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Enantioselective Synthesis of an All-*syn* Four Vicinal Fluorine Motif

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The incorporation of fluorine atoms into organic molecules is well-known to have profound effects on their physical properties.[1] In general terms, highly fluorinated compounds have contributed significantly to materials science,[2] whereas selectively fluorinated compounds have been used effectively in pharmaceutical and agrochemical products[3] and in mechanistic enzymology research.[4] We have been interested in developing novel partially fluorinated motifs to expand the repertoire of fluorinated building blocks in organic chemistry.[5] Organic compounds with two vicinal fluorines have conformations which are influenced by the fluorine *gauche* effect,[6] and it is attractive to consider the level of conformational predictability if longer vicinal fluorine systems are developed which bear multiple fluorine atoms at adjacent stereocenters; such compounds may be considered intermediate between alkanes and perfluoroalkanes, and as a class, their chemistry and behavior remain to be explored.

As an initial contribution to the synthesis of such compounds, we have reported the stereoselective preparation of α,*β*,*γ*-trifluoroalkanes in two diastereoisomeric series (Chart 1).[7] This trifluoro motif has the potential to be incorporated into a variety of performance molecules which rely on conformation to optimize their physical properties.

In this communication, we report a stereoselective synthesis of an all-*syn* four vicinal fluorine motif (Chart 2) as a single enantiomer and in a format which will allow its direct incorporation into larger molecular architectures. Such a motif has prospects for a variety of applications in the design of novel materials such as liquid crystals and self-assembling monolayers or in the preparation of elaborate deoxyfluoro sugar analogues and, in a general sense, broadens the available range of functionalized alkanes.

The synthetic sequence commenced with (*R*)-butadiene monoxide **1** (Scheme 1), which is readily available in enantiomerically pure form (>99% ee) by hydrolytic kinetic resolution of the commercially available racemate according to a Jacobsen protocol.[8] Our synthetic approach required regioselective opening of epoxide **1** with HF at the 2-position, a transformation which has previously been achieved with the racemate.[9] However, the corresponding transformation with a single enantiomer is complicated by the partial S_N1 character of the epoxide ring-opening reaction. Treatment of **1** with HF−triethylamine furnished fluorohydrin **2** with somewhat reduced enantiopurity (80% ee), as determined by Mosher ester analysis.[10] This stereoselectivity could not be improved; however, the loss of enantiopurity was circumvented as described below.

Protection of fluorohydrin **2** gave benzyl ether **3**, a compound which underwent cross metathesis upon treatment with Grubbs' second generation catalyst[11] to furnish the symmetrical alkene **4**. This reaction proceeded in good yield and gave a product with exclusively the *E* double bond geometry. Notably, we were able to exploit an additional stereochemical feature of the metathesis reaction: since the starting material **3** (80% ee) consisted of a 9:1 mixture of (*S*)- and (*R*)-enantiomers, the product **4** was formed as

Chart 1. α,*β*,*γ*-Trifluoroalkanes[7]

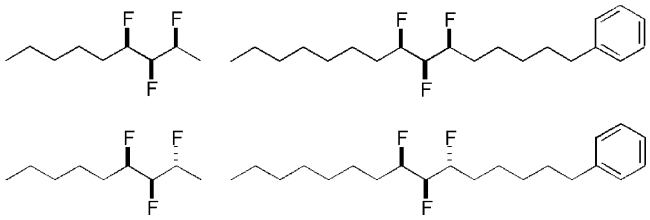
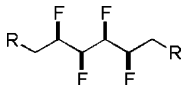
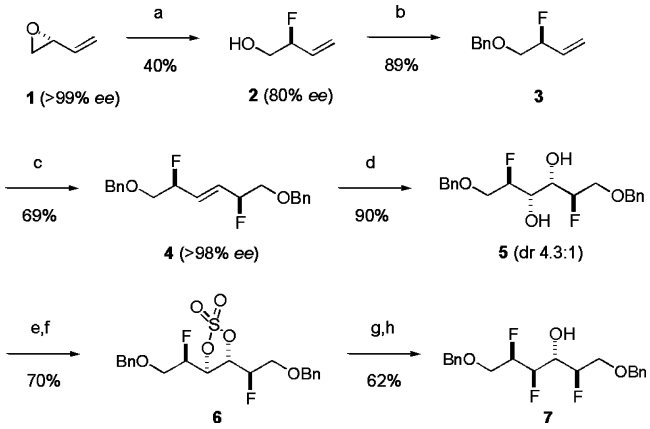


Chart 2. All-*syn* Four Vicinal Fluorine Motif



Scheme 1[a]



[a] Reagents and conditions: (a) $Et_3N{\cdot}3HF$, Na_2SO_4, 70 °C; (b) BnBr, NaH, DMF, 40 °C; (c) Grubbs second generation catalyst, DCM, Δ; (d) $KMnO_4$, $MgSO_4$, EtOH, H_2O, −10 °C; (e) $SOCl_2$, pyridine, DCM, 0 °C; (f) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C; (g) TBAF, MeCN, rt; (h) H_2SO_4, H_2O, THF, rt.

a statistical 81:18:1 mixture of (*S*,*S*)-, (*R*,*S*)-, and (*R*,*R*)-isomers, and straightforward chromatographic removal of the (*R*,*S*)-isomer then allowed the major diastereoisomer to be recovered directly in 98% ee, thereby overcoming the loss of enantiopurity suffered during the epoxide opening step. Furthermore, alkene **4** was amenable to recrystallization, which allowed an enantiomerically pure sample to be recovered. Single-crystal X-ray analysis of **4** confirmed the *E* double bond geometry and the *syn* relationship between the two fluorine substituents.[12]

The next stage of the synthesis required selective dihydroxylation of the double bond of **4** (Scheme 1). Initial attempts at epoxidation or dihydroxylation were hampered by low conversions, presumably due to the rather electron-deficient nature of the double bond. However, treatment of **4** with potassium permanganate gave the required diol **5** in good yield, with the diastereoselectivity of *cis*-dihydroxylation controlled by the two fluorine substituents. The

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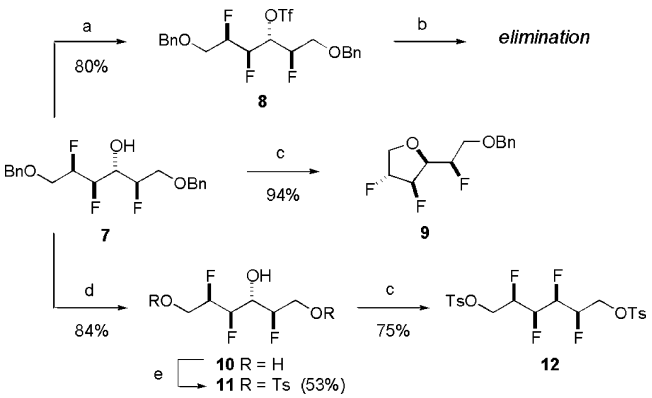
Scheme 2[a]



[a] Reagents and conditions: (a) Tf_2O, pyridine, DCM, −40 °C; (b) TBAF, MeCN, 0 °C; (c) Deoxo-Fluor, 70 °C; (d) H_2, Pd/C, MeOH, rt; (e) TsCl, 2,4,6-collidine, 50 °C.

assignment of the relative stereochemistry of **5** is supported by single-crystal X-ray data.[13]

Diol **5** was next converted to the corresponding cyclic sulfate **6** under standard conditions[14] (Scheme 1), and subsequent ring opening with TBAF gave the trifluoro derivative **7** in good yield, along with a smaller amount of a byproduct arising through a competing elimination pathway.

With the trifluoro alcohol **7** in hand, attention was turned toward the introduction of the fourth fluorine atom. Alcohol **7** was first converted to the corresponding triflate **8** (Scheme 2), but subsequent treatment of **8** with TBAF led predominantly to elimination rather than the desired S_N2 displacement by fluoride. An alternate approach was investigated, in which the free alcohol **7** was treated with excess Deoxo-Fluor reagent[15] or DAST[16] (Scheme 2); unfortunately, however, cyclization occurred to give the tetrahydrofuran derivative **9** as the only reaction product in both cases.[17] In an attempt to suppress this adventitious cyclization on steric grounds, the benzyl ether was replaced by the 2,6-dichlorobenzyl ether protecting group. However, it emerged that formation of the corresponding tetrahydrofuran derivative remained the dominant reaction pathway.

Accordingly, we decided to investigate the tosyl ester as a protecting group (Scheme 2). Hydrogenolysis of **7** gave triol **10**, which was selectively reprotected to give the ditosylate **11**. In this case, **11** was cleanly converted to the desired tetrafluoro compound **12** upon treatment with Deoxo-Fluor at 50 °C. This reaction was not accompanied by the previously observed cyclization, elimination, or loss of the tosyl groups. At 70 °C, conversion to **12** was improved to a satisfactory level, although some elimination products also became apparent at these more forcing conditions.

The all-*syn* tetrafluoro compound **12** was crystalline and proved amenable to single-crystal X-ray analysis (Figure 1), which unambiguously confirmed the absolute configuration of each stereocenter. The crystal structure, which has C_2 symmetry, displays *gauche* relationships between all four fluorines with dihedral angles of 66.7° (F9−C−C−F10) and 59.7° (F10−C−C−F10′) between vicinal fluorines, consistent with the fluorine *gauche* effect. In the crystal packing structure, the aryl and fluoroalkyl groups pack in separate domains, and intermolecular interactions include a hydrogen bond (2.52 Å) from the fluorine atom of C10 (and C10′) to the hydrogen atom at C9 (and C9′) of an adjacent molecule.

In summary, we have described the preparation of an enantiomerically pure all-*syn* four vicinal fluorine motif, which represents

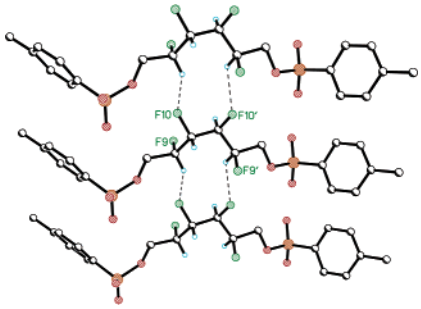


Figure 1. X-ray structure of **12** showing crystal packing arrangement.

an unexplored class of functionalized alkanes and which now has prospects to be directly incorporated into a variety of performance molecules.

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Supporting Information Available: Full experimental procedures and characterization data for all compounds, ^{19}F NMR spectrum of **12**, and crystallographic data for **4**, **5**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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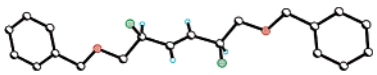
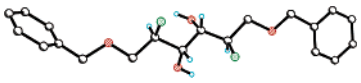
(12) X-ray crystal structure of **4** (see Supporting Information for details):



(13) X-ray crystal structure of **5** (phenyl rings optimized due to disorder in the electron density map; see Supporting Information for details):



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