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α,β,γ-Trifluoroalkanes: A Stereoselective Synthesis Placing Three Vicinal Fluorines along a Hydrocarbon Chain

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Organofluorine compounds have had a huge impact in the design of performance materials with outstanding examples found in pharmaceuticals,[1] agrochemicals[2] and organic materials[3,4] products. In the pharmaceuticals and agrochemicals arena selective fluorination of aromatics or the incorporation of a CF_3 group represents the typical strategy for incorporation of organic fluorine.[5]

Within the materials arena highly fluorinated or perfluorinated compounds have been used as lubricants and polymers for a diversity of products and applications;[6] however the properties of organic materials with an intermediate level of fluorination, and particularly with multiple fluorines at stereogenic centers, have been hardly explored. There is clear evidence that the C−F bond can be exploited as a tool for influencing the conformation of organic molecules, particularly when it is used as a replacement for hydrogen.[7] This is most easily illustrated by the well-known gauche effect which recognizes that 1,2-difluoroethane prefers a gauche over an anti conformation.[8] This gauche preference of vicinal fluorines can also influence the conformation of longer hydrocarbon chains such as *meso*- and (±)-2,3-difluorobutanes and (±)-*erythro*- and (±)-*threo*-9,10-difluorostearic acids.[9] For example in the latter case the *erythro* isomer has a similar conformational stability to the hydrocarbon (stearic acid), whereas the *threo* isomer shows significant conformational disorder. This was attributed to the preference of the vicinal C−F bonds preferring to align gauche to each other in both systems, the former stabilizing and the latter destabilizing the classical *anti-zigzag* conformation of the hydrocarbon chain. Recognizing that the relative stereochemistry of vicinal C−F bonds can have a significant influence on the conformation of hydrocarbons, we have now decided to explore α,β,γ-trifluorohydrocarbons where three fluorines are arranged along a hydrocarbon chain. Such systems have up to four diastereoisomers and eight enantiomers, and clearly any meaningful synthesis to this class of compounds requires stereocontrol, such that the properties of different diastereoisomers can be evaluated. As an initial contribution to the preparation of these compounds, a method for the synthesis of two of the diastereoisomers of the vicinal trifluoro alkyl motif, is described for the two different molecular systems, **1a** and **2a** as well as **1b** and **2b**. In the first instance the racemic diastereoisomers of 2,3,4-trifluorononanes **1a** and **2a** were prepared to develop the synthetic protocol, and the method was then applied to the synthesis of the racemic 6,7,8-trifluoro-1-phenylheptadecanes **1b** and **2b**. The latter route started from allylic alcohol **3b** which derived from a condensation of 6-phenylaldehyde and non-1-yne followed by LAH reduction of the resultant propargylic alcohol **10** (Scheme 2).

The sequential introduction of the fluorine atoms in a stereospecific manner relied heavily on Sharpless cyclic sulfate methodology. Epoxidation of the appropriate allylic alcohols **3** afforded the diastereoisomeric epoxides **4a** and **4a′** or **4b** and **4b′** as a 2:1 mixture for both series. These isomers could be separated in each case to progress toward each of the diastereoisomeric series **a** and **a′** or **b** and **b′**; however it proved more efficient to separate these diastereoisomers after treatment with HF·pyridine. This resulted in a stereo- and, importantly, a completely, regiospecific ring opening and generated the fluorohydrins **5a** and **5a′** or **5b** and **5b′**, retaining the 2:1 mixture. These diastereoisomers were readily separated by silica gel chromatography (Scheme 1).

The vicinal diols of both diastereoisomeric series were then converted to their cyclic sulfates **6a** and **6a′** or **6b** and **6b′** using the method developed by Sharpless, and the sulfates were ring opened, again in both a regio- and stereospecific manner to generate **8a** (or **8b**) and **8a′** (or **8b′**) after in situ hydrolysis of the ring opened difluorosulfates **7a** (or **7a′**) and **7b** (or **7b′**).[10,11] The third fluorine atom was introduced by activation of the remaining alcohol functionality in **8a** (or **8a′**) and **8b** (or **8b′**) to the corresponding triflates **9** followed by a nucleophilic substitution reaction with fluoride ion using TBAF. This reaction led to the desired α,β,γ-trifluoroproducts. The products were always accompanied by elimination products, and despite considerable experimentation the current yield for this final step remains modest. Nonetheless the **1** and **2** diastereoisomers of the products **a** and **b** could be secured after chromatography.

Enantiomerically pure products can be accessed by initiating the synthetic protocol with a Sharpless asymmetric epoxidation/kinetic resolution. This was explored only in the **a** series to confirm the stereochemical course of the first two fluorination reactions in Scheme 1. A Sharpless asymmetric epoxidation on allylic alcohol **3a** and using (+)-DIPT and a limiting (0.5 equiv) amount of ^{t}BuOOH generated the (2*S*,3*R*,4*S*) enantiomer of allylic epoxide **4a′**. The (2*S*,3*R*,4*S*) configuration of this product has been established previously.[12,13] Epoxide **4a′** was then converted to **8a′** as described above, and this crystalline difluoro alcohol proved amenable to X-ray structure analysis[14] (Figure 1).

The resultant structure revealed a stereochemistry consistent with two configurational inversions during formation of each of the α- and γ-C−F bonds. The trifluoroalkane products **1** and **2** are liquids and were not readily amenable to crystallization; however the final fluorination which results from fluoride ion displacement of a triflate is assumed to proceed with an inversion of configuration. Compounds **1a** and **2a** proved to be particularly volatile, but **1b** and **2b** gave materials which were more amenable to longer term storage.

The vicinal trifluoroalkanes were analyzed by ^{19}F NMR spectroscopy, and the resultant data are shown in Table 1. It is most informative to compare the chemical shift of **1b** and **2b**. The configurational arrangement of the fluorines in diastereoisomer **1b** posesses a pseudo symmetry, and consequently the α and γ fluorines have identical chemical shifts, whereas this pseudo symmetry does not exist in diastereoisomer **2b** and each fluorine signal is now well resolved. These spectra reinforce the stereochemical assignments of the two diastereoisomers. For the **1** series the vicinal coupling constants (Table 1) $J^2_{F\alpha-F\beta}$ (**1a** 12.9 Hz and **1b** 12.3 Hz) and $J^2_{F\beta-F\gamma}$ (**1a** 11.2 Hz and **1b** 12.3 Hz) are similar

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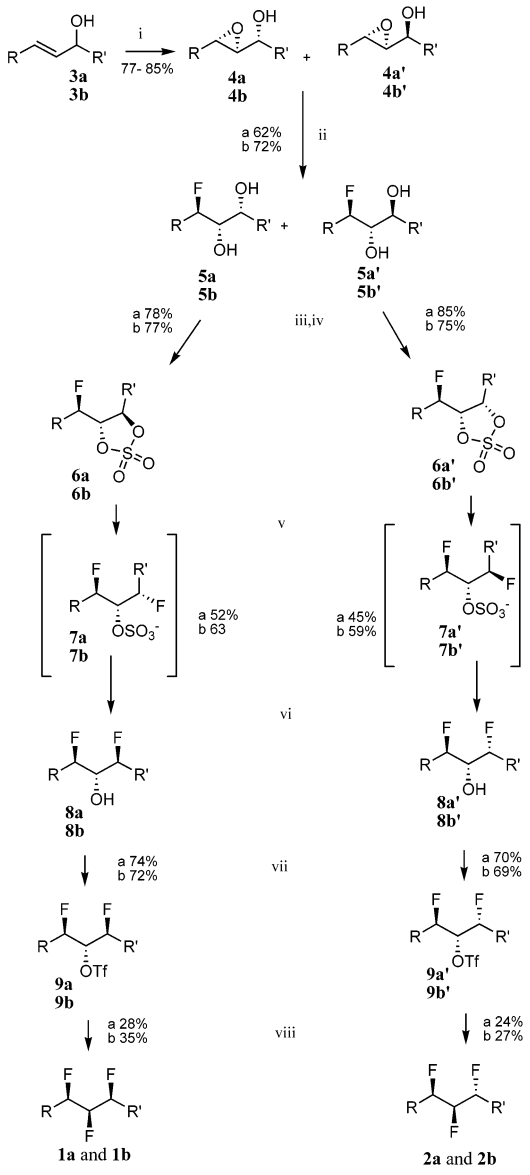
Scheme 1 [a]



[a] Reagents and conditions: **a** R = C_5H_{11}, R′= CH_3, **b** R = C_7H_{15}, R′ = C_5H_{20}Ph. (i) *m*CPBA in DCM, 0 °C 2 h. (ii) HF·pyridine in DCM, 10 °C 4 h. (iii,iv) $SOCl_2$, py. in DCM, 0 °C 45 min then $NaIO_4$/ $RuCl_3$ in CH_3CN/ H_2O, 0 °C 1 h. (v) TBAF in acetone, 0 °C 2 h. (vi) Et_2O/H_2SO_4. (vii) Tf_2O, pyr in DCM, −40 °C 1 h. (viii) TBAF in MeCN, 0 °C 30 min.

suggesting similar gauche relationships between these vicinal substituents. For the **2** series the $J^2_{F\alpha-F\beta}$ values are also similar but larger (**2a** 14.4 Hz and **2b** 14.9 Hz) suggesting an increased anti conformation between the α and β fluorines. This is consistent with an extended hydrocarbon chain forcing the α and β fluorines anti to each other. On the other hand the $J^2_{F\beta-F\gamma}$ values in the **2** series are similar but smaller (**2a** 9.3 Hz and **2b** 9.2 Hz) suggesting a tighter gauche angle between the β and γ fluorines. These coupling constants reveal a close conformational analogy between compounds **1a** and **1b** and between **2a** and **2b**.

Scheme 2

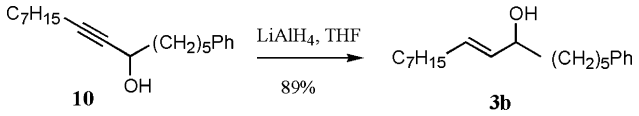


Table 1. $^{19}F\{^1H\}$ NMR ($CDCl_3$) Data for Compounds **1a**−**2b**

	^{19}F chemical shifts (ppm)			^{19}F–^{19}F coupling constants (Hz)		
	F_α	F_β	F_γ	$J_{\alpha-\beta}$	$J_{\beta-\gamma}$	$J_{\alpha-\gamma}$
1a	−189	−199	−207	12.9	11.2	–
2a	−185	−201	−213	14.4	9.3	3.4
1b	−197	197	−207	12.3	12.3	
2b	−194	−200	−212	14.9	9.2	

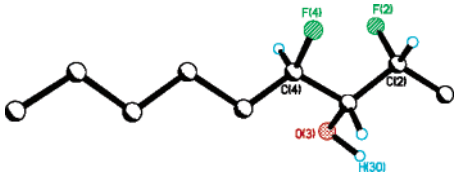


Figure 1. X-ray structure of **8a′** confirming the relative stereochemistry.

This synthetic method offers a new structural motif which can now be incorporated into performance molecules, both in the area of bioactives and in materials, which rely on conformation to optimize their properties.

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Supporting Information Available: Full synthetic protocols and characterization for all compounds and crystallographic data for **8a′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for crystallographic data.

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