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# Cysteine-, Methionine- and Seleno-Cysteine-Proline Chimeras: Synthesis and Their Use in Peptidomimetics Design

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**Adriano Mollica**

**Abstract:** Natural sulphurated amino acids are cysteine and methionine. Their importance in biological processes is largely known. Cysteine, plays a key role due to the thiol group, which represents a nucleophilic and easily oxidizable function. Synthetic methodologies to obtain Cysteine-, Methionine- and Seleno-Cysteine-Proline chimeras are strongly desirable and particularly appealing in the field of organic chemistry.

**Keywords:** Cysteine, methionine, seleno-cysteine proline chimeras, peptidomimetic design, χ-Space, chemical ligation

## 1. INTRODUCTION

In proteins, free Cysteine (Cys) has a hydrophilic character, as hydrogen bond donor, while when covalently bonded each other, Cys residues have a crucial role in determining and stabilizing the conformation of protein and peptides [1, 2]. Methionine (Met) contributes to conformational properties of proteins through the Met-aromatic motif, a hydrophobic interaction that provides an additional stabilization [3].

Structure's modification on peptides is always responsible of changes in their biological activities, because a specific constraint, such as that imposed by unnatural amino acids, may destabilize the interactions between the ligand and the protein.

Methionine is an interesting amino acid residue in biologically active peptides; its conformationally constrained analogues are subdivided into two, well-documented classes (Fig. **1**) [4-8].

Conformational profile of *N*-acetyl, *N'*-methylamide derivatives of *cis*- and *trans*-3-methyl-proline shows an inverse γ-turn structure more stable than that of *cis*-3-methyl-proline [9], furthermore $C\rightarrow C^{\alpha}$ and $N\rightarrow CO^{\tau}$cyclizations are two complementary constraints.

The β-stereocenter of proline amino acid determinates the amino acid side chain orientation in biologically active peptides binding to receptor [10].

To further delineate the molecular interactions of this *C*-terminal amino acid with both binding sites of the human NK-1 tachykinin receptor, Sugase *et al.* [11] have designed constrained analogs of methionine, *i.e.* 3-prolinomethionines. The resulting analogs completely lose NK-1 biological activity [12], a result which may come from the non-accurate fixed value of the $\chi^2$ angle on the pyrrolidine ring. In contrast, 3-prolinoamino acids [13], combine the proline constraint on the peptide backbone (fixed $\chi^1$ angle) with the presence in position 3 (or β) on the pyrrolidine ring of the native amino acid side chain with a flexible $\chi^2$ angle.

Enomoto *et al.* [14] investigated the structural modifications of *N*-mercaptoacyl-*L*-proline and (*4R*)-*N*-mercaptoacyl-thiazolidine-4-carboxylic acid to build efficient leukotriene A4 ($LTA_4$) hydrolase inhibitors. The (2*S*)-3-mercapto-2-methylpropionyl group was chosen for both of them (Fig. **2**).

The insertion of 4-isopropylbenzylthio, 4-*tert*-butylbenzylthio or 4-cyclohexylbenzylthio group with (*S*)-configuration at the C-4 position of proline, gave strong $LTA_4$ hydrolase inhibitors.

The syntheses of 3-proline-methionine and 4-proline-methionine chimeras have been performed via Zinc-enolate cyclization and Mitsunobu reaction in diastereoselective and enantioselective way (Fig. **3**).

## 2. 3-SUBSTITUTED CYSTEINE-PROLINE AND METHIONINE-PROLINE CHIMERAS SYNTHESES

### 2.1. 5-Exo-Trig-Cyclization via Zinc Enolate

The first synthesis of a 3-proline-methionine chimera (3-methylsulfanylmethyl-pyrrolidine-l,2-dicarboxylic acid dimethyl ester) has been described by Udding *et al.* [15] which involves xanthate transfer cyclization of a glycine radical, leading to non-regiospecific and non-diastereoselective reaction.

A more general strategy via Zinc-enolate cyclization, was reported by Karoyan and Chassing [16].

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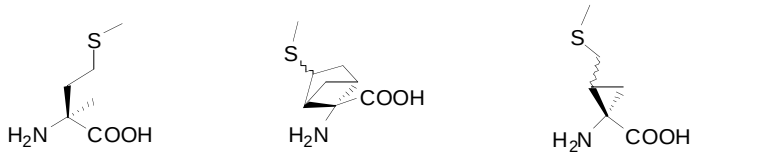


**α-methylmethionine (αMe)** **4-norbornanomethionine ($N_4^Z$ Met and $N_4^E$ Met)** **2,3-methanomethionine ($\Delta_3^Z$ Met and $\Delta_3^E$ Met)**

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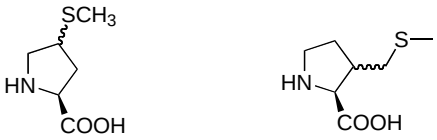



**4-prolinomethionine ($P_4^Z$ Met and $P_4^E$ Met)** **3-prolinomethionine ($P_3^Z$ Met and $P_3^E$ Met)**

**Fig. (1).** Conformationally constrained methionines.

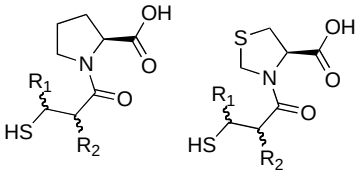



**Fig. (2).** Structures of *N*-mercaptoacyl-*L*-proline and (4*R*)-*N*-mercaptoacylthiazolidine-4-carboxylic acid scaffolds.

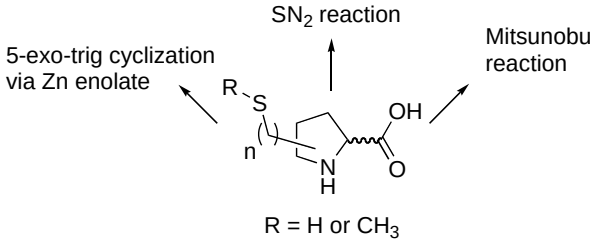



**Fig. (3).** Schematic representation of possible synthetic approaches to Met-Pro and Cys-Pro chimeras.

The organozinc derivative was treated with iodine to give ethyl *cis*-3-iodomethyl-*N*-benzylprolinate, which was alkylated by the sodium salt of methanethiol to yield the *cis*-3-proline-methionine analogs as racemic mixture. A *one-pot* procedure could be also applied modifying the carbanionic species and using an electrophilic sulfur donor, so as the stereogenic center on the *N*-protecting group generates an asymmetric C-2 carbon atom center.

Following Karoyan and Chassing also described the conversion of the *N*-(*o*-methylbenzyl)-prolinomethionine into *N*-(vinyloxycarbonyl)-prolinomethionine (Voc($P_3$)Met), and into *N*-(*tert*-butoxycarbonyl)-prolinomethionine (Boc($P_3$)Met) (Scheme **1**) [17].

The (-)/(+) [But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid ethyl or benzyl ester (-)-**1** and (+)-**1** were prepared by alkylation of (-) or (+)-α-methylbenzylamine with 4-bromobutene and ethylbromoacetate or benzylbromoacetate respectively, in DMSO.

The lithium enolate of (-)-**1** was transmetallated (3 eq. of dried $ZnBr_2$ at -90°C) to yield *cis* diastereoselective cyclization, the reaction mixture was cooled to 0°C and the second transmetallation reaction was carried out (1.2 eq. of CuCN 1M, LiCl in THF at 0°C for 10 min.), then (*S*)-methyl methanesulfonothiolate was added.

Easy cleveage of the cuprozinc compound was achieved giving the 3-methyl-sulfanylmethyl-l-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid ethyl ester **2** in *2S,3R* configuration.

Olofson *et al.* [18] used vinylchloroformate for *N*-dealkylations on product **2**, despite the slow reaction's rate, then voc group was removed from **3** by HCl in dioxane.

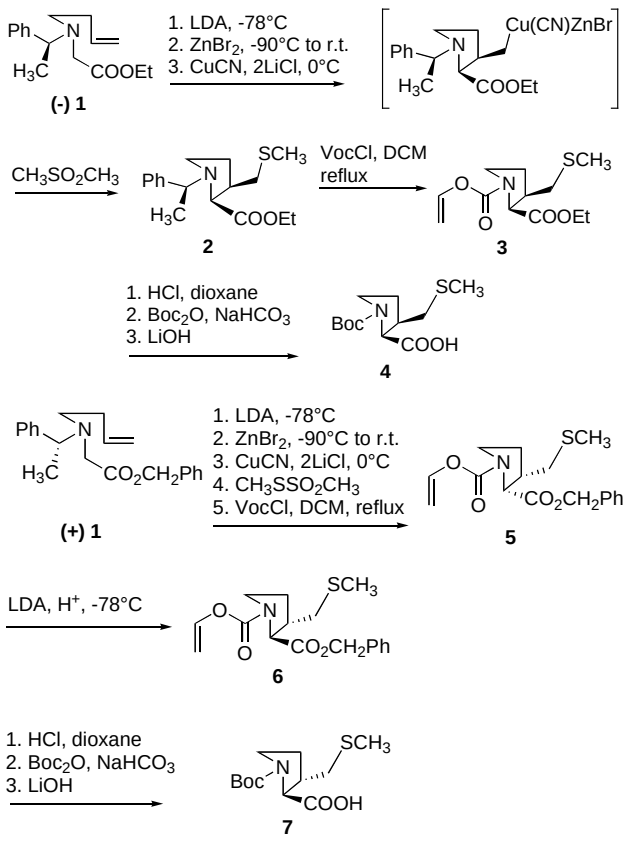
*Tert*-butoxycarbonyl (*N*-Boc) protection and saponification gave (*2S,3R*)-Boc 3-proline-methionine **4** as crude mixture, which was following purified by silica gel chromatography.

An alternative route was proposed starting from (+)-α-methylbenzylamine to give (2*R*,3*S*)-benzyl-Voc-3-proline-methioninate **5**, which was deprotonated by LDA in THF at -78 °C obtaining an inversion of configuration at the $C^{\alpha}$ carbon over 90% (as determined by NMR).

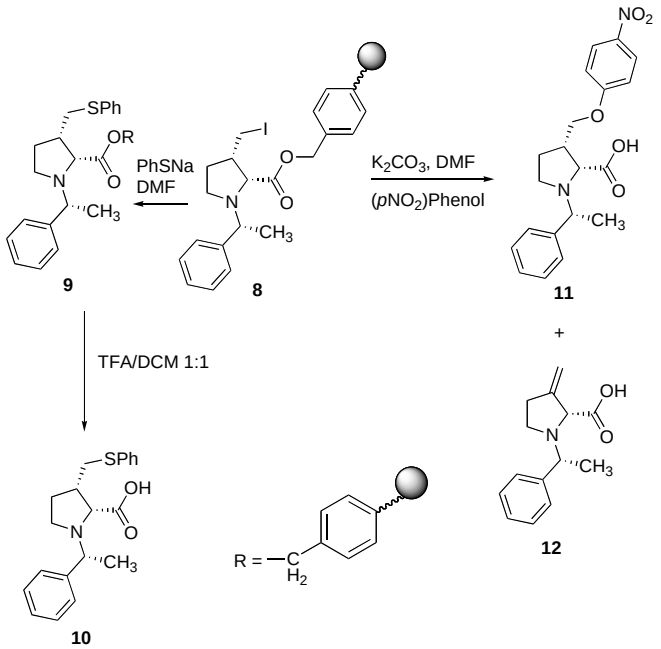
Enantiomerically pure (*2S,3S*)-benzyl-Voc-3-proline-methioninate **6** was isolated after flash chromatography. $Boc_2O$ protection and saponification gave the (*2S,3S*)-Boc 3-proline-methionine **7**.

As a continuation of their studies concerning solid-phase amino-Zinc-enolate cyclization, Karoyan *et al.* [19] explored the iodo derivative **8** functionalization (Scheme **2**).

Compound **8** was reacted with two kinds of nucleophiles sodium thiophenate and *p*-nitrophenol in DMF, at 50°C. In the first case, compound **10** was characterized by mass spectroscopy after cleavage of **9** from the resin while in the second case, 2 eq. of nucleophile were used with $K_2CO_3$ giving nucleophilic substitution of the halogen atom and cleavage of the product from the resin.




**Scheme 1.** Synthesis of (*2S, 3R*)- and (*2S, 3S*)-prolinomethionine [17].

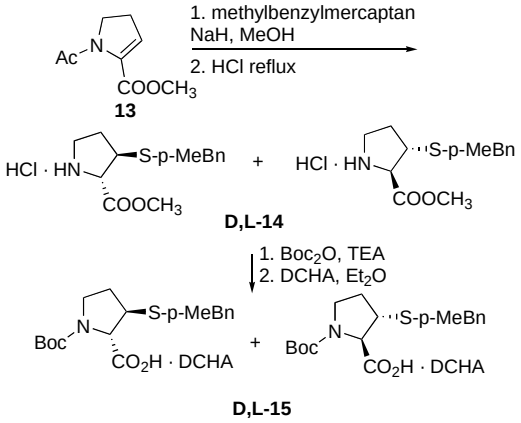



**Scheme 2.** Functionalization of the iodo derivative [19].

Basic conditions applied during the work-up of the reaction cleaved the *p*-nitrophenol ester providing compounds **11** and **12**.

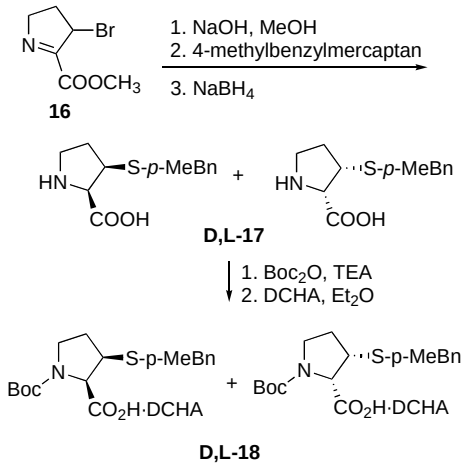
## 2.2. Via Dihydroproline Intermediate Formation

Kolodziej *et al.* [20] reported the synthesis of protected cysteine-proline chimeras to the synthesis of *D,L-N*-Boc-3-mercapto-proline (*D,L*-**15**) (Scheme **3**).




**Scheme 3.** Synthesis of 3-substituted proline reported by Kolodziej *et al.* [20].

Conjugate addition of 4-methylbenzylmercaptan to 2,3-dehydroproline derivative **13**, [21] and hydrolysis in acid conditions, provided the *trans*-diastereomer **14** following ripetitive crystallizations, in 52% yield. Compound **14** was protected with $Boc_2O$ to give derivative **15** as cyclohexylamine salt in 92% yield. In a similar manner, the *cis*-isomers were also obtained (Scheme **4**).



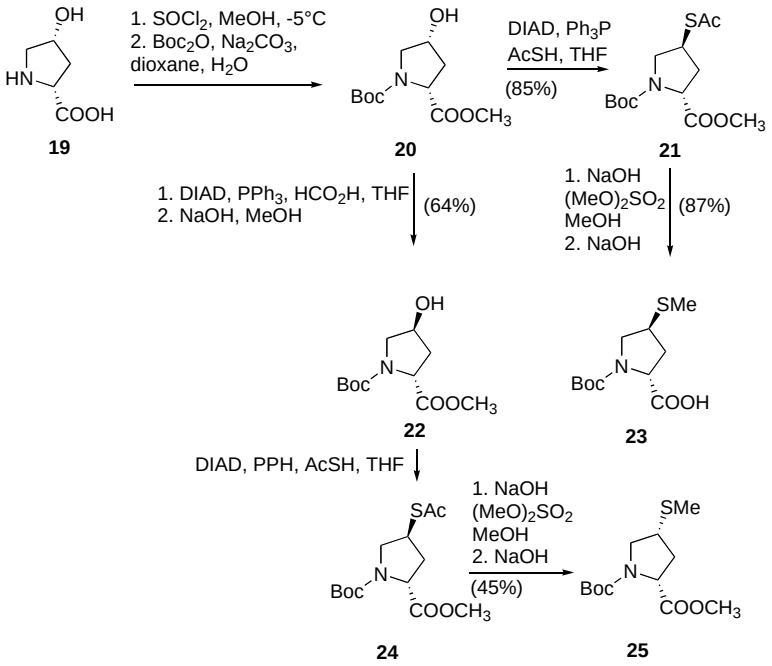

**Scheme 4.** Synthesis of diastereomeric mixture of protected 3-substituted proline [20].

The 3-bromo-l,2-dehydroproline derivative **16** was described by Hausler and Schmidt [22], and used to react with 4-methylbenzylmercaptan in aqueous sodium hydroxide; diastereoselective reduction with $NaBH_4$ provided the *cis*-isomer *D,L*-**17** in an overall yield of 37%.

## 3. 4-SUBSTITUTED CYSTEINE-PROLINE AND METHIONINE-PROLINE CHIMERAS SYNTHESES

### 3.1. Mitsunobu Reaction

Selective CCK-B agonist can be prepared by substitution of the $^{31}$Met residue in Boc-CCK4 ((Boc-Trp$^{30}$-Met$^{31}$-Asp$^{32}$-




**Scheme 5.** Synthesis of 4-substituted Cys-Pro reported by Kolodziej *et al*. [20].

Phe[33]-$NH_2$) with *trans*-3-propyl-proline. At this regard, Kolodziej *et al.* [20] synthesized different Ac-CCK4 analogs containing 3- and 4-(alkylthio)-substituted proline derivatives. A high-yielding synthetic strategy was developed to achieve the *S*-methylated derivatives **23** and **25** (Scheme **5**).

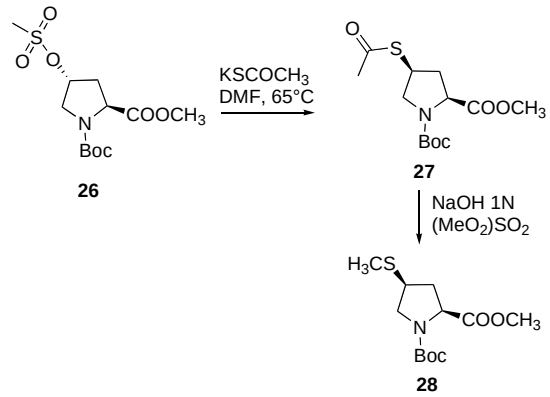
Reaction of compound **20** with thiolacetic acid under Mitsunobu conditions is the key transformation, to provide derivative **21** in 85% yield [23].

Derivative **23** was obtained in a *one-pot* reaction's sequence [23] involving two selective hydrolysis and alkylation, in 60% overall yield from **19**. Mitsunobu inversion of the C-4 carbon of **20** was performed using formic acid, followed by hydrolysis of the formate ester to yield **22** in 64%. Then **25** was obtained in an overall yield of 45% from **19**, following the reaction's sequence described above. Recently Mollica *et al*. [24] investigated new fMLF analogs incorporating chimeric *L*-proline-methionine residues, namely the homochiral *cis*-4(*S*)-methylthio-(*S*)-proline **28** and the heterochiral *trans*-4(*R*)-methylthio-(*S*)-proline **35**, in which γ-thiomethyl-ether functionality is preserved. *Cis*- and *trans*-4-methylthio-proline derivatives can be prepared following different approaches [25].

To obtain *N*-Boc-*cis*-4(*S*)-methylthio-(*S*)-proline **28** and *N*-Boc-*trans*-4(*R*)-methylthio-(*S*)-proline **35**, the *N*-protected *cis*-analog **28** was prepared from 4-hydroxy-*trans*-proline **29** treating the corresponding *N*-Boc-*trans*-4-mesylate **26** with potassium thioacetate, followed by hydrolysis of the derivative **27** and alkylation of the thiol group (Scheme **6**).

The *N*-Boc derivative **29** was prepared to build *N*-Boc-*trans*-analog **34** (Scheme **7**).

In this case, two configurational inversions at C-4 occurred; the first involved the formation of the 4-oxo-analog **30** which, after stereoselective reduction with $NaBH_4$, gave the *N*-Boc-(*2S,4S*)-*cis*-isomer **31**.




**Scheme 6.** Synthesis of *cis*-4(*S*)-methylthio-(*S*)-proline by Mollica *et al.* [24].

## 4. 4-SELENO-CYSTEINE-PROLINE CHIMERAS SYNTHESES

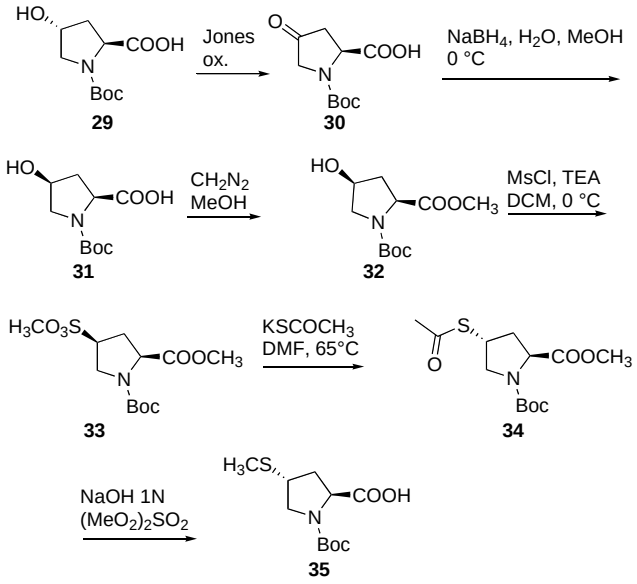
### 4.1. Mitsunobu Reaction

The preparation of Seleno-Cysteine-Pro chimeras is particularly interesting since its use in native chemical ligation (NCL) in several papers [26-29].

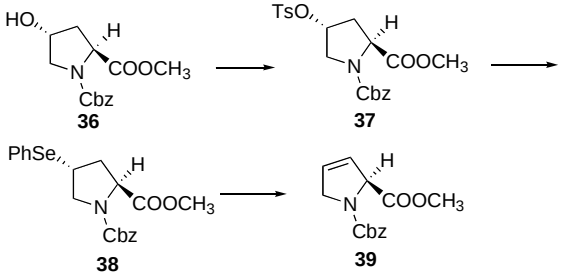
One of the first attempt to synthesize these chimeras was done by Rüeger and Benn for the (*S*)-3,4-dehydroproline starting from (*2S,4R*)-4-hydroxyproline [30], considering that selenoxide elimination can be regioselective if the required 3-ene function could be introduced (Scheme **8**).

This protocol was applied successively by Robinson *et al.* [31] for the synthesis of a series of epoxyprolines and aminohydroprolines.

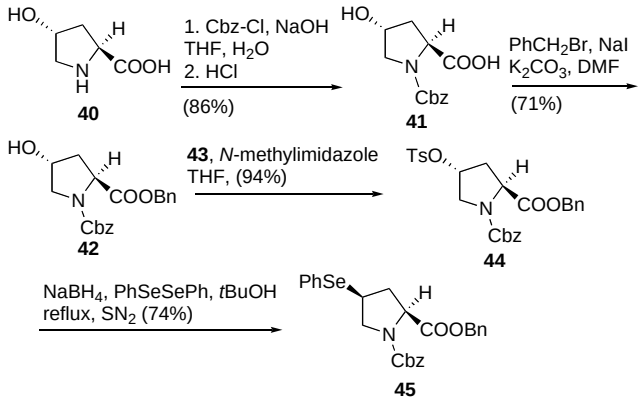
For this purpose, 3,4-dehydro-*L*-proline derivative was prepared from *trans*-hydroxy-*L*-proline **37** using a modified version of the method reported by Rüeger and Benn (Scheme **9**) [30].




**Scheme 7.** Synthesis of *trans*-4(*R*)-methylthio-(*S*)-proline [24].

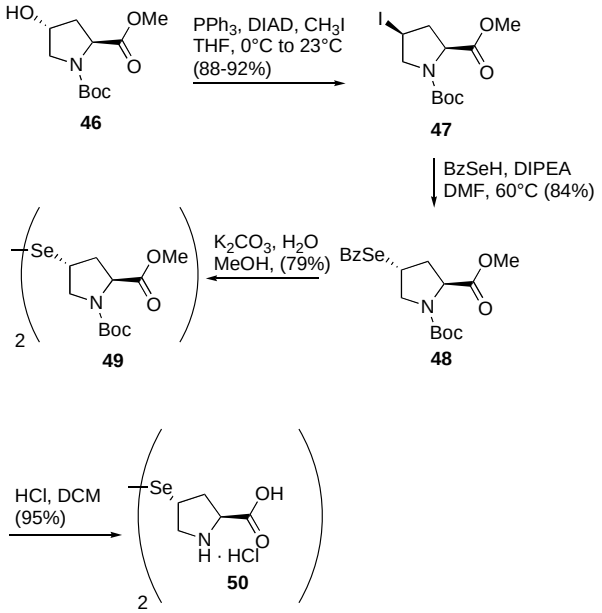



**Scheme 8.** Schematic representation of protocol applied by Rüeger and Benn [30].




**Scheme 9.** Synthesis of intermediate product for Rüeger's procedure [30].

Treatment of derivative **42** with tosyl chloride/pyridine failed to give tosylate **44** in good yield. Then 1-(toluenesulphonyl)-3-methylimidazolium triflate **43** was chosen to prepare product **44** in acceptable yield. Reaction of **44** with PhSeSePh/$NaBH_4$ in *tert*-butanol furnished **45** without transesterification. Durek and Alewood have studied the conversion of thioesters to selenoesters to give highly reactive *C*-terminal ligation partners [32]. Also Metanis *et al.* [33] have described the ligation and the deselenization of peptide-feature *N*-terminal selenocysteine residues. Thus *trans*-seleno-proline, was synthesized for the first time (Scheme **10**).




**Scheme 10.** Synthesis of *trans*-seleno-proline [30].

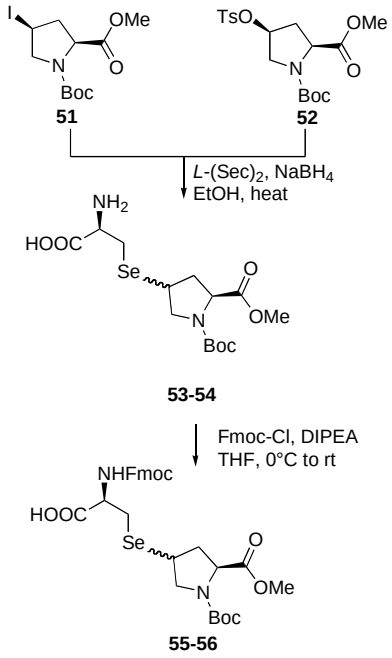
Beginning with the commercially available pyrrolidine **46**, Mitsunobu inversion gave the *cis*-iodo-proline **47**, in good yield. Treatment with selenobenzoic acid provided compound **48** in 84% yield. Removal of the benzoate and saponification occurs in concert to give *N*-Boc seleno-proline dimer **49**, in 79% yield which was finally removed under acidic conditions to afford oxidatively dimerized **50**.

### 4.2. $S_N2$ Reaction

Starting from 4-hydroxylproline, Caputo *et al.* [34] reported a new procedure to prepare sulphur and selenium containing bis α-amino acids. The existing hydroxyl group of *trans*-4-hydroxy-*L*-proline was involved in $S_N2$ process, for which inversion of C-4 configuration occurred. Although *trans* configuration was maintained transforming the hydroxyl group either into its tosyl ester or by substitution with an iodine complex, giving the *cis*-4-iodo-*L*-proline. Cysteinyl nucleophile attack provided *trans*-4-(*S*)-cysteinyl-*L*-proline **53** from compound **51** and *cis*-4-(*S*)-cysteinyl-*L*-proline **54** from derivative **52**; diastereomeric *trans/cis* 4-selenocysteinyl-*L*-prolines **55** and **56** were finally obtained with the addition of selenocysteinyl nucleophile (Scheme **11**) [35].

## 5. CONCLUSION

This review is focused on Met, Cys, and Cys-Seleno Proline chimeras. The most important synthetic strategies reported in literature to prepare these chimeric compounds have been reported and discussed. They are particularly important in peptidomimetics design; for example, Wiśniewski reported a small library of oxytocin analogues [36], which show selectivity to vasopressin receptors and present several chemical modification, including the introduction of *trans*-4-SMe-Pro residue in peptide **57** (Fig. **4**).




**Scheme 11.** Synthesis of bis α-amino acids from 4-hydroxylproline by Caputo *et al*. [34].

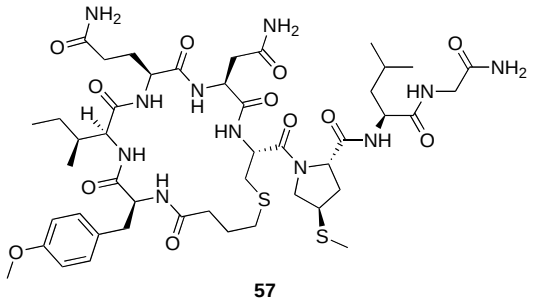



**Fig. (4).** An oxytocin analog containing a Met-Pro chimera residue [36].

This class of compounds can be considered central in the field of peptide-based drug discovery [37], due to the remarkable effects of proline and cysteine on peptides secondary structures.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

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