Molecular Conformation

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Synthesis and Structure of Stereoisomeric Multivicinal Hexafluoroalkanes**

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The properties and functions of organic molecules can be critically influenced by their molecular conformation. New strategies which can influence conformation in a predictable manner are therefore likely to be important for a variety of applications. An emerging strategy for exerting conformational control involves the incorporation of fluorine atoms into the organic framework in a rational and selective manner. Selective fluorination has been a well-known and important strategy in performance organic molecules for many years, with fluorinated compounds finding use in a wide range of applications from materials science[1] to medicine.[2] However, selective fluorination which is specifically used as a tool for conformational control has been exploited only recently, with notable advances in the conformational control of peptides.[3] Organic bound fluorine has an atomic radius between those of hydrogen and oxygen so there is only a minor steric perturbation on replacing fluorine for hydrogen in an alkane.[4] However the C–F bond is polar with a relatively large dipole,[4] and thus it experiences electrostatic interactions with neighboring functional groups including other C–F bonds.[5] It is interesting to consider constructing molecules containing several vicinal fluorine atoms (Figure 1) to study the accumulating interplay between the C–F bonds and how that relates to conformational outcomes.[6] We have been exploring methods for the preparation of such multivicinal fluoroalkanes, and have prepared stereoisomers of compounds containing two,[7] three,[8] and four[9,10] vicinal fluorine atoms, and we have compared their conformations.[6] It emerges that the conformational behavior of these molecules is governed by two "preferences" (Figure 1). The first is the avoidance of conformations which cause 1,3-C–F bonds to align parallel to one another, which is due to an

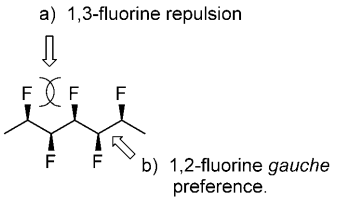
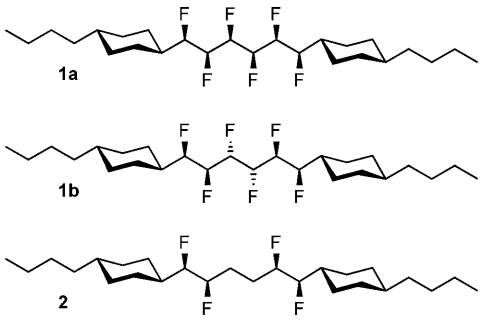


Figure 1. Multivicinal fluoroalkane conformation is governed by a) the avoidance of 1,3-fluorine repulsion and b) the 1,2-fluorine *gauche* effect.

electrostatic repulsion (ca. 3 kcal mol^{-1}).[11,12] The second and weaker preference is the fluorine *gauche* effect,[13] which recognizes the energetic preference (ca. 0.8 kcal mol^{-1}) for vicinal C–F bonds to align *gauche* rather than *anti* to each other.

Having developed an understanding of the conformational behavior of short vicinal fluorine motifs,[6–10] our current research goal is to develop methods for the synthesis of more extended systems and to investigate whether their conformations can be accurately predicted by the preferences described above. The molecular targets **1a**, **1b**, and **2** were thus identified as synthetic objectives for this study. It was



anticipated that the all-*syn* hexafluoroalkane **1a** would adopt a conformation in which all vicinal fluorine atoms are aligned *gauche* with a helical progression of C–F bonds along the carbon backbone.[10] The expected helical conformation of **1a** avoids the 1,3-fluorine repulsion, which would be occasioned by a zigzag conformation. In contrast, the diastereoisomeric target **1b** was expected to exhibit dramatically different conformational behavior. The stereochemical pattern of **1b** should allow it to adopt the zigzag conformation without incurring any 1,3-fluorine repulsion (although the zigzag structure would only partially satisfy the preference for 1,2-fluorine *gauche* alignments). The structurally related tetra-

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fluoroalkane **2** was also expected to prefer the zigzag conformation, as this conformation would deliver the maximum number of 1,2-fluorine *gauche* alignments while the insulating central ethyl linker would preclude any 1,3-fluorine repulsion. Thus, a comparison of the systems **1a**, **1b**, and **2** should reveal the importance of such stereoelectronic interactions. The butanecyclohexyl rings at the periphery of the target molecules were chosen for their ability to impart liquid crystallinity and to aid structural analysis.

A divergent strategy was envisaged for the synthesis of **1a**, **1b**, and **2**, starting from the common precursor **3** (Scheme 1).[14] A Horner–Wadsworth–Emmons reaction of aldehyde **3** with triethyl phosphonoacetate gave α,β-unsaturated ester **4**, and subsequent reduction with diisobutylaluminum hydride generated the allylic alcohol **5**. Alcohol **5** underwent a Sharpless–Katsuki asymmetric epoxidation reaction[15] and furnished the epoxide **6** with 90% *ee*. Oxidation gave the corresponding aldehyde **7**, which underwent a Wittig reaction with methyltriphenylphosphonium bromide to generate allylic epoxide **8**. Epoxide **8** underwent ring opening with triethylamine trihydrofluoride to introduce the first fluorine substituent. Although this reaction required somewhat forcing conditions, the ring-opened product **9** was recovered in satisfactory yield with the desired S_N2 product predominating over potential S_N2' and S_N1 products. Fluorohydrin **9** (90% *ee*) was subjected to a symmetrical cross-metathesis reaction using the second-generation Grubbs catalyst,[16] and generated difluorodiol **10** as a single diastereoisomer (>99% *ee*) after flash chromatography on silica gel. The *E* geometry of alkene **10** was confirmed by X-ray crystallography.[17,18] Both hydroxy groups of **10** were then activated as their corresponding triflates to generate **11**, and double displacement with a fluoride ion gave the tetrafluoroalkene **12** in modest yield, along with various elimination side-products. Despite this, the overall reaction sequence to this point was robust and scalable enough to furnish several grams of the intermediate **12**, which served as a pivotal precursor for diastereoisomers **1a** and **1b** as well as the tetrafluoroalkane **2**: a product of the direct hydrogenation of **12**.

Dihydroxylation of **12** with potassium permanganate furnished the separable diols **13a** and **13b** in a 9:1 diastereoisomeric ratio (Scheme 1).[19] Diols **13a** and **13b** were then progressed through to their respective cyclic sulfates **14a** and **14b**,[20] which were ring-opened with triethylamine trihydrofluoride and gave **15a** and **15b**, respectively. The final fluorine atoms were installed using the Deoxo-Fluor reagent[21] to successfully furnish the hexafluoroalkanes **1a** and **1b** as air-stable, white, crystalline solids.

Crystals of **1a**, **1b**, and **2** were subject to X-ray crystallographic analysis (Figure 2).[17,18] The structure of **1a** does indeed have a helical arrangement of the C–F bonds along the carbon backbone. This arrangement is most obviously appreciated by looking at the arrangement of the C–F bonds along the molecular axis (Figure 2, inset). The six C–F bonds almost complete a full pitch of the helix, falling short by a 40° angle between the first and last bonds. In clear contrast, diastereoisomer **1b** adopts the expected zigzag conformation (Figure 2), in which 1,3-fluorine repulsion is avoided and three out of a possible five fluorine *gauche* alignments are achieved. A similar zigzag conformation emerges for the tetrafluoroalkane **2** (Figure 2), although in this case a slight twist about the long axis of the molecule is observed, presumably as a consequence of dipole relaxation or possibly because of crystal packing forces. The vicinal fluorine atoms of **2** are *gauche* and with the insulating ethyl linkage in place there is no possibility of 1,3-fluorine repulsion.

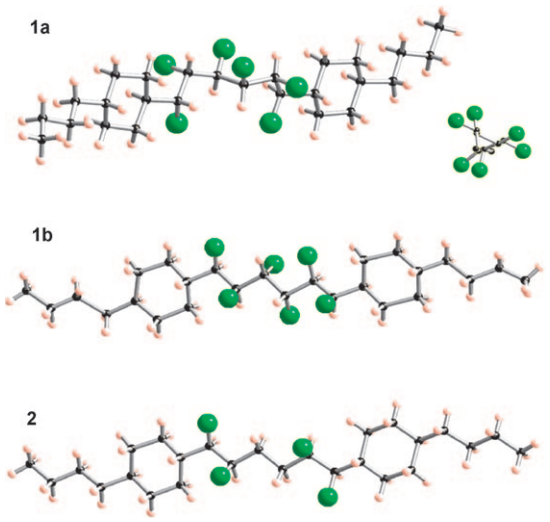
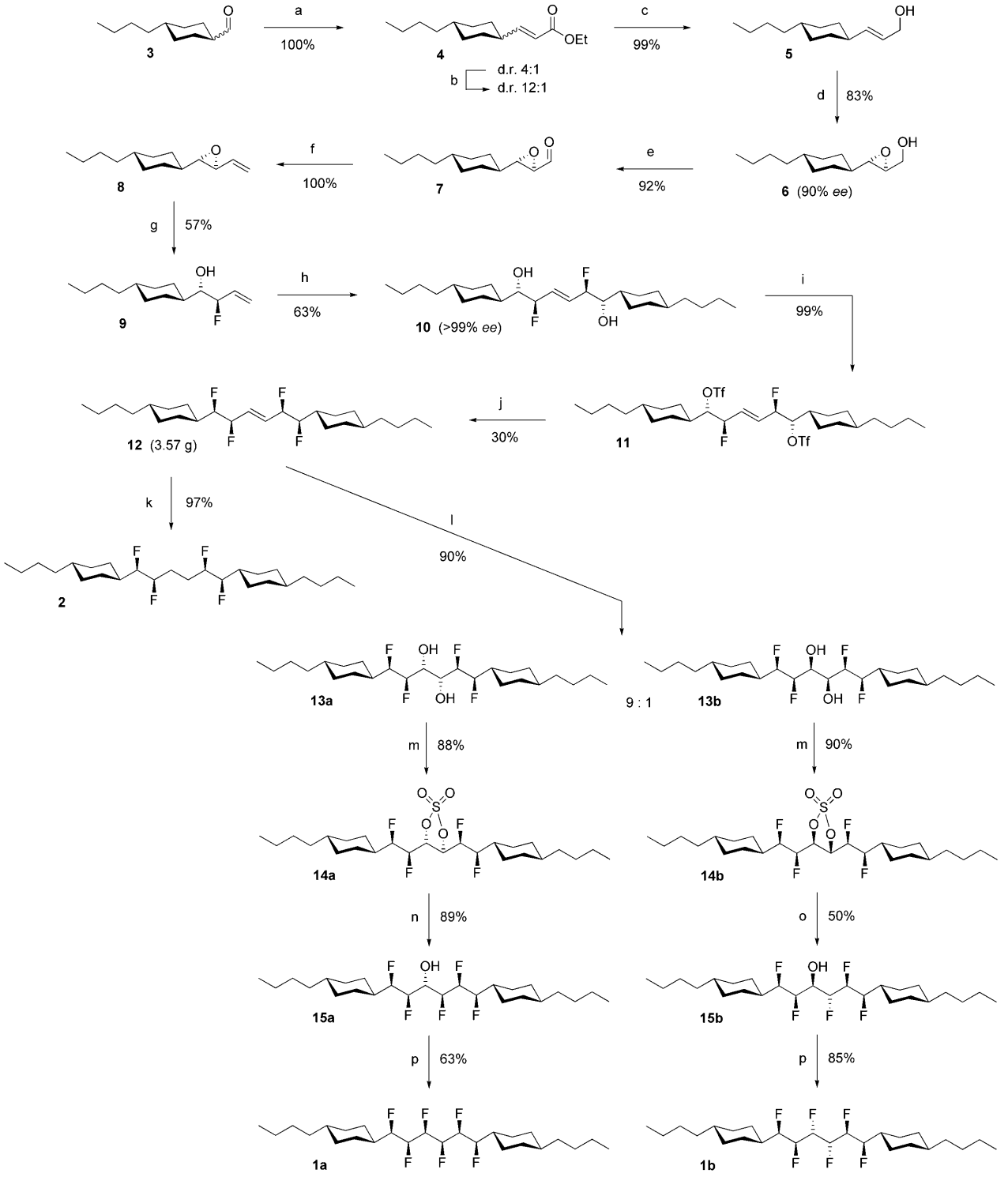


Figure 2. X-ray crystal structures of **1a**, **1b**, and **2**. Structure **1a** (top) has vicinal C–F bonds aligned *gauche* to each other to form a helical pattern as they progress along the carbon backbone (inset: the fluoroalkyl portion of **1a** viewed along the molecular axis). Structure **1b** (middle) shows the carbon backbone in a zigzag conformation with no 1,3-fluorine repulsion. Structure **2** (bottom) shows the carbon backbone in a zigzag conformation but with a slight twist, possibly compensating for a large dipole moment.

The ^1H and ^{19}F NMR spectra of **1a**, **1b**, and **2** were analyzed to obtain information on their conformations in solution. The spectra gave $^3J_{HH}$ and $^3J_{HF}$ coupling constants which were related through Karplus-type curves to the corresponding H-C-C-H and H-C-C-F molecular dihedral angles.[22] In each case (**1a**, **1b**, and **2**) all of the observed ^3J values were consistent with the solid-state conformations.[17] Moreover the $^3J_{HH}$ and $^3J_{HF}$ values of **1a**, **1b**, and **2** were not noticeably affected by changes in temperature or solvent.[17] The NMR spectroscopy results indicate that the solid-state conformations of **1a**, **1b**, and **2** (Figure 2) are intrinsically preferred by each fluoroalkyl chain, with no evidence of any artifacts from competing crystal packing forces.

These findings are reinforced with molecular modeling data obtained from truncated octane models of **1a**, **1b**, and **2**.[17] In the case of the hexafluoroalkanes **1a** and **1b**, the molecular modeling data is unequivocal: at the MP2/6-311+G(2d,p)//B3LYP/6-31G(d) +ZPE level of theory,[23] the helical and zigzag structures clearly emerge as the lowest energy conformers of **1a** and **1b**, respectively. For compound **2**, the linear zigzag conformation is the lowest in energy although there are several other conformers close in energy to this minimum.[17] This finding suggests that the zigzag structure of **2** is somewhat destabilized by a high dipole



Scheme 1. Synthesis of **1a**, **1b**, and **2**. Reagents and conditions: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, RT; b) KOH, EtOH, Δ; c) Diisobutylaluminum hydride, CH_2Cl_2, hexanes or *n*-hexane, −78 °C; d) cumene hydroperoxide, diisopropyl (+)-tartrate, $Ti(OiPr)_4$, molecular sieves (4 Å), CH_2Cl_2, −35 °C; e) Dess–Martin periodinane, CH_2Cl_2, RT; f) Ph_3PCH_2Br, potassium bis(trimethylsilyl)amide, tetrahydrofuran, RT; g) $Et_3N{\cdot}3HF$, MeCN, 120 °C; h) second-generation Grubbs catalyst, CH_2Cl_2, Δ; i) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, RT; j) $Et_3N{\cdot}3HF$, Et_3N, tetrahydrofuran, 50 °C; k) H_2, Pd/C, EtOAc, RT; l) $KMnO_4$, $MgSO_4$, EtOH, CH_2Cl_2, H_2O, 0 °C; m) $SOCl_2$, pyridine, CH_2Cl_2, RT; then $NaIO_4$, $RuCl_3$, MeCN, H_2O; n) $Et_3N{\cdot}3HF$, Et_3N, MeCN, 110 °C; then H_2SO_4, H_2O, tetrahydrofuran, RT; o) $Et_3N{\cdot}3HF$, 120 °C; then H_2SO_4, H_2O, tetrahydrofuran, RT; p) $(MeOCH_2CH_2)_2NSF_3$ (Deoxo-Fluor), CH_2Cl_2, Δ. Tf = trifluoromethanesulfonyl.

moment caused by the positioning of all four fluorine atoms on the same face of the molecule.

In summary, we have described the synthesis of hexafluoroalkanes **1a** and **1b**, which so far contain the longest runs of vicinal fluorine atoms prepared in a controlled stereoselective manner. The related tetrafluoroalkane **2** is also described. The conformational behavior of **1a**, **1b**, and **2** is consistent with two stereochemical preferences: parallel 1,3-C–F bonds are avoided, and *gauche* 1,2-C–F bonds are favored. These preferences explain why runs of all-*syn* contiguous fluorine atoms (e.g. **1a**) induce a helical arrangement of the C–F bonds, whereas in contrast, the *syn-anti-syn-anti-syn* contiguous fluorine pattern (e.g. **1b**) induces a zigzag conformation. Having developed the synthetic methods and established the conformational predictability of these fluoroalkane systems, the foundation is now laid for the future design of performance organic molecules based on this motif. To that end, we are currently investigating the various molecular architectures of molecules including fluorinated liquid crystals and deoxofluorosugar analogues, and the results of these studies will be reported in due course.

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[1] P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.
[2] a) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886.
[3] a) J. A. Hodges, R. T. Raines, *J. Am. Chem. Soc.* **2005**, *127*, 15923 – 15932; b) R. I. Mathad, B. Jaun, O. Flögel, J. Gardiner, M. Löweneck, J. D. C. Codée, P. H. Seeberger, D. Seebach, M. K. Edmonds, F. H. M. Graichen, A. D. Abell, *Helv. Chim. Acta* **2007**, *90*, 2251 – 2273.
[4] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319.
[5] N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. T. Tozer, R. J. Young, *Angew. Chem.* **2007**, *119*, 6008 – 6012; *Angew. Chem. Int. Ed.* **2007**, *46*, 5904 – 5908.
[6] L. Hunter, D. O'Hagan, *Org. Biomol. Chem.* **2008**, *6*, 2843 – 2848.
[7] a) M. Schüler, D. O'Hagan, A. M. Z. Slawin, *Chem. Commun.* **2005**, 4324 – 4326; b) M. Tavasli, D. O'Hagan, C. Pearson, M. C. Petty, *Chem. Commun.* **2002**, 1226 – 1227.
[8] a) M. Nicoletti, D. O'Hagan, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2005**, *127*, 482 – 483; b) M. Nicoletti, M. Bremer, P. Kirsch, D. O'Hagan, *Chem. Commun.* **2007**, 5075 – 5077.
[9] a) L. Hunter, D. O'Hagan, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2006**, *128*, 16422 – 16423; b) L. Hunter, P. Kirsch, J. T. G. Hamilton, D. O'Hagan, *Org. Biomol. Chem.* **2008**, *6*, 3105 – 3108.
[10] L. Hunter, A. M. Z. Slawin, P. Kirsch, D. O'Hagan, *Angew. Chem.* **2007**, *119*, 8033 – 8036; *Angew. Chem. Int. Ed.* **2007**, *46*, 7887 – 7890.
[11] D. Wu, A. Tian, H. Sun, *J. Phys. Chem. A* **1998**, *102*, 9901 – 9905.
[12] A similar steric repulsion occurs if a C–F bond is aligned parallel to a C–C bond in the β position.
[13] L. Goodman, H. Gu, V. Pophristic, *J. Phys. Chem. A* **2005**, *109*, 1223 – 1229.
[14] M. E. Neubert, S. A. Keast, J. M. Kim, K. J. Miller, R. M. Murray, A. G. Norton, R. A. Shenoy, M. E. Walsh, R. G. Petschek, *Liq. Cryst.* **2004**, *31*, 175 – 184.
[15] Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780.
[16] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18 – 29.
[17] See the Supporting Information.
[18] CDCC 721047 (**1a**), 721048 (**1b**), 721049 (**2**), and 721050 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[19] The selectivity of this reaction was substrate-controlled; subsequent efforts to modify the product ratio by using the Sharpless asymmetric dihydroxylation protocol were thwarted by this strong substrate bias.
[20] Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538 – 7539.
[21] G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, *Chem. Commun.* **1999**, 215 – 216.
[22] C. Thibaudeau, J. Plavec, J. Chattopadhyaya, *J. Org. Chem.* **1998**, *63*, 4967 – 4984.
[23] Gaussian 03 (Revision D.01): M. J. Frisch et al., Gaussian, Inc., Wallingford, CT, **2004**.

