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Diastereoselective Synthesis of 2,3,4,5,6-Pentafluoroheptanes

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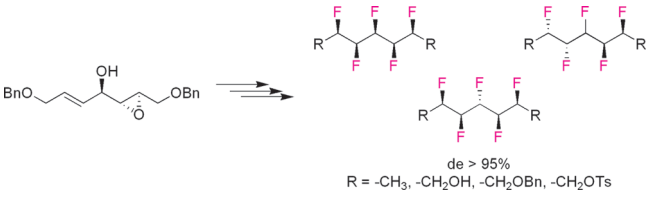

A stereocontrolled synthesis of alkanes containing five contiguous fluorine atoms is presented. The compounds were prepared by sequential fluorination of diastereoisomeric alcohol-diepoxides. The chemistry involved epoxide ring-opening with $HF \cdot NEt_3$ and deshydroxyfluorination reactions of free alcohols with Deoxo-Fluor. The fluorination reactions were all highly stereospecific, with all five fluorines being incorporated in three sequential steps. Three different diastereoisomers of the 2,3,4,5,6-pentafluoroheptyl motif were prepared as heptane-1,7-diol derivatives, a structural format amenable for incorporation of the vicinal pentafluoro scaffold into larger molecular architectures.

The introduction of fluorine atoms can have a significant influence on the physical and chemical behavior of organic molecules and as a consequence the strategy is widely used in optimizing structure activity relationships in medicinal[1−3] and agrochemicals[4] development as well as in organic materials.[5] Fluorine is often regarded as an isostere of hydrogen; however, its high electronegativity induces stereoelectronic and electrostatic consequences when such a change is made.[6] The incorporation of fluorine has therefore emerged as an important tool in the design for example of performance materials such as liquid crystals.[7] Current challenges exist in placing fluorine at a stereogenic center, rather than the incorporation of fluoroaryl and CF_3 groups, and rapid progress is being made.[8,9] Our focus has been to investigate strategies for the synthesis of molecules containing fluorine atoms at adjacent stereogenic centers and this has led to the study of a new class of multivicinal fluoroalkanes, which consist of sequential fluoromethylene (CHF) groups.[10] This structural motif is intermediate in structure between alkanes and perfluoroalkanes. Stereocontrolled syntheses of such motifs require the controlled introduction of the C−F bonds and we have recently reported the preparation of different diastereoisomers of tetra- and hexafluoro compounds such as **1** and **2** (Figure 1).[11−14]

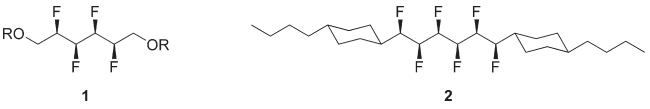

FIGURE 1. Tetra- and hexavicinal fluorine motifs. The *all-syn* isomers only are illustrated.

It emerged from these studies that individual stereoisomers display very different conformational behavior. In this Note we report the stereoselective synthesis of three unique diastereoisomers **3a**−**c** of 2,3,4,5,6-pentafluoroheptane-1,7-diol (Figure 2). These diols represent novel building blocks and have the potential to allow the incorporation of this pentafluoro motif in larger molecular architectures.

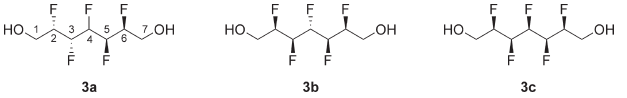

FIGURE 2. Pentafluoroalkane diastereoisomers.

To access diastereoisomers **3a**−**c** a synthesis was developed that incorporated stereochemical flexibility. Starting from propargyl alcohol **4**, the key allylic epoxide **7** was prepared in an enantioselective manner by using a protocol of Schreiber and Trost (Scheme 1).[15−17] A subsequent epoxidation was carried out with *m*CPBA to provide a mixture of

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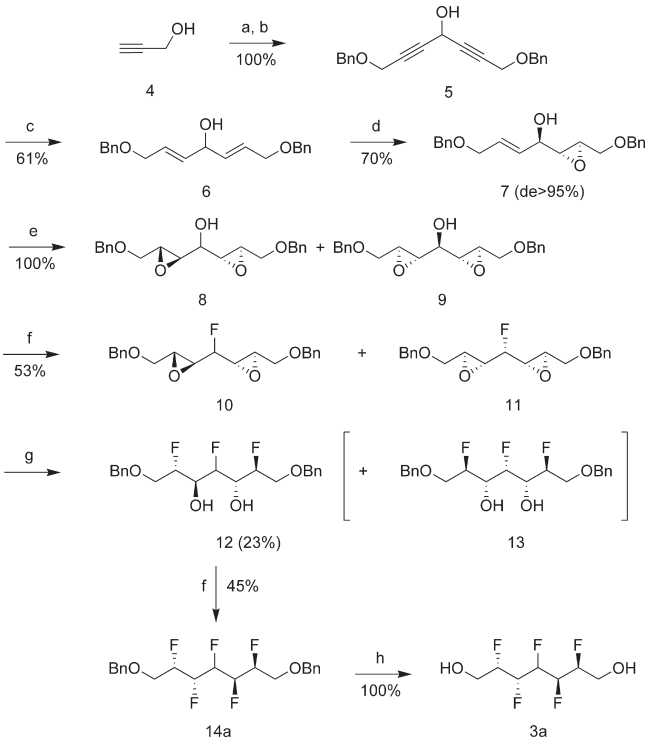
SCHEME 1. Synthesis of the Five Vicinal Fluorine Motif 3a[a]

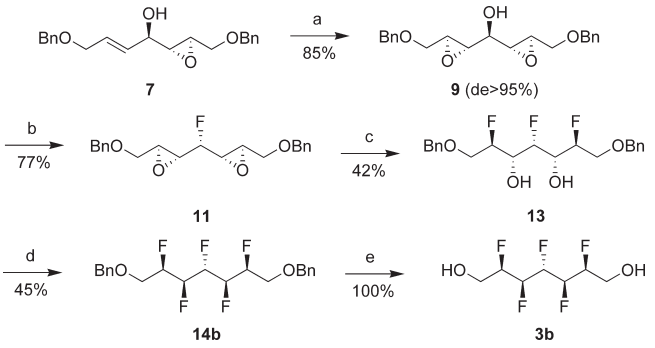


[a]Reagents and conditions: (a) NaH, BnBr, DMF; (b) *n*BuLi, THF, −78 °C, EtOCHO; (c) Red-Al, THF, −40 °C; (d) *t*BuOOH, Ti(O*i*Pr)$_4$, D(−)DIPT, DCM, −20 °C; (e) *m*CPBA, DCM, 0 °C; (f) Deoxo-Fluor, DCM, rt; (g) $Et_3N\cdot 3HF$, neat, 150 °C, overnight, sealed reactor; (h) H_2, Pd/C, MeOH.

the two diastereoisomers **8** and **9**. This mixture was treated with Deoxo-Fluor ($(MeOCH_2CH_2)_2NSF_3$). converting the free alcohol to fluorine, in the presence of the epoxides, and generating **10** and **11** in a 68:32 diastereoisomeric ratio. Treatment then with $Et_3N\cdot 3HF$, under forcing conditions, allowed two additional fluorines to be introduced in one step, despite a modest yield. Nucleophilic ring-opening of the epoxides occurs exclusively away from the central fluorine. Diastereoisomers **12** and **13** could be easily separated by chromatography. Fluorine substitutions of the two remaining hydroxyl groups of **12** generated **14a** in a moderate yield, although advantageously two fluorines were installed in this step. Finally hydrogenolysis of the peripheral benzyl ethers furnished diol **3a**. Although this synthesis suffers from some modest yields, it is emphasized that the five fluorine atoms were incorporated in a stereospecific manner in three successive steps, to give a stereochemically pure product **14a**.

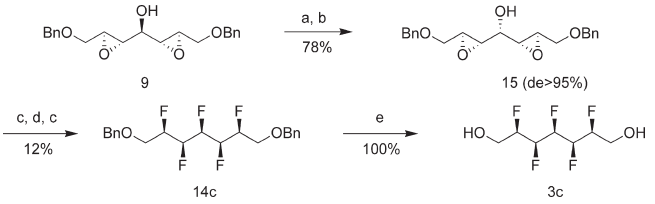
The synthesis of diastereoisomer **3b** was achieved as illustrated in Scheme 2. A Sharpless epoxidation enabled conversion of **7** to the *meso* diepoxide **9**, as a single stereoisomer.[18] Then, the previous reaction sequence [(i) dehydroxyfluorination; (ii) epoxide opening; (iii) didehydroxyfluorination; (iv) hydrogenation] allowed completion of the synthesis of **3b**. However, intermediate **13** was more resistant than **12** in the difluorination reaction and mild heating was required for successful substitution to generate **14b**. This gave rise to some

SCHEME 2. Synthesis of Five Vicinal Fluorine Motif 3b[a]



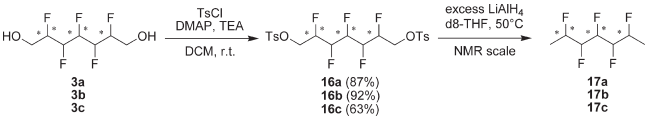
[a]Reagents and conditions: (a) *t*BuOOH, Ti(O*i*Pr)$_4$, L(+)DIPT, DCM, −20 °C; (b) Deoxo-Fluor, DCM, rt; (c) $Et_3N\cdot 3HF$, neat, 150 °C, overnight, sealed reactor; (d) Deoxo-Fluor, THF, reflux; (e) H_2, Pd/C, MeOH.

SCHEME 3. Synthesis of Five Vicinal Fluorine Motif 3c[a]



[a]Reagents and conditions: (a) DIPAD, PPh_3, *p*-$(NO_2)C_6H_4CO_2H$, toluene, −25 °C; (b) K_2CO_3, MeOH; (c) Deoxo-Fluor, DCM, rt; (d) $Et_3N\cdot 3HF$, neat, 150 °C, overnight, sealed reactor; (e) H_2, Pd/C, MeOH.

SCHEME 4. Synthesis of Ditosylates 16 and Pentafluoroheptanes 17



elimination side products, although these could be removed by chromatography.

Execution of the synthesis of the *all-syn* diastereoisomer **3c** required a configurational inversion of the central hydroxyl group of diepoxide alcohol **9** (Scheme 3). A Mitsunobu reaction was successfully employed to achieve this generating isomer **15** in good yield.[19] The *all-syn* pentafluoro isomer **3c** was then prepared following the synthesis protocols described for **3a** and **3b**.

With the diastereoisomers of the pentadiols **3a**−**c** in hand, each was converted to its corresponding ditosylate **16a**−**c**, to generate activated intermediates for further functionalization. It was also attractive to use these ditosylates to prepare the parent pentafluoroheptane alkanes. Thus the individual ditosylates **16a**−**c** were then treated with $LiAlH_4$ to achieve a smooth conversion to the individual 2,3,4,5,6-pentafluoroheptanes **17a**−**c** (Scheme 4). These heptanes are volatile and were prepared at an anylatical level in deuterated solvents, such that they could be analyzed directly by NMR.

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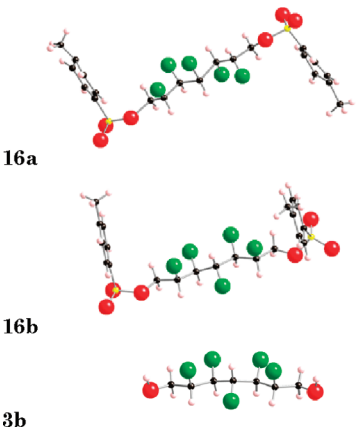

FIGURE 3. Crystal structures of **16a**, **16b**, and **3b**.

Ditosyls **16a** and **16b** and the diol **3b** were crystallized and a suitable crystal of each was used for X-ray structure analysis as shown in Figure 3. The structures confirm the relative configuration of each stereoisomer, consistent with configurational inversions during each C−F bond formation. The structure of the ditosylate **16a** indicates that the molecule adopts an extended zigzag chain conformation resulting in two sets of *gauche* C−F relationships at C2/C3 and C5/C6. The central C(4)−F bond adopts one *gauche* and one *anti* relationship relative to each of its vicinal C−F bonds. This conformation is close (1.56 kcal mol^{-1} above) to the energy minimum of the parent heptane as determined by DFT calculations at the B3LYP/6-31G(d) level of theory.[20] The calculated structures are illustrated in Figure 4, where the extended structure is presumably more compatible with unit cell packing.

A comparison of the structures of **3b** and **16b**, the diol and ditosylate of the same diastereoisomeric series, shows that they also adopt extended zigzag main chain conformations in the solid state with two pairs of *gauche* C−F bonds at C2/C3 and C5/C6. The central fluorine on C4 orients *anti* to each of its vicinal fluorines and there is perhaps unexpectedly a 1,3 F···F interaction between the C−F bond on C3 and C5. This is anticipated to be a repulsive interaction due to dipole alignment. Computational analyses of the corresponding pentafluoroheptane **17b** revealed a more twisted structure as the global minimum in the gas phase (Figure 4); however, the observed extended conformation revealed in the X-ray structures of **3b** and **16b** (Figure 3) is calculated to be only 1.4 kcal mol^{-1} higher in energy and again this latter conformation is presumably adopted in the solid state, due to its symmetry, and its relatively low energy.

The *all-syn* diol **3c** is the only diol of the three that is a liquid at room temperature and despite considerable effort we were unable to obtain a suitable crystal of the corresponding ditosyl derivative **16c**, which in our hands remained an amorphous solid. The extended zigzag conformer of the parent heptane **c** is now calculated to be 8.43 kcal mol^{-1} higher in energy than the minimum (Figure 4), and is clearly a strained structure with fluorine−fluorine repulsion, so the extended ditosyl structure **16c** is unlikely to be amenable to crystallization unlike **16a** and **16b**. The calculated minimum energy conformer of **17c** has all of the fluorine atoms *gauche*

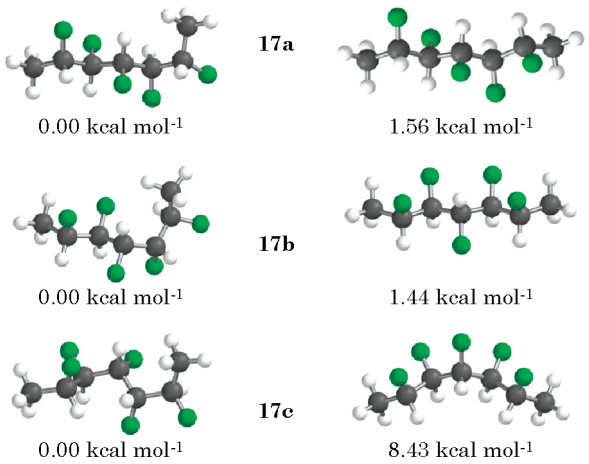

FIGURE 4. DFT calculated (B3LYP/6-31G(d)) minimum zero energy conformation (left) for heptanes **17** and the extended linear conformation (right), similar to that observed in the X-ray structures.

to each other in a helical arrangement, similar to previous observations for the *all-syn* tetra and hexa series.[11−14] However, this low energy conformer does not crystallize presumably because it lacks sufficient symmetry for unit cell packing. NMR indicates (see below) too that the molecule is dynamic in solution indicating competing low-energy conformers.

Some insight into the conformations in solution of these diastereoisomers can be gleaned from ^{1}H and ^{19}F NMR coupling constants ($^{3}J_{HH}$ and $^{3}J_{HF}$). In a similar manner to H/H ($^{3}J_{HH}$) coupling constants, vicinal H/F ($^{3}J_{HF}$) coupling constants obey Karplus-type angular relationships.[21] Compounds **14a** and **3a** have almost identical coupling constants and therefore very similar solution conformations, despite different peripheral functionalities. For each molecule of the **a** series, $^{3}J_{HF}$ values for HC(2)−C(3)F were measured at ∼28 Hz, a large value consistent with a *trans* relationship. On the other hand $^{3}J_{HF}$ for FC(3)−C(4)H had a value of 4.6 Hz, a small value consistent with a tight *gauche* relationship between C−F and C−H bonds. These values suggest a rather stable conformation in solution, similar to that revealed in the X-ray stucture of **16a**.

Diastereoisomers **b** and **c** have molecular symmetry and they generate second order ^{1}H and ^{19}F NMR spectra, which require simulation to extract the coupling constants (see the Supporting Information). Diastereoisomers **14b** and **3b** have vicinal $^{3}J_{HF}$ couplings for HC(2)−C(3)F measured at 23.7 and 26.6 Hz, respectively, whereas values for FC(3)−C(4)H were recorded at 12.1 and 10.2 Hz, respectively. These are consistent with the observed solid state structure as a major contributor, but the lower *anti* and higher *gauche* values suggest a more dynamic molecule in solution with other conformers contributing, lowering (*anti*) and raising (*gauche*) the values relative to the **a** series. For stereochemical series **c** we could not obtain any X-ray structural information. The DFT theory study suggested that the linear extended structure is energetically unfavorable and that this diastereoisomer will prefer a helical stucture (Figure 4). ^{19}F NMR gave three $^{3}J_{HF}$ coupling constants of between 21 and

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22 Hz indicating a conformationally dynamic structure and suggesting a number of contributing low-energy conformers in solution.

In conclusion, the synthesis of three diastereoisomers of a pentavicinal fluoroalkane was demonstrated as a novel motif in organic chemistry. The parent 2,3,4,5,6-pentafluoro heptanes were prepared and the pentafluoro 1,7-diol and 1,7-ditosyl diastereoisomers **a**−**c** were generated armed for incorporation of these building blocks into larger molecular scaffolds.

Experimental Section

General Procedure for Epoxides Opening with HF. A solution of monofluorinated diepoxide (1.20 mmol) in $Et_3N \cdot 3HF$ (3 mL) was heated in a reactor at 150 °C overnight. The mixture was then carefully quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL). Dichloromethane (20 mL) was added and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the crude residue was purified by silica gel chromatography (CH_2Cl_2/EtOAc 100/0 → 95/5) to obtain the desired compound.

General Procedure for the Synthesis of 14. Neat Deoxo-Fluor (1.79 mmol) was added to a solution of trifluorinated diol (0.36 mmol) in dry CH_2Cl_2 (3 mL) at rt. The mixture was stirred overnight under argon. The mixture was diluted with EtOAc (6 mL) then washed with a saturated aqueous solution of $NaHCO_3$ (3 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexane/CH_2Cl_2 100/0 → 40/60) to obtain the pentafluoro product.

Data for 3a: mp 144−147 °C; $[\alpha]^{20}_D$ −2.1 (*c* 0.97, MeOH); IR (neat) ν_{max} (cm^{-1}) 3353, 3174, 2868, 1055; ^1H NMR (CD_3OD, 300 MHz) δ 5.21−4.54 (m, 5H), 4.01−3.74 (m, 4H); ^1H {^{19}F dec} NMR (CD_3OD, 300 MHz) δ 5.13−4.69 (m, 5H), 3.97−3.78 (m, 4H); ^{19}F NMR (CD_3OD, 282 MHz) δ −205.0 (m, 1F), −206.0 (m, 1F), −206.0 (m, 1F), −218.0 (m, 2F); ^{19}F {^1H dec} NMR (CD_3OD, 282 MHz) δ −202.7 (dd, J = 13.4, 2.7 Hz, 1F), −212.7 (dd, J = 8.9, 3.0 Hz, 1F), −216.2 (m, 1F), −217.9 (ddd, J = 13.4, 9.3, 3.5 Hz, 1F), −218.2 (ddd, J = 14.2, 8.9, 3.5 Hz, 1F); ^{13}C NMR (CD_3OD, 75 MHz) δ 94.4 (m, CH), 92.2 (m, CH), 89.9 (m, CH), 61.6 (dd, J = 22.2, 8.6 Hz, CH_2), 60.6 (dd, J = 26.0, 6.6 Hz, CH_2); HRMS (ESI, +ve) *m*/*z* calcd for $C_7H_{11}O_2F_5Na$ [M + Na^+] 245.0577, found 245.0581.

Acknowledgment. We gratefully acknowledge the EPSRC for funding this research.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, X-ray structural information of **3b**, **16a**, and **16b**, and calculation data for **17a**, **17b**, and **17c**. This material is available free of charge via the Internet at http://pubs.acs.org.