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Stereocontrolled Synthesis of Tetrafluoropentanols: Multivicinal Fluorinated Alkane Units for Drug Discovery

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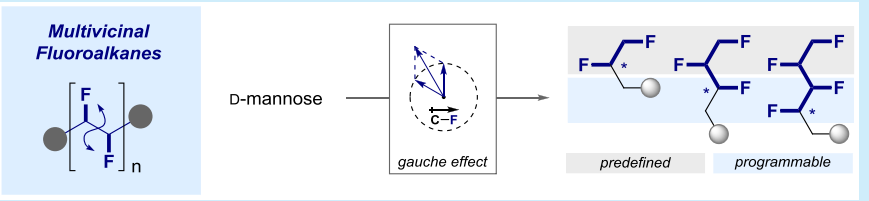
Supporting Information



ABSTRACT: A stereodivergent synthesis of four diastereomeric 2,3,4,5-tetrafluoropentanols is disclosed. X-ray crystallographic analysis reveals conformations that manifest sequential stereoelectronic *gauche* effects ($\sigma_{C-H/C} \rightarrow \sigma_{C-F}^*$), thereby generating topological diversity via subtle C(sp^3)−H to C(sp^3)−F exchange. Two representative tetrafluoro arrays have been incorporated into truncated analogues of Gilenya for the management of relapsing remitting multiple sclerosis. These closely similar multivicinal fluoroalkanes have notably different physicochemical profiles and were found to be stable in the presence of human microsomes.

Multivicinal fluoroalkanes uniquely amalgamate the physicochemical properties of hydrocarbons and perfluorocarbons (Figure 1).[1] The juxtaposition of localized partial charge inversion and comparable van der Waals radii, coupled with fluorine's relative scarcity in Nature, creates a unique environment to facilitate the discovery of novel materials with unexplored function.[2] Unlike the achiral parent compound classes, this organohalogen subset comprises repeating (CHF) stereocenters, thus allowing for the programmed generation of stereoisomers with unique physicochemical properties. This is a consequence of molecular conformation which can be regulated as a function of noncovalent interactions. The venerable *gauche* effect associated with 1,2-difluoroethane is necessarily telescoped in multivicinal fluoroalkanes:[3] this gives rise to a predictable dihedral angle ($\varphi_{FCCF} = 60°$) as a consequence of stabilizing hyperconjugative interactions ($\sigma_{C-H} \rightarrow \sigma_{C-F}^*$). Repulsive 1,3-fluorine interactions also provide a handle and, together, with the *gauche* effect, can be exploited to populate specific conformers as a function of relative configuration.[4] The potential and versatility of multivicinal fluoroalkanes is exemplified by O'Hagan's seminal contributions to understanding the physicochemical behavior of this new class of materials[5] and the stereocontrolled synthesis of a fluorinated analogue of the complex lipid fluorodanicalipin by Carreira and co-workers.[6]

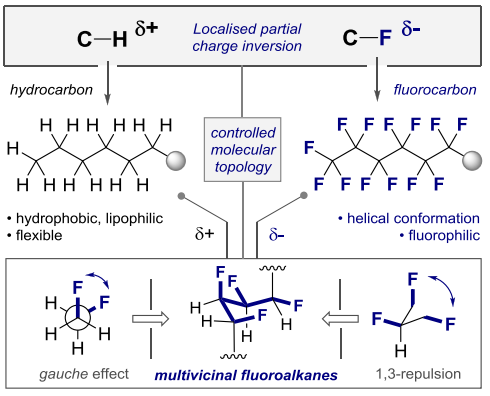


Figure 1. Multivicinal fluoroalkanes as asymmetric building blocks.

By merging these two compound classes, it is possible to explore new areas of chiral, 3D molecular space with enormous potential in the design of novel bioisosteres for drug discovery.[7] Herein, we report a convenient strategy to access four diastereoisomers of 2,3,4,5-tetrafluoropentan-1-ol from inexpensive D-mannitol and demonstrate their structural variation. Preliminary validation of their potential in drug discovery is also presented in the synthesis and physicochemical profiling of analogues of the multiple sclerosis drug, Gilenya.[8]

Our interest in the fluorine *gauche* effect,[3] coupled with our recent disclosure of the catalytic, enantioselective vicinal

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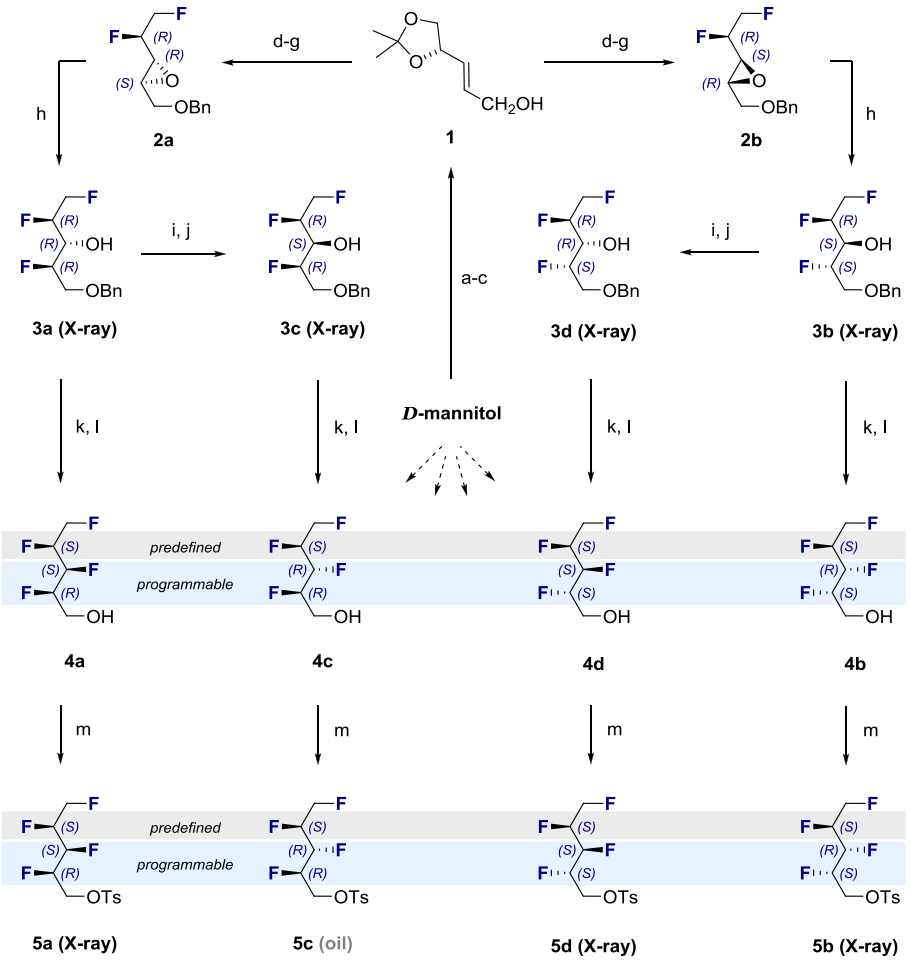
Scheme 1. Synthesis of Tetrafluoropentanols 5a–d[a]



[a]Conditions: (a) D-mannitol, $ZnCl_2$, acetone, rt, 24 h, 88%; (b) (i) $NaIO_4$, $NaHCO_3$,H_2O, rt, 4 h, then (ii) K_2CO_3, $(EtO)_2P(O)CH_2CO_2Et$, H_2O, 0 °C to rt, 18 h, 70%; (c) DIBAL-H, THF, −78 °C to rt, 18 h, **1** 90%; (d) $Ti(O^iPr)_4$, (*)-DIPT, ^{t}BuOOH, CH_2Cl_2, −25 °C, 64 h, 72/85%; (e) BnBr, NaH, TBAI, THF, 0 °C to rt, 20 h, 86/77%; (f) acetic acid (70%), rt, 18 h, 89/79%; (g) Deoxofluor (50% in THF), CH_2Cl_2, 0 °C to rt, 20 h, 73% **2a**, 84% **2b**; (h) NEt_3·3HF, 120 °C, 20 h, 89% **3a**, 80% **3b**; (i) Tf_2O, pyridine, CH_2Cl_2, −10 °C to rt, 2 h, then (j) $NaNO_2$, DMF, 50 °C, 3 h, 72% **3c**, 59% **3d**; (k) Deoxofluor (50% in THF), CH_2Cl_2, 0 °C to rt, 22 h, 76/75/73/85%; (l) Pd/C, H_2, Et_2O, rt, 18 h, 98% **4a**, 98% **4b**, 74% **4c**, 80% **4d**; (m) TsCl, NEt_3, DMAP, rt, 18 h, 76% **5a**, 89% **5b**, 76% **5c**, 77% **5d**. For full experimental details, see the Supporting Information.

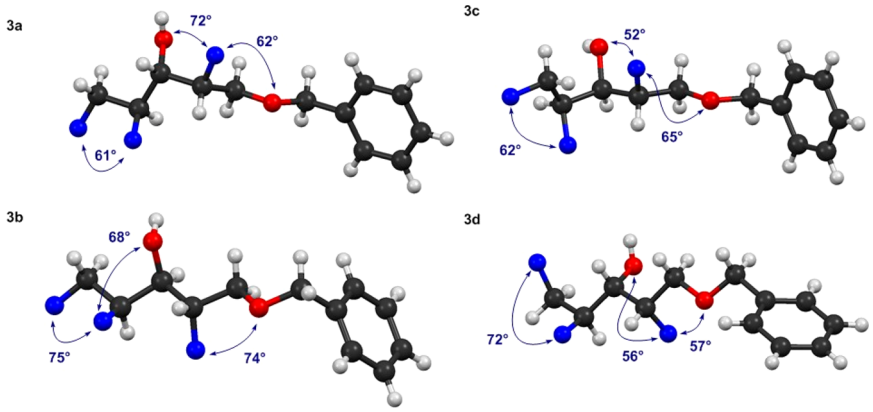


Figure 2. X-ray analyses of alcohols **3a–d** showing selected *gauche* dihedral angles.

difluorination of alkenes,[9,10] motivated us to explore larger congeners of the 1,2-difluororoethylene unit in the context of focused molecular design. As the 1,2,3,4-tetrafluorobutylene motif may be considered as the first higher homologue of the parent 1,2-difluoroethylene unit, a stereodivergent route to access the various diastereoisomers starting from inexpensive D-mannitol was devised (Scheme 1).

Allylic alcohol **1**[11] (see Supporting Information) was processed to compounds **2a** and **2b** via four-step synthetic sequences. Reagent-controlled Sharpless asymmetric epoxida-

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tion provided access to both epoxyalcohol diastereoisomers.[12] Subsequent protecting group manipulation provided the corresponding 1,2-diols, which were suitable substrates for fluorine incorporation. Following the conditions reported by Shreeve and co-workers,[13] 1,2-difluoroalkanes **2a** and **2b** were generated in 73 and 84%, respectively. Exposing epoxides **2a** and **2b** to neat $NEt_3 \cdot 3HF$ at 120 °C for 18 h generated trifluorides **3a** and **3b** in a highly regio- and stereoselective manner (89 and 80%, respectively). To access the four possible tetrafluorinated stereoisomers **4a−d**, configurational inversion of the hydroxyl group in **3a** and **3b** was performed via a two-step procedure involving triflation and treatment with sodium nitrite to generate **3c** and **3d**.[14]

All four diastereoisomers (**3a−d**) were crystalline, allowing the absolute configuration to be confirmed by X-ray analysis (Figure 2). In all four scenarios, F−C−C−F/OH dihedral angles were observed that satisfy the torsional requirements for the stereoelectronic *gauche* effect. Interestingly, in the case of **3a** and **3c**, the characteristic zigzag conformation of the chain is distorted to avoid repulsive 1,3-interactions. This is mitigated in structures **3b** and **3d** due to the 1,3-*anti* relationship of the fluorine atoms.

Installation of the final fluorine substituent via invertive substitution required an excess of Deoxofluor to generate the tetrafluoro motif (up to 85% yield). Cleaveage of the benzyl ether using palladium on charcoal under a H_2 atmosphere in diethyl ether liberated the 2,3,4,5-tetrafluoropentanols as highly volatile solids (sublimation at $\sim 10^{-2}$ mbar and ambient temperature). To address this volatility issue and provide a useful handle for further functionalization, tosylates **5a−d** were prepared. In three cases, it was possible to perform single-crystal diffraction analysis to unequivocally establish the relative and absolute configuration of products **5a**, **5b**, and **5d**. As is evident from Figure 3, the final deoxyfluorination event proceeds with inversion of configuration, and the structures adopt conformations in which the stereoelectronic *gauche* effects manifest themselves. It is interesting to note that, in the case of the all-*syn* system **5a**, a linear zigzag conformation is observed despite the repulsive 1,3-interaction.

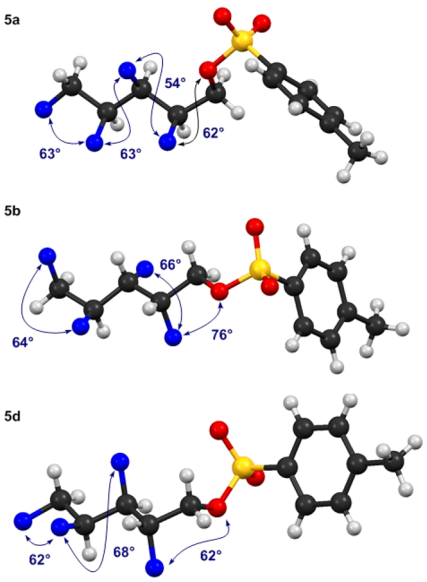


Figure 3. X-ray analyses of tosylates **5a**, **5b**, and **5d** showing selected *gauche* dihedral angles.

In the *syn−anti* diastereoisomer **5b**, two *gauche* alignments are evident from the solid-state analysis. An additional fluorine−oxygen *gauche* conformation can also be observed, and there is no appreciable distortion of the carbon chain.

When considering the tetrafluoro motif as its two constituent 1,2-difluoroethylene units, the internal *gauche* relationships contrast sharply with the 2,3-*anti* relationship in the center of the structure. This phenomenon is also present in derivative **5d**, where a single *anti* relationship is wedged between three discrete *gauche* effects. These structural data demonstrate that subtle changes in closely similar structures can have profound effects on conformational variation. This is evident from an inspection of the extended packing array of tetrafluorides **5a** and **5b** (Figure 4; for full structure analysis, see the Supporting Information).

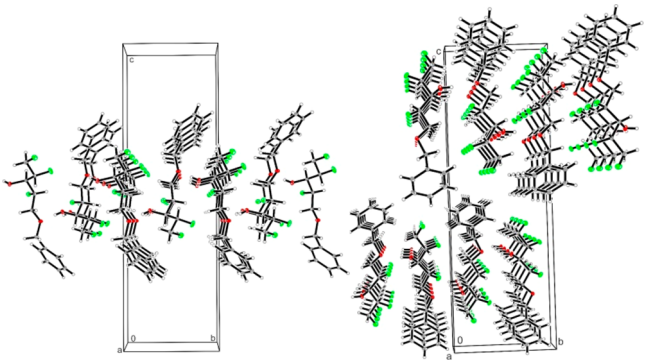
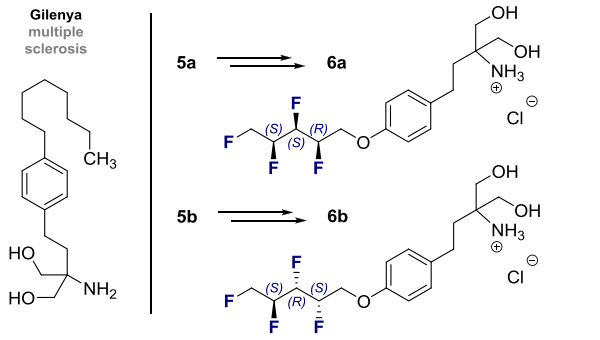


Figure 4. Extended packing arrays of the all-*syn* diastereoisomer **5a** (left) and *syn,anti* diastereoisomer **5b** (right).

To explore the potential of these motifs in modulating the physicochemical profiles of small molecule drugs, the tetrafluoro arrays in **5a** and **5b** were incorporated into an analogue of the multiple sclerosis drug Gilenya (Figure 5).

Whereas both candidates **6a** and **6b** displayed comparable log $D_{7.4}$ values (0.4 and 0.6), notable differences in aqueous



Entry	Log $D_{7.4}$	Solubility (pH7.4, μM)	Rat Hepatocytes Cl_{int} (μL/min/10^6 cells)	(Hu Plasma Bind Bioreclamation) Mean Protein binding (% free)
Gilenya[8]	3.5	2	12.8	0.24
6a	0.4	925	3.010	55
6b	0.6	563	1.730	54

Figure 5. Comparison of the physicochemical properties of multivicinal fluoroalkanes **6a** and **6b** with Gilenya.

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solubility were observed at pH 4.7 (925 vs 563 μM). Both compounds were found to be stable in the presence of human microsomes [Cl_{int} (μM/min/mg <4.5), and similar low intrinsic clearance rates in rat hepatocytes were observed. As expected, the fluorinated systems displayed physicochemical profiles very different than that of the parent drug Gilenya,[8] further underscoring the potential of multiply fluorinated motifs in functional small molecule design.[15]

In conclusion, a stereodivergent route to four diastereoisomers of the 1,2,3,4-tetrafluoro motif is disclosed from an inexpensive, chiral pool starting material. Whereas the configuration of the penultimate C(sp^3)−F unit is predetermined by the sugar, the adjoining, contiguous centers can be programmed to facilitate access to four discrete diastereoisomers. Solid-state structural analysis reveals a predisposition to adopt conformations that allow for stabilizing hyperconjugative interactions of the type ($\sigma_{C-H/C} \rightarrow \sigma_{C-F}^*$). These sequential *gauche* effects give rise to subtle changes in structural topology and physicochemical properties. Given the biosisosteric nature of C(sp^3)−H and C(sp^3)−F bonds, multivicinal fluoroalkanes are a versatile class of materials to explore 3D chemical space.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02662.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1941733−1941739 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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