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"SUSTAINABLE SYNTHESIS OF CICLOPENTENE DERIVATIVES THROUGH MULTICOMPONENT REACTIONS IN CONTINUOUS FLOW REGIME."

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“Hacer es la mejor manera de decir”
José Martí

To my mother and my little sister

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List of Abreviatures

DHP	Dihydropyran heterocyclic ring
dr	Diasteromeric ratio
ee	Enatiomeric excess
3,5 DNBA	3,5 dinitrobenzoic acid
MCR	Multicomponent reaction
IMCR	Isocyanide multicomponent reaction
P-3CR	Passerini three component reaction
Ugi-4CR	Ugi four component reaction
Ugi-4C-3CR	Ugi four center three component reaction
MW	Microwaves
BPR	Backpressure regulator
TFE	2,2,2-trifluoroethanol
THP	Tetrahydropyridine
DCM	Dichloromethane
THF	Tetrahydrofuran
2 Me-THF	2-Methyltetrahydrofuran
DMC	Dimethyl carbonate

List of Tables

TABLE 2.1- Optimization studies for the Organocatalytic Reaction…….26
TABLE 2.2- Optimization studies for the Continuous Flow 4-Center 3-Component Ugi's Reaction…….31
TABLE 2.3- Complete assignments of ^{1}H NMR and ^{13}C for compound **6j**..…35
TABLE 2.4- Comparison between microwave synthesis and continuous flow regime of compound **6a**……...42
TABLE 2.5- Sustainability evaluation of the designed methodology…….43

List of Figures

FIGURE 1.1- Numbers of papers published on Green Chemistry between 2010-2019 , according to the Web of Science.....1
FIGURE 1.2- Principles of Green Chemistry……...…….……2
FIGURE 1.3- General classification of the activation mode in organocatalysis……..3
FIGURE 1.4-Examples of biologically active compounds obtained through organocatalyzed Michael's reactions……8
FIGURE 1.5- Comparison between multi-step synthesis and MCR…….....9
FIGURE 1.6-Applications of MCRs in chemistry……..10
FIGURE 1.7- Examples of active pharmaceutical ingredients (APIs) compounds obtained by flow methods……...14
FIGURE 1.8- Principals zones of a typical flow continuous system……..14
FIGURE 1.9- Applications of the Flow Chemistry……..…16
FIGURE 1.10- Applications of cyclopentene-derived compounds…….22
FIGURE 2.1- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3**.....28
FIGURE 2.2- Chiral stationary-phase HPLC analysis of compound **3**……...30
FIGURE 2.3- Flow continuous system used in the MCR……...31
FIGURE 2.4- ^{1}H NMR spectra in $CDCl_3$ of compound **6a**.....34
FIGURE 2.5- HRMS spectra of compound **6j**……..….36
FIGURE 2.6- Sequential synthesis of cyclopentene derivatives…….37
FIGURE 2.7- Chromatogram and mass spectrum for the detection of compound **7** by GC-MS…….....41
FIGURE 2.8- Synthesis of continuous flow regime on a larger scale……42
FIGURE 3.1- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6a**.....47
FIGURE 3.2- Chiral stationary-phase HPLC analysis of compound **6a**…….48
FIGURE 3.3- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6b**……50
FIGURE 3.4- Chiral stationary-phase HPLC analysis of compound **6b**…….51
FIGURE 3.5- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6c**……...….53
FIGURE 3.6- Chiral stationary-phase HPLC analysis of compound **6c**…….54
FIGURE 3.7- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6d**……...….56
FIGURE 3.8- Chiral stationary-phase HPLC analysis of compound **6d**…….57
FIGURE 3.9- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6e**……59
FIGURE 3.10- Chiral stationary-phase HPLC analysis of compound **6e**……...60
FIGURE 3.11- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6f**……..62
FIGURE 3.12- Chiral stationary-phase HPLC analysis of compound **6f**……...63

FIGURE 3.13- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6g**……..65
FIGURE 3.14- Chiral stationary-phase HPLC analysis of compound **6g**……...66
FIGURE 3.15- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6h**……..68
FIGURE 3.16- Chiral stationary-phase HPLC analysis of compound **6h**……...69
FIGURE 3.17- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6i**……...71
FIGURE 3.18- Chiral stationary-phase HPLC analysis of compound **6i**……72
FIGURE 3.19- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6j**……..74
FIGURE 3.20- COSY and NOESY NMR spectra in $CDCl_3$ of compound **6j**…….….75
FIGURE 3.21- HMBC and superimposed ^{13}C- DEPT 135 NMR spectra in $CDCl_3$ of compound **6j**……....76
FIGURE 3.22- HRMS spectra of compound **6j**……..……77
FIGURE 3.23- Chiral stationary-phase HPLC analysis of compound **6j**……...78
FIGURE 3.24- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6k**……..80
FIGURE 3.25- Chiral stationary-phase HPLC analysis of compound **6k**……...81
FIGURE 3.26- ^{1}H and ^{13}C NMR spectra in $CDCl^3$ of compound **6l**……...83
FIGURE 3.27- Chiral stationary-phase HPLC analysis of compound **6l**……84
FIGURE 3.28- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6m**……86
FIGURE 3.29- Chiral stationary-phase HPLC analysis of compound **6m**…....87
FIGURE 3.30- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6n**……..89
FIGURE 3.31- Chiral stationary-phase HPLC analysis of compound **6n**……...90
FIGURE 3.32- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6o**……..92
FIGURE 3.33- Chiral stationary-phase HPLC analysis of compound **6o**……...93
FIGURE 3.34- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6p**…….……95
FIGURE 3.35- Chiral stationary-phase HPLC analysis of compound **6p**……...96
FIGURE 3.36- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6q**……..…...98
FIGURE 3.37- Chiral stationary-phase HPLC analysis of compound **6q**……...99
FIGURE 3.38- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6r**……..…..101
FIGURE 3.39- Chiral stationary-phase HPLC analysis of compound **6r**…….102
FIGURE 3.40- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6s**……....104
FIGURE 3.41- Chiral stationary-phase HPLC analysis of compound **6s**…….105
FIGURE 3.42- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6t**……107
FIGURE 3.43- Chiral stationary-phase HPLC analysis of compound **6t**…....108
FIGURE 3.44- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3**……..……110
FIGURE 3.45 - Chiral stationary-phase HPLC analysis of compound **3**…....111

List of Schemes

SCHEME 1.1- β-functionalization of α, β-unsaturated aldehydes……..……..4
SCHEME 1.2-Proposed mechanism for β-functionalization of α, β-unsaturated aldehydes……...4
SCHEME 1.3- Intermediaries in the β-functionalization of α, β-unsaturated aldehydes…….…….5
SCHEME 1.4- Synthesis of 3,4 functionalized dihydropyrans……6
SCHEME 1.5- Proposed mechanism for the synthesis of 3,4 functionalized dihydropyrans……6
SCHEME 1.6- Synthesis of 3,4 chiral dihydropyrans……...……7
SCHEME 1.7- Proposed mechanism for the synthesis of 3,4 chiral dihydropyrans……....8
SCHEME 1.8- Examples of MCRs……10
SCHEME 1.9- Multi-component reaction of Passerini……...11
SCHEME 1.10- Multicomponent reaction of Ugi……...11
SCHEME 1.11- Proposed mechanism of the Ugi-4CR……...11
SCHEME 1.12- Multicomponent reaction of Ugi-Smile……12
SCHEME 1.13- Proposed mechanism of the Ugi-Smile's reaction……12
SCHEME 1.14- Microwave-assisted synthesis of linear peptoids……..13
SCHEME 1.15- Synthesis of linear and cyclic peptoids via Ugi-4CR in continuous flow system……...16
SCHEME 1.16-Synthesis of α-amino-1,3-dicarbonyl compounds through continuous flow methods……17
SCHEME 1.17- Synthesis one-pot of hydroquinolin-5-ones using organocatalysis and MCR……18
SCHEME 1.18- Proposed mechanism for the synthesis of hydroquinolin-5-ones……..19
SCHEME 1.19- One-pot synthesis of THP derivatives merging organocatalysis and MCR……20
SCHEME 1.20- Proposed mechanism for the synthesis of THP derivatives…..20
SCHEME 2.1- Methodology proposed for the synthesis of cyclopentene derivatives……24
SCHEME 2.2- Catalytic cycle of Michael's addition of α-cyanoketones to α,β-unsaturated aldehydes……..…25
SCHEME 2.3- Proposed mechanism for the multicomponent stage…….……40

Resumo

"SÍNTESE SUSTENTÁVEL DE DERIVADOS DE CICLOPENTENO ATRAVÉS DE REAÇÕES MULTICOMPONENTES EM REGIME DE FLUXO CONTÍNUO"

A química sustentável ganhou relevância nos últimos anos, não apenas na indústria de química fina, mas também, em síntese orgânica. Essa nova concepção da química, permite o desenvolvimento de processos de maneira ambientalmente mais amigáveis, através da minimização na geração resíduos, reduzindo a manipulação de reagentes químicos perigosos – no entanto, essa abordagem estimula o uso de substratos e solventes "sustentáveis ou verdes". Nesse contexto, o uso de fluxo contínuo em síntese orgânica foi estendido a uma taxa exponencial, devido as várias aplicações na síntese de derivados de produtos naturais de interesse para indústria farmacêutica. De forma a contribuir com a área, esse projeto tem por objetivo desenvolver uma nova metodologia estereosseletiva para síntese de ciclopentenos tetrasubstituídos através de uma abordagem mais sustentável. Nesse sentido, elegemos a combinação de organocatálise e reações multicomponentes como ferramentas de síntese. Ambas metodologias permitem o emprego de solventes verdes, bem como, a incorporação de técnicas de fluxo contínuo na substituição dos métodos em batelada. A etapa multicomponente representou avanços significativos no desenvolvimento de uma metodologia mais sustentável. Finalmente, a metodologia desenhada pode ser considerada como um protocolo sustentável para a síntese de análogos de produtos naturais, enantiomericamente enriquecidos, de maneira rápida e eficiente.

Abstract

“SUSTAINABLE SYNTHESIS OF CICLOPENTENE DERIVATIVES THROUGH MULTICOMPONENT REACTIONS IN CONTINUOUS FLOW REGIME”

Sustainable chemistry has gained relevance in recent years, not only in the fine chemical industry, but also in organic synthesis. This new conception of chemistry allows the development of environmentally friendly processes, by minimizing waste generation as well as in reducing the handling of hazardous chemical reagents. However, this approach encourages the use of "sustainable or green" substrates and solvents. In this context, the use of continuous flow has been extended at an exponential rate in organic synthesis, due to the various applications to the synthesis of derivatives of natural products of interest to the pharmaceutical industry. In order to contribute in the area, this project aimed to develop a new stereoselective methodology for the synthesis of tetrasubstituted cyclopentenes through sustainable approach. Combination of organocatalysis and multicomponent reactions as synthesis tools was chosen. Both methodologies allowed the use of green solvents, as well as the incorporation of continuous flow techniques in the substitution of batch methods. The multicomponent stage represented significant advances in the development of a more sustainable methodology. Finally, the designed methodology can be considered as a sustainable protocol for the synthesis of analogues of natural products, enantiomerically enriched, quick and efficiently.

Summary

Chapter 1.……..……1
1.1-Introduction……1
1.2-Organocatalysis……...3
1.2.1-Michael's reaction in Organocatalysis…….5
1.3-Multicomponent reactions……...9
1.3.1-Multicomponent Ugi's Reaction……..11
1.3.2-MCR in Continuous Flow Regime……...13
1.3.2.1-Flow Chemistry……...13
1.3.2.2-Ugi's Reaction in Continuous Flow Regime……..16
1.3.3-Sequential Combination of Organocatalyzed and Multicomponent Reactions……...18
1.4-Project Aims…….……22

Chapter 2. Results and discussion……...24
2.1-Proposed methodology……..24
2.2-Organocatalytic Stage……...25
2.3-Multicomponent Stage……..31
2.3.1-Reaction screening……...37
2.3.2-Mechanism proposal for the multicomponent stage……40
2.4-Evaluation of the proposed methodology…….42
2.4.1-Sustainability evaluation of the proposed methodology……..43
2.5-Conclusions……...……44

Chapter 3. Experimental Section…….45
3.1-General Remarks…….……..45
3.2-Experimental Section…….….45
3.2.1-General sequencial synthesis procedure in continuous flow regime……..…….….45
3.2.2-General procedure for the synthesis of compound **3**……...109
References……..……...…112

Chapter 1.

1.1-Introduction

Sustainable chemistry has gained relevance in recent years, not only in industry but also in chemical synthesis. This has been reflected by the number of papers published in the last decade (2010-2019), which have increased continuously and steadily, from 904 papers in 2010 to more than 2600 in 2019, with a total accumulated of 17932 papers (FIGURE 1.1).

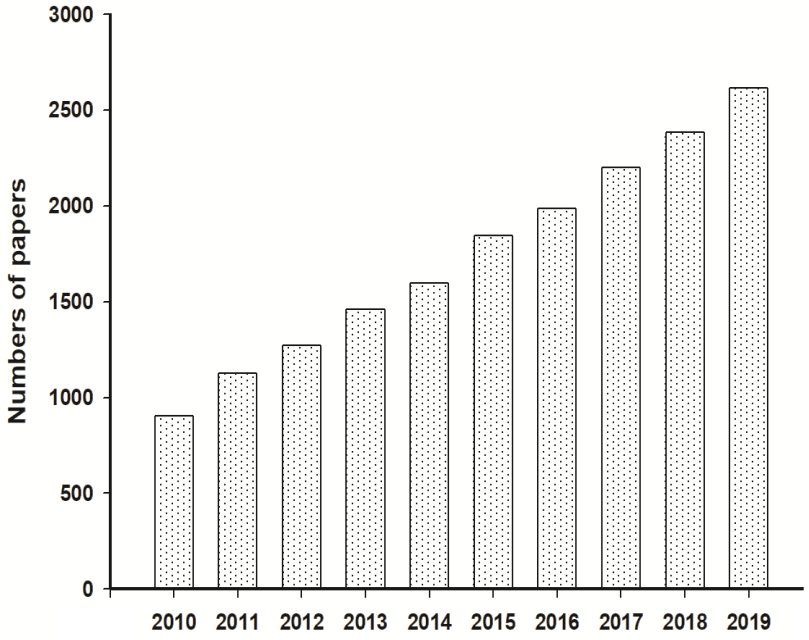


FIGURE 1.1- Numbers of papers published on Green Chemistry between 2010-2019 , according to the Web of Science.

This new conception of chemistry draws a guide to develop products and processes in a responsible, conscious and environmentally-friendly way, following the foundations of the “green chemistry” formulated by Anastas and Werner in the late 90's.[1] These principles promote the development of new methodologies in chemical processes through the efficient use of energy, minimizing waste by reducing the use of hazardous chemical compounds and by encouraging the use of non-toxic or “green” substrates and solvents (FIGURE 1.2).

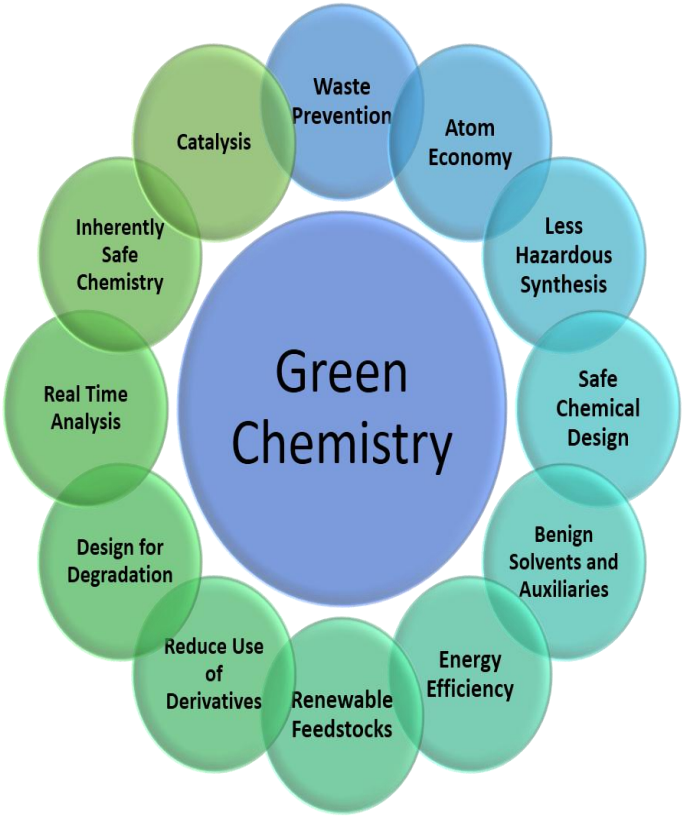


FIGURE 1.2- Principles of Green Chemistry.

Solvents largely define the sustainability of a chemical synthesis and have a great influence on the cost and safety of the process; hence the use of "green" solvents obtained from biomass and its derivatives become important in chemical production.[2]

There are various methods to determine the environmental impact of a specific solvent or solvent mixture and estimate the amount of its emissions. The first method, the environmental, health and safety (EHS) evaluation method,[3] is a detection method with the objective of identifying the potential risks of chemical products. The second method, the solvent life cycle (LCA) evaluation method,[4] can be used for a more detailed evaluation of emissions to the environment from production to final disposal. These techniques, together with other computational analysis models,[5,6] made it possible to prepare the GSK's Sustainable Solvent Guide,[7] which includes a wide variety of solvents, their properties and its impact on the environment. Some of the most used green solvents in modern chemistry are alcohols (ethanol, 2-propanol,), esters (ethyl acetate, isopropyl acetate), carbonates (dimethyl carbonate, diethyl carbonate), among others.[7]

At present, the use of green solvents has been of great interest in the development of more sustainable synthetic strategies than the existing strategies. In this context, organocatalysis and multicomponent reactions occupy a special place in modern organic synthesis.

1.2-Organocatalysis

Since 2000, the field of organocatalysis has developed at a very rapid pace, and is being explored by many researchers around the world. According to MacMillan,[8] organocatalysts are small organic molecules that are used as catalysts in chemical synthesis.

This new methodology has been implemented very quickly due to the advantages offered by organocatalysts: low cost, they are not toxic and stable in atmospheric conditions and in the majority of solvents, making experimental operations simpler.

The interaction of organocatalysts with the substrate is called the "activation mode". The activation modes can be covalent and non-covalent (FIGURE 1.3).[9] In the covalent activation mode, the formation of a covalent bond occurs between the substrate and the organocatalyst within the reaction medium. Examples of these organocatalysts are aminocatalysts[10] and carbenes[11].

In the non-covalent activation mode, interactions between the substrate and the organocatalyst can occur through hydrogen bonds or the formation of ion pairs. In this context, some examples of organocatalysts are thioureas and phosphoric acids[12], as well as chiral bases such as cinchonas alkaloids and phase transfer catalysts[13].

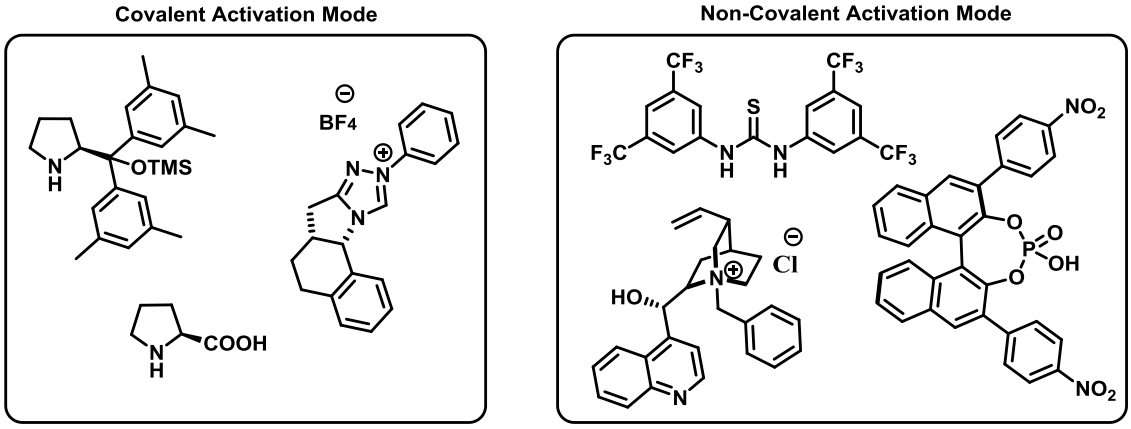
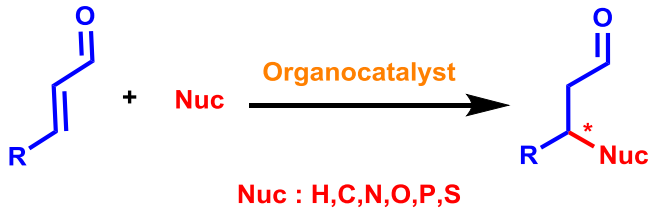
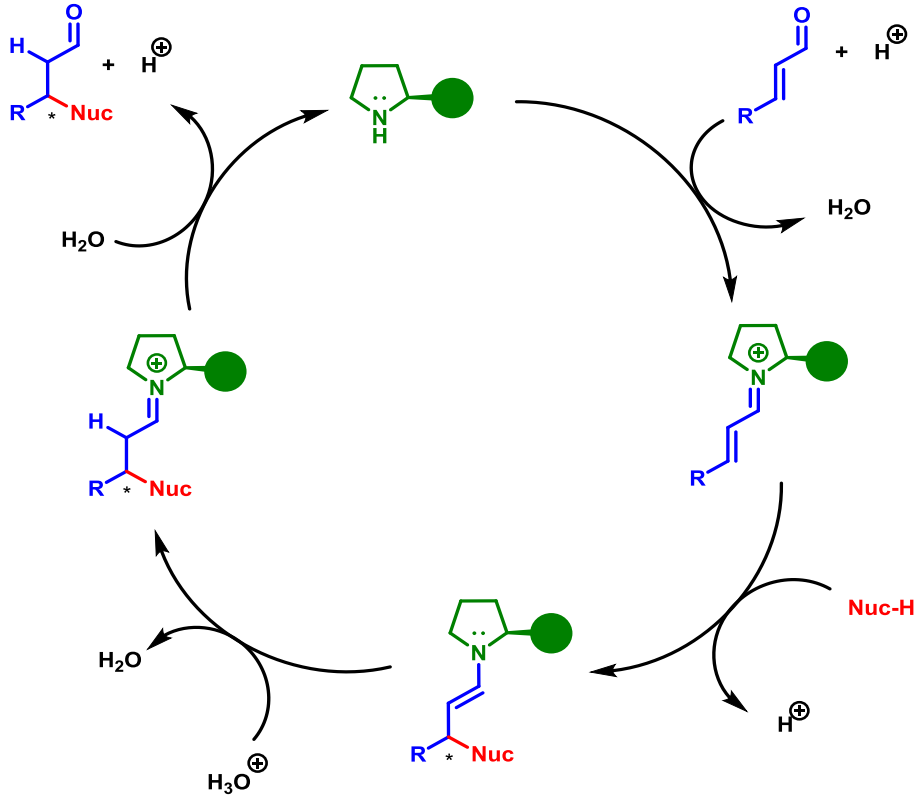


FIGURE 1.3- General classification of the activation mode in organocatalysis.

Within the repertoire of existing organocatalysts in the literature, chiral secondary amines have acquired considerable interest due to their use in the functionalization of carbonyl compounds, especially in β-positions of α,β-unsaturated aldehydes.[14] The enantioselective insertion of various nucleophilic species constitutes a very versatile way to form new C-C and C-heteroatom bonds (SCHEME 1.1).



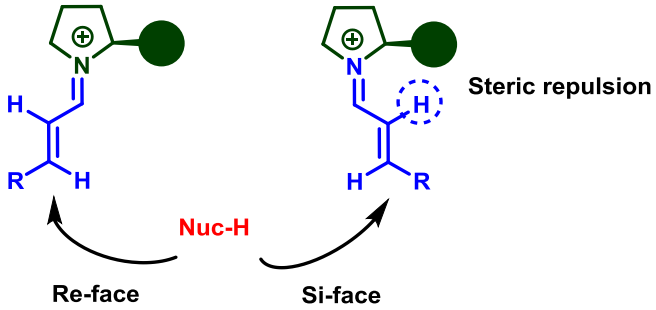
SCHEME 1.1- β-functionalization of α,β-unsaturated aldehydes.



SCHEME 1.2- Proposed mechanism for β-functionalization of α,β-unsaturated aldehydes.

The catalytic cycle begins with the condensation of the catalyst (chiral secondary amine) and the α,β-unsaturated aldehyde, forming as an intermediate, a conjugated iminium ion, that is the reactive species in the β-functionalization. Attacking a nucleophile to the β-carbon atom of the iminium ion leads to the formation of a β-functionalized enamine, which is in tautomeric equilibrium with the corresponding iminium ion. Finally, the hydrolysis of the iminium ion releases the functionalized β-product and the organocatalyst, which can catalyze a new reaction cycle[15] (SCHEME 1.2).

The structure and reactivity of the iminium ion have been extensively studied through various theoretical and experimental methods.[16] The results show an energetic favor for the trans-trans iminium ion as a single molecule and in the transition state as compared to cis-trans iminium ion (SCHEME 1.3). This conformation leads to a Re-face attack of the nucleophile while the Si-face approach is unfavorable because of steric repulsion. The control of the configuration of both double bonds and the direction of the nucleophilic attack (mainly because the steric hindrance of the catalyst protects the Si-face), constitute a determining aspects in the enantioselectivity of the reaction.[15]

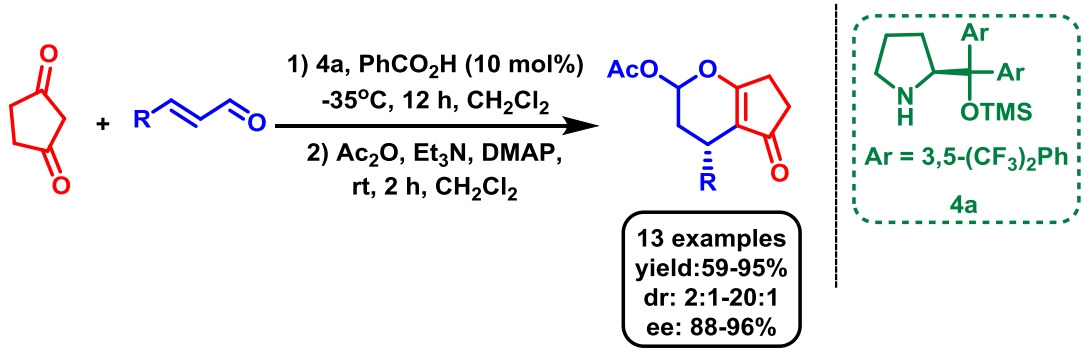


SCHEME 1.3- Intermediaries in the β-functionalization of α,β-unsaturated aldehydes.

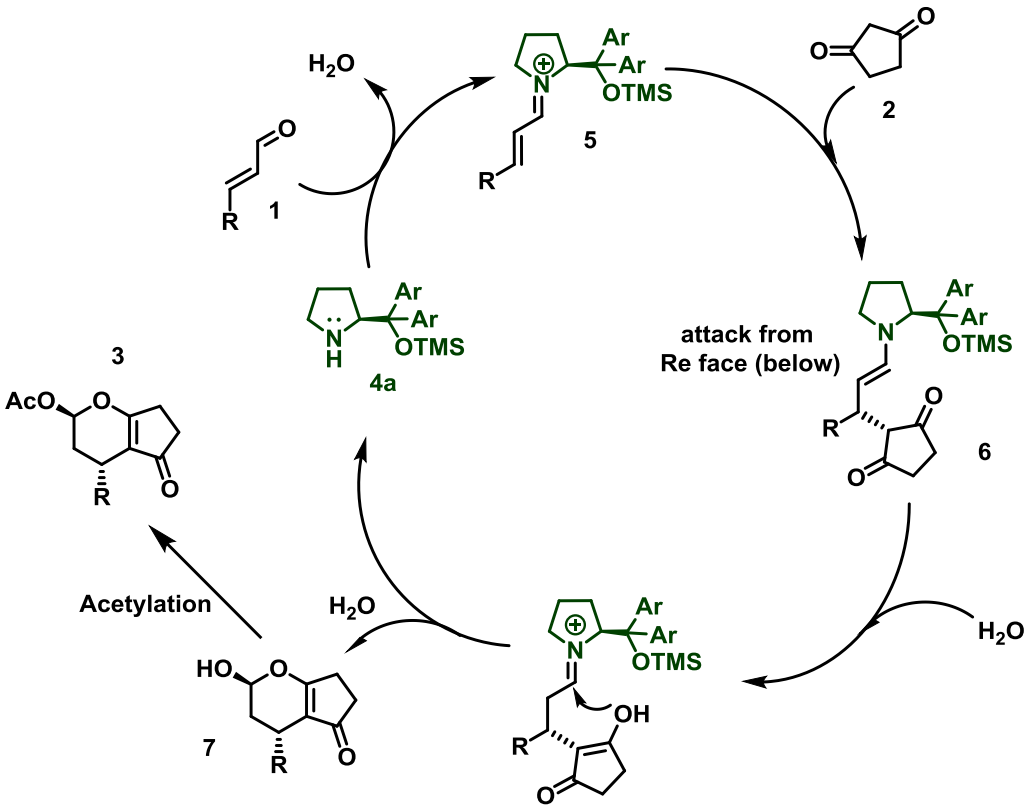
1.2.1-Michael's reaction in Organocatalysis

The synthesis of optically active compounds from the formation of new bonds (C-C and C-heteroatom) together with the creation of stereogenic centers in an enantioselective manner continues to be a very attractive research area for synthetic chemists. In this context, the addition of organocatalyzed Michael's reaction via iminium ion has become a very useful tool for obtaining a variety of chiral compounds, including natural products or molecular fragments of its central structure.[17] An example of these structures is the dihydropyran heterocyclic ring (DHP), found in numerous naturally-occurring products and biologically active compounds of pharmacological interest.[18-22]

In 2008, Franke et al[23] reported Michael's addition of 1,3 cyclopentadione to α,β-unsaturated aldehydes followed by acetylation to form a family of 3,4 dihydropyrans with yields of 59-95 % and high enantioselectivity (88-96% ee). This reaction proceeds under slightly acidic conditions and in the presence of a secondary amine as a catalyst (SCHEME 1.4).



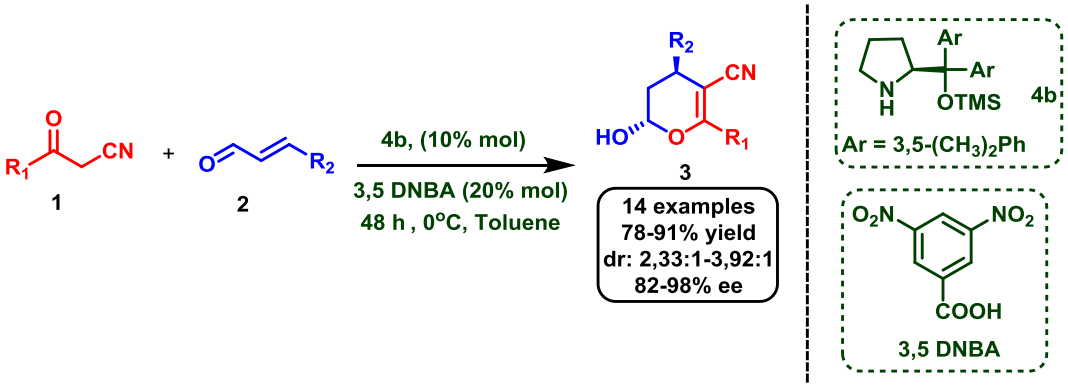
SCHEME 1.4- Synthesis of 3,4 functionalized dihydropyrans.



SCHEME 1.5- Proposed mechanism for the synthesis of 3,4 functionalized dihydropyrans.

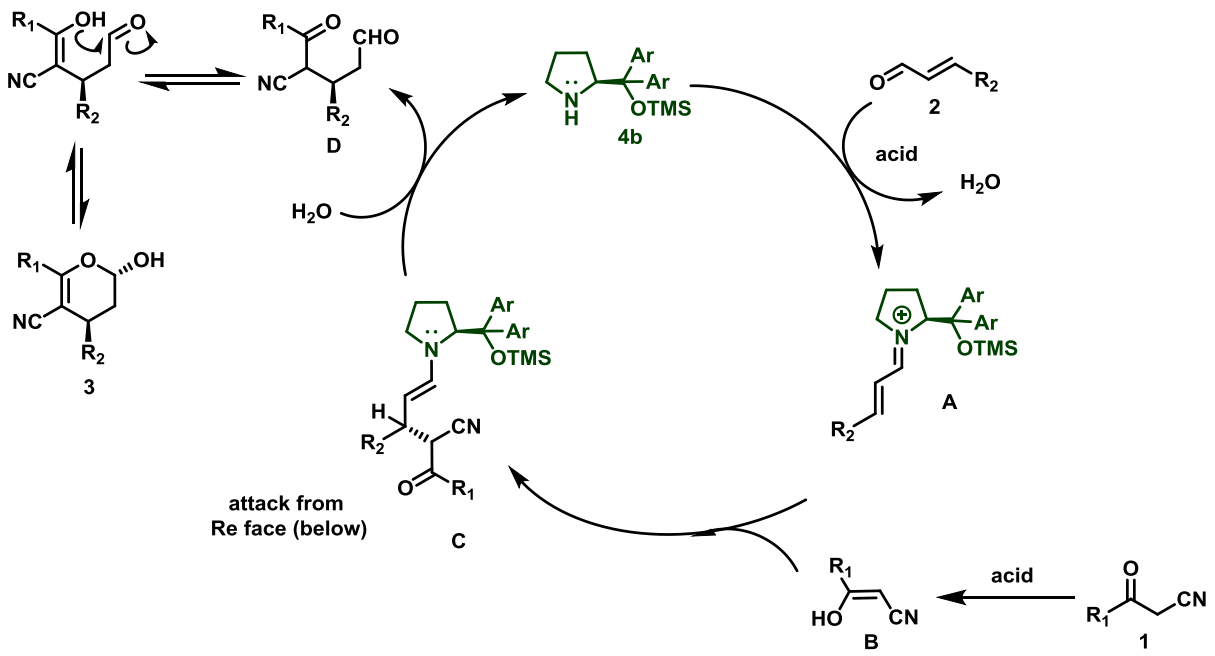
The α,β-unsaturated aldehyde **1** is transformed by the reaction between catalyst **4a** and nucleophile **2** in the Michael's adduct **6**. The stereocenter formed in the catalytic cycle is controlled by a Re-face attack of the nucleophile on the β-carbon atom of the iminium ion **5**, because the Si-face is protected by the C2 substituent on the pyrrolidine ring of the catalyst. After the formation of the stereocenter, the catalyst is released by cyclization to result in hemiacetal **7**, which is easily acetylated to provide the desired product **3** (SCHEME 1.5).

In 2014, Niu et al[24] described Michael's asymmetric addition of α-cyanoketones to α,β-unsaturated aldehydes using L-diphenylprolinol trimethylsilyl ether as catalyst. The reaction is carried out in the presence of 3,5 dinitrobenzoic acid (3,5 DNBA), obtaining a variety of 3,4 chiral dihydropyrans with yields of 78-91% and high enantioselectivity (up to 98% ee) (SCHEME 1.6).



SCHEME 1.6- Synthesis of 3,4 chiral dihydropyrans.

The mechanism begins with the reaction of catalyst **4b** with the α,β-unsaturated aldehyde **2** to form the iminion ion **A**. The nucleophilic attack of intermediate **B** (obtained from α-cyanoketone **1** in acidic medium) to the iminion ion **A** generates, *in situ*, another intermediate **C**, which will then undergo hydrolysis to give intermediate **D**. The stereocenter formed in the catalytic cycle is controlled by a nucleophilic Re-facial attack in the plane of the iminium ion because the substituent of carbon 2 in the pyrrolidine ring of the catalyst protects the Si-face from the attack, this, being frequent when TMS-protected proline derivatives are used as organocatalysts.[25-28] Later, the catalyst is released by cyclization to form intermediate **D**, which after the steps of enolization and intramolecular addition finally generates the desired product **3** (SCHEME 1.7).



SCHEME 1.7- Proposed mechanism for the synthesis of 3,4 chiral dihydropyrans.

Michael's organocatalytic reaction is of great importance in obtaining biologically active compounds with various therapeutic properties and high structural diversity such as: (S)-Rolipram, a phosphodiesterase inhibitor[29], (S)-Baclofen, a potent gamma-aminobutyric acid (GABA) receptor agonist[30] and (-)-Paroxetine, an antidepressive drug[31](FIGURE 1.4). However, the use of more environmentally friendly solvents could be a very novel alternative to develop the organocatalytic process from a more sustainable perspective.[32]

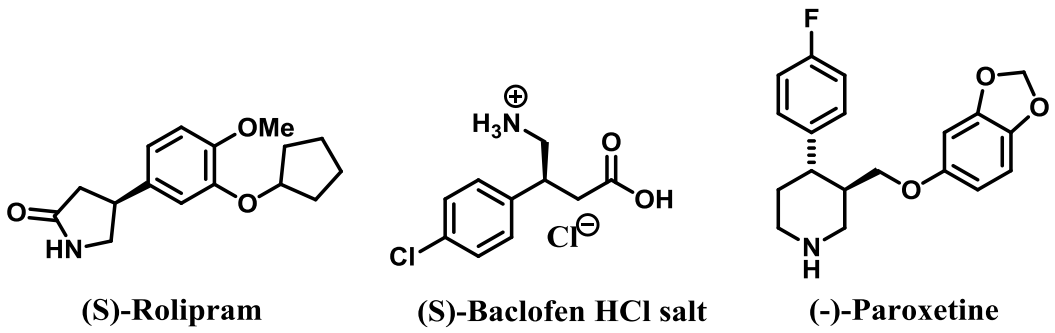


FIGURE 1.4-Examples of biologically active compounds obtained through organocatalyzed Michael's reactions.

1.3-Multicomponent reactions

Multicomponent reactions (MCRs) constitute one of the most attractive transformations in synthetic organic chemistry. These are defined as reactions in which three or more reagents, in a one-pot manner, react by means of several sequential stages forming a product that contains essentially all the atoms of the starting materials.[33]

MCRs are generally characterized as condensation reactions with high atomic economy, which occur under mild conditions, sustainable solvents and without the need to use an inert atmosphere, generating products with greater diversity and molecular complexity.[34]

MCRs have great advantages compared to traditional multi-step syntheses (FIGURE 1.5). In MCRs, a molecule is assembled in a single chemical step by mixing the corresponding starting materials unlike the traditional synthetic efforts, which involves multiple sequential steps. In this way, high levels of atomic efficiency and lower generation of waste can be achieved and time and energy are saved, avoiding the isolation and purification of synthetic intermediaries that require a lot of time.[35]

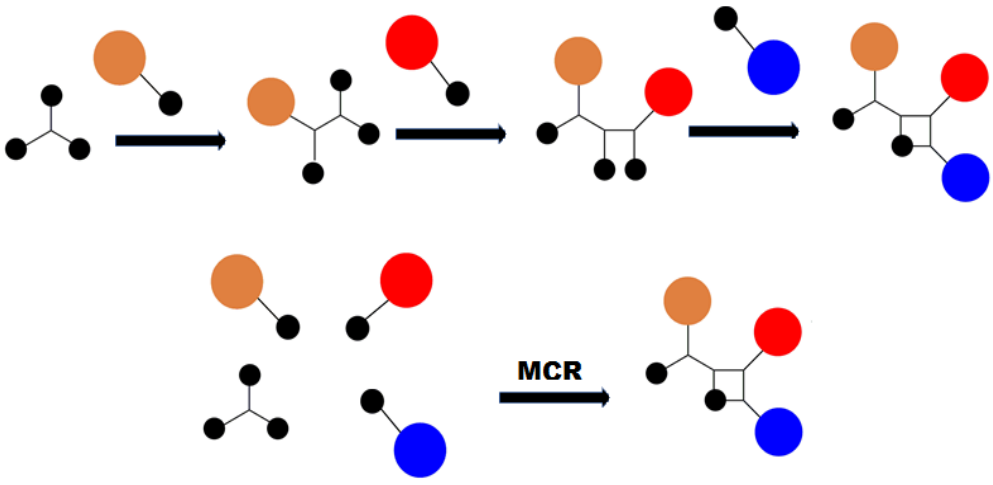


FIGURE 1.5- Comparison between multi-step synthesis and MCR.

MCRs provide quick and easy access to various compounds with applications in different areas of chemistry (FIGURE 1.6).

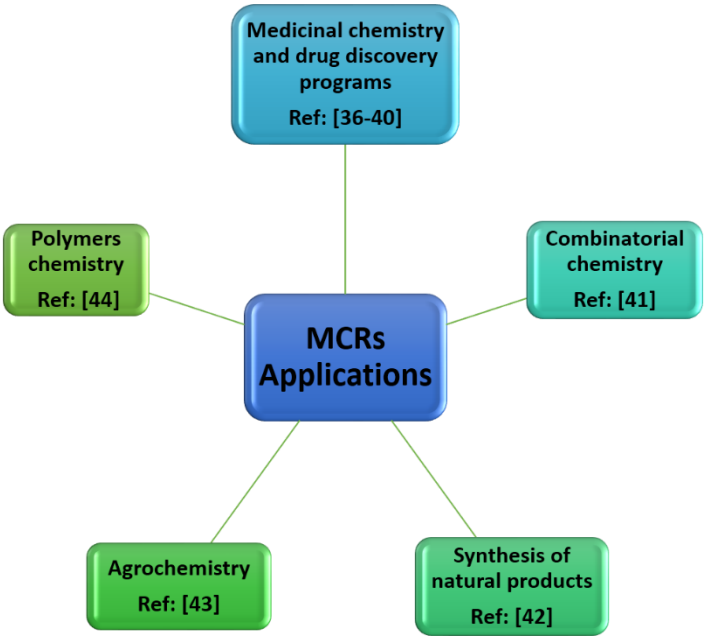
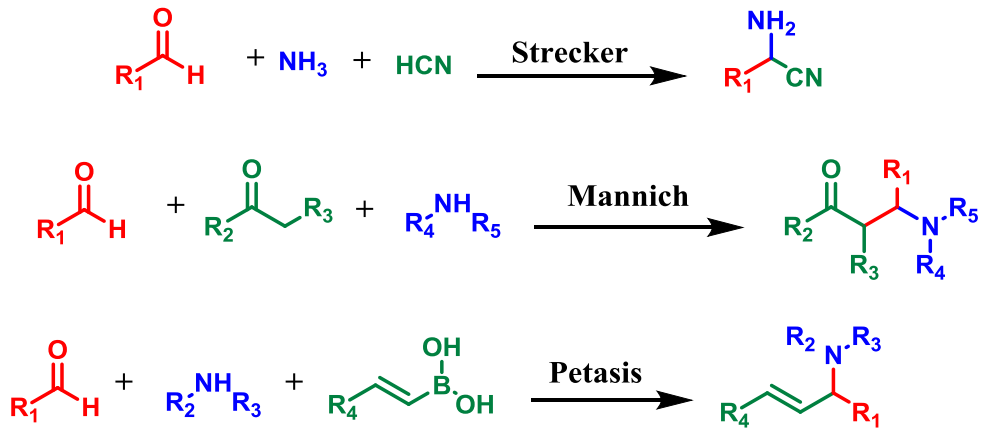


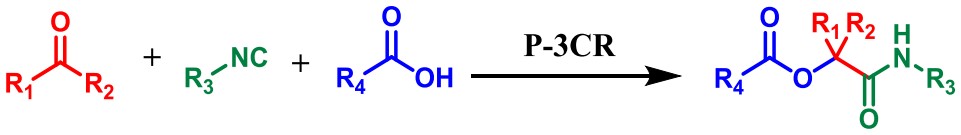
FIGURE 1.6-Applications of MCRs in chemistry.

There is a wide variety of multicomponent reactions that combine the reactivity of various organic functions, such as the Strecker, Mannich, Petasis' reactions, among others[45] (SCHEME 1.8).



SCHEME 1.8- Examples of MCRs.

Within the MCRs, the isocyanide-based reaction (IMCR) such as the Passerini's three-components reaction (P-3CR) and the Ugi's four-components reaction (Ugi-4CR), occupy a privileged place due to the reactivity of the divalent carbon atom of the isocyanides towards nucleophiles and electrophiles compounds, which then converts isocyanides into exceptional chemical species.[46]

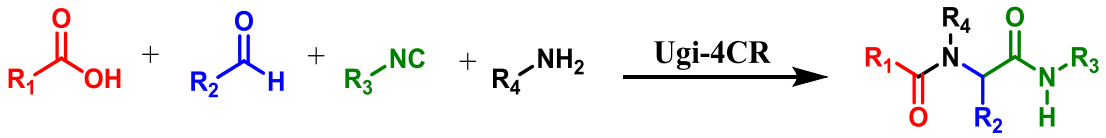


SCHEME 1.9- Multicomponent reaction of Passerini.

Specifically, the Ugi's reaction has been extensively studied and is widely used in synthetic chemistry.

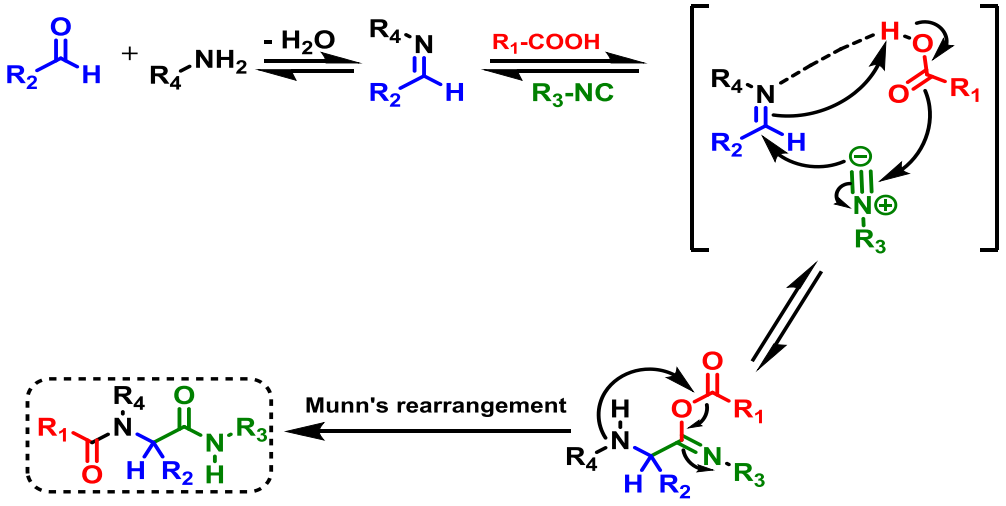
1.3.1-Multicomponent Ugi's Reaction

The Ugi's reaction was described by Ivar Ugi in 1959.[47] In this reaction, an aldehyde, a primary amine, a carboxylic acid and an isocyanide are combined to give way to a single reaction product, from the four starting components (SCHEME 1.10).



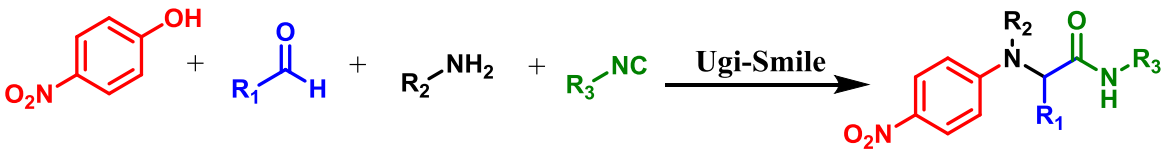
SCHEME 1.10- Multicomponent reaction of Ugi.

The general mechanism of this reaction, first involves the *in situ* formation of an imine from the aldehyde and the primary amine. Then the nucleophilic attack of the isocyanide component to this imine occurs, followed by the addition of the carboxylic acid to give rise to an α-adduct. Finally, an intramolecular rearrangement of this intermediate occurs (Munn's rearrangement) to obtain variously N-substituted dipeptides derivatives.[48] This mechanism was verified experimentally by Neto et al[35] and is the most accepted to date (SCHEME 1.11).

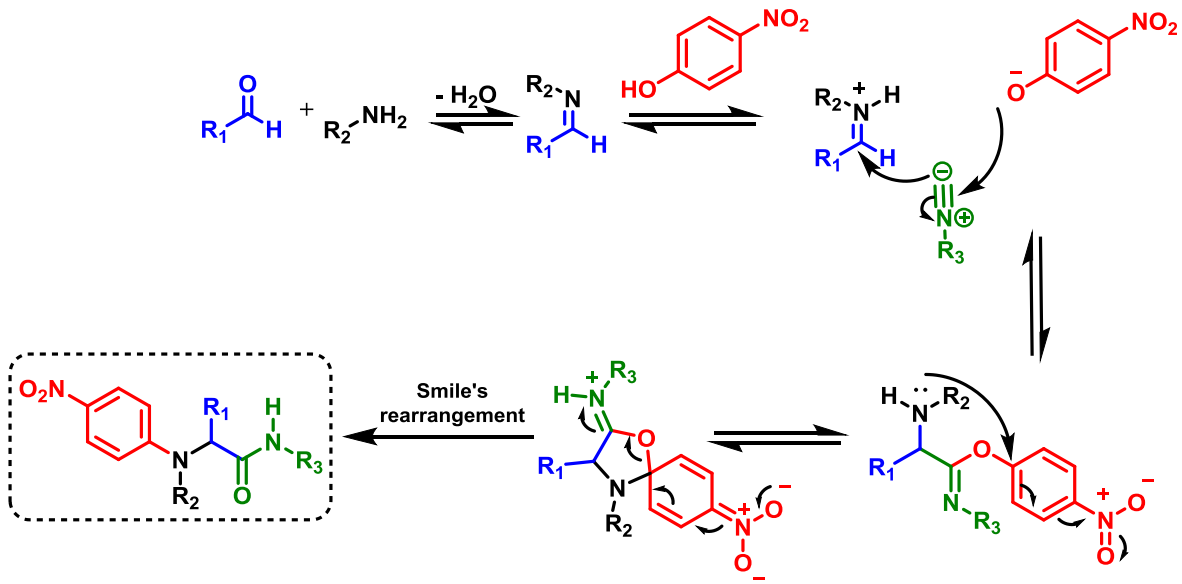


SCHEME 1.11- Proposed mechanism of the Ugi-4CR.

Among the modifications made to the reaction of Ugi, one of the most important is to replace the acid component of the classical reaction with a phenol that contains an electron-withdrawing group.[49] This substitution modifies the last stage of the reaction mechanism, the Munn's rearrangement and leads to a new Smiles's type rearrangement, giving rise to the reaction known as Ugi-Smiles (SCHEME 1.12).



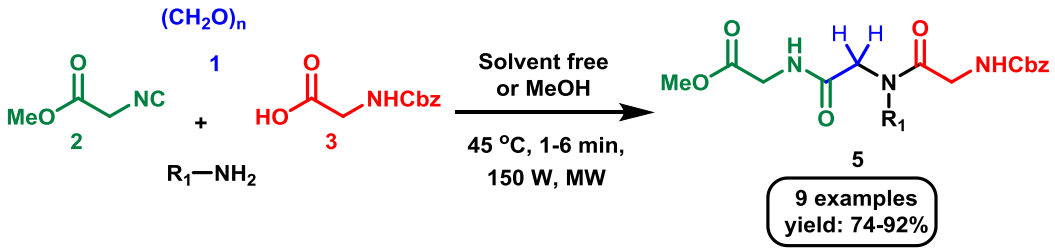
SCHEME 1.12- Multicomponent reaction of Ugi-Smile.



SCHEME 1.13- Proposed mechanism of the Ugi-Smile's reaction.

The reaction of four components of Ugi has played an important role in obtaining biologically active compounds with very diverse pharmacological properties.[50-55] Similarly, the use of more efficient heating sources such as microwaves (MW) have allowed accelerating chemical reactions, leading to cleaner processes with higher yields.[56-58]

Barreto and co[59] reported a fast and efficient route in MW for the synthesis of linear peptoids through the reaction of Ugi four components (SCHEME 1.14). The synthesized peptoids served as starting material to obtain other compounds with greater diversity and structural complexity and potential biological interest.



SCHEME 1.14- Microwave-assisted synthesis of linear peptoids.

This one-pot methodology led to yields of 75-92% and very small reaction times (1-6 min) when compared to traditional heating forms (oil baths). Similarly, it offers several advantages such as the absence of solvents and operational simplicity, contributing to sustainability and greater security for high-speed and small-scale synthesis. However, the need to carry out reactions under conditions of high pressures and temperatures in laboratories, with a homogeneous mixer and heating throughout the vessel (avoiding the appearance of dead zones) many times above the boiling point of the solvent used , safely and directly scalable to the industry, has led to the transfer of MW technology towards a continuous flow methods.[60]

1.3.2-MCR in Continuous Flow Regime

1.3.2.1-Flow Chemistry

At present, the use of flow chemistry in organic synthesis has been extended at an exponential rate due to its varied applications in the pharmaceutical industry, especially in the synthesis of derivatives of natural products and active ingredients (APIs) in automated systems.[61] For examples, Artemisinin, an antiparasitic (highly effective for the treatment of malaria),[62] Rac-Oxomaritidine, which is a naturally-occurring alkaloid with cytotoxic properties[63] and Olanzapine, a drug used in the treatment of bipolar disorder and schizophrenia[64] (FIGURE 1.7).

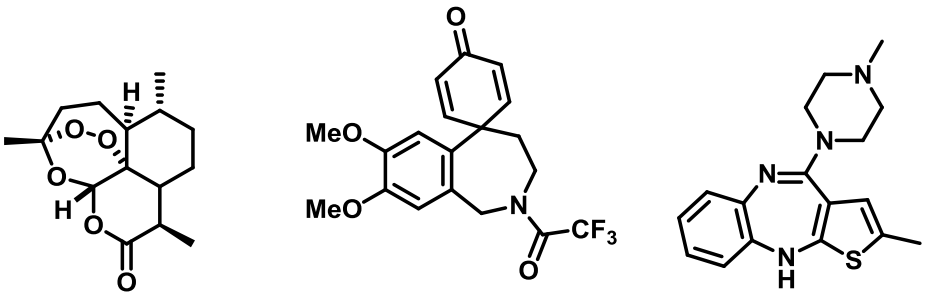


FIGURE 1.7- Examples of active pharmaceutical ingredients (APIs) compounds obtained by flow methods.

Continuous flow technology has been implemented in several laboratories occupying a relevant space in modern synthesis. In general, continuous flow systems are composed of modules and accessories that can be divided into five main areas: reagent and solvent inlet, mixing, reactor, pressure regulation and finally, the collection of the desire product.[65] In addition, the analysis and purification zones can also be integrated into these systems[66,67] (FIGURE 1.8).

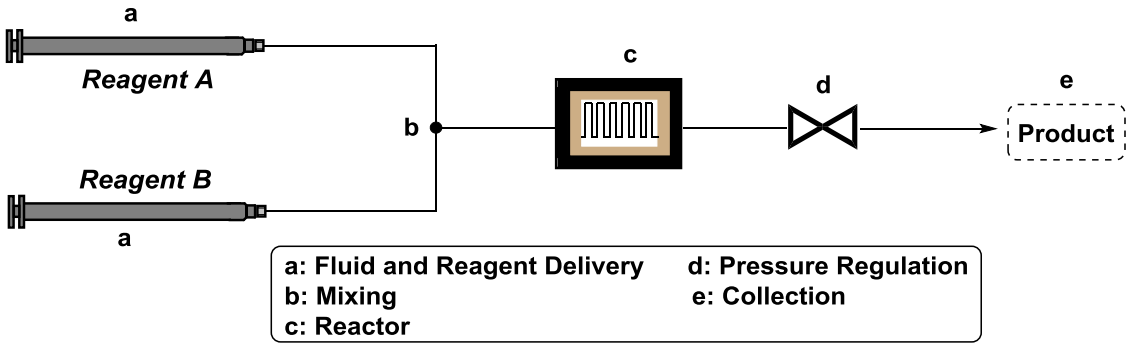


FIGURE 1.8- Principals zones of a typical flow continuous system.

The reagents and solvents enter the continuous flow system through high-pressure pumps, which can be of three types: peristaltic pumps, HPLC or syringe pumps. The choice of the type of pump to be used is related to the flow rate and pumping accuracy required for each fluid.[68]

The mixing of the reagents occurs through the mixing devices that can be found in various formats. The most common for laboratory scale are the T, Y or Quad mixers for micromixing two or three solutions.[69]

The reactor is the central unit of each continuous flow system where it occurs the chemical reaction. The reactors can be divided into three main types: tubular, microchips and packed bed columns (solid support).

The reactors are generally made of various materials such as glass, silicone, ceramic, fluoropolymers (Polytetrafluoroethylene, PTFE and Perfluoroalkoxy alkanes, PFA) or stainless steel. The choice of the reactor as well as its material depend on the characteristics of the reaction. Stainless steel reactors are more suitable for high temperature and pressure processes, while other reactors made of PFA are more used for photochemical reactions. [70]

The pressure regulators are connected usually before the collection of the product in the end of the flow continuous system and they ensure a constant pressure throughout the process. There are two types of pressure regulators: predetermined fixed cartridges and adjustable pressure regulators, the latter can be handled during the process without the need to interrupt the flow.[71] Operating under a backpressure regulator also allows solvents to be heated above their atmospheric boiling points, affording opportunities for improved reaction kinetics.[65]

Flow technology offers great advantages compared to batch methods: better control over mixing and fluid heating operations, use of small amounts of reagents and solvents, minimizing waste generated, low reaction times, efficient use of energy, easy scaling and security, contributing to more sustainable and green processes.[72,73]

Continuous flow methods can be applied in various areas of synthetic chemistry and especially in multicomponent reactions (FIGURE 1.9). Within the MCRs reported in a continuous flow regime, the Ugi’s reaction deserves special attention.

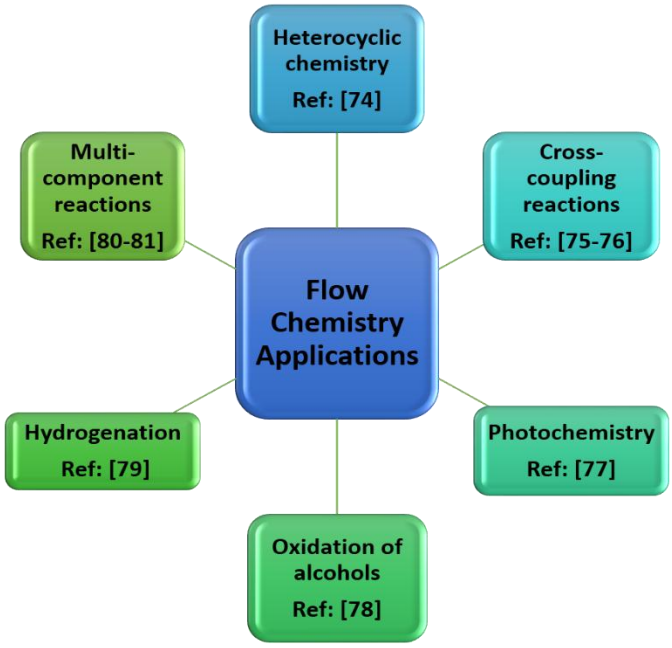
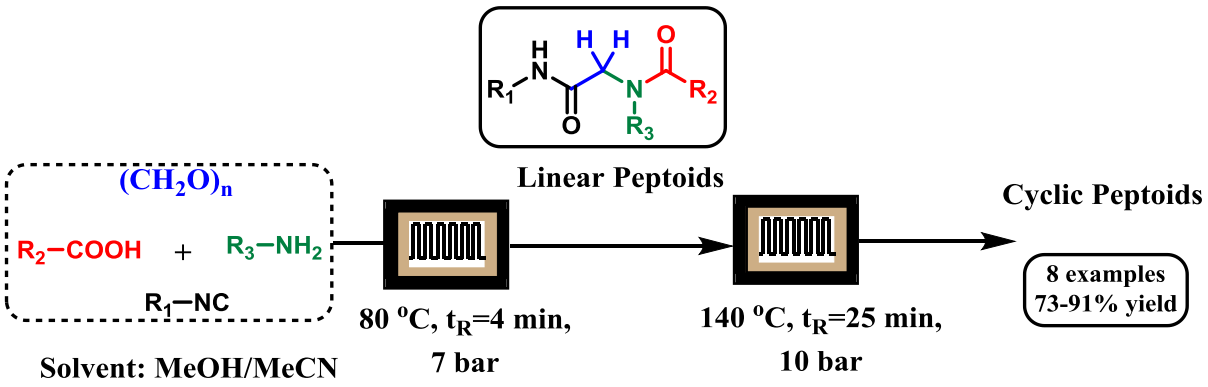


FIGURE 1.9- Applications of the Flow Chemistry.

1.3.2.2-Ugi's Reaction in Continuous Flow Regime

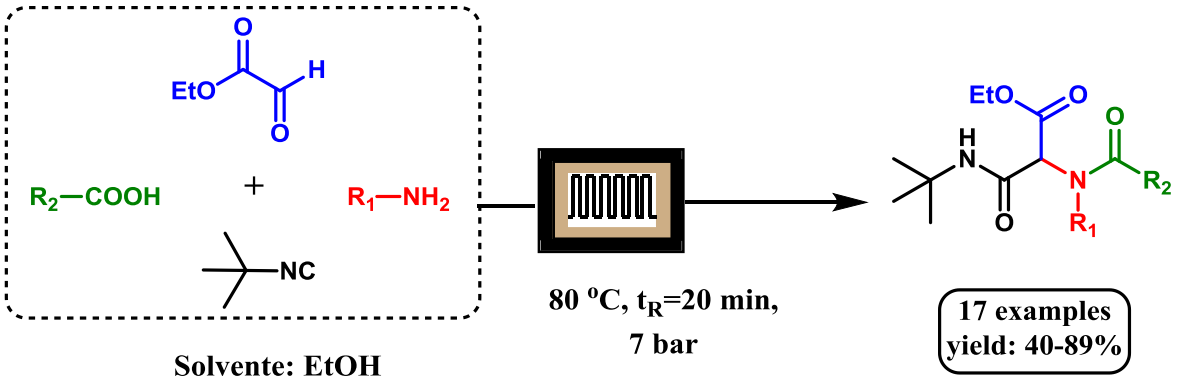
In 2015, Salvador and co-workers[82] developed a very interesting strategy for the synthesis of linear and cyclic peptoids using flow methods. The fundamental transformation of this process is the formation of linear peptoids through an Ugi-4CR and subsequent macrocyclization to give rise to cyclic peptoids (Scheme 1.15).



SCHEME 1.15- Synthesis of linear and cyclic peptoids via Ugi-4CR in continuous flow system.

Continuous flow technology was applied at all stages of the process: from the generation of starting materials (acid, amine and isocyanide), the Ugi's reaction and subsequent macrocyclization. The authors succeeded in coupling the multi-step flow system conveniently, without the need to isolate and purify the intermediates formed at each reaction stage. This methodology led to a single process that generates the desired products quickly and with yields of 73-91%.

A strategy to synthesize α-amino 1,3 dicarbonyl compounds by Ugi's reaction using a microchip type reactor was described by Vasconsuelos et al[83] (SCHEME 1.16).



SCHEME 1.16-Synthesis of α-amino 1,3 dicarbonyl compounds through continuous flow methods.

Various α-amino 1,3 dicarbonyls compounds were obtained with yields of 40-89% , some with the possibility of being used as precursors for the synthesis of new 1,2,3 triazole compounds.

It is important to note that the use of an environmentally friendly solvent such as ethanol and flow techniques helps to develop the process from a greener perspective. In addition, the use of a backpressure regulator at the outlet of the microreactor allows the process to be carried out at a temperature higher than the boiling point of the solvent without affecting the results obtained.

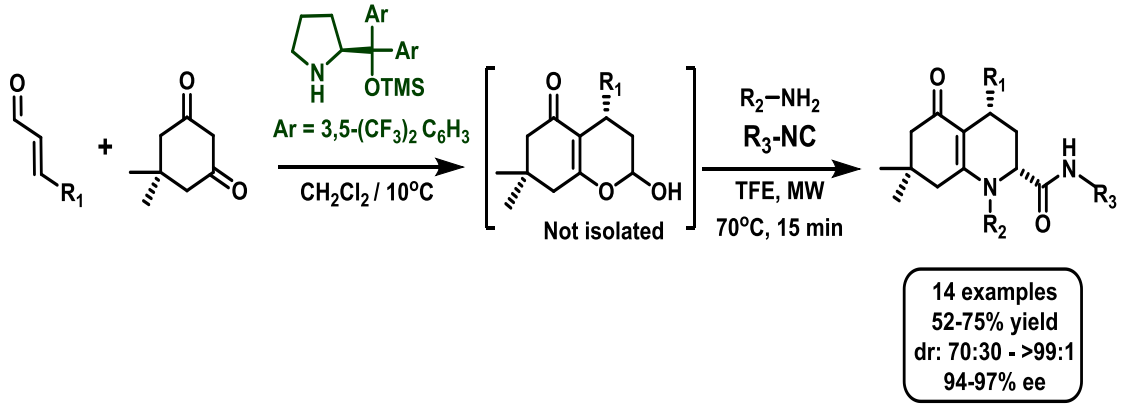
1.3.3-Sequential Combination of Organocatalyzed and Multicomponent Reactions

Asymmetric organocatalysis is of vital importance for the synthesis of different enantiomerically enriched molecules and chiral building blocks. Similarly, multicomponent reactions are used as a powerful tool to obtain natural products and biologically active compounds. As a consequence, new chemical bonds with high chemical efficiency are formed, generating high levels of diversity and structural complexity.[84]

However, most MCRs have some drawbacks in relation to enantio and diasteroselectivity due to competition with competing reactions that can occur spontaneously in an appropriate solvent and at room temperature, as well as the complexity of the reaction mechanism, among other factors.[85]

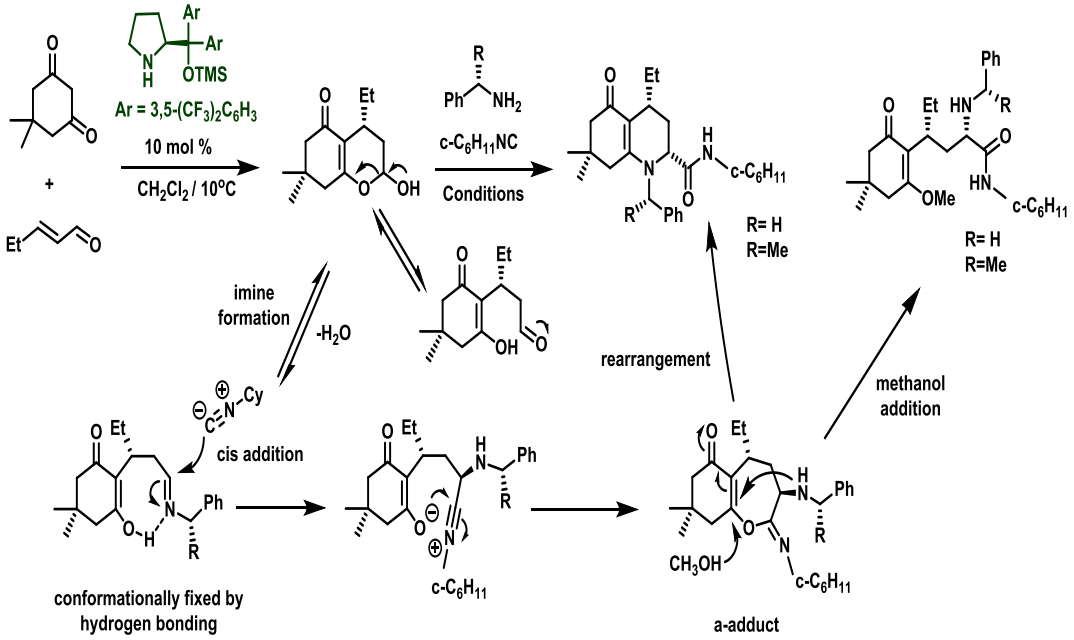
To solve these limitations and obtain enantiomerically-pure or enriched products, the combination of organocatalysis and multicomponent reactions was adopted as a strategy, obtaining satisfactory results in our group[86,87] and Banfi's team[88]. The combination of these two methodologies has proved to be efficient, expanding the repertoire of stereoselective synthesis.

In their work, Echemendía and colleagues[89] described a one-pot pathway for the synthesis of hydroquinolin-5-ones derivatives that effectively combines an organocatalytic reaction followed by a multicomponent reaction (SCHEME 1.17).



SCHEME 1.17- Synthesis one-pot of hydroquinolin-5-ones using organocatalysis and MCR.

Michael's addition of a dicarbonyl compound to α,β-unsaturated aldehydes first forms an enantiomerically-enriched intermediate. Subsequently, the multicomponent stage in MW occurs through an Ugi-type reaction with three components and four reaction centers to generate the desired products. This methodology allowed to obtain a series of hydroquinolin-5 ones with yields of 52-75% and high enantioselectivity (94-97% ee).

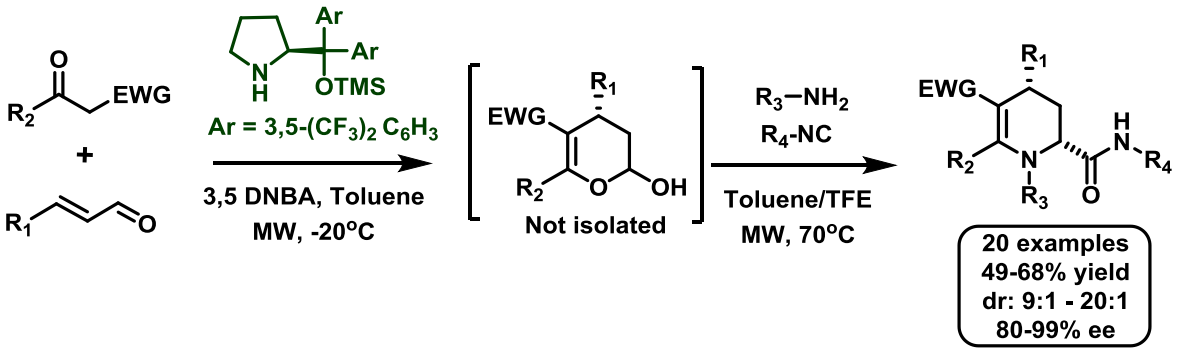


SCHEME 1.18- Proposed mechanism for the synthesis of hydroquinolin-5-ones.

It is important to note that the use of apolar solvents such as toluene and dichloromethane in the multicomponent stage did not lead to product formation. However, protic polar solvents such as TFE and methanol did favor the process in both cases, as expected for this type of reaction.[45,48]

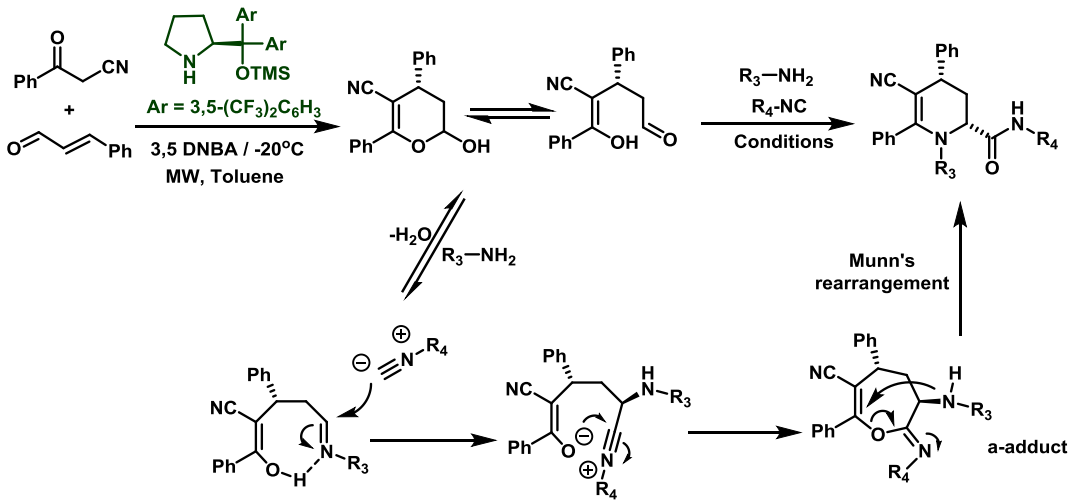
The use of methanol allowed for obtaining a mixture of final products as a result of the competition between the reorganization of the α-adduct (that is, the migration of the amine) and the addition of methanol. This is given because the α-adduct is a rigid and fused bicycles with very low conformational flexibility, which can discourage the migration of the amine and allows the attack of a nucleophilic solvent such as methanol. To solve this problem, TFE is used, as it allows for obtaining only the desired product.

Based on that protocol, a sequential procedure via one-pot synthesis of tetrahydropyridine derivatives (THP) was recently published by our group[90] (SCHEME 1.19).



SCHEME 1.19- One-pot synthesis of THP derivatives merging organocatalysis and MCR.

In this case, Michael's asymmetric addition occurs between an α-substituted carbonyl compound with electron-withdrawing groups and an α,β-unsaturated aldehyde to form a hemiacetal, in the presence of a proline-derived catalyst (Jørgensen's catalyst) and 3,5 dinitrobenzoic acid. Then the multicomponent stage is carried out without isolating the previously generated hemiacetal, which allows to obtain the desired products with yields of 49-68% and with high enantio (80-99% ee) and diasteroselectivity (9:1 to 20:1 dr) using MW energy.



SCHEME 1.20- Proposed mechanism for the synthesis of THP derivatives.

The proposed mechanism for the multicomponent stage was studied through theoretical calculations, initially starting from the hemiacetal generated in the previous organocatalytic stage. The sequence begins with the addition of the amine to the hemiacetal to form an imine that has an intramolecular hydrogen bond. Later, the nucleophilic addition of the isocyanide occurs to generate the α-adduct that will undergo an intramolecular rearrangement (Munn's rearrangement) resulting in the desired product (SCHEME 1.20).

It is important to note that this novel method allows each of the components to varies in both reaction stages, increasing the structural and complex diversity of the products obtained. In addition, the use of MW in each reaction step of the synthesis allowed to reduce reaction times significantly up to 50 minutes and obtain products with high enantiomeric purity in a fast and efficient manner. However, the use of less environmentally harmful solvents in chemical synthesis continues to be an alternative that should be further explored with a view to developing more sustainable methodologies.

1.4-Project Aims

The combination of organocatalytic and multicomponent reactions has proven to be a very effective tool in organic synthesis. With organocatalysis, it is possible to generate a reactive intermediate with high enantioselectivity and subsequently, in the multicomponent step, the complexity and structural diversity of the process is increased. This new approach can be considered a protocol for *rapid and efficient synthesis of analogs of enantiomerically enriched natural products,* which represents the *general objective* of this project.

Cyclopentene derivatives have relevant biological properties and have been widely found in naturally-occurring molecules, as well as synthetic compounds with therapeutic and medicinal properties. Examples of which are (-) -Neplanocin A that has antiviral activity[91] and natural products Laurokamurene A and B with cytotoxic properties, isolated from the sea-weed of the genus *Laurencia* that inhabited in China.[92] Another is Vibralactone, an inhibitor of the pancreatic lipase enzyme, obtained from fungal cultures of the *Boreosterum vibrans* species.[93] (FIGURE 1.10).

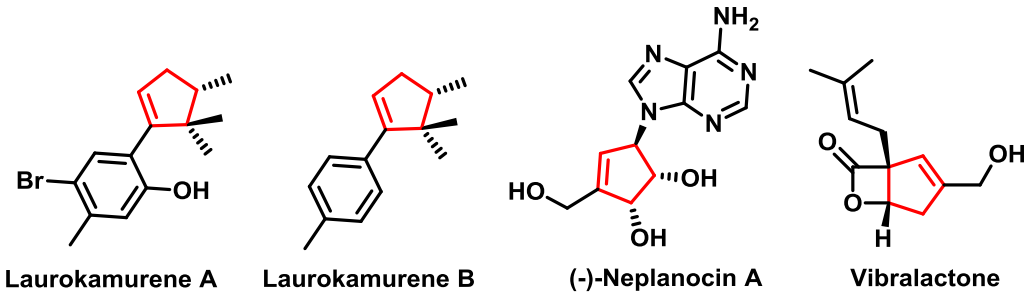


FIGURE 1.10- Applications of cyclopentene-derived compounds.

The synthesis of these biologically active compounds could also be achieved through this protocol. Similarly, the use of environmentally friendly solvents in each reaction step and the incorporation of continuous flow techniques replacing batch methods (for example, the MW) in the multi-component stage, constitute less explored modification procedures in synthetic chemistry and it represents significant advances in the development of more sustainable methodologies.

Considering these criteria, we defined the following as *specific objectives:*

1-Develop a fast and efficient methodology for the synthesis of cyclopentene derivatives with high enantio and diasteroselectivity, through the combination of organocatalysis and multicomponent reactions.

2-Evaluate the sustainability and effectiveness of the strategy developed from the use of green solvents and continuous flow methods in the multicomponent step.

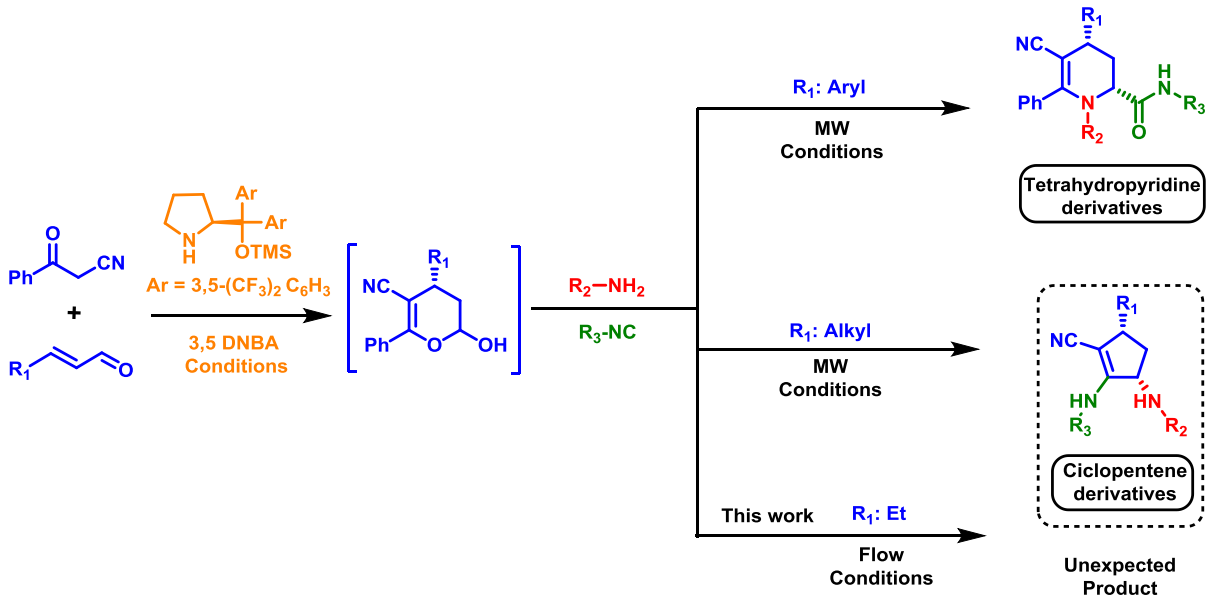
Chapter 2. Results and discussion

2.1-Proposed methodology

The combination of organocatalysis and multicomponent reactions has been a methodology studied carefully in our research group. In a published paper[90] a strategy is developed for the organocatalyzed addition of benzoylacetonitrile to an α,β-unsaturated aldehyde that contains aryl-groups as substituent to generate a hemiacetal *in situ*, followed by a multicomponent Ugi's reaction after adding the amine and isocyanide, to give rise to tetrahydropyridine derivatives (THP).

Following the same procedure with the aim of expanding the variety of aldehyde used, an α,β-unsaturated aldehydes with different alkyl-substituents were studied and surprisingly the expected final product (six-membered ring heterocyclic compounds) was not obtained, a new product is being isolated which contained a five-membered cyclopentene ring (SCHEME 2.1).

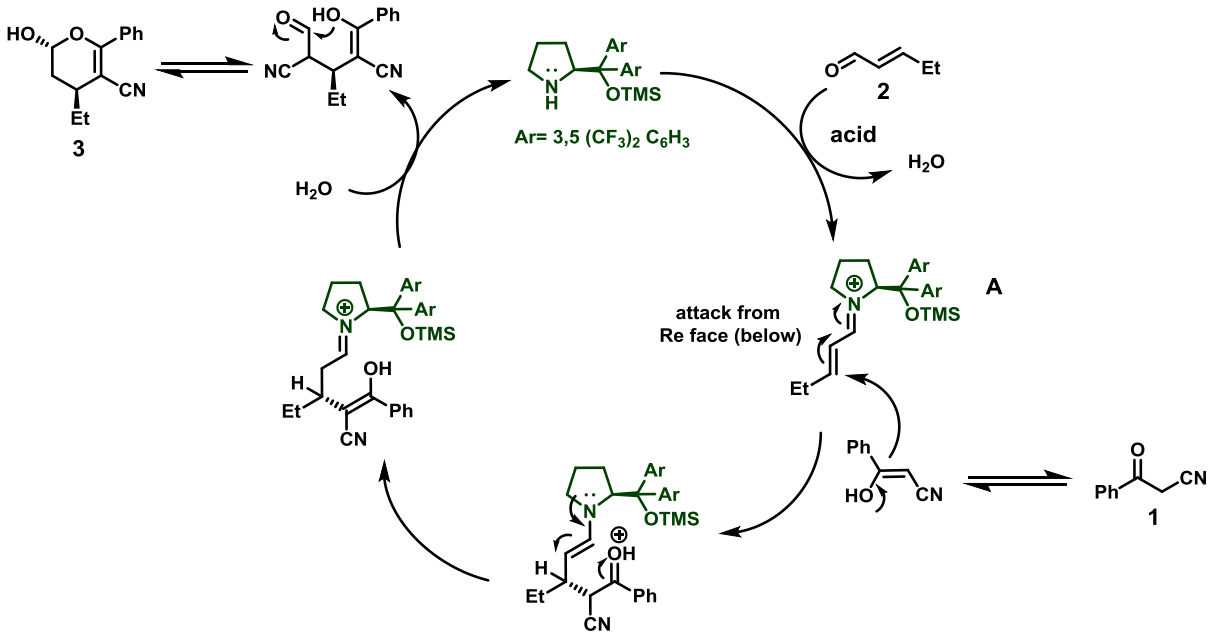
The methodology proposed in this project continues the research developed in our group and it is based on the development of a combinatorial strategy of an organocatalyzed Michael's addition and a multicomponent Ugi's reaction with three components and four reaction centers, to generate a series of cyclopentene derivatives with high enantioselectivity (SCHEME 2.1). In addition, the application of flow chemistry in the multicomponent stage and the use of green solvents will allow the synthesis to develop in a sustainable manner and with high yields.



SCHEME 2.1- Methodology proposed for the synthesis of cyclopentene derivatives.

2.2-Organocatalytic Stage

The first stage is the organocatalytic reaction where a conjugate addition of an α-cyanoketone **1** and an α,β-unsaturated aldehyde **2** occurs to generate an enantiomerically-enriched hemiacetal **3**, by means of covalent activation via iminium ion and through a Re-face attack from nucleophile **1** to intermediate **A** (SCHEME 2.2). At this stage, we rely on the strategy published by the Shang's group[24] and the procedures developed independently by Rueping and co-workers[94] and Jørgensen et al.[23]

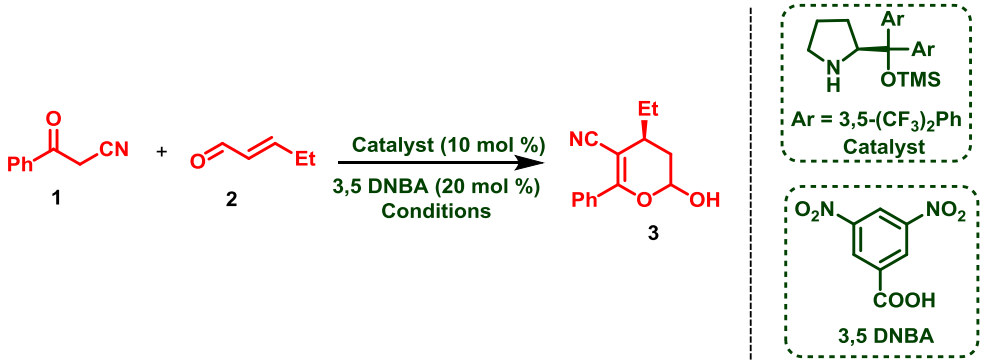


SCHEME 2.2- Catalytic cycle of Michael's addition of α-cyanoketones to α,β-unsaturated aldehydes.

First, the reaction conditions reported by the authors were evaluated and optimized. [24] Benzoylacetonitrile and trans-2-pentenal were initially selected for the organocatalyzed conjugate addition in the presence of 10 mol % of the Jørgensen's catalyst ((S)-α, α-bis [3,5-bis (trifluoromethyl) phenyl]-2-pyrrolidinemethanol trimethylsilyl ether) and 20 mol % of 3,5 dinitrobenzoic acid (3,5 DNBA).

The parameters studied were the solvent and the temperature while the reaction time being maintained in 48 hours in all the cases evaluated. The results obtained are shown in TABLE 2.1.

TABLE 2.1- Optimization studies for the Organocatalytic Reaction.



Entry	Solvent	T/(ºC)	t/(h)	Yield 3 (%) [a]	dr (%) [b]	ee (%) [c]
1	Toluene	-20	48	79	2.1:1	96
2	$CHCl_3$	-20	48	79	1.9:1	99
3	DCM	-20	48	63	2.1:1	98
4	2 Me-THF	-20	48	91	1.9:1	90
5	THF	-20	48	85	1.9:1	84
6	p-Cymene	-20	48	86	1.9:1	98
7	EtOH [d]	-20	48	83	1.8:1	92
8	**DMC [d]**	**10**	**48**	**89**	**2.1:1**	**97**
9	EtOH[d]	10	48	76	2.3:1	76
10	DMC+EtOH (1:1 v/v) [d]	10	48	80	4.4:1	94
11	EtOH[d]	rt	48	70	2.1:1	68

General reaction conditions: 0.15 mmol of benzoylacetonitrile (1 equiv), *trans*-2-pentenal (0.18 mmol, 1.2 equiv), Jørgensen'catalyst (0.015 mmol, 0.1 equiv) and 3,5 dinitrobenzoic acid (0.03 mmol, 0.2 equiv) in solvent (1.0 mL) for 48 h. [a]: Yield of the isolated product after column chromatography. [b]: The d.r was determined by ^{1}H NMR analysis of the crude reaction. [c]: Enantiomeric excess of the major diastereoisomer was determinated by chiral HPLC analysis.
[d]: Green solvents. Ar=3,5-$(CF_3)_2$-C_6H_3, DCM=dichloromethane, THF = tetrahydrofuran, 2Me-THF=2-Methyltetrahydrofuran, DMC= dimethyl carbonate.

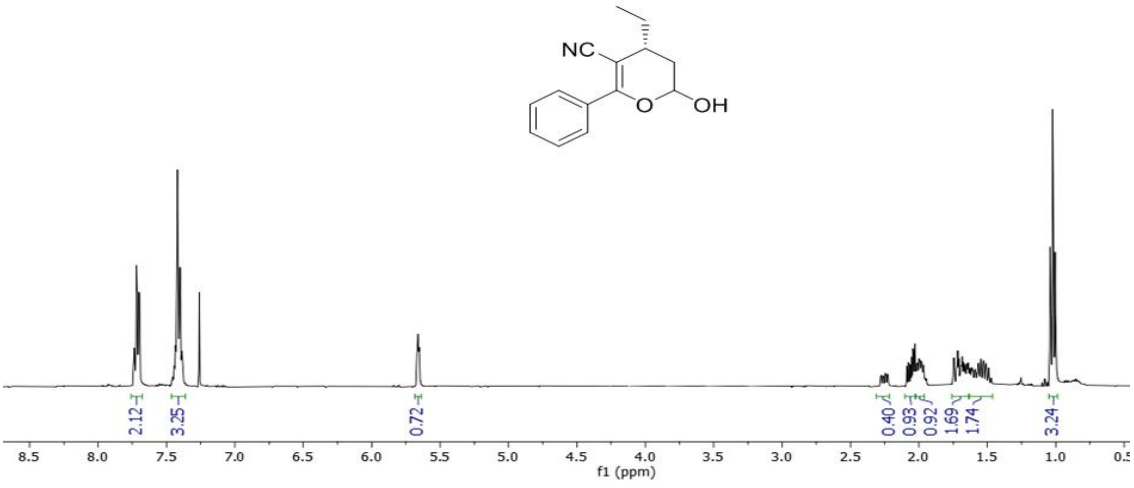
Initial experiments at a temperature of -20ºC with toluene as solvent allowed for obtaining product **3** with a yield of 79% and 96% ee as an inseparable mixture of two diasteroisomers (entry 1). Keeping the temperature constant, a series of solvents (entries 2-7) were examined, including EtOH which is considered a green solvent (entry 7), obtaining high yields and enantioselectivity in most cases and the best results at that temperature (entry 6).

Further study with other sustainable solvents and/or mixtures of solvents but with an increase in the reaction temperature to 10ºC (entries 8-10), revealed that the use of dimethyl carbonate (DMC) in the reaction was the optimal option (entry 8), giving a yield of 89% and enantioselectivity of 97% ee. Finally, when carrying out the reaction at ambient conditions in an EtOH solvent, it showed very low enantioselectivity values (entry 11).

These results contribute to making the reaction greener, allowing an efficient use of energy (variation of the reaction temperature in the order of 30ºC) and reduction of hazardous waste.

It is important to note that in the organocatalytic stage, dr was not significantly influenced by the variation of solvent and temperature.

The compound **3** synthesized in the organocatalytic stage was characterized by ^{1}H NMR and ^{13}C NMR techniques (FIGURE 2.1).



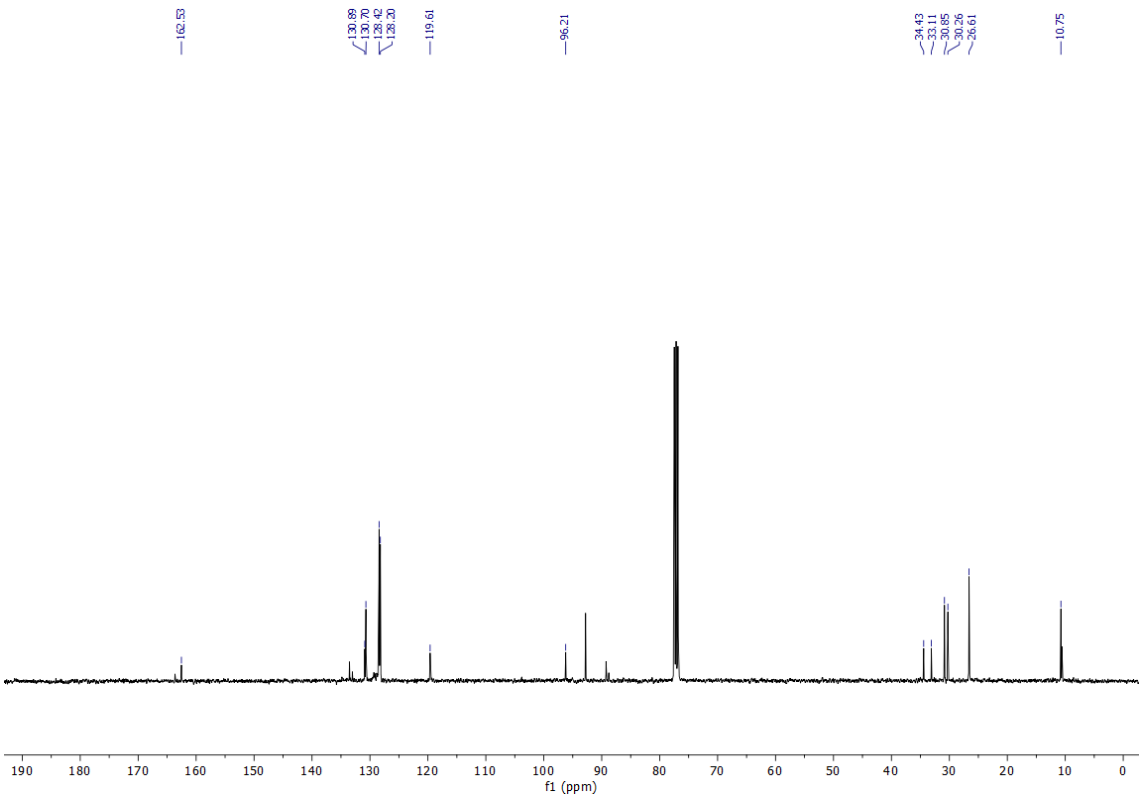


FIGURE 2.1- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3**.

As shown in the figure, the spectroscopic characterization of ^{1}H NMR corroborates the obtaining of the desired product. The multiplets appearing at 7.76 ppm and 7.46 ppm that integrate 2H and 3H respectively can be observed in the most unshielded region of the spectrum, indicating the presence of a mono-substituted aromatic ring. In addition, a signal appears that integrates 1H around 5.7 ppm that corresponds to the hemiacetal anomeric proton.

Signals corresponding to the carbon-linked protons with sp3 hybridization appear in the most shielded area of the spectrum. In this sense, multiplets that integrate 1H and 2H are observed, as well as the triplet that integrates 3H around 1.03 ppm, which corresponds to the CH_3 group of the carbon chain linked to the stereogenic center.

It should be noted that using chloroform as a deuterated solvent, it was only possible to identify the closed structure of the compound, which indicates that the balance between both structures (open and closed) has a greater proportion in the balance of the isomer in the form of hemiacetal (structure closed).

In the case of the ^{13}C NMR spectrum, 14 carbons appears equivalent to the number of carbons present in the structure of the compound. The signals of aromatic carbons (119-131ppm) can be observed, as well as the quaternary carbons of the C-C double bond in the hemiacetal ring. It is also important to note the presence of the aliphatic carbons (CH_2 and CH_3) that appear between 10.8-34.4 ppm.

Finally, the information obtained by both spectra shows that hemiacetal **3** was successfully formed. In analogy to the stereochemistry previously defined by Niu et al[24] through X-ray crystallography analysis, the absolute configuration of the asymmetric center C-4 of hemiacetal **3** was assigned as **S**.

Although this compound has two asymmetric centers, only the main diasteroisomers could be identified in the chromatograms obtained by chiral HPLC analysis (FIGURE 2.2). This is explained by the rapid exchange of the anomeric carbon configuration, which occurs through the balance between the closed form (hemiacetal) with the open form (hydroxy-aldehyde), which makes it difficult to separate the four stereoisomers by chiral HPLC analysis.

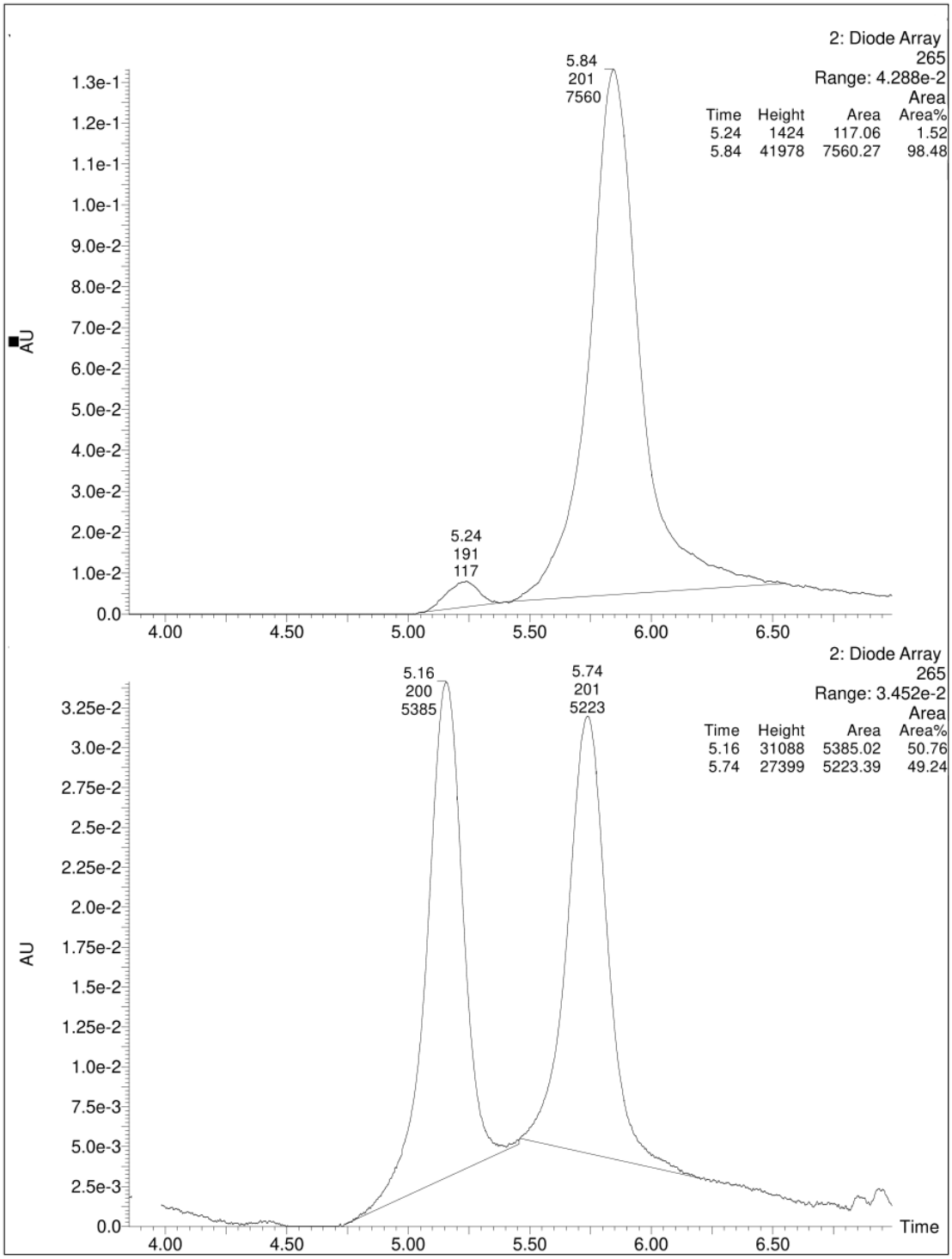


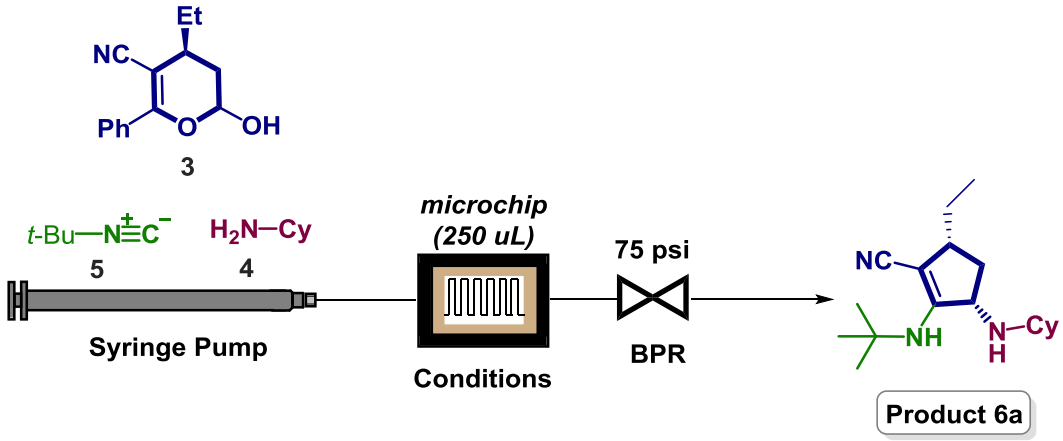
FIGURE 2.2- Chiral stationary-phase HPLC analysis of compound **3.**

2.3-Multicomponent Stage

After having established the optimal conditions in the organocatalytic stage and having synthesized compound **3**, the Ugi-type multicomponent reaction was studied. The hemiacetal **3** obtained was reacted together with a primary amine **4** (cyclohexylamine) and an isocyanide **5** (tert-butyl isocyanide) using a continuous flow system that was assembled for this purpose (FIGURE 2.3). The results obtained during this procedure are shown in TABLE 2.2.

FIGURE 2.3- Flow continuous system used in the MCR.

TABLE 2.2- Optimization studies for the Continuous Flow 4-Center 3-Component Ugi's Reaction.



Entry	Solvent	T (ºC)	t_R (min)	Yield 6a (%) [a]	dr (%) [b]	ee (%) [c]
1	TFE	70	20	75	5.3:1	>99
2	TFE	70	15	72	5.4:1	>99
3	TFE	70	10	74	5.3:1	>99

4	TFE	75	20	73	5.4:1	>99
5	TFE	75	15	79	5.3:1	>99
6	TFE	75	10	77	5.2:1	>99
7	TFE	80	15	81	5.3:1	>99
8	TFE	80	10	87	7.2:1	>99
9	TFE	85	10	79	5.2:1	>99
10	EtOH [d]	80	10	82	20:1	>99
11	1-Butanol [d]	80	10	78	17:1	97
12	1-Propanol [d]	80	10	75	15:1	93
13	2-Propanol [d]	80	10	70	18:1	>99
14	DMC+EtOH (1:1 v/v) [d]	80	10	89	20:1	98
15	**DMC+EtOH (1:1 v/v) [d,e]**	**80**	**10**	**86**	**20:1**	**98**

General reaction conditions: 0.15 mmol of hemiacetal (1 equiv), cyclohexylamine (0.15 mmol, 1 equiv) and *tert*-butyl isocyanide (0.15 mmol, 1 equiv) in solvent (1.0 mL). [a]: Yield of the isolated product after column chromatography. [b]: The d.r was determined by ^{1}H NMR analysis of the crude reaction. [c]: Enantiomeric excess of the major diastereoisomer was determinated by chiral HPLC analysis. [d]: Green solvents. [e]: Sequential synthesis of product **6a** from the organocatalytic reaction step without isolating hemiacetal **3**. Ar =3,5-$(CF_3)_2$-C_6H_3, DMC=dimethyl carbonate, TFE=trifluoroethanol.

We began the study of the standard reaction in TFE at 70ºC and residence time of 20 minutes, obtaining the desired product **6a** with a yield of 75% and excellent enantioselectivity (> 99% ee) while the dr of the reaction was 5.3:1 (entry 1). Then the influence of temperature and residence time was evaluated without varying the solvent used (entries 2-9) and it was obtained that the best option in TFE was that with the highest values of yield and dr (entry 8), while the enantioselectivity of the product remained excellent.

Having established the best conditions of temperature and residence time in the microreactor, further experiments were carried out with a view to determining which green solvent or mixture of solvents was the most appropriate for the reaction (entries 10-14). The mixture of solvent DMC+EtOH (1:1 v/v) gives the best results (entry 14). This led us to the hypothesis of formulating the synthetic route sequentially for the entire process (entry 15), this being the optimal condition to obtain the product **6a** with a yield of 86% and excellent enantiomeric purity (98% ee) and diasteroselectivity (20:1 dr).

It is important to note that the presence of the secondary amine catalyst used in the organocatalytic stage did not interfere with the multicomponent step, since no product that included this fragment was detected.

The use of various types of alcohols that are protic polar solvents is crucial to the success of the multicomponent stage as is known for Ugi-type reactions based on isocyanides.[34]

In other hands, the implementation of flow chemistry at this stage led to the experiments of temperatures very close and even higher than the boiling point of solvents, which could be achieved with the use of a backpressure regulator installed at the exit of the microreactor, avoiding the evaporation of the solvent inside the system, which could affect the tests carried out.

As shown in FIGURE 2.4, the structural assignment of compound **6a** can be performed unequivocally using ^{13}C and proton NMR spectroscopic techniques. In accordance with the figure, characteristic signals are observed that indicate the presence of the different molecular fragments of the structure. For example, a signal of a wide singlet appears around 5.65 ppm in the most unshielded area of the spectrum, corresponding to the NH bound to sp2 carbon of the cyclic structure. Next, a doublet doublet with 10.6 and 7.1 Hz coupling constants appears at 3.60 ppm, which can be assigned to the H-3 that is next to a CH_2 whose protons are diastereotopic because neighbouring stereogenic center. On the other hand, in the most shielded region of the spectrum, around 2.65 ppm a doublet triplet appears that corresponds to the hydrogen linked to carbon 5. Similarly, a singlet can be seen that integrates at 9H and that corresponds to the *tert*-butyl group provided by the isonitrile and that is present in the structure of the carbocycle. Likewise shown above, signals indicating the presence of more than one carbon sp2 can be inferred through the ^{13}C spectrum, as well as signals from the aliphatic carbons of the methyl and methylene groups of the structure.

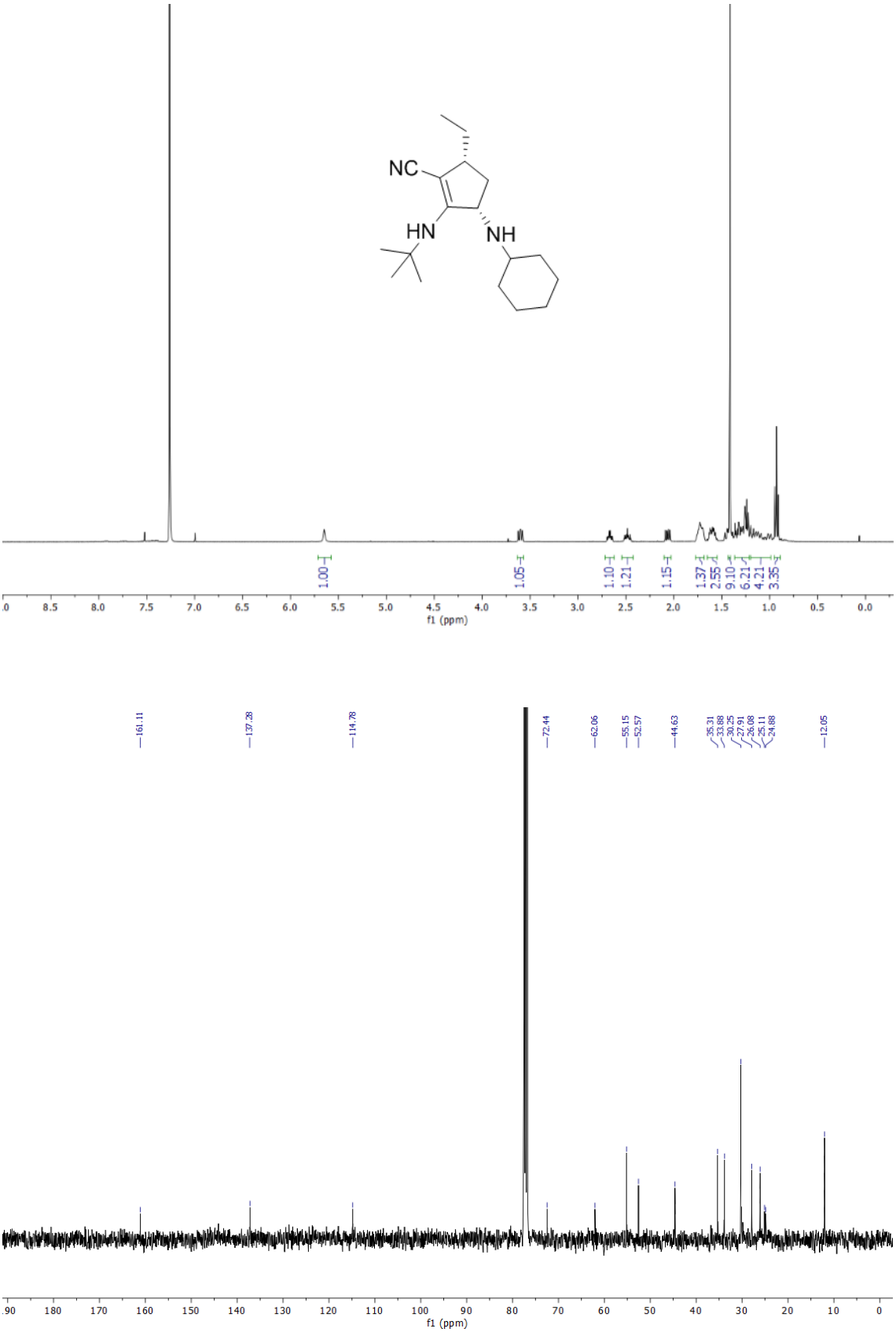


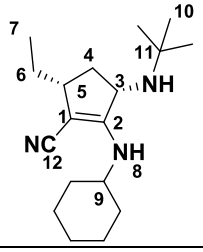
FIGURE 2.4- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6a**.

A more correct assignment of the synthesized compounds is achieved using two-dimensional spectroscopic techniques. As shown in TABLE 2.3, the full characterization for compound **6j** is presented. The analysis of the proton NMR spectrum confirms the presence of the amine fragment incorporated in the structure. This can be affirmed due to the signal that appears around 1.10 ppm, which corresponds to a singlet that integrates to 9H and which is typical of the tert-butyl group. A doublet that integrates at 1H and corresponds to H-8 linked to the neighbouring amine to the double bond can also be observed at a chemical shift close to 5.2 ppm. In the 3.8 ppm, a multiplet appears that integrates one and corresponds to the H-9. For its part, the COSY spectrum shows the correlations between the neighbouring protons present in the structure.

The ^{13}C spectrum clearly shows the presence of the cyanide group, in a chemical shift of 121 ppm. This dislocation can be explained by the presence of a triple bond that is neighbouring the cyclopentene ring. On the other hand, the aliphatic zone shows the presence of sp3 hybridization carbons present in the structure, highlighting the chemical shifts of 70.6 ppm corresponding to the quaternary C-2, also in 30.6 ppm a signal appears that can be attributed to the tert-butyl group present in the molecule.

Together with this spectrum, a multi-pulse experiment was conducted to determine the presence of the CH, CH_2 and CH_3 groups. To this end, a Distortionless Enhancement by Polarization Transfer 135 experiment was performed. In this way, the exact number of primaries to quaternaries carbons is detected. With this technique, four quaternary carbons, seven CH_2 and a total of five CH and CH_3 were assigned. Similarly, with the help of HMBC experiments we determine the heteronuclear couplings present in the structure.

TABLE 2.3- Complete assignments of ^{1}H NMR and ^{13}C for compound **6j.**



Position	**^{1}H NMR: δ(ppm), *J*(Hz)**	**^{13}C NMR: δ(ppm)**
1	-	70.7
2	-	160.1

3	3.61 (dd, *J* = 9.9/ 7.3 Hz)	57.5
4	2.08 (ddd, *J* = 12.4/ 7.2/1.0 Hz); 1.39-1.28 (m)	40.6
5	2.60 (td, *J* = 8.2/ 5.1 Hz)	43.5
6	1.49-1.41 (m, 4H)	24.2
7	0.93 (t, *J* = 7.4 Hz)	12.1
8	5.18 (d, *J* = 8.1 Hz)	-
9	3.83-3.71 (m,1H)	51.0
10	1.07 (s, 9H)	30.6
11	-	50.7

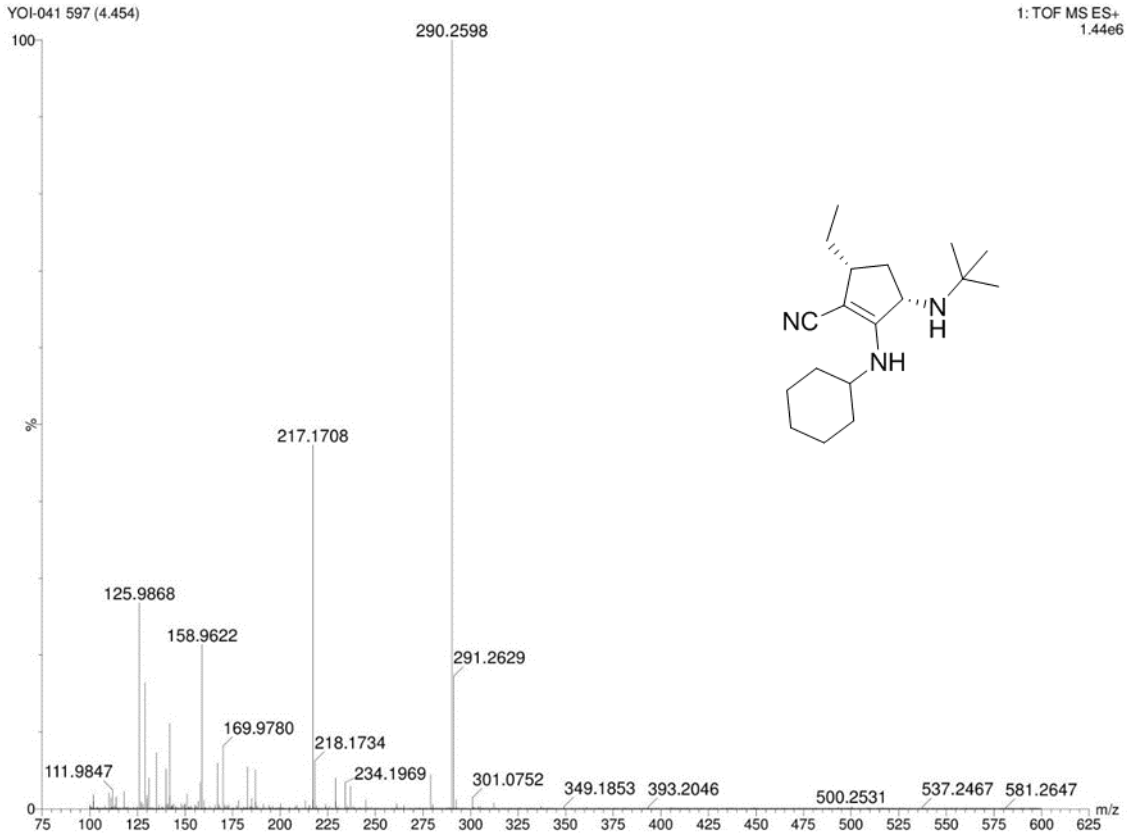
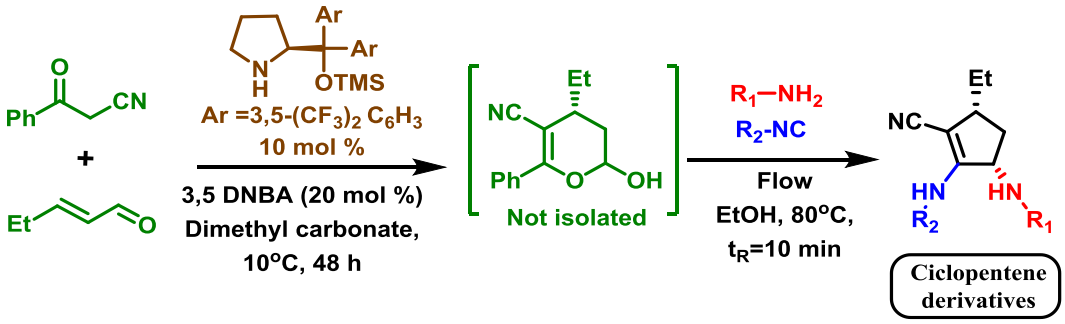


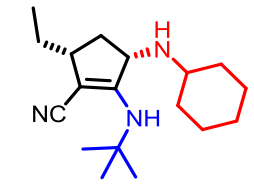
FIGURE 2.5- HRMS spectra of compound **6j.**

The structure of compound **6j** was further corroborated from the high-resolution mass spectrum (HRMS) as shown in the FIGURE 2.5. An intense peak corresponding to the mass of compound **6j** plus a hydrogen [M+H] is observed and its value is 290.2598, while the calculated mass is 290.2596.

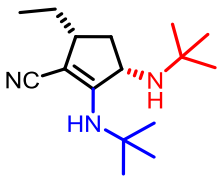
2.3.1-Reaction screening



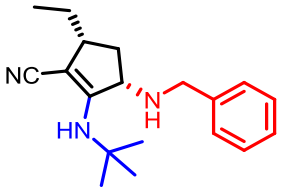
Sequencial Organocatalytic Conjugate Addition / 4 Center - 3 Components Ugi's Reaction



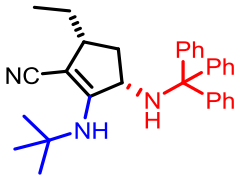
6a, 86%, 20:1 dr, 98% ee



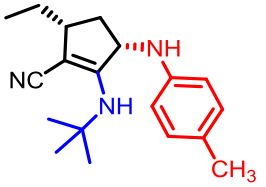
6b, 89%, 20:1 dr, 96% ee



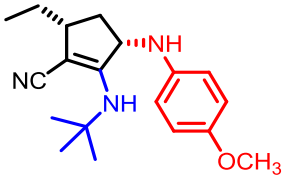
6c, 77%, 9,2:1 dr, 94% ee



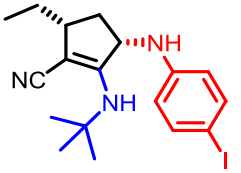
6d, 81%, 20:1 dr, 88% ee



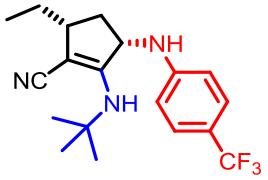
6e, 84%, 5:1 dr, >99% ee



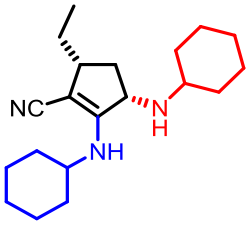
6f, 70%, 20:1 dr, >99% ee



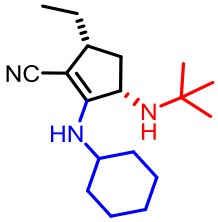
6g, 80%, 13,6:1 dr, 92% ee



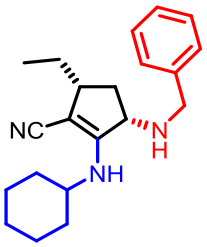
6h, 62%, 20:1 dr, 92% ee



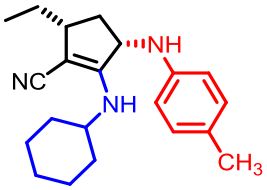
6i, 91%, 20:1 dr, >99% ee



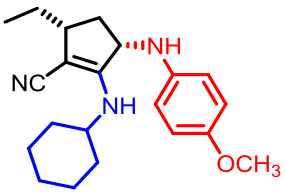
6j, 86%, 20:1 dr, 86% ee



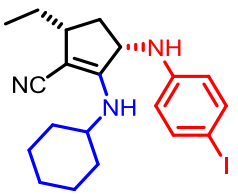
6k, 82%, 20:1 dr, 86% ee



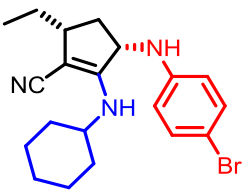
6l, 90%, 20:1 dr, 92% ee



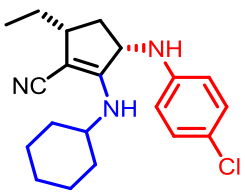
6m, 82%, 20:1 dr, >99% ee



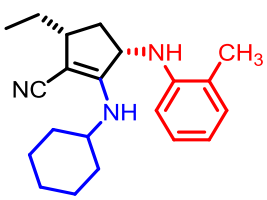
6n, 87%, 20:1 dr, 96% ee



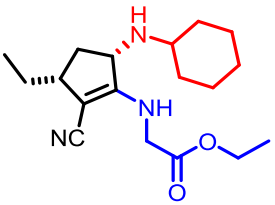
6o, 75%, 20:1 dr, 96% ee



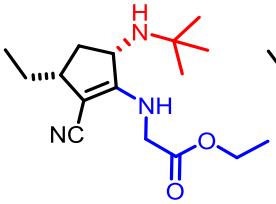
6p, 79%, 20:1 dr, 96% ee



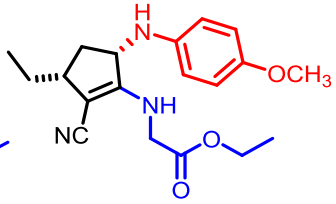
6q, 72%, 20:1 dr, 96% ee



6r, 74%, 20:1 dr, >99% ee



6s, 76%, 20:1 dr, 98% ee



6t, 53%, 20:1 dr, 96% ee

FIGURE 2.6- Sequential synthesis of cyclopentene derivatives.

Following this methodology, a series of cyclopentene derivatives **(6a to 6t)** were synthesized from the variation of two structural elements: the amine and the isocyanide, which are incorporated in the multicomponent step (FIGURE 2.6). In the procedure, the hemiacetal generated *in situ* in the organocatalytic stage was not isolated. Instead, EtOH solvent, the amine and isocyanide components were added to it, ensuring a MCR in a continuous flow system.

The products were obtained with an enantioselectivity of 86-99% ee, a diasteroselectivity of 5:1-20:1 dr and yields of 53-91%, through the incorporation of a variety of aliphatic and aromatic amines, as well as commercially available isocyanides.

When tert–butyl isocyanide and several aliphatic amines (cyclohexylamine, tert–butylamine, benzylamine and tritylamine) were used, the respective compounds **6a to 6d** were obtained, with yields of 77-89% and high diasteroselectivity (9.2:1 to 20:1 dr, 88-98% ee) while the compound **6d** being the one with the lowest enantioselectivity with 88% ee.

It is important to note that when very bulky amines were used as in the case of compounds **6a**, **6b** and **6d**, higher yields (86%, 89% and 81% respectively) and excellent diasteroselectivity (20:1 dr) were obtained, in comparison with the amine of the product **6c** (77% yield, 9.2:1 dr) which is the least impeded of all analyzed.

Maintaining the same isocyanide but using aromatic amines para–substituted with donor groups (p–toluidine and p–methoxyaniline) as well as electron–withdrawing groups (p–iodoaniline and p–trifluoromethylaniline) led to products **6e to 6h** respectively. In the case of compounds **6e** (84% yield) and **6g** (80% yield) yields similar to aliphatic amines were obtained, while compounds **6f** (70% yield) and **6h** (62% yield) it were lower.

The diasteroselectivity was excellent in the cases of compounds **6f at 6h** (13.6:1 to 20:1 dr) while in the case of product **6e** (5:1 dr) it decreased considerably. The enantioselectivity declined relatively compared to aliphatic amines when anilines were used with electron–withdrawing groups: compounds **6g** (92% ee) and **6h** (92% ee) while in the cases of anilines with donor groups it was totally the opposite, obtaining enantiomerically–pure products **6e** (99% ee) and **6f** (99% ee).

It was observed that the use of less nucleophilic anilines (such as p–trifluoromethylaniline) resulted in compound **6h** with a very low yield (62%) compared to the other amines studied. This behavior is because the nucleophilicity of the aromatic amine influences the formation of the imine during the multicomponent reaction. In the case of compound **6h**, this process is very disadvantaged, which hinders the yields obtained.

By using a less bulky isonitrile such as cyclohexyl isocyanide, as well as aliphatic amines (cyclohexylamine, tert–butylamine and benzylamine respectively), products **6i to 6k** were obtained with yields of 82-91% and excellent diasteroselectivity (20:1 dr). Unexpectedly, the enantioselectivity decreased significantly in compounds **6j** and **6k** being 86% ee in both cases, while product **6i** was obtained enantiomerically–pure (99% ee) and with the highest yield (91%) after being purified.

The evaluation of aromatic amines in this case (p–toluidine, p–methoxyaniline, p–iodoaniline, p–bromoaniline, p–chloroaniline and o–toluidine) generated products **6l to 6q** with yields of 72-90%. The diasteroselectivity was excellently maintained (20:1 dr) and the enantioselectivity (92-99% ee) was increased when compared to the aliphatic amines studied.

The product **6m** was obtained enantiomerically–pure (82% yield, 99% ee) and the enantioselectivities values of the aromatic amines with electron–withdrawing groups in –para position **(6n to 6p)** were equal between them (96% ee) and higher than the amine with donor group in the same position as in compound **6l** (92% ee).

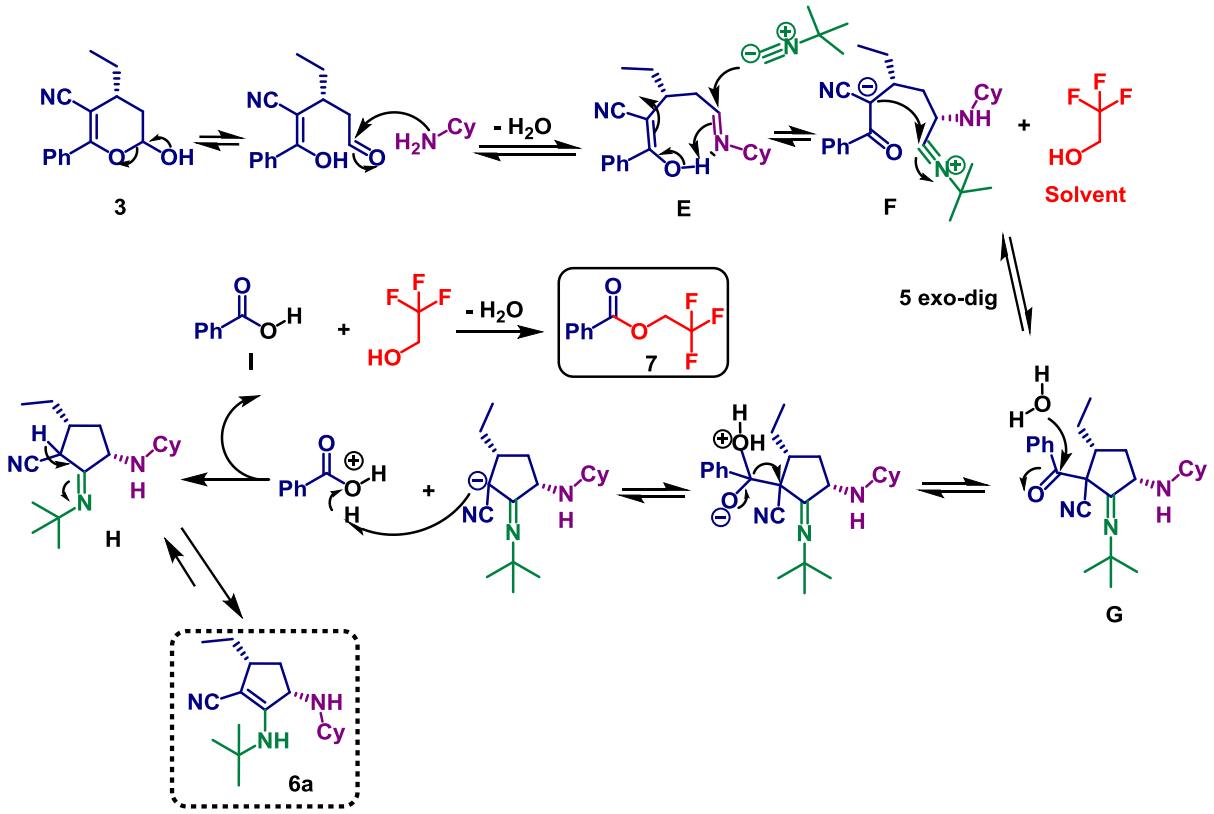
The comparison between anilines with methyl groups in –ortho positions, compound **6q** (72% yield, 20:1 dr, 96% ee) and –para position, compound **6l** (90% yield, 20:1 dr, 92% ee), showed that the –para product is obtained with greater yield than the –ortho product, but with lower enantiomeric purity, while the diasteroselectivity being maintained excellent in both cases.

The use of an isonitrile derived from glycine (ethyl isocyanoacetate) with aliphatic (cyclohexylamine and tert–butylamine) and para–substituted aromatic amines with a donor group (p–methoxyaniline), led to the obtaining of compounds **6r to 6t** respectively, with excellent diasteroselectivity (20:1 dr). The aliphatic amines **6r** (74% yield, 99% ee) and **6s** (76% yield, 98% ee) were obtained with yields and enantioselectivities greater than the aromatic amine **6t** (53% yield, 96% ee). This behavior is due to aromatic amines being less

nucleophilic than aliphatic and less reactive, negatively influencing the formation of imine and therefore decreases the efficiency of the reaction.

It is also evident that the change of the bulky character between the aliphatic amines (cyclohexylamine and tert–butylamine) does not influence the yield of the **6r** (74%) and **6s** (76%) products.

2.3.2-Mechanism proposal for the multicomponent stage



SCHEME 2.3- Proposed mechanism for the multicomponent stage.

The proposed mechanism for the multi-component stage in the formation of cyclopentene derivatives appears in SCHEME 2.3. The first step is the formation of imine **E** through a direct attack of cyclohexylamine on the open form of hemiacetal **3** obtained in the organocatalytic step, with subsequent water removal. Later, the imine forms a conformationally rigid eight-membered ring that has an intramolecular hydrogen bond.[90]

The nucleophilic addition of the isocyanide component to the C-N double bond of the imine opens the cycle, resulting in a highly reactive intermediate **F** containing a negatively charged nucleophilic carbon and a C-N triple bond belonging to the isocyanide, where the electrophilic carbon atom

exhibits sp hybridization. Compound **F** undergoes a 5–exo–dig type intramolecular cyclization favored according to the Baldwin's Rules. The attack occurring at the innermost atom (specifically the carbon atom) and generating intermediate **G**, containing a very thermodynamically stable five-membered ring.

The nucleophilic attack of the water formed during the process to the double exocyclic C-O (carbonyl) bond of intermediate **G**, followed by an intramolecular rearrangements, leads to the formation of compounds **H** and **I**. Then, intermediate **I** reacts with the TFE solvent to generate product **7**, which was detected by GC-MS corroborating the proposed mechanistic sequence (FIGURE 2.7).

Finally, tautomerization of compound **H** occurs, leading to the formation of the more thermodynamically stable product **6a**, which correspond to the final structures of the products obtained.

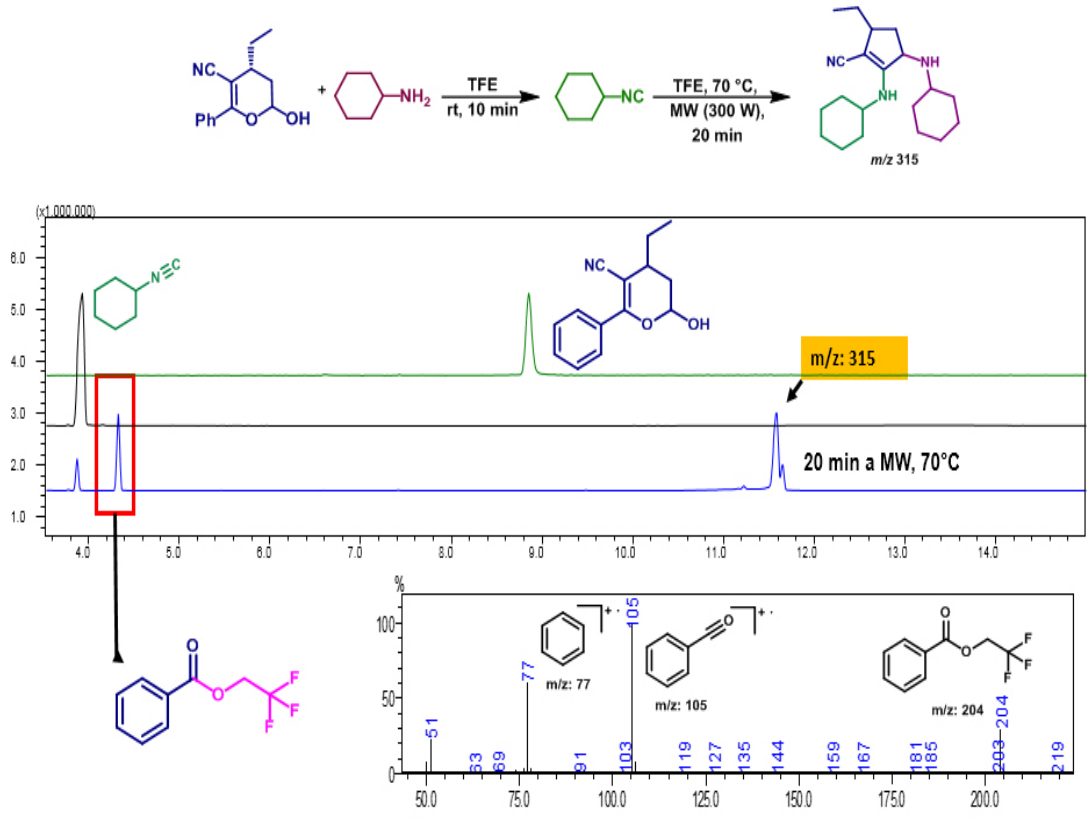


FIGURE 2.7- Chromatogram and mass spectrum for the detection of compound **7** by GC-MS.

2.4-Evaluation of the proposed methodology

After obtaining the optimal conditions in the continuous flow system, a subsequent study was carried out using the microwave technique to compare the synthesis efficiency in the microreactor. The reaction conditions established in both cases were temperature of 70 °C and time of 20 min to avoid overheating of the EtOH solvent. The results obtained are shown in the TABLE 2.4.

TABLE 2.4- Comparison between microwave synthesis and continuous flow regime of compound **6a**.

Entry	Conditions	Yield 6a (%)[a]	dr (%)[b]	ee (%)[c]
1	Microwave (70°C, 20 min)	78	18:1	97
2	Flow chemistry (70°C, t_R=20 min)	84	16.8:1	96

[a]: Yield of the isolated product after column chromatography. [b]: The d.r was determined by ^{1}H NMR analysis of the crude reaction. [c]: Enantiomeric excess of the major diastereoisomer was determinated by chiral HPLC analysis.

The results obtained shows that continuous flow technology has a higher performance than in the case of MW, maintaining the enantiomeric purity and high diasteroselectivity values.

In addition, the synthesis of continuous flow regime on a larger scale (FIGURE 2.8) resulted in 1.8 mmol of starting material (benzoylacetonitrile) being able to be continuously converted into the cyclopentene derivative (1.49 mmol, 431 mg) for approximately 6 hours of infusion rate. The above proved that the benefit of this methodology would be able to be adopted in the pharmaceutical industry.

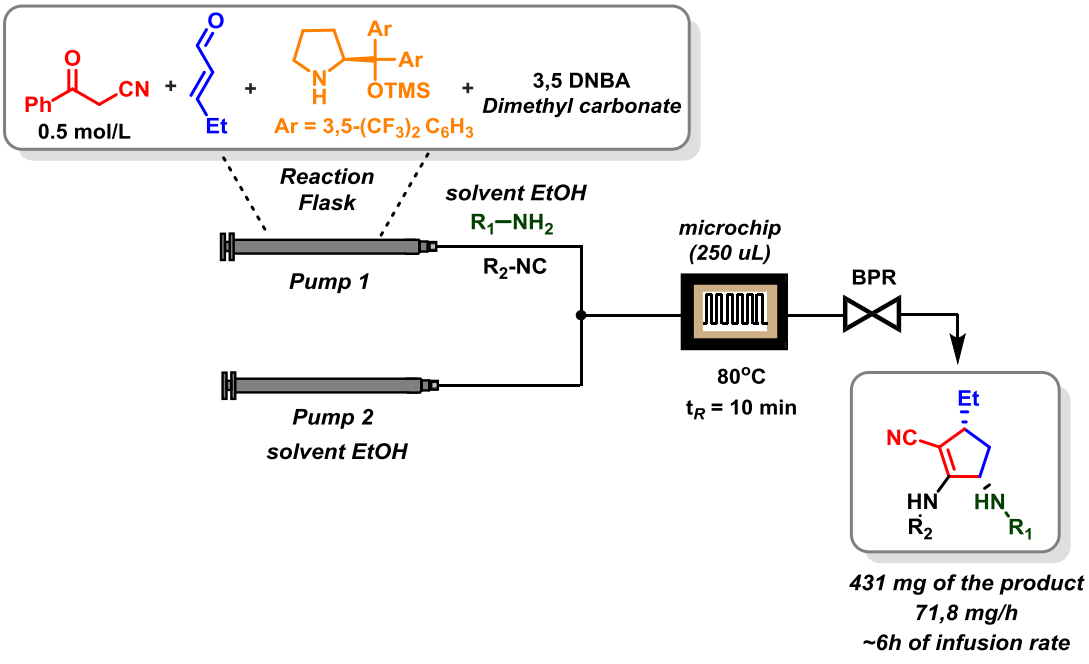


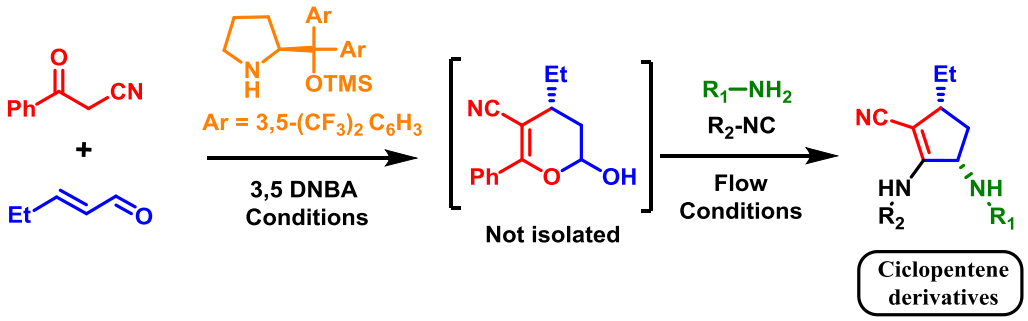
FIGURE 2.8- Synthesis of continuous flow regime on a larger scale.

2.4.1-Sustainability evaluation of the proposed methodology

The sustainability evaluation of the designed methodology was carried out using the existing green metrics: factor E, atomic economy (AE), and mass intensity (MI).[95] Factor E was selected because it is widely used in the pharmaceutical industry and is applied to multi-step processes. It also leads to a much more rigorous and comprehensive evaluation of the process since it takes into account all the components (reagents, solvents and auxiliaries) that are involved in the synthesis, as well as the yield of the final product obtained.

In this way, factor E can be determined through the division of the mass of waste-considered to total mass of materials used minus the mass of product-and the mass of product formed (Table 2.5).

TABLE 2.5- Sustainability evaluation of the designed methodology.



Compound	n (mmol)	eq	M (g/mol)	m (mg)	Density (g/cm^3)	V (mL)
Benzoylacetonitrile	0.15	1.0	145.16	21.77		
Trans-2 pentenal	0.18	1.2	84.12	15.14	0.86	
Jørgensen'catalyst	0.015	0.1	597.51	8.96		
3,5-dinitrobenzoic acid	0.03	0.2	212.12	6.36		
DMC (Solvent)				1069	1.069	1.0
Cyclohexylamine	0.15	1.0	99.17	14.88	0.865	
Tert-butyl isocyanide	0.15	1.0	83.13	12.47	0.735	
EtOH (Solvent)				789	0.789	1.0
Product **6a** (86% yield)			289.47	37.5		
Total mass				**1937.58**		
E factor				**50.67**		

The results obtained show that the calculated Factor E (50.67) is located within the segment of the pharmaceutical industry (25 to more than 100) and very close to the maximum value obtained in the case of fine chemistry (5 to 50)[96], therefore the designed methodology can be considered efficient and sustainable.

Similarly, it is an evidence that the amount of solvents used in the synthesis have a significant influence on the calculation of factor E. Hence, there is a need for proper use in synthetic chemistry.

2.5-Conclusions

From the results obtained in this work, it can be concluded that: a highly stereoselective sequential procedure was developed in the synthesis of cyclopentene derivatives through the combination of organocatalysis and multicomponent reactions. The use of environmentally friendly solvents and continuous flow methods contribute to obtaining these products in a sustainable and efficient way and to the development of new synthetic strategies in green chemistry.

Finally, the designed methodology can be considered as a protocol to synthesize enantiomerically-enriched natural products analogues fast and efficiently.

Chapter 3. Experimental Section

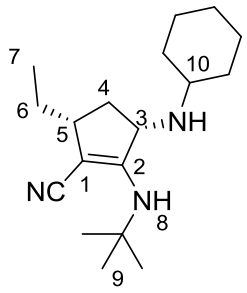
3.1-General Remarks

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. The following abbreviations were used for spin multiplicity: s = singlet, bs = broad singlet, d = doublet, t =triplet, td =triplet of doublets, q = quartet, dd = double of doublets, ddd = double of doublet of doublets, m = multiplet. 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). 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. Chiral HPLC chromatograms were obtained on an apparatus with an Ultraperformance Convergence Chromatography (Waters ACQUITY UPC ^{2} ™) using Daicel Chiralpak OD, AD and OZ columns (2.5 μm, 3 mm x 150 mm) as chiral stationary phases. Optical rotations were measured with a Polarimeter at 589 nm, 20 °C. The Syringe Pump was a Cole-Palmer apparatus 74900 Series model. The Microreactor was a high pressure and temperature glass microchip (250 μL) obtained from the Syrris Asia Flow Chemistry System.

3.2-Experimental Section

3.2.1-General sequencial synthesis procedure in continuous flow regime:

To a solution of Jørgensen's catalyst (0.015 mmol, 0.1 equiv.), 3,5 dinitrobenzoic acid (0.03 mmol, 0.2 equiv.) and *trans*-2 pentenal (0.18 mmol, 1.2 equiv.) in dimethyl carbonate (1.0 mL) was added benzoylacetonitrile (0.15 mmol, 1.0 equiv.). The resulting solution was stirred for 48h at 10 °C. Ethanol (1.0 mL), the amine (0.15 mmol, 1.0 equiv.) and the isocyanide (0.15 mmol, 1.0 equiv.) were added and the reaction mixture were injected into the microreactor at 80°C and residence time of 10 min by a syringe pump until the steady state condition is reached.



Compound 6a: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), cyclohexylamine (17.2 µL, 0.15 mmol) and tert-butyl isocyanide (17.0 µL, 0.15 mmol), were reacted according to the general procedure. Flash column chromatography purification (n-hex/AcOEt 6:1) afforded compound **6a** (37.3 mg, 86%) as a yellow oil.

$[\alpha]_D^{20}$ -12.8 (c 0.7, acetone, 20°C). Rf = 0.34 (n-hex/AcOEt 5:1). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ = 5.65 (brs, 1H, H-8); 3.60 (dd, *J*= 10.6/7.1, 1H, H-3); 2.67 (td, *J*=8.4/ 4.8,1H, H-5); 2.54-2.43 (m, 1H, H-10); 2.07 (dd, *J*=12.3/7.1, 1H, H-4a); 1.78-1.67 (m, 1H, H-4b); 1.64-1.55 (m, 2H); 1.41 (s, 9H, H-9); 1.36-1.21 (m, 6H); 1.20-0.99 (m, 4H); 0.94 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 12.0 (CH_3), 24.9, 25.1, 26.1, 27.9 (CH_2), 30.2 (CH_3), 33.9, (CH_2), 35.3, 44.6, 52.6 (CH), 55.1, 62.1 (CH_2), 72.4, 114.8, 137.3, 161.1 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{18}H_{32}N_3$ 290.2596; found: 290.2599

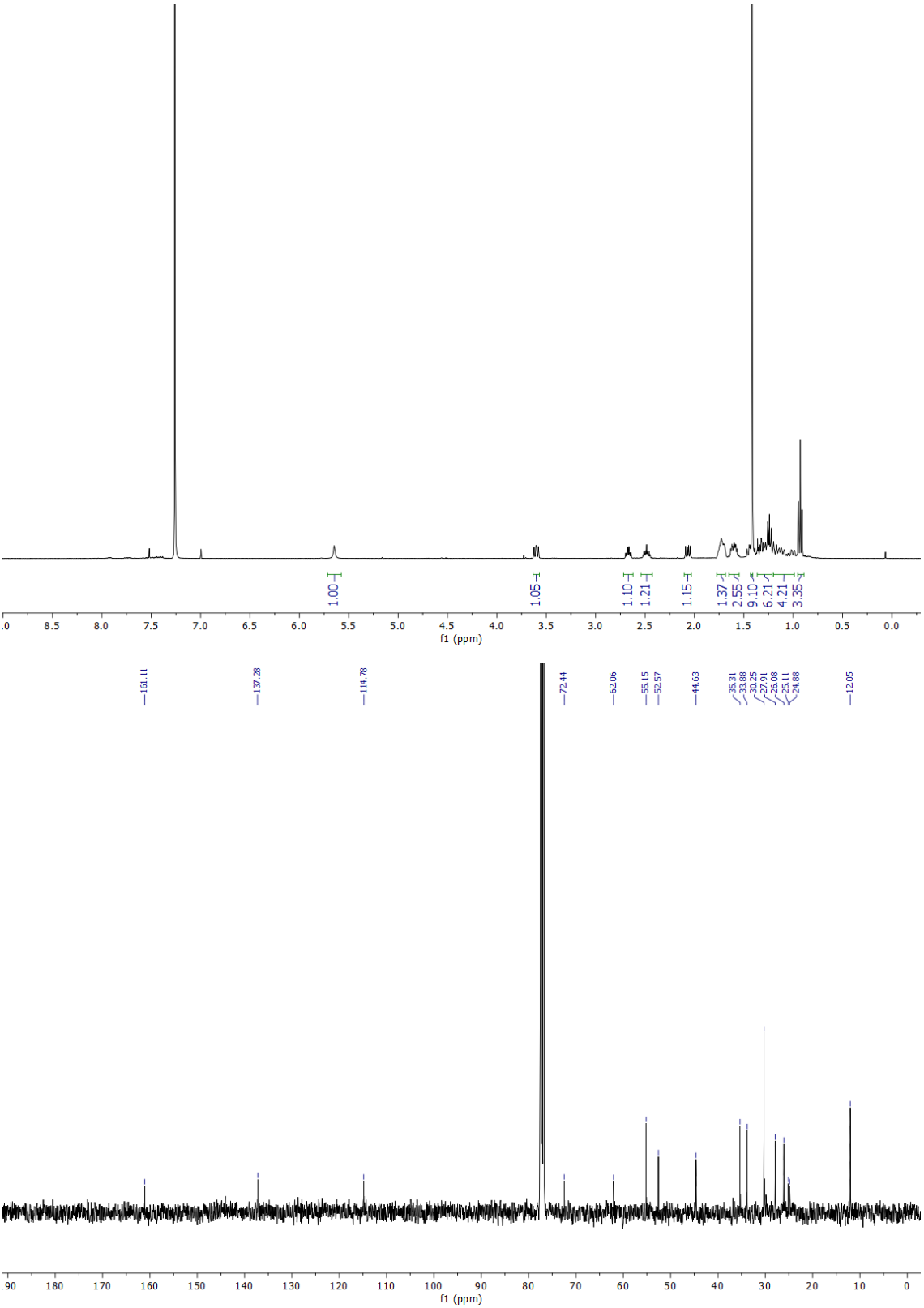


FIGURE 3.1- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6a**.

Chromatograms of Compound 6a

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (CH_3CN 95%) at 1.0 mL/min, UV-detection at $\lambda = 265$ nm:

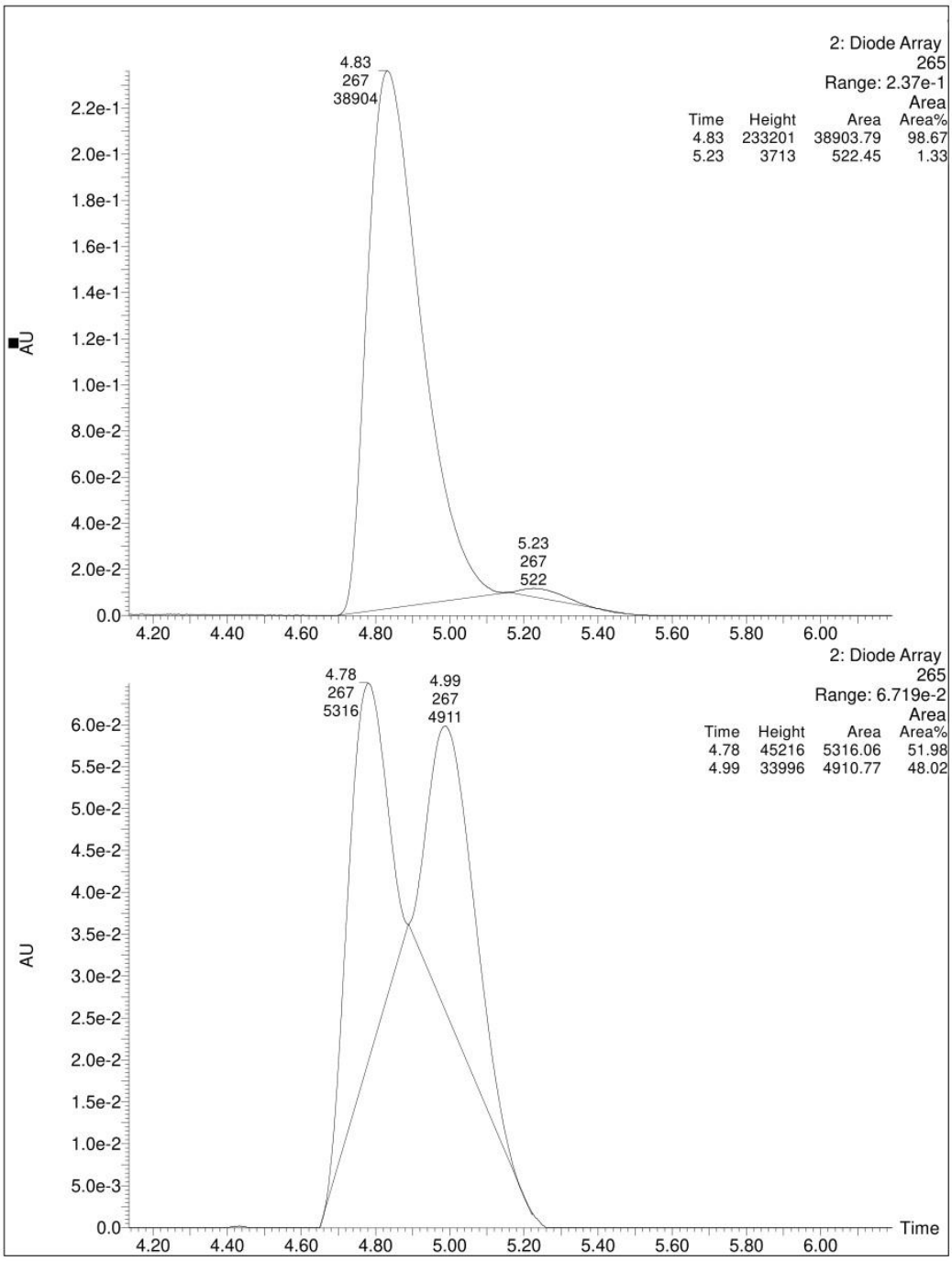
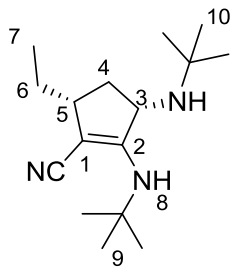


FIGURE 3.2- Chiral stationary-phase HPLC analysis of compound **6a.**



Compound 6b: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), *tert*-butylamine (15.8 µL, 0.15 mmol), and *tert*-butyl isocyanide (17.0 µL, 0.15 mmol), were reacted according to the general procedure . Flash column chromatography purification (*n*-hex/AcOEt 10:1) afforded compound **6b** (35.1 mg, 89%) as a pale yellow solid. $[\alpha]_D^{20}$ 12.3 (*c* 0.7, acetone, 20°C). R_f = 0.49 (*n*-hex/AcOEt 5:1). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ = 5.68 (s, 1H, H-8); 3.55(dd, *J*=10.6/7.1, 1H, H-3); 2.64 (td, *J*=8.4/ 4.8,1H, H-5); 2.08 (dd, *J*=12.3/7.1, 1H, H-4a); 1.66-1.54 (m, 1H, H-4b); 1.41 (s, 9H, H-9); 1.38-1.28 (m, 2H, H-6); 1.09(s, 9H, H-10); 0.94 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 10.9 (CH_3), 27.6 (CH_2), 30.1, 30.4 (CH_3), 40.7 (CH_2), 42.3 (CH), 50.6, 51.1 (C), 59.2 (CH), 70.9, 123.1, 158.3(C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{16}H_{30}N_3$: 264.2440; found: 264.2445

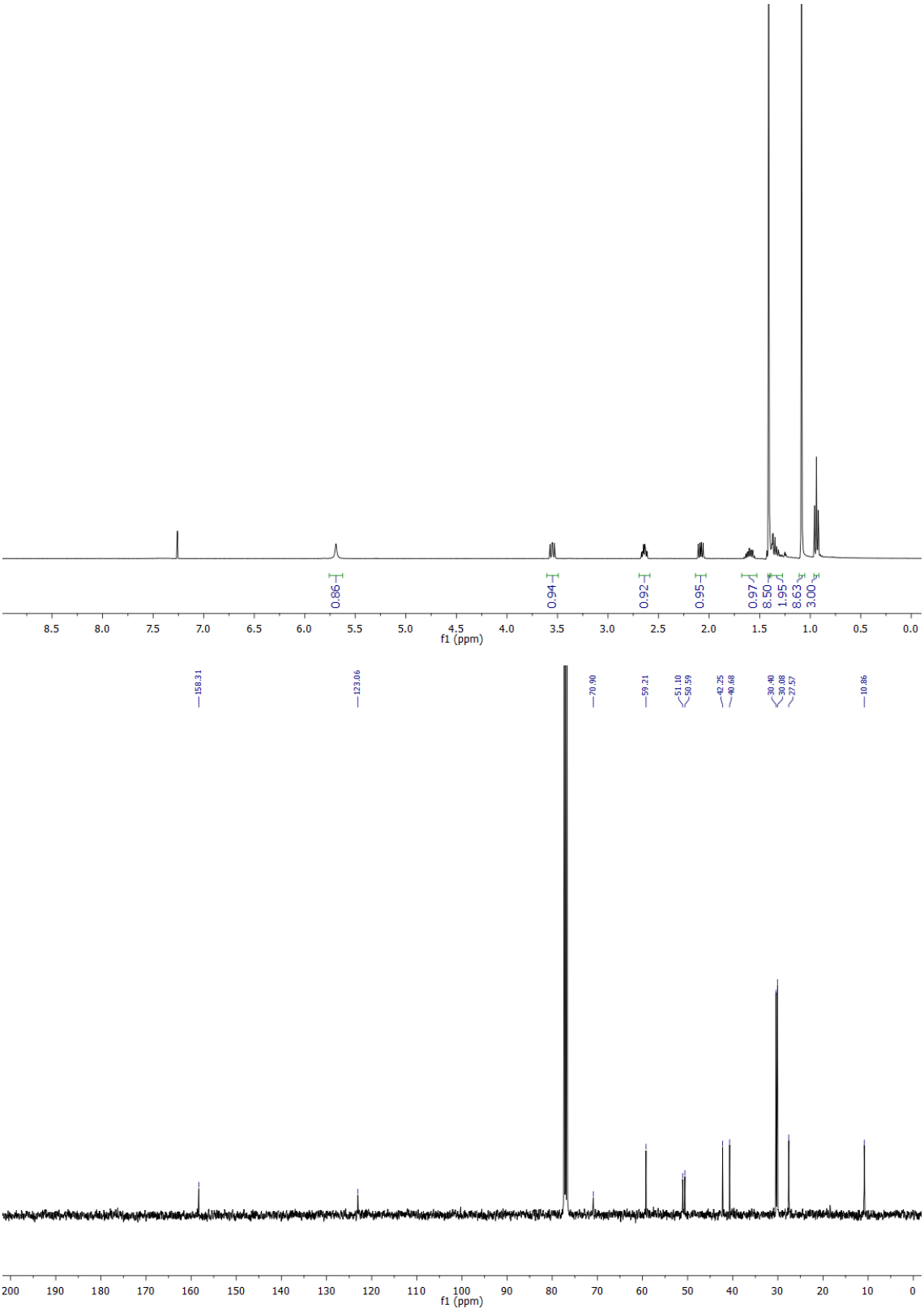


FIGURE 3.3- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6b.**

Chromatograms of Compound 6b

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (CH_3CN 95%) at 1.0 mL/min, UV-detection at λ = 265 nm:

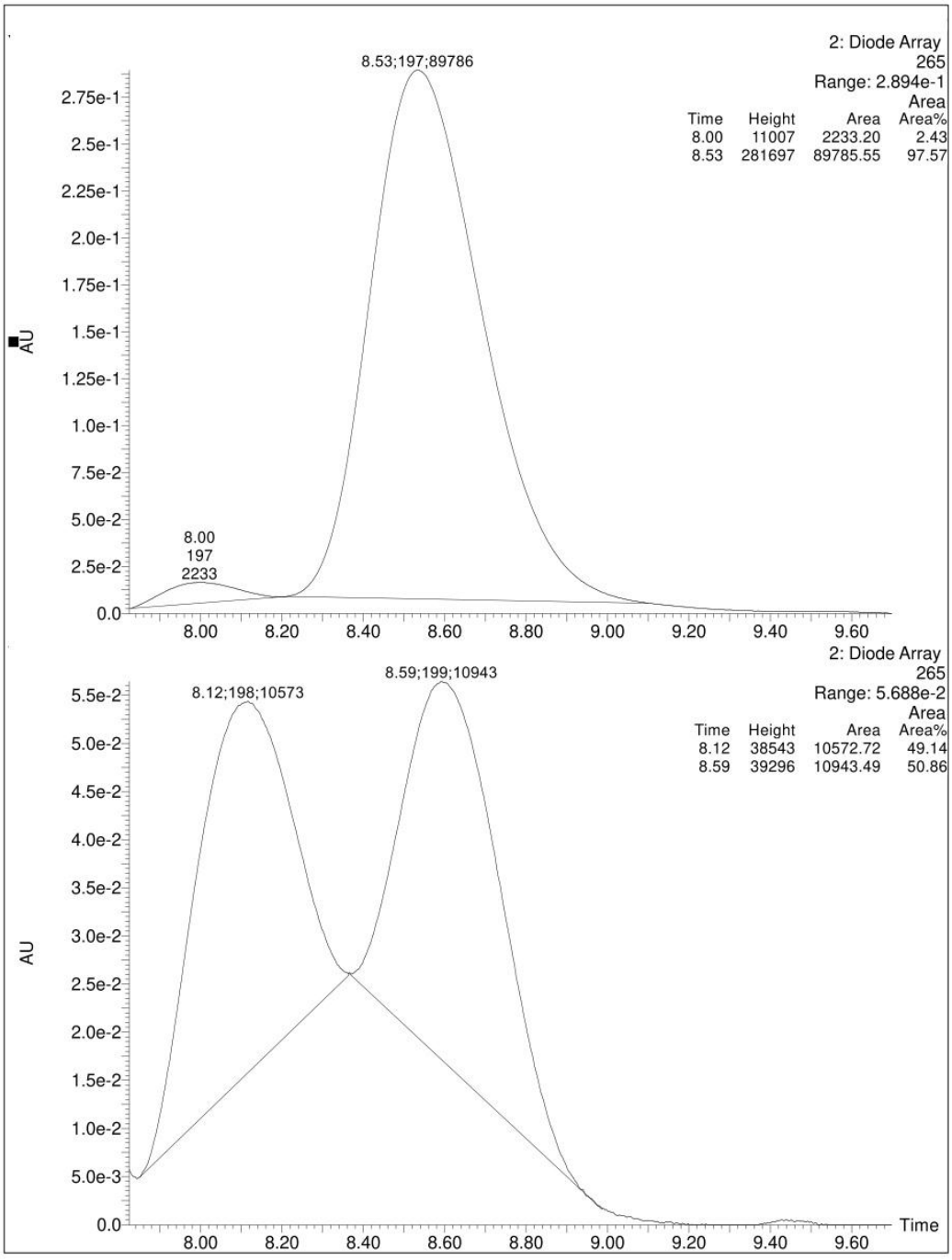
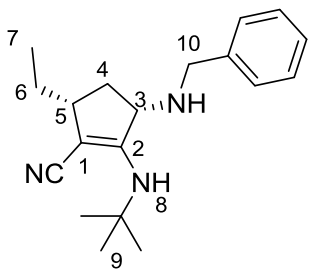


FIGURE 3.4- Chiral stationary-phase HPLC analysis of compound **6b**.



Compound 6c: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), benzylamine (16.4 µL, 0.15 mmol), and *tert*-butyl isocyanide (17.0 µL, 0.15 mmol), were reacted according to the general procedure. Flash column chromatography purification (*n*-hex/AcOEt 5:1) afforded compound **6c** (34.4 mg, 77%) as a white solid.

$[\alpha]_D^{20}$-19.0 (*c* 0.7, acetone, 20°C). R_f = 0.40 (DCM/MeOH 10:1). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ = 7.36-7.25 (m, 5H, Ph); 5.65 (s, 1H, H-8); 5.31(s, 2H, H-10); 3.75 (d, *J* = 7.4 Hz, 1H); 3.68 (dd, *J* = 9.9/7.6 Hz, 1H, H-3); 2.72 (td, *J*=8.0/ 4.9,1H, H-5); 2.06-1.93 (m, 1H, H-4a); 1.69-1.53 (m, 1H, H-4b);1.42 (s, 9H, H-9); 1.35-1.21 (m, 2H, H-6); 0.92 (t, *J* = 7.4 Hz, 2H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.8 (CH_3), 28.0 (CH_2), 30.2 (CH_3), 34.8 (CH_2), 44.8 (CH), 50.8 (C), 51.5 (CH_2), 63.9, 72.8, 123.1 (C), 126.6, 127.4, 128.2, 128.6 (CH), 146.2, 156.7(C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{19}H_{28}N_3$: 298.2283; found: 298.2280

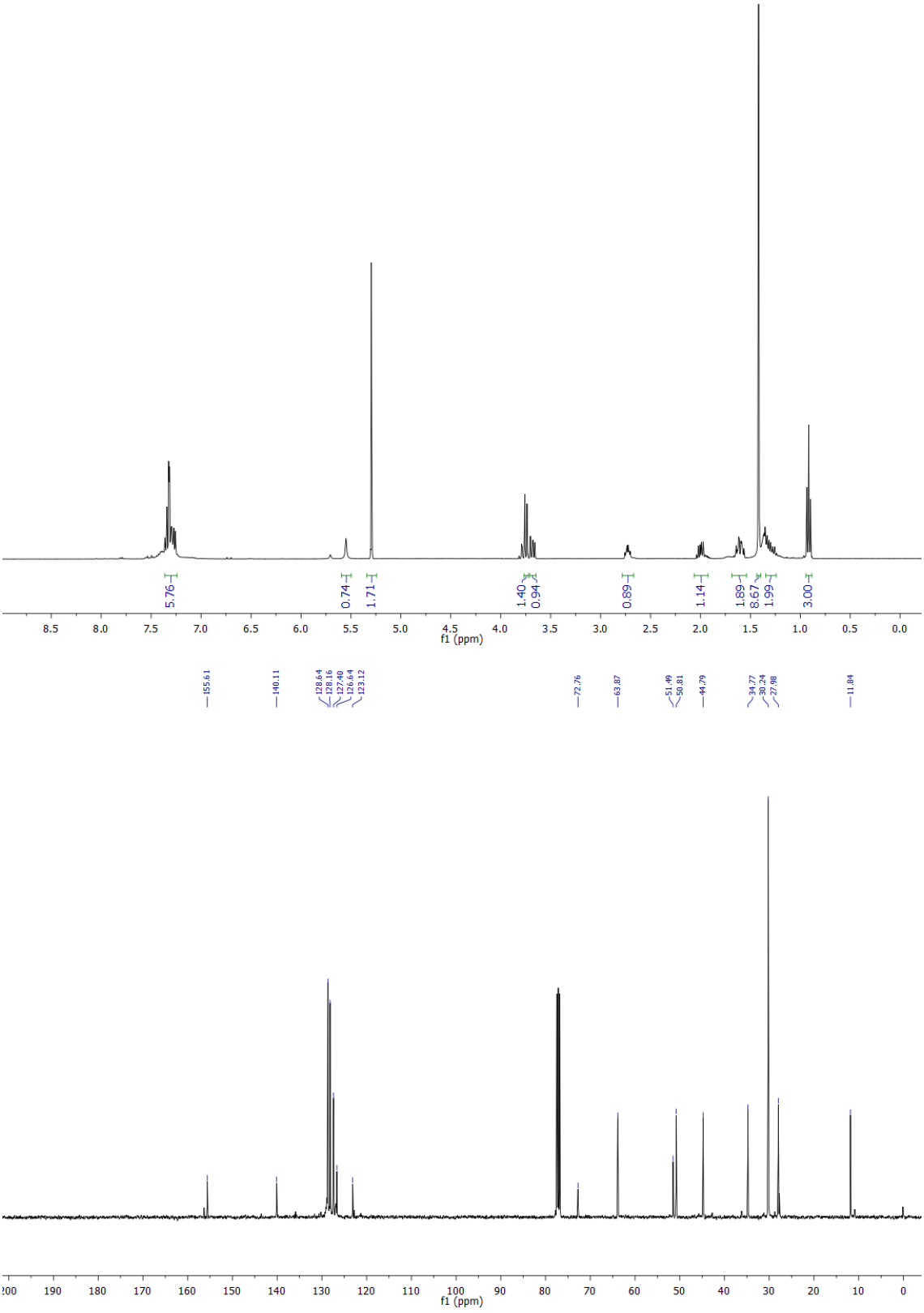


FIGURE 3.5- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6c.**

Chromatograms of Compound 6c

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (CH_3CN 95%) at 1.0 mL/min, UV-detection at λ = 265 nm:

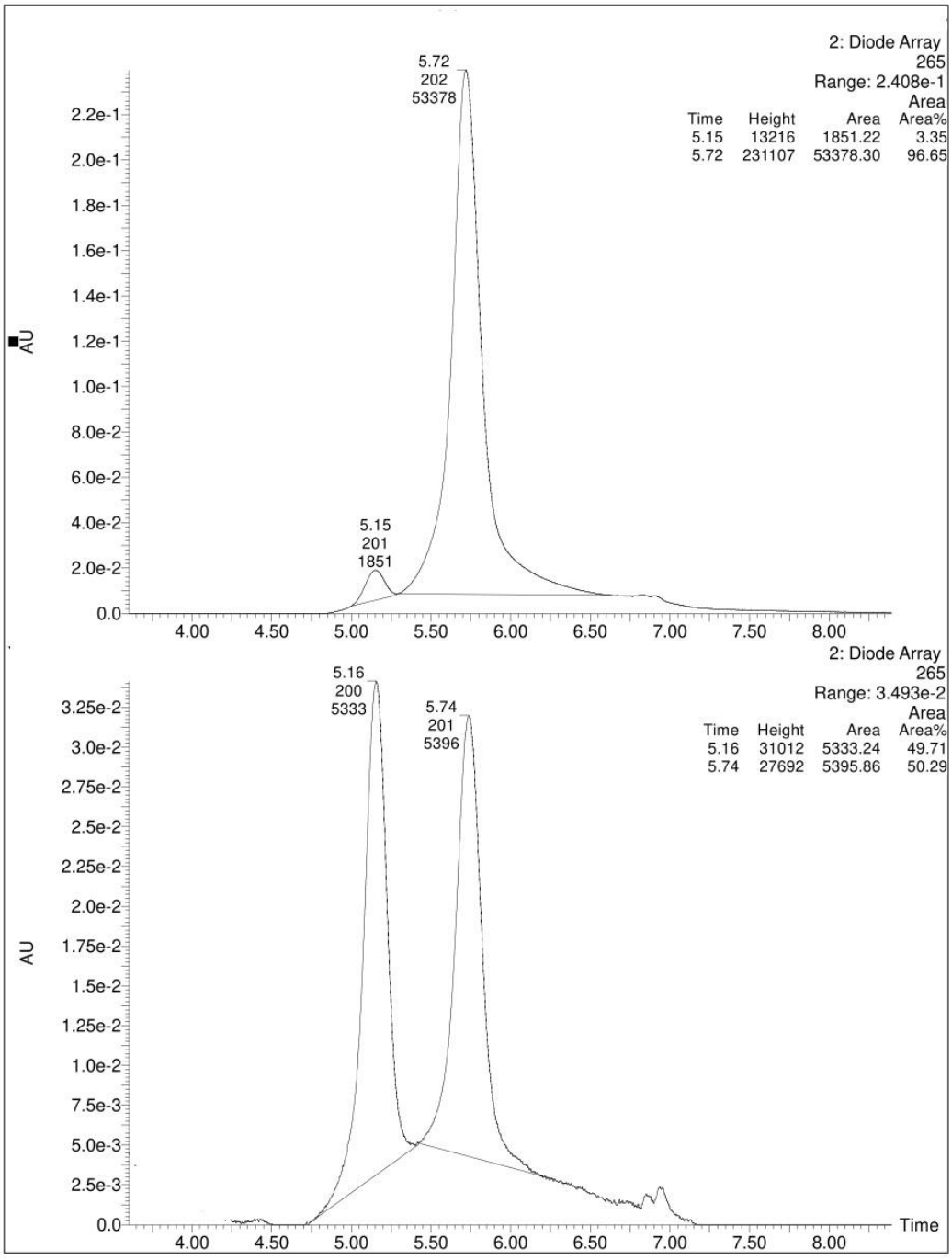
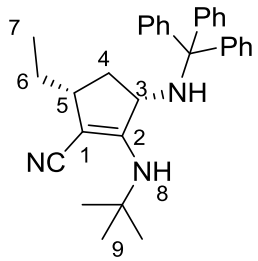


FIGURE 3.6- Chiral stationary-phase HPLC analysis of compound **6c.**



Compound 6d: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), triphenylmethylamine (38.9 mg, 0.15 mmol), and *tert*-butyl isocyanide (17.0 µL, 0.15 mmol), were reacted according to the general procedure. Flash column chromatography purification (*n*-Hex/AcOEt 8:1) afforded compound **6d** (52.8 mg, 81%) as a white solid. $[\alpha]_D^{20}$ -15.6 (*c* 0.7, acetone, 20°C). R_f = 0.38 (*n*-Hex/AcOEt 6:1). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ = 7.40-7.35 (m, 6H, Ph); 7.25-7.20 (m, 6H, Ph); 7.19-7.14 (m, 3H, Ph); 6.15 (s, 1H, H-8); 3.62(dd, *J*=10.5/7.1, 1H, H-3); 2.62 (td, *J*=8.2/ 4.8,1H, H-5); 1.67-1.55 (m, 2H, H-4); 1.46 (s, 9H, H-9); 1.34-1.21 (m, 2H, H-6); 0.57 (t, *J* = 7.4 Hz, 2H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 12.0 (CH_3), 26.8 (CH_2), 30.4 (CH_3), 36.9 (CH_2), 44.1 (CH), 51.6, 60.2, 70.6, 123.3 (C), 126.8, 128.1, 128.7 (CH), 146.2, 156.7(C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{31}H_{36}N_3$: 450.2909; found:

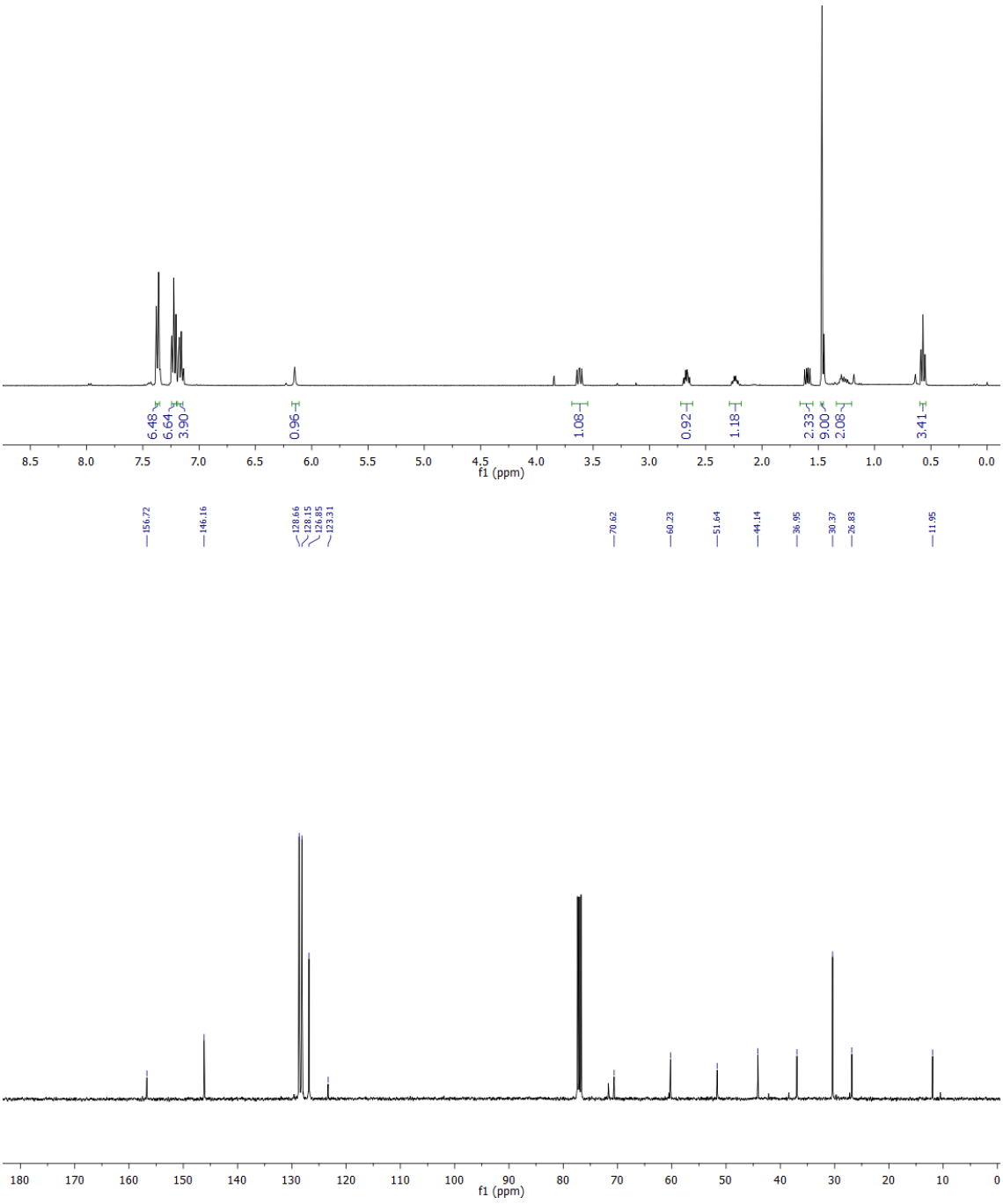


FIGURE 3.7- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6d.**

Chromatograms of Compound 6d

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (*i*-PrOH 65%) at 1 mL/min, UV-detection at λ = 265 nm:

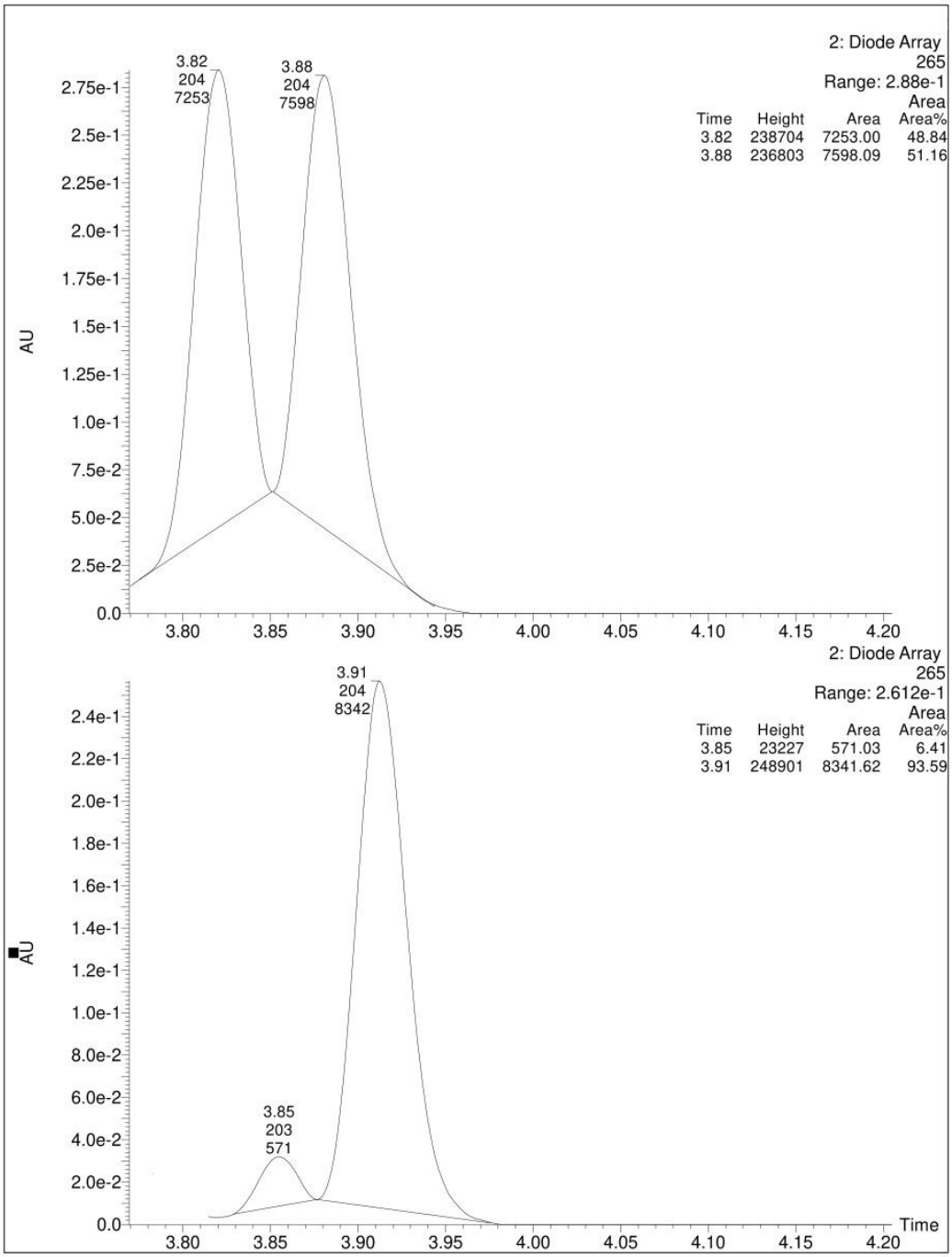
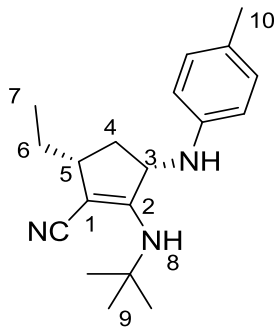


FIGURE 3.8- Chiral stationary-phase HPLC analysis of compound **6d.**



Compound 6e: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 μL, 0.18 mmol), 4-methylaniline (16.1 μL, 0.15 mmol) and tert-butyl isocyanide (17.0 μL, 0.15 mmol) were reacted according to the general procedure . Flash column chromatography purification (n-hexane/EtOAc 8:1) afforded compound **6e** (37.4 mg, 84%) as a yellow oil. $[\alpha]_D^{20}$ -16.0 (c 0.6, acetone, 20ºC). Rf = 0.38 (n-hexane/ EtOAc 3:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =7.02 (d, *J* = 8.0 Hz, 2H, Ph); 6.58 (d, *J* = 7.8 Hz, 2H, Ph); 5.08 (s, 1H, H-8); 4.42 (t, *J* = 8.0 Hz, 1H, H-3); 3,48 (brs, 1H); 2.87-2.71 (m, 1H, H-4a); 2.29 (s, 3H, H-10); 1.97-1.90 (m, 1H, H-4b); 1.85-1.75 (m, 1H); 1.74-1.61 (m, 1H); 1.42 (s, 9H, H-9); 0.95 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.6 (CH_3), 20.5, 28.0 (CH_2), 30.3 (CH_3), 33.8, (CH_2), 42.7 (C); 44.5, 52.0 (CH), 61.7 (CH_3), 74.6 (C), 114.8 (CH), 122.4, 128.6 (C), 130.0 (CH), 144.0, 155.5 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{19}H_{28}N_3$: 298.2283; found: 298.2286

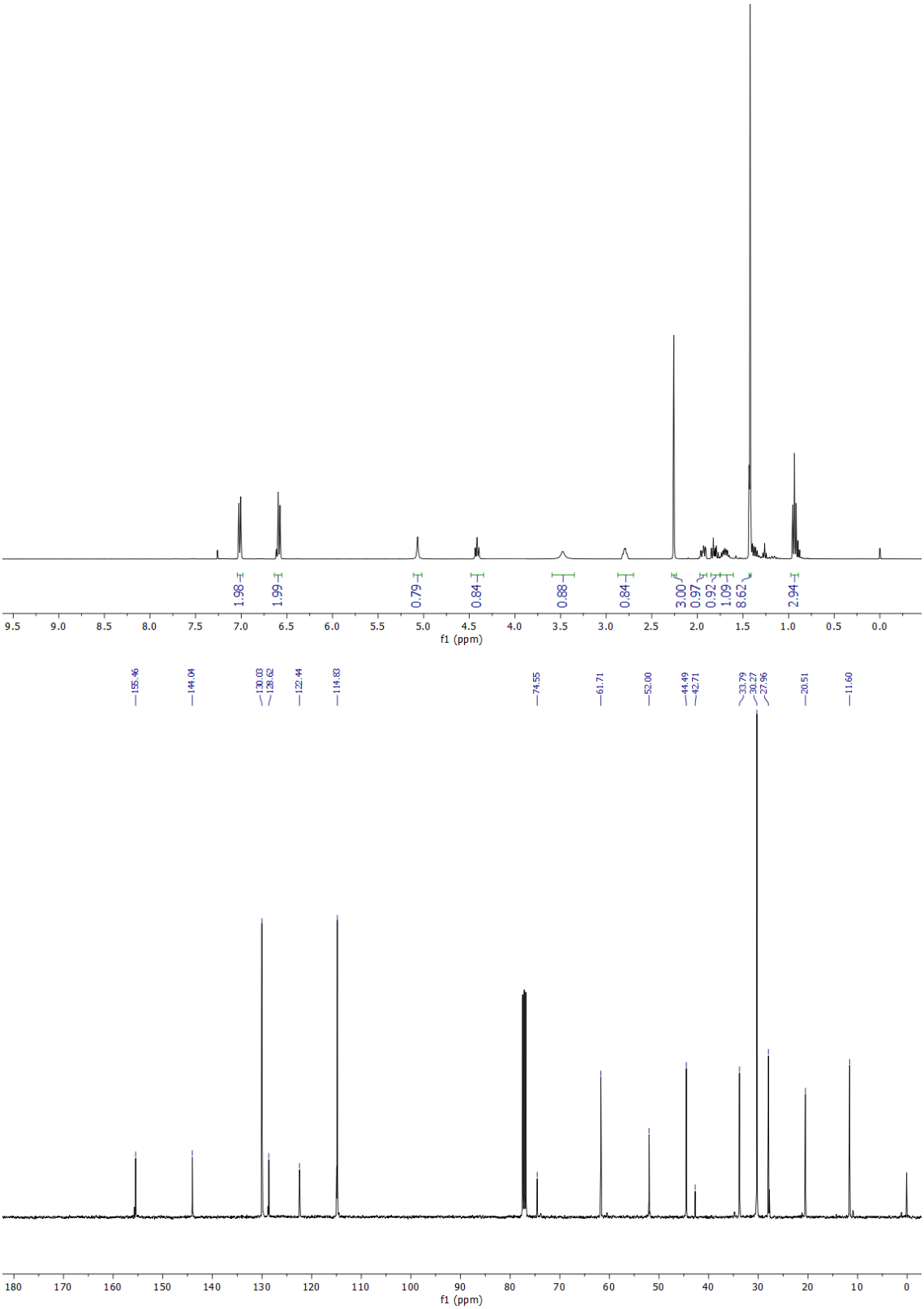


FIGURE 3.9- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6e.**

Chromatograms of Compound 6e

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OD column (CH_3CN 80%) at 1.0 mL/min, UV-detection at $\lambda = 265$ nm:

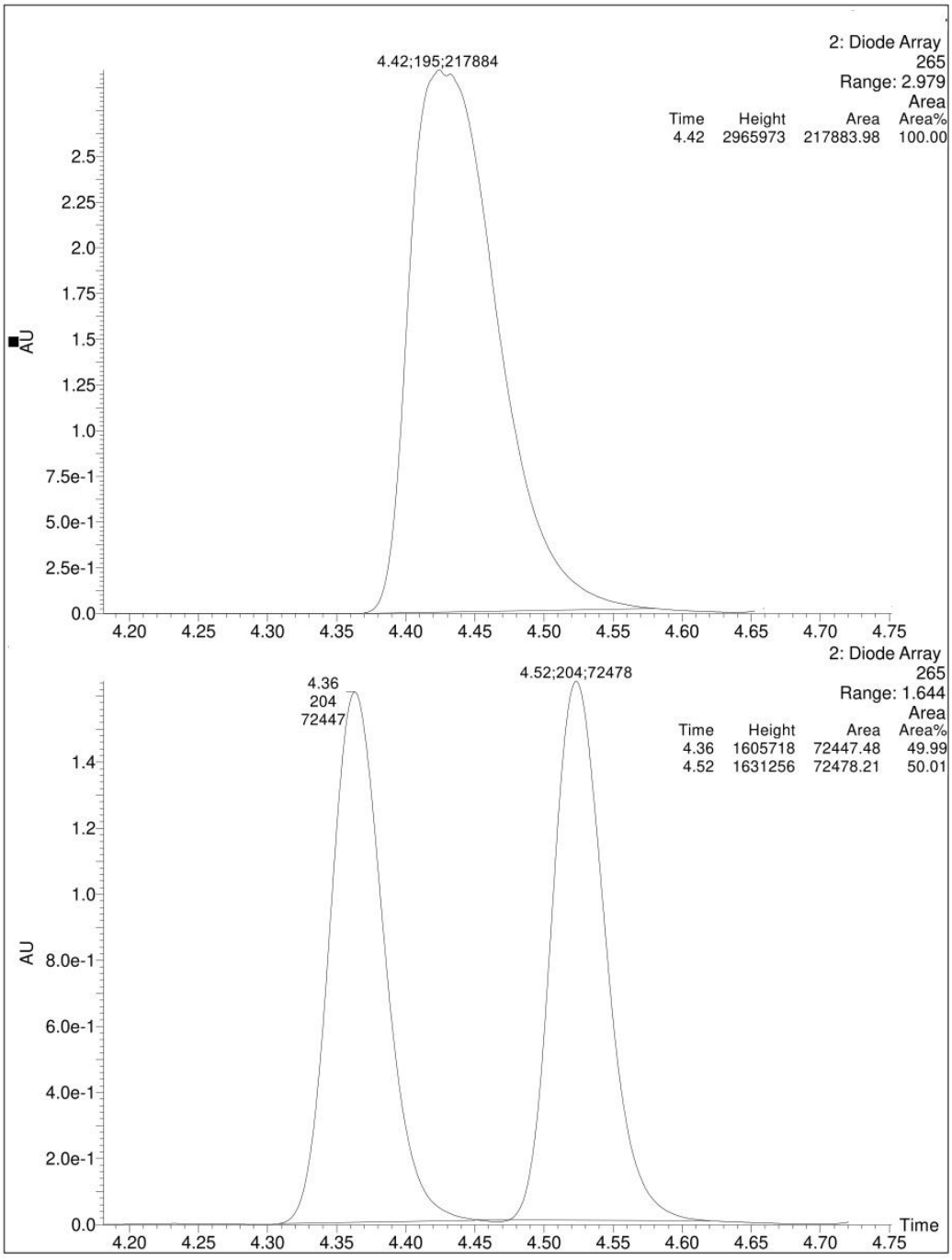
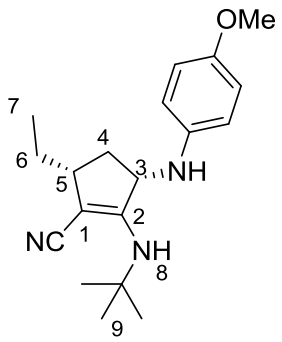


FIGURE 3.10- Chiral stationary-phase HPLC analysis of compound **6e.**



Compound 6f: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), 4-methoxyaniline (18.4 mg, 0.15 mmol) and tert-butyl isocyanide (17.0 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 6:1) afforded compound **6f** (32.8 mg, 70%) as a yellow oil.

$[\alpha]_D^{20}$ -14.0 (c 0.8, acetone, 20ºC). Rf = 0.38 (n-hexane/ EtOAc 3:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =6.81-6.76 (m, 2H, Ph); 6.67-6.58 (m, 2H, Ph); 5.16 (s, 1H, H-8); 4.39 (t, *J* = 8.1 Hz, 1H, H-3); 3,75 (s, 3H, OMe); 2.83-2.74 (m, 2H, H-4); 1.97-1.89 (m, 1H); 1.40 (s, 9H, H-9); 0.93 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.6 (CH_3), 28.0 (CH_2), 30.3 (CH_3), 33.7(CH_2), 44.5, 51.9, 55.8 (CH), 62.4 (CH_3), 74.3 (C), 115.0, 116.3(CH), 122.5 (C), 140.2, 153.4, 155.4 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{19}H_{28}N_3O$: 314.2232; found: 314.2235

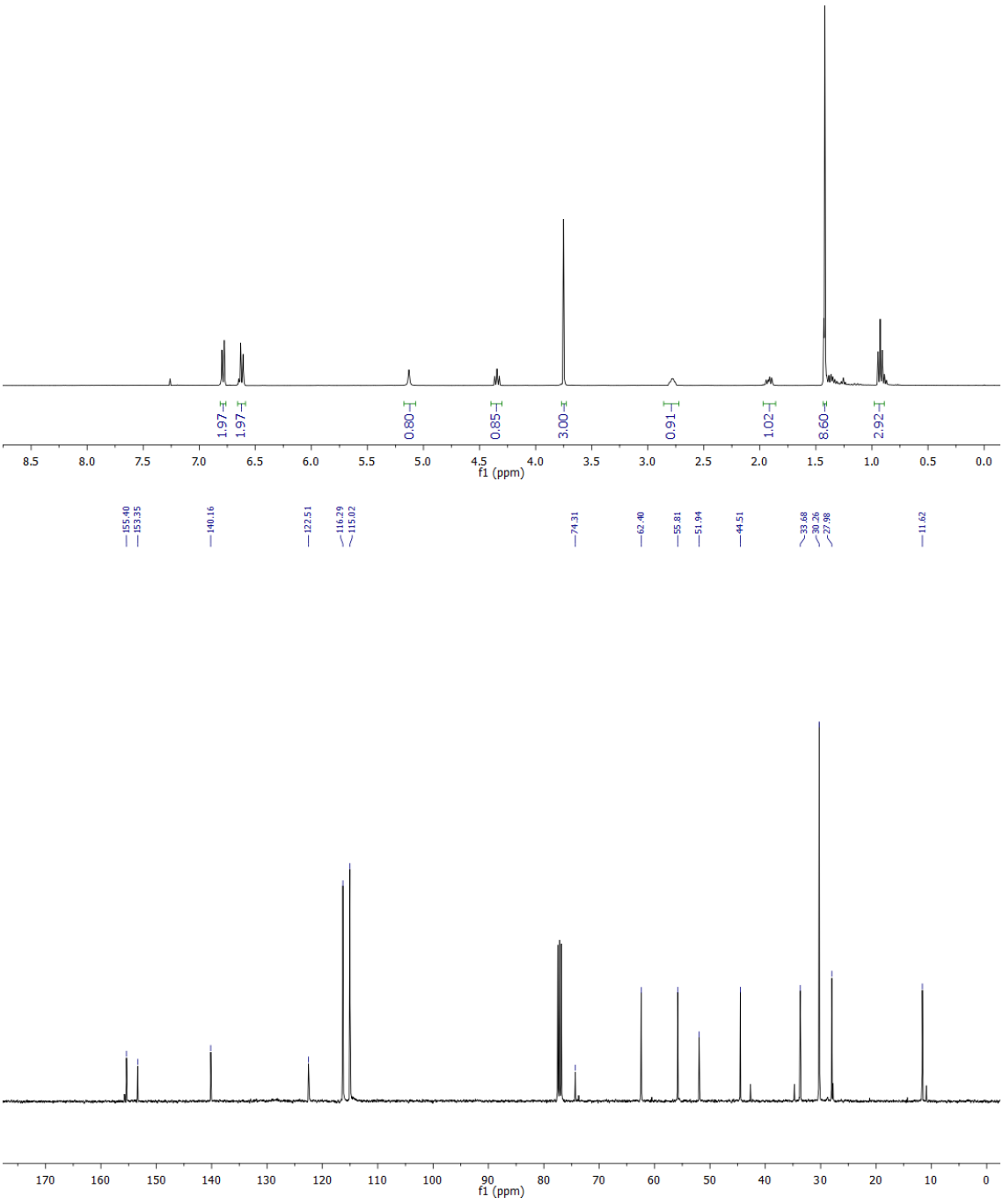


FIGURE 3.11- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6f.**

Chromatograms of Compound 6f

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OD column (CH_3CN 80%) at 1.0 mL/min, UV-detection at $\lambda = 265$ nm:

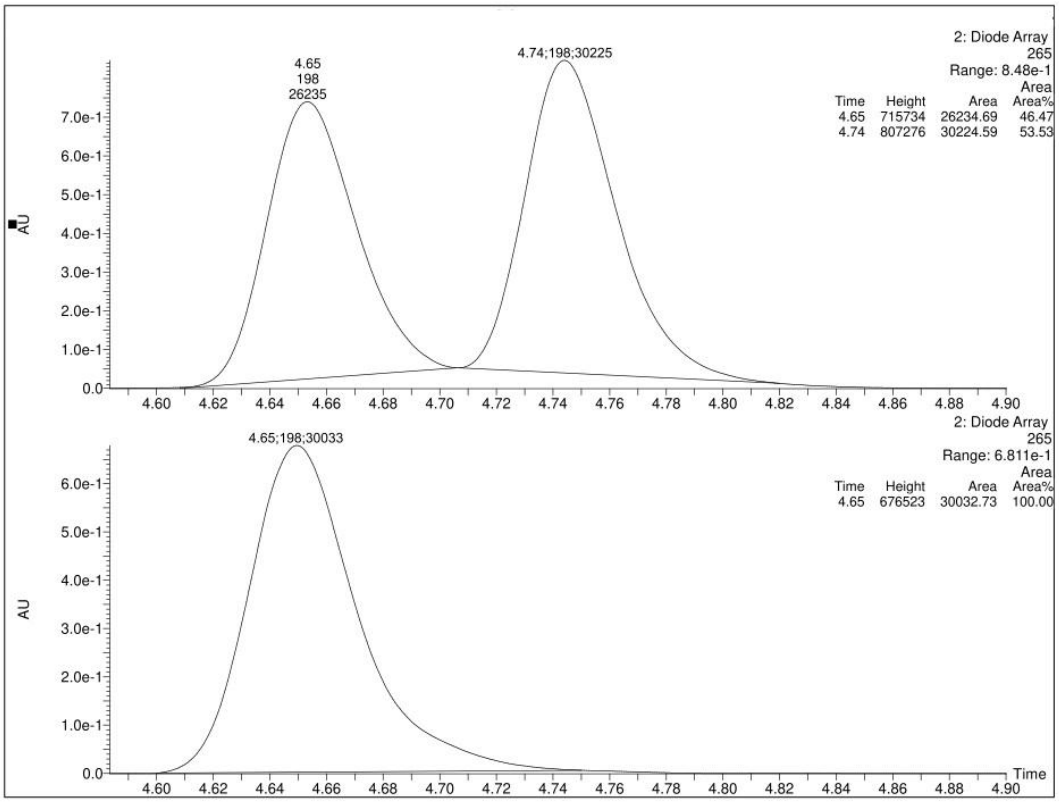
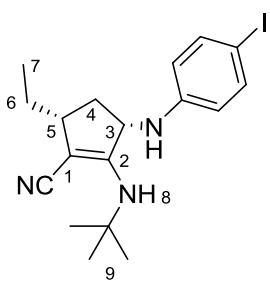


FIGURE 3.12- Chiral stationary-phase HPLC analysis of compound **6f.**



Compound 6g: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), 4-iodoaniline (32.9 mg, 0.15 mmol) and *tert*-butyl isocyanide (17.0 µL, 0.15 mmol), were reacted according to the general procedure. Flash column chromatography purification (*n*-hexane/EtOAc 8:1) afforded compound **6g** (49.2 mg, 80%) as a yellow oil. $[\alpha]_D^{20}$ -8.8 (*c* 0.5, acetone, 20°C). R_f = 0.46 (*n*-hexane/ EtOAc 3:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =7.45 (d, *J* = 8.6 Hz, 2H, Ph); 6.44 (d, *J* = 8.7 Hz, 2H, Ph); 4.89 (s, 1H, H-8); 4.41 (t, *J* = 7.9 Hz, 1H, H-3); 3.80-3.62 (m, 1H); 2.90-2.69 (m, 1H); 1.96-1.80 (m, 2H); 1.76-1.65 (m, 1H); 1.39 (s, 9H, H-9); 0.93 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.5 (CH_3), 27.9(CH_2), 30.2 (CH_3), 33.5 (CH_2), 44.4 (CH); 52.2 (C); 61.1 (CH), 75.6, 80.1 (C), 116.6 (CH), 122.0 (C), 138.2 (CH); 146.0, 154.9 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{18}H_{25}IN_3$: 410.1093; found: 410.1012

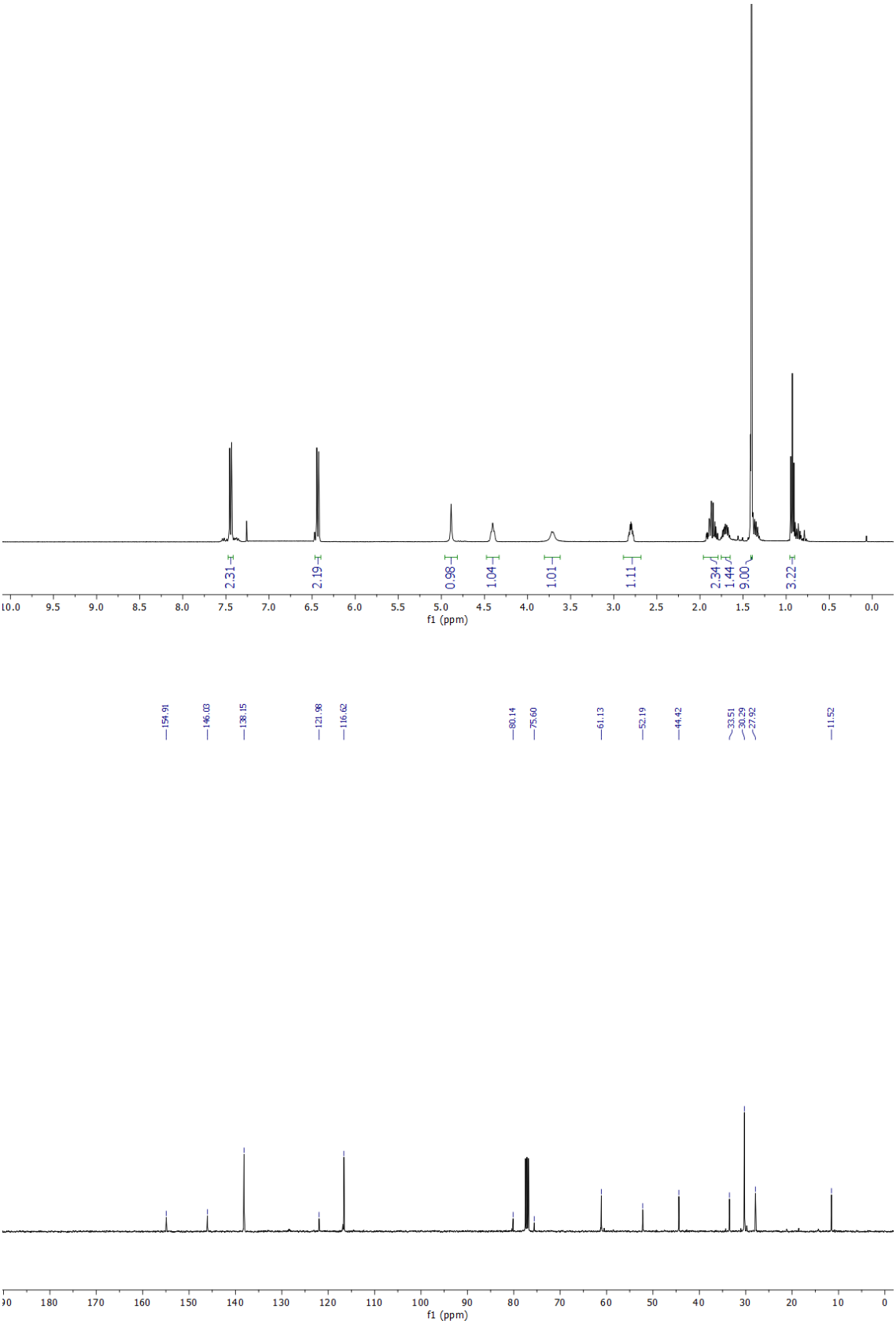


FIGURE 3.13- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6g.**

Chromatograms of Compound 6g

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OD column (*i*-PrOH 80%) at 1.0 mL/min, UV-detection at λ = 265 nm:

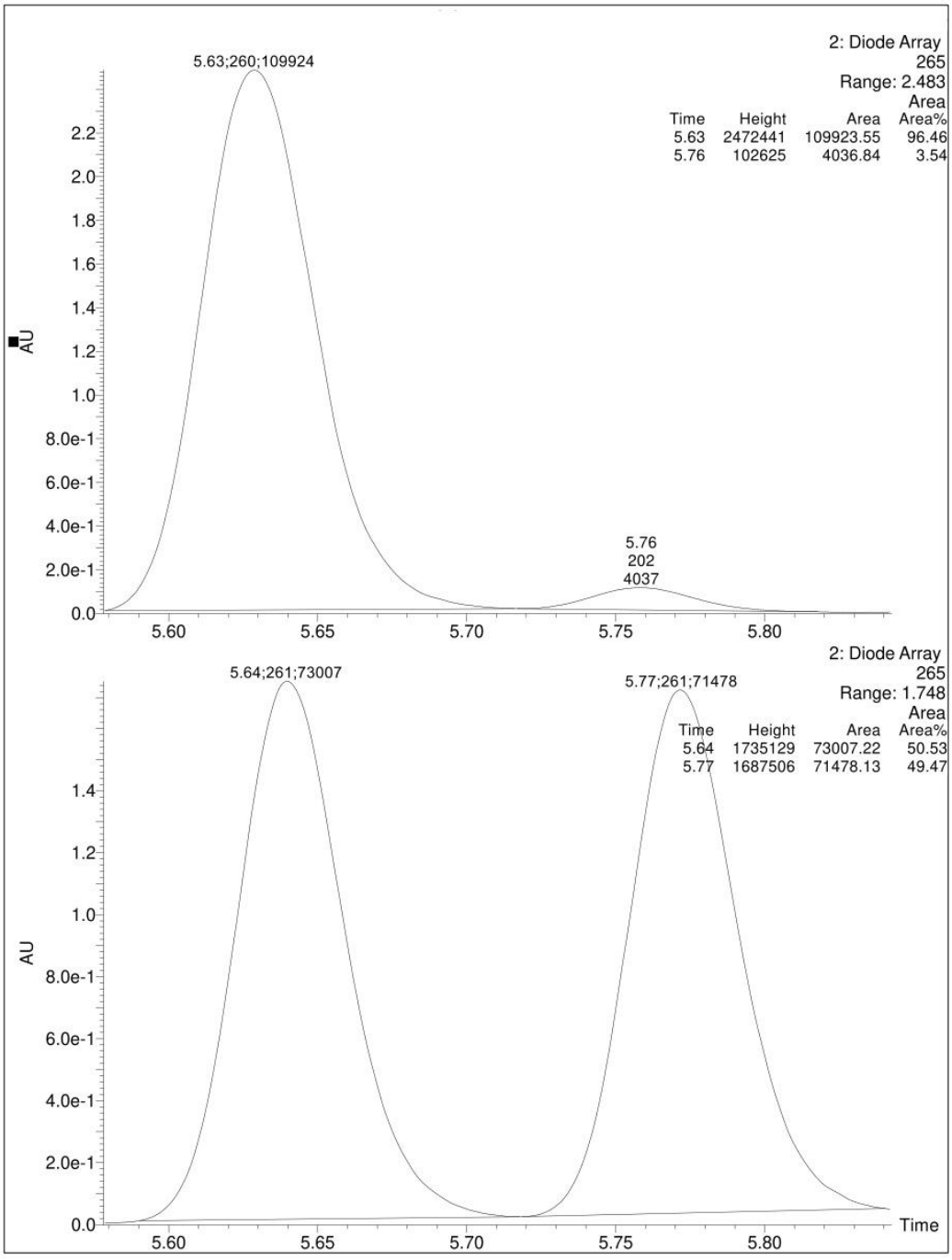
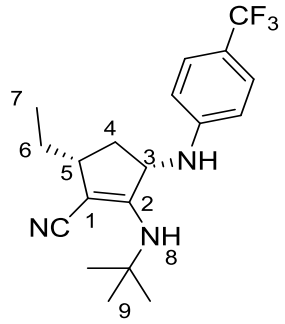


FIGURE 3.14- Chiral stationary-phase HPLC analysis of compound **6g.**



Compound 6h: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), 4-(trifluoromethyl) aniline (18.8 µL, 0.15 mmol) and tert-butyl isocyanide (17.0 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 5:1) afforded compound **6h** (32.7 mg, 62%) as a brown oil.

$[\alpha]_D^{20}$-15.5 (c 0.6, acetone, 20ºC). Rf = 0.35 (n-hexane/ EtOAc 3:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =7.37 (d, *J* = 8.4 Hz, 2H, Ph); 6.57 (d, *J* = 8.8 Hz, 2H, Ph); 4.72 (s, 1H, H-8); 4.39 (t, *J* = 8.0 Hz, 1H, H-3); 2.77-2.67 (m, 1H, H-5); 1,84-1,74 (m, 2H, H-4); 1.69-1.57 (m, 1H); 1.32 (s, 9H, H-9); 0.94 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.5 (CH_3), 27.9 (CH_2), 30.3 (CH_3), 33.7(CH_2), 42.8, 44.4, 52.3 (CH), 60.8, (C), 113.5 (CH) 113.8 (C), 114.3, 121.8, 126.9, (CH), 149.1, 154.8 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{19}H_{25}F_3N_3$: 352.2001; found: 352.2006

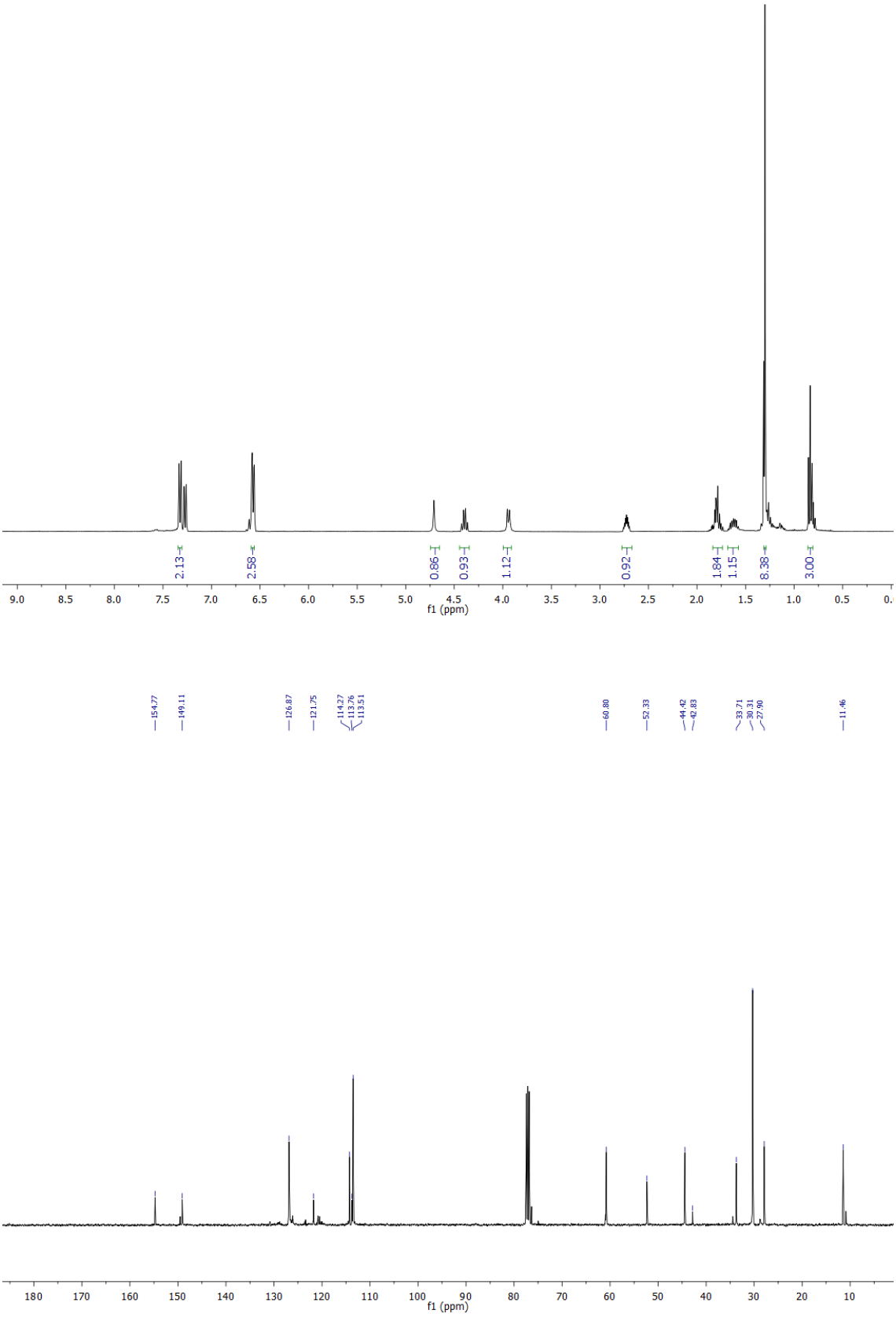


FIGURE 3.15- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6h.**

Chromatograms of Compound 6h

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (MeOH 73%) at 1.0 mL/min, UV-detection at λ = 265 nm:

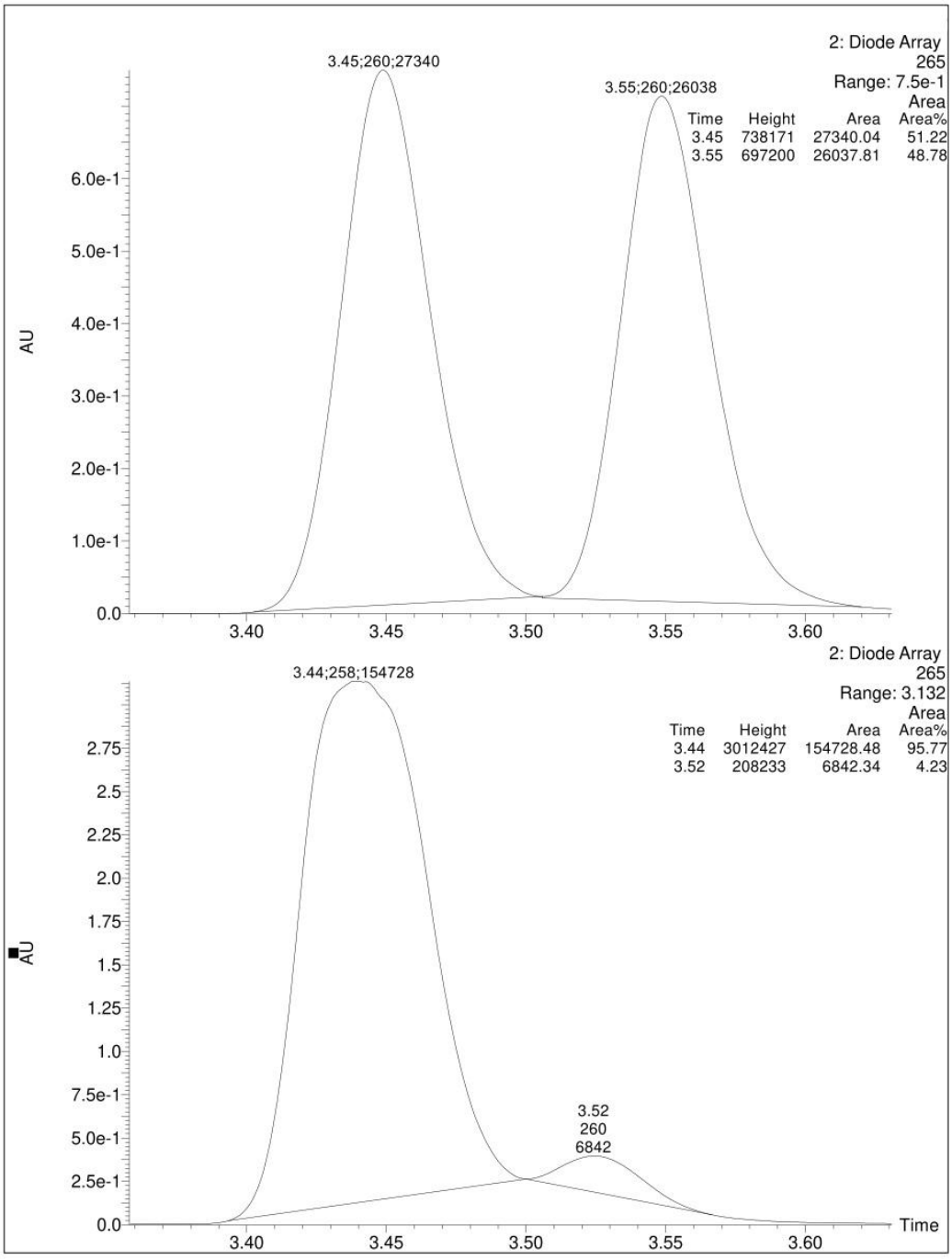
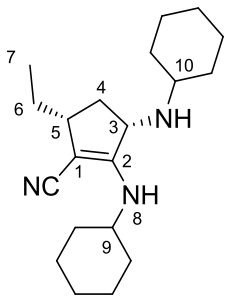


FIGURE 3.16- Chiral stationary-phase HPLC analysis of compound **6h.**



Compound 6i: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), cyclohexylamine (17.2 µL, 0.15 mmol) and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 5:1) afforded compound **6i** (43.1 mg, 91%) as a pale yellow oil.

$[\alpha]_D^{20}$ -12.4 (c 0.5, acetone, 20ºC). Rf = 0.36 (n-hexane/ EtOAc 6:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 5.12 (d, *J* = 8.7 Hz, 1H, H-8); 3.81-3.70 (m, 1H, H-9); 3.65 (dd, *J* = 9.4/ 7.2 Hz, 1H, H-3); 2.68-2.59 (m, 1H, H-5); 2.52-2.41 (m, 1H, H-10); 1.94-1.66 (m, 7H); 1.64-1.34 (m, 8H); 1.33-1.06 (m, 11H); 0.92 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$):** δ = 11.9 (CH_3), 24.2, 24.4, 24.8, 25.0, 25.6, 26.0, 28.0, 33.4, 33.6, 35.2, 37.5 (CH_2), 43.5, 51.4, 54.9, 60.2, 71.4 (CH), 121.5, 159.3 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{20}H_{34}N_3$: 316.2757; found: 316.2755

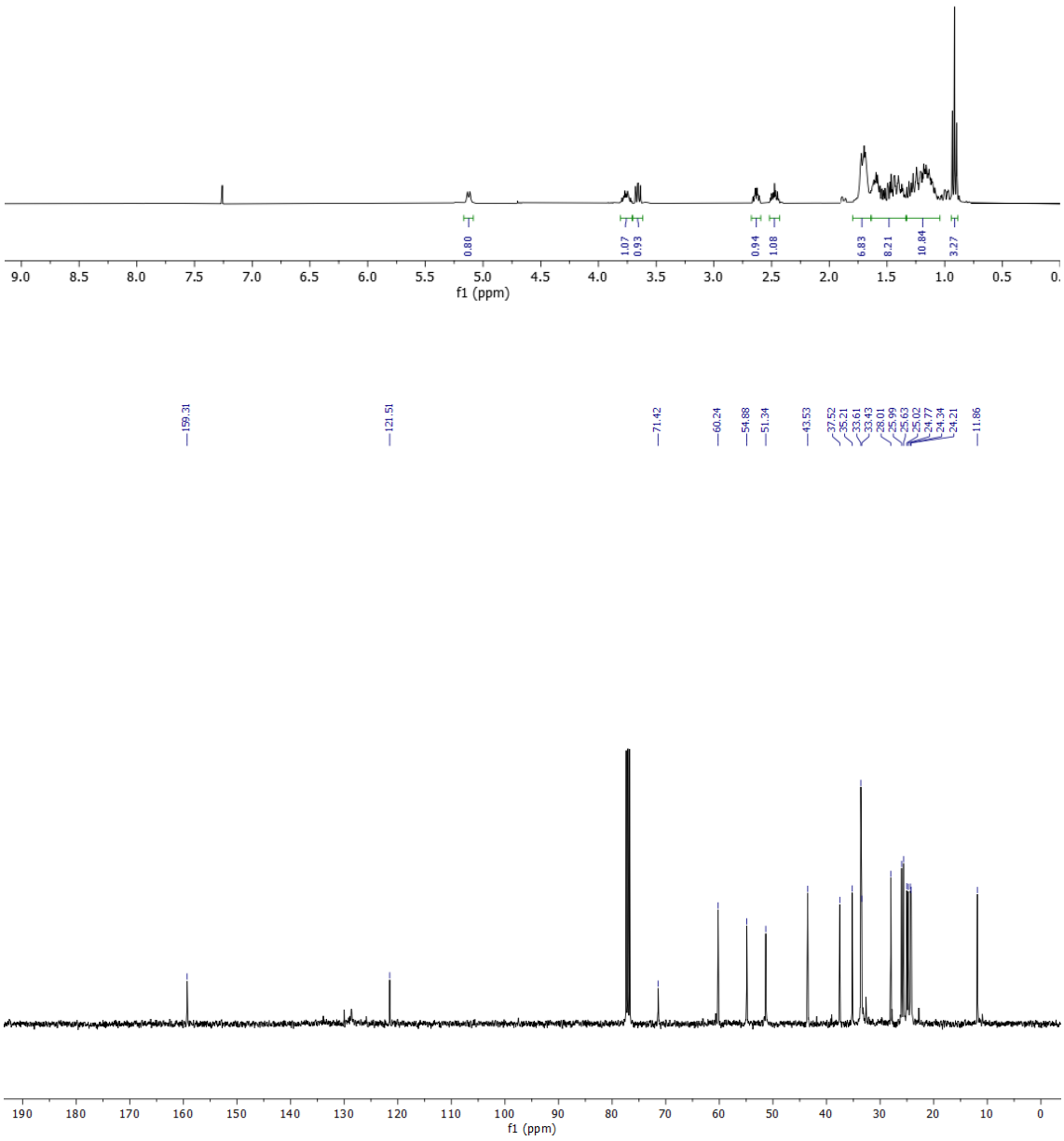


FIGURE 3.17- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6i.**

Chromatograms of Compound 6i

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (CH_3CN 80%) at 1.0 mL/min, UV-detection at $\lambda = 265$ nm:

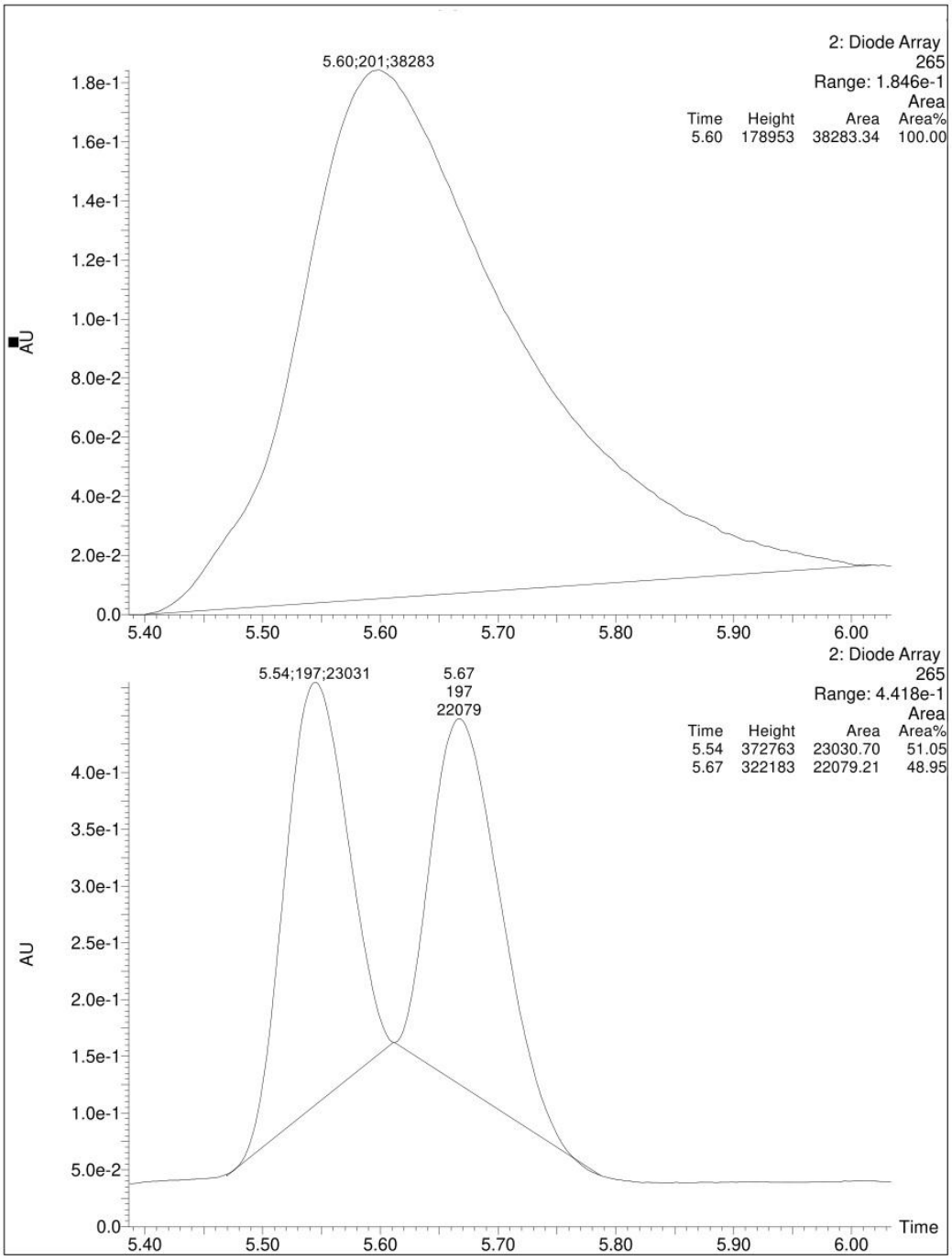
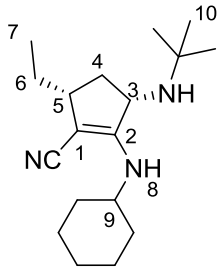


FIGURE 3.18- Chiral stationary-phase HPLC analysis of compound **6i.**



Compound 6j: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), *tert*-butylamine (15.8 µL, 0.15 mmol), and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure . Flash column chromatography purification (*n*-hexane/EtOAc 5:1) afforded compound **6j** (37.4 mg, 86%) as a pale yellow oil.

$[\alpha]_D^{20}$ -10.3 (*c* 0.4, acetone, 20°C). R_f = 0.40 (*n*-hexane/ EtOAc 3:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 5.18 (d, *J* = 8.1Hz, 1H, H-8); 3.83-3.71 (m,1H, H-9); 3.61 (dd, *J* = 9.9/ 7.3 Hz, 1H, H-3); 2.60 (td, *J* = 8.2/ 5.1 Hz, 1H, H-5); 2.08 (ddd, *J* = 12.4/ 7.2/1.0 Hz, 1H, H-4a); 2.05-1.96 (m, 2H); 1.73-1.64 (m, 2H); 1.63-1.51 (m, 2H); 1.49-1.41 (m, 4H); 1.39-1.28 (m, 1H, H-4a); 1.26-1.11 (m, 4H); 1.07 (s, 9H, H-10); 0.93 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 12.1 (CH_3), 24.2, 24.3, 25.8, 28.1 (CH_2), 30.6 (CH_3), 33.4, 33.7, 40.6 (CH_2), 43.5, 50.7, 51.2, 57.5 (CH), 70.7, 121.8, 160.1 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{18}H_{32}N_3$: 290.2596; found: 290.2598

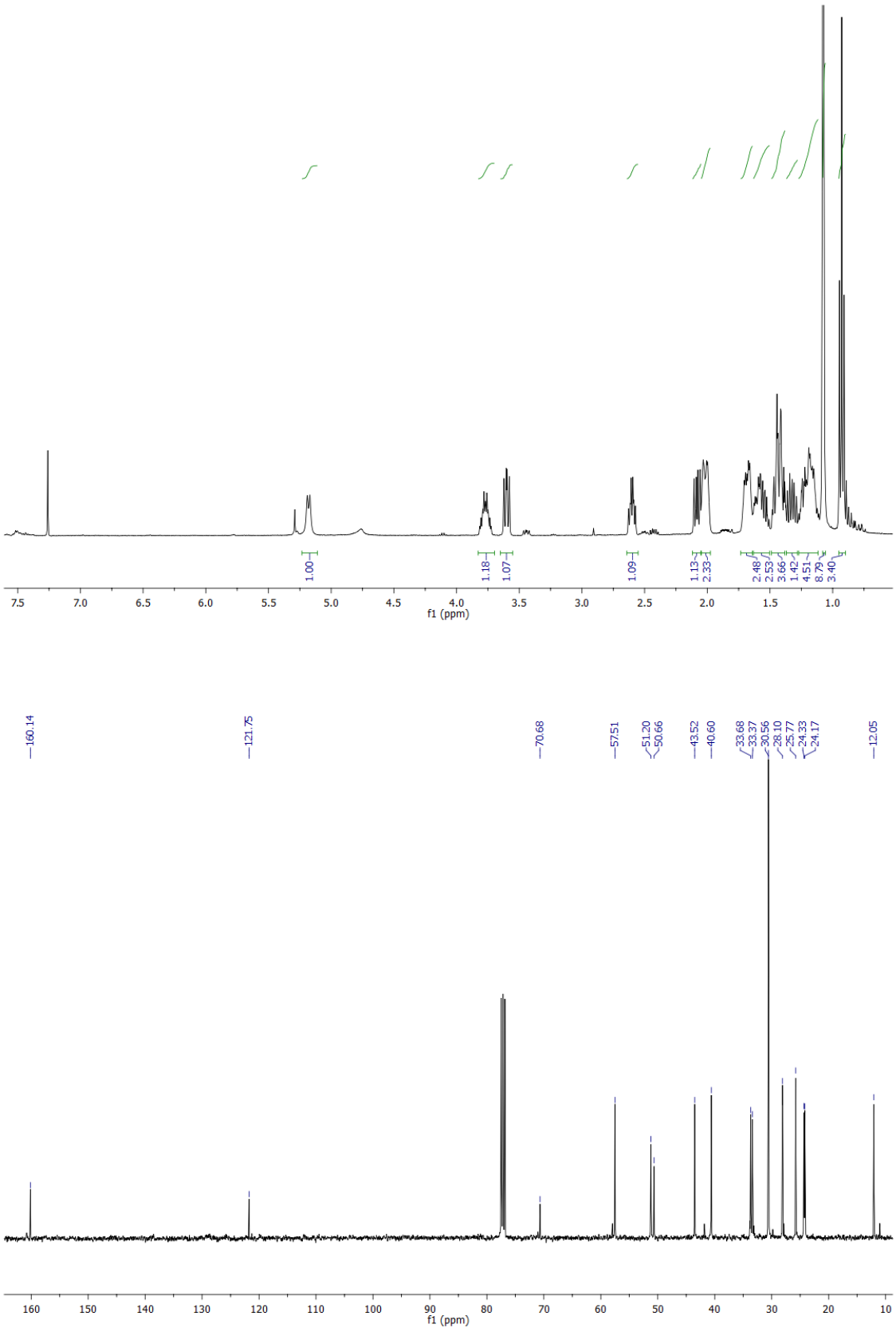


FIGURE 3.19- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6j.**

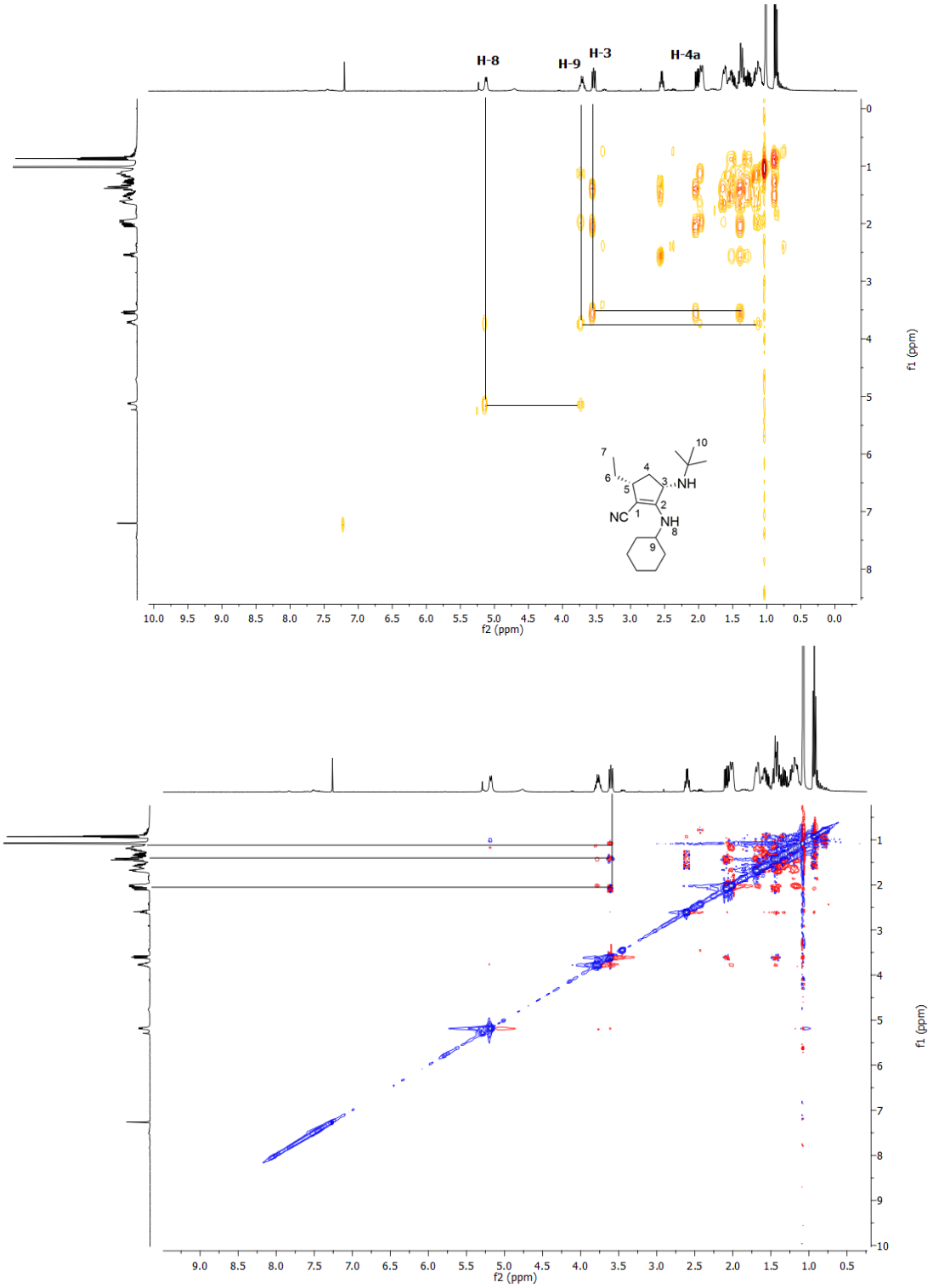


FIGURE 3.20- COSY and NOESY NMR spectra in $CDCl_3$ of compound **6j.**

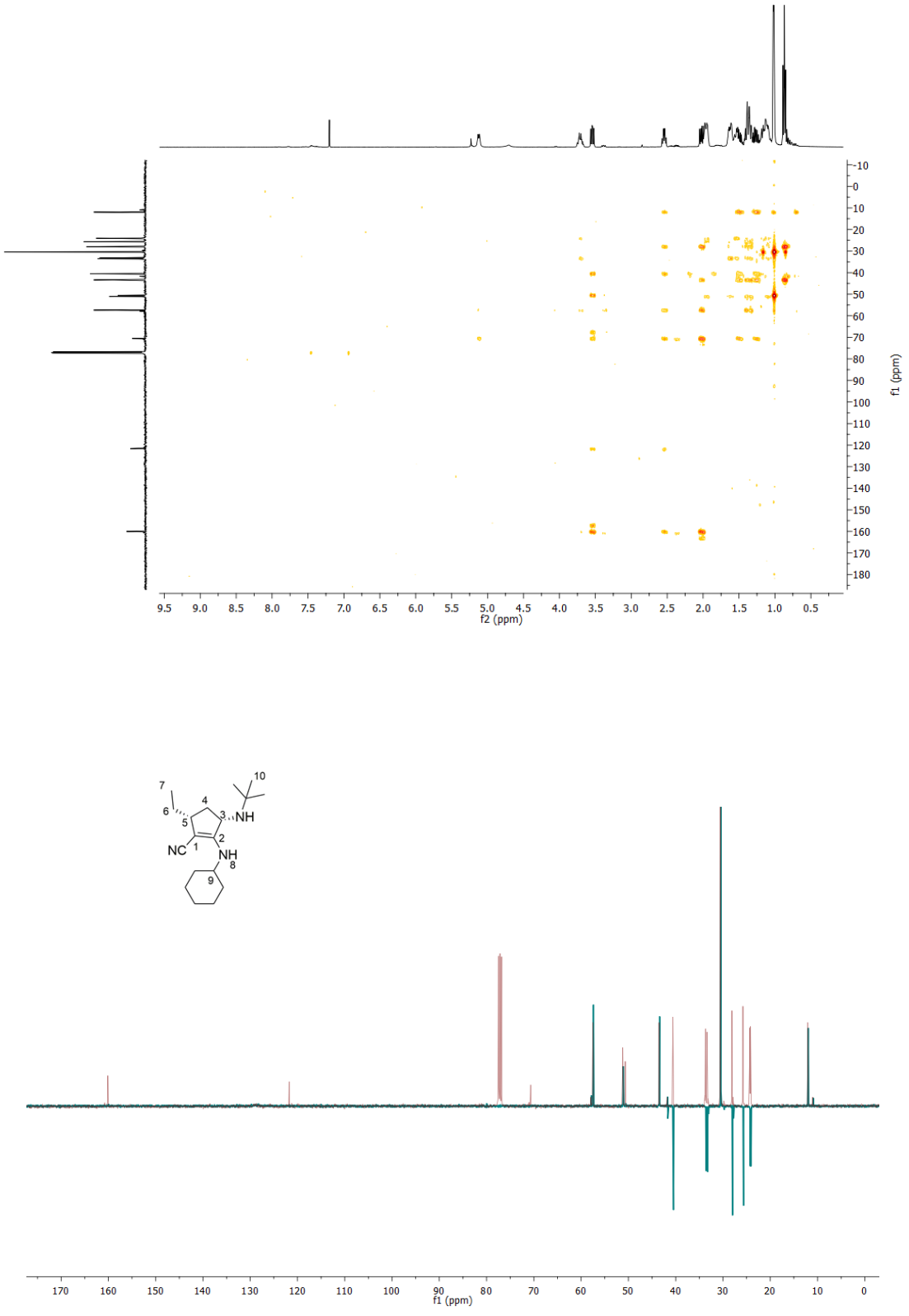


FIGURE 3.21- HMBC and superimposed ^{13}C- DEPT 135 NMR spectra in $CDCl_3$ of compound **6j.**

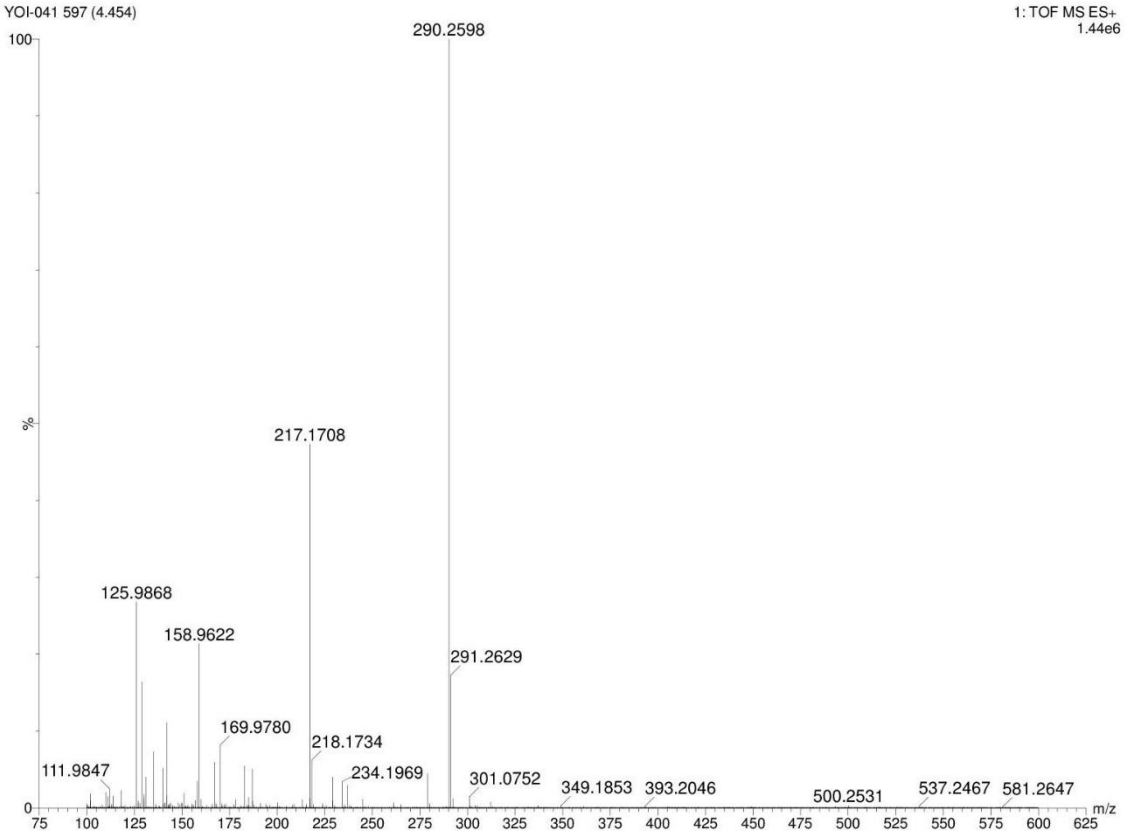


FIGURE 3.22- HRMS spectra of compound **6j.**

Chromatograms of Compound 6j

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (CH_3CN 95%) at 1.0 mL/min, UV-detection at λ = 265 nm:

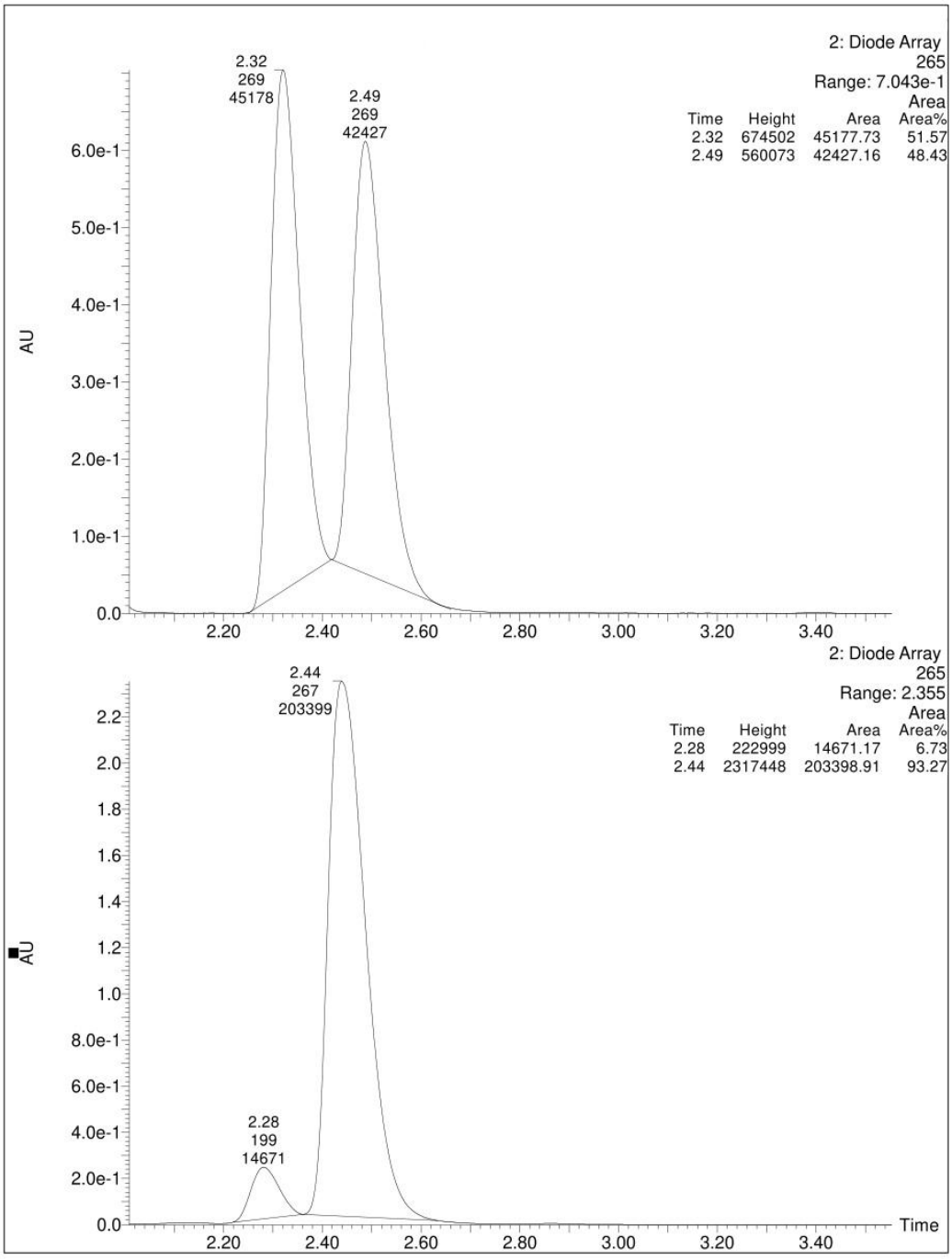
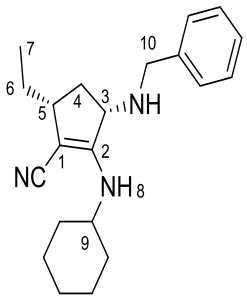


FIGURE 3.23- Chiral stationary-phase HPLC analysis of compound **6j.**



Compound 6k: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), benzylamine (16.4 µL, 0.15 mmol), and ethyl cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (*n*-hexane/EtOAc 4:1) afforded compound **6k** (39.8 mg, 82%) as an orange oil.

$[\alpha]_D^{20}$ -9.2 (*c* 0.5, acetone, 20°C). R_f = 0.32 (*n*-hexane/ EtOAc 4:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.78- 7.46 (m, 5H, Ph); 5.78 (d, *J* = 8.6 Hz, 1H, H-8); 5.35 (s, 2H, H-10); 3.58 (m, 2H, H-3, H-9); 3.51-3.32 (m, 1H, H-5); 2.62 (td, *J* = 8.8/5.4 Hz, 1H, H-4a); 1.81 (d, *J* = 7.9/5.2 Hz, 1H, H-4b); 1.77-1.59 (m, 6H); 1.56-1.34 (m, 4H); 1.27-1.18 (m, 2H); 0.82 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.8 (CH_3), 24.3, 24.4, 25.7, 28.2, 33.7, 35.7, 37.0 (CH_2), 43.9, 50.9 (CH), 51.5 (CH_2), 53.5, 62.4 (CH), 121.3 (C), 127.4, 128.2, 128.6, 128.9 (CH), 140.1, 158.1 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{21}H_{30}N_3$: 324.2440; found: 324.2443

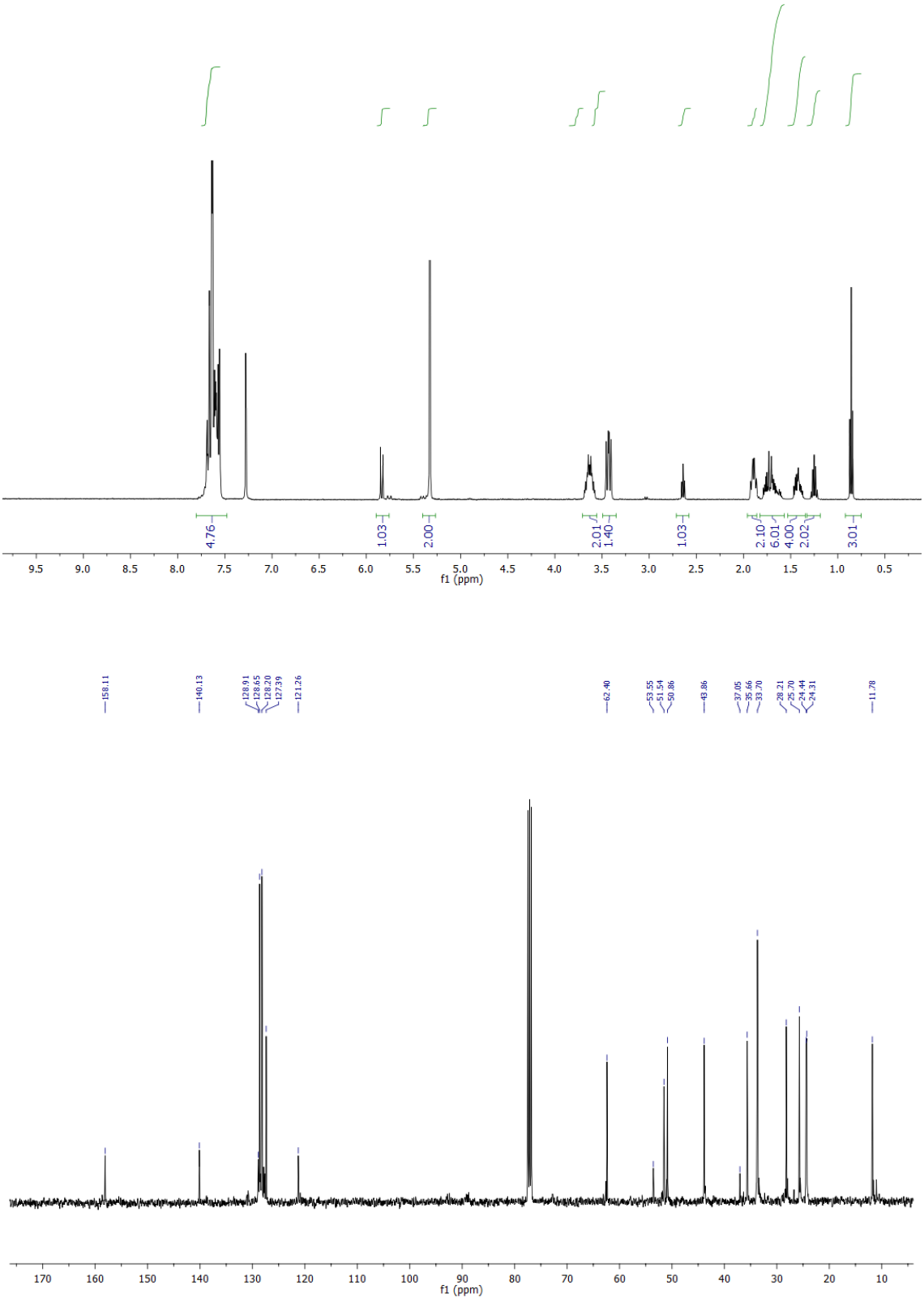


FIGURE 3.24- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6k.**

Chromatograms of Compound 6k

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OD column (*i*-PrOH 85%) at 1.0 mL/min, UV-detection at λ = 265 nm:

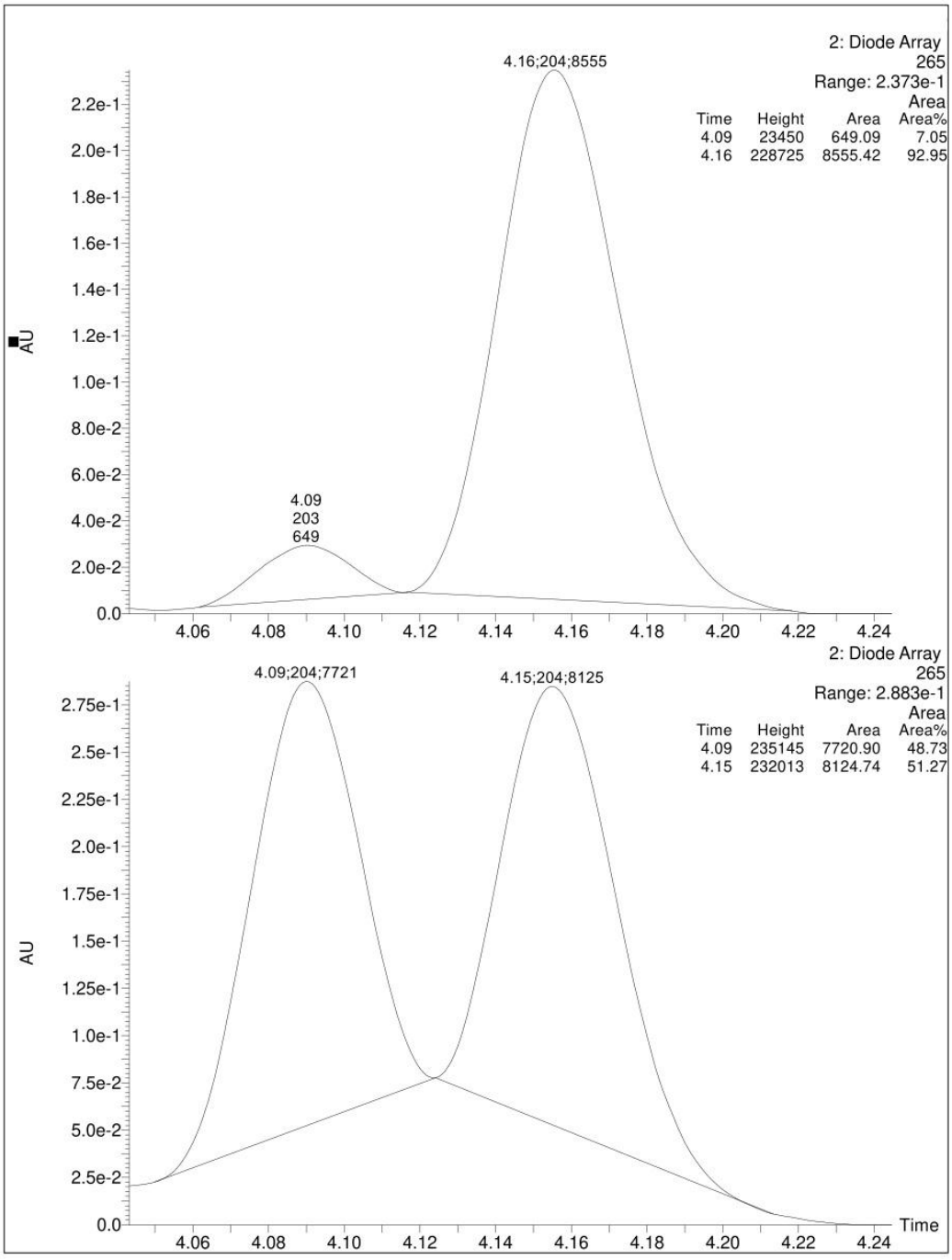
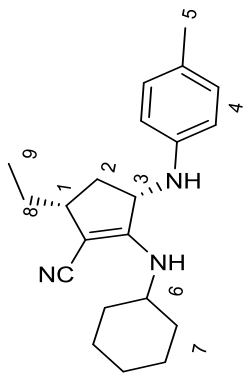


FIGURE 3.25- Chiral stationary-phase HPLC analysis of compound **6k.**



Compound 6l: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), p-toluidine (16.5 µL, 0.15 mmol) and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 4:1) afforded compound **6l** (44 mg, 90%) as a pale brown oil. $[\alpha]_D^{20}$ -7.9 (c 0.5, acetone, 20ºC). Rf = 0.76 (n-hexane/ EtOAc 7:3). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.0 (d, 2H, *J*= 7.91 Hz, H-4); 6.57 (m, 2H, H-4); 4.68 (d, *J*= 7.80, N-H); 4.43 (t, 1H, *J*= 8.69 Hz, H-3); 3.73-3.83 (m, 1H, H-6); 2.71-2.78 (m, 1H, H-1); 2.00 (s, 3H, H-5); 2.00-2.09 (m, 2H, H-2), 1.92-2.00 (qd, 1H, *J*= 2.47 and 7.73 Hz, H-8); 1.76-1.84 (m,1H, H-8), 1.56-1.72 (m, 4H, H-7), 1.29-1.47 (m, 3H, H-7), 1.03-1.21 (m, 3H, H-7), 0.92 (t, 3H, H-9) .**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = (ppm) 11.5, 20.4, 24.1, 24.3, 25.5, 27.8, 28.0, 33.6, 34.7, 43.5, 51.8, 59.8, 114.4, 120.7 (CN), 128.4, 129.9, 144.0, 157.5 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{21}H_{30}N_3$: 324.2440; found: 324.2445

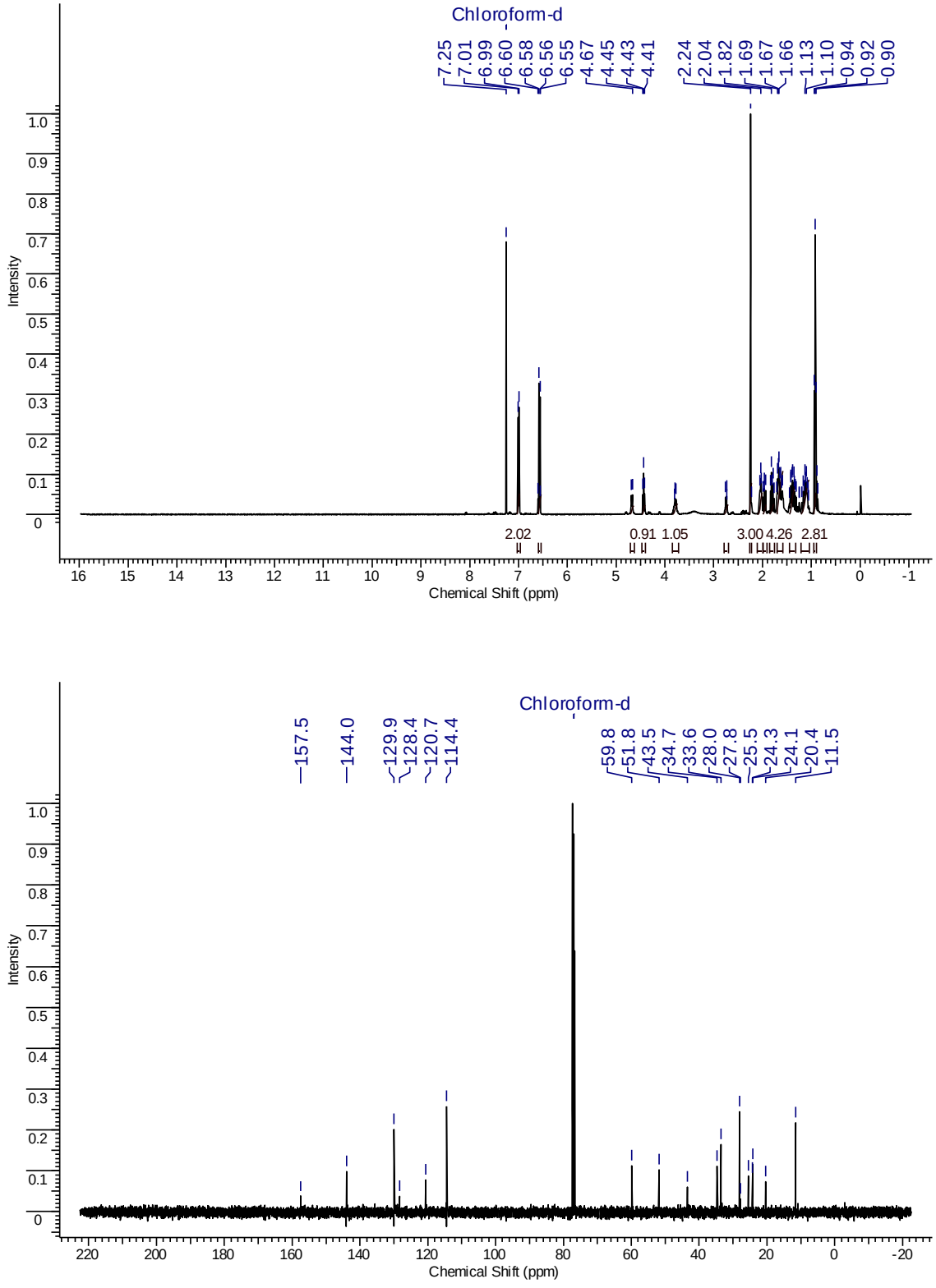


FIGURE 3.26- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6l.**

Chromatograms of Compound 6l

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (CH_3CN 80%) at 1.0 mL/min, UV-detection at λ = 265 nm:

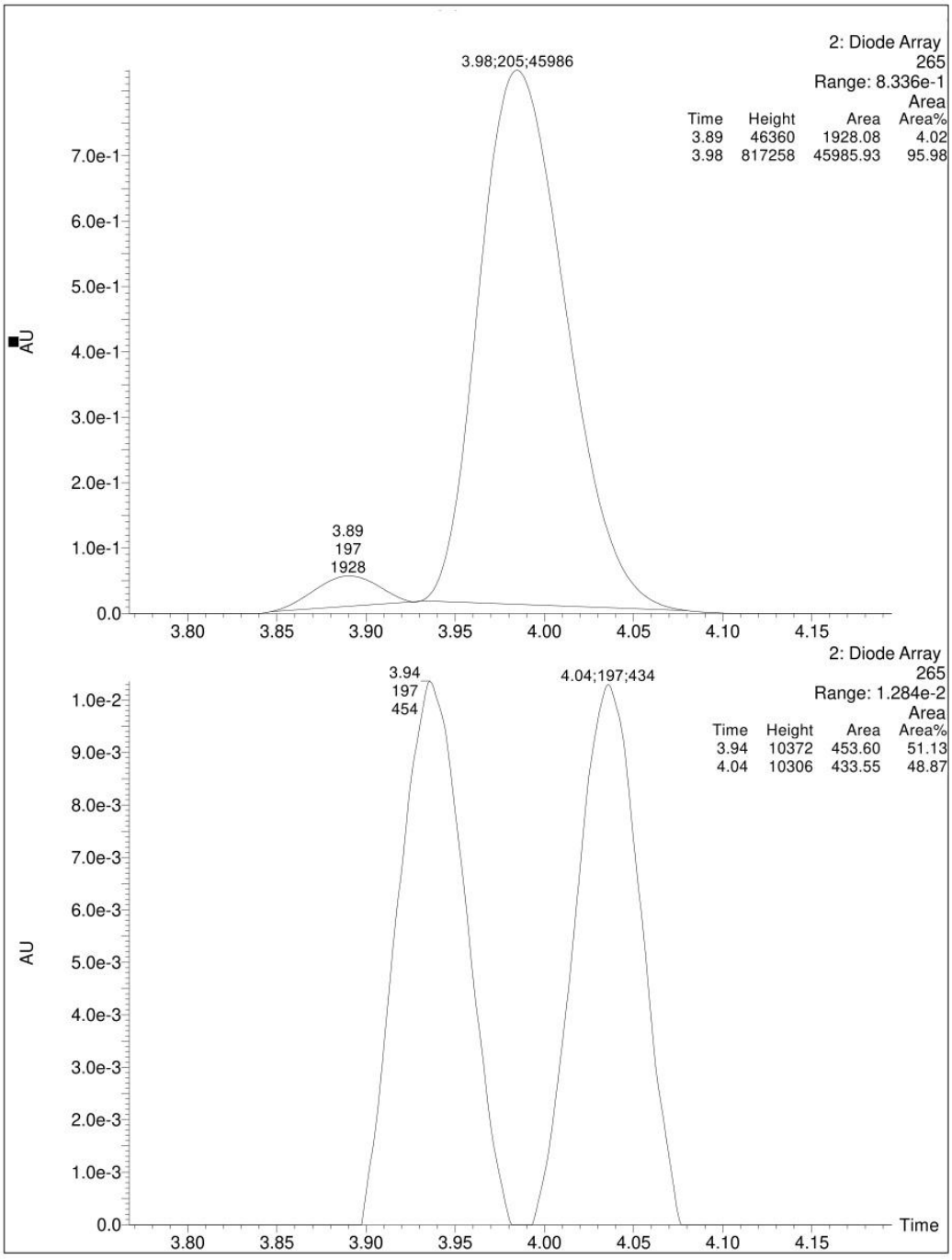
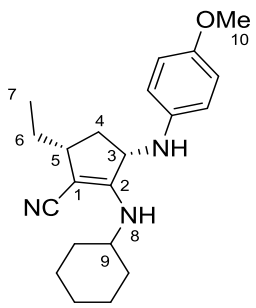


FIGURE 3.27- Chiral stationary-phase HPLC analysis of compound **6l.**



Compound 6m: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), p-anisidine (18.4 mg, 0.15 mmol) and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 5:1) afforded compound **6m** (41.6 mg, 82%) as a brown oil.

$[\alpha]_D^{20}$ −11.7 (c 0.6, acetone, 20ºC). Rf = 0.36 (n-hexane/ EtOAc 4:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =7.24-7.20 (m, 2H, Ph); 7.16-6.82 (m, 2H, Ph); 5.98 (d, *J* = 8.2 Hz, 1H, H-8); 4.52-4.38 (m, 1H, H-9); 4.13 (t, *J* = 7.2 Hz, 1H, H-3); 3.68 (s, 3H, H-10); 2.29-2.09 (m, 2H, H-4); 2.00-1.92 (m, 2H); 1.85-1.57 (m, 6H); 1.55-1.39 (m, 4H); 1.28-1.10 (m, 1H); 0.89 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.5 (CH_3), 24.2, 24.3, 25.5, 28.1, 33.5, 33.6, 34.6 (CH_2), 43.5, 51.8 (CH), 55.7 (CH_3), 60.5 (CH), 73.7, 114.1 (C), 115.0, 115.9 (CH), 120.7 (C), 140.2 (CH), 153.2, 157.2 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{21}H_{30}N_3O$: 340.2389; found: 340.2391

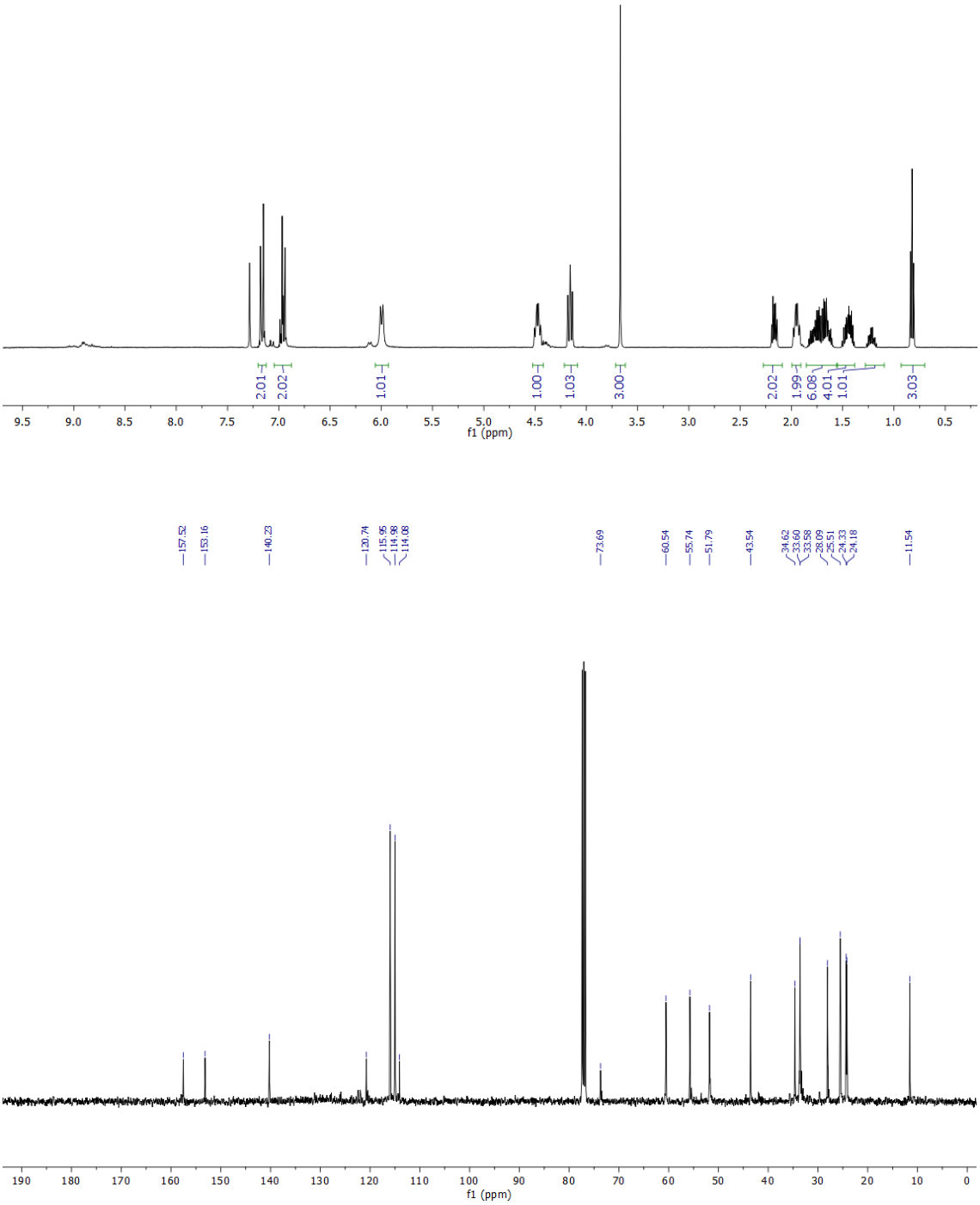


FIGURE 3.28- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6m.**

Chromatograms of Compound 6m

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (MeOH 90%) at 1.0 mL/min, UV-detection at λ = 265 nm:

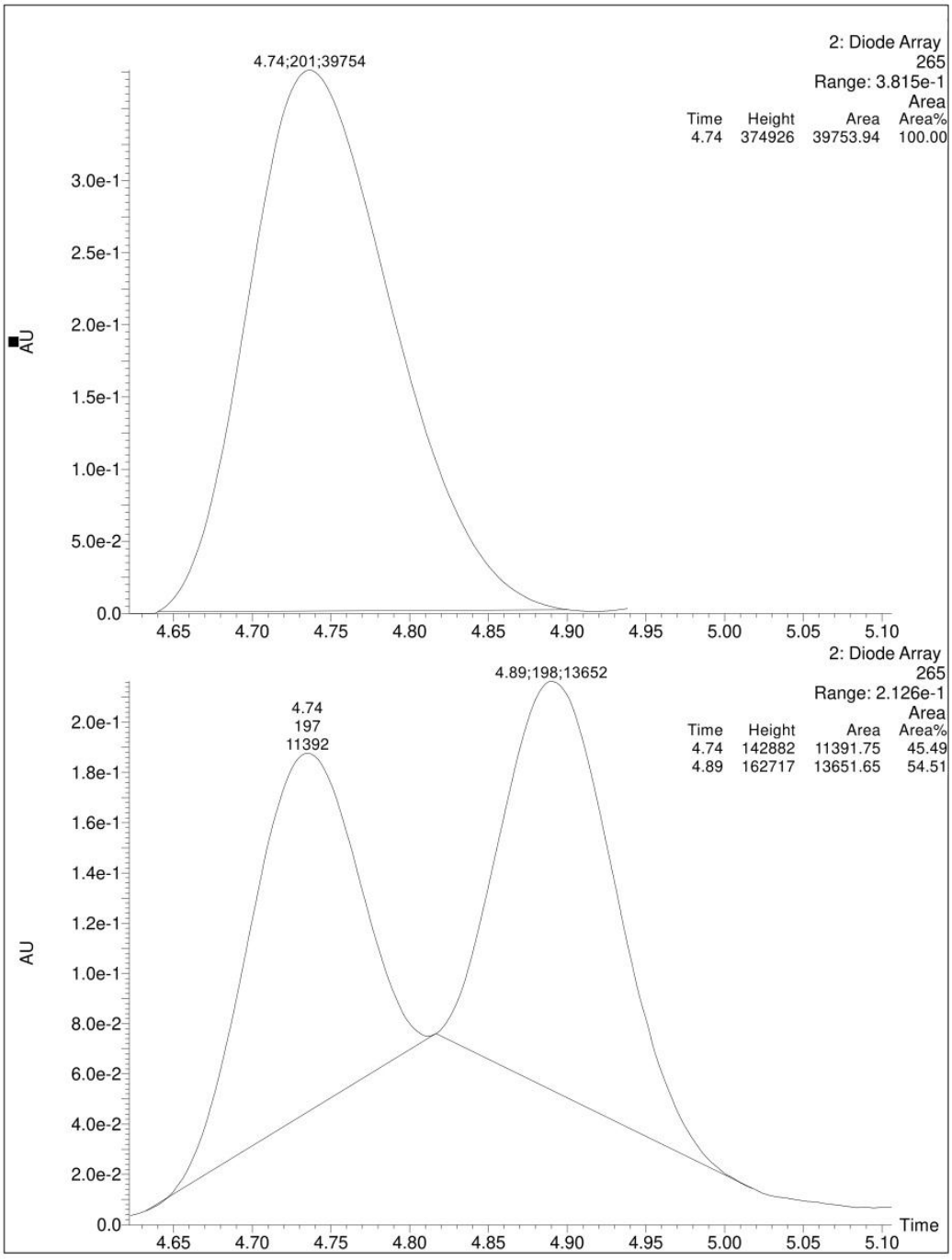
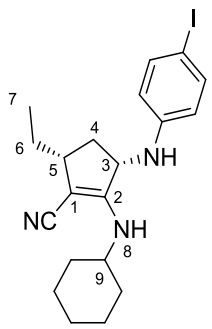


FIGURE 3.29- Chiral stationary-phase HPLC analysis of compound **6m.**



Compound 6n: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), 4-bromoaniline (25.8 mg, 0.15 mmol) and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 6:1) afforded compound **6n** (57.3 mg, 87%) as an pale yellow solid. $[\alpha]_D^{20}$−20.2 (c 0.6, acetone, 20oC). Rf = 0.35 (n-hexane/ EtOAc 5:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =7.38 (d, *J* = 8.5 Hz, 2H, Ph); 6.37 (d, *J* = 8.6 Hz, 2H, Ph); 4.54 (d, *J* = 8.6 Hz, 1H, H-8); 4.38 (t, *J* = 7.5 Hz, 1H, H-3); 3.74-3.62 (m, 1H, H-9); 2.77-2.66 (m, 1H); 2.05-1.94 (m, 2H); 1.91-1.71 (m, 2H, H-4); 1.68-1.52 (m, 4H); 1.41-1.23 (m, 3H); 1.14-0.97 (m, 3H); 0.89 (t, *J* = 7.3 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 10.4 (CH_3), 23.2, 23.3, 24.4, 26.7, 27.0, 28.7, 32.6 (CH_2), 33.3, 42.5, 50.9 (CH), 58.3, 78.8 (C) 115.3 (CH), 116.3 (C), 119.3, 125.0, 137.0 (CH), 145.0, 157.5 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{20}H_{27}IN_3$: 436.1250; found: 436.1258

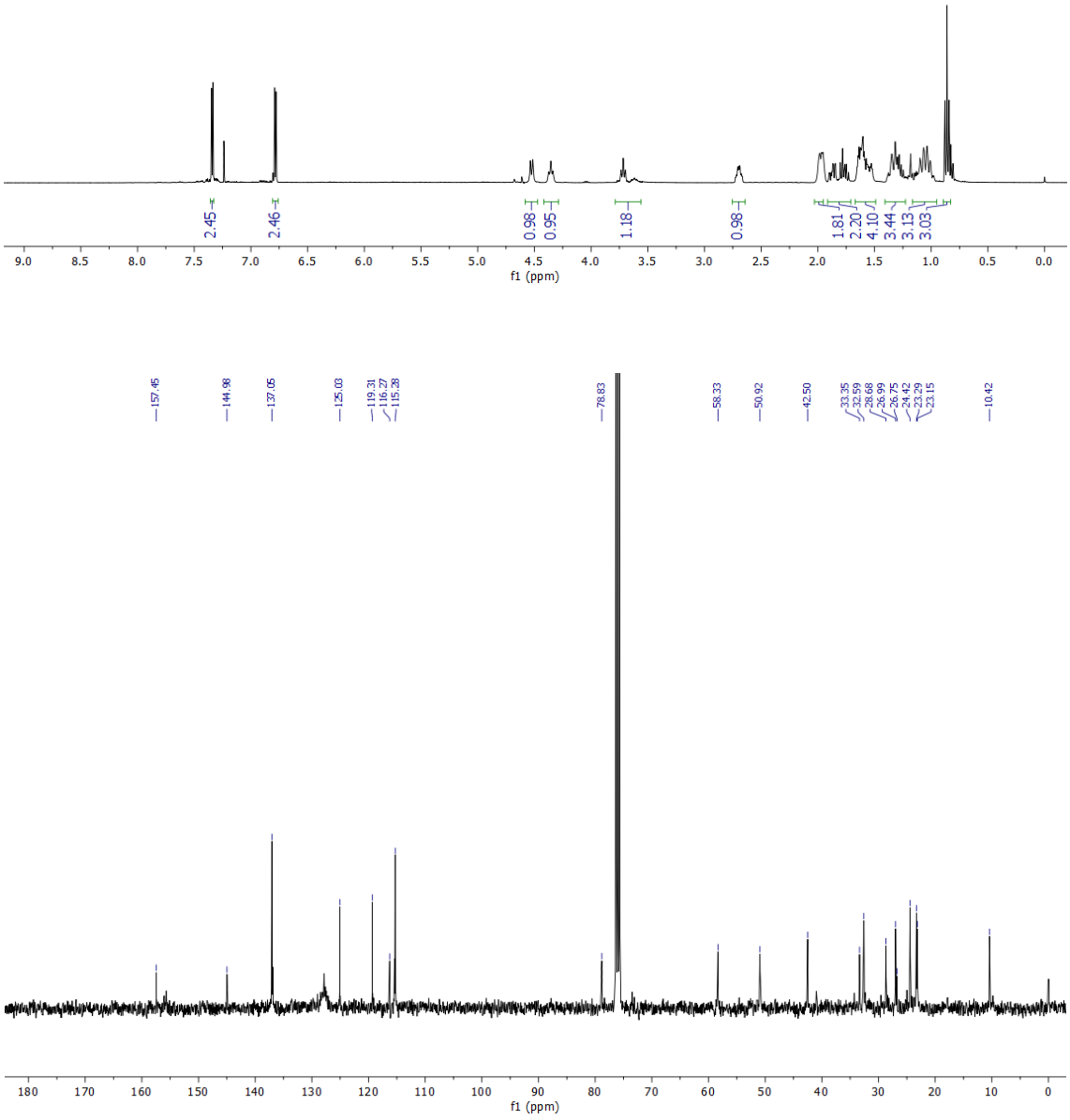


FIGURE 3.30- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6n.**

Chromatograms of Compound 6n

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OD column (*i*PrOH 90%) at 1.0 mL/min, UV-detection at λ = 265 nm:

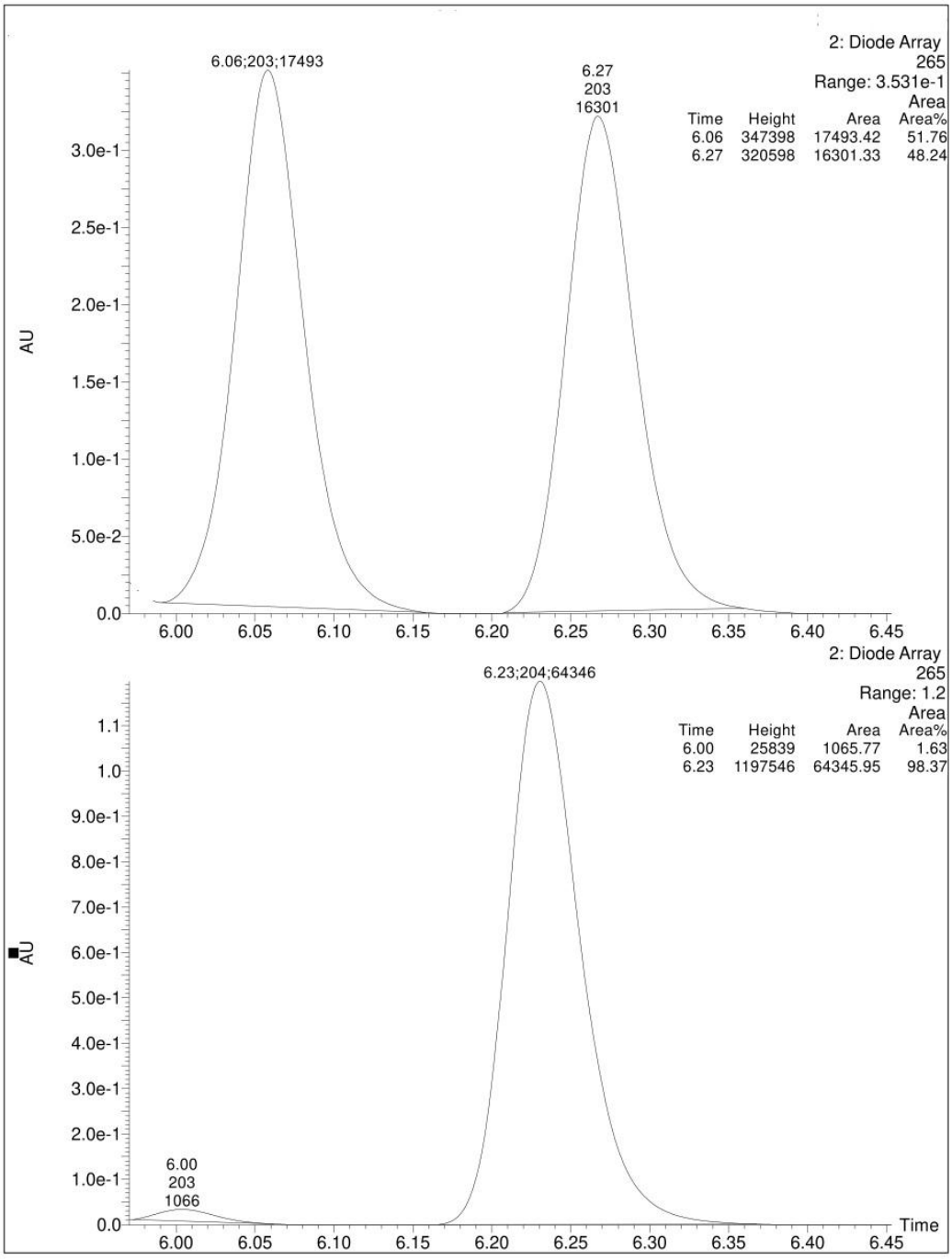
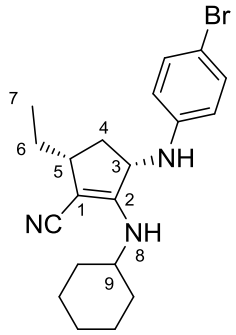


FIGURE 3.31- Chiral stationary-phase HPLC analysis of compound **6n.**



Compound 6o: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), 4-bromoaniline (25.8 mg, 0.15 mmol) and cyclohexylisocyanide (18.7 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 5:1) afforded compound **6o** (45.5 mg, 75%) as an dark yellow oil. $[\alpha]_D^{20}$ −15.4 (c 0.6, acetone, 20ºC). Rf = 0.39 (n-hexane/ EtOAc 4:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =7.23-7.17 (m, 2H, Ph); 7.51-6.43 (m, 2H, Ph); 4.52 (d, *J* = 8.6 Hz, 1H, H-8); 4.36 (t, 1H, H-3); 3.75-3.61 (m, 1H, H-9); 2.76-2.65 (m, 1H); 2.03-1.93 (m, 2H); 1.91-1.71 (m, 2H, H-4); 1.67-1.51 (m, 4H); 1.41-1.23 (m, 3H); 1.14-0.97 (m, 3H); 0.86 (t, *J* = 7.3 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.6 (CH_3), 24.3, 24.4, 25.6, 28.1, 33.7, 34.5, 35.4 (CH_2), 42.1, 43.6, 52.0, 59.6 (CH), 74.5, 110.7 (C), 115.9, 120.5, 132.3 (CH), 145.5, 156.9 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{20}H_{27}BrN_3$: 388.1388; found: 388.1392

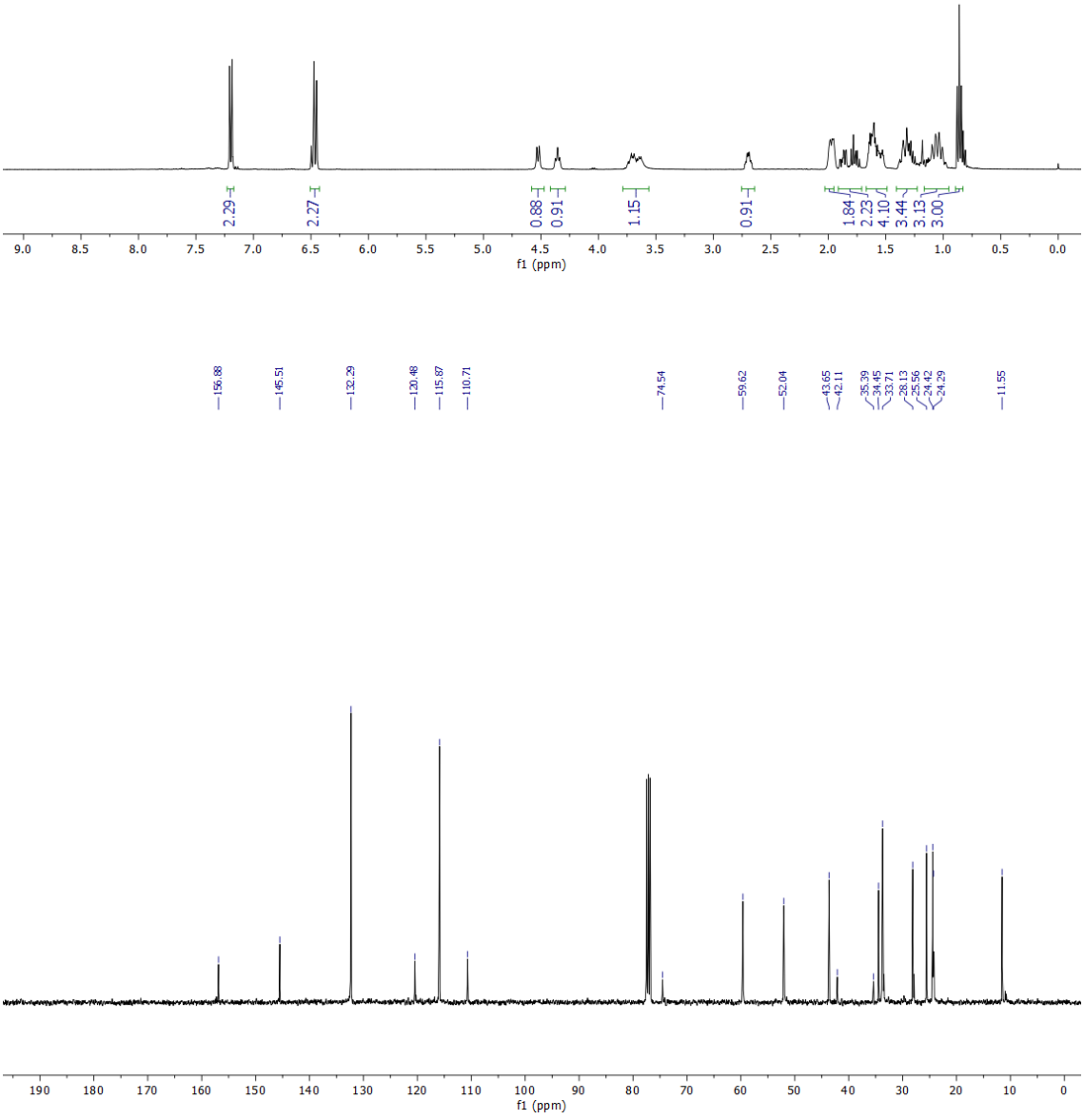


FIGURE 3.32- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6o**.

Chromatograms of Compound 6o

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (*i*PrOH 68%) at 1 mL/min, UV-detection at $\lambda = 265$ nm:

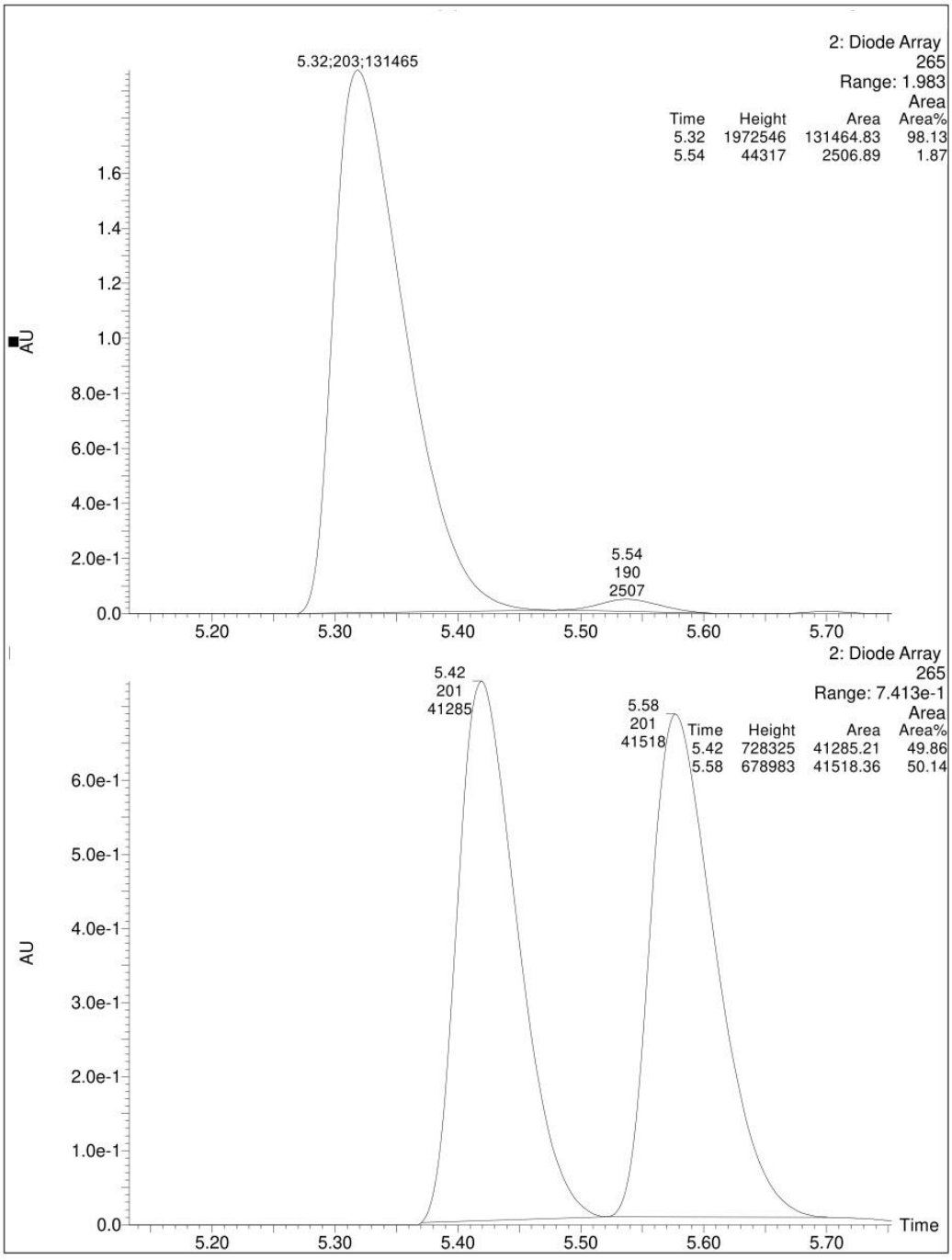
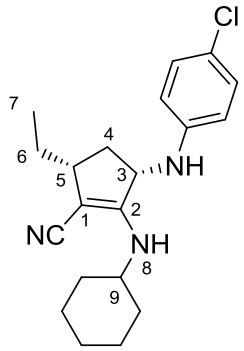


FIGURE 3.33- Chiral stationary-phase HPLC analysis of compound **6o.**



Compound 6p: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 μL, 0.18 mmol), 4-chloroaniline (19.1 mg, 0.15 mmol) and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 5:1) afforded compound **6p** (40.7 mg, 79%) as a brown oil. $[\alpha]_D^{20}$ -8.9 (c 0.5, acetone, 20°C). Rf = 0.53 (n-hexane/ EtOAc 8:2). **^{1}H NMR (400 MHz, $CDCl_3$)** : δ= 7.14 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.64 (d, *J* = 8.6 Hz, 1H, H-8), 4.38 (t, *J* = 8.2 Hz, 1H, H-3), 3.89 – 3.74 (m, 1H), 3.50 (brs, 1H, NH), 2.83 – 2.54 (m, 1H), 2.17 – 1.77 (m, 4H), 1.76 – 1.55 (m, 4H), 1.49 – 1.04 (m, 7H), 0.92 (t, *J* = 7.4 Hz, 3H, H-7). **^{13}C NMR (100 MHz, $CDCl_3$)** δ= 156.7 (C-2), 144.9 (C), 129.3 (CH), 123.7 (C), 120.4 (CN), 115.5 (C), 115.4 (CH), 74.5 (CN), 59.7, 51.9, 43.6, 34.4, 33.6, 28.0, 25.5, 24.3, 24.2, 11.5 (C-7). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{20}H_{26}ClN_3$: 344.1888; found: 344.1906

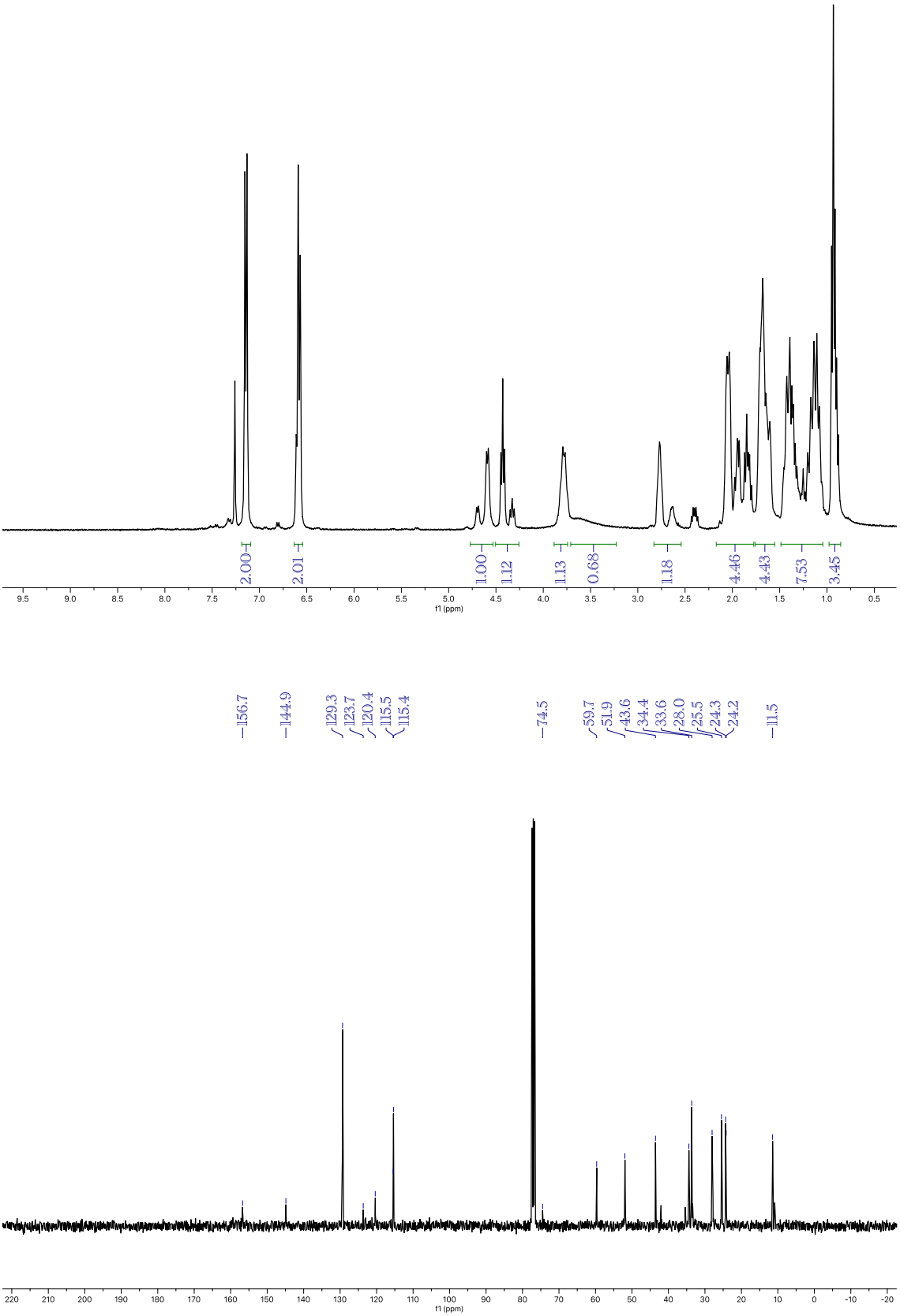


FIGURE 3.34- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6p.**

Chromatograms of Compound 6p

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (*i*PrOH 95%) at 0.5 mL/min, UV-detection at λ = 265 nm:

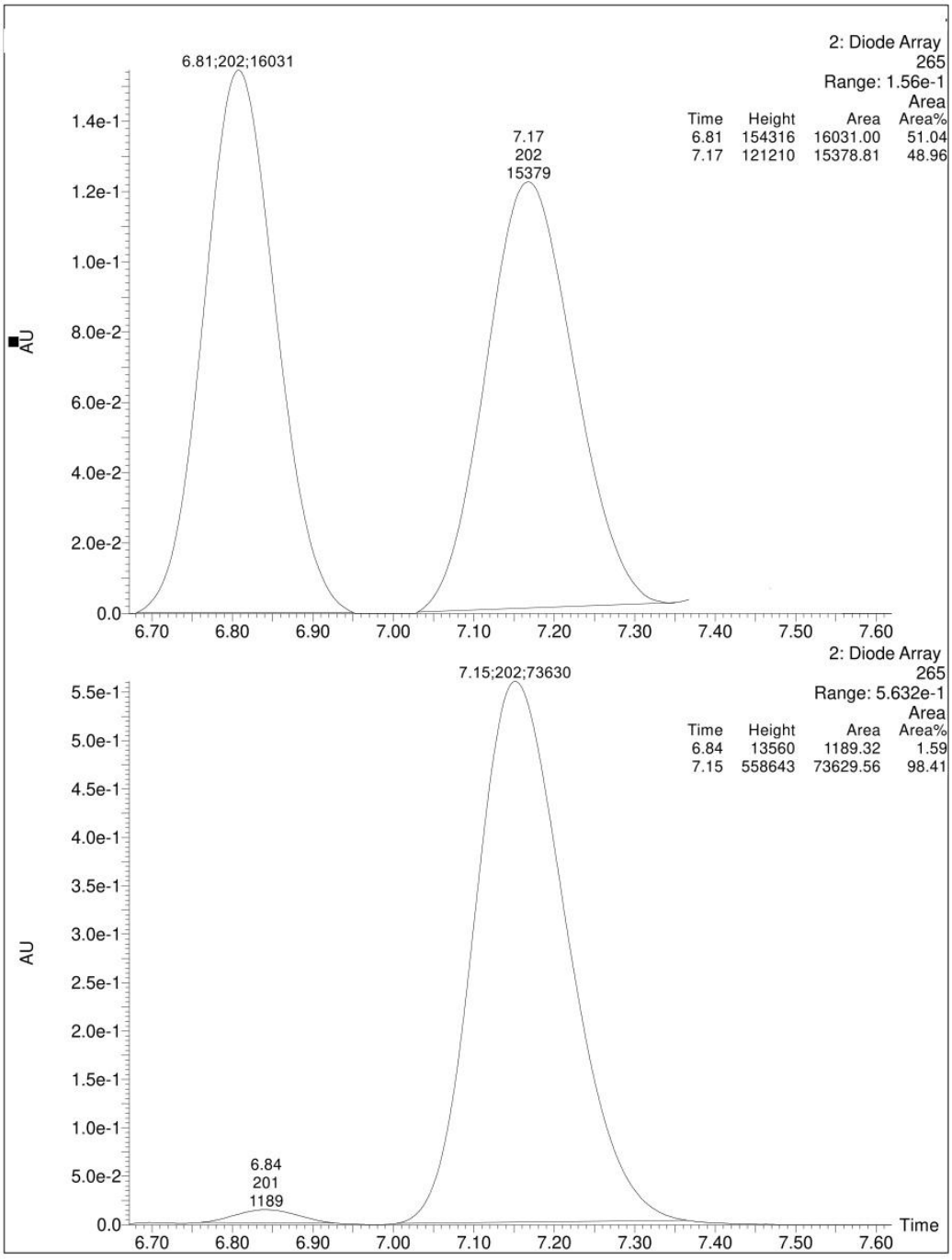
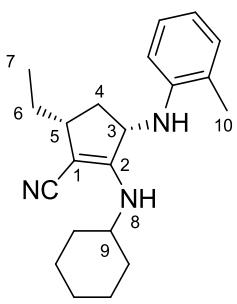


FIGURE 3.35- Chiral stationary-phase HPLC analysis of compound **6p.**



Compound 6q: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 μL, 0.18 mmol), 2-aminotoluene (16.0 μL, 0.15 mmol) and cyclohexylisocyanide (18.7 μL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (*n*-hexane/EtOAc 6:1) afforded compound **6q** (34.8 mg, 72%) as an pale orange oil. $[\alpha]_D^{20}$ -7.2 (*c* 0.5, acetone, 20°C). R_f = 0.42(*n*-hexane/ EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.20-7.04 (m, 2H, Ph); 6.78-6.70 (m, 1H, Ph); 6.67(d, *J* = 8.0 Hz, 1H, Ph); 4.65 (d, *J* = 7.9 Hz, 1H, H-8); 4.54 (t, *J* = 7.9 Hz, 1H, H-3); 3.87-3.63 (m, 1H, H-9); 2.89-2.72 (m, 1H); 2.15 (s, 3H, H-10); 2.07-2.00 (m, 2H); 1.89-1.79 (m, 1H); 1.73-1.58 (m, 4H); 1.21-1.06 (m, 3H); 0.94 (t, J = 7.4 Hz, 3H, H-7).^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 17.8 (CH_3), 24.3, 24.4, 25.6, 28.2, 29.8, 33.7, 35.5 (CH_2), 43.7, 51.9, 59.4 (CH), 74. 5, 111.4 (C), 118.6, 120.6, 123.3, 127.4 (CH), 130.8, 144.6, 157.6 (C). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{21}H_{30}N_3$: 324.2440; found: 324.2436

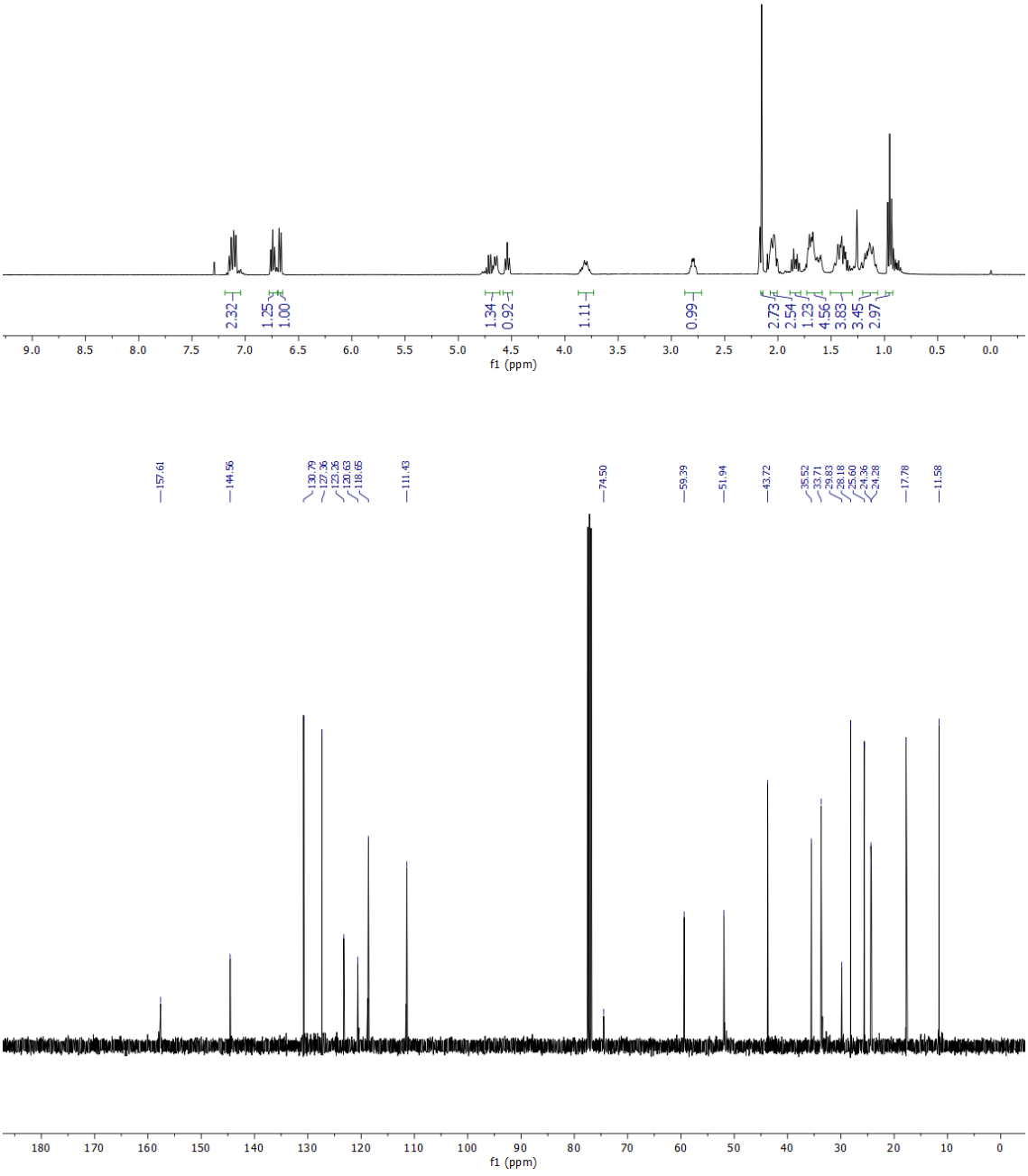


FIGURE 3.36- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6q.**

Chromatograms of Compound 6q

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OD column (*i*PrOH 80%) at 1.0 mL/min, UV-detection at λ = 265 nm:

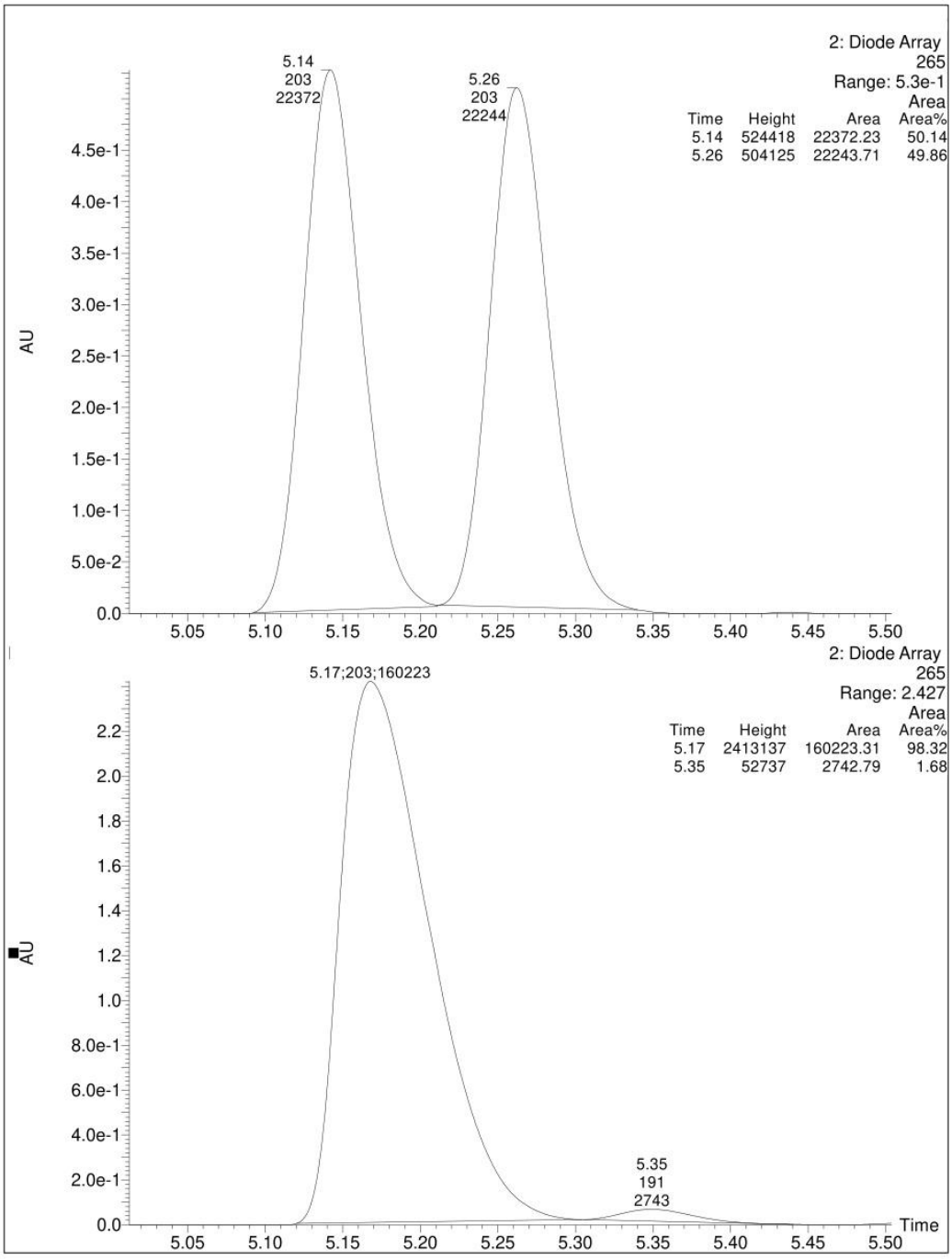
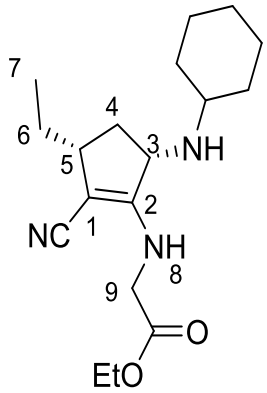


FIGURE 3.37- Chiral stationary-phase HPLC analysis of compound **6q.**



Compound 6r: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), cyclohexylamine (17.2 µL, 0.15 mmol) and ethyl isocyanoacetate (16.4 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/ EtOAc 4:1) afforded compound **6r** (35.4 mg, 74%) as a yellow oil.

$[\alpha]_D^{20}$-9.9 (c 0.5, acetone, 20ºC). Rf = 0.37 (n-hexane/ EtOAc 2:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =5.68 (t, *J* = 5.3 Hz, 1H, H-8); 4.27 (d, *J* = 5.3 Hz, 2H, H-9); 4.23 (q, *J* = 7.0 Hz, 2H, CH_2-OEt); 3.76 (dd, *J* = 9.7/7.5 Hz, 1H, H-3); 2.63 (td, *J* = 8.1/5.2 Hz, 1H); 2.55-2.44 (m, 1H); 2.12-1.99 (m, 1H); 1.78-1.66 (m, 3H); 1.62-1.48 (m, 4H); 1.31 (t, *J* = 7.0 Hz, 3H); 1.25-1.11 (m, 3H); 1.08-0.97 (m, 3H); 0.93 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.9 (CH_3), 14.3, 24.8, 25.1, 26.1, 27.9, 33.7 (CH_2), 35.3 (CH_3), 43.7 (CH_2), 45.2, 55.2, 60.3 (CH), 61.8 (CH_2), 120.6, 129.2, 160.5 (C), 170.1 (C=O). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{18}H_{30}N_3O_2$: 320.2338; found: 320.2339

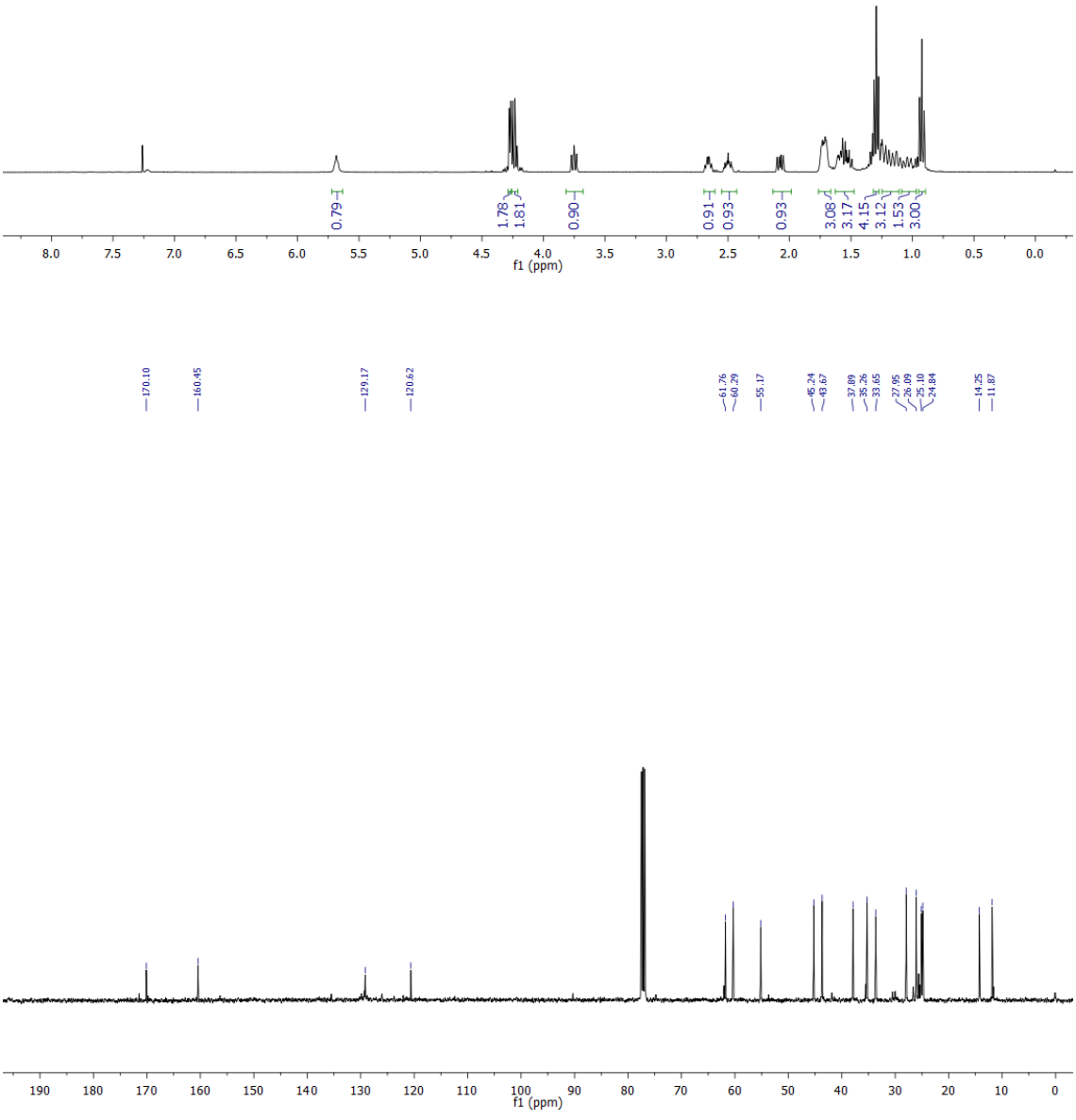


FIGURE 3.38- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6r.**

Chromatograms of Compound 6r

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (MeOH 80%) at 1.0 mL/min, UV-detection at λ = 265 nm:

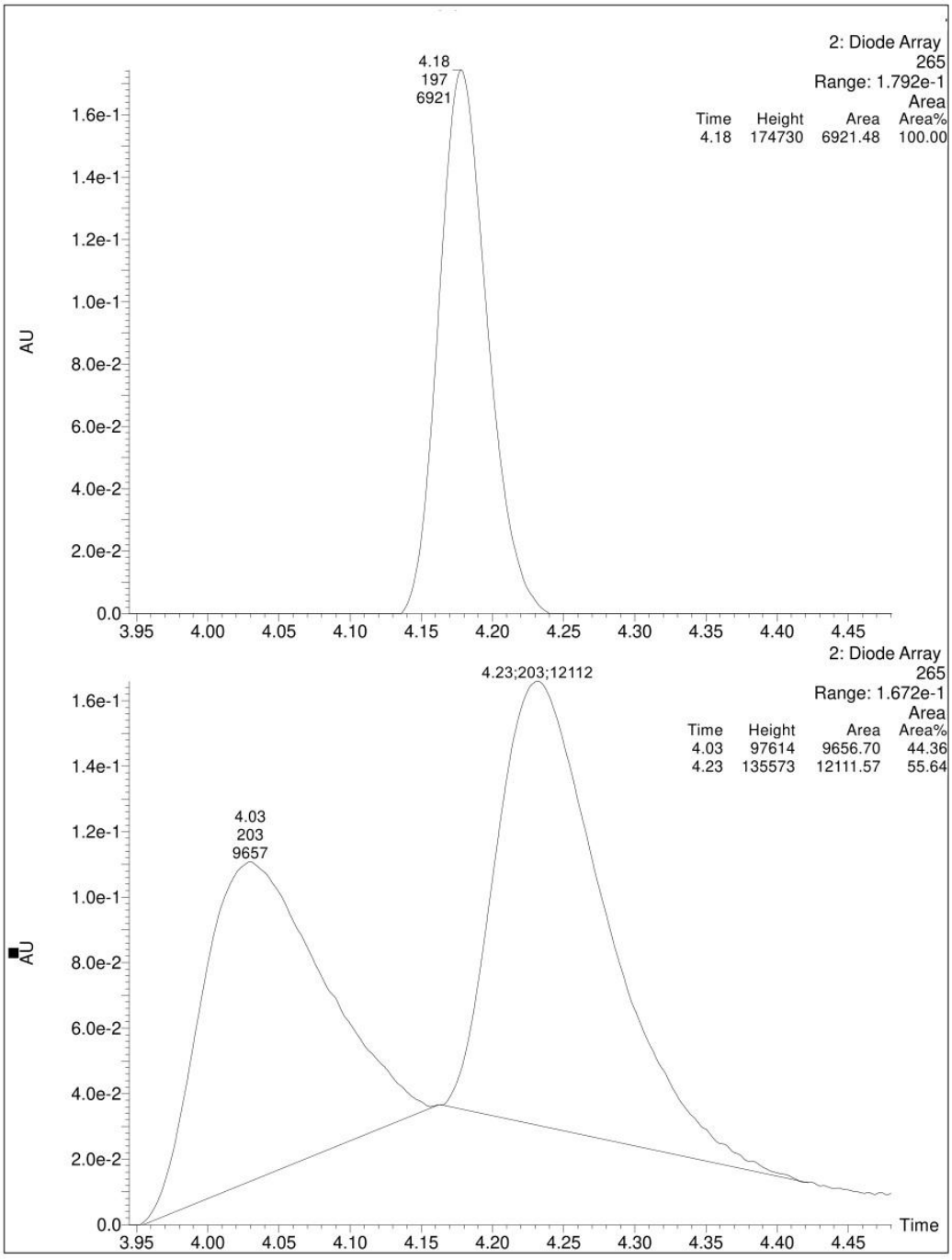
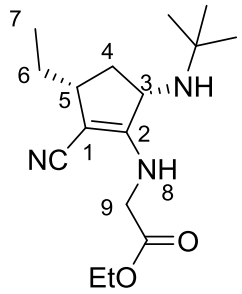


FIGURE 3.39- Chiral stationary-phase HPLC analysis of compound **6r.**



Compound 6s: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), tert-butylamine (15.8 µL, 0.15 mmol), and ethyl isocyanoacetate (16.4 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (n-hexane/EtOAc 4:1) afforded compound **6s** (33.4 mg, 76%) as a brown oil.

$[\alpha]_D^{20}$ -11.6 (c 0.5, acetone, 20ºC). Rf = 0.38 (n-hexane/ EtOAc 2:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 5.75 (t, *J* = 5.6 Hz, 1H, H-8); 4.27 (d, *J* = 5.5Hz, 2H, H-9); 4.24 (q, *J* = 6.9 Hz, 2H, CH_2-OEt); 3.70 (dd, *J* = 9.8/7.3 Hz, 1H, H-3); 2.62 (td, *J* = 8.3/5.2 Hz, 1H); 2.11 (dd, *J* = 12.6/7.3 Hz, 1H, H-4a); 1.62-1.43 (m, 2H); 1.40-1.32 (m, 1H); 1.31 (t, *J* = 7.0 Hz, 3H, CH_3-OEt); 1.10 (s, 9H); 0.93 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.9 (CH_3), 14.2, 27.9 (CH_2), 30.5 (CH_3), 40.7, 43.5 (CH_2), 45.2 (CH_3), 50.8 (CH), 57.4 (CH_2), 61.7 (CH), 73.8, 120.8, 161.1 (C), 170.1 (C=O). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{16}H_{28}N_3O_2$: 294.2182; found: 294.2185

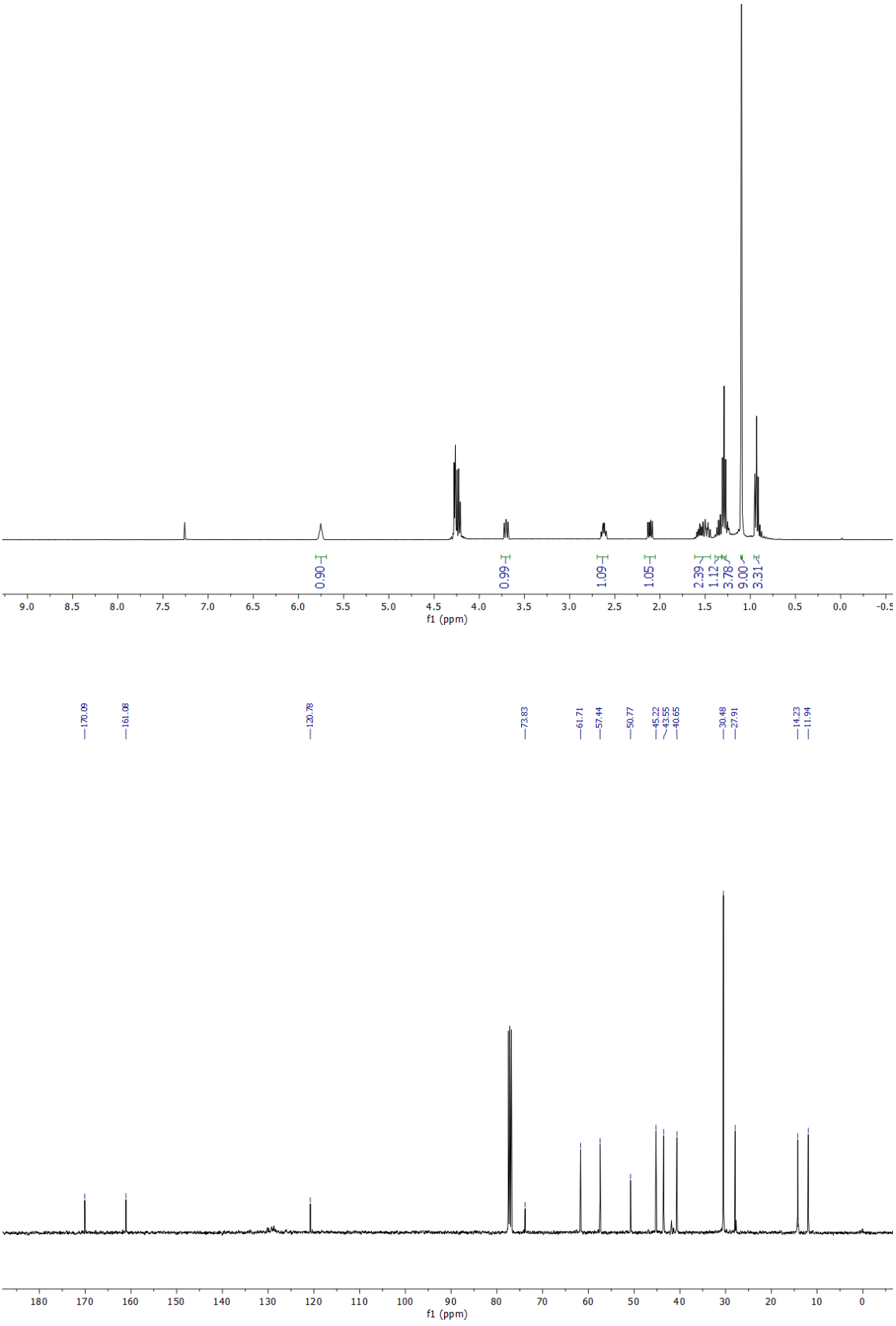


FIGURE 3.40- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6s.**

Chromatograms of Compound 6s

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (MeOH 95%) at 1.0 mL/min, UV-detection at λ = 265 nm:

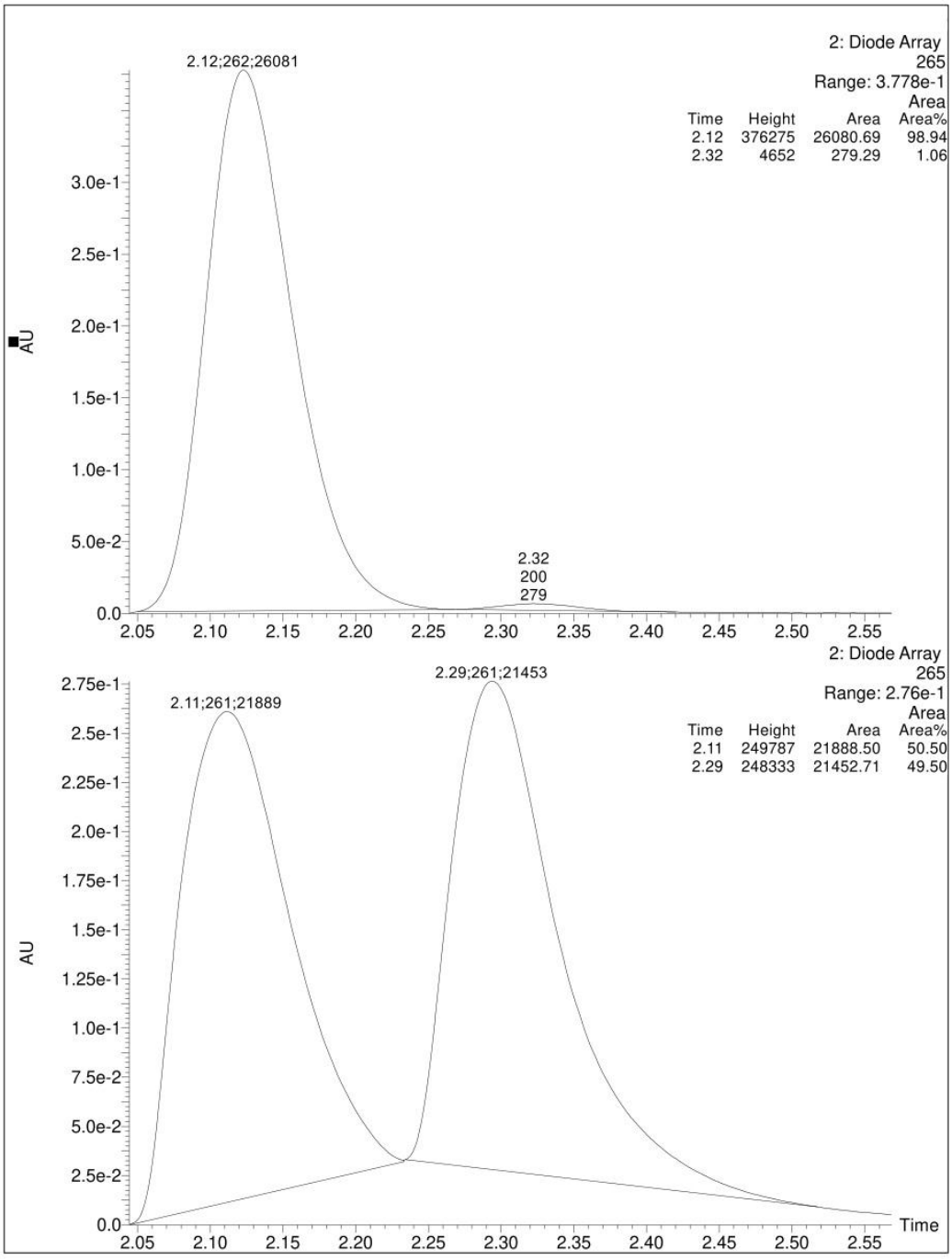
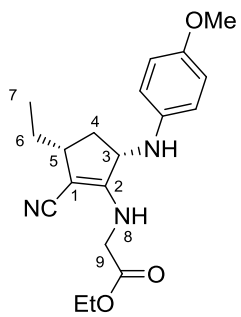


FIGURE 3.41- Chiral stationary-phase HPLC analysis of compound **6s.**



Compound 6t: Benzoylacetonitrile (21.8 mg, 0.15 mmol), trans-2 pentenal (17.6 µL, 0.18 mmol), 4-methoxyaniline (18.4 mg, 0.15 mmol) and ethyl isocyanoacetate (16.4 µL, 0.15 mmol) were reacted according to the general procedure. Flash column chromatography purification (*n*-hexane/EtOAc 10:1) afforded compound **6t** (27.3 mg, 53%) as a dark brown oil.

$[\alpha]_D^{20}$ -16.3 (*c* 0.5, acetone, 20°C). R_f = 0.51 (*n*-hexane/ EtOAc 2:1). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ =6.78 (d, *J* = 8.8 Hz, 2H, Ph); 6.63 (d, *J* = 8.7 Hz, 2H, Ph); 5.32 (t, *J* = 5.8 Hz, 1H, H-8); 4.46 (t, *J* = 7.4 Hz, 1H, H-3); 4.28 (q, *J* = 5.2 Hz, 2H, OCH_2CH_3); 4.23 (d, *J* = 7.1 Hz, 2H, H-9); 3.74 (s, 3H, OMe); 2.82-2.69 (m, 1H); 2.03-1.95 (m, 1H); 1.87-1.78 (m, 1H); 72-1.59 (m, 1H); 1.40-1.32 (m, 1H); 1.29 (t, *J* = 7.1 Hz, 3H); 0.93 (t, *J* = 7.4 Hz, 3H, H-7).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 11.5 (CH_3), 14.2, 28.0, 35.2, 43.7 (CH_2); 45.4, 55.8 (CH_3), 60.3, 61.9 (CH), 76.3 (C), 115.1, 116.0 (CH), 116.9, 119.8 (C), 140.2 (CH), 153.3, 158.7 (C), 169.9 (C=O). HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{19}H_{26}N_3O_3$: 344.1914; found: 344.1923

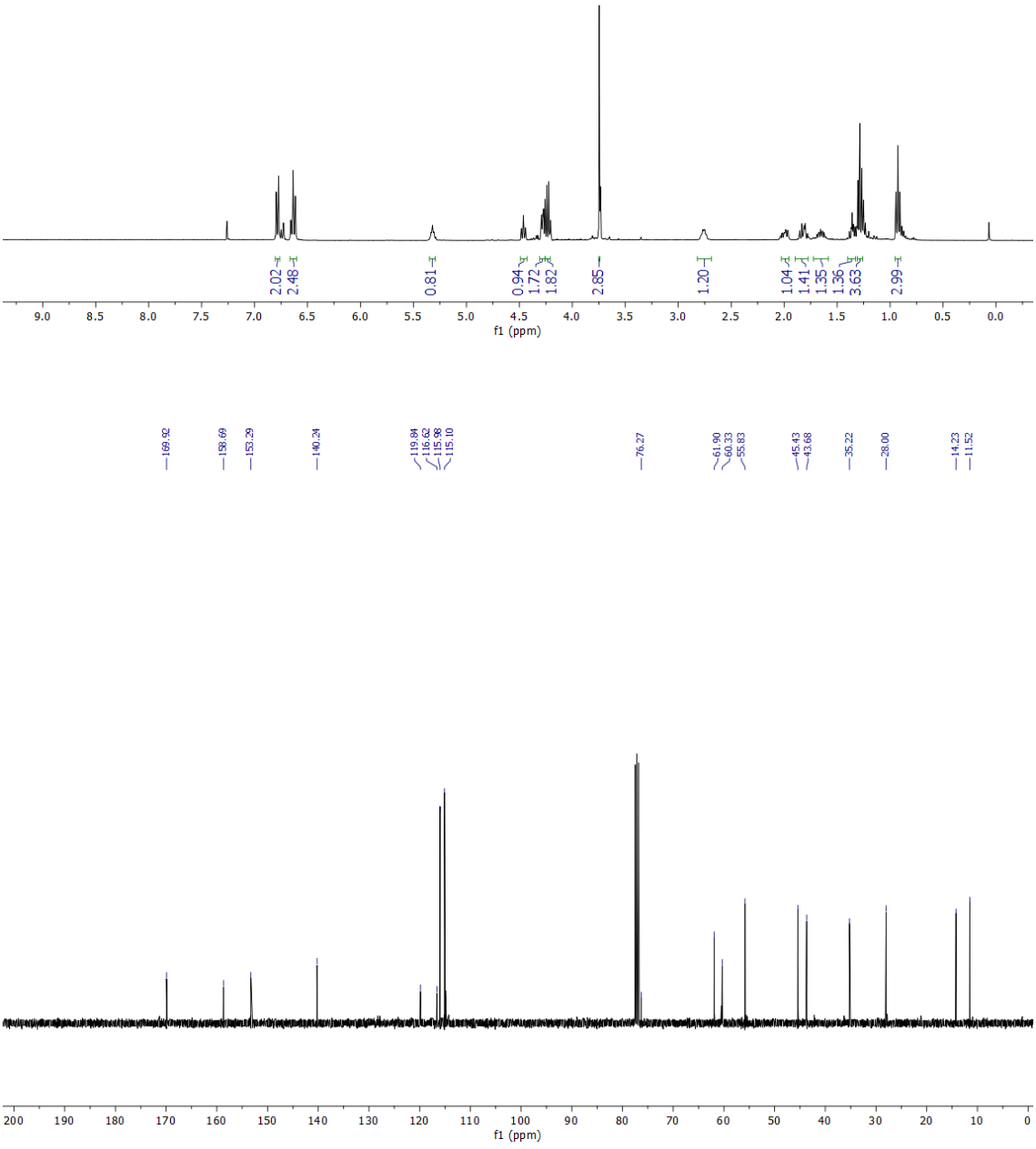


FIGURE 3.42- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **6t.**

Chromatograms of Compound 6t

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel AD column (*i*PrOH 76%) at 1.0 mL/min, UV-detection at λ = 265 nm:

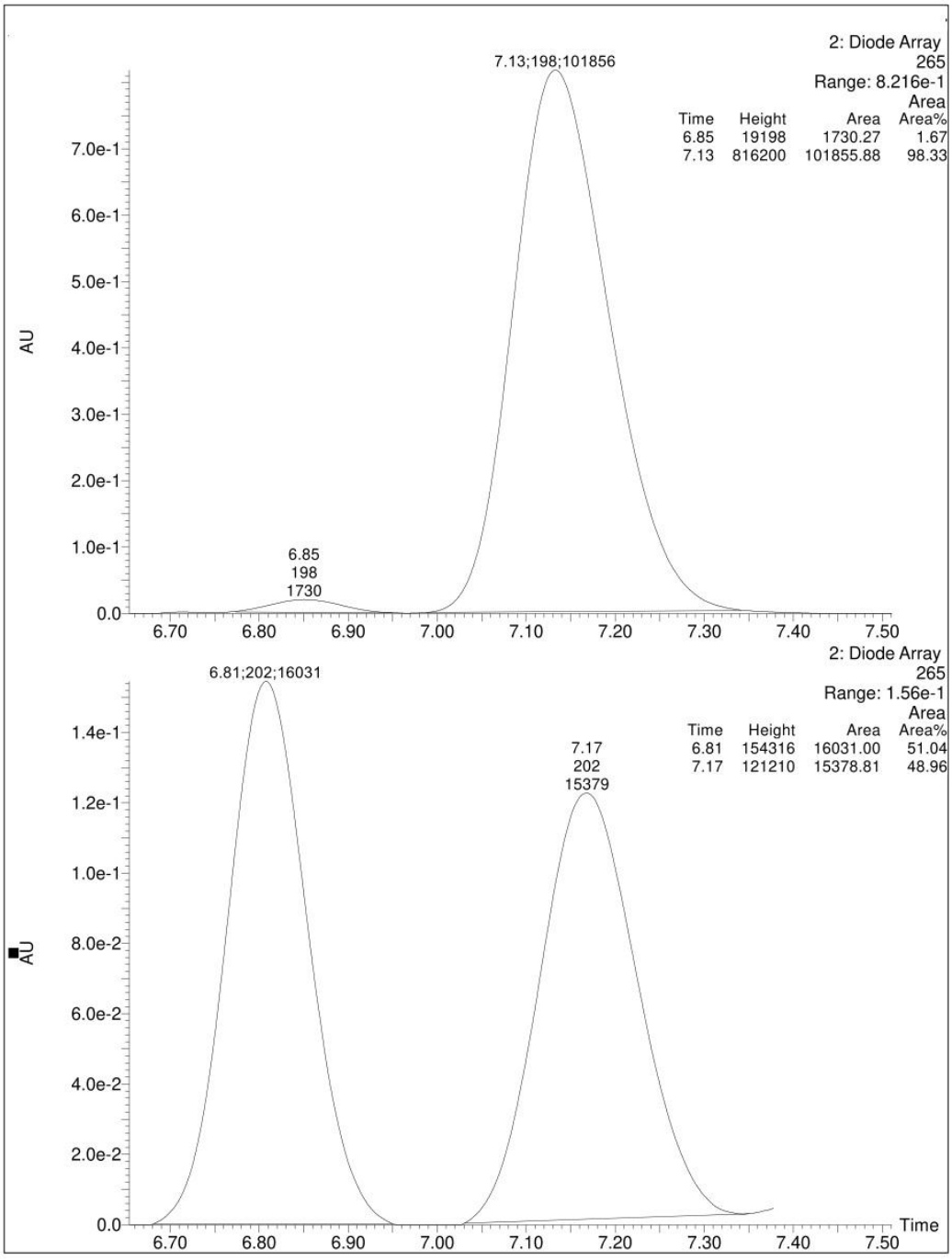
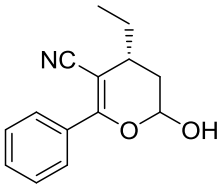


FIGURE 3.43- Chiral stationary-phase HPLC analysis of compound **6t.**

3.2.2-General procedure for the synthesis of compound 3: To a solution of Jørgensen's catalyst (0.015 mmol, 0.1 equiv.), 3,5-dinitrobenzoic acid (0.03 mmol, 0.2 equiv.) and *trans*-2 pentenal (0.18 mmol, 1.2 equiv.) in dimethyl carbonate (1.0 mL) was added benzoylacetonitrile (0.15 mmol, 1.0 equiv.). The resulting solution was stirred for 48h at 10 °C.



Compound 3: Benzoylacetonitrile (290.32 mg, 2 mmol), trans-2 pentenal (234.8 μL, 2.4 mmol), Jørgensen's catalyst (119.5 mg, 0.2 mmol) and 3,5 dinitrobenzoic acid (84.84 mg, 0.4 mmol) were reacted according to the general procedure. Flash column chromatography purification (*n*-hexane/EtOAc 8:1) afforded the compound **3** (418.5 mg, 91%) as a yellow solid.

$[\alpha]_D^{20}$ 4.0 (*c* 0.5, acetone, 20°C). R_f = 0.23 (*n*-hexane/ EtOAc 8:2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.76 – 7.67 (m, 2H), 7.46 – 7.34 (m, 3H), 5.66 (dd, *J* =4.1 Hz, 1H, OH), 2.30 – 2.21 (m, 1H), 2.10 – 2.03 (m, 1H), 2.02 – 1.96 (m, 1H), 1.76 – 1.64 (m, 2H), 1.63 – 1.43 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.5, 130.9, 130.7, 128.4, 128.2, 119.6, 96.2, 34.4, 33.1, 30.9, 30.3, 26.6, 10.8. HRMS (ESI-FT-QQTOF) m/z $[M+H]^+$ calcd for $C_{14}H_{16}NO_2$: 230.1181; found: 230.1176

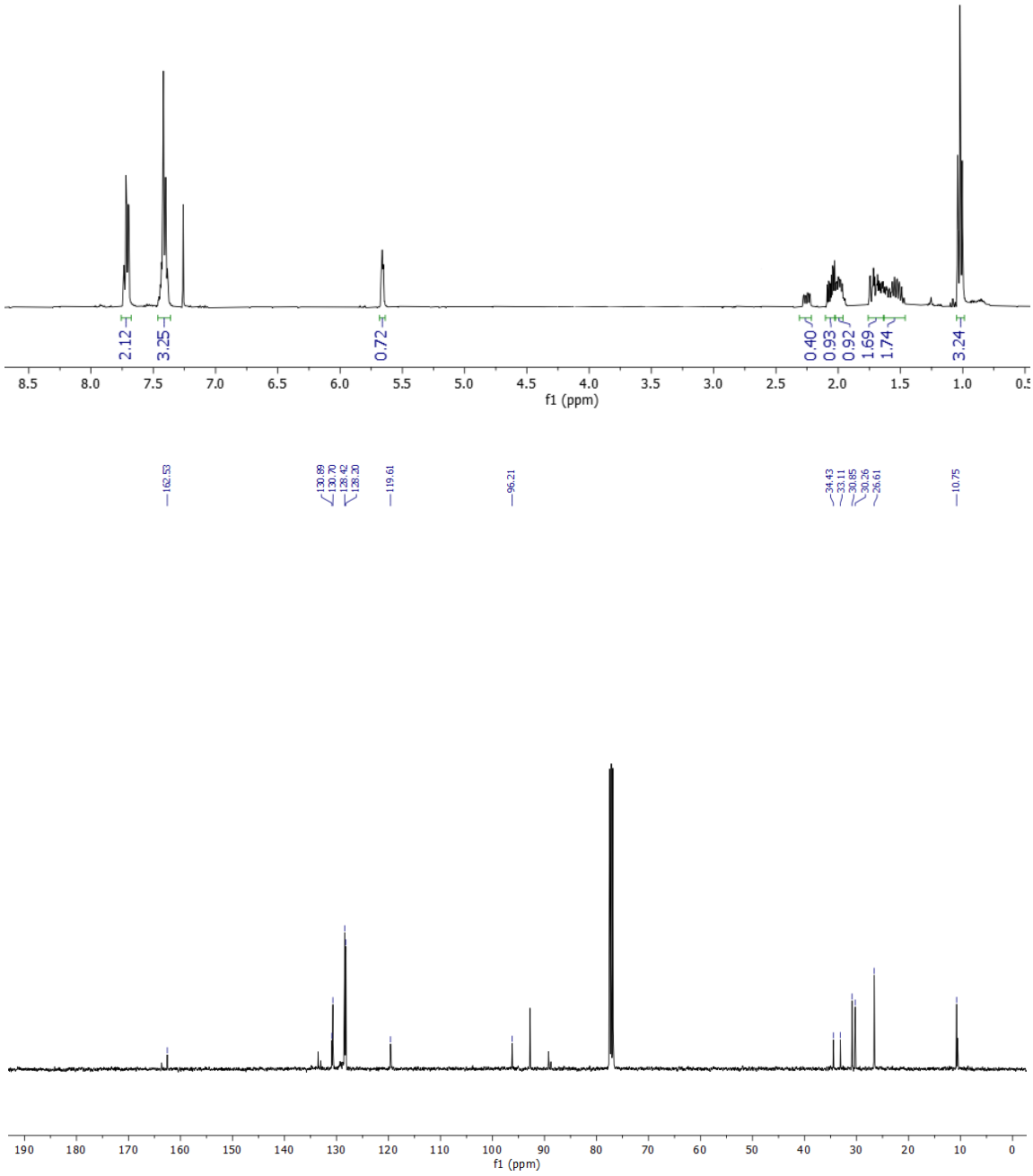


FIGURE 3.44- ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3.**

Chromatograms of Compound 3

The enantiomeric excess was determined by chiral stationary phase UHPLC using a Chiralcel OZ column (CH_3CN 95%) at 1.0 mL/min, UV-detection at $\lambda = 265$ nm:

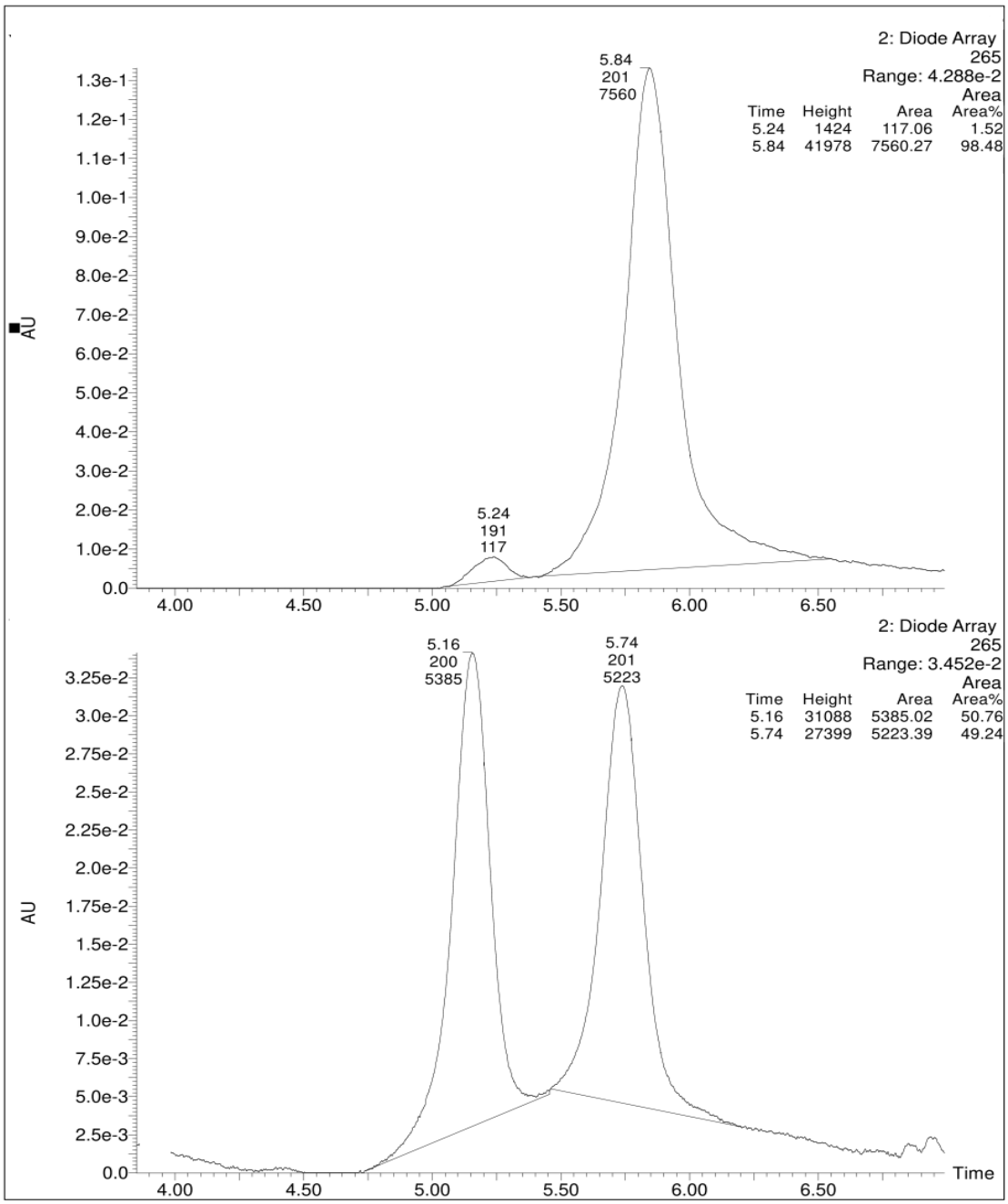


FIGURE 3.45- Chiral stationary-phase HPLC analysis of compound **3.**

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