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Synthesis of L-4,4-Difluoroglutamic Acid via Electrophilic Difluorination of a Lactam

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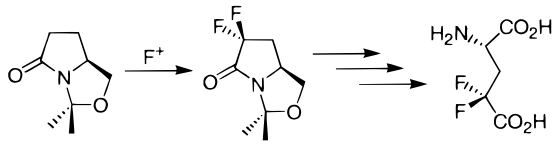
ABSTRACT



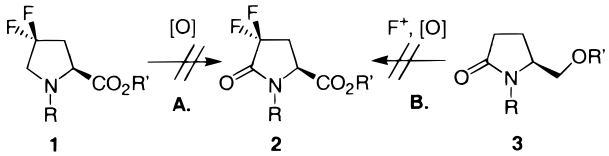
An enantiomerically pure bicyclic lactam proved to be an excellent substrate for electrophilic difluorination using *N*-fluorobenzenesulfonimide. The resulting difluorinated lactam can be easily converted into L-4,4-difluoroglutamic acid. To the best of our knowledge, this is the first example of a synthetically useful electrophilic difluorination of an unactivated lactam.

Our laboratory is interested in studying the biochemical and physiological properties of fluorine-containing molecules. Specifically, fluorinated glutamic acids have been used to probe the enzymatic poly-γ-glutamylation and corresponding hydrolysis of folates and antifolates.[1] In these biochemical experiments, stereochemically pure substrates are most informative.

4,4-Difluoroglutamic acid is an attractive unnatural amino acid target because it can be used as is or easily converted to 4,4-difluoroglutamine, 4,4-difluoroornithine, and other derivatives arising from regioselective reaction at the CF_2-CO_2R carboxyl group.[2] A stereoselective synthesis of L-4,4-difluoroglutamate[3,4] has been reported, but it requires a commercially unavailable starting material that is costly and difficult to prepare. As a result, biochemical studies from this laboratory have relied on material arising from an alternate synthesis which produces a mixture of both fluoroglutamate enantiomers.[1d]

A method for synthesizing fluoroglutamates previously found to be effective involves DAST-mediated fluorination of an appropriate oxoproline followed by RuO_4-mediated oxidation of the heterocycle to a lactam.[5] The resulting fluorinated pyroglutamate derivatives can be easily converted to the corresponding acyclic amino acids. Unfortunately, this strategy could not be applied to the synthesis of L-4,4-difluoroglutamic acid. The required enantiomerically pure difluorinated proline **1**[6] was completely resistant to RuO_4 oxidation (Scheme 1, path A), and thus the conversion to **2** was unsuccessful.[7] Presumably, this is due to the strong

Scheme 1



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electron-withdrawing effect of the difluoromethylene group adjacent to the site of oxidation.

Electrophilic fluorination using so-called "N−F" reagents has grown in popularity and application in recent years as a method for the selective fluorination of activated aromatics, alkenes, and enolates.[8] We envision electrophilic fluorination of a pyroglutamate-derived lactam enolate as a means to synthesize fluoroglutamic acids substituted in the 4-position while completely avoiding the problematic RuO_4 oxidation.

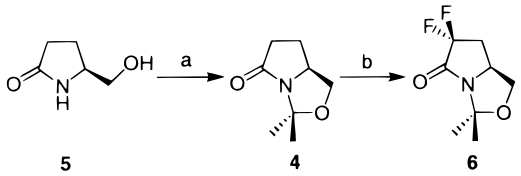
Despite increased use of these reagents, reports of electrophilic N−F *di*fluorinations in the literature are few in number. Recently, success was reported in the difluorination of benzylic phosphonates, nitriles, sulfonates, and tetrazoles.[9] Such reactions appear to be dependent on the acidity of the hydrogens being replaced,[10] which must be great enough to enable formation of the required α-fluoro carbanion intermediate. According to this argument, the fact that the carbanions in these benzylic substrates are stabilized by resonance with unsaturated functionality on either side probably plays a role in the success of their difluorination. An early study supports such an acidity argument and reports low yields for the difluorination of relatively less acidic alkyl amides and esters.[11] Indeed, all examples of electrophilic N−F difluorinations of amide enolates we have found in the literature involve compounds with additional unsaturated functionality in the β-position relative to the amide carbonyl.[12] In apparent contrast to this generalization is another report of the successful electrophilic N−F difluorination of an unactivated lactone.[13] While the α-CH protons of an ester are more acidic than an amide,[14] this result was nonetheless encouraging in the context of the present work.

A series of monocyclic compounds corresponding to **3** with various combinations of protecting groups (R, R′) was synthesized, and NFSi-mediated difluorination was attempted using a wide variety of strong bases and reaction conditions. Unfortunately, these attempts to access **2** were also unsuccessful (Scheme 1, path B) and the reaction conditions used resulted primarily in monofluorinated products.[15]

Ultimately, the bicyclic lactam **4** was focused on as a difluorination substrate. This compound is attractive because it is easily available in chirally pure form and has both its nitrogen and oxygen atoms protected simultaneously by a single moiety. Most importantly, this compound has been dialkylated sequentially (LDA/MeI) in excellent yields.[16]

The synthesis and fluorination of **4** is shown in Scheme 2. The sequence starts with the well-known chiral pyroglutaminol **5** obtained in two steps from L-glutamic acid using the method of Pickering et al.[17] Protection and ring closure was accomplished with 2,2-dimethoxypropane (DMP) using a modification of the procedure of Allen et al.[18] Lactam **4** was treated with 1.1 equiv of LDA followed by 1.3 equiv of NFSi at −78 °C to give a mixture of monofluorinated diastereomers in a 1.2:1.0 ratio and 59% total yield. The mixture was subjected to the same fluorination conditions a second time, and the difluorinated product **6** was obtained in 71% yield.

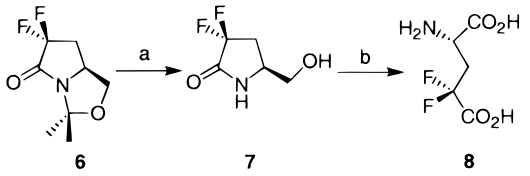
Scheme 2



a. DMP, TsOH, $PhCH_3$ 80-90°C (83%) b. 1) LDA, NFSi, THF -78°C (59%). 2) LDA, NFSi, THF -78°C (71%).

The conversion of compound **6** to L-4,4-difluoroglutamic acid **8** is outlined in Scheme 3.[19] It was anticipated that this might be carried out in only two steps via RuO_4-mediated oxidation of the cyclic ether of **6** to a lactone followed by acid hydrolysis. Unfortunately, treatment of **6** with RuO_4 led to the undesired, but not unprecedented,[20] hydroxylation of the chiral bridgehead CH carbon. Therefore, the difluorinated bicyclic lactam was cleanly deprotected with acetic acid in

Scheme 3



a. AcOH / CH_3CN / H_2O, 90°C (75%) b. 1) H_2CrO_4, acetone 2) 6N HCl, reflux (45%, 2 steps).

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acetonitrile−water to yield difluoropyroglutaminol **7**. Initially, aqueous oxidation of **7** with O_2 and a platinum catalyst was investigated, but the reaction was found to be sluggish and inconsistent. Instead, **7** was successfully oxidized with the Jones reagent in acetone, and the resulting difluoropyroglutamate intermediate was hydrolyzed with aqueous HCl. After neutralization and crystallization, the desired fluoroamino acid **8** was obtained.

In summary, electrophilic fluorination of the bicyclic lactam **4**, obtained in three steps from L-glutamic acid, results in the difluorinated derivative **6**. This result represents the first synthetically useful "N−F"-mediated difluorination of an unactivated amide that we are aware of. A straightforward three-step sequence converts **6** to the title compound L-4,4-difluoroglutamic acid **8**. All reaction steps proceed in good yield and utilize only readily available starting materials and reagents.[21]

Clearly, this fluorination chemistry is not limited only to the application described here. These new reactions provide a general route to other difluorinated amides, esters, carboxylic acids, and various derivatives which can be utilized and expanded upon in the future. Further optimization of the electrophilic fluorination reaction is now underway including the investigation of a one-pot difluorination procedure.

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Supporting Information Available: Descriptions of experimental procedures and characterization data for compounds **6**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) A recently published abstract also describes a synthesis of the title compound involving elaboration of a difluoroolefin, but published experimental details are unavailable at this time (Richards, N. G. J.; Ding, Y. Presented at the 218th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, New Orleans, LA, August 1999; Paper MEDI 244).