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New applications of fluorinated building blocks

A. Abouabdellah, L. Boros, F. Gyenes, J.T. Welch *

Department of Chemistry, State University of New York, Albany, NY 12222, USA

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Abstract

A new and versatile synthesis of optically active α-fluoromalonamide derivatives from enantiomerically pure 3-fluoro-2-azetidinones is described. A fluorinated retroamide isostere based on these α-fluoromalonamides was introduced into a small peptidomimetic for use as an HIV-1 protease inhibitor. The same strategy was employed in efforts to prepare a novel trifluorostatone-type peptidomimetic.

Keywords: Fluorinated building blocks; Fluoromalonamide derivatives; Fluoroazetidinones; Optical activity; Peptidomimetics; HIV-1 protease inhibitor

1. Introduction

The incorporation of fluorine into molecules may result in a profound change in the physical properties of these molecules. These changes may in turn have effects on the biological activity of the fluorinated molecules [1,2]. Of selectively fluorinated molecules, fluoro-β-lactams are a good example of the effect of selective fluorination on modifying biological activity. Fluorinated β-lactams are especially effective not as antibiotics but in the inhibition of β-lactamases and human leukocyte elastase [3,4]. The preparation of fluorinated penicillins and cephalosporins has been reviewed and their biological activity described [4,5].

2. Application of the fluoro-β-lactams in the preparation of peptidomimetics

When available, optically active fluoro-β-lactams may serve as starting materials for asymmetric syntheses. In a simple example, hydrolysis of the lactam moiety led to construction of β-amino-acids directly. In this manner, the difluoro-substituted derivative of β-aminodeoxystatine was prepared [6]. Hydrolysis of the β-lactam under basic conditions and deprotection of nitrogen atom gives the statine analogue. Such a peptide was tested as human plasma Renin inhibitor.

We propose to employ fluorinated β-lactams to prepare a difluorostatone analogue which has also found valuable use as a synthetic amino-acid. From X-ray crystallographic data it was established that the proteases isolated from both HIV-1 and HIV-2 are dimeric structures [7]. The HIV-proteases are thought to act via a catalytic mechanism similar to that of other aspartyl proteases, whereby transfer of a proton from an aspartyl residue to a carbonyl group is accompanied by the addition of water to form a *gem*-diol intermediate [8]. Among the transition-state analogues incorporating isosteric residues that are not cleavable by the enzyme are the reduced amide types [9], hydroxyethylene-containing analogues [10], norstatine derivatives [11], dihydroxyethylene [12] and phosphorus esters [13]. However among all the inhibitors reported the difluoroketone types [14] have extraordinarily low MICs, less than 0.1 nmol [14b]. This potency is no doubt related to the facility with which difluoroketones form *gem*-diols and therefore resemble the native transition state in the proteolysis transformation.

These potent analogues still suffer the distinct liability of being susceptible to the action of proteases. Our approach to overcoming this weakness involved the employment of 'retro-inverso' peptide isosteres, a strategy for the preparation of biologically relevant peptidomimetics which has been growing [15]. The reversal of peptide bonds accompanied by the introduction of the appropriate enantiomerically configured amino-acids can result in the construction of a peptide analogue which is resistant to enzymatic degradation but exhibits

* Corresponding author.

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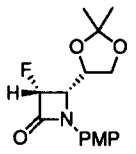
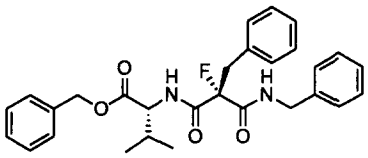
enhanced potency or improved selectivity. Unfortunately, the preparation of optically pure peptide analogues containing an alkylmalonamide residue, *m*Xaa [1], has been encumbered by the configurational lability of the malonyl unit under both neutral and basic conditions. The preparation of optically pure fluorinated malonamides, *mF*Xaa, which are configurationally fixed may overcome this problem. The retroamide functionality will improve bioavailability without diminishing the enzyme inhibitory properties of the analogues.

Optically pure fluorinated β-lactams such as **1** may be converted into *mF*Phe for incorporation into **2**, an analogue of 2-(benzyloxycarbonylvalylamino)-4,4-difluoro-1,7-diphenyl-3-hydroxy-5-keto-heptane (**3**), a remarkably potent HIV-1 protease inhibitor [14a]. Concurrently we wished to extend this strategy to the preparation of the trifluoroketone analogue **4** which may bind more effectively than the difluorostatone types to both HIV-1 and HIV-2 protease and show lower IC_{50} values.



1



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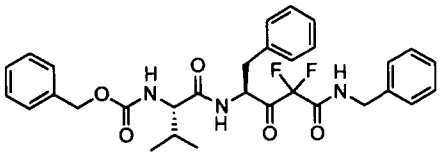

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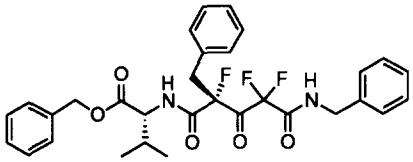

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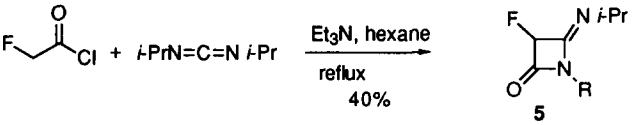
2.1. Synthesis

β-Lactams have been prepared by the cyclization of amides, ester enolate–imine condensations or [2+2] cycloadditions. The most frequently used starting materials for fluoro-β-lactam synthesis are α-fluoro-substituted derivatives of carboxylic acids, often commercially available or readily accessible by fluorination of α-hydroxy- or α-amino-acids.

[1] *m*Xaa is defined according to Ref. [1] as the malonyl residue corresponding to the indicated amino-acid residue. *mF*Xaa is used in this article to refer to the fluorinated malonyl residue.

2.1.1. The fluoroketene–imine condensation

In 1968, Brady and Hoff reported [16] that reaction of fluoroacetyl chloride with diisopropylcarbodiimide in the presence of triethylamine led to the formation of 3-fluoro-1-isopropyl-4-isopropylimino-2-azetidinone (**5**) [Eq. (1)].

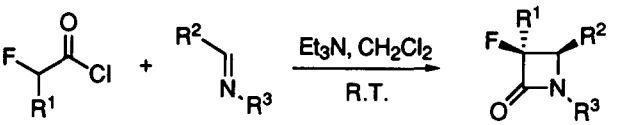


5

(1)

The authors postulated the involvement of fluoroketene in this reaction. However, the [2+2] cycloaddition to cyclopentadiene is the only evidence for presence of the fluoroketene (vide infra).

We have previously reported the fluoroketene–imine condensation to be a highly stereoselective process [17]. A number of 3-fluoro-β-lactams have been synthesized with *cis* stereochemistry in the ring [Eq. (2)].



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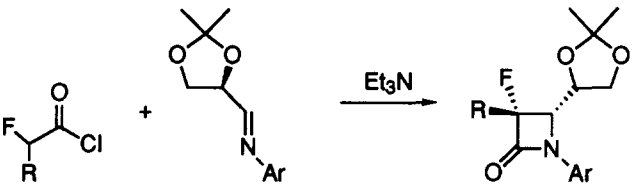
(2)

The reaction was very stereoselective, especially in the case of condensation with the optically active imine **7** derived from (*R*)-glyceraldehyde acetonide [18]. A single diastereoisomer of 3-fluoro-2-azetidinone (**1**) was formed in fair yield and in a d.e. of not less than 99% [Eq. (3)].

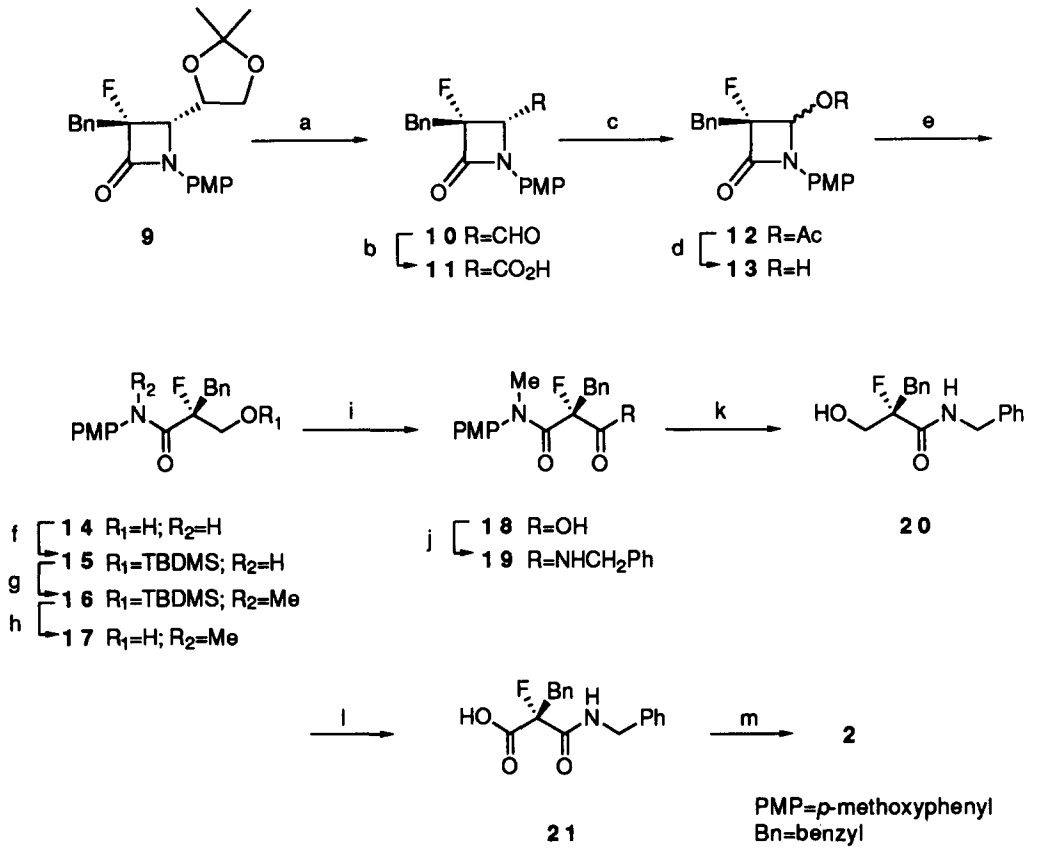


7
Ar = 4-MeOPh

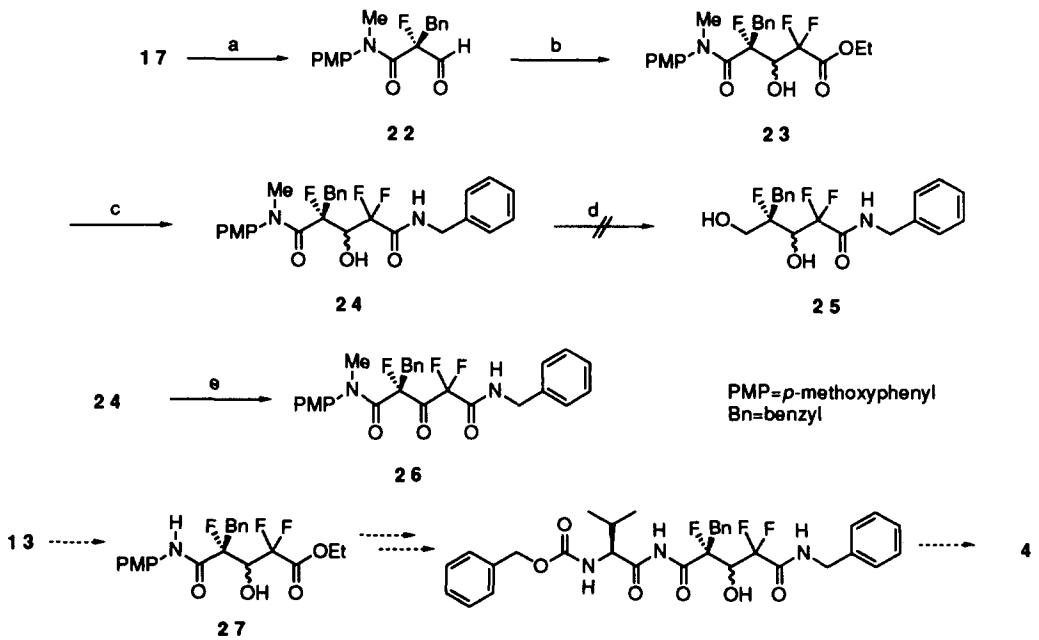
1 R=H
8 R=Ph

(3)

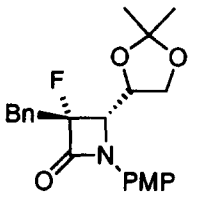
While formation of the β-lactams is an essential prerequisite to further transformation, the ability to substitute the β-lactam with stereocontrol is also a necessary requirement for the employment of β-lactams in synthesis. Optically active α-benzyl-α-fluoromalonic acid derivatives have been synthesized using the fluoro-β-lactam **9** as a chiral building block [19].



Scheme 1. Reagents and conditions: (a) H_5IO_6, Et_2O, 90%; (b) $KMnO_4$, K_2CO_3, THF/H_2O, 90%; (c) lead tetraacetate, DMF/AcOH, 72%; (d) aq. NaOH, MeOH, 96%; (e) $NaBH_4$, EtOH, 95%; (f) TBDMS-Cl, imidazole, DMF, 100%; (g) NaH, DMSO, MeI, 93%; (h) TBAF, THF, 91%; (i) Jones'reagent, 80%; (j) benzylamine, DCC, HOBt, 79%; (k) DIBAL-H, ^{n}BuLi, THF, 88%; (l) Jones'reagent, 77%; (m) (D)-Val-*O*-benzyl, DCC, HOBt, 77%.



Scheme 2. Reagents and conditions: (a) Swern, 85%; (b) Zn(2 equiv.), Ag(OAc)(0.3 equiv.), $BrCF_2CO_2Et$, Me_2AlCl (1.5 equiv.), THF, 60%; (c) benzylamine, Me_3Al, 85%; (d) DIBAL-H, ^{n}BuLi, THF; (e) Dess–Martin 95%.



9

Functionalization of 3-fluoro-β-lactam was performed by alkylation at the C-3 position [18]. Optically pure β-lactam **1** as well as its diastereomer were deprotonated with LDA at −90 °C and alkylated to give exclusively *cis*-substituted products.

The very high stereoselectivity of this alkylation is the result of steric effects. The large substituent at C-4 directs electrophilic attack from the opposite face of the ring. Only with non-sterically demanding electrophiles such as D_2O or H_2O was the *cis/trans* ratio attenuated and then only to 5:1.

2.1.2. Retroamide synthesis

Benzylation was effected in greater than 60% yield according to the above methods [18]. In a single-pot transformation, deprotection and oxidative cleavage was effected with periodic acid [20] to form **10** in 90% yield (Scheme 1). Oxidation to acid **11** was followed by Hunsdiecker decarboxylation to **12** with lead tetraacetate [21] in 65% yield for the two steps. Saponification of acetate **12** revealed the aminal **13** which was readily reduced to alcohol **14**. Protection of the alcohol with t-butyldimethylchlorosilane formed **15** in nearly quantitative yield for the three steps combined. At this point the termini of the building block must be differentiated to facilitate the reductive removal of the *p*-methoxyphenyl blocking group. Since the target molecule **20** contains an *N*-benzyl amide, it was determined that conversion of the *p*-methoxyphenyl anilide to a tertiary amide was necessary to activate that carbonyl toward reduction in the presence of the secondary benzyl amide. Conversion of **15** to **16** was effected with methyl iodide upon deprotonation of *p*-methoxyphenyl anilide with sodium hydride in dimethylsulfoxide [22]. Following deprotection of the alcohol function in the usual manner with *tetra*-n-butylammonium fluoride in THF, Jones oxidation of **17** yielded acid **18**. Benzylamine was coupled to the acid in the presence of dicyclohexylcarbodiimide and hydroxybenzotriazole to form **19** in 79% yield. Selective reduction of the tertiary *N*-methyl-*p*-methoxyphenylanilide was possible using a complex reducing agent prepared in situ from n-butyllithium and diisobutylaluminum hydride [23]. Complete reduction to the alcohol was possible by the addition of sodium borohydride to the reaction mixture. Alcohol **20** was formed in 88% yield. Jones oxidation (77%) and coupling with the unnatural amino-acid *O*-benzyl D-valine under the previously described conditions [24] yielded the target compound **2** in 77% yield.

It was necessary to employ the unnatural D-configuration of the amino-acid in order for the substrate to retain the topological features of **3** since the normal N–C progression of the peptide was inverted by the *mF*Phe isostere. Introduction of this Phe analogue allows us to incorporate the P_1 [25] benzyl side-chain matching the known selectivity of HIV-1 protease [26] and the P_2 valine identified as dramatically improving activity of the previously described analogues [14a]. This compound as well as the corresponding L-valine analogue are currently undergoing biological tests.

The attempted oxidation of alcohol **17** to the aldehyde **18** by Collin's reagent failed (Scheme 2). However oxidation under the conditions of Swern went smoothly, forming the aldehyde in 85% yield. The Reformatsky reagent drived from ethyl α-bromo-α,α-difluoroacetate under the conditions of Curran [27] added smoothly to the aldehyde to give the alcohol (60% yield). The trimethylaluminum-assisted formation of the benzamide **24** proceeded in 85% yield [28]. Unfortunately at this point diamide **24** was resistant to reduction with the ate complex previously employed. We considered that the presence of the hydroxy residue might be interfering with the reaction and sought to remove it by oxidation. Potassium permanganate modified by copper(II) sulfate was ineffective in oxidizing the alcohol to the ketone. However Dess–Martin reagent smoothly converted the alcohol into the target ketone in quantitative yield. Unfortunately this transformation also failed to facilitate the desired reduction. Further transformations of the trifluoro alcohol **25** and the related compound **27** are currently under investigation.

Acknowledgments

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