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# A Stereocontrolled Synthesis of Monofluoro Ketomethylene Dipeptide Isosteres

Robert V. Hoffman* and Junhua Tao

Department of Chemistry and Biochemistry

New Mexico State University

Las Cruces, NM 88003-0001

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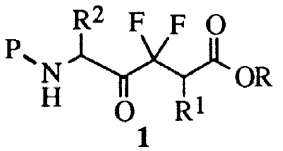
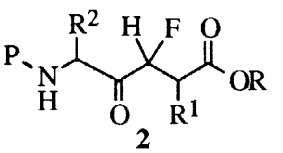
**Abstract:** A simple, stereocontrolled synthesis of monofluoro ketomethylene dipeptide isosteres has been developed. The method is short (6 steps) and diastereoselective (85-95% de) and enantioselective (>95% ee). 

The incorporation of fluorine into biologically active molecules can induce unique changes in the physical, chemical, and biological properties of the parent compound.[1] Fluorinated peptide mimetics are particularly interesting,[2] since they contain fluorine-activated electrophilic carbonyl groups which react readily with active site nucleophiles such as hydroxyl groups (serine proteases), thiol groups (cysteine proteases), or water (aspartate or metallo proteases) to produce transition state analogs in the active site.[3]

While fluorinated ketones have been incorporated at the ends of peptide chains,[3,4] incorporating fluoroketone isostere units *within* the peptide chain is not common. Difluorostatone analogs have been studied as difluorinated dipeptide mimetics;[5] however, few examples of true difluoroketomethylene dipeptide isosteres **1** are extant,[6] and only a single example of a monofluoroketomethylene dipeptide isostere **2** has been reported.[7] The latter could be very interesting peptide mimetics since they are true peptide isosteres whose binding region can be extended in both the P and P' directions. Moreover the carbonyl group is only partially hydrated (≈ 20-50%) upon treatment with water, so that interaction with several different types of proteases is possible.



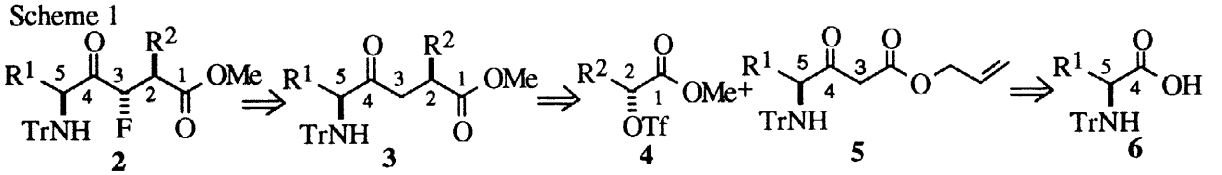
**1**



**2**

Based on our synthesis of ketomethylene peptide isosteres,[8] and our synthesis of monofluoro ketomethylene peptide isostere core units using Selectfluor® for electrophilic fluorination,[9] we envisioned a stereoselective synthesis of monofluoroketomethylene peptide isosteres **2** shown retrosunthetically in Scheme 1. The stereoselective fluorination of **3** requires unprecedented 1,3-allylic stereocontrol by an N-tritylamino group.

Scheme 1



**2** **3** **4** **5** **6**

Tritylated amino acids **6**[10] containing branched, unbranched and heteroatom containing side-chains were converted to allyl β-ketoesters **5**[11] (55-75%), alkylated with scalemic triflates **4**[8] and decarboxylated to provide tritylated ketomethylene isosteres **3**[12] in good yields (50-60%) (Scheme 2). Allyl esters were superior to *t*-butyl esters because palladium[0] not only cleaved the allyl group selectively but also catalyzed the decarboxylation to

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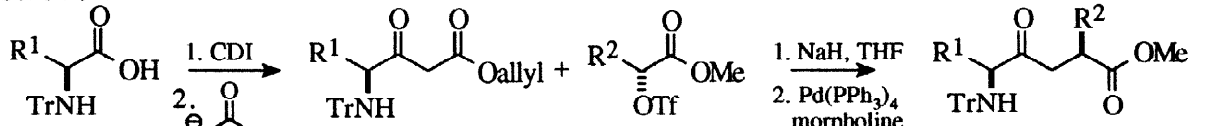
give **3**.[13] The (*R*)-enantiomer of triflate **4** produces the (*R*) configuration at C-2 of **3** which has the same stereochemical sense as a normal dipeptide.

Scheme 2




**6a** $R^1$=i-Bu
**6b** $R^1$= $CH_3$
**6c** $R^1$= Bn

**5a-c** (65-70%)

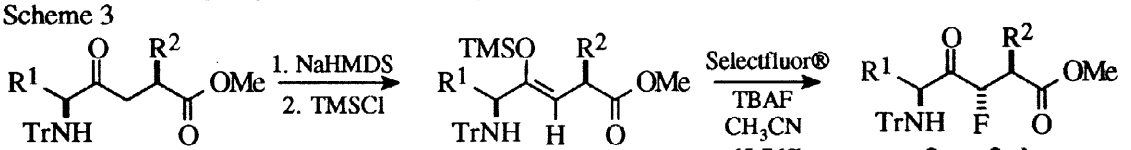
**4a** $R^2$= $CH_3$ (R)
**4b** $R^2$= $CH_2C_6H_{11}$ (R)
**4c** $R^2$= i-Bu (R)
**4d** $R^2$= n-Pr (R)

**3aa, 3ab, 3bc, 3cd**

(2*R*, 5*S*)-Isosteres **3aa, 3ab, 3bc, 3cd** were converted to the corresponding *Z*-TMS enol ethers **7** using NaHMDS-TMSCl. It is known that bulky nitrogen substituents on amino ketones promote enolate formation regiospecifically distal from the α-amino group by removal of the α'-proton.[14] Moreover only one vinyl proton signal was seen in the nmr spectra of **7** indicating a single double bond geometry was produced in every case. The use of NaHMDS under kinetic conditions[15] allows the *Z*- geometry to be assigned to **7**.

Treatment of **7** (without purification) with Selectfluor®[16] in the presence of TBAF produced monofluoro ketomethylene dipeptide isosters **2** in generally good yields (65-76%) (Scheme 3).[13] Noteworthy is that *only a single diastereomer was evident in the nmr spectrum of the monofluorinated products* **2**. Thus the N-trityl amino group and/or the C-alkyl group (or both) exert significant stereocontrol in the electrophilic fluorination of **7**

Scheme 3

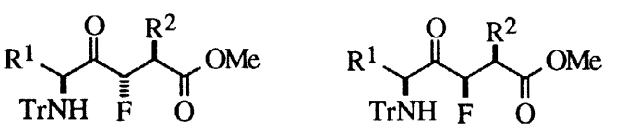



**3aa, 3ab, 3bc, 3cd**

**7**

**2aa, 2ab, 2bc, 2cd**

The nmr signal of the C-3 proton was used to tentatively assign the configuration of the products. The single diastereomers of **2** produced by the fluorination of **7** had the C-3 signal at δ≈ 4.4-4.9 with $J_{H-H}$ = 7-8 Hz. The two possible diastereomers of **2** are shown below. Since the absolute configuration at C-2 and C-5 are known, only the configuration of the fluorine atom at C-3 is variable. Conformations about the 2-3, 3-4, and 4-5 bonds of **2** ($R_1$, $R_2$=$CH_3$) were evaluated computationally (AM1). For **2***S,S,S* there are three conformations of lowest energy which are 1.7-3.0 kcal /mole more stable than the next lowest energy conformer, and they all had a dihedral angle of 179.5° between the C-2 and C-3 protons. For **2***S,R,S* the conformation of lowest energy was also 2.5 kcal more stable than the next lowest energy conformation and had a dihedral angle of 83.2° between the C-2 and C-3 protons. A vicinal coupling constant $J_{H-H}$ = 7-8 Hz found in the product is consistent with the 179.5° dihedral angle found for **11***S,S,S* diastereomer. (Similar results were found for $R^1$= *i*-Pr, $R^2$ = Me.)

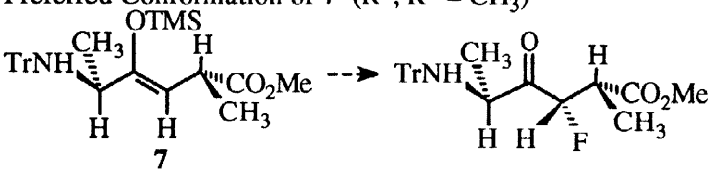



**2** (2*S*,3*S*,5*S*) 2(2*S*,3*R*,5*S*)

Conformational analysis of the TMS-enol ether **7** provides an explanation for this stereoselection, at least in an operational manner. Using $R_1$, $R_2$= $CH_3$ for calculational simplicity, the preferred conformation of **7**, which lies 3 kcal/mol lower than the next lowest-energy conformer (AM1), minimizes $A_{1,2}$ interactions and has both the

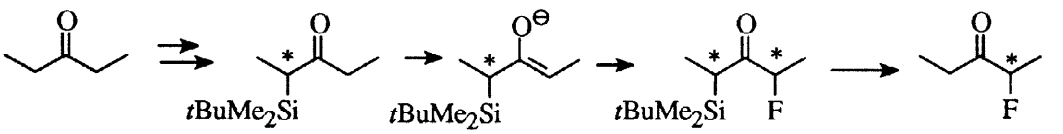
N-trityl group at C-5 and the methyl group at C-2 (which is larger than the methyl carboxylate group[17]) above one face of the enol double bond. Approach of the fluorinating agent from the face opposite the trityl and methyl groups leads to the observed stereochemistry. More work is needed to verify and extend this model; however, the results suggest that the bulky N-tritylamino group plays a significant role in controlling the facial selectivity and may act in concert with the alkyl group at C-2.

Figure 1. Preferred Conformation of **7** ($R^1$, $R^2 = CH_3$)




Electrophilic fluorination of a TMS enol ether by $XeF_2$ was used previously to access a monofluoroketomethylene peptide isostere but was non-stereoselective.[7] The present method is much shorter and is highly diastereoselective for the examples studied thus far. Other methods for the electrophilic asymmetric synthesis of α-fluoroketones has been the object of several recent studies.[18,19] In general asymmetric fluorinating agents derived from camphor are used to fluorinate ketone enolates.[18] This approach, however, generally gives modest enantioselectivity (< 75% ee). Enders recently described the electrophilic fluorination of chiral α-silylketone enolates.[19] The α-silyl group provides good stereocontrol for fluorination at the α'-position and is subsequently removed (Scheme 4). High de's are found for cyclic ketones. Lower de's (67-89%) are found for acyclic ketones but both enantiomers can be produced by choosing either the Z- or E-enolate geometry.

Scheme 4




The present work has similar elements in that a bulky group (N-tritylamino) at the α-position is used to direct fluorination at the α'- position. The results have also allowed a working model to be proposed to rationalize the stereoselection. However, the complex functional and chiral environment encountered here requires further work to fully understand the structural factors which control diastereoselection. Moreover the use of an N-tritylamino group for 1,3-allylic stereocontrol could have wider applications as well.

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