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Sequential Deoxyfluorination Approach for the Synthesis of Protected α,β,γ-Trifluoro-δ-amino Acids

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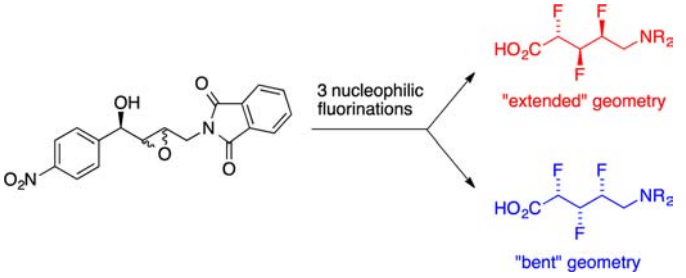
ABSTRACT



Backbone-homologated amino acids have been synthesized, containing three vicinal fluorine atoms placed stereospecifically along the carbon chain. Different trifluoro stereoisomers are found to have contrasting conformations, consistent with known stereoelectronic effects associated with C−F bonds.

The incorporation of fluorine atoms into organic molecules can have a dramatic impact on the substances' physical and chemical properties.[1] For example, fluorine substituents can lead to higher hydrophobicity and greater metabolic stability, and they can affect the pK_a of nearby functional groups. These effects have been put to good use in the pharmaceuticals arena: so much so that approximately 20% of drugs currently on the market are organofluorine compounds.[2] Fluorine atoms can also affect the conformations of organic molecules, since the highly polarized C−F bond participates in a variety of stereoelectronic interactions with adjacent functional groups (**1**−**3**, Figure 1).[3] This concept has been applied to optimize the properties of a variety of organofluorine molecules in which conformation influences function, such as peptides,[4] organocatalysts,[5] liquid crystals,[6] and bioactive small molecules.[7] For example, we have synthesized α,β-difluoro-γ-aminobutyric acids (**4**, Figure 1);[8] the different

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(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.
(2) (a) Hagmann, W. K. J. *Med. Chem.* **2008**, *51*, 4359. (b) Purser, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(3) Hunter, L. *Beilstein J. Org. Chem.* **2010**, DOI: 10.3762/bjoc.6.38.
(4) (a) Schüler, M.; O'Hagan, D.; Slawin, A. M. Z. *Chem. Commun.* **2005**, 4324. (b) Mathad, R. I.; Gessier, F.; Seebach, D.; Jaun, B. *Helv. Chim. Acta* **2005**, *88*, 266.
(5) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11860.
(6) (a) Nicoletti, M.; Bremer, M.; Kirsch, P.; O'Hagan, D. *Chem. Commun.* **2007**, 5075. (b) Hunter, L.; Kirsch, P.; Slawin, A. M. Z.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 5457.
(7) (a) Khrimian, A. P.; Oliver, J. E.; Waters, R. M.; Panicker, S.; Nicholson, J. M.; Klun, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 37. (b) Winkler, M.; Moraux, T.; Khairy, H. A.; Scott, R. H.; Slawin, A. M. Z.; O'Hagan, D. *ChemBioChem* **2009**, *10*, 823. (c) Bucher, C.; Sparr, C.; Schweizer, W. B.; Gilmour, R. *Chem.—Eur. J.* **2009**, *15*, 7637. (d) O'Hagan, D. *Future Med. Chem.* **2011**, *3*, 189. (e) Myers, A. G.; Barbay, J. K.; Zhong, B. J. *Am. Chem. Soc.* **2001**, *123*, 7207. (f) Massa, M. A.; Spangler, D. P.; Durley, R. C.; Hickory, B. S.; Connolly, D. T.; Witherbee, B. J.; Smith, M. E.; Sikorski, J. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1625.
(8) (a) Hunter, L.; Jolliffe, K. A. J.; Jordan, M. J. T.; Jensen, P.; Macquart, R. B. *Chem.—Eur. J.* **2011**, *17*, 2340. (b) Wang, Z.; Hunter, L. J. *Fluorine Chem.* **2012**, *143*, 143.

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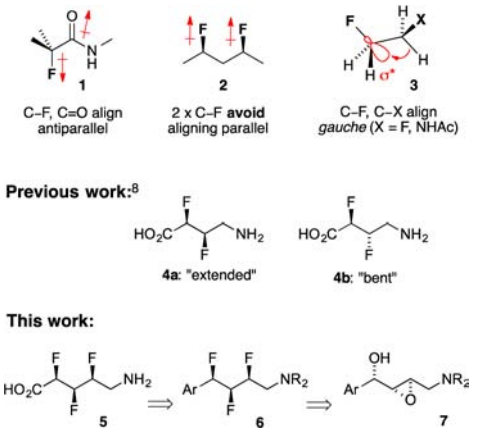


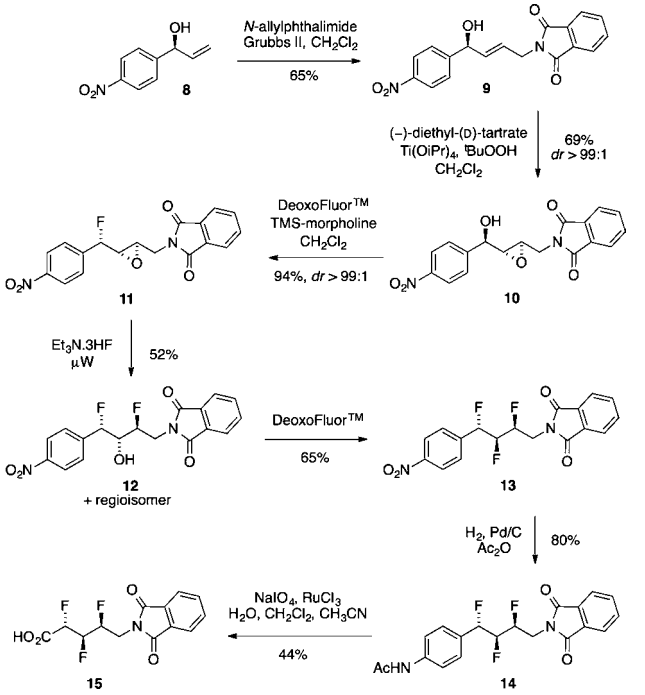
Figure 1. Fluorination affects molecular conformation (**1**–**3**); this concept is exploited by **4a**/**b** which have shape-dependent biological activity. Structure **5** is a target of this work.

stereoisomers of **4** have different preferred conformations, and this has led to applications of **4a**/**b** as subtype-selective GABA receptor ligands and as components of shape-controlled peptides.[9]

In a conceptual extension of this work, we recently became interested in the hypothetical α,*β*,*γ*-trifluoro-*δ*-aminopentanoic acid structure (**5**, Figure 1). We recognized that if such a *δ*-amino acid were incorporated into a peptide, it would preserve the same backbone length as a dipeptide of α-amino acids. At the same time, a peptide containing **5** could showcase all of the stereoelectronic effects outlined in Figure 1 (i.e., structures **1**–**3**) within the same molecule. The presence of three vicinal stereocenters should allow several different isomers (and hence, several different molecular shapes) to be created, with potential applications as, for example, *β*-turn elements in bioactive peptidomimetics. For these reasons, we were motivated to attempt a synthesis of some of the stereoisomers of **5**.

We reasoned that the trifluoro moiety of **5** could potentially be created via a sequential nucleophilic deoxyfluorination approach (Figure 1), based on methods developed by O'Hagan and co-workers for the synthesis of other multivicinal fluoroalkane systems in which the fluoroalkyl moieties are flanked by alkyl, arylalkyl, or tosylate groups.[10,11] Thus, an epoxy alcohol (**7**) could be subjected to deoxyfluorination, followed by epoxide opening with fluoride, followed by deoxyfluorination of the newly formed alcohol group, to deliver the required vicinal trifluoro moiety (**6**). Meanwhile, we reasoned that the amino group of **5** should be protected throughout, and that an aryl group

Scheme 1. Synthesis of *anti*,*syn* Trifluoroamino Acid **15**



could serve as a latent carboxylic acid until the end of the synthesis.[4a,8,12] Finally, variation of the stereochemistry of **7** should allow different isomers of **5** to be created.

We initially targeted the *anti*,*syn* diastereoisomer **15** (Scheme 1). Cross-metathesis of the enantiopure allylic alcohol **8**[13] with excess *N*-allylphthalimide delivered the disubstituted alkene **9** in good yield and exclusively as the *E* isomer. Asymmetric epoxidation[14] of **9** then furnished the epoxy alcohol **10** in good yield and with a diastereoisomeric ratio of greater than 99:1. The stage was now set for **10** to undergo three sequential nucleophilic fluorination reactions.[10] The first fluorination was performed by treating **10** with bis(2-methoxyethyl)aminosulfur trifluoride (DeoxoFluor), and this delivered the benzylic fluoride **11** in excellent yield. Benzylic deoxyfluorination reactions are often challenging due to competing S_N2 and S_N1 reaction mechanisms, but in this case the presence of an aryl nitro group, along with the additive TMS-morpholine,[15] ensured that the S_N1 mechanism was suppressed and the fluorination occurred with clean inversion of stereochemistry.

The second fluorination reaction (**11**→**12**, Scheme 1) was also challenging, due to the forcing conditions required to effect epoxide ring-opening. After considerable optimization, we found that treatment of **11** with neat triethylamine trihydrofluoride under microwave irradiation

(9) (a) Yamamoto, I.; Jordan, M. J. T.; Gavande, N.; Doddareddy, M. R.; Chebib, M.; Hunter, L. *Chem. Commun.* **2012**, *48*, 829. (b) Hunter, L.; Butler, S.; Ludbrook, S. B. *Org. Biomol. Chem.* **2012**, *10*, 8911. (c) Hunter, L. *Chim. Oggi* **2012**, *30*, 20.

(10) Brunet, V. A.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2009**, DOI: 10.3762/bjoc.5.61.

(11) (a) Hunter, L.; O'Hagan, D. *Org. Biomol. Chem.* **2008**, *6*, 2843. (b) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2005**, *127*, 482.

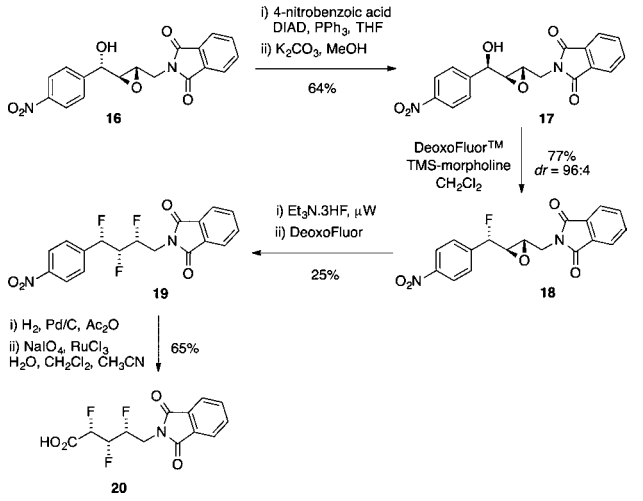
(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(13) (a) Stambasky, J.; Malkov, A. V.; Kocovsky, P. *J. Org. Chem.* **2008**, *73*, 9148. (b) George, S.; Narina, S. V. *Tetrahedron* **2006**, *62*, 10202.

(14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(15) (a) Bio, M. M.; Waters, M.; Javadi, G.; Song, Z. J.; Zhang, F.; Thomas, D. *Synthesis* **2008**, 891. (b) Bresciani, S.; O'Hagan, D. *Tetrahedron Lett.* **2010**, *51*, 5795.

Scheme 2. Synthesis of all-*syn* Trifluoroamino Acid **20**



delivered the desired difluoro alcohol **12**, along with the regioisomeric α,*β*-difluoro-*γ*-hydroxy compound (not shown), in moderate combined yield. The regioisomers of **12** were inseparable, but this was inconsequential because when both compounds were subsequently treated as a mixture with neat DeoxoFluor, they converged to deliver the desired *anti,syn* trifluoro product **13** in good yield. The aryl nitro group played another important role during the conversion of **12** into **13**: it suppressed neighboring group participation of the aryl group, a process which has caused undesired 1,2 aryl migration in related homobenzylic deoxyfluorination reactions with systems lacking a nitro group.[8,10]

With the trifluoro compound **13** in hand, the final task was to oxidize the aryl moiety to give the target carboxylic acid **15**. However the nitro group of **13**, having served a valuable purpose to this point, now posed a complication because only electron-rich aromatic groups are readily oxidized to carboxylic acids.[12] Therefore, we resolved to convert the nitro group of **13** into the corresponding aniline via hydrogenation. Isolation of the aniline derivative was not possible because it was susceptible to benzylic defluorination,[16] but performing the hydrogenation reaction in acetic anhydride as solvent allowed us to trap the hydrogenated product as the corresponding acetanilide **14** in good yield. Finally, we were gratified to discover that **14** could be readily converted into the target carboxylic acid **15**, albeit in moderate yield due to difficulties associated with the chromatographic purification of **15**.

Having successfully completed the synthesis of the *anti, syn* trifluoro amino acid **15** (Scheme 1), we next turned our attention to the all-*syn* target **20** (Scheme 2). This required as the starting material the all-*syn* epoxy alcohol **17**. We discovered that **17** could not be obtained directly via a Sharpless asymmetric epoxidation reaction,[14] due to

(16) (a) Hudlicky, M. J. *Fluorine Chem.* **1989**, *44*, 345. (b) Gamble, A. B.; Garner, J.; Gordon, C. P.; O'Conner, S. M. J.; Keller, P. A. *Synth. Commun.* **2007**, *37*, 2777. (c) Chung, D. S.; Kim, C. K.; Lee, B.-S.; Lee, I. *Tetrahedron* **1993**, *49*, 8359.

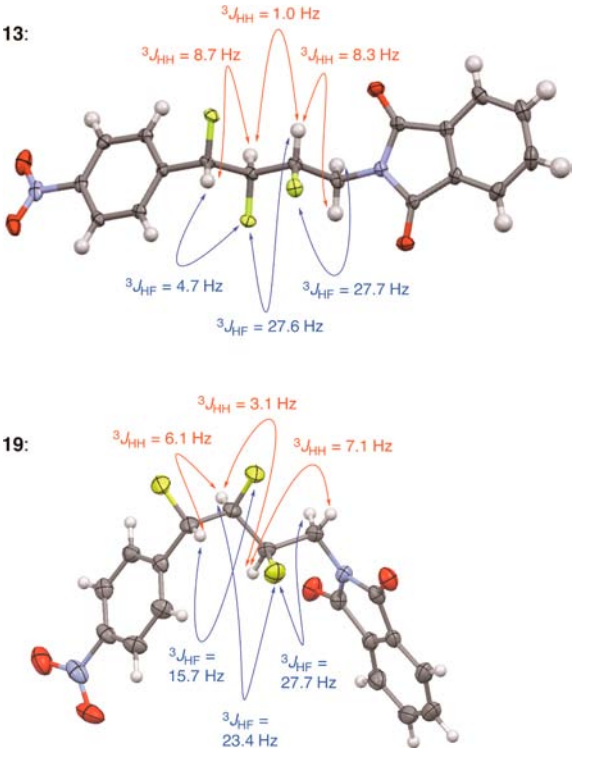


Figure 2. Crystal structures of the diastereoisomeric trifluoro compounds **13** and **19** and selected coupling constants from the corresponding ^{1}H NMR spectra.

a substrate−catalyst mismatch effect. However, we were able to employ **16** as an alternate starting material (Scheme 2), and inversion of the alcohol stereocenter via a Mitsunobu hydrolysis sequence[17] successfully delivered the requisite compound **17**. The first fluorination reaction provided fluoroepoxide **18** in good yield, along with a small quantity of the S_N1 product (not shown). The fluoroepoxide **18** was then carried through a four-step sequence analogous to that described in Scheme 1, to eventually deliver the all-*syn* target **20**.

Having completed our synthetic efforts, we were interested to compare the conformational behavior of the newly created, isomeric trifluoro motifs. We initially focused our attention on the precursors **13** and **19**, since both of these compounds are crystalline solids that were amenable to X-ray crystallographic analysis (Figure 2). A clear contrast is immediately evident in the overall backbone conformations of **13** and **19** in the solid state. The *anti,syn* isomer **13** adopts an extended zigzag conformation, which places the *β*-C−F and *γ*-C−F bonds *gauche* to one another (64°) and the *γ*-C−F bond *gauche* to the vicinal C−N bond (63°). These observations accord with the known preference of C−F bonds to align *gauche* to vicinal electronegative substituents (e.g., **3**, Figure 1).[3] The α-C−F and *β*-C−F bonds of structure **13** are aligned *anti* (177°), but this is

(17) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. *Chem. Rev.* **2009**, *109*, 2551.

unsurprising because the other possible staggered conformers about the Cα−Cβ bond of **13** would incur dipolar or steric repulsions (e.g., **2**, Figure 1).

The solid-state conformation of the all-*syn* isomer **19** (Figure 2) is very different from that of **13**. The carbon backbone of **19** has a bent geometry, which places all of the vicinal C−F and C−N bonds *gauche* to their neighbors (59°, 72°, 66°) while avoiding parallel 1,3-C−F alignments. The bent structure of **19** is reminiscent of geometries previously observed in other all-*syn* multivicinal fluoroalkanes,[6,11,18] and is fully consistent with the known conformational effects associated with C−F bonds (Figure 1).[3]

To confirm that the observed conformations of **13** and **19** (Figure 2) are intrinsically preferred by the fluoroalkyl chains rather than being an artifact of crystal packing forces, we analyzed the ^{1}H NMR solution spectra of **13** and **19** (Figure 2). The vicinal H,H and H,F coupling constants of **13** all clearly fall within ranges typically associated with either *gauche* or *anti* alignments,[19] and in every case the suggested dihedral angle is fully consistent with the solid-state structure. This confirms that the extended structure is the intrinsically preferred conformation of **13**, and that there is relatively little conformational disorder even in solution. For compound **19**, the overall pattern of larger and smaller coupling constants once again suggests that the crystal structure accurately represents the minimum energy conformation. However, the coupling constants of **19** are somewhat more intermediate in magnitude than those of **13**, suggesting that more conformational averaging may be occurring for **19**.

Elucidating the conformational behavior of amino acids **15** and **20** is not straightforward because they are not crystalline solids and their NMR spectra contain broad and overlapping NMR signals. However, a preliminary *J*-based analysis suggests that the different trifluoro amino acid isomers also have contrasting conformations: the *anti*, *syn* trifluoro amino acid **15** seems to adopt an extended geometry while the all-*syn* isomer **20** prefers a bent shape.[20] Further work is ongoing in our laboratory to more comprehensively investigate the conformations of these amino acids and their analogs.

In summary, we have synthesized two novel δ-amino acid derivatives (**15**, **20**), each of which contains three vicinal fluorine atoms placed stereospecifically along the backbone. Notable features of our synthetic approach to these small but densely functionalized targets include the successful stereochemical control throughout, and an expedient method for converting a nitroaryl moiety into a carboxylic acid group. The conformations of two precursor trifluoro compounds (**13**, **19**) have been compared in the solution and solid states, and it emerges that the different diastereoisomers have strikingly different conformations, consistent with known stereoelectronic effects associated with C−F bonds. This suggests that the amino acids **15** and **20** may have valuable applications as components of shape-controlled bioactive peptides in the future.

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Supporting Information Available. Synthetic procedures, characterization data, crystallographic information, and reproductions of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) (a) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422. (b) Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7887.

(19) (a) Ihrig, A. M.; Smith, S. L. *J. Am. Chem. Soc.* **1970**, *92*, 759. (b) Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1998**, *63*, 4967.

(20) See the Supporting Information.