

## Amino acids with fluorinated olefinic motifs – synthetic approaches

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In dedication to Professor Zbigniew Czarnocki on the occasion of his 66<sup>th</sup> anniversary

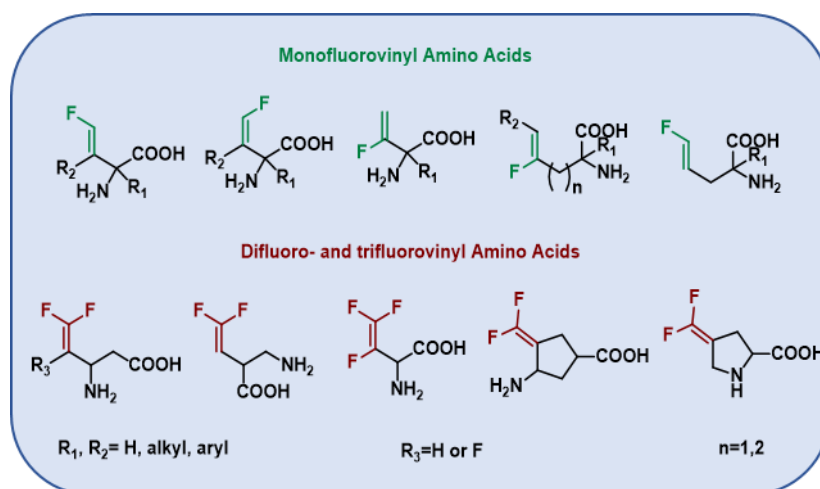
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### Abstract

Peptidomimetics are molecules related to natural peptides that have an artificial unit incorporated in their structure. Such structural modifications, mimicking properties of natural amino acids, can be responsible for differently pronounced activity. Among others, amino acid derivatives with fluorinated olefinic motifs can act as building blocks in the synthesis of complex molecules with potential biological activity. Therefore, the synthetic approaches to the fluorinated olefinic moiety amino acids are of interest to organic chemists. There are different synthetic methods yielding fluorinated olefins having significant value in the synthesis of amino acid derivatives. This mini review describes the latest achievements in the synthesis of amino acids bearing mono-, di- or trifluorovinyl moiety.



**Keywords:** Monofluorovinyl moiety, difluorovinyl moiety, trifluorovinyl moiety, amino acids, peptidomimetics, biological activity

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## 1. Introduction

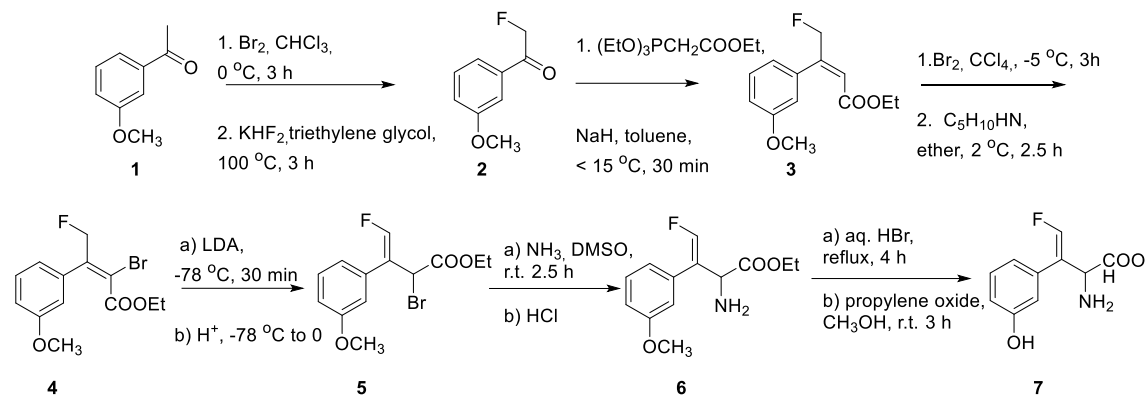
The incorporation of fluorine to an organic molecule often induces remarkable changes in their biophysical properties including solubility, lipophilicity, conformational and metabolic stability as well as chemical reactivity.<sup>1,2</sup> The changes in reactivity have far-reaching consequences. Incorporation of fluorine often affects a molecule's bond energy, acidity and basicity, ability to form hydrogen bonds and its geometry.<sup>3-6</sup> Therefore, the incorporation of fluorine or fluoroalkyl moieties into molecules is broadly used in the synthesis of drugs and biologically active compounds.<sup>7,8</sup> This is one of the reasons why fluorination methods are widely studied in synthetic organic chemistry.

Fluorinated amino acids as well as fluorinated peptides have been widely studied and used in the design and synthesis of novel pharmaceuticals. They are very useful building blocks with regards to the synthesis of bioactive compounds. The big interest in the synthesis of fluorinated amino acids and peptides is also notable in the literature. Recently, in 2019 Professor Kocsch published a broad review about the synthetic methods of fluorinated amino acids.<sup>9</sup> Additionally, synthetic approaches were also discussed earlier by the Kocsch group in 2008.<sup>10</sup> Since the synthetic approaches to amino acids having fluorinated olefinic fragments were not well covered, we present herein, a short overview of the synthetic methods of amino acids bearing a fluorinated olefin. There are various successful syntheses that afford fluorinated olefins, and some have significant methodological value to synthetic chemists in the preparation of fluorinated amino acid libraries.

## 2. Monofluoroolefinic Amino Acid Derivatives

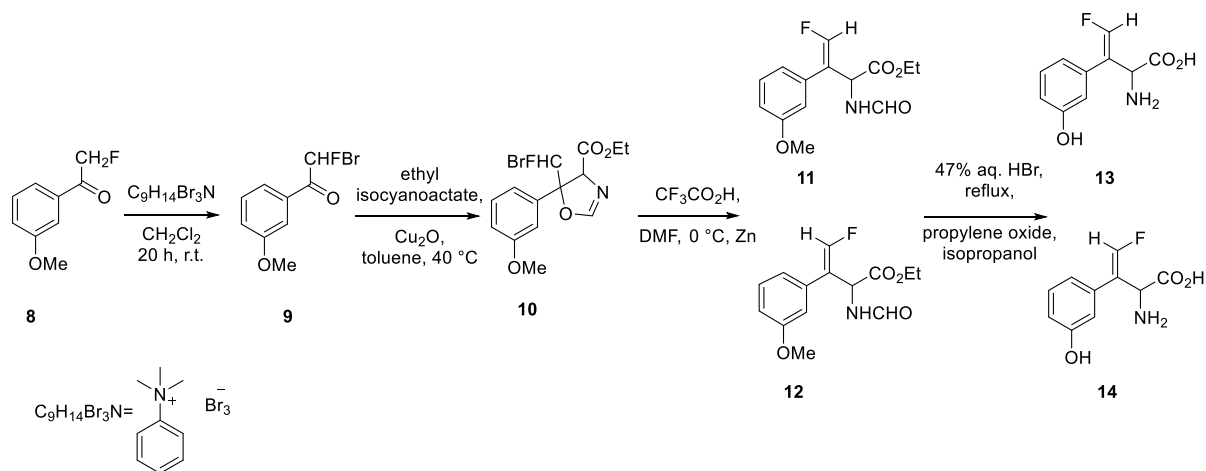
The monofluorovinyl moiety is often considered isosteric to the peptide bond. As such, due to the electronic similarity, it can replace the amide bond in peptides. Furthermore, the incorporation of fluorovinyl moieties in simple amino acids can strongly affect their bioactive properties and, therefore, this is a common strategy used in the design and synthesis of amino acid derivatives.

The early synthesis of (*E*)- $\beta$ -(fluoromethylene)-*m*-tyrosine was reported by McDonald *et al.* in 1984.<sup>11</sup> The first step required the bromination followed by further fluorination by  $\text{KHF}_2$ . Compound **2** was obtained in 54% yield and was further treated with triethyl phosphonoacetate in the presence of NaH to yield **3**, as a mixture of *Z*- and *E*-isomers in 8:1 ratio and 80% yield. After subsequent bromination and dehydrobromination by piperidine, compound **4** was obtained that was further treated with LDA to give the *E*-bromide **5**. Subsequent reaction of bromide **5** with ammonia in DMSO gave amine **6** in 20% yield. After deprotection of **6** the final product **7** bearing monofluorovinyl moiety was synthesized as a colorless powder in good 86% yield (Scheme 1).



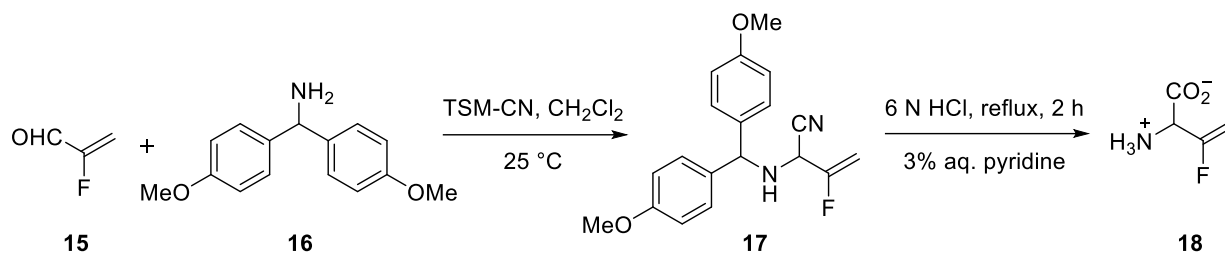
**Scheme 1.** Multi-step synthesis of *(E)*-β-(fluoromethylene)-*m*-tyrosine (**7**).

McDonald's procedure employed a Wittig-type reaction and led to the *E*-isomer only. One year later, the same group offered another method called the "isocyanoacetate route" which gave both isomers.<sup>12</sup> This procedure involved fluoroketone **8** as a starting material which was first treated with phenyltrimethylammonium tribromide to form product **9** in 87% yield. Subsequent, condensation with ethyl isocyanoacetate in the presence of Cu<sub>2</sub>O as catalyst gave a mixture of diastereoisomers **10**. Next, the formed oxazoline **10** was protonated by trifluoroacetic acid which led to oxazoline ring opening. Furthermore, activated zinc has been used and compounds **11** and **12** were formed. The last step involved the refluxing in 47% aqueous solution of HBr and the treatment of propylene oxide. It finally resulted in the *(E)*-isomer **13** as a colorless powder and the *(Z)*-isomer **14** as a yellowish powder in equal 28% yields (Scheme 2).



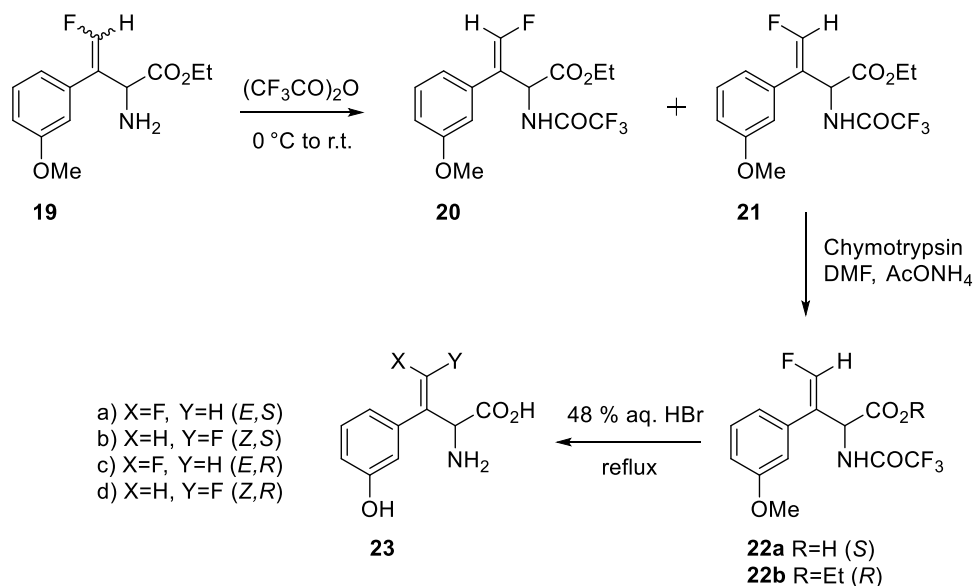
**Scheme 2.** Synthesis of *(E)*- and *(Z)*- fluoromethylene-*m*-tyrosine via the isocyanoacetate route.

The synthesis of 3-fluorovinylglycine (**18**) was reported by Thornberry *et al.*<sup>13</sup> (Scheme 3). The monofluorovinyl group from starting material 2-fluoroacrolein (**15**) has been transferred in the reaction with 4,4'-dimethoxybenzhydramine (**16**) into the desired product. First, the aldehyde was transformed into cyanoamine and subsequent treatment with refluxing 6N HCl and elution with aqueous pyridine yielded the desired monofluorovinyl compound **18** in 25-30%.



**Scheme 3.** Synthesis of 3-fluorovinylglycine (**18**).

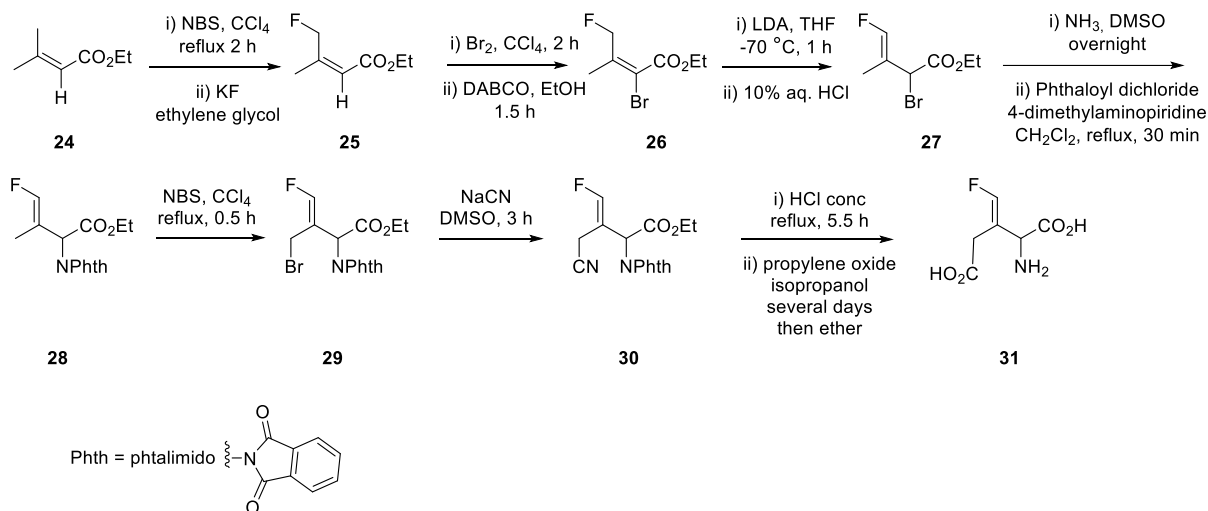
The method established by McDonald was further studied by Lacan *et al.*<sup>14</sup> The protected derivative of **19** was prepared according to the previously described Wittig-type reaction. Subsequently, treatment of the starting material **19** with trifluoroacetic anhydride yielded (*E*)- and (*Z*)-trifluoroacetyl derivatives **20** and **21** in the 85:15 ratio. Next, these isomers were separated by subjecting them to  $\alpha$ -Chymotrypsin. This enzyme specifically catalyzed only the hydrolysis of the (*E*)-isomer **21** while there was no interaction between Chymotrypsin and (*Z*)-isomer **20**. As a result, the compounds **22a** and **22b** were formed. Deprotection was achieved by HBr-mediated hydrolysis and yielded **23a** and **23b** (or **23c** and **23d**) in equal amounts. The product mixture was separated by HPLC (Scheme 4).



**Scheme 4.** Synthesis of (*E*)- and (*Z*)-3-fluoromethylene-*m*-tyrosines.

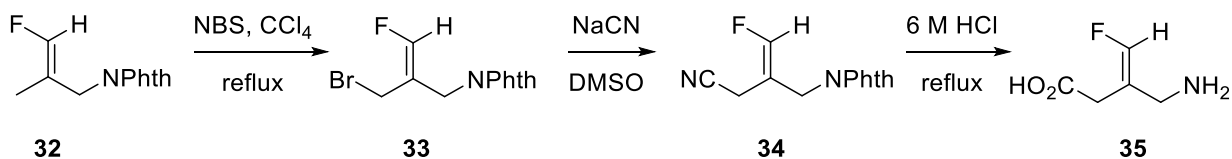
McDonald's group continued studies on synthetic methodology, and in 1985 proposed the synthesis of (*E*)- $\beta$ -fluoromethyleneglutamic acid according to a similar method.<sup>15</sup> The final product was prepared in 11 steps from ethyl 3,3-dimethylacrylate (**24**) (Scheme 5). First, the substrate was brominated (total 57% yield) and then fluoride exchange took place. The prepared product **25** was obtained as a mixture of isomers in 50% yield. Further the bromination and subsequent dehydrobromination process transformed **25** into **26** in 69% yield. Then, isomerization led to form only the *E*-isomer **27**. The exchange of bromine with phthaloyl dichloride in the presence of dimethyl sulfoxide saturated with ammonia and 4-aminopyridine enabled to obtain *N*-protected amino acid derivative **28** in 13% yield. After bromination of methyl group, the compound **29** was synthesized as a mixture of *Z*- and *E*- isomers in 2:1 ratio. Finally, the use of sodium cyanide yielded **30**,

treatment of which with concentrated HCl, then propylene oxide and isopropanol, after several days allowed the formation of the target product **31** in an excellent 95% yield. This multistep synthesis gave access to desired fluoro derivative of glutamic acid.



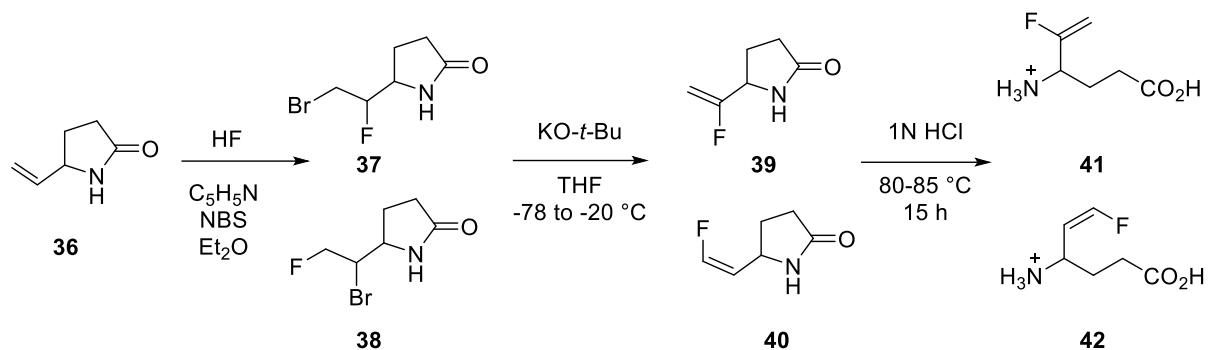
**Scheme 5.** Multi-step synthesis of (*E*)- $\beta$ -fluoromethyleneglutamic acid.

Similarly, McDonald and Bey presented a general route to fluoroallyl amino acids by modifying the *N*-protected substrate bearing fluorovinyl moiety.<sup>16</sup> The starting phthalimide **32** (Scheme 6) was treated with NBS affording bromide as a mixture of *E/Z*-isomers. Next, only the *Z*-isomer **33** was used in the reaction with sodium cyanide and was transformed to the corresponding nitrile **34**. A subsequent hydrolysis with hydrochloric acid yielded amino acid **35** as a final product.



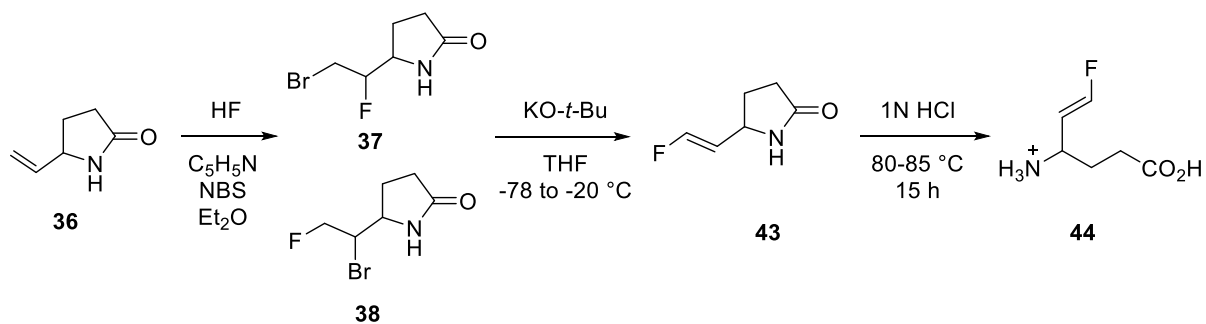
**Scheme 6.** Synthesis of (*Z*)-fluorovinyl amino acid using phthalimide method.

The synthesis of amino-fluoro-hexenoic acids has been studied by Kolb *et al.* They used 5-ethenyl-2-pyrrolidynone (**36**) as starting material.<sup>17</sup> In the first step, substrate reacted with HF in the presence of pyridine and NBS to obtain (bromofluoroethyl)pyrrolidinones as a mixture of isomers **37/38** in ratio 25:75. The next step involved elimination of HBr and led to the formation of fluorovinyl compounds **39** and **40** in 50% yield. Finally, after separation of the isomers **39** and **40** and acid hydrolysis gave the desired compounds **41** and **42**, respectively (Scheme 7).



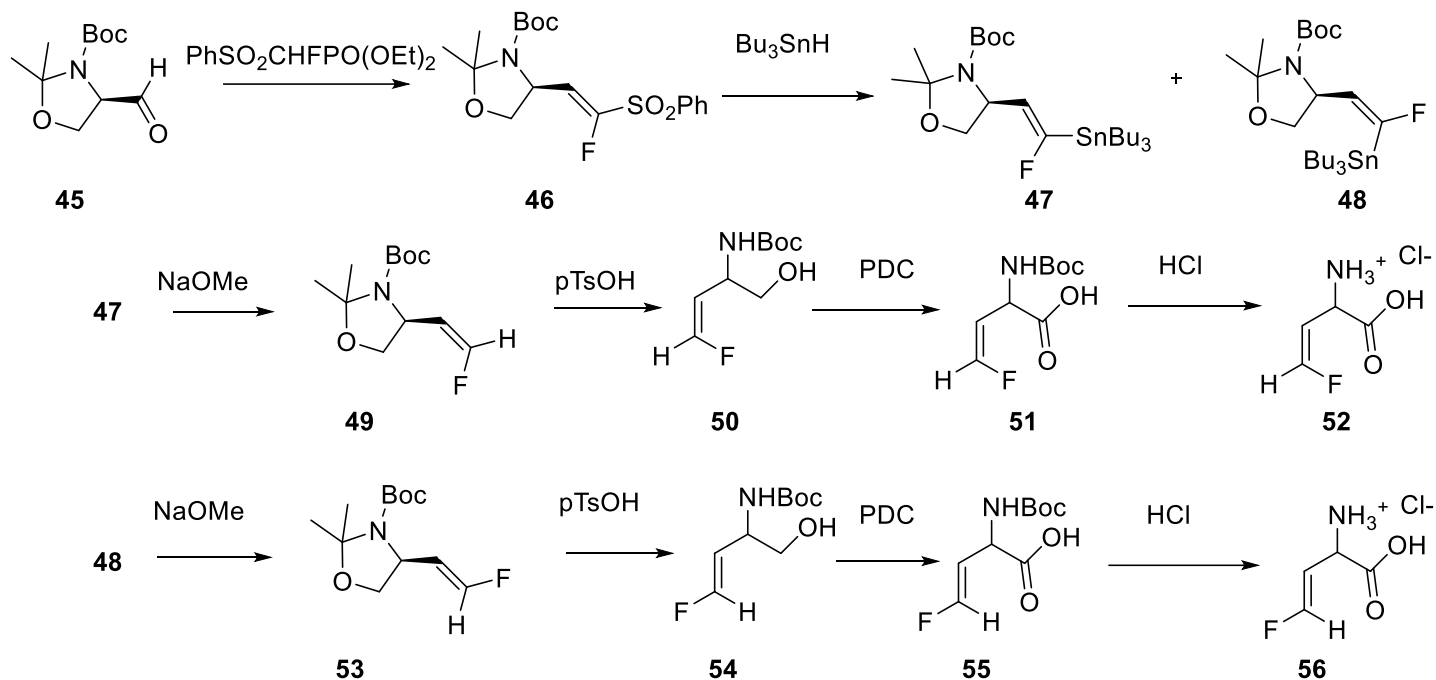
**Scheme 7.** Synthesis of 4-amino-5-fluoro-5-hexenoic acid (**41**) and (*Z*)-4-amino-6-fluoro-5-hexenoic acid (**42**) hydrochloride salts.

The synthesis described above was further investigated by Silverman *et al.* in 1996.<sup>18</sup> They also proposed the synthetic scheme to yield compound **42** (Scheme 7). In contrast to the Kolb's synthesis, they isolated the (*E*)-(5-fluorovinyl)-2-pyrrolidinone (**43**) which is a precursor to the desired (*E*)-4-amino-6-fluoro-5-hexenoic acid (**44**) (Scheme 8).



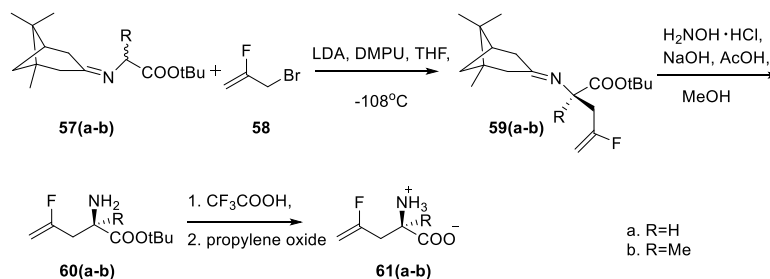
**Scheme 8.** Synthesis of (*E*)-4-amino-6-fluoro-5-hexenoic acid.

McCarthy *et al.* published the synthesis of fluorovinyl amino acids according to HWE (Horner-Wadsworth-Emmons) procedure.<sup>19</sup> The starting aldehyde **45** was condensed with McCarthy's reagent to form vinylsulfone, which was subsequently treated with  $\text{Bu}_3\text{SnH}$ . The mixture of isomers **47** and **48** was obtained in 60 and 11% yields, respectively (Scheme 9). These isomers were separated and treated with sodium methanolate. The isopropyl group was removed by *p*-toluenesulfonic acid and **50** and **54** were obtained in 50 and 34% yield, respectively. Finally, the alcohols **50** and **54** were oxidized to the carboxylic acid in the presence of PCC and the Boc protective group was removed. Products **52** and **56** were obtained in 75 and 78% yields, respectively.



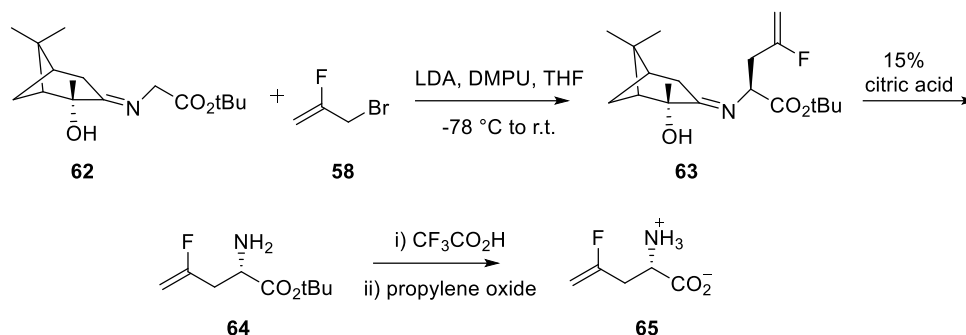
**Scheme 9.** Synthesis of amino acids **52** and **56**.

The research presented by Laue *et al.* involved the enantioselective synthesis of fluoroolefin amino acid derivatives.<sup>20</sup> Fluoroolefins are known as the amide bond isosteres, where the carbon - fluorine bond mimics the carbonyl moiety.<sup>21</sup> As a starting material camphor derivatives of glycine **57a** and alanine **57b** have been used (Scheme 10). The first step involved alkylation with 3-bromo-2-fluoropropene (**58**) and formation of alkylated product **59a** in 86% and **59b** in 64% yields, respectively. Further transamination, acid hydrolysis and treatment with propylene oxide allowed the formation of (*R*)-(+)-2-amino-4-fluoropent-4-enoic acid (**61a**) (59% yield and 94% ee) which is as an isostere for asparagine and (*R*)-(+)-2-amino-4-fluoro-methylpent-4-enoic acid (**61b**) in 59% and 61% ee.



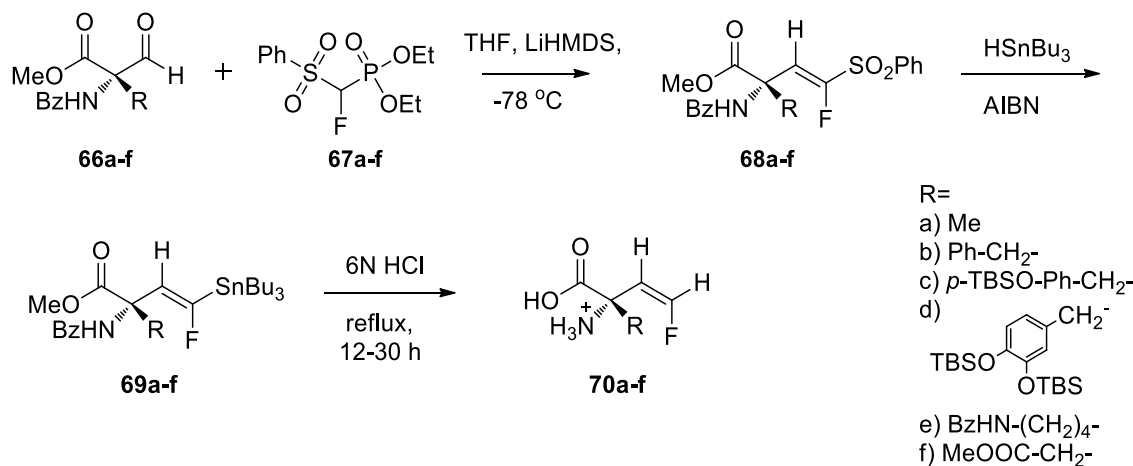
**Scheme 10.** Enantioselective synthesis of asparagine isostere **61a** and its analogue **61b**.

The earlier described method was further investigated also by Laue *et al.*<sup>22</sup> The first step involved alkylation of compound **62** by 3-bromo-2-fluoropropene (**58**) at -78 °C and allowed the formation of **63** in 73% yield and diastereoselectivity above 97%. Further acid hydrolysis caused partial racemization and compound **64** was obtained with 83% enantioselectivity. Finally, deprotection of carboxylic group by  $\text{CF}_3\text{CO}_2\text{H}$  led to desired (*S*)-2-amino-4-fluoropent-4-enoic acid (**65**) (Scheme 11).



**Scheme 11.** Synthesis of  $\gamma$ -fluorinated  $\alpha$ -amino acid.

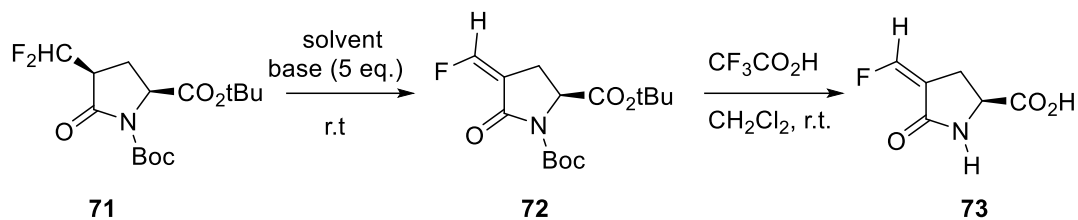
Another example of synthetic approach has been presented by Berkowitz *et al.*<sup>23</sup> They reported the three-step synthesis of six fluorovinyl amino acid derivatives employing Horner-Wadsworth-Emmons reaction protocol. As a starting reactant diethyl  $\alpha$ -fluoro- $\alpha$ -(phenylsulfonyl)-methyl phosphonate (**67**) (McCarthy's reagent) was used with corresponding aldehydes **66a-f** in the presence of the LiHMDS as a strong base. The reaction was carried out in  $-78\text{ }^\circ\text{C}$  and led to (*E*)- $\alpha$ -fluorovinyl sulfones **68a-f** in good to excellent yield (52-93%) and unusual diastereoselectivity - each compound was obtained as a single geometric isomer (*E*). The next step included the stereospecific interchange of sulfone to stannane **69**. The last step involved protodestannylation, deprotection of amine and carboxylic group with hydrochloric acid and allowed formation of (*Z*)- $\alpha$ -(2'-fluoro)vinyl amino acids **70a-f** in yields ranging from 52% for **70f** and 93% for DOPA derivative **70d** (Scheme 12).



**Scheme 12.** Synthesis of amino acids with (*2'**Z*)-fluorovinyl moiety.

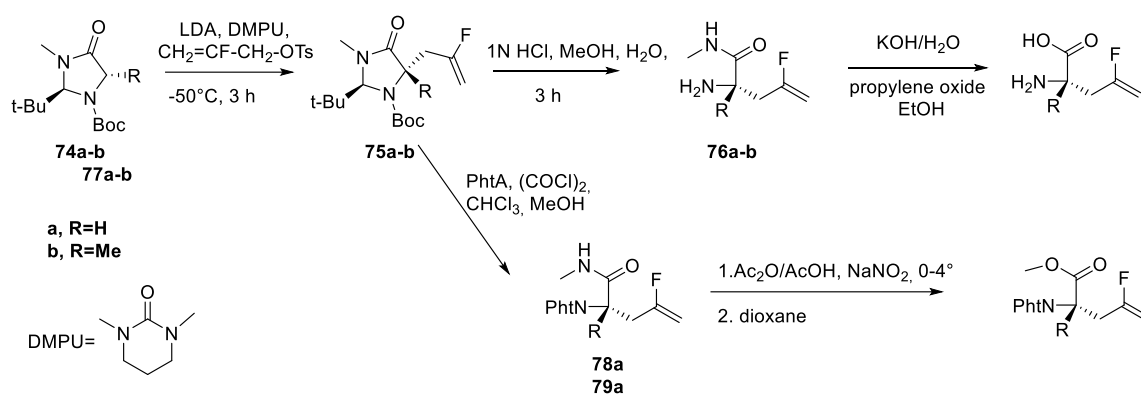
In 2004 Qiu *et al.* described for the first time the dehydrofluorination process of (*2S,4S*)-*tert*-butyl-*N*-*tert*-butoxycarbonyl-4-difluoromethylpyroglutamate (**71**).<sup>24</sup> The starting material **71** was synthesized from *trans*-4-hydroxy-*L*-proline.<sup>15,16</sup> The reaction course was tested with the use of different bases in CH<sub>2</sub>Cl<sub>2</sub>. Triethylamine led to the formation of the desired product in 90% yield, while the use of pyridine yielded **72** only in less than 3%. The effect caused by the use of different solvent in the reaction was also investigated in presence of NEt<sub>3</sub> as a base. The best results (90% yield) were obtained for CH<sub>3</sub>CN and CH<sub>2</sub>Cl<sub>2</sub>. Finally, deprotection with CF<sub>3</sub>CO<sub>2</sub>H allowed getting the desired 4-monofluoromethylenyl-*L*-pyroglutamic acid (**73**) in 72% yield (Scheme 13).





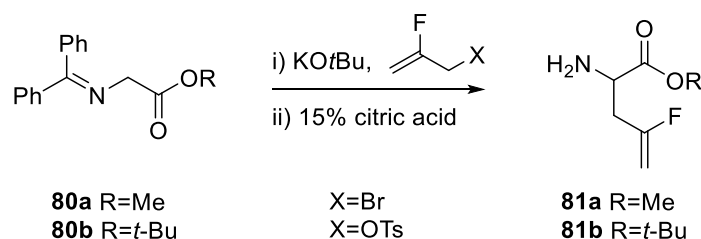
**Scheme 13.** Synthesis of 4-monofluoromethylenyl-*L*-pyroglutamic acid by the dehydrofluorination reaction.

Shendage *et al.* reported the selective and efficient synthesis of  $\gamma$ -fluoro- $\alpha$ -amino acids from (*S*)-Boc-BMI **74a-b**<sup>27</sup> (Scheme 14). The first step included asymmetric alkylation of **74a-b** with fluorovinyl tosylate in the presence of LDA as a base and led to the products **75a-b** in 89 and 84% yield, respectively. These compounds were then transformed with the use of HCl/MeOH/H<sub>2</sub>O to *N'*-methylamides **76a-b** in 43 and 63% yields, respectively. The final products **77a-b** were obtained after basic hydrolysis and treatment of propylene oxide in ethanol. After basic hydrolysis of the amide bond of **76a**, partial racemization was observed in the formed compound **77a**. To minimize this effect, **75a** was treated with phthalic anhydride and oxalyl chloride which allowed the formation of the amide **78a** in 89% yield. The amide bond was further removed by thermal decomposition of the in situ generated *N'*-nitrosoamide and the desired product  $\gamma$ -fluoro- $\alpha$ -amino methyl ester **79a** was obtained in 91% yield (Scheme 14).



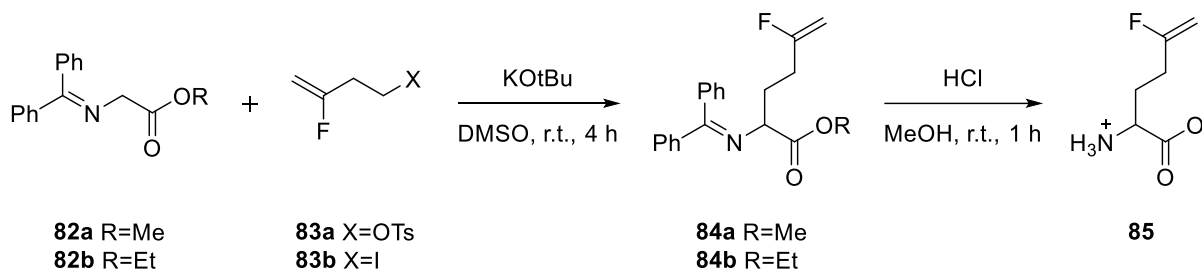
**Scheme 14.** Asymmetric synthesis of  $\gamma$ -fluoro- $\alpha$ -amino acids.

In 2013 Haufe<sup>28</sup> reported the synthesis of fluoroallyl amino acid derivatives which were used to synthesize 2-amino-4-fluoropent-4-enoic acid esters **81a-b** (Scheme 15). This process included alkylation of imine **80a** with 2-fluoroallyl bromide and imine **80b** with corresponding tosylate. The desired products **81a** and **81b** were obtained in 83 and 96% yields, respectively.



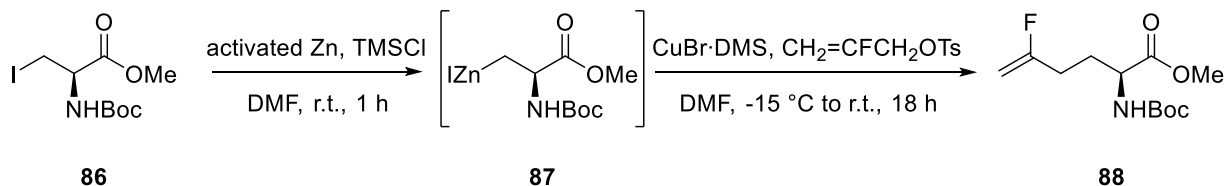
**Scheme 15.** Synthesis of 4-fluoro-2-amino acid esters **81a-b**.

Later, Haufe developed the synthesis which involved methyl or ethyl benzhydrylidene glycinate **82a** and **82b** as starting materials (Scheme 16).<sup>28</sup> As a reagent, the use of 2-fluoro-4-iodobut-1-ene (**83b**) led to the formation of **84a** and **84b** with rather low yields from 11 to 16%, respectively. 2-Fluoro-4-tosyl-but-1-ene (**83a**) allowed to obtain higher quantities of **84a** and **84b**. The final step included deprotection of carboxylic group and formation of the 2-amino-5-fluorohex-5-enoic acid in 20% yield for R=Me or 56% yield for R=Et (**85**).



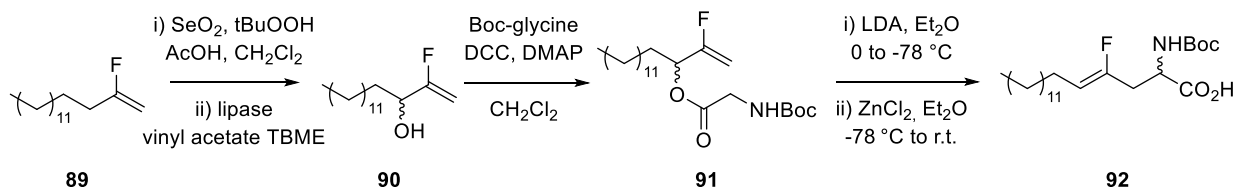
**Scheme 16.** Synthesis of fluoroallyl amino acid by alkylation of imine.

Due to the low yields of the previous synthesis, Haufe prepared methyl *N*-Boc-(*S*)-2-amino-5-fluorohex-5-enoate (**88**) according to Jackson's procedure with zinc reagents.<sup>29</sup> The alanine iodo-derivative **86** in the presence of activated zinc led to the formation of intermediate **87** and its further treatment with CuBr and alkylation with tosylate yielded product **88** in 61% (Scheme 17).



**Scheme 17.** Zinc-activated synthesis of fluorinated allylalanine derivative **88**.

Furthermore, Haufe *et al.* synthesized amino acid derivatives with monofluorovinyl side chain.<sup>30</sup> The first step involved oxidation of the starting material by SeO<sub>2</sub> (Scheme 18). Further condensation of the generated fluorinated alcohol **90** with *N*-Boc-glycine allowed the formation of the amino ester enolate. Subsequently, the Claisen rearrangement occurred affording the desired product **92** in 86% yield.



**Scheme 18.** Synthesis of amino acid **92**.

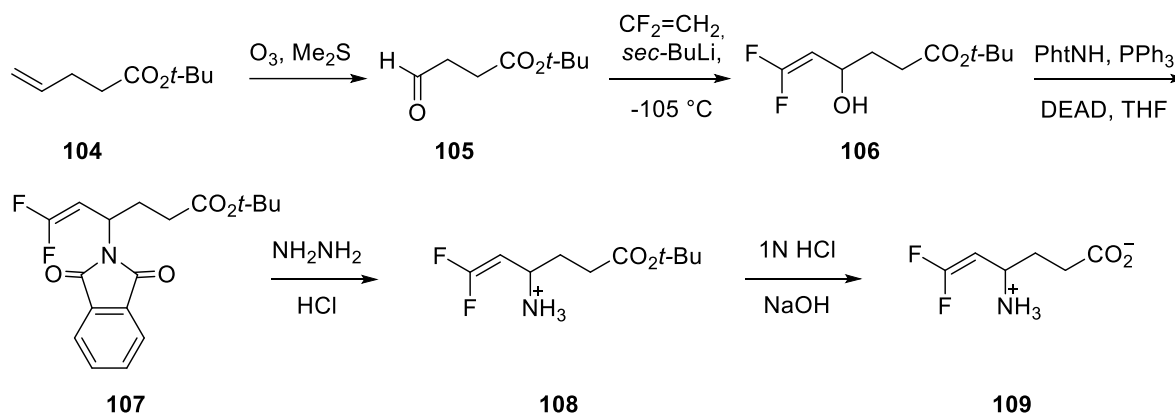
The synthesis of  $\beta,\gamma$ -unsaturated amino acids has been reported by Berkowitz.<sup>31</sup> In the proposed procedure the carboxyl and amino groups are retained, but also the fluorovinyl side chain bonded to the  $\alpha$ -carbon is present. In 2004 Berkowitz *et al.* described the synthesis of such compounds by the Horner-



### 3. Difluoro- and Trifluoro Amino Acid Derivatives

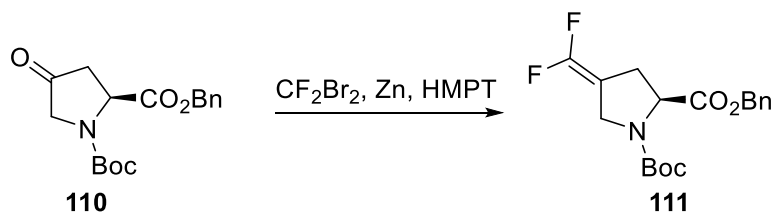
Access to the difluoro- and trifluorovinyl derivatives is discussed below. The di- and trifluorovinyl groups are very special components in medicinal chemistry and can be widely used in the design of drugs, owing to their metabolic stability.

The synthesis of 4-amino-6,6-difluoro-5-hexenoic acid from 4-oxobutanoic acid *tert*-butyl ester, was described by Kolb *et al.* (Scheme 21).<sup>17</sup> Ozonolysis of the starting ester afforded the aldehyde **105**, that can be treated with 1,1-difluoroethene to give the difluorinated alcohol **106**. Furthermore, alcohol **106** can be converted into the phthalimide **107** that, on mild acid hydrolysis in the presence of hydrazine, gives the amino ester hydrochloride **108** which, after ester hydrolysis, was transformed to the desired product **109**.



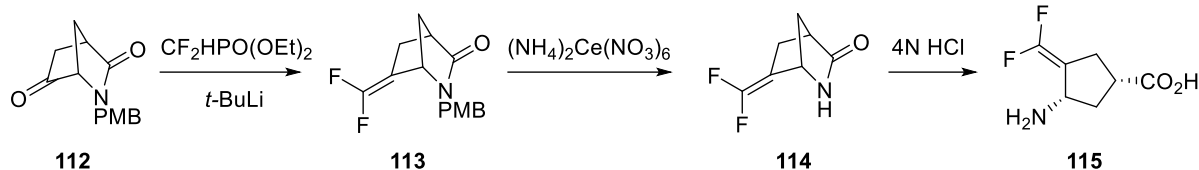
**Scheme 21.** Synthesis of 4-amino-6,6-difluoro-4-hexenoic acid **109**.

Qui *et al.* proposed the synthesis of benzyl (2*S*)-*N*-Boc-4-difluoromethyleneproline (**111**) (Scheme 22).<sup>25</sup> The reaction proceeded by addition of  $CF_2Br_2$  to the carbonyl moiety of the substrate **110** and subsequent treatment with zinc and HMPT which yielded the target derivative of proline **111** in 48% yield. This compound has been obtained as an intermediate for further synthesis of its hydrogenated analogue *N*-Boc-*cis*-4-difluoro-methyl-*L*-proline.



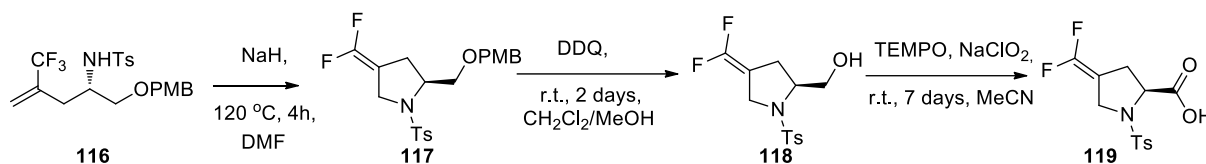
**Scheme 22.** Synthesis of benzyl (2*S*)-*N*-Boc-4-difluoromethyleneproline **111**.

In 2003 Pan *et al.* synthesized the unsaturated difluoro-substituted amino acid **115** (Scheme 23) using a Horner-Wadsworth-Emmons reaction as a key reaction step. Further treatment with cerium ammonium nitrate and acid hydrolysis in the final step yielded the amino acid **115** with a difluoroalkene moiety.<sup>32</sup>



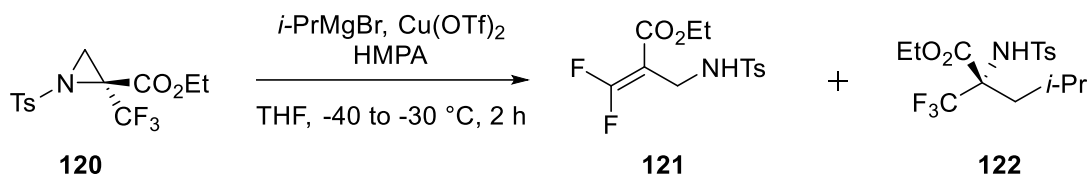
**Scheme 23.** Synthesis of (1S,3S)-3-amino-4-difluoro-methylene-1-cyclopentanoic acid (**115**).

The synthesis of 4-difluoromethylene proline **119** was described by Ichikawa *et al.*<sup>33</sup> The three-step procedure involved treating the starting material **116** with NaH, removal of the PMB group with DDQ and further oxidation of the generated alcohol **118** with  $\text{NaClO}_2$  in the presence of TEMPO. This route led to the desired product **119** in 93% yield and 99% enantioselectivity (Scheme 24).



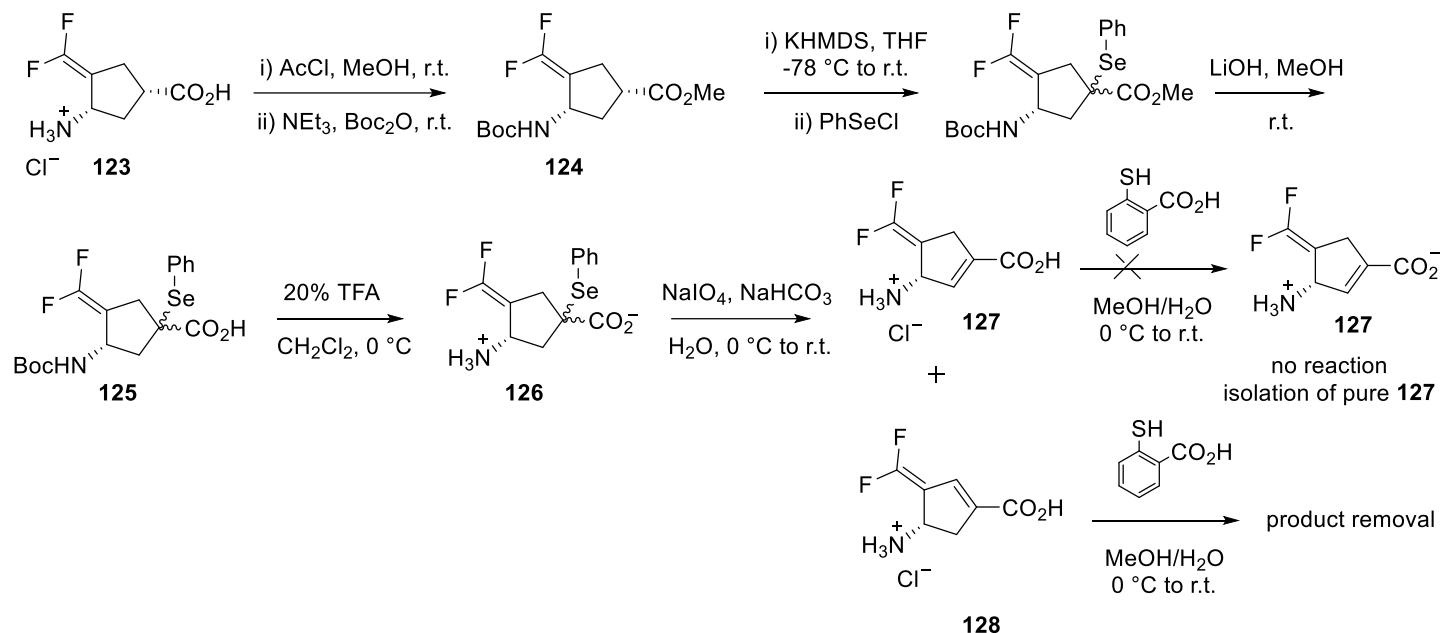
**Scheme 24.** Synthesis of 4-difluoromethylene proline **119**.

The synthesis of ethyl 3,3-difluoro-2-N-tosylamino-2-propenoate (**121**) (Scheme 25) was presented by Katagiri *et al.*<sup>34</sup> The reaction of aziridine **120** with Grignard reagent led to the formation of the desired amino acid derivative **121** as the major product (68%) together with a minor side product **122** (16%).



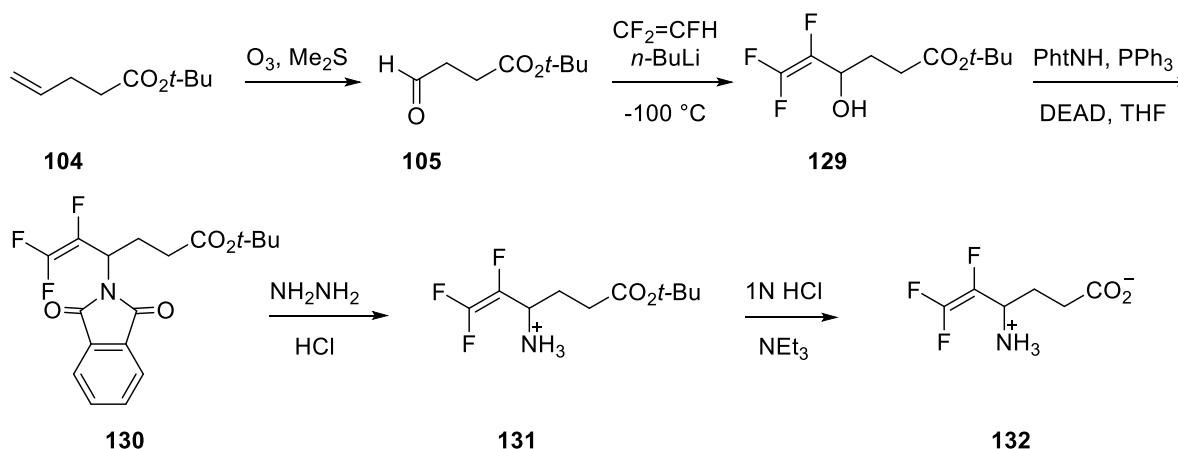
**Scheme 25.** Reaction of aziridine **120** with a Grignard reagent.

Recently, Juncosa *et al.* reported the synthesis of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid from its saturated analogue CPP-**115** (Scheme 26, cf. Scheme 23).<sup>35</sup> The first step included the protection of both amino and carboxylic group. Then, after using potassium hexamethyldisilazane and PhSeCl, the phenylselenenyl group was introduced to the  $\alpha$ -carbon. Next, deprotection of amino and carboxylic groups and elimination of PhSe-group furnished a mixture of the hydrochlorides of isomers **127** and **128** in a 5:3 ratio, respectively. One of the isomers, **128**, turned out to be more reactive and was removed by a selective modification using a soft thiol nucleophile. Finally, the isomer **127** was isolated as a pure product.



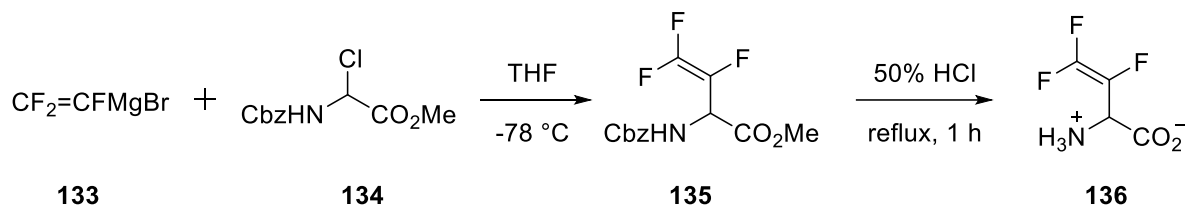
**Scheme 26.** Synthesis of (S)-3-Amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (**127**).

As shown before, in 1987 Kolb *et al.*<sup>17</sup> described the synthesis of 4-amino-5,6,6-trifluoro-5-hexenoic acid (**132**) according to the procedure presented earlier (Scheme 21). In comparison to the synthesis of difluorinated derivative **109** they used 1,1,2-trifluoroethene in the second step and triethylamine in the final route (Scheme 27).



**Scheme 27.** Synthesis of 4-amino-5,6,6-trifluoro-5-hexenoic acid **132**.

The preparation of trifluorovinyl amino acid **136** (Scheme 28) was presented by Castelhamo *et al.*<sup>36</sup> This route involved condensation of the Grignard reagent **133** with *N*-protected 2-chloroglycine methyl ester **134** and further acidic hydrolysis.



**Scheme 28.** Synthesis of trifluorovinyl amino acid **136**.

## 4. Conclusions

The idea, that peptidomimetics, as analogues of natural peptides, can be useful alternative in therapy is well known. The expected differences in their biological activity are attributed to the “artificial” unit incorporated to the original peptide chain. Also, the fact, that fluorine introduced to organic molecules, can dramatically change their properties is generally known. Besides changes of physical properties such as hydrophilicity, lipophilicity, the reactivity and stability can also be influenced by the incorporation of fluorine(s) in a molecule. It affects bond energy, acidity and basicity, hydrogen bond formation and, what is very important - the geometry of the molecule. Among others, introducing fluorine substituted vinyl units into poly-amino acid chain are of special interest. The presence of fluorine(s) at vinylic moieties and their precise location can significantly impact their properties. This general idea, however, requires quite challenging synthetic methods to prepare such “imaginary beautiful” molecules. This short review presents recent synthetic approaches and achievements on synthesis of amino acid derivatives bearing fluorine-substituted olefinic motifs.

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## List of Abbreviations

**2,2,6,6-TMP**- 2,2,6,6-Tetramethylpiperidine  
**AIBN**- Azobisisobutyronitrile  
**Boc**- *tert*-Butyloxycarbonyl group  
**Cbz**- Benzyloxycarbonyl group  
**DCC**- *N,N'*-Dicyclohexylcarbodiimide  
**DDQ**- 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone  
**DMAP**- 4-Dimethylaminopyridine  
**DMF**- Dimethylformamide  
**DMPU**- *N,N'*-Dimethylpropyleneurea  
**DMS**- Dimethyl sulfide  
**DMSO**- Dimethyl sulfoxide

**HMPT**- Hexamethylphosphoramide  
**LDA**- Lithium diisopropylamide  
**LiHMDS**- Lithium bis(trimethylsilyl)amide  
**LiTMP**- Lithium tetramethylpiperidide  
**NBS**- *N*-Bromosuccinimide  
**PCC**- Pyridinium chlorochromate  
**PMB**- *p*-Methoxybenzyl group  
**(S)-Boc BMI**- 2-*tert*-Butyl-3-methylimidazolidin-4-one  
**TEMPO**- (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl  
**TFA**- Trifluoroacetic acid  
**TMSCl**- Trimethylsilyl chloride

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