Tetrahedron Letters, Vol.31, No.50, pp 7297-7300, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

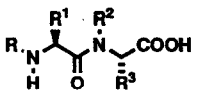
FLUOROOLEFIN DIPEPTIDE ISOSTERES - I.

The Synthesis of GlyΨ(CF=CH)Gly and Racemic PheΨ(CF=CH)Gly

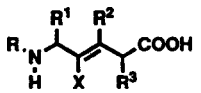
Thomas Allmendinger [a] *, Pascal Furet [b] and Ernst Hungerbühler [a]
[a] Central Research Laboratories, [b] Pharmaceuticals Division
Ciba-Geigy AG, CH-4002 Basel, Switzerland

Summary: The syntheses of Gly-Gly and racemic Phe-Gly fluoroolefin dipeptide isosteres are described, the first examples of a new class of peptide analogues.

The use of non-hydrolyzable amide isosteres is an established approach [1,2] to overcoming one of the major drawbacks in the use of peptides as therapeutic agents, namely their rapid degradation by peptidases. One known approach is to use the trans-olefinic as amide mimic, which is geometrically equivalent to the amide bond in its most stable (transoid) conformation [3]. Several contributions to the synthesis and application of this class of compounds 1 have been made [4].

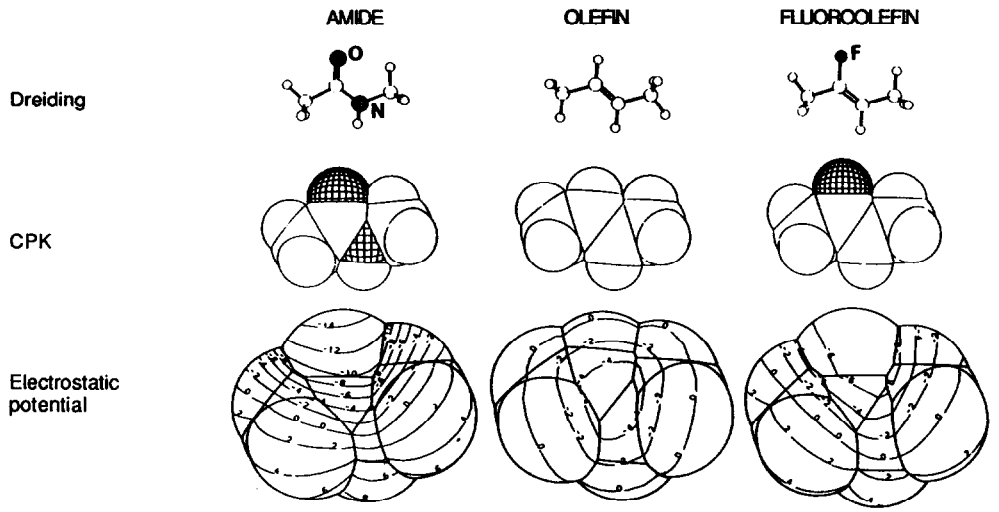


Dipeptide

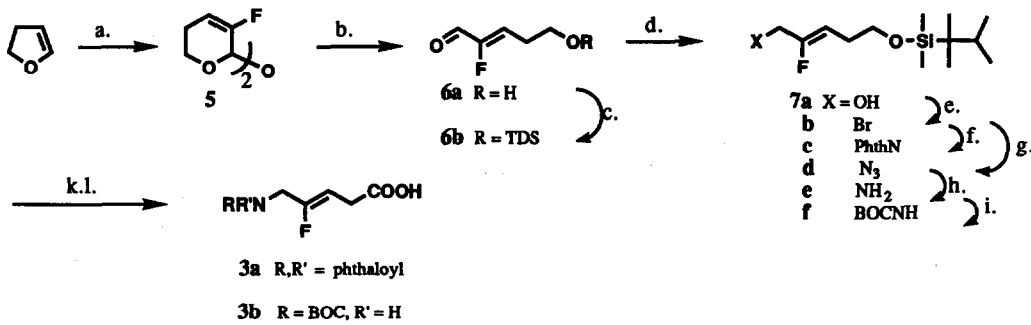


1 X=H
2 X=F

We have calculated the molecular profiles of N-methyl acetamide, trans-2-butene and 2-fluoro-2(Z)-butene as simple models of the peptide bond (see figure 1). Their comparison suggests that the fluoroolefin unit is an even better



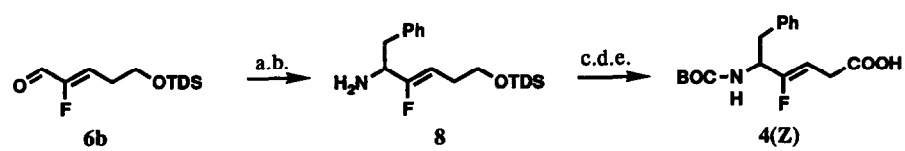
amide bond substitute mimicking both steric and electronic features of the peptide bond. Dipole moment calculations enabled Abraham [7] to reach the same conclusion, though attempts to synthesize the corresponding dipeptide isostere **2** have not, until now, been successful [8]. In this letter we describe the preparation of the first examples of fluoroolefin isosteres **3** (Gly-Gly mimic) and **4** (Phe-Gly analogue), the latter in both the E and Z configuration at the fluoroolefin double bond.



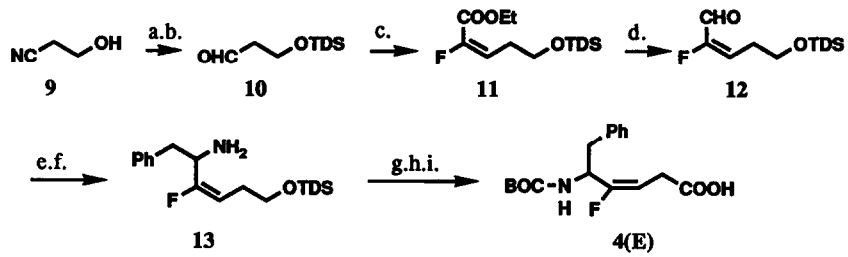
Scheme 1. a. $CHCl_2F$, CH_2Cl_2, 50% NaOH, $PhCH_2NEt_3Cl$, 41%; b. aq. HCl, dioxane, reflux, 34%; c. TDS-Cl, imidazole, DMF, rt, 65%; d. DIBAH, toluene, -70°, 80%; e. CBr_4, Ph_3P, CH_2Cl_2, 0°, 50%; f. K-phthalimide, DMF,50°, 55%; g. NaN_3, DMF, rt, 64%; h. LAH, ether, rt, 80%; i. $(BOC)_2O$, CH_2Cl_2, 85%; k. R, R'=Phth: 1% HCl in EtOH, R=BOC, R'=H: Bu_4NF; l. Jones oxidation, 68%.

As summarized in scheme 1 the Gly-Gly fluoroolefin dipeptide isostere **3** was synthesized from cyclic acetal **5**, obtained by the procedure of Dehmlow [9]. Compound **5** was then subjected to acid catalyzed hydrolysis which occurred with concomitant double bond[10] isomerisation to give the Z configurated α,β-unsaturated aldehyde **6a**. Further elaboration as detailed in scheme 1[11] ultimately afforded the N-protected amino acids **3a** and **3b** [13].

The Phe-Gly isostere **4(Z)** was prepared starting with the aldehyde **6b** (scheme 2). Thus treatment with lithium hexamethyldisilazide [14] at -25°C to form the corresponding silylimine followed by in situ addition of benzylmagnesium chloride and aqueous work up afforded the amine **8** in 48% yield. After protection of the amino group, deprotection and oxidation of the alcohol functionality, the N-BOC protected dipeptide isostere **4(Z)** was obtained as a racemate[13]. In order to study the significance of the double bond geometry we also synthesized the corresponding **4(E)** isomer by a similar reaction sequence (scheme 3). The silyloxypropanal **10**, prepared from 3-hydroxy-propionitrile **9**, was fluoroolefinated using triethylphosphonofluoro acetate [15] to get the E-configurated ester **11** which was further reduced to the aldehyde **12**, the double bond isomer of the before mentioned aldehyde **6b**. In situ silylimine formation and Grignard addition furnished the amine **13**, which was transformed in three further steps to **4(E)**.



Scheme 2. a. $LiN(SiMe_3)_2$, THF, hexane, -25°; b. $PhCH_2MgCl$, ether, -70°, 48%; c. $(BOC)_2O$, CH_2Cl_2, rt, 100%; d. Bu_4NF, THF, rt, 96%; e. Jones oxidation, 68%.



SCHEME 3. a. TDS-Cl, DBU, CH_2Cl_2, 80%; b. DIBAH, toluene, -70° to -20°, 65%; c. $(EtO)_2PO$-CHF-COOEt, LDA, THF, -70°, 76%; d. DIBAH, toluene, -70°, 72%; e. $LiN(SiMe_3)_2$, -25°; f. $PhCH_2MgCl$, 14%; g. $(BOC)_2O$, CH_2Cl_2, rt, 86%; h. Bu_4NF, THF, rt, 77%; i. Pt/C, O_2, 28%.

In sharp contrast to pure olefin dipeptide isosteres, where the double bond easily migrates into conjugation to the carbonyl group [16], the fluoroolefin analogues **3** and **4** and their derivatives are resistant toward such isomerisations, clearly indicating the stabilizing effect of fluorine to the double bond [17].

In conclusion we have established a simple route to the first fluoroolefin dipeptide isosteres that mimic the Gly-Gly and Phe-Gly peptides. A generalization of the shown synthetic scheme to AA-Gly fluoroolefin dipeptide mimics is possible by changing the organometallic species added to the silylimine intermediate. Further examples, alternative routes and biological applications are published in the accompanying paper and elsewhere [18].

Acknowledgment: The helpful commentary of our colleagues Dr. Robert W. Lang and Dr. Hans Greuter as well as the laboratory skills of Gisela Geiger, Andrea Zingg, Hans Ofner and Guenther Bartsch are gratefully acknowledged.

References

1. A.Spatola in B. Weinstein (Editor), Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Vol. 7, Marcel Dekker, New York, 1983, pp. 267-357.
2. D. Tourwé, *Janssen Chimica Acta* **1985**, *3*, 3.
3. M.M. Hann , P.G. Sammes, P.D. Kennewell and J.B. Taylor, *J.Chem.Soc., Chem.Commun.* **1980**, 234; *Perkin Trans. I* **1982**, 307.
4. a. M.T. Cox, D.W. Heaton and J. Horbury, *J.Chem.Soc., Chem. Commun.* **1980**, 799. b. M.T. Cox, J.J. Gormley, C.F. Hayward and N.N. Petter, *ibid* **1980**, 800. c. N.J. Miles, P.G. Sammes, P.D. Kennewell and R. Westwood, *J. Chem. Soc., Perkin Trans. I* **1985**, 2299. d. A. Spaltenstein, P.A. Carpino, F. Miyake and P.B. Hopkins, *J.Org.Chem.* **1987**,*52*, 3759. e. Y.-K. Shue, G.M. Carrera, Jr. and A.M. Nadzan, *Tetrahedron Lett.* **1987**, 3225. f. Y.-K. Shue, M.D. Tufano and A.M. Nadzan, *ibid* **1988**, 4041. g. J.K. Whitesell and R.M. Lawrence, *Chirality*, **1989**, *1*, 89.
5. The molecular electrostatic potentials were calculated in the monopole approximation using atomic charges derived from a Mulliken population analysis on MNDO wave functions. The potentials are displayed as isovalue contour lines on expanded Van der Waals surfaces of the molecules [6] (extra atomic radius of 1.5 A). Negative and positive values correspond to regions of attraction and repulsion respectively for a unitary positive charge.

6. N.C. Cohen, *ACS Symp. Ser.* **1979**, *112*, 371-381.
7. R.J. Abraham, S.L.R. Ellison, P. Schonholzer and W.A. Thomas, *Tetrahedron* **1986**,*42*, 2101.
8. S.L.R. Ellison, PhD. Thesis, University of Liverpool, UK, 1984.
9. E.V. Dehmlow and K. Franke, *Liebigs. Ann. Chem.* **1979**, 1456.
10. Schlosser described the preparation of specifically Z-configurated α-fluoro-α,β-unsaturated aldehydes by a similar process: Y. Bessière, D.N.-H. Savary and M. Schlosser, *Helv. Chim. Acta* **1977**,*60*, 1739.
11. TDS: Thexyldimethylsilyl protecting group [12].
12. Hj. Wetter and K. Oertle, *Tetrahedron Lett.* **1985**, *26*, 5515.
13. All new compounds show correct elemental analysis and/or molecular ion using mass spectroscopy. Some physical data are listed below.

Table 1: ^{1}H NMR data (300MHz, $CDCl_3$) of some compounds **RR'CH-CF=CH-CH_2-R"**

No	R	R'	R"	mp	1-H	3-H	4-H	CH_2O (R")	CH_2Ph	NH OH	J 3-F
6a	O		CH_2OH	-	9.13	6.16	2.63	3.60	-	3.5	32.5
6b	O		CH_2OSi	-	9.20	6.04	2.54	3.70	-	-	33
7a	OH	H	CH_2OSi	-	4.11	4.91	2.31	3.60	-	1.65	36.5
7b	Br	H	CH_2OSi	-	3.93	5.06	2.31	3.60	-	-	35
7c	PhthN	H	CH_2OSi	-	4.36	4.93	2.28	3.55	-	-	36
-	NH_2	H	CH_2OSi	-	3.27	4.73	2.28	3.58	-	1.36	37
-	PhthN	H	CH_2OH	64	4.40	4.97	2.36	3.65	-		36
3a	PhthN	H	COOH	154	4.41	5.16	3.12	-	-		34
3b	BOCNH	H	COOH		3.85	5.03	3.15	-	-	4.90	35
8	NH_2	CH_2Ph	CH_2OSi	-	3.56	4.70	2.27	3.52	2.73;298	1.50	38
-	BOCNH	CH_2Ph	CH_2OSi	-	4.45	4.66	2.26	3.49	2.95	4.73	37
-	BOCNH	CH_2Ph	CH_2OH	-	4.45	4.59	2.30	3.53	2.92;3.01	4.78	36.5
4(Z)	BOCNH	CH_2Ph	COOH	105	4.46	5.05	3.10	-	2.88;3.08	6.32	37
12	O		CH_2OSi	-	9.75	6.23			-	-	18
13	NH_2	CH_2Ph	CH_2OSi	-	3.86	5.00	1.90	3.27	2.86		22
-	BOCNH	CH_2Ph	CH_2OH	-	4.60	5.06	2.12	3.40	2.92	4.92	
4(E)	BOCNH	CH_2Ph	COOH	-	4.63	5.24	3.00	-	2.70-3.05		20

Table 2: ^{13}C chemical shifts and C-F coupling constants of some compounds **RR'CH-CF=CH-CH_2-CH_2-OSi**

No	R	R'	C1	C2	C3	C4	C5	CH_2Ph
6b	O		183.4 (25)	156.8 (260)	128.5 (11)	34.3	60.7	-
8	NH_2	CHPh	54.4 (29)	161.4 (254)	101.9 (14)	34.2	62.2	41.1
-	BOCNH	CHPh	53.0 (26)	157.2 (257)	103.7	34.2	62.0	38.9

14. G. Cainelli, D. Giacomini, M. Panunzio, G. Martelli and G. Spunta, *Tetrahedron Lett.* **1987**, *28*, 5369.
15. H. Machleidt and R. Wessendorf, *Liebigs Ann. Chem.* **1964**, *674*, 1.
16. H. Duplaa , G. v.Sprecher and W. Schilling, personal communication.
17. W.R. Dolbier, Jr., K.S. Medinger, A. Greenberg and J.F. Liebman, *Tetrahedron* **1982**, *38*, 2415.
18. a) T. Allmendinger, 199th ACS National Meeting, Boston, Massachusetts, 1990.
    b) E. Hungerbühler, 200th ACS National Meeting, Washington D.C., 1990.

(Received in Germany 10 July 1990)