Adam Mickiewicz Univeristy in Poznań

Faculty of Chemistry

Department of Synthesis and Structure of Organic Compounds

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Doctoral dissertation

SYNTHESIS AND PROPERTIES OF FLUORINATED AMINO ACID DERIVATIVES

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Table of contents

1. Introduction

Fluorine is a very reactive chemical element which belongs to the 17th group of the periodic table (The Halogens). Gaseous fluorine was firstly obtained in 1886 by Henri Moissan, who was awarded for his achievements the Nobel Prize in 1906. Until 1943 natural products containing fluorine atoms were not known. Moreover, sodium monofluoroacetate, the first isolated natural fluorinated compound has been observed to be extremely toxic. Fluorine is the 13th most common element in the Earth's crust, however, natural organic compounds containing fluorine are extremely rare. This may be puzzling, but the answer is simple related to chemical properties of fluorine. Bond C-F is one of the strongest chemical bonds, and its biological formation/breaking would require extremely activated intermediates that are difficult to produce under biological conditions[1]. Fluorine displays some extreme properties. It is the most electronegative element **(**electronegativity value equals to 4.0 in the Pauling's scale), the smallest atomic radii (0.5741 Å) [2] among and non-noble-gases and non-hydrogen chemical elements, and the highest reduction potential (2.87 V). It forms the most reactive bond in a diatomic molecule existing under normal conditions [3] and is highly reactive with almost all chemical elements, even including noble gases. The variety of these properties transfer onto the compounds with fluorine atom(s), imparting unique persistence and unbelievable utility in plenty of applications, including medicinal chemistry and drug synthesis.

In recent years, intensive progress has been made in the chemistry of organic fluorine compounds, and new discoveries are proving to be revolutionary in different fields. For example, fluorine is used to produce highly stable materials like Teflon and other fluoropolymers, which are widely used in several applications. Fluorine is also a key player in the production of fluoropharmaceuticals. For instance, fluoroquinolones are used as antibiotics and fluorodeoxyglucose is used for imaging purposes by PET [4,5].

Nowadays it is not suprising that the electronegativity, atomic size, lipophilicity of fluorinated groups can dramatically incluence chemical and physical properties, including, metabolic stability and solubility compared to their non-fluorinated analogue. For example, the substitution of $–CH_3$ group for $–CF_3$ can radically chcange the chemical properties of a molecule [6]. Even a single fluorine atom can

completely change the biological effects of a natural product. Overall, the effect of fluorine on the biological activity of organic compounds is still rather unpredictable.

Fluorinated compounds are considered as fundamental ingredients in protein/peptide engineering and in drug discovery. A new class of organofluorine building blocks is used for construction of the unique and bioactive materials. Incorporation of fluorine atom to the organic molecules represents one of the most powerful modern design strategies to impart amino acids and peptides with unique functionality, empowering them for widespread application in the medicinal chemistry, biochemistry and medicine [4,5].

Amino acids are chemical compounds with two functional groups - amino and carboxyl- and they play a key role as building blocks in living organisms. Amino acids combine with each other forming proteins. Proteins are the basic building part of the human's organism and are composed of amino acids bonded with the peptide bond. The amino acids that make up the proteins in our bodies are all *L*,α-amino acids. The 20 amino acids that are found in living cells (protein amino acids) display a wide range of chemical versatility. The chemical properties of the amino acids in proteins determine the biological activity of the whole protein. Proteins control all cellular processes and catalyze most of the reactions. Humans can produce ten of the twenty amino acids.

The peptide bond undergoes non-enzymatic, spontaneous hydrolysis with the half-life equal to 400 years[7]. It is a resonance hybrid of three structures (Fig. 1).

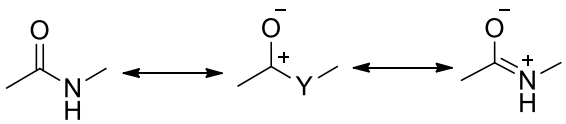


Figure 1. Resonance structures of peptide bond [8].

Unfortunately, in living organisms, amide bond is less stable due to the activity of the proteolytic enzymes. This problem can be overcome by looking for the chemical compounds, which are structurally alike to those possessing peptide moiety. Isosteres (isosteric molecules – molecules with similar/identical space arrangement; by definition isosteres are atoms, molecules or ions of similar size, containing the same number of atoms and valence electrons) are one example of such solution. Isosteres

are molecules or ions which have similar shape as well as electronic properties. They imitate the parent structure; therefore they are sometimes called “mimetics”. Moreover, these new protein-like molecules can be resistant to rapid proteolysis. Substitution of the peptide bond with a different, non-hydrolyzable moiety, can reinforce the peptide’s stability, what might be important for example in drug application. Some examples of peptide bond isosteres are presented below (Fig. 2)[9]. Replacement of one isostere to another allows to achieve desired chemical or physical properties without introducing steric perturbation in the parent structure.

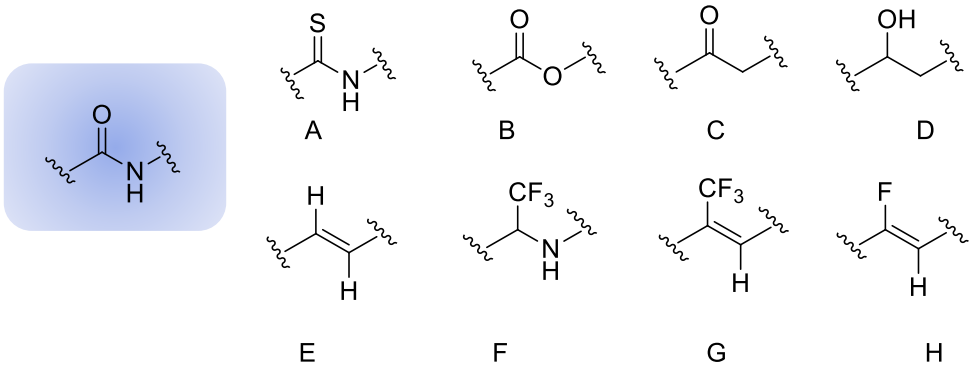


Figure 2. Peptide bond isosteres.

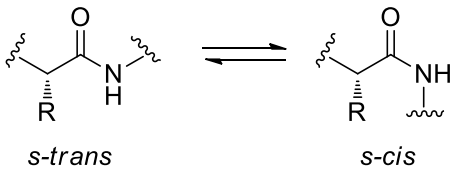
Among them, monofluorovinyl moiety is one of the examples of peptide bond isosteres (Fig. 2-H).

2. Literature

2.1. Fluorovinyl moiety

Fluorovinyl moiety is of one of the examples of mimics in peptides. It is structurally similar to the peptide bond: monofluoroalkene is a rigid structure with a double bond; the fluorine atom has partial negative charge (due to polarized C-F bond) and can play a role of an acceptor of hydrogen bond [10]. We can also visualized a hydrogen bond, where oxygen atom plays a role as an acceptor and N-H group a role of a donor. Moreover, in the nature, amide bond exists as two isomeric forms: *s-cis* as well as *s-trans* which can be at equilibrium [11], however mainly the *s-trans* isomer is preferred due to the smaller steric hindrance. Only in the proline molecule, the *s-cis* isomer is favoured [12]. Monofluorovinyl moiety can selectively mimic one of above-mentioned isomers, because there exists no equilibrium between these two isomers. Therefore, (*Z*)-fluoroalkene mimics the *s*-trans amide bond, whereas (*E*)-fluoroalkene mimics the *s*-cis isomer (Fig. 3) [13].

Amide bond:



Fluorovinyl bond:

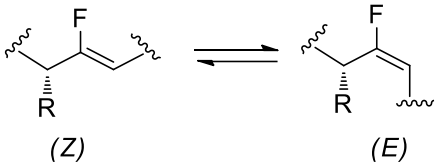


Figure 3. Conformations of amide and fluorovinyl bond.

Highly electronegative fluorine atom imitates the carbonyl oxygen atom and causes the dipole moment of such molecule to be similar to the value calculated for the amide linkage (Tab.1) [14].

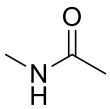
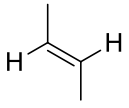
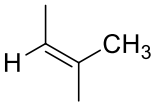
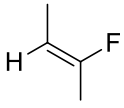
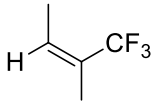
Moiety					
μ [D]	3.6	0.1	0.2	1.4	2.3

Table 1. Dipole moments (μ) of peptide bond and selected olefinic isosteres.

Amide bond, because of existing as resonance forms, is considered having partly double bond character which is responsible for the slightly difficult rotation around this bond. A negative charge is placed on the oxygen atom (Fig. 4).

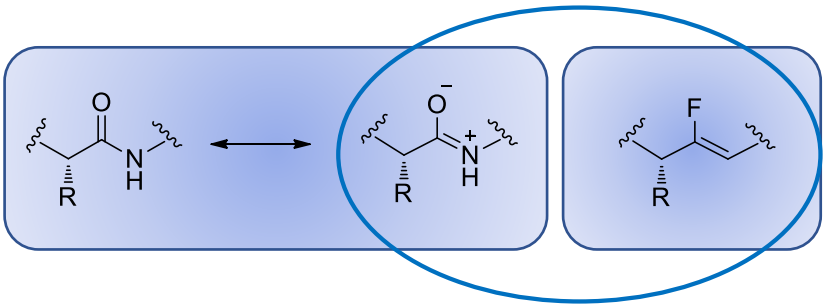


Figure 4. Fluorovinyl moiety as a peptide bond isostere [9].

Among many fluorine-containing molecules, those with monofluoroolefinic group are very important and they are often used in bioactive molecules and pharmaceuticals [15]. For instance, Tamoxifen is a drug used in the treatment for estrogen-dependent breast tumor, but one drawback of this drug is the increased risk of endometrial tumors. The fluorovinyl tamoxifen derivative (Fig.5, A) was very active against the MCF7 (estrogen-dependent breast adenocarcinoma) cell line [16].

Next example, where the introduction of a fluorine atom to a double bond of a natural chemical compound leads to a strong inhibition of the enzymatic system is fluoroconiferin which is a strong lignification inhibitor (Fig. 5, B) [17,18].

Among the biologically active compounds with a monofluorinated alkene moiety, active factor Xa inbibitor (Fig. 5, C). can be also mentioned. Xa factor is a serine proteinase which cleaves prothrombin to thrombin. This enzyme plays an important role in blood coagulation, therefore factor Xa has proven to be an attractive target for the development of new anticoagulants used in the treatment of thrombotic disorders [19].

Fourthly, the novel fleroxacin analogue with fluorovinyl moiety was presented as showing antibacterial activity (Fig. 5, D) [20].

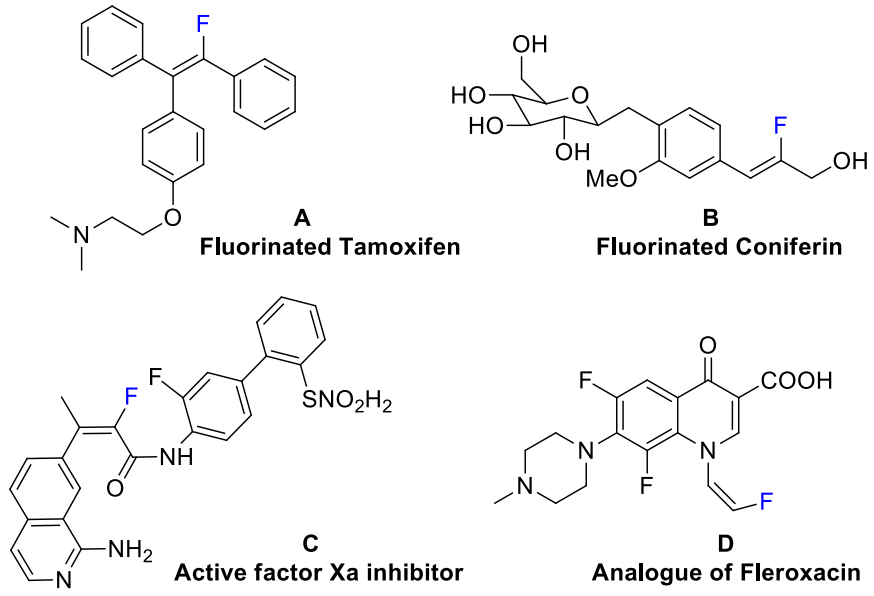


Figure 5. Structures of biologically active fluoroolefins.

2.2. Monofluorovinyl group – synthetic preparation

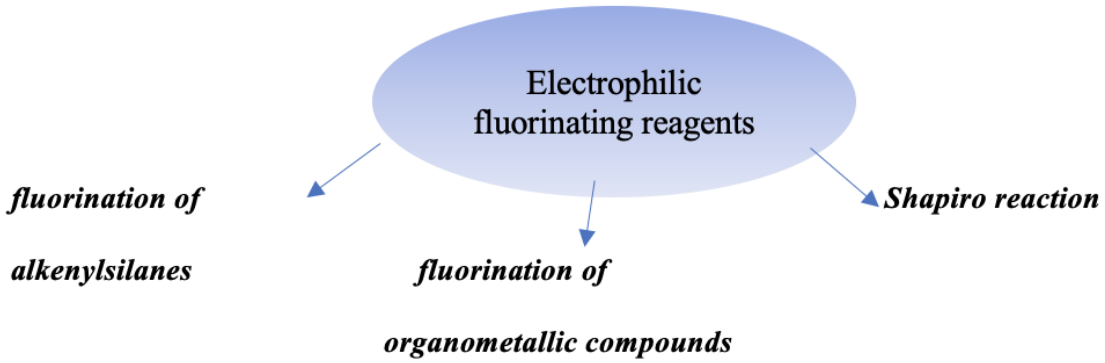
Compounds with fluorovinyl moiety are an interesting group in protein biochemistry because they can retain the original bioactivity as a parent structure and very often have additional biological activity [21]. Many methods of their synthesis have been described in the literature. Generally, they can be divided into two approaches:

- reactions using electrophilic or nucleophilic fluorinating agents,
- olefination reactions with fluorinated building blocks.

Moreover, in the literature there are also scientific reports on the stereoselective synthesis of monofluorovinyl compounds using transition metals [22].

2.2.1. Reactions using electrophilic reagents

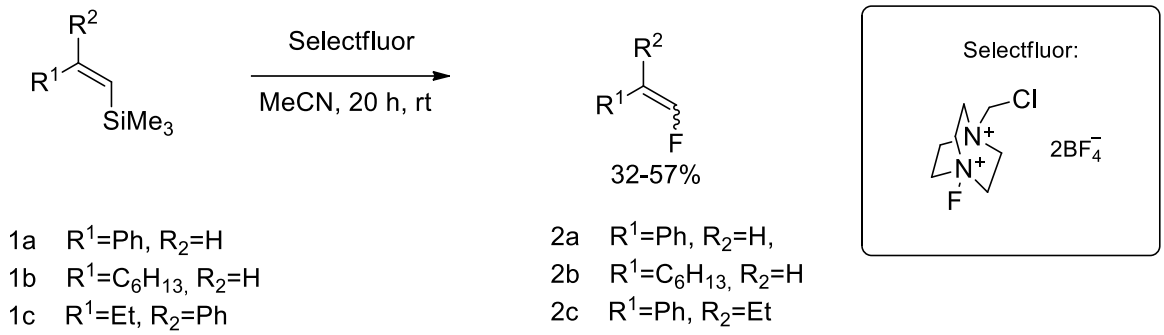
Generally, the synthesis of fluoroalkenes where electrophilic reagents were used, can be divided into three groups:



2.2.1.1. Fluorination of alkenylsilanes

Functionalized fluoroalkyl and alkenylsilanes have been recently widely employed for the synthesis of the versatile organofluorine compounds over the last years[23]. The use of electrophilic fluorination reagent like Selectfluor is one of the possibilities of introducing a fluorine atom into alkenylsilane derivatives into the vinylic position. In the literature, the reactions of a series of alkenyltrimethylsilanes with Selectfluor have been described (Scheme 1, 1a-c). As a result of the

reported reactions, products 2a-c were obtained in the isolated yield of 32, 45, 57%, respectively, with the ratio of *Z:E* isomers of 65:35, 80:20 and 58:42, respectively [24].

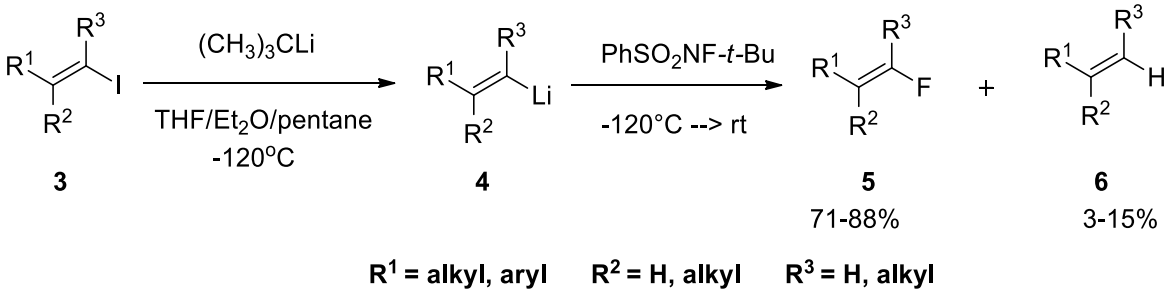


Scheme 1. Fluorodesilylation of vinylsilanes.

2.2.1.2. Fluorination of organometallic compounds

The formation of new carbon−fluorine bond with controlled regiochemistry and tolerance of various functional groups is still a synthetical challenge. Organofluorine compounds can be obtained by electrophilic fluorination of organometallic compounds, containing magnesium or lithium atom.

For example, the introduction of a fluorine atom to the alkene is possible when *N-tert*-butyl-*N*-fluoro-sulfonamide is used and double-bonded halides, in particular iodides, which allow to obtain the desired fluoroolefins in just two stages in good yields (Scheme 2) [25].

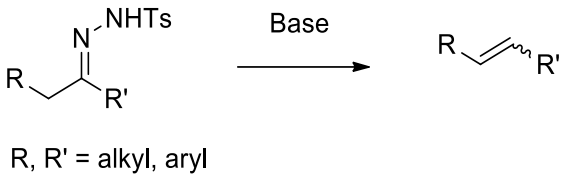


Scheme 2. Electrophilic fluorination of organolithium compounds.

A lithium compound **4** is formed from the corresponding alkenyl iodide by metal-halogen exchange. This compound reacts at low temperature with $PhSO_2NF$-*t*-Bu and product **5** is obtained predominantly (71% to 88% yield). Compound **6** is always formed as a by-product in yield of 3% to 15% depending on the iodide used.

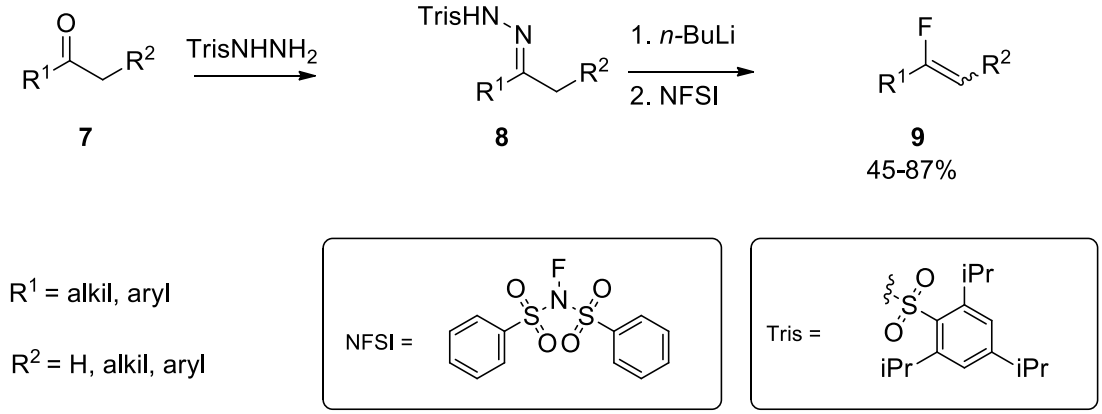
2.2.1.3. Shapiro reaction

Shapiro reaction is very convenient synthetical tool for preparing numerous olefinic compounds from ketones and aldehydes *via* sulfonylhydrazones [26]. This reaction allows to introduce the double bond into the molecule in the presence of a strong base (Scheme 3). These methods allow preparation not only of simple molecules with a double bond but also larger, complex systems that could express biological activity. Numerous compounds have been synthesized with the use of this methodology including molecules with fluoroolefinic moiety [27, 28].



Scheme 3. The general procedure of Shapiro reaction.

This reaction allow to obtain the fluoroolefins by electrophilic fluorination where NFSI is the fluorinating reagent [29] (Scheme 4). Several structurally diverse alkyl and aryl ketones can be used in this methos. As a result of the reaction, both internal and terminal fluoroalkenes are possible to be obtained in yields ranging from 45% to 87% (Scheme 4, **9**).



Scheme 4. The synthesis of fluoroalkenes via Shapiro reaction.

2.2.2. Reactions using nucleophilic reagents

The formation of fluoroolefins using nucleophilic fluorinating reagents is based on the condensation of the reagent R-CY(-)-F (Fig. 9) with a chemical compound with carbonyl moiety. This reaction can be divided into three groups depending on the reagent used. In modified Horner-

Wadsworth-Emmons reaction (HWE) the monofluorinated phosphonates react with aldehydes, where Y=P(O)(OR)$_2$ [30, 31, 32] where R=alkil/aryl group. In case when Y=SiR$_3$ the reaction is called fluoro-Peterson olefination [33]; and finally, when Y=SO$_2$Ar the reaction is named Julia-Kocienski coupling [34] .

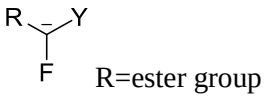
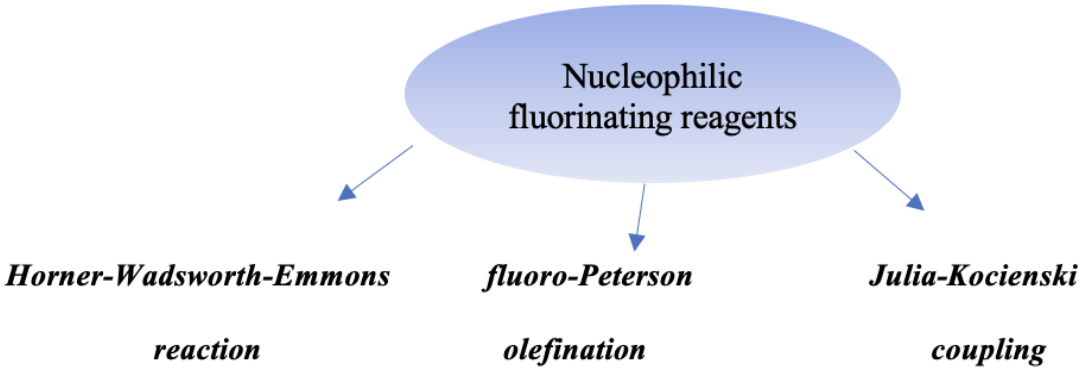
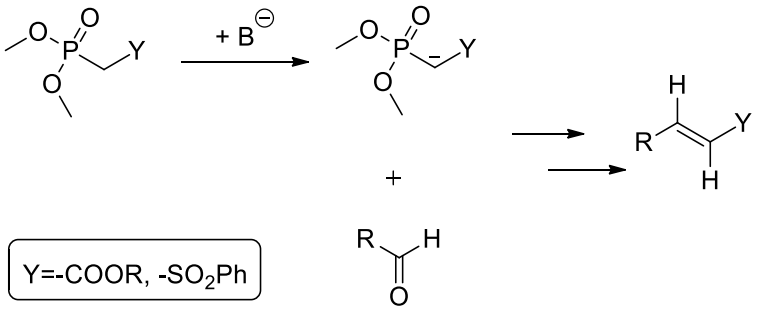


Figure 6. Reagent used in nucleophilic fluoromethylene reactions of carbonyl compounds.



2.2.2.1. Horner-Wadsworth-Emmons reaction

In the Horner-Wadsworth-Emmons (HWE) reaction the aldehydes or ketones undergoes condensation with phosphonate carbanions (ylides) yielding (*E*)-alkene as a major product of this synthesis [35] (Scheme 5).



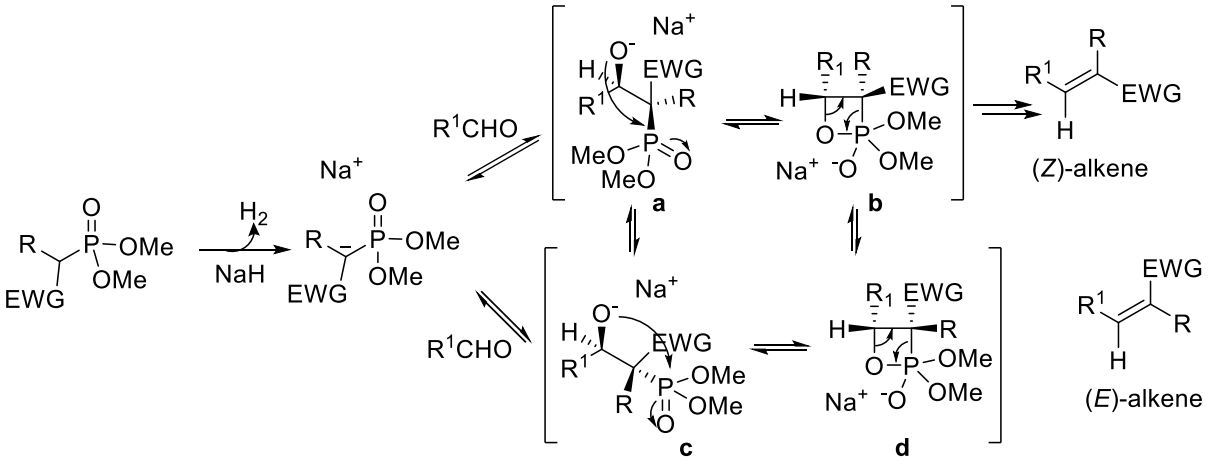
Scheme 5. General scheme of the Horner-Wadsworth-Emmons reaction.

2.2.2.1.1. History

The reaction between aldehydes/ketones and carbanions was firstly described in 1958 by Horner[36] and further being modified in 1961 by Emmons and Wadsworth[37]. There can be distinguished three different reaction conditions depending on the generated carbanion. The carbanions can be made from phosphine oxides (Horner conditions), phosphonates (Wadsworth-Emmons conditions) and phosphonoamides (Corey conditions)[38]. High nucleophility and basicity, as well as easy removal of co-product (due to extraction with water) are common advantages of these reactions.

2.2.2.1.2. Reaction mechanism

The HWE reaction begins with the deprotonation of the α-carbon atom in the phosphonate and formation of the phosphonate carbanion (Scheme 6). The second step, nucleophilic addition of the carbanion onto the aldehyde/ ketone is the rate-limiting step. If R=H, the intermediate products assigned as a,b as well as c,d can be transformed into each other. At the end of the reaction, the phosphonate is eliminated and the final olefinic product is formed.



Scheme 6. HWE reaction mechanism.

2.2.2.1.3. Modifications of the HWE reaction

The HWE reaction has been modified over the last years due to the necessity of reducing reaction's cost, due to environmental aspects and generally making it easier to perform. In 1983, Still and Gennari prepared macrocyclic (*Z*)-alkenes via the intramolecular HWE reaction [39]. In opposite to the classic HWE conditions, they used trimethyl phosphonopropionate in the presence of potassium *tert*-butanolate and saturated aldehydes with branched chains in the α-position. They obtained trisubstituted unsaturated esters in high (*Z*)-selectivity.

Six years later, Villieras and co-workers revealed that one-pot reaction with potassium carbonate or sodium hydroxide solution in deuterated water at ambient temperature leads to preparation of α-deuterated alkenes in high yields (above 90%) [40].

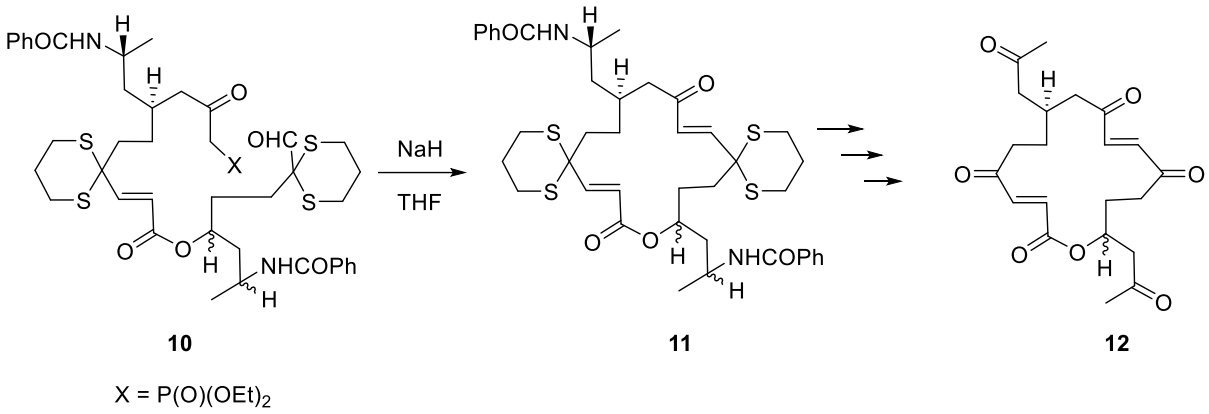
Wipf and Henninger elaborated the solid-phase HWE reaction [41]. The olefination products can be easily saparated from the co-products soluble in water. Wipf's group used the Wang resin to synthesize peptide mimetics with (*E*)-alkene moiety.

In 2002, Inanaga's group used silica gel, which turned out to be a perfect HWE reaction medium because it can be recovered and reused without loss of its activity [42]. The reaction was conducted at ambient temperature without the solvent. The desired products were only washed with an appriopriate solvent, because formed co-product retained on the silicagel. It is worth mentioning that this protocol is very eco-friendly because of short time of reaction, solvent-free conditions and reuse of silica gel.

In 2010, Ando and co-workers proposed the HWE reaction which was carried out without the solvents and in the presence of DBU. They used many structurally different aldehydes and obtained (*E*)-alkens in high yield (above 87%) and stereoselectivity (E:Z ratios raning from 97:3 to >99:1). This method is safe, environmentally friendly, does not require expensive catalysts as well as bases. Moreover, high (*E*)-selectivity and the ease of work-up make this method very valuable [43].

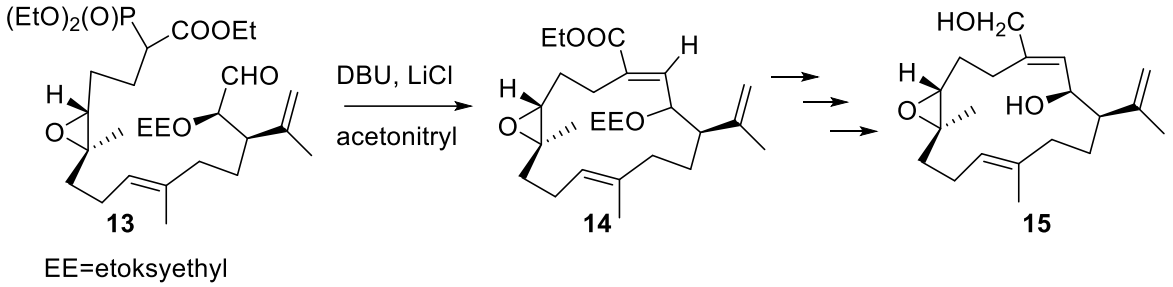
2.2.2.1.4. Applications of the HWE reaction

The HWE reaction is commonly used to obtain the biologically active compounds. For instance, the natural antibiotic (-)-vermiculine was synthesized in 1978 by Burri and co-workers. The synthetic procedure was a multi-step sequence, where the HWE reaction played an important role and allowed to obtain the multi-membered ring (Scheme 7)[44].



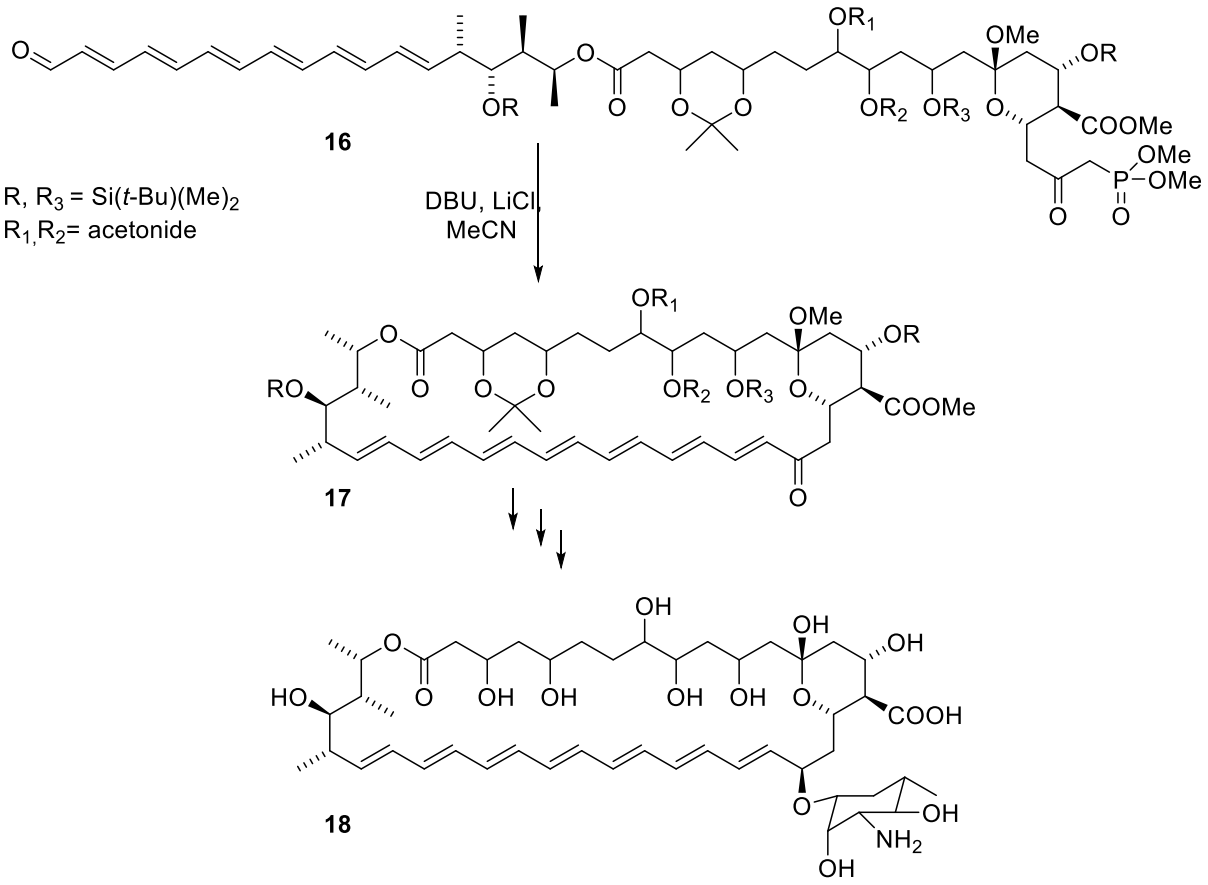
Scheme 7. Synthetic scheme of the (-)-vermiculine.

Eight years later, Tius and Fauq proposed the synthesis of (-)-Asperdiol (**15**) due to intermolecular HWE reaction. Asperdiol is a natural product which was isolated from the Caribbean gorgonians. It showed activity against the P-388 lymphocytic leukemia and a few other cancer cell lines. The total synthesis of (-)-Asperdiol was a multi-step procedure where compound **13** in the presence of DBU and lithium chloride yielded ester **14**. Several further steps allowed to obtain the desired product **15** having the anticancer activity[45] (Scheme 8).



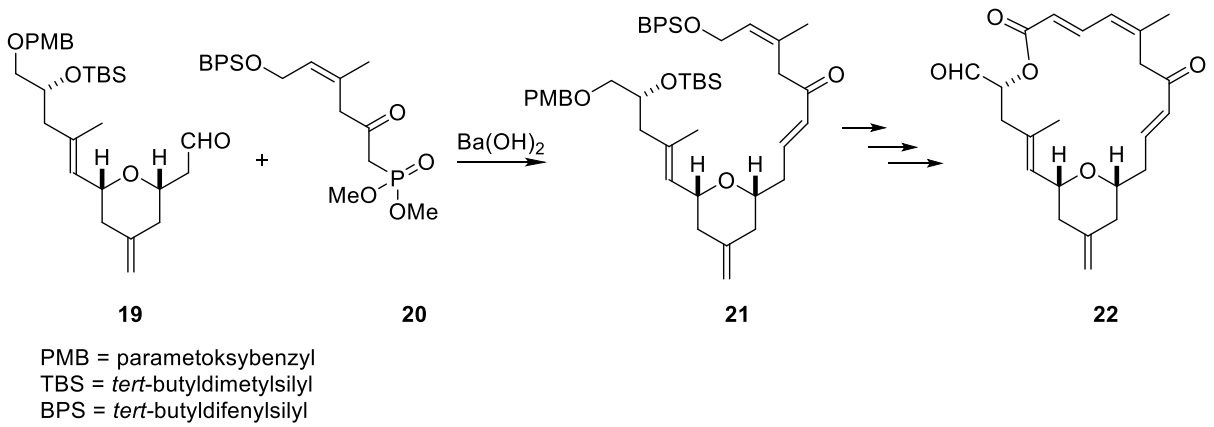
Scheme 8. Synthetic scheme of (-)-Asperdiol.

In 1988 Ogawa's group proposed the synthesis of Amphoterycin B which is an antifungal antibiotic with macrocyclic poliene fragment and many hydroxyl groups. In the synthetic route, the aldehyde group condenses with α-phosphoryl carbanion at both ends of the chain (Scheme 9).



Scheme 9. Synthetic scheme of Amphoterycin B.

The next example is the (+)- Dactylolid, which is a cytotoxic metabolite. This compound can be isolated from sponges of the Dactylospongia group [46]. In 2005 Sanchez and Keck reported the first total synthesis one of this chemical compound with the HWE reaction and further macrocyclisation (Scheme 10). [47]

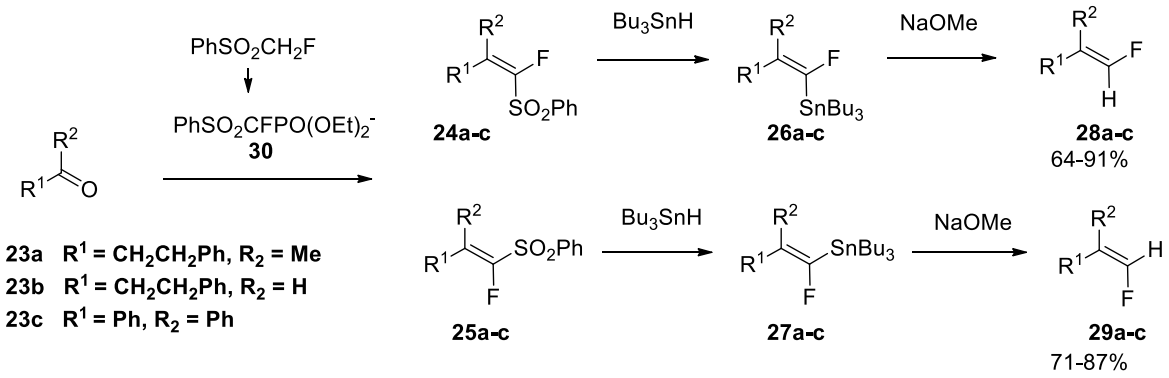


Scheme 10. Synthetic scheme of (+)-Dactylolid.

2.2.2.1.5. Synthesis of fluorinated olefinic compounds using HWE reaction (examples)

HWE reaction is successfully used to synthesize fluoroolefinic compounds. The products which are formed can act as both (*Z*) and (*E*)-alkenes [48, 49]. Fortunately, huge steric hindrance of the phosphonate, replacement THF with DMF, higher temperature of the reaction system favor the formation of (*E*)-products. Usually, the reaction is carried out in the presence of a strong base such as *n*-butyllithium, potassium *tert*-butoxide, sodium hydride, or lithium bis(trimethylsilyl)amide and is some cases, the aldehyde may undergo racemization, aldol condensation or even decomposition due to strong basic conditions. Therefore, the literature data show that a weaker base such as DBU or diisopropylethylamine in acetonitrile can also be used, but in the presence of lithium chloride [50, 51, 52].

The first example of obtaining fluorovinyl compounds following HWE methodology is the synthetic path presented in Scheme 11. Aldehydes **23b** and ketones **23a** and **23c** reacted with carbanion **30** generated in situ from fluoromethylphenyl sulfone and diethylchlorophosphate. Fluorovinylsulphones **24-25a-c** were obtained, which in turn were converted to fluorvinylstannanes. Finally, in the presence of sodium methoxide, the desired products **28a-c** and **29a-c** were obtained in yields ranging from 64% to 91% [30].



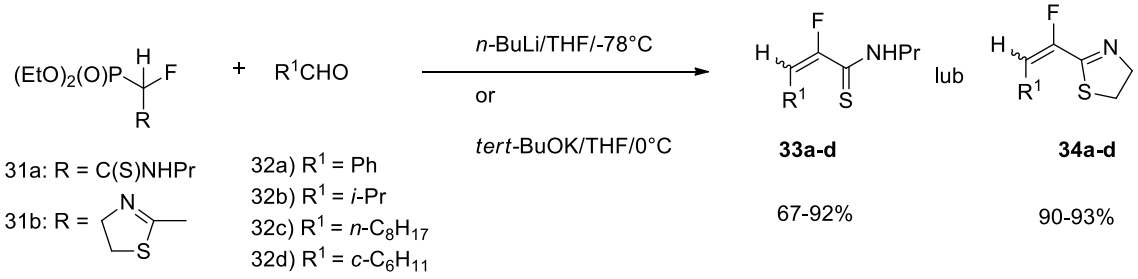
Scheme 11. Scheme of the synthesis of fluorovinyl compounds by HWE reaction.

In the second example, the HWE reaction was carried out using structurally diverse aldehydes and two different bases: *n*-BuLi (method I) and *tert*-Bu-OK (method II) [31]. In the case of using procedure I and substrate **31a** (Scheme 12), the aromatic product **33a** was obtained in 92% yield and as a mixture of E/Z isomer in the ratio equal to 65:35. In the case of the aliphatic derivatives **33b-d**, the (*E*)-alkene predominates because E/Z selectivity equals to 4/1. The yield was slightly lower, in a range from 67% to 72%. The use of method I and substrate **31b** enabled the formation of products **34a-d** in higher

selectivity (E/Z= 95:5) and higher yield (90% to 93%). When the second method was used, the yields of products **33** and **34** were similarly high as in procedure I, but a significant decrease in the selectivity of the products **34a-d** was observed (E/Z= 75:25) (Tab. 2).

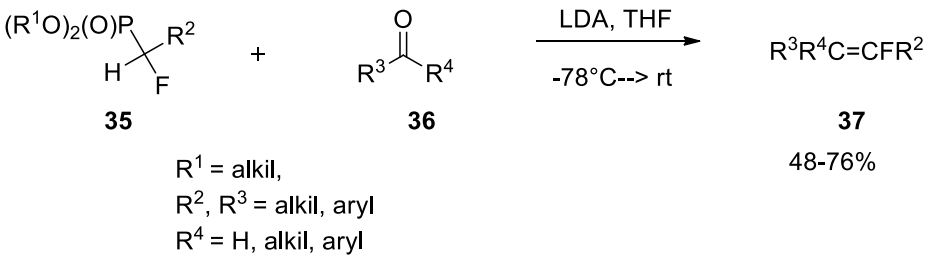
	Method I	**Method II**
Base	*n*-BuLi	*Tert*-Bu-OK
Yield [%] of aromatic product 25a	92	93
Selevtivity E/Z ratio of product 25a	65:35	60:40
Yield [%] of aliphatic products 25b-d	67-72	60-72
Selevtivity E/Z ratio of products 25b-d 26a-d	4:1 95:5	3:2 75:25
Yield [%] of products 26a-d	90-93	88-93

Table 2. Comparision of the yields and selectivity of two HWE reaction conditions leading to fluorinated unsaturated thioamides and thioazoles.



Scheme 12. The synthesis of α-fluoro-α,β-unsaturated thioamides and thiazoles.

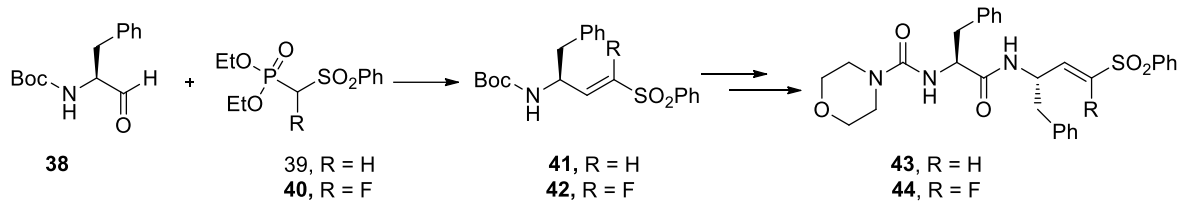
Another example of HWE reaction is the one-pot synthesis (Scheme 13) of fluoroolefins **37** by reaction of the phosphonate $(R_1O)_2P(O)CFHR_2$ with different carbonyl compounds [32]. A lot of desired structures **37** were obtained in yields ranging from 48% to 76%. The highest stereoselectivity (E/Z= 1:99) was observed for the chemical compound $(C_2F_5)(OEt)C{=}CFPh$.



Scheme 13. Synthesis of fluoroolefins with the general formula $R^3R^4C{=}CFR^2$.

2.2.2.1.6. Synthesis of fluorinated olefinic amino acid derivatives using HWE reaction

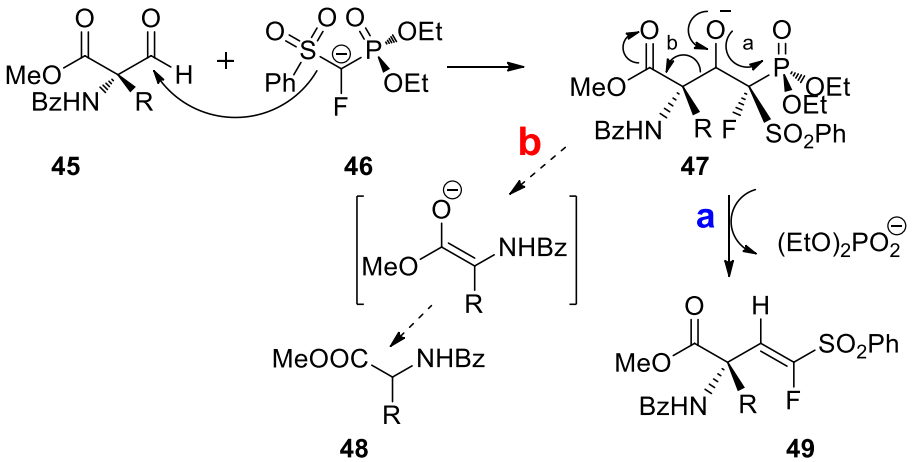
HWE method have been also found in the synthesis of fluorinated alkenyl amino acid derivatives. In the first described example, *N*-tert-butoxycarbonyl-phenylalaninal (**38**) reacted with the carbanion of compound **40** which is called McCarthy's reagent ((diethyl-1-fluoro-1-(phenylsulfonyl)methylphosphonate) (Scheme 14). NaH was used as the deprotonating agent when R_1 = H and succesfully only the (*E*) isomer was selectively obtained in 52% yield. LiHMDS was used when R_1 = F and a 1:1 mixture of (*Z*)- and (*E*)-fluorovinyl sulfones was obtained. The deprotonated fluorovinyl sulfone was further coupled with a carboxylic acid to give a peptidomimetic with a fluoroolefinic group **43-44** [53].



38 39, R = H **40**, R = F **41**, R = H **42**, R = F **43**, R = H **44**, R = F

Scheme 14. The synthesis of amino acid derivatives via HWE reaction.

In 2004, Berkowitz and co-workers [54] reported the synthesis of florinated olefinic amino acids. The carboxyl group of the amino acid was only protected with methyl group and the aldehyde group in the side chain was subjected to the condensation. The coupling of structurally diverse aldehydes with severe steric hindrances was conducted. The main purpose of this work was to study the stereoselectivity of the reaction and to check whether the *β*-alkoxyphosphonate undergoes the desired HWE reaction or "Retro-Claisen" condensation which is a competitive reaction (Scheme 15).

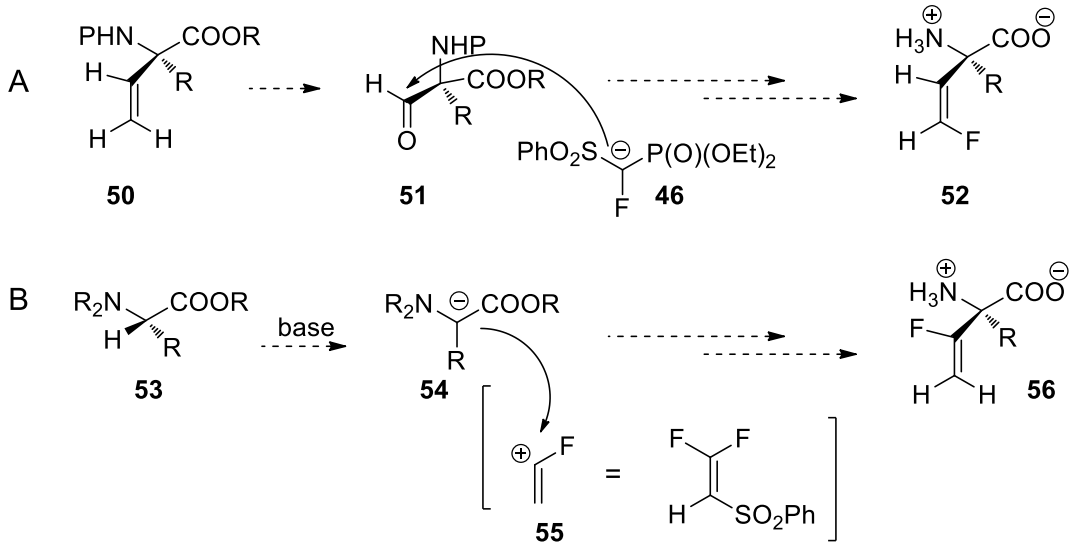


45 **46** **47** **48** **49**

Scheme 15. The competitive reaction between HWE (a), and Claisen condensation (b).

The research revealed that for sterically crowded aldehydes, no mixture of E/Z isomers is formed, and the target structures were obtained as pure isomers. Such high level of diastereoselectivity is unique when it comes to the condensation of aldehyde groups using the above-mentioned phosphonate carbanion, and this phenomenon occurs probably due to the presence of a quaternary center at the α-position to the carbonyl group in the aldehyde. Generally, a competitive "Retro-Claisen" reaction is observed in these types of reactions, but when such sterically crowded amino acid derivatives are used, the HWE condensation pathway dominates for all amino acids, apart from aspartate. It is the first attempt to synthesize such compounds by HWE reaction using McCathy's reagent. The product contains a fluorine atom in the 2' position of the vinyl chain.

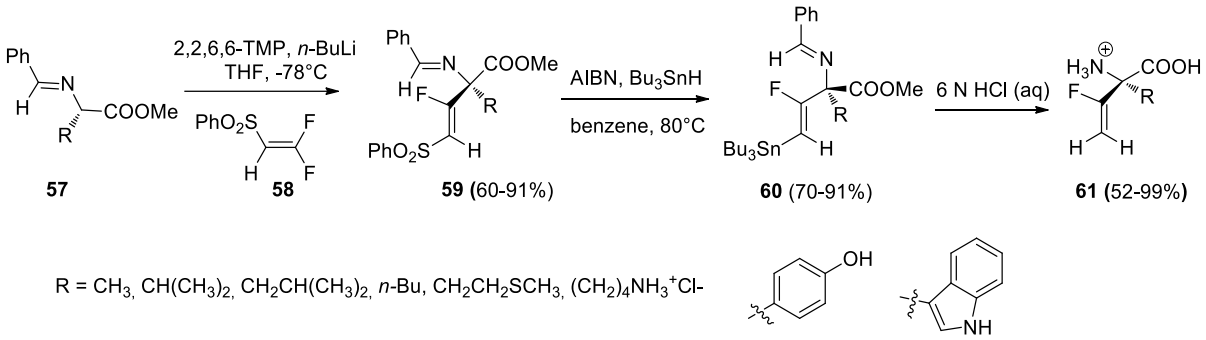
Berkowitz group [55] decided to look for a new way of synthesis, in which the fluorine atom will be introduced in the 1' position of the amino acid. Therefore, the synthesis of quaternary β,γ-unsaturated amino acids was reported. The carbonyl and amino groups in the α-position was retained and the fluorovinyl side chain was attached to the α-carbon atom (Scheme 16, A and B). The novelty of this method is the use of an electrophilic fluorinating agent.



Scheme 16. The synthesis of fluorovinyl amino acids using nucleophilic (A) and electrophilic (B) fluorinating agents.

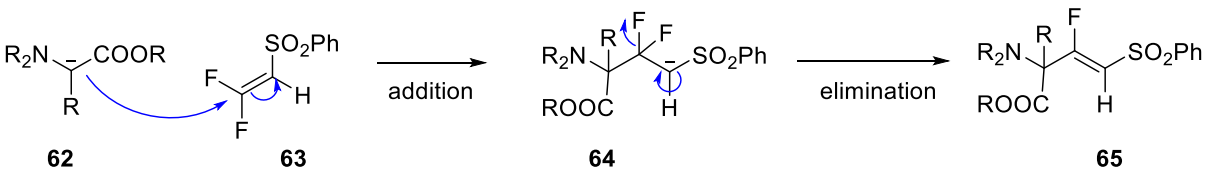
Berkiwitz and co-workers developed a viable (1'-fluoro)vinyl cation which can condense with amino acid-derived enolates. β-difluorovinyl phenyl sulfone was chosen as a perfect candidate and it can be written as $CH_2=CF^+$ (fluorovinyl cation) to simplify the reaction scheme.

The amino acid derivatives (Scheme 17, **57**) reacted with LiTMP generated *in situ* and difluorovinyl sulfone **58** to form compounds **59** in isolated yields ranging from 60 to 91%. In the next step, α-(1'-fluoro)vinylphenylsulfones were treated with $HSnBu_3$ in the presence of AIBN and products **60** were obtained in good isolated yields (70-91%). Finally, the acid removal of -$SnBu_3$ group and the hydrolysis of the ester group, lead to form the desired α-(1'-fluoro)vinyl amino acid hydrochlorides **61** in good to excellent yields.



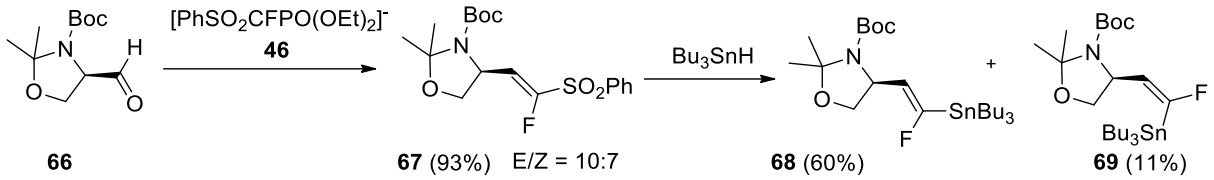
Scheme 17. The synyhesis of α-(1'-fluoro)vinylic amino acids.

In the reaction mechanism (Scheme 18), the AA-derived enolate **62** is added to the β,β-difluorovinyl pheyl sulfone **63**. In the next step, the F^- ion is eliminated and α-(1′-fluoro)vinyl sulfone derivatives **64** is formed, which in turn reacted with Bu_3SnH in the presence of AIBN as presented above. Final hydrolysis yields the target amino acid derivative with a fluorovinyl group **65**.



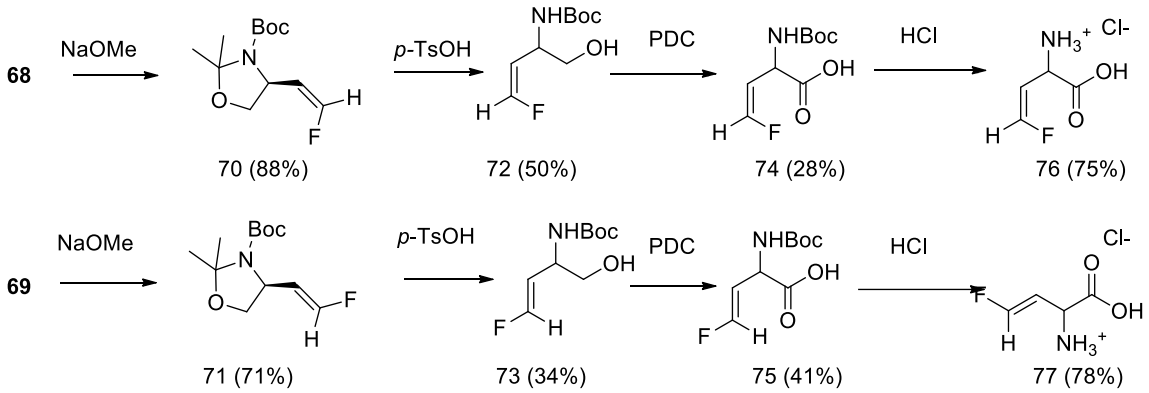
*Scheme 18. Mechanism of α-(1'-Fluoro)vinylation of AA-Derived Enolates **62** with β,β-difluorovinyl pheyl sulfone **63**.*

In the last example of fluorovinyl amino acid synthesis by HWE reaction, the starting aldehyde (Scheme 19, **66**) was converted to the mixture of fluorvinyl sulfones **67** (E/Z ratio = 10:7), which in turn was treated with Bu_3SnH.



Scheme 19. The synthesis of fluorovinylstannanes.

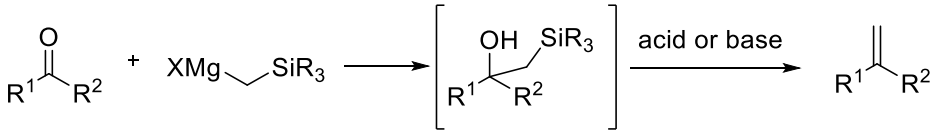
A mixture of isomers **68** and **69** was separated by flash chromatography and each one reacted with sodium methoxide in the next step (Scheme 20). The isopropylidene group was removed using *p*-toluenesulfonic acid. Then, the alcohol was oxidized to a carboxylic acid in the presence of pyridine dichromate and the Boc protecting group was removed by HCl, yielding the target amino acids **76** and **77** in 75% and 78% [30].



Scheme 20. The synthesis of fluorovinyl amino acids.

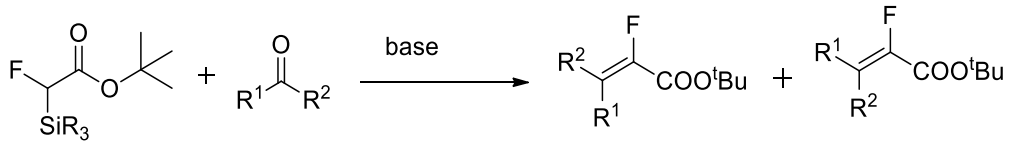
2.2.2.2. Fluoro-Peterson olefination

The Peterson olefination was discovered in 1968 [56]. This reaction allows to obtain alkenes from α-silylcarbanions (Scheme 21). The intermediate *β*-hydroxysilane can be isolated and the elimination step may be performed later. One charateristic key of this reaction is that it can be used to prepare either *trans*- or *cis*-alkenes depending on the conditions employed. Treatment of the *β*-hydroxysilane with base allows to obtain alkene, while treatment of the same β-hydroxysilane with acid leads to form alkene of different stereochemistry [57].



Scheme 21. The general scheme of Peterson olefination.

The Peterson olefination can be also used to obtain the fluoroolefins. Lin and Welch proposed the fluoro-Peterson reaction where *tert*-butyl α-fluoro-α-(trialkylsilyl)acetate was used (Scheme 22, **78**) as well as different aliphatic and aromatic carbonyl compounds **79**. NaHMDS, LDA, or the LDA/*tert*-Bu-OK system were used as a bases. In the case of using this method, *Z*-isomers of **80** were obtained as major products, which is opposite to the HWE reaction, where the *E*-isomer predominates [33]. The isolated yields of a mixture of isomers varied from 23% to 88% and the highest yield was obtained for R^1 = H and R^2 = o-$CH_3C_6H_4$ and LDA/*tert*-Bu-OK.

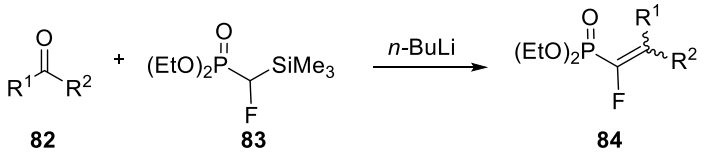


78 **79** **80** (*Z*) **81** (*E*)

base = LDA, NaHMDS, LDA/*tert*-BuOK
R^1 = H, Me
R^2 = alkil n>2, aryl

Scheme 22. The scheme of fluoro-Peterson olefination.

Another example of Peterson olefination that leads to form the fluoroalkenes was investigated by two groups [58]. Waschbüsch and co-workers prepared the α-fluorovinylphosphonates as a mixture of *E*- and *Z*-isomers [59]. The reaction with aromatic aldehydes and lithium α-fluoro-α-trimethylsilylmethylphosphonate yielded the vinyl phosphonates *E*-selectively whilst the reaction with ketones allowed to form fluorinated *Z*-alkenes (Scheme 23) [60]. Keeney group used an analogous procedure [61].



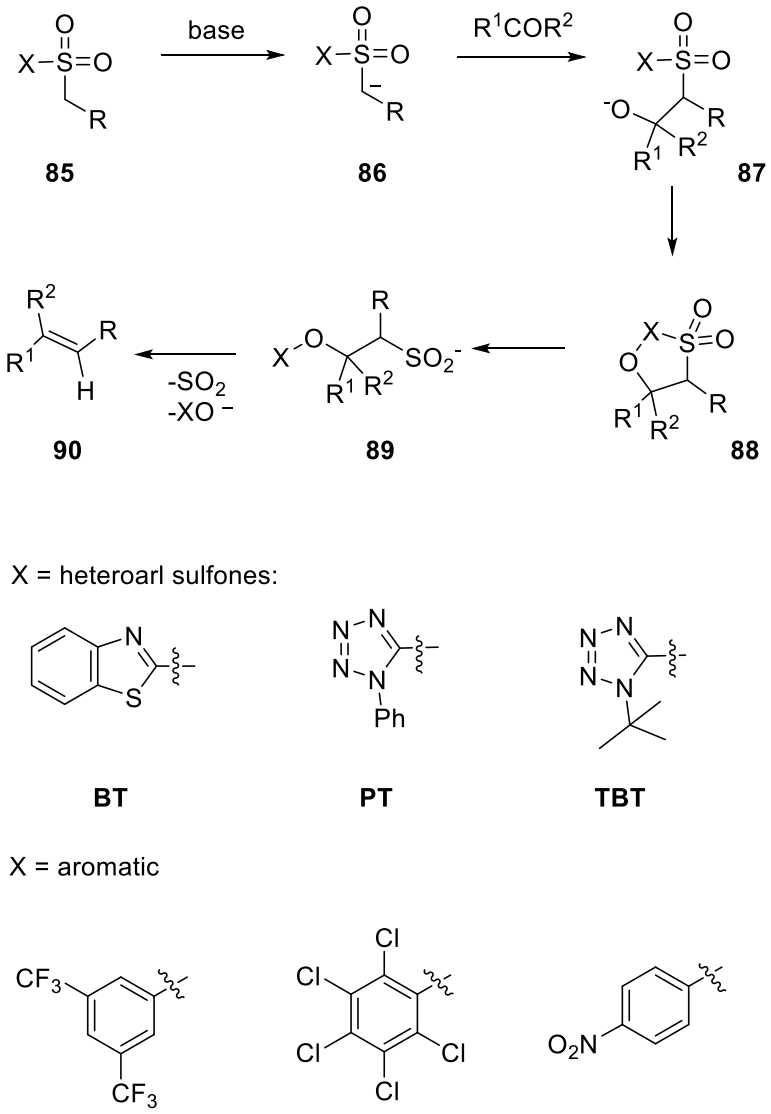
82 **83** **84**

R^1	R^2	yield [%]	*E:Z*
C_6H_5	H	81	74:26
p-$MeOC_6H_4$	H	91	70:30
2-furyl	H	92	80:20
2-thienyl	H	93	78:22
2-pyridinyl	H	52	85:15
(-)carvone		87	0:100
2-Me-c-C_6H_9		62	0:100

Scheme 23. Peterson olefination of α-silyl phosphorus stabilised carbanions.

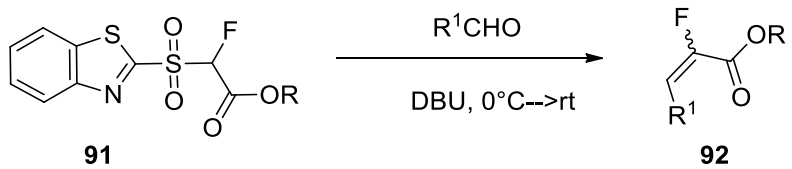
2.2.2.3. Julia-Kocienski olefination

The Julia–Kocienski coupling provides a versatile platform for the preparation of compounds with fluorovinyl moiety. This reaction is also called modified or one-pot olefination and is a useful method for the introduction of unsaturation [62]. The modified Julia–Kocienski olefination hinges on the use of heteroaryl sulfones [63] or electron-deficient aryl sulfones [64] (Scheme 24). Sulfones with 1-phenyl-1H-tetrazol- 5-yl (PT) and benzothiazol-2-yl (BT) are widely used in this synthesis. In the mechanism, the deprotonation of the sulfone by the base lead to the formation of carbanion **86** and subsequently to β-alkoxy sulfone **87**. Then, a spirocyclic intermediate **88** is formed which is opened via cleavage of a C–S bond. Finally, the elimination of SO_2 and aryl- or heteroaryl alkoxide yields the desired olefin **90**.



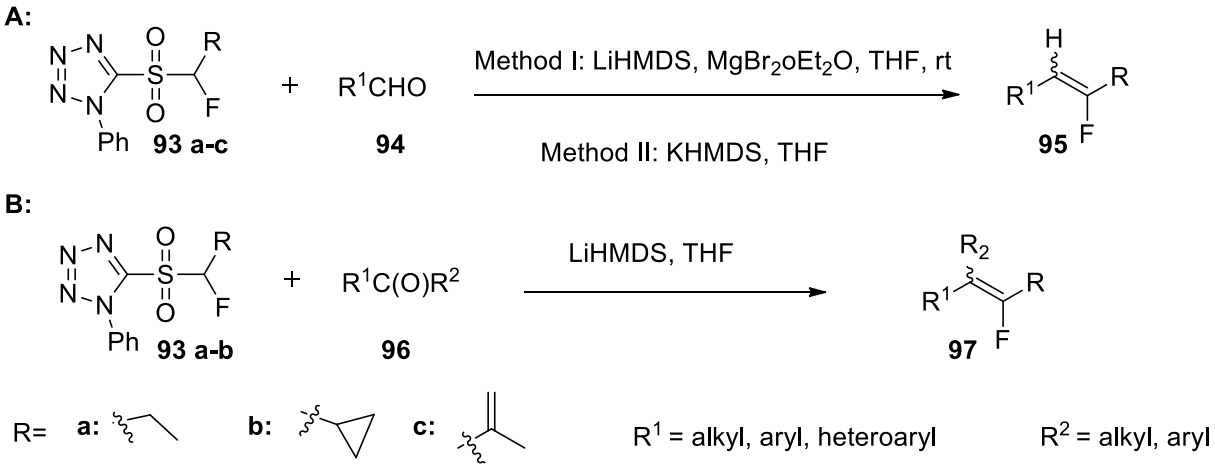
Scheme 24. The general mechanism of the Julia-Kocienski olefination.

In the literature are presented numerous scientific reports on the synthesis of fluoroolefins using the Julia-Kocienski reagent. For instance, in 2006, the synthesis of α-fluoroacrylates nas been published (Scheme 25). The reaction resulted in a few fluorinated products **92** in high yields (65% to 99%) depending on the structure of the substituent R in the compound **91**. For more bulky groups, like R = *tert*-Bu, the yields ranged from 75% to 99%. When R substituent was ethyl group, the yield ranged from 65% to 94%, and when R = 8-fluoromenthyl, the yields were from 70% to 92% [65].



Scheme 25. The synthesis of α-fluoroacrylates via Julia-Kocienski olefination

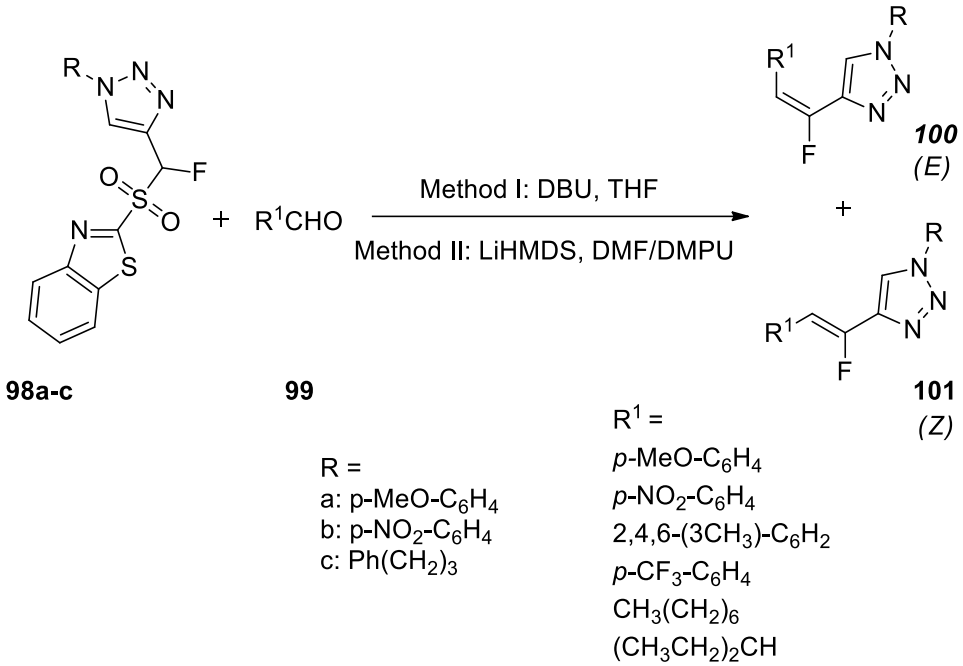
Three years later, the synthesis of fluoroolefins using the Julia-Kocienski coupling was proposed by Zajc and Ghosh (Scheme 26, A). The reaction was carried out in the presence of LiHMDS and $MgBr_2 \bullet OEt_2$ or in the presence of KHMDS. In the case of using lithium salt, the majority of isomers (*Z*) were obtained in yields ranging from 0 to 94%. When potassium salt was used (*E*)-isomers were produced in 64% to 90% yield. For dialkyl, aryl-alkyl and diaryl ketones **96,** fluoroolefins were obtained in better yields ranging from of 71% to 99% (Fig. 30B) [66].



Scheme 26. Condensation of fluorinated sulfone derivatives (1a-c) with aldehydes and ketones.

Fluoroolefins can be also obtained by coupling of fluorosulfones with aldehydes. The Julia-Kocienski reagent (Scheme 27, **98**) was implemented using two different reaction conditions: DBU and

THF (method I) and - LiHMDS in the DMF/DMPU system (method II) [34]. In the first synthesis (with DBU), the (*E*)-isomers **100** were obtained with high selectivity. This selectivity depended on the structure of the aldehyde and on the thiazole reagent.



Scheme 27. Condensation of sulfones 1a-c with the aldehydes.

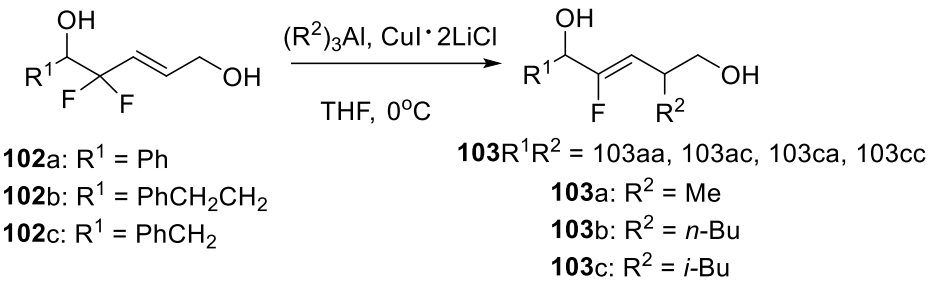
The best results were obtained for aromatic aldehydes (yields from 47% to 90%). In case of using the aliphatic substrates, the yields of the reaction were lower when bulky groups were present, because then the addition of Julia-Kocienski reagent to the aldehyde occurs more slowly. In comparison to the first method, the second method led to form the (*Z*) isomers predominantly (Tab.3)

	Method I	**Method II**
Reaction conditions	DBU, THF, reflux	LiHMDS, DMF/DMPU, -78ºC
Aromatic products		
Yields [%]	52-85	47-90
E:Z ratio	57:43 to 87:13	1:9 (average)
Aliphatic products		
Yields [%]	3-61	57-68
E:Z ratio	60:40	30:70 to 20:80

Table 3. Comparison of two methods leading to form the 4-fluorovinyl-1,2,3-triazoles.

2.2.3. S_N2' reaction of α,α-difluoroallyl and organocopper compounds

Alternative for the incorporation of a fluorine atom into the structures of organic compounds is the reaction between α,α-difluoroallyl compounds and organocopper reagents. The first example is the reaction between (*E*)-4,4-difluoro-5-hydroxyallyl compounds **102a-c** in the presence of trialkylaluminum and CuI•2LiCl (Scheme 28). This procedure leads to form selectively the (*Z*)-4-fluorohomoallyl alcohols **103** in yields ranging from 65% to 98% [67].

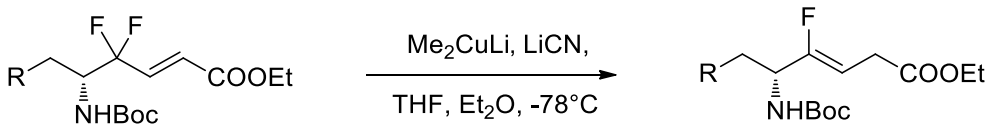


102a: R^1 = Ph
102b: R^1 = $PhCH_2CH_2$
102c: R^1 = $PhCH_2$

103R^1R^2 = 103aa, 103ac, 103ca, 103cc
103a: R^2 = Me
103b: R^2 = *n*-Bu
103c: R^2 = *i*-Bu

Scheme 28. The reaction of (E)-4,4-difluoro-5-hydroxyallyl alcohols with R_3Al in the presence of copper(I) ions.

The next example shows the synthesis of (*Z*)-fluoroalkenes dipeptide isosteres using Me_2CuLi and LiCN. As a result of the reaction, fluoroolefinic derivatives were obtained in yields of 84% for compound **105a** and 89% for **105b** (Scheme 29) [68].



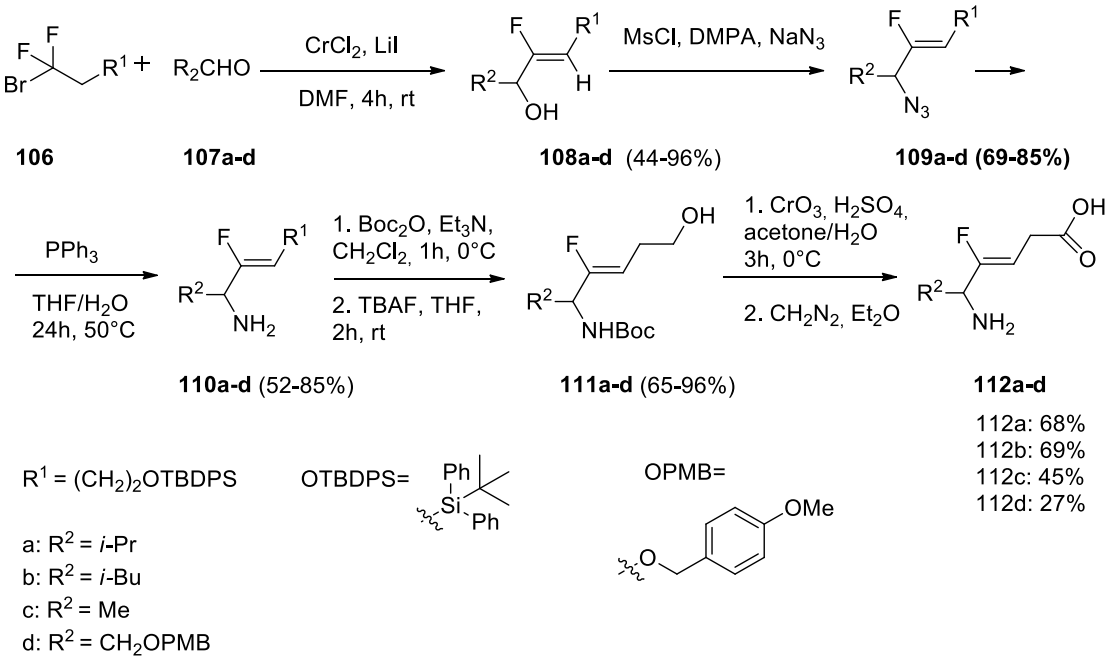
104a: R = Ph
104b: R = OBzl

105a
105b

Scheme 29. The synthesis of fluoroolefinic dipeptide derivatives.

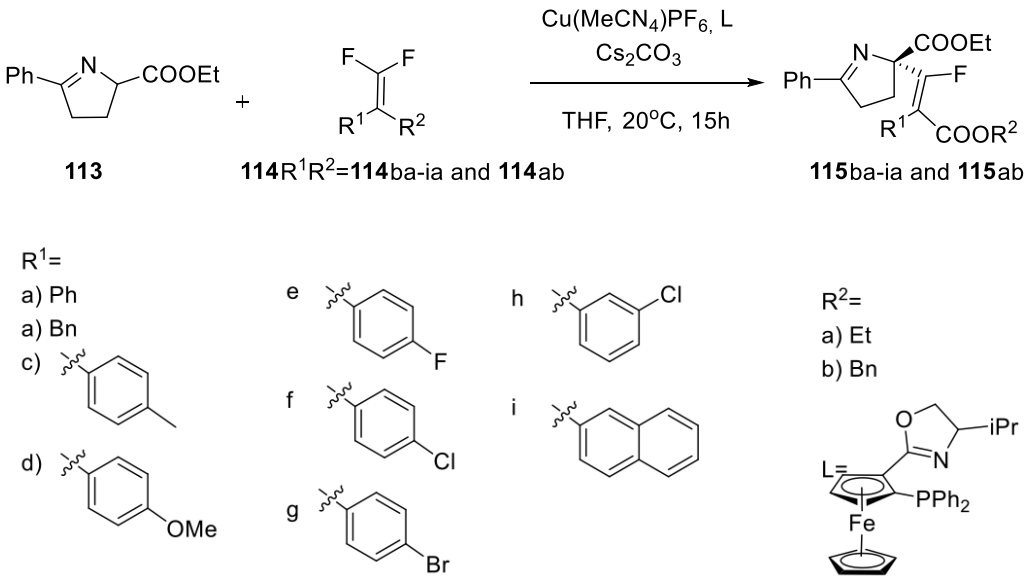
2.2.4. Stereoselective synthesis using transition metal compounds

Another method of creating fluoroalkene compounds is the reductive coupling of molecules bearing the -$CBrF_2$ moiety with aldehydes in the presence of Cr(II) ions (Scheme 30). In the first step, a series of (*E*)- or (*Z*)-β-fluoroallyl alcohols were prepared which were in turn converted into azides. In the next step, the -N_3 group was reduced to the –NH_2 group using triphenylphosphine. The amines were then protected with the –Boc moiety, and subsequently the -OH group was oxidized to carboxylic acids using acidic solution of chromium(VI) oxide and the –Boc protecting group was removed. Fluoroalkene dipeptides were obtained in yields ranging from 27% when R^2=CH_2OPMB and 69% when R^2=*i*-Bu (Scheme 30, **112a-d**) [22].



Scheme 30 The synthesis of peptidomimetics with fluoroolefinic moiety.

At the beginning of 2023, a new work of Wang appeared where a Cu-catalyzed enantioselective fluoroalkenylation of imino esters was presented. This reaction proceeds under mild contidions in the presence of the chiral ligand i-Pr-Phosferrox. Ethyl 5-phenyl-3,4-dihydro-2H-pyrrole-2-carboxylate (**113**) underwent a nucleophilic addition with gem-difluoroalkenes **114** and this protocol lead to form (*E*)-tetrasubstituted monofluoroalkenes predominantly in good yields (43-80%) and excellent enantioselectivities (ee>98%) [69].



Scheme 31. Enantioselective copper-catalyzed synthesis of monofluoroalkenes.

2.3. Peptidomimetics

Peptides are polymers made up of amino acids bonded with amide group -CONH-. Oligomers of amino acids which are composed of up to 30 to 50 monomer building blocks are named as peptides. "Protein" term is preferred for any members of this polymer that exists above this limit [70]. Peptide moiety is barely flexible. Therefore, each amino acid can take on several conformations. Because of this, proteins and peptides are very flexible and can adopt multiple spatial configurations.

Peptidomimetics are chemical compounds whose essential elements "mimic" a natural protein or peptide in tridimensional space (Fig. 8 A, B) and they can produce the same effect in biological systems and moreover, they can retain the ability to interact with the desired targets. In natural peptides there are a lot of disadvantages which can be overcome by the replacement of a natural peptide with peptidomimetics, including poor bioavalability and susceptibility to rapid proteolysis. These properties often can be improved. Therefore, mimetics of proteins have great potential in drug synthesis and drug discovery [71].

Peptidomimetics are created by changing the parent peptides with the purpose of obtaining molecules which are more suitable for clinical development and are extensively used in medicinal chemistry [72].

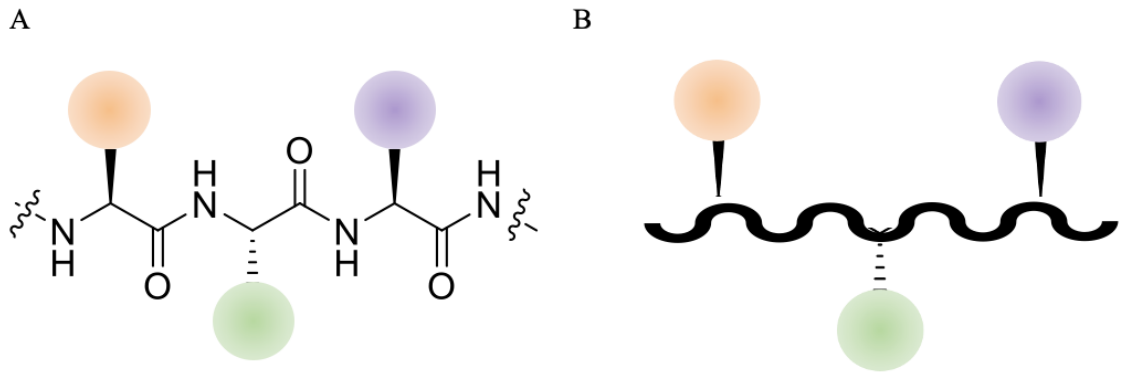


Figure 8. Graphic comparision of peptides (A) and peptidomimetics (B).

Incorporation of a fluorine atom to an organic compounds can change its physicochemical properties as well as reactivity. This modification is often used in the synthesis of drugs and biologically active compounds [73,74]. Fluorinated compounds which are biologically active are resistant to alkalis and acids, metabolic degradation and even oxidation, because the bond formed between carbon and fluorine atom is the strongest bond that a carbon atom can form with another chemical element (Tab. 4). The steric

and/or polar similarity of the fluorine atom to other atoms (or groups of atoms) causes that fluorinated organic compounds can be used as analogs of amino acids, amides, ethers or alcohols [75].

C-X bond			
Energy of dissociation [kcal/mol]	79	99	116

Table 4. Comparison of dissociation energy of carbon atom bonds with selected chemical elements [76].

In order to prevent protein hydrolysis, new compounds mimicking the functions and properties of the amide bond are sought. One of the examples of mimics in peptides is replacing the peptide bond with fluorovinyl group. It has been shown that introducing fluorine atom/s was being very good tolerated by the various proteins and peptides and does not cause steric perturbation in the structure of a parent peptide [77]. Moreover, the employment of ^{19}F-labeled chemical compounds represents interesting approach due to signal sensitivity of fluorine atom and lack of background signals on NMR spectra. Replacement of peptide bonds with non-hydrolyzable mimetic is one of the most promising approaches toward overcoming the major drawbacks of peptides [78] .

2.3.1. Biological activity of peptidomimetics with fluoroolefinic group

Organofluorine compounds, due to their biological properties and wide application in organic synthesis, occupy a significant place in the chemistry of drugs [79, 80].The fluorovinyl moiety is often present in biologically active molecules and has recently been an interesting part in the research and development of the pharmaceutical industry. Bioisosteres of peptide bonds are often used to change bioavailability due to changing their solubility in the lipid layer, resulting in faster transport through membranes [81, 82]. Moreover, they can reduce toxicity or modify the starting compound and subsequent changes in its metabolism.

In the literature, there are few examples of peptidomimetics where the peptide bond has been replaced with a fluorovinyl one. The first example which is worth mentioning presents the analogs of *N*-substituted glycylpyrrolidines and piperidines (Fig. 9, A). The second, is the fluoroolefinic proline derivatives (Fig. 9, B). It was reported that they can inhibit dipeptyl peptidases II and IV and are used as hypoglycemic agents in the treatment of type II diabetes [83].

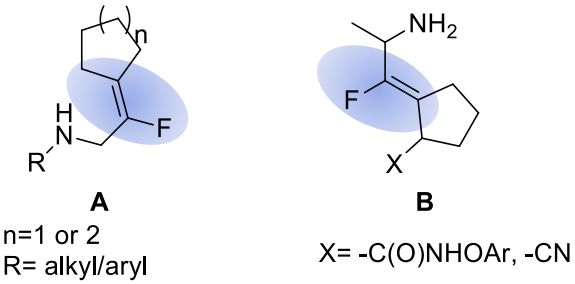


Figure 9. Fluoroolefin analogs of N-substituted glycylpyrrolidines and piperidines (A) and proline fluoroolefin derivative (B) .

Among the well-known fluoroolefin inhibitors we can distinguish a BMS-790052 inhibitor (Fig. 10, A) of the NS5A protein which blocks a different protein that is essential in the replication of the hepatitis C virus. Chang designed and synthesized a new HCV NS5A inhibitor, which is a peptidomimetic where the peptide bond is replaced with a fluoroolefin moiety (Fig. 10, B) and proved that the introduction of this group is associated with a very strong inhibitory effect on the HCV virus [21].

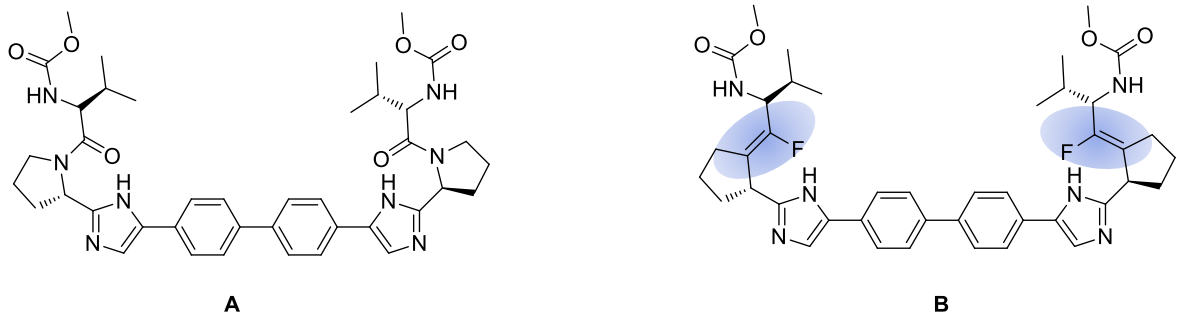


Figure 10. BMS-790052 inhibitor of the NS5A protein (A) and its peptidomimetic with a fluoroolefin moiety (B).

Another example of a biologically active fluorovinyl compound was synthesized by McCarthy's group [30]. It is called Tezacitabine [84] (Fig. 11) and acts as a bioprecursor of the ribonucleotide reductase inhibitor.

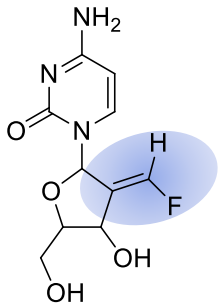
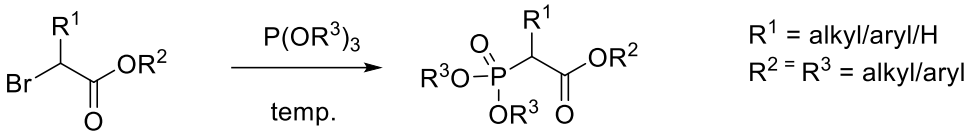


Figure 11. The structure of Tezacitabine.

2.4. Arbuzov reaction

The Michael-Arbuzov reaction is a useful method for the preparation of α-ketophosphonates from trialkyl or triaryl phosphites and acyl, alkyl or aryl halides. This reaction is very versatile and plays an important role for the formation of P-C bond to yield phosphonates, phosphinates and phosphine oxides (Scheme 32). Dialkylphosphonate, a substrate necessary to the Horner-Wadsworth-Emmons reaction, can be easily synthesized with the use of Michael-Arbuzov reaction, where triethyl phosphite reacts with α-bromoester at higher temperature (above 100ºC). [85]

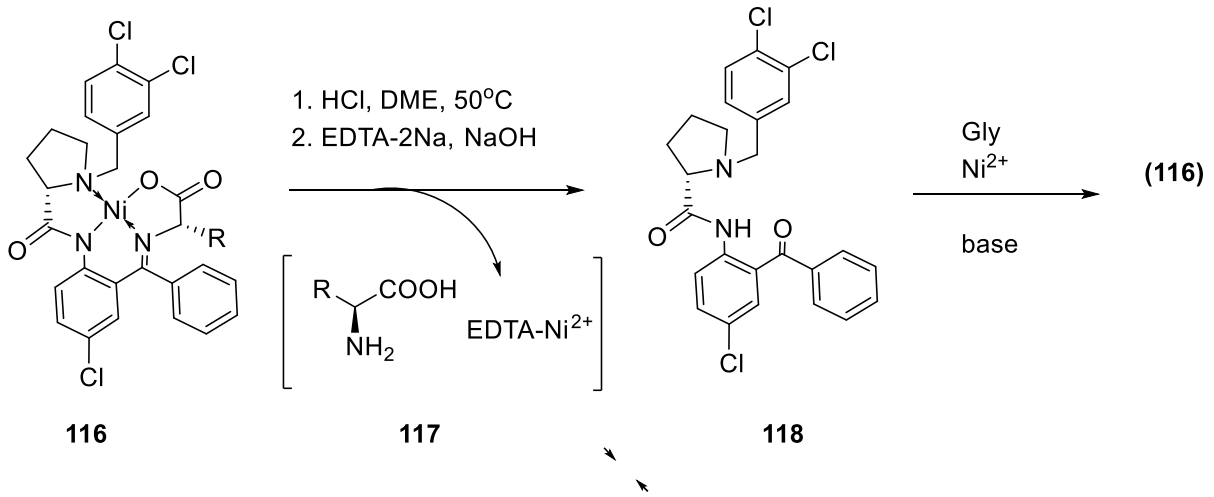


Scheme 32. The general scheme of the Michael-Arbuzov reaction.

2.5. Synthesis of fluorinated amino acids using chiral Ni(II) complexes

The history of Nickel(II) complexes used in the synthesis of amino acids dates back to the eighties of the twentieth century. Chiral Ni(II) complexes have been introduced as a facile, useful tools in the synthesis of different amino acids on a gram-scale. Using uniform approach and similar starting materials makes this method highly beneficial.

Using these complexes, many structurally diverse amino acids can be obtained. The advantages of this method undoubtedly include the high yields of the products created, high selectivity of the reaction and large scale. An additional advantage is the possibility of recovering and reusing the catalyst (Scheme 33) due to disassembling of the homologation products under acidic conditions. It allows to recover and reuse of the corresponding chiral ligands. The ligand **118** is precipitated and filtered and can react again with Gly, nickel(II) salt in the presence of a base to form the desired complex **116.**



*Scheme 33. Recovering of the Ni(II) catalyst **116**.*

Ni(II) complexes can be easily obtained in a gram-scale from (S)- or (R)-proline-containing ligands [86], [87]. The desired AAs can be obtained from the same starting material in only two steps. Alkylated Ni(II) complexes can be conventionally transformed to the derivatives of higher AAs via alkyl halide alkylation [88], Mannich [89], aldol [90], Michael [91], [92] addition reactions, as well as various multi-step transformations [93]. Homologation products can be disassembled under acidic conditions.

Nickel(II) complexes are constantly modified, most often in order to increase the diastereoselectivity of the alkylation reaction. For this purpose, various substituents are introduced on the benzyl group of the proline chiral auxiliary (Fig. 12). In general, some of these modified Ni(II)

complexes were found efficient for stereoselective (ee 95%) syntheses of α-methyl-α-amino acids. Some of the Ni(II) complex derivatives perform better when alkylated with allyl or aryl bromides. This topic is being explored all the time and currently the appropriate modified Ni(II) complex is being adapted to the specific homologation reaction.

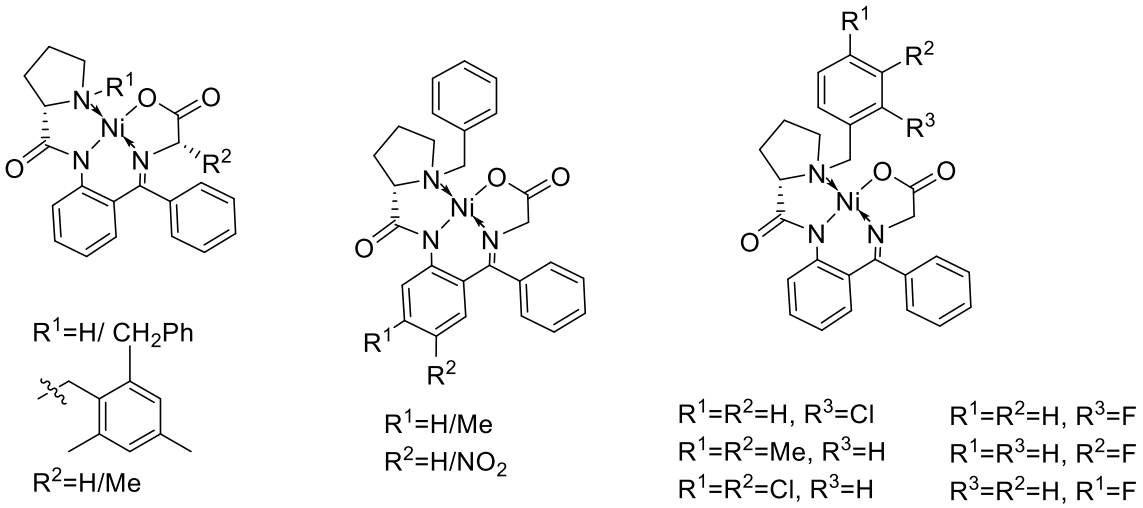


Figure 12. Examples of chiral nickel(II) complexes used in amino acid syntheses.

Nickel(II) complexes allow to obtain many alkyl and aryl amino acid derivatives [94–96] symmetrically R,R-disubstituted amino acids [88], as well as fluorinated derivatives (Tab. 5).

α,β-diamino acids are an important groups of compounds commonly found in nature as structural motifs of biologically relevant molecules. Fluorinated derivative of these chemicals, (2S,3S)-β-(trifluoromethyl)-α,β-diamino acid can be obtained through the Mannich addition to PMP-protected imine using nickel(II) complex (Tab. 5, entry 1) and subsequent disassembly of the nickel(II) complex under acidic conditions [89].

Another example is the large-scale (greater than 150g) synthesis of 2-amino-4,4,4-trifluorobutanoic acid (Tab.5, entry 2) which is a bioisostere of leucine moiety. This method starts with the preparation of the alkylated Ni(II) complex with CF_3–CH_2–I under basic conditions which in turn is disassembled and enantiomerically pure (>99% ee) 2-amino-4,4,4-trifluorobutanoic acid is formed, which can be converted to the *N*-Fmoc derivative [97].

Fluorinated amino acids (AAs) play very important role in the peptide chemistry. In 2022 Koksch group published a paper [98], which presented a strategy for the gram-scale synthesis of a series

of fluorinated AAs which were obtained in enantiopure form (99%ee). This work provides a unified synthesis of diverse range of eight aliphatic fluorinated AAs in only two steps. This AAs vary widely in degree of fluorination and steric structure (Tab. 5, entry 3-10).

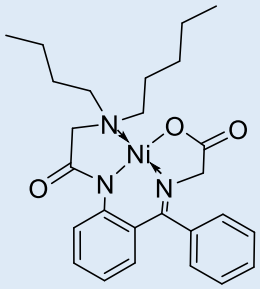
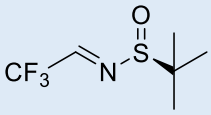
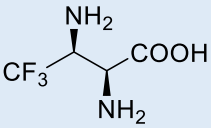
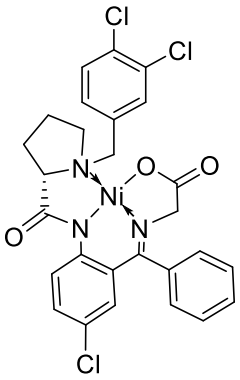
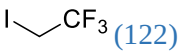
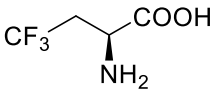
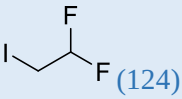
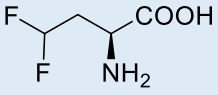
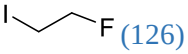
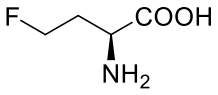
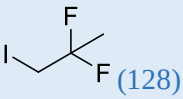
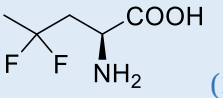
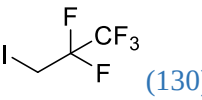
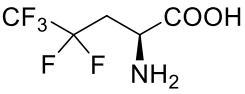
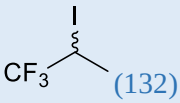
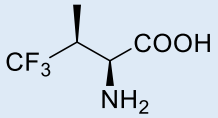
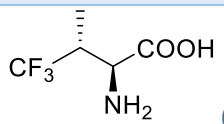
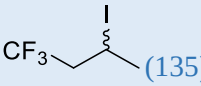
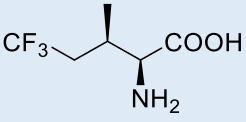
Glutamic acid (Glu) and its derivatives (glutamine, pyroglutamic acid) are important for biological activity of peptides. (*2S, 3R*) as well as (*2S,3S*)-3-trifluoromethylpyroglutamic acid (Tab.5, entry 11, 12 respectively) can be synthesized via simple, multi-gram synthesis between nickel(II) complex and ethyl crotonates [99,100]. This method includes Michael addition reaction and Ni(II) complex followed by acidic decomposition of the addiction products. Using the same method, two new fluorinated glutamic acids (*2S,3S,4R*)-26 as well as (*2S,3S*)-28 were synthesized [92].

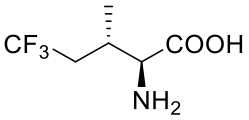
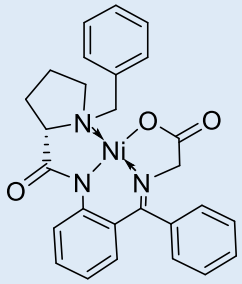
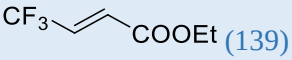
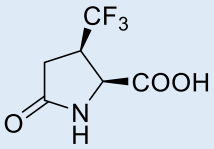
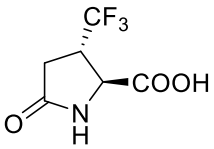
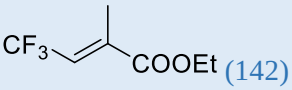
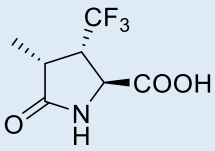
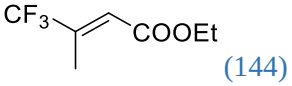
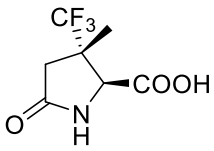
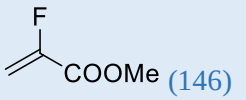
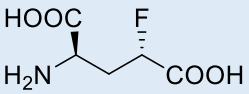
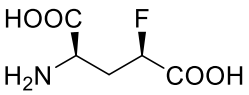
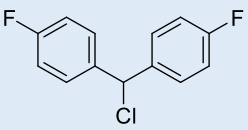
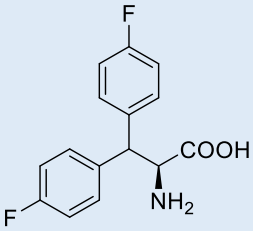
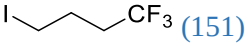
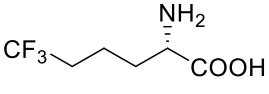
Another example is the synthesis of (*2S,4R*)- and (*2S,4S*)-F-glutamic acid (Tab. 5, entry 15,16). The fluorinated derivatives of proteinogenic amino acids play an important role in medicinal chemistry. Stereoselective fluorination of the amino acids can drastically change the characteristic of the parent structures influencing their chemical and biological activities. Glutamic acid is a central nervous system neutrotransmitter. The effect of introducing a fluorine atom into the C-4 position of glutamic acid was studied in terms of biosynthesis of folate poly-c-glutamate and the role of analogs of antifolates in the cytotoxic action. In one of the key steps, the C-terminal carboxyl group glutamate is activated by the enzyme before the peptide coupling. Therefore, the introduction of one or more fluorine atoms in the C-4 position of the side chain may interfere with biological processes [101].Therefore, Belokon and co-workers proposed a novel synthetic protocol for the preparation of the (*2S,4R*)- and (*2S,4S*)-FGlu via Michael reaction of methyl α-fluoroacrylate and Ni(II) complex and acidic disassembly of the final product [102].

A fluorinated analog of β,β-diphenylalanine plays an important role as an intermediates for the synthesis of DPP IV inhibitors. The diastereometically pure (S)-2-amino-3,3-bis-(4-fluorophenyl)propanoic acid (**150**) has been isolated in 95% yield. It was obtained due to the reaction of Ni(II) complex with $(4\text{-}FC_6H_4)_2CHCl$) and subsequent acidic hydrolysis [96,103].

Linear **ω**-(trifluoromethyl)-containing α-amino acids can also be obtained due to reaction with **ω** -trifluoromethyl alkyl iodides and nickel(II) complexes. At the end, the acidic hydrolysis was performed to afford enantiomerically pure 2-amino-6,6,6-trifluorohexanoic acid (**152**) in 96% yield. The yields of

the reaction decreased with the alkyl chain length because of the increasing electronic effect of the -CF_3 group. Methylated derivative of **152** was also diastereoselectively obatained in 75% yield using the same method with modified Ni(II) complex (Tab.5, entry 19) [104].

Nickel(II) complex	Entry	Second reactant	Fluorinated amino acid
 (119)	1	 (120)	 (121)
 **(116a)**	2	 (122)	 (123)
	3	 (124)	 (125)
	4	 (126)	 (127)
	5	 (128)	 (129)
	6	 (130)	 (131)
	7	 (132)	 (133)
	8		 (134)
	9	 (135)	 (136)

	10		 (137)
 **(138)**	11	 (139)	 (140)
	12		 (141)
	13	 (142)	 (143)
	14	 (144)	 (145)
	15	 (146)	 (147)
	16		 (148)
	17	 (149)	 (150)
	18	 (151)	 (152)

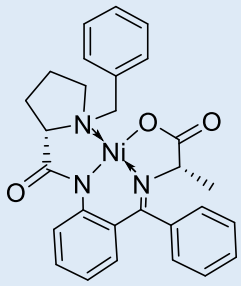
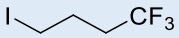
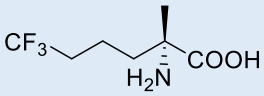
 **(153)**	19	 (154)	 (155)

Table 5. Fluorinated amino acid derivatives obtained from the reaction of different chiral Ni(II) complexes.

3. Objectives of the research

Fluorinated organic compounds are an attractive group of molecules that are widely used mainly in medicinal chemistry. Introducing a fluorine atom into molecules of known, biologically active structures can dramatically improve their properties. Literature reports indicate that the fluorovinyl bond is a mimetic of the peptide bond, which has a number of advantages. This moiety is less susceptible to proteolysis and can increases the bioavailability of the parent molecule. Therefore, it seems justified to undertake such a topic, aimed at obtaining new derivatives of this type.

The main goal of this work was to develop of the total, multi-step procedure leading to obtaining fluorovinyl derivatives of amino acids, which can be used as building blocks for further syntheses. The Horner-Wadsworth-Emmons (HWE) reaction was chosen as the reaction that enables the introduction of the fluorovinyl bond into the organic molecules. Literature data showed that phenylalanine derivatives were modified in this way, therefore this amino acid was selected for testing reaction an as a starting material. In the next step, if the developed method was successful, the plans were to use other L,α-amino acids and modify them in accordance with the developed procedure. Full spectroscopic characterization was also one of the key elements of the doctoral thesis.

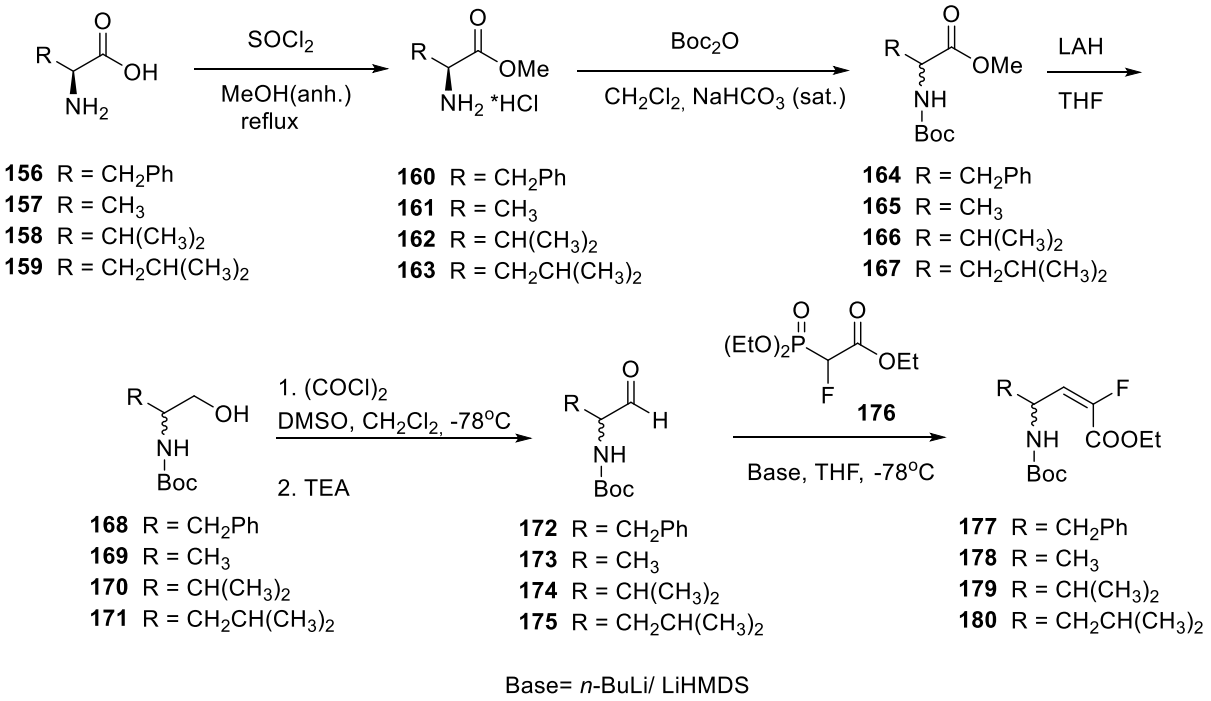
The aim of the work was also to optimize the appropriate crystallization conditions to be able to analyze their structure using X-ray. Synthetic research was also planned to be supplemented with mechanistic studies, which would facilitate a better understanding of the ongoing processes and changes.

An additional issue was to obtain fluorovinyl derivatives with a phosphonate group, as well as the use of the Shapiro reaction, which could be a tool for obtaining chemical compounds with a fluorovinyl group.

4. Results and discussion

4.1. Synthesis of fluoroolefinic amino acids

The synthesis path leading to the formation of fluorinated amino acid derivatives **177-180** has been developed (Scheme 34). Starting from pure L,α-amino acids, the carboxyl group was esterified, because the reduction of the ester group -COOR is easier to carry out than the reduction of the carboxylic moiety [105]. The amino group was then protected with a tert-butoxycarbonyl group. The next step included reduction and subsequent oxidation to the aldehyde group using the Swern conditions. The final reaction, crucial for this procedure, was the Horner-Wadsworth-Emmons reaction which allowed to obtain the desired fluorovinyl amino acids.



156 R = CH_2Ph
157 R = CH_3
158 R = $CH(CH_3)_2$
159 R = $CH_2CH(CH_3)_2$

160 R = CH_2Ph
161 R = CH_3
162 R = $CH(CH_3)_2$
163 R = $CH_2CH(CH_3)_2$

164 R = CH_2Ph
165 R = CH_3
166 R = $CH(CH_3)_2$
167 R = $CH_2CH(CH_3)_2$

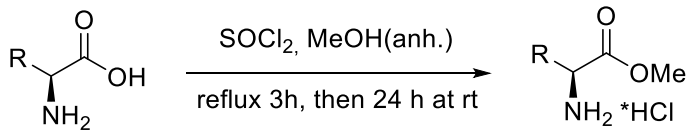
168 R = CH_2Ph
169 R = CH_3
170 R = $CH(CH_3)_2$
171 R = $CH_2CH(CH_3)_2$

172 R = CH_2Ph
173 R = CH_3
174 R = $CH(CH_3)_2$
175 R = $CH_2CH(CH_3)_2$

177 R = CH_2Ph
178 R = CH_3
179 R = $CH(CH_3)_2$
180 R = $CH_2CH(CH_3)_2$

Scheme 34. The synthetic pathway leading to the fluorovinyl amino acid derivatives.

4.1.1. Synthesis of methyl ester hydrochlorides



156 R = CH_2Ph
157 R = CH_3
158 R = $CH(CH_3)_2$
159 R = $CH_2CH(CH_3)_2$

160 R = CH_2Ph
161 R = CH_3
162 R = $CH(CH_3)_2$
163 R = $CH_2CH(CH_3)_2$

Scheme 35. General scheme of the esterification reaction.

Esterification was the first step of the synthesis and L-phenylalanine (**156)**, L-alanine (**157)**, L-valine (**158)**, L-leucine (**159)** were used as starting materials. The reaction was carried out in anhydrous methanol in the presence of thionyl chloride for 3 hours at reflux followed by 24 hours at room temperature, with monitoring the progress of the reaction by TLC [106]. The post-reaction mixtures were purified by repeated evaporation of methanol and then diethyl ether on a rotary evaporator. All methyl ester hydrochlorides were obtained as solids in excellent isolation yields (Tab. 6) and were fully spectroscopically characterized.

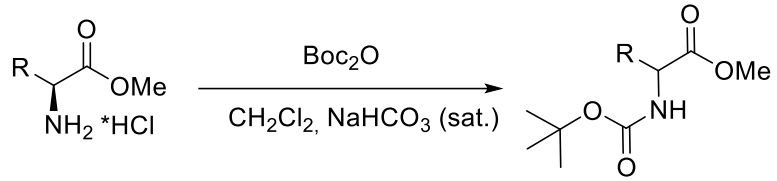
Number of product	Name of product	Reaction yield GC-MS [%]	Isolated yield [%]	Product characterization
160	*L*-phenylalanine methyl ester hydrochloride	100	99	White solid; **TLC**: $CHCl_3$:MeOH = 95:5 (v:v), Rf = 0.7
161	*L*-alanine methyl ester hydrochloride	Insoluble in solvents used in GC-MS analysis	99	Yellow solid **TLC**: $CHCl_3$:MeOH = 85:15 (v:v), Rf = 0.33
162	*L*-valine methyl ester hydrochloride	100	99	Pink solid, **TLC**: 50% SSE in AcOEt (v:v), Rf = 0.4,
163	*L*-leucine methyl ester hydrochloride	100	99	Yellow solid **TLC**: $CHCl_3$:MeOH = 1:9 (v:v), Rf = 0.8

*Table 6. Characterization of the methyl ester hydrochlorides **160-163.***

4.1.2. Synthesis of *N*-(*tert*-Butoxycarbonyl)-amino acid methyl esters

In the next step, the amino group had to be protected, to prevent any interference with the subsequent stages of the reaction. The benzyl group was first introduced as protecting group. Using benzyl bromide dibenzylation of the amino group occurred. However, using benzaldehyde in the presence of TEA and subsequent reduction with $NaBH_4$ allowed to attach one benzyl group to the $–NH_2$ moiety. In the future studies, prepared fluorovinyl amino acid derivatives may be used as potential biologically active compounds, for example as cathepsin C inhibitors, therefore for biological research, the amino group should be deprotected. Removing of the benzyl group takes place by reaction with hydrogen in the presence of a metal catalyst. Hydrogenation reaction however, may cause hydrogenation

of the double bond of the fluorovinyl moiety. Therefore, this idea has been abandoned, and the benzyl group was replaced with a *tert*-butoxycarbonyl group. The amino protection reaction with a *tert*-butoxycarbonyl group can be carried out with di-*tert*-butyl dicarbonate in the presence of a base. Two different reaction procedures were tested. In the first one, anhydrous triethylamine and inert conditions as well as water-free dichloromethane were used. In the second case, an aqueous solution of sodium hydrogen carbonate and reaction in a two-phase system, using dichloromethane as the second solvent were used. Both reactions gave similar results, so in large scale, due to the simplified conditions the procedure with $NaHCO_3$ as the base (Scheme 36) has been used.



160 R = CH_2Ph
161 R = CH_3
162 R = $CH(CH_3)_2$
163 R = $CH_2CH(CH_3)_2$

164 R = CH_2Ph
165 R = CH_3
166 R = $CH(CH_3)_2$
167 R = $CH_2CH(CH_3)_2$

Scheme 36. General scheme of the N-Boc protection of amine group.

The post-reaction mixture always consisted of the product and unreacted, excess of Boc_2O, which had to be separated each time using a chromatographic column. It has been tried to carry out these reactions using the equimolar amount of amino acid methyl ester hydrochlorides and Boc_2O, but despite increasing reaction time, the unreacted amino acid methyl ester was still present in the reaction mixture. Therefore this reaction should always be carried out with an excess of Boc_2O [107,108]. Fortunately, the removal of Boc_2O was possiblie by column chromatography with 98:2 hexane:ethyl acetate mixture (v:v) as an eluent. All products, *N*-Boc amino acid methyl esters, were obtained as colorless oils (Tab. 7).

Number of product	Name of product	Isolated yield [%]	Product characterization
164	*N*-Boc-phenylalanine methyl ester	95	Colourless liquid **TLC**: hexane:AcOEt = 6:1 (v:v), Rf = 0.85
165	*N*-Boc-alanine methyl ester	80	Colourless liquid **TLC**: hexane:AcOEt = 7:3 (v:v), Rf = 0.65
166	*N*-Boc-valine methyl ester	90	Colourless liquid **TLC**:hexane:AcOEt = 7:3 (v:v), Rf = 0.71
167	*N*-Boc-leucine methyl ester	89	Colourless liquid **TLC**: hexane:AcOEt = 9:1 (v:v) Rf = 0.25

Table 7. Characterization of the N-Boc amino acid methyl esters ***164-167.***

4.1.3. Synthesis of *N*-(*tert*-Butoxycarbonyl)-amino alcohols

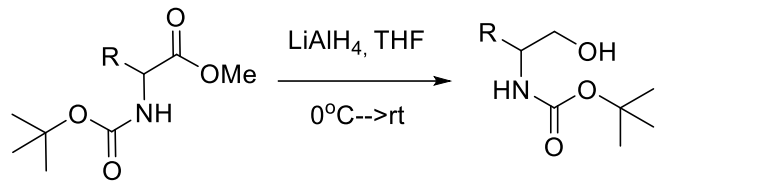
The developed synthetic path required the formation of an aminoalcohol at a certain stage, therefore, several attempts were made to reduce the carboxyl group.

The reduction of phenylalanine with lithium aluminum hydride [109] was used firstly and the conversion of the substrate (amino acid) was only 3% (confirmed by GC-MS analysis). This reaction was repeated several times using three different sources of lithium aluminium hydrides. The reaction time was also extended; however, the maximum yield of the product was 20%.

The literature also describes the possibility to reduce amino acids and their derivatives with sodium borohydride in the presence of iodine [110]. Many attempts were made to reduce phenylalanine using the above-mentioned reagents, but the reaction did not occur. A boiling THF has been used and $NaBH_4$ remained undissolved throughout the reaction.

Moreover, a third idea was a reaction of *N*-boc-phenylalanine with a borane dimethyl sulfide complex (BH_3*SMe_2) but this reaction also failed.

Therefore, the carboxylic group was first transformed into an ester group and then subjected to a reduction reaction with LAH (Scheme 37).



164 R = CH_2Ph
165 R = CH_3
166 R = $CH(CH_3)_2$
167 R = $CH_2CH(CH_3)_2$

168 R = CH_2Ph
169 R = CH_3
170 R = $CH(CH_3)_2$
171 R = $CH_2CH(CH_3)_2$

Scheme 37. General scheme of the reduction of N-Boc-amino acid methyl esters.

The reduction of *N*-Boc methyl esters **164-167** of used amino acids were carried out and, in each case, excellent results were obtained (100% conversion of substrates). The post-reaction mixtures were analyzed by GC-MS and each time some contamination has been seen [111].

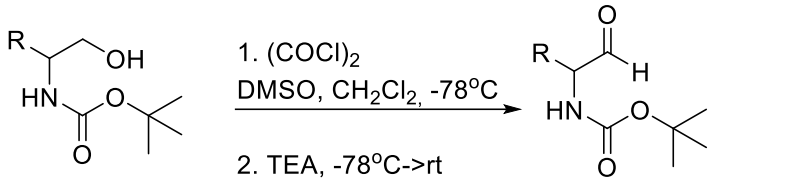
Another problem was the low isolated yield of the products after extraction in the water/diethyl ether system. Unfortunately, most of the product remains in the aqueous phase, despite the use of other solvents instead of diethyl ether (ethyl acetate, chloroform, dichloromethane). Finally, the crude product was used directly after filtration and evaporation of the solvent for further stages. All the obtained alcohols were solids (Tab. 8).

Number of product	Name of product	Isolated yield [%]	Product characterization
168	*N*-Boc-phenylalaninol	87	White solid **TLC**: hexane:AcOEt = 1:1, (v:v), Rf = 0.6
169	*N*-Boc-alaninol	67	White solid **TLC**: Hexane:AcOEt = 1:1, (v:v), Rf = 0.55
170	*N*-Boc-valinol	63	Pinkish solid **TLC**: Hexane:AcOEt = 3:7(v:v), Rf = 0.70
171	*N*-Boc-leucinol	70	White solid, **TLC**: Hexane:AcOEt = 1:1 (v:v), Rf = 0.54

*Table 8. Characterization of the N-Boc amino alcohols **168-171***

4.1.4. Synthesis of *N*-(*tert*-Butoxycarbonyl)-amino aldehydes. Swern oxidation

The next step of the synthesis was Swern oxidation. Generally, this reaction allows to oxidize primary or secondary alcohols to the aldehydes or ketones using oxalyl chloride, dimethyl sulfoxide, and an organic base [112–114].The reaction is known for its mild conditions and wide functional group tolerance. Dimethyl sulfide, one of the by-products has a strong odor even at low concentrations and carbon monoxide (another by -product formed) are highly toxic, so the reaction must be carried out in a fume hood. The reaction should be kept below -60 °C to avoid side reactions [115,116].



168 R = CH_2Ph
169 R = CH_3
170 R = $CH(CH_3)_2$
171 R = $CH_2CH(CH_3)_2$

172 R = CH_2Ph
173 R = CH_3
174 R = $CH(CH_3)_2$
175 R = $CH_2CH(CH_3)_2$

Scheme 38. General scheme of the Swern oxidation of N-Boc amino alcohols.

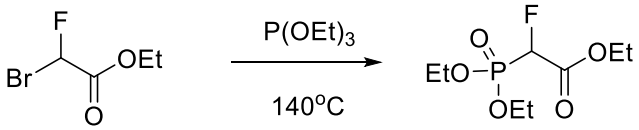
Firstly, *N*-Boc-phenylalaninol was first used to test the reaction conditions. The reaction was carried out under conditions described in the literature [117,118] (Scheme 38), however the product formation was only around 50% yield (GC-MS analysis). The reaction was carefully analyzed in order to increase the reaction yield. Crucial issue is that dimethyl sulfoxide is quite hygroscopic and quickly absorbs water from the atmosphere. The reaction conditions were changed, e.g. the reaction time was extended, but still mixture of the product and unreacted alcohol were obtained in reaction mixture. Finally, it is known that oxalyl chloride, while stored, tends to hydrolyze to oxalic acid. This results in less Me_2SCl^+ agent being formed than expected upon activation of DMSO by oxalyl chloride. This led to the conclusion that more base equivalents had to be added before the deprotonation-oxidation step. This is why, the number of triethylamine equivalents was changed from recommended 4 to 6 and the desired aldehyde was synthesized with 100% alcohol conversion. The final aldehydes **172-175** were used in the next step without further purification (Tab. 9).

Number of product	Name of product	Isolated yield [%]	Product characterization
172	*N*-Boc-phenylalaninal	78	White solid **TLC**: hexane:EtOAc = 7:3, (v:v), Rf = 0,55
173	*N*-Boc-alaninal	80	White solid **TLC**: hexane:EtOAc = 8:2, (v:v), Rf = 0.28
174	*N*-Boc-valinal	57	White solid **TLC**: hexane:EtOAc = 8:2, (v:v), Rf = 0.52
175	*N*-Boc-leucinal	80	White solid **TLC**: hexane:EtOAc = 8:2, (v:v), Rf = 0.56

*Table 9. Characterization of the N-Boc amino aldehydes **172-175**.*

4.1.5. Arbuzov reaction

A reaction between ethyl bromofluoroacetate and triethyl phosphite was carried out (Scheme 39) to get access to the triethyl 2-fluoro-2-phosphonoacetate (**176**) which is necessary as a reagent for the HWE reaction.



184 **176**

Scheme 39. Scheme of the Arbuzov reaction of trietyhyl phosphite and ethyl bromofluoroacetate.

To avoid removing excess of triethyl phosphite, the reaction with stoichiometric number of substrates was carried out but unfortunately, the GC-MS chromatogram showed unreacted substrates (Fig. 13). It means that an excess of triethyl phosphite has been necessary, as it most likely that it shifts the reaction equilibrium toward products.

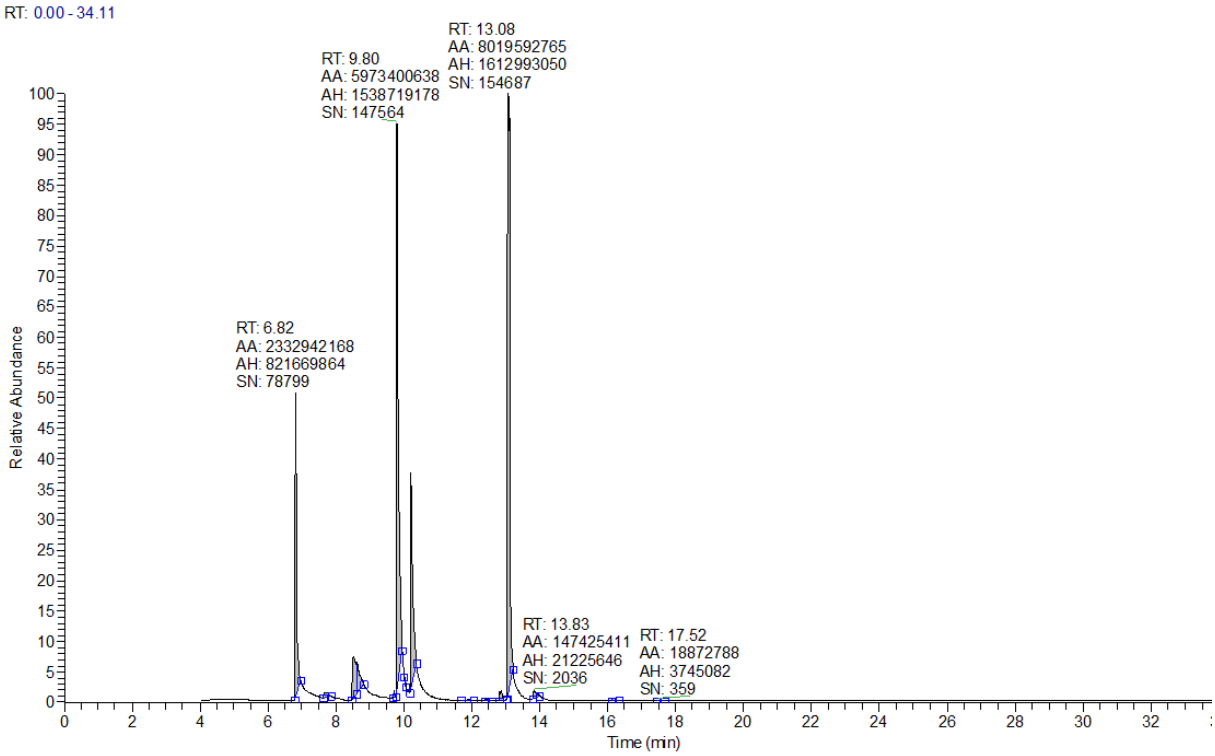


Figure 13. GC-MS chromatogram of the mixture after the Arbuzov reaction, in which an equimolar mixture of substrates was used. 6.82 min- ethyl bromofluoroacetate, 9.80 min- triethyl phosphite, 13.08 min- reaction product.

The excess of triethyl phosphite could not have been separated using simple distillation (as suggested in the literature [119]) or using column chromatography (hexane:ethyl acetate mixture as eluent). The reaction product is quite polar, so it was purified on a column chromatography with chloroform : methanol as eluting phase. Finally, the pure product was isolated.

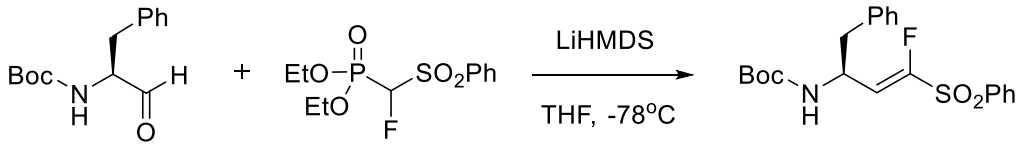
Moreover, to improve the reaction yield and shorten the reaction time performed this reaction has been performed under the microwave radiation (150ºC, 100W). Nevertheless, the reaction yield was lower (49%) in comparision to 80% yield of the standard reaction at 140ºC. An attempt was also made to carry out this reaction using a cheaper substrate (ethyl chlorofluoroacetate instead ethyl bromofluoroacetate), but the yield of the reaction was low (29%).

4.1.6. Horner-Wadsworth-Emmons reaction

After successfull preparation of the aldehydes **172-175**, the HWE reaction was the final and the most challenging step, since the fluorovinyl moiety is introduced at this stage. Different conditions are reported in the literature to carry out this reaction. The literature analysis shows, that the most frequently chosen solvent was THF or DME, and the base was *n*-BuLi, LiHMDS or LDA. The reaction was always carried out under inert conditions, using anhydrous solvents and temperature -78ºC. First, an appriopriate phosphonate solution was prepared followed by the addition of the base at a temperature below zero °C. A carbanion was generated which then reacts with the added aldehyde [31,120,121].

4.1.6.1. HWE reaction of the *N*-(*tert*-Butoxycarbonyl)-phenylalaninal

The first reaction tests were done with the use of phenylalanine derivative as a starting material. The reaction conditions were based on the Steert and co-workers work [53],who used the same substrate, *N*-Boc-phenylalaninal (**172**) and subjected it to the HWE reaction (Scheme 40). They obtained selectively the vinyl sulfone **186** in 52% isolated yield as a single *E*-isomer.



172 **185** **186**

*Scheme 40. Scheme of the HWE reaction of N-Boc-phenylalaninal and sulfone **185**.*

Therefore, in the case of phenylalanine derivative **172**, THF was used as a solvent and two different bases were tested: LiHMDS (generated in situ from *n*-BuLi and HMDS) and *n*-BuLi. Fortunately, these conditions allowed to obtain the desired product with fluorovinyl moiety (Fig. 14).

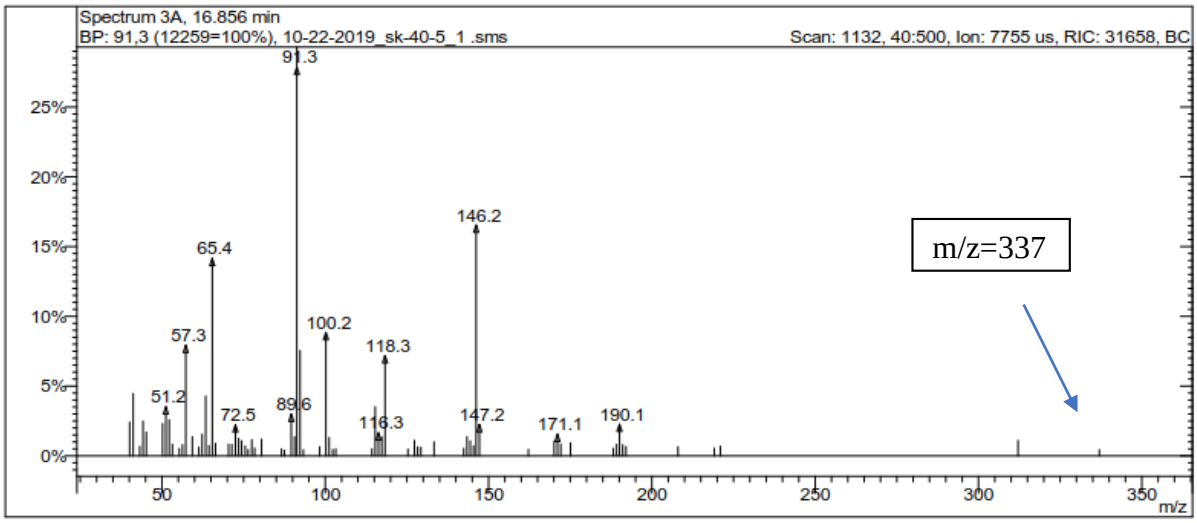
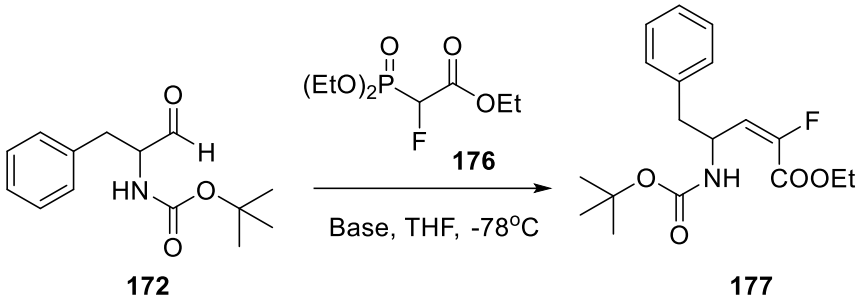


Figure 14. MS spectrum of the reaction mixture HWE reaction of N-Boc-phenylalaninal.

The reaction yields were higer when *n*-buthyllithium was used (34% isolated yield compared to 23%) (Tab. 10). Another solvent was also tested, which was DME, but it did not change the overall yield of the reaction.

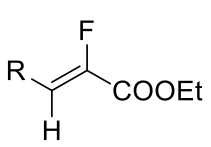


Base	Yield of 177 (GC-MS) [%]	Isolated yield of 177 [%]
n-BuLi	92	34
LiHMDS	73	23

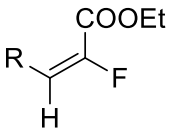
Table 10. Comparision of the yield of products after HWE reaction.

It was the first attempt to synthesize and purify such fluorovinyl derivative and such results implies that some optimization of the purification conditions was necessary.

After obtaining the desired product, it was necessary to analyze the structure and find out whether the *E* or *Z* isomer was formed. In the literature, the coupling constants of the hydrogen and fluorine atoms at the double bond have anakytical value to describe H-F geometry at this bond. It can be concluded that the coupling constant for the *Z*-isomer is more than 30 Hz and for the *E*-isomer it is less, around 20 Hz [122] (Tab. 11).



(a)
Z-isomer



(b)
E-isomer

(187) R = CH_3
(188) R = CH_2CH_3
(189) R = $CH(CH_3)_2$
(190) R = $C(CH_3)_3$
(191) R = CH=CHPh

Structure symbol	J_{H-F} [Hz]		Structure symbol	J_{H-F} [Hz]
187a	33.0		187b	21.2
188a	33.3		188b	21.5
189a	33.7		189b	21.9
190a	38.7		190b	28.4
191a	31.08		191b	19.34

Table 11. The literature data of the vinylic H-F coupling constants (J_{H-F}) of Z and E α,β-unsaturated esters (a) and (b)

^{19}F NMR spectrum showed a doublet with a coupling constant equal to 20.4 Hz (Fig. 15), which would suggest the formation of *E* isomer. Moreover, the HWE reaction is known as a reaction leading mainly to the *E*-product.

William R. Dolbier's Book [123] also presents the H-F coupling constants of fluorovinyl systems and, for example, the three-bond H-F coupling constant of *E*-1-fluoropentene is 18.6 Hz, and for the *Z* isomer it is 44 Hz.

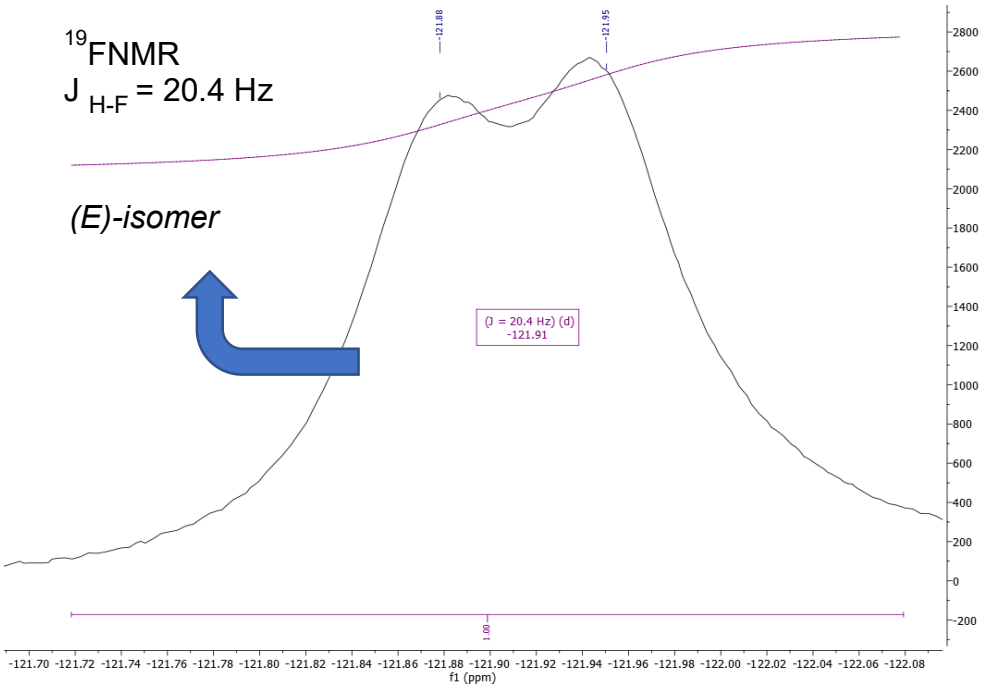


*Figure 15. ^{19}F NMR spectrum of the product **177**.*

First fluorovinyl amino acid derivative **177** was successfully synthesized and its structure has been confirmed by NMR spectroscopic analysis. The same synthetic approach was applied to modified alanine, valine as well as leucine.

4.1.6.2. HWE reaction of the *N*-(*tert*-Butoxycarbonyl)-alaninal

In case of alanine derivative **178**, directly after the Horner-Wadsworth-Emmons reaction, two spots were present on the TLC plate. The ^{19}F NMR spectrum also revealed two doublets with different coupling constants- the first one had a value of 18.38 Hz, and the second 6.28 Hz. Upon longer standing, a crystal was formed. The ^{19}F NMR spectrum was repeated and only one doublet with coupling constant equal to 6.28 Hz was observed. The crystal structure was determined by X-Ray analysis (Fig. 16) , which confirmed that the linear derivative **178** was fully converted into the cyclic form of the lactam **182** (Scheme 41).

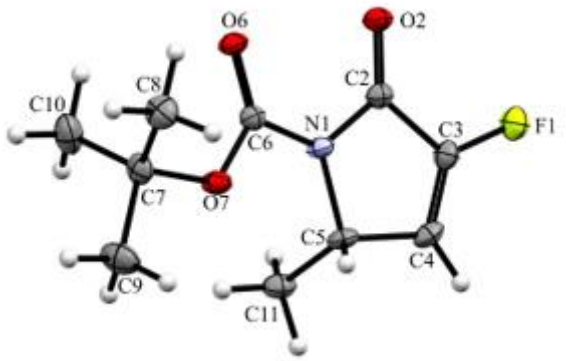
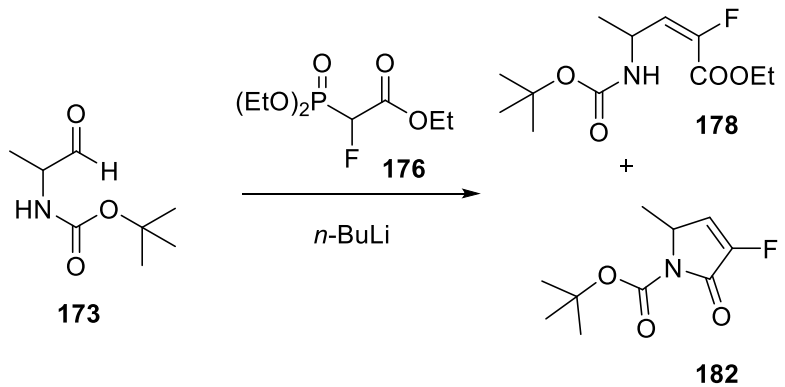


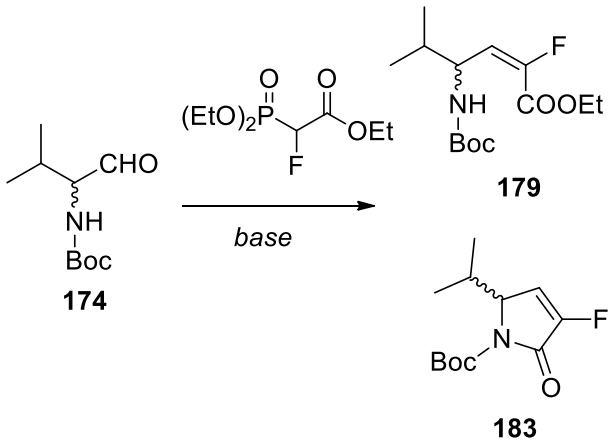
*Figure 16. Assymetric unit of the crystal structure of the lactam **182**.*



*Scheme 41. The HWE reation of N-Boc-alaninal (**173**).*

4.1.6.3. HWE reaction of the *N-(tert*-Butoxycarbonyl)-valinal

In the case of the HWE reaction with the valine derivative **174**, two spots were also observed on the TLC plate directly after the reaction corresponding to a mixture of both forms (linear and cyclic) with the coupling constants J_{H-F} = 6.58 Hz for cyclic derivative and J_{H-F} = 21.16 Hz for the linear one. Given this background, further analysis of the cyclization process was done as well as different crystallization methods to get the pure lactams. In order to obtain the cyclic fluorovinyl derivative of valine crystallization was carried out, using solvents such as: methanol, ethyl acetate, diethyl ether, dichloromethane, as well as mixtures of hexane: ethyl acetate and chloroform: methanol in various, variable proportions. None of these methods yielded satisfactory results. For this reason, the influence of the base on the ratio of the created fluorivinyl derivatives was examined. When *n*-BuLi was used, directly after the reaction the mixture of olefine **179** and cyclic form **183** were obtained in a ratio of 1:0.32. When LiHMDS was used, the ratio **179 : 183** was equal to 0.55:1 (Tab. 12). Fortunately, it was possible to determine the crystal structure of valine analogue (Fig. 17).



Base	179: 183*
***n*-BuLi**	1:0.32 (more linear form)
LiHMDS	0.55:1 (more cyclic form)

*Determined on the ^{19}F NMR analysis.

Table 12. Comparision of the obtained product's ratio depending on the base used.

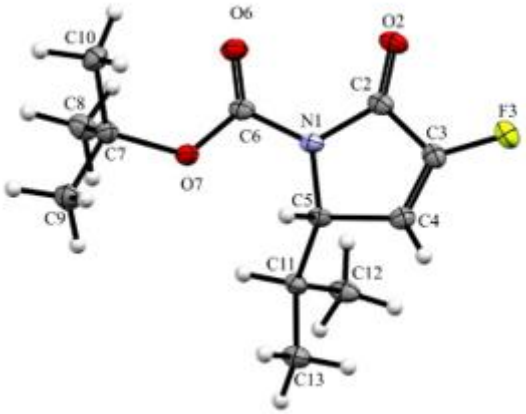
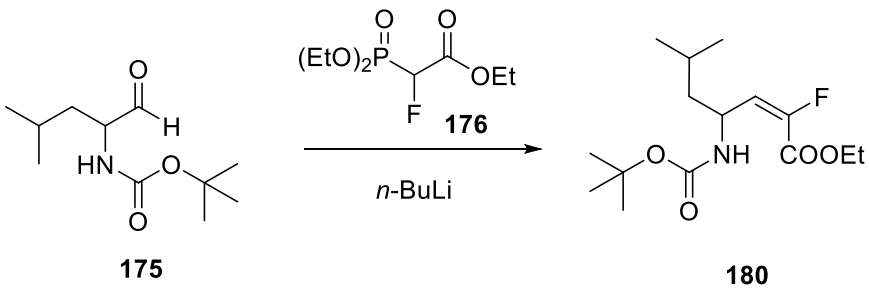


*Figure 17. Assymetric unit of the crystal structure of the lactam **183**.*

4.1.6.4. HWE reaction of the *N*-(*tert*-Butoxycarbonyl)-leucinal

L,α-leucine was subjected to a similar modification and finally, after the HWE reaction, only a linear fluorovinyl derivative was obtained (Scheme 42). Despite many attempts of crystallization, no cyclic derivative has been obtained so far.



Scheme 42. The HWE reaction of N-Boc-Leucinal.

The formation of a linear product was confirmed by ^{1}H, ^{13}C and ^{19}F NMR analysis. A doublet with a couplig constant J=20.89 Hz was obtained in the ^{19}F NMR spectrum (Fig. 18).

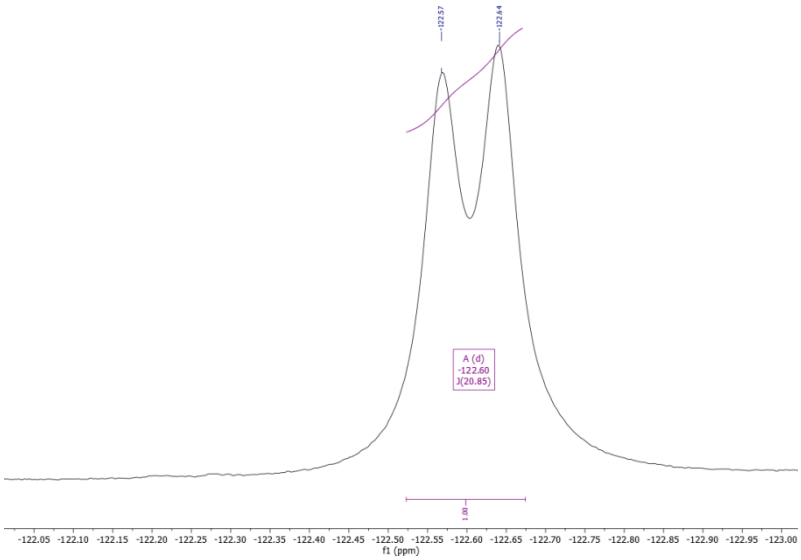
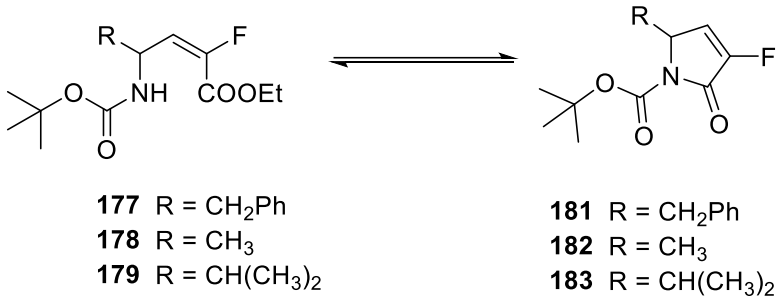


*Figure 18. ^{19}F NMR spectrum of product **180**: δ -122.60 (J = 20.89 Hz).*

4.2. Crystal structures



177 R = CH_2Ph
178 R = CH_3
179 R = $CH(CH_3)_2$

181 R = CH_2Ph
182 R = CH_3
183 R = $CH(CH_3)_2$

*Scheme 43. Cyclization of the linear products **177-179** to lactams **181-183.***

After obtaining cyclic fluorovinyl derivatives of alanine and valine, many attempts were made to obtain fluorovinyl derivatives of phenylalanine (Scheme 43). Immediately after the HWE reaction, only a linear product was obtained. Crystallization by slow evaportion of the solvent did not lead to the formation of the cyclic form. Therefore, one of the most modern methods of obtaining crystals, namely crystallization by sublimation (Fig. 19) was applied. This method is a useful method for growing crystals from vapor. For this purpose, a small amount of a linear phenylalanine derivative was placed in a special vessel under vacuum and heated it until the product was completely sublimated on a specially cooled surface. Unfortunately, this method also failed to obtain crystals.

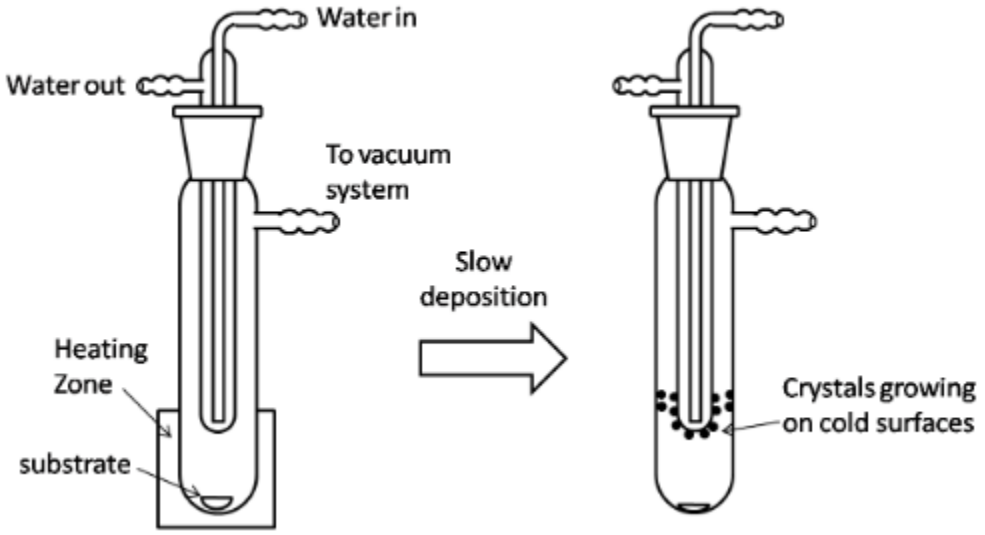


Figure 19. Crystallization by sublimation apparatus.

Finally, diffusion crystallization with two solvents was tested. The sample was dissolved in methanol and placed it in a vial with diethyl ether. The system was closed and left. This method was successful and practically 100% cyclic derivative of phenylalanine was obtained. A cyclization reaction

of the linear derivative **177** took place and a lactam crystal **181** was obtained. After some time, it turned out that the linear derivative of phenylalanine is also able to cyclize itself (Fig. 20), but it takes much longer time (several weeks) than in the case of alanine and valine derivative, where the cyclic analogue is formed immediately after the reaction. It can be concluded that steric hindrance of the amino acid side chain affects the rate of cyclization.

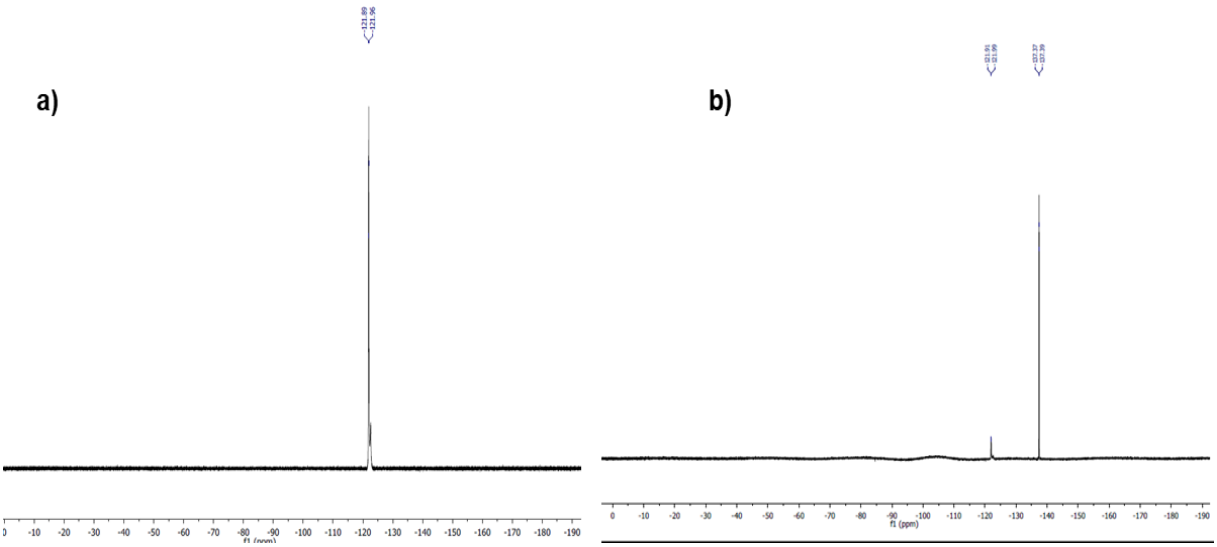


*Figure 20. Comparision of ^{19}F NMR spectra of a sample measured directly after HWE reaction (a) and after two weeks crystallization process (ratio: **177/181** = 0.3:1) (b). Signals: (a) δ = –121.90 ppm (J = 20.28 Hz) (b) δ = –121.89 ppm (J = 20.28 Hz), –137.39 ppm (J = 6.01 Hz).*

Although the benzyl group is too large for cyclization to occur, the hydrogen bonds formed between the molecules cause that such an arrangement favors the stabilization of the crystal structure (Fig. 21).

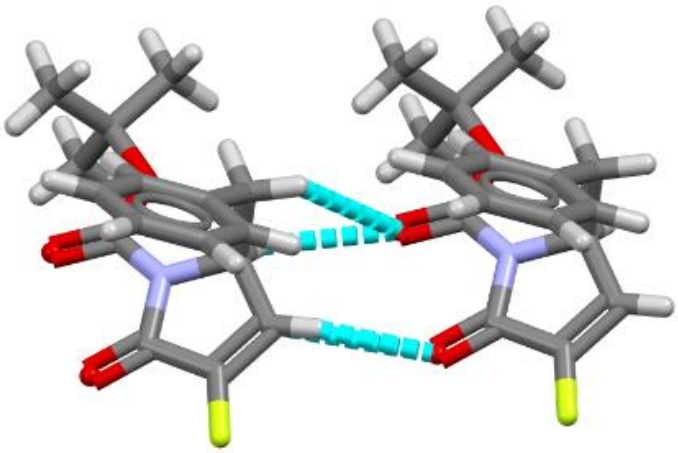


Figure 21. Hydrogen bonding between phenylalanine fluorovinyl derivative molecules.

Interestingly, all the obtained lactams **181-182** as well as **183** were not enantiomerically pure (Fig. 22), even though pure *L*-amino acids were used as starting material. This finding was confirmed by X-ray analysis, which showed the presence of both enantiomers in the crystal lattice (Fig. 23).

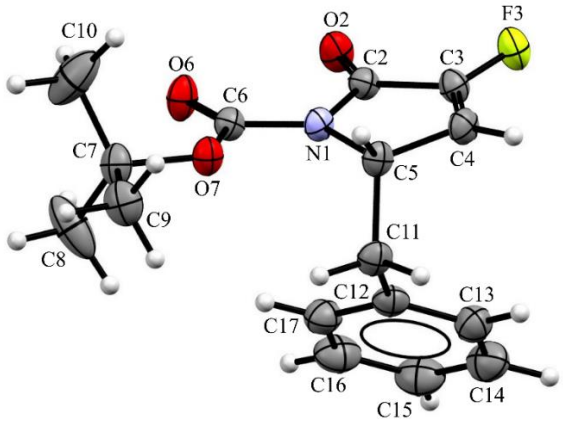


*Figure 22. Assymetric unit of the crystal structure of the lactam **181**.*

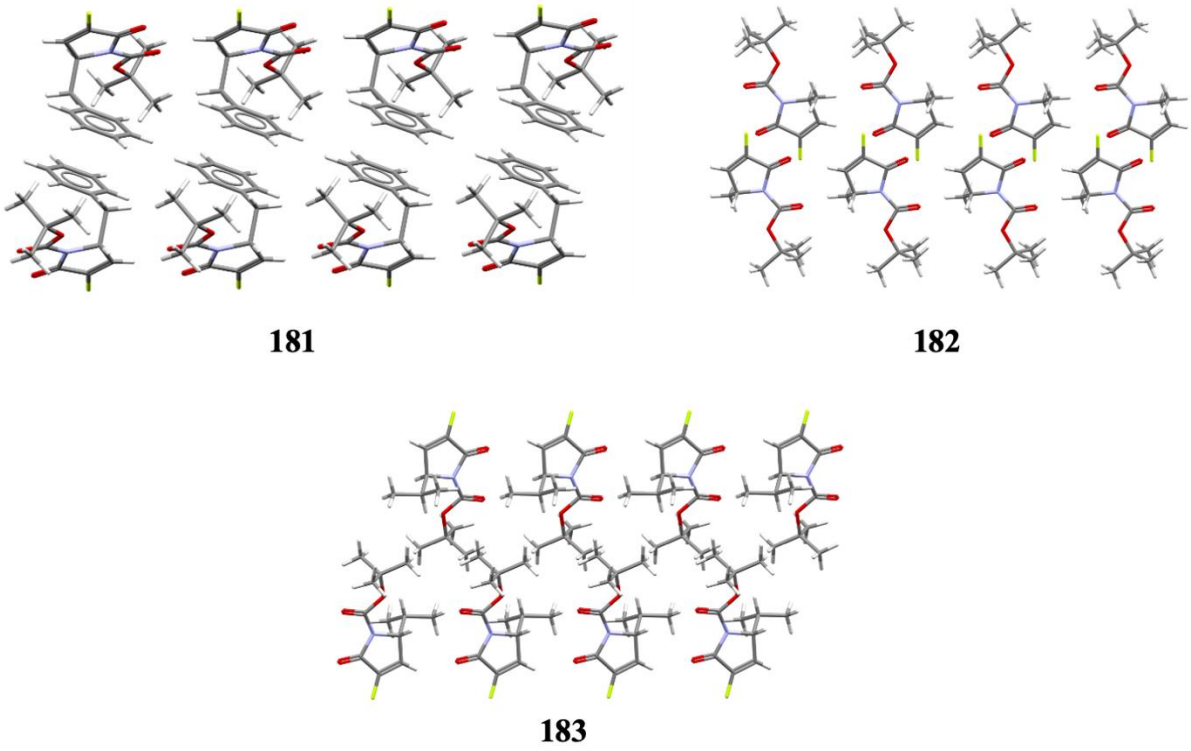


*Figure 23. Fragments of the crystal lattices of lactams **181,182,183**, showing the relative position of the molecules with R (lower) and S (upper) configuration running along the [010] direction.*

The crystals of the linear form of fluorovinyl amino acid derivatives were not obtained. The isolated crystals always correspond to the lactams. An analogous cyclization reaction has been described for aspartic acid derivatives [124]. However, considering phenylalanine as the parent structure, such phenomenon has not been described so far. There are reports of linear, non-fluorinated derivatives

of phenylalanine, but none of them show a tendency to cyclization or are produced by other synthetic routes [125–131]. However, there are reports of a tendency to cyclization of fluorinated derivatives of various amino acids such as valine, glycine, proline, but never at this reaction stage [132] . To date, only cyclic derivatives of these amino acids without the Boc protecting group have been described in the literature [133].

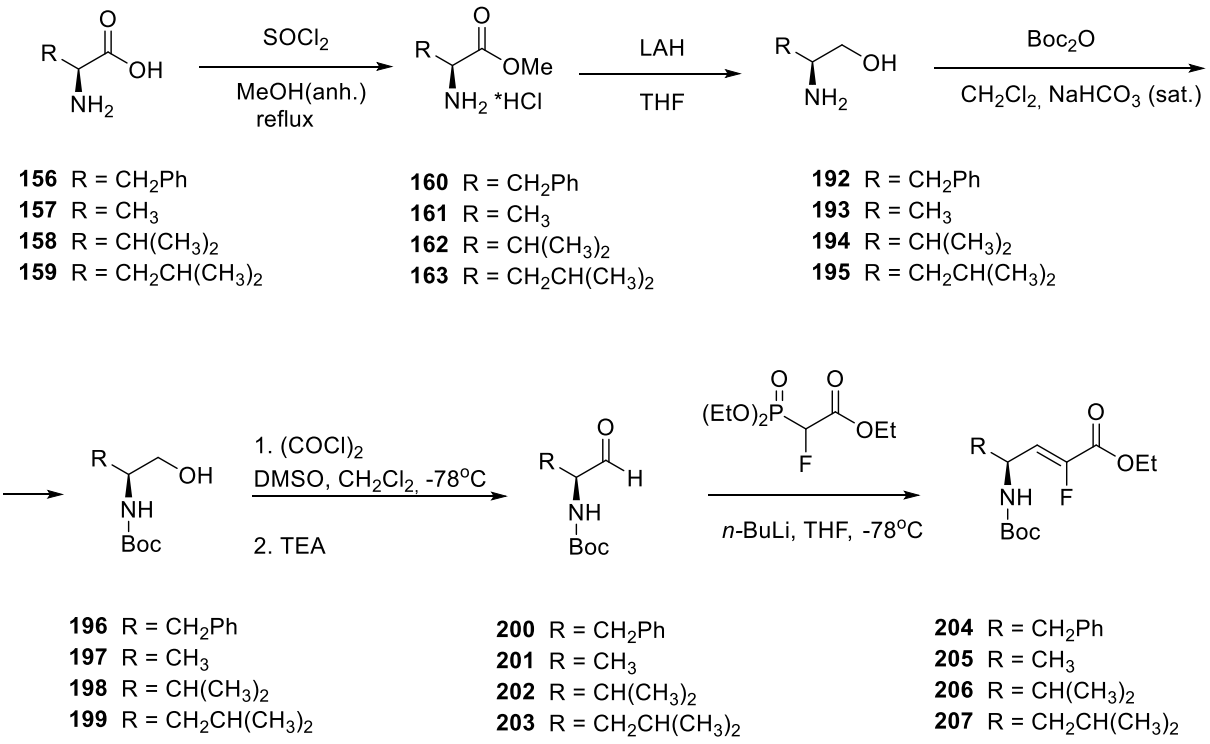
4.3. Stereoselective synthesis of fluoroolefinic amino acids

After finding the formed lactams as racemic mixtures, the possible racemization path was studied. The enantiomeric purity of the starting amino acids, amino acid methyl esters, alcohol, aldehyde as well as fluorovinyl derivatives was veryfied (Tab. 13). The crystal structure of the *Boc*-protected phenylalanine methyl ester (**164**) was also obtained, which was previously deposited in the CCDC database by Oguz et al. [134] as a mixture of both enantiomers (preliminary measurement of the crystal showed the same parameters of the unit cell to those already published in the CCDC crystalligraphy database). This confirmed assumptions that racemization takes place at this stage during Boc-protection of the $-NH_2$ group, probably via enolization. The *N*-Boc-alaninol (**168**), *N*-Boc-alaninal (**172**) and all the cyclic fluorovinylic lactams were obtained as a racemate (Tab. 13).

Amino acid or amino acid derivative	X-ray analysis results
Amino acid	S-enantiomer
Amino acid methyl ester	S-enantiomer
***N*-Boc amino acid methyl ester**	racemate
***N*-Boc alcohol**	racemate
***N*-Boc aldehyde**	racemate
Fluorovinyl amino acid derivative	racemate

Table 13. Configuration of the products obtained in each step of the synthetic procedure confirmed by the X-ray analysis of the crystal structures.

Therefore, it was decided to slightly modify the synthetic procedure (Scheme 44) and the obtained amino acid methyl esters were firstly reduced to remove the carbonyl group, and then the obtained amino alcohols **192-195** were reacted with Boc_2O. Further steps remained unchanged.



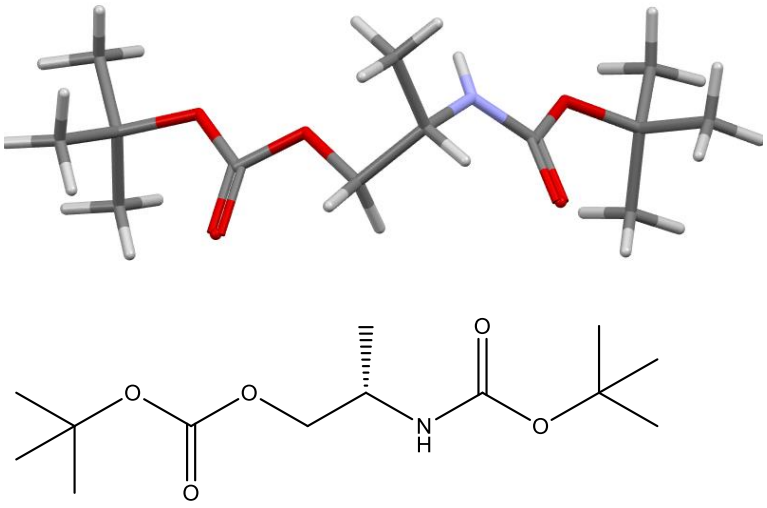
Scheme 44. Synthesis path proceeding without racemization.

4.3.1. Synthesis of amino alcohols

In the case of alanine, the alcohol formed after reduction of alanine methyl ester hydrochloride is very polar, which was not conducive to post-reaction processing - this product could not be extracted into any organic solvent which is immiscible with water. The product also did not elute off the chromatographic column, even using reverse phase silica gel. Therefore, the product was used in the next step without further puritication.

4.3.2. *Boc*-protection of amino alcohols

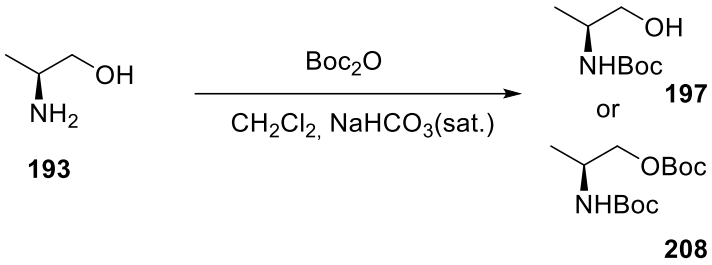
The X-ray examination of the (S)-*N*-Boc-phenylalaninol (**196)** confirmed that it is a pure enantiomer. So far, protecting reactions using Boc_2O have been carried out with an excess of this reagent (according to literature procedures the excess of Boc_2O shifts the equilibrium towards the products) [135]. There are however reports in which the synthesis of *N*-Boc-alaninol was carried out with equimolar amount of Boc_2O and the alcohol **193** [136,137]. Therefore, it was decided to carry out such reaction to avoid separation of excess Boc_2O on the column chromatography. The expected product was obtained and was directly used for the next step. The effect of the amount of base used on the course of this chemical reaction was also investigated. Interestingly, in one case alaninol with both: the amino and the hydroxyl group protected was obtained. To determine in which case such product is formed, six reactions were conducted in which the amounts of the base and Boc_2O were changed (Tab. 14). In the case of reaction number 2 (stoichiometric amount of Boc_2O and a small amount of base), both the $-NH_2$ group as well as -OH were protected. The structure was crystallographically confirmed (Fig. 24). In the rest of the trials (Tab. 14, entry 1 and 3-6) only the amino group was protected.



Space group $P2_12_12_1$

*Figure 24. Assymetric unit of the crystal structure of tert-butyl (S)-(1-((tert-butoxycarbonyl)oxy)propan-2-yl)carbamate (**208**).*

The table below shows the conditions of the test reactions. (S)-2-aminopropan-1-ol (**193**) was used (0.1717g) in each of 1-6 reactions and the following amounts of Boc_2O and base were also used (Tab. 14).



	1	2	3	4	5	6
Boc_2O (mass)	Deficiency (0.3g)	Stoichiometric number of moles of Boc_2O and alcohol **193** (0.5g)	Excess (0.8g)	Deficiency (0.3g)	Stoichiometric number of moles of Boc_2O and alcohol **193** (0.5g)	Excess (0.8g)
$NaHCO_3$ saturated solution (volume)	Deficiency (0.80ml)	Deficiency (0.80ml)	Deficiency (0.80ml)	Excess (1.20ml)	Excess (1.20ml)	Excess 1.20ml)

*Table 14. Boc-protection conditions of the (S)-2-aminopropan-1-ol (**193**).*

Interestingly, such compound does not appear in the literature at all, nor is it in the Cambridge Stuctural Database [138]. Two cases of protecting the -OH group with a *tert*-butoxycarbonyl group were found. The first reaction takes place in protic ionic liquids [139]. The second paper showed alcohols reacted with Boc_2O in the presence of $Mg(ClO_4)_2$ and even under these conditions it was not possible to block the -OH group (the ethers were obtained instead) [140]. Therefore, obtaining such structure **208** under the proposed conditions is surprising and unprecedented.

4.3.3. Horner-Wadsworth-Emmons reaction

To confirm that the developed path is stereoselective, an X-ray analysis of the phenyalalanine fluorovinyl derivative obtained by this method was carried out and the study showed that the cyclic form of one S-enantiomer was formed (Fig. 25)

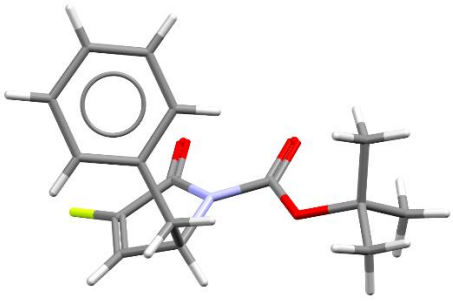
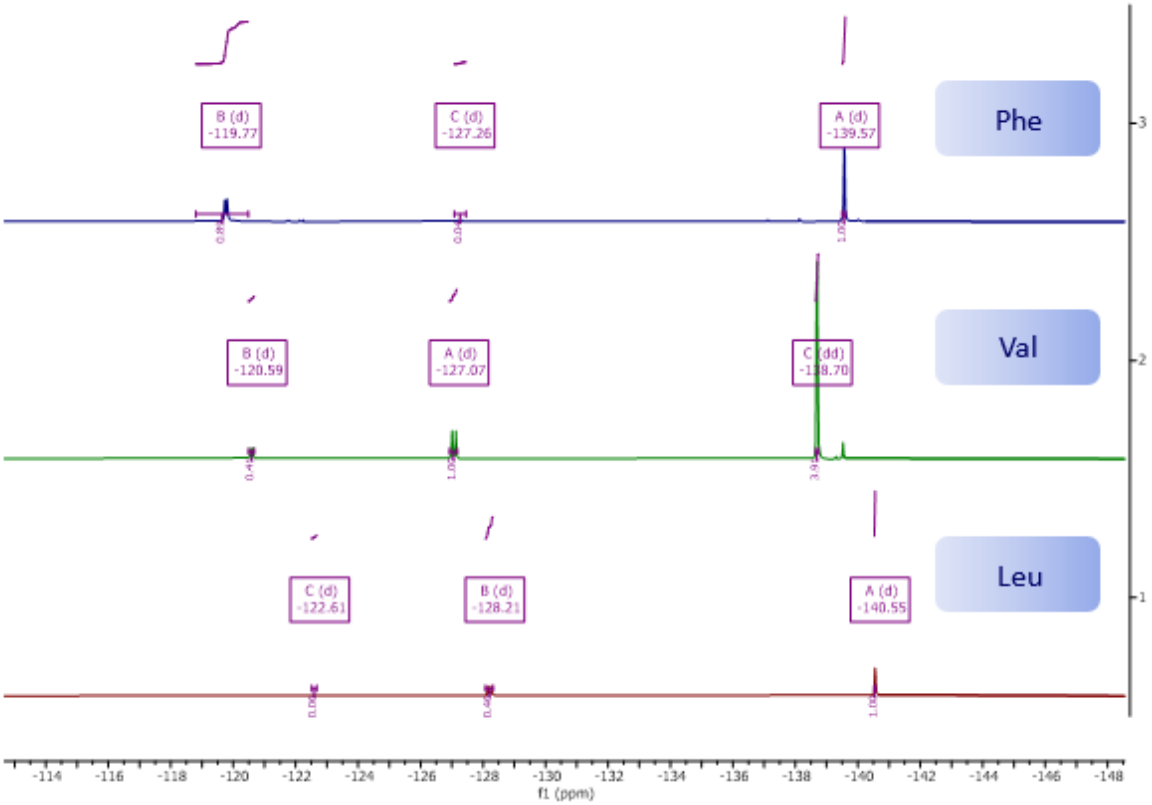


*Figure 25. Assymetric unit of the crystal structure of the S-enantiomer of lactam **181.***

HWE reactions were carried out for *S*-amino acid derivatives (Phe, Val, Leu) - it turned out that using pure enantiomers, the HWE reaction leads to different products - mainly cyclic forms and a small amount of linear *Z* isomers (which has not happened before) (Tab. 15) .



Fluorovinyl amino acid derivative of:	(*E*)-isomer linear form	(*Z*)-isomer linear form	Cyclic form (lactam)
Phe	-119.77, d, J = 21.0 Hz	-127.26 ppm, d, J = 33.8 Hz	-139.57 ppm, d, J = 6.4 Hz
Val	-120.59 ppm, d, J = 22.0	-127.07 ppm, d, J = 34.3 Hz	-138.70 ppm, d, J = 6.6 Hz
Leu	-122.61 ppm, d, J = 21.3 Hz	-128.21 ppm, d, J = 34.1 Hz	-140.55 ppm, d, J = 6.4 Hz

Table 15. *Comparision of the* ^{19}F *NMR signals of samples after HWE reaction.*

The ratio of the isomers obtained after the HWE reaction was different depending on the amino acid derivative used, however, in each case a mixture of both form has been obtained (Tab. 16).

Fluorovinyl amino acid derivative of:	Isomer E:isomer Z: cyclic form ratio determined on the ^{19}F NMR spectrum
Phe	0.75:0.01:1
Val	0.10:0.23:1
Leu	0.04:0.52:1

Table 16. Ratio of the Isomer E:isomer Z: cyclic form of the fluorovinyl derivatives of Phe, Val and Leu.

Moreover, *N*-Boc-leucinal was obtained using above-mentioned procedure and its structure was examined using the X-Ray method. This aldehyde turned out to be a racemic mixture again. Therefore, the search for reasons for second racemization began. Two references that summarize the stereochemistry of various oxidation methods, including the Swern oxidation, may have helped.

The work of Myers and coworkers [141] showed how the side chain of an amino acid derivative affects the degree of racemization in the Swern reaction in the presence of triethylamine as a base. The conclusion was that the Swern reaction causes racemization to varying degrees depending on the nature of the side chain group of the *N*-protected amino alcohol. Such observations explain why in some cases of the studies discussed in this doctoral dissertation complete racemization was observed (like for leucine derivative), and in some cases one of the enantiomers predominated.

Moreover, there are some literature reports showing how the base influences the stereochemistry of the Swern oxidation [142]. For example, the use of diisopropylethylamine as base produces less racemization, but the rate of oxidation can be unacceptably slow and in epimerization-prone cases products of high ee are not obtained.

Therefore, it was decided to use different oxidation method to obtain pure enantiomers of the desired products. According to the literature, the Dess-Martin oxidation afford the products of more than 90% ee [141].

Thus the procedure which would lead in any case (irrespective of the structure, protecting groups, side chains of the aldehyde used) to small degree of racemization would be the same as above (Scheme 44), but replacing the Swern oxidation with a Dess-Martin oxidation.

4.4. S-cis and *s-trans* conformations of fluorovinyl amino acid derivatives

During the analysis of the ^{19}F NMR spectra after the HWE reaction, it was remarkable that for each obtained fluorovinyl linear derivative, one large doublet was observed and always a smaller doublet with a similar value of the coupling constant was present next to it (Fig. 26). Smaller signals occurred as singlets when the sample was measured in $CDCl_3$ and as doublets when the sample was measured in DMSO-d^6. Such situation took place for the obtained *E* and *Z* isomers.

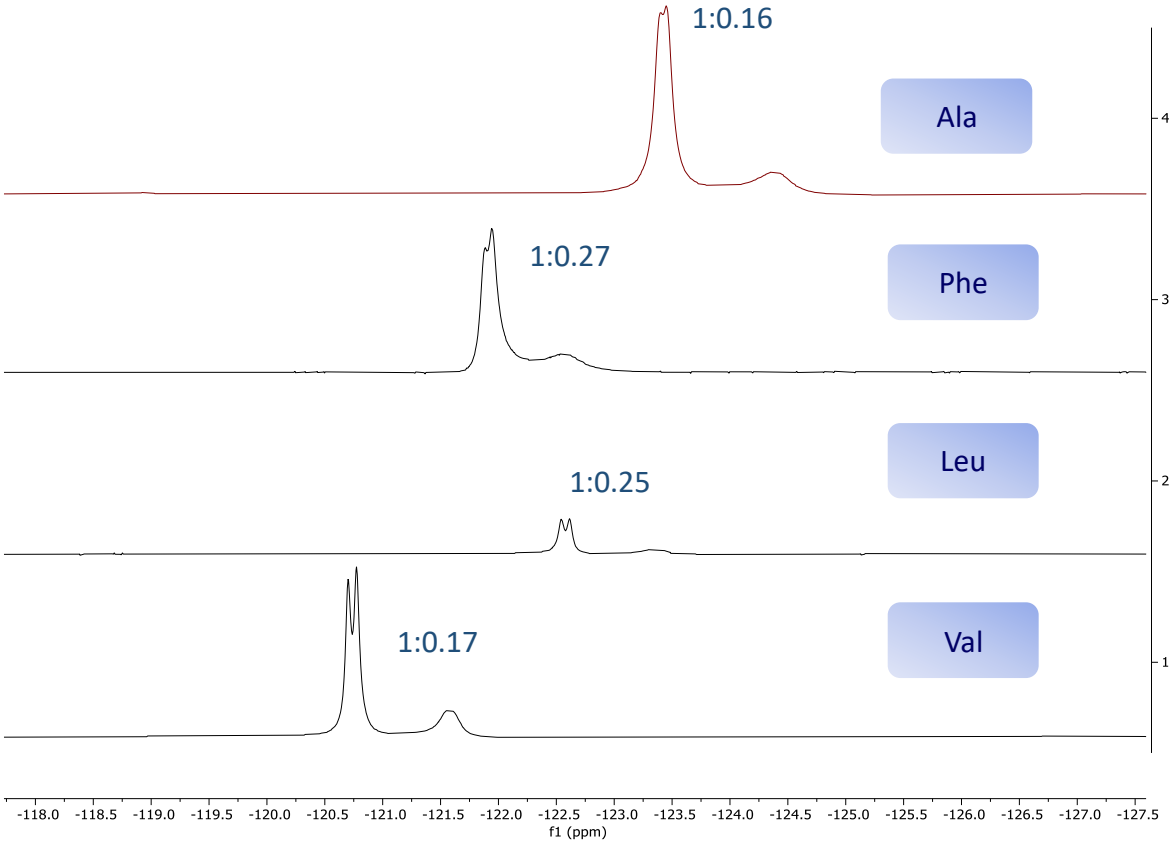


Figure 26. Comparision of the ^{19}F NMR spectra of linear fluorovinyl derivative of (from the top) alanine, phenylalanine, leucine, and valine.

Therefore, the spectra in different temperatures for the fluorovinyl derivative of phenylalanine were measured. The first sample was measured at room temperature and ^{19}F NMR spectrum showed two doublets side by side at a ratio of 1:0.27 and at the second measurement at +60ºC where only one doublet was left (Fig. 27).

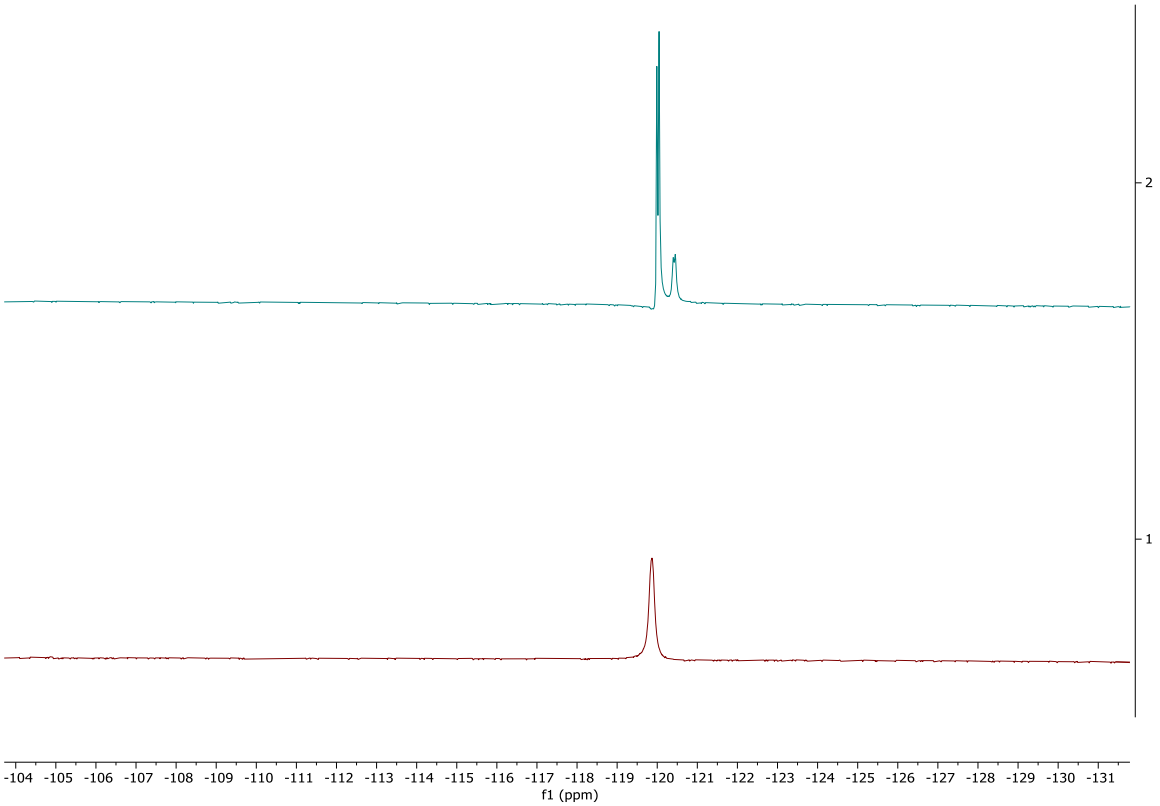
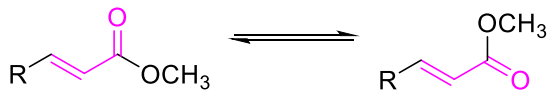


*Figure 27. Comparision of the ^{19}F NMR spectra of fluorovinyl phenylalanine derivative **177** measured at room temperature (upper spectrum) and at 60°C (lower spectrum).*

The explanation of this fact is based on the the publication that describes the possibility of isomerism in α,β-unsaturated esters [143]. These compounds can exist as *s-cis* or *s-trans* isomers (Scheme 45). Moreover, the tert-butoxycarbonyl (Boc) group can also form rotamers, what is another alternative to explain this phenomenon.



s-cis *s-trans*

Scheme 45. s-cis (on the left) and s-trans (on the right) possible isomers of α,β-unsaturated esters.

The research revealed that, depending on the temperature or state of matter, these compounds can occur as *s-cis* or *s-trans* conformation in variable amounts, which is also confirmed by the above-presented ^{19}F NMR spectra measured at different temperatures.

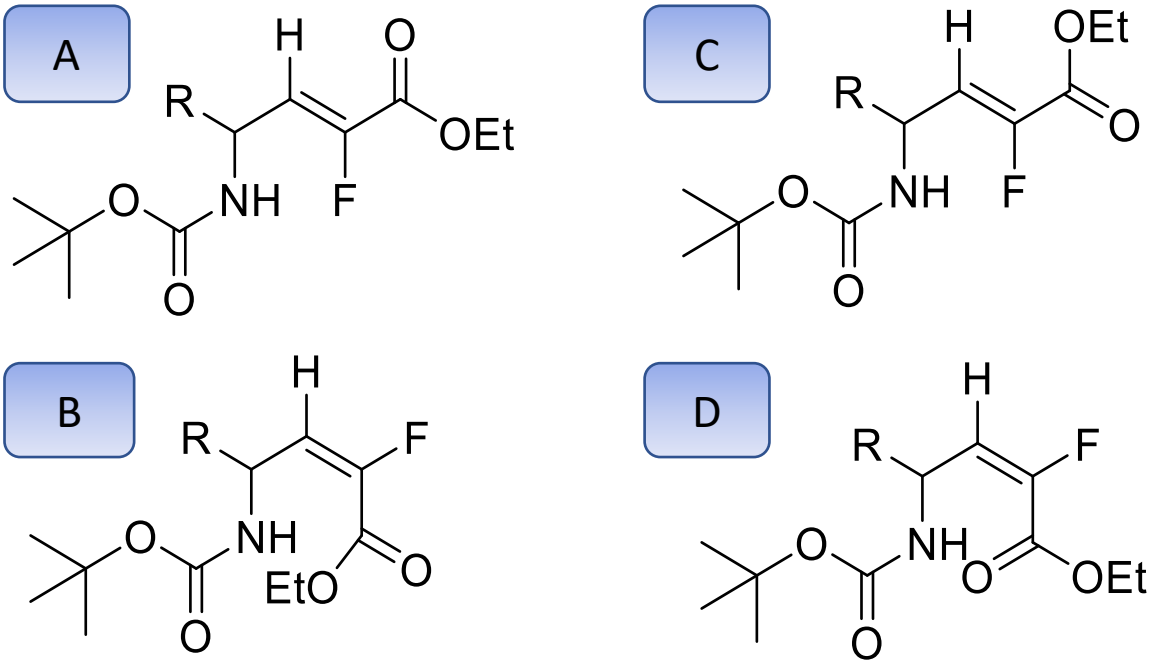


Figure 28. S-cis (A,D) and s-trans (B,C) conformations of E- (C,D) and Z-isomers (A,B) of fluorovinyl amino acid derivatives ***177-180.***

In the case of the *E* isomer (Fig. 28), it can be assumed that the larger doublet in the ^{19}F NMR spectrum comes from the *s-cis* conformation, due to the hydrogen bonds that can form between the -NH group and the carbonyl group of the ester moiety (Fig. 29). Such a phenomenon has already been described in the literature, where a six-membered ring was formed due to hydrogen bonds [144]. In the case of the fluorovinyl derivatives studied in this work, a seven-membered ring would be formed.

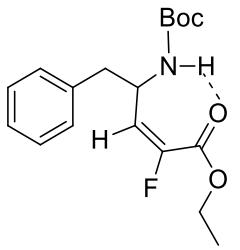
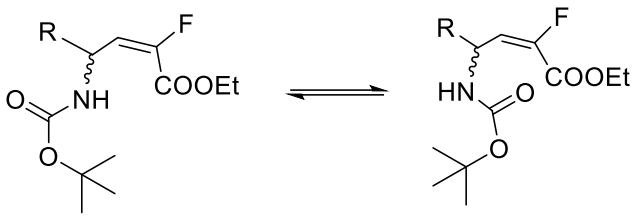


Figure 29. Possible hydrogen bonding between –NH and carbonyl oxygen atom in s-cis E-isomer of phenylalanine fluorovinyl derivative ***177.***

On the other side, nitrogen atom undergoes a phenomenon which is called ‘inversion’ giving two rotamers (Fig. 30) [145,146]. In this case, the –COO- part on the Boc group gets flipped over leaving the rest of the molecule in its orginial place. However, the ability to form romaters by the Boc group cannot affect the number and value of signals in the ^{19}F NMR spectrum, therefore the phenomenon of the

occurrence of two signals very close to each other in the ^{19}F NMR spectrum with high probability may be caused by possible *s-cis* and *s-trans* conformations within the group fluorovinyl as described above.

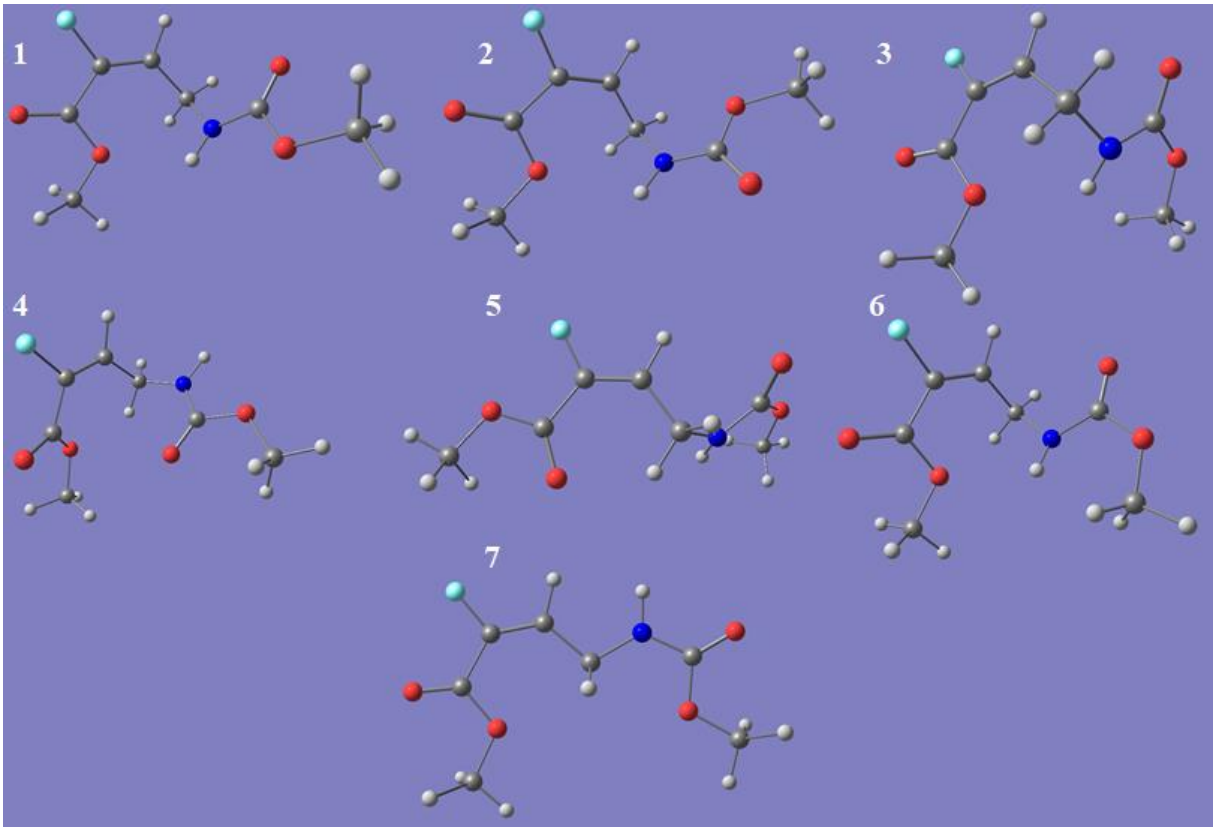


R=CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

Figure 30. Boc group's possible rotamers.

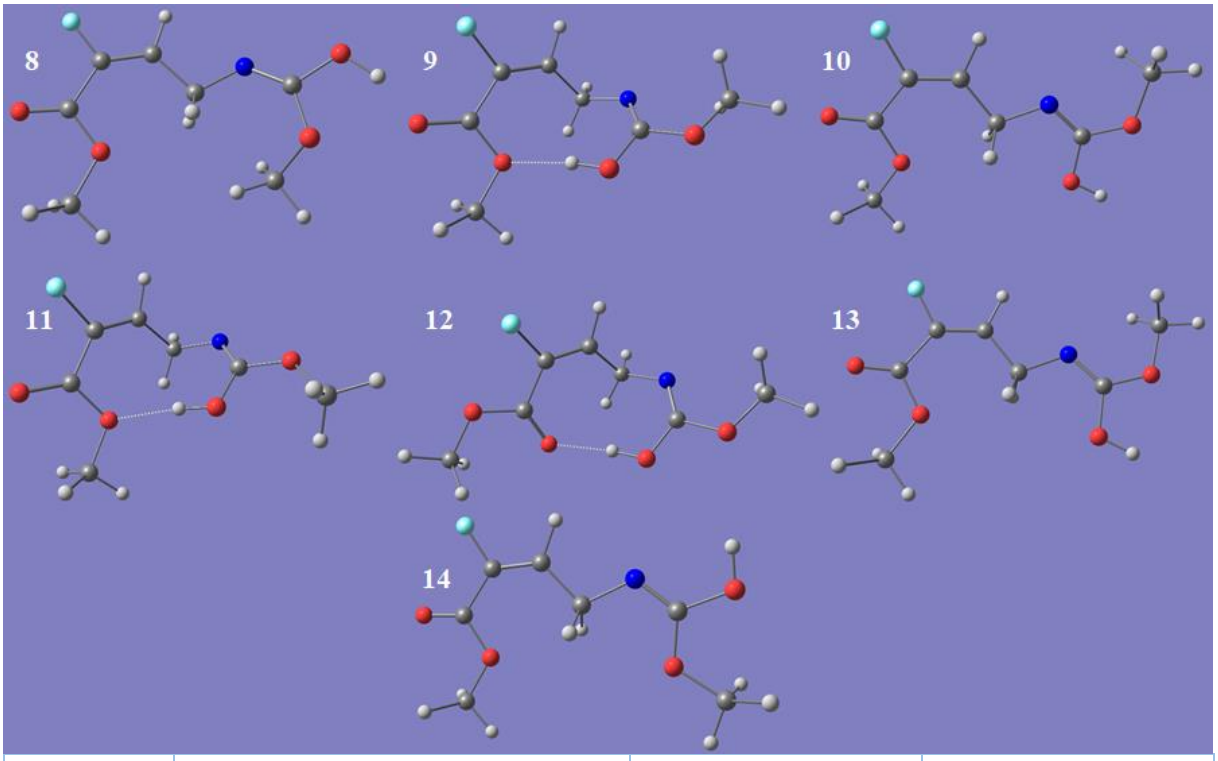
4.5. Computer assisted mechanistic studies

To further investigate the observed cyclization, DFT computational methods were used to model the thermodynamics of likely reaction pathways. The molecule chosen for the calculations was a fluorovinyl derivative of phenylalanine, however, to simplify the calculations, the benzyl group was replaced by a hydrogen atom and *tert*-butoxy and ethoxy groups by methoxy group. Various combinations of conformations were investigated to determine the minimal energy pathways for all cyclization reactions. To optimize all the structures Gaussian 09 was used at the M06 level of theory with the 6–31+G** basis set and the calculations of frequency were carried out at the same level of theory. The energies of conformers of the linear form (Tab. 17), iminol (Tab. 18) and cyclic form (Tab. 19) were presented in Hartree energy (E_h) and converted to kcal/mole by multiplying E_h times 627.5095. Conformer 1 has the lowest energy and the energy difference for the remaining conformers was calculated in relation to its energy value. In the case of cyclic structures, the energy of the methanol molecule was added, because only molecules with the same molecular formula can be compared.



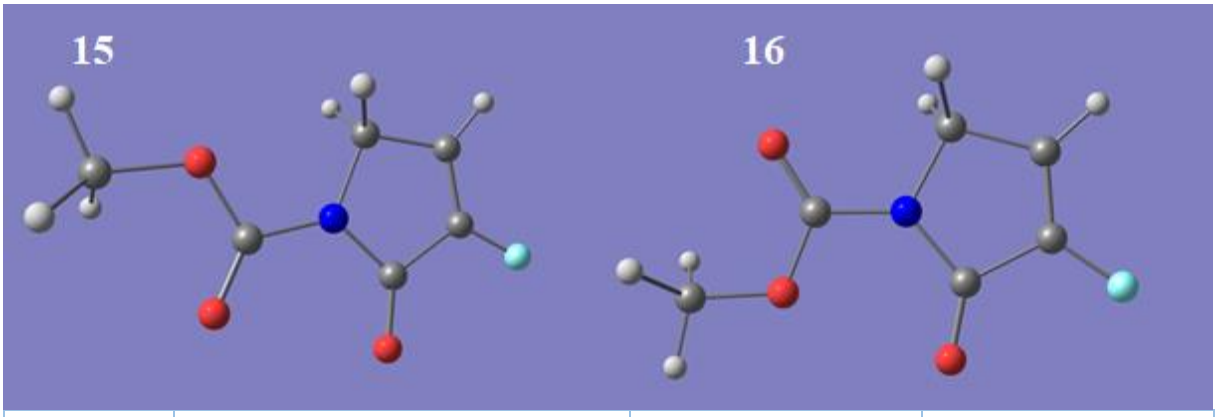
Conformer number	E_h	E [kcal/mol]	ΔE [kcal/mol]
MeOH	-115.661661827	-72578.7915822	-
1	-727.902765641	-456765.900516	0.000000
2	-727.900571884	-456764.523913	1.376603
3	-727.890375478	-456758.125571	7.774945
4	-727.902695094	-456765.856247	0.044269
5	-727.893140937	-456759.860923	6.039593
6	-727.890375477	-456758.125570	7.774946
7	-727.897676766	-456762.707199	3.193317

Table 17. Calculated energy values for linear conformers 1-7.



Conformer number	E_h	E [kcal/mol]	ΔE [kcal/mol]
8	-727.854189335	-456735.418423	30.482093490
9	-727.870361814	-456745.566807	20.333709279
10	-727.871520222	-456746.293719	19.606797254
11	-727.863159056	-456741.047008	24.853508350
12	-727.876628180	-456749.499011	16.401505083
13	-727.871520132	-456746.293662	19.606853730
14	-727.868811001	-456744.593657	21.306859169

Table 18. Calculated energy values for iminol conformers 8-14.

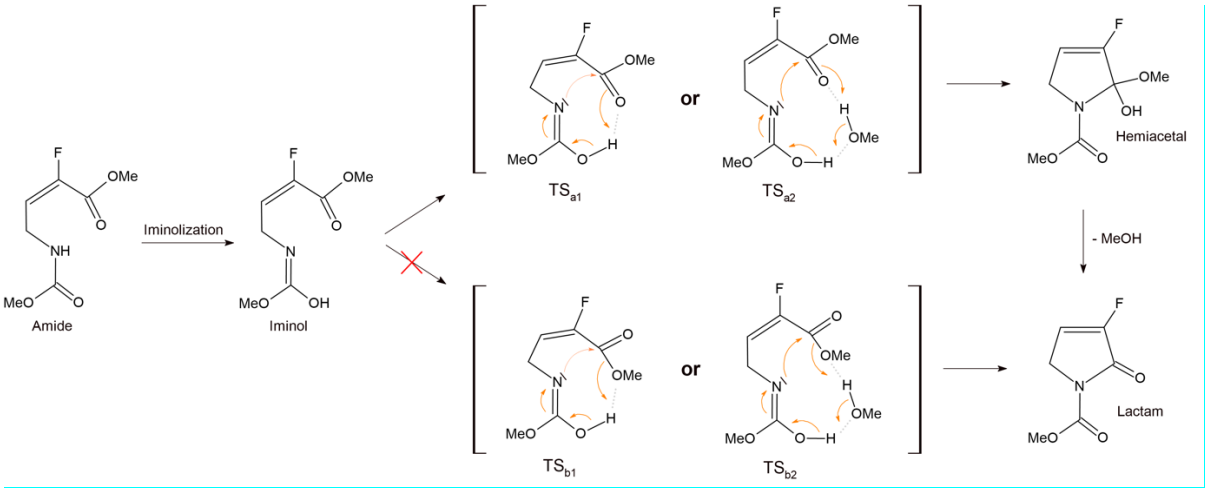


Conformer number	E_h	E [kcal/mol]	ΔE [kcal/mol]
15	-612.218161658+(-115.661661827) = -727.879823485	-456751.504095	14.396420771
16	-612.22141343+(-115.661661827) = -727.883075257	-456753.544613	12.355902771

Table 19. Calculated energy values for cyclic conformers 15-16.

The first step is common to all the considered mechanisms. Initially, the amide group undergo iminolization. In the next step, a conformational change occurs, followed by a nucleophilic attack of the iminol nitrogen on the carboxylic carbon, yielding hemiacetal or lactam forms. Thus, four mechanisms were considered, two of which ran through transition states marked TSa1, TSa2, TSb1 and TSb2 (Scheme 46). The first two transition states involve the mechanism of cyclization via a hemiacetal intermediate as described in the literature [124]. The last two transition states lead directly to the lactam.

Two versions of these reaction paths were also considered in more detail: with or without the participation of one methanol molecule. However, it is conceivable that more solvent molecules could assist in this mechanism.



Scheme 46. Considered mechanism for the observed cyclization.

As it results from the energy profiles of the studied reaction paths (Fig. 31), transition states leading to hemiacetal intermediates (TSa1 or TSa2) are preferred, because these are about 10 kcal/mol less than transition states leading directly to the lactam. These results indicate that the observed cyclization most likely goes via a hemiacetal intermediate.

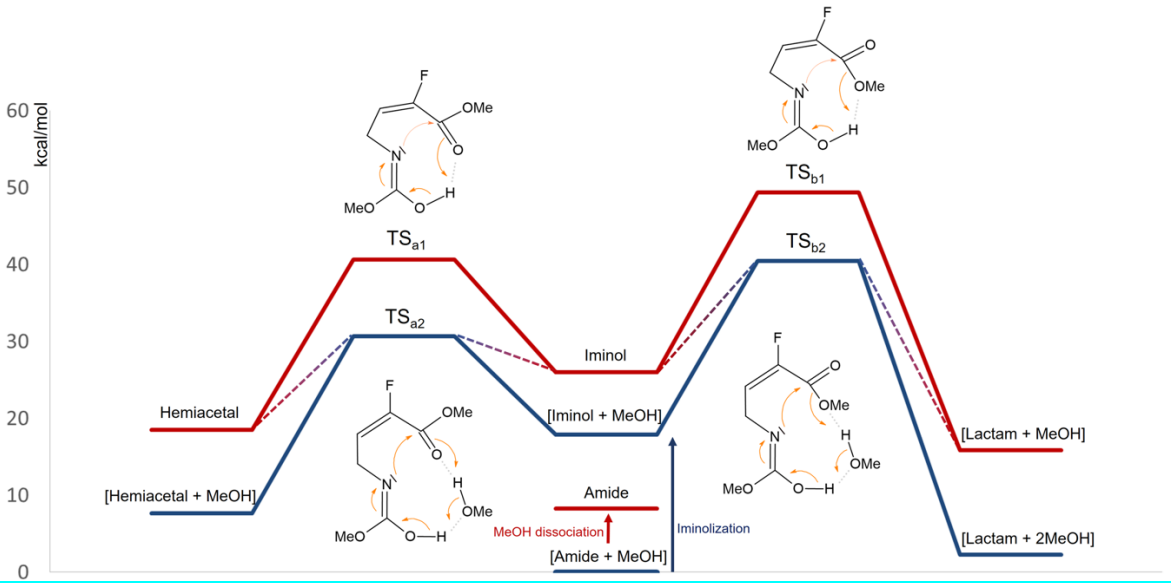


Figure 31. Energy profiles for considered reaction pathways.

The same calculations were performed for the model molecule without the fluorine atom. The obtained results are similar to those obtained for the fluorinated derivative (Fig. 32). The application of the polarizable continuum model (PCM) method with methanol or ether as solvent gave results consistent with those obtained in the gas phase. Unfortunately, the lack of observed cyclization for

derivatives without a fluorine atom cannot be explained by thermodynamics in the simplified model which has been used.

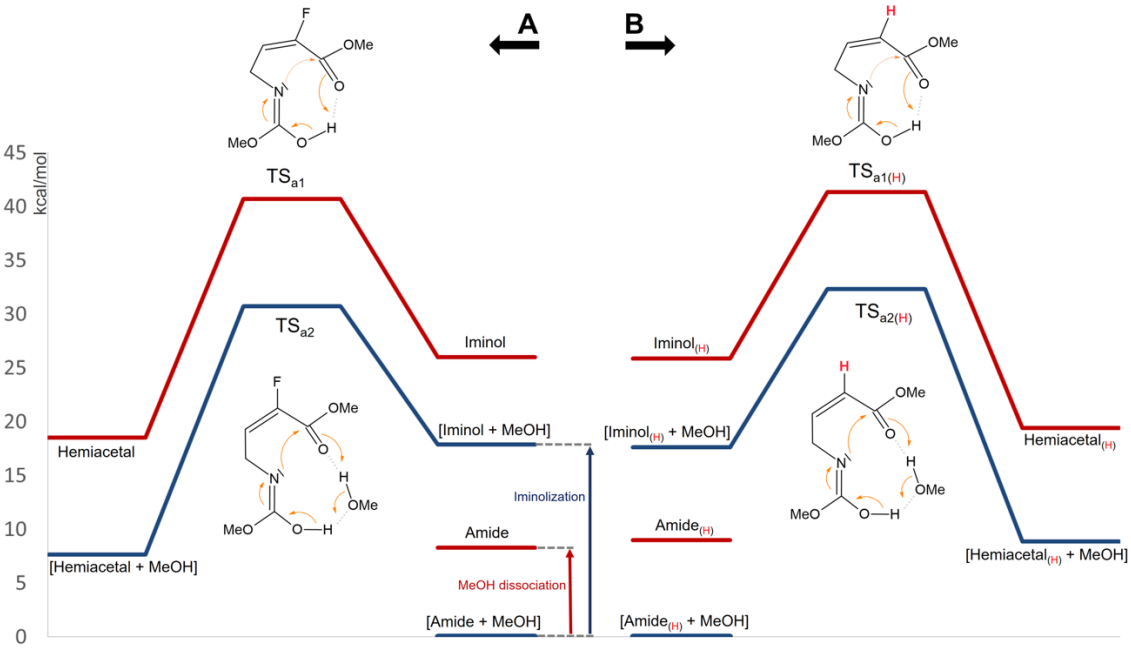


*Figure 32. Energy profiles for reactions leading to the hemiacetal intermediate in case for **A**: fluorinated; and **B**: non-fluorinated model molecule.*

It is worth noting that the geometry of the double bond affects the cyclization process. The linear monofluorovinyl derivative of phenylalanine **177** was obtained as *E*-isomer and it means that ester and amine group are on the same side of the double bond, which facilitates cyclization. The non-fluorinated analog **209** described in literature also has *E*-configuration, but in this case the ester and amine moieties are on opposite sides of each other from the double bond. Therefore, the geometry of the double bond may be one of the key factors that explain why such cyclization does not occur in the case of phenylalanine derivatives without a fluorine atom (Fig. 33).

177 **209**

*Figure 33. Geometry of fluorinated **177** and non-fluorinated **209** monofluorovinyl derivative of phenylalanine.*

4.6. Shapiro reaction- attempts to obtain fluorinated peptidomimetic

The very first research idea was the synthesis of the fluorovinyl peptidomimetic (Fig. 34) with phosphonate group which can mimic the carboxyl group. This compound can be potential inhibitor of Cathepsin C.

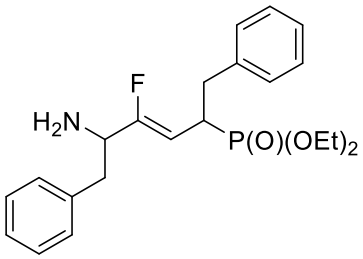
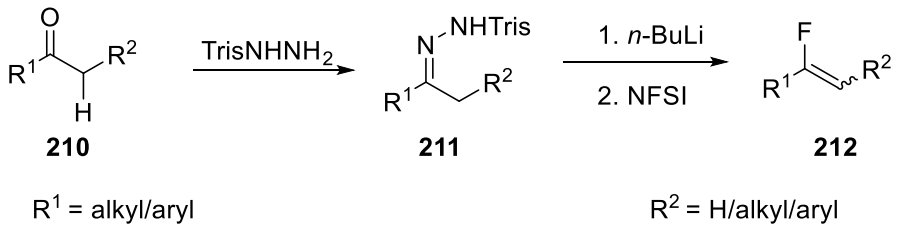


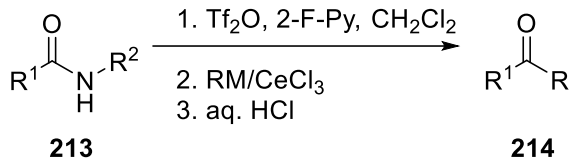
Figure 34. The structure of fluorovinyl peptidomimetic- a potential inhibitor of cathepsin C.

The plan required design of specific synthetic procedures which seem to be challenging due to the lack of the literature reports which could be adopted. Nevertheless, based on Altman's research [147] the synthetic procedure which could possibly lead to the desired product was developped. The fluoroalkenes were prepared via Shapiro reaction. It was the first reported direct access to the fluorinated peptidomimetics (Scheme 47).



Scheme 47. The general procedure leading to the fluoroalkenes via Shapiro reaction.

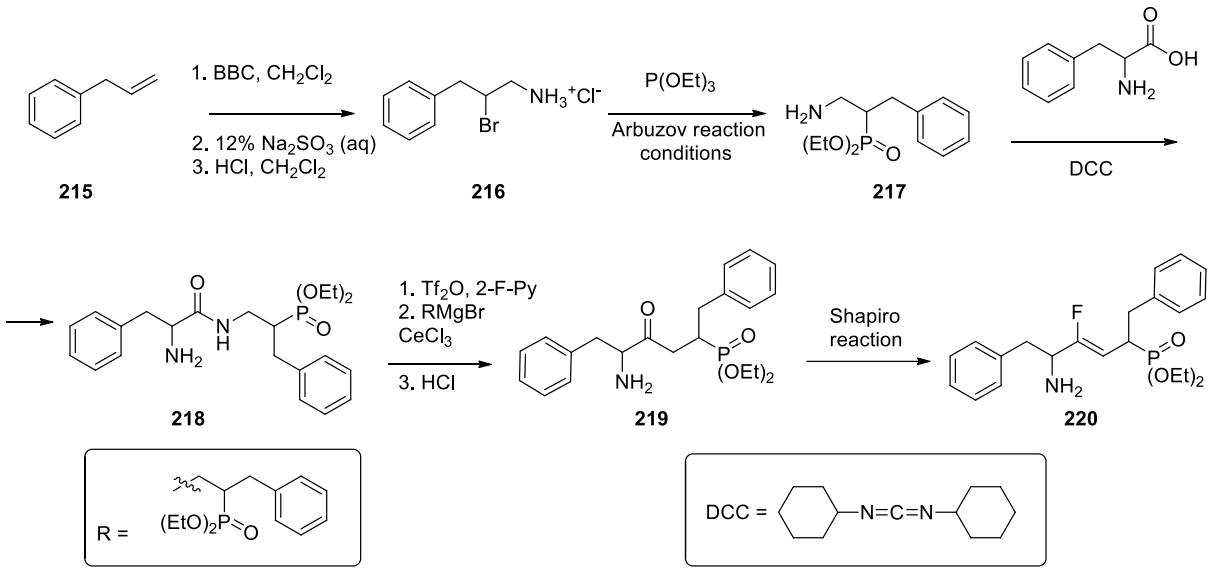
The above-mentioned work seemed to be very easy. However, the synthesis of the starting ketone was also very challenging. Fortunatelly, in 2012 Huang group reported the conversion of the secondary amides directly into ketons (Scheme 48) [148].Therefore, the synthesis of an appriopriate ketone seemed to be possible.



Tf_2O = trifluoromethanesulfonic anhydride
2-F-Py = 2-fluoropyridine
RM = organometallic compound

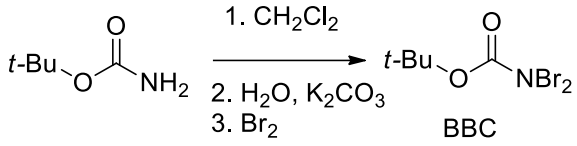
Scheme 48. Direct transformation of amides into ketones.

To take all these publications into account, the synthetic stategy leading to the peptidomimetic with fluorovinyl moiety was created (Scheme 50). Firstly, allylbenzene reacts with BBC to get the aminobromide derivative which in turns was subjected to the Arbuzov reaction with triethyl phosphite. The next step includes the condensation with phenylalanine in the presence of DCC. The peptide moiety is subsequently converted into ketone and the final step- Shapiro reaction- leads to the desired product.



Scheme 50. The synthetic procedure leading to the peptidomimetic with fluoroolefinic group.

At the beginning, the allylbenzene reacted with BBC leading to the product **216** (Scheme 50). BBC **222** is a useful reagent for aminobromination of terminal alkenes and was firstly described in 2001 by Klepacz and Zwierzak. According to the literature data, this reagent can be easily obtained by bromination of *tert*-butyl carbamate **221** [149] (Scheme 51).



221 **222**

Scheme 51. The synthetic scheme of BBC.

Based on the literature the reaction was carried out several times, however each time the reaction parameters (concentration, reaction time) or the amount of reagents (more bromine) have been changed. The problem was the discoloration of the product during evaporation of the solvent on the rotary evaporator (BBC should be brown). Therefore, a method where the BBC comes out as a precipitate was used and precipitate was filtered and dried in air. It retained its brown color, which could suggest the formation of the desired product. However, the spectroscopic analysis was quite problematic, because both the substrate and the product give the same signals in the ^{1}H- and ^{13}C NMR spectra. Only GC-MS analysis or IR spectroscopy could confirm the formation of the product. The chromatogram below (Fig. 35) shows the synthesized BBC. Moreover, the absorption at ν ~3500 cm^{-1} had disappeared after the reaction; therefore, it can be assumed that the $–NH_2$ was converted into the $–NBr_2$.

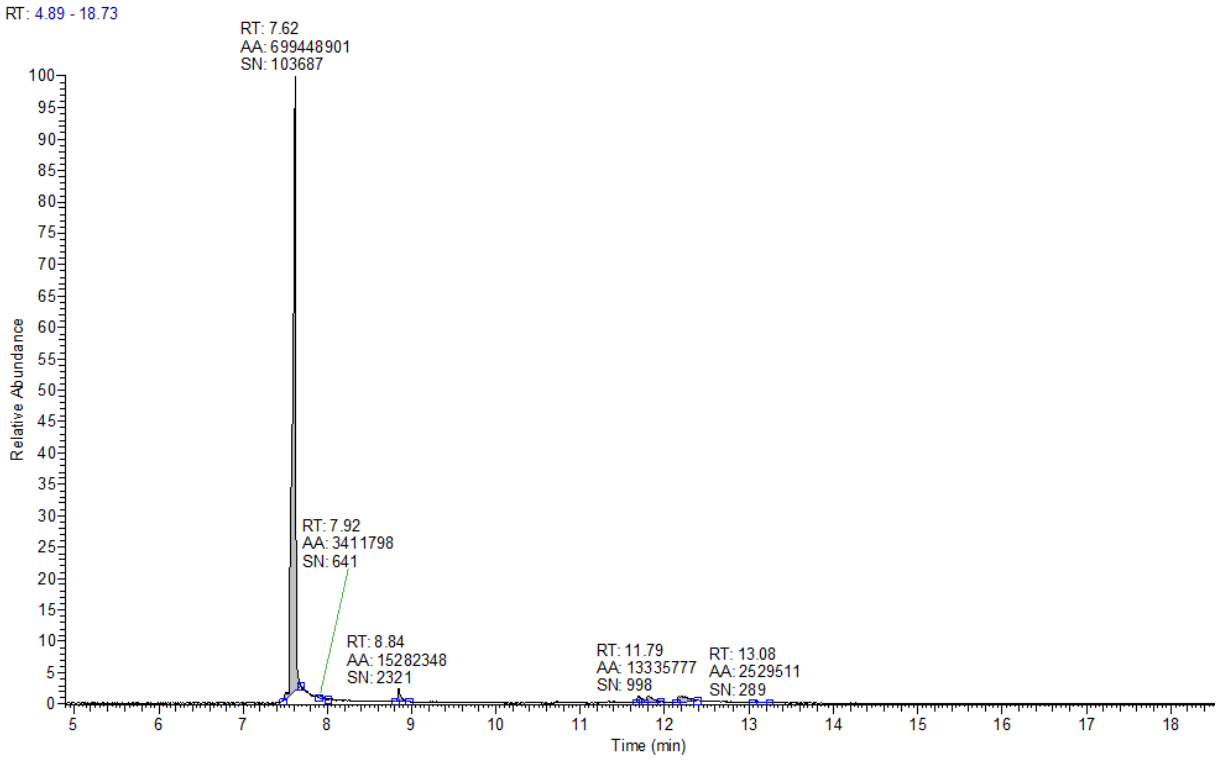
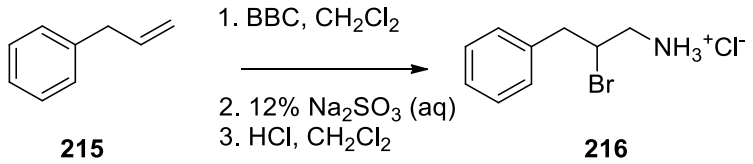


Figure 35. The chromatogram of the synthesized BBC.

The second step was the reaction between BBC and allylbenzene (Scheme 52). According to the literature, BBC reacts smoothly with a variety of terminal alkenes in an anti- Markovnikov fashion and leads to the formation of β-bromoamines upon reduction with aqueous solution of Na_2SO_3. Therefore, BBC was dissolved in dichloromethane and then allylbenzene was added. The reaction mixture was refluxed for 2 hours. Then the flask was cooled to 5°C and 12% solution of Na_2SO_3 was added. The last step involved the acid hydrolysis which should have led to the β-bromoamine hydrochloride.



Scheme 52. The reaction of allylbenzene and BBC.

Unfortunately, the analysis of the reaction mixture showed that most likely the reaction did not take place. Many products were formed (GC-MS analysis) and none of the mass decays corresponds to the decay of the expected product (Fig. 36).

The authors indicated that the β-bromo-*N*-Boc-amines (products which are formed after reduction with Na_2SO_3) were not isolated just to minimize undesired side reaction. These chemical compounds were immediately deprotected by gaseous HCl. Therefore, such information indicates that this reaction is very susceptible to the formation of by-products. This reaction was repeated, and more equivalents of BBC were used. Unfortunately, despite all the efforts, the product was not obtained. Therefore, it was an interest in other methods of synthesizing different fluorovinyl amino acid derivatives.

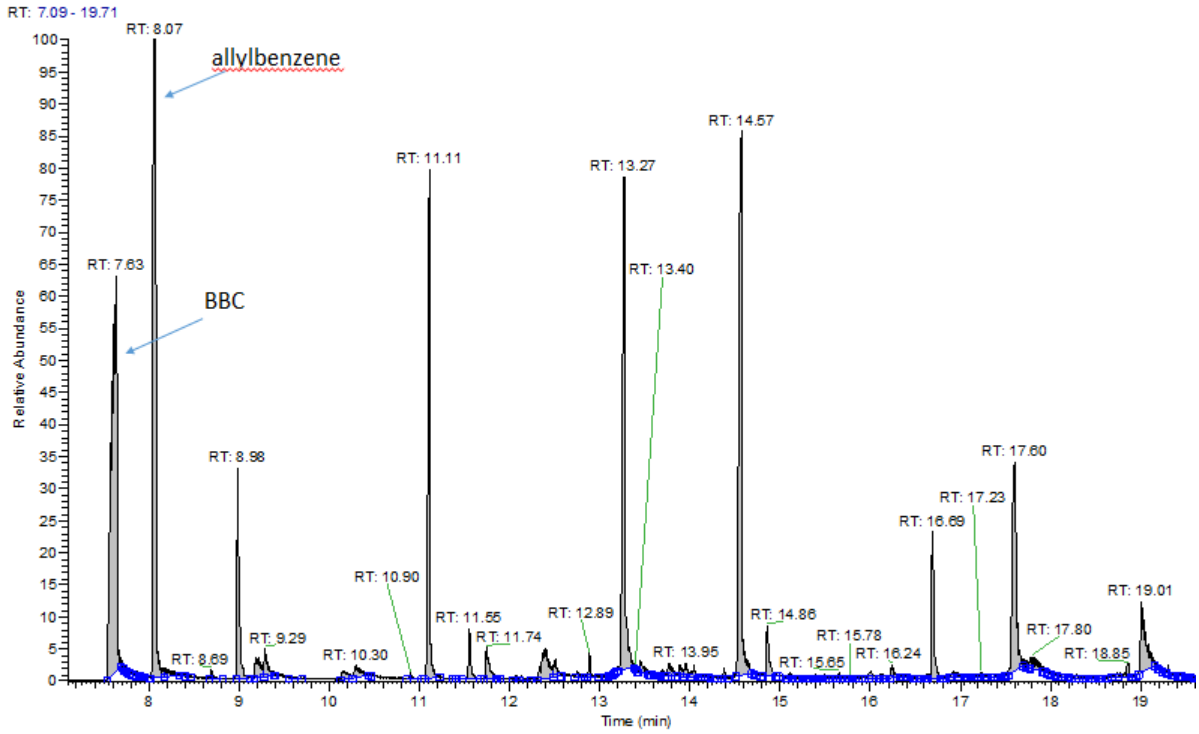
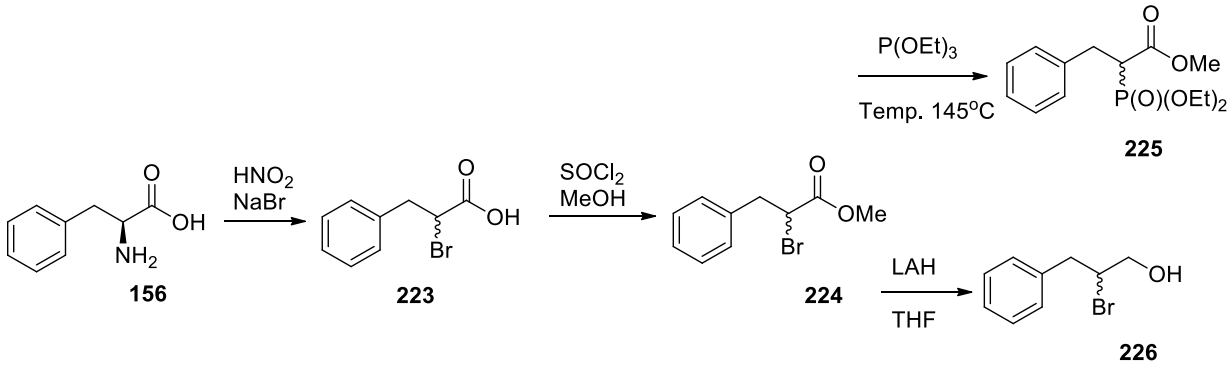
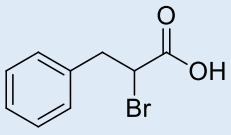
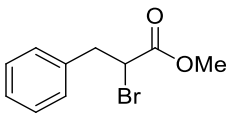


Figure 36. Chromatogram of the reaction mixture of BBC and allyl benzene.

4.7. Synthesis of bromo-derivatives of amino acids

Another idea was the synthesis of phosphonate derivatives of amino acids as a substrate for further HWE reaction (Tab. 20). Therefore, a synthetic pathway was developed that starts with the conversion of the amino group of phenylalanine into -Br using diazonium salts [150]. This reaction step was successful and the resulting 2-bromo-3-phenylpropanoic acid (**223**) was fully characterized by spectroscopy. The next step was esterification with thionyl chloride in methanol, which also led to the formation of the desired product **224**, but the yields of this reaction were low (9%). The ester formed was used for two alternative reactions. The first was an Arbuzov reaction with triethyl phosphite, but no product formation was observed. Even despite more equivalents of triethyl phosphite were added and the reaction time was extended from the recommended 5.5 hours to 9 hours, no satisfactory result was observed. Therefore, it was decided to subject the methyl ester of 2-bromo-3-phenylpropanoic acid (**224**) to the reduction reaction [151]. Unfortunately, despite repeated attempts, it was not possible to obtain the desired product.



Nr	Structure	Reaction conditions	Yield GC-MS[%]	GC MS (EI, 70Ev) m/z (rel. Int, %)	Other reports
223		[Phe]:[NaBr]:[$NaNO_2$]= 1:3.5:1.25 2.5M H_2SO_4 = 1.3ml/1mmol 6 h, rt	78	229.0 (3), 148.9 (20), 130.9 (77), 91.0 (46), 77.0 (22)	**TLC**: Cy/EtOAc/AcOH =99:1 Rf = 0.75
224		[**223**]:[$SOCl_2$] (mmol) = 1:1,7, MeOH (anhydrous) = 4ml/1mmol reflux 3 h, next 48h, rt	64	243.0 (M+, 5), 163,1 (65), 131.3 (100), 103.3 (23)	**TLC**: heksan:EtOAc = 7:3 Rf=0.4

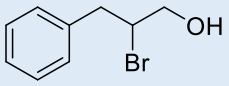
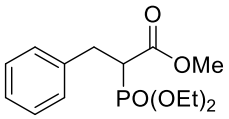
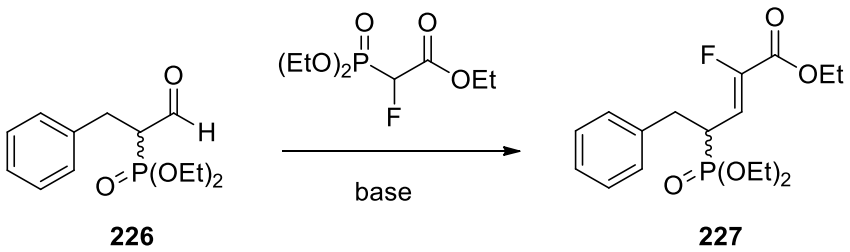
226		[**224**]:[LAH] (mmol) = 1:1.1, THF (anhydrous) = 5.4ml/1mmol, rt Then 10% KOH	-	Unable to distinguish the product	^{1}H NMR analysis: Unable to distinguish the structure
225		[**224**]:[$P(OEt)_3$] (mmol) = 1:1.5, 6h 140ºC, without solvent	0	Substrates only	The reaction did not occur

Table 20. Characteristics of reactions using phenylalanine bromo- derivatives

It was planned that phosphonate **225** could be reduced to alcohol and then oxidized to aldehyde. The same aldehyde was supposed to be made from derivative **226** by Arbuzov reaction with triethyl phosphite and subsequent oxidation. This aldehyde with a phosphonate group could be in turn subjected to HWE reaction to obtain a compound **227** with a fluorovinyl moiety (Scheme 53).



226 **227**

*Scheme 53. HWE reaction of diethyl (1-oxo-3-phenylpropan-2-yl)phosphonate (**226**).*

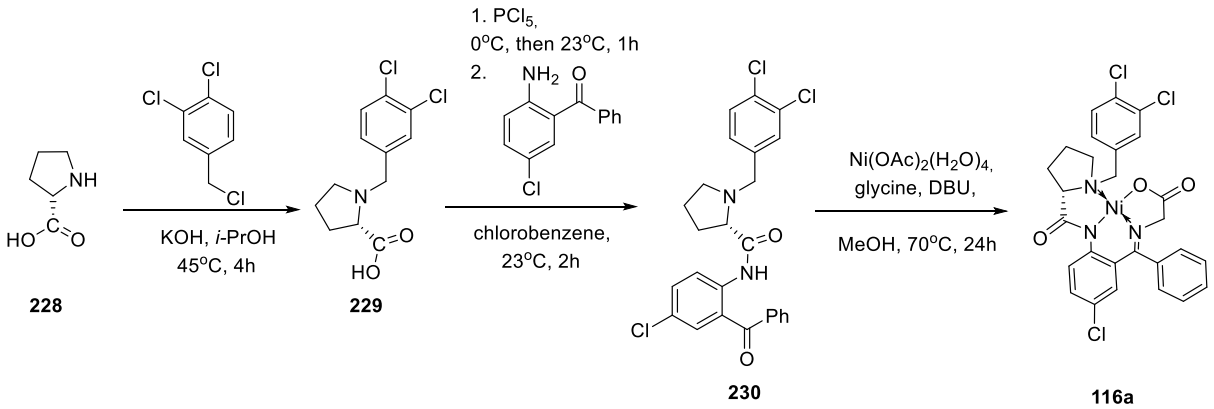
Several different attempts have been made to obtain fluorovinyl amino acid derivatives with a phosphonate moiety, including the use of the Shapiro reaction. The conditions or ingredients were not suitable and these reasons caused the above-mentioned reactions to fail.

4.8. Synthesis of fluorinated amino acids using chiral Ni(II) complex

4.8.1. The synthesis of chiral nickel(II) complex

From January to April 2023 I was doing a doctoral internship in the research group of Prof. Beate Koksch at Freie University of Berlin. The project was focused on the synthesis of fluorinated amino acid derivatives.

The first part of the project was the synthesis of a chiral nickel(II) complex according to the three-step sequence described in the literature [152,153]. This synthesis was carried out on a large gram scale (Tab. 21). A 30 g of proline was used at the beginning of this procedure and finally, 77 g of chiral nickel complex (231) was obtained and the structure was characterized by ^{1}H NMR and ^{13}C NMR. The percentage yields of the reaction obtained at each stage of the synthesis were satisfactory in comparison to the literature yields [98,154–156].

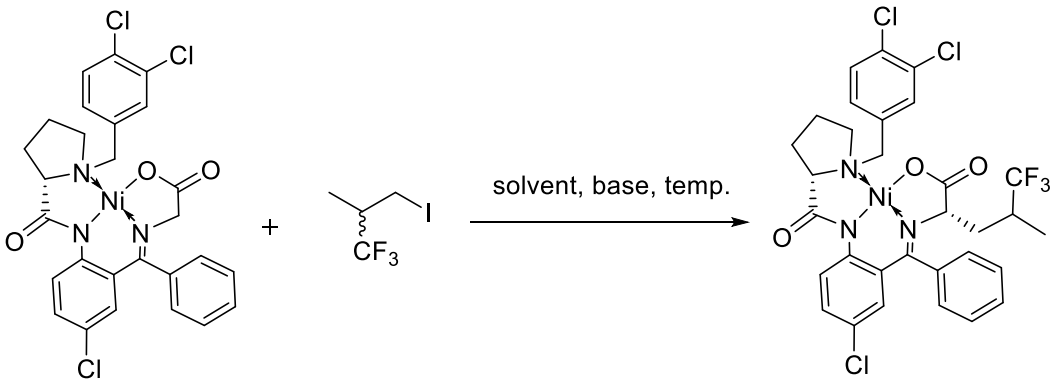


Reaction step	Mass of the product [g]	Percentage yield [%]	Appearance
First	63.63	87.8	White solid
Second	83.22	77	Slightly yelowish solid
Third	86.5	77	Red solid

Table 21. The masses, percentage yield and appearance of the products obtained according to the Romoff's procedure.

4.8.2. The synthesis of 2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5,5,5- trifluoro-4-methylpentanoic acid = FmocTfLeu

The second part of the project was the synthesis of the Fmoc- protected trifluoroleucine due to two reaction steps. First step included alkylation of the nickel(II) complex via 1,1,1-trifluoro-2-methyl iodopropane (**231**) (Scheme 54).



116a **231** **232ab**

Scheme 54. The chemical reaction of chiral Ni(II) complex and 1,1,1-trifluoro-2-methyliodopropane.

Many test reactions were carried out, checking how the solvent, temperature, type and amount of the base used affect the yield of the created product. The analysis of table 22 shows that the highest yields of the created product were obtained when sodium hydride was used as the base and DMF as the solvent at the temperature of 0ºC. The percentage yield was determined by the ^{19}F NMR spectra using 2-chloro-4-fluorotoluene as an internal standard.

Entry	Base [eq]	Solvent [2.5ml/mmol of Ni-complex]	Temp [ºC]	Yield [%]
A	1 eq DBU	THF	0	0
B	1 eq KOH	MeOH	0	0
C	2 eq NaH	DMF	0	40
D	1.3 eq NaH	MeCN	rt	11

Table 22. Screening Conditions for the Alkylation Step Using 1,1,1-trifluoro-2-methyl-iodopropane.

Therefore, the reaction carried out under these conditions has been examined in a wider range and the influence of temperature, concentration (volume of the solvent used per the same number of millimoles of the Ni(II) complex) as well as the amount of sodium hydride was checked. The analysis

of table 23 shows that the use of 1.3 equivalent of sodium hydride and 5 ml of DMF per each mmol of Ni(II) complex at the temperature of 0ºC allowed to obtain the product in 60% yield (Tab. 23. Entry 1). Literature data shows that such yield is satisfactory for this type of reaction with the use of a nickel complex because the highest yields recorded in the literature so far were 60% [98]. Therefore, it was decided to finish the research for the best reaction conditions, as these turned out to be fully satisfactory. For the screening reactions, 50 mg of nickel complex was used. Therefore, the same reaction was carried out, but on a larger scale, using 2.5 g of nickel complex, testing whether the yield of this reaction is the same when maximizing the scale. As it turned out, the same yield results were obtained (Tab. 23, entry 2). The product was obtaines as a mixture of two main diastereoisomers **232a** and **232b.**

entry	Reaction number	NaH [eq]	DMF [ml/mmol of Ni-complex]	Temp [ºC]	Yield [%]*
1	SK-1	1.3	5	0	60
2	SK-1BS (bigger scale)	1.3	5	0	62
3	SK-2	3	2.5	0	31
4	SK-3	1.3	2.5	rt	7
5	SK-4	3	2.5	rt	36
6	SK-5	1.3	2.5	0	41
7	SK-6	3	5	0	33
8	SK-7	1.3	5	rt	51
9	SK-8	3	5	rt	24
10	SK-9	1.3	5	-10	20

Table 23. Screening conditions for the alkylation step using 1,1,1-trifluoro-2-methyl-iodopropane.

It can also be concluded from the analysis of table 23 that such general trend comes from these results: using lower concentration (5ml/mmol of Ni-complex) caused better yields, (for example comparision of entry 1 and 6, 3 and 7, 4 and 8). Only for entry 5 and 9 this system did not work.

It is also worth mentioning the method of calculating the yield of the created product. 2-chloro-4-fluorotoluene was used as an internal standard and signals on the ^{19}F NMR spectra from the product and from the standard were integrated. The molecule of an internat standard contains one fluorine atom and the product molecule contains three. Thus, if the integration ratio of product:reference signals was

3:1, the yield would be 100%. If this ratio was different, the yield was recalculated proportionally. For example, in the Fig. 37 the integration ratio of reference 232a:232b = 1:1:0.92, which equals to the total 64% yield.

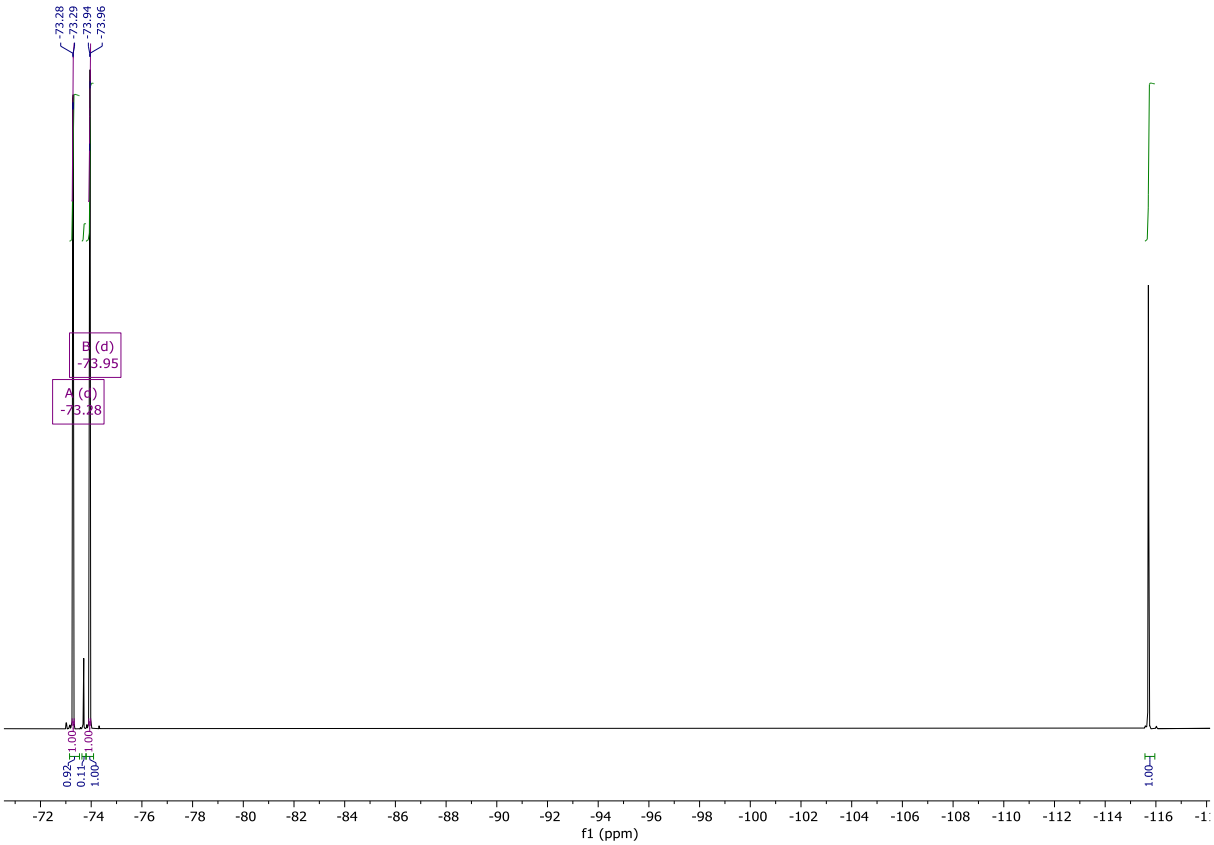


*Figure 37. ^{19}F NMR spectrum of reaction mixture **232ab** in $CDCl_3$: q, -115.71 ppm J = 7.5Hz (reference) and d, -73.28 ppm, J = 8.20 Hz (diastereoisomer 232b) -73.95 ppm 8.7 Hz (diastereoisomer 232a)*

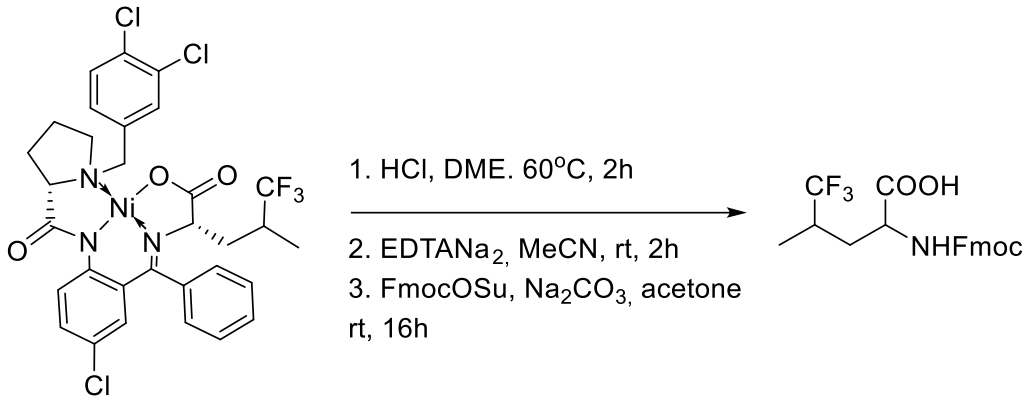
Since the product was formed as a mixture of two diastereoisomers, the separation of them was perfomed using a column chromatography. A mixture of chloroform and acetone was used ($CHCl_3$:acetone = 30:1 (v:v)) as an eluent (Tab. 24). Distaereoisomers were successfully separated and characterized by ^{1}H, ^{13}C and ^{19}F NMR. The isolated yield was equal to the yield calculated on the analysis of the ^{19}F NMR spectra (60%).

Structure number	TLC (chloroform:acetone = 6:1 v:v)
232a	Rf = 0.56
232b	Rf = 0.50

Table 24. Comparision of the retention factors (Rf) of diastereoisomer 232a and 232b.

The absolute configuration of the diastereoisomers has not yet been determined, but this product (232a, 232b) forms large crystals that will allow the determination of the final structure using X-ray and crystallographic analysis.

The second step of the synthesis of Fmoc-Tf-Leu was one-pot hydrolysis of alkylated nickel(II) complex and subsequent Fmoc protection of amine group (Scheme 55).



232a/232b **233a/233b**

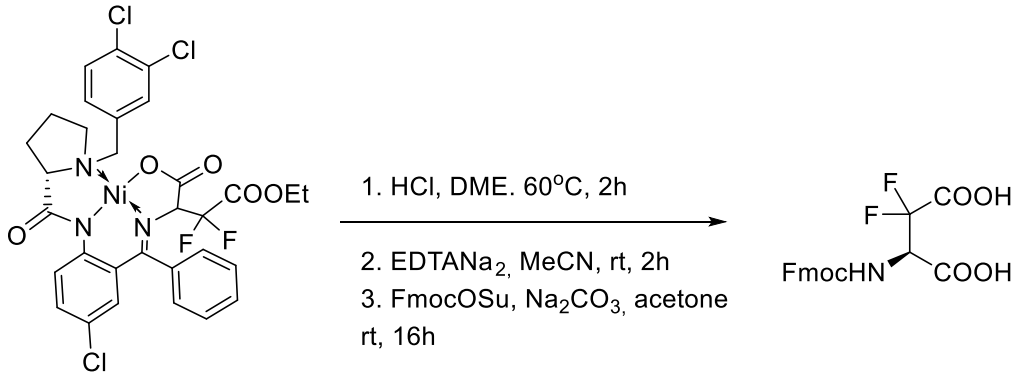
Scheme 55. Scheme of the synthesis of Fmoc-Tf-Leu.

This reaction was performed on each diastereoisomer **232a** and **232b**, yielding products **233a** and **233b**, whose structure was fully analyzed spectroscopically after purification by column chromatography. In the future, the obtained fluorinated derivatives of amino acids will be used for solid phase peptide synthesis (SPPS). Interestingly, for each of the obtained products, it was necessary to select completely different purification conditions on the chromatographic column. Product **233a** was purified using chloroform/methanol misture ($CHCl_3$-> $CHCl_3$/10% MeOH v:v) and product **233b** was purified only using hexane and gradually increasing the polarity of the eluent by adding ethyl acetate (hexane-> hexane:ethyl acetate 8:2 v:v).

4.8.3. The synthesis of 3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2,2-difluoro-4-oxo-4-(prop-1-en-1-yloxy)butanoic acid = Fmoc-Df-Asp-OAll

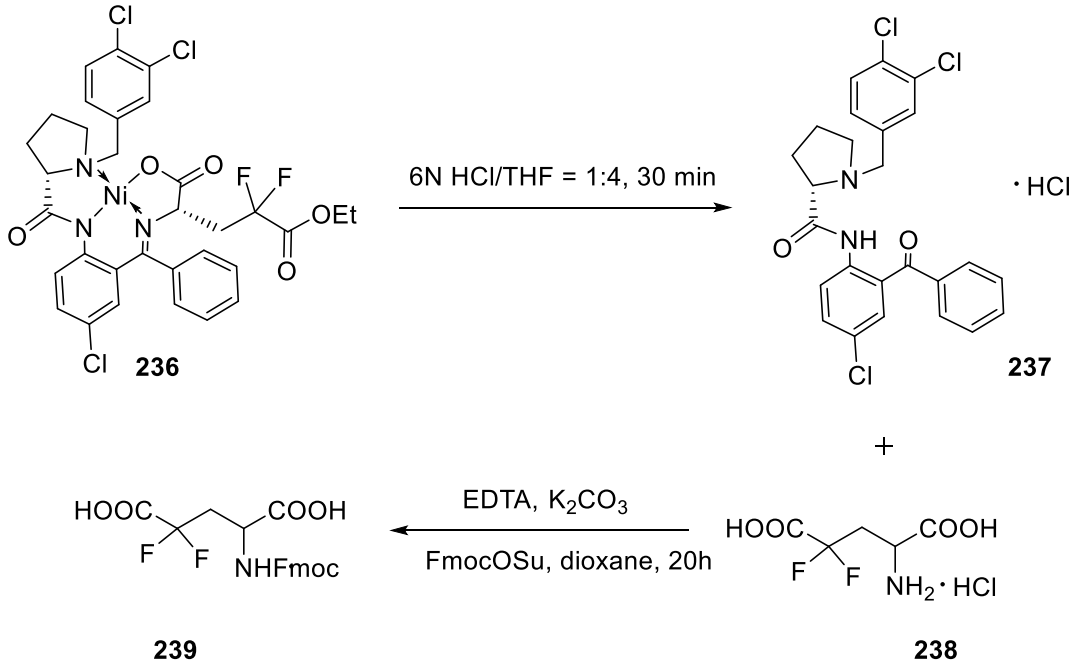
The second aim of the research was the synthesis of Fmoc-Df-Asp-OAll which could be one of the substrates for the SPPS. Obtaining such derivative could be demanding due to the presence of two fluorine atoms in the alpha position to the carbonyl group. This meant that the hydrogen atom located at the stereogenic center was very acidic and such molecule could easily decompose. Therefore, several different methods were used. First of all a „standard" procedure (which was described above to obtain

Fmoc-Tf-Leu) was implemented to obtain F-moc protected difluoroaspartic acid (**235**) (Scheme 56) which in turn could be subjected to the OAll protection of the carboxylic group. As a starting material **234** was applied and this compound was synthesised previously by prof. Koksch's research group.



Scheme 56. The synthesis of Fmoc-Df-Asp

Unfortunalelly, this reaction did not work. Several peaks on HPLC analysis were seen, whereas in other cases (for different amino acid derivatives) only one peak was observed [98] and ^{1}H NMR spectrum showed more signals than expected. Moreover, after addition of acetone, two phases were observed. Thererefore, this method has been slightly modified and dioxane was employed instead of acetone according to the publication of Soloshonok's group [86]. They used a similar procedure to obtain a difluorinated derivative of glutamic acid (Scheme 57).



Scheme 57.The synthesis of Fmoc-DfGlu by Soloshonok's group.

These methods were compared (Tab. 25) and there were slight differences in the hydrolysis stage (temperature and acid concentration) and in the protection of the amino group, a different solvent and a different base were used.

Comparision of Solonoshonok and Koksch conditions	**Koksch** [98]	**Soloshonok** [86]
hydrolysis	3M HCl, DME, 60^{0}C	6M HCl, THF, rt
F-moc protection step/ Base used	Na_2CO_3	K_2CO_3
F-moc protection step/ solvent used	H_2O/acetone	dioxane

Table 25. Comparision of the reaction conditions leading to difluorinated derivative of amino acids.

Therefore, this procedure was repeated with dioxane instead of acetone. After addition of dioxane, two phases were not observed. Finally, the reaction mixture was purified using column chromatography ($CHCl_3$-> 10%MeOH) and the ^{1}H, ^{19}F and ^{13}C NMR analysis was done. The desired product was not obtained because ^{19}F NMR spectrum showed a singlet (δ = -112.02 ppm) (Fig. 38) when there should have been a doublet of doublets. Similarly, the ^{1}H NMR analysis indicated that the desired product was not formed because there were many more signals than expected, among which there were no signals from the desired product.

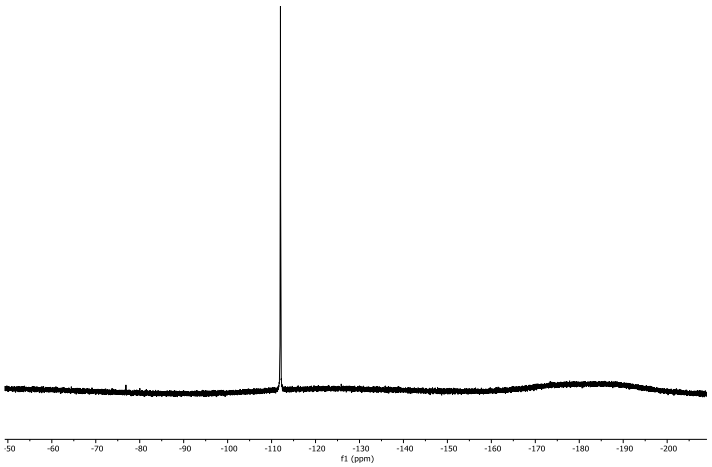
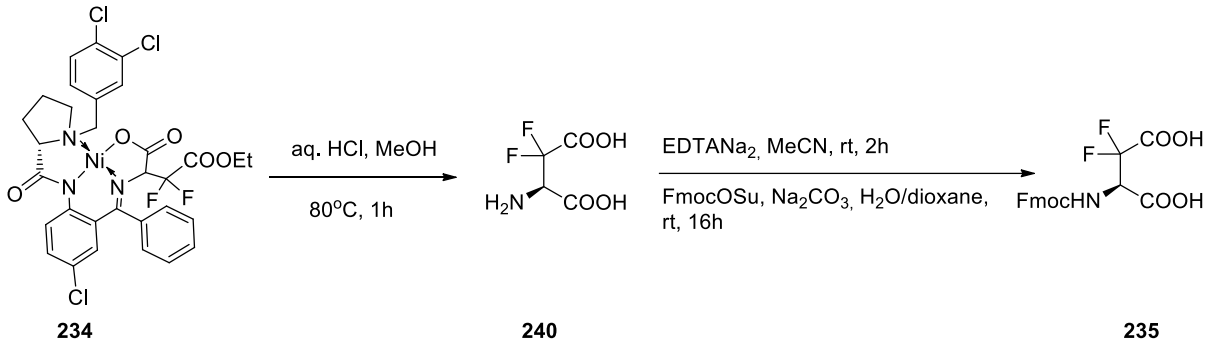


*Figure 38. ^{19}F NMR spectrum (s,-112.02 ppm) of the reaction mixture after hydrolysis and F-moc protection of **234**.*

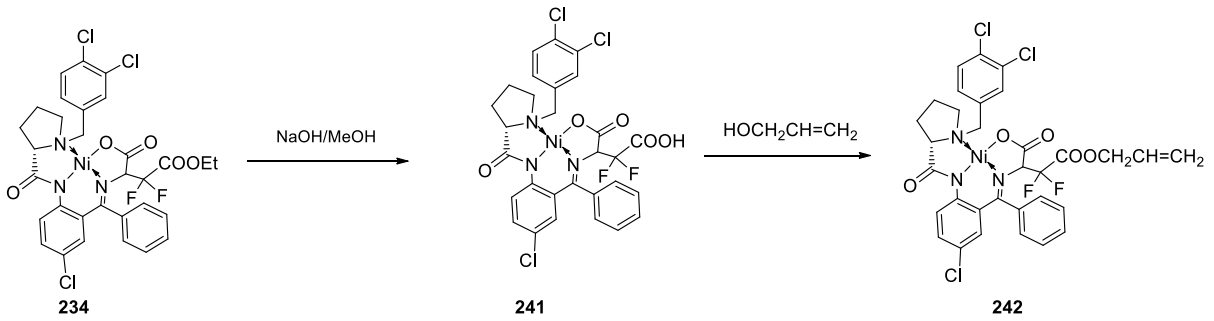
This reaction was repeated with the isolation of the α-difluoro-aspartic acid (Scheme 58) to check at which stage the problems occur - whether it is the hydrolysis stage or the F-moc protection stage. The product after hydrolysis was applied to a Dowex ion-exchange column. The column has been

washed with CH_2Cl_2 several times and then several times with H_2O (till the colourless eluent). The product was dissolved in an aqueoud solution of hydrochloric acid (pH of the solution was below its isoeectric point, approximately the pH was equal to 5), placed on the chromatography column, washed with water to remove all the impurities and finally washed with 5% of ammonia [4]. The difluoroaspartic acid was obtained in 50% yielad as a white solid. The structure was confirmed by ^{1}H, ^{19}F and ^{13}C NMR analysis. This result indicates that the hydrolysis step was not a problem. The product (α-difluoro-aspartic acid) was subjected to the reaction with $EDTANa_2$ and FmocOSu. The reaction mixture was purified, and NMR analysis was done. Again, the desired product was not obtained because ^{19}F NMR spectrum showed a singlet (δ = -76.83 ppm) instead of doublet of doublets.



Scheme 58. The synthesis of Fmoc-Df-Asp due to acidic hydrolysis, isolation of the Df-Asp and subsequent F-moc protection.

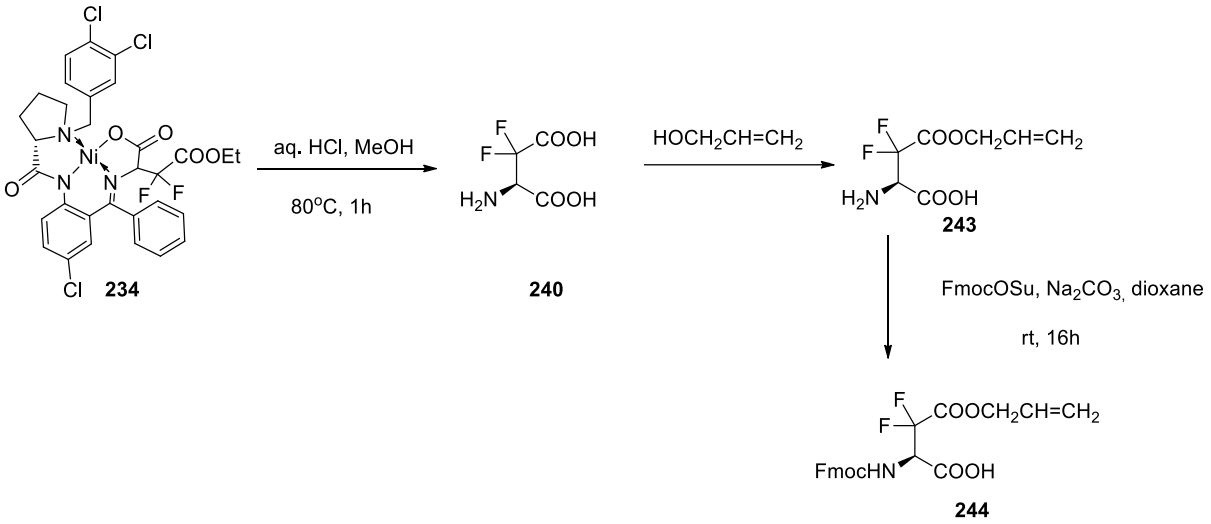
Consequently, it was decided to run this reaction in a different way via mild basic hydrolysis (according to the procedure [157]) and subsequent protection of the –COOH group (Scheme 59).



*Scheme 59. Mild basic hydrolysis of the alkylated Ni(II) complex **234** and allyl protection of the carboxylic group*.

Unfortunately, the product of the reaction was impossible to identify, most likely decomposition or formation of many by-products took place. As a result, it can be assumed that basic conditions of the reaction, even mild basic conditions, can cause decomposition of the product. For that reason,

summarizing the previous experiments, it was possible to develop an alternative synthesis route (Scheme 60) on their basis. It consists of three stages, where first the acidic hydrolysis takes place, then one of the carboxyl groups is selectively protected by the -OAll group [158] and finally Fmoc protection of the amine group. The results of these studies were not completed due to the end of the internship, however, previous struggles and experiences allowed the development of the most likely response path and allowed to determine at what stage complications occur.



*Scheme 60. The syntesis of Fmoc-Df-Asp-OAll **244** via three-step procedure.*

To conclude, the best conditions for the alkylation of Ni-complex by 1,1,1-Trifluoro-2-methyl-iodopropane were selected and the alkylated Nickel(II) complex was obtained in 60% yield. Moreover, two diastereoisomers were separated. Finally, two stereochemically pure forms of Fmoc-TfLeu were synthesized and the structures were confirmed by NMR spectroscopic analysis.

The second part of the research was the synthesis of Fmoc-Df-Asp-OAll. This endeavour has been highly challenging and although the final product could not be isolated in substantial yield, these efforts layed a solid foundation for the establishment of a new synthetic route. Therefore, this synthesis may be realized via this three step sequence. First of all, hydrolysis of the alkylated Ni(II)-complex, then protection of the –COOH group with the allyl group and finally Fmoc protection of the amine group.

5. Experimental section

5.1. General remarks

5.1.1. Chemical reagents and solvents

5.1.1.1. Organic solvents	Supplier
C_6H_{12}	**STANLAB**
Hexane	
C_4H_8O	**WITKO**
Tetrahydrofurane	
CH_2Cl_2	**WITKO**
Dichloromethane	
CH_3OH	**STANLAB**
Methanol	
$(C_2H_5)_2O$	**POCH BASIC**
Diethyl ether	
$CH_3COOC_2H_5$	**STANLAB**
Ethyl acetate	
$CHCl_3$	**STANLAB**
Chloroform	
$CDCl_3$	**SIGMA ALDRICH**
Deuterated chloroform	
C_2D_6OS	**SIGMA ALDRICH**
Deuterated dimethyl sulfoxide	
CH_3OCH_3	**STANLAB**
Acetone	
$(CH_3)_2CHOH$	**STANLAB**
Isopropyl alcohol	

5.1.1.2. Organic reagents

$SOCl_2$ **SIGMA ALDRICH**

Thionyl chloride

$C_{10}H_{18}O_5$ **FLUOROCHEM**

Di-*tert*-butyl decarbonate

C_2H_6OS **SIGMA ALDRICH**

Dimethyl sulfoxide

$(COCl)_2$ **SIGMA ALDRICH**

Oxalyl chloride

$(C_2H_5)_3N$ **SIGMA ALDRICH**

Anhydrous triethylamine

$C_6H_{19}NSi_2$ **SIGMA ALDRICH**

Hexamethyldisilazane

C_4H_9Li **SIGMA ALDRICH**

n-Buthyllithium

$(C_2H_5O)_3P$ **SIGMA ALDRICH**

Triethyl phosphite

$BrCH_2COOC_2H_5$ **SIGMA ALDRICH**

Ethyl bromoactetate

5.1.1.3. Inorganic reagents

$NaHCO_3$ **EUROCHEM**

Sodium hydrogen carbonate

NaCl **EUROCHEM**

Sodium chloride

Na_2SO_4 **EUROCHEM**

Anhydrous sodium sulphate

SiO_2 **FLUKA**

Silica

H_2O ---

Distill water

$LiAlH_4$ **SIGMA ALDRICH**

Lithium aluminium hydride

KOH **STANLAB**

Potassium hydroxide

CO_2 ---

Solid carbon dioxide

HCl **STANLAB**

Hydrochloric acid (conc.)

CaH_2 **SIGMA ALDRICH**

Calcium hydride

HCl **CHEMAT**

Hydrogen chloride in diethyl ether

Ar ---

Argon

5.1.1.4. Mixtures and solutions

SSE- a mixture of 400ml of ethyl acetate, 200ml of isopropanol and 100 ml of water. The mixture was extracted and the upper layer was collected. It is a polar eluent used in the TLC analysis [159,160].

$KMnO_4$ solution used for TLC staining. 2g potassium permanganate, 13 g potassium carbonate was dissolved in 200mL od distill water.

5.2. Methods of analysis and identification of chemical compounds

5.2.1. Nuclear Magnetic Resonance (NMR) spectroscopy

^1H, ^{13}C, ^{19}F NMR were recorded on a VARIAN Mercury 300 MHz or Varian VNMR-S 400 MHz Spectrometer. Chemical shifts are reported as δ values (ppm). NMR spectra were recorded in deuterated solvents $CDCl_3$ or DMSO-d^6 and calibrated using an internal reference: TMS (^1H), $CDCl_3$ (^{13}C) and $CFCl_3$ (^{19}F). Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet. Coupling constants (*J*) are given in Hz.

5.2.2. Gas Chromatography-Mass Spectrometry (GC-MS)

Mass spectra (MS) were carried out with gas chromatography- mass spectrometry (Varian 4000 GC-MS chromatograph).

5.2.3. Melting point analysis

Melting points were measured on a Stuart SMP 10 apparatus.

5.2.4. Infrared spectroscopy (IR)

Infrared (IR) spectra were recorded on a Jasco FT/IR-4600 FT-IR Spectrometer and the samples were prepared as neat fine powders.

5.2.5. X-Ray structural analysis

Single crystal X-ray analyses were performed on an Xcalibur Ruby or Oxford Diffraction Xcalibur diffractometer and the some of the crystals were kept at 100 K by a Cryosystem device.

The low-temperature measurement was conducted on an Oxford Diffraction SuperNova diffractometer with monochromatic CuKα radiation, equipped with a CryoJet cooling system. Intensity data were collected at 100K using a Rigaku XtaLAB Synergy-R diffractometer with a rotating anode X-ray Source and a Cryostream cooling system. Data collection and data reduction were performed using the CrysAlis PRO software[35]. Further data processing was carried out using Olex2. The crystal structure for the aforementioned compounds was solved and refined using ShelXT[36] and ShelXL[37], respectively. For all structures, non-hydrogen atoms were refined anisotropically. In **(181)**, **(182)**, and **(183)** hydrogen atoms were derived from a difference Fourier map and refined freely. In **(173)** and in one of the two molecules, in the **(11)** asymmetric unit, the hydrogen atoms of the methyl and hydroxymethyl groups located at the chiral center were positioned with geometric constraints. The others were located on the difference Fourier map and allowed to refine isotropically. CCDC 2040718 **(181)**, 2116143 **(182)**, 2116146 **(183)**, 2116157 **(173)** and 2116174 **(169)**.

5.2.6. High Resolution Mass Spectrometry (HR-MS)

HRMS data for mass determination was collected. Measurements were performed using QTOF mass spectrometer (Impact HD, Bruker Daltonics) in the positive ions mode.

5.2.7. Thin Layer Chromatography (TLC)

Thin-layer chromatography (TLC) was carried out on 0.25 mm Merck TLC silica gel 60 F254 plates using ethyl acetate, hexane, methanol, chloroform or SSE as eluents and with detection by UV light or with stain solution (Potassium Permanganate).

5.2.8. Optical Rotations

The optical rotations were measured on a Polarimeter PERKIN-ELMER 243B at specific wavelength λ = 589 nm (sodium D-line) at at 20 ºC in a 1 dm-cell. In all cases the concentration of the solution was given as g/dL.The specific rotation are indicated in (deg·cm^2)/g.

5.3. DFT computations

Gaussian 09[28] was used to fully optimize all the structures reported in Scheme 31 and Scheme 32 at the M06 level of theory[29] with the 6-31+G** basis set.[30] Frequency calculations were carried out at the same level of theory. Transition structures were located using the Berny algorithm with the NoEigenTest request. Intrinsic reaction coordinate (IRC) calculations were used to confirm the connectivity between transition structures and minima [161]. Various combinations of conformations were examined to determine minimum energy pathways for all cyclization reactions. The polarizable continuum model (PCM) [162–164] was used to simulate methanol and ether as solvents.

5.4. General experimental procedures

General procedure I (GPI)- esterification of amino acids

General procedure II (GPII)- NH_2-protection od amino acid methyl esters with Boc_2O

General procedure III (GPIII)- reduction of amino acid methyl esters with LAH

General procedure IV (GPIV)- Swern oxidation of *N*-Boc-aminoalcohols

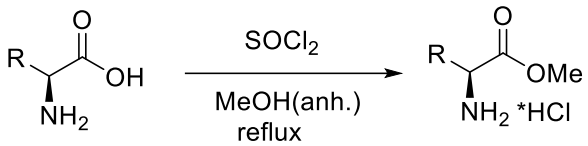
General procedure V (GPV)- Horner-Wadsworth-Emmons reaction of *N*-Boc-aminoaldehydes in the presence of *n*-BuLi

General procedure V (GPV)- Horner-Wadsworth-Emmons reaction of *N*-Boc-aminoaldehydes in the presence of LiHMDS

General procedure VI (GPVI)- reduction of amino acid methyl ester hydrochlorides with LAH

General procedure VII (GPVII)- *N*-Boc protection of amino alcohols

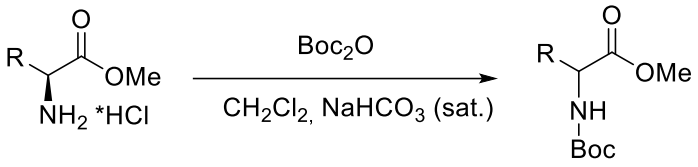
5.4.1. Synthesis of amino acids methyl esters hydrochlorides general procedure I (GPI)



R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

Thionyl chloride (1.7 equiv.) was dissolved in cold anhydrous methanol (4ml/1 mmol of amino acid) under argon atmosphere. Then, solid amino acid (1 equiv.) was added to the reaction mixture and was heated under the reflux for 3 hours and next 24 hours stirring at room temperature. Finally, the solvent was evaporated, and the reaction mixture was quenched three times with methanol and three times with diethyl ether. At the end, a solid substance has precipitated.

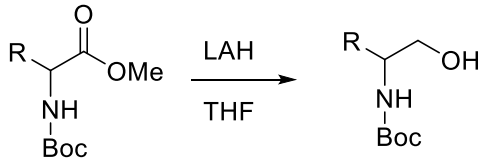
5.4.2. Synthesis of *N*-(*tert*-Butoxycarbonyl)-amino acids methyl esters - general procedure II (GPII)



R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

In a round-bottomed flask, methyl ester hydrochloride (1 equiv.) was dissolved in dichloromethane (2ml of dichloromethane per each 1mmol of the substrate). Then, di-*tert*-butyl-di-carbonate 1.5 equiv.) and saturated solution of sodium bicarbonate (1ml $NaHCO_{3(aq)}$ per each 1 ml of Boc_2O) was added and the reaction mixture was stirring for 3 hours at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was washed with deionized water. The water layer was quenched 3 times with dichloromethane. The combined organic layers were died over anhydrous sodium sulphate. Next, the solvent was removed under vacuum. The excessive reactant (Boc_2O) was removed by column chromatography (silica gel, hexane→ ethyl acetate). The combined fractions were collected, and the solvent was evaporated. All the Boc-protected methyl esters were obtained as a colourless oils.

5.4.3. Synthesis of *N*-(*tert*-Butoxycarbonyl)-amino alcohols- general procedure III (GPIII)

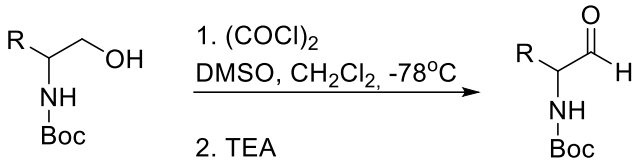


R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

A round-bottomed flask was immersed in an ice bath and LAH (3 equiv.) and freshly distilled THF (15ml of a solvent per each mmol of *N*-Boc methyl ester) was added under argon atmosphere. Then, solid amino acid derivative (1 equiv.) was added slowly, the ice-bath was removed, and the reaction mixture was stirring for 24 hours at room temperature. After the completion of the reaction (monitored by TLC), the additional LAH was neutralized with 10% solution of KOH. The mixture was filtered, and the solvent was removed under vacuum. The crude material was dissolved in diethyl ether

and extracted three times with distilled water. The combined organic layers were died over anhydrous sodium sulphate and the solvent was removed under vacuum.

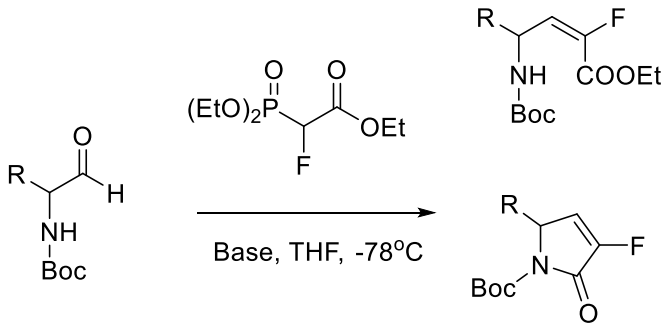
5.4.4. Synthesis of *N*-(*tert*-Butoxycarbonyl)-amino aldehydes general procedure IV (GPIV)



R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

To a solution of $(COCl)_2$ (1.2 equiv.) in freshly distilled dichloromethane at -78°C under argon atmosphere was added a solution of DMSO (2 equiv.) in dichloromethane dropwise. After 1 hour of stirring, a solution of alcohol (1 equiv.) in dichloromethane was added. After 1 hour, trimethylamine (4 equiv.) was added dropwise. The reaction mixture was stirred 30 min at -78°C then slowly allowed to warm to room temperature. The reaction mixture was extracted three times with 1% solution of hydrochloric acid, then three times with distilled water, saturated dolution of sodium hydrogencarbonate and sodium chloride. The collected organic layers were died over anhydrous sodium sulphate, and the solvent was evaporated under vaccum.

5.4.5. Horner-Wadsworth-Emmons reaction- general procedure V and VI (GPV) and (GPVI)



R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

Base= *n*-BuLi/ LiHMDS

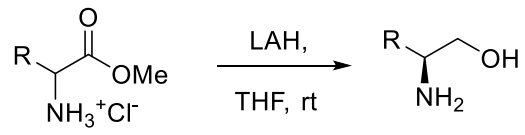
Horner–Wadsworth–Emmons Reaction with *n*-BuLi; General Procedure V (GPV):

To a solution of triethyl 2-fluoro-2-phosphonoacetate (1.2 equiv.) in anhydrous THF (5mL) under argon atmosphere at –78 °C (dry ice/isopropanol bath), *n*-butyllithium (1.2 equiv., 2.5 M in hexane) was added dropwise. After 30 minutes, *N*-Boc-aldehyde (1 equiv.) in THF (10 mL/3 mmol of aldehyde) was added dropwise. After 2 hours stirring, the THF was evaporated, and the residue was dissolved in diethyl ether and extracted with 1% hydrochloric acid. The organic layer was then dried over anhydrous Na_2SO_4, filtrated, and concentrated to form the crude product, which was purified by column chromatography on silica gel (*n*-hexane to *n*-hexane/EtOAc 8:2, v/v) to give the desired fluorovinyl amino acid derivative **177-180.**

Horner–Wadsworth–Emmons Reaction with LiHMDS; General Procedure VI (GPVI):

To a dry 100 mL round-bottom flask that was purged with argon, anhydrous THF (10 mL) was added and LiHMDS was generated in situ by adding n-BuLi (1.05 equiv., 2.5 M in hexane) and HMDS (1.05 equiv.). The reaction mixture was cooled to –78 °C (dry ice/isopropanol bath) and stirred for 1 h. Triethyl 2-fluoro-2-phosphonoacetate (1.3 equiv.) was then added and the reaction mixture was stirred for 1 h before a solution of aldehyde (1 equiv.) in THF was added dropwise. After 2 h stirring at –78 °C, the reaction was warmed to room temperature and quenched three times with 1% solution of HCl and extracted three times with diethyl ether. The organic layers were collected, dried over anhydrous sodium sulfate, filtrated, and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 98:2 to 1:1) to give the desired fluorovinyl amino acid derivatives **179** and **183**.

5.4.6. Synthesis of amino alcohols- general procedure VI (GPVI)

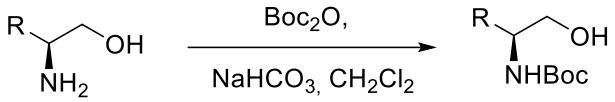


R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

Lithium aluminium hydride (3.2 equiv.) was added to amino acid methyl ester hydrochloride (1 equiv.) in dru THF (5mL/1mmol of ester). After stirring for 18 hours at room temperaturę, water and 10%

solution of KOH were added slowly. The reaction mixture was extracted with ethyl acetate. The organic layers were collected, dried oved anhydrous Na_2SO_4 and the solvent was evaporated using vacuum.

5.4.7. *N*-Boc protection of amino alcohols- Synthesis of (S)- *N*-(*tert*-Butoxycarbonyl)-amino alcohols- general procedure VII (GPVII)



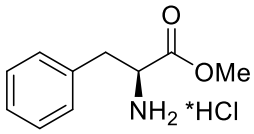
R = CH_2Ph, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

Saturated solution of sodium hydrogen carbonate (0.4mL per each 1mmol of amino alcohol) was added to a solution of amino alcohol (1 equiv.) and Boc_2O (1.5 equiv.) in dichloromethane (2.5ml per/1mmol of amino alcohol) and the resulting mixture was stirred at room temperature for 3 hours. The organic layer was separated and the aqueous layer was extracted with dichloromethane two Times. The combind organic layers were dier over anhydrous Na_2SO_4 and the excessive Boc_2O was removed by column chromatography (hexane→ethyl acetate).

5.5. Synthesis of amino acids methyl esters hydrochlorides

5.5.1. Synthesis of L-phenylalanine methyl ester hydrochloride (160)

According to the GPI, L-phenylalanine (1g, 0.006mol) was transformed to L-phenylalanine methyl ester hydrochloride.



Appearance: White solid

TLC: $CHCl_3$:MeOH = 95:5(v:v), Rf = 0.7

Yield: 99% (1.3 g, 0.0060mol)

Mp: 156-160 °C [165]

^{1}H NMR (403 MHz, DMSO.-d^6): δ = 3.35 (dd, J = 5.43, 14.10 Hz, 1H, CH_2), 3.45 (dd, J = 6.84, 14.09 Hz, 1H, CH_2), 3.67 (s, 3H, OCH_3), 4.41 (t, J = 6.04 Hz, 1H, CH), 4.41 (t, J = 6.04 Hz, 1H, CH), 7.24-7.30 (m, 5H, C_6H_5), 8.75 (s, 3H, NH_3^+).

^{13}C NMR (101 MHz, DMSO-d^6): δ = 35.98 (CH_2), 52.68 (CH), 53.32 (CH_3), 127.39-134.7 (C_6H_5), 169.48 ($\underline{C}OOCH_3$).

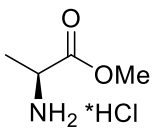
GC-MS (EI, 70Ev) m/z (rel. Int, %): 180.0 (M+, 8), 120.1 (100), 103.2 (17), 91.3 (45), 88.4 (86).

IR (neat): νmax 2842, 2700, 2620, 1742, 1583, 1483, 1446, 1290, 1238, 1211, 1083, 1061, 741, 700 cm^{-1}.

The NMR spectra were in good agreement with literature [106].

5.5.2. Synthesis of L-alanine methyl ester hydrochloride (161)

According to the GPI, L-alanine (1g, 0.0117mol) was transformed to L-alanine methyl ester hydrochloride.



Appearance: White solid

TLC: $CHCl_3$:MeOH = 85:15(v:v), Rf = 0.33

Yield: 99% (1.56 g, 0.0117 mol)

Mp: 103-105°C [166]

^{1}H NMR (403 MHz, DMSO-d^6): δ = 1.41 (d, 3H, J = 7.21 Hz, CH_3), 3.72 (s, 3H, OCH_3), 4.03 (q, 1H, J = 7.17 Hz, CH), 8.66 (s, 3H, NH_3^+).

^{13}C NMR (101 MHz, DMSO-d^6): δ = 15.80 (CH_3), 47.94 (CH), 52.98 (OCH_3), 170.50 ($\underline{C}OOCH_3$).

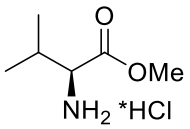
GC-MS (EI, 70Ev) m/z (rel. Int, %): 88.0 (1.5), 44.0 (100), 42.3 (10), 36.0 (17.5), 18.0 (16.5).

IR (neat): νmax 3427, 2957, 2709, 1747, 1590, 1458, 1389, 1328, 1251, 1208, 1117, 974, 904, 754 cm^{-1}.

The NMR spectra were in good agreement with literature [106].

5.5.3. Synthesis of L-valine methyl ester hydrochloride (162)

According to the GPI, L-valine (1g, 0.0085mol) was transformed to L-valine methyl ester hydrochloride.



Appearance: White solid

TLC: 50% SSE in AcOEt (v:v), Rf = 0.4

Yield: 99% (1.43 g, 0.0085mol)

Mp: 168-170°C [165]

^{1}H NMR (403 MHz, DMSO-d^6): δ = 0.92 (d, 3H, J = 6.89 Hz, CH_3), 0.97 (d, 3H, J = 6.85 Hz, CH_3), 2.17 (m, 1H, $C\underline{H}(CH_3)_2$)), 3.74 (s, 3H, OCH_3), 3.83 (s, 1H, $C\underline{H}$-NH_3^+), 8.63 (s, 1H, NH_3^+).

^{13}C NMR (101 MHz, DMSO-d^6): δ = 17.46 (CH_3), 18.39 (CH_3), 29.17 ($\underline{C}H(CH_3)_2$), 52.56 (OCH_3), 57.11 (CHNH), 169.06 ($\underline{C}OOCH_3$).

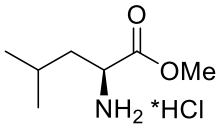
GC-MS (EI, 70Ev) m/z (rel. Int, %): 88.04 (27), 74.05 (7), 72.08 (100), 56.09 (9), 55.08 (38).

IR (neat): νmax 3418, 2992, 2673, 2615, 1700, 1571, 1465, 1379, 1341, 1334, 1107, 1069, 639 cm^{-1}.

The NMR spectra were in good agreement with literature [167] .

5.5.4. Synthesis of L-leucine methyl ester hydrochloride (163)

According to the GPI, L-leucine (1g, 0.0076mol) was transformed to L-leucine methyl ester hydrochloride.



Appearance: White solid

TLC: TLC: $CHCl_3$:MeOH = 1:9 (v:v), Rf = 0.8

Yield: 99% (1.38 g, 0.0076mol)

Mp: 134-136 °C [168]

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.98 (d, 6H, J = 5.75 Hz, CH_3), 1.86 (m, 1H, C<u>H</u>$(CH_3)_2$)), 1.96 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.10 (s, 1H, CH), 8.80 (s, 3H, NH_3^+).

^{13}C NMR (101 MHz, CDCl3): δ = 22.13 (CH_3), 22.46 (CH_3), 24.55 (<u>C</u>H$(CH_3)_3$), 39.60 (CH_2), 51.92 (OCH_3), 53.25 (CH), 170.31 (<u>C</u>$OOCH_3$).

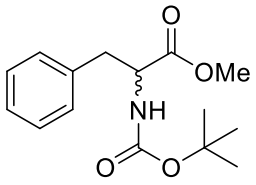
IR (neat): νmax 2926, 2854l, 2627, 1594, 1513, 1393, 1345, 1254, 948 cm^{-1}.

The NMR spectra were in good agreement with literature [106].

5.6. *N*-(*tert*-Butoxycarbonyl)-protection of amino acid methyl ester hydrochlorides

5.6.1. Synthesis of *N*-(*tert*-Butoxycarbonyl)-phenylalanine methyl ester (164)

According to the GPII, L-Phenylalanine methyl ester hydrochloride (1.3g, 0.0060mol) was transformed to N-Boc-phenylalanine methyl ester



Appearance: Colourless liquid

TLC: hexane:AcOEt = 6:1 (v:v), Rf = 0.85

Yield: 95% (1.60 g, 0.0058mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.41 (s, 9H, $(CH_3)_3$), 3.04 (dd, 1H, J = 6.25, 13.81 Hz, CH_2), 3.12 (dd, 1H, J = 5.84, 13.57 Hz, CH_2), 3.71 (s, 3H, OCH_3), 4.59 (dd, 1H, J = 6.06, 13.92 Hz, CH), 4.97 (d, 1H, J = 7.16) 7.11-7.30 (m, 5H, C_6H_5).

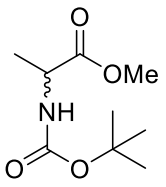
^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.42 $(CH_3)_3$, 38.47 (CH_2), 52.36 (OCH_3), 54.52 (CH), 80.05 ($\underline{C}(CH_3)$), 127.15-136.30 (C_6H_5), 155.19 ($\underline{C}OO(CH_3)_3$), 172.48 ($\underline{C}OOCH_3$).

GC MS (EI, 70Ev) m/z (rel. Int, %): 206.0 (7), 162.0 (59), 120.2 (90), 91.2 (100), 88.3 (85).

The NMR spectra were in good agreement with literature [169], [170].

5.6.2. Synthesis of *N*-(*tert*-Butoxycarbonyl)-alanine methyl ester (165)

According to the GPII, L-alanine methyl ester hydrochloride (1.59g, 0.0117mol) was transformed to *N*-Boc-alanine methyl ester.



Appearance: Colourless liquid

TLC: hexane:AcOEt = 7:3 (v:v), Rf = 0.65

Yield: 80% (1.81 g, 0.0089mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.36 (d, 3H, J = 7.20 Hz, CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 3.73 (s, 3H, OCH_3), 4.30 (m, 1H, CH), 5.05 (s, 1H, NH).

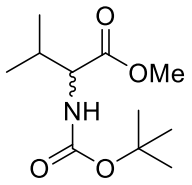
^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.79 (CH_3), 28.43 $(CH_3)_3$, 49.25 (CH), 52.45 (OCH_3), 82.71 ($\underline{C}(CH_3)_3$) 155.21 ($\underline{C}OOC(CH_3)_3$), 173.99 ($\underline{C}OOCH_3$).

GC-MS (EI, 70Ev) m/z (rel. Int, %): 144.07 (16), 130.01 (6), 102.03 (16), 88.01 (32), 69.98 (8), 59.03 (33), 57.02 (100).

The NMR spectra were in good agreement with literature [170].

5.6.3. Synthesis of *N*-(*tert*-Butoxycarbonyl)-valine methyl ester (166)

According to the GPII, L-valine methyl ester hydrochloride (1.43g, 0.0085mol) was transformed to *N*-Boc-valine methyl ester.



Appearance: Colourless liquid

TLC: hexane:AcOEt = 7:3 (v:v), Rf = 0.71

Yield: 90% (1.78 g, 0.0077mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.88 (d, 3H, J = 6.89 Hz, CH_3), 0.95 (d, 3H, J = 6.85 Hz, CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 2.11 (m, 1H, $C\underline{H}(CH_3)_2$)), 3.73 (s, 3H, OCH_3), 4.21 (dd, 1H, J=4.84, 9.15 Hz, $C\underline{H}$-NH), 5.01 (d, 1H, J = 8.38 Hz, NH).

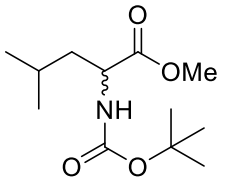
^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.74 (CH_3), 19.12 (CH_3), 28.44 ($C(\underline{C}H_3)_3$), 31.45 ($\underline{C}H(CH_3)_2$), 52.19 (OCH_3), 58.64 ($\underline{C}$H-NH), 79.91 ($\underline{C}(CH_3)_3$), 155.79 ($\underline{C}OOC(CH_3)_3$), 173.08 ($\underline{C}OOCH_3$).

GC-MS (EI, 70Ev) m/z (rel. Int, %): 172.07 (16), 158.03 (2), 130,06 (17), 116.06 (63), 72.06 (77), 57.06 (100).

The NMR spectra were in good agreement with literature [170].

5.6.4. Synthesis of *N*-(*tert*-Butoxycarbonyl)-leucine methyl ester (167)

According to the GPII, L-leucine methyl ester hydrochloride (1.43g, 0.0085mol) was transformed to N-Boc-leucine methyl ester.



Appearance: Colourless liquid

TLC: hexane:AcOEt = 9:1 (v:v) Rf = 0.25

Yield: 89% (1.67 g, 0.0068mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.92 (d, 3H, J = 2.72 Hz, CH_3), 0.94 (d, 3H, J = 2.62 Hz, CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.50 (m, 2H, CH_2), 1.68 (m, 1H, $CH(CH_3)_2$), 3.70 (s, 3H, OCH_3), 4.3 (m, 1H, CHNH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.86 (CH_3), 22.82 (CH_3), 24.75 ($CH(CH_3)_3$), 28.29 ($(CH_3)_3$), 41.81 (CH_2), 51.98 (CH), 52.17 (OCH_3), 79.82 ($C(CH_3)_3$), 155.39 ($COOC(CH_3)_3$), 174.03 ($COOCH_3$).

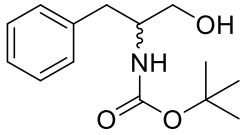
GC-MS (EI, 70Ev) m/z (rel. Int, %): 186.06 (13), 144.08 (16), 130.07 (67), 86.08 (80), 57.06 (100).

The NMR spectra were in good agreement with literature [170].

5.7. Reduction of *N*-(*tert*-Butoxycarbonyl)-amino esters

5.7.1. Synthesis of *N*-(*tert*-Butoxycarbonyl)-phenylalaninol (168)

According to the GPIII, *N*-Boc-phenylalanine methyl ester (0.5g, 0.0018mol) was reduced to *N*-Boc-phenylalaninol.



Appearance: White solid

TLC: hexane:AcOEt = 1:1, (v:v), Rf = 0.6

Yield: 89% (0.39 g, 0.0016mol)

Mp: 95-96°C [171]

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.45 (s, 9H, $(CH_3)_3$), 2.87 (d, 2H, J = 7.20, $C\underline{H}_2$-C_6H_5), 3.58 (dd, 1H, J = 5.35, 10,86 Hz, $C\underline{H}_2OH$), 3.70 (dd, 1H, J = 3.65, 11.07 Hz, $C\underline{H}_2OH$), 3.90 (s, 1H, NH), 4.79 (d, 1H, J = 7.40 Hz, CH), 7.23-7.36 (m, 5H, C_6H_5).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.47 $(CH_3)_3$, 37.57 ($\underline{C}H_2C_6H_5$), 53.86 (CH), 64.54 (CH_2OH), 79.88 ($\underline{C}(CH_3)$), 126.67-137.91 (C_6H_5), 156.30 ($\underline{C}OO(CH_3)_3$).

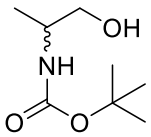
GC-MS (EI, 70Ev) m/z (rel. Int, %): 198.5 (10), 178.0 (10), 160.0 (14), 91.3 (100), 60.2 (89).

IR (neat): 3356, 2920, 2853, 1685, 1370, 1008 cm^{-1}.

The NMR spectra were in good agreement with literature [172].

5.7.2. Synthesis of *N*-(*tert*-Butoxycarbonyl)-alaninol (169)

According to the GPIII, N-Boc-alanine methyl ester (0.5g, 0.0024mol) was reduced to N-Boc-alaninol.



Appearance: White solid

TLC: Hexane:AcOEt = 1:1, (v:v), Rf = 0.55

Yield: 89% (0.28 g, 0.0016mol)

Mp: 55-57°C [173]

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.14 (d, 3H, J = 6.79 Hz, CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 3.49 (dd, 1H, J = 6.18, 10.94 Hz, CH_2), 3.62 (dd, 1H, J = 3.81, 10.94 Hz, CH_2), 3.75 (m, 1H, CH), 4.67 (s, 1H, NH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.44 (CH_3), 28.51 $(CH_3)_3$, 48.77 (CH), 67.28 (CH_2), 79.85 ($\underline{C}(CH_3)_3$) 156.51 ($\underline{C}OOC(CH_3)_3$).

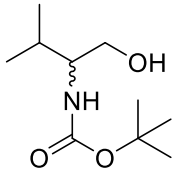
GC-MS (EI, 70Ev) m/z (rel. Int, %): 144.08 (22), 120.08 (4), 102.04 (14), 88.01 (32), 60.08 (4), 59.10 (36), 57.02 (100).

IR (neat): 3355, 2931, 2852, 1679, 1526, 1340, 1070 cm^{-1}.

The NMR spectra were in good agreement with literature [172].

5.7.3. Synthesis of *N*-(*tert*-Butoxycarbonyl)-valinol (170)

According to the GPIII, N-Boc-valine methyl ester (0.5g, 0.0022mol) was reduced to *N*-Boc-valinol.



Appearance: White solid

TLC: Hexane:AcOEt = 3:7,(v:v), Rf = 0.70

Yield: 63% (0.28 g, 0.0014mol)

Mp: 50-52°C

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.93 (d, 3H, J = 6.18 Hz, CH_3), 0.95 (d, 3H, J = 6.72 Hz, CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 1.82 (m,1H, $C\underline{H}(CH_3)_2$), 2.17 (s, 1H, OH), 3.42 (s, 1H, NH) 3.65 (ddd, 2H, J = 5.08, 11.02, 17.50 Hz, CH_2OH), 4.65 (dd, 1H, J = 4.84, 9.15 Hz, $C\underline{H}$-NH).

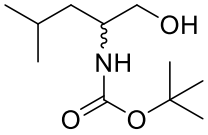
^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.65 (CH_3), 19.63(CH_3), 28.51 ($C(\underline{C}H_3)_3$), 29.74 ($\underline{C}H(CH_3)_2$), 58.24 ($\underline{C}$H-NH), 64.52 (CH_2), 79.74 ($\underline{C}(CH_3)_3$), 157.04 ($\underline{C}OOC(CH_3)_3$).

GC MS (EI, 70Ev) m/z (rel. Int, %): 172.09 (12), 160.06 (2), 130,06 (14), 116.05 (43), 72.07 (78), 57.06 (100)

The NMR spectra were in good agreement with literature [172].

5.7.4. Synthesis of *N*-(*tert*-Butoxycarbonyl)-leucinol (171)

According to the GPIII, N-Boc-leucine methyl ester (0.5g, 0.0020mol) was reduced to *N*-Boc-leucinol.



Appearance: White solid

TLC: Hexane:AcOEt = 1:1,(v:v), Rf = 0.54

Yield: 70% (0.31 g, 0.0014mol)

Mp: 104-105°C [174]

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.92 (d, 3H, J = 0.78 Hz, CH_3), 0.94 (d, 3H, J = 0.94 Hz, CH_3), 1.32 (m, 2H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.67 (m, 1H, $C\underline{H}(CH_3)_2$)), 3.29 (s, 1H, NH), 3.49 (J = 5.56, 10.81 Hz, $C\underline{H}_2OH$), 3.62 (dd, 1H, J = 3.73, 11.00 Hz, $C\underline{H}_2OH$).

^{13}C NMR (101 MHz, CDCl3): δ = 22.27(CH_3), 23.12 (CH_3), 24.84 ($\underline{C}H(CH_3)_3$), 28.45 (($\underline{C}H_3)_3$), 40.60 (CH_2), 50.89 (CH), 66.12 (CH_2OH), 79.33 ($\underline{C}(CH_3)_3$), 156.61 ($\underline{C}OOC(CH_3)_3$).

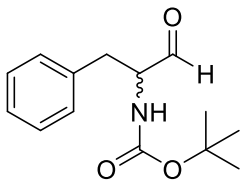
GC MS (EI, 70Ev) m/z (rel. Int, %): 186.12 (8), 144.09 (7), 130.08 (38), 86.09 (64), 57.06 (100).

The NMR spectra were in good agreement with literature [172].

5.8. Oxidation of *N*-(*tert*-Butoxycarbonyl)-amino alcohols

5.8.1. Synthesis of *N*-(*tert*-Butoxycarbonyl)-phenylalaninal (172)

According to the GPIV, *N*-Boc-phenylalaninol (0.39g, 0.0016mol) was oxidized to *N*-Boc-phenylalaninal.



Appearance: White solid

TLC: hexane:EtOAc = 7:3, (v:v), Rf = 0.55

Yield: 78% (0.30 g, 0.0012mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.43 (s, 9H, $(CH_3)_3$), 3.11 (d, 2H, J = 6.70, $C\underline{H}_2$-C_6H_5), 4.42 (m, 1H, CH), 5.05 (bs, 1H, NH), 7.14-7.34 (m, 5H, C_6H_5), 9.63 (s, 1H, CHO).

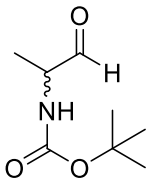
^{13}C NMR (101 MHz, $CDCl_3$): δ = 38.39 $(CH_3)_3$, 35.60 ($\underline{C}H_2C_6H_5$), 60.91 (CH), 80.34 ($\underline{C}(CH_3)$), 127.22-135.90 (C_6H_5), 155.90 ($\underline{C}OO(CH_3)_3$), 199.96 (CHO).

GC MS (EI, 70Ev) m/z (rel. Int, %): 193.5 (12), 164.0 (33), 120.2 (100), 91.5 (53), 57.3 (60).

The NMR spectra were in good agreement with literature [175].

5.8.2. Synthesis of *N*-(*tert*-Butoxycarbonyl)-alaninal (173)

According to the GPIV, *N-Boc*-alaninol (0.28g, 0.0016mol) was oxidized to *N-Boc*-alaninal.



Appearance: White solid

TLC: hexane:EtOAc = 8:2, (v:v), Rf = 0.28

Yield: 80% (0.23g, 0.0013mol)

^{1} H NMR (400 MHz, $CDCl_3$): δ= 1.33 (d, 3H, J = 7.38 Hz, CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 4.22 (m, 1H, $C\underline{H}$-NH), 5.11 (d, 1H, J = 8.40 Hz, NH), 9.55 (s, 1H, CHO).

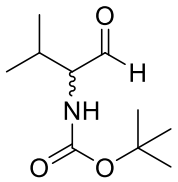
^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.99 (CH_3), 28.42 ($(CH_3)_3$, 55.65.77 (CH), 80.23 ($\underline{C}(CH_3)_3$) 155.43 ($\underline{C}OOC(CH_3)_3$), 199.87 (CHO).

GC MS (EI, 70Ev) m/z (rel. Int, %): 144.09 (12), 100,02 (3), 89.06 (7), 88.03 (23), 59,06 (45), 57,09 (100), 44.08 (56).

The NMR spectra were in good agreement with literature [175].

5.8.3. Synthesis of *N*-(*tert*-Butoxycarbonyl)-valinal (174)

According to the GPIV, *N*-Boc-valinol (0.28g, 0.0014mol) was oxidized to *N*-Boc-valinal.



Appearance: White solid

TLC: hexane:EtOAc = 8:2, (v:v), Rf = 0.52

Yield: 57% (0.16g, 0.0008mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.93 (d, 3H, J = 6.98 Hz, CH_3), 1.02 (d, 3H, J = 6.98 Hz, CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 2.27 (m, 1H, $C\underline{H}(CH_3)_2$)), 4.24 (dd, 1H, J = 4.33, 7.58 Hz, $C\underline{H}$-NH), 5.08 (d, 1H, J = 8.38 Hz, NH), 9.63 (s, 1H, CHO).

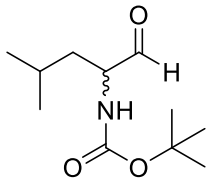
^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.68 (CH_3), 19.19 (CH_3), (28.40 ($C(\underline{C}H_3)_3$), 29.17 ($\underline{C}H(CH_3)_2$), 64.75 ($\underline{C}$H-NH), 80.08 ($\underline{C}(CH_3)_3$), 155.69 ($\underline{C}OOC(CH_3)_3$), 200.95 (CHO).

GC MS (EI, 70Ev) m/z (rel. Int, %): 172.06 (9), 116.04 (49), 98.04 (10), 72.05 (86), 59.05 (28), 57.05 (100).

The NMR spectra were in good agreement with literature [175].

5.8.4. Synthesis of *N*-(*tert*-Butoxycarbonyl)-leucinal (175)

According to the GPIV, N-Boc-leucinol (0.31g, 0.0014mol) was oxidized to *N*-Boc-leucinal.



Appearance: White solid

TLC: hexane:EtOAc = 8:2, (v:v), Rf = 0.56

Yield: 80% (0.25g, 0.0012mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.89 (d, 6H, J = 6.61 Hz, CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 1.58 (m, 1H, $C\underline{H}(CH_3)_2$)), 1.70 (m, 1H, $C\underline{H}(CH_3)_2$)), 1.70 (m, 2H, CH_2), 4.15 (m, 1H, $C\underline{H}NH$), 5.09 (d, 1H, J = 7.60 Hz, NH), 9.51 (s, 1H, CHO).

^{13}C NMR (101 MHz, $CDCl^3$): δ = 22.27(CH_3), 23.12 (CH_3), 24.84 ($\underline{C}H(CH_3)_3$), 28.45 (($\underline{C}H_3)_3$), 40.60 (CH_2), 50.89 (CH), 66.12 (CH_2OH), 79.33 ($\underline{C}(CH_3)_3$), 156.61 ($\underline{C}OOC(CH_3)_3$).

The NMR spectra were in good agreement with literature [176].

The compound **203** was obtained using Dess-Martin periodinane according to the procedure below:

Dess-Martin periodinane (0.27g, 064mmol) were suspended in 1.35 mL of dichloromethane, then within 40 minutes a solution of *N*-Boc-leucinol (0.126g, 0.573mmol) in 1.35 mL of dichloromethane was metered in. The reaction mixture and it was stirred for 2 hours at ambient temperature. Then, the it was combined with 2 mL of 20% $KHCO_3$ and 2mL of 10% $Na_2S_2O_3$ solution. The mixture was stirred for 20 min at ambient temperature, the phases were separated and the organic layers were washed with 20% $KHCO_3$ solution and water. The organic phase was dried and the solvent was evaporated using rotary evaporator. This gave (S)-*N*-Boc-leucinal (**203**) (0.1g, 82%) as a slightly yiellowish solid.

$[\alpha]_D^{20}$ = -8.5 (c = 1.00 g/dL, $CHCl_3$)

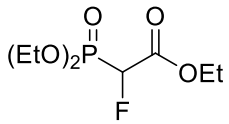
5.9. Synthesis of triethyl 2-fluoro-2-phosphonoacetate (176)

Triethyl phosphite (0.631g, 0.65ml, 3.8mmol) was added to the ethyl bromofluoroacetate (0.5g, 2.7mmol) and was placed in Schlenk rotaflo. The reaction mixture was stirred and heated at 145 °C for 6 hours. The compound was purified by silica gel column chromatography (mobile phase: chloroform). Fractions containing the compound were combined and the solvent was evaporated under vacuum.

Appearance: colourless oil

TLC: hexane:EtOAc = 1:5, (v:v), Rf = 0.56

Yield: 78% (0.511g, 2.1mmol)



^{1}H NMR (403 MHz, *CDCl$_3$*) δ = 1.39 – 1.32 (m, 9H, CH_3), 4.30 – 4.21 (m, 4H, CH_2), 4.34 (q, *J* = 7.1 Hz, 2H, $COOCH_2$), 5.20 (dd, *J* = 47.0, 12.5 Hz, 1H, CH).

^{19}F NMR: -210.48 (dd, $^{2}J_{P\text{-}F}$ = 71.8, $^{2}J_{F\text{-}H}$ = 47.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.20 ($COOCH_2\underline{C}H_3$), 16.45 (CH_3), 16.51 (CH_3), 62.60 ($COO\underline{C}H_2CH_3$), 64.40 (t, J = 6.5Hz, CH_2), 85.17 (dd, $J_{C\text{-}F}$ = 196.4, $J_{C\text{-}P}$ = 158.5, CH), 164.8 (d, J= 21.8Hz, C=O).

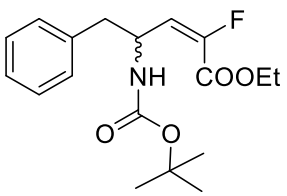
GC MS (EI, 70Ev) m/z (rel. Int, %): 242.1 (M+, 37), 158.7 (40), 131.0 (45), 99.2 (100), 65.1 (82).

The NMR spectra were in good agreement with literature [177,178].

5.10. Horner-Wadsworth-Emmons reactions

5.10.1. Synthesis of ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-5-phenylpent-2-enoate (177)

According to the GPV, N-Boc-phenylalaninal (0.70g, 0.0028mol) was converted to ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-5-phenylpent-2- enoate.



Appearance: White solid

TLC: hexane:EtOAc = 8:2, (v:v), Rf = 0.52

Yield: 34% (0.32g, 0.0009mol)

Mp: 131–134 °C

$[\alpha]_D^{20}$ = ±0.0 (c = 0.65 g/dL, $CHCl_3$)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.17 Hz, 3H, $C\underline{H}_3CH_2$), 1.31 (s, 9H, $(CH_3)_3$), 2.87 (d, *J* = 6.62 Hz, 2H, $C\underline{H}_2$-C_6H_5), 4.23 (q, *J* = 7.14 Hz, 2H, $CH_3C\underline{H}_2$), 4.57 (s, 1H, NH), 5.16 (ddt, *J* = 9.23 Hz, 6.70, 1.19 Hz, 1H, C<u>H</u>NH), 5.81 (dd, *J* = 9.36, 20.06 Hz, 1H, CH=CF), 7.13-7.28 (m, 5H, C_6H_5).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.23 (s, ($\underline{C}H_3CH_2$), 28.43 (s, $(CH_3)_3$), 41.07 (s, ($\underline{C}H_2C_6H_5$), 48.39 (s, CHNH), 61.92 (s, $CH_3\underline{C}H_2$), 79.80 (s, ($\underline{C}(CH_3)_3$), 123.88 (d, *J* = 18.00 Hz, <u>C</u>H=CF), 123.88 (s, $CH_2CH_2(CH)CH_2\underline{C}H_2$), 126.95 (s, $\underline{C}H_2CH_2(CH)CH_2CH_2$), 128.68 (s, $CH_2CH_2(CH)\underline{C}H_2CH_2$), 129.65 (s, $CH_2CH_2(CH)\underline{C}H_2CH_2$), 136.88 (s, $CH_2CH_2(\underline{C}H)CH_2CH_2$), 147.15 (d, *J* = 259.00 Hz, CH=<u>C</u>F), 155.11 (s, $\underline{C}OO(CH_3)_3$), 160.56 (d, *J* = 35.30 Hz, $\underline{C}OOCH_2CH_3$).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –121.90 (d, J = 20.28 Hz, CH=CF).

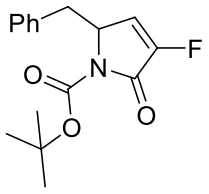
GC MS (EI, 70 eV): m/z (%) = 246.09 (5), 190.06 (18), 146.06 (37), 118.03 (13), 57.03 (100).

IR (neat): 3321, 2976, 1717, 1685, 1662, 1530, 1376, 1325, 1312, 1227, 1161, 1132, 1109, 1011, 749, 701 cm^{-1}.

ESI-MS: m/z [M + Na]+ calc for $C_{18}H_{24}FNO_4Na$: 360.1587; found: 360.1591.

5.10.2. Synthesis of 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-benzyl-1H-pyrrol-2(5H)-one (181)

Upon standing at room temperature, **177** crystallized to the cyclic form of lactam **181** (diffusion crystallization MeOH/Et_2O).



Appearance: White crystalline solid

TLC: hexane:EtOAc = 8:2, (v:v), Rf = 0.41

Yield: 80% (0.22g, 0.0008mol)

Mp: 124-127 °C

^{1}H NMR (403 MHz, dmso-d^{6}): δ = 1.38 (s, 9H, $(CH_3)_3$), 2.73 (m, 2H, C$\underline{H}_2$-C_6H_5), 3.57 (m, 1H, CHN), 6.28 (m, 1H, CH=CF), 7.13-7.36 (m, 5H, C_6H_5).

^{13}C NMR (101 MHz, dmso-d^{6}): δ = 27.67 (s, $(CH_3)_3$), 36.08 (d, *J* = 2.12 Hz, ($\underline{C}H_2C_6H_5$), 55.88 (d, *J* = 4.35 Hz, CHNH), 82.86 (s, ($\underline{C}(CH_3)_3$), 122.31 (d, *J* = 4.07 Hz, $\underline{C}$H=CF), 127.52 (s, $CH_2CH_2(CH)CH_2\underline{C}H_2$), 126.86 (s, $\underline{C}H_2CH_2(CH)CH_2CH_2$), 128.15 (s, $CH_2CH_2(CH)\underline{C}H_2CH_2$), 129.67 (s, $CH_2CH_2(CH)\underline{C}H_2CH_2$), 134.52 (s, $CH_2CH_2(\underline{C}H)CH_2CH_2$), 148.35 (s, $\underline{C}OO(CH_3)_3$), 149.27 (d, *J* = 271.05 Hz, CH=$\underline{C}$F), 160.24 (d, *J* = 32.82 Hz, $\underline{C}$OCF).

^{19}F NMR (283 MHz, dmso-d^{6}): δ = –139.58 (J = 6.41 Hz, CH=CF).

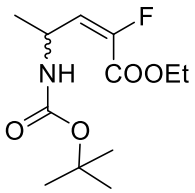
GC MS (EI, 70 eV): m/z (%) = 281.11 (8), 221.10 (11), 161.02 (28), 91.10 (30), 57.10 (100).

IR (neat): 3327, 3090, 2977, 2931, 1768, 1718, 1685, 1672, 1532, 1369, 1351, 1325, 1284, 1228, 1156, 1110, 1013, 986, 951, 896, 778, 750, 698 cm^{-1}.

ESI-MS: m/z $[M + Na]^+$ calcd for $C_{16}H_{18}FNO_3$: 314.1169; foun-d: 314.1169.

5.10.3. Synthesis of ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-2-pentenoate (178)

According to the GPV, *N*-Boc-alaninal (0.50g, 0.0029mol) was converted to ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-2-pentenoate



Appearance: pale-yellow oil

TLC: hexane:EtOAc = 7:3, (v:v), Rf = 0.63

Yield: 90% (0.68g, 0.0026mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.85 Hz, 3H, CH_3), 1.34 (t, J = 7.14 Hz, 3H, $C\underline{H}_3CH_2$), 1.41 (s, 9H, $(CH_3)_3$), 4.27 (q, J = 7.14 Hz, 2H, $CH_3C\underline{H}_2$), 4.69 (bs, 1H, NH), 5.04 (m, 1H, C$\underline{H}$NH), 5.81 (dd, J = 8.85, 20.02 Hz, 1H, CH=CF).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.20 (s, ($\underline{C}H_3CH_2$), 20.88 (CH_3), 28.78 (s, $(CH_3)_3$), 42.00 (s, CHNH), 61.80 (s, $CH_3\underline{C}H_2$), 80.39 (s, ($\underline{C}(CH_3)_3$), 124.70 (d, *J* = 17.30 Hz, $\underline{C}$H=CF), 146.55 (d, *J* = 256.60 Hz, CH=$\underline{C}$F), 154.24 (s, $\underline{C}OO(CH_3)_3$), 160.21 (d, *J* = 32 Hz, $\underline{C}OOCH_2CH_3$).

^{19}F NMR (283 MHz, $CDCl_3$): δ= -123.43 (d, J=18.38 Hz, CH=CF).

GC MS (EI, 70Ev) m/z (rel. Int, %): 246.06 (1), 190.04 (4), 161.09 (12), 132.03 (62), 57.09 (100).

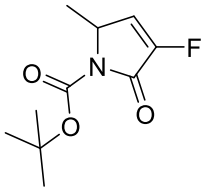
IR (neat): νmax 3360, 1727, 1683, 1666 cm^{-1}.

ESI-MS: m/z $[M + Na]^+$ calcd for $C_{12}H_{20}FNO_4$: 284.1274; found: 284.1269.

The NMR spectra were in good agreement with literature [179]

5.10.4. Synthesis of 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-methyl-1H-pyrrol-2(5H)-one (182)

Upon standing at room temperature, **178** crystallized to the cyclic form of lactam **182** (Et_2O traces, 100%).



Appearance: Colourless crystalline solid

TLC: hexane:EtOAc = 7:3, (v:v), Rf = 0.55

Yield: 99% (0.56g, 0.0026mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 1.47 (dd, 3H, J = 6.53, 1.18 Hz, CH_3), 1.56 (s, 9H, $C(CH_3)_3$), 4.53 (pd, 1H, J = 6.52, 2.46 Hz, CHN), 6.37 (dd, 1H, J = 2.46, 0.65 Hz, CH=CF).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.47 (s, CH_3), 28.21 (s, $(CH_3)_3$), 52.09 (s, CHNH), 83.98 (s, ($\underline{C}(CH_3)_3$), 122.12 (d, J = 3.66 Hz, $\underline{C}$H=CF), 148.98 (s, $\underline{C}OO(CH_3)_3$), 150.58 (d, *J* = 276.59 Hz, CH=$\underline{C}$F), 160.75 ($\underline{d}$, *J* = 35.09 Hz, $\underline{C}$OCF).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -138.74 (d, J = 6.28 Hz, CH=CF).

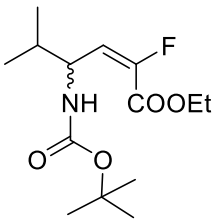
GC MS (EI, 70Ev) m/z (rel. Int, %): 190.1 (5), 161.1 (23), 146.2 (30), 132.3 (100), 57.2 (68).

IR (neat): νmax 3350, 2979, 1787, 1693, 1514, 1367, 1325, 1155, 1048, 857 cm^{-1}.

ESI-MS: m/z $[M + Na]^+$ calcd for $C_{10}H_{14}FNO_3$: 238.0856; found: 238.0850.

5.10.5. Synthesis of ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-5-methylhex-2-enoate (179)

According to the GPV, *N*-Boc-valinal (0.40g, 0.0020mol) was converted to ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-5-methylhex-2- enoate.



Appearance: White solid

TLC: hexane:EtOAc = 8:2 , (v:v), Rf = 0.67

Yield: 72% (0.207g, 0.0007mol)

A single crystal of **183** was selected and its structure was solved; however, the resulting material was a mixture of both forms **179** and **183**. Ethyl 4-(*tert*-butoxycarbonylamino)-2-fluoro-5-methylhex-2-enoate (**179**) data analyzed from mixture **179**/**183** (ratio 1:0.32).

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.92 (m, 6 H, $CH(C\underline{H}_3)_2$), 1.35 (t, J = 7.15, 7.15 Hz, 3H, $C\underline{H}_3CH_2$), 1.41 (s, 9H, $(CH_3)_3$), 1.85 (s, 1H, $C\underline{H}(CH_3)_2$), 4.30 (m, 2H, $CH_3C\underline{H}_2$), 4.66 (bs, 1H, NH), 4.85 (m, 1H, C<u>H</u>NH), 5.74 (dd, J = 21.30, 9.68 Hz, 1 H, CH=CF).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.15 (s, $\underline{C}H_3CH_2$), 18.23 (s, $CH(\underline{C}H_3)_2$), 18.88 (s, $CH(\underline{C}H_3)_2$), 28.42 (s, $(CH_3)_3$), 29.78 (s, $\underline{C}H(CH_3)_2$), 61.82 (s, CHNH), 79.52 (s, $CH_3\underline{C}H_2$), 82.39 (s, $\underline{C}(CH_3)_3$), 122.70 (d, *J* = 17.34 Hz, <u>C</u>H=CF), 147.55 (d, *J* = 256.61 Hz, CH=<u>C</u>F), 155.24 (s, $\underline{C}OO(CH_3)_3$), 161.21 (d, *J* = 32.10 Hz, $\underline{C}OOCH_2CH_3$).

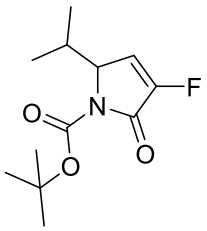
^{19}F NMR (283 MHz, $CDCl_3$): δ = -120.74 (d, 21.16 Hz, CH=CF).

GC MS (EI, 70Ev) m/z (rel. Int, %): 246.05 (4), 190.04 (23), 146.05 (60), 118.03 (13), 57.08 (100).

ESI-MS: m/z $[M + Na]^+$ calcd for $C_{14}H_{24}FNO_4$: 312.1587; found: 312.1582.

5.10.6. Synthesis of 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-isopropyl-1H-pyrrol-2(5H)-one (183)

Upon standing at room temperature, **179** crystallized to the cyclic form of lactam **183** (Et_2O traces).



Appearance: White solid

TLC: hexane:EtOAc = 8:2, (v:v), Rf = 0.60

Yield: 53% (0.071g, 0.0003mol)

Data analyzed from mixture **179/183** (ratio 0.55:1).

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.69 (d, J = 6.88 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 1.07 (d, J = 7.06 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 1.55 (s, 9H, $(CH_3)_3$), 2.63 (m, 1H, C$\underline{H}(CH_3)_2$), 4.46 (m, 1H, CHN), 6.37 (m, 1H, CH=CF).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.71 (s, CH($\underline{C}H_3$)$_2$), 19.55 (s, CH($\underline{C}H_3$)$_2$),), 28.18 (s, $(CH_3)_3$), 28.65 (d, *J* = 1.99 Hz, $\underline{C}H(CH_3)_2$, 60.79 (d, *J* = 3.03 Hz, CHNH), 83.94 (s, ($\underline{C}(CH_3)_3$), 117.84 (d, *J* = 3.88 Hz, $\underline{C}$H=CF), 149.21 (s, $\underline{C}OO(CH_3)_3$), 151.41 (d, *J* = 276.93 Hz, CH=$\underline{C}$F), 160.61 (d, *J* = 36.04 Hz, $\underline{C}$OCF).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -136.48 (d, J = 6.58 Hz, CH=CF).

GC MS (EI, 70 eV): m/z (%) = 187.01 (2), 170.02 (12), 145.01 (27), 127.00 (18), 101.03 (32), 57.07 (100).

ESI-MS: m/z $[M + Na]^+$ calcd for $C_{12}H_{18}FNO_3$: 266.1169; found: 266.1157.

According to the GPVI, *N*-Boc-valinal (0.20g, 0.0010mol) was converted to the mixture of:

ethyl 4-(*tert*-Butoxycarbonylamino)-2-fluoro-5-methylhex-2- enoate

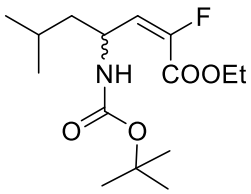
yield: 65% (0.079g, 0.0003mol)

and 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-isopropyl-1H-pyrrol-2(5H)-one

yield: 33% (0.048g, 0.0002mol).

5.10.7. Synthesis of ethyl 4-(*tert*-butoxycarbonylamino)-2-fluoro-6-metylhept-2-enoate (180)

According to the GPV, *N*-Boc-leucinal (0.14g, 0.0007mol) was converted to ethyl 4-(*tert*-butoxycarbonylamino)-2-fluoro-6-metylhept-2-enoate.



Appearance: White solid

TLC: hexane:EtOAc = 7:3, (v:v), Rf = 0.57

Yield: 88% (0.175g, 0.0006mol)

^{1}H NMR (403 MHz, $CDCl_3$): δ = 0.94 (d, 3H, $CH_2CH(C\underline{H}_3)_2$), 0.96 (d, 3H, $CH_2CH(C\underline{H}_3)_2$), 1.35 (t, *J* = 7.17 Hz, 3H, $C\underline{H}_3CH_2$), 1.41 (s, 9H, $(CH_3)_3$), 1.65 (m, 2H, $C\underline{H}_2CH(CH_3)_2$), 4.31 (q, *J* = 7.14 Hz, 2H, $CH_3C\underline{H}_2$), 4.59 (bs, 1H, NH), 5.04 (m, 1H, C<u>H</u>NH), 5.76 (dd, *J* = 9.35, 20.21 Hz, 1H, CH=CF).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.26 (s, ($\underline{C}H_3CH_2$), 21.98 (s, $CH_2CH(\underline{C}H_3)_2$), 23.16 (s, $CH_2CH(\underline{C}H_3)_2$), 24.77 (s, $CH_2\underline{C}H(CH_3)_2$), 28.45 (s, $(CH_3)_3$), 44.22 (s, $\underline{C}H_2CH(CH_3)_2$), 45.52 (s, CHNH), 61.86 (s, $CH_3\underline{C}H_2$), 79.60 (s, ($\underline{C}(CH_3)_3$), 124.78 (d, *J* = 17.26 Hz, <u>C</u>H=CF), 147.05 (d, *J* = 256.45 Hz, CH=<u>C</u>F), 155.11 (s, $\underline{C}OO(CH_3)_3$), 160.61 (d, *J*=35.62 Hz, $\underline{C}OOCH_2CH_3$).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -122.60 (*J*=20.89 Hz, CH=CF).

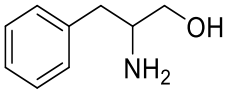
GC MS (EI, 70Ev) m/z (rel. Int, %): 190.0 (23), 160.1 (25), 146.1 (100), 118.0 (55), 57.0 (60).

IR (neat): νmax 3314, 2950, 2930, 1725, 1682, 1541, 1365, 1323, 1238, 1016 cm^{-1}.

5.11. Reduction of amino acid methyl ester hydrochlorides

5.11.1. Synthesis of 2-amino-3-phenylpropan-1-ol (192)

According to the GPVI, L-phenylalanine methyl ester hydrochloride (0.15g, 0.7mmol) was transformed into **2-amino-3-phenylpropan-1-ol**



Appearance: light yiellow oil, crystallized on standing

TLC: $CHCl_3$:MeOH = 1:9, (v:v), Rf = 0.20

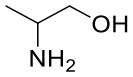
Yield: 80% (0.084g, 0.55mmol)

Mp: 92-94 ºC

The TLC and melting point data were in good agreement with [180].

5.11.2. Synthesis of 2-aminopropan-1-ol (193)

According to the GPVI, L-alanine methyl ester hydrochloride (1.00g, 7.13mmol) was transformed into 2-aminopropan-1-ol. The prodyct was nor extracted from the reaction mixture using ethyl acetate. To obtain the desired product, KOH was added, the solution was filtered, washed with THF and the solvent was evaporated to give the crude product.



Appearance: white solid

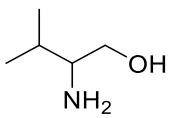
TLC: ethyl acetate:MeOH = 10:1, (v:v), Rf = 0.10

Yield: 81% (0.43g, 5.73mmol)

The TLC data was in good agreement with [181].

5.11.3. Synthesis of 2-amino-3-methylbutan-1-ol (194)

According to the GPVI , L-valine methyl ester hydrochloride (0.67g, 4.011mmol) was transformed into 2-amino-3-methylbutan-1-ol.



Appearance: colourless oil, crystallized to a white solid upon standing.

TLC: CH_2Cl_2:MeOH = 4:1, (v:v), Rf = 0.40

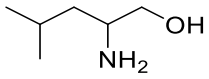
Yield: 32% (0.13g, 1.26mmol)

Mp: 32-34 ºC

The TLC and melting point data were in good agreement with [182]**.**

5.11.4. Synthesis of 2-amino-4-methylpentan-1-ol (195)

According to the GPVI, L-leucine methyl ester hydrochloride (2.00g, 0.011mol) was transformed into 2-amino-4-methylpentan-1-ol.



Appearance: white solid

TLC: $CHCl_3$:MeOH = 85:15, (v:v), Rf = 0.25

Yield: 79% (1.01g, 8.66mmol)

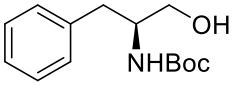
Mp: 66-69 ºC

The TLC and melting point data were in good agreement with [183].

5.12. *N*-Boc protection of amino alcohols

5.12.1. Synthesis of (S)-*N*-(*tert*-Butoxycarbonyl)-phenylalaninol (196)

According to the GPVII, 2-amino-3-phenylpropan-1-ol (0.13g, 0.86mmol) was transformed into (S)-*N*-Boc-phenylalaninol



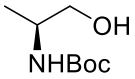
Yield: 93% (0.20g, 0.0008mol)

$[\alpha]_D^{20}$ = -18.3 (c = 1.00 g/dL, $CHCl_3$)

All obtained analysis results were the same as for compound 168.

5.12.2. Synthesis of (S)-*N*-(*tert*-Butoxycarbonyl)-alaninol (197)

2-aminopropan-1-ol (0.1717g, 2.3mmol) was transformed into (S)-*N*-Boc-alaninol according to the GPVII, but the number of moles of Boc_2O were equal to the number of moles of amino alcohol. The final product did not have to be purified of excess Boc_2O.

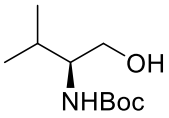


Yield: 75% (0.30g, 1.7mmol)

All obtained analysis results were the same as for compound 169.

5.12.3. Synthesis of (S)-*N*-(*tert*-Butoxycarbonyl)-valinol (198)

According to the GPVII , 2-amino-3-methylbutan-1-ol (0.47g, 4.56mmol) was transformed into (S)-*N*-Boc-valinol

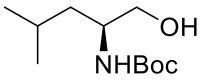


Yield: 77% (0.72g, 3.5mmol)

All obtained analysis results were the same as for compound 170.

5.12.4. Synthesis of (S)-*N*-(*tert*-Butoxycarbonyl)-leucinol (199)

According to the GPVII , 2-amino-4-methylpentan-1-ol (1.26g, 0.01mol) was transformed into (S)-*N*-Boc-leucinol.



Yield: 82% (1.92g, 8.8mmmol)

All obtained analysis results were the same as for compound 171.

5.13. Synthesis of fluorinated amino acids using chiral nickel(II) complex

5.13.1. Synthesis of nickel(II)-[N-[[5-Chloro-2-[[[(S)-1-[(3,4dichlorophenyl)methyl]-2-pyrrolidinyl-κN]carbonyl]aminoκN]phenyl]phenylmethylene]-glycinato(2-)-κN, κO] – Glycine−Ni(II) Ligand Complex

First step: Synthesis of (3,4-dichlorobenzyl)-L-proline (229)

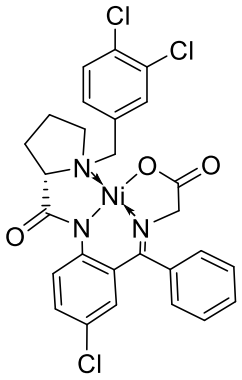
L-Proline (30.0g, 0.26 mol, 1 equiv.) as well as potassium hydroxide (30.7g, 0.55mol, 2.1 equiv.) were dissolved in isopropanol (260 mL) at 45ºC. Then, 3,4-dichlorobenzyl chloride (39.6 mL, 0.28 mol, 1.1 equiv.) was added and the reaction mixture was stirred for 4 h at 45ºC. The solution turned orange. Then, the pH was adjusted to 5 with concentrated HCl and then methanol (434.8mL) was added. The reaction mixture was stirred for 16 h at 45ºC and the precipitated potassium chloride was filtered and washed with an methanol/isopropanol mixture (2:3). The filtrate was concentrated under reduced pressure. At the end, the product was filtered, washed with acetonitrile and dried in vacuo. The (3,4-dichlorobenzyl)-L-proline was obtained as a white solid substance (63.63g, 0.23mol, 88%).

Second step: Synthesis of N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide (230)

Compound **229** (63.0 g, 0.23 mol, 1 equiv.) was dissolved in chlorobenzene (440 mL) and then cooled to 0 °C under argon protection. Then PCl_5 (48 g, 0.23 mol, 1 equiv.) was added slowly. The mixture was stirred for 40 min at 0°C and then was warmed to the room temperaturę. In the next step, 2-amino-5-chlorobenzophenone (50.91 g, 0.23 mol, 1 equiv.) was added and the mixture was stirring at room temperature for 2 h. This reaction was quenched by methanol (40 mL),further stirring for 1 h and the crude product was precipitated, filtered and washed with chlorobenzene (80 mL) as well as acetone (2 * 200 mL). The filtrated solution was concentrated leading to further precipitation of crude product which was was filtered and washed with acetone (2 * 250 mL). The product was dried in vacuo at 45 °C. The solid product was washed with MeOH (200mL), filtered and dried in vacuo at 45 °C. The N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2- carboxamide was obtained as slightly yellowish needles (83 g, 0.17 mol, 77%).

Third step: Synthesis of chiral Ni(II) complex (116a)

A compound **230** (83g, 0.17 mol, 1 equiv.), $Ni(OAc)_2*4H_2O$ (83.93g, 0.33mol, 2 equiv.) and glycine (26g, 0.33mol, 2 equiv.) was dissolved in methanol (780mL). The green suspension was stirred at room temperature and then DBU (114.15 mL, 0.85 mol, 5 equiv.) was added. The suspension was warmed to 75 °C and stirred for 72 h. Afterwards, the reaction was quenched by 6% solution of acetic acid (846 mL) and the reaction mixture was further stirring for 3 h. The final product was filtered, washed with water (582 mL) and a water/methanol-mixture (1:1) (582 mL) and then dried in vacuo at 55 °C. The Nickel(II)-[N-[[5-Chloro-2-[[[(S)-1-[(3,4dichlorophenyl)methyl]-2- pyrrolidinyl-ϰN]carbonyl]aminoκN]phenyl]phenylmethylene]-glycinato(2-)-ϰN, ϰO] – Glycine–Ni(II) Ligand Complex **116a** was obtained as a red solid (86.7 g, 0.13 mol, 77%). [184]

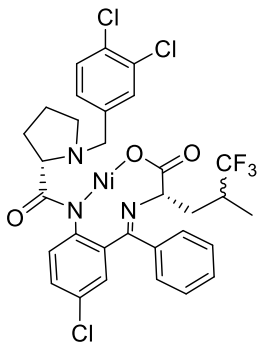


^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.13 – 1.67 (m, 2H), 2.36 – 2.26 (m, 1H), 2.56 – 2.48 (m, 1H), 3.53 – 3.20 (m, 1H), 3.76 – 3.67 (m, 2H), 3.80 (s, 1H), 3.90 – 3.86 (m, 1H), 4.37 (d, J = 12.8 Hz, 1H), 6.76 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 7.20 (dd, J = 9.2, 2.4 Hz, 1H), 7.26 (d, J = 6.3 Hz, 1H), 7.70 – 7.44 (m, 3H), 7.80 – 7.75 (m, 1H), 8.20 (dd, J = 9.1, 1.2 Hz, 1H), 8.61 (dd, J = 8.1, 2.1 Hz, 1H), 8.79 (d, J = 2.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.81, 30.95, 58.65, 62.96, 70.85, 122.93, 126.39, 130.15, 130.24, 130.40, 131.09, 131.08, 132.09, 132.26, 132.45, 133.18, 133.35, 133.54, 133.85, 134.01, 134.67, 138.66, 140.95, 174.41, 176.97, 180.97.

5.13.2. Synthesis of Ni(II)- Schiff Base complex of TfLeu (232)

Chiral nickel(II) complex **116a** (2.5g, 4.15 mmol, 1.0 equiv) was dissolved in dry, degassed DMF (5 mL/mmol = 20.75mL) under an argon atmosphere. Alkyl iodide **231** (1037mg, 4.36 mmol,1.05 equiv) and then NaH (216mg 60% dispersion in mineral oil, 5.40 mmol, 1.3 equiv) were added to the solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Then 1mL of H_2O was added to the solution, and the reaction mixture was stirred for 1 h. The precipitated product was filtered from the reaction mixture and dried under high vacuum. The desired product was obtained as red solid (1.78g, 60%). The product was a mixture of both diastereoisomers which were separated using colum chromatography (eluent: $CHCl_3$:acetone = 30:1 (v:v)).



^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.46 (d, J = 6.8Hz, 3H), 3.21 (d, J = 12.6Hz, 1H), 3.37 (dd, J = 11.3, 5.6Hz, 1H), 3.52-3.55 (m, 1H), 3.61-3.69 (m, 1H), 3.82 (dd, J = 12.1, 3.9 Hz, 1H), 4.32 (d, J = 12.6 Hz, 1H), 6.59 (d, J = 2.6Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 7.12 (dd, J = 9.3, 2.6 Hz, 1H), 7.32 (d, J = 7.0 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.50-7.52 (m, 1H), 7.55-7.60 (m, 2H), 7.77 (dd, J = 8.2, 2.1 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H), 8.88 (d, J = 2.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 11.10, 24.06, 30.94, 34.52 (q, J = 26.0 Hz), 36.60, 58.64, 63.07, 67.26, 71.39, 124.52, 126.00 (q, J = 282.0 Hz), 127.31, 127.34, 127.52, 129.56, 130.05, 130.61, 131.21, 132.14, 132.49, 132.70, 133.54, 133.73, 134.99, 140.73, 170.38, 177.92, 180.11.

First diastereoisomer **232a**

TLC: Rf = 0.56 (chloroform:acetone = 6:1 v:v)

Yield: (0.8177 g, 27%)

^{19}F NMR (283 MHz, $CDCl_3$): δ = -73.95, d, J = 8.88Hz.

Second diastereoisomer **232b**

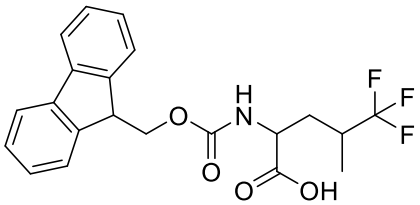
TLC: Rf = 0.50 (chloroform:acetone = 6:1 v:v)

Yield: (0.8290 g, 28%)

^{19}F NMR (283 MHz, $CDCl_3$): δ = -73.27, d, J = 9.31 Hz

5.13.3. Synthesis of 2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-5,5,5-trifluoro-4-methylpentanoic acid = FmocTfLeu (233)

The alkylated Ni(II) complex **232a and 232b** (100 mg, 0.14 mmol, 1.0 equiv) was dissolved in DME (3.33 mL/mmol=0.46mL) and aqueous HCl solution (3M, 0.23 Ml, 0.7 mmol, 5.0 equiv) was added. The reaction mixture was stirred for 2 h at 60 °C. The reaction mixture was cooled to room temperature, and the precipitated ligand was filtered from the solution, washed with H_2O and dried under high vacuum. The filtrate was concentrated under reduced pressure and then MeCN (0.28mL) and EDTA Na_2 (52mg, 0.14 mmol, 1.0 equiv) were added to the filtrate. The reaction mixture was stirred at 23 °C for 2 h. The pH of the solution was treated with aq. NaOH solution to pH 7, and Na_2CO_3 (0.03g, 0.28 mmol, 2.0 equiv) was added to the mixture. FmocOSu (47.38mg, 0.14 mmol, 1.0 equiv) was dissolved in acetone (1mL) and added dropwise to the reaction solution. After 16 h of stirring at room temperature, the mixture of solvents was removed under reduced pressure, H_2O (1 Ml) was added, and the mixture was treated with aq. HCl (6M) to pH 2. The resulting solution was extracted with EtOAc, the organic phases were combined and dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography to yield **233a and 233b** as a slightly yiellowish solid.



^{1}H NMR (600 MHz, MeOH-d^4): δ = 1.16 (d, J = 7.0 Hz, 3H), 1.64-1.69 (m, 1H), 2.18-2.24 (m, 1H), 2.39-2.49 (m, 1H), 4.21-4.26 (m, 2H), 4.38 (d, J = 7.1 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.67 (t, J = 7.1 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.25, 33.85, 35.19, 47.28, 50.98, 51.86, 67.31, 120.20 (2C), 125.11 (d, J =, 2C), 127.50 (2C), 127.75 (q, J = 280.4 Hz), 127.95 (2C), 141.50 (2C), 143.75 (d, J = 22 Hz, 2C), 156.02, 175.72.

First diastereoisomer **233a**

TLC: Rf = 0.21 (SSE)

Yield: (53mg, 96%)

Column chromatography contidions: $CHCl_3$-> $CHCl_3$+10% MeOH

^{19}F NMR (283 MHz, MeOH-d^4): δ = -74.51, d, J = 9.22 Hz.

Second diastereoisomer **233b**

TLC: Rf = 0.16 (SSE)

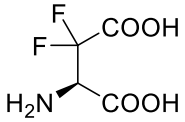
Yield: (50mg, 91%)

Column chromatography contidions: Hexane->hexane:ethyl acetate (8:2 v:v)

^{19}F NMR (283 MHz, MeOH-d^4): δ = -74.90, d, J = 9.30 Hz.

5.13.4. Synthesis of 3-amino-2,2-difluorosuccinic acid (α-difluoro aspartic acid) (235)

200mg of **234** was added at 70ºC to a mixture of aq. HCl (6M, 2.30 mL, 14mmol, 50equiv) and MeOH (2.40 mL). The resulting reaction mixture was refluxed for 1h. After cooling to room temperature, the solvent wa removed under reduced pressure. The residue was dissolved in aqueous solution of ammonia (1M, 10mL) and washed with dichloromethane (3x30mL). The organic solvents were collected, dried over Na_2SO_4, filtered and concentrated in vacuo to afford the ligand **118**. The aqueous phase was concentrated and dissolved in water (5mL) and the pH was adjusted to pH 6. The reaction mixture was purified using 2g of Dowex 50x2 100 ion-exchange column (washed several times with dichloromethane and then several times with H_2O (till the colourless eluent). The column was refill several times with water and then washed with 5% of ammonia aqueous solution [155]. Water fractions and ammonia franctions were collected separately. The desired product was obtained as a white solid.



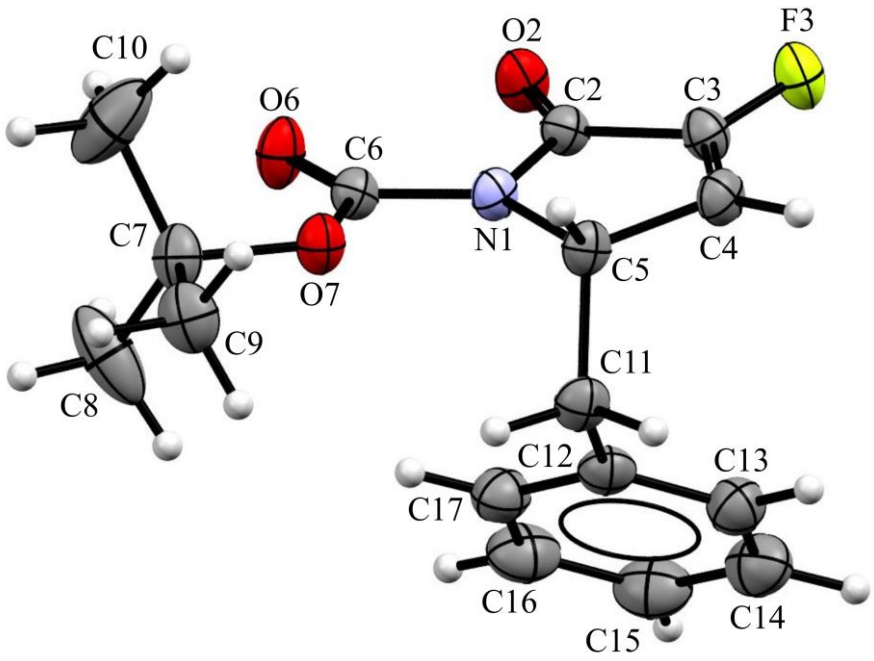
Yield: 40.7mg, 87%

^{1}H NMR (600 MHz, D_2O): δ = 3.61 (dt, J = 6.2, 2.3 Hz, 1H)

^{13}C NMR (101 MHz, D_2O): δ = 55.60, 112.83, 165.77 (2C).

5.14. X-ray analysis of the crystal structures

(R/S)- 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-benzyl-1H-pyrrol-2(5H)-one (181)



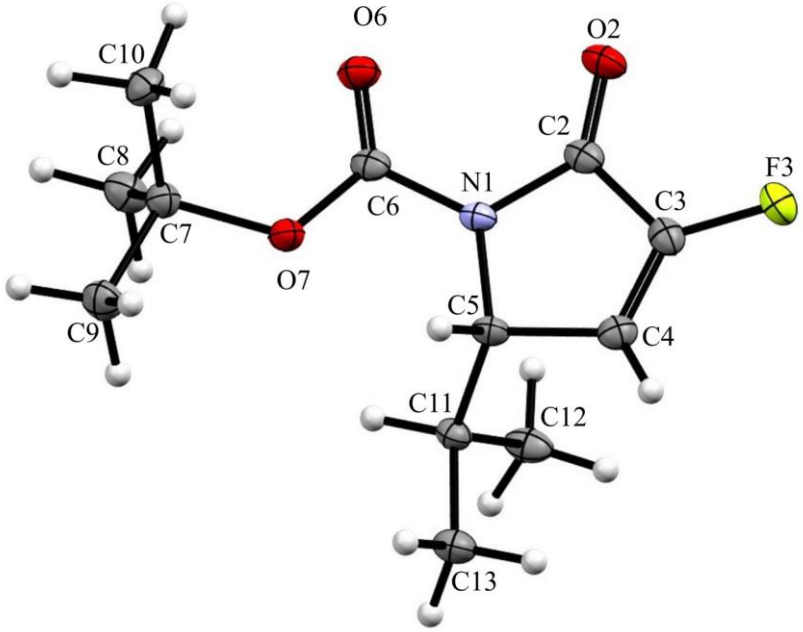
Asymmetric part of a unit cell, showing the molecule with the (S) configuration for the determined crystal structure of the **181** racemate.

Selected crystallographic data: space group $P2_1/c$, unit cell parameters a = 6.5298(1) Å, b = 15.6868(3) Å, c = 15.2735(3) Å, β = 100.195(2)°, V = 1539.79(5) $Å^3$

Selected geometrical parameters:

F3—C3	1.3347(14) Å
C3—C4	1.3196(17) Å
C5—C4	1.4968(17) Å
N1—C5	1.4790(13) Å
N1—C2	1.3935(15) Å
N1—C6	1.3958(15) Å
C2—N1—C6	123.92(9)°
F3—C3—C2	118.19(10)°
N1—C5—C11	112.41(9)°

(R/S)- 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-isopropyl-1H-pyrrol-2(5H)-one (183)



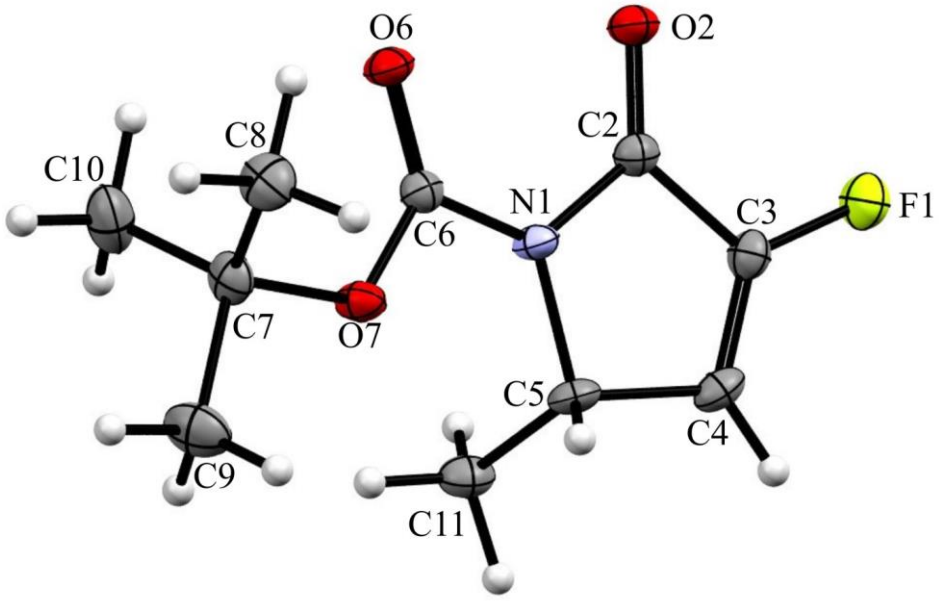
Asymmetric part of a unit cell, showing the molecule with the (S) configuration for the determined crystal structure of the **183** racemate.

Selected crystallographic data: space group $P2_1/n$, unit cell parameters a = 9.56966(17) Å, b = 6.21787(10) Å, c = 20.9605(4) Å, β = 90.3386(17)°, V = 1247.19(4) $Å^3$.

Selected geometrical parameters:

F3—C3	1.345(2) Å
C3—C4	1.314(3) Å
C5—C4	1.501(3) Å
N1—C5	1.483(2) Å
N1—C2	1.403(2) Å
N1—C6	1.399(2) Å
C2—N1—C6	123.06(15)°
F3—C3—C2	118.59(17)°
N1—C5—C11	112.38(15)°

(R/S)- 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-methyl-1H-pyrrol-2(5H)-one (182)



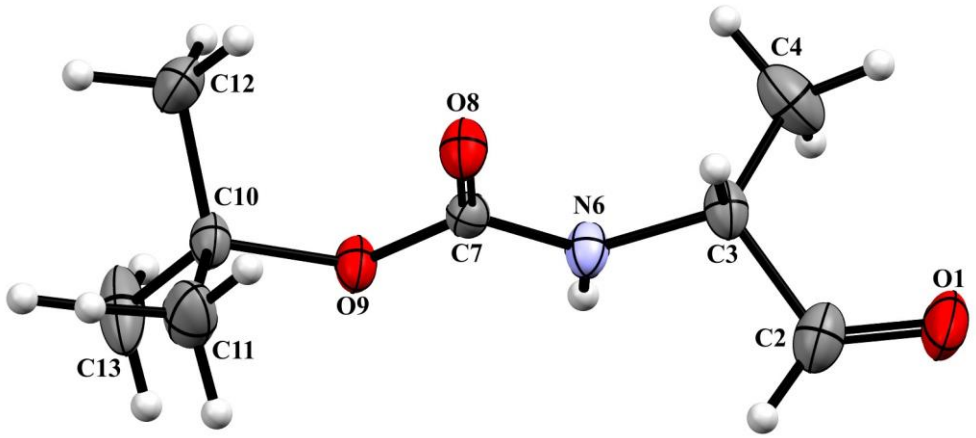
Asymmetric part of a unit cell, showing the molecule with the (S) configuration for the determined crystal structure of the **182** racemate

Selected crystallographic data: space group $P2_1/n$, unit cell parameters a = 6.5538(3) Å, b = 8.3652(4) Å, c = 20.4576(8) Å, β = 95.291(4)°, V = 1116.80(9) $Å^3$.

Selected geometrical parameters:

F3—C3	1.340(2) Å
C3—C4	1.314(2) Å
C5—C4	1.497(2) Å
N1—C5	1.487(2) Å
N1—C2	1.393(2) Å
N1—C6	1.394(2) Å
C2—N1—C6	124.12(11)°
F3—C3—C2	118.18(12)°
N1—C5—C11	111.47(11)°

(R/S)- *N*-(*tert*-Butoxycarbonyl)-alaninal (172)



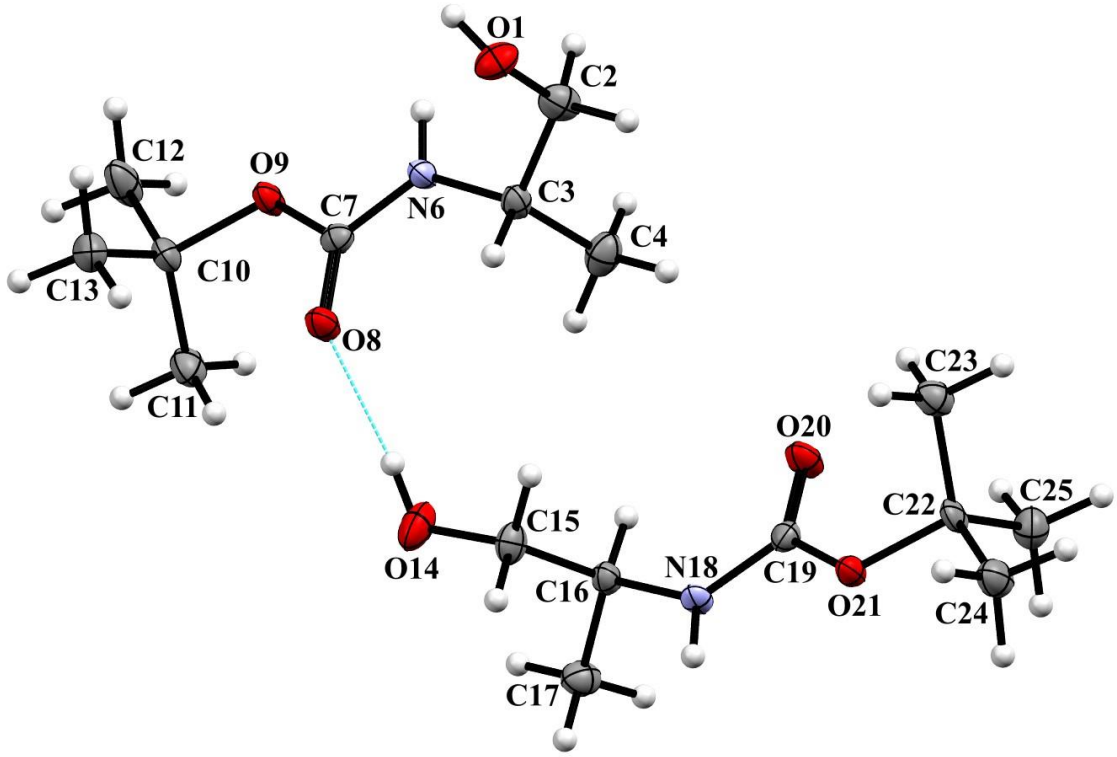
Asymmetric part of a unit cell, showing a molecule with the (R) configuration of the determined crystal structure of the AlaCHO racemate. A fragment of the structure related to the disorder of the methyl group and the aldehyde oxygen atom at the C3 carbon atom has been omitted.

Selected crystallographic data: space group $P2_1$, unit cell parameters a = 10.4142(8) Å, b = 9.5214(5) Å, c = 10.8071(9) Å, β = 115.240(10)°, V = 969.30(14) $Å^3$.

Selected geometrical parameters:

O8—C7	1.2163(15) Å
O9—C7	1.3462(14) Å
N6—C7	1.3494(15) Å
N6—C3	1.4487(15) Å
C2—O1	1.198(2) Å
O8—C7—O9	125.69(11)°
O8—C7—N6	124.89(11)°
O1—C2—C3	120.10(16)°

(R/S)- *N*-(*tert*-Butoxycarbonyl)-alaninol (168)



Asymmetric part of the unit cell, constituting a fragment of the AlaCHO crystal structure. A fragment of the structure related to the disorder of the methyl and hydroxymethyl groups at the C3 carbon atom has been omitted.

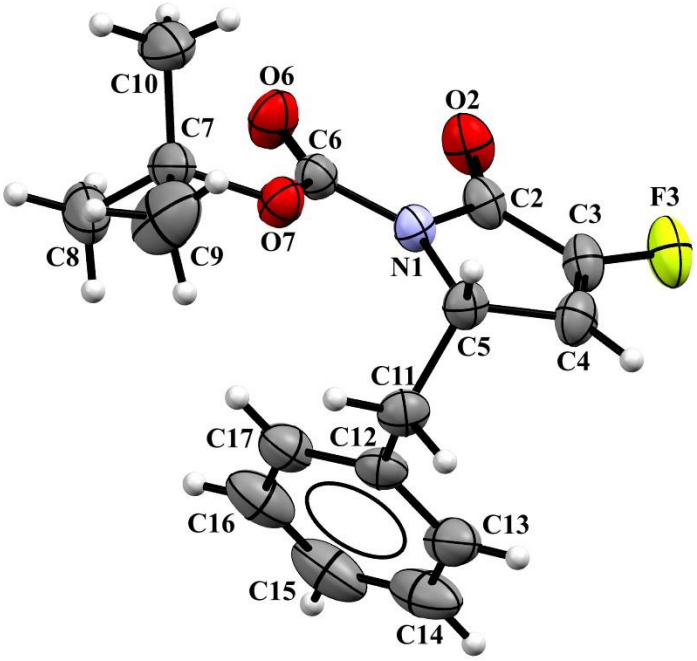
Selected crystallographic data: space group $P2_1/n$, unit cell parameters a = 10.6707(5) Å, b = 9.3460(3) Å, c = 10.8953(5) Å, β = 118.909(6)°, V = 951.17(8) $Å^3$.

Selected geometrical parameters:

O8—C7	1.239(4) Å
O9—C7	1.336(4) Å
N6—C7	1.349(2) Å
N6—C3	1.449(2) Å
C2—O1	1.198(2) Å
O8—C7—O9	125.7(1)°
O8—C7—N6	124.9(1)°
O1—C2—C3	120.1(2)°

O20—C19	1.215(5) Å
O21—C19	1.352(4) Å
N18—C19	1.343(4) Å
N18—C16	1.455(4) Å
O14—C15	1.425(4) Å
O20—C19—O21	125.2(4)°
O20—C19—N18	125.4(4)°
O14—C15—C16	110.7(3)°

(S)- 1-(*tert*-Butoxycarbonylamino)-3-Fluoro-5-benzyl-1H-pyrrol-2(5H)-one (S enantioner of 181)



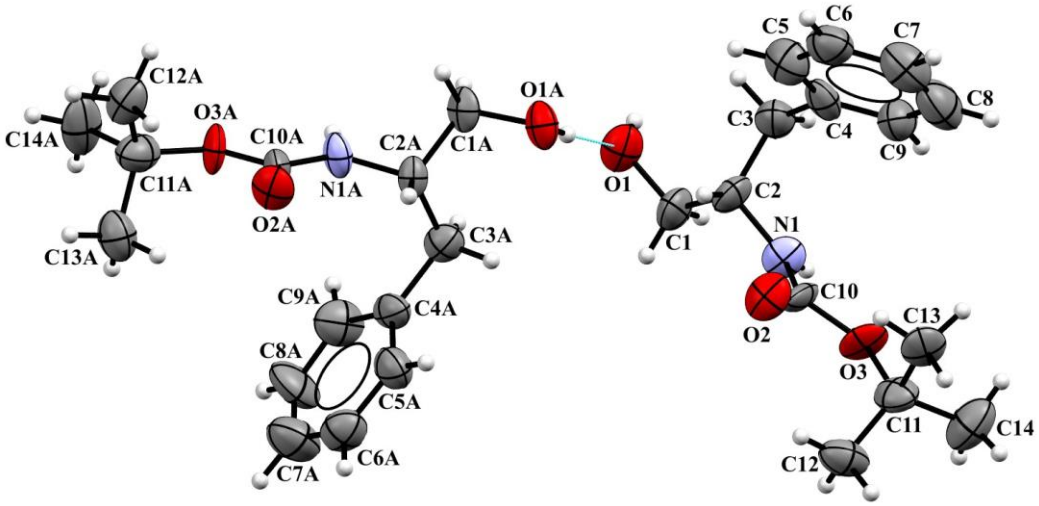
Asymmetric part of the (S)-**181** unit cell.

Selected crystallographic data: space group $P2_12_12$, unit cell parameters a = 6.3452(1) Å, b = 13.4439(3) Å, c = 18.4576(5) Å, V = 1574.51(6) Å^3.

Selected geometrical parameters:

F3—C3	1.341(3) Å
C3—C4	1.294(4) Å
C5—C4	1.491(4) Å
N1—C5	1.478(3) Å
N1—C2	1.396(3) Å
N1—C6	1.387(3) Å
C2—N1—C6	124.1(2)°
F3—C3—C2	118.3(3)°
N1—C5—C11	113.2(2)°

(S)- *N*-(*tert*-Butoxycarbonyl)-phenylalaninol (196).



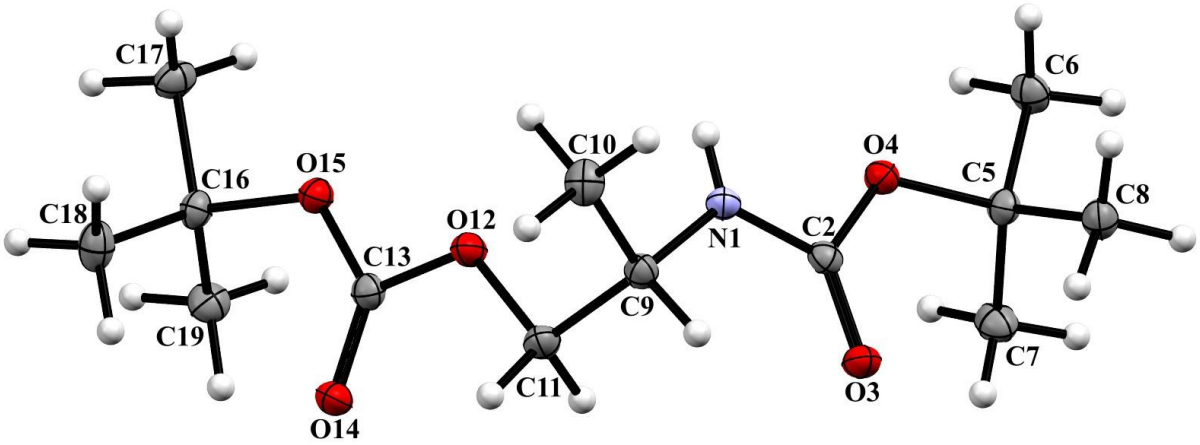
Asymmetric part of the unit cell, composed of two molecules **(S)-196.**

Selected crystallographic data: space group *C2*, unit cell parameters a = 28.285(2) Å, b = 5.1995(5) Å, c = 19.9273(18) Å, β = 95.019(8)°, V = 2919.4(4) Å^3.

Selected geometrical parameters:

O1—C1	1.41(2) Å
O1A—C1A	1.44(2) Å
N1—C2	1.42(3) Å
N1A—C2A	1.42(2) Å
N1—C10	1.33(4) Å
N1A—C10A	1.28(3) Å
O2—C10	1.23(4) Å
O2A—C10A	1.25(4) Å
O1—C1—C2	112.5(19)°
O1A—C1A—C2A	115.1(17)°
O2—C10—N1	129(3)°
O2A—C10A—N1A	128(3)°

(S)- *Tert*-butyl (S)-(1-((tert-butoxycarbonyl)oxy)propan-2-yl)carbamate (208).



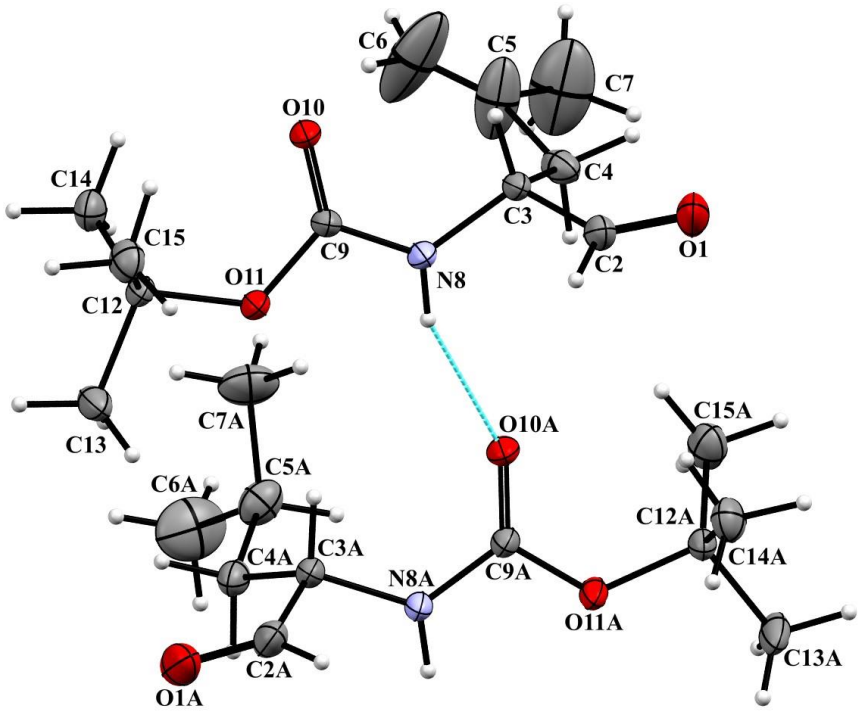
Asymmetric part of the unit cel.

Selected crystallographic data: space group $P2_12_12$, unit cell parameters a = 5.9133(2) Å, 11.4649(4) Å, 23.0995(9) Å, V = 1566.04(10) Å^3.

Selected geometrical parameters:

N1—C2	1.346(3) Å
O3—C2	1.215(3) Å
O4—C2	1.355(3) Å
O12—C13	1.329(3) Å
O14—C13	1.206(3) Å
O15—C13	1.323(3) Å
C10—C9—C11	111.8(2)°
N1—C9—C10	110.1(2)°
N1—C9—C11	111.3(2)°

(R/S)- *N*-(*tert*-Butoxycarbonyl)-leucinal (175)



A fragment of the crystal structure of the LeuCHO racemate, which is an asymmetric part of the unit cell, which consists of (R)-LeuCHO and (S)-LeuCHO molecules..

Selected crystallographic data: space group $P\bar{1}$, unit cell parameters a = 9.3840(4) Å, b = 10.6407(7) Å, c = 14.4113(12) Å, α = 105.583(7)°, β = 97.541(5)°, γ = 90.534(4)°, V = 1372.62(17) Å^3.

Selected geometrical parameters:

C2-O1	1.175(5) Å
C9-O10	1.210(4) Å
C9-O11	1.347(4) Å
C2A-O1A	1.176(6) Å
N8A-C9A	1.445(5) Å
C9A-O11A	1.338(5) Å
C12-O11-C9	121.9(3)°
O1-C2-C3	125.5(5)°
C12A-O11A-C9A	121.7(3)°
O1-C2-C3	125.6(6)°

5.15. NMR spectra of the obtained products

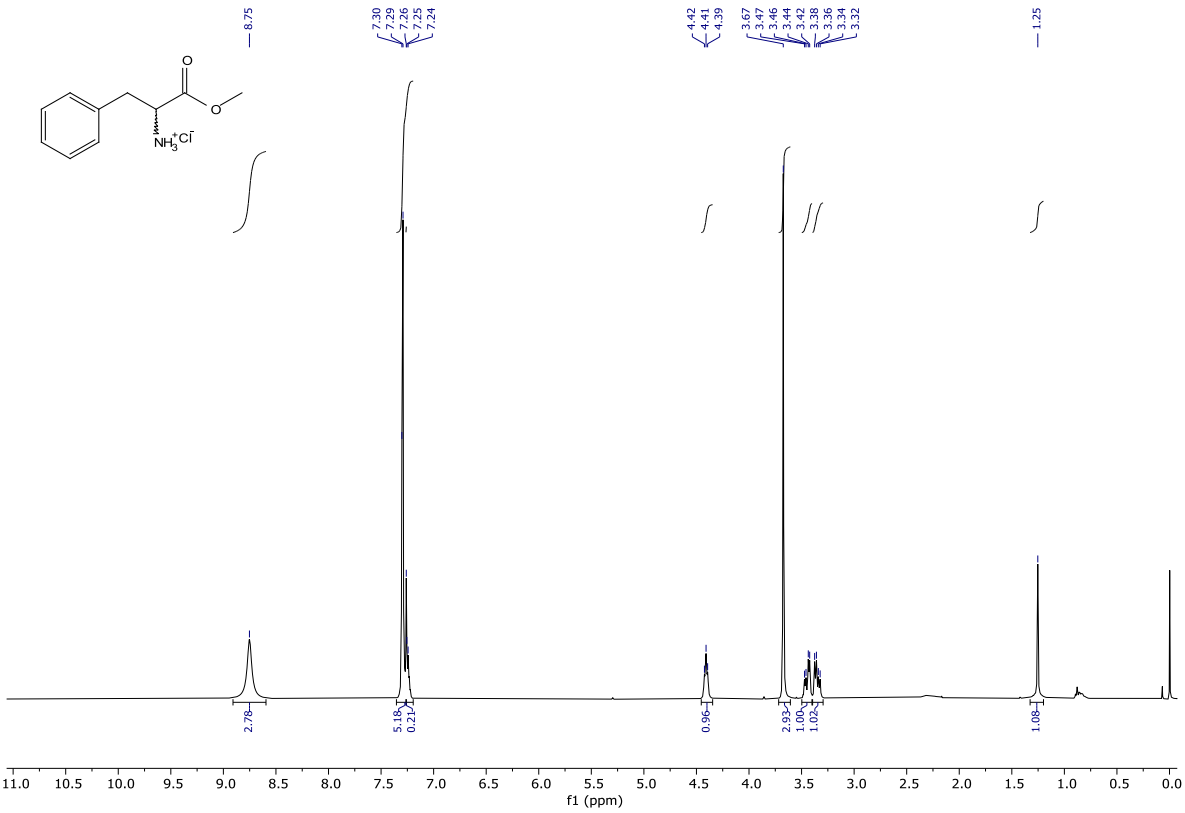


Fig. 39. [1]HNMR spectrum of compound 160.

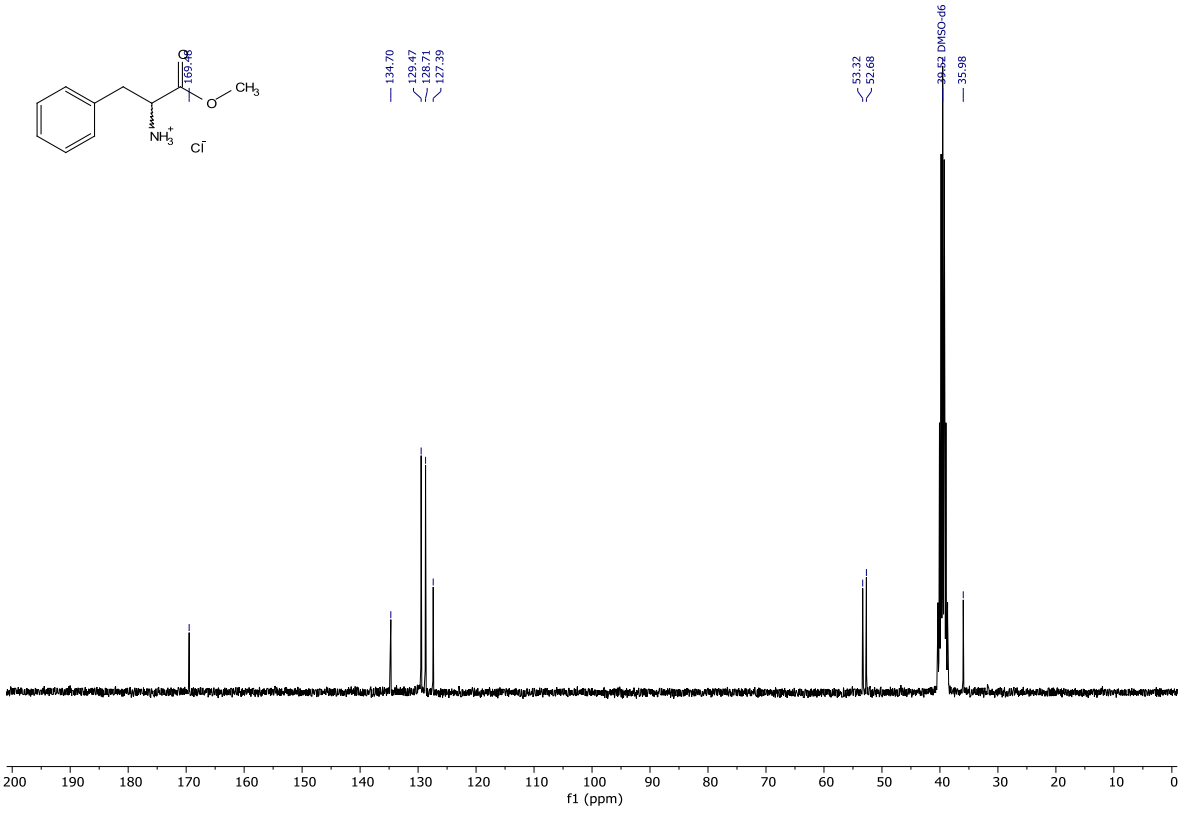


Fig. 40. [13]CNMR spectrum of compound 160.

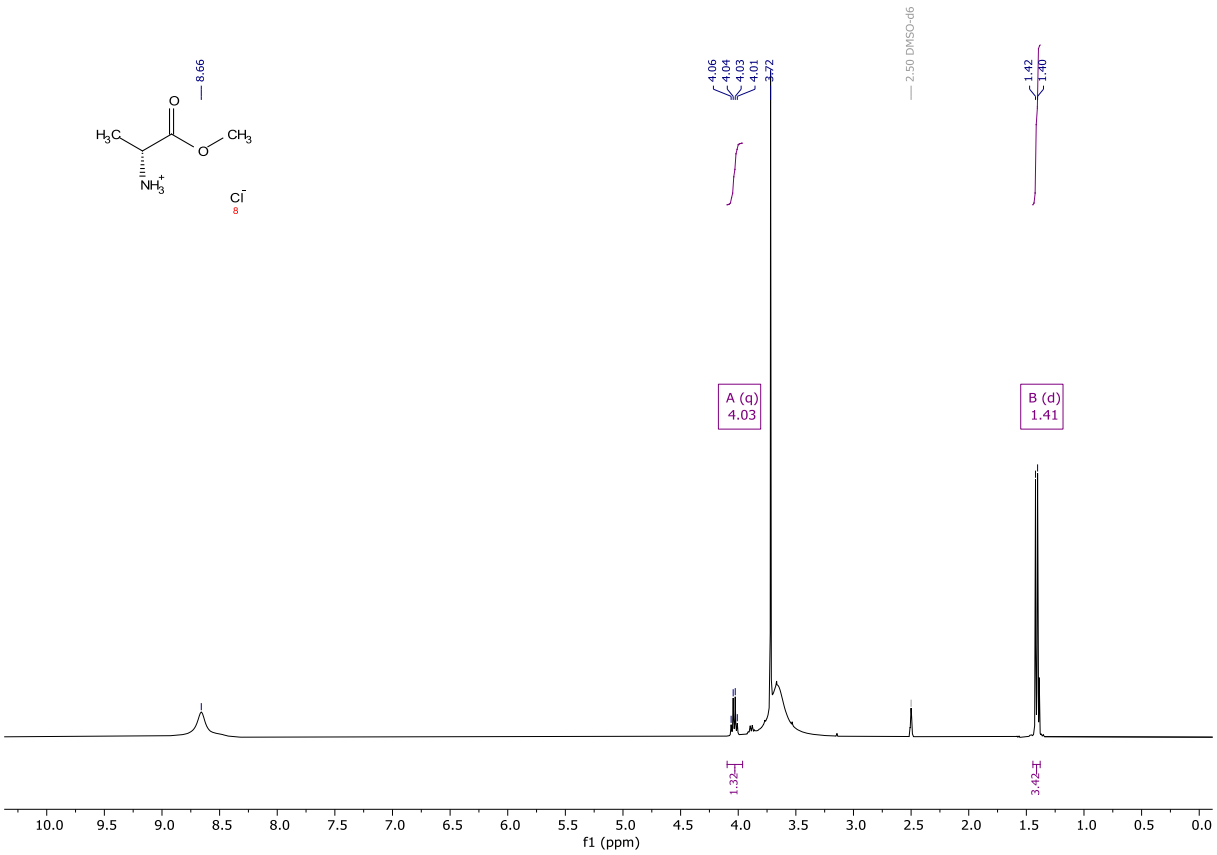


Fig. 41. [1]HNMR spectrum of compound 161.

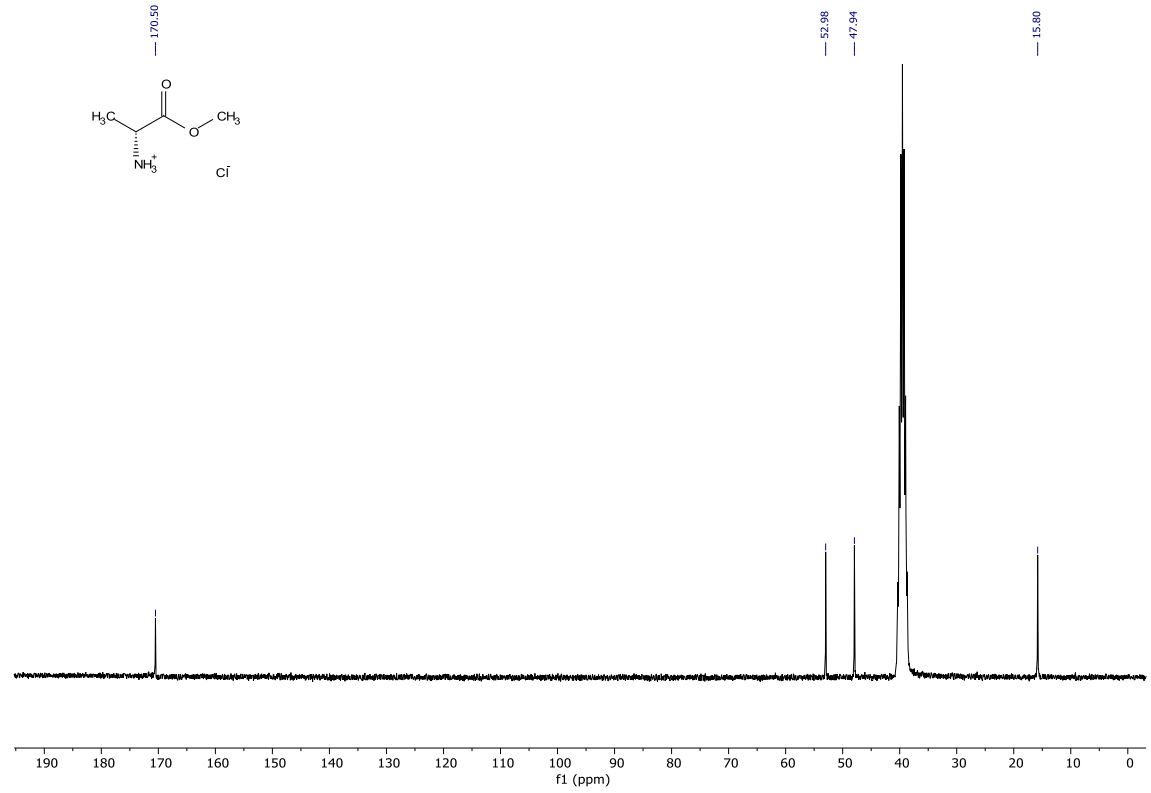


Fig. 42. [13]CNMR spectrum of compound 161.

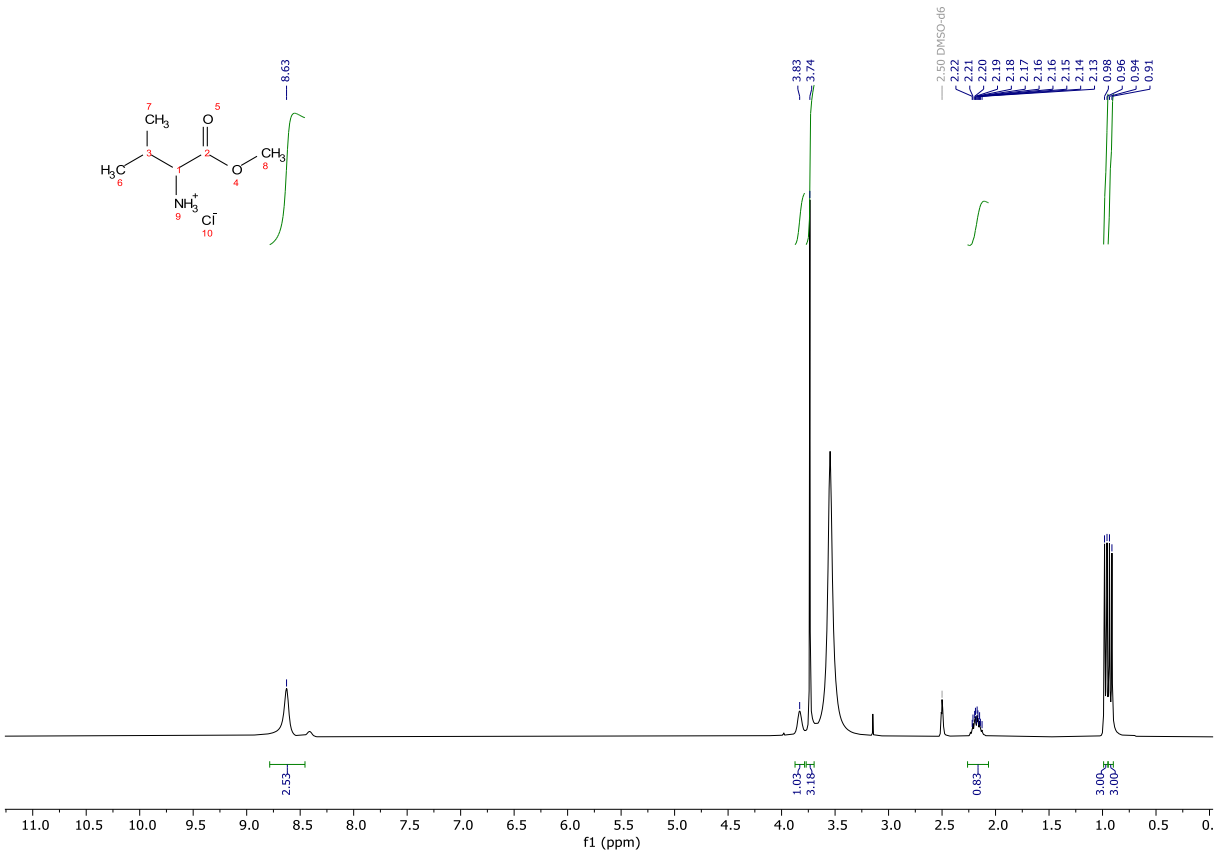


Fig. 43. [1]HNMR spectrum of compound 162.

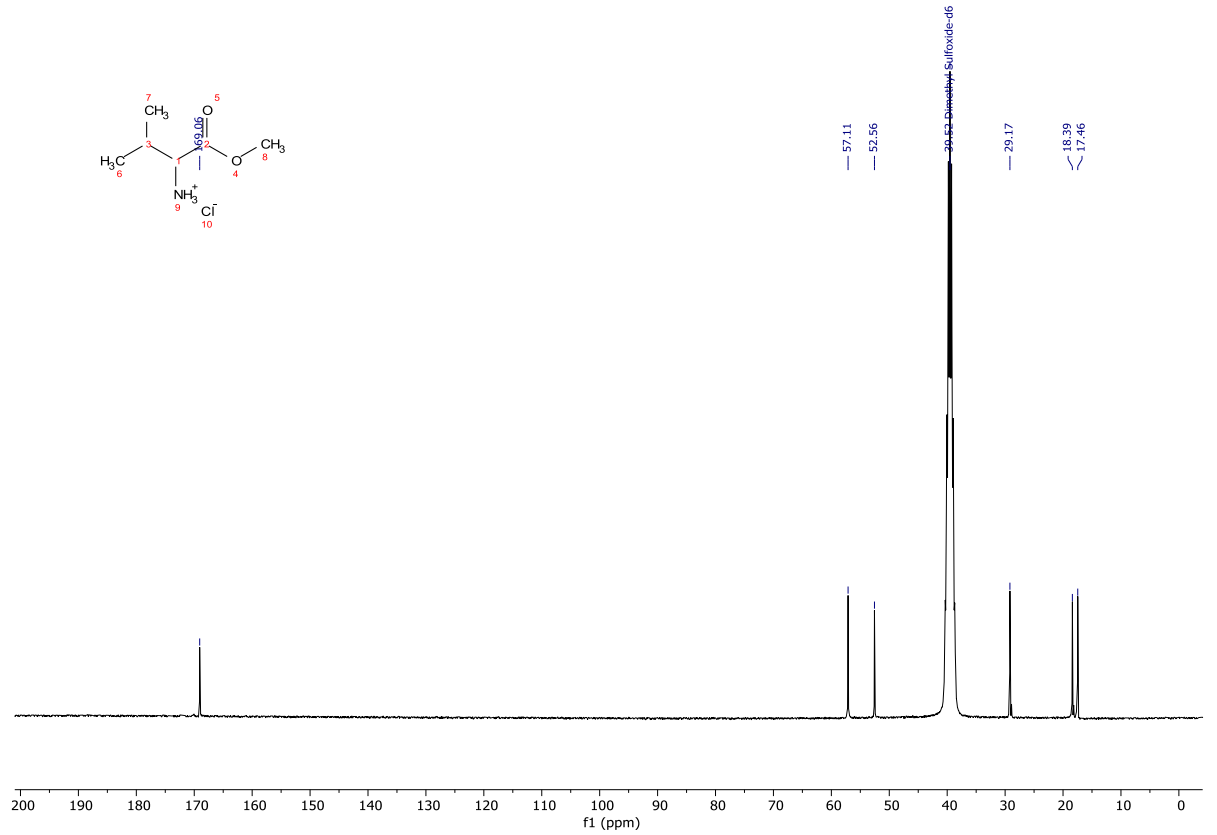


Fig. 44. [13]CNMR spectrum of compound 162.

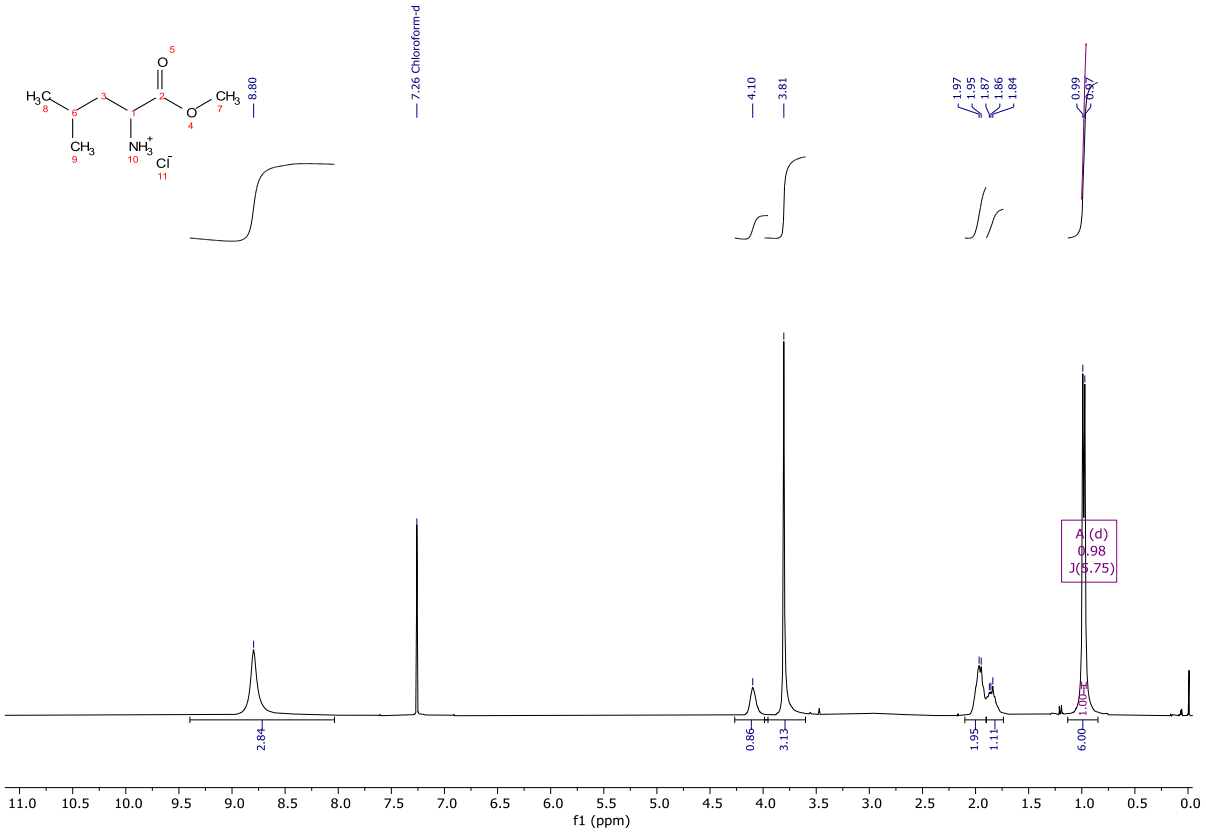


Fig. 45. [1]HNMR spectrum of compound 163.

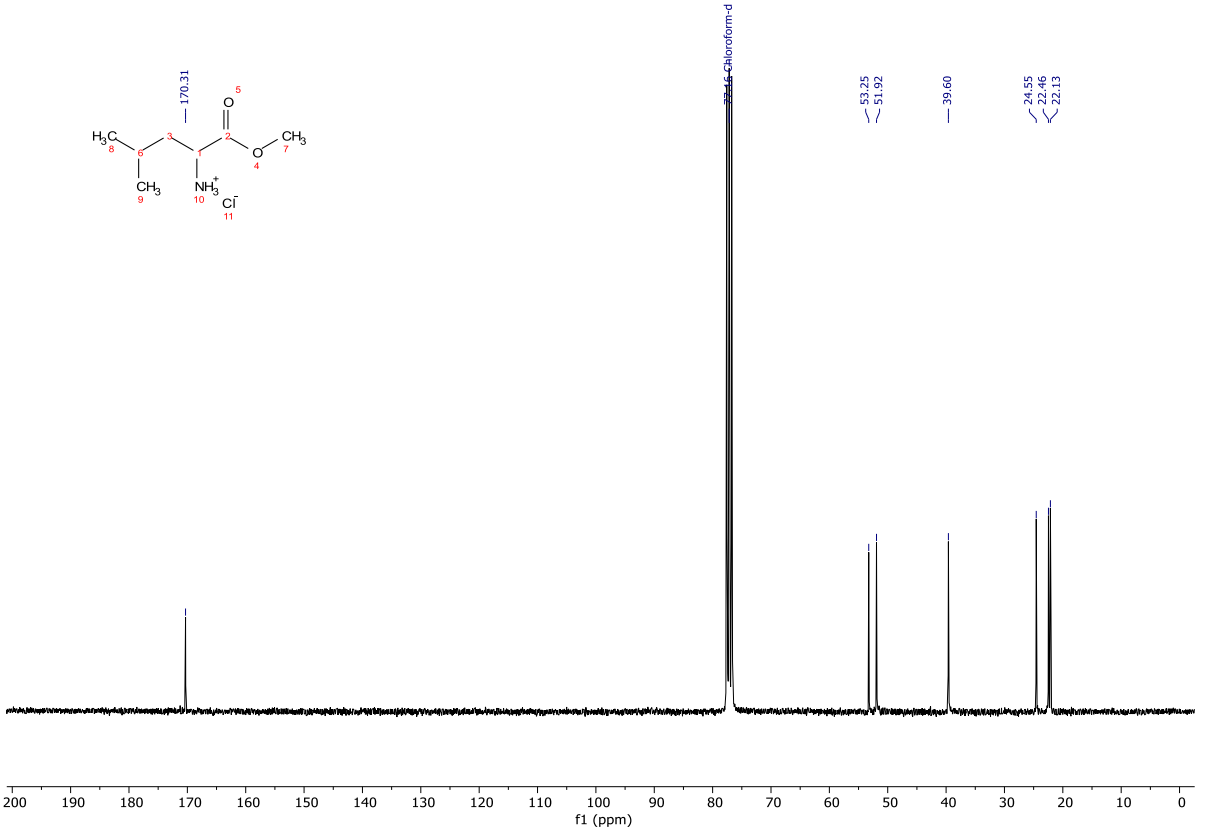


Fig. 46. [13]CNMR spectrum of compound 163.

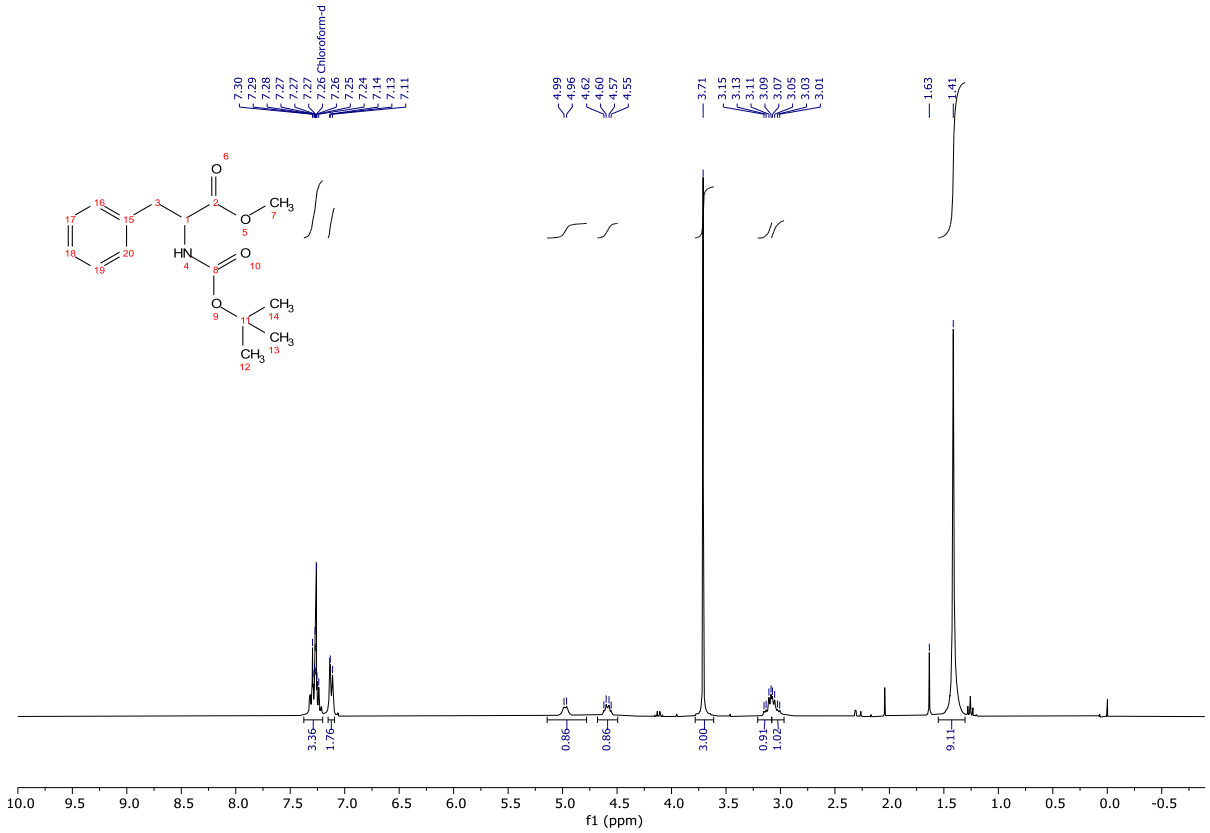


Fig. 47. [1]HNMR spectrum of compound 164.

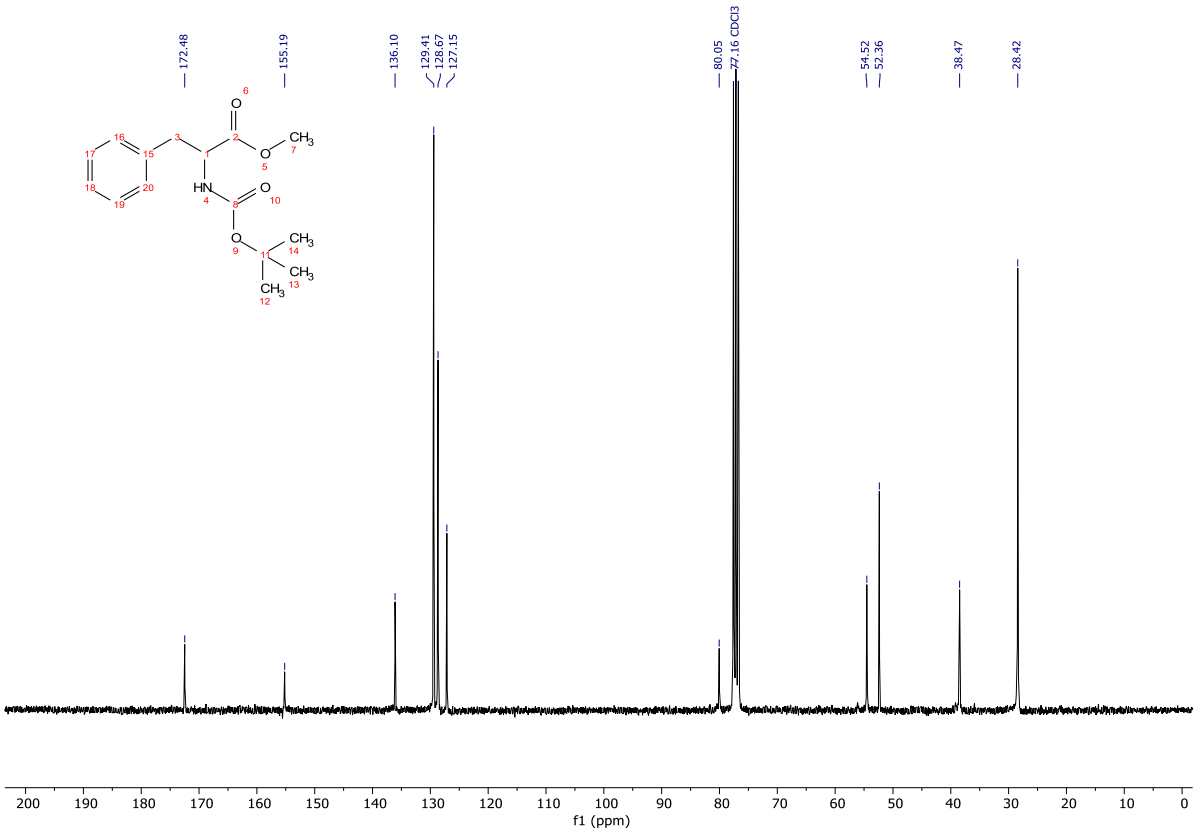


Fig. 48. [13]CNMR spectrum of compound 164.

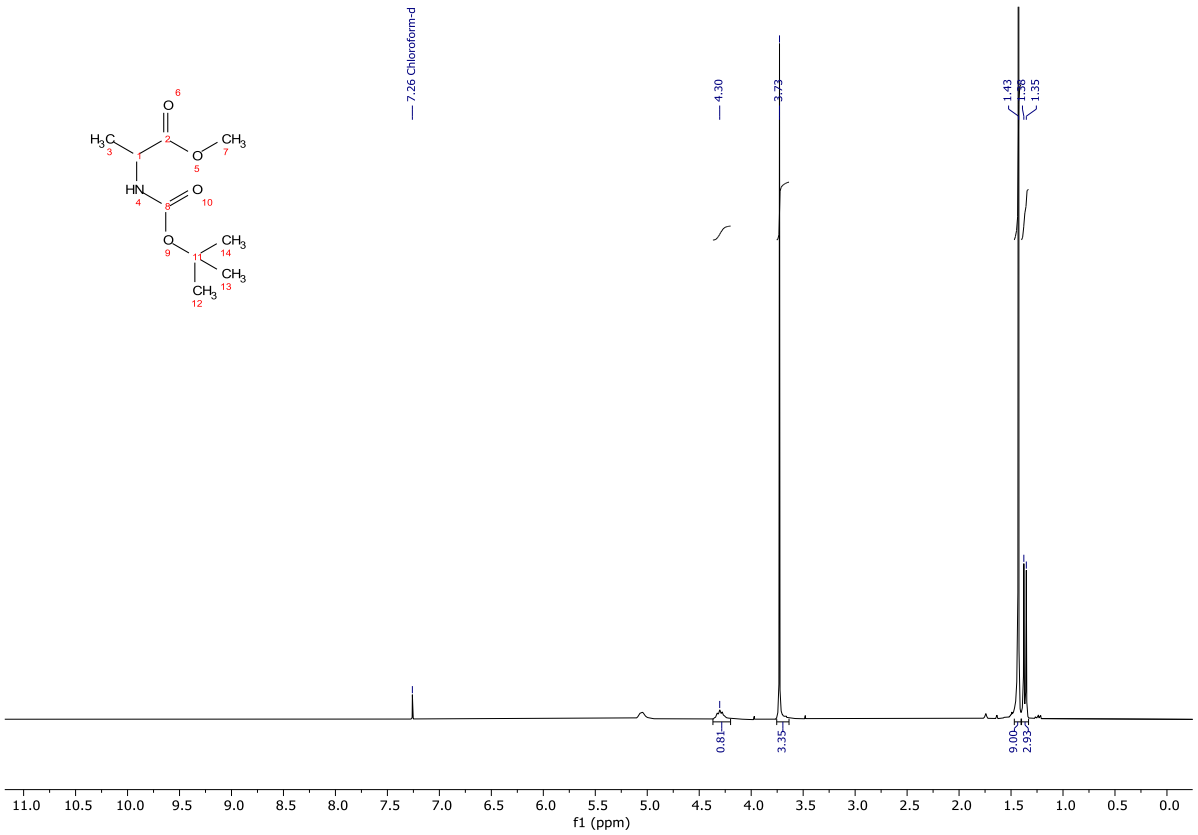


Fig. 49. [1]HNMR spectrum of compound 165.

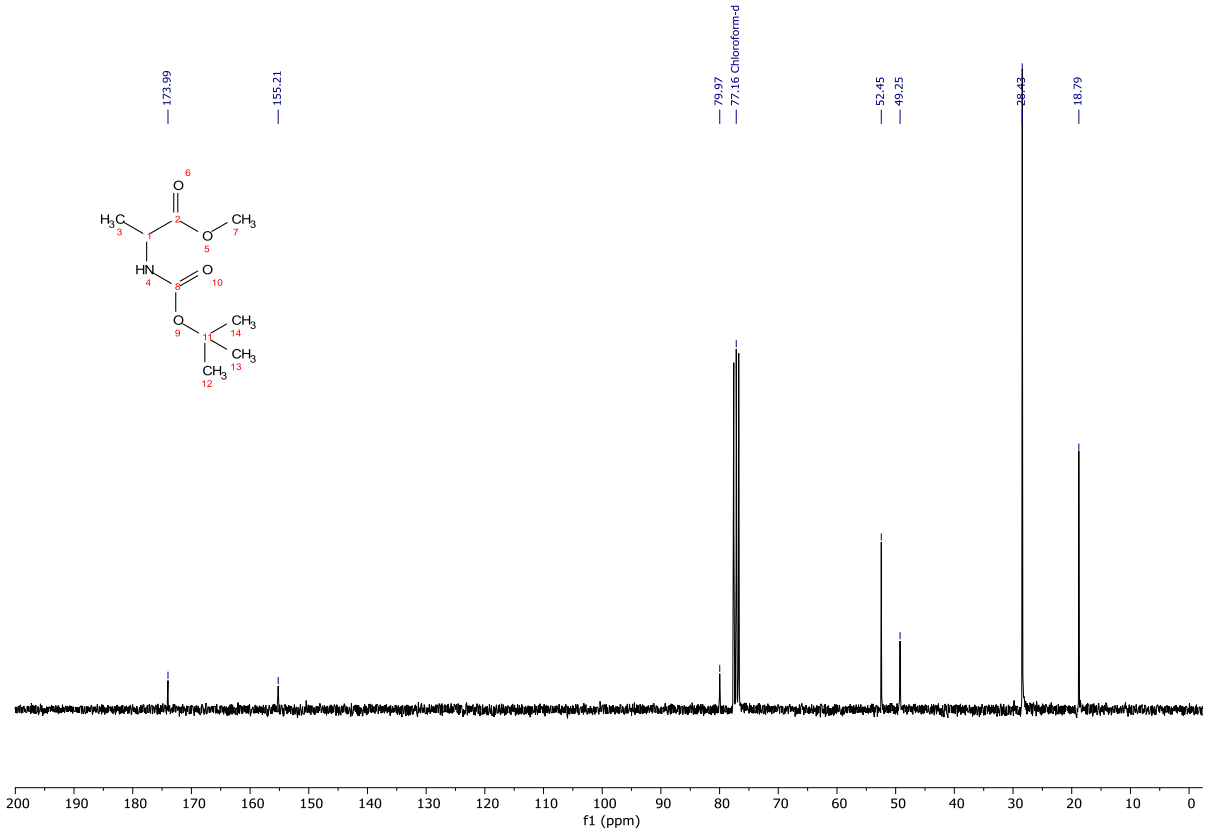


Fig. 50. [13]CNMR spectrum of compound 165.

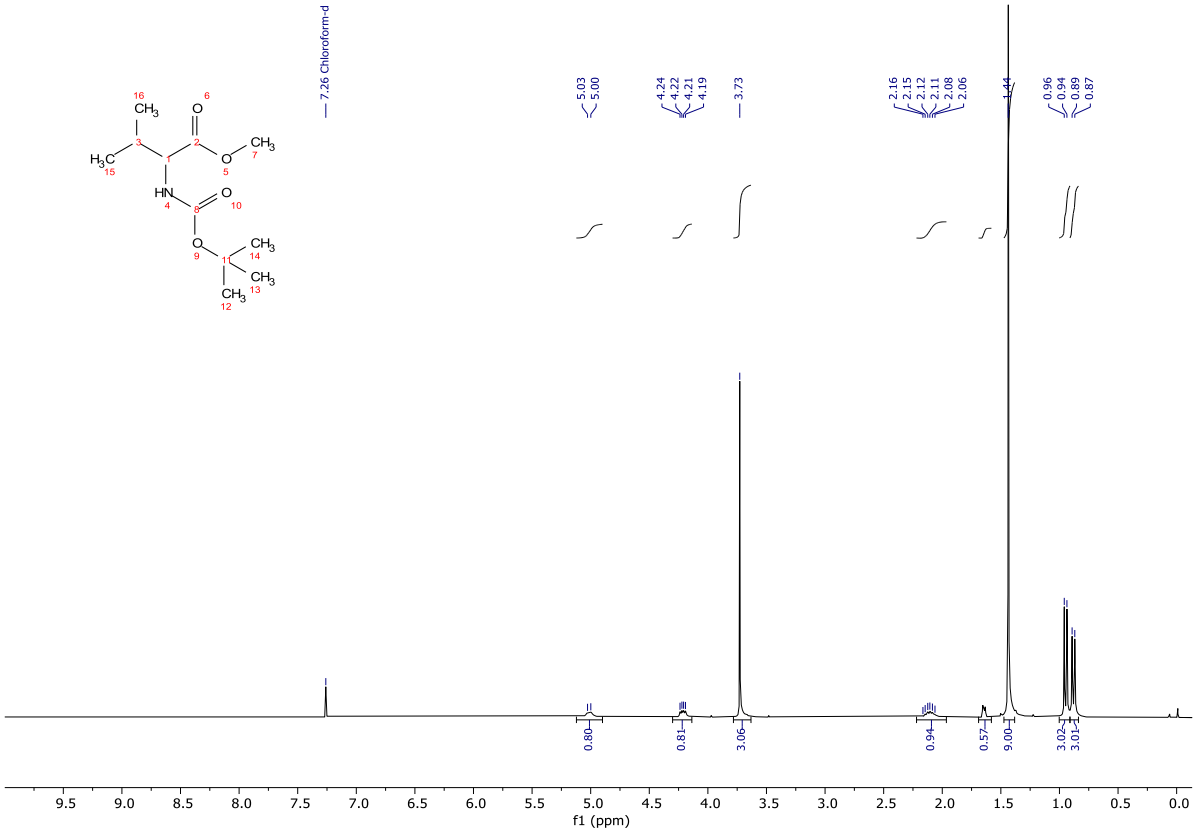


Fig. 51. [1]HNMR spectrum of compound 166.

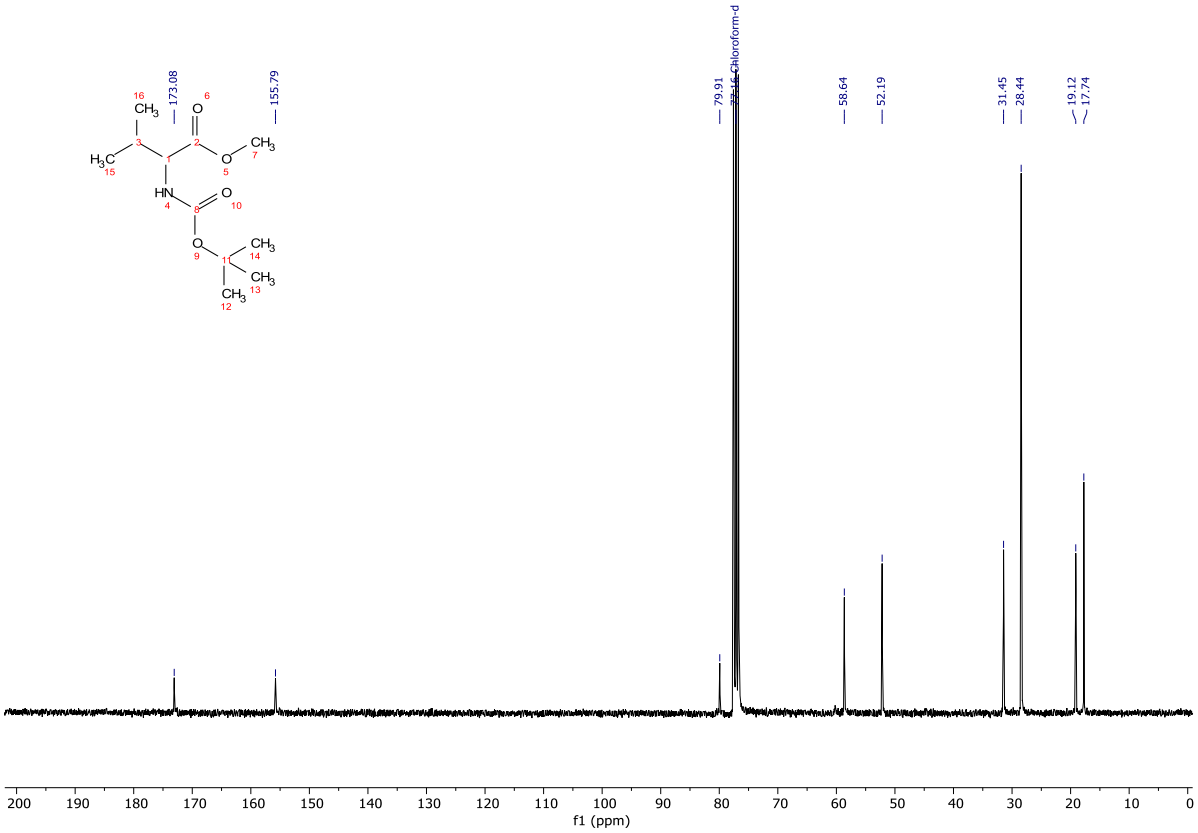


Fig. 52. [13]CNMR spectrum of compound 166.

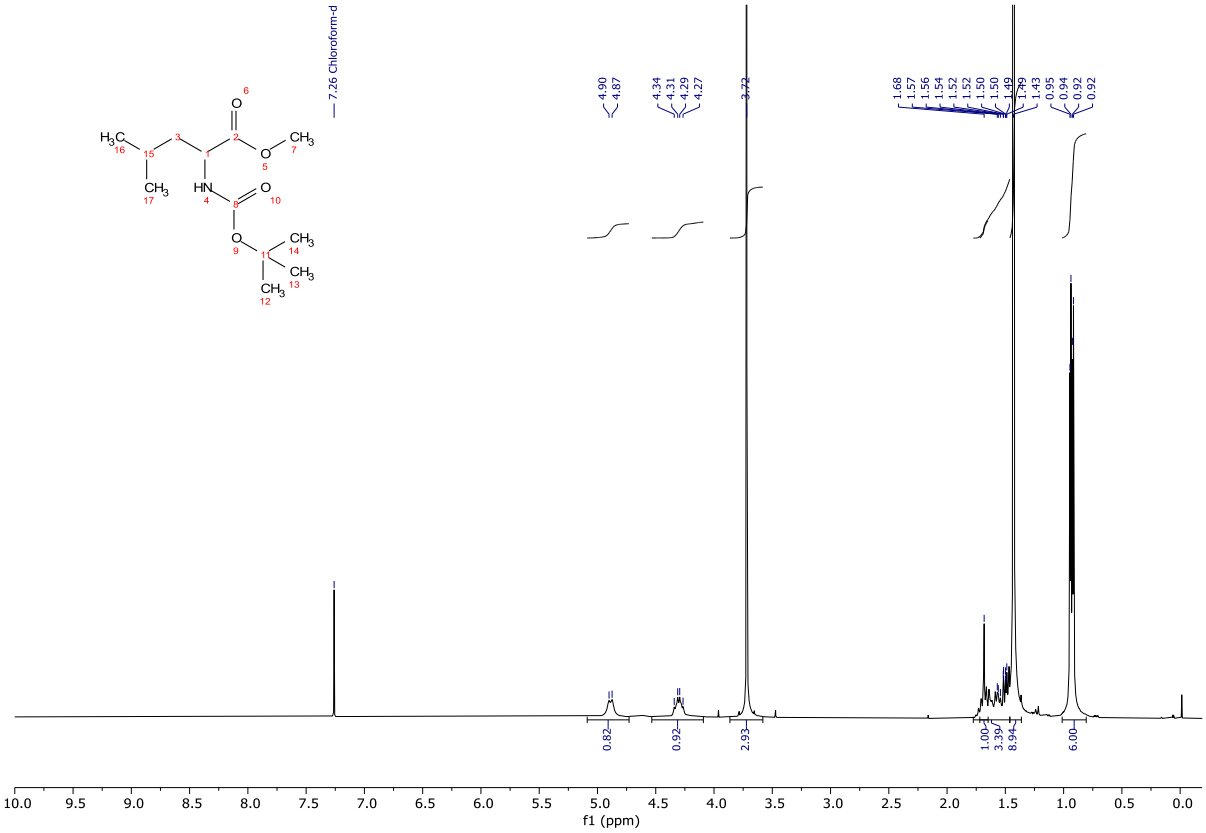


Fig. 53. [1]HNMR spectrum of compound 167.

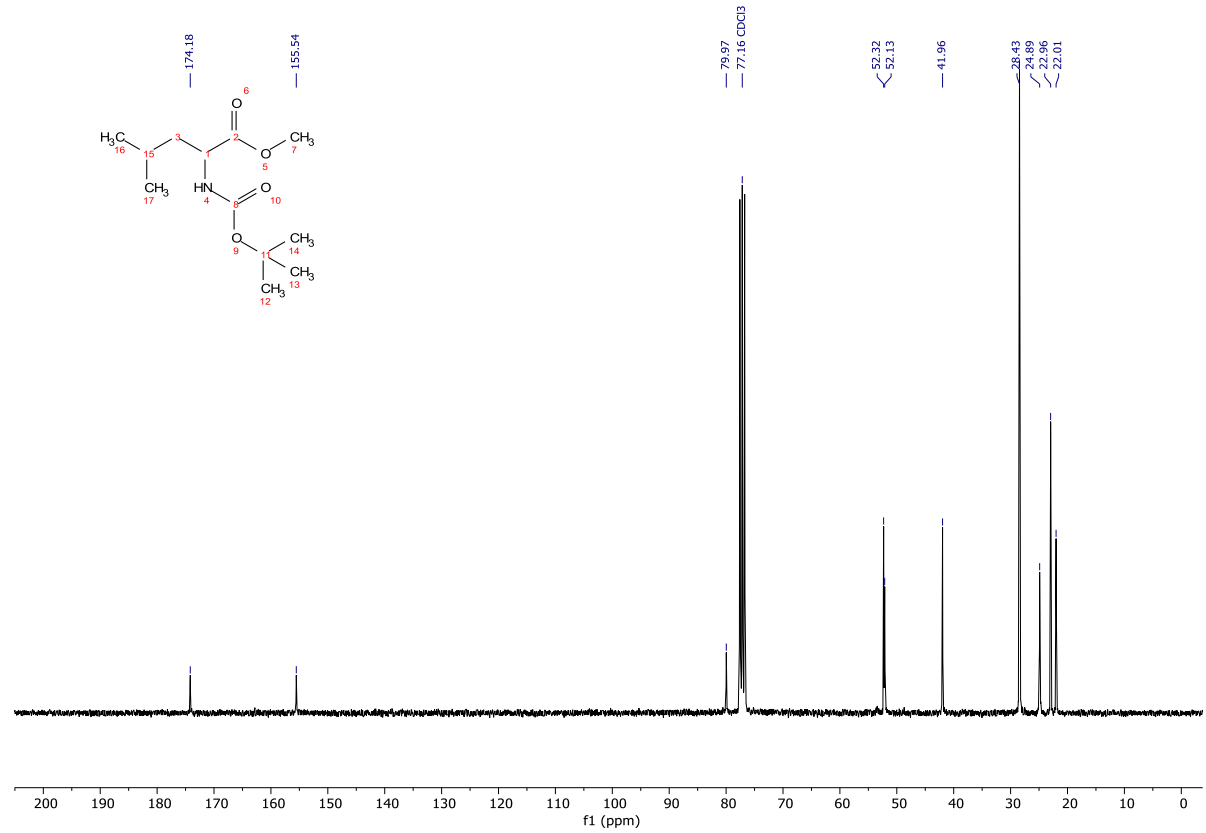


Fig. 54. [13]CNMR spectrum of compound 167.

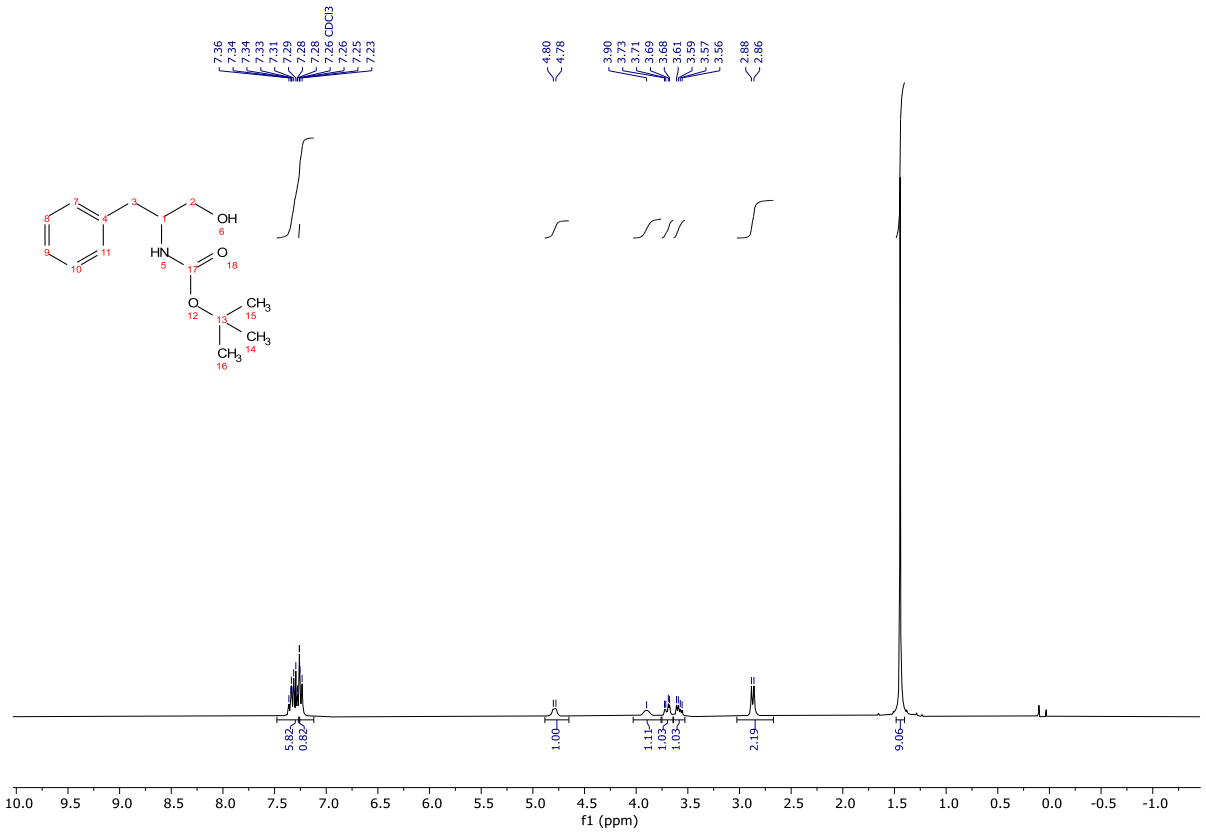


Fig. 55. [1]HNMR spectrum of compound 168.

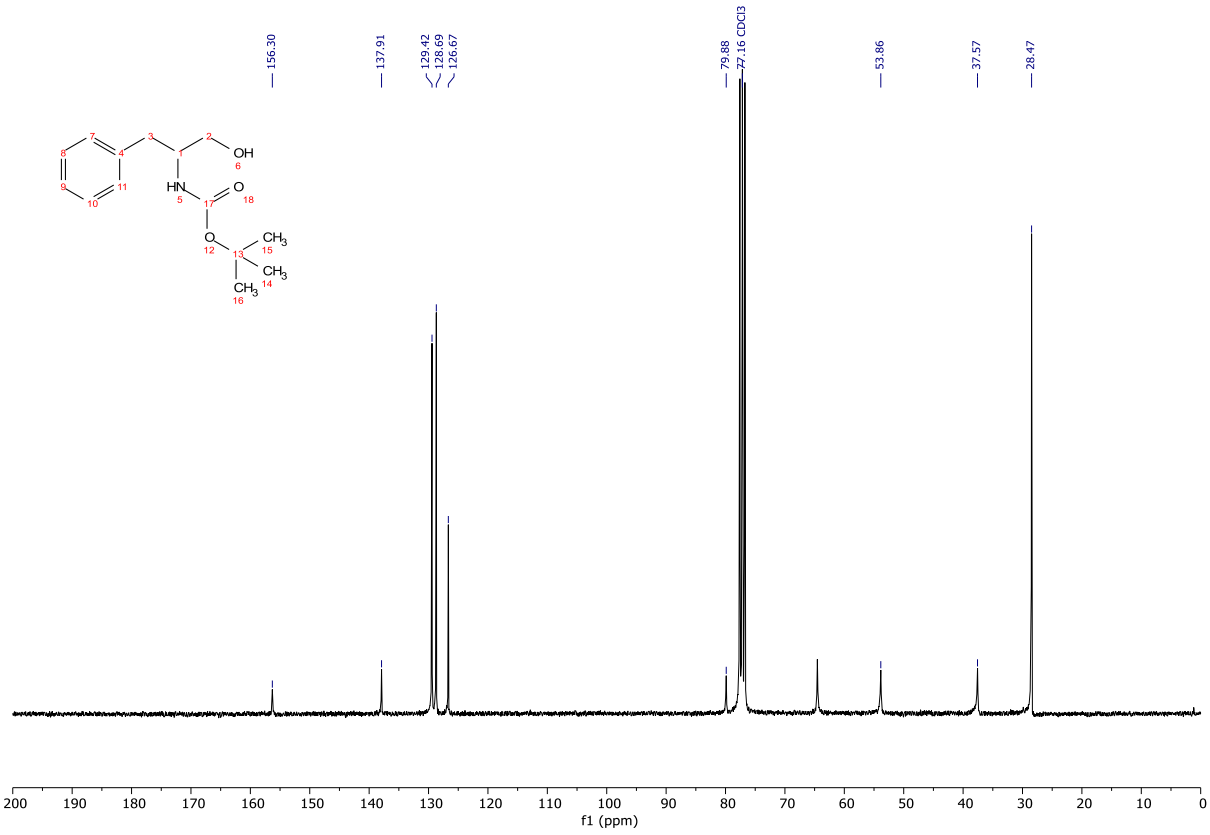


Fig. 56. [13]CNMR spectrum of compound 168.

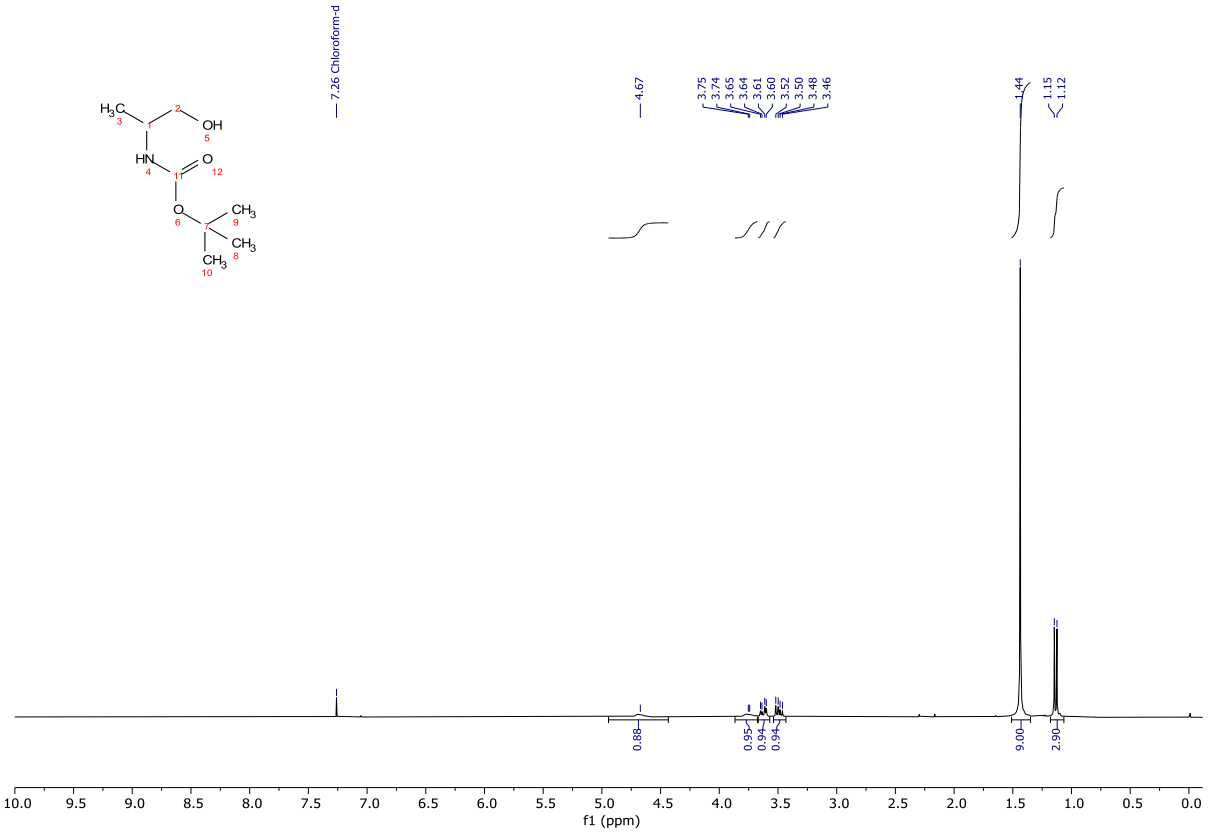


Fig. 57. [1]HNMR spectrum of compound 169.

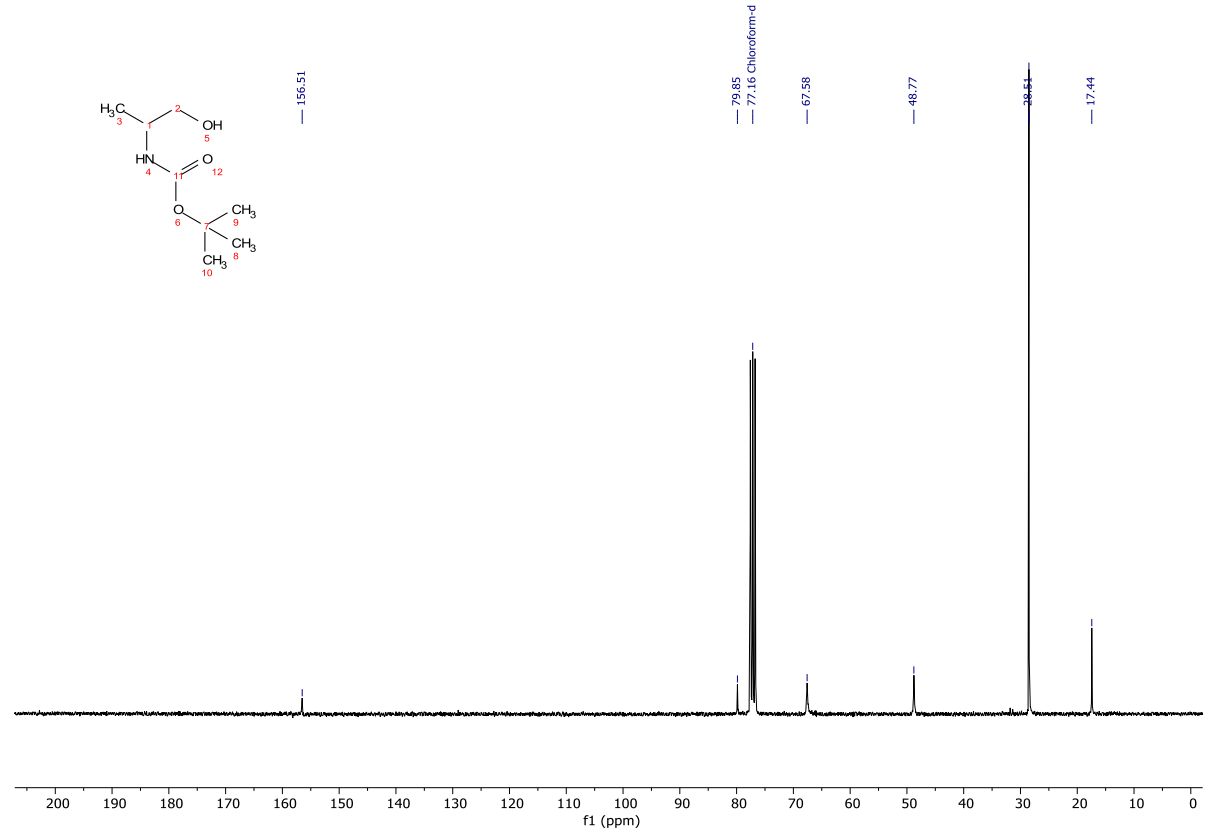


Fig. 58. [13]CNMR spectrum of compound 169.

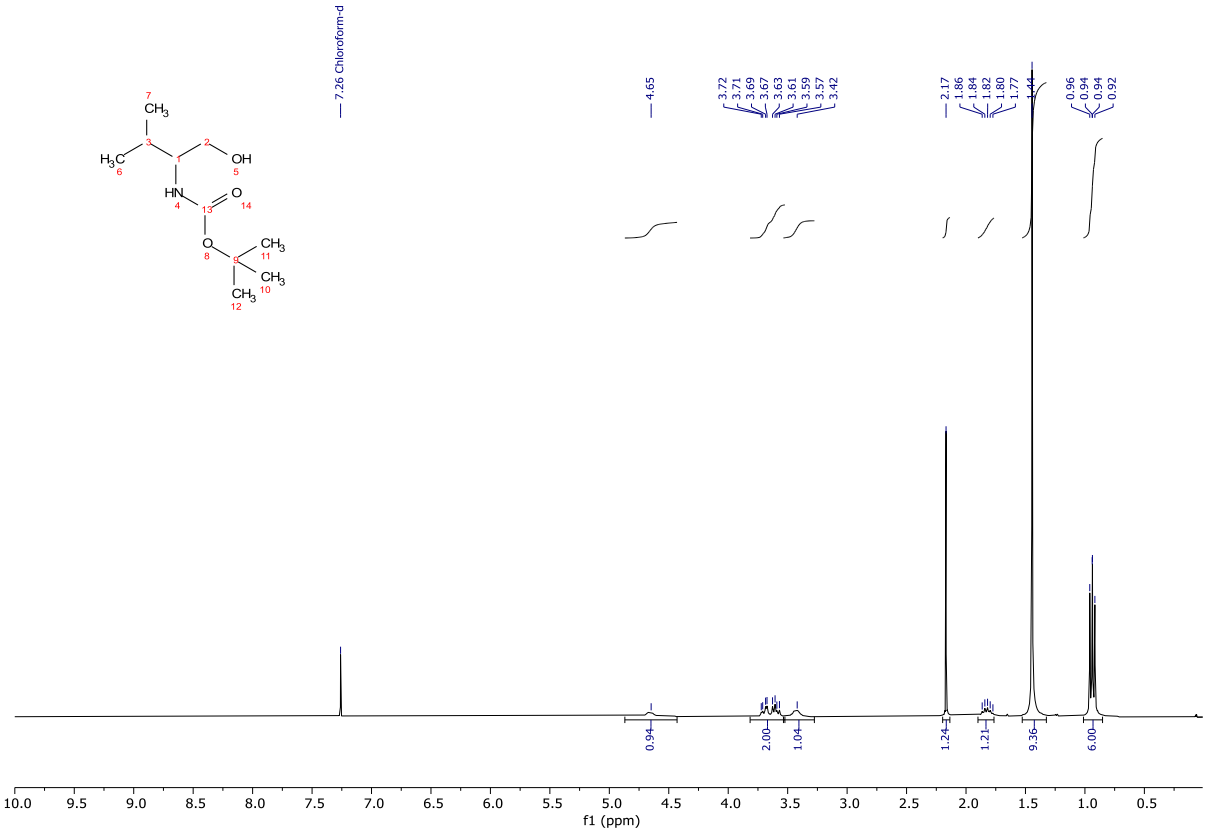


Fig. 59. [1]HNMR spectrum of compound 170.

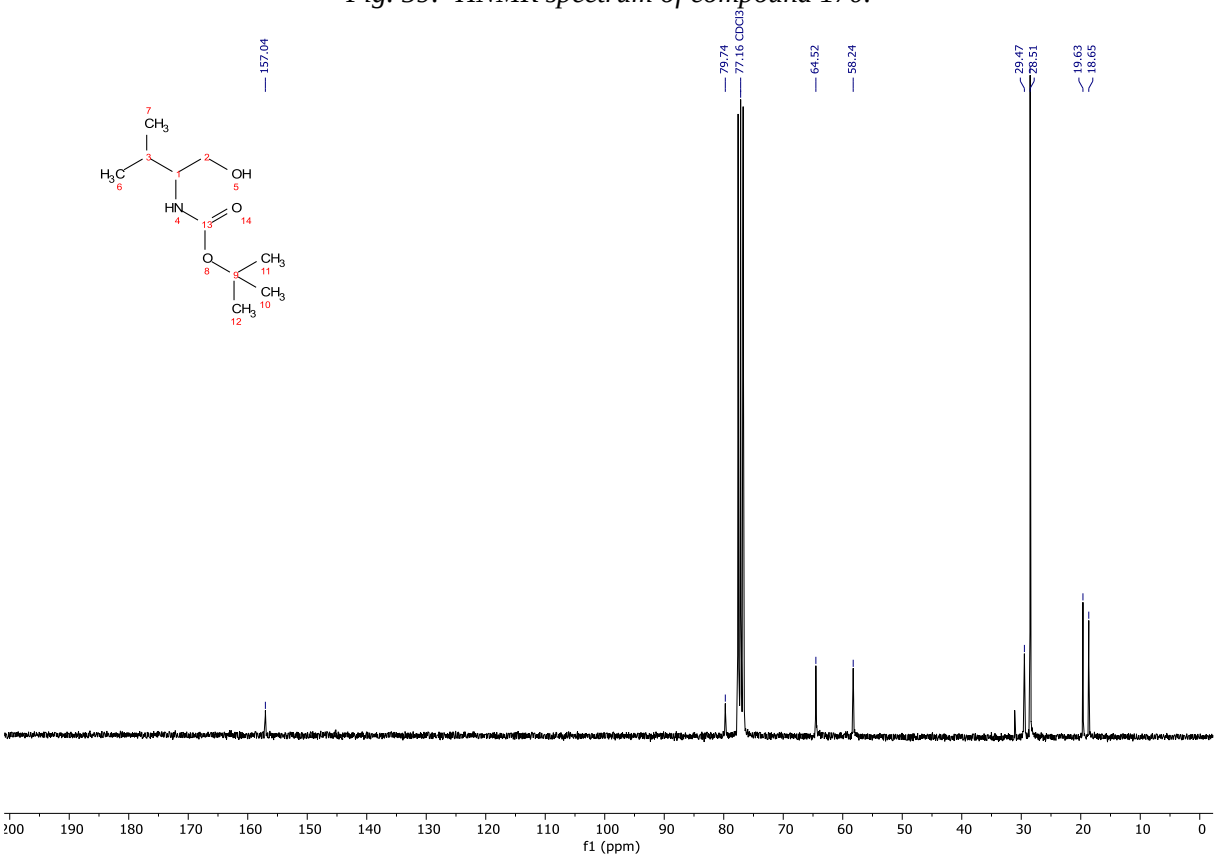


Fig. 60. [13]CNMR spectrum of compound 170.

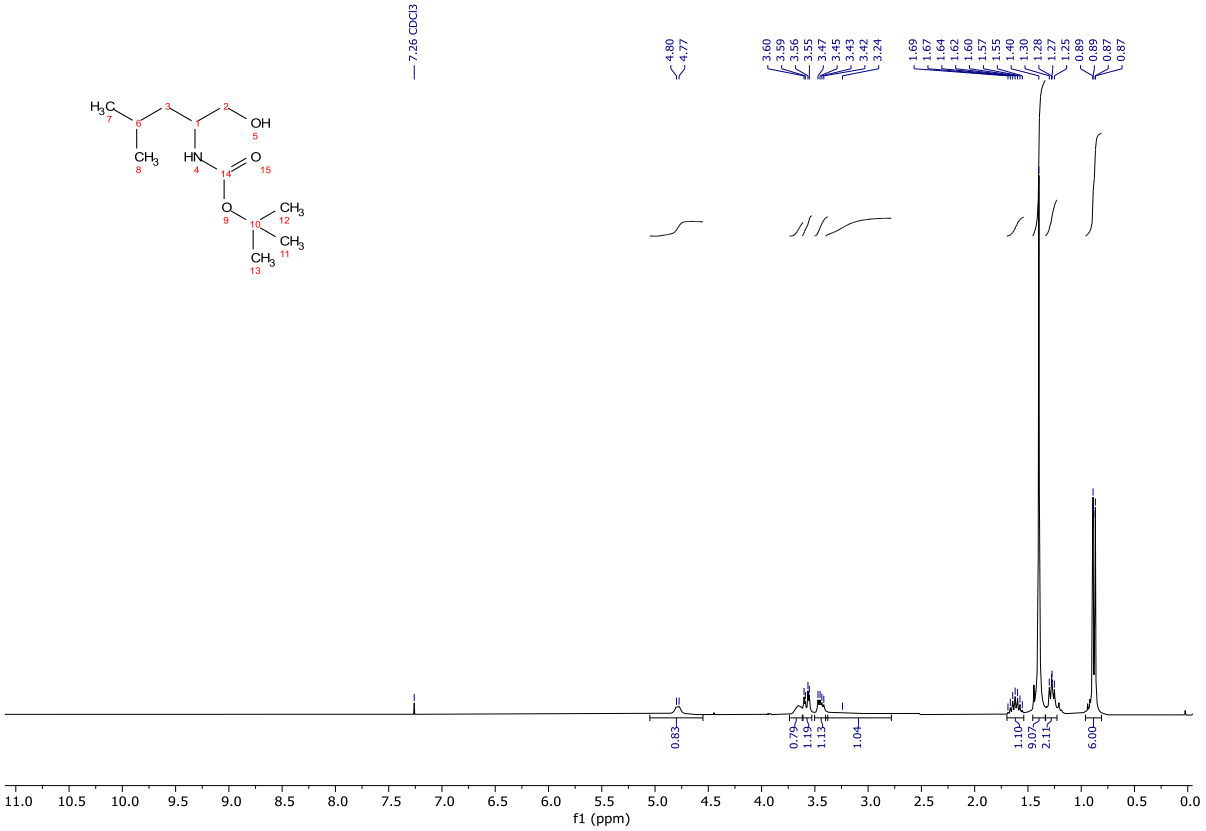


Fig. 61. [1]HNMR spectrum of compound 171

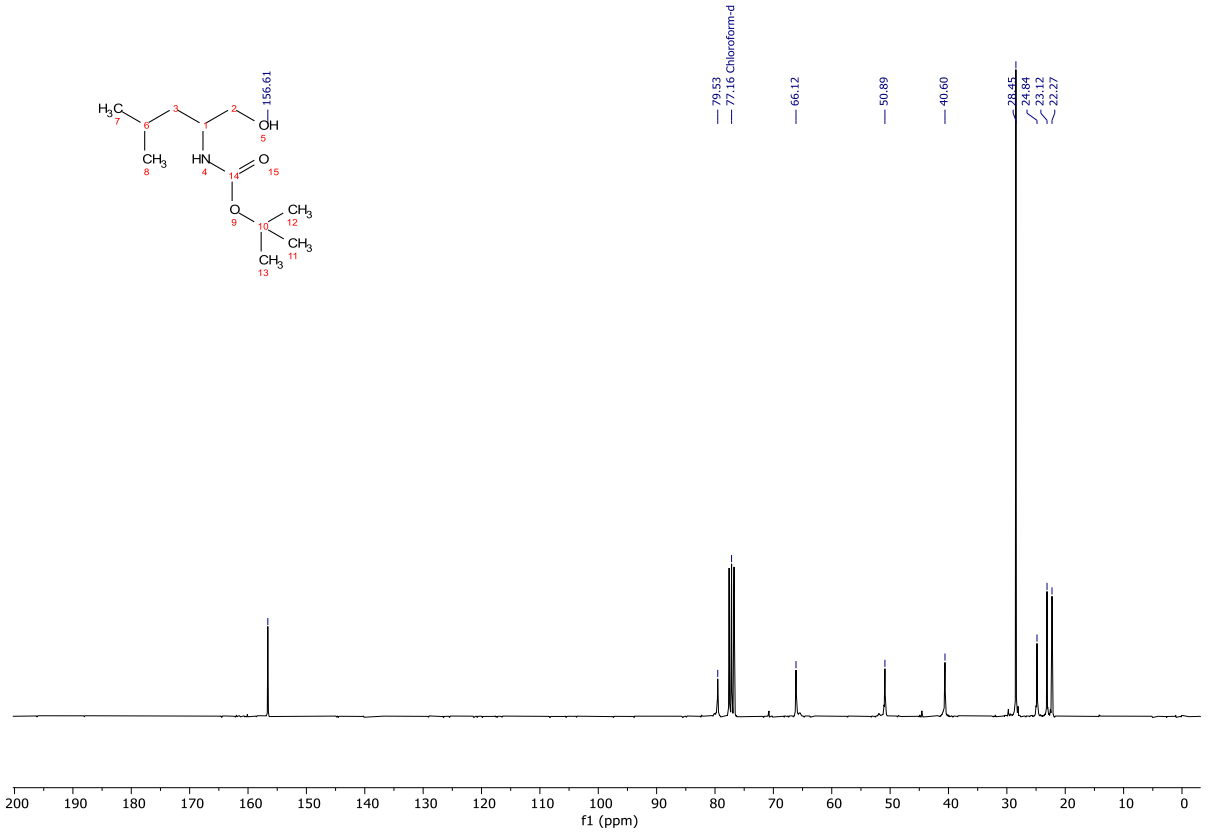


Fig. 62. [13]CNMR spectrum of compound 171.

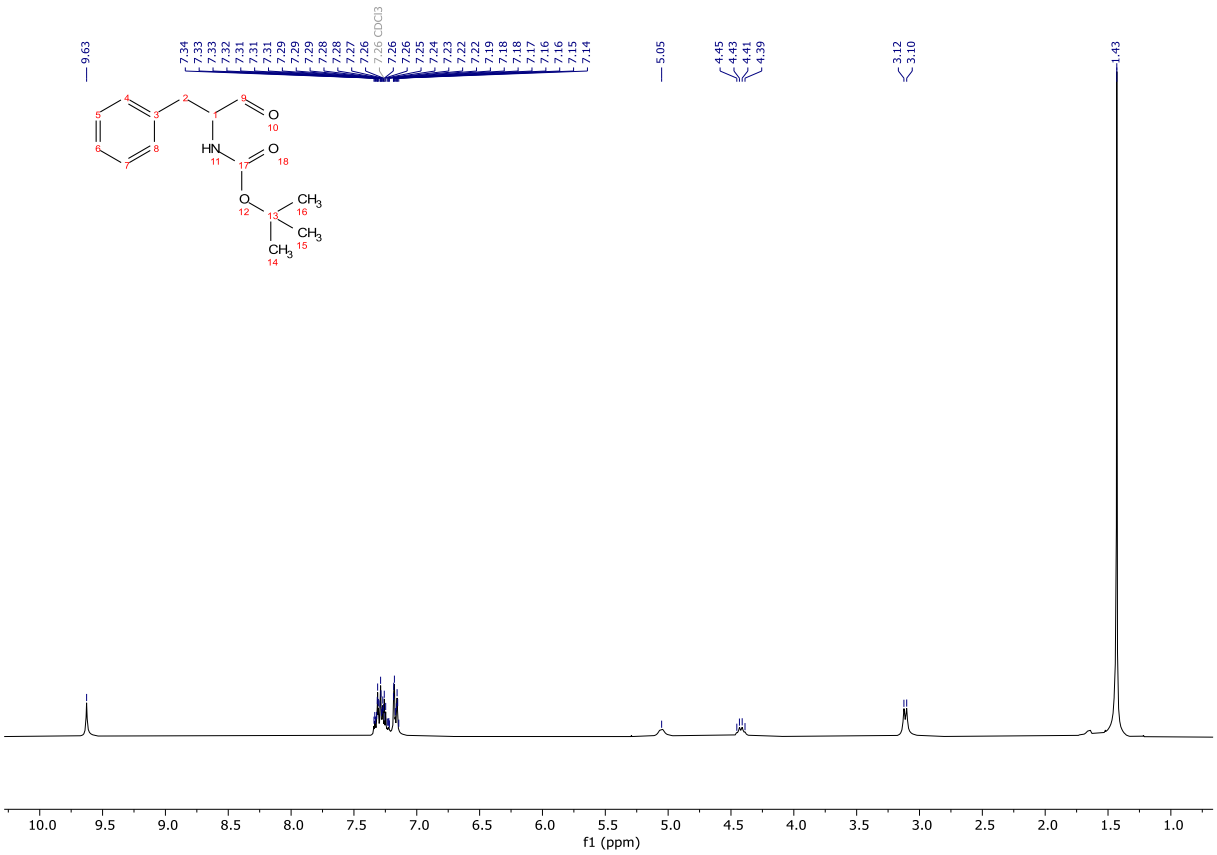


Fig. 63. [1]HNMR spectrum of compound 172.

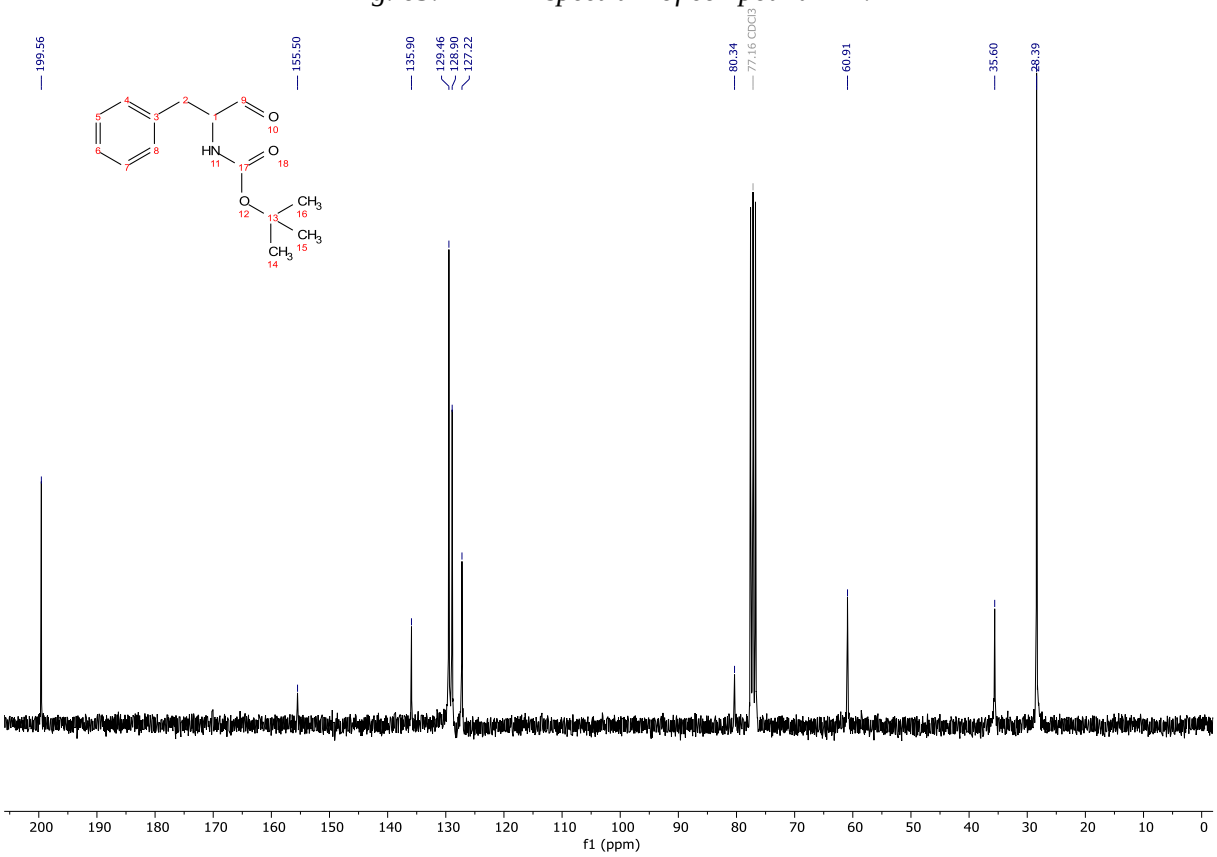


Fig. 64. [13]CNMR spectrum of compound 172.

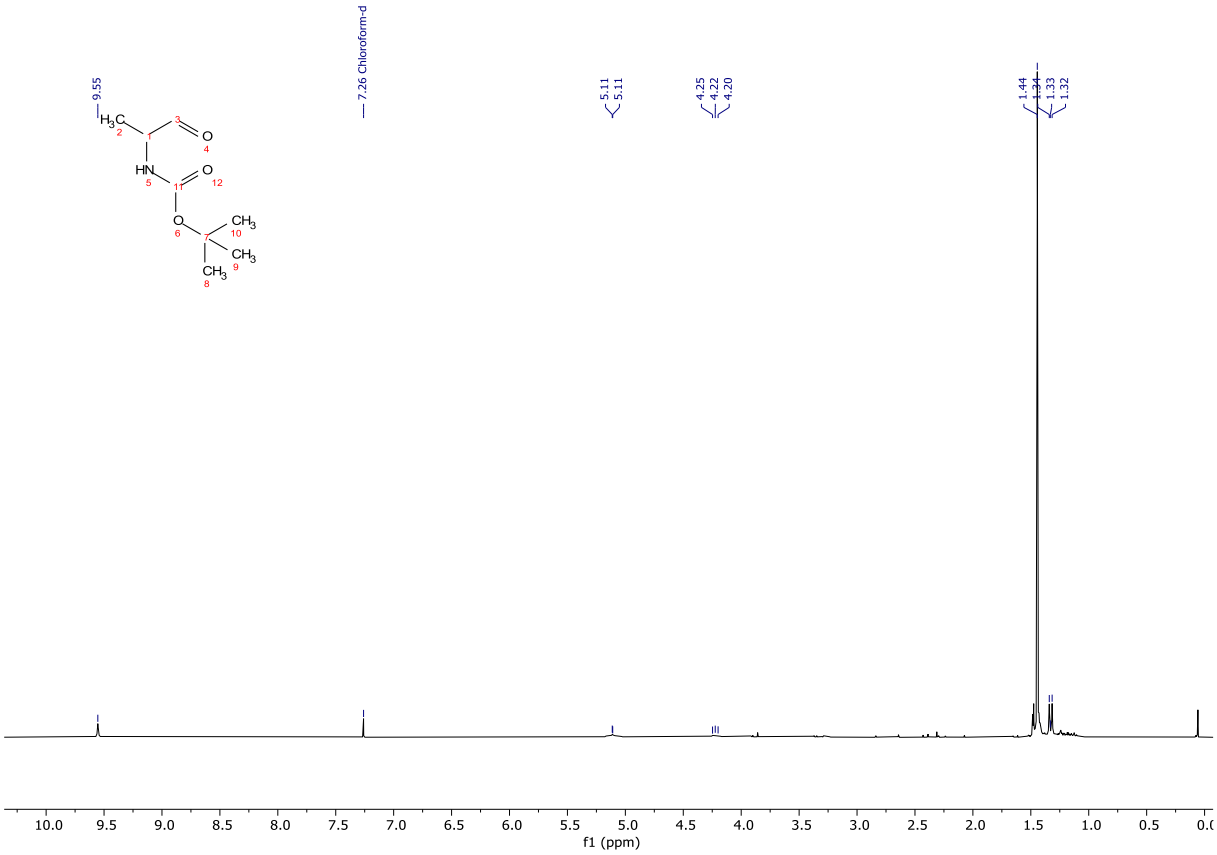


Fig. 65. [1]HNMR spectrum of compound 173.

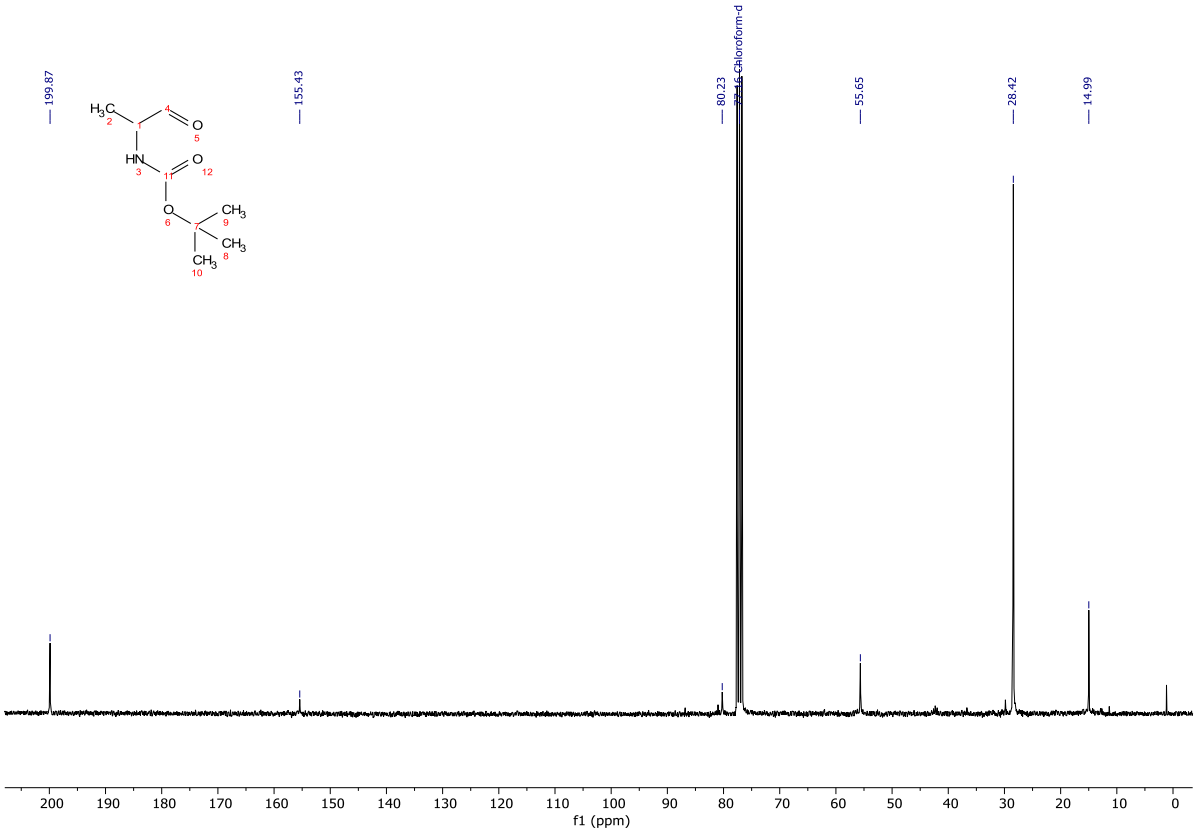


Fig. 66. [13]CNMR spectrum of compound 173.

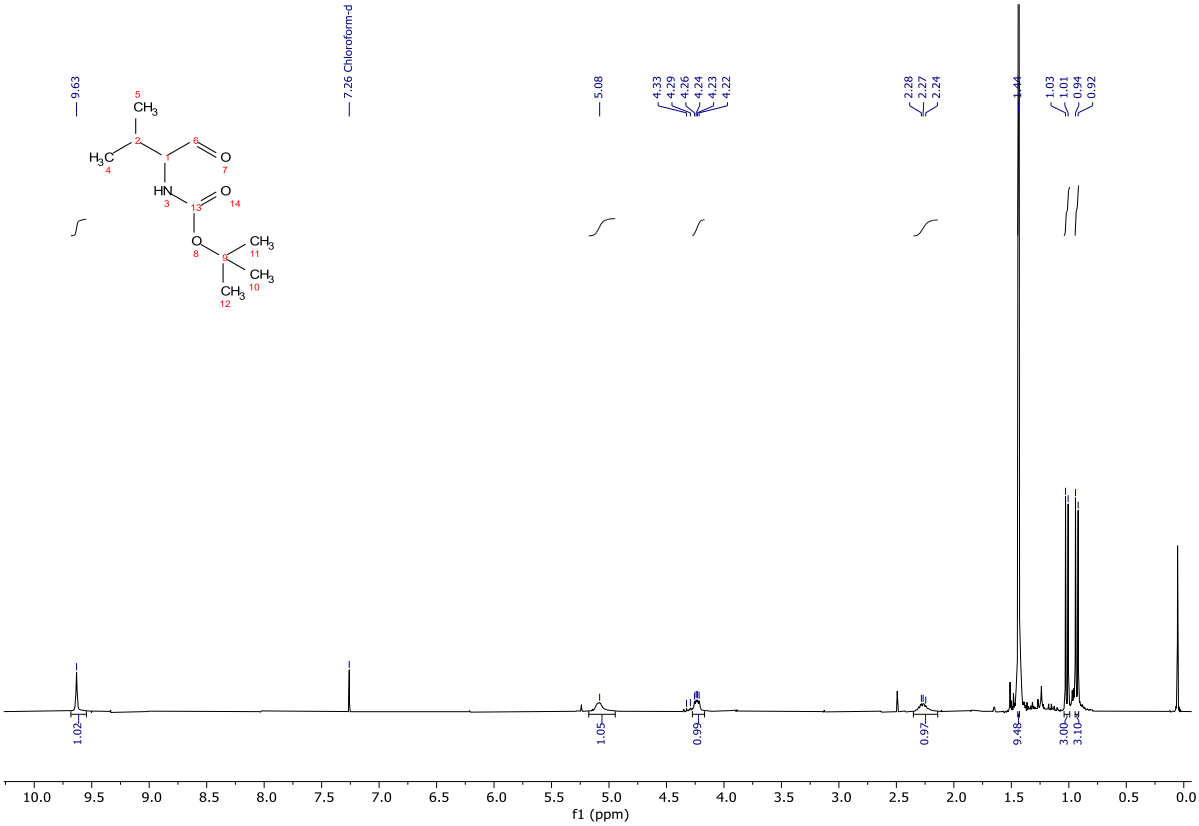


Fig. 67. [1]HNMR spectrum of compound 174.

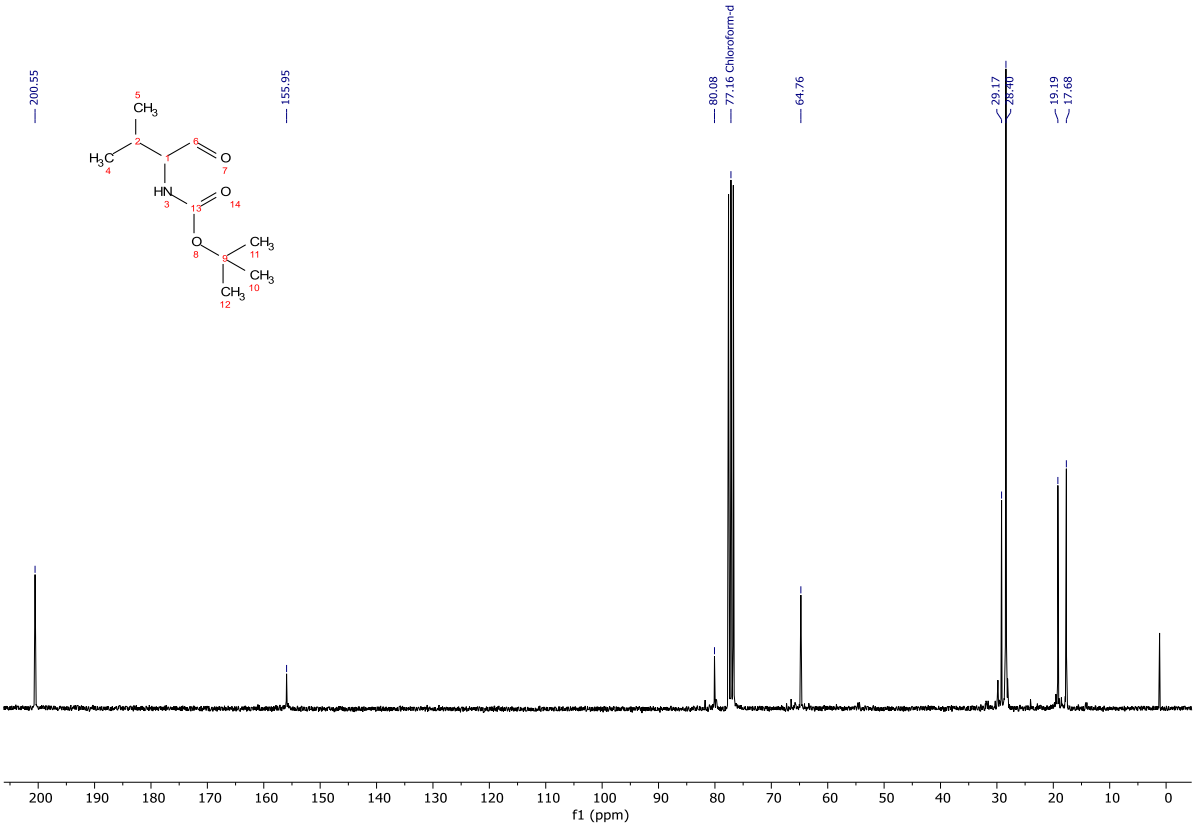


Fig. 68. [13]CNMR spectrum of compound 174.

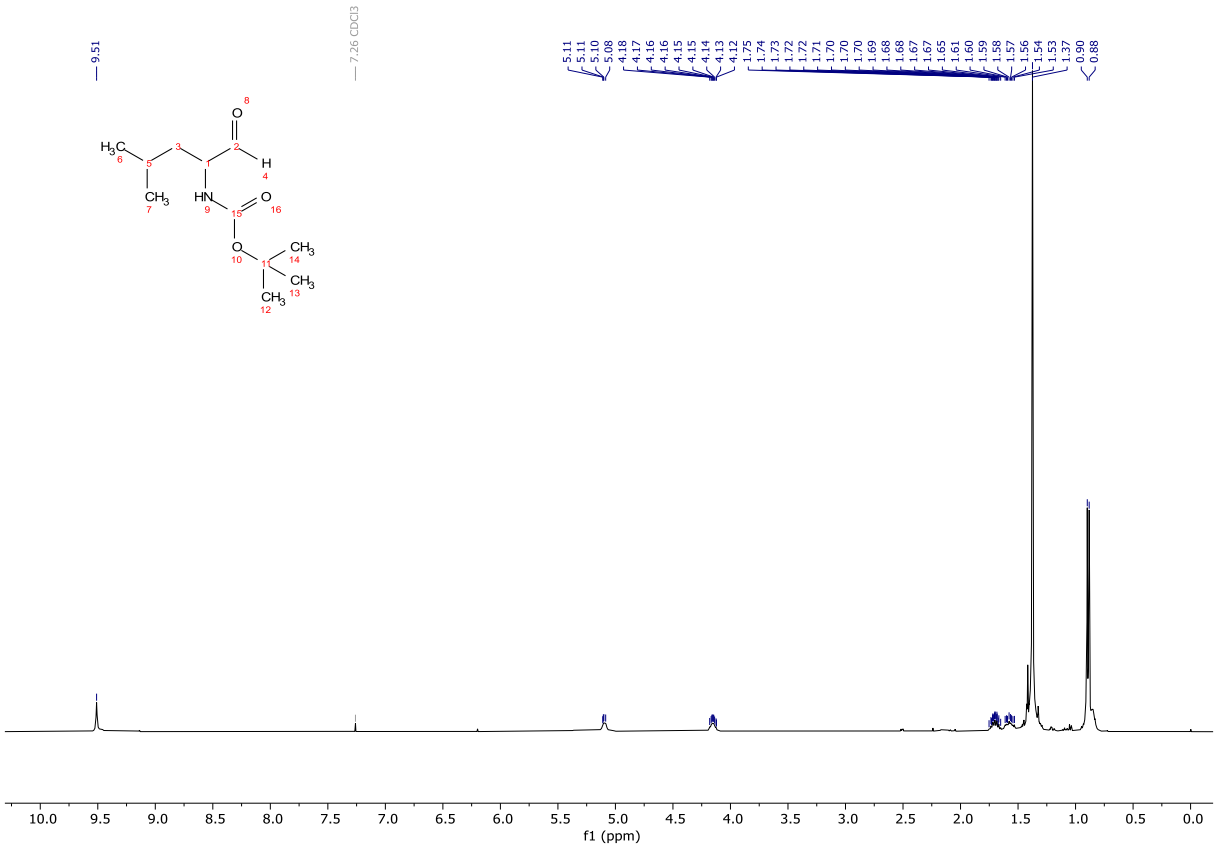


Fig. 69. [1]HNMR spectrum of compound 175.

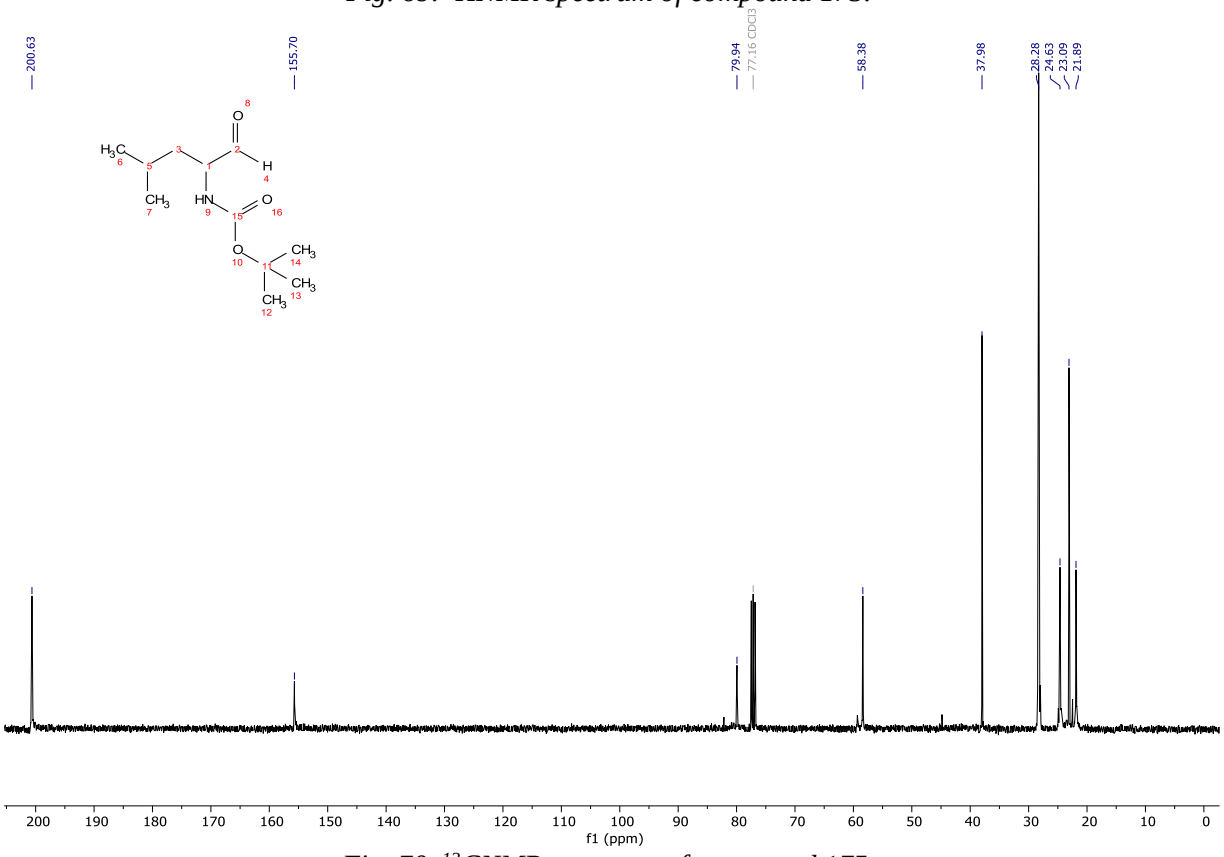


Fig. 70. [13]CNMR spectrum of compound 175.

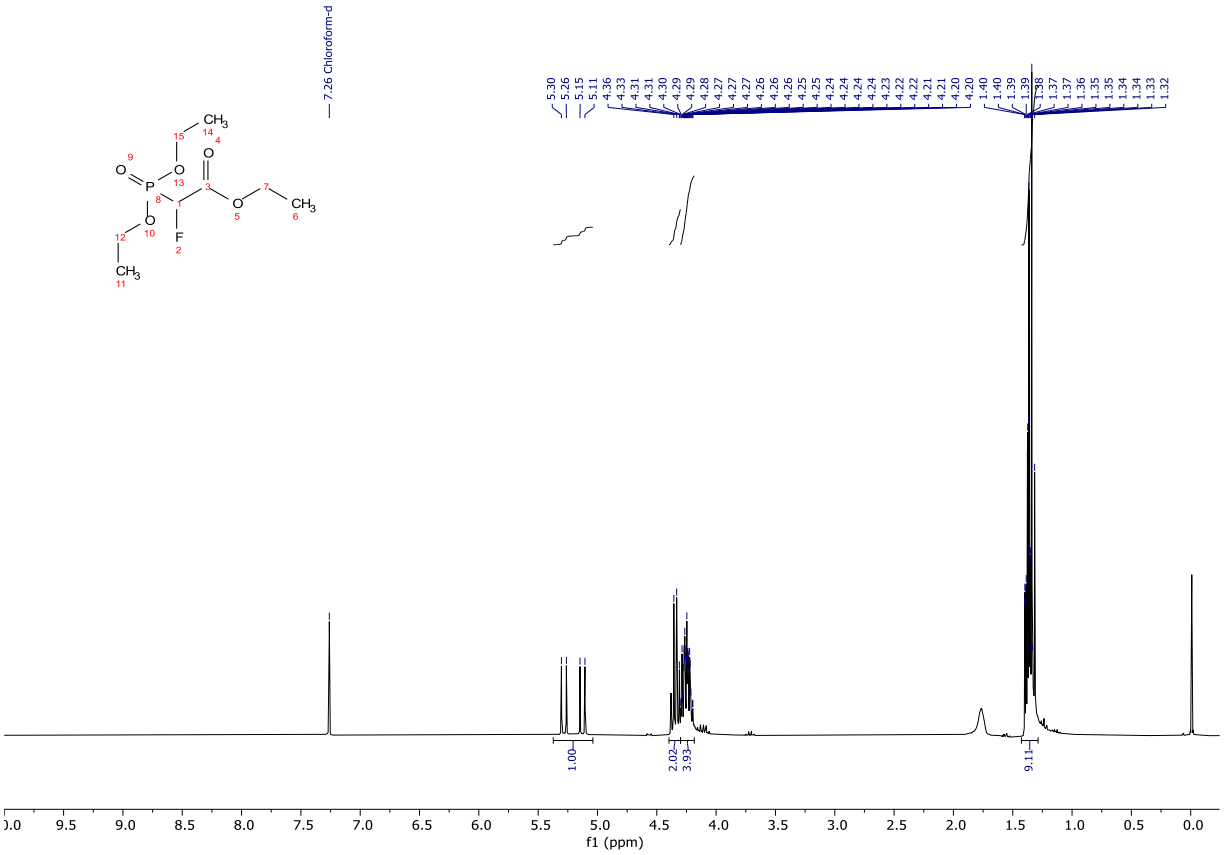


Fig. 71. [1]HNMR spectrum of compound 176.

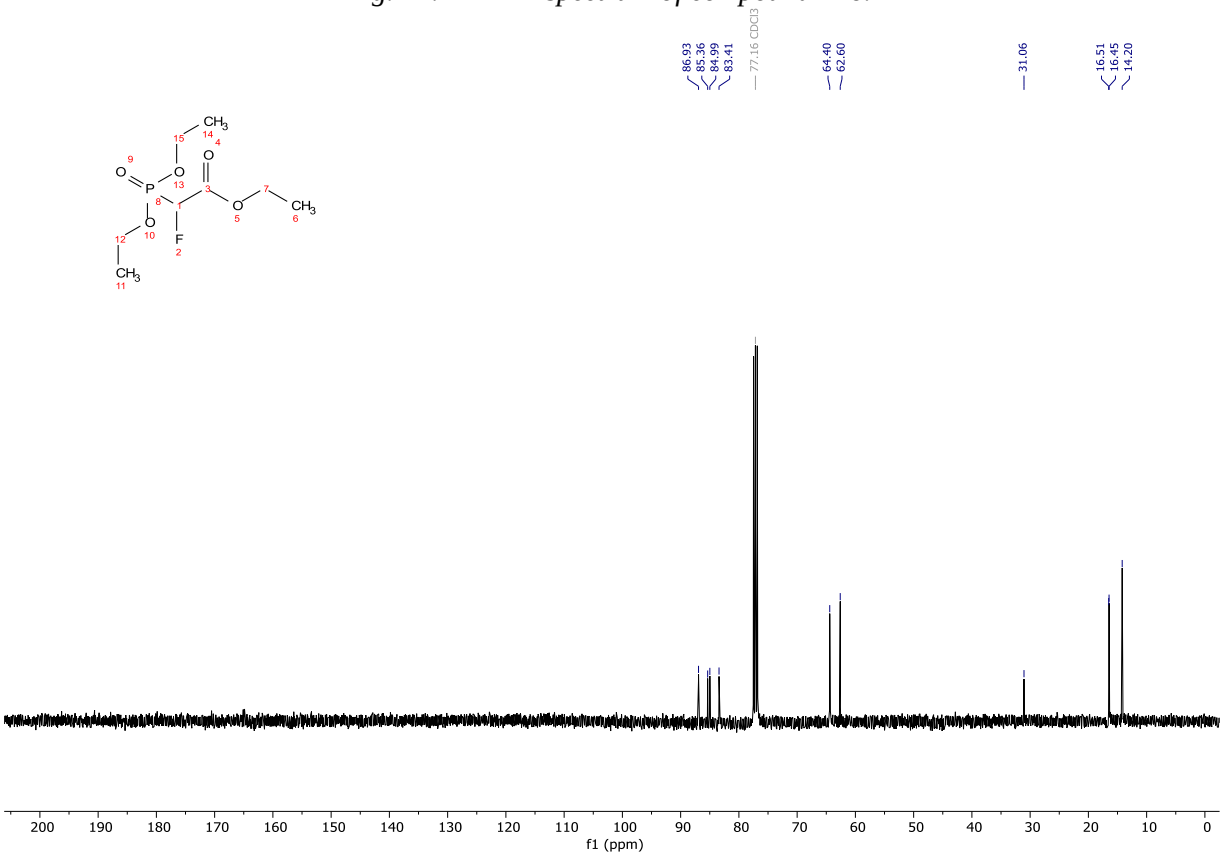


Fig. 72. [13]CNMR spectrum of compound 176.

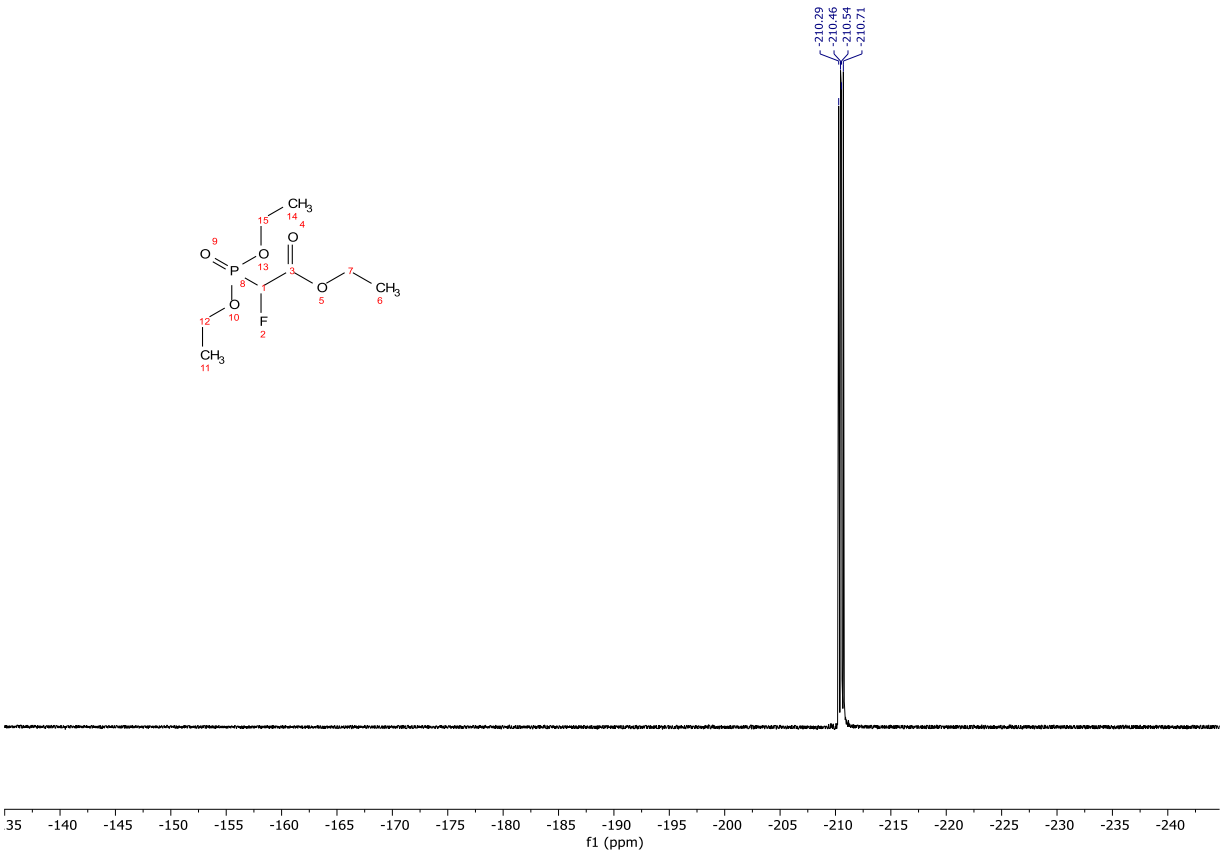


Fig. 73. ^{19}FNMR spectrum of compound 176.

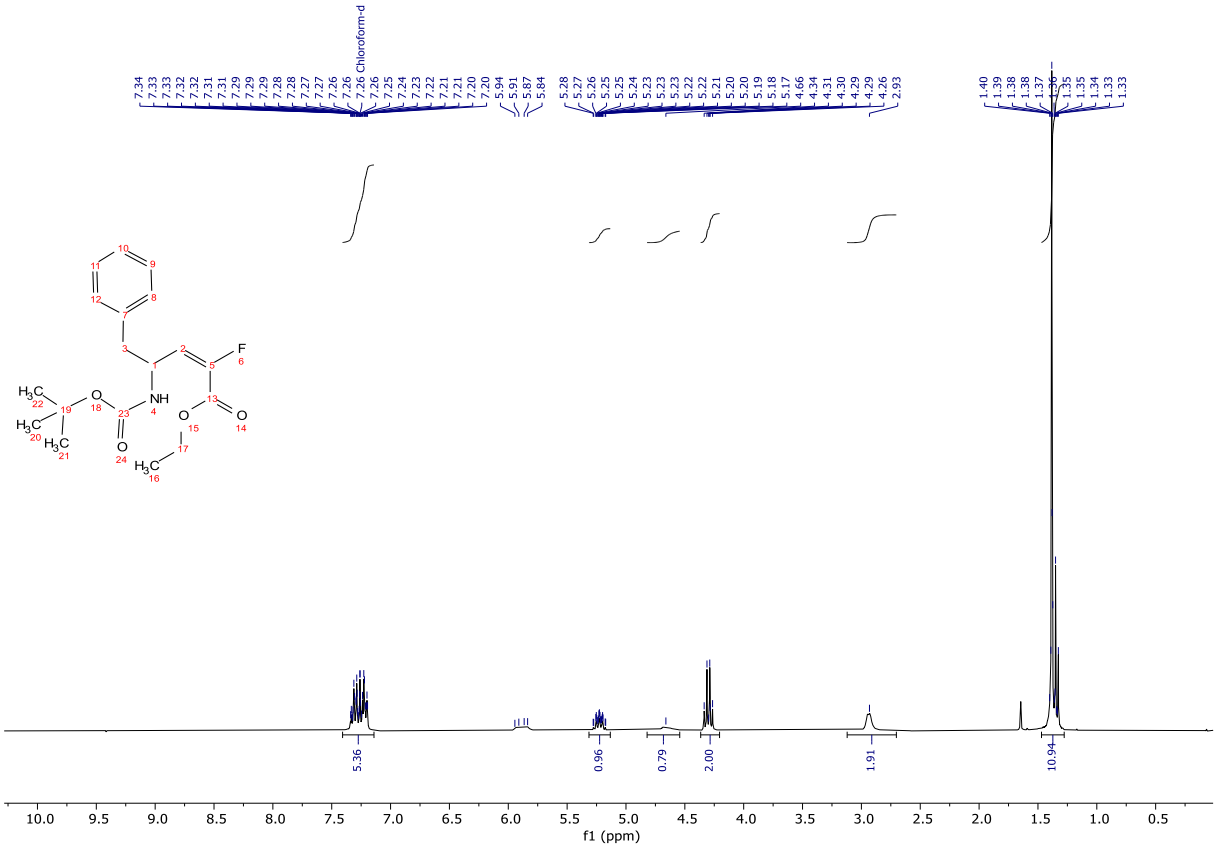


Fig. 74. [1]HNMR spectrum of compound 177.

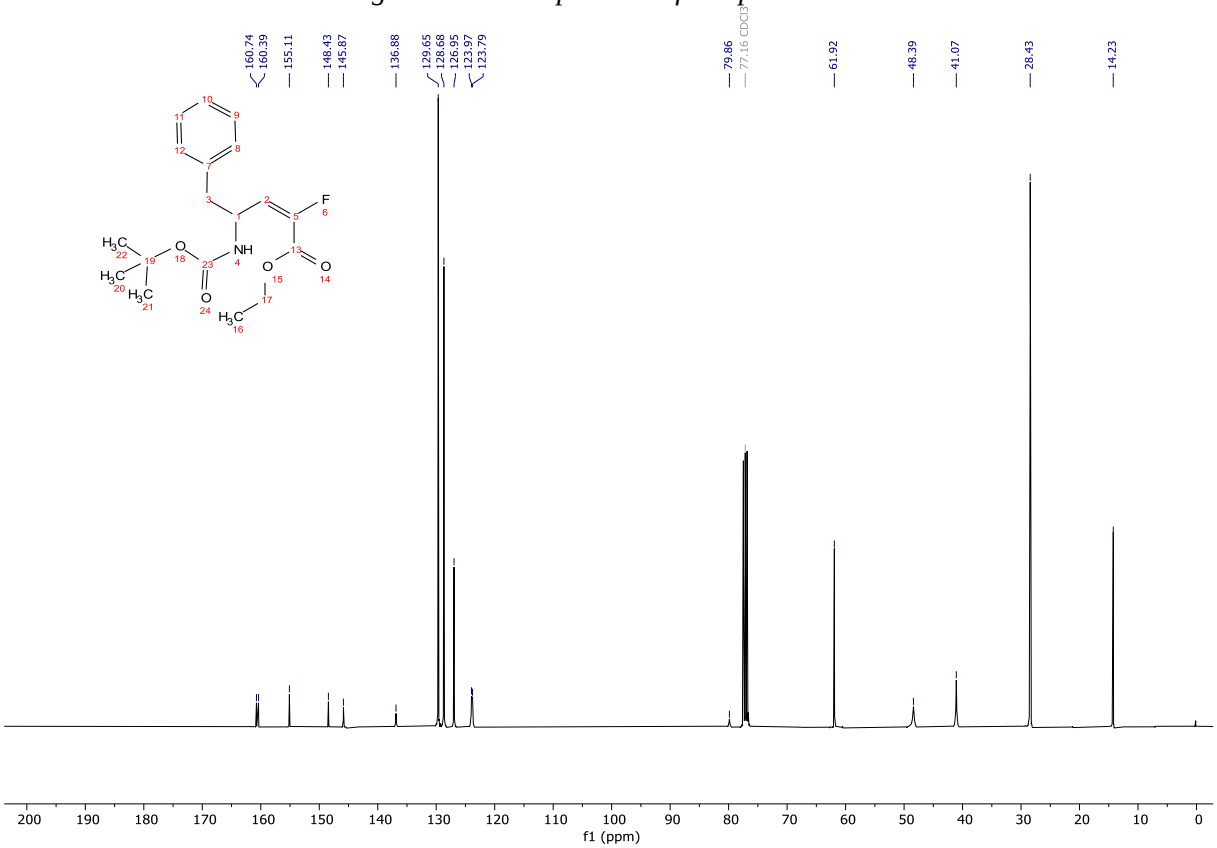


Fig. 75. [13]CNMR spectrum of compound 177.

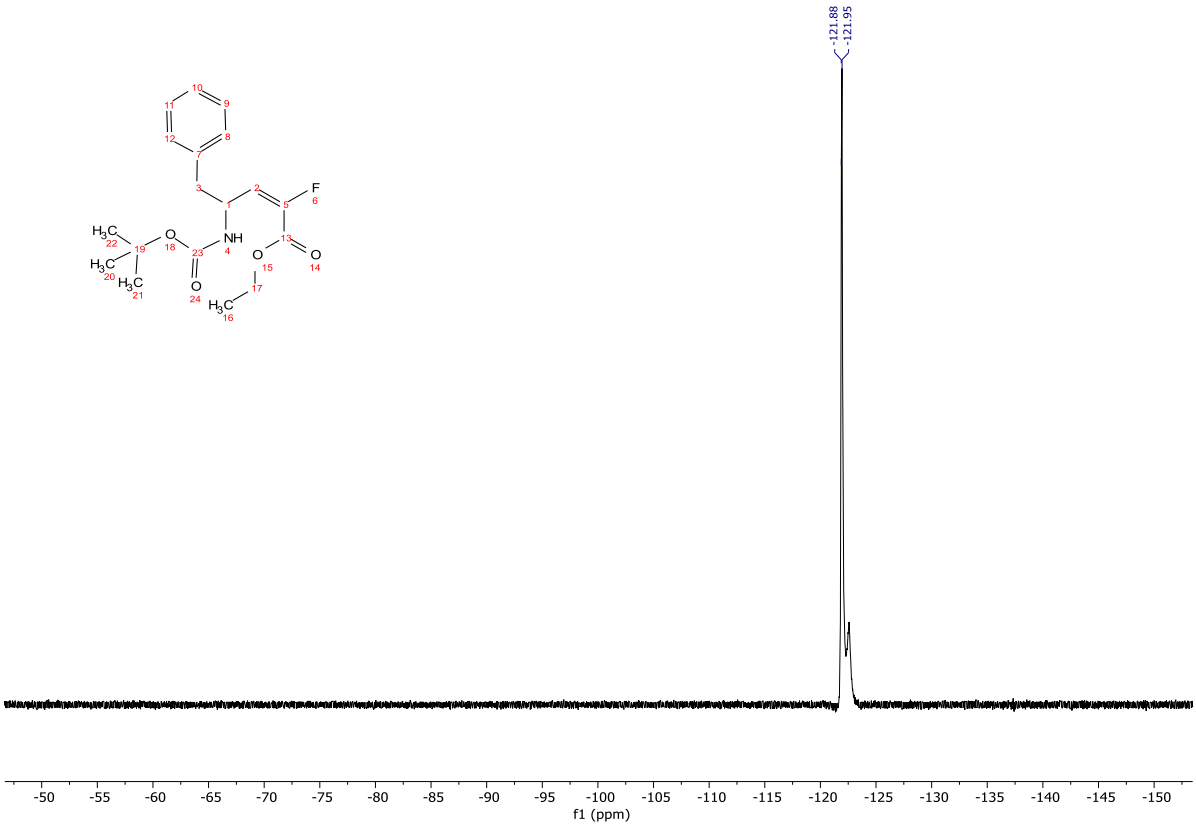


Fig. 76. ^{19}FNMR spectrum of compound 177.

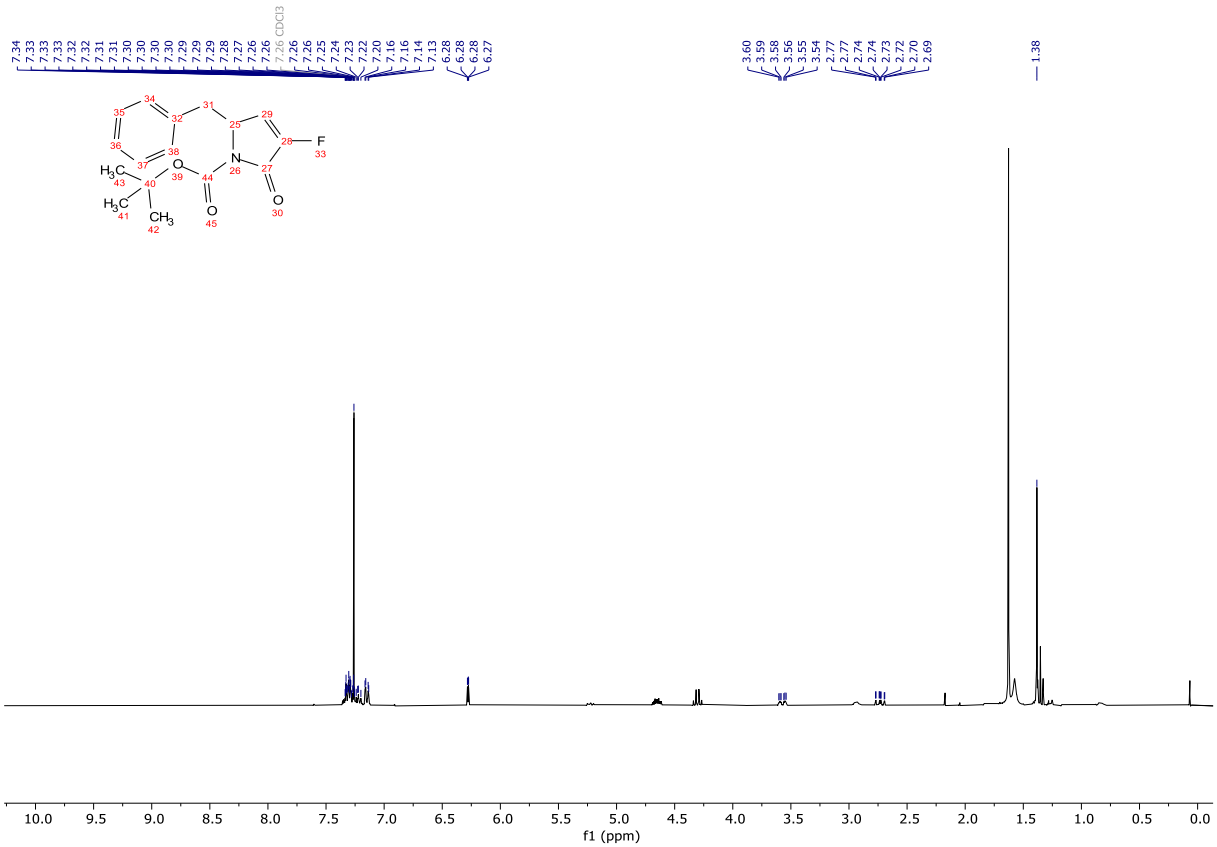


Fig. 77. [1]HNMR spectrum of compound 181.

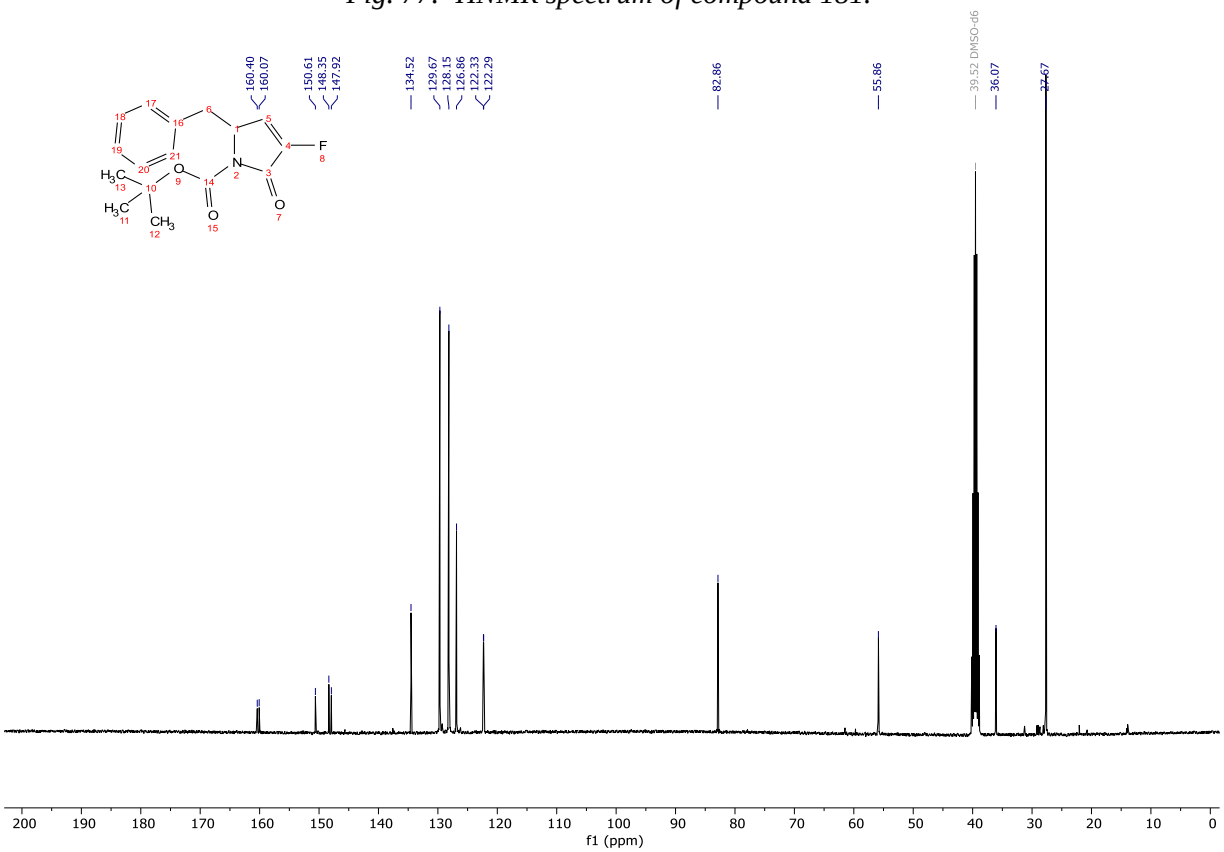


Fig. 78. [13]CNMR spectrum of compound 181.

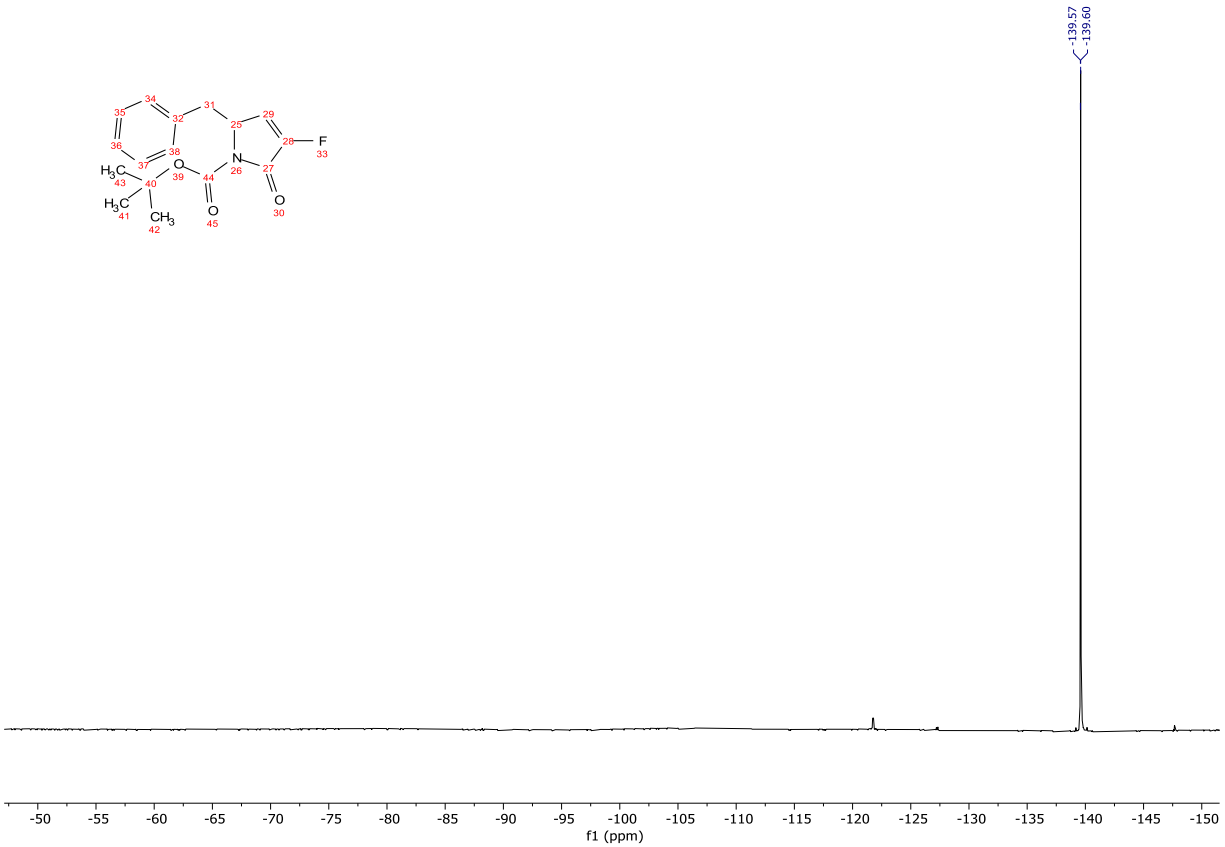


Fig. 79. ^{19}FNMR spectrum of compound 181..

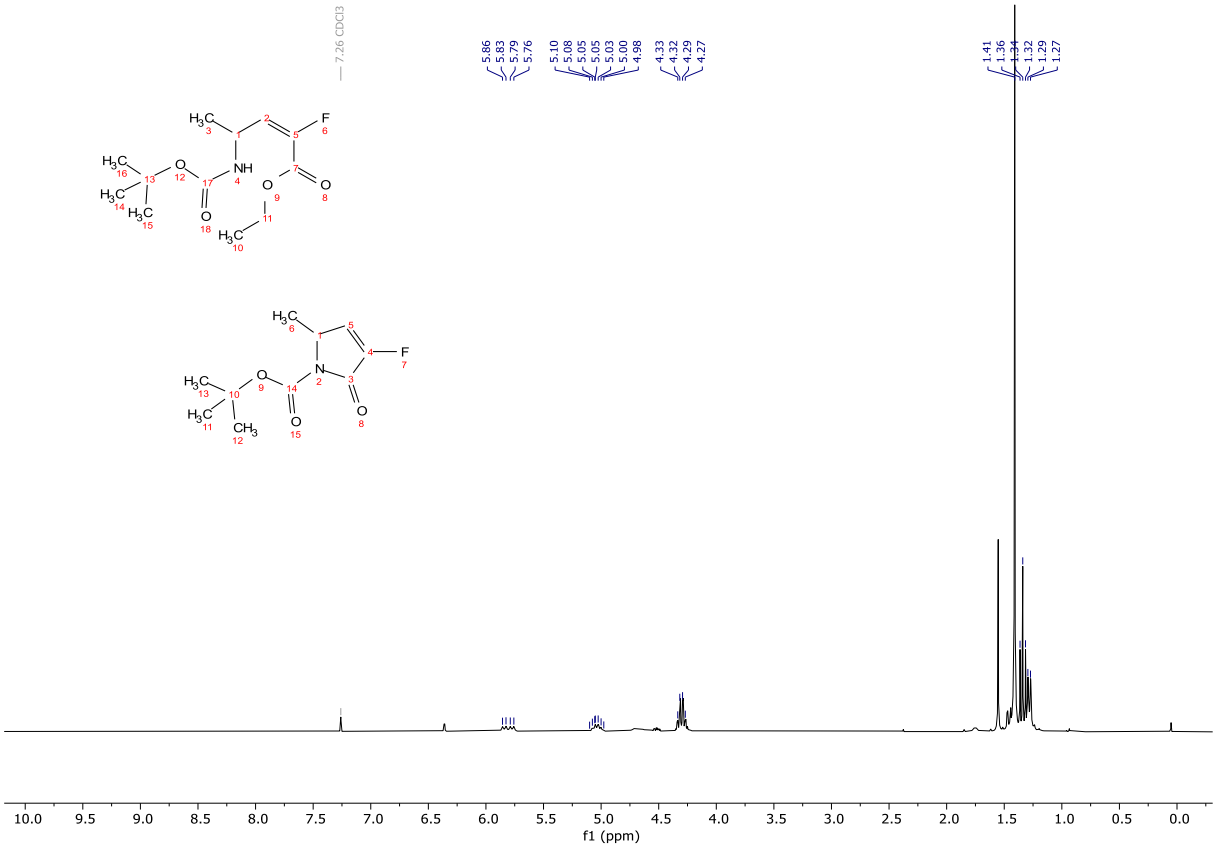


Fig. 80. [1]HNMR spectrum of the mixture 178/182.

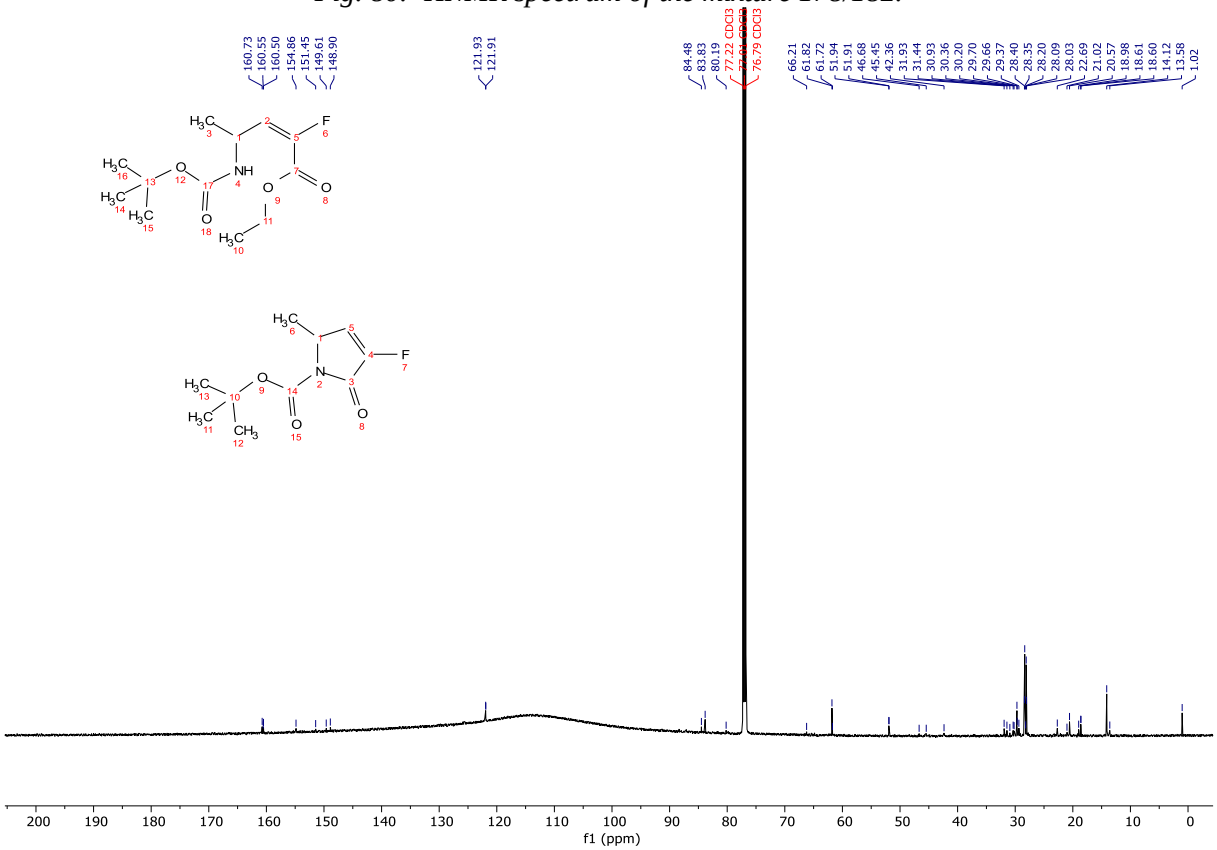


Fig. 81. [13]CNMR spectrum of the mixture 178/182.

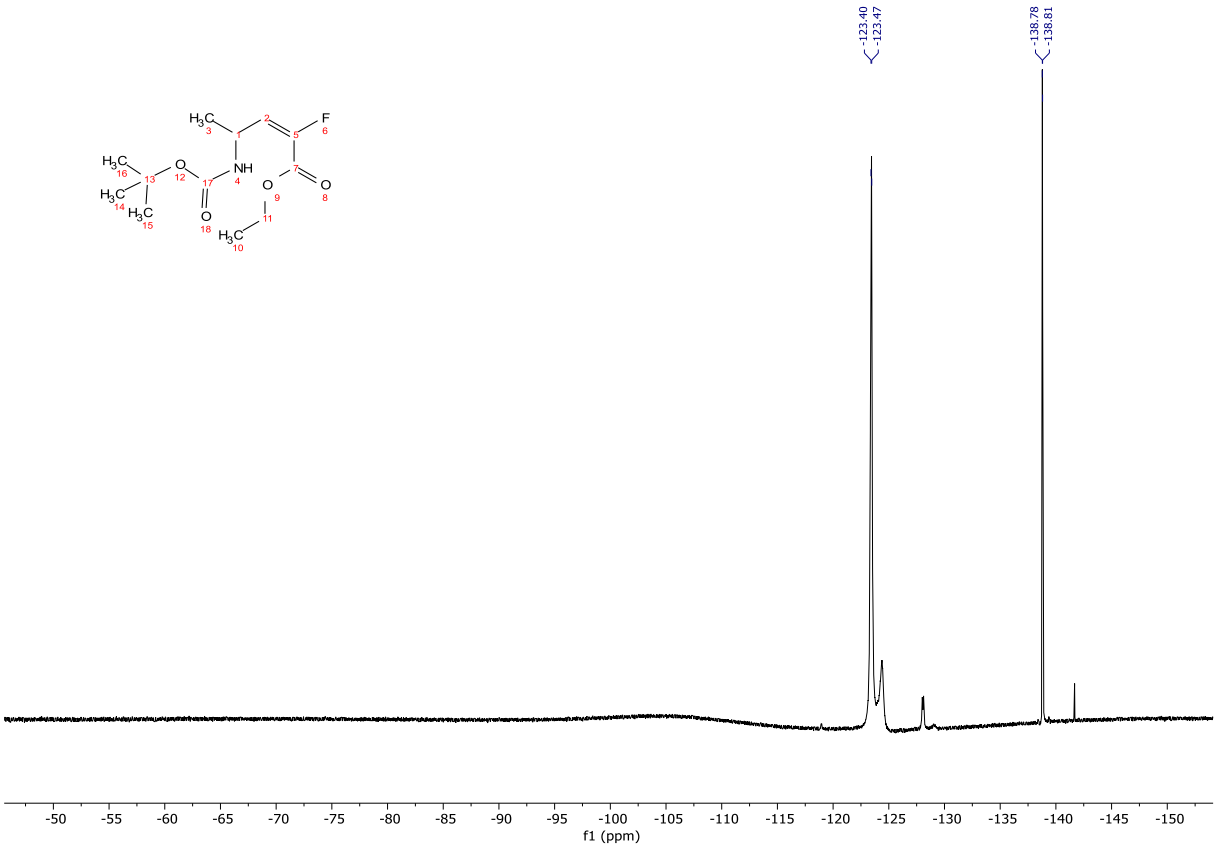


Fig. 82. ^{19}FNMR spectrum of the mixture 178/182.

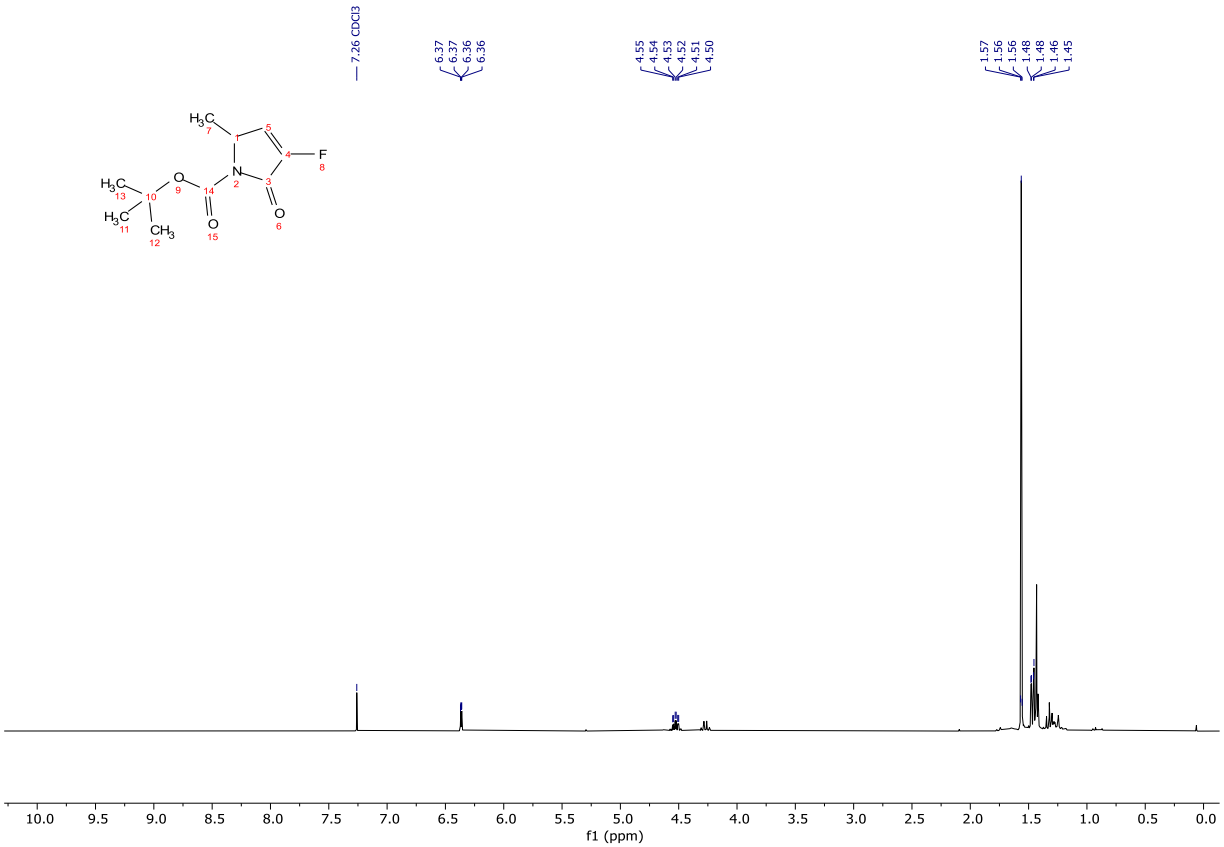


Fig. 83. [1]HNMR spectrum of compound 182.

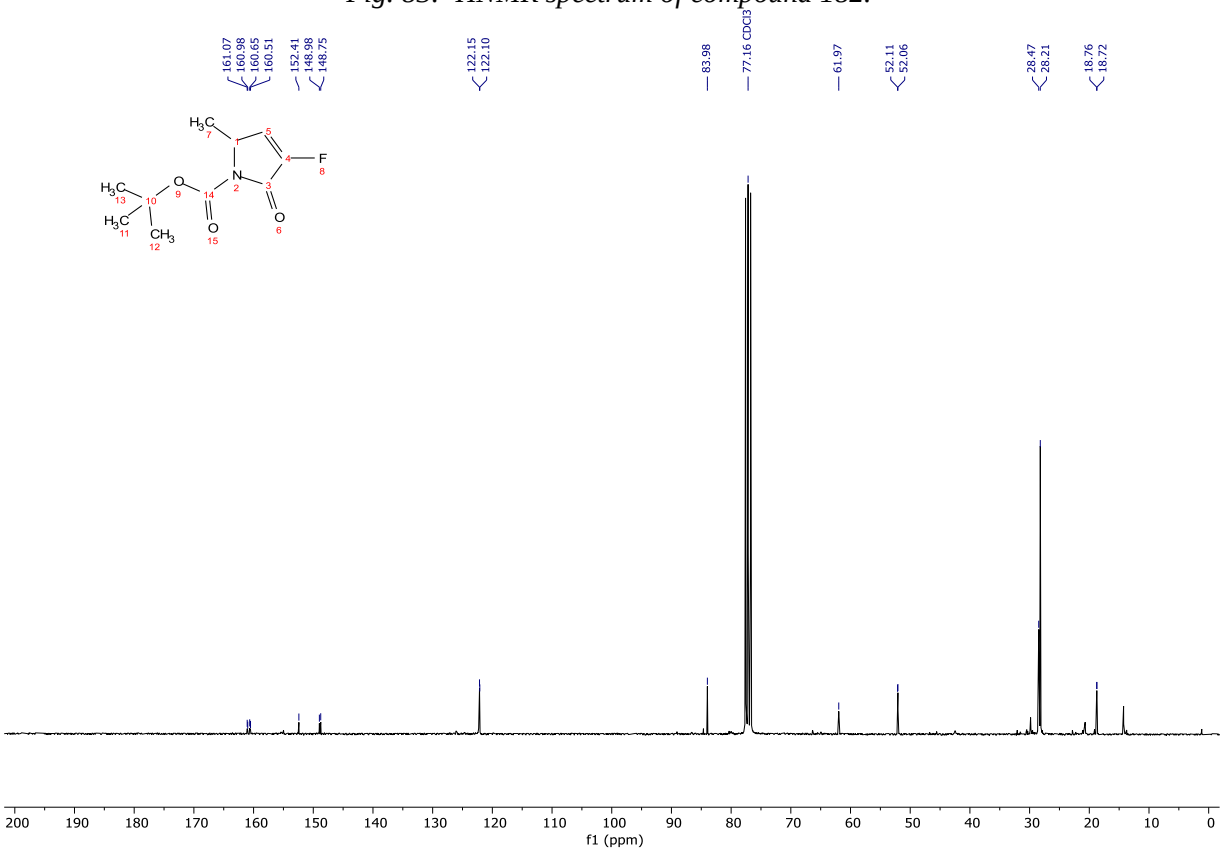


Fig. 84. [13]CNMR spectrum of compound 182.

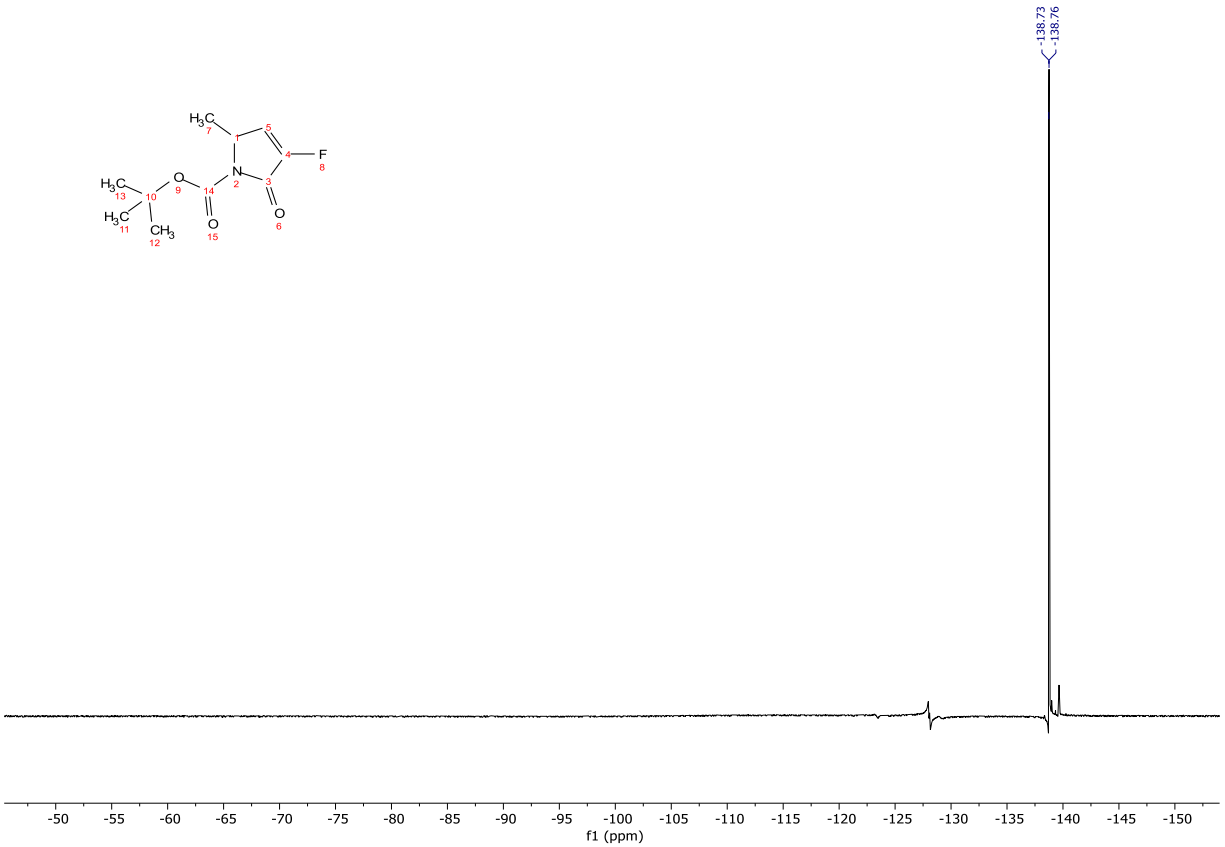


Fig. 85. [19]FNMR spectrum of compound 182.

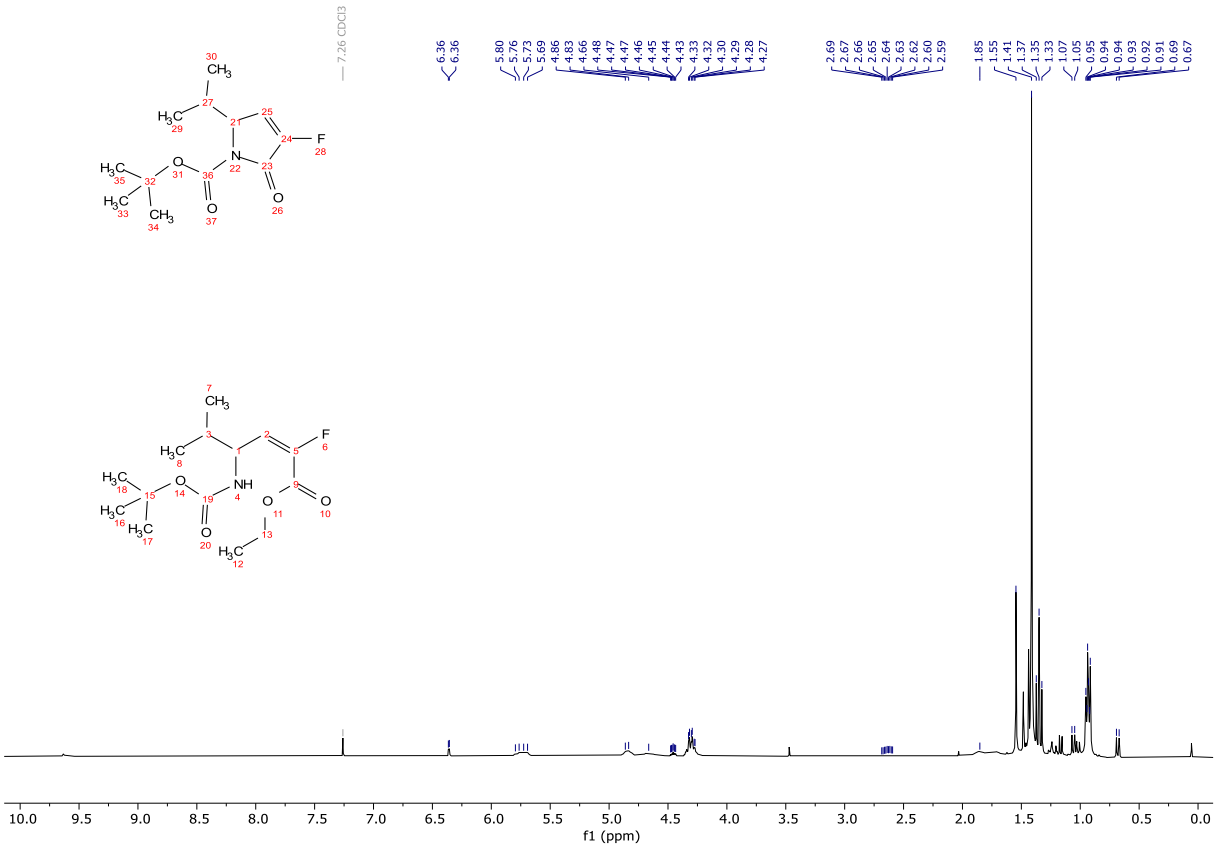


Fig. 86. [1]HNMR spectrum of the mixture 179/183.

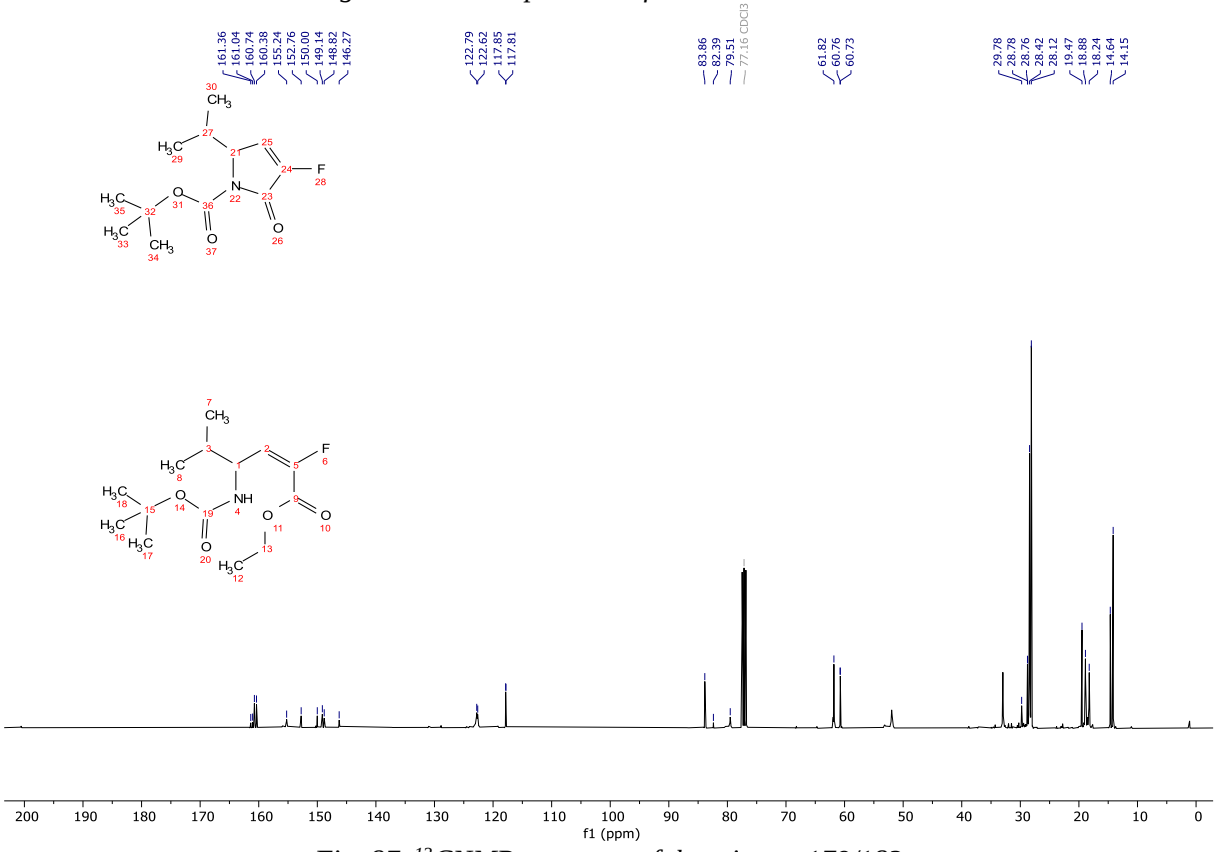


Fig. 87. [13]CNMR spectrum of the mixture 179/183

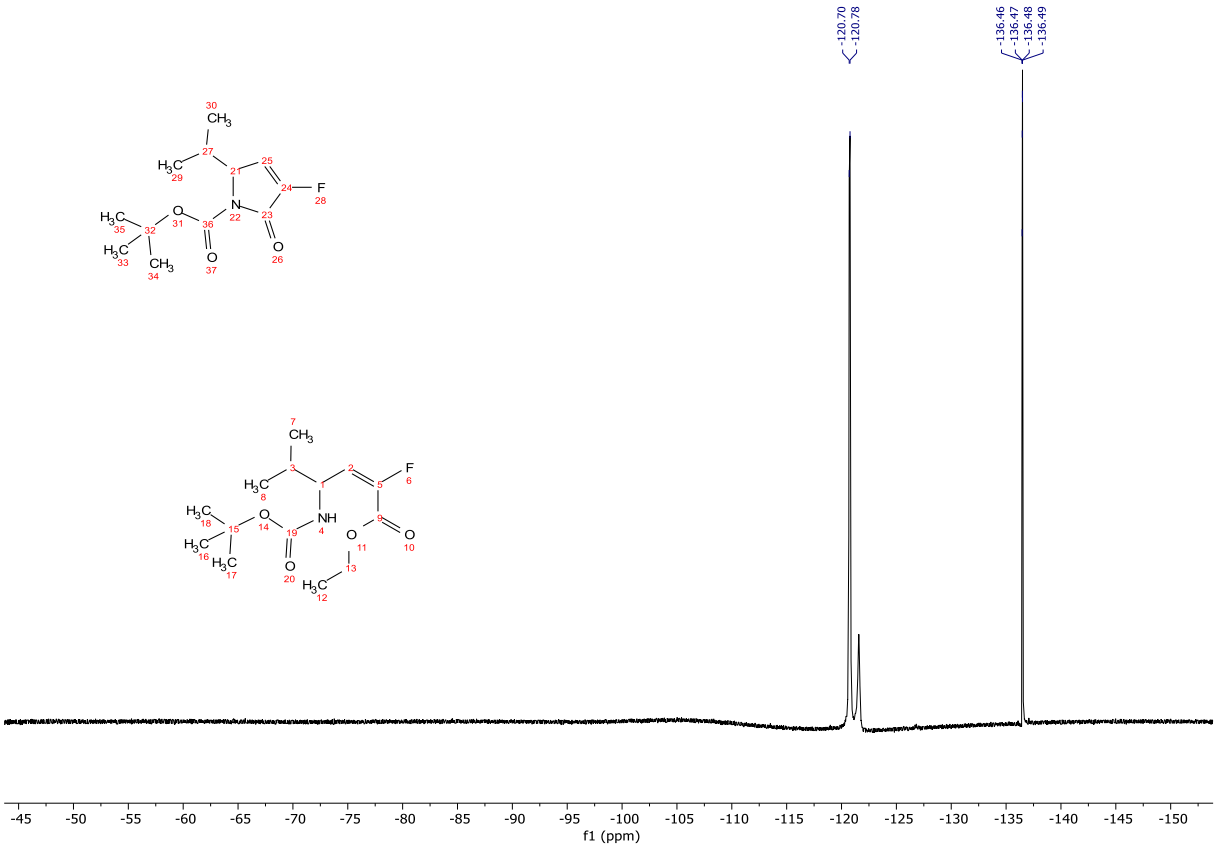


Fig. 88. [19]FNMR spectrum of the mixture 179/183

1.

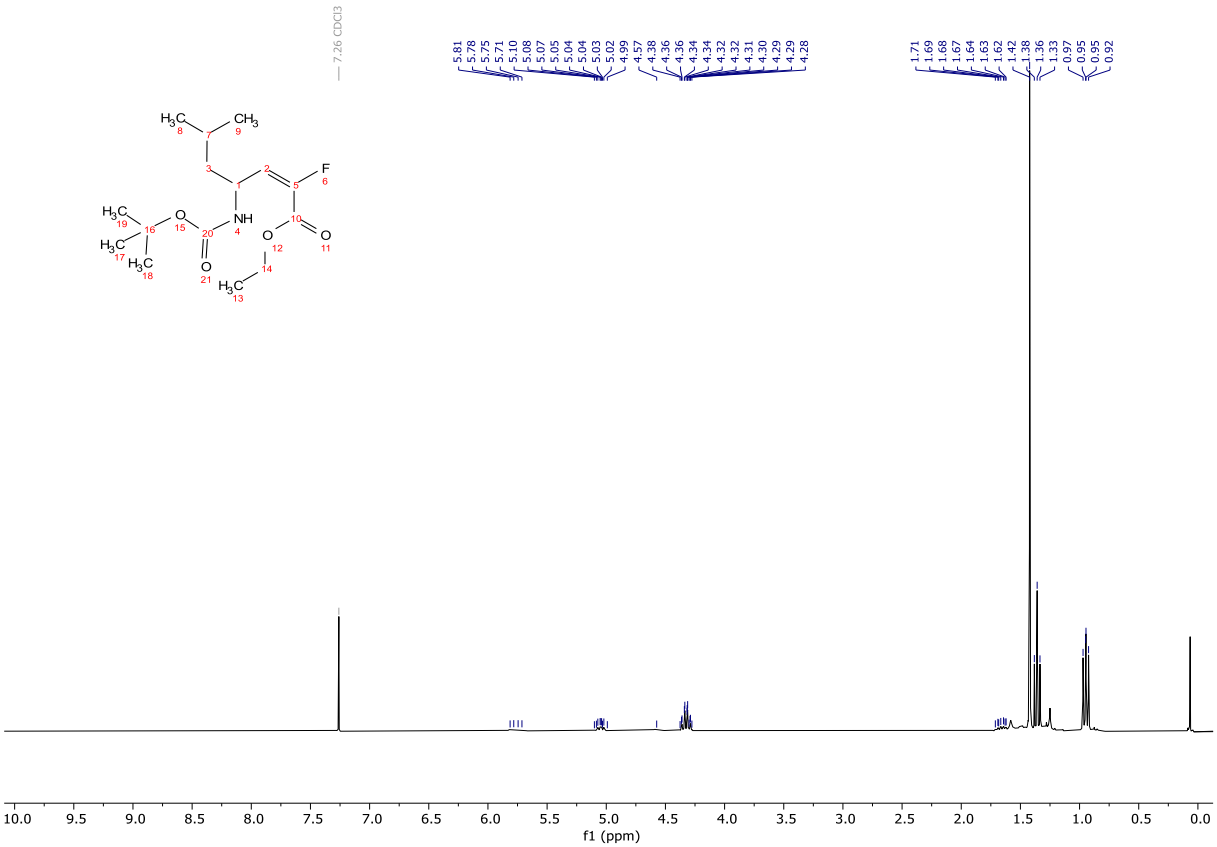


Fig. 89. [1]HNMR spectrum of compound 180.

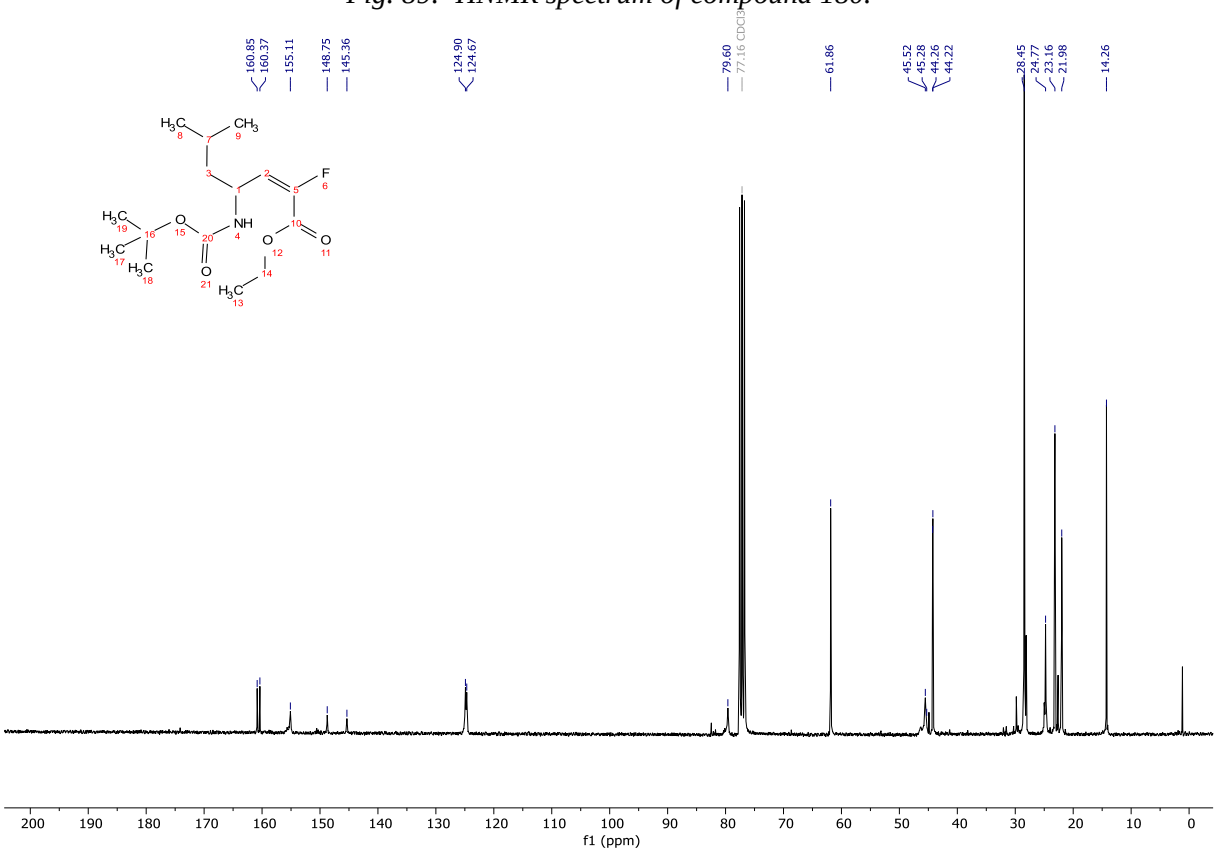


Fig. 90. [13]CNMR spectrum of compound 180.

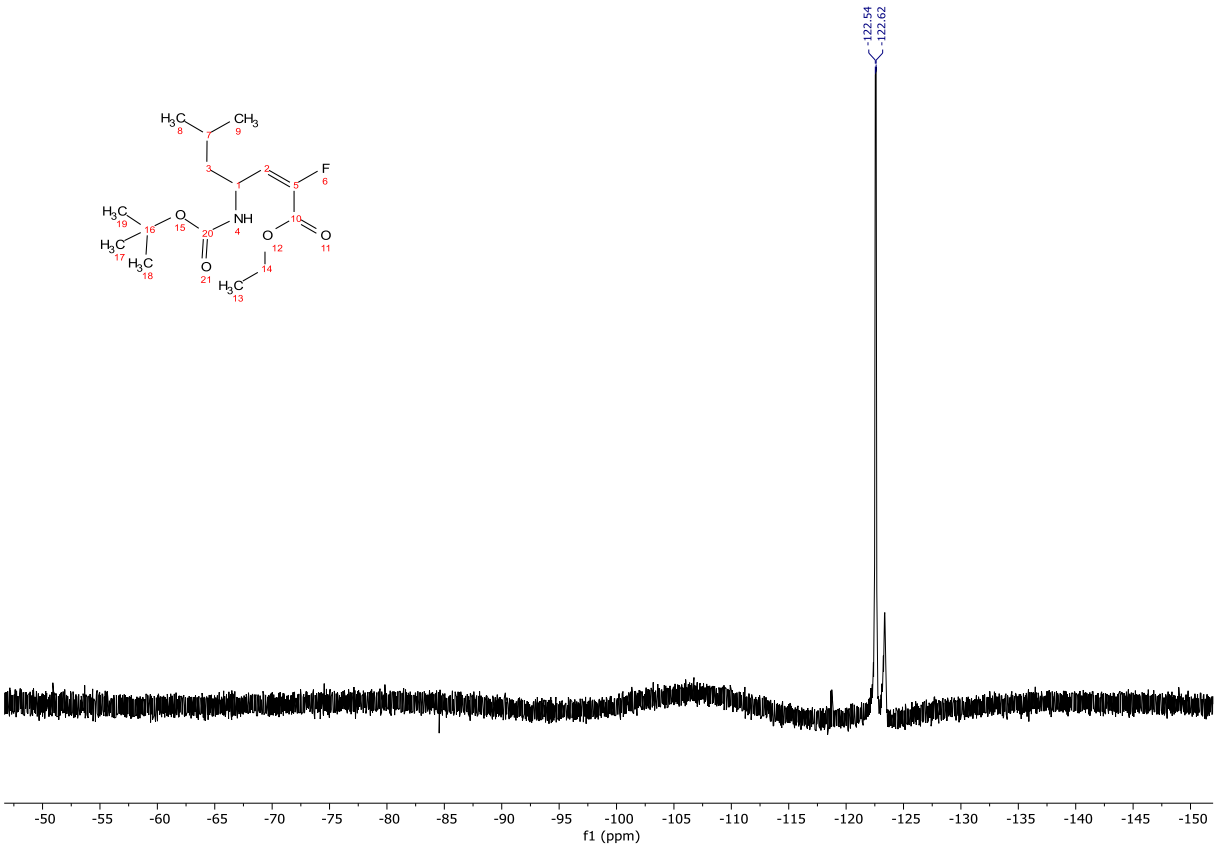


Fig. 91. ^{19}FNMR spectrum of compound 180.

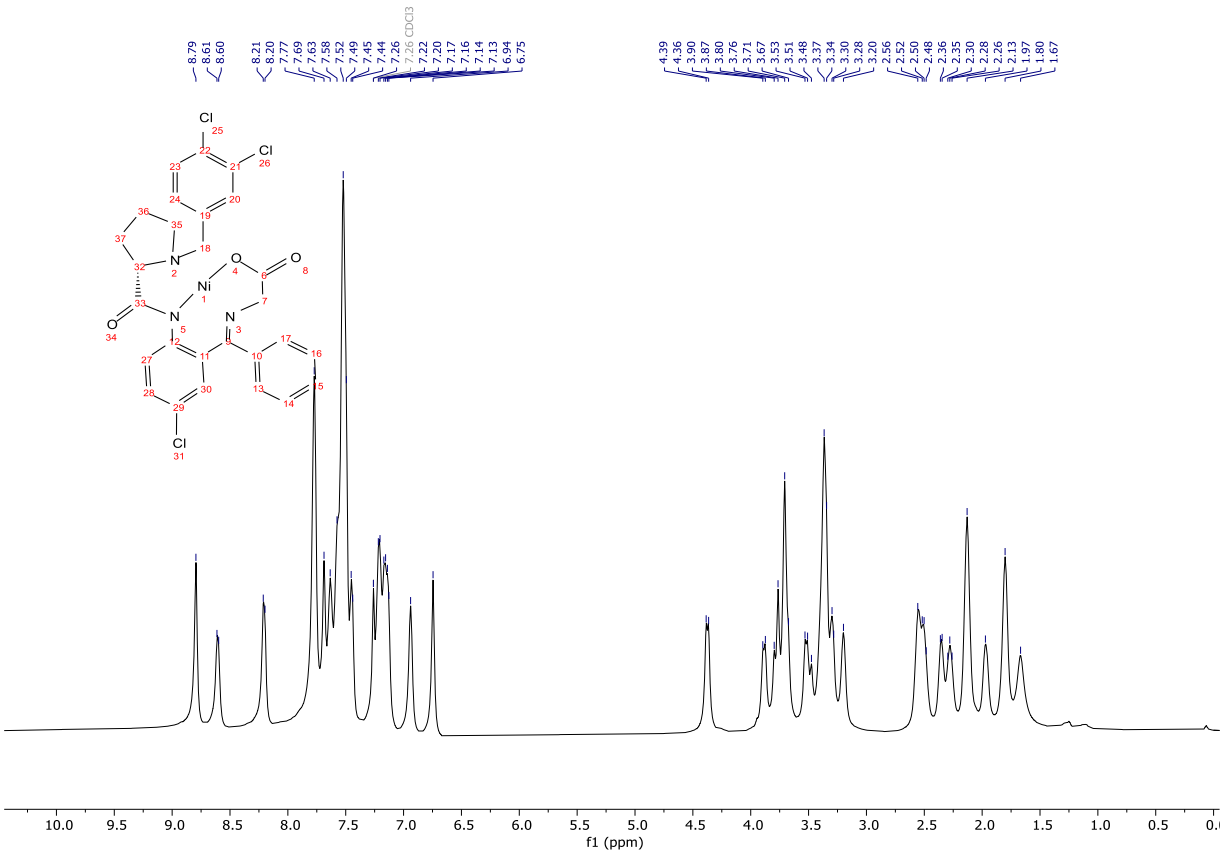


Fig. 92. [1]HNMR spectrum of compound 116a.

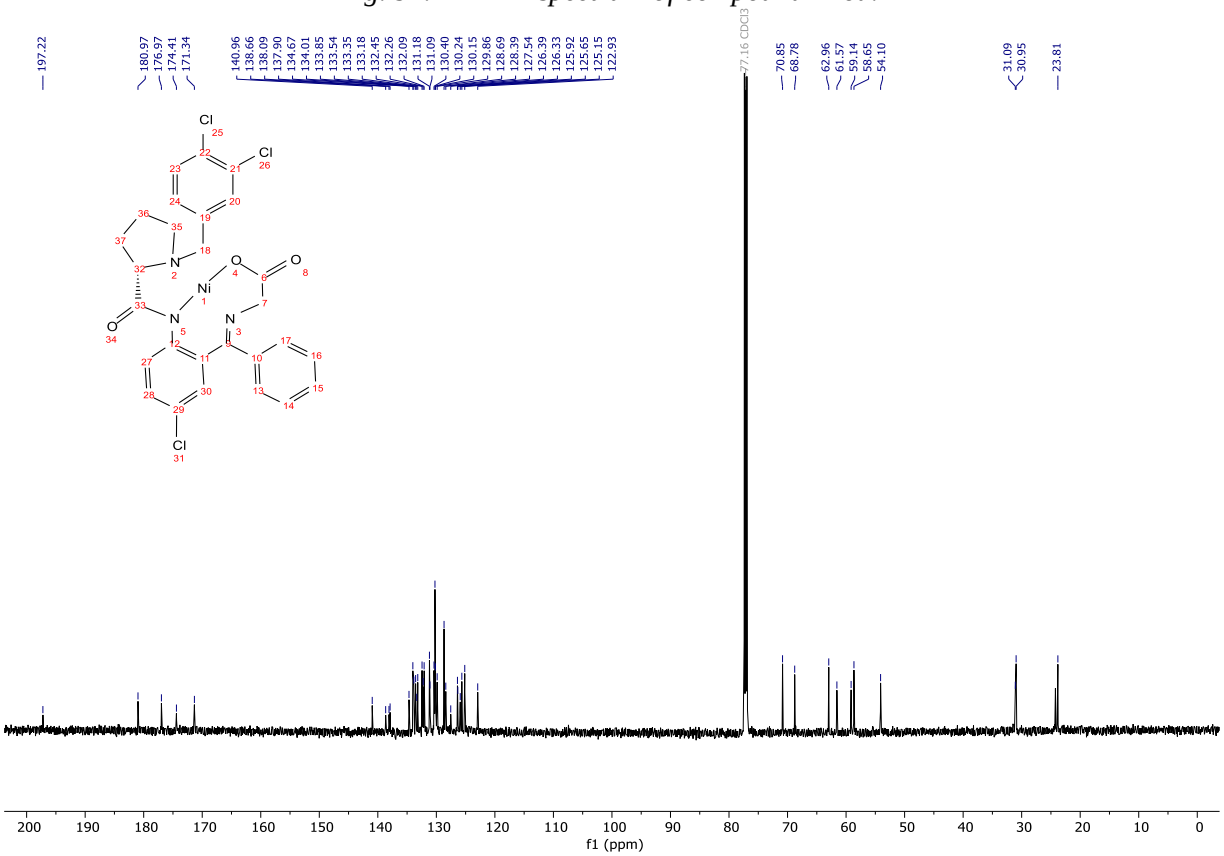


Fig. 93. [13]CNMR spectrum of compound 116a.

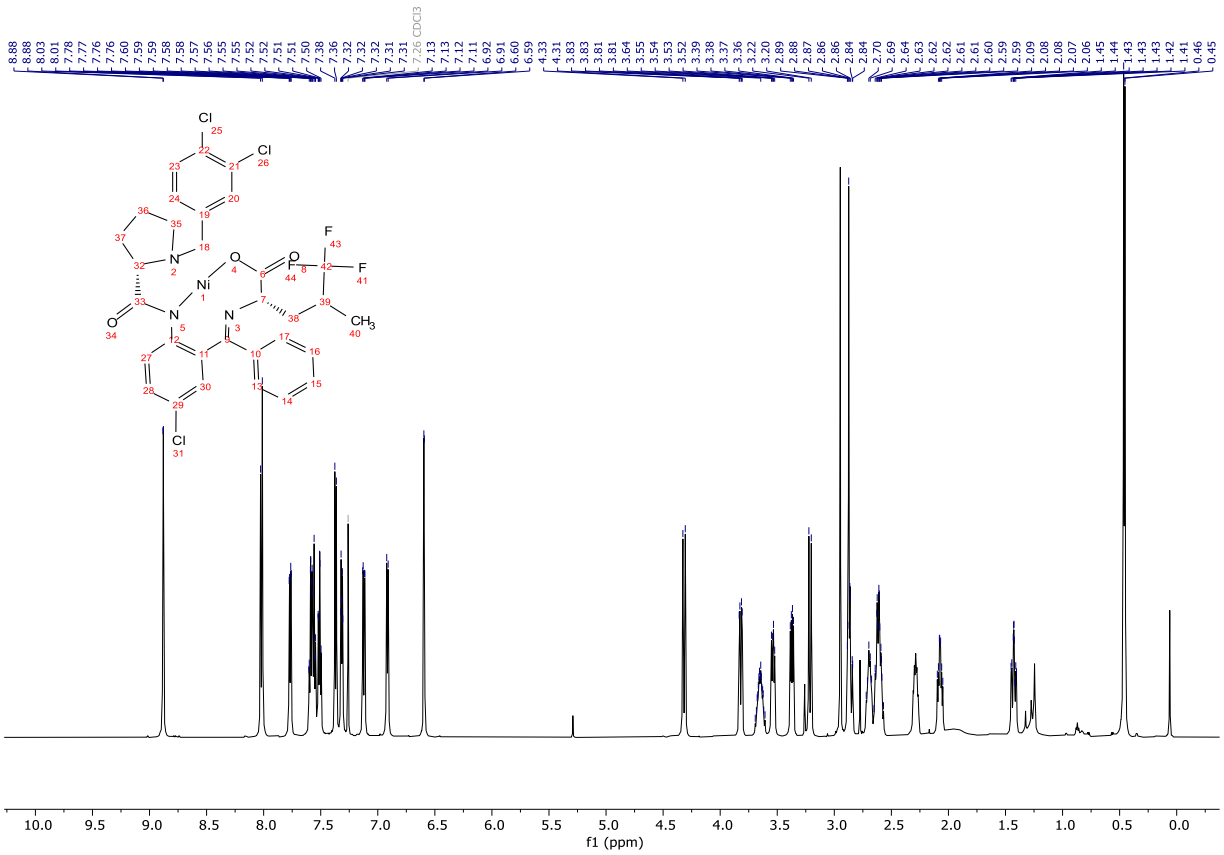


Fig. 94. [1]HNMR spectrum of compound 232a.

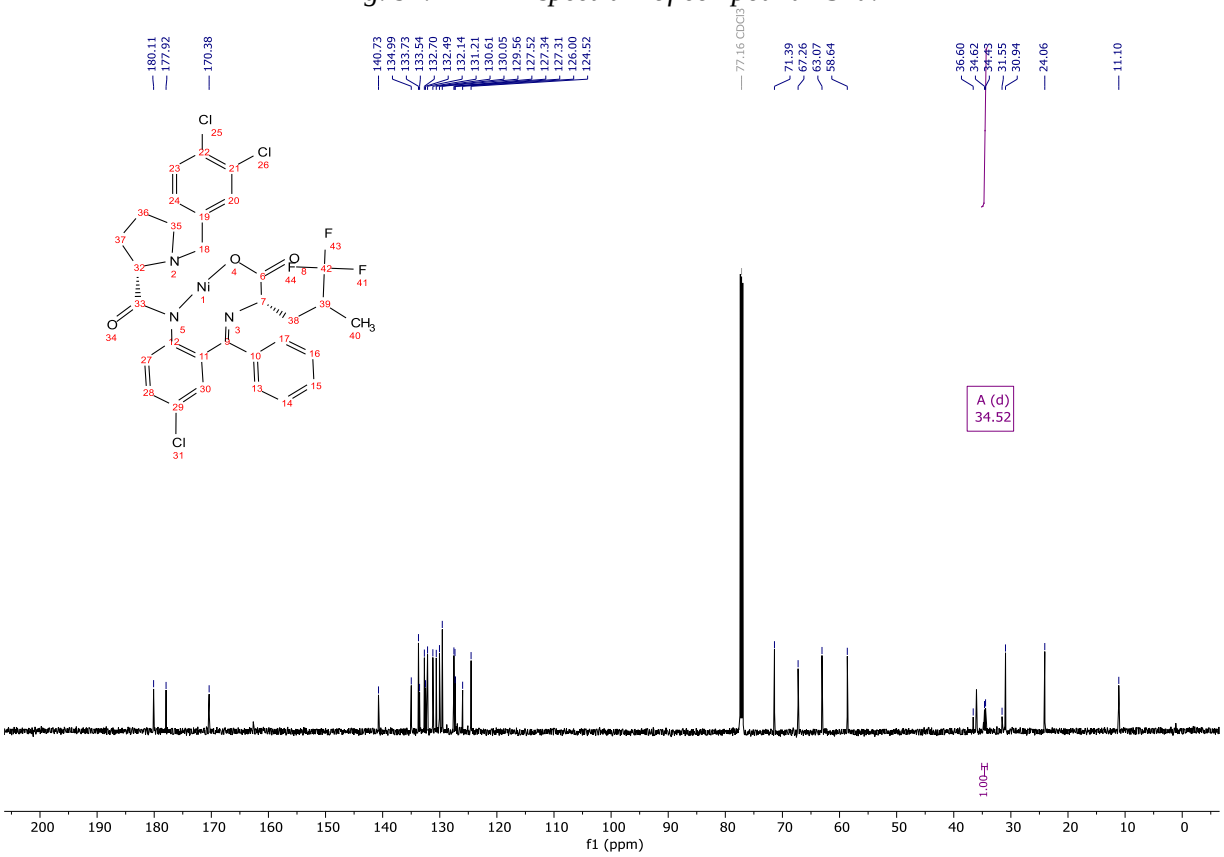


Fig. 95. [13]CNMR spectrum of compound 232a.

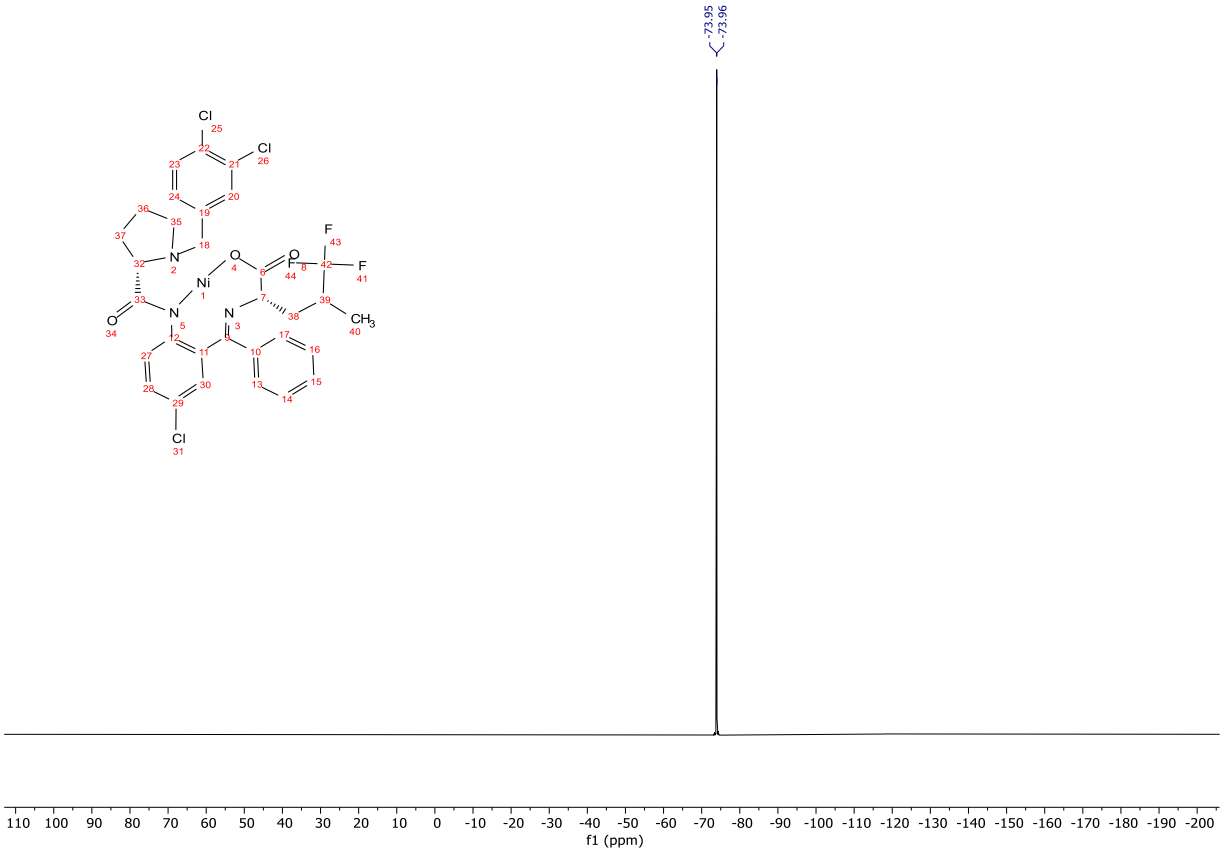


Fig. 96. [19]FNMR spectrum of compound 232a.

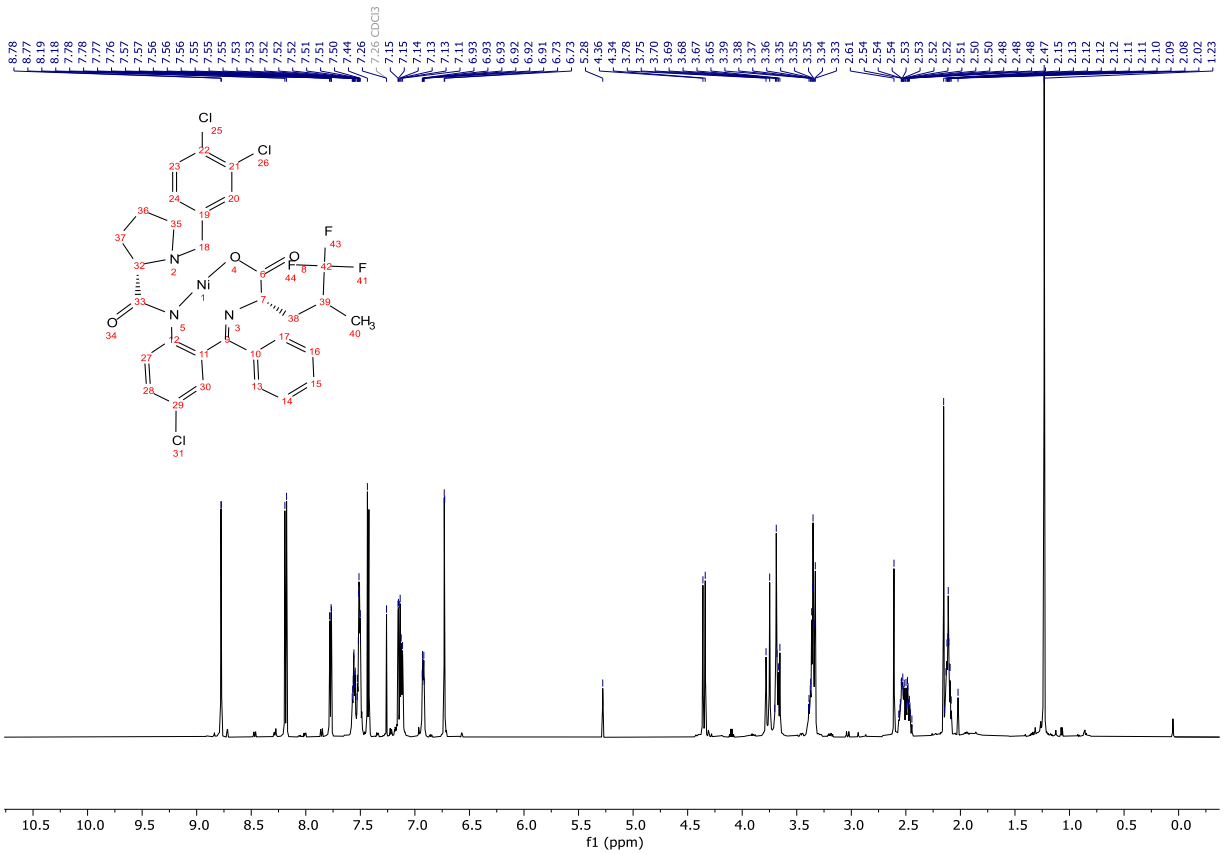


Fig. 97. [1]HNMR spectrum of compound 232b.

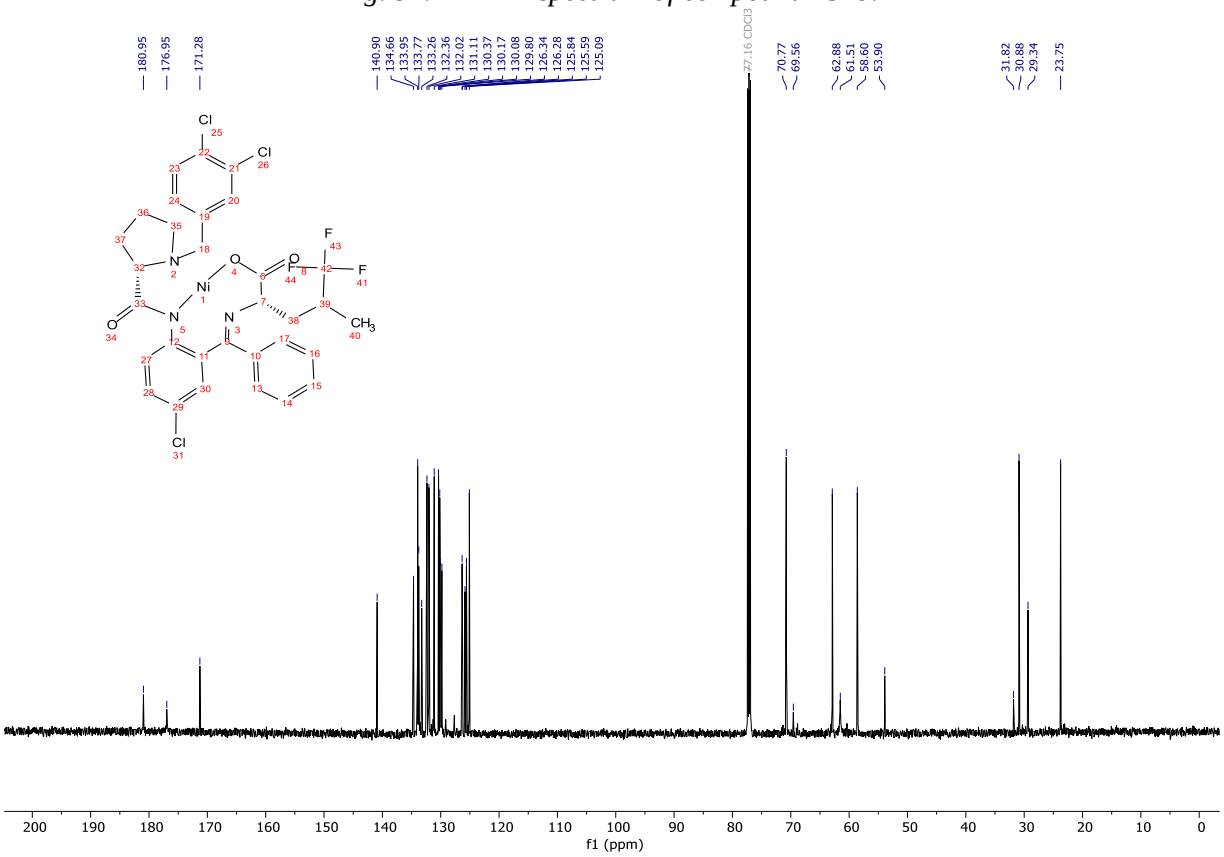


Fig. 98. [13]CNMR spectrum of compound 232b.

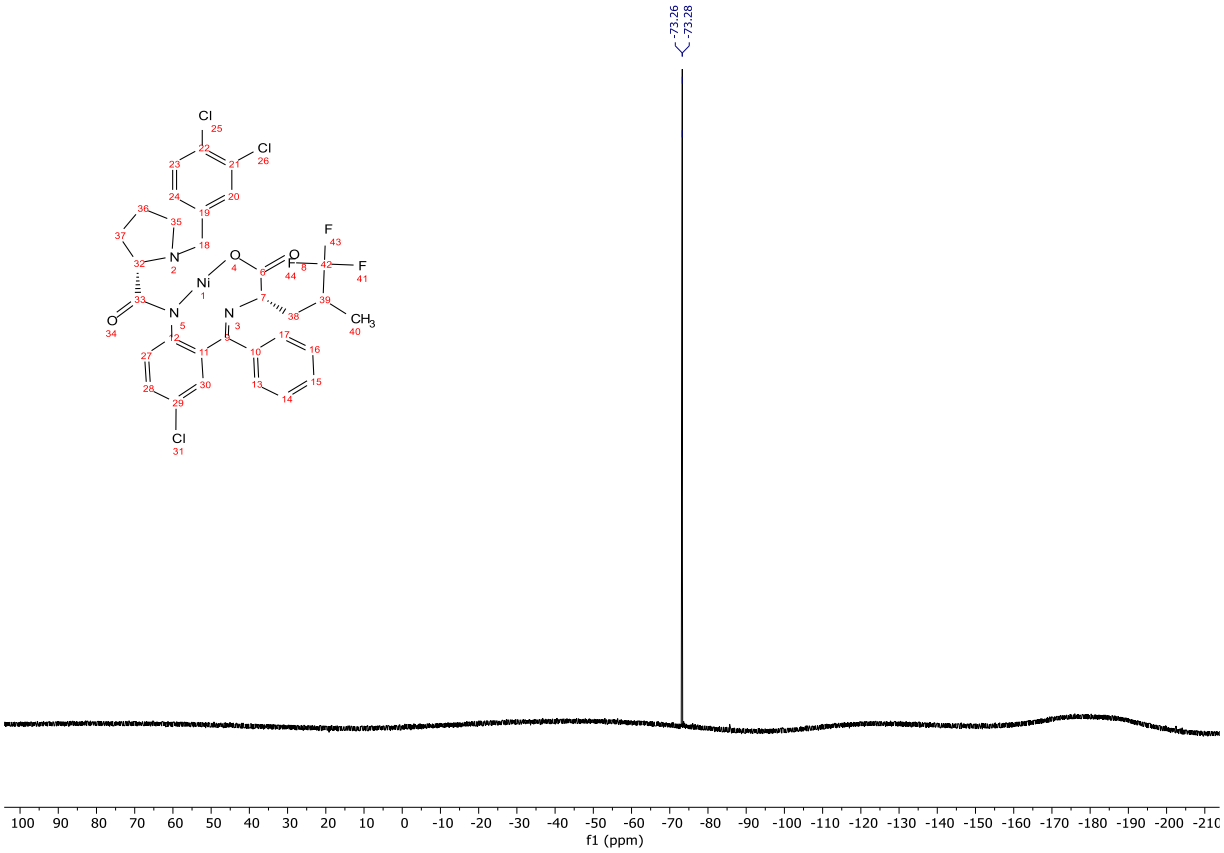


Fig. 99. [19]FNMR spectrum of compound 232b.

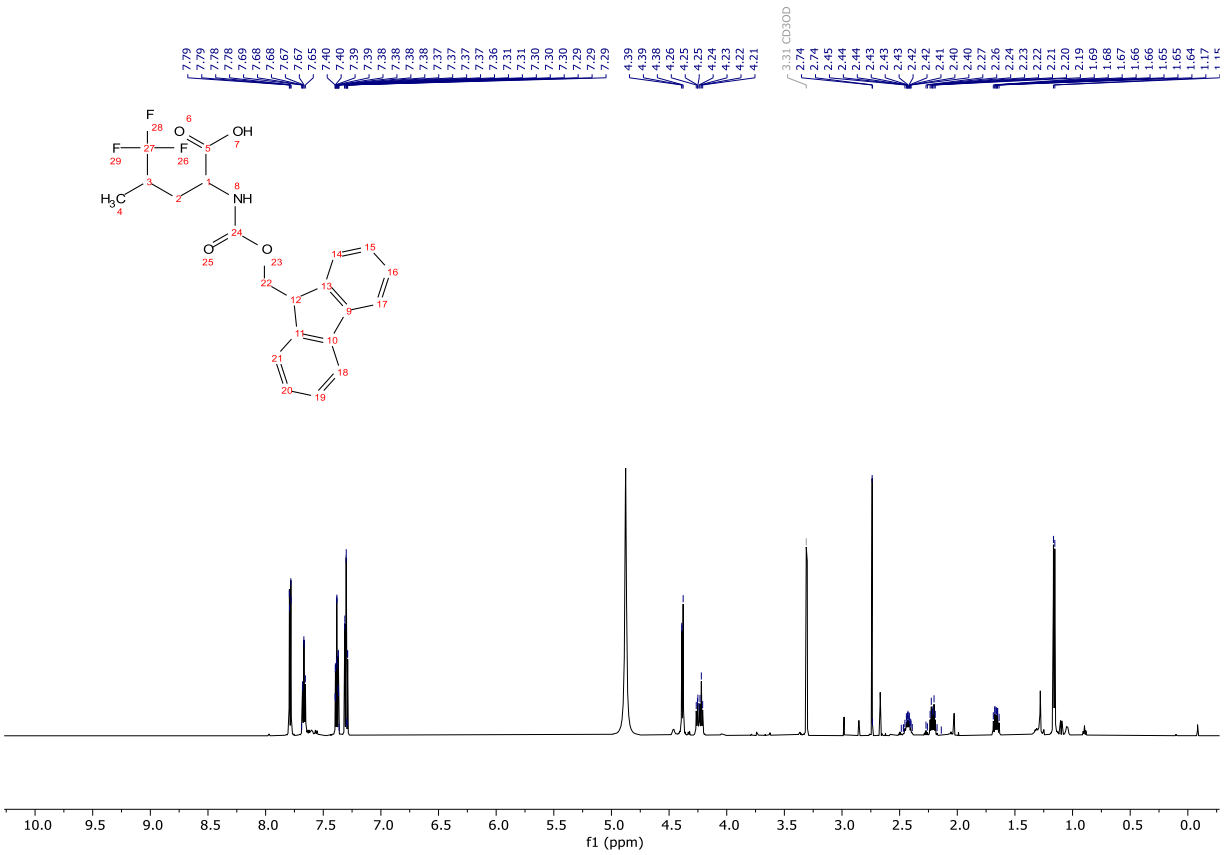


Fig. 100. [1]HNMR spectrum of compound 233a.

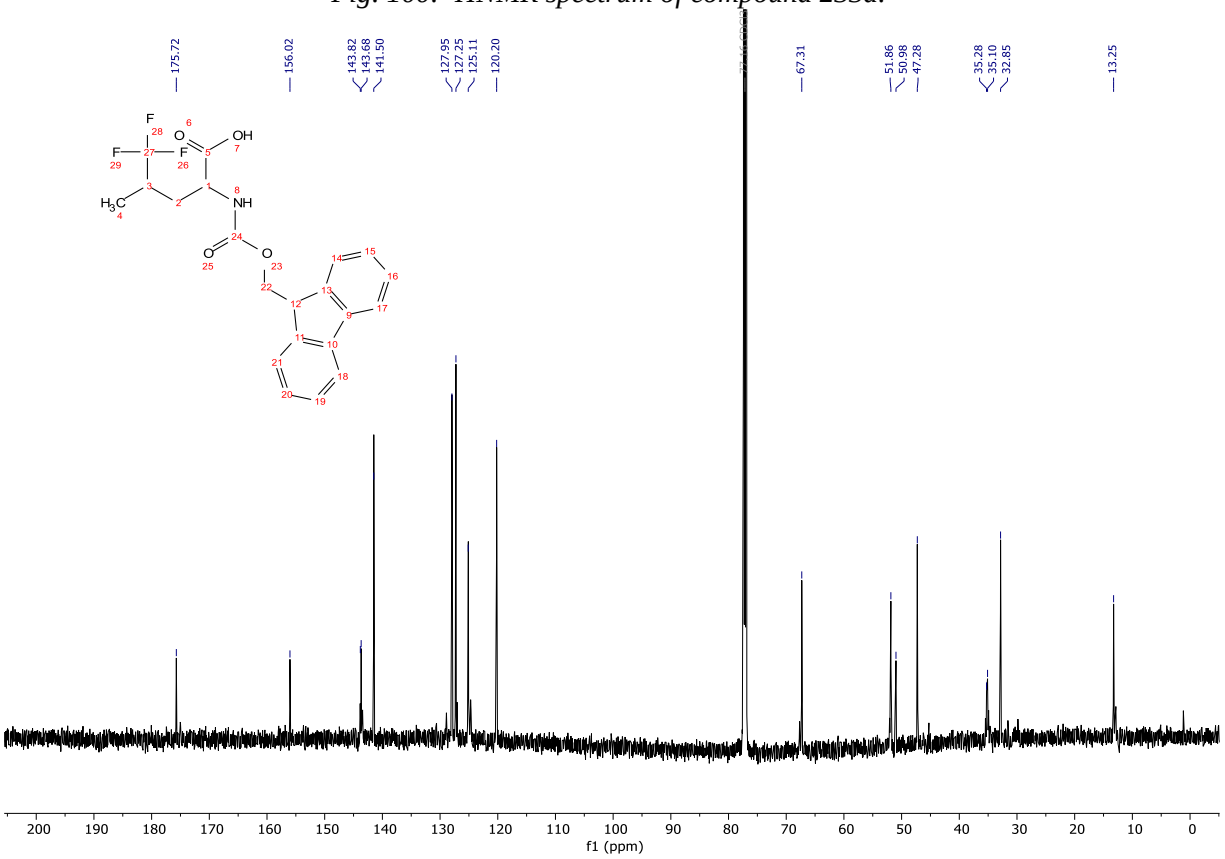


Fig. 101. [13]CNMR spectrum of compound 233a.

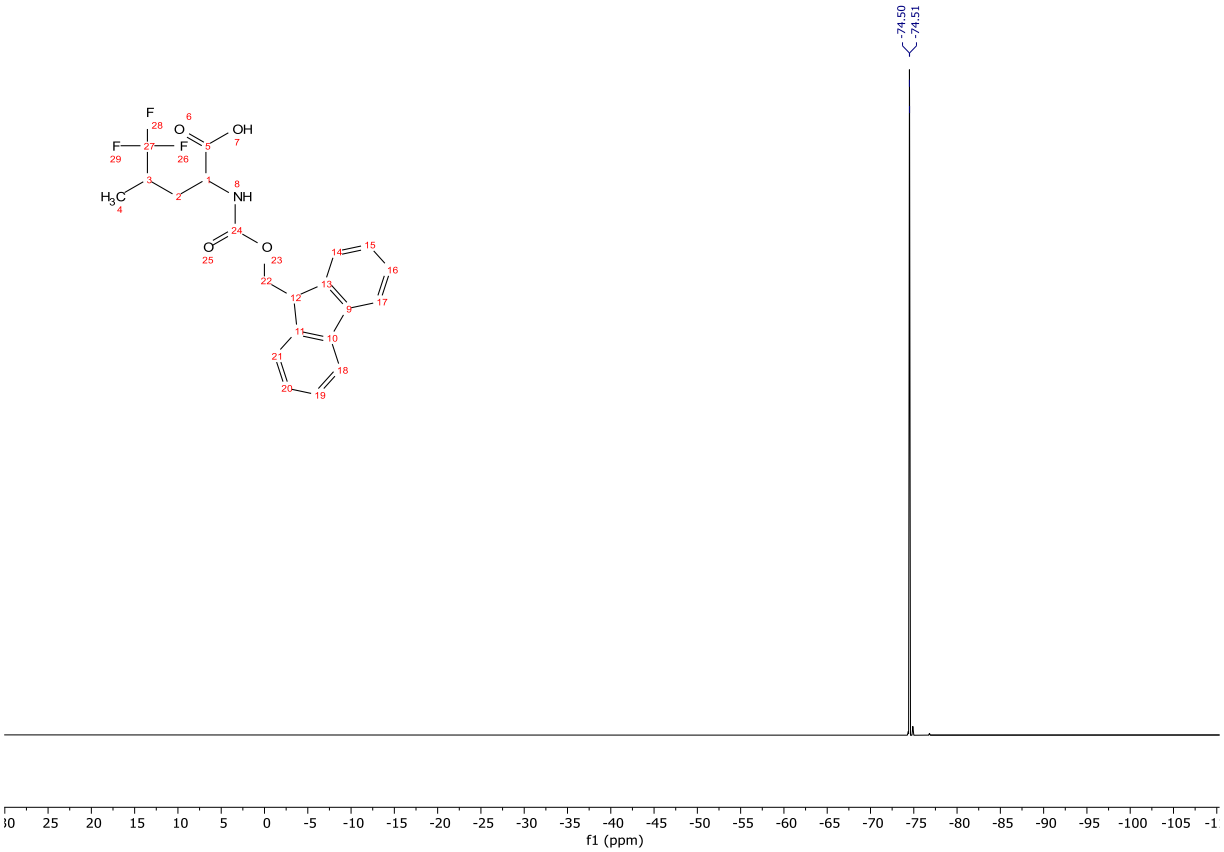


Fig. 102. ^{19}FNMR spectrum of compound 233a.

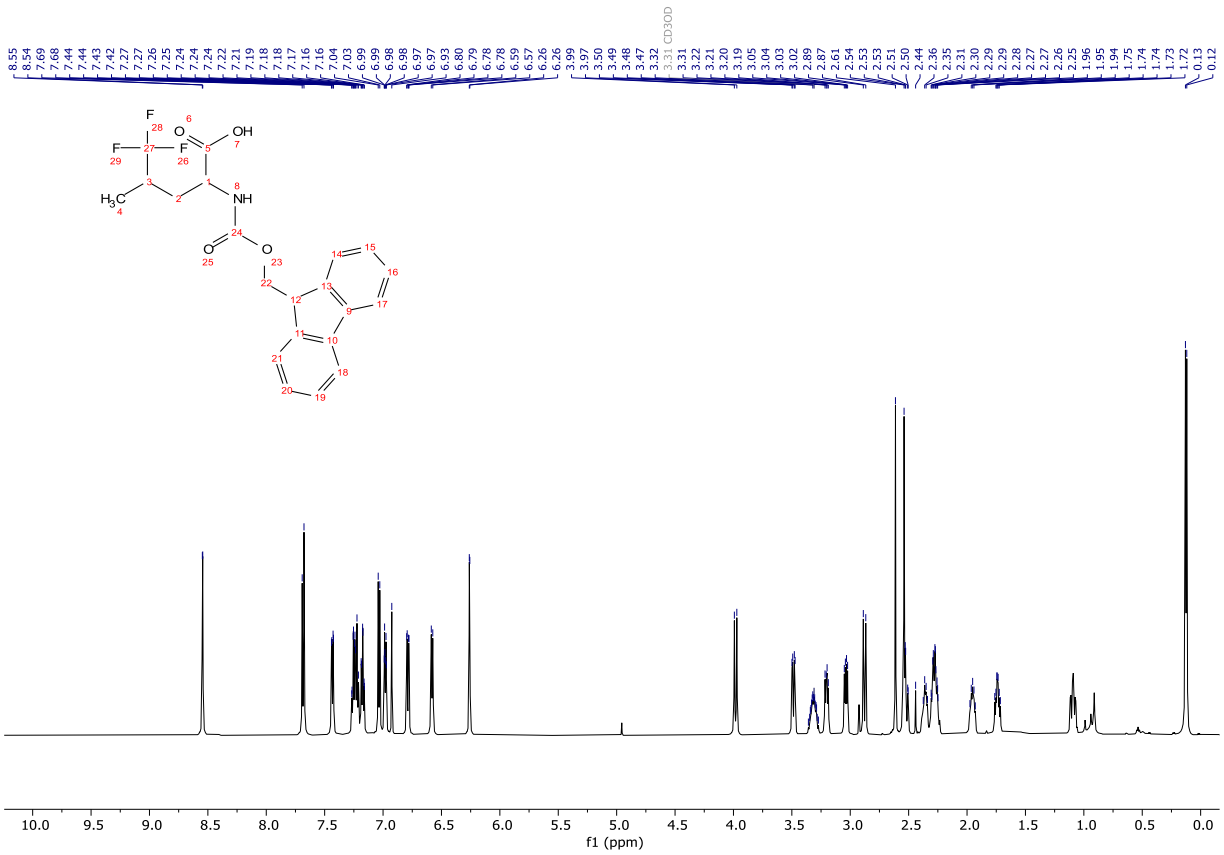


Fig. 103. [1]HNMR spectrum of compound 233b.

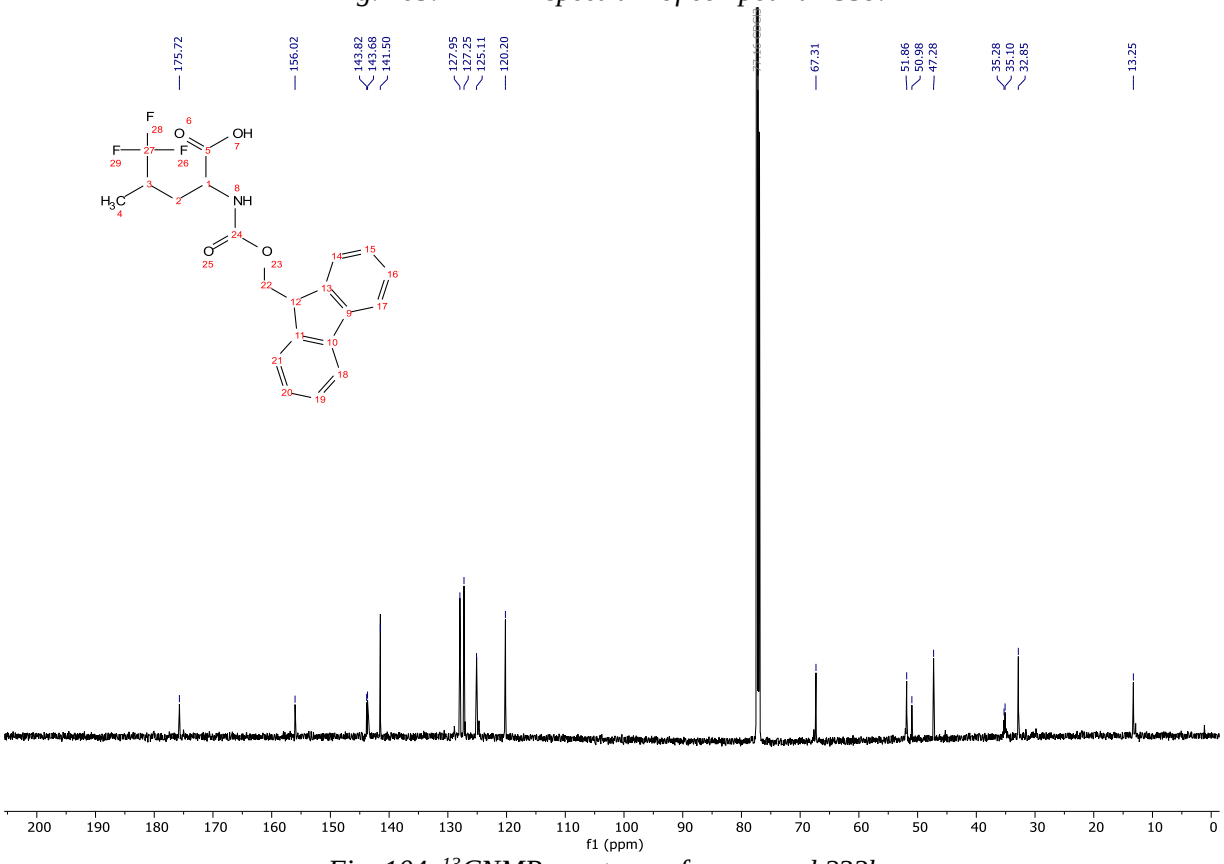


Fig. 104. [13]CNMR spectrum of compound 233b.

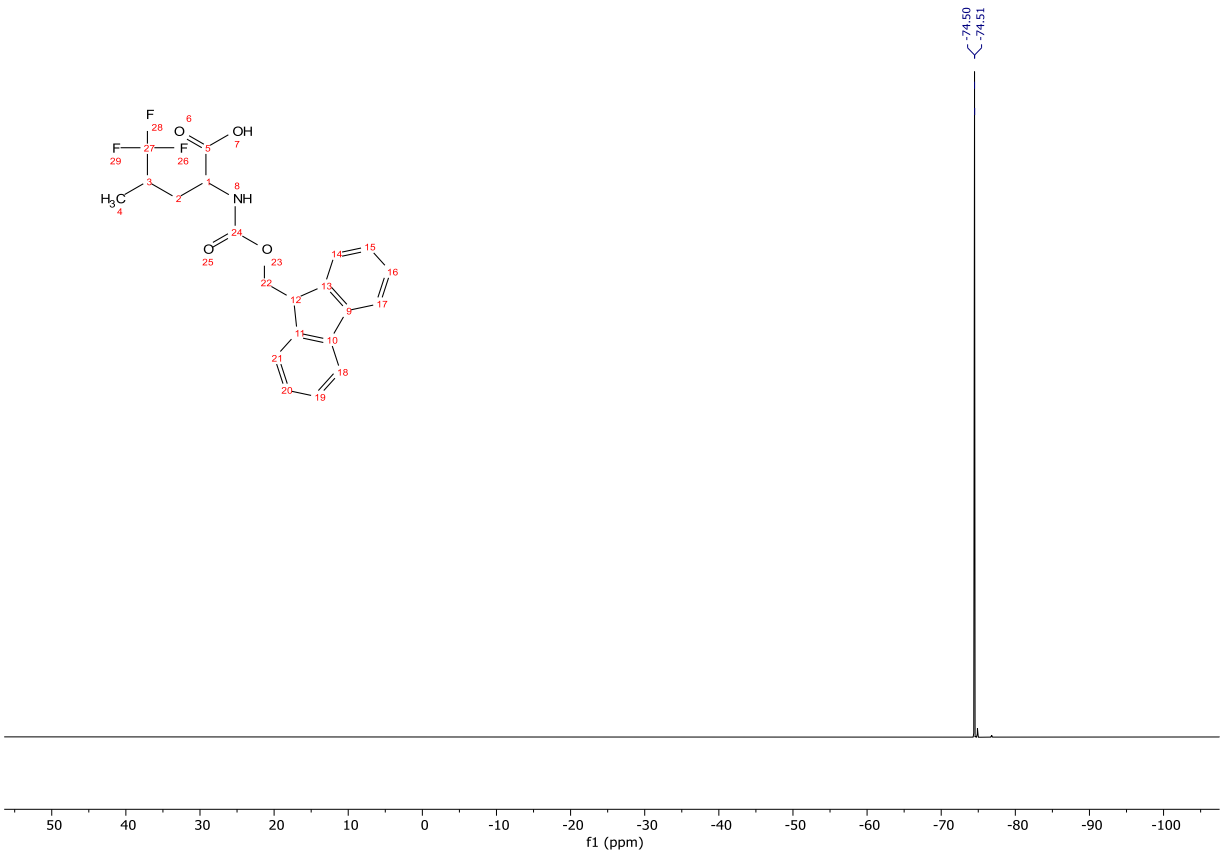


Fig. 105. ^{19}FNMR spectrum of compound 233b.

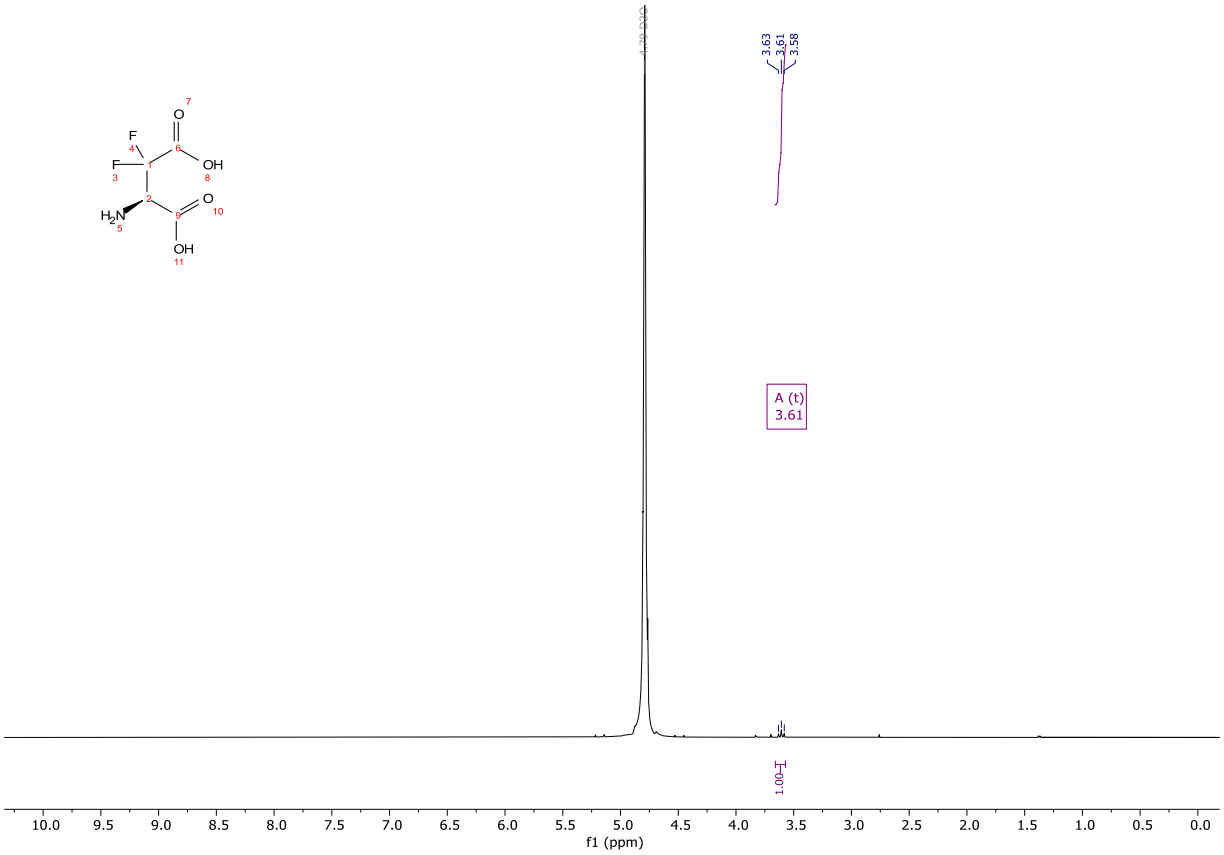


Fig. 106. [1]HNMR spectrum of compound 235.

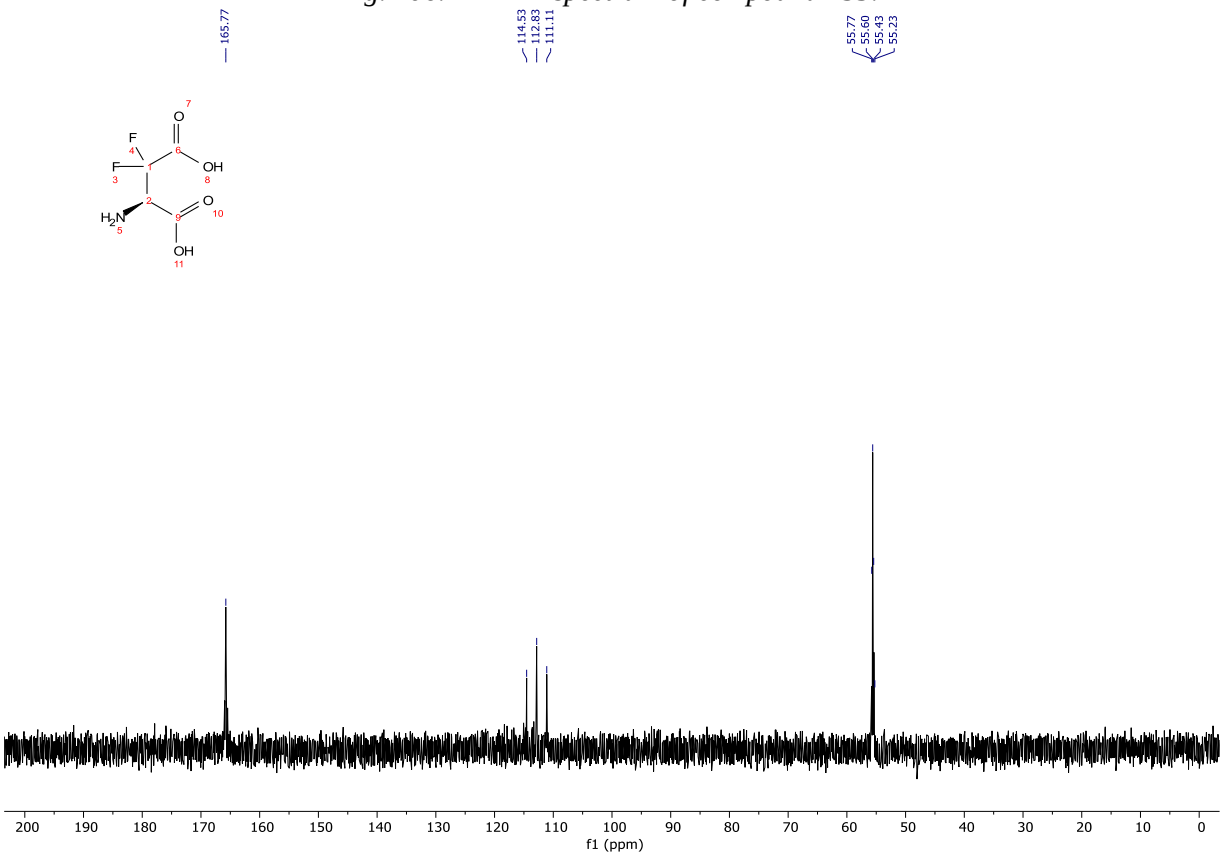


Fig. 107. [13]CNMR spectrum of compound 235.

6. Summary

Organic compounds with fluorovinyl bond are an attractive group of chemical compounds that can play a role as peptide mimetics. The fluorovinyl bond "mimics" the peptide bond, however, literature reports show that it is more resistant to rapid proteolysis and may increase the bioavailability of the target molecule. Therefore, the use of fluorovinyl derivatives seems to be an interesting and attractive idea, because such compounds can be used as, for example, inhibitors of many enzymes, such as for example, Cathepsin C, and can also be used as precursors for further syntheses of peptides.

The doctoral thesis focused on practical organic synthesis. Its main goal was to develop an efficient method of obtaining new amino acid derivatives with a fluorovinyl moiety. The scope of tasks performed as part of the doctoral thesis included the design of the structure of desired compounds, and then the selection of an effective and efficient method of their synthesis. The developed procedure consisted of five stages, and structurally diverse amino acids were used, without reactive side chains, such as alanine, phenylalanine, leucine and valine.

The implementation of the above-mentioned tasks required the use of standard techniques used in organic chemistry laboratories. The synthesis was carried out using the classical solution method, using temperature conditions dictated by the type of chemical reaction. Each of the carried out chemical reactions was optimized in terms of the amount of solvent used (concentration of reagents), temperature, reaction time or oxygen access (or inert atmosphere of argon). Extraction, filtration, crystallization and column chromatography were used to purify the post-reaction mixtures. The progress of the reaction was monitored by TLC, adjusting the polarity of the eluent.

The structures of the obtained compounds were confirmed by spectroscopic measurements: infrared spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H, ^{13}C, ^{19}F NMR), as well as chromatographic methods, such as gas chromatography coupled with mass detection. The structures of the compounds that formed the crystals were confirmed by X-ray analysis.

7. Conclusions

As part of the doctoral thesis, an efficient, effective procedure for obtaining fluorovinyl derivatives of amino acids was developed. The desired chemical compounds were obtained using a five-step synthesis, which included Horner-Wadsworth-Emmons (HWE) reaction as a key step allowing the introduction of the fluorovinyl bond.

The obtained amino acid derivatives were fully characterized after each step of the synthesis, and the greatest attention was focused on the analysis of products with fluorovinyl group.The paper not only presents the synthesis of fluorinated amino acid derivatives, but also reports the formation of fluorinated lactams by the self-driven cyclization of the linear minofluorivinylic derivatives of amino acids. Such chemical compounds, to my best knowledge, have not been described so far and are undoubtedly a novelty in organic synthesis.

The analysis of spectroscopic data, specifically the H-F coupling constants at the double bond, suggest that the HWE reactions led to the obtaining of fluorovinyl derivatives of amino acids as *E*-isomers in majority.

During doctoral research, it was also proved that the reaction of protecting the amino group with the *tert*-butoxycarbonyl group can lead to racemization when there is a carbonyl group of the amino acid in the molecule. This problem can be overcome by reversing the reaction steps and getting rid of the carbonyl group. The research also showed an interesting fact that under specific reaction conditions, the Boc_2O can react with both the amino and hydroxyl groups. Such a phenomenon has not been reported in the literature so far, which undoubtedly constitutes an interesting supplement to the research.

The influence of the base used in the HWE reaction on the yield and type of products created was also investigated. The use of *n*-BuLi allowed to obtain products in higher yields (on average by 20% more than in the case of using LiHMDS), and in the case of the valine derivative, it allowed to obtain more linear form **179** than the lactam derivative **183**.

Cyclic fluorovinyl derivatives (lactams) have a tendency to form crystals, therefore, as part of the research, many attempts have been made to obtain the largest possible crystals using various crystallization methods. The difficculty of some crystallization forced to search for less classic methods

for obtaining crystals, such as crystallization by sublimation or diffusion crystallization in a system of two different solvents.

As part of the doctoral thesis, fluorinated derivatives of amino acids with the F-moc group were also synthesized using a chiral nickel(II) complex. Such obtained new, fluorinated derivatives can be used as substrates for the synthesis of solid phase peptide synthesis (SPPS).

The results appearing in the course of the research were tried to be explained using, among others, ^{19}F NMR measurements at higher and lower temperatures than 25ºC. Using this method, it was possible to explain the additional signals appearing in the ^{19}F NMR spectrum of each obtained fluorovinyl derivative. The results of the measurements indicate that, most likely, in α,β-unsaturated carbonyl systems, the presence of *s-cis* and *s-trans* isomers may be responsible for the observed signals, the ratio and number of which changes depending on the temperature.

The cyclization that took place was one of the most suprising issues encountered during the research, especially since such a phenomenon has not yet been described in the scientific literature. Therefore, using the DFT methods, it was decided to examine these situations more deeply and the most probable mechanism of the occurring cyclization was determined. It has been established that cyclization most likely runs via hemiacetal as an intermediate. The results of the calculations also showed the position of the amino and ester groups at the double bond for the cyclization to be possible at all. Theoretical research was a good complement to practical research.

8. Abstract

Recently, much attention has been paid to the synthesis of amino acid analogs that have diverse groups which can be isosteres of the peptide bond. Such chemicals, generally called peptidomimetics, are commonly used in medicinal chemistry and pharmacology research due to the better stability of such molecules and often better pharmacokinetic properties compared to the original natural peptides. In addition, the conduction of the fluorine atom(s) can significantly affect the properties of the final product, changing its lipophilicity, conformation, metabolic stability, solubility, as well as chemical reactivity.

The PhD thesis focused on the fluorovinyl group as a peptide bond mimetic. One of the main goals was the synthesis of amino acid derivatives containing fluorovinyl bonds as a starting material that can be used for further oligopeptide synthesis. The monofluorovinyl group, due to its electronic and structural similarity, is treated as an isostere of the peptide bond and can clearly influence biological properties. The structural similarity of the two groups is due to the observation that the amide bond can be represented as a hybrid of two resonance structures. In an amide bond, the lone electron pair of the nitrogen atom is delocalized, which makes the C-N bond have the properties of a double bond. Moreover, bond length, angle and rigidness are very similar in fluoroalkenes and amides. The fluorine atom can also mimic the carbonyl oxygen atom, due to the similarity of the van der Waals radius (1.47 Å for the fluorine atom and 1.52 Å for the oxygen atom).

Taking into account the above aspects, it becomes justified to undertake a topic aimed at obtaining new derivatives of this type.

The planned synthesis pathway was based on amino acid modification. *L*,α-amino acids such as alanine, phenylalanine, valine and leucine were used as starting chemicals. In the first stage, methyl ester hydrochlorides derived from the starting amino acids were formed. In the next step, the amino group was protected with a *tert*-butoxycarbonyl group, followed by reduction with lithium aluminum hydride to obtain *N*-Boc-aminoalcohols, which in turn were subjected to Swern oxidation. The aldehyde derivatives of amino acids obtained in this way were subjected to the key Horner-Wadsworth-Emmons (HWE) reaction with ethyl 2-diethoxyphosphoryl-2-fluoroacetate in the presence of a strong base, such

as *n*-butyllithium or lithium hexamethyldisilazane. This was the last stage of the planned synthesis, which enabled the introduction of the fluorovinyl moiety into the structure of amino acid derivatives.

The influence of different bases on the HWE reaction yield and on the type of products formed was investigated. It was also found that in the case of amino acid derivatives with smaller side groups, such as alanine and valine, formation of a mixture of linear and cyclic forms is observed immediately after the HWE reaction.

During the research, it turned out that the linear fluorovinyl derivatives of amino acids obtained by the above-mentioned procedure can, under certain conditions, cyclize to lactams, forming crystals whose structure could be determined using X-ray analysis. According to the literature date, these are the first derivatives of this type obtained so far.

X-ray analysis of the lactams confirmed that they were synthesized in the form of a racemic mixture, although the starting substrates were L-α-amino acids. Therefore, it was decided to identify in which of the synthetic steps racemization may occur. Crystals of each of the products obtained at a particular stage of the synthesis were obtained and it turned out that the methyl ester hydrochlorides are pure (*S*)-enantiomers, while the products formed as a result of NH_2-protection with the Boc group (*N*-Boc-amino acid methyl esters) are in the racemic form. Therefore, the analysis showed that racemization occurs during the reaction with Boc_2O, most likely due to enolization. Therefore, another method of synthesis was developed, proceeding without racemization, by switching the sequence of the synthesis steps. Amino acid methyl ester hydrochlorides were reduced with LAH to remove the carbonyl group, and then the resulting amino alcohols were protected with a -Boc group. The crystal of N-Boc-phenylalaninol obtained in this way turned out to be a pure (S)-enantiomer, which confirmed the effectiveness of the planned synthesis. In addition, a fluorovinyl derivative of phenylalanine in the form of a lactam was obtained by this method, the structure of which was also confirmed by X-Ray analysis and which also turned out to be a pure (S)-enantiomer.

The ability to cyclize of the fluorovinyl derivatives was really interesting and such phenomenon has not been reported in the scientific literature so far, and it was decided to explore this topic using DFT calculations. It allowed to identify the most likely mechanism for cyclization and determined that it occurs via a hemiacetal as an intermediate.

As part of the doctoral thesis, fluorinated amino acid derivatives in the form of F-moc derivatives were also synthesized, which will be building blocks for the solid phase peptide synthesis (SPPS). For this purpose, a chiral nickel(II) complex was used, which enables the production of a number of structurally diverse fluorinated amino acids.

In conclusion, the paper reports the synthesis of fluorovinyl derivatives of amino acids and their conversion into lactams. Such chemical compounds, to my best knowledge, have not yet been reported in the scientific literature. In addition, the DFT method was used to present the most likely mechanism of the occurring cyclization. As part of the doctoral thesis, it was also paid an attention to the stereochemistry of the created products.

9. Streszczenie

W ostatnich czasach wiele uwagi poświęca się syntezie analogów aminokwasów, które posiadają zróżnicowane grupy, mogące stanowić izostery wiązania peptydowego. Takie związki chemiczne, ogólnie zwane peptydomimetykami, są powszechnie stosowane w chemii leków oraz w badaniach farmakologicznych, ze względu na lepszą stabilność takich cząsteczek oraz często lepsze właściwości farmakokinetyczne w porównaniu do naturalnych peptydów. Ponadto, prowadzenia atomu/ów fluoru może znacząco wpłynąć na właściwości finalnego produktu, zmieniając jego lipofilowość, konformacje, stabilność metaboliczną, rozpuszczalność, a także reaktywność chemiczną.

W pracy doktorskiej skupiono się na grupie fluorowinylowej jako mimetyka wiązania peptydowego. Jednym z głównych celów była synteza pochodnych aminokwasów, zawierających wiązania fluorowinylowe jako materiał wyjściowy, który może być wykorzystywany do dalszej syntezy oligopeptydów. Grupa monofluorowinylowa, ze względu na jej elektronowe i strukturalne podobieństwo, jest traktowana jako izoster wiązania peptydowego i może wyraźnie wpłynąć na właściwości biologiczne. Podobieństwo strukturalne tych dwóch grup wynika z obserwacji, że wiązanie amidowe może być przedstawione jako hydryda struktur rezonansowych. W wiązaniu amidowym, wolna para elektronowa atomu azotu jest zdelokalizowana, co powoduje, że wiązanie C-N ma właściwości wiązania podwójnego. Ponadto, długość wiązań, kąty czy sztywność są bardzo podobne we fluoroalkenach oraz amidach. Atom fluoru może także naśladować karbonylowy atom tlenu, ze względu na podobieństwo promienia van der Waalsa (1.47 Å dla atomu fluoru i 1.52 Å dla atomu tlenu).

Biorąc pod uwagę powyższe aspekty, uzasadnionym staje się podejmowanie tematyki mającej na celu otrzymanie nowych pochodnych tego typu.

Zaplanowana ścieżka syntezy bazowała na modyfikacji aminokwasów. Jako początkowe związki chemiczne użyto L,α-aminokwasy, takie jak alanina, fenyloalanina, walina oraz leucyna. W pierwszy etapie doszło do utworzenia chlorowodorków estrów metylowych pochodzących ze startowych aminokwasów. W kolejnym kroku nastąpiła protekcja grupy aminowej grupą tert-butoksykarbonylową, a następnie redukcja glinowodorkiem litu celem otrzymania *N*-Boc-aminoalkoholi, które z kolei zostały poddane utlenianiu Swerna. Otrzymane w ten sposób aldehydowe pochodne aminokwasów poddano kluczowej reakcji Hornera-Wadswortha-Emmonsa (HWE) z 2-dietoksyfosforylo-2-fluorooctanem etylu

w obecności silnej zasady, jak *n*-butylolit, czy heksametylodisilazan litu. Był to ostatni etap zaplanowanej syntezy, który umożliwił wprowadzenie ugrupowania fluorowinylowego do struktury pochodnych aminokwasów.

Zbadano także wpływ różnych zasad na wydajność reakcji HWE oraz na rodzaj tworzonych produktów. Stwierdzono, że w przypadku pochodnych aminokwasów z mniejszymi grupami bocznymi, jak alanina i walina, bezpośrednio po reakcji HWE obserwuje się tworzenie mieszaniny formy liniowej i cyklicznej.

W toku badań okazało się, że otrzymane wyżej wymienioną procedurą liniowe, fluorowinylowe pochodne aminokwasów mogą w określonych warunkach cyklizować do laktamów, tworząc przy tym kryształy, których strukturę można było określić przy użyciu badań rentgenograficznych. Jak wynika z analizy literaturowej, dotychczas, są to pierwsze otrzymane tego typu pochodne.

Analiza X-Ray laktamów potwierdziła, że występują one w postaci mieszaniny racemicznej, mimo,że wyjściowe substraty były *L*-α-aminokwasami. Podjęto zatem próbę identyfikacji, w którym z etapów syntezy może dochodzić do racemizacij. Otrzymano kryształy każdego z produktów otrzymywanego na poszczególnym etapie syntezy i okazało się, że chlorowodorki estrów metylowych są czystymi (*S*)-enancjomerami, natomiast produkty powstające w wyniku NH_2-protekcji grupą Boc (estry metylowe *N*-Boc-aminokwasów) występują w formie racematu. Z przeprowadzonej analizy wynikło zatem, że podczas reakcji z Boc_2O dochodzi do racemizacji, najprawdopodobniej wskutek enolizacji. Opracowano zatem kolejną metod syntezy, tym razem przebiegającą bez racemizacji, zamieniając kolejnością etapy syntezy. Chlorowodorki estrów metylowych aminokwasów zredukowano LAH-em, by usunąć grupę karbonylową, a następnie otrzymane aminoalkohole zabezpieczono grupą – Boc. Otrzymany w ten sposób kryształ *N*-Boc-fenyloalaninolu okazał się czystym (*S*)-enancjomerem , co potwierdziło skuteczność zaplanowanej syntezy. Ponadto, otrzymano tą metodą fluorowinylową pochodną fenyloalaniny w postaci laktamu, której strukturę również potwierdzono analizą X-Ray i która okazała się również być czystym (*S)*-enancjomerem.

Zainteresowanie w badaniach zwróciła nieodnotowana dotychczas w literaturze naukowej zdolność do cyklizacji fluorowinylowych pochodnych i zdecydowano się zgłębić ten temat wykorzystując

obliczenia DFT. Pozowoliły one ustalić najbardziej prawdopodobny mechanizm cyklizacji i ustalono, że dochodzi do niej przez hemiacetal jako produkt przejściowy.

W ramach pracy doktorskiej zsyntetyzowano także fluorowane pochodne aminokwasów w postaci *F-moc* pochodnych, które stanowić będą bloki budulcowe do syntezy peptydów na podłoży stałym. Wykorzystano w tym celu chiralny kompleks niklu(II), który umożliwia otrzymywanie szeregu zróżnicowanych strukturalnie fluorowanych aminokwasów.

Podsumowując, praca przedstawia syntezę fluorowinylowych podchodnych aminokwasów oraz ich przekształcenie w laktamy. Takie związki chemiczne, zgodnie z moją wiedzą, nie zostały dotychczas odnotowane w literaturze naukowej. Ponadto, wykorzystano metodę DFT do zaprezentowania najbardziej prawdopodobnego mechanizmu zachodzącej cyklizacji. W ramach pracy doktorskiej zwrócono również uwagę na stereochemię tworzonych produktów.

LIST OF ABBREVIATIONS

ºC	Celsius degree
μ	dipole moment
Å	Angstrom (10^{-10} m)
AAs	amino acids
AIBN	azobis(isobutyronitrile)
Ala	alanine
Boc	*N-tert*-butoxycarbonyl group
BBC	*tert*-Butyl N,N-dibromocarbamate
BT	benzothiazol-2-yl group
d	doublet
DCC	N,N'-Dicyclohexylcarbodiimide
dd	doublet of doublets
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DME	dimethoxyetanol
DMF	dimethylformamide
DMPU	*N,N'*-Dimethylpropyleneurea
DMSO	dimethylsulfoxide
DPP	dipeptidyl peptidase
ee	enantiometic excess
Equiv.	equivalents
EWG	electron withdrawing group
GC-MS	Gas chromatography-Mass spectroscopy
HCV	Hepatitis C virus
HWE	Horner-Wadsworth-Emmons reaction
H	hours
Hz	Herz
IR	Infrared spectroscopy

J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Leu	leucine
LiHMDS	lithium hexamethyldisilazane
LiTMP	lithium tetramethylpiperidide
m	multiplet
MCF7	estrogen-dependent breast adenocarcinoma
mg	miligram
mL	milliliter
mp	melting point
n-BuLi	*n*-Buthyllithium
NFSI	*N*-fluorobenzenesulfonimide
NMR	Nuclear Magnetic Rezonance
PDC	pyridine dichromate
PET	positron emission tomography
Phe	phenylalanine
ppm	parts per milion
PT	1-phenyl-1H-tetrazol- 5-yl group
s	singlet
SPPS	solid phase peptide synthesis
T	temperature
t	triplet
TLC	Thin Layer Chromatography
Tert-Bu-OK	potassium *tert*-butoxide
THF	tetrahydrofuran
Val	valine

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