Electrophilic Fluorination of Pyroglutamic Acid Derivatives: Application of Substrate-Dependent Reactivity and Diastereoselectivity to the Synthesis of Optically Active 4-Fluoroglutamic Acids

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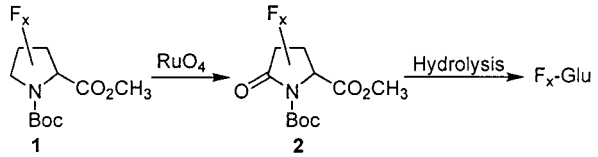
Electrophilic fluorination of enantiomerically pure 2-pyrrolidinones (**4**) derived from (L)-glutamic acid has been investigated as a method for the synthesis of single stereoisomers of 4-fluorinated glutamic acids. Reaction of the lactam enolate derived from **9** with NFSi results in a completely diastereoselective monofluorination reaction to yield the monocyclic trans-substituted α-fluoro lactam product **21**. Unfortunately, a decreased kinetic acidity in **21** and other structurally related monofluorinated products renders them resistant to a second fluorination. In contrast, the bicyclic lactam **12** is readily difluorinated under the standard conditions described to yield the α,α-difluoro lactam **24**. The difference in reactivity between the two types of related lactams is attributed mainly to the presence or lack of a steric interaction between the base used for deprotonation and the protecting group present in the pyrrolidinone substrates. This conclusion was reached based on analysis of the X-ray crystal structure of **21**, molecular modeling, and experimental evidence. The key intermediates **21** and **24** are converted to (2*S*,4*R*)-4-fluoroglutamic acid and (2*S*)-4,4-difluoroglutamic acid, respectively.

Introduction

Fluorinated amino acids are powerful molecular tools for bioorganic and medicinal chemists. The substitution of fluorine for hydrogen within the natural amino acid structure can impart dramatic, yet predictable, effects on chemical reactivity and is sterically conservative enough so that the resulting product is often still active in biological systems. Because of this fact, fluoroamino acids and larger molecules containing them have enjoyed widespread popularity and use in applications such as biochemical probes, alternate enzyme substrates, and enzyme inhibitors.[1,2] A consequence of this popularity is the existence of a large body of literature describing methods for the synthesis of these compounds.[3,4] Despite this progress, there remains a strong demand for improved strategies and synthetic routes.

This laboratory is interested in studying the biochemical and physiological effects of incorporating fluorine-containing glutamic acids into folates and antifolates in terms of their ability to enhance or hinder the formation and hydrolysis of poly-γ-glutamate conjugates.[5−9] In such investigations, the most valuable data are obtained from experiments utilizing synthetic substrates which are stereochemically pure. Thus, efficient and stereoselective routes to a variety of fluoroglutamate isomers are desired. One previously effective synthetic method relies on the general strategy shown in Scheme 1. Protected fluorinated prolines **1** are obtained by reaction of the corresponding oxygenated heterocycles with DAST and then converted to pyroglutamate derivatives **2** via oxidation with RuO_4. A final one-step hydrolysis of the protecting groups and lactam ring gives the desired fluoroglutamate products. Application of this strategy resulted in the synthesis of (2*S*,4*S*)-4-fluoroglutamic acid[7,10] and (2*RS*)-3,3-difluoroglutamic acid[11] for use as peptide building blocks and substrates in biochemical experiments.

Scheme 1



Unfortunately, the DAST/RuO_4 method cannot be applied to the synthesis of (2*S*)-4,4-difluoroglutamic acid. Synthesis of the necessary enantiomerically pure di-

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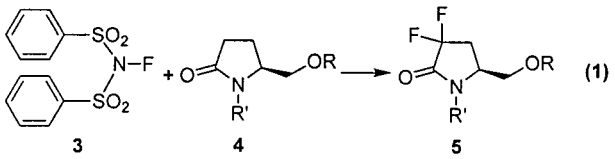
fluorinated proline[12,13] and application of the strategy shown in Scheme 1 was unsuccessful due to the complete failure of the RuO_4 ring oxidation.[14] This result is consistent with an oxidation mechanism proceeding through a carbocation intermediate as suggested by Lee,[15] although evidence for alternate possibilities has been reported.[16] In any case, it is clear that the strongly electron-withdrawing CF_2 group produces an insurmountable destabilizing effect on this transformation. In addition, even in the cases of fluorinated proline derivatives where RuO_4 oxidation is successful, the transformation suffers from the problem of extended reaction times and inconsistent yields.

Electrophilic fluorination using so-called "N−F" reagents is a method emerging in recent years for the selective introduction of fluorine at electron-rich centers such as alkenes, aromatics, and carbanions.[17,18] These reagents are usually stable solids which can be used with standard laboratory glassware and lack the high reactivity, corrosiveness, and toxicity of earlier sources of positive fluorine. One such compound possessing particular popularity and commercial availability is *N*-fluorobenzenesulfonimide (NFSi, **3**).[19] Electrophilic fluorination of pyroglutamate-derived lactam enolates was envisioned as a means to provide fluoroglutamates substituted in the 4-position while completely avoiding the problematic RuO_4 ring oxidation. It was anticipated that treatment of a compound such as **4** with a deprotonation/NFSi fluorination sequence would lead to an intermediate **5** (eq 1) which could be converted to the desired (*2S*)-4,4-difluoroglutamic acid as a single stereoisomer.



3 **4** **5** (1)

Electrophilic fluorination of enolates is advantageous in that it can utilize a large body of existing carbanion chemistry. Reactions of electrophiles with enolates of lactams related to the general structure **4** having various combinations of protecting groups are numerous in the literature and generally proceed with significant diastereoselectivity. The major products of such monosubstitutions most commonly contain the two ring substituents in a trans relationship to each other.[20] Thus, it may be possible to use electrophilic fluorinations or other substitutions for the synthesis of monofluorinated 4-fluoroglutamates while taking advantage of this stereochemical bias to control the configuration at the site of fluorination and avoiding the problematic RuO_4 ring oxidation.

This report describes the investigation of electrophilic fluorination of pyroglutamate-derived pyrrolidinone lactams with NFSi and its application to the synthesis of fluorinated glutamic acids.

Results

Synthesis of Fluorination Substrates. The synthetic routes utilized in preparing the protected lactams for this work are shown in Scheme 2. These pathways illustrate a general strategy for obtaining a wide variety of N,O-protected pyroglutaminols. This class of compounds was selected as substrates in preference to protected pyroglutamates and acyclic glutamates based on some unpromising preliminary results involving N-Boc pyroglutamate ethyl ester and concerns over unwanted side reactions such as α-carbon racemization which are possible in the presence of an excess of various strong bases.[21] Path A allows access to trityl or silyl ether protection at the primary alcohol (R) with any desired amide protecting group (R′). Path B results in benzyl or 4-methoxybenzyl (PMB) protected amides (R′) and any desired ether protecting group for the alcohol (R). The starting material in every case is L-glutamic acid, which makes these pathways attractive for use on larger scales. Utilization of this starting material ultimately results in the same natural L, or 2*S*, configuration in the final products. While this configuration is of greatest interest for most biological studies, the use of D-glutamic acid and the same chemistry should provide access to the corresponding D-fluoroglutamate stereoisomers. Various examples and combinations of each type of protection were prepared and examined as fluorination substrates.

Monofluorination of Lactam Substrates. To study the reactivity and diastereoselectivity of the electrophilic fluorination reaction, each substrate was subjected to a set of standardized monofluorination conditions which are described in the Experimental Section. The results, derived from NMR analysis (^1H, ^{19}F) and material recovered after chromatography, are summarized in Table 1. With only one exception (**10**), successful diastereoselective monofluorination was observed. In general, substrates with benzyl protecting groups for the amide led to higher yields and greater diastereoselectivity than those protected with a Boc carbamate. Interestingly, there was no particular correlation between the degree of diastereoselectivity and the size of the oxygen protecting group. There were also no predictable trends based on whether this group was an alkyl or silyl ether.

Clear exceptions to these general trends were compounds **9** and **10** which both contain a trityl ether. Subjecting **10** to these conditions led mainly to unchanged starting material while monofluorination of **9**, although low-yielding, showed complete diastereoselectivity and produced only a single monofluorinated product. An X-ray crystal structure of this product was obtained, and the fluorine was found to be in a trans relationship with respect to the protected hydroxymethyl group across the lactam ring.[22] By comparison of ^1H and

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(22) Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 166557. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Scheme 2

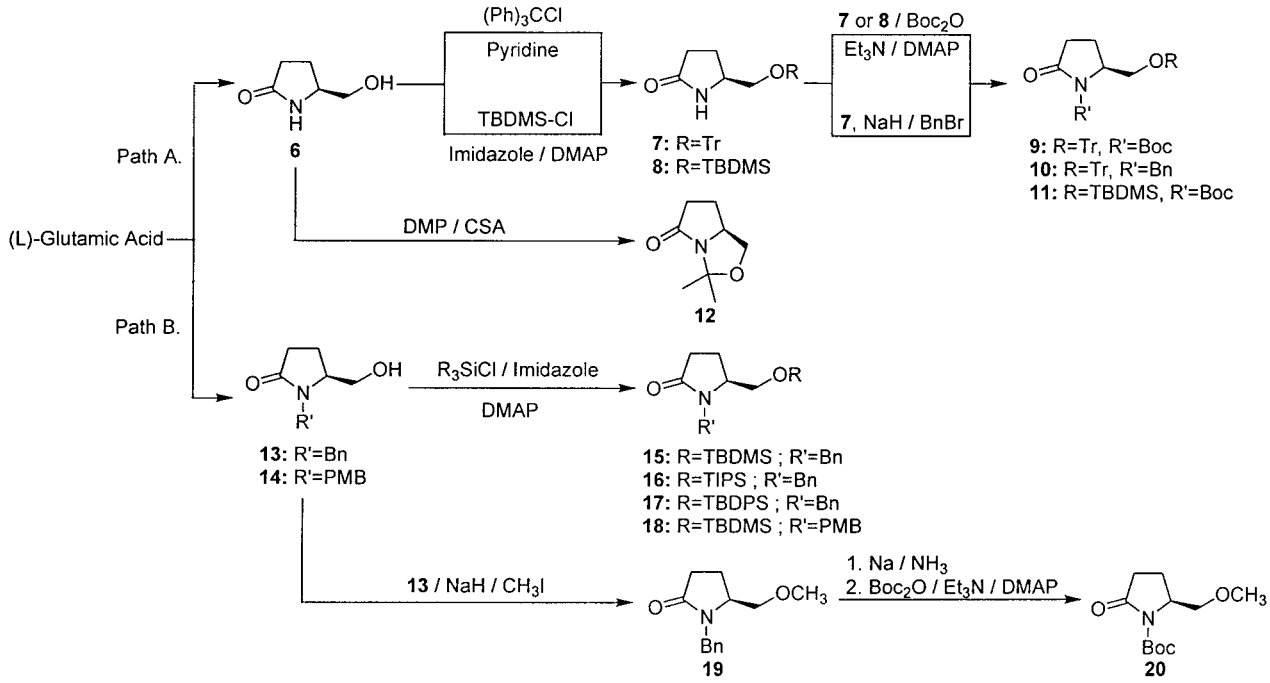
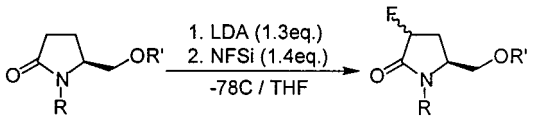


Table 1. Summary of Lactam Monofluorinations with NFSi[a]



compound	R	R′	% yield[b]	isomer ratio[c]
15	Bn	TBDMS	68	5.7:1.0[d]
17	Bn	TBDPS	66	3.3:1.0
16	Bn	TIPS	>50[e]	4.9:1.0
19	Bn	CH_3	70	5.7:1.0
10	Bn	$C(Ph)_3$	0	N/A
18	4-(MeO)-Bn	TBDMS	64	4.9:1.0
11	Boc	TBDMS	40	1.6:1.0
20	Boc	CH_3	<38[f]	1.7:1.0
9	Boc	$C(Ph)_3$	20	single isomer
12	N/A	N/A [bicylic]	59	1.2:1.0

[a] See Experimental Section for details. [b] Total yield of all fluorinated products. [c] Determined by NMR analysis of crude reaction mixtures. The trans isomer is the major product in each case. [d] Based on material recovered after chromatography. [e] Yield based on incomplete recovery of products after chromatography. [f] Yield based on complete recovery of products plus an inseparable impurity after chromatography.

^{19}F NMR coupling patterns and chemical shifts to this known diastereomer, the major products in all of the other standard monofluorination reactions were assigned to have the trans relative stereochemistry as well.

Difluorination of Lactam Substrates. During the course of examining the monofluorination of the monocyclic lactam **9**, it was noted that even in cases where an excess of base and NFSi was used, difluorinated products were not observed. Unfortunately, this observation continued when many subsequent deliberate attempts at difluorination under the standard conditions (Table 1 and Experimental Section) and closely related variants failed to yield any of the desired difluorinated lactam corresponding to **5** (eq 1).

In addition to these standard conditions, a number of other attempts were made to carry out electrophilic difluorinations of the lactam substrates. A recent report[23] described the electrophilic difluorination of the Corey lactone using NFSi. Consistent with the results here, difluorination of the lactone was not observed following simple treatment of the substrate with base followed by NFSi. Instead, it required a large excess of reagents and, most importantly, the presence of $ZnCl_2$ or $MnBr_2$. As a positive control, electrophilic difluorination of a commercial sample of the Corey lactone was attempted, and the reaction proceeded as described in the literature. Unfortunately, these same conditions did not result in difluorination of either unsubstituted (**9**, **15**) or trans-monofluorinated (**21**, **22**) pyrrolidinone lactams. A summary of these efforts is shown in Table 2. A trace of the desired product was periodically detected in the crude reaction mixture by ^{19}F NMR, but even this poor result was difficult to reproduce, and it was never possible to isolate, purify, and characterize any difluorinated monocyclic lactams.

In dramatic contrast to these results was the reactivity of the bicyclic substrate **12** toward difluorination. Under the standard monofluorination conditions (Table 1) it gave a good yield of monofluorinated product, but the least diastereoselectivity of any substrate examined. However, the most important observation regarding **12** was the appearance of a difluorinated product in the reaction mixture when an excess of LDA and NFSi was used, indicating a greater reactivity of **12** toward difluorination. This greater reactivity was confirmed when sequential treatment of **12** and then the monofluorinated intermediate **23** (Scheme 3) with the standard monofluorination conditions led to good yields of the difluorinated lactam **24**. Compound **24** was then converted in three steps to (2*S*)-4,4-difluoroglutamic acid providing a practical and efficient route to this stereochemically pure fluoroamino acid which was described in detail in a previous publication from this laboratory.[24]

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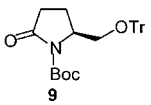
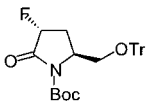
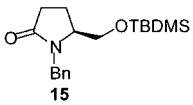
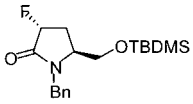
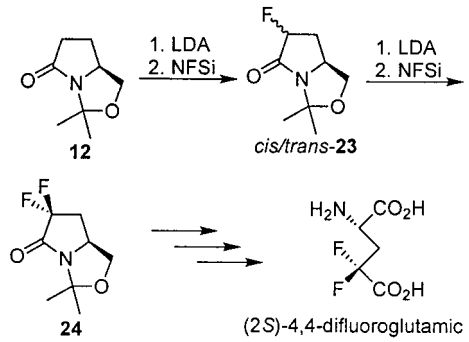
Table 2. Summary of Unsuccessful Electrophilic Difluorination Experiments[a]

Compound	Difluorination Conditions[b] Reagent (Equivalents Used)
 **9**	a. KHMDS (5.0), $MnBr_2$ (4.0), NFSi (4.0) b. KDA (3.0), NFSi (4.0)
 **21**	a. LiHMDS (1.4), NFSi (1.6), (3:1 THF / HMPA) b. KHMDS (2.5), $ZnCl_2$ (2.0), NFSi (2.5) c. KDA (1.5), NFSi (1.5)
 **15**	a. NaHMDS (2.2), NFSi (2.2) b. KHMDS (5.0), $MnBr_2$ (4.0), NFSi (4.0)
 **22**	a. KDA (1.0), NFSi (1.0)

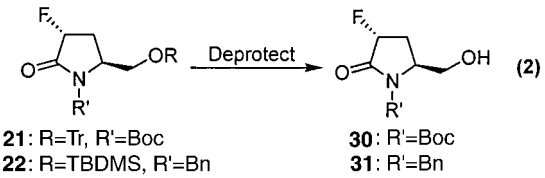
[a] Results were obtained by examination of the ^1H and ^{19}F NMR spectra of the crude reaction mixtures. The syntheses of **9** and **15** are outlined in Scheme 2. The monfluorinated derivatives **21** and **22** were obtained as shown in Scheme 4 and Table 1 (**15** → **22**), respectively. [b] All reactions were run in THF unless noted otherwise.

Scheme 3



Synthesis of (2*S*,4*R*)-4-Fluoroglutamic Acid. The completely diastereoselective monofluorination of **9** revealed great promise for the development of a synthetic route to (2*S*,4*R*)-4-fluoroglutamic acid, but the initial low yields required improvement. The reaction was examined in detail with respect to the base, temperature, dilution, reagent stoichiometry, and even reagent sources. The final successfully optimized procedure (Scheme 4, path A) used to obtain **21** (See Experimental Section) consistently gives yields of nearly 60% while maintaining the absolute trans diastereoselectivity.

Development of a method to convert **21** to (2*S*,4*R*)-4-fluoroglutamic acid was not straightforward. It was originally assumed that the best strategy to convert protected monofluorinated pyroglutaminols to fluoroglutamates involved initial selective deprotection of the oxygen protecting group as shown in eq 2. A partially protected intermediate, **30** or **31**, could then be oxidized to the required carboxylic acid while still maintaining



sufficient solubility in common organic solvents to allow for easy product extraction, isolation, and purification. Unfortunately, the best monofluorination substrate **9**, which yields a completely diastereoselective fluorination, contains protecting groups with very similar reactivity.

A wide variety of attempts were made to selectively remove the trityl group from **21** in good yield, although none were successful. These experiments included the use of protic acids (HCl, CSA, citric acid, formic acid), Lewis acids (BCl_3,[25] Et_2AlCl,[26] $Yb(OTf)_3$,[27]) hydrogenolysis (H_2/Pd−C, H_2/$Pd(OH)_2$, HCO_2NH_4/Pd−C), and others (CAN, CAN−SiO_2,[28] I_2/MeOH[29]). In some cases, the appearance of only the desired product **30** was observed initially, but it was soon followed by the undesired product in which both protecting groups had been removed at a rate such that a good yield of **30** could not be obtained in a single reaction step. Attempts to increase the yield of **30** by altering the reaction conditions were not successful.

An alternative to the use of **21** as a key intermediate was compound **22** which was derived from **15** and easily separated from its minor cis diastereomer in the crude fluorination reaction mixture (Table 1) using silica gel chromatography. Removal of the TBDMS ether (TBAF) to yield **31** then oxidation (RuO_4) and alkylation (CH_2N_2) to the corresponding methyl ester proceeded cleanly in good yields, but subsequent removal of the benzyl group was problematic. The only method which proved to be successful was a dissolving metal reduction ($Na/NH_{3(liq)}$), but these conditions caused undesired reduction of the C−F bond.

Conservative protecting group substitutions based on compound **9** designed to increase the difference in reactivity between the two different groups were envisioned, and two more protected pyroglutaminols were prepared. The first contained a 4,4′-dimethoxytrityl (DMT) ether instead of the trityl ether (R = DMT, R′ = Boc)[30] and the second contained a Cbz group instead of Boc (R = Tr, R′ = Cbz).[31] Unfortunately, attempted monofluorination of these analogues resulted in a mixture of multiple products and was not pursued further.

Ultimately, it became clear that conversion of **21** to (2*S*,4*R*)-4-fluoroglutamic acid would have to take place as shown in Scheme 5 via simultaneous removal of both protecting groups followed by a single-phase oxidation in a polar solvent. Thus, the Boc and trityl groups were removed with either aqueous HCl in MeOH or anhydrous trifluoroacetic acid (TFA) in the presence of triethylsilane to give the deprotected pyroglutaminol **27**. Oxidation of

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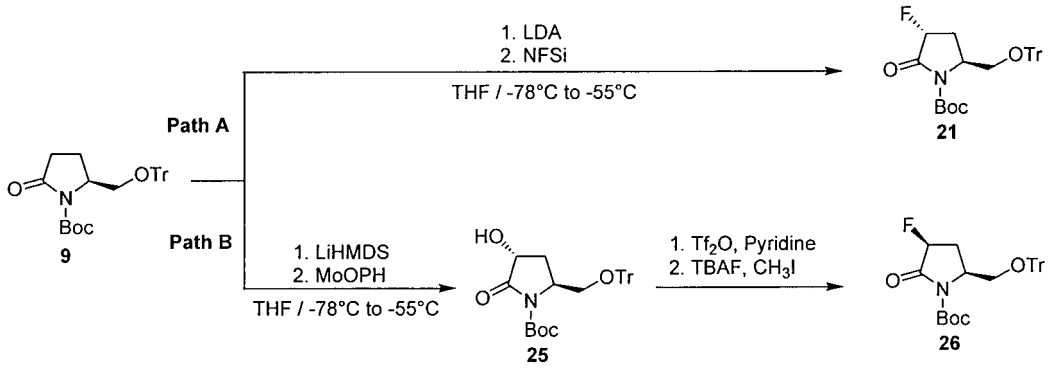
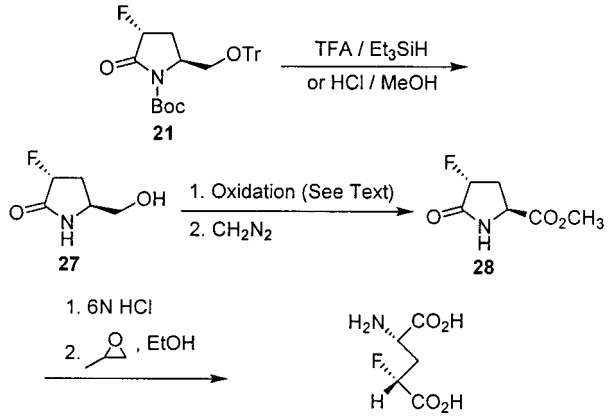
(28) Hwu, J. R.; Jain, M. L.; Tsai, F. Y.; Tsay, S. C.; Balakumar, A.; Hakimelahi, G. H. *J. Org. Chem.* **2000**, *65*, 5077.
(29) Wahlstrom, J. L.; Ronald, R. C. *J. Org. Chem.* **1998**, *63*, 6021.
(30) Prepared from **6** by reaction with DMT-Cl (1.1 equiv) and pyridine (1.3 equiv) in CH_2Cl_2 followed by Boc protection according to the method used for **9**.
(31) Prepared from **7** by deprotonation with LiHMDS (1.1 equiv) in THF at −78 °C followed by reaction with Cbz-Cl (1.2 equiv).

Scheme 4



Scheme 5



small polar alcohols such as **27** to the corresponding carboxylic acids in good yield with convenient product isolation is a challenge. Initially, aqueous oxidation of **27** with O_2 and a platinum catalyst[32] was investigated, but the reaction was found to be sluggish and inconsistent. Both a single-phase RuO_4 oxidation in aqueous acetone[33] and the Jones reagent under standard conditions consumed the starting material, but the reaction was not clean, and a mixture of undesired byproducts was formed. Similar problems regarding the oxidation of polar molecules have been encountered in the area of carbohydrate chemistry. In some cases, these have been overcome utilizing catalytic TEMPO and stoichiometric hypochlorite as a primary oxidant.[34] Treatment of **27** with TEMPO/NaBr/NaOCl in deionized water kept basic (pH $\geq$ 10) with aqueous NaOH[35] resulted in a complex mixture of products. Spectroscopic analysis of the product mixture gave evidence of NaOCl-mediated N-chlorination of the amide in **27** followed by elimination and further decomposition in the strongly basic medium. Thus, such undesired chlorination reactions should be considered when substrates with unprotected N−H bonds are involved. An alternative to hypochlorite as a primary oxidant when utilizing TEMPO is bis-acetoxyiodobenzene (BAIB).[36,37] A variety of experiments involving the TEMPO/BAIB combination were carried out, but unfortunately this method also was found to be inconsistent and problematic for the conversion of the alcohol **27** to the corresponding carboxylic acid. Finally, success was achieved by returning to the TEMPO/NaOCl system and using a milder reaction medium. When this oxidation was carried out in a mixture of acetone and 5% aqueous $NaHCO_3$, the desired acid product was obtained cleanly without any of the previously observed undesired byproducts. Also successful was the application of a method utilizing catalytic chromium trioxide (CrO_3) and periodic acid (H_5IO_6) in wet acetonitrile[38] and modification of the reported standard procedure to avoid an aqueous−organic partition in the workup step. The crude carboxylic acid product was esterified to give **28** which could be isolated and purified by standard silica gel chromatography. A final HCl hydrolysis followed by propylene oxide neutralization of the crude amino acid hydrochloride gave the desired product (2*S*,4*R*)-4-fluoroglutamic acid **29** as a single stereoisomer.

Indirect Cis Fluorination of Chiral Pyroglutaminols. Due to the trans directing effect observed for the reaction of electrophiles with enolates derived from lactams such as **9**, it is not possible to synthesize (2*S*,4*S*)-4-fluoroglutamic acid directly via electrophilic fluorination because the required intermediate contains a cis relationship between the incoming fluorine and the substituent at the existing chiral center.

The conversion of aliphatic alcohols to alkyl fluorides with inversion of configuration is often successful as a strategy for selective fluorination. Thus, it was proposed that a diastereoselective electrophilic hydroxylation of **9** followed by fluorination with stereochemical inversion could provide access to the cis-substituted intermediate **26** while still taking advantage of the strong trans directing effect present in this substrate. A similar strategy had been attempted previously for the synthesis of intermediates which could be converted into fluoroglutamates.[39] In the present case, the electrophilic hydroxylation of the lactam enolate of **9** with a good yield and high stereoselectivity had already been reported.[40] Thus, deprotonation of **9** and reaction with MoOPH[41] according to the literature method as shown in Scheme 4 gave the trans-substituted alcohol **25**. The diastereo-

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selectivity of this reaction was analogous to that of the corresponding fluorination (**9** → **21**) and none of the cis-substituted alcohol was observed within the limit of NMR detection while analyzing the crude reaction mixture.

Reaction of **25** with either DAST or Deoxo-Fluor[42] produced the desired product, but in low yields. Instead of pursuing these reagents further, the alcohol was converted to the corresponding triflate, and reaction with a nucleophilic fluoride source was investigated. Treatment of the triflate with an excess of TBAF solution at −78 °C led to the formation of an initial reversible adduct characterized by a bright yellow color and a new spot observed by TLC. A quench of the reaction at this point led to the recovery of the original triflate starting material. However, when the reaction solution was allowed to slowly warm and stir at room temperature, the desired cis-substituted product **26** was observed by NMR. During experiments designed to trap the initially formed adduct, hypothesized to involve reversible addition of fluoride to the electron deficient lactam carbonyl, it was discovered that addition of iodomethane to the reaction mixture before warming to room-temperature resulted in a cleaner substitution reaction with less undesired side products.

Development of this route to **26** (Scheme 4, path B) provides the key component required for an alternate synthesis of (2*S*,4*S*)-4-fluoroglutamic acid utilizing a diastereoselective electrophilic pyrrolidinone enolate substitution and avoiding the problematic RuO_4 oxidation. Utilization of the chemistry shown in Scheme 5 for the synthesis of (2*S*,4*R*)-4-fluoroglutamic acid should allow for conversion of **26** to the diastereomeric (2*S*,4*S*)-4-fluoroglutamic acid. The most important use of the cis-substituted compound **26**, however, was as a tool for examining the reactivity differences with respect to difluorination between the monocyclic and bicyclic substrates used in this work (see Discussion).

Discussion

The development of convenient and readily available sources of electrophilic fluorine over the past decade has led to a rapidly expanding body of new literature describing their application in organic synthesis. In this work, it was proposed that the use of electrophilic fluorination of reduced pyroglutamic acid derivatives would provide an efficient route to single stereoisomers of 4-fluoroglutamic acids and eliminate the need for a problematic RuO_4 oxidation associated with an earlier route to these compounds.[7,10] Of particular interest was (2*S*)-4,4-difluoroglutamic acid, a target which was readily available only in racemic form.[8] However, the ability to control the stereochemistry of electrophilic monofluorinations leading to single stereoisomers of 4-fluoroglutamic acid was also an attractive concept.

The electrophilic monofluorinations of the substrates shown in Table 1 proceed, with the exception of the bicyclic lactam **12**, with significant diastereoselectivity. Consistent with numerous other substitution reactions of optically active 5-substituted-2-pyrrolidinone lactam enolates appearing in the literature, the major products of these fluorinations have a trans relationship between the fluorine and the substituent at the adjacent chiral center. This finding provides further evidence that existing carbanion chemistry can be transferred successfully to electrophilic fluorination reactions. The origin of the facial selectivity in pyrrolidinone alkylations and substitutions has been investigated in particular detail in recent years.[43−45] While some debate still remains, it is clear that the selectivity results from a combination of steric, torsional, and electronic effects. It is not surprising that compound **12**, the fluorination substrate with the least steric differentiation between the two faces of its lactam ring, also exhibits the least diastereoselectivity in monofluorination. In sharp contrast is the completely diastereoselective monofluorination of **9**, which might initially be attributed strictly to steric hindrance from the bulky triphenylmethyl protecting group. However, Table 1 includes a variety of other ethers ranging in size from the equally bulky TBDPS to the much smaller methyl. These other compounds also show diastereoselectivity in fluorination, but the magnitude is much less relative to **9**, and this selectivity does not vary significantly with ether size. This provides evidence that contributions in addition to steric factors are also likely to play a role in determining the degree of diastereoselectivity observed in **9**. Thus, good to excellent levels of diastereoselectivity can be obtained with the proper choice of protecting groups, although it may not always be possible to predict the absolute best combination a priori. The most striking result of these experiments, illustrated in Scheme 6, is the dramatic difference in reactivity with respect to electrophilic difluorination between protected monocyclic pyroglutaminols and the bicyclic pyrrolidinone **12**. To explain this difference, the questions of why the monocyclic lactams such as **9** cannot be difluorinated under these reaction conditions and what factors in **12** make it more reactive toward difluorination must be addressed.

It is now well established that the ease of electrophilic fluorination using N−F reagents for a given substrate depends strongly on the acidity of the hydrogen being replaced. Accordingly, active methylene groups in malonates are the most reactive and can be converted to the corresponding difluoromethylene derivatives even by reaction with only the N−F reagent and no added base.[46] Protons positioned next to an amide carbonyl are much less acidic, and therefore electrophilic fluorination at this position is expected to be more difficult. In fact, prior to the experiments reported here an electronic reaction search utilizing CAS SciFinder and Beilstein Crossfire yielded only a single example of the synthesis of an α,α-difluoroamide using N−F reagents involving a substrate which did not contain an additional activating group such as a carbonyl in the *β*-position.[47] Even in this single example, the substrate was a small unfunctionalized molecule and the yield was moderate at best. With respect to esters and lactones, the case in the literature was found to be largely the same, but a report of the N−F-mediated electrophilic difluorination of the Corey lactone in good yield[23] proved that such a reaction is

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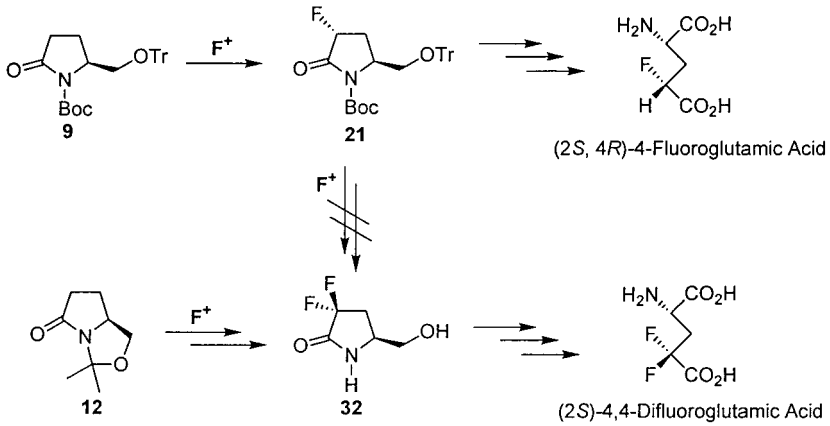
Scheme 6



indeed possible. Despite the fact that esters are more acidic than amides,[48] this result served as a significant inspiration prior to beginning this study.

The success in monofluorination of **9** clearly indicates that the acidity and reactivity of this compound, and other related monocyclic lactams from Table 1, are sufficient to allow deprotonation and reaction with NFSi. Given the strong connection between electrophilic fluorination and acidity, it is reasonable to assume that the failure to fluorinate **21** and other related monofluorinated monocyclic compounds (e.g., **22**) a second time (Table 2) is related to a decreased kinetic acidity of the fluoromethylene CHF proton in such intermediates relative to the corresponding methylene CH_2 protons in the original unfluorinated starting material. Despite its high electronegativity, it has been demonstrated that fluorine substitution can actually be a destabilizing factor for resonance-stabilized sp^2-hybridized carbanion formation when it is directly bonded to the carbon developing the negative charge.[49,50] Because of this α-fluoro carbanion effect, some fluorinated molecules are actually less acidic than their corresponding protio analogues. This effect should apply in compounds such as **21**, rendering them less acidic and more difficult to fluorinate a second time. However, the same effect will also be present in the bicyclic monofluorinated substrate **23** and therefore cannot explain the difference in reactivity between these two compounds.

The rate of deprotonation from a position next to a carbonyl depends on stereoelectronic, torsional, and steric effects.[51] Since the X-ray crystal structure of **21** is available, the structural and electronic features of this monocyclic 2-pyrrolidinone can be qualitatively evaluated and compared to the bicyclic lactam as shown in Figure 1. The transition state for CH deprotonation is stabilized by the stereoelectronic "CH-π-overlap effect". This stabilization results from orbital alignment between the CH σ bond to be broken, and therefore the p orbital of the developing anion, and the carbonyl π system. Maximum stabilization occurs when these orbitals are exactly aligned, which is the case when the dihedral angle between the proton being removed and the carbonyl oxygen is 90°. Figure 1A shows the Newman projection between C2 and C3 in **21**. The important H−C(3)−C(2)−O dihedral angle is 66.3°, a deviation from the ideal 90° for maximum orbital overlap in the transition state. Figure 1B shows the position occupied by the base during deprotonation of this intermediate. It is expected that the bulky bases used in these experiments (Tables 1 and 2) would encounter significant destabilizing steric repulsion from the trityl or any of the other ether protecting groups used in the monocyclic fluorination substrates. This is verified by noting that the crystal structure of **21** shows the trityl group is indeed positioned over the top face of the lactam ring. This final factor is very significant because if it is accepted that one fluorine will not significantly affect the conformation of **9** vs **21** then the deprotonation of the nonfluorinated substrate **9** will face nonideal stereoelectronic factors, but it can take place from the face opposite the trityl ether and not encounter the unfavorable steric interactions created by this large group. This is consistent with the experimental result that **9** can be fluorinated but the trans-substituted monofluorinated **21** cannot (Scheme 6). Thus, in addition to the desirable role it plays in directing the diastereoselectivity of monofluorination, a steric effect due to the ether protecting group in monocyclic pyroglutaminols appears to be responsible for the failure of the attempted electrophilic difluorinations (Table 2).

This explanation can be strengthened experimentally by noting that the major factor proposed to limit difluorination, an unfavorable steric interaction between the base and ether protecting group on the top face of the lactam ring, will only apply in the case of trans-substituted monofluorinated lactams such as **21**. Therefore, the corresponding cis-substituted lactam **26** should exhibit a greater reactivity than **21** under these conditions and difluorination should be possible. Indeed, when a sample of **26** obtained through the hydroxylation−fluorination method (Scheme 4) was subjected to the standard monofluorination conditions, the observed result was very different from that seen with **21**. The ^{19}F NMR spectrum of the resulting crude reaction mixture showed, in addition to a number of minor unidentified signals, three prominent resonances corresponding to the desired difluorinated lactam (δ −25 ppm), the trans-substituted lactam **21** (δ −110 ppm) and the cis-substituted starting material **26** (δ −108 ppm) in a ratio of 2:2:1. A mass spectrum of this mixture also served to verify the presence of these products which were not separable by silica gel chromatography. Clearly, unlike the monofluorinated substrates shown in Table 2, com-

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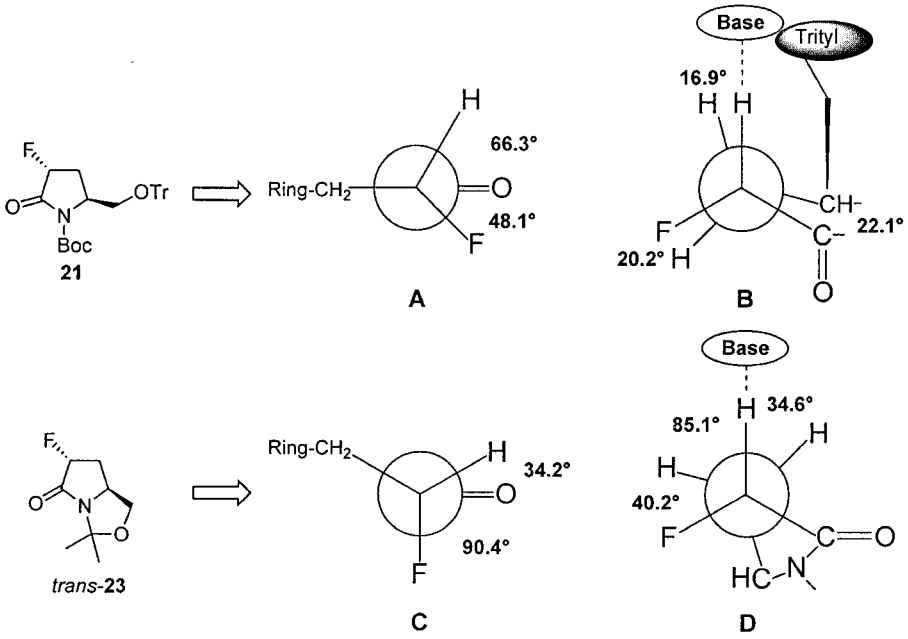

Figure 1. Newman projections through the C2−C3 (A,C) and C3−C4 (B,D) bonds of the X-ray crystal structure of **21** and the MM2 molecular mechanics model of *trans*-**23**.

pound **26** is deprotonated under these conditions, and the resulting enolate can react with NFSi resulting in difluorination. In addition, under the reaction conditions used, it appears that not all of the enolate generated was able to react with NFSi. Instead, some of it was reprotonated upon quenching to yield the epimerized product **21**. The completely diastereoselective monofluorination of **9** indicates that the top face of the *O*-trityl-protected lactam enolate ring may be too hindered to react with the bulky NFSi, but this must not be the case for the smaller proton donors (NH_4^+, H_3O^+) used to quench the reaction.

To complete the analysis, the factors outlined for the failure of substrates such as **9** to form difluorinated products must either be absent in the bicylic **12**, or other factors unique to this substrate which offset the decrease in kinetic acidity upon monofluorination must be present. Given the reactivity difference just described between the cis- and trans-substituted monofluorinated pyrrolidinones, some difluorination of bicyclic **23** might be expected since it is obtained from **12** as a near equal mixture of both cis and trans diastereomers (Table 1). On the basis of the yield of the difluorination step to give the product **24**, though, it is obvious that both stereoisomers of **23** have the ability to be difluorinated. By this same argument it might be suggested that difluorinated lactams should have been observed in the experiments summarized in Table 1 since cis-substituted lactams were present for many of the substrates after addition of NFSi to the reaction. It is likely, however, that difluorination was not observed since only a small excess of base was used and, in addition to the deprotonation/fluorination reaction, there is also a decomposition pathway between NFSi and the strong bases utilized in these experiments which serves to consume the reagents.[52]

The true nature of the concept of amide resonance has been the subject of a debate in recent years.[53] Accompanying this debate has been the study and characterization of distorted amides which possess either a significantly pyramidalized nitrogen, a perpendicularly twisted C(O)−N bond, or both. These distortions break the resonance interaction between the nitrogen lone pair and the amide carbonyl resulting in functional groups which are better described based on their reactivity and physical properties as amino-ketones than amides. As such, protons adjacent to the carbonyl of a distorted amide should be more acidic than those of a normal resonance-stabilized amide. Therefore, it was proposed that the constraints of the bicyclic system in **12** might adversely affect the amide resonance and make the α-protons more acidic than those in corresponding monocyclic pyrrolidinones. The crystal structure of **21** indicates that the amide nitrogen is almost perfectly planar with the three groups deviating from planarity by only 0.017 Å. In contrast, MM2 molecular mechanics and semiempirical PM3 modeling of **12** and the corresponding monofluorinated intermediates indicate a more distinct pyramidalization of the amide nitrogen which supports the hypothesis of a lack of amide resonance in **12**. However, the spectroscopic data contradict this. The ^{13}C NMR chemical shift is a reflection of the charge density around the carbon atom. Accordingly, distorted amides which lack electron donation from nitrogen are characterized by larger downfield carbonyl ^{13}C chemical shifts relative to planar amides. The average of the amide carbonyl ^{13}C chemical shift for every substrate in Table 1 except for the bicyclic **12** is 175.58 ± 0.28 ppm. The ^{13}C carbonyl chemical shift for **12** is 171.58 ppm. This represents a significant difference between **12** and the rest of the substrates, but the shift of **12** is *upfield* from the rest and not consistent with decreased amide resonance. The carbonyl IR absorption frequency is also diagnostic for evaluating the extent of amide distortion. The amide carbonyl of **12** absorbs at 1686 cm^{-1} which is consistent with a normal nontwisted lactam.

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To help evaluate stereoelectronic effects, an energy-minimized MM2 molecular mechanics model of *trans*-**23** was calculated for comparison with the crystal structure of **21**. Figures 1C and 1D illustrate the Newman projections of this model corresponding to those for the crystal structure of **21** in Figures 1A and 1B. As shown in Figure 1C, the calculated H−C(3)−C(2)−O dihedral angle is 34.2° which would correspond to much *less* CH-π-overlap stabilization for deprotonation from the top face relative to **21**. Therefore, what is probably the most important factor in this analysis is shown in Figure 1D. In contrast to **21**, deprotonation of *trans*-**23** will not face any steric hindrance between the base and a bulky ether protecting group because of the bicylic structure. Thus, the evidence is strong that decreased unfavorable steric interactions give *trans*-**23** a kinetic acidity sufficient to allow electrophilic difluorination.

In summary, it has been demonstrated that the 3,5-cis-substituted monofluorinated pyrrolidinones used in this work (**26**, *cis*-**23**) can be deprotonated, and the resulting lactam enolates will react with NFSi leading to difluorination. In the case of 3,5-trans-substituted monofluorinated pyrrolidinones, the bicyclic *trans*-**23** can also be deprotonated and fluorinated a second time but monocyclic substrates such as **21** cannot. Because monofluorinated lactams with a trans relationship between substituents are the major products produced from electrophilic monofluorination of substrates such as **9**, these monocyclic compounds do not allow for successful electrophilic difluorination. Only the bicylic **12** provides access to the necessary difluorinated lactam intermediate **24** enroute to (2*S*)-4,4-difluoroglutamic acid.

This work has demonstrated that electrophilic difluorination and diastereoselective electrophilic monofluorination of pyroglutamic acid derivatives can be used to synthesize (2*S*)-4,4-difluoroglutamic acid and (2*S*,4*R*)-4-fluoroglutamic acid. These new synthetic routes utilize only readily available reagents and avoid a problematic RuO_4 oxidation while providing products which are stereochemically pure. Ironically, in the process of developing a solution to this long-standing oxidation problem, other oxidation difficulties were encountered in the conversion of an alcohol to a carboxylic acid within a small polar molecule. This problem was ultimately solved, and the methods and process used should be of interest to others synthesizing unnatural amino acids and encountering similar challenges. Finally, given the utility of pyroglutamic acid derivatives, this chemistry and the various intermediates involved should be of interest for many applications in organofluorine chemistry beyond the amino acid syntheses reported here.

Experimental Section

General Methods. Thin-layer chromatography (TLC) was performed with standard Sigma-Aldrich brand silica gel 60 F-254 plates. Column chromatography was performed with silica gel 60 (230−400 mesh). Melting points were obtained on a Thomas-Hoover Mel-Temp apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on Bruker AVANCE DRX300 and DRX500 spectrometers using the X-WinNMR software. Chemical shifts are reported in parts per million (ppm) upfield or downfield from tetramethylsilane (internal standard for ^{1}H and ^{13}C) or trifluoroacetic acid (external standard for ^{19}F). Infrared spectra were obtained on a Nicolet 5-DX spectrometer. Mass spectra were obtained with a VG 70−250-S mass spectrometer made by Micromass (UK) and an Opus data system. X-ray crystal structure was obtained by the X-ray facility of the Department of Chemistry, The University of Michigan. Elemental analyses were obtained from the CHN/AA service of the Department of Chemistry, The University of Michigan. Molecular modeling was done using Spartan software from Wavefunction, Inc. and Cambridge Software's Chem3D Pro for Microsoft Windows.

(*S*)-5-(Hydroxymethyl)-2-pyrrolidinone **6** was synthesized by the method of Pickering et al.[54] (Scheme 2, path A) or purchased from Sigma-Aldrich. (*S*)-5-(*tert*-Butyldimethylsiloxymethyl)-1-(*tert*-butyloxycarbonyl)-2-pyrrolidinone **11** was synthesized from **6** via intermediate **8** using a minor modification of the method of Ikota.[55] (*S*)-5-(Hydroxymethyl)-1-(phenylmethyl)-2-pyrrolidinone **13** and (*S*)-5-(hydroxymethyl)-1-(4-methoxyphenylmethyl)-2-pyrrolidinone **14** were synthesized by modification of the procedure reported by Olsen et al.[56] (Scheme 2, path B). (*S*)-5-(Methoxymethyl)-1-(phenylmethyl)-2-pyrrolidinone **19** was synthesized from **13** as described by Brena-Valle et al.[20] Oxodiperoxymolybdenum(pyridine)−(hexamethylphosphoric triamide) (MoOPH) was prepared by the method of Vedejs and Larsen.[41] *N*-Fluorobenzenesulfonimide was obtained from Honeywell International, Inc. Solutions of *n*-butyllithium were obtained from Fisher-Acros. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Dichloromethane was freshly distilled from calcium hydride. Pyridine was distilled after heating 5 h at reflux over barium oxide. Diisopropylamine was distilled from sodium hydroxide. 1,1,1,3,3,3-Hexamethyldisilazane was distilled from calcium hydride. All other reagents and starting materials were obtained from Sigma-Aldrich or Fisher-Acros and used without further purification. Air- and moisture-sensitive reactions were run in flame- or oven-dried (T > 100 °C overnight) glassware under an atmosphere of dry nitrogen or argon.

(S)-5-(Trityloxymethyl)-2-pyrrolidinone (7). Compound **6** (1.0 g, 8.8 mmol) and triphenylmethyl chloride (3.64 g, 13.05 mmol, 1.5 equiv) were stirred in anhydrous pyridine (15 mL). The reaction was heated to 100 °C under a condenser and drying tube for 3 h. The mixture was cooled to rt and then slowly poured into vigorously stirred ice−water. Stirring of this mixture continued for 10 min until a yellow gum was deposited in the cloudy white water. This gum was washed and decanted with freshwater three times and then dissolved in CH_2Cl_2. This organic layer was washed with water and brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the resulting orange oil was partially purified using silica gel column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 19:1) to give a light yellow solid which contained the desired tritylated product plus a trace of residual pyridine. The product NMR spectrum matched that of authentic material obtained from Aldrich, and the sample was used for Boc protection without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 1H), 2.14 (m, 1H), 2.30 (m, 2H), 2.99 (t, 1H, J = 9.2 Hz), 3.20 (dd, 1H, J = 9.2, 3.9 Hz), 3.86 (m, 1H), 6.07 (br, 1H), 7.24−7.42 (m, 15H).

(S)-1-(*tert*-Butyloxycarbonyl)-5-(trityloxymethyl)-2-pyrrolidinone (9). Compound **7** (2.7 g, 7.6 mmol) was dissolved in CH_2Cl_2 (35 mL), and to the stirred solution were added Boc_2O (3.3 g, 15.2 mmol, 2 equiv), DMAP (1.0 g, 8.4 mmol, 1.1 equiv), and Et_3N (1.0 g, 9.9 mmol, 1.3 equiv). The solution was stirred at rt for 3 d. The reaction was diluted with CH_2Cl_2 (30 mL) and washed with water and then brine. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a dark orange oil which was purified by silica gel column chromatography (hexanes/EtOAc, 4:1) to give the desired product as a pale yellow solid (3.79 g, 8.3 mmol, 94% yield (two steps from **6**)). R_f = 0.43 (hexanes/EtOAc, 3:2); mp 113−115 °C (lit. 118−119 °C);[40] $[\alpha]^{23}_D = -32.3$ (c 1.05, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.94−2.11 (m, 2H), 2.44 (m, 1H), 2.78 (m, 1H), 3.10 (dd, 1H, J

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= 9.4, 2.7 Hz), 3.48 (dd, 1H, *J* = 9.4, 4.5 Hz), 4.26 (m, 1H), 7.29 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8, 28.4, 32.6, 58.0, 64.5, 83.1, 87.3, 127.6, 128.3, 129.0, 144.0, 150.1, 175.5; FAB-MS (3-nba with Na^+) *m/e* (rel intensity) 479.9 (MNa^+, 100.0), 380.0 (100.0), 165.0 (42.8), 136.0 (38.0), 106.0 (35.7); FAB−HRMS (3-nba with Na^+) *m/e* calcd for $C_{29}H_{31}NO_4Na$ (MNa^+) 480.2151, found 480.2146.

(*S*)-1-Phenylmethyl)-5-(trityloxymethyl)-2-pyrrolidinone (10). Compound **7** (200 mg, 0.56 mmol) was dissolved in THF and cooled to 0 °C. Dry NaH (18 mg, 0.73 mmol, 1.3 equiv) was slowly added. The mixture was stirred for 10 min after complete addition of the NaH, and then benzyl bromide (125 mg, 0.73 mmol, 1.3 equiv) was added. The flask was warmed to rt and allowed to stir overnight. The reaction was quenched with the slow addition of H_2O, and the solvents were removed in vacuo. The resulting residue was partitioned between EtOAc and H_2O. After separating layers, the aqueous layer was extracted further with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give an orange residue which was purified by silica gel column chromatography (hexanes/EtOAc, 3:2) to give the desired product as a colorless semisolid in quantitative yield. R_f = 0.55 (hexanes/EtOAc, 3:2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.93−2.11 (m, 2H), 2.41 (m, 1H), 2.63 (m, 1H), 3.15 (dd, 2H, *J* = 10.0, 3.7 Hz), 3.19 (dd, 1H, *J* = 10.0, 4.2 Hz), 3.65 (d, 1H, *J* = 15.0 Hz), 4.98 (d, 1H, *J* = 15.0 Hz), 7.03−7.40 (m, 20H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.0, 30.7, 44.5, 56.9, 63.4, 87.1, 127.4, 127.6, 128.1, 128.8, 136.8, 143.7, 175.7; CI-MS (NH_3) *m/e* (rel intensity) 448.3 (MH^+, 100.0), 243.1 (22.4), 206.1 (34.7), 188.1 (12.8); CI−HRMS (NH_3) *m/e* calcd for $C_{31}H_{30}NO_2$ (MH^+) 448.2276, found 448.2255.

(5*S*)-2,2-Dimethyl-8-oxo-1-aza-3-oxa-bicyclo[3.3.0]-octane (12). Compound **6** (10.4 g, 90.3 mmol) was dissolved in 2,2-dimethoxypropane (DMP) (40 mL), and camphorsulfonic acid (CSA) (500 mg, cat.) was added. The solution was refluxed for 4 h, and then the volatile components (DMP, MeOH) were removed in vacuo. Fresh DMP was added, and the mixture was again refluxed for 4 h. The process of evaporation and restarting was repeated a total of three times. After the final evaporation, the remaining residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$, water, and then brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the desired product as a pale yellow oil (12.3 g, 79 mmol, 87% yield). R_f = 0.52 (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 3H), 1.67 (s, 3H), 1.76 (m, 1H), 2.17 (m, 1H), 2.53 (m, 1H), 2.81 (m, 1H), 3.45 (t, 1H, *J* = 8.8 Hz), 4.08 (dd, 1H, *J* = 8.1, 5.6 Hz), 4.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 23.9, 24.5, 27.0, 37.4, 61.8, 70.0, 91.4, 171.6; EI-MS (70 ev) *m/e* (rel intensity) 155.1 (M^+, 1.9), 140.1 (M^+ − 15, 100.0), 98.1 (19.9), 84.0 (14.2), 70.1 (12.2); EI−HRMS (70 ev) *m/e* calcd for $C_8H_{13}NO_2$ (M^+) 155.0946, found 155.0941.

General Procedure for the Silation of *N*-Benzyl-Protected 5-(Hydroxymethyl)-2-pyrrolidinones (15−18). The free alcohol (**13** or **14**), imidazole (1.3 equiv), and DMAP (0.1 equiv) were dissolved in CH_2Cl_2, and then TBDMS-Cl, TIPS-Cl, or TBDPS-Cl (1.3 equiv) was added. The solutions were stirred at rt for 30 min, and a white precipitate was visible. The reaction was diluted with CH_2Cl_2 and H_2O and transferred to a separatory funnel. After separation of layers, the remaining aqueous layer was extracted further with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give the crude product which was purified by silica gel column chromatography.

(*S*)-5-(*tert*-Butyldimethylsiloxymethyl)-1-(phenylmethyl)-2-pyrrolidinone (15). Synthesized via the general procedure and purified by eluting with hexanes/EtOAc (1:1) to give the desired product as a colorless oil in quantitative yield. R_f = 0.48 (hexanes/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.70−2.04 (m, 2H), 2.37−2.55 (m, 2H), 3.50 (m, 2H), 3.66 (m, 1H), 4.03 (d, 1H, *J* = 15.0 Hz), 4.99 (d, 1H, *J* = 15.0 Hz), 7.23−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −5.4, 18.4, 21.7, 26.0, 30.6, 44.7, 58.5, 63.6, 127.6, 128.2, 128.8, 137.1, 175.8; CI-MS (NH_3) *m/e* (rel intensity) 320.3 (MH^+, 100.0); CI−HRMS (NH_3) *m/e* calcd for $C_{18}H_{30}NO_2Si$ (MH^+) 320.2045, found 320.2040.

(*S*)-1-(Phenylmethyl)-5-(triisopropylsiloxymethyl)-2-pyrrolidinone (16). Synthesized via the general procedure and purified by eluting with hexanes/EtOAc (3:2) to give the desired product as a colorless oil (90% yield). R_f = 0.33 (hexanes/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (m, 21H), 2.02 (m, 2H), 2.30 (m, 1H), 2.54 (m, 1H), 3.53 (m, 1H), 3.66 (m, 1H), 3.77 (m, 1H), 4.04 (d, 1H, *J* = 15.0 Hz), 5.06 (d, 1H, *J* = 15.0 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.0, 18.1, 21.7, 30.6, 44.7, 58.5, 64.0, 127.6, 128.2, 128.8, 137.1, 175.8; CI-MS (NH_3) *m/e* (rel intensity) 362.5 (MH^+, 100.0), 170.2 (35.5), 154.2 (25.5); CI−HRMS (NH_3) *m/e* calcd for $C_{21}H_{36}NO_2Si$ (MH^+) 362.2515, found 362.2517.

(*S*)-5-(*tert*-Butyldiphenylsiloxymethyl)-1-(phenylmethyl)-2-pyrrolidinone (17). Synthesized via the general procedure and purified by eluting with hexanes/EtOAc (4:1) to give the desired product as a colorless oil (93% yield). R_f = 4.8 (hexanes/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 2.01 (m, 2H), 2.42 (m, 1H), 2.59 (m, 1H), 3.47−3.68 (m, 3H), 3.74 (d, 1H, *J* = 15.0 Hz), 4.99 (d, 1H, *J* = 15.0 Hz), 7.42 (m, 15H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.3, 21.6, 27.0, 30.7, 44.6, 58.2, 63.9, 127.6, 128.0, 128.8, 130.1, 130.2, 133.0, 135.8, 135.9, 136.9, 175.8; CI-MS (NH_3) *m/e* (rel intensity) 444.6 (MH^+, 100.0), 274.4 (16.3), 207.3 (22.2); CI−HRMS (NH_3) *m/e* calcd for $C_{28}H_{34}NO_2Si$ (MH^+) 444.2359, found 444.2345.

(*S*)-5-(*tert*-Butyldimethylsiloxymethyl)-1-(4-methoxyphenylmethyl)-2-pyrrolidinone (18). Synthesized via the general procedure and purified by eluting with hexanes/EtOAc (1:1) to give the desired product as a colorless oil (93% yield). R_f = 0.38 (hexanes/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.90 (m, 2H), 2.36 (m, 1H), 2.50 (m, 1H), 3.49 (m, 2H), 3.67 (m, 1H), 3.79 (s, 3H), 3.96 (d, 1H, *J* = 14.8 Hz), 4.95 (d, 1H, *J* = 14.8 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 7.18 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −5.4, 18.4, 21.7, 26.0, 30.7, 44.1, 55.5, 58.3, 63.6, 114.1, 129.2, 129.5, 159.1, 175.7; CI-MS (NH_3) *m/e* (rel intensity) 350.3 (MH^+, 100.0), 230.2 (19.4), 136.1 (17.0), 121.1 (25.5); CI−HRMS (NH_3) *m/e* calcd for $C_{19}H_{32}NO_3Si$ (MH^+) 350.2151, found 350.2140.

(*S*)-1-(*tert*-Butyloxycarbonyl)-5-(methoxymethyl)-2-pyrrolidinone (20). THF (8 mL) was added to a flask containing a glass stir bar which was then cooled to −78 °C in a dry ice-^{i}PrOH bath. NH_3 (10 mL) was condensed into the flask and the mixture continued to stir at −78 °C. A solution of compound **19** (730 mg, 3.3 mmol) in THF (5 mL) was added slowly in portions along with the periodic addition of sodium so that a deep blue color persisted in the reaction mixture. After complete addition of the starting material, the reaction stirred for an additional 10 min before the remaining sodium was slowly quenched with ^{n}BuOH. The flask was warmed to rt and the NH_3 evaporated. The remaining solvents were removed in vacuo, and the resulting white residue was dissolved in water. This aqueous solution was brought to pH = 7.0 with 3.0 M HCl, and then it was repeatedly extracted with CH_2Cl_2 until TLC analysis indicated that the extracts no longer contained the product. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give a light yellow oil which was purified by silica gel column chromatography (EtOAc/MeOH, 9:1) to give the desired deprotected amide as a colorless oil (240 mg, 1.86 mmol, 56% yield). R_f = 0.38 (EtOAc/MeOH, 9:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.77 (m, 1H), 2.16−2.38 (m, 3H), 3.29 (dd, 1H, *J* = 9.4, 7.4 Hz), 3.37 (s, 3H), 3.40 (dd, 1H, *J* = 9.4, 4.3 Hz), 3.83 (m, 1H), 7.10 (br, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.1, 29.8, 53.8, 59.1, 76.2, 178.5; EI-MS (70 eV) *m/e* (rel intensity) 129.1 (M^+, 4.5), 84.1 (100.0), 45.0 (10.5), 41.0 (31.05); EI−HRMS (70 ev) *m/e* calcd for $C_6H_{11}NO_2$ (M^+) 129.0789, found 129.0788. The intermediate secondary amide (200 mg, 1.55 mmol) was dissolved in CH_2Cl_2, and DMAP (189 mg, 1.55 mmol, 1.0 equiv), Et_3N (202 mg, 2.0 mmol, 1.3 equiv), and Boc_2O (474 mg, 2.17 mmol, 1.4 equiv) were added. The mixture stirred at rt for 24 h, and then the solution was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The resulting crude residue was purified by silica gel column chromatography (hexanes/EtOAc, 3.5:1.5), and the desired product was obtained as a colorless oil (350 mg, 1.52 mmol, 98% yield, 55% yield from **19**). R_f = 0.38 (hexanes/EtOAc, 3:2);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 9H), 2.07 (m, 2H), 2.39 (m, 1H), 2.69 (m, 1H), 3.35 (s, 3H), 3.50 (dd, 1H, J = 9.6, 3.1 Hz), 3.57 (dd, 1H, J = 9.6, 5.0 Hz), 4.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.5, 28.2, 32.2, 57.4, 59.5, 73.6, 83.1, 150.1, 175.1; CI-MS (NH_3) *m/e* (rel intensity) 230.0 (M + H^+, 1.7), 147.0 (65.9), 130.0 (100.0); CI−HRMS (NH_3) *m/e* calcd for $C_{11}H_{20}NO_4$ (MH^+) 230.1392, found 230.1390.

General Method for Electrophilic Monofluorination of Lactams (Table 1). A solution of LDA (1.3 equiv) in THF (4−5 mL) was prepared and cooled to −78 °C. A solution of the lactam substrate in THF (4−5 mL) was then added slowly. The resulting mixture was stirred for 90 min at −78 °C and then a solution of NFSi (1.4 equiv) in THF (4−5 mL) was added. After 30 min, the reaction was quenched at −78 °C with saturated aqueous NH_4Cl and then allowed to warm slowly to rt. The solvents were removed in vacuo, and the resulting residue was partitioned between EtOAc and H_2O. After separation of the EtOAc layer, the aqueous layer was further extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give a residue which was analyzed by NMR and purified by silica gel column chromatography.

(3*R*,5*S*)-1-(*tert*-Butyloxycarbonyl)-3-fluoro-5-(trityloxymethyl)-2-pyrrolidinone (21). Diisopropylamine (1.59 g, 15.73 mmol, 1.8 equiv) was added to THF (100 mL), and the mixture was cooled to −78 °C in a dry ice−^{i}PrOH bath. A solution of ^{n}BuLi (895 mg, 8.73 mL, 13.98 mmol, 1.6 equiv) (1.6M) was slowly added, and the resulting solution was stirred for 1 h. A solution of **9** (4.0 g, 8.74 mmol) in THF (7 mL) was added slowly. The resulting light yellow solution was stirred at −78 °C for 45 min and then at −55 °C for 5 min. A solution of NFSi (4.13 g, 13.11 mmol, 1.5 equiv) in THF (15 mL) was then added, and the reaction was allowed to stir at −55 °C for 35 min. The reaction was quenched with saturated aqueous NH_4Cl, and the flask was warmed to rt. The THF was removed in vacuo, and the resulting residue was partitioned between EtOAc and H_2O. After separating layers, the aqueous layer was extracted further with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to leave an orange residue which was purified by two sequential silica gel columns: #1 (hexanes/EtOAc, 4:1), #2 ($CHCl_3$/EtOAc, 19:1) to give the desired product as a white solid (2.4 g, 5.0 mmol, 57% yield). The samples for elemental analysis and X-ray crystal structure determination were obtained by crystallization in EtOH. R_f = 0.40 (hexanes/EtOAc, 4:1); mp 130−134 °C; $[\alpha]^{23}_D$ = −1.63 (*c* 0.61, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 2.32 (m, 2H), 2.97 (dd, 1H, J = 9.9, 2.1 Hz), 3.66 (dt, 1H, J = 9.9, 2.6, 2.2 Hz), 4.27 (d, 1H, J = 9.1 Hz), 5.56 (dt, 1H, J = 53.1, 8.9 Hz), 7.29 (m, 15H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.2, 30.7 (d, $^2J_{C-F}$ = 18.9 Hz), 54.5, 63.6, 84.1, 86.9, 88.2 (d, $^1J_{C-F}$ = 187 Hz), 127.6, 128.3, 128.6, 143.4, 149.5, 169.7 (d, $^2J_{C-F}$ = 20.8 Hz); ^{19}F NMR ($CDCl_3$, 282.38 MHz) δ −110.6 (dd, J = 53.6, 25.4 Hz); FAB-MS (3-nba with Na^+) *m/e* (rel intensity) 498.0 (MNa^+, 61.6), 398.0 (69.5), 243.0 (100.0), 136.0 (25.6); FAB−HRMS (3-nba with Na^+) *m/e* calcd for $C_{29}H_{30}FNO_4Na$ (MNa^+) 498.2056, found 498.2054. Anal. Calcd for $C_{29}H_{30}FNO_4$: C, 73.24; H, 6.36; N, 2.95. Found: C, 72.84; H, 6.27; N, 2.84.

(3*R*,5*S*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxy-5-(trityloxymethyl)-2-pyrrolidinone (25). 1,1,1,3,3,3-Hexamethyldisilazane (314 mg, 1.95 mmol, 3.0 equiv) was added to THF (4 mL), and the solution was cooled to −78 °C in a dry ice−^{i}PrOH bath. A solution of ^{n}BuLi (115 mg, 1.12 mL, 1.8 mmol, 2.8 equiv) (1.6 M) was added dropwise and the mixture stirred for 35 min. A solution of compound **9** in THF (2 mL) was added dropwise over 5 min. The mixture stirred for 30 min at −78 °C and then 5 min at −55 °C before solid MoOPH (425 mg, 0.98 mmol, 1.5 equiv) was added in one portion. The bright yellow reaction mixture was stirred for 30 min before it was quenched with saturated aqueous NH_4Cl. The flask was warmed to rt, and the THF was removed in vacuo. The resulting residue was partitioned between EtOAc and H_2O. After separating layers, the aqueous layer was extracted further with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to leave a residue which was purified by silica gel column chromatography (hexanes/EtOAc, 3:2) to give the desired product as a white solid (189 mg, 0.40 mmol, 61% yield). R_f = 0.42 (hexanes/EtOAc, 1:1); mp = 92−95 °C; IR (thin film) 3450 cm^{-1} (b, OH); ^{1}H NMR ($CHCl_3$, 500 MHz) δ 1.51 (9H, s), 2.06 (1H, m), 2.36 (1H, dd, J = 12.6, 8.6 Hz), 2.73 (1H, d, J = 1.9 Hz), 3.06 (1H, dd, J = 9.8, 2.4 Hz), 3.57 (1H, dd, J = 9.8, 3.5), 4.23 (1H, m), 4.77 (1H, m), 7.22−7.46 (15H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.1, 31.7, 54.9, 63.8, 70.0, 83.7, 87.4, 127.4, 128.2, 128.7, 143.5, 149.5, 175.7; FAB-MS (na with Na^+) *m/e* (rel intensity) 496.1 (MNa^+, 24.7), 396.1 (34.6), 243.1 (100.0); FAB−HRMS (na with Na^+) *m/e* calcd for $C_{29}H_{31}NO_5Na$ (MNa^+) 496.2100, found 496.2104.

(3*S*,5*S*)-1-(*tert*-Butyloxycarbonyl)-3-fluoro-5-(trityloxymethyl)-2-pyrrolidinone (26). A solution of alcohol **25** (200 mg, 0.42 mmol) and pyridine (99.7 mg, 1.26 mmol, 3.0 equiv) in CH_2Cl_2 was cooled to 0 °C, and triflic anhydride (142 mg, 0.50 mmol, 1.2 equiv) was added dropwise. After 20 min the reaction was diluted with CH_2Cl_2 and poured into half-saturated aqueous NaCl. The organic layer was washed (2×) with saturated aqueous $CuSO_4$, dried (Na_2SO_4), and filtered. The solvent was removed in vacuo to give the desired intermediate triflate in quantitative yield as a pale yellow solid which was used without further purification.[57] ^{1}H NMR ($CHCl_3$, 300 MHz) δ 1.52 (s, 9H), 2.28−2.43 (m, 2H), 3.04 (dd, 1H, J = 10.1, 2.0 Hz), 3.74 (dd, 1H, J = 10.1, 2.1 Hz), 4.30 (dd, 1H, J = 8.4, 1.7 Hz), 5.95 (t, 1H, J = 9.4 Hz), 7.22−7.37 (m, 15H); ^{19}F NMR ($CDCl_3$, 282.38 MHz) δ 1.34 (s). The triflate (100 mg, 0.16 mmol) was dissolved in THF and cooled to −78 °C. A commercial solution of TBAF (1.0 M in THF) (320 μL, 0.32 mmol, 2.0 equiv) was added dropwise. After 15 min, methyl iodide (45.4 mg, 0.32 mmol, 2.0 equiv) was also added. After 30 min, the solution was allowed to warm gradually to rt and stir for 24 h. The resulting solution was diluted (2:1) with EtOAc and half-saturated aqueous $NaHCO_3$ was added dropwise with vigorous stirring. After separation of layers, the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and condensed in vacuo to give the crude product as an orange residue. The desired product was purified by silica gel column chromatography (hexanes/EtOAc, 3:2) and obtained as a white solid (55 mg, 0.12 mmol, 72% yield from the triflate). The sample for elemental analysis was obtained by crystallization in EtOH. R_f = 0.46 (hexanes/EtOAc, 3:2); mp = 104−106 °C; $[\alpha]^{23}_D$ = −75.8 (*c* 0.55, MeOH); ^{1}H NMR ($CHCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.30−2.48 (m, 1H), 3.34 (d, 2H, J = 4.9 Hz), 4.24 (m, 1H), 4.98 (ddd, 1H, J = 51.8, 7.8, 4.1 Hz), 7.21−7.43 (m, 15H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.8, 28.1, 55.4, 64.0, 84.1, 87.0, 88.5 (d, $^1J_{C-F}$ = 185 Hz), 127.4, 128.1, 128.8, 143.7, 149.4, 168.8 (d, $^2J_{C-F}$ = 20.1 Hz); ^{19}F NMR ($CDCl_3$, 282.38 MHz) δ −108.0 (m, J = 52, 27, 3.0 Hz); FAB-MS (NBA with Na^+) *m/e* (rel intensity) 498.3 (MNa^+, 28.21), 398.2 (29.0), 243.2 (100.0), 154.1 (19.5), 136.1 (12.7); FAB−HRMS (NBA with Na^+) *m/e* calcd for $C_{29}H_{30}FNO_4Na$ (MNa^+) 498.2056, found 498.2054. Anal. Calcd for $C_{29}H_{30}FNO_4$: C, 73.24; H, 6.36; N, 2.95. Found: C, 73.07; H, 6.28; N, 2.95.

(3*R*,5*S*)-3-Fluoro-5-hydroxymethyl-2-pyrrolidinone (27). Deprotection Method A. Compound **21** (2.73 g, 5.74 mmol) was stirred at rt in 3% concentrated HCl in MeOH for 48 h. The pH of the solution was adjusted to 7.0 with saturated aqueous $NaHCO_3$. The now cloudy solution was condensed in vacuo to give a white residue. This residue was triturated with CH_2Cl_2/MeOH (5:1), and the resulting suspension was filtered to remove the insoluble solids. Evaporation of the filtrate in vacuo left another white solid residue which was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 5:1) to give the desired product as a white solid (554 mg, 4.16 mmol, 73% yield). R_f = 0.51 (CH_2Cl_2/MeOH, 5:1); mp 111−113 °C; $[\alpha]^{23}_D$ = +94.1 (*c* 1.01, MeOH); ^{1}H NMR (MeOH-d_4, 300 MHz) δ 2.20 (m, 2H), 3.47 (m, 2H), 3.75 (m, 1H), 5.12 (dt, 1H, J = 53.8, 6.5 Hz); ^{13}C NMR (MeOH-d_4, 75.5 MHz) δ 32.5 (d, $^2J_{C-F}$ = 20.7 Hz), 54.9, 65.2, 90.1 (d, $^1J_{C-F}$ = 180.7 Hz), 175.5 (d, $^2J_{C-F}$ =

(57) The triflate is unstable at room temperature and should be used immediately or stored in a freezer (<0 °C).

20.1 Hz); ^{19}F NMR (MeOH-d_4, 282.38 MHz) δ −113.22 (ddd, J = 54, 29, 13 Hz); DCI-MS (NH_3) m/e (rel intensity) 151.1 (82.4), 134.1 (MH^+, 100.0) 114.1 (5.2); DCI−HRMS (NH_3) m/e calcd for $C_5H_9FNO_2$ (MH^+) 134.0617 found 134.0612. Anal. Calcd for $C_5H_8FNO_2$: C, 45.11; H, 6.06; N, 10.52. Found: C, 44.70; H, 6.02; N, 10.36.

Deprotection Method B. Compound **21** (1.0 g, 2.10 mmol) was dissolved in CH_2Cl_2, and the solution was cooled to 0 °C. Triethylsilane (1.1 g, 9.45 mmol, 4.5 equiv) was added followed by the dropwise addition of anhydrous TFA (2.4 g, 21 mmol, 10 equiv). The resulting solution stirred at 0 °C for 2 h. The solvent and volatile components were removed in vacuo to give a white solid residue. Silica gel column chromatography (CH_2Cl_2/MeOH, 5:1) of this crude material and concentration of the fractions containing the desired product (R_f = 0.51) gave a white solid which contained the desired product plus a minor inseparable impurity with a total mass corresponding to greater than 100% yield. This material exhibited the following NMR signals in addition to those reported for pure **27** in method A: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.96 (m, D_2O exchange); ^{19}F NMR (DMSO-d_6, 282.38 MHz) δ −1.22 (s). This material can be carried on for oxidation and esterification without further purification.

(2*S*,4*R*)-4-Fluoro-5-oxo-pyrrolidine-2-carboxylic Acid Methyl Ester (28). Oxidation Method A. Compound **27** (217 mg, 1.63 mmol) was dissolved in acetone (23 mL) and cooled to 0 °C in an ice−water bath before 5% aqueous $NaHCO_3$ (5 mL), NaBr (34 mg, 0.33 mmol, 0.2 equiv), and TEMPO (25 mg, 0.16 mmol, 0.1 equiv) were added with vigorous magnetic stirring. A solution of household bleach (365 mg, 4.9 mmol, 3.0 equiv NaOCl) was slowly added dropwise over 2 h to the white nonhomogeneous mixture. After complete addition, the mixture stirred for an additional 1 h. The remaining excess oxidant was quenched with the addition of ^{i}PrOH and stirring for 15 min. The mixture was acidified to pH = 3−4 using 1 M aqueous $KHSO_4$ and testing with pH indicator paper. The flask was warmed to rt, and all solvents were removed in vacuo to give a crude white solid residue.

Oxidation Method B. Compound **27** (30 mg, 0.23 mmol) was dissolved in wet acetonitrile (1.4 mL, 0.75 vol % H_2O) and cooled to 0 °C in an ice−water bath. A stock solution containing H_5IO_6 (128 mg, 0.56 mmol, 2.5 equiv) and CrO_3 (0.24 mg, 2.42 μmol, 1.1 mol %) in wet acetonitrile (1.4 mL, 0.75 vol. % H_2O) was slowly added dropwise over 40 min. After complete addition the mixture was stirred for an additional 45 min before being quenched with aqueous phosphate buffer (prepared by dissolving 600 mg of Na_2HPO_4 in 10 mL of H_2O). The solvents were removed in vacuo to give a crude solid residue.

Esterification of the Crude Carboxylic Acid. Methanol was added to the solid residues obtained from either oxidation method which contained the crude carboxylic acid and inorganic salts. After the mixture was stirred vigorously to dissolve the desired carboxylic acid product, the insoluble solids were filtered, and the resulting filtrate was stirred and cooled to 0 °C in an ice−water bath. This solution was treated dropwise with portions of CH_2N_2 in Et_2O[58] until TLC analysis (CH_2Cl_2/MeOH, 5:1) indicated the complete loss of starting material and the formation of a new higher R_f product. Any remaining CH_2N_2 was destroyed with a solution of acetic acid in Et_2O. The flask was warmed to rt and the solvents were removed in vacuo. The crude product was obtained by triturating the residue with EtOAc, filtering the insoluble salts, and condensing the filtrate in vacuo. Finally, the desired ester product was purified by silica gel column chromatography (EtOAc) to give **28** as a colorless oil with yields of approximately 70% in two steps from **27** utilizing either oxidation method. R_f = 0.5 (EtOAc); $[\alpha]^{23}_D$ = +94.6 (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54−2.68 (m, 2H), 3.79 (s, 3H), 4.39 (m, 1H), 5.14 (ddd, 1H, J = 52.5, 7.3, 6.3 Hz), 7.62 (br, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 32.2 (d, $^2J_{C-F}$ = 21.6 Hz), 52.9, 53.1, 87.3 (d, $^1J_{C-F}$ = 184.4 Hz), 171.7, 172.6 (d, $^2J_{H-F}$ = 20.0 Hz); ^{19}F NMR ($CDCl_3$, 282.38 MHz) δ −116.01 (m); CI-MS (NH_3) m/e (rel intensity) 179.1 ($[M + NH_4]^+$, 100.0), 162.1 (MH^+, 30.2); CI-HRMS (NH_3) m/e calcd for $C_6H_9FNO_3$ (MH^+) 162.0566 found 162.0573. Anal. Calcd for $C_6H_8FNO_3 \cdot 0.25\ H_2O$: C, 43.51; H, 5.17; N, 8.46. Found C, 43.69; H, 5.10; N, 8.41.

(2*S*,4*R*)-4-Fluoroglutamic Acid (29). Compound **28** (171 mg, 1.06 mmol) was dissolved in 6 N aqueous HCl and refluxed for 4 h. The solution was cooled and evaporated to dryness in vacuo. The resulting solid was dissolved in distilled H_2O and again evaporated to dryness (2×) to give the crude fluoroglutamate hydrochloride salt. The salt was dissolved in a minimum of 95% EtOH and cooled to 0 °C with magnetic stirring in an ice−water bath. An excess of propylene oxide was added dropwise to the solution, and a precipitate formed. After 20 min all the volatile components were removed in vacuo. The resulting tan solid was crystallized from H_2O/EtOH, washed with cold Et_2O, and dried to give the neutralized fluoroglutamate product (104 mg, 0.63 mmol, 60% yield). mp = 173−175 °C (lit. mp = 182−183 °C dec);[10] $[\alpha]^{23}_D$ = +36.8 (c 0.90, 1N HCl) (lit. $[\alpha]^{25}_D$ = +33.17 (c 1, 1N HCl));[10] ^{1}H NMR (D_2O, 300 MHz) δ 2.31−2.42 (m, 1H), 2.50−2.65 (m, 1H), 4.13 (dd, 1H, J = 6.8, 6.1 Hz), 5.17 (ddd, 1H, J = 50.2, 10.3, 2.8 Hz); ^{13}C NMR (D_2O, 75.5 MHz) δ 33.1 (d, $^2J_{C-F}$ = 20.6 Hz), 51.3, 87.93 (d, $^1J_{C-F}$ = 180.5 Hz), 172.1, 174.3 (d, $^2J_{C-F}$ = 21.5 Hz); ^{19}F NMR (D_2O, 282.38 MHz) δ −110.14 (ddd, J = 51, 37, 15 Hz); DCI-MS (NH_3) m/e (rel intensity) 165.1 ($[M + NH_4 - H_2O]^+$, 100.0); DCI−HRMS (NH_3) m/e calcd for $C_5H_{10}FN_2O_3$ ($[M + NH_4 - H_2O]^+$) 165.0675 found 165.0678. Anal. Calcd for $C_5H_8FNO_4$: C, 36.37; H, 4.88; N, 8.48. Found: C, 35.99; H, 5.12; N, 8.51.

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Supporting Information Available: ORTEP plot of compound **21** and X-ray crystallographic data. This information is available free of charge on the Internet at http://pubs.acs.org.

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(58) Ethereal solutions of diazomethane were carefully prepared in a fume hood using Diazald and a procedure based on those outlined in Aldrich Technical Bulletin AL-180.