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"MERGING ORGANOCATALYTIC AND MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC SCAFFOLDS AND HYBRID MOLECULES."

Radell Echemendía Pérez*

Tese apresentada como parte dos requisitos para obtenção do título de DOUTOR EM CIÊNCIAS, área de concentração: QUÍMICA ORGÂNICA.

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“All we have to decide is what to do with the time that is given us.”

J.R.R. Tolkien

The Fellowship of the Ring

To my dear mother “Gordi”, my father “Pipo”, my Tata, my uncle Rolo and my lover Wall.

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List of Abreviatures

AC	Asymmetric Catalysis
ACN	Acetonitrile
CPA	Chiral Phosphoric Acid
DCM	Dichloromethane
DFT	Density Functional Theory
dr	Diasteromeric ratio
DNBA	3,5-dinitrobenzoic acid
ee	Enatiomeric excess
GBB-3CR	Groebke-Bieynamé-Blackburn three component reaction
HB	Hydrogen bonding
HM	Heck-Mizoroki
HOMO	Highest occupied molecular orbital
IMCR	Isocyanide multicomponent reaction
LUMO	Lowest unoccupied molecular orbital
MCR	Multicomponent reaction
NOE	Nuclear overhauser effect
P-3CR	Passerini three component reaction
SI	Steric interaction
S_NAr	Nucleophilic aromatic substitution
S_N2	Bimolecular nucleophilic substitution
TFE	2,2,2-trifluoroethanol
THP	Tetrahydropyridine
TS	Transition state
U-3CR	Ugi three component reaction
U-4CR	Ugi four component reaction
U4C-3CR	Ugi four center three component reaction
U5C-4CR	Ugi five center four component reaction

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RESUMO

“COMBINAÇÃO DE REAÇÕES ORGANOCATALÍTICAS E MULTICOMPONENTES PARA A SÍNTESE DE SISTEMAS HETEROCÍCLICOS E MOLECULAS HÍBRIDAS”. Pequenas moléculas orgânicas enantiomericamente puras ou enriquecidas são materiais de partida chave em síntese orgânica. Os blocos de construção quirais estão em alta demanda na síntese total de produtos naturais complexos e na descoberta e desenvolvimento de drogas, bem como, na produção de pesticidas, fragrâncias e materiais avançados. Nesse sentido, metodologias organocatalíticas emergiram como um terceiro pilar da catálise assimétrica e, possuem posição de destaque no desenvolvimento de métodos mais sustentáveis. De maneira similar, reações multicomponentes (RMCs) apresentam-se como uma poderosa ferramenta para a síntese de compostos heterocíclicos bioativos e análogos de produtos naturais. Aldeídos quirais são componentes chave em RMCs estereocontroladas, os métodos para a funcionalização assimétrica de compostos carbonílicos são relevantes para o desenvolvimento de novas abordagens multicomponentes estereosseletivas.

Nos últimos anos, nosso grupo e o grupo de Banfi vêm explorando o potencial da organocatálise para gerar compostos enantiomericamente enriquecidos com o poder sintético das RMCs na diversificação desses compostos quirais.

Neste trabalho descrevemos metodologias altamente estereosseletivas para a síntese de hídridos de produtos naturais a partir de um procedimento organocatalítico - one-pot sequencial - seguido de uma reação multicomponente. Efetivamente, o procedimento compreende uma adição conjugada organocatalisada de compostos metileno ativos (1,3-dicarbonilas e α-cianocetonas) a aldeídos α,β-insaturados para a formação de hemiacetais assimétricos contendo grupos funcionais ortogonais. Após esse primeiro evento, de forma sequencial e one-pot é implementada uma reação multicomponente intramolecular baseada em isocianeto. Através do emprego desta abordagem foi possível sintetizar híbridos de produtos naturais, incluindo até quatro fragmentos moleculares diferentes, tais como, unidades hidroquinolinona, tetrahidropiridina, peptídeos, lipídeo e glicosídeo

ABSTRACT

“MERGING ORGANOCATALYTIC AND MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC SCAFFOLDS AND HYBRID MOLECULES”. Small enantiomerically pure or enriched organic molecules are key starting materials in organic synthesis. Chiral building blocks are in high demand in the overall synthesis of complex natural products and in the discovery and development of drugs as well as in the production of advanced pesticides, fragrances and materials. In this sense, organocatalytic methodologies have emerged as a third pillar of asymmetric catalysis and have a prominent position in the development of more sustainable methods. Similarly, multicomponent reactions (MCRs) present themselves as a powerful tool for the synthesis of bioactive heterocyclic compounds and analogues of natural products. Chiral aldehydes are key components in stereocontrolled MCRs, methods for the asymmetric functionalization of carbonyl compounds are relevant for the development of novel multicomponent stereoselective approaches.

In recent years, our group and the Banfi group have been exploring the potential of organocatalysis to generate compounds enantiomerically enriched with the synthetic power of MCRs in the diversification of these chiral compounds.

In this work we describe a highly stereoselective methodology for the synthesis of natural product hybrids from an organocatalytic tandem procedure, followed by a multicomponent reaction. Effectively, the procedure comprises an organocatalysed conjugate addition of active methylene compounds (1,3-dicarbonyls and α ester or cyanoketones) to α,β-unsaturated aldehydes to form asymmetric hemiacetals containing orthogonal functional groups. Next, an isocyanate based intramolecular multicomponent reaction is implemented. Through the use of this approach it was possible to synthesize hybrids of natural products, including up to four different molecular fragments, such as hydroquinoline, tetrahydropyridine, peptides, lipid and glycoside units

Summary

Chapter 1

1. Chapter 1

1.1 Introduction

The origin of life on Earth is one of the greatest and most fascinating puzzles of mankind. Scientists generally assume that it evolved in a stepwise process with increasing complexity, but fundamental questions of how exactly that happened remain essentially unanswered. One part of this big puzzle that is of particular interest for many chemists is the origin of biological chirality. We certainly know that chirality is the source of diverse phenomena at the macro- and microscopic level and is responsible of a large number of catalytic reactions, and these are the origin of asymmetry in our body and culture.[1]

The biological machinery made up from the basic building blocks of life - chiral amino acids, sugars, and lipids - is susceptible to enantioselective interactions. Biological systems are thus commonly capable of differentiating between enantiomeric forms of chiral molecules, including odorants, pheromones, agrochemicals, environmental pollutants and, most importantly, drug compounds. The two different enantiomers of a compound may have distinctly different effects on a given biological system. For instance, (*S*)-citalopram is a potent agent against major depression, panic disorder, whereas its (*R*)-enantiomer is much less active (FIGURE 1.1).[2]

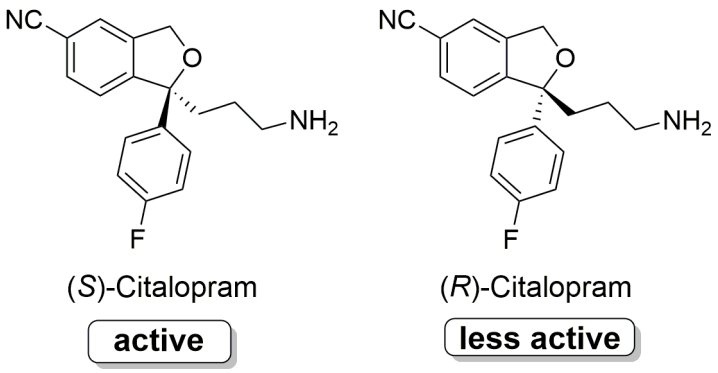


FIGURE 1.1.1- Enatiomers of Citalopram

In chemical synthesis, much effort has been directed towards the development of asymmetric transformations to access optically active products.[3] This could be achieved by the use of three main alternative strategies:

1. *To start from a pure enantiomer of a natural product (chiral pool).*
2. *To use one resolution method to obtain pure enantiomers from the racemate.*
3. *To employ a stereoselective synthesis.*

The enantioselective construction of C-C bonds is a fundamental goal of Modern Organic Synthesis. There are strict regulations for the employment of enantiopure compounds in Pharmaceuticals, Agrochemicals and in other sectors of fine chemical industry. [4]Then, new improvements over the known methodologies to obtain enantiopure compounds are done continuously.

Stereoselective synthesis bridges organic and medicinal chemistry, biology and medicine, as well as material science and physics providing a crucial platform for the drug and natural product synthesis, drug discovery, and drug developments.[5,6] Stereoselective synthesis is the science concerned with the construction of structurally complex organic molecules from readily available starting materials by a series of rationally designed stereoselective synthetic transformations. It includes the generation of one or more stereogenic centers, starting from achiral precursors, either under substrate control using a chiral auxiliary, under reagent control using a chiral reagent, by the use of a chiral catalyst, or by employing so-called absolute asymmetric synthesis, which involves a total spontaneous resolution.

From the above mentioned methods, a chiral catalyst controlled stereoselective synthesis (asymmetric catalysis), it's a chemical process, in which the formation of a new stereogenic center is controlled by chirality of small amounts of an optically active reagent that accelerates this process without being destroyed.[7] During this process, the catalyst is reused, improving efficiency and avoiding waste. The preferences for asymmetric catalysis (AC) are in agreement with low cost and environmental concerns.

For decades, in the generally accepted view there are two classes of efficient asymmetric catalysts: enzymes and synthetic metal complexes.[8] These catalyst are cluster in the pillars of AC (FIGURE 1.2); 1) Biocatalysis: where enzymes, which possess high molecular weight, are employed, and 2) metal catalysis: using transition metals and organic chiral ligands to induce asymmetry. After the turn of the century, a new class of catalysis was born, using small organic molecules without presence of metal trace knowing as organocatalysis and has been established as the third pillar of AC.[9]

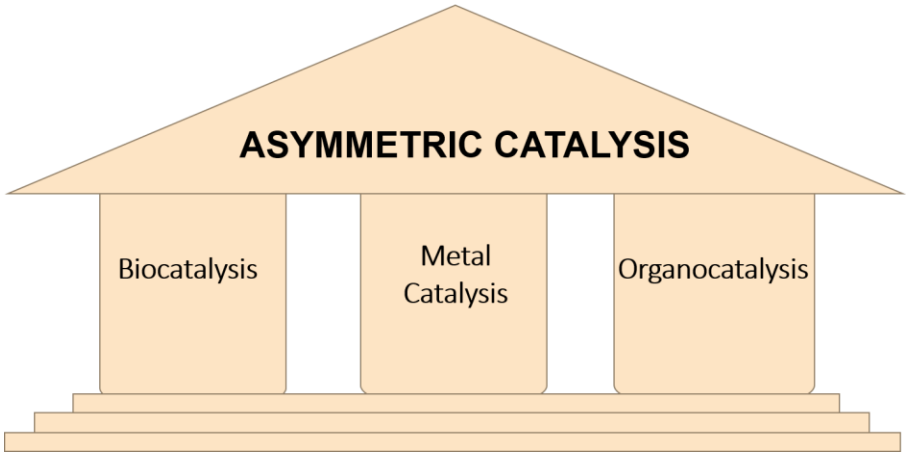


FIGURE 1.1.2-The three pillars of asymmetric catalysis: Biocatalyis, Metal Catalysis and Organocatalysis.

1.2 Organocatalysis

The use of small organic molecules as catalysts, the so called “organocatalysts,” has been widely explored by scientists around the world since its definition by MacMillan in 2000.[10]

The rapid growth of this methodology is mainly due to numerous advantages that organocatalysis offer for synthetic organic chemistry. The organocatalysts are often of low cost, non-toxic, insensitive to moisture, and allow the preparation of both enantiomers from the chiral pool, thus leading to broad possibilities for structural modification. Besides that, reactions are performed under an aerobic atmosphere, avoiding inert atmosphere, and oxygen-free solvents make the experimental operations considerably simpler.

The organocatalysts can be classified by means of their interaction with the substrate, the so-called ‘mode of activation’. In organocatalysis, there are two large activation modes: the covalent; and the non-covalent.[11]

The covalent activation mode is characterized by the formation of a covalent bond between the substrate and the catalyst, thus increasing the interaction among the substrate and the reagent in the reaction medium.[11] For instance, aminocatalysts[12] and carbenes[13] belong in this category. In the case of non-covalent organocatalysis, the interactions between the substrate and the catalyst can occur via hydrogen bonds (e.g., thioureas and phosphoric acids)[14] or ionic interactions (e.g., phosphoric acids, chiral bases such as cinchona alkaloids and phase-transfer catalysts), (FIGURE 1.3).[15]

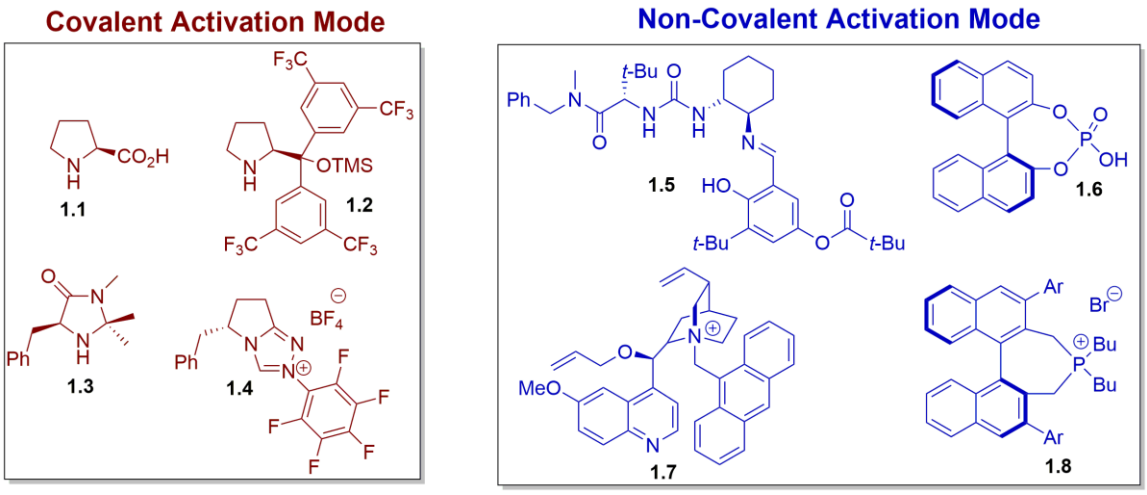


FIGURE 1.2.1- Activation modes in organocatalysis.

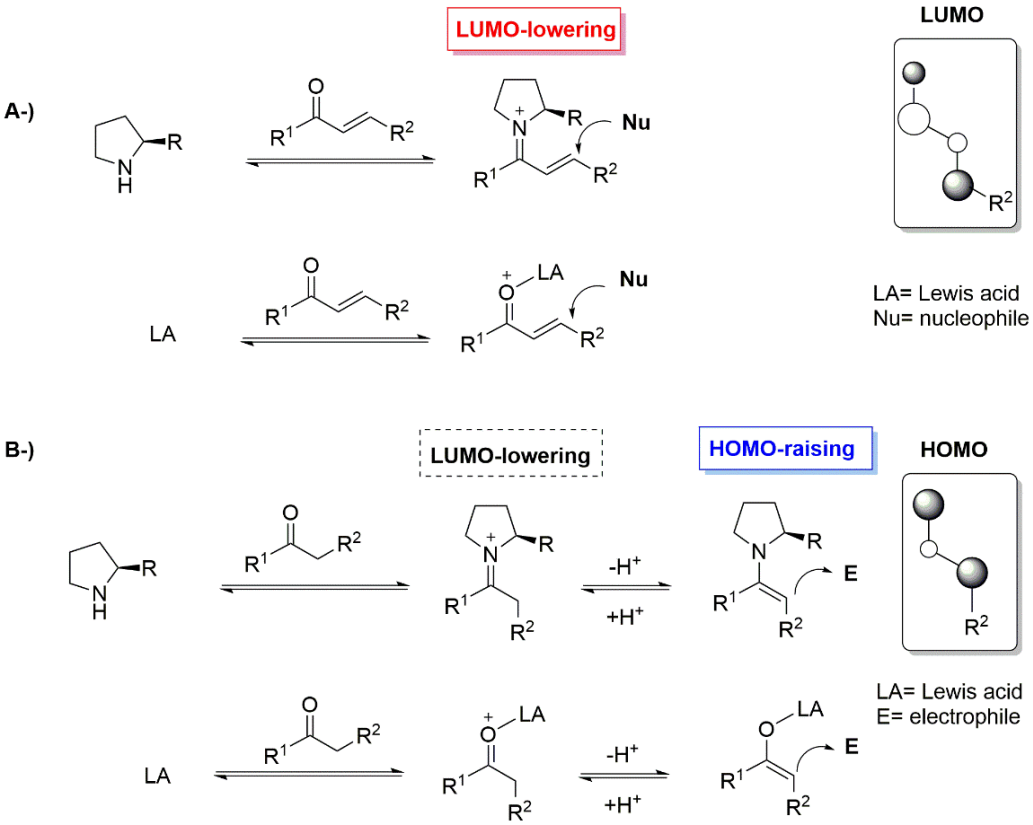
1.3 Aminocatalysis

The enantioselective transformations of carbonyl compounds using chiral primary and secondary amines as efficient organocatalyst, is known as “asymmetric aminocatalysis”.

The roots of modern aminocatalysis trace back to the pioneering work of Knoevenagel, who, at the turn of the 19th century, found that primary and secondary amines, as well as their salts, catalyze the aldol condensation of β-ketoesters or malonates with aldehydes or ketones.[16] In the first half of the 19th century, Kuhn and Fischer and Marschall discovered that amines and amine salts also catalyze aldol addition and condensation reactions.[17]

The principle for aminocatalytic activation emulates the mechanism of the activation of carbonyl compounds by Lewis acids. This is a well-established strategy for enantioselective catalysis, in which rate acceleration occurs through the reversible binding of the Lewis acid to isolated or conjugated π systems, thereby resulting in a redistribution of the electronic density toward the positively charged metal center.[18] The reversible condensation of a chiral secondary amine with carbonyl compounds to form positively charged iminium ion intermediates mimics the electronic situation of the π orbitals in Lewis acid catalysis. [12] Thus, the energy of the lowest unoccupied molecular orbital (LUMO) of the system is effectively lowered. For conjugated π systems, the electronic redistribution induced by the iminium intermediates facilitates nucleophilic additions, including conjugate additions and pericyclic reactions (LUMO activation). In the case of isolated π systems, the

lowering of the LUMO energy increases the acidity of the α proton. This induces a fast deprotonation, which leads to the generation of the enamine-a nucleophilic enolate equivalent (HOMO activation). Here too, the raising of the energy of the highest occupied molecular orbital (HOMO) leads to activation of the carbonyl compounds, similar to the generation of activated nucleophiles by Lewis acids (SCHEME 1.1).[12]



SCHEME 1.1- Activation modes of carbonyls compounds by Lewis acids and by aminocatalysis.

Based on these modes of activation for carbonyl enantioselective functionalization motivated scientists to develop and improve new catalysts underlying the sense of rational design including the pyrrolidine core (FIGURE 1.4).[19,20,21,22,23,24] In contrast researchers have recognized that chiral primary amines offer new opportunities for expanding the applicability and synthetic potential of aminocatalysis.[25] In particular, 9-amino(9-deoxy)-epi-cinchona alkaloids, primary amines easily derived from natural sources, have enabled the stereoselective functionalization of a variety of sterically hindered carbonyl compounds, which cannot

be functionalized using secondary amines and which are often unsuccessful substrates for metal-based approaches too.

The disadvantage on the synthesis of some of these catalysts remains on the multip-step linear synthesis and the drastic reaction conditions required. Those conditions provide low atom economy and global yield, with tedious purifications. Significant challenges remain in this area, including optimization, simplicity, and green synthetic routes to obtain new efficient organocatalysts.

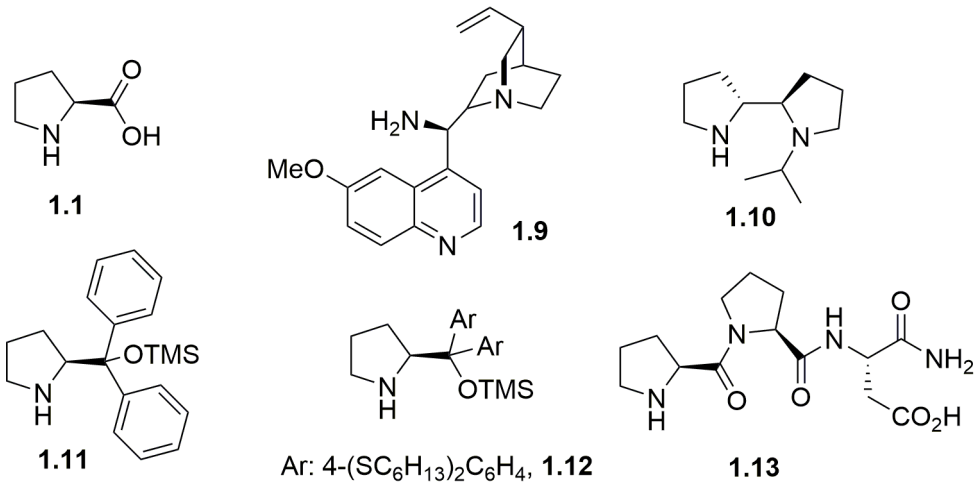


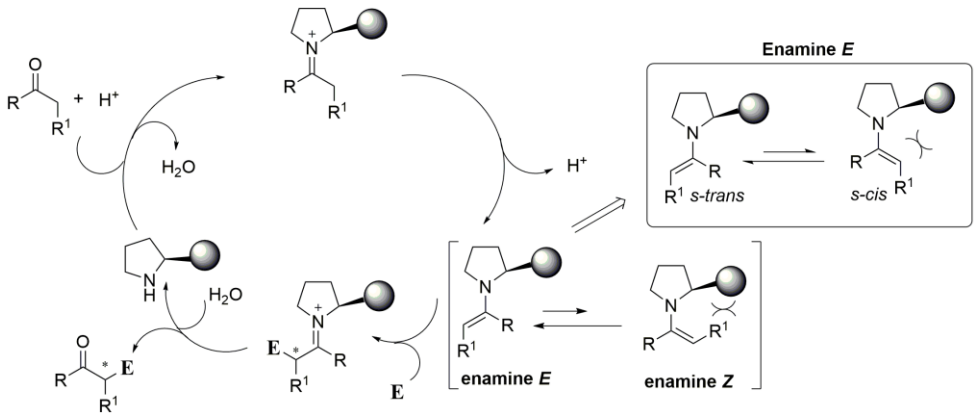
FIGURE 1.3.1- Different types of amino-catalysts.

1.3.1 Enamine catalysis

The application of secondary amines (i.e., pyrrolidine-type catalyst) to generate chirality and catalyze the direct asymmetric Aldol, Michael and Mannich reactions has been extensively exploited in the last decade. In general, this type of catalysts can activate aldehydes and ketones in a covalent way via enamines formation, which react with a determined electrophile to form C-C, C-S, C-N, C-X (X=F, Cl, Br) bonds with good efficiency and stereoselectivity.[26,27,28,29,30]

The enamine formation is produced between pyrrolidine ring and the correspondent aldehyde or ketone as shown in the catalytic cycle (SCHEME 1.2), where the enamine formed has two possible configurational isomers (E and Z), in a thermodynamic equilibrium. Unless other general and specific interactions favours the enamine Z, the enamine E is energetically most favoured and always the formation of this conformation is predominantly. Two rotational isomers (s-trans and s-*cis*) exist in the enamine E, where by steric interactions the most favourable is the s-*trans*-enamine E. It is generally accepted that the s-*trans* enamine is the most

stable conformer, where the double bond is situated in the opposite direction to the bulky group located in the 2-position of the pyrrolidine ring.[31]



SCHEME 1.2- Pyrrolidine-catalyzed activation cycle of enamine.

The *s-trans* conformer has also been considered as the most reactive intermediate until now. So far, the role of the pyrrolidine ring is to activate the oxo component increasing the energy of the HOMO of the substrate when the enamine is formed but not in the trajectory of the electrophile in the formation of the new stereogenic C-C bond. The trajectory of the electrophile depends on the side group attached to the pyrrolidine ring.

The trajectory of the incoming electrophile has traditionally been proposed to follow either of the two different models based on the nature of catalysts. As shown in FIGURE 1.5, the model A exhibit the induction of stereoselectivity by a hydrogen bonding (HB) interaction, and the model B shows the approach of the electrophile ruled by steric interaction (SI).

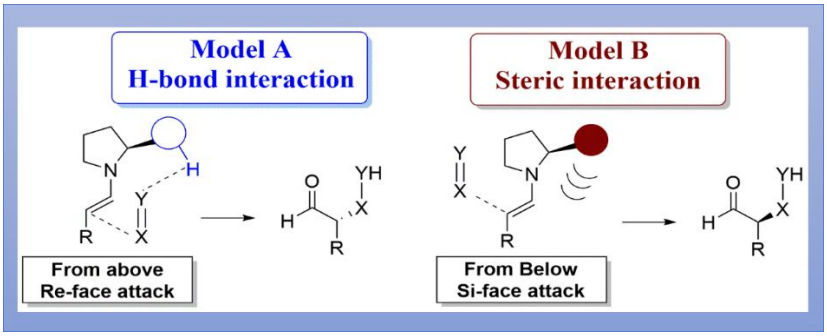


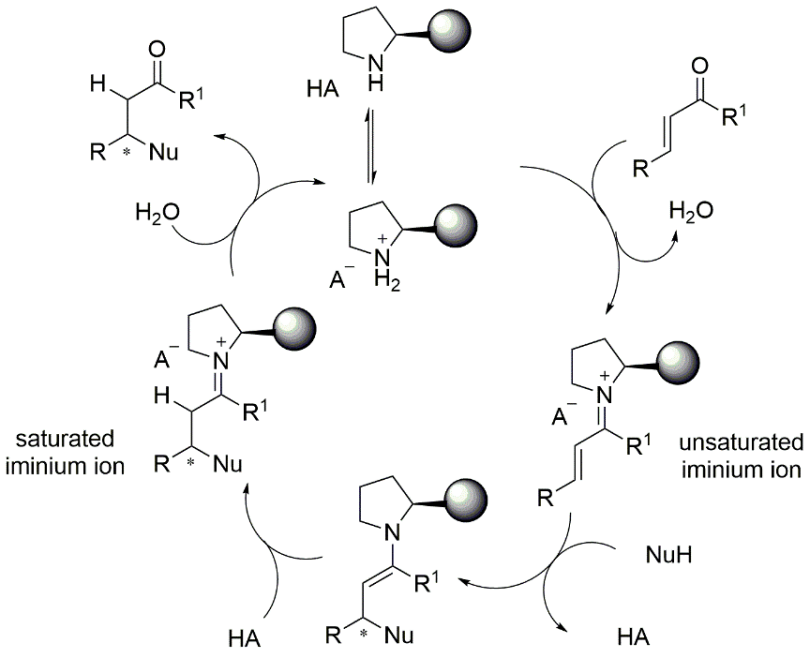
FIGURE 1.3.2- Aminocatalytic route via enamine activation.

In general, catalysts with a HB directing group (i.e. -CO_2H, -OH, -$CONH_2$) at the position 2 of the pyrrolidine ring, follows model A (e.g. see **1.1** and **1.13** FIGURE 1.4). In contrast, bulky substituents in the position 2 of pyrrolidine ring (i.e. -2Ph, -2PhCF_3) where the steric hindrance blocks one face of the enamine, are in agreement with model B of induction of stereoselectivity (e.g. see **1.9**-**1.12** FIGURE 1.4).

1.3.2 Iminium catalysis

Together with enamine catalysis, iminium catalysis is the most prominent activation mode in asymmetric aminocatalysis. Initial work on these mode of activation was carried out on cycloadditions but it was rapidly extended to Michael reactions,[32] nitrone additions,[33] Friedel-Crafts alkylations[34] and is now established as a general strategy for the asymmetric conjugate addition of nucleophiles at the β-position of α,β -unsaturated carbonyl compounds

The β-functionalization of α,β-unsaturated carbonyl compounds draws close parallels to enamine chemistry. The “standard” catalytic cycle for a chiral pyrrolidine-catalyzed β-functionalization of an α,β-unsaturated carbonyl compound (SCHEME 1.3) begins with the acid-promoted condensation of the carbonyl with the amine to form an unsaturated iminium ion, more electrophilic than the starting unsaturated carbonyl. This reactive intermediate suffers then the addition of the nucleophile at the β-position, leading to a β-functionalized enamine in tautomeric equilibrium with an iminium ion. Hydrolysis of this intermediate releases both the product and the chiral ammonium salt, which can re-enter in the catalytic cycle.[35]



SCHEME 1.3- Chiral amine-catalyzed β-functionalization via iminum catalysis.

Although chiral amines with hydrogen-bond directing groups like those shown in FIGURE 1.4 can be used in iminium catalysis,[36] usually best results are obtained with amines substituted with bulky non acidic groups In this case, the stereochemical outcome of the addition to enals can usually be predicted by the transition state (FIGURE 1.6), that implies the attack of the nucleophile by the opposite face to the bulky amine substituent in the energetically favored *s-trans* conformer of the (*E*)-configured unsaturated iminium ion.[37] A related transition state model, in which the diene or the 1,3-dipole also approaches the less hindered face of the (*E*)-iminium ion, rationalizes the observed outcome of iminium-catalyzed asymmetric cycloadditions.

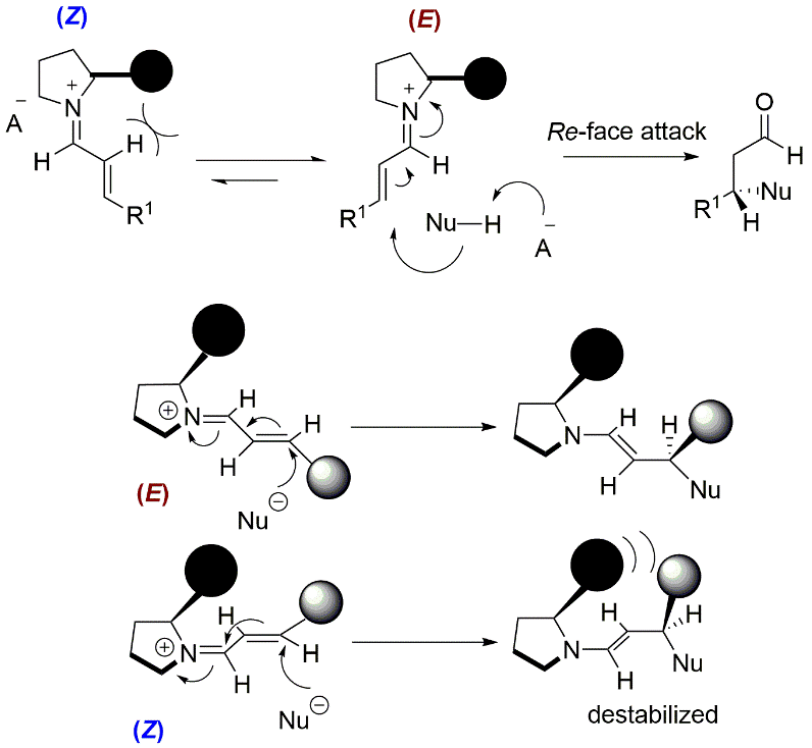


FIGURE 1.3.3- Nucleophilic attack to (E)- and (Z)-iminium ions.

In this model (FIGURE 1.6), the (*E*)-iminium ion intermediates are assumed to react with nucleophiles faster than the (Z)-isomers, so that the stereochemical outcome of the reaction is independent of the (*E*):(*Z*) ratio in solution. The less stable (*Z*)-iminium isomers are shown to be kinetically favoured. The higher reactivity of the (*E*)-iminium ion is explained by the degree of steric repulsion developing between the aldehyde β-substituent and the large substituent on the heterocycle along the reaction coordinate upon nucleophilic attack.

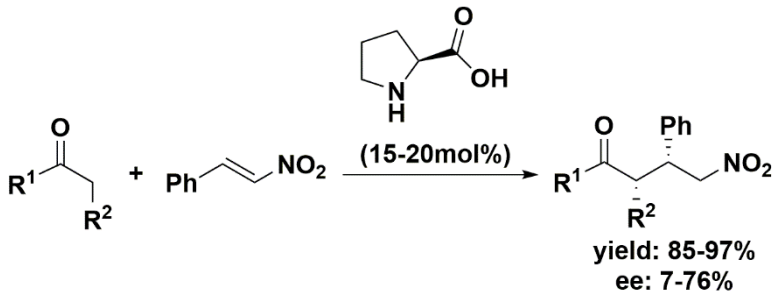
1.4 Organocatalytic asymmetric Michael reaction

Making C-C bonds, along with the creation of stereogenic carbon centers, continues to be an appealing and demanding area of research, and processes in which compounds are synthesized in optically active form are of growing interest.

In this context, the organocatalytic asymmetric Michael reaction is one of the most useful methods for the of C–C and C-X (carbon- heteroatom) bond formation. Several chiral primary and secondary amines have been shown to catalyze the enantioselective Michael reaction of enolizable carbonyl compounds to

electron-deficient olefins via formation of an intermediate enamine species. One of the most studied transformations of this conjugate addition is the reaction of aldehydes and ketones with nitroalkenes, which results in the formation of functionalized adducts with remarkable potential in organic synthesis, owing to the synthetic versatility of the nitro group.

The first attempts in this field involved the proline catalyzed Michael reaction of ketones and nitrostyrene.[38] In those cases, the obtained yields and diastereoselectivities were remarkably high, although only moderate enantioselectivities were obtained (SCHEME 1.4). Since these pioneering studies, a surplus of other modified chiral amines have been employed in order to improve the results furnished by the proline-catalyzed reaction.

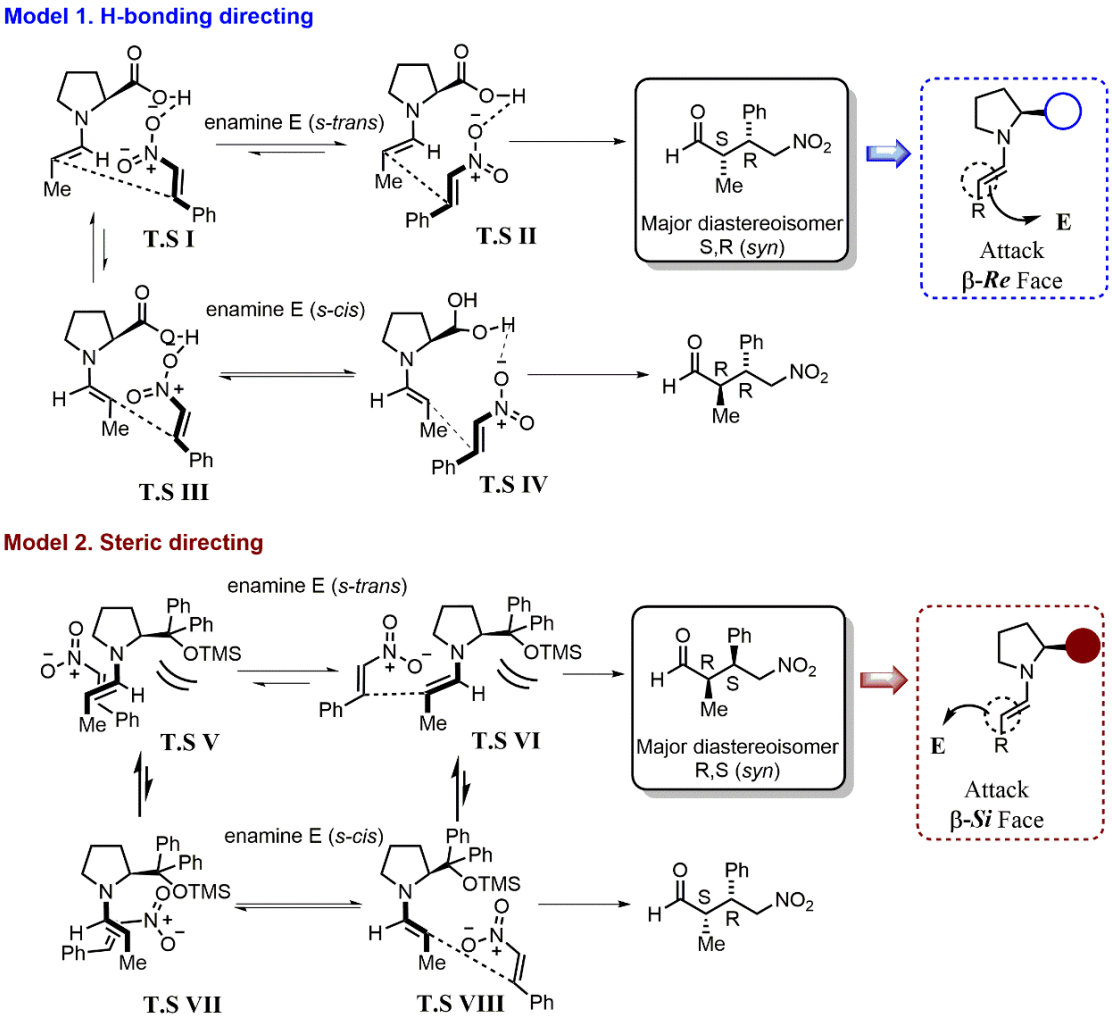


SCHEME 1.4- First attempt in proline catalyzed Michael reaction.

A plethora of studies shown that the substituent attached to the pyrrolidine core is important in the enantio- and diastereoselectivity of the Michael adducts. Four possible transition states (TS) can be drawn for both models (model 1 and model 2, SCHEME 1.5). These TS show that even with the possibility to form the *s-cis*-enamine E (TS **III** and **IV**), the equilibrium is displaced to the formation of the most stable *s-trans*-enamine E (**TS I** and **II**) of both models, and therefore, the difference in terms of energy between these TS determines the course of stereoselectivity. The model 1, also known as Houk-List model,[39,40] illustrate an hydrogen bond between the proton of the carboxylic acid and the oxygen of nitro group at the β-nitrostyrene. This HB guide the β-nitrostyrene to the *Re* face of the enamine by a *like* approach, thus forming the *S,R*-diastereomer as the major product. On the other hand, model 2 is determined by steric interaction, the bulky group attached to pyrrolidine core produces a steric hindrance capable of approaching the *Si* face of enamine to β-nitrostyrene and thus produce the inversed *R,S*-configuration

of Michael product. Either one, model 1 or model 2 lead to the formation of the major diasteroisomer *syn*.

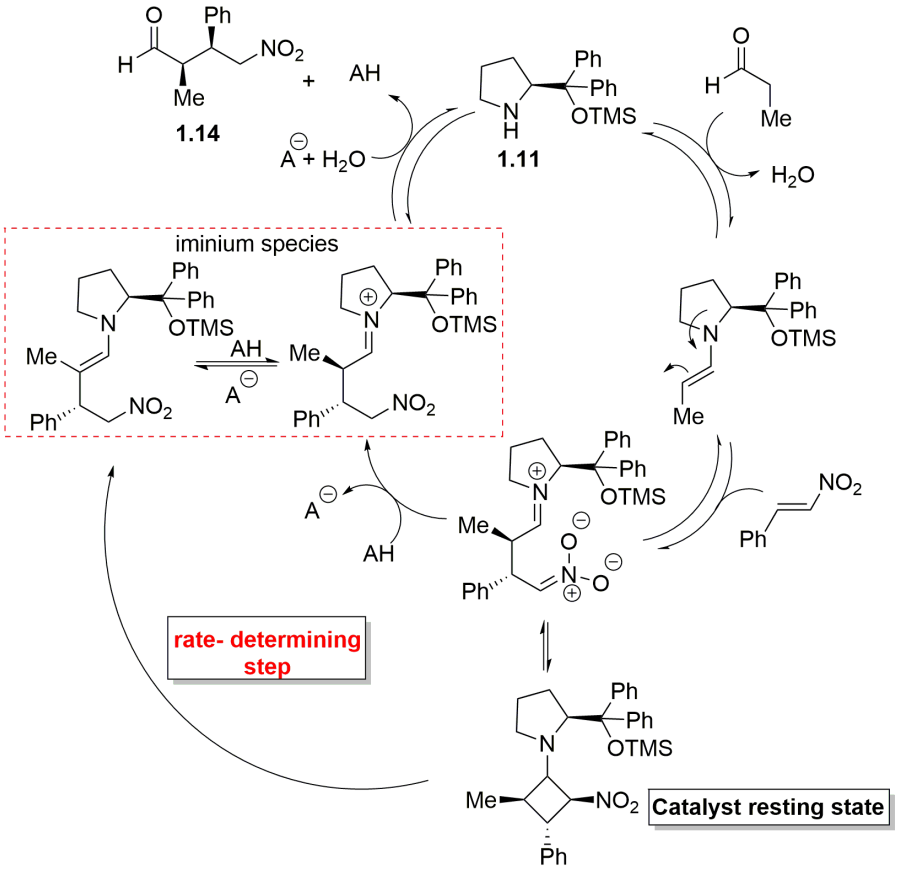
Two factors are important for good stereoselection: 1) one face of the enamine must be less accessible; 2) the equilibrium between the enamine rotamers must be well displaced to the one side.



SCHEME 1.5- Proposal transition states by HB and SI in the Michael addition.

The mechanism of the addition of linear aldehydes to nitroolefins has been discussed by many authors, and it is still an open discussion. The most accepted by the scientific community mechanism, was proposed by Blackmond in 2011 (SCHEME 1.6).[41,42] In this work, the conjugate addition of propanal to β-nitrostyrene, catalyzed by diarylprolinol silyl ether **1.11**, reveals that the formation of the product is the rate-determining step of the reaction, rather than enamine formation as mentioned before. The cyclobutane intermediate (SCHEME 1.6), called as `parasitic intermediate´ during the catalytic cycle, is significant to keep the high

stereoselectivity in the final product. Interestingly, this parasitic intermediate, which should delay the reaction, is considered to be important in the stereoselectivity.

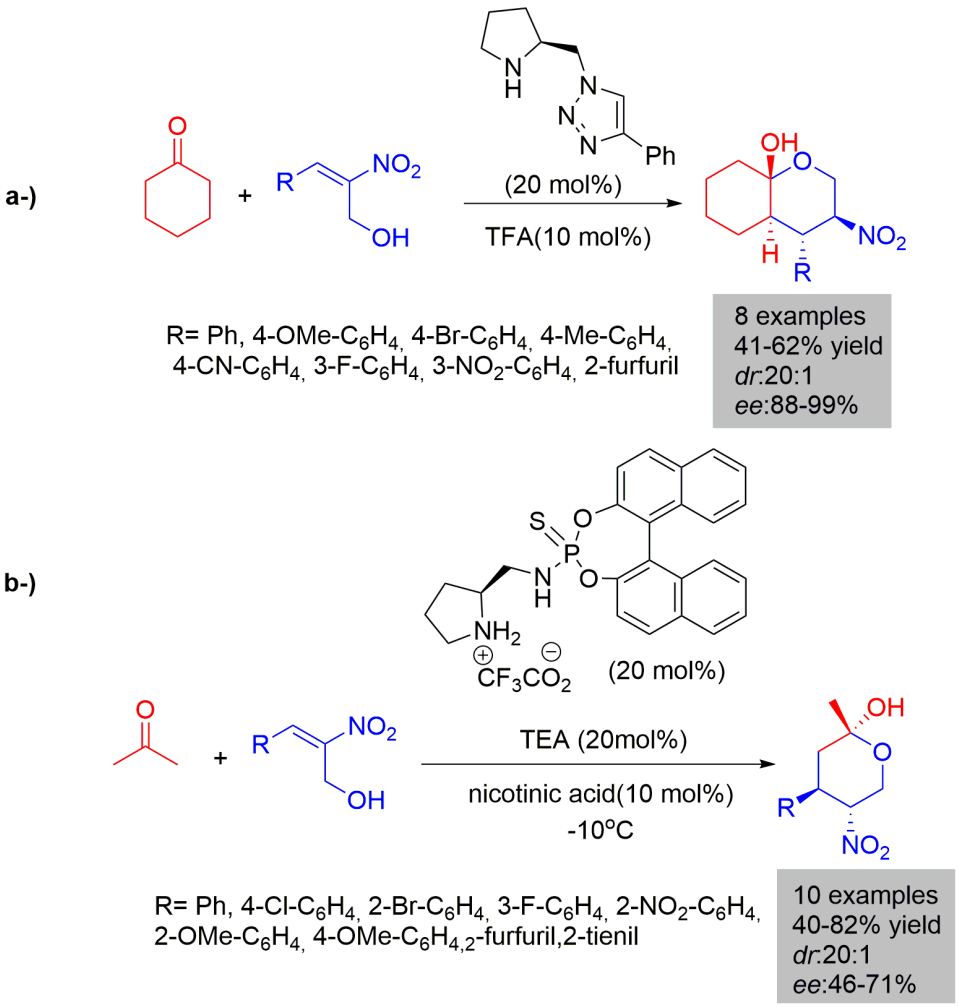


SCHEME 1.6-Proposed catalytic cycle for the Michael addition of aldehydes to nitrostyrene.

The Michael reaction have been also directed towards the target- and diversity oriented synthesis,[43] in which many new substrates and approaches have been attempted. In this context, applying the organocatalytic asymmetric Michael reaction for the synthesis of natural products or molecular fragments of their core structure is of vital importance.[44] One of the most crucial structure present in numerous natural products and biologically active compounds is the tetrahydropyran (THP) heterocyclic ring.[45]

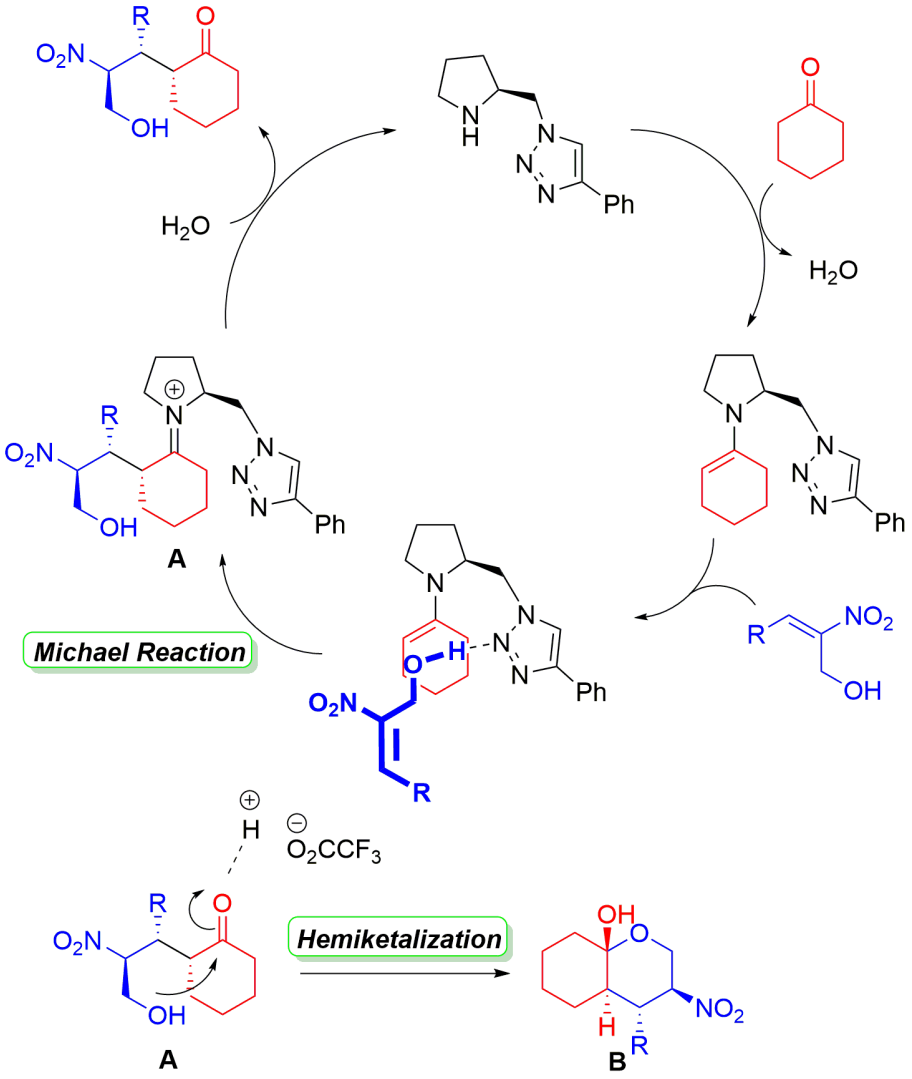
In 2009, Chandrasekhar et al. developed a domino Michael/hemiketalization reaction catalyzed by a triazole-based organocatalysts.[46] This procedure led to a new class of tetrahydropyrans with moderate yields (41–62%) and good to excellent enantioselectivities (88–99% ee) in the absence of a solvent (SCHEME 1.7 a). According to the authors the cyclohexanone can be activated with the secondary amine organocatalyst to perform a Michael adition to the nitro-olefins. This intermediate **A** can subsequently undergo an acid catalysed

hemiketalization reaction, in the presence of trifluoroacetic acid, to afford the final product **B** (SCHEME 1.8).



SCHEME 1.7-Synthesis of THPs via domino Michael/hemiketalization.

Successively, Wang, Zhou and their co-workers used a pyrrolidine-based thiophosphoramide (20 mol%) as organocatalyst for the same reaction sequence (SCHEME 1.7 b).[47] The procedure shows moderate results of enantioselectivity. The products were obtained with god yields and diasteroselectivity. Even though the mechanism was not reported, the authors speculated a bifunctional activation of the substrates (ketone and nitro-olefin). The pyrrolidine function can form an enamine while the acidic N-H of the phosphoramide organocatalyst, can coordinate and orientate the nitroalkene to facilitate the enantioselective attack of the enamine nucleophile.



SCHEME 1.8-Organocatalytic Michael/hemiacetalization mechanism.

1.5 One-pot reactions in organic synthesis

The definition of a *one-pot* reaction encompasses several concepts that describe multiple-step reactions that occur sequentially in the same reaction vessel and without isolation of the intermediates, for instance: domino and tandem reactions.[48] More recently, the term pot economy was introduced in order to broaden the concept of *one-pot* reactions covering other sequential processes.

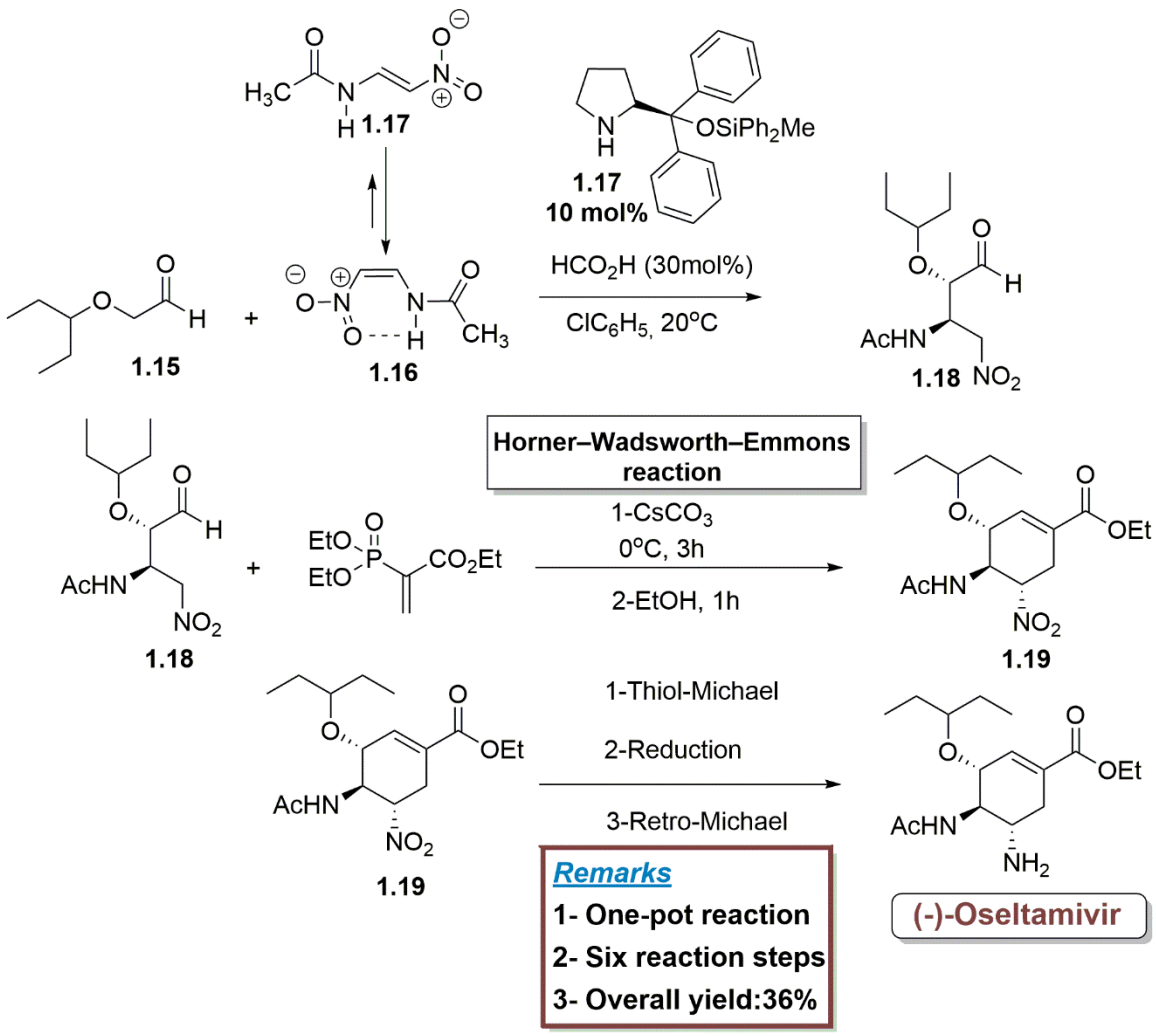
The domino reaction is a process involving two or more transformations that result in the formation of new bonds (carbon-carbon or carbon-heteroatom), which must occur under the same reaction conditions from the beginning without addition of reagents, solvents or catalysts during the reaction. In addition, the reaction steps are carried out in a fixed chronological order, in which a certain

transformation occurs only as a result of an earlier stage.[49] From this concept, multicomponent reactions are classified as a subgroup of domino reactions that contains least three components and most of the atoms of the reactants are incorporated into the final product.[50]

Tandem reactions, instead, are sequential transformations that occur, according to the definition itself, "one after another", in which, for example, two functionalities in the same molecule react with other components independently or when conditions change reactions to occur, such as temperature modification, addition of other reagents, catalysts or solvent exchange. [51] However, in some cases it is not possible to perform several reactional steps in a one-pot manner, due, for example, to the incompatibility of by-products, excess reactants or catalysts in the later steps of the synthesis. Then, an alternative aiming to perform multi-step synthesis minimizing residues and purification steps is the use of telescope processes in which the intermediates are subjected to washes or filtrations but are not isolated at each step of the synthesis.

The one-pot synthesis has been widely used as an efficient approach to achieve biological active molecules. In the growing field of organocatalysis, organocatalysts are particularly effective reagents in achieving a one-pot, multi-step synthesis. This is evidenced by a dramatic increase of impressive syntheses over the past decade.[52] The synthesis of (-)-oseltamivir reported by Hayashi and co-workers is an example of this strategy.[53] The one-pot synthesis of (-) - oseltamivir as illustrated in **SCHEME 1.9** was performed in six steps without purification of any of the intermediates and without evaporation or exchange of solvents. The first step consists of an organocatalyzed Michael reaction, interestingly, the nitro compound **1.16** exits exclusively as *Z* isomer due the strongest intramolecular hydrogen bond. Another interesting feature is related with the *anti*-product **1.18** of the Michael reaction. The authors postulated that intramolecular HB plays a key role in this observation.

The second setp of this synthesis is a Horner-Wadsworth-Emmons (HWE) reaction resulting in the cyclized intermediate **1.19** which after a thiol-Michael, a reduction of the nitro group and *retro*-Michael, provided the (-)-oseltamivir in an overall yield of 36%. This synthesis represents the first example of a stereochemically complex drug being synthesized in a single reactor, in significant yield, without the need to evaporate or swap solvents.



SCHEME 1.9- Synthesis of (-)-oseltamivir.

1.6 Multicomponent reactions

Multicomponent reactions (MCRs) constitutes one of the most attractive transformations in synthetic organic chemistry. MCRs belong to one-pot reactions employing at least three starting materials which react each other to form a product, where basically all the atoms are present in the newly formed product.[54]

The MCRs have a plethora of advantages compared with traditional multistep synthesis. In MCRs, a molecule is assembled in one convergent chemical step by simply mixing the corresponding starting materials as opposed to traditional ways with multiple sequential steps. In this way, very high levels of atom efficiency can be reached, while avoiding time-consuming isolation and purification of synthetic intermediates.

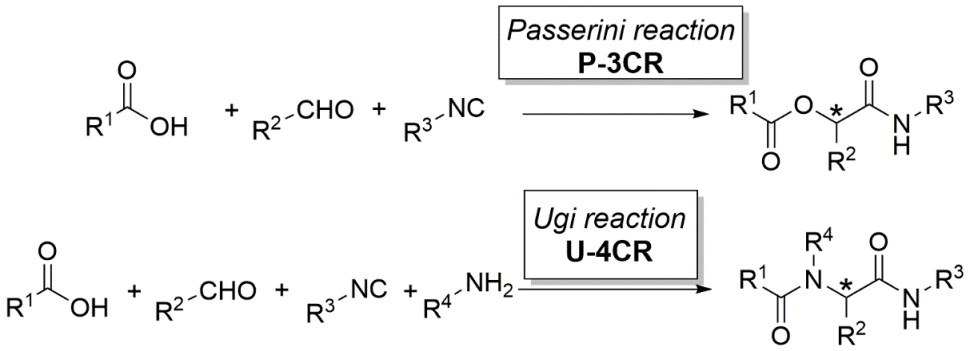
The rapid and easy access to biologically relevant compounds by MCRs and the scaffold diversity of MCRs has been recognized by the synthetic community in industry and academia as a preferred method to design and discover biologically active compounds.

There is a wide variety of multicomponent reactions that combine the reactivity of several organic functions, such as the reactions of Strecker, Biginelli, Mannich, Petasis, among others.[55] In multicomponent chemistry, the isocyanide multicomponent reactions had a privileged place because of the reactivity of isonitrile component.

1.7 Isocyanide based multicomponent reactions

The isocyanide group is an unusual functionality, which may react with electrophiles, nucleophiles, and radicals under various conditions, giving rise to different primary imine adducts. Therefore, the use of isocyanide in synthetic organic chemistry play a crucial role in the generation of chemical diversity, which has been exploited both in organic and medicinal chemistry, and in polymer science.[56] The chemistry of isocyanides is characterized by the lifted diversity of transformations that includes hundreds of multicomponent reactions, as well as very large numbers of oligomerizations and polymerizations. Many of these reactions have been employed as an initial step in numerous preparative methods, and especially for the syntheses of various heterocycles.[57]

The isocyanide based multicomponent reactions (IMCR) are particularly interesting because of the exceptional reactivity of the functional group of the isocyanide. Today most IMCR relates to the classical reactions of Passerini and Ugi (SCHEME 1.10). Other IMCRs also responsible for inducing high levels of structural diversity and complexity are the Groebke-Bieynamé-Blackburn three component reaction (GBB-3CR),[58, 59,60] the Orrru three component reaction.[61]

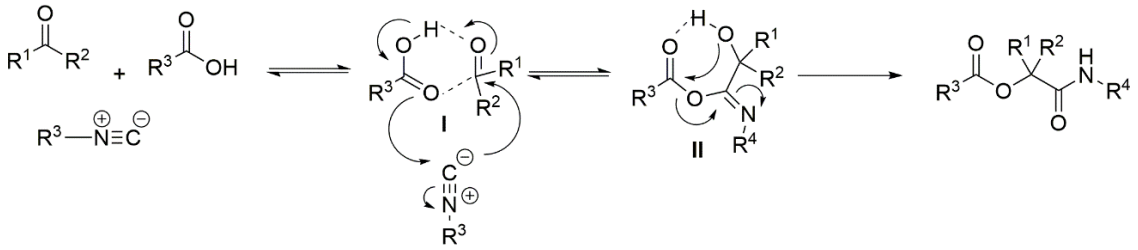


SCHEME 1.10- Passerini and Ugi multicomponent reactions.

1.7.1. Passerini reaction

The Passerini reaction is the first IMCR and plays a central role in combinatorial chemistry today. This multicomponent reaction involves an aldehyde or ketone, an isocyanide, and a carboxylic acid and offers direct access to α-acyloxy carboxamides.

The exact mechanism is a subject of some uncertainty, the most accepted proposal is that the isonitrile is inserted into the carbonyl compound which is activated by hydrogen bonding through the acid component (intermediate I). Then, the nucleophilic oxygen of the carboxyl attacks the carbon of the isonitrile, forming a seven-membered cyclic intermediate (II), which finally undergoes an intramolecular transacylation rearrangement, this reaction step is irreversible and shifts from the equilibrium towards the desired product (SCHEME 1.11).[62]

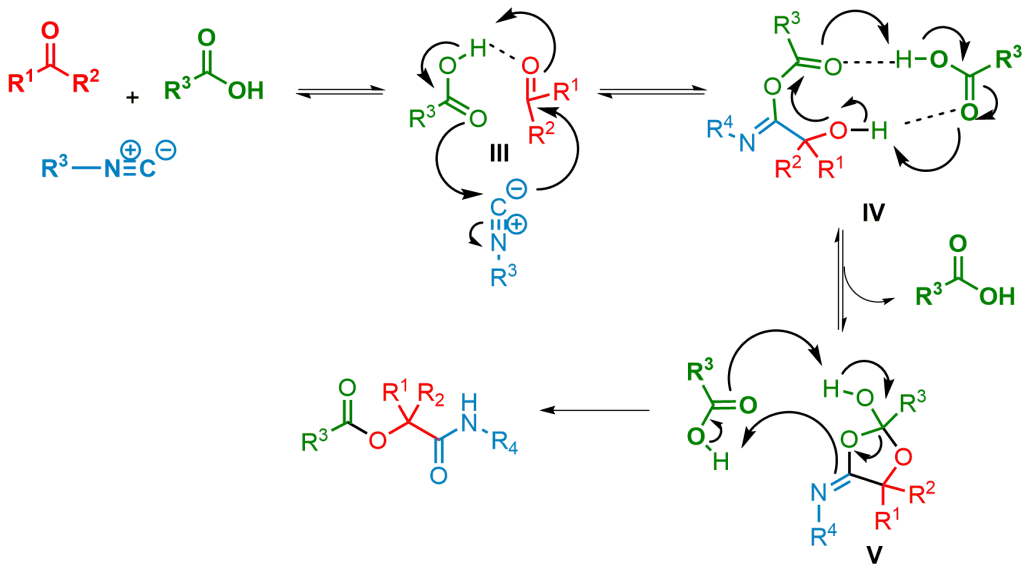


SCHEME 1.11- Possible mechanism of the Passerini reaction.

More recent studies, propose through theoretical calculations that although Passerini's reaction has three components, there is the participation of a second molecule of carboxylic acid as a fourth component in the reaction mechanism.[63] The first step occurs from the hydrogen bonding interaction of the carbonyl component and the carboxylic acid, this intermediate (III) reacts with

isonitrile and the resulting structure (IV) coordinates with the carboxylic acid (SCHEME 1.12).

The authors have shown that the rearrangement of intermediate IV that would lead directly to the final product has a high energy barrier, so the formation of V is favored. Then, a carboxylic acid molecule assists in the V rearrangement, providing α-acyloxycarboxamide (SCHEME 1.12).

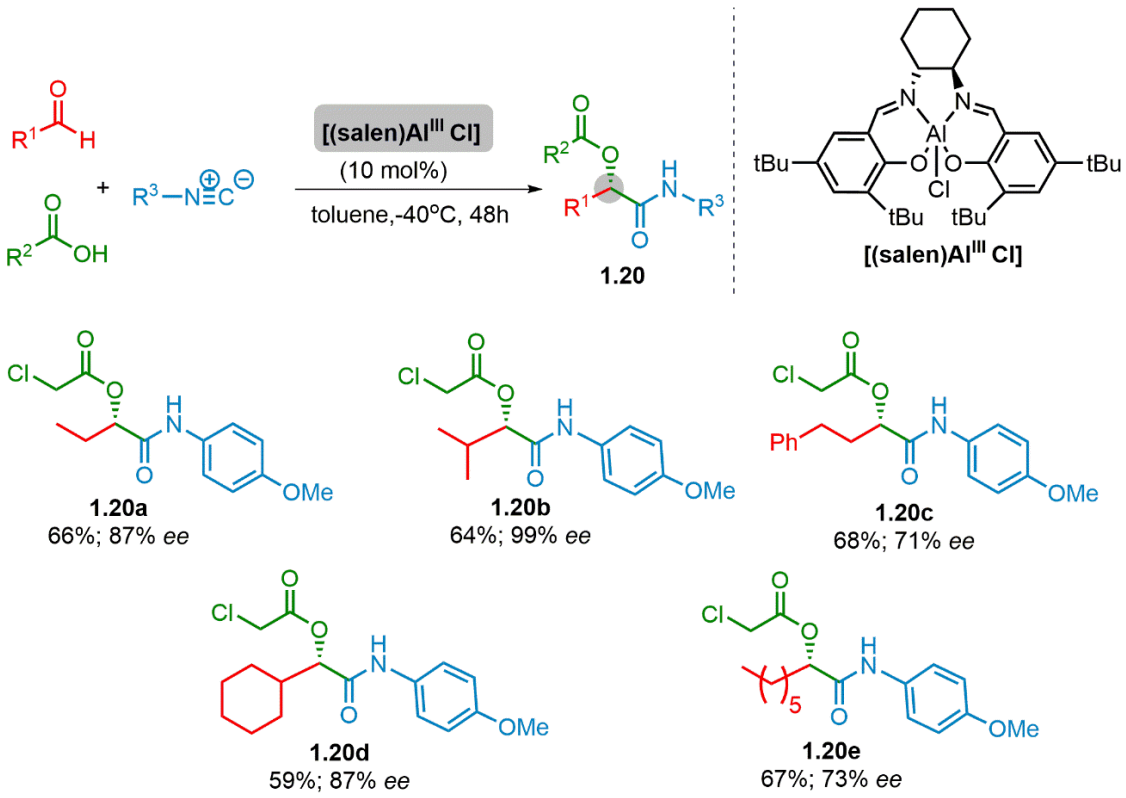


SCHEME 1.12- The Passerini reaction mechanism proposed by theoretical calculations.

One of the main limitations of IMCR as synthetic tools is the typical lack of stereocontrol. For instance, when the carbonyl component of the Passerini reaction has different substituents, the product obtained has an asymmetric center and under normal reaction conditions (achiral ambient) the racemate is formed. The use of components that already have defined stereogenic center is one of the strategies to induce the asymmetry of the new center formed in the reaction. Another strategy is the use of metal complex as Lewis acids for the stereogenic control.

Wang et al proposed the use of metal complexes with only one coordination site acting as Lewis acids to promote the enantioselective Passerini reaction using aliphatic aldehydes.[64] Different metallic salts were tested, such as $MnCl_3$, $CrCl_3$, $Ti(OiPr)_4$, and Et_2Zn. Among the catalysts evaluated, [(salen) $Al^{III}Cl$] provided compounds with the best enantiomeric excess and yields (SCHEME 1.13). The best reaction conditions were at -40 °C, 10 mol % of the chiral catalyst and for 48h. The use of both linear and branched aliphatic aldehydes provide the α-

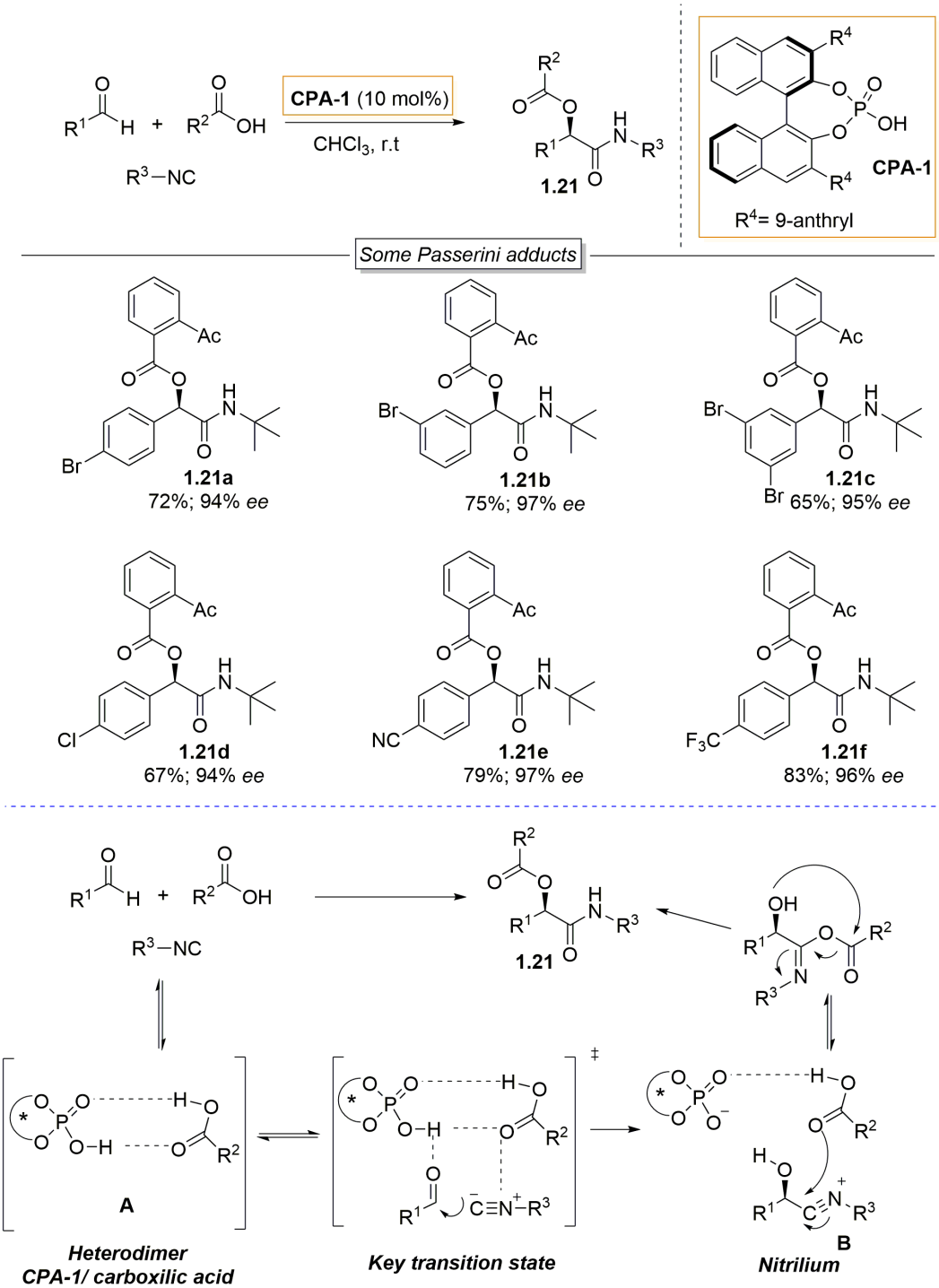
acyloxycarboxamides with excellent enantioselectivities and the selectivity of the reaction increased when an aliphatic isocyanide was changed for a less reactive aromatic one. [65]



SCHEME 1.13- Enantioselective Passerini reaction catalyzed by [(salen) AlIIICl].

In 2015 Zhang et al. proposed the use of chiral phosphoric acids as organocatalysts to promote the Passerini reaction enantioselectively by means of the activation of the carboxylic acid allowing the amplification of the scope of the components, since the reactions with metallic complexes presented certain limitations in relation to the aldehydes employed.[66] The proposed mechanism starts with the formation of a heterodimer with phosphoric acid (CPA-1) and the carboxylic acid, which participates in the simultaneous activation of the aldehyde and the carboxylic acid, which participates in the simultaneous activation of the aldehyde and isonitrile by hydrogen bonding and ionic interaction (intermediate **A**), leading to the formation of the intermediate nitrile **B**, to which the carboxylate is added followed by rearrangement of intramolecular transacylation affording the Passerini adduct (**1.21**). In this work a wide variety of aromatic, aliphatic and α, β-unsaturated substrates - aldehydes were used; aromatic and aliphatic carboxylic acids, including bulky

substituents such as trityl and adamantyl; and aliphatic isonitriles, with good yields and enantiomeric excesses (SCHEME 1.14).



SCHEME 1.14- Enantioselective Passerini reaction with chiral phosphoric acid organocatalyst.

As showed above, a variety of substituted aromatic aldehydes were successfully employed. The authors suggest that the position and the electronic

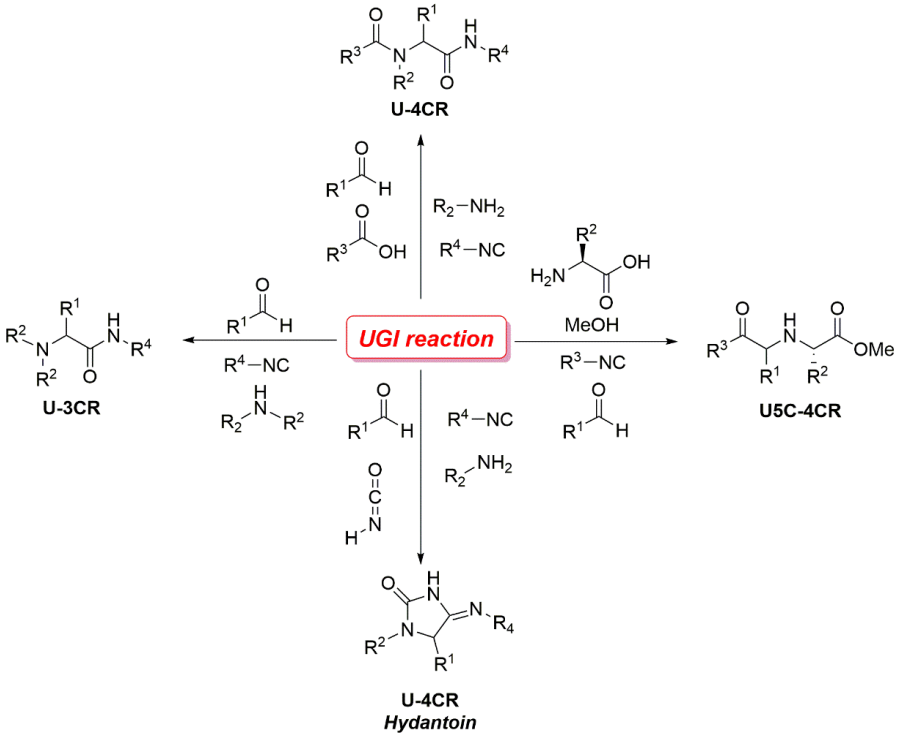
property of the substituents for aromatic rings have a very limited effect on the stereoselectivity of the process.

This report represents a very exciting and promising result regarding the efficient exploration of the stereochemical diversity, an issue of great importance for the preparation of libraries of compounds.

1.7.2. Ugi multicomponent reaction

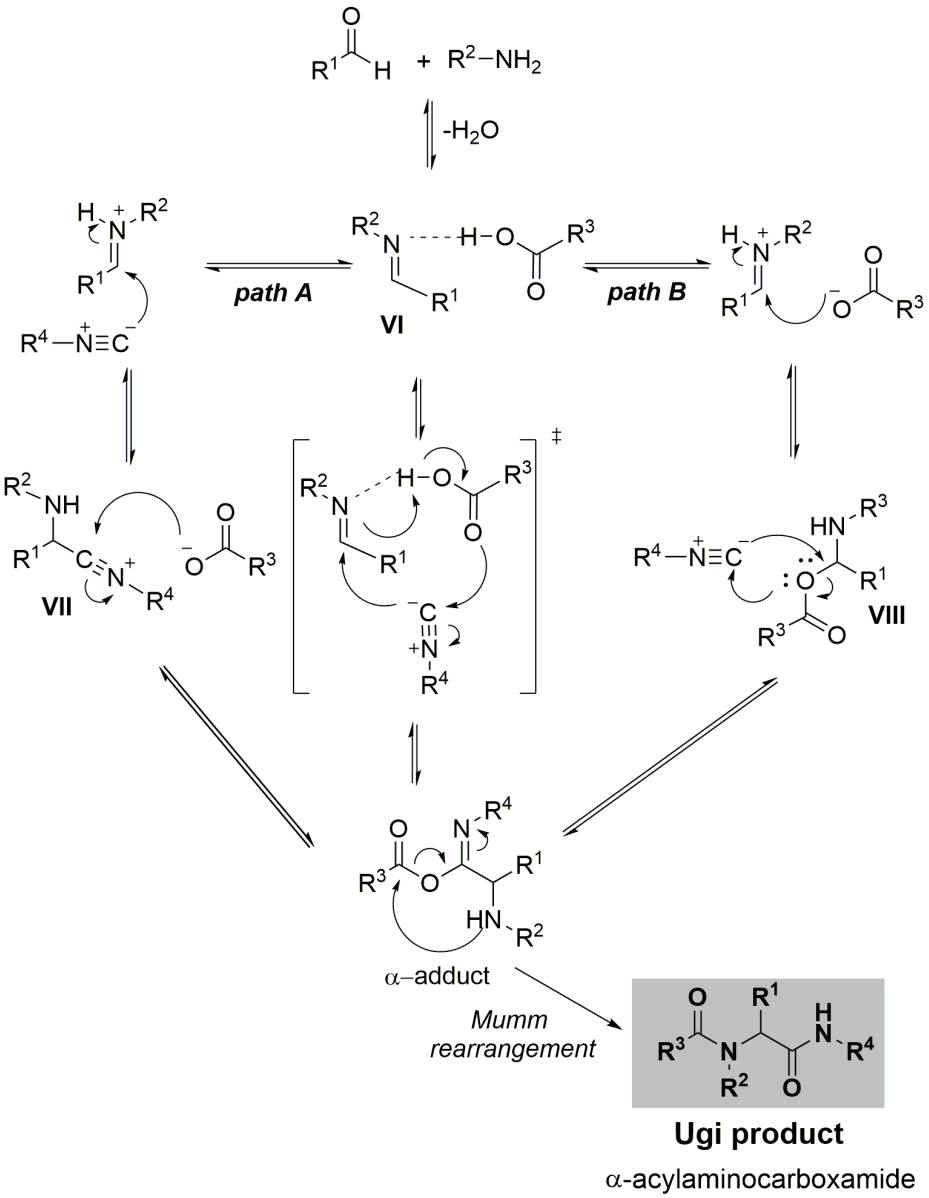
The Ugi reaction was first described by Ivar Ugi in 1959. This MCR (U-4CR) furnishes α-acylamino amides by one-pot methodology, combining oxo-substrates, carboxylic acids, amines and isocyanides.

Since its discovery, the Ugi reaction has become one of the most exploited reactions, presenting various modifications in the quantity and variety of components, such as reaction with three (Ugi-3C) components employing, for example, preformed imines or secondary amines in this case the acid component is not used. The Ugi reaction is widely used in the formation of heterocycles, as in the 4-component version in which the carboxylic acid is replaced by an isocyanate, leading to formation of hydantoins. There are other versions of Ugi-4C that have five reactive centers, reactions in which amino acids are used (in this case, two distinct functions in the same molecule participate in the reaction) and methanol as a solvent that also participates in the reaction.[67,68]



SCHEME 1.15- Examples of modifications for the Ugi reaction.

In the literature there are different mechanistic proposals for the Ugi reaction and all of them have in common the initial formation of an imine (VI), then the obtaining of the α-adduct is described by three different paths: a) the protonated imine undergoes nucleophilic attack of isonitrile carbon resulting in intermediate VII and subsequent addition of the carboxylate; b) occurs the addition of the carboxylate to the iminium ion forming intermediate VIII, followed by the insertion of isonitrile ; c) a transition state similar to that of the Passerini reaction is proposed in which the imine is activated by the carboxylic acid by hydrogen bonding and then the isonitrile is added to the carbon of the imine and concomitantly undergoes the nucleophilic attack of the carboxylate. Then, the α-adduct passes through the Mumm rearrangement, an intramolecular acylation followed by a hydroxylimine- amide rearrangement, irreversible reaction stage resulting in the α-acylaminocarboxamide (SCHEME 1.16).[69]

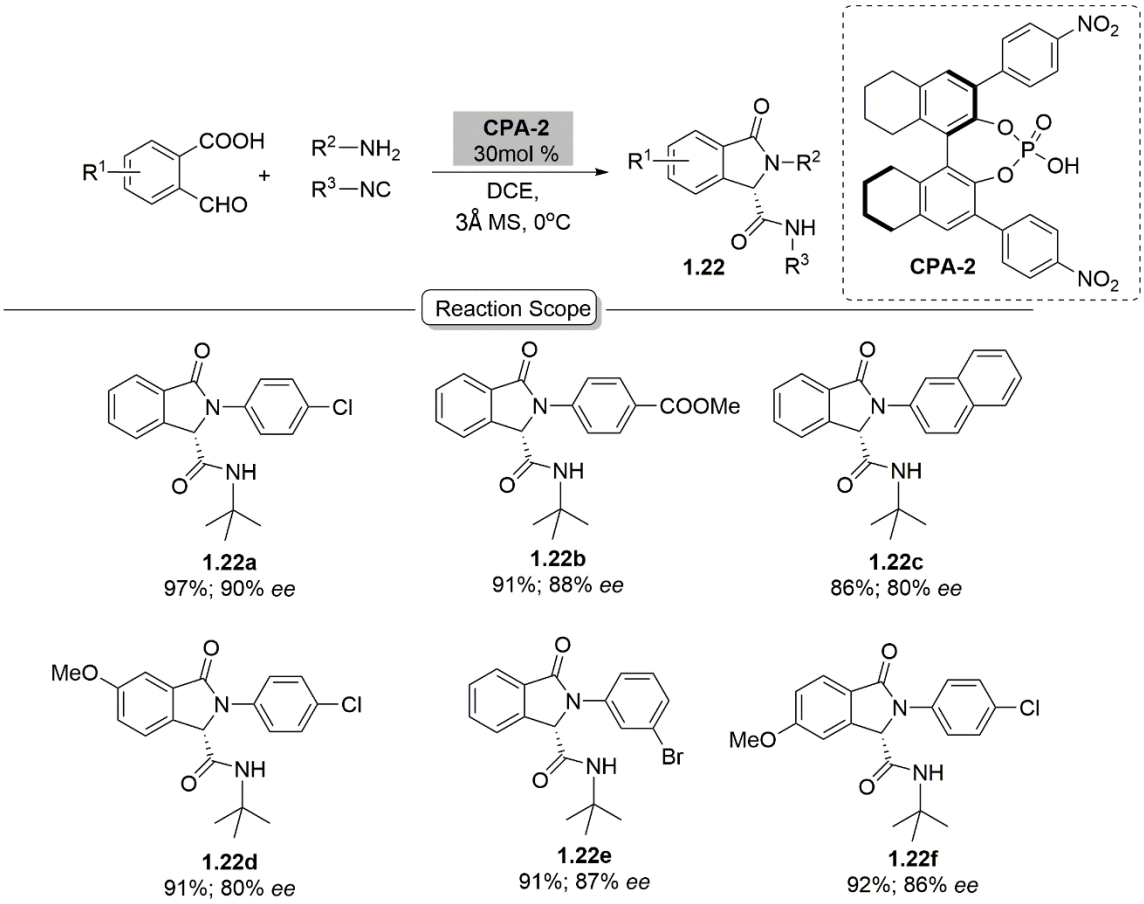


SCHEME 1.16- Mechanistic proposal for the Ugi four component reaction.

Similarly, in the Ugi reaction there is also the formation of an asymmetric center when the carbonyl component has different substituents, however, enantioselective Ugi reactions have several limitations. [69]

A few years ago, Zhang et al.[70] reported the first catalytic enantioselective Ugi four-center three-component reaction, with the use of a chiral phosphoric acid (CPA-2) leading to compounds **1.22a-f**. The authors suggested from experimental evidence that the control of the enantioselectivity promoted by phosphoric acid is more related to the dynamic kinetic resolution of the α-adduct than with the addition step of isonitrile (which leads to α-adduct formation). It has also been observed that the tautomerization rate is greater than the Mumm

rearrangement rate, suggesting that in the tautomerization step the catalyst may also play an important role in the stereochemical control.

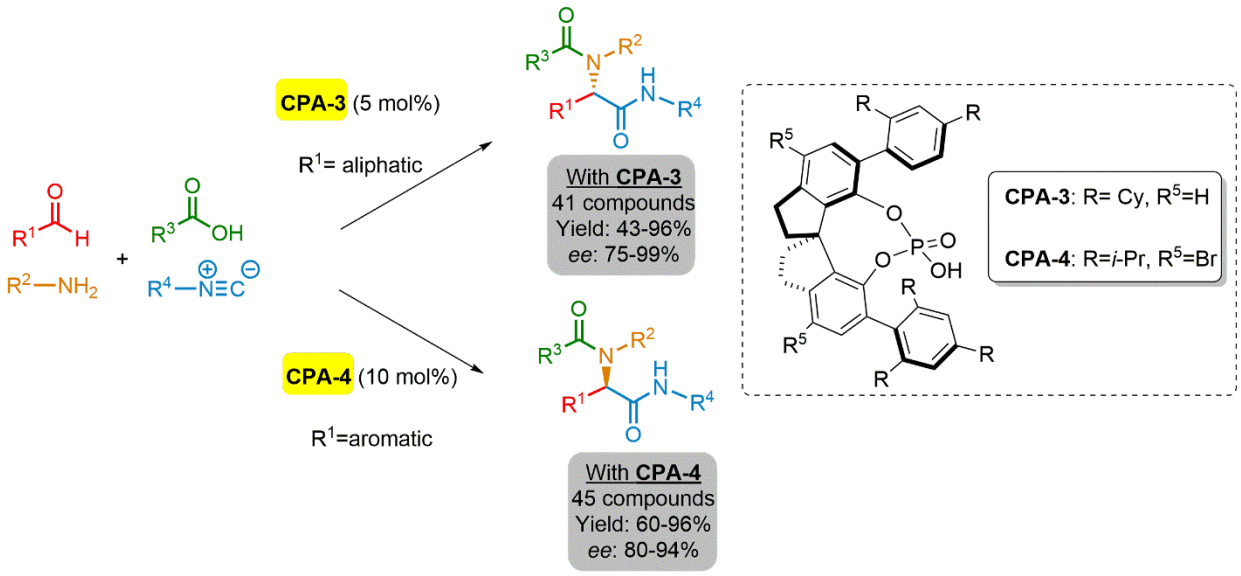


SCHEME 1.17- Enantioselective Ugi four center three component reaction with chiral phosphoric acid.

More recently, the Tan group reported an enantioselective organocatalytic four-component Ugi reaction.[71] In this extraordinary report the catalytic asymmetric Ugi-4CR was accomplished with two different 1,1′-spirobiindane-7,7′-diol (SPINOL) as organocatalysts. The reaction exhibited broad substrate compatibility and good to excellent enantioselectivity. The authors obtained a small *N*-substituted dipeptide library of 86 compounds, which are otherwise challenging to obtain via conventional methods, from four achiral building blocks in excellent yields (SCHEME 1.18).

According to the authors,[71] activation of the imine might be accomplished by CPA-carboxylic acid heterodimer catalysis via a bifunctional activation mode, which was supported by experiments (carboxylic acids with varying

pKa values and steric properties yielded products with a range of *ee* values) and density functional theory (DFT) calculations.



SCHEME 1.18- Enantioselective organocatalytic Ugi four component reaction.

Despite this relevant reports the enantioselective Ugi and Passerini reaction is not a slight task. There are some difficulties associated with these two reaction, that can be summarized by the following.[69]

1- *Competition from background reactions, as both P-3CR and U-4CR occur spontaneously in an appropriate solvent at room temperature.*

2- *Difficulty in chemoselective activation of carbonyl or imine function by a Lewis acid (LA) due to the Lewis basicity of the other components.*

3- *Coordination of isocyanide to metal is known to divert the reaction pathway of isocyanides.*

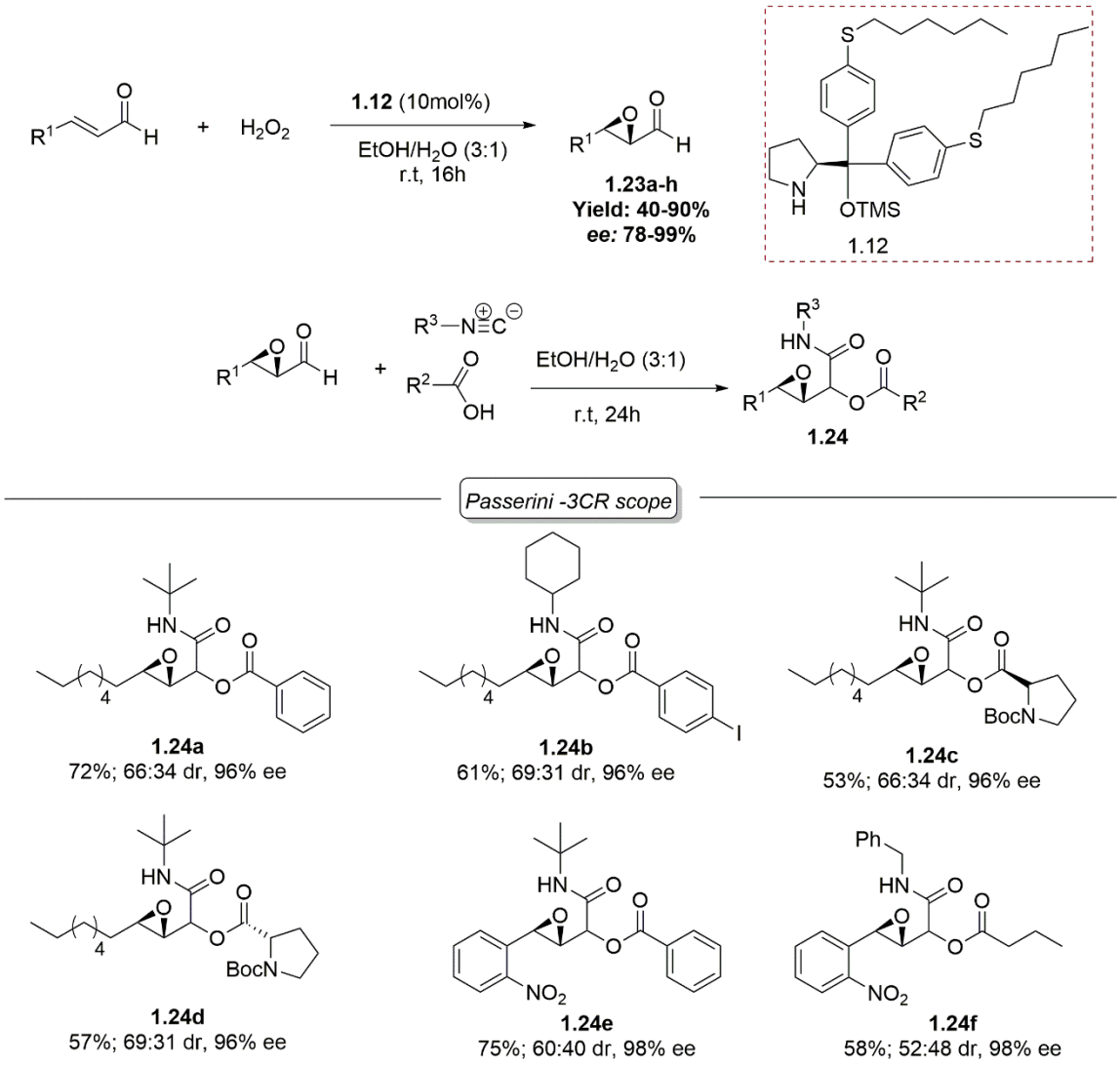
4- *The complexity of the reaction mechanism.*

To overcome this restraint, giving access to enantiopure MCR products there is another possibility directed to the use of chiral, enantiomerically pure inputs different from the widely used chiral pools (i.e., amino acids or sugars).

1.8 Sequential combination of organocatalysis and multicomponent reactions

As mentioned before, nowadays there is an emerging topic dealing with the combination of organocalysis with IMCRs to develop new stereoselective transformations. Looking at the repertoire of IMCRs, one realizes the presence of the carbonyl component, i.e. ketones or aldehydes, in these reactions. Only recently, early efforts have been directed towards implementation of an aminocatalytic asymmetric functionalization of such carbonyl functionalities followed by a subsequent IMCR.[72] Aminocatalysis has been successfully applied in the different asymmetric functionalization (α, β, γ and even ε) of carbonyls compounds. Hence, combination of aminocatalysis with the available repertoire of IMCRs provides unlimited possibilities for scaffold generation. Some reports referring to this combination are in development by our group and some articles have been published.

The Banfi´s [73] and our group realized the advantages of the conjugation of multicomponent reactions with organocatalytic process to the efficient exploration of stereochemical space. In these sense, our group describe a tandem nucleophilic epoxidation of α,β-unsaturated aldehydes followed by the P-3CR to access a green process of a new library of epoxy-peptides **1.24** (SCHEME 1.19).[74] Excellent enantioselectivity of epoxides **1.23** (>90% *ee*) were obtained employing catalyst **1.12** in a greener mixture of solvents. The *dr*. determined was very low because of the poor stereoselectivity of the Passerini reaction carried out in the second step. Further studies of the carboxylic acid substrate (compounds **1.24c** and **1.24d**) afforded similar diasteroselectivity and yield. The authors pointed that there are no incompatible interactions between the chiral epoxy aldehyde and the chiral acid. Overall, these results introduce more levels of molecular complexity for the synthesis of a novel family of epoxy-peptidomimetics. This work also comprised the first report of a one-pot organocatalytic multicomponent reaction sequence based on an asymmetric epoxidation reaction and a Passerini-3CR.

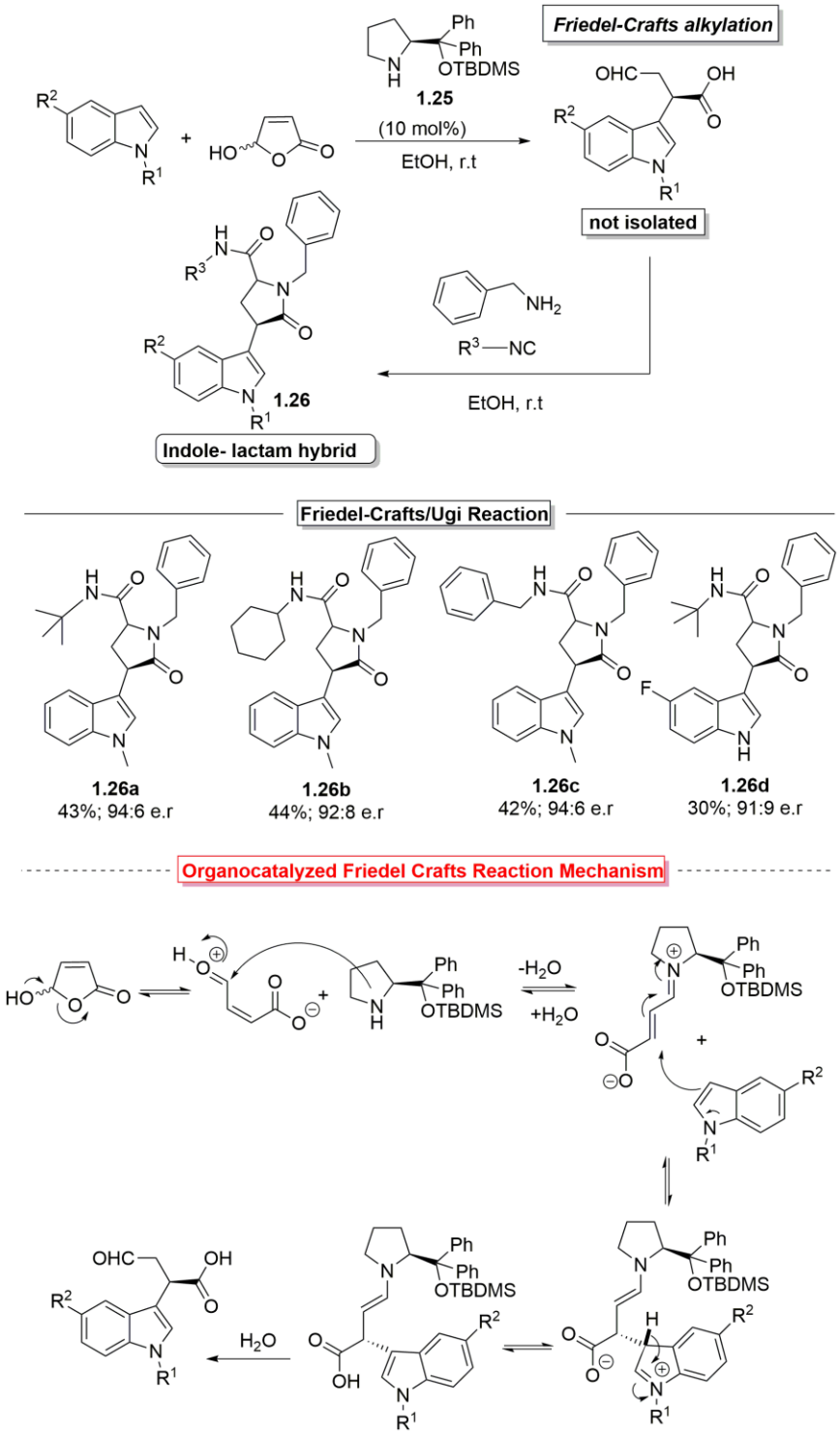


SCHEME 1.19- Organocatalytic-P-3CR reaction for the synthesis of epoxy-peptides.

Another interesting combination of IMCR with organocatalysis is the one-pot reaction of Friedel-Crafts indole alkylation followed by an Ugi 4-center 3-component reaction (U4C-3CR) as shown in **SCHEME 1.20**. In this case, chiral lactams (**1.26**) were obtained.[75] The 5-hydroxyfuran-2-one was used as α,β-unsaturated aldehyde for the organocatalytic LUMO activation mode in the Friedel-Crafts indole alkylation. The corresponding Friedel-Crafts adducts were obtained in short reaction times (3h), good enantiomeric ratio (up to 95:5) and high yields.

Once, having demonstrated the usefulness of 5-hydroxyfuran as an electrophilic, it was implemented a sequential organocatalytic intramolecular U4C-3CR, for the synthesis of lactam (**1.26**). It was obtained in high yield (77%) and enantiomeric relation er. (94:6). However, the dr. obtained (1:4:1) was poor, which is

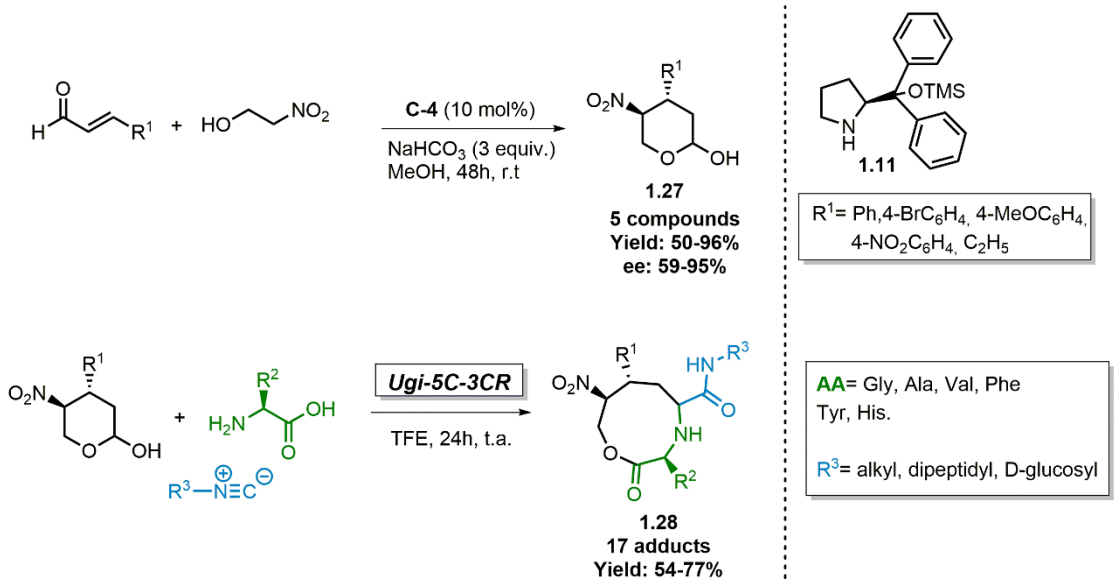
attributed to the new stereogenic center formed in a racemic manner in the Ugi reaction (SCHEME 1.20).



SCHEME 1.20- Organocatalytic and sequential Friedel-Craft Ugi reaction.

More recently, our group reported the use of asymmetric hemiacetals in multicomponent reactions.[76] An organocatalyzed conjugated addition of α, β-

unsaturated aldehydes and 2-nitroethanol was performed to obtain asymmetric 2-hydroxytetrahydropyrans **1.27** as chiral bifunctional substrates. These asymmetric hemiacetals were used as oxo-component for the Ugi reaction. Several amino acids and isocyanides where utilized to afford a small family of cyclic depsipeptide mimics (**1.28**) with low diasteroselectivity. This case is an example of the Ugi reaction which employs three components and has five reactive centers, two of which are present in the hemiacetal plus two in the amino acid and isonitrile (SCHEME 1.21).



SCHEME 1.21- The use of asymmetric hemiacetals in the Ugi reaction.

While on the contrary the multicomponent step showed pitiful diastereoselectivity, the overall strategy proved an exceptional complexity-generating ability with the creation of three new stereocenters and the incorporation of four components into the final cyclic depsipeptide scaffolds. The entity of a nitro group makes these compounds appropriate for further derivatization such as reduction and coupling to amino acids for enlarging the peptide chain by the western part.

1.9 Objectives: Chapter 1

In an attempt to further demonstrate the potential of this concept, this chapter focuses on the development of sequential organocatalytic multicomponent sequences leading to structurally varied heterocyclic compounds. Considering the need of chiral starting materials to pursuit stereoselective intramolecular I-MCRs, we focused on methodologies where the organocatalytic processes provide the enantiomerically enriched compounds having two functionalities capable to react in a subsequent MCR. In especial, we will focus on developing variations of the Ugi reaction, as this class of I-MCR is considered a wonderful tool to generate cyclic compounds.

For this aim, we envisioned to employ hemiacetal, previously prepared by organocatalysis, as chiral bifunctional scaffolds aiming at performing subsequent multicomponent steps capable to generate cyclic compounds. Such organocatalytic/multicomponent sequences will rely on initial Michael conjugate additions followed by Ugi-type reactions (FIGURE 1.7).

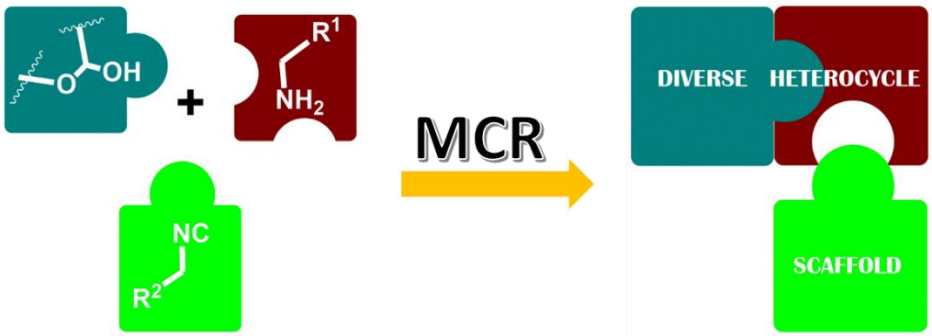


FIGURE 1.9.1- General methodology of the chapter.

1.10 Results and discussion: Chapter 1

1.10.1 Stereoselective organocatalytic multicomponent reaction sequence for the synthesis of hydroquinolinone

The generation and decoration of privileged natural product scaffolds is a successful strategy for obtaining libraries of bioactive compounds.[77] Scaffold decoration entails the utilization of both combinatorial and rationally designed approaches to functionalize biologically validated molecular targets. Scaffold generation, in contrast, focuses on the application of methodologies capable of generating structures which cover a larger part of the chemical and biological space. Since scaffold generation is pivotal during the early stage of drug discovery, issues like chemical efficiency, stereocontrol, and easy diversification are crucial in process development. Relevant strategies for exploring the broader chemical space by targeting dissimilar chemotypes, either previously validated by nature or derived from chemist`s synthetic expertise.

As shown in FIGURE 1.8, the initial objective is the organocatalytic synthesis of enantio-rich chromenone and its subsequent utilization in an isocyanide based multicomponent reaction. The result of this synthethic desing is a small family of hidroquinolin-5-one.

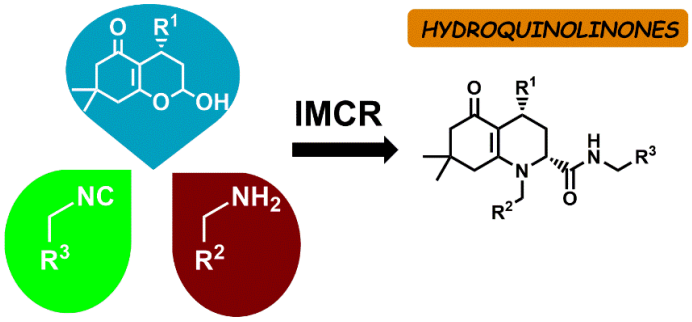


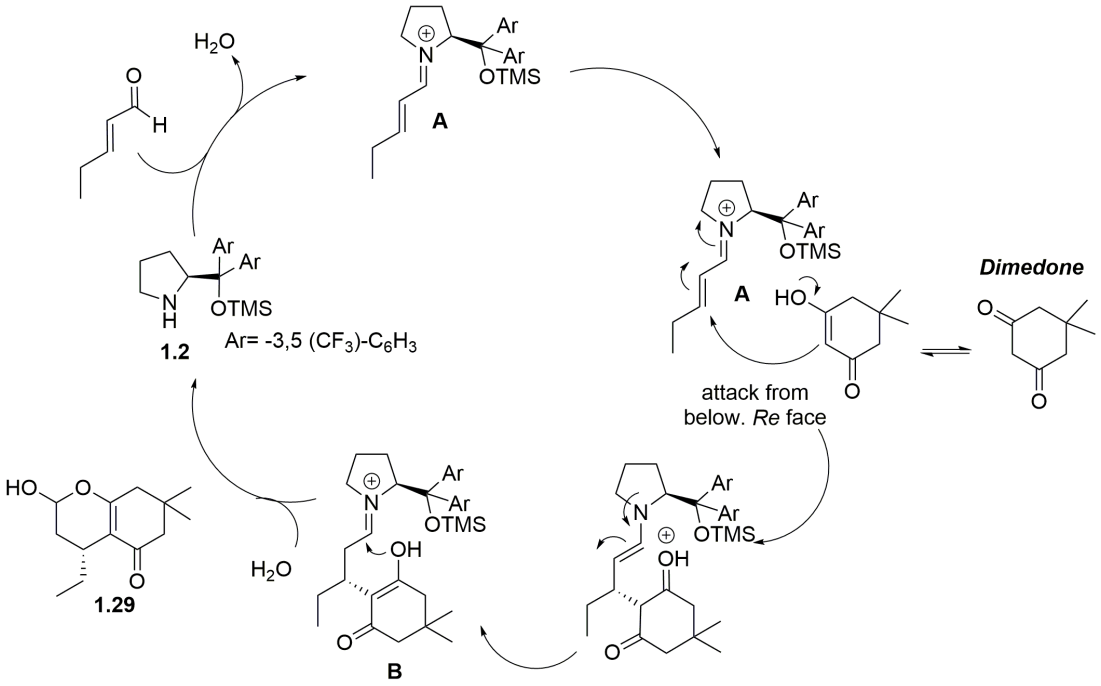
FIGURE 1.10.1- Isocyanide based multicomponent reaction approach for the synthesis of hydroquinolinones.

This chapter describes a highly stereoselective approach for the one-pot synthesis of a natural product-like based on the hydroquinoline platform. The approach involves an asymmetric organocatalytic conjugate addition of dicarbonyl

compounds to α,β-unsaturated aldehydes, followed by a new intramolecular 4-center 3-component reaction including amine and isocyanide components.

We formulated two main selection criteria for the organocatalytic and multicomponent approaches. First, the organocatalytic process should provide enantiomerically enriched hemiacetal suitable for a subsequent I-MCR. Second, we aimed at utilizing intramolecular I-MCRs, as these typically provide better stereocontrol as compared to their intermolecular versions. As mentioned above, the first procedure is an organocatalytic cascade developed independently by Rueping [78] and Jørgensen.[79]

The cascade process comprises the asymmetric conjugate addition of 1,3-cycloalkanediones to α,β-unsaturated aldehydes followed by acetalization. This organocatalytic reaction occurs via iminium ion activation mode where catalyst **1.2** lowers the energy of the LUMO orbital of the α,β-unsaturated aldehyde to permit the attack of the nucleophile (1,3-dione). Steric shielding produced by the organocatalyst blocks the *Si*-face of the α,β-unsaturated aldehyde. The stereocenter formed in the catalytic cycle is controlled by a *Re*-face attack of the nucleophile on the planar iminium ion **A** (SCHEME 1.22). The *Re*- face of the β-carbon atom in the iminium-ion intermediate is favoured for approach of the nucleophile owing to the bulk of the C2-substituent in the pyrrolidine ring of the catalyst. After the formation of the stereocenter, the catalyst is released by cyclization to form the hemiacetal **1.29** (SCHEME 1.22).



SCHEME 1.22- Proposed catalytic cycle one-pot Michael addition of α,β-unsaturated aldehydes and 1,3-cyclopentadione.

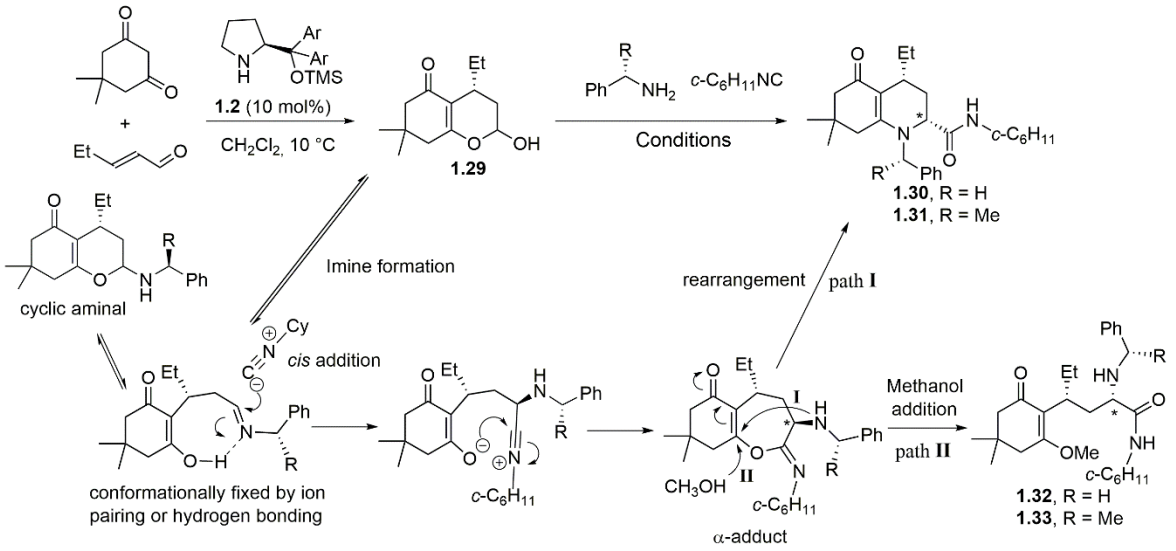
According with the authors,[78] we tried to reproduce the conditions reported; dimedone and *trans*-2-pentenal were initially selected for the organocatalytic conjugate addition with 10 mol% of catalyst diarylprolinol silyl ether **1.2** in dichloromethane for 48h. The TABLE 1.1 shows the consecutive organocatalytic and multicomponent process. Both racemic and enantiomerically enriched **1.29** were prepared and subsequently subjected to the I-MCR by treatment with a primary amine and an isocyanide. Such a multicomponent process is considered an enol Ugi type reaction,[80] which has been previously implemented with heterocyclic and conjugated enols [80b,c] as isosteric replacement of the carboxylic acid component. However, neither intramolecular variants of this type of I-MCR nor combinations with a pre-MCR organocatalytic process have been reported so far.

Initial experiments using methanol, toluene, or dichloromethane in the second reaction step were unsatisfactory as the first solvent gave a mixture of products and the two latter ones did not lead to any product formation (entries 1-4, 6 and 7, TABLE 1.1). Products **1.30**, **1.31** and **1.32**, **1.33** were formed in a ratio of about 1.5:1 when methanol was used, as a result of the competition between the rearrangement of the α-adduct (i.e., migration of the amine component) and the addition of methanol to the conjugated position.

As displayed in TABLE 1.1, the intermediate α-adduct is a rigid, fused bicyclic system, in which the low conformational flexibility may disfavor the amine migration, thus enabling the attack of a nucleophilic solvent like methanol. To circumvent this problem, 2,2,2, trifluoroethanol (TFE) was used, which led to 2-amido-hydroquinolin-6-one **1.30** as the sole product in good yield (entry 5, TABLE 1.1). Importantly, the use of microwave irradiation enabled the reaction to proceed in similar chemical efficiency and significantly shorter reaction times, i.e. 15 min at 70°C (entry 8, TABLE 1.1). Since the second step did not proceed in dichloromethane (DCM), we evaluated the possibility of implementing a *one-pot* sequence by addition of TFE after formation of organocatalytic product **1.29**, thus carrying out the second step in the solvent mixture DCM/TFE (1:1, v/v). To our delight, both yield and stereoselectivity remained high in this one-pot process comprising the organocatalytic step and the I-MCR (entries 9 and 10, TABLE 1.1). Importantly, the presence of secondary amine catalyst **1.2** did not interfere in the IMCR, as no product including this fragment was detected.

A key feature of this approach is the different stereochemical outcome derived from variation of primary amine. As illustrated in TABLE 1.1, the use of benzyl amine led to almost no diastereoselectivity in the I-MCR, producing **1.30** as a mixture of diastereoisomers (entries 1 and 5). Conversely, the utilization of the chiral (*S*)-α-methylbenzyl amine provided enantiomerically pure product **1.31** with an excellent diastereoselectivity (>99:1). Interestingly, the diastereomeric ratio of product **1.32** correlates with the enantiomeric ratio of intermediate **1.29**, confirming the great stereocontrol of the multicomponent step with the use of a chiral amine.

TABLE 1.1- Optimization study and concise reaction mechanism for the one-pot organocatalytic conjugate addition/Ugi-4C-3CR sequence to 2-amido-hydroquinolin-5-ones.

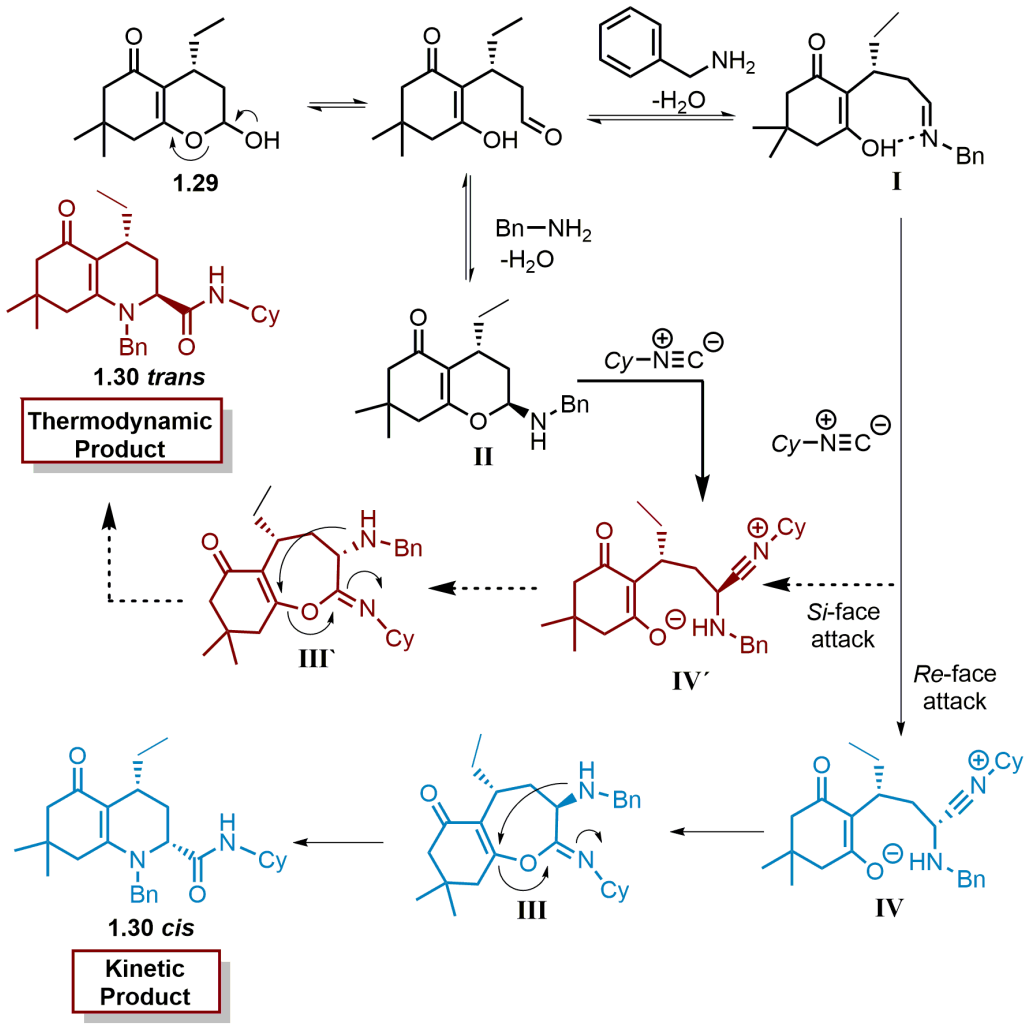


Entry [a]	R	Conditions [b]	Yield (%) [c] 1.30-1.31/1.32-1.33	*dr.* (*syn*/*anti*) [d] 1.30-1.31	ee (%) [e] 1.30-1.31
1 [f]	H	MeOH, RT	39/25	54:46	**92**
2 [g]	H	MeOH, MW	40/27	60:40	**>99**
3 [g]	H	Toluene, MW	n.r.	-	**-**
4 [f]	H	CH_2Cl_2, RT	n.r.	-	**-**
5 [f]	H	TFE, RT	77/0	58:42	**93**
6 [g]	Me	MeOH, MW	42/28	>99:1	**>99**
7 [f]	Me	CH_2Cl_2, RT	n.r.	-	**-**
8 [g]	Me	TFE, MW	75/0	>99:1	**>99**
9 [f,h]	Me	CH_2Cl_2/TFE, RT	64/0	>99:1	**>99**
10 [g,h]	**Me**	**CH_2Cl_2/TFE, MW**	**71/0**	**>99:1**	**>99**

a) First step performed with dimedone (1 equivalents) and *trans* -2-pentenal (1.3 equivalents). b) Second step performed either with benzyl or (*S*)-α-methylbenzyl amine (1.3 equivalents) and cyclohexylisocyanide (1.3 equivalents). c) Yield of isolated product over two steps. d) Determined by ^{1}H NMR spectroscopic analysis. e) Determined by chiral-stationary phase HPLC analysis. f) Conducted at room temperature for 36 h. g) Conducted under MW for 15 min at 70 °C. h) Addition of TFE to the reaction mixture containing CH_2Cl_2 to make a 1:1 (v/v) mixture. TFE: Trifluoroethanol. Ar: 3,5-(CF_3)-C_6H_3.

Taking a close look into the mechanism proposal for the hydroquinoline-5-one formation (SCHEME 1.23), we formulate two possible reaction pathway. The first step in both cases is the imine formation through a direct attack of benzylamine to the open hemiacetal form of **1.29** with subsequently water elimination. Later, the imine could be present as two equilibrium structure; a conformationally rigid seven-member ring **I** featuring an intramolecular hydrogen-bond (pathway 1) and stable cyclic aminal **II** (pathway 2). In the case of intermediate **I** the hydrogen-bond based

conformer presents two of the bulkier substituents in the pseudo-equatorial position in a cyclic saddle-like conformation. The later one pathway involves an S_N2 mechanism to achieve the thermodynamically stable **1.30** *trans* product, but with a high energy barrier. This reaction rather occurs through a low energy transition state facilitating then a concerted asynchronous reaction pathway affording the kinetically **1.30** *cis* product. The first step involves a proton transfer to the imine, followed by formation of the C-C bond. The α-adduct **III** is readily formed from the alkoxy attack to the nitrilium-ion in **IV**. Finally, a concerted migration of the exocyclic amine to the nitrile conjugate position and cleavage of C-O bond afford the hydroquinoline-5 one product.



SCHEME 1.23- Mechanism proposal for the isocyanide based multicomponent reaction.

The FIGURE 1.9 clearly demonstrate the two possible attack of isocyanide to the cyclic intermediate **I**. Attack from the *Si*-face is sterically not favoured. On the other hand, the *Re*-face approximation of the isonitrile is less hindered and consequently more possible. This conformation **I** is the key for understanding the experimental diastereoselectivity. The isocyanide can clearly preference for the *Re* face that leads to the formation of the favoured diastereoisomer. This intermediate is also responsible of for the orientation of the enol and isocyanide π-systems by a stabilizing non-covalent interaction.

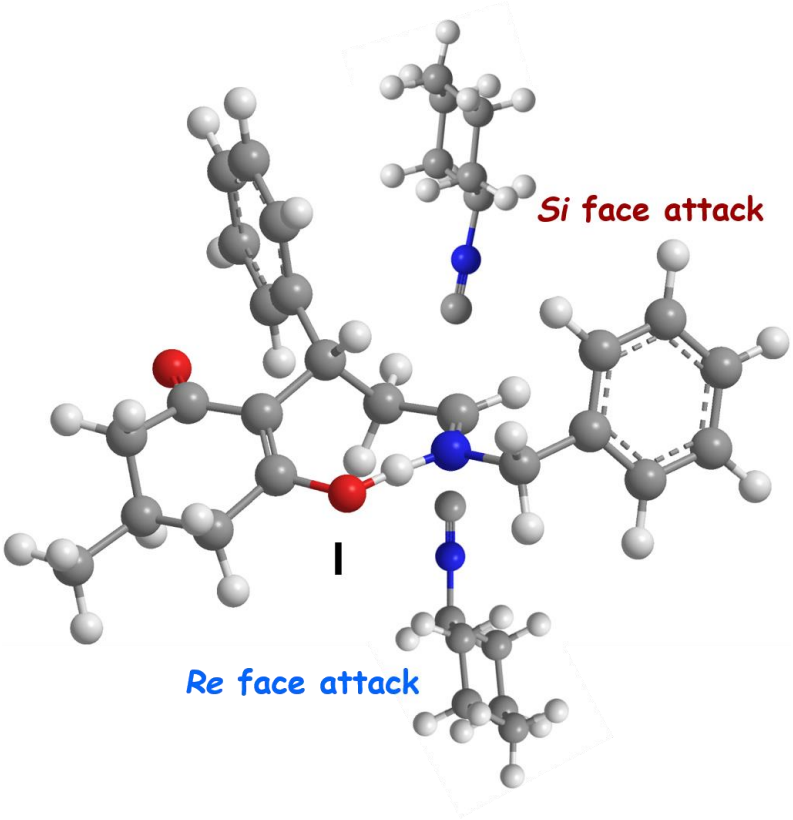


FIGURE 1.10.2- Isocyanide attack to the *Re* and *Si* faces of intermediate **I**.

The relative configuration of hydroquinolin-5-ones **1.30** and **1.31** was determined by NMR analysis on the basis of the absolute configuration at C-4 of intermediate **1.29**, as previously assessed by X-ray analysis.[78] The solid-state structures showed the axial orientation (directing toward the α face) of the substituent at position 4 in product **1.29**. In a first instance, the two diastereoisomers of compound **1.30** derived from benzyl amine were isolated and analyzed by NMR. In the major stereoisomer of **1.30** (and also in the only one of **1.31**), various nuclear overhauser effect (NOE) correlations between hydrogens of the ethyl chain at position 4 and the substituent at position 2 were found. Similarly, strong NOE

correlations were observed between the amide substituent at position 2 and one of the geminal methyl groups of the fused bicyclic skeleton (FIGURE 1.9).

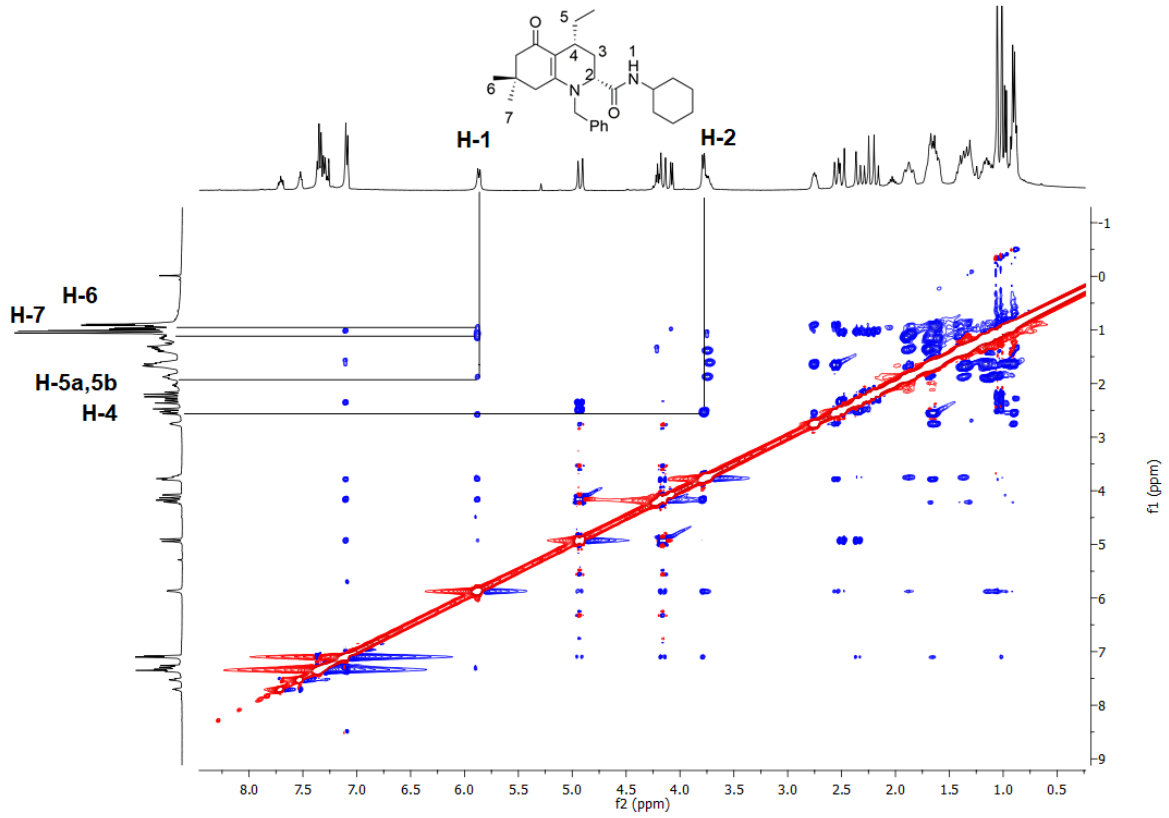


FIGURE 1.10.3- NOESY spectra of diasteroisomer *cis* of compound **1.30**.

These results unambiguously prove the *cis* configuration in which both substituents at positions 2 and 4 have a pseudo-axial orientation directing toward the α-face of the hydroquinolin-6-one skeleton. As highlighted in FIGURE 1.10, these NOE couplings are only possible due to the 1,3 and 1,5-diaxial interactions of the amide substituent at C-2 and the substituent at position 4 and the geminal axial methyl group, respectively. In contrast, the minor stereoisomer of compound **1.30** showed a strong NOE correlation between the hydrogen at C-2 and the ethyl group at C-4, indicating the *trans* configuration of substituents at positions 2 and 4. As shown in TABLE 1.1, the diastereoselection of this process derives from the preferential addition of the isocyanide to the conformational fixed imine (or iminium ion) by the same face of ethyl group (cis addition). Further enolate addition leads to the α-adduct featuring the trans disposition between the ethyl group and the exocyclic amine moiety. Finally, migration of the amine (rearrangement) generates the piperidine ring with the *cis* configuration of the amide substituent at C-2 with

respect to the ethyl group at C-4. A further evidence that the stereocontrol lies at the isocyanide addition step is that the acyclic side-product **1.33**, derived from methanol addition, was obtained with the same diastereoselectivity of **1.31**, whilst formation of side-product **1.32** proceeded with poor stereoselection, as resulted for **1.30**. To get deeper insight into stereoselectivity, we turned to implement the reaction sequence with variation of the four different components.

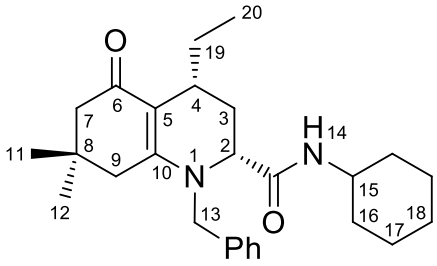
The NMR characterization of the hydroquinoline-5-ones is not a very easy task, to this end the compound **1.30** was selected for full characterization (TABLE 1.2). The ^{1}H NMR spectra of compound **1.30**, allow us to confirm the presence of the isocyanide and amine fragment in the molecule. For instance, the region of hydrogen bonding to Csp^2 hybridization, appears two multiplets signals from 7.38-7.27 and 7.10 ppm corresponding to five hydrogen of the aromatic ring. The chemical shift of 5.83 ppm is a doublet with a coupling constant of 8.1 Hz which correspond to amide hydrogen H-14. At δ of 4.86 and 4.17 ppm appears the benzylic protons 13a and 13b off the methylene group. The chemical shifts off 3.79 and 3.73 ppm correspond to the H-2 and H-15 respectively. These protons also show correlation in the COSY spectra with H-4 and H-17. The COSY diagram also shows correlation between the amide hydrogen with H-2 and H-16.

The ^{13}C NMR spectra clearly shows at 190 ppm, the presence of the ketone carbonyl group close to an unsaturated system, attributed to C-6. The carboxyl group of amide bond appears at 170 ppm. The aromatic region of the spectra has the existence of eight carbons, corresponding with the benzyl group and the quaternary carbons of the unsaturated system.

Since only two carbonyl groups are in compound **1.30**, by heteronuclear multiple-bond correlation (HMBC) we determined that these signals correlates with two shifts 2.76 ppm (H-4) and 2.56 (H-3) ppm. Also at 155 ppm is an heteronuclear correlation with 2.56 ppm, indicating that this carbon corresponds to C-5.

A correlation with shifts 28.7, 28.4 and 12.1 pm was identified by HSQC and correspond to the CH_3 of C-11,12 and 20 respectively and associated to the chemical shift of the hydrogen spectra; 1.05, 1.02 and 0.89 ppm. The HSQC spectra also facilitate the identification of C-12 at 24.7 ppm with a direct correlation with the multiplet at 0.98 ppm.

TABLE 1.2- ^{1}H NMR and ^{13} C shifts assigments for comound **1.30**.

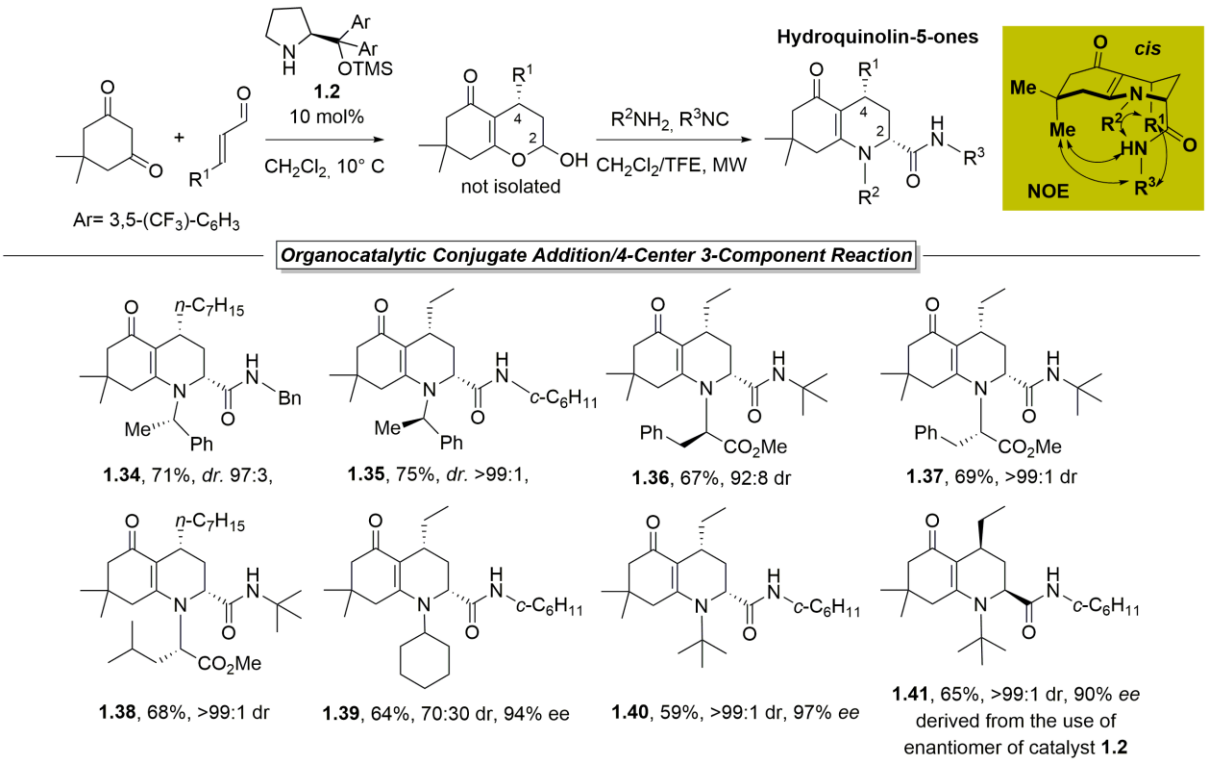


Position	^{1}H NMR: δ(ppm), *J*(Hz)	^{13}C NMR: δ(ppm)
2	3.79 (d, *J* =6.5)	60.6
3	2.56 (d, *J* =14.1); 1.74-1.65 (m)	33.0
4	2.76 (m)	30.3
5	-	155.0
6	-	194.4
7	2.27 (d, *J* =16.1); 2.18 (d, *J* =16.2)	50.2
8	-	33.1
9	2.50 (d, *J* =16.1); 2.34 (d, *J* =16.2)	32.4
10	-	136.6
11	1.02 (s)	28.7
12	1.05 (s)	28.4
13	4.86 (d, *J* =17.0); 4.17 (d, *J* =17.0)	53.9
14	5.83 (d, *J* =8.1)	-
15	3.73 (m)	48.4
16	1.74-1.65 (m); 1.42-1.32 (m)	25.8
17	1.74-1.65 (m); 1.41-1.32	25.4
18	1.20-1.11 (m)	24.9
19	0.98 (m)	24.3
20	0.89 (t, *J* =5.2)	12.1

The scope of the one pot organocatalytic- multicomponent reaction was performed under the optimized conditions, that is, first step performed with dimedone and different aliphatic aldehydes for 48 h. Second step performed with either aliphatic amines or amino acid and isocyanides in microwave for 15 min at 70°C.

As shown in SCHEME 1.24, several hydroquinolin-5-ones were produced by variation of three structural elements, i.e. the aldehyde incorporated in the organocatalytic step, as well as the amine and isocyanide in the I-MCR. As before, the one-pot processes were performed without isolation of intermediate

hemiacetal **1.29**, but simply carrying out the subsequent I-MCR through addition of TFE, the amine and isocyanide components immediately after completion of the organocatalytic step.



SCHEME 1.24- One-pot synthesis of hydroquinolin-5-one.

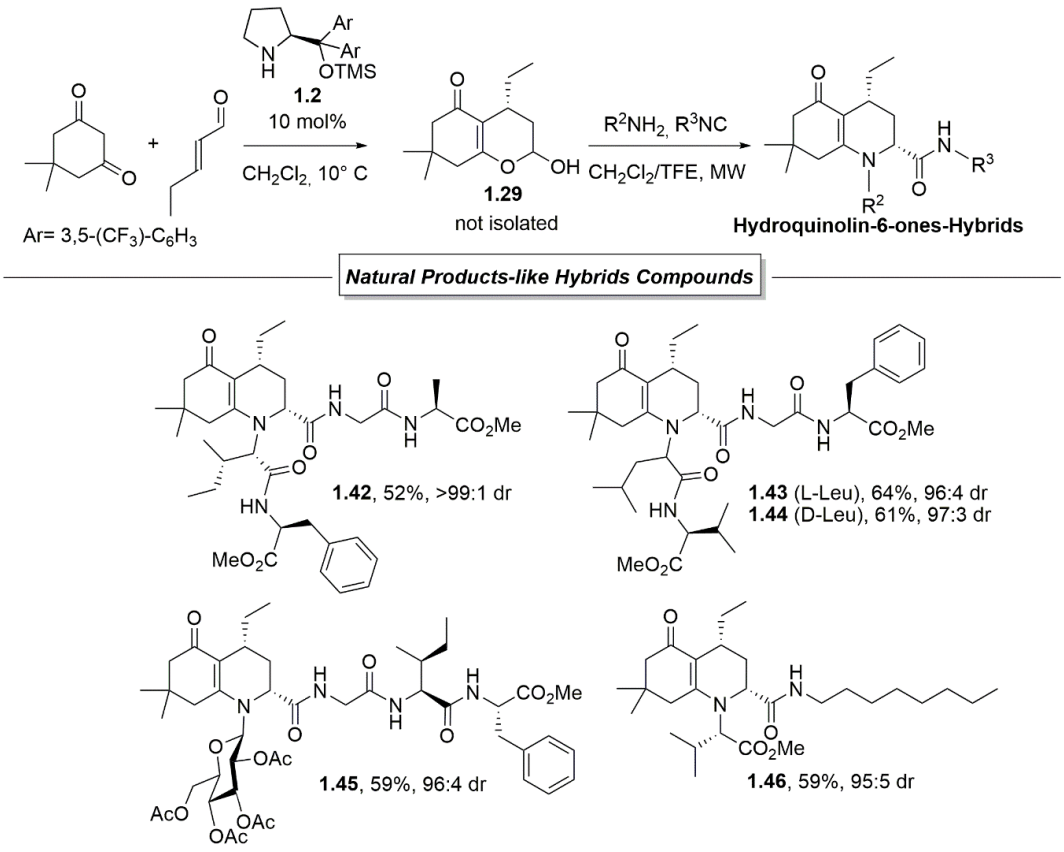
The stereoselectivity of the multicomponent sequence leading to hydroquinolin-5-ones **1.34** proved once more to be excellent when the amine is chiral (α-MeBn and amino acids). As before, NMR evidences proved the cis configuration for major isomers. The use of either *S* or *R*-α-methylbenzyl amine as well as either D- or L-amino acid methyl esters provided the same stereo-differentiation to the cis isomers of compounds **1.34**-**1.38**.

An interesting result was obtained when the bulky character of the achiral amine was increased from cyclohexyl to *tert*-butyl amine. Thus, cyclohexylamine gave compound **1.39** with moderate diastereoselectivity (*dr*. 70:30, 94% *ee*), while the highly crowed *tert*-butyl amine rendered **1.40** with excellent diastereoselectivity (*dr*. 99>1, 97% *ee*). This confirms that not only chiral amines, but also achiral ones with great steric congestion at the α-position can induce stereoselection in this I-MCR. A further experiment proceeding via the enantiomer of intermediate hemiacetal **1.29** (prepared using the enantiomer of catalyst **1.2**) resulted

in the highly stereoselective formation of compound **1.41** (*dr*. 99>1, 90% *ee*), which is the enantiomer of **1.40** (*dr*. 99>1, 97% *ee*) as revealed by chiral-stationary phase HPLC and optical rotation analysis. This result confirms the great stereofacial selectivity (*cis* addition) when a bulky, eventually chiral amine is used.

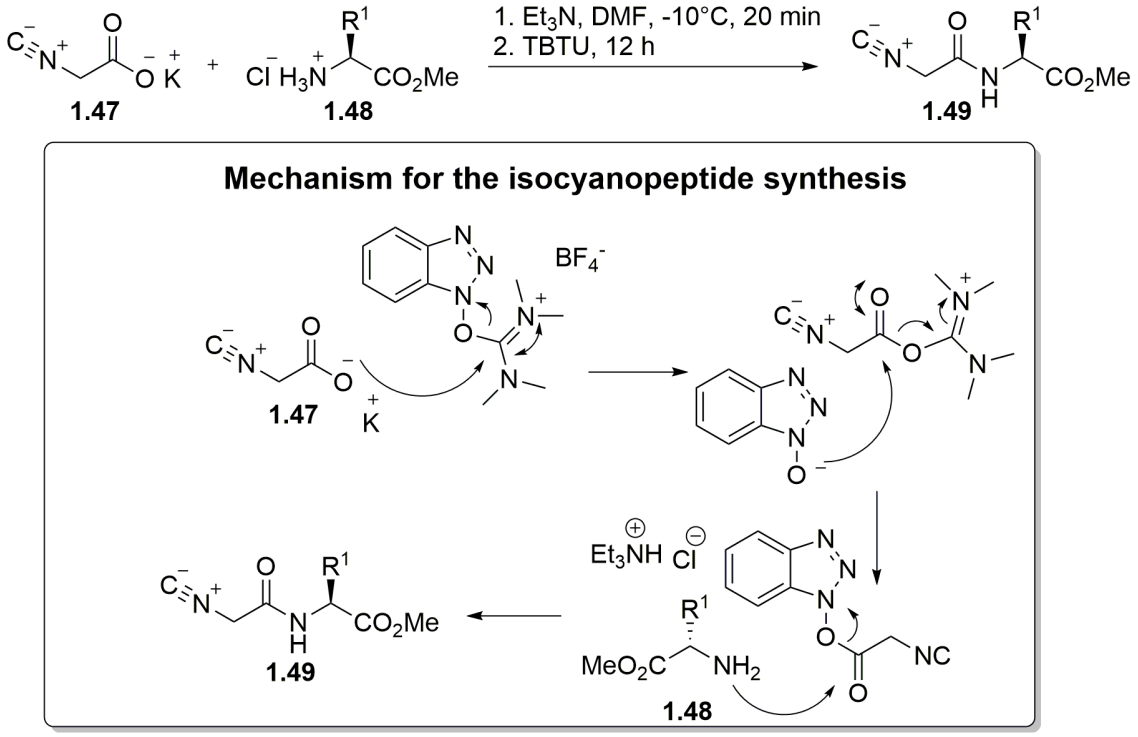
1.10.2 Stereoselective organocatalytic multicomponent synthesis of Natural Product- like hybrids.

Having demonstrated the efficacy of the organocatalytic/ I-MCR sequence for the stereoselective preparation of molecular hybrids, we focused on the generation of further skeletal diversity and complexity through variation of the amine and isocyanide components. To this end, we investigated the possibility of incorporating natural product fragments of peptidic, lipidic, and saccharidic nature into piperidine-based hybrid architectures. The SCHEME 1.25 illustrates the one-pot approach leading to the hydroquinolin-5-one **1.42**-**1.46** utilizing the enantiomerically enriched chromenone **1.29**.



SCHEME 1.25- One-pot stereoselective synthesis of natural product hybrids including hydroquinolinone lipidic, peptidic, and sacharidic moieties.

The isocyanopeptides with the sequences CN-Gly-Ala-OMe, CN-Gly-Phe-OMe and CN-Gly-Ile-OMe used to achieved the hydroquinoline-5-ones **1.42**-**1.45** respectively were synthesized following a previous reported procedure.[81] A typical peptide coupling procedure of the methyl esters of aminoacids or the peptide (for CN-Gly-Ile-OMe) with potassium isocyanoacetate salt, in presence of the coupling reagent 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) afford the isocyanide derived products (SCHEME 1.26).

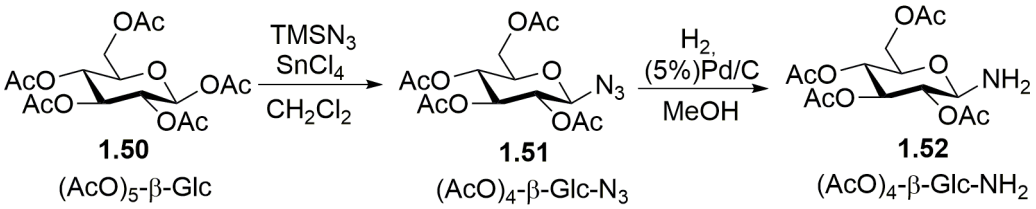


SCHEME 1.26- General synthetic route for isocyanopeptide synthesis.

According to the SCHEME 1.26, the peptide coupling starts with the activation of the potassium salt of isocyanide. The coupling and activating group TBTU is a well-established reagent for this purpose because it plays a dual role of activating group and recemisation suppressant.[82]

For the synthesis of hydroquinoline hybrid **1.45**, the synthetic route for β-glucosyl amine ($(AcO)_4$-β-Glc-NH_2) was needed. In these case a two-step reaction procedure was employed (SCHEME 1.27). In the first one, the formation of the $(AcO)_4$-β-Glc-N_3 was achieved using $SnCl_4$ and trimethylsilyl azide ($TMSN_3$). The use of a Lewis acid activates the acetate group in the anomeric carbon of **1.50** which is eliminated through a neighbouring group effect. The cyclic intermediate is attacked

by the azide group generating the compound **1.51**. The second step of the synthesis is a catalytic hydrogenation (5% Pd-C, MeOH) to obtain the desire amine **1.52**.



SCHEME 1.27- Synthesis of β-glucosyl amine.

The synthesis of the isocyanopeptides and sacharidic amine allow us to introduce diversity and complexity into the hydroquinoline core (see SCHEME 1.25). As before, enantiomerically pure hybrids were produced in an excellent diastereomeric ratio, with the cis isomers as major products. The use of epimeric dipeptides having either L- or D-Leu at the *N*-terminus generates the hybrids **1.43** and **1.44** respectively, and both feature the cis configuration. Albeit the complexity of the isocyanide or amine component, the yields of the novel natural products like compounds were very good. This procedure also furnished complex natural products moieties in one pot. Compounds like **1.42**, **1.45**, **1.46** constitute a rapid way for the assembly of lipo and glycol-peptidomimetics.

1.11 Conclusions: Chapter 1

A highly stereoselective and one-pot sequence leading to complex natural product-like was developed. Hydroquinolin-5-ones were obtained in a yield range of 59-75% and high stereoselectivity (dr. >99:1, >99% ee). From a synthetic point of view, the present approach can be regarded as an asymmetric multicomponent ligation process that integrates up to four different molecular fragments into a single skeleton. This report confirms that the asymmetric aminocatalytic functionalization of carbonyl compounds is an effective pre-MCR process capable of providing enantiomerically enriched building blocks for subsequent multicomponent diversification. The versatility of this diversity-oriented strategy relies on the vast number of 1,3-dicarbonyls and α,β-unsaturated aldehydes that could be combined with amines and isocyanides of biomolecular nature. Such a facile variation of reaction components combines with the great levels of molecular

complexity available with low synthetic cost. This procedure provides a rapid generation of diversity and complexity with the formation of four new covalent bonds. Finally, we envision that other iminium, enamine and N-heterocyclic carbene organocatalytic processes may be combined with varied MCRs, hence expanding the repertoire of stereoselective multicomponent cascade reactions.

Chapter 2

2. Chapter 2

2.1 Introduction: Chapter 2

In this chapter will be discussed the development of a sequential procedure comprising two cascade events that lead to novel and structurally complex tetrahydropyridines (THPs) in high enantio and diastereoselectivity. The process encloses an asymmetric Michael addition to α,β-unsaturated aldehydes followed by I-MCRs (FIGURE 2.1). Thus, this chapter is organized in a short introduction about the importance of THP heterocycles and the different synthetic methods for obtain this compounds. We also discuss about the metal-mediated post-Ugi transformations for heterocyclic scaffolds construction, followed then by the chapter objective's, results and discussion and final remarks.

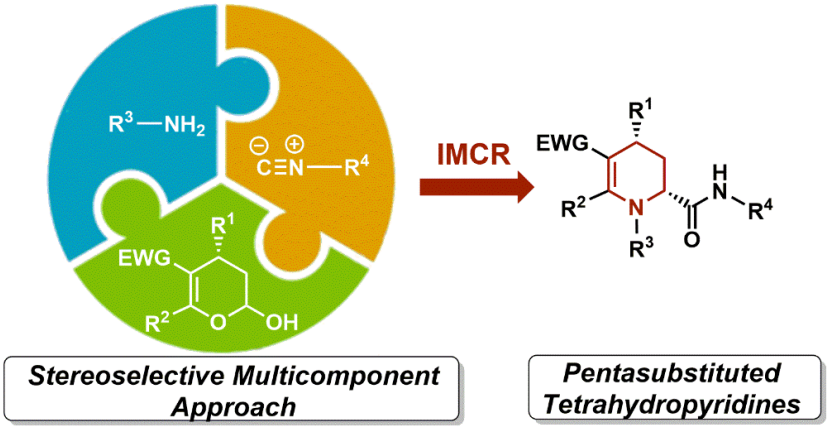


FIGURE 2.1.1- General methodology of the synthesis of THPs.

2.2 Importance of Tetrahydropyridines

The THPs have been recognized as a major constituent of naturally occurring alkaloid. In recent years have received massive attention as a promising building block for numerous natural and synthetic molecules. This nitrogen-containing heterocycle are among the most common structural motifs in bioactive compounds.[83] These compounds are important heterocycles present in many molecules of natural and non-natural origins. For instance, alkaloids such as **2.1** isolated from *Leuconotis griffithii* display moderate cytotoxicity against drug-sensitive and vincristine-resistant

human KB cells.[84] Other compounds such as 1-(1,4,5,6-tetrahydropyridin-2-yl)ethanone **2.2**[85] and betanin **2.3**[86] are used in food industry, as aroma and dye, respectively (FIGURE 2.2). Furthermore (*E*)-Pandamarilactonine-32 (**2.4**) is an alkaloid obtained from *Pandanus amaryllifolius*, whose extracts have been used as flavours but also in traditional medicine in Asia, because of their antioxidant, antibiofilm, and anti-inflammatory activities.

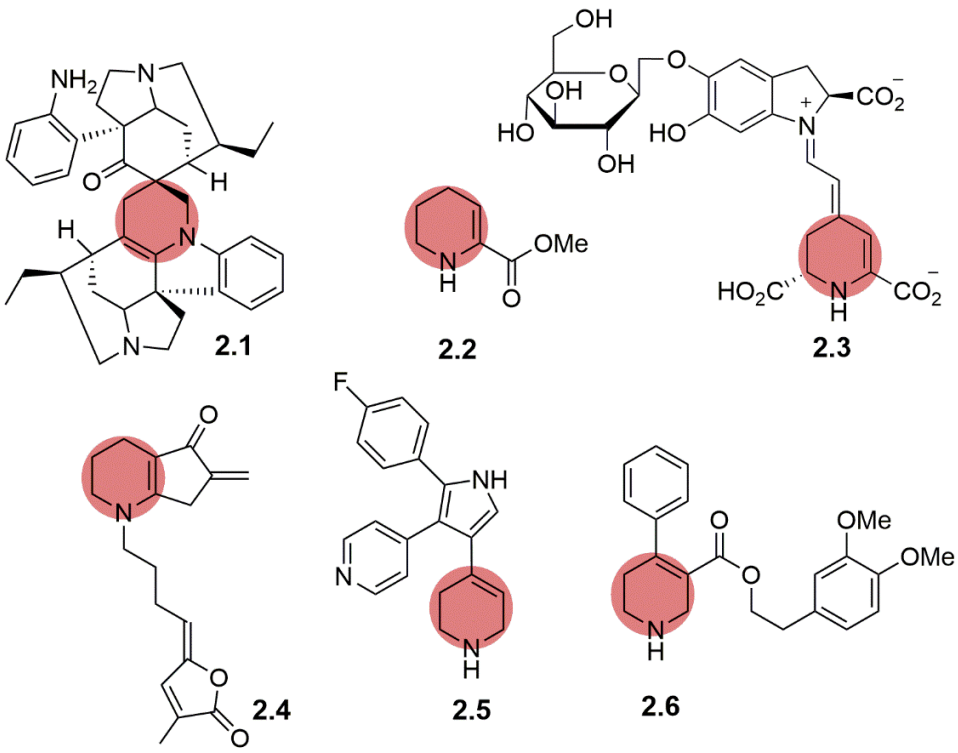


FIGURE 2.2.1- Examples of natural and non-natural tetrahydropyridines derivatives compounds.

On the other hand, non-natural THPs are also of great interest. For example, compound **2.5** bearing a THP ring attached to a pyrrole nucleus can act as an antiinflammatory agent with superior activities compared to the corresponding piperidine and pyridine analogues.[87] The ester **2.6**, function as an antagonist for M5 muscarinic acetylcholine receptor, a potential target for the treatment of drug abuse.[88]

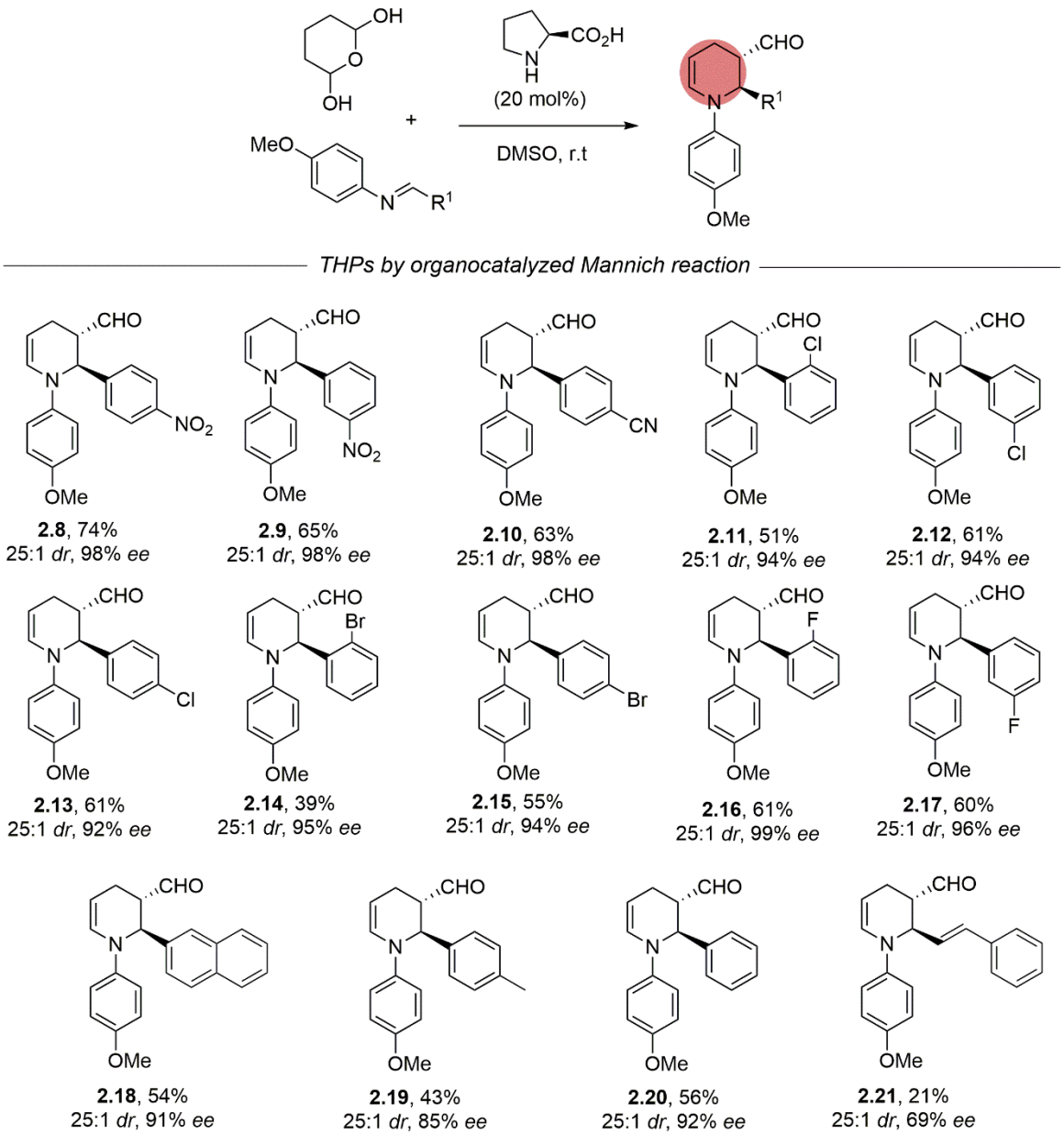
Apart from that, compounds with THP molecular fragment have found to possess another biological and medicinal activities such as antimicrobial,[89] anti-influenza,[90] analgesic,[91] hyperglycemic,[92] antimalarial,[93] etc.

2.3 Synthetic strategies for the asymmetric preparation of THP

As was previously mentioned THP compounds basically contain a heterocyclic fragment made up of a cyclohexene ring possessing nitrogen as hetero atom. They can be substituted at almost all the six position of heterocyclic ring providing huge variety of its derivatives. Since THPs non-planar ring comprise Csp^3 carbon atoms, many of them are chiral, rendering the development of methods to control them. To overcome these loads, the concept of MCRs and organocatalysis has emerged some extremely powerful strategies to achieve stereocontrol.

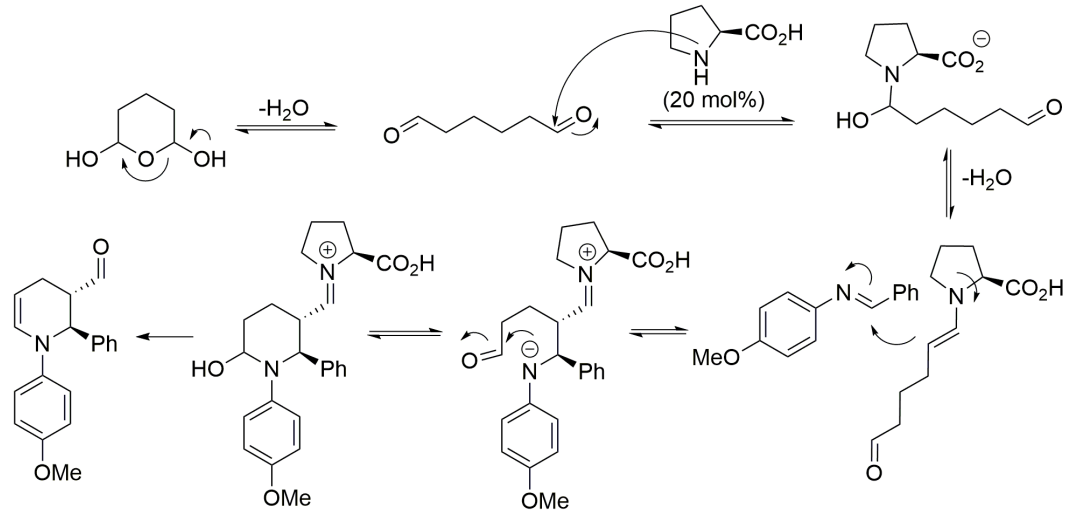
One of the must adopted methods not only in organic synthesis in general, but also more specifically in organocatalysis is the Mannich reaction, which constitute an addition of an enol or enolate to an imine.[94] In this sense, the first strategy to attain THPs via a Mannich reaction was to use 1,5-dialdehydes synthetic equivalents in the presence of proline derivatives. In 2008, Xu and co-workers showed that inexpensive aqueous tetrahydro-2H-pyran-2,6-diol could interact with (*S*)-proline **1.1** to afford an intermediate enamine able to trap diversely substituted *N*-(*p*-methoxyphenyl) aldimines (SCHEME 2.1).[95]

The authors suggest that initial Mannich reaction is followed by hemiaminal formation and dehydration to afford 1,2,3,4-THPs (SCHEME 2.1) in moderate yields but with complete diastereoselectivities and very high enantiomeric excesses.



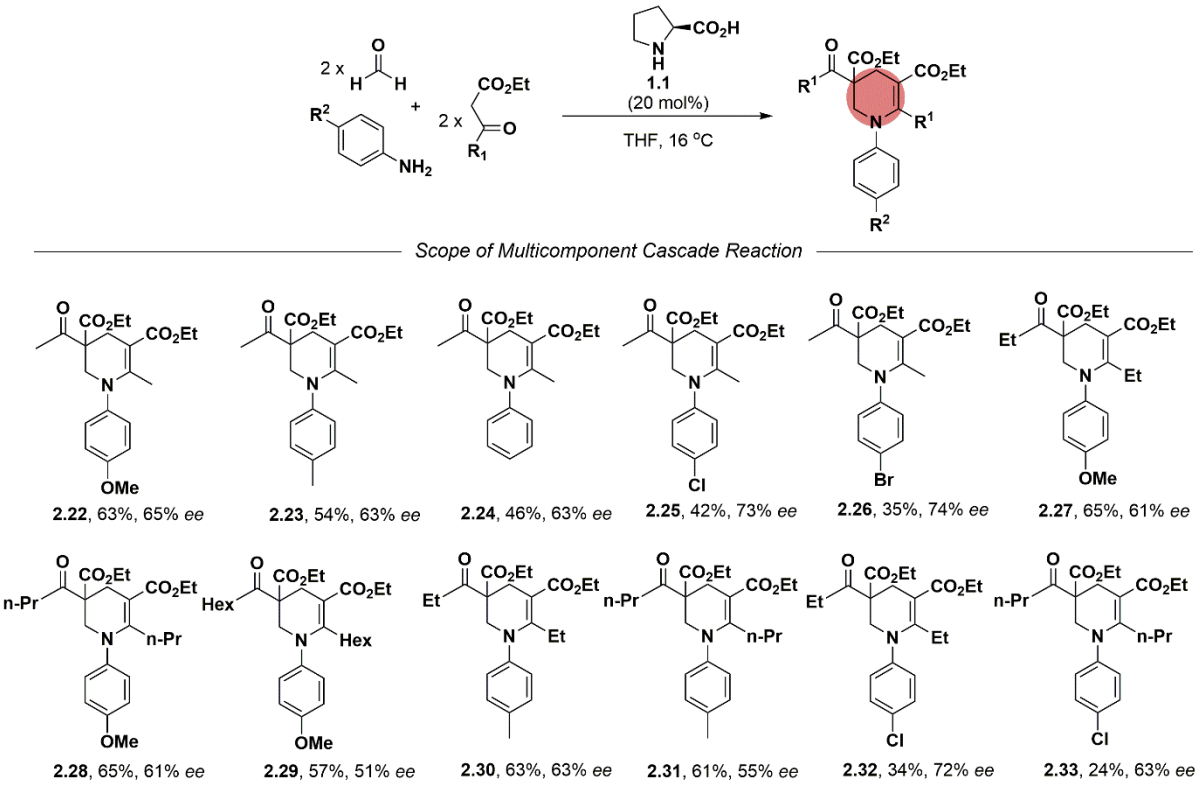
SCHEME 2.1- Synthesis of THPs by (S)-proline-catalyzed Mannich reaction.

Remarkably, organocatalysts that do not hold an acidic proton failed to provide the final product, pointing towards a bifunctional activation mode where the carboxylic acid function interacts with the nitrogen atom of the imine. The aldimines obtained from enals or aliphatic aldehydes performed very poorly compared to their aromatic congeners. The SCHEME 2.2 illustrate the mechanism for the proline organocatalyzed Mannich reaction. Initially 2,6-diol could interact with (S)-proline to afford an intermediate enamine able to trap diversely substituted N-(*p*-methoxyphenyl)aldimines. The initial Mannich reaction is followed by hemiaminal formation and dehydration to afford 1,2,3,4-THPs.



SCHEME 2.2- Mechanism for the THP synthesis using the Mannich reaction.

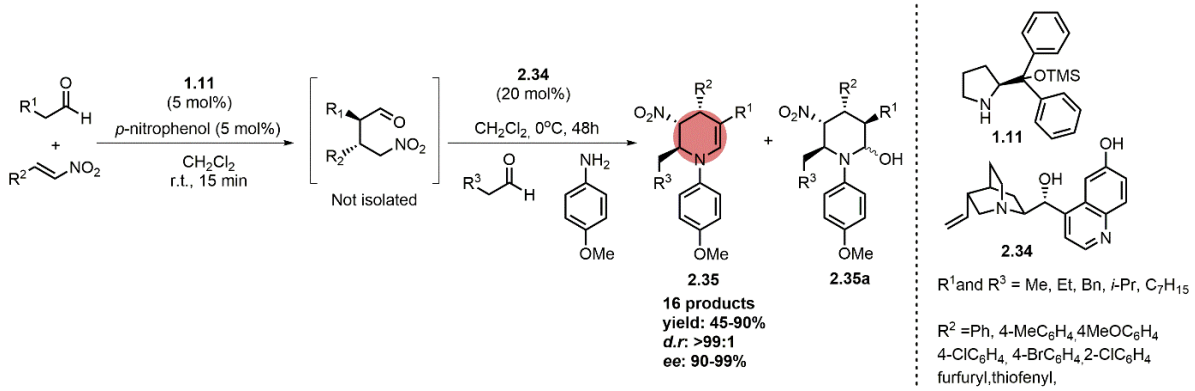
In 2011 Xu et. al.[96] reported the cascade a multicomponent combination of two molecules of linear -keto esters, two molecules of formaldehyde and substituted anilines could assemble in a pseudo-five-component reaction, in the presence of proline **1.1** to deliver 1,4,5,6-THPs **2.22-2.33** in moderate yields and enantiomeric excesses, the absolute configuration of which has not been determined (SCHEME 2.3). The authors claim that the enantioselective step consists in the addition of a chiral but not configurationally stable proline-derived enamine to the imine. As expected, the generation of multiple covalent ligations during the reaction was very efficient. In this course three C-C bonds and two C-N bonds were formed.



SCHEME 2.3- Proline-catalyzed pseudo-five-component synthesis of 1,4,5,6-THPs.

Nitroolefins are exceptionally efficient Michael acceptors for enantioselective organocatalysis and they can serve as the starting point to prepare enantioenriched THPs. The group of Sun and Lin published a study where nitroolefins were at first combined with enolizable aldehydes in the presence of secondary amine organocatalyst **1.11** and p-nitrophenol as cocatalys.[97] In a second time, an *aza*-Henry reaction followed by cyclization delivered the 1,2,3,4-THPs **2.35** and **2.35a**. In the first case, the imine engaged in the aza-Henry reaction catalyzed by **2.34** was produced in situ by adding *p*-methoxy aniline that combines with the excess aldehyde obtained as the Michael product (SCHEME 2.4). The formation of compound **2.35a** it is barely formed in comparison with **2.35** (20:1 ratio) affording an excellent chemeoselectivity.

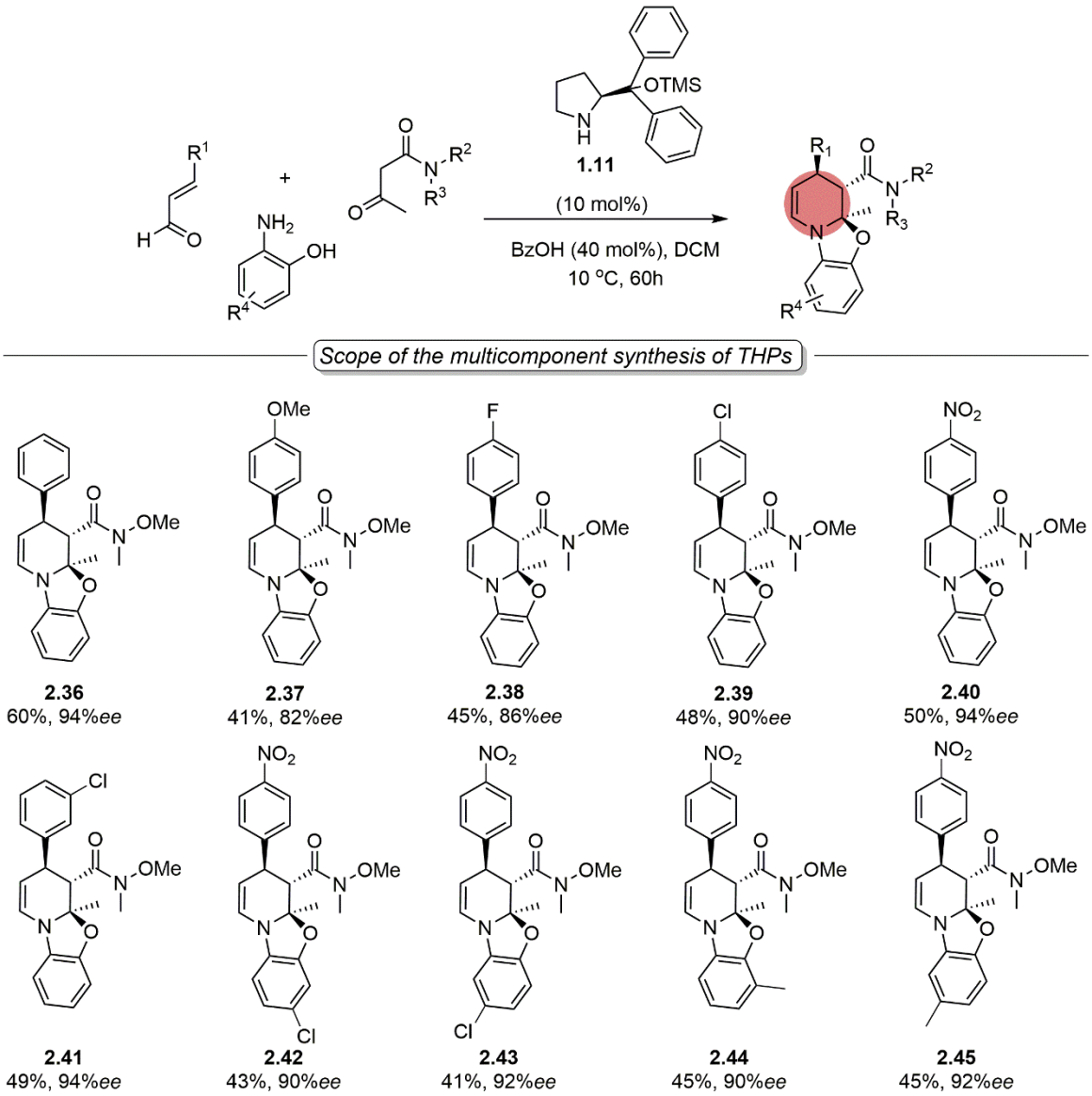
The authors pointed that β-aryl-nitroethylenes with an electron donating or an electron-withdrawing group could be converted in the corresponding THP with moderate yields and excellent enantioselectivity. This dual-catalyst-promoted asymmetric cascade reaction were observed for a broad spectrum of substrates under mild conditions.



SCHEME 2.4- Synthesis of THPs initiated by a Michael addition and with dual-catalyst asymmetric cascade.

In 2015 the Constantieux´s group investigated the potential regioselectivity of a multicomponent organocatalytic Michael addition of α,β unsaturated aldehydes with dicarbonyl compounds.[98] The starting point of this transformation was the combination of the above mentioned ones and a functionalized amine (SCHEME 2.5).

With aromatic enals as electrophiles and 2-aminophenols as the third reaction partner, the THPs were formed in moderate yields, notably better with more activated Weinreb -ketoamides, but with very high stereoselectivities (SCHEME 2.5). The THP final compounds obtained from an enal bearing an electron-donating group in *para* position was obtained with slightly reduced enantiomeric excess, electron-neutral and -poor enals afforded products with good enantioselectivities; *meta*-substitution was also well tolerated, as shown for product, but, in the case of *ortho*-substituted cinnamaldehydes or aliphatic enals, the reaction was sluggish, with only small amounts of product identified. This work represents the first route to Δ^2-substituted tetrahydropyridines based on an enantioselective MCR. The moderate yield reported is comprehensive in view of the complexity of the MCR that installs four new bonds, but with complete regioselectivities and very high diastereoselectivity.



SCHEME 2.5- Use of tertiary -ketoamides as pronucleophiles to the synthesis of THP.

2.4 Metal-catalyzed post-Ugi reactions for the synthesis of heterocyclic scaffolds

As mentioned before the Ugi-4CR is by far one of the most extraordinary multicomponent reaction leading to high structural and molecular complexity. The U-4CR has remained as one of the highly investigated reactions for generating multifunctional adducts, owing to the mildness of the reaction conditions, the wide application scope and the high variability associated with it. Moreover, it provides an opportunity for an innumerable of post-transformations depending on the

functional groups introduced during the MCR, thus leading to the synthesis of several pharmacologically important heterocyclic scaffolds, mostly in two operational steps. Besides the well-known post-Ugi transformations such as Ugi-deprotection cyclization (UDC), acid–base catalyzed cyclizations, cycloadditions, macrolactonizations, SNAr and SN_2 reactions,[99] the metal-catalyzed transformations directed towards the synthesis of diverse heterocyclic scaffold is a very attractive field. Due the very extensive literature about metal-catalyzed post-Ugi transformations, this section is limited to Ugi-Heck and Ugi-arylations reactions.

2.4.1 Ugi- Heck reactions

The Heck–Mizoroki cross-coupling (HM) reaction is an important part of the synthetic chemist's toolbox and it has been applied to a huge variety of substrates. This transformation belongs to the family of Pd-cross coupling reactions. Usually, palladium- (II) species are chosen as starting material because of their higher stability. Such compounds are then reduced in situ to palladium (0) species which enter the catalytic cycle. The reaction mechanisms are quite well understood and, especially in the case of Pd complexes, are considered to be organometallic in nature, taking place in the coordination sphere of the metal. Although, generally speaking, there are two types of Pd cross coupling reaction that have become important in organic synthesis (FIGURE 2.3).

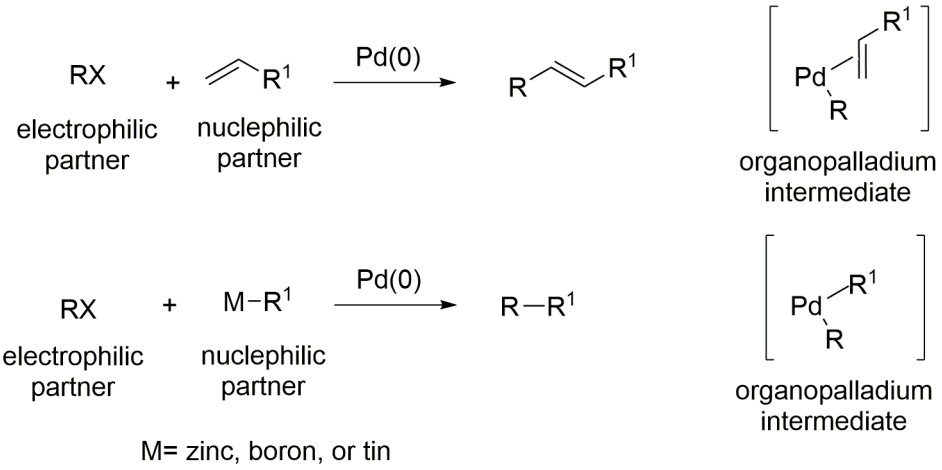


FIGURE 2.4.1- General catalytic cycle for the Pd cross-coupling reactions.

In the specific case of the HM after the oxidative addition, the palladium(II) species react with the olefin (nucleophilic partner). This results in a

carbometallation reaction to generate palladium(II) alkyl complex. Elimination of palladium hydride from complex furnishes the desire product and base assisted elimination of HX from palladium(II) complex regenerates the active palladium (0) catalyst to regenerate the catalytic cycle again (FIGURE 2.4).

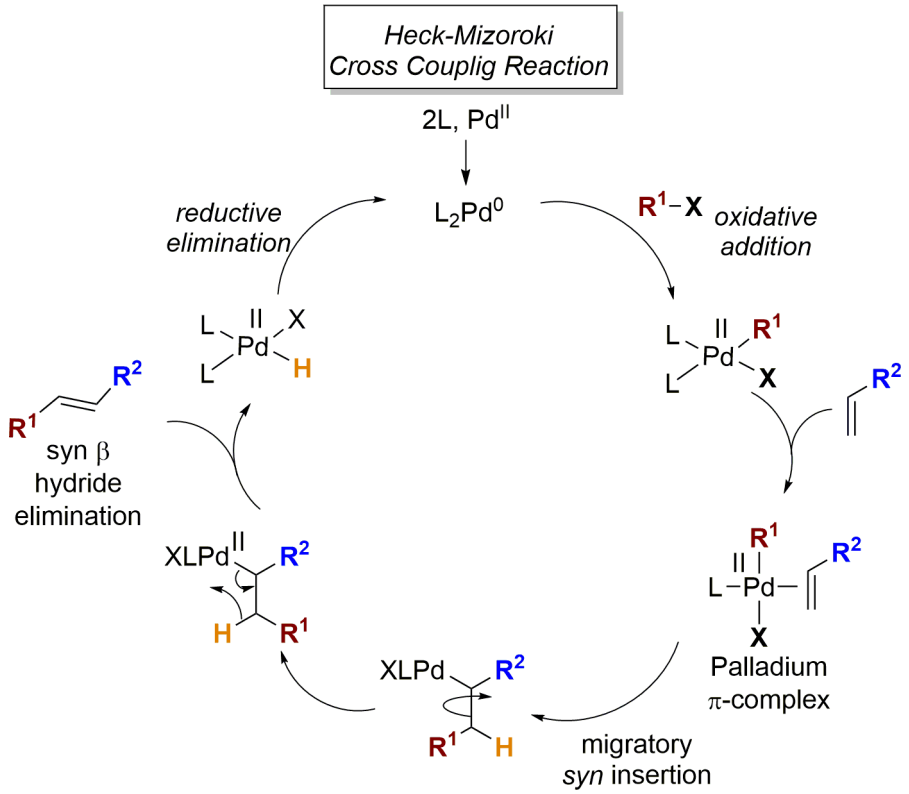
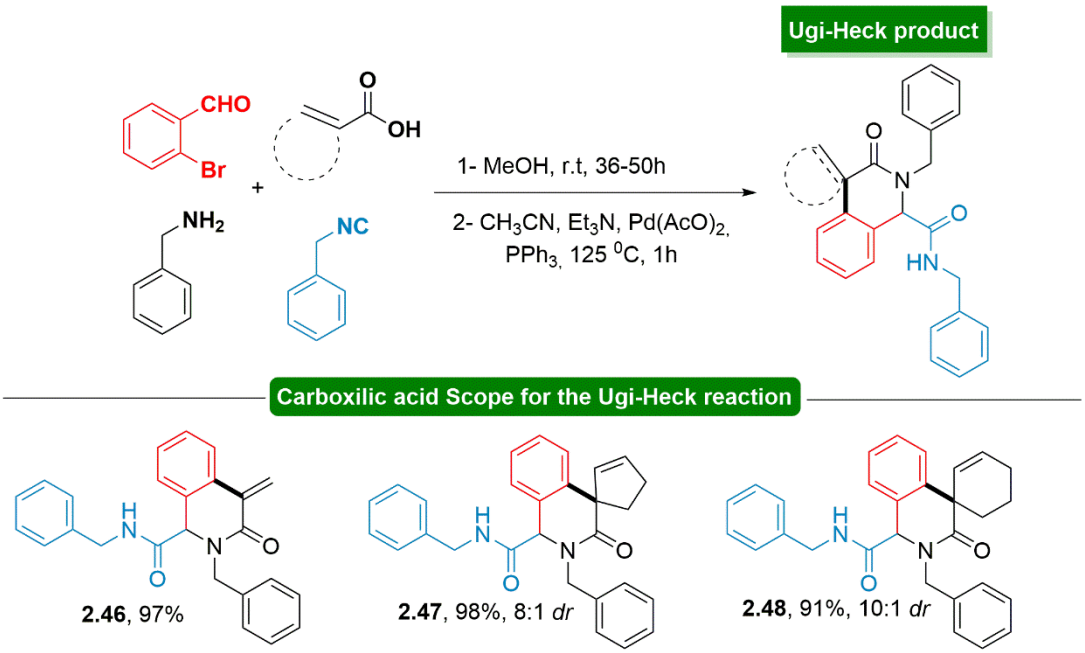


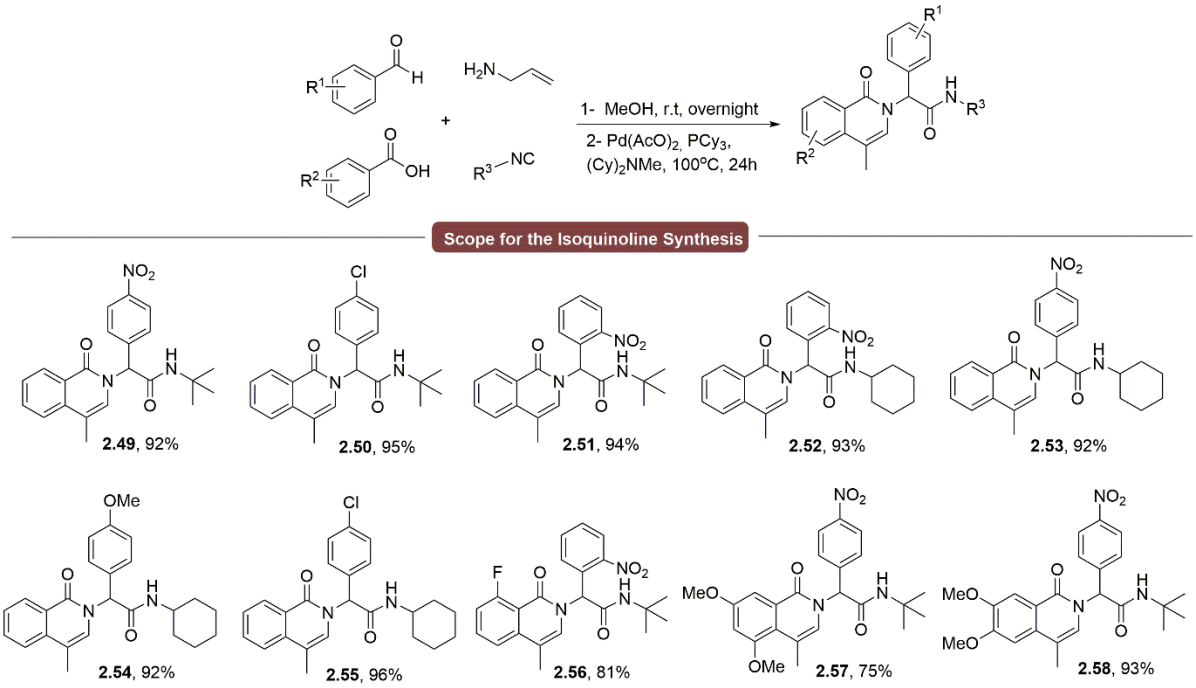
FIGURE 2.4.2- Heck-Mizoroki reaction mechanism.

The combination of the Heck reaction, with the Ugi reaction has been employed for the synthesis of pharmacologically important scaffolds. An interesting report by Gracias and co-workers in a sequential one-pot Ugi–Heck cyclization approach, whereby the ring size and periphery features of the products were effectively controlled based on the choice of the bi-functional starting materials (SCHEME 2.6).[100] Utilizing *o*-bromo benzaldehyde with unsaturated acids as alkene source, isoquinolines **2.46**-**2.48** with an olefin-containing spirocyclic system or an α,β-unsaturated system were obtained using $Pd(OAc)_2$ as catalyst, PPh_3 as ligand, Et_3N as base in MeCN at 125°C under microwave irradiation for 1 h.



SCHEME 2.6- Sequential Ugi-Heck reaction for the synthesis of isoquinolines.

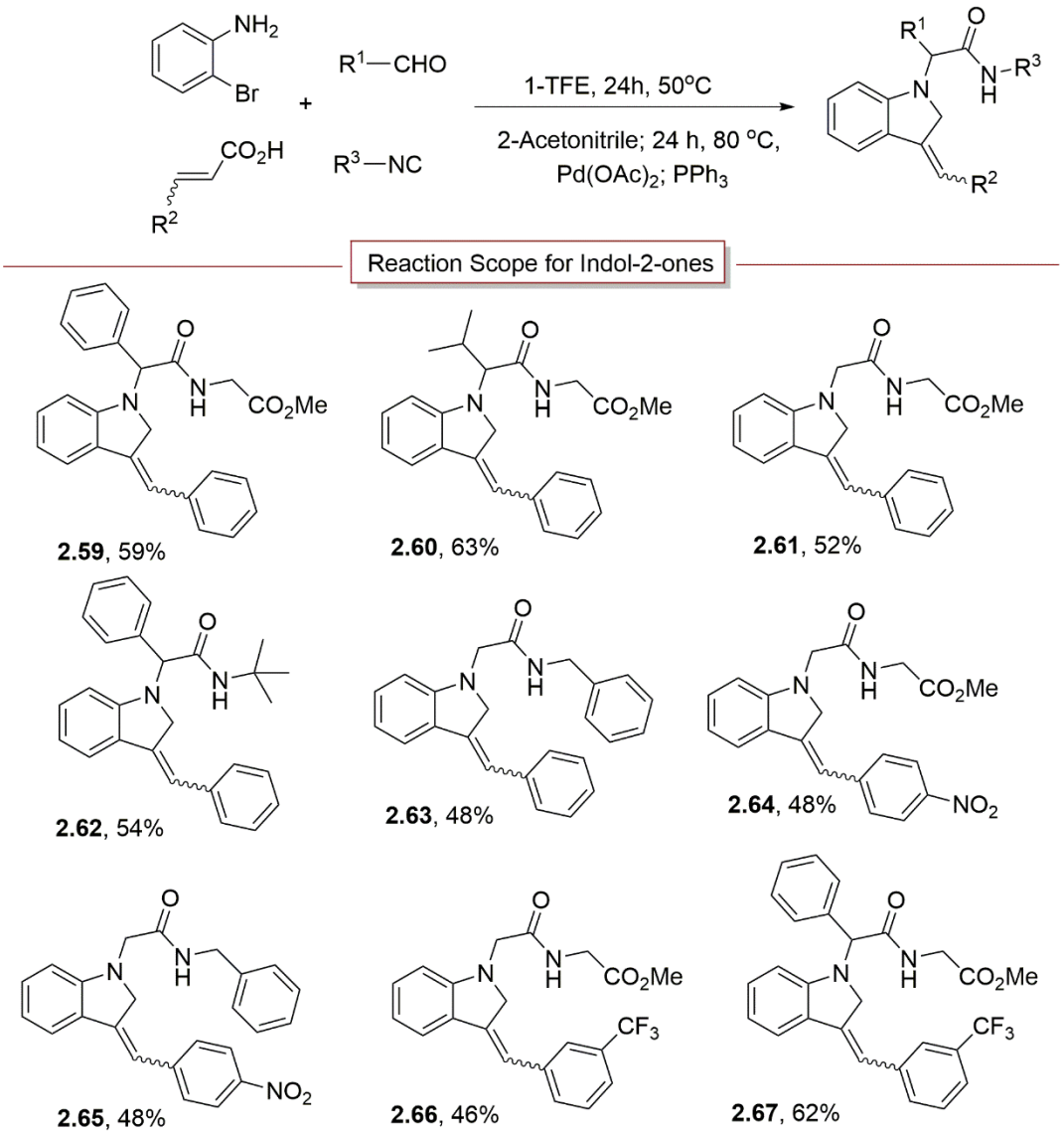
Another example of the HM reaction for the synthesis isoquinoline scaffolds was elaborated by Yan and co-workers.[101] The first step in this sequence is a Pd-catalyzed intramolecular Heck reaction followed by a Pd-catalyzed double bond isomerisation of the Ugi adduct generated by reacting N-allylamine either with o-halobenzoic acids or with *o*-halobenzaldehydes (SCHEME 2.7). The catalytic system consisting of $Pd(OAc)_2$, PCy_3 and *N*-methyldicyclohexylamine as unique base in dimethylacetamide (DMA) provided access to a variety of isoquinolines in good to excellent yields.



SCHEME 2.7- Synthesis of substituted isoquinoline compounds.

The indole scaffold belongs to a class of heterocycle which display important biological activities. Therefore, the synthesis and functionalization, of indoles have been the object of research for over one and half century.[102]

Umkehrer and co-workers[103] developed an efficient Ugi–Heck combination for combinatorial library production of indol-2-ones bearing four points of diversity using acrylic acids (SCHEME 2.8) as one of the Ugi substrates. In this novel one-pot solution phase synthesis, the starting materials for Ugi reaction were stirred at 50ºC for 24 h in TFE (polar protic). Afterwards, the solvent was changed to MeCN and 10 mol% of Pd-catalyst was added which provided the desired products in moderate yields after 16–24 h of stirring at 80ºC. The synthetized compounds (**2.59**-**2.67**), were isolated as isomeric mixtures with moderate to good yields.



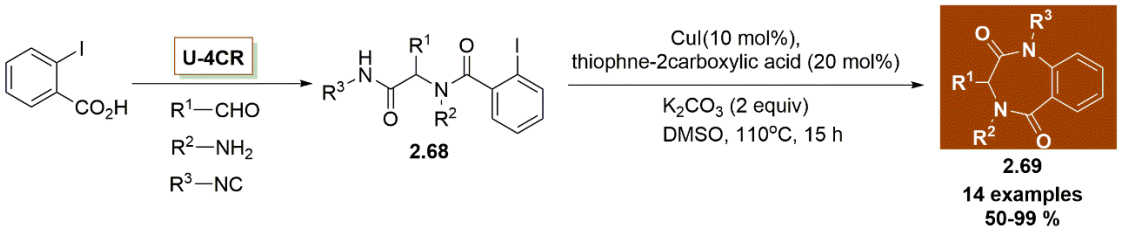
SCHEME 2.8- Synthesis of indolones via one-pot Ugi-Heck.

2.4.2 Ugi- Arylation reactions

In order to increase the construction of pharmaceutically relevant cyclic scaffolds intramolecular (C-, O- and N-) arylation reactions have been combined with the Ugi-4CR.

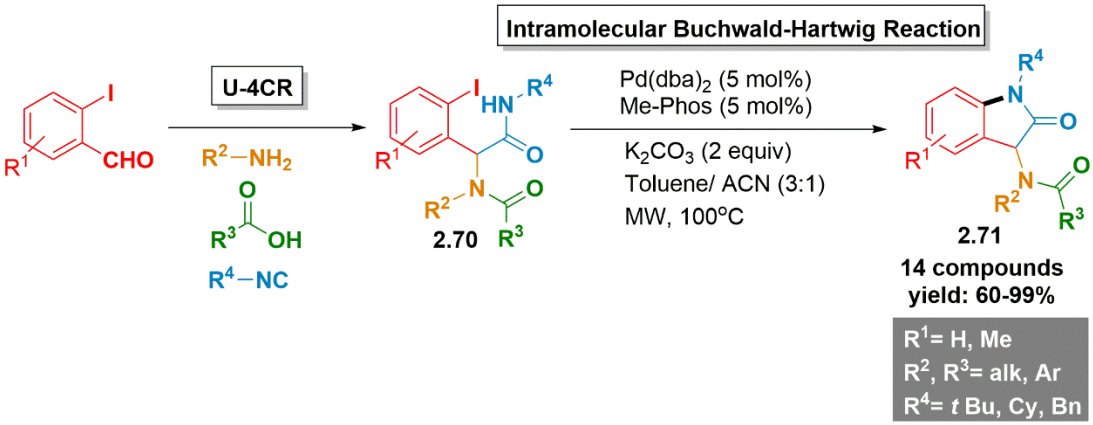
In 2004, Zhu and co-workers[104] described an efficient methodology for the construction of two differen heterocyclic scaffolds from the linear Ugi-adduct **2.68** (SCHEME 2.9). They exploiting the different catalytic behavior of Pd- and Cu-catalysts. While Pd triggered a domino intramolecular N-arylation/C–H activation/ aryl–aryl bond-forming process, Cu promoted only the intramolecular N-arylation leading to the formation of 1,4-benzodiazepine-2,5- diones **2.69**. The optimized

reaction conditions involved the use of CuI as catalyst and thiophene-2-carboxylic acid as a ligand in DMSO at 110 °C for 15 h.



SCHEME 2.9- Cu(I)-catalyzed synthesis of 1,4-benzodiazepine-2,5-diones.

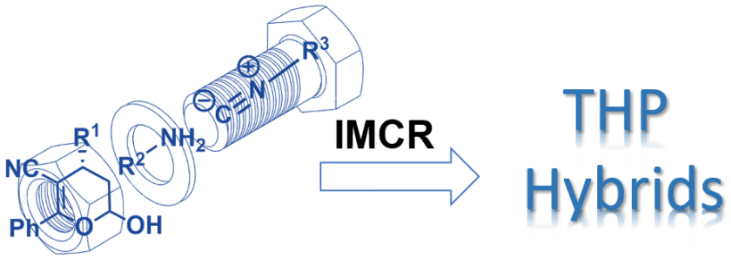
A few years later, the authors have reported an efficient methodology to access functionalized oxindoles **2.71** via Pd-catalyzed intramolecular amidation (intramolecular Buchwald–Hartwig reaction) of Ugi substrates **2.70** under microwave irradiation (SCHEME 2.10).[105] Initially, the cyclization was tried with a Cu-catalyst; however, the yield could not be increased beyond 42%. Thereafter, the reaction was optimized under using $Pd(dba)_2$ as the catalyst and Me-Phos as the ligand of choice, giving the 2-oxindoles in moderate to excellent yields (60–99%). Sterically hindered amides and iodides were well tolerated and no competitive C–H activation process leading to formation of dihydrophenanthridine was observed in the course of reaction.



SCHEME 2.10- Palladium-catalyzed intramolecular Buchwald-Hartwig reaction.

2.5 Objectives: Chapter 2

The THP skeleton as mentioned above is of wide occurrence in natural alkaloids and medicinally important synthetic compounds. The synthesis of this compounds could be achieved by an organocatalytic cascade and multicomponent sequences. Inspired by this successfully process, we aimed in this chapter to extending the scope of a powerful Ugi-type MCR described by our group to the stereoselective synthesis of THPs. This I-MCR encompasses the condensation of a bifunctional substrate (hemiacetal), having an aldehyde and a conjugated enol, with an amine and an isocyanide.



2.6 Results and discussion: Chapter 2

2.6.1 Stereoselective sequential organocascade and multicomponent approach for the synthesis of THP

We describe the development of a sequential procedure comprising two cascade events that lead to novel and structurally complex THPs in high enantio and diastereoselectivity. As shown in FIGURE 2.5 our strategy differs from previously reported examples [97,98] in both the initial organocatalytic conjugate addition and the final cyclization step, which comprises a new isocyanide-based MCR (I-MCR). Hence, we prove that the amine and the isocyanide are the key components for the generation of structural diversity and complexity at this novel THP scaffold.

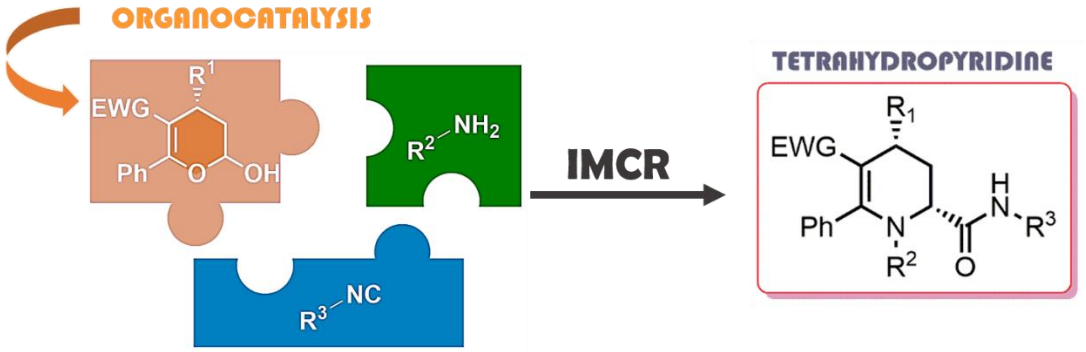
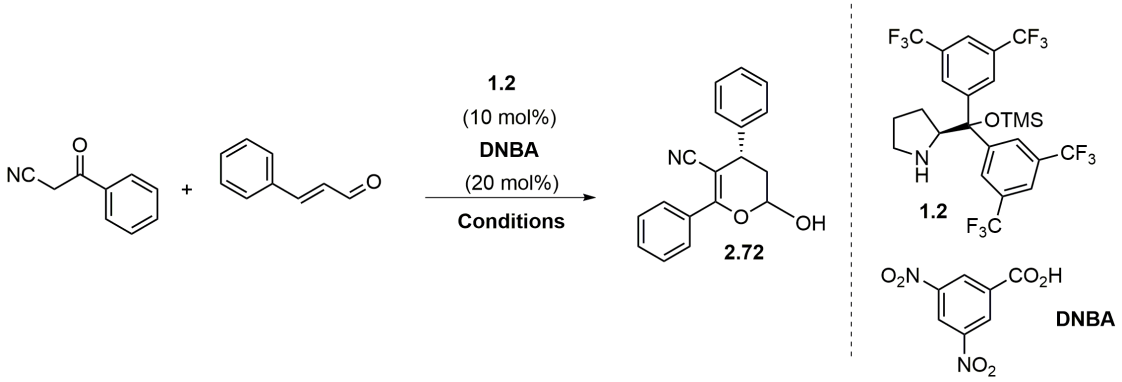


FIGURE 2.6.1- One-pot multiple bond-forming for the stereoselective synthesis of chiral tetrahydropyridines.

We previously mentioned that the use of enantiopure chiral aldehydes derived from organocatalytic transformations as substrates in stereoselective MCRs is an emerging field of research.[106] In this chapter we adapt the protocol of one-pot cascade approaches comprising asymmetric Michael additions to α,β-unsaturated aldehydes followed by I-MCRs to THP synthesis.

The first issue consists in the optimization of the organocatalytic conjugate addition of benzoyl acetonitrile to cinnamaldehyde using 10 mol% of **1.2** as organocatalyst and 20 mol% of 3,5-dinitrobenzoic acid with some modifications of the previously reported procedure[107] i.e., changed the solvent, catalyst and reaction time (TABLE 2.1).

TABLE 2.1- Optimization of the organocatalytic step.

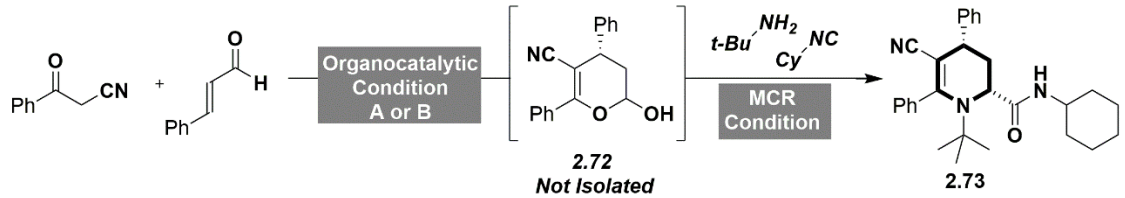


Entry	Solvent	Temp. /^{o}C	Time / h	Yield 2.72 (%)[b]	*ee* (%)[c]
1[a]	Toluene	0	48	70	90
2[a]	DCM	-10	3	40	92
3[a]	Toluene	-20	20	80	95
4[a]	DCM	-20	20	65	91
5[d]	Toluene	-20 (MW)	0.5	70	96

[a]Reaction performed with **1.12** (10 mol%), 3,5- dinitrobenzoic acid (20 mol%), cinnamaldehyde (0.10 mmol; 1 eq), benzoacetonitrile (0.15 mmol; 1.5 eq). [b] Determined after purification. [c] *e.e* was determined by HPLC analysis on a chiral stationary phase column. [d] Reaction performed with **1.12** (10 mol%), 3,5- dinitrobenzoic acid (20 mol%), cinnamaldehyde (0.10 mmol; 1 eq), benzoacetonitrile (0.15 mmol; 1.5 eq) in tolulene under microwave irradiated (300 W) at -20 ^{0}C for 30 min.

In this case the better conditions for the organocatalytic process were the corresponding to entry 5, albeit, the use of toluene at -20 ^{o}C could for 20 h it is also an excellent condition. This results lead us to hypothesised a one-pot formulation for the overall process.

TABLE 2.2- Optimization Studies for the One-Pot Organocatalytic Conjugate Addition/4-Center 3-Component Reaction.



Entry[c]	Solvent	Temp(°C)	Time (min)	Yield **2.73** (%)[d]	*dr* **2.73**[e]	*ee* **2.73** (%)[f]
1[a,g]	TFE	70	5	40	20:1	96
2[a,g]	TFE	70	10	60	20:1	96
3[a,g]	TFE	70	15	65	20:1	96
4[a,g]	TFE	70	20	71	20:1	96
5 [a,g]	TFE	70	40	76	10:1	96
6 [a,g]	TFE	60	20	65	20:1	96
7 [a,g]	TFE	85	20	61	9:1	96
8[a,g]	EtOH	70	20	35	9:1	96
10[a,g]	THF	70	20	23	9:1	96
11[a,g]	Toluene	70	20	36	9:1	96
12[b,g]	TFE	70	20	69	20:1	96

[a] **Condition A**: Reaction performed with catalyst **1.12** (10 mol%), 3,5- dinitrobenzoic acid (20 mol%), cinnamaldehyde (0.10 mmol; 1 eq), benzoacetonitrile (0.15 mmol; 1.5 eq) in tolulene at -20^0 C for 20h. [b] **Condition B**: Reaction performed with catalyst **1.12** (10 mol%), 3,5- dinitrobenzoic acid (20 mol%), cinnamaldehyde (0.10 mmol; 1 eq), benzoacetonitrile (0.15 mmol; 1.5 eq) in tolulene under microwave irradiated (300 W) at -20 ^{0}C for 30 min. [c] Reactions performed on 0.15 mmol scale and 2.0 mL total volume of solvent under microwave irradiation [d] Isolated yields after purification. [e] d.r. was determined by ^{1}H NMR analysis of the crude product. [f] *ee* was determined by HPLC analysis on a chiral stationary phase column. [g] Multicomponent reaction performed with addition of amine (0.15 mmol), isocyanide (0.15 mmol) and a mixture toluene/Solvent (1:1), with MW irradiation 20 min,70 ^{0}C.

Alternatively, we found that this first step could also be carried out under microwave irradiation (300 W) at -20 ^{o}C for only 30 min in good yield and excellent enantioselectivity. As depicted in TABLE 2.2, the subsequent multicomponent step was performed by adding trifluoroethanol (TFE) to the solution of cyclic hemiacetal **2.72** to reach a toluene/TFE 1:1 (v/v) solvent mixture, followed by addition of the amino and isocyanide components and stirring under microwave irradiation at 70 ^{o}C for 20 min.

The use of TFE - a polar protic solvent - is crucial for the success of the multicomponent event, as it is known from Ugi-type reactions based on isocyanides.[108] However, other nucleophilic alcohols such as MeOH and EtOH are not permitted, as a concomitant conjugate addition of the solvent can take place.

Overall, the one-pot procedure is completed within 50 min -i.e., the first organocatalytic reaction for 30 min and the multicomponent one for 20 min - to furnish the THP derivatives in good yields after purification.

The FIGURE 2.6 illustrate the proton NMR spectra for the tetrahydropyridines **2.73**. Taking close look, we can appreciate a few signals that allow us to see at1.11 ppm a singlet integrated to 9H of the *tert*-butyl group incorporated by the amine component. It is also noted at 5.4 ppm a doublet integrated to 1H and with a coupling constant of 8.1 Hz that correspond to NH of the amide bond formation.

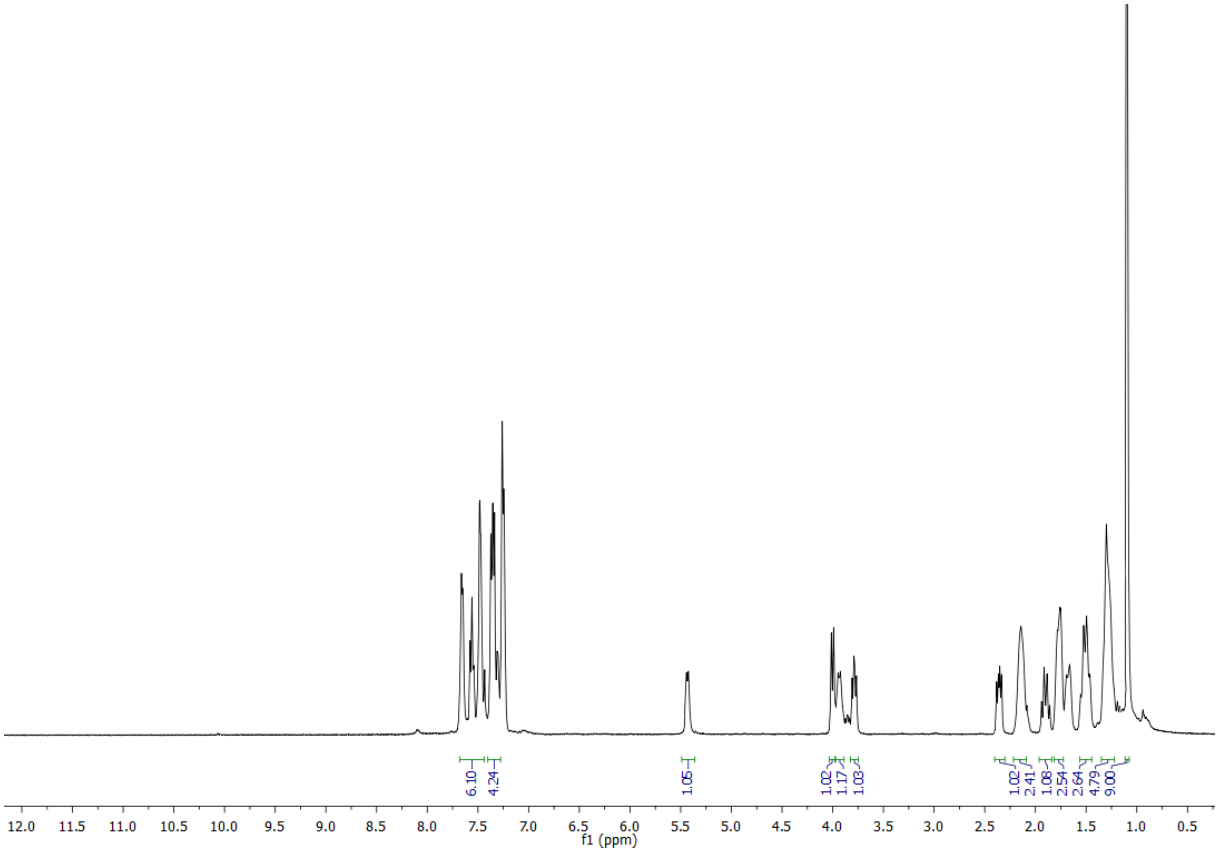
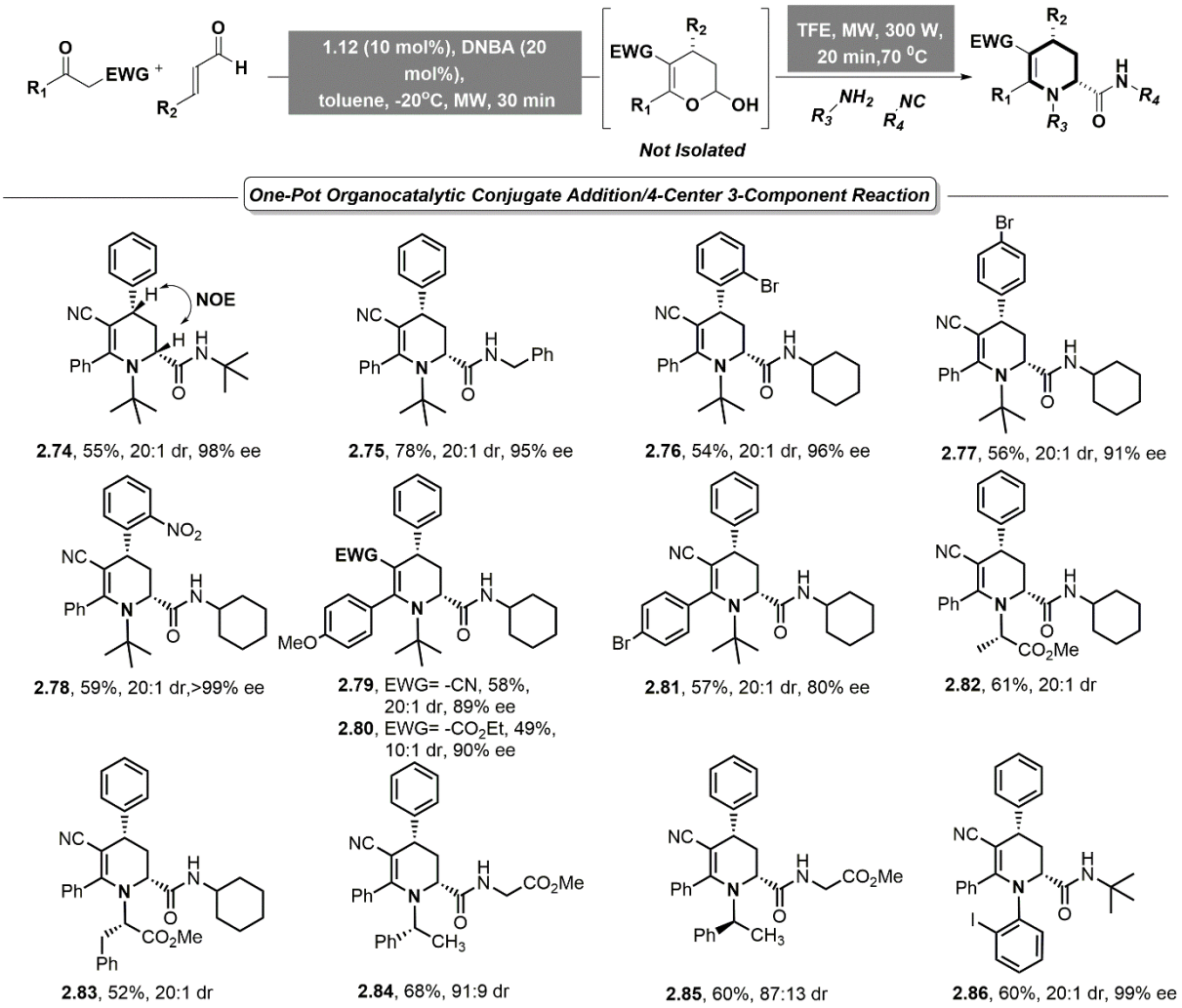


FIGURE 2.6.2- ^{1}H NMR spectra for compound **2.73**.

As shown in SCHEME 2.11, THPs (**2.74**- **2.81** and **2.86**) were produced with good to excellent enantio and diastereoselectivity by incorporating a variety of aliphatic and aromatic amines as well as commercially available isocyanides. Of note, the use of bulky amines, e.g., t-Bu and *o*-substituted aniline, led to excellent enantio and diastereoselectivies. Alternatively, the employment of chiral amines, such as the *R* and *S*-methylbenzyl amines as well as alanine and phenylalanine

methyl esters, furnished the THPs (**2.82** - **2.85**) in enantiopure form and excellent diastereoselectivity.

While the substrate scope of the amino and isocyanide components is remarkable, including amino acids and isocyanoacetate derivatives, the one-pot procedure worked well only with α,β-unsaturated aldehydes bearing an aryl substituent as R^1. Thus, the THPs were readily produced either using cinnamaldehyde and their derivatives (**2.76**, **2.77** and **2.78**), but they could not be obtained when R^1 was an aliphatic substituent. Furthermore, this protocol also allowed the introduction of molecular diversity by means of substituted β-keto nitriles and a β-keto ester analog. Gratifying, compounds **2.79**, **2.80** and **2.81** were obtained in good yield and high stereoselectivity.



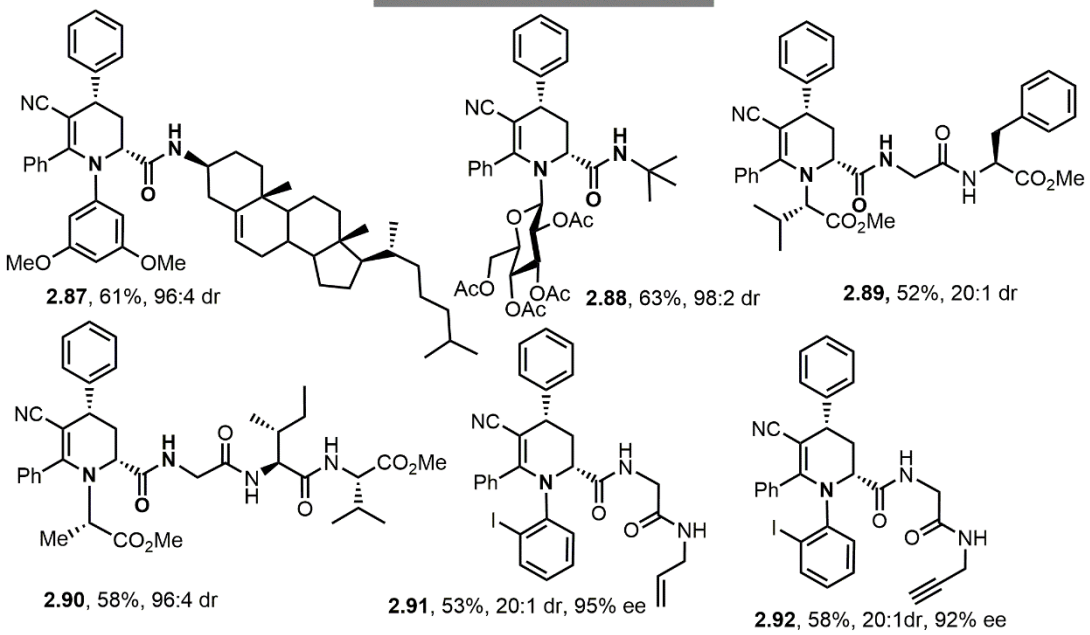
SCHEME 2.11- Organocascade and multicomponent synthesis of THP.

2.6.2 Stereoselective synthesis of chimeric THP derivatives

The conjugation of THPs to other chemically or biologically relevant molecules is a common approach in the pursuit of interesting biomedical and chemical applications.[109] This conjugation could also mimicry the bioactivity of natural occurring molecules and also improve the performance of the separate building blocks.

Based on this statement the structural diversity and complexity derived from the variation of the amino and isocyanide components are notable, thus enabling the preparation of chimeric THP derivatives incorporating very complex biomolecular fragments.

As depicted in the SCHEME 2.12, enantiomerically pure chimeric THP derivatives were efficiently produced in one-pot by reaction of cyclic hemiacetal **2.72** – derived from the organocatalytic step – with amine and isocyanides of steroidal, peptidic and monosaccharidic nature. Thus, THP-cholesterol derivative **2.87** was obtained with excellent diastereoselectivity by incorporation of cholesteryl isocyanide[110] and 3,5-dimethoxyaniline. The synthesis of *N*-glycosyl THP **2.88**, using peracetylated glucosyl amine, proved the possibility of incorporating sugar residues also with excellent diastereoselectivity. Similarly, the THP-peptide chimeras **2.89** and **2.90** – featuring the heterocycle embedded midway the peptide skeleton – were produced almost as a single stereoisomer using amino acid methyl esters and peptides as amino and isocyanide components, respectively. The use of functionalized isocyanoacetates[111] furnished another class of hybrid compounds **2.91** and **2.92** with allyl and propargyl scaffolds. The yields and enantioselectivities were excellent taking into consideration that four new bond are formed and complexity of the final product.

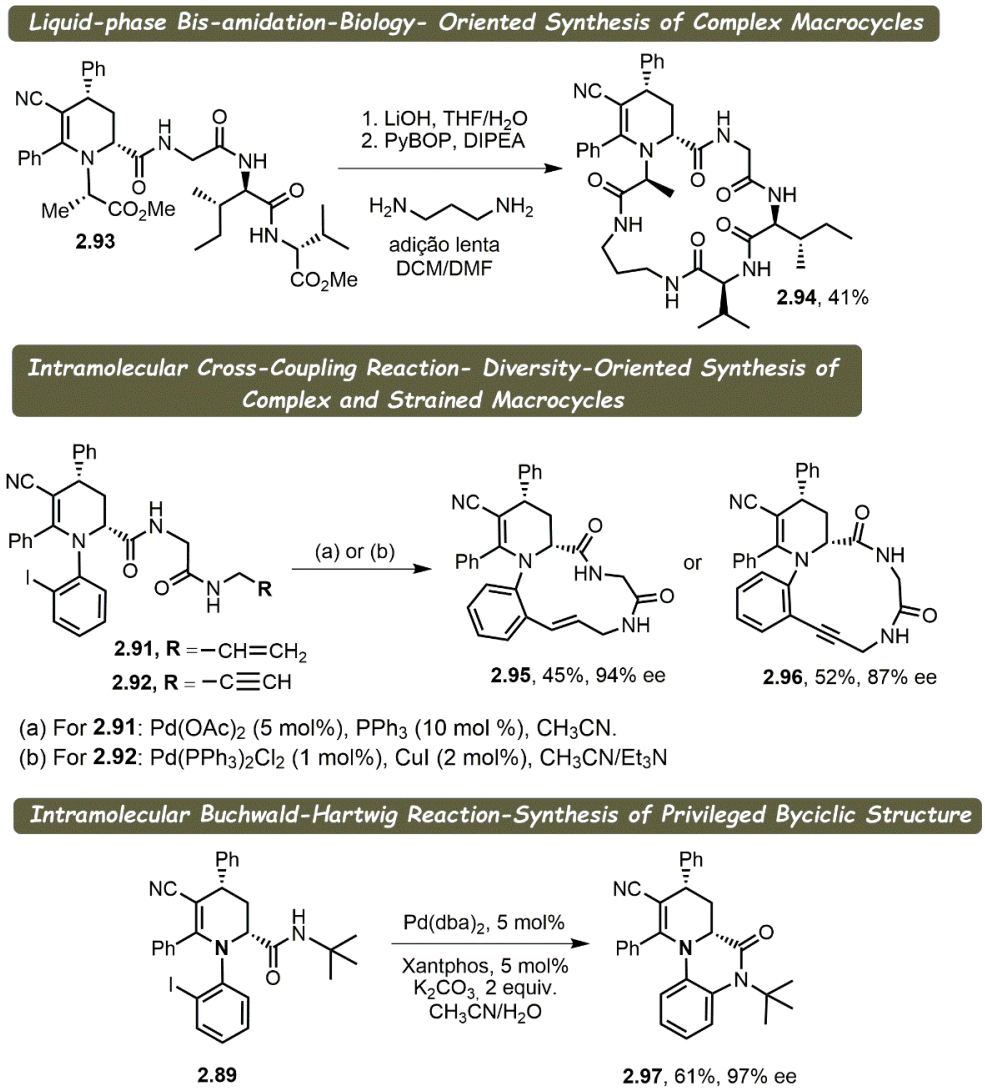


SCHEME 2.12- Small collection of THP-Chimeric compounds.

2.6.3 Novel post MCR derivatizations

In the previous section was mentioned the importance of the conjugation and synthesis of THP-hybrid compounds. We mentioned also that post-modifications of the U-4CR provide the synthesis of diverse and relevant scaffolds.

In this context, to extend the synthetic applications of this sequential multi bond-forming approach, we turned to implement post-MCR (macro)cyclization procedures. For this, we took advantage of the functionalities installed at R^3 and R^4 of the THP ring during the I-MCR.



SCHEME 2.13- Synthesis of THP conjugates by post-MCR derivatization.

As depicted in SCHEME 2.13, the THP-peptide chimera **2.90** was subjected to mild saponification (compound **2.93** is obtained) and subsequent macrocyclization with ethylendiamine by a double lactamization using PyBOP/DIPEA to produce the chimeric THP-peptide macrocycle **2.94** in 41% overall yield. The design of compounds **2.91** and **2.92** – incorporating propenyl and propargyl peptide substituents, respectively, as well as an *o*-iodo-phenyl group at the neighboring position – aimed at conducting subsequent Pd-catalyzed ring closing reactions. Thus, macrocycles **2.95** (45% yield) and **2.96** (52% yield) were obtained by Heck and Sonogashira cyclization protocols, respectively.[100,112] Finally, THP **2.89** was submitted to intramolecular Pd-catalyzed *N*-arylation using typical Buchwald-Hartwig conditions[113] to render the polycyclic THP derivative [114]**2.97** in 61% yield.

These interesting modifications achieved in this section, were planned by the incorporation of different functional group during the multicomponent

synthesis. Notice that for compound **2.96** a little racemisation occurred during the Sonogashira coupling. The formation of the macrocyclic compounds **2.95** and **2.96** were detected by ^{1}H NMR. For instance, the *trans* isomer of compound **2.95** was the compound detected, in this case the alkene protons appear as a doublet in 6.8 ppm and with coupling constant of 15 Hz, indicating the *trans* configuration of the final product.

2.7 Conclusions: Chapter 2

Summarizing, we have developed a powerful one-pot approach comprising an organocatalytic cascade followed by a multicomponent reaction, which was successfully used for the stereoselective synthesis of THPs and chimeric derivatives including peptidic, saccharidic and steroidal substituents. The method proved good to excellent enantio- and diastereoselectivity with the use of bulky and chiral amines. The installation of suitable functionalities at the THP skeleton enabled post-multicomponent macro- and polycyclizations, by means of lactamization and Pd-catalyzed ring closing procedures.

Chapter 3

3. Experimental Section

3.1 Experimental Section of Chapter 1

General Remarks

Melting points are uncorrected. 1H NMR and 13C NMR spectra were recorded at 400 MHz for 1H and 100 MHz for 13C, respectively. Chemical shifts (δ) are reported in parts per million relatives to the residual solvent signals, and coupling constants (J) are reported in hertz. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (Hybrid linear ion trap–orbitrap FT-MS and QqTOF/MS – Microtof – QII models). Flash column chromatography was carried out using silica gel 60 (230-400 mesh) and analytical thin layer chromatography (TLC) was performed using silica gel aluminum sheets. Visualization of the compounds was achieved by UV , vanillin solution or $KMnO_4$ .HPLC chromatograms were obtained on an apparatus with a LC-10AT Pump, SPD-10AUV-Vis Detector, SCL-10A System Controller, using a Chiralpak AD-H (4,6 mmØ × 250 mmL, particle size 5 µm), Chiralpak OD-H (4,6 mmØ × 250 mmL, particle size 5 µm), Chiralpak OJ-H (4,6 mmØ × 250 mmL, particle size 5 µm), Chiralpak AS-H (4.6 mmØ × 250 mmL, particle size 5 µm). Optical rotations were measured with a Polarimeterat 589 nm, 20 °C.

3.1.1 General one-pot reaction procedure A

The 1,3-dicarbonyl compound (0.25 mmol, 1 equiv.) was added to a stirring solution of catalyst **1.12** (0.025 mmol, 0.1 equiv.) and α,β-unsaturated aldehyde (0.33 mmol, 1.3 equiv) in CH_2Cl_2 (0.5 mL) at 10 ^oC in a 10 mL glass tube. The reaction mixture was stirred at that temperature for 48h and then allowed to reach room temperature. Trifluoroethanol (0.5 mL), the amine (0.33 mmol, 1.3 equiv.) and the isocyanide (0.33 mmol, 1.3 equiv.) were added and the glass tube was sealed and introduced in the microwave reactor. NEt_3 (0.33 mmol) was added when α amino acid and peptide methyl ester hydrochlorides were employed as amino components. The flask was irradiated for 15 min (300 W) under high-speed magnetic stirring, while the temperature was raised up to 70 °C. The reaction course was

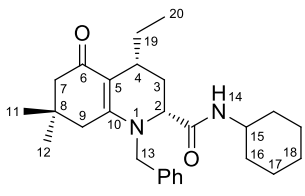
monitored by TLC, and additional cycles of 15 min were applied in cases of poor consumption of the starting material. The volatiles were concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

3.1.2 General one-pot reaction procedure B

The 1,3-dicarbonyl compound (0.25 mmol, 1 equiv.) was added to a stirring solution of catalyst **1.12** (0.025 mmol, 0.1 equiv.) and α,β-unsaturated aldehyde (0.33 mmol, 1.3 equiv) in CH_2Cl_2 (0.5 mL) at 10 ºC. The reaction mixture was stirred at that temperature for 48 h and then allowed to reach room temperature. Trifluoroethanol (0.5 mL), the amine (0.33 mmol, 1.3 equiv.) and the isocyanide (0.33 mmol, 1.3 equiv.) were added and the reaction mixture was stirred at room temperature for 36 h. The volatiles were concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

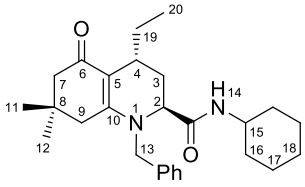
3.1.3 One Pot Synthesis of hidroquinolin-6-ones 1.30-1.46

Compound 1.30: Dimedone (35 mg, 0.25 mmol), trans-2-pentenal (32 µL, 0.33 mmol), benzylamine (36 µL, 0.33 mmol) and cyclohexylisocyanide (41 µL, 0.33 mmol) were reacted according to the general one-pot procedure A. Flash column chromatography purification (n-hexane/EtOAc 1:1) afforded the diastereomers cis (47.5 mg, 45%) and trans (34 mg, 32%) of compound 5a as pale yellow oils.



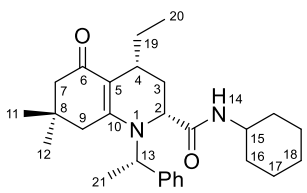
cis: R_f = 0.33 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -62.1 (*c* 6.0, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.27 (m, 3H, Ph); 7.10 (d, *J* = 7.2 Hz, 2H, Ph); 5.83 (d, *J*=8.1 Hz, 1H, H-14); 4.86 (d, *J*= 17.0 Hz, 1H, H-13a); 4.17 (d, *J* = 17.0 Hz, 1H, H-13b); 3.79 (d, *J*= 6.5Hz, 1H, H-2); 3.73 (m, 1H, H-15); 2.76 (m, 1H, H-4); 2.56 (d, *J* = 14.1 Hz, 1H, H-3a); 2.50(d, *J* = 16.1 Hz, 1H, H-9a); 2.34 (d, *J* = 16.2 Hz, 1H, H-9b); 2.27 (d, *J* = 16.1 Hz, 1H, H-7a); 2.18 (d, *J* = 16.2 Hz, 1H, H-7b); 2.04 (m, 1H); 1.93-1.85 (m, 2H, H-16a); 1.74-1.65 (m, 4H, H-19a, H-3b, H-17a); 142-1.32 (m, 4H, H-16b, H-17b); 1.20-1.11 (m, 2H, H-18); 1.05 (s, 3H, H-12); 1.02 (s, 3H, H-11);

0.98 (m, 1H, H-19b); 0.89 (m, 3H, H-20). The *cis* configuration was assigned based analysis of the NOESY spectrum. Important NOE contacts are: between H-14 (NH) and H-12 (axial methyl) as well as between H-14 and H-19 (methylene of the axial ethyl group). There are also NOE contacts between H-4 and H-2. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 194.4, 170.0 (C=O), 155.0, 136.6 (C), 129.2, 128.0, 126.0 (CH), 112.4 (C), 60.6 (CH), 53.9, 50.0 (CH_2), 48.4 (CH), 40.8 (CH_2), 33.1 (C), 33.0, 32.4 (CH_2), 30.3 (CH), 28.7, 28.4 (CH_3), 25.8, 25.6, 24.9, 24.7, 24.3(CH_2), 12.1 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 423.30011 $[M+H]^+$; calcd. for $C_{27}H_{39}N_2O_2$: 423.30060.



***trans*:** R_f = 0.16 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -33.3 (*c* 5.4, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 3H, Ph); 7.12 (d, *J* = 7.1 Hz, 2H, Ph); 5.54 (d, *J* = 8.6 Hz, 1H, H-14); 4.85 (d, *J* = 16.9 Hz, 1H, H-13a); 4.12 (d, *J* = 16.9 Hz, 1H, H-13b); 3.78 (m, 1H, H-15); 3.71 (dd, *J* = 10.3/5.0 Hz, 1H, H-2); 2.79 (m, 1H, H-4); 2.45 (d, *J* = 16.4 Hz, 1H, H-9a); 2.39 (d, *J* = 16.5 Hz, 1H, H-9b); 2.23 (d, *J* = 16.3 Hz, 1H, H-7a), 2.18 (d, *J* = 16.0 Hz, 1H, H-7b); 2.02 (m, 1H); 1.98 (m, 1H, H-3a); 1.92 (m, 1H, H-3b); 1.88 (m, 2H, H-16a); 1.71-1.54 (m, 5H, H-19a, H-17); 1.43-1.25 (m, 4H, H-16b, H-18); 1.17 (m, 1H, H-19b); 1.05 (s, 3H, H-12); 1.01 (s, 3H, H-11); 0.87 (t, *J* = 7.4 Hz, 3H, H-20). The *trans* configuration was assigned based analysis of the NOESY spectrum. Important NOE contacts are: between axial H-2 and H-12 (axial methyl) as well as between axial H-2 and H-19 (methylene of the axial ethyl group). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 170.7 (C=O), 156.9, 136.4 (C), 131.0, 129.1, 129.0, 128.0, 126.7 (CH), 112.7 (C), 59.5 (CH), 52.0, 49.3 (CH_2), 48.4 (CH), 40.9, 33.1 (CH_2), 32.1 (C), 30.5 (CH_2), 30.3 (CH), 29.1, 28.3 (CH_3), 27.6, 26.9, 25.5, 24.8, 23.8 (CH_2), 11.6 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 423.30012 $[M+H]^+$; calcd. for $C_{27}H_{39}N_2O_2$: 423.30060.

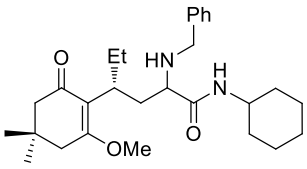
Compound 1.31



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), (*S*)-α-methylbenzylamine (43μL, 0.33 mmol) and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.31** (82 mg,

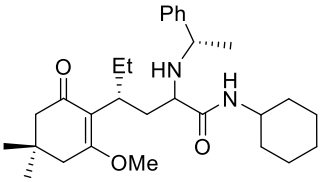
75%, isomer *cis*) as a pale yellow oil. R_f = 0.36 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -42.3 (*c* 3.5, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.21 (m, 3H, Ph); 7.07 (m, 2H, Ph); 6.00 (d, *J* = 8.3Hz, 1H, H-14); 5.15 (q, *J* = 7.0 Hz, 1H, H-13); 3.65 (m, 1H, H-15); 3.52 (dd, *J* = 6.0/1.8 Hz, 1H, H-2); 2.72 (m, 1H, *J* = 15.4 Hz, H-9a); 2.42 (m, 1H, H-4); 2.33 (d, *J* = 15.5 Hz, 1H, H-9b); 2.25 (m, 1H, H-9a); 2.22 (m, 1H, H-3a); 2.21(m, 2H, H-7); 1.86 (m, 2H, H-16a); 1.74 (m, 1H, H-17a); 1.64-1.56 (m, 4H, H-16b, 17b); 1.54 (d, *J* = 7.0 Hz, 3H, H-21); 1.37-1.23 (m, 2H, H-18); 1.12 (s, 3H); 1.07 (s, 3H); 0.92 (m, 1H, H-3b); 0.81-0.69 (m, 5H, H-19, H-20).^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 170.9 (C=O), 154.4, 139.1 (C), 128.8, 128.2, 126.9 (CH), 115.4 (C), 56.3, 54.9 (CH), 50.1, 48.2, 43.2(CH_2), 33.3 (C), 32.7(CH), 32.55, 31.1(CH_2), 30.5, 26.2(CH_3), 25.6(CH), 25.4, 24.8, 24.7, 23.3(CH_2), 17.7, 11.9 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 437.31629 $[M+H]^+$; calcd. for $C_{28}H_{41}N_2O_2$: 437.31684.

Compound 1.32



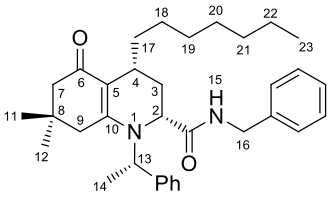
Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), benzylamine (36μL, 0.33 mmol) and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A using MeOH as solvent of the second multicomponent step. Flash column chromatography purification (*n*-hexane/EtOAc 9:1) afforded diastereomeric mixtures of **1.30** (41 mg, 42%) and **1.32** (28 mg, 25%) as colorless oils. **1.32:** R_f = 0.47 (*n*-hexane/EtOAc 9:1). dr: 74:26. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73, 9.49 (2×d, *J* = 9.4 Hz, 1H); 7.27-7.18 (m, 5H, Ph); 3.91-3.79 (m, 2H); 3.66-3.61 (m, 1H); 3.55 (s, 3H, OCH_3); 2.80, 2.60 (2×m, 1H); 2.48-2.37 (m, 3H); 2.19 (t, *J* = 13.8 Hz, 1H); 1.92-1.87 (m, 2H); 1.81-1.74 (m, 1H); 1.69-1.60 (m, 3H); 1.56-1.45 (m, 4H); 1.26-1.05 (m, 6H); 1.05, 1.04 (2×s, 3H); 1.03, 1.02 (2×s, 3H); 0.89, 0.77 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6 (C=O), 173.2 (C=O), 164.8 (C), 140.2 (C), 128.7 (2×CH), 128.5 (2×CH), 127.6 (CH), 110.6 (C), 59.9 (CH_3), 52.5 (CH_2), 51.9 (CH_2), 50.9 (CH), 48.8 (CH), 45.9(CH_2), 41.3 (C), 36.2 (CH), 35.6 (CH_2), 34.6 (CH_2), 33.8 (CH_2), 32.0 (CH_2), 29.8 (CH_3), 28.1 (CH_3), 25.6 (CH_2), 25.2 (CH_2), 13.0 (CH_2), 11.9 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 455.3279 $[M+H]^+$; calcd. for $C_{28}H_{43}N_2O_3$: 455.3274.

Compound 1.33



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), (*S*)-α-methylbenzylamine (43μL, 0.33 mmol)and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A using MeOH as solvent of the second multicomponent step. Flash column chromatography purification (*n*-hexane/EtOAc 9:1) afforded **1.31** (46 mg, 42%) and **1.33** (33 mg, 28%) as colorless oils. **1.33:** R_f = 0.47 (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (d, *J* = 9.8 Hz); 7.31-7.19 (m, 5H, Ph); 3.79 (q, *J* = 6.6 Hz, 1H); 3.78 (m, 1H); 3.57 (s, 3H, OCH_3); 3.46 (t, *J* = 6.7 Hz, 1H); 2.78 (br. m, 1H); 2.49-2.39 (m, 3H); 2.16 (d, *J* = 14.7 Hz, 1H); 2.00 (m, 1H); 1.83 (ddd, *J* = 13.0/7.2/3.0 Hz, 1H); 1.76-1.69 (m, 2H); 1.57-1.45 (m, 6H); 1.38 (d, *J* = 6.5 Hz, 1H); 1.34-1.31 (m, 1H); 1.27 (d, *J* = 6.5 Hz, 3H); 1.24-1.15 (m, 2H); 1.06 (s, 3H); 1.04 (s, 3H); 1.07-0.96 (m, 5H); 0.71 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4 (C=O), 173.2 (C=O), 165.6 (C), 144.6 (C), 128.6 (2×CH), 127.5 (2×CH), 126.7 (CH), 109.7 (C), 58.1 (CH), 55.6 (CH_3), 51.9 (CH_2), 51.2 (CH_2), 48.9 (CH), 45.9 (CH), 41.0 (C), 36.3 (CH), 35.4 (CH_2), 34.4 (CH_2), 33.8 (CH_2), 29.8 (CH_2), 28.2 (CH_3), 28.1 (CH_3), 25.6 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 25.1 (CH_3), 11.5 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 469.3436 $[M+H]^+$; calcd. for $C_{29}H_{45}N_2O_3$: 469.3430.

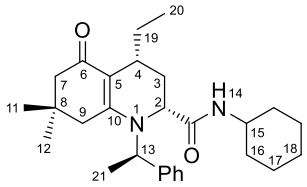
Compound 1.34



Dimedone (35 mg, 0.25 mmol), *trans*-2-decenal (61μL, 0.33 mmol), (*S*)-α-methylbenzylamine (43μL, 0.33 mmol)and benzylisocyanide (32.5 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.34** (79 mg, 71%, isomer *cis*) as a pale yellow oil. R_f = 0.50 (*n*-hexane/EtOAc 2:1). $[\alpha]_D^{20}$ -3.34 (*c* 5.5, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.28 (m, 6H, Ph); 7.23 (m, 2H, Ph); 7.13 (m, 2H, Ph); 6.26 (t, *J* = 5.2 Hz, 1H, H-15); 5.16 (q, *J*= 6.9 Hz, 1H, H-13); 4.42 (dd, *J* = 14.1/5.4 Hz, 1H, H-16a); 4.26 (dd, *J* = 14.1/5.2 Hz, 1H, H-16b); 3.66(d, *J* = 4.4 Hz, 1H, H-2); 2.69 (d, *J* = 15.5 Hz, 1H, H-9a); 2.60 (m, 1H, H-4); 2.29(d, *J* = 12.0 Hz, 1H, H-3a); 2.26 (d, *J* = 15.8 Hz, 1H, H-9b); 2.23(s, 2H, H-7); 1.56 (d, *J* = 7.0 Hz, 3H, H-14); 1.50 (m, H, H-17a); 1.36 (m, 1H, H-18a); 1.30-1.16 (m, 9H,

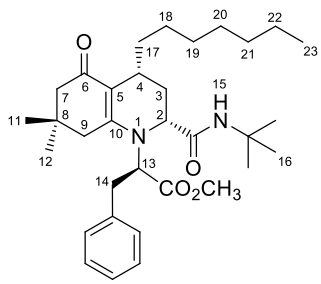
H-19, H-18b, H-20, H-21, H-22); 1.09 (s, 3H, H-11); 0.87 (m, 1H, H-3b); 0.85 (m, 3H, H-23); 0.83 (s, 3H, H-12); 0.82 (m, 1H, H-17b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 171.8 (C=O), 154.4, 139.3, 137.2 (C), 131.0, 129.0, 128.8, 128.3, 128.2, 128.0, 126.8 (CH), 115.3 (C), 56.2, 54.8 (CH), 50.0, 44.5, 42.9 (CH_2), 32.7 (C), 32.4, 32.0 (CH_2), 30.7 (CH_3), 29.7, 29.4 (CH_2), 28.5 (CH), 27.2 (CH_2), 26.0 (CH_3), 24.2, 22.7 (CH_2), 17.6, 14.2 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 515.36321 $[M+H]^+$; calcd. for $C_{34}H_{47}N_2O_2$: 515.36279.

Compound 1.35



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), (*R*)-α-methylbenzylamine (43μL, 0.33 mmol) and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.35** (82 mg, 75%) as a pale yellow oil. R_f = 0.36 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -10.36 (*c* 4.0, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.21 (m, 5H, Ph); 5.78 (d, *J* = 8.1Hz, 1H, H-14); 5.19 (q, *J*= 6.9 Hz, 1H, H-13); 3.83 (dd, *J*= 5.8/1.4 Hz, 1H, H-2); 3.39-3.36 (m, 1H, H-15); 2.73-2.62 (m, 2H, H-9a); 2.59 (dd, *J* = 11.8/5.9 Hz, 1H, H-4); 2.53 (d, *J* = 15.5 Hz, 1H, H-9b); 2.28 (s, 2H, H-7); 1.44 (d, *J* = 7.0 Hz, 3H, H-21); 1.41-1.32 (m, 2H); 1.24 (dd, *J* = 11.5/6.7 Hz, 2H); 1.19 (s, 1H, H-11); 1.16 (d, *J* = 8.2 Hz, 2H); 1.12 (s, 3H, H-12); 0.88 (t, *J* = 7.0 Hz, 3H, H-20); 0.84-0.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 170.0 (C=O), 154.3, 139.1 (C), 129.4, 129.2, 128.8, 128.4, 127.2 (CH), 118.1 (C), 57.3, 54.8 (CH), 50.4, 48.2, 44.1, 32.9 (CH_2), 32.8 (C), 31.4 (CH), 31.1(CH_2), 29.4, 26.6 (CH_3), 25.9, 25.7, 25.0, 24.7 (CH_2), 16.5, 12.3 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 437.31580 $[M+H]^+$; calcd. for $C_{28}H_{41}N_2O_2$: 437.31626.

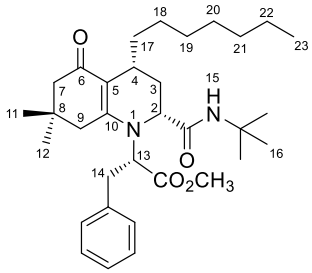
Compound 1.36



Dimedone (35 mg, 0.25 mmol), *trans*-2-decenal (61 μL, 0.33 mmol), D-phenylalanine methyl ester hydrochloride (97mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol) and *t*-butylisocyanide (37 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.36** (72 mg, 67%,

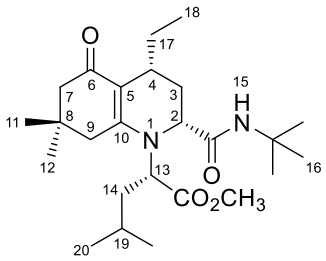
isomer *cis*) as a pale yellow oil. R_f = 0.55 (*n*-hexane/EtOAc 2:1). $[\alpha]_D^{20}$ 25.3 (*c* 1.10, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29-7.23 (m, 3H, Ph); 7.13 (m, 2H, Ph); 6.19 (s, 1H, H-15); 4.69 (t, *J*= 7.2 Hz, 1H, H-13); 4.01 (d, *J* = 4.3 Hz, 1H, H-2); 3.75(s, 3H, CH_3O); 3.26 (dd, *J* = 14.0/7.5 Hz, 1H, H-14a); 2.84 (dd, *J* = 14.0/6.9 Hz, 1H, H-14b); 2.66 (d, *J* = 14.6 Hz, 1H, H-3a); 2.60 (m, 1H, H-4); 2.27 (d, *J* = 15.3 Hz, 1H, H-9a); 2.18 (d, *J* = 16.8 MHz 1H, H-7a); 2.13 (d, *J* = 15.3 Hz, 1H, H-9b); 2.05(d, H, *J* = 16.7 Hz, H-7b); 1.47 (m, 1H, H-17a); 1.46 (m, 1H, H-18a); 1.40 (m, 1H, H-3b); 1.28 (s, 9H, H-16); 1.31-1.17 (m, 9H, H-18b, H-19, H-20, H-21, H-22); 1.05 (s, 6H, H-11, H-12); 0.98 (m, 1H, H-17b); 0.85 (t, *J* = 6.9 Hz, H-23).^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 170.4, 169.6 (C=O), 153.4, 136.2 (C), 129.3, 129.2, 128.1, 127.4 (CH), 117.1(C), 62.8, 56.1 (CH), 52.9 (CH_3), 51.9 (C), 49.9, 42.6, 35.8, 32.6 (CH_2), 32.5 (C), 32.1 (CH_2), 30.8 (CH_3), 29.6, 29.5, 27.5 (CH_2), 26.2 (CH_3), 24.5 (CH_2), 22.8 (CH_3), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 539.38367 $[M+H]^+$; calcd. for $C_{33}H_{51}N_2O_4$: 539.38433.

Compound 1.37



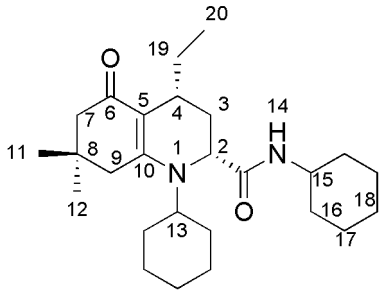
Dimedone (35 mg, 0.25 mmol), *trans*-2-decenal (61 μL, 0.33 mmol), L-phenylalanine methyl ester hydrochloride (97 mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol)and *t*-butylisocyanide (37 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.37** (74 mg, 69%, isomer *cis*) as a pale yellow oil. R_f = 0.50 (*n*-hexane/EtOAc 2:1). $[\alpha]_D^{20}$ -12.5 (*c* 1.10, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.24 (m, 3H, Ph); 7.15 (m, 2H, Ph); 6.17 (s, 1H, H-15); 4.68(t, *J* = 7.2 Hz, 1H, H-13); 4.05(d, *J* = 4.5 Hz, 1H, H-2); 3.73 (s, 3H, CH_3O); 3.24 (dd, *J* = 14.0/7.5 Hz, 1H, H-14a); 2.83 (dd, *J* = 14.0/7.0 Hz, 1H, H-14b); 2.68-2.55 (m, 2H); 2.29 (d, *J* = 14.4 Hz, 1H, H-9a); 2.22 (d, *J* = 7.5 MHz 1H); 2.18-2.24 (m, 1H); 2.08 (d, H, *J* = 16.6 Hz, H-7b); 1.46 (m, 1H, H-17a); 1.44 (m, 1H, H-18a); 1.36 (m, 1H, H-3b); 1.29 (s, 11H); 1.26-1.21 (m, 9H); 1.04 (s, 6H, H-11, H-12); 0.97 (m, 1H, H-17b); 0.85 (t, *J* = 7.0 Hz, H-23). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 170.3, 169.5 (C=O), 153.3, 136.2 (C), 130.9, 129.2, 128.7, 127.2 (CH), 62.7, 55.9 (CH), 52.7 (CH_3), 50.9 (C), 49.8, 42.5, 32.6, 32.5 (CH_2), 32.3 (C), 31.9 (CH_2), 30.7 (CH_3), 29.5, 29.4, 28.3 (CH_2), 27.3 (CH_3), 26.0 (CH_2), 24.4 (CH_3), 22.7 (CH_2), 14.1 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 539.38330 $[M+H]^+$; calcd. for $C_{33}H_{51}N_2O_4$: 580.38433.

Compound 1.38



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), L-leucine methyl ester hydrochloride (60 mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol)and *t*-butylisocyanide (37 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.38** (74 mg, 68%) as a pale yellow oil. R_f = 0.33 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -12.3 (*c* 1.10, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23 (br s, 1H, H-13); 3.80 (br s, 1H, H-2); 3.74 (s, 3H); 2.62 (d, *J* = 13.8 Hz, 1H, H-3); 2.26 (d, *J* = 16.9 Hz, 1H, H-7); 2.20 (d, *J* = 16.8 Hz, 1H, H-7); 2.10 (d, *J* = 15.3 Hz, 1H, H-9); 1.90 (br s, 2H); 1.73-1.55 (m, 4H); 1.49-1.39 (m, 2H); 1.31 (s, 9H); 1.08 (d, *J* = 16.8 Hz, 3H); 0.99 (dd, J=6.3/2.9 Hz, 6H); 0.91 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 171.6, 170.2 (C=O), 153.9, 116.7 (C), 62.2, 52.6 (CH), 51.2 (CH_3), 50.1 (CH), 45.2 (C), 42.5 (CH_2), 32.6 (C), 30.2 (CH), 29.7, 28.5 (CH_2), 28.3 (CH_3), 26.7 (CH_2), 25.4 (CH_3), 25.1, 23.2 (CH_2), 22.9, 22.3, 11.7 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 435.32068 $[M+H]^+$; calcd. for $C_{25}H_{43}N_2O_4$: 435.32173.

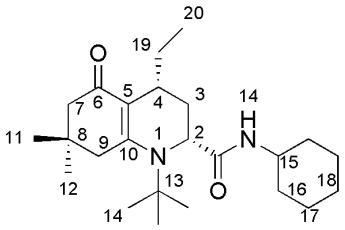
Compound 1.39



Dimedone (35 mg, 0.25 mmol), trans-2-pentenal (32 μL, 0.33 mmol), cyclohexylamine (38μL, 0.33 mmol) and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (n-hexane/EtOAc 1:1) afforded compound **1.39** (66 mg, 64%) as a pale yellow oil. Rf = 0.26 (n-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -4.9 (*c* 0.6, methanol, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (d, *J* = 8.1Hz, 1H, H-14); 3.93 (d, *J*= 6.0/1.6 Hz, 1H, H-2); 3.71 (m, 1H, H-13); 3.66-3.62 (m, 1H, H-15); 2.67 (d, *J* = 13.7 Hz, 1H, H-9a); 2.59-2.52 (m, 1H); 2.48 (d, *J*= 8.4 Hz, 1H, H-3a); 2.43 (m, 1H); 2.17(m, 2H, H-7); 1.85 (m, 1H, H-3b); 1.78 (m, 6H); 1.64 (m, 4H); 1.55 (m, 4H); 1.35 (s, 2H, H-9); 1.39 (m, 4H); 1.12 (s, 3H, H-12); 1.08 (d, 4H); 1.06 (s, 3H, H-11); 0.89 (t, 3H, H-20). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 170.9 (C=O), 154.3, 115.7, 58.6, (C), 55.9, 54.5, 50.4, 49.8 (CH_2), 47.9 (CH), 42.5, 30.0, 32.8 (CH_2), 32.4(C), 32.3, 32.2 (CH), 31.0, 30.9, 30.8, 30.4, 30.2 (CH_2), 29.2 (CH), 26.1, 25.9, 25.6, 25.4, 25.3, 25.1 (CH_2), 24.6 (CH_3),

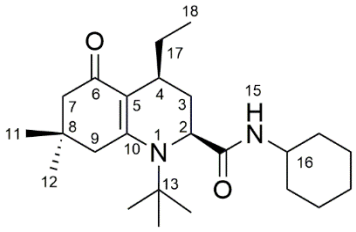
24.5, 24.2 (CH_2), 11.8, 10.6 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 415.63175 $[M+H]^+$; calcd. for $C_{26}H_{43}N_2O_2$: 415.63188.

Compound 1.40



Dimedone (35 mg, 0.25 mmol), trans-2-pentenal (32 μL, 0.33 mmol), *tert*-butylamine (35μL, 0.33 mmol) and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (n-hexane/EtOAc 1:1) afforded compound **1.40** (57 mg, 59%) as a pale yellow oil. Rf = 0.31 (n-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ -1.85 (*c* 5.4, methanol, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (d, *J* = 8.1Hz, 1H, H-14); 4.27 (dd, *J*= 5.8/2.4 Hz, 1H, H-2); 3.73-3.63 (m, 1H, H-15); 2.67 (d, *J* = 15.6 Hz, 1H, H-9a); 2.65 (dd, *J* = 13.9/2.3 Hz, 1H, H-3a); 2.56-2.52 (m, 1H, H-4); 2.49 (dd, *J* = 15.1/1.5 Hz, 1H, H-7a); 2.18 (d, *J* = 16.0 Hz, 1H, H-9b); 1.86 (m, 1H, H-3b); 1.79 (m, 2H, H-16); 1.66 (m, 2H); 1.60 (m, 2H); 1.45 (s, 9H, H-14); 1.32 (m, 4H); 1.14 (m, 1H); 1.08 (s, 3H, H-11); 1.05 (s, 3H, H-12); 1.06 (m, 1H); 0.88 (t, *J* = 16.0 Hz, 3H, H-20). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 171.3 (C=O), 155.8, 118.7, 60.9, (C), 57.2, 50.5, 48.3, 46.3 (CH_2), 33.1 (CH), 32.9 (C), 30.6, 29.8 (CH), 26.8, 25.4, 25.3, 24.9, (CH_2), 24.8, 24.7, 23.9, 11.7 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 389.58342 $[M+H]^+$; calcd. for $C_{24}H_{41}N_2O_2$: 389.58357.

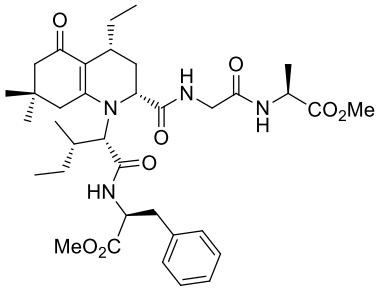
Compound 1.41



Dimedone (35 mg, 0.25 mmol), trans-2-pentenal (32 μL, 0.33 mmol), *tert*-butilamine (35μL, 0.33 mmol) and cyclohexylisocyanide (41 μL, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (n-hexane/EtOAc 1:1) afforded compound **1.41** (63 mg, 65%) as a pale yellow oil. Rf = 0.31 (nhexane/EtOAc 1:1). +2.5 (*c* 6.4, methanol, 20°C). 1H NMR (400 MHz, CDCl3): δ = 6.07 (d, *J* = 8.1Hz, 1H, H-14); 4.27 (dd, *J*= 5.8/2.4 Hz, 1H, H-2); 3.73-3.63 (m, 1H, H-15); 2.67 (d, *J* = 15.6 Hz, 1H, H-9a); 2.65 (dd, *J* = 13.9/2.3 Hz, 1H, H-3a); 2.56-2.52 (m, 1H, H-4); 2.49 (dd, *J* = 15.1/1.5 Hz, 1H, H-7a); 2.18 (d, *J* = 16.0 Hz, 1H, H-9b); 1.86 (m, 1H, H-3b); 1.79 (m, 2H, H-16); 1.66 (m, 2H); 1.60 (m, 2H); 1.45 (s, 9H, H-14); 1.32 (m, 4H); 1.14 (m, 1H); 1.08 (s, 3H, H-11); 1.05 (s, 3H, H-12); 1.06 (m, 1H);

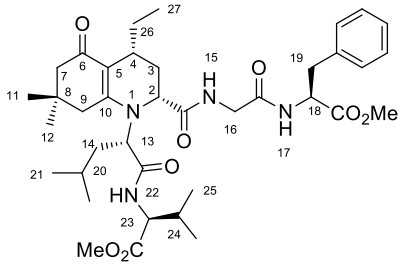
0.88 (t, *J* = 16.0 Hz, 3H, H-20). 13C NMR (100 MHz, CDCl3): δ = 195.5, 171.3 (C=O), 155.8, 118.7, 60.9, (C), 57.2, 50.5, 48.3, 46.3 (CH2), 33.1 (CH), 32.9 (C), 30.6, 29.8 (CH), 26.8, 25.4, 25.3, 24.9, (CH2), 24.8, 24.7, 23.9, 11.7 (CH3). HRMS (ESI-FTQQTOF) *m/z*: 389.58342 [M+H]+; calcd. for C24H41N2O2: 389.58357.

Compound 1.42



Dimedone (**1**, 35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), HCl·Ile-Phe-OMe (109 mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol) and CN-Gly-Ala-OMe (56 mg, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **1.42** (89 mg, 52%) as a pale yellow amorphous solid. R_f = 0.43 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{20}$ 10.7 (*c* 6.15, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22-7.11 (m, 5H, Ph); 7.02 (m, 1H, N*H*); 6.85 (m, N*H*); 4.78 (m, 1H); 4.54 (m, 1H), 4.26 (m, 1H), 4.21 (m, 1H), 3.71 (s, 3H, OCH_3); 3.69 (s, 3H, OCH_3); 3.23 (dd, *J* = 14.1/4.7 Hz, 1H); 3.13-3.06 (m, 1H); 2.89 (d, *J* = 5.6 Hz, 1H); 2.78 (d, *J* = 15.8 Hz, 1H); 2.55 (m, 1H); 2.33 (m, 1H); 2.19-2.03 (m, 2H); 1.67 (m, 2H); 1.39 (d, *J* = 7.2 Hz, 3H); 1.18 (s, 3H); 1.04 (m, 1H); 0.98 (s, 3H); 0.92 (d, *J* = 6.7 Hz, 3H); 0.84-0.74 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 173.1, 172.4, 171.4, 169.8, 167.8 (C=O), 154.3, 137.1 (C), 130.9, 129.1, 120.0, 128.5, 126.8 (CH), 115.5 (C), 64.9, 56.5, 54.7 (CH), 53.3, 52.8 (CH_3), 49.9 (CH_2), 48.5 (CH), 47.8, 47.0 (CH_2), 45.1, 40.6 (CH), 37.7, 37.0 (CH_2), 34.1 (C), 31.7, 30.3 (CH_2), 29.2, 28.4 (CH_3), 27.7 (CH_2), 19.1, 18.3, 16.1 12.6, 11.4 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 669.38477 $[M+H]^+$; calcd. for $C_{36}H_{53}N_4O_8$: 669.38579.

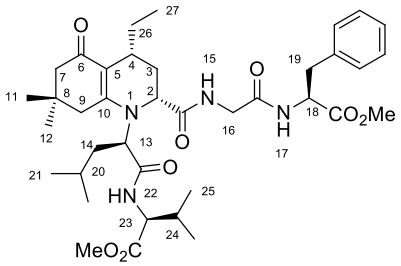
Compound 1.43



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), HCl·Leu-Val-OMe (92 mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol)and CN-Gly-Phe-OMe (81 mg, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:2) afforded compound **1.43** (111 mg, 64%) as a pale yellow amorphous solid. R_f = 0.37 (*n*-hexane/EtOAc 1:3). $[\alpha]_D^{20}$ 14.8 (*c* 1.10, acetone, 20°C).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.10 (m, 3H, Ph); 7.08-7.01 (m, 2H, Ph);

6.41 (d, *J* = 7.0 Hz, 1H, H-17); 4.85 (dd, *J* = 13.8/6.4 Hz, 1H, H-18); 4.33 (dd, *J* = 8.1/5.8 Hz, 1H, H-23); 4.05 (dd, *J* = 7.4/6.0 Hz, 1H, H-2); 3.98 (d, *J* = 5.0 Hz, 2H, H-16); 3.78 (dd, *J* = 7.6/5.7 Hz, 1H, H-13); 3.74 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 3.15 (dd, *J* = 13.9/6.2 Hz, 1H, H-19a); 3.08 (dd, *J* = 13.8/6.8 Hz, 1H, H-19b); 2.69 (m, 1H, H-4); 2.54 (m, 1H, H-3a); 2.30 (d, *J* = 5.0 Hz 1H, H-9a); 2.26-2.22 (d, *J* = 5.0 Hz, 1H, H-9b); 2.19 (d, *J* = 3.6 Hz, 1H, H-7a); 2.18 (m, 1H, H-24); 2.13 (d, *J* = 3.6 Hz, 1H, H-7b); 1.96-1.90 (m, 1H, H-14a); 1.76 (m, 1H, H-3b); 1.65 (m, 1H, H-20); 1.62 (m, 1H, H-14b); 1.57-1.52 (m, 1H, H-26a); 1.02 (s, 6H, H-11, H-12); 0.96 (d, *J* = 6.7 Hz, 6H, H-21); 0.93 (d, *J* = 6.7 Hz, 6H, H-25); 0.85 (t, *J* = 7.1 Hz, 3H, H-27);0.84 (m, 1H, H-26b).^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 173.0, 172.4, 171.8, 171.6, 167.8 (C=O), 156.1, 135.6 (C), 129.3, 128.7, 127.3 (CH), 112.9 (C), 65.6, 63.6, 58.5, 53.4 (CH), 52.5, 52.2 (CH_3), 50.5, 43.1, 41.4, 38.8, 37.8 (CH_2), 30.4, 29.8 (CH), 29.4, 26.8 (CH_3), 25.9 (CH_2), 25.8 (CH), 24.9 (CH_2), 23.1, 22.7, 19.1, 18.2, 11.8 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 696.40871 $[M+H]^+$; calcd. for $C_{38}H_{57}N_4O_8$: 696.40857.

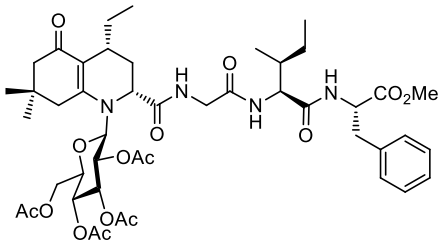
Compound 1.44



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), HCl·Leu-Val-OMe (92 mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol)and CN-Gly-Phe-OMe (81 mg, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 1:2) afforded compound **1.44** (104 mg, 61%) as a pale yellow amorphous solid. R_f = 0.38 (*n*-hexane/EtOAc 1:3). $[\alpha]_D^{20}$ 10.5 (*c* 1.15, acetone, 20°C).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.6 Hz, 1H, H-22); 7.25-7.22 (m, 3H, Ph); 7.13-7.09 (m, 2H, Ph); 6.72 (d, *J* = 6.0 Hz, 1H, H-15); 6.69 (s, 1H, H-17); 4.82 (dd, *J* = 14.3/6.6 Hz, 1H, H-18); 4.42 (dd, *J* = 8.3/5.6 Hz, 1H, H-23); 4.35 (dd, *J* = 7.5/6.0 Hz, 1H, H-13); 4.14-4.08 (m, 1H, H-2); 3.81 (d, *J* = 5.0 Hz, 2H, H-16); 3.68 (s, 3H, OCH_3); 3.66 (s, 3H, OCH_3); 3.15 (dd, *J* = 13.9/6.2 Hz, 1H, H-19a); 3.06 (dd, *J* = 13.8/6.8 Hz, 1H, H-19b); 2.59 (m, 1H, H-4); 2.53 (m, 1H, H-3a); 2.45 (d, *J* = 5.0 Hz 1H, H-9a); 2.35-2.32 (m, 1H, H-9b); 2.30 (d, *J* = 3.7 Hz, 1H, H-7a); 2.25-2.20 (m, 1H, H-7b); 2.19 (m, 1H, H-24); 1.99-1.89 (m, 1H, H-14a); 1.68 (m, 1H, H-26a); 1.60 (d, *J* = 6.3 Hz, 1H, H-3b); 1.57-1.52 (m, 1H, H-14b); 1.12 (s, 6H, H-11, H-12); 0.95 (d, *J* = 6.9 Hz, 6H, H-21); 0.93 (d, *J* = 6.7 Hz, 6H, H-25); 0.85 (t, *J* = 7.0 Hz, 3H, H-27); 0.84 (m, 1H, H-26b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 173.1 172.5, 172.1, 171.7,

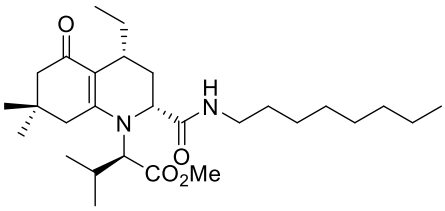
168.6 (C=O), 156.5, 136.4 (C), 129.6, 129.1, 129.0, 127.6 (CH), 116.4 (C), 61.3, 58.5, 55.2, 53.9 (CH), 52.7, 52.6 (CH_3), 50.5, 43.8 (CH_2), 43.0 (CH), 41.5 (C), 39.3, 39.1 (CH), 38.3, 32.9, 31.1 (CH_2), 30.7, 26.6, 25.9 (CH_3), 25.6 (CH), 25.1, 23.4, 22.7, 19.7, 18.7, 12.0 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 696.40971 $[M+H]^+$; calcd. for $C_{38}H_{57}N_4O_8$: 696.40882.

Compound 1.45



Dimedone (**1**, 35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), β-D-glucosyl amine (114.5 mg, 0.33 mmol), and CN-Gly-Ile-Phe-OMe (118 mg, 0.33 mmol) were reacted according to the general procedure B. Flash column chromatography purification (CH_2Cl_2/EtOAc 5:1) afforded compound **1.45** (134 mg, 59%) as a pale yellow amorphous solid. R_f = 0.37 (CH_2Cl_2/EtOAc 5:1). $[\alpha]^{20}_D$ 12.5 (*c* 1.10, acetone, 20°C) ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.30-7.22 (m, 4H, Ph, N*H*); 7.09 (d, *J* = 6.5 Hz, 2H, Ph); 6.99 (d, *J* = 8.2 Hz, 1H, N*H*); 6.36 (d, *J* = 7.8 Hz, 1H, N*H*); 5.37 (m, 1H); 5.27 (m, 1H); 5.10 (dd, *J* = 10.3/5.1 Hz, 1H); 5.04 (t, *J* = 9.7 Hz, 1H); 4.91-4.85 (m, 1H); 4.77 (m, 1H); 4.33-4.18 (m, 5H); 4.10 (dd, *J* = 18.0/8.3 Hz, 2H); 3.73 (s, 3H, OCH_3); 3.15 (dd, *J* = 13.9/5.7 Hz, 1H); 3.07 (dd, *J* = 13.9/6.3 Hz, 1H); 2.65-2.56 (m, 2H); 2.26-2.13 (m, 4H); 2.08, 2.06, 2.02, 2.01 (4×s, 12H, 4×Ac); 1.91 (m, 1H); 1.85 (br. m, 1H); 1.74-1.67 (m, 2H); 1.60-1.52 (m, 2H); 1.40 (br. s, 2H); 1.24 (s, 3H); 1.16-1.09 (m, 2H); 1.04 (t, *J* = 5.0 Hz, 3H); 1.01 (s, 3H); 0.98 (d, *J* = 6.7 Hz, 3H); 0.92-0.84 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 171.5, 170.7, 170.6, 170.4, 169.9, 169.5, 169.1, 168.4(C=O), 162.3, 135.4(C), 130.9, 129.2, 128.8, 128.7, 127.3(CH), 113.7(C), 84.4, 79.9, 73.0, 71.1, 70.3, 68.6 (CH), 62.4 (CH_2), 57.8, 53.1 (CH), 52.5 (CH_3), 51.00 (CH), 45.1, 42.6 (CH_2), 42.5 (CH), 42.4 (CH_2), 37.8 (C), 37.3, 32.1 (CH_2), 29.7, 28.8 (CH_3), 27.9, 24.8 (CH_2), 20.80, 20.62, 19.15, 15.17, 11.63, 11.21 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 913.44263 $[M+H]^+$; calcd. for $C_{46}H_{65}N_4O_{15}$: 913.44409.

Compound 1.46



Dimedone (35 mg, 0.25 mmol), *trans*-2-pentenal (32 μL, 0.33 mmol), L-valine methyl ester hydrochloride (46.2 mg, 0.33 mmol), Et_3N (46 μL, 0.33 mmol), and *n*-octilisocyanide (46 mg, 0.33 mmol) were reacted according to the general procedure A. Flash column chromatography purification (*n*-hexane/EtOAc 2:1) afforded compound **1.46** (97.7 mg, 58%) as a pale yellow oil. R_f = 0.32 (*n*-hexane/EtOAc 1.5:1). $[\alpha]_D^{20}$ -27.46 (*c* 2.50, acetone, 20°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12-8.02 (m, 2H); 6.94-6.90 (m, 2H); 4.66 (m, 1H); 4.22 (m, 1H); 4.16-4.08 (m, 3H); 3.78-3.68 (m, 2H); 3.61 (s, 3H); 3.30-3.22 (m, 1H); 3.16 (d, *J* = 4.3 Hz, 1H); 2.58-2.43 (m, 4H); 2.24-2.11 (m, 4H); 2.08 (s, 3H); 2.04-1.97 (m, 2H); 1.92-1.84 (m, 2H); 1.49-1.43 (m, 5H); 1.42-1.35 (m, 2H); 1.07-1.00 (m, 5H); 0.97-0.85 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 173.7, 172.0, 166.3 (C=O), 163.1, 158.7 (C), 126.9 (CH), 123.7, 118.3 (C), 114.6 (CH), 108.5 (C), 100.9, 66.7 (CH), 64.2 (CH_2), 60.7 (CH), 52.3 (CH_3), 51.1 (CH), 38.9 (CH_2), 35.1 (CH), 32.2, 31.4, 29.9, 26.3 (CH_2), 19.9, 17.7, 15.4, 14.6, 11.2 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 674.38396 $[M+H]^+$; calcd. for $C_{36}H_{56}N_3O_7S$: 674.38390.

3.2 Experimental Section of Chapter 2

3.2.1 General Aspects and Materials

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in parts per million relatives to the residual solvent signals, and coupling constants (*J*) are reported in hertz. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (Hybrid linear ion trap–orbitrap FT-MS /MS – and QqTOF Microtof – QII models). Reagents and materials were of the highest commercially available grade and used without further purification. Flash column chromatography was carried out using silica gel 60 (230-400 mesh) and analytical thin layer chromatography (TLC) was performed using silica gel aluminum sheets. Visualization of the compounds was achieved by UV or KMnO4. HPLC chromatograms were obtained on an apparatus with an LC-10AT Pump, SPD-10AUV-Vis Detector, SCL-10A System Controller, using a Chiralpak AD-H (4,6 mmØ × 250 mmL, particle size 5 μm), Chiralpak OD-H (4,6 mmØ × 250 mmL, particle size 5 μm), Chiralpak OJ-H (4,6 mmØ × 250 mmL, particle size 5 μm), Chiralpak AS-H (4,6 mmØ × 250 mmL, particle size 5 μm) columns as chiral stationary phases Optical rotations were measured with a Polarimeterat 589 nm, 20 °C.

3.2.2 General one-pot reaction procedure A

To a solution of **1.12** (0.01 mmol, 0.1 equiv.), 3,5-dinitrobenzoicacid (0.02 mmol, 0.2 equiv.), and α,β-unsaturated aldehyde (0.10 mmol, 1.0 equiv.) in toluene (1.0 mL) was added α-cyanoketones (0.15 mmol, 1.5 equiv.) at 0^{o}C. The resulting solution was stirred for 48h. 2,2,2-trifluoroethanol (1.0 mL), the amine (0.15 mmol, 1.5 equiv.) and the isocyanide (0.15 mmol, 1.5 equiv.) were added in a 10 mL glass tube and introduced in the microwave reactor. NEt_3 (0.15 mmol, 1.5 equiv.) was added when α-amino acid and peptide methyl ester hydrochlorides were employed as amino components. The flask was irradiated for 20 min (300 W) under high-speed magnetic stirring, while the temperature was raised up to 70 °C. The reaction course was monitored by TLC, and additional cycles of 5 min were applied in cases of poor

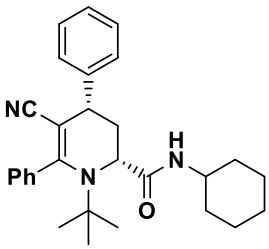
consumption of the starting material. The volatiles was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

3.2.3 General one-pot reaction procedure B

To a solution of **1.12** (0.01 mmol, 0.1 equiv.), 3,5-dinitrobenzoicacid (0.02 mmol, 0.2 equiv.), and α,β-unsaturated aldehyde (0.10 mmol, 1.0 equiv.) in toluene (1.0 mL) was added α-cyanoketones (0.15 mmol, 1.5 equiv.) and was irradiated for 30 min (300 W) under high-speed magnetic stirring at -20 ^{o}C. 2,2,2-trifluoroethanol (1.0 mL), the amine (0.15 mmol, 1.5 equiv.) and the isocyanide (0.15 mmol, 1.5 equiv.) were added and the glass tube was sealed. NEt_3 (0.15 mmol, 1.5 equiv.) was added when α-amino acid and peptide methyl ester hydrochlorides were employed as amino components. The flask was irradiated for 20 min (300 W) under high-speed magnetic stirring, while the temperature was raised up to 70 °C. The reaction course was monitored by TLC, and additional cycles of 5 min were applied in cases of poor consumption of the starting material. The volatiles was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

3.3 Sequential and Organocascade synthesis of tetrahydropyridine compounds 2.73-2.92

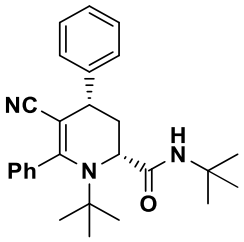
Compound 2.73



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), *tert*-butylamine (15.7 μL, 0.15 mmol), and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 4:1) afforded compound **2.73** (30.5 mg, 69%, isomer

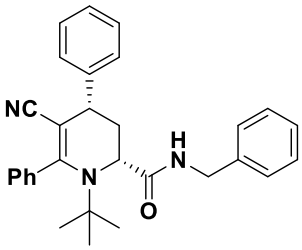
cis) as a yellow oil. $[\alpha]_D^{20}$ −2.4 (*c* 0.5, acetone, 20°C). R_f = 0.38 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74-7.42 (m, 6H); 7.39-7.28 (m, 4H); 5.43 (d, *J* = 8.1 Hz, 1H); 4.00 (d, *J* = 8.9 Hz, 1H); 3.97-3.90 (m, 1H,); 3.79 (dd, *J* = 10.1, 7.0 Hz, 1H); 2.36 (dd, *J* = 12.3, 7.0 Hz, 1H); 2.16-2.10 (m, 2H); 1.96-1.85 (m, 1H); 1.82-1.72 (m, 2H); 1.56-1.45 (m, 2H); 1.35-1.22 (m, 4H); 1.10 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.7, 30.5, 33.3, 33.8, 44.6, 47.3, 50.7, 51.3, 57.2, 69.7, 115.5, 116.1, 121.1, 123.7, 126.5, 126.9, 127.5, 128.7, 129.1, 129.3, 131.5, 133.3, 144.5, 149.8, 156.5, 160.9. HRMS (ESI-FT-QQTOF) *m/z*: 442.2869 $[M+H]^+$; calcd. for $C_{29}H_{36}N_3O$: 442.2858. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 5.6 min, t_R (minor)= 6.6 min, 96% ee.

Compound 2.74



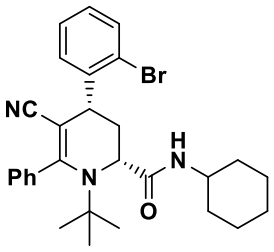
Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), *tert*-butylamine (15.7 μL, 0.15 mmol), and *tert*-butyl isocyanide (16.9 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 5:1) afforded compound **2.74** (23.0 mg, 55%, isomer *cis*) as a yellow oil. $[\alpha]_D^{20}$ −6.8 (*c* 0.4, acetone, 20°C). R_f = 0.40 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.28 (m, 6H); 7.24-7.14 (m, 4H); 5.05 (brs, 1H); 4.74 (ddd, *J* = 7.9, 7.0, 0.8 Hz, 1H); 4.13-4.06 (m, 1H,); 2.69 (dt, *J* = 12.0, 7.0 Hz, 1H); 1.49 (s, 9H), 1.47 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3, 30.4, 41.8, 43.2, 47.2, 48.3, 52.3, 117.4, 21.7, 126.8, 126.9, 127.2, 127.7, 128.5, 128.8, 129.2, 131.3, 143.7, 147.8, 156.9, 162.9. HRMS (ESI-FT-QQTOF) *m/z*: 416.2711 $[M+H]^+$; calcd. for $C_{27}H_{34}N_3O$: 416.2702. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OJ-H column (*n*-hexane/*i*-PrOH 95:5) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 18.7 min, t_R (minor)= 33.7 min, 98% ee.

Compound 2.75



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), *tert*-butylamine (15.7 μL, 0.15 mmol), and benzyl isocyanide (18.3 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/ EtOAc 5:1) afforded compound **2.75** (35.1 mg, 78%, isomer *cis*) as a dark yellow oil. $[\alpha]_D^{20}$ −6.7 (*c* 0.5, acetone, 20°C). R_f = 0.40 (*n*-hexane/CH_2Cl_2 1:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 12H); 7.24-7.16 (m, 3H); 5.71 (brs, 1H); 3.99 (d, *J* = 8.8 Hz, 1H); 3.75 (dd, *J* = 12.4, 5.0 Hz, 1H); 3.70 (d, *J* = 5.0 Hz, 1H); 3.63 (d, *J* = 10.9 Hz, 2H); 2.14 (m, 1H); 1.93 (m, 1H); 1.42 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3, 39.4, 48.1, 48.6, 50.9, 51.7, 63.6, 63.9, 71.5, 122.7, 126.6, 126.9, 127.4, 127.5, 127.7, 127.8, 128.1, 128.2, 128.7, 139.9, 143.8, 144.3, 156.7. HRMS (ESI-FT-QQTOF) *m/z*: 450.2551 $[M+H]^+$; calcd. for $C_{30}H_{32}N_3O$: 450.2545. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.5 mL/min, UV-detection at λ= 254 nm: t_R (major)= 15.6 min, t_R (minor)= 17.3 min, 95% ee.

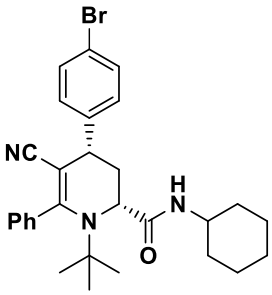
Compound 2.76



Benzoylacetontrile (21.8 mg, 0.15 mmol), *o*-bromo-cinnamaldehyde (19.9 mg, 0.10 mmol), *tert*-butylamine (15.7 μL, 0.15 mmol), and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded compound **2.76** (28.1 mg, 54%, isomer *cis*) as a pale yellow solid. $[\alpha]_D^{20}$ −2.2 (*c* 0.6, acetone, 20°C). R_f = 0.36 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83-7.76 (m, 1H); 7.66-7.52 (m, 2H); 7.50-7.41 (m, 2H); 7.37-7.11 (m, 3H); 7.05-6.96 (m, 1H); 5.42 (d, *J* =

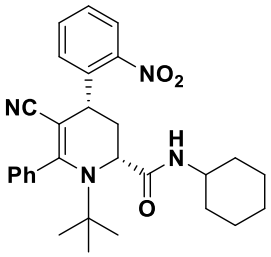
8.5 Hz, 1H); 4.21 (d, *J* = 9.0 Hz, 1H); 3.92-3.78 (m, 1H); 3.46 (dd, *J* = 10.2, 7.1 Hz, 1H); 2.19-2.11 (m, 1H); 2.10-1.97 (m, 2H); 1.84-1.73 (m, 1H); 1.72-1.61 (m, 2H); 1.47-1.32 (m, 2H); 1.27-1.09 (m, 4H); 0.95 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.4, 25.7, 30.5, 33.2, 33.9, 43.2, 47.0, 50.7, 51.4, 56.5, 67.5, 112.7, 120.9, 125.9, 127.5, 128.1, 128.9, 128.8, 129.2, 132.2, 133.3, 133.5, 133.8, 142.7, 147.3, 155.8. HRMS (ESI-FT-QQTOF) *m/z*: 520.1971 $[M+H]^+$; calcd. for $C_{29}H_{35}BrN_3O$: 520.1964. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.5 mL/min, UV-detection at λ= 254 nm: t_R (major)= 13.1 min, t_R (minor)= 14.5 min, 96% ee.

Compound 2.77



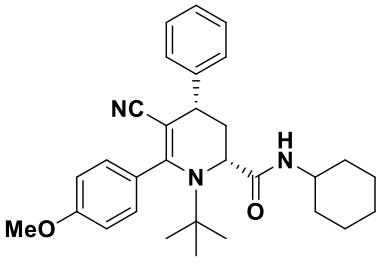
Benzoylacetontrile (21.8 mg, 0.15 mmol), *trans*-4-bromocinnamaldehyde (19.9 mg, 0.10 mmol), *tert*-butylamine (15.7 µL, 0.15 mmol), and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded compound **2.77** (29.1 mg, 56%, isomer *cis*) as a pale yellow solid. $[\alpha]_D^{20}$ −1.3 (*c* 0.4, acetone, 20°C). R_f = 0.38 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94-7.85 (m, 1H); 7.65-7.47 (m, 3H); 7.45-7.35 (m, 3H); 7.11-7.05 (m, 2H); 5.42 (d, *J* = 8.6 Hz, 1H); 3.94-3.83 (m, 2H); 3.69 (dd, *J* = 10.2, 7.1 Hz, 1H); 2.29-2.21 (m, 1H); 1.91-1.79 (m, 1H); 1.77-1.67 (m, 2H); 1.66-1.59 (m, 2H); 1.54-1.38 (m, 2H); 1.32- 1.16 (m, 4H); 1.05 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.3, 25.7, 30.5, 33.3, 33.8, 44.5, 46.9 , 50.8, 51.4, 57.2, 69.2, 120.3, 120.9, 124.3, 128.7, 128.8, 129.2, 129.9, 131.8, 132.6, 133.5, 143.6, 148.0, 155.9, 161.1. HRMS (ESI-FT-QQTOF) *m/z*: 520.1970 $[M+H]^+$; calcd. for $C_{29}H_{35}BrN_3O$: 520.1964. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AS-H column (*n*-hexane/*i*-PrOH 90:10) at 0.5 mL/min, UV-detection at λ= 254 nm: t_R (major)= 6.1 min, t_R (minor)= 6.9 min, 91% ee.

Compound 2.78



Benzoylacetontrile (21.8 mg, 0.15 mmol), *trans*-2-nitrocinnamaldehyde (17.7 mg, 0.10 mmol), *tert*-butylamine (15.7 µL, 0.15 mmol), and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 5:1) afforded compound **2.78** (28.7 mg, 59%) as a yellow solid. $[\alpha]_D^{20}$ −2.3 (*c* 0.5, acetone, 20°C). R_f = 0.32 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08-8.04 (m, 2H); 7.91 (dd, *J* = 8.1, 1.3 Hz, 1H); 7.68-7.59 (m, 2H); 7.53-7.46 (m, 3H); 3.45-7.38 (m, 1H); 5.91 (dd, *J* = 7.6, 3.2 Hz, 1H); 5.39 (d, *J* = 8.7 Hz, 1H); 4.84 (dd, *J* = 7.9, 5.8 Hz, 1H); 3.93-3.79 (m, 1H); 2.84-2.75 (m, 1H); 2.16-2.12 (m, 1H); 1.79-1.58 (m, 4H); 1.50-1.32 (m, 3H); 1,25 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 24.2, 25.5, 30.5, 33.4, 33.7, 39.3, 44.9, 52.3, 56.5, 60.5, 78.4, 119.2, 124.9, 128.1, 128.5, 128.75, 129.1, 130.0, 133.8, 133.9, 136.1, 138.2, 144.7, 149.8, 156.8, 167.6. HRMS (ESI-FT-QQTOF) *m/z*: 487.2721 $[M+H]^+$; calcd. for $C_{29}H_{35}N_4O_3$: 487.2709. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OJ-H column (n-hexane/i-PrOH 90:10) at 1.0 mL/min, UV-detection at λ= 254 nm: t_R (major)= 45.5 min, t_R (minor)= 53.2 min, >99% ee.

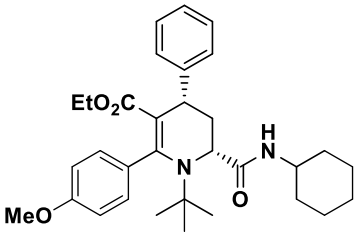
Compound 2.79



4-Methoxybenzoylacetontrile (26.4 mg, 0.15 mmol), cinnamaldehyde (12.6 µL, 0.10 mmol), *tert*-butylamine (15.7 µL, 0.15 mmol), and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded compound **2.79** (27.4 mg, 58%) as a yellow solid. $[\alpha]_D^{20}$ −2.6 (*c* 0.6, acetone, 20°C). R_f = 0.34 (*n*-hexane/

EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91-7.84 (m, 1H); 7.38-7.33 (m, 1H); 7.25-7.19 (m, 2H); 7.17-7.10 (m, 4H); 6.94-6.90 (m, 1H); 5.30 (d, *J* = 8.4 Hz, 1H); 3.89 (d, *J* = 8.9 Hz, 1H); 3.82 (s, 3H); 3.67 (dd, *J* = 10.1/ 7.1 Hz, 1H); 2.27-2.21 (m, 1H); 2.07-1.98 (m, 2H); 1.83-1.75 (m, 1H); 1.70-1.61 (m, 2H); 1.44-1.34 (m, 2H); 1.23-1.11 (m, 4H); 0.98 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.3, 25.8, 30.6, 33.4, 33.8, 44.6, 47.4, 50.8, 51.3, 57.3, 69.8, 114.1, 121.1, 123.8, 123.7, 126.5, 126.9, 128.5, 128.7, 129.3, 131.3, 131.8, 133.3, 144.6, 149.1, 155.9, 160.9. HRMS (ESI-FT-QQTOF) *m/z*: 472.2971 $[M+H]^+$; calcd. for $C_{30}H_{38}N_3O_2$: 472.2964. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel AD-H column (n-hexane/i-PrOH 80:20) at 1.0 mL/min, UV-detection at λ= 254 nm: t_R (minor)= 31.7 min, t_R (major)= 37.1 min, 89% ee.

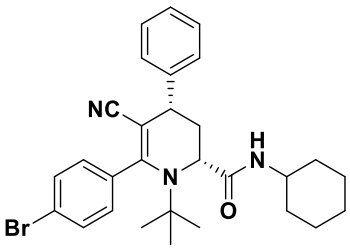
Compound 2.80



To a solution of Jørgensen catalyst (9.0 mg, 0.015 mmol), benzoic acid (4 mg, 0.03 mmol), and cinnamaldehyde (12.6 μL, 0.10 mmol) in dichloromethane (1.0 mL) was added ethyl 3-(4-methoxyphenyl)-3-oxopropionate (28.7 μL, 0.15 mmol) and was irradiated for 30 min (300 W) under high-speed magnetic stirring at -20 °C. 2,2,2-trifluoroethanol (1.0 mL), *tert*-butylamine (15.7 μL, 0.15 mmol), and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were added and the glass tube was sealed. The flask was irradiated for 20 min (300 W) under high-speed magnetic stirring, while the temperature was raised up to 70 °C. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded compound **2.80** (38.1 mg, 49%, isomer *cis*) as a yellowish oil. $[\alpha]_D^{20}$ −17.4 (*c* 0.5, EtOH, 20°C). R_f = 0.38 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.60 (m, 2H); 7.53-7.41 (m, 5H); 7.25-7.10 (m, 2H); 6.24 (d, *J* = 6.9 Hz 1H); 4.52-4.48 (m, 1H); 4.18 (q, *J* = 7.8 Hz, 2H); 3.72 (s, 3H); 3.58-3.50 (m, 1H); 3.23-3.15 (m, 1H); 2.60-2.50 (m, 1H); 2.32-2.10 (m, 6H); 1.88-1.76 (m, 2H); 1.73-1.56 (m, 3H);1.47 (t, *J* = 7.5 Hz, 3H); 1.292 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.8, 27.2, 29.5, 29.8, 31.1, 32.1, 32.9, 37.2, 45.1, 54.3, 56.7, 63.3, 77.5, 85.2, 105.9, 110.1, 115.3, 116.9, 118.6, 120.6, 125.1, 129.2, 129.6,

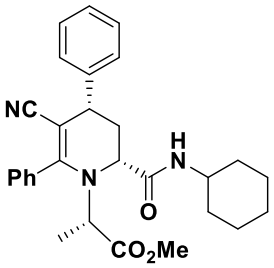
139.0, 140.3, 148.3, 155.1, 169.4, 174.0. HRMS (ESI-FT-QQTOF) *m/z*: 519.3229 $[M+H]^+$; calcd. for $C_{32}H_{43}N_2O_4$: 519.3223. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 95:5) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 15.5 min, t_R (minor)= 17.2 min, 90% ee.

Compound 2.81



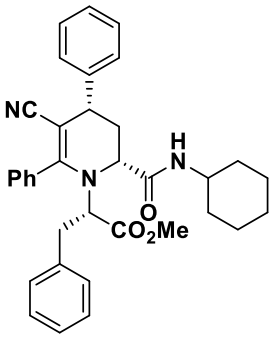
4-Bromobenzoyacetontrile (33.6 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), *tert*-butylamine (15.7 μL, 0.15 mmol), and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 4:1) afforded compound **2.81** (29.7 mg, 57%) as a pale yellow solid. $[\alpha]_D^{20}$ −1.6 (*c* 0.5, acetone, 20°C). R_f = 0.35 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.27 (m, 4H); 7.25-6.97 (m, 5H); 5.29 (d, *J* = 8.1 Hz, 1H); 3.77 (d, *J* = 9-0 Hz, 1H); 3.74-3.60 (m, 1H); 3.54 (dd, *J* = 10.1, 7.1 Hz, 1H); 2.31-2.23 (m, 1H); 2.05-1.80 (m, 3H); 1.75-1.62 (m, 5H); 1.60-1.48 (m, 1H); 1.37-1.26 (m, 2H); 1,15 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 24.0, 25.5, 30.2, 33.1, 33.5, 44.3, 47.1, 50.5, 51.0, 57.0, 69.5, 120.8, 125.1, 126.2, 126.6, 127.5, 127.9, 128.4, 128.9, 129.2, 129.9, 131.8, 132.4, 144.2, 160.7. HRMS (ESI-FT-QQTOF) *m/z*: 520.1978 $[M+H]^+$; calcd. for $C_{29}H_{35}BrN_3O$: 520.1964. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (n-hexane/i-PrOH 97:3) at 1.0 mL/min, UV-detection at λ= 254 nm: t_R (major)= 12.6 min, t_R (minor)= 16.6 min, 80% ee.

Compound 2.82



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), alanine methyl ester hydrochloride (20.9 mg, 0.15 mmol), Et_3N (21 μL, 0.15 mmol) and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 2:1) afforded compound **2.82** (28.8 mg, 61%, isomer *cis*) as a pale yellow oil. $[\alpha]_D^{20}$ −14.4 (*c* 5.0, acetone, 20°C). R_f = 0.32 (*n*-hexane/EtOAc 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56-7.24 (m, 6H); 7.21-7.13 (m, 3H); 5.59 (d, *J*= 8.2 Hz, 1H); 4.01 (dd, *J*= 8.6, 1.4 Hz, 1H); 3.86 (m, 1H); 3.72 (s, 3H); 3.37 (q, *J* = 7.0 Hz, 1H); 2.18-2.03 (m, 2H); 2.01-1.90 (m, 1H); 1.81-1.71 (m, 2H); 1.68-1.55 (m, 2H); 1.46 (d, *J* = 12.0 Hz 1H); 1.30 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 24.2, 25.6, 25.9, 33.5, 33.6, 40.4, 47.6, 51.5, 52.2, 54.2, 61.7, 71.2, 102.5, 113.7, 120.6, 125.0, 126.6, 126.9, 127.9, 128.6, 129.8, 130.5, 132.5, 134.6, 144.0, 159.1, 176.4. HRMS (ESI-FT-QQTOF) *m/z*: 472.2618 $[M+H]^+$; calcd. for $C_{29}H_{34}N_3O_3$: 472.2601. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 8.8 min, >99:1 *dr*.

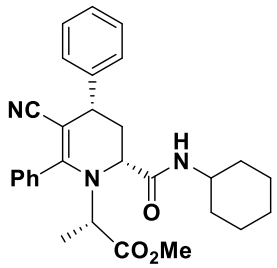
Compound 2.83



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), HCl Phe-OMe (32.3 mg, 0.15 mmol), Et_3N (21.0 μL, 0.15 mmol) and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure B. Flash

column chromatography purification (*n*-hexane/EtOAc 4:1) afforded compound **2.83** (28.5 mg, 52%, isomer *cis*) as a pale yellow solid. $[\alpha]_D^{20}$ −5.3 (*c* 0.5, acetone, 20°C). R_f = 0.33 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.35 (m, 7H); 7.29-7.12 (m, 8H); 4.81 (d, *J* = 7.9 Hz, 1H); 4.47 (t, *J* = 7.1 Hz, 1H); 4.15 (d, *J* = 4.9 Hz, 1H); 3.70 (s, 3H); 3.60 (m, 1H); 3.48 (t, *J* = 7.6 Hz, 1H); 3.12 (dd, *J* = 13.9, 6.8 Hz, 1H); 2.58 (dd, *J* = 14.0, 6.8 Hz, 1H); 2.35-2.27 (m, 2H); 2.22-2.12 (m, 2H); 1.82-1.60 (m, 6H); 1.56-1.50 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 24.5, 25.7, 33.4, 36.1, 39.7, 39.9, 45.6, 47.4, 51.6, 52.4, 60.1, 61.5; 67.5, 111.4, 116.2, 123.8, 126.9, 127.3, 128.6, 128.7, 128.8, 128.9, 129.2, 129.3; 131.5, 133.4, 144.4, 149.8, 149.7, 156.5, 158.9, 175.6. HRMS (ESI-FT-QQTOF) *m/z*: 548.2910 $[M+H]^+$; calcd. for $C_{35}H_{38}N_3O_3$: 548.2913. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 19.2 min, t_R (minor)= 23.4 min, 99:1 *dr*.

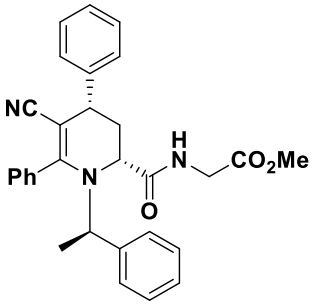
Compound 2.84



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), alanine methyl ester hydrochloride (20.9 mg, 0.15 mmol), Et_3N (21 μL, 0.15 mmol) and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 2:1) afforded compound **2.84** (28.8 mg, 61%, isomer *cis*) as a pale yellow oil. $[\alpha]_D^{20}$ −14.4 (*c* 5.0, acetone, 20°C). R_f = 0.32 (*n*-hexane/EtOAc 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56-7.24 (m, 6H); 7.21-7.13 (m, 3H); 5.59 (d, *J*= 8.2 Hz, 1H); 4.01 (dd, *J*= 8.6, 1.4 Hz, 1H); 3.86 (m, 1H); 3.72 (s, 3H); 3.37 (q, *J* = 7.0 Hz, 1H); 2.18-2.03 (m, 2H); 2.01-1.90 (m, 1H); 1.81-1.71 (m, 2H); 1.68-1.55 (m, 2H); 1.46 (d, *J* = 12.0 Hz 1H); 1.30 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 24.2, 25.6, 25.9, 33.5, 33.6, 40.4, 47.6, 51.5, 52.2, 54.2, 61.7, 71.2, 102.5, 113.7, 120.6, 125.0, 126.6, 126.9, 127.9, 128.6, 129.8, 130.5, 132.5, 134.6, 144.0, 159.1, 176.4. HRMS (ESI-FT-QQTOF) *m/z*: 472.2618 $[M+H]^+$; calcd. for $C_{29}H_{34}N_3O_3$: 472.2601. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H

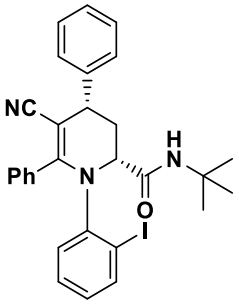
column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 8.8 min, >99:1 *dr*.

Compound 2.85



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), (*R*)-α-methylbenzylamine (37.3 μL, 0.15 mmol), and methyl isocyanoacetate (13.6 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded compound **2.85** (28.8 mg, 60%, isomer *cis*) as a pale yellow oil. $[\alpha]_D^{20}$ −2.1 (*c* 0.6, acetone, 20°C). R_f = 0.40 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.21 (m, 12H); 7.18-7.04 (m, 3H); 5.93 (brs, 1H); 4.36 (m, 2H); 3.97 (m, 2H); 3.84 (brs, 4H); 2.04 (m, 1H); 1.83 (m, 1H); 1.39 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 41.4, 44.9, 47.6, 48.6, 52.8, 56.8, 61.1, 74.6, 119.8, 126.4, 126.6, 126.8, 127.4, 127.9, 128.7, 129.1, 143.6, 144.3, 145.7, 160.6, 170.4. HRMS (ESI-FT-QQTOF) *m/z*: 480.2290 $[M+H]^+$; calcd. for $C_{30}H_{30}N_3O_3$: 480.2287. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (minor)= 22.8 min, t_R (major)= 30.8 min, 87:13 *dr*.

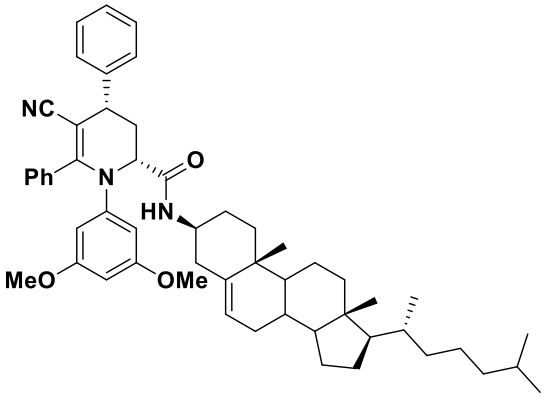
Compound 2.86



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), 2-iodoaniline (32.8 mg, 0.15 mmol), and *tert*-butyl isocyanide (16.9 μL, 0.15 mmol)

were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 4:1) afforded compound **2.86** (33.7 mg, 60%, isomer *cis*) as amorphous white solid. $[\alpha]_D^{20}$ −6.2 (*c* 0.5, acetone, 20°C). R_f = 0.39 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74-7.52(m, 5H); 7.49-7.21 (m, 7H); 7.20-6.98 (m, 2H); 5.57 (s, 1H); 4.68 (dd, *J* = 6.9, 5.2 Hz, 1H); 4.39-4.25 (m, 1H); 4.10 (dd, *J* = 7.0, 4.5 Hz, 1H); 2.60 (m, 1H); 1.48 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1, 41.6, 43.0; 47.1, 52.1, 73.7, 121.6, 122.7, 124.1, 126.7, 126.9, 127.1, 127.2, 127.6, 128.7, 129.9, 130.1, 131.4, 134.1, 140.3, 141.7, 143.6, 148.1, 157.0, 157.7, 180.5. HRMS (ESI-FT-QQTOF) *m/z*: 562.1369 $[M+H]^+$; calcd. for $C_{29}H_{29}IN_3O$: 562.1355. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OJ-H column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (major)= 28.3 min, t_R (minor)= 41.9 min, 99% ee.

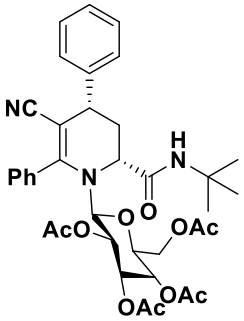
Compound 2.87



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), 3, 5 dimethoxy aniline (22.7 mg, 0.15 mmol), and cholesterol isocyanide (59.3 mg, 0.15 mmol) were reacted according to the general procedure B. The reaction was concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (3 mL). The product was recrystallized by addition of MeOH and collected by vacuum filtration to afforded compound **2.87** (49.3 mg, 61%, isomer *cis*) as a yellow solid. $[\alpha]_D^{20}$ −2.9 (*c* 0.5, acetone, 20°C). R_f = 0.40 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.32 (m, 2H); 7.31-7.21 (m, 5H); 7.19-7.06 (m, 6H); 5.87 (s, 1H); 5.75 (d, *J* = 2.7 Hz, 1H); 5.33 (s, 1H); 4.77 (d, *J* = 8.2 Hz, 1H); 4.49 (t, *J* = 7.2 Hz, 1H); 4.02-3.95 (m, 1H); 3.84-3.75 (m, 3H); 3.66 (s, 6H); 2.43-2.30 (m, 1H); 2.18-2.10 (m, 1H); 2.09-1.98 (m, 3H); 1.96-1.84 (m, 3H), 1.82-1.71 (m, 3H), 0.84 (d, *J* = 6.4 Hz, 6H), 0.80 (s, 3H), 0.78 (s, 3H), 0.6 (s, 3H) .^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 17.6, 18.4, 19.9, 21.5,

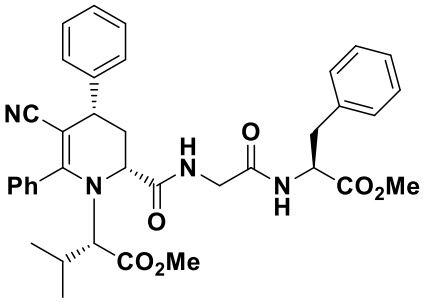
21.8, 22.8, 23.3, 27.0, 27.2, 28.5, 28.7, 29.0, 30.8, 34.8, 35.2, 35.6, 36.0, 38.3, 38.5, 38.7, 38.9, 41.3, 46.6, 48.8, 52.3 54.2, 55.0, 55.6, 58.2, 59.7, 60.1, 89.9, 92.1, 118.9, 121.6, 124.7, 125.8, 126.1, 126.4, 127.6, 127.7, 128.9, 129.0, 132.9, 138.5 142.7, 147.2, 157.5, 160.8. HRMS (ESI-FT-QQTOF) *m/z*: 808.5429 $[M+H]^+$; calcd. for $C_{54}H_{70}N_3O_3$: 808.5417. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.8 mL/min, UV-detection at λ= 254 nm: t_R (minor)= 9.7 min, t_R (major)= 12.0 min, 96:4 *dr*.

Compound 2.88



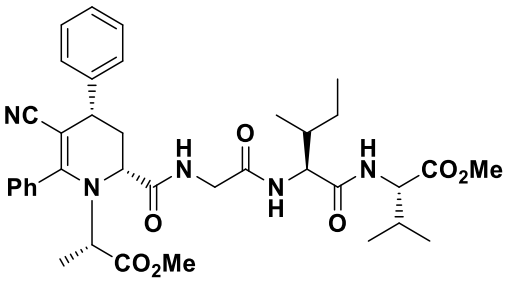
Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), 2,3,4,6-tetra-O-acetyl-β -D-glucopyranosylamine (52.1 mg, 0.15 mmol), and *tert*-butyl isocyanide (16.9 μL, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 2:1) afforded compound **7** (21.8 mg, 63%, isomer *cis*) as a yellow solid. $[\alpha]_D^{20}$ −3.9 (*c* 0.4, acetone, 20°C). R_f = 0.37 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68-7.57 (m, 1H); 7.51-7.35 (m, 6H); 7.30- 7.12 (m, 3H); 5.90 (s, 1H); 5,45 (t, *J* = 7.5 Hz, 1H); 5.30 (t, *J* = 7.5 Hz, 1H); 5.15 (dd, *J* = 10.0, 9.5 Hz, 1H); 4.98 (dd, *J* = 9.4, 9.5 Hz, 1H); 4.60 (dd, *J* = 9.0, 9.5 Hz, 1H); 4.28 (d, *J* = 9.0 Hz, 1H); 4.24 (dd, *J* = 12.0, 4.9 Hz, 1H); 4.10 (dd, 1H); 3.80-3.60 (m, 1H); 3.48 (t, *J* = 7.0 Hz, 1H); 2.78-2.46 (m, 1H), 2.14, 2.12, 2.01, 1.97 (4×s, 12H); 1.48 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 22.7, 26.2, 27.3, 30.2, 35.4, 41.6, 43.0, 47.0, 48.1, 52.2, 62.0, 69.4, 71.2, 72.5, 73.6, 82.8, 84.8, 121.7, 126.1, 126.8, 126.9, 127.1, 127.6, 128.1, 128.7, 129.9, 143.7, 156.9, 167.9, 168.5, 169.3, 170.3, 171.1. HRMS (ESI-FT-QQTOF) *m/z*: 690.3039 $[M+H]^+$; calcd. for $C_{37}H_{44}N_3O_{10}$: 690.3026. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel AS-H column (*n*-hexane/*i*-PrOH 90:10) at 1.0 mL/min, UV-detection at λ= 290 nm: t_R (major)= 13.5 min, t_R (minor)= 18.3 min, 98:2 *dr*.

Compound 2.89



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), HCl Val-OMe (25.1 mg, 0.15 mmol), Et_3N (21 μL, 0.15 mmol), and CN-Gly-Phe-OMe (36.9 mg, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded compound **2.89** (33.1 mg, 52%, isomer *cis*) as a pale brown oil. $[\alpha]_D^{20}$ −1.3 (*c* 0.5, acetone, 20°C). R_f = 0.33 (*n*-hexane/ EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 6H, Ph); 7.25-7.19 (m, 3H, Ph); 7.18-7.08 (m, 6H, Ph); 6.37 (d, *J* = 7.7 Hz, 1H); 6.17 (t, *J* = 5.8 Hz, 1H); 4.95 (dd, *J* = 13.7, 6.0 Hz, 1H); 4.28 (d, *J* = 5.8 Hz, 2H); 4.12 (m, 1H); 4.02 (dd, *J* = 7.8, 4.0 Hz, 1H) 3.77 (m, 1H); 3.73 (s, 3H); 3.72 (s, 3H); 3.16 (m, 2H); 3.07 (d, *J* = 5.2 Hz, 1H); 2.04 (m, 3H); 1.99 (m, 2H); 1.26 (t, *J* = 7.1 Hz, 1H); 0.95 (d, *J* = 6.8 Hz, 3H); 0.90 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 19.4, 31.6, 37.9, 39.9, 46.3, 47.8, 52.0, 52.4, 53.4, 61.8, 64.4, 75.4, 119.9, 120.1, 126.7, 126.9, 127.2, 127.5, 128.1, 128.3, 128.7, 128.9, 129.0, 129.1, 129.2, 135.6, 142.2, 143.3, 160.3, 167.8, 171.6, 175.8. HRMS (ESI-FT-QQTOF) *m/z*: 637.3031 $[M+H]^+$; calcd. for $C_{37}H_{41}N_4O_6$: 637.3026. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 1.0 mL/min, UV-detection at λ= 254 nm: t_R (major)= 22.6 min, 99:1 *dr*.

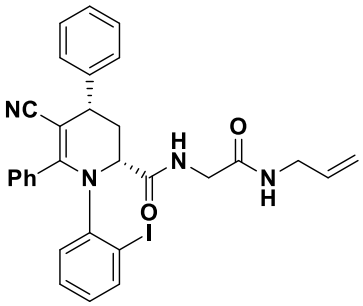
Compound 2.90



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), HCl Ala-OMe (20.9 mg, 0.15 mmol), Et_3N (21.0 μL, 0.15 mmol), and CN-Gly-Ile-Val-OMe (46.7 mg, 0.15 mmol) were reacted according to the general procedure B. Flash

column chromatography purification (*n*-hexane/EtOAc 1:3) afforded compound **2.90** (39.1 mg, 58%, isomer *cis*) as a pale yellow solid. $[\alpha]_D^{20}$ −5.2 (*c* 0.5, acetone, 20°C). R_f = 0.29 (*n*-hexane/ EtOAc 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76-7.60 (m, 2H); 7.55-7.46 (m, 5H); 7.23-7.02 (m, 3H); 6.33 (d, *J* = 6.8 Hz, 1H); 6.16 (t, *J* = 5.7 Hz, 1H); 6.12 (t, *J* = 5.8 Hz, 1H); 5.76 (t *J* = 5.8 Hz, 1H); 4.70-4.62 (m, 1H); 4.55-4.60 (m, 2H); 4.52-4.47 (m, 1H); 4.28 (d, *J* = 7.1 Hz, 1H); 4.12 (d, *J* = 8.2 Hz, 1H); 3.74 (2xs, 6H); 3.49 (q, *J* = 7.0 Hz, 1H); 2.51 (m, 1H); 2.26-2.12 (m, 2H); 2.09-1.97 (m, 1H); 1.60-1.55 (m, 1H); 1.51(d, *J* = 7.0 Hz, 3H); 1.46-1.30 (m, 1H); 1.09 (d, *J* = 7.0 Hz, 6H); 0.90 (d, *J* = 6.8 Hz, 6H); 0.80 (t, *J* = 2.5 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 15.3, 17.9, 18.9, 19.8, 37.5, 46.4, 47.1, 52.1, 52.2 54.1, 56.2, 57.3, 57.9, 58.0, 61.7, 62.3, 75.2, 119.7, 120.1, 126.7, 126.8, 126.9, 127.5, 128.3, 128.6, 128.7, 130.1, 143.0, 143.5, 161.0, 168.6, 170.9, 172.2, 176.1. HRMS (ESI-FT-QQTOF) *m/z*: 674.3565 $[M+H]^+$; calcd. for $C_{37}H_{48}N_5O_7$: 674.3554. The diastereomeric ratio was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.7 mL/min, UV-detection at λ= 254 nm: t_R (major)= 13.8 min, t_R (minor)= 21.8 min, 96:4 *dr*.

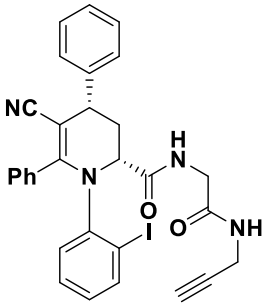
Compound 2.91



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), 2-iodoaniline (32.8 mg, 0.15 mmol), and N-allyl-2-isocyanoacetamide (18.6 mg, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 5:1) afforded compound **2.91** (31.9 mg, 53%, isomer *cis*) as amorphous yellow solid. $[\alpha]_D^{20}$ −10.6 (*c* 0.5, acetone, 20°C). R_f = 0.41 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (ddd, *J* = 7.6, 3.6, 1.3 Hz, 1H); 7.42-7.38 (m, 1H); 7.35-7.31 (m, 4H); 7.20-7.07 (m, 6H); 6.54 (dd, *J* = 6.9, 5.5 Hz, 1H); 6.47-6.42 (m, 1H); 6.28 (t, *J* = 6.3 Hz, 1H); 5.81-5.77 (m, 1H); 5.76-5.68 (m, 1H); 5.15-5.03 (m, 2H); 4.69 (t, *J* = 7.6 Hz, 1H); 4.21 (dd, *J* = 5.2, 2.4 Hz, 2H); 4.03 (t, *J* = 5.8 Hz, 1H); 3.87-3.80 (m, 2H); 2.21 (dd, *J* = 7.7, 5.9 Hz, 2H).^{13}C

NMR (100 MHz, $CDCl_3$): δ = 39.5, 42.2, 46.3, 47.7, 59.6, 78.3, 87.2, 112.3, 117.0, 120.5, 126.8, 127.0, 127.2, 127.4, 128.4, 128.6, 128.8, 129.2, 129.5, 129.9, 130.1, 133.4, 139.5, 143.2, 145.5, 156.5, 159.3, 167.7, 170.6. HRMS (ESI-FT-QQTOF) *m/z*: 603.1268 $[M+H]^+$; calcd. for $C_{30}H_{28}IN_4O_2$: 603.1257. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OD-H column (*n*-hexane/*i*-PrOH 90:10) at 0.7 mL/min, UV-detection at λ= 254 nm: t_R (major)= 19.2 min, t_R (minor)= 24.4 min, 95% ee.

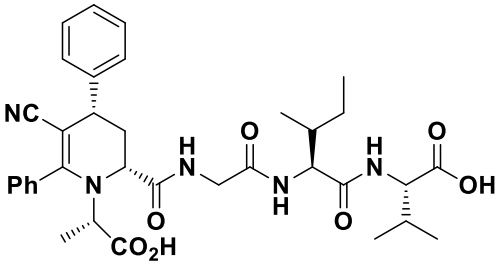
Compound 2.92



Benzoylacetontrile (21.8 mg, 0.15 mmol), cinnamaldehyde (12.6 μL, 0.10 mmol), 2-iodoaniline (32.8 mg, 0.15 mmol), and 2-Isocyano-*N*-(prop-2-yn-1-yl)acetamide (18.3 mg, 0.15 mmol) were reacted according to the general procedure B. Flash column chromatography purification (*n*-hexane/EtOAc 4:1) afforded compound **2.92** (34.8 mg, 58%, isomer *cis*) as yellow solid. $[\alpha]_D^{20}$ −10.1 (*c* 0.5, acetone, 20°C). R_f = 0.32 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76-7.67 (m, 3H); 7.63-7.24 (m, 9H); 7.10-6.94 (m, 2H); 6.12-5.80 (m, 1H); 5.30-5.13 (m, 1H); 4.46 (d, *J* = 5.8 Hz, 2H); 4.24 (dd, *J* = 5.4, 2.6 Hz, 2H); 4.00 (dd, *J* = 7.1, 2.9 Hz, 1H); 3.65-3.59 (m, 1H); 3.52-3.48 (m, 1H); 2.65-2.54 (m, 1H); 2.31 (t, *J* = 2.6 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 39.4, 46.2, 47.6, 59.6, 68.4, 71.9, 78.9, 79.0, 87.1, 112.3, 118.5, 120.5, 126.2, 126.9, 127.0, 128.8, 128.9, 128.2, 129.6, 130.1, 139.5, 143.2, 145.6, 159.6, 167.9, 170.7. HRMS (ESI-FT-QQTOF) *m/z*: 601.1128 $[M+H]^+$; calcd. for $C_{30}H_{26}IN_4O_2$: 601.1100. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OJ-H column (n-hexane/i-PrOH 90:10) at 1.0 mL/min, UV-detection at λ= 300 nm: t_R (minor)= 20.4 min, t_R (major)= 21.7 min, 92% ee.

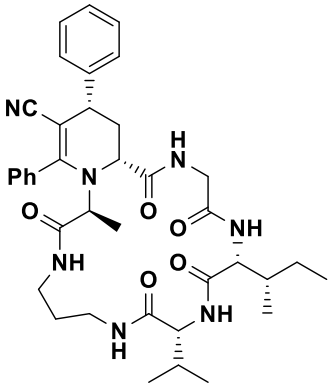
3.4 Synthesis of the THP- Chimeric molecules 2.94-2.97

Compound 2.93. Methyl ester removal procedure for compound 2.90



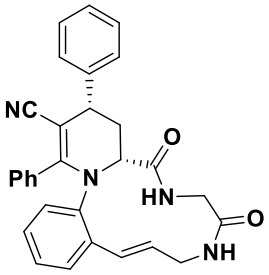
The THP-peptide chimeric **2.90** (30.0 mg, 0.04 mmol) was dissolved in THF/H_2O (2:1, 5 mL) and LiOH (5.7 mg, 0.24 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h and then acidified with aquouse 10% $NaHSO_4$ to pH 3. The resulting phases were separated and the aqueous phase was additionally extracted with EtOAc (2×10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the ***C*-deprotected THP-peptide 2.93** (22.7 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82-7.75 (m, 1H); 7.70-7.57 (m, 1H); 7.49-7.21 (m, 8H); 5.58 (d, *J* = 6.8 Hz, 1H); 4.64 (d, *J* = 6.0 Hz, 1H); 4.56 (t, *J* = 5.9 Hz, 1H); 4.51-4.47 (m, 2H); 4.43-4.39 (m, 1H); 4.33-4.29 (m, 1H); 4.20 (dd, *J* = 6.9, 5.7 Hz, 1H) 4.11(m, 1H); 4.00 (d, *J* = 8.2 Hz, 1H); 3.48 (m, 1H); 2.65 (m, 1H); 2.15-2.06 (m, 4H); 1.35 (d, *J* = 7.0 Hz, 3H); 1.25 (d, *J* = 7.0 Hz, 3H); 1.18 (t, *J* = 7.1 Hz, 1H); 0.96 (d, *J* = 6.8 Hz, 6H); 0.85 (t, *J* = 2.5 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 15.6, 17.9, 18.4, 19.4, 25.9, 30.2, 38.0, 41.4, 42.3, 46.4, 47.8, 56.6, 57.3, 57.8, 62.1, 75.2, 119.7, 120.1, 126.7, 126.8, 126.9, 127.5, 128.4, 128.6, 128.7, 130.4, 143.0, 143.8, 161.0, 168.6, 171.9, 172.2, 176.1. HRMS (ESI-FT-QQTOF) *m/z*: 646.3235 $[M+H]^+$; calcd. for $C_{35}H_{44}N_5O_7$: 646.3240.

Compound 2.94



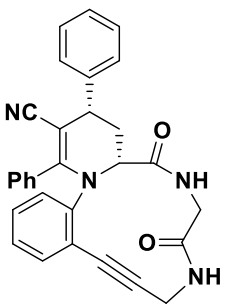
The ***C*-deprotected THP-peptide 2.93** (22.6 mg, 0.035 mmol), PyBOP (41.6 mg, 0.070 mmol) and DIEA (41.8 µL, 0.210 mmol) are suspended in CH_2Cl_2/DMF (100 mL). 1,3-Diaminopropane (3.4 µL, 0.035 mmol) is syringed in portion wise and the resulting solution is stirred at room temperature for 12h. The reaction mixture is concentrated and then diluted with 20 mL EtOAc, transferred to a separatory funnel and sequentially washed with 5% aqueous solution of $KHSO_4$ (2×10 mL) and 5% aqueous suspension $NaHCO_3$ (2×10 mL) and brine (3x10 mL). The organic phase is dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) furnished the chimeric THP-peptide macrocycle **2.94** (11.2 mg, 41%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.78-7.61 (m, 1H); 7.57-7.33 (m, 9H); 6.21 (m, 1H); 5.86 (d, *J* = 6.8 Hz, 1H); 5.42 (d, *J* = 6.0 Hz, 1H); 4.64 (t, *J* = 5.9 Hz, 1H); 4.57 (m, 1H); 4.47-4.42 (m, 2H); 4.39-4.26 (m, 1H); 4.20-4.00 (m, 1H); 4.02 (dd, *J* = 6.9, 5.7 Hz, 1H) 3.53(m, 2H); 3.25 (m, 2H); 3.18 (m, 1H); 2.85-2.80 (m, 1H); 2.59-2.43 (m, 4H); 1.82 (t, *J* = 7.0 Hz, 3H); 1.20 (d, *J* = 7.0 Hz, 3H); 0.96 (d, *J* = 6.8 Hz, 6H); 0.85 (t, *J* = 3.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 15.8, 17.6, 18.6, 19.9, 25.9, 27.3, 30.7, 32.4, 37.7, 40.2, 41.2, 42.6, 43.3, 44.1, 56.7, 58.3, 59.8, 62.2, 74.2, 111.6, 118.6, 126.7, 127.1, 127.5, 127.8, 128.1, 128.9, 129.8, 131.7, 144.5, 146.8, 165.9, 168.4, 171.7, 173.8, 177.4. HRMS (ESI-FT-QQTOF) *m/z*: 684.3869 $[M+H]^+$; calcd. for $C_{38}H_{50}N_7O_5$: 684.3873.

Compound 2.95



A mixture of **2.91** (60.2 mg, 0.100 mmol), palladium(II) acetate (1.1 mg, 0.005 mmol), triphenyl phosphine (2.6 mg, 0.010 mmol) and triethylamine (34.7 µL, 0.250 mmol) in acetonitrile (2mL) was heated to 120 °C for 45 min (300W). Flash column chromatography purification (*n*-hexane/EtOAc 6:1) afforded compound **2.95** (21.4 mg, 45%) as amorphous white solid. R_f = 0.50 (*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 7.2, 4.6 Hz, 1H); 7.48-7.39 (m, 1H); 7.38-7.29 (m, 4H); 7.28-7.15 (m, 6H); 6.82 (dd, *J* = 6.7, 5.1 Hz,1H); 6.77-6.72 (m, 1H); 6.62 (d, *J* = 15.1 Hz, 1H); 6.36 (brs, 1H); 5.93-5.70 (m, 2H); 4.76 (t, *J* = 7.7 Hz,1H); 4.28 (dd, *J* = 5.4, 2.5 Hz, 2H); 4.11 (t, *J* = 6.0 Hz, 1H); 3.95-3.86 (m, 2H); 2.31-2.25 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.3, 46.4, 47.1, 47.8, 59.7, 87.3, 112.4, 117.1,120.0, 120.6, 126.9, 127.1, 127.3, 127.5, 128.5, 128.7, 128.9, 129.0, 129.3, 129.7, 130.1, 133.2, 133.5, 139.6, 143.3, 145.6, 156.6, 159.4, 167.8, 170.7. HRMS (ESI-FT-QQTOF) *m/z*: 475.2139 $[M+H]^+$; calcd. for $C_{30}H_{27}N_4O_2$: 475.2134. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel OJ-H column (*n*-hexane/*i*-PrOH 90:10) at 1.0 mL/min, UV-detection at λ= 254 nm: t_R (major)= 8.8 min, t_R (minor)= 17.0 min, 94% ee.

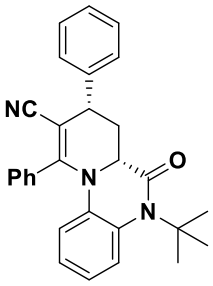
Compound 2.96



A solution of **2.92** (121 mg, 0.20 mmol), $Pd(PPh_3)_2Cl_2$ (1.4 mg, 0.002 mmol) and CuI (1.0 mg, 0.004 mmol) in Et_3N/CH_3CN (1:1, 4.0 mL) was heated at 100 °C for 3h under N_2 atmosphere. The reaction mixture was poured into water and extracted with

DCM, then the combined organic phases were concentrated *in vacuo* and purified by column chromatography (*n*-hexane/EtOAc 5:1) to afford compound **2.96** (49.1 mg, 52%) as brown oil. R_f= 0.37 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91-7.52 (m, 4H); 7.49 -7.21 (m, 7H); 7.169-6.69 (m, 3H); 6.13 (t, *J* = 7.0 Hz, 1H); 5.62 (m, 1H); 5.03 (d, *J* = 5.8 Hz, 2H); 4.70 (d, *J* = 6.1 Hz, 2H), 4.17(d, *J* = 6.9 Hz, 1H); 3.85 (t, *J* = 7.0 Hz, 1H); 3.78 (d, *J* =6.9 Hz, 1H); 2.65-2.50 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 37.5, 39.5, 46.3, 47.7, 59.6, 72.0, 87.1, 90.1, 91.0, 112.4, 118.6, 119.9, 120.6 126.3, 126.9, 127.1, 128.5, 128.9, 129.1, 129.3, 129.6, 133.5, 139.6, 143.3, 145.6, 159.6, 167.9, 169.9. HRMS (ESI-FT-QQTOF) *m/z*: 473.1989 $[M+H]^+$; calcd. for $C_{30}H_{25}N_4O_2$: 473.1978. The enantiomeric excess was determined by chiral stationary phase HPLC using a Chiralcel IA column (*i*-PrOH) at 1.0 mL/min, UV-detection at λ= 254 nm: t_R (minor)= 3.6 min, t_R (major)= 3.7 min, 87% ee.

Compound 2.97



To a solution of **2.89** (56.1 mg, 0.1 mmol), in toluene/acetonitrile (*v*/*v* = 3/1 c= 50 mM, ca 2mL), was added K_2CO_3 (27.7 mg, 0.2 mmol), $Pd(dba)_2$ (2.7 mg, 0.005 mmol) and XantPhos (2.9, 0.005 mmol) in a teflon-capped vial. The sealed vial is then subjected to micro-wave heating (150W, 100°C) for 1 h. After cooling to room temperature, the catalyst and salt were removed by filtration through a short pad of Celite. The filtrate was concentrated to dryness and purified by flash column chromatography (*n*-hexane/EtOAc 4:1) to afford compound **2.97** (26.4 mg, 61%) as an amorphous white solid. R_f = 0.35 (*n*-hexane/ EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.07 (m, 11H); 6.97-6.68 (m, 3H); 4.15 (t, *J* = 7.3 Hz, 1H); 3.90 (t, *J* = 7.0 Hz, 1H); 2.89 (dd, *J* = 7.5, 2.8 Hz, 1H); 2.16 (dd, *J* = 7.0, 2.9 Hz, 1H); 1.39 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9, 42.0, 43.4, 49.7, 51.8, 94.5, 116.6, 119.8, 121.5, 125.4, 126.9, 127.6, 128.4, 129.0, 129.1, 130.5, 134.8, 139.4, 141.7, 143.4, 145.3, 147.9, 151.3, 152.9, 157.6, 158.5, 169.1. HRMS (ESI-FT-QQTOF) *m/z*: 456.2069 $[M+Na]^+$; calcd. for $C_{29}H_{27}N_3NaO$: 456.2052. The enantiomeric excess was determined by chiral

stationary phase HPLC using a Chiralcel OJ-H column (*n*-hexane/*i*-PrOH 80:20) at 0.7 mL/min, UV-detection at λ= 254 nm: t_R (minor)= 10.6 min, t_R (major)= 14.6 min, 97% ee.

3.5 Selected Spectra and Chromatograms of Chapter 1

FIGURE 3.5.1-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of the diastereomer cis of compound **1.30**.

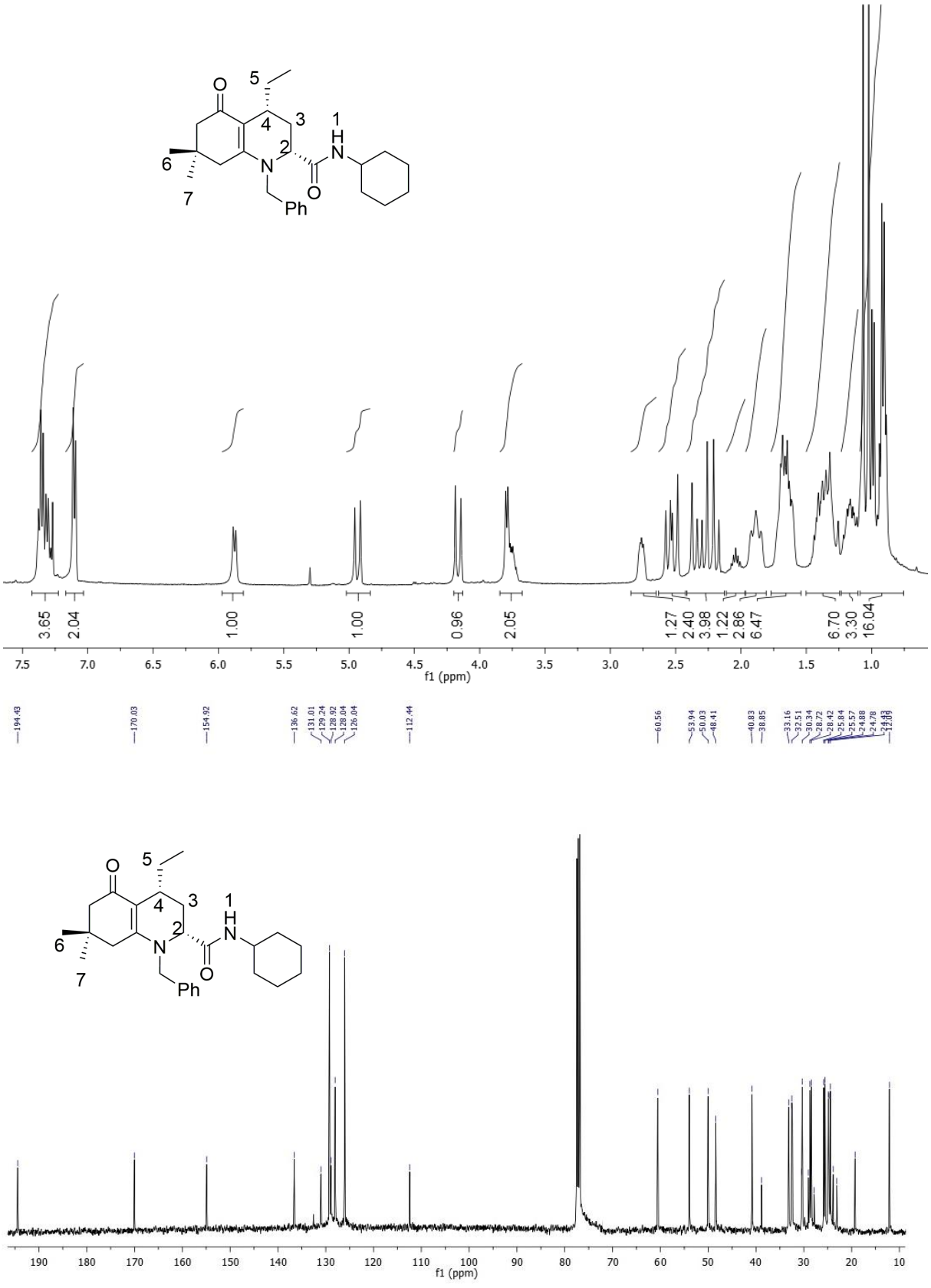


FIGURE 3.5.2- COSY and NOESY spectra in $CDCl_3$ of the diastereomer cis of compound **1.30**.

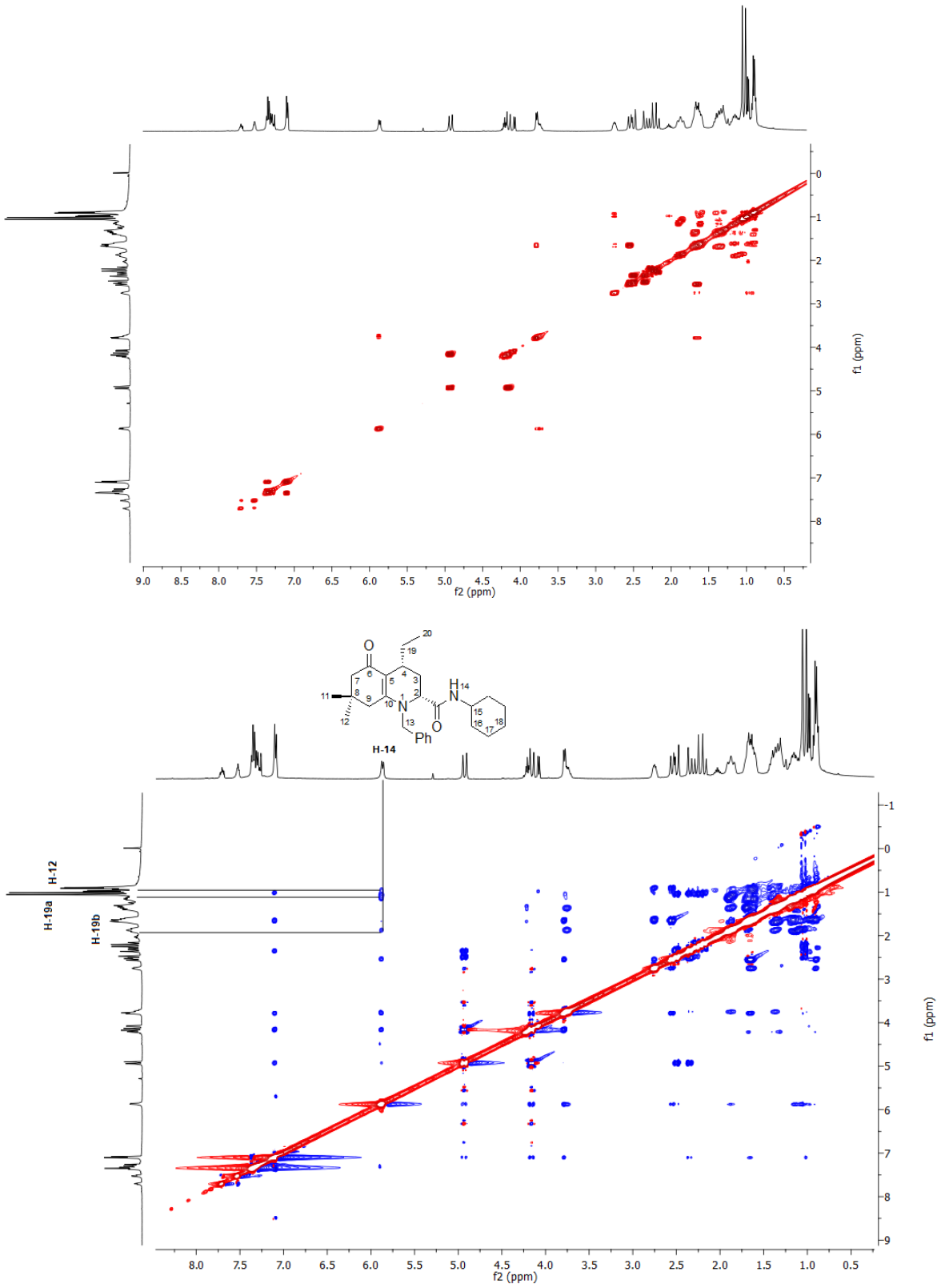


FIGURE 3.5.3-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of the diastereomer trans of compound **1.30**.

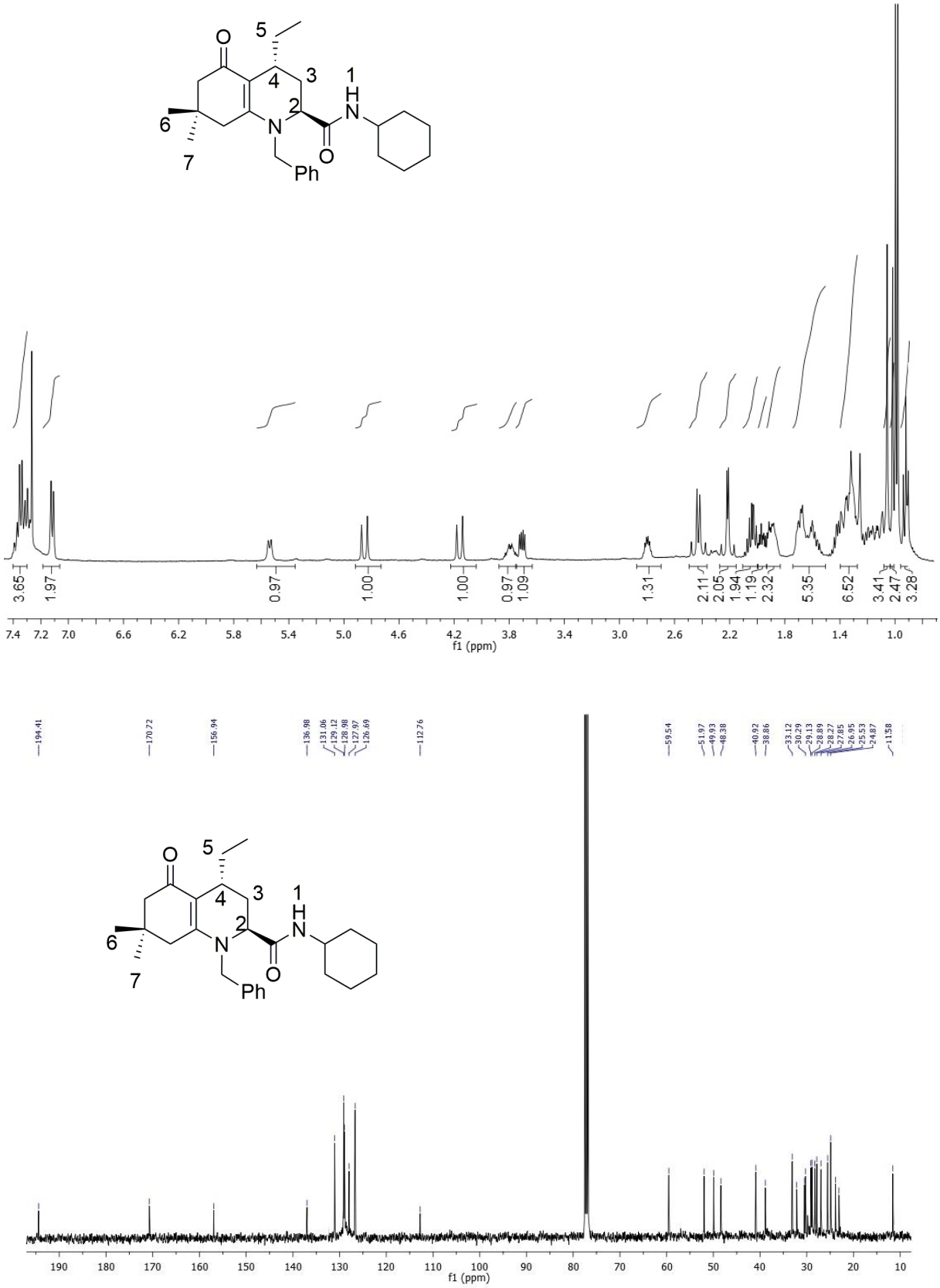
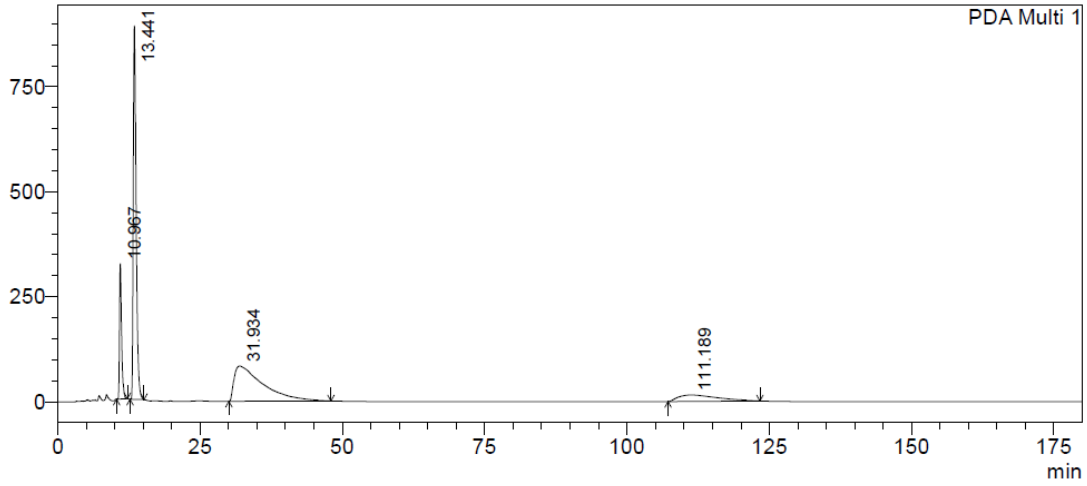
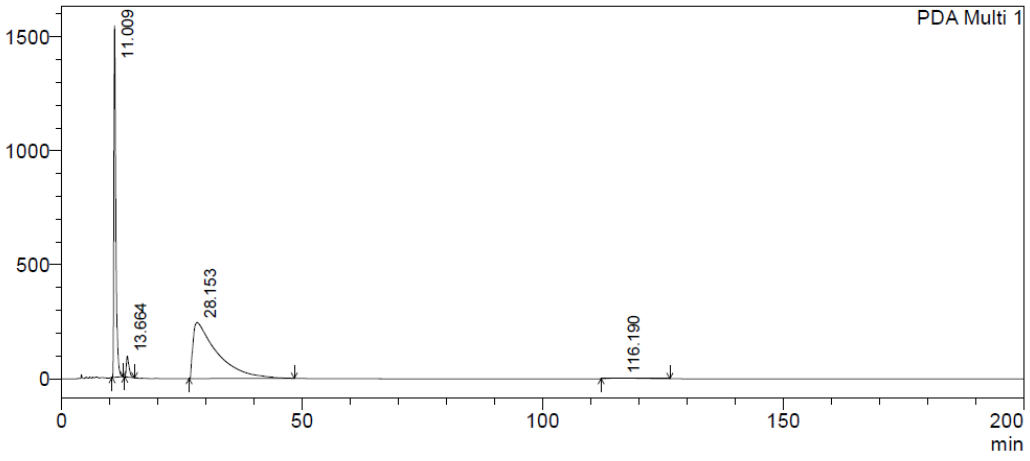


FIGURE 3.5.4- Chiral stationary-phase HPLC analysis of the mixture of diastereomers of **1.30**; n-hexane/i-PrOH 90:10 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	10.967	8494989	322142	11.148
2	13.441	30903885	888932	40.555
3	31.934	29549949	84019	38.778
4	111.189	7254400	15551	9.520
Total		76203223	1310645	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	11.009	45121046	1542300	33.319
2	13.664	3652498	92501	2.697
3	28.153	85163596	245563	62.888
4	116.190	1484218	3402	1.096
Total		135421357	1883766	100.000

FIGURE 3.5.5-^{1}H and ^{13}C NMR spectra in CDCl3 of compound **1.31**.

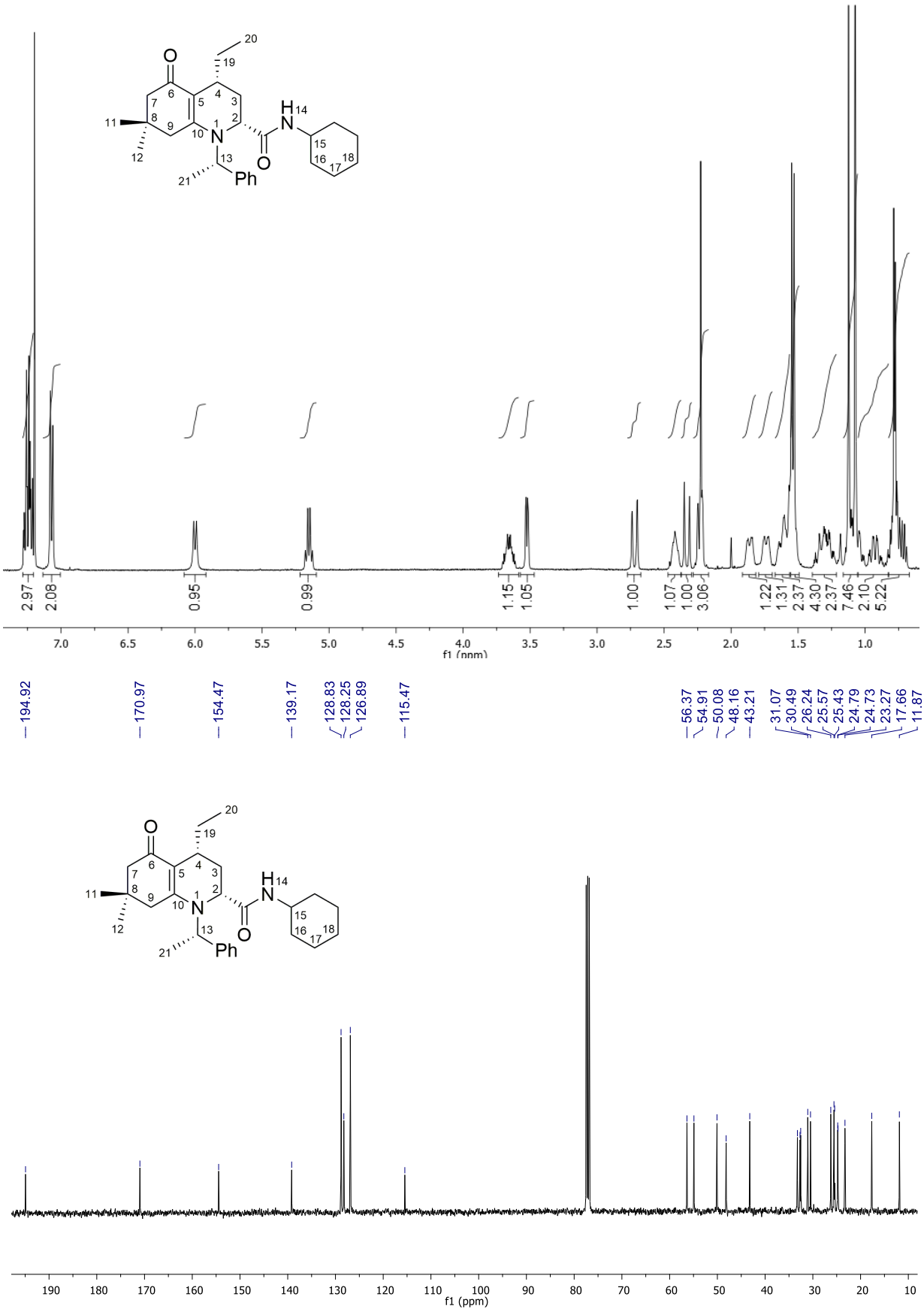
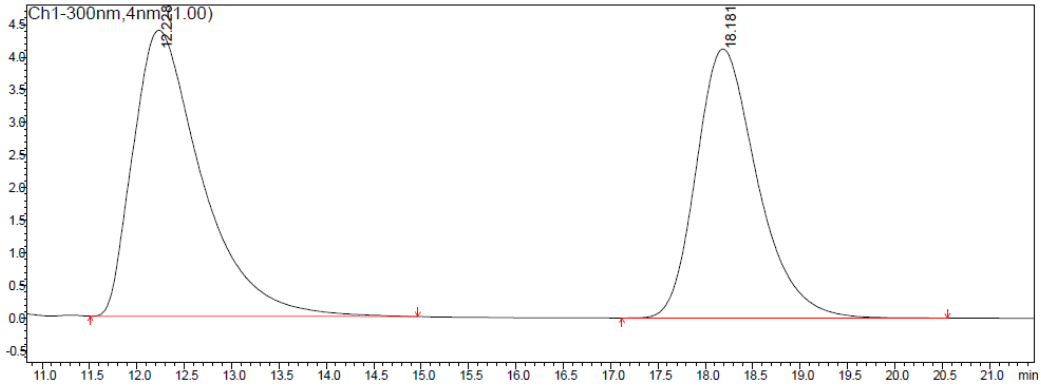
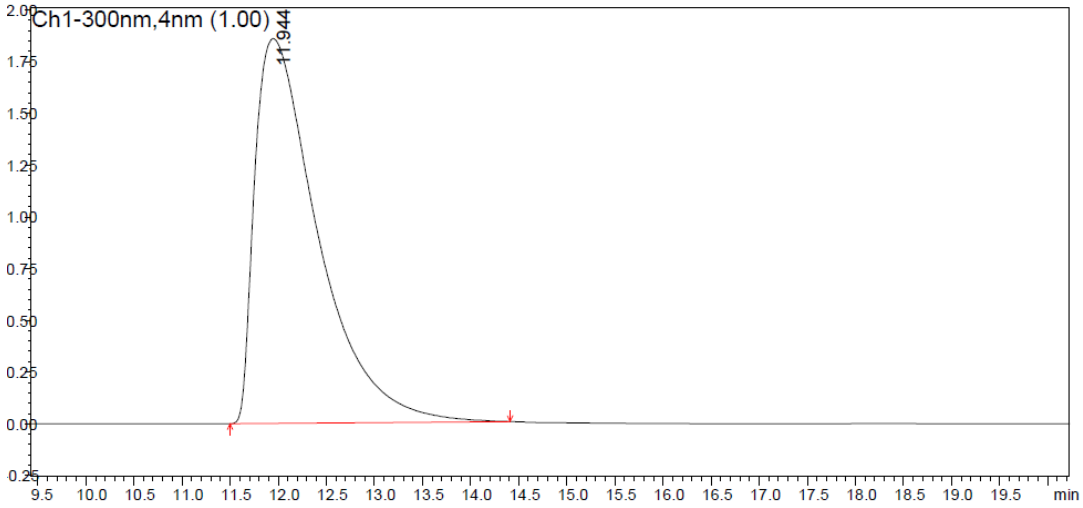


FIGURE 3.5.6- Chiral stationary-phase HPLC analysis of compound **1.31**; n-hexane/i-PrOH 90:10 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

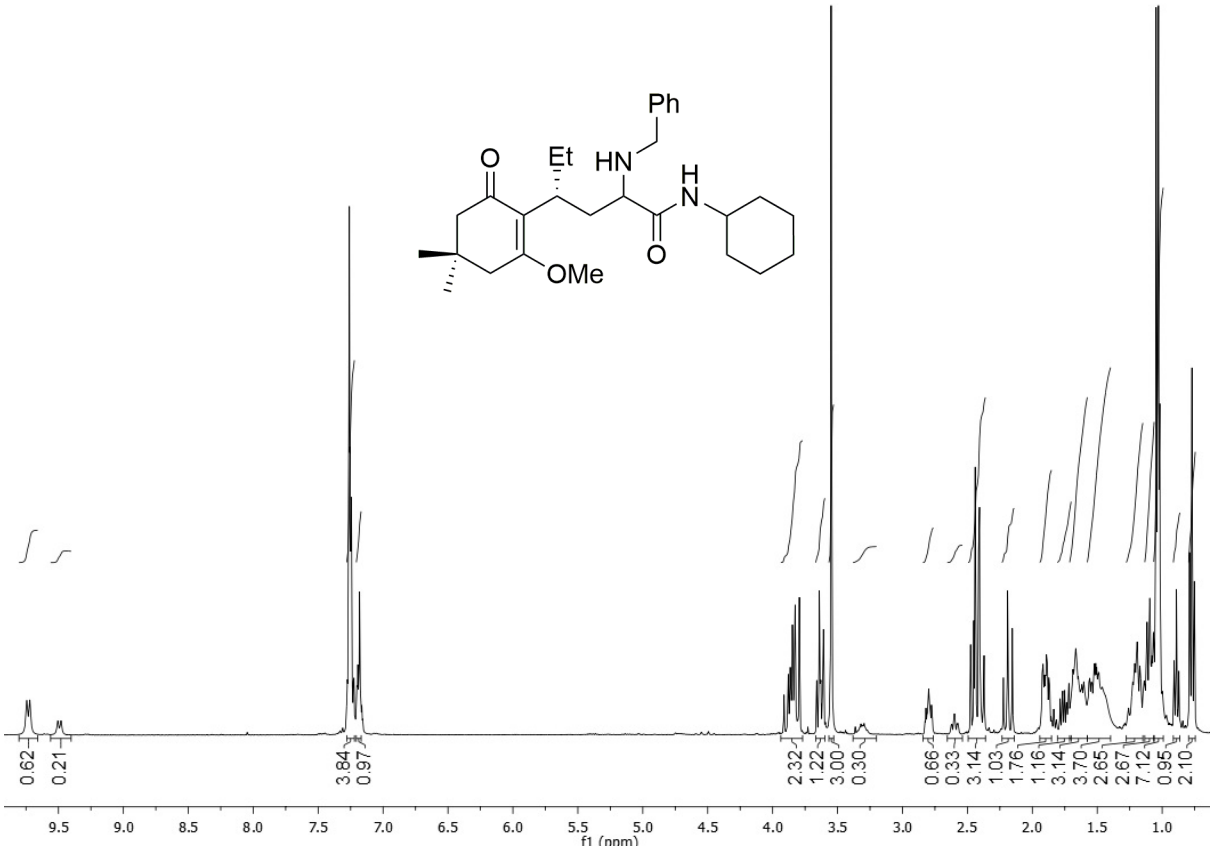
Peak#	Ret. Time	Area	Height	Area %
1	12.228	22038058	438186	54.376
2	18.181	18490616	412362	45.624
Total		40528674	850549	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	11.944	85012511	1858220	100.000
Total		85012511	1858220	100.000

FIGURE 3.5.7-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.32**.



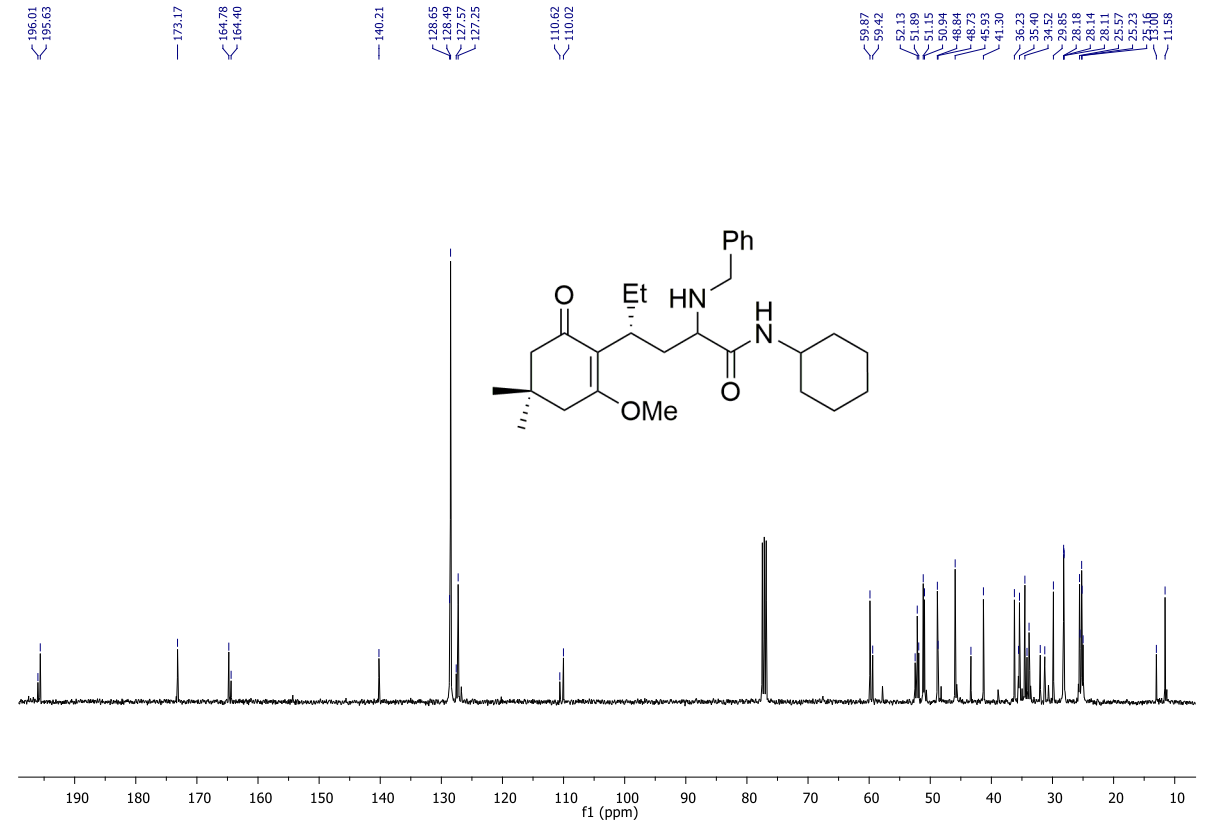


FIGURE 3.5.8-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.33**.

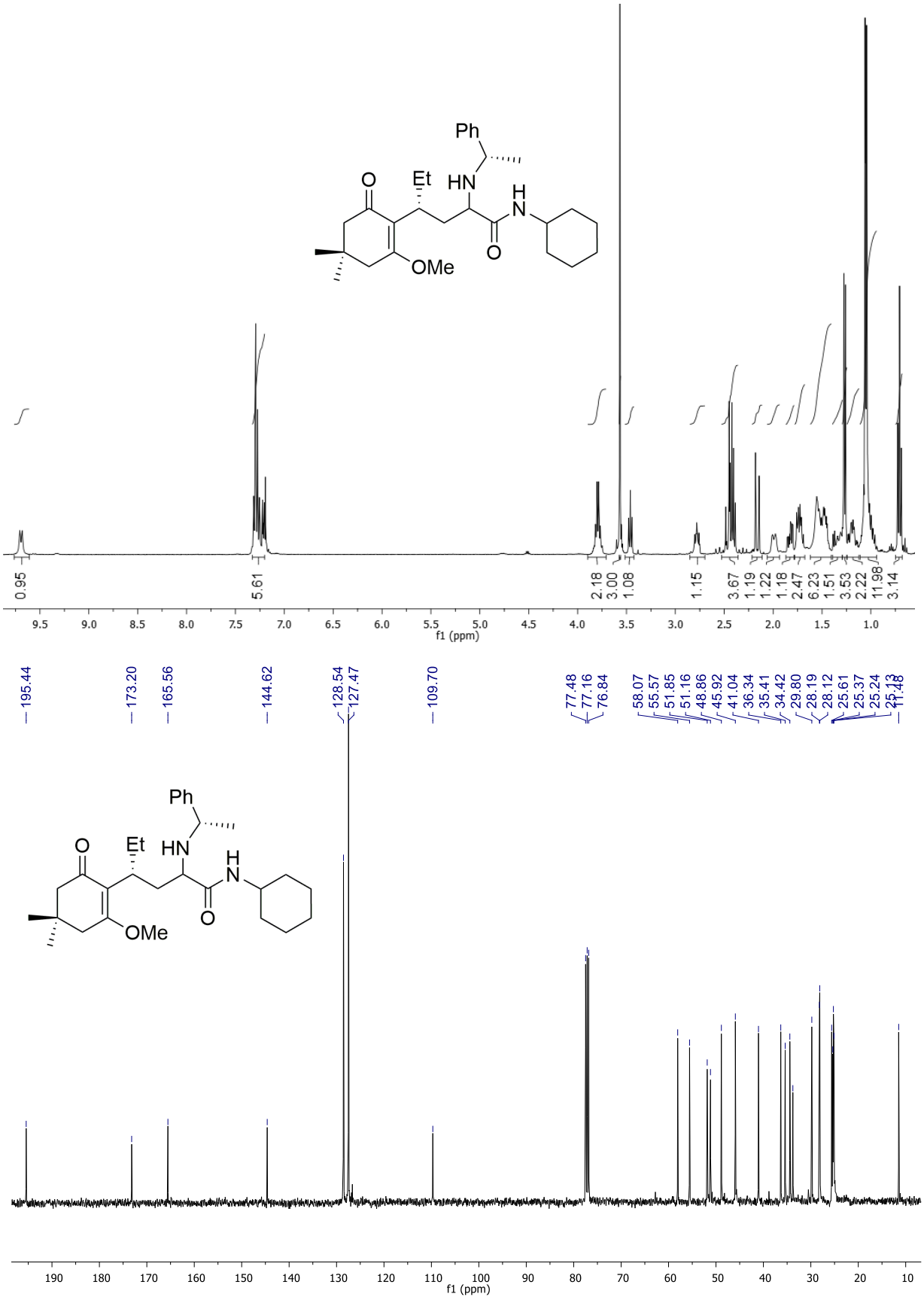


FIGURE 3.5.9-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.34**.

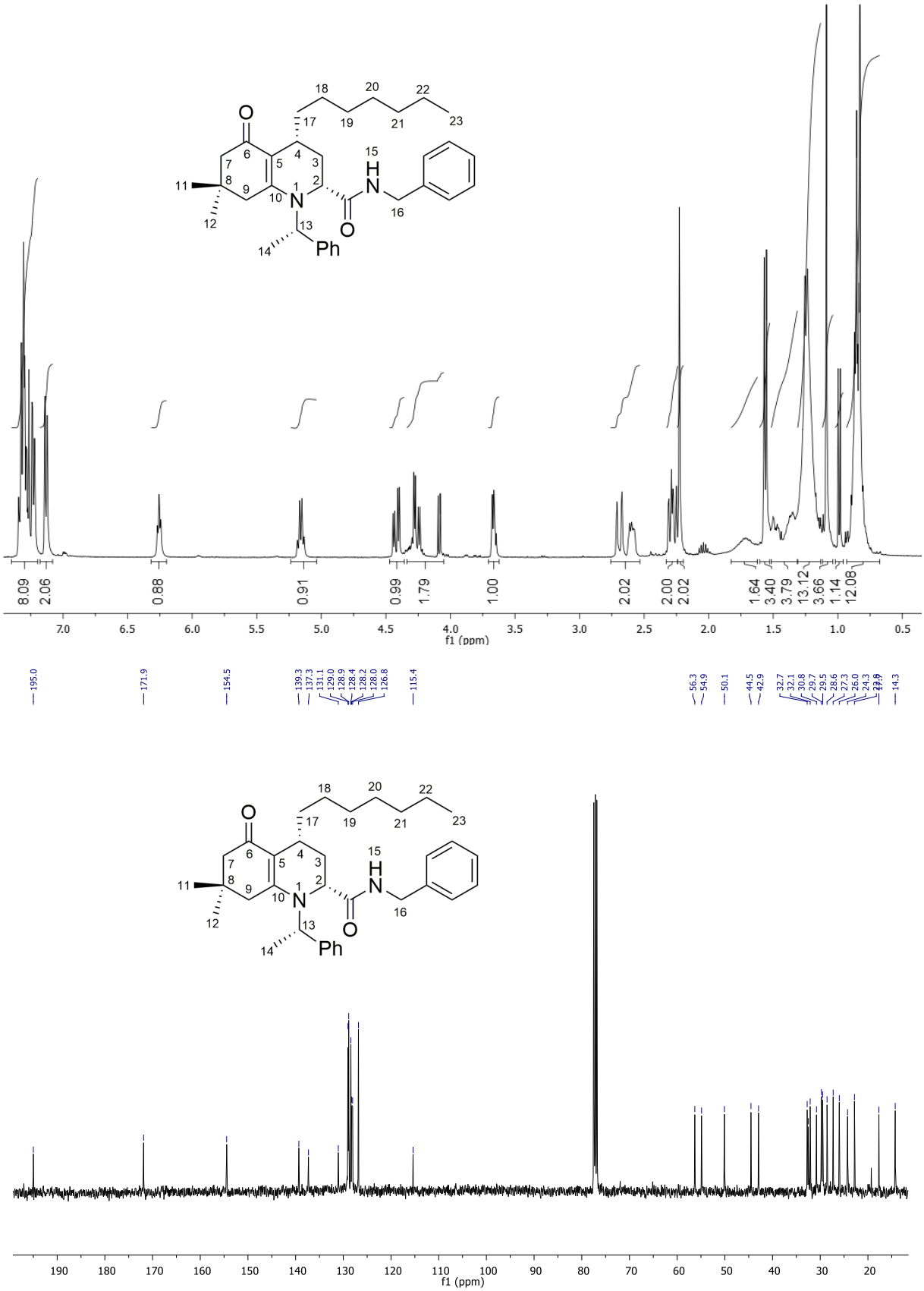
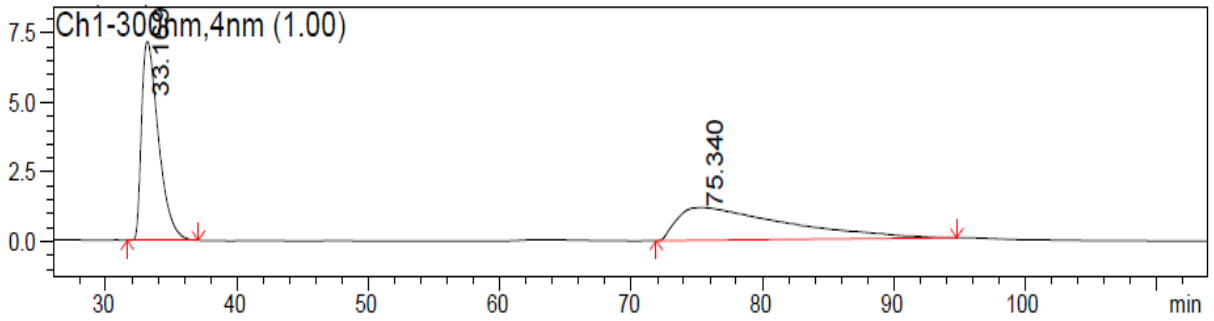
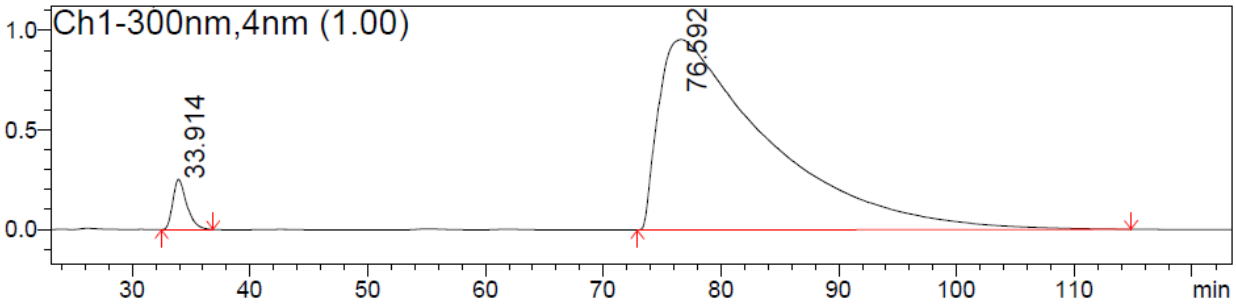


FIGURE 3.5.10- Chiral stationary-phase HPLC analysis of compound **1.34**; n-hexane/i-PrOH 90:10 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	33.169	64570743	717418	48.748
2	75.340	67886796	119241	51.252
Total		132457538	836660	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	33.914	2095780	25349	3.254
2	76.592	62319177	95801	96.746
Total		64414957	121150	100.000

FIGURE 3.5.11-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.35**.

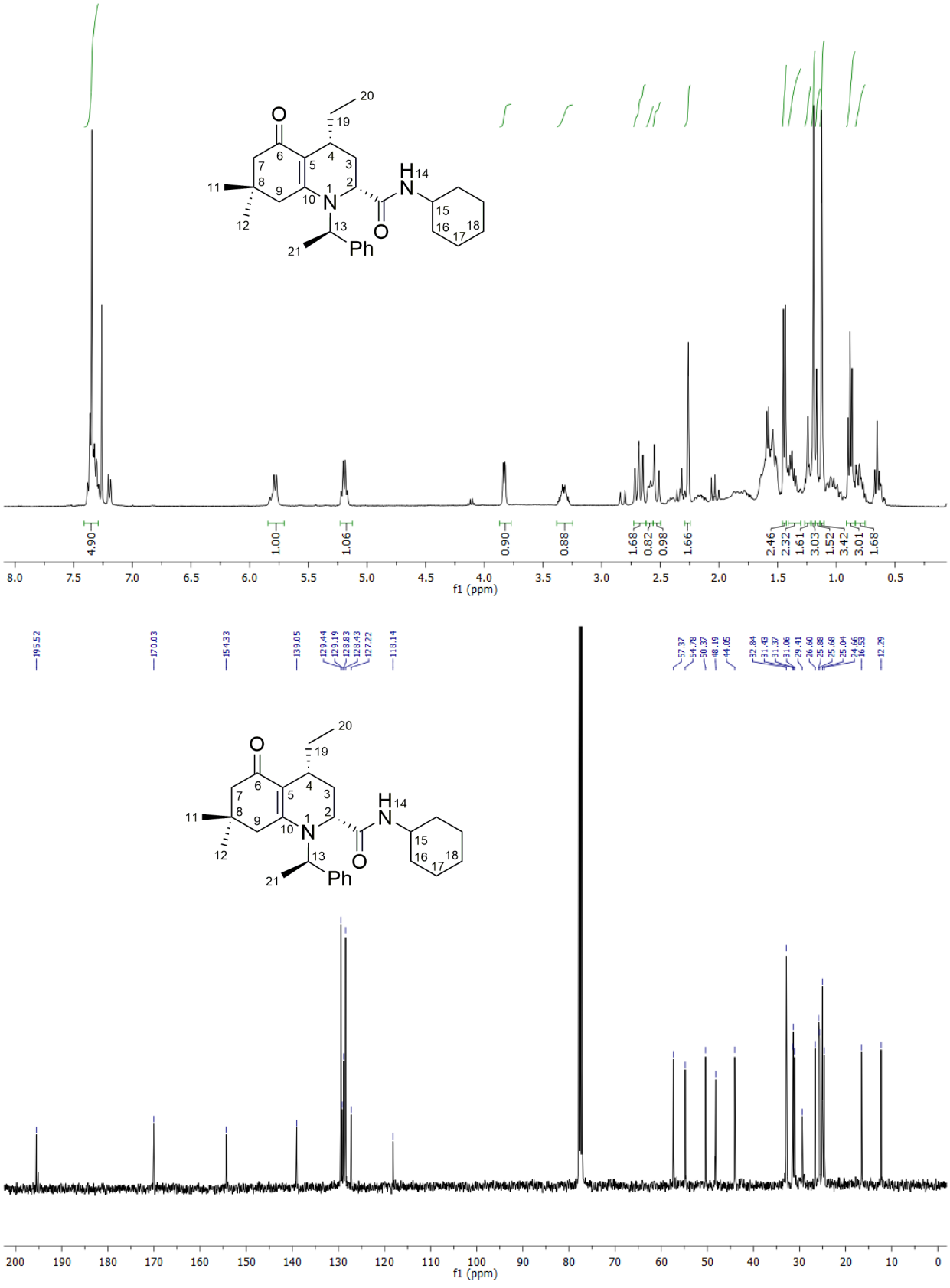


FIGURE 3.5.12-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.36**.

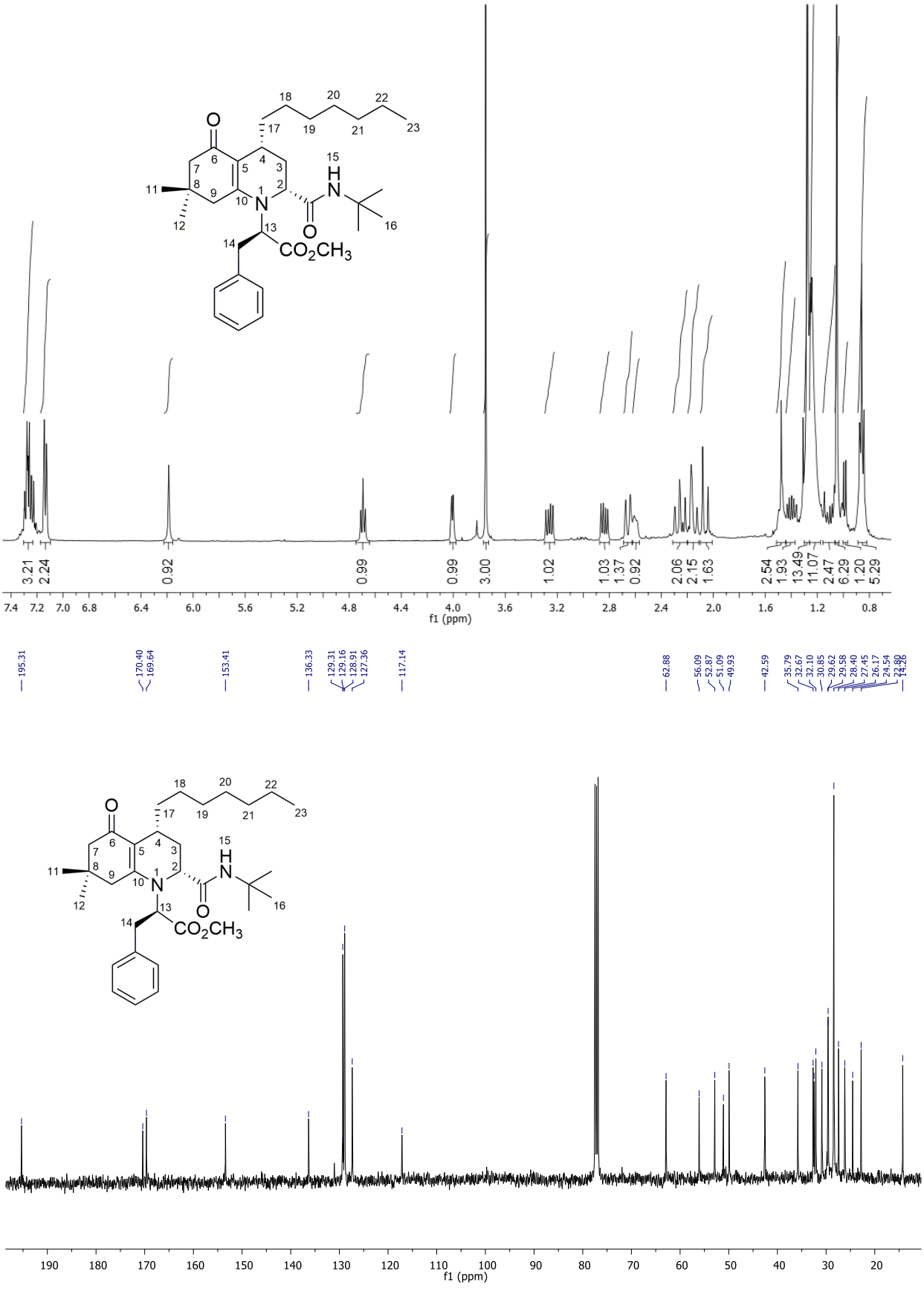
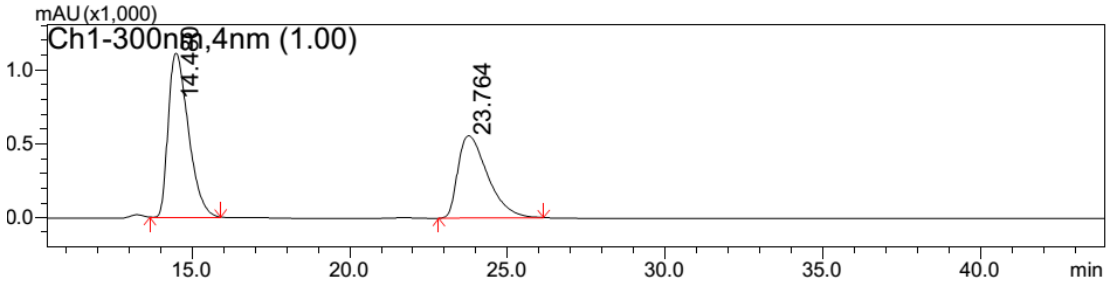
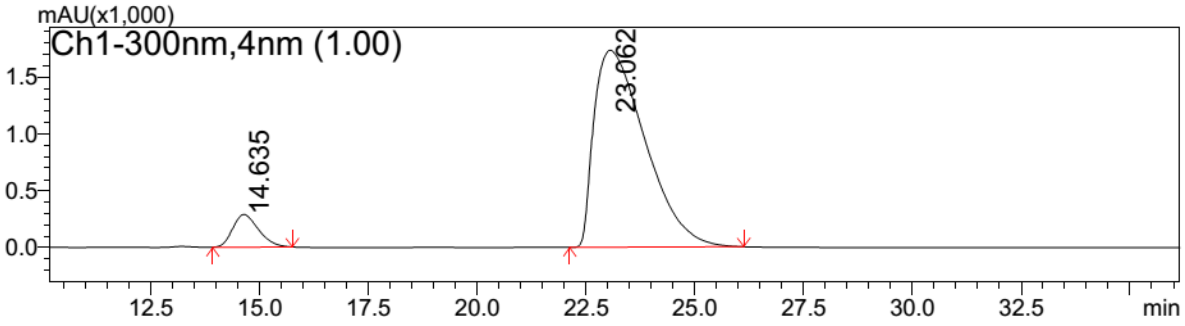


FIGURE 3.5.13- Chiral stationary-phase HPLC analysis of compound **1.36**; n-hexane/i-PrOH 95:5 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.480	49303850	1110013	57.328	66.506
2	23.764	36699587	559037	42.672	33.494
Total		86003438	1669049	100.000	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.635	11940311	286696	7.750	14.209
2	23.062	142121644	1730991	92.250	85.791
Total		154061955	2017687	100.000	100.000

FIGURE 3.5.14-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.37**.

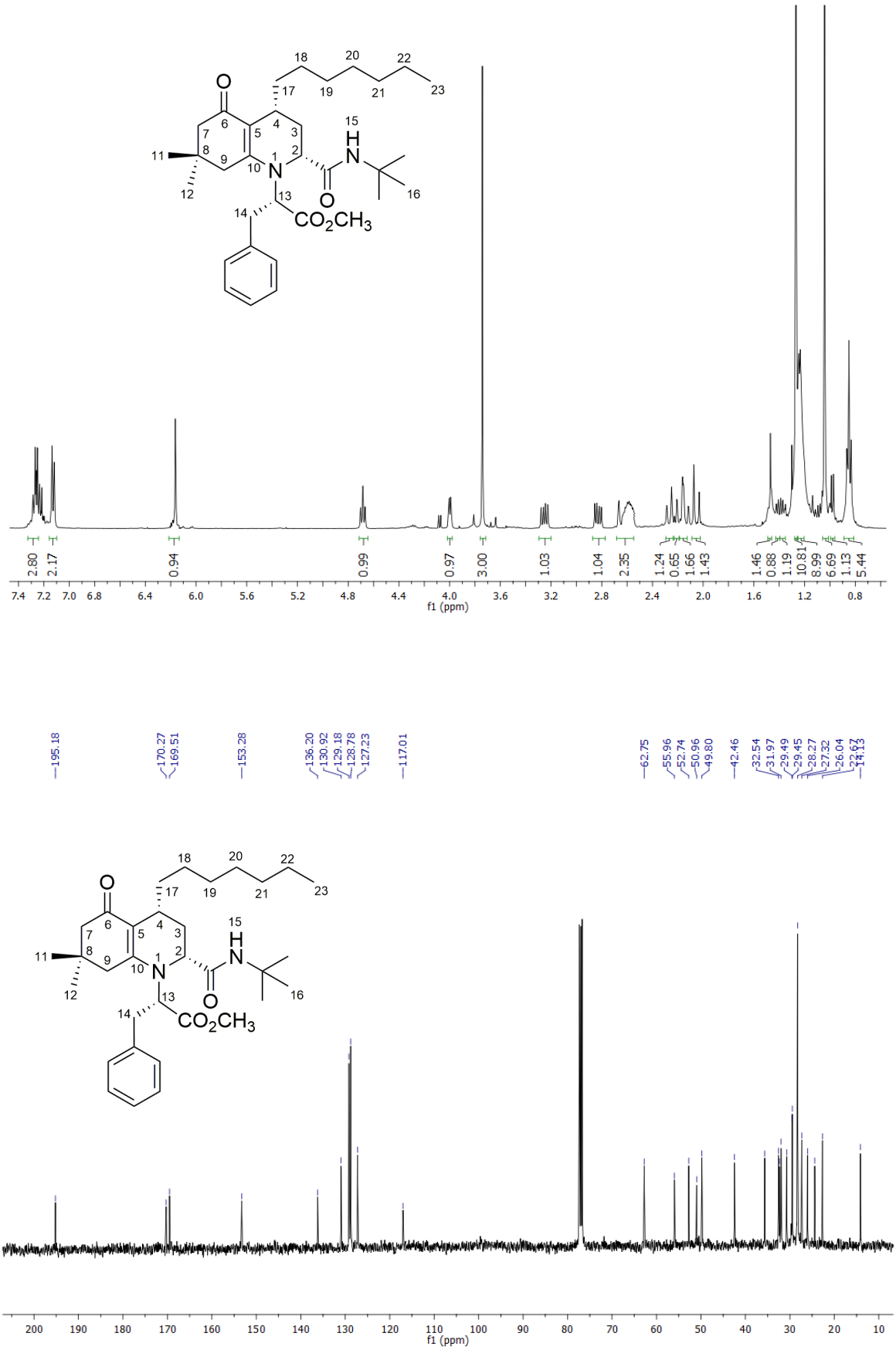
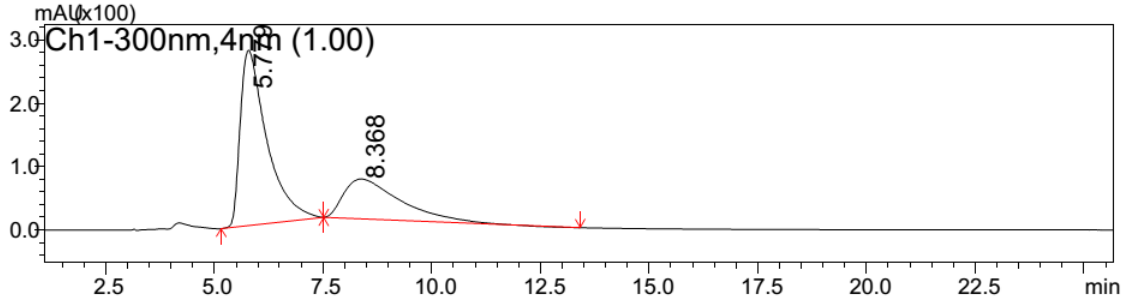
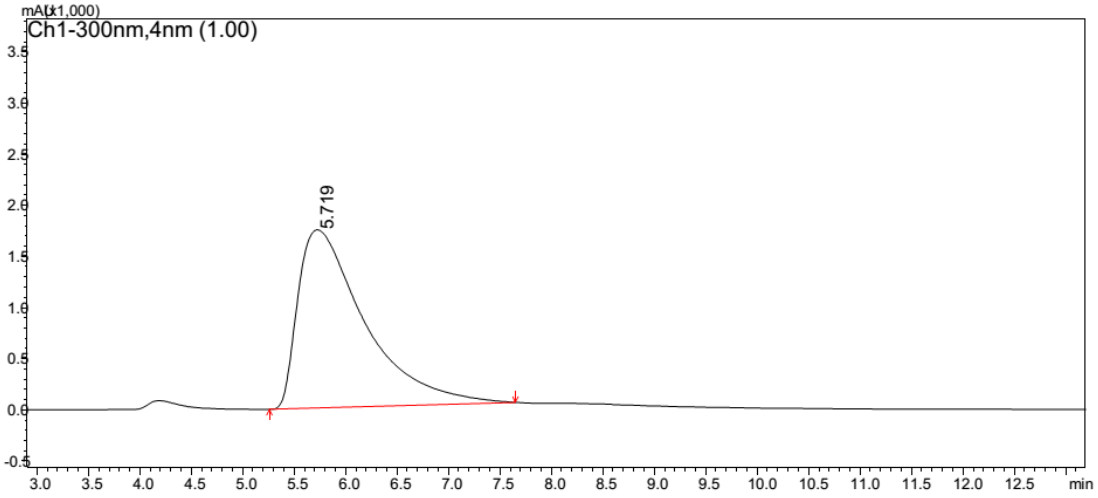


FIGURE 3.5.15- Chiral stationary-phase HPLC analysis of compound **1.37**; n-hexane/i-PrOH 95:5 OJ-H at 1 mL/min.



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.779	11829329	276781	67.252	81.495
2	8.368	5760320	62849	32.748	18.505
Total		17589649	339630	100.000	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.719	78844686	1743990	100.000	100.000
Total		78844686	1743990	100.000	100.000

FIGURE 3.5.16-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.38**.

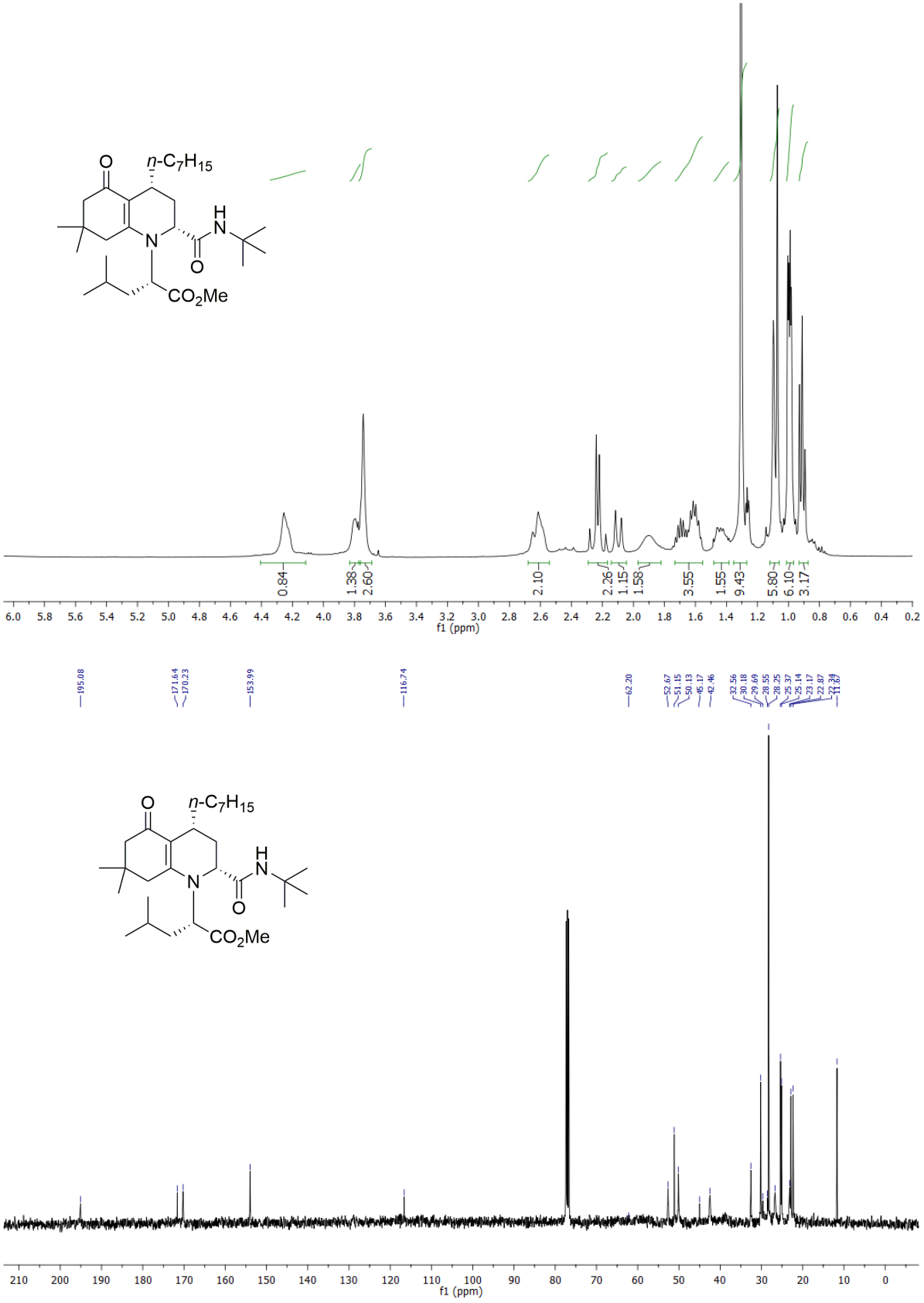
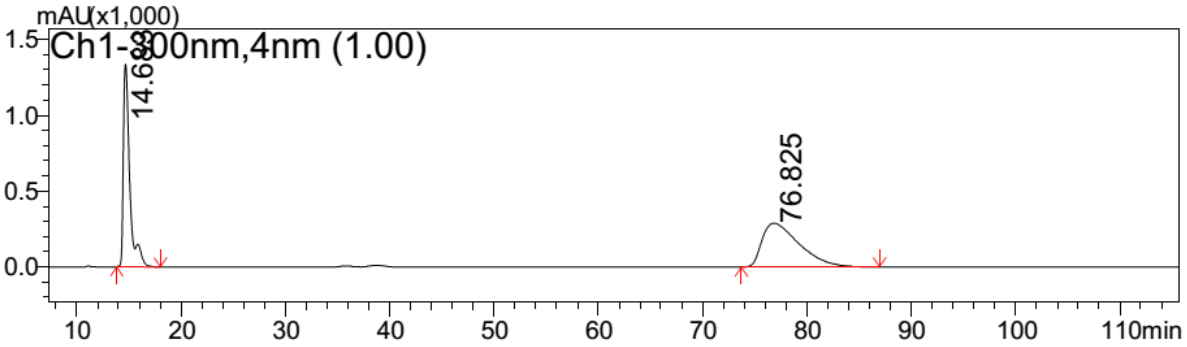
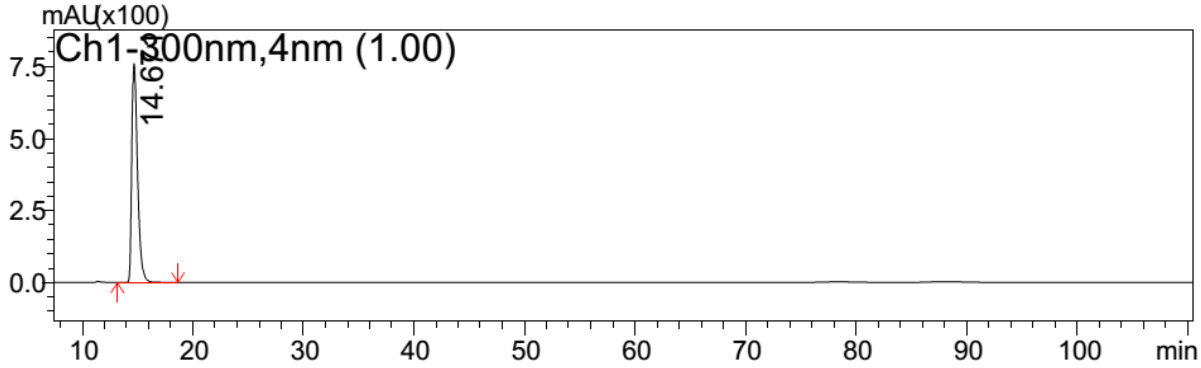


FIGURE 3.5.17- Chiral stationary-phase HPLC analysis of compound **1.38**; n-hexane/i-PrOH 95:5 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.683	56876558	1335259	44.273	82.249
2	76.825	71590958	288184	55.727	17.751
Total		128467516	1623443	100.000	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.671	27378842	760913	100.000	100.000
Total		27378842	760913	100.000	100.000

FIGURE 3.5.18-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.39**.

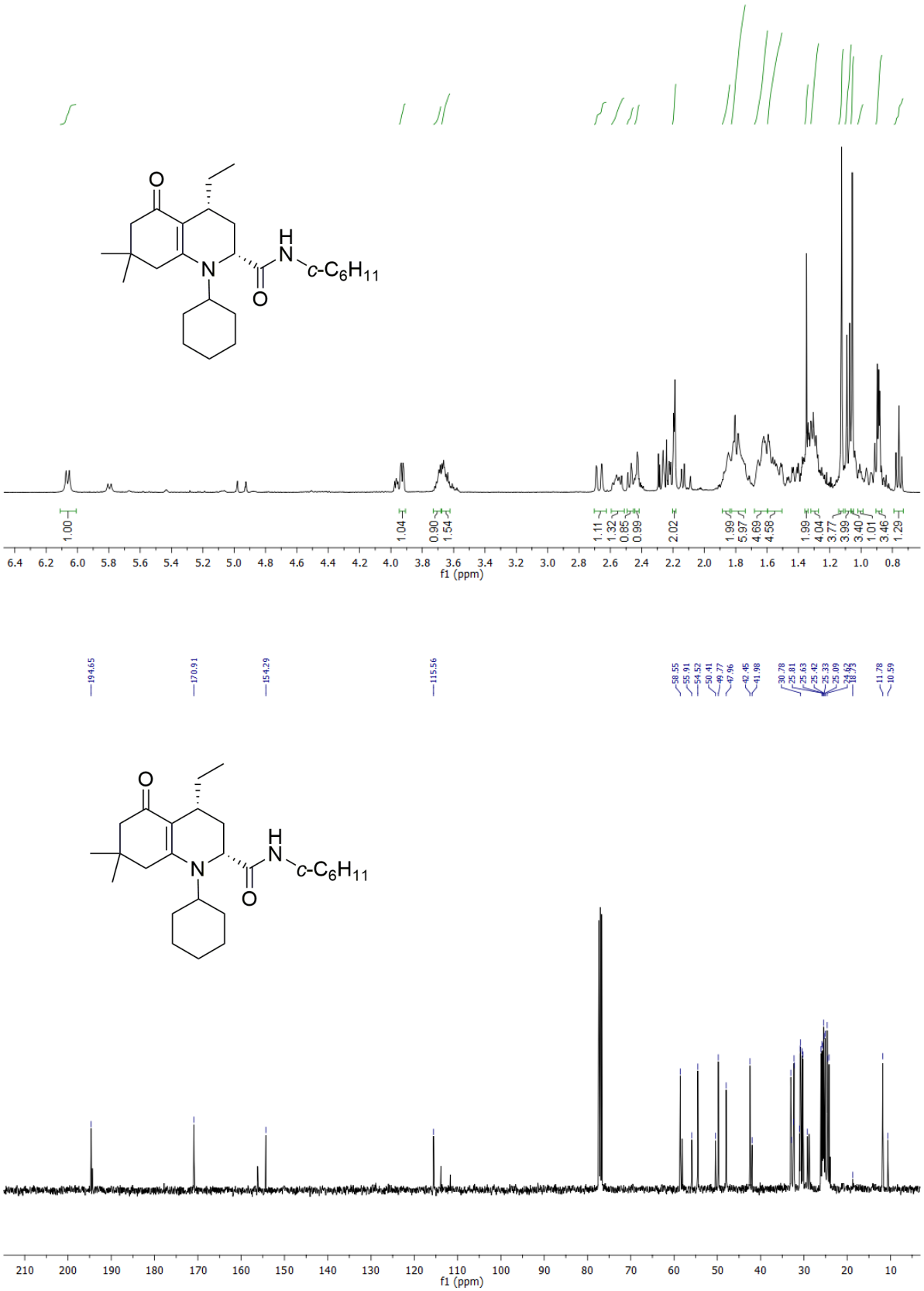
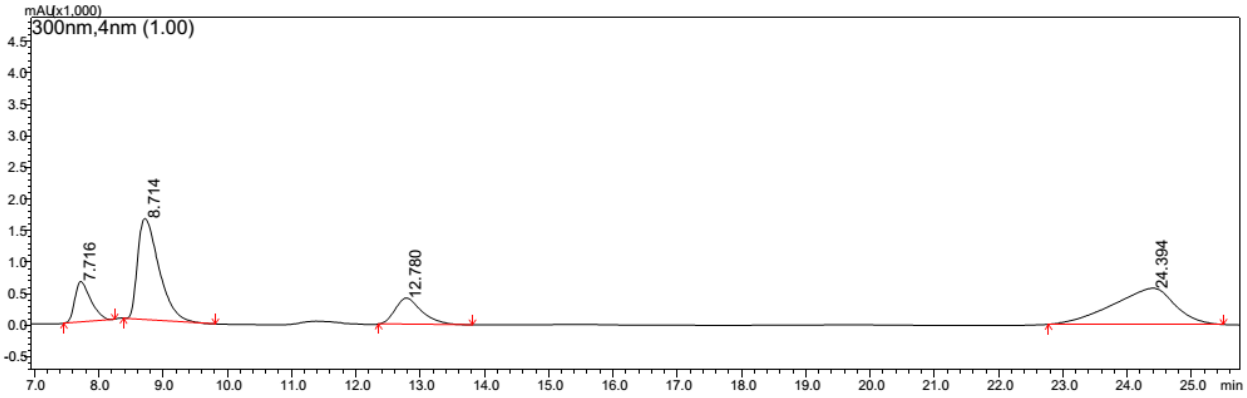
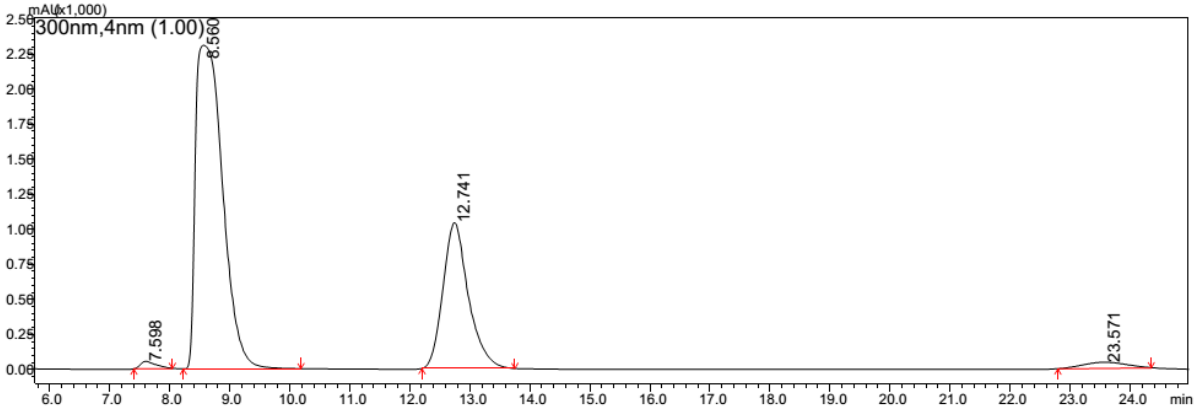


FIGURE 3.5.19- Chiral stationary-phase HPLC analysis of compound **1.39**; n-hexane/i-PrOH 90:10 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.716	10914310	639213	11.092	19.821
2	8.714	37019109	1599663	37.622	49.602
3	12.780	11932123	413288	12.126	12.815
4	24.394	38532006	572820	39.160	17.762
Total		98397549	3224984	100.000	100.000



PDA Ch1 300nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.598	943182	52559	0.887	1.526
2	8.560	72612800	2307800	68.264	66.999
3	12.741	30632945	1040159	28.799	30.197
4	23.571	2180922	44009	2.050	1.278
Total		106369849	3444527	100.000	100.000

FIGURE 3.5.20-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.40**.

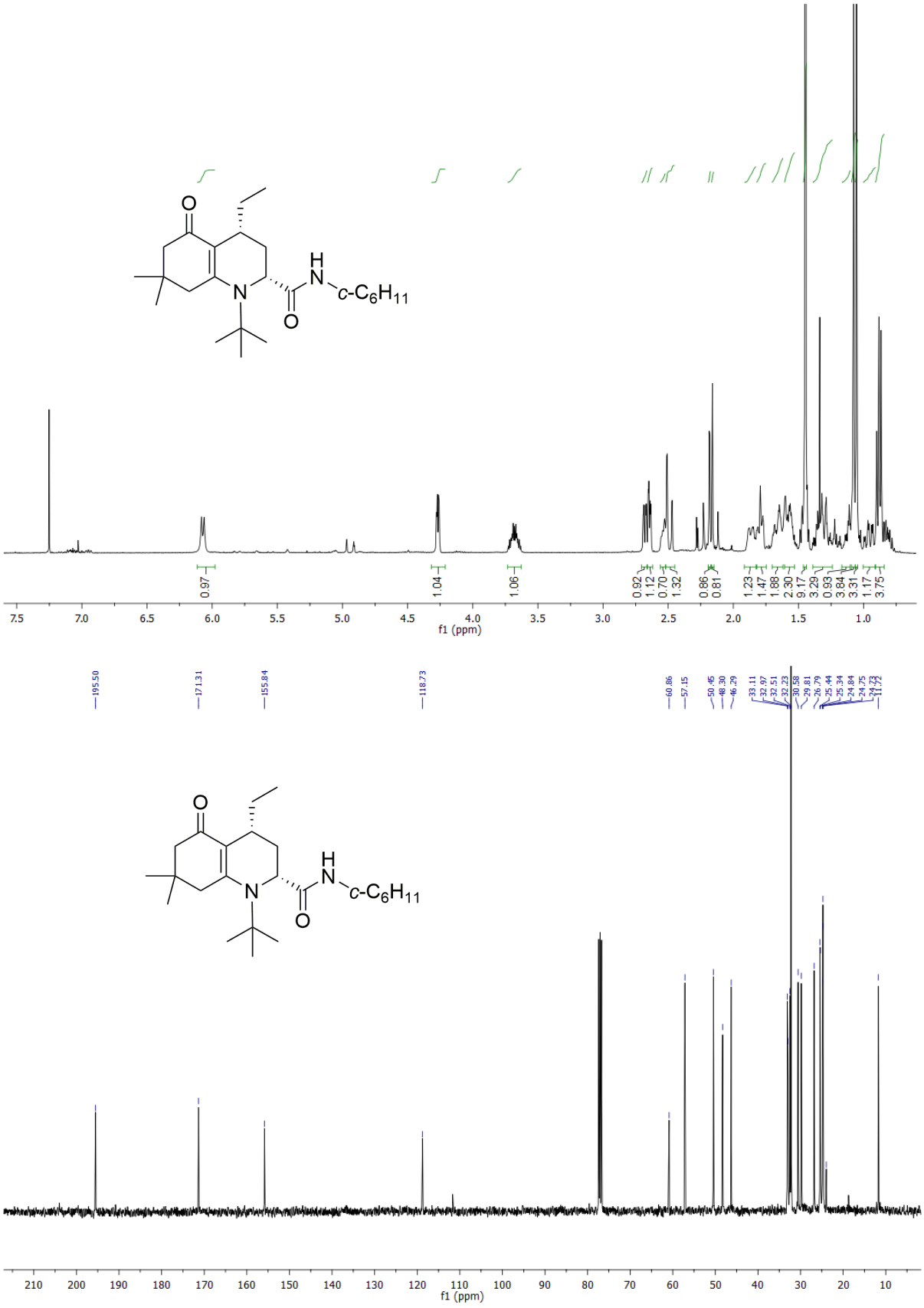
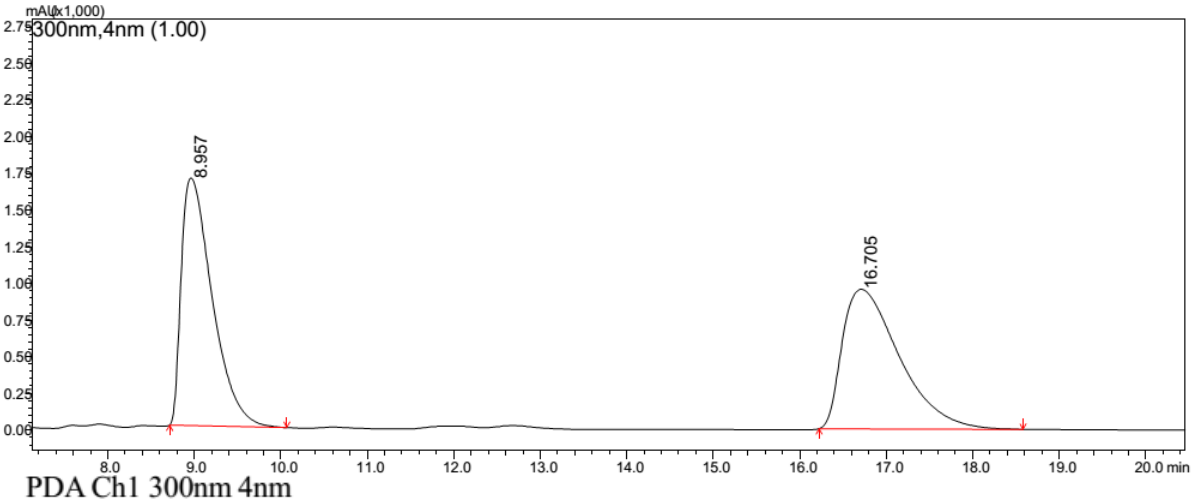
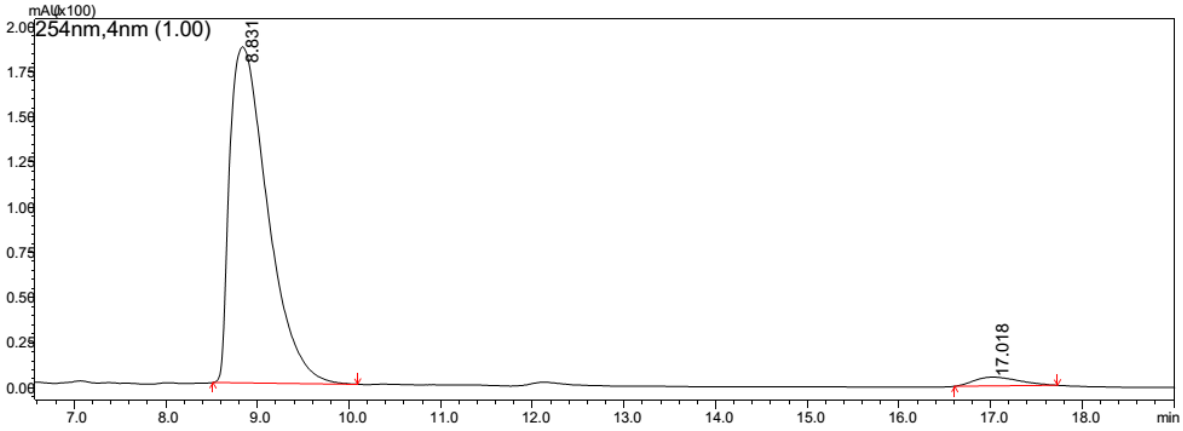


FIGURE 3.5.21- Chiral stationary-phase HPLC analysis of compound **1.40**; n-hexane/i-PrOH 90:10 AD-H at 1 mL/min.



PDA Ch1 300nm 4nm

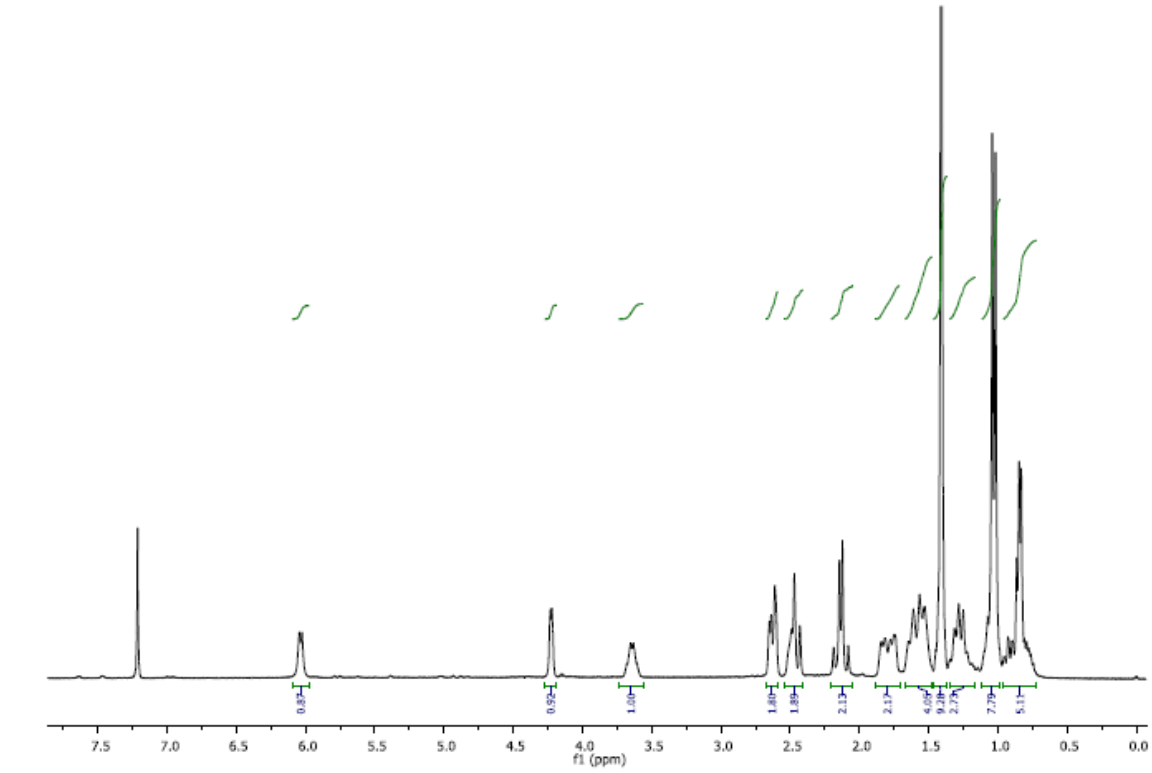
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.957	41938213	1688683	50.177	64.197
2	16.705	41642233	941778	49.823	35.803
Total		83580446	2630461	100.000	100.000



PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.831	5342503	185967	96.996	97.443
2	17.018	165464	4879	3.004	2.557
Total		5507967	190847	100.000	100.000

FIGURE 3.5.22- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.41**.



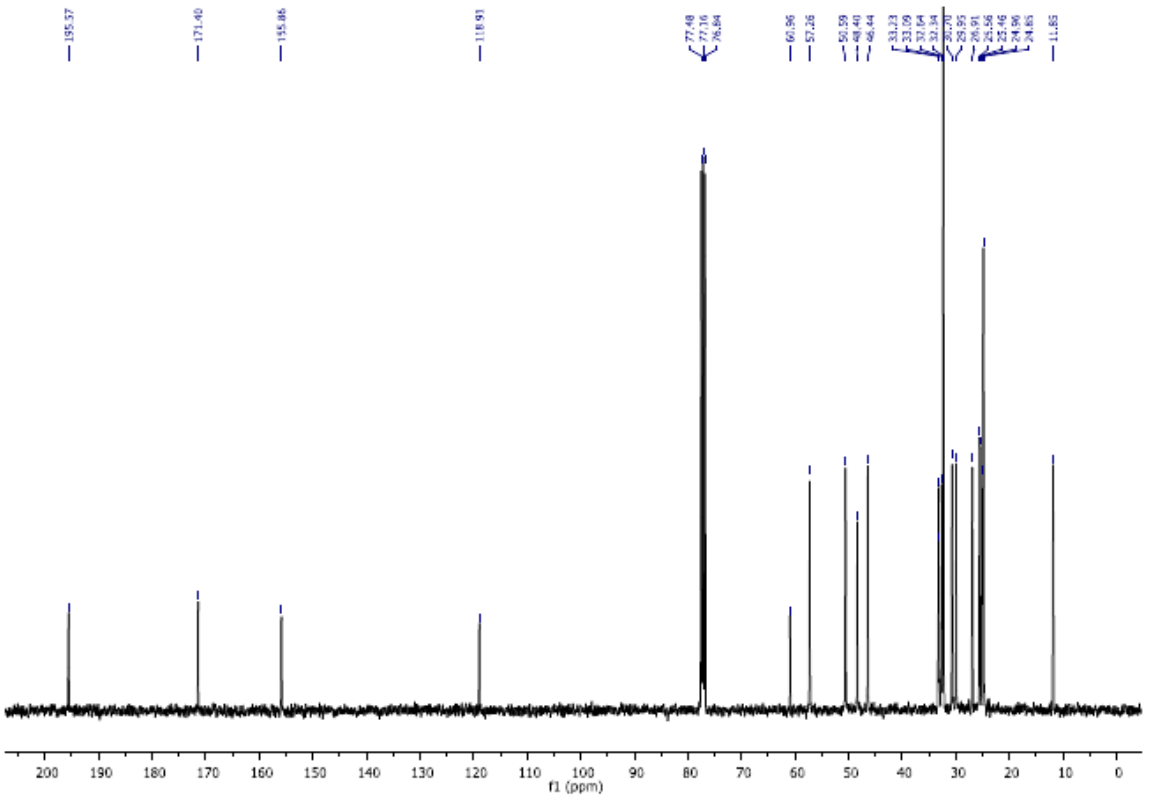
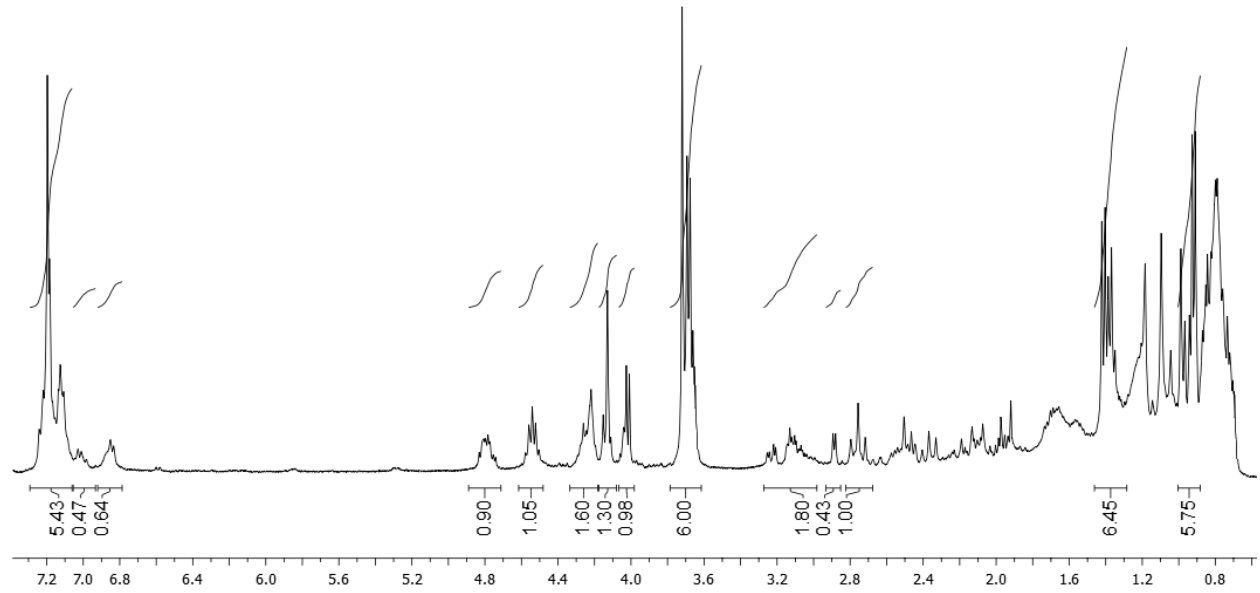


FIGURE 3.5.23-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.42**.



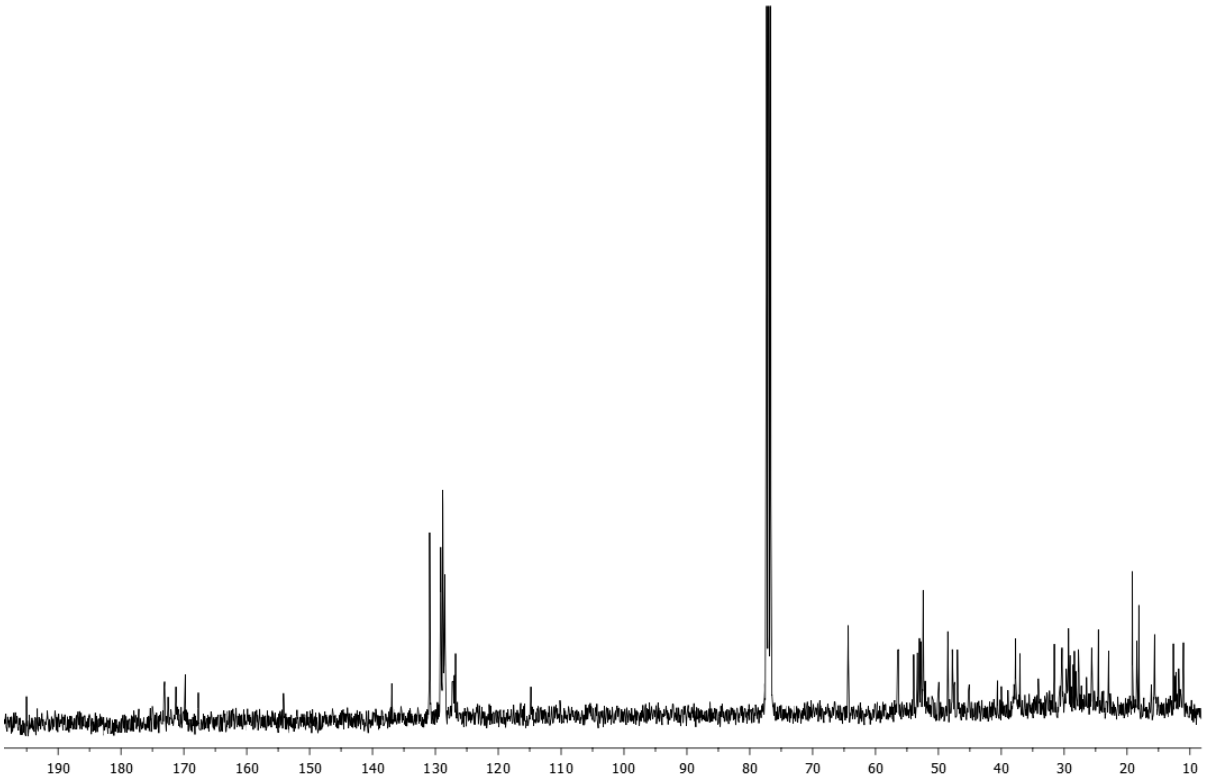
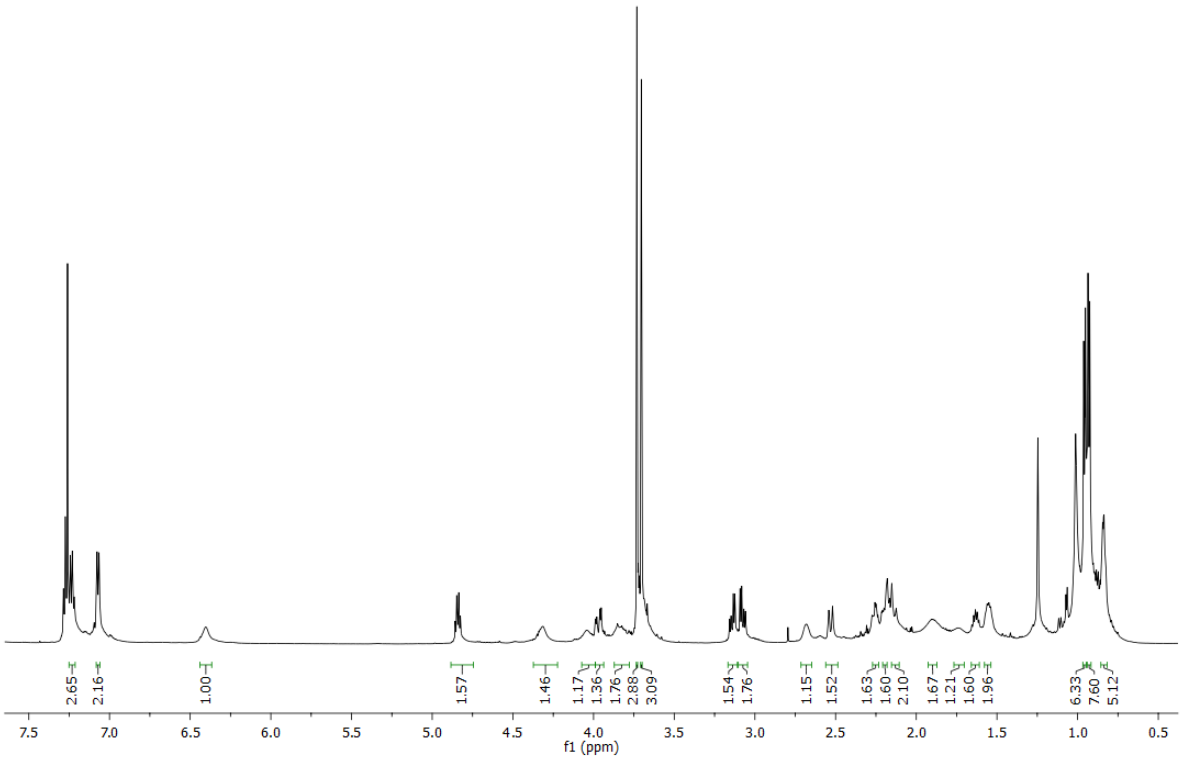


FIGURE 3.5.24- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.43**.



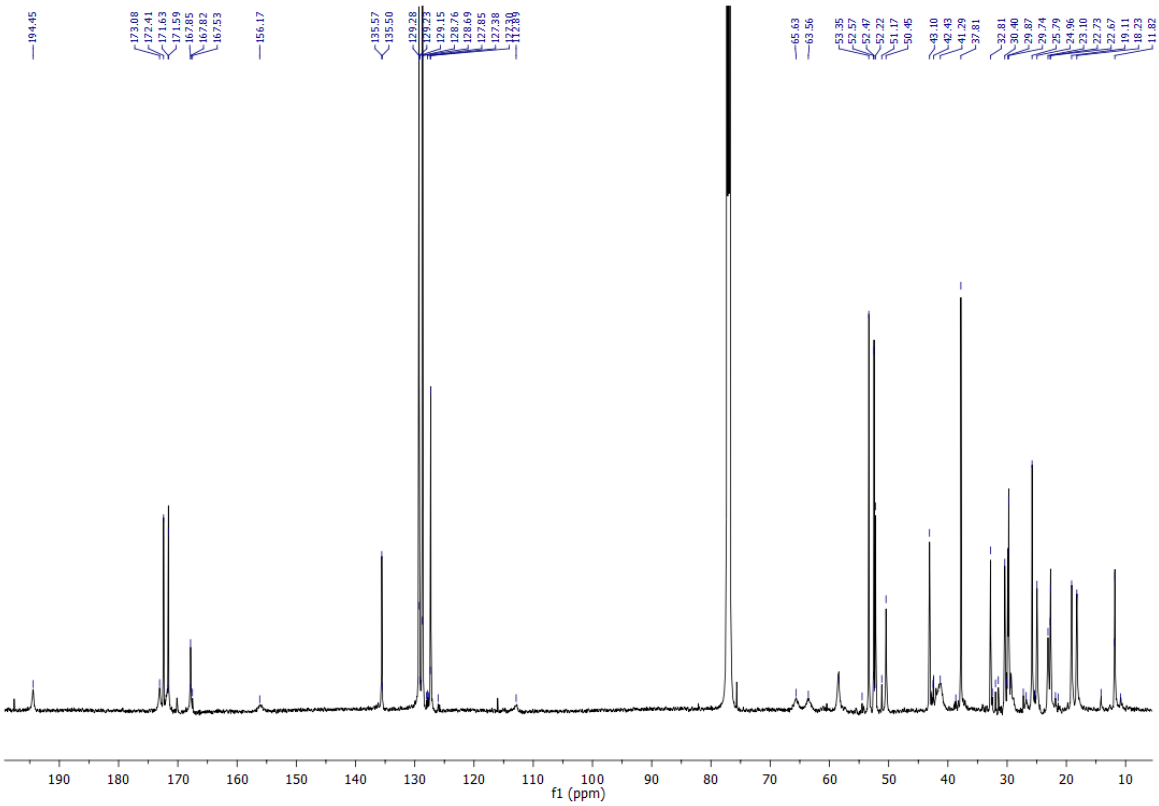
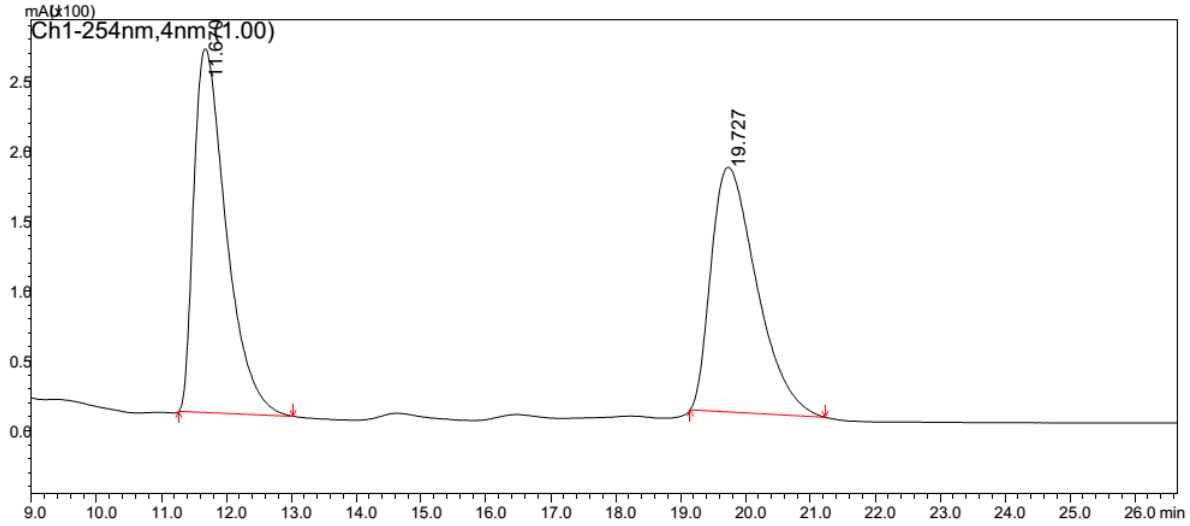
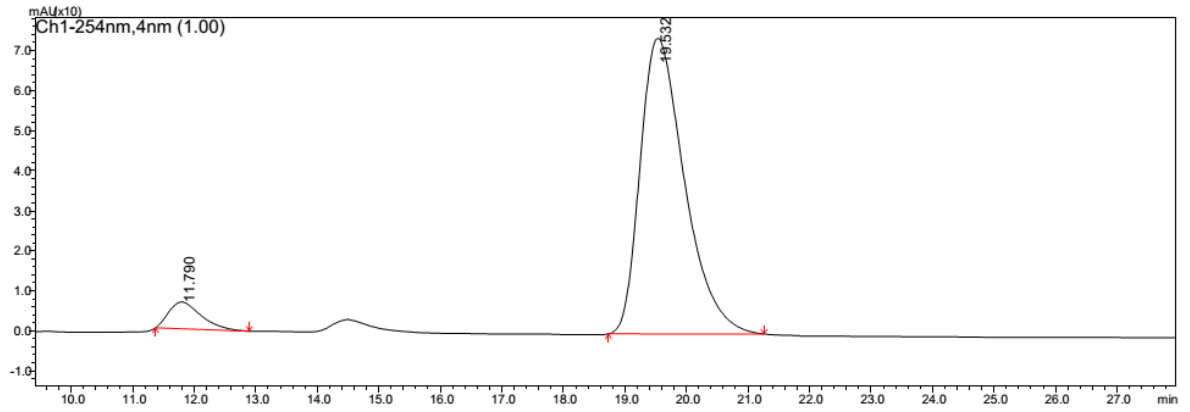


FIGURE 3.5.25- Chiral stationary-phase HPLC analysis of compound **1.43**; n-hexane/i-PrOH 95:5 AD-H at 1 mL/min.



PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.670	9022928	260087	51.354	59.791
2	19.727	8547156	174904	48.646	40.209
Total		17570083	434990	100.000	100.000



PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.790	242971	6658	6.151	8.268
2	19.532	3707410	73871	93.849	91.732
Total		3950381	80529	100.000	100.000

FIGURE 3.5.26- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1.45**.

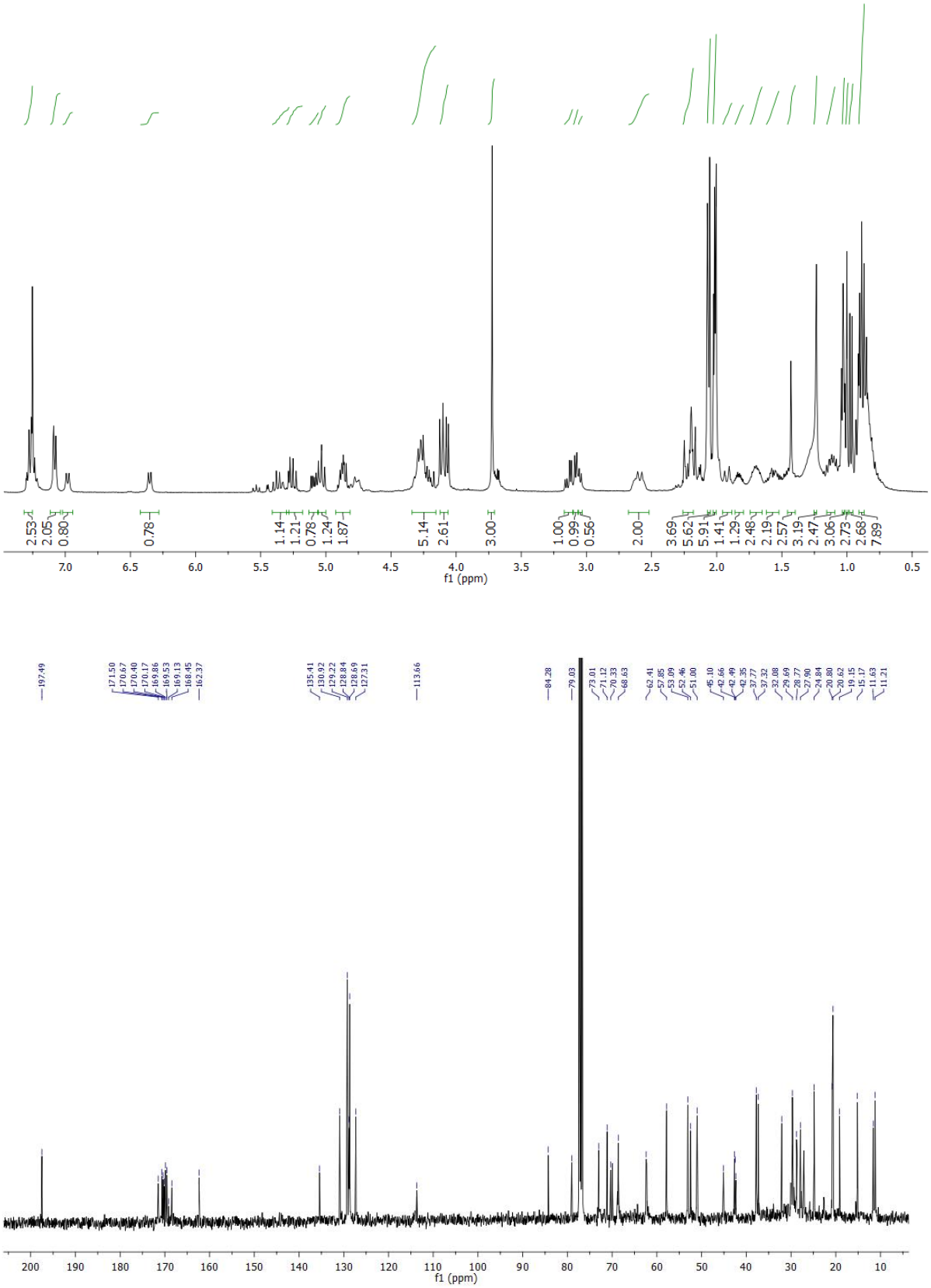
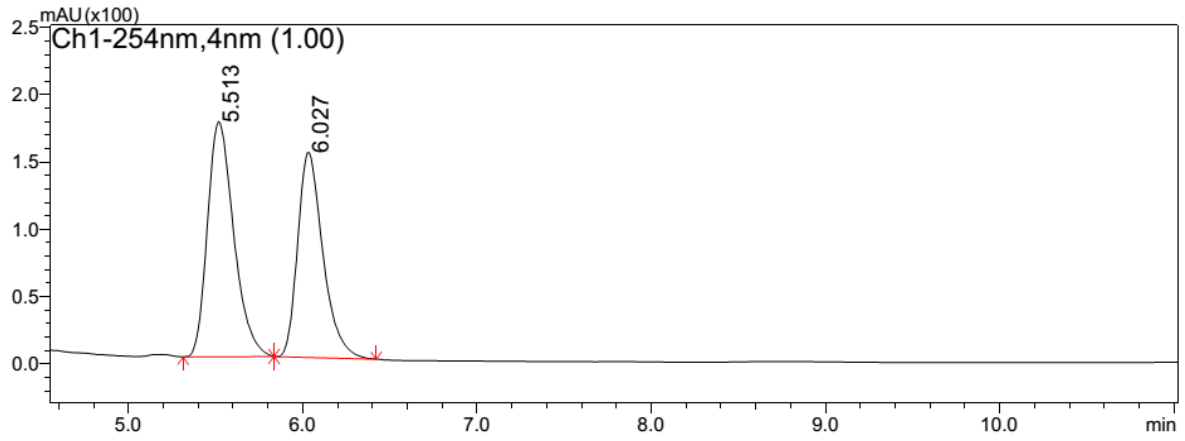
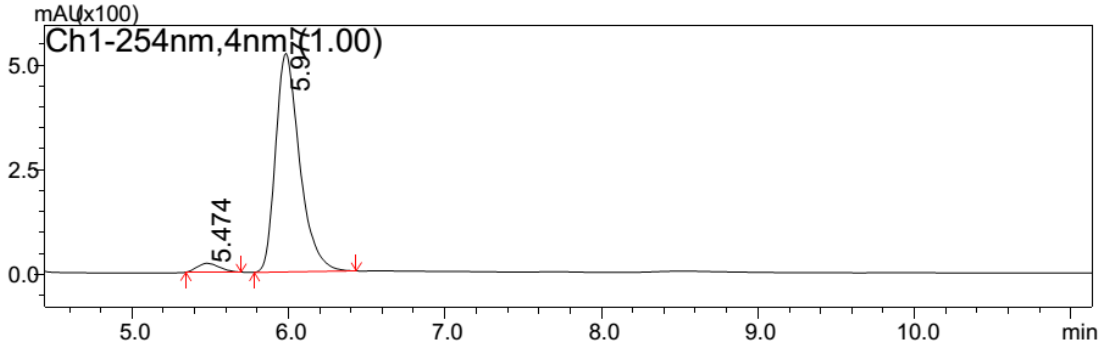


FIGURE 3.5.27- Chiral stationary-phase HPLC analysis of compound **1.45**. n-hexane/i-PrOH 90:10 OJ-H at 1 mL/min.



PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.513	1830097	174815	54.380	53.479
2	6.027	1535310	152068	45.620	46.521
Total		3365408	326883	100.000	100.000



PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.474	214847	21544	3.692	3.955
2	5.977	5604148	523129	96.308	96.045
Total		5818995	544673	100.000	100.000

3.6 Selected Spectra and Chromatograms of Chapter 2

FIGURE 3.6.1-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.73**.

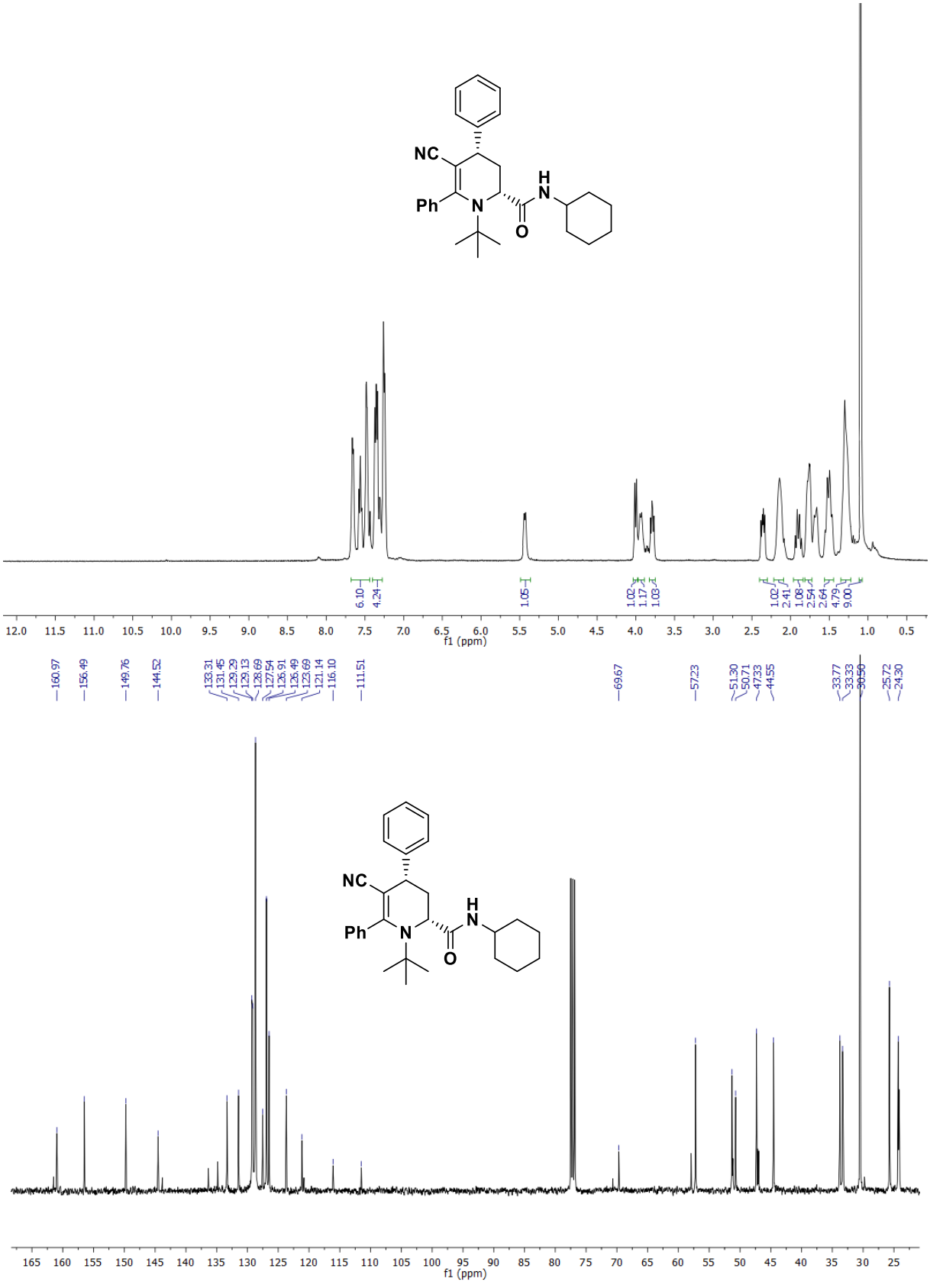


FIGURE 3.6.2-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.74**.

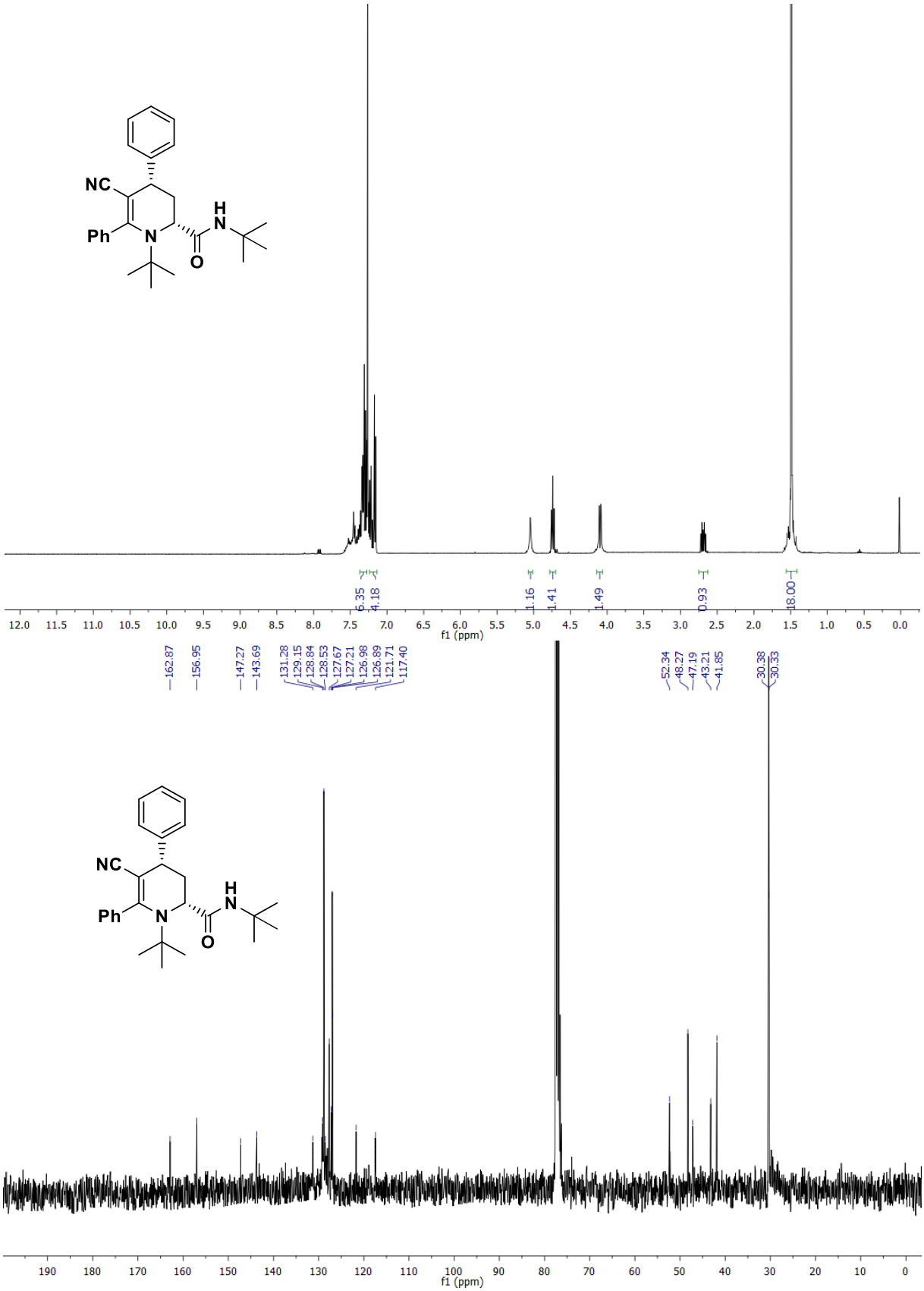


FIGURE 3.6.3-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.75**.

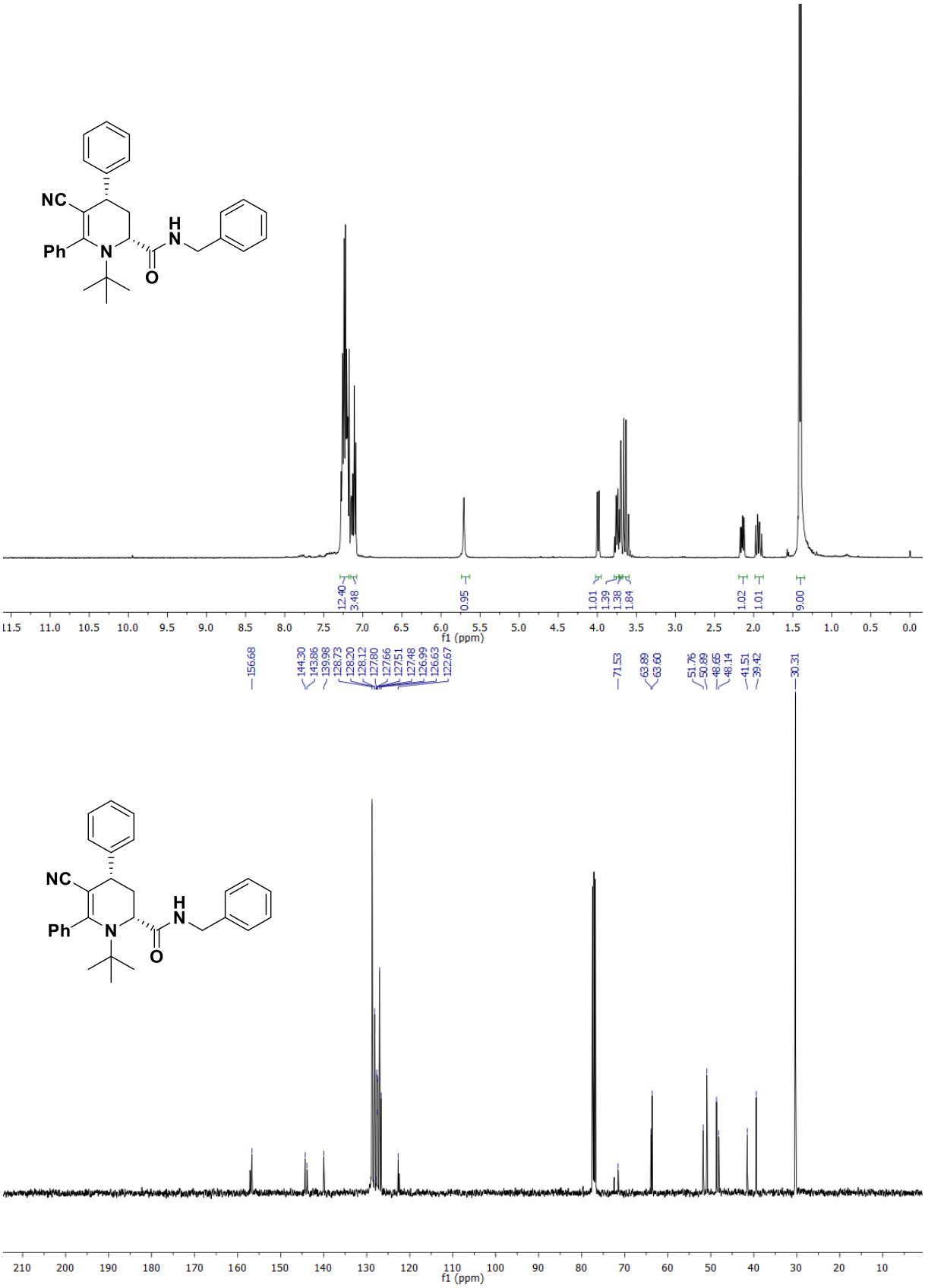


FIGURE 3.6.4-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.76**.

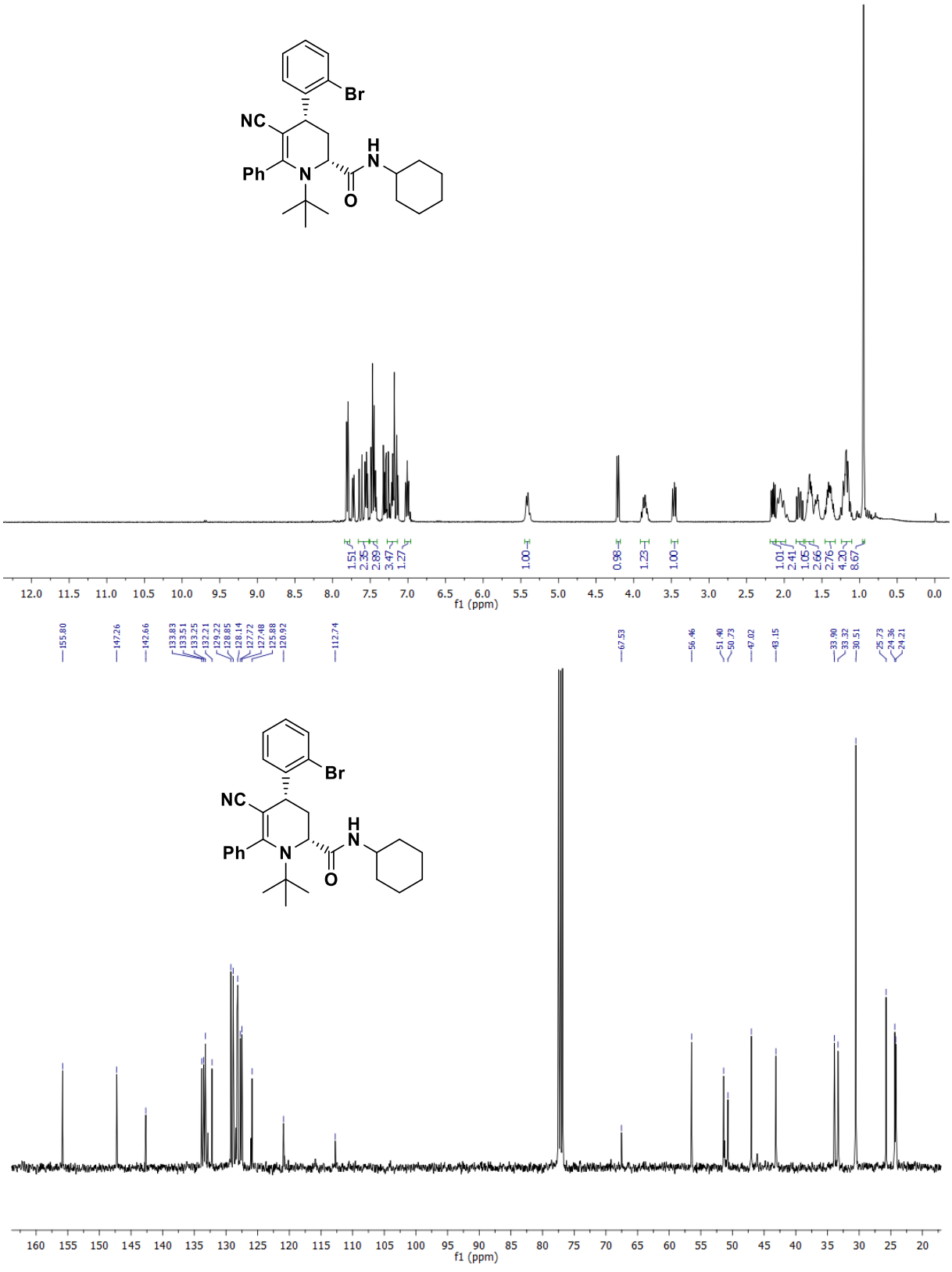


FIGURE 3.6.5-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.77**.

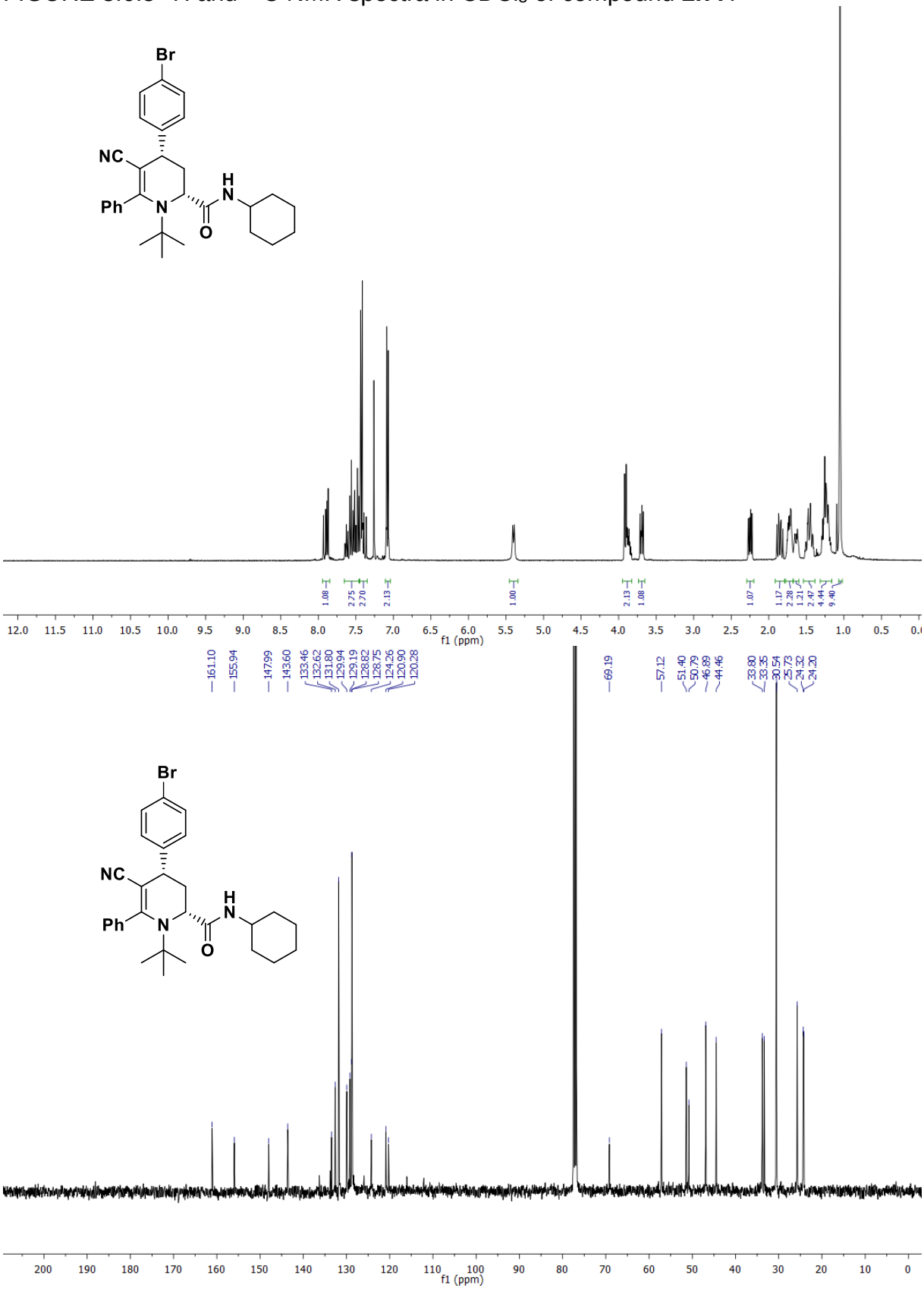


FIGURE 3.6.6-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.78**.

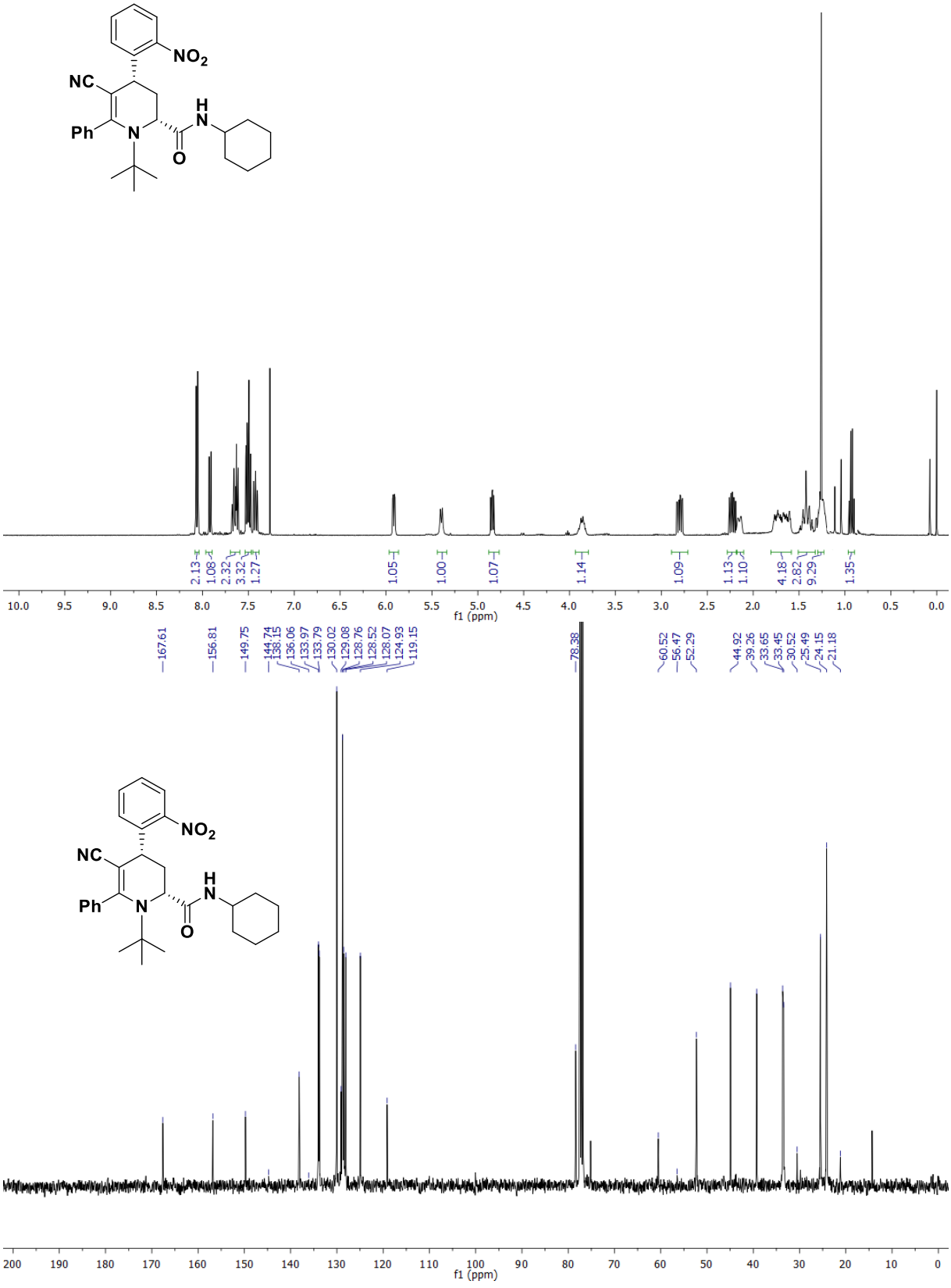


FIGURE 3.6.7-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.79**.

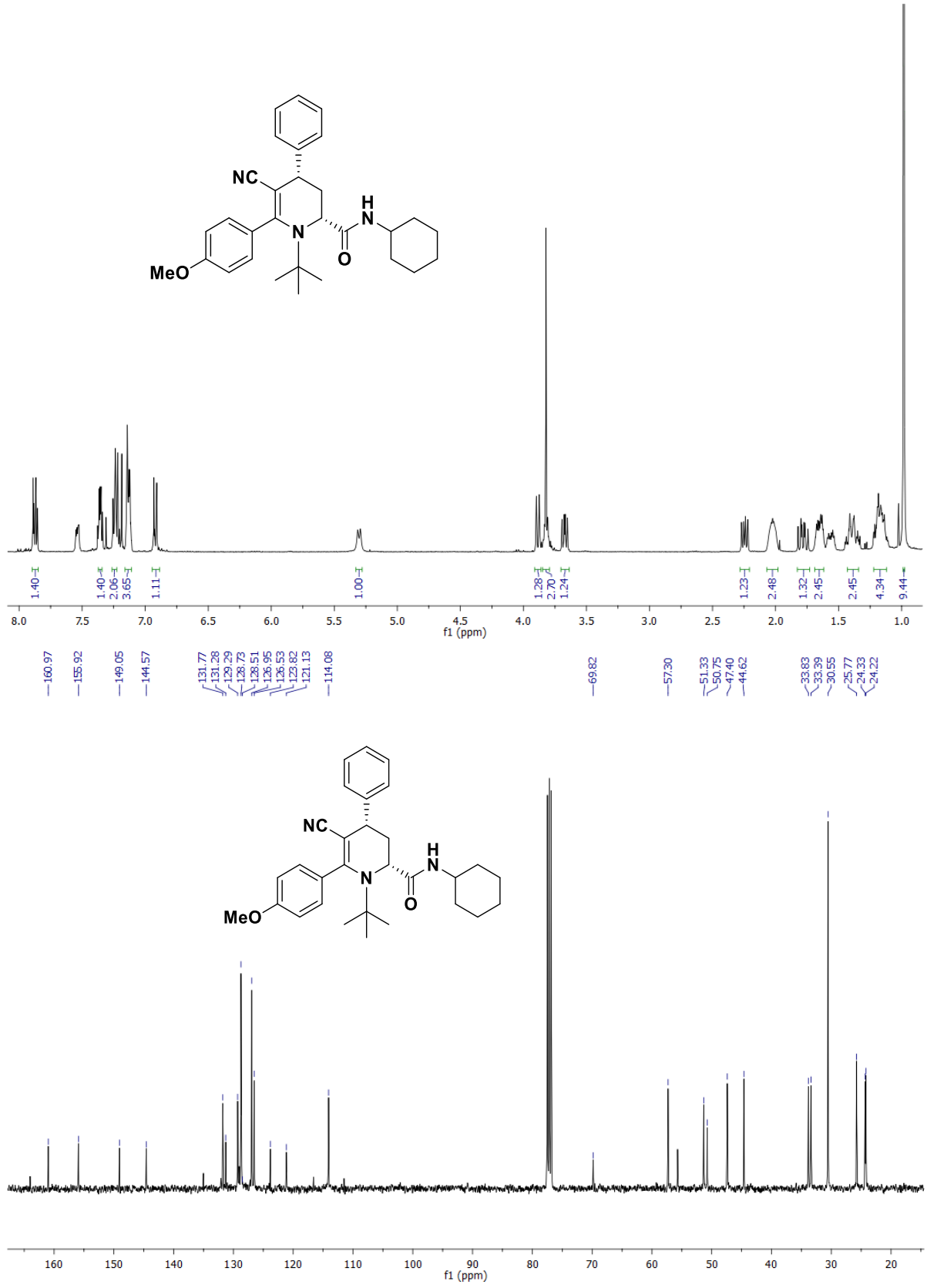
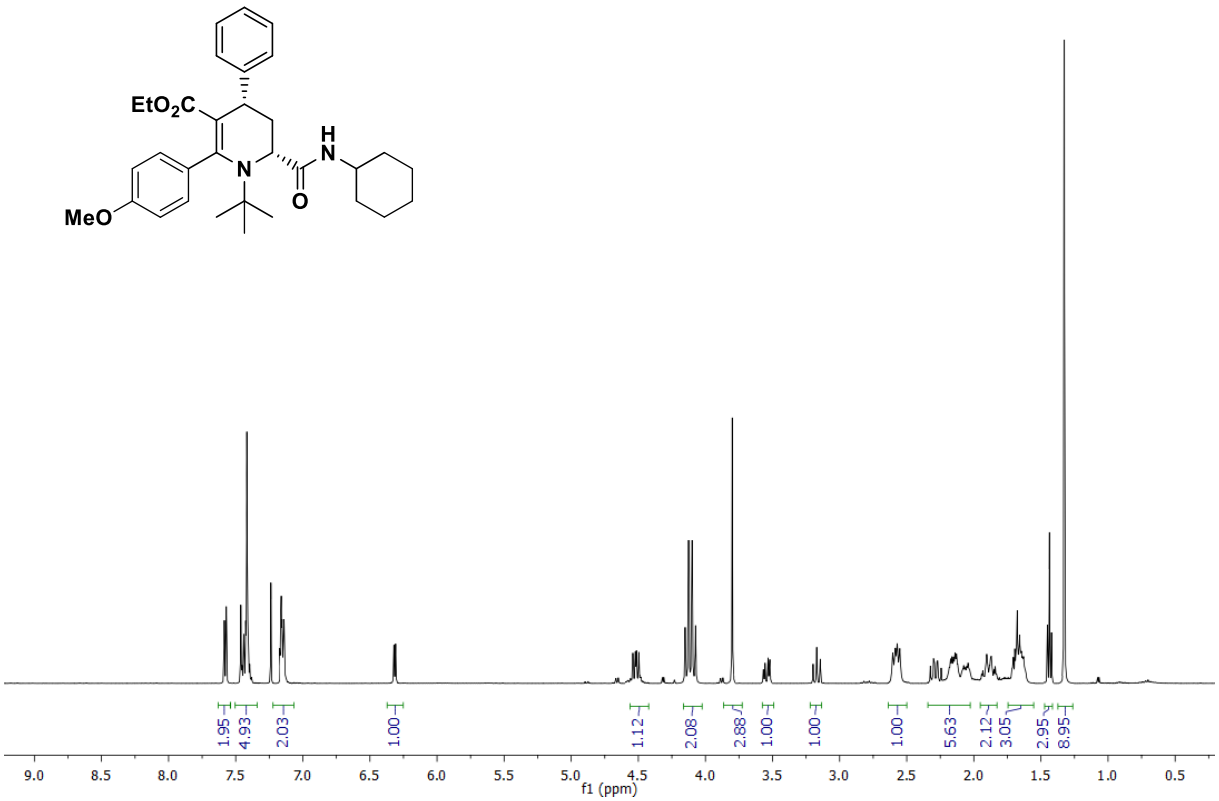


FIGURE 3.6.8-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.80**.



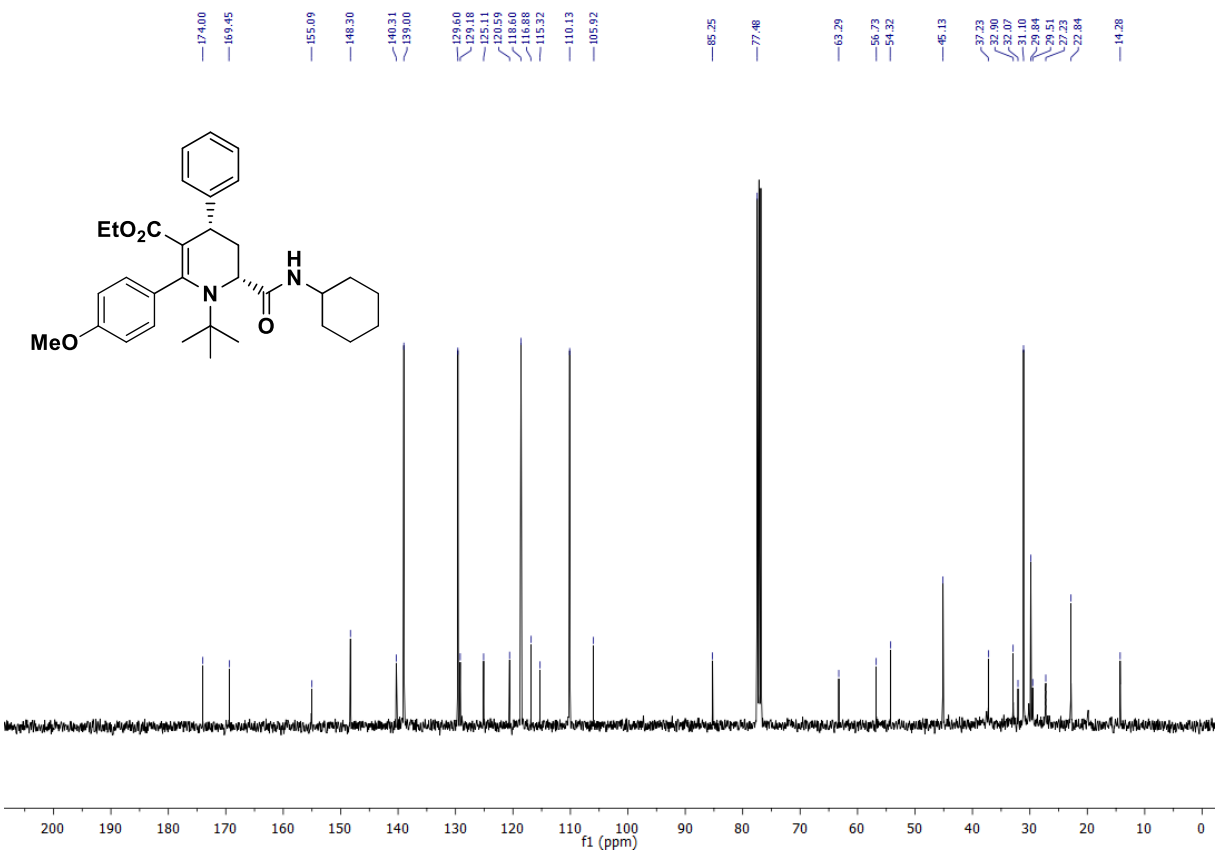


FIGURE 3.6.9-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.81**.

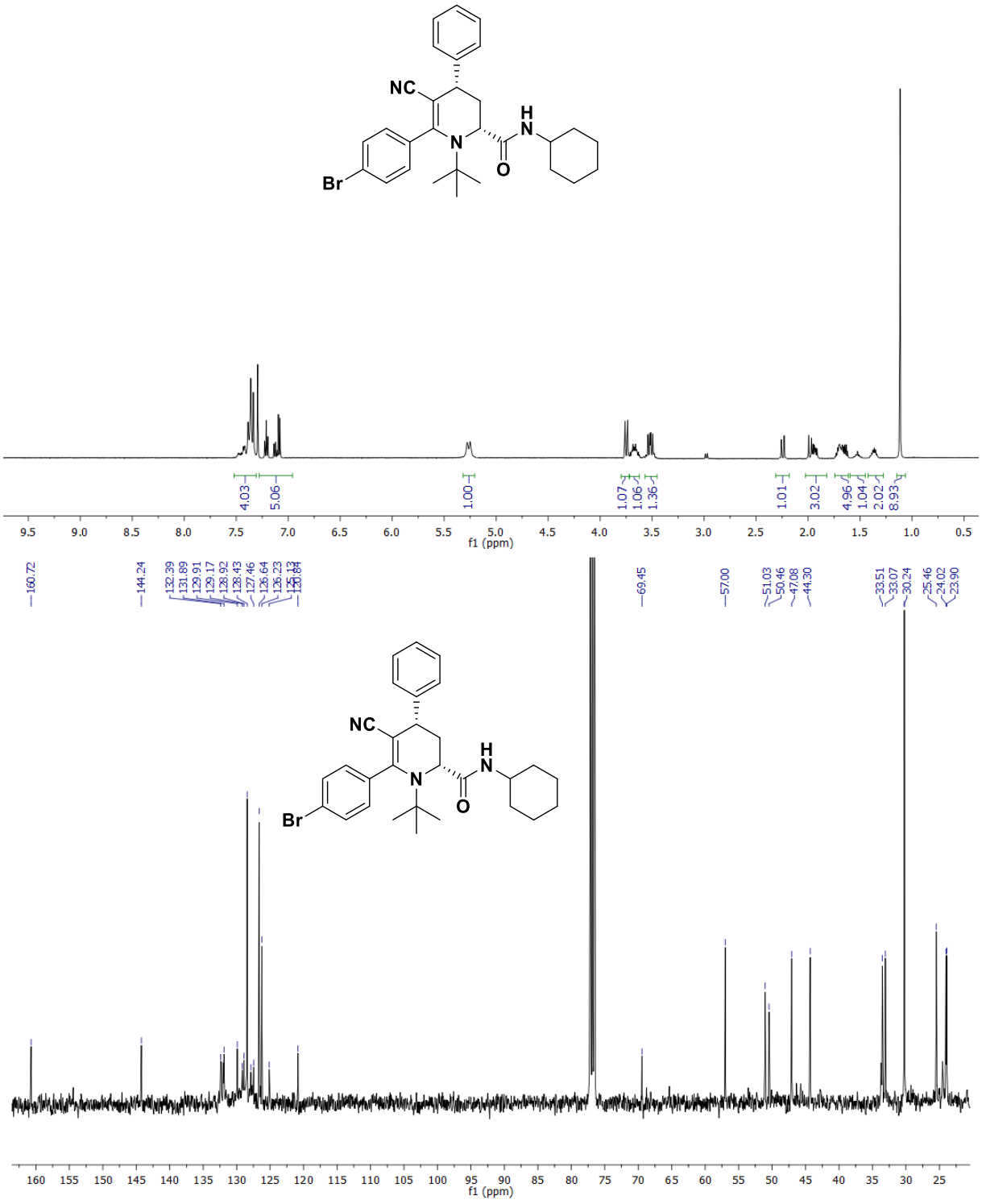


FIGURE 3.6.10-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.82**.

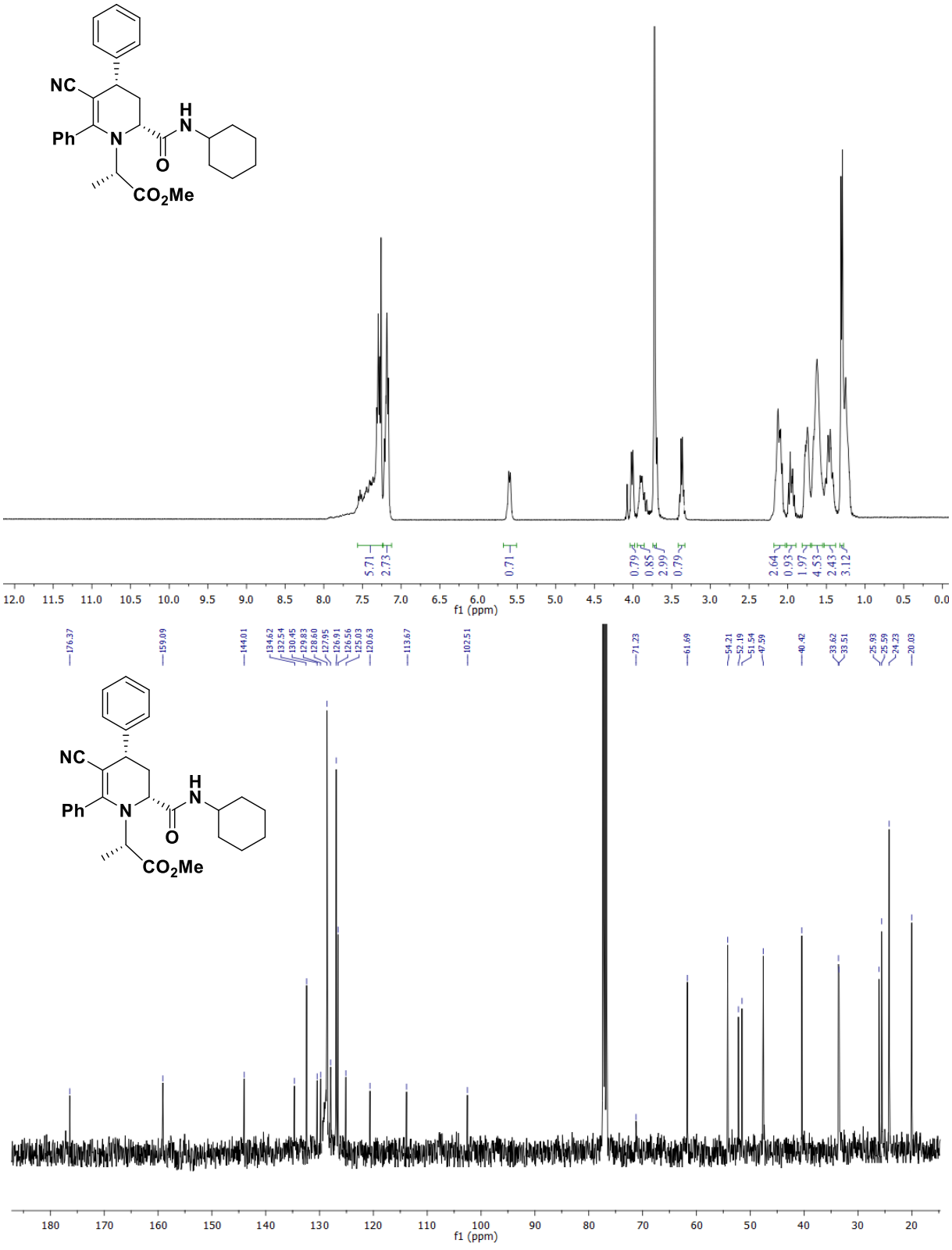
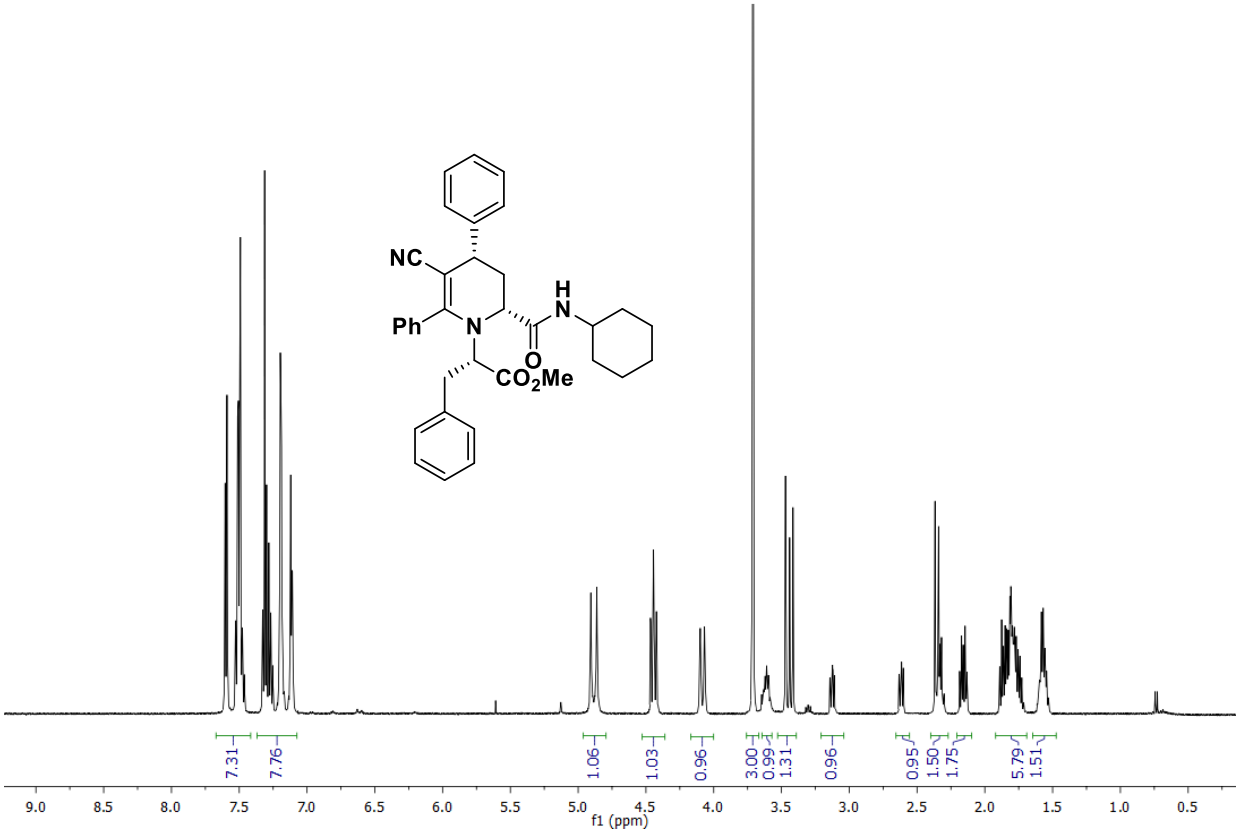


FIGURE 3.6.11-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.83**.



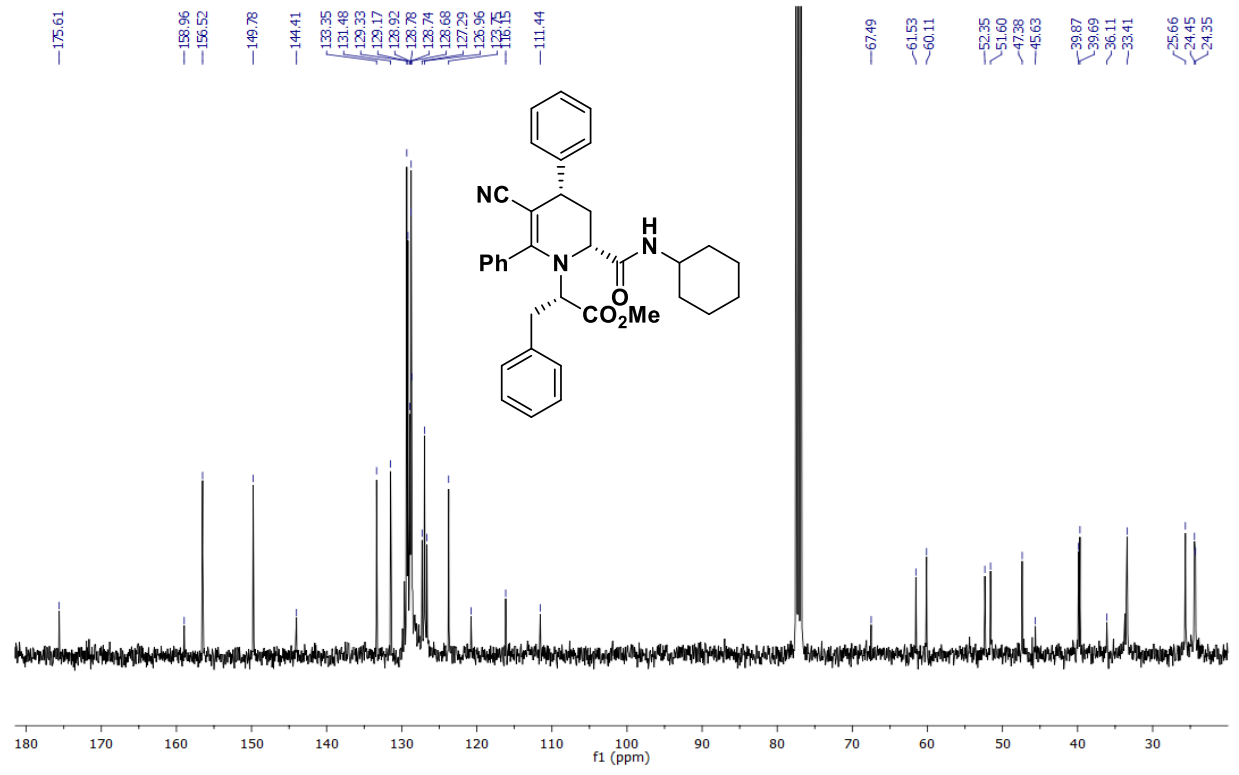


FIGURE 3.6.12-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.84**.

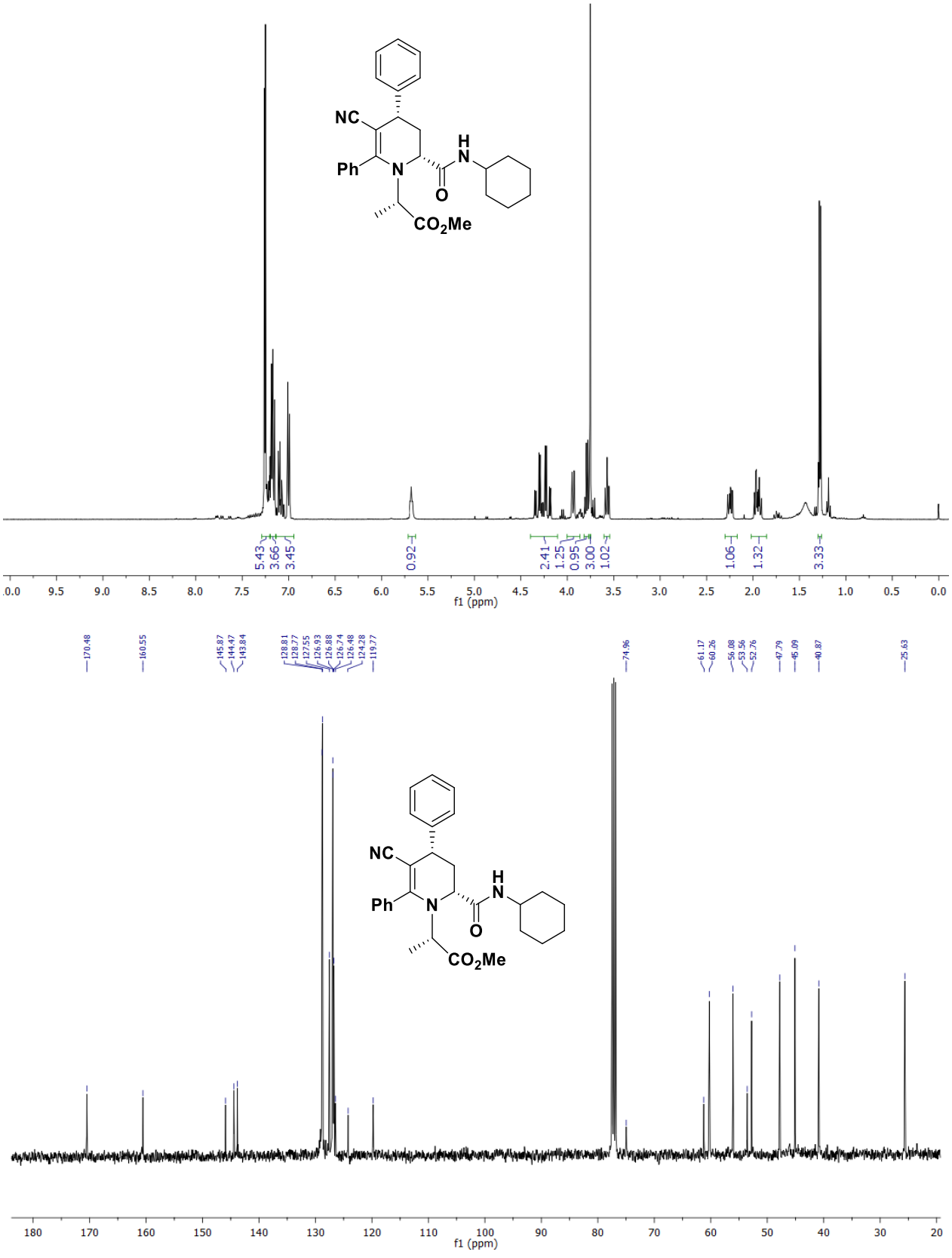
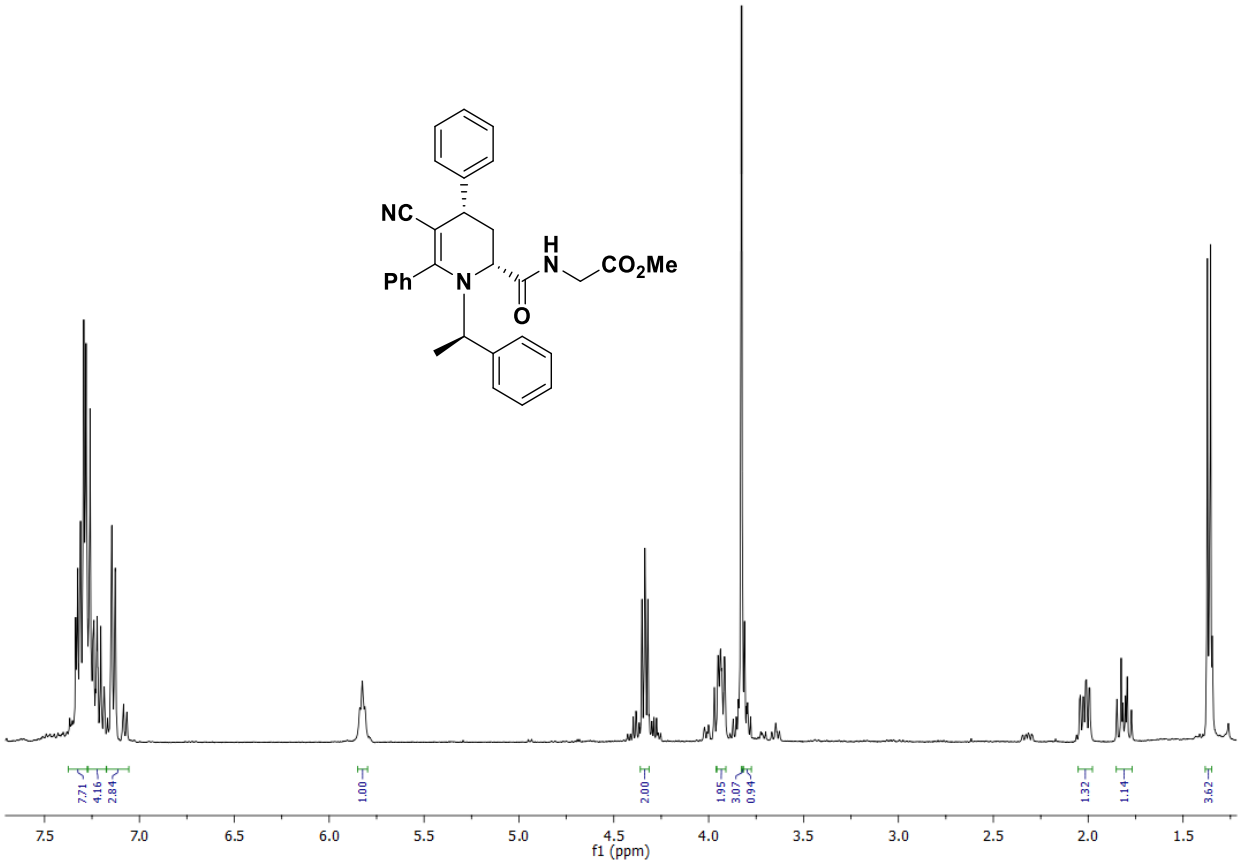


FIGURE 3.6.13-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.85**.



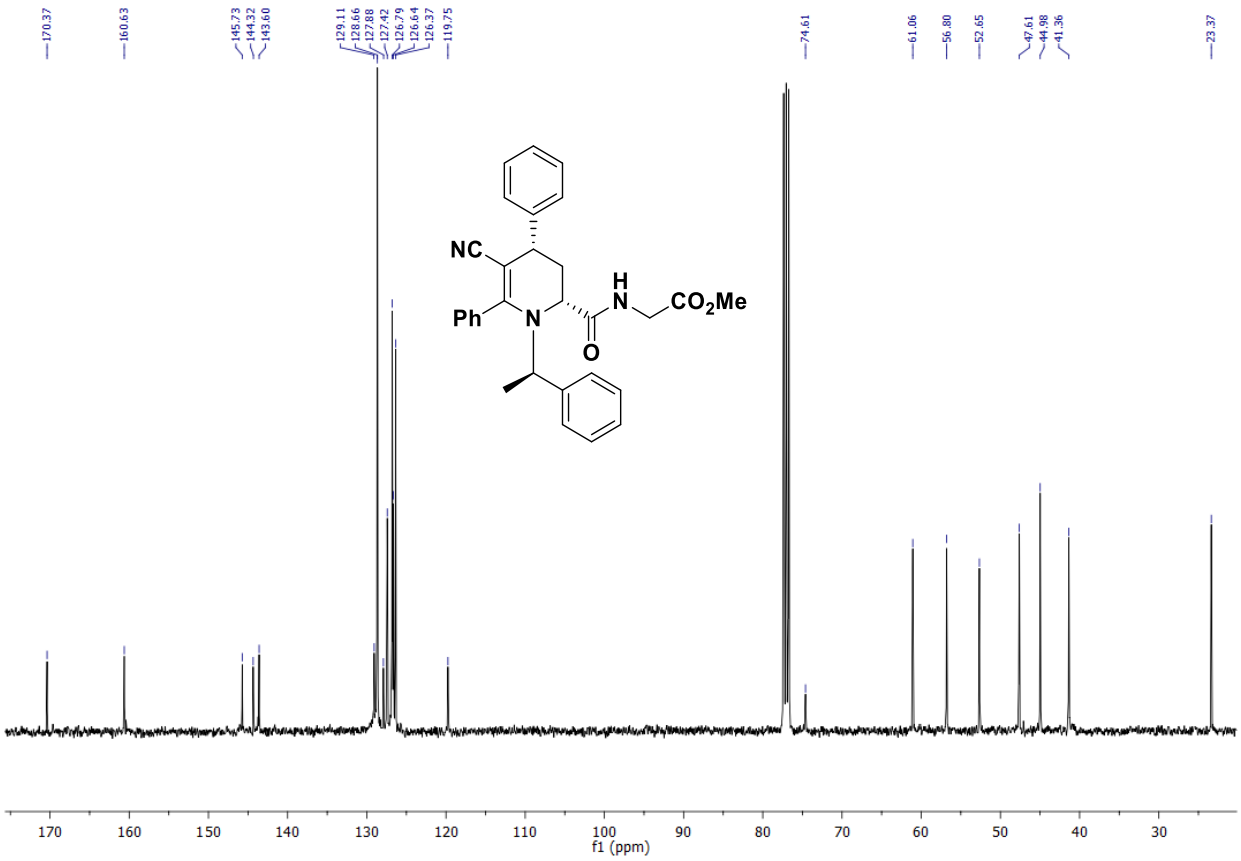


FIGURE 3.6.14-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.86**.

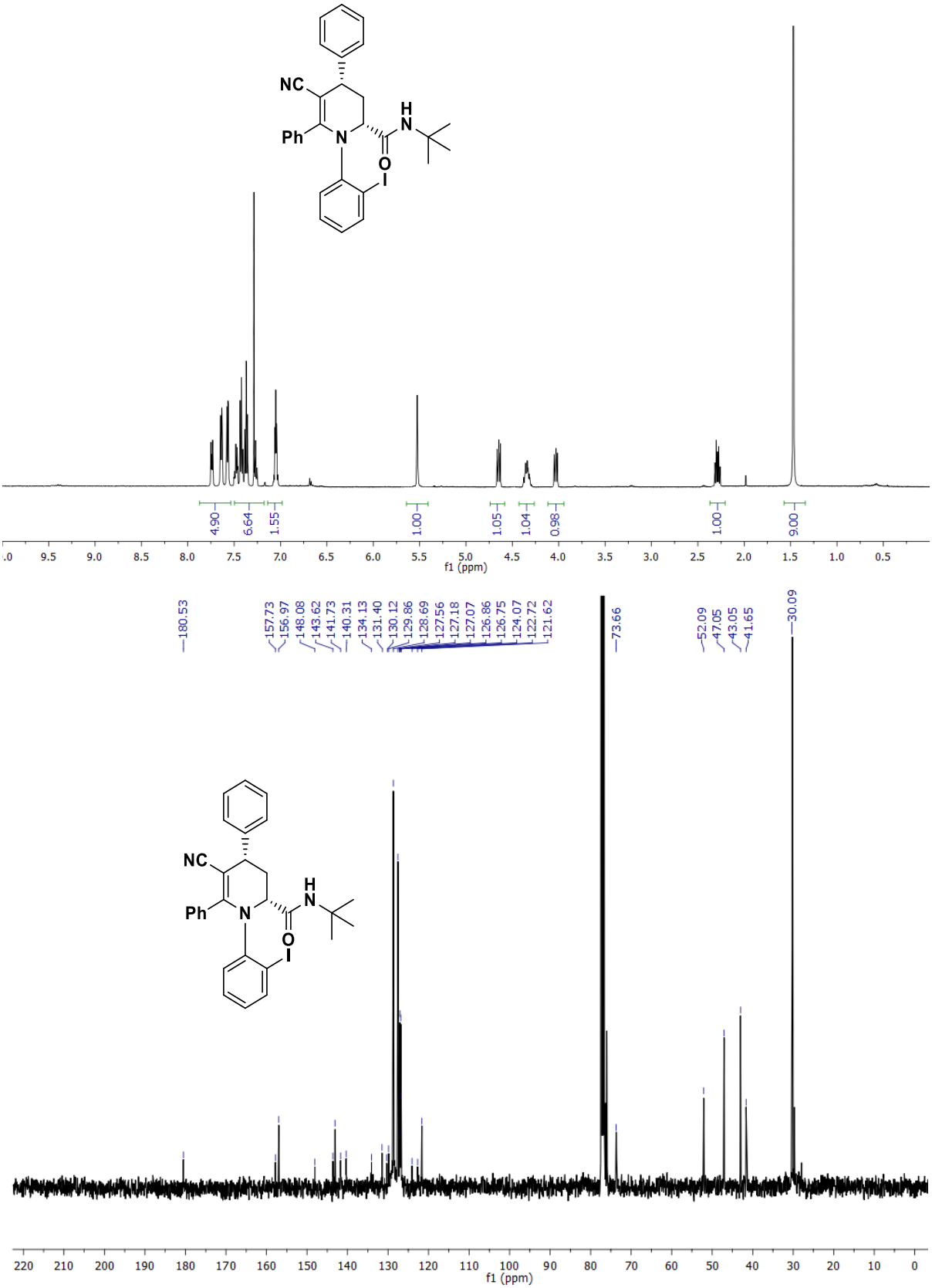


FIGURE 3.6.15-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.87**.

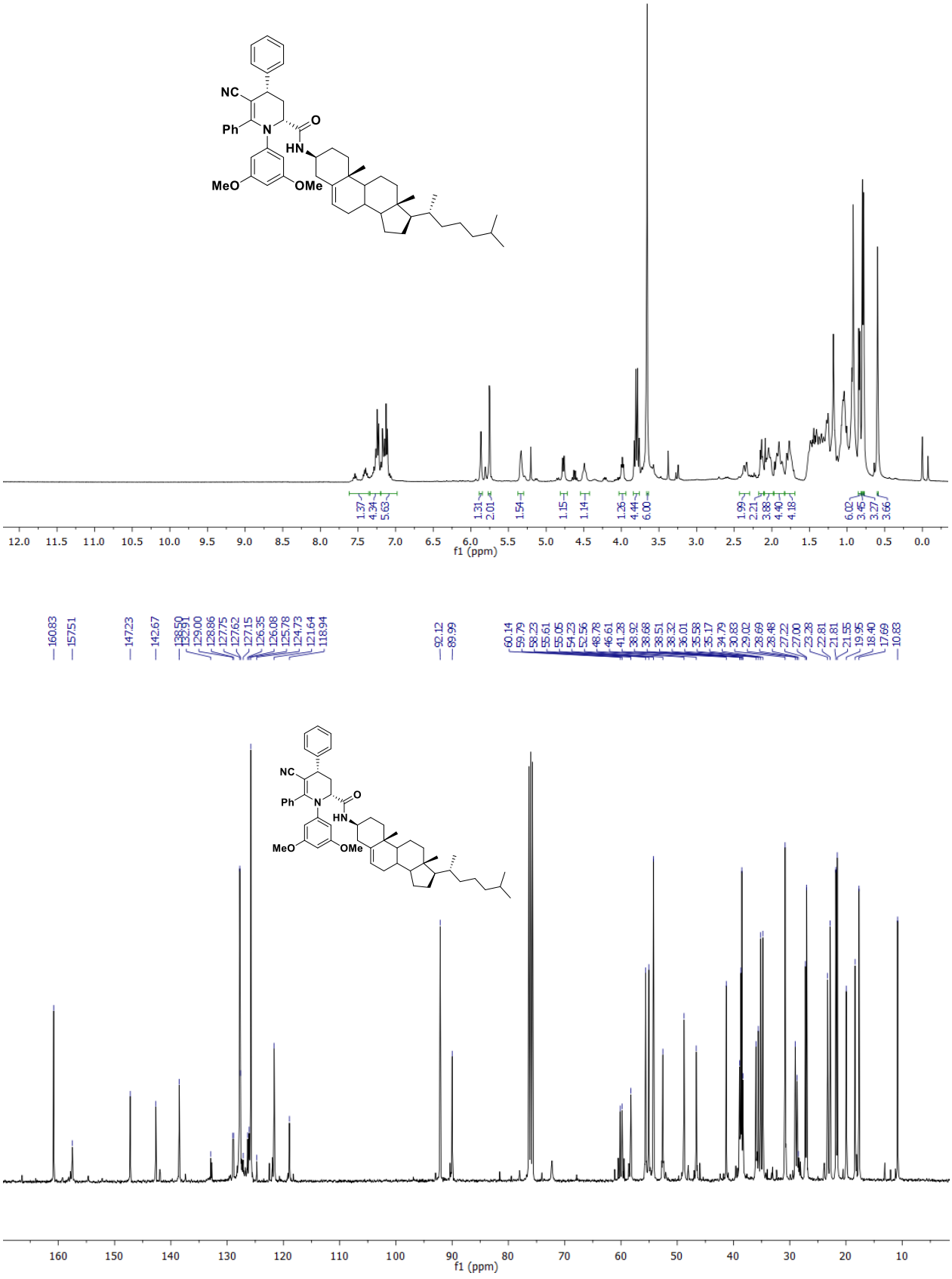


FIGURE 3.6.16-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.88**.

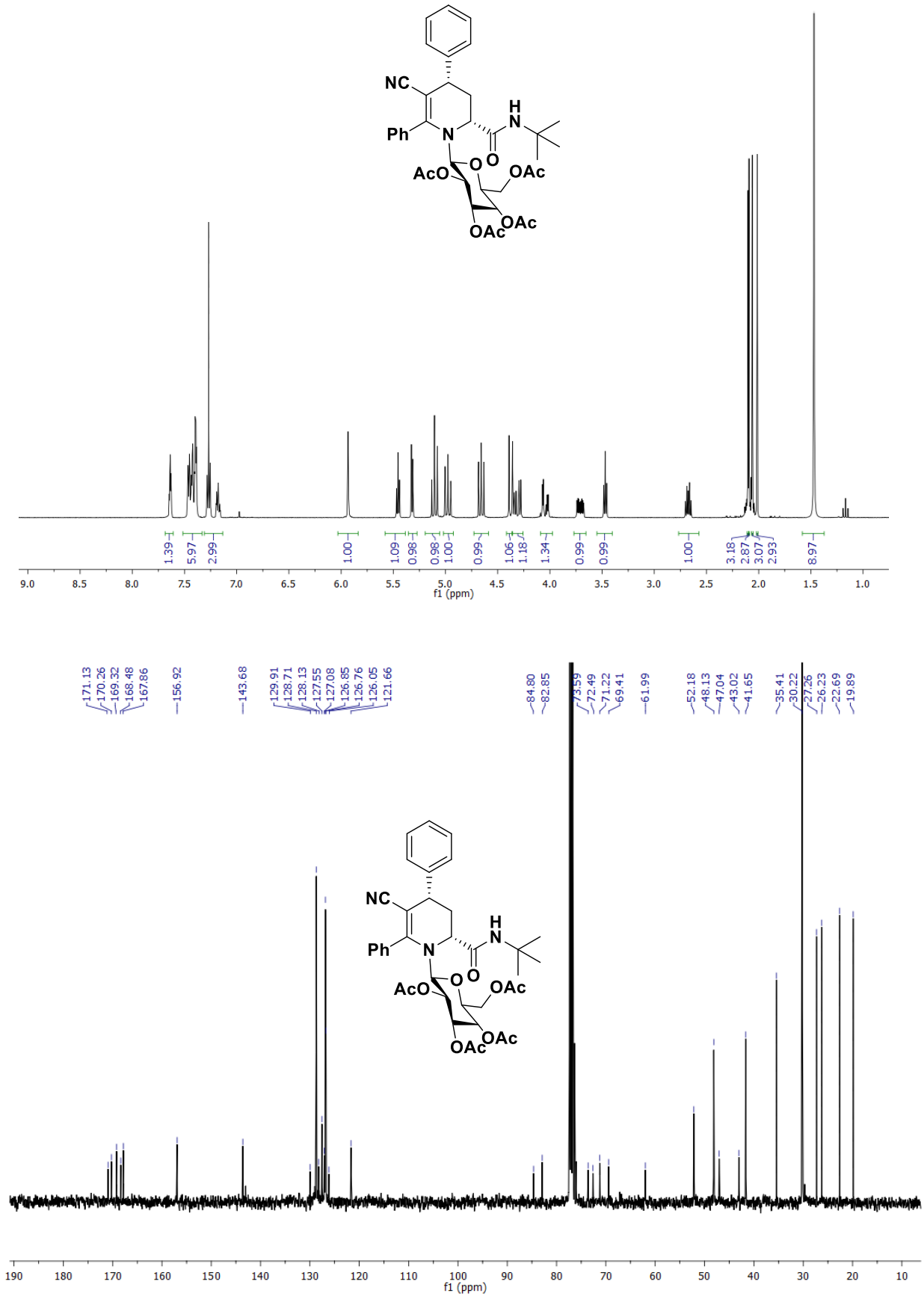


FIGURE 3.6.17-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.89**.

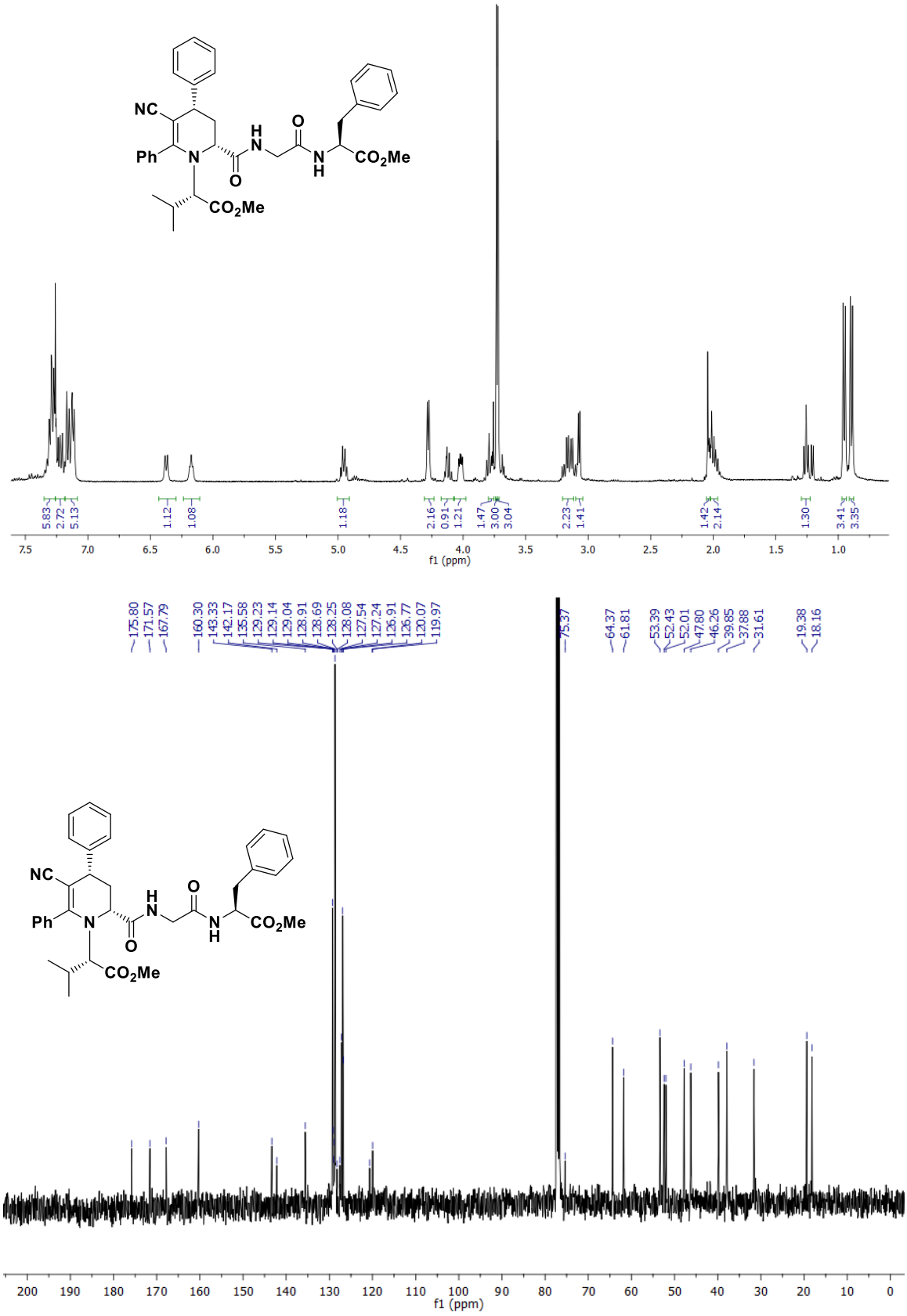
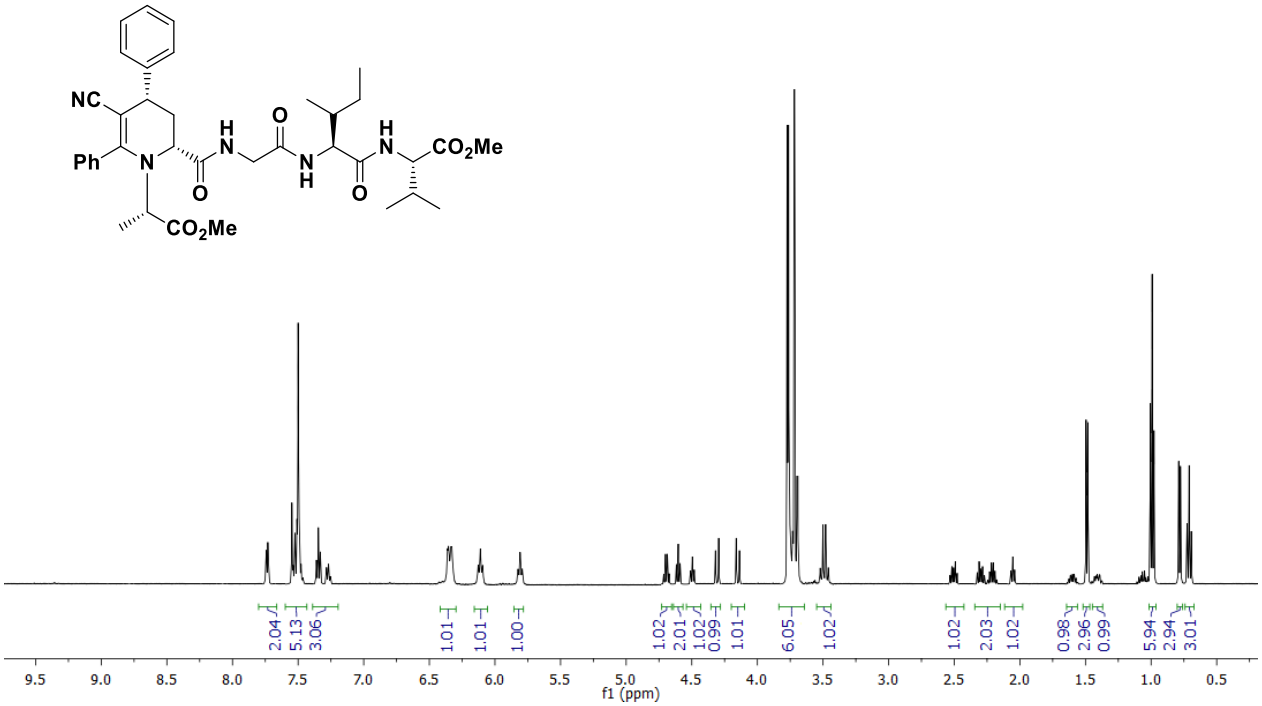


FIGURE 3.6.18-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.90**.



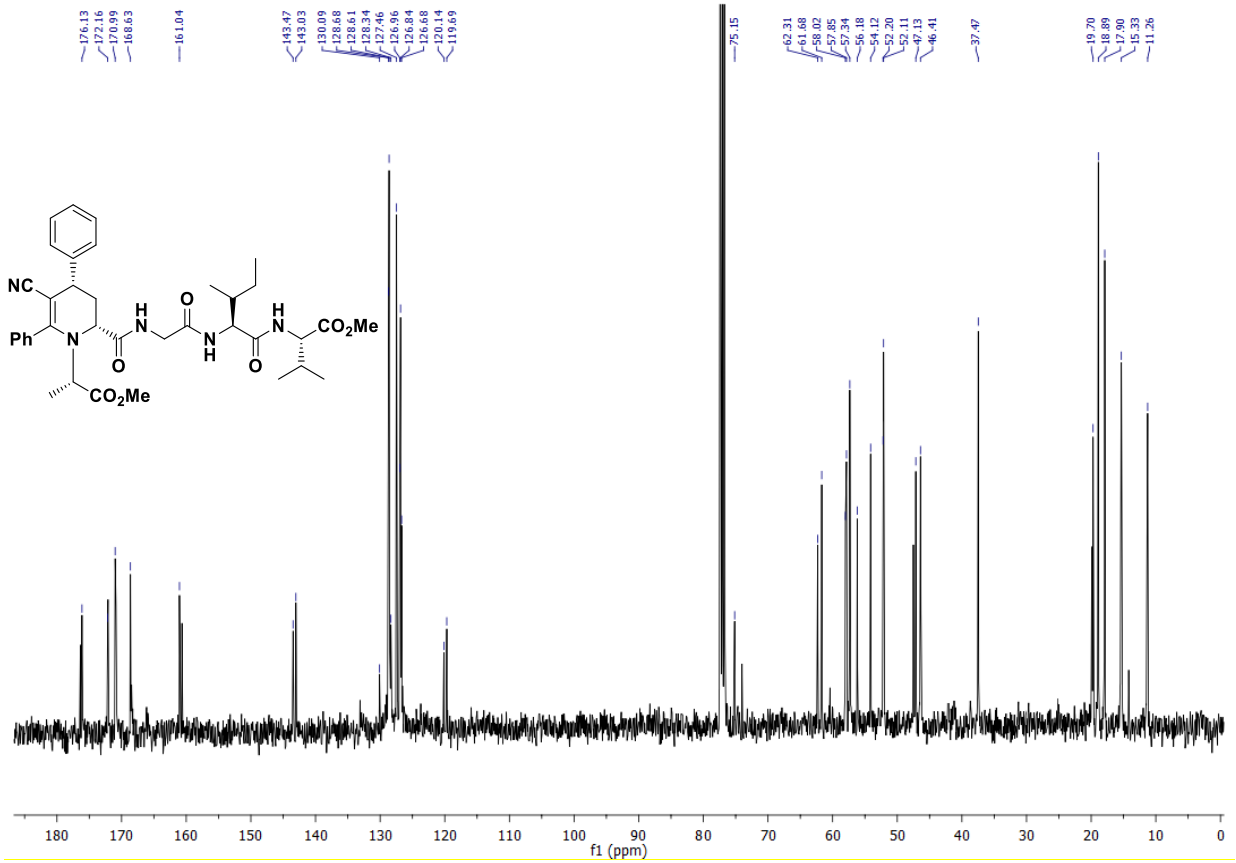
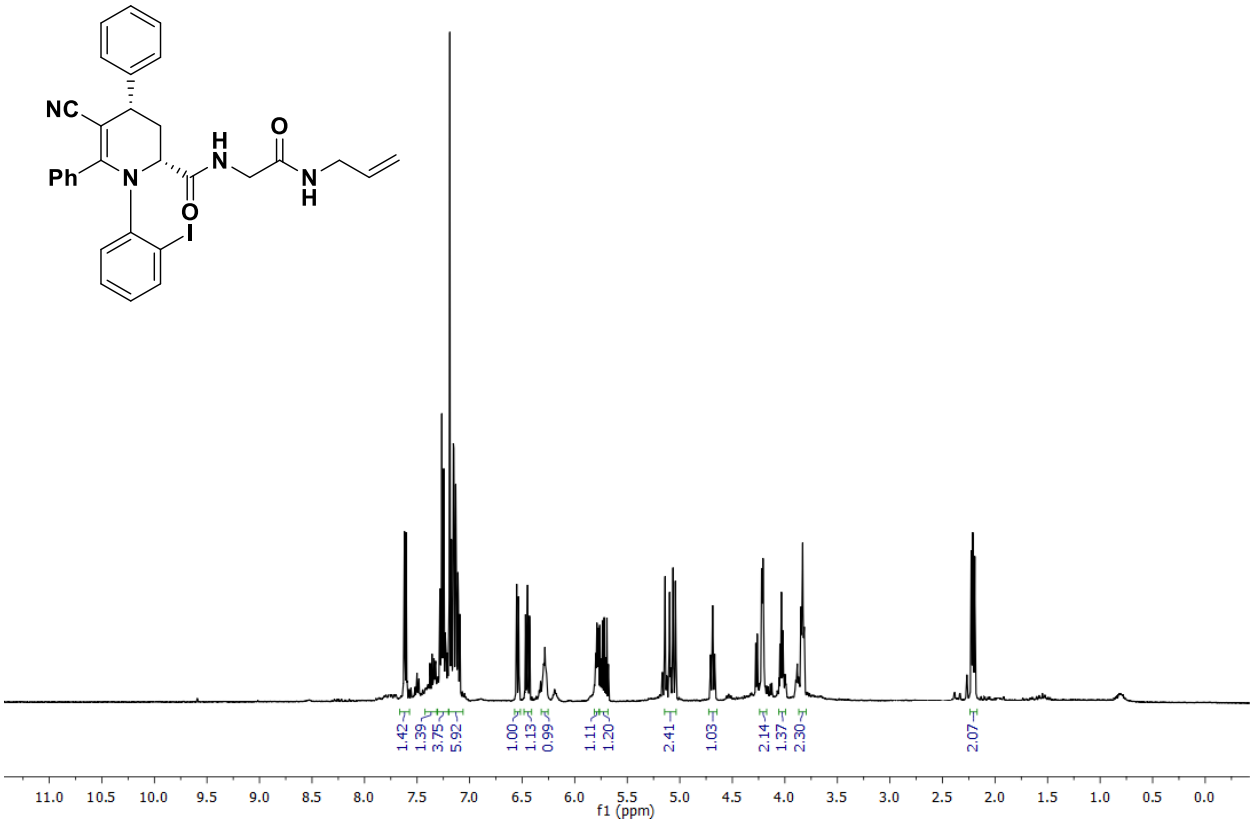


FIGURE 3.6.19-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.91**.



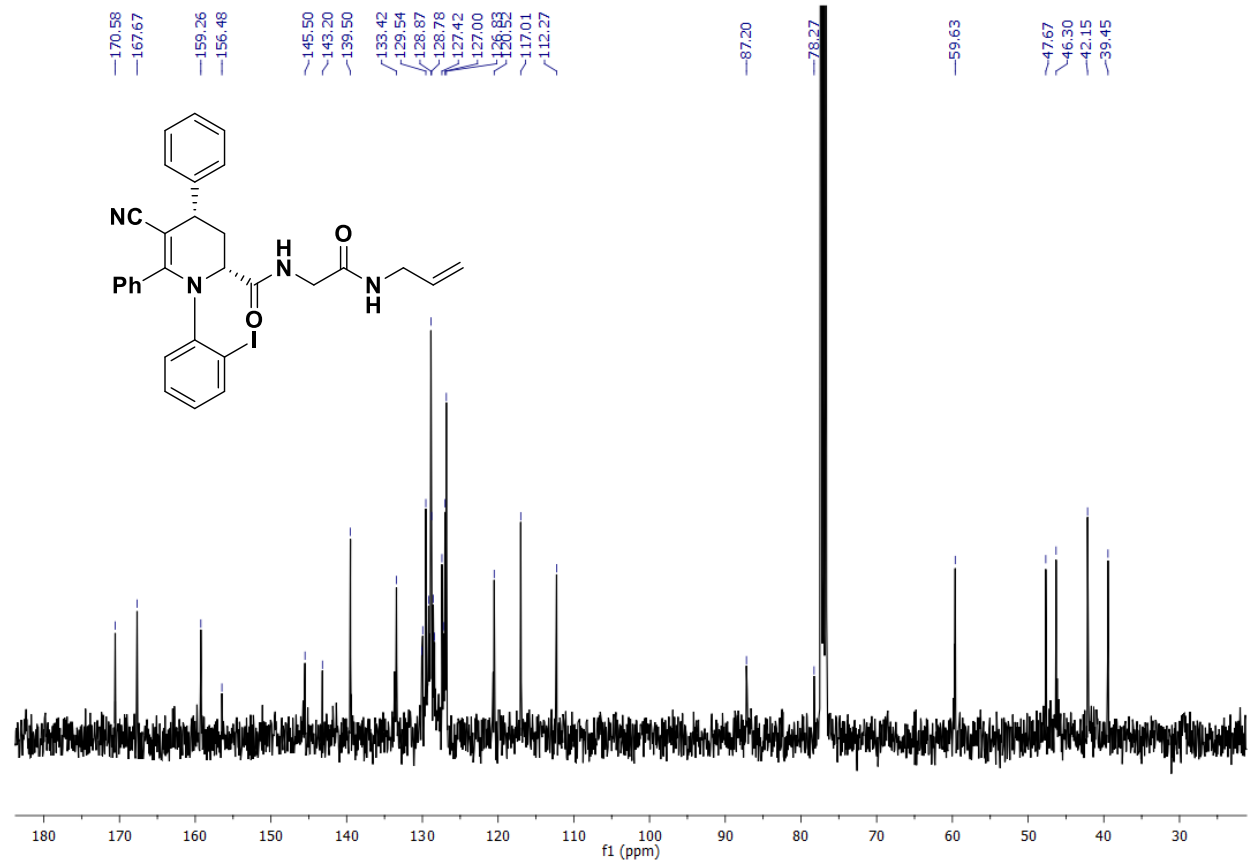
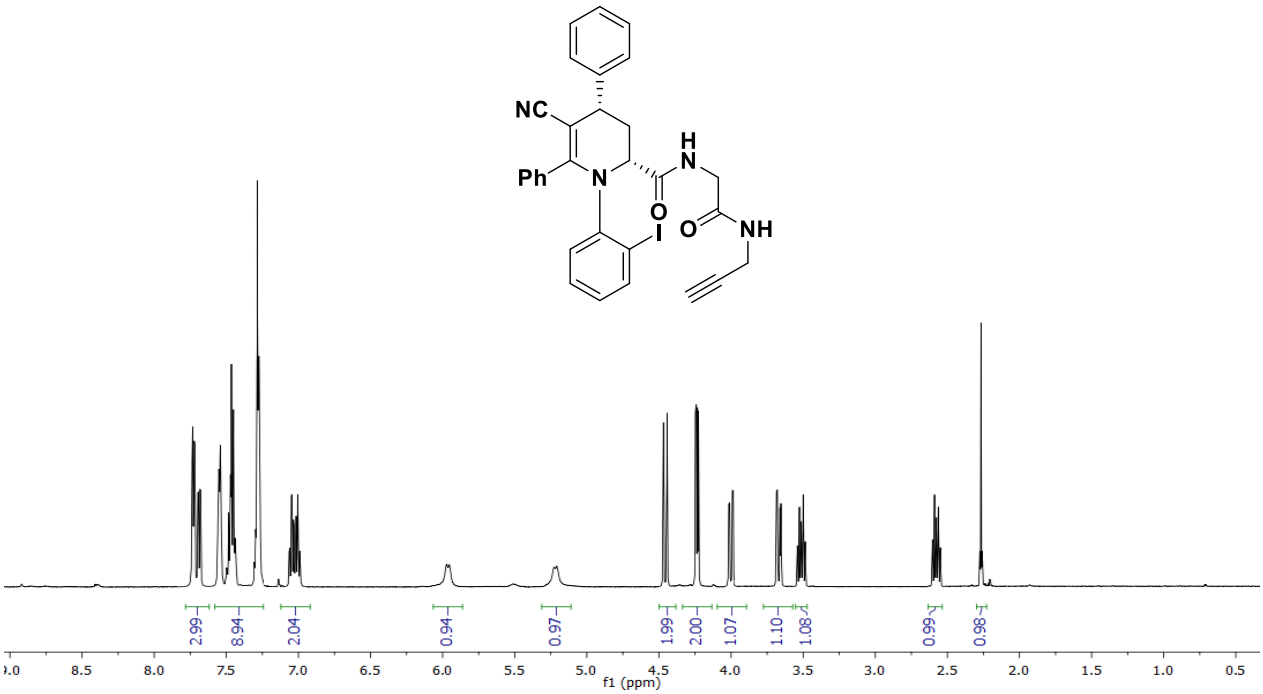


FIGURE 3.6.20-^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2.92**.



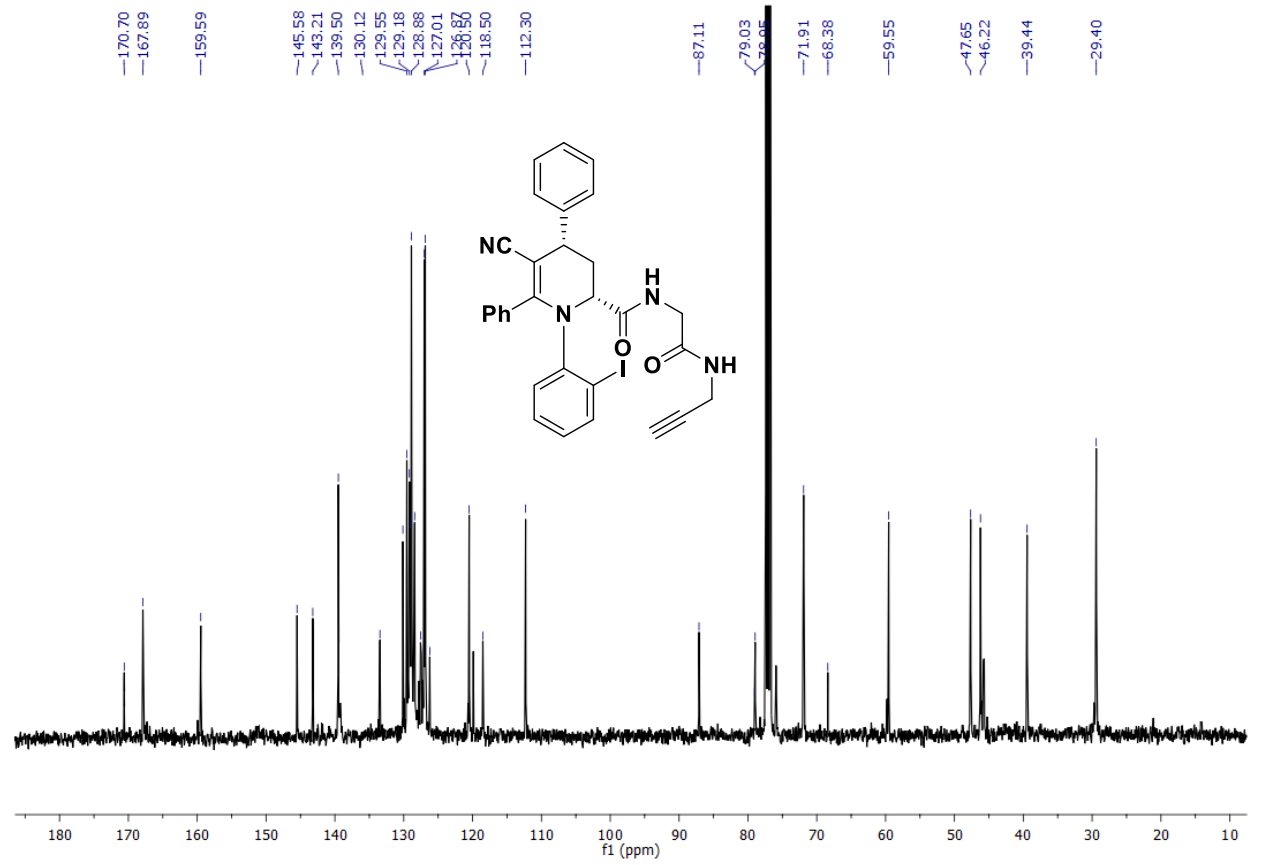
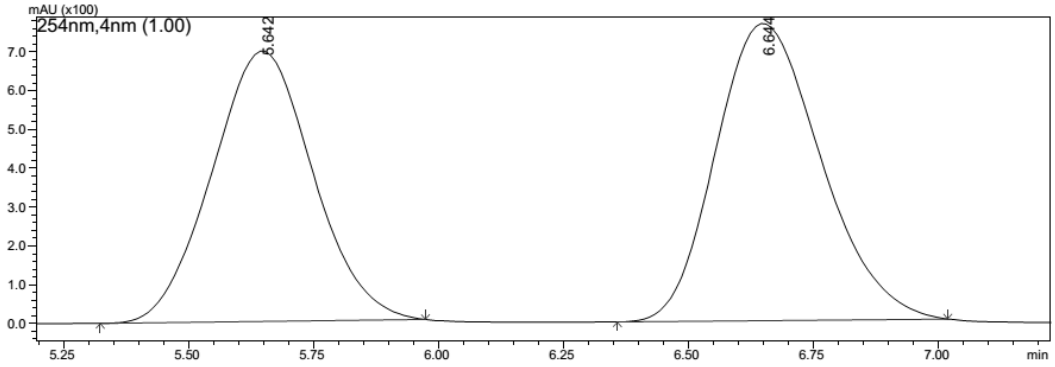
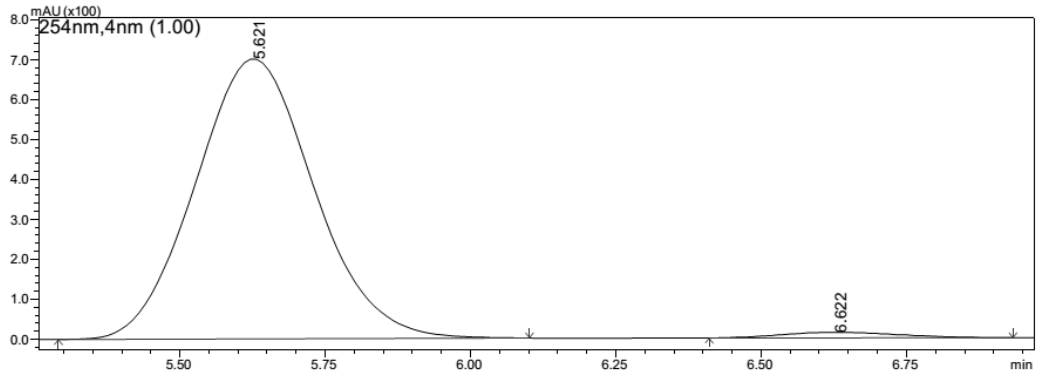


FIGURE 3.6.21- Chiral stationary-phase HPLC analysis of compound **2.73**. OD-H column (n-hexane/iPrOH 90:10) at 0.8 mL/min.

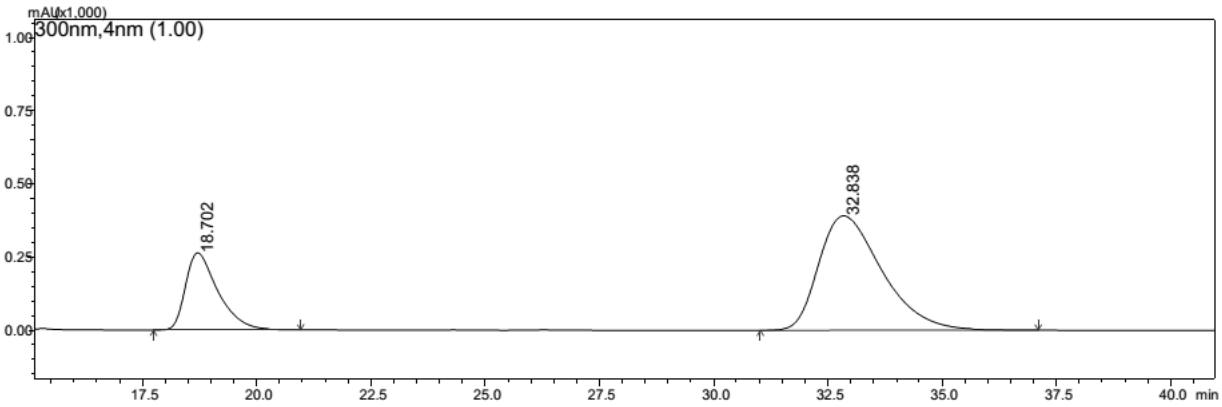


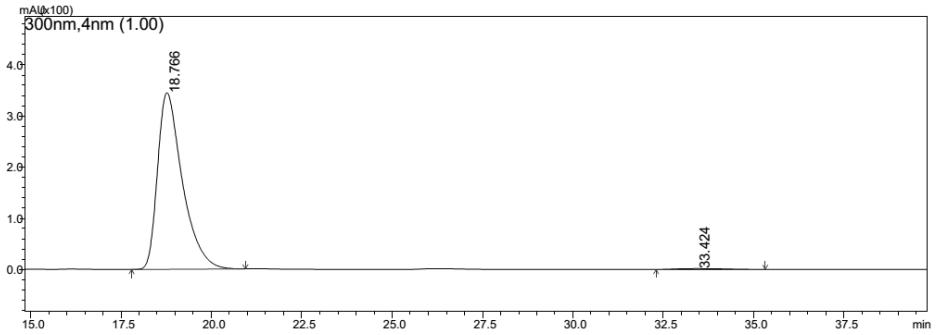


PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.621	9945319	700393	98.041	98.049
2	6.622	198761	13933	1.959	1.951
Total		10144081	714326	100.000	100.000

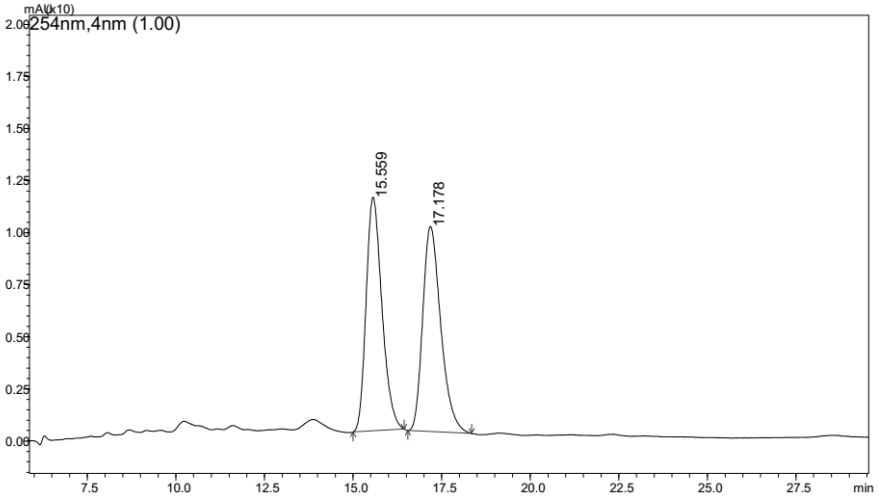
FIGURE 3.6.22- Chiral stationary-phase HPLC analysis of compound **2.74**. OJ-H column (n-hexane/iPrOH 95:5) at 0.8 mL/min.

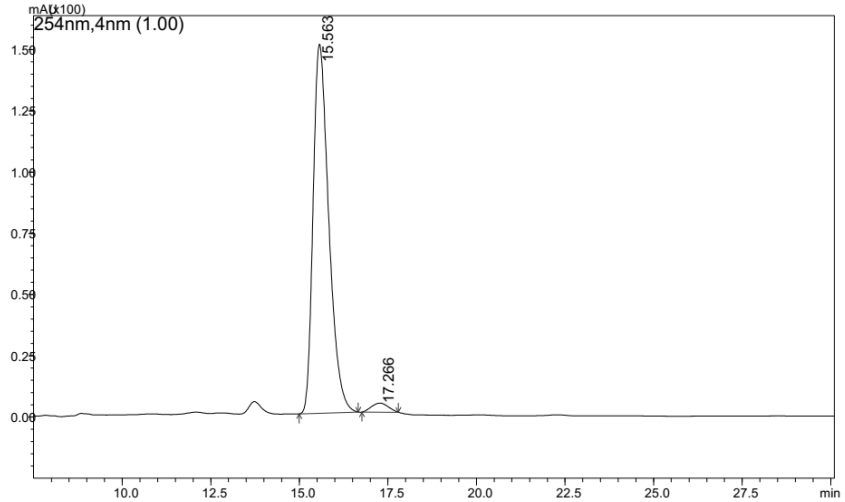




Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.766	16500835	344984	99.219	99.558
2	33.424	129861	1531	0.781	0.442
Total		16630696	346516	100.000	100.000

FIGURE 3.6.23- Chiral stationary-phase HPLC analysis of compound **2.75**. AD-H column (n-hexane/iPrOH 90:10) at 0.5 mL/min.

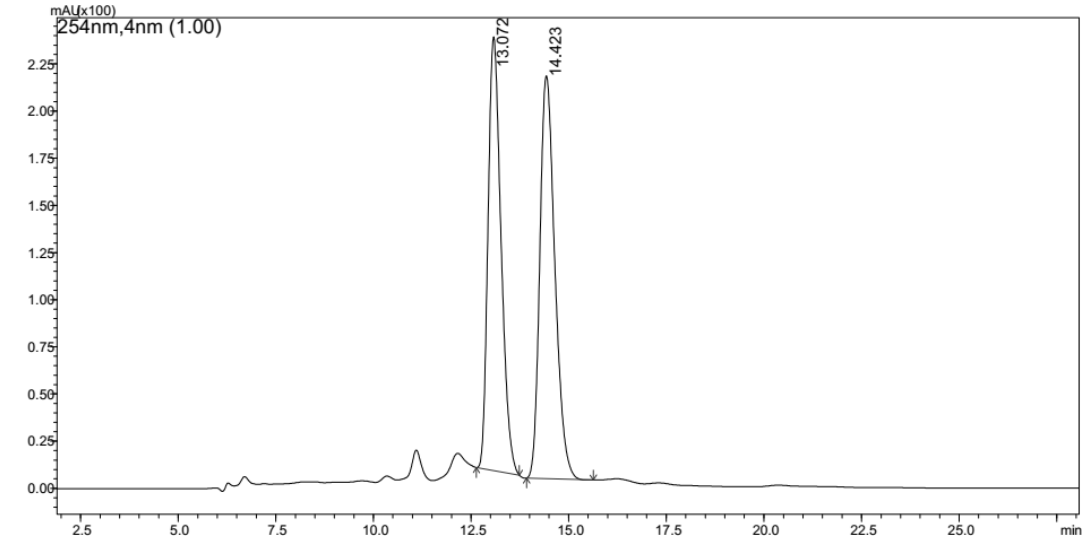


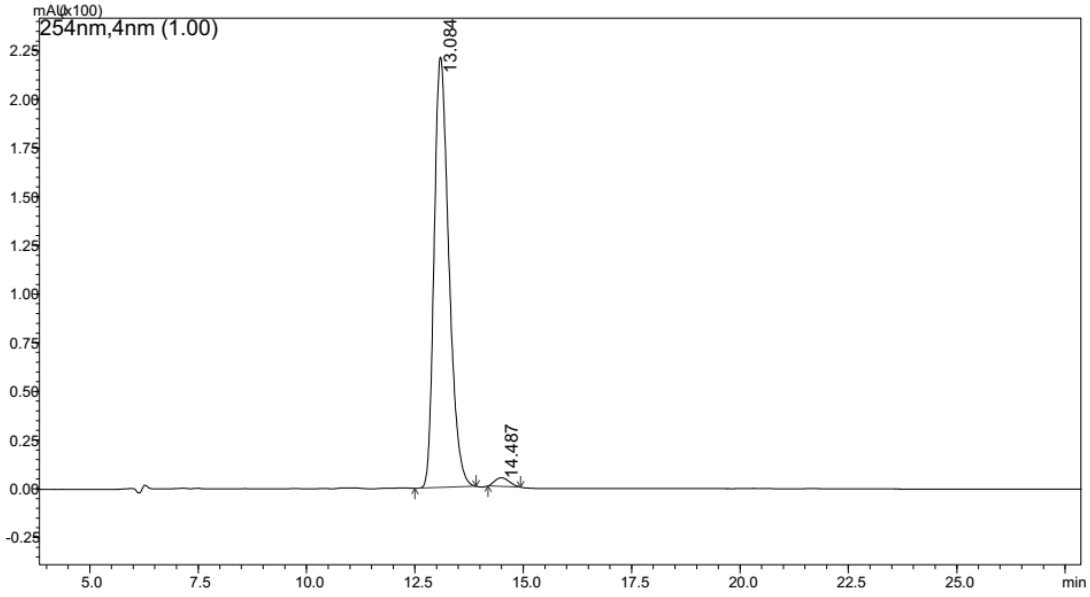


PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.563	4639313	150582	97.476	97.629
2	17.266	120141	3656	2.524	2.371
Total		4759453	154239	100.000	100.000

FIGURE 3.6.24-Chiral stationary-phase HPLC analysis of compound **2.75**. AD-H column (n-hexane/iPrOH 90:10) at 0.5 mL/min.





PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.084	5222760	221151	98.087	98.032
2	14.487	101867	4440	1.913	1.968
Total		5324626	225591	100.000	100.000

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