Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6231–6234

TETRAHEDRON LETTERS

Synthesis of (*E*)- and (*Z*)-fluoro-olefin analogues of potent dipeptidyl peptidase IV inhibitors

Pieter Van der Veken, István Kertèsz, Kristel Senten, Achiel Haemers and Koen Augustyns*

Department of Medicinal Chemistry, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium

Received 15 May 2003; accepted 20 June 2003

Abstract—(*E*)- and (*Z*)-fluoro-olefin analogues of potent dipeptidyl peptidase IV inhibitors were synthesized. A Wadsworth–Horner–Emmons reaction, followed by amide formation and reduction of the amide were used for the construction of the α-fluoro-α,β-unsaturated amine functionality.

1. Introduction

Dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5., CD26) is a serine peptidase cleaving off dipeptides from the amino terminus of peptides or proteins with proline or alanine at the penultimate position. Since prolylamides are known to play a critical role in peptide structure and function, and because of their high resistance towards non-specific enzymatic hydrolysis, the few enzymes capable of cleaving this structural motif have always attracted considerable scientific attention. As a result of this research, it was shown that DPP IV-inhibition can be used as a new tool for controlling type II diabetes.[1] Typically, these inhibitors possess a dipeptide skeleton with a free amino terminus and a pyrrolidine ring attached to an electrophilic site for Ser-OH scavenging such as a carbonitrile or a boronic acid (Fig. 1).

The stability of these compounds is compromised due to reaction of the electrophilic group with the free amino terminus, a process analogous to the well-known diketopiperazine formation in peptide chemistry. This problem can possibly be overcome by changing the amide bond in the parent structure by a more rigid function that stabilizes the '*trans*' conformation of the inhibitor. This '*trans*' conformation is presumed necessary for enzyme binding.[2] As early as 1986, the fluoro-olefin group was proposed as a superior rigid isosteric and isoelectronic replacement for the amide bond, an assumption also supported by more recent theoretical studies.[3] Furthermore, the introduction of a fluoro-olefin function might have pronounced effects on the pharmacokinetic characteristics of these compounds compared to their parent amide compounds. This concept was used by the group of Welch in synthesizing fluoro-olefin analogues of two known inhibitors with alanyl-ψ[C(F)=C)]-proline structure (Fig. 1). Although no general and unambiguous conclusions considering the effect on inhibitory activity of introducing the fluoro-olefin group in these compounds can be drawn from only two examples, Welch could experimentally verify that there is indeed significant enzyme affinity for these peptidomimetics.[4]

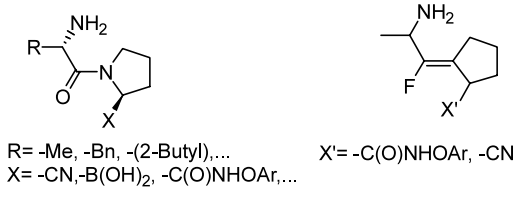


Figure 1. Typical structure for DPP IV inhibitors (left) and existing (*Z*)-fluoro-olefin mimetics (right).

Our research on fluoro-olefin analogues of prolyl-derived DPP IV inhibitors was focused on *N*-substituted glycylprolylanalogues (Fig. 2).

Members of this group of compounds have been selected for different clinical trials for the management of type II diabetes.[5] Since the (*E*)-isomers of the existing fluoro-olefin inhibitors have never been synthesized, our compounds offer the opportunity to rigorously examine the *cis*,*trans* selectivity of DPP IV. The *N*-substituent groups in our compounds (2-phenylethyl-, 1-

* Corresponding author. Tel.: +32-(0)3-8202703; fax: +32-(0)3-8202739; e-mail: koen.augustyns@ua.ac.be

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01542-9

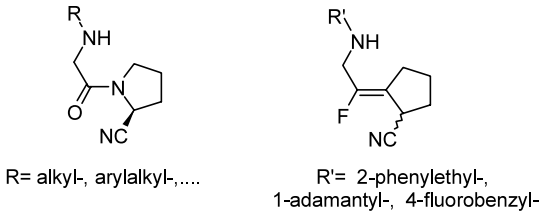


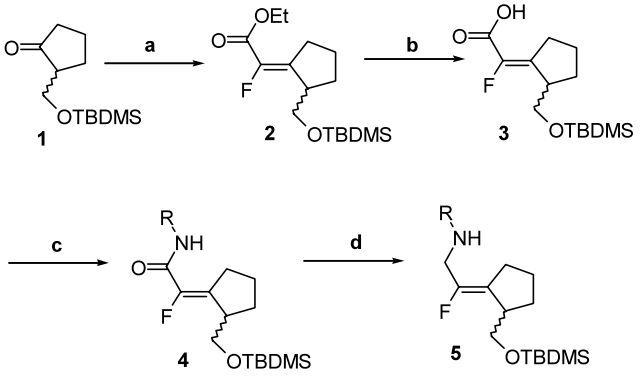
Figure 2. Newer DPP IV inhibitors (left) and synthesized fluoro-olefin mimetics (right).

adamantyl-, and 4-fluorobenzyl-) were chosen according to the activity data for the parent structures obtained from patent literature.[6]

2. Results and discussion

Similar to Welch, racemic TBDMS-protected (2-hydroxymethyl)cyclopentanone was chosen as the starting material for the construction of the pseudodipeptide skeleton (Scheme 1).

Contrary to Welch's Peterson olefination methodology for the introduction of the fluoro-olefin moiety, we decided to use the much easier accessible Wadsworth–Horner–Emmons reagent ethyl (diethoxyphosphoryl)(fluoro)acetate, obtained in high yield from the Arbuzov reaction between triethylphosphite and ethyl bromofluoroacetate. Although this Wadsworth–Horner–Emmons reagent has been used numerous times with aldehydes, its reactivity towards ketones is



Scheme 1. Construction of the β-fluoro-β,γ-unsaturated amine group. Synthetic steps for the (*E*)-isomers are identical. *Reagents and conditions*: (a) 1. NaH, Et_2O, 0°C, 2. ethyl(diethoxyphosphoryl)(fluoro)acetate, 4 h, 74% ($E/Z=1.3$); (b) KOH, $MeOH/H_2O$, 8 h, 98%/97%;[a] (c) TBTU, DIPEA, RNH_2, CH_2Cl_2, 4 h, 85–87%/84–91%;[b] (d) 1. $POCl_3$ (4 equiv.), DIPEA (1 equiv.), CH_2Cl_2, 0°C, 2 h, 2. $LiAlH_4$ (2 equiv.), Et_2O, 0°C.[c]

[a]Yields separated by '/' are for *E*- and *Z*-isomers, respectively.

[b]Yields for *E*- and *Z*-isomers fall within the indicated range.

[c]The crude reaction products were used in the next steps without purification.

largely undocumented.[7] The reaction was optimized with cyclopentanone and the successful outcome of the reaction seems to be very much confined to specific reaction conditions and the use of NaH as base (Table 1).

The yield of the reaction (74%) with compound **1** and the E/Z isomeric ratio (1.3) were comparable to the results reported for this reaction when using the Peterson reagent *tert*-butyl α-fluoro-α-trimethylsilylacetate. Double bond isomers were separated by column chromatography; the structural identity of these isomers was determined by NMR spectroscopy.[8]

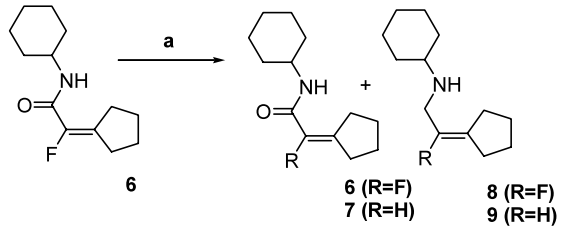
The fluoro-olefin products **2** were then subjected to alkaline hydrolysis in almost quantitative yield and coupled to the appropriate amine using the standard peptide coupling reagent TBTU. For the subsequent reduction, one literature precedent was present of the successful $LiAlH_4$ mediated transformation of an α-fluoro-α,β-unsaturated amide into the corresponding amine in ethereal solution.[9] As a test, these conditions were applied to compound **6**, obtained in a similar way starting from cyclopentanone (Scheme 2). After reacting for four days, the reaction mixture which still contained a considerable amount of starting material was quenched. Using an extractive work-up, amide and amine components were separated and the latter were Boc-protected to allow chromatographic separation. However, it was found that the yield of the desired product (3%) was unacceptably low and that the very slow reaction was accompanied by extensive defluorination (Table 2, first entry).

Contrary to our results, Bartlett and Otake only mention the defluorinated analogue of their target amine in 3–6% yield.

In order to find reaction conditions that suppress this side reaction, different aluminium hydride-based reductants were tested on model compound **6**.

Table 1. Optimizing the Wadswoth–Horner–Emmons reaction with cyclopentanone

Base	Conditions	Yield (%)
KO*t*-Bu	DMF/0°C	12
LDA	THF/−78°C	<5
n-BuLi	THF/−78°C	0
KHMDS	THF/−78°C	0
NaH	THF/0°C	70
NaH	Et_2O/0°C	84



Scheme 2. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O.

As seen from Table 2, $POCl_3$-preactivation which turns the amide bond in a more reactive chloro-imidate, followed by $LiAlH_4$ reduction is a superior method and was adopted in the synthesis of our target fluoro-olefin peptidomimetics. To prevent acidolytic cleavage of the TBDMS group by HCl produced during the reaction with $POCl_3$, 2 equiv. of DIPEA were added to the reaction mixture. After reduction, the crude amines **5** were Boc-protected, followed by selective acidic hydrolysis of the TBDMS group and chromatographic purification of the resulting alcohols (Scheme 3).

The Jones oxidation protocol was then used for the synthesis of the acids **12**, followed by activation with *iso*-butylchloroformate and transformation into the corresponding primary amides **13**. Dehydration in high yield gave the protected carbonitriles **14**. Contrary to the very recently published synthesis of a carbonitrile fluoroolefin inhibitor by Welch's group (Fig. 1), the use of the standard $POCl_3$/imidazole dehydrating agent did not result in low yields for this step for any of the products.

The same holds true for the acidolytic deprotection of the Boc-group which was done using TFA and provided final products **15**. Although a cyclization reaction, similar to the inactivation reaction described for amide inhibitors might be expected for the deprotected (*E*)-isomers, these compounds were stable for at least 96 h in aqueous or methanolic solution (controlled by HPLC).

3. Conclusion

We have shown that fluoro-olefin analogues of glycyl-prolylcarbonitriles can be prepared from cyclopentanones with a Wadsworth–Horner–Emmons reaction. Yields and *E*/*Z* isomeric ratio are comparable with the Peterson olefination method. A generally applicable method for the clean transformation of both (*E*)- and (*Z*)-α-fluoro-α,β-unsaturated amides into the corresponding amines was developed. The synthesized compounds will be of importance as DPP IV inhibitors and for the study of the selectivity of DPP IV for a '*trans*' P_2–P_1 bond.

Table 2. Comparison of reduction methods for model α-fluoro-α,β-unsaturated amide **6**

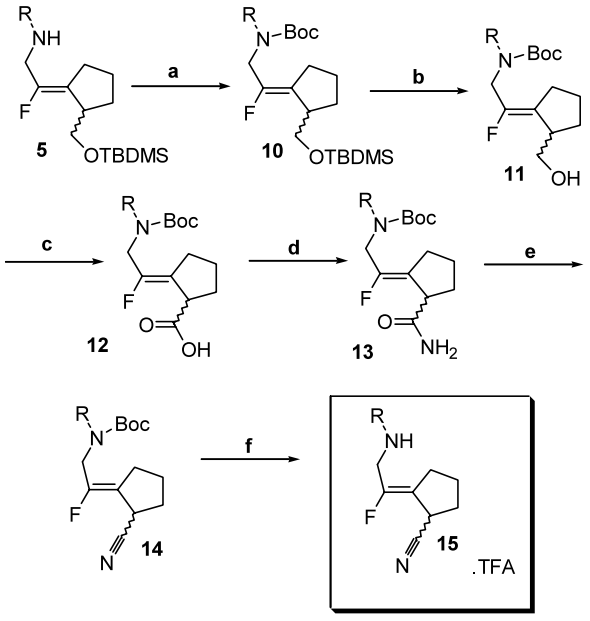
Reducing agent	Conditions	Yield (%)	
		8	**9**
$LiAlH_4$[a]	Et_2O/0°C to rt/96 h	3	6
$LiAlH_4/AlCl_3$ (3:1)[b]	Et_2O/0°C to rt/6 h	65	22
$LiAlH_4/ZnCl_2$ (2:1)[c]	a. Et_2O/0°C to rt/4 h	74	6
	b. THF/0°C to rt/4 h	72	6
$AlH_3 \cdot Et_3N$	Et_2O/0°C to rt/8 h	51	19
1. $POCl_3$/2. $LiAlH_4$[d]	a. 1. DCM/rt/1 h		
	2. Et_2O/0°C to rt/3 h	92	3
	b. 1. DCM/rt/1 h		
	2. THF/0°C to rt/3 h	79	4

[a] Reaction was stopped before completion, remainder 22% of **6**, 61% of **7**.

[b] In situ formation of alane: $3LiAlH_4+AlCl_3 \rightarrow 4AlH_3+3LiCl$.

[c] In situ formation of alane and zincane: $2LiAlH_4+ZnCl_2 \rightarrow 2AlH_3+ZnH_2+2LiCl$.

[d] $POCl_3$ reacts with amides, forming a reactive chloro-imidate.



Scheme 3. Synthesis of target compounds. The synthetic methods for the (*E*)-isomers are identical. (a) $(Boc)_2O$, DIPEA, CH_2Cl_2, 6 h;[a] (b) $AcOH/H_2O/THF$ (3:1:1), 12 h, 21–69%/41–72%;[b] (c) Jones oxidation, 1 h, 78–94%;[c] (d) 1. *i*-ButOC(O)Cl, DIPEA, CH_2Cl_2, 0°C, 15 min, (2) NH_4OH (10 equiv.), 67–91%;[c] (e) $POCl_3$/imidazole, pyridine, −10°C, 30 min, 85–93%;[c] (f) TFA/CH_2Cl_2 (1:1), 30 min, 88–94%.[c]

[a]The crude reaction products were used in he next steps without purification.

[b]This is the combined yield of the reduction, Boc-protection, and TBDMS-removal steps. Low yields were found for compounds with R = 1-adamantyl, probably due to ineffective Boc-protection caused by steric factors.

[c]Yields for *E*- and *Z*-isomers fall within the indicated range.

Acknowledgements

P. Van der Veken is a Fellow of the Institute for the Promotion of Innovation by Science and Technology in Flanders. I. Kertèsz thanks the European Community for his appointment as a Marie Curie Fellow.

References

1. Augustyns, K.; Bal, G.; Thonus, G.; Belyaev, A.; Zhang, X. M.; Bollaert, W.; Lambeir, A. M.; Durinx, C.; Goossens, F.; Haemers, A. *Curr. Med. Chem.* **1999**, *6*, 311–327.
2. Fischer, G.; Heins, J.; Barth, A. *Biochim. Biophys. Acta* **1983**, *742*, 452–462.
3. (a) Abraham, M. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101–2110; (b)

Biomedical Frontiers of Fluorine Chemistry; Cieplak, P.; Kollman, P. A.; Radomski, J. P. *ACS Symp. Ser. 639*; American Chemical Society: Washington, DC, 1996, 143–156.

4. (a) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291–304; (b) Lin, J.; Toscano, P. J.; Welch, J. T. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 14020–14024; (c) Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003**, *11*, 207–215; (d) Biomedical Frontiers of Fluorine Chemistry; Welch, J. T.; Lin, J.; Boros, L. G.; DeCorte, B.; Bergmann, K.; Gimi, R. *ACS Symp. Ser. 639*; American Chemical Society: Washinton, DC, **1996**, 129–142.
5. (a) Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Dunning, B. E.; Mangold, B. L.; Mone, M. D.; Russel, M. E.; Weldon, S. C.; Hughes, T. E. *J. Med. Chem.* **2002**, *45*, 2362–2365; (b) Hughes, T. E.; Russel, M. E.; Bolognese, L.; Li, X.; Burkey, B. F.; Wang, P. R.; Villhauer, E. B. NVP-LAF237, A Highly Selective and Long-Acting Dipeptidyl Peptidase IV Inhibitor, *Abstracts from the ADA 62nd Scientific Sessions*; 62nd Annual Meeting and Scientific Sessions, San Francisco, 6/14-6/18; American Diabetes Association: Washington, DC, 2002; 272-OR, A67.
6. Villhauer, E. B. US Patent 6,124,305, 2000.
7. Burton, D. J.; Yang, Z. Y.; Qiu, W. M. *Chem. Rev.* **1996**, *96*, 1641–1715.
8. ^{1}H–^{1}H NOESY experiments (400 MHz) on compounds **5** were indicative in assigning fluoro-olefin geometries. Characteristic NOEs were seen between the NH-proton and cyclopentyl-protons. These results were confirmed by comparing our ^{1}H and ^{13}C NMR spectra for the aldehyde derived of compound **1** with data provided by Welch in Ref. 4a. The aldehyde was synthesized by coupling acid **3** to *N*-methoxy-*N*-methylamide using TBTU, followed by $LiAlH_4$-reduction of the resulting Weinreb-amide. During the reduction, no defluorination occurred. *E*- and *Z*-isomers were separated by silica gel flash chromatography, using hexanes/ethylacetate 49:1 as the eluent.
9. Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107–3111.