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Organofluorine Chemistry: Synthesis and Conformation of Vicinal Fluoromethylene Motifs

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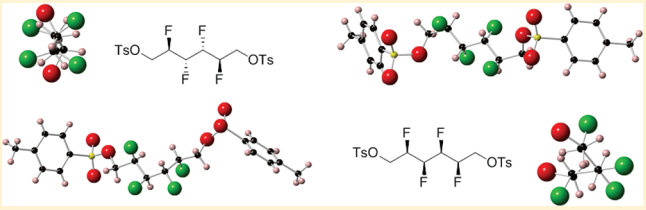
ABSTRACT: The C−F bond is the most polar bond in organic chemistry, and thus the bond has a relatively large dipole moment with a significant −ve charge density on the fluorine atom and correspondingly a +ve charge density on carbon. The electrostatic nature of the bond renders it the strongest one in organic chemistry. However, the fluorine atom itself is nonpolarizable, and thus, despite the charge localization on fluorine, it is a poor hydrogen-bonding acceptor. These properties of the C−F bond make it attractive in the design of nonviscous but polar organic compounds, with a polarity limited to influencing the intramolecular nature of the molecule and less so intermolecular interactions with the immediate environment. In this Perspective, the synthesis of aliphatic chains carrying multivicinal fluoromethylene motifs is described. It emerges that the dipoles of adjacent C−F bonds orientate relative to each other, and thus, individual diastereoisomers display different backbone carbon chain conformations. These conformational preferences recognize the influence of the well-known *gauche* effect associated with 1,2-difluoroethane but extend to considering 1,3-fluorine−fluorine dipolar repulsions. The synthesis of carbon chains carrying two, three, four, five, and six vicinal fluoromethylene motifs is described, with an emphasis on our own research contributions. These motifs obey almost predictable conformational behavior, and they emerge as candidates for inclusion in the design of performance organic molecules.



INTRODUCTION

It was Linus Pauling who first highlighted the C−F bond as the most polar in organic chemistry, an observation which emerged from his evaluation of electronegativity differences between bonding elements and his recognition that fluorine is the most electronegative of the elements.[1] A number of consequences follow from this, particularly that the C−F bond has significant ionic character and that it is the strongest bond (BDE = 105.4 kcal mol^{-1}) in organic chemistry (Figure 1). Thus, fluorinated compounds, and particularly those with a high level of fluorination, have high chemical and thermal stability. The bond has a relatively large dipole; e.g., fluoromethane has a dipole moment of 1.8 Dy (Figure 1). However, despite the polarity of the C−F bond, the high electronegativity of fluorine compresses its lone pairs and thus organic bound fluorine is a weak hydrogen bond acceptor. It follows that when fluorine is introduced into an organic molecule, it provides an electronic torque through the molecule but it does not generally enhance intermolecular interactions between molecules in the way nitrogen and oxygen do through hydrogen bonding. Thus, molecules emerge of higher polarity but lower viscosity after substitution of fluorine for hydrogen. Fluorinated compounds fall into two broad classes: those that are heavily fluorinated such as perfluorocarbon materials and polymers, most extremely represented by poly(tetrafluoroethylene) (Teflon) or those that are selectively fluorinated, e.g., with −F or $-CF_3$, typical of bioactives found in pharmaceutical and agrochemical products. We have been interested in the synthesis and properties of molecules with an intermediate level of fluorination and in particular a class of compounds containing sequential fluoromethylene (−CHF−) groups.[2] Runs of fluoromethylenes along a carbon chain generate stereogenic centers, and thus, one of the challenges in studying such materials is the requirement to prepare them as single stereoisomers or at least as racemates. It was of interest to assess how the polar C−F bonds would orientate relative to each other in extended systems, and in this Perspective we describe the synthesis of compounds with two, three, four, five, and six sequential fluoromethylene groups. As a starting point in considering the preferred conformations of such compounds, it is useful to revisit the *gauche* effect which recognizes that 1,2-difluoroethane **1** has a small preference for a *gauche* rather than an *anti* conformation (Figure 1).[3] The *gauche* preference has its origin in ${}^{C-H}\sigma_{(HOMO)}$ to ${}^{C-F}\sigma^*_{(LUMO)}$ hyperconjugation, which occurs when vicinal C−H bonds orientate antiperiplanar to C−F bonds. The effects are relatively weak, but in certain *gauche* conformations two mutually reinforcing interactions can be accommodated and a stabilization of ∼0.8 kcal mol^{-1} is found.

When two C−F bonds are placed 1,3 to each other on a carbon chain, e.g., in 1,3-difluoropropane **2**, then they experience dipolar repulsion particularly when the C−F bonds are coaligned.[4] This repulsion is maximal at around 3.0 kcal mol^{-1} and is a significant influence; thus, conformations where the 1,3−C-F bonds turn away from each other are favored (Figure 1). It has emerged from this research program that linear chains of stereoisomers where the fluorines are

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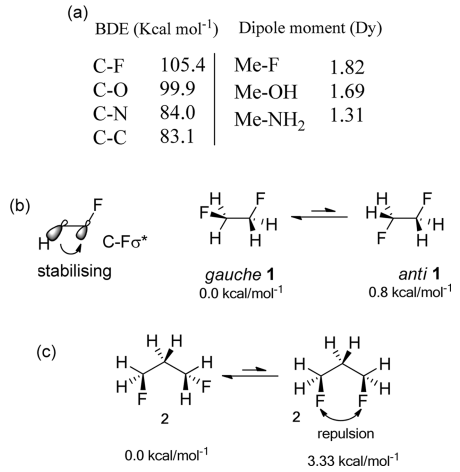


Figure 1. Some features of the C−F bond. (a) Comparison with the bond dissociation energies (BDE) and dipole moments with nitrogen, oxygen, and carbon. (b) 1,2-Difluoroethane **1** has a lowest eneregy *gauche* conformer due to hyperconjugative $^{C-H}\sigma_{(HOMO)}$ to $^{C-F}\sigma^*_{(LUMO)}$ interactions. (c) The lowest energy conformer of 1,3-difluoropropane **2** avoids dipolar repulsion between the C−F bonds.

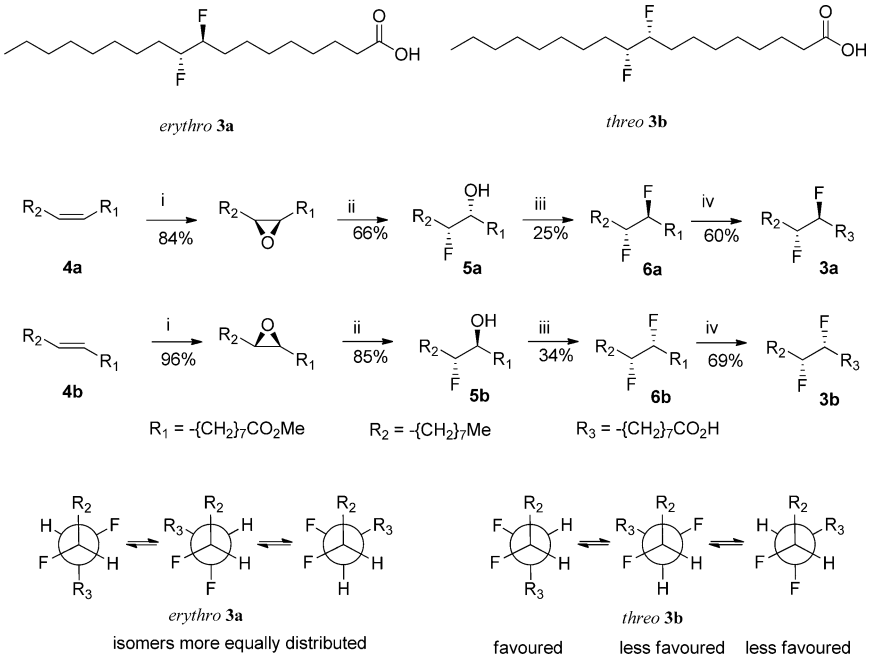
all-syn tend to form helical arrangements because adjacent C−F bonds orientate *gauche* to each other and those positioned 1,3 turn away from each other. This is particulary obvious in the *all-syn* isomers with four, five, and six sequential C−F bonds described below. The following sections describe our excursions into the synthesis of this class of compound and the results are presented progressively with the synthesis of stereoisomers containing an increasing number of sequential fluoromethylene groups, from two to six.

TWO FLUORINES

Our first introduction to vicinal fluorine compounds came about when we prepared and compared the melting points of *erythro*-**3a** (mp 68 °C) and *threo*-**3b** (mp 87 °C) 9,10-difluorostearic acids.[5] These compounds were synthesized by adaption of a strategy of Schlosser[6] from the corresponding *cis*- and *trans*-oleic acid methyl esters **4** by epoxidation, HF ring-opening, and the DAST treatment of the corresponding fluorohydrins **5a** or **5b** as illustrated in Scheme 1. The fluorination step with DAST gave rise to the vicinal difluoro products **6a** and **6b** with complete stereointegrity but with some olefin side products; however, these were readily removed by treatment with ozone and then chromatography.

Purification of the resultant fatty acids **3a** and **3b** after ester hydrolysis gave nice white waxy solids. The melting points of these 9,10-difluorostearic acid diastereoisomers were evaluated by careful DSC analysis, which showed a 20 °C difference in their melting points (67−69 °C for *erythro* **3a** and 86−88 °C for (±)-*threo*-**3b**). This was somewhat surprising given the identical high molecular mass of these materials and the preconceived expectation that their properties would be dominated by the fatty acid nature of the molecules. The only difference between these two molecules is the stereogenicity of a single C−F bond, and this gives rise to a significant melting point difference. In order to gain further insight into the properties of these stereoisomers, they were deposited on a water subphase, and Langmuir isotherms were recorded which record pressure area relationships on the surface for a given amount of material.[5] The *threo* isomer **3b** has an isotherm very similar to stearic acid itself indicating an extended aliphatic chain on the surface. However, for the *erythro* isomer **3a**, a significant surface pressure exists with a much more expanded surface area. This is an indication that the molecules of the *erythro* isomer **3a** are much more disordered on the surface. This disorder is consistent with the initial observation that the *erythro* isomer

Scheme 1[a]



[a]Key: (i) *m*-CPBA (1.3 equiv), CH_2Cl_2, rt, 21 h; (ii) HF·pyridine (1.5 equiv), CH_2Cl_2, rt, 15 min (a)/ 4 h (b); (iii) DAST (1.6 equiv), CH_2Cl_2, −78 °C to rt, 5 h (a)/1 h (b); (iv) NaOH−MeOH, reflux, 18 h.

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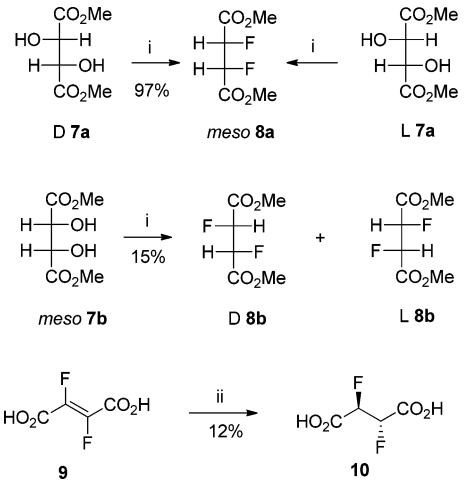
has a lower melting point. We rationalize this observation as a manifestation of the *gauche* effect. For the *threo* isomer **3b**, an extended zigzag structure accommodates two antiperiplanar C−H to C−F relationships which stabilize the *anti* zigzag conformation (favored Newman projection for *threo*-**3b** in Figure 1); however, for the *erythro* isomer **3a** an *anti* zigzag conformation of the aliphatic chain would place the vicinal C−F bonds antiperiplanar to each other. However, rotation of the FC−CF bond such that the main chain becomes disordered allows favorable C−H/C−F *gauche* interactions to compete with disfavored 1,4-H,H interactions (of R^1 and R^2 groups in the staggered Newman projections for **3a**, Figure 1), and thus, the chain more easily accesses all staggered conformations and becomes disordered. These observations with 9,10-difluorostearic acids alerted us to the power of influencing the properties of organic aliphatics by placing C−F bonds adjacent to each other with a defined stereochemistry and prompted a research program exploring these motifs more extensively.

It became a focus to prepare other vicinal difluoro motifs. We placed some effort into preparing the *erythro* and *threo* isomers of 2,3-difluorosuccinic acid **10**.[7] Hudlicky in 1980[8a] followed by Yagupolskii's laboratory in the Ukraine in 1981[8b] had reported the direct dehydroxyfluorination of tartaric acid methyl esters **7** using SF_4/HF, and this approach generated the corresponding vicinal difluoro products **8** in good yield (Scheme 2).[8] By this method, one of the dehydroxyfluorination steps proceeds with a retention of configuration; thus, both D- and L-tartaric acid esters **7a** generate *meso*-1,2-difluorosuccinic acid methyl ester **8a**, and notably, enantiomerically pure 1,2-difluorosuccinic acid methyl ester **8b** is not accessible. Conversely, *meso*-tartarate **7b** generates racemic (±)-1,2-difluorosuccinic acid methyl ester **8b**. The optimum conditions use SF_4/HF. This is a dangerous reagent composition requiring specialist isolation precautions, and we shied away from using these conditions. Hudlicky[9] had some some limited success in the synthesis of 2,3-difluorosuccinic acid **10** by hydrogenation of 2,3-difluorofumaric acid **9**, but the yields were low (Scheme 2). Schlosser has prepared *syn*- and *anti*-diastereoisomers of vicinal difluorides from *cis*- and *trans*-epoxides by HF·NEt_3 ring-opening and then DAST treatment of the resulting fluorohydrins.[6] However, this method did not prove suitable for the preparation of 1,2-difluorosuccinic acids.[7]

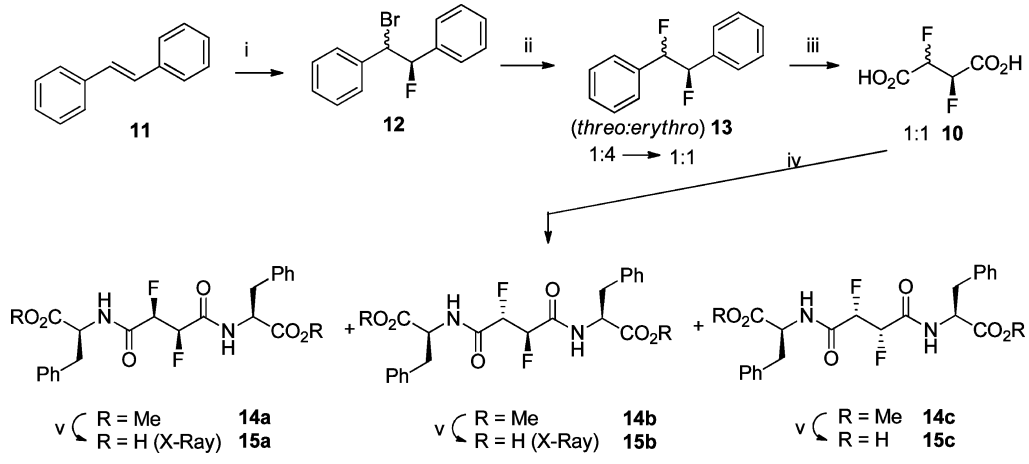
Our initial approach to **10** explored fluorination of the cyclic sulfate of tartaric acid stereoisomers, but fluorination led to extensive elimination products, and in the end this was not fruitful. A more successful approach[7] involved bromofluorination of stilbene **11** followed by silver fluoride (AgF) treatment of product **12** to generate a mixture of *erythro*- and *threo*-1,2-difluoro-1,2-diphenylethanes **13**. (Scheme 3). It also emerged that there was no advantage is using either *cis*- or *trans*-stilbene **11** to bias the generation of the different diastereoisomers. In each case, the *erythro* product was always predominant indicating a significant intermediate carbocation formation during the reaction favoring *erythro*-**13** as the thermodynamic product. The isomers could be separated either by crystallization, which amplified the *erythro*-**13** product, or by chromatography to obtain the minor *threo*-**13** stereoisomer. *erythro*- and *threo*-**13** were then used as precursors for the synthesis of their corresponding 2,3-difluorosuccinic acids **10**, a process that was achieved by oxidation of the aryl rings. The conditions used involved ozone/H_2O_2 in acetic acid with modest to good transformations (45% yield). The resultant *erythro*- and *threo*-succinic acids **10** were crystalline solids, and both were subjected to X-ray structure analysis (Figure 2). The two diastereoisomers of **10** have very different main chain conformations. In each case, the C−F bonds lie *gauche* to each

Scheme 2[a]



[a]Key: (i) SF_4 (4 equiv), HF (8 equiv), 90 °C, 5h; (ii) Pd/C, H_2.

Scheme 3[a]



[a]Key: (i) NBS, HF/pyr, Et_2O; (ii) AgF, 73%; (iii) O_3, AcOH, H_2O_2, 45%; (iv) PheOMe, EDCI, HOBt, DMF, 83%; (v) aq HCl−acetone, 100%.

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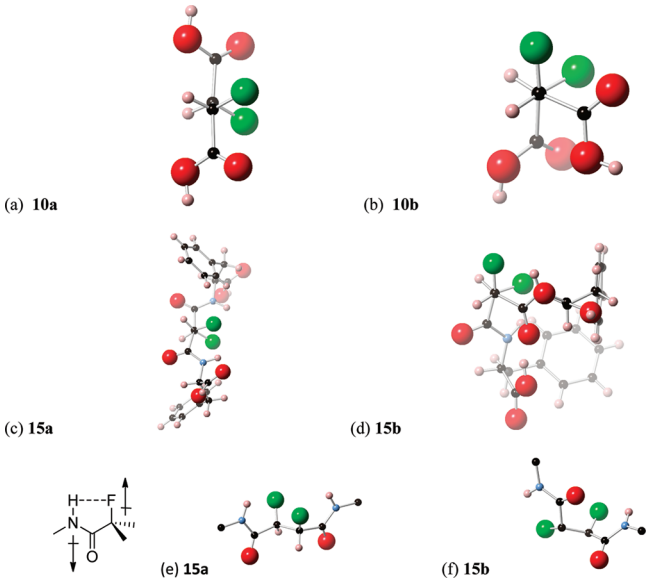


Figure 2. X-ray structures of (a) *threo*-**10a** and (b) *erythro*-**10b** 2,3-difluorosuccinic acids. In both cases, the C−F bonds lie *gauche* to each other. This conformation is maintained for both diastereoisomeric series in the structures of the peptides (c) *threo*-**15a** and (d) *erythro*-**15b** which retain the 2,3-difluorosuccinate core. The peptidic structures also have a clear antiplanar relationship between each C−F bond and the amide carbonyl as a result of dipolar relaxation as highlighted in (e) and (f).

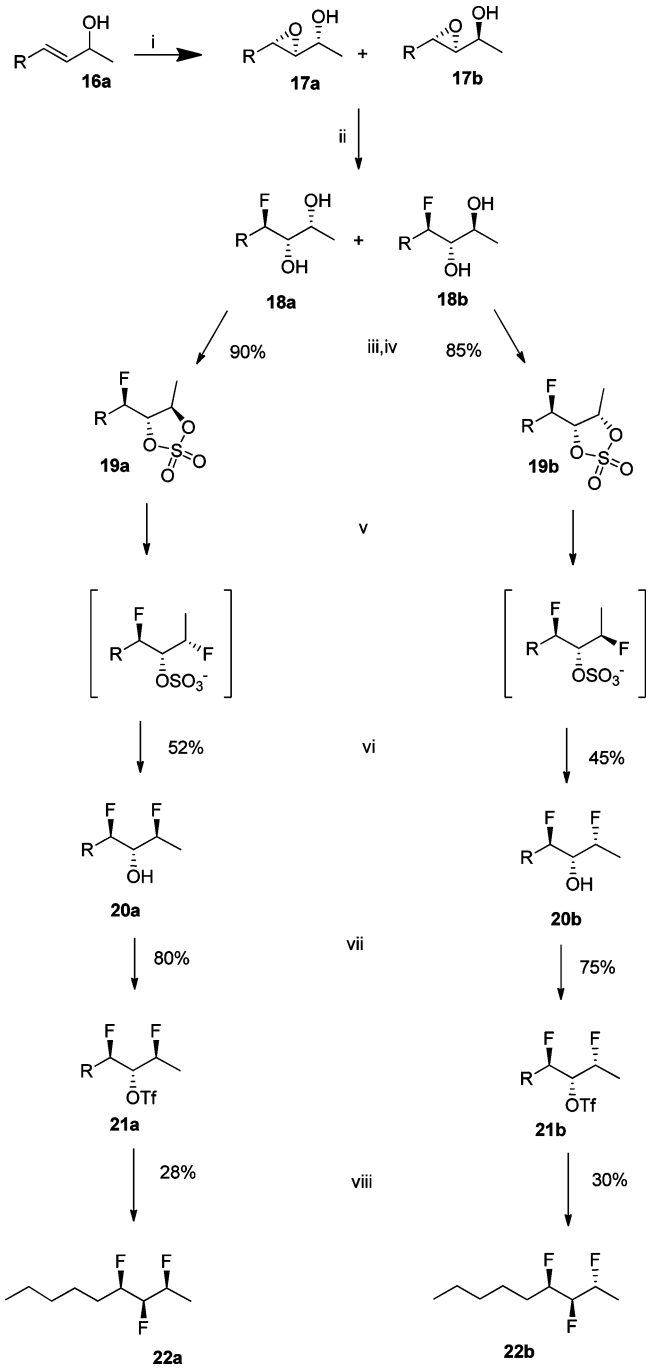
other and antiperiplanar to a vicinal C−H bond, consistent with hyperconjugative C−H to C−F stabilization influencing these conformations.

α-Fluoroamides adopt a particularly favorable conformation where the C−F bond orientates *anti* to the amide carbonyl to relax the opposing dipoles.[10] Thus, it was anticipated that amides with the 2,3-difluorosuccinate core **15a** and **15b** would adopt this conformation at each amide bond, and the anticipated *gauche* preference along the linking difluorosuccinate moiety should allow prediction of the overall conformation of such a peptidic molecule. Accordingly a 1:1 (*erythro*/*threo*) mixture of 2,3-difluorosuccinic acid **10** was reacted with (*S*)-L-phenylalanine methyl ester to give three methyl ester diastereoisomers **14a**−**c**.[11] Chromatography separated the three isomers. The *threo*-**14a** and the *eyrthro*-**14b** isomers were hydrolyzed to their corresponding dicarboxylic acids **15a** and **15b**, respectively, and the resultant X-ray structures of these stereoisomers are shown in Figure 2. Stereoisomer **15a** has a twisted carbon linker (difluorosuccinate), whereas stereoisomer **15b** has an extended *anti* zigzag structure. These structures maintain the conformational preferences of their precursor succinic acid diastereoisomers **10a** and **10b** demonstrating the enduring influence of the C−F bond configuration on the conformations. Also each C−F bond aligns antiparallel to the adjacent amide carbonyl as highlighted in substructures (e) and (f) in Figure 2 for **15a** and **15b**, respectively.

THREE FLUORINES

Placing three fluoromethylene groups adjacent to each can generate up to eight stereoisomers, and thus concise routes are required to access individual entities. Our first approach to this class of molecules elaborated allylic alcohol **16a**.[12] Reaction with *m*-CPBA generated two epoxy alcohol stereoisomers **17a** and **17b** which were directly fluorinated with HF·pyridine. The fluorination proved to be stereo- and regiospecific and gave the resultant fluorohydrins **18a** and **18b** as a mixture as shown in Scheme 4. The diastereoisomers could be separated by chromatography and were were progressed through cyclic sulfate/fluorination protocols to introduce the second fluorine.[13] Fluorination was regiospecific with nucleophilic attack to the peripheral C−O bond of the cyclic sulfate generating **20a** and

Scheme 4[a]



[a](i) *m*-CPBA in DCM, 0 °C 2 h; (ii) HF·pyridine in DCM, −10 °C 4 h; (iii) thionyl chloride, pyridine, DCM, 0 °C 45 min; (iv) $NaIO_4$/ $RuCl_3$ in CH_3CN/H_2O, 0 °C 1 h; (v) TBAF in acetone, 0 °C, 2 h; (vi) Et_2O/ H_2SO_4 20; (vii) Tf_2O, pyridine in DCM, −40 °C 1 h; (viii) TBAF in acetonitrile, 0 °C, 30 min.

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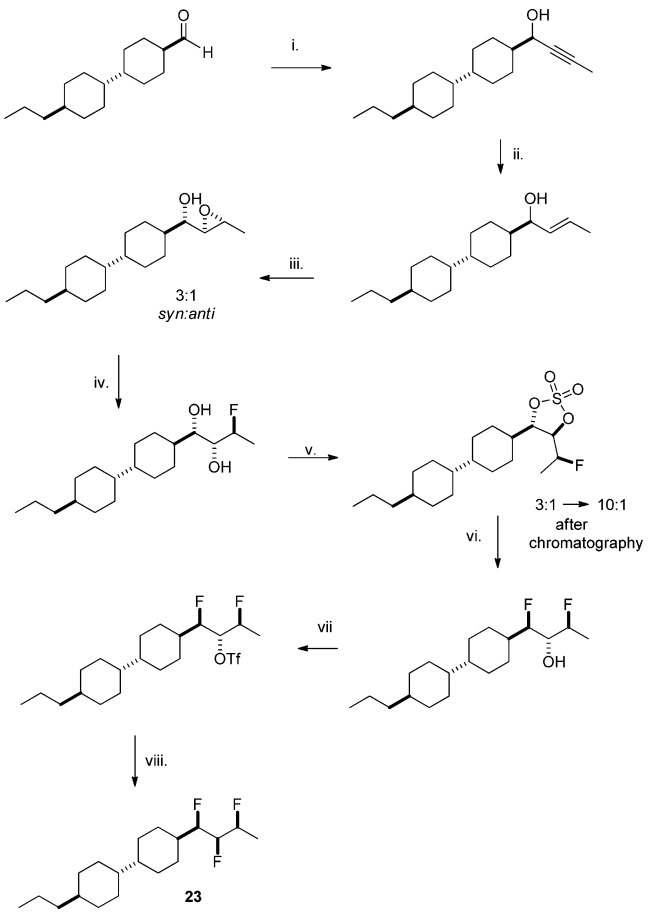
20b. The third fluorine was then introduced by triflation followed by fluoride ion displacement. This synthesis approach was used to prepare the 2,3,4-trifluorononanes **22a** and **22b** as shown in Scheme 4 and also longer chain trifluorophenylpentadecanes.[12] The route was also used to prepare the liquid crystalline candidate **23** containing three vicinal fluorines (Scheme 5). The routes in Schemes 4 and 5 required five

Scheme 5[a]

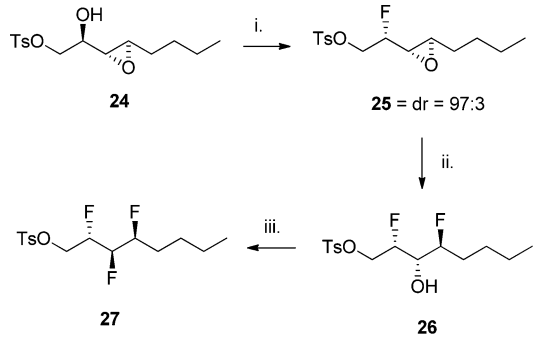


[a](i) nBuLi/propyne, $CeCl_3$, THF, −78 °C, 27%; (ii) $LiAlH_4$, THF, 0 °C, 59%; (iii) *m*-CPBA, DCM, 0°C, 95%; (iv) HF/Pyr, DCM, −5 °C; (v) $SOCl_2$, Pyr then $NaIO_4$, $RuCl_3$, 53%; (vi) TBAF, 27%; (vii) Tf_2O, Pyr, DCM, −40 °C, 37%; (viii) TBAF, THF/MeCN, 11%.

chemical steps from the epoxy alcohol, and in these cases the products were racemic.

In an effort to develop a more direct, three-step route to an enantiomerically pure trifluoro motif, an approach was explored which involved dehydroxyfluorination of the Sharpless-derived epoxy alcohol **24** to generate fluoroepoxide **25** with an inversion of configuration as shown in Scheme 6.[14] The reaction proceeds with high diastereoselectivity. Epoxide ring-opening with HF/Pyr gave difluorohydrin **26**, and then dehydroxyfluorination introduced the third fluorine to give **27** in three steps. This approach proved straightforward with good regio- and stereointegrity for each step, certainly for the diastereoisomer series shown in Scheme 6. However, the *all-syn* diastereoisomer of **27** proved more challenging to prepare by this route. Fluorination of the *all-syn*-isomer of epoxy alcohol **24** (not shown) resulted primarily in rearrangement byproduct, and then subsequent fluorination of the recovered fluoro

Scheme 6[a]



[a](i) Deoxo-Fluor, DCM, 40 °C, 83%; (ii) HF·pyridine, DCM, −60 °C, 56%; (iii) Deoxo-Fluor, DCM, 60 °C, 48%.

epoxide was also inefficient. Thus, the efficiency of this route is very specific to the stereochemical series shown in Scheme 6.

Most recently, we have prepared fluorinated analogues **28a** and **28b** of the hexose sugars D-glucose and D-arabinose, respectively, where three of the hydroxyl groups have been replaced by fluorine atoms, but conserving the stereochemistry of the original sugar.[15] Although there has been significant interest in preparing selectively fluorinated monosaccharides to explore the relative importance of hydrogen bonding in sugar−protein interactions, these are unique in that three OH to F exchanges have been made.[16] The synthetic route to these sugars is illustrated in Scheme 7. The route starts with a non-stereoselective epoxidation of allylic fluoride **29** and then ring-opening with $(HF)_3Et_3N$. The resultant difluorohydrin diastereoisomers **31a** and **31b** are separated and progressed either to the D-glucose **28a** or the D-altrose **28b** analogue by a series of relatively efficient transformations. In particular, the third fluorine is introduced in a substitution reaction on **31** of high stereointegrity using Deoxo-Fluor. Deprotection of the penultimate acetal/aldehydes **34a** or **34b** gave the sugars **28a** or **28b** as white crystalline solids, and both were subjected to X-ray crystallography, establishing their structural and stereochemical integrity.[15]

In many ways, these are sufficiently mutated structures that they can hardly be classed as sugar analogues, but none the less the D-glucose analogue **28a** was transported across red blood cells at a similar rate to D-glucose itself and the cell membrane protein (Glut 1 transporter) did distinguish the α- and β-anomers of this sugar and also transported the arabinose sugar analogue **28b** at a slower rate.[15] Thus these molecules were differentially recognized by the protein and do appear to conserve some of the characteristics of their parent sugar structures in this transmembrane assay.

■ FOUR FLUORINES

The research program progressed toward the synthesis of tetrafluoro motifs. Initially, three linear single enantiomers **35a−c** of this structural class were prepared.[17−20] The synthesis route to the *all-syn* isomer **35a** is shown in Scheme 8 and utilized a Grubbs second-generation metathesis reaction as a key step in the route. This involved a self-coupling metathesis reaction of allyl fluoride **38**, itself generated from the enantiopure epoxide **36**[21] after ring-opening with $HFNEt_3{\cdot}HF$ to give **37** followed by benzyl ether protection. Ring-opening to **37** resulted in a slight loss of enantiopurity (80% ee); however, since **38** consisted of a 9:1 mixture of (*S*)- and (*R*)-enan-

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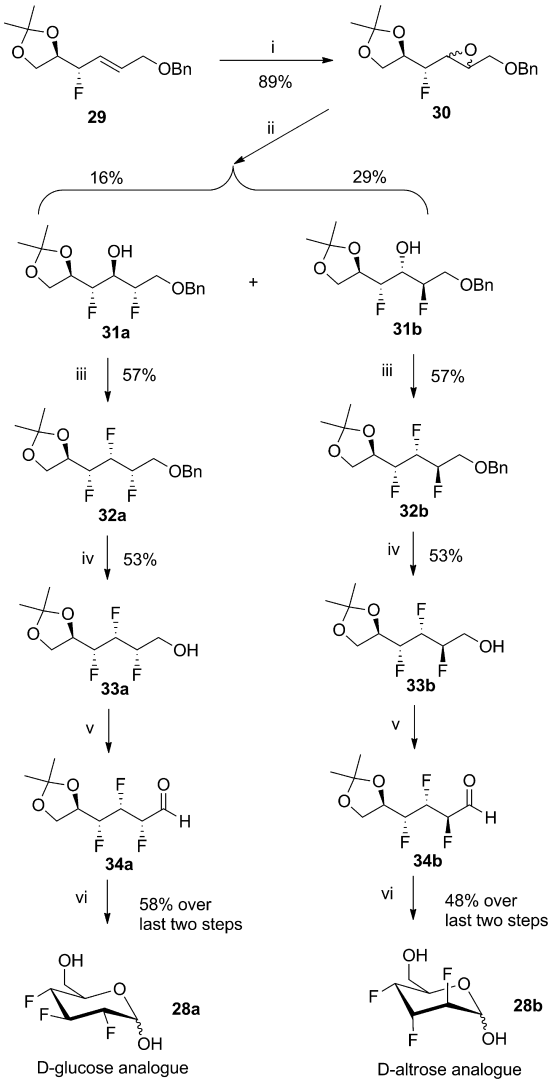
Scheme 7[a]

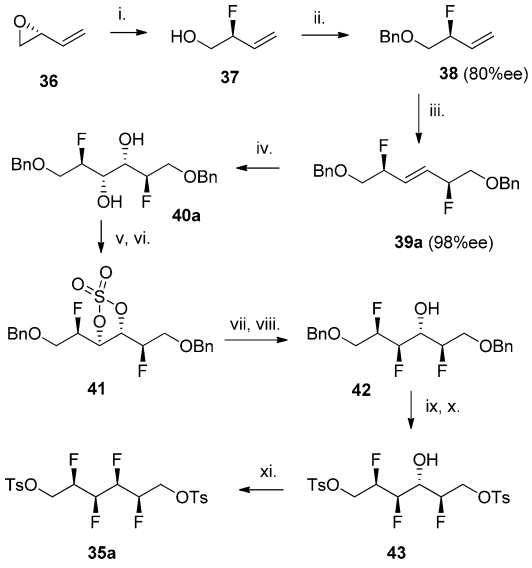


[a](i) *m*-CPBA, CH_2Cl_2, rt, 5 d; (ii) $(HF)_3Et_3N$, CH_2Cl_2, MW, up to 140 °C, 21 h; (iii) Deoxo-Fluor CH_2Cl_2, reflux, 15 h; (iv) $NaBrO_3$/$Na_2S_2O_4$, EtOAc, H_2O, rt, 1 h; (v) Dess–Martin periodinane, rt, CH_2Cl_2, 0.5 h; (vi) $SnCl_2$, CH_2Cl_2, rt, 1 h.

tiomers, the metathesis product **39** was formed as a statistical 81:18:1 mixture of (*S*,*S*)-**39a**, (*R*,*S*)-**39b**, and (*R*,*R*)-**39c**. Chromatography allowed removal of the diastereoisomer (*R*,*S*)-**39b** leaving only the major and minor enantiomers **39a** and **39c** in the product mixture but now in 98% ee; therefore, the loss in enantiopurity during epoxide ring-opening was recovered. Dihydroxylation of the electron-deficient double bond of **39a** required $KMnO_4$, and this favored *anti* attack (*anti*/*syn*, 4.3:1) away from the fluorine atoms to give diol **40a**, which could be separated from the minor *syn*-diastereoisomer **40b** by chromatography.

Cyclic sulfate formation to **41**, followed by hydrogen fluoride ring-opening, enabled a relatively efficient conversion to generate trifluoro alcohol **42**. At this stage, the benzyl ethers were replaced for tosyl groups and then the final fluorine was introduced in a dehydroxyfluorination reaction of **43** with Deoxo-Fluor. This gave the *all-syn* tetrafluoro isomer **35a** which was crystallized and structure solved by X-ray analysis (Figure 3). The solid-state conformation has all of the C–F bonds *gauche*

Scheme 8. Synthetic Route to Vicinal Tetrafluoro Compounds[a]



[a](i) $Et_3N{\cdot}3HF$, Na_2SO_4, 70 °C, 40%; (ii) BnBr, NaH, DMF, 40 °C, 89%; (iii) Grubbs (II) catalyst, DCM, 30 °C, 69%; (iv) $KMnO_4$, $MgSO_4$, EtOH, H_2O, DCM, −10 °C, 90%; (v) $SOCl_2$, pyridine, DCM, 0°C; (vi) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C, 70% over two steps; (vii) TBAF, MeCN, rt; (viii) H_2SO_4, H_2O, THF, rt, 62% over two steps; (ix) H_2, Pd/C, MeOH, rt; (x) TsCl, 2,4,6-collidine, 50 °C, 45% over two steps; (xi) Deoxo-Fluor, 70 °C, 75%.

to each other. If this isomer adopted a main chain *anti* zigzag conformation, then there would be two repulsive 1,3 C–F bond interactions; thus the chain twists to the observed lower energy isomer. This is very different to isomer **35b**, prepared from the minor dihydroxylation product **40b**. The X-ray-derived structure (Figure 3) of **35b** reveals an extended *anti* zigzag conformation, which can be achieved as there are no such 1,3-C–F repulsive bond interactions in this extended conformation.

In all, three different tetrafluoromethylene stereoisomers were prepared as their ditosylates **35a–c**,[19,20] and these compounds were converted on an analytical scale in $CDCl_3$ for an NMR study to the corresponding 2,3,4,5-tetrafluorohexanes **44a–c** by treatment with $LiAlH_4$, in a reaction which was remarkably smooth, giving the alkanes in almost quantative conversions as illustrated in Scheme 9. Detailed ^1H and ^{19}F NMR analyses, particularly observing vicinal $^3J_{HF}$ coupling constants revealed very different solution conformations for the three isomers. In addition, the solution conformations of the ditosyl precursors **35a–c** and the corresponding 2,3,4,5-tetrafluorohexane steroisomers **44a–c** were very similar, indicating that the relative C–F bond stereochemistry dictates the conformation, not the tosyl groups. Additionally, the three 2,3,4,5-tetrafluorohexane stereoisomers had very different retention times with gas chromatography, indicating that they have distinct polarities most probably arising due to their average molecular dipole moments, and that unique relative stereochemistry leads to unique physical properties.

It became attractive to prepare a cyclohexane ring carrying four contigious fluorine atoms, and in particular to prepare the *all-syn* isomer of 1,2,3,4-tetrafluorocyclohexane **45**. Isomer **45** has a calculated dipole moment of 4.91 Dy, which is polar for an aliphatic organic material, as a consequence of all of

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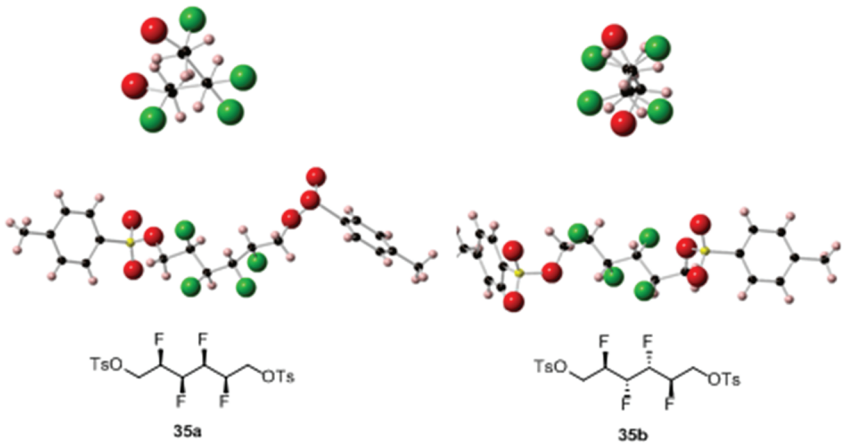
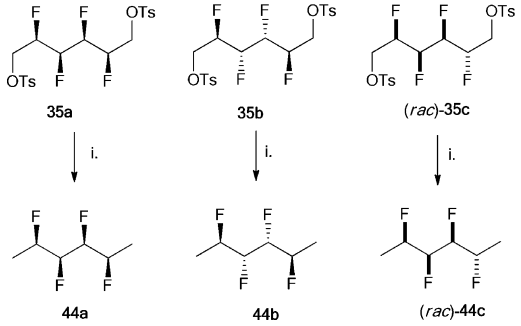


Figure 3. X-ray structures of tetrafluorostereoisomers **35a** and **35b**. The all-syn isomer **35a** adopts a helical arrangement of the C−F bonds, which all lie 60° (*gauche*) to each other. By contrast, tereoisomer **35b** adopts an *anti* zigzag backbone as there are no 1,3-C−F bond repulsive interactons in that conformation.

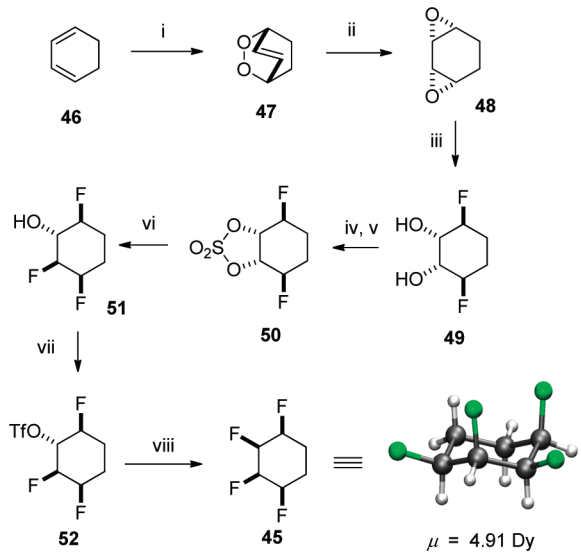
Scheme 9[a]



[a]Key: (i) $LiAlH_4$, quantative transformations carried out on an NMR scale in $CDCl_3$.

the fluorine atoms lying above the plane of the cyclohexane ring. The synthetic route to the compound is illustrated in Scheme 10.[22] The route exploited the known preparation of endoperoxide **47** by singlet oxygen cycloaddition with cyclohexadiene **46**.[23] Disproportionation of endoperoxide **47** to generate *syn*-diepoxide **48** was achieved in a reaction catalyzed by $Ru(PPh_3)_3Cl_2$.[24] With the *syn*-diepoxide **48** in hand, it was then subjected to ring-opening with $Et_3N{\cdot}3HF$ to prepare the difluorohydrin **49** as a single stereo- and regioisomer. Cyclic sulfate methodology was used to generated **50**, and then fluoride ion ring-opening gave the trifluorohydrin alcohol **51**. Activation of the alcohol moiety gave triflate ester **52**, and then displacement with fluoride generated the *all-syn* tetrafluorocyclohexane **45**. This compound was a nice crystalline solid (mp = 83 °C) presumably as a consequence of its polarity, and the resultant X-ray structure is shown in Scheme 10. The anticipated chair conformation emerged conspiciously with two 1,3-diaxial C−F bonds. Cyclohexane **45** is formally a nonchiral *meso* stereoisomer; however, it becomes chiral in the solid-state chair conformation. Ring interconversion gives enantiomeric forms, and the unit cell is composed of enantiomeric dimers. Low-temperature ^{19}F NMR (200 K) resolved all four of the fluorine atoms as ring interconversion was sufficiently slow on the NMR time scale, and a large coupling constant ($^4J_{FF}$ = 29 Hz) was observed between the two diaxial fluorine atoms. However, the magnitude of this coupling constant is too large

Scheme 10. X-ray Structure and Synthesis of Tetrafluorocyclohexane 45[a]



[a]Key: (i) $(PhO)_3P$, O_3, CH_2Cl_2, −78 °C then **x**, CH_2Cl_2, −78 °C → −25 °C; (ii) $Ru(PPh_3)_3Cl_2$, CH_2Cl_2, 0 °C → rt, 46% from two steps; (iii) $Et_3N.3HF$, 90°C; (iv) $SOCl_2$, Pyr, CH_2Cl_2, 0 °C; (v) $NaIO_4$, $RuCl_3{\cdot}xH_2O$, MeCN, H_2O, 35% from three steps; (vi) $Et_3N{\cdot}3HF$, 120 °C, 70%; (vii) Tf_2O, pyridine, rt; (viii) $Et_3N{\cdot}3HF$, 120 °C, 35% over two steps.

for a standard $^4J_{FF}$ coupling constant and is clearly a consequence of a through-space rather than a through-bond coupling, as the distance (~2.8 Å) between the two axial fluorines is within van der Waals contact distance.

■ FIVE FLUORINES[25]

The preparation of individual stereoisomers of a linear pentafluoromethylene motif was explored, and three unique stereoisomers **53a−c** have been prepared.[24] The routes to these three stereoisomers started from the bis-allylic alcohol **54** as a common precursor, a compound already described in the literature.[26,27] The synthetic routes to these isomers are shown in Schemes 11−13. Scheme 11 illustrates an initial synthesis route which involved an asymmetric epoxidation to **55** followed

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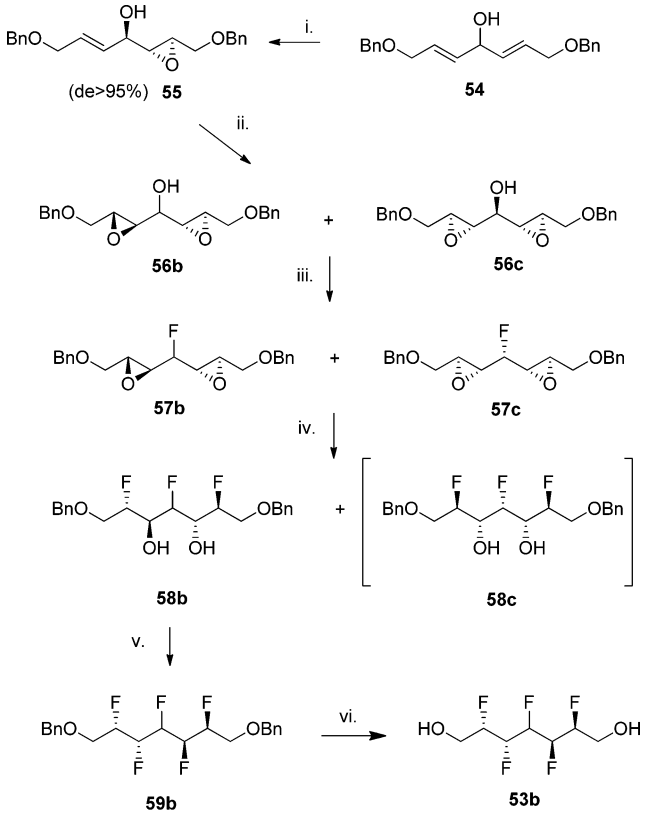
Scheme 11[a]

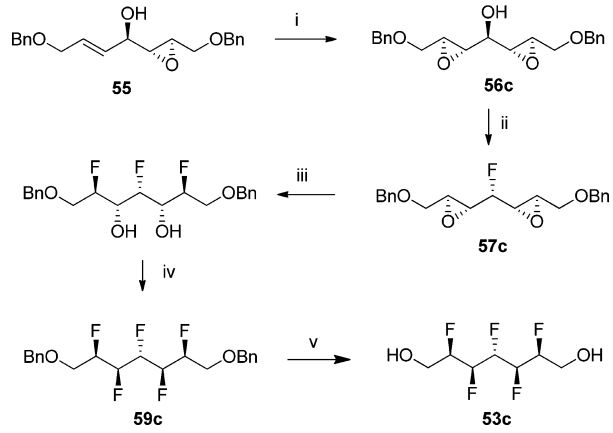


[a]Key: (i) *t*BuOOH, Ti(O*i*Pr)$_4$, D(−)DIPT, DCM, −20 °C, 70%; (ii) *m*-CPBA, DCM, 0 °C, 100%; (iii) Deoxo-Fluor, DCM, rt, 53%; (iv) $Et_3N{\cdot}3HF$, neat, 150 °C, overnight, sealed reactor, 23%; (v) Deoxo-Fluor, DCM, rt, 45%; (vi) H_2, Pd/C, MeOH, 100%.

by an *m*-CPBA epoxidation to generate diastereoisomeric products **56b** and **56c**. Fluorination of the central alcohol moiety, with an inversion of configuration, using Deoxo-Fluor, was achieved without any complication from the epoxides, which were robust enough to withstand ring-opening. This gave the fluorodiepoxide diastereoisomers **57b** and **57c**, which could be separated by chromatography. Double-epoxide ring-opening with $Et_3N{\cdot}3HF$, of the *anti* epoxide stereoisomer **57b**, generated the trifluorodiol **58b**, which was taken directly to the pentafluoro product **59b** by treatment with Deoxo-Fluor, in a double dehydroxyfluorination reaction, also with good stereointegrity, at both reaction centers. Hydrogenation of the peripheral benzyl ethers of **59b** then gave the desired petrafluorodiol **53b**. Diastereoisomers **53a** and **53c** were prepared in an analogous manner. However, in order to access these stereoisomers it proved more efficient to generate epoxide stereoisomer **56b** by Sharpless methodology for the second epoxidation, rather than by separation of diastereoisomeric mixtures from an *m*-CPBA reaction as outlined in Scheme 11. Accordingly, a Sharpless epoxidation, catalyzed by D-(+) DIPT, was carried out on allylic alcohol **55**. This sequence of two enantiomerically controlled epoxidations generated the *meso* diepoxide diol **56c**. Progress through the chemical steps as before and summarized in Scheme 12 generated a second stereoisomer **53c** of this series.

In order to generate the all *syn*-stereoisomer **53a**, it was anticipated that the route to **53c** could be manipulated but

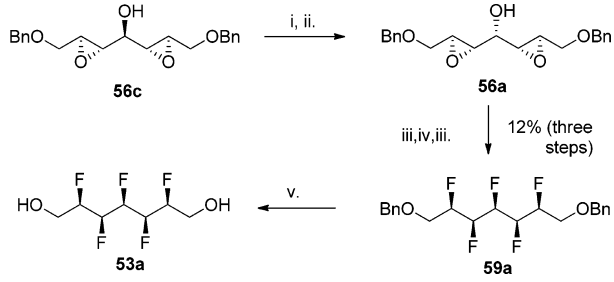
Scheme 12[a]



[a](i) *t*BuOOH, Ti(O*i*Pr)$_4$, L(+)DIPT, DCM, −20 °C, 85%; (ii), Deoxo-Fluor, DCM, rt, 77%; (iii) $Et_3N{\cdot}3HF$, neat, 150 °C, 16 h, sealed reactor, 42%; (iv) Deoxo-Fluor, THF, reflux, 45%; (v) H_2, Pd/C, MeOH, 100%.

with a necessary configurational inversion of the central alcohol moiety. This was achieved by carrying out a Mitsunobu inversion on the diepoxy alcohol **56c** as illustrated in Scheme 13 and then progressing through the

Scheme 13[a]



[a]Key: (i) DIPAD, PPh_3, *p*-$(NO_2)C_6H_4CO_2H$, toluene, −25 °C; (ii) K_2CO_3, MeOH, 78% over two steps; (iii) Deoxo-Fluor, DCM, rt; (iv) $Et_3N{\cdot}3HF$, neat, 150 °C, overnight, sealed reactor; (v) H_2, Pd/C, MeOH, 100%.

fluorination steps as previously described to give **53a**. Overall, the strategy proved relatively starightforward, and this series of pentafluoromethylene stereoisomers could be subjected to both solution- and solid-state conformational analysis by NMR and X-ray crystallography, respectively. Diol **53a** was the only diol of the three that was a liquid at room temperature, and despite persistant attempts we were unable to crystallize the ditosyl derivative of this *all-syn* stereoisomer. DFT calculations for the *all-syn* 2,3,4,5-tetrafluoroheptanes **60a** argue strongly against an extended *anti* zigzag structure, as there are four 1,3-dipolar repulsive interactions, and this is calculated to raise the energy of that conformer by 8.43 kcal mol^{-1} relative to the twisted/helical structure where all of the C−F bonds are *gauche* to each other. NMR analysis indicates the dominance of the helical structure for **60a** in solution (Figure 4). This helical arrangement for the *all-syn* isomers of these fluoromethylene structure motifs is

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most apparent in the next section where the *all-syn* hexafluoro motif is considered.

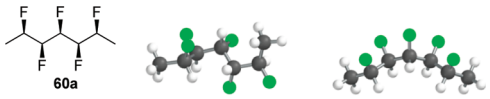
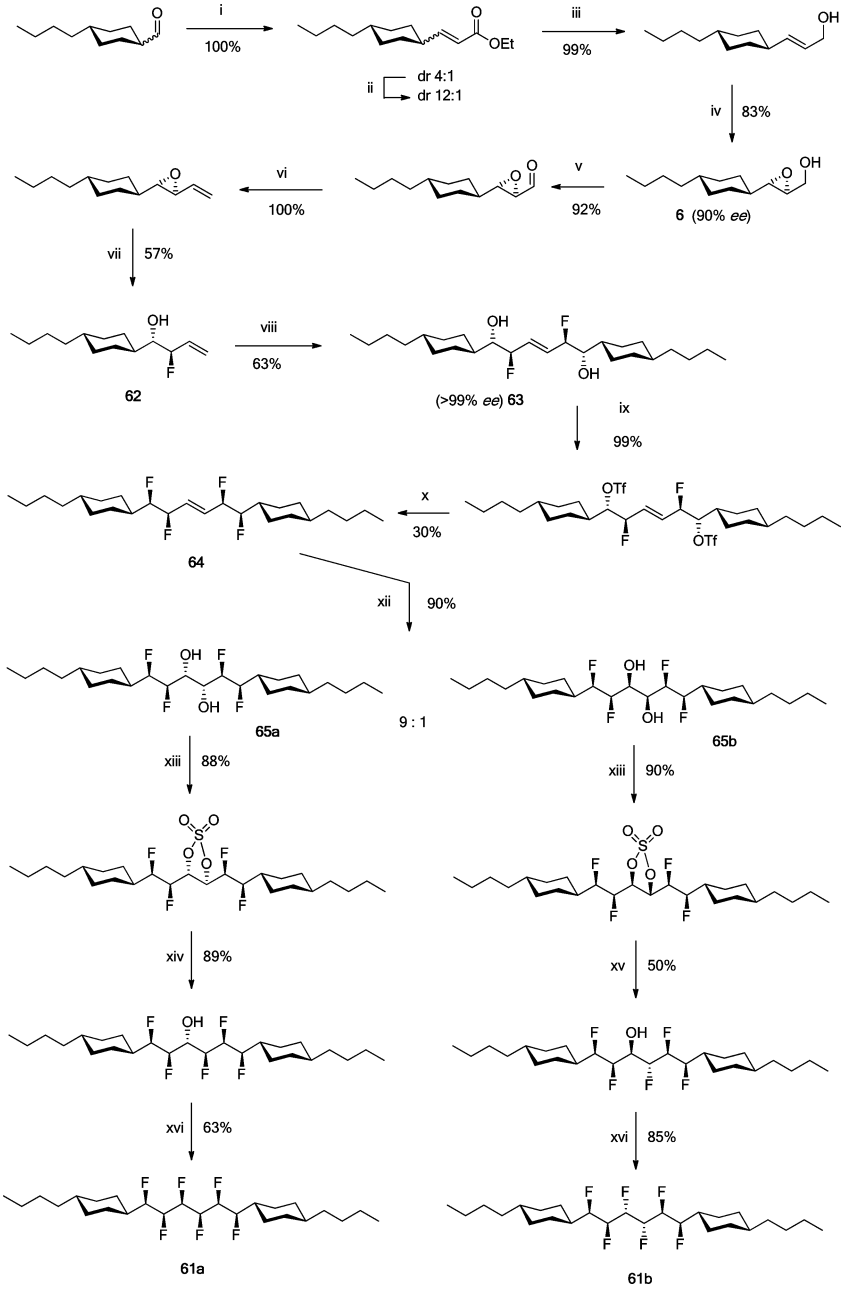


Figure 4. DFT calculated (B3LYP/6-31G(d)) minimum zero energy conformation (left) for heptane **60a** and the extended linear conformation (right).

SIX FLUORINES[28]

The most advanced motifs of the fluoromethylene series that we have prepared are the hexafluoro stereoisomers **61a** and **61b**. It was particularly attractive to prepare the *all-syn* stereoisomer **61a** to explore the influence of the stereochemistry on the helical nature of this motif, a feature that had been emerging from observations in the tetra- and penta-stereoisomers. The most significant interaction for inducing a helical conformation is 1,3-C−F dipolar repulsion, but stereoisomer **61b** avoids any such interactions in the extended

Scheme 14[a]



[a]Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, rt; (ii) KOH, EtOH, D; (iii) diisobutylaluminium hydride, CH_2Cl_2, hexane, −78 °C; (iv) Cumene hydroperoxide, diisopropyl (+)-tartrate, $Ti(O^iPr)_4$, molecular sieves, CH_2Cl_2, −35 °C; (v) Dess−Martin periodinane, CH_2Cl_2, rt; (vi) Ph_3PCH_2Br, potassium bis(trimethylsilyl)amide, THF, rt; (vii) $Et_3N{\cdot}3HF$, MeCN, 120 °C; (viii) Grubbs 2nd generation catalyst, CH_2Cl_2, D; (ix) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, rt; (x) $Et_3N{\cdot}3HF$, Et_3N, THF, 50 °C; (xi) H_2, Pd/C, EtOAc, rt; (xii) $KMnO_4$, $MgSO_4$, EtOH, CH_2Cl_2, H_2O, 0 °C; (xiii) $SOCl_2$, pyridine, CH_2Cl_2, rt; then $NaIO_4$, $RuCl_3$, MeCN, H_2O; (xiv) $Et_3N.3HF$, Et_3N, MeCN, 110 °C; then H_2SO_4, H_2O, THF, rt; (xv) $Et_3N{\cdot}3HF$, 120 °C; then H_2SO_4, H_2O, THF, rt; (xvi) bis(2-methoxyethylamino)sulfur trifluoride [Deoxo-Fluor], CH_2Cl_2.

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anti zigzag conformation. These two stereoisomers therefore offered the potential to explore just how predictive conformational preferences can be with the fluoromethylene motifs. At the outset, it was attractive to append a crystallizable motif to the periphery of the structures such that conformations could be explored both by NMR and X-ray crystallography. The butylcyclohexane motif was selected as such alkylcyclohexanes[29] have been used quite widely in liquid crystalline motifs and starting materials were available on scale. The synthetic route to the vicinal hexafluoro motifs is summarized in Scheme 14. The key step involved a self-metathesis reaction on the vinylfluorohydrin **62**, which generated exclusively the *E*-olefin **63**. A double dehydroxyfluorination of **63** proceeding by triflation and then fluoride displacement generated the tetrafluoro olefin **64** and provided an intermediate which was a branchpoint for preparation of the two diastereoisomers **61a** and **61b**. The double bond in **64** has reduced nucleophilicity as it is flanked by two C−F bonds and was resistant to AD-mix dihydroxylations and standard epoxidation methodologies; however, permanganate was sufficiently reactive to mediate dihydroxylation. This was a relatively efficient reaction and generated the diastereoisomeric diols **65a** and **65b** in a 4:1 ratio. Separation of these diastereoisomers by chromatography allowed each to progress independently to the target hexafluoro stereoisomers **61a** and **61b**, following cyclic sulfate methodology and dehydroxyfluorinations, as practiced for several of the preceding syntheses and as summarized in Scheme 14.

Both **61a** and **61b** proved to be nice crystalline solids, and they were each amenable to X-ray crystallography. The resultant structures are shown in Figure 5. It is immediately

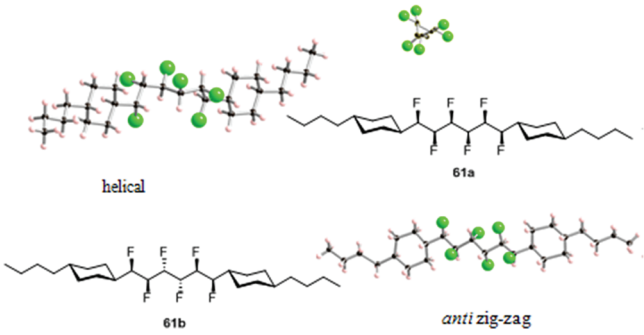

Figure 5. X-ray structures of vicinal hexafluorostereoisomers **61a** and **61b**. The *all-syn* isomer **61a** adopts a helical arrangement to avoid 1,3 repulsive C−F bond interactions, and as a result all of the vicinal C−F bonds lie approximately at 60° to each other. The upper inset highlights only the C−F bonds of **61a** looking along the molecular axis. Stereoisomer **61b** adopts an *anti* zigzag structure as there are no repulsive C−F bond interactions in this conformation.

obvious that the *all-syn* stereoisomer **61a** adopts a helical arrangement of C−F bonds along the carbon chain, with each adjacent C−F bond rotated by approximately 60° (*gauche*) to the next. By contrast for stereoisomer **61b**, the carbon chain adopts a classical *anti*zigzag conformation. This is most satisfactory as there are no 1,3-dipolar repulsions in this conformation. By contrast, if isomer **61a** were to adopt this conformation, then this would necessitate four 1,3-C−F dipolar repulsions, and thus, such a conformation is avoided. The ^{1}H and ^{19}F NMR spectra of the two stereoisomers were analyzed to obtain information on the solution conformations. The second-order spectra yielded $^{3}J_{HH}$ and $^{3}J_{HF}$ coupling constants which were related through Karplus-type curves to the corresponding H−C−C−H and H−C−C−F molecular dihedral angles.[30] In each case, the observed ^{3}J values were consistent with the solid-state conformations. For example, in stereoisomer **61a** the vicinal $^{3}J_{HH}$ coupling for HC(1)−C(2)H was measured at 0.6 Hz consistent with a *gauche* relationship between the hydrogens, whereas the value for HC(2)−C(3)H is 7.1 Hz, more consistent with an *anti* relationship between the hydrogens. Similar trends are observed for $^{3}J_{HF}$ vicinal coupling constants. Again for stereoisomer **61a** the $^{3}J_{HF}$ value for FC(1)−C(2)H is recorded at 29.7 Hz, a large value consistent with a *trans* relationship, and 14.0 Hz for FC(2)−C(3)H, which is consistent with a *gauche* relationship between C−H and C−F bonds. Moreover the $^{3}J_{HH}$ and $^{3}J_{HF}$ values were not noticeably affected by changes in temperature or solvent, suggesting that the observed solid-state conformations are also the significant ones in solution.

■ CONCLUSION

This Perspective has outlined the recent past activity of the research group in preparing alkane chains carrying adjacent fluoromethylene groups. The resultant multivicinal fluoroalkane motifs are collectively a previously unexplored class of organofluorine compounds. Synthetic strategies for introducting fluorine have involved epoxide or cyclic sulfate ring-opening with HF reagents or fluoride ion sources, or fluorodehydroxylation reactions, and for motifs containing more than three fluorines then single stereoisomers were prepared in each case. The individual stereoisomers of the same molecular series can display very different favored conformations, and it emerges that chains will orient to minimize 1,3-C−F···F−C dipolar repulsion as the dominant factor influencing the favored conformation. Most notably the *all-syn* isomers of multivicinal fluoroalkanes adopt a helical arrangement of the C−F bonds as they progress along the chain. Synthetic access to these structural motifs remains challenging, but if synthesis strategies can be improved, such as the recent developments which are emerging in epoxide ring-opening strategies[31] and reagent development in deoxyfluorinations,[32] then multivicinal fluoroalkanes emerge as attractive candidates as performance organic materials, as they have low viscosity but can have high orientated polarity. Such properties are attractive for liquid crystal display development and the linear helical compounds when placed under stress have the potential to uncoil with a concomitant increase in dipole moment, an attractive property for piezo- and pyroelectric materials. Work toward more efficient syntheses and applications of these materials is ongoing in our laboratory.

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Notes

The authors declare no competing financial interest.

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David O'Hagan is currently Professor of Organic Chemistry at the University of St. Andrews in Scotland, where he has research interests in organofluorine chemistry and biochemistry. He studied undergraduate chemistry at the University of Glasgow and did his Ph.D work at Southampton University. After a postdoctoral period with Heinz G. Floss at the Ohio State University, he took up his first academic position at the University of Durham in 1986. He moved to his current position at St. Andrews University in 2000.

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