Tetrahedron Letters, Vol.31, No.50, pp 7301-7304, 1990
Printed in Great Britain

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

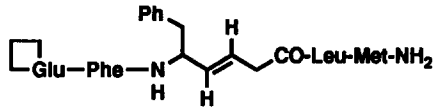
FLUOROOLEFIN DIPEPTIDE ISOSTERES[1] - II. Enantioselective Synthesis of both Antipodes of the Phe-Gly Dipeptide Mimic

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

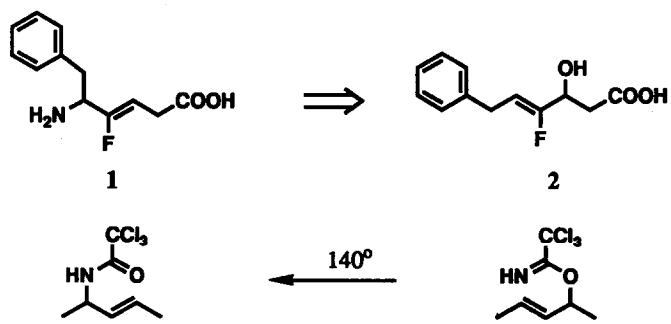
Abstract. The addition of optically active ester enolates to α-fluoro-α,β-unsaturated aldehydes and formal S_N2' substitution of an allylic hydroxyl group thus formed by a trichloro-acetamido group via Overman rearrangement constitutes a new general route to fluoroolefin dipeptide isosteres in enantiomerically pure form. This methodology was applied for the preparation of both enantiomers of the PheΨ(CF=CH)Gly dipeptide mimic which were further elongated to substance P analogues.

The neuropeptide substance P (SP) has generated a great deal of interest during the recent years [2]. A large number of analogues which cannot be cleaved by peptidases have been designed, prepared and tested. A recent example is a C-terminal hexapeptide **A** in which the amide bond between Phe-Gly is replaced by the isosteric trans configured double bond [3].

SP: Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe—Gly-Leu-Met-NH_2

A: 

As we have established a synthetic route to the new class of fluoroolefin dipeptide isosteres [1] we chose SP as our first target molecule to gain an insight into the utility of these isosteres. This letter deals with the enantioselective synthesis of both antipodes of **1**, the fluoroolefin dipeptide isostere of the Phe-Gly region of SP.

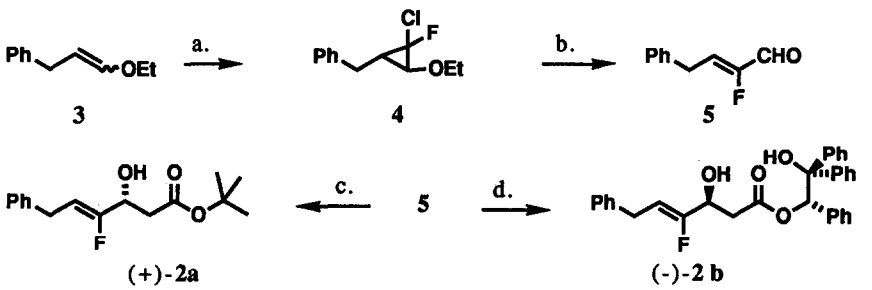


Scheme 1

From the retrosynthetic scheme 1, it is evident that the hetero Cope-rearrangement of allylic iminoesters, pioneered originally by Overman [4] would serve as an ideal method for the introduction of a nitrogen functionality into the fluorinated

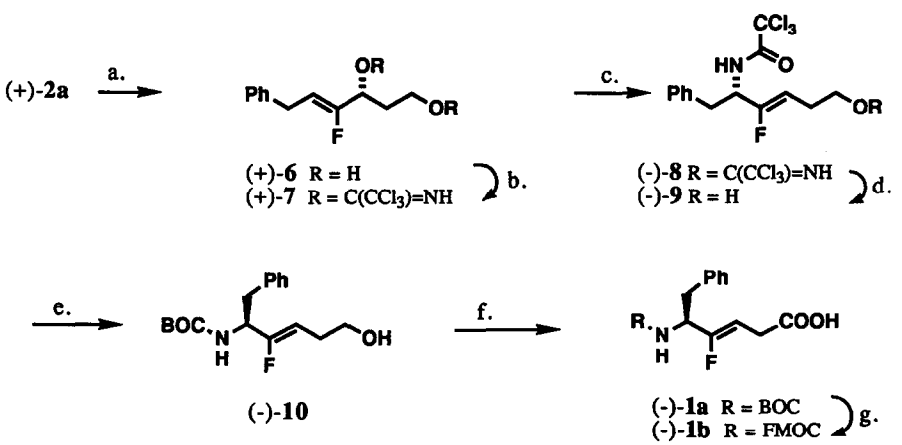
templates. In the case of optically active **2** the transfer of chirality should lead to optically active products. The preparation of derivatives of the hydroxy acid **2** is outlined in scheme 2.

The known enol ether [5] **3** was converted to the chlorofluorocarbene adduct **4**, which was solvolyzed to the fluorinated unsaturated aldehyde **5** by a method of Schlosser [6,7]. The optically active (R)- and (S)-hydroxy-esters (+)-**2a** and (-)-**2b** were prepared by the addition of the diacetone glucose modified titanium enolate of tert.-butyl acetate [9] and the bis-lithiated (S)-(2-hydroxy-1,2,2-triphenylethyl) acetate [(S)-HYTRA] [10] respectively.



Scheme 2. a. $CHCl_2F$, 60% KOH, 18-crown-6, 68%; b. H_2O, sodium dodecylsulfate, reflux, 61%; c. $Cp(DAG\text{-}O)_2Ti\text{-}O\text{-}C(\text{-}OBu^t)=CH_2$, toluene, -70°, 80%, ee=93%; d. (S)-HYTRA, 2 LDA, -70°, 90%, ee>90%..

The hydroxy-esters could not be rearranged directly via their trichloro-acetimidates due to the facile elimination to the corresponding dienes. Therefore they were first reduced to the diols **6** (see scheme 3, showing the sequence only for one enantiomer) and treated with catalytic amounts of sodium hydride and two equivalents of trichloro acetonitrile to give the bis-iminoesters **7** which were subsequently rearranged in refluxing xylene to the acetamide **8**. The unaffected primary iminoester group was cleaved with sulfuric acid in methanol affording the alcohol **9**.

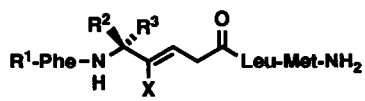


Scheme 3. a. LAH, ether, 78%; b. 1. cat. NaH, hexane, THF, 2. Cl_3CCN, ether; c. xylene, 140°, 73% (from **6**); d. H_2SO_4, MeOH, 98%; e. 1. NaOH, H_2O, MeOH, 2. $(BOC)_2O$, CH_2Cl_2, 81%; f. Jones oxidation, 76%; g. 1. HCl, dioxane, 2. FMOC-OSu, NEt_3, 61%.

After cleavage of the trichloro acetamide the amino alcohol was protected as its N-tert.-butyloxycarbonyl derivative **10**, which was oxidized to the acid **1a** [11]. After changing the protecting groups (BOC to FMOC) of the enantiomeric acids (-)- and (+)-**1a** yielding the building blocks (-)- and (+)-**1b**, they were elongated to the full sequence of SP and to the hexapeptide analogues. The peptide chains were assembled by the Fmoc solid phase approach [12] on a polystyrene based trialkoxy-diphenylamine resin [13]. Using analogous conditions as for regular Fmoc amino acids, units of the type **1b** were incorporated without noticeable changes in coupling yields. The substance P analogues **11**, **12**, **13** and **14** were characterized by FAB-MS and showed significant biological activity (see table and reference [14]).

In a receptor binding assay, compound **11** is almost as active as SP itself whereas its diastereomere **12** binds 10 times weaker. This ratio is reflected in the binding affinities of the hexapeptide analogues **13** and **14**. Compared to the olefinic analogue **15**, the fluoroolefin derivative **13** binds more than 10 times stronger to the SP-receptor which supports the working hypothesis [1]. In contrast to the behaviour of non-fluorinated analogues which easily undergo isomerisation of the double bond to give α,β-unsaturated amides[15], the double bond in compounds **1a**, **1b**, **11-14** and the corresponding intermediates was stable towards all basic or acidic reaction conditions employed, thus indicating the stabilizing effect of fluorine on the double bond [16].

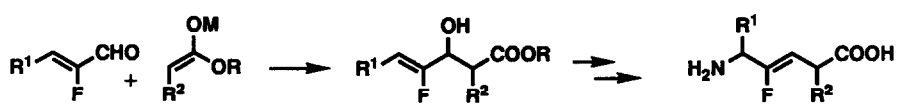
Table: Receptor binding of substance P and some analogues



No	R^1	R^2	R^3	X	IC_{50}
SP					1.3 nM
11	Arg-Pro-Lys-Pro-Gln-Gln-	CH_2Ph	H	F	2 nM
12	"	H	CH_2Ph	F	20 nM
13	pyro-Glu-	CH_2Ph	H	F	0.8 µM
14	"	H	CH_2Ph	F	10 µM
15*	"	CH_2Ph	H	H	>10 µM **

* one diastereomer of **A** corresponding to the natural *S*-configuration
** 20 % inhibition at 10 µM.

In conclusion the aldol reaction of α-fluoro-α,β-unsaturated aldehydes and ester enolates followed by the introduction of a nitrogen functionality by an Overman rearrangement represents a general synthetic route, which allows the preparation of a wide variety of fluoroolefin dipeptide isosteres.



They exhibit a higher chemical stability and, in a first example, a higher receptor binding affinity compared to the known trans-olefin isostere.

Acknowledgement. The skillful assistance of Gisela Geiger and Hans Ofner as well as helpful discussions with Dr. Robert W. Lang, Dr. Hans Greuter, Dr. Stuart Mickel and Dr. W. Schilling are gratefully acknowledged.

References

1. Part I: T. Allmendinger, P. Furet and E. Hungerbühler, previous article.
2. a) R. Porter and M. O'Connor (Ed.), "Substance P in the Nervous System", Ciba Foundation Symposium 91 (1982); b) L. Barthó and P. Holzer, *Neuroscience* **1985**, *16*, 1; c) G. Drapeau, P. D'Orléans-Juste, S. Dion, N.-E. Rhaleb, N.-E. Rouissi and D. Regoli, *Neuropeptides* **1987**, *10*, 43; d) P. Ward, G. B. Ewan, C. C. Jordan, S. J. Ireland, R. M. Hagan and J. R. Brown, *J. Med. Chem.* **1990**, *33*, 1848.
3. M.T. Cox, J.J. Gormley, C.F. Hayward and N.N. Petter, *J. Chem. Soc.*, Chem. Commun. **1980**, 800.
4. L.E. Overman, *J. Am. Chem Soc.* **1976**, *98*, 2901.
5. J.F. Normant, A. Commercon, M. Bourgain and J. Villieras, *Tetrahedron Lett.* **1975**, 3833.
6. Y. Bessière, D.N.-H. Savary and M. Schlosser, *Helv. Chim. Acta* **1977**, *60*, 1739.
7. Alternatively **5** can be obtained by DIBAH reduction of the ester $PhCH_2CH{=}CF\text{-}COOEt$ [8].
8. T. Allmendinger, in preparation.
9. R.O. Duthaler, P. Herold, W. Lottenbach, K. Oertle and M. Riediker, *Angew. Chem.* **1989**, *101*, 490; *Angew. Chem.,Int. Ed. Engl.* **1989**, *28*, 495.
10. R. Devant, U. Mahler and M. Braun, *Chem. Ber.* **1988**, *121*, 397.
11. The specific optical rotations ($[\alpha]_D^{20}$, measured in $CHCl_3$ at a concentration of about 1%) of the intermediates are the following: (+)-**2a** : $+10.5^o$; (-)-**2b**: -148.4^o; (+)-**6**: $+13^o$, (-)-**6**: -13.6^o; (-)-**8**: -11.8^o, (+)-**8**: $+12.3^o$; (-)-**9**: -18.7^o, (+)-**9**: $+18.5^o$; (-)-**10**: -4.5^o, (+)-**10**: $+3.9^o$; (-)-**1a**: -7.9^o, (+)-**1a**: $+7.7^o$.
12. E. Atherton, H. Fox, D. Harkiss, C.J. Logan, R.C. Sheppard and B.J. Williams, *J. Chem. Soc., Chem. Commun.* **1978**, 537.
13. H. Rink, *Tetrahedron Lett.* **1987**, *28*, 3787.
14. T. Allmendinger, 199th ACS National Meeting, Boston, Massachusetts, 1990, Abstr. number.FLUO 0006.
15. H. Duplaa, G. von Sprecher and W. Schilling, personal communication.
16. W.R. Dolbier, Jr., K.S. Medinger, A. Greenberg and J.F. Liebman, *Tetrahedron* **1982**, *38*, 2415.

(Received in Germany 10 July 1990)