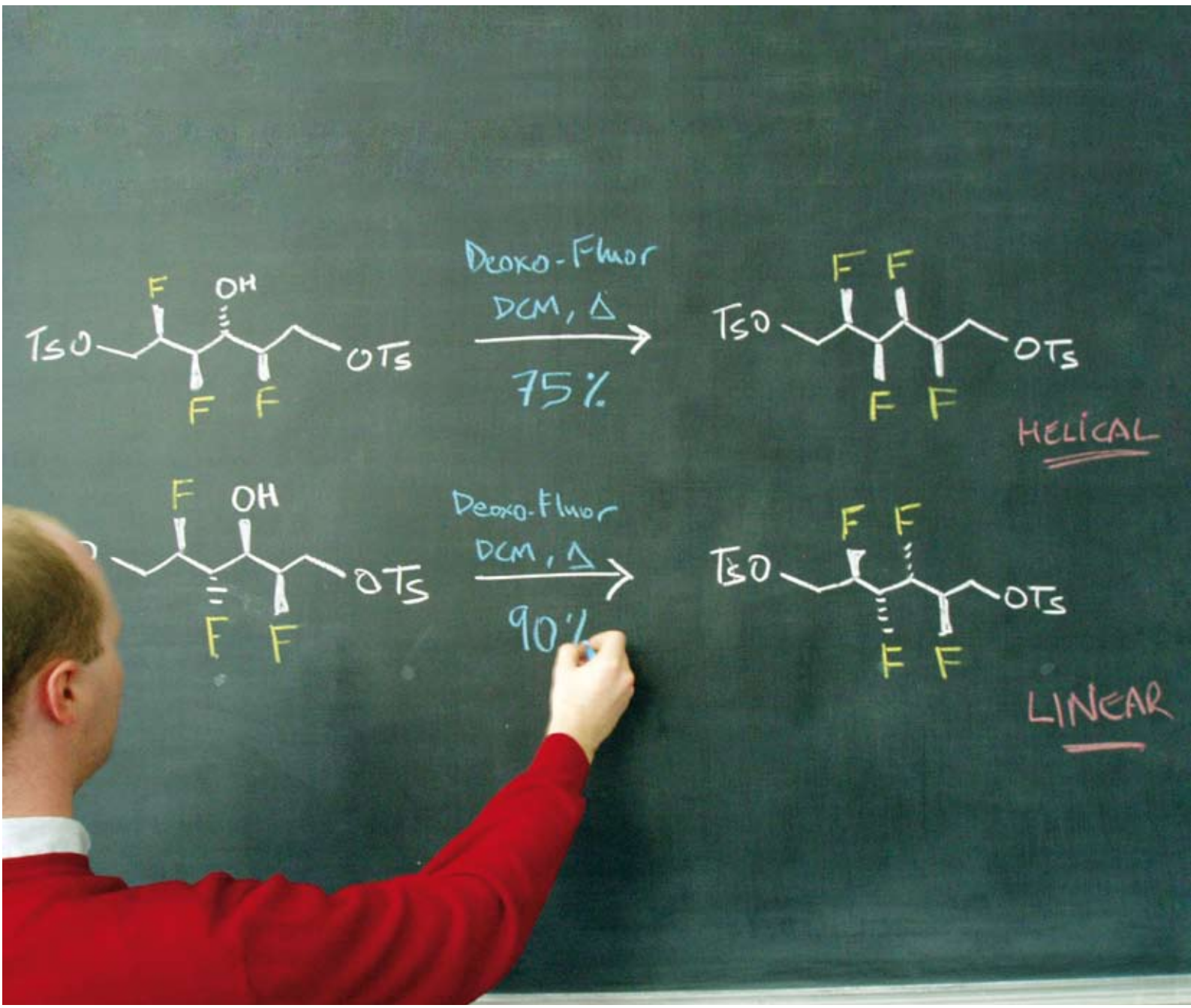
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 6 | Number 16 | 21 August 2008 | Pages 2829–3016



ISSN 1477-0520

RSC Publishing

EMERGING AREA

Luke Hunter and David O'Hagan
Multi-vicinal fluoroalkanes: a new class of organofluorine compounds

Chemical Science

In this issue...

1477-0520(2008)6:16;1-H

Multi-vicinal fluoroalkanes: a new class of organofluorine compounds

Luke Hunter and David O'Hagan*

Received 4th June 2008, Accepted 11th June 2008
First published as an Advance Article on the web 9th July 2008
DOI: 10.1039/b809432b

"Multi-vicinal fluoroalkanes" are straight-chain alkanes in which each adjacent carbon atom is bonded to one fluorine atom. Such molecules may be regarded as intermediate in structure between alkanes and perfluoroalkanes. The alternate fluoromethylene groups also generate stereogenic centres, which need to be controlled during synthesis. This review will describe our recent progress in the preparation of such single isomer motifs and the study of the conformational behaviour of this new class of organofluorine compounds.

Introduction

The fluorine atom is the most electronegative on the Pauling–Allred scale, and the incorporation of fluorine for hydrogen in organic compounds can have profound effects on the resultant physical and chemical properties.[1] This has led to fluorine's special status as an extreme element in, for example, medicinal chemistry, where single fluorine atoms are commonly used as a replacement for hydrogen in 'fluorine screens' during structure–activity relationship enhancements.[2] Selective fluorination has also led to the improved properties of materials such as organic liquid crystals.[3] At the other end of the spectrum, high levels of fluorination have enhanced the properties of materials where, for example, perfluoroalkanes have found applications as wide temperature range lubricants and surface coatings.[4]

Despite the numerous applications of fluorine in organic chemistry, there is a class of fluoro-organic compounds that has been hardly explored. "Multi-vicinal fluoroalkanes" (*e.g.* Fig. 1) are straight-chain alkanes in which each adjacent carbon atom is bonded to one fluorine atom. These compounds are conceptually intermediate between alkanes and perfluoroalkanes, but an important distinguishing feature of the multi-vicinal fluoroalkanes is the stereochemical complexity that they possess. Different diastereoisomers might be expected to exhibit different conformational behaviour and they potentially have a role in the development and optimisation of performance molecules such as liquid crystals or self-assembling monolayers.

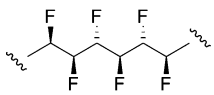


Fig. 1 A multi-vicinal fluoroalkane.

This review describes our recent progress in preparing specific structural motifs of this class of compound. Synthetic approaches, conformational studies and the first measurements of physical properties are presented.

Synthetic approaches

The synthesis of multi-vicinal fluoroalkanes presents a challenge of stereochemical control. Furthermore, the synthetic routes need to be flexible enough to provide access to different diastereoisomers, such that the properties of the stereoisomers can be compared.

Centre for Biomolecular Sciences and School of Chemistry, University of St Andrews, St Andrews, United Kingdom. E-mail: do1@st-andrews.ac.uk; Fax: +44 1334 463808; Tel: +44 1334 463800

Luke Hunter

Luke Hunter obtained his BSc (Hons) at the University of Sydney in 2000, and he completed a PhD at the same institution in 2004 under the supervision of Dr Craig Hutton. In 2005 he joined the laboratory of Professor David O'Hagan at the University of St Andrews. His research interests include the stereoselective synthesis of functional molecules such as bioactive natural products and fluorinated liquid crystals.

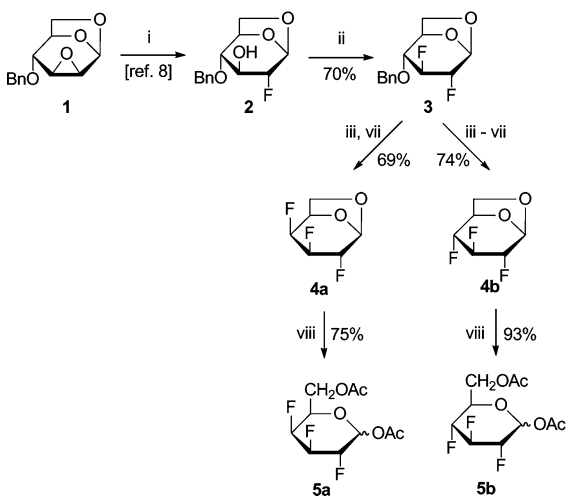
David O'Hagan

David O'Hagan studied chemistry at the University of Glasgow (1982). He moved to the University of Southampton to carry out a PhD (1985) with John A. Robinson, then spent a postdoctoral year at Ohio State University with Heinz G. Floss. In 1986 he was appointed to the University of Durham. In 2000 he moved to his current position at the University of St Andrews where he has broad interests in organofluorine chemistry.

There are several methods reported for the synthesis of vicinal difluoro motifs,[5,6] and so the next goal was to develop methodology for the synthesis of three and four vicinal fluorine motifs.

Three vicinal fluorines

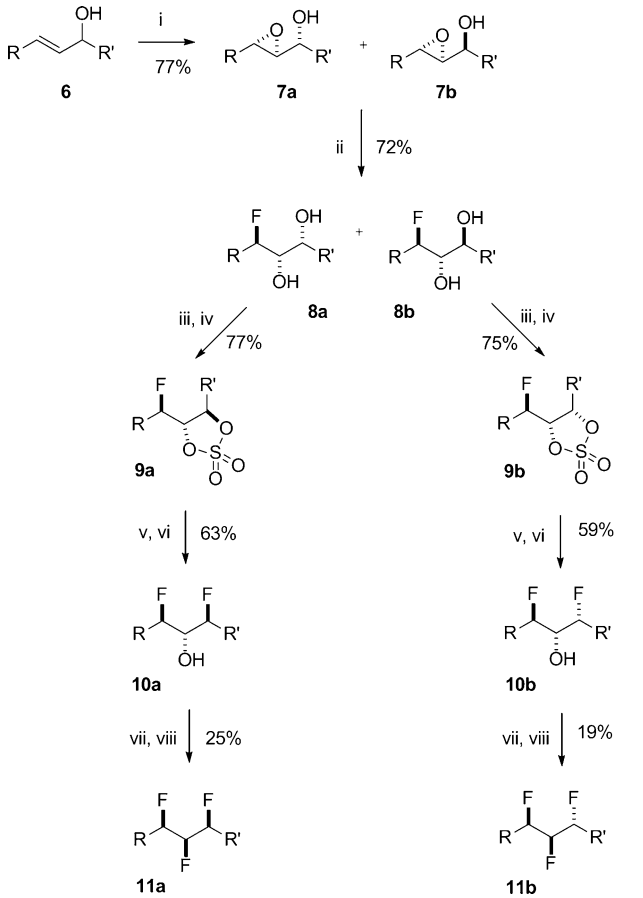
To our knowledge, the only previous example of the stereoselective synthesis of compounds containing more than two vicinal fluorines was reported by Sarda and co-workers.[7] They achieved the sequential substitution of three hydroxyl groups by fluorine to prepare the di-acetate derivatives of glucose and galactose (Scheme 1).



Scheme 1 Synthetic route to trifluoro deoxysugar analogues.[7] (i) KHF_2, $(HOCH_2)_2$, Δ; (ii) diethylaminosulfur trifluoride [DAST], PhMe, Δ; (iii) H_2, Pd/C, EtOAc, r.t.; (iv) Tf_2O, pyridine, DCM, r.t.; (v) $PhCO_2Na$, DMF, 80 °C; (vi) NaOMe, MeOH, r.t.; (vii) DAST, DCM, Δ; (viii) Ac_2O, H_2SO_4, r.t.

Moving forward from these early results[7] (Scheme 1), we aimed to develop more flexible methods that could be adapted to access different diastereoisomeric series and longer runs of vicinal fluorines within a variety of molecular architectures.

Our initial synthetic route to vicinal trifluoro isomers is illustrated in Scheme 2.[9] The racemic allylic alcohol **6** was treated with *m*CPBA to give a 2 : 1 mixture of epoxy alcohols **7a** and **7b**. These compounds were then ring-opened in what emerged to be a highly stereoselective manner, by treatment with HF·pyridine, giving the separable fluoro diols **8a** and **8b**. The fluoro diol **8a** was then converted to the corresponding cyclic sulfate **9a** under Sharpless conditions,[10] and **9a** was then ring-opened with TBAF in another highly stereo- and regio-selective reaction, giving the difluoro alcohol **10a**. The final hydroxyl group was then activated as its triflate, and displacement with TBAF then afforded the vicinal trifluoro stereoisomer **11a**. This substitution reaction was always plagued by elimination side-reactions, hence the modest yield in this final step. Nevertheless, the methodology was robust enough to provide both stereoisomers **11a** and **11b** (the latter *via* fluoro diol **8b**). Although in this case the products were obtained in racemic form, an enantioselective option was also demonstrated by initiating the synthetic route with a Sharpless asymmetric epoxidation/kinetic resolution.

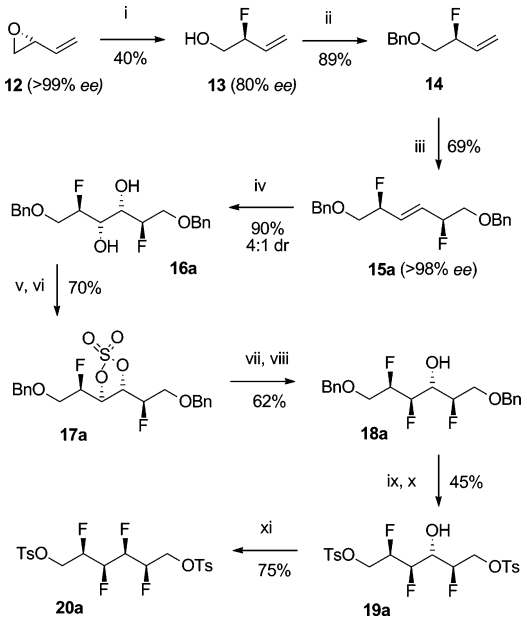


Scheme 2 New synthetic route to vicinal trifluoro compounds.[9] R = C_7H_{15}; R′ = $C_5H_{10}Ph$; (i) *m*CPBA, DCM, 0 °C; (ii) HF·pyridine, DCM, 10 °C; (iii) $SOCl_2$, pyridine, DCM, 0 °C; (iv) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C; (v) TBAF, acetone, 0 °C; (vi) H_2SO_4, Et_2O, r.t.; (vii) Tf_2O, pyridine, DCM, −40 °C; (viii) TBAF, MeCN, 0 °C.

Four vicinal fluorines

The synthesis of a four vicinal fluorine motif was next addressed. It was important to develop an enantioselective route that could be adapted to afford different tetrafluoro diastereoisomers and a more efficient method of installing the final fluorine atom was needed. Also, it was desirable to produce the tetrafluoro motif in a format which would allow its subsequent incorporation into larger molecular architectures. The chosen synthetic route is illustrated in Scheme 3.[11]

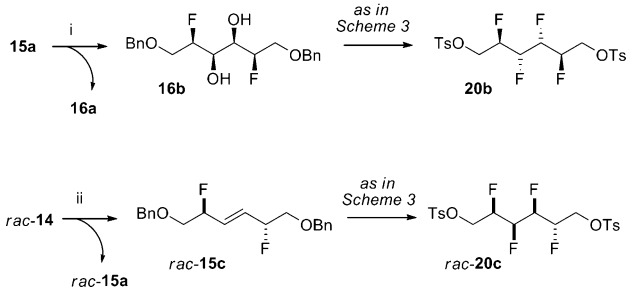
The synthesis began with the enantiopure epoxide **12**, which is readily accessed *via* hydrolytic kinetic resolution of the racemate.[12] Nucleophilic ring-opening[13] of **12** with $Et_3N{\cdot}3HF$ gave predominantly the desired 2-fluoro product **13**, but in reduced optical purity (80% ee). The fluoroalcohol **13** was then protected as a benzyl ether, and the ether was subjected to a symmetrical cross-metathesis reaction using the Grubbs second generation catalyst.[14] Notably, the symmetry of this reaction provided a satisfactory solution to the earlier loss of enantiopurity, because the major (*syn*) product **15a** could be separated from the minor (*anti*) product by silica gel chromatography, giving **15a** in >98% ee. The resultant difluoroalkene **15a** was then treated with potassium permanganate to give the difluorodiol **16a** as a separable 4 : 1 diastereoisomeric mixture. The major difluorodiol stereoisomer



Scheme 3 Synthetic route to vicinal tetrafluoro compounds.[11] (i) $Et_3N{\cdot}3HF$, Na_2SO_4, 70 °C; (ii) BnBr, NaH, DMF, 40 °C; (iii) Grubbs second generation catalyst, DCM, Δ; (iv) $KMnO_4$, $MgSO_4$, EtOH, H_2O, DCM, −10 °C; (v) $SOCl_2$, pyridine, DCM, 0 °C; (vi) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C; (vii) TBAF, MeCN, r.t.; (viii) H_2SO_4, H_2O, THF, r.t.; (ix) H_2, Pd/C, MeOH, r.t.; (x) TsCl, 2,4,6-collidine, 50 °C; (xi) bis(2-methoxyethyl)aminosulfur trifluoride [Deoxo-Fluor™], 70 °C.

16a was then converted to the corresponding cyclic sulfate **17a**, and was then subjected to ring-opening with TBAF to provide the trifluoroalcohol **18a**. Unfortunately, the final fluorine atom could not be installed at this stage because the desired substitution of the hydroxyl group was out-competed by undesired elimination or rearrangement reactions under a variety of conditions. However, this problem was circumvented by switching the protecting groups from benzyl ethers to tosyl esters prior to the final fluorination reaction. The conversion to tosyl esters was also advantageous in generating crystalline products suitable for X-ray structure analysis. Thus, the ditosylate **19a** could be treated with Deoxo-Fluor™ to successfully provide the tetrafluoro target **20a** in good yield.

It was also possible to adapt this method to the synthesis of two other tetrafluoro diastereoisomers **20b** and **20c**[15] (Scheme 4).



Scheme 4 Synthesis of other tetrafluoro diastereoisomers.[15] (i) $KMnO_4$, $MgSO_4$, EtOH, H_2O, DCM, −10 °C; (ii) Grubbs second generation catalyst, DCM, Δ.

Conformational behaviour

Having established synthetic routes to compounds containing two, three and four vicinal fluorine motifs, the conformational behaviour of these compounds was explored. They provide sufficiently short motifs to investigate the fundamental conformational relationships between the 1,2- and 1,3-fluorines. In particular, it was interesting to compare the preferred conformations of diastereoisomeric compounds within the same structural series.

The fluorine *gauche* effect[16] is clearly expected to impact on 1,2-fluorine relationships,[17] an effect which has already been shown to significantly influence the conformation of diastereoisomeric 9,10-difluorostearic acids[18] and difluoro pseudopeptides[6] (Fig. 2). *Erythro* and *threo* 9,10-difluorostearic acids **21** have very different physical properties: for example, the melting point of **21a** is *ca.* 20 degrees higher than that of **21b**.[18] In the case of *threo*-**21a**, the chain prefers an extended zig-zag confomation, because in that conformation, the fluorines are *gauche* with respect to each other. In *erythro*-**21b**, however, when the chain is extended, the fluorines are *anti*, and the two preferences compete, resulting in conformational disorder and a lowering of the melting point. In the case of the peptidic compounds **22**,[6] both solid and solution state analyses indicate that the backbone conformations are very different, accommodating the fluorine *gauche* preference for each diastereoisomer.

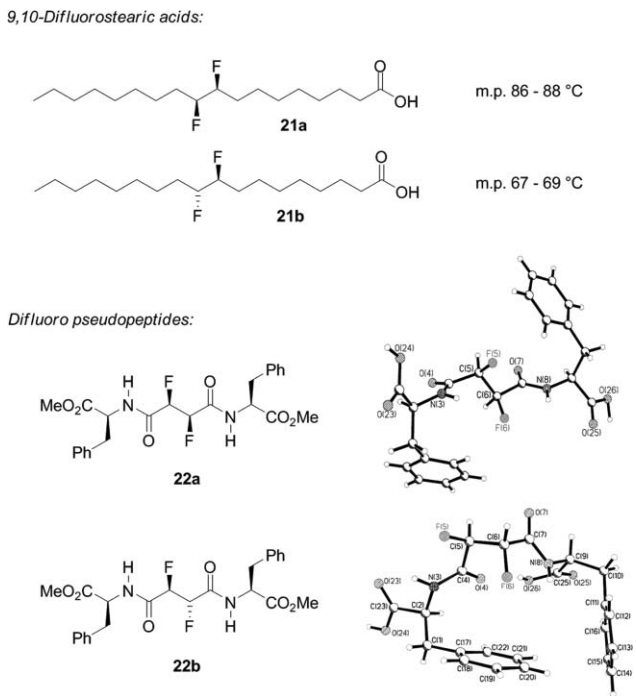


Fig. 2 The fluorine *gauche* effect influences the conformation of 1,2-difluoro compounds **21** and **22**.

When studying compounds with three and four vicinal fluorines, a new effect emerges in addition to the fluorine *gauche* effect. This is revealed most obviously in the all-*syn* trifluoro stereoisomer **11a** (Fig. 3). If this compound adopts a linear conformation, then the two "outside" C–F bonds are constrained to align parallel to one another. However, this arrangement is energetically unfavourable because the parallel C–F dipoles repel each other, incurring

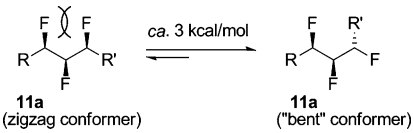


Fig. 3 The all-*syn* trifluoro compound **11a** prefers a "bent" conformation, which avoids any 1,3-F · · · F repulsion.

an energy penalty of *ca.* 3 kcal mol^{-1}.[19] A more favourable conformation is obtained by rotating one C–C bond such that the molecule avoids the 1,3-F · · · F repulsion but still orientates each pair of vicinal fluorines *gauche* to each other. This 1,3-repulsion is also predicted in the calculated preferred conformations of 1,3-difluoropropane[19] and *cis*-1,3-difluorocyclohexane,[20] arising presumably as a combination of dipole and lone pair repulsion.

This 1,3-F · · · F repulsion is demonstrated in studies of novel fluorinated liquid crystal molecules (Fig. 4),[21] which were synthesised by adapting the methodology presented in Scheme 2. In the case of the difluoro liquid crystal **23**, the fluoroalkyl tail prefers the extended zig-zag conformation shown, consistent with a fluorine *gauche* effect. Both fluorine atoms are positioned on the same face of the molecule and as a result, compound **23** has a substantial molecular dipole moment perpendicular to the long axis of the molecule, and this is reflected in the negative value of the observed dielectric anisotropy of this compound. In the case of the all-*syn* trifluoro liquid crystal **24** (Fig. 4), this molecule has a lower negative dielectric anisotropy than predicted, indicating a lower dipole, inconsistent with an extended zig-zag conformation. Compound **24** cannot adopt the extended zig-zag conformation because it incurs 1,3-F · · · F repulsion. Instead, the carbon chain is forced to adopt a "bent" conformation. The three fluorines are not presented to the same face and a lower than anticipated dielectric anisotropy value is observed.

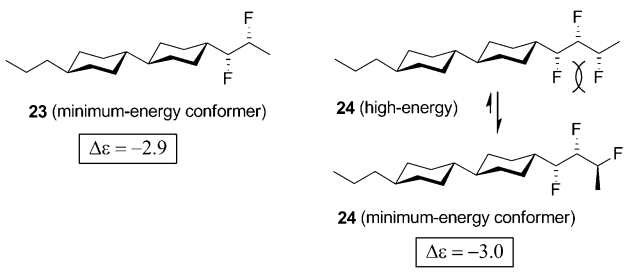


Fig. 4 Comparing the liquid crystal properties of **23** and **24** illustrates the importance of 1,3-F · · · F repulsion.[21]

It emerges that avoidance of 1,3-F · · · F repulsion is the dominant force influencing the preferred conformation of these vicinal trifluoro compounds. The same effect dictates the conformational behaviour of the tetrafluoro stereoisomers **20a**, **20b** and **20c** (Schemes 3 and 4).[15] They all have different carbon chain backbone conformations. Due to the presence of the tosylate groups, each of compounds **20a–c** is crystalline, and each solid-state structure was elucidated by X-ray crystallography (Fig. 5). The all-*syn* isomer **20a** adopts a "bent" conformation in which each pair of vicinal C–F bonds is aligned *gauche*, and no 1,3-F · · · F repulsions are present. This conformation places the fluorine atoms in a helical arrangement about the carbon backbone. In contrast, the *anti–syn–anti* isomer **20b** adopts a linear conformation in the

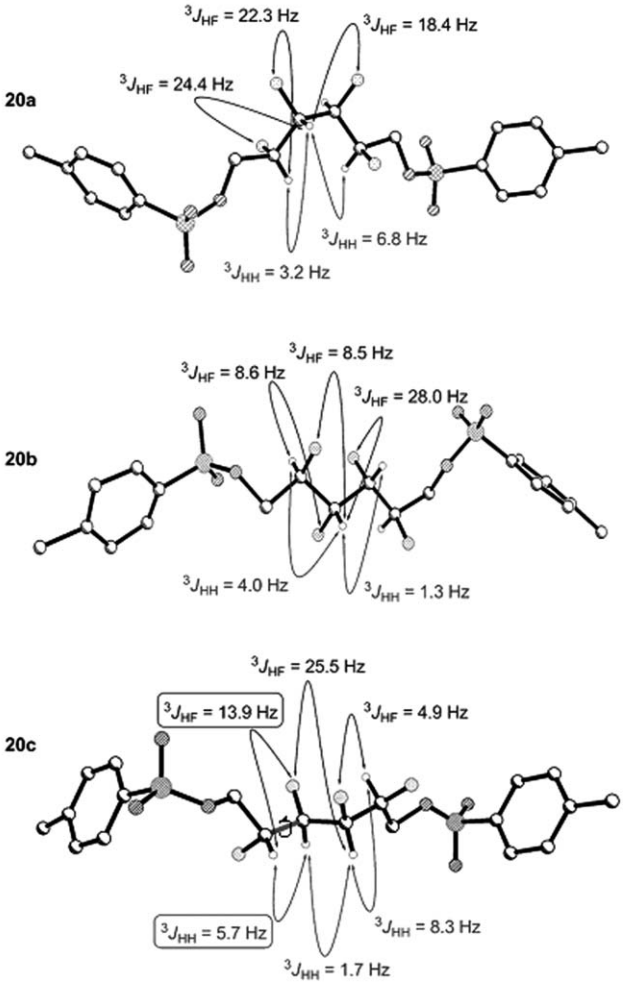


Fig. 5 Crystal structures of **20a–c**.[15] Selected coupling constants from the corresponding ^{1}H NMR spectra ($CDCl_3$) are superimposed on the structures; values that suggest differences between the solid- and solution-state conformations are highlighted in boxes. The solution conformation of **20c** is obtained by rotating the highlighted C–C bond through ~120°.

solid state, which precludes two of the possible three fluorine *gauche* alignments. Finally, the *syn–syn–anti* isomer **20c** adopts a conformation in which each pair of vicinal fluorines is aligned approximately *gauche*, but with dihedral angles, which vary considerably from the ideal value of 60°.

The observed solid-state conformation of **20c** (Fig. 5) is somewhat unexpected, since it entails a 1,3-F · · · CH_2 repulsion. This implies that the fluoroalkyl chain of **20c** is being forced into a strained conformation by the crystal packing forces, which are dominated by the tosyl groups rather than the fluoroalkyl portion of the molecule. It became important to investigate the solution-state conformations of **20a–c** in order to examine the intrinsic conformational preferences of the fluoroalkyl chains themselves. To that end, the ^{1}H- and ^{19}F-NMR spectra of **20a–c** were analysed, providing maps of $^3J_{HH}$ and $^3J_{HF}$ values (Fig. 5), which could be related *via* Karplus curves to the corresponding molecular dihedral angles.[22] This analysis revealed that for both **20a** and **20b**, the solid-state conformations are also preferred in solution. However, for isomer **20c**, the solution conformation is different from the solid-state structure: in solution, **20c** undergoes one C–C bond rotation

resulting in the loss of one fluorine *gauche* alignment to avoid the 1,3-F $\cdots$ CH_2 repulsion.

For each of the isomers **20a–c** (Fig. 5), the NMR studies were validated by molecular modelling experiments.[15] Calculations at the MP2/6-311+G(2d,p) level of theory confirmed that the observed solution structures of **20a–c** corresponded to the minimum-energy conformation of each fluoroalkyl chain. Furthermore, using molecular modelling, it was also possible to investigate more extended fluoroalkyl systems. For example, the all-*syn* compound **25** (Fig. 6) containing 12 vicinal fluorines was built *in silico.*[15] When forced into an extended zig-zag conformation, compound **25** adopts a very strained conformation that suffers from multiple 1,3-F $\cdots$ F repulsions, a conformation which is unrealistic in the solution or solid state. In contrast, when the molecule is allowed to relax to its minimum-energy structure, a helical conformation results in which all 1,3-repulsions are avoided whilst *gauche* alignments between each pair of vicinal C–F bonds are maintained. This helix has a pitch of *ca.* 5.9 Å and requires six fluoromethylene units for one complete turn.

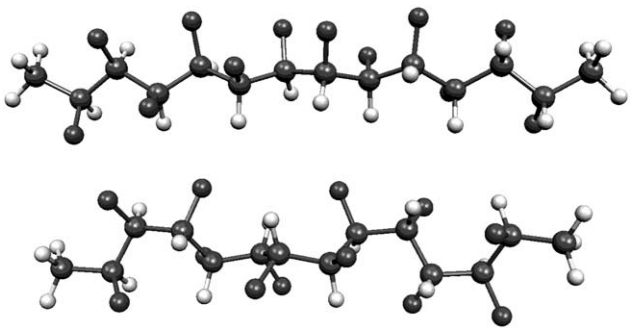


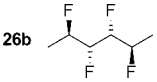
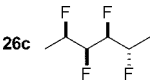
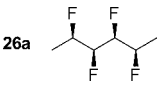
Fig. 6 The model system all-*syn* $CH_3(CHF)_{12}CH_3$ **25** with its strained zig-zag conformation (top) and the helical minimum-energy conformation (bottom).[15]

Physical properties

Even the most basic physical properties of multi-vicinal fluoroalkanes have remained unexplored until recently. The fluoroalkanes described in this review thus far are not suitable for investigating physical parameters such as boiling point, polarity, hydrophobicity and solubility, because these molecules contain functional groups that mask the intrinsic physical properties of the fluoroalkyl chains themselves. Therefore, the preparation of multi-vicinal fluoroalkanes in the absence of other functional groups emerged as an objective.

As an initial contribution in this area, the tetrafluorohexane compounds **26a–c** (Table 1) were investigated.[23] Hexanes **26a–c** were prepared by treating the ditosylates **20a–c** (Schemes 3 and 4) with excess $LiAlH_4$. It is noteworthy that these reductions did not yield any obvious side-products and the fluoroalkyl groups are surprisingly robust under the forcing reaction conditions employed. Tetrafluorohexanes **26a–c** were examined by GC-MS and compared with reference standards of hexane and perfluorohexane (Table 1). This analysis revealed that all three of the fluoroalkanes **26a–c** were more polar, eluting later than the reference compounds, consistent with higher molecular dipole moments due to the polarised C–F bonds.

Table 1 GC-MS data for tetrafluorohexanes **26a–c**[23]

Compound	Dipole (D)[a]	Retention time/min
Perfluorohexane	0.09	10.2
Hexane	0.00	14.8
26b 	0.25	17.6
26c 	3.54	18.9
26a 	2.19	19.4

[a] Dipole moment calculated for the minimum-energy conformer.

Furthermore, and perhaps unexpectedly, significant differences in retention time are also observed within the series **26a–c** (Table 1), indicating that the physical properties of the different diastereoisomers can vary markedly despite their identical connectivities and constitutions. The relative GC elution order of **26a–c** seems to correlate approximately with the molecular dipole moment calculated for each minimum-energy conformer, but this interpretation is complicated since conformational mobility causes the dipole moments of **26a–c** to fluctuate.

Conclusions

In this review, we have described some recent progress in the study of multi-vicinal fluoroalkanes, a hitherto unexplored class of organofluorine compounds. Synthetic access to a variety of molecules containing three and four vicinal fluorines has been established, and the conformational behaviour of these compounds has been investigated using NMR, X-ray crystallography and molecular modelling. It emerges that avoidance of 1,3-F $\cdots$ F and 1,3-F $\cdots$ CH_2 repulsive interactions are the dominant drivers dictating the preferred conformation of multi-vicinal fluoroalkanes, with the fluorine *gauche* effect exerting a more subtle conformational influence. Finally, some initial exploration of the physical properties of multi-vicinal fluoroalkanes relative to hydrocarbons and perfluoroalkanes has also been presented.

In the future, it will be valuable to further develop the synthetic methods described here, so that longer runs of multi-vicinal fluorine diastereoisomers within a variety of functional molecular architectures (*e.g.* liquid crystals and fluorosugar analogues) can be accessed. Work towards these goals is currently underway in our laboratory.

Acknowledgements

The authors would like to thank Dr Marcello Nicoletti and Dr Martin Schueler, past members of the research group at St Andrews who made valuable early contributions to this research, and Dr Peer Kirsch and Dr Matthias Bremmer at Merck Liquid Crystals who have taken a close interest in these studies. We also acknowledge EPSRC for funding.

References

1 P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, Germany, 2004; R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, UK, 2004.
2 K. Mueller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.
3 M. Hird, *Chem. Soc. Rev.*, 2007, **36**, 2070; P. Kirsch, A. Hahn, R. Fröhlich and G. Haufe, *Eur. J. Org. Chem.*, 2006, 4819.
4 G. G. Hougham, P. E. Cassidy, K. Johns and T. Davidson, *Fluoropolymers: Synthesis and Properties*, Kluwer Academic, Norwell, MA, USA, 1999.
5 R. F. Merritt, *J. Am. Chem. Soc.*, 1967, **89**, 609; T. Chia, N. C. Yang and C. L. Chernick, *J. Am. Chem. Soc.*, 1964, **86**, 5021; A. I. Burmakov, L. A. Motnyak, B. V. Kunshenko, L. A. Alexeeva and L. M. Yagupolskii, *J. Fluorine Chem.*, 1981, **19**, 151; M. Hudlicky, *J. Fluorine Chem.*, 1983, **23**, 241; R. P. Singh and J. M. Shreeve, *J. Fluorine Chem.*, 2002, **116**, 23; G. S. Lal, G. P. Pez, R. J. Pesari and F. M. Prozonic, *Chem. Commun.*, 1999, 215; G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic and H. S. Cheng, *J. Org. Chem.*, 1999, **64**, 7048; B. Hulin, S. Cabal, M. G. Lopaze, M. A. Van Volkenburg, K. M. Andrews and J. C. Parker, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4770; C. G. Caldwell, P. Chen, J. He, R. E. Parmee, B. Leiting, F. Marsilio, R. A. Patel, J. K. Wu, G. J. Eiermann, A. Petrov, H. He, K. A. Lyons, N. A. Thornberry and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1265; G. S. Lal, E. Labach and A. Evans, *J. Org. Chem.*, 2000, **65**, 4830; G. Olah, *J. Org. Chem.*, 1979, **44**, 3872; S. Rozen, *J. Org. Chem.*, 1986, **51**, 3607; M. Hudlicky, *J. Fluorine Chem.*, 1983, **23**, 241.
6 D. O'Hagan, H. S. Rzepa, M. Schüler and A. M. Z. Slawin, *Beilstein J. Org. Chem.*, 2006, **2**, 19.
7 P. Sarda, F. C. Escribano, R. J. Alves, A. Olesker and G. Lukacs, *J. Carbohydr. Chem.*, 1989, **8**, 115.
8 J. Pacák, Z. Točík and M. Cerný, *J. Chem. Soc. D*, 1969, 77.
9 M. Nicoletti, D. O'Hagan and A. M. Z. Slawin, *J. Am. Chem. Soc.*, 2005, **127**, 482.
10 Y. Gao and K. B. J. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538.
11 L. Hunter, D. O'Hagan and A. M. Z. Slawin, *J. Am. Chem. Soc.*, 2006, **128**, 16422.
12 S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. J. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.
13 A. Hedhli and A. J. Baklouti, *J. Fluorine Chem.*, 1995, **70**, 141.
14 A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. J. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.
15 L. Hunter, A. M. Z. Slawin, P. Kirsch and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2007, **46**, 7887.
16 N. C. Craig, A. Chen, K. H. Suh, S. Klee, G. C. Mellau, B. P. Winnewisser and M. Winnewisser, *J. Am. Chem. Soc.*, 1997, **119**, 4789.
17 T. Hamatani, S. Matsubara, H. Matsuda and M. Schlosser, *Tetrahedron*, 1988, **44**, 2875.
18 M. Tavasli, D. O'Hagan, C. Pearson and M. C. Petty, *Chem. Commun.*, 2002, 1226.
19 D. Wu, A. Tian and H. Sun, *J. Phys. Chem. A*, 1998, **102**, 9901.
20 V. G. S. Box and L. L. Box, *J. Mol. Struct.*, 2003, **649**, 117.
21 M. Nicoletti, M. Bremer, P. Kirsch and D. O'Hagan, *Chem. Commun.*, 2007, 5075.
22 A. M. Ihrig and S. L. Smith, *J. Am. Chem. Soc.*, 1970, **92**, 759; C. Thibaudeau, J. Plavec and J. Chattopadhyaya, *J. Org. Chem.*, 1998, **63**, 4967.
23 L. Hunter, P. Kirsch, J. D. Hamilton and D. O'Hagan, *Org. Biomol. Chem.*, 2008, DOI: 10.1039/B807449f.