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A Systematic Investigation of Lipophilicity Modulation by Aliphatic Fluorination Motifs

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Abstract.

Optimization of compound lipophilicity is a key aspect of drug discovery. The aim of this work was to compare the lipophilicity modulations induced by 16 distinct known and novel fluoroalkyl motifs on three parent models. Fifty fluorinated compounds, with 28 novel experimental aliphatic log*P* values, are involved in discussing various lipophilicity trends. As well as confirming known trends, a number of novel lipophilicity reducing motifs are introduced. Tactics to reduce lipophilicity are discussed, such as "motif extensions" and "motif rearrangements", including with concomitant extension of the carbon chain, as well as one-

and two-fluorine 'deletions' within perfluoroalkyl groups. Quantum chemical log*P* calculations (SMD-MN15) based on solvent-dependent 3D conformational analysis gave excellent correlations with experimental values, superior to Clog*P* predictions based on 2D structural motifs. The availability of a systematic collection of data based on a small number of parent molecules illustrates the relative lipophilicity modulations of aliphatic fluorination motifs.

Introduction.

Fluorine introduction is a much-used operation in the drug development optimization process.[1-4] While any change in molecular structure will have an impact on a number of properties, this is particularly pronounced for fluorination. This is due to the high electronegativity of fluorine, resulting in a highly polar C–F bond with concomitant strong inductive effect and low polarizability of the fluorine lone pairs,[5] without leaving much of a steric footprint. The efficiency of fluorine introduction for property optimization is exemplified by statistics on the proportion of commercial drugs, or drugs currently in clinical trials, that are fluorinated.[6-8] The vast advances that are continuing to be made in synthetic organofluorine chemistry[9-17] have accelerated its use and, with the emergence of late stage fluorination methodologies,[18,19] this is set to continue. The increased understanding of the stability of fluorinated motifs, especially when heteroatoms are involved,[20-22] will further enhance its successful application.

Lipophilicity is an important property that is affected by fluorination. While fluorine introduction on aromatic rings generally leads to a lipophilicity increase, the influence of aliphatic fluorination on lipophilicity is more complex.[2,4] This is best illustrated by $CH_3 \rightarrow CF_3$ exchange, which can result in a lipophilicity increase or decrease, which can be in both cases quite significant (see below). Given the need to keep lipophilicity within optimal boundaries during optimization,[23-29] the possibility to use aliphatic fluorination for lipophilicity reduction

purposes is an attractive prospect. New fluorine-containing motifs continue to be introduced that are suitable for this purpose, with recent examples being the (Ar)-SCF_2CH_3 and (Ar)-OCF_2CH_3 groups by O'Hagan,[30] and the $–OCH_2(CF_2)_nCH_3$ (n = 2,3) groups from our lab.[31] In addition, lipophilicities of some known motifs such as a 1,2-difluoroethyl group, which has been demonstrated to be very efficient in lipophilicity reduction (see below),[32,33] and the CF_2H group, which has additional interest as 'lipophilic hydrogen bond donor',[34,35] have been investigated in detail. In this context, the availability of a toolbox of "fluorinated motifs" from which the medicinal chemist can pick and choose for optimal effect would be of great practical use, and the understanding of the lipophilicity impact of diverse fluorinated motifs, with or without modifying the chain lengths involved, will be of great benefit in medicinal chemistry.

The process of understanding the influence of aliphatic fluorination on lipophilicity was pioneered by the Müller/Carreira group (Figure 1, series **A**–**C**), by investigating a series of compounds with increasing fluorine content, such as **A1–A5**.[36] Using a combination of dipole moment and fluorine hydrophobic surface considerations, they explained the decrease in lipophilicity upon monofluorination by the C–F dipole introduction. Given that a trifluoromethyl group has approximately the same dipole moment as a C–F group, but a larger hydrophobic surface, a higher log*P* would be expected compared to monofluorination. The dipole moment of a CF_2-group is slightly larger than that of a single C–F, but the expected log*P* decrease is overridden by the log*P* increase caused by the larger hydrophobic surface area. The lower lipophilicities of a vicinal over a geminal difluoro motif could nicely be explained by the higher vector sum of the two C–F dipoles for a ca. 60° (*gauche* dihedral) angle compared to a ca. 110° (bond) angle.[32,37] Subsequently, through the synthesis of Gilenya® derivatives with alkyl side chains of various lengths, Gilmour has further demonstrated the lower log*P* of 1,2-difluoroethyl groups compared to their ethyl and trifluoroethyl counterparts.[33] Müller also pointed out that the lipophilicity increase resulting from aliphatic

chain extension is compensated when a CF_2 group is simultaneously replaced by a vicinal difluoro group (e.g. compare **A3**, **A4** with **B4**–**B6**).[32] Such observations are of great interest as these represent liponeutral bulk increases.

Although their lipophilicity range is three orders of magnitude apart, the fluorinated propoxy side chains in series **C** and the corresponding propanols (series **D**, Figure 1) display the same lipophilicity trend,[38] except that now the trifluorinated **D4** shows a slightly increased log*P* compared to propanol **D1**. For the ethanol series (**E**, Figure 1)[38] and the proline ester series (**F**, Figure 1),[39] this log*P* increase for the trifluorinated analogues is even more pronounced, with the difluorinated derivatives in series **E** and **F** being as lipophilic as their nonfluorinated parents. In these cases, the decrease in polarizability of the oxygen lone pairs caused by the inductive effect of the trifluoromethyl group has a log*P* increasing effect (similar to how aromatic fluorination increases lipophilicity). In addition, with a C2-chain, there is always a conformation in which a C–F dipole is antiperiplanar to the C–O dipole. Furthermore, the lipophilicity range of series **D**–**F** (from -0.75 to +0.55 log*P* units) is much lower compared to that of series **C** (+2.3 to +2.9 log*D* units). Hence, the relative contribution of the dipole is much reduced, in contrast to the volume contribution, a consideration already recognized by Müller through the lipophilicity comparison across the log*P* scale of a set of trifluoromethylated compounds with their methylated analogues.[36] Interestingly, Rafique et al. reported the log*D* of a number of CF_3CH_2OAr/FCH_2CH_2OAr matched molecular pairs (not shown), with Ar representing 4-pyridyl rings having a range of (non-conjugated) substituents, in which the trifluoromethylated derivative is not always the most lipophilic one although all compounds are within a narrow lipophilicity range.[40]

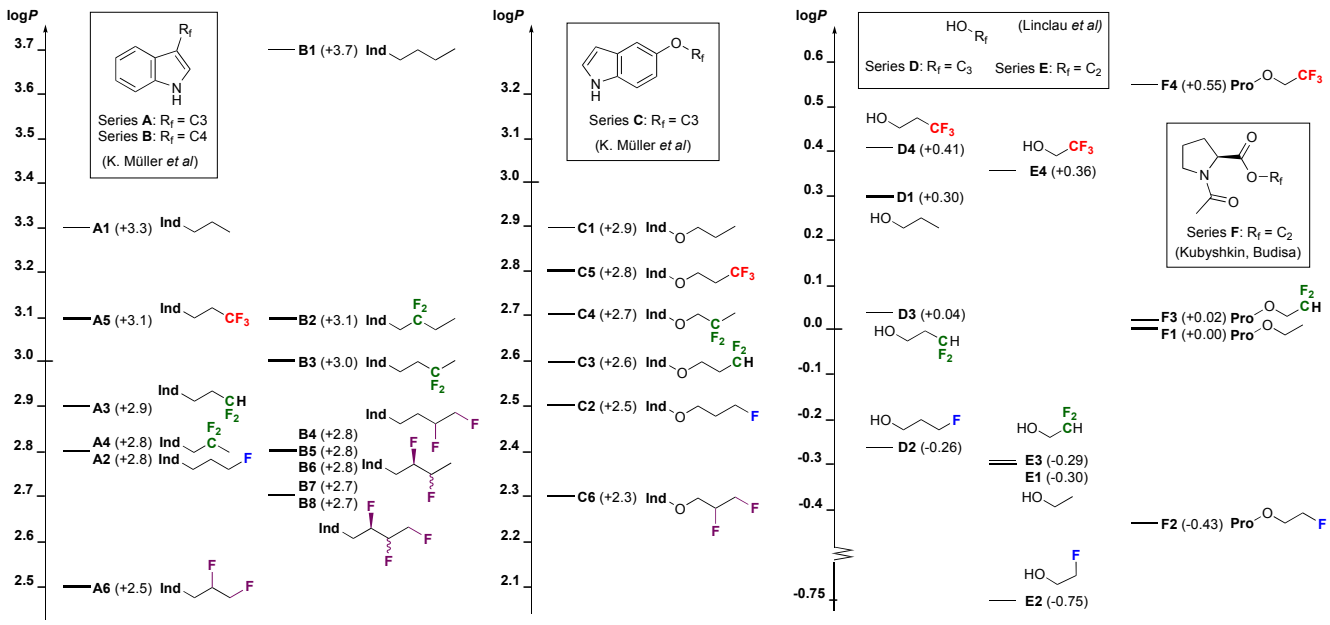


Figure 1. A selection of relevant precedence of aliphatic fluorination and lipophilicity featuring different fluorination patterns for given 'parent' (nonfluorinated) compounds **A**–**F**.

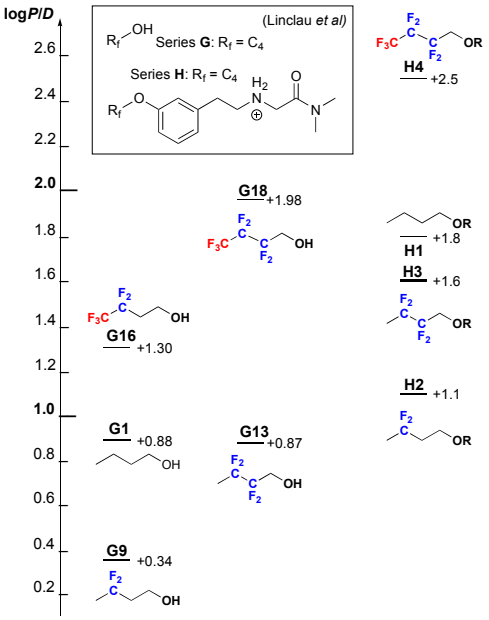


Figure 2. Log*P*/*D* values of derivatives obtained by internal polyfluorination of the parent compounds **G1** and **H1**.

Based on the observation that there is a large log*P* decrease when terminal pentafluorination is changed to a CF_2 motif at the penultimate chain position (Figure 2, compare **G16** with **G9**), our group established that this remains the case even with longer perfluoroalkyl moieties (e.g. **G18→G13**).[31] Interestingly, the tetrafluorinated **G13** has a similar lipophilicity as its nonfluorinated parent **G1**. Very similar observations were made when such butoxy groups were introduced in a druglike molecule, such as evenamide **H1**,[31] a schizophrenia drug currently in phase II clinical trials.[41]

The availability of measured lipophilicity data of matched molecular pairs (or matched molecular series) is of great interest for qualitative evaluation about the relative effect of a given motif on lipophilicity, and more importantly, as a collective body of data to extract trends and gain understanding of the effects at work. The reporting of experimental log*P* data is very valuable[27,29] as inputs to validate/optimize computational log*P* prediction algorithms, or to obtain correlations of their predictions with the experiment.

Here, we report experimental octanol-water shake flask log*P* values of 50 saturated fluorinated aliphatic compounds involving, in total, 16 different aliphatic fluorination motifs introduced on three "parent" alcohol models. Our choice for alkanols as model compounds is based on the aforementioned interplay of the polar C–F bond with an electronegative functional group, which affects its resulting lipophilicity modulation. Given that the magnitude of fluorine's lipophilicity modulating effect is also dependent on the lipophilicity of the nonfluorinated parent compound, it is important that different motifs can be compared when substituted on the same framework, hence the limited number of nonfluorinated 'parents'. Two nonfluorinated 'parents' are linear alkanols (Figure 3): 1-butanol (BuOH, log*P* +0.88) and 1-pentanol (1-PentOH, log*P* +1.51). Positional isomers which have the fluorination motif at different carbon atoms are investigated systematically for the CHF and CF_2-motifs. For this purpose, 2-pentanol (2-PentOH, log*P* +1.19) is also included as a parent substrate. Around half of the log*P* values

are new, and the precedent is included to have as large a data set as possible to facilitate discussion and allow comparison between different motifs, and positioning of motifs vs a polar alcohol group.

Results.

Lipophilicity results.

The direct determination of log*P* values was conveniently achieved by a ^{19}F NMR based method developed by our group, which is suitable for measuring the octanol/water partition coefficients *P* of (fluorinated) non-UV active substrates.[31] The use of an internal standard as a mixture with the compound of interest obviates the need for accurate weight/partition volume/sample volume measurements. Potential quantitative integration issues due to the solvent-dependence of the relaxation time are minimized by selecting a sufficiently long relaxation delay for the NMR experiments (D1-setting).

The results of the lipophilicity measurements are shown in Figure 3, together with previously measured values of analogues. The difference in lipophilicity with the nonfluorinated parent is indicated.

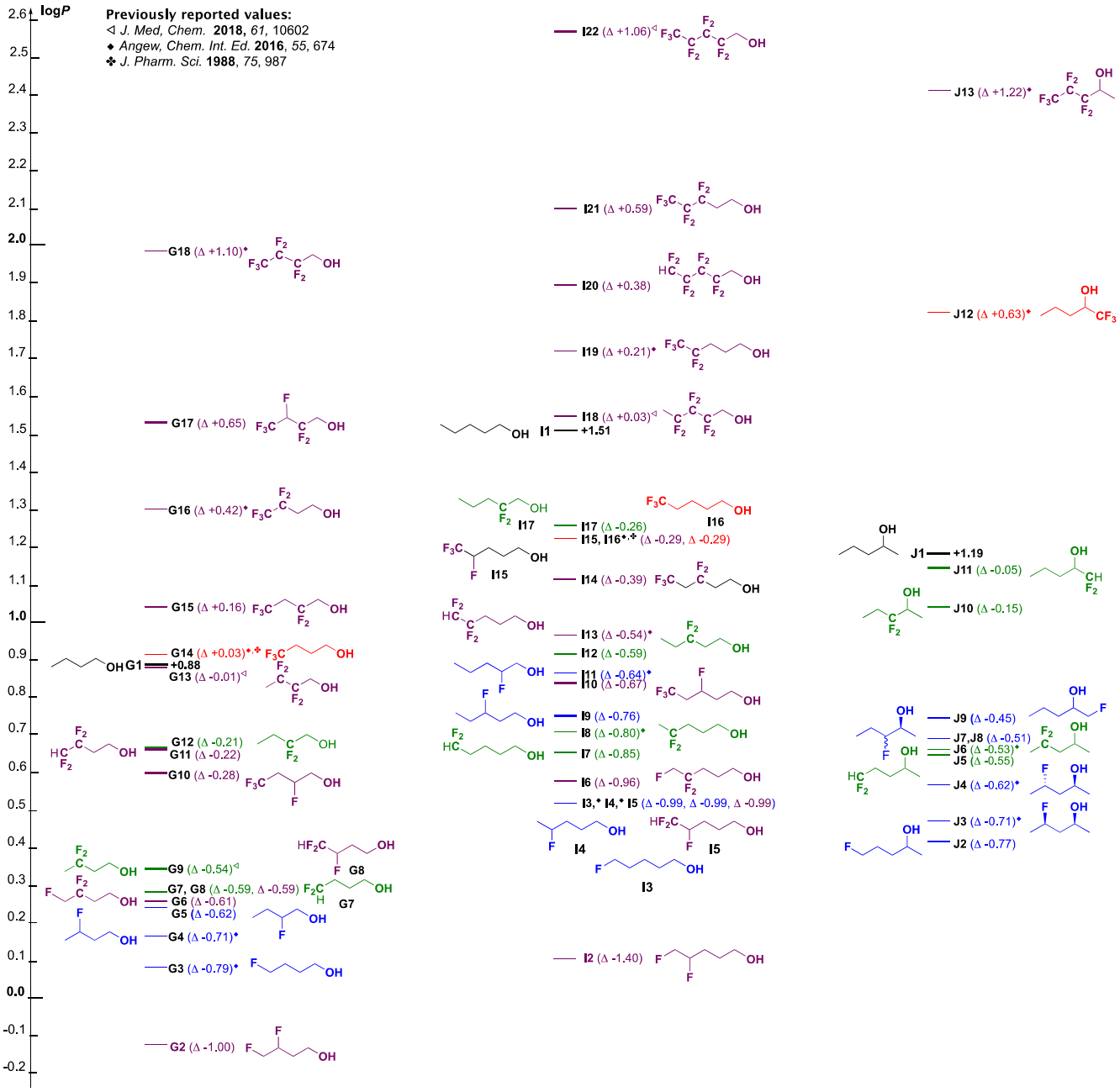


Figure 3. Summary table with new log*P* data, together with previously reported values for completion.[31,38,42] Color coding: blue, monofluorinated; green, *gem*-difluorinated; red, a (single) CF_3 group; purple, multifluorinated (fluorination at more than one carbon atom). The difference in log*P* value with the corresponding nonfluorinated parent compounds **G1**, **I1**, **J1** (depicted in black) is given (See Figure S1 for a list of all log*P* values).

Discussion

The discussion of the data is organized by motif. First, mono- and geminal difluorination will be discussed, then vicinal fluorination motifs, followed by skipped motifs. A number of compound series will be discussed, and finally correlations will be shown with a number of log*P* prediction methods.

Monofluorination and geminal difluorination.

The data for all monofluorinated and geminal difluorinated analogues is shown in Figure 4. As expected, monofluorination of acyclic alkanols results in a systematic decrease in lipophilicity when compared to their respective parent compound. This decrease is clearly dependent on the relative position of the fluorination and the alcohol functional group (cf. the series **G3**,**4**,**5**; **J2**,**3**,**4**,**7**,**8**,**9**, and **I3**,**4**,**9**,**11**). The β-monofluorinated analogues **G5**, **J7–9** and **I11** all have the highest log*P* values within their respective families. This is explained by the proximity of the fluorination site to the hydroxyl group, resulting in a higher reduction in polarizability of the oxygen lone pairs, as well as a possible conformation where the C–O/C–F dipoles counteract. Monofluorination at the methyl group (**J9**) causes a slightly lower reduction in lipophilicity compared to internal monofluorination (**J7**/**J8**). Unfortunately, due to partial ^{19}F NMR signal overlap in the aqueous solvent, the lipophilicity of the individual diastereomers **J7** and **J8** could not be determined (the stereoisomers were not separable), although qualitatively the values appear to be very similar (the average value is given, see SI section 4.3.2). An increasing number of methylene groups between the OH and F groups leads to a further reduction in lipophilicity. For **I3** and **I4**, the decrease in lipophilicity is quite substantial ($\Delta\log P_{\mathbf{I1\text{-}I3,4}}$ –0.99). Compounds **J3** and **J4** were obtained in diastereomerically pure form, and the lower lipophilicity of the *syn*-diastereomer **J3** can be explained by the comparatively larger stabilization of its most polar conformation (featuring parallel C–O and

C–F bonds) in water compared to that of **J4** (and the opposite for the less polar conformers in octanol).[38]

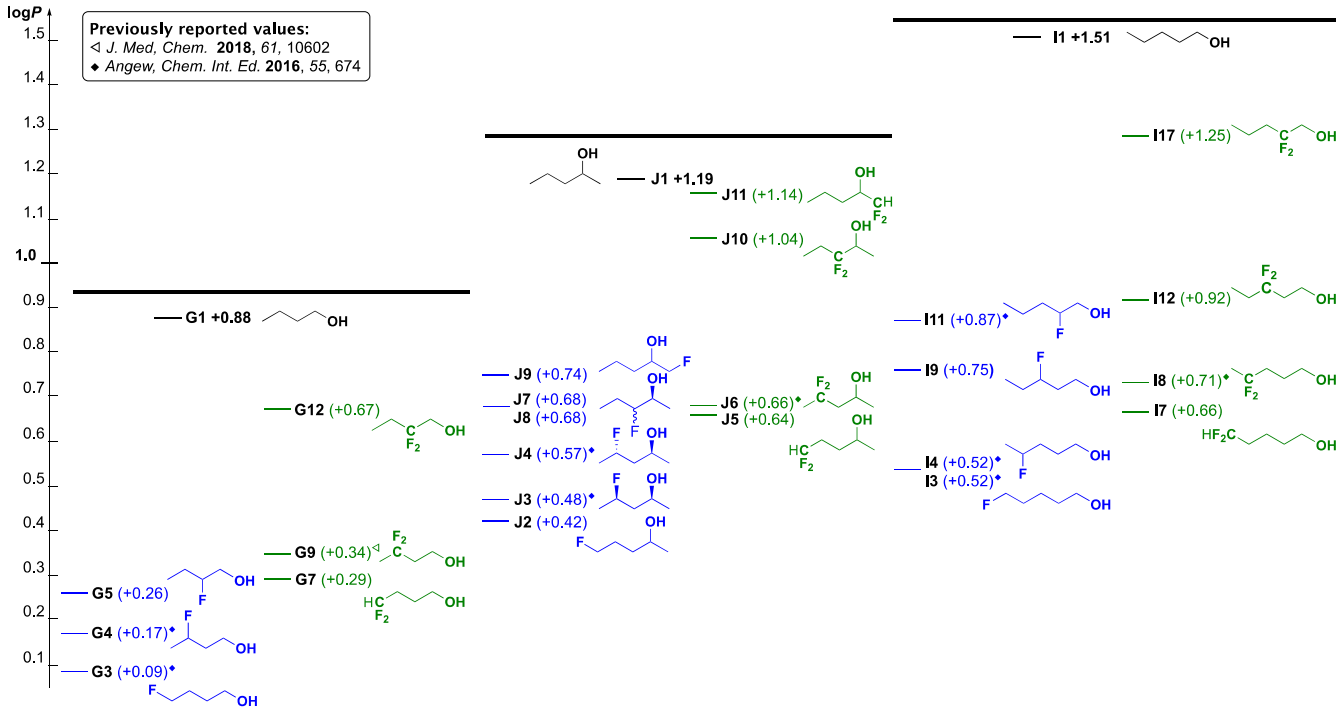


Figure 4. Systematic mono- and difluorinated lipophilicity series of the parent compounds 1-butanol (**G1**), 2-pentanol (**J1**) and 1-pentanol (**I1**). Color coding: blue, monofluorinated; green, *gem*-difluorinated.

All the geminal difluorinated alkanols are more lipophilic than their corresponding monofluorinated congeners, which conforms to Müller's 'rule'[37] that the influence of the larger CF_2-dipole moment (compared to C–F) is counterbalanced by an increased hydrophobic surface. For the compounds in Figure 4, the increase from the monofluorinated congeners is about 0.15-0.20 log*P* units, except for the vicinal difluorohydrins where the difference is up to 0.40 log*P* units. This can be explained by the larger polarizability reduction of the alcohol lone pairs by a CF_2-group, as well as by the increased probability that the C–O dipole is antiperiplanar with a C–F dipole (compared to monofluorination). Nevertheless, all *gem*-

difluorinated compounds investigated in this study still have a lower lipophilicity in comparison to their respective nonfluorinated parent compound. As with the monofluorinated derivatives, their lipophilicity progressively decreases with fluorination further from the alcohol group. Indeed, the β-difluorination analogues **G12**, **J10**, **J11** and **I17** all have the highest log*P* values within their respective families. In the 2-PentOH family, just like for the monofluorination, the internal β-difluorination **J10** causes a larger log*P* decrease compared to its terminal counterpart **J11**. For matched compound pairs featuring internal CF_2 and terminal CF_2H groups, Müller already noted that there was little difference in their log*P* values.[32] In our data set involving longer aliphatic chains, we show that this remains true only when CF_2H compounds are compared with compounds having CF_2 groups at the penultimate carbon atom (cf. **I7** and **I8** for the PentOH family, **J5** and **J6** for the 2-PentOH family, and **G7** and **G9** for the BuOH family). For CF_2 groups further away from the final carbon atom the difference is much more significant, because of the influence of the polar alcohol group. In all cases, compounds having a RCH_2CF_2H group are slightly less lipophilic than their congeners with a RCF_2CH_3 group (compare **G7** and **G9**; **J5** and **J6**; and **I7** and **I8**).

In longer chains such in 1-pentanol, the increase in lipophilicity in comparing C–F with CF_2 is roughly compensated when moving one bond further away from the alcohol group. For example, 3-fluoropentan-1-ol **I9** has a similar log*P* as 4,4-difluoropentan-1-ol **I8**.

Vicinal fluorination series.

Two series featuring vicinal fluorination motifs at the terminal position of the alkyl chain are shown in Figure 5. In general, the lipophilicity increases with increasing number of fluorine atoms present in the motif, and it is notable that only the compounds with the fully fluorinated pentafluoroethyl motif (**G16**, **I19**) have a larger lipophilicity than their nonfluorinated parents. The introduction of vicinal difluorination causes significant reductions in lipophilicity (–1.00

log*P* unit for **G2**, –1.40 log*P* units for **I2**). This is in keeping with Müller's analysis,[32] and with Gilmours's Gilenya® examples (there was a 1.7 log*P* unit decrease between the respective CH_2–CH_3 and CHF–CH_2F Gilenya® analogues).[33] The differences in log*P* tend to slightly increase between compounds having 2 vs 3, 3 vs 4 and 4 vs 5 fluorines present. For motifs with the same number of fluorines, their internal arrangement has an impact on the log*P*. For the vicinal trifluorination motifs, which have been considered by Müller in the context of polarity prediction,[43] this impact is small (Δlog*P* 0.02-0.06, and reverses between BuOH (**G6**/**G8**) and PentOH (**I5**/**I6**)), but there is a larger difference between the two vicinal tetrafluorinated motifs (Δlog*P* 0.25, **I13**/**I15**).

In all cases, for series where the fluorine count at a particular carbon is increasing whilst keeping that at the other carbon of the motif constant (e.g. consider **I2**→**I5**→**I15** or **I6**→**I13**→**I19**), the log*P* increases. This is further elaborated in the SI (Figures S2-S3).

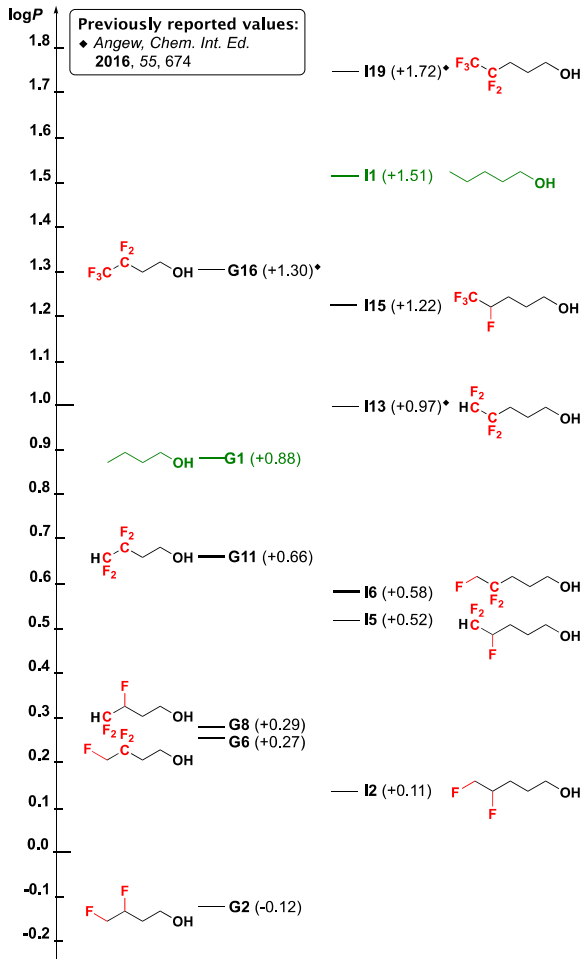
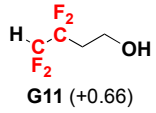
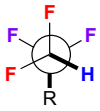
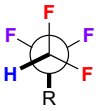
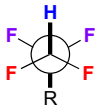
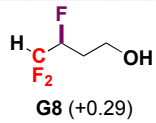
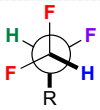
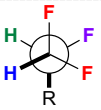
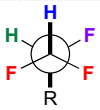
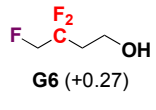
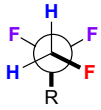
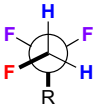
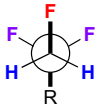
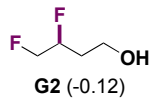
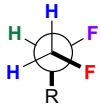
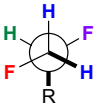
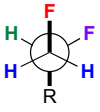


Figure 5. Systematic exploration of all $C_2H_xF_{(5-x)}$ motifs.

The vicinal fluorination motifs in **G2**/**I2**, **G6**/**I6**, **G8**/**I5**, and **G11**/**I13** feature different conformations upon rotation of the bond between the fluorinated carbons and, given the polarity of the various C–F bonds present, it was of interest to explore the impact of their conformations on the lipophilicity. Hence, conformational analysis in water and octanol medium was carried out for the corresponding butanol derivatives (Table 1).

Table 1. Calculated[a] dipole moments and conformational distribution of selected vicinal fluorinated butanols in the octanol and the water phase. The repartition of the *g*(+), *g*(–) and *t*

conformers (defined by the H(F)-C_4–C_3-C_2 dihedral angle) is given. For full details, see Tables S8-S11.

Compound[b] ($\log P$)[c] μ_t (D)[d]	$\Delta\mu_t$[d] (D)	$g(+)$ p[e]	$g(+)$ μ_s[f] (D)	$g(-)$ p[c]	$g(-)$ μ_s[f] (D)	t p[c]	t μ_s[f] (D)	NMR analysis (% antiperiplanar)
 **G11** (+0.66)								[h]
Oct: 3.13	**-0.60**	26%	4.25	26%[g]	4.25	47%	1.88	
Wat: 3.73		35%	4.45	35%[g]	4.45	30%	2.08	
 **G8** (+0.29)								$^3J_{H3\text{-}H4}$ (oct) 3.3 Hz (41%) $^3J_{H3\text{-}H4}$ (wat) 2.8 Hz (31%)
Oct: 3.48	**-0.42**	41%	3.56	33%	4.20	25%	2.42	$^3J_{F3\text{-}H4}$ (oct) 7.4 Hz (33%)
Wat: 3.90		31%	3.58	50%	4.58	19%	2.58	$^3J_{F3\text{-}H4}$ (wat) 9.0 Hz (50%)
 **G6** (+0.27)								$^3J_{H4\text{-}F3}$ (wat) 13.2 Hz (39%) $^3J_{H4\text{-}F3}$ (oct): *J*-values could not be determined
Oct: 3.69	**-0.46**	24%	2.76	24%[g]	2.76	52%	4.56	
Wat: 4.15		22%	2.93	22%[g]	2.93	55%	5.14	
 **G2** (-0.12)								[h]
Oct: 3.74	**-0.30**	38%	3.12	0.0%	2.24	62%	4.10	
Wat: 4.04		36%	3.95	0.0%	2.34	64%	4.09	

[a]Calculated at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium. [b]*t*-Conformer shown. [c] Experimental *logP*. [d]Weighted by the relative populations of each conformer: $\mu_t=\mu_{oct}-\mu_{wat}$ (t = total). [e]Sum of all conformers with a given H(F)-C_4-C_3-C_2 dihedral angle. [f]Weighted dipole moment of the conformers with the H(F)-C_4-C_3-C_2 dihedral angle as shown: μ_s (s = subset). [g]Structure with equivalence of the *g*(+) and *g*(-) conformations. [h]Not investigated.

In all cases, the "total" molecular dipole moment μ_t (weighed across *all* conformations) in the octanol phase is lower than that in the water phase (cf. $\Delta\mu_t$), which reflects the expected higher populations of apolar conformers in the octanol phase due to its lower dielectric constant. This difference is clearly significant for the tetrafluorinated **G11**.

The data were then further refined to provide insight into the contribution of the fluorinated motif: the fluorohydrin conformations are grouped according to the three possible C3-C4 rotational minima. Their respective population in both the octanol and water phases, and the corresponding weighted dipole moment μ_s of these subsets of conformers are given. The magnitude of μ_s is determined by the two main contributors, the fluorinated motif and the alcohol group, and the contribution of the former is easily seen. For example, for **G11**, all C–F dipole moments in the *t*-conformers are opposed so the $\mu_s(t)$ value is much lower than that of the (equivalent) *g* conformations, where only two C–F bonds are antiperiplanar. For **G8**, the *g*(+)- and *t*-conformations each have two C–F dipoles opposed, but their corresponding μ_s values (for a given phase) are different, which is due to a different relative average orientation of the C–O–H dipoles. Still, both values are lower than that of the $\mu_s(g(-))$ value, as there the three C–F dipoles point into the same direction (vector sum ~$2.16\mu_{(C-F)}$). For a given motif conformation, the μ_s values are typically lower for the octanol phase, which is attributed to the aforementioned conformational differences across the C1-C2 and C2-C3 bonds (higher population of apolar conformations in the octanol phase).

The conformational population data show that there is considerable difference in the influence of the medium on the conformational profile of the fluorinated motifs. For the compounds bearing two fluorines at the C-terminal position, **G11** and **G8**, the motif conformer populations in water are very different from those in octanol. For **G11**, the population of the more apolar trans conformation significantly increases going from water to octanol (from 30% to 47%, a ca. 60% increase). Similarly for **G8**, the populations of the two less polar *g*(+) and *t* conformations both increase by around 30% each. Conversely, with only one fluorine at the C-terminal position (**G6** and **G2**), there is minimal influence of the medium on the motif conformer population. Hence, for these compounds, despite the overall conformational profile in the two phases being clearly different (as shown by the $\Delta\mu_t$ values), the different solvent

polarities do not influence the conformational behavior of these fluorination motifs: regardless the medium, for **G2** there is 36-38% of *g*(+), 62-64% of *t*, and 0% *g*(–) population (similar consideration for **G6**). In other words: the dielectric constant of the medium has no impact on the conformational distribution of the motif, despite the different dipole moments of these conformations (e.g. compare **G6**(*t*) and **G6**(*g*)). This could be explained by additional factors that stabilize conformations, over and above dipole stabilization by the dielectric constant of the medium, such as steric effects, and by stereoelectronic effects such as the fluorine gauche effect, which is a stabilizing $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation. The latter was investigated further.

The energies of hyperconjugations operating in these motifs can be estimated through NBO analysis by calculating the charge transfer from the corresponding bonding to the antibonding orbitals, $E^{(2)}_{\sigma \rightarrow \sigma^*}$, reported in Table S15. As expected, the stabilization by $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation is larger than a $\sigma_{C-C} \rightarrow \sigma^*_{C-F}$ hyperconjugation, which in turn is larger than a $\sigma_{C-F} \rightarrow \sigma^*_{C-F}$ hyperconjugation. Furthermore, the calculations show that the $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation energy roughly decreases with the extent of additional fluorination in the order **G2**→**G6**→**G8**→**G11**. Hence, the *g* conformations of **G11** are stabilized by one weak $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ (ca. 14 kJ mol^{-1}) and $\sigma_{C-C} \rightarrow \sigma^*_{C-F}$ hyperconjugation (ca. 6 kJ mol^{-1}). For **G8**, the *g*(–) conformation exhibits two $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugations (ca. 17 kJ mol^{-1}), and the *t*-conformation only one (ca. 17 kJ mol^{-1}). The *g*(+) and again the *g*(–)-conformations have a weaker C–C mediated hyperconjugation (ca. 9 kJ mol^{-1}). For **G6**, the *t*-conformer has one C-H (ca. 21 kJ mol^{-1}) and one C–C (ca. 8 kJ mol^{-1}) mediated hyperconjugation, while its *g*(+) conformer only has one C-H mediated one (ca. 20 kJ mol^{-1}). Finally, compound **G2** only occupies conformations that have either two C-H mediated hyperconjugations (ca. 21 kJ mol^{-1} in *g*(+)), or one C-H and one C-C mediated hyperconjugations (ca. 21 and 12 kJ mol^{-1} in *t*). The latter is the most populated, which may be due to the lower amount of steric congestion.

Hence, we qualitatively suggest that the larger F-gauche stabilization in **G2** would make it the dominant force in both phases, while for **G11** the smaller fluorine gauche stabilization would be of the same order of magnitude as the interactions that destabilize polar conformations in apolar phases, resulting in a 'chameleon' character in which the molecule adopts polar or apolar conformations depending on the dielectric constant of the medium. Nevertheless, crystal structures containing -CF_2CF_2H groups show that this motif was present as a *g* conformation.[44-47] The calculations of the motif conformations in **G8** and **G11** correspond reasonably well to the relative energies of the respective conformations for 1,1,2-trifluoro and 1,1,2,2-tetrafluoroethane as calculated with MP2/6-31+G*.[48]

A correlation of these calculated populations with the solution-phase populations through a (qualitative) *J*-value NMR analysis (see SI section 8 for full details) was possible for **G8**. Using (octanol-saturated) D_2O and (water-saturated) octanol as solvents, the $^3J_{H3\text{-}H4}$ value measured in the octanol phase (3.3 Hz) is larger compared to the value in the water phase (2.8 Hz), and vice versa for the $^3J_{F3\text{-}H4}$ values (7.4 vs 9.0 Hz). This is consistent with the population differences of conformers containing antiperiplanar H3-H4 and F3-H4 dihedral angles (see Table 1, last column). For **G6**, the coupling constants in water-saturated octanol could not be determined due to signal overlap.

'Skipped' fluorination.

A small number of 'skipped' fluorination motifs, with a methylene group separating the fluorinated carbons, are shown in Figure 6. In all cases the motif contains a trifluoromethyl group.

While in both cases skipped tetrafluorination leads to a lower log*P* than skipped pentafluorination, a key difference between the butanol and the pentanol series is their relative

position with the nonfluorinated parent: the pentafluorinated **G15** has a higher log*P* than butanol **G1**, while **I14** has a much lower lipophilicity than **I1**. This can be explained by the proximity of the motif to the alcohol group (cf. Figure 4: β,β-difluorination leads to a much higher log*P* than γ,γ-difluorination, see Figure S4 for further analysis).

Conformational analysis in water and octanol medium of some skipped fluorination motifs, calculated on the 1-pentanol chain are given in Table 2. Following the analysis for the vicinal motifs, the conformations are grouped according to the three possible C3-C4 rotational minima, hence the data refer to the conformational profile of the skipped fluorination motif.

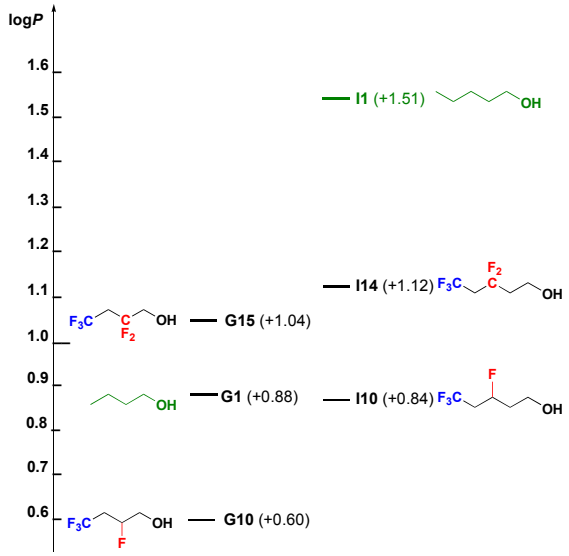
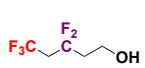
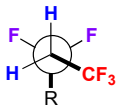
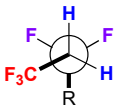
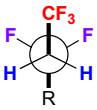
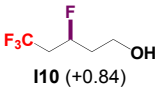
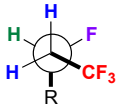
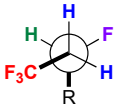
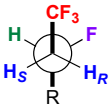
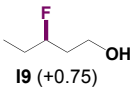
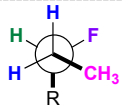
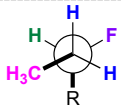
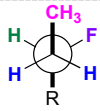


Figure 6. Skipped fluorination motifs.

Table 2. Calculated[a] dipole moments and conformational distribution of the skipped fluorinated pentanols **I10** and **I14** in the octanol and the water phase, next to the monofluorinated **I9**. The repartition of the *g*(+), *g*(-) and *t* conformers (defined by the F_3C-C_4-C_3-C_2 or H_3C-C_4-C_3-C_2 dihedral angle) is given. For full details see Tables S12-S14.

Compound[b]	*g*(+)	*g*(–)	*t*	NMR

($\log P$)[c] μ_t (D)[d]	$\Delta\mu_t$[d] (D)	p[e]	μ_s[f] (D)	p[c]	μ_s[f] (D)	p[c]	μ_s[f] (D)	analysis (% antiperiplanar)
 **I14** (+1.12)								$^3J_{H4\text{-}F3}$ (wat) 15.6 (37%) $^3J_{H4\text{-}F3}$ (oct) 15.5 (39%)
Oct: 3.81	**-0.30**	26%	2.87	26%[g]	2.87	47%	4.86	
H_2O: 4.11		21%	3.06	21%[g]	3.06	57%	4.92	
 **I10** (+0.84)								$^3J_{H3\text{-}H4R}$ (wat) 9.0 Hz (97%) $^3J_{H3\text{-}H4S}$ (wat) 2.7 Hz (2%) $^3J_{F3\text{-}H4R}$ (wat) 16.5 Hz (1%) $^3J_{F3\text{-}H4S}$ (wat) 33.6 Hz (97%)
Oct: 4.45	**-0.42**	2%	2.45	3%	3.44	94%	4.54	
H_2O: 4.87		1%	2.16	2%	3.58	97%	4.93	
 **I9** (+0.75)								[h]
Oct: 2.58	**-0.57**	13%	2.88	21%	2.96	56%	2.39	
H_2O: 3.15		27%	3.32	16%	3.29	56%	3.02	

[a]Calculated at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium. [b]*t*-Conformer shown. [c]Experimental *logP*. [d]Weighted by the relative populations of each conformer: $\mu_t=\mu_{oct}-\mu_{wat}$ (t = total). [e]Sum of all conformers with a given H(F)-C_4-C_3-C_2 dihedral angle. [f]Weighted dipole moment of the conformers with the $H_3(F_3)C$-C_4-C_3-C_2 dihedral angle as shown: μ_s (s = subset). [g]Structure with equivalence of the *g*(+) and *g*(-) conformations. [h]Not investigated.

In line with the results described for the vicinal fluorination motifs, a lower averaged molecular dipole moment is found in the octanol phase than in the water phase for these three fluoropentanol derivatives. The grouping of the conformations along the three possible motif conformational minima reveals interesting differences between **I10** and **I14**. There is a broad population distribution for the skipped pentafluorinated motif, while the opposite is observed for the skipped tetrafluorination motif, for which the *t*-conformer is by far the most stable conformer. The destabilization of the *t*-conformer of **I14** is most likely due to the linear 1,3-repulsions between the CF_2 and CF_3 groups,[49] although *t*-**I10** also features such an interaction.

As a separate point of interest, the conformational profile of **I10** was compared with that of **I9**, in which the trifluoromethyl group is replaced with a methyl group. Again, there is much more conformational disorder to a level close to that of **I14**. The estimated hyperconjugation

contributions (Table S16) for **I9** ($\sigma_{C-H4} \rightarrow \sigma^*_{C-F3}$ ca 25 kJ mol^{-1} and $\sigma_{C4-C5} \rightarrow \sigma^*_{C-F}$ ca 14 kJ mol^{-1}) are much higher than those calculated for **I14** ($\sigma_{C-H4} \rightarrow \sigma^*_{C-F3}$ ca 20 kJ mol^{-1} and $\sigma_{C-C} \rightarrow \sigma^*_{C-F}$ ca 10 kJ mol^{-1}). Hence, the electronic stabilization of the *g*-conformers is higher for **I9**, and is now able to compete with the steric destabilization between the methyl and R-groups.

For **I10**, the populations of the *t*-conformers is only slightly reduced in the octanol phase, despite their weighted dipole moment being much higher than that of the *g*-conformers. For **I9**, for which all conformer subsets have similar averaged dipole moments in water, only the *g*-conformers show variation in population between the solvents.

^{1}H and ^{19}F NMR analysis (see SI section 8 for a detailed discussion) was possible for **I10** and **I14**, and is fully consistent with the calculated conformational profile. For **I10**, the dominant *anti*-conformation of the skipped tetrafluorinated motif in **I10** is clearly demonstrated. In water, the very different vicinal couplings of H3 to the two diastereotopic H4 protons, which are averaged over all conformations, indicate a biased conformational profile, with the 9.0 Hz coupling relating to an antiperiplanar arrangement between H3 and what must be the H4(*R*) proton (cf. the corresponding Newman projection in Table 2), and a *gauche* arrangement between H3 and the H4(*S*) proton. Hence, this H4(*S*) proton must then predominantly be antiperiplanar with the fluorine at C3, which is indeed borne out with the large vicinal H-F coupling. Unfortunately, due to signal overlap, the corresponding *J*-values in water-saturated octanol could not be obtained. For **I14**, the $^{3}J_{H4-F3}$ values in the octanol and water phases are essentially the same (within the error limit), which is what was expected given their very similar (averaged) antiperiplanar disposition between the H4 and F3 nuclei.

Fluorinated motif extension (no change in carbon framework)

As indicated in the introduction, there are many reasons for fluorine introduction as part of the drug development process. In the context of lipophilicity control, it can be of interest to have knowledge whether the log*P* of a candidate that already contains fluorine can be further reduced by introducing additional fluorines. The possibility of fluorinated motif extension for that purpose, where fluorine is introduced at other carbons than those already fluorinated, is explored in Figures 7 and 8 (further introduction of fluorine at an already fluorinated carbon is expected to lead to a lipophilicity increase).

The extension of the monofluorination in **I3** and **I4** by a vicinal C–F group (Figure 7), leading to **I2**, leads to a significant log*P* reduction. The same operation starting from the difluorinated structures **I7** and **I8**, leading to **I5**/**I6**, still leads to a log*P* decrease, albeit much smaller. The extension of the monofluorination in **I3** and **I4** by two geminal C–F bonds, leading to **I5**/**I6**, is either liponeutral or slightly log*P* enhancing. In contrast, the same operation starting from the difluorinated structures **I7** and **I8**, leading to **I13**, now leads to a significant log*P* increase. Hence, extension with a single fluorine leads to an overall increase in polarity that outweighs the introduction of hydrophobic surface, while the opposite is the case when extending with two geminal C–F bonds.

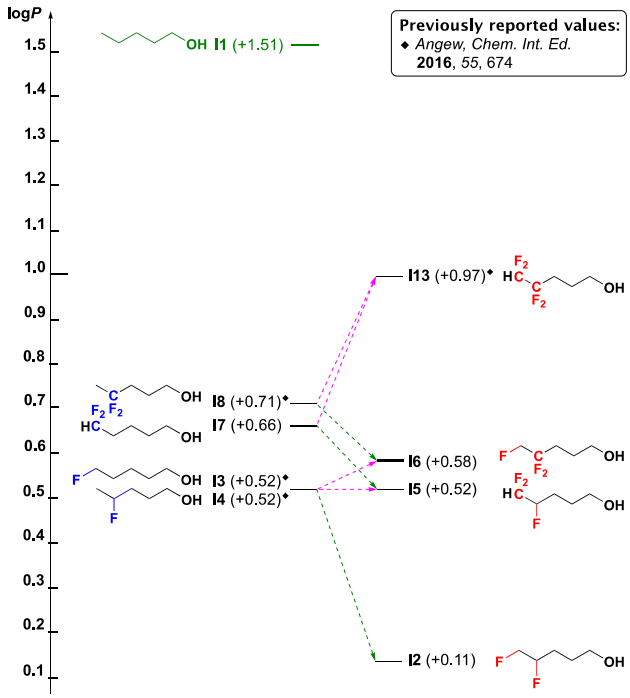


Figure 7. F-motif extension of mono- and geminal difluorinated motifs (See Figure S7 for BuOH).

The extension of a trifluoromethyl group is illustrated in Figure 8. Introducing a C–F group in the vicinal position, leading to **I15**, is liponeutral, but a large log*P* reduction is observed when the C–F group is added in the β-position, leading to **I10**. The comparative operations with a *gem*-difluoro motif lead to very different results: the vicinal pentafluorination (**I19**) leads to a very large log*P* increase, while the skipped pentafluorinated **I14** has a reduced log*P*. Hence, comparing the lipophilicity of the vicinal and skipped motifs with the same number of fluorines shows that the latter have a lower lipophilicity. This may be rationalized by C–F dipole annihilation in the vicinal motif, and by the polarized C–H bonds of the CH_2-group within the skipped fluorination motif (the chemical shift of $CF_3\mathbf{CH_2}CF_2$- protons is 2.88 ppm, compared to 2.15 ppm for a methylene group adjacent to a pentafluoroethyl group).

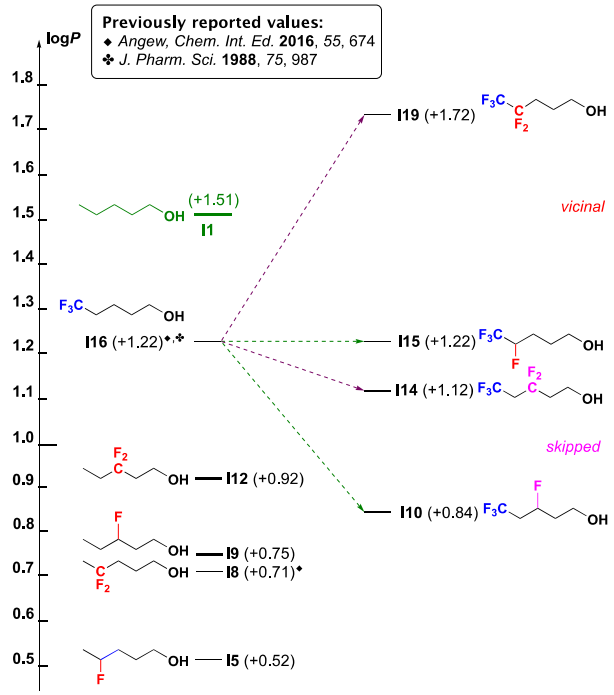


Figure 8. Motif extension involving a trifluoromethyl group. (see Figure S8 for BuOH).

The "reverse" motif extension operation, i.e. extending a mono- or difluorinated motif (cf. **I5**, **I8**, **I9**, **I12**) with a trifluoromethyl motif always leads to a log*P* increase which can be very large (e.g. **I8**→**I19**: +1.01 log*P* units) or very modest (e.g. **I9**→**I10**: +0.09 log*P* units).

Fluorine motif reorganization (same numbers of fluorines, same carbon framework)

In motif reorganization, the fluorine atoms of a given motif are re-distributed on the same carbon skeleton. The trend identified by Müller (Figure 1)[32] regarding the lower lipophilicity of vicinal difluorinated compounds compared to the corresponding geminal analogues is also observed here (Figure 9). The vicinal difluorinated **I2** has a much lower log*P* than **I7**/**I8**, with a difference of up to -0.6 log*P* units for the latter. A similar observation is made for the butanol compounds (compare **G2** with **G7**/**G9**, see Figure S9).

Interestingly, our data show that a similar operation for a trifluoromethyl group, i.e. changing a "geminal" trifluorinated motif to the corresponding vicinal trifluorinated motifs, also results in a significant decrease in lipophilicity (**I16→I5**/**I6**), with log*P* differences of up to -0.7 units.

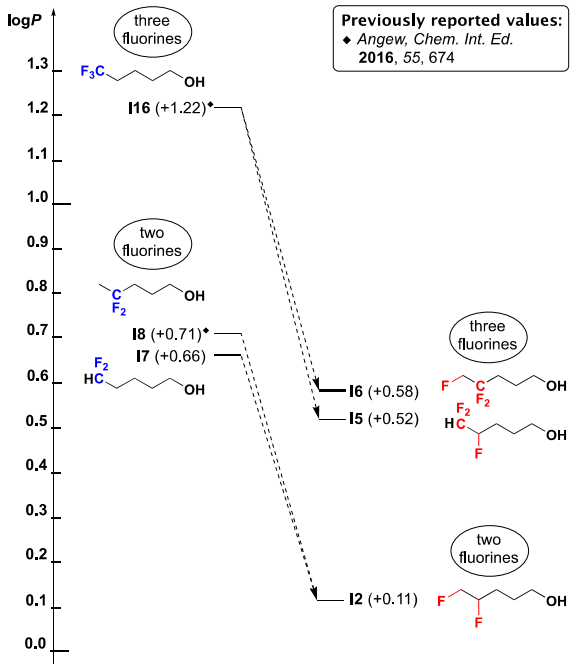


Figure 9. Motif reorganizations (See Figure S9 for the BuOH series).

As a further observation, Müller's data in Figure 1 show that converting a $–CH_2–CF_3$ group to a vicinal $–CHF–CH_2F$ group leads to a reduction in lipophilicity. In proposing the vicinal difluoroethylidene group as a bioisostere for a trifluoromethyl group, Gilmour has further demonstrated that this reduction is substantial when modifying the aliphatic side chain of Gilenya® in this way, and showed that >1 log*P* unit reductions are possible in side chains of varying lengths.[33] The 1.11 log*P* decrease observed going from **I16→I2** fully agrees with Gilmour's data.

Fluorine 'deletions' from perfluoroalkyl groups

As shown above in Figure 1, a CF_2H motif leads to a lower lipophilicity than a CF_3 motif.[36,38,39] Hence, converting the widely used CF_3 group into a CF_2H group can be used to achieve a reduction in lipophilicity. Indeed, the same observation was made for **I16** and also for **I15** (Figure 10). Such a lipophilicity reduction operation will be of even more interest when working with larger perfluoroalkyl motifs. Our group had already shown that a significant log*P* reduction can be thus obtained for a pentafluoroethyl group (compare **I19** with **I13**),[31] and this observation is confirmed for the butanol series (**G16**→**G11**). In both cases, the tetrafluorinated compounds have a much lower lipophilicity than the nonfluorinated parents, which has precedent in the literature.[50]

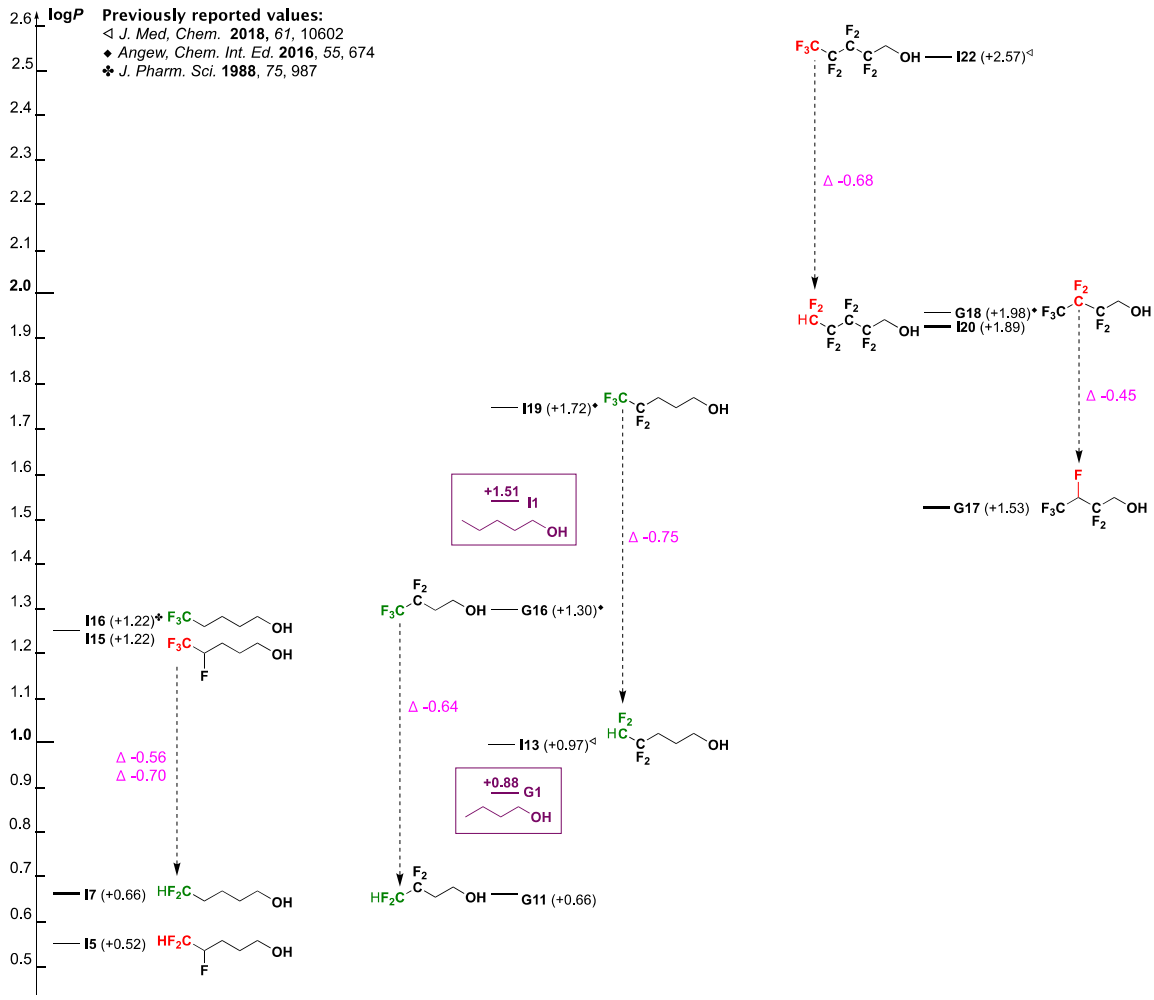


Figure 10. Single fluorine 'deletions' from perfluoroalkylated carbon motifs.

Even for a nonafluorinated 'ponytail' as in **I22**, replacing a terminal C–F bond with a C–H bond to give an octafluorinated motif as in **I20** leads to a large log*P* reduction. Removing an internal fluorine from a perfluoroalkyl group also leads to a log*P* reduction: compare **G18** with commercially available **G17**.

The 'deletion' of two geminal fluorines from a perfluorinated moiety also reduces the lipophilicity, as expected from comparing a pentafluorinated with a trifluorinated compound (Figure 11). Very large log*P* reductions are achieved by replacing an internal CF_2 group of a perfluoroalkyl group by a CH_2 group as shown by comparing **G18** with **G15** and **I21** with **I14**.

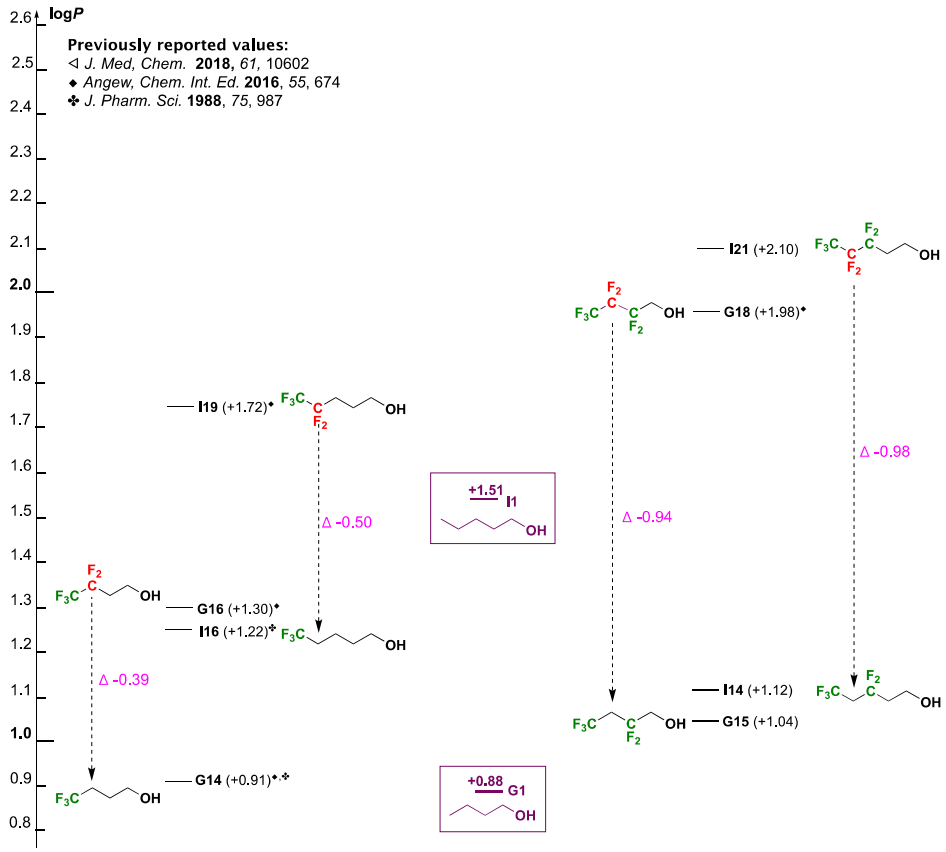


Figure 11. Geminal fluorination 'deletion' effects.

Finally, as illustrated in Figure 2 above, this type of operation with the trifluoromethyl group of a polyfluoroalkyl moiety also leads to a drastic lipophilicity reduction, and all the relevant examples are gathered in Figure S10.

Chain extension

Extending the size of an aliphatic substituent is sometimes required to fill hydrophobic pockets in binding sites. However, the addition of methyl groups, or the insertion of methylene groups, usually leads to an increase in lipophilicity, which is often undesired. Hence, it is of interest to have a panel of extensions available that do not lead to such a log*P* increase. As mentioned in the introduction, Müller had identified that aliphatic chain extension is liponeutral when a CF_2 group is simultaneously replaced by a vicinal difluoro group,[32] and our group has shown that extending a terminal polyfluorinated group by a (nonfluorinated) methyl group even leads to a log*P* reduction (summarized in Figure S11).[31]

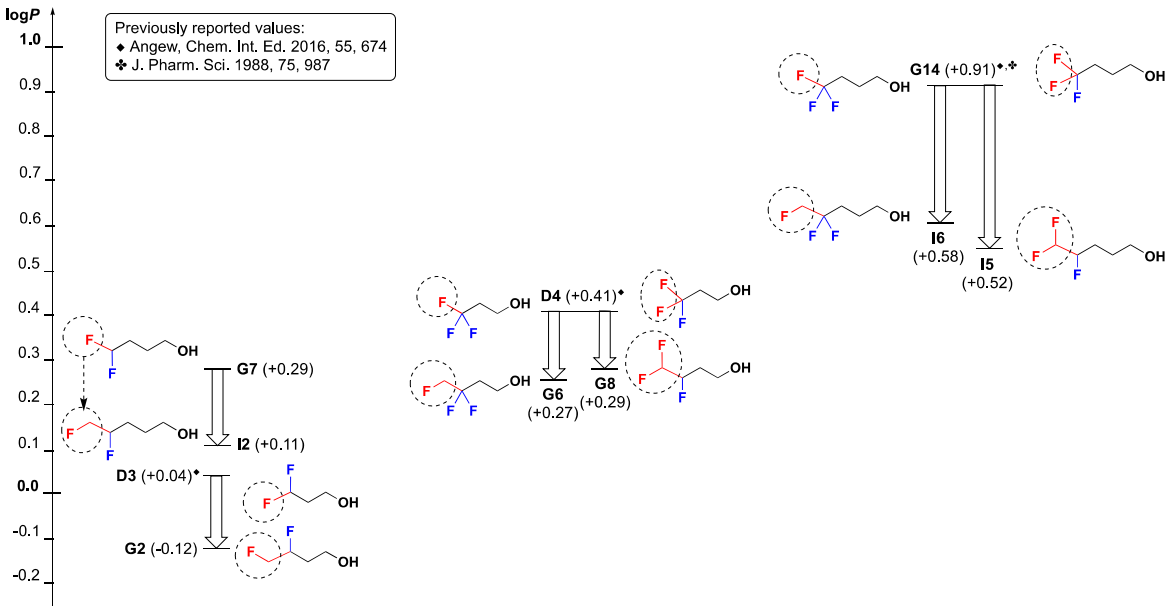


Figure 12. Chain extensions with motif rearrangements that result in log*P* reduction.

Our data (Figure 12) show that chain extension with simultaneous modification of a CF_2H group into a CHF-CH_2F group leads to a small log*P* reduction (cf. **G7→I2** and **D3→G2**, Figure 12). In addition, our data also show that chain extension of a trifluoromethylated compound is also possible with concomitant log*P* reduction using similar operations. Changing a C–F with a fluoromethyl group reduces the log*P*: the log*P* of 3,3,3-trifluoropropanol **D4** is higher than that of 3,3,4-trifluorobutanol **G6** (Δ 0.14 units) and that of 4,4,4-trifluorobutanol **G14** is higher than that of 4,4,5-trifluoropentanol **I6** (Δ 0.33 units). In addition, carrying two fluorine atoms forward with the extra methyl group also leads to a lipophilicity reduction: compare the log*P*'s of **D4** and **G14** with those of **G8** and **I5** respectively. The latter has a log*P* reduction of 0.39 log*P* units.

We also observed that chain extension of a vicinal pentafluoroethyl group by insertion of a methylene group leads to a lipophilicity reduction (Figure 13).

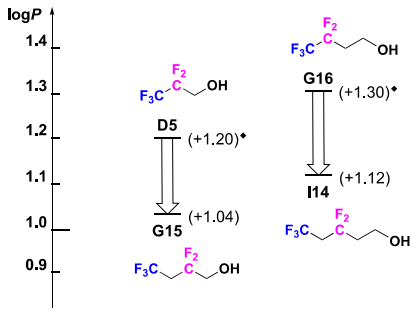


Figure 13. Chain extension of pentafluoroethyl motifs resulting in log*P* reduction.

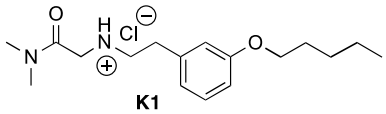
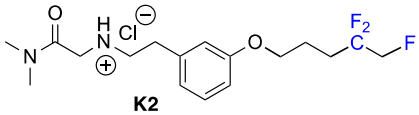
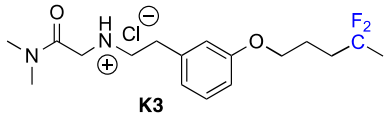
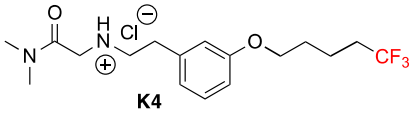
Even more interesting is how extension of nonfluorinated chains can be achieved without log*P* increase by exploiting fluorination. The scope is huge: from the summary table (Figure 3), it is easily seen that 1-butanol **G1** (log*P* +0.88) has a higher lipophilicity than many fluorinated 1-

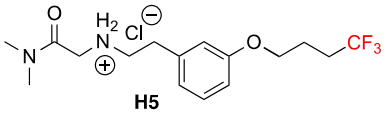
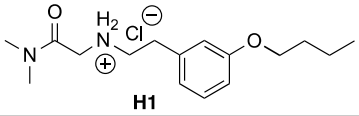
pentanol derivatives (namely **I2**–**I11**). Equally, 1-propanol **D1** (log*P* +0.30) has a higher lipophilicity than many fluorinated 1-butanols (**G2**–**G8**). Remarkably, given that the log*P* of 1-pentanol **I1** (+1.51) is so much larger than that of 1-propanol **D1** (+0.30), chain extension of the latter by two carbon atoms having terminal vicinal difluorosubstitution, as in 4,5-difluoropentanol **I2** (log*P* +0.11), still leads to a lipophilicity reduction.

Further analysis of log*P* trends is given in the SI (Section 2.1)

Finally, lipophilicity trends for a vicinal trifluorinated motif were further investigated by incorporation in the evenamide analogue **K1** (Table 3). Because of the presence of the ammonium group, log*D* values were measured at pH 7.4, this time using AstraZeneca's routine shake-flask method involving UV-detection for concentration determination. The change in p$K_{a(H)}$ of the amine due to the fluorination of the remote alkoxy group is expected to be very minimal and this factor was thus assumed to have a negligible influence on the log$D_{7.4}$ of the evenamide analogues.

Table 3. Analysis of fluorinated motifs when incorporated in evenamide **H1** and analogue **K1**.

Structure	log$D_{7.4}$[a]	Solubility[b] (μM)	PPB[c] (%free)	Hu Mics CLint[d]	Rat Heps Clint[e]	hERG[f] (μM)
 **K1**	+2.3[31]	779	23	29	91	1.8
 **K2**	+1.6	870	47	<3	34	15
 **K3**	+1.7[31]	1000	49	7	38	7.6
 **K4**	+2.3	>1000	28	10	105	9.6

 H5	+1.9	900	47	<3	52	18
 H1	+1.8[31]	782	45	13	82	9.4

[a]log$D_{7.4}$ determined by shake flask method; [b]Solubility of compounds in aqueous phosphate buffer at pH 7.4 after 24 h at 25 ˚C; [c]Determined from DMSO stock solution by equilibrium dialysis in 10% human plasma supplied by Quintiles; [d]Rate of metabolism (µL/min/mg) determined from DMSO stock solution in human microsomes; [e]Rate of metabolism (µL/min/10^6 cells) determined from DMSO stock solution in isolated rat hepatocytes diluted to 1x10^6 cells/mL; [f]Inhibition of the hERG tail current was measured using a plate-based planar patch clamp system (IonWorks™).

The log*D* value of the nonfluorinated evenamide analogue **K1** is +2.3.[31] Introduction of the vicinal trifluorination motif to obtain **K2** led to a significant log*D* decrease (0.6 log*D* units), in line with the log*P* difference between **I1** and **I6** (Δ 0.93 units, Figure 5). Motif extension going from **K3** to **K2** leads to a reduction in log*D* (Δ 0.1 unit), which is similar to the difference observed for the corresponding alkanols **I8** and **I6** (0.13 log*P* units, Figure 7). Motif rearrangement from **K4** to **K2** reduces the log *D* by 0.6 units, in line with a similar reduction in log*P* between the corresponding alkanols **I16** and **I6** (Δ 0.64 units, Figure 9). Finally, chain extension with concomitant motif rearrangement (**H5** to **K2**) leads to a 0.3 log*D* unit reduction, again very similar to the 0.31 log*P* unit reduction between the corresponding alkanols **G14** and **I6**, Figure 12), and in contrast to a 0.5 log*D* unit increase when simply extending the butyl chain in **H1** to a pentyl chain in **K1**. Hence, the log*P* trends that were obtained upon introducing these fluorinated motifs in the butanol and pentanol models are fully replicated in the log$D_{7.4}$

trends of a pharmaceutically relevant drug candidate when they are introduced as part of an aromatic butoxy/pentoxy chain.

The introduction of the fluorine atoms lead to an increase in aqueous solubility. Human plasma protein binding clearly correlates with the lipophilicity (cf. **K1**/**K4** and **K2**/**K3**/**H1**/**H5**). Metabolic stability studies (human microsomes and rat hepatocytes) generally showed an increased stability of the fluorinated derivatives towards oxidative degradation, with only one exception, **K4**, which showed similarly high metabolism with rat hepatocytes compared with **K1**. With respect to inhibition of the hERG receptor, all of the fluorinated analogues showed lower IC_{50}'s than the corresponding compounds with the same chain length (cf. **K2**/**K3**/**K4** with **K1** and **H5** with **H1**).

Lipophilicity prediction

Müller's two-parameter model involving dipole moment and hydrophobic volume considerations is a useful means for rapid log*P* predictions.[32,37] The difference in the number of fluorine atoms *m* has a 'volume' contribution of +0.3•*m*, and a dipole difference has a polarity contribution expressed in 'units' of $\bullet\mu_{C-F}$. For example, the ~0.4 log*P* difference between **G2** and **G6** is in accordance with this model, given the negligible dipole contribution (the averaged calculated dipole moments for **G2** and **G6** are very similar, cf. Table 1), and **G2** contains one less fluorine atom. Compound **G6** is about 0.25 D more polar than **G8**, with an equal number of fluorines, hence the model predicts the log*P* value to be lower for **G6** by about 0.1 log*P* units (0.25 D ~$0.1\bullet\mu_{C-F}$).

However, DFT calculations taking into account 3D conformational preferences in water and in octanol clearly show an often significant difference between the averaged dipole moments of a given compound in octanol and in water, reflecting its different conformational profiles

between these solvents. In addition, a more accurate description of compound solubility in a given phase, that does not rely on prior experimental data, is given by the relative free energy in solution.

While there are a plethora of methods available for log*P* prediction, typically based on 2D substructure and property-based methods,[51,52] there is excellent precedent for lipophilicity prediction using quantum chemical calculations,[53,54] including for nonfluorinated[55] and fluorinated[56] alkanols. The description of octanol as a continuum solvent is challenging to model. This is not only because of the significant amount of water dissolved in this solvent (the water solubility in octanol is 48.91 mg g^{-1} at 25 °C,[56] which is 26 mol% !), but also because of octanol self-association phenomena in the liquid state which leads to a non-uniform dispersion of the water in octanol.[52,58] Nevertheless, the SMD model was reported to give the best correlations (as opposed to the C-PCM and IEF-PCM implicit models) for a series of nonfluorinated aliphatic alcohols within a benchmark of 6 different DFT funtionals.[55] Recently, Ho and coworkers found that implicit solvent models outperformed explicit solvent models in the log*P* prediction of a set of fluorinated alcohols, with the SMD model also giving the best result.[56] However, to their surprise, fragment-based prediction methods were found to give mean and maximum absolute errors about two times smaller compared to the implicit solvent models.[56]

The DFT conformational analysis of the compounds above, carried out in water and *n*-octanol, was performed using the SMD model, but with the MN15 functional, which to the best of our knowledge has yet to be employed for log*P* calculations. However, we have found that this functional best describes molecular interactions involving fluorohydrins, and hence octanol/water partition coefficients were estimated from the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ Gibbs energies, used here for the conformational analysis in both water and *n*-octanol medium at 298 K. These calculated $\log P_{theor}$ values are given in Table S4,

and a correlation with the experimental values is given in Figure 14a. While the absolute values and variation range are far from the experimental values (a slope of 2.098 is obtained), an excellent correlation between experimental and theoretical trends is observed ($r^2 = 0.957$). Indeed, the experimentally found decreases in lipophilicity upon *vic*-difluorination (**G2**/**I2**), upon going from the pentafluorinated (**G16**/**I19**) to the tetrafluorinated motifs (**G11**/**I13**), and upon going from the nonafluorinated **I22** to the terminal methylated hexafluorinated **I18**, are in agreement with the calculated logP_{theor} values. The very similar values between the internally polyfluorinated **G13**/**I18** and their nonfluorinated parents that were determined experimentally are also reproduced theoretically, even though the calculations slightly overestimate the lipophilicities of **G13** and **I18**. However, with the C-terminal trifluorination of **I9**, leading experimentally to a slight increase of lipophilicity in **I10**, the calculations show a log*P* decrease. Hence, despite the absolute values and variation range being still far from the experimental values, the evolution of lipophilic properties are appropriately reproduced, with any inherent errors due to the inadequate description of the solvation models (e.g. "pure" solvents rather than wet octanol and water with small amounts of octanol) only introducing a proportional, as opposed to a random error.

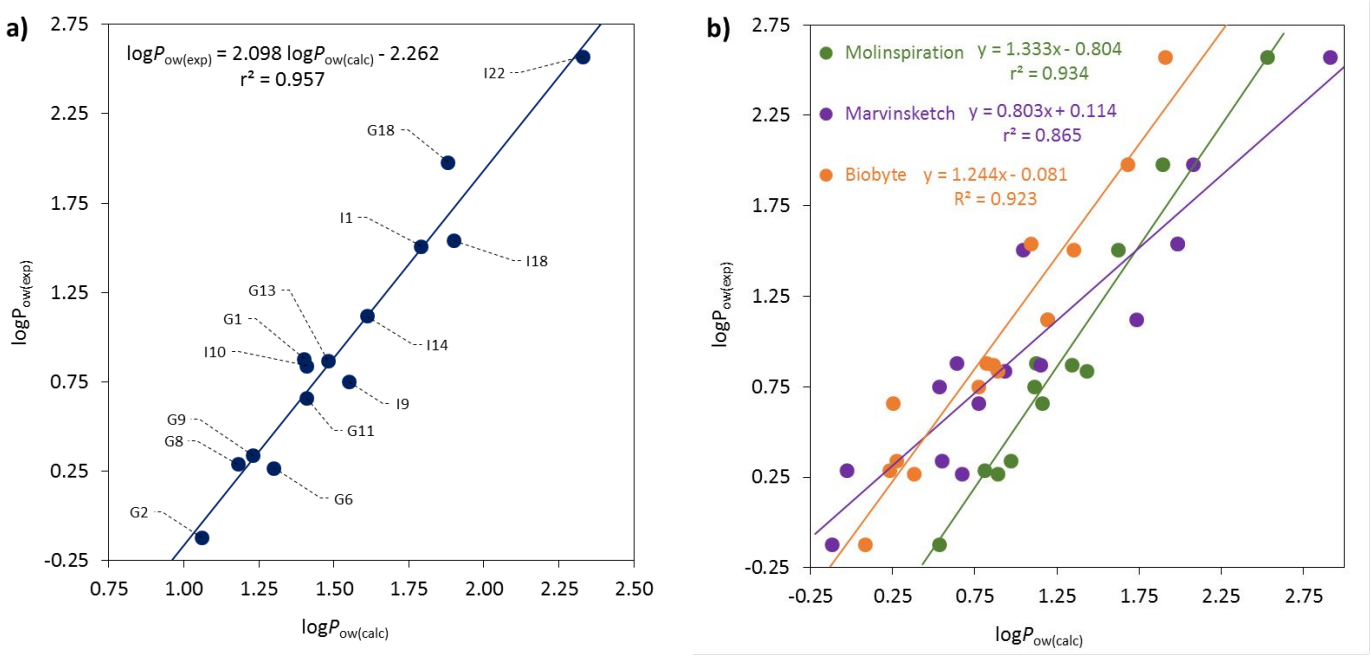


Figure 14. a) Correlation between the logP_{theor} values, calculated after obtaining the (weighted) solvation energies in octanol and water, with the experimental log*P* data for a subset of fluorohydrins. **b)** Correlation between the Clog*P* values obtained with three web-based calculators, with the experimental log*P* values for the same fluorohydrin subset.

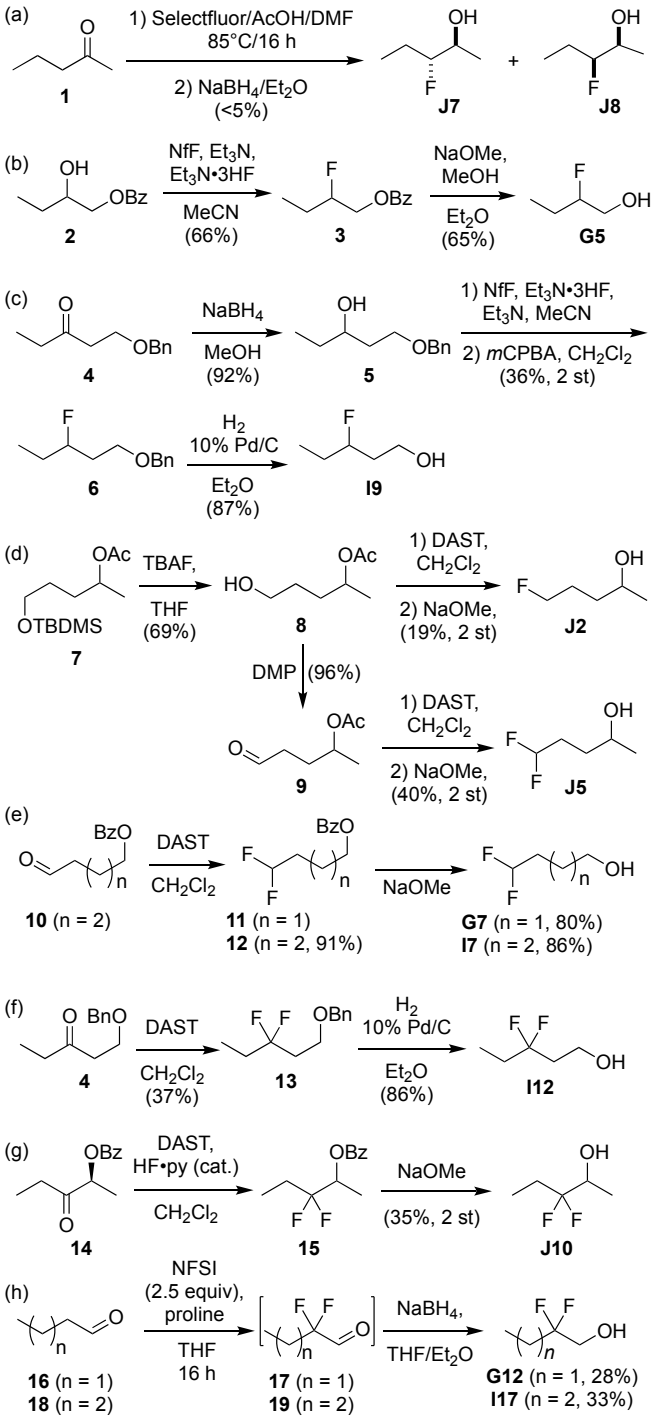
As a comparison with the free energy of solvation log*P* calculation method, the graph in Figure 14b shows correlations with Clog*P* values, obtained by three web-based programs for the same compound subset. The Molinspiration method gives the best correlation (RMSE 0.934), closely followed by Biobyte.

In addition, the calculated lipophilicity (Clog*P*) values for all compounds as listed in Figure 3 were obtained from a number of calculation programmes (Tables S1-S3). While there were usually large differences with the experimental values for individual compounds, some of the calculation programmes gave correlations with RMSE of >0.9.

Chemistry.

The synthesis of the targets with fluorination at a single carbon atom is given in Scheme 1. The diastereomers **J7** and **J8** were obtained as an inseparable mixture from electrophilic fluorination of 2-pentanone, followed by reduction. The electrophilic fluorination also led to ca. 10% of primary fluoride and trace amounts of *gem*-difluorinated byproducts. Fluorine introduction for targets **G5** and **I9** (Scheme 1b,c) was achieved by NfF-mediated deoxyfluorination[59,60] of precursors **2**[61] and **5**, the latter obtained by reduction of ketone **4**.[62] Deoxyfluorination of **5** was accompanied by elimination leading to alkene side products (in a 1:0.4 ratio), which were conveniently removed by treatment of the mixture with *m*CPBA. Finally, protecting group removal through benzoate transesterification and benzyl ether hydrogenolysis afforded the desired products **G5** and **I9**. The final monofluorinated target **J2** (Scheme 1d) was obtained by DAST-mediated deoxyfluorination of **8**, which was obtained by silyl ether cleavage of **7**,[63] and acetate methanolysis.

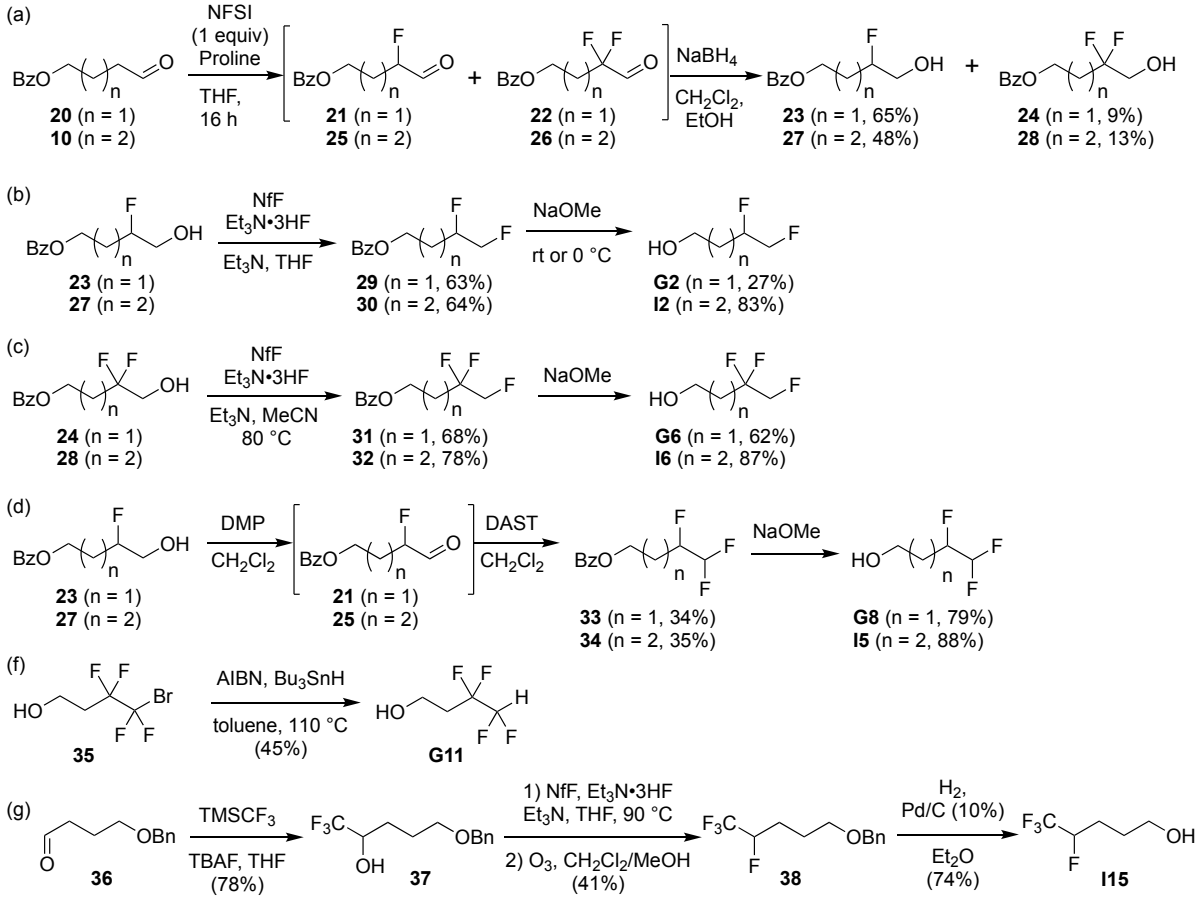
The geminal difluorinated targets were mostly synthesized by DAST mediated deoxofluorination. Aldehyde **9** was obtained by DMP oxidation of **8** (Scheme 1d), and subjected to DAST followed by acetate methanolysis to give **J5**. Similarly, the difluorinated **12**, **13**, and **15** (Scheme 1e-g) were obtained from aldehyde **10**[64] and ketones **4**[62] and **14**.[65] Deprotection of **11**[66] – **13** and **15** led to targets **G7**, **I7**, **I12**, and **J10**. Some elimination product (6%, 3,4-isomer, not shown) was observed with the deoxofluorination of **14**, which could only be separated after the deprotection step. Finally, the synthesis of both **G12** and **I17** (Scheme 1h) was achieved *via* electrophilic fluorination of the aldehydes **16** and **18** with NFSI. Due to the volatility of the compounds involved, the literature procedure[67] was adapted in that no change of solvent to CH_2Cl_2/EtOH was performed, and instead the mixture was diluted with Et_2O during the extraction procedure and, after drying with $MgSO_4$, $NaBH_4$ was added to effect the reduction step directly.



Scheme 1. Synthesis of model compounds with fluorination at a single carbon.

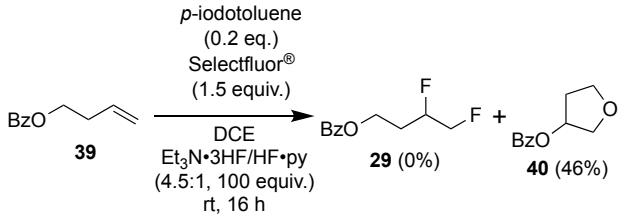
The synthesis of targets with fluorination at vicinal positions is given in Scheme 2. The electrophilic fluorination of the benzyloxyalkanals **20**[68] and **10** (Scheme 2a) under conditions developed by MacMillan *et al*.[69] and Barbas *et al*.[70] was the basis for the synthesis of most

members of this class. For both starting materials, the use of 1 equiv. of NFSI led mainly to monofluorinated alcohols **23** and **27** following aqueous work up, change of solvent to CH_2Cl_2/EtOH, and aldehyde reduction. In our hands, the use of a substoichiometric amount of L-proline gave mainly the difluorinated products, exclusively so if 2.2 equiv. of NFSI was used, in which case **24** was isolated in 40% yield (not shown). Following a method used by the Carreira/Müller group,[22] the vicinal difluorinated targets **G2** and **I2** (Scheme 2b) were obtained by NfF mediated deoxyfluorination of **23** and **27**, followed by alcohol deprotection. Interestingly, when the benzoate deprotection was carried out at room temperature, a low yield of **G2** was obtained. While this could be due to the volatility of **G2**, cyclization to a tetrahydrofuran byproduct was also possible. Müller has reported that *N*-(4-fluorobutyl) piperidines are prone to cyclization,[22] and our group has experienced that distillation of 4-fluoropentan-1-ol led to partial (20%) cyclization.[38] Hence, for **30** the reaction was carried out at 0 °C to give **I2** in 83% yield.



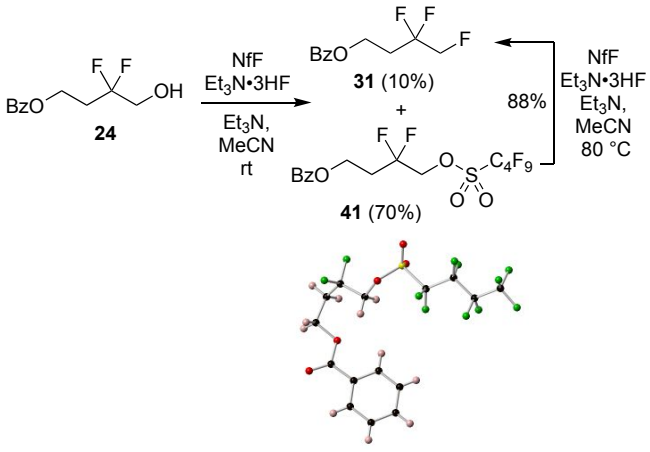
Scheme 2. Synthesis of model compounds with fluorination at vicinal carbon atoms.

It should be noted that novel, catalytic, vicinal difluorination methodology to access vicinal alkenes has become available,[71,72] including enantioselective variants.[73,74] However, when the Gilmour conditions[71] were attempted (Scheme 3), only a trace amount of fluorinated products were observed, with **40** isolated as the major product in a yield of 46%. While the outcome of this reaction was unexpected, reaction of **39** with (dibenzoyloxyiodo)benzene and palladium (II) diacetate was reported to lead to the same outcome.[75]



Scheme 3. Attempted direct vicinal difluorination to **G2**.

The synthesis of the trifluorination motif as in targets **G6** and **I6** (Scheme 2c) was achieved by deoxyfluorination of a β,β-difluorinated primary alcohol,[76,77] but other methodology is available.[78] Starting from **24**, the introduction of the primary fluorine atom using NfF deoxyfluorination at room temperature only led to **31** in 10% yield, with 70% of the crystalline nonaflate **41** (Scheme 4). This reflects the deactivating influence of the adjacent CF_2 group on an S_N2 reaction.[79-81] However, reaction of the nonaflate with Et_3N•3HF at elevated temperature gave **31** in excellent yield. Hence, submitting **24** (and **28**) to NfF with Et_3N•3HF at the same temperature (Scheme 2c) gave the desired **31** (and **32**) directly in 68% (and 78%) yields. In comparison, reaction of **24** with DAST at room temperature did lead to **31** in 60% yield, but required a 5 day reaction time, and a reduced yield of 56% when conducted at 40 °C over 16h (not shown). Targets **G6** and **I6** were then obtained following benzoate methanolysis (at rt).



Scheme 4. Deactivation of a CF_2 group for deoxyfluorination. Crystal structure of **41** shown.

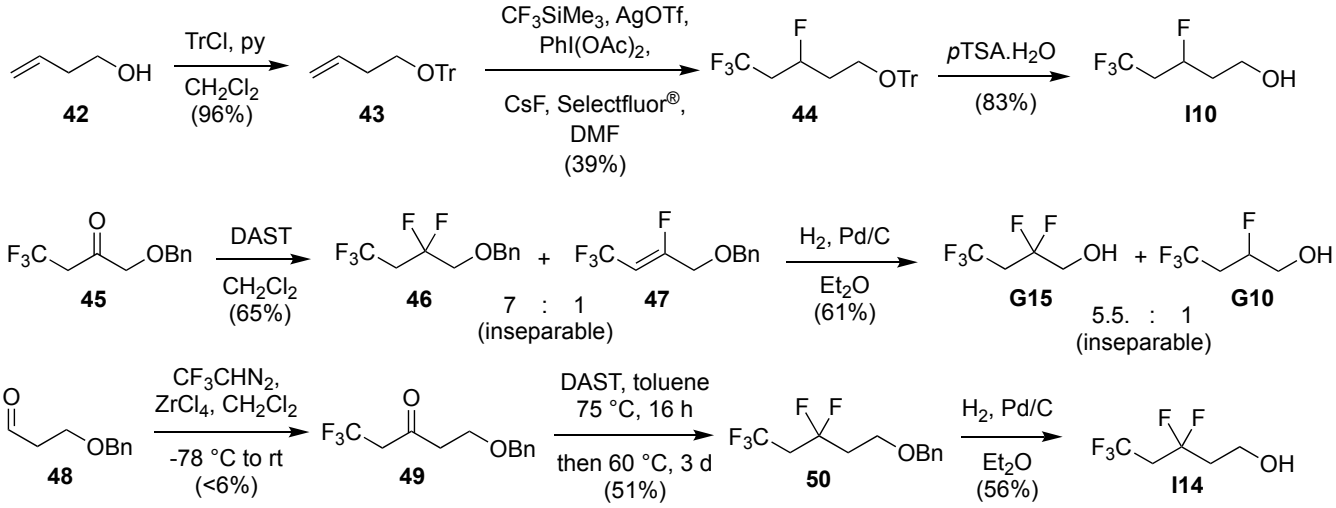
Precedent for the incorporation of the other vicinal trifluorinated motif $RCHFCHF_2$ into organic substrates usually employs trifluoroethylene as a fluorinated building block.[82,83] Here, its synthesis was achieved via DMP-mediated oxidation of **23**/**27** (Scheme 2d) to the fluoroaldehydes **21**/**25**, followed by immediate treatment with DAST to give **33**/**34** in moderate yields. Deprotection then resulted in the isolation of **G8** and **I5**.

The vicinal tetrafluorinated motif was synthesized from the commercially available **35** (Scheme 2f), and **G11** was directly obtained by a radical reduction procedure. Synthetic methodology towards vicinal tetrafluorinated compounds has recently been reviewed,[10] and new methodology for the synthesis of CF_2CF_2H motifs has recently been published.[83]

The other tetrafluorinated target **I15** (Scheme 2g) was synthesized from known[84] aldehyde **36**. Trifluoromethyl addition using the Ruppert-Prakash reagent[85] led to **37**, and the resulting alcohol was then fluorinated under heating, to give **38**. This led to significant elimination (ratio S_N2/E2 1.2:1), and elimination products were removed by ozonolysis. Alcohol deprotection then gave **I15**.

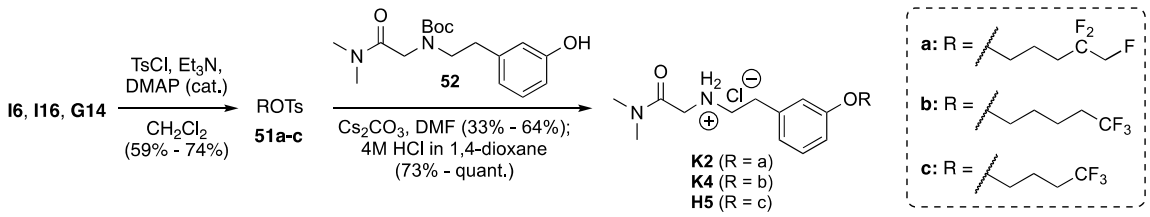
Finally, the synthesis of targets with a skipped fluorination motif is shown in Scheme 5. Trityl protection of commercially available **42** was performed before subjecting the product to silver-mediated oxidative fluorotrifluoromethylation developed by Qing et al.[86] Acidic cleavage of the trityl group yielded the tetrafluorinated alcohol **I10**. For the skipped pentafluorinated motif, the ketone **45**[87] was subjected to deoxyfluorination with DAST providing the desired **46**, together with the fluoroalkene elimination side product **47**, as an inseparable mixture. Hydrogenolysis of the benzyl ethers with concomitant hydrogenation of the alkene **47** was performed in Et_2O to give **G15** and **G10** as a mixture in a 5.5:1 ratio, which again proved

inseparable by column chromatography. However, given that the ^{19}F resonances of **G15** and **G10** were baseline-separated, their lipophilicity could be determined from the mixture. Hence, the synthesis of pure **G10** using Qing's methodology[86] was not carried out. For the synthesis of the skipped pentafluorinated target **I14**, aldehyde **48** was subjected to Carreira's homologation chemistry with trifluoromethyl diazomethane, which was generated in situ from trifluoroethylamine hydrochloride.[87] This provided **49** in a low yield (in contrast to the synthesis of **45**, for which the same methodology was used), but sufficient quantities were obtained for our purposes. Deoxofluorination with DAST proceeded slowly to give **50**, which was then deprotected to yield **I14** in reasonable yield.



Scheme 5. Synthesis of model compounds with skipped fluorination motifs.

Evenamide analogues **K2**, **K4**, **and H5** were synthesized from known **52** (Scheme 6),[31] by aryl ether formation with tosylates **51a**–**c**, prepared from their corresponding alcohols, followed by Boc hydrolysis.



Scheme 6. Synthesis of evenamide analogues.

Conclusions

Monofluorination of aliphatic chains leads to a large reduction in lipophilicity, which becomes less pronounced the closer the fluorine is positioned to the alcohol group. The same observation is made for geminal difluorination, with the latter always being more lipophilic compared to its monofluorinated congeners, but for the examples investigated, still less lipophilic than the nonfluorinated parent alkanols.

When fluorination is considered at two vicinal carbon atoms, the log*P* increases with increasing number of fluorines, but only the fully fluorinated pentafluoroethyl containing compounds have a larger log*P* than the parent nonfluorinated compound. The internal arrangement of the fluorines across the two carbons of the motif affects the log*P* value to some degree. Skipped fluorination motifs involving a CF_3 group, in which a CH_2- group separates the fluorinated carbons, were also investigated. Here, even the pentafluorinated motif in the pentanol series leads to a large lipophilicity reduction. This is not the case in the BuOH series, due to the proximity of the motif to the alcohol functional group, illustrating the importance of considering motif positions close to electronegative functional groups.

Whereas 'adding' fluorines to an already fluorinated carbon typically increases the log*P*, this is not always the case when more fluorines are added in the vicinal or skipped positions, which we coin 'motif extension'. The change in lipophilicity strongly depends on the fluorination level of the original motif. For all the examples investigated, extending a motif with a C–F

bond in the vicinal position causes a negligible (CF_3 motif), small (CF_2 motif), or large (CF motif) log*P* decrease (which in itself is smaller than the decrease in log*P* caused by monofluorination at the same positions in the parent alcohol). Extending a motif with a *gem*-difluoro motif results in a very large (CF_3 motif), large (CF_2 motif), or negligible/small increase (CF motif) (this compares to a decrease in log*P* when starting from the parent alcohol). However, extending a CF_3 motif with skipped C–F or CF_2 fluorination leads to a decrease in log*P*. A 'motif reorganization' refers to a motif extension without an increase in fluorine atoms. In all cases, converting a geminal to a vicinal motif leads to a significant lipophilicity reduction. Reducing the fluorine count of a motif ('fluorine deletions') decreases log*P*. In the examples investigated, single fluorine deletion from a perfluoroalkylated motif (CF_3, C_2F_5, C_3F_7, C_4F_9), and double internal deletion from a $CF_3CF_2CF_2$ to $CF_3CH_2CF_2$ motif, leads to large or very large log*P* reductions.

Finally, fluorination can be exploited to achieve chain extensions without concomitant lipophilicity increase. Starting from a non-fluorinated alkyl chain, introduction of many possible aliphatic F-motifs (with up to 4 fluorines) allows for one-carbon extension without log*P* increase, and vicinal difluoro motif introduction even allows a two-carbon extension without log*P* increase. Starting from an existing polyfluorinated motif, chain extension with concomitant conversion of a geminal polyfluorinated motif to a vicinal motif, or of a vicinal perfluorinated to a skipped motif, also leads to lipophilicity reduction.

3D Conformational analysis (SMD-MN15) showed that the conformational profile of the -$CHFCH_2F$ and -CF_2CH_2F motifs are very similar between the octanol and water phases, while the -$CHFCF_2H$ and -CF_2CF_2H motifs have 'chameleon'-like character, as their conformational distribution is very much dependent on the medium. This leads to a larger averaged dipole moment differences between the phases. Interestingly, the skipped -$CHFCH_2CF_3$ motif appears

very rigid, with ca. 95% of the population in the linear conformation, in both octanol and water phases.

It is shown that available web-based Clog*P* programs based on 2D structures perform well in predicting the effects of fluorine introduction on lipophilicity across a range of motifs, over almost three orders of magnitude in partition coefficient. However, DFT based prediction produced a tighter correlation albeit on a smaller subset. The reliance of this method on 3D conformational analysis and relative energies of solvation will benefit accuracy, although the approximation introduced by the necessary use of a continuum solvent model, especially for water-saturated octanol, will be a limiting factor.

This extensive dataset of aliphatic fluorination motifs enables a full overview of how their introduction affects lipophilicity, and we hope will facilitate lipophilicity optimization efforts in drug discovery programs. The opportunities for lipophilicity modulation by aliphatic fluorination motifs will stimulate further research in this area.[88]

Experimental Section.

General Methods. All chemical reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were purchased from commercial sources. All glassware was flame-dried under vacuum and cooled under Ar prior to use. Water or air sensitive reactions were performed under inert atmosphere, using dry solvents. Reactions were monitored by TLC (Merck Kieselgel 60 F_{254}, aluminium sheet) and spots were visualized by UV and/or by exposure to a basic solution of $KMnO_4$, followed by brief heating. Flash column chromatography was performed on silica gel (Merck silica gel 60, particle size 40–63 μm). All reported solvent mixtures are volume measures. Nuclear magnetic resonance spectra were recorded using either a Bruker Ultrashield 400 MHz or 500 MHz spectrometer. The chemical

shift (δ) is given in ppm using the residual solvent peak as an internal standard. The coupling constants (*J*) are given in Hertz (Hz). IR spectra were recorded on a Thermo Scientific™ Nicolet iS5 as films and absorption peaks are given in cm^{-1}. Low resolution electrospray mass spectra were recorded with a Waters Acquity TQD mass tandem quadrupole mass spectrometer. HRMS spectra were measured on a Bruker Daltonics MaXis time of flight (TOF) mass spectrometer or, for volatile compounds, a Thermo MAT900 XP double focusing sector mass spectrometer. All compounds subjected to biological assays were of >95% purity (liquid chromatography–UV).

Determination of log*P*

Lipophilicities of the fluorinated alkanols were determined using a previously published protocol:[38] 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 $^{19}F\{^{1}H\}$ NMR experiments, NMR parameters were set as follows: D1 30 sec for the octanol sample, D1 60 sec 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. Log*P* values of non-fluorinated compounds were taken from the literature.

Calculations

The calculations were carried out with the Gaussian16 program.[89] The conformational analysis of the various compounds investigated was performed with the MN15 functional[90,91] in combination with the triple-zeta quality aug-cc-pVTZ basis set. Scans along the various rotatable bonds: C-C, C-O, and O-H bonds of the compounds have systematically been conducted. The solvent effects (octanol and water) were taken into account using the SMD solvation continuum model.[92] The vibrational spectrum of each optimized conformer was computed to confirm its nature of true minimum and to obtain the correction to the free energies. Single point calculations at the SMD/MN15/aug-cc-pVTZ were finally carried out to obtain refined electronic energy values. The relative populations, p_i, of the various conformers were evaluated at 298K from the computed free energies through a Boltzmann distribution (Eq. (1)).

$$p_i = \frac{e^{-\Delta G_i / RT}}{\sum_{i=1}^{n} e^{-\Delta G_i / RT}} \quad (1)$$

The theoretical molecular dipole moments were then computed for each conformer, and were weighted according to these populations (either for the compound as a whole or within a conformer series as in Tables 1,2). The fluorohydrin lipophilicity was then estimated from the above results through the calculations of the weighted SMD Gibbs energies obtained in water and in *n*-octanol at 298.15 K to obtain the standard free energy associated with the transfer between these two solvents. The octanol/water partition coefficient was then calculated

according to Eq(2), and following the procedure proposed by Ribeiro for chloroform/water partition coefficient calculations:[93]

$$\log P = -\frac{\Delta G^{o}_{o/w}}{2.303RT} = -\frac{G^{o}_{o} - G^{o}_{w}}{2.303RT} \quad (2)$$

Synthesis

Compounds **1**, **16**, **18**, **35**, **42**, **48**, **G17**, **I20**, and **J13** were commercially available, and the syntheses of **2**,[61] **4**,[62] **7**,[63, 94] **10**,[64] **11**,[22] **14**,[95] **20**,[68] **36**,[84] **39**,[96] **45**,[87] **J9** and **J11**[97] were achieved according to published procedures.

General procedure A for tosylate formation

To a solution of alcohol (1.0 equiv) in CH_2Cl_2 (3.2 mL/mmol alcohol) was added Et_3N (1.1 equiv), DMAP (0.1 equiv) and tosyl chloride (1.1 equiv) at rt under inert atmosphere. After 1 h stirring, the reaction was quenched with 2M aq. HCl (3.2 mL/mmol) and the layers were separated. The organic layer was washed with aq. sat. $NaHCO_3$ (3.2 mL/mmol), dried over Na_2SO_4, concentrated, and purified via column chromatography (SiO_2, 10/90 -> 20/80 acetone/hexane) to afford the desired tosylate **51**.

General Procedure B for Aryl Ether Formation via the Tosylate

To a solution of **52** (1.0 or 1.1 equiv) and the tosylate **51** (1 equiv) in DMF was added Cs_2CO_3 (2 equiv) at rt under inert atmosphere. After 16 h, the solvent was removed *in vacuo.* The residue was dissolved in water (30% v/v of DMF volume) and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and the resulting oil was purified by column chromatography (1:1, EtOAc/ heptane) to afford the ether **53**, which was used directly in the next step.

General Procedure C for Boc-Deprotection

To the Boc-protected amine **53** was added 4 M HCl in dioxane (0.5 mL) at rt under inert atmosphere. The reaction was concentrated after complete consumption of starting material as confirmed by mass-spec analysis (roughly 4 h). The residue is then dissolved in CH_2Cl_2 (5 mL) and concentrated 3 times. The salt was then stirred in Et_2O (10 mL), filtered, further rinsed with Et_2O (10 mL) and dried to afford the evenamide analogues **K2**, **K4**, **H5** as the pure HCl salt.

2-Fluorobutyl benzoate (3): To a solution of **2**[61] (1.60 g, 1 equiv) in MeCN (25 mL) was added Et_3N (6.89 mL, 6 equiv), Et_3N•3HF (2.68 mL, 2 equiv) and nonafluorobutane-1-sulphonyl fluoride (2.96 mL, 2 equiv). After 16 h, the mixture was quenched with sat. aq. $NaHCO_3$ (70 mL) and diluted with CH_2Cl_2 (100 mL). The organic phase was collected and washed with 2M HCl (70 mL), sat. aq. $NaHCO_3$ (70 mL) and brine. The organic layer was dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (5:95 acetone/hexane) to yield **3** as a colorless oil (1.06 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.1, 1.0 Hz, 2H, H_{Ar}), 7.63–7.55 (m, 1H, H_{Ar}), 7.46 (t, J = 7.6 Hz, 2H, H_{Ar}), 4.86–4.65 (m, 1H, H2), 4.57–4.33 (m, 2H, H1), 1.91–1.65 (m, 2H, H3), 1.07 (t, J = 7.5 Hz, 3H, H4) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3 (C = O), 133.2 (C_{Ar}), 129.8 (C_{Ar}), 129.7 (C_{Ar}×2), 128.4 (C_{Ar}×2), 92.5 (d, J = 172.4 Hz, C2), 65.9 (d, J = 22.7 Hz, C1), 24.7 (d, J = 21.3 Hz, C3), 9.2 (d, J = 5.9 Hz, C4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -188.1 (dtdd, J = 48.6, 27.0, 22.5, 17.3 Hz, 1F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -188.1 (s, 1F) ppm; IR (neat) 2972 (w), 2883 (w), 1719 (s), 1451 (m), 1267 (s), 707 (s) cm^{-1}; HRMS (CI) for $C_{11}H_{13}FO_2$ $[M+H]^+$, calculated 197.09723, found 197.09604.

1-(Benzyloxy)pentan-3-ol (5): To a solution of **4**[62] (2.33 g, 1 equiv) in MeOH (40 mL), $NaBH_4$ (0.92 g, 2 equiv) was added portionwise at 0 °C. The reaction mixture was allowed to warm to room temperature and after 30 min, the reaction mixture was quenched with water (30 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic

phases were dried over Na_2SO_4 and concentrated to afford **5** as a colorless oil (2.16 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H, H_{Ar}), 4.54 (s, 2H, PhC$\underline{H}_2$), 3.81–3.62 (m, 3H, H1 + H3), 2.85 (s, 1H, OH), 1.82–1.68 (m, 2H, H2), 1.56–1.43 (m, 2H, H4), 0.95 (t, J = 7.5 Hz, 3H, H5) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.9 (C_{Ar}), 128.4 (C_{Ar}×2), 127.7 (C_{Ar}), 127.6 (C_{Ar}×2), 73.3 (Ph$\underline{C}H_2$), 72.8 (C3), 69.3 (C1), 35.9 (C2), 30.2 (C4), 9.9 (C5) ppm. Data consistent with literature.[98]

1-Benzyloxy-3-fluoropentane (6): To a solution of **5** (2.08 g, 1 equiv) in MeCN (32 mL) was added Et_3N (8.99 mL, 6 equiv), Et_3N•3HF (3.50 mL, 2 equiv) and nonafluorobutane-1-sulphonyl fluoride (3.20 mL, 2 equiv). After 16 h, the reaction was quenched with sat. aq. $NaHCO_3$ until pH 7 and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (1:19 acetone/petroleum ether 40–60 °C) to yield a mixture of **6** and elimination byproducts (1.31 g, 1:0.4 respectively). This mixture was dissolved in CH_2Cl_2 (25 mL), followed by portionwise addition of *m*CPBA (0.97 g, 2 equiv) at 0 °C. After 16 h, the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (1:19 Et_2O/petroleum ether 40–60 °C) to yield **6** as a colorless oil (0.75 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H, H_{Ar}), 4.73–4.54 (m, a doublet with 49.5 Hz can be observed, 1H, H3), 4.55 (d, J = 11.9 Hz, 1H, PhC$\underline{H}$H'), 4.51 (d, J = 11.9 Hz, 1H, PhCH$\underline{H}$'), 3.68–3.57 (m, 2H, H1), 1.96–1.78 (m, 2H, H2), 1.72–1.59 (m, 2H, H4), 0.99 (t, J = 7.5 Hz, 3H, H5) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.4 (C_{Ar}), 128.4 (C_{Ar}×2), 127.6 (C_{Ar}×2), 127.6 (C_{Ar}), 92.7 (d, J = 167.3 Hz, C3), 73.1 (Ph$\underline{C}H_2$), 66.3 (d, J = 4.4 Hz, C1), 35.1 (d, J = 21.3 Hz, C2), 28.3 (d, J = 20.5 Hz, C4), 9.3 (d, J = 5.9 Hz, C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -184.4– -184.0 (m, 1F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -184.1

(s, 1F) ppm; IR (neat) 3065 (w), 2967 (m), 2879 (m), 1363 (m), 1097 (s), 930 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{17}FNaO$ $[M+Na]^+$, calculated 219.1156, found 219.1156.

5-Hydroxypent-2-yl acetate (8): To a stirred solution of **7**[94,63] (16.80 g, 1 equiv) in THF (100 mL), was added TBAF (1M in THF, 92 mL, 1.1 equiv) dropwise at 0 °C over 30 min. The reaction was stirred at 0 °C for 30 min, before allowing to warm to room temperature. After 2 h, the reaction mixture was quenched by the dropwise addition of sat. aq. NH_4Cl (150 mL) at 0 °C. After 30 min of vigorous stirring, the aqueous phase was extracted with EtOAc (3×300 mL) and the combined organic layers were dried over $MgSO_4$. The crude oil was purified with column chromatography (1:9 acetone/petroleum ether 40–60 °C) to afford **8** as a slightly orange oil (7.80 g, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.90–4.87 (m, 1H, H2), 3.67 (t, J = 6.0 Hz, 2H, H5), 2.04 (s, 3H, CH_3, Ac), 1.71–1.50 (m, 4H, H3 + H4), 1.42 (br. s, 1H, OH), 1.23 (d, J = 6.4 Hz, 3H, H1) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8 (C = O), 70.7 (C2), 62.5 (C5), 32.2 (C3 or C4), 28.5 (C3 or C4), 21.3 (CH_3, Ac), 20.0 (C1) ppm. Data consistent with literature.[99]

5-Oxopent-2-yl acetate (9): To a solution of **8** (2.02 g, 1 equiv) in CH_2Cl_2 (20 mL) was added DMP (8.40 g, 1.4 equiv) portionwise at 0 °C. The reaction mixture was allowed to warm to room temperature and after 45 min, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and the crude oil was purified with column chromatography (1:3 EtOAc/pentane) to afford **9** as a colorless oil (1.89 g, 96%), which was immediately subjected to the next step (^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, J = 1.3 Hz, 1H, H5), 4.93 (sxt, J = 6.3 Hz, 1H, H2), 2.50 (td, J = 7.3, 1.3 Hz, 2H, H4), 2.03 (s, 3H, CH_3, Ac), 1.95–1.84 (m, 2H, H3), 1.25 (d, J = 6.2 Hz, 3H, H1) ppm).

5,5-Difluoropentyl benzoate (12): To a solution of **10**[64] (3.27 g, 1 equiv) in CH_2Cl_2 (30 mL), DAST (4.0 mL, 1.9 equiv) was added dropwise at 0 °C. After 60 h the reaction was quenched with sat. aq. $NaHCO_3$ until pH 7. The aqueous phase was extracted with CH_2Cl_2 (2×150 mL), the organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (5:95 EtOAc/petroleum ether 40–60 °C) to afford **12** as a pale-yellow oil (3.23 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H, H_{Ar}), 7.58 (tt, J = 7.4, 1.3 Hz, 1H, H_{Ar}), 7.49–7.43 (m, 2H, H_{Ar}), 5.85 (tt, J = 57.6, 4.4 Hz, 1H, H5), 4.36 (t, J = 6.4 Hz, 2H, H1), 2.01–1.81 (m, 4H, H2 + H3), 1.71–1.60 (m, 2H, H4) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9 (C = O), 133.3 (C_{Ar}), 130.6 (C_{Ar}), 129.8 (C_{Ar}×2), 128.7 (C_{Ar}×2), 117.4 (t, J = 239.3 Hz, C5), 64.7 (C1), 34.0 (t, J = 20.9 Hz, C4), 28.5 (C2), 19.2 (t, J = 5.5 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.3 (dt, J = 57.2, 17.3 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -116.3 (s, 2F) ppm; IR (neat) 2959(w), 1714 (s), 1451 (m), 1269 (s), 1094 (s), 1026 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{14}F_2NaO_2$ $[M+Na]^+$, calculated 251.0854, found 251.0853.

1-Benzyloxy-3,3-difluoropentane (13): To a solution of **4**[62] (2.23 g, 1 equiv) in CH_2Cl_2 (35 mL), DAST (3.07 mL, 2 equiv) was added dropwise at 0 °C. The reaction mixture was heated 40 °C and after 48 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ until pH 7 was reached. The aqueous phase was extracted with CH_2Cl_2 (3×100 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$ and concentrated. The crude oil was purified by column chromatography (5:95 acetone/petroleum ether 40–60 °C) to yield **13** as a pale-yellow oil (0.91 g, 37%), as well as allowing for **4** (1.12 g, 50%) to be reclaimed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H, H_{Ar}), 4.53 (s, 2H, PhC$\underline{H}_2$), 3.67 (t, J = 6.7 Hz, 2H, H1), 2.20 (tt, J = 16.2, 6.7 Hz, 2H, H2), 1.90 (tq, J = 16.8, 7.6 Hz, 2H, H4), 1.03 (t, J = 7.5, 3H, H5) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.0 (C_{Ar}), 128.4 (C_{Ar}×2), 127.7 (C_{Ar}), 127.6 (C_{Ar}×2), 124.8 (t, J = 240.3 Hz, C3), 73.2 (Ph$\underline{C}$H$_2$), 64.3 (t, J = 5.9 Hz, C1), 36.2 (t, J =

25.7 Hz, C2), 30.0 (t, J = 25.7, C4), 6.6 (t, J = 5.5, C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.9 (quin, J = 16.5 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -98.9 (s, 2F) ppm; IR (neat) 2982 (br. w), 2888 (w), 1374 (m), 1102 (s), 940 (s), 737 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{16}F_2NaO$ $[M+Na]^+$, calculated 237.1061, found 237.1055.

3,3-Difluoropent-2-yl benzoate (15): To a solution of **14**[95] (5.0 g, 1 equiv) in CH_2Cl_2 (15 mL) was added DAST (6.4 mL, 2 equiv) dropwise at 0 °C. The reaction was heated to 40 °C and after 24 h, 10 drops of HF•py was added. The reaction was heated to 40 °C for 24 h, then cooled to 0 °C and quenched with sat. aq. $NaHCO_3$ until pH 7 was reached. The aqueous layer was then extracted with CH_2Cl_2 (3×75 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude oil was purified by column chromatography (1:19 Et_2O/pentane) to afford **15** and the corresponding elimination byproduct (3-fluoropent-3-en-2-yl benzoate **53**) as a mix of inseparable products with a 94:6 ratio by ^{19}F NMR, which was used in the next step.

Data for 15: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.02 (m, 2H, H_{Ar}), 7.67–7.56 (m, 1H, H_{Ar}), 7.52–7.44 (m, 2H, H_{Ar}), 5.48–5.23 (m, 1H, H2), 2.10–1.83 (m, 2H, H4), 1.45 (d, J = 6.6 Hz, 3H, H1), 1.07 (t, J = 7.5 Hz, 3H, H5) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.3 (C = O), 133.4 (C_{Ar}), 129.8 (C_{Ar}×2), 129.6 (C_{Ar}), 128.5 (C_{Ar}×2), 122.7 (dd, J = 246.5, 242.8 Hz, C3), 70.0 (dd, J = 34.5, 28.6 Hz, C2), 26.5 (t, J = 24.9 Hz, C4), 13.4 (t, J = 2.9 Hz, C1), 5.7 (dd, J = 6.6, 5.1 Hz, C5)ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2– -112.2 (m, 1F, F3'), -113.8– -115.0 (m, 1F, F3'') ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -111.8 (d, J = 250.6 Hz, 1F, F3'), -114.4 (d, J = 251.4 Hz, 1F, F3'') ppm; IR (neat) 2990 (w), 2948 (w), 1723 (s), 1265 (s), 1097 (s), 965 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{14}F_2NaO_2$ $[M+Na]^+$, calculated 251.0854, found 251.0853.

Selected data for byproduct 53: ^{1}H NMR (400 MHz, $CDCl_3$) δ benzoyl group not visible due to overlap with major product, 5.63 (dq, J = 17.6, 6.6 Hz, 1H, H2), 5.02 (dq, J = 36.3, 6.8 Hz,

1H, H4), 1.65 (dd, J = 7.2, 2.3 Hz, 1H, H5), 1.52 (d, J = 6.7 Hz, 1H, H1) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.4 (ddd, J = 36.4, 17.3, 3.5 Hz, 1F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -126.4 (s, 1F) ppm; HRMS (ESI+) for $C_{12}H_{13}FNaO_2$ $[M+Na]^+$, calculated 231.0792, found 231.0791.

3-Fluoro-4-hydroxybutyl benzoate (23) and 3,3-difluoro-4-hydroxybutyl benzoate (24): A solution of NFSI (10.73 g, 1 equiv) and proline (4.02 g, 1 equiv) in THF (40 mL) and *i*-PrOH (5 mL) was stirred for 15 min before the addition of a solution of **20**[68] (6.72 g, 1 equiv) in THF (5 mL). After 16 h, Et_2O (50 mL) was added and the reaction mixture was cooled to -78 °C. After 30 min at -78 °C, the reaction mixture was directly filtered through a silica plug, eluting with cold Et_2O (75 mL). The organic mixture was washed with sat. aq. $NaHCO_3$ (3×50 mL), brine and dried over $MgSO_4$ and concentrated. The resultant crude oil was dissolved in EtOH (48 mL) and CH_2Cl_2 (72 mL), followed by addition of $NaBH_4$ (6.62 g, 5 equiv) in one portion. After 30 min, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl (300 mL) stirring vigorously for 30 min. The reaction mixture was then diluted with CH_2Cl_2 (250 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3×150 mL) and the combined organic phases washed with $NaHCO_3$ (2×150 mL), brine and dried over $MgSO_4$. The crude was concentrated and purified by column chromatography (3:7 acetone/petroleum ether 40–60 °C) to yield **23** as a colorless oil (4.83 g, 65%) and **24** as a pale-yellow oil (0.72 g, 9%).

Data for 23: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.00 (m, 2H, H_{Ar}), 7.65-7.56 (m, 1H, H_{Ar}), 7.53–7.43 (m, 2H, H_{Ar}), 4.85 (ddddd, J = 49.3, 8.7, 5.9, 3.9, 3.0 Hz, 1H, H3), 4.59–4.39 (m, 2H, H1), 3.94–3.68 (m, 2H, H4), 2.28–2.00 (m, 2H, H2), 1.89 (br. t, J = 7.1, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4 (C = O), 133.1 (C_{Ar}), 130.0 (C_{Ar}), 129.6 (C_{Ar}×2), 128.4 (C_{Ar}×2), 91.5 (d, J = 168.7 Hz, C3), 64.8 (d, J = 22.0 Hz, C4), 60.7 (d, J = 5.1 Hz, C1), 30.4 (d, J = 20.5 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -192.7 (app. dddq, J = 49.3,

26.0, 23.4, 15.6 Hz, 1F) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -192.7 (s, 1F) ppm; IR (neat) 3447 (br. w), 2965 (w), 2945 (w), 1716 (s), 1271 (s), 1111 (s), 1070 (s) cm^{-1}; HRMS (CI) for $C_{11}H_{14}FO_3$ $[M+H]^+$, calculated 213.09215, found 213.09212.

Data for 24: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.00 (m, 2H, H_{Ar}), 7.61–7.54 (m, 1H, H_{Ar}), 7.49–7.42 (m, 2H, H_{Ar}), 4.56 (t, J = 6.5 Hz, 2H, H1), 3.86 (td, J = 12.8, 6.8 Hz, 2H, H4), 2.48 (tt, J = 16.3, 6.4 Hz, 2H, H2), 1.94 (br. t, J = 7.0 Hz, 1H, OH) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4 (C = O), 133.2 (C_{Ar}), 129.8 (C_{Ar}), 129.6 (C_{Ar}×2), 128.5 (C_{Ar}×2), 122.2 (t, J = 242.1 Hz, C3), 64.3 (t, J = 31.9 Hz, C4), 58.7 (t, J = 5.9 Hz, C1), 32.8 (t, J = 24.6 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.6 (tt, J = 16.13, 12.8 Hz, 2F) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -107.6 (s, 2F) ppm; IR (neat) 3444 (br. w), 2961 (w), 2938 (w), 1714 (s), 1271 (s), 1110 (m), 1069 (m) cm^{-1}; HRMS (CI) for $C_{11}H_{13}F_2O_3$ $[M+H]^+$, calculated 231.08273, found 231.08249.

4-Fluoro-5-hydroxypentyl benzoate (27) and 4,4-difluoro-5-hydroxypentyl benzoate (28): A solution of NFSI (6.12 g, 1 equiv) and proline (2.23 g, 1 equiv) in THF (45 mL) and *i*-PrOH (5 mL) was stirred for 15 min before the addition of a solution of **10**[64] (4.00 g, 1 equiv) in THF (5 mL). After 16 h, Et_2O (50 mL) was added and the reaction mixture was cooled to -78 °C. After 30 min the reaction mixture was filtered through a silica plug, eluting with cold Et_2O (50 mL). The organic mixture was washed with sat. aq. $NaHCO_3$ (2×50 mL), brine and dried over $MgSO_4$ and concentrated. The resultant crude oil was dissolved in EtOH (40 mL) and CH_2Cl_2 (60 mL) before the addition of $NaBH_4$ (3.67 g, 5 equiv) in one portion. After 30 min, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl (50 mL) stirring vigorously for 30 min. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phases washed with $NaHCO_3$ (50 mL), brine and dried over $MgSO_4$. The crude was

concentrated and purified by column chromatography (3:7 EtOAc/heptane) to yield **27** as a colorless oil (2.12 g, 48%) and **28** as a pale-yellow oil (0.60 g, 13%).

Data for 27: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.00 (m, 2H, H_{Ar}), 7.59–7.54 (m, 1H, H_{Ar}), 7.47–7.42 (m, 2H, H_{Ar}), 4.74–4.57 (m, 1H, H4), 4.44–4.31 (m, 2H, H1), 3.83–3.66 (m, 2H, H5), 2.10–1.59 (m, 5H, H2 + H3 + OH) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.6 (C = O), 133.0 (C_{Ar}), 130.2 (C_{Ar}), 129.5 (C_{Ar}×2), 128.4 (C_{Ar}×2), 94.1 (d, J = 169.1 Hz, C4), 64.9 (d, J = 22.1 Hz, C5), 64.4 (C1), 27.7 (d, J = 21.1 Hz, C3), 24.5 (d, J = 4.6 Hz, C2) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ -190.4– -190.9 (m, 2F) ppm; ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ -190.6 (s, 2F) ppm; IR (neat) 3427 (br. w), 2955 (m), 2876 (w), 1714 (s), 1271 (s), 1110 (m), 709 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{15}FNaO_3$ $[M+Na]^+$, calculated 249.0897, found 249.0898.

Data for 28: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06–8.02 (m, 2H, H_{Ar}), 7.60–7.53 (m, 1H, H_{Ar}), 7.47–7.42 (m, 2H, H_{Ar}), 4.38 (t, J = 6.3 Hz, 2H, H1), 3.78 (t, J = 12.6 Hz, 2H, H5), 2.20–1.98 (m, 4H, H2 + H3), 1.93 (br. s, 1H, OH) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.5 (C = O), 133.0 (C_{Ar}), 130.1 (C_{Ar}), 129.6 (C_{Ar}×2), 128.4 (C_{Ar}×2), 122.9 (t, J = 241.8 Hz, C4), 64.2 (t, J = 32.2 Hz, C5), 64.1 (C1), 30.1 (t, J = 24.4 Hz, C3), 21.4 (t, J = 4.6 Hz, C2) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ 109.0 (tt, J = 17.3, 12.6 Hz, 2 F) ppm; ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ -109.0 (s, 2F) ppm; IR (neat) 3445 (br. w), 2959 (w), 2941 (w), 1716 (s), 1271 (s), 1111 (m), 709 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{14}F_2NaO_3$ $[M+Na]^+$, calculated 267.0803, found 267.0802.

3,4-Difluorobutyl benzoate (29): To a solution of **23** (1.00 g, 1 equiv) in THF (20 mL) was added Et_3N (3.94 mL, 6 equiv), Et_3N•3HF (1.50 mL, 2 equiv) and nonafluorobutane-1-sulphonyl fluoride (1.70 mL, 2 equiv). After 4 h, the reaction was quenched with sat. aq. $NaHCO_3$ until pH 7 and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (7:3 CH_2Cl_2/petroleum ether 40–60 °C) to yield

29 as a colorless oil (0.64 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.03 (m, 2H, H_{Ar}), 7.62–7.56 (m, 1H, H_{Ar}), 7.49–7.43 (m, 2H, H_{Ar}), 5.06–4.80 (m, 1H, H3), 4.75–4.42 (m, 4H, H1 + H4), 2.30–2.02 (m, 2H, H2) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3 (C = O), 133.2 (C_{Ar}), 129.9 (C_{Ar}), 129.6 (C_{Ar}×2), 128.4 (C_{Ar}×2), 88.8 (dd, J = 173.9, 19.8 Hz, C3), 83.8 (dd, J = 174.6, 22.7 Hz, C4), 60.3 (d, J = 5.1 Hz, C1), 29.7 (dd, J = 21.3, 6.6 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -191.7– -192.2 (m, 1F, F3), -230.9 (tdd, J = 47.3, 21.7, 13.0 Hz, 1F, F4) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -191.9 (d, J = 13.0 Hz, 1F, F3), -230.9 (br. d, J = 13.0 Hz, 1F, F4) ppm; IR (neat) 2964 (w), 2908 (w), 1715 (s), 1452 (m), 1270 (s), 1109 (s) cm^{-1}; HRMS (ESI+) $C_{11}H_{12}F_2NaO_2$ $[M+Na]^+$, calculated 237.0698, found 237.0698.

4,5-Difluoropentyl benzoate (30): To a solution of **27** (1.00 g, 1 equiv) in THF (15 mL) was added Et_3N (3.70 mL, 6 equiv), Et_3N•3HF (1.44 mL, 2 equiv) and nonafluorobutane-1-sulphonyl fluoride (1.59 mL, 2 equiv). After 16 h, the reaction was quenched with sat. aq. $NaHCO_3$ (40 mL) and diluted with Et_2O (50 mL). The organic phase was collected and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic layers were washed with aq. HCl (2M, 30 mL), brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude was purified by column chromatography (1:19 EtOAc/heptane) to yield **30** as a colorless oil (0.65 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.97 (m, 2H, H_{Ar}), 7.64–7.56 (m, 1H, H_{Ar}), 7.53–7.41 (m, 2H, H_{Ar}), 4.96–4.67 (m, 1H, H4), 4.67–4.45 (m, 2H, H5), 4.46–4.33 (m, 2H, H1), 2.18–1.66 (m, 4H, H2 + H3) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5 (C = O), 133.0 (C_{Ar}), 130.1 (C_{Ar}), 129.5 (C_{Ar}×2), 128.4 (C_{Ar}×2), 91.2 (dd, J = 173.5, 19.4 Hz, C4), 83.9 (dd, J = 174.6, 23.5 Hz, C5), 64.2 (C1), 26.9 (dd, J = 21.3, 6.6 Hz, C3), 24.3 (d, J = 4.4 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -190.0– -190.6 (m, 1F, F4), -230.6 (tdd, J = 46.8, 20.8, 13.9 Hz, 1F, F5) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -190.3 (d, J = 13.9 Hz, 1F, F4), -230.6 (d, J = 13.9 Hz, 1F, F5) ppm; IR (neat) 2959 (w), 2906 (w), 1714 (s), 1270 (s),

1109 (m), 709 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{14}F_2NaO_2$ $[M+Na]^+$, calculated 251.0854, found 251.0850.

3,3,4-Trifluorobutyl benzoate (31): To a solution of **24** (570 mg, 1 equiv) in MeCN (15 mL) was added Et_3N (2.07 mL, 6 equiv), Et_3N•3HF (0.83 mL, 2 equiv) and nonafluorobutane-1-sulphonyl fluoride (0.89 mL, 2 equiv). The reaction was heated to 80 °C and after 16 h, was quenched with sat. aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (3:7 Et_2O/pentane) to yield **31** as a pale-yellow oil (391 mg, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–7.97 (m, 2H, H_{Ar}), 7.65–7.54 (m, 1H, H_{Ar}), 7.51–7.41 (m, 2H, H_{Ar}), 4.57 (t, J = 6.2 Hz, 2H, H1), 4.54 (dt, J = 46.1, 11.7 Hz, 2H, H4), 2.50 (ttd, J = 16.4, 6.5, 2.4 Hz, 2H, H2) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2 (C = O), 133.2 (C_{Ar}), 129.7 (C_{Ar}), 129.6 (C_{Ar}×2), 128.5 (C_{Ar}×2), 119.9 (td, J = 243.0, 23.1 Hz, C3), 81.5 (dt, J = 179.0, 36.7 Hz, C4), 58.2 (t, J = 5.9 Hz, C1), 32.6 (t, J = 24.2 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.1 (tdt, J = 16.4, 15.4, 12.1 Hz, 2F, F3), -234.2 (tt, J = 46.2, 15.4 Hz, 1F, F4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -108.1 (d, J = 15.6 Hz, 2F, F3), -234.2 (t, J = 15.6 Hz, 1F, F4) ppm; IR (neat) 2971 (w), 2912 (w), 1718 (s), 1268 (s), 1110 (m), 1053 (m) cm^{-1}; HRMS (ESI+) for $C_{11}H_{11}F_3NaO_2$ $[M+Na]^+$, calculated 255.0603, found 255.0605.

3,3,4-Trifluorobutyl benzoate (31, from 41): To a solution of **41** (40 mg, 1 equiv) in MeCN (2 mL) was added Et_3N (0.07 mL, 6 equiv) and Et_3N•3HF (0.03 mL, 2 equiv). The reaction was heated to 80 °C and after 16 h was quenched with sat. aq. $NaHCO_3$ (5 mL), followed by extraction with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (3:7 Et_2O/petroleum ether 40–60 °C) to yield **31** as a colorless oil (16 mg, 88%).

4,4,5-Trifluoropentyl benzoate (32): To a solution of **28** (0.54 g, 1 equiv) in MeCN (15 mL) was added Et_3N (1.85 mL, 6 equiv), HF•Et_3N (0.72 mL, 2 equiv) and nonafluorobutane-1-sulphonyl fluoride (0.79 mL, 2 equiv). The reaction was heated to 80 °C and after 16 h, was quenched with sat. aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude was purified by column chromatography (1:19 EtOAc/heptane) to yield **32** as a pale-yellow oil (0.42 g, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.01 (m, 2H, H_{Ar}), 7.62–7.55 (m, 1H, H_{Ar}), 7.49–7.43 (m, 2H, H_{Ar}), 4.48 (dt, J = 46.5, 11.5 Hz, 2H, H5), 4.40 (t, J = 6.2 Hz, 2H, H1), 2.26–1.95 (m, 4H, H3 + H4) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4 (C = O), 133.1 (C_{Ar}), 130.0 (C_{Ar}), 129.6 (C_{Ar}×2), 128.4 (C_{Ar}×2), 120.7 (td, J = 241.4, 22.0 Hz, C5), 81.6 (dt, J = 178.3, 37.4 Hz, C4), 63.9 (C2), 29.9 (t, J = 23.8 Hz, C3) 21.2 (t, J = 4.8 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6 (tdt, J = 16.5, 15.6, 11.5 Hz, 2F, F4), -234.3 (tt, J = 46.2, 15.4 Hz, 1F, F5) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -109.6 (d, J = 15.6 Hz, 2F, F4), -234.3 (t, J = 15.6 Hz, 1F, F5) ppm; IR (neat) 2969 (w), 2901 (w), 1716 (s), 1269 (s), 1110 (m), 709 (s) cm^{-1}; HRMS (ESI+) for $C_{12}H_{13}F_3NaO_2$ $[M+Na]^+$, calculated 269.0760, found 269.0760.

3,4,4-Trifluorobutyl benzoate (33): To a solution of **23** (1.00 g, 1 equiv) in CH_2Cl_2 (20 mL) was added DMP (2.99 g, 1.5 equiv). After 1 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (2:1, Et_2O/petroleum ether 40–60 °C) to afford the intermediate **21**, which was immediately dissolved in CH_2Cl_2 before the dropwise addition of DAST (1.10 mL, 2.5 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and after 16 h, was quenched with sat. aq. $NaHCO_3$ until pH 7. The aqueous layer was then extracted with CH_2Cl_2 (3×20 mL) and

the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography (7:3 CH_2Cl_2/petroleum ether 40–60 °C) to afford **33** (0.38 g, 34% over 2 steps) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.01 (m, 2H, H_{Ar}), 7.63–7.56 (m, 1H, H_{Ar}), 7.50–7.43 (m, 2H, H_{Ar}), 5.91 (tdd, J = 54.7, 5.6, 3.7 Hz, H4), 4.95–4.64 (m, a doublet with 46.9 Hz can be observed, 1H, H3), 4.63–4.42 (m, 2H, H1), 2.36–2.14 (m, 2H, H2) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2 (C = O), 133.2 (C_{Ar}), 129.8 (C_{Ar}), 129.6 (C_{Ar}×2), 128.5 (C_{Ar}×2), 113.3 (td, J = 244.5, 31.2 Hz, C4), 87.5 (dt, J = 177.5, 27.1 Hz, C3), 59.6 (d, J = 3.7 Hz, C1), 27.7 (dt, J = 20.5, 2.9 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -129.6 (dddd, J = 297.8, 54.7, 12.1, 8.7 Hz, 1F, F4'), -133.3 (ddt, J = 297.8, 54.7, 12.1 Hz, 1F, F4''), -203.26– -203.72 (m, 1F, F3) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -129.6 (dd, J = 297.8, 11.7 Hz, 1F, F4'), -133.3 (dd, J = 297.8, 13.4 Hz, 1F, F4''), -203.5 (t, J = 13.4 Hz, 1F, F3) ppm; IR (neat) 2975 (w), 2910 (w), 1717 (s), 1270 (s), 1069 (s), 1069 (s) cm^{-1}; HRMS (EI) for $C_{11}H_{11}F_3O_2$ [$M^{\cdot+}$], calculated 232.07057, found 232.07216.

4,5,5-Trifluoropentyl benzoate (34): To a solution of **27** (0.90 g, 1 equiv) in CH_2Cl_2 (15 mL) was added DMP (2.53 g, 1.5 equiv). After 1 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (8 mL) and sat. aq. $NaHCO_3$ (8 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (3:1, Et_2O/petroleum ether 40–60 °C) to afford the intermediate **25**, which was immediately dissolved in CH_2Cl_2 before the dropwise addition of DAST (1.62 mL, 3 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and after 16 h, was quenched with sat. aq. $NaHCO_3$ until pH 7. The aqueous layer was then extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography (1:1 CH_2Cl_2/petroleum ether 40–60 °C) to afford **34** (0.34 g, 35%

over 2 steps) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.02 (m, 2H, H_{Ar}), 7.62–7.54 (m, 1H, H_{Ar}), 7.49–7.43 (m, 2H, H_{Ar}), 5.83 (tdd, J = 54.9, 5.5, 3.8 Hz, 1H, H5), 4.74–4.49 (m, 1H, H4), 4.47–4.32 (m, 2H, H1), 2.17–1.78 (m, 4H, H2 + H3) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5 (C = O), 133.0 (C_{Ar}), 130.1 (C_{Ar}), 129.5 (C_{Ar} x 2), 128.4 (C_{Ar} x 2), 113.5 (td, J = 244.3, 31.5 Hz, C5), 89.9 (dt, J = 176.8, 26.8 Hz, C4), 64.0 (C1), 25.0 (dt, J = 20.5, 3.3 Hz, C3), 23.8 (d, J = 2.9 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -129.5 (dddd, J = 297.4, 55.0, 11.7, 9.5 Hz, 1F, F5), -132.9 (ddt, J = 297.4, 55.0, 12.1 Hz, 1F, F5'), -201.9– -201.4 (m, 1F, F4) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -129.5 (dd, J = 297.4, 12.1 Hz, 1F, F5), -132.9 (dd, J = 297.6, 13.7 Hz, 1F, F5'), -201.7 (t, J = 12.6 Hz, 1F, F4) ppm; IR (neat) 2967 (w), 1715 (s), 1270 (s), 1069 (s), 709 (s) cm^{-1}; HRMS (EI) for $C_{12}H_{13}F_3O_2$ [$M^{\cdot+}$], calculated 246.08622, found 246.08425.

5-Benzyloxy-1,1,1-trifluoropentan-2-ol (37): A solution of 4-benzyloxy-1-butanal **36**[84] (4.94 g, 27.7 mmol, 1.0 equiv) in anhydrous THF (50 mL) under argon was cooled to -10 °C, followed by addition of $TMSCF_3$ (4.50 mL, 30.4 mmol, 1.1 equiv) and dropwise addition of TBAF solution (2.8 mL, 1M in THF, 2.8 mmol, 0.1 equiv). The reaction mixture was warmed to room temperature and stirred for 1 h, followed further addition of more TBAF solution (28 mL, 1M in THF, 28.0 mmol, 1.01 equiv). The resulting mixture was stirred at room temperature overnight. On the following day, the reaction mixture was quenched with aq. 1M HCl solution (100 mL), followed by extraction with EtOAc (3×100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography (5/95 – 10/90 acetone/40-60 °C petroleum ether) to afford the desired product **37** (5.36 g, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.42 (5H, m, H_{Ar}), 4.56 (2H, s, CH_2Ph), 3.86 - 3.98 (1H, m, H-2), 3.77 (1H, br. s, -O*H*), 3.49 - 3.62 (2H, m, H-5 + H-5'), 1.89 - 1.99 (1H, m, H-3), 1.80 - 1.89 (2H, m, H-4 + H-4'), 1.65 - 1.76 (1H, m, H-3') ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.5 (s, C_{Ar}), 128.5 (s, CH$_{Ar}$×2), 127.9 (s, CH$_{Ar}$), 127.8

(s, CH_{Ar}×2), 125.2 (q, *J* 281.9 Hz, C-1), 73.3 (s, CH_2Ph), 70.3 (q, *J* 30.8 Hz, C-2), 69.8 (s, C-5), 27.6 (q, *J* 1.8 Hz, C-3), 25.4 (s, C-4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.7 (3F, d, *J* 6.9 Hz, CF_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -79.7 (3F, s, CF_3) ppm; IR (neat) 3389 (br. m), 3095 (w), 3068 (w), 3040 (w), 2937 (m), 2863 (m), 1457 (m), 1277 (s), 1167 (s), 1133 (s), 1087 (s), 1032 (m) cm^{-1};HRMS (EI) for $C_{12}H_{15}F_3O_2$ [$M^{\bullet+}$] calcd, 248.10187; found, 248.10342.

1-Benzyloxy-4,5,5,5-tetrafluoropentane (38): To a sealed tube reactor were added **37** (1.73 g, 6.97 mmol, 1.0 equiv), anhydrous THF (10 mL), Et_3N (5.61 mL, 40.25 mmol, 5.77 equiv), $Et_3N{\cdot}3HF$ (2.18 mL, 13.37 mmol, 1.92 equiv) and perfluoro-1-butanesulfonyl fluoride (2.42 mL, 13.5 mmol, 1.93 equiv) under argon. The reaction mixture was stirred at 90 °C overnight, and then monitored by TLC analysis. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and slowly quenched with sat. aq. $NaHCO_3$ solution (100 mL), followed by extraction with CH_2Cl_2 (3×100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography (40/60 CH_2Cl_2/40-60 °C petroleum ether) to afford a mixture of desired product **38** and alkene byproducts. To this mixture were added CH_2Cl_2 (20 mL) and MeOH (5 mL). The solution was cooled to -78 °C, and bubbled with ozone in O_2 until the reaction mixture turned slightly blue. The reaction mixture was then bubbled with O_2 for 30 min, followed by addition of dimethyl sulphide (2 mL). The resulting mixture was stirred at room temperature overnight. On the following day, the solvent was removed by rotary evaporation under reduced pressure inside a fume hood. The crude mixture was purified by repeated flash chromatography (20/80 – 30/70 CH_2Cl_2/40-60 °C petroleum ether) to isolate the desired product **38** (738 mg, 41%) as a colourless oil. IR (neat) 3092 (w), 3065 (w), 3031 (w), 2940 (m), 2869 (m), 1457 (m), 1366 (m), 1283 (s), 1176 (s), 1155 (s), 1099 (s), 1026 (m), 983 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.41 (5H, m, H_{Ar}), 4.60 - 4.81 (1H, m, H-4, a doublet with *J* 46.8 Hz was observed),

4.55 (1H, d, *J* 12.7 Hz, PhC*H*H'), 4.52 (1H, d, *J* 12.7 Hz, PhCH*H'*), 3.48–3.63 (2H, m, H-1 + H-1'), 1.73–2.04 (4H, m, H-3 + H-3' + H-2 + H-2') ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 138.2 (s, C_{Ar}), 128.4 (s, CH_{Ar}×2), 127.7 (s, CH_{Ar}), 127.6 (s, CH_{Ar}×2), 122.9 (qd, *J* 281.0, 25.7 Hz, C-5), 88.4 (dq, *J* 183.4, 34.1 Hz, C-4), 73.0 (s, PhCH_2), 69.0 (s, C-1), 25.3 (dq, *J* 20.5, 1.5 Hz, C-3), 24.4 (d, *J* 2.9 Hz, C-2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.8 (3F, dd, *J* 10.8, 6.1 Hz, CF_3), -202.0 - -201.4 (1F, m, CH*F*) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -79.8 (3F, d, *J* 11.1 Hz, CF_3), -201.7 (1F, q, *J* 11.1 Hz, CH*F*) ppm; HRMS (EI) for $C_{12}H_{14}F_4O$ [$M^{\bullet+}$]: calcd, 250.09753; found, 250.09880.

Attempted direct vicinal difluorination leading to 3-oxacyclopentyl benzoate (40): To a Teflon tube was added a solution of **39**[96] (100 mg, 1 equiv) and *p*-iodotoluene (24 mg, 0.2 equiv) in DCE (1.3 mL). A solution of Et_3N•3HF (0.76 mL) and HF•Py (0.55 mL) was then added, followed by Selectfluor® (302 mg, 1.5 equiv). After 16 h, the reaction was quenched with sat. aq. $NaHCO_3$ until pH 7. The aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over $MgSO_4$. The crude mixture was concentrated and purified by column chromatography (1:4 acetone/petroleum ether 40–60 °C) to yield **40** as a colorless oil (0.50 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–7.97 (m, 2H, H_{Ar}), 7.66–7.54 (m, 1H, H_{Ar}), 7.51–7.42 (m, 2H, H_{Ar}), 5.57 (ddt, *J* = 6.4, 4.3, 2.0Hz, 1H, H1), 4.08–3.96 (m, 3H, H3' + H4), 3.93 (td, *J* = 8.3, 4.4 Hz, 1H, H3''), 2.37–2.24 (m, 1H, H2'), 2.23–2.12 (m, 1H, H2'') ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3 (C=O), 133.1 (C_{Ar}), 130.0 (C_{Ar}), 129.63 (C_{Ar}×2), 128.4 (C_{Ar}×2), 75.4 (C1), 73.2 (C4), 67.2 (C3), 33.0 (C2) ppm. Data consistent with literature.[100]

4-Benzoyloxy-2,2-difluorobutyl nonafluorobutanesulfonate (41): To a solution of **24** (50 mg, 1 equiv) in MeCN (2 mL) was added Et_3N (0.18 mL, 6 equiv), Et_3N•3HF (0.07 mL, 2 equiv) and nonafluorobutane-1-sulfonyl fluoride (0.08 mL, 2 equiv). After 16 h the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), followed by extraction with CH_2Cl_2 (3×10 mL).

The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude was purified by column chromatography (3:7 Et_2O/petroleum ether 40–60 °C) to yield **41** as colourless crystals (77 mg, 70%) and **31** a colourless oil (5 mg, 10%). Mp: 55–57 °C (Et_2O/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.01 (m, 2H, H_{Ar}), 7.65–7.56 (m, 1H, H_{Ar}), 7.51–7.44 (m, 2H, H_{Ar}), 4.68 (t, J = 11.5 Hz, 2H, H4), 4.58 (t, J = 6.1 Hz, 2H, H1), 2.52 (tt, J = 16.0, 6.1 Hz, 2H, H2) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1 (C = O), 133.4 (C_{Ar}), 129.6 (C_{Ar}×2), 129.4 (C_{Ar}), 128.5 (C_{Ar}×2), 118.7 (t, J = 245.0 Hz, C3), 73.0 (t, J = 34.8 Hz, C4), 57.8 (t, J = 5.9 Hz, C1), 33.0 (t, J = 23.5 Hz, C2) ppm (nonafluorobutane sulfonate carbons not visible due to multiple fluorine-fluorine couplings); ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.9 (t, J = 8.7 Hz, 3F), -105.7 (tt, J = 15.6, 12.1 Hz, 2F, F3), -110.3 (t, J = 13.9 Hz, 2F), -121.3– -121.5 (m, 2F), -126.0– -126.2 (m, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -80.9 (br. t, J = 9.5 Hz, 3F), -105.7 (s, 2F, F3), -110.3 (t, J = 13.9 Hz, 2F), -121.3– -121.5 (m, 2F), -126.0– -126.1 (m, 2F) ppm; IR (neat) 2964 (w), 2918 (w), 1722 (s), 1422 (s), 1238 (s), 1199 (m), 1142 (s) cm^{-1}; HRMS (ESI+) for $C_{15}H_{11}F_{11}NaO_5S$ $[M+Na]^+$, calculated 535.0044, found 535.0055.

1-Trityloxybut-3-ene (43): To a solution 3-buten-1-ol **42** (0.80 g, 1 equiv) and pyridine (1.35 mL, 1.05 equiv) in CH_2Cl_2 (33 mL), was added trityl chloride (3.40 g, 1.1 equiv). After 20 h, the reaction mixture was washed with sat. aq. $NaHCO_3$ (2×30 mL), water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (1:19 CH_2Cl_2/petroleum ether 40-60 °C) to **43** as a colorless oil (3.34 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.43 (m, 6H, H_{Ar}), 7.34–7.27 (m, 6H, H_{Ar}), 7.26–7.20 (m, 3H, H_{Ar}), 5.86 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H, H3), 5.13–4.98 (m, 2H, H4), 3.13 (t, J = 6.8 Hz, 2H, H1), 2.38 (q, J = 6.8 Hz, 2H, H2) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.3 (C_{Ar}×3), 135.6 (C3), 128.7 (C_{Ar}×6), 127.7 (C_{Ar}×6), 126.9 (C_{Ar}×3), 116.3 (C4), 86.4 ($\underline{C}Ph_3$), 63.2 (C1), 34.6 (C2) ppm; IR (neat) 3058 (w), 2924 (w), 1448 (s), 1068 (s), 695

(s) cm^{-1}; HRMS (EI) for $C_{23}H_{22}O$ [$M^{\cdot+}$], calculated 314.16652, found 314.16555. ^1H NMR data consistent with literature.[101]

1-Trityloxy-3,5,5,5-tetrafluoropentane (44): To a solution of Selectfluor® (6.08 g, 3 equiv) in DMF (70 mL) was added $PhI(OAc)_2$ (1.85 g, 1 equiv), AgOTf (2.94 g, 2 equiv) and CsF (1.73 g, 2 equiv) at -50 °C. A solution of **43** (1.80 g, 1 equiv) in DMF (10 mL) was added, followed by CF_3SiMe_3 (2.52 mL, 3 equiv). The reaction was allowed to warm to -20 °C and after 5 h was allowed to warm to room temperature. After 16 h, the reaction was quenched with water (80 mL) and the aqueous phase was extracted with Et_2O (3×100 mL). The combined organic phases were washed with water, brine, dried over Na_2SO_4 and concentrated. The crude oil was purified by column chromatography (1:4 CH_2Cl_2/petroleum ether 40-60 °C) to **44** as a colorless oil (0.90 g, 39%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 6H, H_{Ar}), 7.39–7.32 (m, 6H, H_{Ar}), 7.31–7.26 (m, 3H, H_{Ar}), 5.12 (dtt, J = 49.0, 8.0, 4.0 Hz, 1H, H3), 3.39–3.20 (m, 2H, H1), 2.63–2.24 (m, 2H, H4), 2.11–1.81 (m, 2H, H2) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.9 (C_{Ar} x 3), 128.5 (C_{Ar} x 6), 127.8 (C_{Ar} x 6), 127.1 (C_{Ar} x 3), 125.4 (qd, J = 277.3, 2.9 Hz, C5), 86.9 ($\underline{C}Ph_3$), 85.4 (dq, J = 172.1, 3.3 Hz, C3), 58.8 (d, J = 5.1 Hz, C1), 39.4 (qd, J = 28.5, 22.4 Hz, C4), 35.4 (d, J = 21.3 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.2 (q, J = 10.4 Hz, 3F, F5), -183.4–-182.9 (m, 1F, F3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -64.2 (d, J = 8.1 Hz, 3F, F5), -183.2 (q, J = 8.1 Hz, 1F, F3) ppm; IR (neat) 3059 (w), 2932 (w), 1449 (s), 1256 (s), 1135 (s), 1072 (s), 697 (s) cm^{-1}; HRMS (EI) for $C_{24}H_{22}F_4O$ [$M^{\cdot+}$], calculated 402.16013, found 402.16171.

1-Benzyloxy-2,2,4,4,4-pentafluorobutane (46): To a solution of **45**[87] (2.3 g, 1 equiv) in CH_2Cl_2 (35 mL), DAST (4.37 mL, 3 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and after 16 h, was quenched with sat. aq. $NaHCO_3$ until pH 7. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated. The crude oil was purified by column

chromatography (1:4 CH_2Cl_2/hexane) to yield an inseparable mixture of **46** and **47** as a pale-yellow oil in a ratio of 7:1 respectively (1.64 g, 65%).

Data for 46: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.31 (m, 5H, H_{Ar}), 4.64 (s, 2H, PhC$\underline{H}_2$), 3.72 (t, J = 12.4 Hz, 2H, H1), 2.90 (tq, J = 14.6, 10.2 Hz, 2H, H3) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.7 (C_{Ar}), 128.6 (C_{Ar}×2), 128.2 (C_{Ar}), 127.9 (C_{Ar}×2), 123.7 (qt, J = 276.7, 5.8 Hz, C4), 118.9 (tq, J = 244.7, 3.1 Hz, C2), 73.9 (Ph$\underline{C}H_2$), 70.0 (tq, J = 31.7, 1.4 Hz, C1), 37.8 (qt, J = 30.1, 26.5 Hz, C3) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ -61.9 (tt, J = 10.2, 8.9 Hz, 3F, F4), -103.0 (ttq, J = 14.6, 12.4, 8.9 Hz, 3F, F2) ppm; ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ -62.1 (t, J = 8.7 Hz, 3F), -103.2 (q, J = 8.7 Hz, 2F) ppm; IR (neat) 2926 (w), 2876 (w), 1389 (s), 1171 (s), 1119 (s), 1095 (s), 698 (s) cm^{-1}; HRMS (CI) for $C_{11}H_{12}F_5O$ $[M+H]^+$, calculated 255.08028, found 255.08272.

Selected data for 1-benzyloxy-2,4,4,4-tetrafluorobut-2-ene 47: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (dqt, J = 33.4, 7.5, 1.0 Hz, 1H, H3), 4.62 (s, 2H, $PhCH_2$), 4.12–4.04 (m, 2H, H1) ppm (benzoyl resonances not visible due to overlap with major product); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 97.9 (qd, J = 35.8, 5.7 Hz, C3), 73.3 (PhC$\underline{H}_2$), 65.9 (d, J = 34.1 Hz, C1) ppm (other carbons not visible due to overlap with **46**); ^{19}F NMR (471 MHz, $CDCl_3$) δ -57.9 (ddt, J = 16.7, 7.5, 2.2 Hz, 3F, F4), -101.0 (dqt, J = 33.5, 16.7, 6.4 Hz, 1F, F2) ppm; ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ -57.9 (d, J = 16.5 Hz, 3F, F4), -101.0 (q, J = 16.8 Hz, 1F, F2); HRMS (EI) for $C_{11}H_{10}F_4O$ $[M^{\cdot+}]$, calculated 234.06623, found 234.06659.

5-Benzyloxy-1,1,1-trifluoropentan-3-one (49): To a 2 L three-neck round-bottom flask were added 2,2,2-trifluoroethylamine hydrochloride (12.52 g, 92.4 mmol, 5.05 equiv), CH_2Cl_2 (485 mL) and water (16.2 mL). The resulting mixture was cooled to 0 °C, followed by adding $NaNO_2$ (7.65 g, 110.9 mmol, 6.06 equiv). The reaction was stirred further for 1 h at 0 °C behind a blast shield, and the water layer was removed by using a separating funnel. The organic layer was transferred to a new 2 L two-neck flask and cooled immediately to -78 °C. To this solution

were added 3-benzyloxypropanal **48** (3.0 g, 18.3 mmol, 1.0 equiv) and $ZrCl_4$ (14.02 g, 60.2 mmol, 3.29 equiv). The reaction mixture was then stirred at -78 °C and warmed up very slowly to room temperature by the ambient environment overnight. On the following day, the reaction was quenched by MeOH (100 mL) and sat. aq. $NaHCO_3$ solution (150 mL), followed by extraction with CH_2Cl_2 (200 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude mixture was repeatedly purified by chromatography (50/50 – 60/40 CH_2Cl_2/hexane) to afford the desired product **49** (~90% purity, 272 mg, < 6%) as a yellow oil. IR (neat) 3092 (w), 3068 (w), 3037 (w), 2942 (w), 2875 (m), 1732 (s), 1457 (w), 1417 (m), 1372 (s), 1268 (s), 1106 (s), 1035 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 - 7.39 (5H, m, H_{Ar}), 4.52 (2H, s, PhCH_2), 3.77 (2H, t, *J* 6.1 Hz, H-5), 3.29 (2H, q, *J* 10.3 Hz, H-2), 2.80 (2H, t, *J* 6.1 Hz, H-4) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.7 (q, *J* 2.6 Hz, C-3), 137.7 (s, C_{Ar}), 128.4 (s, CH_{Ar}×2), 127.8 (s, CH_{Ar}), 127.7 (s, CH_{Ar}×2), 123.5 (q, *J* 277.3 Hz, C-1), 73.4 (s, PhCH_2), 64.7 (s, C-5), 46.7 (q, *J* 28.2 Hz, C-2), 43.5 (q, *J* 2.1 Hz, C-4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (3F, t, *J* 10.4 Hz, CF_3) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -62.7 (3F, s, CF_3) ppm; HRMS (EI) for $C_{12}H_{13}F_3O_2$ [$M^{\bullet+}$]: calcd, 246.08622; found, 246.08619.

1-Benzyloxy-3,3,5,5,5-pentafluoropentane (50): To a solution of **49** (250 mg, 1.02 mmol, 1.0 equiv) in anhydrous toluene (10 mL) was added DAST (1.0 mL, 7.57 mmol, 7.42 equiv) at 0 °C. The resulting mixture was stirred at 75 °C for 16 h. On the following day, the reaction was cooled to room temperature, and additional DAST (2.0 mL, 15.14 mmol, 14.84 mmol) was added. The reaction mixture was stirred at 60 °C for 3 d. Upon completion as indicated by TLC analysis, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (100 mL) and slowly quenched with sat. aq. $NaHCO_3$ solution (150 mL), followed by extraction with CH_2Cl_2 (100 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified by chromatography (20/80

CH_2Cl_2/hexane) to afford the desired product **50** (140 mg, 0.52 mmol, 51%) as a colourless oil. This product was used directly in the next step. ^{13}C NMR data were not recorded as extended NS was needed to provide a good S/N ratio for pentyl carbon signals (*see* **I14** for its pentyl carbon signals and multiplicity). IR (neat) 3095 (w), 3071 (w), 3034 (w), 2943 (w), 2878 (m), 1411 (m), 1277 (m), 1234 (s), 1167 (s), 1099 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 - 7.41 (5H, m, H_{Ar}), 4.53 (2H, s, PhCH_2), 3.69 (2H, t, *J* 6.2 Hz, H-1), 2.86 (2H, tq, *J* 14.9, 10.3 Hz, H-4), 2.30 (2H, tt, *J* 15.9, 6.1 Hz, H-2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.8 (3F, tt, *J* 10.3, 9.2 Hz, CF_3), -94.9 - -94.6 (2F, m, CF_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -61.6 (3F, t, *J* 9.1 Hz, CF_3), -94.5 (2F, q, *J* 9.2 Hz, CF_2) ppm; HRMS (EI) for $C_{12}H_{13}F_5O$ [$M^{\bullet+}$]: calcd, 268.08811; found, 268.08921.

4,4,5-Trifluoropentyl tosylate (51a): Using general procedure A with 4,4,5-trifluoropentan-1-ol **I6** (98 mg) in CH_2Cl_2 (3.5 mL), **51a** was obtained as a colourless oil (121 mg, 59%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H, H_{Ar}), 7.37 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 4.41 (dt, *J* = 46.7, 11.1 Hz, 2H, H5), 4.11 (t, *J* = 6.1 Hz, 2H, H1), 2.47 (s, 3H, PhC$\underline{H}_3$), 2.09–1.88 (m, 4H, H2 and H3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.0 (C_{Ar}), 132.8 (C_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 120.3 (td, *J* = 242.5, 22.7 Hz, C9), 81.6 (dt, *J* = 178.6, 37.2 Hz, C5), 69.3 (C1), 29.3 (t, *J* = 23.8 Hz, C3), 21.6 (Me), 21.3 (t, *J* = 4.4 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -234.3 (tt, *J* = 48.1, 15.6 Hz, 1F, F5) , -110.4 (m, 2F, F4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -234.3 (t, *J* = 15.6 Hz, 1F, F5), -110.0 (d, *J* = 13.9 Hz, 2F, F4) ppm; HRMS (ESI^+) for $C_{12}H_{15}F_3NaO_3S$ $[M + Na]^+$, calcd 319.0586; found 319.0591.

5,5,5-Trifluoropentyl tosylate (51b): Using general procedure A with 5,5,5-trifluoropentan-1-ol **I16** (1.00 g) in CH_2Cl_2 (25 mL), **51b** was obtained as a colourless oil (1.40 g, 67%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d *J* = 8.0 Hz, 2H, H_{Ar}), 7.37 (dd, *J* = 8.6, 0.6, 2H, H_{Ar}), 4.05 (t, *J* = 6.1 Hz, 2H, H1), 2.46 (s, 3H, PhC$\underline{H}_3$), 2.10–1.98 (m, 2H, H2 or H4), 1.77–1.71 (m, 2H, H2 or H4), 1.65–1.57 (m, 2H, H3) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.9 (C_{Ar}), 132.9

(C_{Ar}), 129.8 (CH_{Ar}), 127.6 (CH_{Ar}), 126.9 (q, J = 281.7 Hz, C5), 69.5 (C1), 33.0 (q, J = 29.1 Hz, C4), 27.8 (C2), 21.9 (Me), 18.2 (q, J = 2.9 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6 (t, J = 11.3 Hz, 3F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -66.6 (s, 3F) ppm; HRMS (ESI$^+$) for $C_{12}H_{15}F_3NaO_3S$ $[M + Na]^+$, calcd 319.0586; found 319.0593.

4,4,4-Trifluorobutyl tosylate (51c): Using general procedure A with 4,4,4-trifluorobutan-1-ol **G14** (1.00 g) in CH_2Cl_2 (25 mL), **51c** was obtained as a colourless oil (1.62 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H, H_{Ar}), 7.37 (d, J = 8.0 Hz, 2H, H_{Ar}), 4.09 (t, J = 6.1 Hz, 2H, H1), 2.47 (s, 3H, PhC$\underline{H}_3$), 2.23–2.11 (m, 2H, H2 or H3), 1.96-1.89 (m, 2H, H3 or H2) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.1 (C_{Ar}), 132.7 (C_{Ar}), 130.0 (CH_{Ar}), 127.9 (CH_{Ar}), 126.6 (q, J = 275.8 Hz, C4), 68.3 (C1), 30.1 (q, J = 29.8 Hz, C3), 21.9 (q, J = 2.9 Hz, C2), 21.6 (C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.7 (t, J = 10.4 Hz, 3F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -66.7 (s, 3F) ppm; HRMS (ESI$^+$) for $C_{11}H_{13}F_3NaO_3S$ $[M + Na]^+$, calcd 305.0430; found 305.0433.

3,4-Difluorobutan-1-ol (G2): To a solution of **29** (0.59 g, 1 equiv) in Et_2O (20 mL), NaOMe (25% in MeOH, 1.26 mL, 2 equiv) was added. After 16 h, the reaction was quenched with aq. HCl (2M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the organic phases were collected, washed with brine, and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (1:9 CH_2Cl_2/Et_2O) to afford **G2** as a pale-yellow oil (81 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (dddddd, J = 48.9, 22.0, 8.9, 5.1, 4.2, 2.3 Hz, 1H, H3), 4.72–4.38 (m, 2H, H4), 3.85 (br. t, J = 4.9 Hz, 2H, H1), 2.08–1.77 (m, 2H, H2), 1.59 (br. s, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 89.6 (dd, J = 172.4, 19.8 Hz, C3), 84.2 (dd, J = 173.9, 22.0 Hz, C4), 58.3 (d, J = 5.1 Hz, C1), 32.8 (dd, J = 20.5, 6.6 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -191.6– -192.2 (m, 1F, F3), -230.1 (tdd, J = 47.6, 21.9, 13.0 Hz, 1F, F4) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -191.9 (d, J = 13.0 Hz, 1F, F3), -230.1 (d, J = 13.0 Hz, 1F, F4) ppm; IR (neat) 3371 (br. w),

2931 (m), 2853 (w), 1152 (m), 1072 (s), 1045 (s), 688 (s) cm^{-1}; HRMS (CI) for $C_4H_9F_2O$ $[M+H]^+$, calculated 111.06160, found 111.06206.

2-Fluorobutanol (G5): To a solution of **3** (0.98 g, 1 equiv) in Et_2O (15 mL), NaOMe (25% in MeOH, 2.28 mL, 2 equiv) was added. After 18 h, the reaction was quenched with aq. HCl (2M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the organic phases were collected washed with brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (CH_2Cl_2) to afford **G5** as a pale-yellow oil (297 mg, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (ddddd, J = 49.4, 7.93, 6.2, 5.1, 3.0 Hz, 1H, H2), 3.80–3.58 (m, 2H, H1), 1.94 (br. s, 1H), 1.80–1.49 (m, 2H, H3), 1.00 (t, J = 7.5 Hz, 3H, H4) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 95.9 (d, J = 167.3 Hz, C2), 64.7 (d, J = 22.0 Hz, C1), 24.1 (d, J = 20.5 Hz, C3), 9.2 (d, J = 5.9 Hz, C4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -190.7 (dtdd, J = 49.4, 27.7, 23.4, 16.5 Hz, 1F) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -190.7 (s, 1F) ppm; IR (neat) 3346 (br. w), 2972 (w), 2884 (w), 1464 (w), 1058 (s), 843 (s) cm^{-1}; HRMS (CI) for $C_4H_{10}FO$ $[M+H]^+$, calculated 93.07102, found 93.07046.

3,3,4-Trifluorobutan-1-ol (G6): To a solution of **31** (500 mg, 1 equiv) in Et_2O (15 mL), NaOMe (25% in MeOH, 0.99 mL, 2 equiv) was added dropwise. After 16 h, the reaction was quenched with aq. HCl (1M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the organic phases were collected and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was then purified by column chromatography (CH_2Cl_2) to afford **G6** as a pale-yellow oil (171 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (dt, J = 46.6, 11.9 Hz, 2H, H4), 3.92 (t, J = 5.9 Hz, 2H, H1), 2.26 (ttd, J = 16.7, 6.0, 2.3 Hz, 2H, H2), 1.64 (br. s, 1H, OH) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 120.7 (td, J = 242.3, 22.4 Hz, C3), 81.8 (dt, J = 178.1, 35.7 Hz, C4), 56.4 (t, J = 5.9 Hz, C1), 36.0 (t, J = 22.7 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.1 (tdt, J = 16.7, 15.4, 11.9 Hz, 2F, F3), -234.6 (ttt, J = 46.2, 15.4, 2.3 Hz, 1F, F4) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -108.1 (d, J = 13.9 Hz, 2F, F3),

-234.6 (t, J = 13.9 Hz, 1F, F4) ppm; IR (neat) 3365 (br. w), 2974 (w), 2905 (w), 1105 (m), 1049 (s), 917 (s) cm^{-1}; HRMS (CI) for $C_4H_8F_3O$ $[M+H]^+$, calculated 129.05277, found 129.0521.

4,4-Difluorobutan-1-ol (G7): To a solution of **11**[22] (3.00 g, 1 equiv) in Et_2O (30 mL), NaOMe (25% w/w in MeOH, 6.41 mL, 2 equiv) was added dropwise. After 4 h, the reaction was neutralised with aq. HCl (2M, 20 mL) and the aqueous phase was washed with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated (750 mbar, 30 °C). The crude oil was purified by column chromatography (CH_2Cl_2) to **G7** as a pale-yellow oil (1.24 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (tt, J = 57.0, 4.0 Hz, 1H H4), 3.72 (td, J = 5.6, 4.9, 2H, H1), 2.11–1.86 (m, 2H, H3), 1.81–1.66 (m, 2H, H2), 1.41 (br. t, J = 4.9, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 117.2 (t, J = 238.8 Hz, C4), 61.9 (C1), 30.7 (t, J = 21.3 Hz, C3), 25.1 (t, J = 5.1 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.2 (dt, J = 57.2, 18.2 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -116.2 (s, 2F) ppm; IR (neat) 3300 (br, w), 2950 (w), 2900 (w), 980 (s), 1010 (s), 1060 (s), 1110 (s) cm^{-1}; HRMS (EI) for $C_4H_8F_2O$ $[M^{\cdot+}]$, calculated 110.05377, found 110.05350.

3,4,4-Trifluorobutan-1-ol (G8): To a solution of **33** (0.35 g, 1 equiv) in Et_2O (15 mL), NaOMe (25% in MeOH, 0.69 mL, 2 equiv) was added. After 16 h, the reaction was quenched with aq. HCl (2M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the organic phases were collected washed with brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (1:9 CH_2Cl_2/Et_2O) to afford **G8** as a pale-yellow oil (0.15 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (tdd, J = 55.0, 6.1, 3.7 Hz, 1H, H4), 4.94–4.65 (m, 1H, H3), 3.95–3.80 (m, 2H, H1), 2.09–1.87 (m, 2H, H2), 1.53–1.44 (m, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 113.6 (td, J = 243.9, 30.8 Hz, C4), 87.7 (dt, J = 175.7, 27.0 Hz, C3), 57.5 (d, J = 4.1 Hz, C1), 30.8 (dt, J = 20.5, 2.9 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -130.1 (ddt, J = 296.5, 55.5, 10.4 Hz,

1F, F4'), -133.0 (ddt, J = 296.5, 55.5, 12.1 Hz, 1F, F4''), -204.2– -204.6 (m, 1F, F3) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -130.1 (dd, J = 296.5, 12.1 Hz, 1F, F4'), -133.0 (dd, J = 296.5, 13.9 Hz, 1F, F4''), -204.4 (t, J = 13.0 Hz, 1F, F3) ppm; IR (neat) 3362 (br. w), 2971 (w), 2900 (w), 1152 (m), 1068 (s), 1042 (s), 968 (s) cm^{-1}; HRMS (CI) for $C_4H_8F_3O$ $[M+H]^+$, calculated 129.05218, found 129.05293.

2,4,4,4-Tetrafluorobutan-1-ol (G10) and 2,2,4,4,4-pentafluorobutan-1-ol (G15): To a solution of **46** and **47** (0.6 g, 1 equiv) in THF (8 mL) was added a suspension of Pd/C 10% (300 mg) in THF (2 mL). The reaction mixture was degassed with argon and one balloon of hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 5 h. The reaction was then filtered over Celite, which was then rinsed with CH_2Cl_2 (30 mL). The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (9:1 CH_2Cl_2/pentane) to afford **G15** and **G10** as an inseparable mixture, a pale-yellow oil, in a 5.5:1 ratio respectively (225 mg, 61%). **IR** (neat) 3364 (br. w), 2953 (w), 2887 (w), 1389 (s), 1161 (s), 1076 (s), 890 (s) cm^{-1}.

Data for G10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (dsxt, J = 48.3, 3.9 Hz, 1H, H2), 3.97–3.63 (m, 2H, H1), 2.72–2.38 (m, 2H, H3), 1.81 (br. t, J = 6.6 Hz, 1H, OH) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 125.4 (qd, J = 276.3, 4.8 Hz, C4), 87.8 (dq, J = 172.9, 3.1 Hz, C2), 64.0 (d, J = 22.9 Hz, C1), 35.7 (qd, J = 29.3, 23.0 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.3 (td, J = 10.6, 6.9 Hz, 3F), -191.0– -191.4 (m, 1F) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -64.3 (d, J = 6.9 Hz, 3F), -191.2 (q, J = 6.9 Hz, 1F) ppm; HRMS (CI) for $C_4H_5F_4O$ $[M-H]^-$, calculated 145.02710, found 145.02606.

Data for G15: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (td, J = 12.5, 7.1 Hz, 2H, H1), 2.89 (tq, J = 14.5, 10.2 Hz, 2H, H3), 1.93 (br. t, J = 7.0 Hz, 1H, OH) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 123.6 (qt, J = 276.6, 6.0 Hz, C4), 119.1 (tq, J = 244.5, 2.9 Hz, C2), 63.6 (tq, J = 31.5, 1.4 Hz, C1), 37.4 (qt, J = 30.3, 26.7 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.1 (quin, J = 9.5

Hz, 3F), -106.2 (ttq, J = 14.5, 12.6, 9.3 Hz, 2F) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -62.1 (t, J = 8.7 Hz, 3F), -106.2 (q, J = 9.2 Hz, 2F) ppm; HRMS (CI) for $C_4H_6F_5O$ $[M+H]^+$, calculated 165.03333, found 165.03153.

3,3,4,4-Tetrafluorobutan-1-ol (G11): To a solution of 3,3,4,4-tetrafluoro-4-bromobutan-1-ol **35** (3.00 g, 1 equiv) and AIBN (219 mg, 0.1 equiv) in degassed toluene (15 mL) was added Bu_3SnH (5.4 mL, 1.5 equiv). The reaction mixture was refluxed for 16 h, before purification by column chromatography (100:0 to 0:100, pentane/ CH_2Cl_2). The resulting crude was carefully concentrated 750 mbar/30 °C and purified again by column chromatography (10:0 to 8:2, CH_2Cl_2, Et_2O) on a silica gel/K_2CO_3 mix[102] (9:1). The combined fractions were concentrated at 750 mbar/30 °C, which was combined with the concentrate from a second reaction on a 2 g scale. Final careful removal of residual solvent using a Kugelrohr apparatus at 50 °C at atmospheric pressure, **G11** was obtained as a colorless oil (1.47 g, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (tt, J = 53.8, 3.5 Hz, 1H, H4), 3.95 (q, J = 5.9 Hz, 2H, H1), 2.29 (ttt, J = 17.5, 6.2, 1.5 Hz, 2H, H2), 1.65 (t, J = 5.1 Hz, 1H, OH) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 117.7 (tt, J = 246.9, 28.9 Hz, C3), 110.1 (tt, J = 248.9, 39.3 Hz, C4), 55.7 (t, J = 5.5 Hz, C1), 33.2 (t, J = 21.7 Hz, C2) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.8 (tdt, J = 17.5, 3.7, 1.8 Hz, 2F, F3), -136.2 (ddt, J = 53.8, 3.5, 1.8 Hz, 2F, F4) ppm; $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) δ -115.7 (t, J = 1.8 Hz, 2F, F3), -136.2 (t, J = 1.8 Hz, 2F, F4) ppm; IR (neat) 3370 (br. w), 2982 (w), 2908 (w), 1091 (s), 1047 (s), 986 (s) cm^{-1}; HRMS (EI) for $C_4H_6F_4O$ $[M^{\cdot+}]$, calculated 146.03493, found 146.03463.

2,2-Difluorobutan-1-ol (G12): A solution of NFSI (21.88 g, 2.5 equiv) and proline (1.27 g, 0.4 equiv) in THF (45 mL) was stirred for 15 min before the addition of a solution of butanal **16** (2.50 mL, 1 equiv) in THF (5 mL). After 16 h, Et_2O (50 mL) was added and the reaction mixture was cooled to -78 °C. After 30 min the reaction mixture was filtered through a silica plug, eluting with cold Et_2O (100 mL). The organic mixture was washed with sat. aq. $NaHCO_3$

(3×100 mL), brine and dried over $MgSO_4$ and filtered. $NaBH_4$ (10.48 g, 10 equiv) was then added portionwise to the resultant crude solution. After 16 h, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl (300 mL), stirring vigorously for 30 min. The layers were then separated, and the aqueous phase was extracted with Et_2O (3×75 mL). The combined organic phases were washed with $NaHCO_3$ (3×100 mL), brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C, and then concentrated further by short path distillation (to remove THF), before purification by column chromatography (CH_2Cl_2 to 9:1 CH_2Cl_2/Et_2O) to yield **G12** as a yellow oil (0.86 g, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (td, J = 12.8, 6.8 Hz, 2H, H1), 1.96 (tq, J = 17.1, 7.5 Hz, 2H, H3), 1.84-1.90 (m, 1H, OH), 1.05 (t, J = 7.5 Hz, 3H, H4) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 123.5 (t, J = 241.4 Hz, C2), 63.8 (t, J = 31.9 Hz, C1), 26.5 (t, J = 24.6 Hz, C3), 6.1 (t, J = 5.5 Hz, C4) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.0 (tt, J = 17.3, 12.1 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -111.0 (s, 2F) ppm; IR (neat) 3337 (br. w), 2987 (w), 2893 (w), 1072 (s), 1050 (m), 903 (s) cm^{-1}; HRMS (CI) for $C_4H_7F_2O$ [M-H]$^-$, calculated 109.4595, found 109.04886.

2-((3-(4,4,4-Trifluorobutoxy)phenethyl)amino)-*N*,*N*-dimethylacetamide·HCl (H5): Using general procedure B with **52** (1.1 equiv) and **51c** (67 mg) in DMF (2 mL), **53c** was obtained as a colourless gum (46 mg, 49%). According to general procedure C, N-Boc cleavage of **53c** (51 mg, 1 equiv) yielded **H5** as an off-white solid (36 mg, quantitative). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (br s, 2H, NH_2^+), 7.23 (t, J = 8.0 Hz, 1H, H4), 6.89 (d, J = 7.6 Hz, 1H, H5), 6.86 (t, J = 2.1 Hz, 1H, H1), 6.78 (dd, J = 8.2, 1.8 Hz, 1H, H3), 4.00 (t, J = 6.0 Hz, 2H, H13), 3.98 (br s, 2H, H9), 3.37 (m, 2H, H8), 3.28 (m, 2H, H7), 2.97 (s, 3H, H11 or H12), 2.96 (s, 3H, H11 or H12), 2.31 (m, 2H, H15), 2.03 (m, 2H, H14) ppm (see SI for atom numbering); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.3 (C10), 159.0 (C2), 137.8 (C6), 130.1 (C4), 127.1 (q, J = 278.7 Hz, C16), 121.3 (C5), 114.9 (C1), 113.5 (C3), 66.0 (C13), 49.8 (C8), 47.9 (C9), 36.2 (C11 or C12), 35.9 (C11 or C12), 32.5 (C7), 30.7 (q, J = 29.2 Hz, C15), 22.2 (q, J = 2.9 Hz,

C14) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6 (t, J = 10.4 Hz, 3F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -66.6 (s, 3F) ppm; IR (neat): 2925 (br m), 2757 (br m), 1671 (s), 1241 (s), 1151 (m) cm^{-1}; HRMS (ESI$^+$) for $C_{16}H_{24}F_3N_2O_2$ $[M + H]^+$, calcd 333.1784; found 333.1789 (-1.3 ppm error), for $C_{16}H_{24}F_3N_2NaO_2$ $[M + Na]^+$, calcd 355.1604; found 355.1601.

4,5-Difluoropentan-1-ol (I2): To a solution of **30** (0.58 g, 1 equiv) in Et_2O (10 mL), NaOMe (25% in MeOH, 0.86 mL, 1.5 equiv) was added at 0 °C. After 6 h, the reaction was quenched with aq. HCl (2M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the organic phases were collected washed with brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (1:9 Et_2O/CH_2Cl_2) to afford **I2** as a colorless oil (0.26 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88–4.64 (m, a doublet with 49.2 Hz can be observed, 1H, H4), 4.65–4.35 (m, 2H, H5), 3.78–3.65 (m, 2H, H1), 1.91–1.64 (m, 4H, H2 + H3), 1.44 (br. s, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 91.7 (dd, J = 172.8, 19.4 Hz, C4), 84.0 (dd, J = 173.9, 23.5 Hz, C5), 62.2 (C1), 27.9 (d, J = 4.4 Hz, C2), 26.6 (dd, J = 23.1, 6.6 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -189.3– -189.9 (m, 1F, F4), -230.4 (tdd, J = 47.5, 20.4, 13.9 Hz, 1F, F5) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -189.4 (d, J = 13.9 Hz, 1F, F4), -230.2 (d, J = 13.9 Hz, 1F, F5) ppm; IR (neat) 3349 (br. w), 2955 (w), 2881 (w), 1456 (w), 1038 (s), 916 (m) cm^{-1}; HRMS (CI) for $C_5H_{11}F_2O$ $[M+H]^+$, calculated 125.07725, found 125.07576.

4,5,5-Trifluoropentan-1-ol (I5): To a solution of **34** (0.31 g, 1 equiv) in Et_2O (5 mL), NaOMe (25% in MeOH, 0.58 mL, 2 equiv) was added at 0 °C. After 16 h, the reaction was quenched with aq. HCl (2M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the organic phases were collected washed with brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (CH_2Cl_2) to afford **I5** as a colorless oil (0.16 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (tdd, J = 54.9, 5.8, 3.8 Hz, 1H, H5), 4.72–4.45 (m, 1H, H4), 3.82–3.64 (m, 2H, 2H, H1), 2.04–1.66 (m, 4H,

H2 + H3), 1.43 (br. s, 1H, OH) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 113.6 (td, J = 244.3, 31.5 Hz, C5), 90.3 (dt, J = 176.1, 26.8 Hz, C4), 62.1 (C1), 27.3 (d, J = 2.9 Hz, C2), 24.7 (dt, J = 20.5, 2.9 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -129.7 (dddd, J = 296.5, 55.5, 12.1, 9.5 Hz, 1F, F5), -132.8 (dddd, J = 296.5, 54.6, 13.0, 11.3 Hz, 1F, F5'), -201.3– -201.8 (m, 1F, F4) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -129.7 (dd, J = 296.5, 12.1 Hz, 1F, F5), -132.8 (dd, J = 296.5, 13.9 Hz, 1F, F5'), -201.5 (t, J = 12.1 Hz, 1F, F4) ppm; IR (neat) 3349 (br. w), 2960 (w), 2884 (w), 1152 (m), 1058 (s), 980 (w) cm^{-1}; HRMS (CI) for $C_5H_{10}F_3O$ $[M+H]^+$, calculated 143.06783, found 143.06665.

4,4,5-Trifluoropentan-1-ol (I6): To a solution of **32** (0.40 g, 1 equiv) in Et_2O (5 mL), NaOMe (25% in MeOH, 0.55 mL, 1.5 equiv) was added. After 16 h, the reaction was quenched with aq. HCl (2M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the organic phases were collected, washed with brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (1:9 Et_2O/CH_2Cl_2) to afford **I6** as a pale-yellow oil (202 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (dt, J = 46.5, 11.5 Hz, 2H, H5), 3.74 (t, J = 6.2 Hz, 2H, H1), 2.18–1.98 (m, 2H, H3), 1.88–1.75 (m, 2H, H2), 1.33 (br. s, 1H, OH) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 120.9 (td, J = 242.1, 22.7 Hz, C4), 81.6 (dt, J = 178.3, 37.0 Hz, C5), 61.9 (C1), 29.6 (t, J = 23.8 Hz, C3), 24.6 (t, J = 4.0 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.5 (tdt, J = 17.3, 15.2, 11.5 Hz, 2F, F4), -234.5 (ttt, J = 46.0, 15.2, 2.6 Hz, 1F, F5) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -109.5 (d, J = 15.2 Hz, 2F, F4), -234.5 (t, J = 15.2 Hz, 1F, F5) ppm; IR (neat) 3363 (br. w), 2970 (w), 2885 (w), 1197 (m), 1054 (s), 1017 (s), 930 (s) cm^{-1}; HRMS (CI) for $C_5H_{10}F_3O$ $[M+H]^+$, calculated 143.06783, found 143.06737.

5,5-Difluoropentan-1-ol (I7): To a solution of **12** (3.19 g, 1 equiv) in Et_2O (30 mL), NaOMe (25% w/w in MeOH, 6.60 mL, 2 equiv). After 18 h, the reaction was quenched with aq. HCl (1M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the organic

phases were collected and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (CH_2Cl_2 to 9:1 CH_2Cl_2/Et_2O) to afford **I7** as a pale-yellow oil (1.50 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (tt, J = 56.9, 4.4 Hz, 1H, H5), 3.68 (t, J = 6.5 Hz, 2 H, H1), 1.95–1.80 (m, 2H, H4), 1.68–1.52(m, 4H, H2 + H3), 1.34 (br. s, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 117.2 (t, J = 238.8 C5), 62.4 (C1), 33.7 (t, J = 20.91 Hz, C4), 32.0 (C2), 18.5 (t, J = 5.5 Hz, C3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.2 (dt, J = 55.9, 18.0 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -116.2 (s, 2F) ppm; IR (neat) 3333 (br. w), 2940 (w), 2873 (w), 1404 (m), 1121 (s), 1087 (s), 994 (s) cm^{-1}; HRMS (EI) for $C_5H_{10}F_2O$ [$M^{\cdot+}$], calculated 124.06942, found 124.06616.

3-Fluoropentan-1-ol (I9): To a solution of **6** (0.70 g, 1 equiv) in Et_2O (20 mL) was added a suspension of Pd/C 10 wt. % (300 mg) in Et_2O (10 mL). The reaction mixture was degassed with nitrogen and one balloon of hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere. After 16 h, the reaction was then filtered over Celite, which was then rinsed with CH_2Cl_2 (30 mL). The crude was carefully concentrated at 750 mbar/30 °C and purified by column chromatography (9:1 CH_2Cl_2/Et_2O) to afford **I9** as a colorless oil (0.33 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79–4.53 (m, a doublet with 49.2 Hz can be observed, 1H, H3), 3.82 (t, J = 5.8 Hz, 2H, H1), 1.99–1.48 (m, 5H, H2 + H4 + OH), 1.00 (t, J = 7.5 Hz, 3H, H5) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 93.8 (d, J = 165.8 Hz, C3), 59.5 (d, J = 3.7 Hz, C1), 37.4 (d, J = 20.5 Hz, C2), 28.3 (d, J = 20.5 Hz, C4), 9.3 (d, J = 6.6 Hz, C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.5– -184.0 (m, 1F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -183.7 (s, 1F) ppm; IR (neat) 3341 (br. w), 2969 (m), 2884 (m), 1463 (m), 1056 (s), 927 (s) cm^{-1}; HRMS (CI) for $C_5H_{12}FO$ [M+H]$^+$, calculated 107.08667, found 107.08630.

3,5,5,5-Tetrafluoropentan-1-ol (I10): To a solution of **44** (0.90 g, 1 equiv) in CH_2Cl_2 (4.4 mL) and MeOH (2.2 mL), p-TsOH•H_2O (207 mg, 0.05 equiv) was added. After 16 h, the

reaction was quenched with sat. aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the organic phases were collected washed with brine and dried over Na_2SO_4. The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (CH_2Cl_2) to afford **I10** as a colorless oil (298 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (dtt, J = 49.0, 8.5, 3.7 Hz, 1H, H3), 3.86 (dt, J = 6.8, 5.0 Hz, 2H, H1), 2.69–2.31 (m, 2H, H4), 2.09–1.79 (m, 2H, H2), 1.47 (td, J = 5.0, 0.7 Hz, 1H, OH) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 125.4 (qd, J = 276.6, 2.9 Hz, C5), 85.5 (dq, J = 171.3, 3.3 Hz, C3), 58.2 (d, J = 4.4 Hz, C1), 39.5 (qd, J = 28.6, 22.7 Hz, C4), 37.4 (d, J = 20.5 Hz, C2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.3 (td, J = 10.4, 7.4 Hz, 3F, F5), -184.3– -184.8 (m, 1F, F3) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -64.3 (d, J = 7.4 Hz, 3F, F5), -184.5 (q, J = 7.4 Hz, 1F, F3) ppm; IR (neat) 3364 (br. w), 2962 (w), 2898 (w), 1257 (s), 1151 (s), 1130 (s), 1053 (s) cm^{-1}; HRMS (CI) for $C_5H_8F_4O$ $[M+H]^+$, calculated 161.05840, found 161.05551.

3,3-Difluoropentan-1-ol (I12): To a solution of **13** (0.64 g, 1 equiv) in Et_2O (20 mL) was added a suspension of Pd/C 10% (300 mg) in Et_2O (10 mL). The reaction mixture was degassed with nitrogen and one balloon of hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere. After 16 h, the reaction was then filtered over Celite, which was then rinsed with CH_2Cl_2 (30 mL). The crude was carefully concentrated at 750 mbar/30 °C and was purified by column chromatography (9:1 CH_2Cl_2/Et_2O) to afford **I12** as a colorless oil (0.32 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (q, J = 5.9 Hz, 2H, H1), 2.14 (tt, J = 17.0, 6.2 Hz, 2H, H2), 1.91 (tq, J = 16.8, 7.5 Hz, 2H, H4), 1.61 (br. t, J = 7.1 Hz, 1H, OH), 1.04 (t, J = 7.5 Hz, 3H, H5) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 125.4 (t, J = 240.3 Hz, C3), 57.2 (t, J = 5.5 Hz, C1), 38.5 (t, J = 24.2 Hz, C2), 30.2 (t, J = 26.0 Hz, C4), 6.5 (t, J = 5.9 Hz, C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.5 (quin, J = 16.9 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -99.5 (s, 2F) ppm; IR (neat) 3351 (br. w), 2984 (m), 2893

(w), 1375 (m), 1144 (s), 1052 (s), 936 (s) cm^{-1}; HRMS (CI) for $C_5H_{11}F_2O$ $[M+H]^+$, calculated 125.07725, found 125.07681.

3,3,5,5,5-Pentafluoropentan-1-ol (I14): To a solution of **50** (135 mg, 0.50 mmol) in Et_2O (10 mL) was added Pd/C (10 wt. % loading palladium on carbon, 300 mg) under argon. The resulting reaction mixture was degassed with H_2, and stirred under H_2 at room temperature for 2 d. Upon completion as indicated by TLC analysis, the reaction mixture was loaded directly onto a column for purification (100% pentane – 50/50 CH_2Cl_2/pentane – 10/90 Et_2O/CH_2Cl_2) to afford the desired product **I14** in solution, which was concentrated at 700 mbar/35 °C to ca. 2 mL and further dried by slow evaporation at atmospheric pressure to obtain **I14** (50 mg, 56%) as a colourless oil. IR (neat) 3383 (br. m), 2964 (m), 2930 (m), 2860 (w), 1280 (m), 1225 (s), 1167 (s), 1097 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (2H, q, *J* 5.8 Hz, H-1), 2.88 (2H, tq, *J* 14.6, 10.1 Hz, H-4), 2.27 (2H, tt, *J* 16.8, 6.0 Hz, H-2), 1.51 (1H, t, *J* 5.4 Hz, -O*H*) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 123.6 (qt, *J* 276.9, 6.2 Hz, C-5), 120.4 (tq, *J* 243.2, 3.3 Hz, C-3), 56.5 (t, *J* 6.1 Hz, C-1), 41.2 (qt, *J* 29.3, 27.9 Hz, C-4), 38.9 (tq, *J* 23.5, 1.5 Hz, C-2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.9 (3F, tt, *J* 9.7, 9.2 Hz, CF_3), -94.8 - -94.4 (2F, m, CF_2) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -61.9 (3F, t, *J* 9.2 Hz, CF_3), -94.5 (2F, q, *J* 9.2 Hz, CF_2) ppm; HRMS (CI) for $C_5H_8F_5O$ $(M + H)^+$: calcd, 179.04898; found, 179.05001.

4,5,5,5-Tetrafluoropentan-1-ol (I15): To a solution of 1-benzyloxy-4,5,5,5-tetrafluoropentane **38** (660 mg, 2.64 mmol) in Et_2O (30 mL) was added Pd/C (10 wt. % loading palladium on carbon, 350 mg) under argon. The resulting reaction mixture was degassed with H_2, and stirred under H_2 at room temperature overnight. Upon completion as indicated by TLC analysis, the reaction mixture was loaded directly onto a column for purification (50/50 CH_2Cl_2/pentane – 10/90 Et_2O/CH_2Cl_2) to afford the desired product **I15** in solution, which was concentrated at 700 mbar/35 °C to ca. 2 mL and further dried by slow evaporation at atmospheric pressure to obtain **I15** (313 mg, 74%) as a colourless oil. IR (neat) 3092 (w), 3065

(w), 3031 (w), 2940 (m), 2869 (m), 1457 (m), 1366 (m), 1283 (s), 1176 (s), 1155 (s), 1099 (s), 1026 (m), 983 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59–4.83 (1H, m, H-4, a doublet with J 47.0 Hz was observed), 3.63–3.83 (2H, m, H-1 + H-1'), 1.61–2.02 (5H, m, H-3 + H-3' + H-2 + H-2' + O*H*) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 122.8 (qd, J 280.8, 26.0 Hz, C-5), 88.5 (dq, J 183.4, 33.9 Hz, C-4), 61.8 (s, C-1), 27.1 (d, J 2.6 Hz, C-2), 24.8 (dq, J 20.5, 1.6 Hz, C-3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.1 (3F, dd, J 11.3, 6.1 Hz, C*F*$_3$), -201.9– -201.5 (1F, m, CH*F*) ppm; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -79.9 (3F, d, J 11.3 Hz, C*F*$_3$), -201.5 (1F, q, J 11.3 Hz, CH*F*) ppm; HRMS (CI) for $C_5H_9F_4O$ $[M + H]^+$: calcd 161.05840; found, 161.05772.

2,2-Difluoropentan-1-ol (I17): A solution of NFSI (18.31 g, 2.5 equiv) and proline (1.07 g, 0.4 equiv) in THF (45 mL) was stirred for 15 min before the addition of a solution of pentanal **18** (2.47 mL, 1 equiv) in THF (5 mL). After 16 h, Et_2O (50 mL) was added and the reaction mixture was cooled to -78 °C. After 30 min the reaction mixture was filtered through a silica plug, eluting with cold Et_2O (100 mL). The organic mixture was washed with sat. aq. $NaHCO_3$ (3×100 mL), brine and dried over $MgSO_4$ and filtered. $NaBH_4$ (10.48 g, 10 equiv) was then added portionwise to the resultant crude solution. After 16 h, the reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl (300 mL), stirring vigorously for 30 min. The layers were then separated, and the aqueous phase was extracted with Et_2O (3×75 mL). The combined organic phases were washed with $NaHCO_3$ (3×100 mL), brine and dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C, and then concentrated further by short path distillation (to remove THF), before purification by column chromatography (CH_2Cl_2 to 9:1 CH_2Cl_2/Et_2O) to yield **I17** as a yellow oil (0.95 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (td, J = 12.8, 6.6 Hz, 2H, H1), 1.99–1.88 (m, 2H, H3), 1.81 (br. t, J = 6.7 Hz, 1H, OH), 1.54 (tq, J = 8.2, 7.5 Hz, 2H, H4), 0.99 (t, J = 7.4 Hz, 3H, H5) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 123.2 (t, J = 241.4, C2), 64.1 (t, J = 31.9 Hz, C1), 35.3 (t, J = 23.8 Hz, C3), 15.3 (t,

J = 5.1 Hz, C4), 13.9 (C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.8 (tt, J = 17.3, 13.9 Hz, 2F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -108.9 (s, 2F) ppm; IR (neat) 3349 (br. w), 2968 (m), 2880 (w), 1164 (m), 1068 (s), 1010 (s) cm^{-1}; HRMS (CI) for $C_5H_{11}F_2O$ $[M+H]^+$, calculated 125.07772, found 125.07725.

5-Fluoropentan-2-ol (J2): To a stirred solution of DAST (2.50 mL, 2.5 equiv) in CH_2Cl_2 (3 mL), was added **8** (1.08 g, 1 equiv) dissolved in CH_2Cl_2 (3 mL) dropwise at -78 °C. The reaction was allowed to warm to room temperature and after 16 h, DAST (1 mL) was added at 0 °C. After 24 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (60 mL) dropwise at 0 °C and left to stir for 15 min until evolution of CO_2 ceased. The aqueous was extracted with CH_2Cl_2 (3×40 mL) and the combined organic layers were dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and was purified with column chromatography (1:9, Et_2O/pentane) to afford a slightly yellow solution (790 mg). Due to its presumed volatility, the product, 5-fluoropent-2-yl acetate **54**, (containing elution solvents) was used directly for next step without complete removal of the solvent residue. (Selected characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (sxt, J = 6.2 Hz, 1H, H2), 4.57–4.35 (m, a doublet with J = 47.1 was observed, 2H, H5), 2.04 (s, 3H, CH_3, Ac), 1.89–1.61 (m, 4H, H3 + H4), 1.25 (d, J = 6.2 Hz, 3H, H1) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -218.9 (tt, J = 46.7, 24.3 Hz, 1F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -218.9 (s, 1F) ppm). To a stirred solution of **54** (593 mg, ~1 equiv) in Et_2O (5 mL) was added NaOMe (25% w/w in MeOH, 1.8 mL, ~2 equiv). After 1.5 h, the reaction was neutralized with aq. HCl (1 M) until 7 pH. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and purified by column chromatography (1:9 Et_2O/CH_2Cl_2) to afford **J2** as a slightly yellow oil (110 mg, 19%, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61–4.38 (m, a doublet with J = 47.3 was observed, 2H, H5), 3.87 (sxt, J = 6.2 Hz, 1H, H2), 1.98–1.67 (m, 2H, H4), 1.67–1.47 (m, 2H, H3), 1.34 (br. s, 1H,

OH), 1.24 (d, J = 6.2 Hz, 3H, H1) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 84.2 (d, J = 164.3 Hz, C5), 67.6 (C2), 34.8 (d, J = 5.1 Hz, C3), 26.8 (d, J = 19.8 Hz, C4), 23.6 (C1) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -218.2 (tt, J = 46.8, 26.0 Hz, 1F) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -218.0 (s, 1F) ppm; IR (thin film, $CDCl_3$) 3486 (br. w), 2965 (w), 2893 (w), 1424 (s), 1371 (s), 1134 (s) cm^{-1}; HRMS (EI) for $C_5H_{11}FO$ [$M^{\cdot+}$], calculated 106.07884, found 106.07791.

5,5-Difluoropentan-2-ol (J5): To a stirred solution of **9** (1.89 g, 1 equiv) in CH_2Cl_2 (50 mL) was added DAST (3.46 mL, 2 equiv) dropwise at 0 °C. The reaction was allowed to warm to room temperature and after 16 h, was quenched with sat. aq. $NaHCO_3$ until pH 7. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL), dried over $MgSO_4$ and carefully concentrated at 750 mbar/30 °C. The crude was purified with column chromatography (1:19 to 1:9 Et_2O/pentane) to afford a colorless solution (1.60 g). Due to the presumed volatility of this fluorinated product, **55** (containing eluting solvents) was used directly for next step without complete removal of the solvent residue. (Selected characterization data: ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (tt, J = 56.7, 4.3 Hz, 1H, H5), 4.28 (sxt, J = 6.24 Hz, 1H, H2), 2.05 (s, 3H, CH_3, Ac), 2.00–1.79 (m, 2H, H4), 1.77–1.67 (m, 2H, H3), 1.25 (d, J = 6.24 Hz, 3H, H1) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.4 (dt, J = 57.2, 17.3 Hz, 2F) ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -116.4 (s, 2F) ppm). To a stirred solution of **55** (1.60 g, ~1 equiv) in Et_2O (30 mL) was added NaOMe (25% w/w in MeOH, 4.40 mL, ~2 equiv). After 6 h, the reaction was neutralized with aq. HCl (1 M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried with $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and purified by column chromatography (CH_2Cl_2) to afford **J5** as a colorless oil (633 mg, 40%, 2 steps). ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (tt, J = 57.0, 4.3 Hz, 1H, H5), 3.87 (qtd, J = 6.1, 6.0, 4.7 Hz, 1H, H2), 2.16–1.79 (m, 2H, H4), 1.73–1.48 (m, 2H, H3), 1.38 (d, J = 4.6 Hz, 1H, OH), 1.24 (d, J = 6.1 Hz, 3H, H1) ppm; $^{13}C\{^1H\}$ NMR

(101 MHz, $CDCl_3$) δ 117.3 (t, J = 238.8 Hz, C5), 67.3 (C2), 31.2 (t, J = 4.8 Hz, C3), 30.5 (t, J = 21.3 Hz, C4), 23.7 (C1) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.7 (ddt, J = 279.2, 55.5, 17.3 Hz, 1F, F5'), -116.7 (ddt, J = 280.0, 57.2, 17.3 Hz, 1F, F5'') ppm; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -115.7 (d, J = 279.2 Hz, 1F, F5'), -116.7 (d, J = 280.0 Hz, 1F, F5'') ppm; IR (neat) 3346 (br. w), 2971 (w), 2936 (w), 2875 (w), 1120 (s), 1003 (s), 928 (m) cm^{-1}; HRMS (EI) for $C_5H_{10}OF_2$ [$M^{\cdot+}$], calculated 124.06942, found 124.06995.

***rac*-(2*S*,3*R*)-3-Fluoropentan-2-ol (J7) and *rac*-(2*S*,3*S*)-3-fluoropentan-2-ol (J8)**: To a 100 mL two-neck round-bottom flask was added 2-pentanone (1.24 mL, 11.61 mmol, 1.0 equiv), Selectfluor (5.14 g, 14.51 mmol, 1.25 equiv), anhydrous DMF (30 mL) and acetic acid (0.066 mL, 1.16 mmol, 0.1 equiv) under argon. The reaction mixture was stirred at 75 °C overnight and then monitored by ^1H and ^{19}F NMR analysis. Upon completion, the reaction mixture was cooled to room temperature and quenched with sat. aq. $NaHCO_3$ solution (100 mL), followed by extraction using Et_2O (3×100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to ca. 4 mL (at 700 mbar/35 °C). To this solution (containing DMF and Et_2O) was added anhydrous Et_2O (30 mL) under argon, and cooled to -78 °C. $NaBH_4$ (1.32 g, 34.83 mmol) was slowly added at -78 °C. The reaction mixture was warmed to room temperature, followed by addition of 10 drops of EtOH. The reaction was then left at room temperature overnight. On the following day, the solvent of reaction mixture was taken out of the reaction flask, and filtered over a pad of silica gel (CH_2Cl_2 – 3/97 Et_2O/CH_2Cl_2). The filtrate was concentrated to ca. 2 mL (at 700 mbar/35 °C), and further dried by slow evaporation at atmospheric pressure to afford a mixture of the desired products **J7** and **J8** (50 mg, ~75% pure, ratio: **J7**:**J8**: ~1:1, calculated yield < 5% over 2 steps). Note: In $^{19}F\{^1H\}$ NMR spectrum, impurities signals were not overlapped with the desired products signals. Therefore, log*P* measurement is still feasible. ^1H NMR (500 MHz, $CDCl_3$) δ 4.32 (1H, ddt, J 48.5, 9.4, 3.4 Hz, H-3 of **J7** or **J8**), 4.11 - 4.26 (1H, m, H-3 of **J8** or **J7**, a doublet with J 49.1 Hz was observed),

3.85 - 3.95 (1H, m, H-2 of **J7** or **J8**), 3.81 (1H, dquin, *J* 16.0, 6.3 Hz, H-2 of **J8** or **J7**), 2.07 (1H, br. s, -O*H* of **J7** or **J8**), 1.80 (1H, br. s, -O*H* of **J8** or **J7**), 1.56 - 1.76 (4H, m, H-4 and H-4' of **J7** and **J8**), 1.21 (3H, dd, *J* 6.5, 1.3 Hz, H-1 of **J7** or **J8**), 1.20 (3H, dd, *J* 6.5, 0.9 Hz, H-1 of **J8** or **J7**), 1.03 (3H, t, *J* 7.4 Hz, H-5 of **J7** or **J8**), 1.02 (3H, t, *J* 7.4 Hz, H-5 of **J8** or **J7**) ppm; $^{1}H\{^{19}F\}$ NMR (500 MHz, $CDCl_3$) δ 4.32 (1H, dt, *J* 9.2, 3.7 Hz, H-3 of **J7** or **J8**), 4.19 (1H, dt, *J* 6.7, 5.6 Hz, H-3 of **J8** or **J7**), 3.86 - 3.94 (1H, m, H-2 of **J7** or **J8**), 3.81 (1H, quin, *J* 6.3 Hz, H-2 of **J8** or **J7**), 2.07 (1H, br. s, -O*H* of **J7** or **J8**), 1.80 (1H, br. s, -O*H* of **J8** or **J7**), 1.56 - 1.74 (4H, m, H-4 and H-4' of **J7** and **J8**), 1.21 (3H, d, *J* 6.5 Hz, H-1 of **J7** or **J8**), 1.20 (3H, d, *J* 6.5 Hz, H-1 of **J8** or **J7**), 1.03 (3H, t, *J* 7.4 Hz, H-5 of **J7** or **J8**), 1.02 (3H, t, *J* 7.4 Hz, H-5 of **J8** or **J7**) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) *δ* 99.0 (d, *J* 169.5 Hz, C-3 of **J8** or **J7**), 97.6 (d, *J* 170.5 Hz, C-3 of **J7** or **J8**), 69.0 (d, *J* 17.9 Hz, C-2 of **J8** or **J7**), 68.8 (d, *J* 20.0 Hz, C-2 of **J7** or **J8**), 24.2 (d, *J* 21.2 Hz, C-4 of **J7** or **J8**), 23.0 (d, *J* 21.5 Hz, C-4 of **J8** or **J7**), 18.4 (d, *J* 6.0 Hz, C-1 of **J8** or **J7**), 17.4 (d, *J* 6.0 Hz, C-1 of **J7** or **J8**), 9.7 (d, *J* 4.8 Hz, C-5 of **J7** or **J8**), 9.3 (d, *J* 5.0 Hz, C-5 of **J8** or **J7**) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ* -194.6 - -194.2 (1F, m, F-3 of **J7** or **J8**), -195.1 - -194.8 (1F, m, F-3 of **J8** or **J7**) ppm; $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) *δ* -194.4 (1F, s, F-3 of **J7** or **J8**), -194.9 (1F, s, F-3 of **J8** or **J7**) ppm; HRMS (CI) for $C_5H_{12}FO$ $[M + H]^+$: calcd, 107.08667; found, 107.08470.

3,3-Difluoropentan-2-ol (J10): To a stirred solution of the mixture of **15** and **51**, obtained as described above, in Et_2O (30 mL) was added NaOMe (25% w/w in MeOH, 11.0 mL). After 6 h, the reaction was neutralized with aq. HCl (1 M) until pH 7. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried over $MgSO_4$. The crude was carefully concentrated at 750 mbar/30 °C and purified by column chromatography (CH_2Cl_2) to afford **J10** as a colorless oil (1.05 g, 35% over 2 steps starting from **14**). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.93 (ddq, *J* = 18.5, 8.7, 6.5 Hz, 1H, H2), 2.09–1.85 (m, 2H, H4), 1.85–1.80 (m, 1H, OH), 1.29 (d, *J* = 6.6 Hz, 3H, H1), 1.06 (t, *J* = 7.5 Hz, 3H, H5) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz,

$CDCl_3$) δ 124.3 (t, J = 243.9 Hz, C3), 68.9 (t, J = 29.3 Hz, C2), 25.3 (t, J = 24.9 Hz, C4), 16.1 (t, J = 3.7 Hz, C1), 5.7 (t, J = 5.5 Hz, C5) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.7– -115.0 (m, 1F, F3'), -116.7 (ddt, J = 246.2, 23.4, 12.1 Hz, 1F, F3'') ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -114.3 (d, J = 246.2 Hz, 1F, F3'), -116.7 (d, J = 246.2 Hz, 1F, F3'') ppm; IR (neat) 3356 (br. w), 2989 (w), 2949 (w), 2882 (w), 1468 (m), 1106 (s), 957 (s) cm^{-1}; HRMS (CI) for $C_5H_{11}OF_2$ $[M+H]^+$, calculated 125.07725, found 125.07773).

2-((3-(4,4,5-Trifluoropentoxy)phenethyl)amino)-*N*,*N*-dimethylacetamide·HCl (K2): Using general procedure B with **52** (1 equiv) and **51a** (96 mg) in DMF (2 mL), **53a** was obtained as a colourless gum (68 mg, 64%). According to general procedure C, N-Boc cleavage of **53a** (51 mg, 1 equiv) yielded **K2** as an off-white solid (37 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (br s, 2H, NH_2^+), 7.20 (br t, J = 7.4 Hz, 1H, H4), 6.89-6.86 (m, 2H, H5 and H1), 6.77 (d, J = 8.1 Hz, 1H, H3), 4.47 (dt, J = 46.9, 11.4 Hz, 2H, 17), 4.03-4.00 (m, 4H, H13 and H9), 3.38 (br s, 2H, H8), 3.28 (br s, 2H, H7), 2.97 (s, 3H, H11 or H12), 2.94 (s, 3H, H11 or H12), 2.15 (m, 2H, H15), 2.00 (m, 2H, H14) ppm (see SI for atom numbering); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.5 (C10), 159.1 (C2), 138.0 (C6), 129.0 (C4), 121.3 (C5), 120.8 (td, J = 241.3, 22.7 Hz, C16), 115.0 (C1), 113.3 (C3), 81.7 (dt, J = 178.1, 35.5 Hz, C17), 66.8 (C13), 49.7 (C8), 48.3 (C9), 36.5 (C11 or C12), 35.9 (C11 or C12), 32.5 (C7), 29.9 (t, J = 23.8 Hz, C15), 21.6 (t, J = 4.4 Hz, C14) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -234.4 (tt, J = 46.6, 15.0 Hz, 1F, F17), -109.7 (m, 2F, F16) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -234.5 (t, J = 15.6 Hz, 1F, F17), -109.7 (d, J = 15.6 Hz, 2F, F16) ppm; IR (neat): 2924 (br m), 2757 (br m), 1671 (s), 1244 (s), 1165 (m) cm^{-1}; HRMS (ESI$^+$) for $C_{17}H_{26}F_3N_2O_2$ $[M + H]^+$, calcd 347.1941; found 347.1946 (-1.6 ppm error), for $C_{17}H_{26}F_3N_2NaO_2$ $[M + Na]^+$, calcd 369.1760; found 369.1765.

2-((3-(5,5,5-Trifluoropentoxy)phenethyl)amino)-*N*,*N*,-dimethylacetamide·HCl (K4): Using general procedure B with **52** (1 equiv) and **51b** (71 mg) in DMF (2 mL), **53b** was obtained as a colourless gum (32 mg, 33%). According to general procedure C, N-Boc cleavage

of **53b** (51 mg, 1 equiv) yielded **K4** as an off-white solid (27 mg, quantitative). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (br s, 2H, NH_2^+), 7.21 (t, J = 7.6 Hz, 1H, H4), 6.89-6.85 (m, 2H, H5 and H1), 6.77 (d, J = 8.2 Hz, 1H, H3), 4.03-3.96 (m, 4H, H13 and H9), 3.37 (br s, 2H, H8), 3.28 (br s, 2H, H7), 2.97 (s, 3H, H11 or H12), 2.96 (s, 3H, H11 or H12), 2.17 (m, 2H, H16), 1.87-1.73 (m, 4H, H14 and H15) ppm (see SI for atom numbering); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.4 (C10), 159.2 (C2), 137.9 (C6), 127.1 (q, J = 271.6 Hz, C17), 129.9 (C4), 121.2 (C5), 114.9 (C1), 113.4 (C3), 67.2 (C13), 49.8 (C8), 48.2 (C9), 36.4 (C11 or C12), 35.9 (C11 or C12), 33.5 (q, J = 28.5 Hz, C16), 32.5 (C7), 28.3 (C14), 18.9 (q, J = 3.1 Hz, C15) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6 (t, J = 10.4 Hz, 3F) ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -66.6 (s, 3F) ppm; IR (neat): 3466 (m), 2929 (br m), 2789 (br m), 1658 (s), 1285 (s), 1132 (m) cm^{-1}; HRMS (ESI$^+$) for $C_{17}H_{26}F_3N_2O_2$ $[M + H]^+$, calcd 347.1941; found 347.1947 (-1.9 ppm error), for $C_{17}H_{26}F_3N_2NaO_2$ $[M + Na]^+$, calcd 369.1760; found 369.1765.

Supporting Information Available. The supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all novel compounds, ^{19}F NMR spectra of the H_2O and octanol phases of all new fluorohydrin log$P$ measurements, tables with the relative Gibbs energy and populations of the energetic minima of **D1**, **D4-6**, **E1**, **E5**, **E6** (PDF). Molecular formula strings (CSV). The raw data are stored in (to be completed in case of acceptance).

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Abbreviations used.

Ac, acetyl; AIBN, azo bis(isobutyronitrile); Bn, benzyl; Bz, benzoyl; Cat, catalytic; Clog*P*, calculated log*P*; CI, chemical ionisation; DAST, diethylaminosulfur trifluoride; DCE, 1,2-dichloroethane; DMAP, 4-(N,N-dimethylamino) pyridine; DMF, dimethyl formamide; DMP, Dess-Martin periodinane; ESI, electrospray ionisation; Et, ethyl; LC-MS, liquid chromatography-mass spectroscopy; log*P*, lipophilicity; mbar, millibar; *m*CPBA, meta chloroperbenzoic acid; Me, methyl; MHz, megahertz; NfF, nonafluorobutylsulfonyl fluoride; NFSI, N-fluorobenzenesulfonimide; NMR, nuclear magnetic resonance; pTSA, paratoluenesulfonic acid; py, pyridine; rt, room temperature; SMD, solvation model based on

density; TBAF, tetrabutyl ammonium fluoride; Tf, trifluoromethylsulfonyl; TLC, thin layer chromatography; TMS, trimethyl silyl; Ts, tosyl.

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