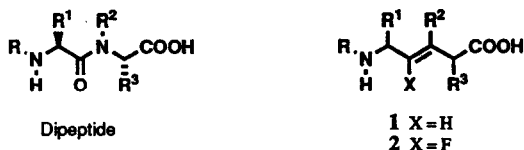


FLUOROOLEFIN DIPEPTIDE ISOSTERES - I. **The Synthesis of GlyΨ(CF=CH)Gly and Racemic PheΨ(CF=CH)Gly**

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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.



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

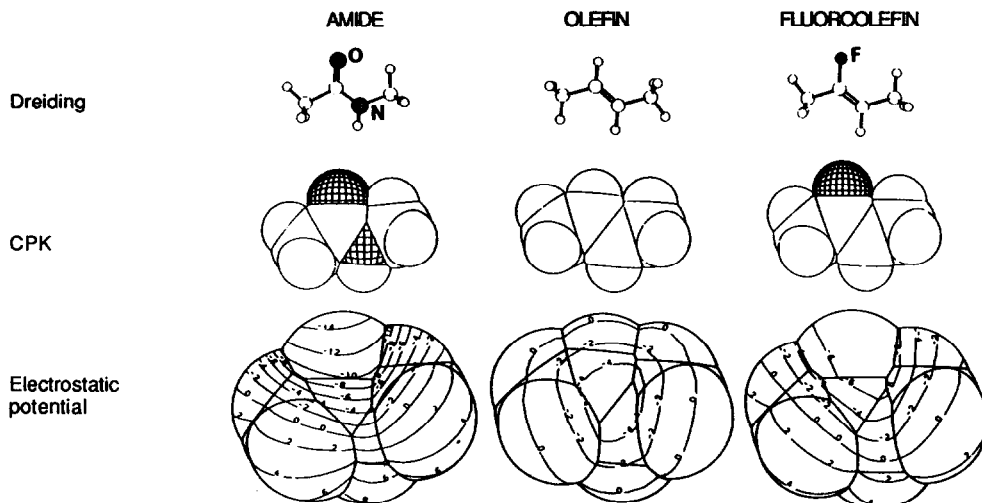
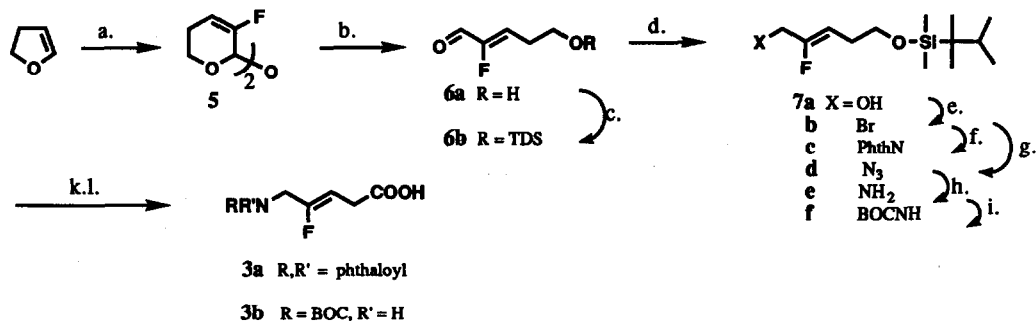


Figure 1: Dreiding and CPK-representation (standard geometries) and electrostatic potential profiles of N-methyl acetamide, trans-2-butene and 2-fluoro-2(Z)-butene ⁵.

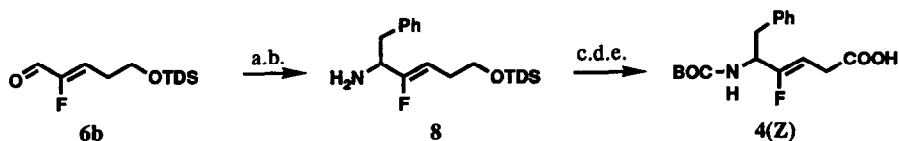
amide bond substitute mimicking both steric and electronic features of the peptide bond. Dipole moment calculations enabled Abraham ⁷ to reach the same conclusion, though attempts to synthesize the corresponding dipeptide isostere 2 have not, until now, been successful ⁸. In this letter we describe the 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.



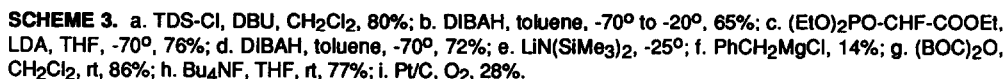
Scheme 1. a. CHCl_2F , CH_2Cl_2 , 50% NaOH, $\text{PhCH}_2\text{NEt}_3\text{Cl}$, 41%; b. aq. HCl, dioxane, reflux, 34%; c. TDS-Cl, imidazole, DMF, rt, 65%; d. DIBAH, toluene, -70° , 80%; e. CBr_4 , Ph_3P , CH_2Cl_2 , 0° , 50%; f. K-phthalimide, DMF, 50° , 55%; g. NaN_3 , DMF, rt, 64%; h. LAH, ether, rt, 80%; i. $(\text{BOC})_2\text{O}$, 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 Dehmow ⁹. Compound 5 was then subjected to acid catalyzed hydrolysis which occurred with concomitant double bond¹⁰ isomerisation to give the Z configured α,β -unsaturated aldehyde 6a. Further elaboration as detailed in scheme 1¹¹ 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 racemate¹³. 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-configured 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. $\text{LiN}(\text{SiMe}_3)_2$, THF, hexane, -25° ; b. PhCH_2MgCl , ether, -70° , 48%; c. $(\text{BOC})_2\text{O}$, CH_2Cl_2 , rt, 100%; d. Bu_4NF , THF, rt, 96%; e. Jones oxidation, 68%.



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 elsewhere¹⁸.

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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 Å). Negative and positive values correspond to regions of attraction and repulsion respectively for a unitary positive charge.

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13. All new compounds show correct elemental analysis and/or molecular ion using mass spectroscopy. Some physical data are listed below.

Table 1: ¹H NMR data (300MHz, CDCl₃) of some compounds RR'¹CH-CF=CH-CH₂-R''

No	R	R'	R''	mp	1-H	3-H	4-H	CH ₂ O (R'')	CH ₂ Ph	NH OH	J 3-F
6a	O		CH ₂ OH	-	9.13	6.16	2.63	3.60	-	3.5	32.5
6b	O		CH ₂ OSi	-	9.20	6.04	2.54	3.70	-	-	33
7a	OH	H	CH ₂ OSi	-	4.11	4.91	2.31	3.60	-	1.65	36.5
7b	Br	H	CH ₂ OSi	-	3.93	5.06	2.31	3.60	-	-	35
7c	PhthN	H	CH ₂ OSi	-	4.36	4.93	2.28	3.55	-	-	36
-	NH ₂	H	CH ₂ OSi	-	3.27	4.73	2.28	3.58	-	1.36	37
-	PhthN	H	CH ₂ OH	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 ₂ Ph	CH ₂ OSi	-	3.56	4.70	2.27	3.52	2.73;298	1.50	38
-	BOCNH	CH ₂ Ph	CH ₂ OSi	-	4.45	4.66	2.26	3.49	2.95	4.73	37
-	BOCNH	CH ₂ Ph	CH ₂ OH	-	4.45	4.59	2.30	3.53	2.92;3.01	4.78	36.5
4(Z)	BOCNH	CH ₂ Ph	COOH	105	4.46	5.05	3.10	-	2.88;3.08	6.32	37
12	O		CH ₂ OSi	-	9.75	6.23	-	-	-	-	18
13	NH ₂	CH ₂ Ph	CH ₂ OSi	-	3.86	5.00	1.90	3.27	2.86	-	22
-	BOCNH	CH ₂ Ph	CH ₂ OH	-	4.60	5.06	2.12	3.40	2.92	4.92	-
4(E)	BOCNH	CH ₂ Ph	COOH	-	4.63	5.24	3.00	-	2.70-3.05	-	20

Table 2: ¹³C chemical shifts and C-F coupling constants of some compounds RR'¹CH-CF=CH-CH₂-CH₂-OSi

No	R	R'	C1	C2	C3	C4	C5	CH ₂ Ph
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

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