REGIOSELECTIVE RING OPENING REACTIONS OF AZIRIDINE-2-PHOSPHONATES AND AZIRIDINE BASED CHIRAL LIGANDS FOR CATALYTIC, ASYMMETRIC AZOMETHINE YLIDE CYCLOADDITIONS AND AZA-HENRY REACTION

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ABSTRACT

REGIOSELECTIVE RING OPENING REACTIONS OF AZIRIDINE-2-PHOSPHONATES AND AZIRIDINE BASED CHIRAL LIGANDS FOR CATALYTIC, ASYMMETRIC AZOMETHINE YLIDE CYCLOADDITIONS AND AZA-HENRY REACTION

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Aziridines are small three-membered heterocyclic compounds. They are important as building blocks for many nitrogen-containing biologically active compounds and as chiral ligands in metal catalyzed asymmetric synthesis of different organic compounds. In the first part of this thesis, we have studied the ring opening reactions of various racemic and chiral aziridine-2-phosphonates. Regioselective aziridine ring opening reaction with HCl formed α-amino-β-chlorophosphonates in 60-95 % yield and the same reaction with alcohols in the presence of H_2SO_4 formed α-amino-β-alkoxyphosphonates in 35-91 % yield.

In the second part of this thesis, we have studied the catalytic performance of aziridine based chiral ligands with a transition metal for 1,3-dipolar cycloaddition (1,3-DC) reaction of azomethine ylides with electron deficient dipolarophiles for the synthesis of highly substituted pyrrolidine derivatives. As the

aziridine based chiral ligands our group synthesized a small library of ferrocenyl aziridinyl methanol (**FAM**) chiral compounds and tested their catalytic performance in different reactions. After screening different transition metals and 12 **FAM** ligands, it was found that Ag-**CFAM4** catalyst system forms pyrrolidine derivatives in up to 95% yield with 99 % ee via the 1,3-DC reaction of azomethine ylides.

Finally, we have also tested the catalytic performance of **FAM** ligands for the aza-Henry reaction which is another important C-C bond-forming process in Organic Chemistry. Optimization studies for this reaction showed that Zn-**PFAM1** catalyst system works better for the addition of nitroalkanes to Boc-substituted imines to give the expected products in up to 88 % yield with 71% ee.

Keywords: Aziridine-2-phosphonates, regioselective ring opening, chiral catalysts, 1,3-dipolar cycloaddition, aza-Henry reaction.

ÖZ

AZİRİDİN-2-FOSFONATLARIN ALANSEÇİCİ HALKA AÇILMA TEPKİMELERİ VE AZİRİDİN BAZLI KİRAL LİGANDLARIN KATALİTİK ASİMETRİK AZOMETİN YLİDLERİN HALKASAL KATILMASINDA VE AZA-HENRY TEPKİMELERİNDE KULLANILMASI

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Aziridinler üçlü halkaya sahip küçük heterohalkalı bileşikleridir. Bu yapılar azot içeren biyolojik olarak aktif bir çok bileşiğin sentezi için önemli başlangıç maddeleridir ve farklı organik bileşiklerin metal katalizörlü asimetrik sentezinde de kiral ligand olarak kullanılmaktadır. Bu tezin ilk kısmında rasemik ve kiral formunda olan farklı aziridin-2-fosfonatların halka açılma tepkimeleri çalışılmıştır. HCl ile alanseçici halka açılma tepkimesi α-amino-β-klorofosfonatları % 60-95 verimle oluşturuken aynı tepkime H_2SO_4 varlığında alkoller ile tekrarlandığında α-amino-β-alkoksifosfonatlar % 35-91 verimle elde edilmiştir.

Bu tezin ikinci kısmında aziridin ana iskeletine sahip kiral ligandların bir geçiş metali varlığında azometin ylidlerin elektronca fakir dipolaraofiller ile 1,3-dipolar halkasalkatılma (1,3-DC) tepkimesi ile çoklu sübstite pirolidin yapılarının elde edilmesindeki performansları araştırılmıştır. Aziridin ana iskeletine sahip olan

ferrosenil aziridinil methanol bileşiklerinden (**FAM**) oluşan küçük bir kiral ligand kütüphanesi grubumuzda oluşturmuş ve farklı tepkimelerde katalizör olarak performanslarını test edilmiştir. Bu çalışmada ise farklı geçiş metalleri ile 12 adet **FAM** kiral ligandının azometin ylidlerin 1,3-DC tepkimesinde taraması yapılmış ve Ag-**CFAM4** katalizör sisteminin pirolidin yapılarını % 95 verim ve % 99'u bulan ee ile oluşturduğu görülmüştür.

Yine bu çalışma kapsamında aynı kiral ligandların performansı Organik Kimyada önemli bir C-C bağı oluşturma tepkimesi olan aza-Henry tepkimesinde denenmiştir. İdeal koşulların belirlenmesi sonucunda en iyi katalizör sisteminin Zn-**PFAM1** olduğu görülmüş ve nitroalkanların Boc-sübstite iminlere eklenmesi sonucunda beklenen ürünler % 88'i bulan verim ve % 71'e varan ee ile izole edilmiştir.

Anahtar Kelimeler: Aziridin-2-fosfonatlar, alanseçici halka açılması, kiral katalizör 1,3-dipolar halkasal katlama, aza-Henry tepkimesi.

A PhD is so much more than a degree. It can break you down into most vulnerable form but has the potential to build you back together to become a resilient, determined, humble, and knowledgeable researcher. This process takes time and patience. Please don't give up on yourself. It's not about getting a degree. It's about becoming who you are meant to be.

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LIST OF ABBREVIATIONS

ABBREVIATIONS

ACN: Acetonitrile

Ar: aryl

BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

δ: chemical shift in parts per million downfield from tetramethylsilane

J: coupling constant

DCM: Dichloromethane

DCE: 1,2-Dichloroethane

1,3-DC: 1,3-Dipolar Cycloaddition

EWG: Electron withdrawing group

FAM: Ferrocenyl Aziridinyl Methanol

HCV: Hepatitis C Virus

HOMO: Highest Occupied Molecular Orbital

HPLC: High Performance Liquid Chromatography

HRMS: High Resolution Mass Spectroscopy

LUMO: Lowest Unoccupied Molecular Orbital

NMR: Nuclear Magnetic Resosnance

POFAM: Phosphorous based Ferrocenyl Aziridinyl Methanol

R_f: retention factor (TLC)

t_R: retention time (HPLC)

TLC: Thin Layer Chromatography

TMS: Tetramethylsilane

CHAPTER 1

INTRODUCTION

1.1 Aziridine: Overview

Aziridines, which are nitrogen containing three membered saturated ring systems (Figure 1) are one of the most valuable three membered heterocyclic compounds in organic chemistry.

Figure 1. Structure of a simple aziridine

Functionalized aziridines are abundantly present in biologically active natural products and synthetic drugs[1] and have been widely used as important intermediates in organic synthesis. The aziridine skeleton can be found in the structures of mitomycins, ficellomycin and azinomycins (Figure 2), which display *in vitro* cytotoxicities[2,3] and display significant *in vivo* antitumor activity.[4] Azinomycin A, in particular, also shows antibiotic activity against both gram positive and gram negative bacteria.[3]

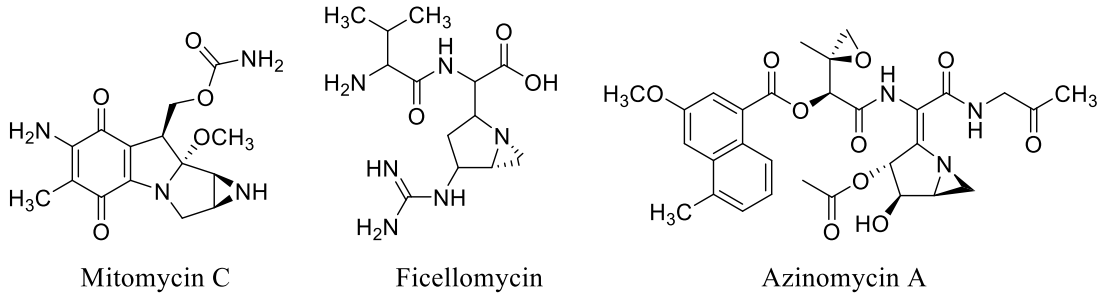
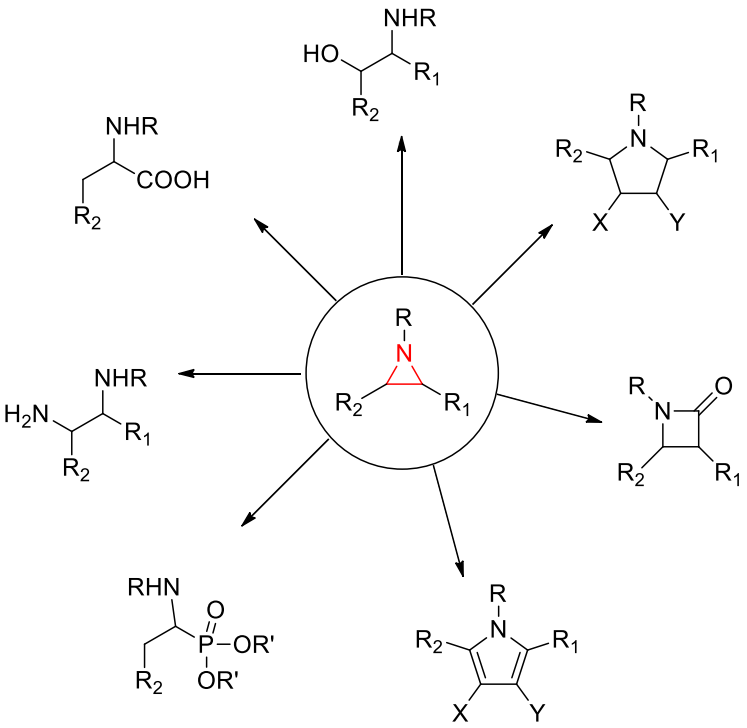


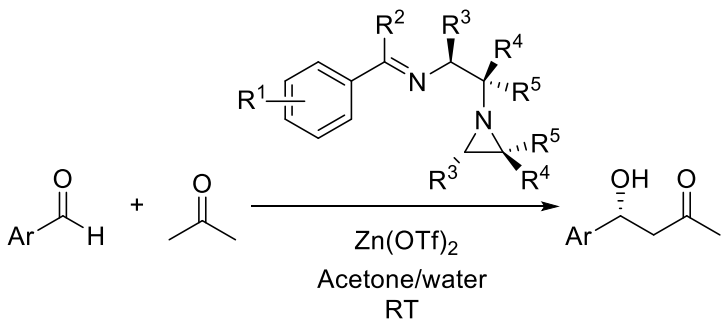
Figure 2. Aziridine compounds with biological activities

Aziridines can also serve as powerful tool for the synthesis of variety of nitrogen containing functionalities. The highly strained ring system of aziridines makes it very advantageous for ring opening reactions with different nucleophiles. Opening the aziridine ring can produce important organic compounds such as amino acids,[5] amino alcohols,[6] pyrrolidines,[7] pyrroles,[8] β-lactams,[9] and oxazoles,[10] as demonstrated in Scheme 1.



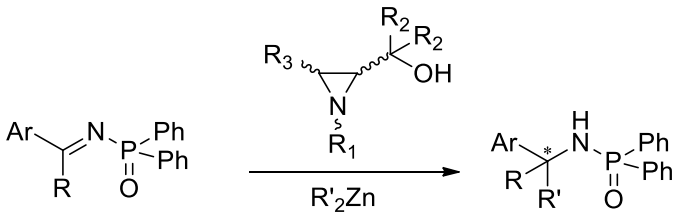
Scheme 1. Aziridine ring opening products

Moreover, with the rapid development of asymmetric synthesis and catalysis, aziridines have been utilized as chiral auxiliary agents and chiral ligands for various organic tranformations.[11] For instance, Chen et al. used chiral aziridine based tridentate ligand for the asymmetric Aldol reaction of aromatic aldehydes and ketones using $Zn(OTf)_2$ as metal source (Scheme 2).[12]



Scheme 2. Asymmetric Aldol reaction with Zn/Tridentate aziridine ligand

Another good example for aziridine based chiral ligands is aziridino alcohol ligands which were used as chiral ligands by Ansderson et al. in enantioselective addition of diethylzinc to imines (Scheme 3).[13]



Scheme 3. Enantioselective addition of diethylzinc to imines using aziridino alcohol ligands

1.2 Ring opening reactions of aziridines

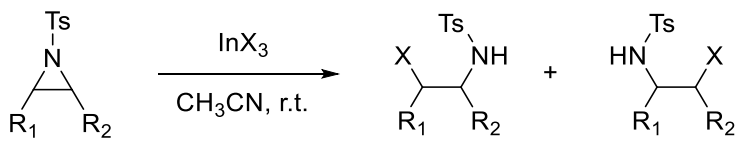
Aziridines, similar to other three-membered heterocycles, are very susceptible to ring opening due to the unique ring strain. Therefore, aziridines are widely used in organic synthesis, acting as precursors to other complex nitrogen containing organic molecules.[14] Based on their activities in the ring opening reactions, aziridines are mainly classified into two different groups as activated and non-activated.

1.2.1 Activated aziridines

Aziridine ring bearing electron withdrawing group on nitrogen atom such as acyl, sulfonyl, phosphoryl, etc. show high activity and easily undergo ring opening reactions with nucleophiles, therefore called activated. The presence of electron withdrawing unit increases ring strain, making it more active for nucleophilic attack. The ring opening reactions of activated aziridines has been intensively studied. In the literature there are many examples of these type of ring-openings with a variety of nucleophiles.[15,16] Although activated aziridines are already prone

to undergo the ring opening with nucleophiles, the reaction could be facilitated in the presence of Lewis acids. Literature findings show that, Lewis acid has been widely used in catalytic ring opening of aziridines with a number of nucleophiles, including alcohols, thiols, azides, nitrile, etc.[16]

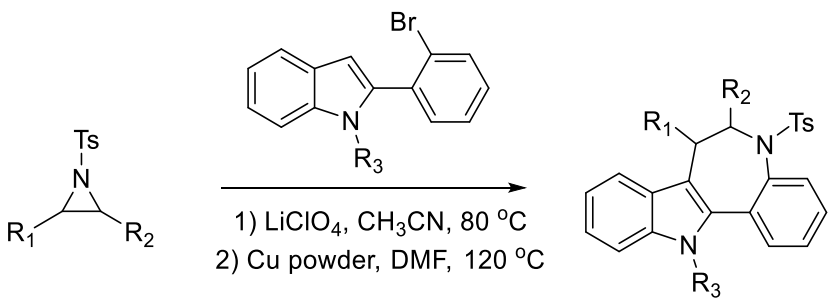
There are number of studies showing ring-opening of activated aziridines by the nucleophilic addition of halogens. Yadav et al. has successfully performed the ring opening of tosyl substituted aziridines by chloride, bromide and iodide nucleophiles using indium (III) halides (Scheme 4).[17,18]



Scheme 4. Ring-opening of aziridine using InX_3

Activated aziridines could be converted to ring opening products, and with further cyclization can produce intriguing products like azepines and indoles.

A recent study of Pradhan et al. on the ring-opening and cyclization of activated aziridines produced azepino-indoles in one-pot and in a stereoselective manner (Scheme 5).[18]

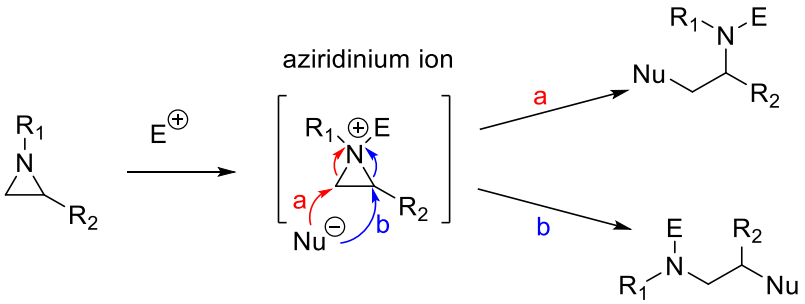


Scheme 5. Synthesis of azepino-aziridines via ring-opening cyclization

1.2.2 Non-activated aziridines

If *N*-functionalities are of electron donating character such as alkyl or aryl groups, then the aziridine ring is classified as non-activated and in order to achieve ring opening product the heterocycle needs to be activated by Lewis acid or protic acid prior to nucleophilic attack.

In recent years, ring-opening products of non-activated aziridines have also attracted considerable attention as valuable intermediates for further synthetic elaboration. Moreover, the intermediate aziridinium ion provides interesting opportunities for the selective synthesis of a variety of functionalized amines.[19]

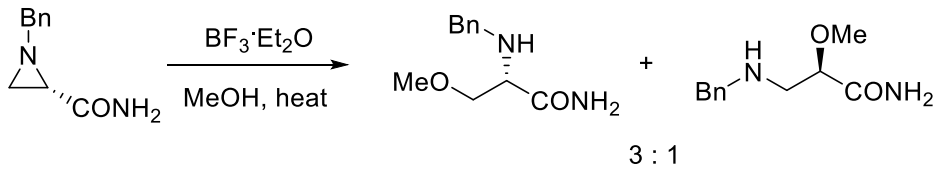


Scheme 6. General ring-opening of aziridine ring

The aziridinium ion can be formed by *N*-functionalization of non-activated aziridines with an electrophile, i.e., Lewis acid or protic acid, which then can easily be opened by different types of nucleophiles. Moreover, if non-symmetric, 2-substituted aziridines are used, the issue of regioselectivity in the ring opening of the corresponding intermediate aziridinium ion becomes important.[20] As it is shown in Scheme 6, the ring opening can occur in two different positions and therefore two different ring-opened amines can be obtained. In other words, if ring opening of intermediate aziridinium ion occur according to path a, α-branched

amine is formed, and if reaction takes place according to path b, β-branched amine can be obtained.

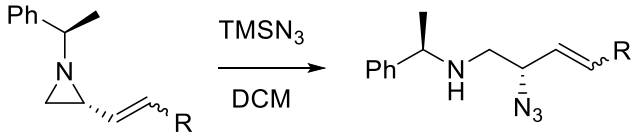
A good example demonstrating formation of both ring-opening products is a study reported by Gotor et al., where the Lewis acid catalyzed ring opening of 2-carbamoylaziridine led to a formation of both α-branched and β-branched amines in 3:1 ratio, respectively (Scheme 7).[21]



Scheme 7. Ring opening of 2-carbamoylaziridine to form isomeric amines

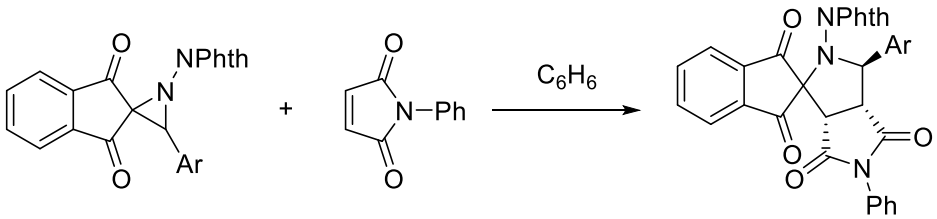
Generally, while aziridine ring is being activated by protic acid or Lewis acids, at the same time, nucleophiles are also coordinated with the acids, reducing their nucleophilicity. As a result, the reactions occur under unfavorable conditions, such as high temperature, long reaction time, and low yields. Under these conditions, the ring-openings usually occur on the less substituted C-N bonds, forming α-branched amine as a major product.

Although the ring opening of aziridine at more substituted carbon center is not common, such examples can be also found in the literature. For example, Lee et al. have performed regioselective ring opening of non-activated aziridines using $TMSN_3$, where azide is introduced to more substituted carbon center of 2-allyl substituted aziridine (Scheme 8).[22]



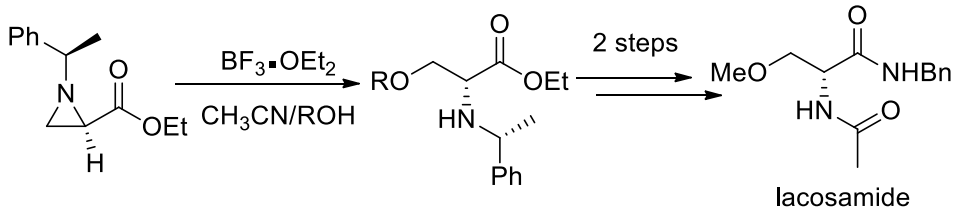
Scheme 8. Ring-opening of non-activated aziridine by $TMSN_3$

Pankova et al. have reported an interesting route for the synthesis of spiro-fused polycyclic compounds via 1,3-dipolar cycloaddition reaction.[23] For that, thermal ring opening of spiro-fused aziridine led to the formation of azomethine ylide, which forms fused pyrrolidine structure with addition of dipolarophile (Scheme 9).



Scheme 9. Ring-opening and 1,3-DC reaction of spiro-fused *N*-phthalimidoaziridines

The ring opening of chiral aziridine-2-carboxylates provides an excellent route for the synthesis of α-amino acids and amino acid derivatives. One good use of aziridine ring opening reaction is seen in the synthesis of the antiepileptic drug (*R*)-lacosamide. The key step is reported to be the ring opening reaction of *N*-alkyl substituted aziridine-(*2R*)-carboxylate with methanol, as shown in Scheme 10.[24]



Scheme 10. Synthesis of (*R*)-lacosamide by ring-opening of aziridines

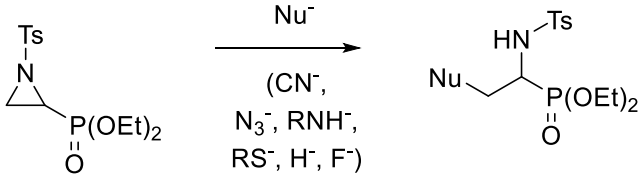
Although the literature has many examples to ring opening reactions of aziridine-2-carboxylates, the same reactions studied with the aziridine-2-phosphonates are limited.

1.2.3 Aziridine-2-phosphonates

Aziridine-2-phosphonates can serve as a useful tool in synthesis of α-aminophosphonic acids, which are the phosphorus analogs of amino acid. Aziridine-2-phosphonates undergo ring-opening reactions like aziridine carboxylates to form α-amino phosphonate derivatives, when followed by the hydrolysis aminophosphonic acids can be obtained. Biological activities of α-aminophosphonic acids are well known.[25]

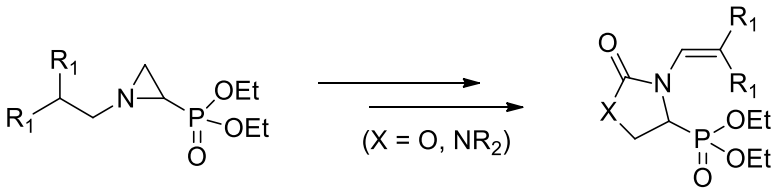
Although there are far less studies on ring-opening of aziridine-2-phosphonates compared to carboxylates, still there are interesting findings in the literature that are worth mentioning.

Dolence et al. reported that the regioselective ring opening of *N*-tosylaziridine-2-phosphonates with carbon, nitrogen, sulfur, hydride, fluoride, and phosphorus nucleophiles could provide the rapid production of a variety of β-substituted α-amino-phosphonates (Scheme 11).[26]



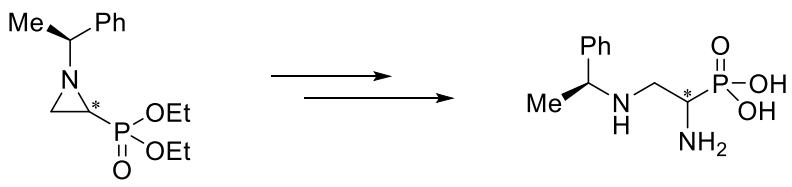
Scheme 11. Ring-opening of tosyl aziridinyl phosphonates with nucleophiles

An interesting ring transformation of aziridine-2-phosphonates to imidazolidinones was reported by Stevens et al.[27] The ring opening of 1-vinyl-2-phosphonoaziridines using methyl chloroformate yields 1-amido-2-chloroethyl phosphonate, which can be converted to corresponding 2-oxazolidinones upon heating in DMSO (Scheme 12).



Scheme 12. Synthesis of 2-oxalidinones from aziridine-2-phosphonates

One other useful application of aziridine ring-opening reaction is selective synthesis of α,β-diaminoethylphosphonic acids from aziridine-2-phosphonates, which was reported by Weglarz-Tomczak et al. along with the study of their biological activities (Scheme 13).[28]



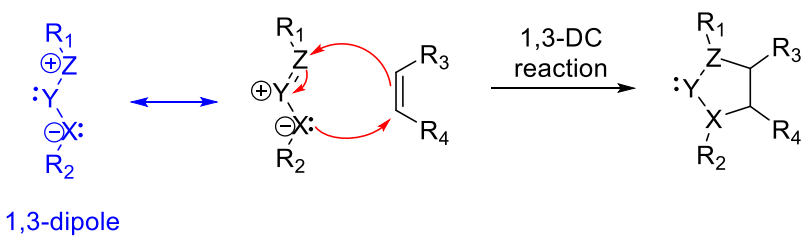
Scheme 13. Synthesis of α,β-diaminoethylphosphonic acid from aziridine-2-phosphonate

In this part we have accepted the challenge to investigate the ring-opening reactions of non-activated aziridine-2-phosphonates, which was not reported in the literature before.

1.3 1,3-Dipolar cycloaddition reaction

1,3-Dipolar cycloaddition reaction (1,3-DC), also known as [3+2] cycloaddition has become one of the fundamental reactions in organic chemistry. It is used in many aspects of chemistry, such as natural product synthesis, material science, biochemistry, etc. In a single step 1,3-DC can provide a five-membered heterocyclic ring by forming two new bonds and up to four new stereocenters.

Mechanistically 1,3-DC reactions work like Diel-Alder reaction; a 1,3-dipole, which bears positive and negative charges at first and third atom, reacts as 4π system with a dipolarophile, delivering 2π electrons, as shown in Scheme 14.



Scheme 14. General representation of 1,3-DC reaction

1.3.1 Types of 1,3-dipoles and dipolarophiles

The 1,3-dipole, also known as an ylide, bears a positive and a negative charge distributed over three atoms and has 4π electrons. The most common atoms incorporated in the 1,3-dipole are nitrogen, carbon, oxygen or sulfur.

Representative examples of some common 1,3-dipoles are shown in Figure 3, but other types of 1,3-dipoles also exist. As represented in Figure 3, 1,3-dipoles are divided into two groups, the allyl anion type which has a bent structure and the propargyl anion type with a linear structure.

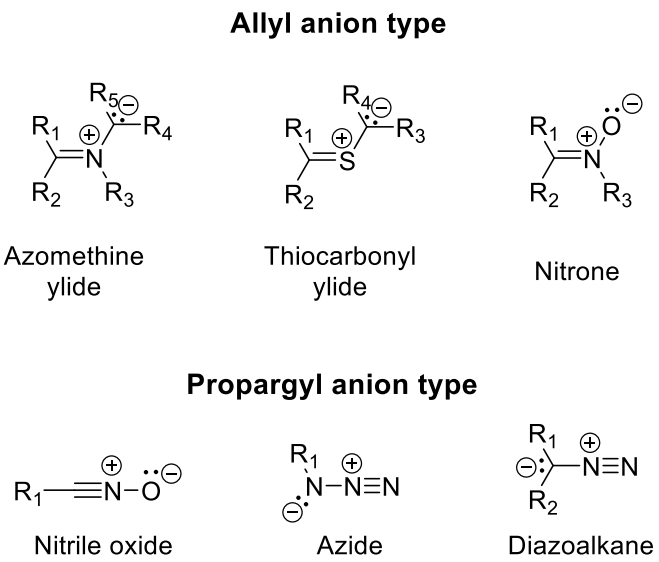


Figure 3. Examples for 1,3-dipoles

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing 2π electrons. Thus, depending on which dipole that is present, *α,β*-unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily (Figure 4). It

must be noted, however, that other 2π-moieties such as carbonyls and imines also can undergo cycloaddition with dipoles.

Figure 4. Examples of common dipolarophiles

Depending on the nature of the dipole and the dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a $LUMO_{(dipolarophile)}$- $HOMO_{(dipole)}$- or a $LUMO_{(dipole)}$-$HOMO_{(dipolarophile)}$ interaction but in some cases a combination of both interactions is involved.[29]

The 1,3-dipolar cycloadditions play a crucial role in the enantioselective preparation of five membered heterocycles. In particular, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with activated olefins has become one of the most useful and well-established methods for the preparation of enantioenriched substituted pyrrolidines, a structural moiety widely present in a large variety of natural products and biologically active compounds.[30]

1.3.2 Importance of pyrrolidine structures

There are many examples for the biologically active pyrrolidines known in the literature. Asymmetric pyrrolidines can be found in the structures of many important drugs such as (-)-kainic acid, (-)-epibatidine, and acromelic acid (Figure 5).

Kainic acid is the kainoid amino acids that are a potent class of neuroexcitant compounds.[31] It has been widely used as a tool in neuropharmacology[32] to stimulate nerve cells and mimic disease states, such as

epilepsy,[33] Alzheimer's disease, and Huntington's chorea.[34] Epibatidine exhibits remarkable analgesic properties being 200 times more potent than morphine,[35] it operates via non-opioid mechanism.[36] Acromelic acid, which is a pyrrolidine carboxylic acid, exhibits remarkably potent neuro-excitatory activity via activation of ionotropic glutamate receptors in the brain.[37]

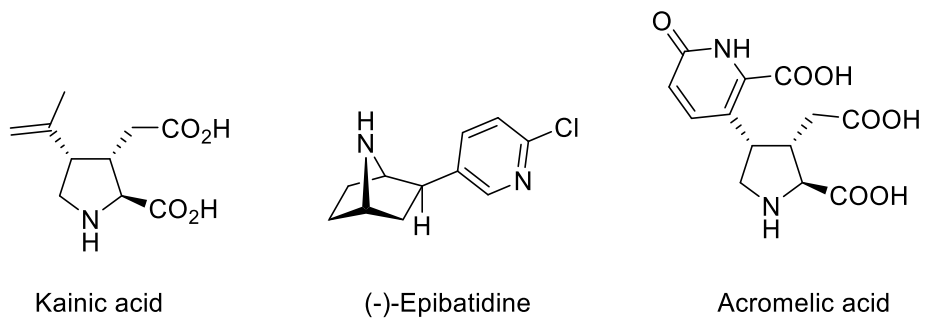
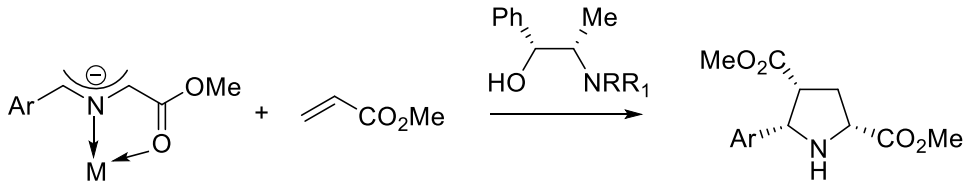


Figure 5. Examples of biologically important pyrrolidine structures

1.3.3 Asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylide

The significance of the pyrrolidine structures has led to a great demand for efficient synthetic methods, especially those producing optically pure pyrrolidine heterocycles. The catalytic asymmetric 1,3-dipolar cycloaddition (1,3-DC) reaction of azomethine ylides with a diverse range of electron-deficient olefin dipolarophiles provides one of the most powerful and expedient approaches for the enantioselective construction of various highly functionalized and stereochemically enriched pyrrolidine derivatives.

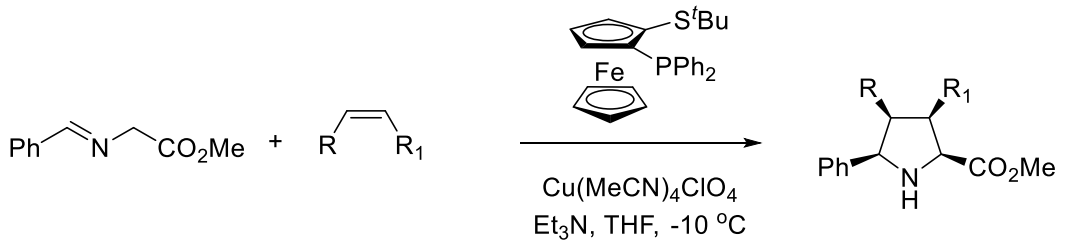
The pioneer work in asymmetric 1,3-DC reactions of azomethine ylides was done by Grigg and Allway in 1991.[38] In this study, $CoCl_2$ and $MgBr_2$ was used with ephedrine as ligand to yield cycloadducts with 60-96 % ee (Scheme 15).



Scheme 15. Asymmetric 1,3-DC reaction done by Grigg and Allway

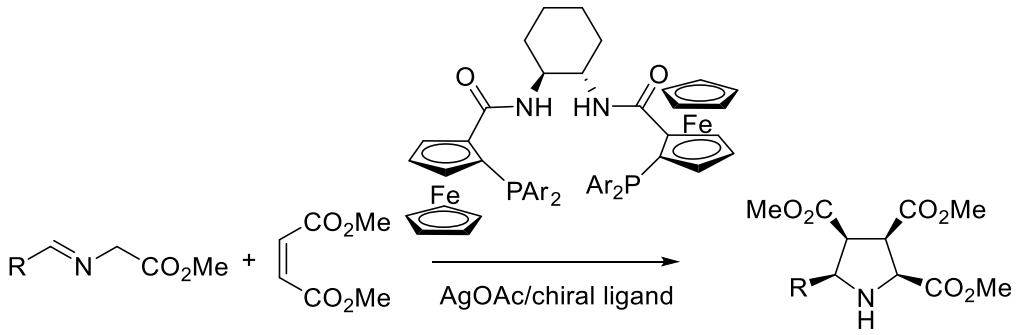
Since then, many different synthetic protocols for asymmetric 1,3-dipolar reaction of azomethine ylides have been developed to date.

One good example for enantioselective 1,3-DC reaction reported by Carretero et al. (Scheme 16).[39] They used planar chiral ferrocene–phosphine ligand (Fesulphos) in the Cu-catalyzed 1,3-DC reaction of azomethine ylide with various alkenes to form cycloadducts in good yield and excellent enantioselectivity, up to 99 % ee and exo selectivity.



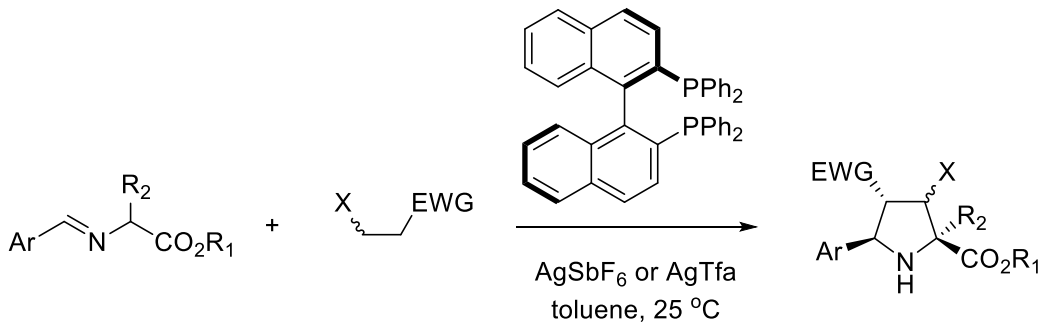
Scheme 16. Enantioselective 1,3-DC using Fesulphos-Cu catalyst

Zhang et.al. have reported the synthesis of aryl and heteroaryl substituted pyrrolidines via 1,3-DC reaction using various well known chiral ligands such as Trost ligand, BINAP, BICP, etc.[40] When using a chiral bis-ferrocenyl amide phosphine ligand shown in Scheme 17, high selectivities and yields were achieved in the reactions with different aryl substrates.



Scheme 17. Synthesis of aryl and heteroaryl substituted pyrrolidines by Zhang et al.

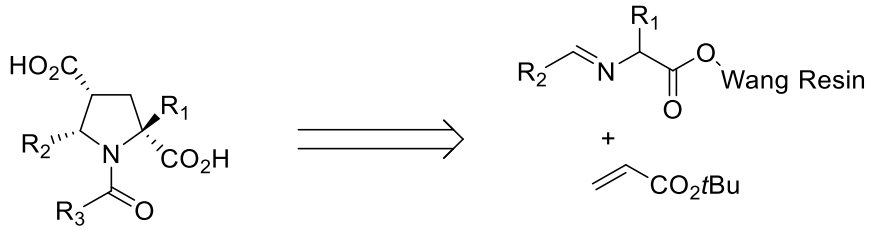
Sansano et al. have reported synthesis of various aryl and heteroaryl substituted pyrrolidines using BINAP-Ag complex (Scheme 18).[41] They have reported over 99 % ee for some products with good selectivities and yields for most of the products. Interesting applications of the developed method was also described in this work for the total synthesis of cis-2,5-disubstituted pyrrolidines.



Scheme 18. Asymmetric 1,3-DC reaction using BINAP-Ag complex

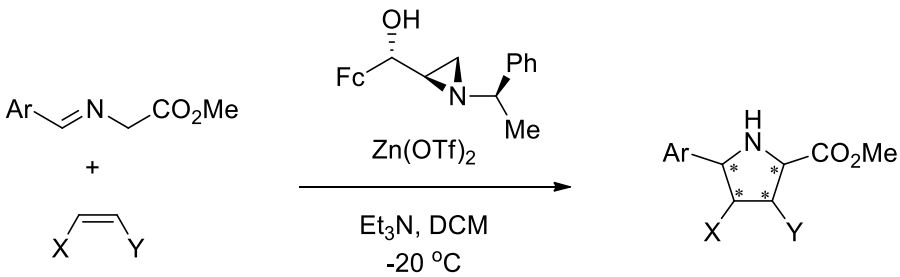
One of the most relevant applications of 1,3-DC reaction is generation of the key intermediate in the preparation of potent and promising inhibitors against hepatitis C virus (HCV), presented by Najera et al.[42] 1,3-DC reaction indicated as a

critical step in the synthesis of the biologically active target pyrrolidine. Desired proline inhibitor can be achieved with additional two steps (Scheme 19).



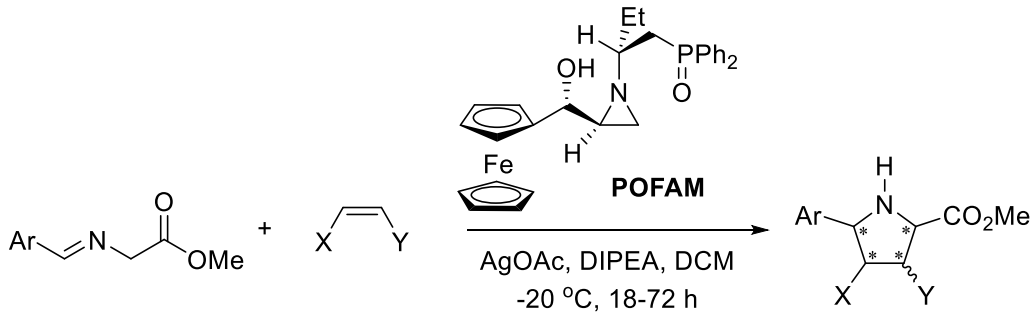
Scheme 19. Retrosynthetic analysis of proline inhibitors

Our group is also involved in performing asymmetric 1,3-DC reactions among other organic transformations. The asymmetric cycloaddition of azomethine ylide with zinc(II)-based catalyst was reported by Dogan et al. (Scheme 20).[43] In this work, enantiorich pyrrolidines were synthesized using ferrocenyl aziridinyl methanol (**FAM**) ligand with zinc triflate salt. Using 10 mol % of zinc salt and 12 mol % of chiral ligand products with high yields up to 94 % and high selectivity, up to 95 % ee, were achieved.



Scheme 20. Asymmetric 1,3-DC reaction with Zn-**FAM** catalyst

Similar study on asymmetric 1,3-DC reaction using aziridine based chiral ligands reported by our group in 2010.[44] Catalytic system using phosphorous derivatives of **FAM** ligands, **POFAM**, with silver metal formed pyrrolidines in up to 99 % yield and 77 % ee (Scheme 21).

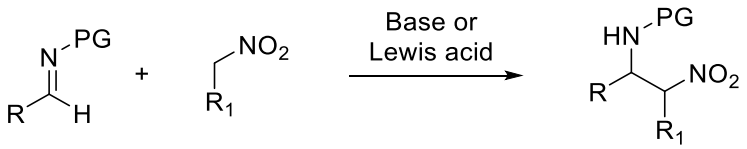


Scheme 21. Asymmetric 1,3-DC reaction using AgOAc-**POFAM** catalyst

Although many intensive efforts have been devoted to developing asymmetric 1,3-DC reaction, still many researchers are interested in new synthetic pathways to overcome the challenges of regio-, diastereo- and enantiocontrol of this reaction. Being one of the interested groups, it was decided to perform 1,3-DC reaction of azomethine ylide with various dipolarophiles using silver salt and chiral ligands of our synthesis. Herein, derivatives of **FAM** ligands, four already reported to the literature and eight new derivatives of **FAM** ligands, were synthesized, and screened in asymmetric 1,3-DC reaction.

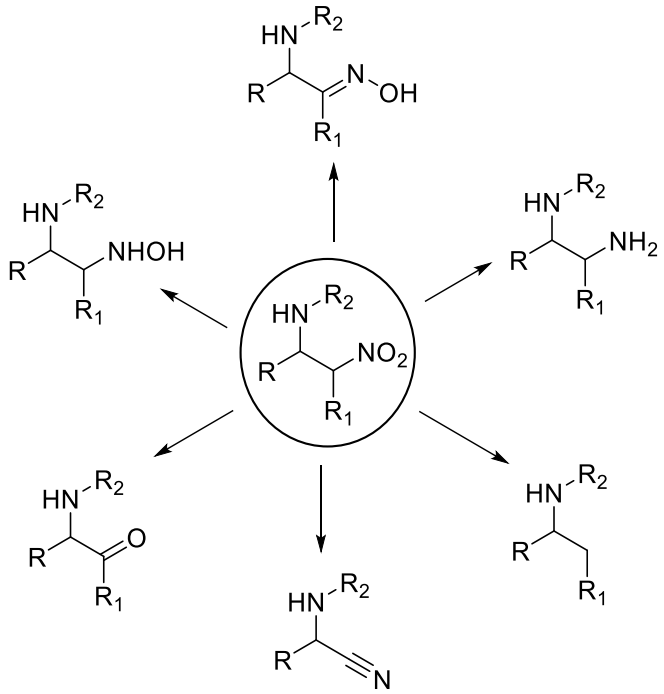
1.4 Importance of aza-Henry reaction

The aza-Henry reaction, also known as nitro-Mannich reaction,[45] is a modified Henry reaction, in which the addition of nucleophilic nitroalkanes to electrophilic imines takes place (Scheme 22).



Scheme 22. General representation for aza-Henry reaction

Aza-Henry reaction is an important C-C bond-forming process, which allows a straightforward entry to a variety of nitrogen-containing chiral/achiral building blocks. Synthetically versatile β-nitroamines formed in this way can be readily converted into a variety of useful compounds such as α-amino acids,[46] vicinal diamines,[47] monoamines,[48] α-amino carbonyls, oximes, hydroxyl amines, nitriles, which can produce various moieties present in biologically active molecules and pharmaceuticals (Scheme 23).[49]

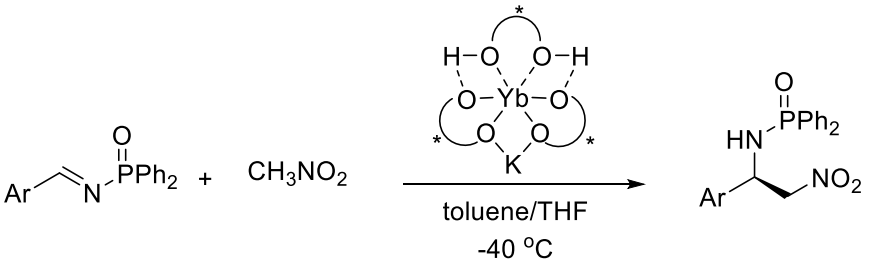


Scheme 23. β-amino nitroalkanes as versatile intermediates

Due to the importance of enantiomerically pure *β*-amino nitroalkanes as versatile intermediates in organic synthesis, a considerable effort has been directed over the last years toward the development of the catalytic asymmetric version of the aza-Henry reaction.[50]

1.4.1 Asymmetric aza-Henry reaction

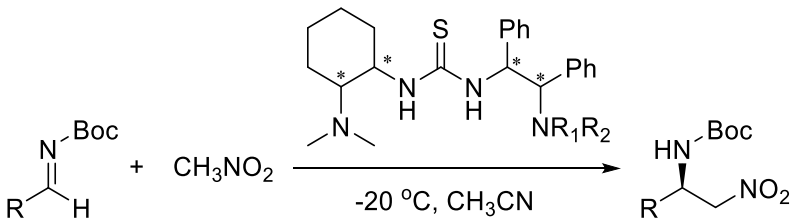
The first asymmetric aza-Henry reaction was reported by Shibasaki and coworkers.[51] In which authors discovered that P=O can coordinate to metal atom of the catalyst, and therefore *N*-phosphonylimine type structures can be used as electrophiles. In their study, they used ytterbium salt with binaphthol ligand (shown in the scheme as semicircles) to achieve 91 % ee and 79 % yield (Scheme 24).



Scheme 24. First asymmetric aza-Henry reaction by Shibasaki

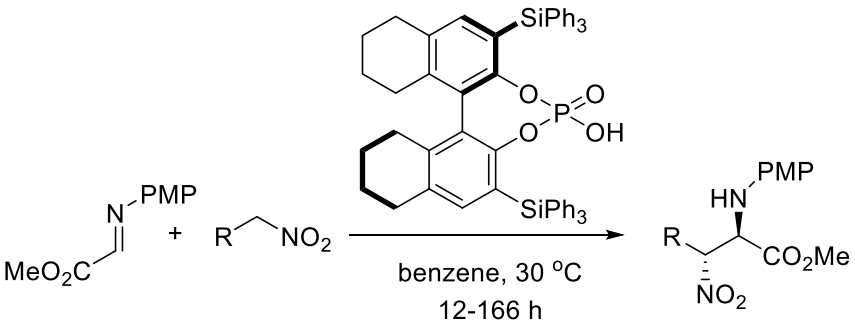
Since then, there has been many developments in this field and there are tremendous number of examples for asymmetric aza-henry reaction with variety of catalysts including both metal catalysts[52] and organocatalysts.[52,53]

A good example for latter is the bifunctional thiourea derivatives, used widely for such organic transformations. Wang et al. have reported asymmetric aza-Henry reaction using bifunctional thiourea catalyst with different nitroalkanes, which resulted in a high selectivity, up to 99 % ee, and high yield (Scheme 25).[45]



Scheme 25. Asymmetric aza-Henry reaction using bifunctional thiourea organocatalyst

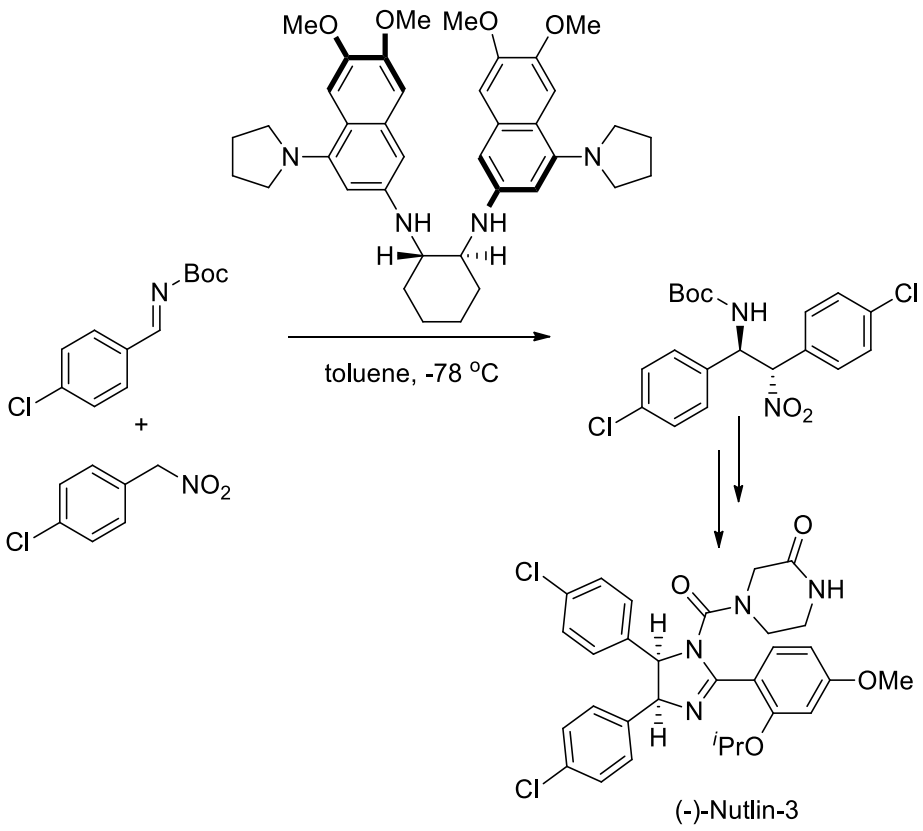
Another organocatalyst widely used in organic transformations, BINOL-derived phosphoric acid which can be also utilized in asymmetric aza-Henry reaction. One example for Brønsted acid catalyzed aza-Henry reaction was reported by Rueping et al. (Scheme 26).[54] In this study, *N*-PMP-*α*-iminoester was used in BINOL-phosphoric acid catalyzed reaction with various nitroalkanes. Yields were good to excellent, 57-93 %, together with high enantiomeric excess 84-92 % ee for major (anti) isomer.



Scheme 26. Asymmetric aza-Henry reaction using Brønsted acid organocatalyst

A good example for the applicational use of aza-Henry reaction can be the synthesis of the potent p53/MDM2 inhibitor (−)-nutlin-3 published by Johnston et al. (Scheme 27).[55] They used chiral bis-amidine catalyst to catalyze reaction between *N*-Boc aryl imine and aryl nitromethane. The resulting *β*-nitroamine was

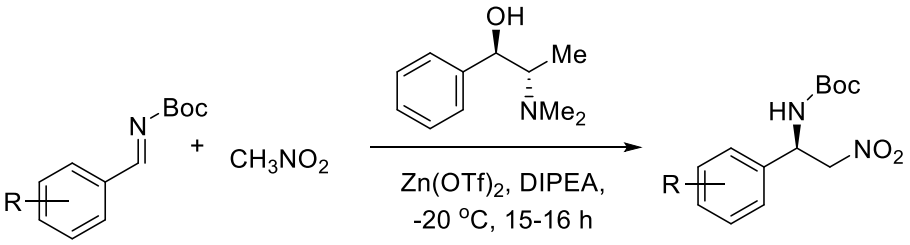
formed in exceptional yield and stereoselectivity, 13:1 dr and 91% ee. Further series of amide bond formations and cyclization form the imidazoline ring furnished (−)-nutlin-3 in 42 % overall yield.



Scheme 27. Aza-Henry reaction in synthesis of (−)-nutlin-3

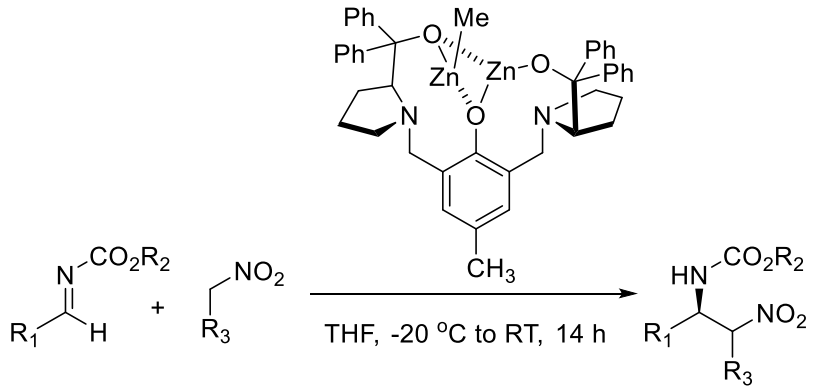
Moderating β-amino nitroalkanes with high enantioselectivities is not an easy with *t*-Boc protected imines and nitromethane by using organocatalysts due to low conversions. Therefore, there are far more examples of enantioselective aza-Henry reaction using metal catalyst, since it is supposed that the dual Lewis acid/Lewis basic functionality should facilitate both formation of the nitronate anion and activation of the imine.[56]

Palomo et al. have reported a use of simple *N*-methylephedrine as chiral ligand in the aza-Hentry reaction of various Boc-protected imines in neat nitromethane (Scheme 28).[57] Apart from chiral ligand and metal source, $Zn(OTf)_2$, DIPEA was used as an additive at low temperature. The product formed in excellent selectivities, 87-99 % ee with acceptable to high yields, 59-98 %. However, reaction with other nitroalkanes other than nitromethane was not reported, and high catalyst loadings were required to achieve good selectivities along with excessive use of nitroalkane.



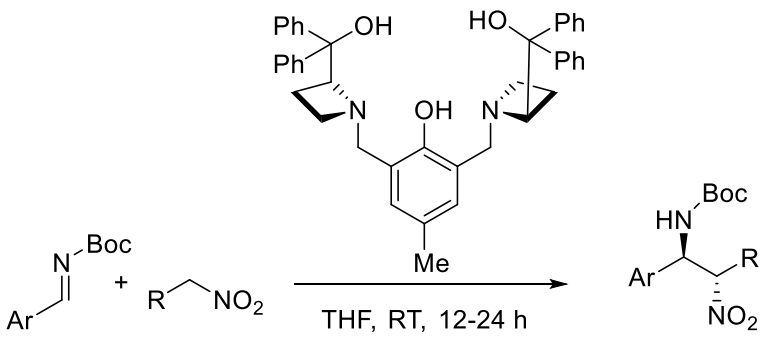
Scheme 28. $Zn(OTf)_2$/*N*-methylephedrine catalyzed aza-Henry reaction

Trost et al. have reported an improved procedure in which Et_2Zn was used as zinc source, to form binuclear zinc complex with chiral ligand, later known as Trost ligand (Scheme 29).[58] This aza-Henry reaction proceeds with high enantioselectivity when various carbamate-protected imines are used, with ee's up to 99 % and yields up to 82 %. The scope of the reaction was also extended to larger nitroalkanes with lower catalyst load and only 2.0 equivalence of nitroalkane. The authors also highlighted the dual Lewis-acid/Lewis-basic functionality of catalyst.



Scheme 29. Asymmetric aza-Henry reaction with bimetallic-zinc/Trost ligand

Most recently, Wang et al. have reported asymmetric aza-Henry reaction of Boc-protected imines under ambient condition using similar dinuclear zinc-AzePhenol catalyst, thus making the process amenable for wide range of applications (Scheme 30).[59]

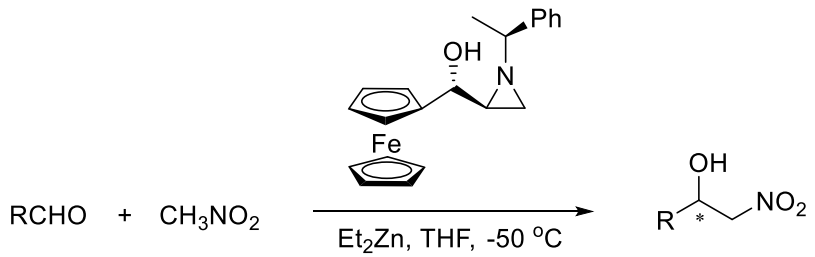


Scheme 30. Asymmetric aza-Henry with dinuclear zinc-AzePhenol catalyst

Although tremendous efforts have already been spent in the literature on establishing a proper reaction condition for aza-Henry reaction, there is still work to be done to achieve the high degrees of stereocontrol, high reactivity, and low catalyst loading. Having that in mind, we wanted to study the performance of **FAM**

ligands in asymmetric aza-Henry reaction of Boc-protected imines with nitroalkanes.

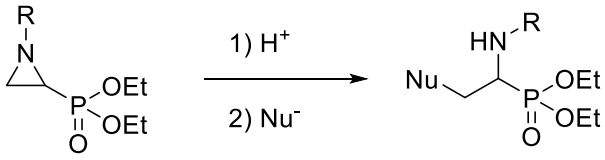
Some derivatives of **FAM** ligands mentioned in this thesis, i.e. **PFAM1-4**, has already been used in asymmetric Henry reaction and reported priorly in the literature by our group (Scheme 31).[60] The fact that this reaction led to products with up to 97 % yield and 91 % ee, made **FAM** ligands a promising candidate as chiral ligand for asymmetric aza-Henry reaction.



Scheme 31. Asymmetric Henry reaction with **FAM** ligand

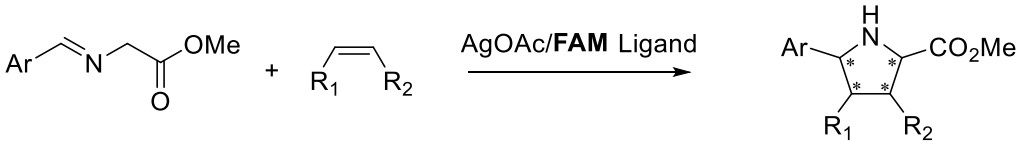
1.5 Aim of the study

The synthesis of both racemic and chiral aziridine-2- phosphonates by using the modified Gabriel-Cromwell reaction and investigation of their biological activities have been studied in previous work.[61] As a continuation of previous work, we are interested in the ring opening reactions of aziridine-2-phosphonates with various nucleophiles. For that purpose, within the first part of the thesis we aimed to study the ring opening reaction of chiral and racemic aziridine-2-phosphonates with different nucleophiles (Scheme 32).



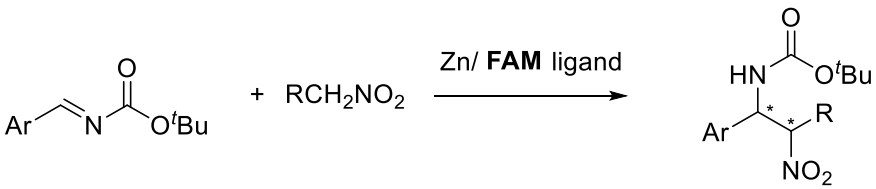
Scheme 32. General scheme for ring-opening of aziridine-2-phosphonate

In the second part of this thesis, we aimed to investigate the potential of aziridine based structures as chiral ligands. For this purpose, we planned to use a small library of 12 **FAM** ligands synthesized by our group for the asymmetric 1,3-dipolar cycloaddition (1,3-DC) reaction of azomethine ylides with dipolarophiles to form pyrrolidines (Scheme 33).



Scheme 33. 1,3-DC reaction using chiral **FAM** ligands and silver salt

As the second metal-catalyzed asymmetric synthesis, we also wanted to test the performance of **FAM** ligands for the aza–Henry reaction using *t*-Boc protected imines and nitroalkanes, **Scheme 34.**



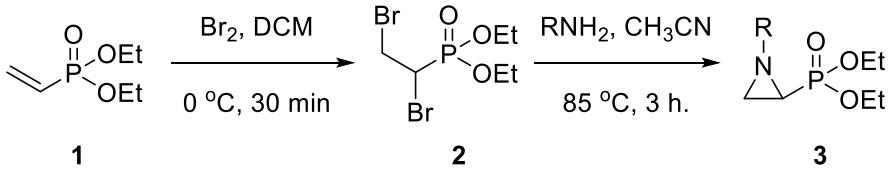
Scheme 34. Asymmetric aza-Henry reaction using Zn-**FAM** ligand catalyst

CHAPTER 2

RESULTS AND DISCUSSION (PART I)

2.1 Synthesis of aziridine-2-phosphonates

For the investigation of ring-opening reactions of aziridine-2-phosphonates with different nucleophiles aziridine-2-phosphonates were synthesized according to the published procedure by our group.[61] First, vinyl phosphonate **1** undergoes bromination reaction to give dibromo phosphonate **2**, which is converted to aziridine **3** through HBr elimination–conjugate addition of RNH_2–S_N2 displacement of α-bromide also known as Gabriel-Cromwell reaction (Scheme 35).



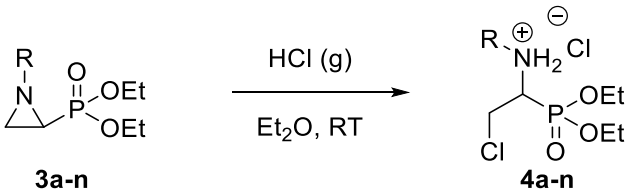
Scheme 35. Synthesis of aziridine-2-phosphonates

By using this method, it was possible to prepare a series of aziridine-2-phosphonates from different amines of racemic, **3a-d**, and chiral nature, **3e-n** (Table 1). To obtain pure diastereomers of chiral aziridines synthesized aziridine-2-phosphonates **3e-n** were separated by silica column chromatography.

2.2 Ring-opening reaction of aziridine-2-phosphonates with HCl

The ring opening reaction of aziridine-2-phosphonates **3** were studied using gaseous HCl generated *in situ*. This reaction opened the aziridine ring regioselectively to give β-chloro-α-amino phosphonates **4**. The results of this study were summarized in Table 1.

Table 1. Ring-opening reaction of aziridine-2-phosphonates with HCl



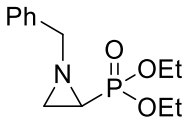
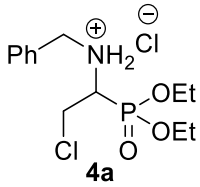
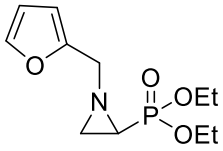
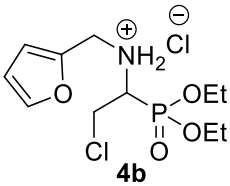
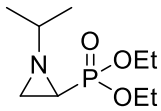
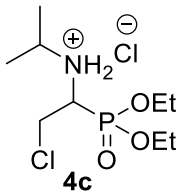
Entry	Aziridine-2-phosphonates	Ring-opened products	Yield[a] (%)
1	 3a	 4a	95
2	 3b	 4b	94
3	 3c	 4c	86

Table 1. Ring-opening reaction of aziridine-2-phosphonates with HCl (*continued*)

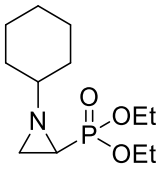
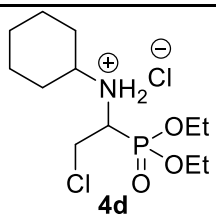
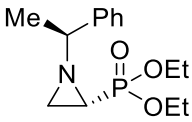
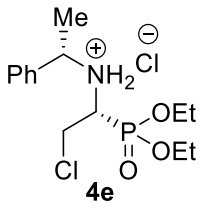
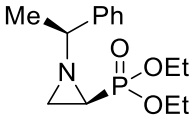
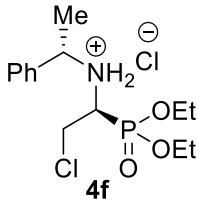
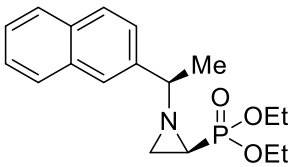
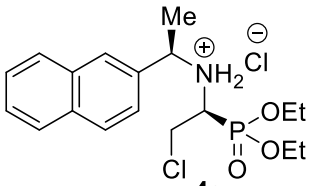
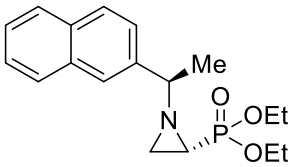
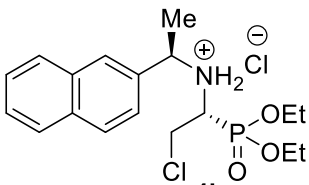
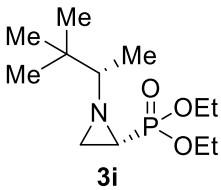
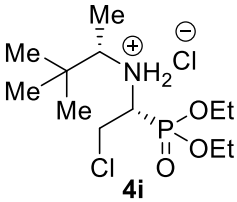
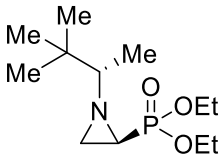
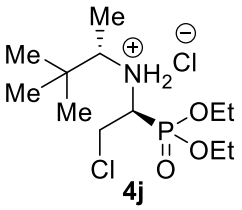
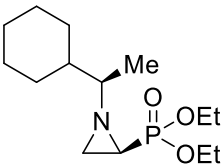
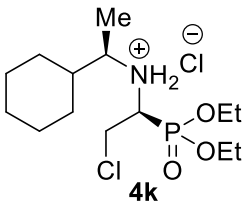
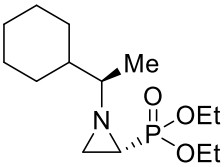
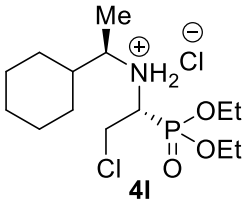
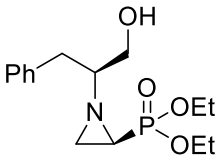
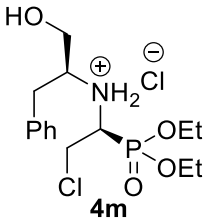
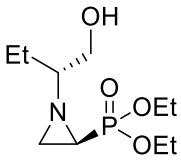
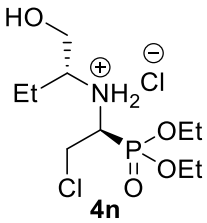
4	 **3d**	 **4d**	93
5	 **3e**	 **4e**	67
6	 **3f**	 **4f**	84
7	 **3g**	 **4g**	95
8	 **3h**	 **4h**	89
9	 **3i**	 **4i**	93

Table 1. Ring-opening reaction of aziridine-2-phosphonates with HCl (*continued*)

10	 **3j**	 **4j**	74
11	 **3k**	 **4k**	79
12	 **3l**	 **4l**	60
13	 **3m**	 **4m**	79
14	 **3n**	 **4n**	87

[a]isolated yield.

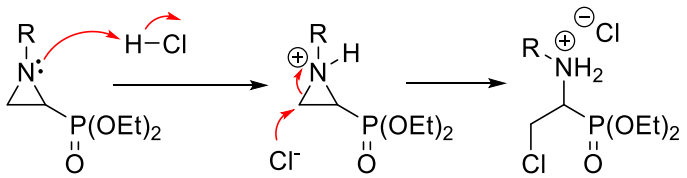
First, the racemic *N*-benzyl substituted aziridine-2-phosphonate **3a** was reacted with HCl in ether which gave a single regioisomer **4a** in 95 % yield (entry 1). After seeing that the ring opening reaction of **3a** takes place smoothly and

efficiently, the other racemic aziridine-2-phosphonates having furfuryl **3b,** isopropyl **3c**, and cyclohexyl **3d** groups on the nitrogen were also subjected to the same reaction. All these reactions led to the expected ring opening products in very good yields (entries 2–4). In repeating the same reaction with the chiral aziridine-2-phophonates **3e-n** (entries 5–14) again the ring opening reaction took place smoothly as expected to yield the corresponding β-chloro-α-aminophosphonates in good to excellent yields, 60–95%.

The ring opening reaction of all aziridine-2-phosphonates **3a-n** with HCl gas takes place in a very short reaction time, at room temperature and mostly with no need for further purification.

2.2.1 Proposed reaction mechanism for the ring opening of aziridine-2-phosphonates with HCl

The proposed mechanism for the aziridine ring-opening reaction is straight forward as shown in Scheme 36.



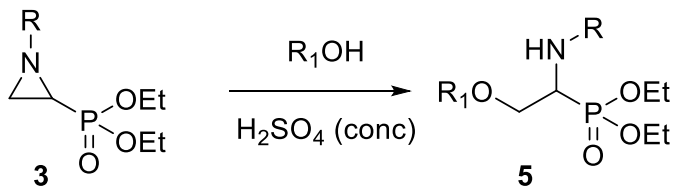
Scheme 36. Proposed mechanism for the ring-opening reaction of aziridine-2-phosphonate with HCl

As it can be seen from the Scheme 36, nitrogen is protonated by HCl and forms an aziridinium ion. Then, chloride ion acts as nucleophile and attacks the aziridine ring from less hindered β-position to form β-chloro-α-amino phosphonate.

2.3 Ring-opening reactions of aziridine-2-phosphonates with alcohols.

The investigation of ring-opening reactions of non-activated aziridines showed that the aziridine ring can be activated with the help of acids such as *p*-toluene sulfonic acid (TsOH) and sulfuric acid. Thus, using TsOH or H_2SO_4 it was possible to do the ring-opening reactions with alcohols successfully. However, the latter showed better yields, therefore all ring-opening reactions were carried out in the presence of H_2SO_4, and the results were summarized in Table 2.

Table 2. Ring-opening of aziridine-2-phosphonates with alcohols



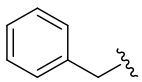
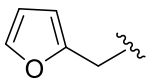
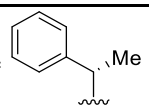
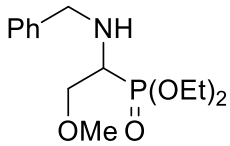
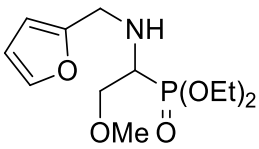
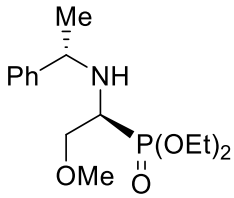
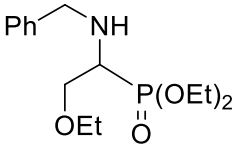
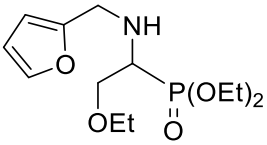
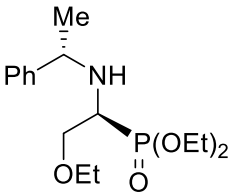
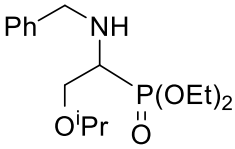
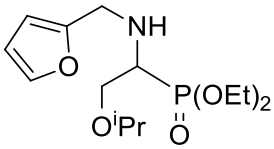
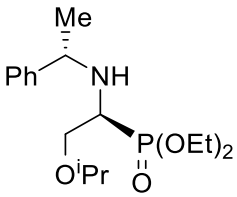
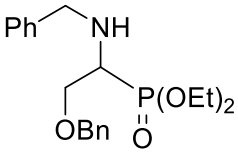
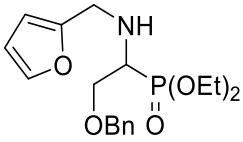
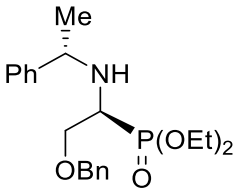
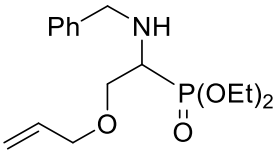
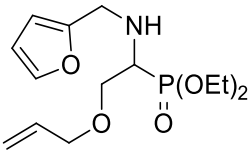
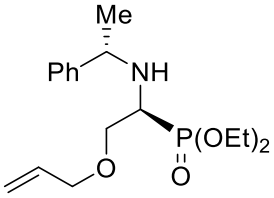
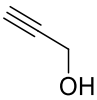
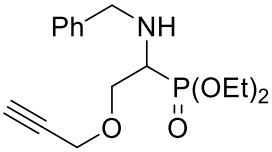
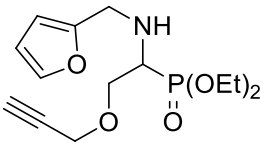
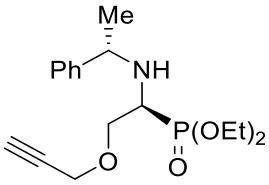
Entry	R_1OH	Aziridine-2-phosphonate/ring opened products		
		R=  **3a**	R =  **3b**	R =  **3f**
1	MeOH	 **5aa**, 91 %	 **5ba**, 84 %	 **5fa**, 86 %
2	EtOH	 **5ab**, 77 %	 **5bb**, 72 %	 **5fb**, 82 %

Table 2. Ring-opening of aziridine-2-phosphonates with alcohols *(continued)*

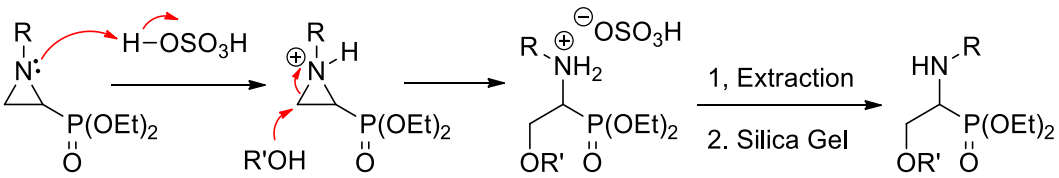
3	^{i}PrOH	 **5ac**, 86 %	 **5bc**, 35 %	 **5fc**, 55 %
4	BnOH	 **5ad**, 43 %	 **5bd**, 81 %	 **5fd**, 53 %
5		 **5ae**, 90 %	 **5be**, 90 %	 **5fe**, 68 %
6		 **5af**, 81 %	 **5bf**, 75 %	 **5ff**, 40 %

As can be seen from Table 2, aziridine-2-phosphonates having three different groups on the nitrogen was studied. Racemic aziridine-2-phosphonates **3a**, **3b** and a chiral aziridine-2-phosphonate **3f** all three gave the ring opening products with methanol in 91%, 84 % and 86 % yield respectively (entry 1). In the case of ethyl alcohol as the nucleophile, the chiral aziridine **3e** gave the highest yield 82 % (entry 2). With secondary alcohol ^{i}PrOH benzyl substituted aziridine **3a** was isolated in 84 % yield and the others were in the acceptable range (entry 3). When

benzyl alcohol was used as the nucleophile, desired β-substituted α-amino phosphonates **5ad**, **5bd** and **5fd** were isolated in 59 %, 81% and 53 % yields respectively (entry 4). Allyl alcohol formed the ring opened products in good yields for the first two aziridines, **3a** (90 %) and **3b** (90 %), and in moderate yield for aziridine **5fe** (68 %, entry 5). Same ring opening reactions were also performed with propargylic alcohol and the expected products **5af** and **5bf** were attained in good yields, 81 % and 75 % respectively, but compound **5ff** was obtained albeit in low yield (40 %, entry 6).

2.3.1 Proposed reaction mechanism for the ring opening of aziridine-2-phosphonates with alcohols

The proposed mechanism for H_2SO_4 mediated ring-opening reaction with alcohols which is similar to ring-opening reaction with HCl. First, nitrogen is protonated by acid and nucleophile present in the medium attacks to the less hindered site. Formed amine salt is removed after extraction and purification on silica gel, as shown in Scheme 37.

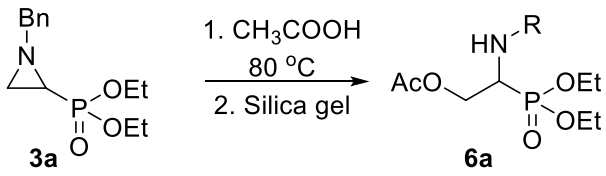


Scheme 37. Proposed mechanism for H_2SO_4 mediated ring-opening

2.4 Ring-opening of aziridine-2-phosphonates with other nucleophiles.

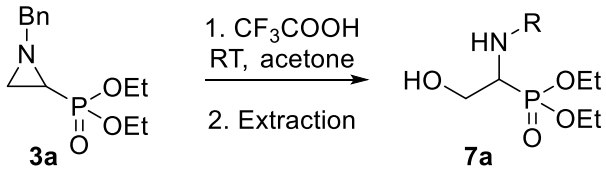
Since it has been established that the presence of a protic acid is enough to activate the aziridine ring, the ring-opening reaction with acetic acid and triflouroacetic acid (TFA) has been tested as well. As for ring-opening with acetic

acid, the formation of expected product **6a** was observed in 96 % yield (Scheme 38).



Scheme 38. Ring-opening reaction with acetic acid

However, ring-opening reaction with TFA did not yield the expected product, instead, hydrolyzed product, β-hydroxy-α-amino phosphonate **7a** was obtained in 82 % yield (Scheme 39).



Scheme 39. Ring-opening with TFA

Trifloroacetate group is highly labile and hydrolysis takes place during flash column chromatography on silica gel as reported in the literature.[62]

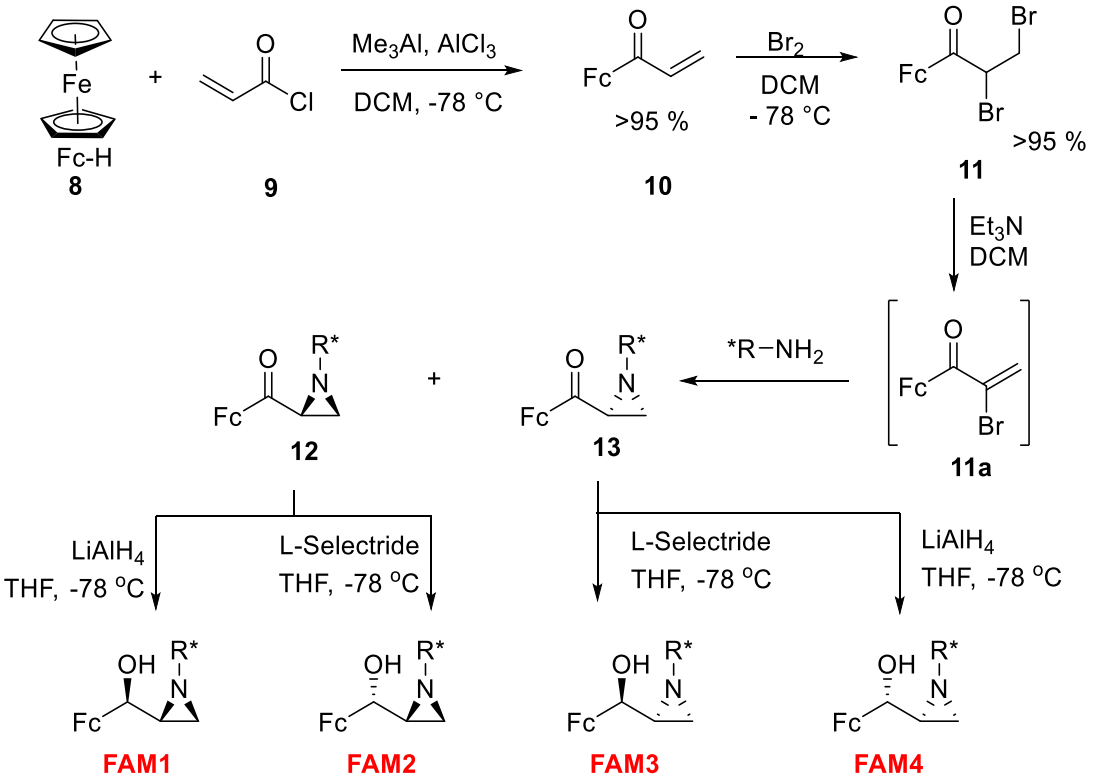
CHAPTER 3

RESULTS AND DISCUSSION (PART II)

3.1 Synthesis of FAM ligands

The small ligand library of chiral aziridinyl based ligands, ferrocenyl aziridinyl methanol (**FAM**) ligands were synthesized according to the procedure previously reported by our group.[63] The synthetic pathway for the synthesis of **FAM** ligands is shown in Scheme 40.

As it can be seen from the Scheme 40, synthesis of **FAM** ligands begins with the reaction of ferrocene **8** and acryloyl chloride **9** in the presence of mixture of $AlCl_3$ and Me_3Al Lewis acids which yields acryloyl ferrocene **10** almost quantitatively. Successful bromination of acryloyl ferrocene at -78 ^oC produces the dibromo compound **11** in excellent yield. Treating dibromo compound with Et_3N eliminates HBr and forms α-bromo compound **11a** which reacts with chiral amine to provide a diastereomeric mixture of ketones **12** and **13** that can be separated easily by silica column chromatography. The reduction of ketone **12** under Luche conditions, using $NaBH_4$ as a reducing agent and $ZnCl_2$ as a chelating agent, forms **FAM1** as the only steroisomer. To obtain **FAM2** having opposite configuration at the alcohol center it was necessary to use L-selectride. Reduction of ketone **13** was not as selective as in the case of ketone **12**. Thus, the use of L-selectride or $LiAlH_4$ both provided **FAM3** and **FAM4** as a mixture that can be separable easily by silica column chromatography.



Scheme 40. Overall reaction pathway for the synthesis of **FAM** ligands

Using synthetic pathway shown in Scheme 40, besides previously reported chiral **PFAM1-4** (R = phenyl, phenyl ferrocenyl aziridinyl methanol) ligands, new derivatives **NFAM1-4** (R = 1-naphtyl, naphthyl ferrocenyl aziridinyl methanol) and **CFAM1-4** (R = cyclohexyl, cyclohexyl ferrocenyl aziridinyl methanol) were also synthesized. For the synthesis of **NFAM** series (*R*)-1-naphthyl ethyl amine was used as chiral amine, while for the **CFAM** series (*R*)-cyclohexyl ethyl amine was utilized. With the synthesis of new **FAM** ligands, we had a small library of twelve chiral ligands shown in Figure 6.

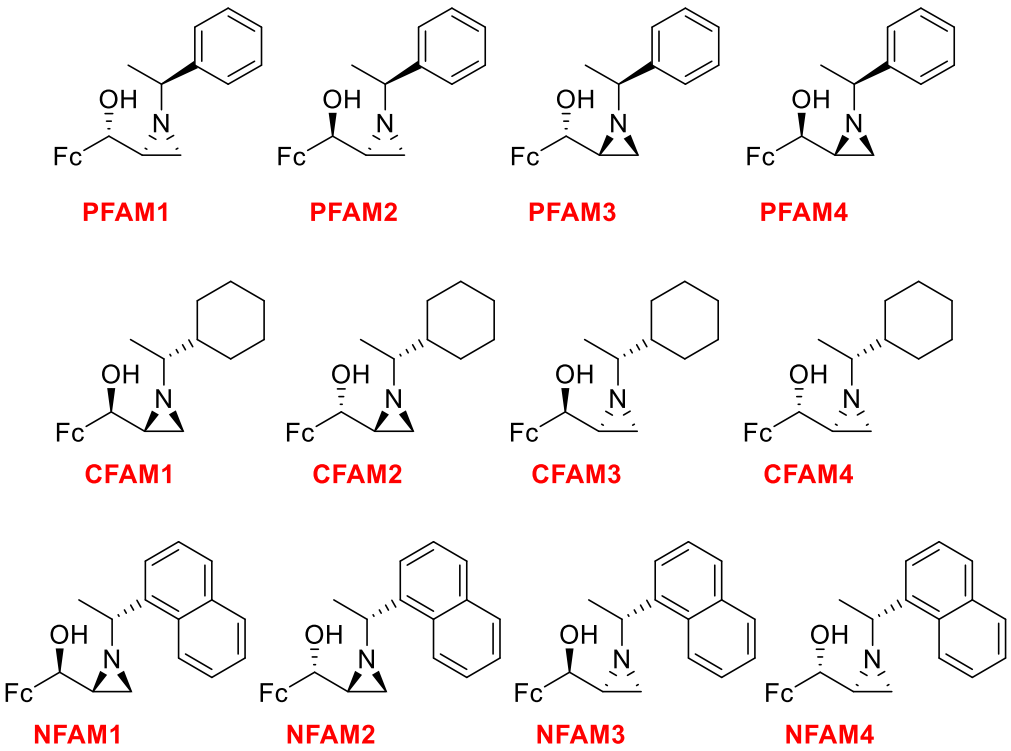
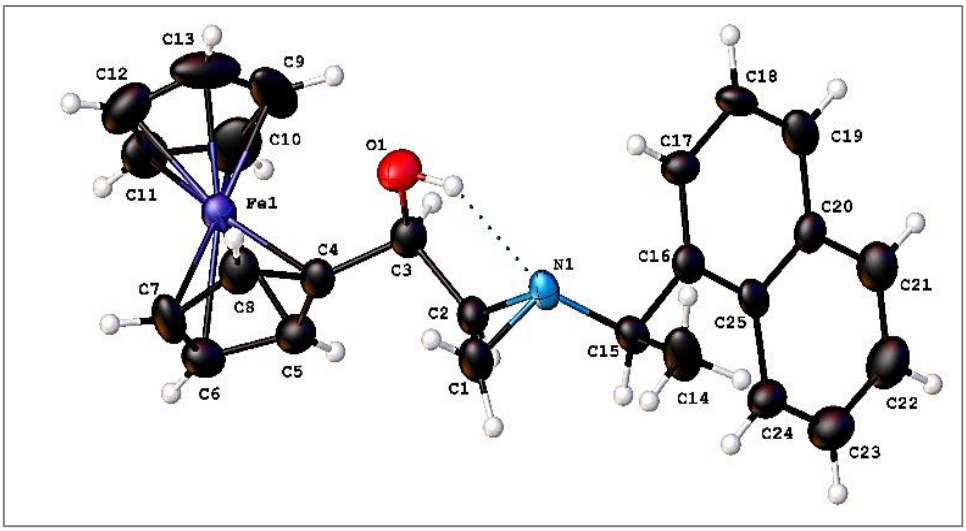


Figure 6. Structure of the **FAM** ligands

The absolute stereochemistries of **FAM** ligands were determined by single crystal *X*-ray analysis. The crystal structure of **PFAM1** was reported in the literature.[43] The absolute stereochemistry of new ligands **NFAM4** and **CFAM3** were also determined by *X*-ray analysis, as shown in Figure 7a and Figure 7b, respectively. Displacement ellipsoids are drawn at the 30 % probability level. The intramolecular interaction is shown by dotted lines.

a)



b)

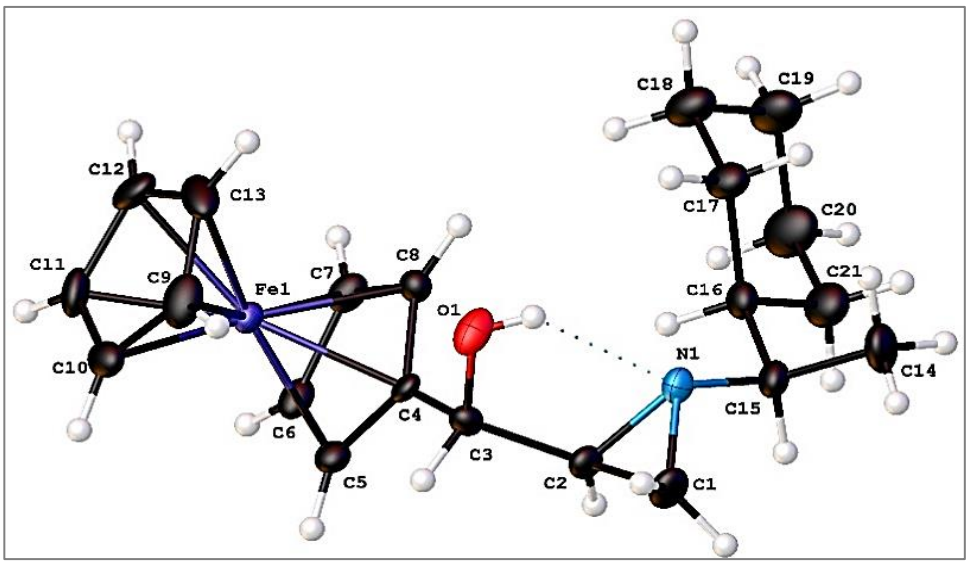


Figure 7. *X*-ray structures of a) **NFAM4** and b) **CFAM3**

The absolute stereochemistry of **NFAM1**, **NFAM2**, **CFAM1** and **CFAM2** at the alcohol center is based on R_f values on TLC and ^{1}H NMR signals of ferrocenyl protons as shown in Figure 8. In Figure 8, for all three ligands, i.e., **PFAM1**, **NFAM1** and **CFAM1**, three protons of the substituted ferrocenyl ring appear on the left-hand side of the big singlet corresponding to five protons of the unsubstituted ferrocenyl ring. On the other hand, for **PFAM2**, **NFAM2** and

CFAM2 one proton of substituted ferrocenyl ring is on the left-hand side and the others are either overlapping or appearing on the right-hand side of the big signal. Based on this observation, since **PFAM1** already confirmed by *X*-ray crystallography, it was concluded that the stereochemistry of **NFAM1** and **CFAM1**, so as **NFAM2** and **CFAM2** are as shown in Figure 6.

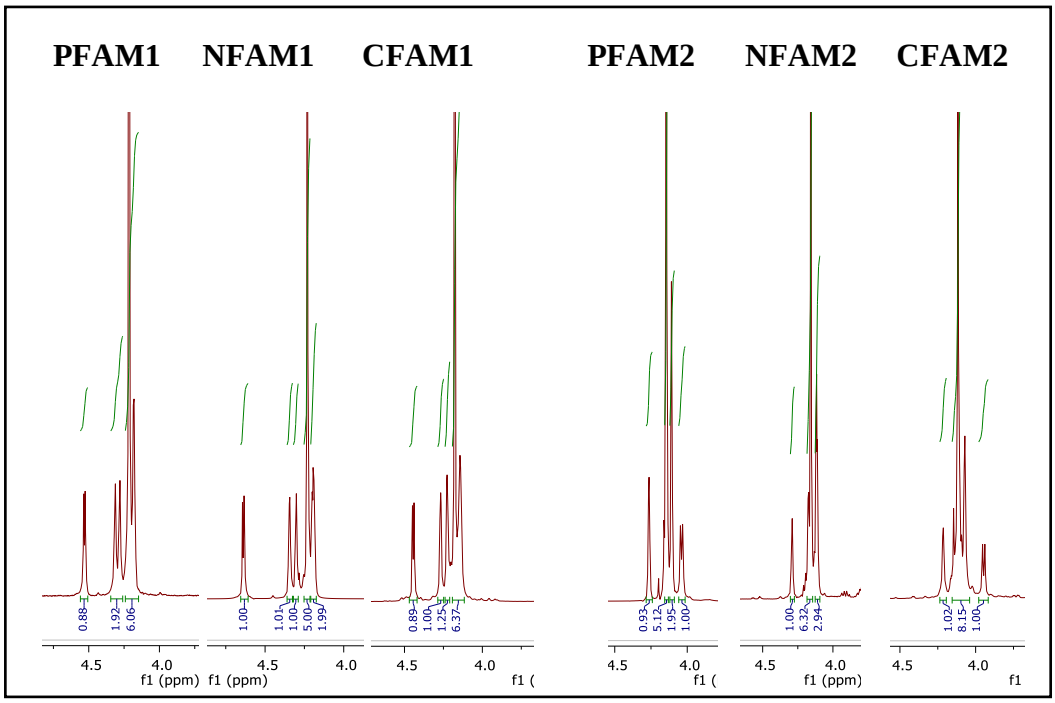


Figure 8. Fraction of the ^{1}H NMR spectrum corresponding to ferrocenyl protons of **FAM1** and **FAM2** ligands

3.2 Optimization studies for 1,3-dipolar cycloaddition reaction

After the synthesis of twelve **FAM** ligands, we were ready to test their performance as a chiral ligand first for the 1,3-dipolar cycloaddition (1,3-DC) reaction of azomethine ylides with electron deficient dipolarophiles. We started optimization studies by ligand screening using an adapted literature procedure.[61]

According to this procedure phenyl substituted imine **14a** and *N*-methylmaleimide were reacted with 10 mol % **FAM** ligand, 5 mol % AgOAc, 1.5 equiv. of dipolarophile, 0.2 M reaction concentration in toluene, and 400 mg 4 Å molecular sieves used as the drying agent for 100 mg imine.[8-10]

3.2.1 Ligand screening

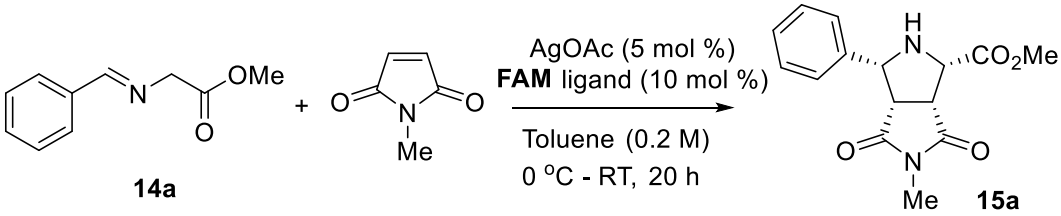
The results of ligand screening studies were summarized in Table 3. As can be seen from the Table 3, in **PFAM** series **PFAM1** showed 79 % yield with selectivity of 73 % ee (entry 1) which is close to that of **PFAM4**, that showed 76 % ee, but only 56 % yield (entry 4). **PFAM2** and **PFAM3** showed lower selectivities with numerical values close to each other, i.e., 43 % and 42 %, respectively (entries 2 and 3).

In case of **CFAM** series, first two ligands showed the selectivities of 60 % and 58 % with high yields over 90 % (entries 5 and 6). Reactions with **CFAM3** and **CFAM4** yielded the products in 78 % ee and 77 % ee, respectively (entries 7 and 8). The latter showed high reaction yield of 96 %.

In **NFAM** series, ligands apart from **NFAM1** showed moderate selectivities, while first isomer gave 71 % ee with 72 % yield (entry 1). As seen in entry 12, **NFAM4** showed the lowest selectivity among these ligands giving only 40 % ee.

It is important to mention that the ligands with opposite configuration at alcohol center give products with opposite stereoselectivity, which are shown with a negative sign in Table 3.

Table 3. Ligand screening for 1,3-DC reaction



14a **15a**

Entry	Ligand	yield[a] (%)	ee[b] (%)
1	**PFAM1**	79	73
2	**PFAM2**	86	-43
3	**PFAM3**	91	42
4	**PFAM4**	56	-76
5	**CFAM1**	94	-60
6	**CFAM2**	92	58
7	**CFAM3**	63	-78
8	**CFAM4**	96	77
9	**NFAM1**	72	-71
10	**NFAM2**	91	67
11	**NFAM3**	70	-45
12	**NFAM4**	81	40

[a]Isolated yield. [b]Determined by chiral HPLC column.

Since **CFAM3**, **CFAM4** and **PFAM1** yielded the product in similar selectivities, above 70 %, for further optimizations the ligand with highest reaction yield was chosen. In other words, **CFAM4** was decided to be the ligand of choice due to good selectivity of 77 % ee with high reaction yield, which is 96 %.

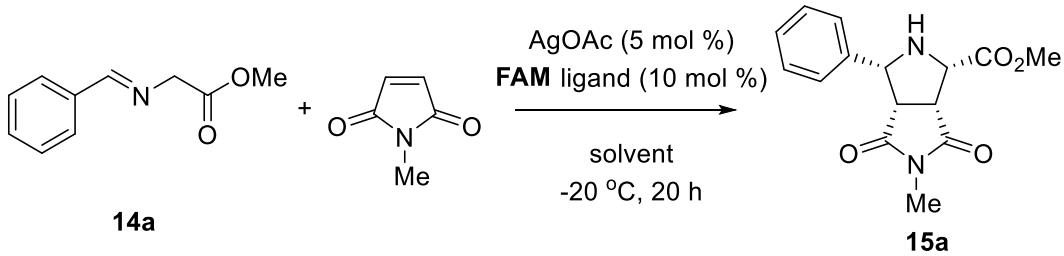
3.2.2 Solvent screening

After determining proper ligand, reaction was repeated with different solvents such as DCM, THF and toluene. In addition, reaction temperature was changed from 0 to -20 °C. The results of these studies are summarized in Table 4.

DCM and THF gave products with close yields and selectivities of 53 % ee and 44 % ee, respectively (entries 1 and 2). The reaction with **CFAM4** in toluene at this temperature showed slight improvement in enantiomeric excess to 80 % together with little decrease in reaction yield (entry 3).

When reaction was carried out with **PFAM1** and **NFAM4** under the same conditions, improvement in selectivity was not observed for the former, yet for the latter the selectivity was improved drastically, from 40 % ee to 70 % ee, together with sharp fall in yield from 81 % to 55 %. As a result, further optimizations were done with the ligand with higher selectivity, i.e., **CFAM4**, in toluene determined to be the reaction solvent.

Table 4. Solvent screening studies for 1,3-DC reaction at -20 °C



Entry	Ligand	Rxn conditions	yield[a] (%)	ee[b] (%)
1	**CFAM4**	DCM (0.2 M)	78	53
2	**CFAM4**	THF (0.2 M)	73	44
3	**CFAM4**	Toluene (0.2M)	89	80
4	**PFAM1**	Toluene (0.2M)	87	73
5	**NFAM4**	Toluene (0.2M)	55	70

[a]Isolated yield. [b]Determined by chiral HPLC column.

3.2.3 Catalyst loading optimizations

To find optimal amount of **FAM** ligand and silver salt that are used in 1,3-DC reaction, different amounts of **CFAM4** and AgOAc, unless stated otherwise, were examined at -20 °C and 0 °C, as summarized in Table 5.

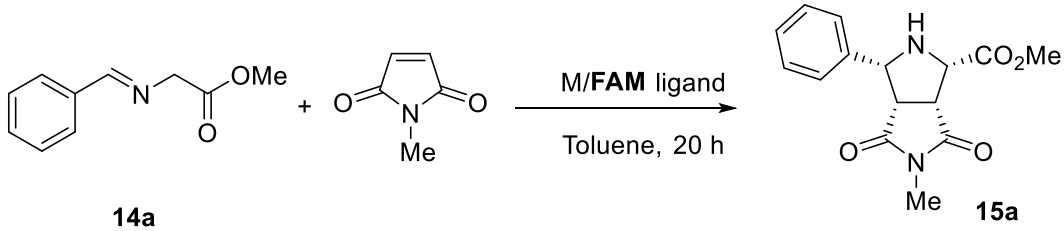
For the reactions at -20 °C increasing the ligand-metal amount did not bring an increase in selectivity, 80 % ee at 10 mol % ligand load (entry 1) and 70 % ee at 20 mol % ligand loads (entry 2). Lowering the ligand load to 5 and 3 mol % resulted in lower yield with almost same ee around 80 % (entry 3 and 4). To achieve higher yield with lower catalyst load, some attempts such as increasing the dipolarophile equivalence from 1.5 to 2.0 (entry 5) and increasing reaction time from 18 h to 24 h were also tried (entry 6). However, all these attempts resulted in decrease in both yield and enantioselectivity.

To increase yield with lower catalyst load three ligands that showed the highest selectivities in ligand screening studies, i.e., **PFAM1**, **CFAM3** and **CFAM4**, were tested at 0 °C-RT conditions with 5 mol % catalyst loads. Under these reaction conditions **CFAM4** ligand yielded the product with 86 % ee in 94 % yield (entry 7). Just to note that decreasing the amount of **PFAM1** did not give a significant change in yield and selectivity (entry 8) while decrease in the amount of **CFAM3** resulted in lessening in selectivity from 78 % ee to 65 % ee (entry 9).

Since **CFAM4** showed an increase in selectivity when the amount was lowered to 5 mol % (entry 7) it was decided to further decrease ligand load. Manipulating the amount of **CFAM4,** it was observed that 3 mol % **CFAM4** with 1.5 mol % AgOAc positively affected both the yield and the enantioselectivity of the product, 95 % and 94 % respectively (entry 10). Further reduction in catalyst amount to 2 mol % ligand and 1 mol % metal salt, resulted in a drop both in yield and ee (entry 11).

In order to examine the performance of other metal sources, the reaction between azomethine ylide and *N*-methylmaleimide was repeated with $Zn(OTf)_2$ and $Cu(CH_3CN)_4BF_4$ commonly used for these reactions. Unfortunately, both metal salts resulted in the formation of racemic products with low yields (entries 12 and 13).

Table 5. Catalyst load optimizations for 1,3-DC reaction



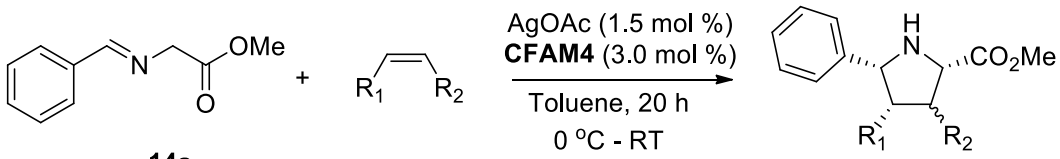
Entry	FAM (mol %)	AgOAc (mol %)	Rxn Temperature	yield[a]	ee[b]
1	20.0	10.0	-20 °C	78	70
2	10.0	5.0	-20 °C	89	80
3	5.0	2.5	-20 °C	42	82
4	3.0	1.5	-20 °C	30	80
5[c]	5.0	2.5	-20 °C	44	55
6[d]	5.0	2.5	-20 °C	33	66
7	5.0	2.5	0 °C - RT	94	86
8[e]	5.0	2.5	0 °C - RT	86	77
9[f]	5.0	2.5	0 °C - RT	74	-65
10	3.0	1.5	0 °C - RT	95	94
11	2.0	1.0	0 °C - RT	81	86
12[g]	6.0	5.0	0 °C - RT	51	rac
13[h]	5.5	5.0	0 °C - RT	28	rac

[a]Isolated yield. [b]Determined by chiral HPLC column. [c]2.0 equiv. of dipolarophile was used. [d]Reaction was carried out for 24 h. [e]**PFAM1** was used as ligand. [f]**CFAM3** was used as ligand. [g]$Zn(OTf)_2$ was used as the metal source. [h]$Cu(CH_3CN)_4BF_4$ was used as the metal source.

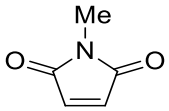
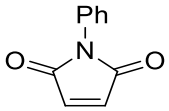
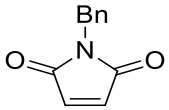
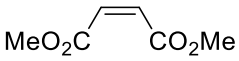
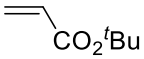
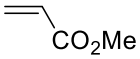
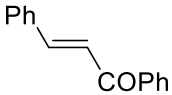
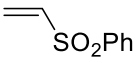
3.2.4 Dipolarophile screening

After setting all reaction parameters 1,3-DC reaction of azomethine ylide was performed with different dipolarophiles as summarized in Table 6. Besides *N*-methylmaleimide, *N*-phenyl and *N*-benzylmaleimides were also tested in 1,3-DC reaction under optimized conditions. As it can be seen from entries 2 and 3, the selectivities of these maleimides were not as high as in the case of *N*-methylmaleimide. The enantioselectivity was 48 % for *N*-benzylmaleimide and 10 % for *N*-phenylmaleimide. When the reaction was carried out with dimethyl maleate 88 % yield and 28 % ee was observed (entry 4). For the reactions with *tert*-butyl and methyl acrylates (entries 5 and 6) the reaction was resulted in moderate yields and low selectivities of 50 % ee for the former and 16 % ee for the latter. The reactions with *trans*-chalcone and vinyl sulfone gave racemic products with low yields (entries 7 and 8).

Table 6. Dipolarophile screening table



14a **15a-22a**

Entry	Product	Dipolarophile	yield[a]	ee[b]
1	**15a**		95	94
2	**16a**		79	10
3	**17a**		91	48
4	**18a**		88	28
5	**19a**		68	50
6	**20a**		51	16
7	**21a**		30	rac
8	**22a**		17	rac

[a]Isolated yield. [b]Determined by chiral HPLC column.

3.2.5 Imine screening

Besides the dipolarophiles, we have also screened the imines obtained by the condensation of glycine methyl ester with different aromatic aldehydes. For that purpose, imines with maleimide dipolarophiles were reacted under optimized reaction conditions. The results of these studies were summarized in Tables 7, 8 and 9.

3.2.5.1 Reaction of different imines with *N*-methylmaleimide

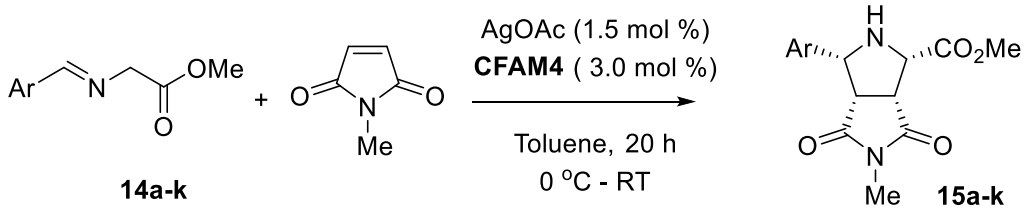
After determining the optimum conditions, 1,3-DC reaction of azomethine ylides obtained from different imines were screened first with *N*-methylmaleimide and the results were summarized in Table 7.

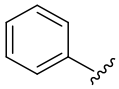
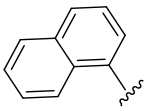
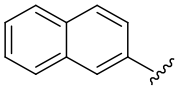
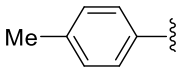
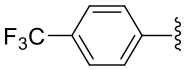
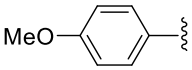
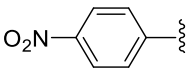
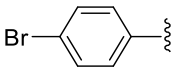
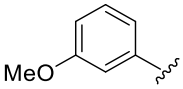
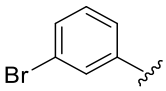
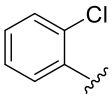
In Table 7, there are two ee values, one is reaction ee after purification of the cycloadducts by flash column chromatography on silica gel and the other one is the ee after recrystallization. The cycloadduct were recrystallized from DCM-Hexane or DCM-Et_2O. Depending on the structure either the major enantiomer crystallized out or remained in the solution.

As shown in Table 7, phenyl substituted imine with *N*-methylmaleimide showed the highest reaction ee of 94 %, therefore, recrystallization was not tried for this cycloadduct (entry 1). In the case of sterically more hindered naphthyl imines (entries 2 and 3) 62 % yield and 65 % ee was obtained for the 1-naphthyl case and 81 % yield and 75 % ee was obtained for the 2-naphthyl case. The ee of both cycloadducts was increased to 90 % and 97 % respectively upon recrystallization. The reaction of *p*-tolyl and *p*-trifluoromethylphenyl substrates yielded products in 50 % and 68 % with an ee of 71 % (increased to 80 %) and 73 % (increased to 96 %) respectively (entries 4 and 5). The effect of both electron donating and withdrawing substituents on the aromatic ring was investigated. Imine with an electron donating methoxy group provided cycloadduct in 65 % yield and

69 % ee (increased to 97 %, entry 6). Strong electron withdrawing nitro group, on the other hand, gave the product in 90 % ee (increased to 99%) with 61% yield (entry 7). The result of *p*-bromophenyl substituted imine was very similar to that of *p*-methoxyphenylimine case, entry 8. Imines with different groups at different possitons of the aromatic ring (*m*-methoxy, *m*-bromo and *o*-chloro), formed the products in 71 %, 91 % and 75 %, yields with moderate selectivities 66 % (increased to 96 %), 76 % (increased to 86 %) and 61 % ee (increased to 90 %), respectively, (entries 9-11).

Table 7. Substrate screening with *N*-methylmaleimide



Entry	Product	Ar	yield[a]	ee[b]	ee recryst
1	**15a**		95	94	94[c]
2	**15b**		62	65	90
3	**15c**		81	75	97[d]
4	**15d**		50	71	80
5	**15e**		68	73	96
6	**15f**		65	69	97[d]
7	**15g**		61	90	>99
8	**15h**		61	65	99[d]
9	**15i**		71	66	96
10	**15j**		91	76	86
11	**15k**		75	61	90

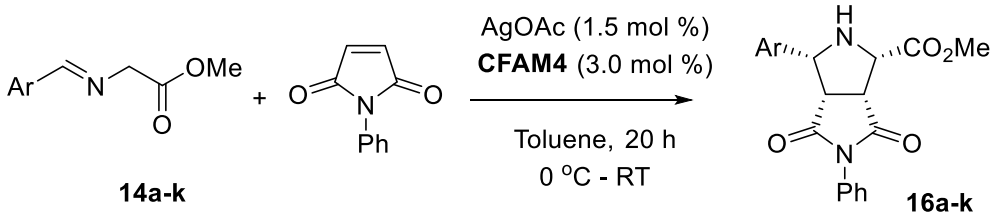
[a]Isolated yield. [b]Determined by chiral HPLC column. [c]ee of reaction. [d]ee of crystals

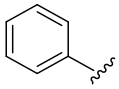
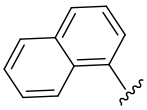
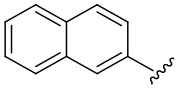
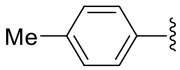
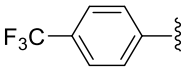
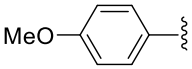
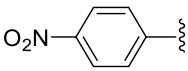
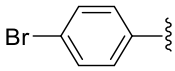
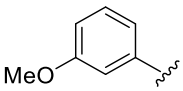
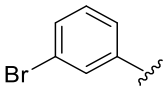
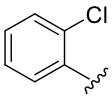
3.2.5.2 Reactions with *N*-phenylmaleimide dipolarophile

Similar work was performed for *N*-phenylmaleimide with each substrate under optimized conditions. The results of these studies are summarized in Table 8. As it can be seen from Table 8, although the yields are reasonably good, the overall selectivities of the reactions are relatively mediocre, compared to studies with two other maleimides. Fortunately, it was possible to increase the ee of all the cycloadducts by recrystallization.

The first reaction of this series was done with phenylimine and *N*-phenylmaleimide which produced the cycloadduct in 79 % yield with 10 % ee (increased to 86 %, entry 1). In the case of the same dipolarophile with naphthylimines corresponding pyrrolidine derivatives were isolated in reasonably good yields but low ee's. Fortunately, it was possible to increase the ee from 45 % to 98 % ee by recrystallization for 1-napthyl case (entry 2) and from 58 % to 99 % for 2-napthyl case (entry 3). When the reaction was performed with the *p*-substituted aromatic imines, in general, the yields were good except the *p*-NO_2 substituted one which formed the product in 19 % yield (entry 7). However, low ee's were obtained for all the other substrates (entries 4-8). On the other hand, it was possible to increase the low ee of all these substrates above 90 % by recrystallization except the *p*-methoxy case which remained at 66 % (entry 6). Repeating the same reaction with *m*-methoxy, *m*-bromo and *o*-chloro substrates cycloadducts were obtained in good yields (entries 9-11) but the enantioselectivities were similar to the previous ones. Once again, it was possible to increase the ee's of these cycloadducts to more than 80 %.

Table 8. Imine screening with *N*-phenylmaleimide



Entry	Product	Ar	yield[a]	ee[b]	ee recryst
1	**16a**		79	10	86
2	**16b**		85	45	98
3	**16c**		86	58	99[c]
4	**16d**		92	46	90[c]
5	**16e**		83	24	96
6	**16f**		86	37	66
7	**16g**		19	36	98
8	**16h**		98	48	97
9	**16i**		85	37	81
10	**16j**		95	47	86
11	**16k**		68	38	93

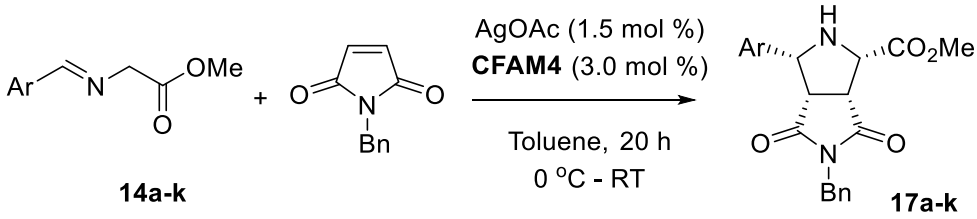
[a]Isolated yield. [b]Determined by chiral HPLC column. [c]ee of crystals.

3.2.5.3 Reactions with *N*-benzylmaleimide dipolarophile

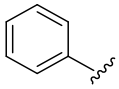
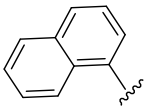
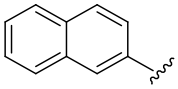
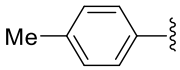
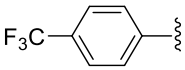
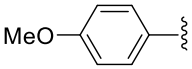
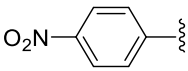
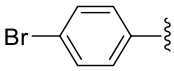
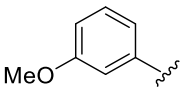
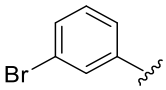
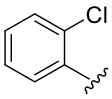
As the third dipolarophile we have used *N*-benzylmaleimide and screened the same imines under optimized reaction conditions. The results of these studies are showed in Table 9.

In this series, while phenyl and 1-naphtyl imines formed the cycloadducts in good yields with low ee's, 2-naphthyl imine formed the cycloadduct in acceptable yield with good ee. For all these cycloadducts recrystallization increased the ee to more than 90 % (entries 1-3). Interestingly, only for 1-naphthyl imine we isolated the product as a diastereomeric mixture with 93/7 *syn/anti* ratio (entry 2). The reaction with *p*-tolyl and *p*-triflomethylphenyl imines gave the cycloadducts in moderate yields with the same ee, 60 %, which increased to 99 % and 85 % respectively (entries 4 and 5). Among the other *p*-substituted imines, *p*-methoxy, *p*-nitro and *p*-chloro, *p*-nitro-substituted imine formed the product in lowest yield but acceptable ee (entries 6-8). By applying a recrystallization process, it was possible to increase ee's from 52 to 86 %, 74 to 93 %, and 73 to 90 % respectively. In the case of *m*-methoxy, *m*-bromo and *o*-chloro-substituted imines, the cycloadducts were isolated in good yields and acceptable ee's (entries 9-11). As in previous series, it was possible to enrich the ee's of the cycloadducts by recrystallization, from 63 to 91 %, 71 to 80 % and 62 to 99 % ee.

Table 9. Substrate screening with *N*-benzylmaleimide



14a-k **17a-k**

Entry	Product	Ar	yield[a]	ee[b]	ee recryst
1	**17a**		91	48	94
2	**17b**		90	60 (dr:93/7)	96
3	**17c**		65	84	98
4	**17d**		68	60	85
5	**17e**		79	60	>99
6	**17f**		90	52	86
7	**17g**		19	74	93
8	**17h**		82	73	90
9	**17i**		84	63	91
10	**17j**		93	71	80
11	**17k**		82	62	>99

[a]Isolated yield. [b]Determined by chiral HPLC column.

3.2.6 Proposed transition state

The structural and sterochemical assignments of the cycloadducts were made by comparing with those found in the literature. Based on the stereochemistry of known compounds, proposed transition state is demonstrated in Figure 9.

According to this transition state, **FAM** ligand, imine and the dipolarophile are coordinated to silver in such a way that the cycloaddition takes place from the *si*-side with respect to imine nitrogen in an *endo*-mode.

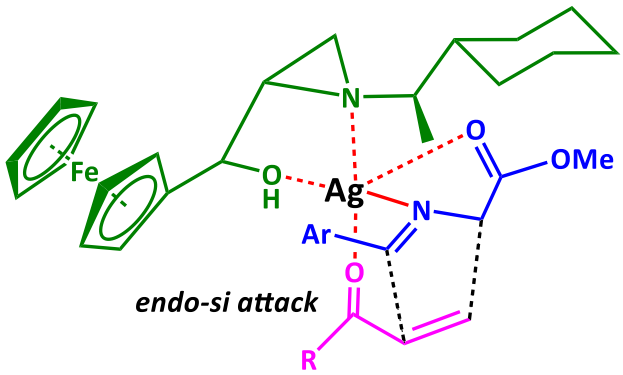


Figure 9. Proposed transition state for Ag-**FAM** catalyzed 1,3-DC reaction

CHAPTER 4

RESULTS AND DISCUSSION (PART III)

4.1 Optimization studies for aza-Henry reaction

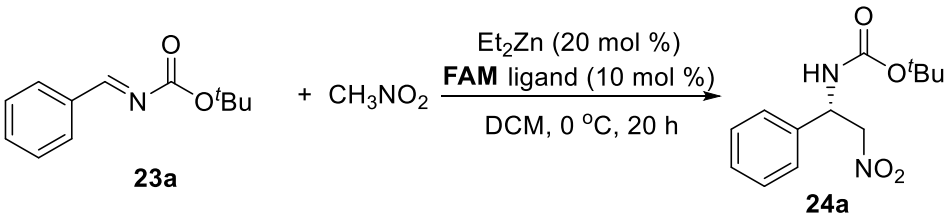
4.1.1 Ligand screening for reaction of Boc-substituted imine with nitromethane

As the first optimization, synthesized **FAM** ligands were screened by modified literature procedure used for asymmetric aza-Henry reaction by using Boc-imine, nitromethane and diethylzinc.[3] The results of these studies were summarized in Table 10.

As can be seen from Table 10, for all **FAM** ligands good yields with low to moderate enantioselectivities were obtained. Similar to 1,3-DC reaction screenings, the ligands of opposite chiralities at alcohol center led to formation of products of opposite stereoselectivity.

The highest yield (88 %) and selectivity (71 % ee) were observed with **PFAM1** ligand (entry 1). Although reasonable yields were achieved using **PFAM2** (entry 2), **CFAM1** (entry 5), **CFAM4** (entry 8), and **NFAM4** (entry 12) their selectivities were low. Therefore, further optimizations were performed by using **PFAM1** ligand.

Table 10. Ligand screening studies for the aza-Henry reaction



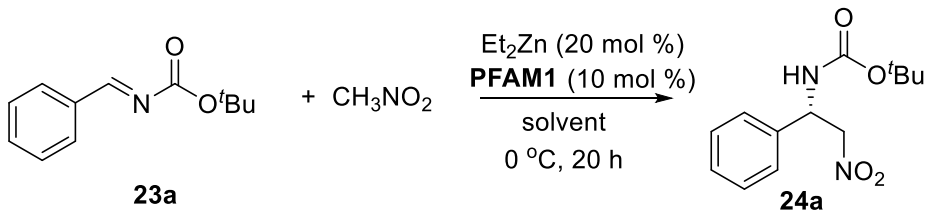
Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**PFAM1**	88	71
2	**PFAM2**	87	60
3	**PFAM3**	73	-25
4	**PFAM4**	68	-52
5	**CFAM1**	89	-35
6	**CFAM2**	70	-17
7	**CFAM3**	71	20
8	**CFAM4**	88	53
9	**NFAM1**	74	-40
10	**NFAM2**	86	-13
11	**NFAM3**	78	20
12	**NFAM4**	87	33

[a]Isolated yield. [b]Determined by chiral HPLC column

4.1.2 Solvent screening studies for the aza-Henry reaction

After selecting proper ligand, solvent screening studies were done using 8 different solvents and the results were summarized in Table 11. Except chloroform (entry 7) yields were reasonable to good but ee's were low for most of the solvents. The promising result was obtained for DCM with 88% yield and 71% ee (entry 1). Therefore, further optimizations were done in DCM.

Table 11. Solvent screening studies



Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	DCM	88	71
2	THF	81	30
3	Et_2O	78	27
4	Toluene	67	27
5	ACN	86	rac
6	DCE	86	40
7	$CHCl_3$	15	18
8	Hexane	88	53

[a]Isolated yield. [b]Determined by chiral HPLC column.

4.1.3 Optimization of reaction conditions in terms of imine–nitromethane ratio, effect of molecular sieves and temperature

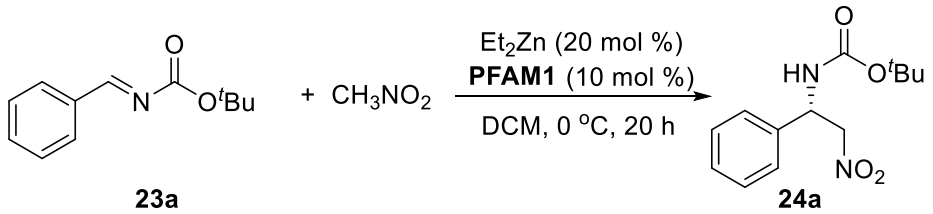
To see the effect of molecular sieves (MS) on the reaction, we have added different amounts of molecular sieves to the reaction medium, the results were summarized in Table 12. Without MS (entry 1) the product was isolated in 81 % yield with 43 % ee. On the other hand, by adding 30 mg of 4Å MS to 100 mg imine solution ee increased to 50 % (entry 2). By doubling the amount of MS 71 % ee was resulted (entry 3). However, further increase in the amount of MS had a negative effect on ee, with 90 mg of 4Å MS ee was 64 % ee and with 120 mg 4Å MS ee was 61 % ee respectively (entries 4 and 5). Low selectivities, around 50 %, were observed when 3Å MS or meshed MS was used (entries 6 and 7).

To find an optimal time for the formation of metal-ligand complexation and nitroalkane addition, stirring time was altered (Table 12). By keeping the metal-ligand complexation time at 30 minutes, we changed the time intervals for the addition of nitromethane and imine to the reaction medium. By adding nitromethane 30 min. after metal-ligand complexation and stirring for 30 min and adding imine at this point, product was isolated in 88 % yield with 71 % ee (entry 3). However, addition of nitromethane and imine together after 30 min complexation lower ee (48 %) was obtained (entry 8). When the imine was added 60 min after nitromethane, further decrease in ee (34 %) was resulted (entry 9).

If no time was spared for the metal-ligand complexation, the product was formed in good yield (93 %) albeit low ee (48 %, entry 10). Giving more time to metal-ligand complexation, yield (88 %) was not affected significantly but the ee remained low (38 %, entry 11).

It was concluded that the optimal time for the reaction was 30 min. for the metal-ligand complexation then addition of nitromethane and another 30 min. for the introduction of the imine at 0 ^{o}C (entry 3). Reaction at room temperature gave low selectivity, only 20 % ee (entry 12). Lowering the temperature to -10 ^{o}C, -20 ^{o}C and -78 ^{o}C resulted in decrease both in yield and ee (entries 13-15).

Table 12. Optimization of aza-Henry reaction conditions



Entry	Rxn conditions	Yield[a] (%)	ee[b] (%)
1	0 °C	81	43
2	30 mg 4Å MS, 0 °C	83	50
3[c]	60 mg 4Å MS, 0 °C	88	71
4	90 mg 4Å MS, 0 °C	78	64
5	120 mg 4Å MS, 0 °C	79	61
6	60 mg 3Å MS, 0 °C	82	47
7	60 mg meshed MS, 0 °C	79	50
8[d]	60 mg 4Å MS, 0 °C	84	48
9[e]	60 mg 4Å MS, 0 °C	87	34
10[f]	60 mg 4Å MS, 0 °C	93	48
11[g]	60 mg 4Å MS, 0 °C	88	38
12	60 mg 4Å MS, RT	73	20
13	60 mg 4Å MS, -10 °C	71	40
14	60 mg 4Å MS, -20 °C	61	30
15	60 mg 4Å MS, -78 °C	39	28

[a]Isolated yield. [b]Determined by chiral HPLC column. [c]Nitromethane was added after 30 min ligand metal complexation time and imine was added after another 30 min. [d]Imine was added together with nitromethane. [e]Imine was added 60 min after nitromethane. [f]Nitromethane was added together with ligand. [g]Nitromethane was added 60 min after the ligand.

4.1.4 Optimization of catalyst load and imine/nitromethane ratio

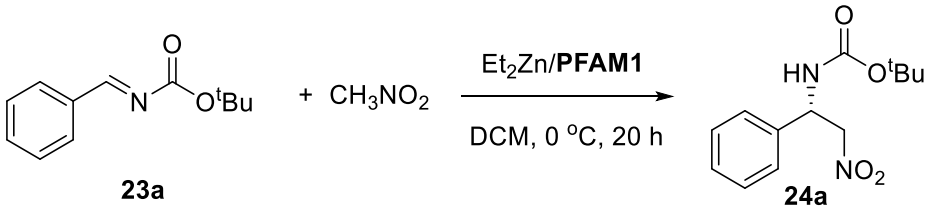
The studies for the catalyst load and nitroalkane equivalence were summarized in Table 13.

To see the effect of catalyst load on reaction selectivity, 40 mol % Et_2Zn and 20 mol % **PFAM1** ligand was used. With this catalyst load both the yield and ee were lower than the the catalyst load which was half of this amount (entries 1 and 2). By using 10 mol % Et_2Zn and 5 mol % **PFAM1** ligand product was obtained as a racemic mixture (entry 3). In keeping the chiral ligand at 10 mol % and varying the amount of Et_2Zn from 15 mol %, 10 mol % and 5 mol % selectivity decreased from 34 %, 20 % to racemic (entries 4-6).

Changing nitromethane equivalence by keeping the catalyst load at 20/10 mol % Zn/**PFAM1** ratio, did not improve the enantioselectivity. The reaction in neat nitromethane resulted in 50 % ee with 90 % yield (entry 7). Using 25 equiv., 10 equiv. and 5 equiv. of nitromethane, 63 %, 47 % and 43 % ee's were achieved respectively (entries 8-10).

Repeating the reaction at 0.1 M and 0.3 M in DCM, did not increase the ee (entries 11 and 12). Therefore, the condition at entry 2 remained as optimal condition for the reaction.

Table 13. Optimization of the catalyst load and nitromethane equivalence



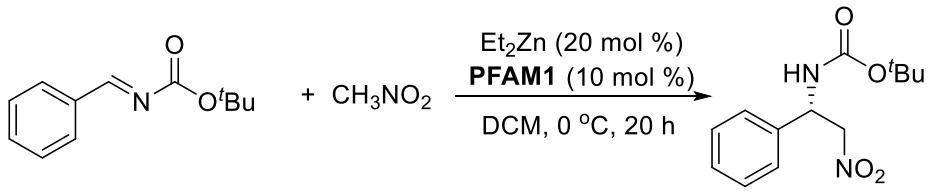
Entry	Imine/ $MeNO_2$	$ZnEt_2$/Ligand (mol %)	Yield[a] (%)	ee[b] (%)
1	1/20	40/20	64	46
2	1/20	20/10	88	71
3	1/20	10/5	80	rac
4	1/20	15/10	87	34
5	1/20	10/10	85	20
6	1/20	5/10	69	rac
7	neat	20/10	91	50
8	1/25	20/10	89	63
9	1/10	20/10	77	47
10	1/5	20/10	65	43
11[c]	1/20	20/10	74	68
12[d]	1/20	20/10	87	44

[a]Isolated yield. [b]Determined by chiral HPLC column. [c]0.1 M in DCM. [d]0.3 M in DCM.

4.1.5 Additive screening for reaction of Boc-protected imine with nitromethane

Lastly, the effect of the additive on the reaction was also studied. For this purpose, different bases, DBU, Hunig's Base, triethyl amine and triphenyl phosphine were used in 5 mol % amounts (Table 14). Only Ph_3P and Et_3N had a positive effect on ee when used in 5 mol % (entries 5 and 8). Further optimizations by changing the amount of these two additives did not bring a positive result in terms of ee therefore, we decided to use 5 mol % Et_3N for the imine screening studies.

Table 14. Additive screening table



23a **24a**

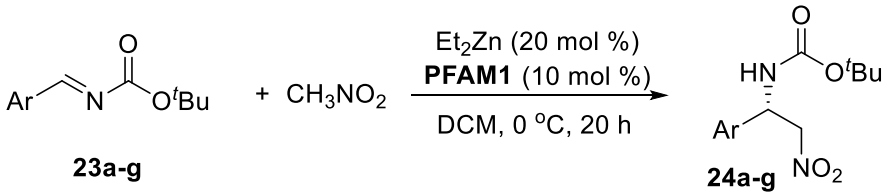
Entry	Additive	Yield[a] (%)	ee[b] (%)
1	-	88	71
2	DBU (5 mol%)	77	rac
3	Hünig's Base (5 mol%)	91	60
4	Ph_3P (2.5 mol%)	73	63
5	Ph_3P (5 mol%)	62	73
6	Ph_3P (10 mol%)	85	65
7	Et_3N (2.5 mol%)	82	60
8	Et_3N (5 mol%)	76	77
9	Et_3N (10 mol%)	77	73
10	Et_3N (20 mol%)	65	50

[a]Isolated yield. [b]Determined by chiral HPLC column.

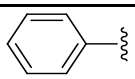
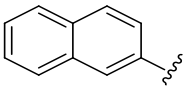
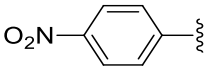
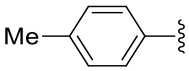
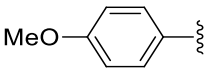
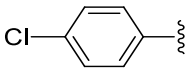
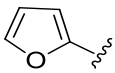
4.1.6 Imine substrate screening for aza-Henry reaction

At this point, the optimized parameters were applied to different *t*-Boc protected imine derivatives with nitromethane and the results were summarized in Table 15. For this purpose, we have synthesized phenyl, 2-naphthyl, *p*-nitrophenyl, tolyl, *p*-methoxyphenyl, *p*-chloro and furyl imines. With all the imines, yields were acceptable to good except for *p*-chloro case which formed the product in 21 % yield without the additive and 23 % with the 5 mol % Et_3N additive (entry 3). The enantioselectivities for the new imines, however, were either very low or none (entries 2-7).

Table 15. Imine substrate screening for aza-Henry reaction with nitromethane



23a-g **24a-g**

Entry	Product	Ar	Yield[a] (%)	ee[b] (%)
1	**24a**		88 (76)	71 (77)
2	**24b**		74 (69)	46 (10)
3	**24c**		21 (28)	6 (10)
4	**24d**		93 (90)	32 (rac)
5	**24e**		76 (83)	rac (rac)
6	**24f**		79	20
7	**24g**		74	16

[a]Isolated yield without additive, numbers in parenthesis were obtained with additive (5 mol % Et_3N). [b]Determined by chiral HPLC column

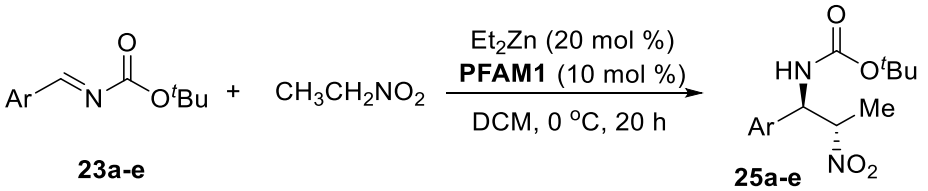
4.1.7 Reaction of Boc-protected imines with nitroethane

In the last part of this study, the optimized parameters were applied to imines bearing different aromatic groups with nitroethane. The results are summarized in Table 16.

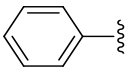
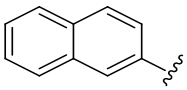
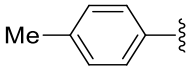
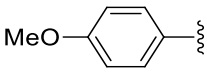
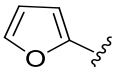
The reaction of phenyl substituted imine with nitroethane formed the product with the highest yield (91 %) with a diastereomeric ratio of 93/7 *anti/syn* (entry 1). The enantioselectivity was found to be 60 % for the major isomer and 10 % for the minor isomer, given in the parenthesis (entry 1). In the case of bulkier 2-naphthyl group, the product was formed in 54 % yield with 73/27 *anti/syn* ratio. The selectivity of the major isomer of this substrate is 34 % (entry 2). Introducing electron donating methoxy group at para position the product was obtained in moderate yield with 79/21 diasteromeric ratio and with a good enantioselectivity of 86 % ee for the *anti*-isomer (entry 4).

The reaction of *p*-tolyl substituted imine provided the product in 74 % yield with 85/15 *anti/syn* ratio and good ee for both diastereomers, 75 % and 82 % respectively (entry 3). Similarly, the reaction of furyl substituted imine gave the product in acceptable yield with with 71/29 diastereomeric ratio and acceptable to excellent ee 64 % for the *anti*-product and more than 99 % for the *syn* product (entry 5).

Table 16. Reaction of Boc-protected imines with nitroethane



23a-e **25a-e**

Entry	Product	Ar	Yield[a] (%)	dr *anti/syn*	ee[b] (%) maj (min)
1	**25a**		91	93/7	60 (10)
2	**25b**		54	73/27	34 (rac)
3	**25c**		74	85/15	75 (82)
4	**25d**		75	79/21	86 (rac)
5	**25e**		69	71/29	64 (>99)

[a]Isolated yield. [b]Determined by chiral HPLC column.

CHAPTER 5

CONCLUSION

In the first part of this thesis, we have investigated the ring-opening reactions of non-activated aziridines with different nucleophiles. Aziridine-2-phosphonates synthesized by the Gabriel-Crowmell reaction was treated with HCl gas bubbled into the ether solution of aziridines. As a result of this process the regioselective ring-opening of aziridines took place to yield β-chloro-α-amino phosphonates in acceptable to good yields 60-95 %.

The ring-opening reaction of aziridine-2-phosphonates was also studied with MeOH, EtOH, ^{i}PrOH, BuOH, allyl alcohol and propargyl alcohol in the presence of H_2SO_4. In all the cases, the ring opening reactions yielded the expected β-alkoxy-α-amino phosphonates regioselectively in moderate to good yields, 35-91 %. The same reaction with neat acetic acid and triflouroacetic acid gave the β-acetoxy- and β-hydroxyaminophosphonates in 96 % and 82 % yields, respectively.

The second part of this thesis consisted of testing the performance of a small library of 12 **FAM** ligands with a transition metal in metal catalyzed asymmetric synthesis. As the first reaction, 1,3-DC reaction of azomethine ylides with various dipolarophiles was tried using silver acetate with **NFAM1-4**, **CFAM1-4** and **PFAM1-4** chiral ligands. After standard optimization studies, various imines were reacted with *N*-methyl-, *N*-phenyl- and *N*-benzylmaleimide used as the dipolarophiles in the presence of Ag-**CFAM4** catalyst system. The yields of the products with *N*-methylmaleimide varied between 50-95 % with the enantioselectivities between 61-94 %. In the case of *N*-phenylmaleimide, 1,3-DC reaction of azomethine ylides provided pyrrolidine derivatives in 19-98 % isolated yield with 10-58 % ee. In the case of *N*-benzylmaleimide, cycloadducts were isolated in 19-93 % yield with 48-84 % ee. The enantiomeric excess values of the

cycloadducts were enriched by recrystallization (mostly around 90 %). In a comparison to previous work,[43] new catalytic system Ag-**CFAM4** proved to work better, since with lower catalyst load (3.0 mol % **CFAM4** - 1.5 mol % AgOAc) selectivity of 94 % ee and 95 % yield in a reaction of phenyl substituted imine with *N*-methyl maleimide. Whereas, the same reaction yielded in 74 % ee using previous catalytic system, i.e. 10 mol % of $Zn(OTf)_2$ and 11 mol % of **PFAM1**.[43]

To test the catalytic performance of **FAM** ligands, we have also studied aza-Henry reaction using Et_2Zn as the metal source. After optimization studies, different substrates on the aromatic ring of the Boc-imines provided the products in 21-93 % yield with no selectivity or low selectivity except the phenyl case which formed the product in 77 % ee.

Reaction of imines with nitroethane was also studied. The products were isolated in acceptable yields (54-91 %) with reasonable diastereoselectivity favoring the *anti*-product. The enantioselectivities of the major isomers were in the range of 34-86 %.

CHAPTER 6

EXPERIMENTAL SECTION

6.1 General consideratation

6.1.1 Materials and instrumentation

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. All solvents were freshly distilled. Products were purified by flash column chromatography on Silica Gel 60 (Merck, 230–400 mesh ASTM). TLC analyses were performed on 250 lm Silica Gel 60 F254 plates. Enantiomeric excess (ee) was determined by chiral HPLC analysis using a chiral stationary phase. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR samples were prepared in $CDCl_3$ and recorded at 400 MHz, 100 MHz and 162 MHz, respectively. ^{1}H NMR data are reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ0.00).

6.2 General procedures

6.2.1 General procedure A. Procedure for the ring opening reaction of aziridine-2-phosphonate with HCl.

HCl (*g*) was generated by slow addition of concentrated HCl (37 %) over concentrated H_2SO_4 (98 %). The *in situ* formed HCl gas was then bubbled into the solution of aziridine-2-phosphonates (200 mg) in diethyl ether (3 mL) at room temperature for about five min at which point the solution became cloudy. Evaporation of diethyl ether gave the highly viscous oily crude β-chloro-α-aminophosphonates **4a-n** which were crystallized from EtOAc-hexane.

6.2.2 General procedure B. Procedure for the ring-opening reaction of aziridine-2-phosphonates with alcohols

Concentrated H_2SO_4 was added drop by drop (50 µl) to a solution of *N*-alkyl substituted aziridine-2-phosphonate (200 mg) in alcohols (3.5 ml) reported in Table 1. The mixture was heated at 80-85 °C until disappearance of the starting material as indicated by TLC. Crude product was purified by flash column chromatography on silica gel using EtOAc as the eluent. For the low boiling alcohols (MeOH, EtOH and ^{i}PrOH) solvent was removed by rotary evaporator and then the crude product was applied to the column. In the case of benzyl alcohol, allyl alcohol and propargyl alcohol, reaction mixture was applied directly to the column. Basic work-up by quenching the reaction mixture with saturated $NaHCO_3$ solution was also tried but the yields were not affected significantly.

6.2.3 General procedure C. Procedure for 1,3-dipolar cycloaddition reaction of azomethine ylides with dipolarophiles

Pre-dried Schlenk tube was charged with ligand and imine under nitrogen atmosphere, dissolved in a proper solvent, and cooled to 0 °C in ice-bath. After 15 mins of stirring silver acetate was added Schlenk tube was wrapped with aluminum foil to keep reaction mixture in the dark. After stirring additional 1-hour 4Å molecular sieves (previously activated by keeping 6-8 h in 100 °C oven) were added, followed by addition of dipolarophile. The resulting mixture was stirred for 2 additional hours at 0 °C and then ice-bath removed to let reaction mixture stir at room temperature for additional 18 hours. The product was purified by silica column chromatography.

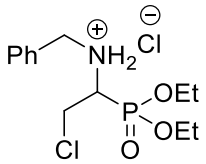
6.2.4 General procedure D: procedure for aza-Henry reaction of Boc-protected imines with nitroalkanes

Pre-dried Schlenk tube with activated 4Å molecular sieves (previously activated by keeping 6-8 h in 100 °C oven) was charged with ligand and Et_2Zn under nitrogen atmosphere, dissolved in a proper solvent, and cooled to 0 °C in cryostat. After 30 mins of stirring nitroalkane was added. After stirring additional 30 min imine was added. The resulting mixture was stirred for 20 additional hours at 0 °C. The product was purified by silica column chromatography.

6.3 Synthesis and characterization of aziridine-2-phosphonate ring-opening products

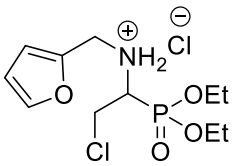
Aziridine ring-opening products **4a-n** were synthesized according to general procedure A, products **5aa-af**, **5ba-bf**, and **5fa-ff** were synthesized according to general procedure B.

6.3.1 Characterization of *N*-benzyl-2-chloro-1-(diethoxyphosphoryl)ethanaminium chloride (**4a**).



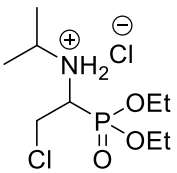
White solid, mp: 194–195 ºC. R_f=0.52 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.2–9.9 (broad singlet, 2H, $[HNH]^+Cl^-$), 7.90-7.68 (m, 2H), 7.50-7.33 (m, 3H), 4.56 (q, J = 13.3 Hz, 2H, benzylic CH_2), 4.40-4.11 (m, 6H), 3.54 (ddd, J =16.0, 6.1, 4.5 Hz, 1H, CHP), 1.39 (td, J = 7.1, 3.0 Hz, 6H, $POCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.6, 129.6, 129.2, 128.6, 64.0 (d, J_{C-P} = 6.8 Hz, $POCH_2$), 63.86 (d, J_{C-P} = 6.8 Hz, $POCH_2$), 52.5 (d, J_{C-P} = 151.5 Hz, CHP), 49.9, 39.7 (CH_2Cl), 16.3 (d, J_{C-P} = 5.4 Hz, $POCH_2CH_3$), 16.29 (d, J_{C-P} = 5.9 Hz, $POCH_2CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 15.3. IR (cm^{-1}): 2982, 2588, 1250, 1012, 976, 748. HRMS-EI (m/z): calculated for $C_{13}H_{22}Cl_2NO_3P$ [M-Cl]: 306.1020, found: 306.1026.

6.3.2 Characterization of 2-chloro-1-(diethoxyphosphoryl)-*N*-(furan-2-ylmethyl)ethanaminium chloride (**4b**).



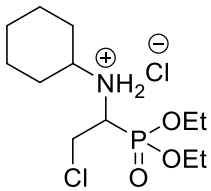
White solid, mp: 116–117 ºC. R_f = 0.50 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.50-9.80 (broad signals, 2H, $[HNH]^+Cl^-$), 7.49 (d, J = 1.2 Hz, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.43 (dd, J = 3.3, 1.8 Hz, 1H), 4.66 (q, J=14.8 Hz, 2H, furfuryl CH_2), 4.40- 4.28 (m, 4H, $POCH_2$), 4.24 (dd, J = 13.2, 4.9 Hz, 2H), 3.62 (dt, J = 15.9, 5.0 Hz, 1H, CHP), 1.41 (td, J = 7.0, 3.4 Hz, 6H, $POCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 144.0, 114.4, 111.1, 64.2 (d, J_{C-P} = 6.4 Hz, $POCH_2$), 53.1 (d, J_{C-P} = 151.8 Hz, CHP), 42.7 (d, J_{C-P} = 2.4 Hz, furfuryl CH_2), 39.7 (CH_2Cl), 16.3 (d, J_{C-P} = 5.4 Hz, $POCH_2CH_3$), 16.1 (d, J_{C-P} = 5.9 Hz, $POCH_2CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 15.1. IR (cm^{-1}): 2981, 2588, 1240, 1012, 746. HRMS-EI (m/z): calculated for $C_{11}H_{20}Cl_2NO_4P$ [M-Cl]: 296.0813, found: 296.0828.

6.3.3 Characterization of *N*-[2-chloro-1-(diethoxyphosphoryl)ethyl]propan-2-aminium chloride (**4c**).



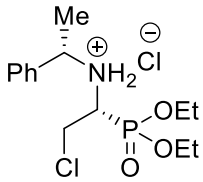
White solid, mp: 138–139 ºC. R_f = 0.47 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 and 8.78 (two broad signals, 2H, $[HNH]^+Cl^-$), 4.47-4.23 (m, 6H), 3.86 (dt, J = 12.7, 6.4Hz, 1H), 3.76 (dt, J = 14.9, 5.4 Hz, 1H, CHP), 1.61 (d, J = 6.5Hz, 3H, CH_3), 1.55 (d, J = 6.5Hz, 3H, CH_3), 1.42 (t, J = 7.0, 3H, $POCH_2CH_3$), 1.41 (t, J = 7.1, 3H, $POCH_2CH_3$). 13C NMR (100 MHz, $CDCl_3$): δ 64.5 (d, J_{C-P} = 6.7Hz, $POCH_2$), 64.2 (d, J_{C-P} = 6.7Hz, $POCH_2$), 54.0 (d, J_{C-P} = 153.1Hz, CHP), 52.1 (CHN), 39.9 (CH_2Cl), 19.9 (CH_3), 18.1 (CH_3), 16.3 (d, J_{C-P} = 5.3Hz, $POCH_2CH_3$), 16.2 (d, J_{C-P} = 5.4 Hz, $POCH_2CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.0. IR (cm^{-1}): 2989, 1252, 1003, 980, 800. HRMS-EI (m/z): calculated for $C_9H_{22}Cl_2NO_3P$ [M-Cl]: 258.1020, found: 258.1024.

6.3.4 Characterization of *N*-[2-chloro-1-(diethoxyphosphoryl)ethyl]cyclohexanaminium chloride (**4d**).



White solid, mp: 128–129 ºC. R_f = 0.57 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.79 and 8.90 (two broad signals, 2H, $[HNH]^+Cl^-$), 4.35-4.13 (m, 6H), 3.72 (dt, J = 15.0, 4.8 Hz, 1H), 3.48 (t, J = 9.7 Hz, 1H), 2.32 (d, J = 9.7Hz, 1H), 2.24 (d, J = 11.8 Hz, 1H), 1.94-1.76 (m, 4H), 1.67 (s, 1H), 1.33 (t, J = 7.0 Hz, 6H, $POCH_2CH_3$), 1.23-1.12 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.6 (d, $J_{C–P}$ = 6.9 Hz, $POCH_2$), 64.3 (d, $J_{C–P}$ = 6.8 Hz, $POCH_2$), 58.8, 53.4 (d, $J_{C–P}$ = 153.2 Hz, CHP), 40.1 (CH_2Cl), 30.1, 28.5, 24.8, 24.7, 16.45 (d, $J_{C–P}$ = 5.4 Hz, $POCH_2CH_3$), 16.41 (d, $J_{C–P}$ = 5.7 Hz, $POCH_2CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 15.7. IR (cm^{-1}): 2937, 1440, 1253, 1009, 964.HRMS-EI (m/z): calculated for $C_{12}H_{26}Cl_2NO_3P$ [M-Cl]: 298.1333, found: 298.1342.

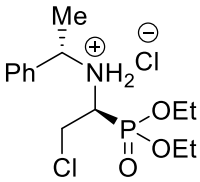
6.3.5 Characterization of (*R*)-2-chloro-1-(diethoxyphosphoryl)-*N*-[(*S*)-1-phenylethyl]ethanaminium chloride (**4e**).



White solid, mp: 70–71 °C. *Rf* = 0.58 (EtOAc). $[\alpha]_D^9$ = –29.86 (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0-10.2 (broad signals, 2H, $[HNH]^+Cl^-$), 7.82 (d, J = 7.1 Hz, 2H), 7.50-7.37 (m, 3H), 5.06 (q, J = 6.4 Hz, 1H, CHN), 4.41 (dq, J = 14.2, 7.1 Hz, 2H, $POCH_2$), 4.35-4.26 (m, 1H), 4.26-4.12 (m, 2H, $POCH_2$), 3.25 (dt, J = 13.6, 5.5 Hz, 1H, CHP), 2.06 (d, J = 6.8 Hz, 3H, CH_3), 1.43 (t, J = 7.0 Hz, 3H, $POCH_2CH_3$), 1.35 (t, J = 7.0 Hz, 3H, $POCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 129.0 (d, $J_{C–P}$ = 13.9 Hz), 128.2 (d, $J_{C–P}$ = 4.1 Hz), 126.0, 64.2 (d, $J_{C–P}$ = 6.7 Hz, $POCH_2$), 63.4 (d, $J_{C–P}$ = 6.6 Hz, $POCH_2$), 59.2 (CHN), 54.1 (d, $J_{C–P}$ = 152.1 Hz, CHP), 40.0 (CH_2Cl), 21.1, 16.2 (d, $J_{C–P}$ = 6.6 Hz, $POCH_2CH_3$), 16.1 (d, $J_{C–P}$ = 6.6 Hz, $POCH_2CH_3$). ^{31}P NMR

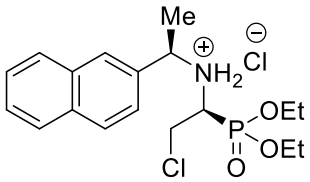
(162 MHz, $CDCl_3$): δ 15.6. IR (cm^{-1}): 2992, 2581, 1251, 1012, 975, 702. HRMS-EI (m/z): calculated for $C_{14}H_{24}Cl_2NO_3P$ [M–Cl]: 320.1177, found: 320.1184.

6.3.6 Characterization of (*S*)-2-chloro-1-(diethoxyphosphoryl)-*N*-[(*S*)-1-phenylethyl]ethanaminium chloride (**4f**).



White crystal (84 % yield), mp: 119.4 °C. *Rf* = 0.67 (EtOAc). $[\alpha]_D^{22}$ = –16 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.9 Hz, 2H), 7.56–7.33 (m, 3H), 4.87 (q, *J* = 6.8 Hz, 1H, –CHPh), 4.47 (td, *J* = 6.7, 12.2 Hz, 1H, $–CH_2Cl$), 4.43–4.13 (m, 4H, $–OCH_2CH_3$), 3.98 (td, *J* = 6.4, 12.4 Hz, 1H, $–CH_2Cl$), 3.62 (dt, *J* = 5.9, 17.5 Hz, 1H, $–CHP(OEt)_2$), 1.96 (d, *J* = 6.8 Hz, 3H, $–CH_3$), 1.38 (t, *J* = 7.0 Hz, 3H, $–OCH_2CH_3$), 1.36 (t, *J* = 7.0 Hz, 3H, $–OCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 129.7, 129.3 (2CH), 128.6 (2CH), 64.7 (d, $J_{C–P}$ = 6.8 Hz, $–OCH_2CH_3$), 64.3 (d, $J_{C–P}$ = 6.9 Hz, $–OCH_2CH_3$), 60.3 (d, $J_{C–P}$ = 4.4 Hz, $–CH_2Cl$), 54.4 (d, $J_{C–P}$ = 149.9 Hz, $–CHPO(OEt)_2$), 39.4 (–CHPh), 20.3 ($–CH_3$), 16.4 (d, $J_{C–P}$ = 5.7 Hz, $–OCH_2CH_3$), 16.3 (d, $J_{C–P}$ = 5.7 Hz, $–OCH_2CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.7. IR (cm^{-1}): 3064, 2981, 2187, 2125, 2013, 1248, 1224, 993, 703. HRMS-EI (m/z): calculated for $C_{14}H_{24}Cl_2NO_3P$ [M^+]: 355.0871 and found: 355.0866.

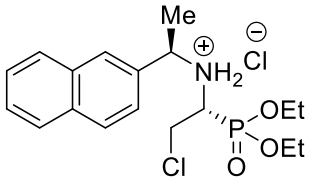
6.3.7 Characterization of (*S*)-2-chloro-1-(diethoxyphosphoryl)-*N*-[(*R*)-1-(naphthalen-2-yl)ethyl]ethanaminium chloride (**4g**).



Viscous oil. R_f = 0.6 (EtOAc). $[\alpha]_D^{10}$ = +3.1 (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.4-10.0 (broad signal, 2H, $[HNH]^+Cl^–$), 8.18-7.94 (m, 3H), 7.89 (dd, *J* = 9.2, 6.2 Hz, 2H), 7.58-7.52 (m, 2H), 5.20 (q, *J* = 7.7 Hz, 1H, CHN), 4.52-4.37 (m, 2H), 4.30-4.05 (m, 4H, $POCH_2$), 3.26 (dt, *J* = 13.3, 5.4 Hz, 1H), 2.10 (d, *J* = 3.7 Hz, 3H, CH_3), 1.45 (t, *J* = 7.0 Hz, 3H, $POCH_2CH_3$), 1.31 (t, *J* = 7.0 Hz, 3H, $POCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.3, 133.5,

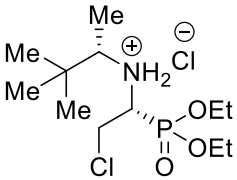
133.0, 129.6, 128.6, 128.1, 127.7, 126.8, 126.6, 124.7, 64.5 (d, J_{C-P} = 6.9 Hz, $POCH_2$), 63.6 (d, J_{C-P} = 6.7 Hz, $POCH_2$), 59.6 (CHN), 54.4 (d, J_{C-P} = 152.0 Hz, CHP), 40.3 (CH_2Cl), 21.3 (CH_3), 16.4 (d, J_{C-P} = 5.6 Hz, $POCH_2CH_3$), 16.3 (d, J_{C-P} = 5.4 Hz, $POCH_2CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.1. IR (cm^{-1}): 2980, 2598, 1249, 1013, 976, 747. HRMS-EI (m/z): calculated for $C_{18}H_{26}Cl_2NO_3P$ [M–Cl]: 370.1333, found: 370.1350.

6.3.8 Characterization of (*R*)-2-chloro-1-(diethoxyphosphoryl)-*N*-[(*R*)-1-(naphthalen-2-yl)ethyl]ethanaminium chloride (**4h**).



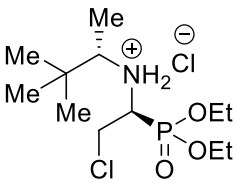
Viscous oil. R_f = 0.65 (EtOAc). $[\alpha]_D^{31}$ = +25.9 (c = 0.043, MeOH), ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.90-7.86 (m, 2H), 7.48 (dd, *J* = 8.5, 1.4 Hz, 2H), 4.99 (q, *J* = 5.7 Hz, 1H, CHN), 4.51 (dd, *J* = 17.6, 11.5 Hz, 1H), 4.35-4.25 (m, 2H, $POCH_2$), 4.16 (dq, *J* = 14.2, 7.1 Hz, 2H, $POCH_2$), 4.05 (td, *J* = 13.2, 4.6 Hz, 1H), 3.57 (ddd, *J* = 17.9, 6.4, 4.9 Hz, 1H, CHP), 1.97 (d, *J* = 6.6 Hz, 3H, CH_3), 1.37 (t, *J* = 7.0 Hz, 3H, $POCH_2CH_3$), 1.29 (t, *J* =7.0 Hz, 3H, $POCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 133.3, 132.9, 129.2, 128.3, 128.0, 127.5, 126.8, 126.5, 124.8, 64.4 (d, J_{C-P} = 6.9 Hz, $POCH_2$), 64.0 (d, J_{C-P} = 6.9 Hz, $POCH_2$), 59.9 (d, J_{C-P} = 5.4 Hz, CHN), 54.1 (d, J_{C-P} = 151.1 Hz, CHP), 39.5 (CH_2Cl), 20.4 (CH_3), 16.1 (t, J_{C-P} = 6.1 Hz, $POCH_2CH_3$ x2). ^{31}P NMR (162 MHz, $CDCl_3$): δ 15.9. IR (cm^{-1}): 2980, 1235, 1039, 951, 745. HRMS-EI (m/z): calculated for $C_{18}H_{26}Cl_2NO_3P$ [M–HCl] [Na]: 392.1158, found: 392.1148.

6.3.9 Characterization of (*R*)-*N*-[(*S*)-2-chloro-1-(diethoxyphosphoryl)ethyl]-3,3-dimethylbutan-2-aminium chloride (**4i**).



Viscous oil, R_f = 0.70 (EtOAc), $[\alpha]_D^{31}$= +21.4 (c = 0.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ4.17-4.07 (m, 4H, $POCH_2$), 3.81 (ddd, *J* = 15.9, 11.6, 4.3 Hz, 1H), 3.71-3.64 (m, 1H), 3.30 (dt, *J* = 20.1, 4.5 Hz, 1H), 2.48 (dd, *J* = 12.6, 6.3 Hz), 1.27 (t, *J* = 7.0 Hz, 6H, $POCH_2CH_3$), 0.91 (d, *J* = 6.4 Hz, 3H, CH_3), 0.84 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ62.9 (d, $J_{C–P}$ = 7.0 Hz, $POCH_2$), 62.5 (d, $J_{C–P}$ = 6.5 Hz, $POCH_2$), 59.7 (d, $J_{C–P}$ = 11.0 Hz, CHN), 54.7 (d, $J_{C–P}$ = 157.1 Hz, CHP), 43.6 (d, $J_{C–P}$ = 5.1 Hz, CH_2Cl), 34.4, 26.3 ($C(CH_3)_3$), 16.4 (d, $J_{C–P}$ = 4.9 Hz, $POCH_2CH_3$ x2), 14.7 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ15.99. IR (cm^{-1}): 2970, 1242, 1024, 965,749. HRMS-EI (m/z): calculated for $C_{12}H_{28}Cl_2NO_3P$ [M–Cl]: 300.1495, found: 300.1484.

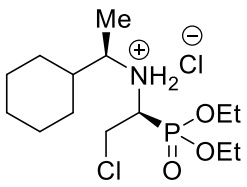
6.3.10 Characterization of (*R*)-*N*-[(*R*)-2-chloro-1-(diethoxyphosphoryl)ethyl]-3,3-dimethylbutan-2-aminium chloride (**4j**).



White solid, mp: 275–276 °C. Rf = 0.67 (EtOAc). $[\alpha]_D^9$ = –32.48 (c = 0.043, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ4.95-4.86 (m, 1H), 4.41-4.32 (m, 3H), 4.32-4.24 (m, 2H), 4.10 (d, *J* = 13.2 Hz, 1H), 3.43 (dd, *J* = 12.4, 5.9 Hz, 1H), 1.51 (d, *J* = 6.6 Hz, 3H, CH_3), 1.42 (q, *J* = 6.8 Hz, 6H, $POCH_2CH_3$ x2), 1.17 (s, *J* = 4.8 Hz, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ64.6 (d, $J_{C–P}$ = 6.8 Hz, $POCH_2$), 64.3, 63.7 (d, $J_{C–P}$ = 6.8 Hz, $POCH_2$), 53.7 (d, $J_{C–P}$ = 154.9 Hz, CHP), 41.4 (d, $J_{C–P}$ = 4.1 Hz, CH_2Cl), 34.0, 26.0 ($C(CH_3)_3$), 16.1 (d, $J_{C–P}$ = 4.6 Hz, $POCH_2CH_3$), 16.0 (d, $J_{C–P}$ = 4.8 Hz, $POCH_2CH_3$), 11.0. ^{31}P NMR (162 MHz,

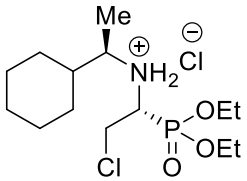
$CDCl_3$): δ 16.1. IR (cm^{-1}): 2973, 2648, 1250, 1013, 980, 763. HRMS-EI (m/z): calculated for $C_{12}H_{28}Cl_2NO_3P$ [M–Cl]: 300.1490, found: 300.1498.

6.3.11 Characterization of (*S*)-2-chloro-*N*-[(*R*)-(1-cyclohexylethyl)-1-(diethoxyphosphoryl)]ethanaminium chloride (**4k**).



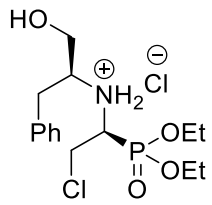
White solid, mp: 182–183 °C. R_f = 0.55 (EtOAc), $[\alpha]_D^{31}$= +14.1 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.29-8.99 (broad signal, 2H, $[HNH]^+Cl^-$), 4.57-4.06 (m, 6H, including $POCH_2$), 3.75 (ddd, J = 11.8, 9.0, 5.9 Hz, 1H), 3.55 (s, 1H), 2.02-1.62 (m, 6H), 1.49-1.36 (m, 9H), 1.35-1.23 (m, 2H), 1.20-1.05 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.7 (d, $J_{C–P}$ = 6.8 Hz, $POCH_2$), 62.4 (d, $J_{C–P}$ = 7.3 Hz, $POCH_2$), 55.5 (d, $J_{C–P}$ = 9.1 Hz, CHN), 53.9 (d, $J_{C–P}$ = 156.1 Hz, CHP), 43.6 (d, $J_{C–P}$ = 6.4 Hz, CH_2Cl), 42.3, 29.4, 27.4, 26.4, 26.2, 26.1, 16.2 (d, $J_{C–P}$ = 7.4 Hz, $POCH_2CH_3$ x2). ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.7. IR (cm^{-1}): 2924, 1240, 1021, 964. HRMS-EI (m/z): calculated for $C_{14}H_{30}Cl_2NO_3P$ [M–Cl]: 326.1646, found: 326.1639.

6.3.12 Characterization of (*R*)-2-chloro-*N*-[(*R*)-(1-cyclohexylethyl)-1-(diethoxyphosphoryl)]ethanaminium chloride (**4l**).



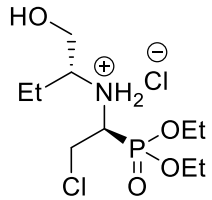
White solid, mp: 101–102 °C. R_f = 0.60 (EtOAc), $[\alpha]_D^{33}$= +0.21 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68-4.48 (m, 1H), 4.45-4.16 (m, 5H), 3.95 (dd, J = 9.9, 4.5 Hz, 1H), 3.49-3.38 (m, 1H), 2.00-1.60 (m, 6H), 1.57-0.96 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.3 (d, $J_{C–P}$ = 6.7 Hz, $POCH_2$), 62.2 (d, $J_{C–P}$ = 6.9 Hz, $POCH_2$), 55.8 (d, $J_{C–P}$ = 5.4 Hz), 54.4 (d, $J_{C–P}$ = 156.8 Hz, CHP), 44.1, 42.7, 29.2, 27.4, 26.2, 26.1, 26.0, 16.2, 16.1 (d, $J_{C–P}$ = 4.5 Hz, $POCH_2CH_3$ x2). ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.4. IR (cm^{-1}): 2925, 1239, 1022, 964. HRMS-EI (m/z): calculated for $C_{14}H_{30}Cl_2NO_3P$ [M–Cl]: 326.1646, found: 326.1663.

6.3.13 Characterization of (*S*)-*N*-[(*S*)-2-chloro-1-(diethoxyphosphoryl)ethyl]-1-hydroxy-3-phenylpropan-2-aminium chloride (**4m**).



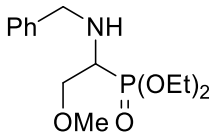
Viscous oil, R_f = 0.29 (EtOAc), $[\alpha]_D^{34}$= –17.7 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H), 4.45-4.05 (m, 6H), 4.03-3.77 (m, 4H), 3.34 (dd, J = 13.7, 6.6 Hz, 1H), 3.16 (dd, J = 13.6, 8.2 Hz, 1H), 1.37 (t, J = 7.0 Hz, 3H, $POCH_2CH_3$), 1.32 (t, J = 7.0 Hz, 3H, $POCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 129.1 (CH x2), 128.7 (CH x2), 127.0, 64.3 (d, $J_{C–P}$ = 6.9 Hz, $POCH_2$), 63.9 (d, $J_{C–P}$ = 6.8 Hz, $POCH_2$), 62.0, 59.0, 54.2 (d, $J_{C–P}$ = 152.3 Hz, CHP), 40.8, 34.8, 16.0 (d, $J_{C–P}$ = 5.6 Hz, $POCH_2CH_3$ x2). ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.0. IR (cm^{-1}): 3314, 2982, 1240, 1014, 977, 702. HRMS-EI (m/z): calculated for $C_{15}H_{26}Cl_2NO_4P$ [M–Cl]: 350.1282, found: 350.1299.

6.3.14 Characterization of (*R*)-*N*-[(*S*)-2-chloro-1-(diethoxyphosphoryl)ethyl]-1-hydroxybutan-2-aminium chloride (**4n**).



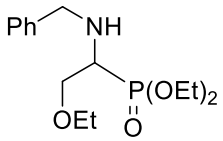
Viscous oil, R_f = 0.22 (EtOAc). $[\alpha]_D^{34}$= –14.86 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49-4.22 (m, 6H), 3.99 (d, J = 5.1 Hz, 2H), 3.93 (d, J = 14.4 Hz, 1H), 3.58 (s, 1H), 2.02-1.88 (m, 2H), 1.42 (t, J = 6.8 Hz, 3H, $POCH_2CH_3$), 1.41 (t, J = 6.9 Hz, 3H, $POCH_2CH_3$), 1.03 (t, J = 7.1Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.4 (d, $J_{C–P}$ = 6.4Hz, $POCH_2$), 64.2 (d, $J_{C–P}$ = 7.1 Hz, $POCH_2$), 62.6, 59.5, 53.1 (d, $J_{C–P}$ = 150.8 Hz, CHP), 40.6, 20.1, 16.0 (d, $J_{C–P}$ = 5.7 Hz, $POCH_2CH_3$ x2), 10.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ 15.2. IR (cm^{-1}): 3288, 2974, 1243, 1013, 977, 794. HRMS-EI (m/z): calculated for $C_{10}H_{24}Cl_2NO_4P$ [M–Cl]: 288.1126, found: 288.1138.

6.3.15 Characterization of diethyl 1-(benzylamino)-2-methoxyethylphosphonate (**5aa**).



Oily compound, R_f = 0.66 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.29 (4 H m), 7.26–7.21 (1 H, m), 4.21–4.10 (4 H, m, $(OCH_2CH_3)_2$), 3.98 (2H, dd, J = 31.6, 13.3 Hz, CH_2Ph), 3.74–3.58 (2H, m, CH_2OMe), 3.33 (3H, s, OCH_3), 3.14 (1H, ddd, J = 14.6, 6.4, 3.7 Hz, CHPO), 1.68 (1H, br. s, NH), 1.34 (6H, dt, J = 1.5, 7.1 Hz, $(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (C), 128.1 (2xCH), 128.0 (2xCH), 126.8 (CH), 70.8 (d, $J_{C–P}$ = 3.3 Hz, CH_2OMe), 61.95 (d, $J_{C–P}$ = 6.7 Hz, $PO(OCH_2CH_3)_2$), 61.91 (d, $J_{C–P}$ = 6.9 Hz, $PO(OCH_2CH_3)_2$), 58.6 (OCH_3), 54.40 (d, $J_{C–P}$ = 154.1 Hz, CHPO), 52.0 (d, $J_{C–P}$ = 7.4 Hz, CH_2Ph), 16.2 (d, $J_{C–P}$ = 5.8 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.6. IR (cm^{-1}): 3449, 2981, 2905, 2852, 1233, 1019, 959, 736. HRMS-EI (m/z): calculated for $C_{14}H_{25}NO_4P$ [M+H]: 302.1521 and found: 302.1529.

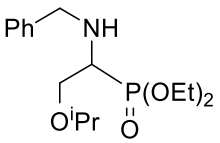
6.3.16 Characterization of diethyl 1-(benzylamino)-2-ethoxyethylphosphonate (**5ab**).



Oily compound, R_f = 0.53 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.25 (5H, m), 4.26–4.10 (4H, m, $(PO(OCH_2CH_3)_2)$, 3.99 (2H, dd, J = 32.3, 13.4 Hz, CH_2Ph), 3.81–3.60 (2H, m, $CH_2OCH_2CH_3$), 3.47 (2H, q, J = 7.0 Hz, CH_3CH_2O), 3.15 (H, ddd, J = 14.2, 6.6, 3.6 Hz, CHPO), 2.60 (1H, br. s, NH), 1.33 (6H, dt, J = 1.5, 7.1 Hz, $(OCH_2CH_3)_2$), 1.18 (3H, t, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (C), 128.0 (4xCH), 127.0 (CH), 68.5 (d, $J_{C–P}$ = 3.4 Hz, $CH_2OCH_2CH_3$), 66.1 (OCH_2CH_3), 61.9 (t, $J_{C–P}$ = 8.1 Hz, $PO(OCH_2CH_3)_2$), 54.3 (d, $J_{C–P}$ = 154.3 Hz, CHPO), 51.9 (d, $J_{C–P}$ = 7.4 Hz, CH_2Ph), 16.14 (d, $J_{C–P}$ = 5.6 Hz, $PO(OCH_2CH_3)_2$), 16.12 (d, $J_{C–P}$ = 5.8 Hz, $PO(OCH_2CH_3)_2$), 14.7 (CH_3CH_2O). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.8. IR (cm^{-1}): 3451, 2977, 2868, 1236, 1020, 958,

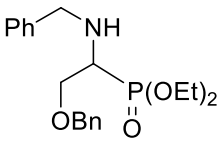
699. HRMS-EI (m/z): calculated for $C_{15}H_{27}NO_4P$ [M+H]: 316.1678 and found: 316.1671.

6.3.17 Characterization of diethyl 1-(benzylamino)-2-isopropoxyethylphosphonate (**5ac**).



Oily compound, R_f = 0.60 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.27 (5H, m), 4.23–4.12 (4H, m, $PO(OCH_2CH_3)_2$), 3.98 (2H, dd, J = 28.7, 13.2 Hz, CH_2Ph), 3.75 (1H, ddd, J = 16.6, 9.8, 3.6 Hz, $CH_2OCH(CH_3)_2$), 3.67–3.53 (2H, m, $CH_2OCH(CH_3)_2$ and $OCH(CH_3)_2$), 3.15 (1H, ddd, J = 14.1, 6.6, 3.6 Hz, CHPO), 2.72 (1H, br. s, NH), 1.33 (6H, dt, J = 0.8, 7.1 Hz, $PO(OCH_2CH_3)_2$), 1.16 (3H, d, J = 4.4 Hz, $OCH(CH_3)_2$), 1.14 (3H, d, J = 4.4 Hz, $OCH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0 (C), 128.2 (4xCH), 126.9 (CH), 72.0 ($OCH(CH_3)_2$), 66.4 (d, $J_{C–P}$ = 3.7 Hz, $CH_2OCH(CH_3)_2$), 62.10 (d, $J_{C–P}$ = 6.7 Hz, $PO(OCH_2CH_3)_2$), 62.06 (d, $J_{C–P}$ = 6.9 Hz, $PO(OCH_2CH_3)_2$), 55.0 (d, $J_{C–P}$ = 154.7 Hz, CHPO), 52.2 (d, $J_{C–P}$ = 7.5 Hz, CH_2Ph), 22.0 ($OCH(CH_3)_2$), 21.9 ($OCH(CH_3)_2$), 16.40 (d, $J_{C–P}$ = 5.6 Hz, $PO(OCH_2CH_3)_2$), 16.41 (d, $J_{C–P}$ = 5.8 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.9. IR (cm^{-1}): 3324, 2974, 1236, 1021, 959, 755, 699. HRMS-EI (m/z): calculated for $C_{16}H_{29}NO_4P$ [M+H]: 330.1834 and found: 330.1840.

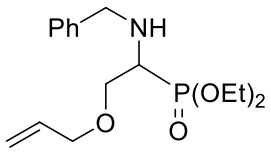
6.3.18 Characterization of diethyl 1-(benzylamino)-2-(benzoyloxy)ethylphosphonate (**5ad**).



Oily compound, R_f = 0.45 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.22 (10H, m), 4.52 (2 H, dd, J = 15.4, 13.2 Hz, OCH_2Ph), 4.20–4.07 (4H, m, $PO(OCH_2CH_3)_2$), 3.97 (2 H, dd, J = 21.1, 13.3 Hz, $NHCH_2Ph$), 3.81 (1H, ddd, J = 16.9, 10.0, 3.6 Hz, CH_2OCH_2Ph), 3.72 (1H, dt, J = 9.9, 6.5 Hz,

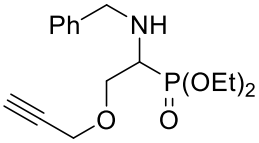
CH_2OCH_2Ph), 3.18 (1H, ddd, J = 15.0, 6.4, 3.6 Hz, CHPO), 1.95 (1H, br. s, NH), 1.30 (6H, dt, J = 8.6, 7.1 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8 (C), 137.8 (C), 128.3, 128.2, 127.6, 126.9, 73.1 (OCH_2Ph), 68.6 (d, J_{C-P} = 3.4 Hz, CH_2OCH_2Ph), 62.2 (d, J_{C-P} = 6.8 Hz, $PO(OCH_2CH_3)_2$), 62.1 (d, J_{C-P} = 6.9 Hz, $PO(OCH_2CH_3)_2$), 54.6 (d, J_{C-P} = 154.7 Hz, CHPO), 52.1 (d, J_{C-P} = 7.8 Hz, CH_2Ph), 16.4 (d, J_{C-P} = 5.9 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.5. IR (cm^{-1}): 3324, 2980, 1238, 1021, 958, 735, 697. HRMS-EI (m/z): calculated for $C_{20}H_{29}NO_4P$ [M+H]: 378.1834 and found: 378.1835.

6.3.19 Characterization of diethyl 2-(allyloxy)-1-(benzylamino)ethylphosphonate (**5ae**).



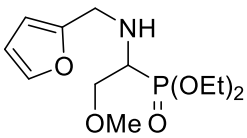
Oily compound, R_f = 0.34 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.28 (4H, m), 7.28–7.21 (1H, m), 5.88 (1H, ddt, J = 16.0, 10.8, 5.6 Hz, CH_2CHCH_2O), 5.27 (1H, dd, J = 17.3, 1.6 Hz, CH_2CHCH_2O), 5.18 (1H, d, J = 10.4 Hz, CH_2CHCH_2O), 4.21–4.10 (1H, m, $PO(OCH_2CH_3)_2$), 4.05–3.92 (4H, m, CH_2CHCH_2O and CH_2Ph), 3.76 (1H, ddd, J = 16.5, 10.0, 3.6 Hz, $CH_2Oallyl$), 3.67 (1H, dt, J = 10.0, 6.5 Hz, $CH_2Oallyl$), 3.16 (1H, ddd, J = 14.6, 6.5, 3.6 Hz, CHPO), 1.99 (1H, br. s, NH), 1.33 (3H, t, J = 7.0 Hz, $PO(OCH_2CH_3)_2$), 1.32 (3H, t, J = 7.1 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (C), 134.1, 128.1, 126.7, 116.9 (CH_2), 71.8 (OCH_2), 68.4 (d, J = 3.5 Hz, CH_2OCH_2 allyl), 61.9 (t, J_{C-P} = 6.9 Hz, $PO(OCH_2CH_3)_2$), 54.4 (d, J_{C-P} = 154.6 Hz, CHPO), 52.0 (d, J_{C-P} = 7.6 Hz, CH_2Ph), 16.29 (d, J_{C-P} = 5.7 Hz, $PO(OCH_2CH_3)_2$), 16.25 (d, J_{C-P} = 5.8 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.5. IR (cm^{-1}): 3324, 2980, 1237, 1021, 958, 736, 699. HRMS-EI (m/z): calculated for $C_{16}H_{27}NO_4P$ [M+H]: 328.1678 and found: 328.1685.

6.3.20 Characterization of diethyl 1-(benzylamino)-2-(prop-2-ynyloxy)ethylphosphonate (**5af**).



Oily compound, *Rf* = 0.42 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.29 (5H, m), 4.24–4.10 (6H, m, $PO(OCH_2CH_3)_2$ and CH_2OCH_2CCH), 4.01 (2H, dd, J = 19.6, 13.3 Hz, CH_2Ph), 3.89 (1H, ddd, J = 17.8, 9.8, 3.5 Hz, $HCCCH_2OCH_2$), 3.75 (1H, dt, J = 9.8, 6.3 Hz, $HCCCH_2OCH_2$), 3.16 (1H, ddd, J = 15.6, 6.2, 3.5 Hz, CHPO), 2.44 (1H, t, J = 2.4 Hz, HCCCH2O), 1.65 (1H, br. s, NH), 1.34 (6H, t, J = 7.0 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (C), 128.2 (4xCH), 126.9 (CH), 79.2 ($HCCCH_2O$), 74.7 ($HCCCH_2O$), 68.1 (d, J = 3.4 Hz, $HCCCH_2OCH_2$), 62.2 (d, $J_{C–P}$ = 6.9 Hz, $PO(OCH_2CH_3)_2$), 62.1 d, $J_{C–P}$ = 7.1 Hz, $PO(OCH_2CH_3)_2$), 58.2 ($HCCCH_2O$), 54.4 (d, $J_{C–P}$ = 154.7 Hz, CHPO), 51.9 (d, $J_{C–P}$ = 8.1 Hz, CH_2Ph), 16.39 (d, $J_{C–P}$ = 5.6 Hz, $PO(OCH_2CH_3)_2$), 16.37 (d, $J_{C–P}$ = 5.8 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.2. IR (cm^{-1}): 3288, 2981, 1232, 1019, 961, 735, 698. HRMS-EI (*m*/*z*): calculated for $C_{16}H_{25}NO_4P$ [M+H]: 326.1521 and found: 326.1530.

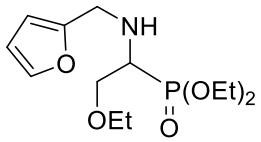
6.3.21 Characterization of diethyl 1-((furan-2-yl)methylamino)-2-methoxyethylphosphonate (**5ba**).



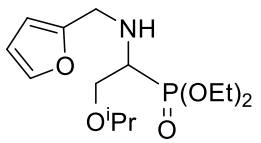
Dark yellow oil, *Rf* = 0.27 (EtOAc). ^{1}H NMR (400 MHz, acetone-*d6*): δ 7.47 (1H, dd, J = 1.9, 1.0 Hz), 6.35 (1H, dd, J = 3.2, 1.8 Hz), 6.27 (1H, d, J = 2.9 Hz), 4.17–4.03 (4H, m, $PO(OCH_2CH_3)_2$), 3.97 (2H, s, CH_2- furyl), 3.63 (1H, ddd, J = 12.5, 10.1, 3.6 Hz, CH_2CHPO), 3.53 (1H, ddd, J = 10.1, 7.5, 6.4 Hz, CH_2CHPO), 3.25 (3H, OCH_3), 3.15 (1H, ddd, J = 13.3, 7.5, 3.5 Hz, CHPO), 2.76 (1H, br. s, NH), 1.28 (3H, t, J = 7.1 Hz, $PO(OCH_2CH_3)_2$), 1.27 (3H, t, J = 7.1 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3 (C), 141.8 (CH), 110.1 (CH), 107.4 (CH), 71.0 (d, $J_{C–P}$ = 3.1 Hz, CH_2OCH_3), 62.3 (d, $J_{C–P}$ = 6.8 Hz,

$PO(OCH_2CH_3)_2$), 58.7 (OCH3), 54.08 (d, J_{C-P} = 155.4 Hz, CHPO), 44.9 (d, J_{C-P} = 7.3 Hz, CH_2-furyl), 16.42 (d, J_{C-P} = 5.7 Hz $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.4. IR (cm^{-1}): 3462, 2982, 1240, 1020, 960, 749. HRMS-EI (*m*/*z*): calculated for calculated for $C_{12}H_{23}NO_5P$ [M+H]: 292.1314 and found: 292.1303.

6.3.22 Characterization of diethyl 1-((furan-2-yl)methylamino)-2-ethoxyethylphosphonate (**5bb**).



Dark yellow oil, *Rf* = 0.32 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (1H, d, *J* = 1.7 Hz), 6.31 (1H, dd, *J* = 3.0, 1.9 Hz), 6.23 (1H, d, *J* = 3.0 Hz), 4.24–4.08 (4H, m, $PO(OCH_2CH_3)_2$), 3.98 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.74–3.60 (2H, m), 3.50–3.38 (2H, m), 3.19 (1H, ddd, *J* = 13.7, 6.4, 4.0 Hz, CHPO), 1.33 (6H, t, *J* = 7.0 Hz, $PO(OCH_2CH_3)_2$), 1.17 (3H, t, *J* = 7.0 Hz CH_3CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (C), 141.8 (CH), 110.0 (CH), 107.5 (CH), 68.6 (d, J_{C-P} = 3.0 Hz, $CH_3CH_2OCH_2$), 66.3 (CH_3CH_2O), 62.5 (d, J_{C-P} = 6.8 Hz, $PO(OCH_2CH_3)_2$), 62.4 (d, J_{C-P} = 7.0 Hz, $PO(OCH_2CH_3)_2$), 53.9 (d, J_{C-P} = 155.6 Hz, CHPO), 44.6 (d, J_{C-P} = 7.4 Hz, CH_2-furyl), 16.32 (d, J_{C-P} = 5.8 Hz, $PO(OCH_2CH_3)_2$), 16.30 (d, J_{C-P} = 5.8 Hz $PO(OCH_2CH_3)_2$), 14.9 (CH_3CH_2O). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.6. IR (cm^{-1}): 3330, 2978, 1242, 1018, 959, 736. HRMS-EI (*m*/*z*): calculated for calculated for $C_{13}H_{25}NO_5P$ [M+H]: 306.1470 and found: 306.1460.

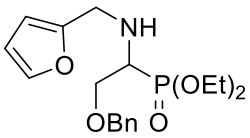


6.3.23 Characterization of diethyl 1-((furan-2-yl)methylamino)-2-isopropoxyethylphosphonate (**5bc**).

Dark yellow oil, *Rf* = 0.38 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (1H, s), 6.31 (1H, dd, *J* = 2.6, 2.0 Hz), 6.23 (1H, d, *J* = 3.0 Hz), 4.22–4.11 (4H, m, $PO(OCH_2CH_3)_2$), 4.00 (2H, dd, *J* = 25.5, 14.5 Hz, CH_2-furyl),

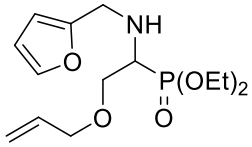
3.77–3.67 (1H, m, iPrOCH$_2$), 3.65–3.51 (2H, m, iPrOCH$_2$ and (CH$_3$)$_2$CHO), 3.20–3.11 (1H, m, CHPO), 2.72 (1H, br. s, NH), 1.33 (6H, t, J = 7.1, PO(OCH$_2$CH$_3$)$_2$), 1.14 (3H, d, J = 6.2 Hz, (CH$_3$)$_2$CHO), 1.10 (3H, d, J = 6.2 Hz, (CH$_3$)$_2$CHO). ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.0 (C), 141.8 (CH), 110.1 (CH), 107.5 (CH), 72.0 (CH$_3$)$_2$CHO), 66.1 (d, J_{C-P} = 2.5 Hz, (CH$_3$)$_2$CHOCH$_2$), 62.6 (d, J_{C-P} = 6.9 Hz, PO(OCH$_2$CH$_3$)$_2$), 62.4 (d, J_{C-P} = 6.8 Hz, PO(OCH$_2$CH$_3$)$_2$), 54.2 (d, J_{C-P} = 155.6 Hz, CHPO), 44.5 (d, J_{C-P} = 7.7 Hz, CH$_2$- furyl), 21.9 (CH$_3$)$_2$CHO), 21.7 (CH$_3$)$_2$CHO), 16.30 (d, J_{C-P} = 5.9 Hz PO(OCH$_2$CH$_3$)$_2$), 16.29 (d, J_{C-P} = 5.8 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (162 MHz, CDCl$_3$): δ 25.7. IR (ATR techniques, cm^{-1}): 3327, 2973, 1241, 1020, 959, 736. HRMS-EI (*m*/*z*): calculated for calculated for C$_{14}$H$_{27}$NO$_5$P [M+H]: 320.1627 and found: 320.1615.

6.3.24 Characterization of diethyl 1-((furan-2-yl)methylamino)-2-(benzyloxy)ethylphosphonate (**5bd**).



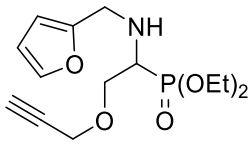
Dark yellow oil, *Rf* = 0.42 (EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39–7.28 (6H, m), 6.30 (1H, dd, J = 3.1, 1.9 Hz), 6.21 (1H, d, J = 2.6 Hz), 4.48 (2H, s, CH$_2$Ph), 4.18–4.09 (4H, m, PO(OCH$_2$CH$_3$)$_2$), 3.97 (2H, dd, J = 20.2, 14.6 Hz CH$_2$-furyl), 3.81–3.67 (2H, m, PhCH$_2$OCH$_2$), 3.22 (1H, ddd, J = 14.0, 6.7, 3.8 Hz, CHPO), 1.81 (1H, br. s, NH), 1.31 (3H, t, J = 7.1 Hz, PO(OCH$_2$CH$_3$)$_2$), 1.29 (3H, t, J = 7.1 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 153.2 (C), 141.7 (CH), 137.7 (C), 128.2 (CH), 127.5 (4xCH), 110.0 (CH), 107.0 (CH), 72.9 (PhCH$_2$O), 68.6 (BnOCH$_2$), 62.2 (d, J_{C-P} = 6.4 Hz, PO(OCH$_2$CH$_3$)$_2$), 62.1 (d, J_{C-P} = 6.6 Hz, PO(OCH$_2$CH$_3$)$_2$), 54.07 (d, J_{C-P} = 156.0 Hz, CHPO), 44.7 (d, J_{C-P} = 7.7 Hz, CH$_2$-furyl), 16.3 (d, J_{C-P} = 5.6 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (162 MHz, CDCl$_3$): δ 25.2. IR (cm^{-1}): 3329, 2981, 2906, 1241, 1020, 959, 735. HRMS-EI (*m*/*z*): calculated for calculated for C$_{18}$H$_{27}$NO$_5$P [M+H]: 368.1627 and found: 368.1610.

6.3.25 Characterization of diethyl 1-((furan-2-yl)methylamino)-2-(allyloxy)ethylphosphonate (**5be**).



Dark yellow oil, *Rf* = 0.32 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (1H, d, *J* = 1.0 Hz), 6.31 (1H, dd, *J* = 3.0, 1.9 Hz), 6.23 (1H, d, *J* = 3.0 Hz), 5.88 (1H, ddd, *J* = 22.8, 10.7, 5.6 Hz, CH_2CHCH_2O), 5.27 (1H, dd, *J* = 17.3, 1.6 Hz, CH_2CHCH_2O), 5.18 (1H, dd, *J* = 10.4, 1.3 Hz, CH_2CHCH_2O), 4.21–4.09 (4H, m, $PO(OCH_2CH_3)_2$), 4.00 (2H, dd, *J* = 20.9, 14.4 Hz, CH_2-furyl), 3.94 (2H, dd, *J* = 4.3, 1.3 Hz, CH_2CHCH_2O), 3.76–3.70 (1H, m, $CH_2CHCH_2OCH_2$), 3.70–3.61 (1H, m, $CH_2CHCH_2OCH_2$), 3.19 (1H, ddd, *J* = 13.8, 6.9, 3.7 Hz, CHPO), 2.07 (1H, br. s, NH), 1.33 (3H, t, *J* = 7.1, $PO(OCH_2CH_3)_2$), 1.32 (3H, t, *J* = 7.0, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (C), 141.7 (CH-furyl), 134.2 (OCH_2CHCH_2), 117.0 (OCH_2CHCH_2), 110.0 (CH-furyl), 107.3 (CH-furyl), 71.8 (OCH_2CHCH_2), 68.5 (d, J_{C-P} = 2.8 Hz, $CH_2OCH_2CHCH_2$), 62.21 (d, J_{C-P} = 6.5 Hz, $PO(OCH_2CH_3)_2$), 62.17 (d, J_{C-P} = 6.9 Hz, $PO(OCH_2CH_3)_2$), 54.0 (d, J_{C-P} = 155.9 Hz, CHPO), 44.7 (d, J_{C-P} = 7.4 Hz, CH_2-furyl), 16.3 (d, J_{C-P} = 5.2 Hz $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.3. IR (cm^{-1}): 3402, 2981, 2909, 1240, 1020, 961, 737. HRMS-EI (*m*/*z*): calculated for calculated for $C_{14}H_{25}NO_5P$ [M+H]: 318.1470 and found: 318.1472.

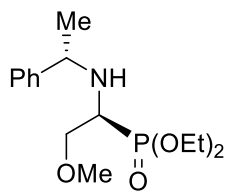
6.3.26 Characterization of diethyl 1-((furan-2-yl)methylamino)-2-(prop-2-ynyloxy)ethylphosphonate (**5bf**).



Dark yellow oil, *Rf* = 0.35 (EtOAc). ^{1}H NMR (400 MHz, acetone-*d6*): δ 7.46 (1H, dd, *J* = 1.9, 1.0 Hz), 6.35 (1H, dt, *J* = 3.9, 1.9 Hz), 6.29–6.24 (1H, m), 4.17 (2H, dd, *J* = 2.4, 1.0 Hz, $HCCCH_2O$), 4.16– 4.06 (4H, m, $PO(OCH_2CH_3)_2$), 3.97 (2H, s, CH_2-furyl), 3.84 (1H, ddd, *J* = 13.0, 10.0, 3.4 Hz, $HCCCH_2OCH_2$), 3.66 (1H, ddd, *J* = 10.0, 7.5, 6.1 Hz, $HCCCH_2OCH_2$), 3.16 (1H, ddd, *J* = 14.1, 7.5, 3.5

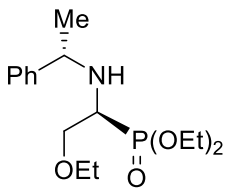
Hz, CHPO), 3.00 (1H, t, J = 2.4 Hz, $HCCCH_2O$), 2.84 (1H, br. s, NH), 1.28 (3H, t, J = 7.1 Hz, $PO(OCH_2CH_3)_2$), 1.27 (3H, t, J = 7.1 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (C), 141.8 (CH), 110.0 (CH), 107.4 (CH), 79.1 ($HCCCH_2O$), 74.8 ($HCCCH_2O$), 68.3 (d, $J_{C–P}$ = 3.2 Hz, $HCCCH_2OCH_2$), 62.33 (d, $J_{C–P}$ = 6.5 Hz, $PO(OCH_2CH_3)_2$), 62.29 (d, $J_{C–P}$ = 6.8 Hz, $PO(OCH_2CH_3)_2$), 58.2 ($HCCCH_2O$), 58.2 (d, $J_{C–P}$ = 155.8 Hz, CHPO), 44.7(d, $J_{C–P}$ = 8.0 Hz, CH_2-furyl), 16.4 (d, $J_{C–P}$ = 5.8 Hz $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.9. IR (cm^{-1}): 3290, 2910, 2982, 1237, 1018, 959, 737. HRMS-EI (*m*/*z*): calculated for calculated for $C_{14}H_{23}NO_5P$ [M+H]: 316.1314 and found: 316.1311.

6.3.27 Characterization of (*R*)-diethyl 1-((*S*)-1-phenylethylamino)-2-methoxyethylphosphonate (**5fa**).



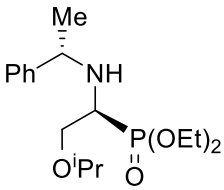
Oily compound, $[\alpha]_D^{29.7}$ = –42.5 (c = 0.025, $CHCl_3$), Rf = 0.49 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.22 (5H, m), 4.22–3.97 (5H, m, CHPh and $PO(OCH_2CH_3)_2$), 3.72 (1H, ddd, J = 25.4, 10.0, 3.6 Hz, CH_3OCH_2), 3.57 (1H, ddd, J = 10.0, 7.5, 4.1 Hz, CH_3OCH_2), 3.38 (3H, s, OCH_3), 2.93 (1H, dt, J = 21.0, 3.8 Hz, CHPO), 2.39 (1H, br. s, NH), 1.35 (3H, d, J = 6.5 Hz, CH_3), 1.32 (3H, t, J = 5.9 Hz, $PO(OCH_2CH_3)_2$), 1.29 (3H, t, J = 5.9, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (C), 128.0 (2xCH), 126.72 (2xCH), 126.70 (CH), 69.7 (CH_3OCH_2), 62.1 (d, $J_{C–P}$ = 6.5 Hz, $PO(OCH_2CH_3)_2$), 61.5 (d, $J_{C–P}$ = 6.7 Hz, $PO(OCH_2CH_3)_2$), 58.7 (OCH_3), 55.1 (d, $J_{C–P}$ = 14.2 Hz, CHPh), 52.3 (d, $J_{C–P}$ = 156.3 Hz, CHPO), 24.3 (CH_3), 16.1 (d, $J_{C–P}$ = 5.9 Hz, $PO(OCH_2CH_3)_2$), 16.0 (d, $J_{C–P}$ = 6.2 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.0. IR (cm^{-1}): 3447, 2978, 2927, 1239, 1022, 960, 701. HRMS-EI (*m*/*z*): calculated for $C_{15}H_{27}NO_4P$ [M+H]: 316.1678 and found: 316.1672.

6.3.28 Characterization of (*R*)-diethyl 1-((*S*)-1-phenylethylamino)-2-ethoxyethylphosphonate (**5fb**).



Oily compound, $[\alpha]_D^{29.6}$ = –43.2 (*c* = 0.025, $CHCl_3$), *Rf* = 0.52 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.21 (5H, m), 4.23–3.95 (5H, m, CHPh and $PO(OCH_2CH_3)_2$), 3.76 (1H, ddd, *J* = 24.3, 10.1, 3.6 Hz, $CH_3CH_2OCH_2$), 3.62 (1H, ddd, *J* = 10.1, 7.6, 4.4 Hz, $CH_3CH_2OCH_2$), 3.58–3.45 (2H, m, CH_3CH_2O), 2.95 (1H, dt, *J* = 20.7, 4.0 Hz, CHPO), 1.35 (3H, d, *J* = 6.5 Hz, CH_3), 1.32 (3H, t, *J* = 5.8 Hz, $PO(OCH_2CH_3)_2$), 1.29 (3H, t, *J* = 5.8, $PO(OCH_2CH_3)_2$), 1.21 (3H, t, *J* = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5 (C), 128.2 (2xCH), 127.0 (2xCH), 126.9 (CH), 67.7 (d, $J_{C–P}$ = 1.8 Hz, $CH_3CH_2OCH_2$), 66.6 (CH_3CH_2O), 62.4 (d, $J_{C–P}$ = 6.5 Hz, $PO(OCH_2CH_3)_2$), 61.7 (d, $J_{C–P}$ = 6.7 Hz, $PO(OCH_2CH_3)_2$), 55.3 (d, $J_{C–P}$ = 14.2 Hz, CHPh), 52.6 (d, $J_{C–P}$ = 156.4 Hz, CHPO), 24.5 (CH_3), 16.3 (d, $J_{C–P}$ = 5.9 Hz, $PO(OCH_2CH_3)_2$), 16.2 (d, $J_{C–P}$ = 6.3 Hz, $PO(OCH_2CH_3)_2$), 14.9 (CH_3CH_2O). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.3. IR (cm^{-1}): 3339, 2976, 2868, 1233, 1023, 959, 701. HRMS-EI (*m/z*): calculated for $C_{16}H_{29}NO_4P$ [M+H]: 330.1834 and found: 330.1830.

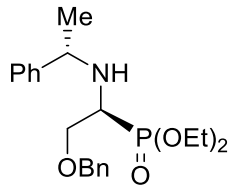
6.3.29 Characterization of (*R*)-diethyl 1-((*S*)-1-phenylethylamino)-2-isopropoxyethylphosphonate (**5fc**).



Oily compound, $[\alpha]_D^{22.4}$= –46.6 (*c* = 0.025, CHCl3), *Rf* = 0.57 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (5H, m), 4.20–3.96 (5H, m, CHPh and $PO(OCH_2CH_3)_2$), 3.75 (1H, ddd, *J* = 25.2, 9.9, 3.7 Hz, $iPrOCH_2$), 3.66–3.54 (2H, m, $iPrOCH_2$ and $(CH_3)_2CHO$), 2.92 (1H, dt, *J* = 20.6, 3.9 Hz, CHPO), 1.35 (3H, d, *J* = 6.5 Hz, CH_3), 1.32 (3H, t, *J* = 6.2 Hz, $PO(OCH_2CH_3)_2$), 1.29 (3H, t, *J* = 5.4, $PO(OCH_2CH_3)_2$), 1.18 (3H, d, *J* = 6.2 Hz, $(CH_3)_2CHO$), 1.16 (3H, d, *J* = 6.2 Hz, $(CH_3)_2CHO$). ^{13}C NMR (100 MHz, $CDCl_3$):

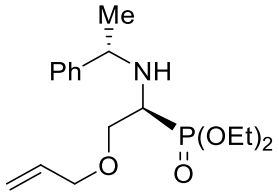
δ 144.6 (C), 128.2 (2xCH), 127.0 (2xCH), 126.9 (CH), 72.0 $(CH_3)_2CHO$), 65.2 (d, $J_{C–P}$ = 2.2 Hz, $CH_3)_2CHOCH_2$), 62.3 (d, $J_{C–P}$ = 6.4 Hz, $PO(OCH_2CH_3)_2$), 61.6 (d, $J_{C–P}$ = 6.7 Hz, $PO(OCH_2CH_3)_2$), 55.3 (d, $J_{C–P}$ = 14.2 Hz, CHPh), 52.8 (d, $J_{C–P}$ = 156.8 Hz, CHPO), 24.6 (CH_3), 21.9 $(CH_3)_2CHO$), 21.8 $(CH_3)_2CHO$), 16.3 (d, $J_{C–P}$ = 6.0 Hz, $PO(OCH_2CH_3)_2$), 16.2 (d, $J_{C–P}$ = 6.4 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.4. IR (cm^{-1}): 3446, 2972, 2928, 1240, 1024, 959, 701. HRMS-EI (*m*/*z*): calculated for $C_{17}H_{31}NO_4P$ [M+H]: 344.1991 and found: 344.1983.

6.3.30 Characterization of (*R*)-diethyl 1-((*S*)-1-phenylethylamino)-2-(benzoyloxy)ethylphosphonate (**5fd**).



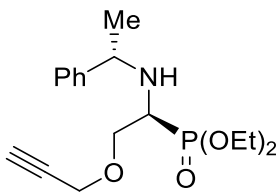
Light yellow oil, $[\alpha]_D^{29.8}$= –51.0 (*c* = 0.025, CHCl3), *Rf* = 0.61 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.22 (10H, m), 4.56 (2H, dd, *J* = 34.7, 12.1 Hz), 4.21–3.94 (5H, m, CHPh and $PO(OCH_2CH_3)_2$), 3.81 (1H, ddd, *J* = 25.7, 10.0, 3.6 Hz, CH_2OCH_2Ph), 3.67 (1H, ddd, *J* = 10.0, 7.5, 4.0 Hz, CH_2OCH_2Ph), 2.94 (1H, dt, *J* = 21.3, 3.7 Hz, CHPO), 2.26 (1H, br. s, NH), 1.32 (3H, d, *J* = 6.5 Hz, CH_3), 1.27 (6H, dd, *J* = 12.5, 7.0 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 137.9, 128.2 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 73.1 (OCH_2Ph), 67.1 ($BnOCH_2$), 62.5 (d, $J_{C–P}$ = 6.5 Hz, $PO(OCH_2CH_3)_2$), 61.8 (d, $J_{C–P}$ = 6.8 Hz, $PO(OCH_2CH_3)_2$), 55.2 (d, $J_{C–P}$ = 14.7 Hz, CHPh), 52.5 (d, $J_{C–P}$ = 157.2 Hz, CHPO), 24.6 (CH_3), 16.3 (d, $J_{C–P}$ = 6.1 Hz, $PO(OCH_2CH_3)_2$), 16.2 (d, $J_{C–P}$ = 6.3 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.9. IR (cm^{-1}): 3328, 2977, 2904, 1241, 1023, 960, 699. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{31}NO_4P$ [M+H]: 392.1991 and found: 392.1981.

6.3.31 Characterization of (*R*)-diethyl 1-((*S*)-1-phenylethylamino)-2-(allyloxy)ethylphosphonate (**5fe**).



Oily compound, $[\alpha]_D^{29.9}$= –43.56 (*c* = 0.025, CHCl3), *Rf* = 0.85 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.21 (5H, m), 5.91 (1H, ddd, *J* = 22.6, 10.7, 5.5 Hz, CH_2CHCH_2O), 5.30 (1H, dd, *J* = 17.2, 1.4 Hz, CH_2CHCH_2O), 5.20 (1H, d, *J* = 10.3 Hz, CH_2CHCH_2O), 4.22–3.96 (7H, m, OCH_2CHCH_2, CHPh and $PO(OCH_2CH_3)_2$), 3.79 (1H, ddd, *J* = 24.7, 10.0, 3.6 Hz, CH_2O-allyl), 3.68–3.59 (1H, m, CH_2O-allyl), 2.94 (1H, dt, *J* = 21.0, 3.8 Hz, CHPO), 2.19 (1H, br. s, NH), 1.36 (3H, d, *J* = 6.5 Hz, CH_3), 1.32 (3H, t, *J* = 5.6 Hz, $PO(OCH_2CH_3)_2$), 1.29 (3H, t, *J* = 5.6 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4 (C), 134.4 (CH_2CHCH_2O), 128.2 (CH), 126.0 (CH phenyl), 116.9 (CH_2CHCH_2O), 72.1 (CH_2CHCH_2O), 67.3 (CH_2Oallyl), 62.4 (d, J_{C-P} = 6.4 Hz, $PO(OCH_2CH_3)_2$), 61.7 (d, J_{C-P} = 6.7 Hz, $PO(OCH_2CH_3)_2$), 55.3 (d, J_{C-P} = 14.4 Hz, CHPh), 52.5 (d, J_{C-P} = 156.7 Hz, CHPO), 24.6 (CH_3), 16.4 (d, J_{C-P} = 6.0 Hz, $PO(OCH_2CH_3)_2$), 16.2 (d, J_{C-P} = 6.3 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.9. IR (cm^{-1}): 3404, 2980, 2929, 1205, 1020, 982, 765, 702. HRMS-EI (*m*/*z*): calculated for $C_{17}H_{29}NO_4P$ [M+H]: 342.1834 and found: 342.1837.

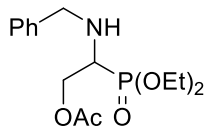
6.3.32 Characterization of (*R*)-diethyl 1-((*S*)-1-phenylethylamino)-2-(prop-2-ynyloxy)ethylphosphonate (**5ff**).



Oily compound, $[\alpha]_D^{22.6}$= –47.70 (*c* = 0.025, CHCl3), *Rf* = 0.60 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.21 (5H, m), 4.27–3.99 (7H, m, HCCCH2O, CHPh and ($PO(OCH_2CH_3)_2$), 3.92 (1H, ddd, *J* = 26.1, 9.8, 3.5 Hz, $HCCCH_2OCH_2$), 3.75–3.66 (1H, m, $HCCCH_2OCH_2$), 2.94 (1H, dt, *J* = 21.5, 3.7 Hz, CHPO), 2.46 (1H, t, *J* = 2.3 Hz, HCC), 1.80 (1H, br. s, NH), 1.36 (3H, d, *J* = 6.5 Hz, CH_3), 1.33 (3H, t, *J* = 7.1 Hz, $PO(OCH_2CH_3)_2$), 1.29 (3H, t, *J* = 6.8 Hz,

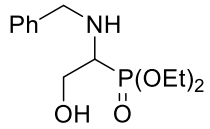
$PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4 (C), 128.3 (CH), 127.1 (CH), 79.4 ($HCCCH_2O$), 74.6 ($HCCCH_2O$), 67.0 (d, J_{C-P} = 2.2 Hz $HCCCH_2OCH_2$), 62.5 (d, J_{C-P} = 6.5 Hz, $PO(OCH_2CH_3)_2$), 61.9 (d, J_{C-P} = 6.7 Hz, $PO(OCH_2CH_3)_2$), 58.4 ($HCCCH_2O$), 55.3 (d, J_{C-P} = 14.6 Hz, CHPh), 52.4 (d, J_{C-P} = 157.4 Hz, CHPO), 24.7 (CH_3), 16.4 (d, J_{C-P} = 5.9 Hz, $PO(OCH_2CH_3)_2$), 16.3 (d, J_{C-P} = 6.2 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.5. IR (cm^{-1}): 3285, 2978, 2097, 1237, 1021, 962, 764, 701. HRMS-EI (*m/z*): calculated for $C_{17}H_{27}NO_4P$ [M+H]: 340.1678 and found: 340.1672.

6.3.33 Synthesis and characterization of diethyl 2-acetoxy-1-(benzylamino)ethylphosphonate (**6a**).



A solution of *N*-benzyl aziridine-2-phosphonate (200 mg) in acetic acid (2 ml) was heated until the disappearance of the starting compound (followed by TLC, 5-6 h). This reaction also works at room temperature at a longer time 16-18 h. The excess acetic acid was evaporated *in vacuo* and then the crude product was purified by column chromatography using EtOAc as the eluent to give compound **6a** in 96% yield as a colorless oil. *Rf* = 0.63 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.23 (5H, m), 4.44 (1H, ddd, *J* = 16.3, 11.6, 3.9 Hz, CH_3COOCH_2), 4.23 (1H, dt, *J* = 11.6, 6.9 Hz, CH_3COOCH_2), 4.20–4.12 (4H, m, $PO(OCH_2CH_3)_2$), 3.99 (2H, t, *J* = 13.7 Hz, CH_2Ph), 3.19 (1H, ddd, *J* = 16.8, 6.6, 3.8 Hz, CHPO), 2.06 (3H, s, $OCOCH_3$), 1.34 (6H, dt, *J* = 7.1, 2.9 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C=O), 139.5 (C), 128.4 (2xCH), 128.3 (2xCH), 127.1 (CH), 63.0 (d, J_{C-P} = 5.8 Hz, CH_2OCO), 62.4 (d, J_{C-P} = 4.9 Hz, $PO(OCH_2CH_3)_2$), 62.3 (d, J_{C-P} = 5.1 Hz, $PO(OCH_2CH_3)_2$), 53.5 (d, J_{C-P} = 152.6 Hz, CHPO), 52.1 (d, J_{C-P} = 8.0 Hz, CH_2Ph), 20.9 (CH_3CO), 16.5 (t, J_{C-P} = 5.4 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.7. IR (cm^{-1}): 3357, 2982, 2929, 1635, 1233, 1016, 960, 728. HRMS-EI (*m/z*): calculated for $C_{14}H_{24}NNaO_5P$ [M+Na]: 352.1295 and found: 352.1312.

6.3.34 Synthesis and characterization of diethyl 1-(benzylamino)-2-hydroxyethylphosphonate (**7a**).

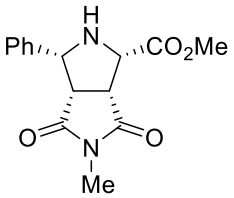


To a solution of *N*-benzyl aziridine-2-phosphonate (200 mg) in acetone (3 ml) was added CF_3COOH (0.1 ml). Then the mixture was stirred at room temperature overnight. In the morning tlc showed no starting material (about 16h). Solvent was evaporated *in vacuo* then the crude product was flash chromatographed on silica gel using EtOAc as the eluent to afford compound **7a** in 82% yield as a colorless oil. *Rf* = 0.43 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.24 (5H, m), 4.25–4.09 (4H, m, $PO(OCH_2CH_3)_2$), 3.96 (2H, dd, J = 39.7, 13.1 Hz, CH_2Ph), 3.82 (1H, ddd, J = 16.4, 11.4, 5.0 Hz, CH_2OH), 3.72 (1H, ddd, J = 11.4, 9.9, 6.2 Hz, CH_2OH), 3.02 (1H, ddd, J = 14.6, 6.2, 5.0 Hz, CHPO), 2.49 (1H, br. s, OH), 1.34 (6H, dd, J = 13.8, 6.9 Hz, $PO(OCH_2CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4 (C), 128.3 (2xCH), 128.2 (2xCH), 127.1 (CH), 62.4 (d, $J_{C–P}$ = 7.0 Hz, $PO(OCH_2CH_3)_2$), 62.1 (d, $J_{C–P}$ = 7.1 Hz, $PO(OCH_2CH_3)_2$), 60.0 (d, J = 4.3 Hz, CH_2OH), 55.7 (d, $J_{C–P}$ = 147.2 Hz, CHPO), 52.0 (d, $J_{C–P}$ = 6.9 Hz, CH_2Ph), 16.4 (t, $J_{C–P}$ = 5.7 Hz, $PO(OCH_2CH_3)_2$). ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.3. IR (cm^{-1}): 3339 (broad), 2980, 2924, 1217, 1020, 960, 735, 698. HRMS-EI (*m*/*z*): calculated for $C_{13}H_{23}NO_4P$ [M+H]: 288.1365 and found: 288.1369.

6.4 Synthesis and characterization of 1,3-dipolar cycloaddition reaction products

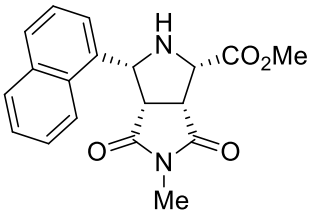
All 1,3-DC reaction products **15a-k**, **16a-k**, **17a-k**, and **18a-22a** were synthesized according to general procedure C. Relative configurations of cycloadducts previously not reported in the literature, were assigned in analogy with those already known, based on our judgement with regard to ^{1}H NMR, HPLC and polarimetry data.

6.4.1 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15a**)



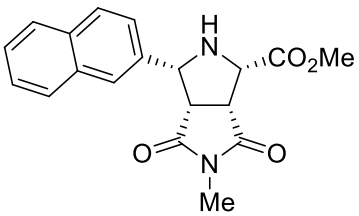
Data are identical with those reported in the literature.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 5H), 4.47 (d, J = 8.6 Hz, 1H), 4.03 (d, J = 6.8 Hz, 1H), 3.86 (s, 3H), 3.54 (t, J = 7.2 Hz, 1H), 3.41 (t, J = 8.1 Hz, 1H), 2.85 (s, 3H), 2.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.8, 170.2, 136.8, 128.5 (2xC), 128.4, 127.1 (2xC), 64.1, 61.7, 52.4, 49.5, 48.3, 25.1. HPLC (Chiralpak AS-H, 1 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 8.7 min, t_{Rmaj}= 13.3 min.

6.4.2 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-3-(naphthalen-1-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15b**)



Data are identical with those reported in the literature.[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 14.5, 8.3 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.52 (dt, J = 18.7, 6.9 Hz, 2H), 7.40 (t, J = 7.7 Hz, 1H), 4.95 (d, J = 8.3 Hz, 1H), 3.96 (d, J = 6.7 Hz, 1H), 3.88 (s, 3H), 3.53 (dt, J = 32.8, 7.6 Hz, 2H), 2.73 (s, 3H), 2.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 174.2, 170.3, 133.4, 133.2, 131.2, 129.1, 128.5, 126.4, 125.7, 125.5, 123.3, 122.3, 61.3, 59.7, 52.3, 47.9, 24.9. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 8.7 min, t_{Rmaj}= 18.4 min.

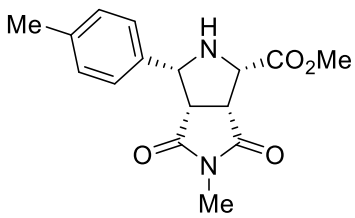
6.4.3 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-3-(naphthalen-2-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15c**)



Data are identical with those reported in the literature.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 6H), 7.48 – 7.40 (m, 4H), 4.60 (d, J = 8.5

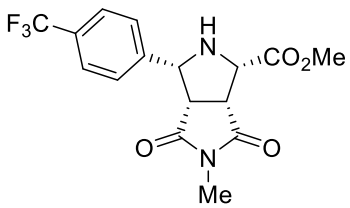
Hz, 1H), 4.06 (d, J = 6.5 Hz, 1H), 3.90 (s, 3H), 3.63 – 3.43 (m, 2H), 2.84 (s, 3H), 2.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 174.7, 170.3, 134.3, 133.4, 133.4, 128.1, 128.1, 127.9, 126.3, 126.2, 125.6, 125.4, 64.1, 61.8, 52.5, 49.4, 48.3, 25.1. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 10.8 min, t_{Rmaj}= 20.0 min.

6.4.4 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15d**)



Data are identical with those reported in the literature.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 4.43 (d, J = 8.6 Hz, 1H), 4.01 (d, J = 6.8 Hz, 1H), 3.86 (s, 3H), 3.53 (t, J = 7.2 Hz, 1H), 3.38 (t, J = 8.1 Hz, 1H), 2.86 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 174.9, 170.3, 138.0, 133.7, 129.2 (2xC), 127.0 (2xC), 64.0, 61.7, 52.4, 49.6, 48.3, 25.1, 21.3. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 70/30, λ 210 nm), t_{Rmin}= 22.6 min, t_{Rmaj}= 27.1 min.

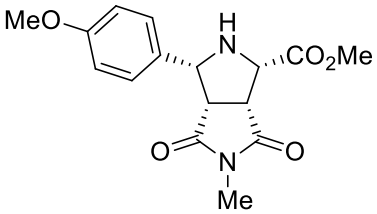
6.4.5 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-4,6-dioxo-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15e**)



White solid, mp: 231–232 °C. $[\alpha]_D^{22.7}$= –26.0 (c = 0.025, $CHCl_3$), Rf = 0.33 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 4.53 (d, J = 8.5 Hz, 1H), 4.07 (d, J = 6.9 Hz, 1H), 3.88 (s, 3H), 3.59 (t, J = 7.3 Hz, 1H), 3.47 (t, J = 8.1 Hz, 1H), 2.87 (s, 3H), 2.43 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 174.5, 170.0, 140.9, 127.6 (4xC), 125.3 (q, J = 3.6 Hz), 63.5, 61.7, 52.5, 49.3, 47.9, 25.2. IR (cm^{-1}): 3343, 3309, 2995, 2844, 1747, 1690, 1439, 1319, 1216, 1119, 821, 695. HRMS-EI (m/z):

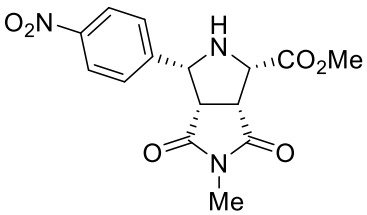
calculated for $C_{16}H_{16}F_3N_2O_4$ [M+H]: 357.1062 and found 357.1067. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 7.5 min, t_{Rmaj}= 11.5 min.

6.4.6 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(4-methoxyphenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15f**)



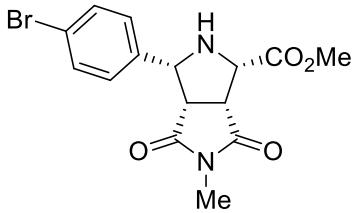
Data are identical with those reported in the literature.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 1H), 6.94 – 6.82 (m, 3H), 4.43 (d, *J* = 8.6 Hz, 1H), 4.01 (d, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.53 (t, *J* = 7.2 Hz, 1H), 3.40 (t, *J* = 8.1 Hz, 1H), 2.86 (s, 3H), 2.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.7, 170.2, 159.7, 138.5, 129.4, 119.4, 113.4, 113.0, 63.9, 61.6, 55.3, 52.3, 49.5, 48.2, 25.0. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 70/30, λ 210 nm), t_{Rmin}= 35.0 min, t_{Rmaj}= 43.6 min.

6.4.7 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-methyl-3-(4-nitrophenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15g**)



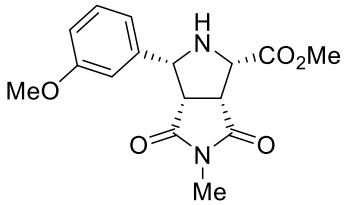
Data are identical with those reported in the literature.[65] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 4.59 (dd, *J* = 8.4, 4.6 Hz, 1H), 4.10 (dd, *J* = 6.8, 4.5 Hz, 1H), 3.89 (s, 3H), 3.61 (t, *J* = 7.3 Hz, 1H), 3.50 (t, *J* = 8.1 Hz, 1H), 2.87 (s, 3H), 2.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.8, 166.7, 148.0, 144.4, 128.2 (2xC), 123.8 (2xC), 63.1, 61.7, 52.6, 49.3, 47.7, 25.3. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 13.8 min, t_{Rmaj}= 18.8 min.

6.4.8 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(4-bromophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15h**)



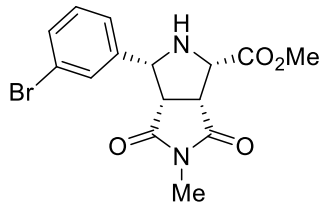
Data are identical with those reported in the literature.[65] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.45 (dd, J = 8.3, 4.7 Hz, 1H), 4.07 – 4.03 (m, 1H), 3.88 (s, 3H), 3.57 (t, J = 7.2 Hz, 1H), 3.42 (t, J = 8.1 Hz, 1H), 2.88 (s, 3H), 2.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 174.6, 170.1, 135.9, 131.6 (2xC), 128.9 (2xC), 122.2, 63.3, 61.6, 52.4, 49.2, 48.0, 25.1. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 9.9 min, t_{Rmaj}= 17.2 min.

6.4.9 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(3-methoxyphenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15i**)



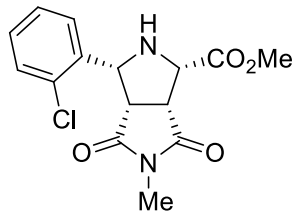
White solid, mp: 164–165 °C. $[\alpha]_D^{22.6}$= –25.52 (c = 0.025, $CHCl_3$), Rf = 0.26 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 1H), 6.98 – 6.82 (m, 4H), 4.44 (d, J = 8.6 Hz, 1H), 4.03 (d, J = 6.7 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.55 (t, J = 7.2 Hz, 1H), 3.41 (t, J = 8.1 Hz, 1H), 2.87 (s, 3H), 2.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.7, 170.2, 159.7, 138.5, 129.4, 119.4, 113.4, 113.0, 63.9, 61.6, 55.3, 52.3, 49.5, 48.2, 25.0. IR (cm^{-1}): 3333, 2986, 2863, 1748, 1693, 1597, 1443, 1382, 1218, 1095, 884, 778, 689. HRMS-EI (m/z): calculated for $C_{16}H_{19}N_2O_5$ [M+H]: 319.1294 and found: 319.1294. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 14.9 min, t_{Rmaj}= 20.7 min.

6.4.10 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(3-bromophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15j**)



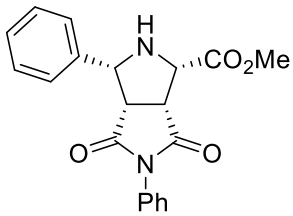
White solid, mp: 191–192 °C. $[\alpha]_D^{23.4}$= –70.08 (*c* = 0.025, $CHCl_3$), *Rf* = 0.43 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 4.44 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.04 (dd, *J* = 6.7, 4.7 Hz, 1H), 3.88 (s, 3H), 3.56 (t, *J* = 7.2 Hz, 1H), 3.42 (t, *J* = 8.1 Hz, 1H), 2.88 (s, 3H), 2.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 174.6, 170.1, 139.3, 131.6, 130.2, 130.0, 126.0, 122.8, 63.3, 61.6, 52.5, 49.3, 48.0, 25.2. IR (cm^{-1}): 3343, 2988, 2901,1771, 1697, 1432, 1382, 1242, 1082, 868, 796. HRMS-EI (*m*/*z*): calculated for $C_{15}H_{16}BrN_2O_4$ [M+H]: 367.0293 and found: 367.0299. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 9.3 min, t_{Rmaj}= 15.1 min.

6.4.11 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(2-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**15k**)



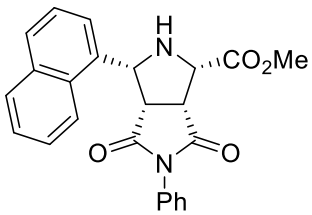
Data are identical with those reported in the literature.[64] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 6.8, 2.5 Hz, 1H), 7.39 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.23 (ddd, *J* = 6.3, 3.4, 2.0 Hz, 2H), 4.72 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 3.70 (t, *J* = 8.1 Hz, 1H), 3.55 (t, *J* = 7.3 Hz, 1H), 2.79 (s, 3H), 2.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.4, 170.2, 135.0, 133.3, 129.2, 129.1, 127.3, 127.0, 61.2, 60.3, 52.3, 47.6, 46.6, 25.0. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 70/30, λ 210 nm), t_{Rmin}= 9.4 min, t_{Rmaj}= 18.3 min.

6.4.12 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16a**)



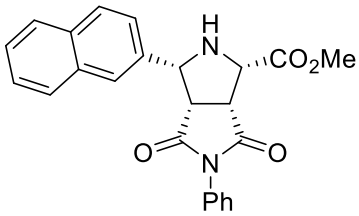
Data are identical with those reported in the literature.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.31 (m, 9H), 7.14 (d, J = 7.9 Hz, 2H), 4.58 (d, J = 8.8 Hz, 1H), 4.11 (d, J = 6.6 Hz, 1H), 3.86 (s, 3H), 3.70 (t, J = 7.2 Hz, 1H), 3.54 (t, J = 8.3 Hz, 1H), 2.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.8, 170.2, 136.8, 131.7, 129.1 (2xC), 128.6, 128.5 (3xC), 127.2 (2xC), 126.2 (2xC), 64.3, 61.9, 52.4, 49.5, 48.4. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 12.6 min, t_{Rmaj}= 20.0 min.

6.4.13 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(naphthalen-1-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16b**)



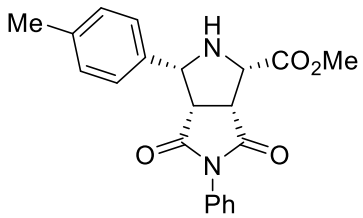
Data are identical with those reported in the literature.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.87 (t, J = 6.6 Hz, 2H), 7.80 (d, J = 8.2 Hz, 1H), 7.61 – 7.42 (m, 3H), 7.29 (dt, J = 24.0, 6.8 Hz, 3H), 7.04 (d, J = 7.7 Hz, 2H), 5.24 (d, J = 7.5 Hz, 1H), 4.20 (d, J = 5.0 Hz, 1H), 3.89 (s, 3H), 3.86 – 3.74 (m, 2H), 2.49 (s, 1H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 173.2, 171.1, 133.5, 133.4, 131.7, 131.3, 129.1, 128.9 (2xC), 128.6, 128.4, 126.4, 126.1 (2xC), 125.7, 125.4, 123.4, 122.5, 61.5, 59.9, 52.3, 48.2, 48.0. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, □ 210 nm), t_{Rmin}= 12.9 min, t_{Rmaj}= 27.2 min.

6.4.14 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(naphthalen-2-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16c**)



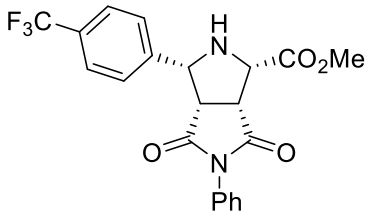
Data are identical with those reported in the literature.[67] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.88 – 7.79 (m, 3H), 7.56 – 7.43 (m, 3H), 7.39 – 7.27 (m, 3H), 7.11 (d, J = 8.0 Hz, 1H), 4.75 (d, J = 8.8 Hz, 1H), 4.17 (d, J = 6.4 Hz, 1H), 3.90 (s, 3H), 3.80 – 3.73 (m, 1H), 3.69 – 3.61 (m, 1H), 2.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.7, 170.2, 134.5, 133.4, 133.3, 131.7 (2xC), 129.1, 128.5, 128.2, 128.0, 127.9, 126.4, 126.2, 126.1 (2xC), 125.7, 125.5, 64.2, 61.9, 52.4, 49.4, 48.4. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 14.2 min, t_{Rmaj}= 31.1 min.

6.4.15 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 4,6-dioxo-5-phenyl-3-(*p*-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16d**)



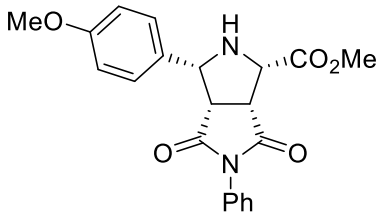
Data are identical with those reported in the literature.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 6H), 7.23 – 7.11 (m, 3H), 4.57 (d, J = 8.7 Hz, 1H), 4.12 (d, J = 6.7 Hz, 1H), 3.87 (s, 3H), 3.76 – 3.68 (m, 1H), 3.61 – 3.49 (m, 1H), 2.49 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.8, 170.2, 138.0, 133.8, 131.7, 129.2 (2xC), 129.0 (2xC), 128.4, 127.0 (2xC), 126.2 (2xC), 64.1, 61.8, 52.3, 49.4, 48.4, 21.2. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 10.2 min, t_{Rmaj}= 18.6 min.

6.4.16 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 4,6-dioxo-5-phenyl-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16e**)



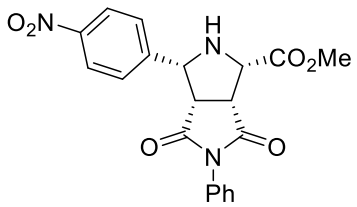
Data are identical with those reported in the literature.[68] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.55 (m, 4H), 7.37 (dt, J = 26.6, 7.3 Hz, 3H), 7.12 (d, J = 8.0 Hz, 2H), 4.65 (d, J = 8.5 Hz, 1H), 4.17 (d, J = 6.7 Hz, 1H), 3.88 (s, 3H), 3.76 (t, J = 7.3 Hz, 1H), 3.62 (t, J = 8.2 Hz, 1H), 2.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.5, 170.0, 140.9, 131.6, 129.3 (2xC), 128.8 (2xC), 127.7, 126.2 (4xC), 125.6 (q, J = 3.6 Hz), 63.8, 62.0, 52.6, 49.3, 48.1. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin} = 9.6 min, t_{Rmaj} = 15.9 min.

6.4.17 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(4-methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16f**)



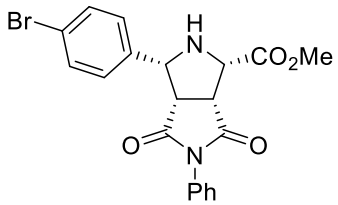
Data are identical with those reported in the literature.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 7.16 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.55 (d, J = 8.8 Hz, 1H), 4.11 (d, J = 6.6 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.70 (t, J = 8.9 Hz, 1H), 3.51 (t, J = 8.3 Hz, 1H), 2.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.9, 170.3, 159.6, 131.7, 129.2 (2xC), 128.7, 128.6, 128.4 (2xC), 126.2 (2xC), 113.9 (2xC), 63.9, 61.9, 55.3, 52.4, 49.5, 48.4. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 210 nm), t_{Rmin} = 16.3 min, t_{Rmaj} = 24.4 min.

6.4.18 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(4-nitrophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16g**)



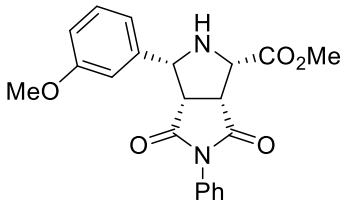
Data are identical with those reported in the literature.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.47 – 7.30 (m, 3H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.71 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.20 (dd, *J* = 6.6, 4.3 Hz, 1H), 3.88 (s, 3H), 3.78 (t, *J* = 7.3 Hz, 1H), 3.65 (t, *J* = 8.2 Hz, 1H), 2.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 173.3, 169.8, 148.0, 144.4, 131.5, 129.3 (2xC), 128.9, 128.2 (2xC), 126.2 (2xC), 123.9 (2xC), 63.3, 62.0, 52.6, 49.2, 47.8. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 210 nm), t_{Rmin}= 16.0 min, t_{Rmaj}= 23.5 min.

6.4.19 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(4-bromophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16h**)



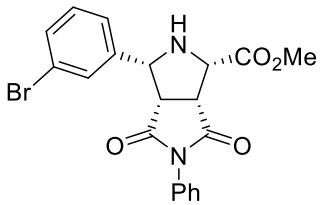
Data are identical with those reported in the literature.[66] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.13 (d, *J* = 7.4 Hz, 2H), 4.54 (d, *J* = 8.7 Hz, 1H), 4.12 (d, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 3.71 (t, *J* = 7.2 Hz, 1H), 3.54 (t, *J* = 8.2 Hz, 1H), 2.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 173.6, 170.0, 135.9, 131.7 (2xC), 131.6, 129.2 (2xC), 129.0 (2xC), 128.7, 126.2 (2xC), 122.4, 63.6, 61.9, 52.5, 49.2, 48.1. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 210 nm), t_{Rmin}= 11.7 min, t_{Rmaj}= 22.6 min.

6.4.20 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(3-methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16i**)



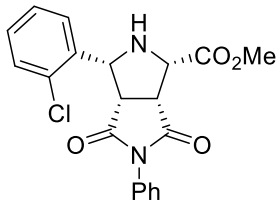
Data are identical with those reported in the literature.[69] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 4H), 7.16 (d, J = 7.6 Hz, 2H), 7.10 – 6.97 (m, 2H), 6.88 – 6.81 (m, 1H), 4.58 (dd, J = 8.8, 5.2 Hz, 1H), 4.13 (dd, J = 6.5, 4.9 Hz, 1H), 3.88 (d, J = 4.4 Hz, 3H), 3.76 (s, 3H), 3.72 (t, J = 7.1 Hz, 1H), 3.56 (t, J = 8.3 Hz, 1H), 2.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 173.7, 170.1, 159.8, 138.5, 131.7, 129.5, 129.1 (2xC), 128.5, 126.2 (2xC), 119.5, 113.7, 113.0, 64.1, 61.9, 55.3, 52.3, 49.4, 48.3. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 12.5 min, t_{Rmaj}= 19.9 min.

6.4.21 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(3-bromophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16j**)



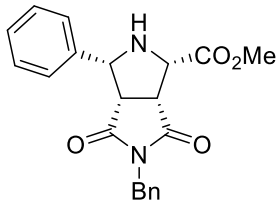
Data are identical with those reported in the literature.[70] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.45 – 7.29 (m, 5H), 7.26 – 7.20 (m, 1H), 7.14 (d, J = 7.4 Hz, 2H), 4.52 (d, J = 8.8 Hz, 1H), 4.09 (d, J = 6.5 Hz, 1H), 3.85 (s, 3H), 3.69 (t, J = 7.1 Hz, 1H), 3.51 (t, J = 8.3 Hz, 1H), 2.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 173.7, 170.0, 139.5, 131.6, 131.6, 130.1 (2xC), 129.2 (2xC), 128.7, 126.3 (2xC), 126.2, 122.8, 63.3, 61.7, 52.5, 49.2, 48.1. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 210 nm), t_{Rmin}= 12.5 min, t_{Rmaj}= 23.8 min.

6.4.22 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 3-(2-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**16k**)



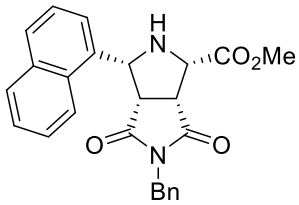
Data are identical with those reported in the literature.[70] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 5.9, 3.5 Hz, 1H), 7.43 – 7.22 (m, 6H), 7.06 (d, J = 8.0 Hz, 2H), 4.83 (dd, J = 8.4, 4.0 Hz, 1H), 4.13 (dd, J = 6.5, 3.8 Hz, 1H), 3.86 (s, 3H), 3.82 (d, J = 8.1 Hz, 1H), 3.71 (t, J = 7.3 Hz, 1H), 2.40 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 173.4, 170.1, 135.1, 133.5, 131.6, 129.4 (2xC), 129.1 (2xC), 128.6, 127.4, 127.1, 126.2 (2xC), 61.6, 60.7, 52.4, 47.8, 46.6. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmin}= 8.2 min, t_{Rmaj}= 14.5 min.

6.4.23 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17a**)



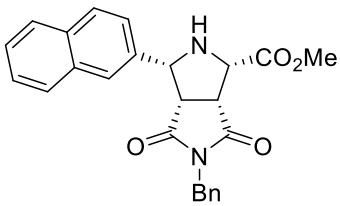
Data are identical with those reported in the literature.[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 6.92 (m, 10H), 4.63 – 4.40 (m, 3H), 4.05 (d, J = 6.9 Hz, 1H), 3.88 (s, 3H), 3.55 (t, J = 7.3 Hz, 1H), 3.38 (t, J = 8.1 Hz, 1H), 2.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 174.3, 170.1, 136.5, 135.7, 129.1, 128.6, 128.4, 128.2, 128.0, 127.2, 64.3, 61.9, 52.4, 49.4, 48.4, 42.6. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 8.2 min, t_{Rmaj}= 14.7 min.

6.4.24 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(naphthalen-1-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17b**)



White solid, mp: 197–198 °C. $[\alpha]_D^{24.9}$= –85.48 (*c* = 0.025, $CHCl_3$), *Rf* = 0.56 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, CDCl3) δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.39 (m, 3H), 7.32 – 7.20 (m, 6H), 5.16 (d, *J* = 8.2 Hz, 1H), 4.52 – 4.38 (m, 2H), 4.16 (d, *J* = 6.5 Hz, 1H), 3.91 (s, 2H), 3.67 (dt, *J* = 27.5, 7.6 Hz, 2H), 2.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 173.8, 170.2, 135.7, 133.4, 132.8, 131.2, 129.2, 128.9, 128.5, 128.4, 127.9, 126.4, 125.7, 125.5, 123.5, 122.3, 61.6, 59.9, 52.4, 48.1, 48.0, 42.5. IR (cm^{-1}): 3340, 2987, 1749, 1698, 1398, 1202, 1125, 702. HRMS-EI (*m*/*z*): calculated for $C_{25}H_{23}N_2O_4$ [M+H]: 415.1658 and found: 415.1637. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), endo: t_{Rmin}= 10.7 min, t_{Rmaj}= 26.3 min, exo: t_{Rmin}= 7.6 min, t_{Rmaj}= 15.5 min.

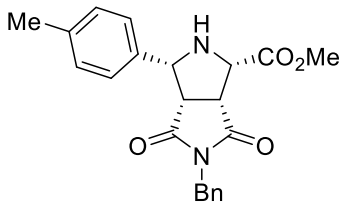
6.4.25 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(naphthalen-2-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17c**)



White solid, mp: 199–200 °C. $[\alpha]_D^{22.6}$= –91.2 (*c* = 0.025, $CHCl_3$), *Rf* = 0.51 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, CDCl3) δ 7.82 – 7.78 (m, 1H), 7.74 – 7.65 (m, 3H), 7.47 – 7.42 (m, 2H), 7.34 – 7.27 (m, 6H), 4.64 – 4.59 (m, 1H), 4.55 – 4.46 (m, 2H), 4.12 – 4.07 (m, 1H), 3.90 (s, 3H), 3.64 – 3.57 (m, 1H), 3.52 – 3.43 (m, 1H), 2.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 174.3, 170.1, 135.7, 133.2, 128.9, 128.6, 128.1, 127.9, 127.8, 126.1, 126.1, 125.7, 125.5, 64.2, 61.9, 52.4, 49.2, 48.3, 42.6. IR (cm^{-1}): 3339, 2979, 1733, 1694, 1346, 1202, 890, 758. HRMS-EI (*m*/*z*): calculated for

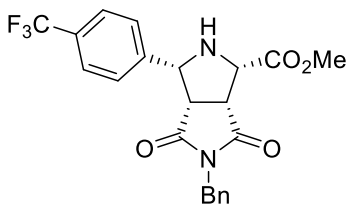
$C_{25}H_{23}N_2O_4$ [M+H]: 415.1658 and found: 415.1640. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 10.2 min, t_{Rmaj}= 26.4 min.

6.4.26 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17d**)



White solid, mp: 158–159 °C. $[\alpha]_D^{22.7}$= –48.64 (*c* = 0.025, $CHCl_3$), *Rf* = 0.64 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 7.03 (s, 4H), 4.53 (dd, *J* = 18.8, 14.0 Hz, 2H), 4.40 (dd, *J* = 8.9, 3.5 Hz, 1H), 4.01 (dd, *J* = 7.3, 3.3 Hz, 1H), 3.87 (s, 3H), 3.53 (t, *J* = 7.3 Hz, 1H), 3.34 (t, *J* = 8.1 Hz, 1H), 2.32 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 174.5, 170.2, 137.9, 135.7, 133.3, 129.1, 129.1, 128.6, 128.0, 127.1, 64.2, 61.9, 52.4, 49.5, 48.4, 42.7, 21.4. IR (cm^{-1}): 3340, 2970, 2900, 1749, 1694, 1399, 1258, 1197, 800. HRMS-EI (*m*/*z*): calculated for $C_{22}H_{23}N_2O_4$ [M+H]: 379.1658 and found: 379.1643. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 7.1 min, t_{Rmaj}= 13.8 min.

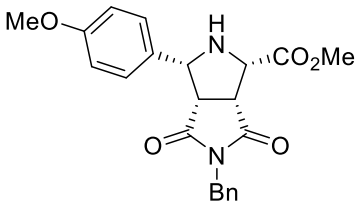
6.4.27 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17e**)



White solid, mp: 189–190 °C. $[\alpha]_D^{24.6}$= –43.44 (*c* = 0.0125, $CHCl_3$), *Rf* = 0.59 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.30 (s, 5H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.52 (dd, *J* = 42.0, 14.0 Hz, 2H) 4.49 (d, *J* = 8.6 Hz, 1H), 4.06 (d, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.58 (t, *J* = 7.3 Hz, 1H), 3.41 (t, *J* = 8.2 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 174.1, 169.9, 140.8, 135.6, 129.1, 128.6, 128.1, 127.6, 125.3 (q, *J* = 3.6 Hz), 63.4, 61.8, 52.4, 49.0, 48.0, 43.7. IR (cm^{-1}): 3347, 2988, 2900, 1744, 1697, 1319, 1126, 1065, 817, 694. HRMS-EI (*m*/*z*): calculated for

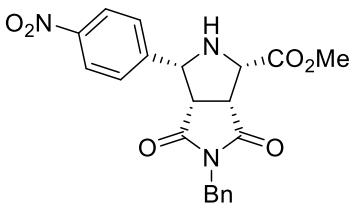
$C_{22}H_{20}F_3N_2O_4$ [M+H]: 433.1375 and found: 433.1365. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 6.0 min, t_{Rmaj}= 10.5 min.

6.4.28 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(4-methoxyphenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17f**)



White solid, mp: 144–145 °C. $[\alpha]_D^{20.8}$= –51.72 (*c* = 0.025, $CHCl_3$), *Rf* = 0.32 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, CDCl3) δ 7.30 (q, *J* = 8.0, 6.0 Hz, 5H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = 14.0 Hz, 1H), 4.45 (d, *J* = 14.0 Hz, 1H), 4.35 (d, *J* = 8.6 Hz, 1H), 3.97 (d, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.49 (t, *J* = 7.3 Hz, 1H), 3.28 (t, *J* = 8.1 Hz, 1H), 2.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 174.5, 170.2, 159.3, 135.7, 129.0, 128.6, 128.4, 128.3, 127.9, 113.7, 63.8, 61.7, 55.1, 52.3, 49.3, 48.3, 42.6. IR (cm^{-1}): 3336, 2988, 2900, 1750, 1695, 1514, 1394, 1252, 1198, 1067, 812. HRMS-EI (*m*/*z*): calculated for $C_{22}H_{23}N_2O_5$ [M+H]: 395.1607 and found: 395.1602. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 11.2 min, t_{Rmaj}= 17.1 min.

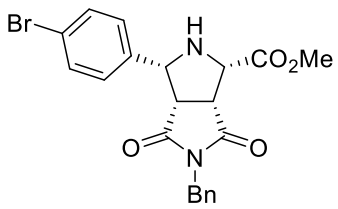
6.4.29 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(4-nitrophenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17g**)



White solid, mp: 201–202 °C. $[\alpha]_D^{21.1}$= –40.88 (*c* = 0.0125, $CHCl_3$), *Rf* = 0.25 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.25 (m, 7H), 4.59 (d, *J* = 14.0 Hz, 1H), 4.55 (d, *J* = 8.6 Hz, 1H), 4.42 (d, *J* = 14.0 Hz, 1H), 4.09 (d, *J* = 6.5 Hz, 1H), 3.90 (s, 3H), 3.61 (t, *J* = 7.3 Hz, 1H), 3.45 (t, *J* = 8.2 Hz, 1H), 2.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 174.0, 169.8, 147.7, 144.2, 135.5, 129.1, 128.7, 128.3,

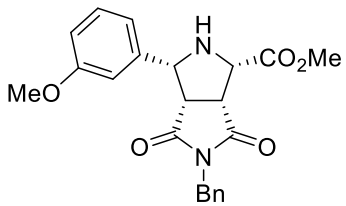
128.1, 123.6, 63.1, 61.8, 52.5, 49.1, 47.8, 42.8. IR (cm^{-1}): 3332, 2946, 2839, 2159, 2030, 1747, 1694, 1514, 1344, 1198, 1079, 858, 744. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{20}N_3O_6$ [M+H]: 410.1352 and found: 410.1345. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 220 nm), t_{Rmin}= 15.6 min, t_{Rmaj}= 21.4 min.

6.4.30 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(4-bromophenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17h**)



White solid, mp: 206–207 °C. $[\alpha]_D^{21.0}$= –49.12 (*c* = 0.025, $CHCl_3$), *Rf* = 0.34 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 7H), 6.99 (d, *J* = 8.4 Hz, 2H), 4.57 (d, *J* = 14.0 Hz, 1H), 4.45 (d, *J* = 14.0 Hz, 1H), 4.39 (d, *J* = 8.6 Hz, 1H), 4.02 (d, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 3.54 (t, *J* = 7.3 Hz, 1H), 3.34 (t, *J* = 8.1 Hz, 1H), 2.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.2, 170.0, 135.6, 135.6, 131.6, 129.1, 128.9, 128.7, 128.1, 122.1, 63.6, 61.8, 52.5, 49.1, 48.1, 42.8. IR (cm^{-1}): 3340, 2988, 2900, 1746, 1698, 1398, 1201, 1126, 890, 698. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{20}BrN_2O_4$ [M+H]: 443.0606 and found: 443.0606. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 220 nm), t_{Rmin}= 9.5 min, t_{Rmaj}= 20.3 min.

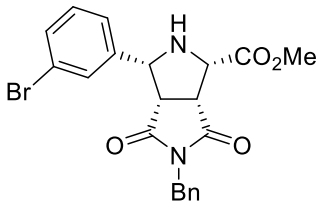
6.4.31 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(3-methoxyphenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17i**)



White solid, mp: 148–149 °C. $[\alpha]_D^{20.5}$= –37.92 (*c* = 0.025, $CHCl_3$), *Rf* = 0.56 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 5H), 7.13 (t, *J* = 8.3 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.74 (d, *J* = 7.4 Hz, 1H), 4.59 – 4.47 (m, 2H), 4.47 – 4.35 (m, 1H), 4.02 (t, *J* = 5.8 Hz, 1H), 3.86 (s,

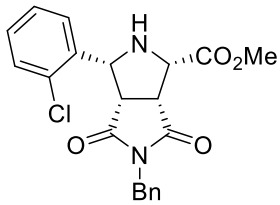
3H), 3.68 (s, 3H), 3.53 (t, J = 7.3 Hz, 1H), 3.36 (t, J = 8.1 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 174.3, 170.1, 159.6, 138.1, 135.7, 129.4, 128.9, 128.7, 127.9, 119.5, 113.6, 112.9, 64.3, 61.9, 55.2, 52.4, 49.4, 48.2, 42.7. IR (cm^{-1}): 3344, 2988, 2901, 1739, 1697, 1402, 1216, 1079, 869, 694. HRMS-EI (m/z): calculated for $C_{22}H_{23}N_2O_5$ [M+H]: 395.1607 and found: 395.1608. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 220 nm), t_{Rmin}= 11.5 min, t_{Rmaj}= 22.0 min.

6.4.32 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(3-methoxyphenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17j**)



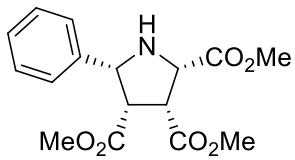
White solid, mp: 120–121 °C. $[\alpha]_D^{22.6}$= –37.04 (c = 0.025, $CHCl_3$), Rf = 0.45 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.23 (m, 7H), 7.06 (d, J = 4.9 Hz, 2H), 4.58 – 4.44 (m, 2H), 4.37 (d, J = 7.9 Hz, 1H), 4.01 (d, J = 5.1 Hz, 1H), 3.85 (s, 3H), 3.52 (t, J = 7.3 Hz, 1H), 3.34 (t, J = 8.1 Hz, 1H), 2.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.1, 169.9, 139.0, 135.6, 131.4, 130.2, 129.9, 128.8, 128.7, 128.0, 126.0, 122.5, 63.42, 61.8, 52.4, 49.1, 47.9, 42.7. IR (cm^{-1}): 3335, 2988, 2901, 1698, 1432, 1394, 1242, 1066, 868, 788, 699. HRMS-EI (m/z): calculated for $C_{21}H_{20}BrN_2O_4$ [M+H]: 443.0606 and found: 443.0608. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 220 nm), t_{Rmin}= 10.2 min, t_{Rmaj}= 19.6 min.

6.4.33 Characterization of (1*S*,3*R*,3a*S*,6a*R*)-methyl 5-benzyl-3-(2-chlorophenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**17k**)



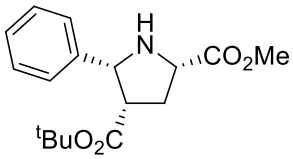
White solid, mp: 158–159 °C. $[\alpha]_D^{24.6}$ = –68.72 (*c* = 0.025, $CHCl_3$), *Rf* = 0.84 (1:1 Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.15 (m, 7H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.71 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.46 (q, *J* = 14.1 Hz, 2H), 4.05 (dd, *J* = 6.6, 4.0 Hz, 1H), 3.86 (s, 3H), 3.67 (t, *J* = 8.1 Hz, 1H), 3.55 (t, *J* = 7.3 Hz, 1H), 2.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 174.1, 170.1, 135.7, 134.8, 133.3, 129.1, 129.1, 128.9, 128.6, 127.9, 127.4, 127.0, 61.5, 60.5, 52.4, 47.8, 46.5, 42.6. IR (cm^{-1}): 3335, 2988, 2900, 1750, 1699, 1434, 1395, 1211, 1054, 759, 704. HRMS-EI (*m*/*z*): calculated for $C_{21}H_{20}ClN_2O_4$ [M+H]: 399.1112 and found: 399.1117. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 60/40, λ 220 nm), t_{Rmin} = 8.8 min, t_{Rmaj} = 16.2 min.

6.4.34 Characterization of (2*S*,3*R*,4*S*,5*R*)-trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**18a**)



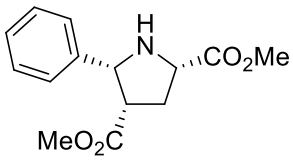
Data are identical with those reported in the literature.[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 4.49 (d, *J* = 6.8 Hz, 1H), 4.17 (d, *J* = 8.9 Hz, 1H), 3.81 (s, 3H), 3.76 – 3.70 (m, 1H), 3.70 (s, 3H), 3.61 – 3.54 (m, 1H), 3.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 171.0, 171.0, 137.2, 128.4 (2xC), 127.8, 126.8 (2xC), 65.5, 62.3, 52.6, 52.2, 51.5, 51.1. HPLC (Chiralpak AS-H, 0.8 mL/min, n-hexane/i-PrOH: 50/50, λ 205 nm), t_{Rmin} = 7.0 min, t_{Rmaj} = 12.2 min.

6.4.35 Characterization of (2*S*,4*S*,5*R*)-4-tert-butyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate (**19a**)



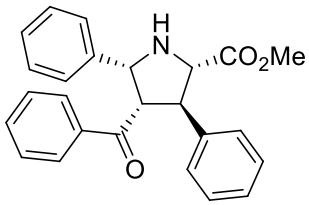
Data are identical with those reported in the literature.[72] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 5H), 4.47 (d, *J* = 7.8 Hz, 1H), 3.95 (t, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.26 (td, *J* = 7.9, 6.1 Hz, 1H), 2.88 (s, 1H), 2.44 (dt, *J* = 13.2, 8.3 Hz, 1H), 2.35 – 2.27 (m, 1H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 171.9, 139.4, 128.2 (2xC), 127.4, 127.3 (2xC), 80.6, 65.6, 60.0, 52.3, 50.3, 34.2, 27.5 (3xC). HPLC (Chiralpak OD-H, 1.0 mL/min, n-hexane/i-PrOH: 80/20, λ 210 nm), t_{Rmaj} = 8.7 min, t_{Rmin} = 12.6 min.

6.4.36 Characterization of (2*S*,4*S*,5*R*)-dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate (**20a**)



Data are identical with those reported in the literature.[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 5H), 4.52 (d, *J* = 7.8 Hz, 1H), 3.98 (t, *J* = 8.1 Hz, 1H), 3.81 (s, 3H), 3.30 (q, *J* = 6.9 Hz, 1H), 3.20 (s, 3H), 2.95 (s, 1H), 2.41 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.0, 139.0, 128.1 (2xC), 127.5, 126.6 (2xC), 65.7, 59.8, 52.2, 51.2, 49.6, 33.2. HPLC (Chiralpak OD-H, 1.0 mL/min, n-hexane/i-PrOH: 85/15, λ 210 nm), t_{Rmaj} = 10.1 min, t_{Rmin} = 14.9 min.

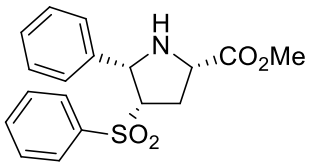
6.4.37 Characterization of (2*S*,3*R*,4*S*,5*R*)-methyl 4-benzoyl-3,5-diphenylpyrrolidine-2-carboxylate (**21a**)



Data are identical with those reported in the literature.[73] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.36 (dt, *J* = 15.0, 6.2 Hz, 5H), 7.24 (t, *J* = 7.6 Hz, 3H), 7.10 (dd, *J* = 17.5, 6.8 Hz, 5H), 5.00 (d, *J* = 8.7 Hz, 1H),

4.52 (t, J = 8.1 Hz, 1H), 4.24 – 4.08 (m, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 173.5, 140.9, 139.1, 137.5, 132.9, 128.9 (2xC), 128.3 (2xC), 128.2 (2xC), 128.2 (2xC), 127.9 (2xC), 127.7, 127.5 (2xC), 127.3, 67.8, 66.8, 60.7, 52.8, 52.4. HPLC (Chiralpak OD-H, 1.0 mL/min, n-hexane/i-PrOH: 80/20, λ 254 nm), t_{Rmin}= 7.8 min, t_{Rmaj}= 15.2 min.

6.4.38 Characterization of (2*S*,4*S*,5*S*)-methyl 5-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (**22a**)

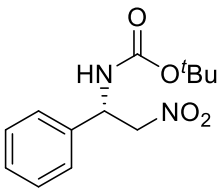


Data are identical with those reported in the literature.[74] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 1H), 7.33 – 7.25 (m, 4H), 7.19 – 7.10 (m, 3H), 4.50 (d, J = 6.6 Hz, 1H), 4.08 – 3.95 (m, 2H), 3.85 (s, 3H), 2.85 (ddd, J = 14.0, 8.0, 5.8 Hz, 1H), 2.66 (dt, J = 14.5, 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 139.4, 135.7, 132.9, 128.9 (2xC), 128.1 (2xC), 128.1 (2xC), 127.9, 127.8 (2xC), 66.7, 64.8, 58.678, 52.7, 31.8. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 50/50, λ 210 nm), t_{Rmaj}= 15.3 min, t_{Rmin}= 22.0 min.

6.5 Synthesis and characterization of aza-Henry reaction products

All aza-Henry reaction products **24a-g** and **25a-e** were synthesized according to general procedure D.

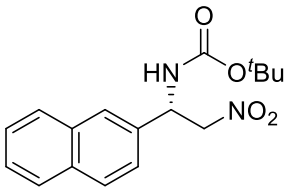
6.5.1 Characterization of *tert*-butyl (*S*)-(2-nitro-1-phenylethyl)carbamate (**24a**)



Data are identical with those reported in the literature.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 5.32 (br, 1H), 4.76 (br, 1H), 4.61 (d, J = 10.9 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 137.0, 129.3, 128.8,

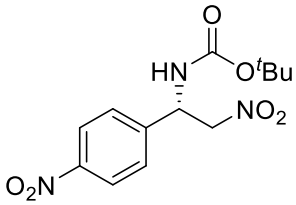
126.4, 80.8, 79.0, 52.9, 28.3. HPLC (Chiralpak AS-H, 1.0 mL/min, n-hexane/i-PrOH: 95/5, λ 210 nm), t_{Rmaj} = 20.8 min, t_{Rmin} = 42.8 min.

6.5.2 Characterization of *tert*-butyl (*S*)-(1-(naphthalen-2-yl)-2-nitroethyl)carbamate (**24b**)



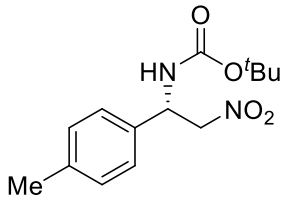
Data are identical with those reported in the literature.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.73 (m, 4H), 7.65 – 7.32 (m, 3H), 5.53 (d, J = 16.7 Hz, 2H), 4.93 (br, 1H), 4.79 (d, J = 8.1 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 134.3, 133.3, 133.3, 129.4, 128.1, 127.8, 126.8, 126.8, 125.7, 123.9, 80.8, 79.0, 53.1, 28.4. HPLC (Chiralpak AD-H, 1.0 mL/min, n-hexane/i-PrOH: 90/10, λ 254 nm), t_{Rmaj} = 18.2 min, t_{Rmin} = 22.8 min.

6.5.3 Characterization of *tert*-butyl (*S*)-(2-nitro-1-(4-nitrophenyl)ethyl)carbamate (**24c**)



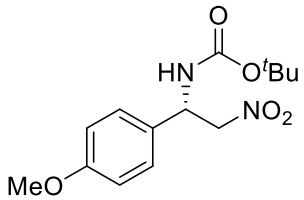
Data are identical with those reported in the literature.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 5.67 (br, 1H), 5.48 (br, 1H), 4.89 (br, 1H), 4.78 (br, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 148.1, 144.3, 127.5, 124.5, 81.5, 78.5, 52.2, 28.4. HPLC (Chiralpak AD-H, 1.0 mL/min, n-hexane/i-PrOH: 90/10, λ 254 nm), t_{Rmaj} = 23.0 min, t_{Rmin} = 47.1 min.

6.5.4 Characterization of *tert*-butyl (*S*)-(2-nitro-1-(*p*-tolyl)ethyl)carbamate (**24d**)



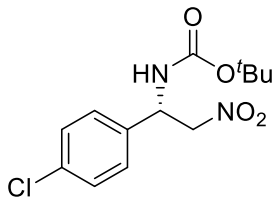
Data are identical with those reported in the literature.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.04 (m, 4H), 5.37 (br, 2H), 4.81 (br, 1H), 4.67 (br, 1H), 2.33 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 138.6, 134.0, 129.9, 126.3, 80.6, 79.0, 52.8, 28.3, 21.2. HPLC (Chiralpak OJ-H, 1.0 mL/min, n-hexane/i-PrOH: 95/5, λ 254 nm), t_{Rmaj} = 26.3 min, t_{Rmin} = 30.0 min.

6.5.5 Characterization of *tert*-butyl (*S*)-(1-(4-methoxyphenyl)-2-nitroethyl)carbamate (**24e**)



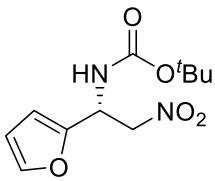
Data are identical with those reported in the literature.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.27 (br, 2H), 4.83 (br, 1H), 4.66 (br, 1H), 3.79 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 154.9, 129.0, 127.7, 114.6, 80.7, 79.0, 55.4, 52.6, 28.4. HPLC (Chiralpak OJ-H, 1.0 mL/min, n-hexane/i-PrOH: 95/5, λ 210 nm), t_{Rmaj} = 53.8 min, t_{Rmin} = 63.2 min.

6.5.6 Characterization of *tert*-butyl (*S*)-(1-(4-chlorophenyl)-2-nitroethyl)carbamate (**24f**)



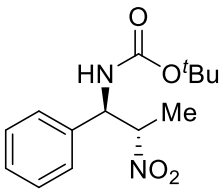
Data are identical with those reported in the literature.[75] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.14 (m, 4H), 5.52 – 4.97 (br m, 2H), 4.82 (br, 1H), 4.70 (br, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 134.7, 129.7, 129.5, 127.9, 81.1, 78.8, 52.3, 28.4. HPLC (Chiralpak AD-H, 1.0 mL/min, n-hexane/i-PrOH: 90/10, λ 210 nm), t_{Rmaj} = 12.8 min, t_{Rmin} = 16.5 min.

6.5.7 Characterization of *tert*-butyl (*R*)-(1-(furan-2-yl)-2-nitroethyl)carbamate (**24g**)



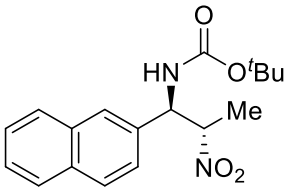
Data are identical with those reported in the literature.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.31 (dd, J = 11.9, 2.4 Hz, 2H), 5.42 (br d, J = 23.2 Hz, 2H), 4.94 – 4.77 (br m, 1H), 4.72 (dd, J = 12.8, 5.6 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 149.6, 142.9, 110.8, 107.9, 80.9, 76.6, 47.3, 28.3. HPLC (Chiralpak OD-H, 1.0 mL/min, n-hexane/i-PrOH: 98/2, λ 220 nm), t_{Rmaj} = 23.4 min, t_{Rmin} = 25.8 min.

6.5.8 Characterization of *tert*-butyl ((1*R*,2*S*)-2-nitro-1-phenylpropyl)carbamate (**25a**)



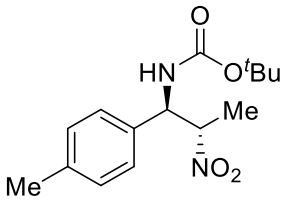
Data are identical with those reported in the literature.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 6H, *syn* and *anti*), 7.26 (d, J = 7.3 Hz, 4H, *syn* and *anti*), 5.71 (br, 1H, *syn*), 5.41 (br, 1H, *anti*), 5.27 – 5.17 (m, 1H, *anti*), 5.13 (br, 1H, *syn*), 4.95 (br, 2H, *syn* and *anti*), 1.52 (d, J = 6.7 Hz, 6H, *syn* and *anti*), 1.42 (s, 9H, *syn*), 1.41 (s, 9H, *anti*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 137.6, 129.1, 128.6, 126.6, 86.9, 80.5, 57.2, 28.4, 17.1. HPLC (Chiralpak AD-H, 1.0 mL/min, n-hexane/i-PrOH: 95/5, λ 210 nm), *syn*: t_{Rmaj} = 19.6 min, t_{Rmin} = 21.3 min, *anti*: t_{Rmaj} = 24.9 min, t_{Rmin} = 32.4 min.

6.5.9 Characterization of *tert*-butyl ((1*R*,2*S*)-1-(naphthalen-2-yl)-2-nitropropyl)carbamate (**25b**)



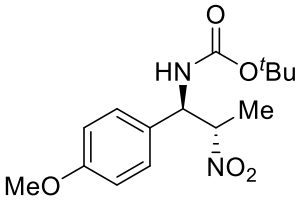
Data are identical with those reported in the literature.[76] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dt, J = 8.5, 4.3 Hz, 6H, *syn* and *anti*), 7.73 (d, J = 7.9 Hz, 2H, *syn* and *anti*), 7.50 (dd, J = 5.2, 2.7 Hz, 4H, *syn* and *anti*), 7.36 (s, 2H, *syn* and *anti*), 5.78 (br, 1H, *syn*), 5.51 (br, 1H, *anti*), 5.45 – 5.35 (m, 1H, *anti*), 5.29 (br, 1H, *syn*), 5.06 (br, 2H, *syn* and *anti*), 1.56 (d, J = 6.5 Hz, 6H, *syn* and *anti*), 1.44 (s, 9H, *anti*), 1.43 (s, 9H, *syn*).^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 134.9, 133.3, 133.2, 129.2, 128.2, 127.8, 126.7, 126.6, 126.1, 123.9, 86.8, 80.6, 57.6, 28.4, 17.3. HPLC (Chiralpak AD + Chiralpak AD-H, 1.0 mL/min, n-hexane/i-PrOH: 90/10, λ 220 nm), *syn*: t_{Rmin} = 34.8 min, t_{Rmaj} = 38.1 min, *anti*: t_{Rmin} = 45.7 min, t_{Rmaj} = 51.2 min.

6.5.10 Characterization of *tert*-butyl ((1*R*,2*S*)-2-nitro-1-(*p*-tolyl)propyl)carbamate (**25c**)



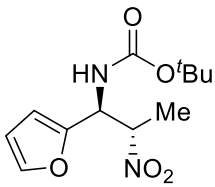
Data are identical with those reported in the literature.[76] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.06 (m, 8H, *syn* and *anti*), 5.57 (br, 1H, *syn*), 5.33 (br, 1H, *anti*), 5.14 (dd, J = 8.7, 6.1 Hz, 1H, *anti*), 5.08 (br, 1H, *syn*), 4.92 (br, 2H, *syn* and *anti*), 2.32 (s, 6H, *syn* and *anti*), 1.52 (d, J = 6.7 Hz, 6H, *syn* and *anti*), 1.42 (s, 9H, *anti*), 1.41 (s, 9H, *syn*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 138.4, 134.5, 129.8, 126.5, 86.9, 80.6, 57.0, 28.3, 21.2, 17.1. HPLC (Chiralpak IA, 1.0 mL/min, n-hexane/i-PrOH: 95/5, λ 220 nm), *syn*: t_{Rmaj} = 14.3 min, t_{Rmin} = 15.9 min, *anti*: t_{Rmaj} = 20.0 min, t_{Rmin} = 22.2 min.

6.5.11 Characterization of *tert*-butyl ((1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitropropyl)carbamate (**25d**)



Data are identical with those reported in the literature.[76] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 6.5 Hz, 2H, *syn*), 7.14 (d, J = 6.8 Hz, 2H, *anti*), 6.88 (d, J = 3.6 Hz, 2H, *syn*), 6.86 (d, J = 3.9 Hz, 2H, *anti*), 5.51 (br, 1H, *syn*), 5.30 (d, J = 8.9 Hz, 1H, *anti*), 5.10 (dd, J = 8.8, 5.9 Hz, 1H, *anti*), 5.04 (br, 1H, *syn*), 4.90 (br, 2H, *syn* and *anti*), 3.79 (s, 3H, *syn*), 3.79 (s, 3H, *anti*), 1.52 (d, J = 6.8 Hz, 6H, *syn* and *anti*), 1.42 (s, 9H, *syn*), 1.41 (s, 9H, *syn*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.66, 129.55, 127.76, 114.52, 114.46, 86.96, 86.06, 56.85, 55.42, 28.38, 17.07. HPLC (Chiralpak AD + Chiralpak AD-H, 1.0 mL/min, n-hexane/i-PrOH: 90/10, λ 220 nm) *syn*: t_{Rmaj} = 38.1 min, t_{Rmin} = 42.3 min, *anti*: t_{Rmaj} = 48.8 min, t_{Rmin} = 51.9 min.

6.5.12 Characterization of *tert*-butyl ((1*S*,2*S*)-1-(furan-2-yl)-2-nitropropyl)carbamate (**25e**)



Data are identical with those reported in the literature.[76] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 2H, *syn* and *anti*), 6.34 – 6.31 (m, 2H, *syn* and *anti*), 6.27 (d, J = 3.2 Hz, 2H, *syn* and *anti*), 5.43 (d, J = 8.1 Hz, 1H, *syn*), 5.32 (s, 1H, *anti*), 5.25 (br, 1H, *syn*), 5.04 (br, 2H, *syn* and *anti*), 4.89 (br, 1H, *anti*), 1.55 (t, J = 7.0 Hz, 6H, *syn* and *anti*), 1.44 (s, 18H, *syn* and *anti*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 150.0, 142.9, 110.7, 108.1, 84.5, 80.78, 51.7, 28.4, 16.4. HPLC (Chiralpak IA, 1.0 mL/min, n-hexane/i-PrOH: 99/1, λ 220 nm), *syn*: t_{Rmin} = 36.2 min, t_{Rmaj} = 43.9 min, *anti*: t_{Rmaj} = 37.5 min, t_{Rmin} = 52.3 min.

REFERENCES

1. Ismail, F. M. D., Levitsky, D. O., Dembitsky, V. M. *Eur. J. Med. Chem.* **2009,** 44, 3373–3387.

2. Zhang, X., Zhou, Y., Wang, H., Guo, D., Ye, D., Xu, Y., Jiang, H., Liu, H. *Adv. Synth. Catal.* **2011**, 353, 1429–1437.

3. Nagaoka, K., Matsumoto, M., Oono, J., Yokoi, K., Ishizeki, S., Nakashima, T. *J. Antibiot.* **1986**, 39, 1527–1532.

4. Ishizeki, S., Ohtsuka, M., Irinoda, K., Kukita, K., Nagaoka, K., Nakashima, T. *Structure* **1987**, 40, 60–65.

5. Beresford, K. J. M., Church, N. J., Young, D. W. *Org. Biomol. Chem.* **2006**, 4, 2888–2897.

6. Hodgson, D. M., Štefane, B., Miles, T. J., Witherington, J. *Chem. Commun.* **2004**, 3, 2234–2235.

7. Ren, W., Zhao, Q., Zheng, C., Zhao, Q., Guo, L., Huang, W. *Molecules* **2016**, 21, 1–15.

8. Wang, S., Zhu, X., Chai, Z. *Org. Biomol. Chem.* **2014**, 12, 1351–1356.

9. Piens, N., D'hooghe, M. *Eur. J. Org. Chem.* **2017**, 2017, 5943–5960.

10. Eastwood, F. W., Perlmutter, P., Yang, Q. *J. Chem. Soc. Perkin Trans.* **1997**, 1, 35–42.

11. Schmidt, F., Keller, F., Vedrenne, E., Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, 48, 1149–1152.

12. Chen, X., Lin, C., Du, H., Xu, J. *Adv. Synth. Catal.* **2019**, 361, 1647–1661.

13. Andersson, P. G., Guijarro, D., Tanner, D. *J. Org. Chem.* **1997**, 62, 7364–

7375.

14. Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*. **2006**, Wiley-VCH Verlag GmbH & Co. KGaA.

15. Sabir, S., Kumar, G., Verma, V. P., Jat, J. L. *ChemistrySelect.* **2018**, 3, 3702–3711.

16. Hu, X. E. *Tetrahedron* **2004**, 60, 2701–2743.

17. Yadav, J. S., Subba Reddy, B. V., Mahesh Kumar, G. *Synlett* **2001**, 9, 1417–1418.

18. Pradhan, S., Shahi, C. K., Bhattacharyya, A., Chauhan, N., Ghorai, M. K. *Org. Lett.* **2017**, 19, 3438–3441.

19. Sun, X., Chen, Y., Wu, N., Kang, C. S., Song, H. A., Jin, S., Fu, Y., Bryant, H., Frank, J. A., Chong, H. S. *RSC Adv.* **2015**, 5, 94571–94581.

20. Stanković, S., D'Hooghe, M., Catak, S., Eum, H., Waroquier, M., Van Speybroeck, V., De Kimpe, N., Ha, H. J. *Chem. Soc. Rev.* **2012**, 41, 643–665.

21. Morán-Ramallal, R., Liz, R., Gotor, V. *Org. Lett.* **2007**, 9, 521–524.

22. Lee, B. K., Kim, M. S., Hahm, H. S., Kim, D. S., Lee, W. K., Ha, H. J. *Tetrahedron* **2006**, 62, 8393–8397.

23. Pankova, A. S., Kuznetsov, M. A. *Tetrahedron Lett.* **2014**, 55, 2499–2503.

24. Jeong, H., Yadav, N. N., Ha, H. J. *Synthesis* **2017**, 49, 1264–1272.

25. Polat-Cakir, S., Beksultanova, N., Dogan, Ö. *Helv. Chim. Acta* **2019**, 102, 1–16.

26. Dolence, E. K., Roylance, J. B. *Tetrahedron Asymmetry* **2004**, 15, 3307–3322.

27. Vanderhoydonck, B., Stevens, C. V. *Tetrahedron* **2007**, 63, 7679–7689.

28. Węglarz-Tomczak, E., Staszewska, K., Talma, M., Mucha, A. *Tetrahedron Lett.* **2016**, 57, 4812–4814.

29. Rispens, M. T., Keller, E., Lange, B. De, Zilstra, R. W. J., Feringa, B. L. *Tetrahedron Asymmetry* **1994**, 5, 607–624.

30. Gupta, R.R. *Topics in Heterocyclic Chemistry* **2008**, Springer-Verlag Berlin Heidelberg

31. Scott, M. E., Lautens, M. *Org. Lett.* **2005**, 7, 3045–3047.

32. McGeer, E. G., McGeer, P. L. *International Review of Neurobiology* **1981**, 22, 173–204.

33. Sperk, G. *Prog. Neurobiol.* **1994**, 42, 1–32.

34. Zaczek, R., Nelson, M. F., Coyle, J. T. *Eur. J. Pharmacol.* **1978**, 52, 323–327.

35. Evans, D. A., Scheidt, K. A., Downey, C. W. *Org. Lett.* **2001**, 3, 3009–3012.

36. Fletcher, S. R., Baker, R., Chambers, M. S., Hobbs, S. C., Mitchell, P. J. *J. Chem. Soc. - Chem. Commun*. **1993**, 0, 1216–1218.

37. Inai, M., Ouchi, H., Asahina, A., Asakawa, T., Hamashima, Y., Kan, T. *Chem. Pharm. Bull.* **2016**, 64, 723–732.

38. Allway, P., Grigg, R. *Tetrahedron Lett.* **1991**, 32, 5817–5820.

39. Cabrera, S., Arrayás, R. G., Carretero, J. C. *J. Am. Chem. Soc.* **2005**, 127, 16394–16395.

40. Longmire, J. M., Wang, B., Zhang, X. *J. Am. Chem. Soc.* **2002**, 124, 13400–13401.

41. Mancebo-Aracil, J., Martín-Rodríguez, M., *Tetrahedron Asymmetry* **2012**,

23, 1596–1606.

42. Nájera, C., Retamosa, M. D. G., Sansano, J. M., De Cózar, A., Cossío, F. P. *European J. Org. Chem.* **2007**, 30, 5038–5049.

43. Dogan, Ö., Koyuncu, H., Garner, P., Bulut, A., Youngs, W. J., Panzner, M. *Org. Lett.* **2006**, 8, 4687–4690.

44. Eröksüz, S., Dogan, Ö., Garner, P. P. *Tetrahedron Asymmetry* **2010**, 21, 2535–2541.

45. Wang, C. J., Dong, X. Q., Zhang, Z. H., Xue, Z. Y., Teng, H. L. *J. Am. Chem. Soc.* **2008**, 130, 8606–8607.

46. Ballini, R., Petrini, M. *Tetrahedron* **2004**, 60, 1017–1047.

47. Wu, J., Wang, D., Wu, F., Wan, B. *J. Org. Chem.* **2013**, 78, 5611–5617.

48. Shen, B., Johnston, J. N. *Org. Lett.* **2008**, 10, 4397–4400.

49. Ferraro, A., Bernardi, L., Fochi, M. *Adv. Synth. Catal.* **2016**, 358, 1561–1565.

50. Pelagalli, A., Pellacani, L., Scandozza, E., Fioravanti, S. *Molecules* **2016**, 21, 1–11.

51. Yamada, K. I., Harwood, S. J., Gröger, H., Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, 38, 3504–3506.

52. Noble, A., Anderson, J. C. *Chem. Rev.* **2013**, 113, 2887-2939.

53. Chou, H. C., Leow, D., Tan, C. H. *Chem. An Asian J.* **2019**, 14, 3803–3822.

54. Rueping, M., Antonchick, A. P. *Org. Lett.* **2008**, 10, 1731–1734.

55. Davis, T. A., Johnston, J. N. *Chem. Sci.* **2011**, 2, 1076–1079.

56. Vesely, J., Rios, R. *Chem. Soc. Rev.* **2014**, 43, 611–630.

57. Palomo, C., Oiarbide, M., Halder, R., Laso, A., López, R. *Angew. Chem. Int. Ed.* **2005**, 45, 117–120.

58. Trost, B. M., Lupton, D. W. *Org. Lett.* **2007**, 9, 8–11.

59. Liu, S., Gao, W. C., Miao, Y. H., Wang, M. C. *J. Org. Chem.* **2019**, 84, 2652–2659.

60. Bulut, A., Aslan, A., Dogan, O. *J. Org. Chem.* **2008**, 73, 7373–7375.

61. Dogan, Ö., Polat-Çakir, S., Beksultanova, N., Altanlar, N., Şimşek, D., Karabıyık, H. *Tetrahedron Asymmetry* **2017**, 28, 324–329.

62. Tamamura, H., Yamashita, M., Nakajima, Y., Sakano, K., Otaka, A., Ohno, H., Ibuka, T., Fujii, N. *J. Chem. Soc. Perkin Trans.* **1999**, 20, 2983–2996.

63. Isleyen, A., Dogan, Ö. *Tetrahedron Asymmetry* **2007**, 18, 679–684.

64. Nájera, C., De Gracia Retamosa, M., Sansano, J. M. *Org. Lett.* **2007**, 9, 4025–4028.

65. Yavuz, S., Özkan, H., Tok, G., Dişli, A. *J. Heterocycl. Chem.* **2013**, 50, 1437–1440.

66. Bai, J. F., Wang, L. L., Peng, L., Guo, Y. L., Ming, J. N., Wang, F. Y., Xu, X. Y., Wang, L. X. *European J. Org. Chem.* **2011**, 23, 4472–4478.

67. Zeng, W., Zhou, Y. G. *Tetrahedron Lett.* **2007**, 48, 4619–4622.

68. Wu, Y., Xu, B., Liu, B., Zhang, Z. M., Liu, Y. *Org. Biomol. Chem.* **2019**, 17, 1395–1401.

69. Bai, X. F., Zhang, J., Xia, C. G., Xu, J. X., Xu, L. W. *Tetrahedron* **2016**, 72, 2690–2699.

70. Shi, J., Zhao, M., Lei, Z., Shi, M. *J. Org. Chem.* **2008**, 73, 305–308.

71. Caleffi, G. S., Larranãga, O., Ferrándiz-Saperas, M., Costa, P. R. R., Nájera,

C., De Cózar, A., Cossió, F. P., Sansano, J. M. *J. Org. Chem.* **2019**, 84, 10593–10605.

72. Kim, H. Y., Shih, H. J., Knabe, W. E., Oh, K. *Angew. Chem. Int. Ed.* **2009**, 48, 7420–7423.

73. Cayuelas, A., Larrañaga, O., Selva, V., Nájera, C., Akiyama, T., Sansano, J. M., De Cózar, A., Miranda, J. I., Cossío, F. P. *Chem. A Eur. J.* **2018**, 24, 8092–8097.

74. Liang, G., Tong, M. C., Wang, C. J. *Adv. Synth. Catal.* **2009**, 351, 3101–3106.

75. Arai, T., Matsumura, E. *Synlett* **2014**, 25, 1776–1780.

76. Handa, S., Gnanadesikan, V., Matsunaga, S., Shibasaki, M. *J. Am. Chem. Soc.* **2010**, 132, 4925–4934.

APPENDICES

8.1 NMR Spectra for aziridine-2-phosphonate ring opening products

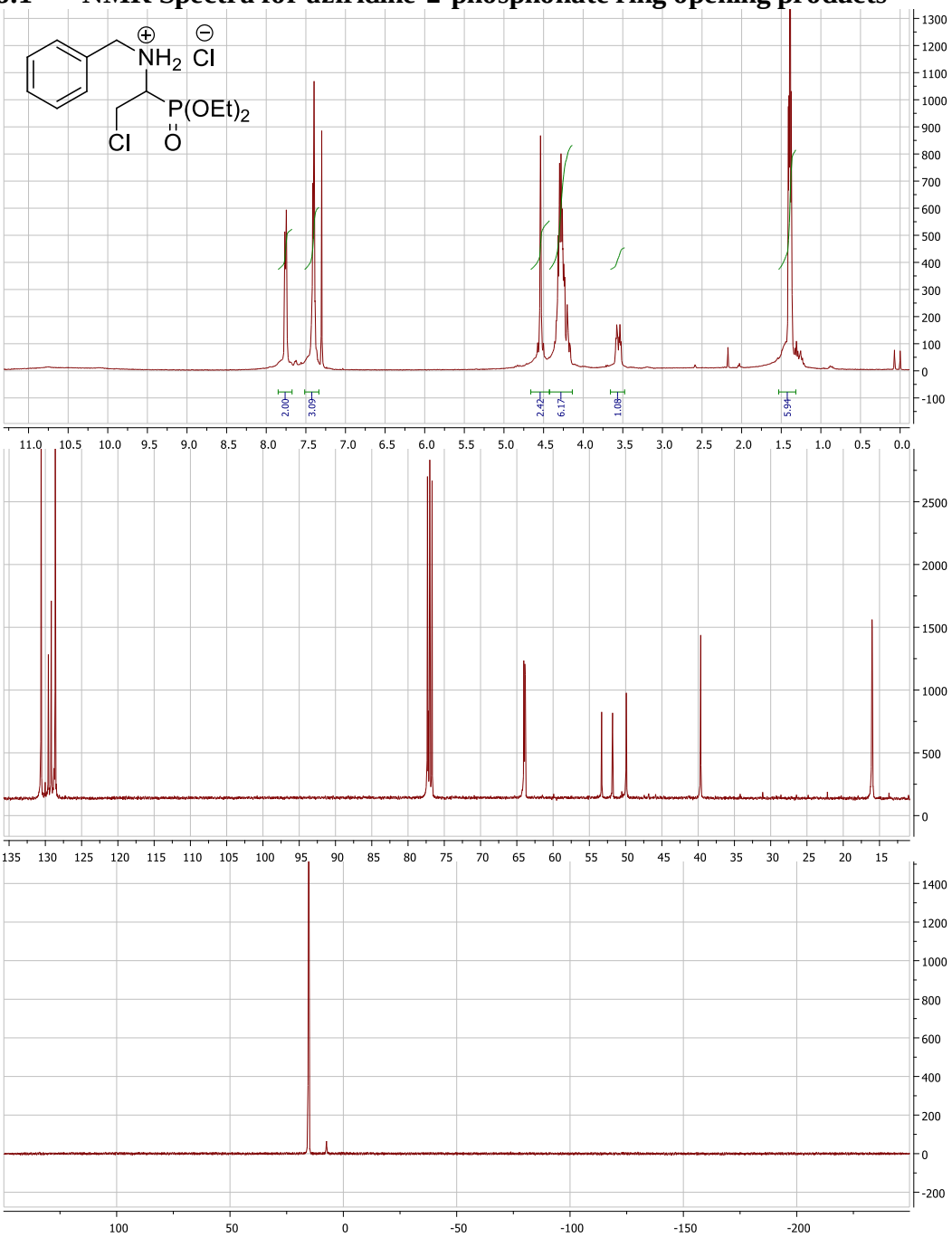


Figure 10. ^{1}H, ^{13}C and ^{31}P spectra of compound **4a**

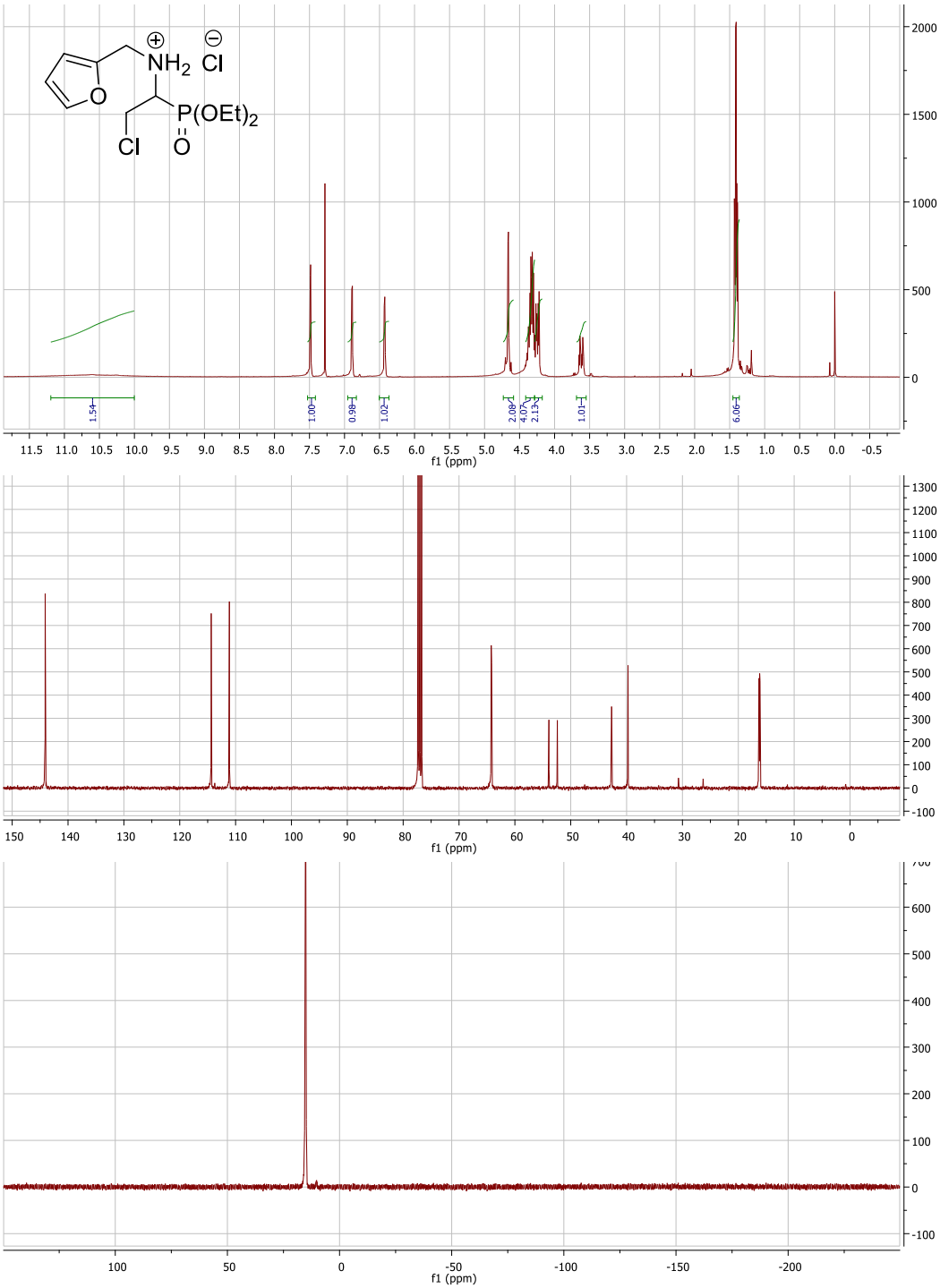


Figure 11. ^{1}H, ^{13}C and ^{31}P spectra of compound **4b**

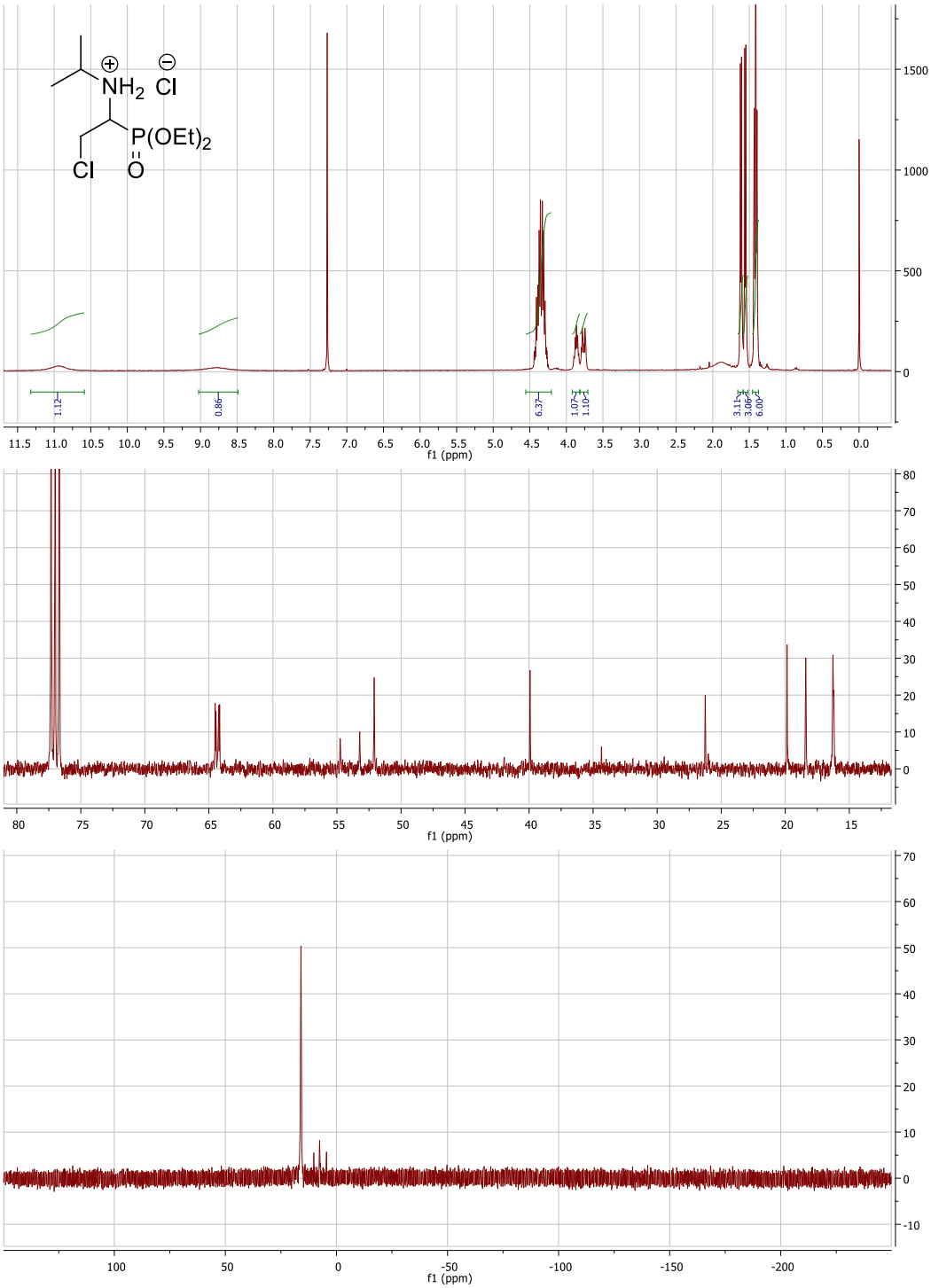


Figure 12. ^{1}H, ^{13}C and ^{31}P spectra of compound **4c**

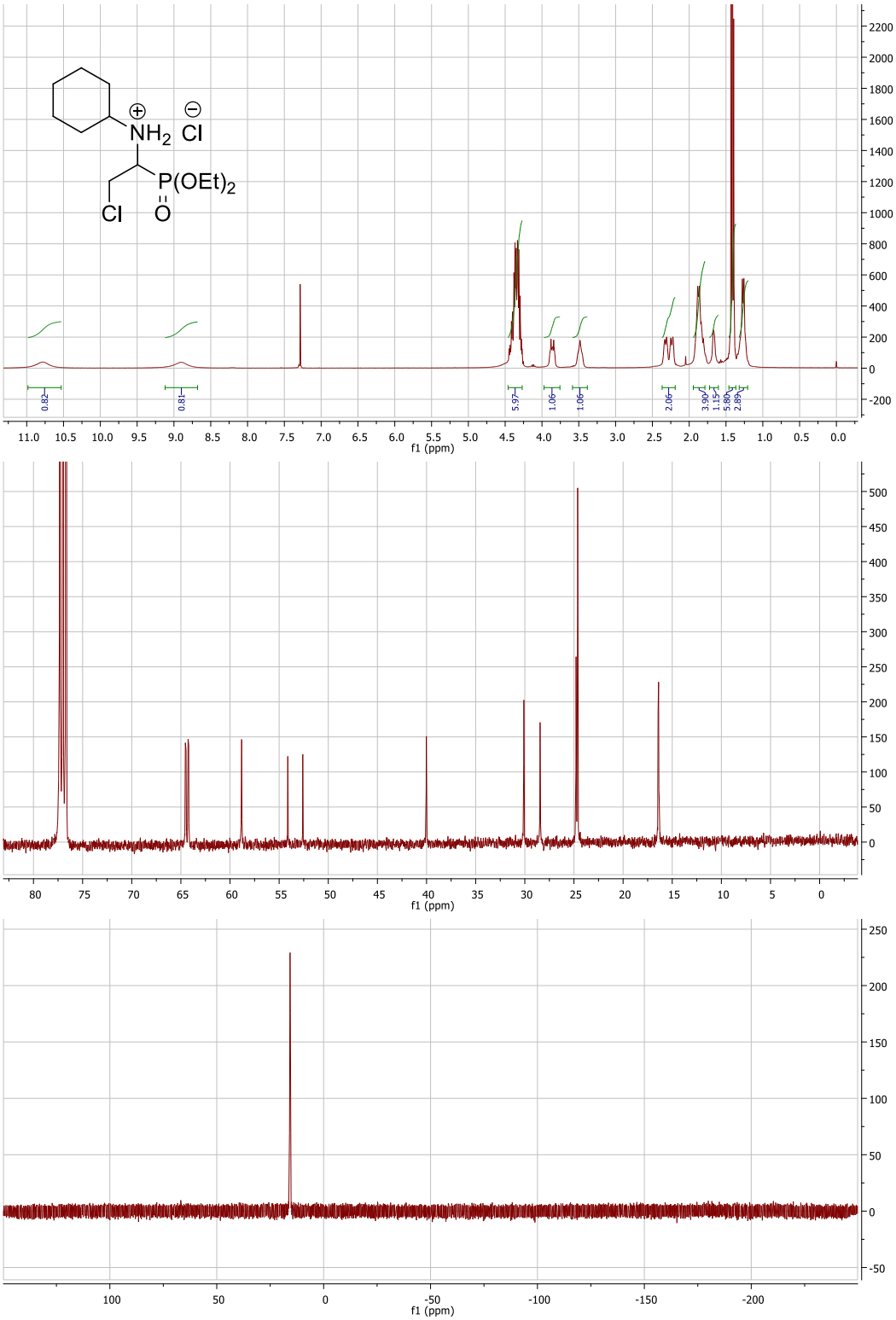


Figure 13. ^{1}H, ^{13}C and ^{31}P spectra of compound **4d**

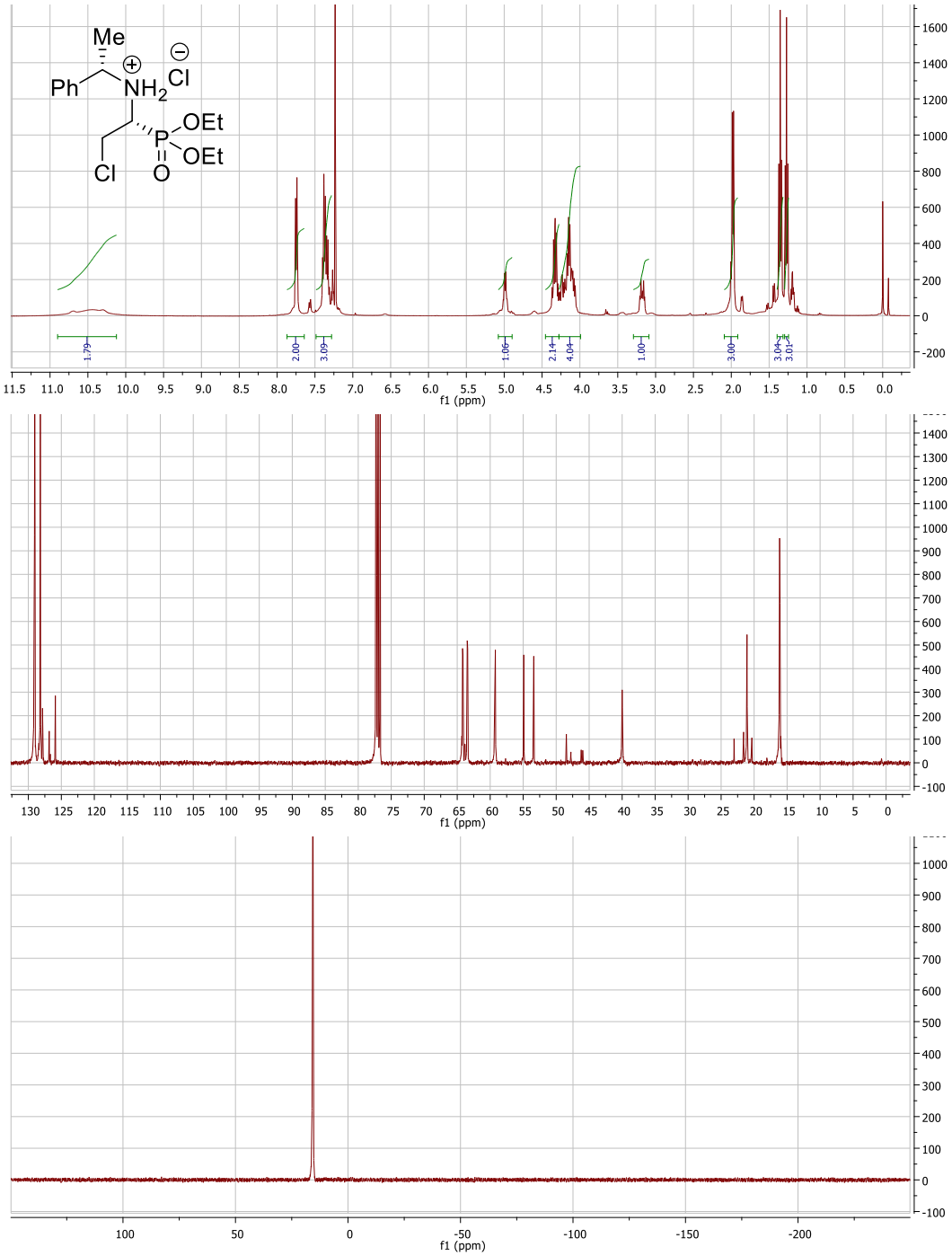


Figure 14. ^{1}H, ^{13}C and ^{31}P spectra of compound **4e**

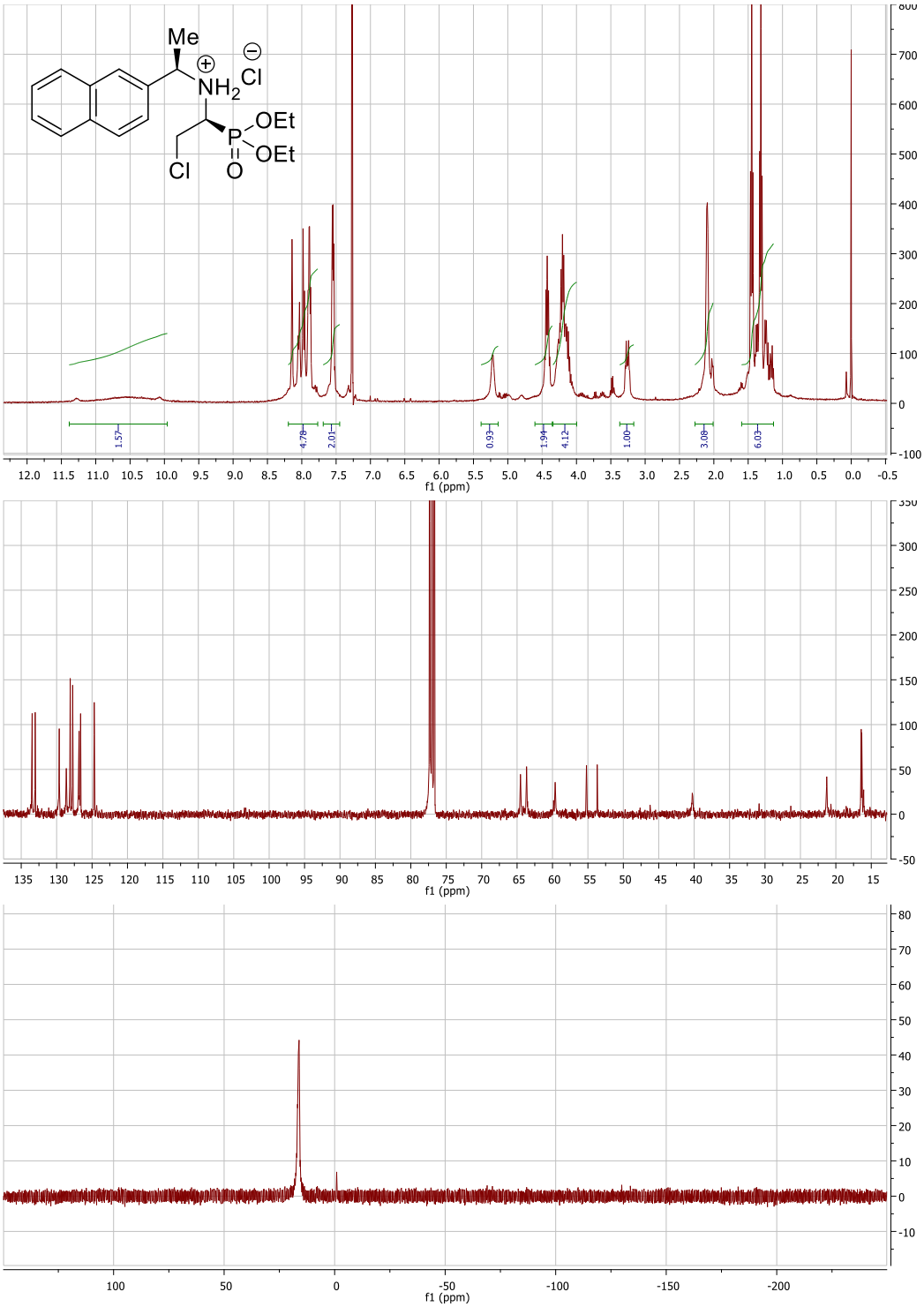


Figure 15. ^{1}H, ^{13}C and ^{31}P spectra of compound **4g**

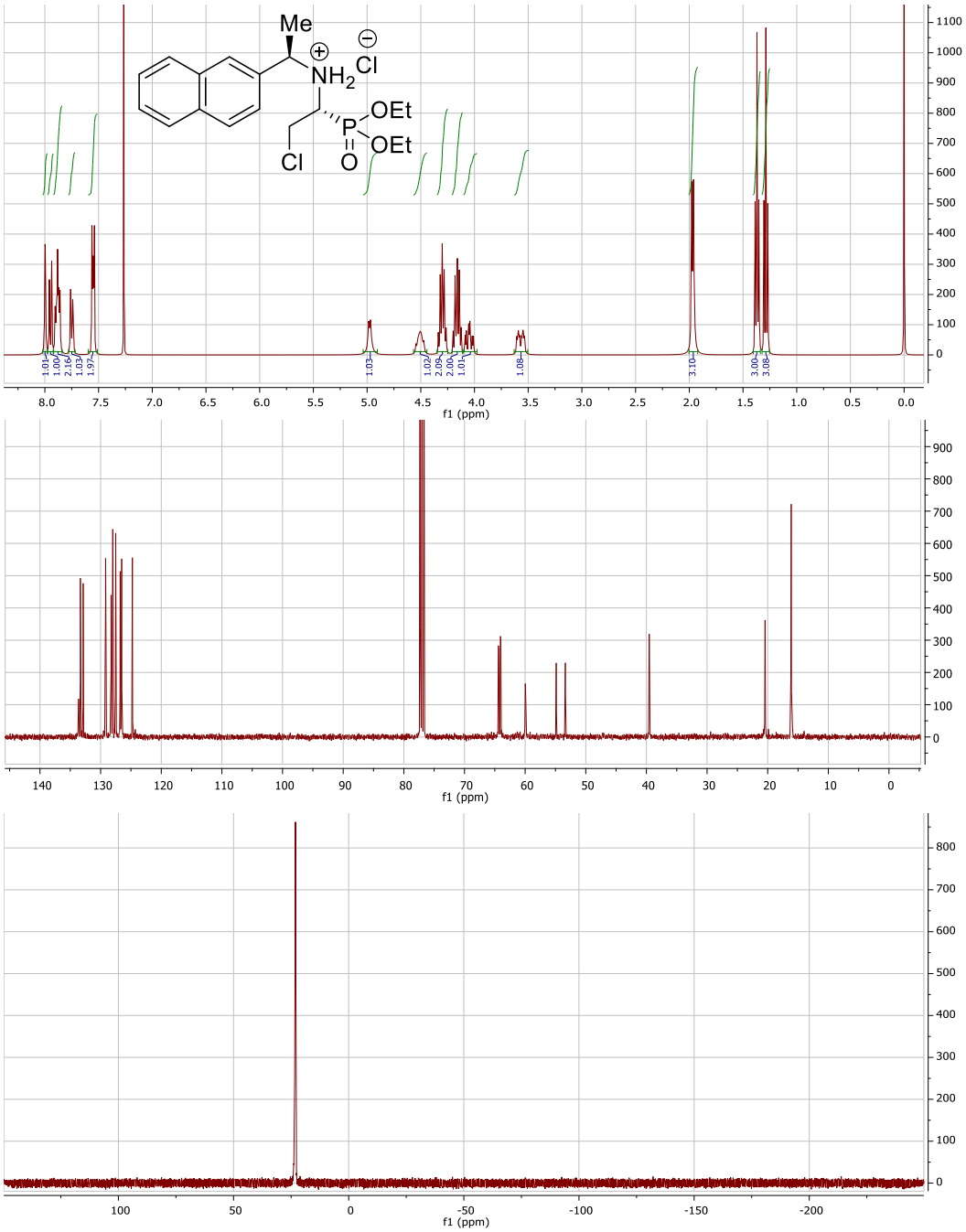


Figure 16. ^{1}H, ^{13}C and ^{31}P spectra of compound **4h**

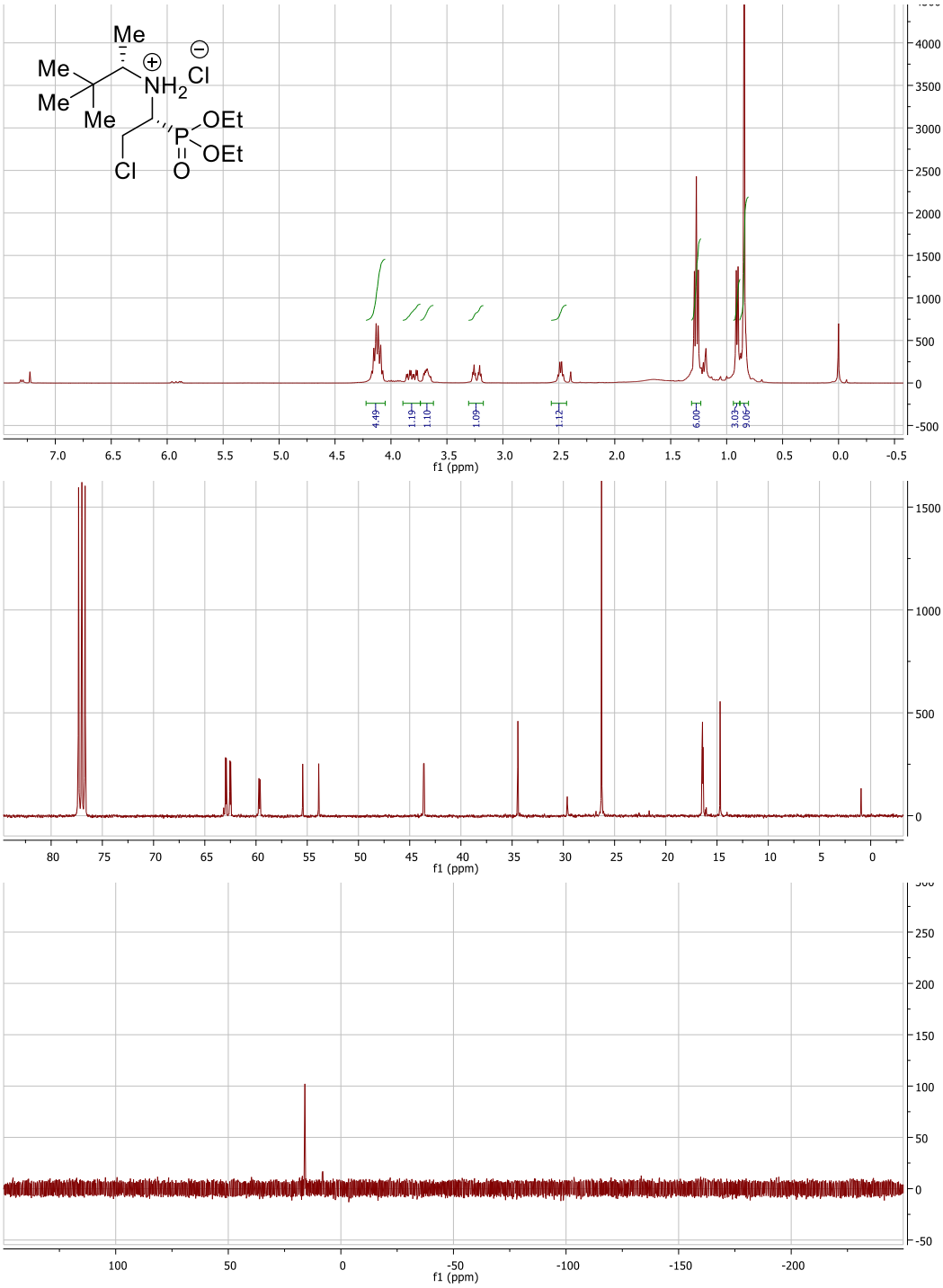


Figure 17. ^{1}H, ^{13}C and ^{31}P spectra of compound **4i**

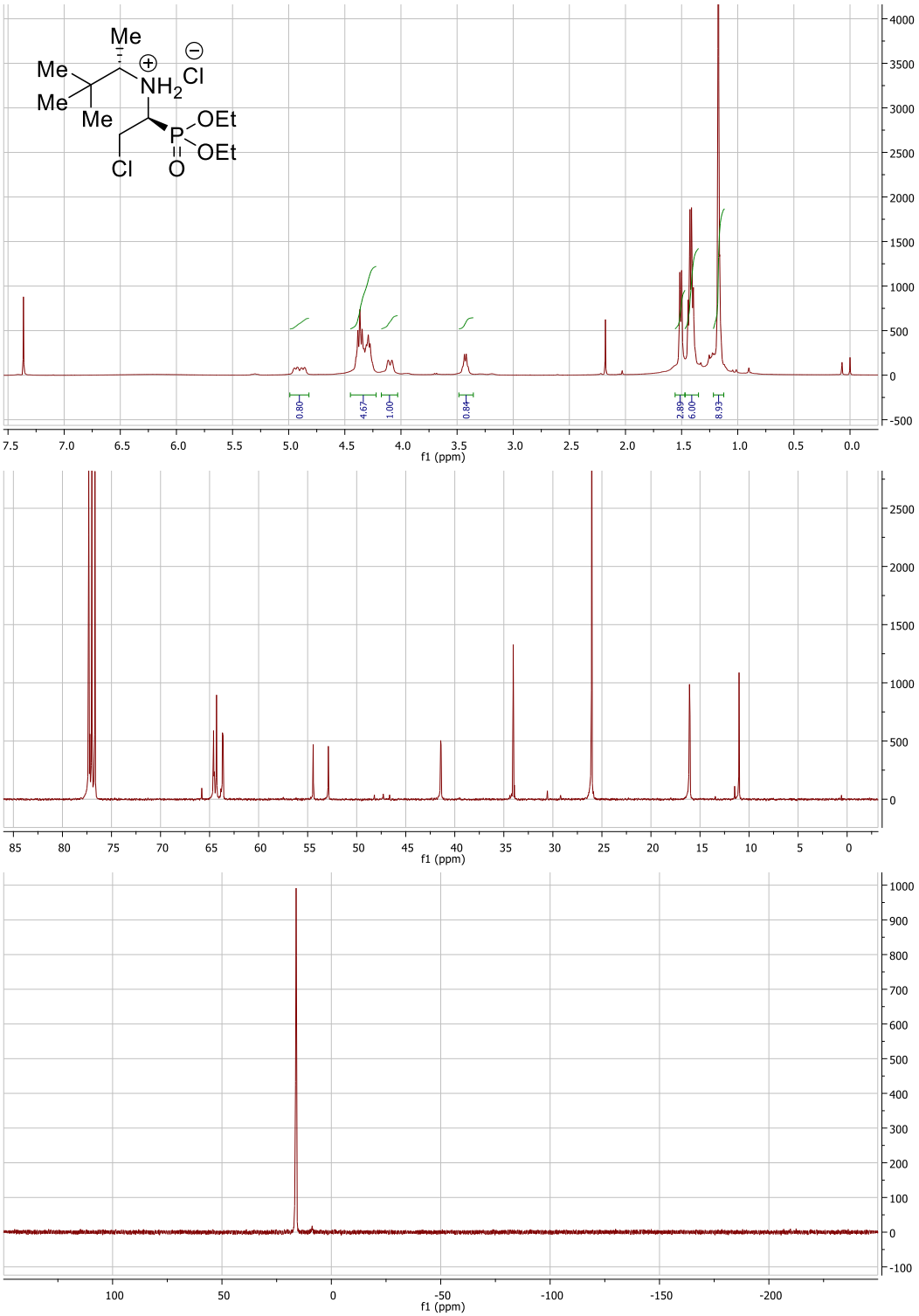


Figure 18. ^{1}H, ^{13}C and ^{31}P spectra of compound **4j**

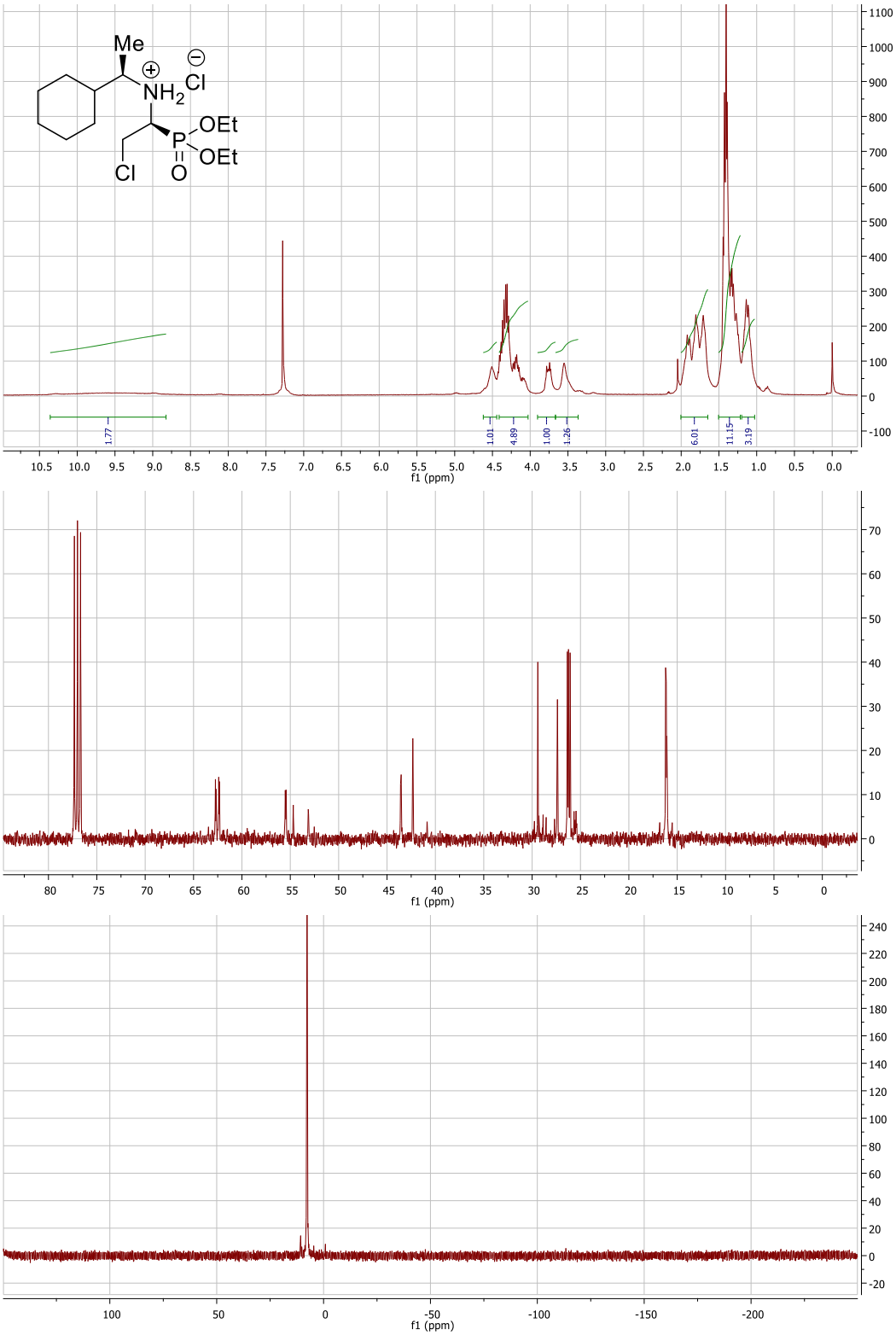


Figure 19. ^{1}H, ^{13}C and ^{31}P spectra of compound **4k**

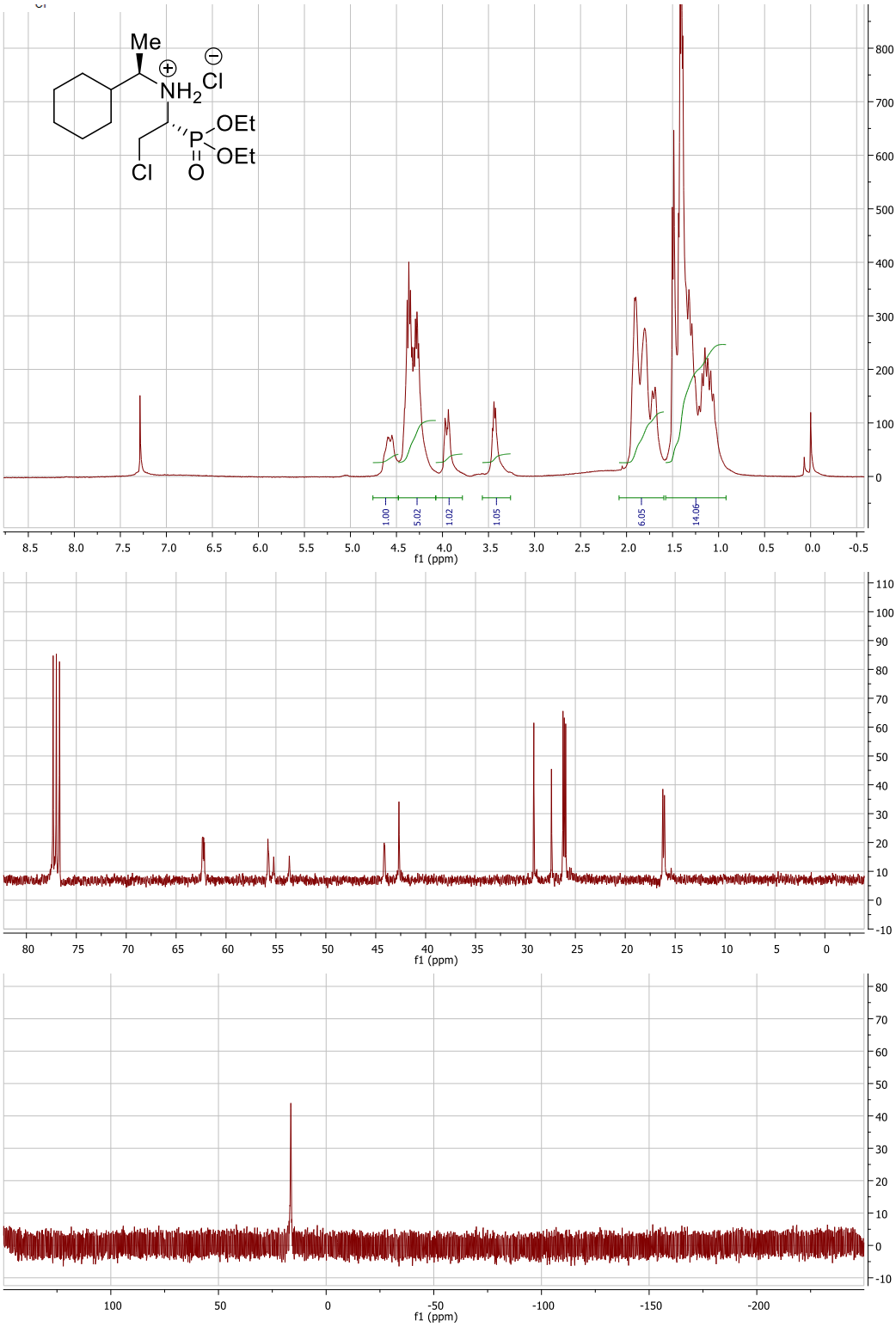


Figure 20. ^{1}H, ^{13}C and ^{31}P spectra of compound **4l**

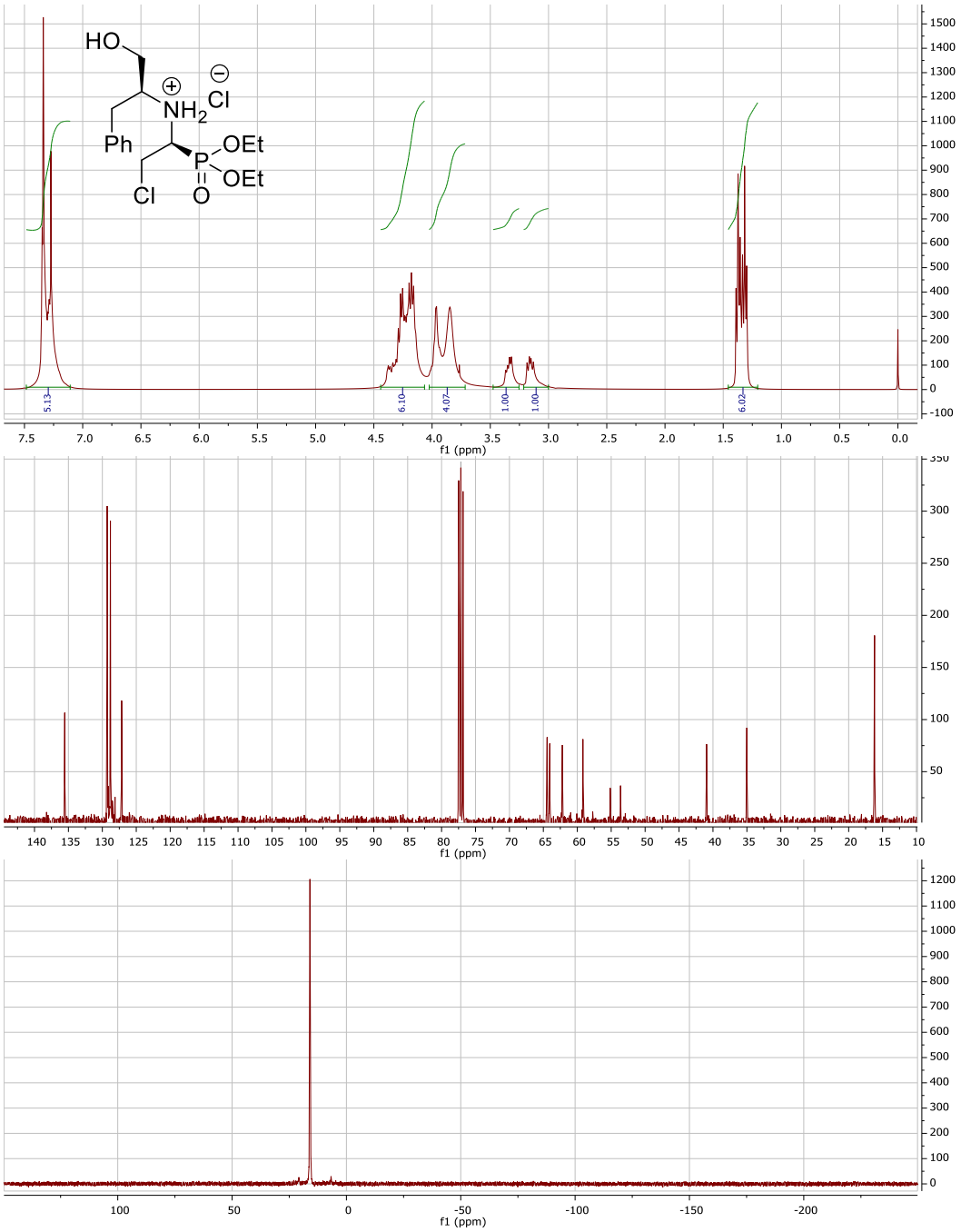


Figure 21. ^{1}H, ^{13}C and ^{31}P spectra of compound **4m**

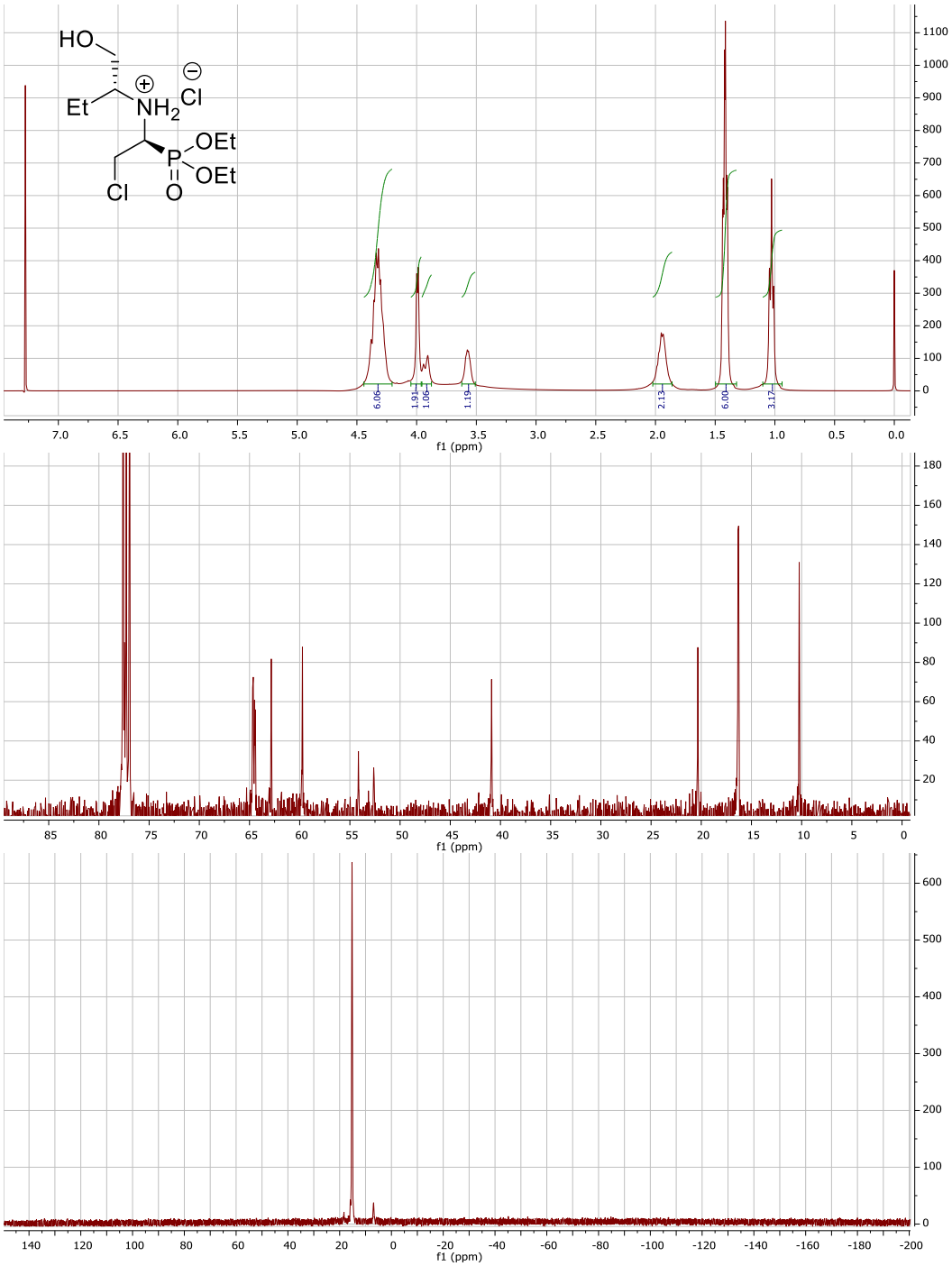


Figure 22. ^{1}H, ^{13}C and ^{31}P spectra of compound **4n**

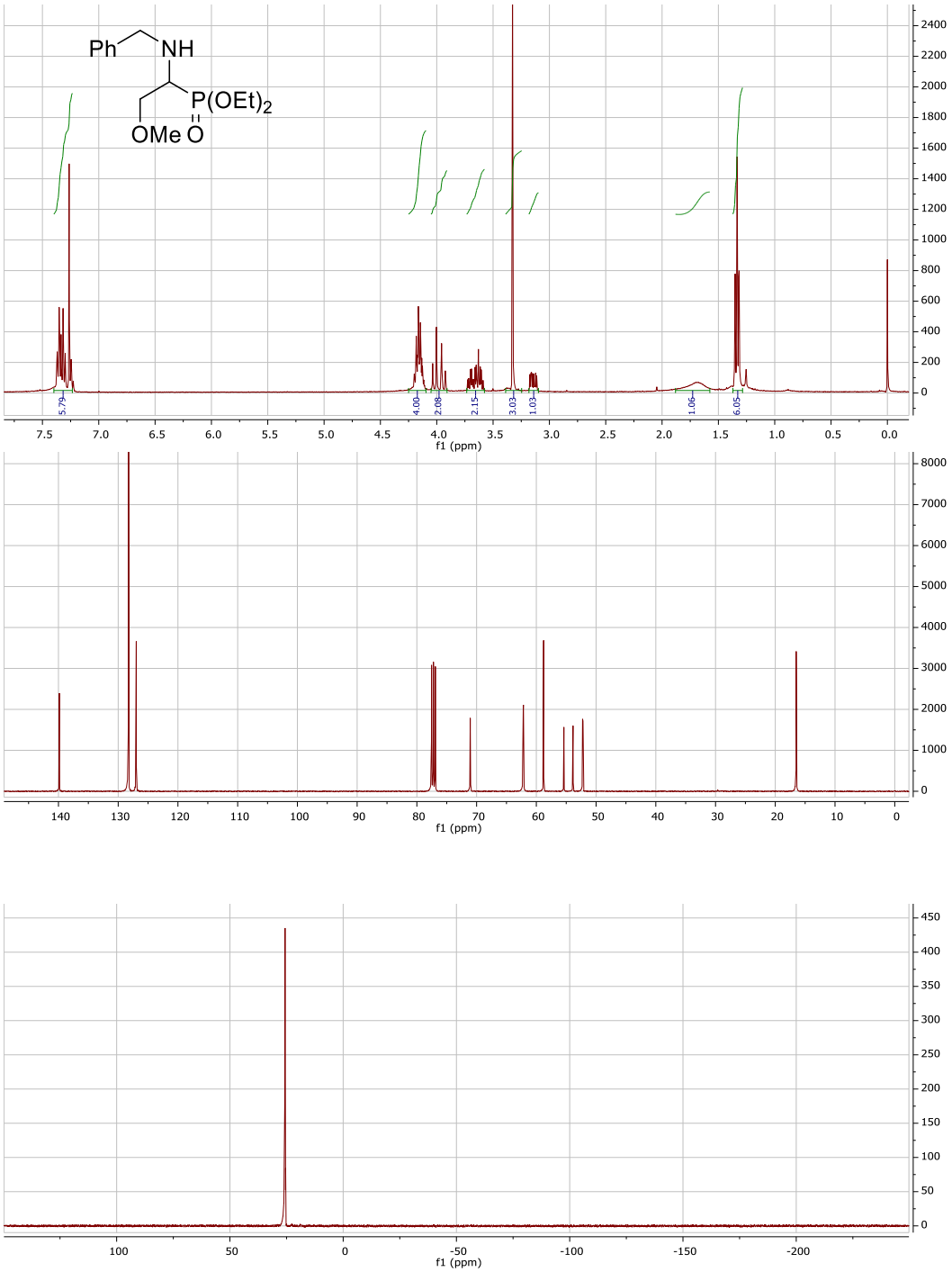


Figure 23. ^{1}H, ^{13}C and ^{31}P spectra of compound **5aa**

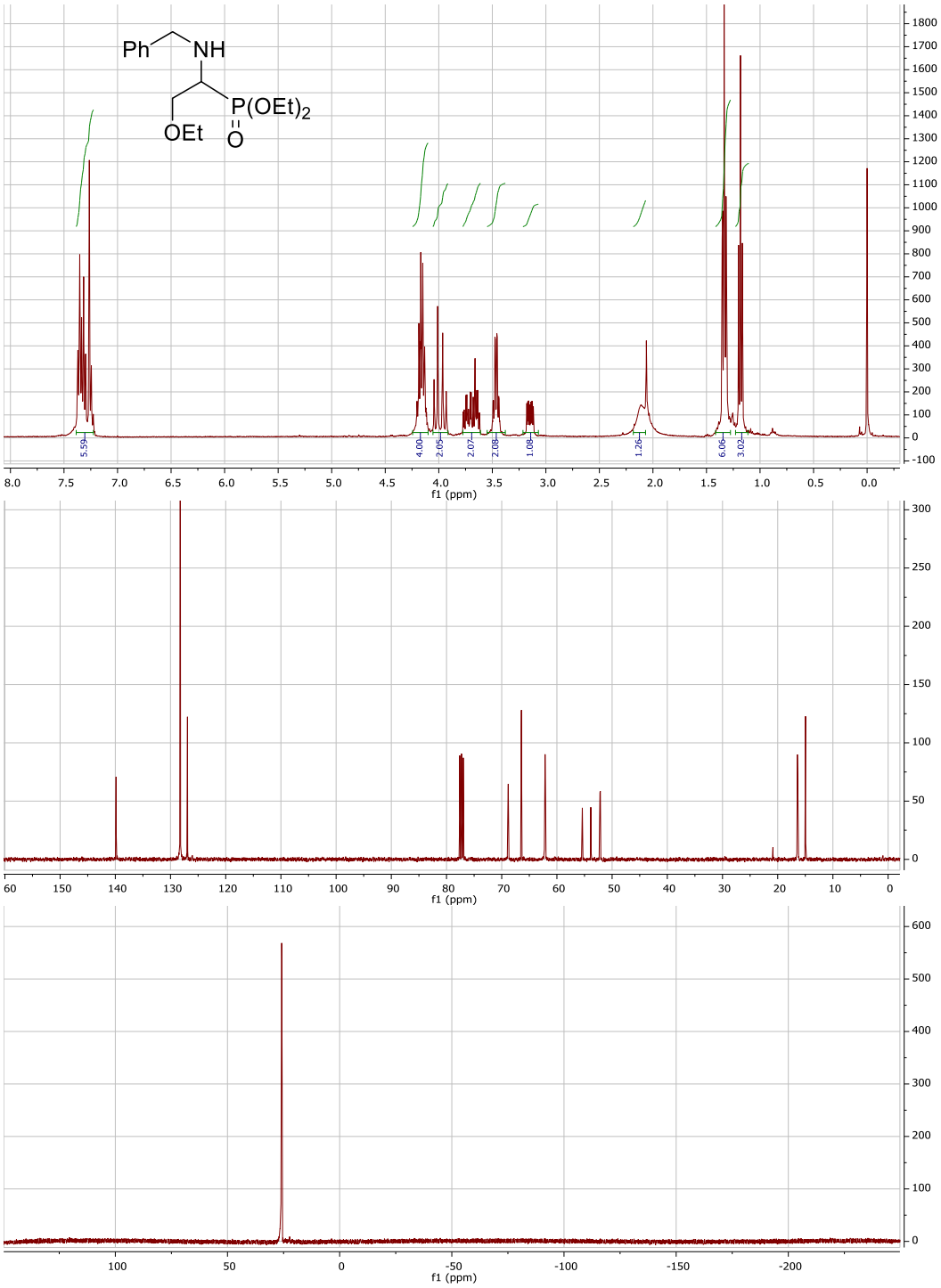


Figure 24. ^{1}H, ^{13}C and ^{31}P spectra of compound **5ab**

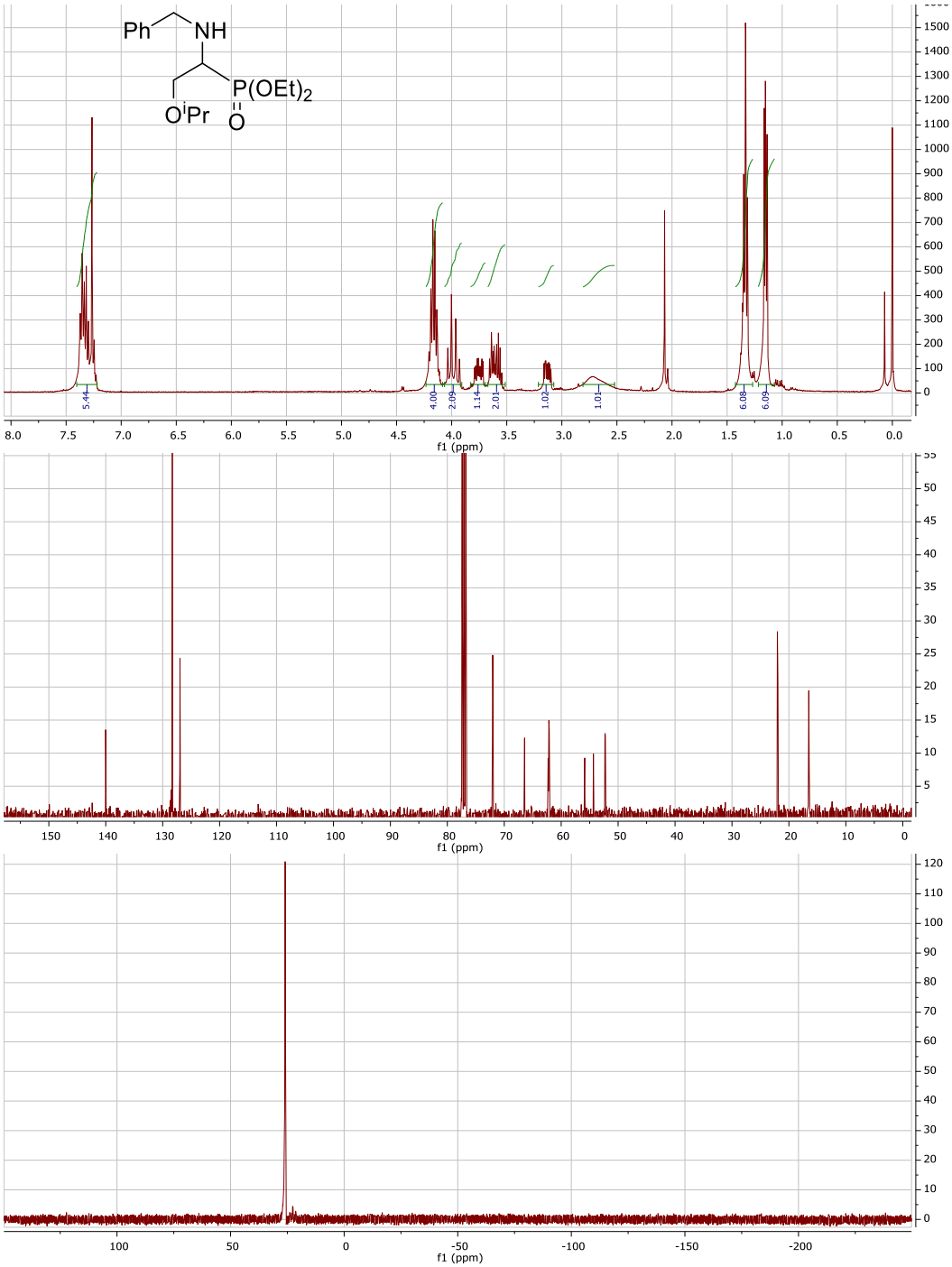


Figure 25. ^{1}H, ^{13}C and ^{31}P spectra of compound **5ac**

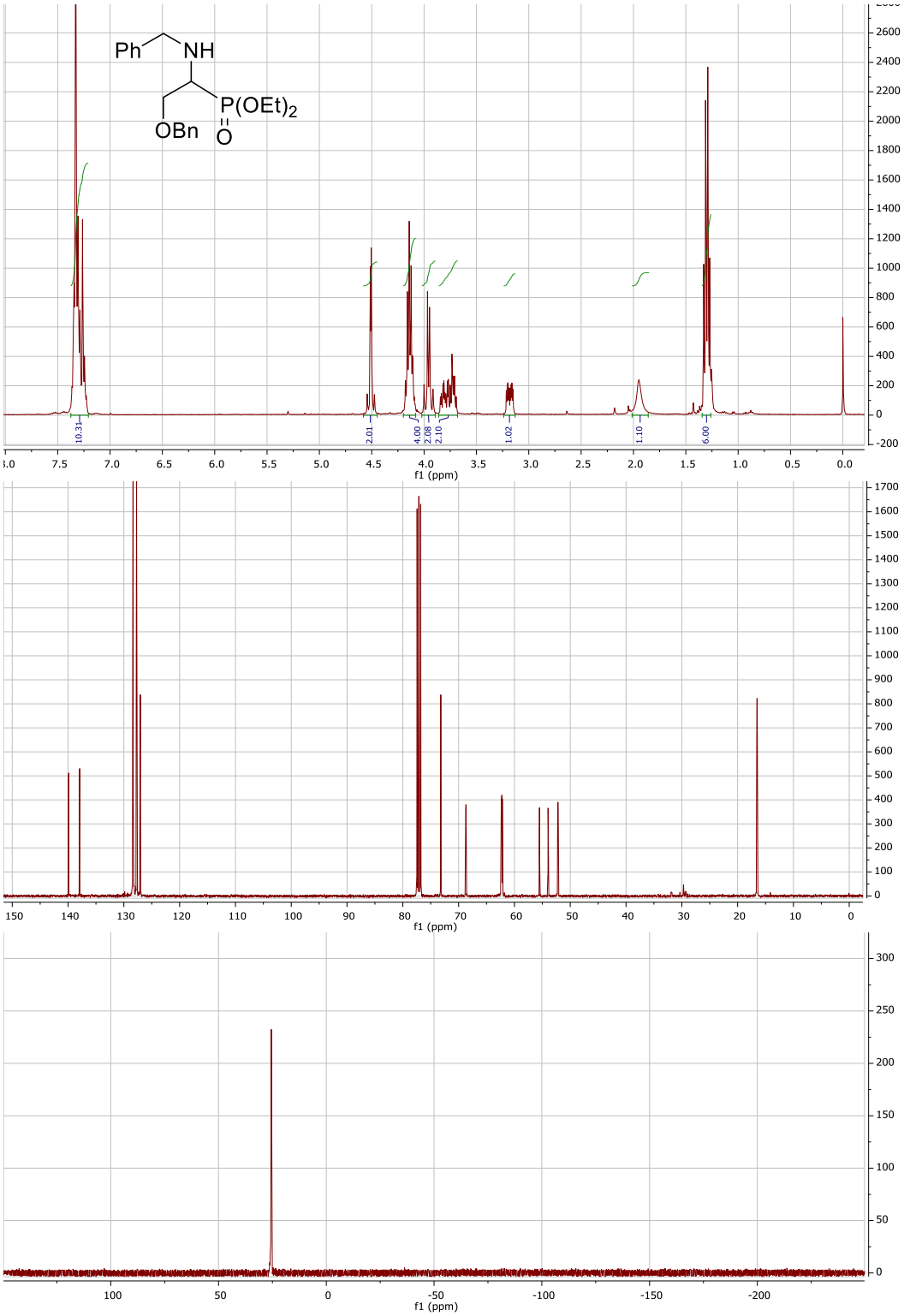
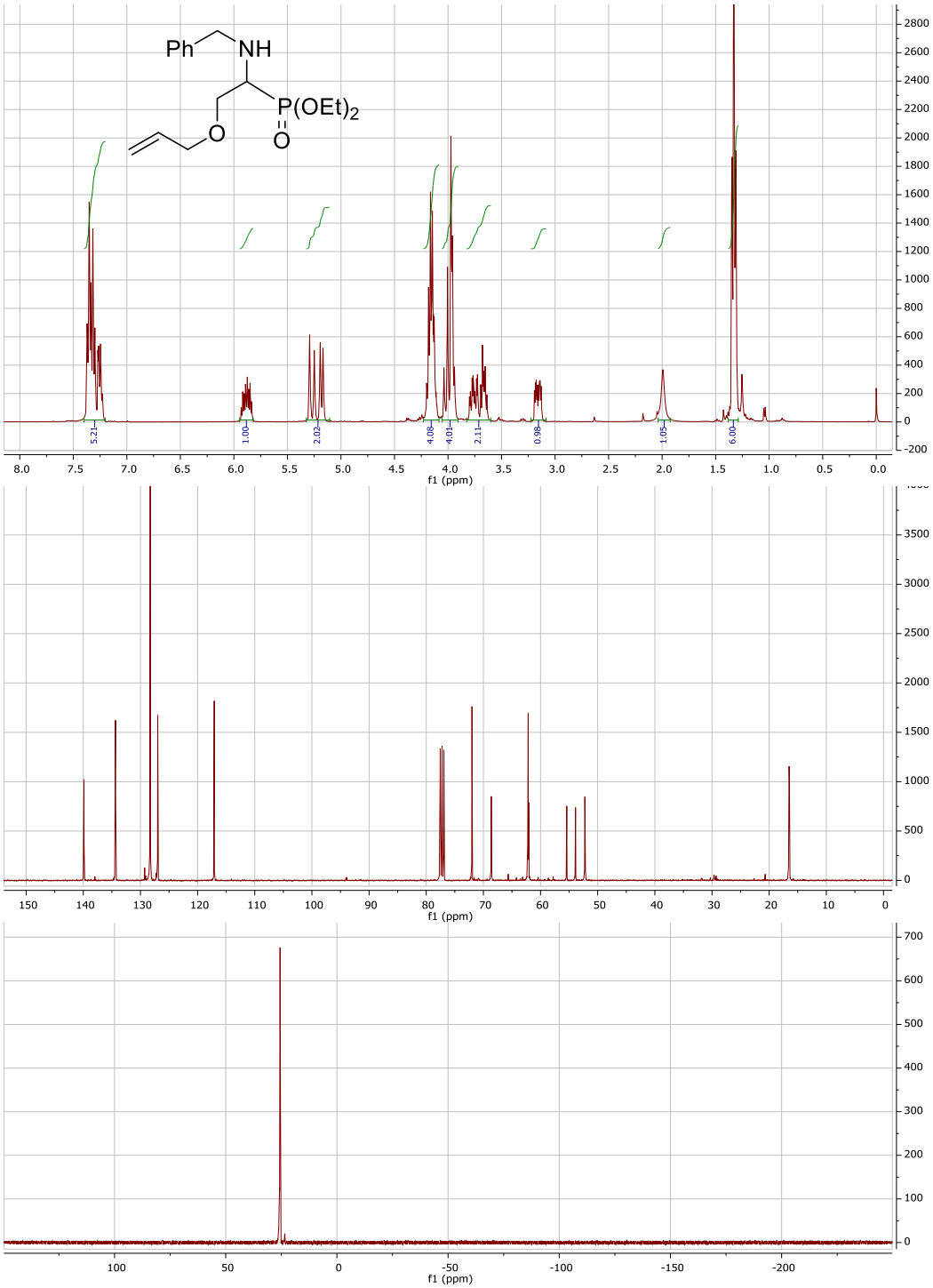


Figure 26. ^{1}H, ^{13}C and ^{31}P spectra of compound **5ad**



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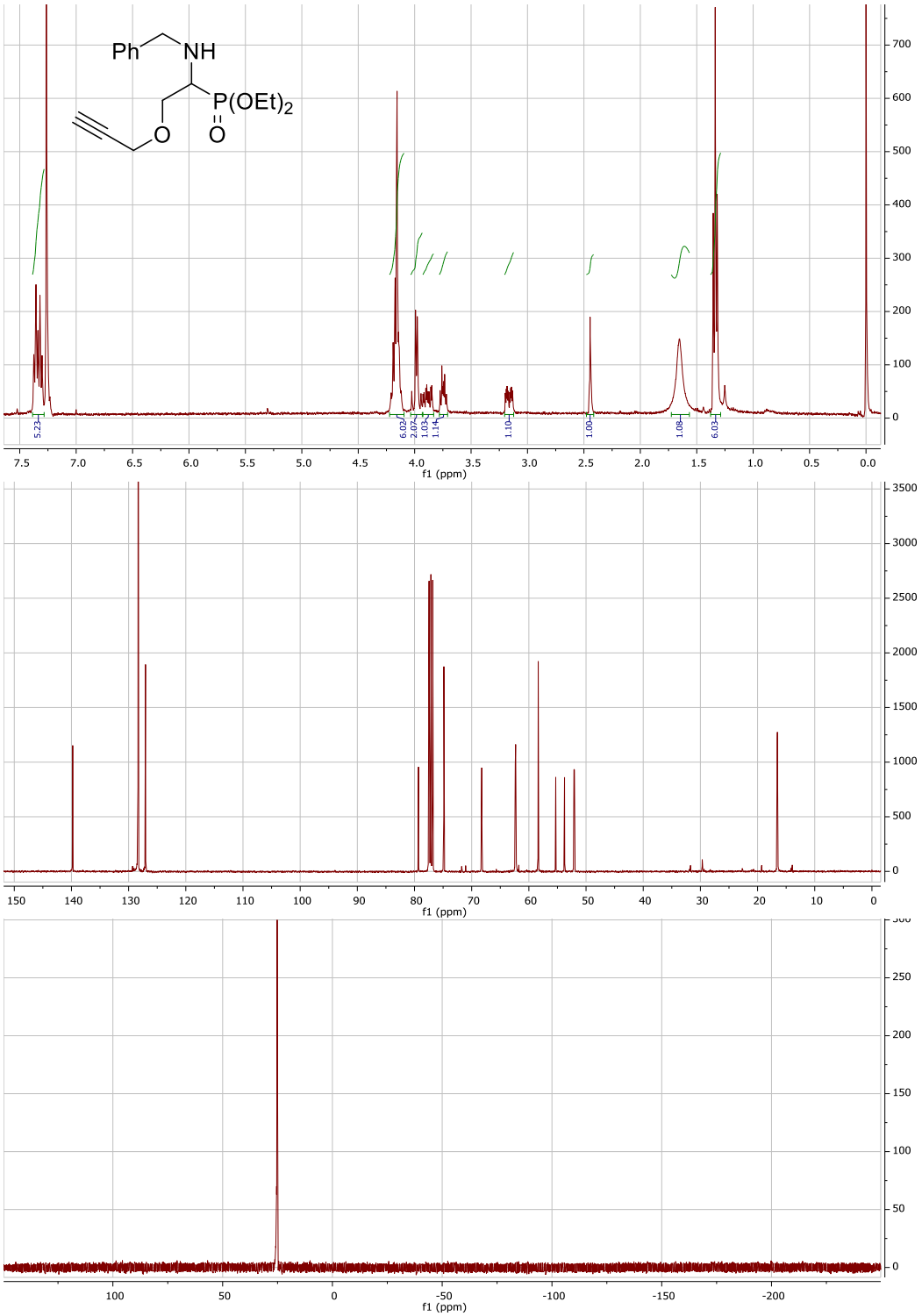


Figure 28. ^{1}H, ^{13}C and ^{31}P spectra of compound **5af**

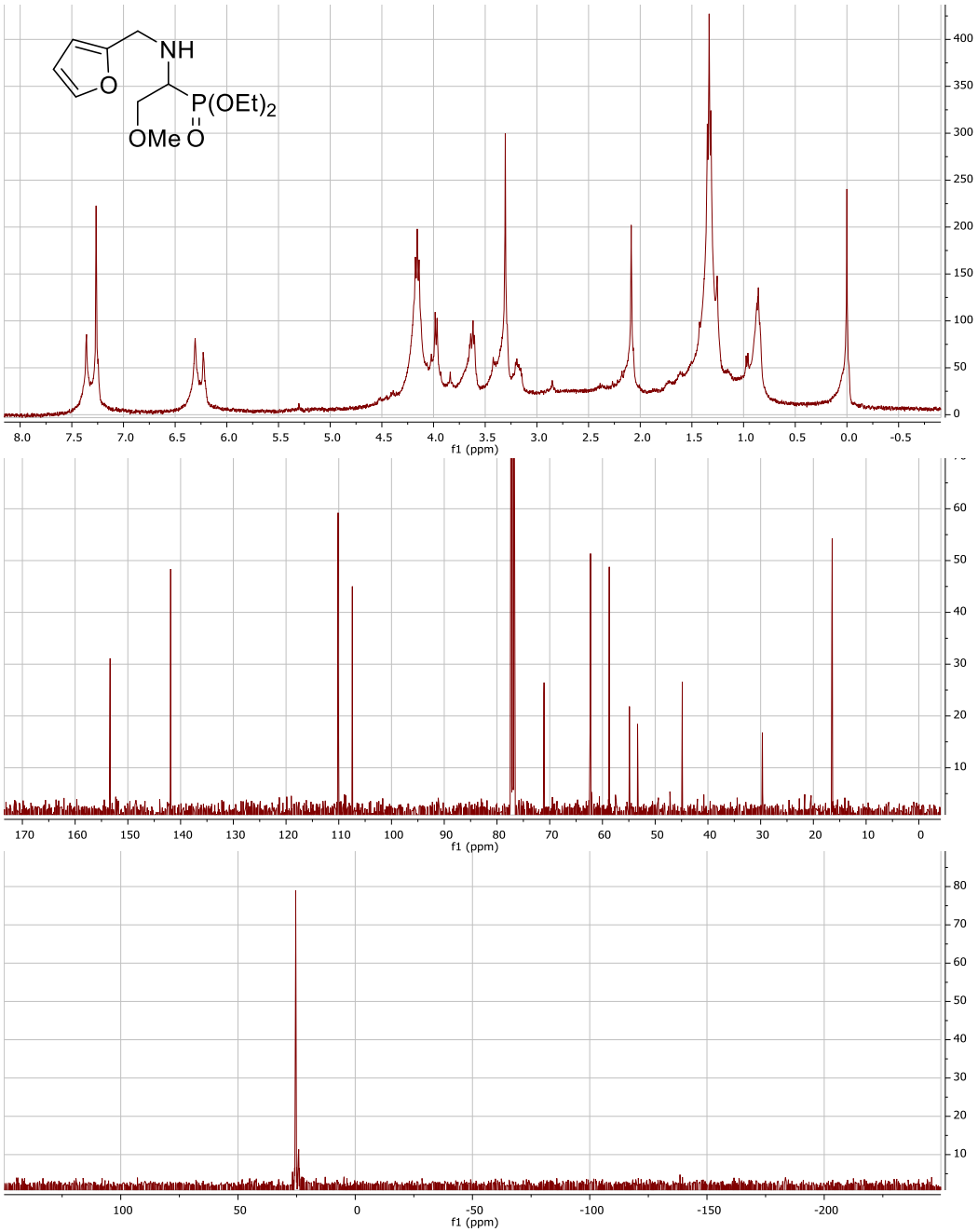


Figure 29. ^{1}H, ^{13}C and ^{31}P spectra of compound **5ba**

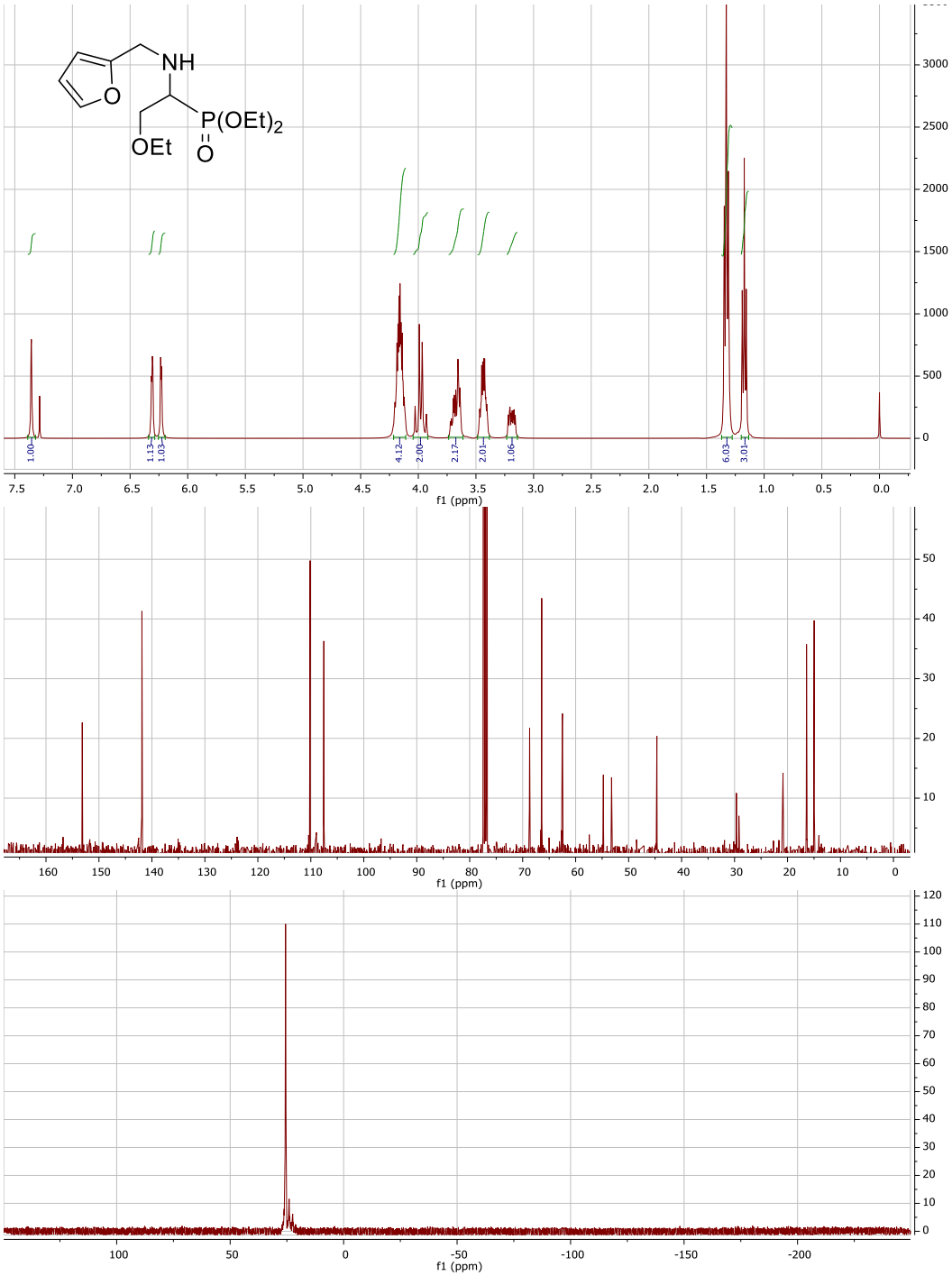


Figure 30. ^{1}H, ^{13}C and ^{31}P spectra of compound **5bb**

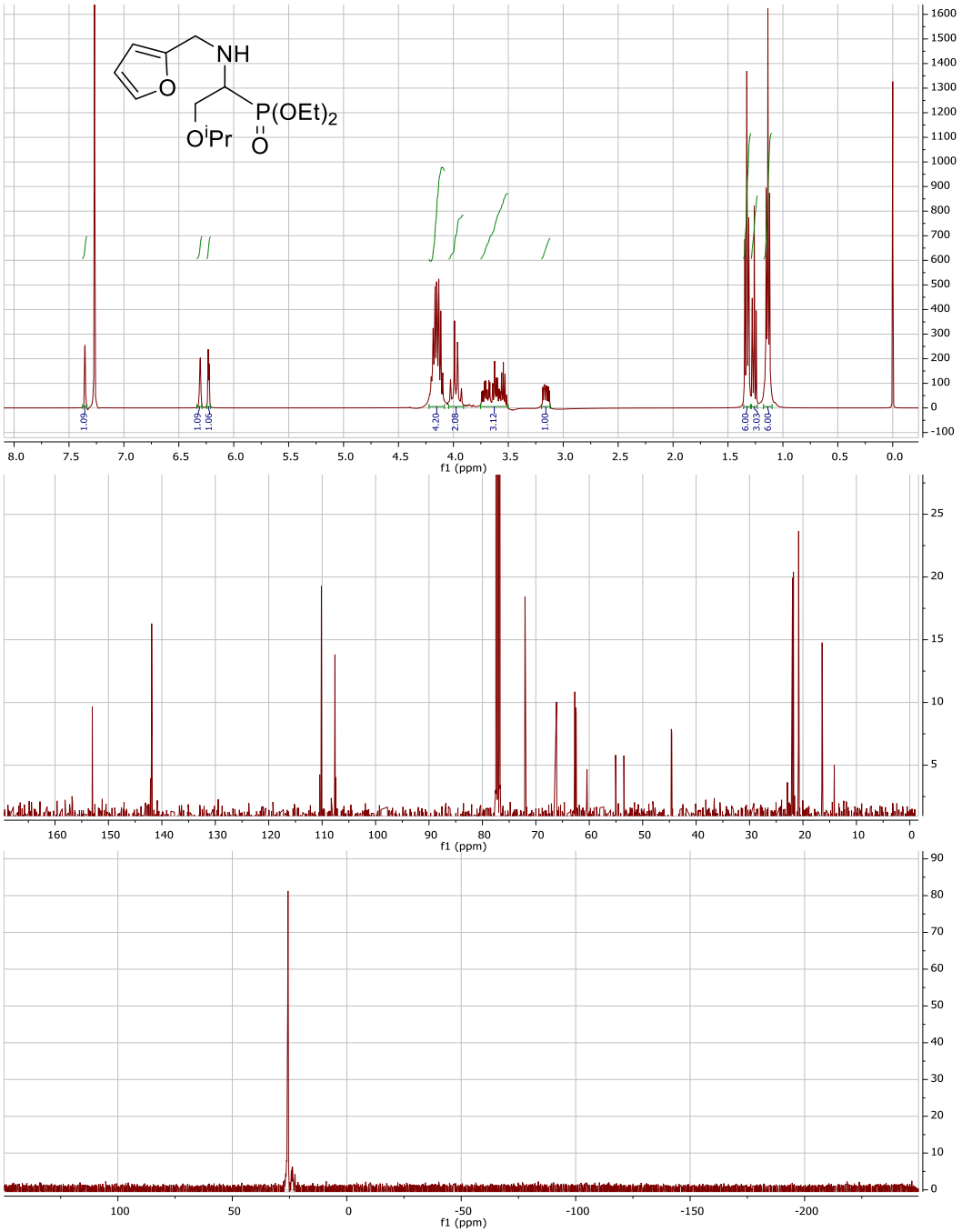


Figure 31. ^{1}H, ^{13}C and ^{31}P spectra of compound **5bc**

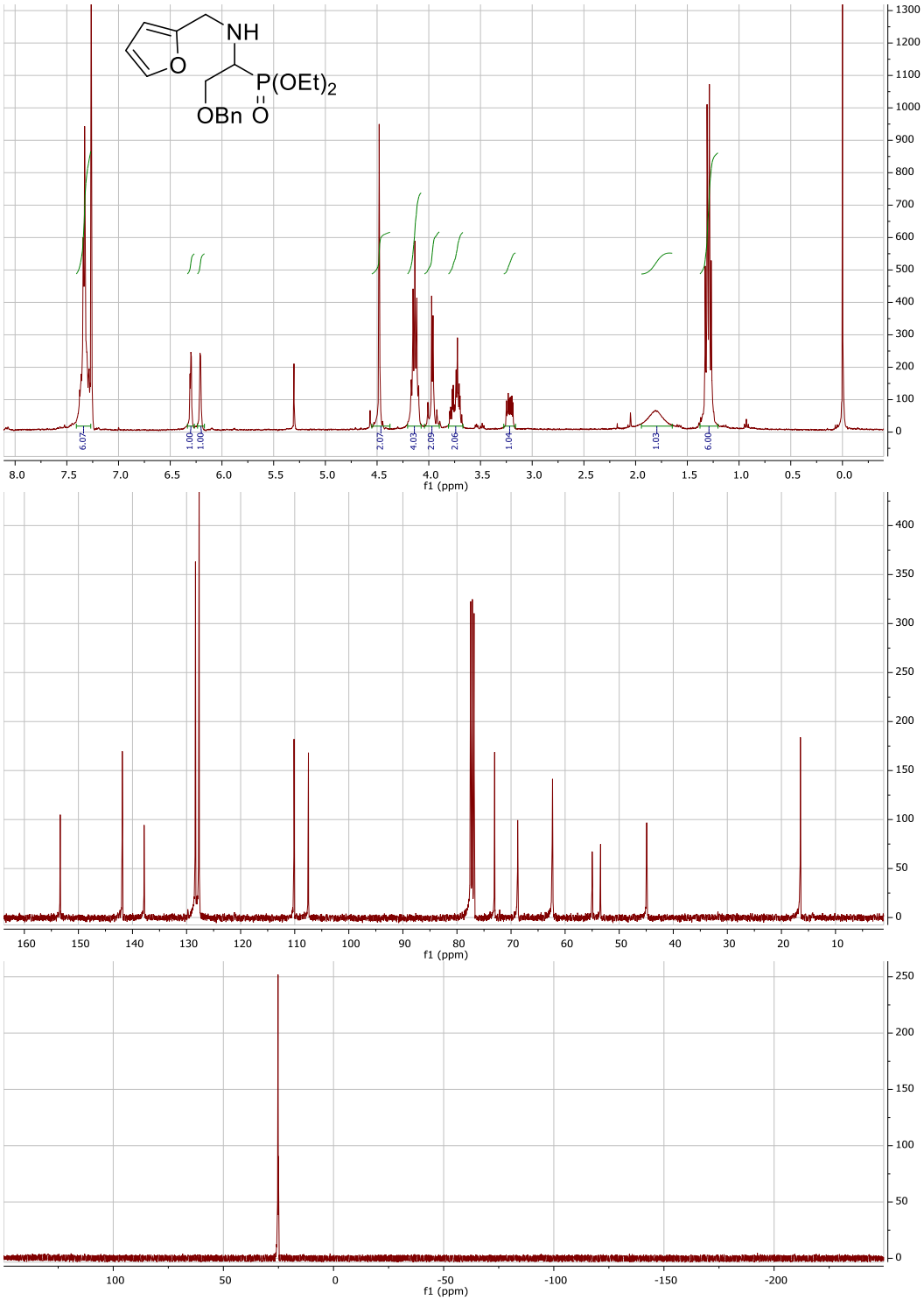


Figure 32. ^{1}H, ^{13}C and ^{31}P spectra of compound **5bd**

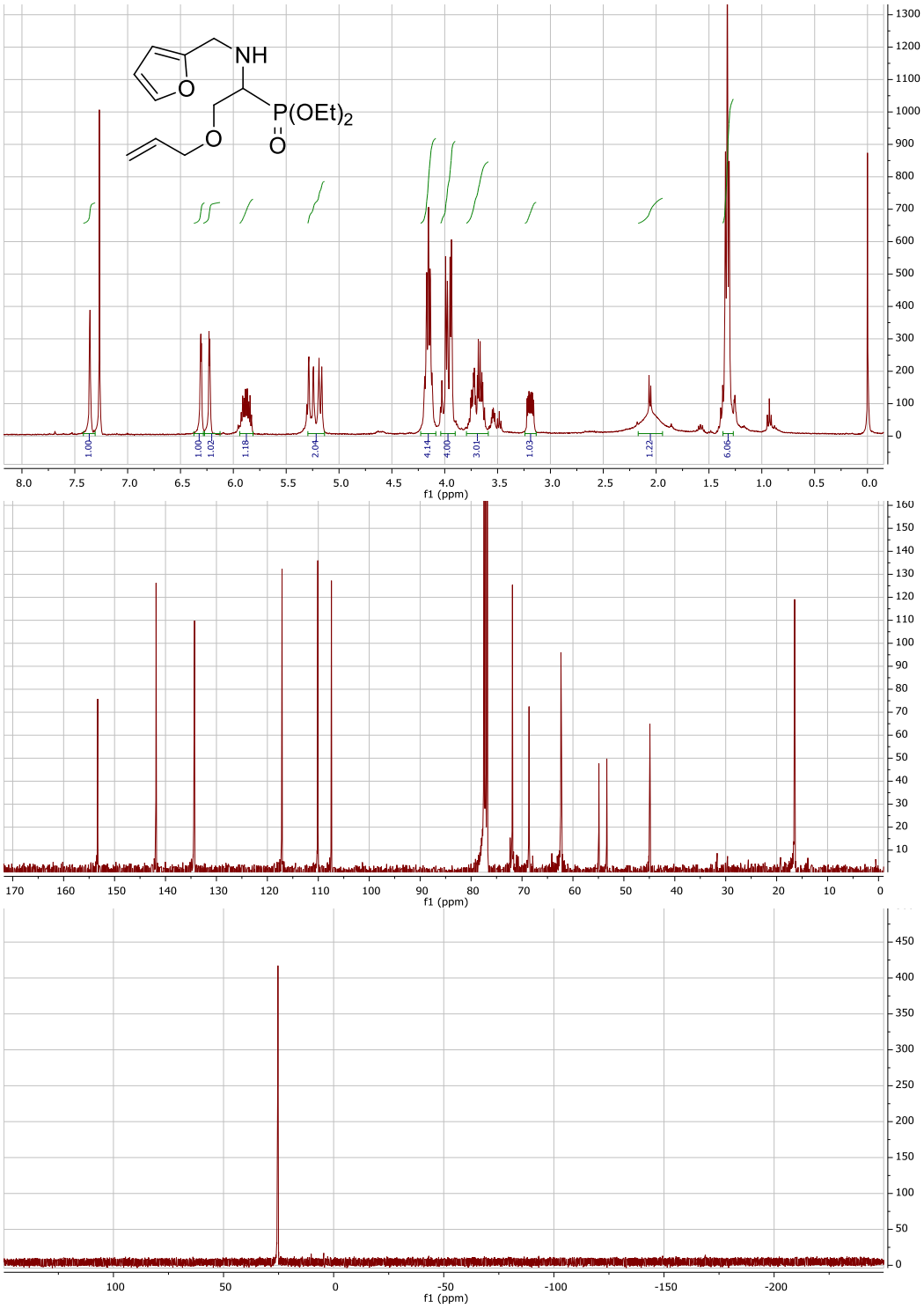


Figure 33. ^{1}H, ^{13}C and ^{31}P spectra of compound **5be**

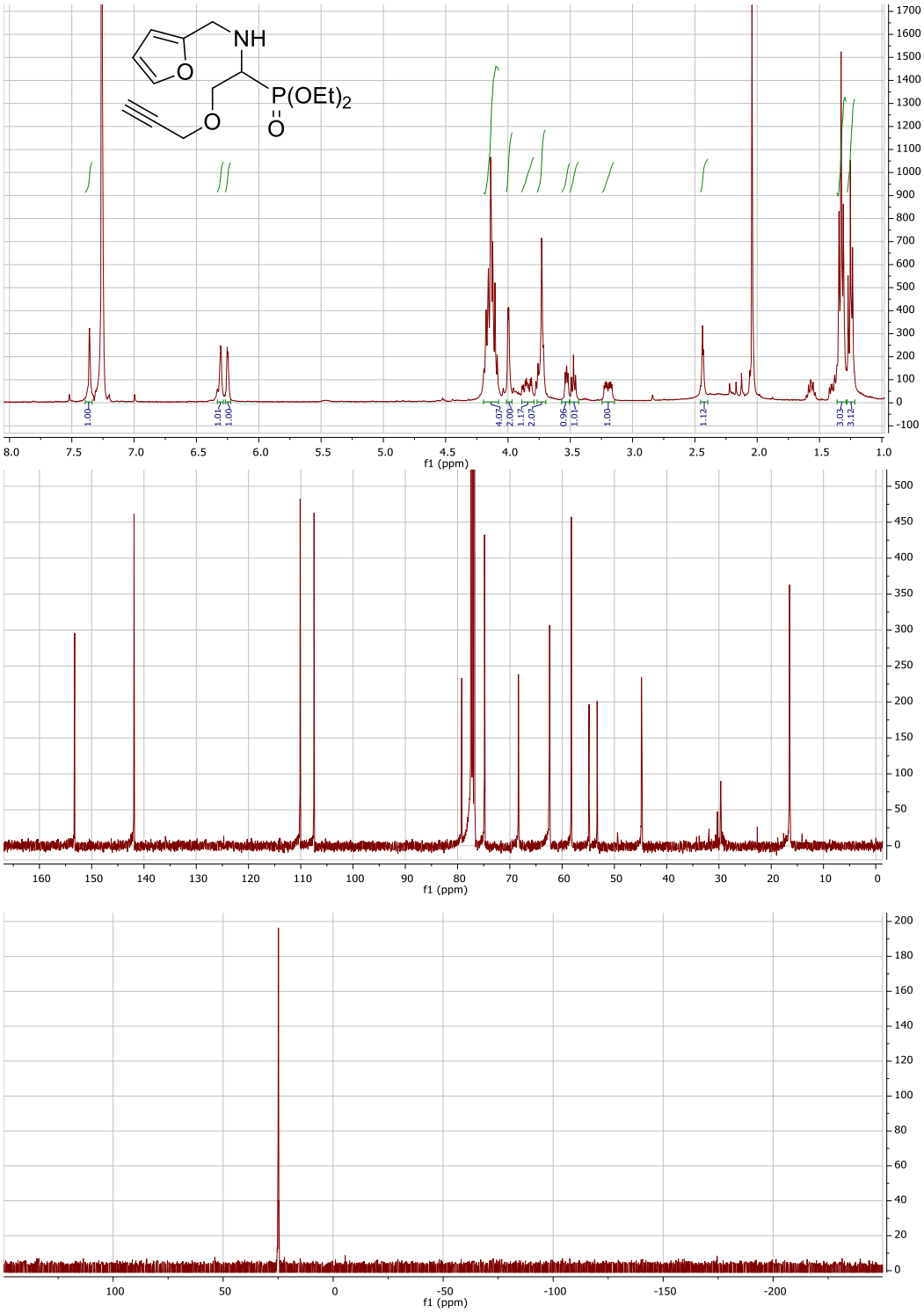
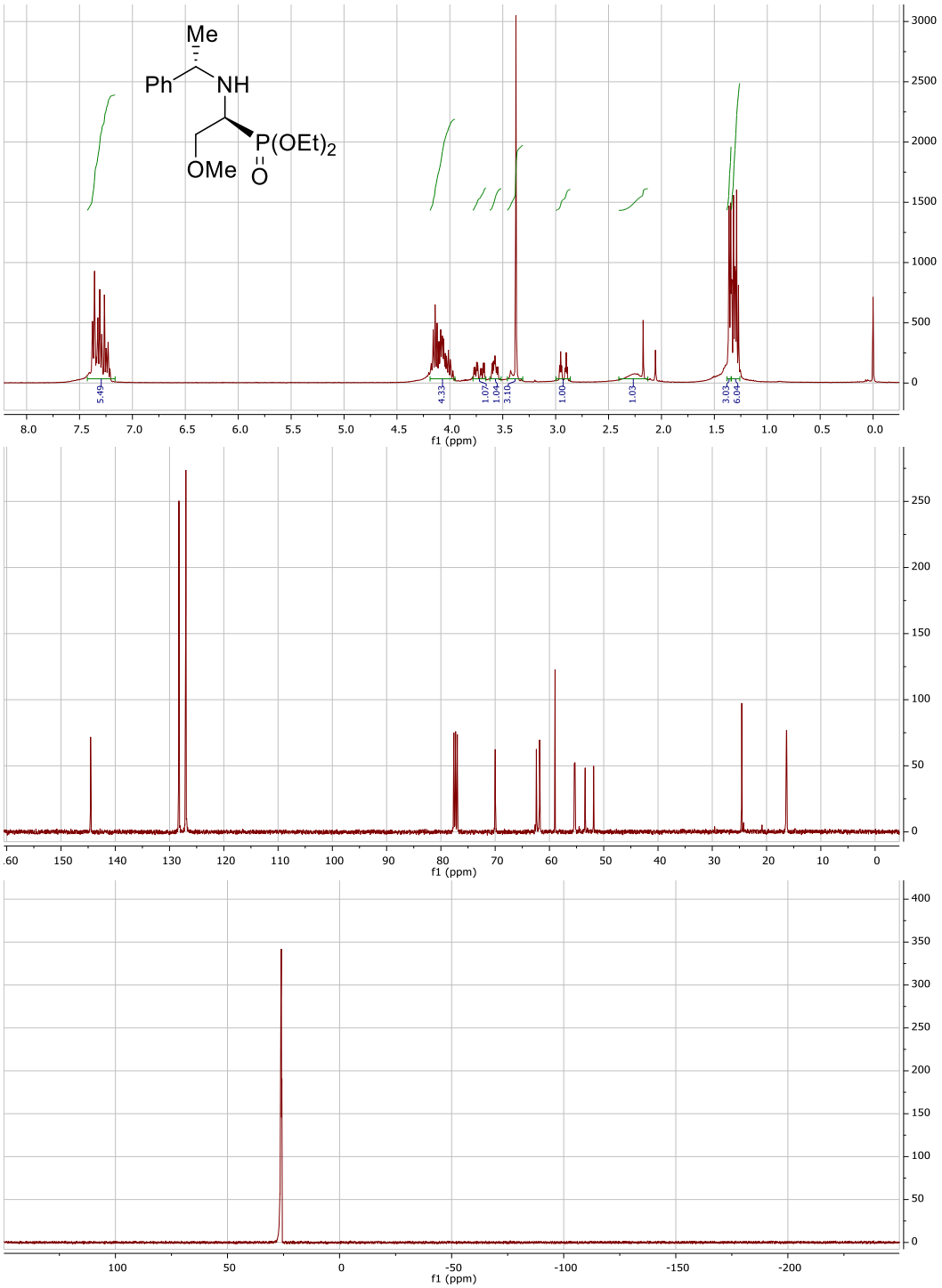


Figure 34. ^{1}H, ^{13}C and ^{31}P spectra of compound **5bf**



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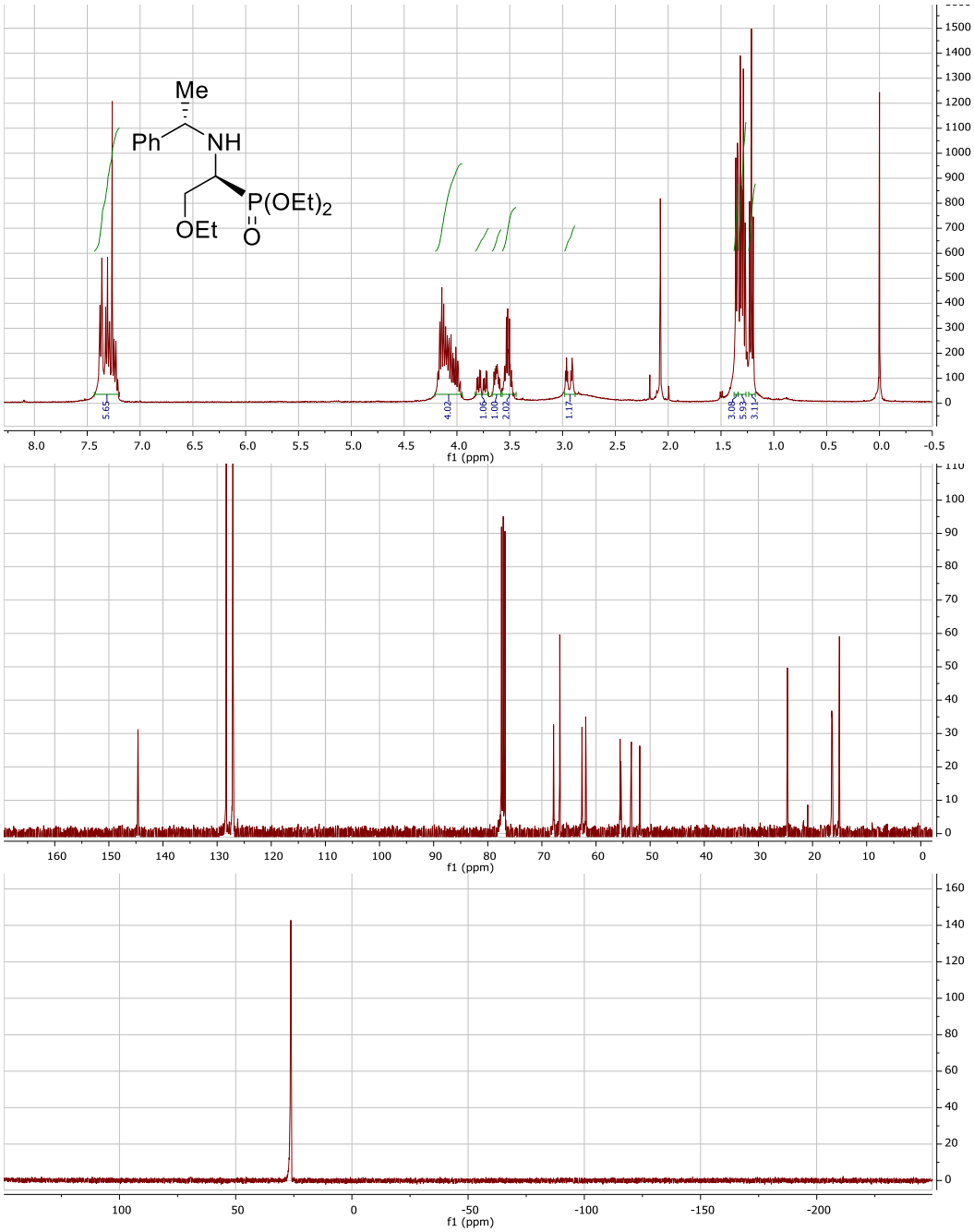


Figure 36. ^{1}H, ^{13}C and ^{31}P spectra of compound **5fb**

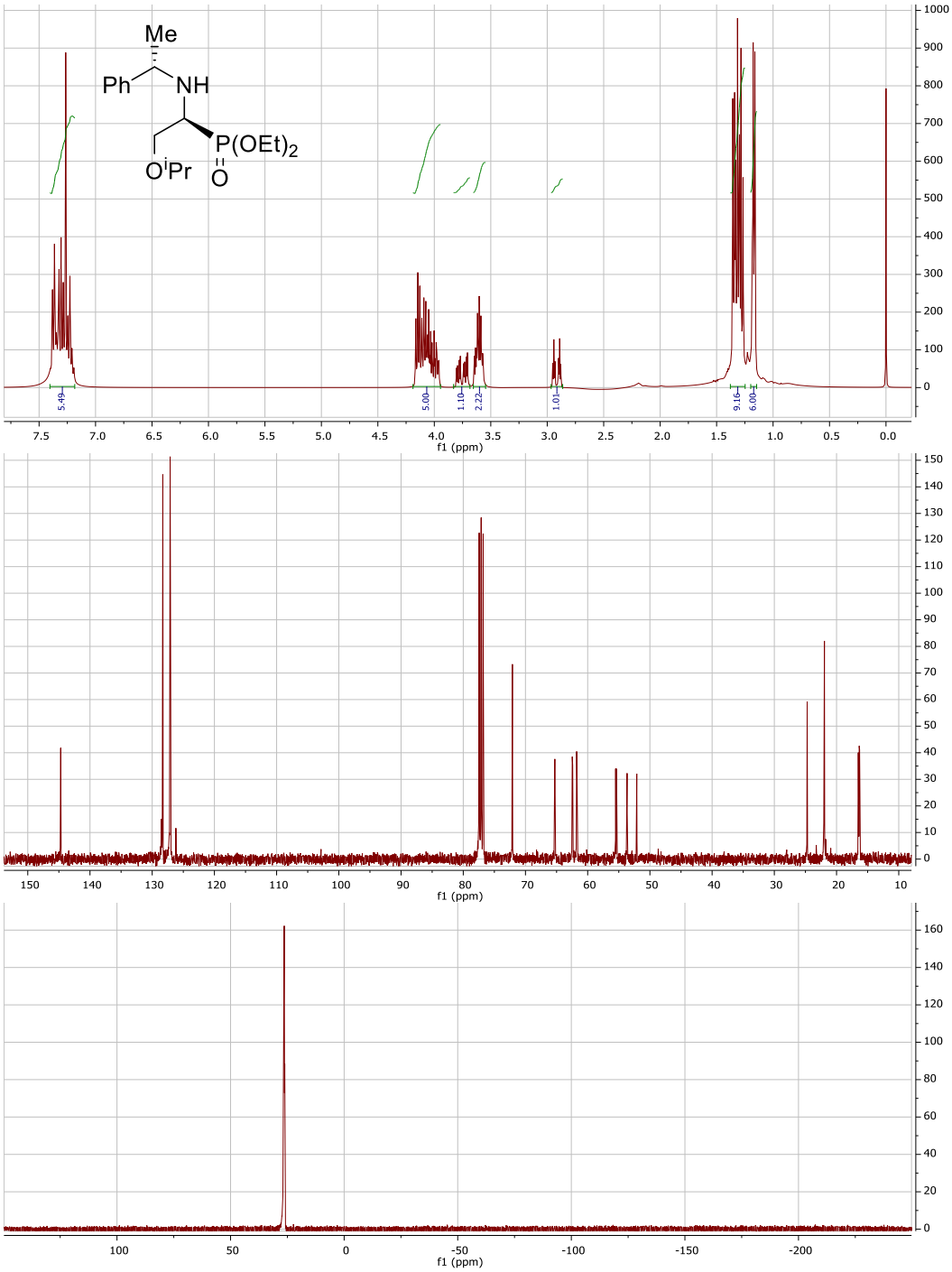


Figure 37. ^{1}H, ^{13}C and ^{31}P spectra of compound **5fc**

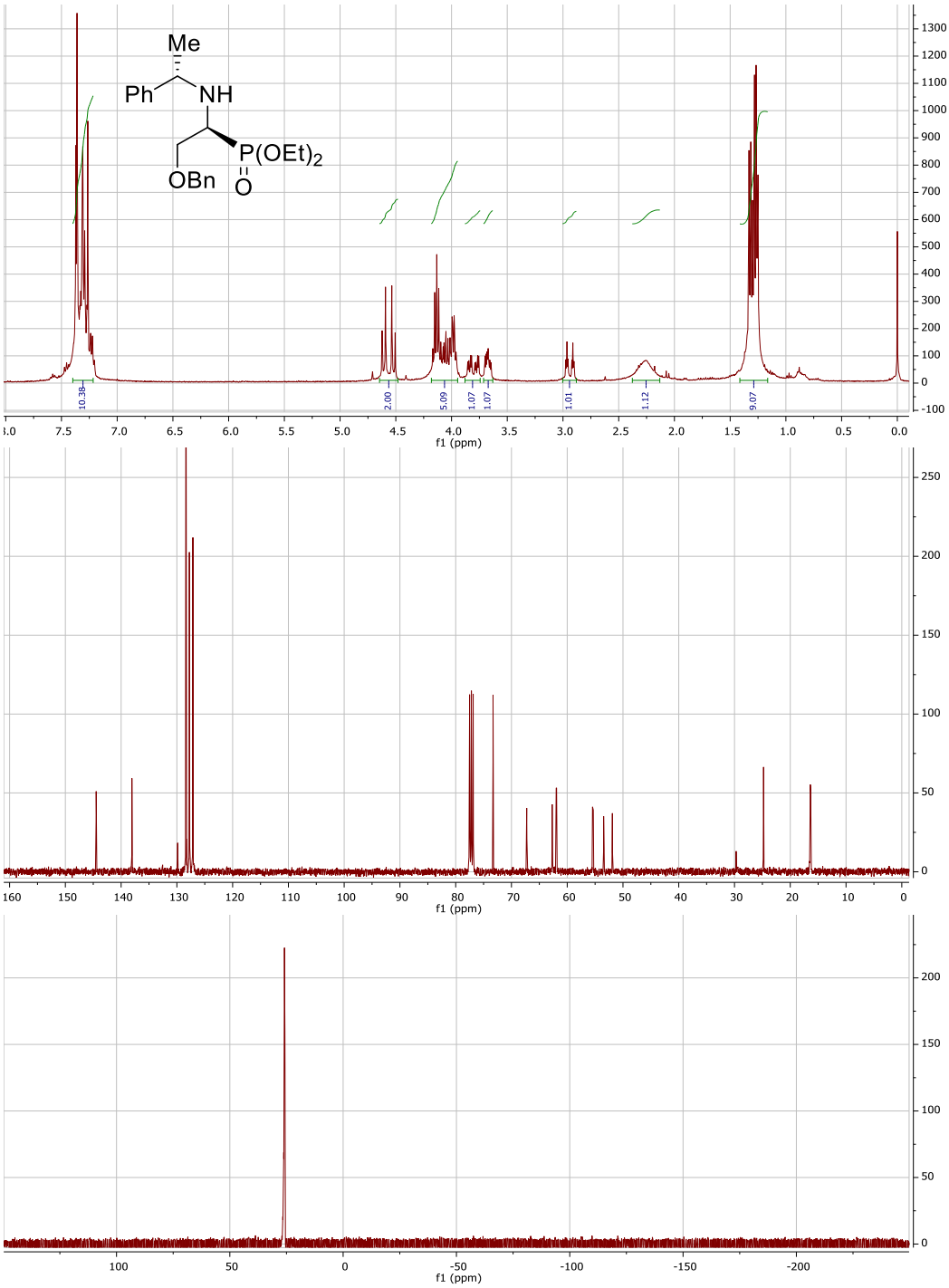
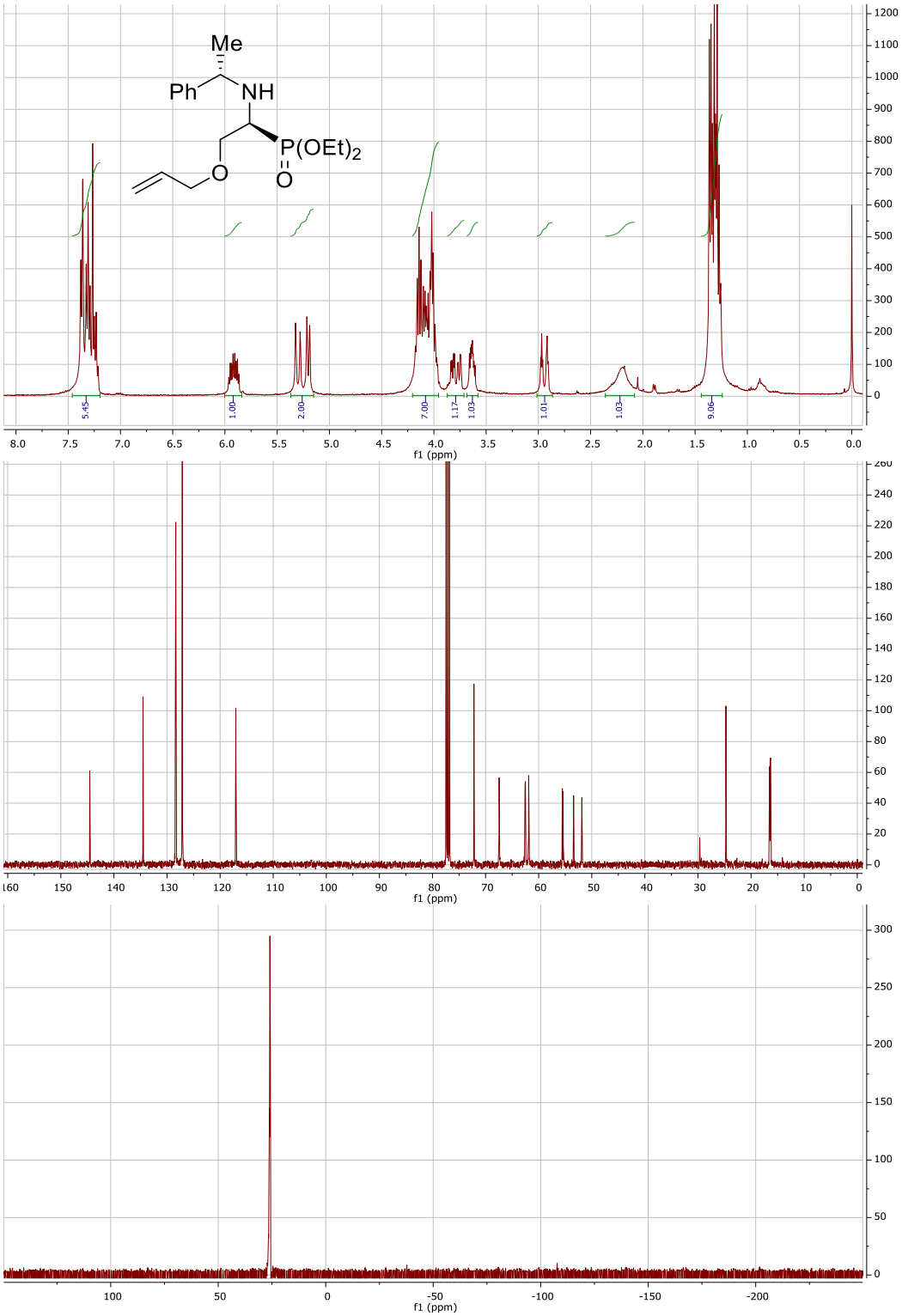


Figure 38. ^{1}H, ^{13}C and ^{31}P spectra of compound **5fd**



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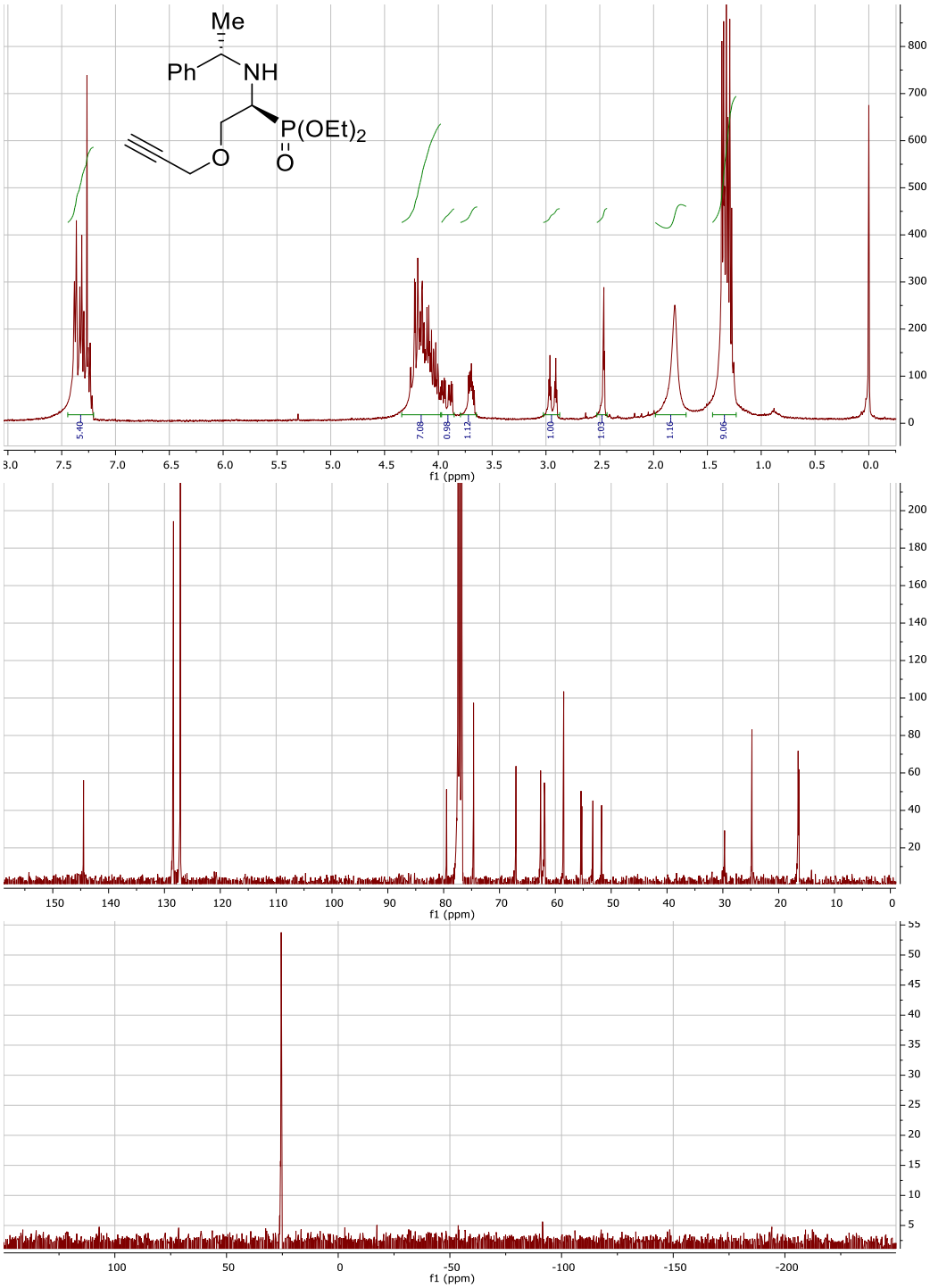


Figure 40. ^{1}H, ^{13}C and ^{31}P spectra of compound **5ff**

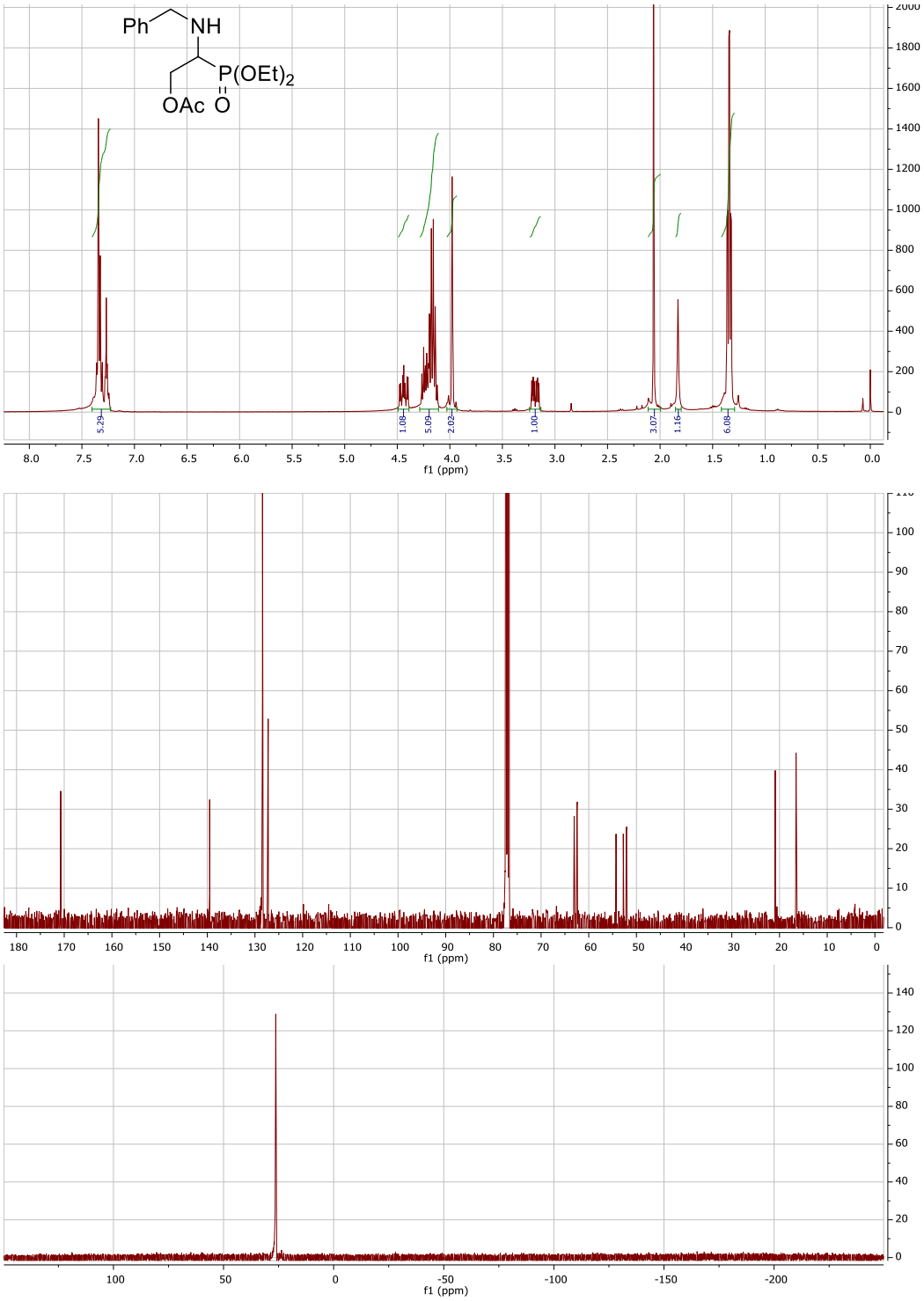


Figure 41. ^{1}H, ^{13}C and ^{31}P spectra of compound **6a**

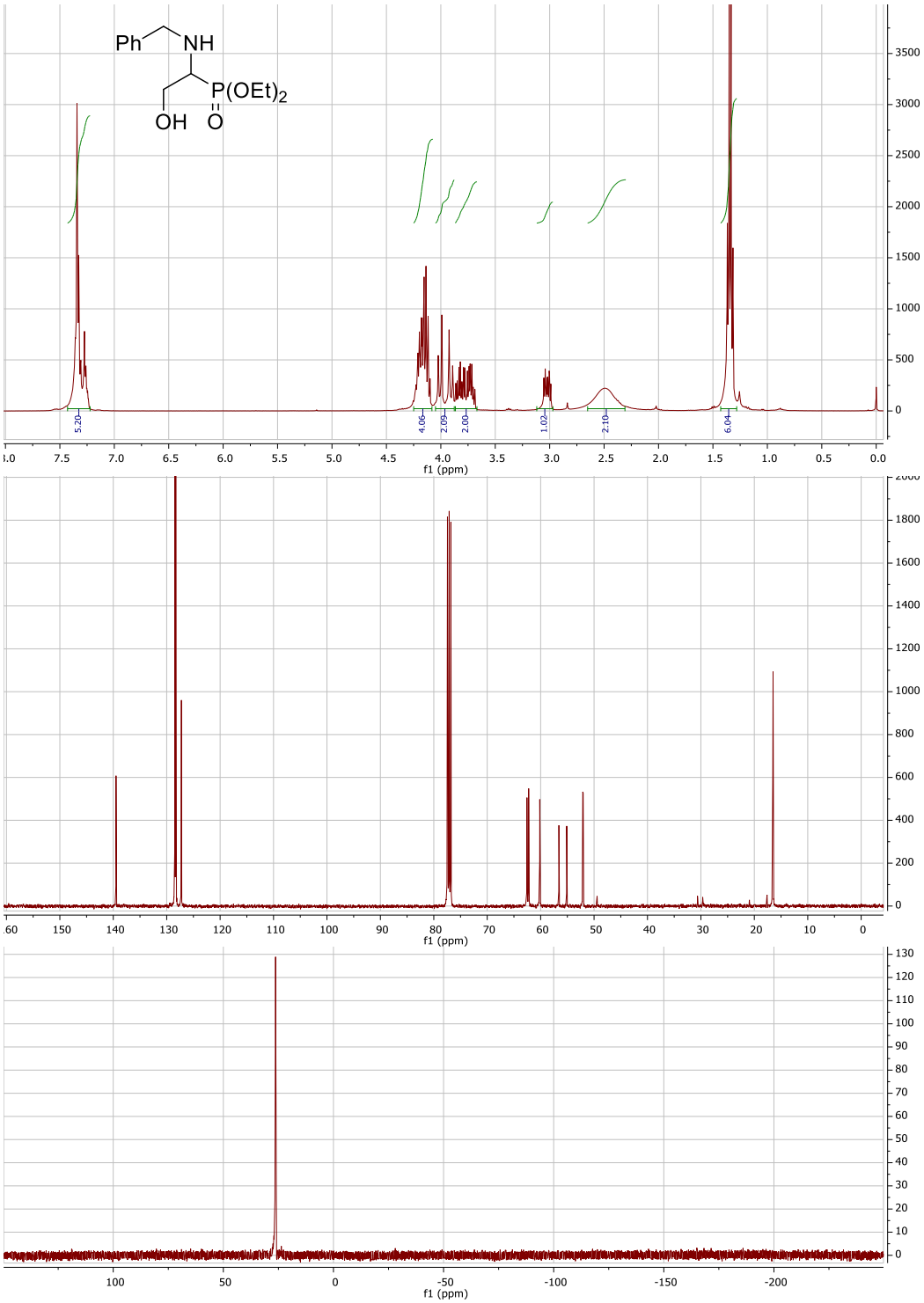


Figure 42. ^{1}H, ^{13}C and ^{31}P spectra of compound **7a**

8.2 Experimental data for 1,3-dipolar cycloaddition reaction products

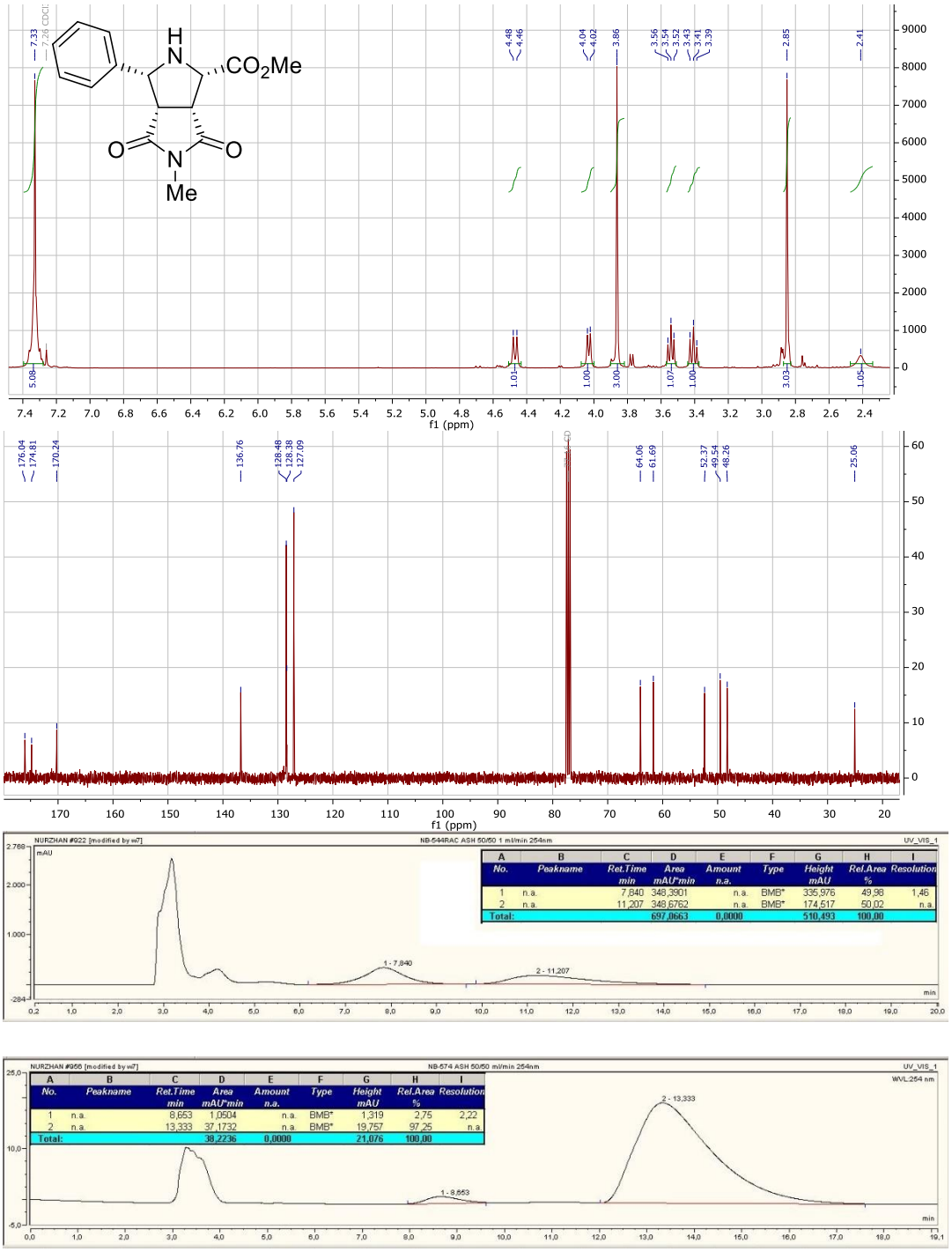
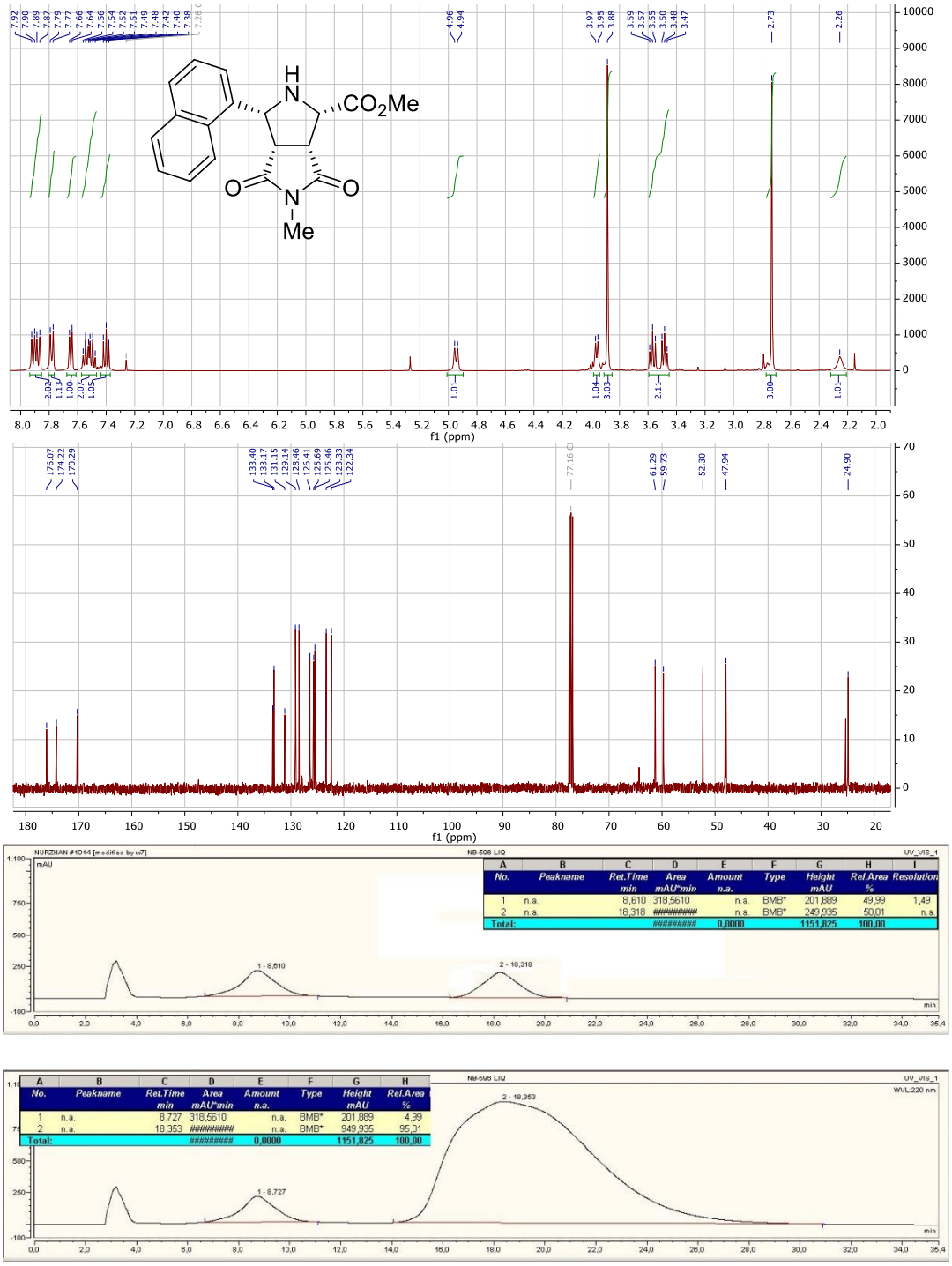


Figure 43. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15a**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,610	318,5610	n.a.	BMB*	201,889	49,99	1,49
2	n.a.	18,318	##########	n.a.	BMB*	249,935	50,01	n.a.
Total:			#########	0,0000		1151,825	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %
1	n.a.	8,727	318,5610	n.a.	BMB*	201,889	4,99
2	n.a.	18,353	##########	n.a.	BMB*	949,935	95,01
Total:			#########	0,0000		1151,825	100,00

Figure 44. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15b**

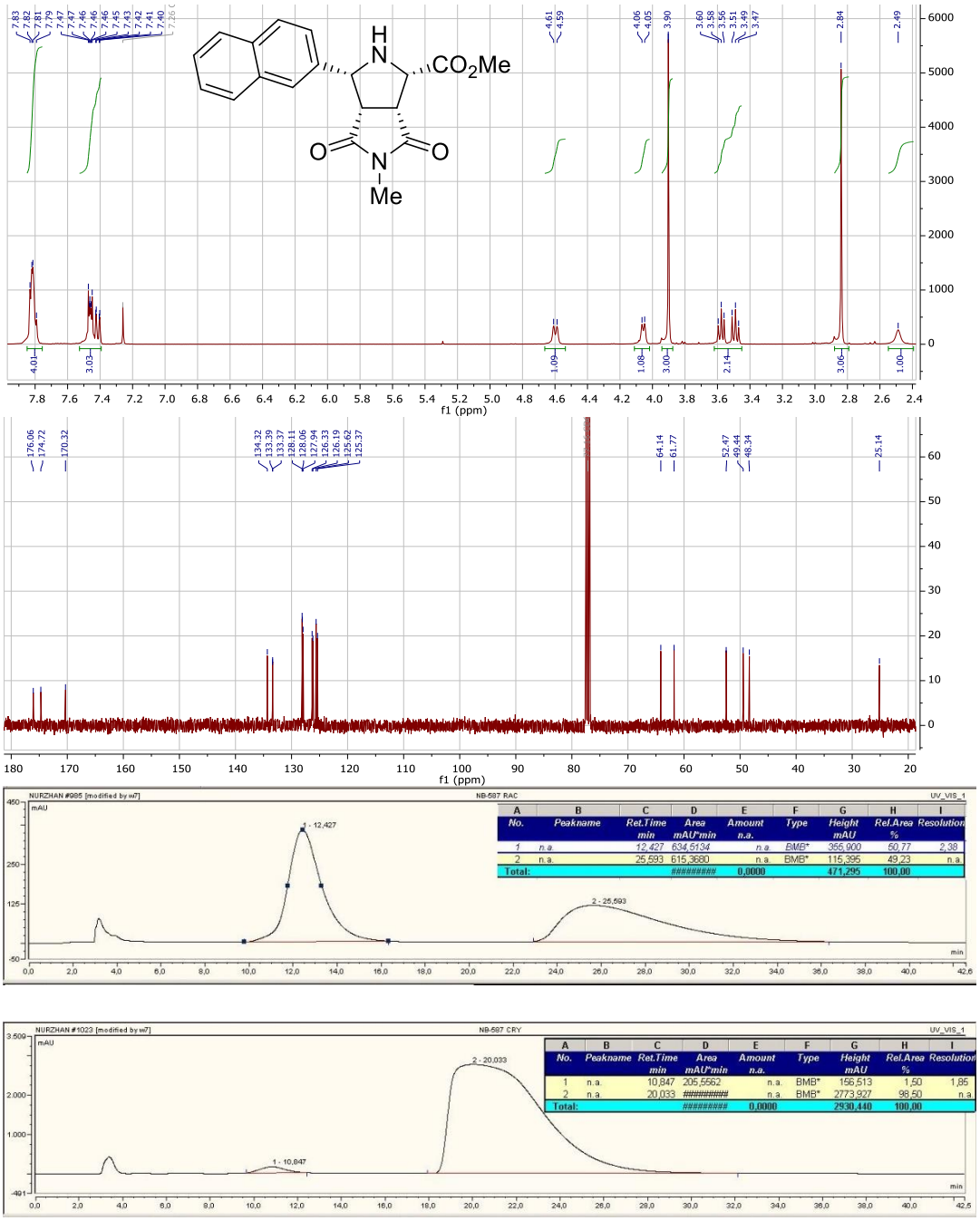


Figure 45. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15c**

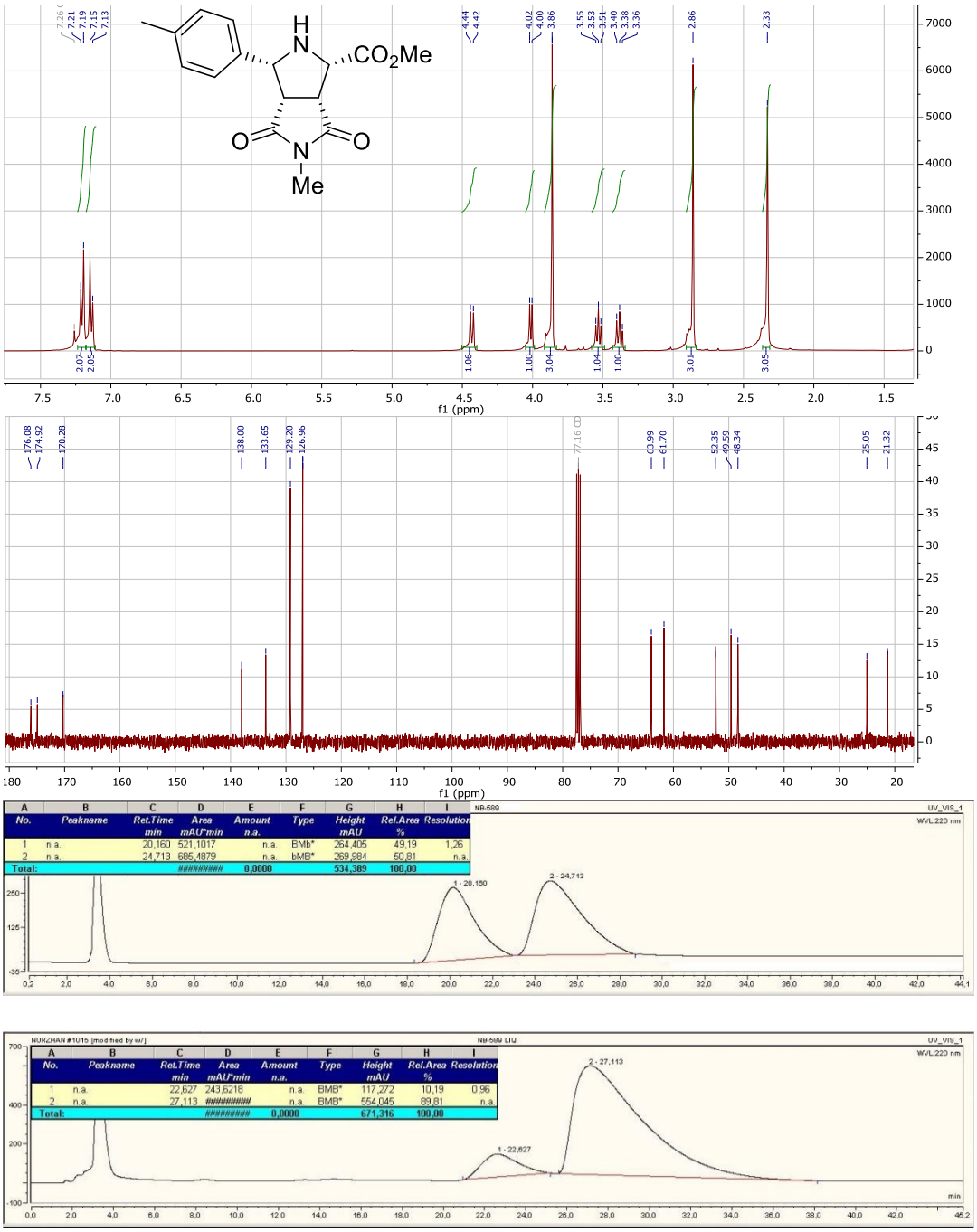


Figure 46. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15d**

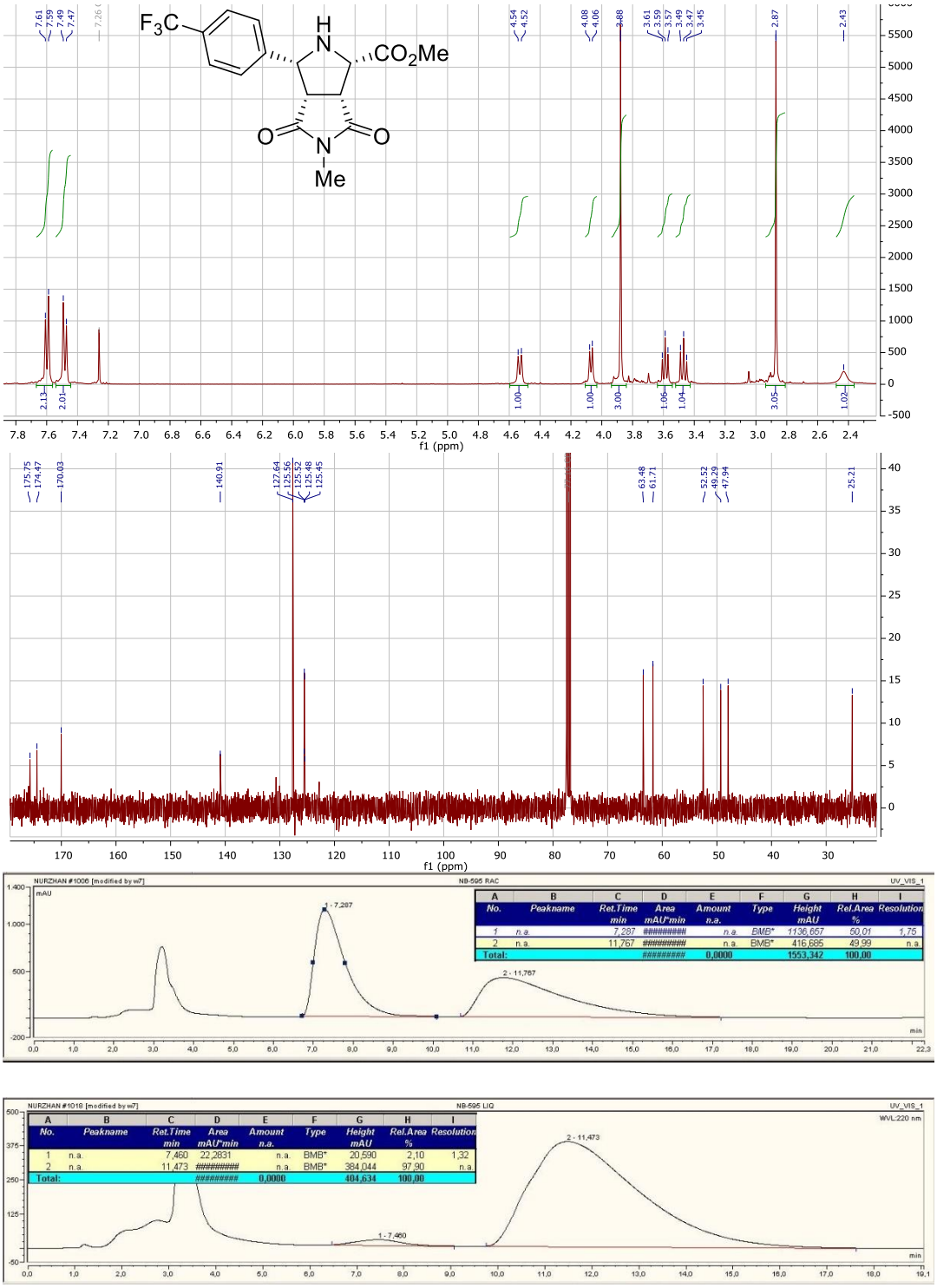


Figure 47. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15e**

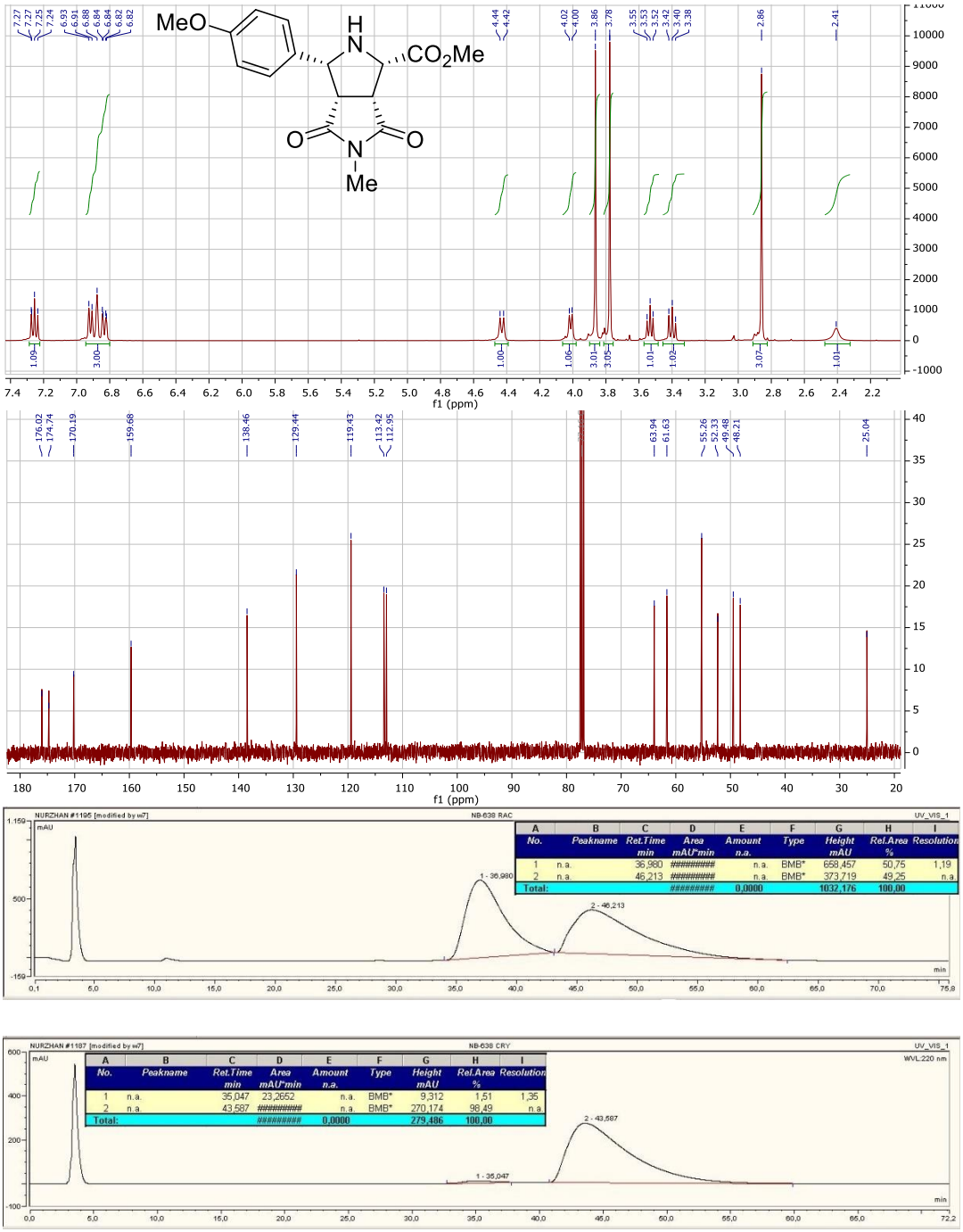


Figure 48. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15f**

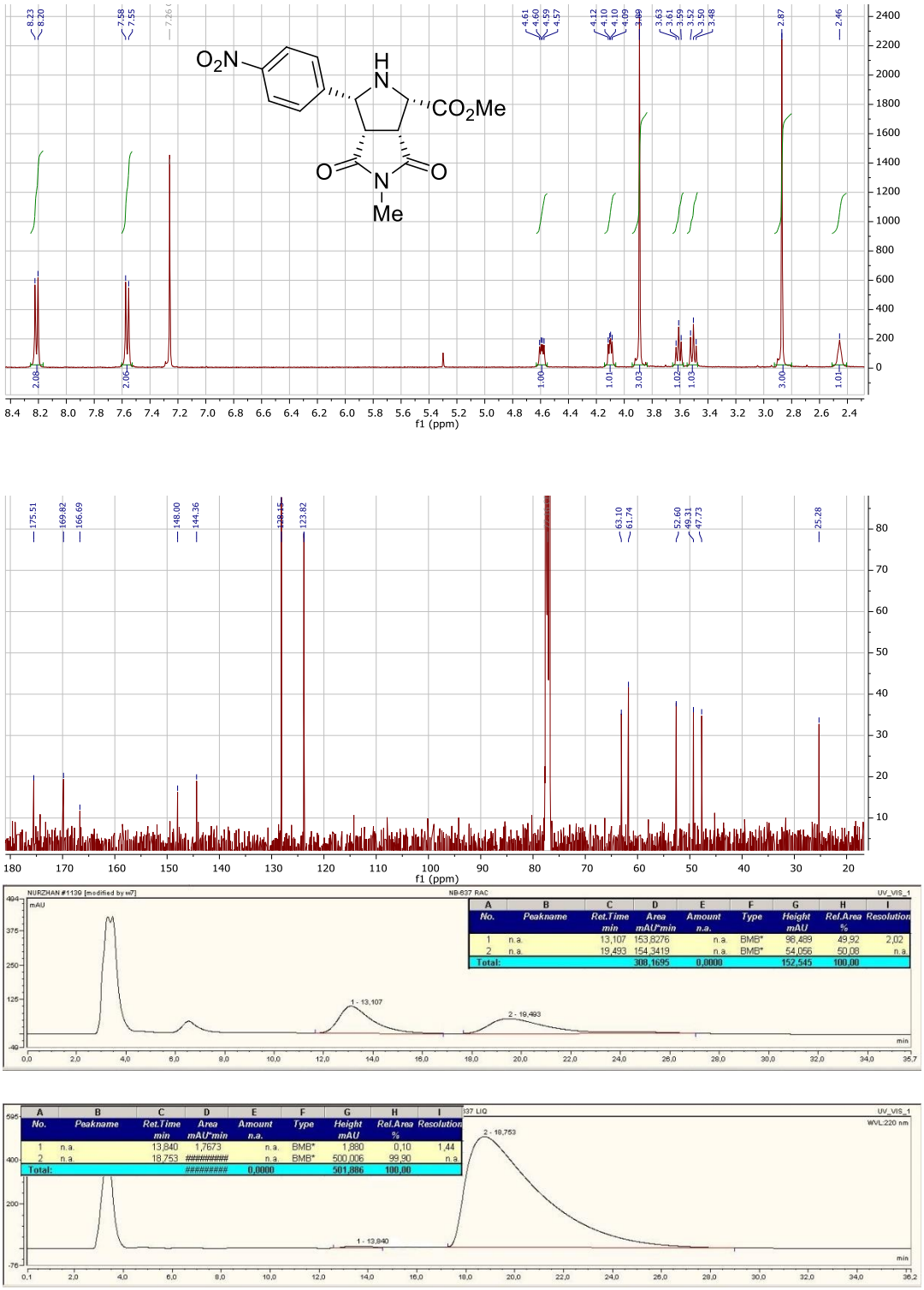


Figure 49. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15g**

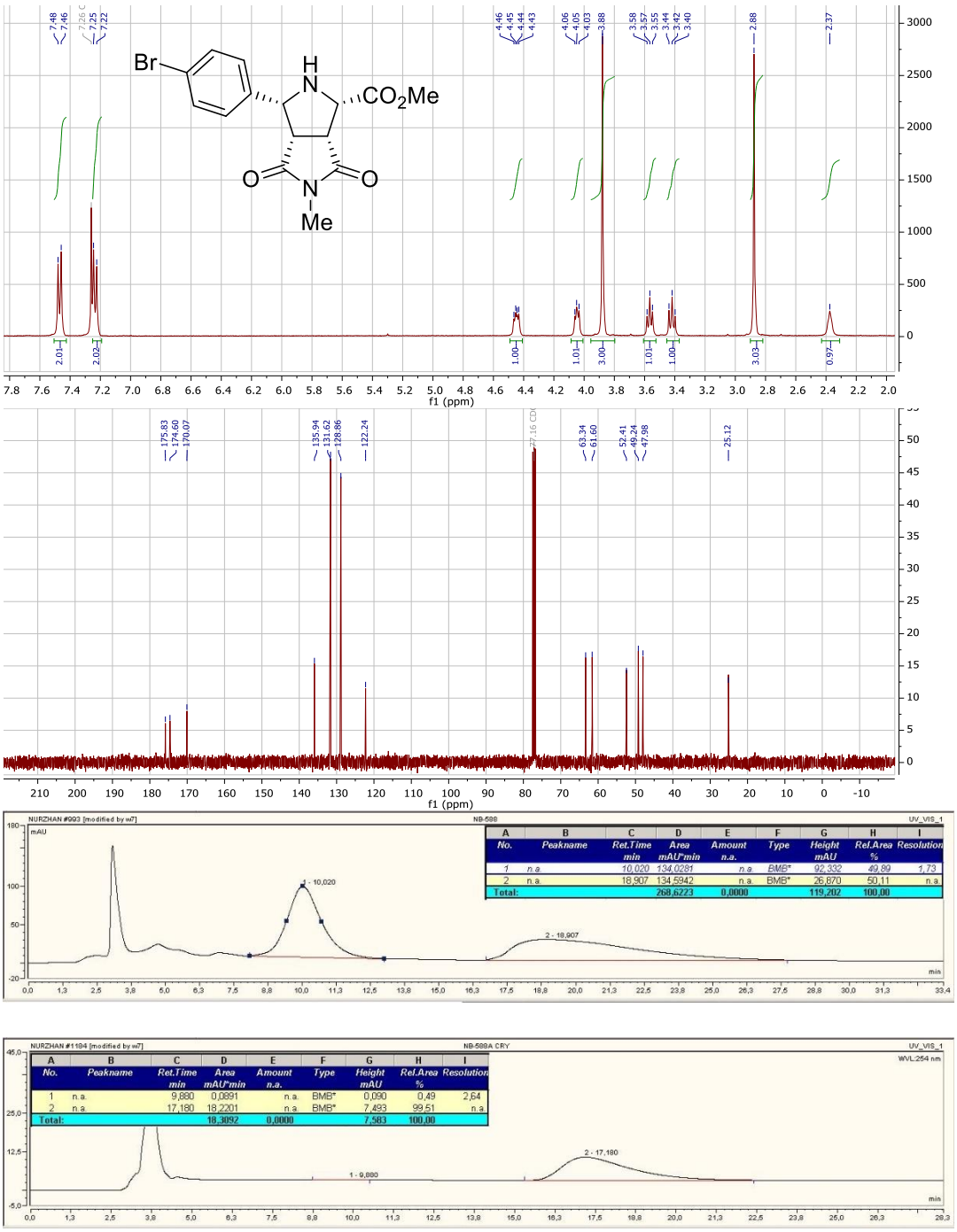


Figure 50. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15h**

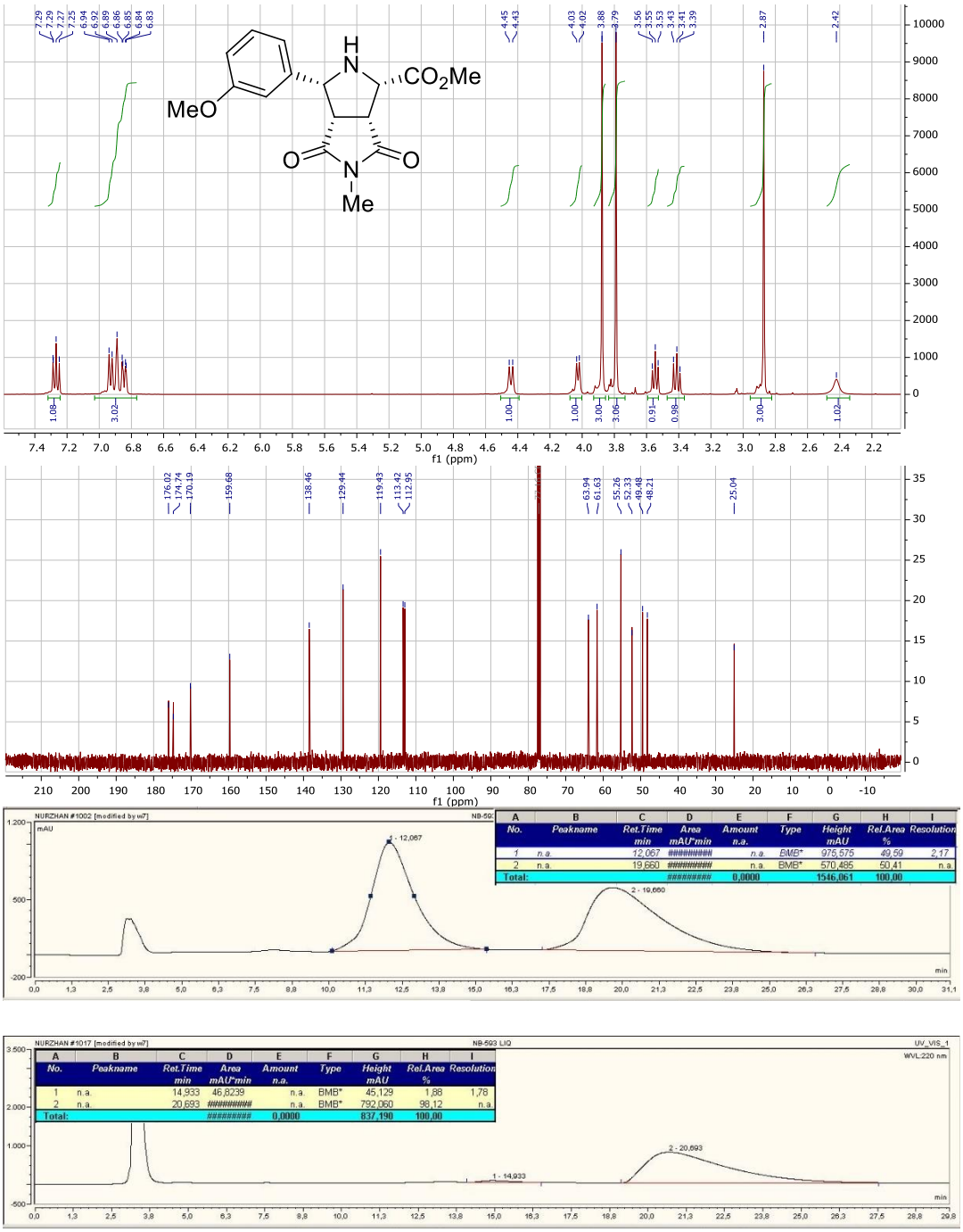


Figure 51. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15i**

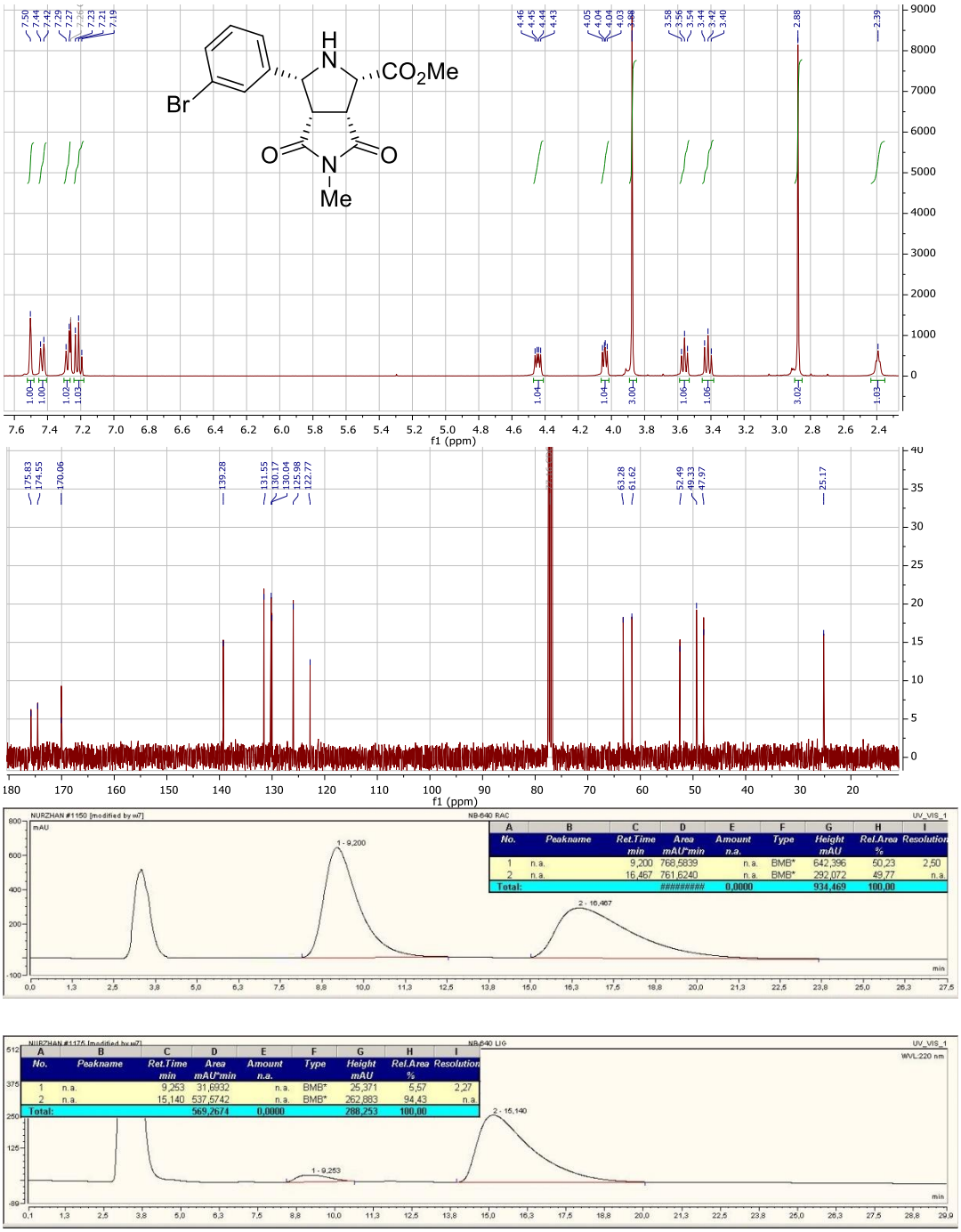


Figure 52. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15j**

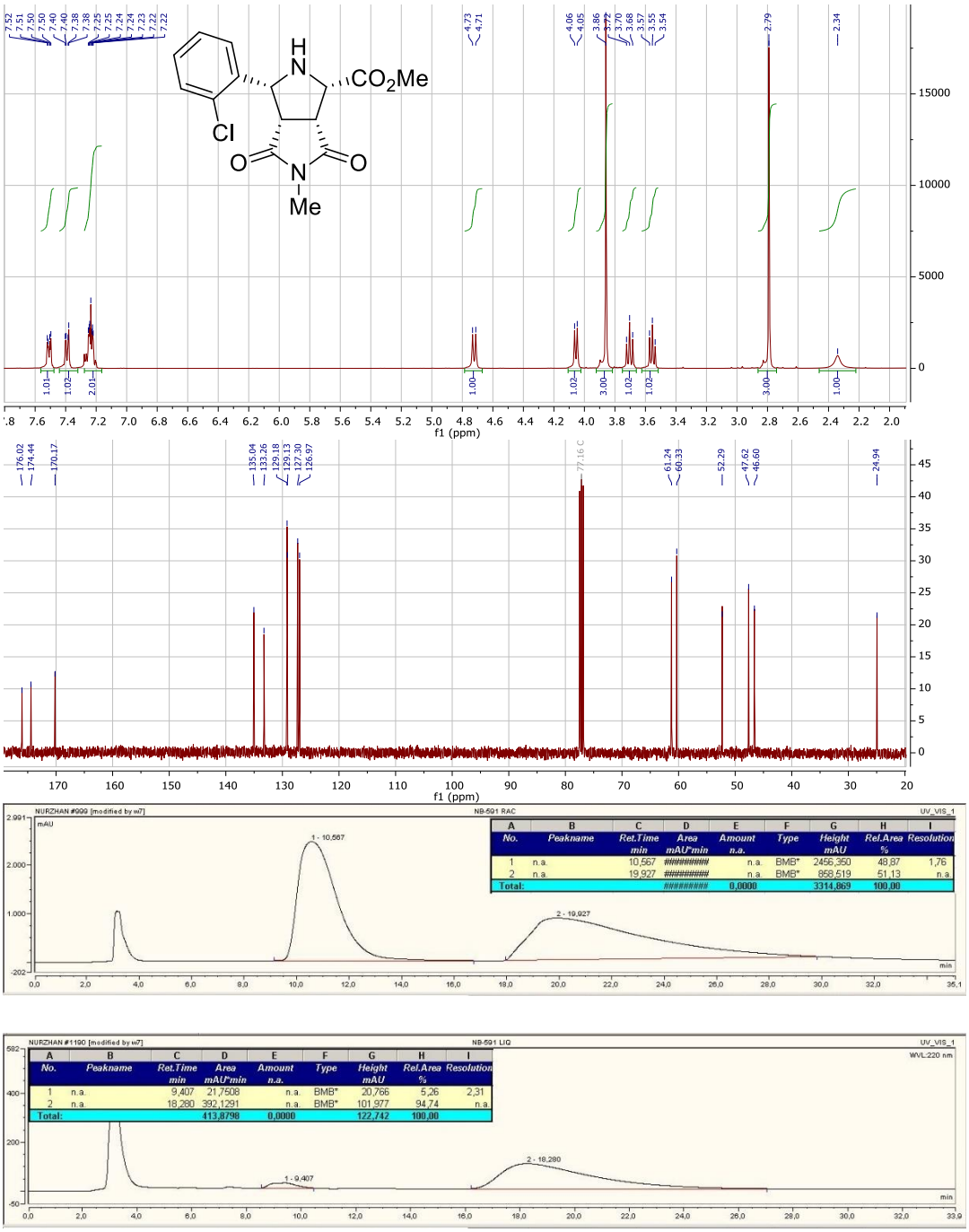
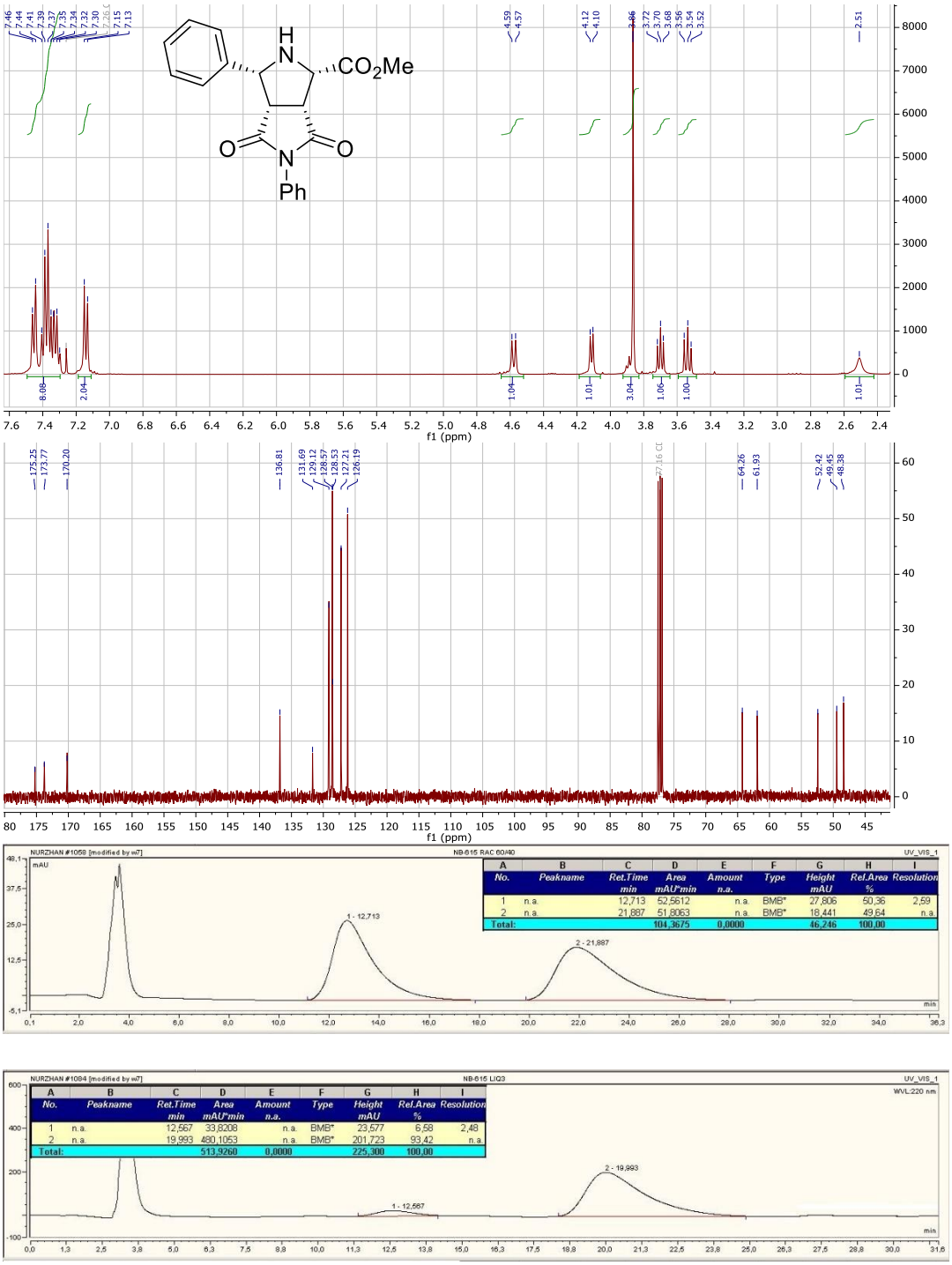


Figure 53. ^{1}H, ^{13}C NMR spectra and HPLC for compound **15k**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Ref.Area %	Resolution
1	n.a.	12,713	52,5612	n.a.	BMB*	27,806	50,36	2,59
2	n.a.	21,887	51,8063	n.a.	BMB*	18,441	49,64	n.a.
Total:			104,3675	0,0000		46,246	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Ref.Area %	Resolution
1	n.a.	12,567	33,8208	n.a.	BMB*	23,577	6,58	2,48
2	n.a.	19,993	480,1053	n.a.	BMB*	201,723	93,42	n.a.
Total:			513,9260	0,0000		225,300	100,00	

Figure 54. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16a**

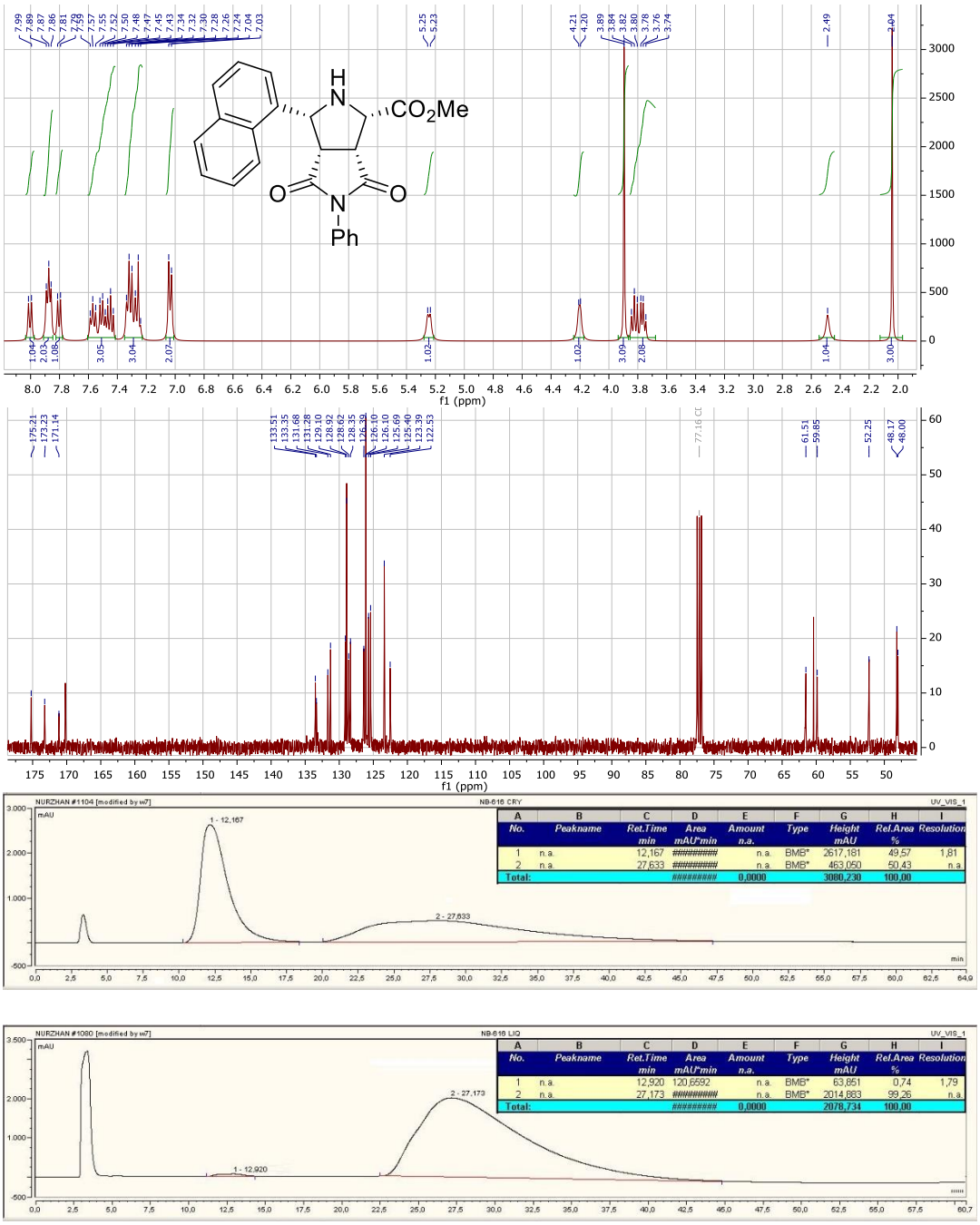


Figure 55. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16b**

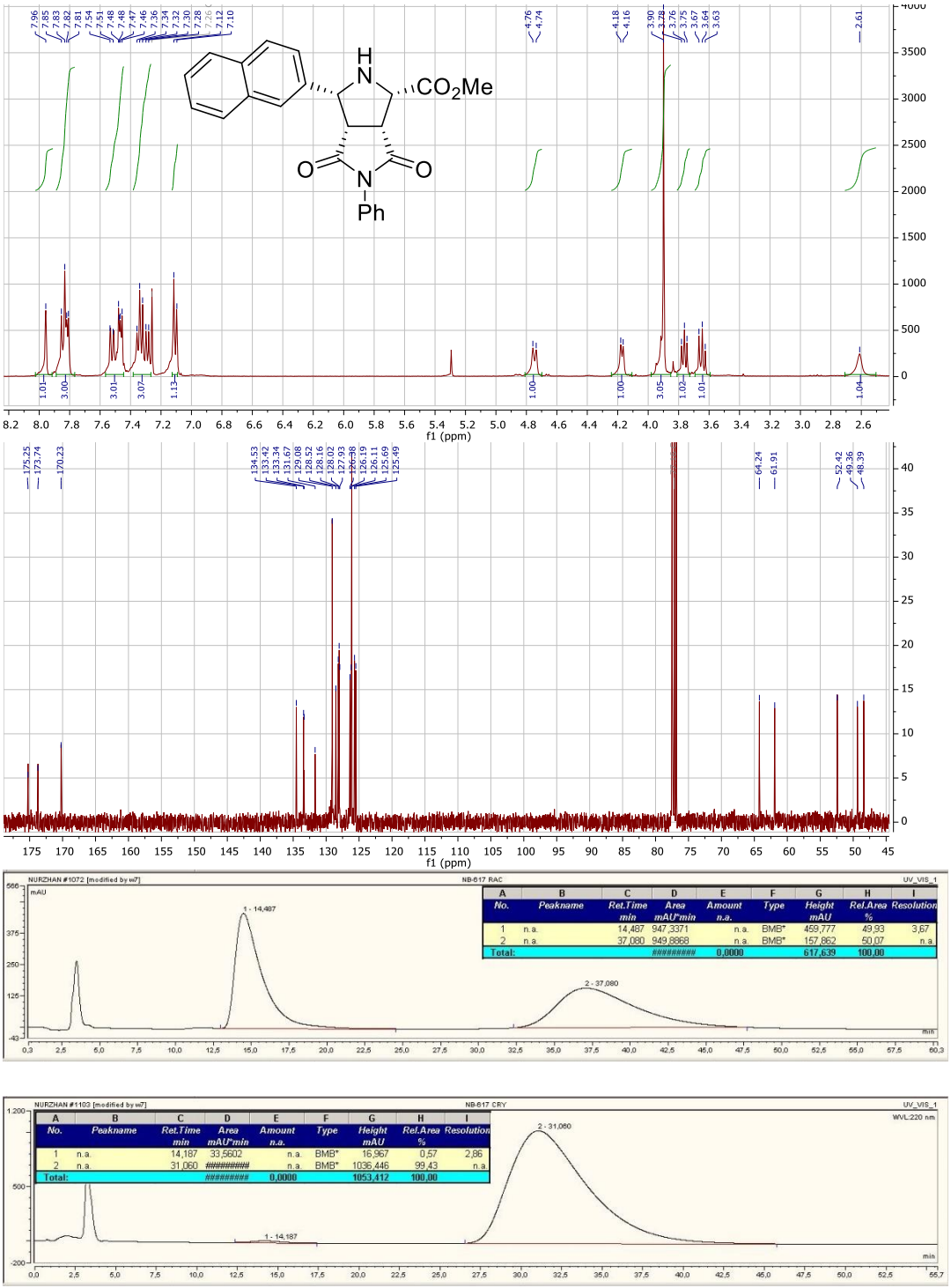


Figure 56. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16c**

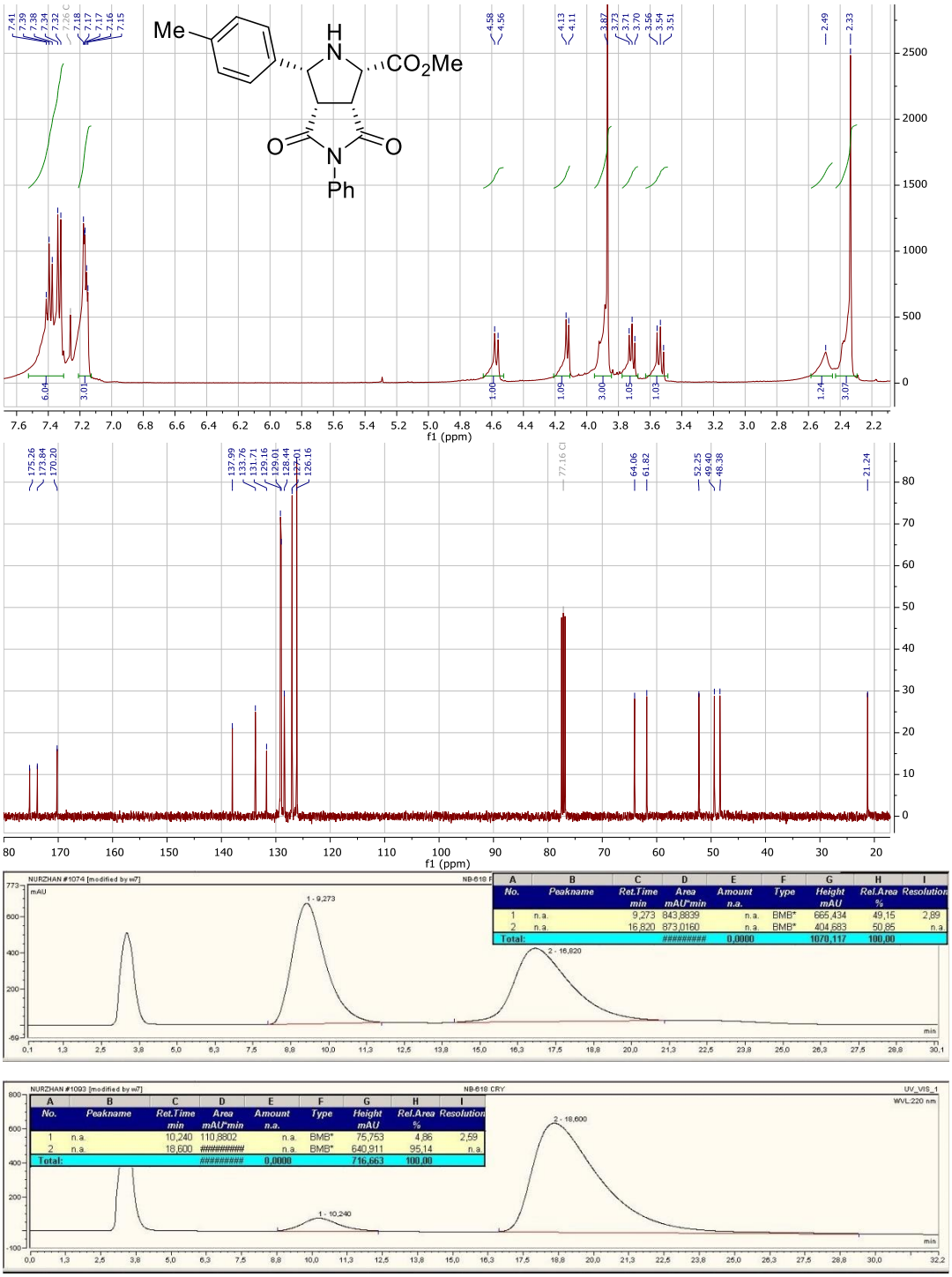


Figure 57. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16d**

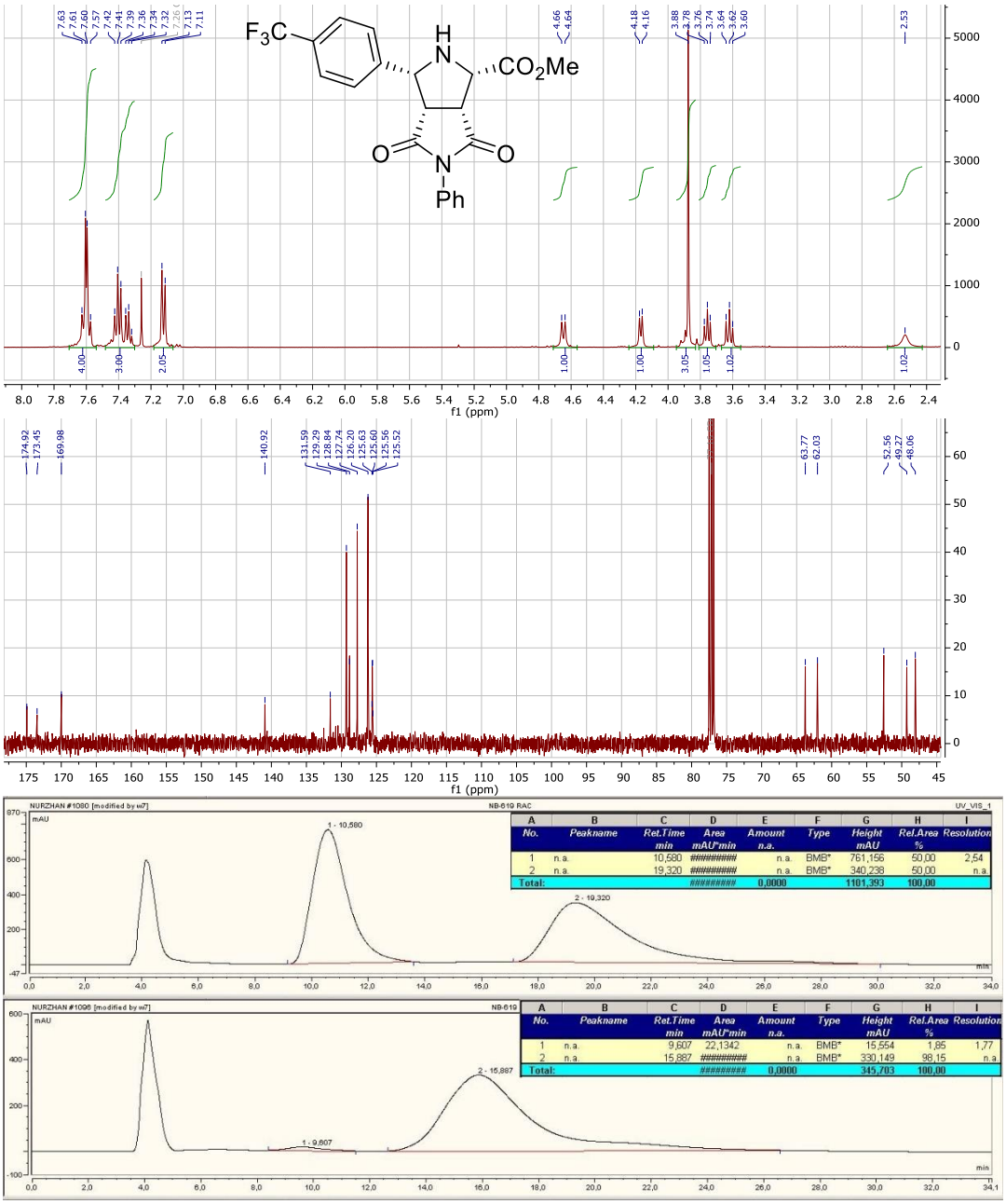
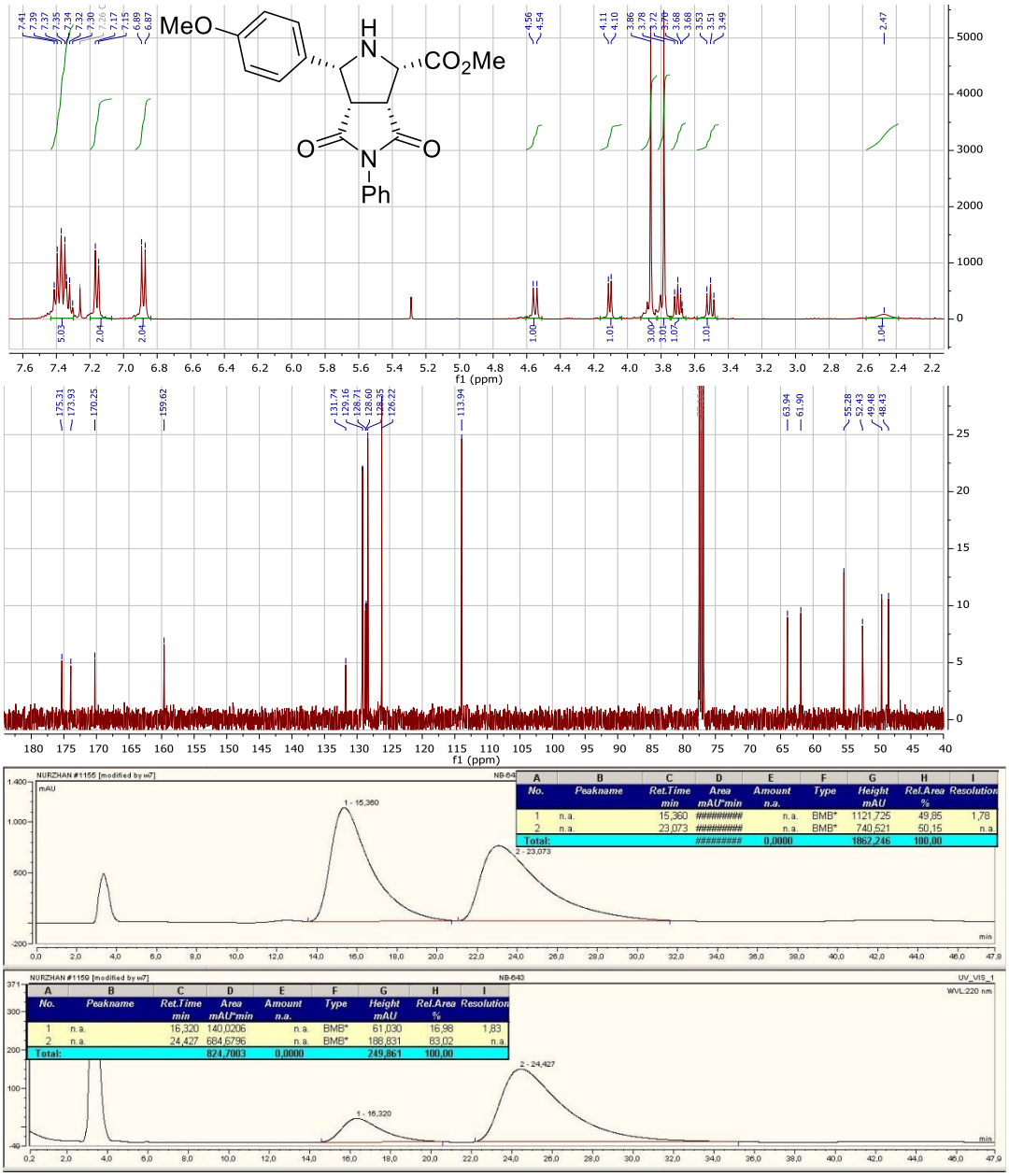


Figure 58. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16e**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	15,360	##########	n.a.	BMB*	1121,726	49,85	1,78
2	n.a.	23,073	##########	n.a.	BMB*	740,521	50,15	n.a.
Total:			#########	0,0000		1862,246	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16,320	140,0206	n.a.	BMB*	61,030	16,98	1,83
2	n.a.	24,427	684,6796	n.a.	BMB*	188,831	83,02	n.a.
Total:			824,7003	0,0000		249,861	100,00	

Figure 59. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16f**

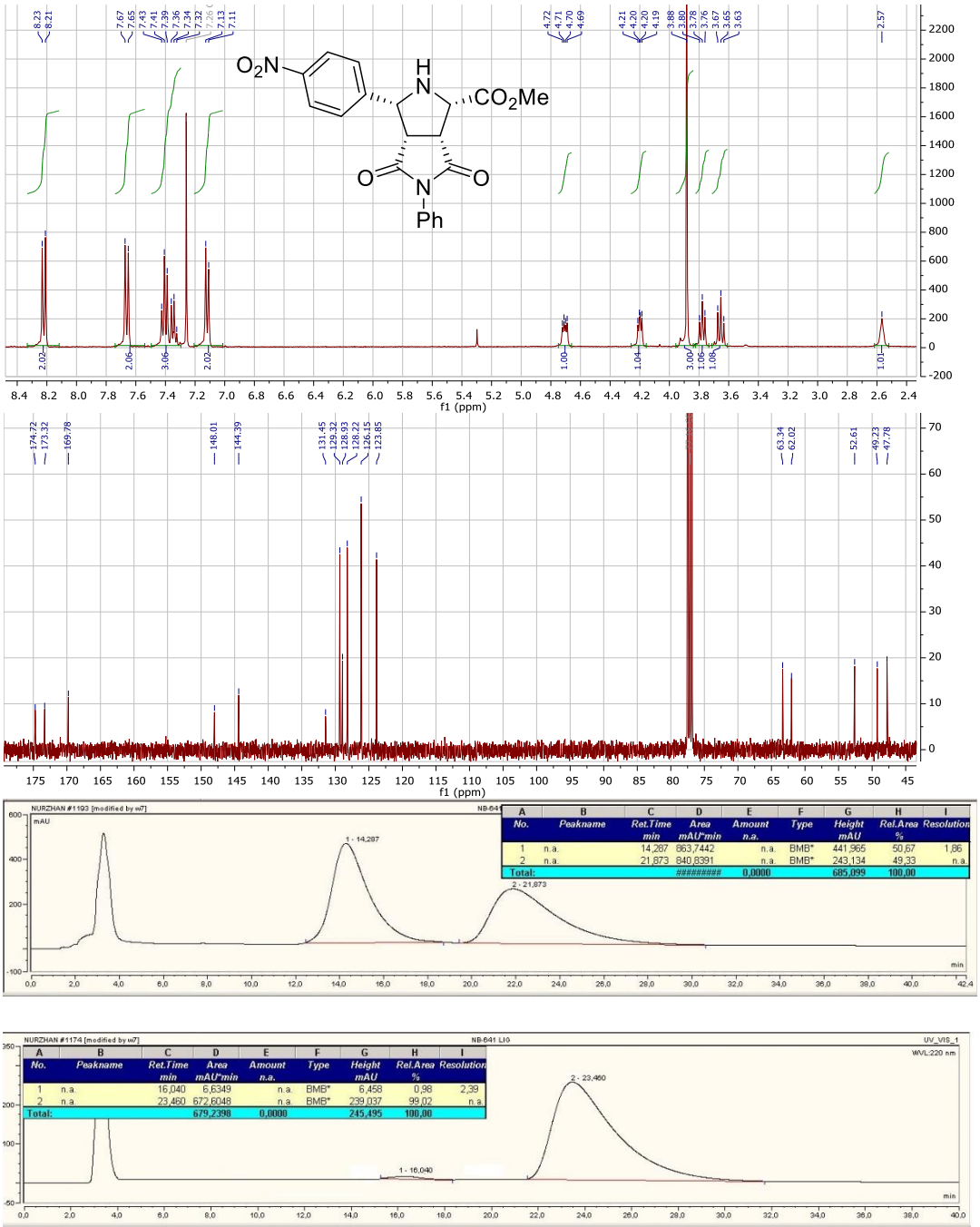


Figure 60. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16g**

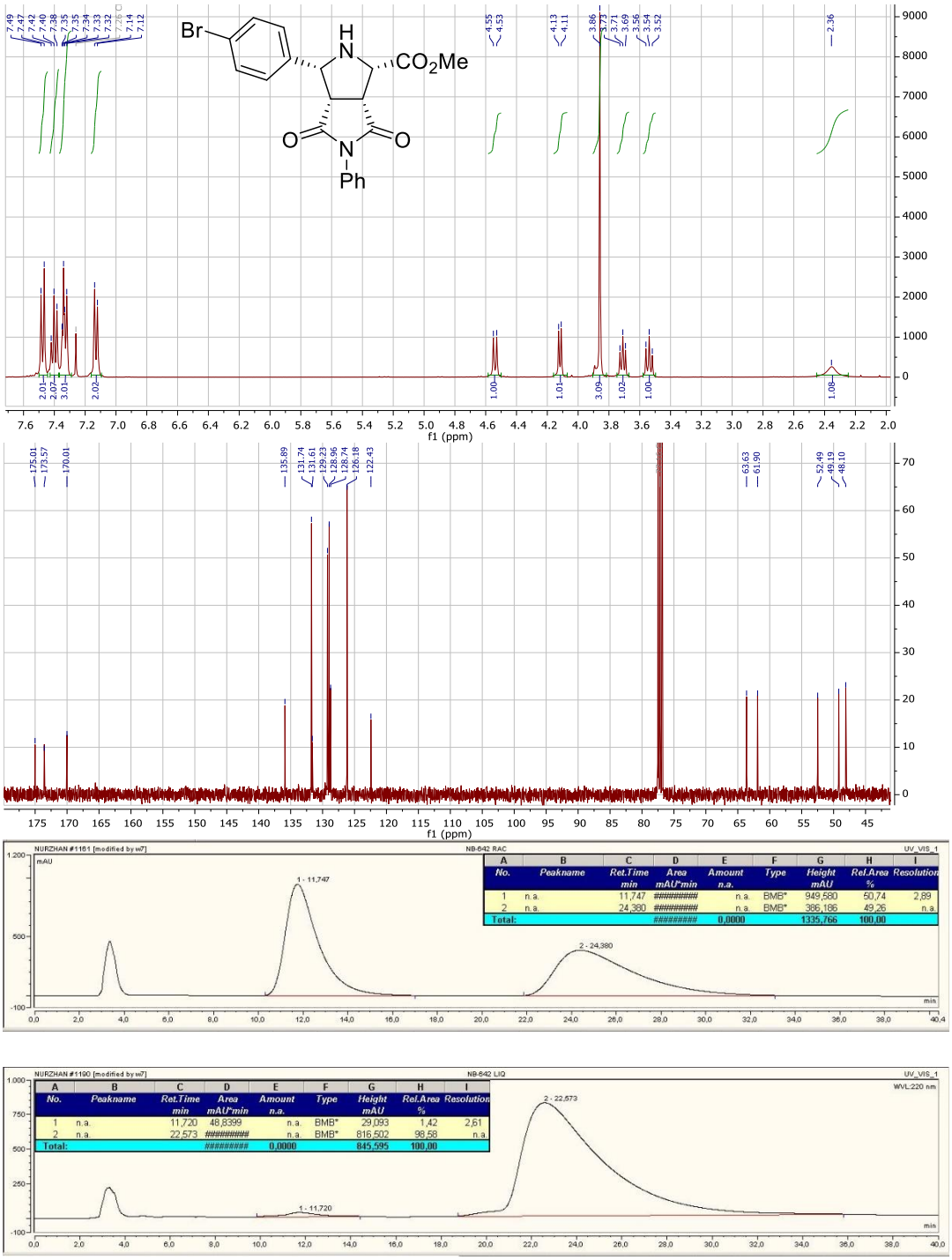


Figure 61. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16h**

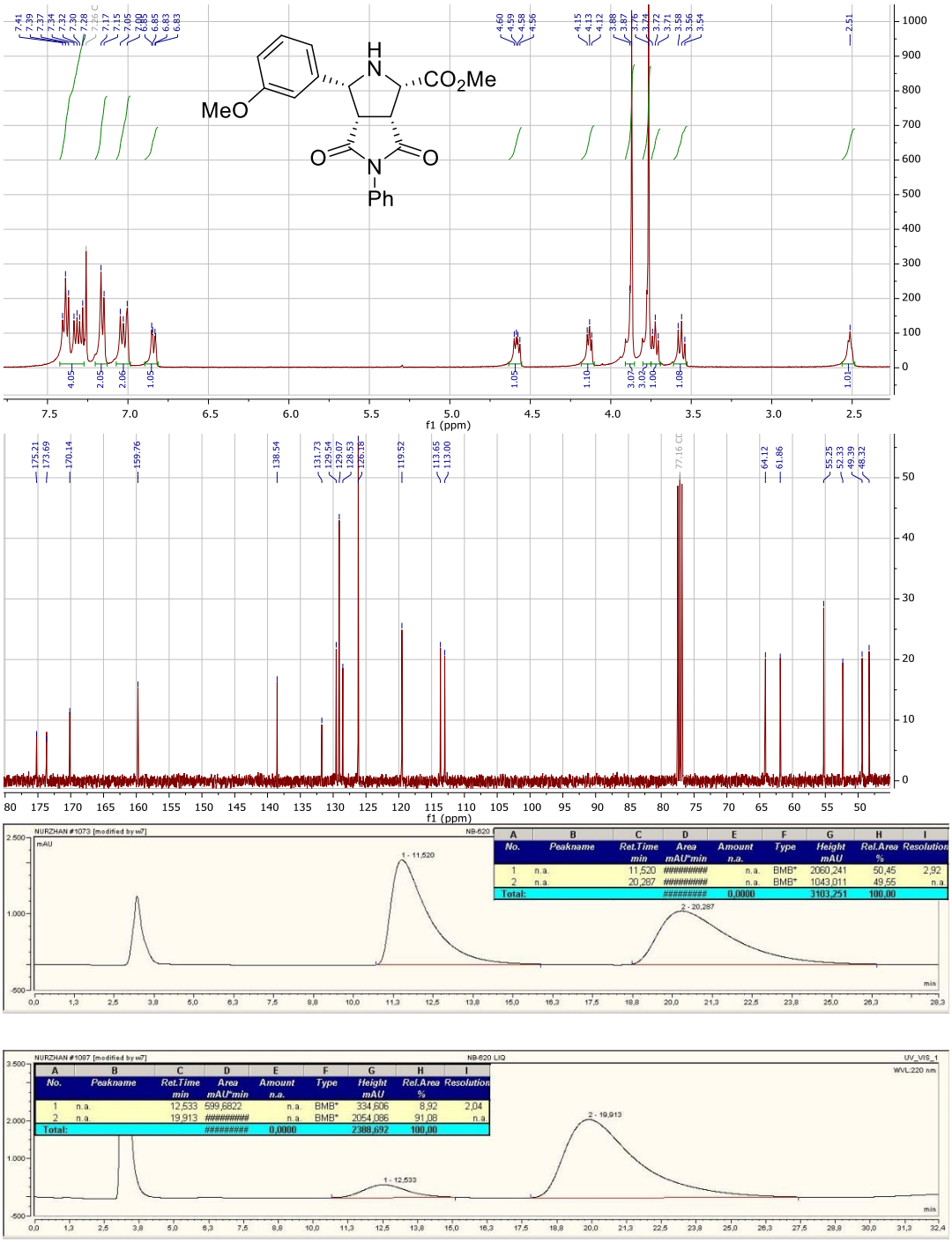


Figure 62. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16i**

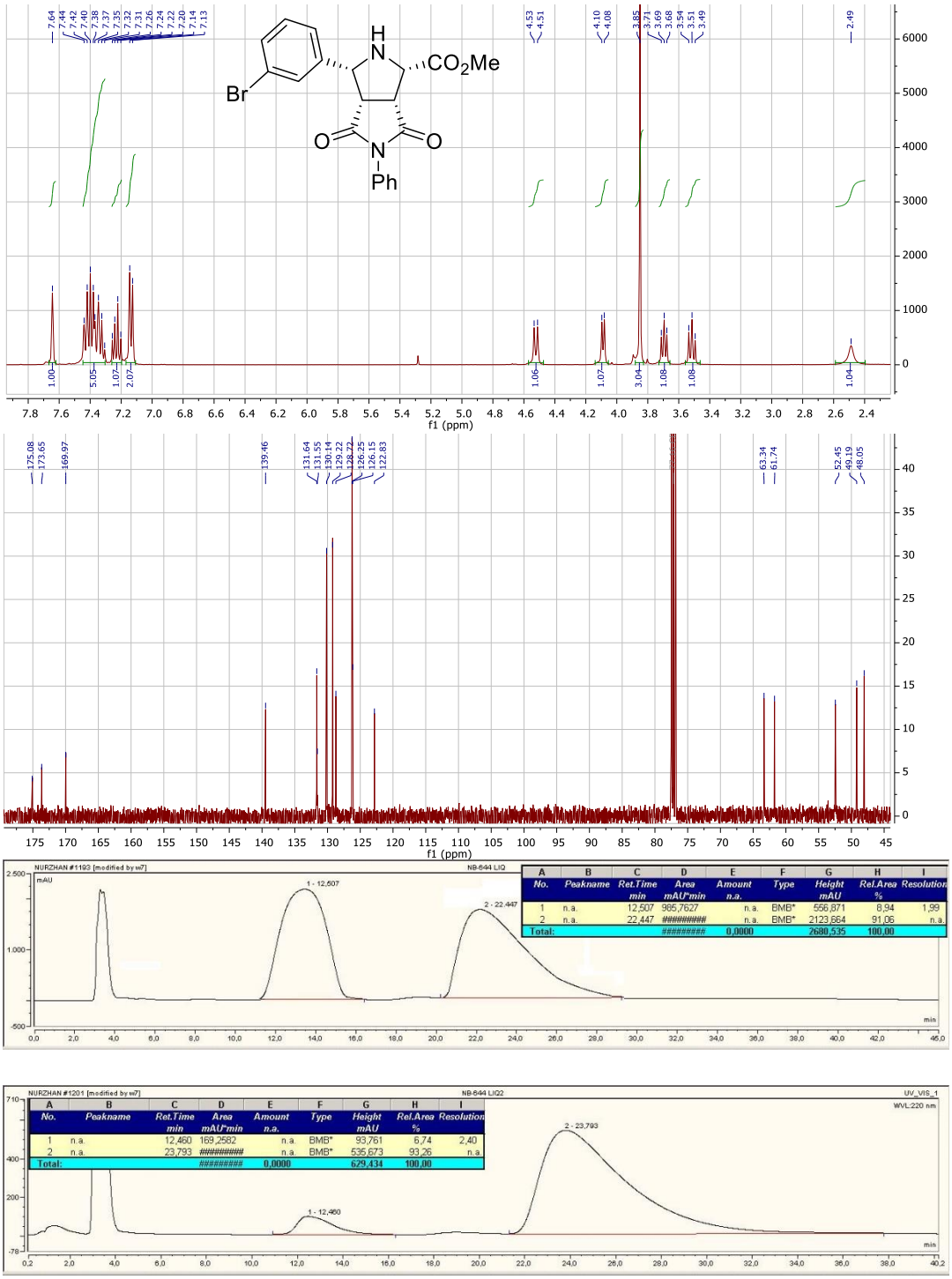


Figure 63. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16j**

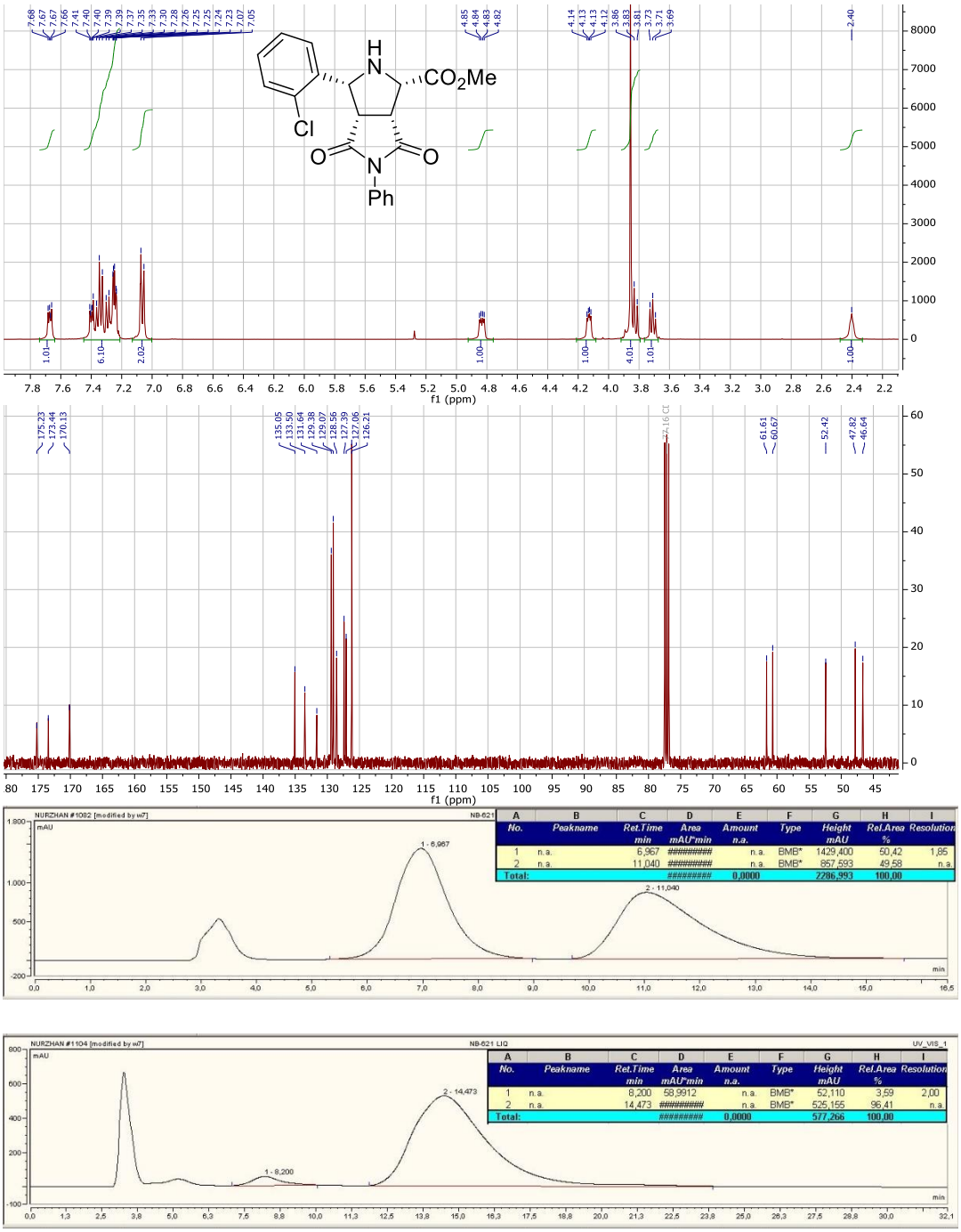
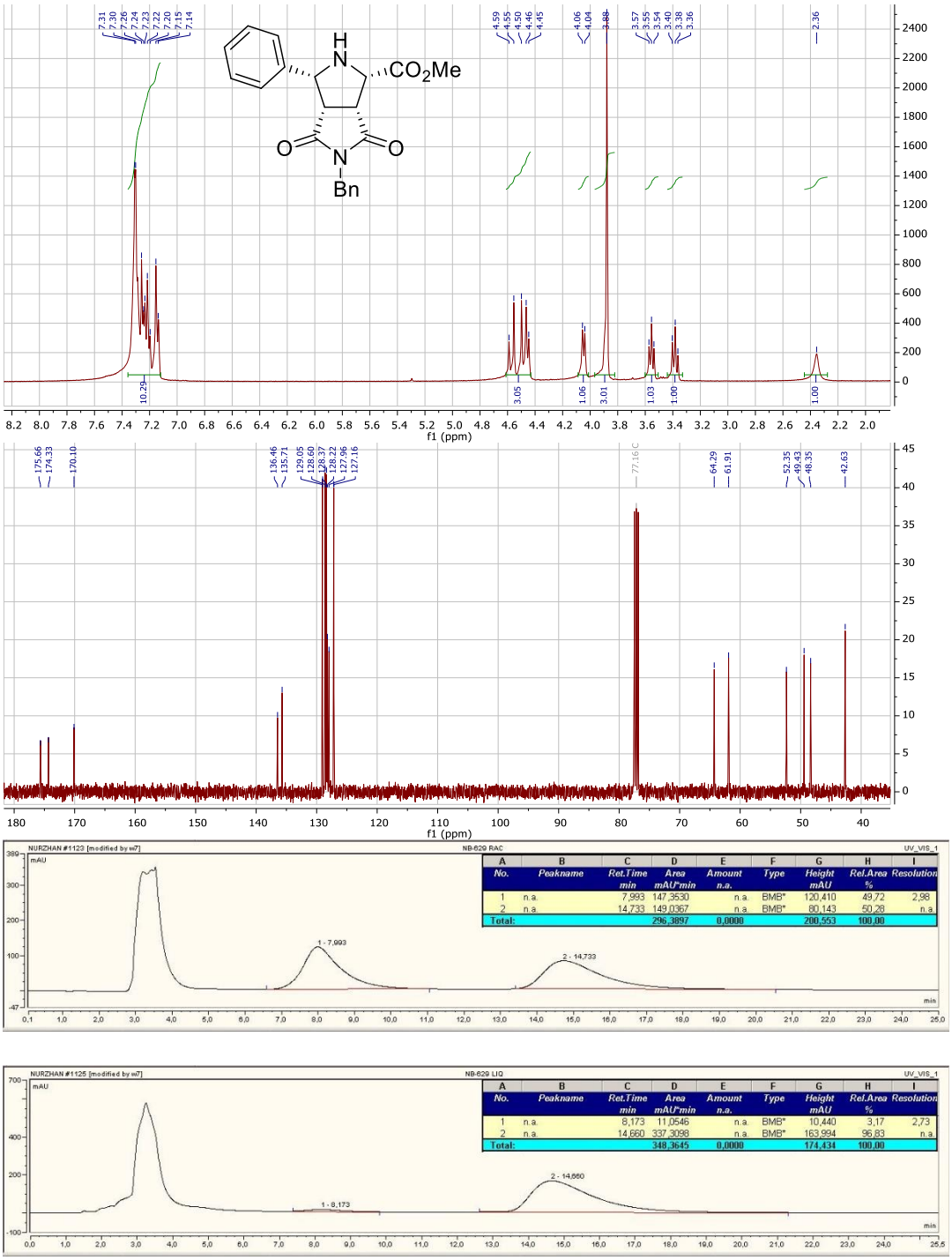


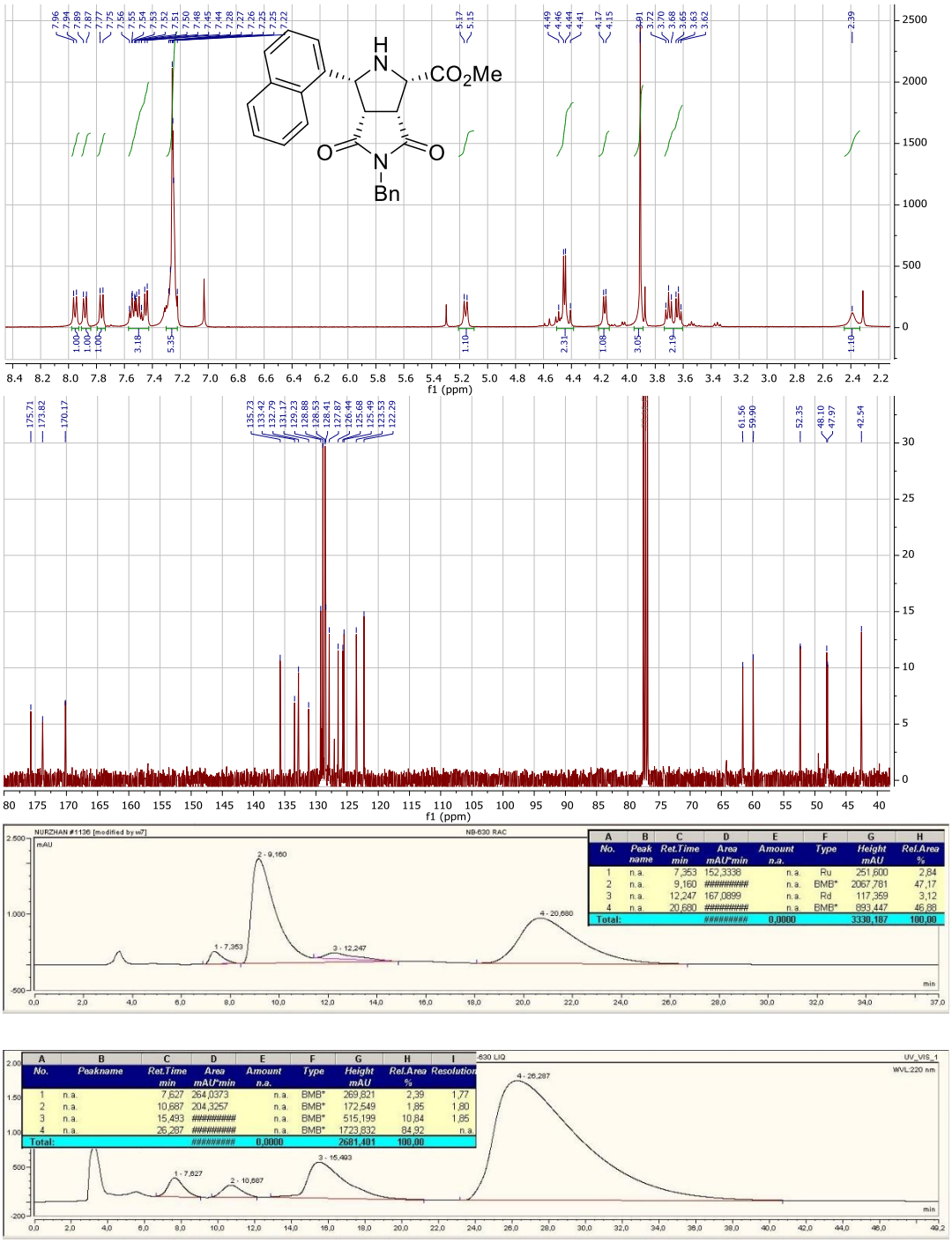
Figure 64. ^{1}H, ^{13}C NMR spectra and HPLC for compound **16k**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	7,993	147,3530	n.a.	BMB*	120,410	49,72	2,98
2	n.a.	14,733	149,0367	n.a.	BMB*	80,143	50,28	n.a.
Total:			296,3897	0,0000		200,553	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,173	11,0546	n.a.	BMB*	10,440	3,17	2,73
2	n.a.	14,660	337,3098	n.a.	BMB*	163,994	96,83	n.a.
Total:			348,3645	0,0000		174,434	100,00	

Figure 65. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17a**



A	B	C	D	E	F	G	H
No.	Peak name	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %
1	n.a.	7,353	152,3338	n.a.	Ru	251,600	2,84
2	n.a.	9,160	#########	n.a.	BMB*	2067,781	47,17
3	n.a.	12,247	167,0899	n.a.	Rd	117,359	3,12
4	n.a.	20,680	#########	n.a.	BMB*	893,447	46,68
Total:			#########	0,0000		3330,187	100,00

A	B	C	D	E	F	G	H	I
No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	7,627	264,0373	n.a.	BMB*	269,821	2,39	1,77
2	n.a.	10,687	204,3257	n.a.	BMB*	172,549	1,85	1,80
3	n.a.	15,493	#########	n.a.	BMB*	515,199	10,84	1,85
4	n.a.	26,287	#########	n.a.	BMB*	1723,832	84,92	n.a.
Total:			#########	0,0000		2681,401	100,00	

Figure 66. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17b**

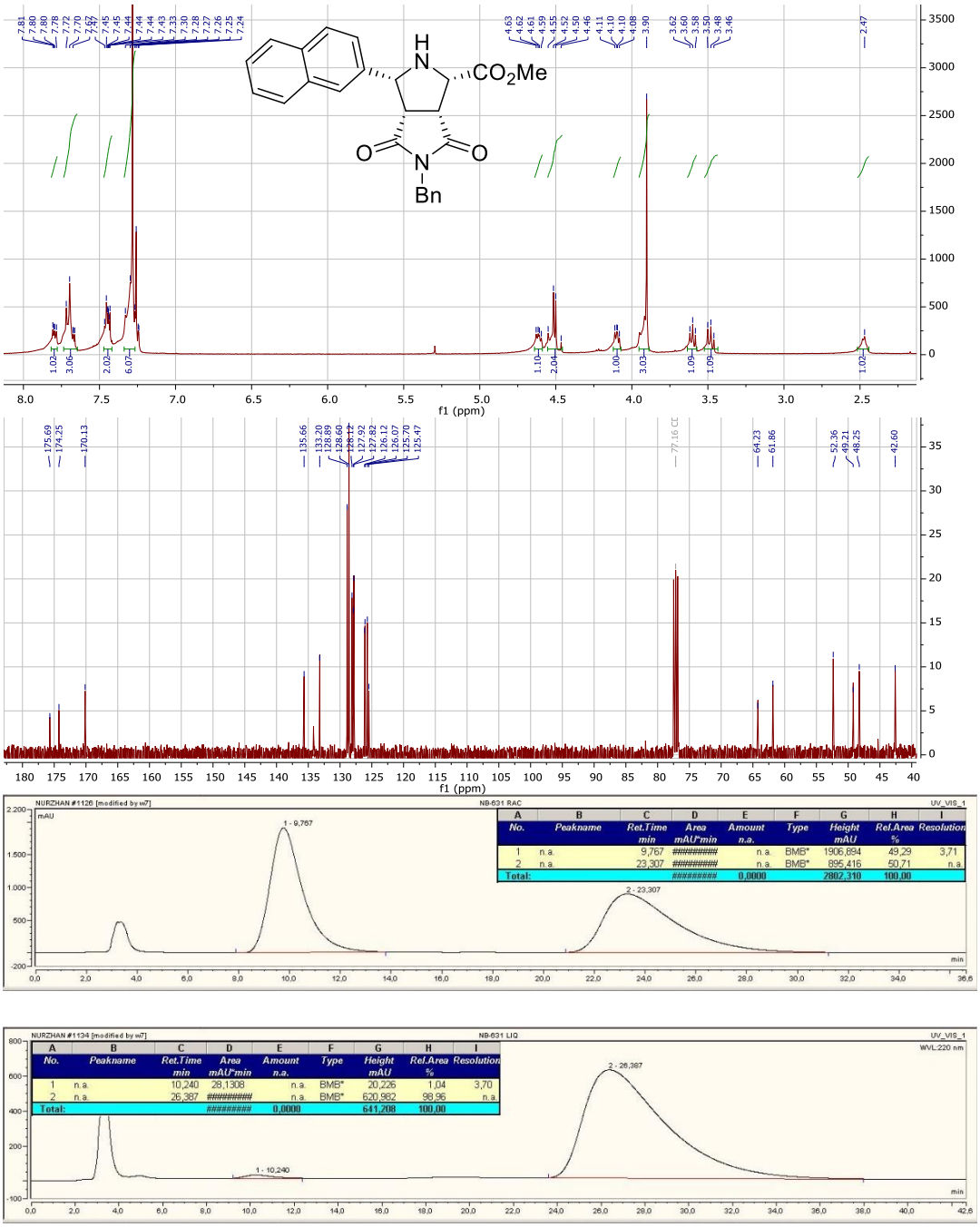


Figure 67. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17c**

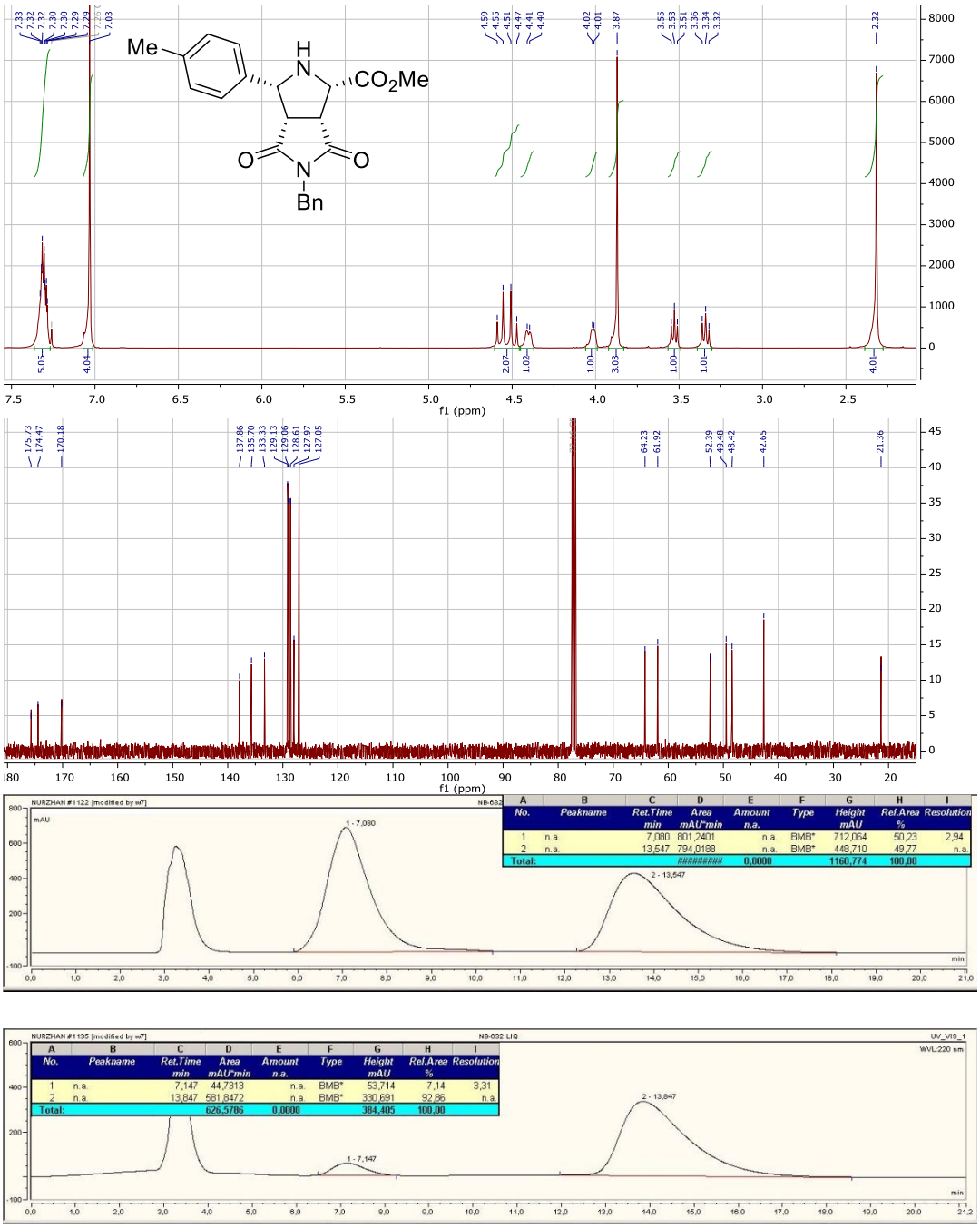


Figure 68. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17d**

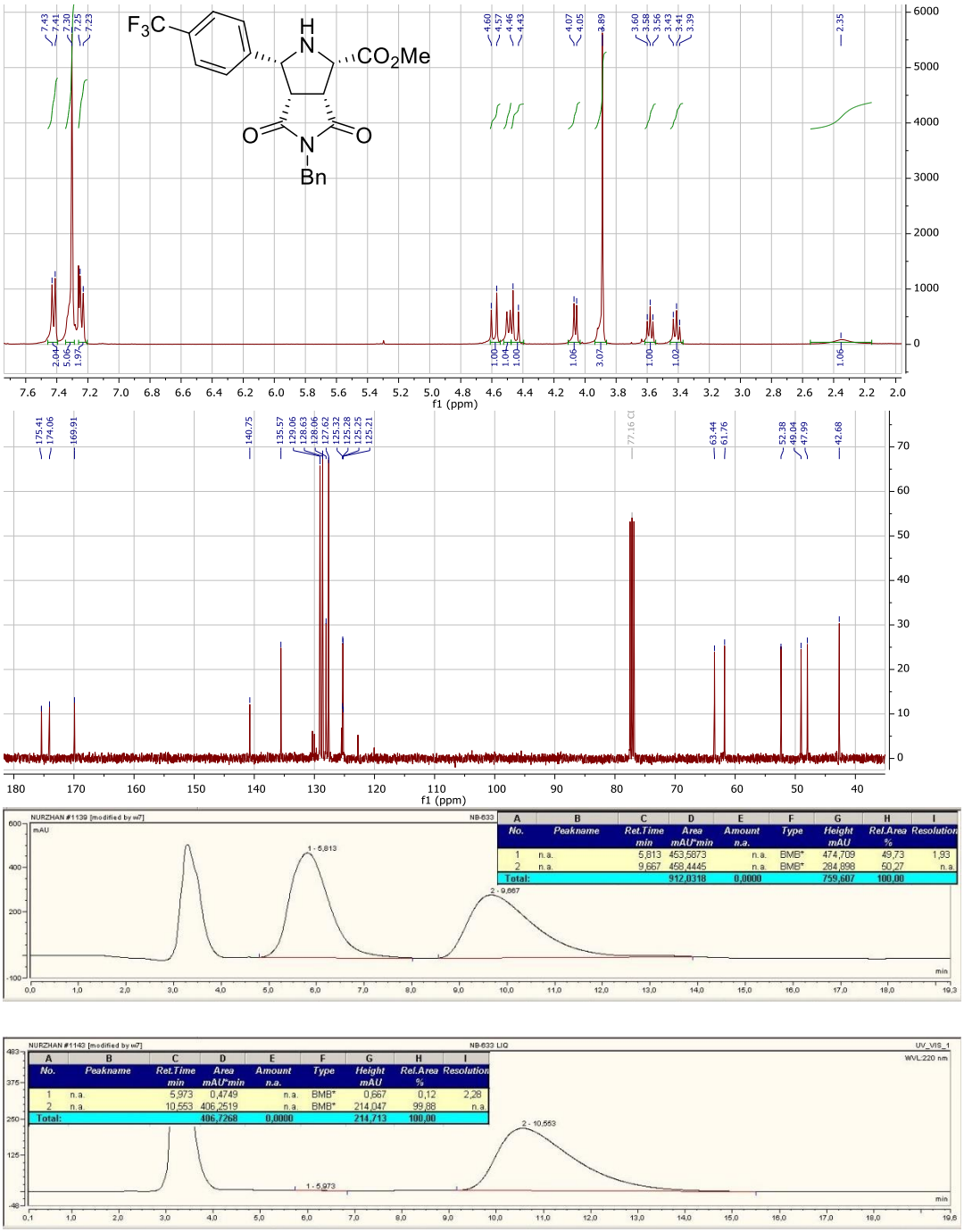


Figure 69. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17e**

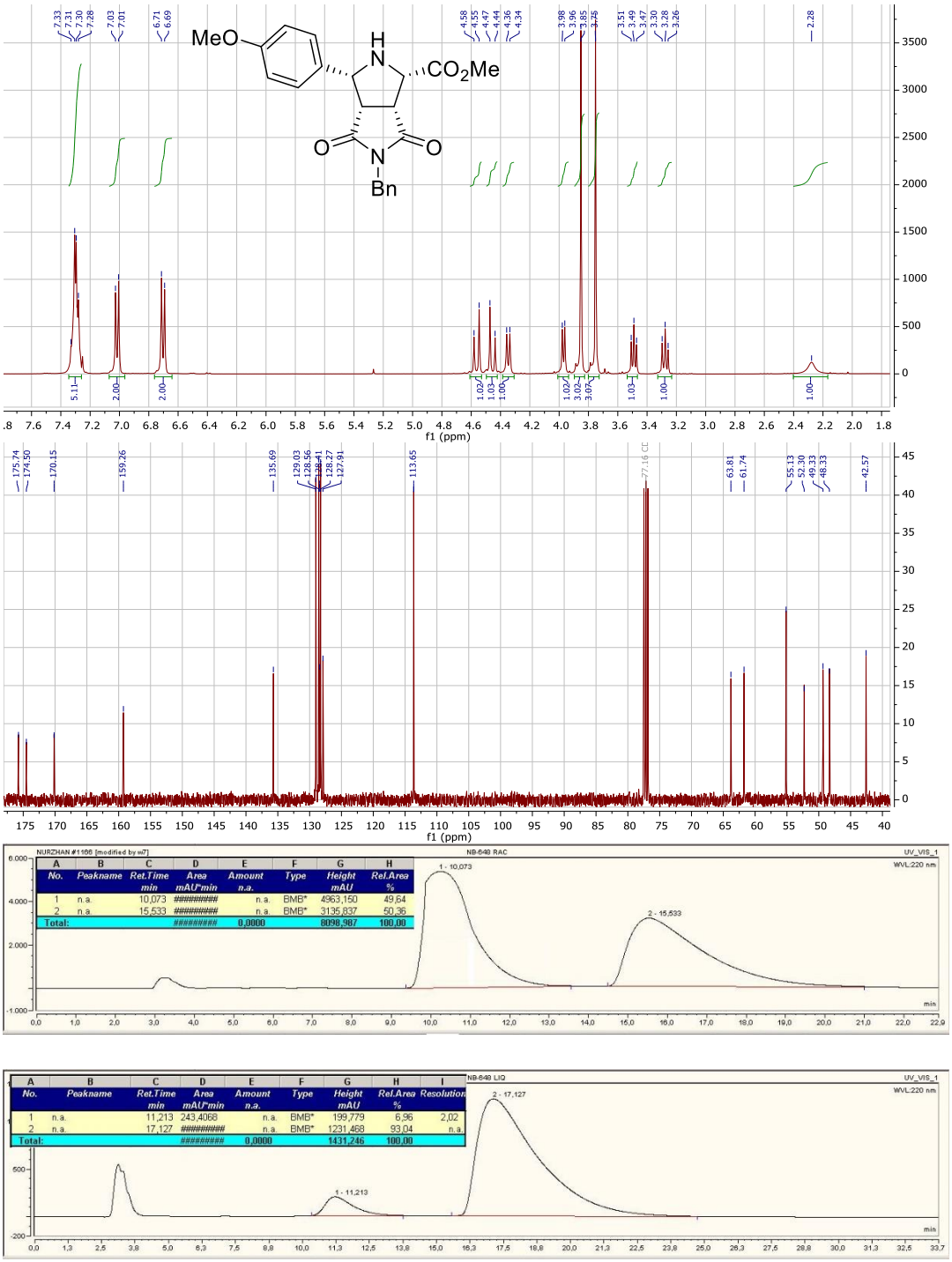


Figure 70. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17f**

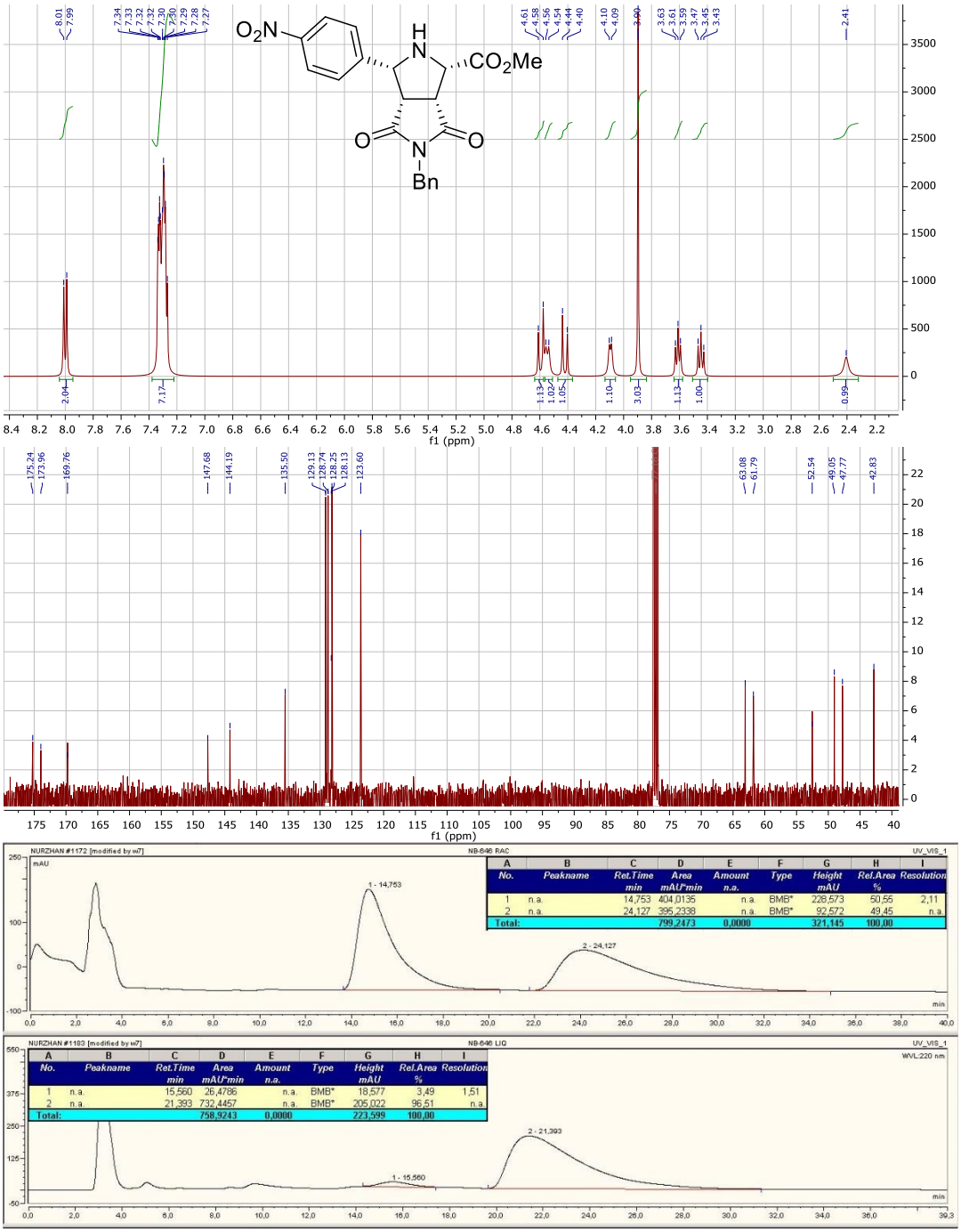


Figure 71. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17g**

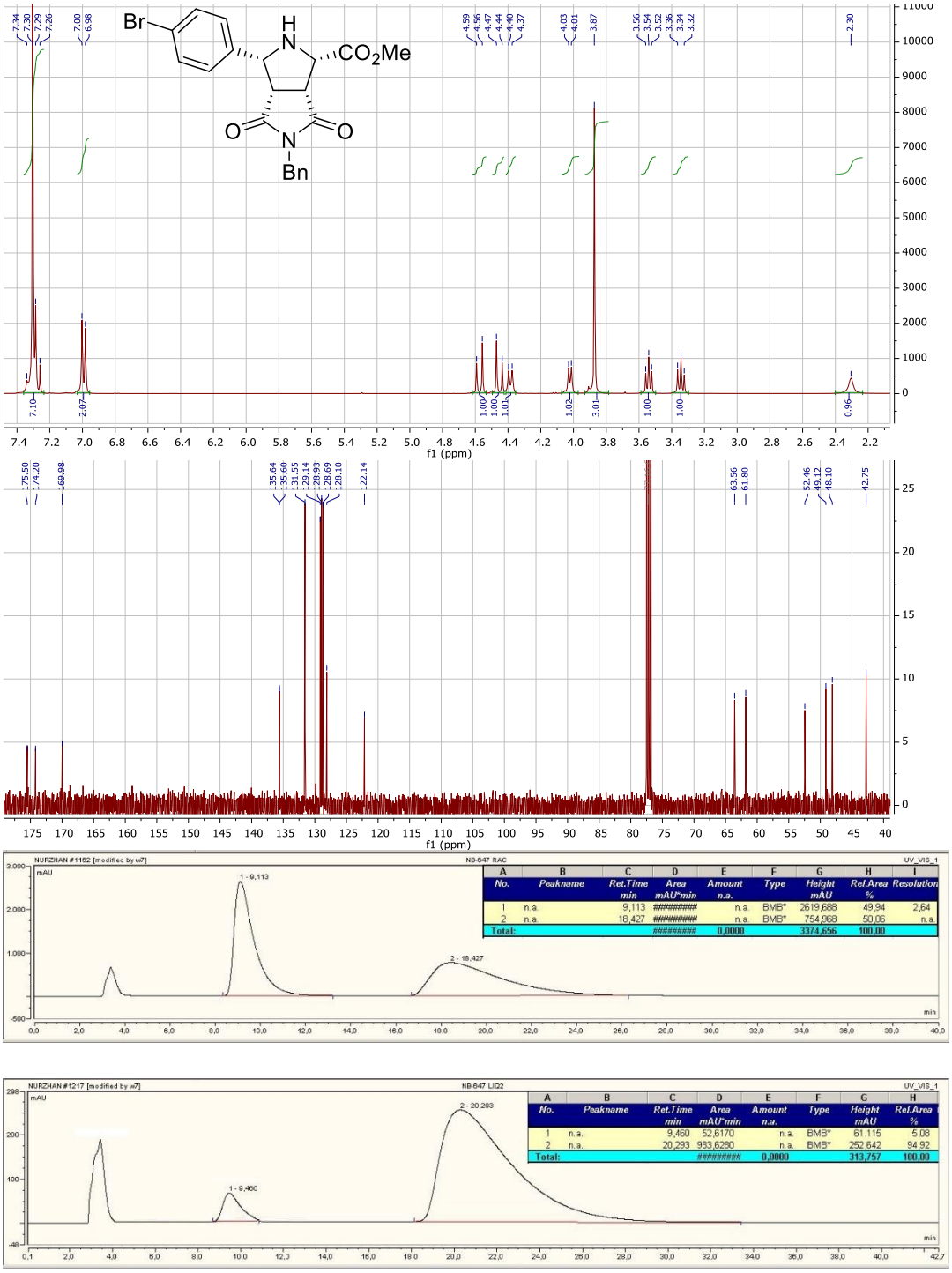


Figure 72. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17h**

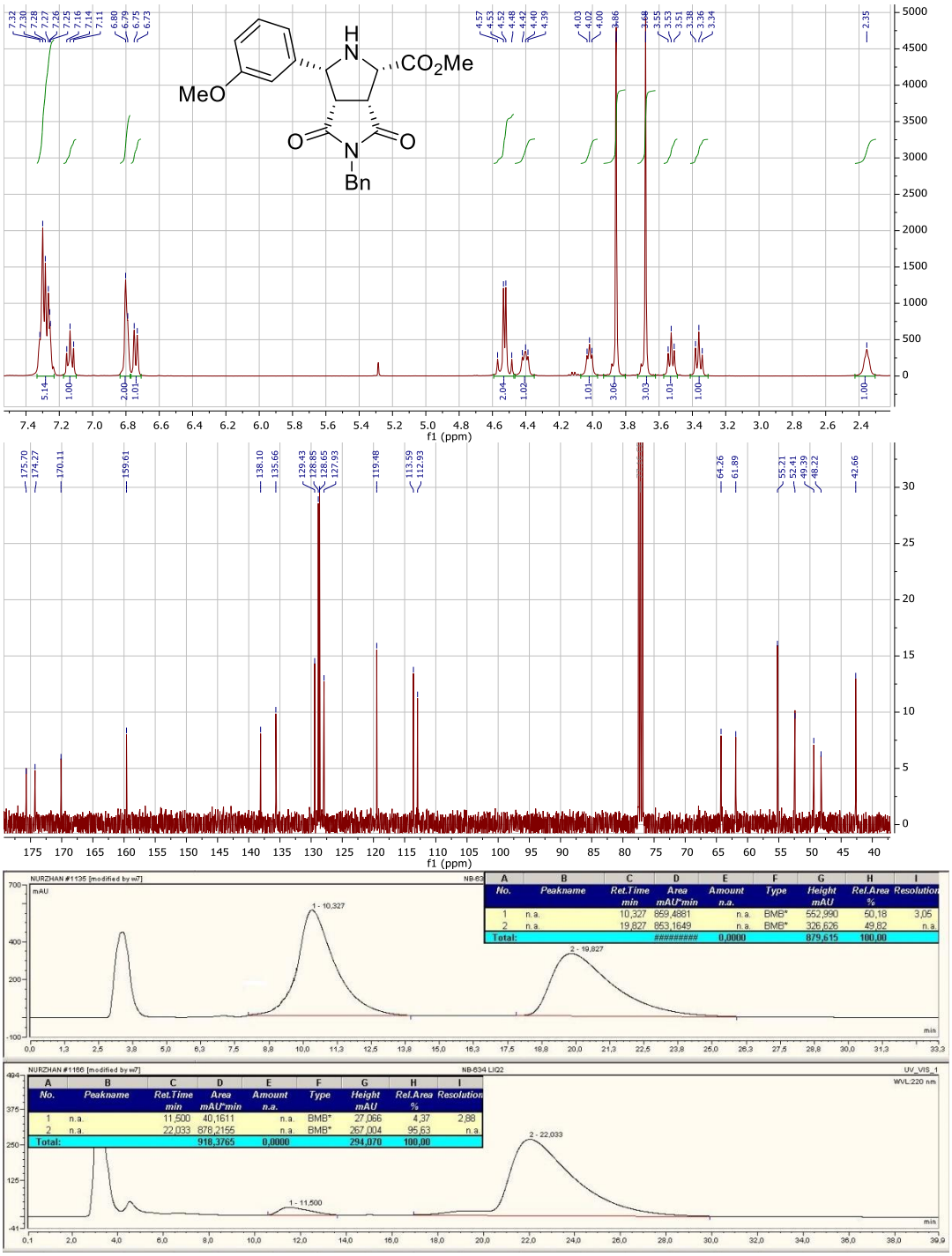
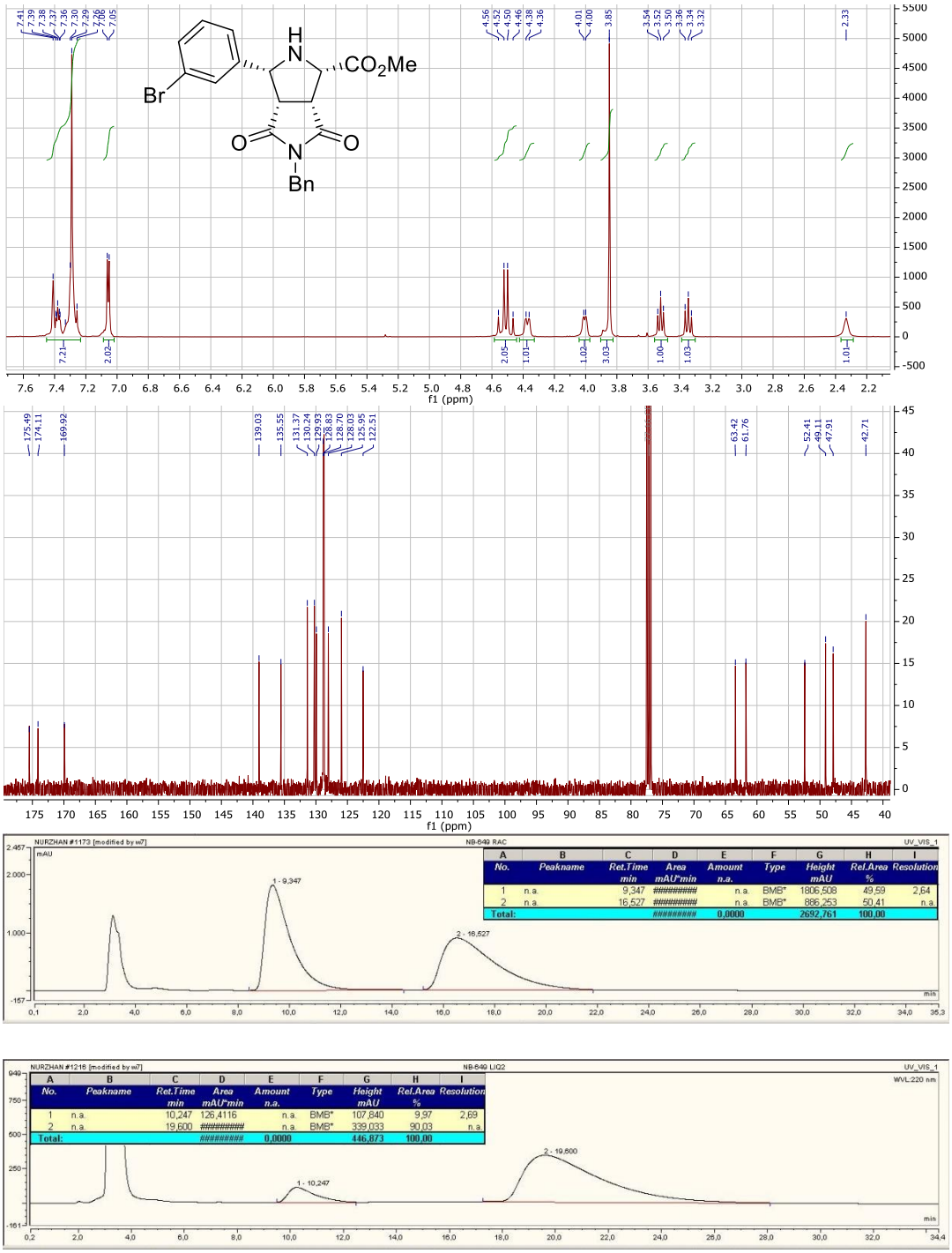


Figure 73. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17i**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	9,347	#########	n.a.	BMB*	1806,508	49,59	2,64
2	n.a.	16,527	#########	n.a.	BMB*	886,253	50,41	n.a.
Total:			#########	0,0000		2692,761	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	10,247	126,4116	n.a.	BMB*	107,840	9,97	2,69
2	n.a.	19,600	#########	n.a.	BMB*	339,033	90,03	n.a.
Total:			#########	0,0000		446,873	100,00	

Figure 74. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17j**

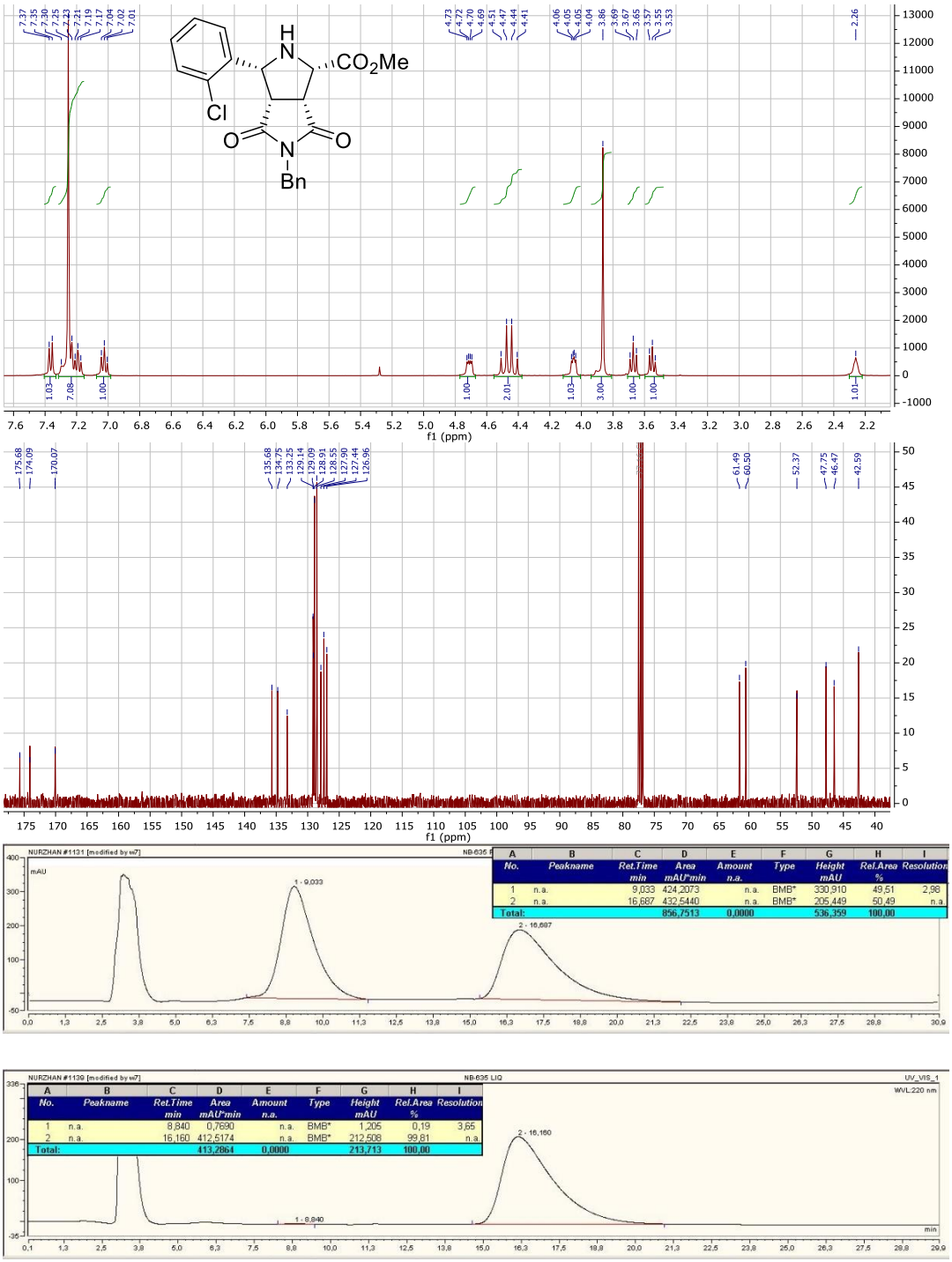
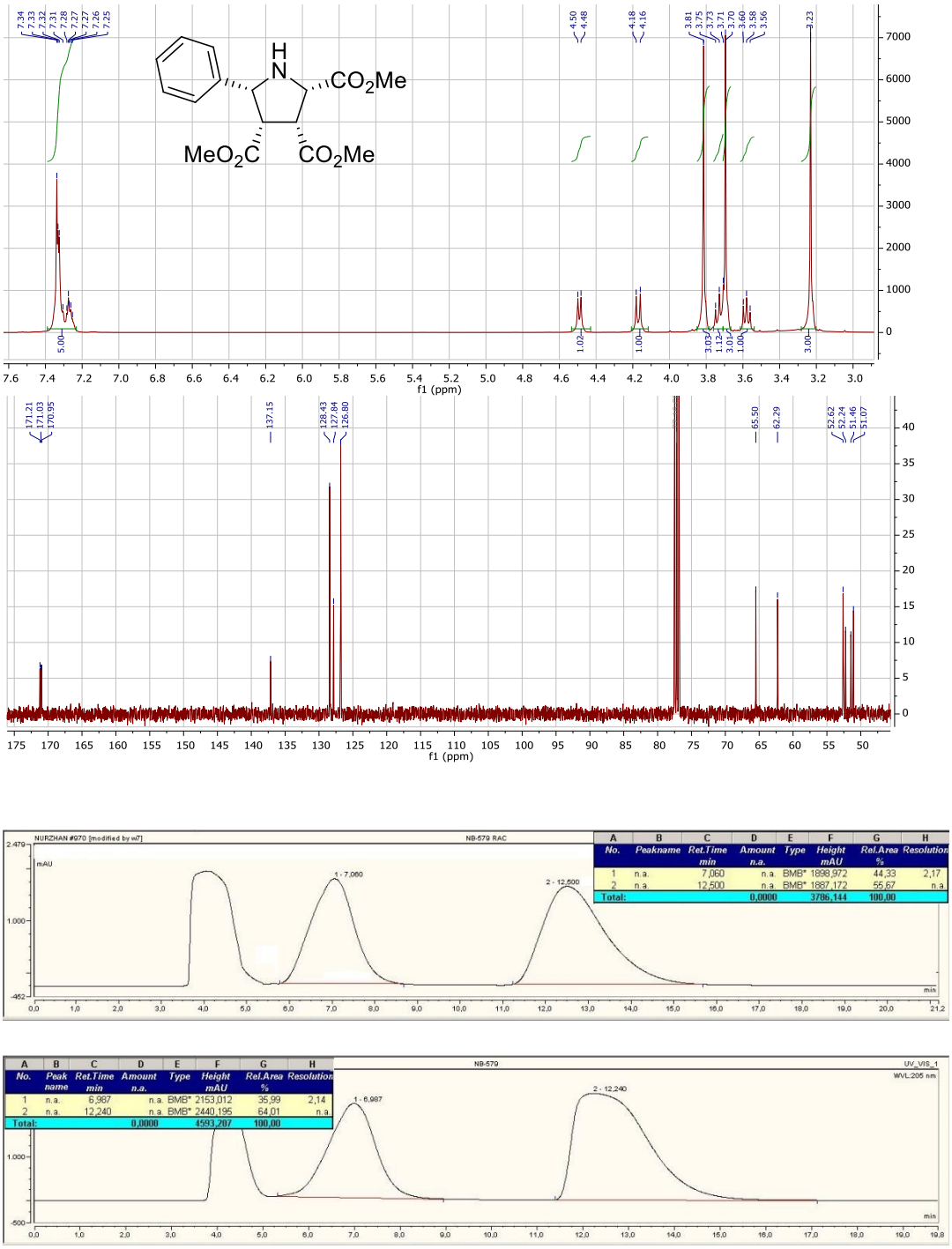


Figure 75. ^{1}H, ^{13}C NMR spectra and HPLC for compound **17k**



No.	Peakname	Ret.Time min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	7,060	n.a.	BMB*	1898,972	44,33	2,17
2	n.a.	12,500	n.a.	BMB*	1887,172	55,67	n.a.
Total:			0,0000		3786,144	100,00	

No.	Peak name	Ret.Time min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	6,987	n.a.	BMB*	2153,012	35,99	2,14
2	n.a.	12,240	n.a.	BMB*	2440,195	64,01	n.a.
Total:			0,0000		4593,207	100,00	

Figure 76. ^{1}H, ^{13}C NMR spectra and HPLC for compound **18a**

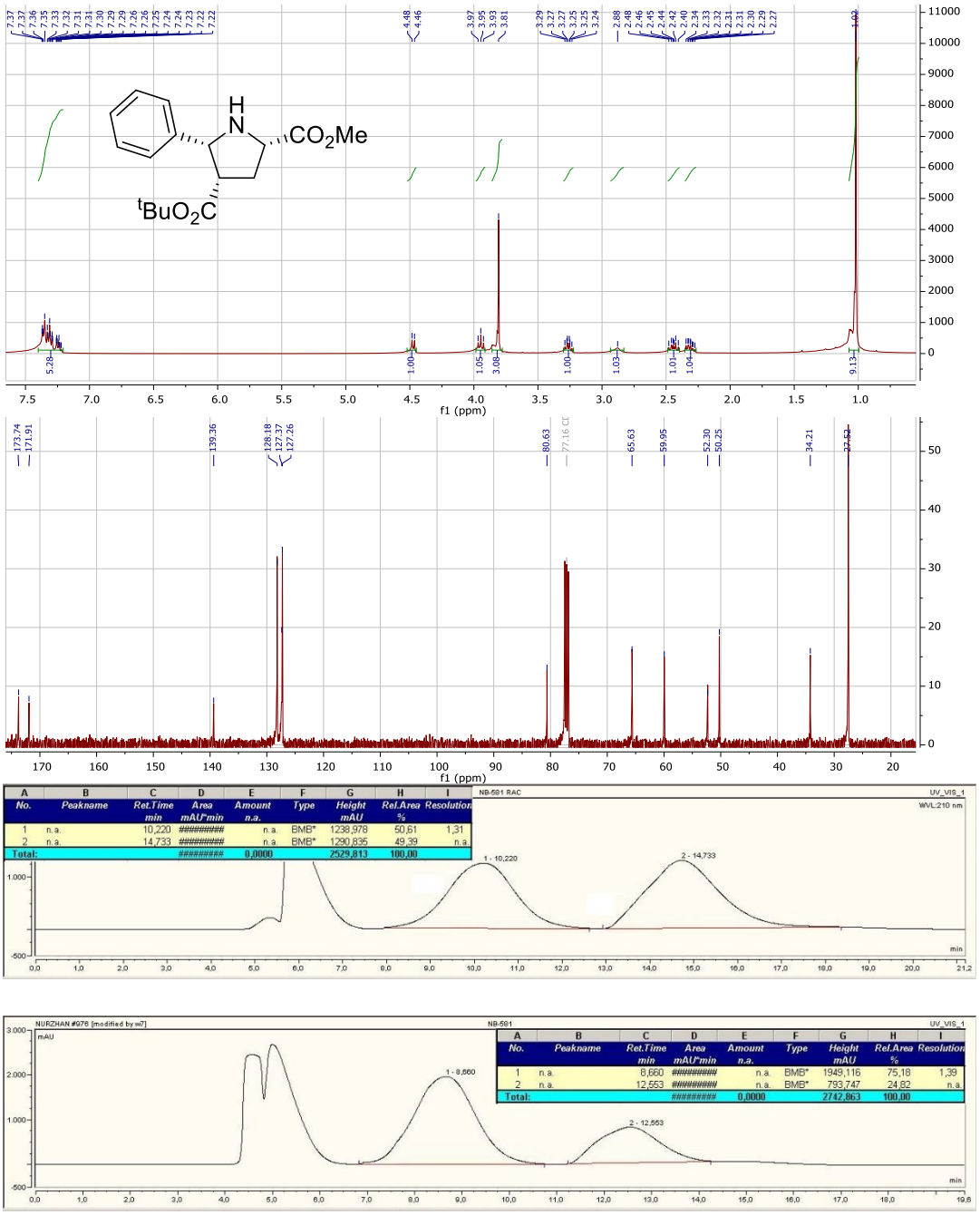


Figure 77. ^{1}H, ^{13}C NMR spectra and HPLC for compound **19a**

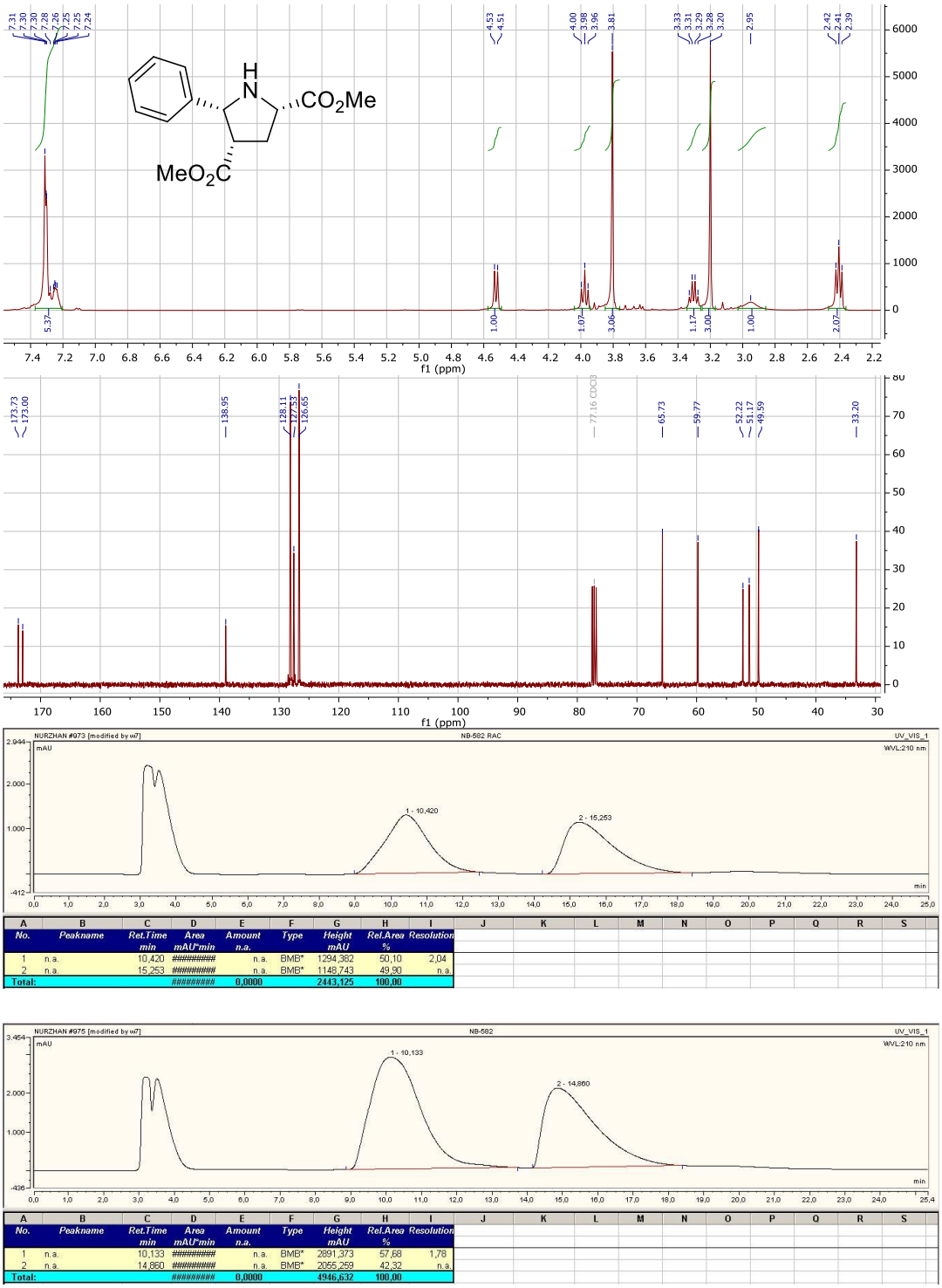
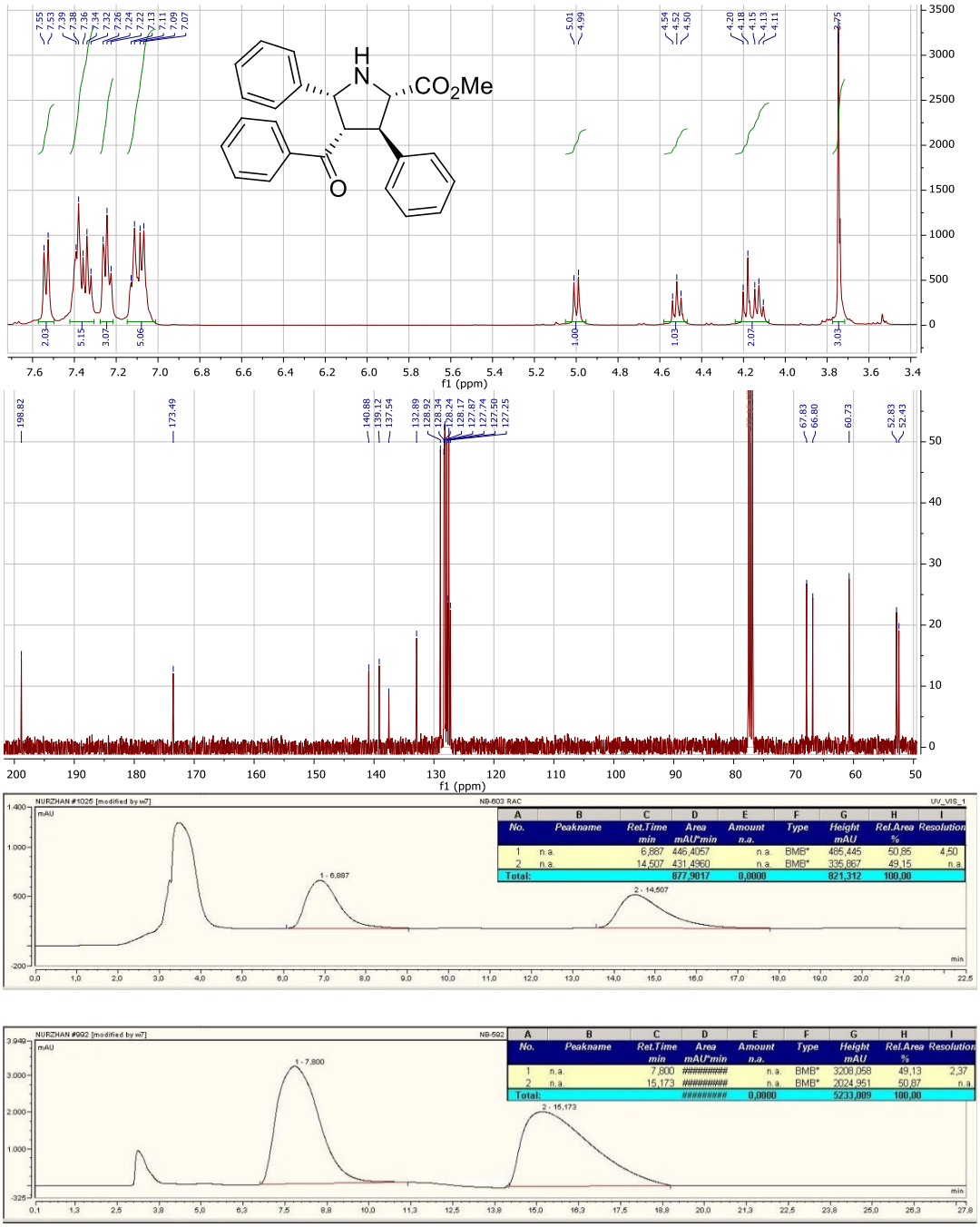


Figure 78. ^{1}H, ^{13}C NMR spectra and HPLC for compound **20a**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	6,887	446,4057	n.a.	BMB*	485,445	50,85	4,50
2	n.a.	14,507	431,4960	n.a.	BMB*	335,867	49,15	n.a.
Total:			877,9017	0,0000		821,312	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	7,800	#########	n.a.	BMB*	3208,058	49,13	2,37
2	n.a.	15,173	#########	n.a.	BMB*	2024,951	50,87	n.a.
Total:			#########	0,0000		5233,009	100,00	

Figure 79. ^{1}H, ^{13}C NMR spectra and HPLC for compound **21a**

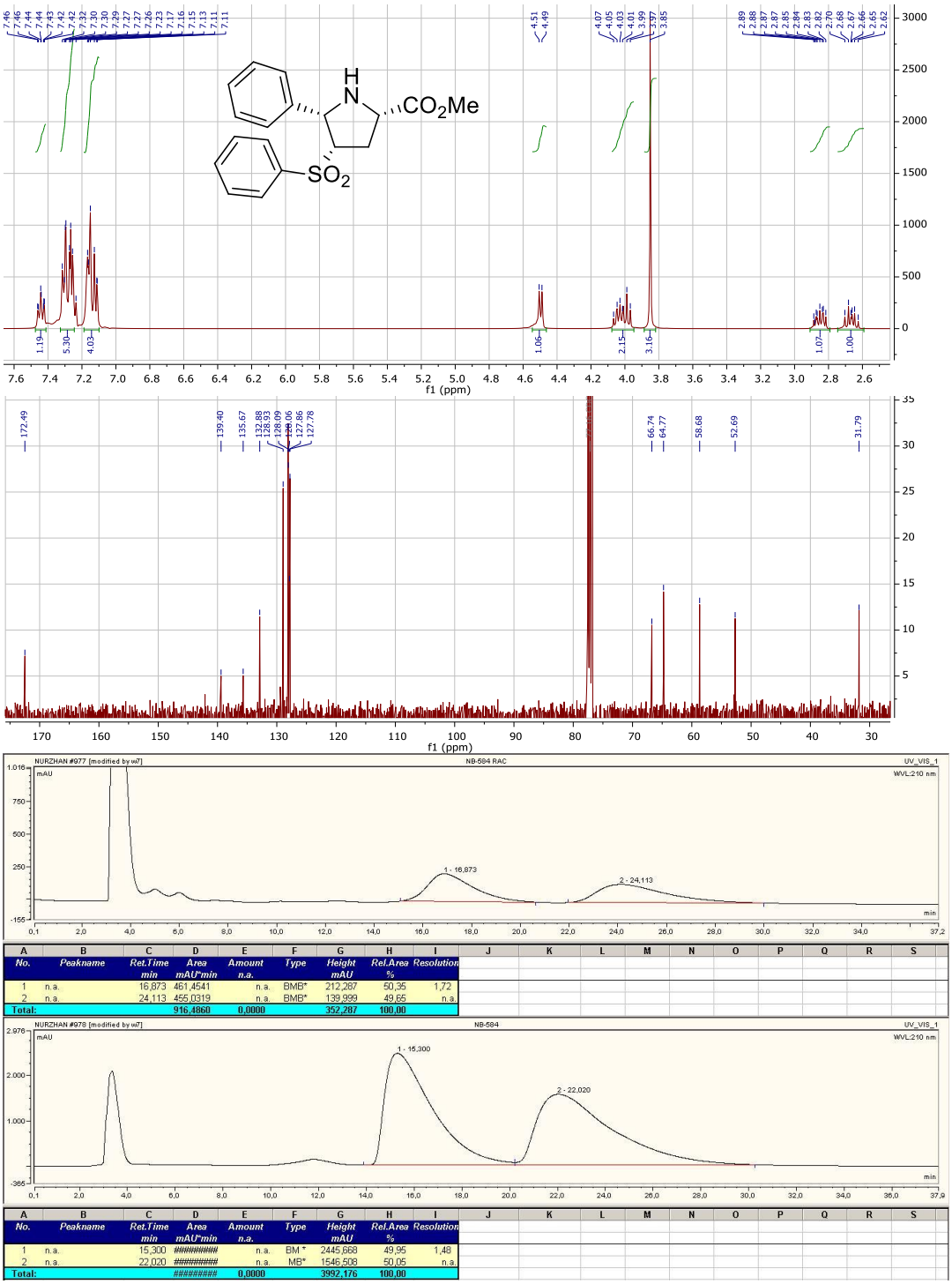
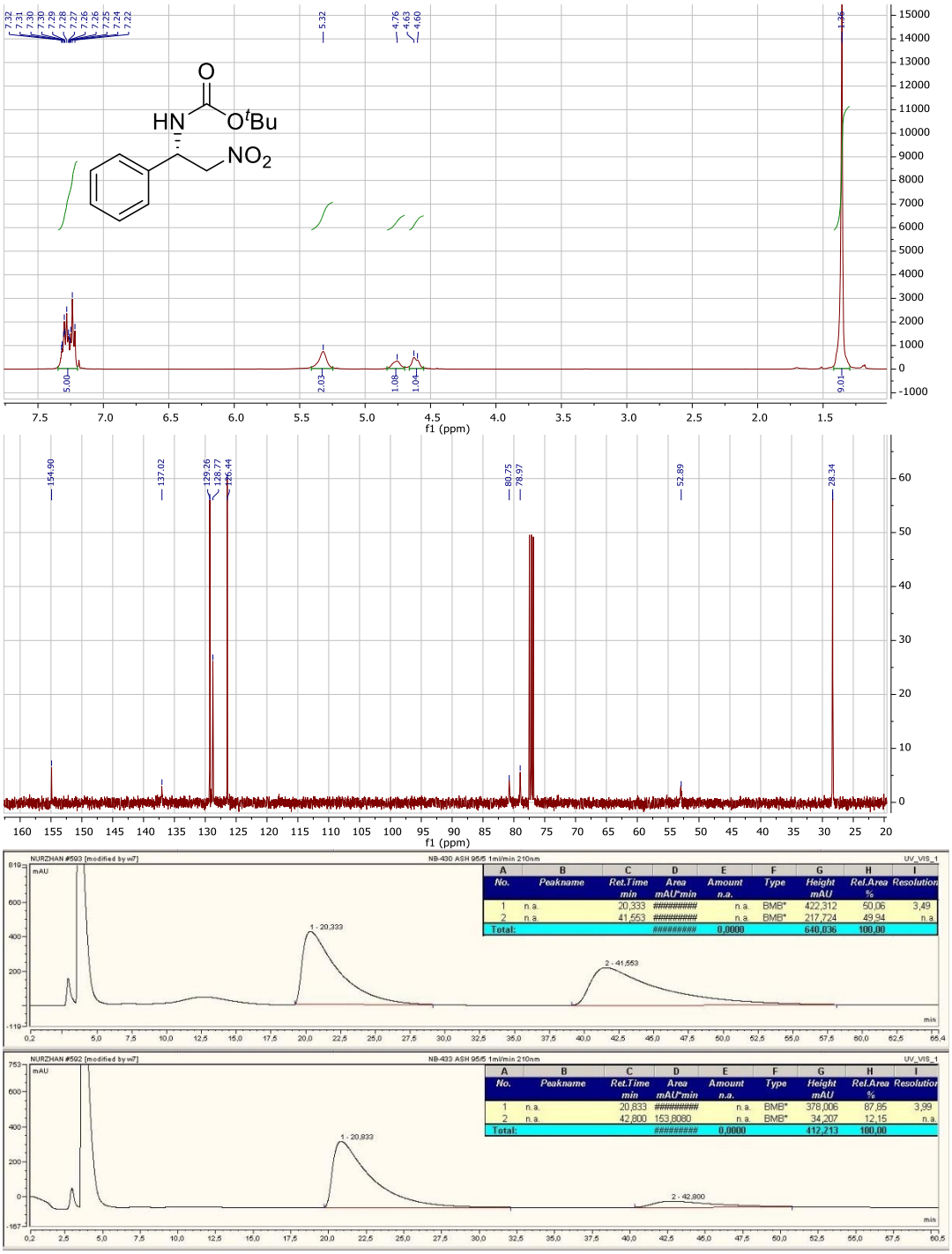


Figure 80. ^{1}H, ^{13}C NMR spectra and HPLC for compound **22a**

8.3 Experimental data for aza-Henry reaction products



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	20,333	#########	n.a.	BMB*	422,312	50,06	3,49
2	n.a.	41,553	#########	n.a.	BMB*	217,724	49,94	n.a.
Total:			#########	0,0000		640,036	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	20,833	#########	n.a.	BMB*	378,006	87,85	3,99
2	n.a.	42,800	153,8080	n.a.	BMB*	34,207	12,15	n.a.
Total:			#########	0,0000		412,213	100,00	

Figure 81. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24a**

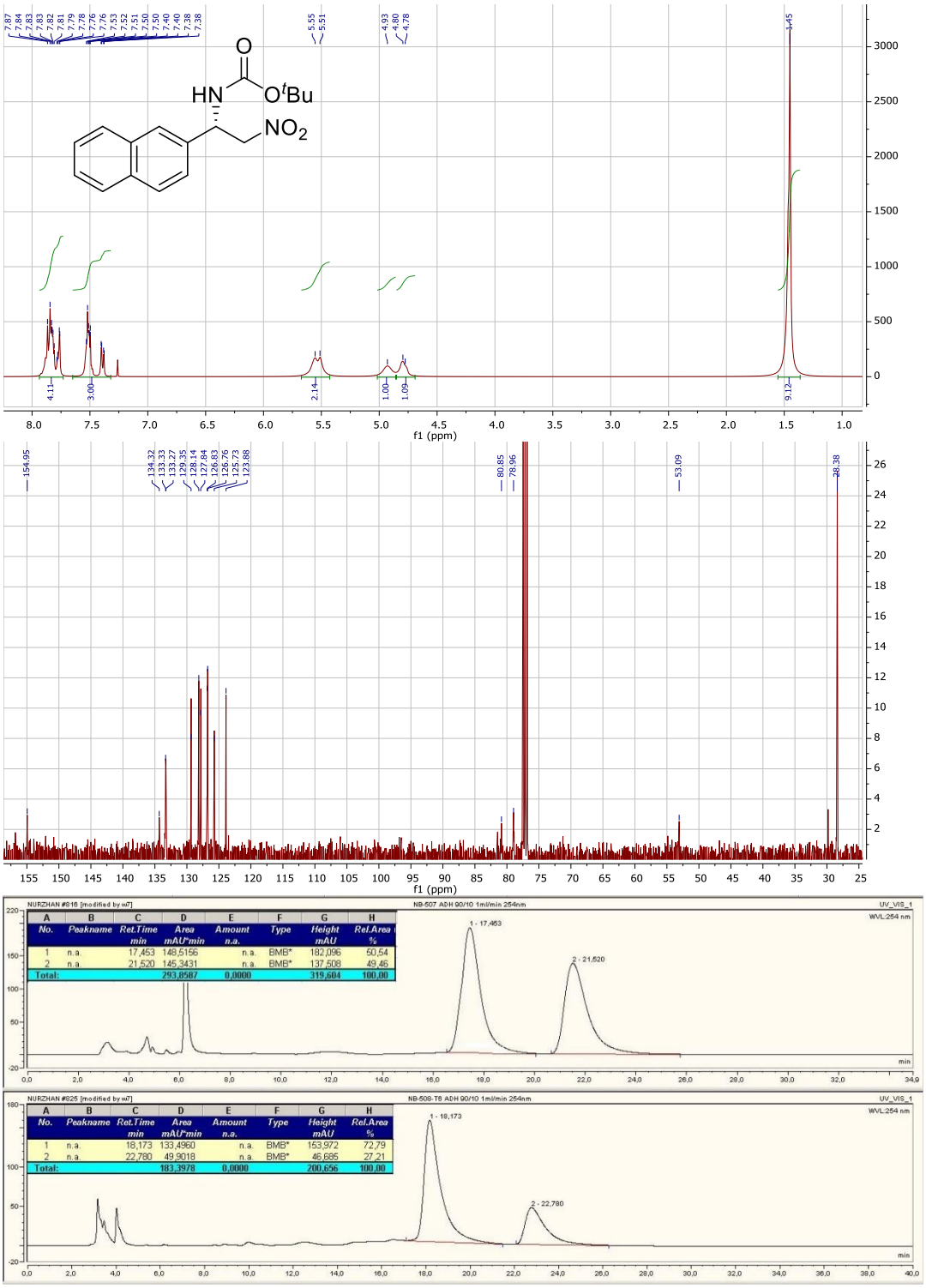
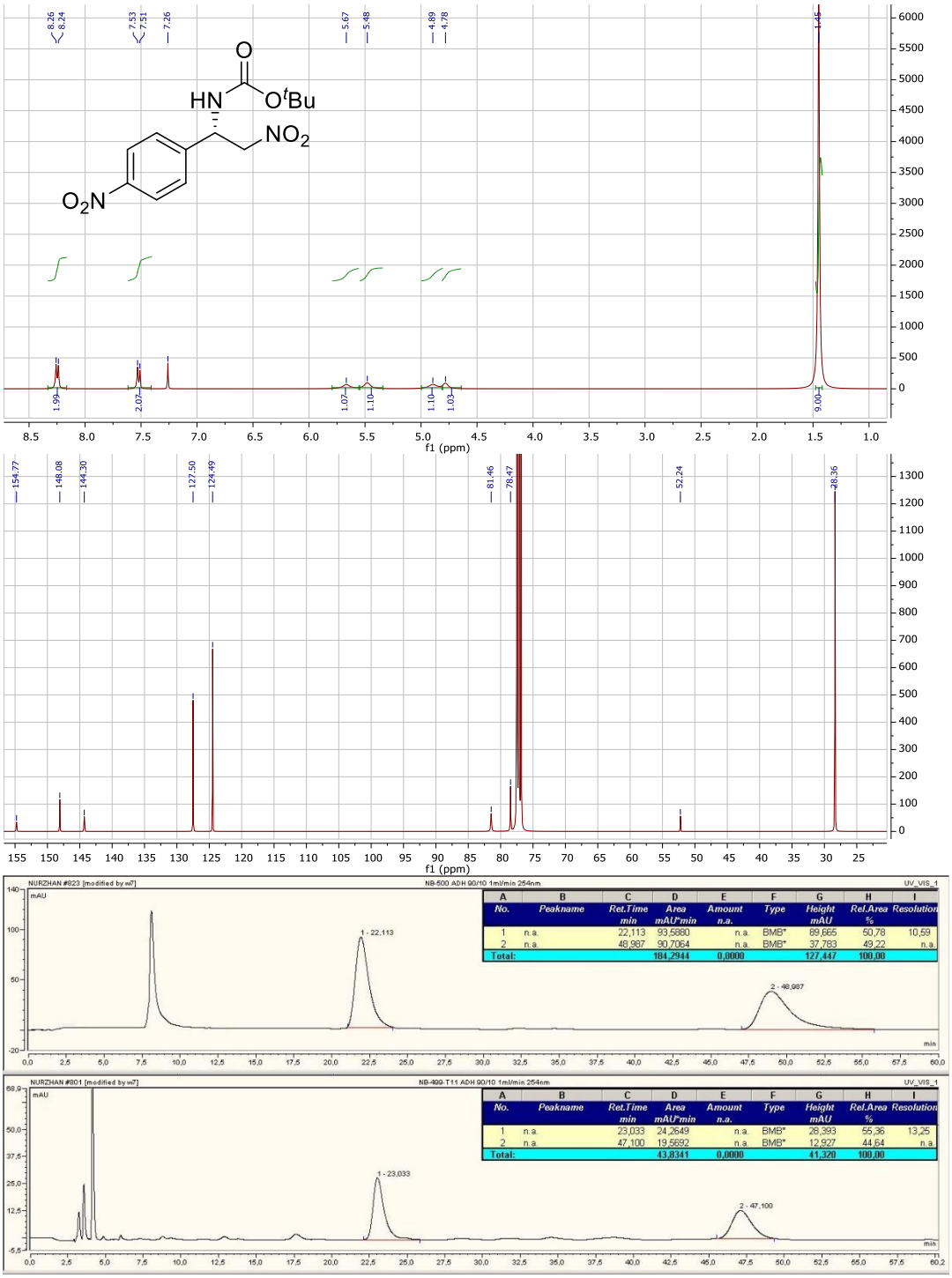


Figure 82. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24b**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	22,113	93,5880	n.a.	BMB*	89,665	50,78	10,59
2	n.a.	48,987	90,7064	n.a.	BMB*	37,783	49,22	n.a.
Total:			184,2944	0,0000		127,447	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23,033	24,2649	n.a.	BMB*	28,393	55,36	13,25
2	n.a.	47,100	19,5692	n.a.	BMB*	12,927	44,64	n.a.
Total:			43,8341	0,0000		41,320	100,00	

Figure 83. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24c**

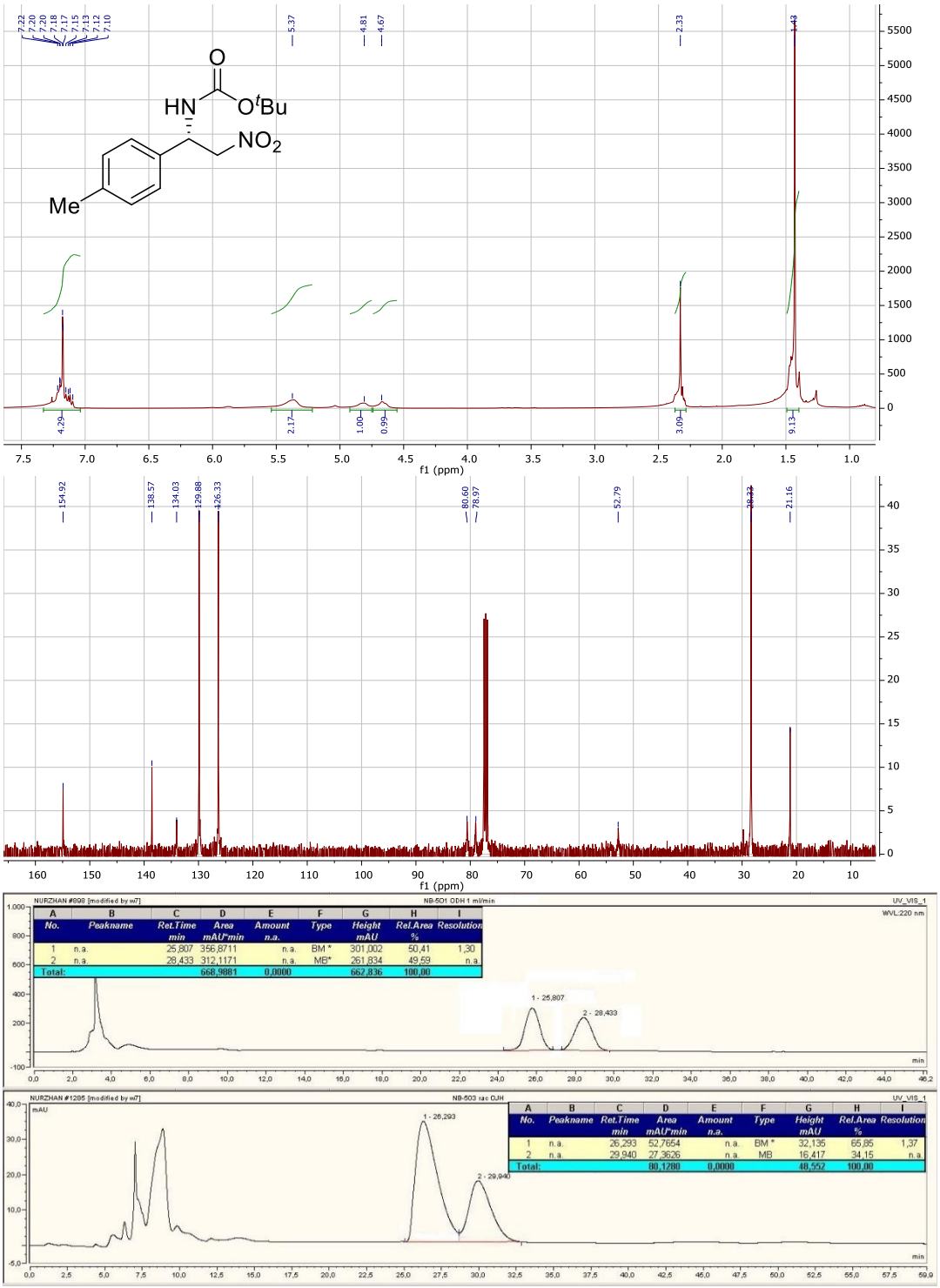
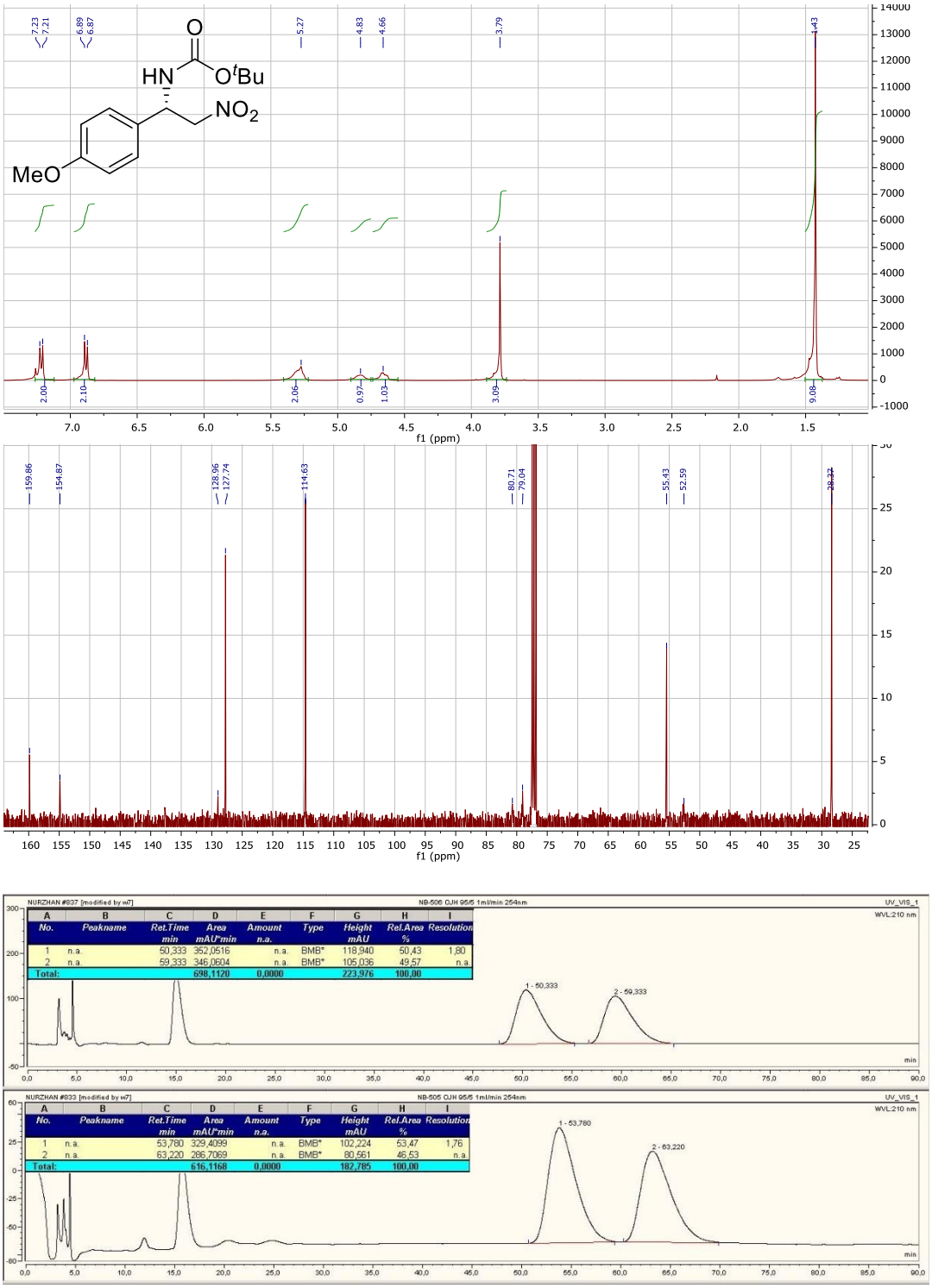


Figure 84. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24d**



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	50,333	352,0516	n.a.	BMB*	118,940	50,43	1,80
2	n.a.	59,333	346,0604	n.a.	BMB*	105,036	49,57	n.a.
Total:			698,1120	0,0000		223,976	100,00	

No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	53,780	329,4099	n.a.	BMB*	102,224	53,47	1,76
2	n.a.	63,220	286,7069	n.a.	BMB*	80,561	46,53	n.a.
Total:			616,1168	0,0000		182,785	100,00	

Figure 85. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24e**

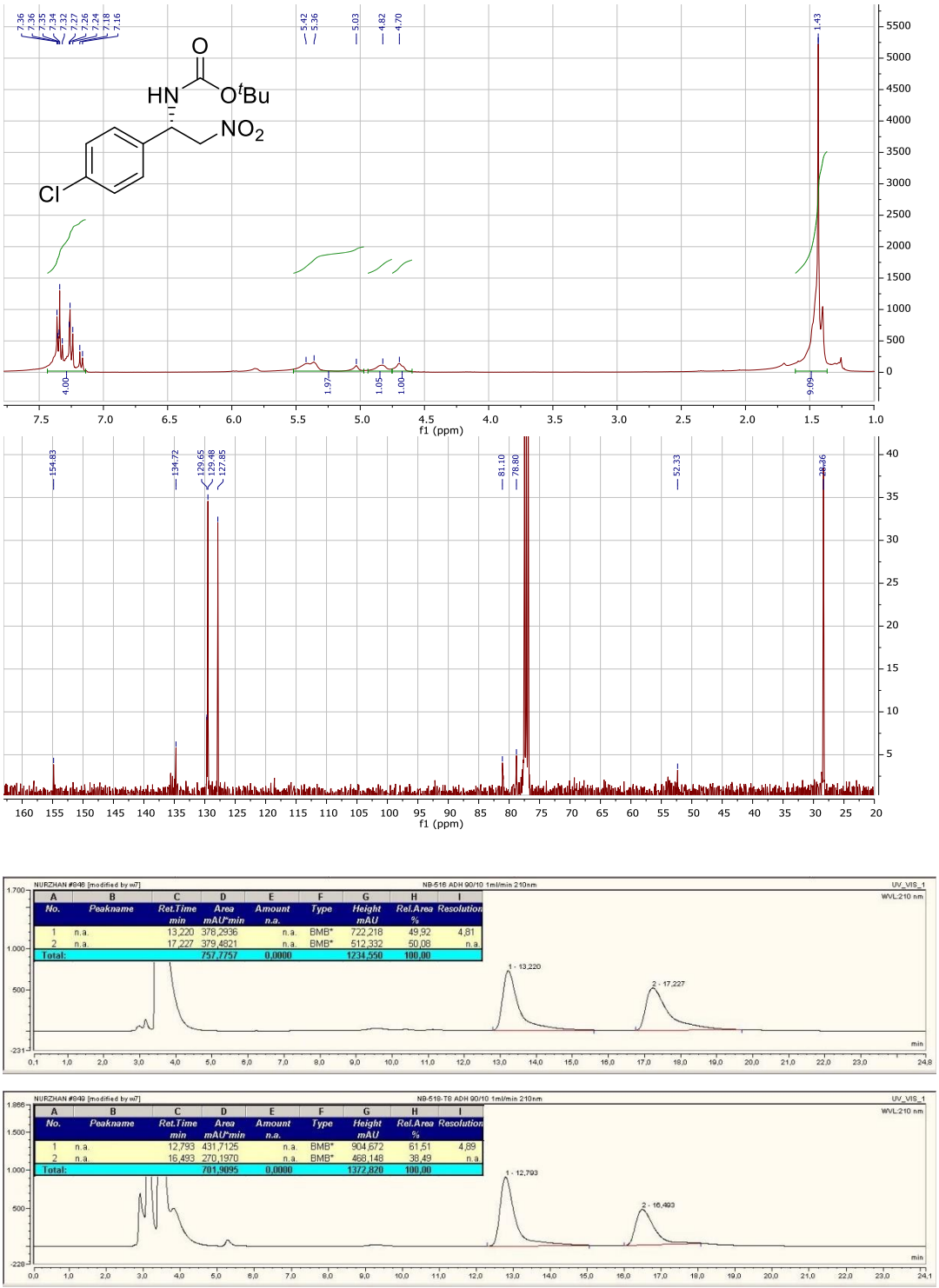


Figure 86. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24f**

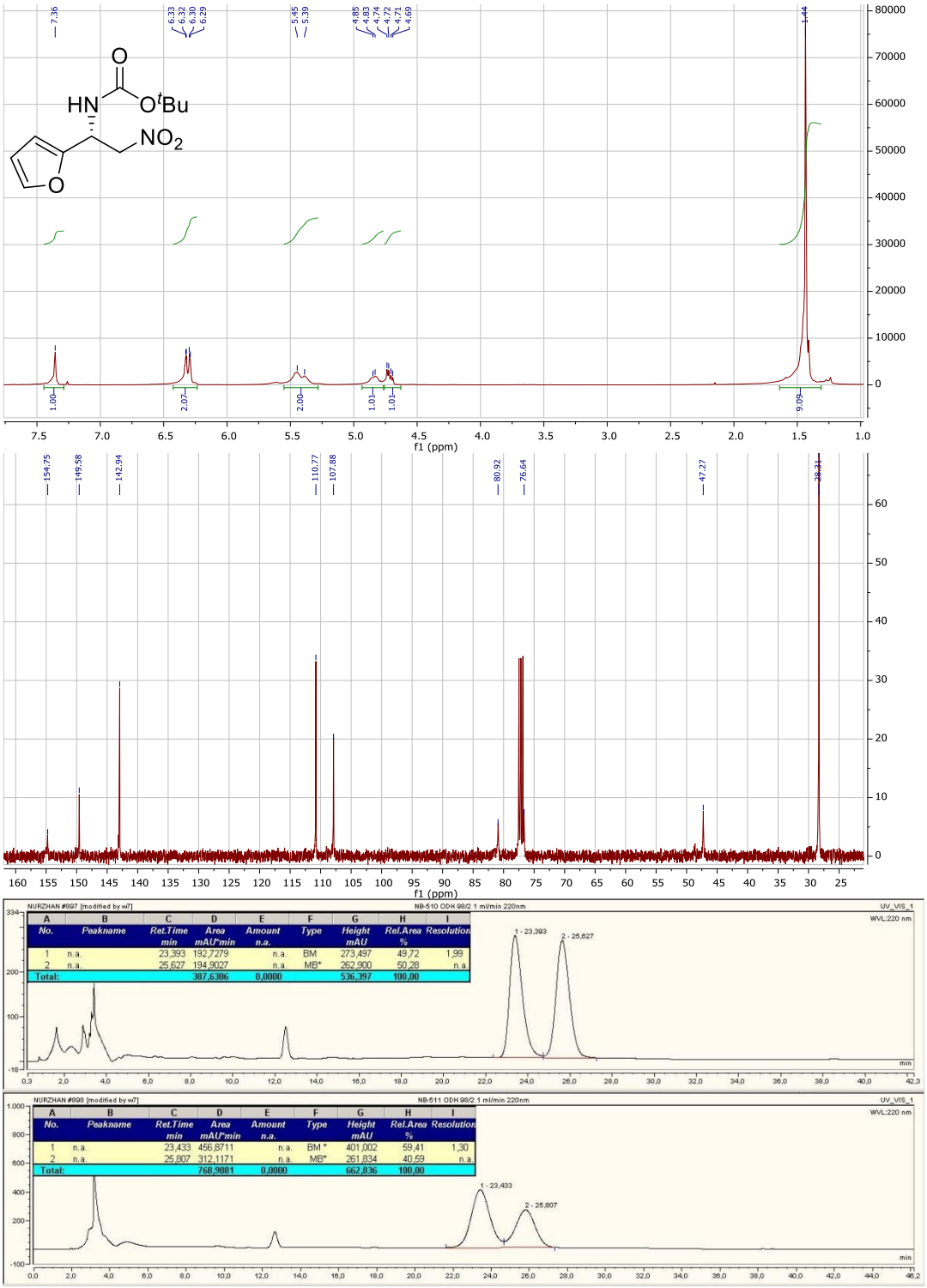


Figure 87. ^{1}H, ^{13}C NMR spectra and HPLC for compound **24g**

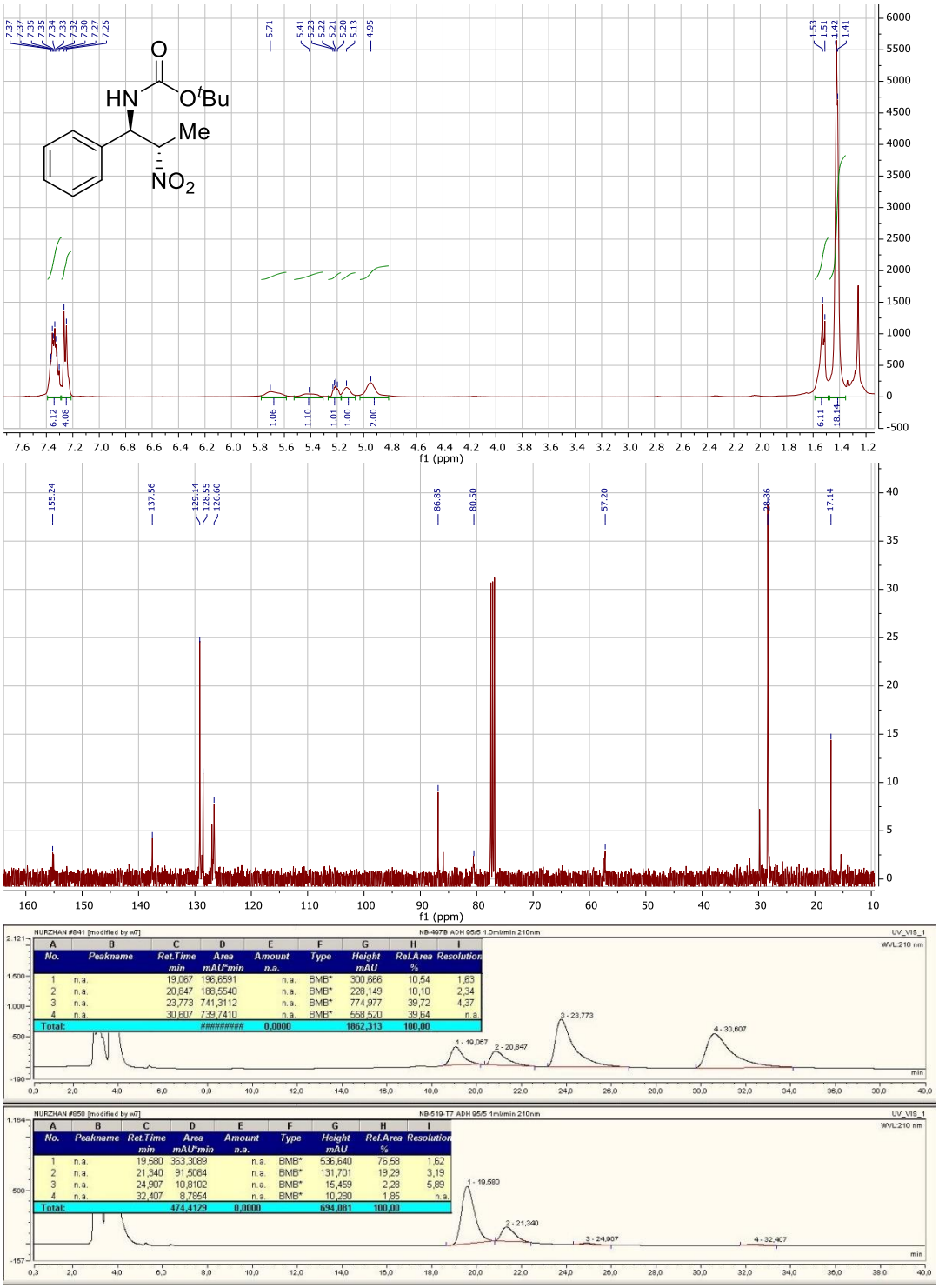


Figure 88. ^{1}H, ^{13}C NMR spectra and HPLC for compound **25a**

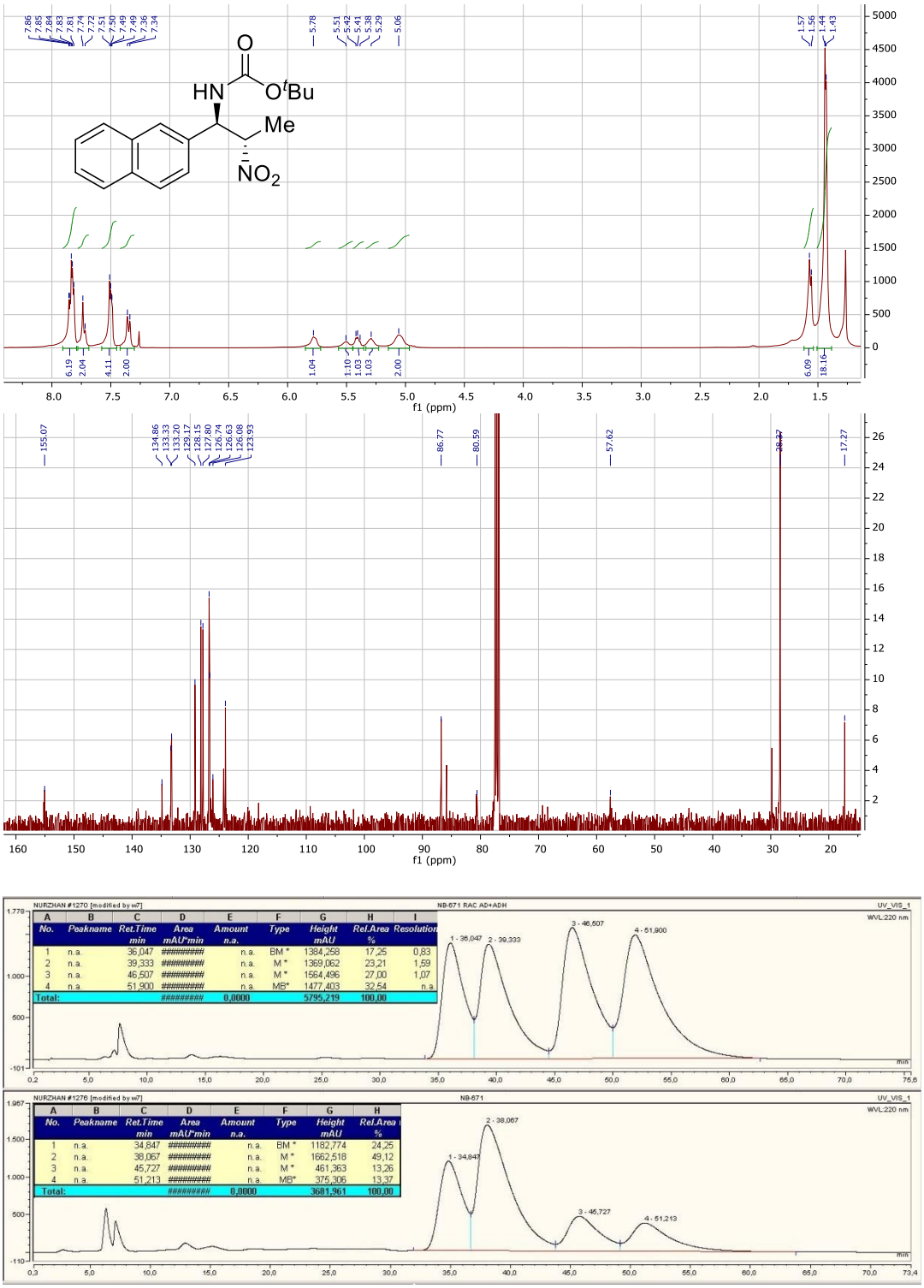


Figure 89. ^{1}H, ^{13}C NMR spectra and HPLC for compound **25b**

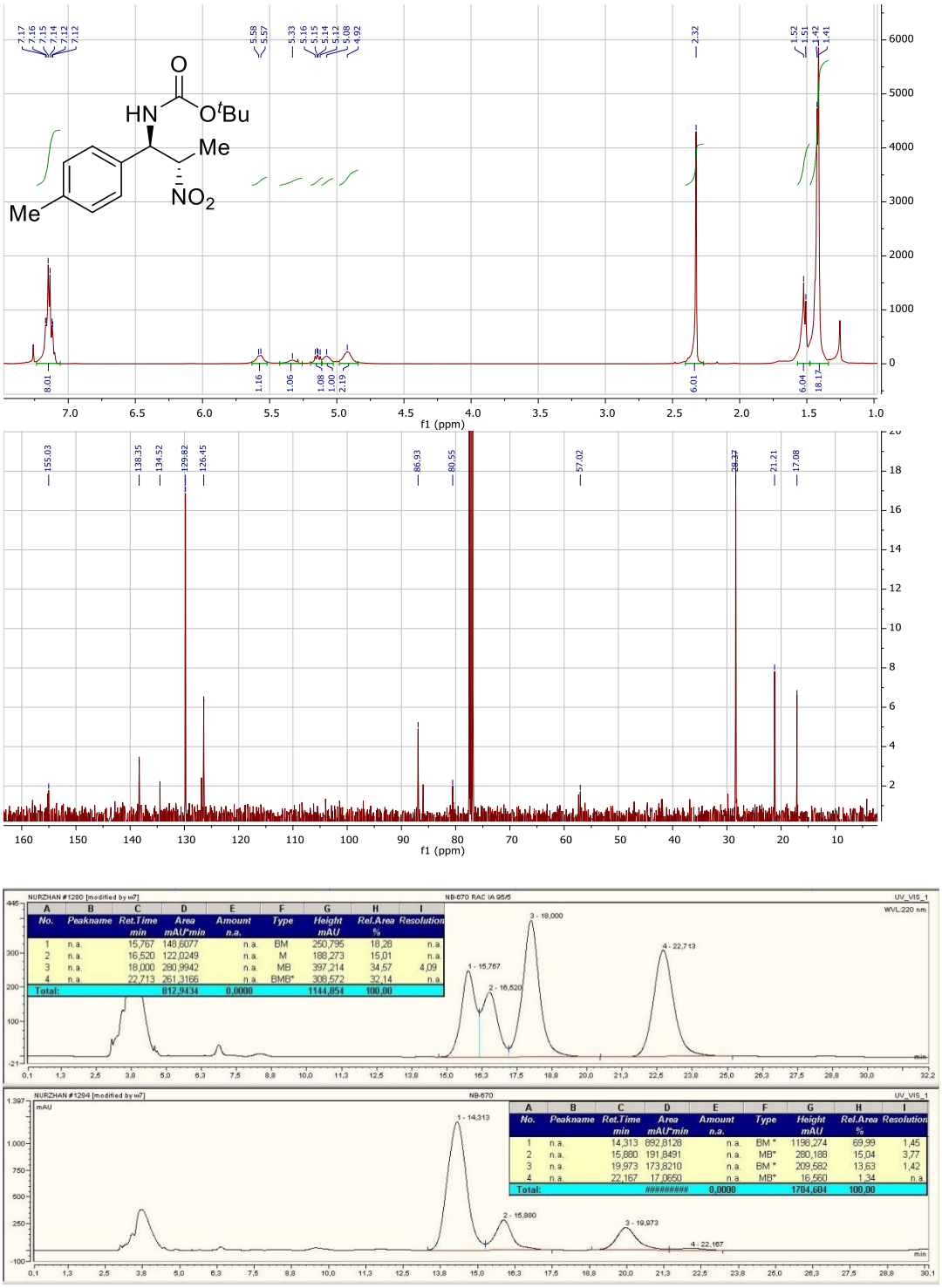


Figure 90. ^{1}H, ^{13}C NMR spectra and HPLC for compound **25c**

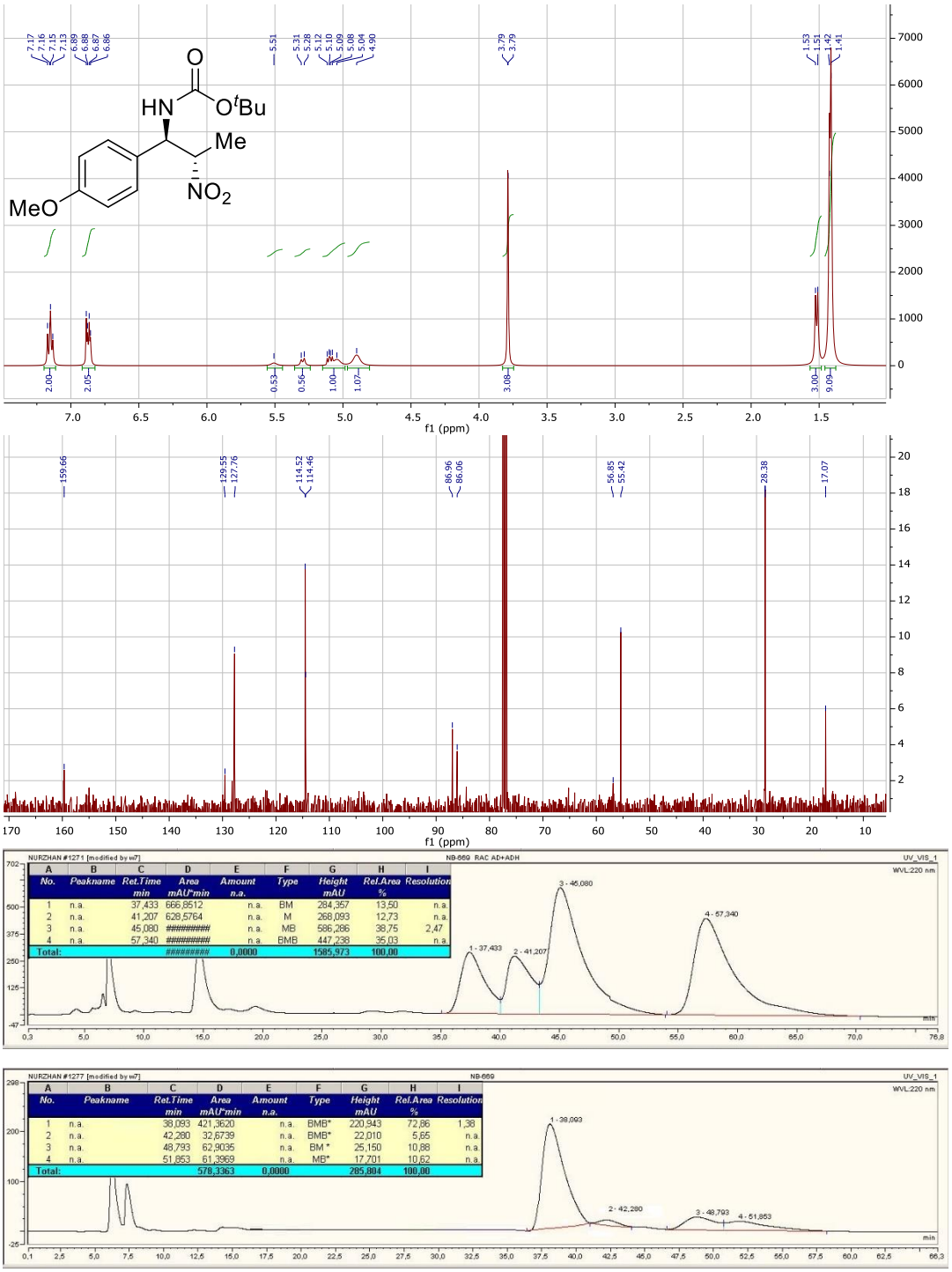


Figure 91. ^{1}H, ^{13}C NMR spectra and HPLC for compound **25d**

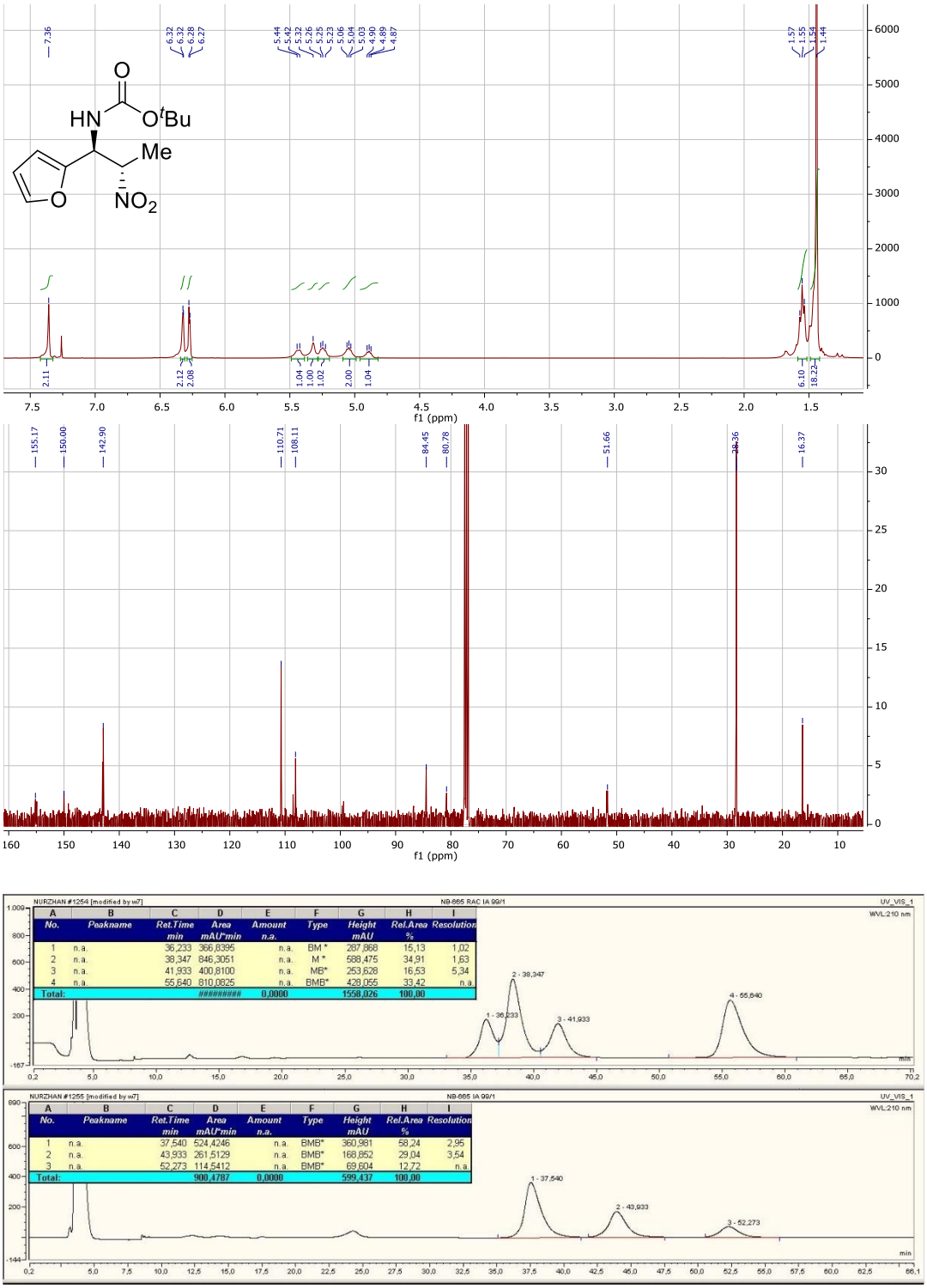


Figure 92. ^{1}H, ^{13}C NMR spectra and HPLC for compound **25**

CURRICULUM VITAE

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EDUCATION

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MS	METU Department of Chemistry	2017
BS	METU Department of Chemistry	2014
High School	Yssyk-Kul Girls' High School	2009

WORK EXPERIENCE

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2014-Present	Department of Chemistry, METU, Ankara, Turkey	2014-Present
2019 Mar.	7th International Drug Chemistry Conference, Antalya, Turkey.	Member of organizing committee
2018 Oct.	4th International Organic Chemistry Conference, Antalya, Turkey.	Member of organizing committee

2017 Oct.-2018 Feb.	METU, Deptartment of Chemistry. Ankara, Turkey	Teaching assistant
2017 Sep.	29th National Chemistry Conference, METU, Ankara, Turkey.	Member of organizing committee
2013 Jul.-Oct.	"Information and Research Center" LTD, Bishkek, Kyrgyzstan	Laboratory Assistant

FOREIGN LANGUAGES

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PUBLICATIONS

1. Polat-Cakir, S., Beksultanova, N., Dogan, Ö. **2019**. Synthesis of Functionalized Novel α-Amino-β-alkoxyphosphonates via Regioselective Ring Opening of Aziridine-2-phosphonates. *Helv. Chim. Acta* 102, 1–16.

2. Polat-Cakir, S., Beksultanova, N., Dogan, Ö. **2018**. Synthesis of β-chloro-α-aminophosphonate derivatives via the regioselective ring opening of unactivated aziridine-2-phosphonates. *Phosphorus. Sulfur. Silicon Relat. Elem*. 0, 1–7.

3. Şen, B., Sevincek, R., Beksultanova, N., Dogan, Ö. **2018**. Synthesis, structural characterization, DFT calculations and Hirshfeld surface analysis of (*R*)-2-((*S*)-2((*S*)-hydroxy(ferrocenyl)methyl)aziridin-1yl)butan-1-ol. *J. Mol. Struct.* 1173, 33–41.

4. Dogan, Ö., Polat Cakir, S., Beksultanova, N., Altanlar, N., Simsek, D., Karabiyik, H. **2017**. Enantioselective synthesis of new chiral 2-aziridinyl phosphonates and studies of their biological activities. *Tetrahedron Asymmetry* 28, 324–329.

5. Beksultanova, N., Gözükara, Z., Araz, M., Bulut, M., Polat-Çakır, S., Aygün, M., Dogan, Ö. **2021**. **FAM**-Ag-catalyzed asymmetric synthesis of heteroaryl-substituted pyrrolidine. *Chirality* 33, 465–478.