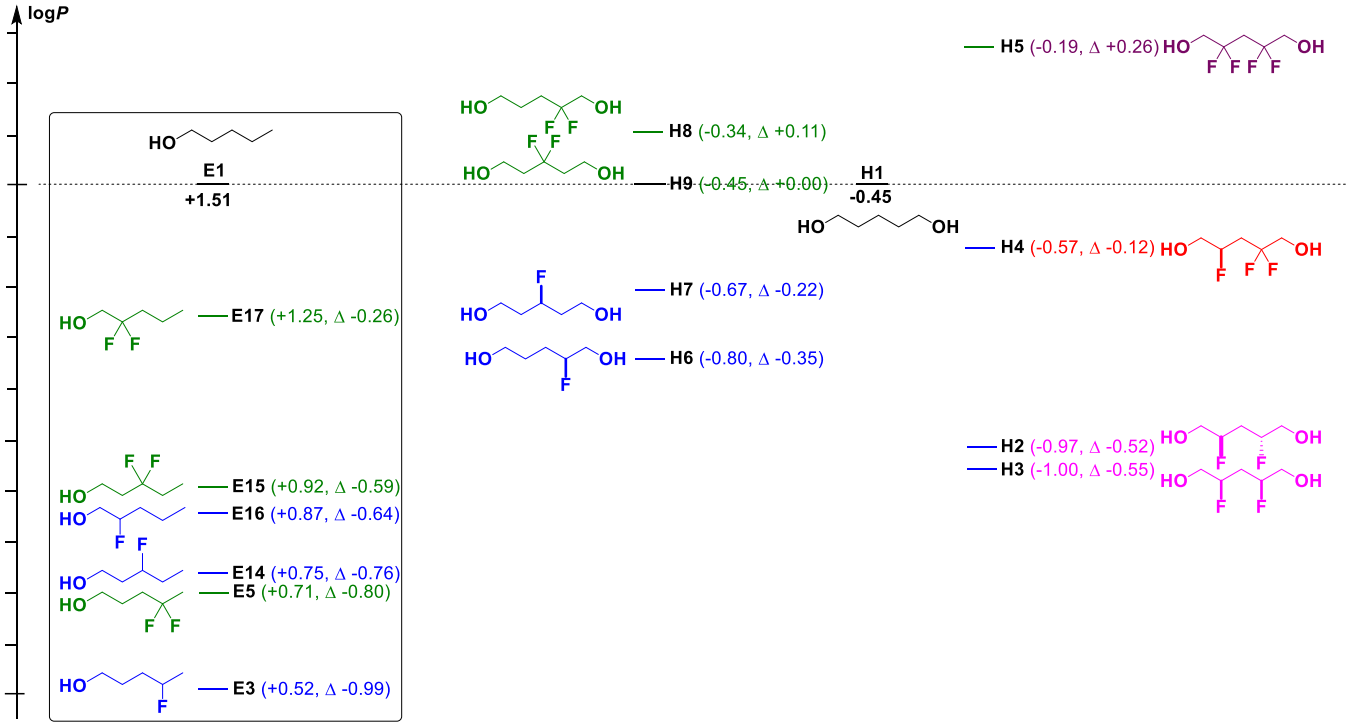

Figure 5. Lipophilicities of fluorinated 1,5-pentanediol derivatives, in comparison to relevant fluorinated 1-pentanols. Lipophilicity scales for the compound series are normalized to their nonfluorinated parents.

lipophilicity decrease. The log *P* of **H4** lies in between that of the monofluorinated **H6** and difluorinated **H8**. Introducing a CF_2 in the skipped position to an existing C−F (**H6** to **H4**) and to an existing CF_2 group (**H8** to **H5**) leads to a log *P* increase, albeit a rather modest one.

A direct comparison of the vicinal and the skipped motifs is given in Figure 6. It is immediately apparent that for a given motif comparison, the lipophilicities of the 1,5-pentanediol compounds are similar to or lower than those of the corresponding 1,4-butanediol analogues despite the extra CH_2 group. This is in stark contrast to the difference between the nonfluorinated **C1** and **H1**. So, the 1,ω-diols with the vicinal and skipped difluoride motifs have similar log *P* values (cf **C2**/**C3** with **H2**/**H3**), and for the tri- and tetrafluorinated versions, the C5 chain compounds have an even lower log *P* (cf **C4** with **H5** and **C5** with **H4**). This can be easily qualitatively explained by dipole arguments: in **C5** and **C4**, there will be abundant conformations with antiperiplanar C−F bonds, while in the skipped motifs, the C−F bonds will polarize antiperiplanar C−H bonds (the chemical shift of the central methylene group in **H5** is 2.67 ppm). The large difference between the skipped tetrafluorinated **H5** and the hexafluorinated **H10** is also worth noting.

The data in Figure 6 are also shown on a normalized scale to the butanediol derivatives (Figure 7), which nicely emphasizes the relative lipophilicity differences in light of a one-carbon chain extension: with mono- or geminal difluorination, there is a lipophilicity increase; with vicinal difluorination, the log *P* remains very similar; and with vicinal tri- and tetrafluorination, a log *P* reduction is obtained.

The difference in lipophilicities between 1,4-butanediol **C1** and 1,5-pentanediol **H1** and that of their stable perfluorinated analogues **C4** and **H10** (Figure 8) is worth noting.

The increase in lipophilicity is much greater when inserting a CF_2 group (**C4** to **H10**) compared to a CH_2 group (**C1** to **H1**). The very similar chemical shift values of the CH_2OH hydrogens in **C4** and **H10** (4.05 vs 4.10, $CDCl_3$) suggest that the tetrafluorinated moiety has a similar effect on alcohol polarizability as the hexafluorinated subunit, indicating that the larger lipophilicity increase upon inserting a difluoromethylene group is due to its larger hydrophobicity vs a methylene group. In comparing hydrocarbon and fluorocarbon containing amphiphilic compounds, differences in critical micelle concentration values led Hatanaka et al. to conclude that the hydrophobicity of a CF_2 group is 1.5 times that of a CH_2 group.[68] However, the context dependence of lipophilicity values does not allow us to derive similar conclusions from the observed lipophilicity differences: with the fluorinated derivatives being more apolar, the relative influence of hydrophobic surface should be reduced, so the log *P* difference could have been expected to be even larger. In addition, there is a further polarity effect at play: in the tetrafluoro motif, all dipoles potentially compensate each other, while this is not possible for the hexafluorinated motif. Hence, the latter motif will be comparatively more polar than the tetrafluorinated motif, indicating that the lipophilicity difference is even smaller than would have been the case if just hydrophobic CH_2 vs CF_2 surface difference considerations were made.

The experimental log *P* values of the 1,4- and 1,5-diol derivatives were also compared with a set of *c*log *P* values (see the Supporting Information for full details). The correlation values of most (fragment-based) calculation methods hovered between 0.8 and 0.9, which is less than that we have typically observed for the fluorinated alkanol derivatives.[23,25]

■ CONCLUSIONS

Lipophilicities of the complete series of vicinal fluorination motifs within the 1,4-butanediol scaffold have been systematically compared with those of the corresponding skipped fluorination motifs within the 1,5-pentanediol scaffold. For

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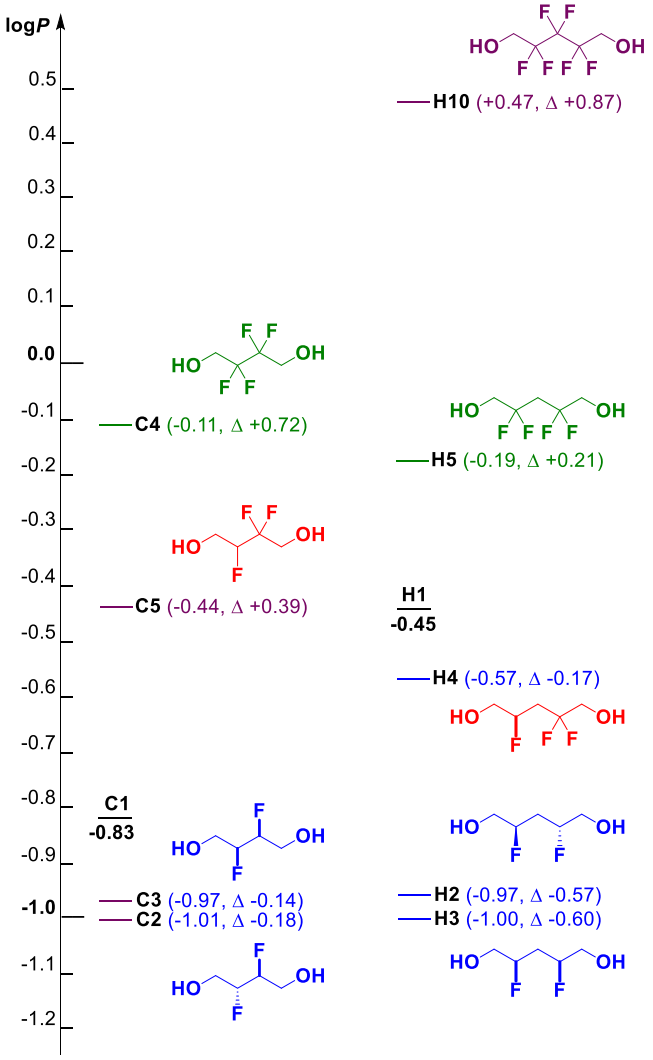

Figure 6. Comparison between vicinal and skipped fluorination motifs.

each of these series, a comparison with all possible monofluorinated and geminal difluorinated analogues is made, and with the perfluorinated analogues. This is the first study comparing the lipophilicities of these motifs.

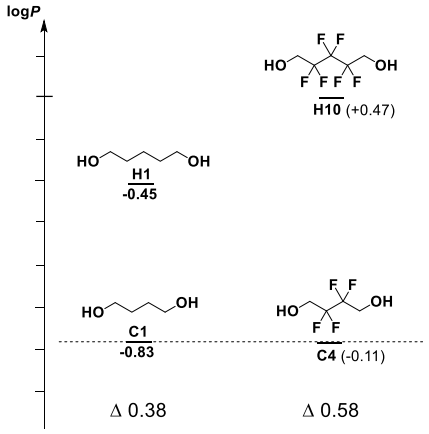

Figure 8. Comparing apparent lipophilicity contributions of CH_2 vs CF_2 groups. Lipophilicity scales for the compound series are normalized to the butanediol derivatives.

The C_2-symmetric skipped difluorinated enantiomers were synthesized from their respective enantiopure glutamic acid building blocks in nine steps, and the *meso*-skipped difluorinated pentanediol was obtained from levoglucosan in eight steps. In both cases, symmetrization to the diol only occurred in the final steps, with these routes generating monoprotected building blocks that would allow facile introduction of these advanced fluorinated substrates in target compounds. The skipped trifluorinated pentanediol was synthesized starting from protected glycidol in six steps, while the skipped tetrafluorinated target was obtained in seven steps from ethyl bromodifluoroacetate.

For both the vicinal and skipped fluorination motifs, log *P* increased with increasing fluorine number. For the vicinal fluorination, only the difluorinated analogue had a lower log *P* compared to the nonfluorinated parent, while for the skipped fluorination, the trifluorinated motif also had a lower log *P*. In absolute values, 1,4-butanediol with vicinal difluorination (*syn* or *anti*) has the same log *P* as 1,5-pentanediol with skipped difluorination (*syn* or *anti*), despite the extra methylene group in the latter (1,5-pentanediol itself has a higher log *P* than 1,4-butanediol). For the corresponding trifluorinated and tetrafluorinated situations, the pentanediols with the skipped motif

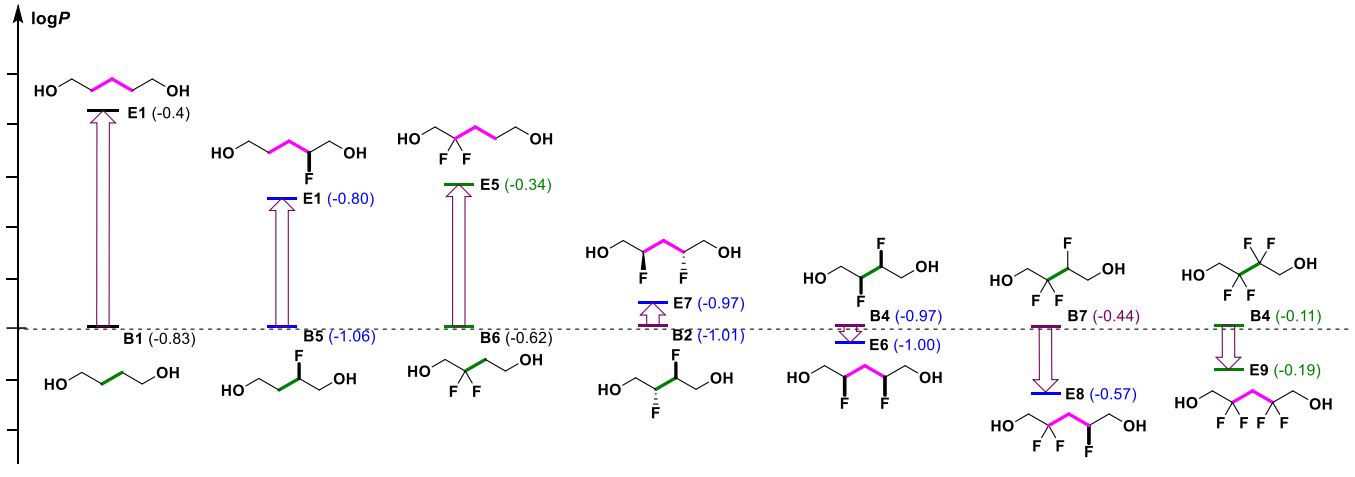

Figure 7. Chain extension with concomitant vicinal to skipped motif reorganization.

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have even lower log *P* values compared to the equivalent butanediols.

Starting from both the monofluorinated and geminal difluorinated 1,4-diols, a small log *P* increase is observed when introducing monofluorination at the adjacent carbons, which is much larger when introducing geminal difluorination at these carbons. In contrast, starting from both the monofluorinated and geminal difluorinated 1,5-diols, introducing monofluorination at the skipped carbon leads to a log *P* decrease, which only becomes a small increase when geminal difluorination is introduced there.

Hence, all of these observations illustrate the greater lipophilicity-reducing power of the skipped motif and emphasize the lipophilicity-increasing power of perfluoroalkylidene moieties.

As an aside, the log *P* difference between the nonfluorinated 1,4-butanediol and 1,5-pentanediol parents was compared with the lipophilicity difference between their stable perfluorinated congeners. This difference is smaller for the nonfluorinated diols (0.38 vs 0.58 log *P* units) and shows the larger hydrophobicity of a CF_2 group compared to a CH_2 group.

The synthetic work toward the skipped building blocks will be of general interest for applications in organic and medicinal chemistry. The insights regarding lipophilicity of the vicinal and skipped motifs will find application in medicinal chemistry, in particular, in drug development involving compounds with hydrocarbon/lipid chain appendages (e.g., many steroids, prostaglandins, etc), as well as taking into account possible metabolic stability issues.[69−71] Finally, the lipophilicity datasets will find application in the development of computational approaches toward lipophilicity estimations.

EXPERIMENTAL SECTION

General Conditions. All air-/moisture-sensitive reactions were carried out under an atmosphere of argon in glassware heated under high vacuum. Where required, reactions were heated using a heating block (DrySyn). All reagents and solvents were bought from commercial sources and used as supplied unless otherwise stated. Flash column chromatography was performed on silica gel (MERCK Geduran 60 Å; particle size, 40−63 μm) under pressure unless otherwise stated. All reported solvent mixtures are volume measures. Reactions were monitored by TLC (MERCK Kieselgel 60 F254, aluminum sheet), visualized under UV light (254 nm), and/or by staining with $KMnO_4$ (10% aq.). Fourier transform infrared (IR) spectra are reported in wavenumbers (cm^{-1}) and were recorded as neat films on a Thermo Scientific Nicolet iS5 spectrometer using neat samples (solid or liquid) unless otherwise stated. Electrospray mass spectra were obtained from a Waters Acquity TQD mass tandem quadrupole mass spectrometer and recorded in *m*/*z* (abundance). HRMS was obtained from a Bruker Daltonics MaXis time-of-flight (TOF) mass spectrometer (ESI), a Bruker Daltonics solariX FT-ICR mass spectrometer equipped with a 4.7T superconducting magnet (**27**, **43**, **44**, **45**, **46**, **H3**), a Thermo MAT900 XP double-focusing sector mass spectrometer (CI), or a LECO Pegasus HRT+ TOF mass spectrometer (EI). Samples were run in HPLC MeOH or MeCN. Optical rotations were recorded on an Optical Activity POLAAR 2001 at 589 nm. Melting points were obtained in an open capillary and are uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ or MeOD using a Bruker Ultrashield 400 or 500 MHz spectrometer. ^1H and ^{13}C chemical shifts (δ) are quoted in ppm relative to residual solvent peaks as appropriate. ^{19}F spectra were externally referenced to $CFCl_3$. The coupling constants (*J*) are given in hertz (Hz). The coupling constants have not been averaged. The NMR signals were designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), spt (septet), m (multiplet), or a combination of the above. For all novel compounds, detailed peak assignment was performed through the combined use of HSQC, HMBC, and COSY NMR experiments as required.

Determination of Log *P*. Lipophilicities of the fluorinated alkanols were determined using a previously published protocol:[27] to a 10 mL pear-shaped flask was added the compound (1.0−10 mg) for log *P* determination, the reference compound (1.0−10 mg, with known log *P* value, e.g., 2,2,2-trifluoroethanol, log *P*: +0.36), water (2 mL), and *n*-octanol (2 mL). The resulting biphasic mixture was stirred (at ±600 rpm) for 2 h at 25 °C and then left without stirring for 16 h at 25 °C to allow phase separation. An aliquot of 0.5 mL was taken from each phase using 1 mL syringes with long needles and added to two separate NMR tubes. A deuterated NMR solvent (0.1 mL, e.g., acetone-d_6) or a capillary tube containing deuterated NMR solvent was added to the NMR tubes to enable signal locking. Because of the volatility of the used compounds, the NMR tubes were sealed using a blowtorch. For NMR samples with directly added deuterated solvent, the tubes were inverted 20 times for mixing. For $^{19}F\{^1H\}$ NMR experiments, NMR parameters were set as follows: D1 30 s for the octanol sample, D1 60 s for the water sample, and O1P centered between two diagnostic fluorine peaks. If needed, an increased number of transients (NS) and/or narrower spectral window (SW) for a good S/N ratio (typically >300) was applied. After NMR data processing, integration ratios ρ_{oct} and ρ_{aq} (ρ_{oct} is defined as the integration ratio between the compound and the reference compound in the octanol sample; likewise for ρ_{aq}) were obtained and used in the equation $\log P_X = \log P_{ref} + \log(\rho_{oct}/\rho_{aq})$ to obtain the log *P* value of the compound. The log *P* measurement of each compound was run in triplicate. The log *P* values of nonfluorinated compounds were taken from the literature where available.

Synthesis. Targets **C4**, **H9**, and **H10** were commercially available.

*(**2R,4S**)-5-((tert-Butyldiphenylsilyl)oxy)-2-fluoropentane-1,4-diol ((**2R,4S**)-**24**).* Synthesized according to a modified procedure of Liotta et al.[52] To a stirred solution of lactone (***S***)-**26**[54] (2.00 g, 5.64 mmol) and NFSI (1.78 g, 5.64 mmol) in dry tetrahydrofuran (THF, 25 mL) at −78 °C, LiHMDS (1 M in THF, 6.80 mL, 6.80 mmol) was added dropwise over 45 min. The solution was stirred at −78 °C for 2 h, then warmed to room temperature (rt), and stirred for 14 h. The reaction was quenched by slow addition of water (0.12 mL), stirred for 30 min, and carefully concentrated in vacuo (bath temperature ≤ 30 °C). The residue was redissolved in CH_2Cl_2 (50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford crude (**2*R*,4*S***)-**25**. This was redissolved in a mixture of dry CH_2Cl_2 (3.4 mL) and EtOH (2.3 mL), to which $NaBH_4$ (0.533 g, 14.1 mmol) was added portionwise at 0 °C. The solution was stirred at rt for 16 h, then cooled to 0 °C, and quenched by cautious addition of sat. aq. NH_4Cl (10 mL). The mixture was stirred vigorously for 30 min at rt. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 40:60) to afford the title compound (**2*R*,4*S***)-**24** as a colorless crystalline solid (1.06 g, 50% over two steps). R_f 0.24 (hexane/EtOAc 40:60); mp 78−79 °C (CH_2Cl_2); $[\alpha]_D^{19}$ −1.3 (c 1.0, $CHCl_3$); IR 3362 (br w), 3071 (w), 2930 (m), 2858 (m), 1427 (m), 1111 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (4H, m, H_{Ph}), 7.49−7.39 (6H, m, H_{Ph}), 4.77 (1H, dqd, *J* = 47.9, 5.7, 3.7 Hz, H_2), 4.01−3.95 (1H, m, H_4), 3.85−3.72 (2H, m, H_1), 3.69 (1H, dd, *J* = 10.3, 3.6 Hz, H_5), 3.59 (1H, dd, *J* = 10.3, 7.2 Hz, $H_{5'}$), 2.80 (1H, d, *J* = 2.5 Hz, OH_4), 2.49 (1H, t, *J* = 5.1 Hz, OH_1), 1.90−1.80 (2H, m, H_3), 1.10 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.5 (C_{Ph}), 132.9 (C_{Ph}), 129.9 (C_{Ph}), 127.8 (C_{Ph}), 91.8 (d, J_{C-F} = 168.7 Hz, C_2), 68.3 (d, J_{C-F} = 5.1 Hz, C_4), 67.5 (C_5), 64.2 (d, J_{C-F} = 22.7 Hz, C_1), 34.1 (d, J_{C-F} = 20.5 Hz, C_3), 26.8 ($C_{tBu,Me}$), 19.2 ($C_{tBu,quat}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −189.7 (dquin, *J* = 48.9, 22.5, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −189.5 (s, F_2) ppm; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{21}H_{29}FNaO_3Si$ 399.1762; found 399.1767.

The synthesis was repeated from (***R***)-**26** (25.0 g, 70.5 mmol) to give (**2*S*,4*R***)-**24** (9.54 g, 36% over two steps). Spectroscopic data were identical except $[\alpha]_D^{19}$ +2.1 (c 1.0, $CHCl_3$).

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*1,6-Di-O-acetyl-2,3,4-trideoxy-2,4-fluoro-ß-D-glucopyranose (**27**).* Synthesized with a procedure of Zottola et al.[72] To a solution of **44** (431 mg, 2.87 mmol, 1.0) in Ac_2O (70 mL) at 0 °C was added TMSOTf (0.104 mL, 0.570 mmol) dropwise. The resulting mixture was stirred at 0 °C for 30 min before being diluted with CH_2Cl_2 (20 mL) and quenched with sat. aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 90:10 to 80:20) to afford the title compound **27** as a light brown solid (682 mg, 2.70 mmol, 94%). R_f 0.23 (hexane/acetone 80:20); IR 1760 (m), 1739 (s), 1245 (s), 1226 (s), 1124 (m), 1095 (m), 1052 (s), 1000 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, α:β 2.20:1.00) δ 6.27 (1H, t, J = 3.8 Hz, $H_{1\alpha}$), 5.74 (1H, dd, J = 7.4, 3.6 Hz, $H_{1\beta}$), 4.66 (1H, ddddd, J = 46.6, 12.0, 5.2, 3.7, 1.5 Hz, $H_{2\alpha}$), 4.53 (1H, ddd, J = 48.4, 10.3, 5.1 Hz, $H_{4\beta}$), 4.51 (1H, dddd, J = 48.4, 10.0, 5.2, 1.4 Hz, $H_{4\alpha}$), 4.45 (1H, ddddd, J = 48.8, 10.7, 7.3, 5.3, 1.1 Hz, $H_{2\beta}$), 4.35 (1H, ddd, J = 12.2, 2.9, 1.5 Hz, $H_{6\beta}$), 4.33 (1H, dt, J = 12.0, 2.5 Hz, $H_{6\alpha}$), 4.23 (1H, ddd, J = 12.4, 4.9, 1.5 Hz, $H_{6'\alpha}$), 4.21 (1H, ddd, J = 12.3, 5.5, 1.6 Hz, $H_{6'\beta}$), 3.95 (1H, dtt, J = 7.2, 4.6, 2.4 Hz, $H_{5\alpha}$), 3.87 (1H, dddd, J = 8.7, 5.6, 4.5, 3.0 Hz, $H_{5\beta}$), 2.77 (1H, dtt, J = 12.7, 7.8, 5.2 Hz, $H_{3eq\beta}$), 2.65 (1H, dquin, J = 10.6, 5.2 Hz, $H_{3eq\alpha}$), 2.22 (1H, dqd, J = 23.0, 11.4, 9.4 Hz, $H_{3ax\alpha}$), 2.19 (3H, s, $H_{Ac\alpha}$), 2.16 (3H, s, $H_{Ac\beta}$), 2.09 (3H, s, $H_{Ac\beta}$), 2.09 (3H, s, $H_{Ac\alpha}$), 2.06 (1H, dtdd, J = 22.9, 12.4, 10.5, 10.4 Hz, $H_{3ax\beta}$) ppm; $^1H\{^{19}F\}$ NMR (500 MHz, $CDCl_3$) δ 6.27 (1H, d, J = 3.6 Hz, $H_{1\alpha}$), 5.74 (1H, d, J = 7.4 Hz, $H_{1\beta}$), 4.67 (1H, ddd, J = 12.0, 5.1, 3.7 Hz, $H_{2\alpha}$), 4.55−4.49 (2H, m, $H_{4\alpha+4\beta}$), 4.45 (1H, ddd, J = 10.7, 7.3, 5.3 Hz, $H_{2\beta}$), 4.35 (1H, dd, J = 12.2, 2.9 Hz, $H_{6\beta}$), 4.33 (1H, dd, J = 12.0, 2.5 Hz, $H_{6\alpha}$), 4.23 (1H, dd, J = 12.3, 4.9 Hz, $H_{6'\alpha}$), 4.21 (1H, dd, J = 12.3, 5.5 Hz, $H_{6'\beta}$), 3.95 (1H, ddd, J = 9.7, 4.9, 2.4 Hz, $H_{5\alpha}$), 3.87 (1H, ddd, J = 8.7, 5.6, 2.9 Hz, $H_{5\beta}$), 2.77 (1H, dt, J = 12.3, 5.2 Hz, $H_{3eq\beta}$), 2.64 (1H, dt, J = 11.2, 5.1 Hz, $H_{3eq\alpha}$), 2.24 (1H, q, J = 11.4 Hz, $H_{3ax\alpha}$), 2.19 (3H, s, $H_{Ac\alpha}$), 2.16 (3H, s, $H_{Ac\beta}$), 2.09 (3H, s, $H_{Ac\beta}$), 2.09 (3H, s, $H_{Ac\alpha}$), 2.05 (1H, ddd, J = 12.3, 10.5, 10.4 Hz, $H_{3ax\beta}$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ 170.56 ($C_{C=O\alpha}$), 170.55 ($C_{C=O\beta}$), 168.94 ($C_{C=O\beta}$), 168.86 ($C_{C=O\alpha}$), 92.7 (dd, $J_{C\text{-}F}$ = 26.1, 0.8 Hz, $C_{1\beta}$), 87.4 (dd, $J_{C\text{-}F}$ = 22.9, 1.27 Hz, $C_{1\alpha}$), 84.9 (dd, $J_{C\text{-}F}$ = 185.5, 10.5 Hz, $C_{2\beta}$), 83.6 (dd, $J_{C\text{-}F}$ = 189.5, 12.2 Hz, $C_{2\alpha}$), 83.4 (dd, $J_{C\text{-}F}$ = 182.4, 10.0 Hz, $C_{4\beta}$), 83.3 (dd, $J_{C\text{-}F}$ = 182.1, 11.7 Hz, $C_{4\alpha}$), 75.3 (dd, $J_{C\text{-}F}$ = 25.0, 0.9 Hz, $C_{5\beta}$), 69.8 (dd, $J_{C\text{-}F}$ = 24.4, 0.8 Hz, $C_{5\alpha}$), 62.1 (d, $J_{C\text{-}F}$ = 1.0 Hz, $C_{6\beta}$), 61.9 ($C_{6\alpha}$), 33.8 (t, $J_{C\text{-}F}$ = 20.5 Hz, $C_{3\beta}$), 30.9 (t, $J_{C\text{-}F}$ = 20.4 Hz, $C_{3\alpha}$), 20.9 ($C_{CH3\text{-}Ac;\beta}$), 20.8 ($C_{CH3\text{-}Ac;\alpha}$), 20.69 ($C_{CH3\text{-}Ac;\beta}$), 20.68 ($C_{CH3\text{-}Ac;\alpha}$) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ −188.5 to −188.6 (m, d_{obs}, J = 48.3 Hz, $F_{4\alpha}$), −189.9 to −190.0 (m, d_{obs}, J = 48.3 Hz, $F_{4\beta}$), −191.0 to −191.2 (m, d_{obs}, J = 48.6 Hz, $F_{2\beta}$), −192.4 (ddddd, J = 46.5, 9.3, 4.7, 3.6, 1.4 Hz, $F_{2\alpha}$) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ −188.6 (d, J = 3.6 Hz, $F_{4\alpha}$), −189.9 (d, J = 5.0 Hz, $F_{4\beta}$), −191.1 (d, J = 5.4 Hz, $F_{2\beta}$), −192.4 (d, J = 3.6 Hz, $F_{2\alpha}$) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{10}H_{14}F_2NaO_5$ 275.0702; found 275.0702.

*5-(Benzyloxy)-4-fluoropentanal (**30**).* To a solution of **47** (538 mg, 2.58 mmol) in a mixture of MeCN (22.1 mL) and water (3.7 mL) at rt was added a solution of $RuCl_3$ in water (2.58 mL, 0.035 M, 0.090 mmol). $NaIO_4$ (1.11 g, 5.17 mmol) was added portionwise over 5 min. The mixture was stirred for 24 h and quenched by slow addition of sat. aq. $Na_2S_2O_3$ (25 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL), washed with sat. brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 70:30) to afford the title compound **30** as a colorless oil (212 mg, 39%). R_f 0.32 (hexane/EtOAc 70:30); IR 3657 (w), 2980 (s), 2889 (m), 1722 (s), 1382 (m), 1092 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (1H, q, J = 1.0 Hz, H_1), 7.39−7.29 (5H, m, H_{Ph}), 4.79−4.61 (1H, m, H_4), 4.59 (2H, s, H_6), 3.61 (2H, dd, J = 22.7, 4.5 Hz, H_5), 2.72−2.57 (2H, m, H_2), 2.06−1.94 (2H, m, H_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.1 (C_1), 137.7 (C_{Ph}), 128.5 (C_{Ph}), 127.8 (C_{Ph}), 127.7 (C_{Ph}), 91.8 (d, $J_{C\text{-}F}$ = 171.7 Hz, C_4), 73.5 (C_{Bn}), 71.5 (d, $J_{C\text{-}F}$ = 22.0 Hz, C_5), 39.2 (d, $J_{C\text{-}F}$ = 3.7 Hz, C_2), 24.1 (d, $J_{C\text{-}F}$ = 21.3 Hz, C_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −188.5 to −188.9 (m, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −188.8 (s, F_4) ppm; HRMS (EI) m/z: $[M^\bullet]^+$ calcd for $C_{12}H_{15}FO_2$ 210.1051; found 210.1052.

*5-((tert-Butyldiphenylsilyl)oxy)-4,4-difluoropentanal (**33**).* To a solution of ester **50** (4.80 g, 11.4 mmol) in CH_2Cl_2 (91 mL) at −78 °C was added DIBAL (1 M in CH_2Cl_2, 13.7 mL, 13.7 mmol) slowly over 15 min, keeping the internal temperature below −60 °C. The reaction was stirred for 3 h, then quenched by slow addition of aq. Rochelle's salt (90 mL), allowed to warm to rt, and stirred for a further 1 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford the title compound **33** as a clear colorless oil (4.36 g, quant.). R_f 0.50 (hexane/EtOAc 70:30); IR 2932 (m), 2858 (m), 1726 (m), 1428 (m), 1106 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, s, H_1), 7.69−7.65 (4H, m, H_{Ph}), 7.49−7.39 (6H, m, H_{Ph}), 3.77 (2H, t, J = 12.0 Hz, H_5), 2.69 (2H, t, J = 7.5 Hz, H_2), 2.35 (2H, tt, J = 17.5, 7.6 Hz, H_3), 1.09 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.1 (C_1), 135.6 (C_{Ph}), 132.4 (C_{Ph}), 130.0 (C_{Ph}), 127.8 (C_{Ph}), 122.6 (t, $J_{C\text{-}F}$ = 242.8 Hz, C_4), 65.1 (t, $J_{C\text{-}F}$ = 34.8 Hz, C_5), 36.3 (t, $J_{C\text{-}F}$ = 3.7 Hz, C_2), 26.7 ($C_{tBu,Me}$), 26.0 (t, $J_{C\text{-}F}$ = 24.9 Hz, C_3), 19.2 ($C_{tBu,quat}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.0 (tt, J = 17.3, 12.1 Hz, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −108.0 (s, F_4) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}F_2NaO_2Si$ 399.1562; found 399.1572.

*(**2R,4S**)-5-((tert-Butyldiphenylsilyl)oxy)-2-fluoro-4-hydroxypentanamide (**38**).* Synthesized according to the procedure of Liotta et al.[52] To a stirred solution of lactone (**S**)-**26**[54] (200 mg, 0.564 mmol) and NFSI (178 mg, 0.564 mmol) in THF (2.5 mL) at −78 °C, LiHMDS (1 M in THF, 0.68 mL, 0.68 mmol) was added dropwise over 1 h. The solution was stirred at −78 °C for 2 h, then warmed to rt, and stirred for 1 h. The reaction was quenched by cautious addition of sat. aq. NH_4Cl (0.1 mL), then diluted with Et_2O (7.5 mL), and washed sequentially with sat. aq. $NaHCO_3$ (2 × 7.5 mL) and sat. brine (7.5 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 90:10 to 0:100) to obtain (**2R,4S**)-**25** (22 mg, 10%) as a white solid and the title compound **38** as a yellow oil (33 mg, 15%). R_f 0.24 (hexane/EtOAc 40:60); IR 3323 (br m), 3071 (w), 2930 (m), 2857 (m), 1679 (s), 1427 (m), 1105 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (4H, m, H_{Ph}), 7.47−7.38 (6H, m, H_{Ph}), 6.34 (1H, br s, NH_2), 6.09 (1H, br s, NH_2), 5.06 (1H, dt, J = 49.2, 6.2 Hz, H_2), 4.07−4.00 (1H, m, H_4), 3.69 (1H, dd, J = 10.3, 4.0 Hz, H_5), 3.60 (1H, dd, J = 10.3, 7.0 Hz, H_5), 2.82 (1H, d, J = 4.8 Hz, OH), 2.14 (2H, dt, J = 24.5, 6.2 Hz, H_3), 1.08 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9 (d, $J_{C\text{-}F}$ = 20.5 Hz, C_1), 135.5 (C_{Ph}), 132.94 (C_{Ph}), 132.91 (C_{Ph}), 129.9 (C_{Ph}), 127.8 (C_{Ph}), 89.2 (d, $J_{C\text{-}F}$ = 191.5 Hz, C_2), 68.4 (d, $J_{C\text{-}F}$ = 4.4 Hz, C_4), 67.3 (C_5), 35.5 (d, $J_{C\text{-}F}$ = 20.5 Hz, C_3), 26.8 ($C_{tBu,Me}$), 19.2 ($C_{tBu,quat}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −186.4 (1F, dtd, J = 49.2, 24.5, 3.5 Hz, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −186.3 (1F, s, F_2) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{21}H_{28}FNNaO_3Si$ 412.1715; found 412.1716.

*(**2R, 4S**)-5-((tert-Butyldiphenylsilyl)oxy)-2-fluoro-4-hydroxypentyl Benzoate ((**2R,4S**)-**39**).* To a solution of (**2R,4S**)-**24** (0.900 g, 2.39 mmol) and Et_3N (0.67 mL, 4.8 mmol) in CH_2Cl_2 (12.0 mL) at 0 °C was added benzoyl chloride (0.28 mL, 2.4 mmol) dropwise over 5 min. The mixture was warmed to rt, stirred for 16 h, and then diluted with CH_2Cl_2 (40 mL). The organic layer was washed with water (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 90:10 to 70:30) to afford the title compound ((**2R,4S**)-**39**) as a yellow oil (0.768 g, 67%). R_f 0.29 (hexane/EtOAc 70:30); $[\alpha]_D^{19}$ −11.6 (c 0.5, $CHCl_3$); IR 3656 (w), 2980 (s), 2889 (m), 1720 (m), 1270 (s), 1111 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09−8.06 (2H, m, H_{Ph}), 7.69−7.66 (4H, m, H_{Ph}), 7.59 (1H, tt, J = 6.9, 1.3 Hz, H_{Ph}), 7.48−7.38 (8H, m, H_{Ph}), 5.10−4.92 (1H, m, d_{obs}, J = 48.3 Hz, H_2), 4.58−4.42 (2H, m, H_1), 4.02−3.95 (1H, m, H_4), 3.72 (1H, dd, J = 10.3, 3.9 Hz, H_5), 3.63 (1H, dd, J = 10.3, 7.1 Hz, $H_{5'}$), 2.59 (1H, d, J = 3.6 Hz, OH), 2.06−1.83 (2H, m, H_3), 1.09 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2 ($C_{C=O}$), 135.5 (C_{Ph}),

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133.2 (C_{Ph}), 132.91 (C_{Ph}), 132.89 (C_{Ph}), 129.9 (C_{Ph}), 129.72 (C_{Ph}), 129.69 (C_{Ph}), 128.4 (C_{Ph}), 127.8 (C_{Ph}), 89.3 (d, $J_{C\text{-}F}$ = 171.7 Hz, C_2), 68.6 (d, $J_{C\text{-}F}$ = 5.1 Hz, C_4), 67.4 (C_5), 65.9 (d, $J_{C\text{-}F}$ = 22.0 Hz, C_1), 34.5 (d, $J_{C\text{-}F}$ = 20.5 Hz, C_3), 26.8 ($C_{tBu,Me}$), 19.2 ($C_{tBu,quat}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −186.6 (dqd, J = 49.0, 24.4, 18.2 Hz, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −186.4 (s, F_2) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{33}FNaO_4Si$ 503.2024; found 503.2029.

The synthesis was repeated from (**2*S*,4*R*)-24** (9.53 g, 25.3 mmol) to give (**2*S*,4*R*)-39** (9.14 g, 75%). Spectroscopic data were identical except $[\alpha]_D^{19}$ +10.2 (c 1.0, $CHCl_3$).

(2R,4R)-5-((tert-Butyldiphenylsilyl)oxy)-2,4-difluoropentyl Benzoate ((2R,4R)-40). To a stirred solution of (**2*R*,4*S*)-39** (584 mg, 1.22 mmol) in dry CH_2Cl_2 (12.2 mL) at 0 °C was added DAST (0.32 mL, 2.44 mmol) dropwise. The solution was stirred at 0 °C for 1 h and then quenched by cautious addition of sat. aq. $NaHCO_3$ (36 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with sat. brine (36 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 100:0 to 70:30) to afford the title compound (**2*R*,4*R*)-40** as a yellow oil (430 mg) containing an unknown impurity, which was taken forward in the next step. An aliquot was further purified by flash column chromatography (Biotage Isolera One, ZIP KP-SIL 5 g Column, hexane/acetone 100:0 to 70:30) for analysis. R_f 0.49 (hexane/EtOAc 70:30); $[\alpha]_D^{26}$ +9.9 (c 1.2, $CHCl_3$, purified sample); IR 3071 (w), 2932 (w), 2858 (w), 1723 (s), 1269 (s), 1111 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.08 (2H, m, H_{Ph}), 7.71−7.67 (4H, m, H_{Ph}), 7.60 (1H, tt, J = 7.5, 1.3 Hz, H_{Ph}), 7.49−7.38 (10H, m, H_{Ph}), 5.11 (1H, dddt, J = 49.3, 9.1, 6.0, 2.9 Hz, H_2), 4.94−4.77 (1H, m, d_{obs}, J = 48.7 Hz, H_4), 4.56 (1H, ddd, J = 24.0, 12.0, 2.9 Hz, H_1), 4.47 (1H, ddd, J = 23.7, 12.6, 5.5 Hz, $H_{1'}$), 3.88 (1H, ddd, J = 19.7, 11.6, 3.7 Hz, H_5), 3.78 (1H, ddd, J = 25.1, 11.6, 4.3 Hz, $H_{5'}$), 2.22−1.96 (2H, m, H_3), 1.08 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1 ($C_{C=O}$), 135.6 (C_{Ph}), 135.5 (C_{Ph}), 133.3 (C_{Ph}), 133.03 (C_{Ph}), 132.96 (C_{Ph}), 129.8 (C_{Ph}), 129.7 (C_{Ph}), 129.6 (C_{Ph}), 128.4 (C_{Ph}), 127.8 (C_{Ph}), 89.6 (dd, $J_{C\text{-}F}$ = 173.1, 3.7 Hz, C_4), 87.7 (dd, $J_{C\text{-}F}$ = 173.1, 3.7 Hz, C_2), 66.1 (d, $J_{C\text{-}F}$ = 22.0 Hz, C_1), 65.6 (d, $J_{C\text{-}F}$ = 23.5 Hz, C_5), 33.7 (t, $J_{C\text{-}F}$ = 20.9 Hz, C_3), 26.7 ($C_{tBu,Me}$), 19.3 ($C_{tBu,quat}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −189.9 to −190.2 (m, F_2), −190.7 to −191.1 (m, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −190.1 (s, F_2), −190.9 (s, F_4) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{32}F_2NaO_3Si$ 505.1981; found 505.1992.

The synthesis was repeated from (**2*S*,4*R*)-39** (9.13 g, 19.0 mmol) to give (**2*S*,4*S*)-40** (7.32 g) containing an unknown impurity, which was taken forward in the next step. Spectroscopic data were identical except $[\alpha]_D^{27}$ −10.4 (c 0.5, $CHCl_3$, purified sample).

(2R,4R)-2,4-Difluoro-5-hydroxypentyl Benzoate ((2R,4R)-41). To a stirred solution of (**2*R*,4*R*)-40** (500 mg) in dry THF (10 mL) at 0 °C was added TBAF (1 M in THF, 1.25 mL, 1.25 mmol) dropwise. The mixture was stirred at rt for 2 h before sat. aq. NH_4Cl (10 mL) was added, and the mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with sat. brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 90:10 to 60:40) to afford the title compound (**2*R*,4*R*)-41** as a yellow solid (195 mg, 56% over two steps). R_f 0.14 (hexane/EtOAc 70:30); $[\alpha]_D^{26}$ +11.1 (c 1.0, $CHCl_3$); mp 51−53 °C (CH_2Cl_2); IR 3328 (br m), 2971 (m), 1727 (m), 1710 (s), 1284 (s) $cm^{-1}cm^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, d, J = 7.1 Hz, H_{Ph}), 7.59 (1H, t, J = 7.5 Hz, H_{Ph}), 7.46 (2H, t, J = 8.2 Hz, H_{Ph}), 5.07 (1H, dddt, J = 48.9, 9.9, 5.6, 2.8 Hz, H_2), 4.87 (1H, dddt, J = 49.3, 9.9, 5.6, 2.9 Hz, H_4), 4.54 (1H, ddd, J = 24.1, 12.8, 2.9 Hz, H_1), 4.44 (1H, ddd, J = 23.8, 12.6, 5.9 Hz, $H_{1'}$), 3.87 (1H, ddd, J = 24.3, 12.5, 2.3 Hz, H_5), 3.71 (1H, ddd, J = 25.1, 12.1, 5.9 Hz, $H_{5'}$), 2.26 (1H, br s, OH), 2.18−1.90 (2H, m, H_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2 ($C_{C=O}$), 133.3 (C_{Ph}), 129.7 (C_{Ph}), 129.5 (C_{Ph}), 128.4 (C_{Ph}), 90.2 (dd, $J_{C\text{-}F}$ = 169.8, 2.6 Hz, C_4), 87.6 (dd, $J_{C\text{-}F}$ = 173.5, 3.3 Hz, C_2), 66.0 (d, $J_{C\text{-}F}$ = 22.0 Hz, C_1), 64.7 (d, $J_{C\text{-}F}$ = 21.3 Hz, C_5), 33.2 (t, $J_{C\text{-}F}$ = 20.9 Hz, C_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −189.8 to −190.2 (m, F_2), −192.7 to −193.1 (m, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −189.9 (s, F_2), −192.8 (s, F_4) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{14}F_2NaO_3$ 267.0803; found 267.0796.

The synthesis was repeated from (**2*S*,4*S*)-40** (7.18 g) to give (**2*S*,4*S*)-41** (2.71 g, 61% over two steps). Spectroscopic data were identical except $[\alpha]_D^{20}$ −10.0 (c 1.0, $CHCl_3$).

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-3-O-phenylthionoformyl-β-D-glucopyranoside (43). To a solution of **28**[56,57] (1.92 g, 11.6 mmol) in CH_2Cl_2 (54 mL) was added pyridine (1.87 mL, 23.1 mmol). The mixture was cooled to 0 °C and *O*-phenyl chorothionoformate (1.92 mL, 13.9 mmol) was added dropwise. The solution was stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 90:10 to 80:20) to afford the title compound **43** as an off-white solid (3.33 g, 95%). R_f 0.26 (petroleum ether/EtOAc 90:10); $[\alpha]_D^{30}$ −54.5 (c 1.0, $CHCl_3$); mp 104−108 °C (not recrystallized); IR 2973 (br w), 2906 (w), 1274 (s), 1207 (s), 1057 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.43 (2H, m, H_{meta}), 7.34 (1H, tt, J = 7.5, 1.1 Hz, H_{para}), 7.15−7.11 (2H, m, H_{ortho}), 5.68−5.66 (1H, m, H_1), 5.63 (1H, tquin, J = 16.0, 1.5 Hz, H_3), 4.87−4.84 (1H, m, H_5), 4.65−4.56 (1H, m, d_{obs}, J = 43.7 Hz, H_4), 4.50 (1H, dq, J = 44.3, 1.1 Hz, H_2), 4.01 (1H, dt, J = 8.1, 1.1 Hz, H_{6endo}), 3.89−3.85 (1H, m, H_{6exo}) ppm; $^1H\{^{19}F\}$ NMR (500 MHz, $CDCl_3$) δ 7.48−7.43 (2H, m, H_{meta}), 7.34 (1H, tt, J = 7.5, 1.1 Hz, H_{para}), 7.14−7.11 (2H, m, H_{ortho}), 5.67 (1H, br t, J = 1.4 Hz, H_1), 5.63 (1H, quin, J = 1.5 Hz, H_3), 4.85 (1H, dq, J = 6.0, 1.7 Hz, H_5), 4.61−4.61 (1H, m, H_4), 4.51−4.50 (1H, m, H_2), 4.01 (1H, dd, J = 8.1, 1.1 Hz, H_{6endo}), 3.87 (1H, dd, J = 8.1, 5.9 Hz, H_{6exo}) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 193.1 ($C_{C=S}$), 153.3 (C_{ipso}), 129.8 (C_{meta}), 127.0 (C_{para}), 121.6 (C_{ortho}), 98.4 (d, $J_{C\text{-}F}$ = 27.9 Hz, C_1), 86.1 (dd, $J_{C\text{-}F}$ = 183.4, 2.9 Hz, C_4), 83.9 (dd, $J_{C\text{-}F}$ = 185.2, 1.8 Hz, C_2), 76.6 (dd, $J_{C\text{-}F}$ = 35.8, 34.1 Hz, C_3), 73.5 (d, $J_{C\text{-}F}$ = 21.3 Hz, C_5), 63.9 (d, $J_{C\text{-}F}$ = 8.8 Hz, C_6) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ −184.2 (ddddd, J = 44.3, 16.1, 10.4, 5.0, 1.4 Hz, F_4), −189.8 (dddd, J = 44.4, 16.1, 2.1, 1.1 Hz, F_2) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ −184.2 (s, F_4), −189.8 (s, F_2) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{12}F_2NaO_4S$ 325.0317; found 325.0316.

1,6-Anhydro-2,3,4-trideoxy-2,4-difluoro-β-D-glucopyranose (44). Synthesized with a procedure of Kirwan et al.[65] To a solution of **43** (3.18 g, 10.5 mmol) in triethylsilane (79.0 mL, 494 mmol) was added benzoyl peroxide (509 mg, 2.10 mmol). The resulting mixture was heated to 120 °C for 1 h. The reaction was cooled to rt, a further aliquot of benzoyl peroxide (509 mg, 2.10 mmol) was added, and the reaction was reheated to 120 °C for 1 h. This was repeated a further three times (five additions in total). The mixture was concentrated in vacuo and diluted with sat. aq. $NaHCO_3$ (75 mL) and CH_2Cl_2 (150 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (3 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/Et_2O 90:10 to 60:40) to afford the title compound **44** as a white powder with a 5% impurity of benzoic acid by mass (1.32 g, 8.35 mmol, 80% calculated for the pure compound). An aliquot was dissolved in CH_2Cl_2, washed three times with sat. $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo for analysis. R_f 0.55 (Et_2O/hexane 70:30); $[\alpha]_D^{27}$ −75.6 (c 0.69, $CHCl_3$); mp 105−109 °C (not recrystallized); IR 2985 (w), 2910 (w), 2371 (w), 2353 (w), 1145 (m), 1064 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (1H, br s, H_1), 4.76 (1H, ddt, J = 7.8, 5.6, 2.7 Hz, H_5), 4.58−4.32 (2H, m, H_{2+4}), 3.85 (1H, dtd, J = 7.9, 5.3, 2.6 Hz, H_{6exo}), 3.75 (1H, dt, J = 8.1, 1.2 Hz, H_{6endo}), 2.34−2.01 (2H, m, $H_{3eq+3ax}$) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 99.1 (d, $J_{C\text{-}F}$ = 25.7 Hz, C_1), 84.9 (dd, $J_{C\text{-}F}$ = 181.9, 1.5 Hz, C_4), 83.3 (dd, $J_{C\text{-}F}$ = 181.2, 1.5 Hz, C_2), 74.5 (d, $J_{C\text{-}F}$ = 19.8 Hz, C_5), 64.1 (d, $J_{C\text{-}F}$ = 7.3 Hz, C_6), 27.6 (t, $J_{C\text{-}F}$ = 22.4 Hz, C_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −180.6 to −181.0 (m, F_4), −186.0 to −186.3 (m, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −180.7 (d, J = 5.2 Hz, F_4),

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−186.0 (d, J = 3.5 Hz, F_2) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_6H_8F_2NaO_2$ 173.0385; found 173.0390.

*(2R,3S,5R)-3,5-Difluorohexane-1,2,6-triol (**45**).* To a solution of **27** (495 mg, 1.96 mmol) in MeOH (4.0 mL) and water (40 mL) at 0 °C was added $NaBH_4$ (742 mg, 19.6 mmol) portionwise. The solution was stirred at rt for 3 h before being cooled to 0 °C for addition of a further portion of $NaBH_4$ (742 mg, 19.6 mmol). The resulting mixture was stirred at rt for 18 h. The reaction was quenched with aq. 1 M HCl (40 mL), and the resulting mixture was stirred for 1 h before being concentrated in vacuo. The residue was redissolved in CH_2Cl_2/acetone, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5 to 80:20) to afford the title compound **45** as a yellow oil (195 mg, 59%). R_f 0.40 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{30}$ −14.5 (c 0.91, MeOH); IR 3340 (br m), 2939 (w), 2359 (w), 1042 (s) cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 4.78 (1H, dqd, J = 48.8, 6.0, 3.3 Hz, H_5), 4.65 (1H, dddd, J = 48.6, 8.3, 6.0, 3.6 Hz, H_3), 3.76−3.57 (5H, m, H_{1+2+6}), 2.21−2.00 (2H, m, H_4) ppm; $^1H\{^{19}F\}$ NMR (500 MHz, MeOD) δ 4.74 (1H, qd, J = 6.0, 3.3 Hz, H_5), 4.62 (1H, ddd, J = 8.3, 6.0, 3.6 Hz, H_3), 3.74−3.64 (4H, m, H_{1+2+6}), 3.59 (1H, dd, J = 11.4, 5.9 Hz, $H_{1'}$), 2.16−2.04 (2H, m, H_4) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, MeOD), δ 91.7 (dd, $J_{C\text{-}F}$ = 169.8, 2.7 Hz, C_5), 90.3 (dd, $J_{C\text{-}F}$ = 170.8, 5.5 Hz, C_3), 72.7 (d, $J_{C\text{-}F}$ = 23.6 Hz, C_2), 63.3 (d, $J_{C\text{-}F}$ = 22.7 Hz, C_6), 62.1 (d, $J_{C\text{-}F}$ = 6.4 Hz, C_1), 32.2 (t, $J_{C\text{-}F}$ = 20.9 Hz, C_4) ppm; ^{19}F NMR (471 MHz, MeOD) δ −189.3 to −189.6 (m, F_5), −191.0 to −191.3 (m, F_3) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, MeOD) δ −189.5 (d, J = 3.2 Hz, F_5), −191.1 (d, J = 2.9 Hz, F_3) ppm; HRMS (ESI) m/z: $[M + Na]^+$, calcd for $C_6H_{12}F_2NaO_3$ 193.0647; found 193.0650.

*(3S,5R)-3,5-Difluorotetrahydro-2H-pyran-2-ol (**46**).* To a solution of **45** (218 mg, 1.28 mmol) in water (20 mL) at 0 °C was added $NaIO_4$ (411 mg, 1.92 mmol). The resulting mixture was warmed to rt and stirred for 3 h before being diluted with water (20 mL) and concentrated in vacuo. The residue was redissolved in acetone/CH_2Cl_2, and the insoluble material was removed by filtration. The filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 80:20) to afford the title compound **46** as a white crystalline solid (151 mg, 84%). R_f 0.32 (hexane/acetone 80:20); $[\alpha]_D^{30}$ +12.9 (c 0.7, $CHCl_3$); mp 65−68 °C (hexane/acetone); IR 3394 (br m), 2949 (w), 1098 (s), 1036 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, α/β 1.00:0.42) δ 5.25 (1H, br d, J = 7.9 Hz, $H_{1\alpha}$), 4.90 (1H, dt, J = 12.2, 2.0 Hz, $H_{1\beta}$), 4.70−4.58 (3H, m, $H_{2\beta+4\alpha+4\beta}$), 4.50 (1H, dq, J = 44.9, 3.4 Hz, $H_{2\alpha}$), 4.15 (1H, ddd, J = 37.1, 13.4, 1.8 Hz, $H_{5ax\alpha}$), 4.15−4.09 (1H, m, $H_{5eq\beta}$), 3.86 (1H, tt, J = 13.5, 2.5 Hz, $H_{5eq\alpha}$), 3.74 (1H, dddt, J = 24.5, 12.5, 2.8, 1.1 Hz, $H_{5ax\beta}$), 3.34 (1H, br s, $OH_{\alpha+\beta}$), 2.50 (1H, dttd, J = 14.4, 11.5, 5.9, 2.1 Hz, $H_{3eq\beta}$), 2.38−2.10 (4H, m, $H_{3\alpha+3ax\beta}$) ppm; $1H\{^{19}F\}$ NMR (500 MHz, $CDCl_3$) δ 5.25 (1H, br d, J = 1.9 Hz, $H_{1\alpha}$), 4.89 (1H, d, J = 1.9 Hz, $H_{1\beta}$), 4.65−4.63 (1H, m, $H_{4\alpha}$), 4.62−4.58 (2H, m, $H_{2\beta+4\beta}$), 4.50 (1H, q, J = 3.2 Hz, $H_{2\alpha}$), 4.15 (1H, dd, J = 13.4, 1.8 Hz, $H_{5ax\alpha}$), 4.12 (1H, ddd, J = 12.4, 4.9, 2.0 Hz, $H_{5eq\beta}$), 3.86 (1H, dt, J = 13.0, 2.5 Hz, $H_{5eq\alpha}$), 3.73 (1H, ddd, J = 12.5, 2.9, 1.0 Hz, $H_{5ax\beta}$), 3.33 (1H, br s, $OH_{\alpha+\beta}$), 2.49 (1H, dtd, J = 14.4, 5.9, 2.1 Hz, $H_{3eq\beta}$), 2.33 (1H, dddt, J = 15.6, 4.7, 3.5, 1.1 Hz, $H_{3eq\alpha}$), 2.22 (1H, dt, J = 15.6, 3.5 Hz, $H_{3ax\alpha}$), 2.19−2.15 (1H, m, $H_{3ax\beta}$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 91.7 (d, $J_{C\text{-}F}$ = 19.3 Hz, $C_{1\beta}$), 91.2 (d, $J_{C\text{-}F}$ = 31.2 Hz, $C_{1\alpha}$), 85.6 (dd, $J_{C\text{-}F}$ = 182.9, 4.0 Hz, $C_{2\beta}$), 84.6 (d, $J_{C\text{-}F}$ = 174.3 Hz, $C_{2\alpha}$), 83.9 (d, $J_{C\text{-}F}$ = 177.4 Hz, $C_{4\alpha}$), 83.2 (dd, $J_{C\text{-}F}$ = 178.3, 4.0 Hz, $C_{4\beta}$), 65.0 (d, $J_{C\text{-}F}$ = 24.1 Hz, $C_{5\beta}$), 61.5 (d, $J_{C\text{-}F}$ = 21.9 Hz, $C_{5\alpha}$), 31.6 (t, $J_{C\text{-}F}$ = 20.7 Hz, $C_{3\beta}$), 28.2 (t, $J_{C\text{-}F}$ = 20.5 Hz, $C_{3\alpha}$) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ −183.7 to −184.1 (m, $F_{4\alpha}$), −185.6 to −185.9 (m, $F_{4\beta}$), −186.5 to −186.8 (m, $F_{2\alpha}$), −200.7 to −201.0 (m, $F_{2\beta}$) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ −183.9 (d, J = 14.3 Hz, $F_{4\alpha}$), −185.8 (d, J = 9.3 Hz, $F_{4\beta}$), −186.7 (d, J = 14.3 Hz, $F_{2\alpha}$), −200.9 (br s, $F_{2\beta}$) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_5H_8F_2NaO_2$ 161.0385; found 161.0389.

*1-(Benzyloxy)-2-fluorohex-5-ene (**47**).* To a solution of **31**[66] (206 mg, 1.0 mmol) in dry THF (4 mL) at rt were added the following in sequence: Et_3N (0.84 mL, 6.0 mmol), $Et_3N{\cdot}3HF$ (0.33 mL, 2.0 mmol), and NfF (0.36 mL, 2.0 mmol). After 24 h, the reaction was quenched by slow addition of sat. aq. $NaHCO_3$ (4 mL). Water (1 mL) was added, and the solution was stirred vigorously for 30 min. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organics were washed with sat. brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 100:0 to 90:10) to afford the title compound **47** as a colorless oil (145 mg, 70%). R_f 0.59 (hexane/EtOAc 80:20); IR 3656 (w), 3067 (w), 2980 (s), 1092 (s), 736 (s), 697 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (5H, m, H_{Ph}), 5.83 (1H, ddt, J = 17.0, 10.3, 6.6 Hz, H_5), 5.07 (1H, dq, J = 17.1, 1.7 Hz, $H_{6'}$), 5.02 (1H, dq, J = 10.2, 1.41 Hz, $H_{6''}$), 4.79−4.62 (1H, m, d_{obs}, J = 49.2 Hz, H_2), 4.61 (2H, s, H_{Bn}), 3.65−3.63 (1H, m, H_1), 3.59−3.57 (1H, m, $H_{1'}$), 2.30−2.12 (2H, m, H_4), 1.90−1.61 (2H, m, H_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) 137.9 (C_{Ph}), 137.4 (C_5), 128.4 (C_{Ph}), 127.71 (C_{Ph}), 127.67 (C_{Ph}), 115.3 (C_6), 92.3 (d, $J_{C\text{-}F}$ = 170.9 Hz, C_2), 73.4 (C_{Bn}), 71.8 (d, $J_{C\text{-}F}$ = 22.0 Hz, C_1), 30.7 (d, $J_{C\text{-}F}$ = 20.5 Hz, C_3), 29.0 (d, $J_{C\text{-}F}$ = 4.4 Hz, C_4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −187.2 (ddtd, J = 48.0, 31.1, 23.7, 15.6 Hz, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −188.0 (s, F_2) ppm; HRMS (EI) m/z: $[M^\bullet]^+$ calcd for $C_{13}H_{17}FO$ 208.1258; found 208.1255.

*5-(Benzyloxy)-2,2,4-trifluoropentan-1-ol (**48**).* To a stirred solution of **30** (212 mg, 1.00 mmol) in dry THF (5 mL) was added L-proline (46 mg, 0.40 mmol). After 5 min, NFSI (788 mg, 2.50 mmol) was added portionwise and the mixture was stirred at rt for 23 h. The reaction mixture was cooled to 0 °C and quenched by slow addition of dimethyl sulfide (0.15 mL, 2.0 mmol). After stirring for 30 min at rt, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 5 mL), sat. brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was redissolved in a mixture of CH_2Cl_2 (6 mL) and EtOH (4 mL) and cooled to 0 °C. $NaBH_4$ (94 mg, 2.5 mmol) was added portionwise, and the mixture was stirred at rt for 30 min. The reaction was quenched at 0 °C by cautious addition of sat. aq. NH_4Cl (10 mL) and stirred vigorously for 30 min at rt. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 70:30) to afford the title compound **48** as a colorless oil (202 mg, 81%). R_f 0.33 (hexane/EtOAc 70:30); IR 3393 (br m), 2980 (m), 1367 (m), 1071 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (5H, m, H_{Ph}), 5.07−4.89 (1H, m, d_{obs}, J = 48.5 Hz, H_4), 4.63 (1H, d, J = 12.1 Hz, H_{Bn}), 4.59 (1H, d, J = 12.1 Hz, H_{Bn}), 3.87−3.78 (2H, m, H_1), 3.73−3.59 (2H, m, H_5), 2.60−2.18 (2H, m, H_3), 1.92 (1H, t, J = 6.9 Hz, OH) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 137.5 (C_{Ph}), 128.5 (C_{Ph}), 127.9 (C_{Ph}), 127.7 (C_{Ph}), 121.9 (t, $J_{C\text{-}F}$ = 242.8 Hz, C_2), 87.8 (ddd, $J_{C\text{-}F}$ = 171.7, 7.3, 3.7 Hz, C_4), 73.6 (C_{Bn}), 71.3 (d, $J_{C\text{-}F}$ = 23.5 Hz, C_5), 64.2 (ddd, $J_{C\text{-}F}$ = 33.0, 29.3, 2.9 Hz, C_1), 35.7 (ddd, $J_{C\text{-}F}$ = 25.7, 24.2, 22.0 Hz, C_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.7 to −104.5 (1F, m, d_{obs}, J = 254.9 Hz, F_2), −108.2 to −109.1 (1F, m, d_{obs}, J = 254.9 Hz, $F_{2'}$), −185.8 to −186.2 (1F, m, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −104.0 (1F, dd, J = 256.6, 5.2 Hz, F_2), −108.5 (1F, dd, J = 254.9, 5.2 Hz, $F_{2'}$), −186.0 (1F, t, J = 4.3 Hz, F_4) ppm; HRMS (EI) m/z: $[M^\bullet]^+$ calcd for $C_{12}H_{15}F_3O_2$ 248.1019; found 248.1019.

*Ethyl 4,4-Difluoro-5-hydroxypentanoate (**49**).* Synthesized with a procedure of Kim et al.[60] Cu powder (3.33 g, 52.4 mmol), ethyl acrylate **35** (2.72 mL, 25.0 mmol), and ethyl bromodifluoroacetate **36** (5.78 mL, 45.1 mmol) were suspended in dry THF (29 mL) and heated to 50 °C. TMEDA (1.87 mL, 12.5 mmol) and AcOH (1.29 mL, 22.5 mmol) were added sequentially, and the mixture was stirred for 1 h before being cooled to rt. MTBE (44 mL) and aq. NH_4Cl (10 wt %, 29 mL) were added, and the mixture was stirred for a further 30 min. The organic phase was separated and filtered through a pad of Celite. The filtrate was washed with aq. NH4Cl 10% (29 mL), dried over $MgSO_4$, and concentrated in vacuo to afford a yellow oil. This was redissolved in a mixture of THF (28 mL) and EtOH (5.6 mL) and cooled to 0 °C. $NaBH_4$ (950 mg, 25 mmol) was added portionwise. The mixture was warmed to rt and stirred for 30 min. The mixture was cooled to 0 °C and quenched by slow addition of

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sat. aq. NH_4Cl (25 mL). After stirring for a further 30 min, the mixture was filtered through a pad of Celite to remove the insoluble solids. The organic solvent was removed in vacuo, and the residue was subsequently extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 80:20) to afford the title compound **49** as a colorless oil (3.20 g, 70% over two steps). R_f 0.10 (hexane/EtOAc 80:20); IR 3449 (br m), 2985 (w), 1716 (s), 1071 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (2H, q, J = 7.2 Hz, $H_{OC\underline{H}_2CH_3}$), 3.73 (2H, t, J = 12.5 Hz, H_5), 2.56 (2H, t, J = 7.5 Hz, H_2), 2.42 (1H, br s, OH), 2.30 (2H, tt, J = 16.8, 7.5 Hz, H_3), 1.28 (3H, t, J = 7.2 Hz, $H_{OCH_2C\underline{H}_3}$) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.8 (C_1), 122.5 (t, $J_{C\text{-}F}$ = 246.5 Hz, C_4), 63.9 (t, $J_{C\text{-}F}$ = 32.3 Hz, C_5), 61.0 ($C_{\underline{O}CH_2CH_3}$), 28.4 (t, $J_{C\text{-}F}$ = 24.9 Hz, C_3), 26.9 (t, $J_{C\text{-}F}$ = 5.1 Hz, C_2), 14.1 ($C_{OCH_2\underline{C}H_3}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.2 (tt, J = 17.3, 12.1 Hz, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −109.2 (s, F_4) ppm; HRMS (EI) m/z: $[M^\bullet]^+$ calcd for $C_7H_{12}F_2O_3$ 182.0749; found 182.0749.

*Ethyl 5-((tert-Butyldiphenylsilyl)oxy)-4,4-difluoropentanoate (**50**).* To a stirred solution of **49** (3.00 g, 16.5 mmol), 1H-imidazole (1.35 g, 19.8 mmol), and DMAP (100 mg, 0.824 mmol) in dry CH_2Cl_2 (83 mL) at 0 °C was added TBDPSCl (5.43 g, 19.8 mmol) portionwise. The reaction mixture was allowed to warm to rt and stirred for 16 h. Water (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 90:10) to afford the title compound **50** as a colorless oil (5.94 g, 86%). R_f 0.59 (hexane/EtOAc 70:30); IR 3657 (m), 2980 (s), 2889 (s), 1736 (s), 1382 (s), 1088 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (4H, m, H_{Ph}), 7.49−7.40 (6H, m, H_{Ph}), 4.18 (2H, q, J = 7.1 Hz, $H_{OC\underline{H}_2CH_3}$), 3.77 (2H, t, J = 12.0 Hz, H_5), 2.57−2.53 (2H, m, H_2), 2.44−2.31 (2H, m, H_3), 1.29 (3H, t, J = 7.1 Hz, $H_{OCH_2C\underline{H}_3}$), 1.09 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.4 (C_1), 135.6 (C_{Ph}), 132.5 (C_{Ph}), 130.0 (C_{Ph}), 127.8 (C_{Ph}), 122.5 (t, $J_{C\text{-}F}$ = 242.8 Hz, C_4), 65.1 (t, $J_{C\text{-}F}$ = 34.1 Hz, C_5), 60.7 ($C_{\underline{O}CH_2CH_3}$), 28.9 (t, $J_{C\text{-}F}$ = 24.2 Hz, C_3), 26.9 (t, $J_{C\text{-}F}$ = 4.8 Hz, C_2), 26.7 ($C_{tBu,Me}$), 19.2 ($C_{tBu,quat}$), 14.2 ($C_{OCH_2\underline{C}H_3}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.5 (tt, J = 17.3, 12.1 Hz, F_4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −108.5 (s, F_4) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{30}F_2NaO_3Si$ 443.1824; found 443.1829.

*5-((tert-Butyldiphenylsilyl)oxy)-2,2,4,4-tetrafluoropentan-1-ol (**51**).* To a stirred solution of **33** (897 mg, 2.38 mmol) in dry THF (12 mL) was added L-proline (109 mg, 0.95 mmol). After 5 min, NFSI (1.88 g, 5.96 mmol) was added portionwise and the mixture was stirred at rt for 19 h. The reaction mixture was cooled to 0 °C and quenched by slow addition of dimethyl sulfide (0.35 mL, 4.8 mmol). After stirring for 30 min at rt, sat. aq. $NaHCO_3$ (25 mL) was added. The aqueous phase was extracted with EtOAc (3 × 25 mL), and the combined organic layers washed with sat. brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oil was redissolved in a mixture of dry CH_2Cl_2 (14.3 mL) and EtOH (9.5 mL) and cooled to 0 °C. $NaBH_4$ (225 mg, 5.96 mmol) was added portionwise, and the mixture was stirred at rt for 30 min. The reaction was quenched at 0 °C by cautious addition of sat. aq. NH_4Cl (25 mL) and stirred vigorously for 1 h at rt. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 80:20) to afford the title compound **51** as a colorless oil (750 mg, 76%). R_f 0.25 (hexane/EtOAc 80:20); IR 3656 (w), 3376 (br w), 2980 (s), 2889 (m), 1382 (m), 1113 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (4H, m, H_{Ph}), 7.49−7.40 (6H, m, H_{Ph}), 3.87 (2H, td, J = 13.0, 7.2 Hz, H_1), 3.82 (2H, t, J = 12.2 Hz, H_5), 2.80 (2H, quin, J = 15.9 Hz, H_3), 1.93 (1H, t, J = 7.3 Hz, OH), 1.09 (9H, s, H_{tBu}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.5 (C_{Ph}), 132.3 (C_{Ph}), 130.0 (C_{Ph}), 127.9 (C_{Ph}), 123.2-118.3 (m, C_{2+4}), 65.3 (t, $J_{C\text{-}F}$ = 33.4 Hz, C_1), 64.3 (t, $J_{C\text{-}F}$ = 30.8 Hz, C_5), 36.5 (quin, $J_{C\text{-}F}$ = 25.3 Hz, C_3), 26.6 ($C_{tBu,Me}$), 19.2 ($C_{tBu,quat}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.9 to −104.3 (m, F_{2+4}) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −104.06 (t, J = 8.7 Hz, F_2), −104.14 (t, J = 8.7 Hz, F_4) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}F_4NaO_2Si$ 437.1530; found 437.1535.

*Diethyl 3-Fluoropentane-1,5-dioate (**54**).* To a solution of **53** (1.0 g, 4.9 mmol) in dry CH_2Cl_2 (49 mL) at 0 °C was added DAST (1.3 mL, 9.8 mmol) dropwise. The solution was stirred at rt for 4 h, then cooled to 0 °C, and quenched by slow addition of sat. aq. $NaHCO_3$ (150 mL). After stirring vigorously at rt for 30 min, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 80:20) to afford the title compound **54** as a yellow oil with a 10% impurity of the elimination byproduct by mass (973 mg, 87% calculated for the pure compound). R_f 0.39 (hexane/EtOAc 70:30); IR 2984 (m), 1731 (s), 1194 (s), 1152 (s), 1024 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (1H, dtt, J = 46.7, 7.3, 5.1 Hz, H_3), 4.19 (2H, q, J = 7.3 Hz, $H_{OC\underline{H}_2CH_3}$), 2.84−2.65 (4H, m, H_{2+4}), 1.29 (3H, t, J = 7.2 Hz, $H_{OCH_2C\underline{H}_3}$) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.4 (d, $J_{C\text{-}F}$ = 6.6 Hz, C_{1+5}), 86.5 (d, $J_{C\text{-}F}$ = 171.7 Hz, C_3), 61.0 ($C_{\underline{O}CH_2CH_3}$), 39.7 (d, $J_{C\text{-}F}$ = 23.5 Hz, C_{2+4}), 14.1 ($C_{OCH_2\underline{C}H_3}$) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −179.3 to −179.7 (m, F_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −184.8 (s, F_3) ppm; HRMS (EI) m/z: $[M^\bullet]^+$ calcd for $C_9H_{15}FO_4$ 206.0949; found 206.0943.

*1,4-Di(benzyloxy)-3-fluorobutan-2-one (**57**).* To a solution of **56**[S1] (2.00 g, 6.57 mmol) in CH_2Cl_2 (65 mL) at rt was added Dess−Martin periodinane (4.18 g, 9.86 mmol) portionwise over 5 min. After 20 h, the mixture was diluted with Et_2O (30 mL), filtered through Celite (eluting with Et_2O), and concentrated in vacuo. To the residue was added sat. aq. $NaHCO_3$ (50 mL) and $Na_2S_2O_3{\cdot}5H_2O$ (3.2 g). The aqueous phase was extracted with EtOAc (3 × 80 mL), and the combined organics were washed with sat. brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (Biotage Isolera One, SNAP KP-SIL 50 g column, hexane/EtOAc 100:0 to 80:20) to afford the title compound **57** as a clear colorless oil (1.56 g, 79%). R_f 0.45 (hexane/EtOAc 70:30); IR 3032 (w), 2867 (w), 1742 (m), 1076 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (10H, m, H_{Ph}), 5.06 (1H, ddd, J = 48.4, 3.7, 2.5 Hz, H_3), 4.65−4.51 (4H, m, H_{Bn}), 4.48 (2H, m, H_1), 3.99−3.83 (2H, m, H_4) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.3 (d, $J_{C\text{-}F}$ = 24.2 Hz, C_2), 137.1 (C_{Ph}), 137.0 (C_{Ph}), 128.48 (C_{Ph}), 128.45 (C_{Ph}), 128.02 (C_{Ph}), 127.98 (C_{Ph}), 127.9 (C_{Ph}), 127.7 (C_{Ph}), 94.8 (d, $J_{C\text{-}F}$ = 187.1 Hz, C_3), 73.7 (C_{Bn}), 73.43 (d, $J_{C\text{-}F}$ = 2.9 Hz, C_1), 73.37 (C_{Bn}), 69.5 (d, $J_{C\text{-}F}$ = 19.1 Hz, C_4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.0 to −203.3 (m, F_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −203.4 (s, F_3) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{19}FNaO_3$ 325.1210; found 325.1217.

*1,4-Di(benzyloxy)-2,2,3-trifluorobutane (**58**).* To a stirred solution of **57** (1.50 g, 4.96 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C was added DAST (3.9 mL, 30 mmol) dropwise. The solution was stirred at rt for 20 h, then cooled to 0 °C, and quenched by slow addition of sat. aq. $NaHCO_3$ (150 mL). After stirring vigorously at rt for 30 min, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (hexane/EtOAc 100:0 to 80:20) to afford the title compound **58** as a clear colorless oil (1.33 g, 83%). R_f 0.54 (hexane/EtOAc 80:20); IR 3031 (w), 2980 (w), 2875 (w), 1113 (s), 1085 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.33 (10H, m, H_{Ph}), 5.14−4.95 (1H, m, H_3), 4.68−4.60 (4H, m, H_{Bn}), 3.99−3.74 (4H, m, H_{1+4}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 137.4 (C_{Ph}), 136.9 (C_{Ph}), 128.50 (C_{Ph}), 128.45 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 127.7 (C_{Ph} + C_{Ph}), 119.0 (td, $J_{C\text{-}F}$ = 247.0, 26.0 Hz, C_2), 89.1 (ddd, $J_{C\text{-}F}$ = 181.9, 33.0, 26.4 Hz, C_3), 74.0 (C_{Bn}), 73.7 (C_{Bn}), 67.6 (ddd, $J_{C\text{-}F}$ = 33.8, 27.1, 1.5 Hz, C_1), 67.0 (ddd, $J_{C\text{-}F}$ = 21.3, 4.4, 2.9 Hz, C_4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.5 (1F, dddt, J = 270.8, 19.4, 12.4, 5.6 Hz, F_2), −120.9 (1F, ddq, J = 270.5, 17.8, 9.7 Hz, $F_{2'}$), −202.4 to −202.8 (1F, m, F_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −115.6 (1F, dd, J = 270.5, 5.2 Hz, F_2), −121.0 (1F, dd, J = 270.5, 12.1 Hz, $F_{2'}$), −202.7 (1F, dd, J = 12.1, 5.2 Hz, F_3)

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ppm; HRMS (EI) m/z: $[M\text{-}CH_2Ph]^+$ calcd for $C_{11}H_{12}F_3O_2$ 233.0784; found 233.0785.

*2,2,3-Trifluorobutane-1,4-diol (**C5**).* To a solution of **58** (600 mg, 1.85 mmol) in dry CH_2Cl_2 (37 mL) at rt, iodotrimethylsilane (0.68 mL, 4.8 mmol) was added dropwise. After 30 min, MeOH (6 mL) was added and the mixture was stirred for a further 30 min. EtOAc (15 mL) and sat. aq. $NaHSO_3$ (5 mL) were added, and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with sat. brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (hexane/acetone 100:0 to 60:40) to afford the title compound **C5** as a crystalline solid (216 mg, 81%). R_f 0.41 (hexane/EtOAc 40:60); mp 52−54 °C (MeOH); IR 3315 (br m), 3200 (br m), 2980 (m) 1229 (m), 1094 (s), 1055 (s) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 4.87−4.68 (1H, m, H_3), 3.95−3.72 (4H, m, H_{1+4}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 121.1 (ddd, $J_{C\text{-}F}$ = 247.2, 245.0, 25.7 Hz, C_2), 179.7 (ddd, $J_{C\text{-}F}$ = 179.7, 32.3, 27.1 Hz, C_3), 61.6 (ddd, $J_{C\text{-}F}$ = 31.5, 27.9, 1.5 Hz, C_1), 60.3 (dt, $J_{C\text{-}F}$ = 21.8, 3.8 Hz, C_4) ppm; ^{19}F NMR (376 MHz, MeOD) δ −119.3 (1F, dddt, J = 266.7, 19.2, 13.2, 6.5 Hz, F_2), −123.5 (1F, ddq, J = 267.0, 13.9, 10.4 Hz, $F_{2'}$), −206.8 to −207.1 (1F, m, F_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, MeOD) δ −119.3 (1F, dd, J = 265.3, 5.2 Hz, F_2), −123.5 (1F, dd, J = 265.3, 10.4 Hz, F_2), −206.9 (1F, dd, J = 12.1, 6.9 Hz, F_3) ppm; HRMS (EI) m/z: $[M\text{-}OH_3]^+$ calcd for $C_4H_4F_3O$ 125.0214; found 125.0209.

*2-Fluorobutane-1,4-diol (**C6**).* To a solution of **59**[23] (500 mg, 2.36 mmol) in Et_2O (25 mL) at rt, NaOMe (25% w/w in MeOH, 1.07 mL, 4.72 mmol) was added dropwise. After 16 h, the reaction mixture was neutralized with aq. HCl (2 M), and the aqueous phase was washed with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and carefully concentrated (30 °C, 750 mbar). The crude mixture was purified by flash column chromatography (Et_2O/acetone 95:5) to afford the title compound **C6** as a pale yellow oil (89 mg, 35%). R_f 0.12 (hexane/EtOAc 40:60); IR 3313 (br m), 2954 (m), 2892 (m), 1054 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87−4.81 (1H, ddddd, J = 48.9, 7.9, 5.5, 4.6, 3.4 Hz, H_2), 3.94−3.66 (4H, m, H_{1+4}), 2.16−1.77 (2H, m, H_3), ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 92.2 (d, $J_{C\text{-}F}$ = 168.0 Hz, C_2), 64.8 (d, $J_{C\text{-}F}$ = 22.7 Hz, C_1), 58.5 (d, $J_{C\text{-}F}$ = 5.9 Hz, C_4), 33.9 (d, $J_{C\text{-}F}$ = 20.5 Hz, C_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −191.5 to −192.0 (m, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −191.8 (s, F_2) ppm; HRMS (EI) m/z: $[M^{\bullet+}]$ calcd for $C_4H_9FO_2$ 108.0581; found 108.0580.

*2,2-Difluorobutane-1,4-diol (**C7**).* To a solution of **60**[23] (150 mg, 0.652 mmol) in Et_2O (10 mL) at rt, NaOMe (25% w/w in MeOH, 0.30 mL, 1.30 mmol) was added dropwise. After 16 h, the reaction mixture was neutralized with aq. HCl (2 M) and the aqueous phase was washed with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and carefully concentrated (30 °C, 750 mbar). The crude mixture was first purified by column chromatography (acetone/petroleum ether 40−60 °C 50:50) and then by HPLC (Et_2O/pentane 95:5) to afford the title compound **C7** as a colorless crystalline solid (22 mg, 27%). R_f 0.16 (hexane/EtOAc 40:60); mp 37−39 °C (MeOH); IR (thin film, $CDCl_3$) 3352 (br w), 2962 (w), 1374 (w), 1262 (m), 1066 (s), 904 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.90 (2H, t, J = 5.6 Hz, H_4), 3.83 (2H, t, J = 12.6 Hz, H_1), 2.69 (1H, br s, OH_1), 2.25 (2H, tt, J = 15.8, 5.6 Hz, H_3), 2.01 (1H, br s, OH_4) ppm; $^1H\{^{19}F\}$ NMR (500 MHz, $CDCl_3$) δ 3.90 (2H, t, J = 5.6 Hz, H_4), 3.83 (2H, s, H_1), 2.69 (1H, br s, OH), 2.25 (2H, t, J = 5.6 Hz, H_3), 2.01 (1H, br s, OH) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 122.9 (t, $J_{C\text{-}F}$ = 242.7 Hz, C_2), 64.4 (t, $J_{C\text{-}F}$ = 33.1 Hz, C_1), 56.9 (t, $J_{C\text{-}F}$ = 6.6 Hz, C_4), 36.8 (t, $J_{C\text{-}F}$ = 24.4 Hz, C_3) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ −105.1 (tt, J = 15.9, 12.7 Hz, F_2) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ −105.1 (s, F_2) ppm; HRMS (CI) m/z: $[M + H]^+$ calcd for $C_4H_9F_2O_2$ 127.0561; found 127.0566.

*(**2S,4S**)-2,4-Difluoropentane-1,5-diol ((**2S,4S**)-**H2**).* To a stirred solution of (**2S,4S**)-**41** (200 mg, 0.82 mmol) in MeOH (4 mL) was added KOH (138 mg, 2.46 mmol) in one portion. The mixture was stirred at rt for 1 h before addition of sat. aq. NH_4Cl (4 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 60:40) to afford the title compound (**2S,4S**)-**H2** as a white crystalline solid (91 mg, 79%). R_f 0.20 (hexane/EtOAc 40:60); $[\alpha]_D^{19}$ −31.2 (c 1, MeOH); mp 115−116 °C (MeOH); IR 3656 (m), 3203 (br m), 2980 (s), 2889 (m), 1382 (m) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 4.80−4.62 (2H, m, d_{obs}, J = 49.6 Hz, H_{2+4}), 3.76−3.56 (4H, m, H_{1+5}), 1.99−1.79 (2H, m, H_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 92.0 (dd, $J_{C\text{-}F}$ = 170.2, 2.9 Hz, C_{2+4}), 65.4 (d, $J_{C\text{-}F}$ = 22.0 Hz, C_1), 34.4 (t, $J_{C\text{-}F}$ = 20.9 Hz, C_3) ppm; ^{19}F NMR (376 MHz, MeOD) δ −191.8 to −192.2 (m, F_{2+4}) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, MeOD) δ −192.1 (s, F_{2+4}) ppm; HRMS (EI) m/z: $[M-CHOH]^+$ calcd for $C_4H_8F_2O$ 110.0543; found 110.0537.

The synthesis was repeated from (**2R,4R**)-**41** (32 mg, 0.13 mmol) to give (**2R,4R**)-**H2** (14 mg, 76%). Spectroscopic data were identical except $[\alpha]_D^{20}$ +29.0 (c 0.15, MeOH).

*2,4-syn-Difluoropentane-1,5-diol (**H3**).* To a solution of **46** (219 mg, 1.59 mmol) in MeOH (20 mL) at 0 °C was added $NaBH_4$ (150 mg, 3.96 mmol) portionwise. The resulting mixture was warmed to rt and stirred for 3 h. The reaction was quenched with aq. 1 M HCl (5 mL), stirred for 1 h, and concentrated in vacuo. The residue was redissolved in CH_2Cl_2/acetone, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 60:40) to afford the title compound **H3** as a white crystalline solid (211 mg, 94%). R_f 0.30 (hexane/acetone 60:40); mp 63−66 °C (not recrystallized); IR 3250 (br m), 2940 (m), 1384 (m), 1068 (s), 1044 (s) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 4.77−4.60 (2H, m, d_{obs}, J = 48.8 Hz, H_{2+4}), 3.76−3.61 (2H, m, H_{1+5}), 2.18 − 1.88 (2H, m, H_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 92.7 (dd, $J_{C\text{-}F}$ = 169.5, 4.4 Hz, C_{2+4}), 64.9 (d, $J_{C\text{-}F}$ = 22.7 Hz, C_{1+5}), 33.9 (t, $J_{C\text{-}F}$ = 21.3 Hz, C_3) ppm; ^{19}F NMR (376 MHz, MeOD) δ −189.2 to −189.5 (m, F_{2+4}) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, MeOD) δ −189.2 (s, F_{2+4}) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_5H_{10}F_2NaO_2$ 163.0541; found 163.0544.

*2,2,4-Trifluoropentane-1,5-diol (**H4**).* To a solution of **48** (180 mg, 0.725 mmol) in dry CH_2Cl_2 (1.5 mL) at rt, iodotrimethylsilane (0.13 mL, 0.94 mmol) was added dropwise. After 30 min, MeOH (2.4 mL) was added. After a further 30 min, sat. aq. sodium bisulfite (1 mL) and EtOAc (5 mL) were added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were washed with sat. brine (1 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash column chromatography (hexane/acetone 100:0 to 60:40) to afford the title compound **H4** as a beige solid (83 mg, 72%). R_f 0.09 (hexane/EtOAc 70:30); mp 60−61 °C (MeOH); IR 3344 (br m), 2955 (w), 1078 (s), 1029 (s) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 4.90−4.72 (1H, m, d_{obs}, J = 49.3 Hz, H_4), 3.76−3.58 (4H, m, H_{1+5}), 2.46−2.12 (2H, m, H_3) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, MeOD) δ 123.7 (td, $J_{C\text{-}F}$ = 242.1, 1.5 Hz, C_2), 90.4 (ddd, $J_{C\text{-}F}$ = 107.9, 5.9, 3.7 Hz, C_4), 65.2 (d, $J_{C\text{-}F}$ = 22.7 Hz, C_5), 64.6 (td, $J_{C\text{-}F}$ = 30.1, 2.2 Hz, C_1), 36.3 (td, $J_{C\text{-}F}$ = 24.2, 22.0 Hz, C_3) ppm; ^{19}F NMR (471 MHz, MeOD) δ −105.4 to −106.2 (1F, m, d_{obs}, J = 251.4 Hz, F_2), −108.4 to −109.2 (1F, m, d_{obs}, J = 251.4 Hz, $F_{2'}$), −188.5 to −188.9 (1F, m, F_4) ppm; $^{19}F\{^1H\}$ NMR (471 MHz, MeOD) δ −105.8 (1F, dd, J = 251.4, 3.5 Hz, F_2), −108.9 (1F, dd, J = 251.4, 5.2 Hz, $F_{2'}$), −188.7 (1F, t, J = 5.2 Hz, F_4) ppm; HRMS (EI) m/z: $[M + H]^+$ calcd for $C_5H_{10}F_3O_2$ 159.0627; found 159.0628.

*2,2,4,4-Tetrafluoropentane-1,5-diol (**H5**).* To a stirred solution of **51** (700 mg, 1.69 mmol) in dry THF (17 mL) at 0 °C was added TBAF (1 M in THF, 2.5 mL, 2.5 mmol) dropwise. The reaction was stirred at rt for 2 h. The reaction mixture was quenched by slow addition of sat. aq. NH_4Cl (20 mL). After vigorous stirring for 15 min, the aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with sat. brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash column chromatography (hexane/acetone 85:15) to afford the title compound **H5** as a white crystalline solid (286 mg, 96%). R_f 0.55 (hexane/acetone 60:40); mp 87−88 °C (MeOH); IR 3657 (w),

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3343 (w), 3248 (w), 2980 (s), 2889 (m), 1387 (m), 1252 (m) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 3.80−3.63 (4H, m, H_{1+5}), 2.67 (2H, quin, J = 16.2 Hz, H_3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 122.5 (tt, $J_{C\text{-}F}$ = 243.7, 4.2 Hz, C_{2+4}), 65.1−64.4 (m, C_{1+5}), 37.3 (quin, $J_{C\text{-}F}$ = 25.1 Hz, C_3) ppm; ^{19}F NMR (376 MHz, MeOD) δ −105.6 to −105.8 (m, F_{2+4}) ppm; $^{19}F\{1H\}$ NMR (376 MHz, MeOD) δ −105.7 (s, F_{2+4}) ppm; HRMS (EI) m/z: $[M + H]^+$ calcd for $C_5H_9F_4O_2$ 177.0533; found 177.0530.

*2-Fluoropentane-1,5-diol (**H6**).* To a stirred solution of **52**[23] (350 mg, 1.55 mmol) in MeOH (7.7 mL) at rt, KOH (261 mg, 4.65 mmol) was added portionwise. After 1 h, sat. aq. NH_4Cl (8 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/acetone 60:40) to afford the title compound **H6** as a yellow oil (65 mg, 34%). R_f 0.14 (hexane/acetone, 60:40); IR 3338 (br m), 2917 (s), 2849 (s), 1462 (w), 1043 (s) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 4.60−4.42 (1H, m, d_{obs}, J = 49.8 Hz, H_2), 3.70−3.54 (4H, m, H_{1+5}), 1.70−1.58 (4H, m, H_{3+4}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 95.6 (d, $J_{C\text{-}F}$ = 169.5 Hz, C_2), 65.3 (d, $J_{C\text{-}F}$ = 22.7 Hz, C_1), 62.7 (C_5), 29.3 (d, $J_{C\text{-}F}$ = 3.7 Hz, C_4), 28.8 (d, $J_{C\text{-}F}$ = 21.3 Hz, C_3) ppm; ^{19}F NMR (376 MHz, MeOD) δ −189.1 to −189.5 ppm; $^{19}F\{^1H\}$ NMR (376 MHz, MeOD) δ −189.4 (s, F_2) ppm; HRMS (EI) m/z: $[M + H]^+$ calcd for $C_5H_{12}FO_2$ 123.0816; found 123.0814.

*3-Fluoropentane-1,5-diol (**H7**).* To a solution of **54** (800 mg, 3.88 mmol) in dry THF (3.9 mL) at 0 °C was added a solution of $LiAlH_4$ (1 M in THF, 5.0 mL, 5.0 mmol) dropwise. The mixture was stirred at rt for 1 h, then cooled to 0 °C, and quenched by dropwise addition of sat. aq. Rochelle's salt (15 mL). EtOAc (15 mL) was added, and the mixture stirred for 1 h. The layers were separated, and the aqueous layer was extracted sequentially with EtOAc (3 × 15 mL) and a mixture of $CHCl_3$/*i*-PrOH (80:20) (3 × 15 mL). The combined organic layers were washed with sat. brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 60:40 to 40:60) to afford the title compound **H7** as a yellow oil (257 mg, 54%). R_f 0.10 (hexane/EtOAc 60:40); IR 3311 (br s), 2955 (m), 1395 (m), 1043 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (1H, dtt, J = 49.8, 8.8, 3.4 Hz, H_3), 3.86−3.82 (4H, m, H_{1+5}), 2.03−1.79 (4H, m, H_{2+4}) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 90.6 (d, $J_{C\text{-}F}$ = 165.1 Hz, C_3), 59.2 (d, $J_{C\text{-}F}$ = 5.1 Hz, C_{1+5}), 37.9 (d, $J_{C\text{-}F}$ = 19.8 Hz, C_{2+4}) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −184.6 (dtt, J = 50.3, 33.0, 17.3 Hz, F_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −187.4 (s, F_3) ppm; HRMS (EI) m/z: $[M + H]^+$ calcd for $C_5H_{12}FO_2$ 123.0816; found 123.0821.

*2,2-Difluoropentane-1,5-diol (**H8**).* To a solution of **55**[23] (0.20 g, 0.80 mmol) in Et_2O (8 mL) at rt, NaOMe (25% w/w in MeOH, 750 μL, 3.6 mmol) was added dropwise. After 16 h, the reaction mixture was filtered through a silica plug (eluting with EtOAc) and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether/acetone, 80:22 to 60:40) to afford the title compound **H8** as a colorless oil (31 mg, 27%). R_f 0.32 (hexane/acetone, 60:40); IR 3331 (br m), 2943 (m), 2883 (m), 1179 (m), 1054 (s), 1004 (s) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 3.65 (2H, t, J = 13.1 Hz, H_1), 3.59 (2H, t, J = 6.5 Hz, H_5), 2.04−1.91 (2H, m, H_3), 1.74−1.67 (2H, m, H_4) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 125.0 (t, $J_{C\text{-}F}$ = 241.0 Hz, C_2), 64.4 (t, $J_{C\text{-}F}$ = 32.3 Hz, C_1), 62.5 (C_5), 31.0 (t, $J_{C\text{-}F}$ = 24.6 Hz, C_3), 26.2 (t, $J_{C\text{-}F}$ = 4.4 Hz, C_4) ppm; ^{19}F NMR (376 MHz, MeOD) δ −109.1 (tt, J = 17.3, 12.1 Hz, F_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, MeOD) δ −109.1 (s, F_2) ppm; HRMS (EI) m/z: $[M - CHOH]^+$ calcd for $C_4H_8F_2O$ 110.0538; found 110.0537.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02810.

^1H, ^{13}C, and ^{19}F NMR spectra of all novel compounds; clog *P* determination of 1,5-pentanediol; comparison of the experimental with the clog *P* values of all fluorinated diols; and experimental log *P* determination data (PDF)

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Notes

The authors declare no competing financial interest.

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