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ASYMMETRIC INDUCTION ON ISOCYANIDE-BASED TRANSFORMATIONS: DEVELOPMENT OF STEREOSELECTIVE UGI-TYPE REACTIONS

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Abbreviations

Ac	Acetyl
Ar	Aromatic group
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	Tert-Butyloxycarbonyl
Bu	Butyl
CPA	Chiral phosphoric acid
Cy	Cyclohexyl
DBA	3,5-Dinitrobenzoic acid
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density Functional Theory
DMC	Dimethyl carbonate
DME	Dimethoxyethane
DPPA	Diphenylphosphoryl azide
dr	Diastereomeric ratio
ee	Enantiomeric excess
ESI	Electronspray ionization
Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
GC	Gas chromatography
HPLC	High Performance Liquid Chromatography
iPr	Isopropyl
Me	Methyl

MOM	Methoxyethoxymethyl
MS	Mass spectrometry
MW	Microwave
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
Phth	Phthalimide
Pin	Pinacol
TBDPS	Tert-butyldiphenylsilyl
TBS	Tert-butyldimethylsilyl
tBu	Tert-butyl
TFA	Trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TRIP	3,3'-bis [(2,4,6-tris(isopropyl)phenyl)]binaphthyl hydrogen phosphate
3Å MS	3Å diameter pore molecular sieves
δ	Chemical shift

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Resumo

INDUÇÃO ASSIMÉTRICA EM TRANSOFMRAÇÕES BASEADAS EM ISOCIANETOS: DESENVOLVIMENTO DE REAÇÕES ESTEREOSSELETIVAS DO TIPO UGI. O desenvolvimento de novas transformações sintéticas que permitam a rápida construção de moléculas estruturalmente complexas, a partir de materiais de partida simples sob ambos os conceitos de diversidade e sínteses orientadas a funções, é extremamente desejável na química orgânica contemporânea. Nesse sentido, as reações multicomponentes (MCRs) aparecem como uma das estratégias mais úteis para gerar rapidamente diversidade estrutural e complexidade molecular. Entre o vasto repertório de MCRs, as reações multicomponentes baseadas em isocianeto (IMCRs) se destacam como uma abordagem poderosa para obter moléculas altamente funcionalizadas com elevada eficiência química, convergência e economia atômica. Como parte de nosso interesse contínuo no desenvolvimento de I-MCRs intramoleculares diastereosseletivas por meio de controle de substrato, foi desenvolvida uma estratégia eficiente, que combina o estereocontrole da organocatálise com o caráter gerador de diversidade de reações multicomponentes, levando a formação de ciclopentenos tetrassubstituídos contendo dois centros estereogênicos. Ainda, com base em nosso recente sucesso no uso de hemiacetais em reações I-MCR controladas por substrato, vislumbramos o desenvolvimento de uma reação assimétrica do tipo Ugi com hemiacetais aquirais usando um ácido de Brønsted quiral como elemento de indução assimétrica. Após uma breve triagem das condições, descobrimos que os ácidos fosfóricos quirais derivados de SPINOL, especialmente usando fenantril como substituinte (59% de rendimento, 66% ee), foram escolhidos como o melhor catalisador nesta triagem inicial.

Abstract

ASYMMETRIC INDUCTION ON ISOCYANIDE-BASED TRANSFORMATIONS: DEVELOPMENT OF STEREOSELECTIVE UGI-TYPE REACTIONS. The design of new synthetic transformations that rapidly allow construction of structurally complex molecules from simple starting materials under both concepts of diversity and function-oriented syntheses is extremely desirable in contemporary organic chemistry. In this regard, multicomponent reactions (MCRs) appear as one of the most useful strategies for quickly generating structural diversity and molecular complexity. Among the vast repertoire of MCRs, isocyanide-based multicomponent reactions (IMCRs) stand out as a powerful approach to achieve highly functionalized molecules with elevated chemical efficiency, convergence and atom economy. As part of our ongoing interest in developing diastereoselective intramolecular I-MCRs based on chiral scaffolds, an efficient strategy has been established, which combines the stereocontrol of organocatalysis with the diversity-generating character of multicomponent reactions, leading to structurally unique cyclopentenyl frameworks containing two stereogenic centers. Based on our recent success into using hemiacetals in substrate-controlled I-MCR reactions, we have envisioned the development of an asymmetric Ugi-type Reaction with achiral hemiacetals using an organocatalytic Brønsted acid as the element of asymmetric induction. After a short screening of conditions, we found out that SPINOL-derived chiral phosphoric acids, especially with phenanthryl as substituent (59% yield, 66% ee), which was chosen as the best catalyst in this initial screening.

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1. Introduction

1.1. Multicomponent Reactions (MCRs)

The multicomponent reactions are defined as chemical reactions in which three or more components come together, in a single reaction vessel, to afford a new product that contains portions of all the components.[1]

These reactions can be categorized as domino processes, which are chemical transformations that comprise at least two consecutive reactions such that each subsequent reaction occurs only in virtue of the chemical functionality formed in the previous step. As a consequence of these features, it is possible to achieve complex chemical structures by employing these synthetic strategies, in a *one-pot* fashion.[2]

The first multicomponent reaction was reported by Strecker in 1850,[3] since then several other new transformations[4] of the kind were developed, some examples are presented in TABLE 1.1.

Among the advantages related to the use of these sustainable synthetic methodologies, there are the high atom economy,[5] multi-bond formation in one step, efficiency and mild conditions. Furthermore, these reactions are convergent and compatible with environmentally benign solvents. Hence, multicomponent reactions are interesting strategies as synthetic tools for the green chemistry point of view, due to its high atom economy, process efficiency, minimizing the overall

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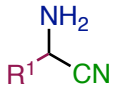
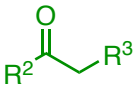
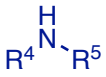
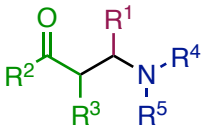
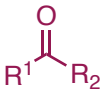
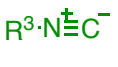
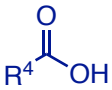
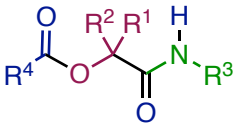
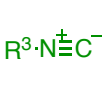
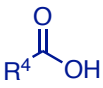
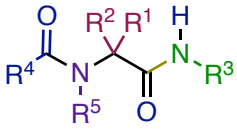
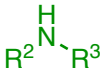
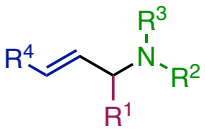
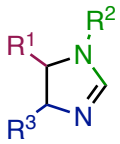
[1] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123.
[2] *(a)* T. J. J Müller, *Top. Heterocycl. Chem.*, 2010, **25**, 25; *(b)* B. Willy, T. J. J. Müller, *Curr. Org. Chem.*, 2009, **13**, 1777; *(c)* J. D. Sunderhaus, S. F. Martin, *Chem Eur. J.*, 2009, **15**, 1300; *(d)* B. B. Toure, D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; *(e)* N. Isambert, R. Lavilla, *Chem. Eur. J.*, 2008, **14**, 8444; *(f)* D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.*, 2007, **36**, 1095; *(g)* D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.*, 2007, **36**, 484.
[3] R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958.
[4] A. Strecker, *Justus Liebigs Ann. Chem.*, 1850, **75**, 27.
[5] B. M. Trost, *Angew. Chem. Int. Ed.*, 1995, **34**, 259.

synthetic steps, functional groups interconversion and avoiding the use of protecting groups.

TABLE 1.1 Highlighted examples of multicomponent reactions

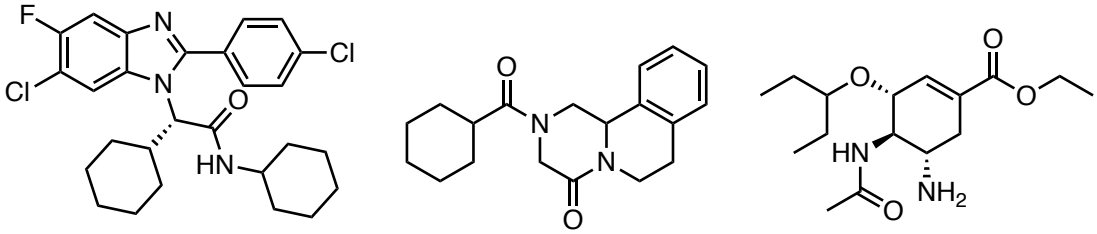
Reaction Year	Components			Product	Waste
Strecker 1850					H_2O
Mannich 1912					H_2O
Passerini 1921					-
Ugi 1959			 		H_2O
Petasis 1993					$B(OH)_3$
Orru 2003					H_2O

However, the biggest of advantage of this class of reactions is certainly the great diversity and structural complexity which is possible to achieve in one single synthetic step. This attribute enables the synthesis of libraries of small molecules in a short period of time, when compared to conventional multistep synthetic approaches.[6] This set of features make them very attractive tools in combinatorial

[6] *(a)* L. F. Tietze, U. Beifuss in Comprehensive organic synthesis. Selectivity, strategy, and efficiency in modern organic chemistry. (B. M. Trost, I. Fleming, Eds.) Pergamon Press, Oxford, England, 1991; (*b*) G. Jones in Organic reactions. John Wiley & Sons, Inc., Hoboken, NJ, 2011, Vol. 15, pp. 204–599.

and medicinal chemistry, as well in development of new materials and catalysts.[7] For these reasons, the pharmaceutical industry, where the rapid and easy access to large libraries of molecules – for biological activity studies – is top priority, has great interest in these transformations.

The importance of them can also be pointed out by increasing number of publications on this topic over the last decades.[8] Moreover, MCRs are also vital steps in the synthesis of some commercial drugs (FIGURE 1.1).[9]



Farnesoid X receptor agonist | Praziquantel | (-)-Oseltamivir

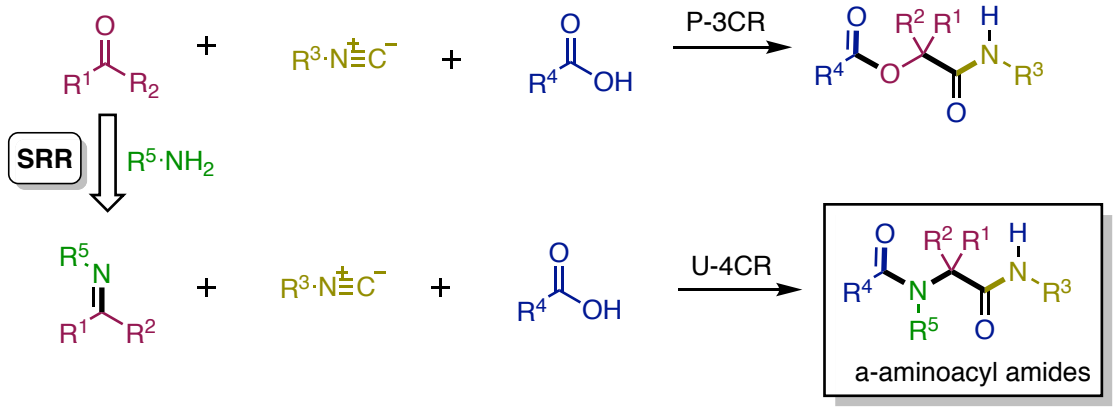
FIGURE 1.1 Examples of drugs synthetized using MCRs.

1.2. Ugi Reaction

The Ugi four-component reaction (U-4CR) was developed by Ivan Karl Ugi in 1959[10] by the substitution of a Single Reactant Replacement (SSR)[11] of the Passerini reaction (P-3CR), the first reported isocyanide-based multicomponent reaction.[12] By introducing a primary amine in the reaction, the aldehyde component was replaced by an *in situ* generated imine (SCHEME 1.1). Thus, this reaction consists in the combination of a carbonyl compound, a primary amine, a

[7] G. Van der Heijden, E. Ruijter, R. V. A. Orru, *Synlett,* 2013, **24**, 666.
[8] *(a)* Herrera, R.P.; Marqués-López, E. Multicomponent Reactions: concepts and applications for Design and synthesis. Eds.; Wiley- VCH: Weinheim, 2015; *(b)* H. Farhid, V. Khodkari, M. T. Nazeri, S. Javanbakhta and A. Shaabani, *Org. Biomol. Chem.*, 2021, **19**, 3318*; (c)* M. J. Buskes, A. Coffin, D. M. Troast, R. Stein, M.-J. Blanco, *ACS Med. Chem. Lett.*, 2023, **14**, 376..
[9] J. Kamalraja, D. Muralidharan, P. Perumal, *Synlett,* 2012, **23**, 2894.
[10] *(a)* I. Ugi, R. Meyr, U. Fetzer, and C. Steinbruckner, *Angew. Chem.*, 1959, **71**, 386; *(b)* I. Ugi and C. Steinbruckner, *Angew. Chem.*, 1960, **72**, 267-268; *(c)* I. Ugi, *Angew. Chem.*, 1962, **74**, 9.
[11] *(a)* B. Ganem, *Acc. Chem. Res.,* 2009, **42**, 463; *(b)* E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.*, 2011, **50**, 6234.
[12] M. Passerini and L. Simone, *Gazz. Chim. Ital.*, 1921, **51**, 126.

carboxylic acid and an isocyanide, rendering peptidomimetics molecules (*α*-aminoacyl amides). It is important to highlight here that just by this simple change, a new element of diversity was introduced in the reaction, thus enhancing the molecular complexity of the final product.



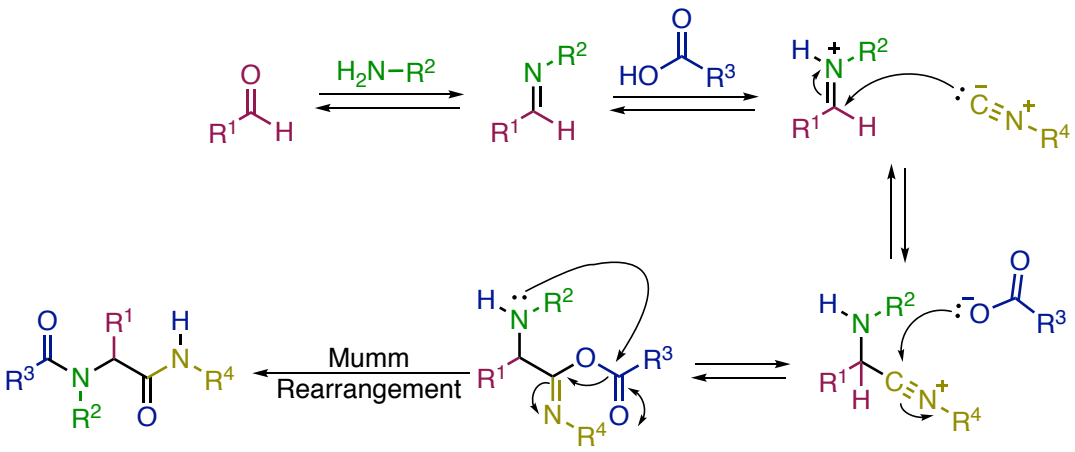
SCHEME 1.1 Development of the Ugi reaction (U-4CR).

The first and most relevant applications of the Ugi reaction were for peptide couplings and *α*-amino acids synthesis.[13] Inspired by this transformation, several research groups worked with much effort to develop new transformations to generate different classes of substances using this reaction as template, especially for the synthesis of heterocyclic molecules.[14]

Due to its great importance for combinatorial chemistry and in the search of new bioactive molecules,[15] there is a huge interest in fully understanding the mechanism of this multicomponent reaction.[16] In this context, Neto and co-workers employed ESI/MS-MS analysis to accumulate experimental insights

[13] *(a)* I. Ugi, *Rec. Chem. Prog.*, 1969, **30**, 289; *(b)* G. Dyker, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 1700.
[14] *(a)* I. Ugi, A. Domling and B. Werner, *J. Heterocycl. Chem.*, 2000, **37**, 647; *(b)* S. Nerdinger and B. Beck, Chemtracts, 2003, **16**, 233; *(c)* J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133.
[15] A. Domling, *Comb. Chem. High Throughput Screen.*, 1998, **1**, 1; *(b)* C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51.
[16] N. Chéron, R. Ramozzi, L. El Kaïm, L. Grimaud, P. Fleurat-Lessard, *J. Org. Chem.*, 2012, **77**, 1361.

regarding the mechanism.[17] This study exhibits two possible pathways for this reaction: differing from which component (the carboxylate or the isocyanide) is doing the nucleophilic attack to the iminium ion, formed after the protonation of the imine. According to the authors, the isocyanide acting as the nucleophilic species is more consistent with the experimental data by the detection of some key intermediates (SCHEME 1.2).

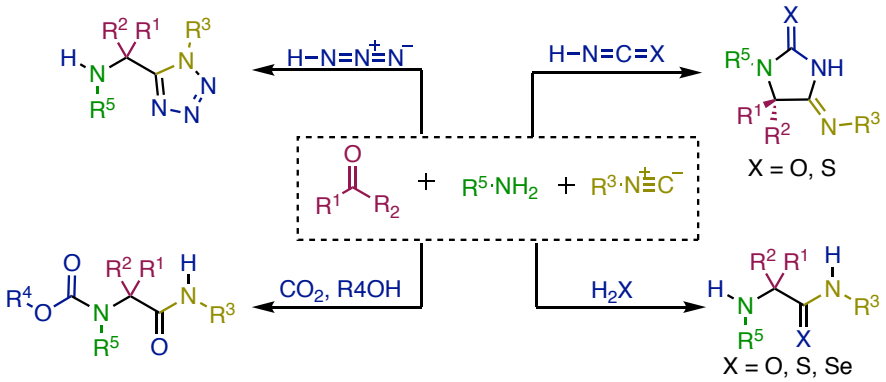


SCHEME 1.2 Proposed mechanism of the Ugi reaction.

1.2.1. Ugi-type Reactions

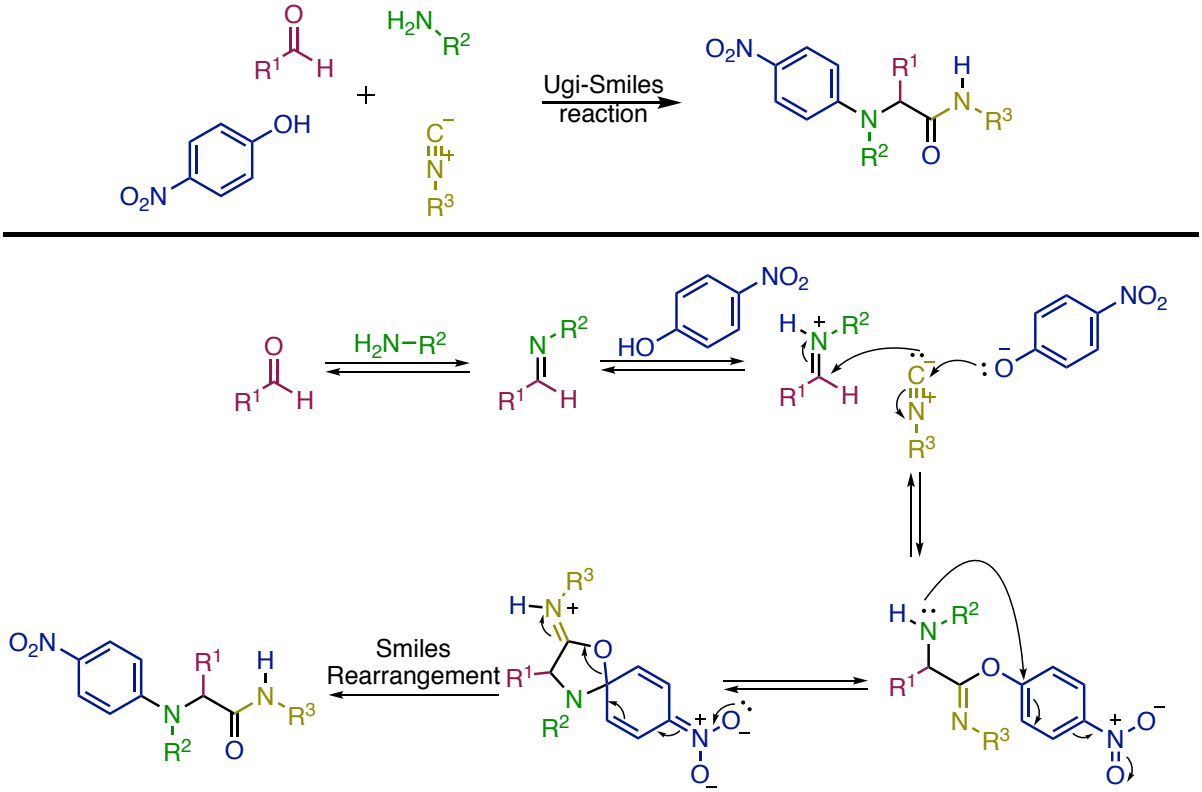
Several other variants of this reaction were developed since its creation, the majority of them by changing one of its components,[18] and by far the most common replaced reagent is the carboxylic acid by another acid component. This simple modification gave rise to the discovery of a big amount of new synthetic methods enabling the preparation of distinct class of molecules, some of those are shown below (SCHEME 1.3).

[17] G.A. Medeiros, W.A. da Silva, G.A. Bataglion, D.A.C. Ferreira, H.C.B. de Oliveira, M.N. Eberlin and B.A.D. Neto, *Chem. Commun.*, 2014, **50**, 338.
[18] Strategic Applications of Named Reactions in Organic Synthesis, L. Kurti and B. Czakó, Elsevier Academic Press, 2005.



SCHEME 1.3 Ugi reaction variants developed by the substitution of the acid component.

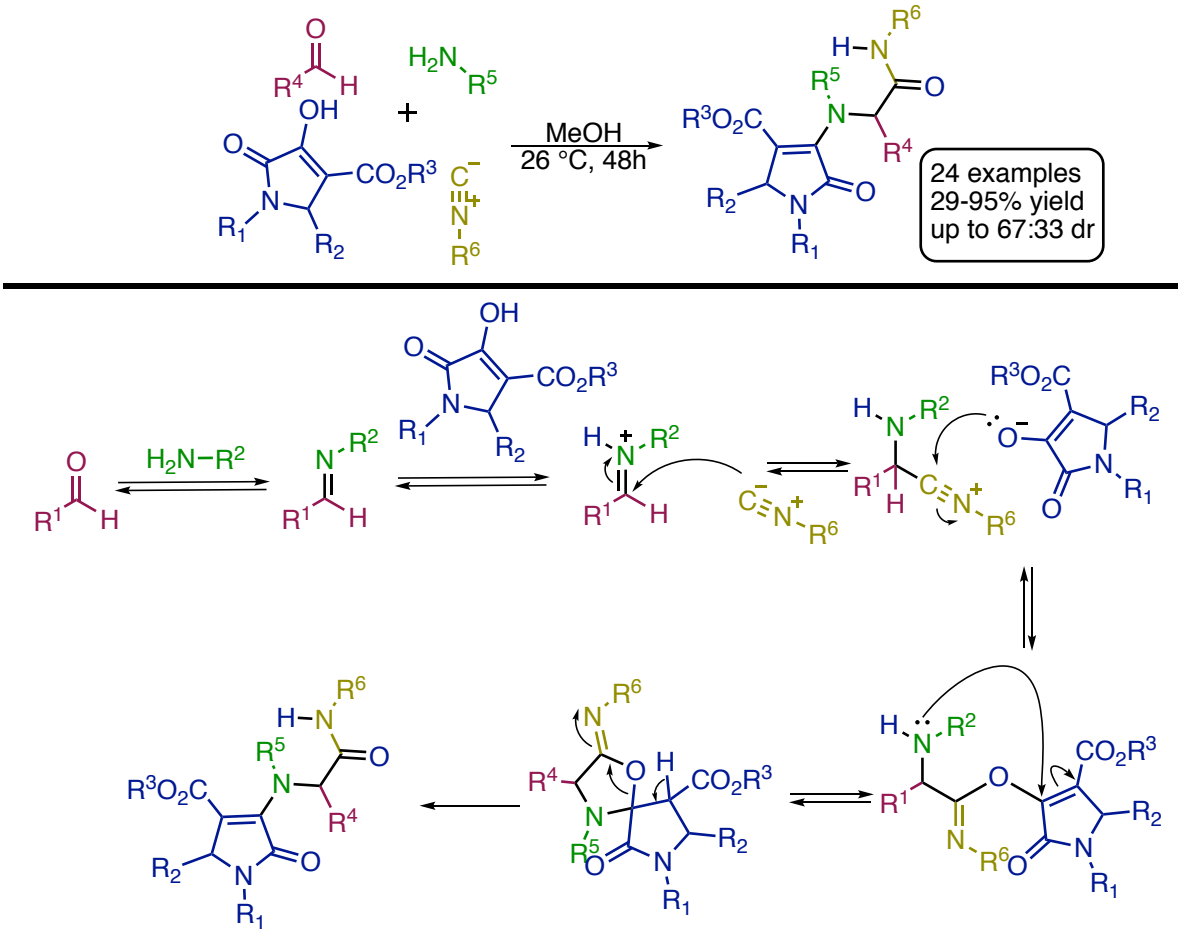
Even though all of those strategies are of great importance and have considerable impact to broaden the synthetic chemical space, one of them stands out, the reaction known as Ugi-Smiles reaction. [19] Through the substitution of the carboxylic of the classic method by a phenol bearing an electron-withdrawing group, El Kaïm and co-workers changed the last step of the mechanism, replacing the Mumm rearrangement for a Smiles rearrangement (SCHEME 1.4).



SCHEME 1.4 Proposed mechanism for the Ugi-Smiles reaction.

[19] L. El Kaim, L. Grimaud and J. Oble, *Angew. Chem. Int. Ed.*, 2005, **44**, 7961.

Following the same principle, an interesting proposal was also developed by Castellano *et al* (SCHEME 1.5).[20] In this case, the authors employed enolic pyrrolidine-2,3-diones as replacement for the acid, this proposal is based on the fact that enol compounds have similar pKa values to phenols,[21] making them acidic enough to protonated imines, and the corresponding enolates are more nucleophilic than carboxylates, allowing it to trap the nitrilium ion formed in this Ugi-type reaction.



SCHEME 1.5 Ugi-type reaction and its mechanistic proposal.

Through this modification, peptidomimetics pyrrolidine – a relevant pharmacophoric group found in natural and pharmaceutical products [22] –

[20] T. G. Castellano, A. G. Neo, S. Marcaccini and C. F. Marcos, *Org. Lett.*, 2012, **14**, 6218.
[21] N. H. Werstiuk, Andrew, D. *Can. J. Chem.*, 1990, **68**, 1467.
[22] *(a)* Thiel, P.; Kaiser, M.; Ottmann, C. *Angew. Chem., Int. Ed.*, 2012, **51**, 2012; (*b)* Rose, R.; Erdmann, S.; Bovens, S.; Wolf, A.; Rose, M.; Hennig, S.; Waldmann, H.; Ottmann, C. *Angew. Chem., Int. Ed.*, 2010, **49**, 4129; (*c)* Armisheva,M.; Kornienko, N.; Gein, V.; Vakhrin,M. *Russ.*

derivatives were prepared with six distinct elements of diversity (R^1-R^6, SCHEME 1.5).

The efficiency of this approach is directly correlated with the structure of the enol components. The conjugated system of the substrate allows the sequence of conjugated addiction/elimination/rearrangement to occur, plus it makes the *retro*-Michael step easier, turning it irreversible, a necessary condition of success on this class of multicomponent reactions.[23]

Albeit the huge applicability of the Ugi reaction and its variants in organic synthesis for the preparation of potential bioactive compounds and drug discovery,[13] the control of the stereochemical course is a challenge to be overcome.[24] In this regard, there are two main strategies to solve this issue: [25] (1) the use of enantioriched chiral starting materials in substrate-controlled reactions and (2) asymmetric induction with chiral catalysts, also known as asymmetric catalysis.

1.3. Diastereoselective Ugi Reactions

The most traditional asymmetry induction strategy in isocyanide-based multicomponent reactions is the use of enantioriched chiral starting materials. As a result of the success of asymmetric induction, then diastereoselective methods are achieved, which can be classified according to the source of the chirality.

1.3.1. Asymmetric Induction using *"chiral pool"*

J. Gen. Chem., 2011, **81**, 1893; (*d*) Jourdan, F.; Kaiser, J. T.; Lowe, D. J. *Synth. Commun.,* 2005, **35**, 2453.

[23] *(a)* L. El Kaim, M. Gizolme.; L. Grimaud, J. Oble *J. Org. Chem.*, 2007, **72**, 4169; (*b)* S. Marcaccini, G. Menchi, A. Trabocchi *Tetrahedron Lett.*, 2011, **52**, 2673.

[24] T. Godet, Y. Bonvin, G. Vincent, D. Merle, A. Thozet, M. Ciufolini, *Org. Lett.,* 2004, **6**, 3281.

[25] A. Dömling, *Chem. Rev.*, 2006, **106**, 17.

Natural products are largely employed as substrates in this sort of approach due to their abundance and easy availability, such as sugars, amino acids, terpenes, alkaloids.

In principle, this strategy can be used for any component of the reaction, nevertheless according to some experimental and theoretical considerations, the best results regarding asymmetric induction on the new stereocenter are obtained by using chiral amines, meanwhile low or no diastereoselectivity is observed for the other components of the Ugi reaction.[25]

Several reports exploit chiral amines to the development of diastereoselective Ugi reactions. Among them, the most successful examples are the ones employing 1-phenylethylamines,[26] α-ferrocenylethylamines[27] and amino sugar derivatives.[28]

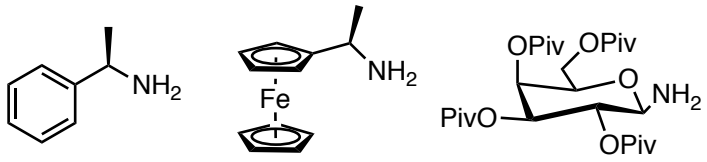
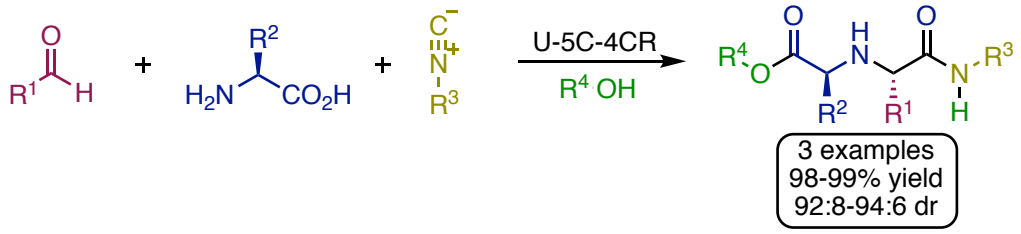


FIGURE 1.2 Examples of chiral amines used in diastereoselective Ugi reactions.

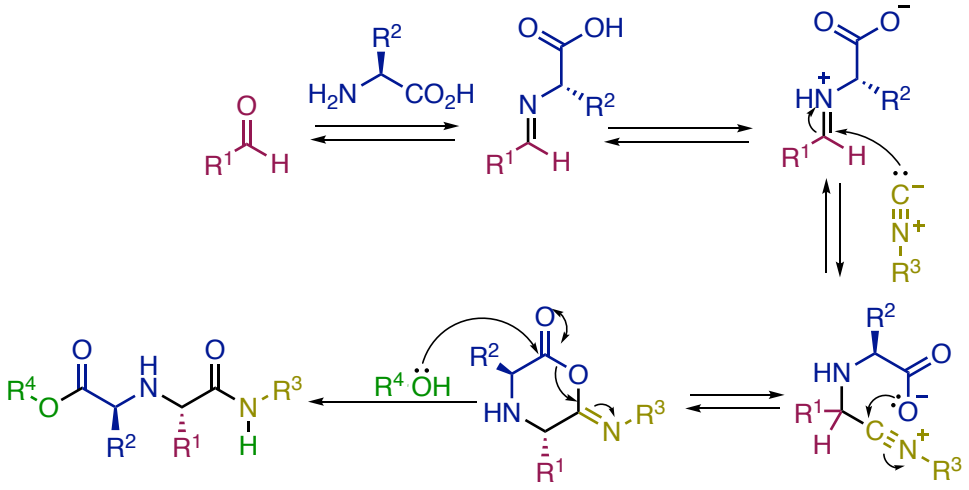
The main advantage associated with this approach is the direct use of a natural and abundant source of chirality, amino acids. In 1996, Ugi and collaborators employed α-amino acids as bifunctional reagents to develop the first Ugi-5-center-4-component reaction (U-5C-4CR) reaction to synthetize α,α'-iminodicarboxylic acid derivatives in excellent yields and diastereoselectivity (SCHEME 1.6).[29]

[26] I. Ugi and G. Kaufhold, *Justus Liebigs Ann. Chem.*, 1967, **709**, 11.
[27] D. Marquarding, P. Hoffmann, H. Heitzer and I. Ugi, *J. Am. Chem. Soc.*, 1970, **92**, 1969.
[28] H. Kunz and W. Pfrengle, *Tetrahedron*, 1988, **44**, 5487.
[29] A. Demharter, W. Hörl, E. Herdtweck and I. Ugi, *Angew. Chem. Int. Ed.*, 1996, **35**, 173.



SCHEME 1.6 First examples of Ugi-5-center-4-component reaction.

Regarding the mechanism of this reaction (SCHEME 1.7), there is first the formation of the imine between the aldehyde and the amine of the amino acid with subsequent nucleophilic attack of the isocyanide – expected to be on the opposite face of amino acid's substituent – followed by the intramolecular attack of the oxygen to the nitrilium ion to form an *O*-acyl amide. Then, an alcoholysis (the fourth component and fifth center of this reaction) of this cyclic intermediate takes place, which leads to a rearrangement to furnish the product of this transformation.



SCHEME 1.7 Proposed mechanism for the U-5C-4CR reaction.

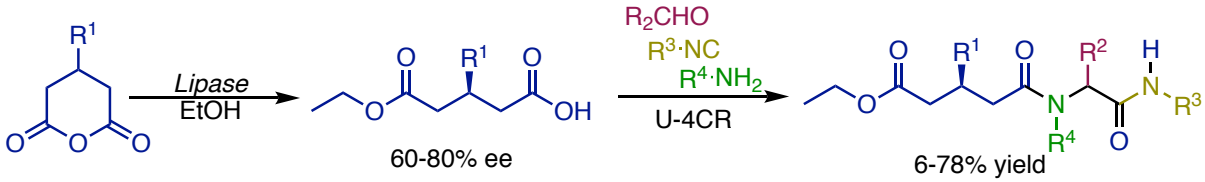
Following the good results obtained by the authors in this first work, this approach was actively applied in several different using α-amino acids,[30] and lately expanded to β-amino acids.[31]

[30] *(a)* I. Ugi, A. Demharter, W. Hörl and T. Schmid, *Tetrahedron*, 1996, **52**, 11657; *(b)* I. Ugi, W. Hörl, C. Hanusch-Kompa, T. Schmid and E. Herdtweck, *Heterocycles*, 1998, **47**, 965; *(c)* S. L. Sollis, *J. Org. Chem.*, 2005, **70**, 4735; *(d)* E. H. B. Silva, F. S. Emery, G. Del Ponte and P. M. Donate, *Synth. Commun.*, 2015, **45**, 1761.

[31] *(a)* A. Basso, L. Banfi, R. Riva and G. Guanti, *Tetrahedron Lett.*, 2004, **45**, 587; *(b)* A. Basso, L. Banfi, R. Riva and G. Guanti, *J. Org. Chem.*, 2005, **70**, 575.

1.3.2. Merging Biocatalysis with the Ugi Reaction

There are several research reports in the literature that exploits biocatalysis as a tool for deracemization, desymmetrization and resolution of organic molecules, therefore this application is well-known and explored.[32] However, the use of this enzymatic catalytic method in combination with a classic multcomponent reation was first reported in 2003 by Ostaszewski and co-workers.[33] In this work, the authors employed enantioriched glutaric monoesters, obtained by the desymmetrization of cyclic anhydrides, as the carboxylic acid component in the Ugi reaction (SCHEME 1.8).



SCHEME 1.8 Seminal work combining biocatalysis and the Ugi reaction.

Enantioriched carbonyl compounds can be easily synthetized by the enzymatic desymmetrization with lipase. However, due to the low stereocontrol that these aldehydes display in these reactions, only intramolecular variants of the Ugi reaction have shown more promising results. [34]

Another important variant of this reaction is the so-called Ugi-Jóullie reaction (SCHEME 1.9). In this approach, the imine is obtained either by combining the aldehyde and the amine in the same molecule, the or oxidation of a cyclic amine. Due to the rigid structure of these cyclic imines, higher level of stereochemical control is usually observed in this variant. [35]

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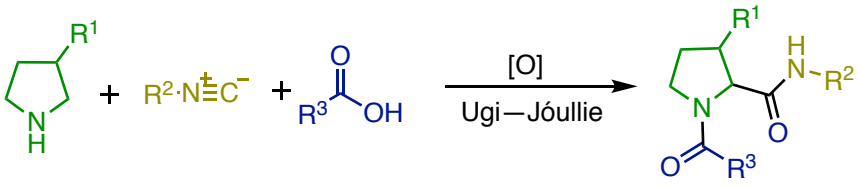
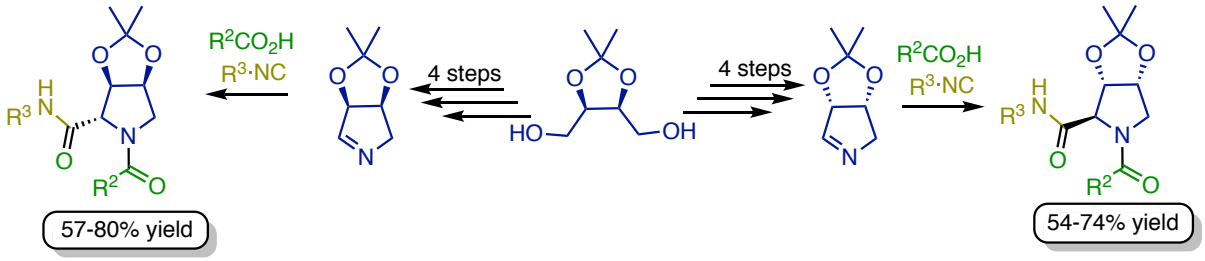
[32] *(a)* C. J. Dunsmore, R. Carr, T. Fleming and N. J. Turner, *J. Am. Chem. Soc.*, 2006, **128**, 2224; *(b)* H. Pellissier, *Tetrahedron*, 2003, **59**, 8291; *(c)* J. H. Schrittwieser and V. Resch, *RSC Adv.*, 2013, **3**, 17602.
[33] *(a)* R. Ostaszewski, D. E. Portlock, A. Fryszkowska and K. Jeziorska, *Pure Appl. Chem.*, 2003, **75**, 413; *(b)* A. Fryszkowska, J. Frelek and R. Ostaszewski, *Tetrahedron*, 2005, **61**, 6064.
[34] L. Banfi, A. Basso, L. Moni and R. Riva, *Eur. J. Org. Chem.*, 2014, 2005.
[35] R. F. Nutt and M. M. Joullié, *J. Am. Chem. Soc.*, 1982, **104**, 5852.



SCHEME 1.9 Ugi-Jóullie reaction.

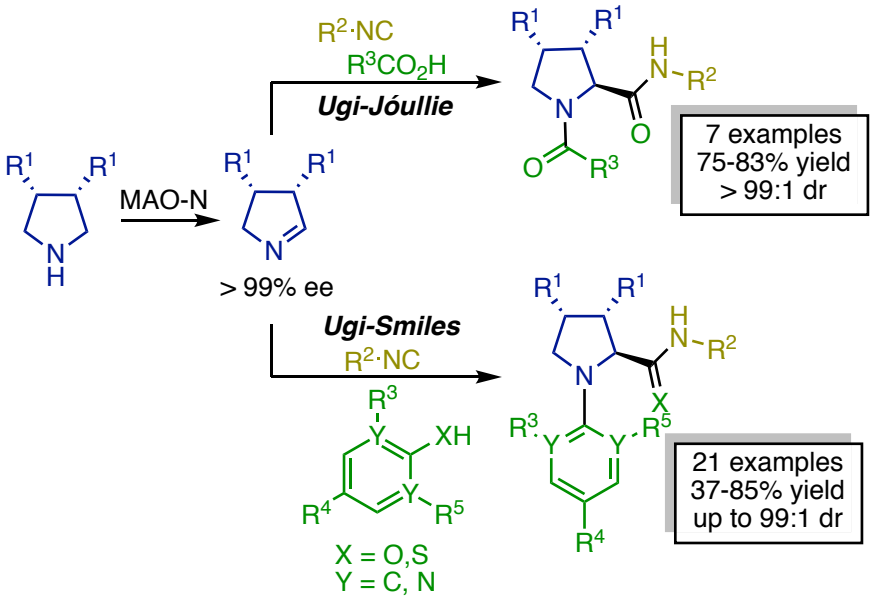
In this regard, Banfi and co-workers [36] envisioned the stereoselective synthesis of pyrrodilines starting from the desymmetrization of diols with lipase (SCHEME 1.10). These compounds showed promising reactivity towards the Ugi-Jóullie, affording both enantiomers in good yields.



SCHEME 1.10 Stereoselective Ugi-Jóullie developed by Banfi *et al.*

Other remarkable work in this field was reported by Orru and Turner,[37] in which pyrrolines, generated via the oxidation of pyrrolidines with the enzyme monoamine oxidase (MAO-N), are employed as substrates in both Ugi-Jóullie[37b] and Ugi-Smiles[38] reactions (SCHEME 1.11).

[36] V. Cerulli, L. Banfi, A. Basso, V. Rocca and R. Riva, *Org. Biomol. Chem.*, 2012, **10**, 1255.
[37] *(a)* V. Köhler, K. R. Bailey, A. Znabet, J. Raftery, M. Helliwell and N. J. Turner, *Angew. Chem. Int. Ed.*, 2010, **49**, 2182; *(b)* A. Znabet, E. Ruijter, F. J. J. de Kanter, V. Köhler, M. Helliwell, N. J. Turner and R. V. A. Orru, *Angew. Chem. Int. Ed.*, 2010, **49**, 5289.
[38] A. Znabet, S. Blanken, E. Janssen, F. J. J. de Kanter, M. Helliwell, N. J. Turner, E. Ruijter, R. V. A. Orru, *Org. Biomol. Chem.*, 2012, **10**, 941.



SCHEME 1.11 Asymmetric synthesis of proline derivatives via MAO-N oxidation and Ugi reactions.

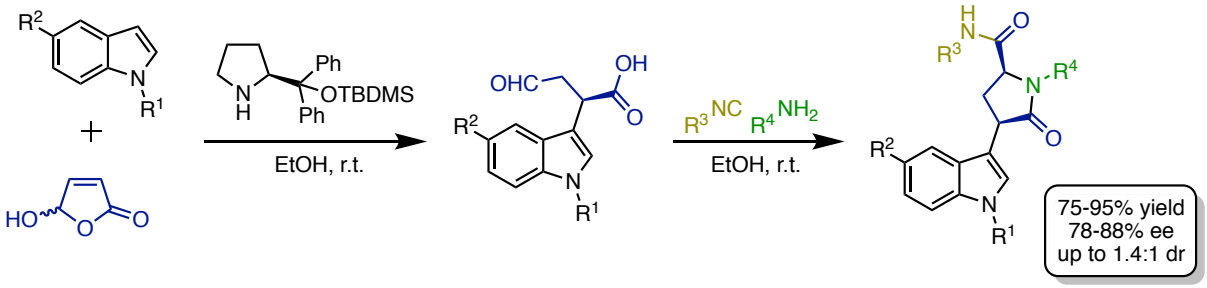
Taking into consideration the number of synthetic steps, it is clear to note the evolution of this strategy compared to the previous one. On the other hand, it is important to mention that through this approach only one of the enantiomers can be synthetized, while the former provides both of the enantiomers in a stereodivergent fashion.

1.3.3. Combination between Organocatalysis and the Ugi Reaction

Organocatalysis also emerges as a powerful strategy for the preparation of enantioriched chiral substrates. In this context, there are a variety of available protocols in the literature showing the enantioselective functionalization, in both α- and β-positions via organocatalytic methods, of aldehydes, which are rather interesting starting materials for multicomponent reactions.[34]

An example of this approach is depicted in the scheme below (SCHEME 1.12), in which the synthesis of pyrrolidinones were synthetized through a

combination of an organocatalytic Friedel-Crafts reaction and a Ugi-4-center-3-component reaction (U-4C-3CR), reported by Riguet.[39]

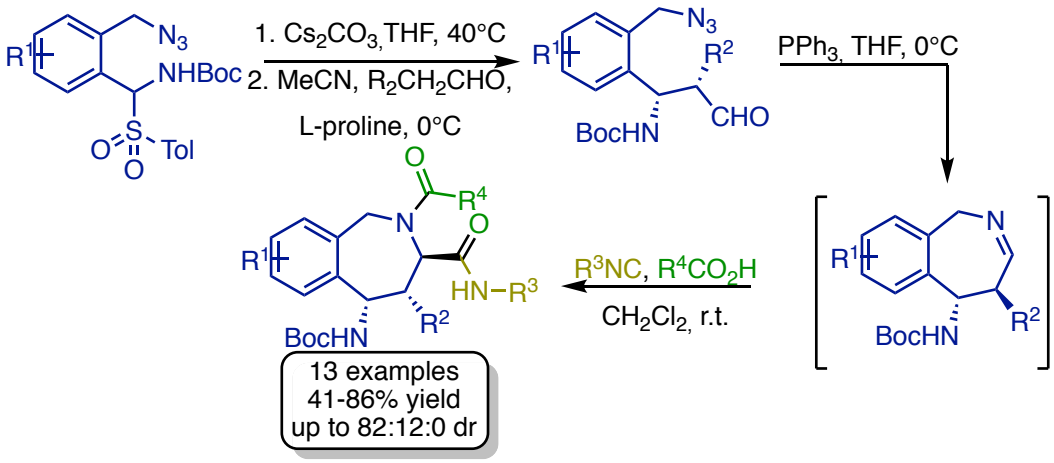


SCHEME 1.12 Pyrrolidinones synthesis via *Friedel-Crafts/Ugi reaction.*

Unfortunately, there was almost no control over the stereochemical course of this transformation, however it shows that combination between organocatalysis and multicomponent is feasible and has potential, whereas the organocatalytic step introduces chirality to the molecule, followed by the Ugi-type reaction, which enhances the molecular diversity and complexity of the final product.

Banfi and co-workers have also contributed to this area by developing the stereoselective synthesis of 2-benzodiazepines with good stereocontrol. Their synthetic route comprehends a sequence of organocatalytic Mannich reaction followed by a Staudinger aza-Wittig (SAW)–Ugi–Joullié reaction.[40]

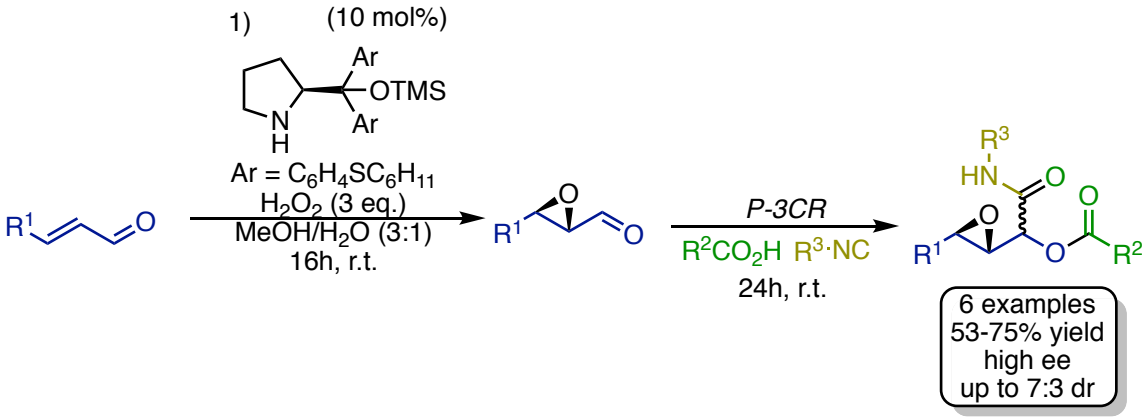
[39] E. Riguet, *J. Org. Chem.*, 2011, **76**, 8143.
[40] L. Moni, A. Basso, L. Banfi, A. Galatini, M. Spallarossa, R. Riva, *J. Org. Chem.,* 2014, **79**, 339.



SCHEME 1.13 Synthesis of 2-benzodiazepines via organocatalytic Mannich–SAW–Ugi–Joullié sequence.

The good diastereo- and enantioselectivity exhibited in this work, and also the diversity of compounds synthetized, are promising results that strengthen the idea of how powerful can be the combination of organocatalysis and multicomponent reactions.

Over the last 10 years, our research group has been using this combination to the diastereoselective synthesis of highly functionalized products. The first report reported in this concern was a sequential methodology that combines an asymmetric epoxidation of *α,β*-unsaturated aldehydes followed by the classic Passerini three-component reaction (SCHEME 1.14).[41]

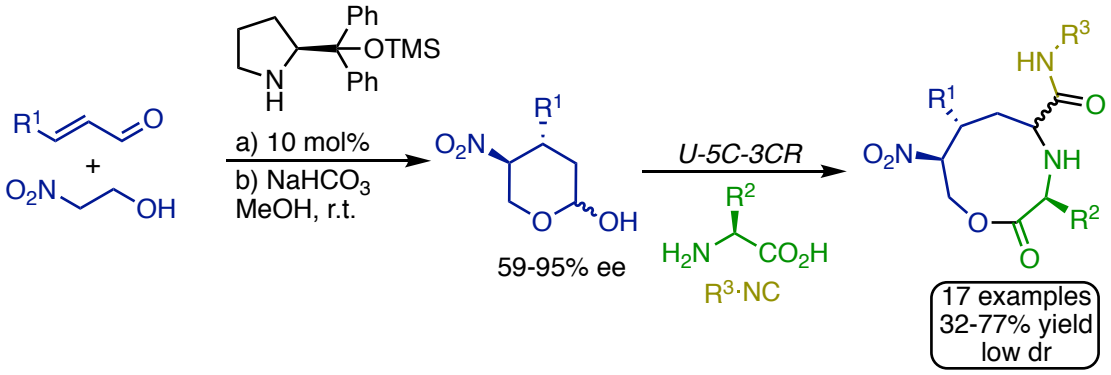


SCHEME 1.14 Sequential organocatalytic asymmetric epoxidation/Passerini reaction.

[41] A. M. Deobald, A. G. Corrêa, D. G. Rivera, M. W. Paixão, *Org. Biomol. Chem.*, 2012, **10**, 7681.

As an attempt of improve the diastereoselectivity of these transformations our group envisioned hemiacetals could solve these issues by the formation of rigid cyclic intermediate capable of enhance the facial selectivity by constraining the possible number of conformations during the isocyanide nucleophilic attack.

Our first work in this regard is shown below, in which De La Torre *et al.*[42] combined the organocatalyzed conjugated addition of 2-nitroethanol to *α,β*-unsaturated aldehydes to form the hemiacetal employed in the Ugi-5C-3CR multicomponent reaction (SCHEME 1.15).



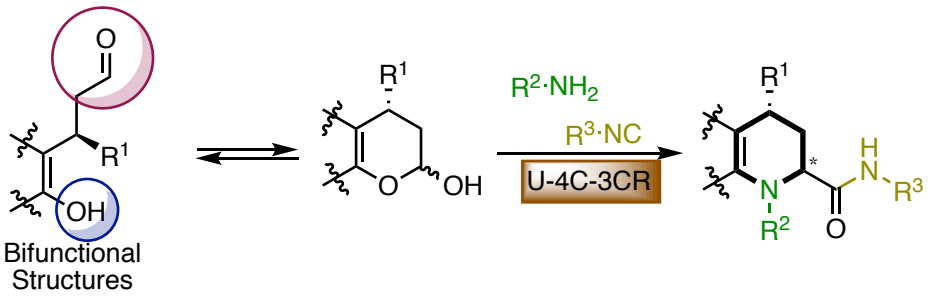
SCHEME 1.15 Our seminal work on the use of hemiacetals in substrate-controlled reactions.

This approach enabled the preparation of cyclic depsipeptides mimics in moderate to good yields. Although the method failed in terms of diastereoselectivity, the protocol was efficient as synthetic tool for the generation of molecular complexity. Furthermore, it is important to mention that three stereocenters were created in the course of this synthetic procedure with high atom economy.

Inspired by these initial results, our research group has been developing stetereoselective variants of isocyanide-based multicomponent reactions over the last decade.[43] Using asymmetric organocatalysis to generate enantioriched hemiacetals as bifunctional structures (both the acid and carbonyl component),

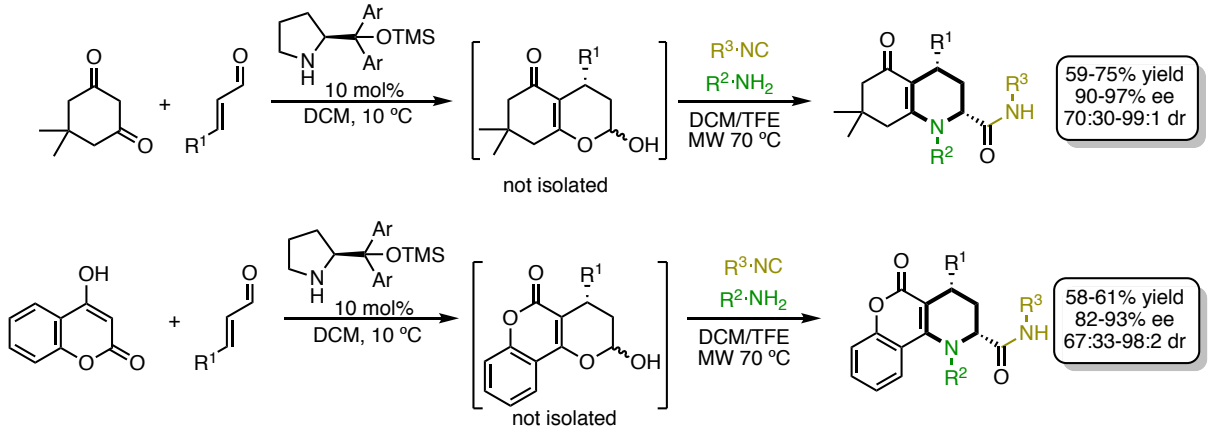
[42] A. F. de la Torre, D. G. Rivera, O. Concepción, R. Echemendia, A. G. Correa, M. W. Paixão, *J. Org. Chem.*, 2016, **81**, 803.
[43] D. G. Rivera and M. W. Paixão, *ACS Symposium Series*, 2017, **1258**, 49.

different *N*-heterocycles were prepared via Ugi-4-center-3-component reactions (SCHEME 1.16), which will be presented in more detail below.



SCHEME 1.16 Hemiacetals in diastereoselective U-4C-3CR reactions.

In 2015, our group developed a highly stereoselective approach for the one-pot synthesis of complex natural product hybrids incorporating fragments of hydroquinolines, chromenes, peptides, glycosides, and lipids (SCHEME 1.17).[44] A organocatalytic Michael addition between α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds produces the hemiacetal that is readily used in the multicomponent step, in this case an Ugi-4-center-3-component reaction.

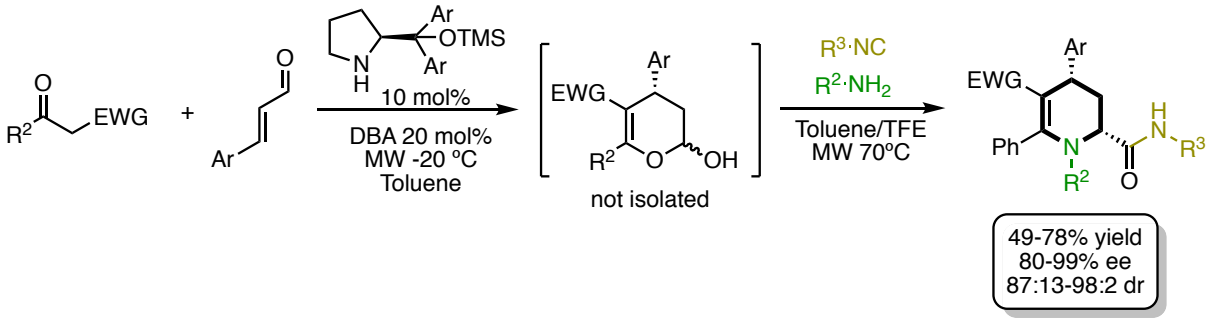


SCHEME 1.17 Natural product-like hybrids via Organocatalysis/U-4C-3CR.

Overall, there is a linkage of the four components to render complex natural product-like structures in good yields and excellent diastereoselectivity, proving the potential of cyclic hemiacetals in the stereocontrol of this sort of Ugi-type reaction.

[44] R. Echemendía, A.F. de la Torre, J.L. Monteiro, M. Pila, A.G. Corrêa, B. Westermann, D.G. Rivera, M.W. Paixão, *Angew. Chem. Int. Ed.*, 2015, **54**, 7621.

A few years later, our group have shown that a similar strategy can be used to the synthesis of complex pentasubstituted tetrahydropyridines in high enantio- and diastereoselectivity (SCHEME 1.18).[45]

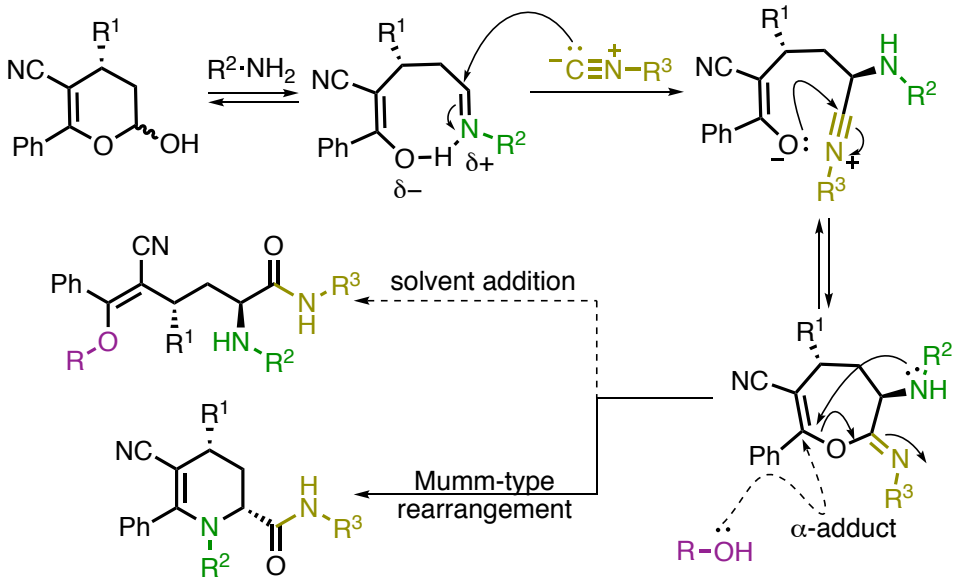


SCHEME 1.18 Stereoselective organocascade/MCR to the synthesis of THPs.

In this work, the authors have performed a deep mechanistic investigation to elucidate the features governing the excellent diastereodiscrimination of the process. According to DFT calculations, during diastereoselectivity-determining step, non-convalent interactions between the isocyanide and the conjugated enol π-system lead the nucleophilic attack via the most sterically crowded face of the imine intermediate. Also, the intramolecular hydrogen-bond formed by the imine and the enol contributes to the stereocontrol, through the formation of a rigid cyclic conformation.

As shown in SCHEME 1.17 and SCHEME 1.18, 2,2,2-trifluoromethylethanol (TFE) was the solvent of choice for both methodologies. During the screening of reaction conditions, the authors observed that other polar protic solvents (crucial for the success of Ugi and Ugi-type reactions),[11b] such as ethanol and methanol, act as reactant by opening the α-adduct and, thus, delivering an acyclic byproduct (SCHEME 1.19). In such cases, TFE had to be used as a solution for this issue, due to its less nucleophilic nature.

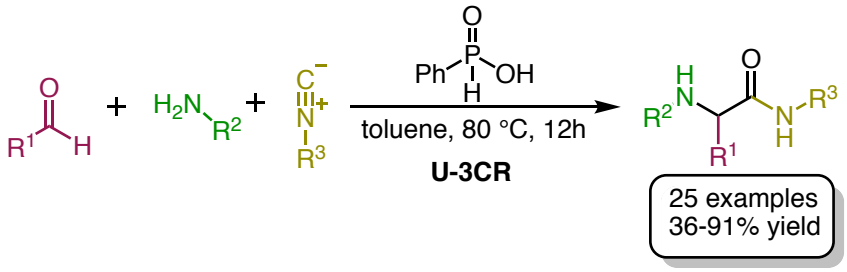
[45] R. Echemendía, G. P. da Silva, M. Y. Kawamura, A. F. de la Torre, A. G. Corrêa, M. A. B. Ferreira, D. G. Rivera, M. W. Paixão, *Chemm. Comm*, 2019, **55**, 286.



SCHEME 1.19 Proposed mechanism for the product and byproduct formation.

1.4. Enantioselective Ugi Reactions

One of the first Ugi catalyzed reactions was developed by List group in 2008, the authors described an Ugi three-component reaction (U-3CR)[46] using a phosphinic acid as a Brønsted acid organocatalyst (SCHEME 1.20).[47]



SCHEME 1.20 Organocatalyzed U-3CR by List and co-workers.

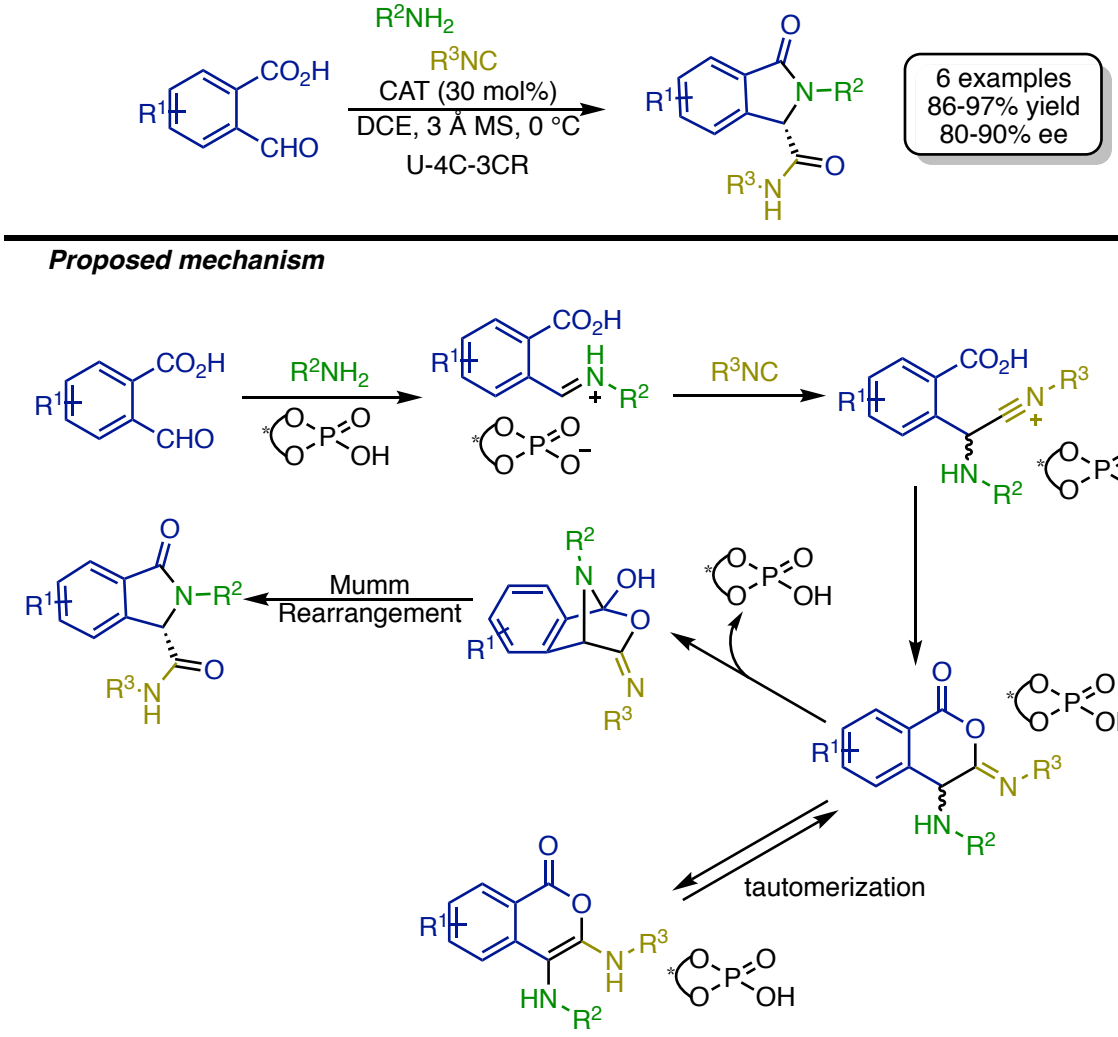
Even though this report presented excellent results in terms of reactivity, its attempt to achieve an enantioselective variant of this transformation shows only low yield and enantioselectivity (15% yield and 18% ee with TRIP as the catalyst). This seminal experiment demonstrates how challenge it is to achieve

[46] J. C. Flores-Reyes, A. Islas-Jácome, E. González-Zamora, *Org. Chem. Front.*, 2021, **8**, 5460. J. C. Flores-Reyes, A. Islas-Jácome, E. González-Zamora, *Org. Chem. Front.*, 2021, **8**, 5460.
[47] S.C. Pan, B. List, *Angew. Chem. Int. Ed.*, 2008, **47**, 3622.

high enantioselectivity in such reaction. In order to fulfill this task, some issues need to be properly handled: (a) avoidance of the uncatalyzed racemic background reaction; (b) succeed in the stereocontrol in the addition of isocyanides to the imine.

In this context, asymmetric Brønsted acid catalysis is a privileged activation mode and there a few successful examples of enantioselective Brønsted acid-catalyzed Ugi-type reactions.[48] A significant breakthrough was described by Wang, Zhu and co-workers, in which the authors have developed a chiral phosphoric acid-catalyzed U-4C-3CR with isocyanides, anilines and 2-formyl benzoic acids (SCHEME 1.21).[49]

[48] Q. Wang, D.-X. Wang, M.-X. Wang, J. Zhu, *Acc. Chem. Res.*, 2018, **51**, 1290.
[49] Y. Zhang, Y.-F. Ao, Z.-T. Huang, D.-X. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.*, 2016, **55**, 5282.

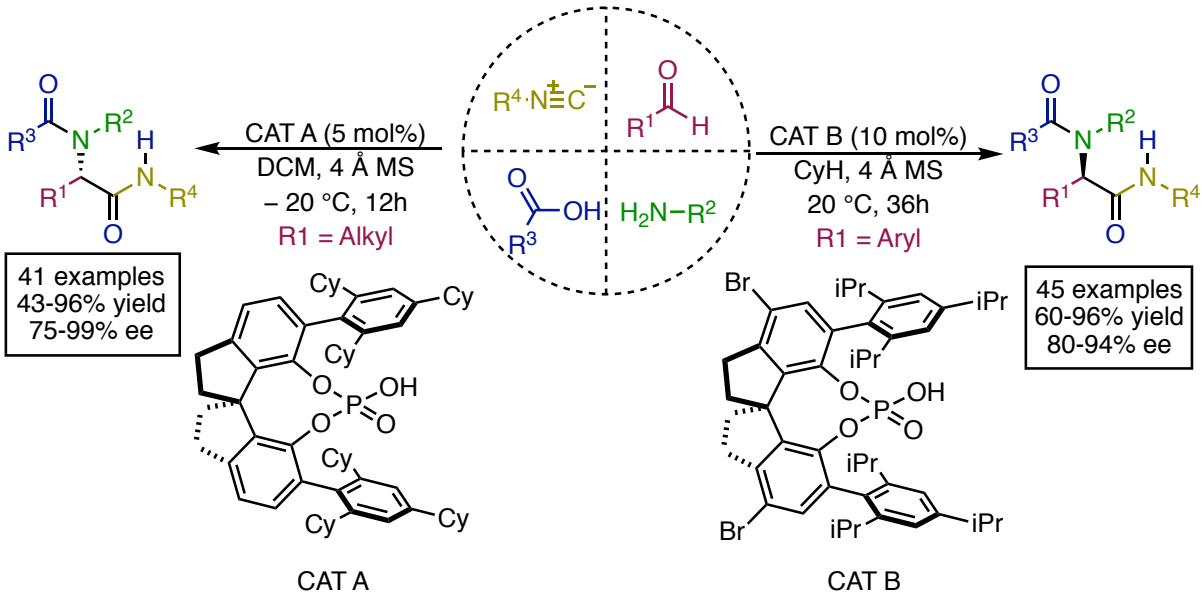


SCHEME 1.21 CPA catalyzed U-4C-3CR by Zhu and co-workers.

After conducting a series of control experiments, they proposed that the mechanism proceeds through an unusual pathway, where the enantioselectivity of the process is a result of a dynamic kinetic resolution (DKR) rather than the C-C bond formation: the imine-enamine tautomerization of the intermediate is faster than the Mumm rearrangement step, therefore the asymmetric protonation of the enamine determines the absolute configuration of the corresponding product. It is also important to highlight that this is the first example of an asymmetric Ugi reaction using carboxylic acid as one of the components.

A few years ago, Houk, Tan and coworkers described the first enantioselective Ugi four-component reaction, rendering α-acylaminoamides by combining the traditional starting materials in a one-pot reaction (SCHEME

1.22).[50] In this report, around 90 examples were prepared in good to excellent enantioselectivity by using two SPINOL-based phosphoric acid derivatives as Brønsted acid organocatalysts, depending on the type of the aldehyde involved in the reaction (alkyl or aryl).

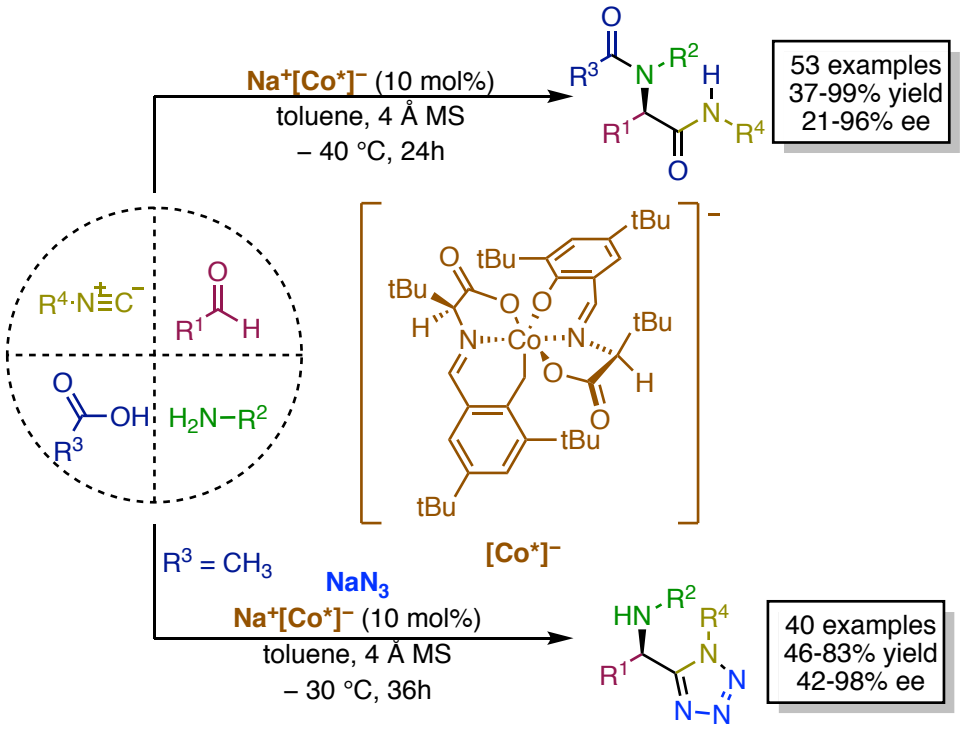


SCHEME 1.22 First enantioselective U-4CR.

This work is an outstanding contribution to the field, providing a simple and efficient method to obtain enantioriched *α*-acylaminoamides that are otherwise hard to synthetize through standard synthetic procedures.

Recently, Cao, Yu and co-workers reported an anionic stereogenic-at-cobalt(III) complexes catalysis strategies for enantioselective Ugi reactions in good to excellent results, including both the classic U-4CR and Ugi-azide reaction (SCHEME 1.23).[51] The anionic catalyst is responsible for the stereocontrol of this protocol by forming an ion pair with the protonated iminium and blocking the *Re*-face while leaving the *Si*-face to the nucleophilic attack of the isocyanide.

[50] J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. Wang, K. N. Houk, B. Tan, *Science*, 2018, **361**, 1087.
[51] B.-B. Sun., K. Liu, Q. Gao, W. Fang, S. Lu, C.-R. Wang, C.-Z. Yao, H.-Q. Cao & J. Yu, *Nat Commun*, 2022, **13**, 7065.



SCHEME 1.23 Transition metal catalyzed Ugi and Ugi-tetrazole reactions.

The key feature of this approach is that a common intermediate – the transient chiral nitrilium ion – is trapped with different terminating agents (carboxylate or azide) to render distinct classes of products under slightly modified reaction conditions using the same catalyst, demonstrating that this procedure has potential to be used as a general method for enantioselective Ugi reaction and its variants.

2. Objectives

The main goals of this work were to exploit the asymmetric induction in isocyanide-based transformations, especially Ugi and Ugi-type reactions.

First, the exploration of hemiacetals in substrate-controlled multicomponent reactions and their influence in the diastereosselctive course of the reaction. In this context, cyclic hemiacetals were synthetized through an asymmetric organocatalyzed method and submitted under similar conditions to a Ugi-4-center-3-component reaction.

In a second moment, chiral phosphoric acid catalysts were evaluated as key element to control the enantioselectivity in U-4C-3CR using achiral hemiacetals as bifunctional substrates, aiming the synthesis of enantioriched *N*-heterocycles.

3. Results and discussion

3.1. Stereoselective Synthesis of Cyclopentenes

3.1.1. Conventional Synthetic Methods

Due to the predominance of polysubstituted cyclopentene and cyclopentane skeletons in bioactive compounds, several strategies have been developed for the stereoselective synthesis of such functionalized rings.

Amongst the numerous methodologies for the synthesis of functionalized cyclopentenes, the phosphine-catalyzed (3 + 2) annulation of allenoates with electron-deficient olefins, first reported by Lu and co-workers in 1995,[52] stands out as the most explored strategy.[53] Therefore, there are several phosphine (3 + 2) annulation methodologies in the literature, including their asymmetric variants.[54] Recently, Lu's group described a phosphine-catalyzed (3 + 2) annulation of electron-poor allenes with activated alkenes for the construction of functionalized cyclopentenes bearing quaternary centers[55] (SCHEME 3.1).

By using a dipeptide multifunctional phosphine catalyst, the authors were successful in controlling both the regio- and stereochemistry of this reaction, affording the functionalized cyclopentenes in high yields. Albeit the reaction displays high efficiency regardless of the substrates' structures, the stereoselectivity of the process is highly substrate dependent. It is necessary to use acrylates with bulky aryl groups as substituents (R^1 and R^2), any aliphatic chain would drop the enantiomeric excess, this trend was reported by the authors during screening of the conditions, furthermore when R^1 = Bn, there was a tremendous erosion on the enantioselectivity (68% ee) of the reaction.

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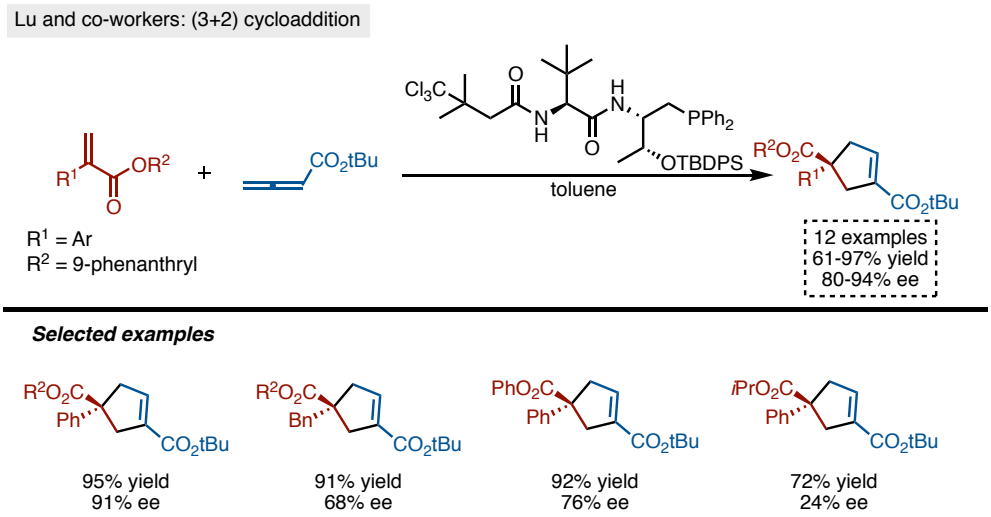
[52] C. Zhang, X. Lu, *J. Org. Chem.*, 1995, **60**, 2906.
[53] Y. Wei, M. Shi, *Org. Chem. Front.*, 2017, **4**, 1876..
[54] S. J. Chen, G. S. Chen, J. W. Zhang, Z. D. Li, Y. L. Zhao, Y. L. Liu, *Org. Chem. Front.*, 2020, **7**, 3399.
[55] X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.*, 2011, **133**, 1726.

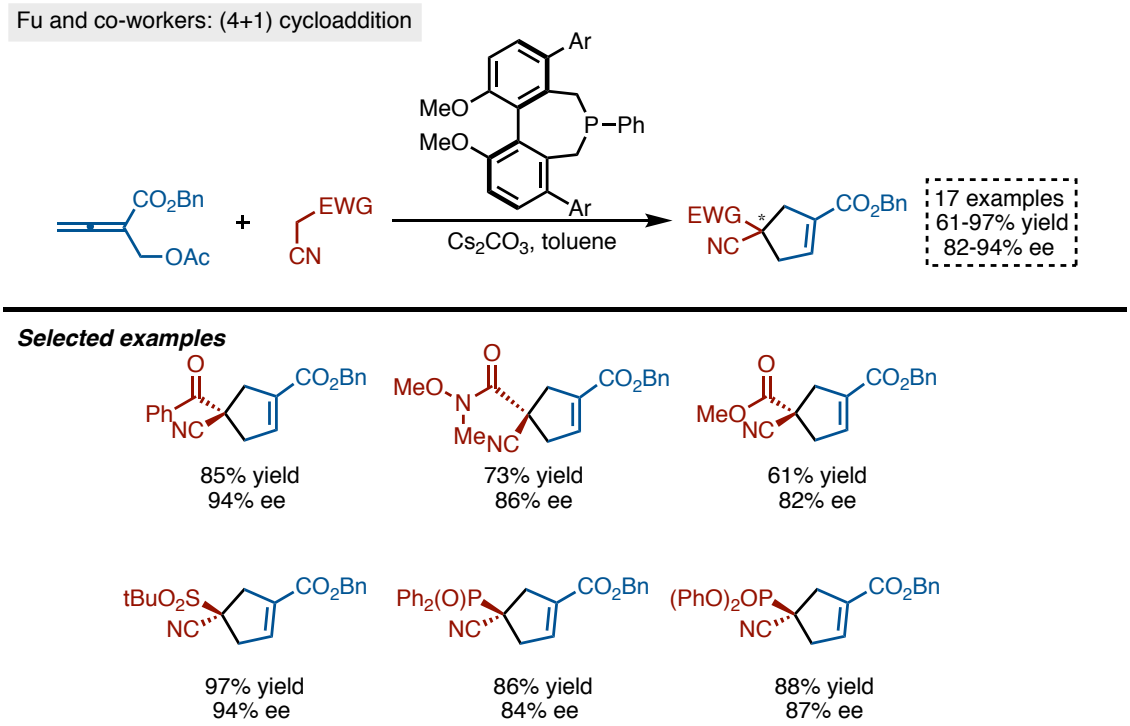


SCHEME 3.1 Enantioselective synthesis of cyclopentenes through (3+2) cycloaddition by Lu and co-workers.

Besides, Fu,[56] Lu,[57,58] Miller[59] and others[60] subsequently developed and expanded the scope of the enantioselective intramolecular formal (3 + 2) cycloaddition between allenoates and activated alkenes to create fused chiral ring scaffolds. Moreover, distinct formal (3 + 2) cycloadditions which have also been useful for the construction of enantioenriched cyclopentene derivatives employed N-heterocyclic carbene (NHC)-catalyzed reactions,[61,62,63] metal carbenoids,[64] and the ring opening of cyclopropanes.[65,66,67]

[56] J. E. Wilson, G. C. Fu, *Angew. Chem., Int. Ed.*, 2006, **45**, 1426.
J. E. Wilson, G. C. Fu, *Angew. Chem., Int. Ed.*, 2006, **45**, 1426.
[57] F. Zhong, X. Han, Y. Wang and Y. Lu, *Angew. Chem., Int. Ed.*, 2011, **50**, 7837.
[58] F. Zhong, G.-Y. Chen, X. Han, W. Yao, Y. Lu, *Org. Lett.*, 2012, **14**, 3764.
[59] B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.*, 2007, **129**, 10988.
[60] H. Ni, W.-L. Chan, Y. Lu, *Chem. Rev.*, 2018, **118**, 9344.
[61] S. Mondal, S. R. Yetra, A. Patra, S. S. Kunte, R. G. Gonnade, A. T. Biju, *Chem. Commun.*, 2014, **50**, 14539.
[62] L. R. Domingo, R. J. Zaragozá, M. Arnó, *Org. Biomol. Chem.*, 2010, **8**, 4884.
[63] B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.*, 2010, **132**, 5345.
[64] H. M. L. Davies, B. Xiang, N. Kong, D. G. Stafford, *J. Am. Chem. Soc.*, 2001, **123**, 7461.
[65] J. Luis-Barrera, V. Laina-Martín, T. Rigotti, F. Peccati, X. Solans-Monfort, M. Sodupe, R. Mas-Ballesté, M. Liras, J. Alemán, *Angew. Chem., Int. Ed.*, 2017, **56**, 7826.
[66] F. J. Sarabia, Q. Li, E. M. Ferreira, *Angew. Chem., Int. Ed.*, 2018, **57**, 11015.
[67] X. Y. Tang. M. Shi, *J. Org. Chem.*, 2010, **75**, 902.

Although less explored, formal (4 + 1) cycloaddition is also a suitable strategy and, according to recent literature,[68,69,70]phosphine[71] and metal catalysis[72] are versatile and powerful approaches for the construction of these five membered ring systems. In 2014, Fu and co-workers disclosed a biphenyl phosphine-catalyzed enantioselective (4 + 1) annulation of allenoates with Michael donors (SCHEME 3.2).[73]

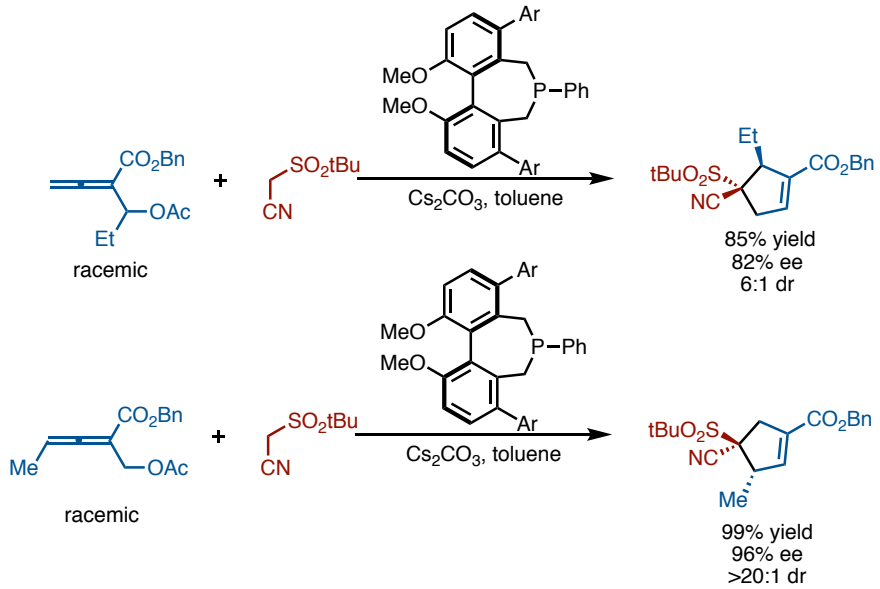


SCHEME 3.2 Asymmetric synthesis of cyclopentenes via enantioselective (4+1) cycloaddition by Fu and co-workers.

This method enables the synthesis of functionalized cyclopentenes with good enantioselectivities and yields. Even though no modification on the allenoates were reported by the authors, a broad scope of Michael donors can be used, such as α-cyano ketones, amides (including Weinreb amide), esters,

[68] H. Zhang and R. Zhou, *Eur. J. Org Chem.*, 2020, **2020**, 4098.
[69] J. R. Chen, X. Q. Hu, L. Q. Lu and W. J. Xiao, *Chem. Rev.*, 2015, **115**, 5301.
[70] X. Tang, H. Ni and Y. Lu, *Org. Chem. Front.*, 2021, **8**, 4485.
[71] R. L. Danheiser, C. Martinez-Davila, R. J. Auchus and J. T. Kadonaga, *J. Am. Chem. Soc.*, 1981, **103**, 2443.
[72] M. J. Behlen and C. Uyeda, *J. Am. Chem. Soc.*, 2020, **142**, 17294.
[73] D. T. Ziegler, L. Riesgo, T. Ikeda, Y. Fujiwara and G. C. Fu, *Angew. Chem., Int. Ed.*, 2014, **53**, 13183.

sulfones, phosphine oxides and phosphonates. Furthermore, the synthesis of highly functionalized products can be achieved either by using racemic substituted allenoates under the same conditions (SCHEME 3.3).

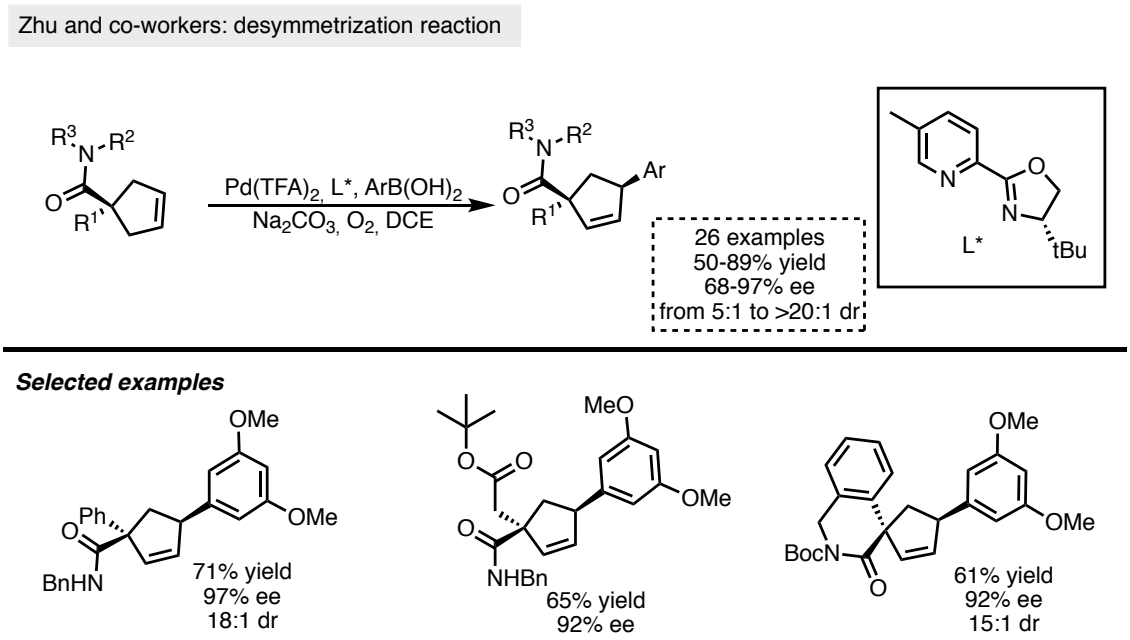


SCHEME 3.3 Scope of substituted allenoates for the asymmetric synthesis of cyclopentenes by Fu and co-workers.

The enantioselective synthesis of pentacyclic cores can also be achieved by desymmetrization reactions. [74] Although there are other approaches for performing such transformation, [75, 76] the most explored is certainly the enantioselective Heck reaction of prochiral cyclopentenes. Correia,[77] Toste[78] and

[74] X. P. Zeng, Z. Y. Cao, Y. H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330.
[75] M. Wadamoto, E. M. Phillips, T. E. Reynolds and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 10098.
[76] S. S. Goh, S. Guduguntla, T. Kikuchi, M. Lutz, E. Otten, M. Fujita and B. L. Feringa, *J. Am. Chem. Soc.*, 2018, **140**, 7052.
[77] *(a)* C. C. Oliveira, E. A. F. Dos Santos, J. H. Bormio Nunes and C. R. D. Correia, *J. Org. Chem.*, 2012, **77**, 8182; *(b)* C. R. D. Correia, C. C. Oliveira, A. G. Salles and E. A. F. Santos, *Tetrahedron Lett.*, 2012, **53**, 3325; *(c)* R. A. Angnes, J. M. Oliveira, C. C. Oliveira, N. C. Martins and C. R. D. Correia, *Chem.–Eur. J.*, 2014, **20**, 13117. *(d)* J. De Oliveira Silva, R. A. Angnes, V. H. Menezes Da Silva, B. M. Servilha, M. Adeel, A. A. C. Braga, A. Aponick and C. R. D. Correia, *J. Org. Chem.*, 2016, **81**, 2010; *(e)* I. U. Khan, S. Kattela, A. Hassan and C. R. D. Correia, *Org. Biomol. Chem.*, 2016, **14**, 9476; *(f)* S. Kattela, G. Heerdt and C. R. D. Correia, *Adv. Synth. Catal.*, 2017, **359**, 260.
[78] C. M. Avila, J. S. Patel, Y. Reddi, M. Saito, H. M. Nelson, H. P. Shunatona, M. S. Sigman, R. B. Sunoj, F. D. Toste, *Angew. Chem., Int. Ed.*, 2017, **56**, 5806.

others[79] have explored and expanded the scope of this type of transformation over the last few years. In this context, Zhu and co-workers recently reported a palladium-catalyzed oxidative Heck reaction between 4,4-disubstituted cyclopentenes and aryl boronic acids (SCHEME 3.4).[80] The success of this strategy is based on the coordination of the palladium complex to the amide moiety of the substrate, delivering the aryl group on the same face of this directing group. This methodology showed good tolerance to a wide range of boronic acids bearing either electron-donating or -withdrawing groups rendering the desired products in high yields and with excellent diastereo- and enantioselectivities. Interestingly, a cyclopentene containing both the amide and ester moieties reacted efficiently with high enantioselectivity (97% ee). This result suggests that the amide is a better directing group then the ester for this transformation. Moreover, spirocyclopentenes can also be efficiently desymmetrized in good yields, although with slightly lower enantioselectivities.



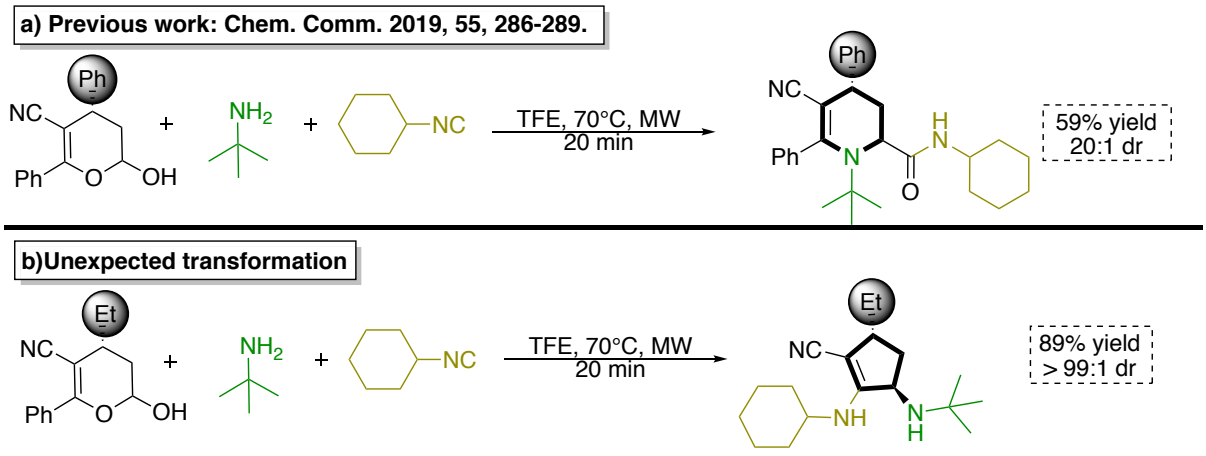
SCHEME 3.4 Desymmetrization of prochiral cyclopentenes via enantioselective Heck reaction by Zhu and co-workers.

[79] *(a)* C. Wu and J. Zhou, *J. Am. Chem. Soc.*, 2014, **136**, 650; *(b)* F. Menard, D. Perez, D. Sustac Roman, T. M. Chapman, M. Lautens, *J. Org. Chem.*, 2010, **75**, 4056.
[80] G. Chen, J. Cao, Q. Wang and J. Zhu, *Org. Lett.*, 2020, **22**, 322.

While these methods provide valuable enantioenriched cyclopentenes, they have limitations that include the multistep synthesis of starting materials and the limited variation of input elements contributing to increased skeletal diversity. These factors may restrict applications in skeletal diversification strategies such as those required in modern drug discovery approaches. Consequently, the design of new transformations enabling the rapid construction of structurally complex carbocycles from simple and available starting materials is of interest in contemporary organic chemistry. [3]

3.1.2. Methodology Development

In an attempt to broaden the substrate scope of a previous publication from our research group and co-workers.[45] In this report, it was observed that hemiacetals bearing aryl groups in the 4-position afforded tetrahydropyridines in good yields and excellent stereoselectivity (SCHEME 3.5a). On the other hand, this desired product was not observed by using hemiacetals with alkyl moieties in the aforementioned position.



SCHEME 3.5 (a) Asymmetric synthesis of tetrahydropyridines; (b) New Ugi-type reaction.

Therefore, we began this work by performing the reaction under the same conditions from the literature, with only one modification: the replacement of the phenyl for the ethyl moiety in the 4-position of the hemiacetal, which was

prepared according to previously described literature procedure.[81] Next, the products of this experiment were isolated and characterized (). As depicted in SCHEME 3.5b, a trisubstituted cyclopentene core was obtained – as the major product – in excellent yield and diastereoselectivity.

3.1.3. Structural determination of the major product

The structure of the isolated product was elucidated with the assistance of standard methods employed in organic synthesis: mass spectroscopy (MS), proton and 13-carbon nuclear magnetic resonance (NMR). The mass spectrum is shown below (FIGURE 3.1) as well as its interpretation.

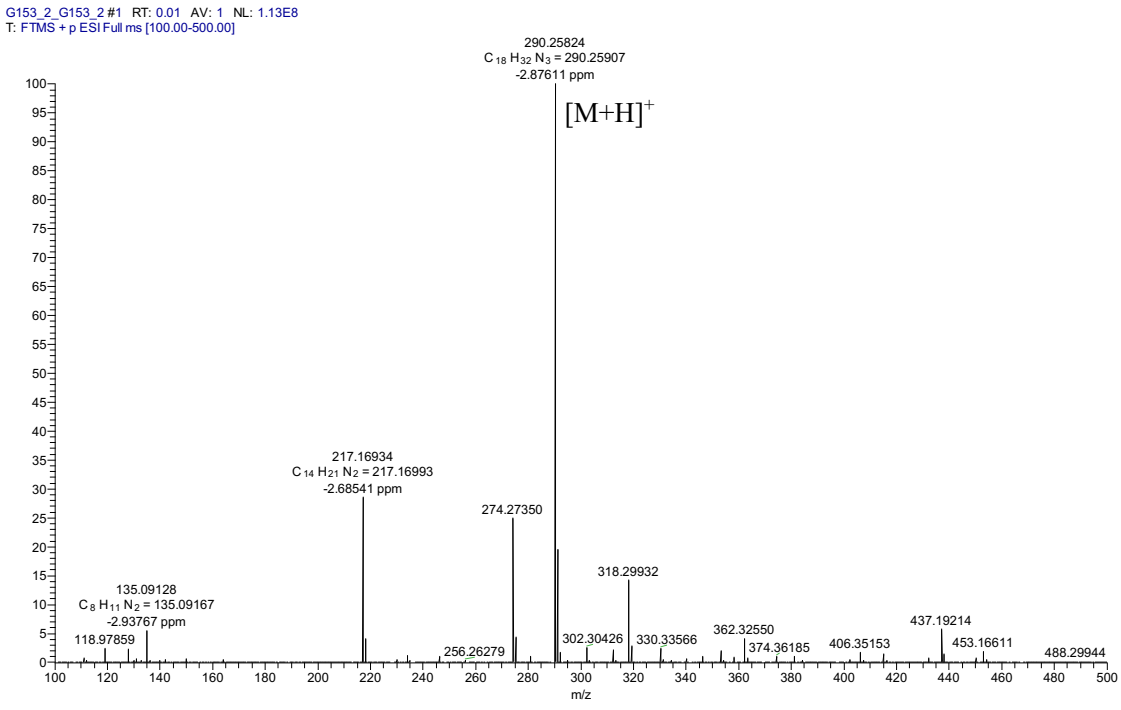
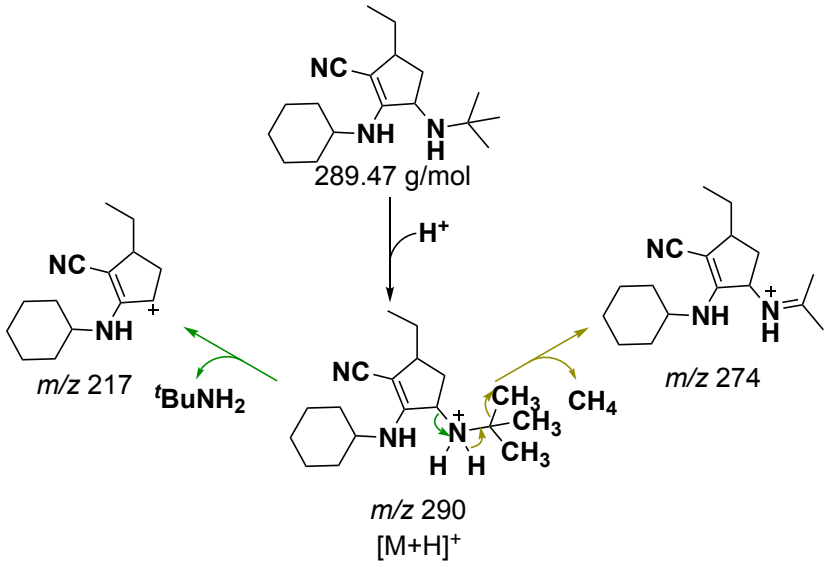


FIGURE 3.1 Mass spectrum of the isolated product from the new transformation.

The mass value of the base peak (*m/z* 290) indicate to a compound with the molecular formula $C_{18}H_{32}N_3$, in agreement with the conjugate acid – $[M+H]^+$ – of the proposed structure. Moreover, there are other two peaks (*m/z* 274 and 217) were assigned as fragments from the base peak (also the molecular peak). The

[81] Z. Niu, X. He e Y. Shang, *Tetrahedron Asymmetry*, 2014, **25**, 796.

fragmentation proposals for these ions are displayed below (SCHEME 3.6): the former of them (*m/z* 274) is an iminium ion, obtained after the β-elimination of a methyl group; the latter is formed by releasing tert-butylamine to render an allylic carbocation, which is stabilized by resonance with the adjacent double bond.



SCHEME 3.6 Fragmentation proposal for the molecular ion m/z 290: MS fragmentation to form the ions m/z 274 (yellow arrows) and 217 (green arrows).

After gathering all this information from the MS analysis, the analyses of the proton (^{1}H) and 13-carbon (^{13}C) NMR were conducted. The ^{1}H NMR data also exhibit signals that corroborate the same proposed structure:

- a triplet ($\delta_H = 0.93$) indicates the presence of the ethyl group of the hemiacetal, as well as the singlet ($\delta_H = 1.07$) and the multiplet between $\delta_H = 1.11$ and 1.74 points out to the incorporation of *t*-butylamine and cyclohexyl isocyanide, respectively, thus, the first conclusion that can be drawn out from this analysis is that all the reaction components were assembled in the product structure;
- signals in the region between $\delta_H = 3.5$ and 5.5 is evidence of protons attached to (or close to) electron-withdrawing heteroatoms (*e.g.* nitrogen and oxygen), also in agreement with the proposal.
- beyond the above observations, the spectrum displays a considerable number of signals with well-defined coupling constants and multiplicity, as shown in

FIGURE 3.2, which is expected rigid cyclic systems due to its lower number of degrees of freedom.

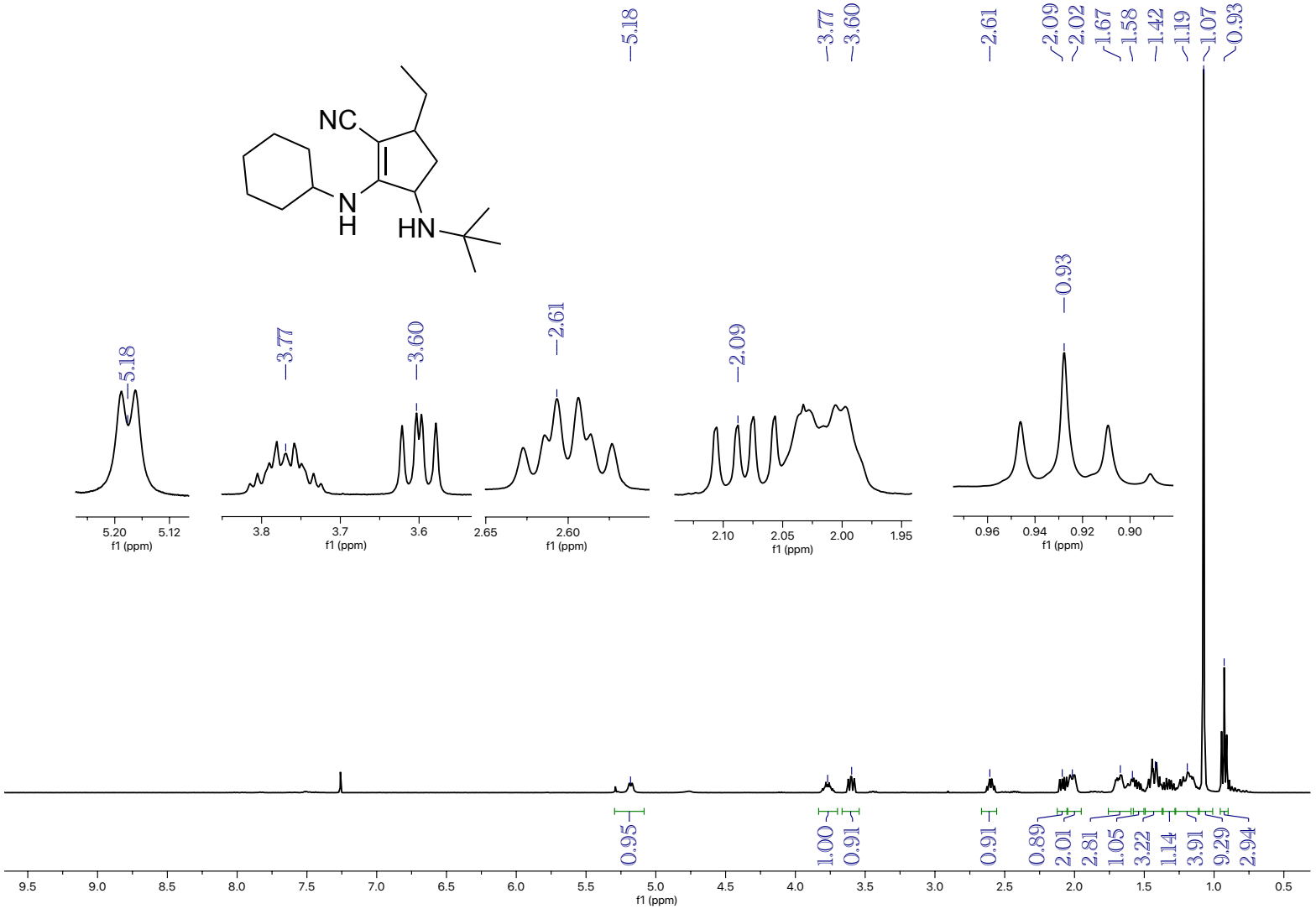


FIGURE 3.2 ^{1}H NMR spectrum of the isolated compound (400 MHz, $CDCl_3$).

Thereafter, the ^{13}C NMR (FIGURE 3.3) analysis was performed, together with DEPT-135 (see Appendix, FIGURE 7.14). Valuable information was extracted by these two analyses, for example: the total amount of nonequivalent carbons (sixteen) along with the number of quaternary carbons (four) and methylene groups (seven). Furthermore, the chemical shifts of some signals provided important insights for the structural determination:

- The quaternary carbon in δ_C = 121.6 shows the presence of the nitrile moiety;
- The huge chemical shift gap between two quaternary carbons (δ_C = 160.0 and 70.6) can be assigned to a highly polarized tetrasubstituted double bond, expected in structures that have substituents with opposite electronic nature (electron-donating and -withdrawing) in α and β-positions, therefore these signals can be attributed to the carbons C-1 and C-2, respectively.

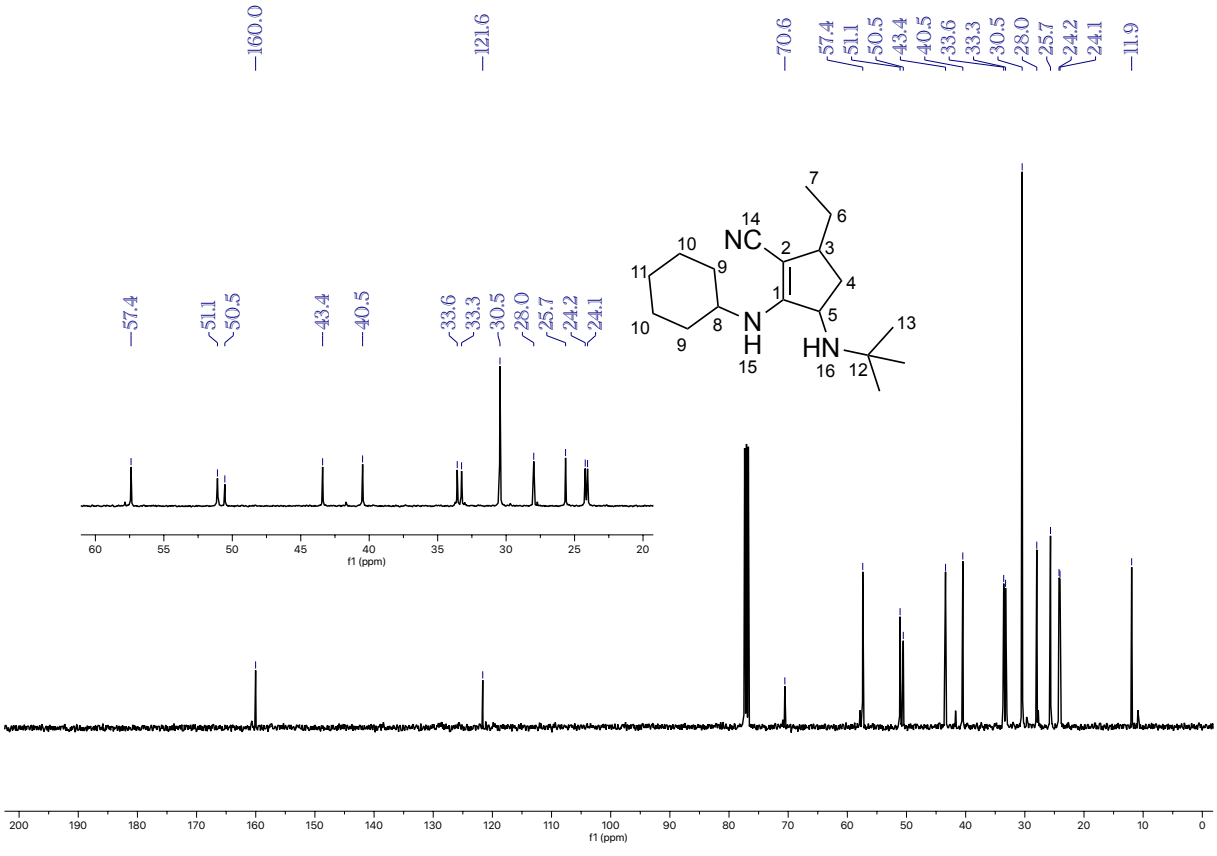


FIGURE 3.3 ^{13}C NMR spectrum of the isolated compound (100 MHz, $CDCl_3$).

It is noteworthy to highlight that all the information gathered so far is in good accordance with the proposed structure, which reinforce our original proposal. However, despite all the important information obtained by the ^{1}H and ^{13}C NMR

analyses, it is not possible to assure the atom connectivity based solely on these experiments. For that reason, two-dimensional NMR experiments were carried out to assist the structural determination of the unknown molecule, the main experiments and its relevant information will be shown below:

- HSQC (*Heteronuclear Single Quantum Coherence*)

Through this experiment it is possible to find correlation between nuclei of two types separated by one bond, being really useful to determine which proton is attached to which carbon.

The analysis of this spectrum (FIGURE 3.4) enabled the attribution of each proton of the molecule to a carbon atom, with the exception of the proton in δ = 5.18, which strongly suggest this proton is the one attached to the nitrogen (H-15, FIGURE 3.3), explaining the absence of correlation, the multiplicity and chemical shift also confirm this hypothesis.

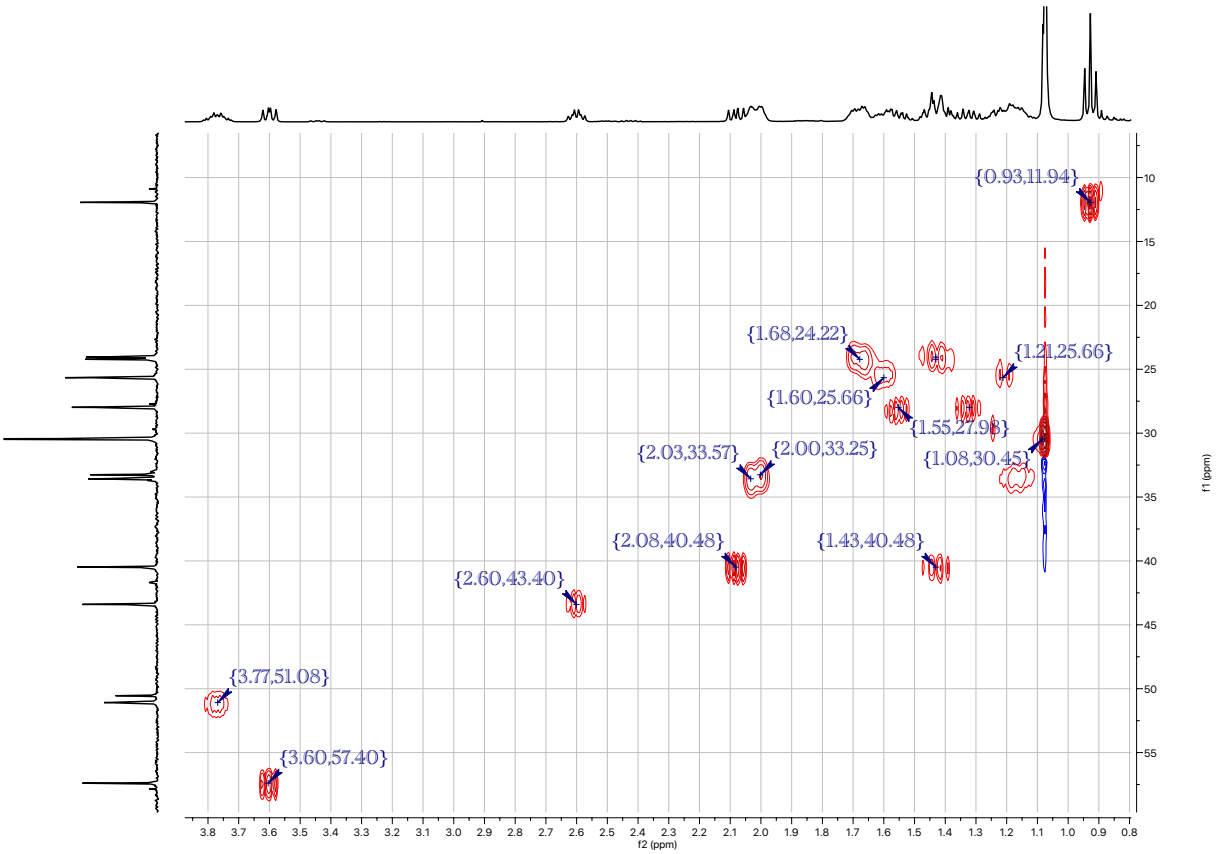
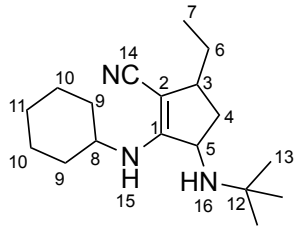


FIGURE 3.4 HSQC spectrum (f1: 100 MHz, f2: 400 MHz, $CDCl_3$) of the isolated product.

The data obtained by the HSQC experiment are summarized in the table below, in which the correlations between ^{1}H - ^{13}C and the chemical shifts of ^{1}H and ^{13}C.

TABLE 3.1 Data extracted from the HSQC experiment



^{13}C	δ_C (ppm)	δ_H (ppm)
5	57,4	3,60 (1H, dd)
8	51,1	3,77 (1H, dddd)
3	43,4	2,60 (1H, dt)
4	40,5	2,08 (1H, dd) and 1,43 (1H, m)
9	33,6	2,03 (2H, m)
9	33,3	2,00 (2H, m)
13	30,5	1,08 (9H, s)
6	28,0	1,55 (1H, m) and 1,32 (1H, m)
11	25,7	1,60 (2H, m)
10	24,2	1,66 (2H, m)
10	24,1	1,68 (2H, m)
7	11,9	0,93 (3H, t)

- HMBC (*Heteronuclear Multiple Quantum Coherence*)

The HMBQ experiment provide correlation between two nuclei over longer ranges of about 2-4 bonds, allowing precisely the connectivity between the atoms. The analysis of this spectrum (FIGURE 3.5) revealed some crucial connections to determine the structure of the product, precisely concerning the carbons with no protons attached, the carbons of the tetrasubstituted double bond, *e.g.,* 1 and 2 (FIGURE 3.3).

Correlations between C-1 and all the hydrogen on the cyclopentene ring (H-3, -4 and -5) suggest this carbon is within the ring, C-2 presents the same correlations, then this conclusion applies to C-2, which has also a correlation with the NH-proton (H-15), indicating proximity between these two fragments from different reactants (hemiacetal

and isocyanide), something that wouldn't be possible in the expected THP product from the previous work.

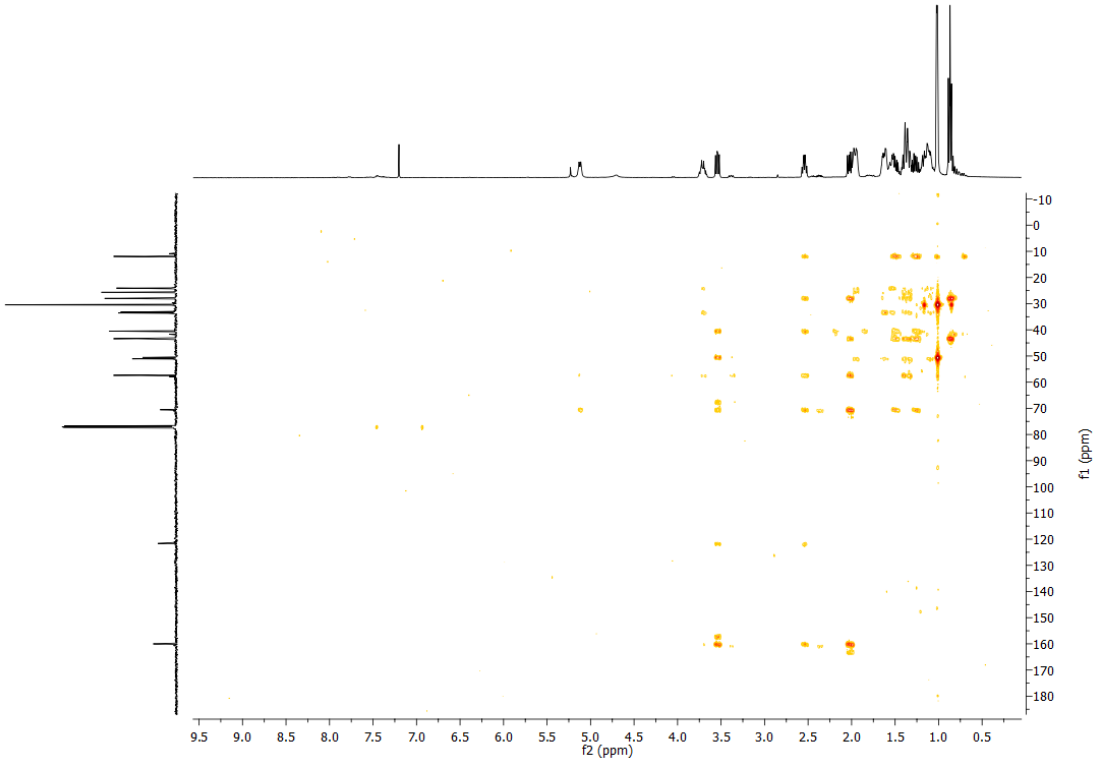


FIGURE 3.5 HMBC spectrum (f1: 100 MHz, f2: 400 MHz, $CDCl_3$) of the isolated product.

The main correlations observed in this experiment are also depicted in the FIGURE 3.6.

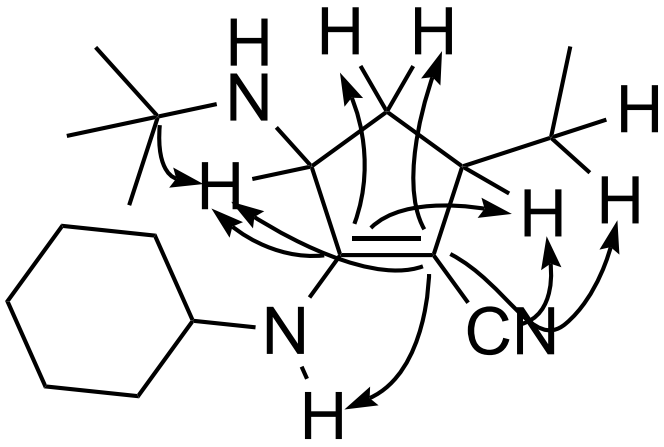
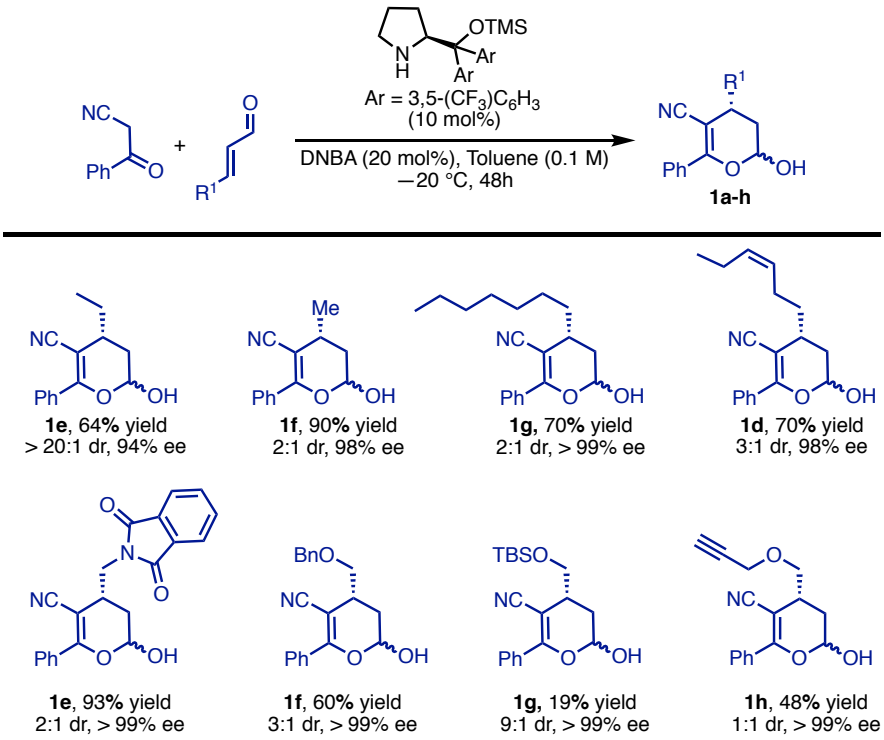


FIGURE 3.6 Main correlations observed in the HMBC spectrum.

Since we have gathered a lot of evidences that corroborates with the proposed structure, it is quite safe to conclude, at this point, that our proposal is consistent with the experimental data.

3.1.4. Synthesis of the hemiacetals **1a-h**

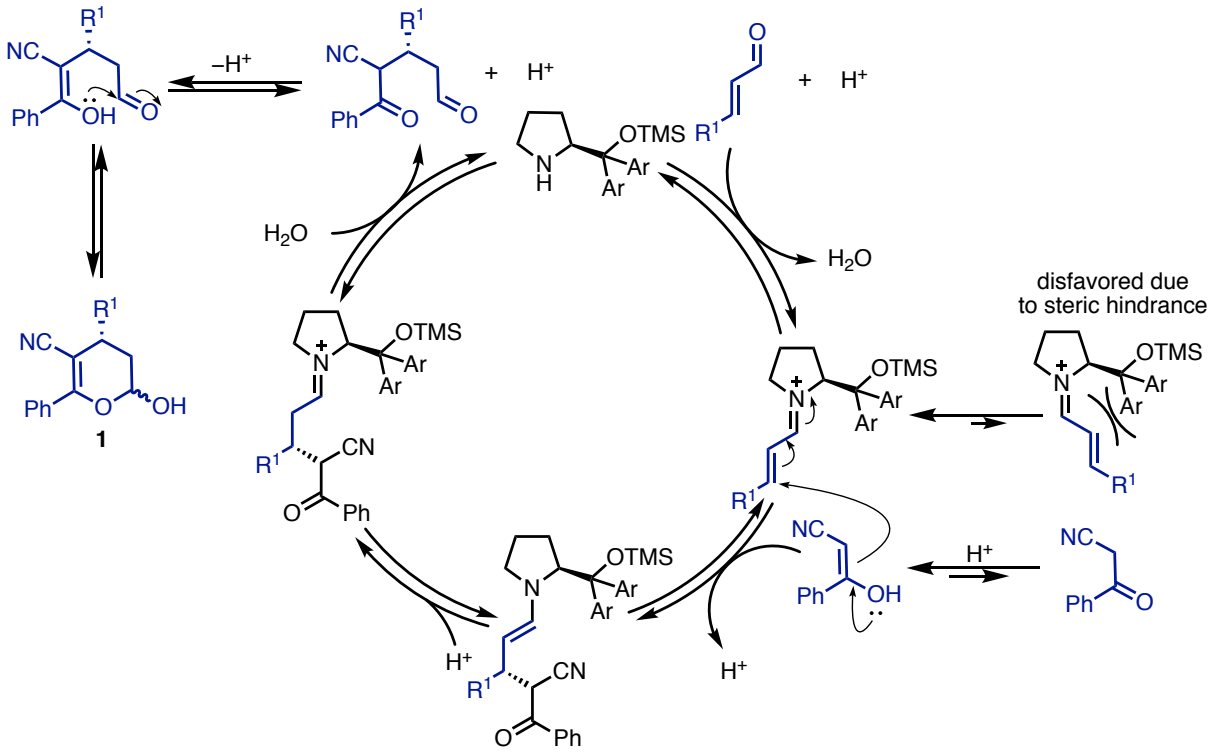
The hemiacetals **1a-h** were prepared via an organocatalyzed Michael addition of benzoylacetonitrile to α,β-unsaturated aldehydes using a prolinol-based catalyst, also known as Jørgensen catalyst (SCHEME 3.7).



SCHEME 3.7 Asymmetric synthesis of the hemiacetals **1a-h**.

As depicted in the SCHEME 3.8, the mechanism of this transformation begins with the condensation between the aminocatalyst and aldehyde in the presence of an acid, releasing water. The newly formed s-*trans* iminium ion is attacked by the enolic form of the benzyolacetonitrile in a 1,4-fashion. The stereocenter formed is controlled by a *Re* facial attack. The Re face of the iminium ion β-carbon atom is favored for the approach of the nucleophile, because of the steric hindrance of the C2-substituent in the pyrrolidine ring of the catalyst which shields the Si face. Then, an enamine is obtained, which is tautomerized to the corresponding iminium ion. After hydrolysis of this species, the catalyst enters to perform a new catalytic cycle, while enolization of

the ketone and intramolecular addiction to aldehyde moiety give the hemiacetal **1** as the final product.

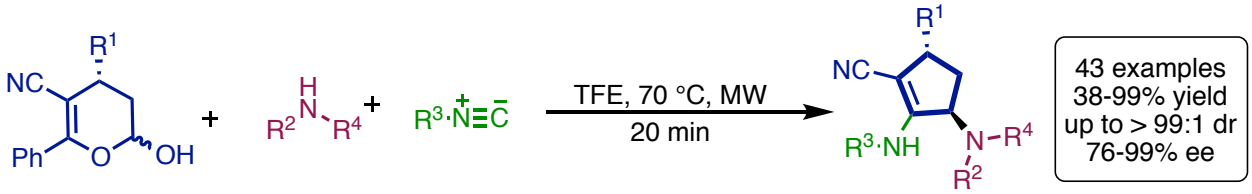


SCHEME 3.8 Mechanism for the asymmetric organocatalytic hemiacetal synthesis.

3.1.5. Scope of the Methodology

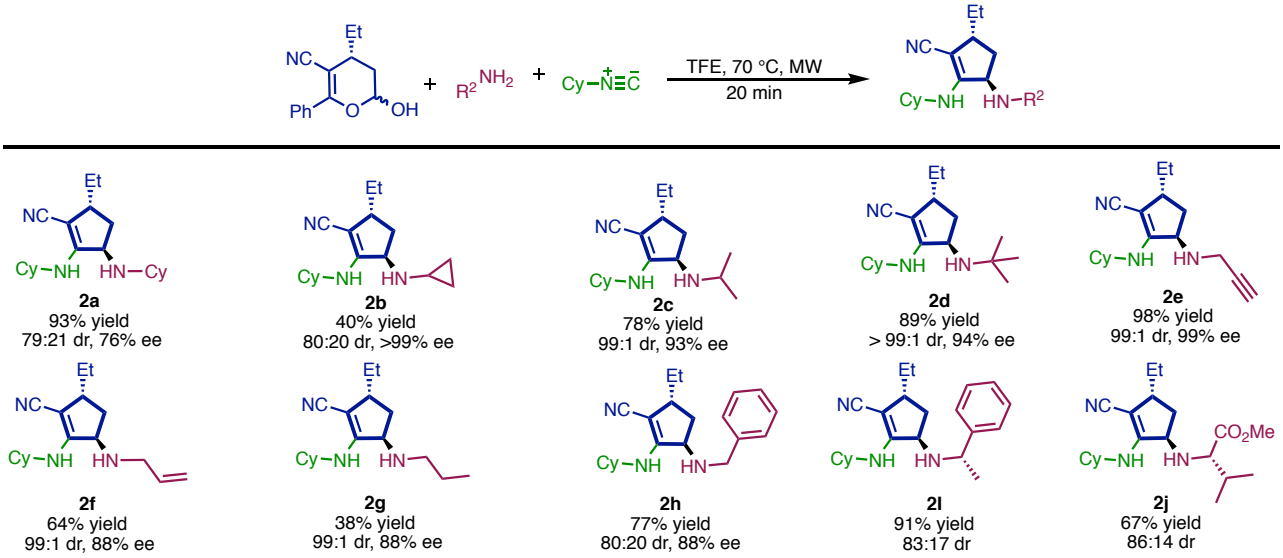
Since, in our first attempt, the reaction proceeded in high yield for the cyclopentenyl product (89%), a variety of substrates were submitted to the same conditions – without any further optimization – in order to solely exploit the generality and limitations of this new transformation.

Broadly speaking, the methodology displayed good efficiency for a wide range of substrates. By using this method, 43 examples were synthetized in moderate to high yields and excellent diastereoselectivity (SCHEME 3.9).



SCHEME 3.9 Developed method for the synthesis of cyclopentenes.

In this context, the influence of the amine component was selected to be the first evaluated component in the reaction protocol. To broaden the substrate scope, a wide range of amines with distinct electronic and steric properties were chosen (SCHEME 3.10), generating a large set of products in good to high yields with excellent stereoselectivity (28 examples, 38–99%, up to >99% ee, up to > 99:1 dr).



SCHEME 3.10 Scope of primary alkyl amines for the developed reaction.

The reaction proved to be efficient for a wide variety of alkylamines – linear, branched, sterically hindered, cyclic and acyclic ones – affording products **2a–g** in moderate to high yields and good stereoselectivities. Additionally, propargyl (**2e**) and allyl (**2f**) amines, which are useful moieties for further orthogonal derivatization, *e.g.*, cross-coupling[82] and metal-catalyzed reactions,[83] as well as bioconjugation, were also amenable to the reaction conditions (**2e** and **2f** in 98% yield, 99:1 dr, 99% ee and 64% yield, 99:1 dr, 88% ee, respectively). Benzyl amine is also a suitable substrate, affording **2h** in 73% yield with 80:20 diastereoselectivity and 86% ee. Moreover, *α*-methylbenzylamine afforded the desired products in both excellent yield and good diastereoselectivity (**2i** in 91% yield, 83:17 dr). Interestingly, L-valine methyl ester

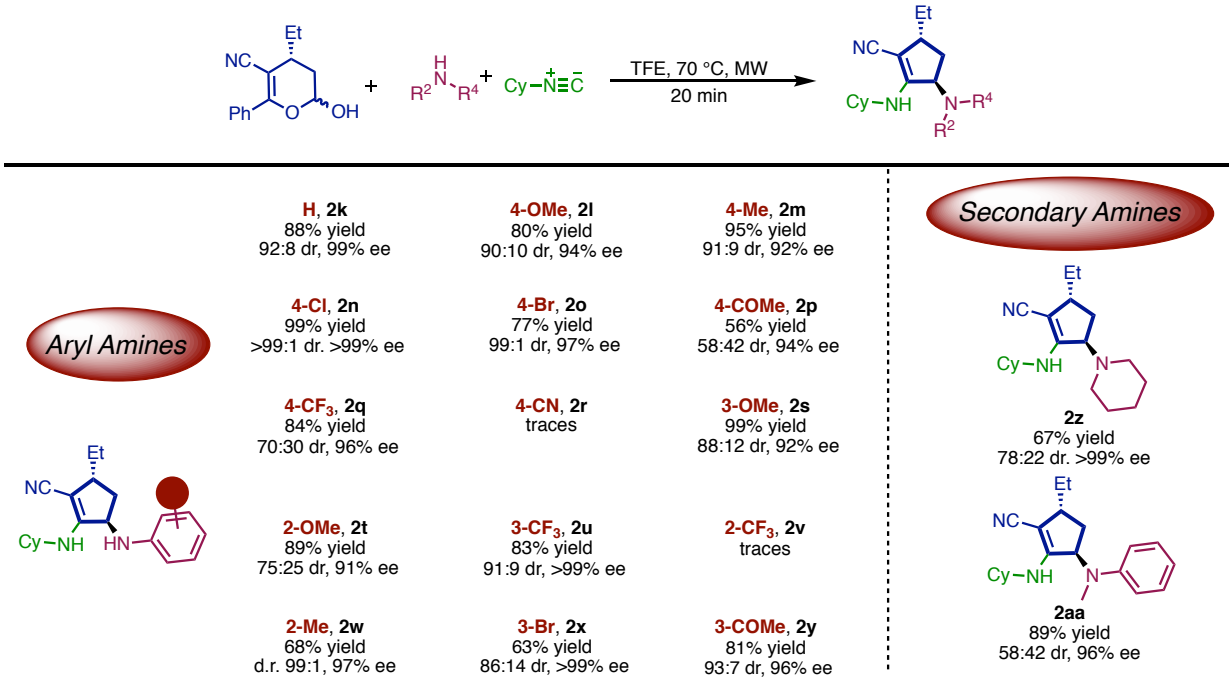
[82] A. Biffis, P. Centomo, A. Del Zotto and M. Zecca, *Chem. Rev.*, 2018, **118**, 2249.
[83] *(a)* J. D. Weaver, A. Recio, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, **111**, 1846; *(b)* C. Nájera, I. P. Beletskaya and M. Yus, *Chem. Soc. Rev.*, 2019, **48**, 4515; *(c)* R. K. Dhungana, S. KC, P. Basnet and R. Giri, *Chem. Rec.*, 2018, **18**, 1314.

displayed promising results in both yield and stereoselectivity (**2j** in 67% yield, 86:14 dr), demonstrating that amino acids can be used as suitable substrates in this procedure.

We were pleased to find that less nucleophilic substituted anilines (SCHEME 3.11) could also be applied in this transformation, affording products in good to excellent yields with high stereoselectivity (56–99% yield, up to 99:1 dr and up to 99% ee). Anilines bearing electron-donating (**2k–m**), halogen (**2n** and **2o**) and some electron-withdrawing (**2p** and **2q**) groups at the *para*-position were also found to be competent substrates for this multicomponent reaction. However, only traces of the product were obtained when employing a strong electron-withdrawing group, *e.g.*, cyano, as an aniline substituent, likely due to its reduced nucleophilicity.

Furthermore, *meta*- and *ortho*-substituted anilines efficiently underwent this transformation (**2s–y**, 63–99% yield and good stereoselectivities). On the other hand, when *ortho*-trifluoromethyl aniline was employed as a substrate, no formation of cyclopentene **2v** was observed. This result can be explained by the hyperconjugative electron-withdrawing nature of the trifluoromethyl group. The *ortho*-methoxy (**2t**) and -methyl (**2w**) derivatives were synthesized in good yields (89% and 68% yield, respectively) and selectivities (75:25 dr, 91% ee and 99:1 dr, 97% ee, respectively). Thus, by analyzing this set of results, it was possible to conclude that the reaction outcome is not significantly influenced by steric hindrance.

We next turned our attention to evaluate the scope of the amino component for secondary amines. Only two examples were prepared in this regard, piperidine and *N*-methylaniline proved to be compatible with the presented method, affording the tertiary amine products (**2z** and **2aa**) in good yields (67 and 89%, respectively), although with a significant decrease in stereoselectivity (up to 78:22).



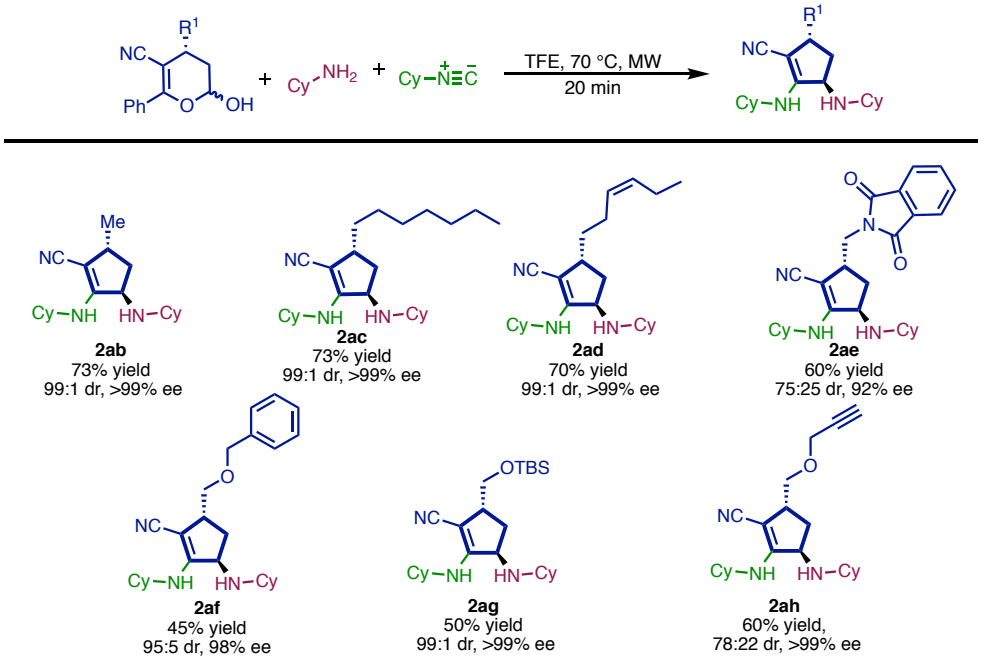
SCHEME 3.11 Scope of anilines (left) and secondary amines (right).

Having examined the reaction scope for the amino component, we focused on defining the scope of the bifunctional component (SCHEME 3.12). A variety of products with different alkyl substituents were produced in moderate to good yields and excellent stereoselectivities (**2ab–2ah**, 45–73% and up to 99:1 dr). The versatility of the method to install functionalized substituents at that position is a clear advantage, as they can be used for further derivatization of the chiral cyclopentenyl scaffold.

The reaction displayed no influence concerning the length of the carbon chain, presenting good yields and stereoselectivity for methyl (**2ab**, 73%, 99:1 dr, >99% ee), heptyl (**2ac**, 73%, 99:1 dr, 99% ee) and (*Z*)-hex-3-enyl (**2ad**, 70%, 99:1 dr, >99% ee) substituted hemiacetals. Subsequently, hemiacetals bearing electronegative heteroatoms (*e.g.*, nitrogen and oxygen) in the side chain show diminished yields under the optimized conditions (**2ae–ah**, 45–60%, up to 99:1 dr, up to >99% ee). These *O*- and *N*-substituted products are far more interesting as synthetic intermediates because they can be deprotected into free amine (**2ae**) and hydroxy groups (**2af** and **2ag**), enabling additional functionalization via conventional synthetic methods.[84] Likewise,

[84] T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, USA, 1999.

product **2ah**, which contains a terminal alkyne, can be easily employed as a substrate in a wide range of chemical transformations, such as Sonogashira coupling[85] and Click reactions.[86] Furthermore, it is noteworthy that this method was compatible with all protecting groups employed (*i.e.*, Bn, TBS and Phth), which is, from the synthetic point of view, a desirable aspect due to the ubiquitous presence of protecting groups in the total synthesis of complex molecules.[87]

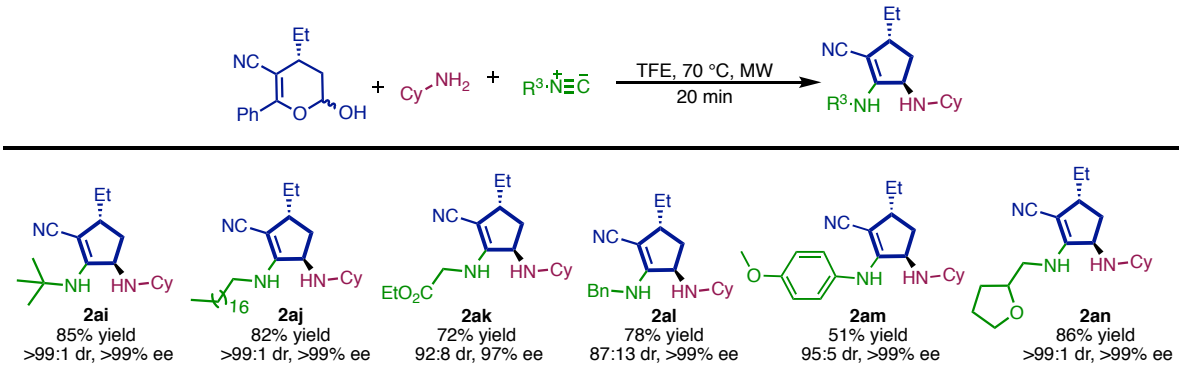


SCHEME 3.12 Scope of hemiacetals for the developed method.

Aiming to better cover the reaction, we evaluated the third component of this reaction: the isocyanide (SCHEME 3.13). Under optimized reaction conditions, five cyclopentenyl derivatives were accessed in moderate to high yields with good diastereo- and enantioselectivities. The method showed good tolerance to both bulky and long alkyl chains, displaying high yields and excellent diastereoselectivity (**2ai** and **2aj** in 85% yield, 99:1 dr and 99% ee, and 82% yield, >99:1 dr and >99% ee). Glycine-derived isocyanide afforded the desired product **2ak** in good yield and excellent stereoselectivity (72% yield, 92:8 dr and 97% ee). Although there is a slight decrease in the stereoselectivity (87:13 dr and >99% ee) upon using benzyl isocyanide, product

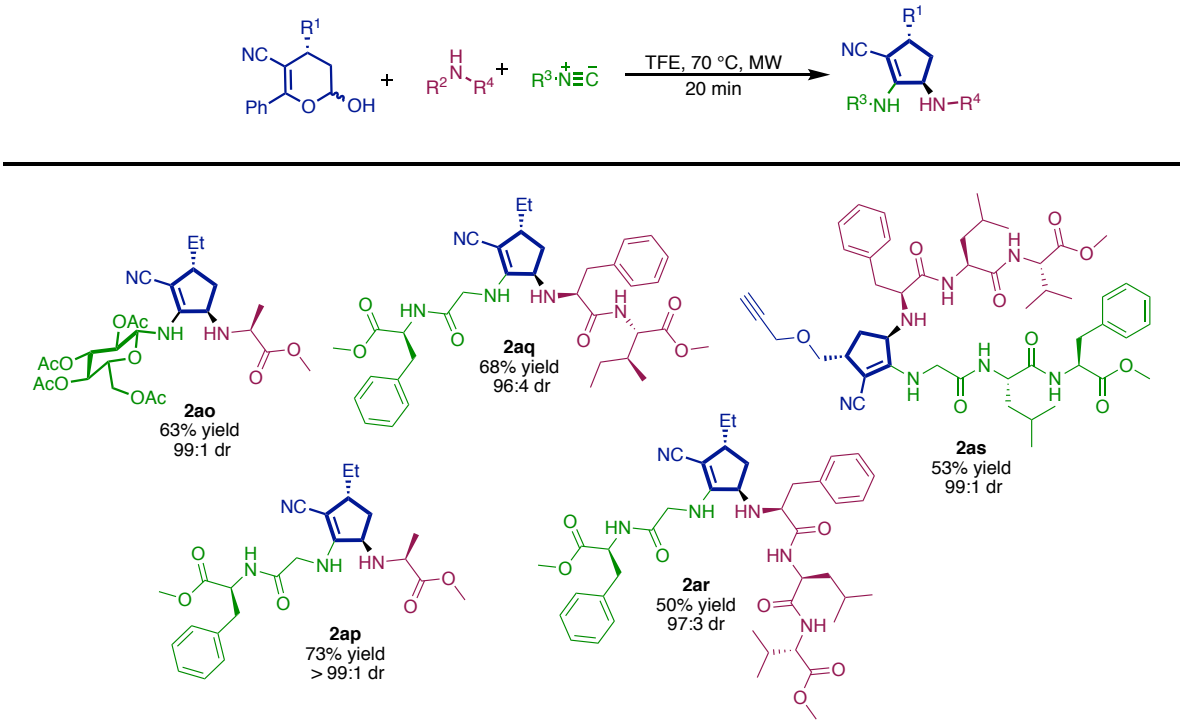
[85] K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46.
[86] P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905.
[87] M. Schelhaas and H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2056.

2al was isolated in 78% yield. An aromatic isocyanide was also evaluated, giving rise to product **2am** in 51% yield and excellent stereoselectivity (95:5 dr and >99% ee). Moreover, the tetrahydrofuran moiety was demonstrated to be compatible with this transformation, generating product **2an** in 86% yield and excellent selectivity (99:1 dr and >99% ee).



SCHEME 3.13 Scope of isocyanides.

To demonstrate the synthetic applicability of this methodology, we focused our efforts on the synthesis of complex molecular hybrids. We further investigated the incorporation of natural product fragments such as peptides and saccharides into the cyclopentenyl core. The isocyanopeptides and peptides were all synthetized as described in the corresponding literature.[44] As depicted in **Erro! Fonte de referência não encontrada.**, glucose, di- and tripeptides derivatives containing the cyclopentenyl scaffold were synthesized by employing the enantioenriched hemiacetal **1** in good yields and excellent diastereoselectivities (**2ao–as**, 50–73%, from 96:4 to >99 : 1 dr).



SCHEME 3.14 Complex structures synthetized via the developed methodology.

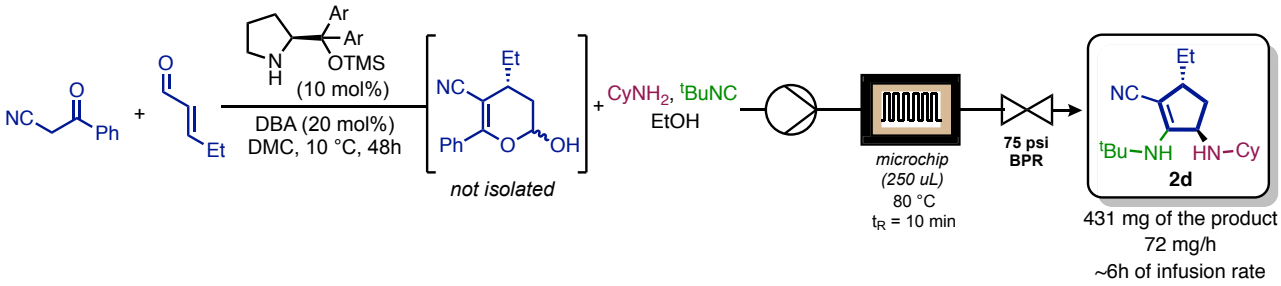
These examples demonstrate the feasibility of the developed method to obtain complex architectures, which shows the great potential of this approach for late-stage modification of peptides.[88] Another important feature is that this multicomponent strategy enables the side-specific insertion of rigid cyclopentenyl structures into peptide side chains, which would modulate the conformation, dynamics, and proteolytic susceptibility of native peptides and, consequently, provide a foundation for sophisticated molecular function.[89] Furthermore, product **2as** can be used as a substrate in cycloaddition reactions with azides – a common strategy employed in bioconjugation[86] – showing that this method can provide a simple, fast and efficient route to link peptides with probes.

Taking advantage of the robustness and practicality of this methodology, we envisioned a one-pot continuous flow procedure (SCHEME 3.15), in which the hemiacetal generated by the organocatalytic Michael addition was directly used in the

[88] E. Lenci and A. Trabocchi, *Chem. Soc. Rev.*, 2020, **49**, 3262

[89] *(a)* M. Goodman, C. Toniolo and J. Falcetta, *J. Am. Chem. Soc.*, 1969, **91**, 1816; *(b)* J. Morlieras, S. Dufort, L. Sancey, C. Truillet, A. Mignot, F. Rossetti, M. Dentamaro, S. Laurent, L. Vander Elst, R. N. Muller, R. Antoine, P. Dugourd, S. Roux, P. Perriat, F. Lux, J.-L. Coll and O. Tillement, *Bioconjugate Chem.*, 2013, **24**, 1584; *(c)* C. Adessi and C. Soto, *Curr. Med. Chem.*, 2005, **9**, 963.

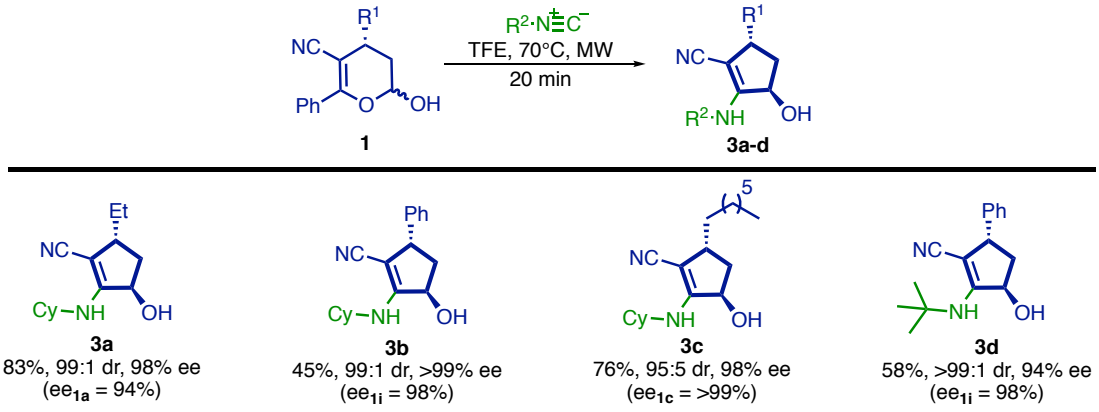
MCR. After optimization, product **2d** was isolated with high yield and excellent selectivity (83% yield, > 99:1 dr and >99% ee), the development and execution of this part of the work was performed by Msc. Yoisel B. Broterson.[90]



SCHEME 3.15 Scaling up of the developed methodology under continuous flow regime.

3.1.6. Passerini-type Reaction

Aiming to extend the scope of this method, we performed the reaction with hemiacetal **1a** under the same previously presented conditions, except in the absence of amine. To our satisfaction, a Passerini-type product **3a** was obtained in good yield and high stereoselectivity (**3a**, 83%, 99:1 dr and 98% ee). Inspired by this result, we then evaluated a narrow scope of substrates for this transformation (SCHEME 3.16).

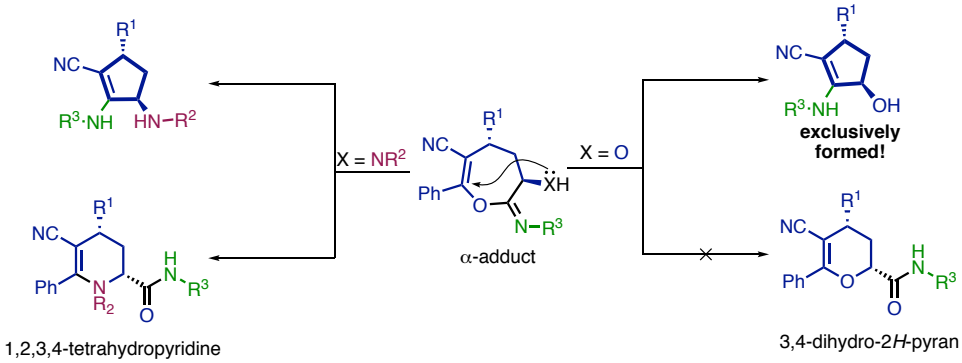


SCHEME 3.16 Scope for the Passerini-type reaction.

In contrast to the limitation described for the synthesis of cyclopentenyl amines, hemiacetals bearing an aryl moiety at the R^1 position are compatible with this new methodology, affording products **3b** (45% yield, 99:1 dr, >99% ee) and **3d** (58% yield,

[90] BROTERSON, Y. B. Sustainable synthesis of ciclopentene derivatives through multicomponent reactions in continuous flow regime. São Carlos, Programa de Pós-Graduação em Química – UFSCar, 2020. Dissertação de mestrado.

>99:1 dr, 94% ee) in moderate yield and excellent stereoselection. A possible explanation for the observed selectivity in this case is based on the difference of nucleophilicity between the oxygen and the nitrogen from the original synthetic method, while the nitrogen is nucleophilic enough to trigger the Mumm-type rearrangement, the less nucleophilic oxygen increases the energetic barrier of this step, disfavoring the formation of the 3,4-dihydro-2*H*-pyran scaffold byproduct (SCHEME 3.17), leading solely to the formation of cyclopentenol products **3**.



SCHEME 3.17 Possible pathways after formation of the α-adduct.

It is possible to note that this reaction shows potential for further improvement, plus the 2-cyclopentenol derivatives are valuable synthetic intermediates widely employed in synthetic programs.[91] Moreover, the relative configuration of the product **3d** was unambiguously confirmed by X-ray analysis (FIGURE 3.7), showing *trans* configuration, which is consistent with the NOESY ^{1}H NMR analysis of compound **2d** (for details, see the FIGURE 7.13). The hemiacetal was prepared according to the literature and its absolute configuration is known, hence the absolute configuration of the new center formed during the multicomponent step could also be determined.

[91] *(a)* D. H. Hua and S. Venkataraman, *Tetrahedron Lett.*, 1985, **26**, 3765; *(b)* M. Asami, M. Ogawa and S. Inoue, *Tetrahedron Lett.*, 1999, **40**, 1563; *(c)* H. Nakagawa, T. Sugahara and K. Ogasawara, *Org. Lett.*, 2000, **2**, 3181; *(d)* T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974.

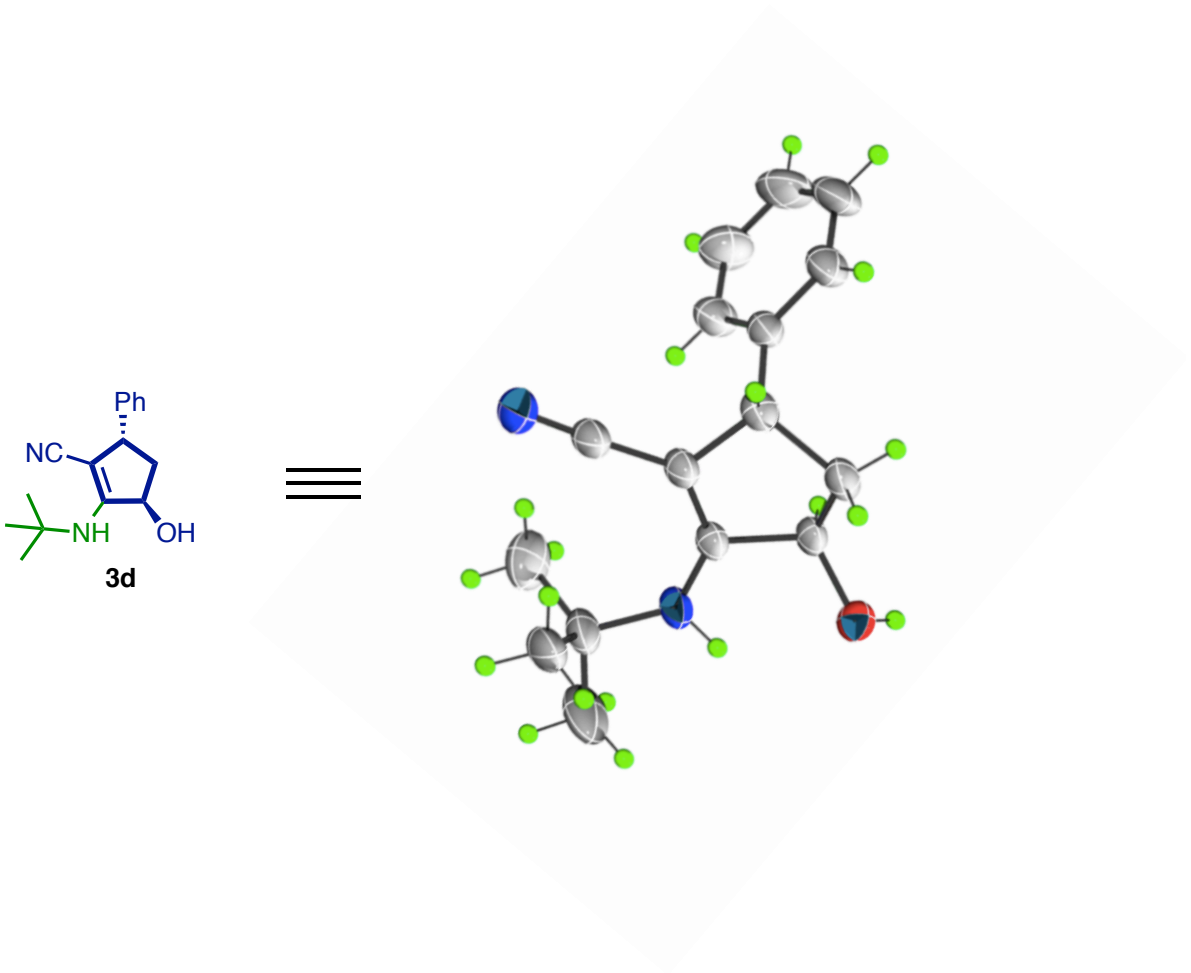
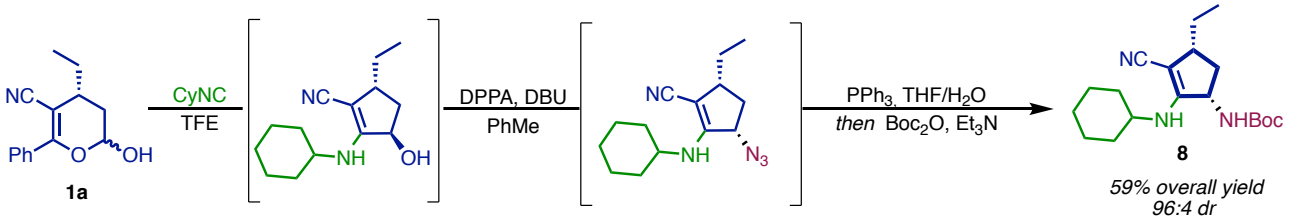


FIGURE 3.7 X-ray structure of the compound **3d** for relative configuration determination.

As an attempt to broaden the applicability of this methodology, we envisioned that the *syn*-diastereoisomer of cyclopentyl amines **2** could be accessed by using Passerini-type cyclopentenols **3** as substrates (SCHEME 3.18). After a sequence of Mitsunobu reaction, Staudinger reduction and Boc protection, compound **8** could be synthesized in excellent selectivity (94:6 dr), although in moderate yield (59%).

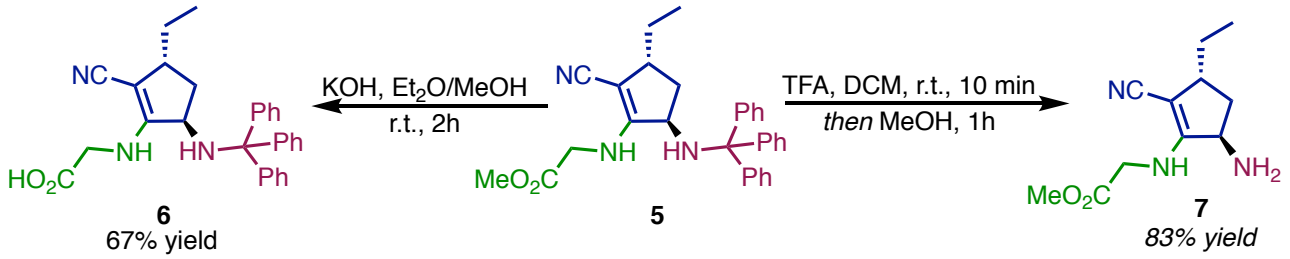


SCHEME 3.18 Synthetic route to obtain the *syn*-diastereoisomer.

3.1.7. Derivatizations

To further show the synthetic potential of this strategy, compound **5** was synthetized using the developed method (58% yield) and submitted to orthogonal deprotection, affording the cyclopentene derivatives **6** and **7** (SCHEME 3.19). First, hydrolysis of the ester in alkaline media gave rise to the carboxylate **6**. Thereafter, the deprotection of the *N*-trityl was performed, affording product **7** containing a primary free amine group that can be used in a wide range of chemical reactions.[92]

Both of these structures are peptidomimetics, and therefore they can be employed as substrates in peptide chemistry. While compound **6** is used as a *C*-terminal dipeptide mimetic, **7** would react in the *N*-terminal position. This example of orthogonal deprotection indicates that compound **5** and derivatives can be employed – regardless of the strategy – in solid-phase peptide synthesis.

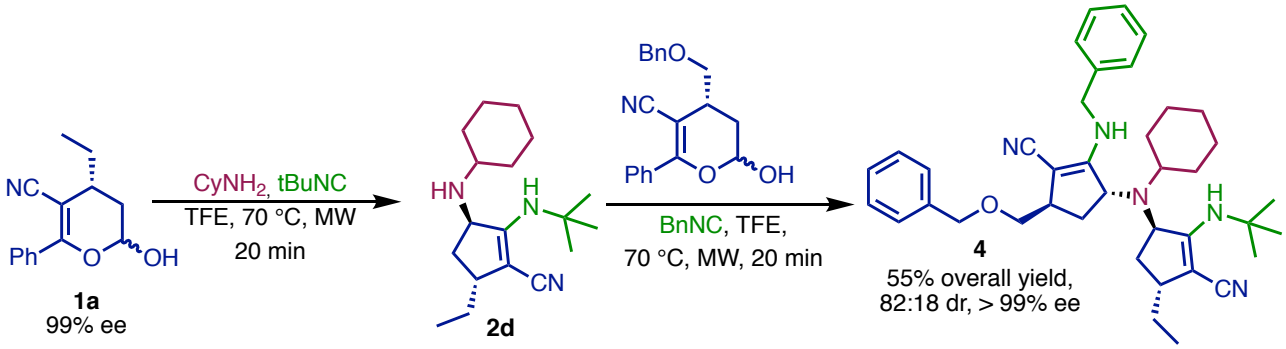


SCHEME 3.19 Orthogonal deprotection of dipeptide-like product **5**.

We envisioned that the products **2** could be further employed as the amino component in a new Ugi-4C-3CR. To this end, product **2d** was obtained by reacting hemiacetal **1a**, cyclohexylamine and tert-butyl isocyanide in a one-pot manner. Compound **2d** was used as the substrate in a second Ugi-4C-3CR with hemiacetal 1f and benzyl isocyanide, generating the tertiary amine **4** in 41% yield (SCHEME 3.20). Once a large library of compounds is synthesized with simple substrates, this strategy becomes an interesting approach for the synthesis of chiral bulky tertiary amines,

[92] *(a)* R. E. Feeney, G. Blankenhorn and H. B. F. Dixon, *Carbonyl-Amine Reactions in Protein Chemistry*, C. B. Anfinsen, J. T. Edsall and F. M. Richards, Academic Press, 1975, vol. 29, pp. 135; *(b)* W. Notz, K. Sakthivel, T. Bui, G. Zhong and C. F. Barbas, *Tetrahedron Lett.*, 2001, **42**, 199; *(c)* Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247; *(d)* F.-S. He, S. Ye and J. Wu, *ACS Catal.*, 2019, **9**, 8943; *(e)* J. T. M. Correia, V. A. Fernandes, B. T. Matsuo, J. A. C. Delgado, W. C. de Souza and M. W. Paixão, *Chem. Commun.*, 2020, **56**, 503.

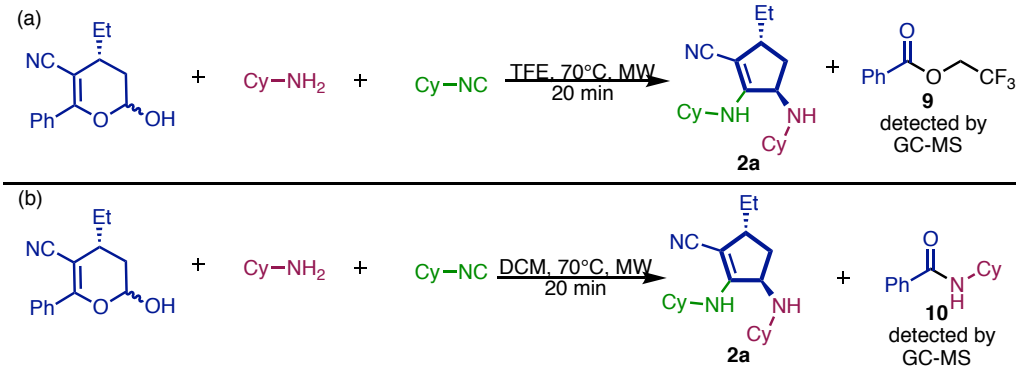
widely used in asymmetric organocatalysis[93] and as ligands for asymmetric transition metal catalysts.[94]



SCHEME 3.20 Two-step synthesis of bulky tertiary amines using the new method.

3.1.8. Study of the Reaction Mechanism

To gain some insights into the possible mechanism of this new approach, some experiments were performed. Initially, the reaction was carried out under the same reaction conditions described and the crude mixture was analyzed by GC-MS (for more details, see section 6.2.10), through which 2,2,2-trifluoroethyl benzoate (**9**, SCHEME 3.21a) was detected.



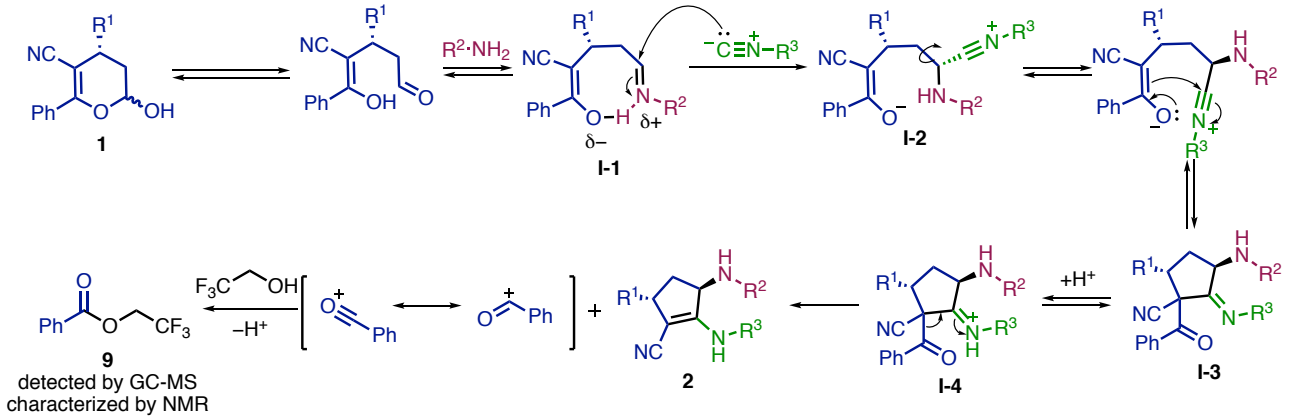
SCHEME 3.21 Control experiments to gather mechanistic information.

The presence of this species drove us to the conclusion that the solvent – 2,2,2-trifluoroethanol – reacts, as a nucleophile, with the ketone moiety present in the substrate. Therefore, we substituted the solvent for dichloromethane (a non-

[93] *(a)* A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; *(b)* S. France, D. J. Guerin, S. J. Miller and T. Lectka, *Chem. Rev.*, 2003, **103**, 2985.
[94] J.-C. Kizirian *Chem. Rev.*, 2008, **108**, 140.

nucleophilic solvent), aiming at the isolation of any intermediate of this transformation. However, under these conditions (SCHEME 3.21b) we observed product formation and instead of by-product **9**, the generation of *N*-cyclohexylbenzamide (**10**) was detected. These results prove that the nucleophilic attack during the elimination of the ketone portion is not a rate determining step (RDS). Also, we assume that the nucleophilicity of the reagent has no influence because both TFE and cyclohexylamine, which are very distinct in nucleophilicity, can play this role.

Based on these experiments and previous literature,[44,45] we proposed a mechanism for this reaction. The hemiacetal **1**, which is in equilibrium with its open enol-aldehyde form, reacts with the amine to render the intermediate **I-1**, a rigid structure possible due to an intramolecular hydrogen bond between the imine and phenol moieties. It is noteworthy to mention that this cyclic conformation has a crucial role in the diastereoselectivity by introducing the conformational rigidity. This species is attacked by the isocyanide to give the nitrilium ion I-2. Next, an intramolecular 5-exo-dig cyclization generates the cyclopentane intermediate I-3. After protonation and elimination of an acylium ion (trapped by the solvent to afford the ester **9**), there is the formation of the observed product **2**.



SCHEME 3.22 Proposed mechanism for the cyclopentenyl amines synthesis.

In collaboration with Ferreira group (DQ/UFSCar), a theoretical investigation using DFT calculations of the most important elementary steps in the MCR was conducted to elucidate the factors that control the observed diastereoselectivity (up to

99 : 1 dr) towards the obtained products (SCHEME 3.23).[95] According to the calculations, attractive non-covalent interactions (NCI) between the isocyanide and the conjugated enol π-system control the diastereoselectivity (FIGURE 3.8), favoring the *Si*-face attack on the imine through the rate- and diastereoselectivity-determining transition state **TS-1** (*Si*-face) over **TS-1′** (*Re*-face).

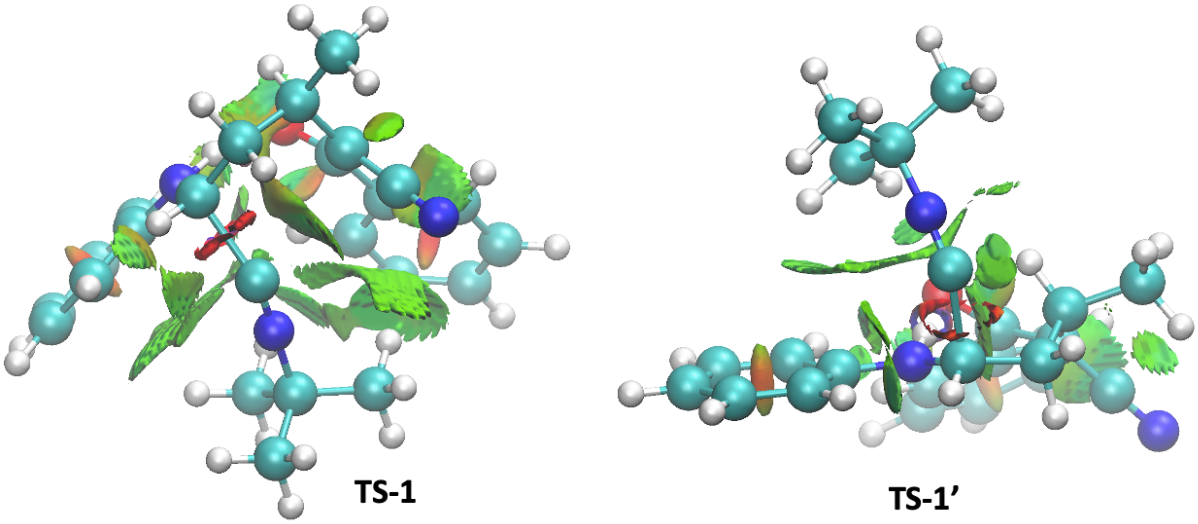


FIGURE 3.8 NCI analysis for the transition states **TS-1** and **TS-1'**. Green surfaces represent attractive interactions and red surfaces are for repulsive interactions.

The computational study shows that **TS-1** is lower in energy than **TS-1′**, giving a theoretical diastereoselectivity of 98:2 at 70 °C in favor of the major diastereoisomer, in excellent agreement with experimental results.

Next, the most intriguing aspect of this transformation was investigated, the unexpected cyclization to furnish the cyclopentenyl moiety **2**. After the formation of intermediate **I-2**, it was expected that the oxygen would attack the electrophilic carbon (C1) of the nitrilium ion via **TS-4**, ultimately affording the possible product **11**. However, the attack of the enolate by the *α*-ketonic carbon (C2) is much lower in energy compared with **TS-4**, corroborating the experimental exclusive formation of **2**.

[95] KAWAMURA, M. W. Estudos mecanísticos de reações de cicloadição e ciclização através de ferramentas experimentais e teóricas. São Carlos, Programa de Pós-Graduação em Química – UFSCar, 2022. Tese de doutorado.

The probable origin of this energy difference is associated with the stabilizing intramolecular hydrogen bond featured in **TS-2** (FIGURE 3.9).

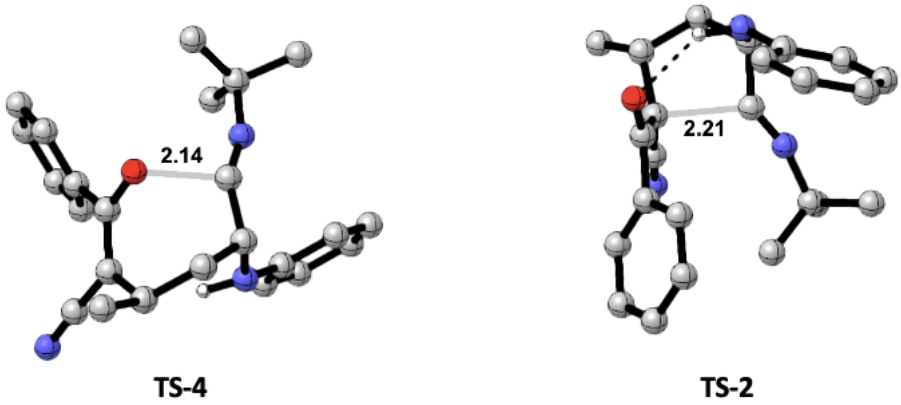


FIGURE 3.9 Comparison between **TS-2** and **TS4**. Gray lines represent the bond formed and the dashed line shows the hydrogen bond in **TS-2**.

Analyzing the competitive attacks of the enolate by the α-ketonic carbon (C2) via **TS-2** and **TS-2′**, both have similar geometries except for the disposition of the NH-Ph group (FIGURE 3.10). The axial arrangement in the **TS-2** conformation brings together the atoms involved in the mentioned hydrogen bond, which is strong enough to overcome the repulsion exerted by the NH-Ph group. Probably for steric reasons, the less hindered **TS-4** is preferred over **TS-2** when using the slightly bulkier –Ph substituent in the R^1 position, justifying the distinct reactivity reported in this work compared to the one reported previously.

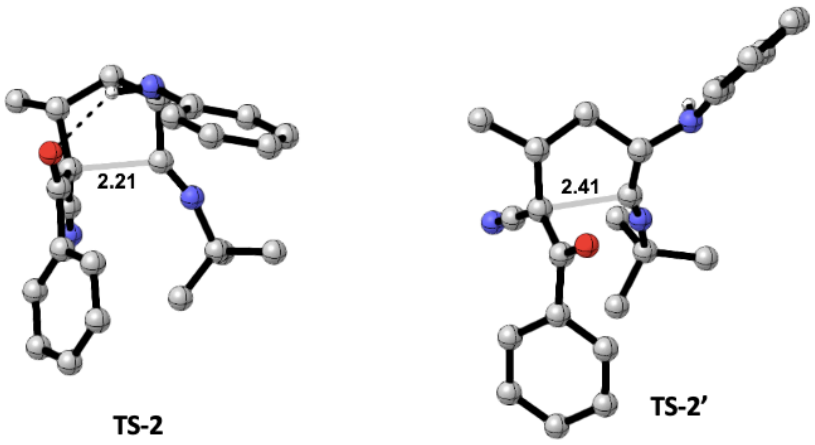
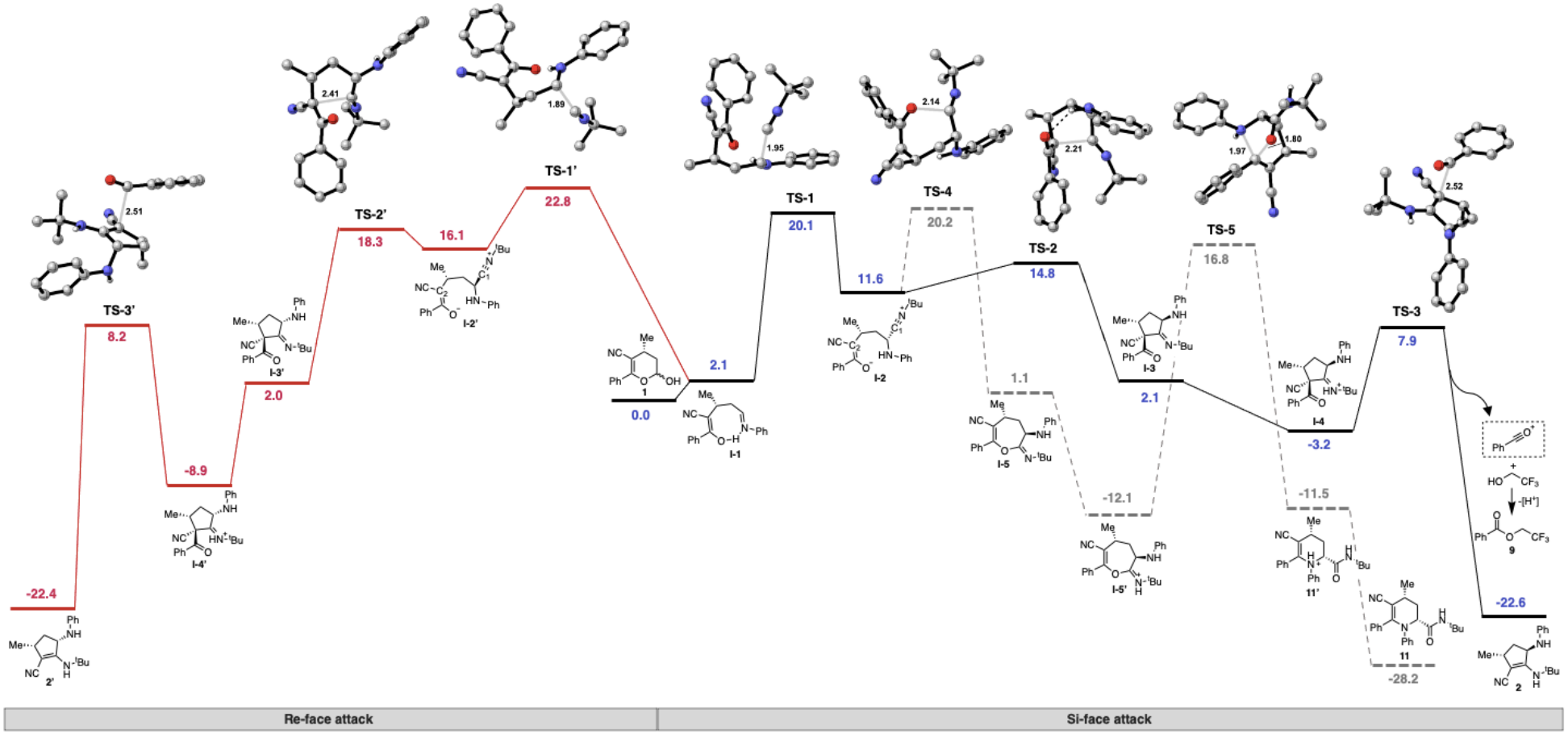


FIGURE 3.10 Comparison between **TS-2** and **TS2'**. Gray lines represent the bond formed and the dashed line shows the hydrogen bond in **TS-2**.

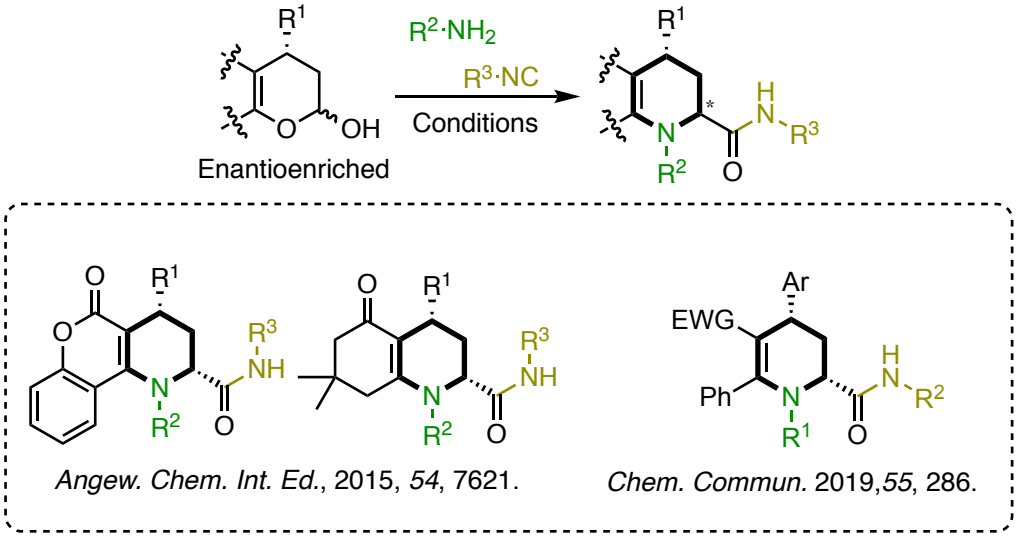
According to this study, the acylium elimination (**TS-3**) proposed is feasible showing low energetic barrier, in agreement with the experimental observation of **9** and **10** (SCHEME 3.21), resulting from the addition of a nucleophilic species to the acylium ion. Also, the acyl transfer mechanism involving the nucleophilic attack of TFE, as well as non-catalyzed pathways were explored but presented much higher energy barrier.



SCHEME 3.23 Proposed mechanism according the DFT calculations.

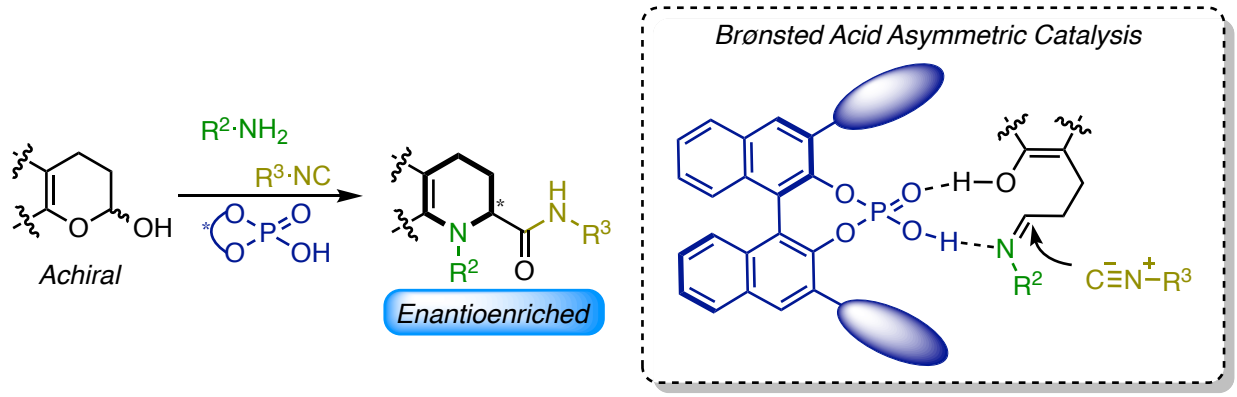
3.2. Synthesis of *N*-heterocycles via Asymmetric Ugi-type Multicomponent Reactions

Recently, our research group has devoted attention on developing asymmetric variants for isocyanide-based multicomponent reactions (I-MCR) through the combination of an asymmetric organocatalytic approach and the employment of enantioriched hemiacetals as a chiral pool to obtaining Ugi-type products in good stereoselecitivity (SCHEME 3.24).



SCHEME 3.24 Synthesis of N-heterocycles with hemiacetals in U-4C-3CR.

This approach proved to be a feasible strategy for the asymmetric synthesis of *N*-heterocycles. However, this type of methodology is only applied when enantioriched starting materials can be used. To fulfill this gap, we intend to develop an asymmetric Brønsted acid organocatalytic Ugi-type Reaction using achiral hemiacetals as starting materials (SCHEME 3.25). This strategy is inspired by the seminal work of Professor List[47] and the recent developed asymmetric Ugi Reaction by the Tan group.[50]

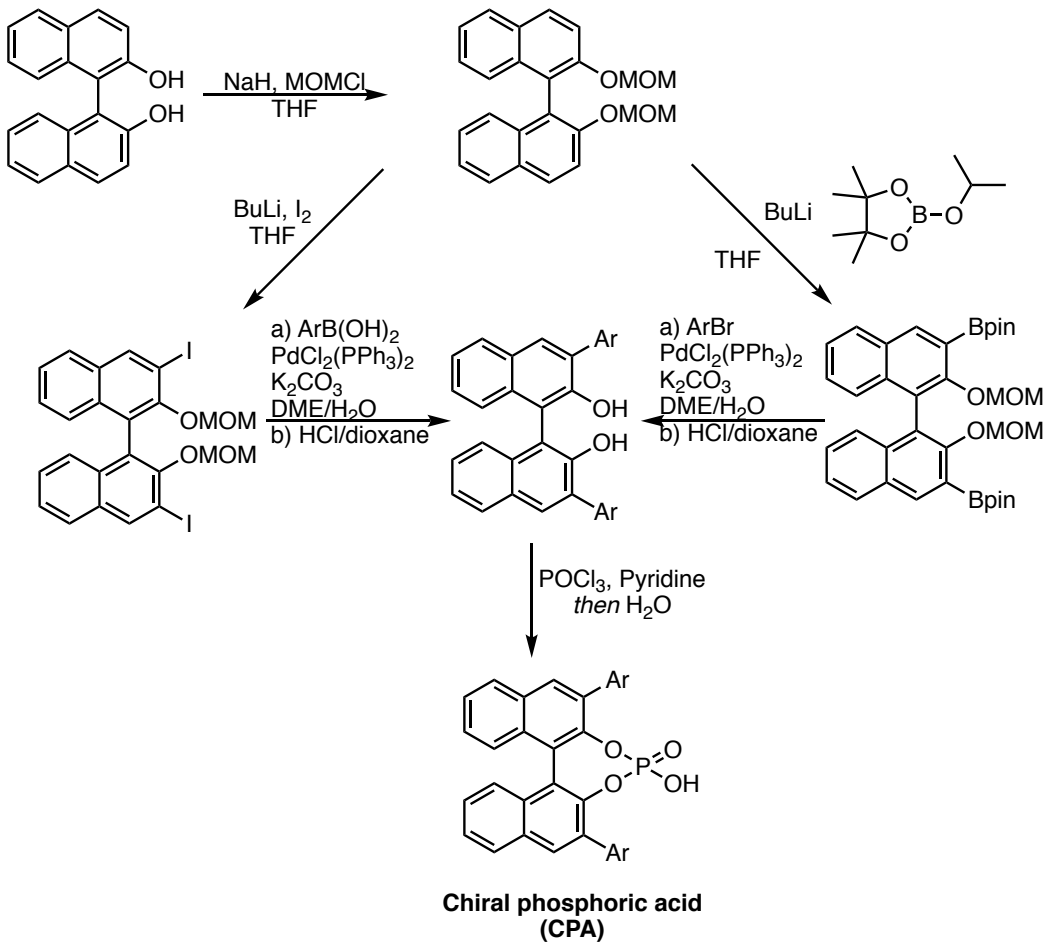


SCHEME 3.25 Proposal of organocatalytic Ugi-type Reactions.

The key point of this strategy is employing CPA as bifunctional catalysts, which can act both as a Lewis base – coordinating with the phenol – and Brønsted acid (to activate the imine for the nucleophilic attack of the isocyanide), mimicking the rigid structure proposed in the previous diastereoselective reports. [44,45]

The syntheses of chiral phosphoric acids (CPAs) are really modular and there are several reports on literature describing their preparation.[96] As shown in SCHEME 3.26, the first step is the protection of the BINOL with the methoxymethyl (MOM) group, followed by an iodination that occurs through ortho-lithiation with butyl lithium (BuLi) and quenching with iodine. This compound is next employed as substrate in a Suzuki coupling with a boronic acid (or ester) – with subsequent deprotection of the MOM group – to furnish the 3,3'-disubstituted BINOL. Alternately, a borate – $B(OR)_3$ – can be used in the lithiation step to quench the organolithium species. In this case, the borylation product obtained can be used as substrate with an aryl bromide in the Suzuki coupling to afford the same BINOL intermediate. It is noteworthy to mention that in some cases the Suzuki coupling is not capable of furnish the desired product in good yields, especially when highly bulky coupling partners are employed, *e.g.*, with 2,4,6-substituted aryl bromides. In such cases, other cross coupling procedures with more reactive organometallic compounds should be used, namely Kumada and Negishi couplings.

[96] A. G. Woldegiorgis, X. Lin, *Beilstein J. Org. Chem.* **2021**, *17*, 2729–.



SCHEME 3.26 Synthesis of BINOL-based chiral phosphoric acids.

The last step of the synthesis is the phosphorylation, which is accomplished by slow addition of the phosphoryl chloride ($POCl_3$) to a mixture modified BINOL and anhydrous pyridine. After full consumption of the BINOL, water is added to hydrolyze the intermediate and render the corresponding chiral phosphoric acid (CPA).

Regarding the synthesis of SPINOL-based catalysts, the synthetic route starts with the synthesis of the SPINOL, which can be done by the following 5-step procedure (SCHEME 3.27):[97]

1) Claisen-Schmidt condensation between acetone and 3-hydroxybenzaldehyde;

2) selective alkene reduction of the α,β-unsaturated ketone;

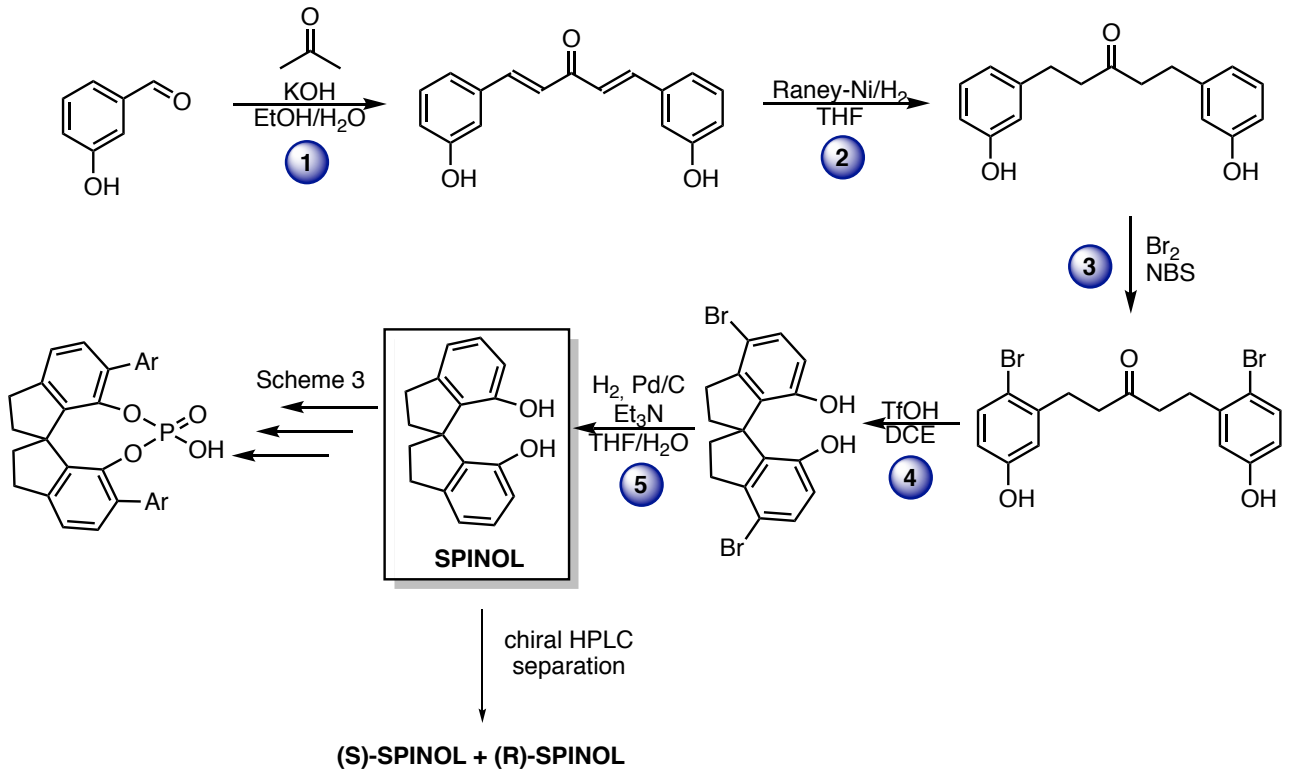
3) bromination of the aromatic ring;

4) cyclization via intramolecular Friedel-Crafts;

[97] S. Li, J.-W. Zhang, X.-L. Li, D.-J. Cheng, B. Tan, *J. Am. Chem. Soc.* **2016**, *138*, 16561.

5) debromination (the bromine is installed to control the selectivity of the Friedel-Crafts step).

After the synthesis of the SPINOL core, all the next steps are the same as described for the BINOL-based catalysts.



SCHEME 3.27 Synthesis of the SPINOL core.

Chiral phosphoric acids (CPAs) have been used as efficient organocatalysts since the first examples were reported by Akiyama[98] and Terada.[99] Although they were originally designed for enantioselective additions to imines, a wide reaction scope has been demonstrated using this type of catalyst.[100] Therefore, several research groups pursued to rationalize the features controlling the stereoselectivity of such catalysts, especially by developing models for the prediction of the stereochemical outcome of CPA-catalyzed reactions.[101] One of first models was the "Quadrant projection"

[98] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.*, 2004, **43**, 1566.
[99] D. Uraguchi, M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356.
[100] X. del Corte, E. M. de Marigorta, F. Palacios, J. Vicario, A. Maestro, *Org. Chem. Front.*, 2022, **9**, 6331.
[101] *(a)* I. D. Gridnev, M. Kouchi, K. Sorimachi, M. Terada, *Tetrahedron Lett.*, 2007, **48**, 497; *(b)* T. Marcelli, P. Hammar, F. Himo, *Chem. – Eur. J.*, 2008, **14**, 8562; *(c)* L. Simón, J. M. Goodman, *J.*

proposed by Terada[101a] and Himo.[101b] In this model (FIGURE 3.11, right), the catalyst is viewed along the C_2-axis, positioning resulting in the aryl substituents on the catalyst occupying two of four quadrants. The preferred TS structure is generally the one where the reactants are positioned in the unoccupied quadrants, providing a simple visual tool for a qualitative understanding of stereoselectivity.

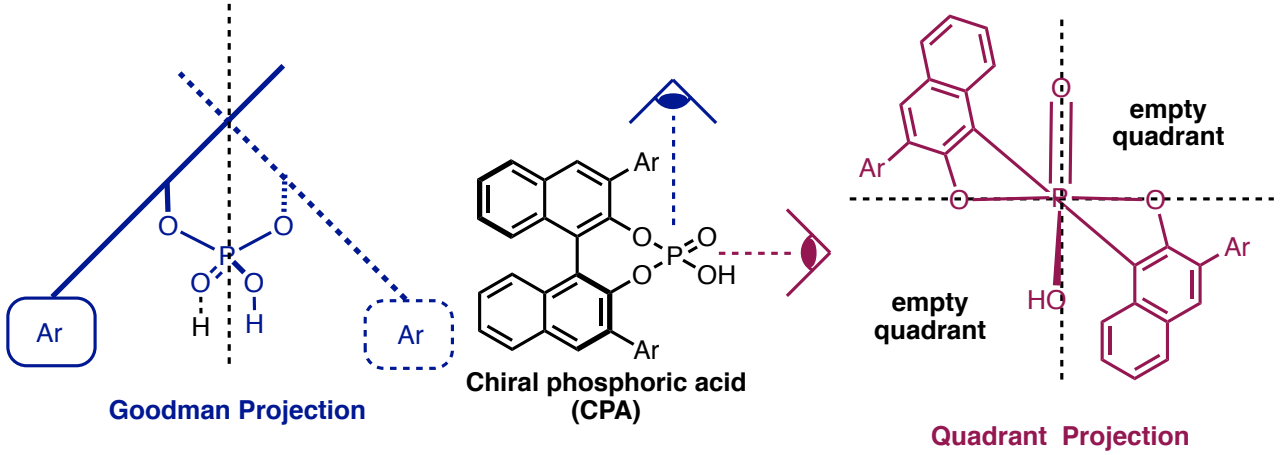


FIGURE 3.11 Goodman and Quadrant projections for a generic CPA catalyst.

Later, Goodman and co-workers[101c] have used this model to develop a general predictive model of imine hydrogenation reactions, known as the "Goodman projection" (FIGURE 3.11, left). In this case, the catalyst is oriented in a way that the BINOL oxygens are in the plane of the page, leaving the phosphoryl group above and below the page along with the 3,3' substituents.

As depicted in the FIGURE 3.12, it is possible to have four different transition states in the Goodman projection: the *N*-substituent of the imine can be pointed away from the bulky aryl substituents – *Type I* – or toward these aryl groups, called *Type II*. Also, the imine can be formed as *E* or *Z* stereoisomers, which is basically defined by steric size of the substituents. In all cases, the nucleophile is attacking from behind.

Org. Chem., 2011, **76**, 1775; *(d)* J. P. Reid, L. Simón, J. M. Goodman, *Acc. Chem. Res.*, 2016, **49**, 1029; *(d)* J. P. Reid, J. M. Goodman, *Chem. Eur. J.,* 2017, **23**, 14248; *(e)* A. Shoja, J. Zhai, J. P. Reid, *ACS Catal.*, 2021, **11**, 11897; *(f)* A. Shoja, J. P. Reid, *J. Am. Chem. Soc.*, 2021, **143**, 7209.

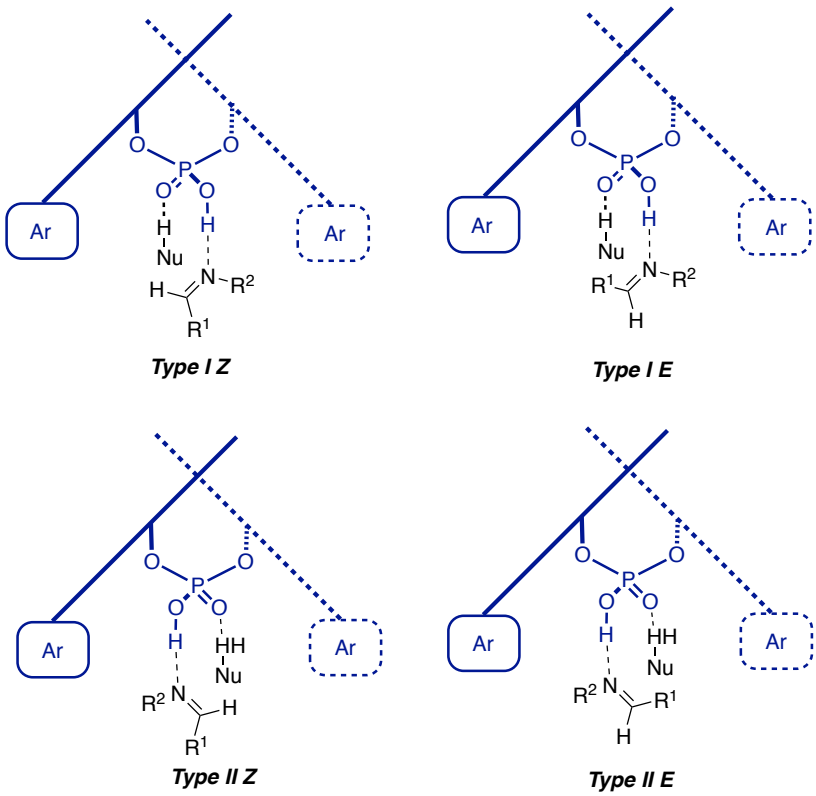


FIGURE 3.12. Transition state models for the prediction of the stereoselectivity with CPA catalysts.

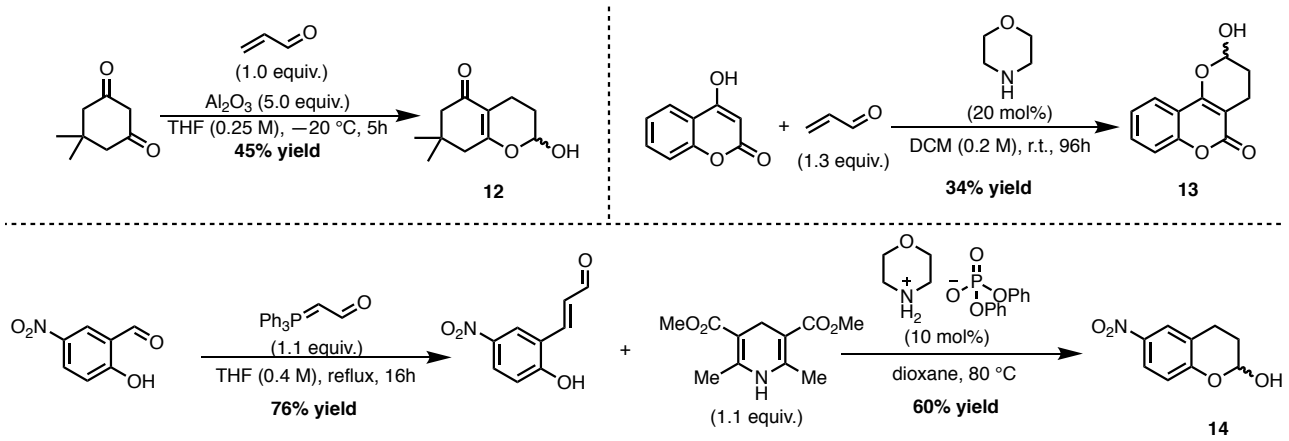
It is important to mention that *Type I Z* pathway is favored in the majority of the cases. Several interactions account for this preference: first, the unfavorable steric clash between the large phenyl substituent and the 3,3′ substituents disfavor the *E* transition state relative to the *Z*; similar steric interactions between the *N*-substituent and the 3,3′ group disfavor *Type II* relative to *Type I.*

3.2.1. Preparation of hemiacetals **12-14**

All the starting materials – hemiacetals – were prepared from slightly modified literature procedures (SCHEME 3.28). The hemiacetals **12** and **13** were prepared in a single step through catalyzed Michael addition to acrolein using dimedone[102] and 4-hydroxycoumarin,[103] respectively. On the other hand, a two-step procedure – a Wittig

[102] *(a)* Y. Nakamura, A. M. Burke, S. Kotani, J. W. Ziller, S D. Rychnovsky*, Org. Lett.* 2010, **12**, 72.
[103] P. T. Franke, B. Richter and K. A. Jørgensen, *Chem. - A Eur. J.* **2008**, *14*, 6317.

reaction [104] with subsequent reduction of the double bond [105] – was necessary to synthetize the hemiacetal **14**.

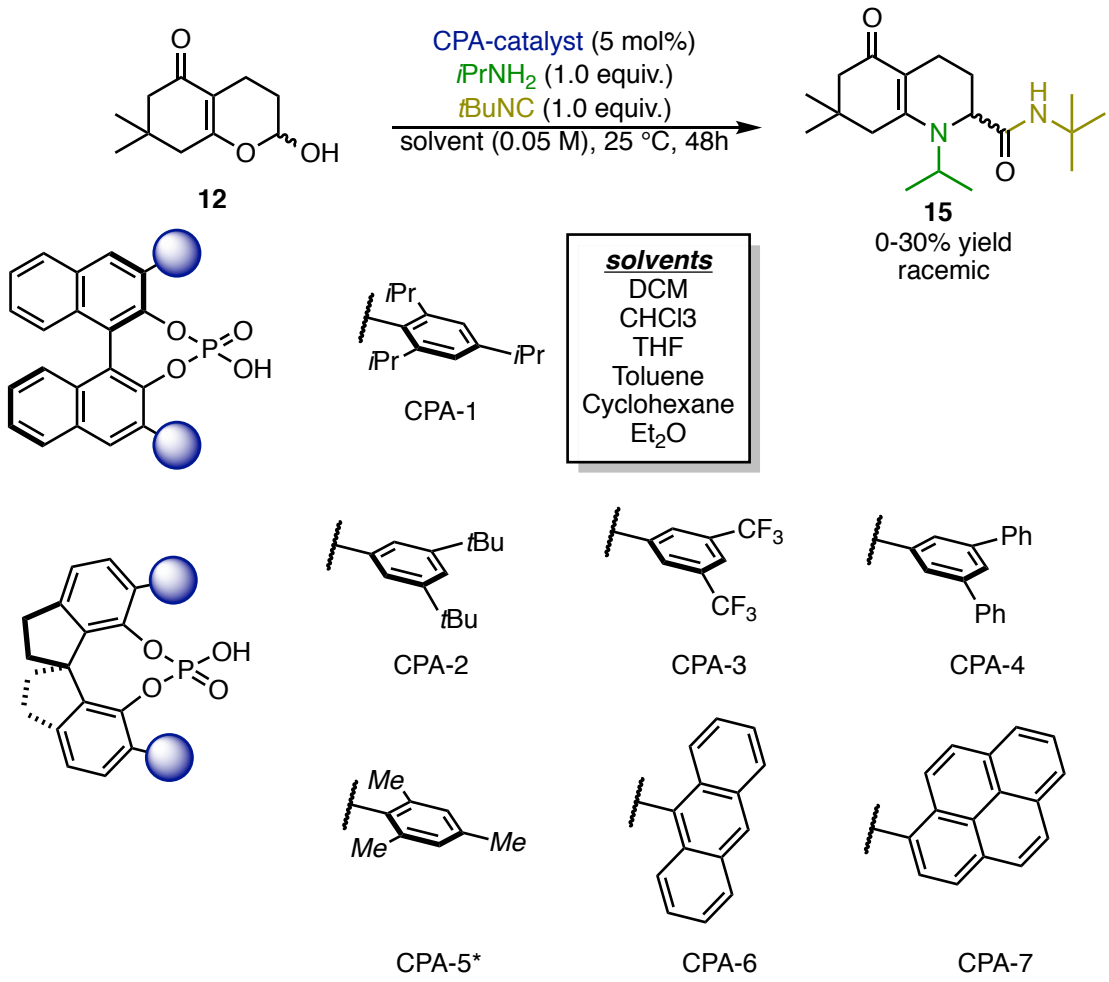


SCHEME 3.28 Synthesis of hemiacetals **12**-**14**.

3.2.1. Initial screening of the reaction conditions

The hemiacetal **12** was chosen as the model substrate for the initial screening of the conditions, due to starting material availability. Even though several different conditions regarding solvent (DCM, $CHCl_3$, THF, toluene, cyclohexane, ethyl ether) and organocatalysts. As shown in SCHEME 3.29, under different reaction conditions the desired product could only be obtained in low yields (0-30 %) and not even traces of enantioselectivity were observed.

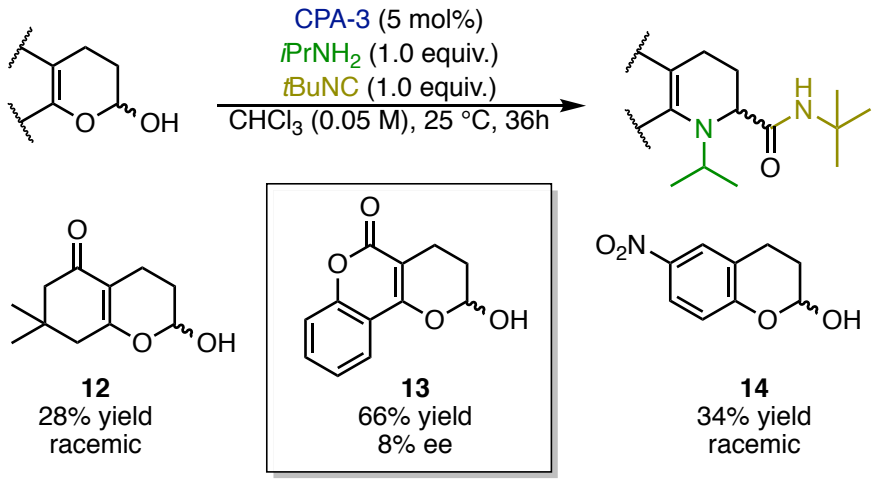
[104] DA SILVA, V. A. F. Síntese de precursores de heterociclos e sistemas cíclicos nitrogenados. São Carlos, Programa de Pós-Graduação em Química – UFSCar, 2018. Dissertação de mestrado.
[105] J. W. Yang, M.T. Hechavarria Fonseca, N. Vignola, B. List, A*ngew. Chem. Int. Ed.*, 2005, **44**, 108.



*(*R*)-catalyst was used.

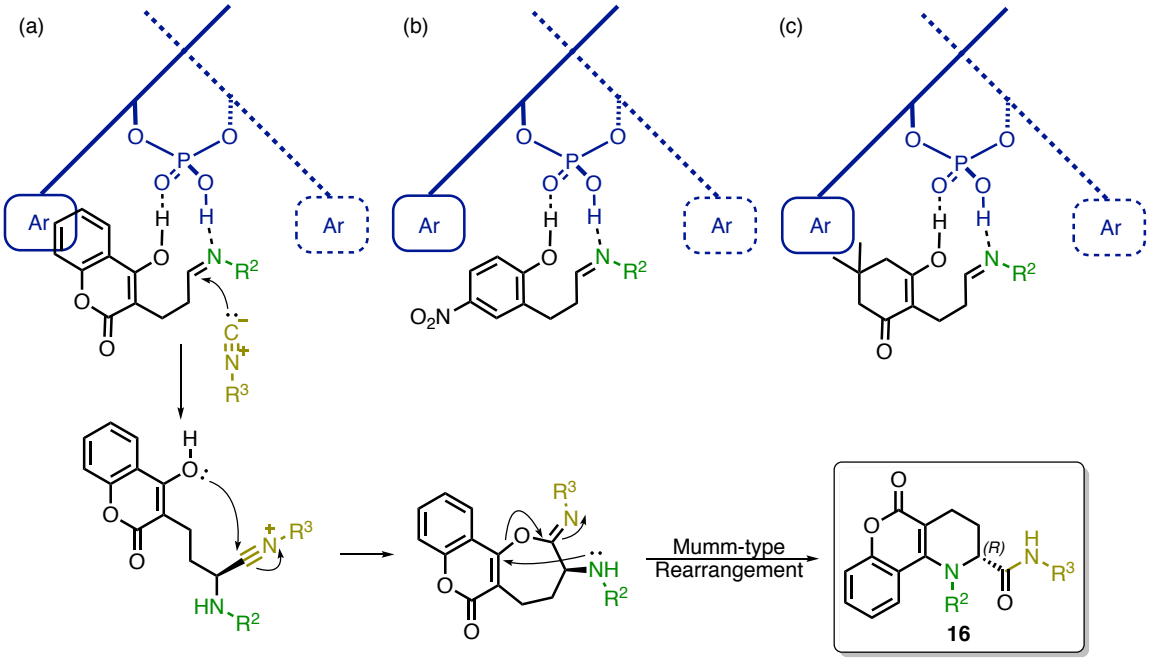
SCHEME 3.29 Initial catalyst and solvent screening for the asymmetric U-4C-3CR.

These results motivated the change of the model substrate: by submitting the all the hemiacetals to similar conditions. Since these compounds have different electronic nature (**12** is purely aliphatic, while **13** and **14** have electron-rich and -poor aromatic rings, respectively), it was also expected that they would render distinct results. Amongst them, the hemiacetal **13** presented better reactivity affording the Ugi-type product in 66% yield and small enantioselectivity, 8% ee (SCHEME 3.30). Therefore, this substrate was further employed in the optimization study.



SCHEME 3.30 Screening of hemiacetal using CPA-3.

As attempt to have a better understanding of the stereoselectivity in these systems and predict the expected absolute configuration for this reaction, an adaptation of the Goodman projection for your reaction was used (SCHEME 3.31).



SCHEME 3.31 Goodman projection for the prediction of the outcome of this reaction.

Since the *E* stereoisomer has no flexibility to interact with the catalyst with both the phenol and the imine, this reaction should undergo through the *Z* isomer, therefore the *Type I Z* transition state was chosen to represent all the cases. By analyzing the model, the imine formed from the hemiacetals **12** and **14** (SCHEME 3.31c and b, respectively) basically doesn't interact with the bulky substituents in the 3,3' position, while the imine formed from hemiacetal **13** (SCHEME 3.31c) is clearly bulkier and

might have non-covalent interactions (attractive or repulsive) with these groups, this insight can be an explanation for the stereoselectivity observed. Additionally, according to this model, the attack of the isocyanide should come from the top face, because the other face is shielded by the bulky substituent on the right side, ultimately rendering the (*R*)-enantiomer of the *N*-heterocycle **16** as the major product.

Next, MS and NMR analysis were carried out to determine if the isolated compound was the desired product. The MS spectrum of the compound **16** (FIGURE 3.13) shows the molecular ion peak for the expected structure, m/z = 342. Moreover, it is possible to observe three other peaks with significant intensity: m/z = 200, 242, 299.

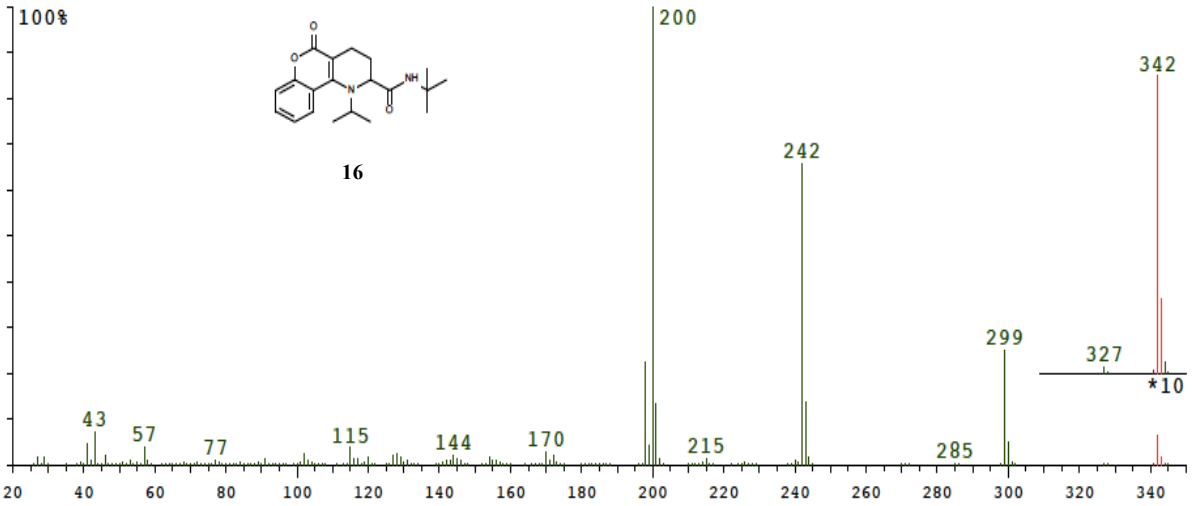
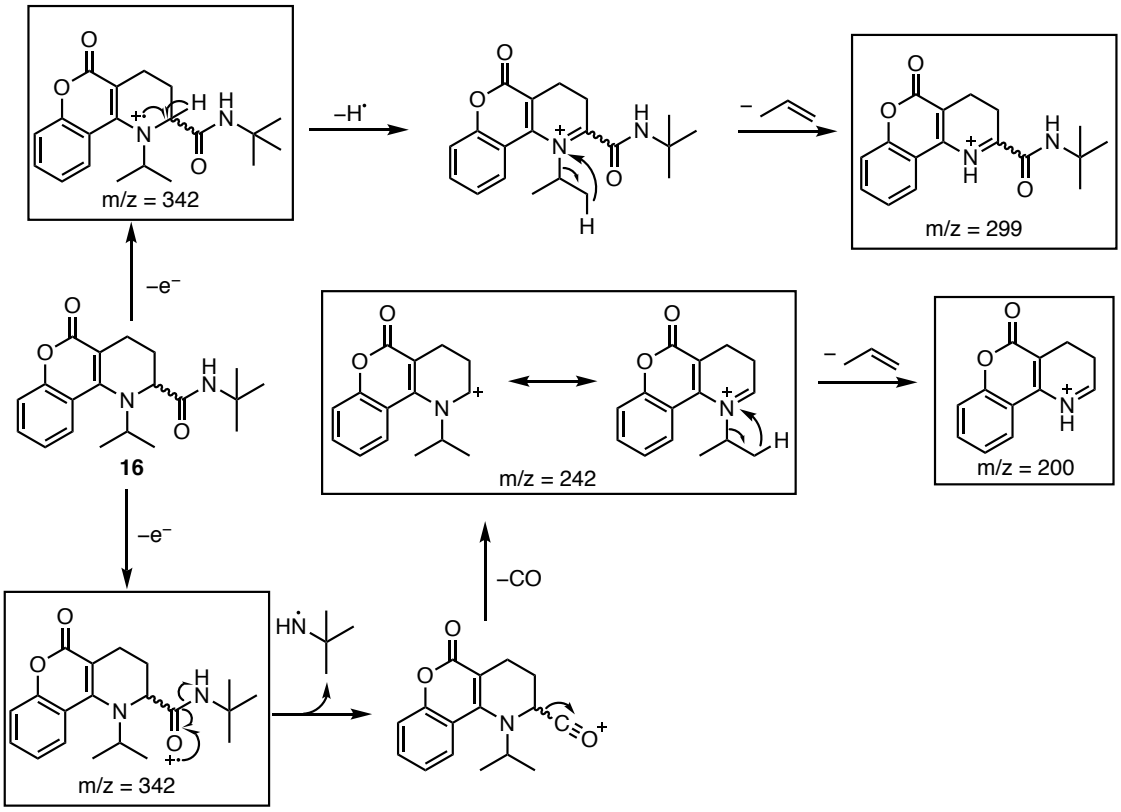


FIGURE 3.13 EI-MS spectrum of the compound 5.

The proposal for these fragmentations is depicted in the SCHEME 3.32, the ion with m/z = 242 is an α-aminocarbocation, which is stabilized by the lone pair of the oxygen to render an iminium, this cation is generated by the oxidation of the amide's oxygen, subsequent α-cleavage of the amide and loss of the carbon monoxide from acylium cation. This cation can further loss propene, through an onium reaction, to afford the ion with m/z = 200. Following another path, the ion with m/z = 299 is formed by the oxidation of the tertiary anime's oxygen and an onium reaction to release propene.



SCHEME 3.32 Proposal for the MS fragmentation of compound **5**.

To gather more information about the structure, the ^{1}H NMR experiment was carried out. After a simple analysis of the spectrum, there are some information that are in accordance with the proposed structure, such as (FIGURE 3.14):

- The two doublets (δ = 1.11 and 1.47 ppm) and the hepadobetet ((δ = 4.32 ppm) indicate the presence of the methyl groups (**11**) and the methine (**10**) of the isopropyl group from the amine;
- The singlet in δ = 1.11 adds up to the incorporation of the methyl groups (**1**) tert-butyl group from the isocyanide;
- The broad singlet (δ = 6.49) is typical of NH from amides, which is also present (**3**) in the desired and proposed structure;
- The doublet of doublets in δ = 3.93 is a typical chemical shift for the hydrogen between amino and carboxylic groups, such as the hydrogen **5** of the proposed structure.

According to these analyses, and checking similar compounds already reported in the literature,[44] it is possible to conclude that the isolated compound is the expected product **16**.

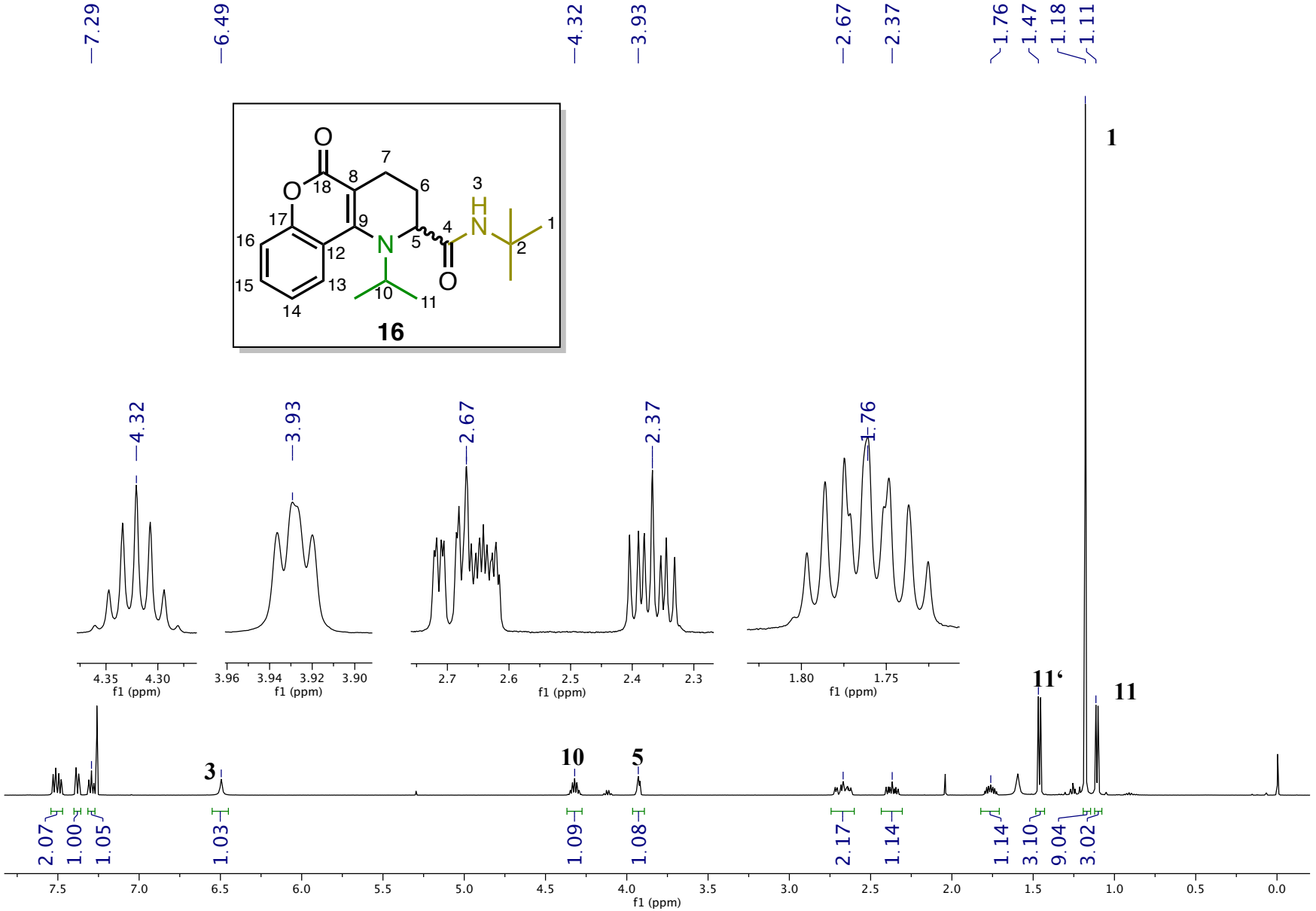
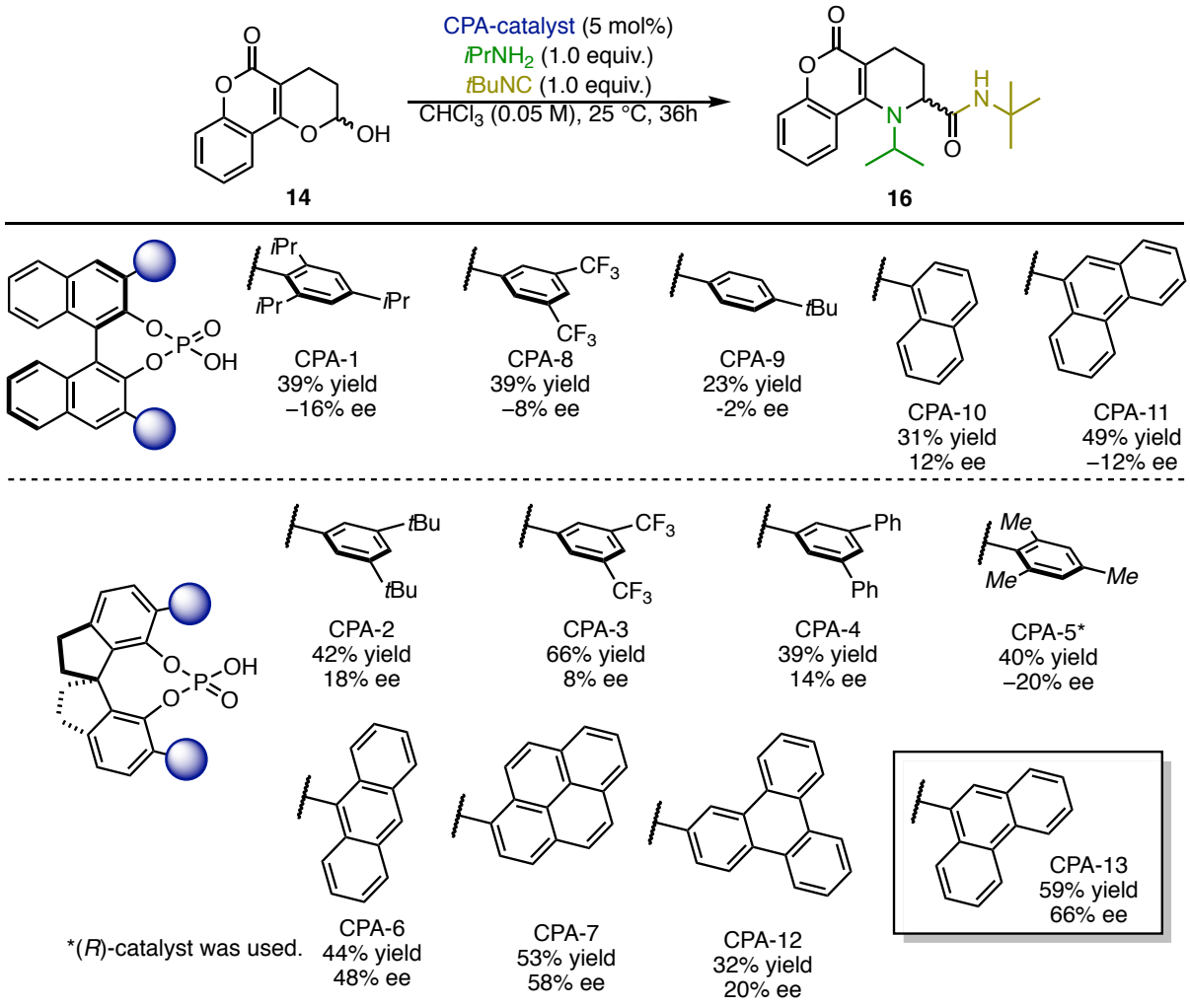


FIGURE 3.14 ^{1}H NMR spectrum of the compound **5** (500 MHz, $CDCl_3$).

Back to the optimization study of the enantioselective MCR, a small set of catalysts were screened (SCHEME 3.33), in general the SPINOL-derived chiral phosphoric acids (CPA) showed better reactivity than the conventional BINOL-derived ones, regarding enantioselectivity the CPAs substituted in the 3,3'-position with polyaromatic rings displayed promising enantioselectivity, especially with phenanthryl as substituent (CPA-13, 66% ee), which was chosen as the best catalyst in this initial screening.



SCHEME 3.33 Catalyst screening for the asymmetric U-4C-3CR using hemiacetal **14**.

After this initial screening, the next step should be evaluating a wide range of solvents, which will be selected as solvent for the screening of other two important parameters: temperature and concentration. At this stage, it is expected that by decreasing both of them should afford better outcomes regarding selectivity, even though these changes can result in an erosion of chemical yield.

Whether none of these modification on the condition lead to better results, a catalyst screening should be considered by testing new catalysts, especially SPINOL-based CPAs with different patterns of polyaromatic substitution and also some modifications at the 4-position. It is also important to mention that there is no linear relationship between catalysts and solvents, which means every promising catalyst has to be submitted to a solvent screening.

4. Conclusion

The structure of unexpected product of the Ugi-type reaction could be unambiguously determined by classic characterization techniques, NMR and MS. The developed method for the diastereoselective synthesis of *trans*-cyclopentenes proved to be efficient and applicable in a broad scope of substrates, affording more than 40 compounds in overall good results. Despite the low dependency on electronic features, electron-poor anilines, bearing strong electron-withdrawing groups, were a limitation of the method and no product could be isolated in such cases.

The protocol was also useful to construct complex structures, displaying a huge potential to be applied as a synthetic tool in both medicinal chemistry and combinatorial chemistry due to its ability of generating molecular complexity and diversity in a single shot. Under continuous flow regime, it was possible to increase the productivity of the reaction, providing almost 0.4 g of product after 6h of infusion.

Additionally, it was possible to synthetize – via Passerini-type reaction – valuable cyclopentenol scaffolds without changing the reaction conditions, which were used as substrate in a one-pot three-step procedure to achieve the complementary diastereoisomer (*cis*) obtained from the developed method.

In accordance with the literature, the nucleophilic attack of the isocyanide on the *Si* face is favored and governed by attractive non-covalent interactions between the isocyanide and the π-enol system of the hemiacetal. The preference for this pathway instead of the reported previously was also explained by DFT calculations, the preferred transition state **TS-2** displays a stabilizing intramolecular hydrogen bond between the amine and the enol, which brings together the atoms involved in the cyclization and also compensates the repulsion exerted by the amine substituent on the axial position. Therefore, this compact

transition is really sensitive to steric effects, what might explain the change for bulkier aryl groups to destabilize **TS-2**, leading the reaction to the THP-pathway (through **TS-4**).

The proposed mechanism is also something to be highlighted, the unexpected rearrangement taking place during the course of this reaction has potential to be applied in the development of new chemical reactions (multicomponent or not) in order to expand the synthetic chemical space.

The results regarding the asymmetric U-3C-4CR show that the proposal is feasible, even though only moderate reactivity (59% yield) and enantioselectivity (66% ee) were obtained using the phenanthryl chiral SPINOL-phosphoric acid derivative (CPA-13) after a short catalyst screening.

Interestingly, SPINOL-based CPAs afforded better results comparing to its BINOL-based counterparts, also polyaromatic substituents (*e.g.* anthracenyl, pyrenyl, phenanthryl) displayed good results. Showing that the next step in the optimization should be the variation of other parameters of interest (temperature and concentration). Whether no improvement is observed, a new catalyst screening has to be done by preparing some SPINOL-based catalysts with polyaromatic substituents (substituted biaryl, chrysene) or substitution on the 4-position.

Furthermore, according to the "adapted" Goodman projection, it was proposed the expected absolute configuration of the *N*-heterocyclic product **16** and explain qualitatively the enantioselectivity obtained by the hemiacetal **13**, when compared to hemiacetals **12** and **14**.

In summary, these results combined illustrate that hemiacetals are promising substrates, due to its rigidity and multiple point of interactions, to use in asymmetric induction strategies, either by substrate or catalyst-controllled reactions.

5. References

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6. Experimental data

6.1. General information

Reagents and materials were purchased from the highest commercially available grade and used without further purification. Flash column chromatography was carried out using silica gel 60 (230-400 mesh) and reactions were monitored using analytical thin layer chromatography (TLC). NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C, unless otherwise noted. Chemical shifts (δ =) are reported in parts per million relatives to the tetramethylsilane (TMS) and coupling constants (*J*) are reported in hertz (Hz). All signals are reported in ppm with the internal reference of residual solvent signals (7.26 or 77.1 ppm for chloroform; 3.31 or 49.0 ppm for methanol). Data are presented as follows: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad, dd = doublet of doublet, dt = doublet of triplet), coupling constant (J/Hz) and integration. The diastereoisomeric ratio (dr) was determined by integration of the ^{1}H NMR spectra of the crude reaction mixture. Only the characterization data for the major isomer is given.

The enantiomeric excess (ee) of products was determined by High Performance Liquid Chromatography (HPLC) or Ultraperformance Convergence Chromatography (UPC^2) analysis. HPLC chromatograms were obtained on an apparatus with a LC-10AT Pump, SPD-10AUV-Vis Detector, SCL-10A System Controller, using a Chiralpak AS-H column (4.6 mmØ × 250 mmL, particle size 5 μm). UPC^2 chromatograms were recorded by Waters ACQUITY UPC^2 using Trefoil CEL2 (2.5 μm, 3 x 15 mm), AMY1 (2.5 μm, 3 x 15 mm) and CEL1 (2.5 μm, 3 x 15 mm) columns as chiral stationary phases with PDA detection. Optical rotations were measured on a PerkinElmer 241 polarimeter at 589 nm and 20 °C, $[\alpha]_D$ values are given in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$; concentration c in g. $(100\ mL)^{-1}$. High resolution mass spectra (HRMS) were performed on a Waters Acquity UPLC H-

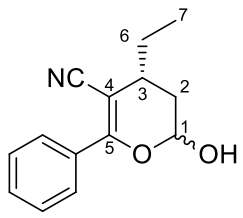
Class System Xevo G2-XS Q-TOF Spectrometer (ESI-Q-TOF). Melting points were determined using a Büchi M-560 Basic Melting Point Apparatus. GC-MS analysis were performed using a Shimadzu GCMS-QP2010S Gas Chromatograph coupled to a MS detector equipped with an Zebron ZB5-MS capillary column (30 m x 0.32 mm, 0.25 μm) under the operation parameters: temperature of inlet of 250 °C, temperature of the interface of 300 °C, temperature ramp of the oven from 50 to 250 °C at a rate of 10 °C min^{-1}.

6.2. Diastereoselective synthesis of cyclopentenes

6.2.1. General procedure for the synthesis of hemiacetals 1a-h

To a solution of Jørgensen catalyst (0.1 equiv.) and 3,5-dinitrobenzoic acid (0.2 equiv.) in toluene (0.1 M) at –20 °C was added the *α*,*β*-unsaturated aldehyde under magnetic stirring. After 20 min, benzoyl acetonitrile was introduced into the reaction mixture. The resulting solution was stirred for 48h at the same temperature. The volatiles were concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

(4*R*)-Ethyl-2-hydroxy-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1a)



Prepared according general procedure using benzoylacetonitrile (888 mg, 6.1 mmol) and pent-2-enal (390 μL, 4.0 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow solid (595 mg, 2.6 mmol, 65% yield, 94% ee). m.p. 66-68 °C. $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 4.0 (*c* 0.5, acetone, 20°C). R_f = 0.23 (*n*-hexane/ EtOAc 4:1).

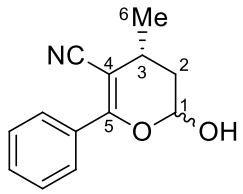
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.67 (m, 2H, Ph), 7.46 – 7.37 (m, 3H, Ph), 5.66 (t, *J* = 3.5 Hz, H-1$_{major}$), 5.47 (d, *J*=8.7, 1H, H-1$_{minor}$), 3.65 (brs, 1H, OH), 2.68 – 2.53 (m, 1H), 2.11 – 1.92 (m, 2H), 1.76 – 1.46 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6 (C-5_{minor}), 162.5 (C-5_{major}), 133.5, 130.9 (minor), 130.7 (major), 128.5(minor), 128.4 (major), 128.3 (minor), 128.2 (major), 119.6 (CN), 96.2 (C-1_{minor}), 92.8 (C-1_{major}), 89.3 (C-4_{major}), 88.8 (C-4_{minor}), 34.4 (C-2_{minor}), 33.1 (C-6_{minor}), 30.8 (C-2_{major}), 30.3 (C-6_{major}), 26.6 (C-3), 10.8 (C-7_{major}), 10.6 (C-7_{minor}).

HRMS (ESI-Q-TOF) *m/z*: 230.1182 $[M+H]^+$; calcd. for $C_{14}H_{16}NO_2$: 230.1176.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 90:10 until 5 min then isocratic 90:10, flow rate = 2 mL/min, 25 °C, λ = 264 nm, t_R = 4.79 min (minor) and t_R = 5.19 min (major), 94% ee.

(4*R*)-2-hydroxy-4-methyl-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1b)



Prepared according general procedure using benzoylacetonitrile (145 mg, 1 mmol) and (*E*)-but-2-enal (165 µL, 2 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a brown oil (193 mg, 0.9 mmol, 90% yield, 2:1 dr, 98% ee). $[\alpha]_D^{20}$ + 5.8 (*c* 0.6, acetone, 20°C). R_f = 0.36 (*n*-hexane/ EtOAc 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.64 (m, 2H, Ph), 7.45 – 7.30 (m, 3H, Ph), 5.56 (t, *J* = 2.5 Hz, 1H, H-1_{major}), 5.39 (d, *J* = 8.6 Hz, 1H, H-1_{minor}), 4.58 (brs, 1H, OH), 2.82 – 2.68 (m, $1H_{major}$), 2.71 – 2.57 (m, $1H_{minor}$), 2.18 (ddd, *J* = 13.5, 6.4, 1.7 Hz, $1H_{minor}$), 2.02 (dt, *J* = 13.6, 5.0 Hz, $1H_{major}$), 1.67 – 1.56 (m, 1H), 1.33 – 1.22 (m, 3H, H-6).

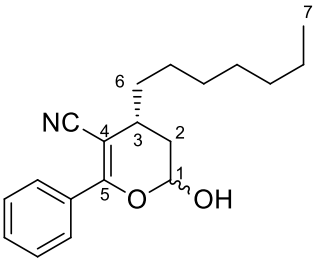
^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.5 (C-5_{minor}), 162.6 (C-5_{major}), 133.4 (Ph_{major}), 133.0 (Ph_{minor}), 130.8 (Ph_{minor}), 130.6 (Ph_{minor}), 128.3 (Ph_{minor}), 128.3 (Ph_{major}), 128.1 (Ph_{major}), 128.1 (Ph_{major}), 119.7 (CN), 95.8 (C-1_{minor}), 92.5 (C-1_{major}), 89.4

(C-5_{major}), 88.8 (C-4_{minor}), 36.2 (C-2_{minor}), 34.3 (C-2_{major}), 28.3 (C-6_{minor}), 24.2 (C-6_{major}), 19.8 (C-3).

HRMS (ESI-Q-TOF) *m/z*: 216.1025 $[M+H]^+$; calcd. for $C_{13}H_{14}NO_2$: 216.1019.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 60:40 in 5 min, flow rate = 1 mL/min, 35 °C, λ = 248 nm, t_R = 4.23 min (minor) and t_R = 4.52 min (major), 98% ee.

(4*R*)-4-heptyl-2-hydroxy-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1c)



Prepared according general procedure using benzoylacetronitrile (87 mg, 0.6 mmol) and (*E*)-dec-2-enal (183 µL, 1 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a brown oil (126 mg, 0.42 mmol, 70% yield, 2:1 dr, > 99% ee). $[\alpha]_D^{20}$ + 1.6 (*c* 0.5, acetone, 20°C). R_f = 0.53 (*n*-hexane/ EtOAc 7:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 – 7.66 (m, 2H), 7.45 – 7.33 (m, 3H), 5.61 (s, 1H, H-1_{major}), 5.42 (t, *J* = 7.2 Hz, 1H, H-1_{minor}), 3.88 (brs, 1H, OH), 2.69 – 2.49 (m, 1H), 2.23 (dd, *J* = 13.4, 6.3 Hz, 1H, H-1_{minor}), 2.04 (dt, *J* = 13.7, 5.2 Hz, 1H, H-1_{major}), 1.97 – 1.83 (m, 1H), 1.78 – 1.58 (m, 1H), 1.51 – 1.17 (m, 11H), 0.89 (t, *J* = 6.6 Hz, 3H, H-7).

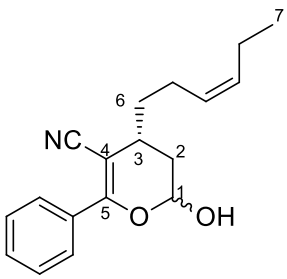
^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6 (C-5_{minor}), 162.5 (C-5_{major}), 133.6 (Ph_{major}), 133.1 (Ph_{minor}), 130.8 (Ph_{minor}), 130.7 (Ph_{minor}), 128.4 (Ph_{major}), 128.3 (Ph_{major}), 128.2 (Ph_{major}), 119.7 (CN), 96.2 (C-1_{minor}), 92.8 (C-1_{major}), 89.4 (C-4_{major}), 88.9 (C-4_{minor}), 33.9 (major), 33.9 (minor), 33.7 (minor), 33.2 (minor), 31.9 (major), 31.5 (major), 29.7 (major), 29.6 (minor), 29.3 (major), 29.2 (major), 26.5 (major), 26.4 (minor), 22.8 (major), 14.2 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 300.1971 $[M+H]^+$; calcd. for $C_{19}H_{26}NO_2$: 300.1958.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 80:20 until 2 min then isocratic 80:20, flow rate

= 0.8 mL/min, 25 °C, λ = 264 nm, t_R = 4.01 min (minor) and t_R = 4.25 min (major), > 99% ee.

(4*R*)-4-((*Z*)-hex-3-en-1-yl)-2-hydroxy-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1d)



Prepared according general procedure using benzoylacetonitrile (44 mg, 0.3 mmol) and (2*E*,6*Z*)-nona-2,6-dienal (96 µL, 0.6 mmol). Obtained after column chromatography purification (*n*-hexane/EtOAc 4:1) as a brown oil (59 mg, 0.21 mmol, 70% yield, 3:1 dr, 98% ee). $[\alpha]_D^{20}$ + 4.2 (*c* 0.5, acetone, 20°C). R_f = 0.61 (*n*-hexane/ EtOAc 7:3).

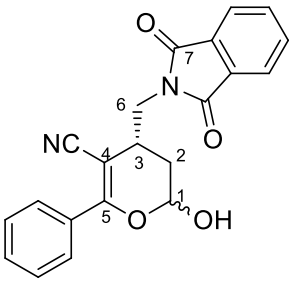
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.63 (m, 2H), 7.52 – 7.38 (m, 3H), 5.65 (t, *J* = 3.4 Hz, 1H, H-1), 5.56 – 5.27 (m, 2H), 3.54 (brs, 1H, OH), 2.79 – 2.56 (m, 1H), 2.26 – 1.94 (m, 6H), 1.84 – 1.41 (m, 3H), 0.98 (td, *J* = 7.5, 1.1 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.4 (C-5), 133.5 (minor), 132.9 (major), 130.9 (Ph_{major}), 130.7 (major), 128.4 (Ph_{major}), 128.3 (Ph_{major}), 128.2 (Ph_{major}), 127.7 (Ph_{minor}), 127.7 (Ph_{minor}), 119.6 (CN_{minor}), 119.5 (CN_{major}), 96.0 (C-1_{minor}), 92.7 (C-1_{major}), 89.4 (C-4_{major}), 89.0 (C-4_{minor}), 33.8 (major), 33.8 (minor), 33.5 (minor), 32.7 (minor), 31.4 (major), 28.8 (major), 24.1 (major), 24.0 (minor), 20.8 (major), 14.4 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 284.3326 $[M+H]^+$; calcd. for $C_{18}H_{22}NO_2$: 284.3345.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 80:20 until 2 min then isocratic 80:20, flow rate = 1 mL/min, 25 °C, λ = 220 nm, t_R = 4.59 min (minor) and t_R = 4.31 min (major), 98% ee.

(4*R*)-4-((1,3-dioxoisoindolin-2-yl)methyl)-2-hydroxy-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1e)



Prepared according general procedure using benzoylacetonitrile (43.5 mg, 0.3 mmol) and (*E*)-4-(1,3-dioxoisoindolin-2-yl)but-2-enal (77.4 mg, 0.36 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a brown oil (101 mg, 0.28 mmol, 93% yield, 2:1 dr, > 99% ee). $[\alpha]_D^{20}$ + 7.4 (*c* 0.5, acetone, 20°C). R_f = 0.36 (*n*-hexane/ EtOAc 7:3).

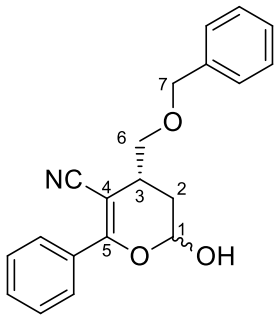
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 – 7.83 (m, 2H, Ph), 7.81 – 7.66 (m, 4H, Ph), 7.54 – 7.33 (m, 3H, Ph), 5.70 (brs, 1H, H-1_{major}), 5.65 (brs, 1H, H-1_{minor}), 4.33 (dd, *J*=13.6, 7.2 Hz, 1H, H-$6a_{minor}$), 4.14 (dd, *J* = 13.7, 5.8 Hz, 1H, H-$6a_{major}$), 3.92 (dd, *J* = 13.8, 7.9 Hz, 1H, H-$6b_{minor}$), 3.81 (dd, *J* = 13.7, 9.5, 1H, H-6_{major}), 3.31 – 3.10 (m, 1H), 2.22 – 1.79 (m, 2H), 1.71 (brs, 1H, OH).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7 (C-7_{minor}), 168.4 (C-7_{major}), 164.1 (C-5_{major}), 164.0 (C-5_{minor}), 134.3 (Ph_{major}), 134.2 (Ph_{minor}), 132.9 (Ph_{minor}), 132.8 (Ph_{minor}), 131.9 (Ph_{minor}), 131.8 (Ph_{minor}), 130.9 (Ph_{major}), 128.4 (Ph_{major}), 128.2 (Ph_{major}), 128.2 (Ph_{major}), 123.6 (Ph_{major}), 119.4 (CN_{minor}), 119.0 (CN_{major}), 94.1 (C-1_{minor}), 92.6 (C-1_{major}), 84.8 (C-4_{minor}), 84.8 (C-4_{major}), 41.6 (C-6_{minor}), 41.2 (C-6_{major}), 31.2 (C-2_{minor}), 30.1 (C-2_{major}), 29.8 (C-3).

HRMS (ESI-Q-TOF) *m/z*: 361.1181 $[M+H]^+$; calcd. for $C_{21}H_{17}N_2O_4$: 361.1183.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, isocratic CO_2/MeOH = 65:35, flow rate = 1 mL/min, 35 °C, λ = 267 nm, t_R = 1.71 min (major) and t_R = 2.15 min (minor), > 99% ee.

(4*R*)-4-((benzyloxy)methyl)-2-hydroxy-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1f)



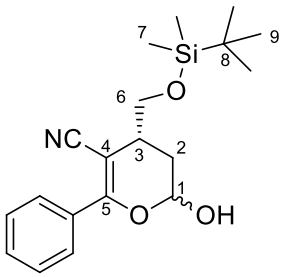
Prepared according the general procedure using benzoylacetonitrile (290 mg, 2.0 mmol) and (*E*)-4-(benzyloxy)but-2-enal (532 mg, 2.0 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as an orange oil (386 mg, 1.20 mmol, 60% yield, 3:1 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 1.1 (*c* 0.5, acetone, 20°C). R_f = 0.10 (*n*-hexane/ EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.69 (m, 2H), 7.48 – 7.27 (m, 8H), 6.89 (d, *J* = 11.2, 1H, OH), 5.66 (s, 1H, H-1a), 5.58 (d, *J* = 11.2 Hz, 1H, H-1b), 4.74 – 4.59 (m, 2H, H-7b), 4.59 (s, 2H, H-7a), 3.98 (dd, *J* = 9.7, 3.2 Hz, 1H, H-6b), 3.77 (dd, *J* = 9.7, 3.4 Hz, 1H, H-6a), 3.69 (dd, *J* = 9.5, 6.5 Hz, 1H, H-6a), 3.53 (dd, *J* = 9.8, 2.3 Hz, 1H, H-6b), 2.92 (qd, *J* = 6.9, 3.4 Hz, 1H, H-3b), 2.82 (d, *J* = 8.5 Hz, 1H, H-3a), 2.44 (ddd, *J* = 13.2, 9.1, 3.5 Hz, 1H, H-2), 2.11 – 2.02 (m, 1H, H-2).

^{13}C NMR (100 MHz, CDCl3) δ = 164.7 (C-5b), 163.8 (C-5a), 138.1 (Ph-a), 136.2 (Ph-b), 133.6 (Ph-a), 133.6 (Ph-b), 133.4 (Ph-a), 130.9 (Ph-b), 130.8 (Ph-a), 128.8 (Ph-b), 128.6 (Ph-a), 128.4 (Ph-b), 128.2 (Ph-b), 127.9 (Ph-a), 127.9 (Ph-a), 127.8 (Ph-b), 119.6 (CN-b), 119.3 (CN-a), 93.2 (C-1a), 91.6 (C-1b), 85.4 (C-4a), 84.1 (C-4b), 74.2 (C-6b), 73.6 (C-6a), 71.3 (C-7a), 71.3 (C-7b), 31.9 (C-3b), 31.5 (C-3b), 31.1 (C-2a), 30.1 (C-3a).

HRMS (ESI-Q-TOF) *m/z*: 344.1443 $[M+H]^+$; calcd. for $C_{20}H_{19}NO_3Na$: 344.1263. The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/MeOH = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 292 nm, t_R = 5.27 min (major) and t_R = 5.40 min (minor), > 99% ee.

(4*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-hydroxy-6-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1g)



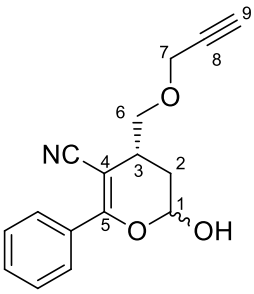
Prepared according the general procedure using benzoylacetonitrile (290 mg, 2.0 mmol) and *(E)*-4-((tert-butyldimethylsilyl)oxy)but-2-enal (400 mg, 2.0 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a yellow oil (132 mg, 0.38 mmol, 19% yield, 9:1 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 2.6 (*c* 0.5, acetone, 20°C). R_f = 0.33 (*n*-hexane/ EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.67 (m, 2H, Ph), 7.49 – 7.36 (m, 3H, Ph), 7.30 – 7.23 (m, 1H), 5.72 (brs, 1H, H-1a), 5.59 (d, *J* = 11.7 Hz, 1H, H-1b), 4.18 (dd, *J*=10.7, 3.0, 1H, H-6b), 3.92 – 3.80 (m, 1H, H-6a), 3.67 (dd, *J* = 10.6, 1.9 Hz, 1H, H-6b), 3.56 (brs, 1H, H-6a), 2.82 – 2.72 (m, 1H, H-2), 2.47 (dddd, *J* = 14.0, 9.1, 3.4, 1.2 Hz, 1H, H-3), 2.18 – 1.92 (m, 1H, H-2), 0.90 (d, *J* = 3.5 Hz, 9H, H-9), 0.16 (d, *J* = 5.6 Hz, 3H, H-7), 0.10 (d, *J* = 3.8 Hz, 3H, H-7).

^{13}C NMR (100 MHz, CDCl3) δ = 165.0 (C-5b), 164.0 (C-5a), 133.7 (Ph-b), 130.8 (Ph-b), 130.6 (Ph-a), 128.4 (Ph-b), 128.3 (Ph-a), 128.2 (Ph-b), 128.1 (Ph-a), 119.7 (CN), 93.4 (C-1a), 91.5 (C-1b), 85.2 (C-4a), 83.8 (C-4b), 65.4 (C-6b), 64.3 (C-6a), 33.6 (C-2b), 33.2 (C-2a), 31.7 (C-8b), 30.0 (C-8a), 25.9 (C-9a), 25.7 (C-9b), 18.3 (C-3), -5.4 (C-7a), -5.6 (C-7b), -5.6 (C-7b).

HRMS (ESI-Q-TOF) *m/z*: 346.1842 $[M+H]^+$; calcd. for $C_{19}H_{28}NO_3Si$: 346.1833. The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/MeOH = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 280 nm, t_R = 3.29 min (major) and t_R = 3.94 min (minor), > 99% ee.

(4*R*)-2-hydroxy-6-phenyl-4-((prop-2-yn-1-yloxy)methyl)-3,4-dihydro-2*H*-pyran-5-carbonitrile (1h)



Prepared according the general procedure using benzoylacetonitrile (145 mg, 1.0 mmol) and *(E)*-4-(prop-2-yn-1-yloxy)but-2-enal (149 mg, 1.2 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow oil (128 mg, 0.48 mmol, 48% yield, 1:1 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 2.2 (*c* 0.5, acetone, 20°C). R_f = 0.08 (*n*-hexane/ EtOAc 4:1).

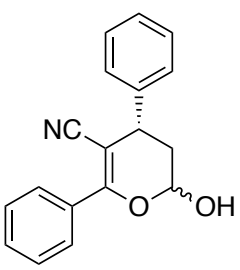
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.67 (m, 2H, Ph), 7.48 – 7.35 (m, 3H, Ph), 6.20 (s, 1H, OH), 5.69 (t, *J* = 3.8 Hz, 1H, H-1a), 5.59 (brs, 1H, H-1b), 4.37 – 4.18 (m, 2H), 4.00 (dd, *J* = 9.6, 3.7 Hz, 1H, H-6a), 3.83 (dd, *J* = 9.4, 3.4 Hz, 1H, H-6b), 3.76 – 3.66 (m, 1H), 2.96 – 2.83 (m, 1H), 2.50 (dd, *J* = 23.0, 2.1 Hz, 1H), 2.42 (dd, *J* = 9.5, 3.8 Hz, 1H, H-2a), 2.12 (dt, *J* = 14.8, 2.6 Hz, 1H, H-2b), 2.05 (dd, *J* = 7.4, 3.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.7 (C-5a), 163.9 (C-5b), 133.5 (Ph-a), 133.3 (Ph-b), 131.0 (Ph-a), 130.8 (Ph-b), 128.4, 128.2, 119.4 (CN-a), 119.2 (CN-b), 93.2 (C-1a), 91.9 (C-1b), 85.2 (C-4a), 84.0 (C-4b), 79.4 (C-8a), 77.9 (C-8b), 76.3 (C-9a), 75.0 (C- 9b), 71.1 (C-6a), 70.9 (C-6b), 59.0 (C-7a), 58.7 (C-7b), 31.8 (C-2a), 31.3 (C-3a), 30.8 (C-2b), 30.0 (C-3b).

HRMS (ESI-Q-TOF) *m/z*: 268.0975 $[M-H]^-$; calcd. for $C_{16}H_{14}NO_3$: 268.0979.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/MeCN = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 300 nm, t_R = 3.64 min (minor) and t_R = 3.74 min (major), > 99% ee.

(4*S*)-2-hydroxy-4,6-diphenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile (1i)



Prepared according procedure of the respective literature.[81] All spectroscopic data are in accordance with the same reference.

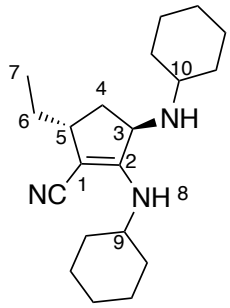
The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, Gradient CO_2/iPrOH = 100:0 to 80:20 until 2 min

then isocratic 80:20, flow rate = 1 mL/min, 25 °C, λ = 220 nm, t_R = 4.13 min (minor) and t_R = 4.50 min (major), 98% ee.

6.2.2. General multicomponent reaction procedure for the synthesis of cyclopentenes 2a-2z/2aa-2as

The hemiacetal **1a-1h** (0.15 mmol, 1 equiv.) was dissolved in trifluoroethanol (0.3 mL), and the amine (0.15 mmol, 1.0 equiv.) was added to this mixture. Triethylamine (0.16 mmol, 1.1 equiv.) was also added to the reaction when α-amino acid and peptide methyl ester hydrochlorides were employed as amino components. After 10 minutes, the isocyanide (0.15 mmol, 1.0 equiv.) was introduced into this solution and the glass tube was sealed. The flask was irradiated for 20 min (300 W) under high-speed magnetic stirring in the microwave reactor, while the temperature was raised up to 70 °C. The volatiles was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

(3*R*,5*R*)-2,3-bis(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2a)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 5:1) as a pale yellow oil (44 mg, 0.14 mmol, 93% yield, 79:21 dr, 76% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 12.4 (*c* 0.5, acetone, 20°C). R_f = 0.36 (*n*-hexane/ EtOAc 6:1).

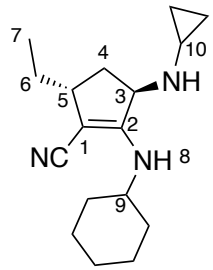
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.11 (d, *J* = 8.0 Hz, 1H, H-8), 3.84-3.71 (m, 1H, H-9), 3.66 (dd, *J* = 9.0/ 7.6 Hz, 1H, H-3), 2.64 (td, *J* = 8.2/5.6 Hz, 1H, H-5), 2.54-2.43 (m, 1H, H-10), 2.09-1.99 (m, 4H), 1.76-1.66 (m, 4H), 1.65-1.32 (m, 8H), 1.28-1.06 (m, 8H), 0.92 (t, J = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.3 (C), 121.4, 71.5, 60.3 54.9, 51.3, 43.5, 37.6 (CH_2), 35.2, 33.6, 33.4, 28.0, 25.9, 25.6, 25.0, 24.8, 24.3, 24.2, 11.8 (CH_3).

HRMS (ESI-Q-TOF) *m/z*: 316.2755 $[M+H]^+$; calcd. for $C_{20}H_{34}N_3$: 316.2757.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, isocratic gradient CO_2/iPrOH = 90:10, flow rate = 1 mL/min, 35 °C, λ = 269 nm, t_R = 3.64 min (minor) and t_R = 3.64 min (major), 76% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-3-(cyclopropylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2b)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclopropylamine (10 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a brown oil (16 mg, 0.06 mmol, 40% yield, 80:20 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 5.6 (*c* 0.5, acetone, 20°C). R_f = 0.37 (*n*-hexane/ EtOAc 4:1).

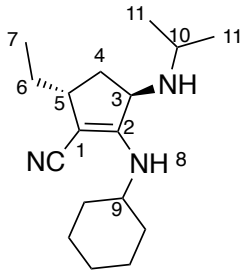
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.92 (d, *J* = 8.3 Hz, 1H, H-8), 3.80 – 3.70 (m, 2H), 2.75 – 2.67 (m, 1H), 2.25 – 2.18 (m, 1H), 2.12 – 1.97 (m, 3H), 1.76 – 1.58 (m, 5H), 1.48 – 1.08 (m, 7H), 0.93 (t, *J* = 7.4 Hz, 3H, H-7), 0.57 – 0.43 (m, 3H), 0.35 – 0.27 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.5 (C-2), 121.2 (CN), 73.2 (C-1), 63.0, 51.7, 44.0, 35.9, 33.7, 33.7, 28.2, 28.1, 25.7, 24.5, 24.4, 11.8 (C-7), 6.8, 6.5.

HRMS (ESI-Q-TOF) *m/z*: 274.2278 $[M+H]^+$; calcd. for $C_{17}H_{27}N_3$: 274.2288.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/MeOH = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 245 nm, t_R = 3.55 min (minor) and t_R = 3.79 min (major), > 99% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(isopropylamino)cyclopent-1-ene-1-carbonitrile (2c)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), isopropylamine (12 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale yellow oil (32 mg, 0.12 mmol, 78% yield, 99:1 dr, 93% ee). $[\alpha]_D^{20}$ – 8.1 (*c* 0.5, acetone, 20°C). R_f = 0.36 (*n*-hexane/ EtOAc 7:3).

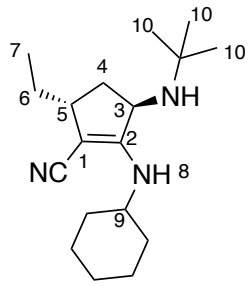
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.10 (d, *J* = 8.7 Hz, 1H), 381 – 3.71 (m, 1H), 3.63 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.88 (hept, *J* = 6.2 Hz, 1H), 2.67- 2.61 (m, 1H), 2.08 – 2.02 (m, 2H), 1.75 – 1.66 (m, 2H), 1.66 – 1.53 (m, 2H), 1.51 – 1.35 (m, 3H), 1.35 – 1.23 (m, 1H), 1.21 – 1.10 (m, 4H), 1.04 (d, *J* = 6.3 Hz, 3H, H-11), 1.00 (d, *J* = 6.1 Hz, 3H, H-11), 0.91 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2 (C-2), 121.6 (CN), 71.7 (C-1), 60.5, 51.5, 46.9, 43.7, 37.3, 33.7, 33.6, 28.1, 25.7, 24.7, 24.5, 24.3, 22.8, 11.9.

HRMS (ESI-Q-TOF) *m/z*: 276.2431 $[M+H]^+$; calcd. for $C_{17}H_{30}N_3$: 276.2434.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/EtOH = 100:0 to 85:15 until 2 min then isocratic 85:15, flow rate = 1 mL/min, 25 °C, λ = 267 nm, t_R = 3.80 min (major) and t_R = 4.45 min (minor), 93% ee.

(3*R*,5*R*)-3-(*tert*-butylamino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2d)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *tert*-butylamine (37 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 5:1) as a pale yellow oil (39 mg, 0.13 mmol, 89% yield, > 99:1 dr, 94% ee). $[\alpha]_D^{20}$ – 10.3 (*c* 0.4, acetone, 20°C). R_f= 0.40 (*n*-hexane/ EtOAc 3:1).

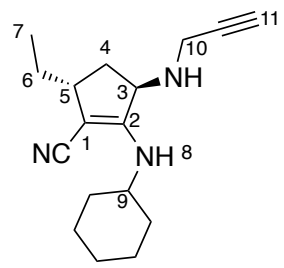
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.18 (d, *J* = 8.6 Hz, 1H, H-8), 3.77 (dtd, *J* = 13.4, 9.3, 3.8 Hz, 1H, H-9), 3.60 (dd, *J* = 10.0, 7.2 Hz, 1H, H-3), 2.60 (td, *J* = 8.3, 5.1 Hz, 1H, H-5), 2.08 (dd, *J* = 12.5, 7.2 Hz, 1H, H-4a), 2.05 – 1.98 (m, 2H), 1.73 – 1.51 (m, 5H), 1.50 – 1.35 (m, 2H), 1.39 – 1.27 (m, 1H), 1.25 – 1.11 (m, 4H), 1.08 (s, 9H, H-10), 0.93 (t, *J* = 7.3 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.1 (C-2), 121.7 (CN), 70.7 (C-1), 57.5, 51.2, 50.7, 43.5, 40.6, 33.7, 33.4, 30.6 (C-10), 28.1, 25.8, 24.3, 24.2, 12.1 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 290.2598 $[M+H]^+$; calcd. for $C_{18}H_{32}N_3$: 290.2596.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, isocratic gradient CO_2/MeCN = 95:5, flow rate = 1 mL/min, 25 °C, λ = 269 nm, t_R = 2.32 min (minor) and t_R = 2.49 min (major), 94% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(prop-2-yn-1-ylamino)cyclopent-1-ene-1-carbonitrile (2e)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), propargyl amine (10 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (40 mg, 0.15 mmol, 98% yield, 99:1 dr, 99% ee). $[\alpha]_D^{20}$ – 4.8 (*c* 0.5, acetone, 20°C). R_f = 0.55 (*n*-hexane/ EtOAc 7:3).

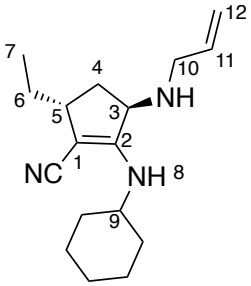
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.93 (d, *J* = 8.7 Hz, 1H, H-8), 3.78 – 3.65 (m, 2H, H-3, H-9), 3.45 – 3.27 (m, 2H, H-10), 2.70 – 2.59 (m, 1H), 2.20 (t, *J*=2.1, 1H, H-11), 2.06 – 1.93 (m, 3H), 1.72 – 1.49 (m, 6H), 1.40 – 1.30 (m, 2H), 1.30 – 1.16 (m, 1H), 1.16 – 1.01 (m, 3H), 0.86 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.3 (C-2), 121.1 (CN), 81.9, 73.3 (C-1), 72.2 (C-11), 62.8, 51.8, 44.0, 36.2, 35.8, 33.7, 28.1, 25.7, 24.5, 24.4, 11.7 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 272.2121 $[M+H]^+$; calcd. for $C_{17}H_{26}N_3$: 272.2121.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 90:10 in 24 min, flow rate = 0.8 mL/min, 25 °C, λ = 254 nm, t_R = 13.40 min (minor) and t_R = 14.35 min (major), 99% ee.

(3*R*,5*R*)-3-(allylamino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2f)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), allylamine (11 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc

4:1) as a pale brown oil (26 mg, 0.10 mmol, 64% yield, 99:1 dr, 88% ee). $[\alpha]_D^{20}$ – 6.3 (*c* 0.5, acetone, 20°C). R_f = 0.39 (*n*-hexane/ EtOAc 7:3).

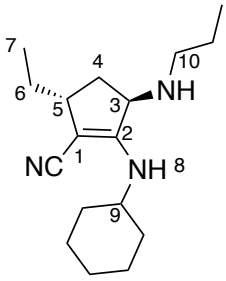
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.86 (ddt, *J* = 16.4, 10.7, 5.9 Hz, 1H, H-11), 5.19 (d, *J* = 17.2 Hz, 1H, H-12), 5.10 (d, *J* = 10.2 Hz, 1H, H-12), 5.05 (d, *J* = 8.7 Hz, 1H, H-8), 3.78 (tq, *J* = 10.1, 4.1 Hz, 1H, H-10), 3.68 (t, *J* = 8.1 Hz, 1H, H-3), 3.30 – 3.12 (m, 2H), 2.68 (q, *J* = 7.9 Hz, 1H), 2.10 – 1.93 (m, 3H), 1.75 – 1.66 (m, 2H), 1.65 – 1.54 (m, 3H), 1.48 – 1.34 (m, 2H), 1.34 – 1.23 (m, 1H), 1.22 – 1.07 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0 (C-2), 136.7 (C-11), 121.3 (CN), 116.3 (C-12), 72.6 (C-1), 62.3, 51.6, 49.4, 43.8, 35.7, 33.7, 33.6, 28.2, 25.7, 24.4, 24.3, 11.8 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 276.2286 $[M+H]^+$; calcd. for $C_{17}H_{28}N_3$: 276.2278.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 85:15 in 9 min, flow rate = 2 mL/min, 25 °C, λ = 254 nm, t_R = 7.28 min (major) and t_R = 8.48 min (minor), 88% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(propylamino)cyclopent-1-ene-1-carbonitrile (2g)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *n*-propylamine (12 µL, 0.15 mmol) and cyclohexyl isocyanide (18.7 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (16 mg, 0.06 mmol, 38% yield, 99:1 dr, 88% ee). $[\alpha]_D^{20}$ + 1.3 (*c* 0.2, acetone, 20°C). R_f = 0.35 (*n*-hexane/ EtOAc 7:3).

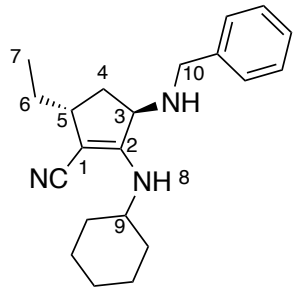
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.15 (d, *J* = 8.6 Hz, 1H, H-8), 3.85 – 3.71 (m, 1H, H-9), 3.69 (t, *J* = 8.1 Hz, 1H, H-3), 2.74 – 2.62 (m, 1H), 2.52 (dddd, *J* = 17.8, 14.2, 11.4, 6.7 Hz, 2H), 2.04 (d, *J* = 11.4 Hz, 2H), 1.96 (ddd, *J* = 12.8, 7.4, 1.9 Hz, 1H), 1.76 – 1.62 (m, 2H), 1.67 – 1.54 (m, 3H), 1.53 – 1.38 (m, 4H), 1.37 – 1.21 (m, 2H), 1.22 – 1.08 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 1H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157-8 (C-2), 121.3 (CN), 72.7 (C-2), 62.7, 51.6, 48.2, 43.9, 35.2, 33.7, 33.6, 28.2, 25.7, 24.4, 24.3, 23.7, 11.9, 11.8 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 274.2445 $[M+H]^+$; calcd. for $C_{17}H_{28}N_3$: 274.2434.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 90:10 in 24 min, flow rate = 0.8 mL/min, 25 °C, λ = 254 nm, t_R = 13.40 min (minor) and t_R = 14.35 min (major), 88% ee.

(3*R*,5*R*)-3-(benzylamino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2h)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), benzylamine (16 µL, 0.15 mmol), and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification as an orange oil (25 mg, 0.12 mmol, 77% yield, 80:20 dr, 88% ee). $[\alpha]_D^{20}$ – 9.2 (*c* 0.5, acetone, 20°C). R_f = 0.32 (*n*-hexane/ EtOAc 4:1).

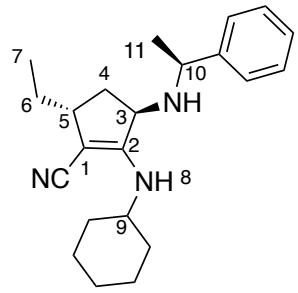
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.25 (m, 5H, Ph), 5.05 (d, *J* = 8.7 Hz, 1H, H-8), 3.82 – 3.69 (m, 4H), 2.74 – 2.67 (m, 1H, H-9), 2.05 – 1.95 (m, 3H), 1.77 – 1.53 (m, 6H), 1.48 – 1.36 (m, 2H), 1.34 – 1.07 (m, 5H), 0.91 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (C-2), 39.9, 128.6, 128.2, 127.4, 121.2 (CN), 72.9 (C-1), 62.4, 51.6, 50.7, 43.9, 35.5, 33.7, 28.2, 25.7, 24.4, 24.3, 11.7 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 324.2443 $[M+H]^+$; calcd. for $C_{21}H_{30}N_3$: 324.2440.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/iPrOH = 100:0 to 60:40 until 5 min then isocratic 60:40, flow rate = 1 mL/min, 35 °C, λ = 269 nm, t_R = 5.32 min (minor) and t_R = 5.47 min (major), 88% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(((*S*)-1-phenylethyl)amino)cyclopent-1-ene-1-carbonitrile (2i)



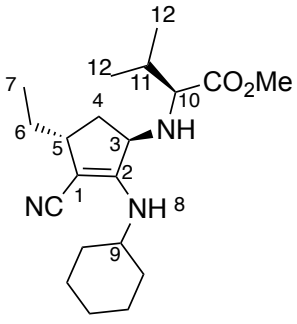
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), (*S*)-α-methylbenzylamine (19 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 5:1) as a brown oil (46 mg, 0.14 mmol, 91% yield, 83:17 dr). $[\alpha]_D^{20}$ – 5.9 (*c* 0.6, acetone, 20°C). R_f = 0.37 (*n*-hexane/ EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.24 (m, 3H, Ph), 7.23 – 7.16 (m, 2H, Ph), 4.86 (d, *J* = 8.7, 1H, H-8), 3.80 (q, *J* = 6.5, 1H, H-10), 3.74 – 3.58 (m, 1H, H-9), 3.28 (t, *J* = 7.6, 1H, H-3), 2.64 – 2.47 (m, 1H), 2.03 – 1.85 (m, 3H), 1.70 – 1.57 (m, 3H), 1.53 – 1.33 (m, 4H), 1.26 (d, *J* = 6.6, 3H, H-11), 1.21 – 1.00 (m, 6H), 0.77 (t, *J* = 7.4, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9 (C-2), 144.9, 128.7, 127.5, 126.9, 121.3 (CN), 72.2 (C-1), 60.4, 56.1, 51.4, 43.7, 36.6, 33.7, 33.6, 28.2, 25.7, 25.6 (C-11), 24.4, 24.3, 11.8 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 338.2596 $[M+H]^+$; calcd. for $C_{22}H_{32}N_3$: 338.2599.

Methyl ((1*R*,4*R*)-3-cyano-2-(cyclohexylamino)-4-ethylcyclopent-2-en-1-yl)-*L*-valinate (2j)



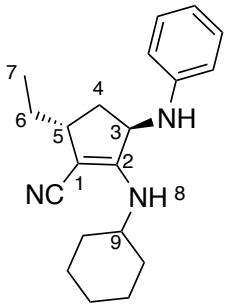
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *L*-valine methyl ester hydrochloride (25 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol) and triethylamine (23 µL, 0.16 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a brown oil (35 mg, 0.10 mmol, 67% yield, 86:14 dr). $[\alpha]_D^{20}$ – 28.2 (*c* 0.6, acetone, 20°C). R_f = 0.33 (*n*-hexane/ EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.27 (d, *J* = 8.4 Hz, 1H, H-8), 3.72 (s, 3H, OMe), 3.63 (t, *J* = 7.7 Hz, 1H, H-3), 3.01 (d, *J* = 5.1 Hz, 1H, H-10), 2.72 – 2.61 (m, 1H, H-9), 2.09 – 2.02 (m, 2H), 1.94 (td, *J* = 13.3 and 6.8 Hz, 1H), 1.76 – 1.69 (m, 4H), 1.63 – 1.56 (m, 3H), 1.38 – 1.17 (m, 7H), 0.94 (d, *J* = 6.8 Hz, 3H, H-12), 0.90 (d, *J* = 6.9 Hz, 3H, H-12), 0.89 (t, *J* = 7.5 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.2 (C=O), 157.6 (C-2), 121.2 (CN), 73.1 (C-1), 63.7, 62.1, 52.1, 51.6, 43.8, 34.8, 33.7, 33.6, 31.9, 27.9, 25.7, 24.4, 24.3, 19.6, 18.4, 11.8 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 348.2654 $[M+H]^+$; calcd. for $C_{22}H_{32}N_3$: 348.2646.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(phenylamino)cyclopent-1-ene-1-carbonitrile (2k)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), aniline (14 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale yellow oil (41 mg, 0.13 mmol, 88% yield, 92:8 dr, 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$–10.1 (*c* 0.6, acetone, 20°C). R_f = 0.35 (*n*-hexane/ EtOAc 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (t, *J* = 7.7 Hz, 2H, Ph), 6.81 (t, *J* = 7.4 Hz, 1H, Ph), 6.68 (d, *J* = 8.0 Hz, 2H, Ph), 4.71 (d, *J* = 8.7 Hz, 1H, H-8), 4.49 (t, *J* = 7.8 Hz, 1H, H-3), 3.89 – 3.70 (m, 1H, H-9), 2.80 – 2.71 (m, 1H), 2.11 – 1.94 (m, 3H), 1.93 – 1.80 (m, 1H), 1.77 – 1.57 (m, 4H), 1.50 – 1.05 (m, 7H), 0.94 (t, *J* = 7.3 Hz, 2H, H-7).

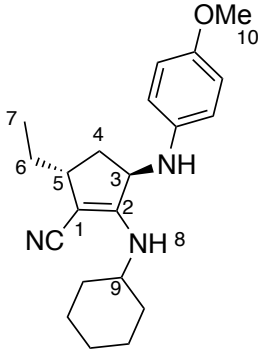
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.2 (C-2), 146.2 (Ph), 129.6 (Ph), 120.7 (CN), 119.3 (Ph), 114.5 (Ph), 74.2 (C-1), 59.7, 52.0, 43.6, 34.7, 33.7, 28.1, 25.6, 24.4, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 310.2283 $[M+H]^+$; calcd. for $C_{20}H_{28}N_3$: 310.2288.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/iPrOH = 100:0 to 60:40 until 5 min then isocratic 60:40, flow rate

= 1 mL/min, 35 °C, λ = 265 nm, t_R = 5.84 min (major) and t_R = 5.99 min (minor), 99% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-((4-methoxyphenyl)amino)cyclopent-1-ene-1-carbonitrile (2l)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *p*-anisidine (18 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 5:1) as a brown oil (41 mg, 0.12 mmol, 80% yield, 90:10 dr, 94% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 11.7 (*c* 0.6, acetone, 20°C). R_f = 0.36 (*n*-hexane/ EtOAc 4:1).

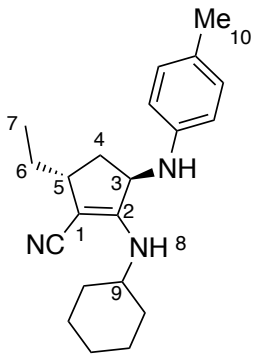
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.24-7.20 (m, 2H, Ph), 7.16-6.82 (m, 2H, Ph), 5.98 (d, *J* = 8.2 Hz, 1H, H-8), 4.52-4.38 (m, 1H, H-9), 4.13 (t, *J* = 7.2 Hz, 1H, H-3), 3.68 (s, 3H, H-10), 2.29-2.09 (m, 2H, H-4), 2.00-1.92 (m, 2H), 1.85-1.57 (m, 6H), 1.55-1.39 (m, 4H), 1.28-1.10 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.2 (C-2), 153.2, 140.2, 120.7, 115.9, 115.0, 114.1 (CN), 73.7 (C-1), 60.5, 55.7, 51.8, 43.5, 34.6, 33.6, 33.5, 25.5, 24.3, 24.2, 11.5 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 340.2391 $[M+H]^+$; calcd. for $C_{21}H_{30}N_3O$: 340.2389.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/iPrOH = 100:0 to 80:20 until 5 min then isocratic 80:20, flow rate = 1 mL/min, 25 °C, λ = 265 nm, t_R = 5.90 min (major) and t_R = 6.01 min (minor), 94% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(*p*-tolylamino)cyclopent-1-ene-1-carbonitrile (2m)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *p*-toluidine (16 μL, 0.15 mmol) and cyclohexyl isocyanide (19 μL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (46 mg, 0.14 mmol, 95% yield, 91:9 dr, 92% ee). $[\alpha]_D^{20}$ – 7.9 (*c* 0.5, acetone, 20°C). R_f = 0.76 (*n*-hexane/ EtOAc 7:3).

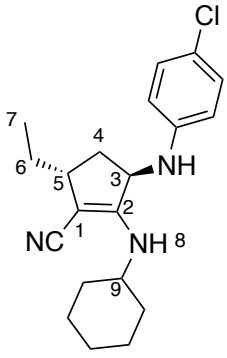
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.01 (d, *J* = 8.6, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.69 (d, *J* = 8.6 Hz, 1H, H-8), 4.44 (t, *J* = 7.9 Hz, 1H), 3.86 – 3.74 (m, 1H), 2.25 (s, 3H, H-10), 2.10 – 2.00 (m, 2H), 1.97 (ddd, *J* = 13.0, 7.6, 2.5 Hz, 1H), 1.81 (dt, *J* = 13.0, 8.3 Hz, 1H), 1.73 – 1.55 (m, 5H), 1.47 – 1.30 (m, 3H), 1.21 – 1.03 (m, 3H), 0.93 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.5 (C-2), 144.0, 130.0, 128.4, 120.7, 114.5, 73.8 (C-1), 59.8, 51.8, 43.5, 34.7, 33.6, 28.1, 25.5, 24.3, 24.2, 20.4, 11.5 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 324.2445 $[M+H]^+$; calcd. for $C_{21}H_{30}N_3$: 324.2434.

The enantiomeric ratio was determined by HLPC analysis using Chiralpak AS-H, isocratic Hex/EtOH = 90:10, flow rate = 0.5 mL/min, 25 °C, λ = 254 nm, t_R = 12.0 min (minor) and t_R = 16.0 min (major), 92% ee.

(3*R*,5*R*)-3-((4-chlorophenyl)amino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2n)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), 4-chloroaniline (19 mg, 0.15 mmol) and cyclohexyl isocyanide (19 μL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a brown solid (51 mg, 0.15 mmol, 99% yield, > 99:1 dr, > 99% ee). m.p. 78-82°C. $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 8.9 (*c* 0.5, acetone, 20°C). R_f = 0.53 (*n*-hexane/ EtOAc 4:1).

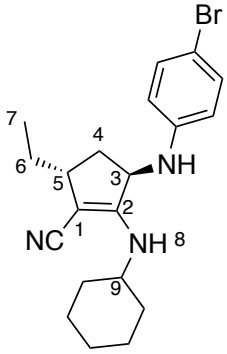
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.64 (d, *J* = 8.6 Hz, 1H, H-8), 4.38 (t, *J* = 8.2 Hz, 1H, H-3), 3.89 – 3.74 (m, 1H), 3.50 (brs, 1H, NH), 2.83 – 2.54 (m, 1H), 2.17 – 1.77 (m, 4H), 1.76 – 1.55 (m, 4H), 1.49 – 1.04 (m, 7H), 0.92 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9 (C-2), 145.0 (C), 129.5 (CH), 123.8 (C), 120.5 (CN), 115.6 (C), 115.5 (CH), 74.6 (CN), 59.8, 52.1, 43.7, 34.5, 33.8, 28.2, 25.6, 24.5, 24.3, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 344.1906 $[M+H]^+$; calcd. for $C_{20}H_{26}ClN_3$: 344.1888.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/MeOH = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 315 nm, t_R = 4.79 min (minor) and t_R = 4.84 min (major), > 99% ee.

(3*R*,5*R*)-3-((4-bromophenyl)amino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2o)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), 4-bromoaniline (26 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 5:1) as a dark yellow oil (45 mg, 0.12 mmol, 77% yield, 99:1 dr, 97% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ $[\alpha]_D^{20}$– 15.4 (*c* 0.6, acetone, 20°C). R_f = 0.39 (*n*-hexane/ EtOAc 4:1).

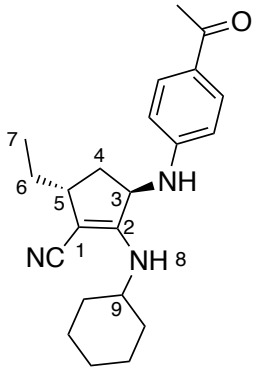
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 8.7, 2H, Ph), 6.46 (d, *J* = 8.7, 2H, Ph), 4.52 (d, *J* = 8.6 Hz, 1H, H-8), 4.36 (t, *J* = 7.8 Hz, 1H, H-3), 3.75-3.61 (m, 1H, H-9), 2.76-2.65 (m, 1H), 2.03-1.93 (m, 2H), 1.91-1.71 (m, 2H, H-4), 1.67-1.51 (m, 4H), 1.41-1.23 (m, 3H), 1.14-0.97 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9 (C-2), 145.5, 132.3, 120.5, 115.9, 110.7 (CN), 74.5 (C-1), 59.6, 52.0, 43.6, 34.5, 33.7, 28.1, 25.6, 24.4, 24.3, 24.2, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 388.1392 $[M+H]^+$; calcd. for $C_{20}H_{27}BrN_3$: 388.1388.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/MeCN = 100:0 to 80:20 until 5 min then isocratic 80:20, flow rate = 1 mL/min, 25 °C, λ = 261 nm, t_R = 5.65 min (major) and t_R = 5.76 min (minor), 97% ee.

(3*R*,5*R*)-3-((4-acetylphenyl)amino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2p)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), 4'-aminoacetophenone (20 mg, 0.15 mmol) and cyclohexyl isocyanide (19 μL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as an orange oil (30 mg, 0.08 mmol, 56% yield, 58:42 dr, 94% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 2.1 (*c* 0.5, acetone, 20°C). R_f = 0.20 (*n*-hexane/ EtOAc 4:1).

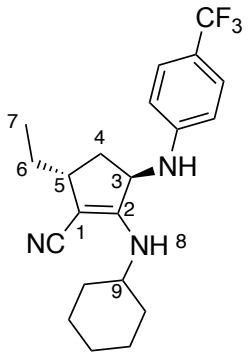
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.6 Hz, 2H, Ph), 6.72 – 6.54 (m, 2H, Ph), 4.67 – 4.42 (m, 2H, H-3, H-8), 3.78 (brs, 1H, NH), 2.82 – 2.76 (m, 1H, H-9), 2.51 (s, 3H, CH_3C=O), 2.10 – 1.77 (m, 4H), 1.80 – 1.57 (m, 4H), 1.48 – 1.21 (m, 3H), 1.21 – 1.06 (m, 3H), 0.94 (t, *J* = 7.2 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.5 (C=O), 156.4 (C-2), 150.8 (C), 130.9 (CH), 128.2 (C), 120.2 (CN), 112.8 (CH), 75.8 (C-1), 59.0, 52.2, 43.7, 34.9, 33.8, 33.7, 28.1, 26.2, 25.5, 24.4, 24.3, 11.5 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 352.2391 $[M+H]^+$; calcd. for $C_{22}H_{29}N_3O$: 352.2383.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 55:45 in 7 min, flow rate = 1 mL/min, 35 °C, λ = 315 nm, t_R = 5.48 min (major) and t_R = 5.66 min (minor), 94% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-((4-(trifluoromethyl)phenyl)amino) cyclopent-1-ene-1-carbonitrile (2q)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), 4-trifluoromethylaniline (19 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 5:1) as a pale orange oil (25 mg, 0.07 mmol, 44% yield, 70:30 dr, 96% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 6.8 (*c* 0.5, acetone, 20°C). R_f = 0.31 (*n*-hexane/ EtOAc 3:1).

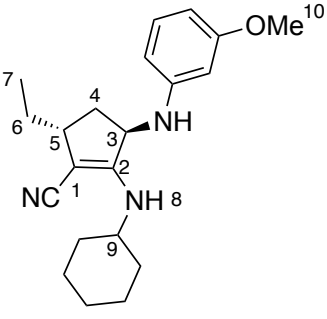
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.81 (d, *J* = 8.6 Hz, 2H, Ph), 7.48 (d, *J* = 8.7 Hz, 2H, Ph), 6.13 (d, *J* = 8.0 Hz, 1H, H-8), 3.92 (t, *J* = 7.9 Hz, 1H, H-3), 3.80-3.68 (m, 1H, H-9), 2.85-2.73 (m, 1H), 2.45-2.40 (m, 1H), 2.27-2.23 (m, 2H), 1.68-1.55 (m, 2H), 1.52-1.42 (m, 2H), 1.40-1.28 (m, 3H), 1.26-1.22 (m, 1H), 1.20-1.12 (m, 3H), 0.90 (t, J = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.5 (C-2), 149.2, 133.8, 126.9 (q, *J* = 3.9 Hz), 124.9 (q, *J* = 270.5 Hz), 120.5 (q, *J* = 33.6 Hz), 120.2 (CN), 114.3, 113.3, 75.0 (C-1), 59.2, 52.2, 43.7, 34.6, 33.8, 33.7, 28.1, 25.5, 24.4, 24.3, 11.5 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 378.2160 $[M+H]^+$; calcd. for $C_{21}H_{27}F_3N_3$: 378.2157.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 60:40 until 5 min then isocratic 60:40, flow rate = 1 mL/min, 35 °C, λ = 265 nm, t_R = 2.90 min (minor) and t_R = 3.07 min (major), 96% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-((3-methoxyphenyl)amino)cyclopent-1-ene-1-carbonitrile (2s)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *m*-anisidine (16 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (50

mg, 0.15 mmol, 99% yield, 88:12 dr, 92% ee). $[\alpha]_D^{20}$ – 5.1 (*c* 0.5, acetone, 20°C). R_f= 0.79 (*n*-hexane/ EtOAc 7:3).

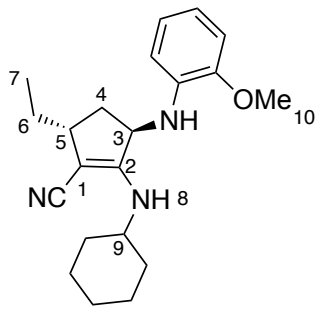
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 – 6.70 (m, 3H), 6.66 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.68 (d, *J* = 8.6 Hz, 1H, H-8), 4.50 (t, *J* = 7.9 Hz, 1H), 3.85 (s, 3H, H-10), 3.85 – 3.73 (m, 1H), 2.83 – 2.72 (m, 1H), 2.11 – 2.00 (m, 2H), 2.00 – 1.76 (m, 2H), 1.79 – 1.54 (m, 4H), 1.48 – 1.31 (m, 3H), 1.23 – 1.03 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.8 (C-2), 147.5, 136.3, 121.3, 120.9, 118.2, 111.7, 110.1, 74.0 (C-1), 59.3, 55.6 (C-10), 52.0, 43.7, 42.1, 34.7, 33.7, 28.2, 25.6, 24.4, 24.3, 11.7 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 340.2380 $[M+H]^+$; calcd. for $C_{21}H_{31}N_3O$: 340.2383.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 85:15 in 2 min then isocratic 85:15, flow rate = 1 mL/min, 25 °C, λ = 266 nm, t_R = 4.62 min (major) and t_R = 5.05 min (minor), 92% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-((2-methoxyphenyl)amino)cyclopent-1-ene-1-carbonitrile (2t)



Prepared according general procedure using hemiacetal **1a** (35 mg, 0.15 mmol), 2-methoxyaniline (15.7 µL, 0.15 mmol) and cyclohexylisocyanide (18.7 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (43 mg, 0.13 mmol, 89% yield, 75:25 dr, 91% ee). $[\alpha]_D^{20}$ – 7.5 (*c* 0.5, acetone, 20°C). R_f= 0.66 (*n*-hexane/ EtOAc 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (t, *J* = 8.1 Hz, 1H), 6.35 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H), 6.27 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 6.21 (t, *J* = 2.3 Hz, 1H), 4.62 (d, *J* = 8.6 Hz, 1H, H-8), 4.47 (t, *J* = 7.7 Hz, 1H), 3.77 (s, 3H, H-10), 3.65 – 3.52 (m, 1H), 2.83 – 2.69 (m, 1H), 2.08 – 2.01 (m, 2H), 1.98 (dd, *J* = 7.6, 2.7 Hz, 1H),

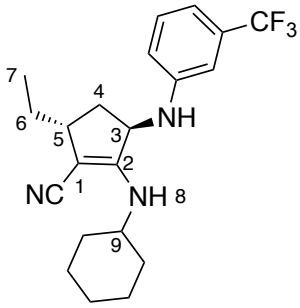
1.83 (dt, *J* = 13.0, 8.1 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.64 – 1.57 (m, 2H), 1.48 – 1.31 (m, 3H), 1.21 – 1.05 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.0, 157.4 (C-2), 148.0, 130.4, 120.7, 107.1, 104.0, 100.5, 74.3 (C-1), 59.6, 55.3 (C-10), 52.0, 43.7, 35.1, 33.8, 33.7, 28.2, 25.6, 24.4, 24.3, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 340.2384 $[M+H]^+$; calcd. for $C_{21}H_{30}N_3O$: 340.2383.

The enantiomeric ratio was determined by HLPC analysis using Chiralpak AS-H, isocratic Hex/EtOH = 90:10, flow rate = 0.5 mL/min, 25 °C, λ = 254 nm, t_R = 25.5 min (major) and t_R = 33.5 min (minor), 91% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-((3-(trifluoromethyl)phenyl)amino) cyclopent-1-ene-1-carbonitrile (2u)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), 3-(trifluoromethyl)aniline (15 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow oil (47 mg, 0.12 mmol, 83% yield, 91:9 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 4.6 (*c* 0.5, acetone, 20°C). R_f = 0.55 (*n*-hexane/ EtOAc 4:1).

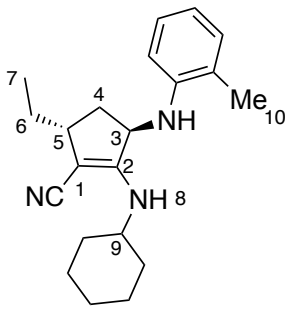
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (t, *J* = 8.0 Hz, 1H), 7.01 (dt, *J* = 8.0, 2.0 Hz 1H), 6.86 (t, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.57 (d, *J* = 8.6 Hz, 1H, H-8), 4.50 (t, *J* = 7.7 Hz, 1H, H-3), 3.94 (brs, 1H, NH), 3.79 (tdd, *J* = 10.3, 8.5, 5.2 Hz, 1H, H-9), 2.79 (ddtd, *J* = 9.5, 4.3, 3.0, 1.5 Hz, 1H, H-5), 2.12 – 2.01 (m, 2H), 1.97 (ddd, *J* = 13.0, 7.7, 3.0 Hz, 1H), 1.86 (dt, *J* = 13.0, 7.7 Hz, 1H), 1.76 – 1.54 (m, 4H), 1.47 – 1.31 (m, 3H), 1.20 – 1.05 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.7 (C-2), 146.9 (C), 131.9 (q, *J* = 32.0 Hz, CH), 130.0, 124.2 (q, *J* = 272.3 Hz, CF_3), 120.4 (CN), 117.0 (CH), 115.3 (q, *J* = 3.9 Hz, CH), 110.5 (q, *J* = 3.6 Hz, CH), 74.8 (C-1), 59.4, 52.1, 43.7, 34.6, 33.7, 33.6, 28.1, 25.5, 24.4, 24.2, 11.5 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 378.2159 $[M+H]^+$; calcd. for $C_{21}H_{26}F_3N_3$: 378.2152.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/EtOH = 100:0 to 60:40 in 5 min, flow rate = 1 mL/min, 35 °C, λ = 318 nm, t_R = 3.81 min (minor) and t_R = 3.88 min (major), > 99% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(*o*-tolylamino)cyclopent-1-ene-1-carbonitrile (2w)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *o*-toluidine (16 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 6:1) as a pale orange oil (25 mg, 0.10 mmol, 68% yield, 99:1 dr, 97% ee). $[\alpha]_D^{20}$ – $[\alpha]_D^{20}$ 7.2 (*c* 0.5, acetone, 20°C). R_f= 0.42 (*n*-hexane/ EtOAc 3:1).

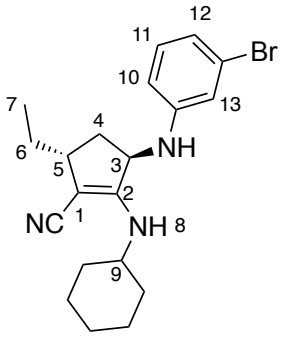
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.20-7.04 (m, 2H, Ph), 6.78-6.70 (m, 1H, Ph), 6.67 (d, *J* = 8.0 Hz, 1H, Ph), 4.65 (d, *J* = 7.9 Hz, 1H, H-8), 4.54 (t, *J* = 7.9 Hz, 1H, H-3), 3.87-3.63 (m, 1H, H-9), 2.89-2.72 (m, 1H), 2.15 (s, 3H, H-10), 2.07-2.00 (m, 2H), 1.89-1.79 (m, 1H), 1.73-1.58 (m, 4H), 1.21-1.06 (m, 3H), 0.94 (t, J = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.6 (C-2), 144.6, 130.8, 127.4, 123.3 (CN), 120.6, 118.6, 111.4, 74.5 (C-1), 59.4, 51.9, 43.7, 35.5, 33.7, 29.8, 28.2, 25.6, 24.4, 24.3, 17.8 (C-10), 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 324.2436 $[M+H]^+$; calcd. for $C_{21}H_{30}N_3$: 324.2440.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/iPrOH = 100:0 to 80:20 in 5 min then isocratic 80:20, flow rate = 1 mL/min, 25 °C, λ = 269 nm, t_R = 5.07 min (major) and t_R = 5.20 min (minor), 97% ee.

(3*R*,5*R*)-3-((3-bromophenyl)amino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2x)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *m*-bromoaniline (26 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow oil (37 mg, 0.10 mmol, 63% yield, 86:14 dr, >99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 3.8 (*c* 0.5, acetone, 20°C). R_f = 0.55 (*n*-hexane/ EtOAc 4:1).

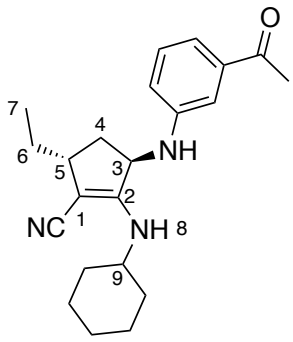
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.04 (t, *J* = 8.0 Hz, 1H, H-11), 6.89 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H, H-10), 6.79 (t, *J* = 2.0 Hz, 1H, H-13), 6.56 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H, H-12), 4.55 (d, *J* = 8.6 Hz, 1H, H-8), 4.44 (t, *J* = 6.7 Hz, 1H, H-3), 3.86 – 3.68 (m, 2H), 2.77 (ddtd, *J* = 8.4, 4.1, 3.1, 1.4 Hz, 1H, H-5), 2.09 – 2.00 (m, 2H), 1.96 (ddd, *J* = 13.0, 7.6, 2.9 Hz, 1H), 1.83 (dt, *J* = 13.0, 8.0 Hz, 1H), 1.77 – 1.57 (m, 5H), 1.48 – 1.31 (m, 3H), 1.26 – 1.04 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.8 (C-2), 147.9 (C), 130.8 (CH), 123.5 (C-Br), 121.7 (CH), 120.4 (CN), 116.9 (CH), 112.8 (CH), 74.8 (C-1), 59.4, 52.0, 43.7, 34.8, 33.7, 33.7, 28.1, 25.6, 24.4, 24.3, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 388.1395 $[M+H]^+$; calcd. for $C_{20}H_{26}ClN_3$: 388.1383.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, isocratic CO_2/EtOH = 80:20, flow rate = 1 mL/min, 35 °C, λ = 250 nm, t_R = 2.33 min (major) and t_R = 3.13 min (minor), > 99% ee.

(3*R*,5*R*)-3-((3-acetylphenyl)amino)-2-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2y)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), 3'-aminoacetophenone (20 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow oil (43 mg, 0.12 mmol, 81% yield, 97:3 dr, 96% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 7.9 (*c* 0.5, acetone, 20°C). R_f = 0.37 (*n*-hexane/ EtOAc 4:1).

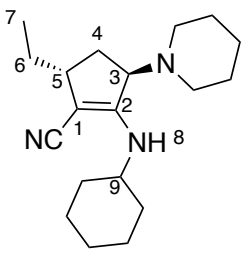
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.20 (m, 3H), 6.91 – 6.81 (m, 1H), 4.58 (d, *J* = 8.7 Hz, 1H, H-8), 4.54 (t, *J* = 7.6 Hz, 1H, H-3), 3.88 – 3.70 (m, 1H, H-9), 2.78 (dq, *J* = 8.2, 4.2, 3.8 Hz, 1H), 2.57 (s, 3H, CH_3C=O), 2.10 – 1.95 (m, 3H), 1.84 (dt, *J* = 13.0, 7.9 Hz, 1H), 1.75 – 1.56 (m, 4H), 1.48 – 1.31 (m, 3H), 1.23 – 1.06 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.4 (C=O), 157.0 (C-2), 147.0 (C), 138.5 (C), 129.8 (CH), 120.4 (CN), 119.4 (CH), 118.8 (CH), 113.02 (CH), 74.9 (C-1), 59.6, 52.1, 43.8, 34.9, 33.8, 33.7, 28.2, 26.8, 25.6, 24.4, 24.3, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 352.2394 $[M+H]^+$; calcd. for $C_{22}H_{29}N_3O$: 352.2383.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/iPrOH = 100:0 to 80:20 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 262 nm, t_R = 5.40 min (major) and t_R = 5.68 min (minor), 96% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(piperidin-1-yl)cyclopent-1-ene-1-carbonitrile (2z)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), piperidine (15 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a brown oil (30 mg, 67% yield, 78:22 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 3.5 (*c* 0.5, acetone, 20°C). R_f = 0.57 (*n*-hexane/ EtOAc 4:1).

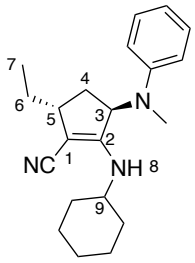
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.17 (d, *J* = 8.7 Hz, 1H, H-8), 3.81 (qt, *J* = 9.2, 3.8 Hz, 1H, H-10), 3.54 (t, *J* = 9.0 Hz, 1H, H-3), 2.54 (dq, *J* = 12.6, 4.5, 3.6 Hz, 1H, H-5), 2.35 (t, *J* = 5.2 Hz, 4H), 2.07 – 1.97 (m, 2H), 1.93 – 1.78 (m, 2H), 1.76 – 1.55 (m, 3H), 1.54 – 1.36 (m, 5H), 0.90 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.6 (C-2), 121.0 (CN), 73.2 (C-1), 70.2, 51.2, 49.9 (C-10), 42.5, 33.9, 33.3, 28.0, 26.7, 25.8, 25.6, 24.6, 24.4, 24.2, 11.0 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 302.2599 $[M+H]^+$; calcd. for $C_{19}H_{31}N_3$: 302.2591.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/MeOH = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 210 nm, t_R = 2.59 min (major) and t_R = 2.68 min (minor), > 99% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-(methyl(phenyl)amino)cyclopent-1-ene-1-carbonitrile (2aa)



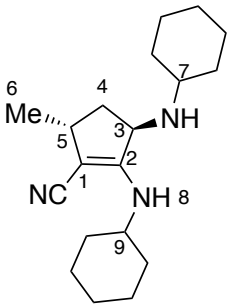
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), *N*-methylaniline (16 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a dark yellow oil (43 mg, 0.13 mmol, 89% yield, 58:42 dr, 96% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 1.1 (*c* 0.5, acetone, 20°C). R_f = 0.70 (*n*-hexane/ EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.19 (m, 2H), 6.92 – 6.77 (m, 3H), 4.76 (t, *J* = 9.1 Hz, 1H, H-3), 4.57 (d, *J* = 10.1 Hz, 1H, H-8), 3.85 (ddt, *J* = 13.9, 9.1, 5.1 Hz, 1H), 2.69 (s, 3H, NCH_3), 2.29 – 1.03 (m, 14H), 0.92 (t, *J* = 7.9 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.6 (C-2), 149.9 (C), 129.5, 120.3 (CN),118.8, 114.5, 74.8 (C-1), 65.7, 51.9, 44.1, 42.2, 34.0, 33.8, 28.6, 28.0, 25.6, 24.6, 24.3, 10.9 (C-7). **HRMS** (ESI-Q-TOF) *m/z*: 324.2443 $[M+H]^+$; calcd. for $C_{21}H_{29}N_3$: 324.2434.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/iPrOH = 100:0 to 70:30 in 10 min, flow rate = 1 mL/min, 35 °C, λ = 280 nm, t_R = 5.91 min (minor) and t_R = 6.02 min (major), 96% ee.

(3*R*,5*R*)-2,3-bis (cyclohexylamino)-5-methylcyclopent-1-ene-1-carbonitrile (2ab)



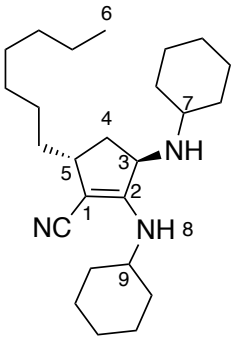
Prepared according the general procedure using hemiacetal **1b** (32 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (32 mg, 0.11 mmol, 73% yield, 99:1 dr, > 99 % ee). $[\alpha]_D^{20}$ – 5.3 (*c* 0.5, acetone, 20°C). R_f= 0.55 (*n*-hexane/ EtOAc 7:3).

^{1}H NMR (400 MH, $CDCl_3$) δ = 5.10 (d, *J* = 8.7 Hz, 1H, H-8), 3.80 – 3.65 (m, 2H), 2.86 – 2.78 (m, 1H), 2.47 (tt, *J* = 10.2, 3.5 Hz, 1H), 2.08 – 1.99 (m, 2H), 1.94 (ddd, *J* = 12.3, 7.1, 1.4 Hz, 1H), 1.85 (d, *J* = 13.0 Hz, 1H), 1.75 – 1.66 (m, 5H), 1.65 – 1.52 (m, 2H), 1.48 – 1.36 (m, 2H), 1.29 – 1.10 (m, 9H), 1.08 (d, *J* = 6.9 Hz, 3H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9 (C-2), 121.3 (CN), 73.1 (C-1), 60.0, 55.0, 51.5, 40.3, 36.8, 35.3, 33.8, 33.5, 26.1, 25.7, 25.1, 24.9, 24.5, 24.3, 20.8 (C-6).

HRMS (ESI-Q-TOF) *m/z*: 302.2589 $[M+H]^+$; calcd. for $C_{19}H_{32}N_3$: 302.2591.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 80:20 until 2 min then isocratic 80:20, flow rate = 1 mL/min, 25 °C, λ = 245 nm, t_R = 4.39 min (major) and t_R = 5.17 min (minor), > 99% ee.



(3*R*,5*R*)-2,3-bis (cyclohexylamino)-5-heptylcyclopent-1-ene-1-carbonitrile (2ac)

Prepared according the general procedure using hemiacetal **1c** (45 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (42 mg, 0.15 mmol, 73% yield, 99:1 dr, >99% ee). $[\alpha]_D^{20}$ – 6.1 (*c* 0.5, acetone, 20°C). R_f= 0.55 (*n*-hexane/ EtOAc 7:3).

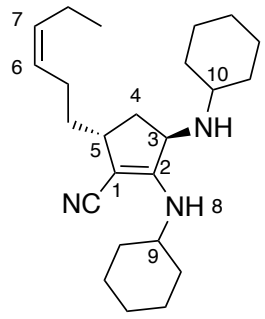
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.11 (d, *J* = 8.7 Hz, 1H, H-8), 3.82 – 3.70 (m, 1H, H-9), 3.66 (dd, *J* = 9.4, 7.1 Hz, 1H, H-3), 2.70 – 2.64 (m, 1H), 2.48 (tt, *J* = 10.5, 3.6 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.75 – 1.67 (m, 4H), 1.66 – 1.58 (m, 2H), 1.55 – 1.35 (m, 4H), 1.35 – 0.98 (m, 22H), 0.87 (t, *J* = 7.4 Hz, 3H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.3 (C-2), 121.7 (CN), 71.9 (C-1), 60.3, 55.0, 51.5, 42.2, 38.1, 35.5, 35.4, 33.8, 33.6, 32.0, 29.9, 29.5, 27.9, 26.1, 25.8, 25.2, 24.9, 24.5, 24.3, 22.8, 14.3 (C-6).

HRMS (ESI-Q-TOF) *m/z*: 386.3534 $[M+H]^+$; calcd. for $C_{25}H_{44}N_3$: 386.3530.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/EtOH = 100:0 to 85:15 in 24 min, flow rate = 0.8 mL/min, 25 °C, λ = 254 nm, t_R = 15.52 min (major) and t_R = 15.28 min (minor), > 99% ee.

(3*R*,5*R*)-2,3-bis (cyclohexylamino)-5-((*Z*)-hex-3-en-1-yl)cyclopent-1-ene-1-carbonitrile (2ad)



Prepared according the general procedure using hemiacetal **1d** (55 mg, 0.15 mmol), cyclohexylamine (17.2 µL, 0.15 mmol) and cyclohexyl isocyanide (18.7 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (39 mg, 0.10 mmol, 70% yield, 99:1 dr, > 99% ee). $[\alpha]_D^{20}$ – 5.7 (*c* 0.5, acetone, 20°C). R_f = 0.74 (*n*-hexane/ EtOAc 7:3).

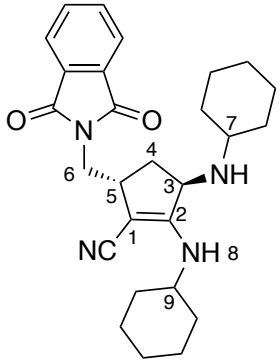
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.42 – 5.25 (m, 2H, H-6, H-7), 5.12 (d, *J* = 8.7 Hz, 1H, H-8), 3.82 – 3.76 (m, 1H, H-9), 3.67 (dd, *J* = 9.4, 7.5 Hz, 1H, H-3), 2.74 – 2.68 (m, 1H), 2.52 – 2.44 (m, 1H), 2.13 – 1.98 (m, 7H), 1.85 (d, *J* = 12.8 Hz, 1H), 1.75 – 1.66 (m, 4H), 1.67 – 1.56 (m, 3H), 1.54 – 1.36 (m, 3H), 1.35 – 1.05 (m, 10H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4 (C-2), 132.1 (C-7, 128.8 (C-6), 121.5 (CN), 71.7 (C-1), 60.3, 55.0, 51.5, 41.8, 37.9, 35.4, 35.3, 33.8, 33.6, 26.1, 25.8, 25.5, 25.1, 24.9, 24.5, 24.3, 20.7, 14.5.

HRMS (ESI-Q-TOF) *m/z*: 370.3215 $[M+H]^+$; calcd. for $C_{24}H_{40}N_3$: 370.3217.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 77:23 until 2 min then isocratic 77:23, flow rate = 1 mL/min, 25 °C, λ = 256 nm, t_R = 4.62 min (major) and t_R = 5.63 min (minor), > 99% ee.

(3*R*,5*R*)-2,3-bis(cyclohexylamino)-5-((1,3-dioxoisoindolin-2-yl)methyl)cyclopent-1-ene-1-carbonitrile (2ae)



Prepared according the general procedure using hemiacetal **1e** (54 mg, 0.15 mmol), cyclohexylamine (17.2 µL, 0.15 mmol) and cyclohexyl isocyanide (18.7 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (40 mg, 0.09 mmol, 60% yield, 75:25 dr, 92% ee). $[\alpha]_D^{20}$ + 0.1 (*c* 0.5, acetone, 20°C). R_f = 0.32 (*n*-hexane/ EtOAc 7:3).

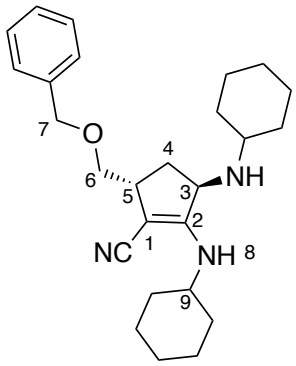
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 – 7.61 (m, 2H), 5.35 (d, *J* = 8.6 Hz, 1H, H-8), 4.12 (q, *J* = 7.0 Hz, 1H), 3.88 – 3.70 (m, 2H, H-6), 3.62 (td, *J* = 13.1, 8.9 Hz, 1H, H-3), 3.23 (q, *J* = 7.8 Hz, 1H), 2.56 – 2.38 (m, 1H), 2.15 (dd, *J* = 12.6, 6.9 Hz, 1H), 2.09 – 1.94 (m, 2H), 1.87 (d, *J* = 13.6 Hz, 1H), 1.75 – 1.65 (m, 5H), 1.65 – 1.57 (m, 2H), 1.50 – 1.34 (m, 3H), 1.33 – 1.00 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.6 (C=O), 160.6 (C-2), 133.9, 132.0, 123.3, 120.5, 67.7 (C-1), 59.6, 54.8, 51.3, 43.1, 41.8, 40.8, 39.3, 36.0, 35.1, 33.5, 25.9, 25.6, 24.9, 24.7, 24.2, 24.1, 14.2

HRMS (ESI-Q-TOF) *m/z*: 447.2760 $[M+H]^+$; calcd. for $C_{27}H_{35}N_4O_2$: 447.2749.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, isocratic CO_2/MeCN = 68:32, flow rate = 1 mL/min, 35 °C, λ = 217 nm, t_R = 3.46 min (major) and t_R = 4.86 min (major), 92% ee.

(3*R*,5*R*)-5-((benzyloxy)methyl)-2,3-bis(cyclohexylamino)cyclopent-1-ene-1-carbonitrile (2af)



Prepared according the general procedure using hemiacetal **1f** (48 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a dark brown oil (28 mg, 0.07 mmol, 45% yield, 95:5 dr, 98% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 5.8 (*c* 0.5, acetone, 20°C). R_f = 0.41 (*n*-hexane/ EtOAc 4:1).

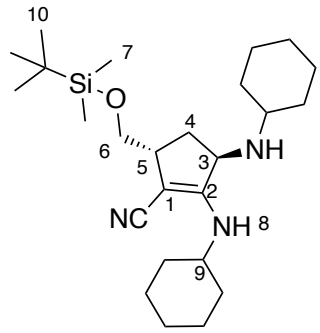
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.17 (m, 5H, Ph), 4.52 – 4.39 (m, 2H), 3.78 – 3.65 (m, 1H), 3.48 (dd, *J* = 9.4, 4.0 Hz, 1H), 3.24 (dd, *J* = 9.4, 7.6 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.52 – 2.39 (m, 1H), 2.24 (dd, *J* = 12.8, 7.4 Hz, 1H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.65 – 1.02 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3 (C-2), 138.6, 128.5, 127.7, 127.7, 121.0 (CN), 73.7, 73.3, 72.7 (C-1), 67.7, 60.2, 55.0, 51.6, 42.6, 35.7, 35.1, 33.7, 33.5, 26.0, 25.7, 25.1, 24.9, 24.4, 24.3.

HRMS (ESI-Q-TOF) *m/z*: 408.3017 $[M+H]^+$; calcd. for $C_{26}H_{37}N_3O$: 408.3009.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/MeOH = 90:10 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 213 nm, t_R = 3.39 min (minor) and t_R = 3.57 min (major), 98% ee.

(3*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3-bis(cyclohexylamino) cyclopent-1-ene-1-carbonitrile (2ag)



Prepared according the general procedure using hemiacetal **1g** (52 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow oil (32 mg, 0.08 mmol, 50% yield, 99:1 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 4.0 (*c* 0.5, acetone, 20°C). R_f = 0.62 (*n*-hexane/ EtOAc 4:1).

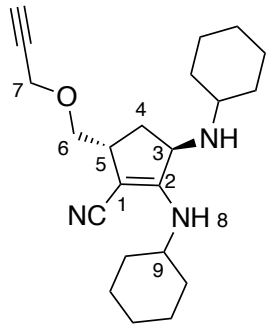
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.29 (brs, 1H, H-8), 3.85 – 3.70 (m, 2H), 3.63 (dd, *J* = 10.0, 3.6 Hz, 1H, H-6), 3.46 (dd, *J* = 10.1, 5.9 Hz, 1H, H-6), 2.84 – 2.75 (m, 1H), 2.54 – 2.43 (m, 1H), 2.28 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.02 (dd, *J* = 11.6, 4.4 Hz, 2H), 1.83 (d, *J* = 11.6 Hz, 1H), 1.76 – 1.65 (m, 6H), 1.65 – 1.55 (m, 2H), 1.50 – 1.34 (m, 3H), 1.31 – 1.04 (m, 8H), 0.87 (s, 9H, H-10), 0.04 (s, 6H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8 (C-2), 121.2 (CN), 67.6 (C-1), 66.0, 65.5, 60.7, 55.1, 51.5, 45.0, 36.0, 35.2, 33.8, 33.7, 33.5, 26.1, 26.1 (C-10), 25.8, 25.2, 24.9, 24.4, 24.4, 18.4, -5.2 (C-7), -5.2 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 432.3412 $[M+H]^+$; calcd. for $C_{25}H_{45}N_3OSi$: 432.3405.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/MeOH = 100:0 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 290 nm, t_R = 3.11 min (major) and t_R = 3.40 min (minor), > 99% ee.

(3*R*,5*R*)-2,3-bis(cyclohexylamino)-5-((prop-2-yn-1-yloxy)methyl)cyclopent-1-ene-1-carbonitrile (2ah)



Prepared according the general procedure using hemiacetal **1h** (40 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 9:1) as a yellow oil (32 mg, 0.09 mmol, 60% yield, 78:22 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 3.8 (*c* 0.5, acetone, 20°C). R_f = 0.34 (*n*-hexane/ EtOAc 4:1).

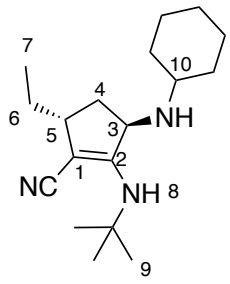
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.29 (d, *J* = 8.7 Hz, 1H, H-8), 4.15 (d, *J* = 2.5 Hz, 2H, H-7), 3.84 – 3.70 (m, 2H), 3.57 (dd, *J* = 9.3, 4.1 Hz, 1H), 3.32 (t, *J* = 8.7 Hz, 1H), 2.94 (td, *J* = 8.2, 4.0 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.41 (t, *J* = 2.5 Hz, 1H), 2.33 (dd, *J* = 12.6, 7.2 Hz, 1H), 2.09 – 1.96 (m, 2H), 1.84 (d, *J* = 12.4 Hz, 1H), 1.76 – 1.61 (m, 6H), 1.51 – 1.33 (m, 4H), 1.25 – 1.01 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8 (C-2), 120.9 (CN), 80.0, 74.4, 72.4, 67.1, 60.2, 58.5, 55.1, 51.5, 42.4, 35.9, 35.3, 33.8, 33.7, 33.5, 26.1, 25.7, 25.1, 24.9, 24.4, 24.3.

HRMS (ESI-Q-TOF) *m/z*: 356.2696 $[M+H]^+$; calcd. for $C_{22}H_{33}N_3O$: 356.2705.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 90:10 to 60:40 in 6 min, flow rate = 1 mL/min, 35 °C, λ = 220 nm, t_R = 3.76 min (minor) and t_R = 4.00 min (major), > 99% ee.

(3*R*,5*R*)-2-(*tert*-butylamino)-3-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2ai)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and *tert*-butyl isocyanide (17 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hex/EtOAc 6:1) as a yellow oil (37 mg, 0.13 mmol, 85% yield, >99:1 dr, >99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 12.8 (*c* 0.7, acetone, 20°C). R_f= 0.34 (*n*-hex/EtOAc 5:1).

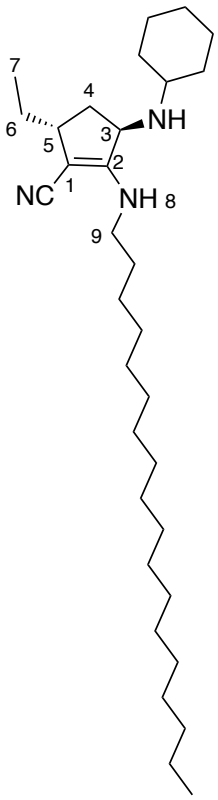
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.67 (s, 1H, H-8), 3.60 (dd, *J* = 10.0, 7.1 Hz, 1H, H-3), 2.66 (td, *J* = 8.4, 4.6 Hz, 1H), 2.48 (tt, *J* = 10.2, 3.7 Hz, 1H), 2.05 (dd, *J* = 12.4, 7.1 Hz, 1H), 1.82 (d, *J* = 12.3 Hz, 1H), 1.77 – 1.66 (m, 3H), 1.64 – 1.54 (m, 2H), 1.40 (s, 9H, H-9), 1.36 – 0.95 (m, 8H), 0.91 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.8 (C-2), 123.5 (CN), 71.4 (C-1), 62.0, 55.1, 51.3, 44.6, 36.7, 35.2, 33.8, 30.2 (C-9), 27.9, 26.0, 25.1, 24.8, 12.0 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 290.2599 $[M+H]^+$; calcd. for $C_{18}H_{32}N_3$: 290.2596.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, isocratic CO_2/MeCN = 95:5, flow rate = 1 mL/min, 25 °C, λ = 265 nm, t_R = 5.84 min (major) and t_R = 5.99 min (minor), >99% ee.

(3*R*,5*R*)-3-(cyclohexylamino)-5-ethyl-2-(octadecylamino)cyclopent-1-ene-1-carbonitrile (2aj)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 μL, 0.15 mmol) and octadecyl isocyanide (42 mg, 0.15 mmol). Obtained after flash chromatography purification (*n*-hexane/EtOAc 20:1) as a brown solid (60 mg, 82% yield, >99:1 dr, > 99% ee). m.p. 40-42 °C. $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 41.8 (*c* 0.5, acetone, 20°C). R_f = 0.60 (*n*-hex/EtOAc 4:1).

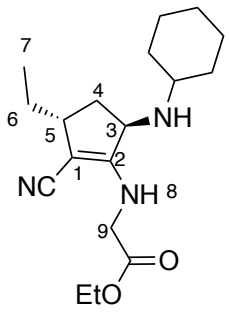
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.18 (s, 1H, H-8), 3.69 (t, *J* = 8.3 Hz, 1H, H-3), 3.52 – 3.37 (m, 2H, H-9), 2.65 (td, *J* = 8.4, 5.5 Hz, 1H), 2.50 (td, *J* = 10.3, 8.6, 5.0 Hz, 1H), 2.06 (dd, *J* = 12.6, 7.3 Hz, 1H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.76 – 1.68 (m, 5H), 1.63 – 1.46 (m, 5H), 1.39 – 1.15 (m, 36H), 0.92 (t, *J* = 7.4 Hz, 3H, H-7), 0.87 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3 (C-2), 121.5 (CN), 72.4 (C-1), 60.3, 55.1, 43.9, 43.7, 37.5, 35.2, 33.6, 32.1, 30.0, 29.8, 29.7, 29.7, 29.5, 28.1 (CH_2), 26.8 (CH_2), 26.1, 25.1, 24.9, 22.8 (CH_2), 14.2 (CH_3), 11.9 (C-7).

HRMS (ESI-Q-TOF) m/z: 486.4796 $[M+H]^+$, calcd. for $C_{32}H_{60}N_3$: 486.4782.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, gradient CO_2/iPrOH = 100:0 to 60:40 until 5 min then isocratic 60:40, flow rate = 1 mL/min, 35 °C, λ = 286 nm, t_R = 5.09 min (major) and t_R = 5.47 min (minor), > 99% ee.

Ethyl ((3*R*,5*R*)-2-cyano-5-(cyclohexylamino)-3-ethylcyclopent-1-en-1-yl)glycinate (2ak)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 µL, 0.15 mmol) and ethyl isocyanoacetate (16 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a yellow oil (22 mg, 0.11 mmol, 72% yield, 92:8 dr, 97% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 9.9 (*c* 0.5, acetone, 20°C). R_f= 0.37 (*n*-hexane/ EtOAc 2:1).

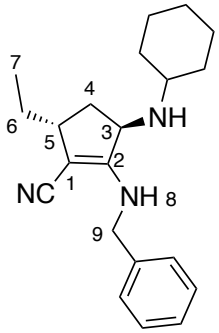
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.76 (s, 1H), 4.31 – 4.19 (m, 4H), 3.78 (t, *J* = 8.1 Hz, 1H, H-3), 2.67 (q, *J* = 7.8 Hz, 1H), 2.52 (tt, *J* = 10.2, 3.7 Hz, 1H), 2.07 (dd, *J* = 12.6, 7.4 Hz, 1H), 1.87 (d, *J* = 12.3 Hz, 1H), 1.79 – 1.67 (m, 3H), 1.63 – 1.47 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 – 1.00 (m, 4H), 0.92 (t, *J* = 7.3 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.1 (C=O), 160.1 (C-1), 120.6 (CN), 75.0 (C-2), 61.8, 60.3, 55.2, 45.2, 43.7, 37.6, 35.1, 33.5, 27.9, 26.0, 25.1, 24.8, 14.3, 11.8 (C-7).

HRMS (ESI-Q-TOF) m/z: 320.2339 $[M+H]^+$; calcd. for $C_{18}H_{30}N_3O_2$: 320.2338.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL2, gradient CO_2/MeOH = 100:60 in 5 min, flow rate = 1 mL/min, 25 °C, λ = 265 nm, t_R = 4.03 min (minor) and t_R = 4.23 min (major), 97% ee.

(3*R*,5*R*)-2-(benzylamino)-3-(cyclohexylamino)-5-ethylcyclopent-1-ene-1-carbonitrile (2al)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 μL, 0.15 mmol) and benzyl isocyanide (19 μL, 0.15 mmol). Obtained after flash chromatography purification (*n*-hexane/EtOAc 20:1) as a brown solid (38 mg, 0.12 mmol, 78% yield, 87:13 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 57.4 (*c* 0.5, acetone, 20°C). R_f= 0.40 (*n*-hex/EtOAc 4:1).

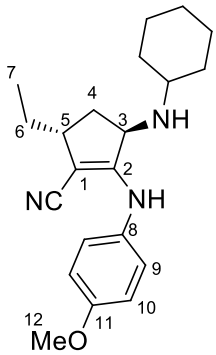
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.27 (m, 5H), 5.42 (brs, 1H), 4.69 (qd, *J* = 14.5, 5.9 Hz, 2H), 3.75 (t, *J* = 8.2 Hz, 1H), 2.69 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.09 (dd, *J* = 12.6, 7.3 Hz, 1H), 1.83 (d, *J* = 13.0 Hz, 1H), 1.71 (d, *J* = 9.5 Hz, 3H), 1.64 – 1.49 (m, 3H), 1.37 – 1.03 (m, 7H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6 (C-2), 138.4, 128.9, 127.8, 127.7, 121.2 (CN), 73.5 (C-1), 60.3, 55.2, 43.7, 37.9, 35.3, 33.6, 26.1, 25.2, 24.9, 11.9 (C-7).

HRMS (ESI-Q-TOF) m/z: 324.2433 $[M+H]^+$, calcd. for $C_{21}H_{30}N_3$: 324.2434.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, isocratic CO_2/MeOH = 85:15, flow rate = 1 mL/min, 35 °C, λ = 286 nm, t_R = 1.67 min (minor) and t_R = 1.80 min (major), > 99% ee.

(3*R*,5*R*)-3-(cyclohexylamino)-5-ethyl-2-((4-methoxyphenyl)amino)cyclopent-1-enecarbonitrile (2am)



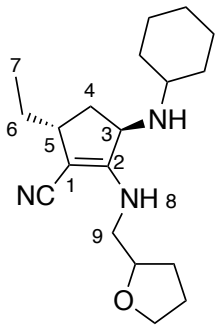
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 μL, 0.15 mmol) and *p*-methoxyphenyl isocyanide (20 mg, 0.15 mmol). Obtained after flash chromatography purification (*n*-hexane/EtOAc 4:1) as an orange oil (25 mg, 0.08 mmol, 51% yield, 95:5 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 8.5 (*c* 0.5, acetone, 20°C). R_f = 0.36 (*n*-hex/EtOAc 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, *J* = 8.8 Hz, 2H, H-9), 6.92 – 6.82 (m, 3H, H-10 and NH), 3.89 (t, *J* = 8.1 Hz, 1H, H-3), 3.79 (s, 3H, H-12), 2.71 (td, *J* = 8.2, 5.2 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.12 (dd, *J* = 12.7, 7.2 Hz, 1H), 1.88 (d, *J* = 12.8 Hz, 1H), 1.83 – 1.68 (m, 1H), 1.66 – 1.53 (m, 3H), 1.41 – 1.01 (m, 7H), 0.95 (t, *J* = 7.4, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.4 (C-2), 157.3 (C-11), 131.7 (C-8), 125.4 (C-9), 119.1 (CN), 114.0 (C-10), 76.5 (C-1), 60.7, 55.5, 55.3, 44.1, 37.4, 35.2, 33.6, 28.0, 26.0, 25.1, 24.9, 11.9 (C-7).

HRMS (ESI-Q-TOF) m/z: 340.2308 $[M+H]^+$, calcd. for $C_{21}H_{30}N_3O$: 340.2383. The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, isocratic CO_2/MeOH = 90:10, flow rate = 1 mL/min, 35 °C, λ = 286 nm, t_R = 3.44 min (minor) and t_R = 3.78 min (major), > 99% ee.

(3*R*,5*R*)-3-(cyclohexylamino)-5-ethyl-2-(((tetrahydrofuran-2-yl)methyl)amino) cyclopent-1-ene-1-carbonitrile (2an)



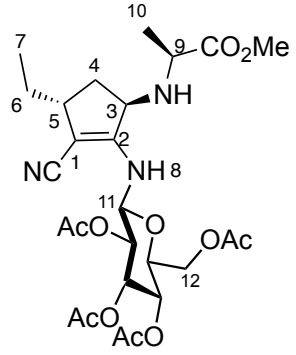
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), cyclohexylamine (17 μL, 0.15 mmol) and 2-(isocyanomethyl)tetrahydrofuran (17 μL, 0.15 mmol). Obtained after flash chromatography purification (*n*-hexane/EtOAc 4:1) as a brown oil (41 mg, 0.13 mmol, 86% yield, >99:1 dr, > 99% ee). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 48.0 (*c* 0.5, acetone, 20°C). R_f = 0.17 (*n*-hex/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.54 (d, *J* = 18.5 Hz, 1H), 4.11 (qd, *J* = 7.4, 3.0 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.82 – 3.66 (m, 3H), 3.48 – 3.32 (m, 1H), 2.70 – 2.60 (m, 1H), 2.49 (tt, *J* = 10.3, 3.7 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.95 – 1.80 (m, 3H), 1.77 – 1.65 (m, 3H), 1.63 – 1.45 (m, 4H), 1.35 – 0.97 (m, 7H), 0.92 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9 (C-2), 121.6 (CN), 77.7 (C-1), 68.5, 60.2, 55.1, 47.7, 43.6, 37.7, 35.1, 33.5, 28.8, 28.7, 28.1, 26.1, 26.0, 25.1, 24.9, 11.9 (C-7).

HRMS (ESI-Q-TOF) m/z: 318.2538 $[M+H]^+$, calcd. for $C_{19}H_{32}N_3O$: 318.2540. The enantiomeric ratio was determined by UPC^2 analysis using Trefoil AMY1, isocratic CO_2/iPrOH = 70:30, flow rate = 1 mL/min, 35 °C, λ = 267 nm, t_R = 1.41 min (major) and t_R = 1.62 min (minor), > 99% ee.

(2*S*,3*S*,4*S*,5*S*,6*S*)-2-(acetoxymethyl)-6-(((3*R*,5*R*)-2-cyano-3-ethyl-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)amino)cyclopent-1-en-1-yl)amino)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (2ao)



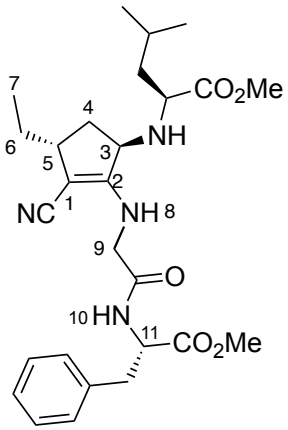
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), HCl.NH_2-Ala-OMe (21 mg, 0.15 mmol), triethylamine (23 μL, 0.16 mmol), and *β*-D-glucosyl isocyanide (54 mg, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 2:1) as a pale yellow oil (53 mg, 0.09 mmol, 63% yield, 99:1 dr).$[\alpha]_D^{20}$ $[\alpha]_D^{20}$ –14.4 (*c* 0.6, acetone, 20°C). R_f= 0.40 (*n*-hexane/ EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.62 (brs, 1H, H-8), 5.30 (t, *J* = 9.3 Hz, 1H), 5.23 (t, *J* = 9.0 Hz, 1H), 5.15 (t, *J* = 9.7 Hz, 1H), 5.05 (t, *J* = 9.3 Hz, 1H), 4.30 (dd, *J* = 12.4, 4.2 Hz, 1H, H-12b), 4.19 (d, *J* = 12.0 Hz, 1H, H-12a), 4.03 – 3.87 (m, 2H), 3.76 (s, 3H, OMe), 3.55 (q, *J* = 7.1 Hz, 1H, H-9), 2.73 (brs, 1H), 2.08 (d, *J* = 5.6 Hz, 6H), 2.02 (d, *J* = 5.5 Hz, 6H), 1.94 – 1.86 (m, 1H), 1.80 (d, *J* = 6.7 Hz, 1H), 1.74 – 1.60 (m, 1H), 1.43 (d, *J* = 7.0 Hz, 3H, H-10), 1.36 – 1.20 (m, 1H), 1.13 – 0.97 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8 (C=O), 170.8 (C=O), 170.3 (C=O), 170.0 (C=O), 169.7 (C=O), 158.6 (C-2), 118.0 (CN), 81.9 (C-11), 73.5, 72.0, 71.0, 68.3, 68.2, 62.0, 61.8, 53.2, 45.1, 33.3, 28.1, 20.9, 20.8, 20.7, 18.1, 11.4 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 568.2509 $[M+H]^+$; calcd. for $C_{26}H_{38}N_3O_{11}$: 568.2506.

Methyl ((1*R*,4*R*)-3-cyano-4-ethyl-2-((2-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)amino)cyclopent-2-en-1-yl)-*L*-leucinate (2ap)



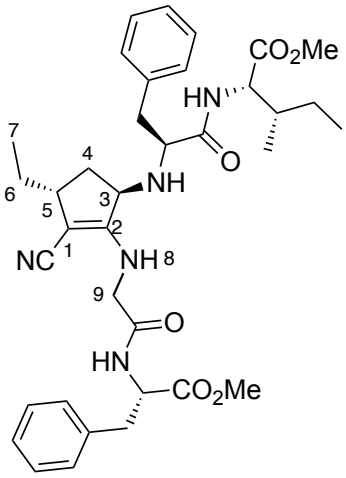
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), HCl.NH_2-Leu-OMe (27 mg, 0.15 mmol), triethylamine (23 μL, 0.16 mmol) and CN-Gly-Phe-OMe (37 mg, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 1:1) as a yellow oil (55 mg, 0.11 mmol, 73% yield, >99:1 dr).$[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 19.8 (*c* 0.6, acetone, 20°C). R_f = 0.33 (*n*-hexane/ EtOAc 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.26 (m, 3H, Ph), 7.11 (d, *J* = 7.0 Hz, 2H, Ph), 6.57 (d, *J* = 7.9 Hz, 1H, H-10), 6.12 (brs, 1H, H-8), 4.95 (dt, *J* = 8.1, 5.9 Hz, 1H, H-11), 4.20 (t, *J* = 6.0 Hz, 2H, H-9), 3.73 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.64 (t, *J* = 7.2 Hz, 1H), 3.35 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.14 (t, *J* = 5.6 Hz, 2H), 2.72 (hept, *J* = 4.0 Hz, 1H), 1.89 (brs, 1H), 1.83 (ddd, *J* = 12.9, 7.5, 3.4 Hz, 1H), 1.74 – 1.57 (m, 2H), 1.52 – 1.44 (m, 1H), 1.43 – 1.35 (m, 1H), 1.31 – 1.19 (m, 2H), 0.92 – 0.86 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4 (C=O), 171.8 (C=O), 168.3 (C=O), 159.1 (C-2), 135.8, 129.4, 128.8, 127.3, 120.3 (CN), 77.4 (C-1), 62.0, 57.6, 53.4, 52.5, 52.4, 46.6, 43.9, 42.3, 38.0, 35.8, 27.8, 24.9, 23.0, 21.8, 11.6 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 499.2925 $[M+H]^+$; calcd. for $C_{27}H_{39}N_4O_5$: 499.2920.

Methyl ((1*R*,4*R*)-3-cyano-4-ethyl-2-((2-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)amino)cyclopent-2-en-1-yl)-*L*-phenylalanyl-*L*-isoleucinate (2aq)

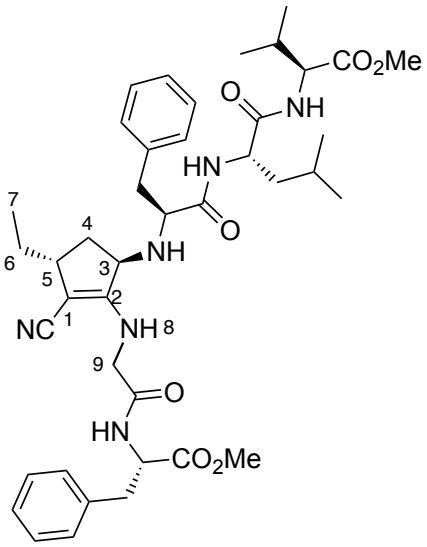


Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), HCl Phe-Ile- OMe (33 mg, 0.15 mmol), triethylamine (23 μL, 0.16 mmol) and CN-Gly-Phe-OMe (37 mg, 0.15 mmol). Obtained after flash column chromatography purification (DCM/MeOH 15:1) as a light yellow oil (64 mg, 0.10 mmol, 68% yield, 96:4 dr). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 7.7 (*c* 0.7, acetone, 20°C). R_f = 0.40 (DCM/MeOH 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 9.1 Hz, 1H, NH), 7.36 – 7.27 (m, 5H, Ph), 7.26 – 7.17 (m, 3H, Ph), 7.13 (d, *J* = 7.1 Hz, 2H, Ph), 6.64 (d, *J* = 7.9 Hz, 1H, NH), 6.28 (brs, 1H, H-8), 4.93 (dt, *J* = 8.2, 5.9 Hz, 1H), 4.58 (dd, *J* = 9.2, 4.6 Hz, 1H), 4.24 (dd, *J* = 17.2, 6.2 Hz, 1H), 4.09 (dd, *J* = 17.3, 5.8, 1H), 3.70 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.27 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.20 – 3.06 (m, 3H), 2.73 (s, 1H), 2.33 (s, 1H), 2.00 – 1.88 (m, 1H), 1.65 – 1.48 (m, 2H), 1.47 – 1.36 (m, 1H), 1.38 – 1.26 (m, 1H), 1.27 – 1.19 (m, 1H), 1.17 – 1.04 (m, 1H), 0.96 – 0.88 (m, 6H), 0.87 – 0.80 (m, 1H), 0.76 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 173.3 (C=O), 173.2 (C=O), 171.9 (C=O), 168.7 (C=O), 162.8 (C-2), 136.3, 135.8, 129.4, 129.3, 129.1, 128.8, 127.6, 127.3, 119.3 (CN), 77.4 (C-1), 62.7, 62.6, 56.5, 53.5, 52.6, 52.5, 46.8, 43.6, 39.4, 38.1, 37.9, 34.2, 27.5, 25.2, 15.8, 11.7, 11.1.

HRMS (ESI-Q-TOF) *m/z*: 646.3609 $[M+H]^+$; calcd. for $C_{36}H_{48}N_5O_6$: 646.3605.

Methyl ((1*R*,4*R*)-3-cyano-4-ethyl-2-((2-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)amino)cyclopent-2-en-1-yl)-*L*-phenylalanyl-*L*-leucyl-*L*-valinate (2ar)



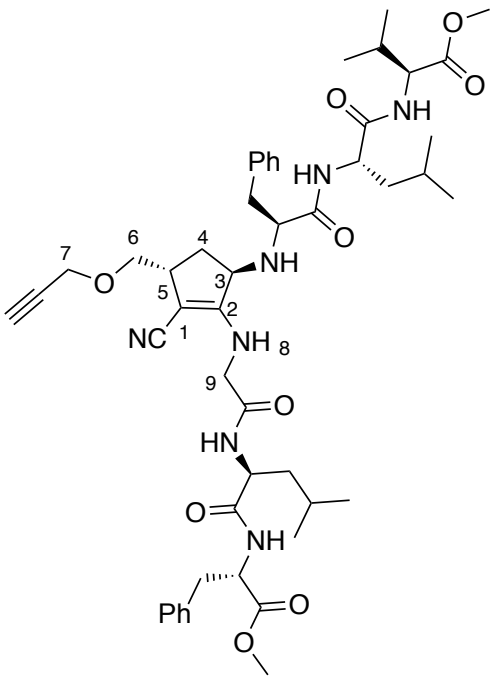
Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), HCl.NH_2-Phe-Leu-Val-OMe (64 mg, 0.15 mmol), triethylamine (23 μL, 0.16 mmol), and CN-Gly-Phe-OMe (37 mg, 0.15 mmol). Obtained after flash column chromatography purification (DCM/MeOH 10:1) as a pale yellow oil (56 mg, 0.08 mmol, 50% yield, 97:3 dr). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 5.2 (*c* 0.5, acetone, 20°C). R_f = 0.17 (DCM/MeOH 99:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.33 – 7.30 (m, 2H), 7.26 – 7.20 (m, 6H), 7.15 – 7.13 (m, 2H), 6.92 (s, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 4.92 (dt, *J*=7.9, 6.0, 1H), 4.57 (q, *J* = 8.4 Hz, 1H), 4.50 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.17 (dd, *J* = 19.1, 5.2, 1H), 4.05 (dd, *J* = 17.1, 5.9 Hz, 1H), 3.74 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.23 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.14 (d, *J* = 6.0 Hz, 2H), 2.95 (s, 1H), 2.88 (s, 1H), 2.65 – 2.47 (m, 1H), 2.25 – 2.08 (m, 3H), 1.75 – 1.54 (m, 6H), 0.97 (d, *J* = 6.5 Hz, 6H), 0.95 – 0.91 (m, 3H), 0.88 (d, *J* = 6.9 Hz, 7H), 0.71 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 173.1 (C=O), 172.2 (C=O), 172.0 (C=O), 168.8 (C=O), 162.7 (C-1), 136.9, 136.1, 129.4, 129.2, 129.1, 128.7, 127.5, 127.2, 119.3 (CN), 63.2 (C-2), 62.9, 57.4, 53.5, 52.4, 52.4, 51.5, 46.9, 43.3, 41.7, 39.6, 38.2, 34.8, 31.4, 27.4, 25.0, 23.1, 22.0, 19.0, 17.8, 11.1 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 745.4286 $[M+H]^+$; calcd. for $C_{41}H_{57}N_6O_7$: 745.4289.

Methyl ((1*R*,4*R*)-3-cyano-2-((2-(((*S*)-1-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)amino)-4-((prop-2-yn-1-yloxy)methyl)cyclopent-2-en-1-yl)-*L*-phenylalanyl-*L*-leucyl-*L*-valinate (2as)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol), TFA.NH_2-Phe-Leu-Val-OMe (76 mg, 0.15 mmol) and CN-Gly-Leu-Phe-OMe (54 mg, 0.15 mmol). Obtained after flash chromatography purification as a brown oil (70 mg, 0.08 mmol, 52% yield, 99:1 dr). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ – 5.0 (*c* 0.5, acetone, 20°C). R_f = 0.47 (DCM/MeOH 9:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 9.0, 1H, NH), 7.33 (t, *J* = 7.4, 2H, Ph), 7.31 – 7.21 (m, 6H, Ph), 7.13 (d, *J* = 7.2, 2H, Ph), 6.88 (brs, 1H, NH), 6.59 (d, *J* = 7.8, 1H, NH), 6.51 (d, *J* = 8.8, 1H, NH), 6.22 (brs, 1H, NH), 4.82 (dt, *J* = 7.9, 6.1, 1H), 4.58 (q, *J* = 8.4, 1H), 4.49 (dd, *J* = 8.8, 4.9 Hz, 2H, H-9), 4.16 (dd, *J* = 17.0, 6.1, 1H), 4.06 (d, *J* = 2.3, 1.6, 2H, H-7), 4.00 (dd, *J* = 17.2, 5.9, 1H), 3.73 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.47 – 3.40 (m, 2H), 3.38 (dd, *J* = 10.4, 3.8, 1H), 3.27 (dd, *J* = 9.3, 6.7, 1H), 3.21 (dd, *J* = 13.7, 3.7, 1H), 3.12 (dd, *J* = 6.2, 4.3, 2H), 2.62 (s, 3H), 2.39 (t, *J* = 2.3, 1H, H-10), 2.17 (pd, *J* = 6.9, 4.8, 1H), 1.86 – 1.79 (m, 2H), 1.69 – 1.59 (m, 6H), 1.56 – 1.48 (m, 2H), 0.97 (d, *J* = 3.8, 3H), 0.96 (d, *J* = 3.9, 3H), 0.92 – 0.88 (m, 12H).

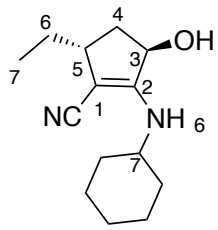
^{13}C NMR (150 MHz, $CDCl_3$) δ = 173.9 (C=O), 173.0 (C=O), 172.1 (C=O), 171.8 (C=O), 171.6 (C=O), 169.0 (C=O), 160.2 (C-2), 137.0, 135.9, 129.4, 129.3, 129.1, 128.8, 127.5, 127.3, 119.0 (CN), 79.7 (C-1), 74.7, 71.7, 63.3, 62.8, 58.5, 57.4, 53.5, 52.5, 52.4, 51.8, 51.4, 46.9, 42.1, 41.7, 41.4, 41.1, 39.9, 37.8, 33.3, 31.4, 25.0, 24.8, 23.1, 23.0, 22.3, 22.1, 19.1, 17.8.

HRMS (ESI-Q-TOF) m/z: 898.5079 $[M+H]^+$, calcd. for $C_{49}H_{68}N_7O_9$: 898.5073.

6.2.3. General reaction procedure for the synthesis of cyclopentenols 3a-d

The hemiacetal **1** (0.15 mmol, 1 equiv.) was dissolved in trifluoroethanol (0.3 mL), the isocyanide (0.15 mmol, 1.0 equiv.) was introduced into this solution and the glass tube was sealed. The flask was irradiated for 20 min (300 W) under high-speed magnetic stirring in the microwave reactor, while the temperature was raised up to 70 °C. The volatiles was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

(3*R*,5*R*)-2-(cyclohexylamino)-5-ethyl-3-hydroxycyclopent-1-ene-1-carbonitrile (3a)



Prepared according the general procedure using hemiacetal **1a** (34 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (29 mg, 0.12 mmol, 83% yield, 99:1 dr, 98% ee). $[\alpha]_D^{20}$ – 1.1 (*c* 0.5, acetone, 20°C). R_f = 0.32 (*n*-hexane/ EtOAc 7:3).

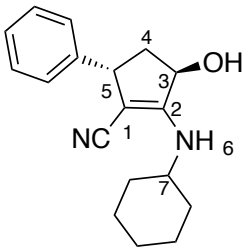
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.62 (t, *J* = 7.2 Hz, 1H, H-3), 4.56 (d, *J* = 8.6 Hz, 1H, H-6), 3.83 – 3.64 (m, 1H), 2.86 – 2.69 (m, 1H), 2.13 – 1.95 (m, 2H), 1.89 – 1.67 (m, 4H), 1.68 – 1.58 (m, 2H), 1.48 – 1.36 (m, 2H), 1.34 – 1.22 (m, 1H), 1.22 – 1.09 (m, 3H), 0.91 (t, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (C-2), 120.5 (CN), 75.9 (C-1), 75.4 (C-3), 52.0, 43.4, 38.3, 33.8, 33.8, 28.3, 25.7, 24.5, 24.4, 11.5 (C-7).

HRMS (ESI-Q-TOF) *m/z*: 235.1799 $[M+H]^+$; calcd. for $C_{14}H_{23}N_2O$: 235.1805.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 85:15 until 2 min then isocratic 85:15, flow rate = 1 mL/min, 25 °C, λ = 290 nm, t_R = 5.21 min (minor) and t_R = 5.82 min (major), 98% ee.

(3*R*,5*S*)-2-(cyclohexylamino)-3-hydroxy-5-phenylcyclopent-1-ene-1-carbonitrile (3b)



Prepared according the general procedure using hemiacetal **1i** (42 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (19 mg, 0.07 mmol, 45% yield, 99:1 dr, > 99% ee). $[\alpha]_D^{20}$ – 3.4 (*c* 0.5, acetone, 20°C). R_f = 0.34 (*n*-hexane/ EtOAc 7:3).

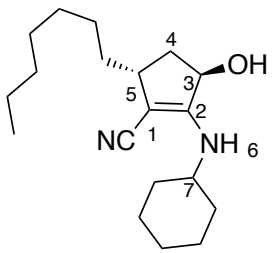
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.26 (m, 3H), 7.28 – 7.16 (m, 2H), 4.79 (t, *J* = 7.4 Hz, 1H, H-3), 4.09 (d, *J* = 8.7 Hz, 1H, H-6), 3.92 – 3.78 (m, 1H, H-7), 2.32 – 2.07 (m, 3H), 1.86 – 1.64 (m, 5H), 1.53 – 1.39 (m, 2H), 1.30 – 1.11 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8 (C-2), 143.7, 128.7, 126.8, 126.7, 120.0 (CN), 75.3 (C-3), 74.9 (C-1), 52.0, 47.4, 42.2, 33.8, 33.6, 25.5, 24.3, 24.3.

HRMS (ESI-Q-TOF) *m/z*: 283.1815 $[M+H]^+$; calcd. for $C_{18}H_{22}N_2O$: 283.1805.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 85:15 until 2 min then isocratic 85:15, flow rate = 1 mL/min, 25 °C, λ = 290 nm, t_R = 7.49 min (minor) and t_R = 9.71 min (major), > 99% ee.

(3*R*,5*R*)-2-(cyclohexylamino)-5-heptyl-3-hydroxycyclopent-1-ene-1-carbonitrile (3c)



Prepared according the general procedure using hemiacetal **1c** (45 mg, 0.15 mmol) and cyclohexyl isocyanide (19 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown oil (35 mg, 0.11 mmol, 76% yield, 95:5 dr, 98% ee). $[\alpha]_D^{20}$ – 1.8 (*c* 0.5, acetone, 20°C). R_f = 0.61 (*n*-hexane/ EtOAc 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.67 (d, *J* = 8.5 Hz, 1H, H-6), 4.60 (t, *J* = 7.2 Hz, 1H, H-3), 3.78 – 3.64 (m, 1H, H-7), 2.82 – 2.73 (m, 1H), 2.73 – 2.52 (m, 1H),

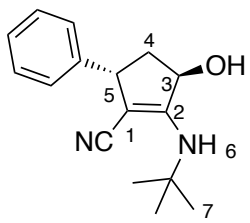
2.09 – 2.00 (m, 1H), 1.98 (ddd, *J* = 13.2, 7.4, 2.6 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.77 – 1.66 (m, 2H), 1.66 – 1.51 (m, 2H), 1.46 – 1.32 (m, 2H), 1.33 – 1.08 (m, 14H), 0.86 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.4 (C-2), 120.8 (CN), 75.5 (C-3), 74.1 (C-1), 52.0, 42.0, 38.4, 35.8, 33.7, 33.7, 32.0, 29.8, 29.4, 27.5, 25.6, 24.4, 24.3, 22.7, 14.2.

HRMS (ESI-Q-TOF) *m/z*: 305.2581 $[M+H]^+$; calcd. for $C_{19}H_{33}N_2O$: 305.2587.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 85:15 until 2 min then isocratic 85:15, flow rate = 1 mL/min, 25 °C, λ = 254 nm, t_R = 5.72 min (minor) and t_R = 6.23 min (major), 98% ee.

(3*R*,5*S*)-2-(*tert*-butylamino)-3-hydroxy-5-phenylcyclopent-1-ene-1-carbonitrile (3d)



Prepared according the general procedure using hemiacetal **1i** (42 mg, 0.15 mmol) and *tert*-butyl isocyanide (17 µL, 0.15 mmol). Obtained after flash column chromatography purification (*n*-hexane/EtOAc 4:1) as a pale brown solid (22 mg, 0.09 mmol, 58% yield, > 99:1 dr, 94% ee). $[\alpha]_D^{20}$ – 4.4 (*c* 0.5, acetone, 20°C). R_f = 0.26 (*n*-hexane/ EtOAc 7:3).

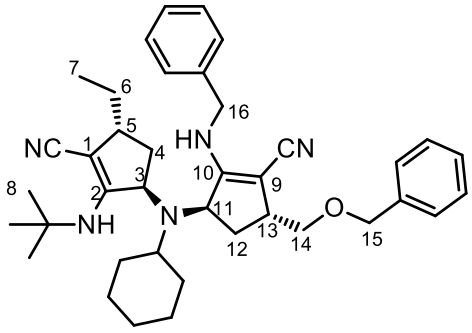
^{1}H NMR (400 MHz, Acetone-d_6) δ = 7.24 – 7.14 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 3H), 5.40 (s, 1H, H-6), 4.60 (t, *J* = 11.7 Hz, 1H, H-3), 3.94 (t, *J* = 8.4 Hz, 1H, H-5), 2.09 – 1.92 (m, 2H, H-4), 1.36 (s, 9H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.0 (C-2), 143.7, 128.9, 127.0, 126.9, 121.7 (CN), 76.5 (C-3), 74.1 (C-1), 52.4, 48.3, 41.9, 30.4.

HRMS (ESI-Q-TOF) *m/z*: 257.1641 $[M+H]^+$; calcd. for $C_{16}H_{21}N_2O$: 257.1648.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/iPrOH = 100:0 to 85:15 until 2 min then isocratic 85:15, flow rate = 1 mL/min, 25 °C, λ = 254 nm, t_R = 5.32 min (minor) and t_R = 6.04 min (major), 94% ee.

6.2.4. Synthesis of the bulky tertiary amine 4



The hemiacetal **1a** (34 mg, 0.15 mmol), was dissolved in trifluoroethanol (0.3 mL) and cyclohexylamine (17 mg, 0.15 mmol) was added to the mixture under magnetic stirring at room temperature. After 10 minutes, tert-butyl isocyanide (17 μL, 0.15 mmol) was dissolved in the reaction mixture. The flask was sealed and irradiated for 20 min under high-speed magnetic stirring in the microwave reactor (300 W), while the temperature was raised up to 70 °C. Then hemiacetal **1f** (48 mg, 0.15 mmol) was added to the mixture and stirred at room temperature for 10 min. Benzyl isocyanide (19 μL, 0.15 mmol) was introduced to this solution and the mixture was irradiated again under the same conditions above. The product **4** was obtained after flash chromatography purification as a brown oil (38 mg, 0.06 mmol, 41% yield, 82:18 dr, > 99% ee). $[\alpha]_D^{20}$ – 1.9 (*c* 0.5, acetone, 20°C). R_f = 0.60 (*n*-hexane/ EtOAc 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.28 (m, 12H),4.78 – 4.63 (m, 3H), 4.58 (s, 2H), 3.99 – 3.83 (m, 2H), 3.70 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.52 (dd, *J* = 9.4, 6.2 Hz, 1H), 2.92 – 2.82 (m, 1H), 2.64 – 2.51 (m, 1H), 2.48 – 2.23 (m, 1H), 2.16 (dt, *J* = 12.1, 7.5 Hz, 1H), 2.10 – 1.95 (m, 1H), 1.79 – 1.67 (m, 3H), 1.64 – 1.50 (m, 4H), 1.42 (s, 9H, H-), 1.33 – 1.25 (m, 4H), 1.21 – 1.08 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H, H-7).

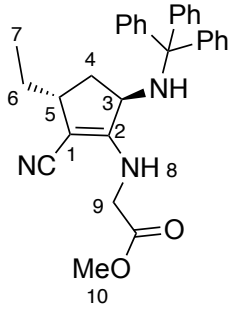
^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9 (C-10), 154.9 (C-2), 138.6, 137.7, 129.1, 128.5, 128.2, 127.9, 127.7, 127.6, 122.7 (CN), 119.6 (CN), 73.7 (C-1), 73.5 (C-9) 73.4 (C-15), 72.2 (C-14), 63.5, 62.1, 54.2, 52.0, 48.6 (C-16), 43.6, 40.2, 35.6, 30.3 (C-8), 30.2, 30.0, 28.0, 26.3, 25.4, 11.9 (C-7).

HRMS (ESI-Q-TOF) m/z: 606.4169 $[M+H]^+$, calcd. for $C_{39}H_{52}N_5O$: 606.4166.

The enantiomeric ratio was determined by UPC^2 analysis using Trefoil CEL1, gradient CO_2/MeCN = 100:0 to 60:40 in 5 min then isocratic 60:40, flow rate = 1

mL/min, 35 °C, λ = 286 nm, t_R = 4.84 min (major) and t_R = 5.48 min (minor), >99% ee.

6.2.5. Synthesis of methyl ((3*R*,5*R*)-2-cyano-3-ethyl-5-(tritylamino)cyclopent-1-en-1-yl)glycinate (5)



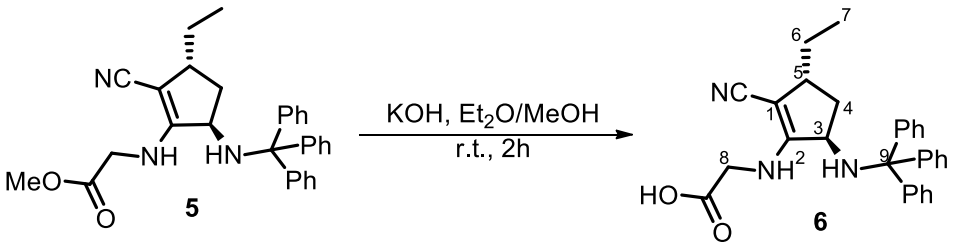
Prepared according the general procedure for the synthesis of cyclopentenyl amines using hemiacetal **1a** (133 mg, 0.58 mmol), tritylamine (150 mg, 0.58 mmol) and methyl isocyanoacetate (56 µL, 0.58 mmol). Obtained after flash chromatography purification as a yellow solid (157 mg, 58% yield, 0.34 mmol). m.p.: 76-81 °C. $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ + 35.6 (*c* 0.5, acetone, 20°C). R_f= 0.27 (*n*-hex/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8.0 Hz, 5H), 7.24 – 7.09 (m, 10H), 6.15 (t, *J* = 5.1 Hz, 1H, H-8), 4.39 – 4.24 (m, 2H, H-9), 3.77 (s, 3H, H-10), 2.27 – 2.13 (m, 1H), 1.27 – 1.13 (m, 2H), 0.95 – 0.62 (m, 2H), 0.55 (t, *J* = 7.4 Hz, 3H, H-7), 0.38 (dd, *J* = 12.7, 6.8 Hz, 1H, H-4a).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.7 (C=O), 160.6 (C-2), 146.3, 128.8, 128.3, 126.9, 120.7 (CN), 75.2, 70.7, 58.8, 52.8, 45.4, 43.3, 38.0, 27.0, 11.9 (C-7).

HRMS (ESI-Q-TOF) m/z: 488.2756 $[M+Na]^+$, calcd. for $C_{30}H_{31}N_3O_2Na$: 488.2308.

6.2.6. Procedure for ester deprotection of compound 5



The compound **5** (73 mg, 0.15 mmol) was dissolved in Et_2O/MeOH (10:1, 2 mL). Next, KOH (9 mg, 1.0 equiv.) was added to this mixture under magnetic at room temperature. After 2 hours, the solvent was removed and the residue suspended

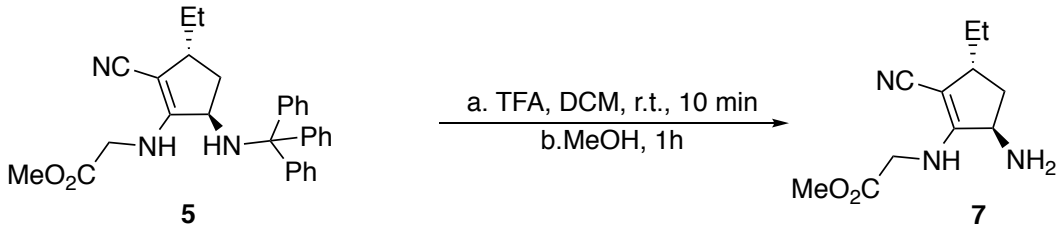
in EtOAc (20 mL) and washed with 0.5 M citric acid solution (2x10 mL). The carboxylic acid **6** was obtained after flash chromatography purification as a yellow oil (54 mg, 76% yield). R_f= 0.30 (DCM/MeOH 9:1).

^{1}H NMR (400 MHz, CD_3OD) δ = 7.58 (d, *J* = 7.9 Hz, 6H), 7.30 (t, *J* = 7.7 Hz, 6H), 7.20 (t, *J* = 7.2 Hz, 3H), 4.18 – 4.05 (m, 2H, H-8), 3.76 (dd, *J* = 10.4, 6.7 Hz, 1H, H-3), 2.22 (dd, *J* = 13.4, 8.2 Hz, 1H, H-5), 1.97 – 1.55 (m, 1H), 1.30 – 1.14 (m, 1H), 1.08 – 0.85 (m, 3H), 0.67 (dd, *J* = 12.8, 5.4 Hz, 3H, H-7), 0.40 (dd, *J* = 12.7, 6.7 Hz, 1H, H-4a).

^{13}C NMR (100 MHz, CD_3OD) δ = 175.9 (C=O), 163.9 (C-2), 148.1, 130.1, 129.0, 127.5, 123.0 (CN), 71.7 (C-9), 71.4 (C-1), 59.6 (C-3), 48.8 (C-8), 44.4 (C-5), 38.2 (C-4), 28.1 (C-6), 12.2 (C-7).

HRMS (ESI-Q-TOF) m/z: 450.2184 $[M-H]^-$, calcd. for $C_{29}H_{28}N_3O_2$: 450.2187.

6.2.7. Procedure for the trityl deprotection of compound 5



5 **7**

The compound **5** was added to a solution of TFA (60% v/v) in DCM (0.8 mL) under magnetic stirring at room temperature for 10 min, and methanol (0.5 mL) was added to the reaction. After 1h, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with water (2x20 mL). Aqueous solution was adjusted until pH = 10 with NaOH 1M, and extracted with EtOAc (3x 20 mL), the organic solvent was removed under reduced pressure. The amine **7** was obtained after flash chromatography purification as a yellow solid (29 mg, 83% yield). m.p.: 104-110 °C. R_f= 0.37 (DCM/MeOH 9:1).

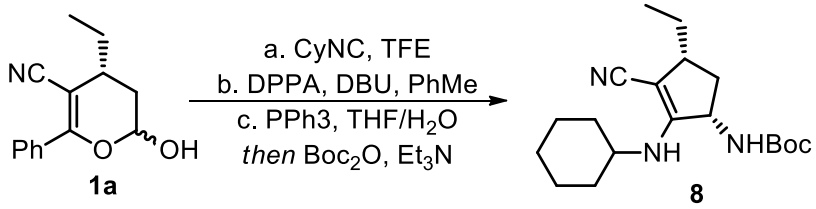
^{1}H NMR (400 MHz, CD_3OD) δ = 4.31 – 4.25 (m, 3H), 3.81 (s, 3H), 3.01 (qd, *J* = 7.3, 3.9 Hz, 1H), 2.08 (ddd, *J* = 14.5, 7.2, 2.7 Hz, 1H), 1.96 (dt, *J* = 14.6, 7.5

Hz, 1H), 1.78 (dqd, *J* = 14.8, 7.5, 4.1 Hz, 1H), 1.34 (ddd, *J* = 15.5, 13.7, 7.6 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ = 171.9, 155.5, 119.3, 81.7, 57.4, 53.2, 46.2, 45.2, 34.0, 28.4, 10.8.

HRMS (ESI-Q-TOF) m/z: 246.1207 $[M+Na]^+$, calcd. for $C_{11}H_{17}N_3O_2Na$: 246.1213.

6.2.8. One-pot procedure for the synthesis of *cis*-cyclopentenyl amine 8



Step a): the cyclohexyl isocyanide (127 µL, 1 mmol) was added to a solution of the hemiacetal **1a** (229 mg, 1 mmol) in trifluoroethanol (2 mL) at room temperature. The flask was sealed and irradiated for 20 min (300 W) under high-speed magnetic stirring in the microwave reactor, while the temperature was raised up to 70 °C. The volatiles were concentrated under reduced pressure and the resulting crude product was used without further purification.

Step b): the crude product was dissolved in toluene (4 mL) and 0.43 mL (2.0 equiv.) of diphenylphosphoryl azide (DPPA) was added to the solution under magnetic stirring at room temperature. After 5 minutes, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 0.3 mL, 2.0 equiv.) was added to this mixture and allowed to react for 24 hours. The solvent was evaporated under reduced pressure and product used in the next step.

Step c): the crude product was dissolved in THF (10 mL) and triphenylphosphine (2.0 equiv, 525 mg) was added. After 1 hour under magnetic stirring at room temperature, water (1 mL) was introduced and the mixture was allowed to react. After 24 hours, triethylamine (3.0 equiv, 0.2 mL) and Boc_2O (3.0 equiv, 0.32 mL)

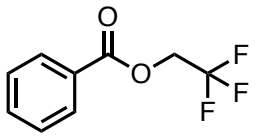
were added to the reaction mixture. After 24 hours, the solvent was removed under reduced pressure and the residue dissolved in EtOAc (30 mL), washed with water (2x20 mL) and concentrated. The compound **8** was obtained after flash chromatography purification (*n*-hexano/EtOAc) as a yellow oil (90 mg, 59% yield, 96:4 dr). $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ -62.8 (*c* 0.5, acetone, 20°C). R_f = 0.50 (*n*-hex/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.21 (d, *J* = 7.0 Hz, 1H), 4.56 (s, 2H), 3.74 (qd, *J* = 9.4, 4.7 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.48 – 2.39 (m, 1H), 2.06 – 1.90 (m, 2H), 1.88 – 1.76 (m, 1H), 1.71 – 1.53 (m, 4H), 1.48 – 1.38 (m, 11H), 1.30 – 1.01 (m, 5H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0, 156.7, 120.4, 80.7, 74.0, 56.3, 51.6, 43.1, 35.5, 33.6, 33.3, 28.4, 25.7, 24.1, 24.0, 11.0.

HRMS (ESI-Q-TOF) m/z: 334.2407 $[M+H]^+$, calcd. for $C_{19}H_{32}N_3O_2$: 334.2489.

6.2.9. Characterization NMR data of compound **9**



9

All the spectroscopic data are in accordance with the literature.[106]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.70 (q, *J* = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.1, 134.0, 130.2, 128.8, 128.5, 123.2 (q, *J* = 277 Hz), 60.9 (q, *J* = 37 Hz).

[106] *(a)* F. de Nanteuil, E. Serrano, D. Perrotta, J. Waser, *J. Am. Chem. Soc.*, 2014, **136**, 6239; *(b)* X. Chen, S. Hu, R. Chen, J. Wang, M. Wu, H. Guo, S. Sun, *RSC Adv.*, 2018, **8**, 4571.

6.2.10. GC-MS chromatograms and mass fragmentation analyses

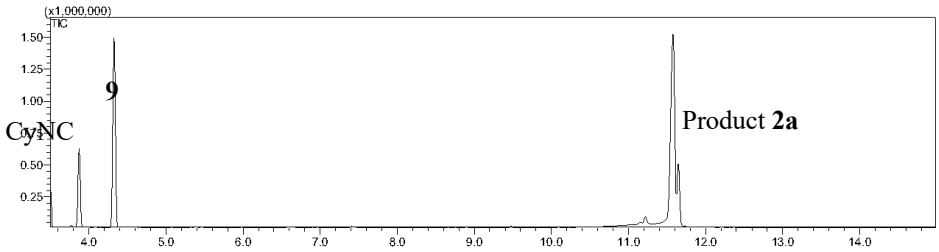


FIGURE 6.1 Chromatogram of crude reaction mixture of compound **2a** in TFE.

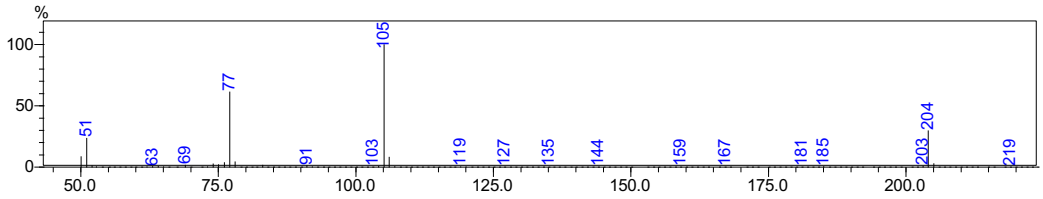
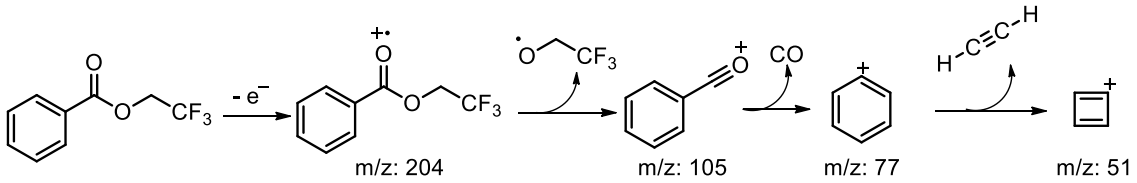


FIGURE 6.2 MS Spectrum of compound **9**.



SCHEME 6.1 Fragmentation proposal of compound **9**.

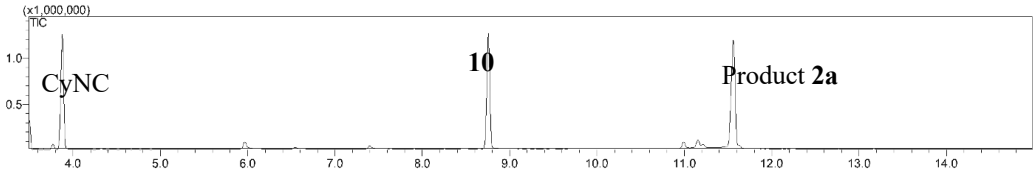


FIGURE 6.3 Chromatogram of the crude reaction mixture of compound **2a** in DCM.

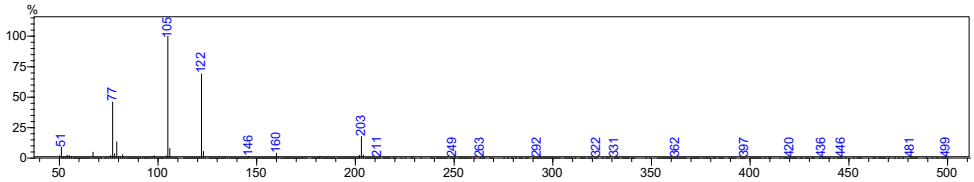
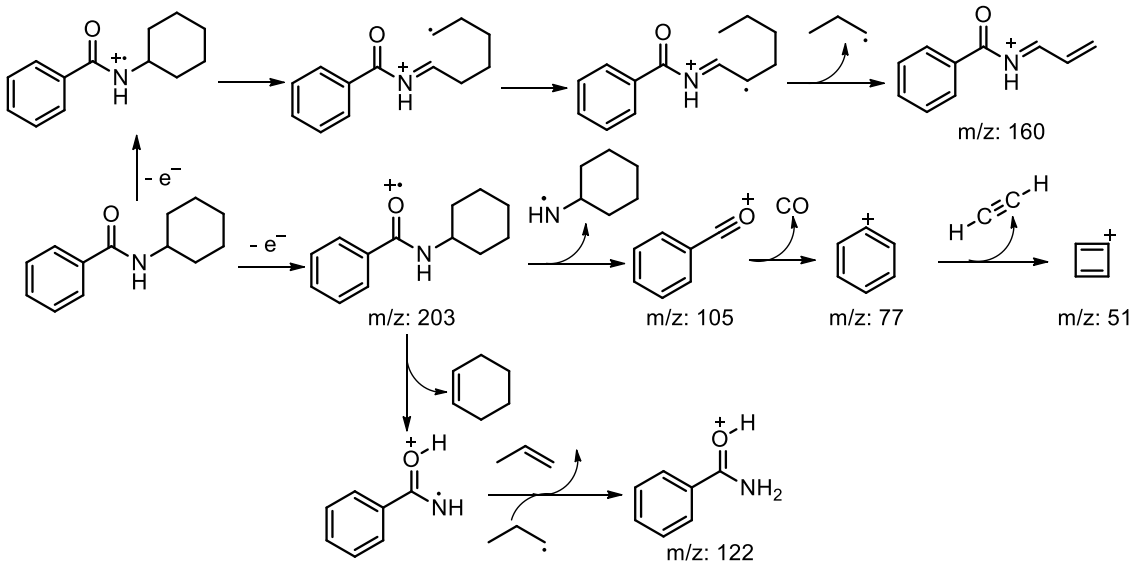
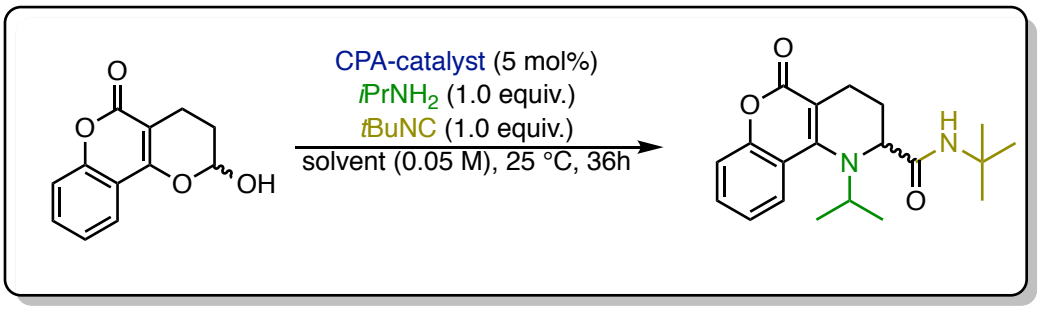


FIGURE 6.4 MS Spectrum of compound **10**.



SCHEME 6.2 Fragmentation proposal of compound **10**.

6.3. Asymmetric Ugi-4-Center-3-Component (U-4C-3CR)



In an oven-dried glass vial (5 mL), hemiacetal (0.05 mmol), amine (1 equiv.) and chiral phosphoric acid (5 mol%) were dissolved in the solvent (0.05 M). The resulting mixture was stirred at room temperature for 15 minutes and then the isocyanide (1 equiv.) was added to the mixture in one portion. The reaction was stirred at the same temperature for 36 h. The reaction was stopped by dilution in $CDCl_3$ and subsequently analyzed by NMR. **^{1}H NMR** (500 MHz, CDCl3) δ = 7.55 – 7.46 (m, 2H), 7.38 (dd, J = 8.2, 1.2 Hz, 1H), 7.29 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 6.49 (brs, 1H), 4.32 (hept, J = 6.7 Hz, 1H), 3.93 (dd, J = 5.1, 3.3 Hz, 1H), 2.73 – 2.60 (m, 2H), 2.37 (ddd, J = 18.1, 11.6, 7.0 Hz, 1H), 1.76 (ddt, J = 13.2, 11.5, 5.5 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.18 (s, 9H), 1.11 (d, J = 6.6 Hz, 3H).

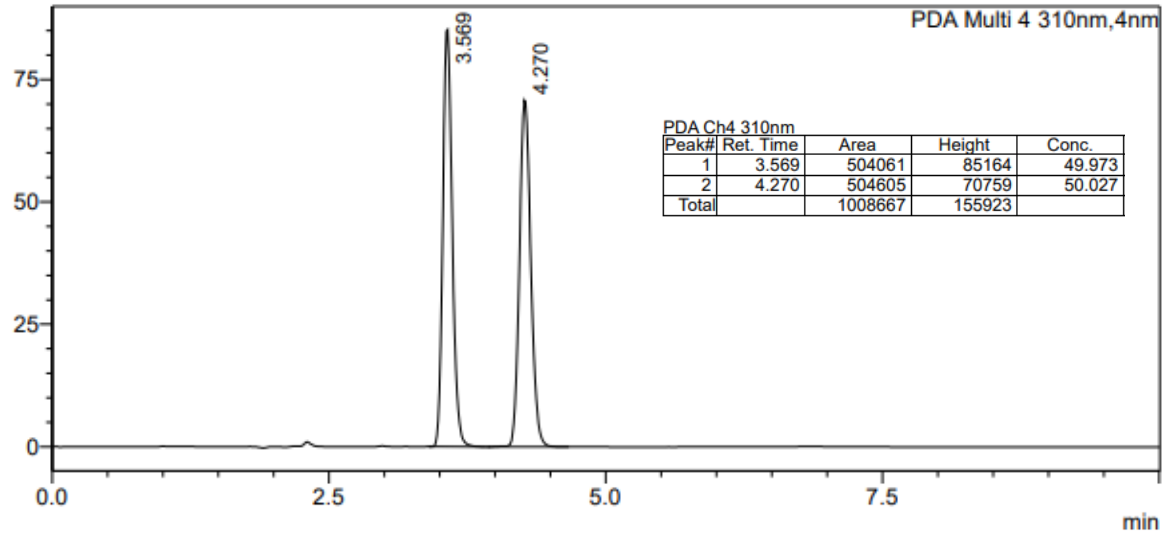
^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 162.1, 153.0, 151.2, 130.7, 123.8, 122.9, 118.3, 116.9, 110.5, 54.2, 53.9, 51.1, 28.7, 21.4, 21.0, 20.0, 18.7.

Product isolation (preparative TLC): using 50% EtOAc in hexanes.

TLC condition: Rf: 0.23 in 30% EtOAc in hexanes.

Reaction monitoring: Reaction was monitored by quenching after 36h and analysis of crude reaction mixture by adding internal standard (dibromomethane).

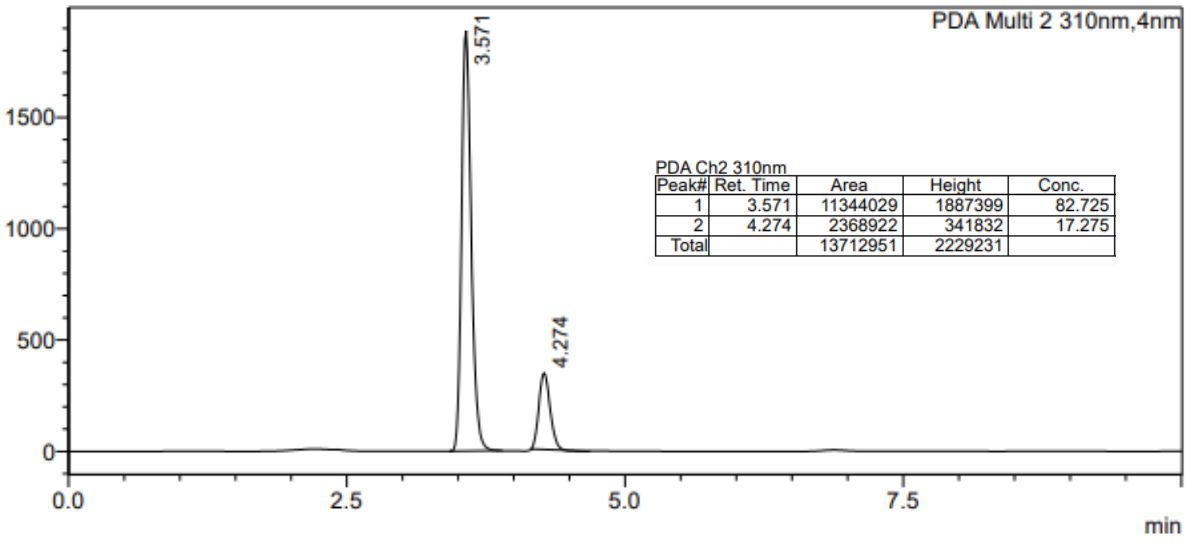
HPLC trace



PDA Ch4 310nm

Peak#	Ret. Time	Area	Height	Conc.
1	3.569	504061	85164	49.973
2	4.270	504605	70759	50.027
Total		1008667	155923	

FIGURE 6.5 HPLC chromatogram for the separation of the racemate of the compound **5**.



PDA Ch2 310nm

Peak#	Ret. Time	Area	Height	Conc.
1	3.571	11344029	1887399	82.725
2	4.274	2368922	341832	17.275
Total		13712951	2229231	

FIGURE 6.6 HPLC chromatogram for the separation of the reaction product **5** with CPA-13.

HPLC conditions: column Chiralpak IC (150 mm x 4.6 mm), isocratic H_2O/MeCN (15:85), flow rate = 1 mL/min, 35 °C, λ = 310 nm.

7. Appendix

7.1. NMR Spectra

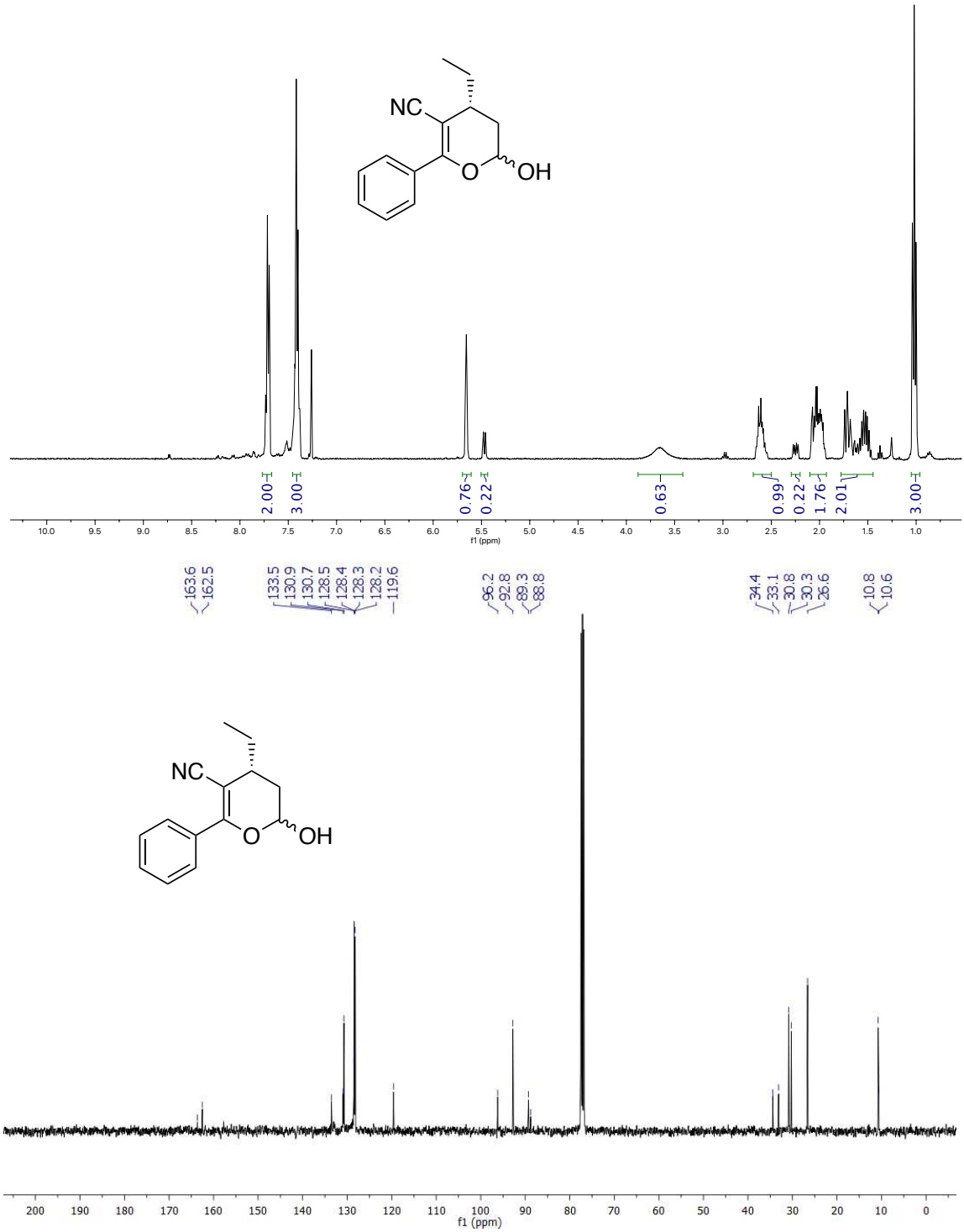


FIGURE 7.1 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1a**.

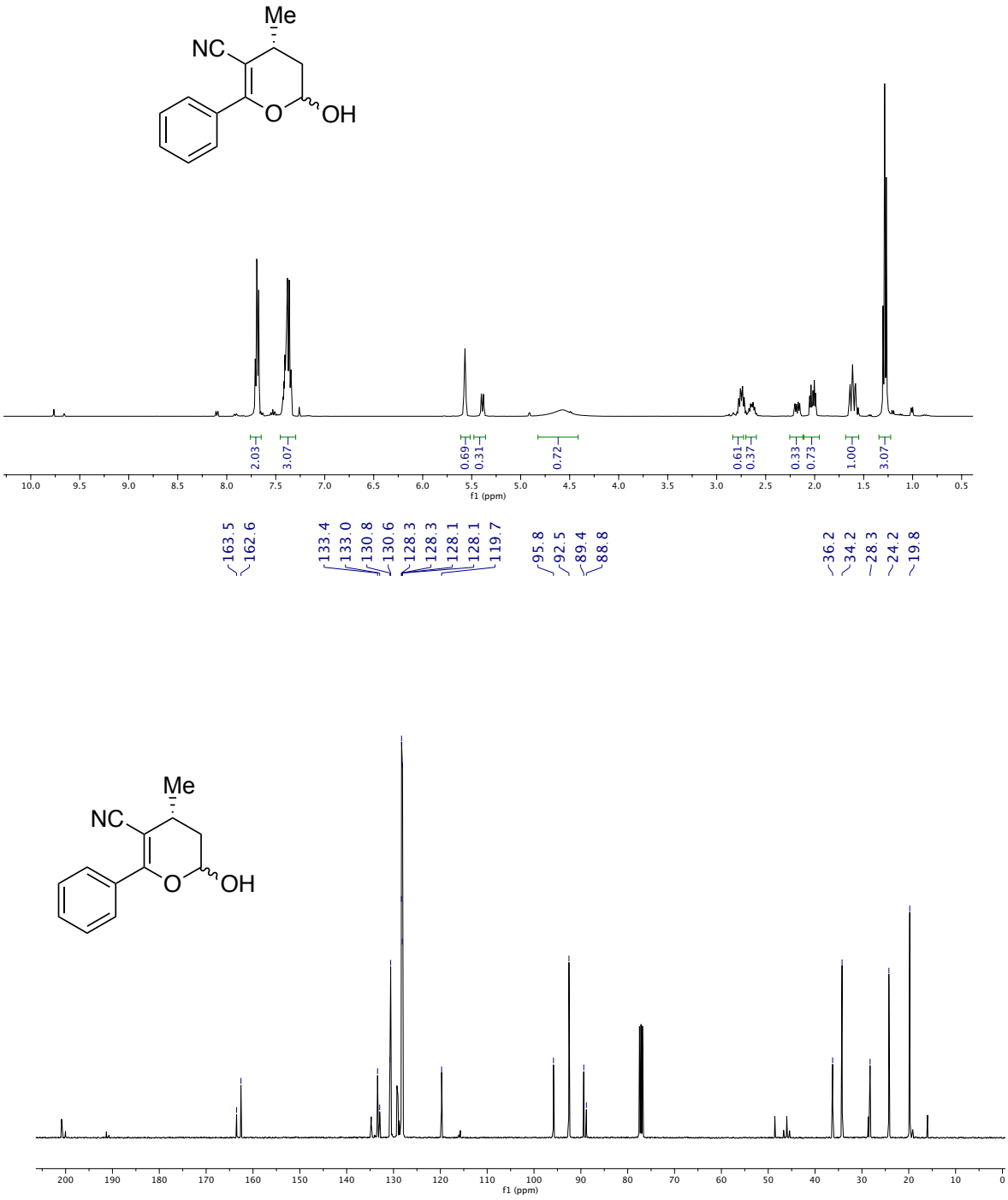


FIGURE 7.2^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1b**.

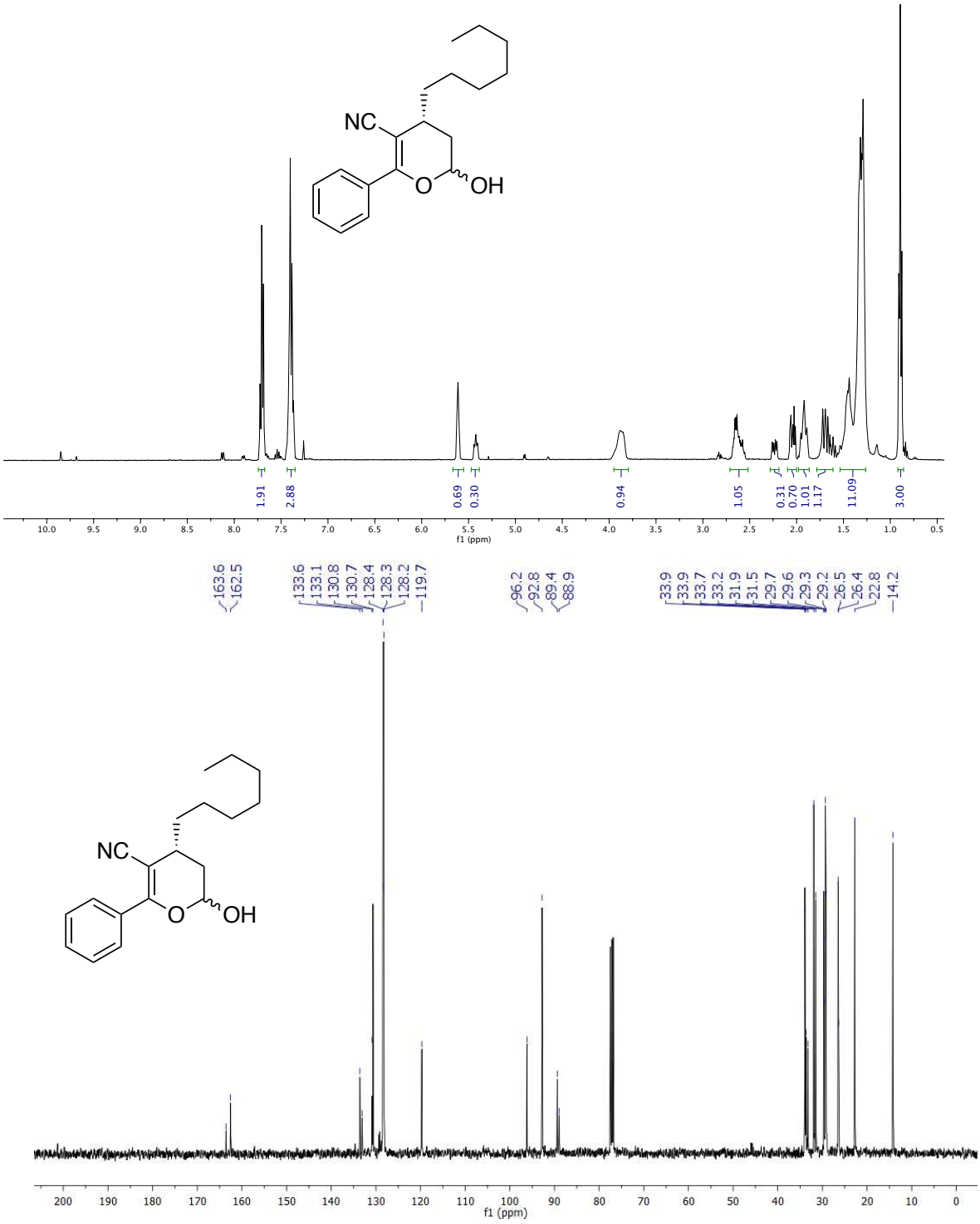


FIGURE 7.3 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1c**.

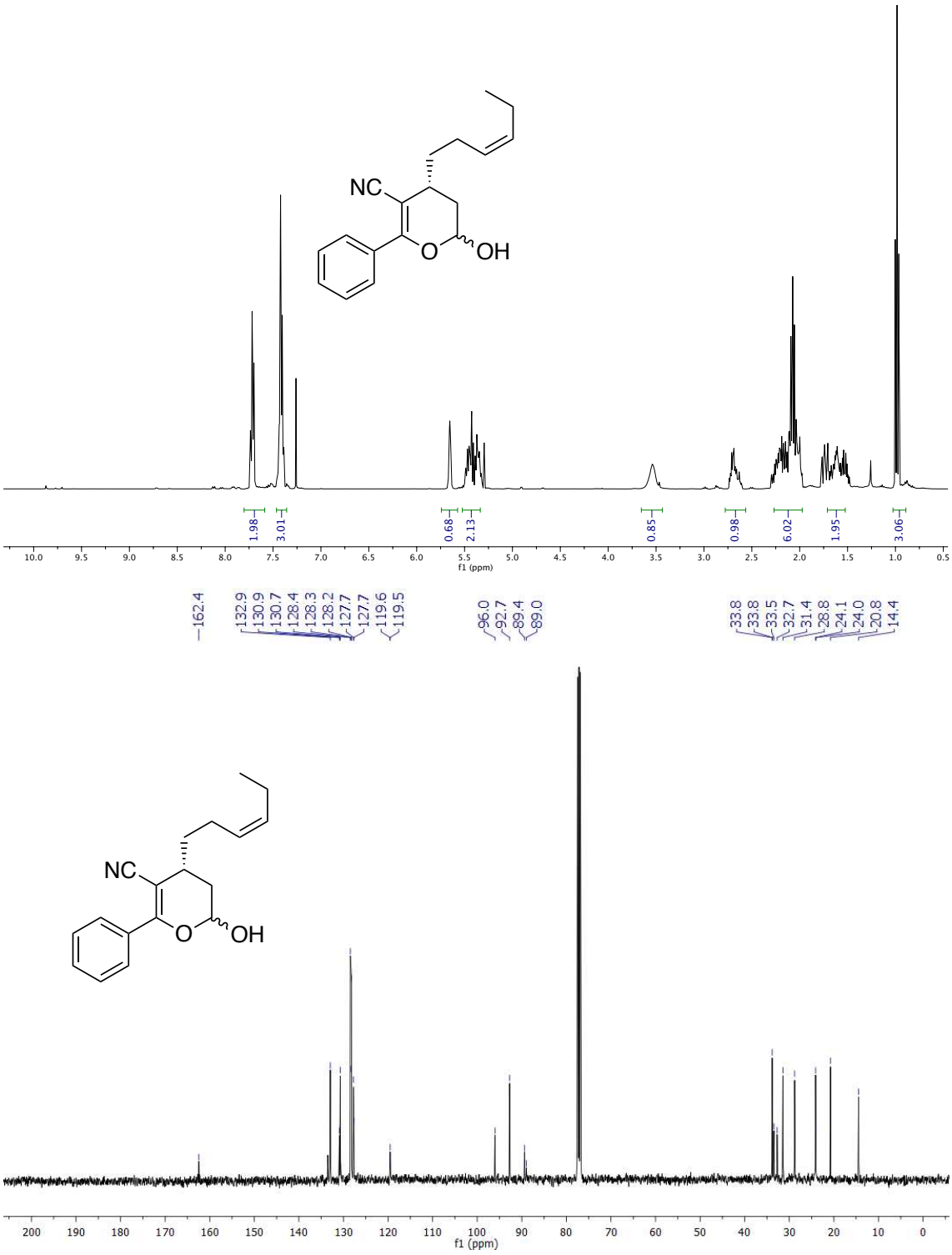


FIGURE 7.4 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1d**.

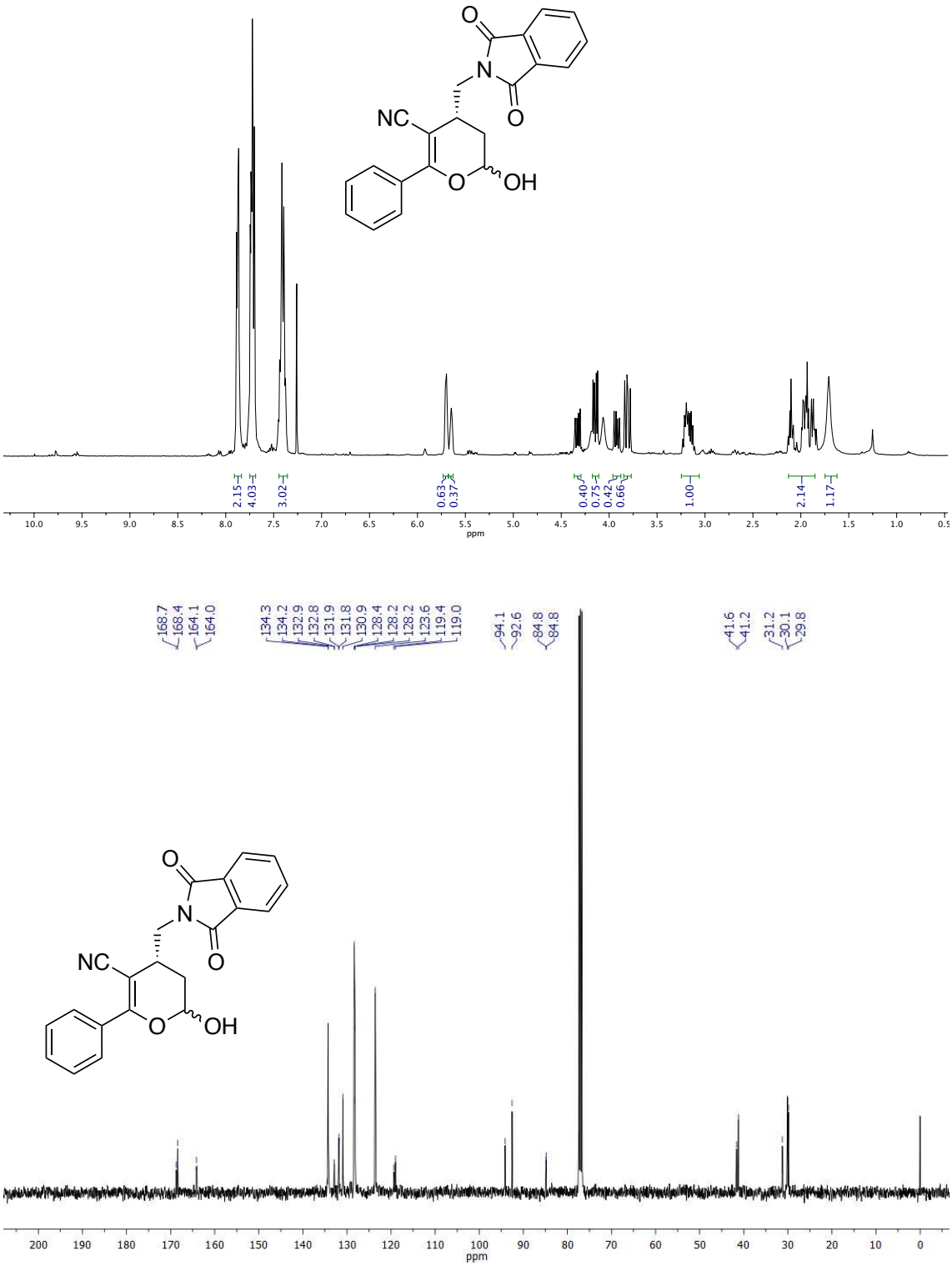


FIGURE 7.5 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1e**.

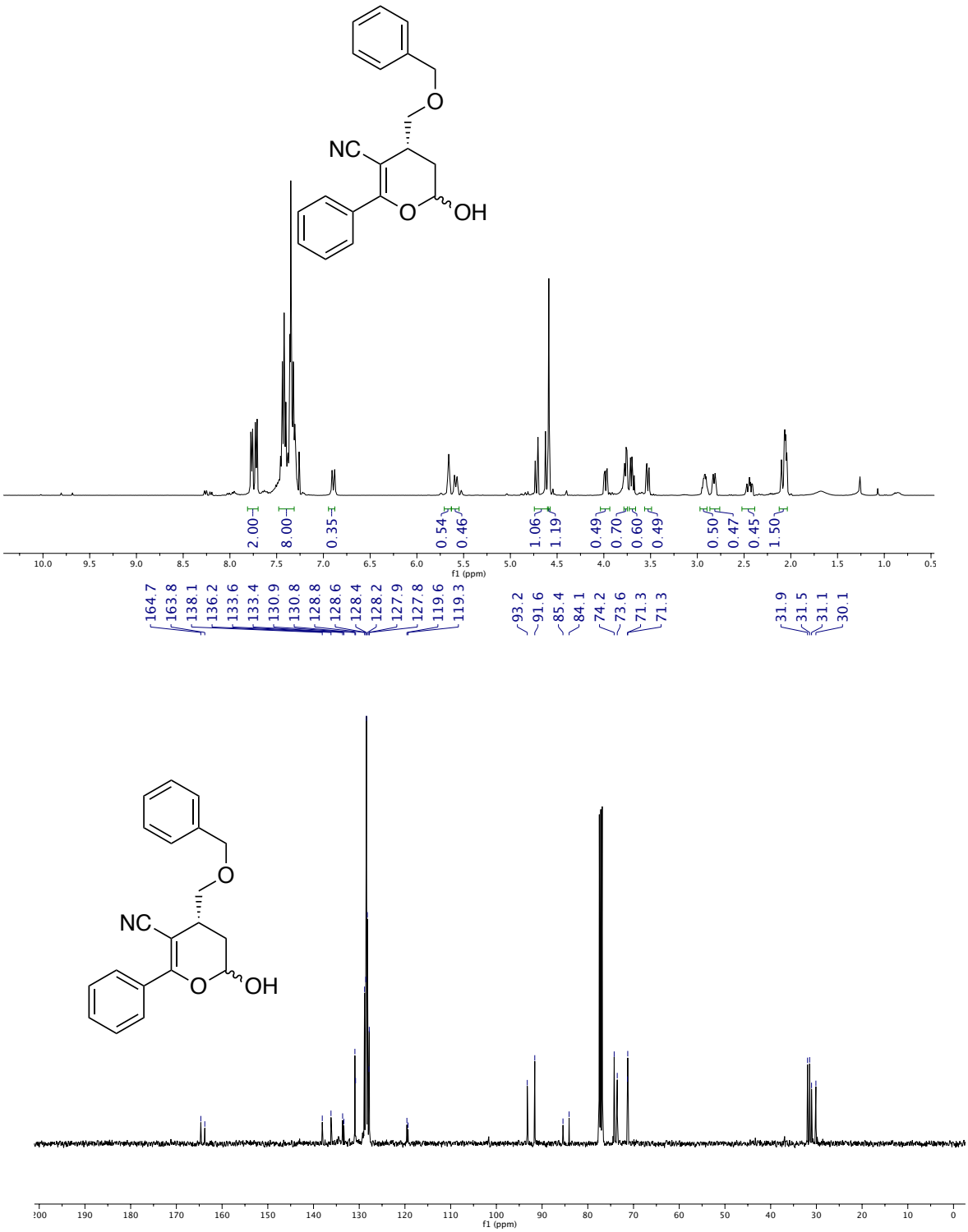


FIGURE 7.6 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1f.**

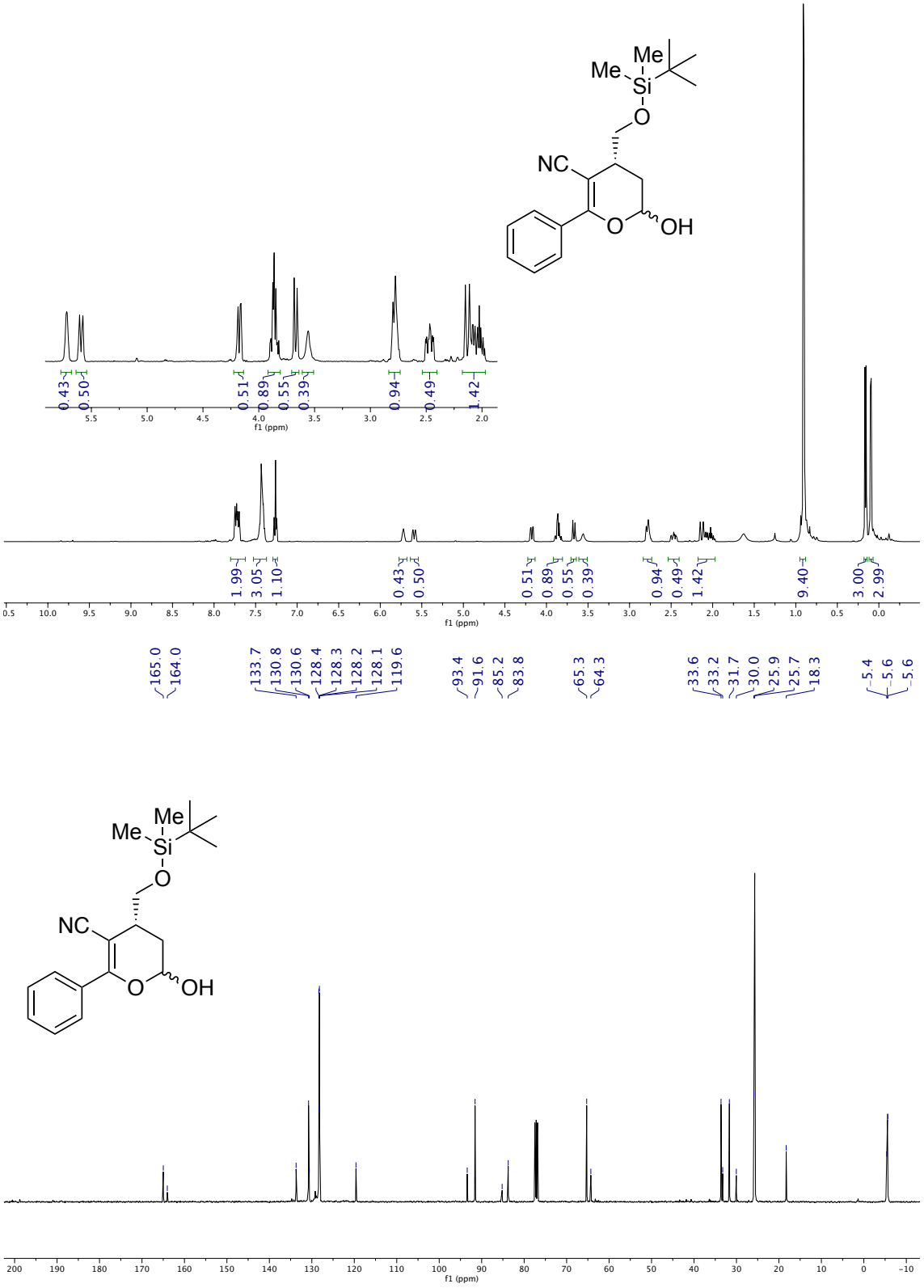


FIGURE 7.7 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1g.**

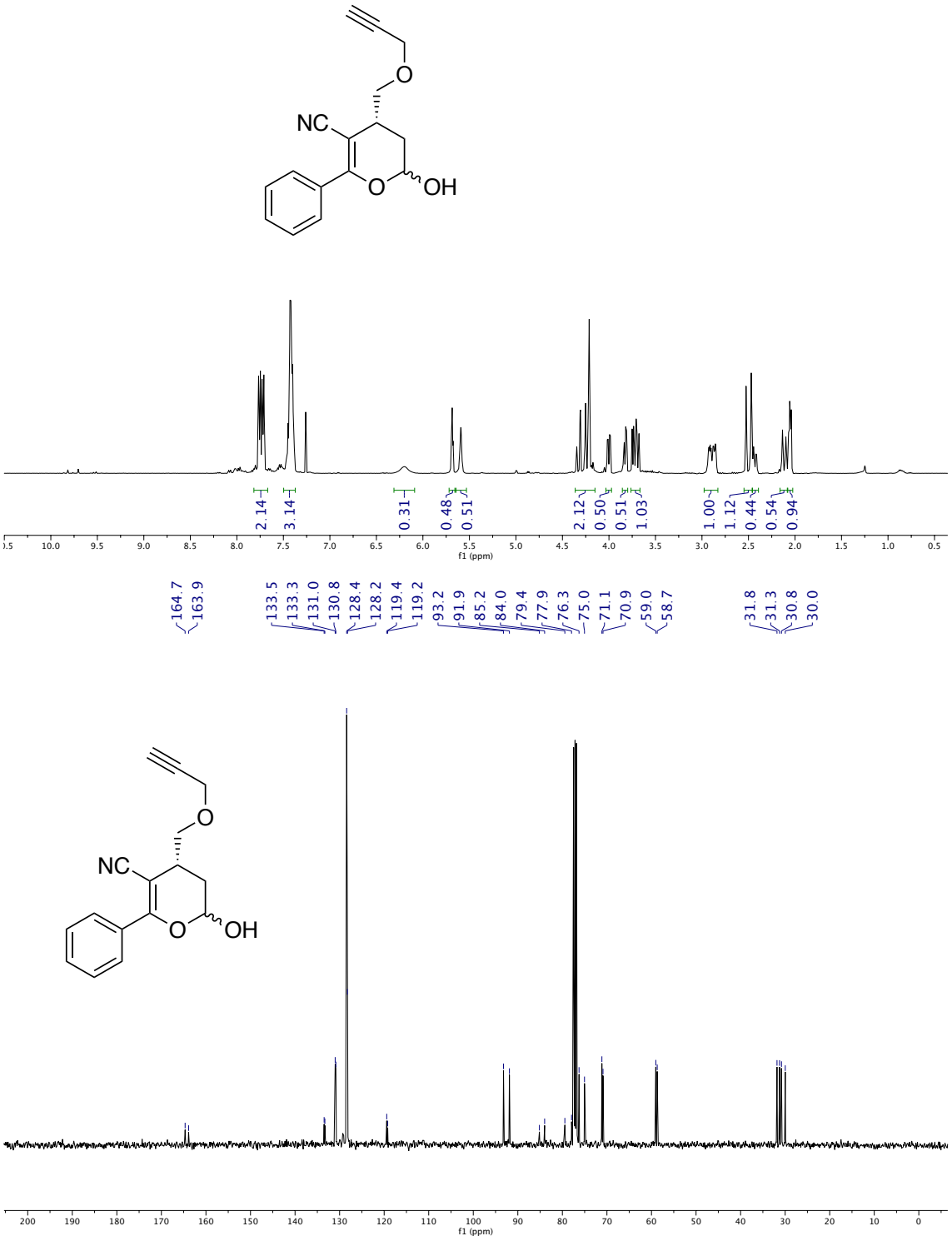


FIGURE 7.8 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **1h.**

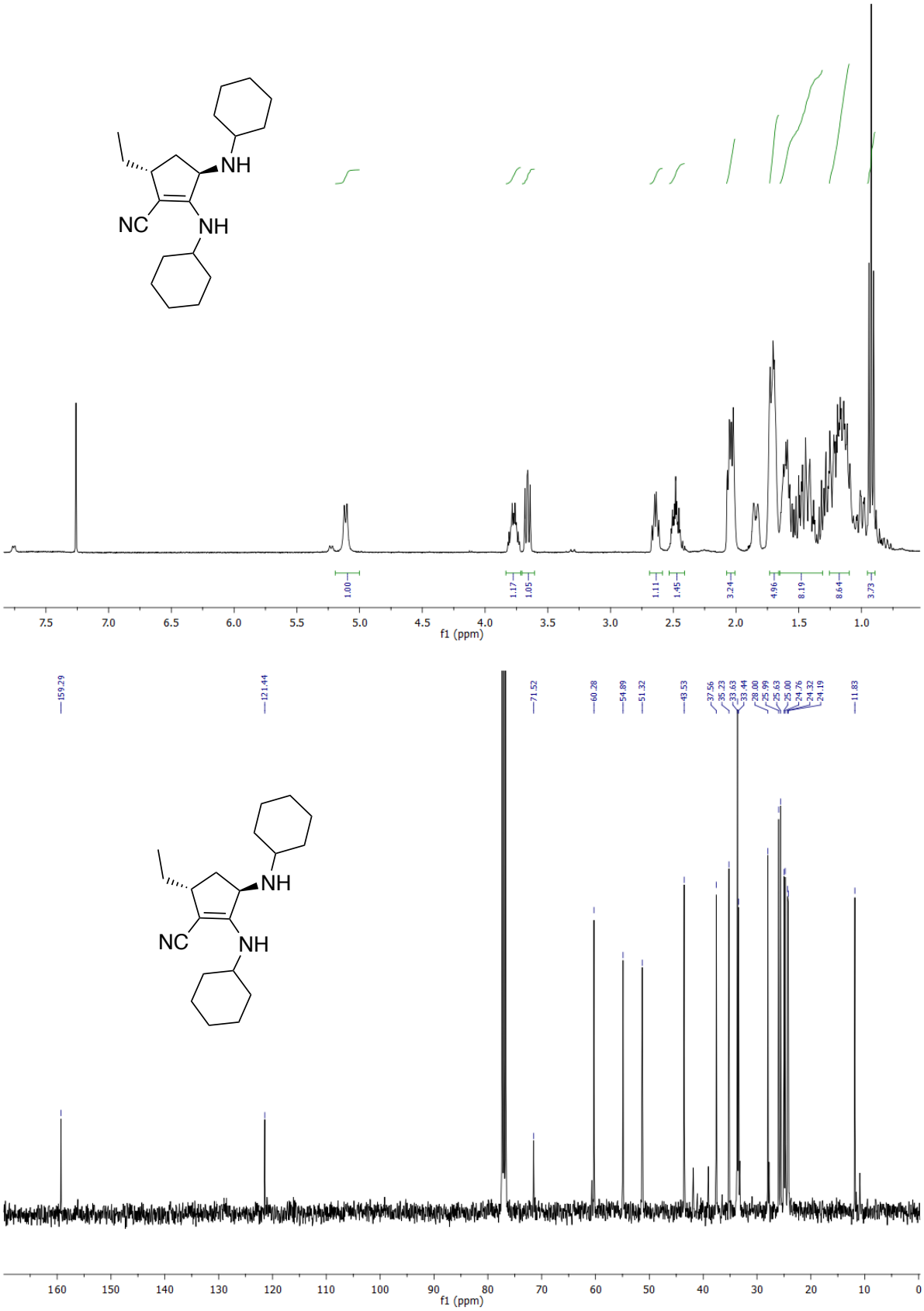


FIGURE 7.9 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2a.**

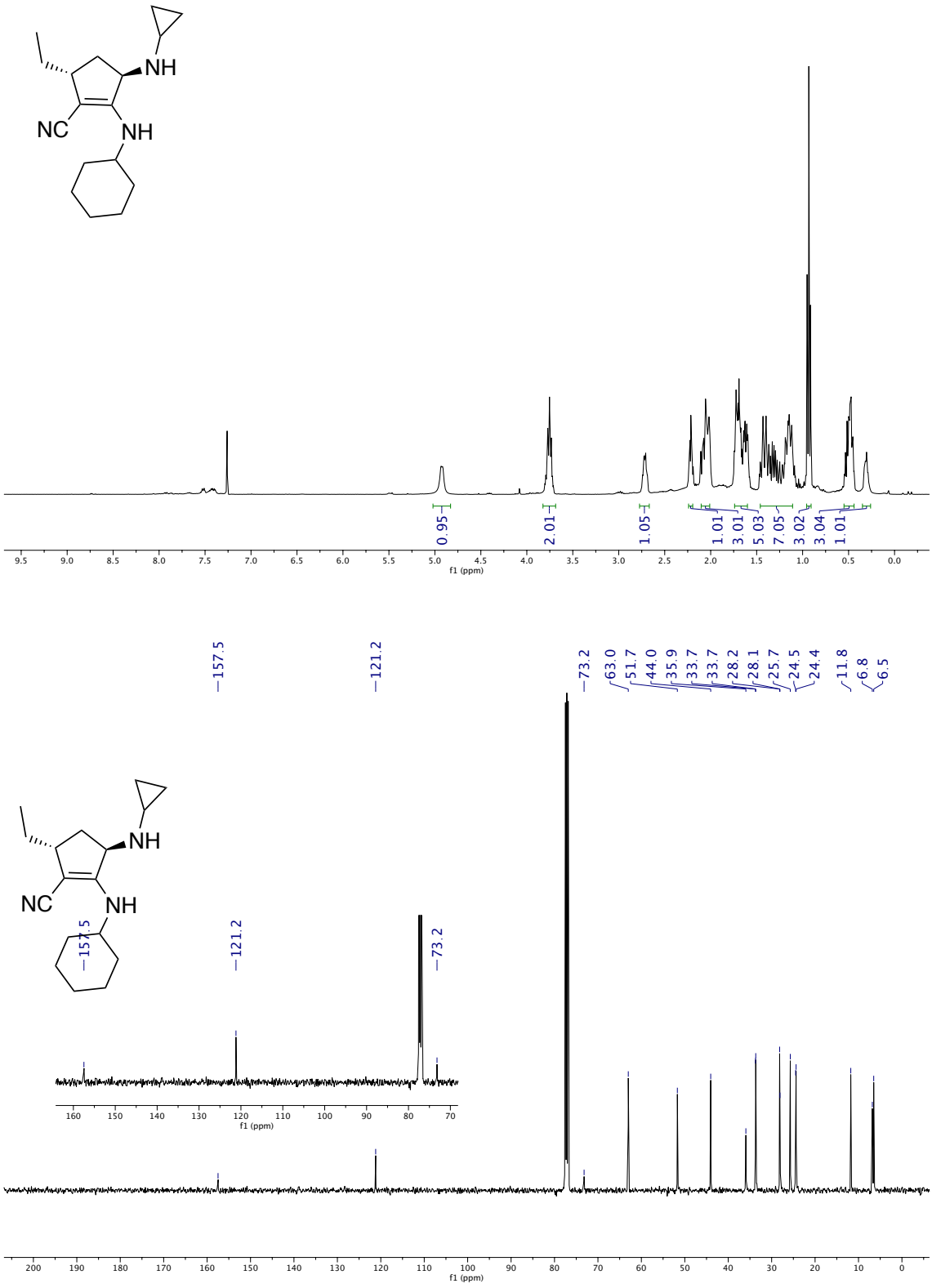


FIGURE 7.10 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2b.**

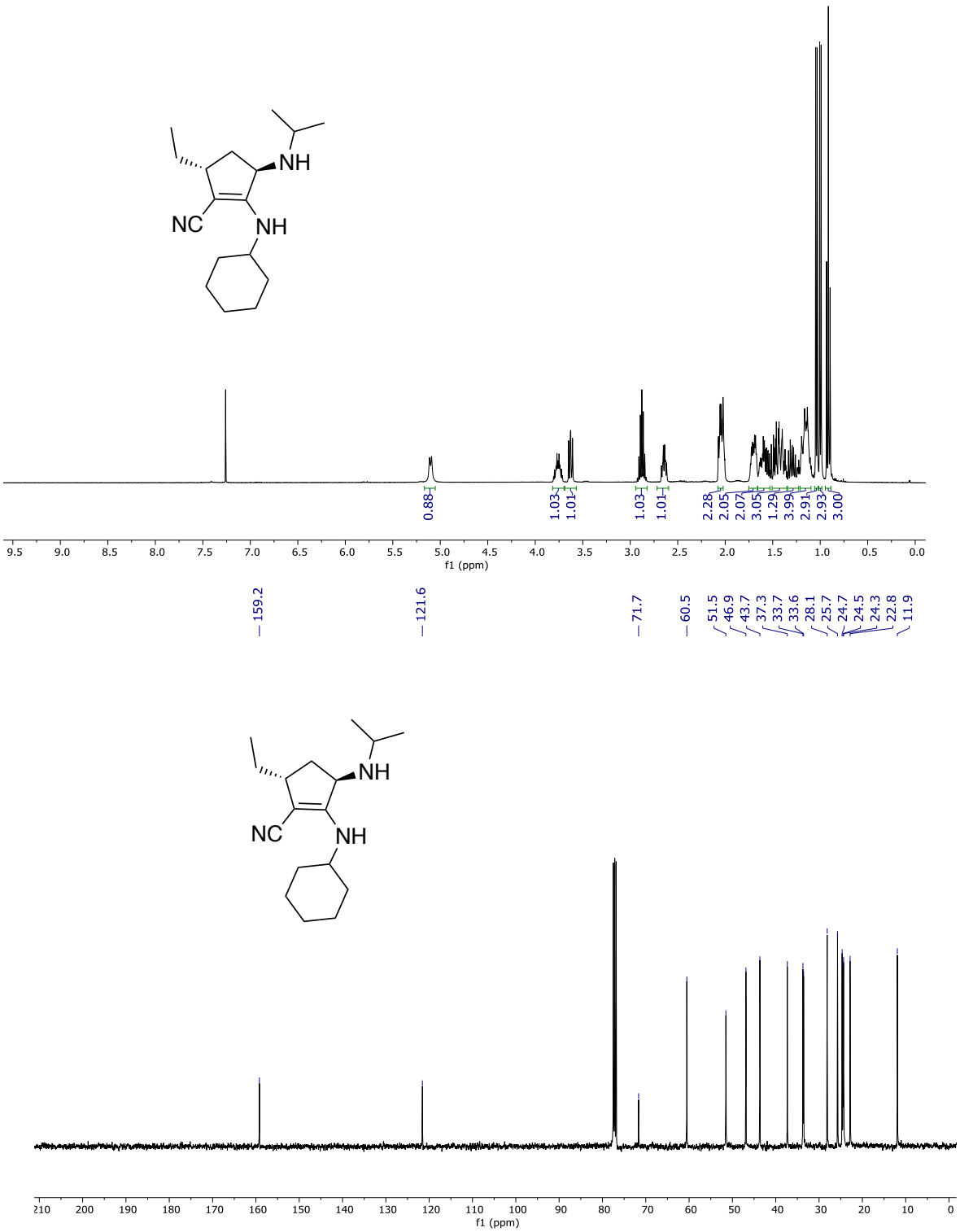


FIGURE 7.11 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2c**.

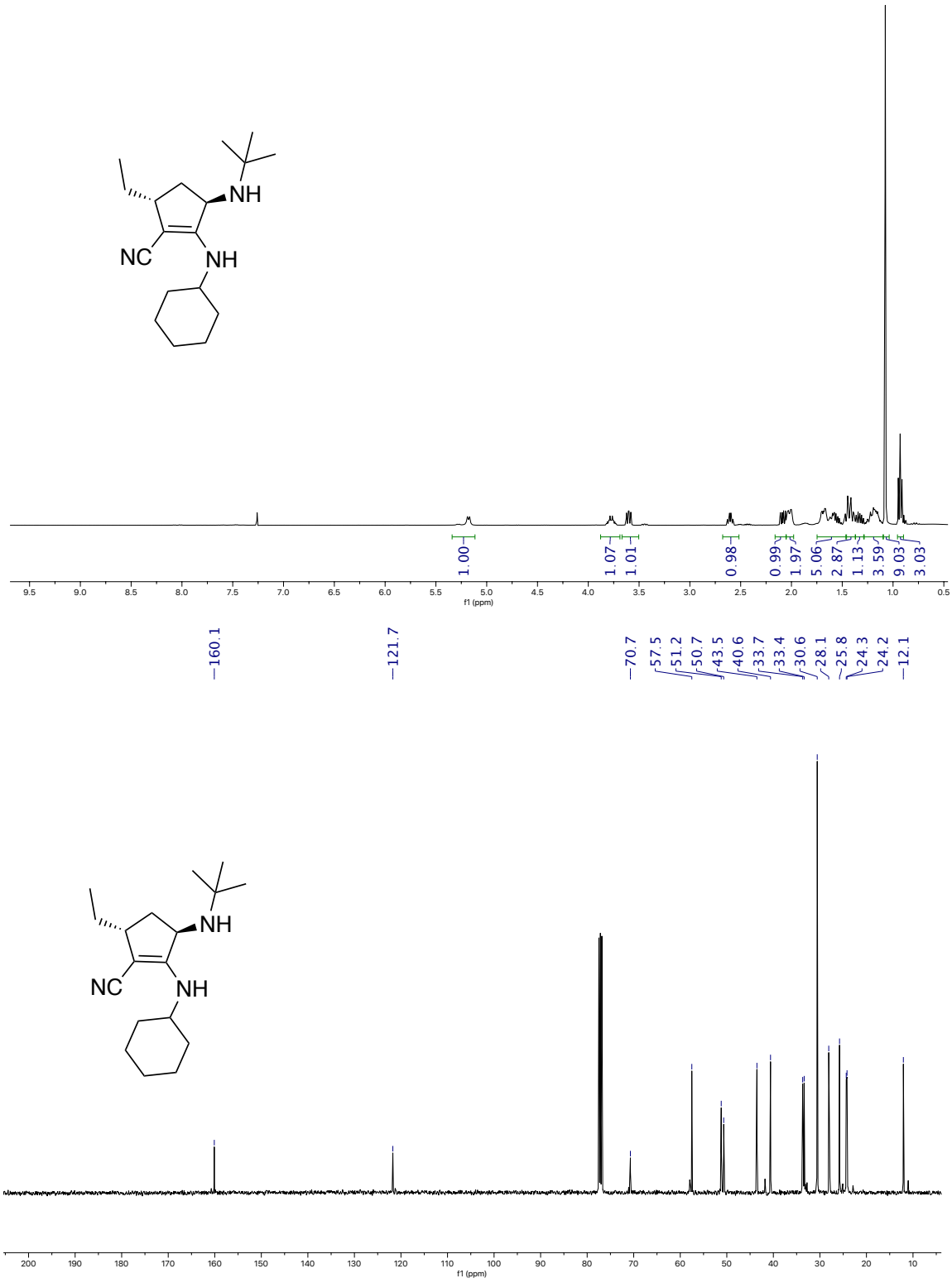


FIGURE 7.12 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2d**.

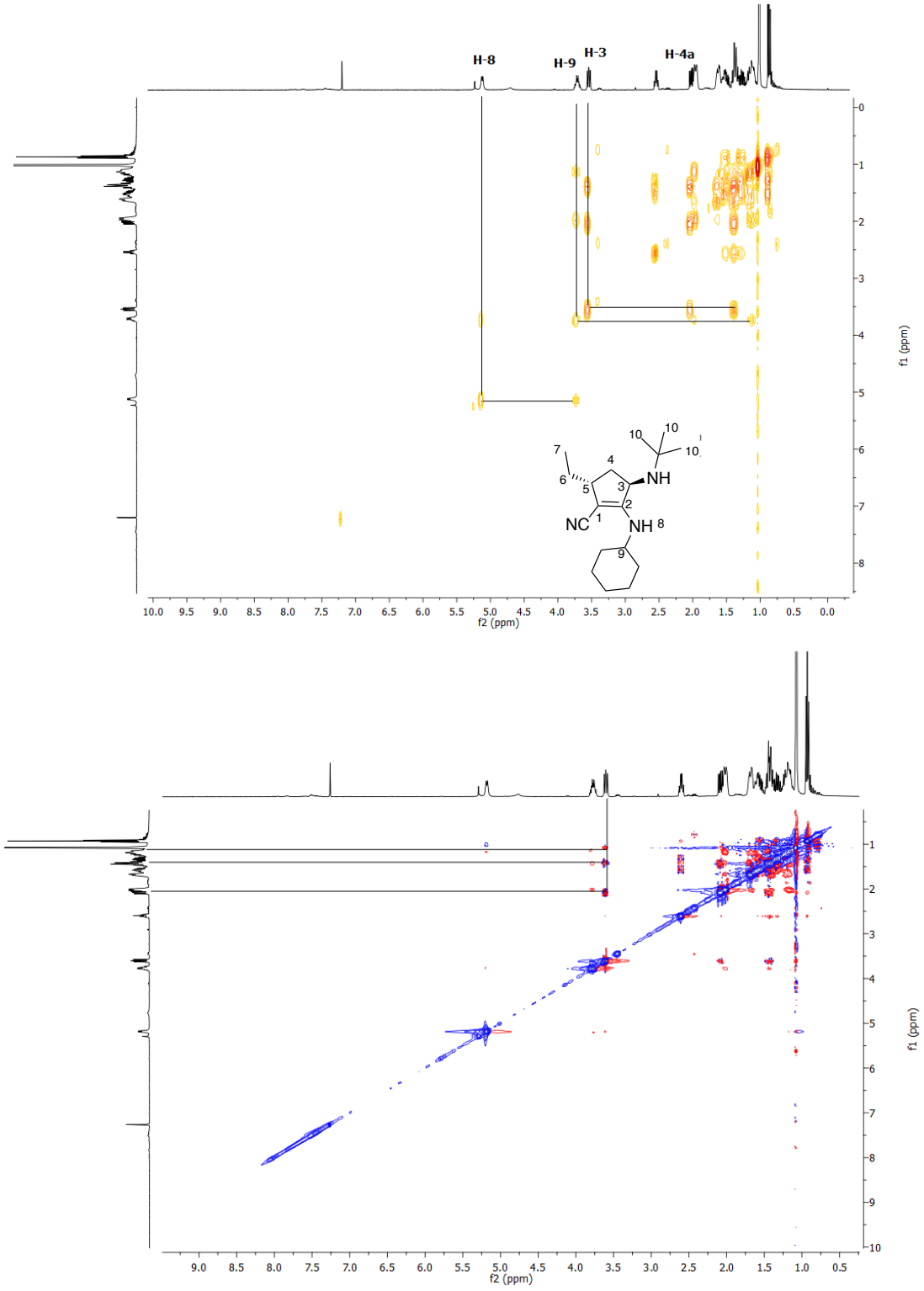


FIGURE 7.13 COSY and NOESY NMR spectra in $CDCl_3$ of compound **2d**.

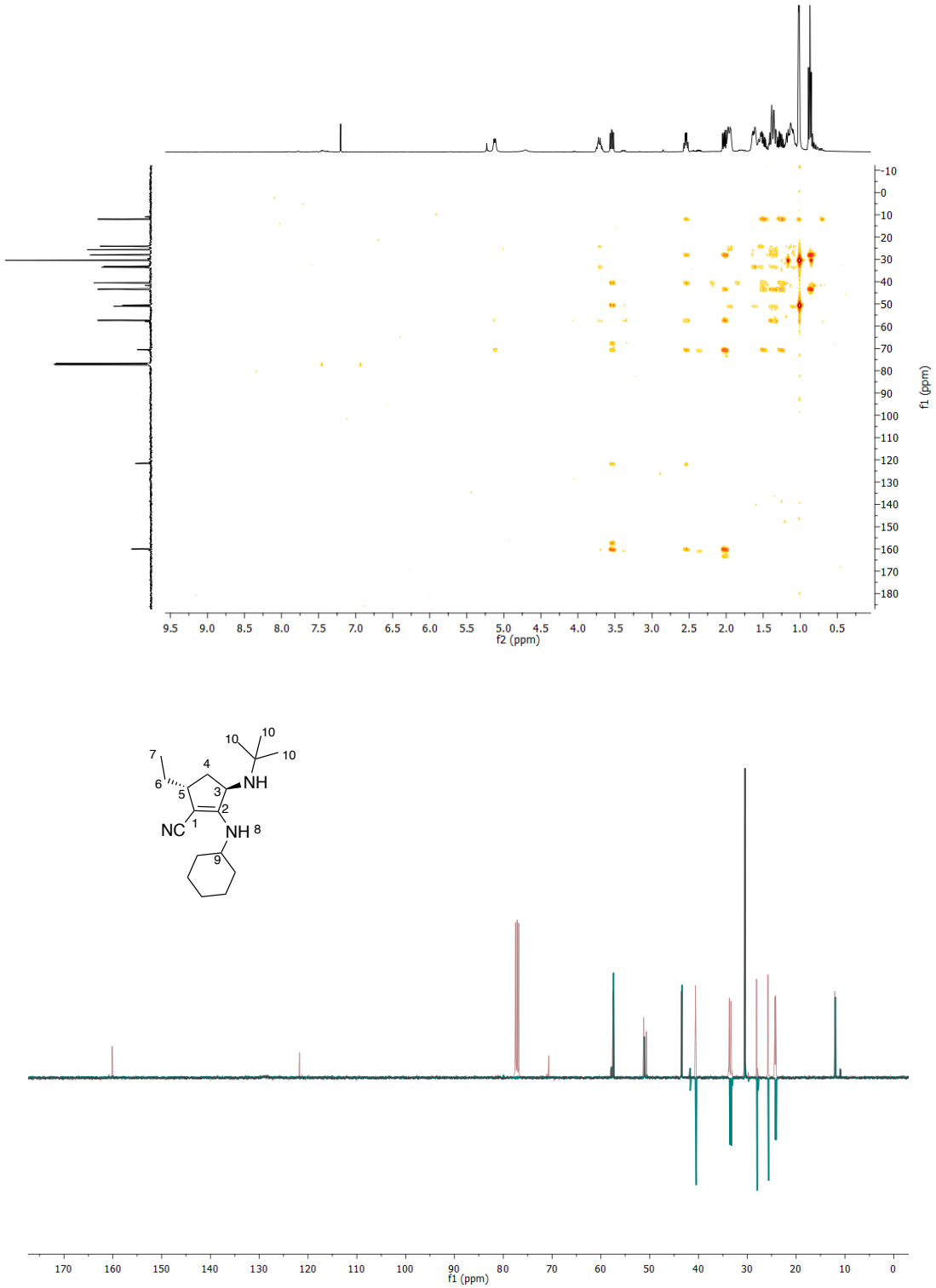


FIGURE 7.14 HMBC and superimposed ^{13}C-DEPT 135 NMR spectra in $CDCl_3$ of compound **2d**.

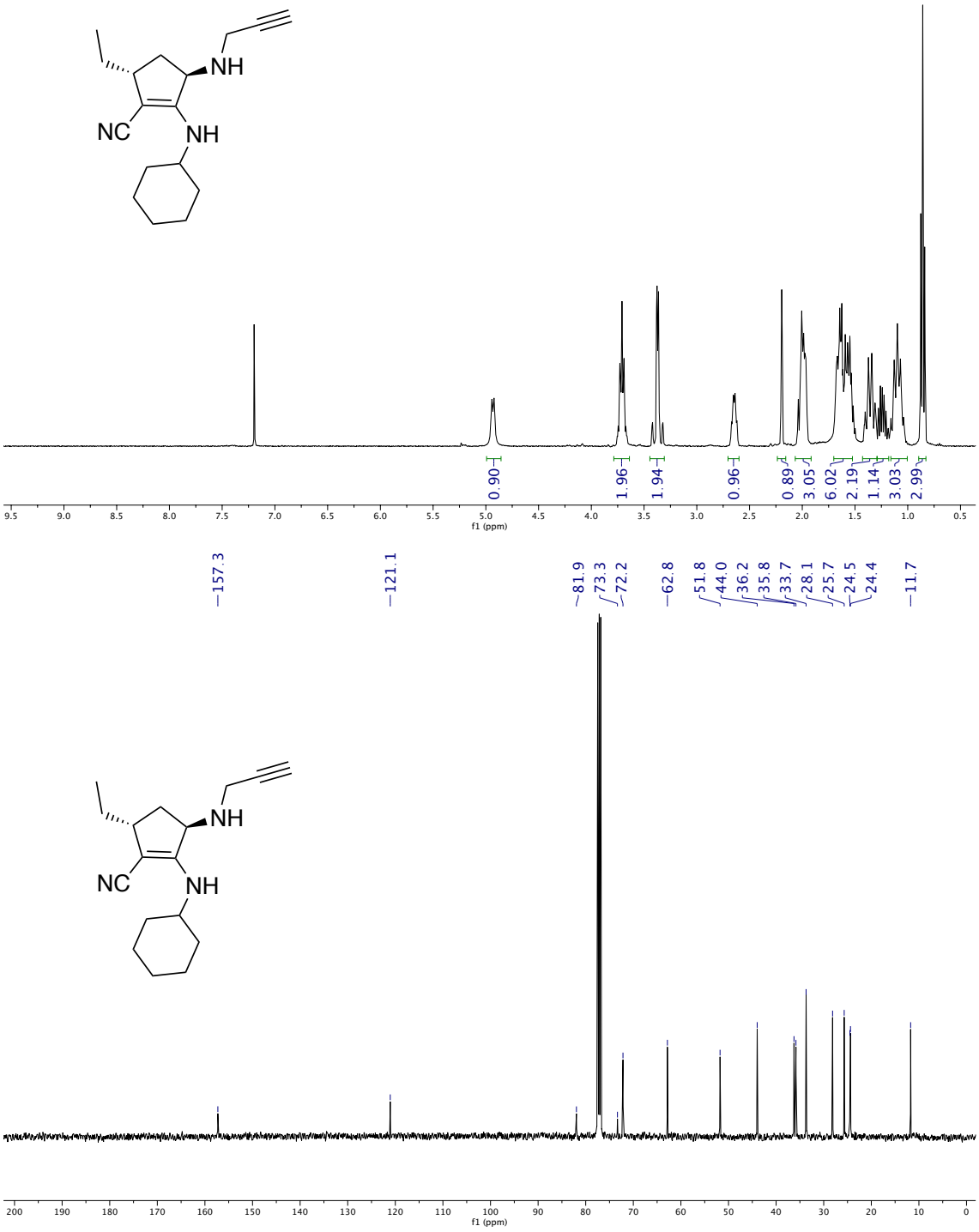


FIGURE 7.15 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2e**.

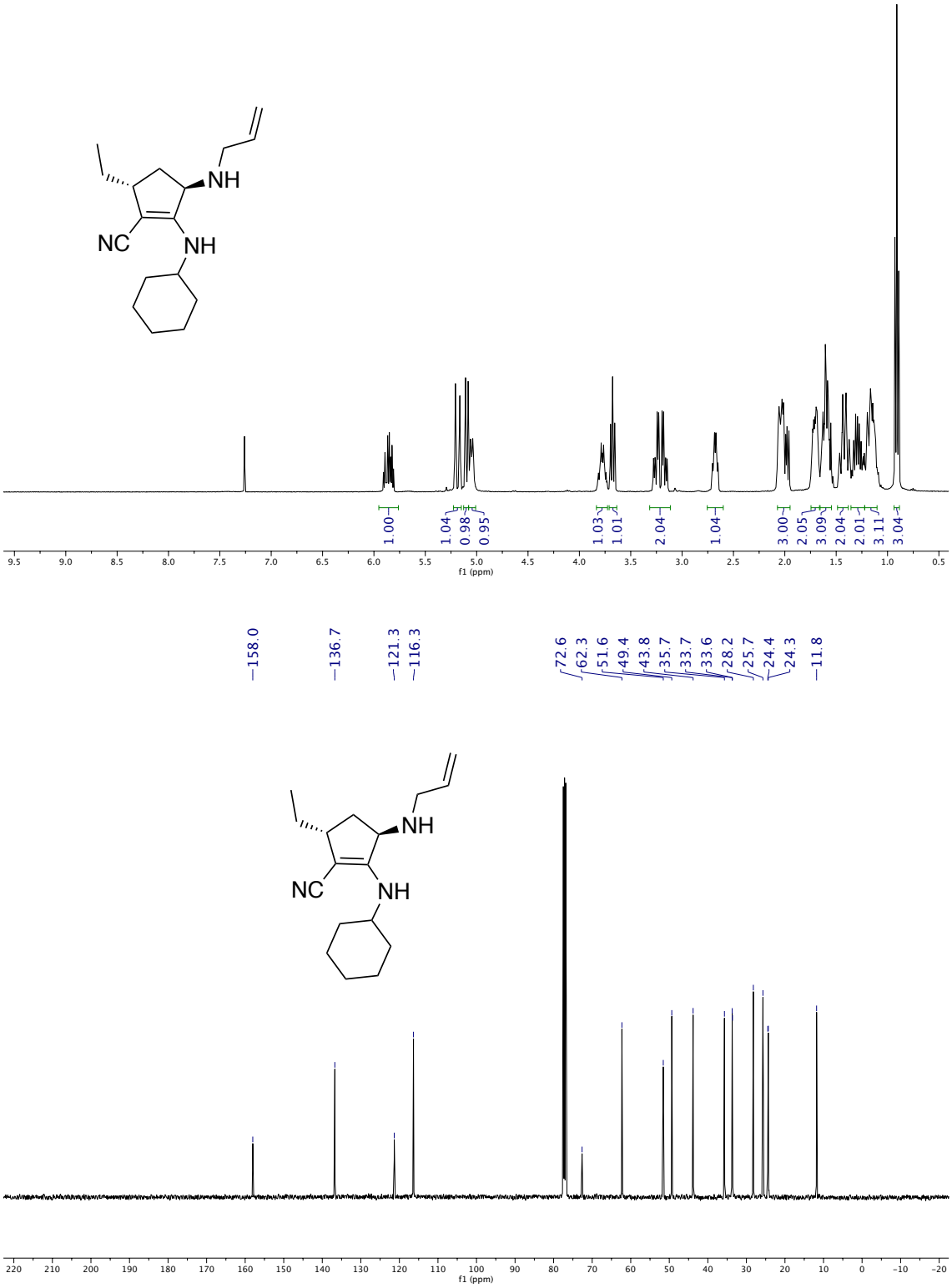


FIGURE 7.16 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2f**.

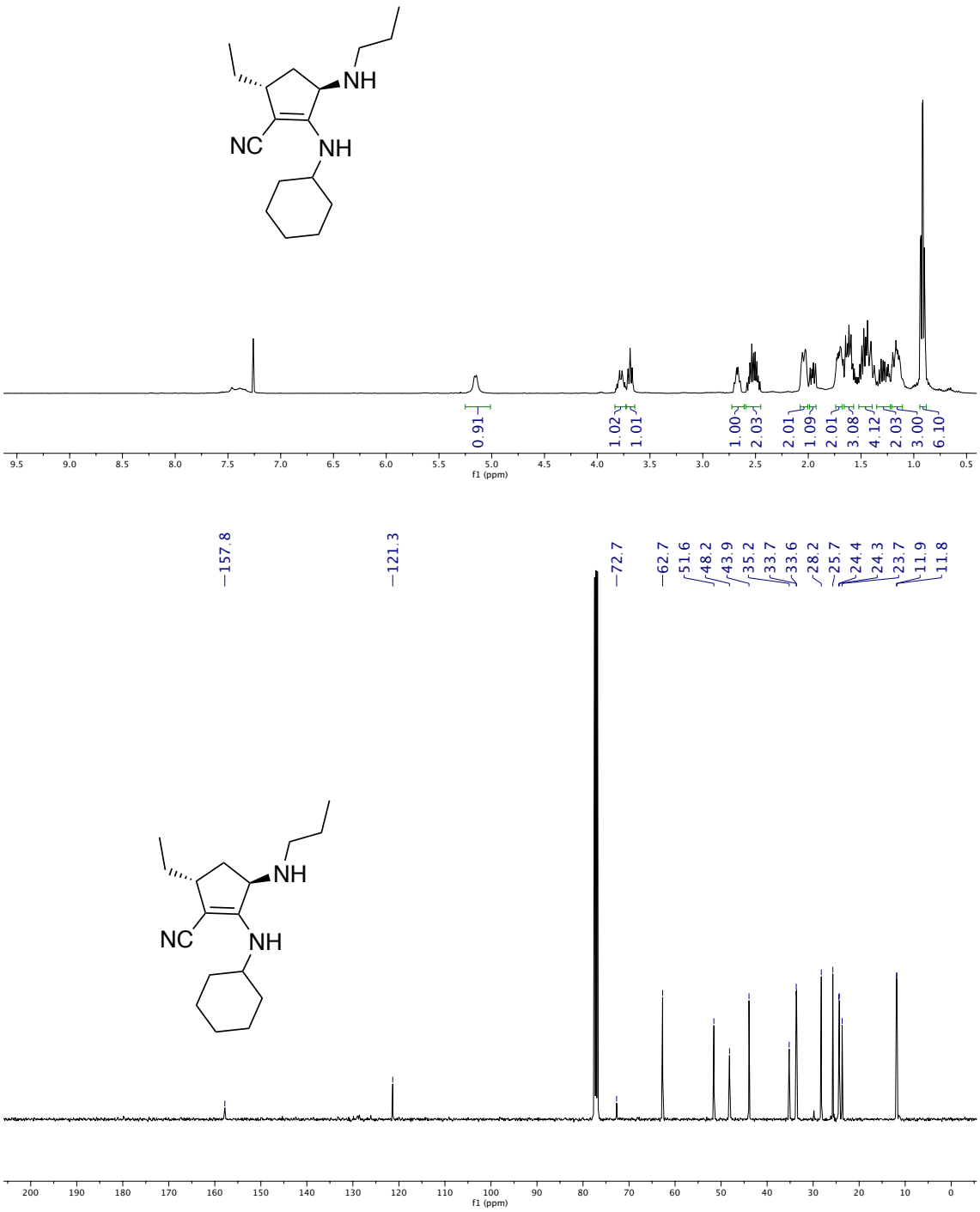


FIGURE 7.17 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2g**.

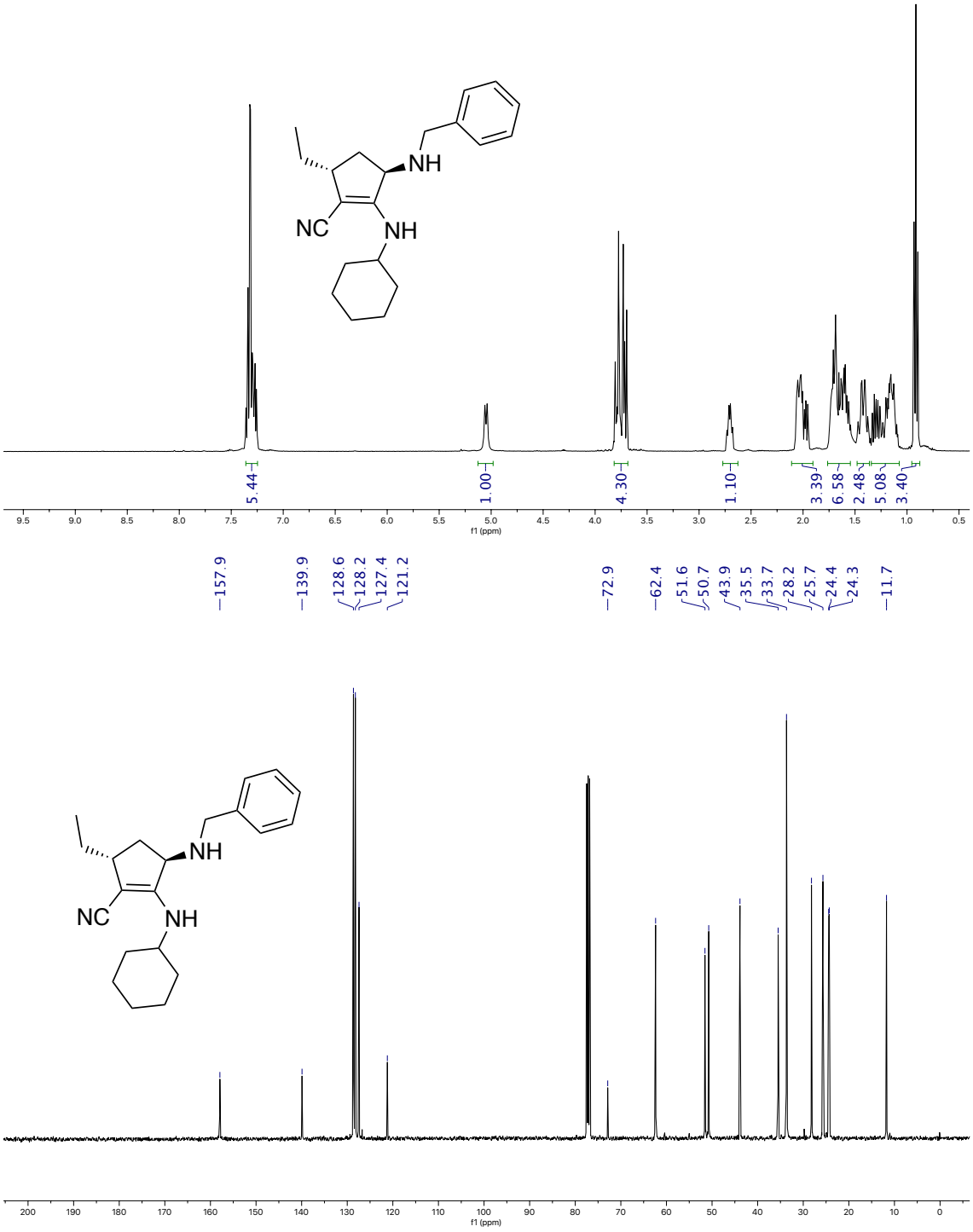


FIGURE 7.18 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2h**.

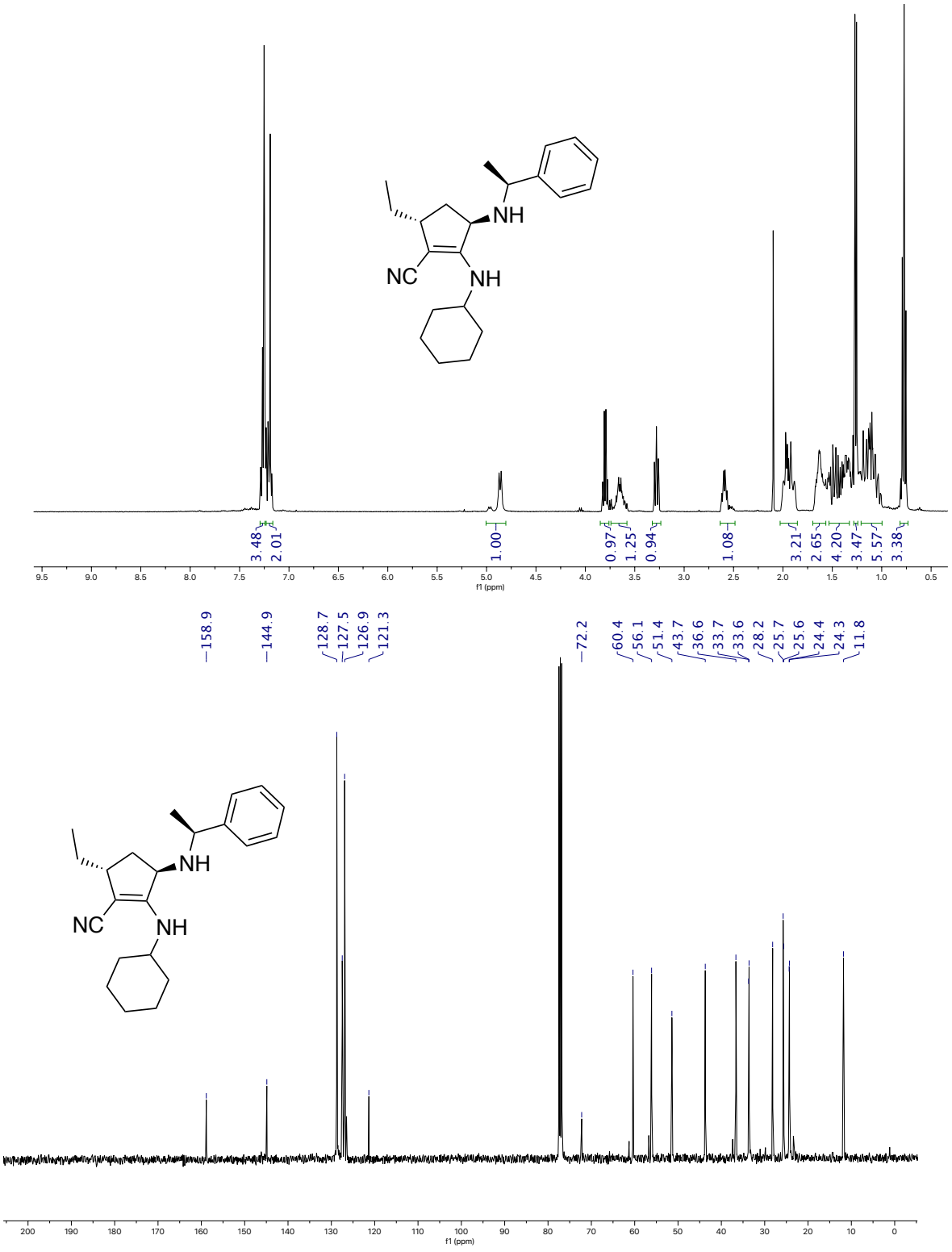


FIGURE 7.19 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2i**.

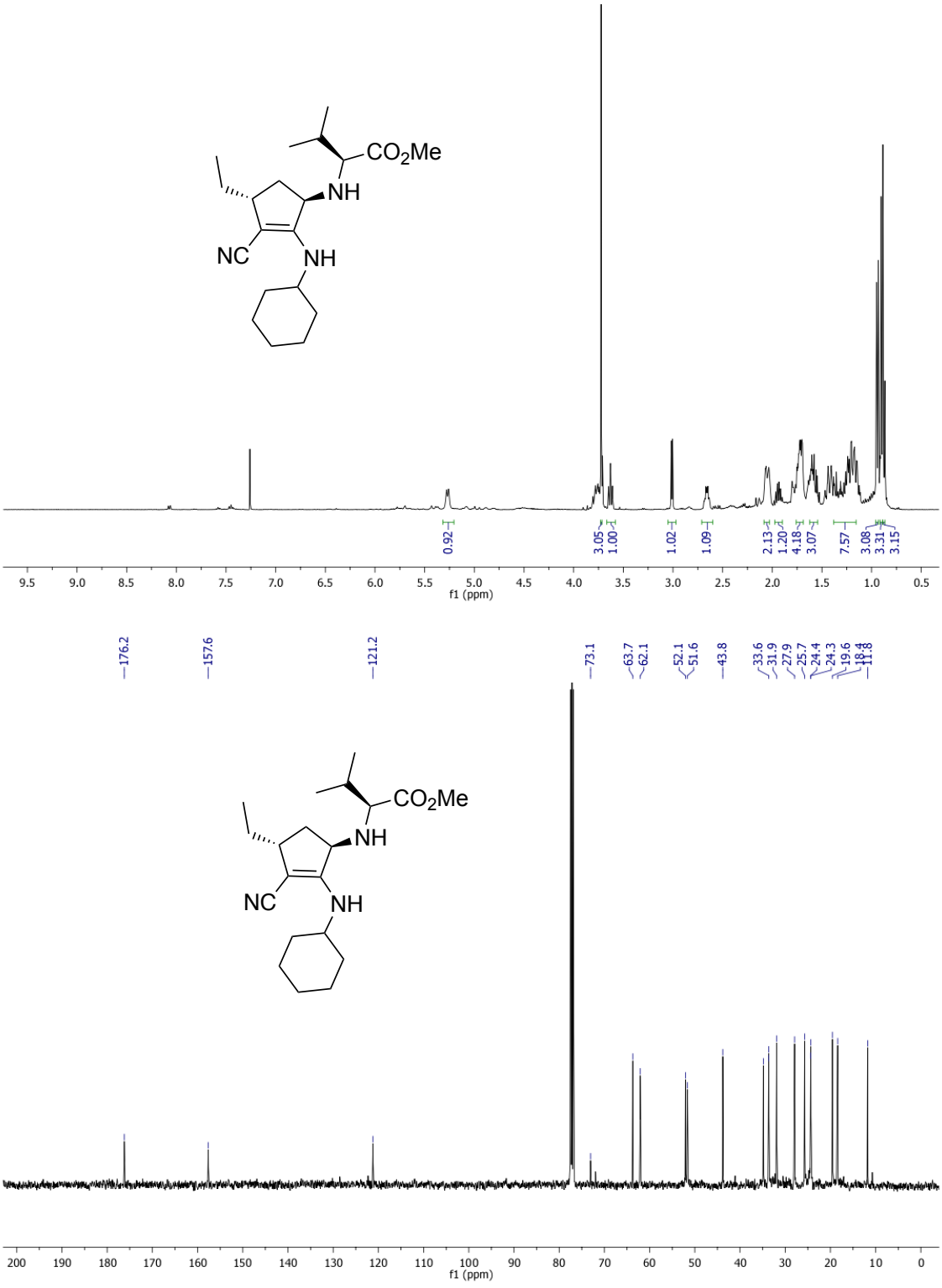


FIGURE 7.20 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2j**.

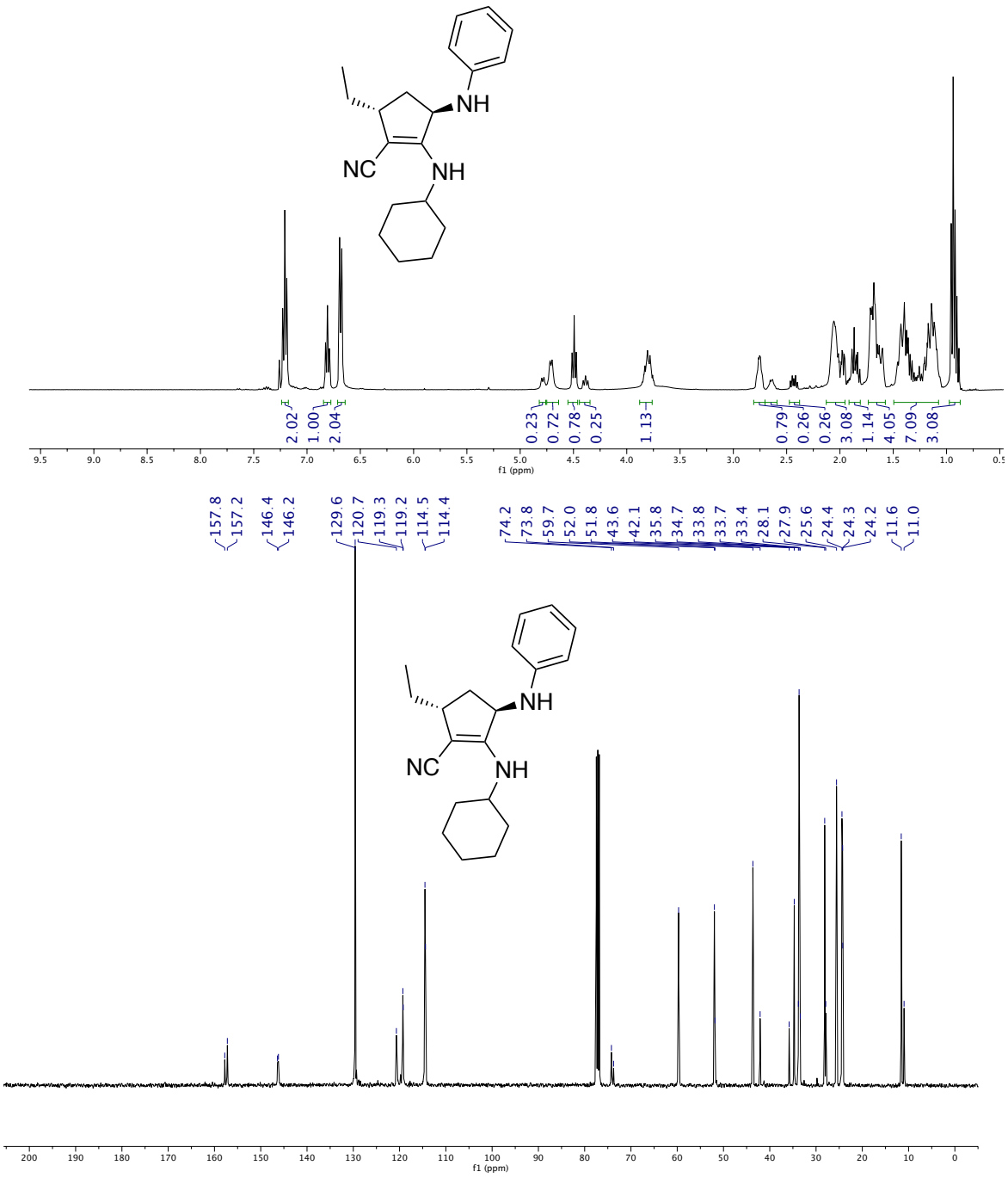


FIGURE 7.21 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2k**.

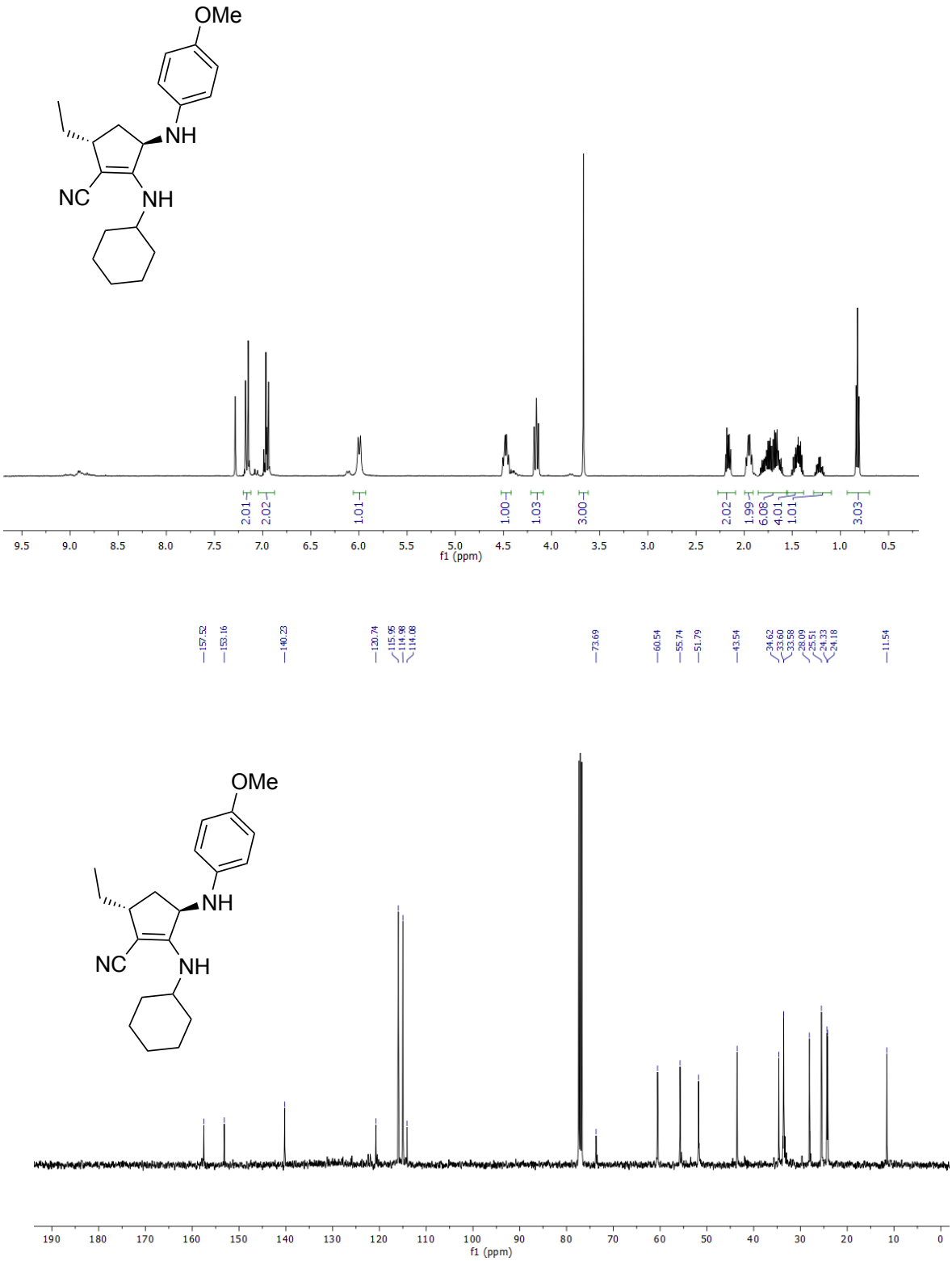


FIGURE 7.22 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2l**.

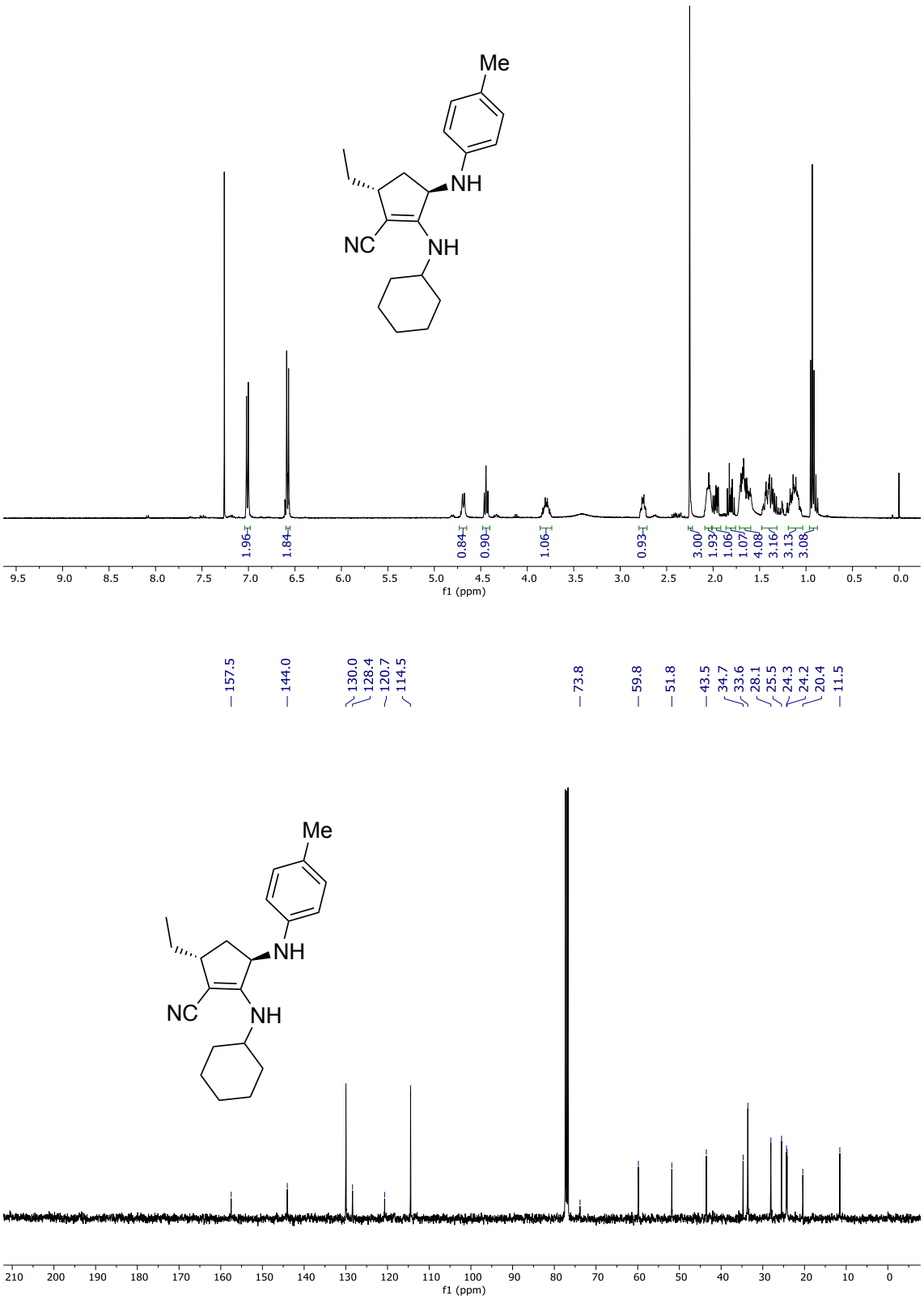


FIGURE 7.23 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2m**.

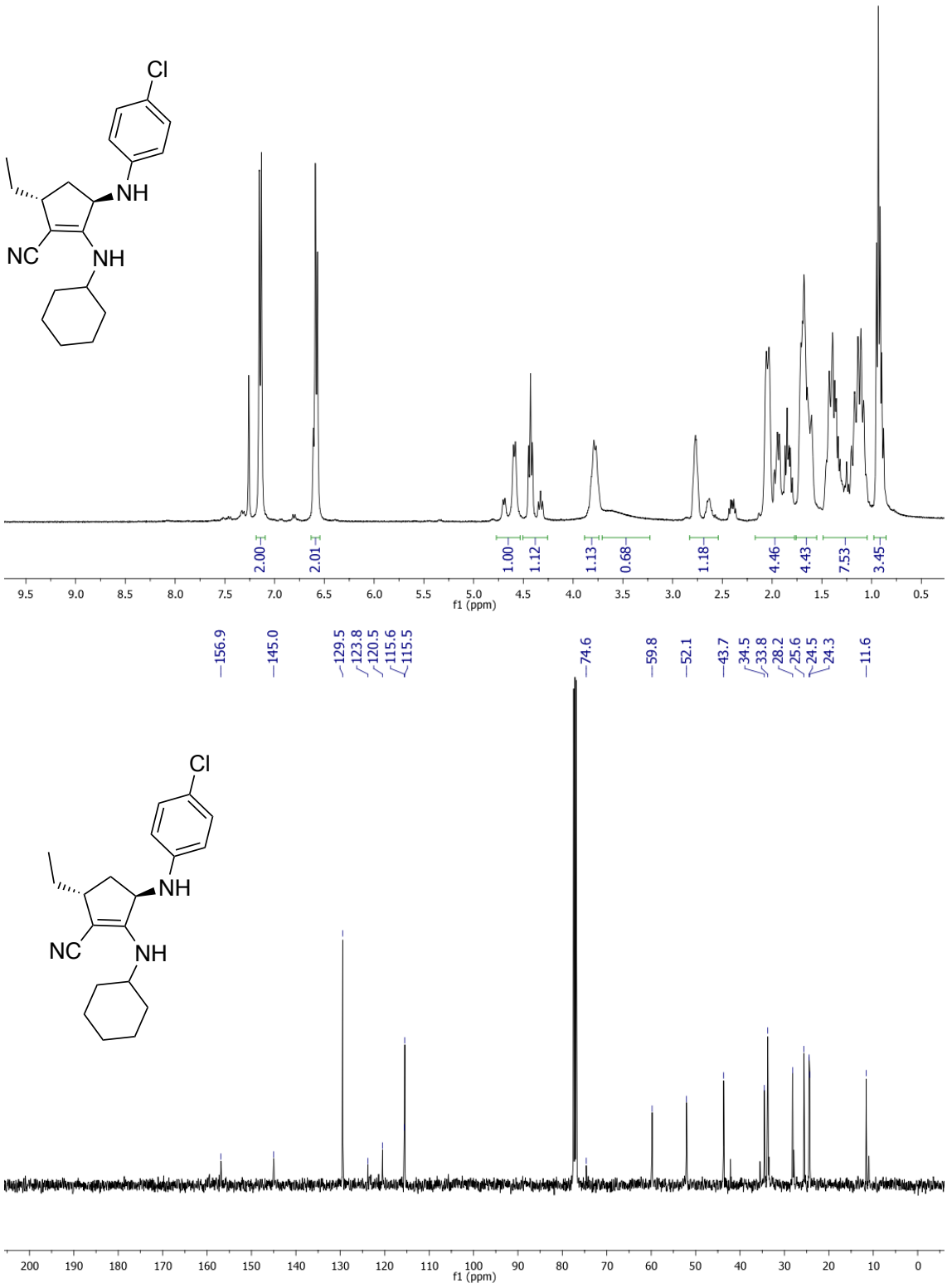


FIGURE 7.24 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2n**.

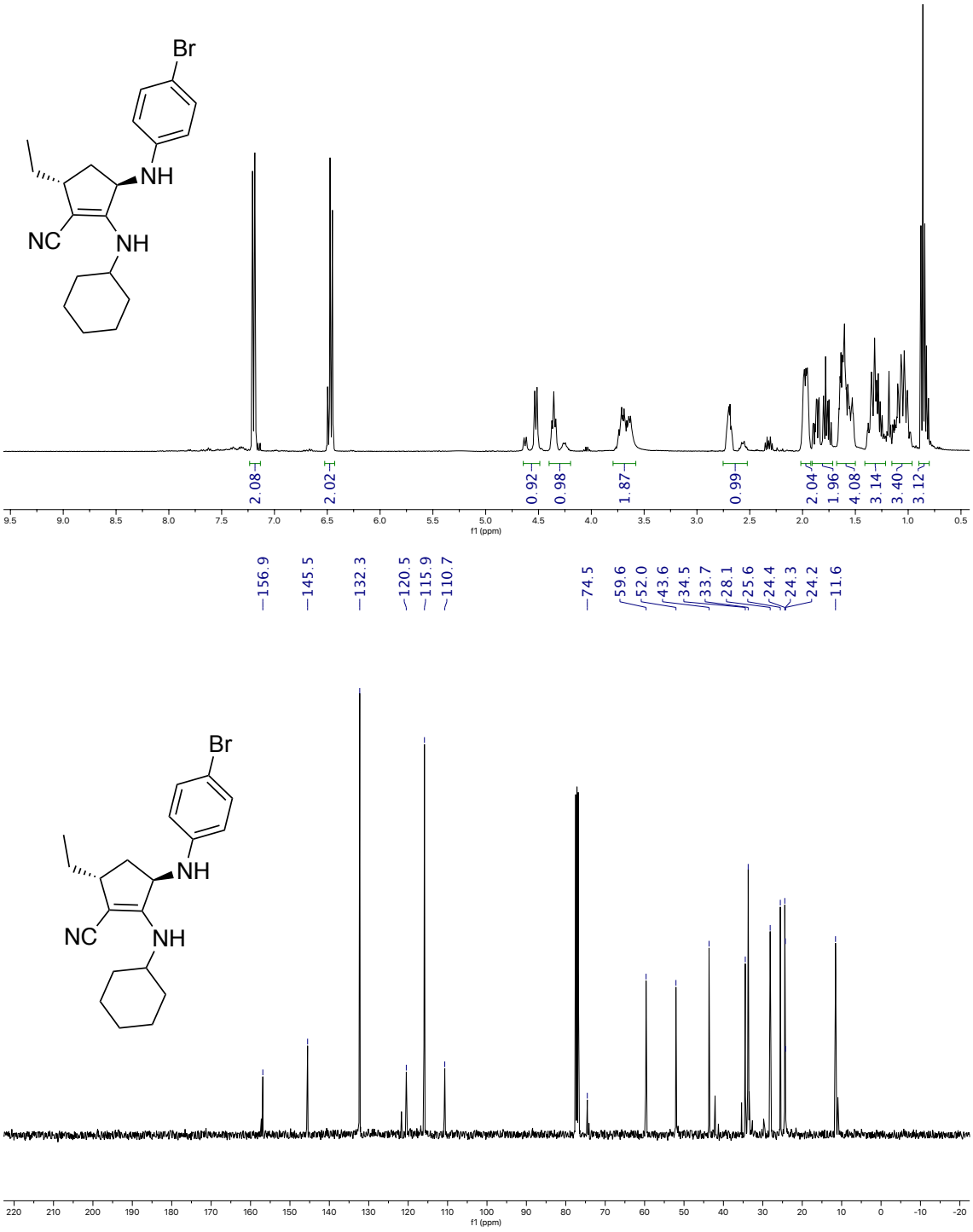


FIGURE 7.25 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2o.**

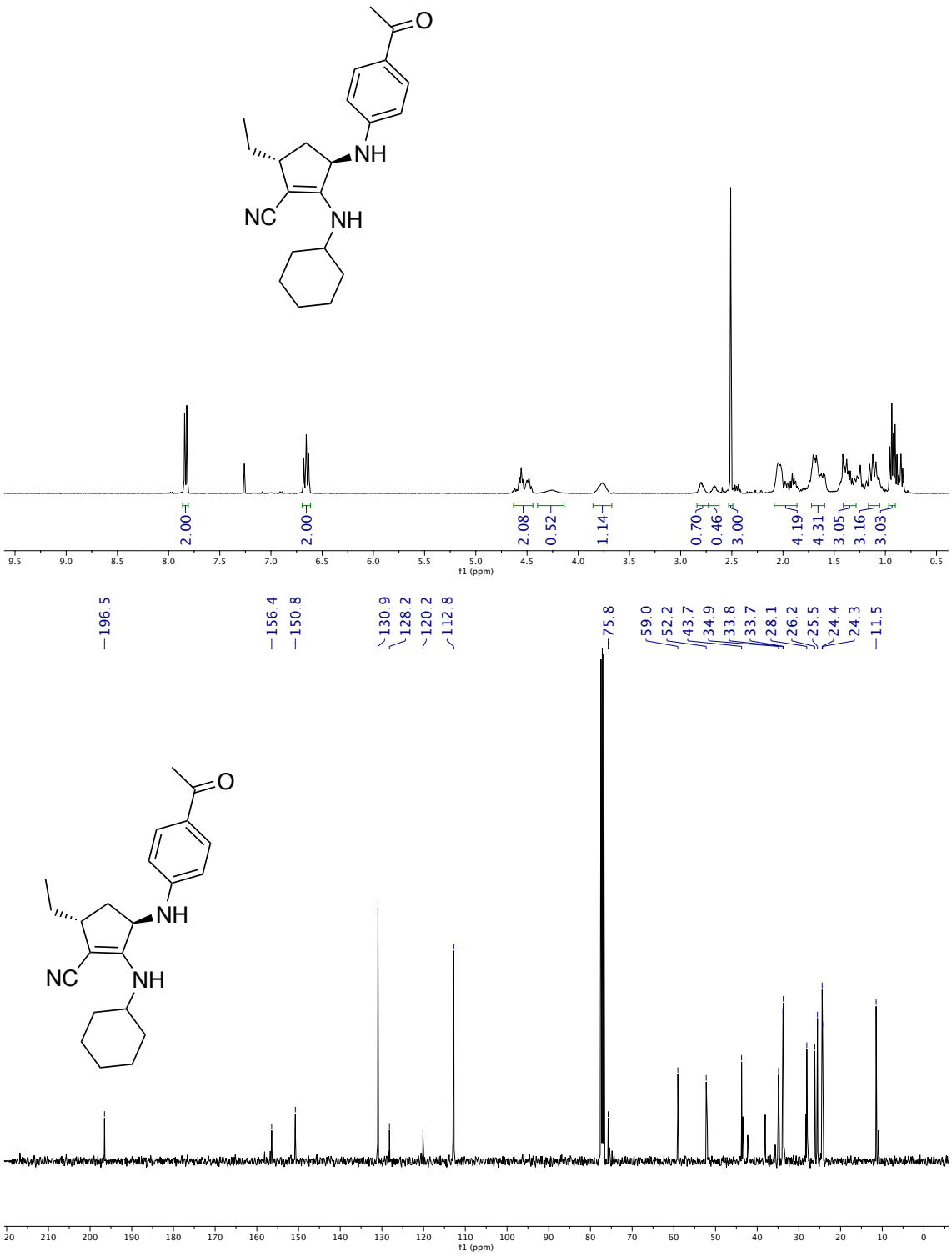


FIGURE 7.26 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2p.**

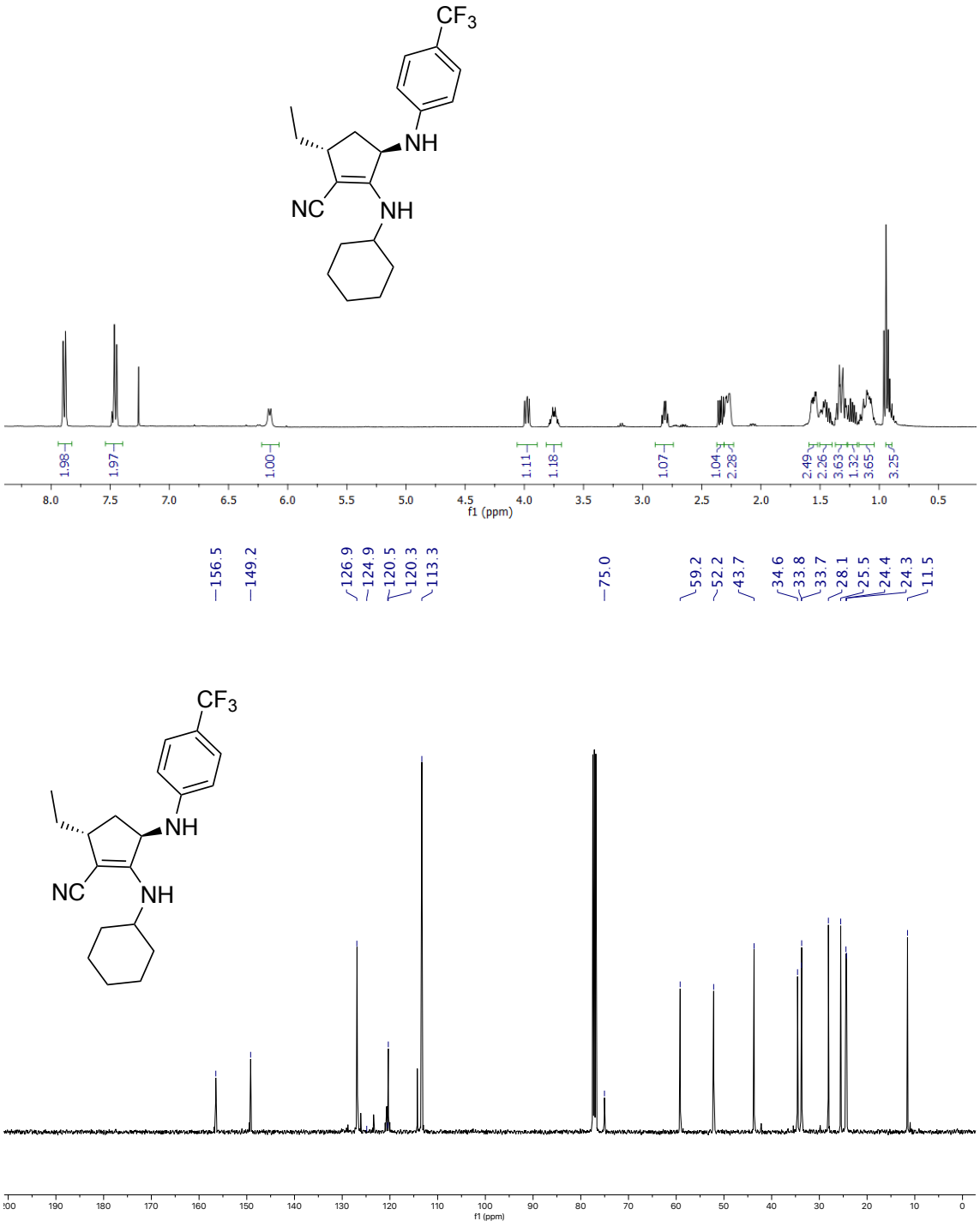


FIGURE 7.27 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2q**.

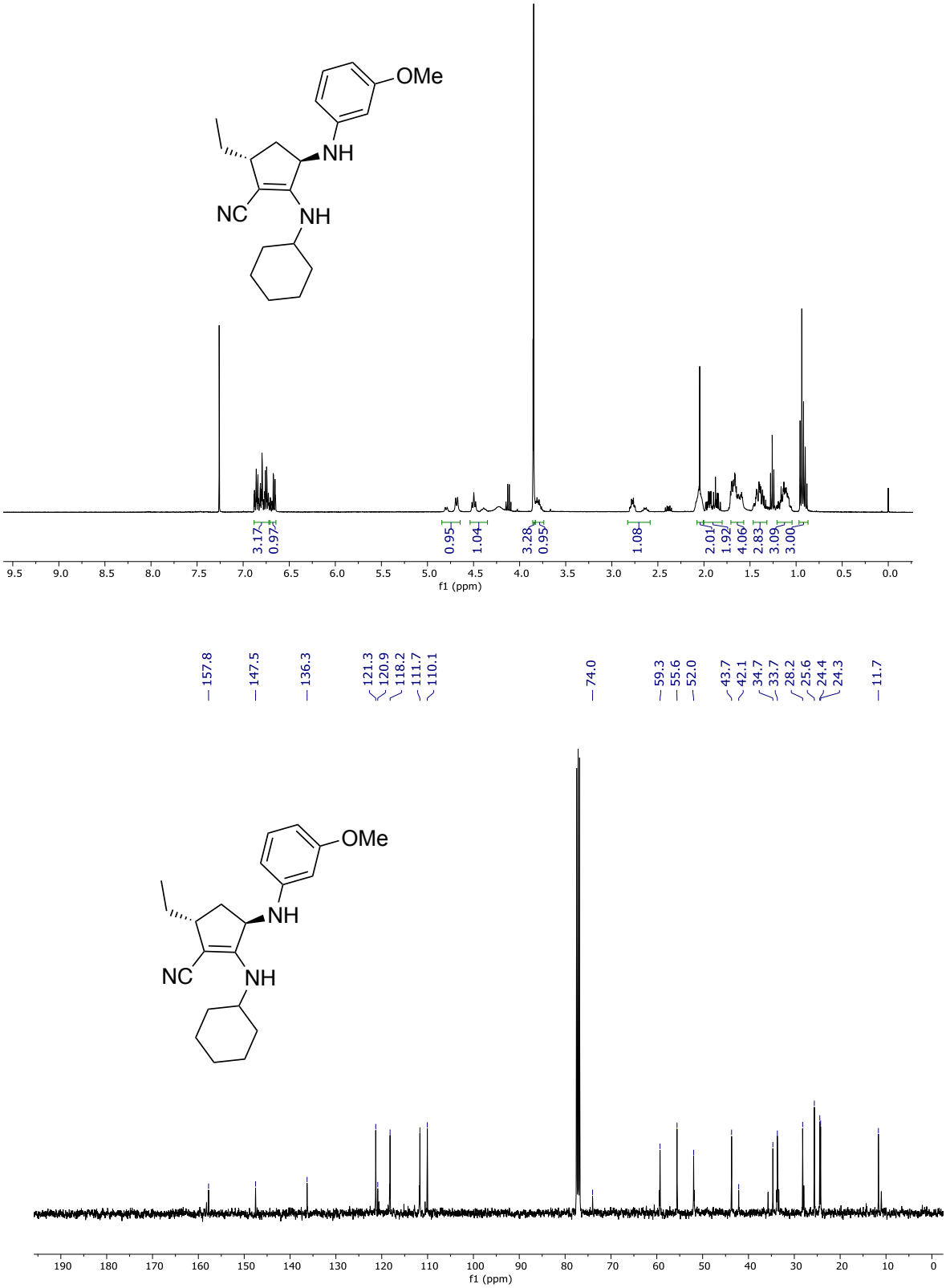


FIGURE 7.28 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2s**.

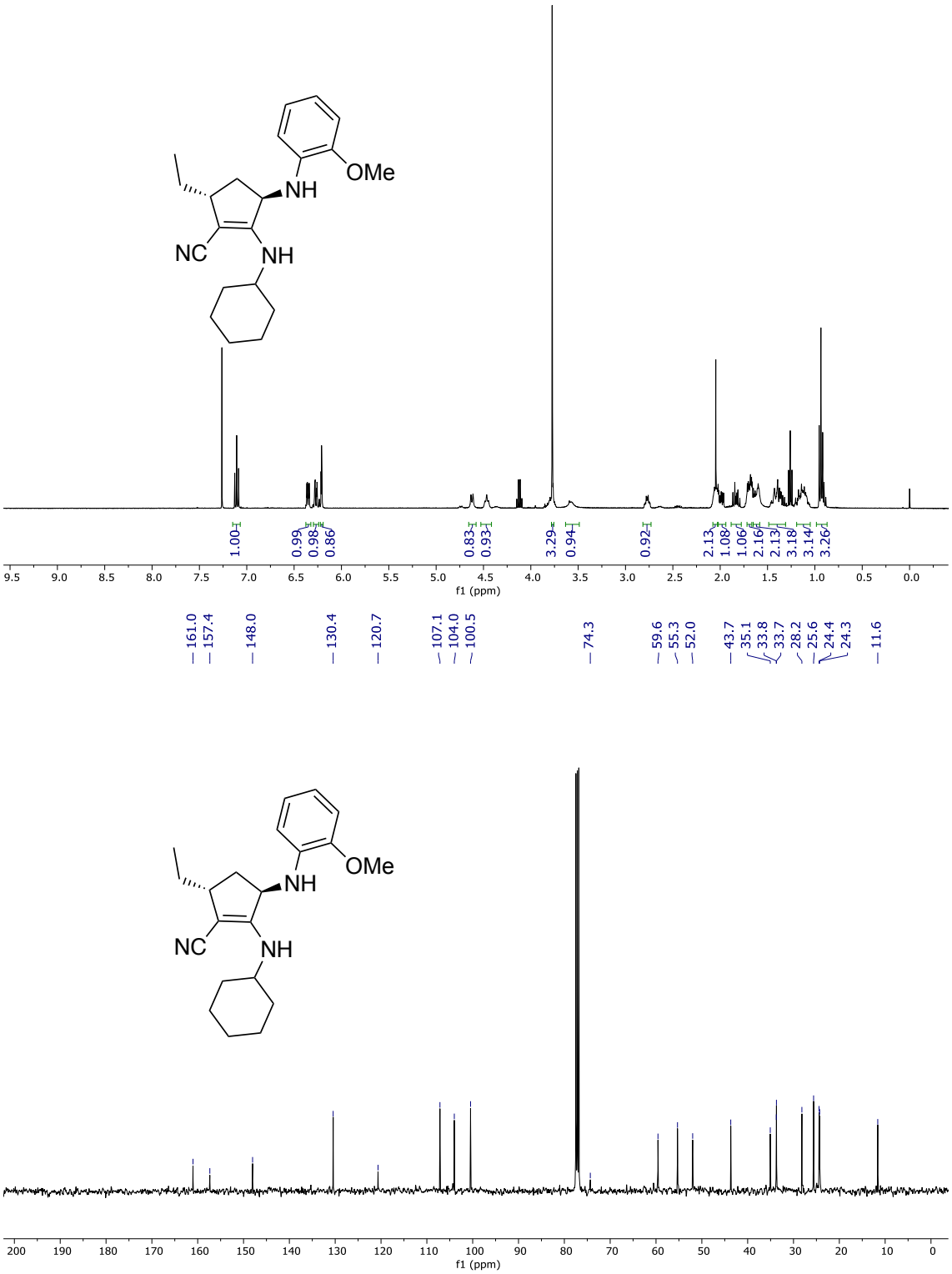


FIGURE 7.29 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2t**.

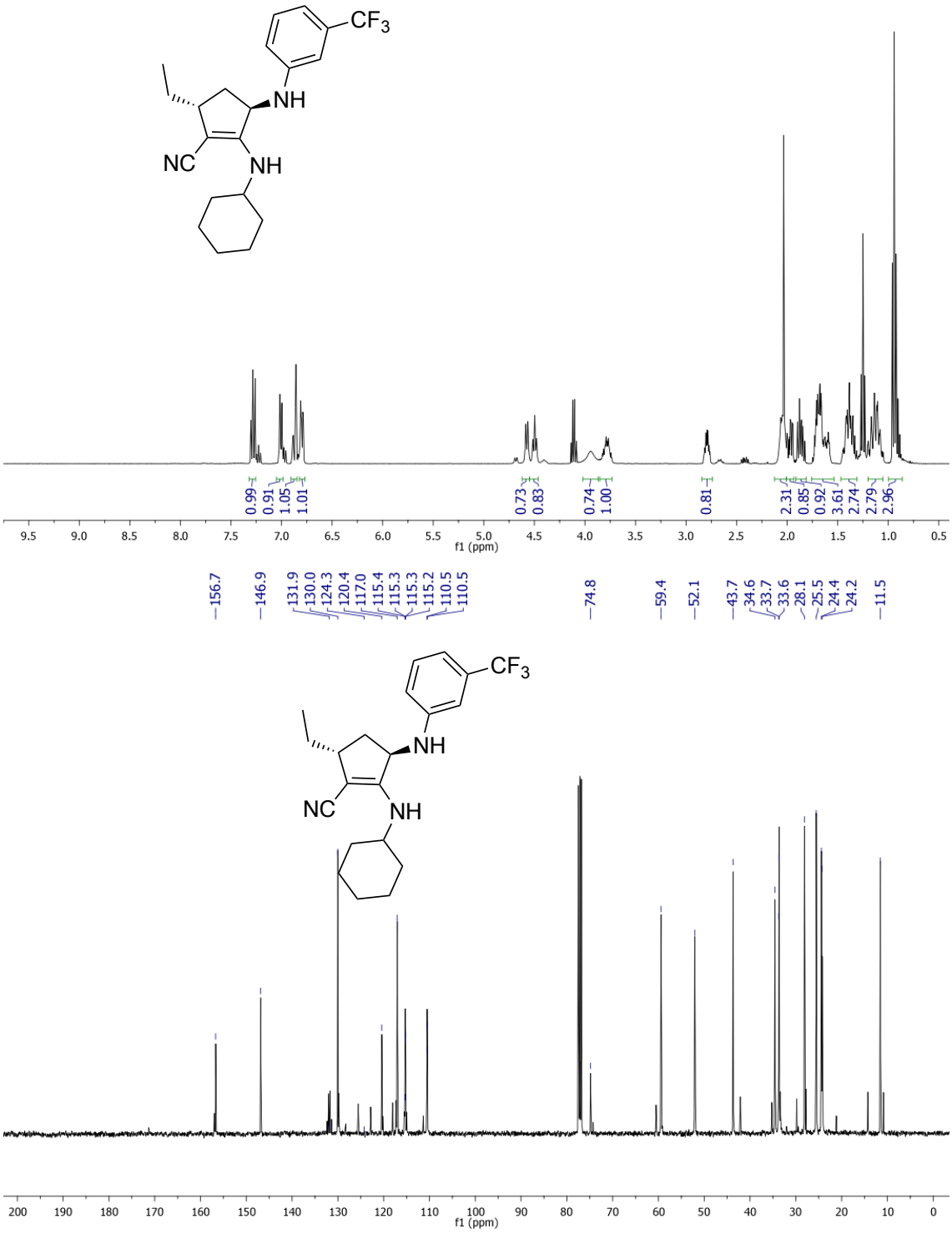


FIGURE 7.30 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2u.**

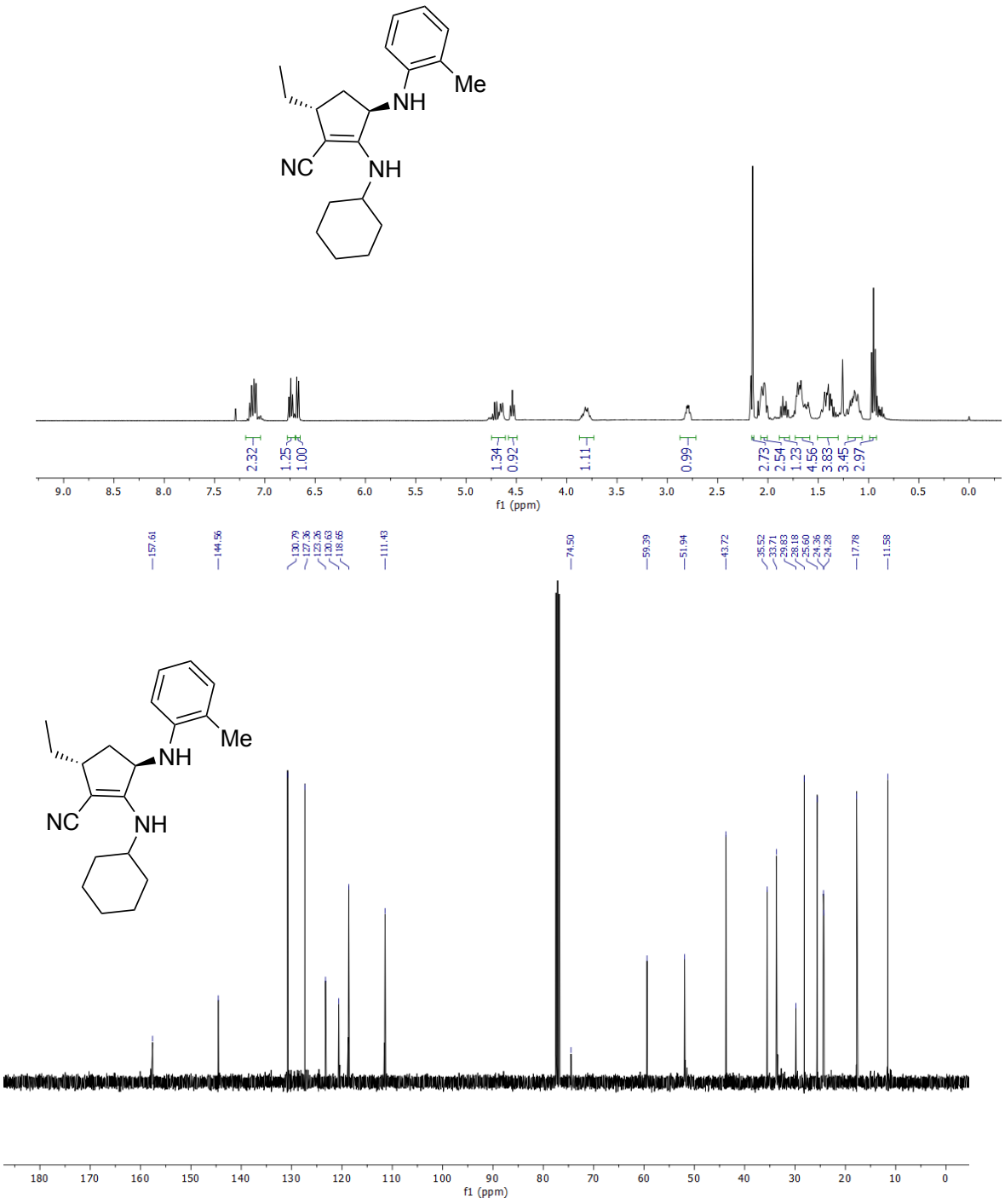


FIGURE 7.31 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2w.**

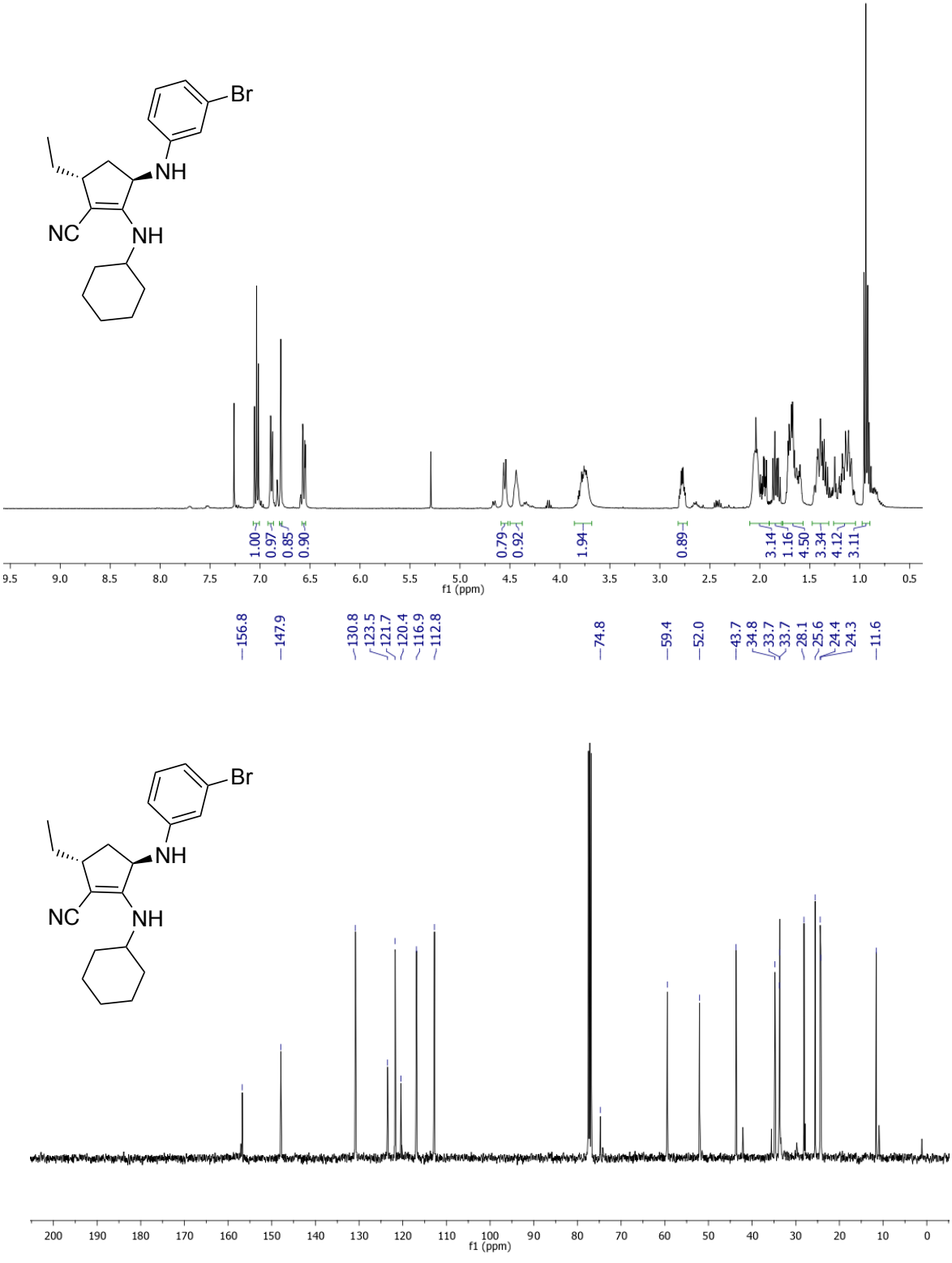


FIGURE 7.32 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2x.**

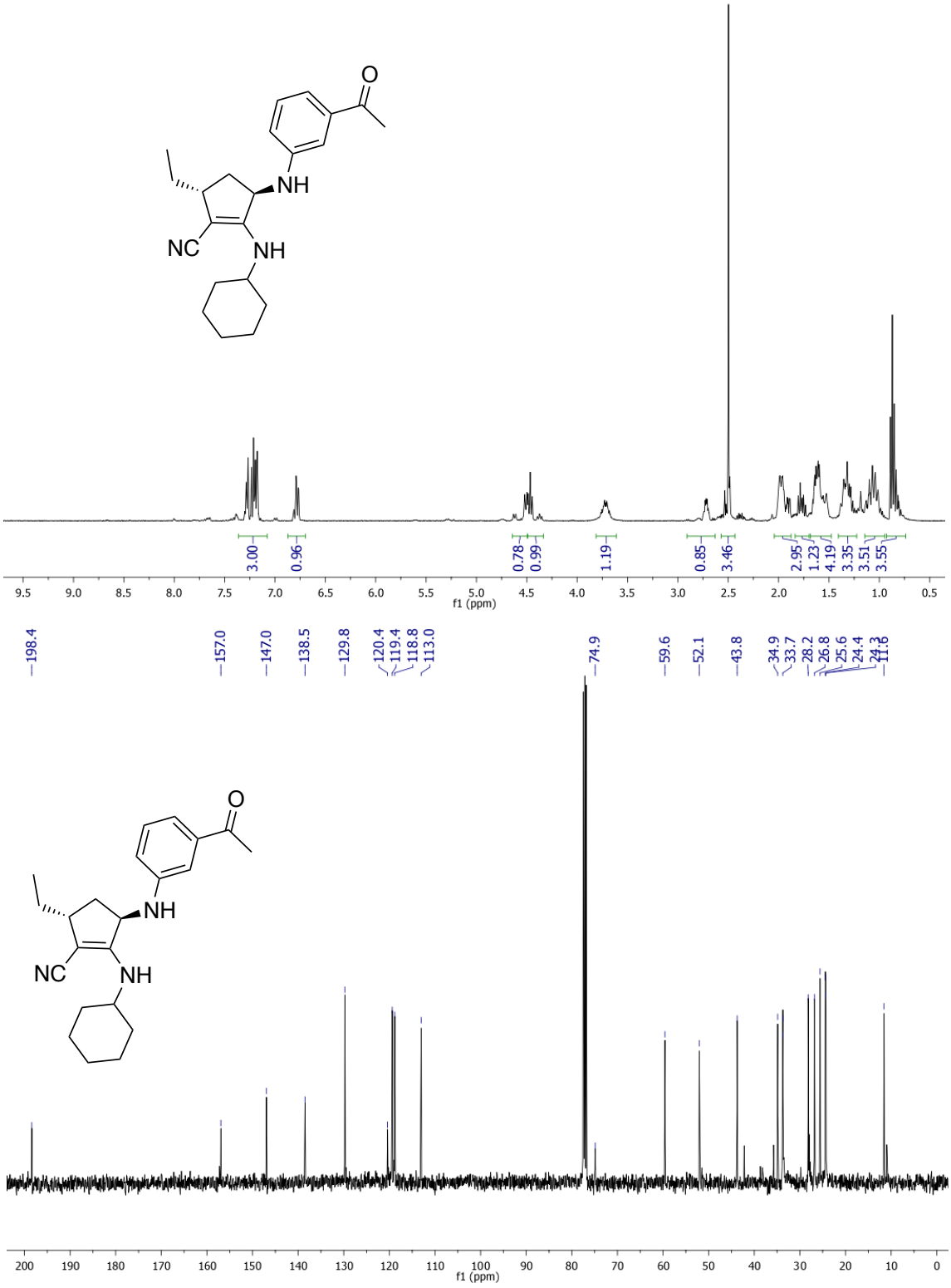


FIGURE 7.33 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2y.**

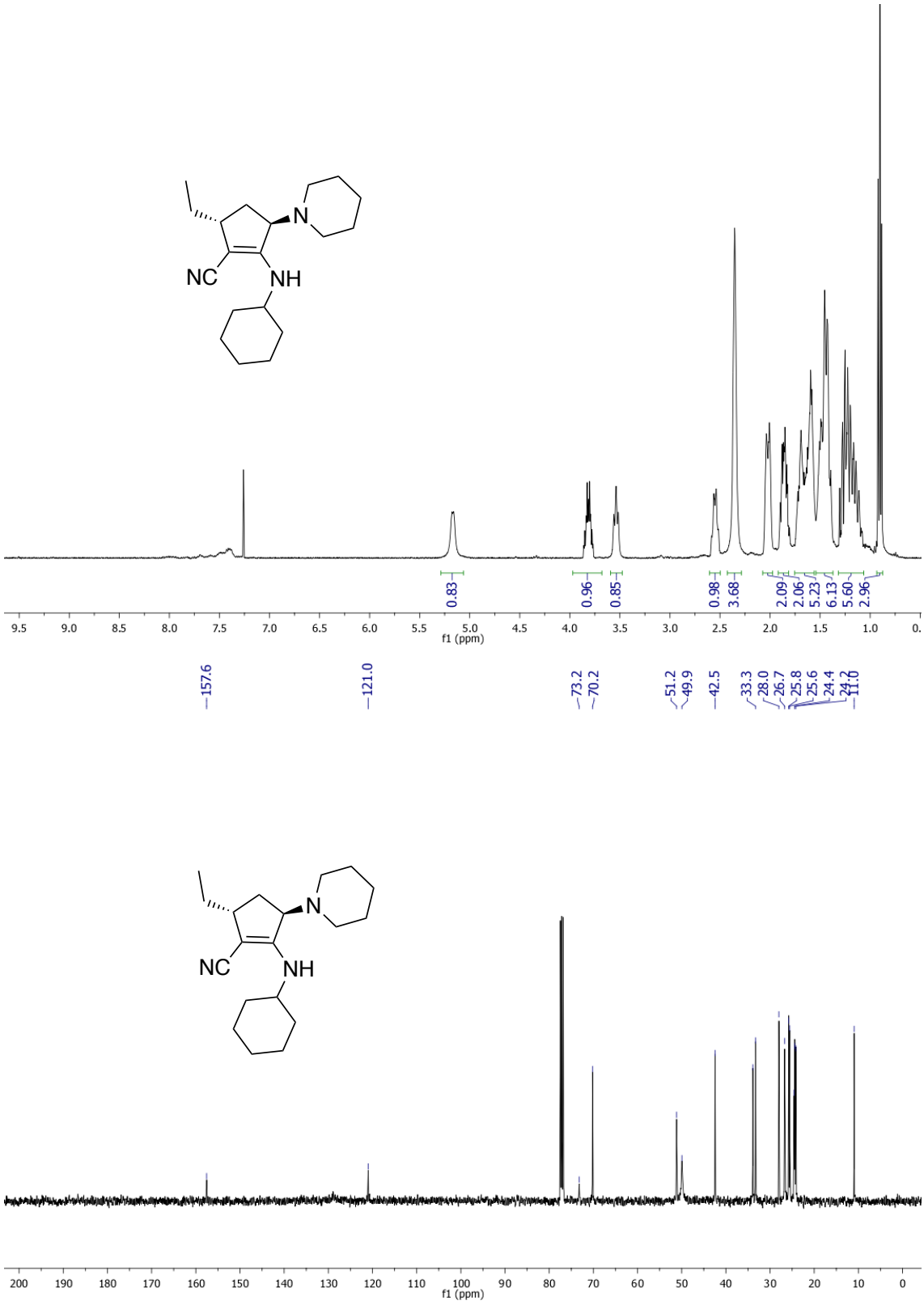


FIGURE 7.34 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2z.**

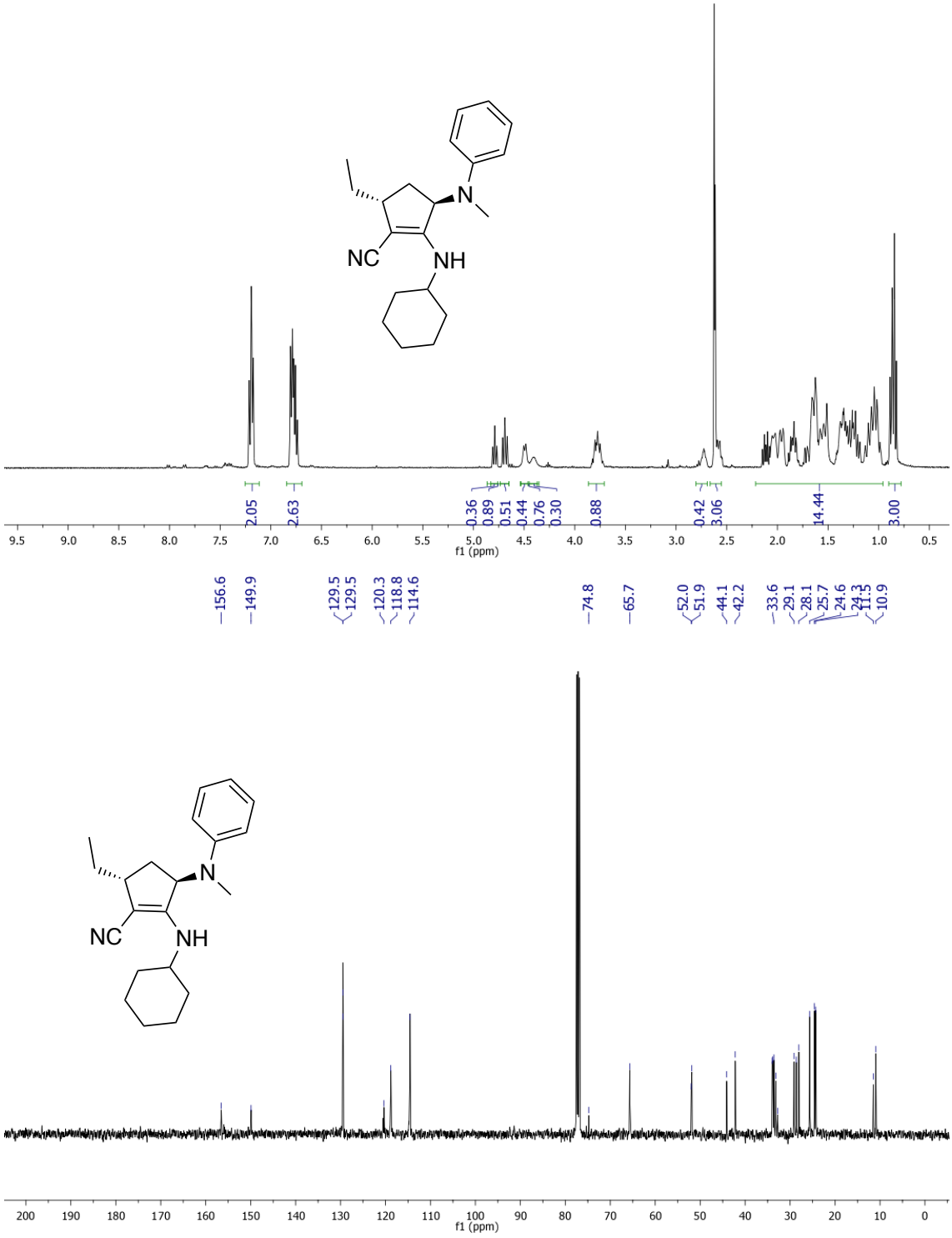


FIGURE 7.35 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2aa.**

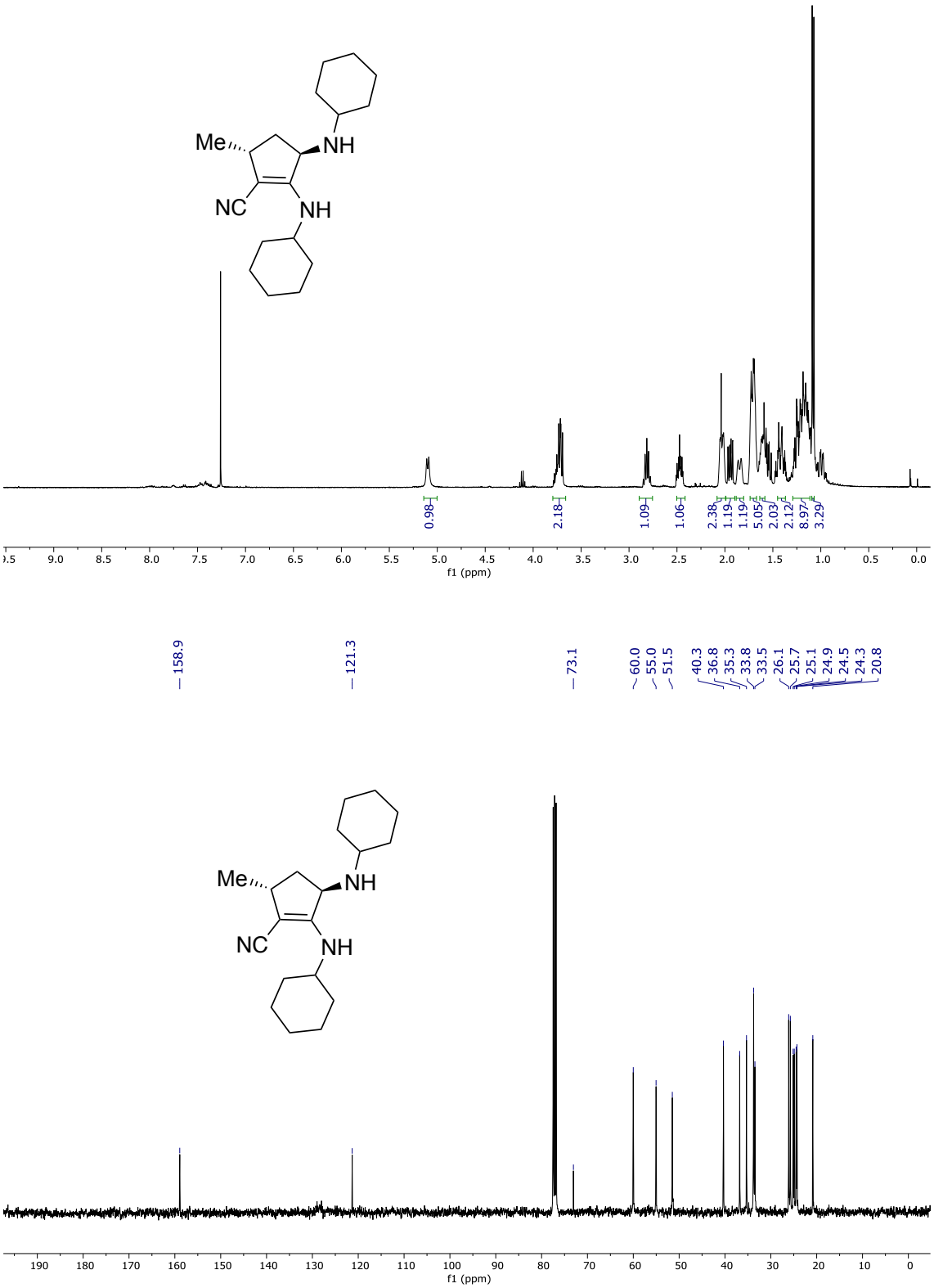


FIGURE 7.36 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ab**.

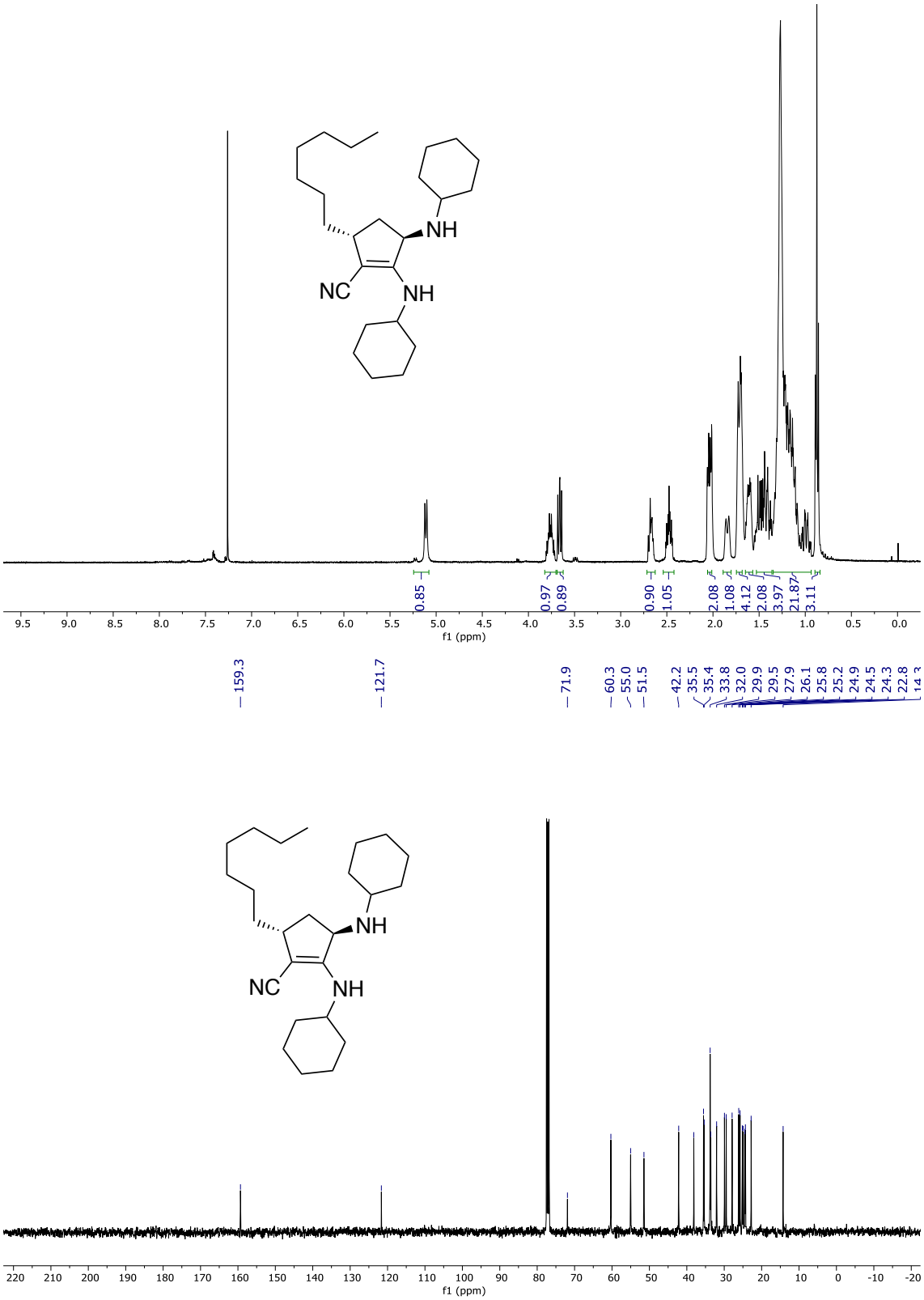


FIGURE 7.37 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ac**.

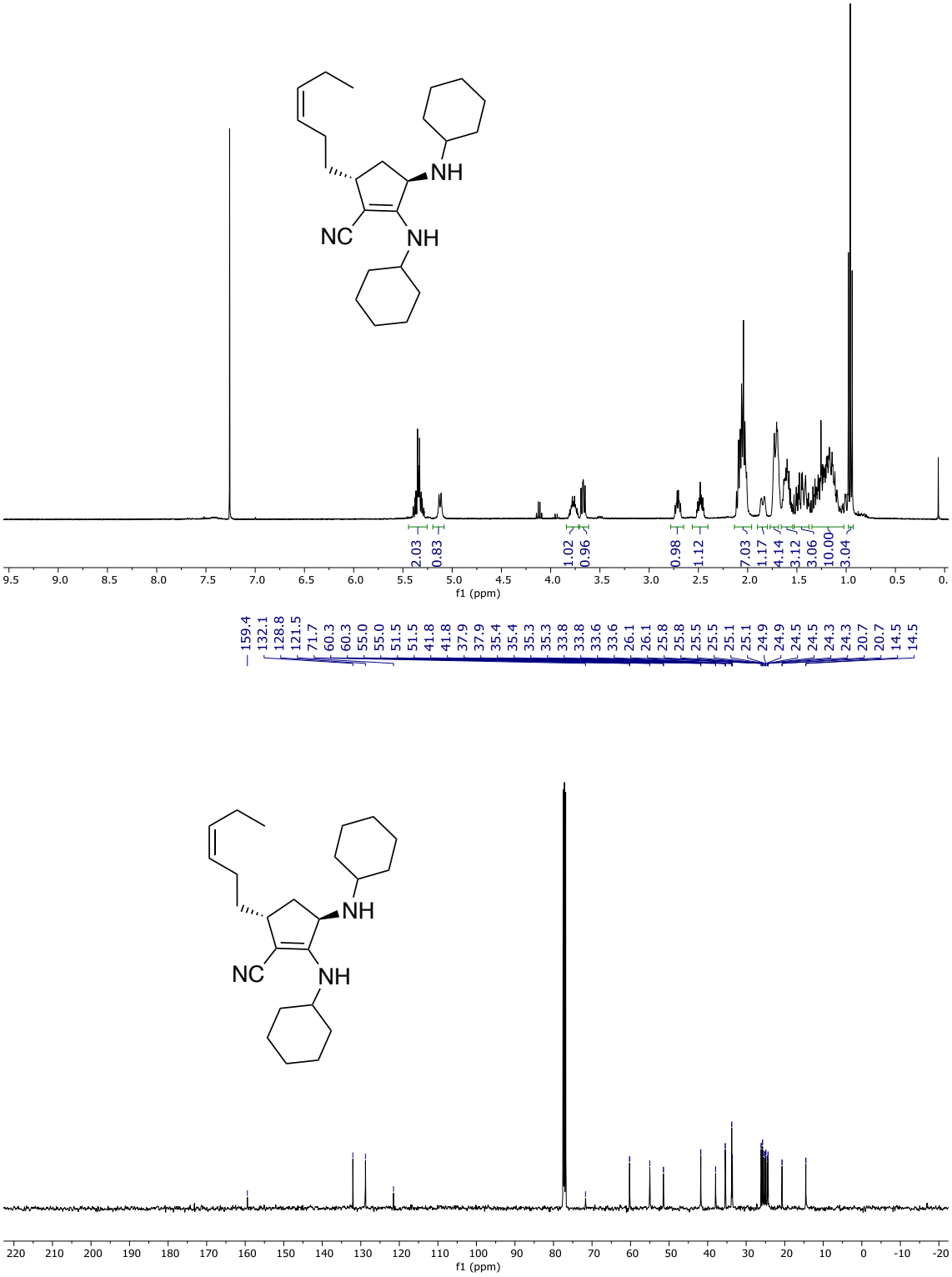


FIGURE 7.38 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ad**.

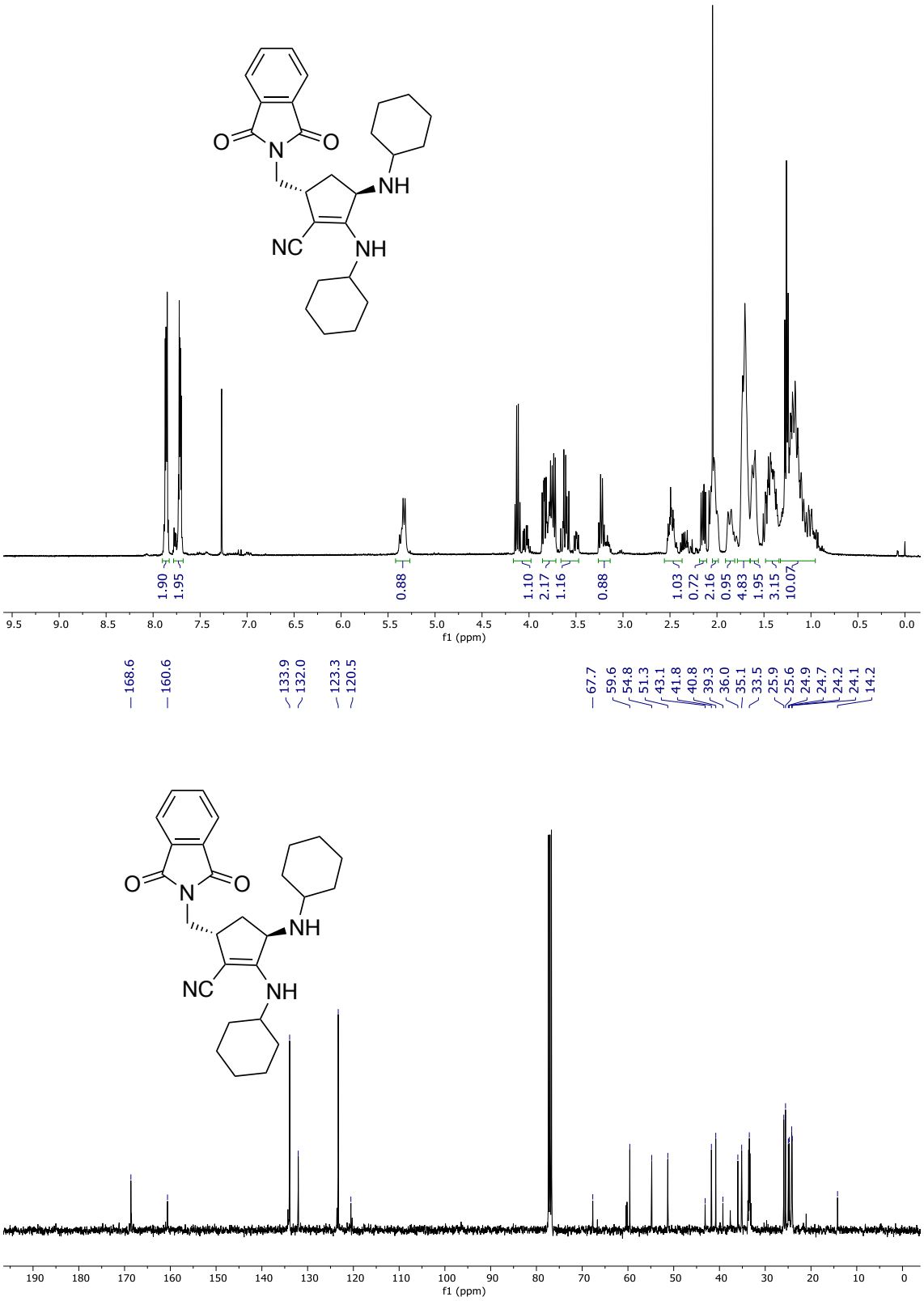


FIGURE 7.39 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ae**.

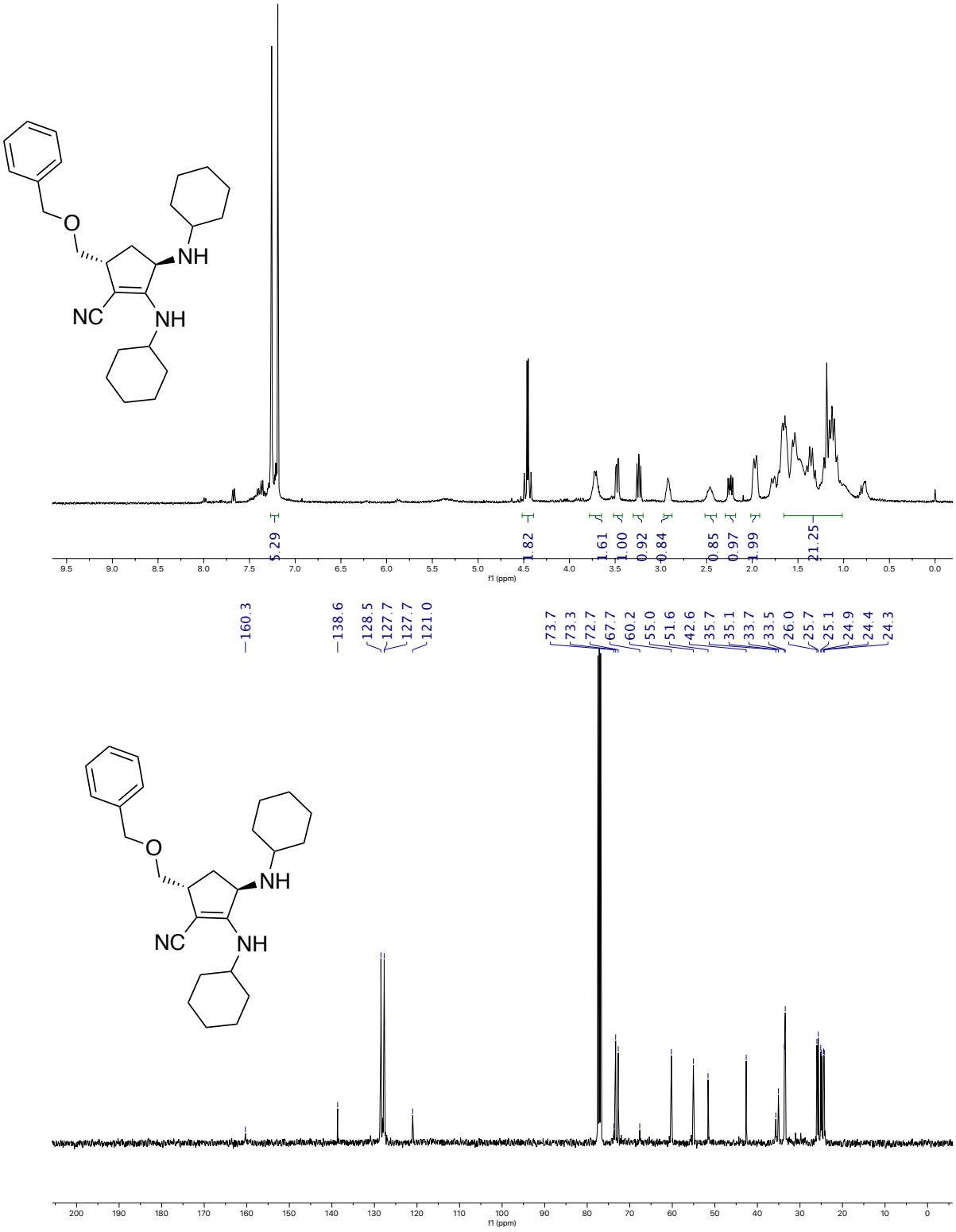


FIGURE 7.40 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2af**.

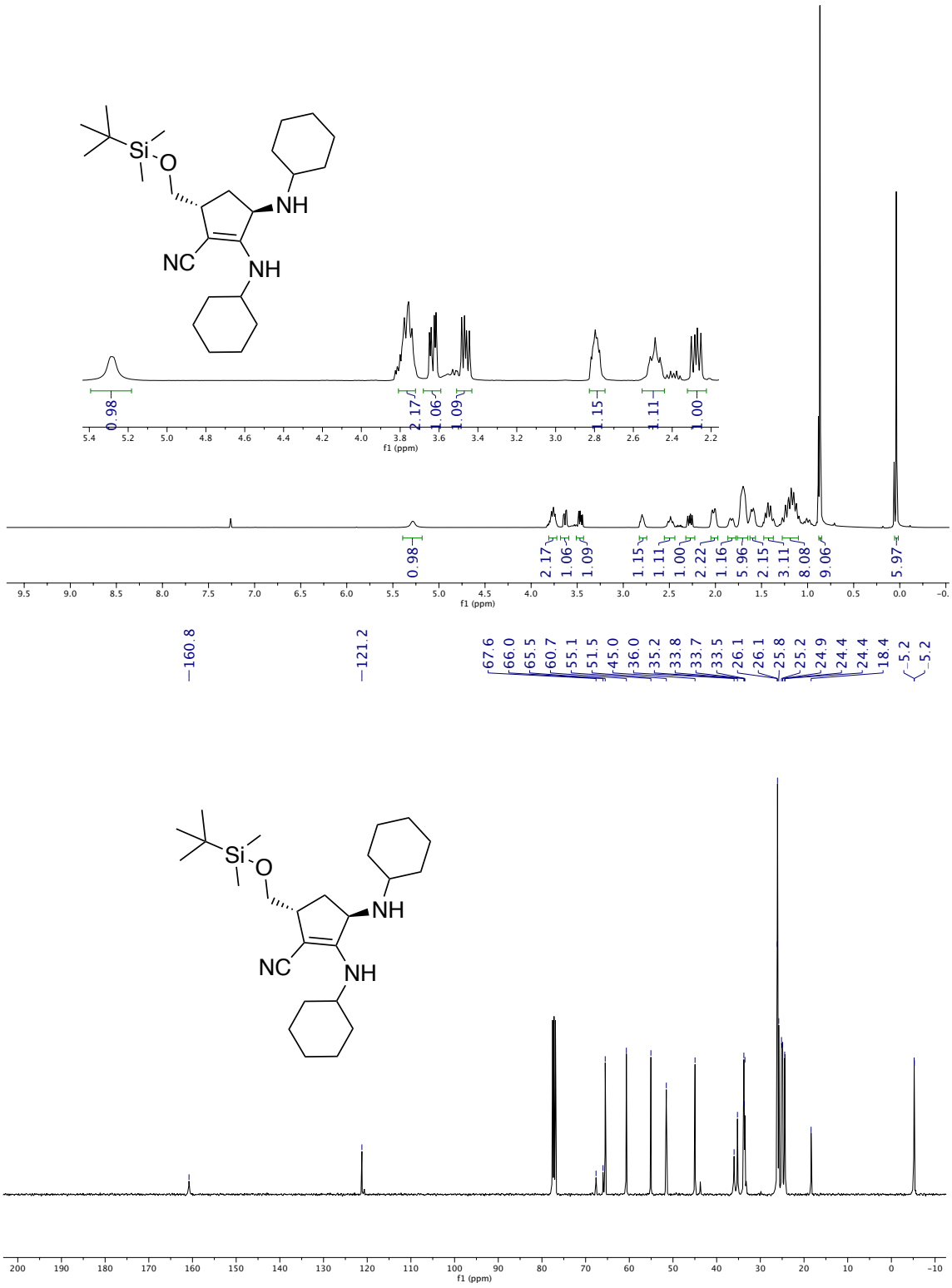


FIGURE 7.41 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ag**.

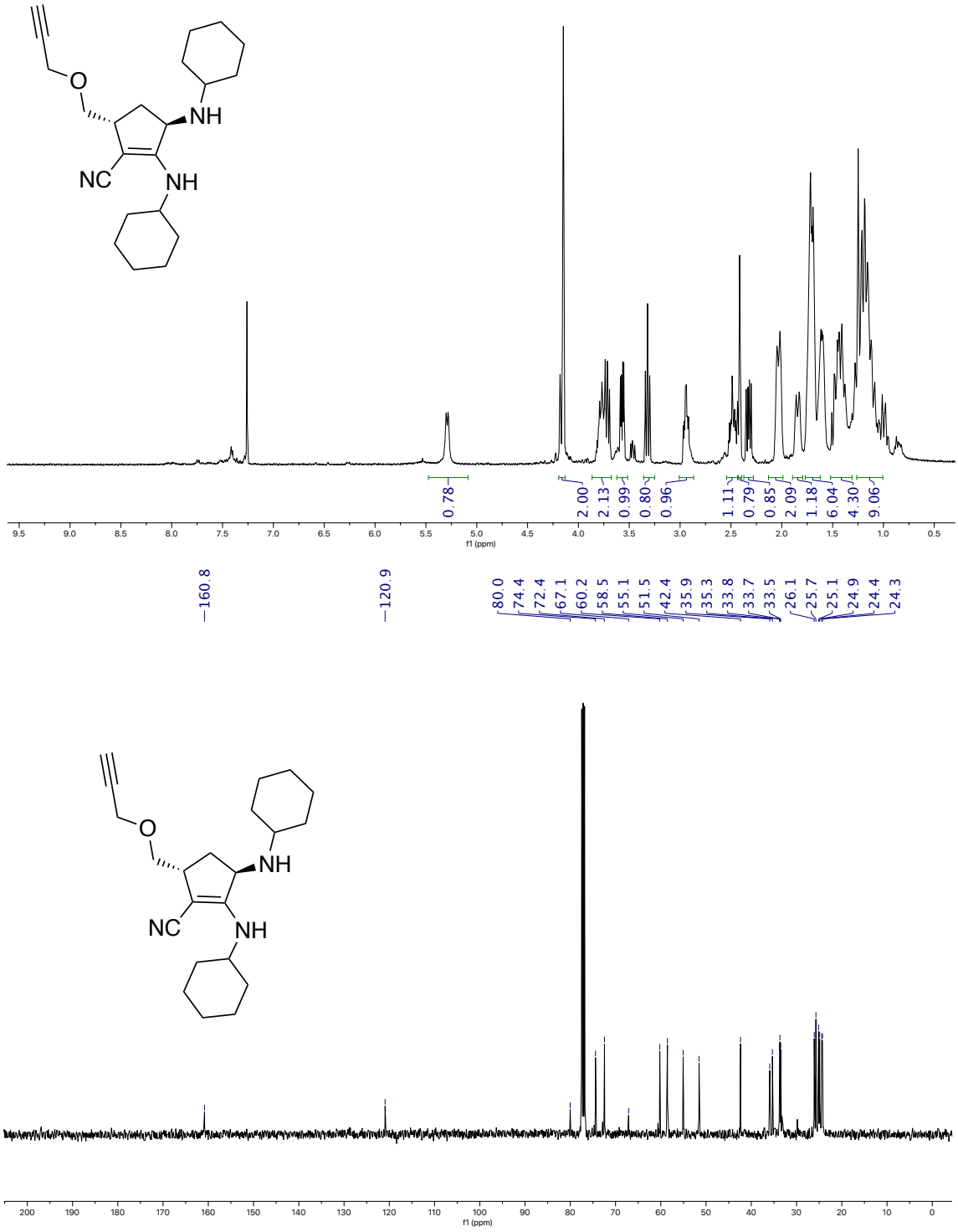


FIGURE 7.42 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ah**.

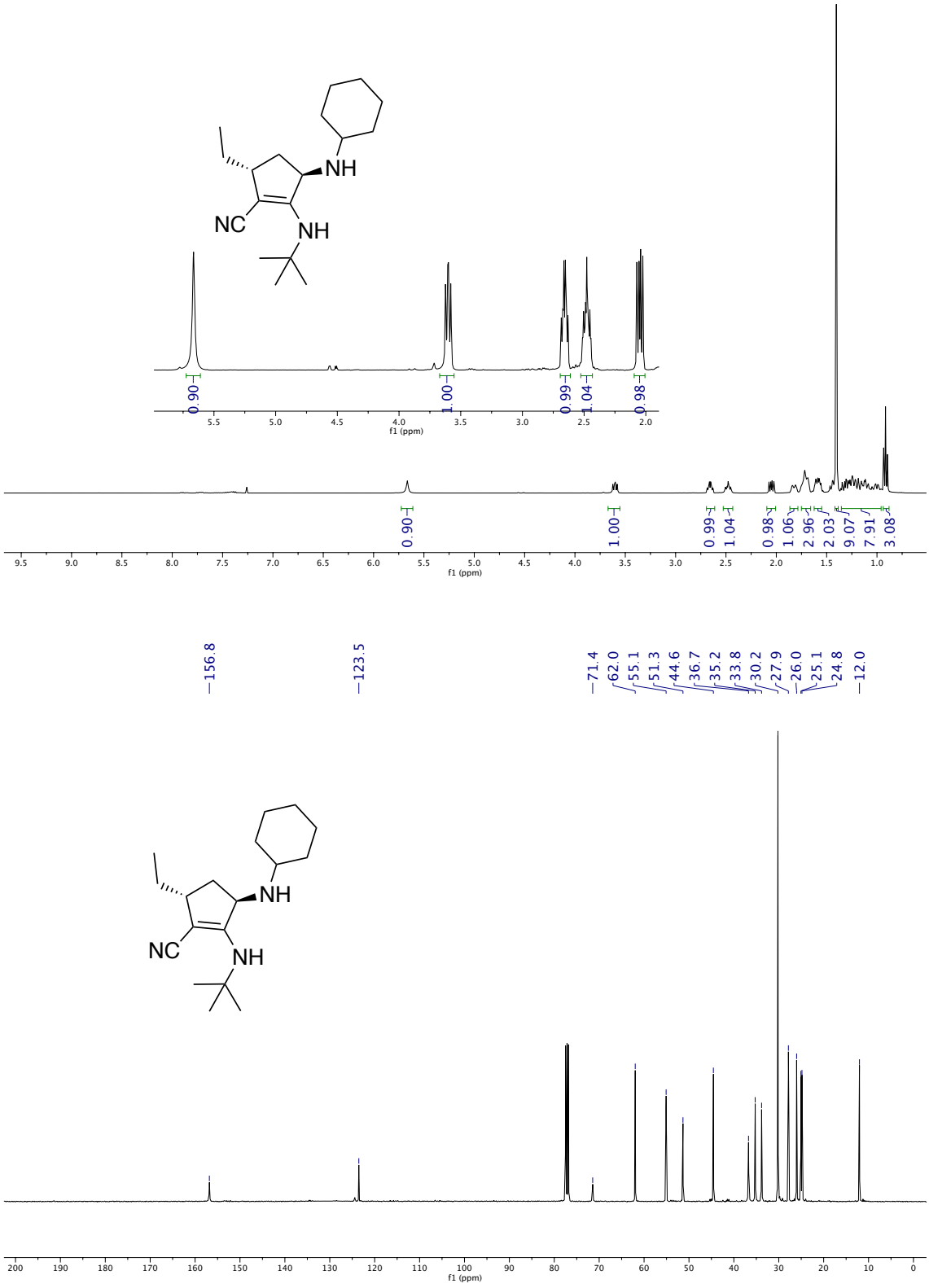


FIGURE 7.43 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ai**.

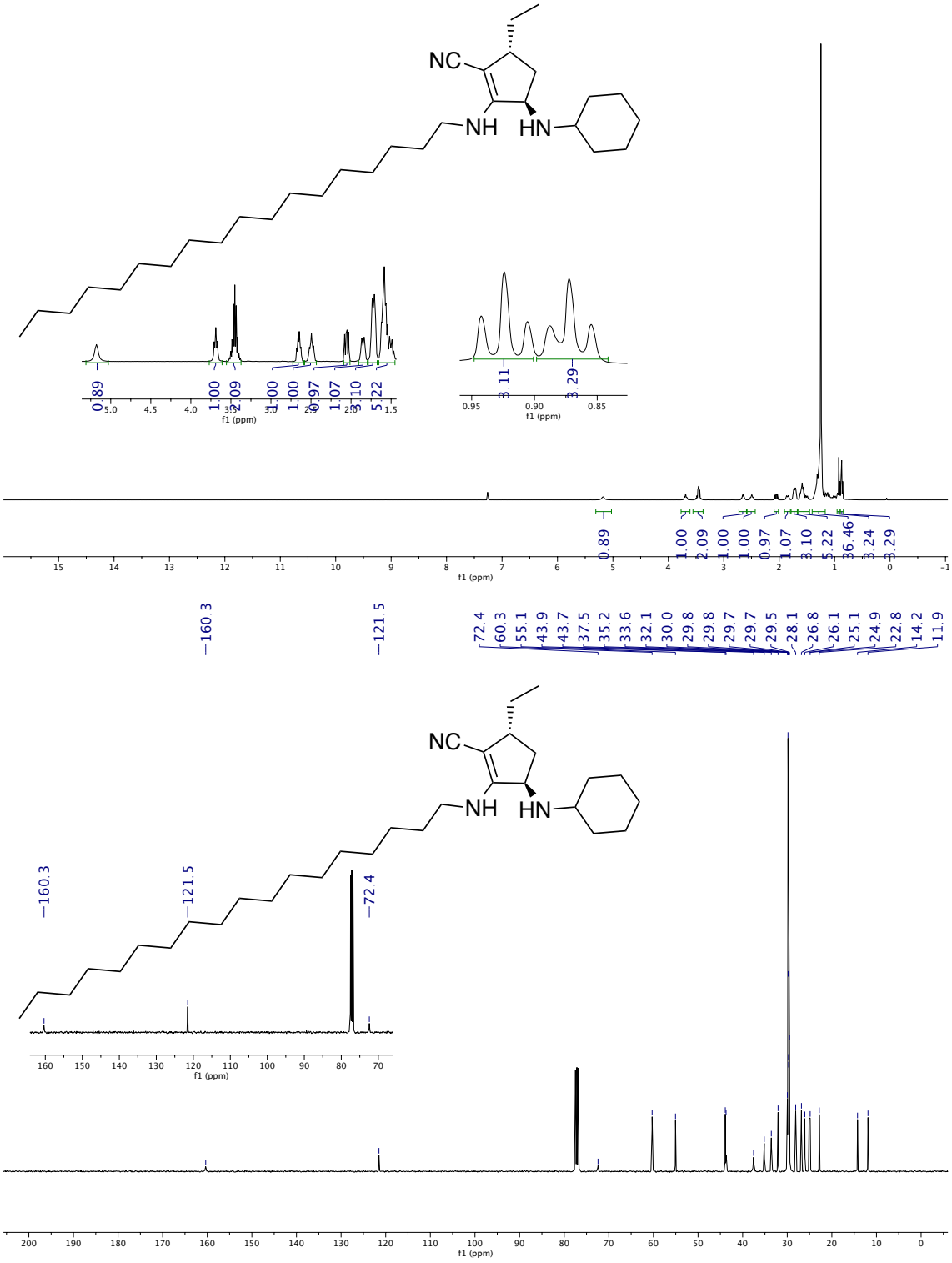


FIGURE 7.44 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2aj.**

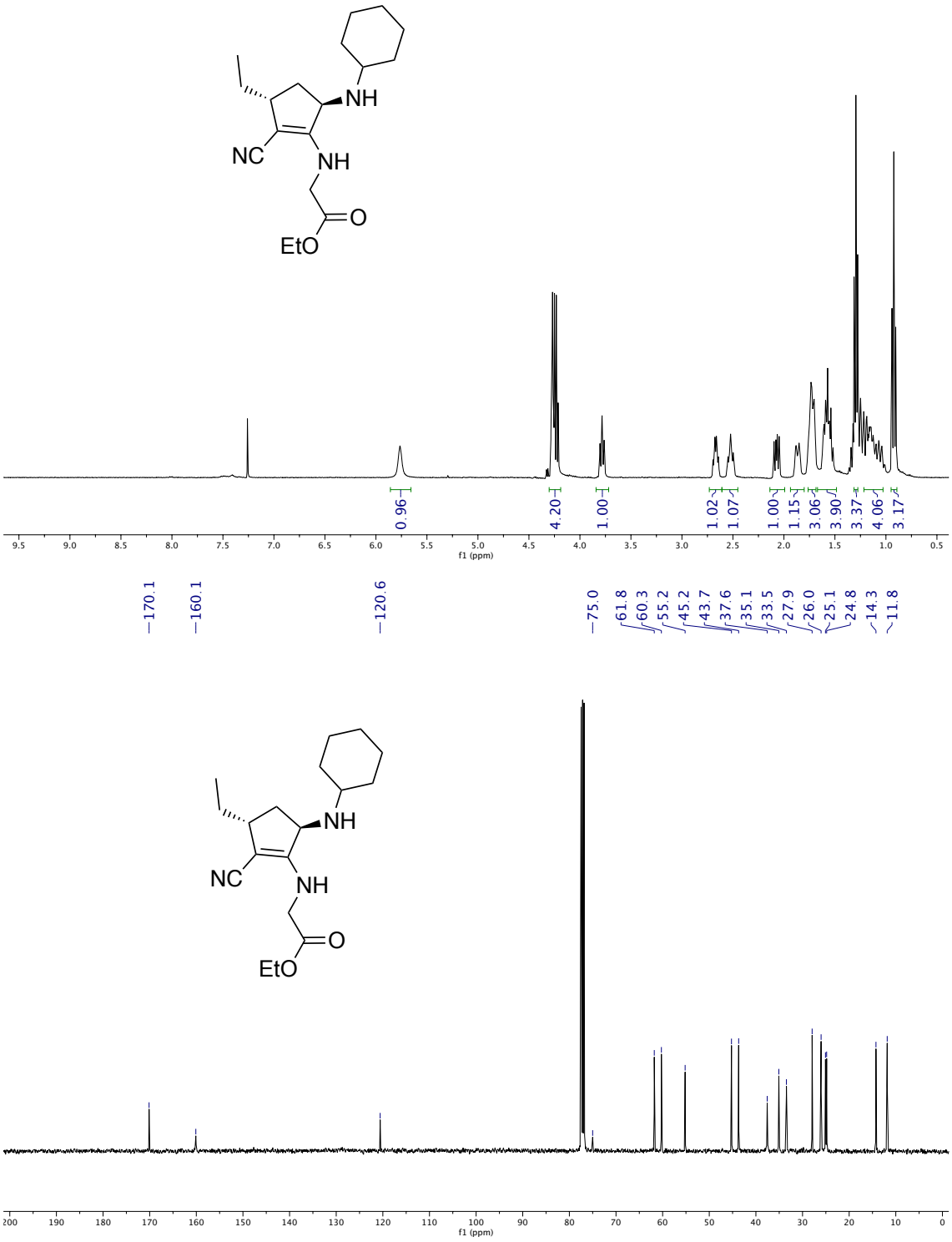


FIGURE 7.45 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ak**.

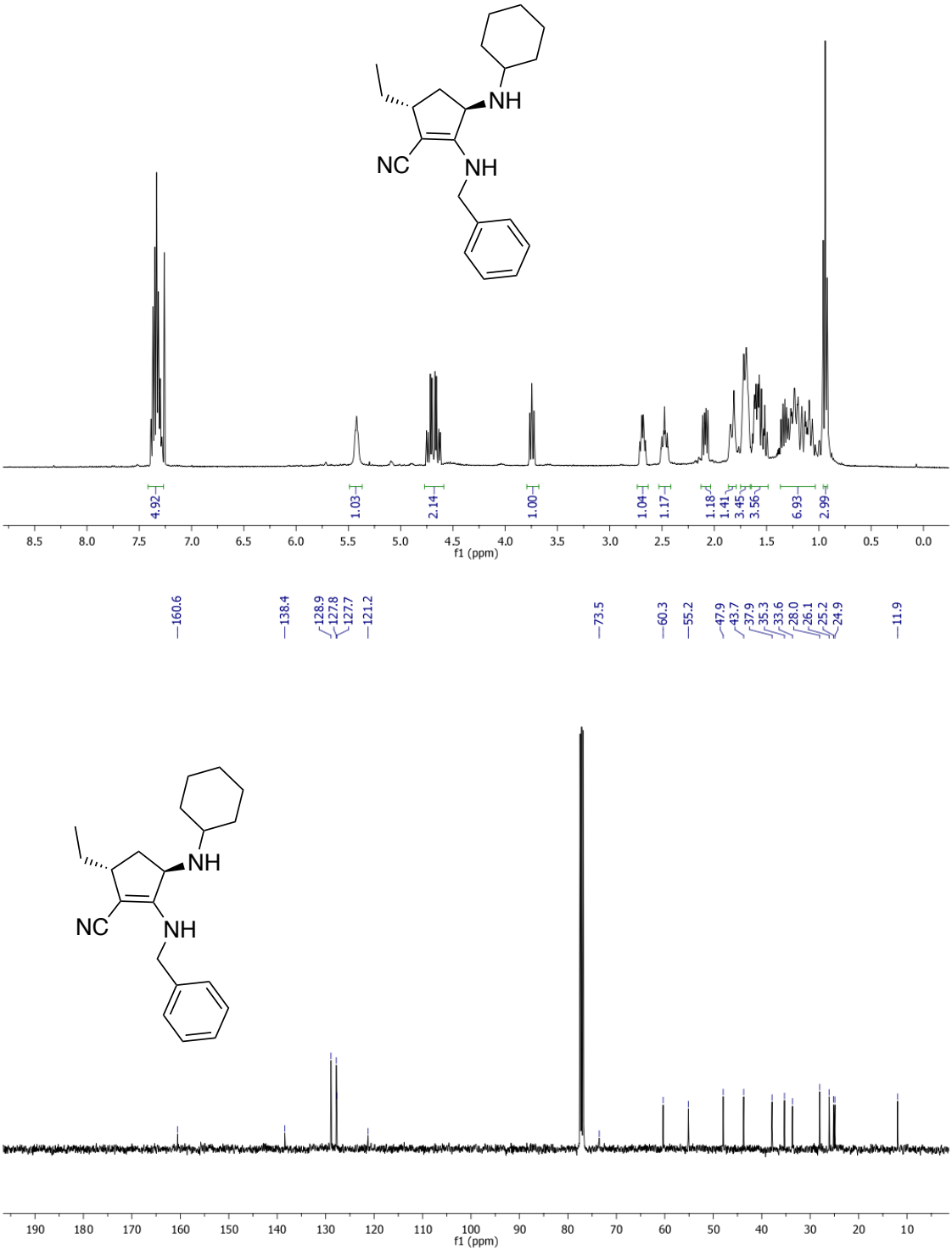


FIGURE 7.46 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2al.**

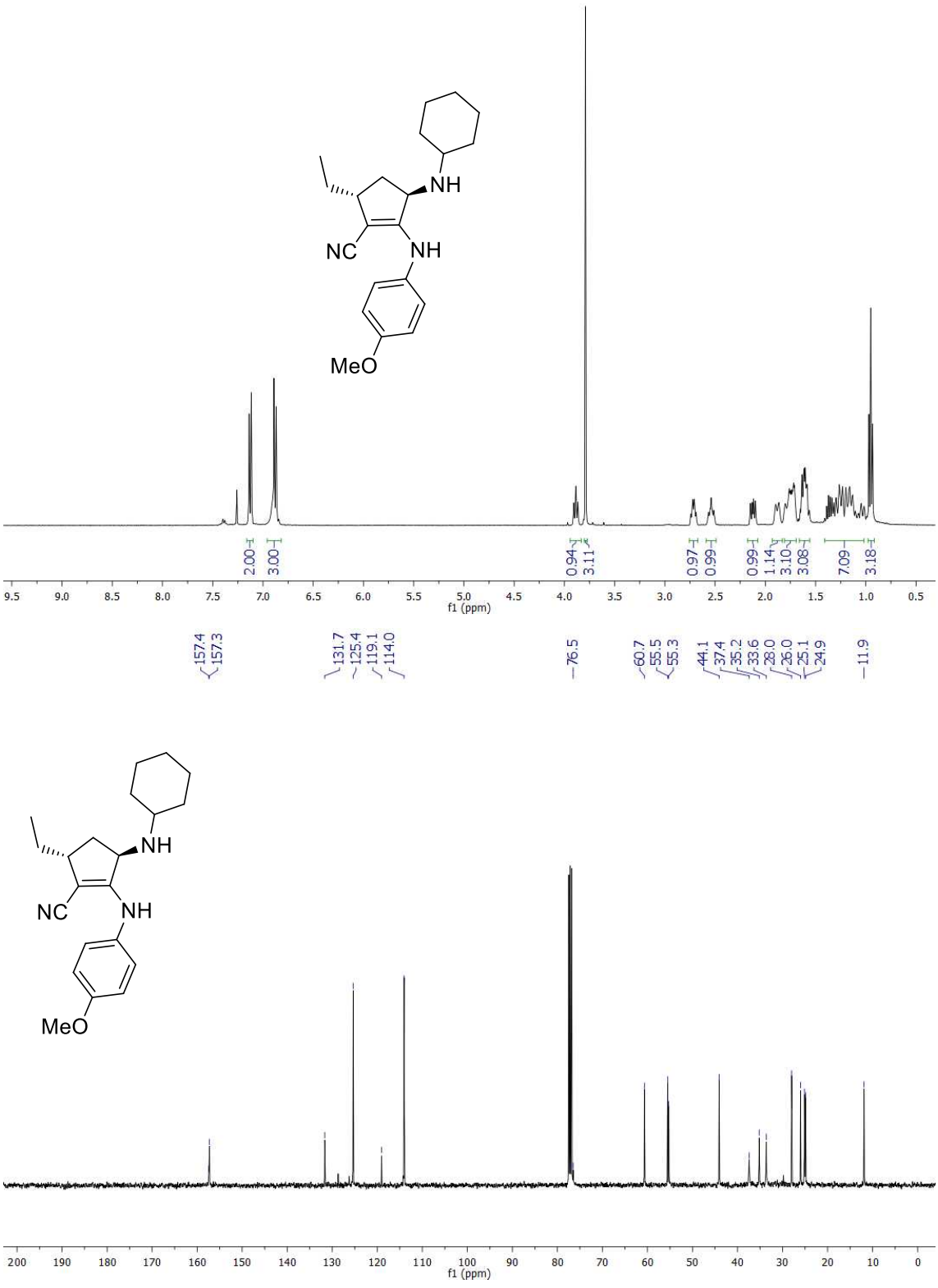


FIGURE 7.47 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2am.**

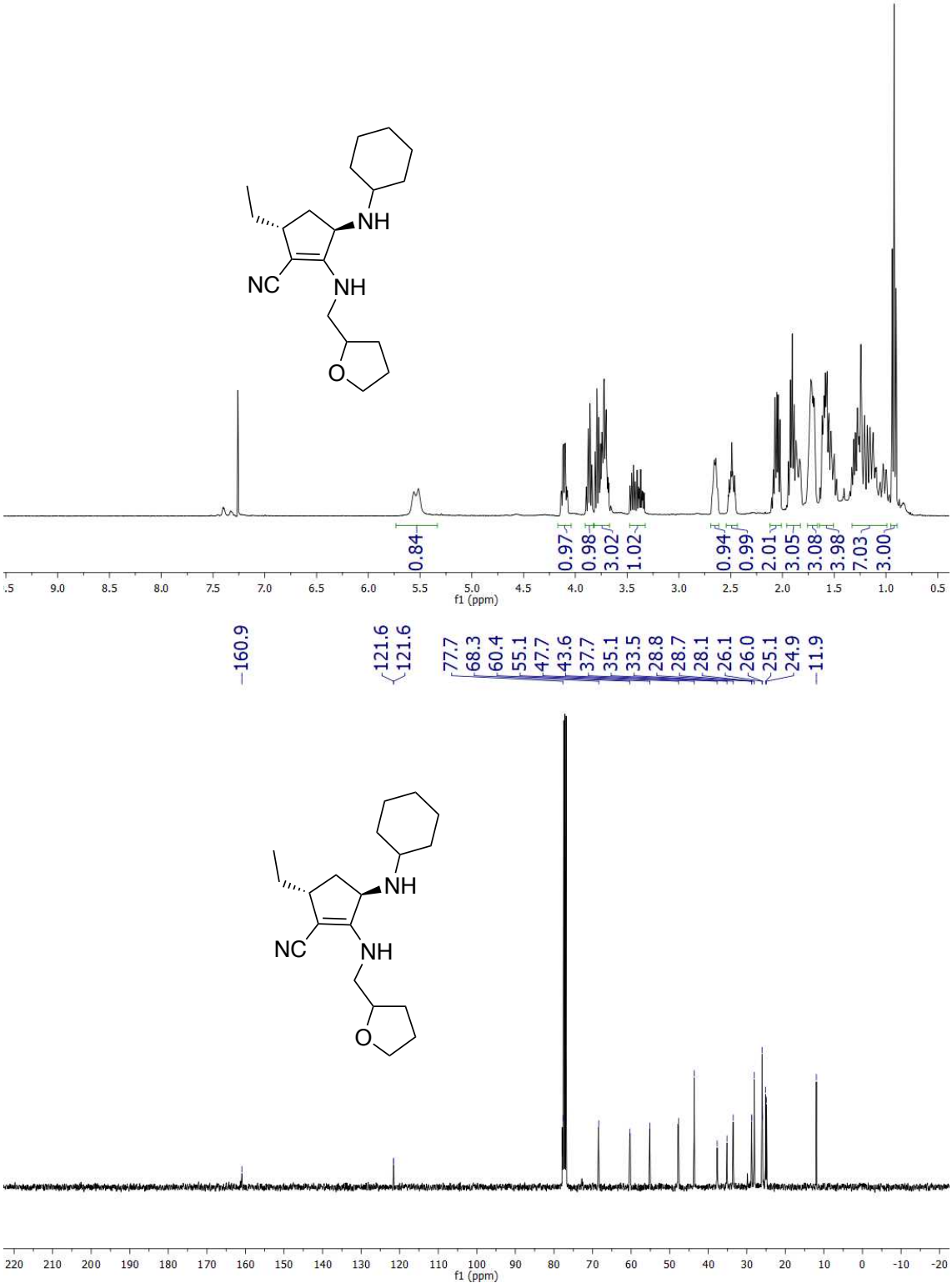


FIGURE 7.48 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2an.**

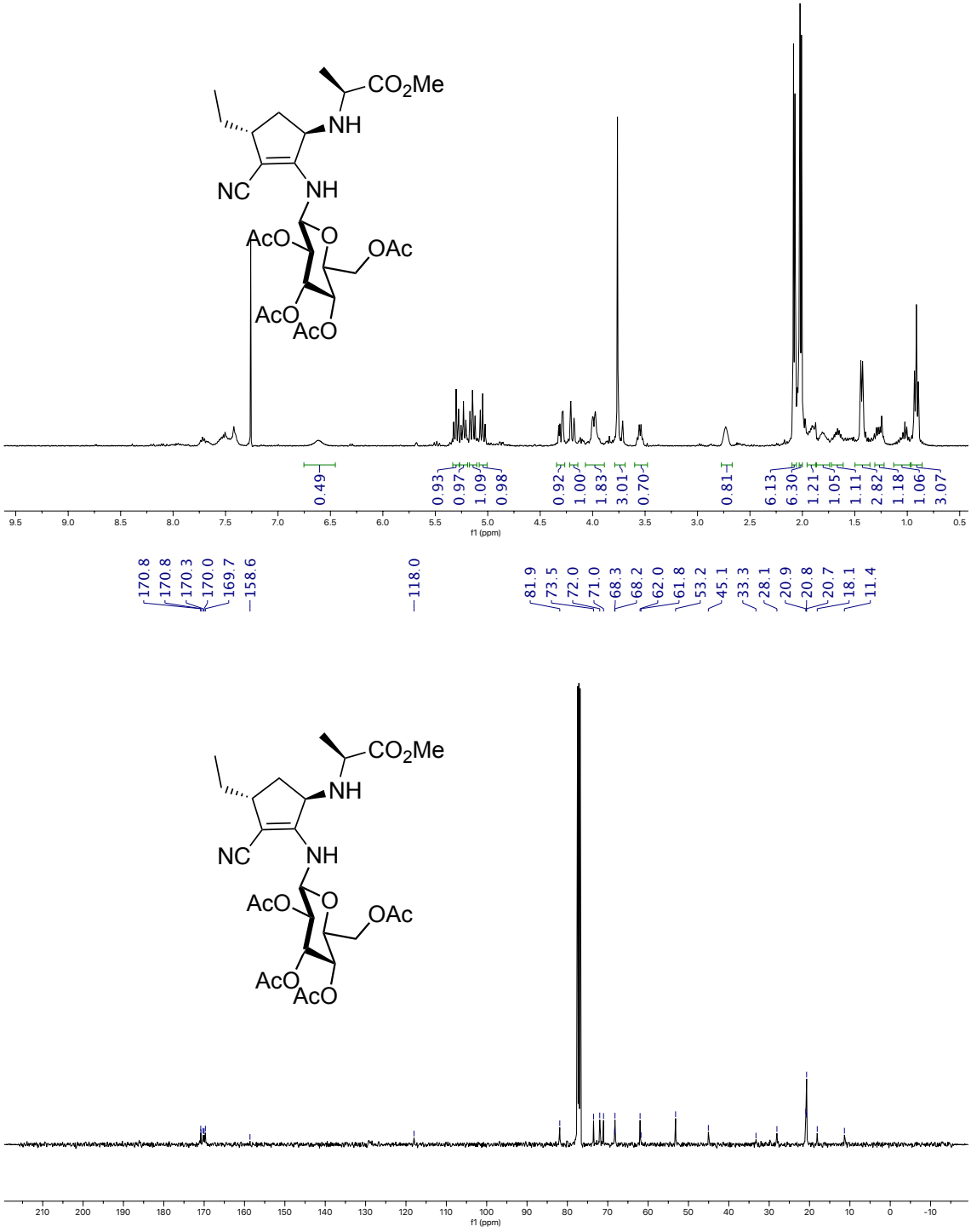


FIGURE 7.49 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ao**.

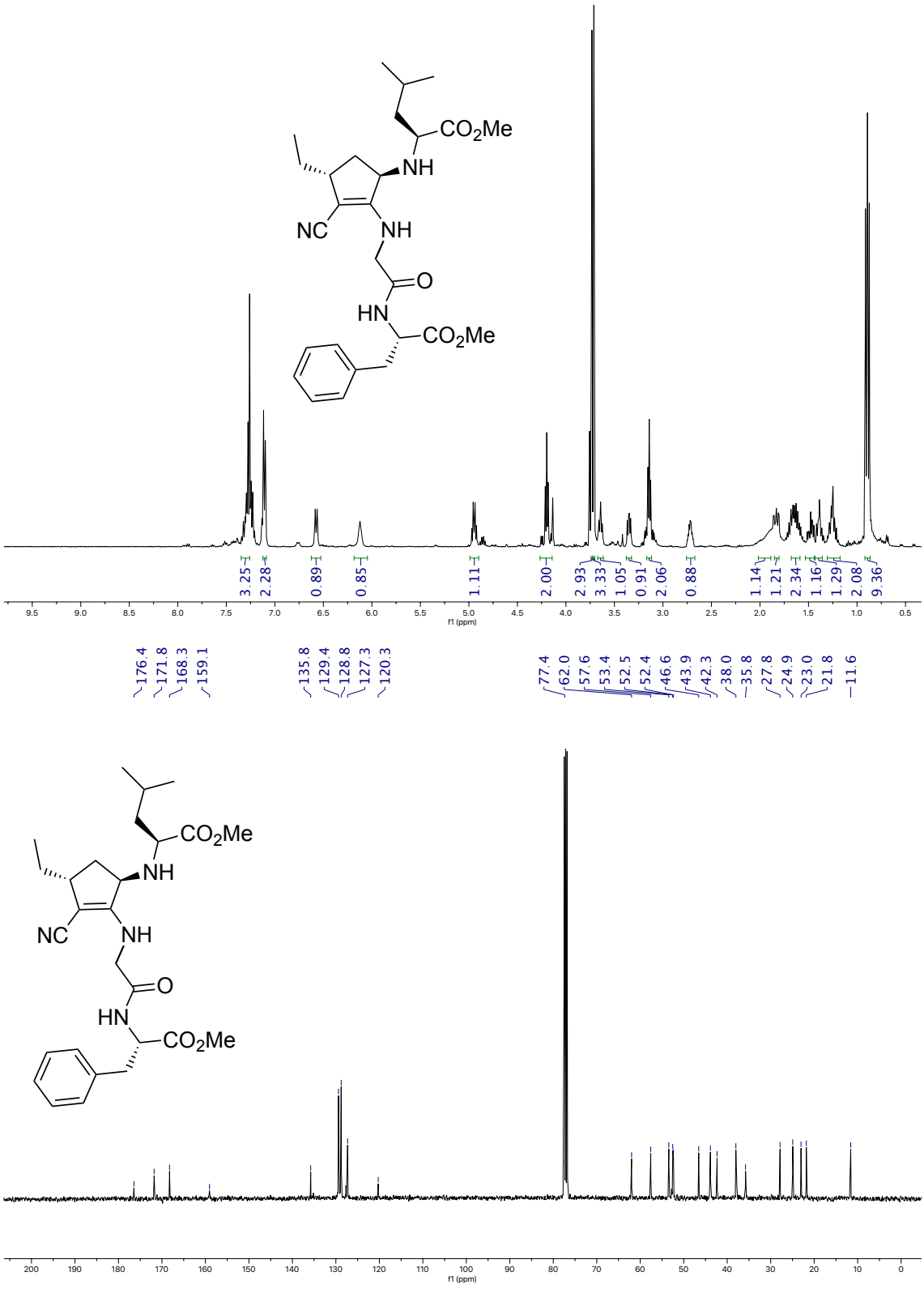


FIGURE 7.50 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ap**.

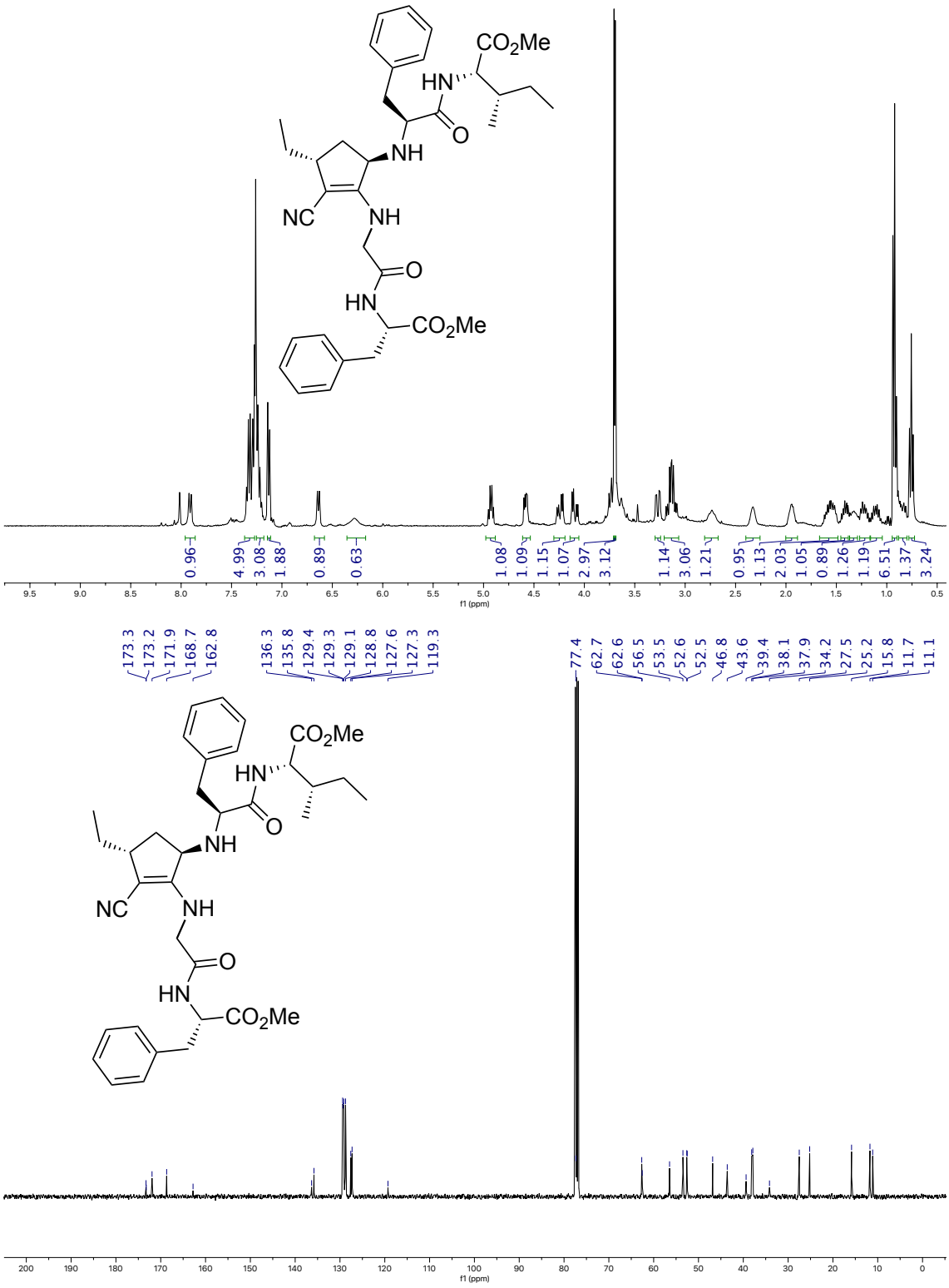


FIGURE 7.51 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2aq**.

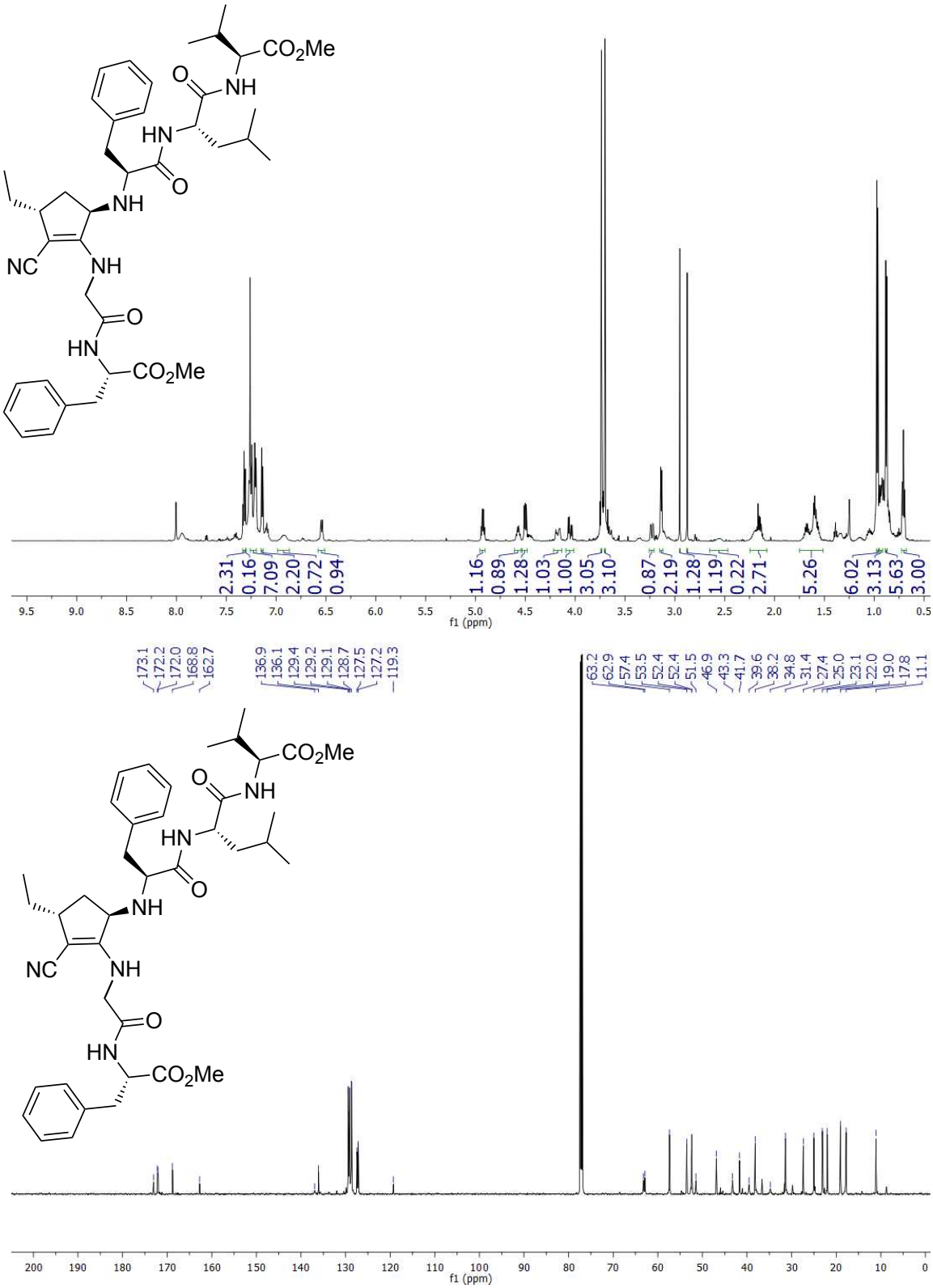


FIGURE 7.52 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2ar**.

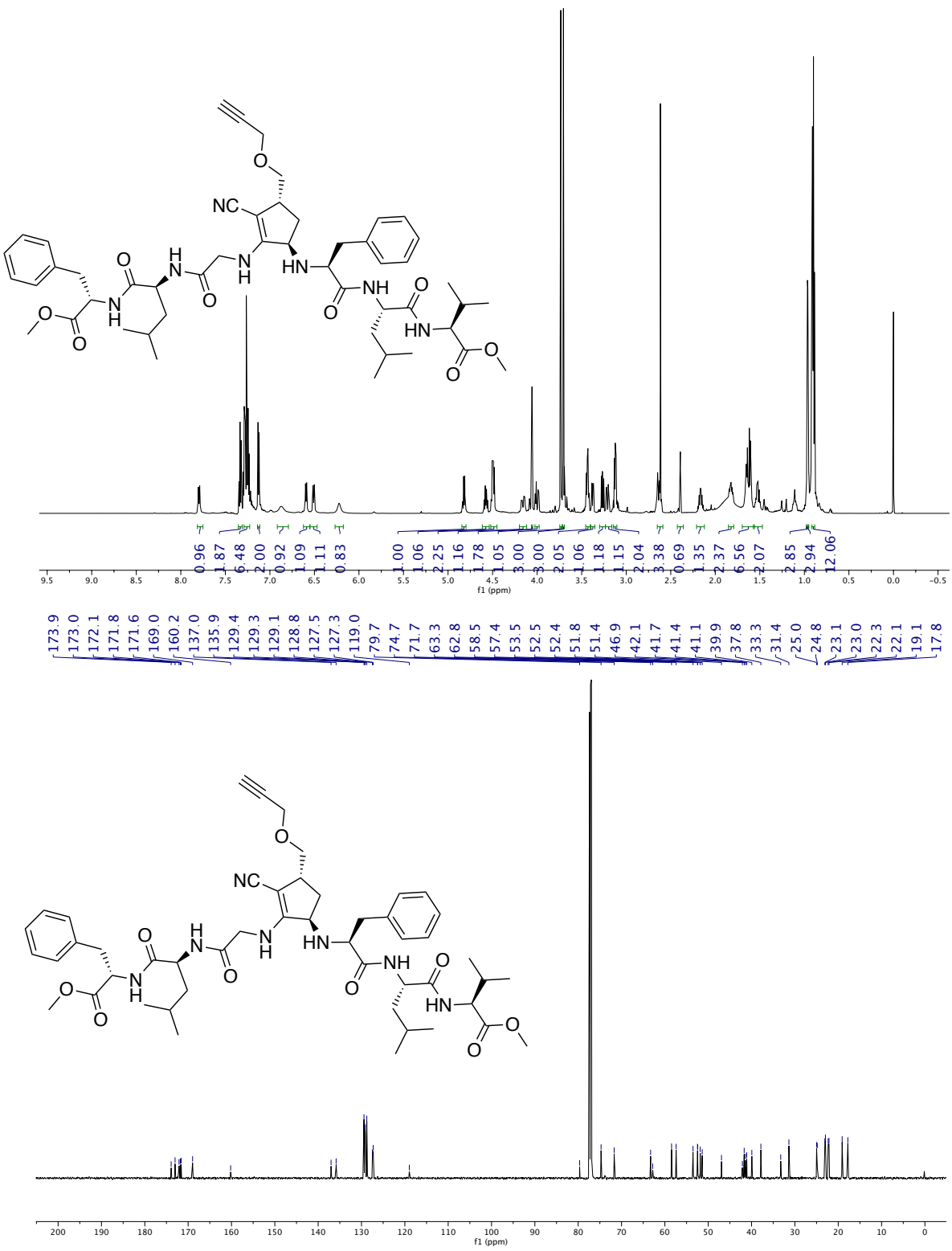


FIGURE 7.53 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **2as**.

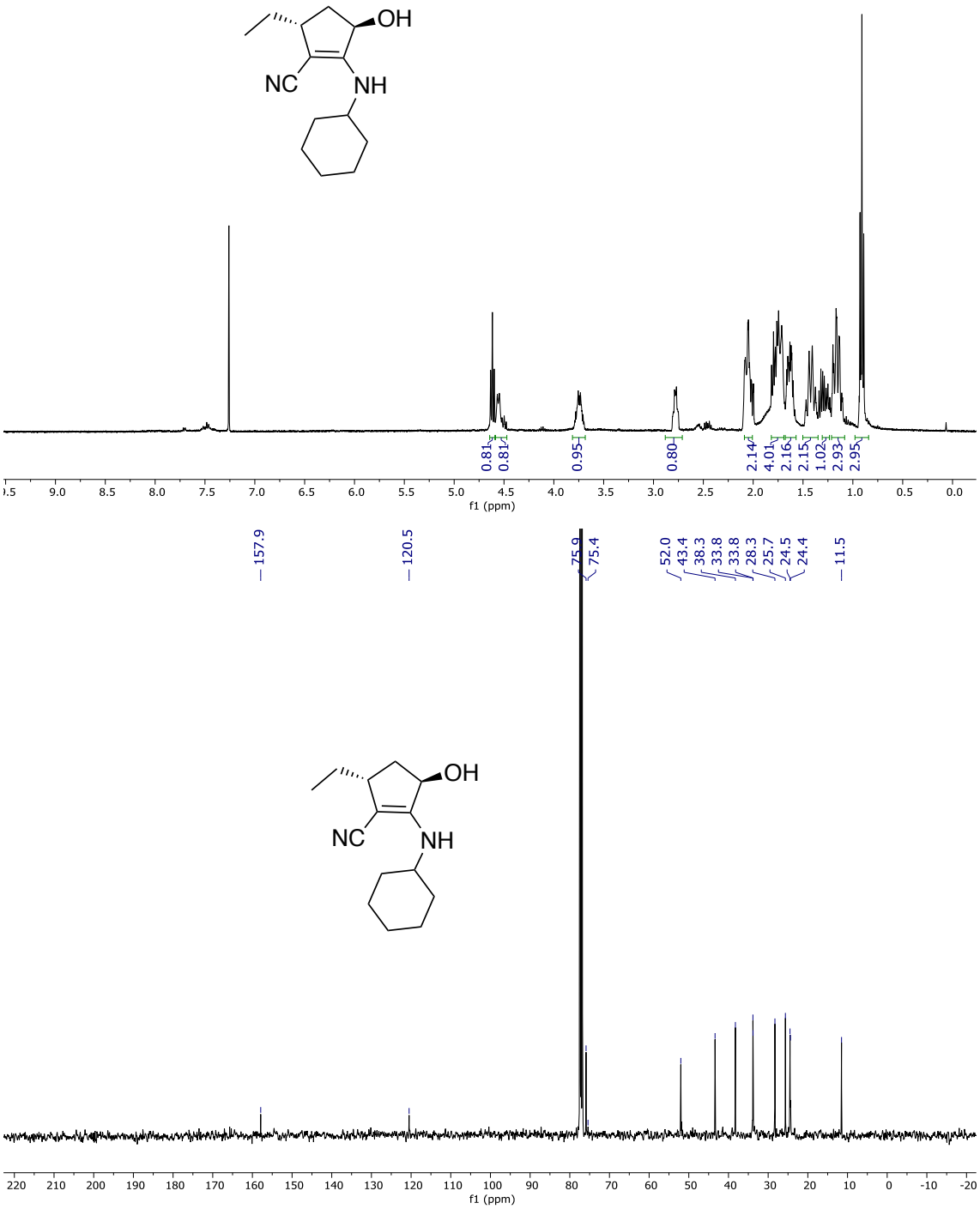


FIGURE 7.54 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3a**.

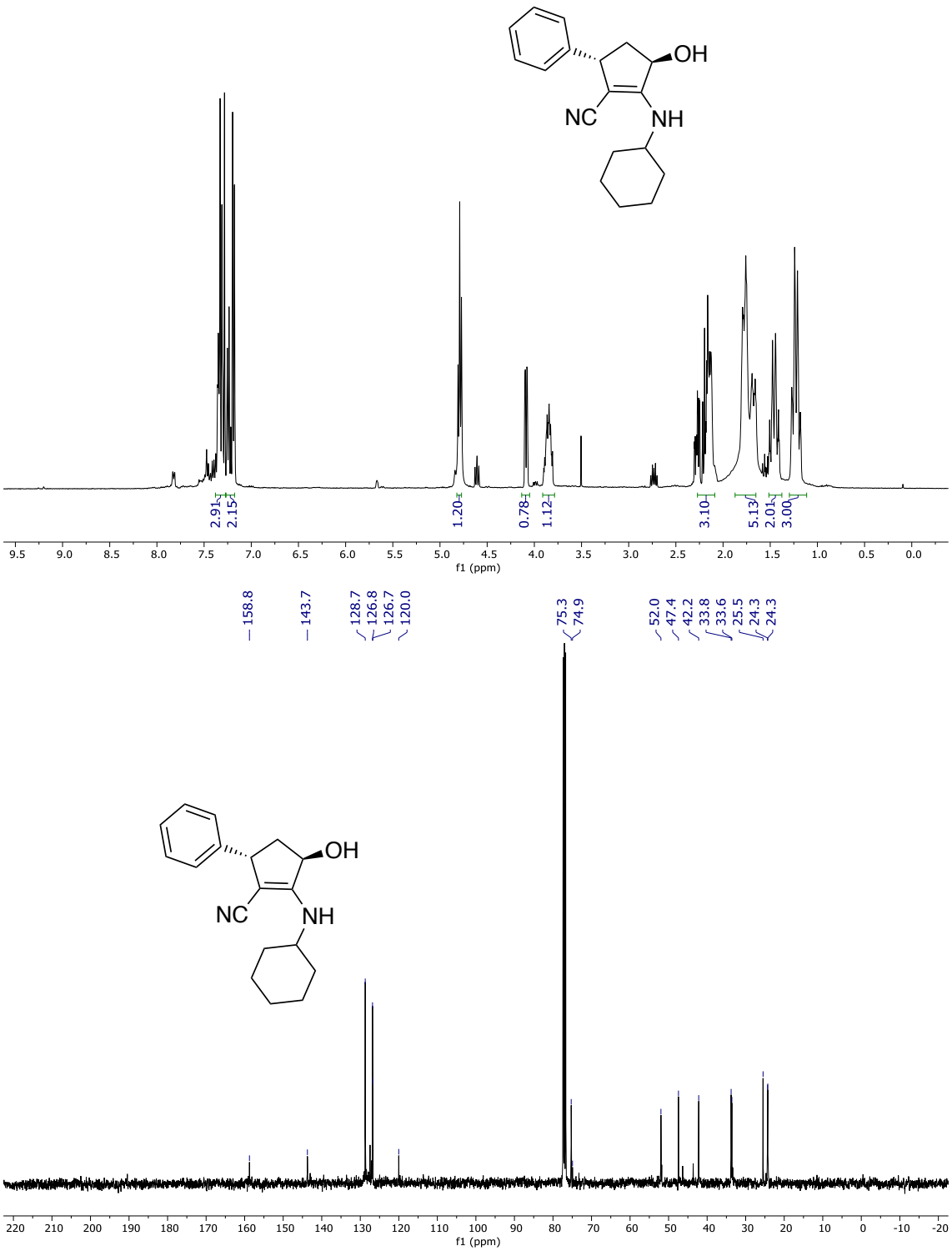


FIGURE 7.55 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3b**.

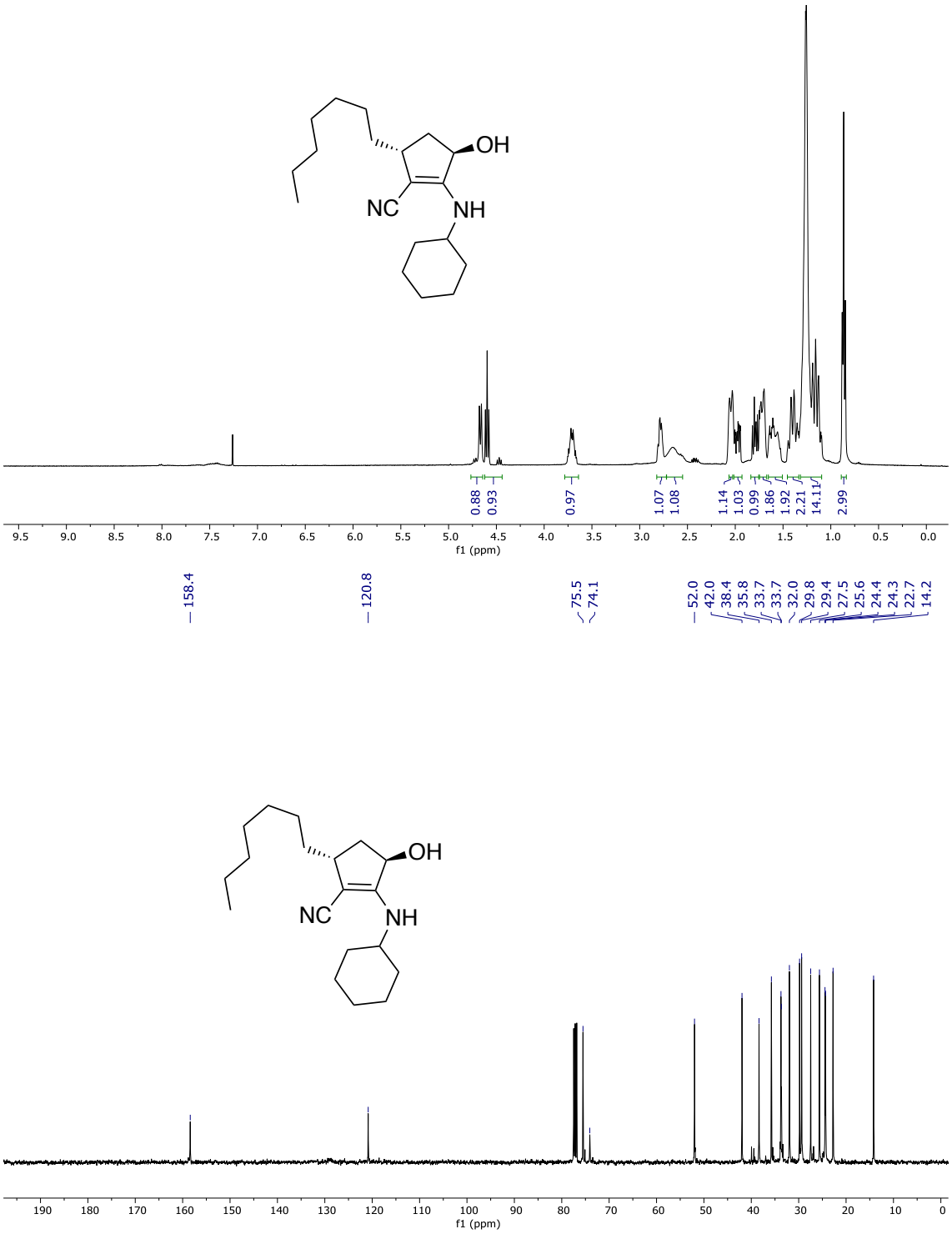


FIGURE 7.56 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **3c**.

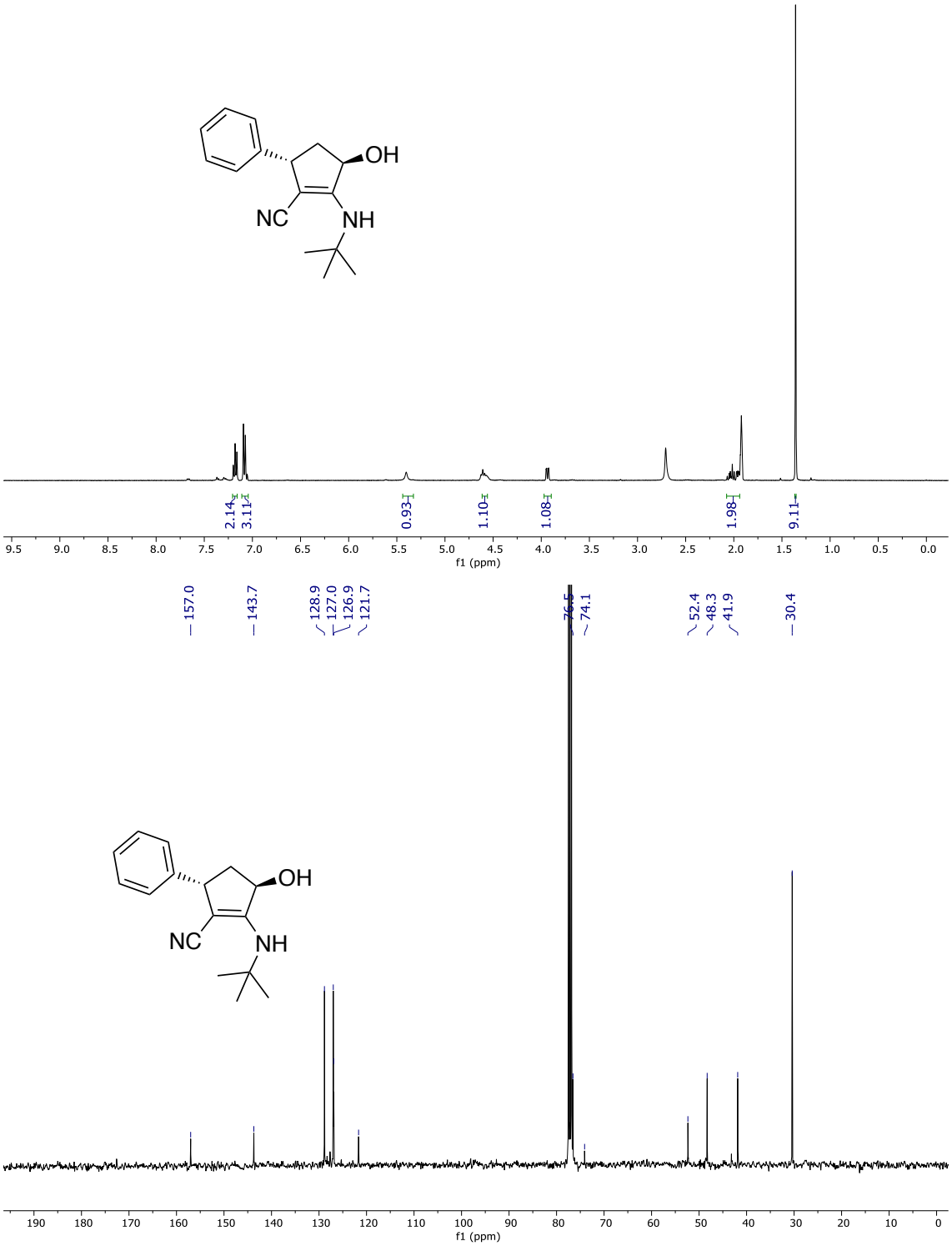


FIGURE 7.57 ^{1}H and ^{13}C NMR spectra in acetone-d^{6} and $CDCl_3$, respectively, of compound of **3d**.

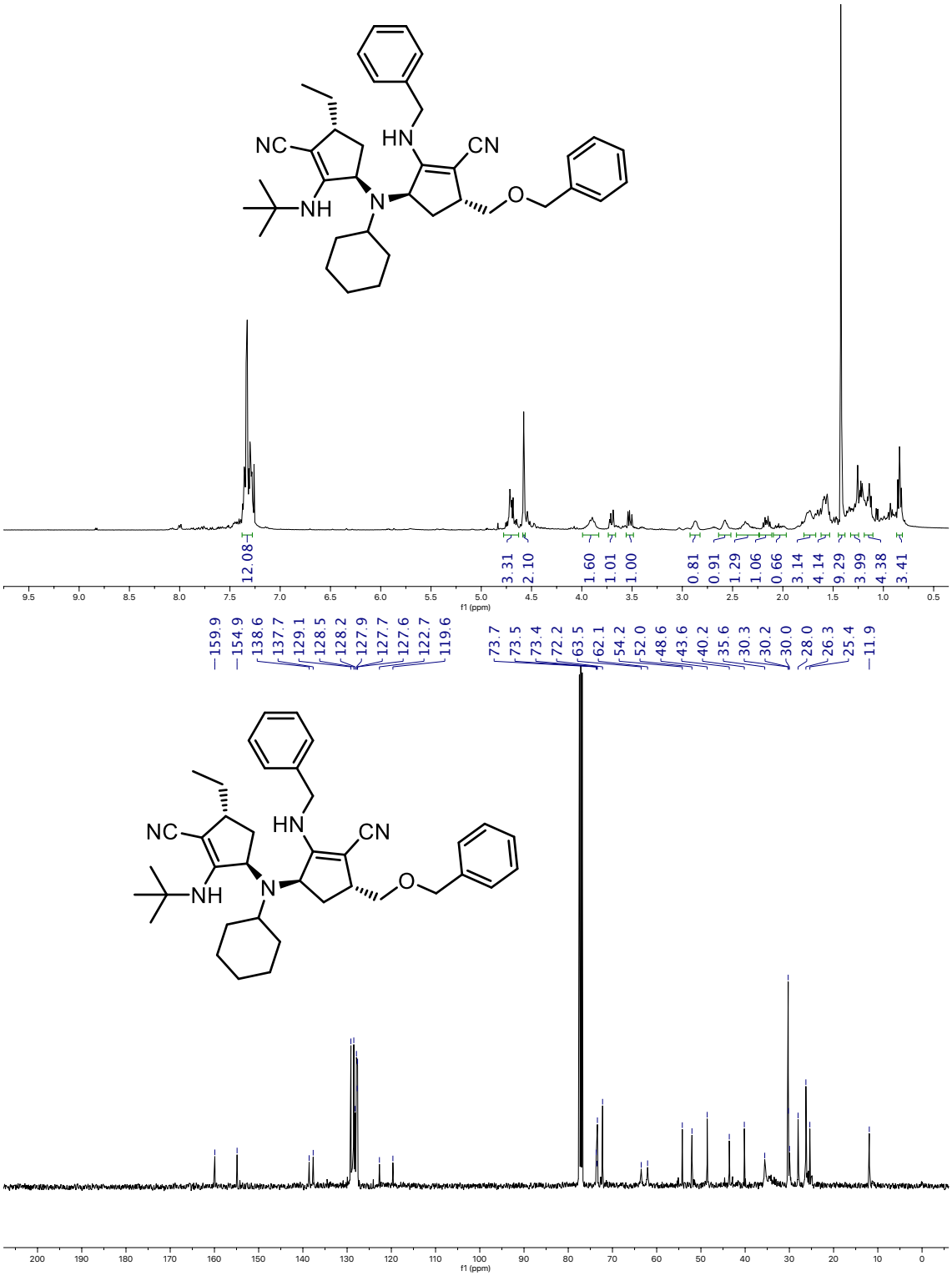


FIGURE 7.58 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **4**.

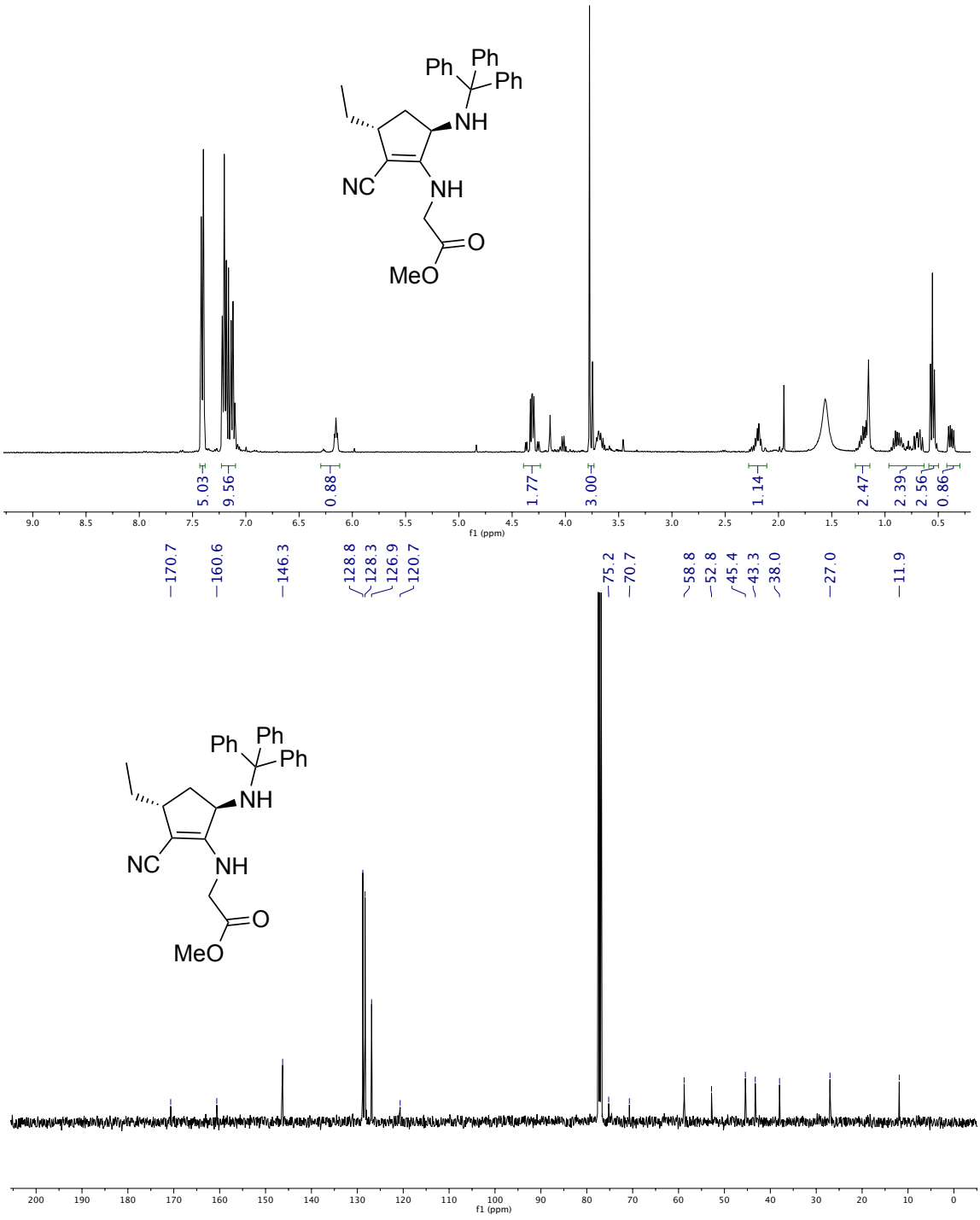


FIGURE 7.59 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **5**.

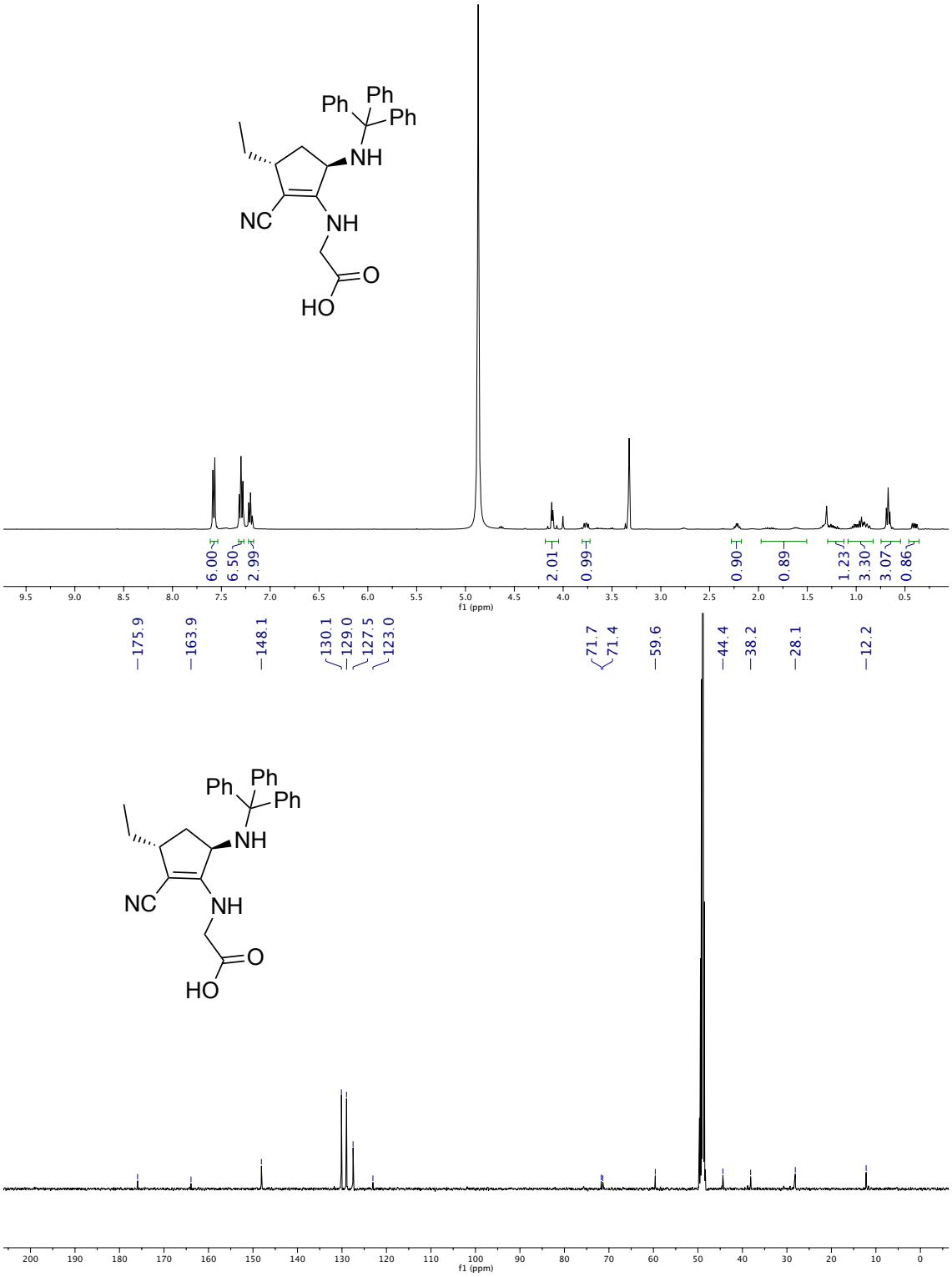


FIGURE 7.60 ^{1}H and ^{13}C NMR spectra in CD_3OD of compound **6**.

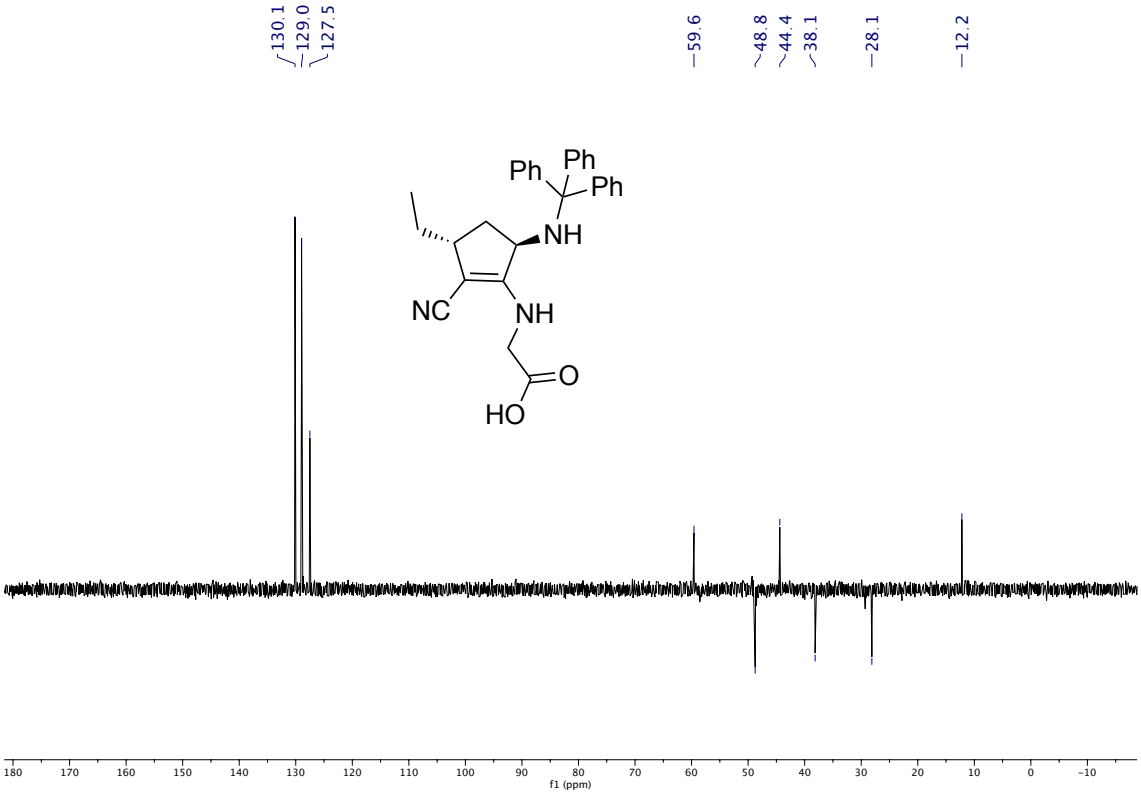


FIGURE 7.61 ^{13}C DEPT 135 spectrum in CD_3OD of compound **6**.

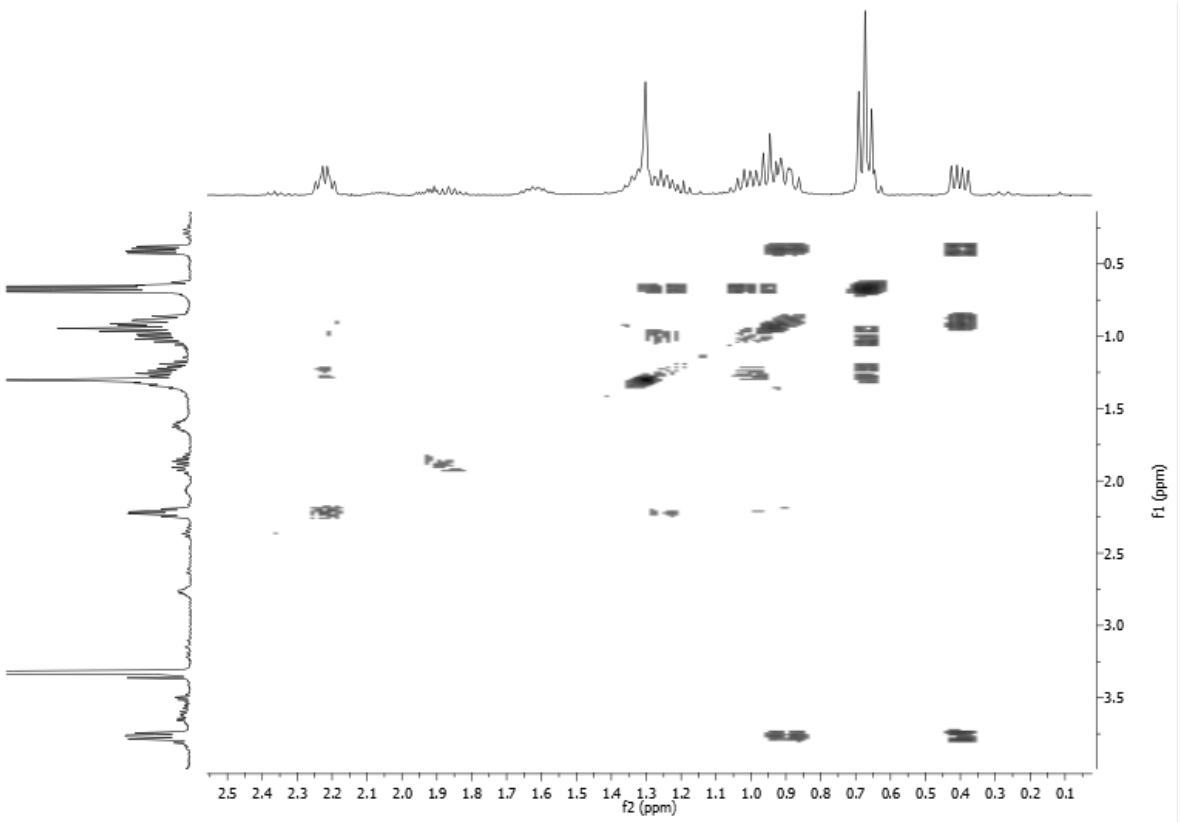


FIGURE 7.62 ^{1}H COSY spectrum in CD_3OD of compound **6**.

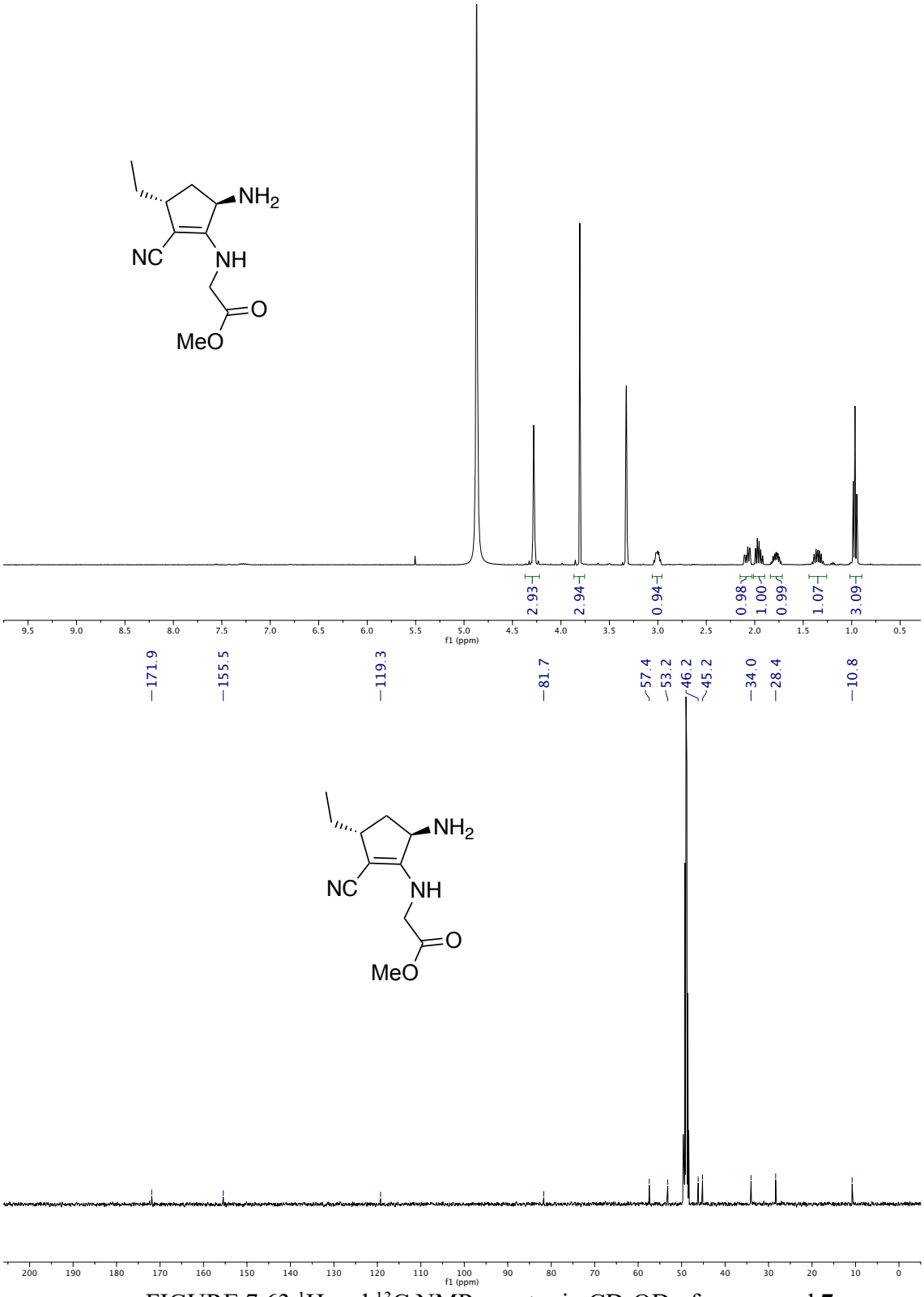


FIGURE 7.63 ^{1}H and ^{13}C NMR spectra in CD_3OD of compound **7**.

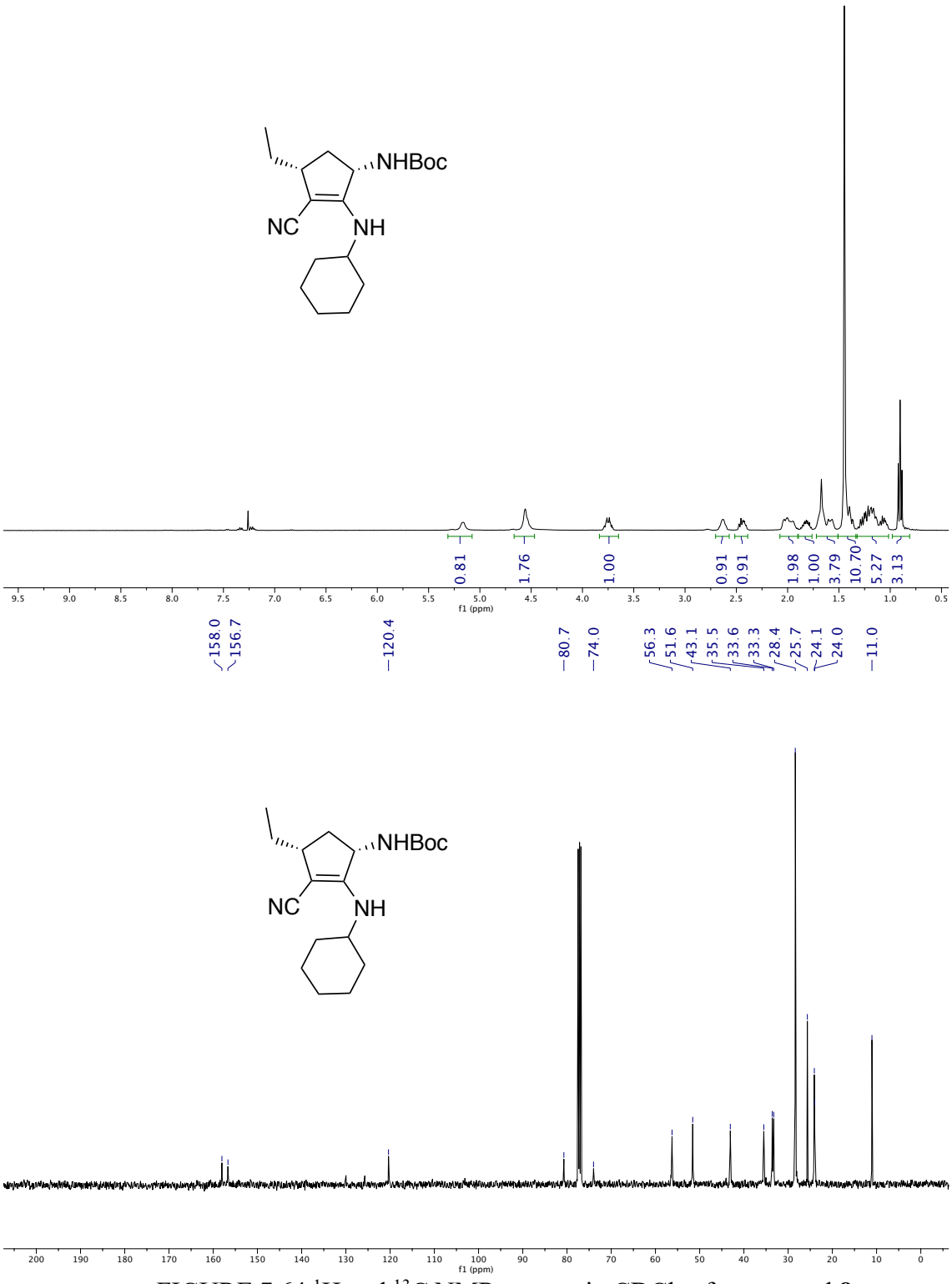


FIGURE 7.64 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **8**.

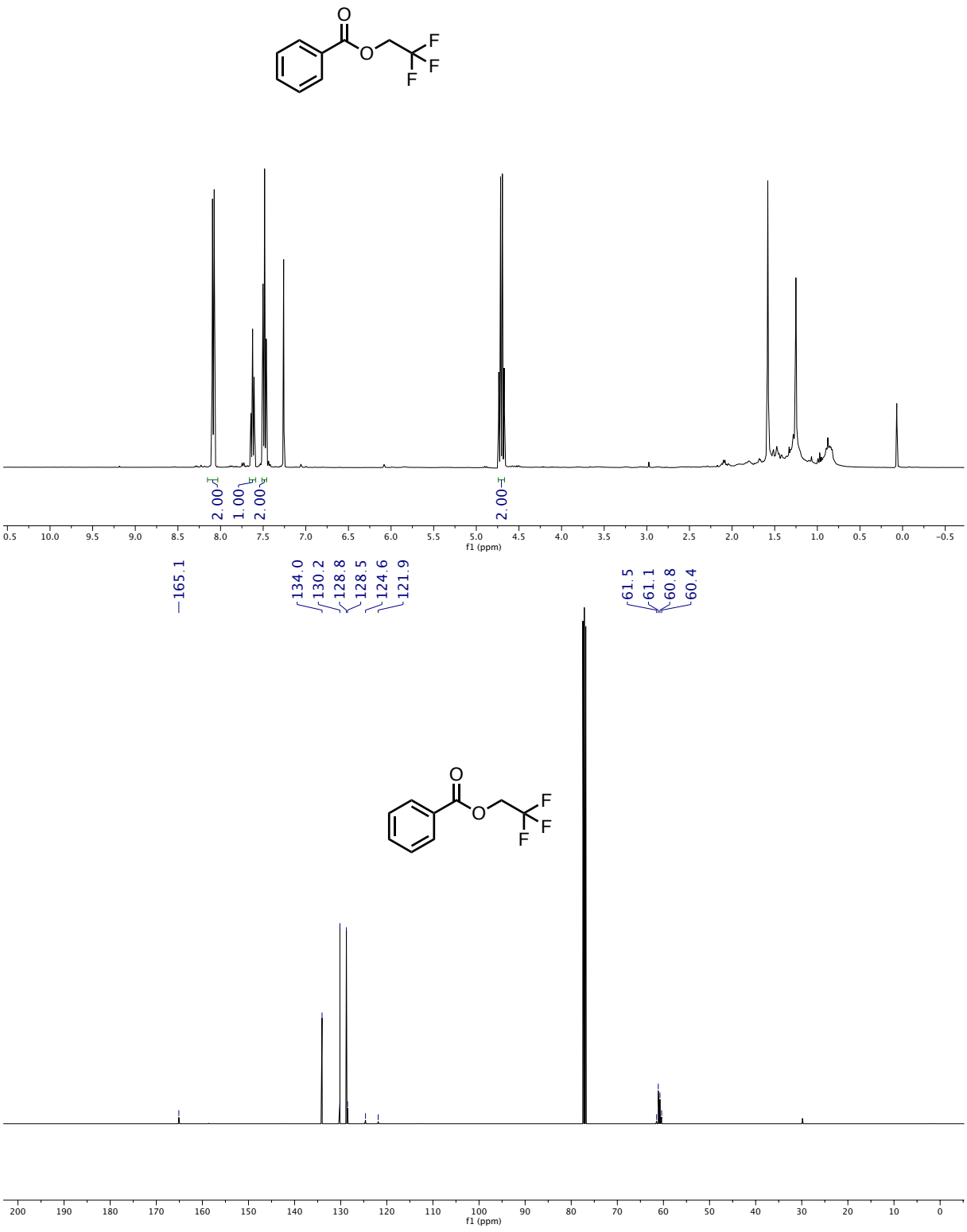


FIGURE 7.65 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **9**.

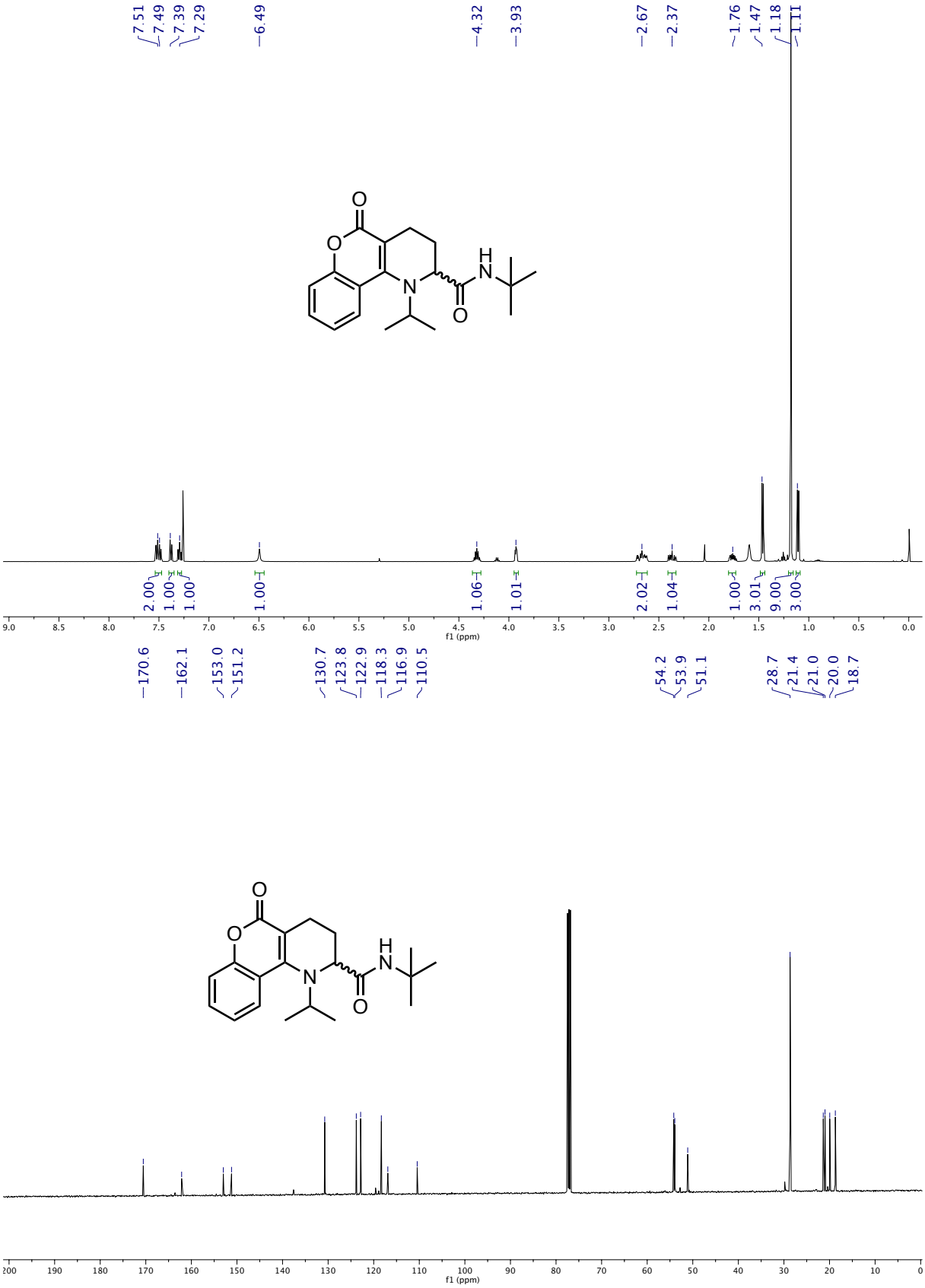


FIGURE 7.66 ^{1}H and ^{13}C NMR spectra in $CDCl_3$ of compound **16** (500 and 100 MHz).

7.2. UPC² and HPLC chromatograms

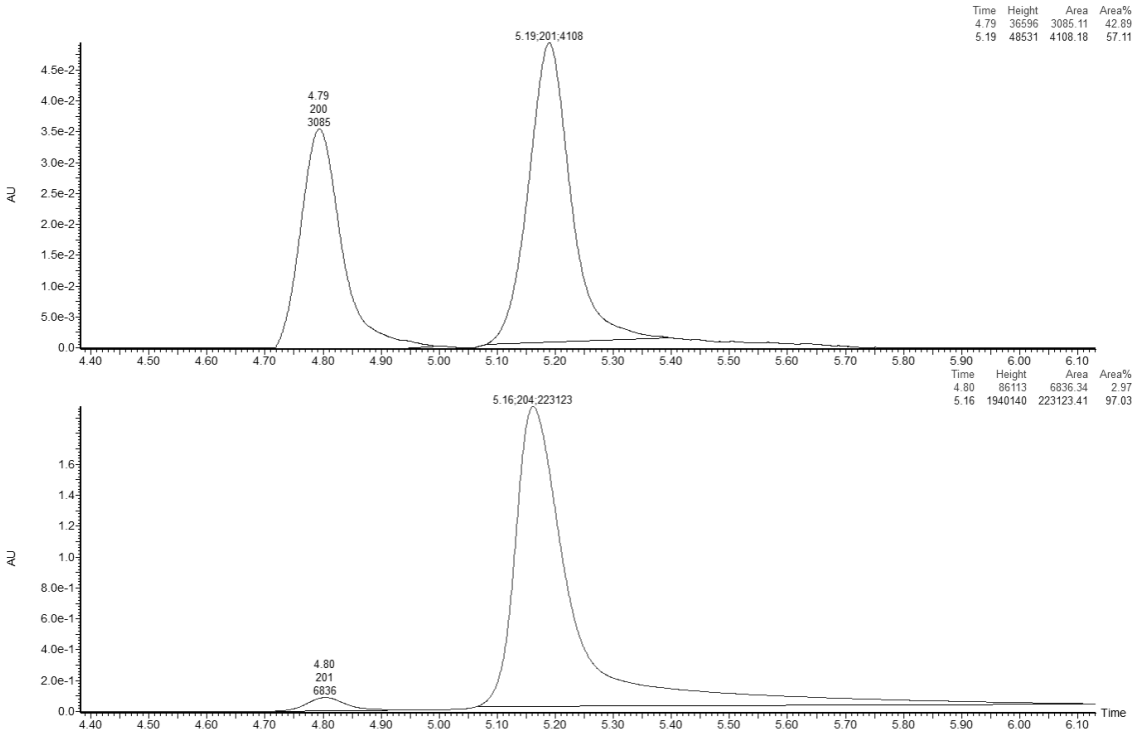


FIGURE 7.67 Chromatograms of compound **1a**.

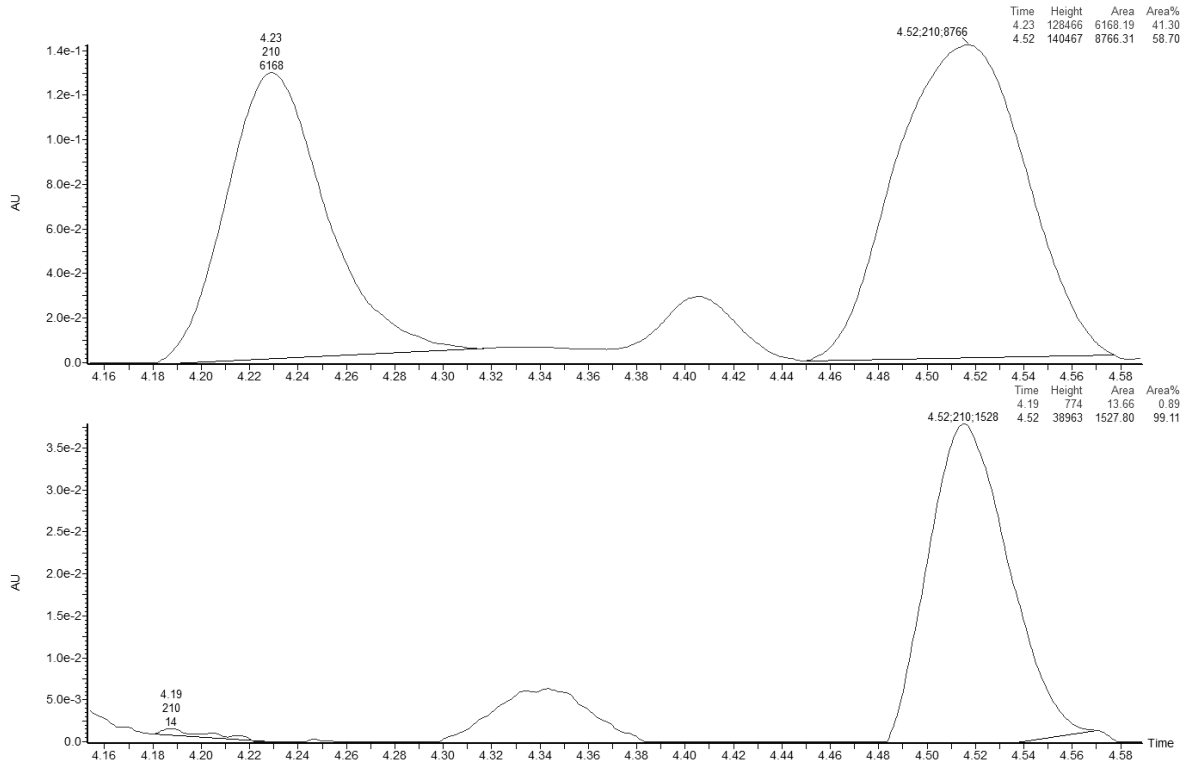


FIGURE 7.68 Chromatograms of compound **1b**.

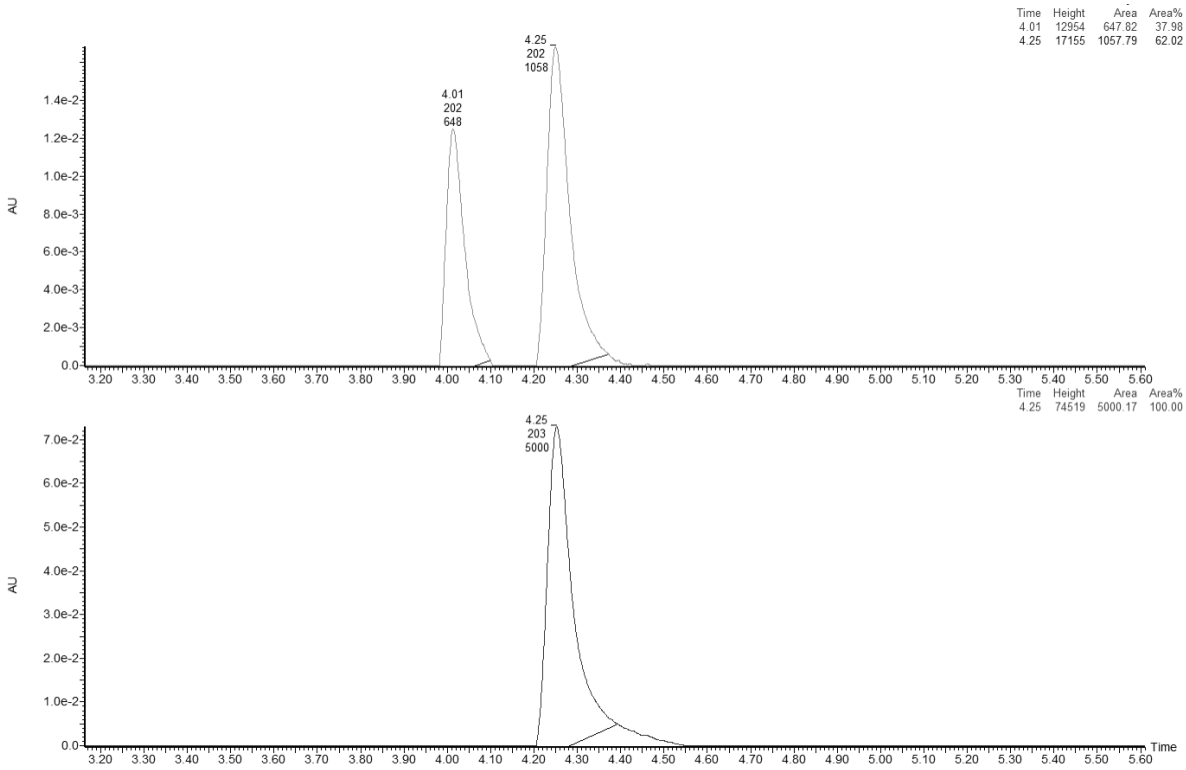


FIGURE 7.69 Chromatograms of compound **1c**.

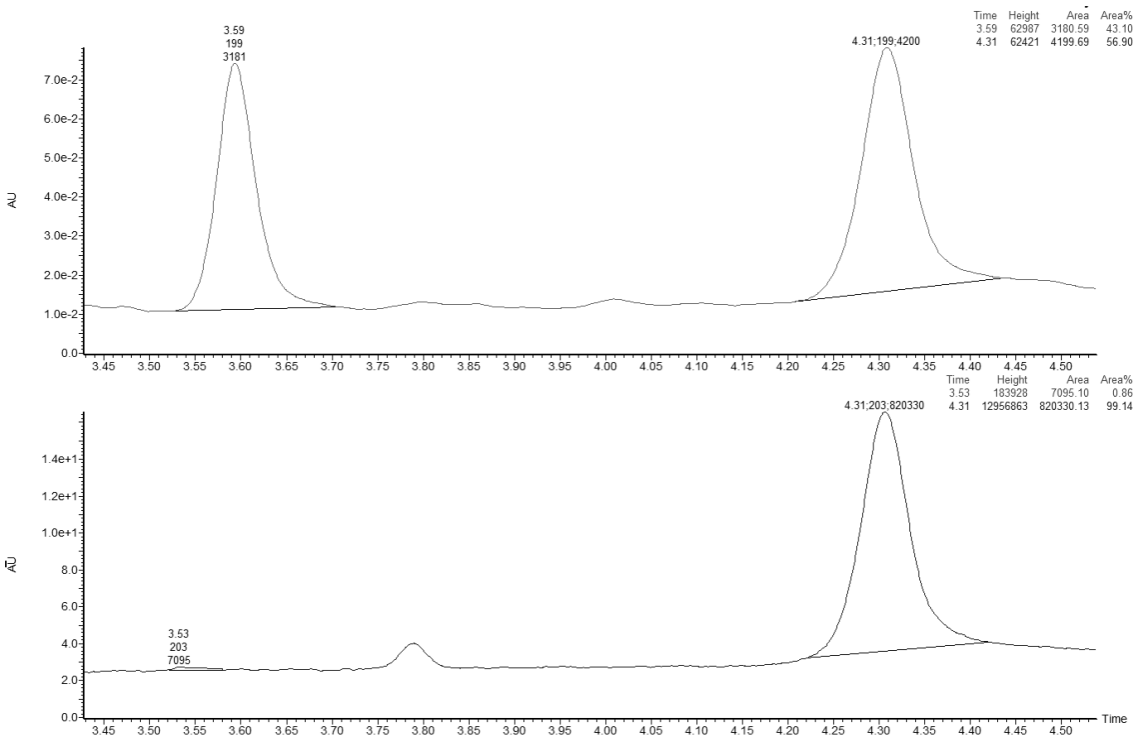


FIGURE 7.70 Chromatograms of compound **1d**.

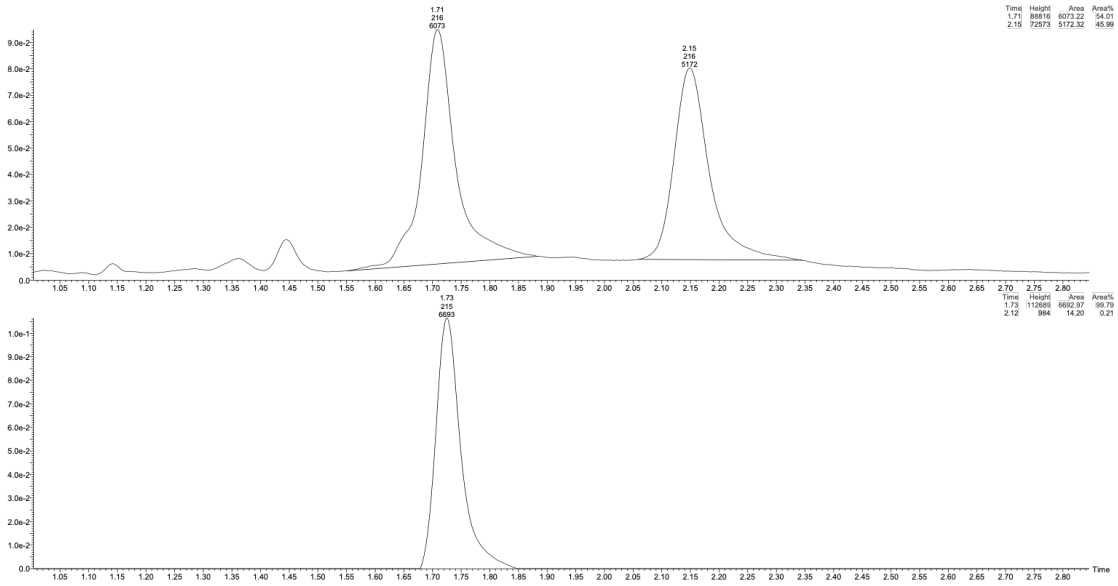


FIGURE 7.71 Chromatograms of compound **1e**.

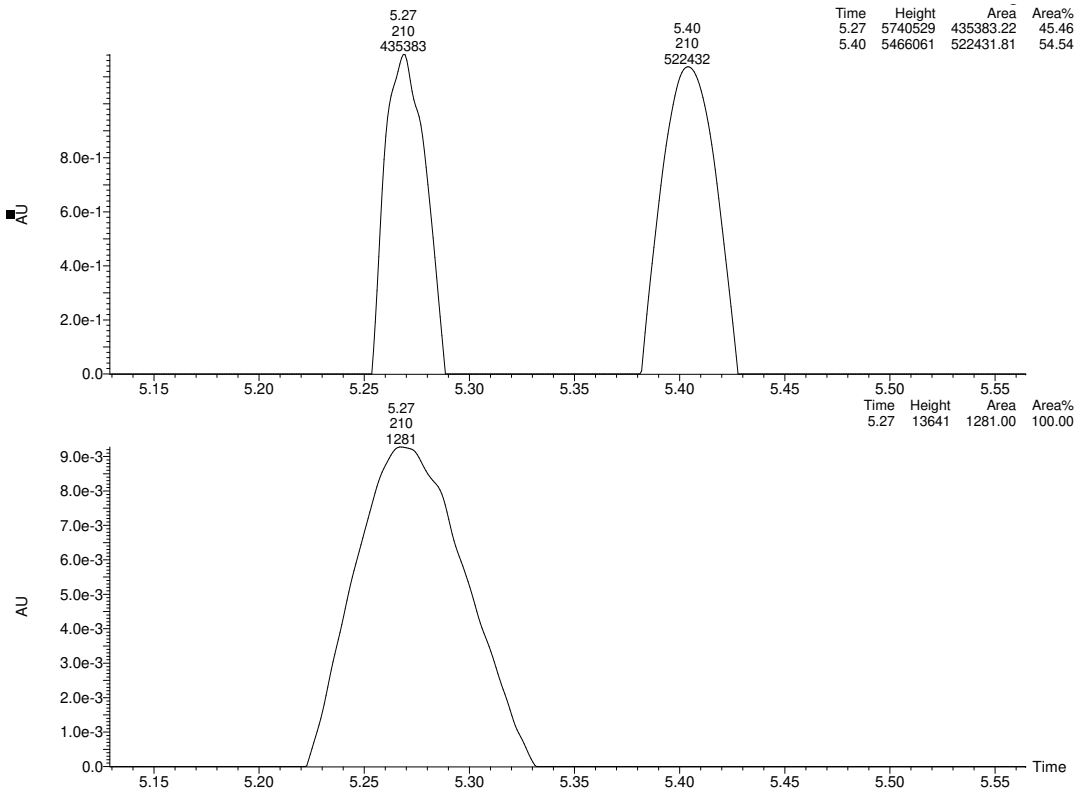


FIGURE 7.72 Chromatograms of compound **1f**.

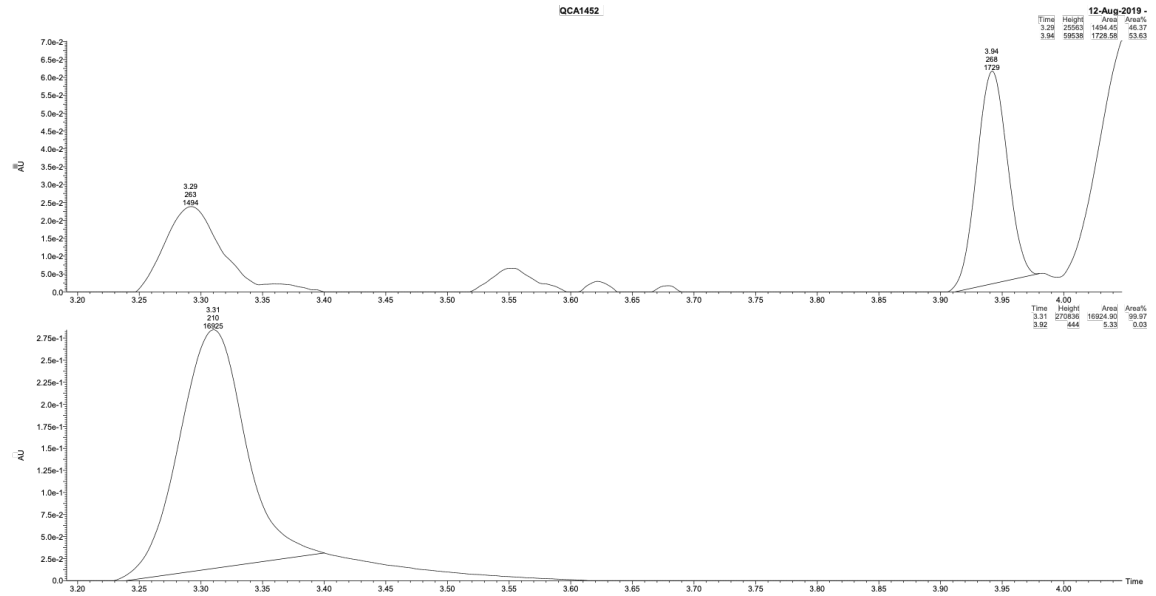


FIGURE 7.73 Chromatograms of compound **1g**.

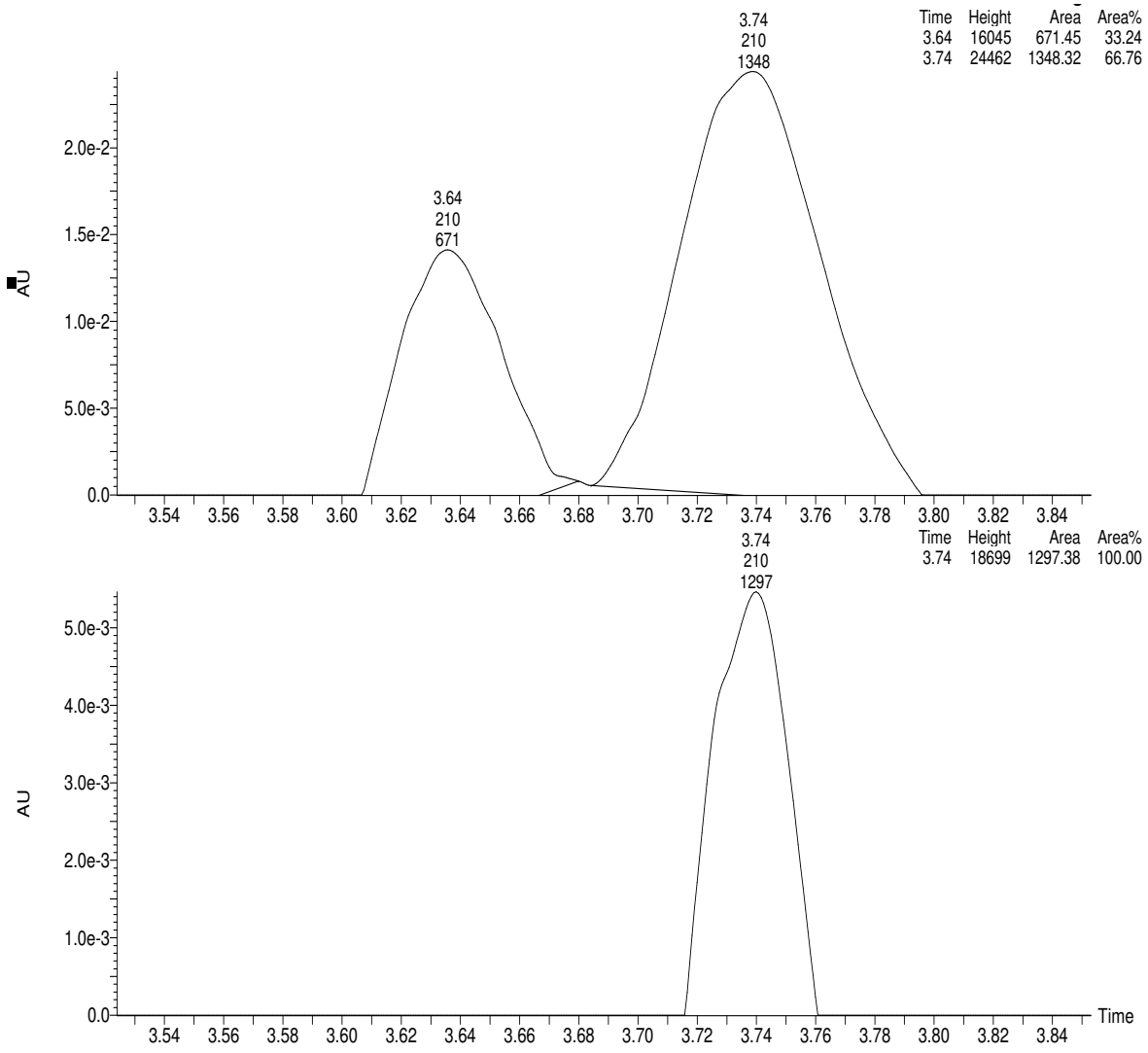


FIGURE 7.74 Chromatograms of compound **1h**.

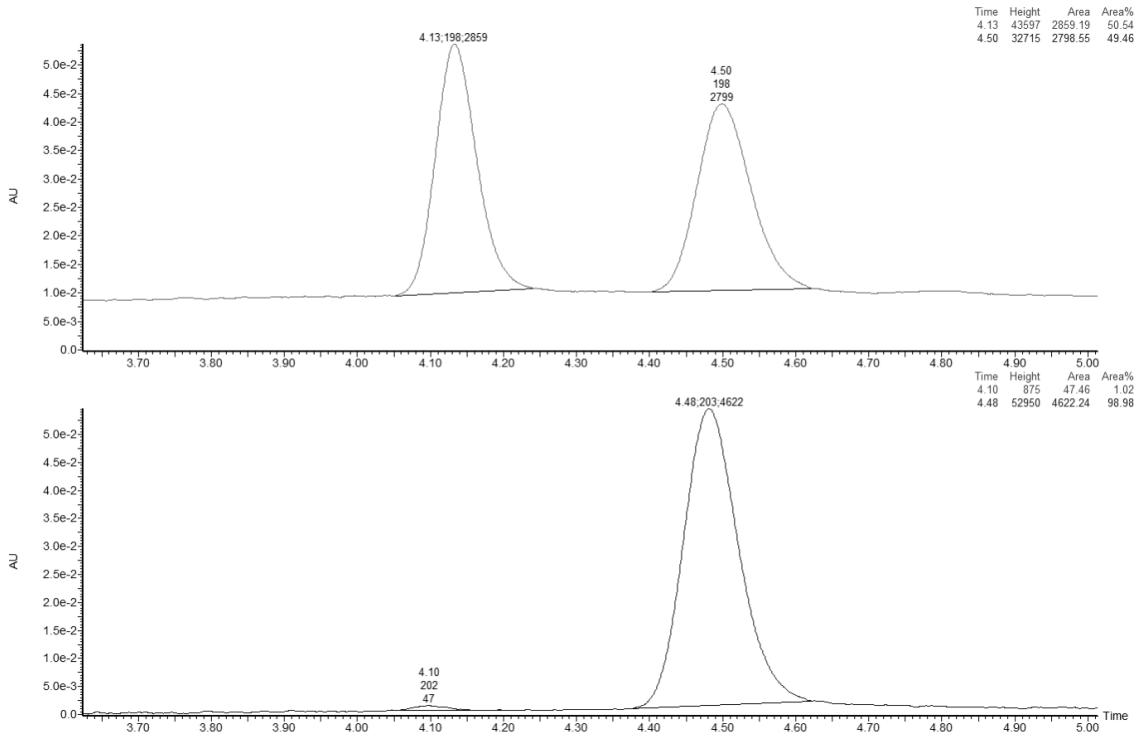


FIGURE 7.75 Chromatograms of compound **1i**.

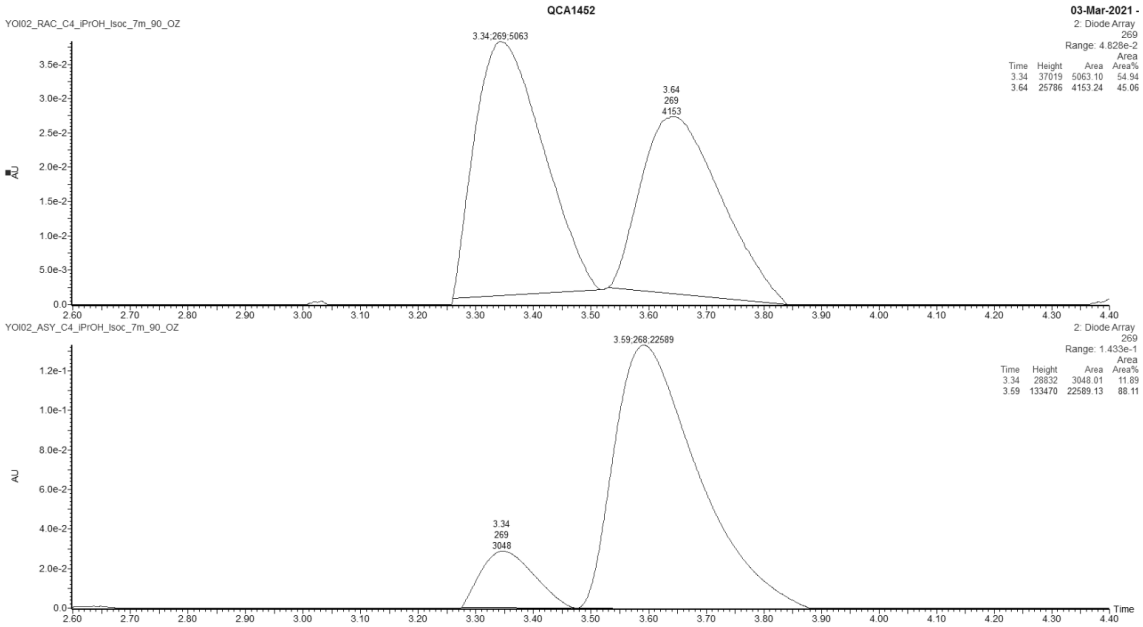


FIGURE 7.76 Chromatograms of compound **2a**.

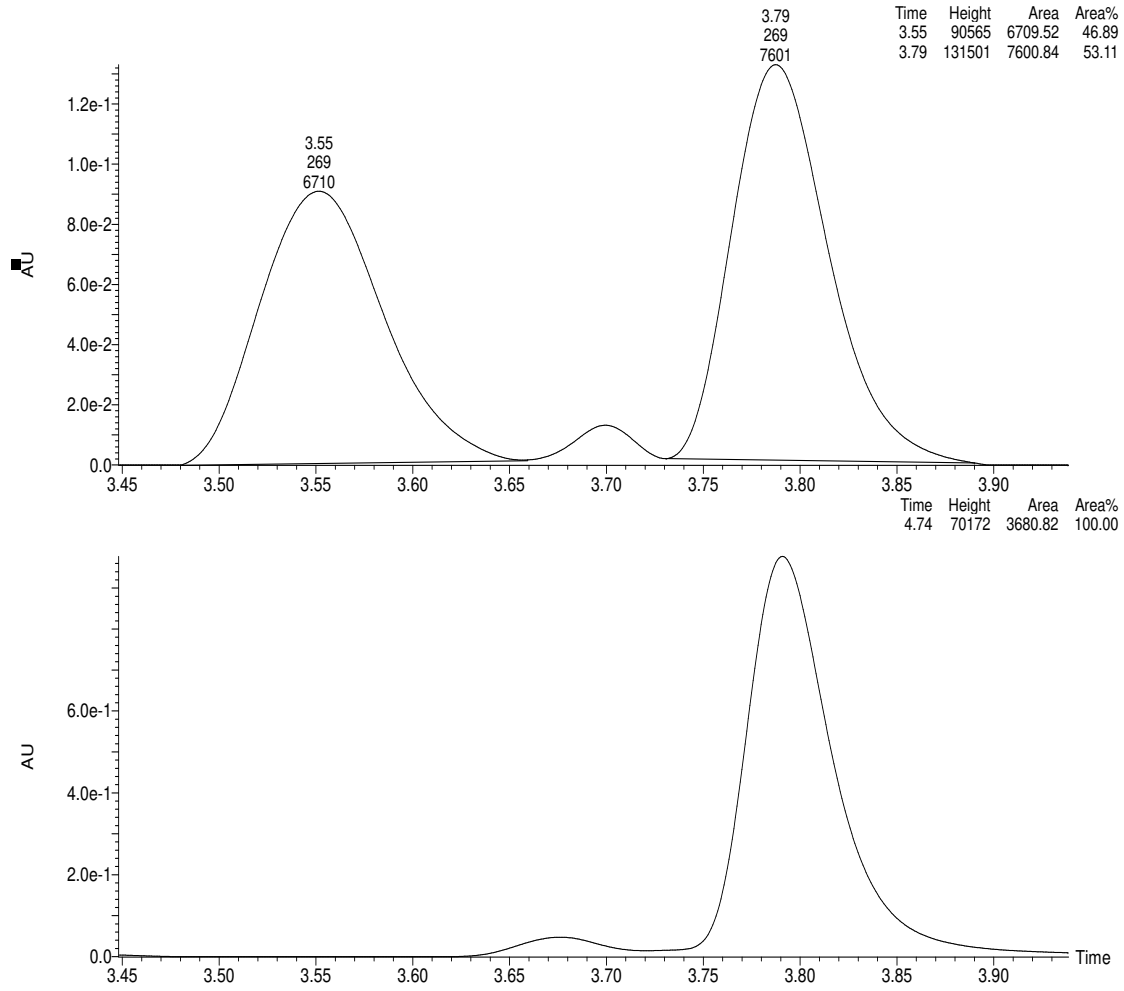


FIGURE 7.77 Chromatograms of compound **2b**.

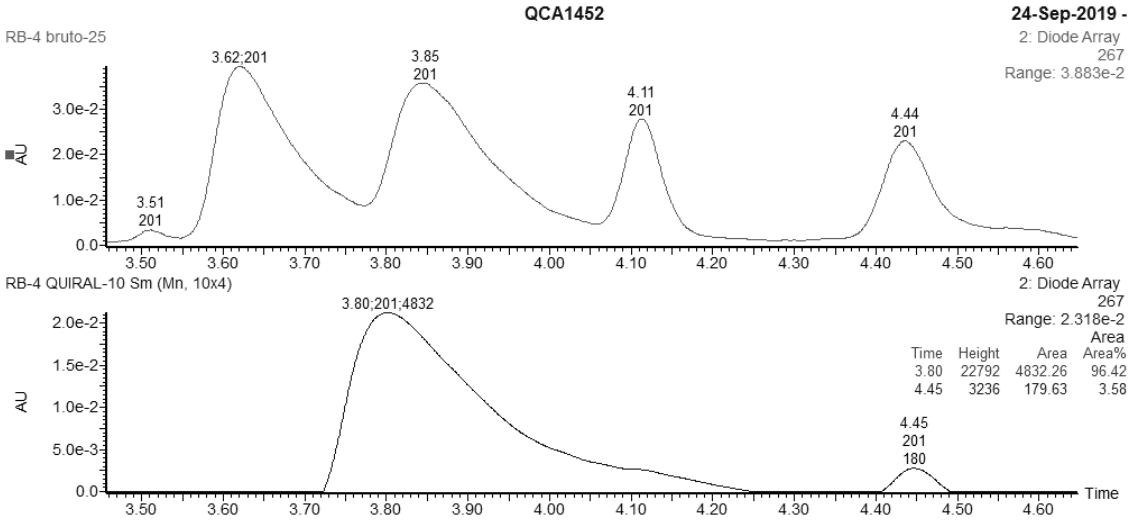


FIGURE 7.78 Chromatograms of compound **2c**.

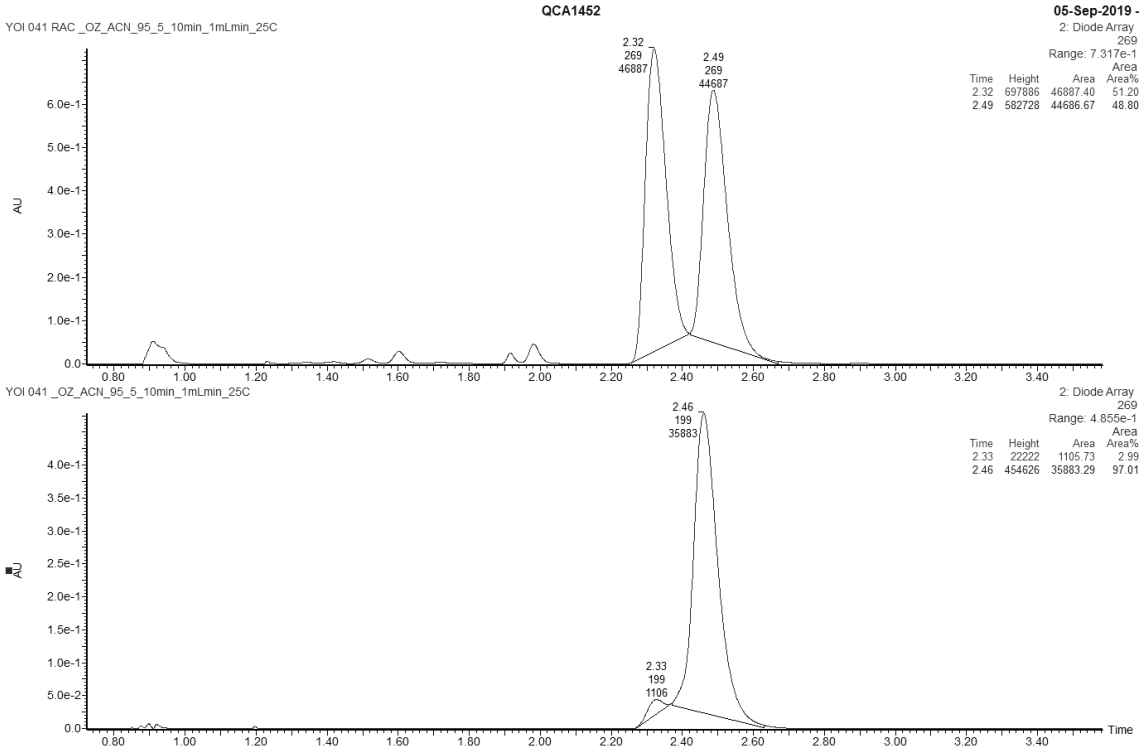


FIGURE 7.79 Chromatograms of compound **2d**.

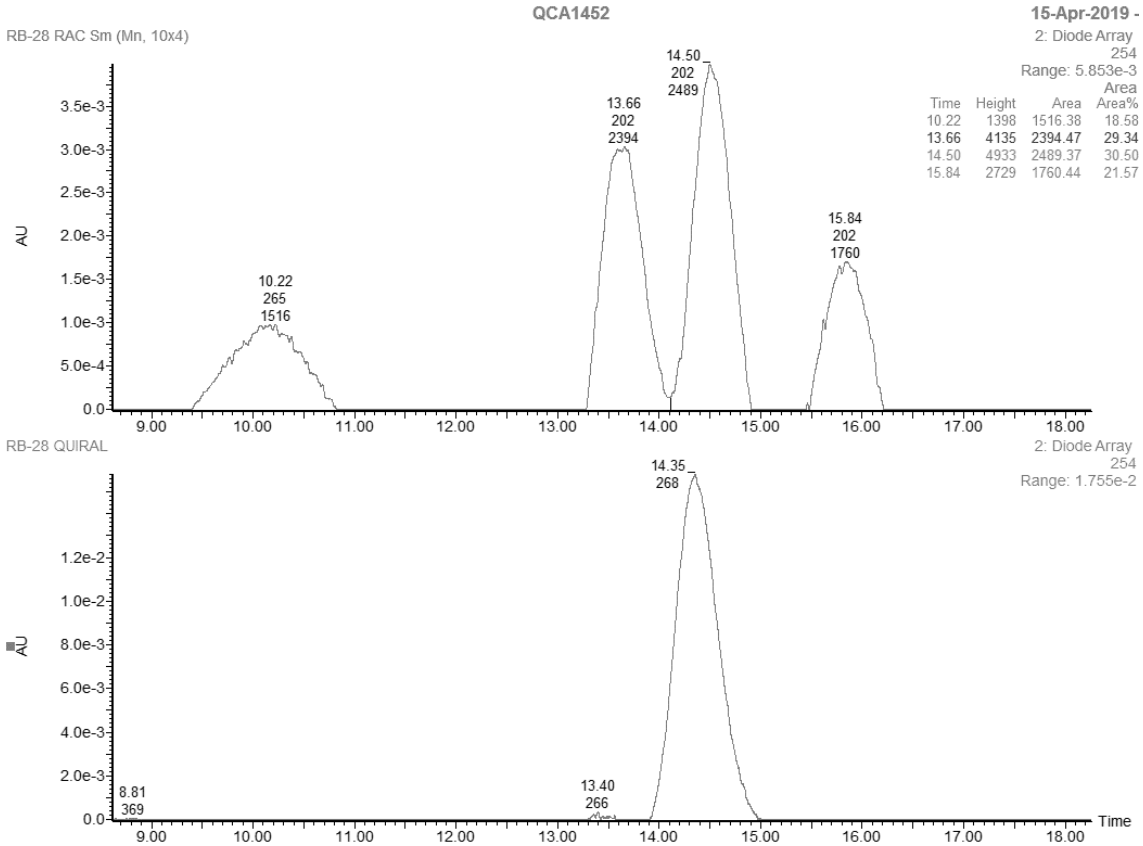


FIGURE 7.80 Chromatograms of compound **2e**.

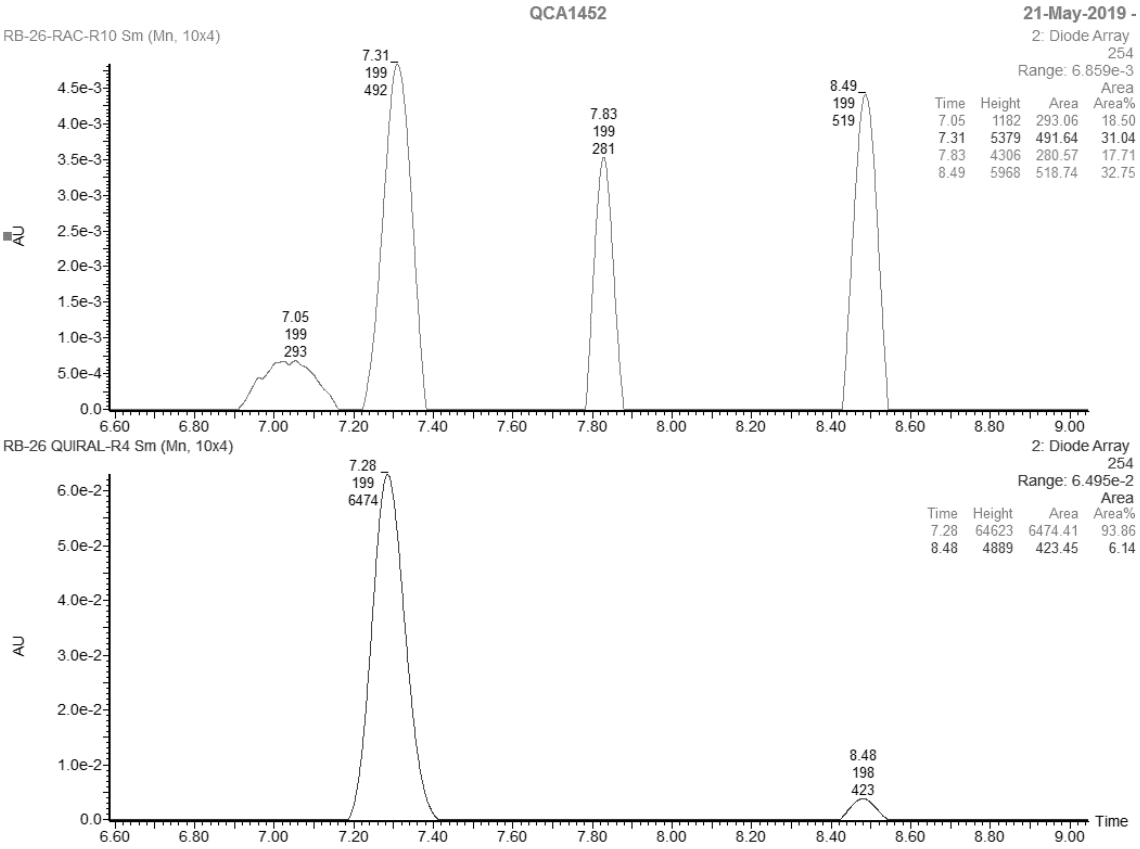


FIGURE 7.81 Chromatograms of compound **2f**.

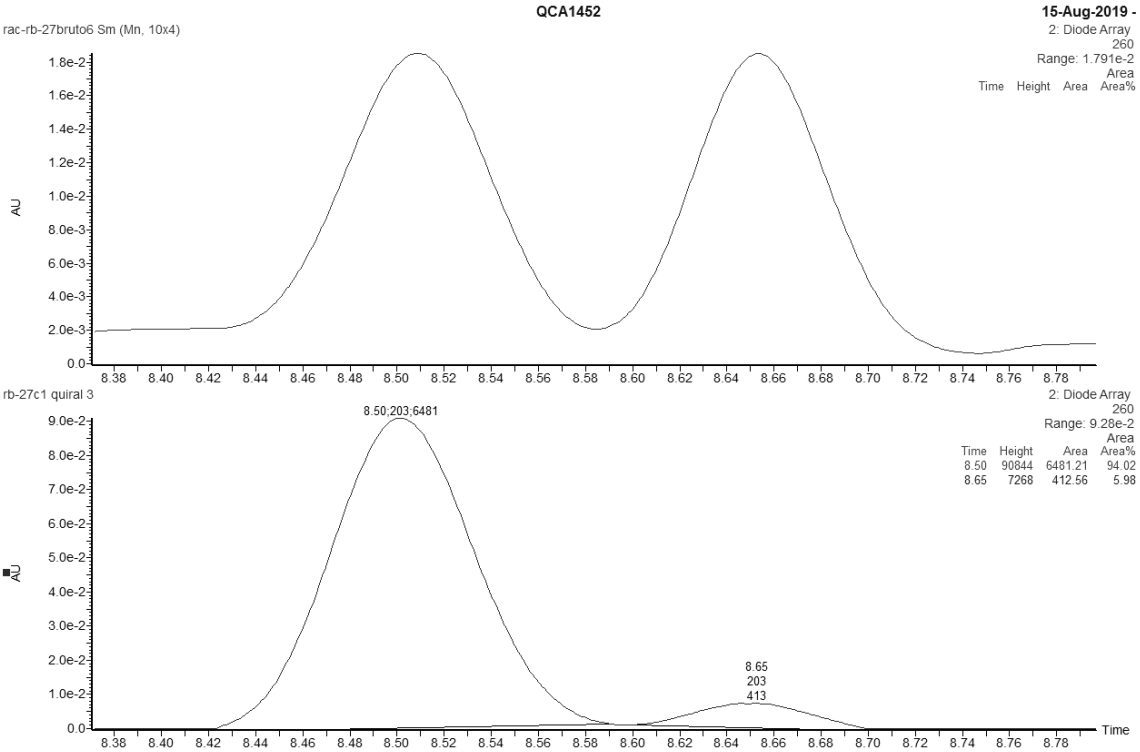


FIGURE 7.82 Chromatograms of compound **2g**.

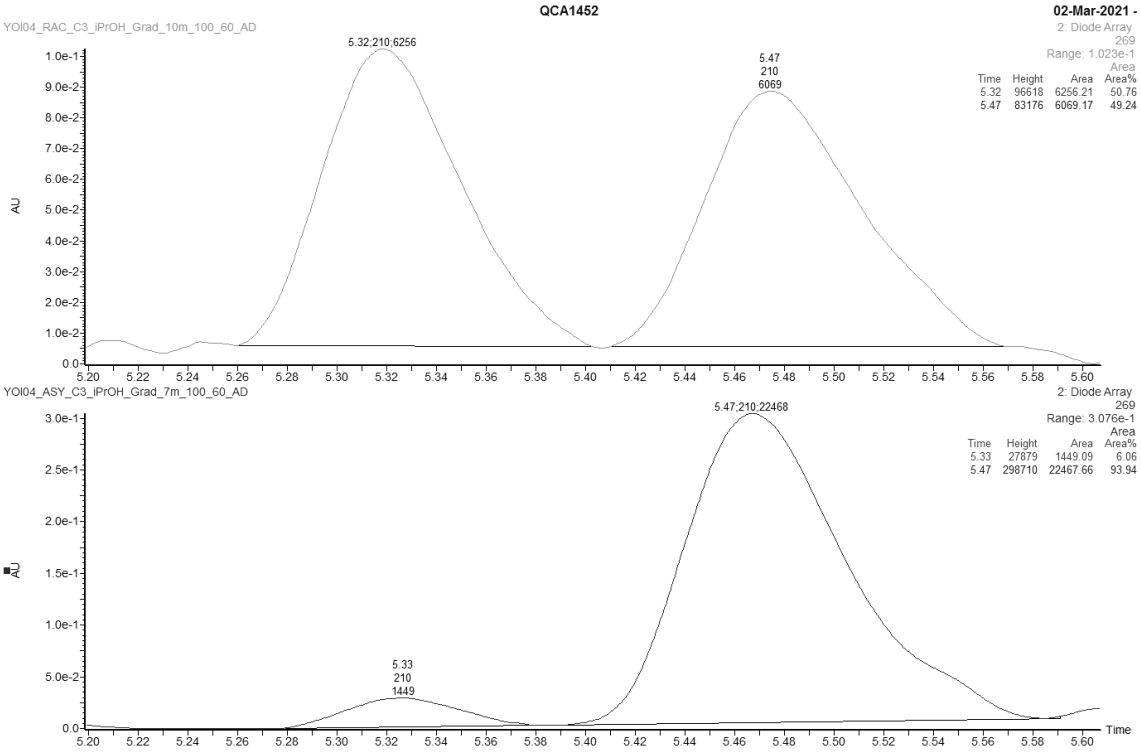


FIGURE 7.83 Chromatograms of compound **2h**.

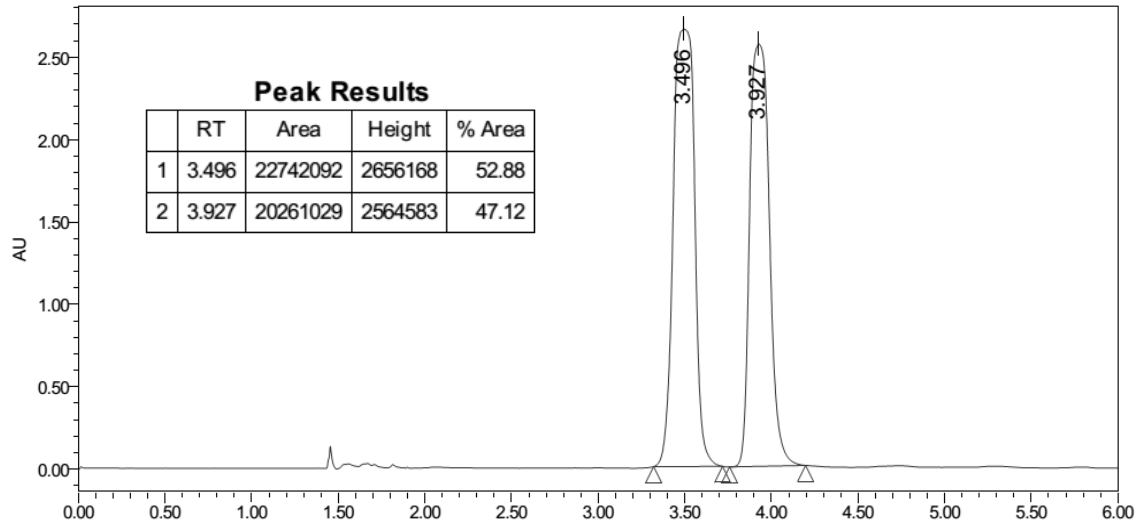


FIGURE 7.84 Chromatograms of compound **2i**.

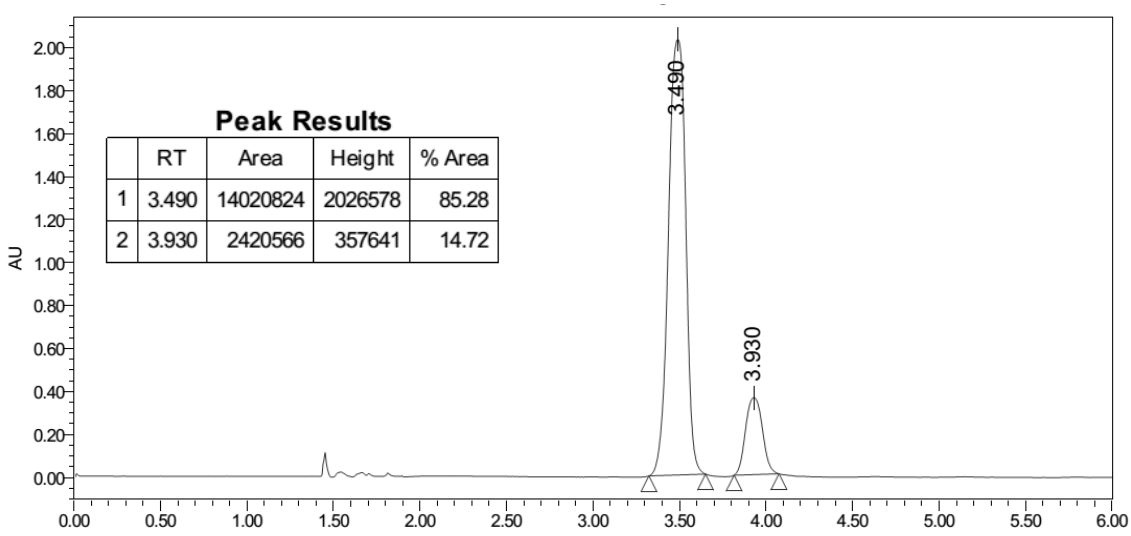


FIGURE 7.85 Chromatograms of compound **2j.**

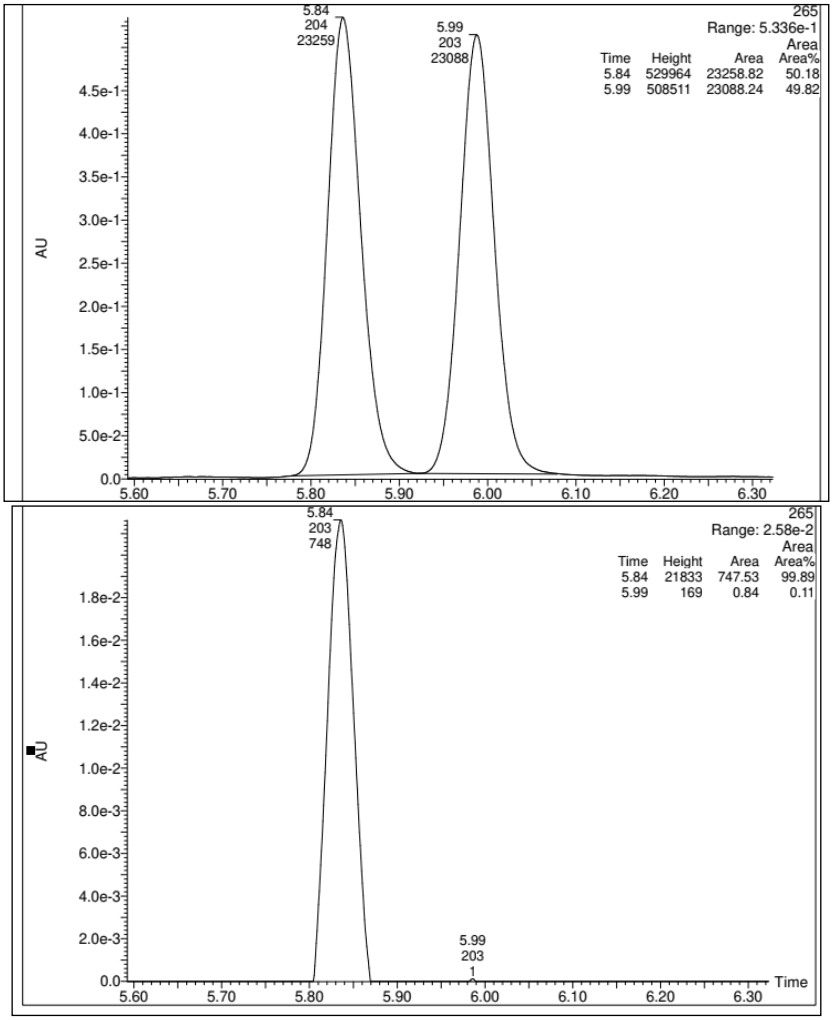


FIGURE 7.86 Chromatograms of compound **2k**.

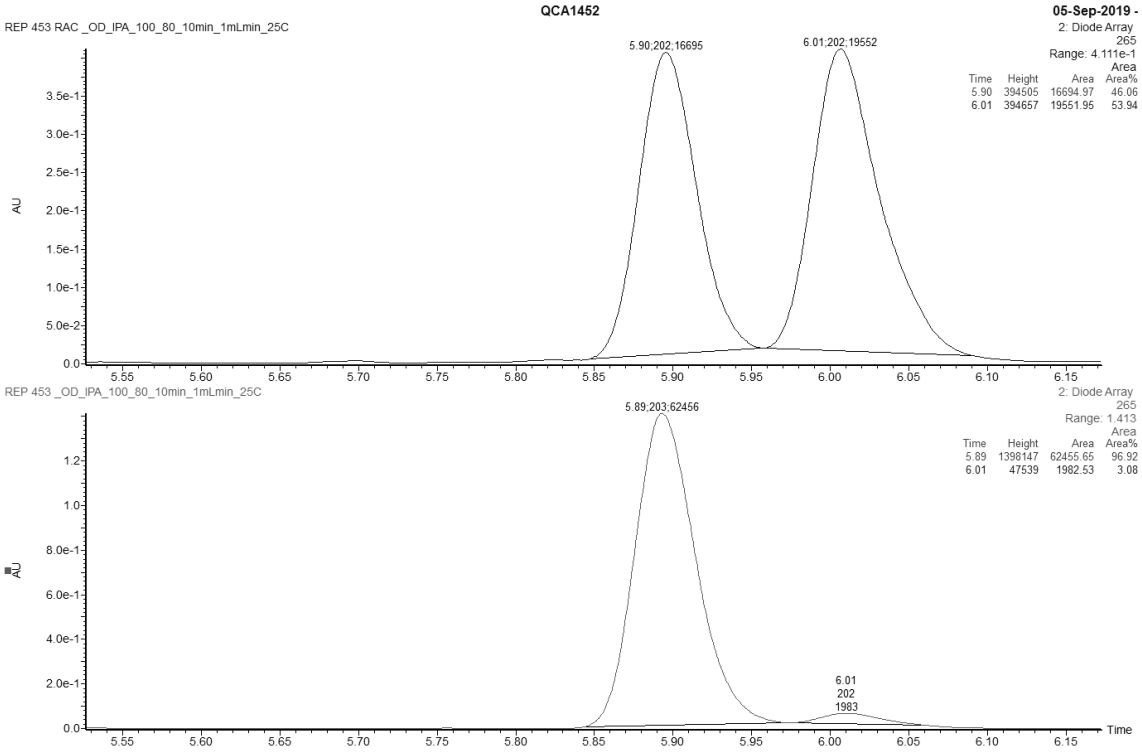


FIGURE 7.87 Chromatograms of compound **2l**.

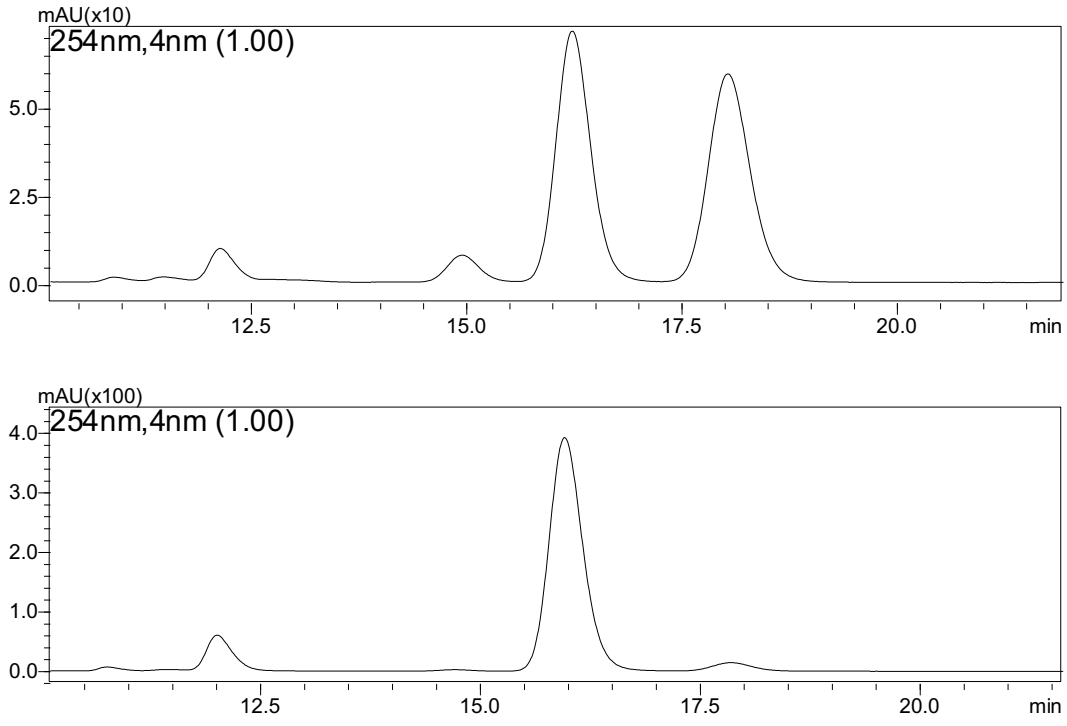


FIGURE 7.88 Chromatograms of compound **2m**.

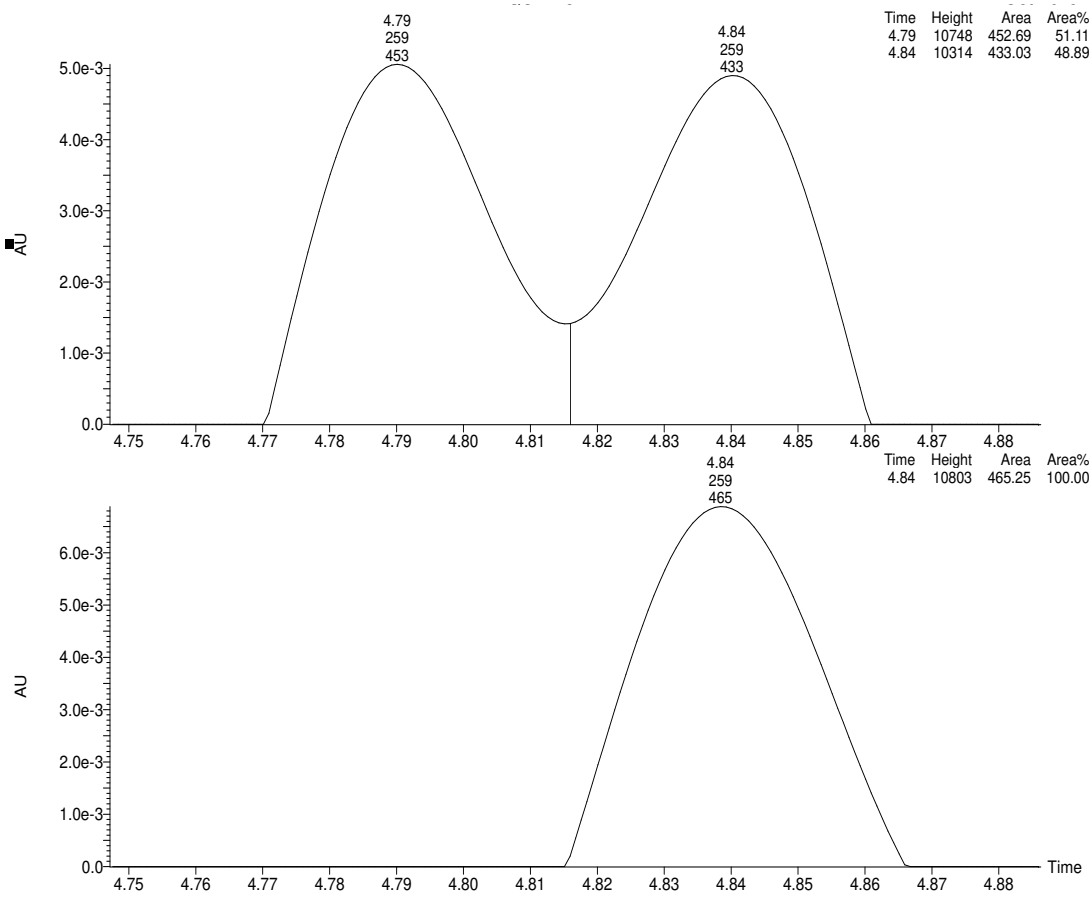


FIGURE 7.89 Chromatograms of compound **2n**.

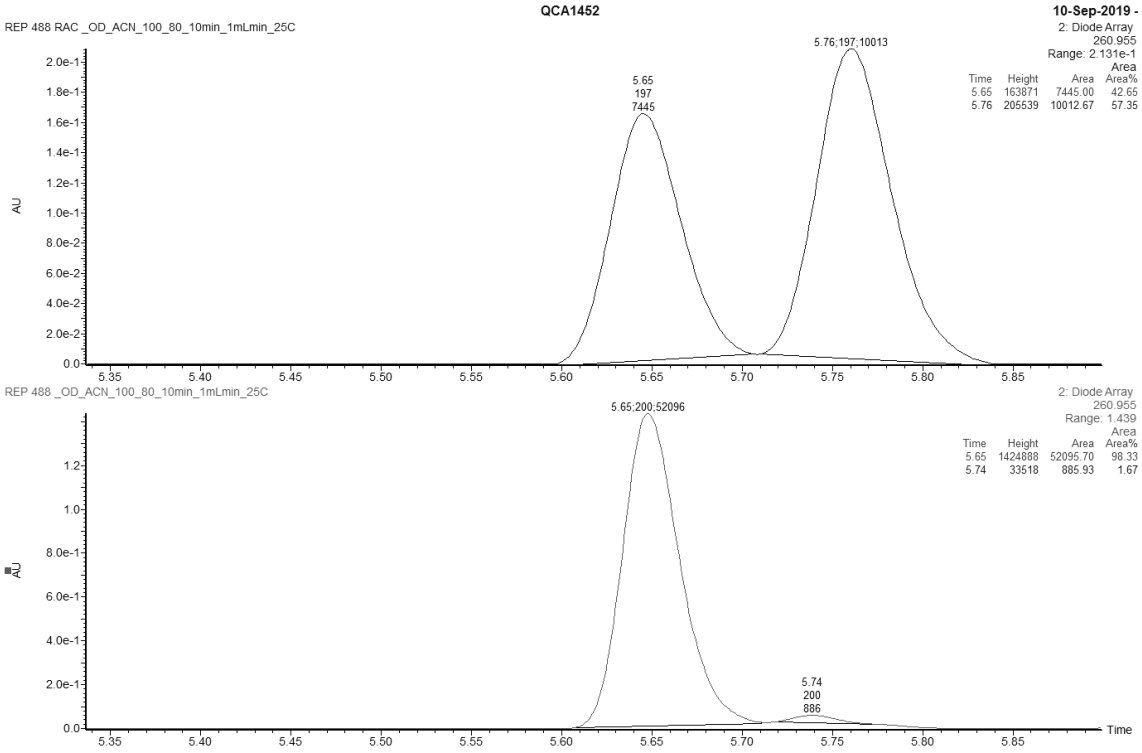


FIGURE 7.90 Chromatograms of compound **2o**.

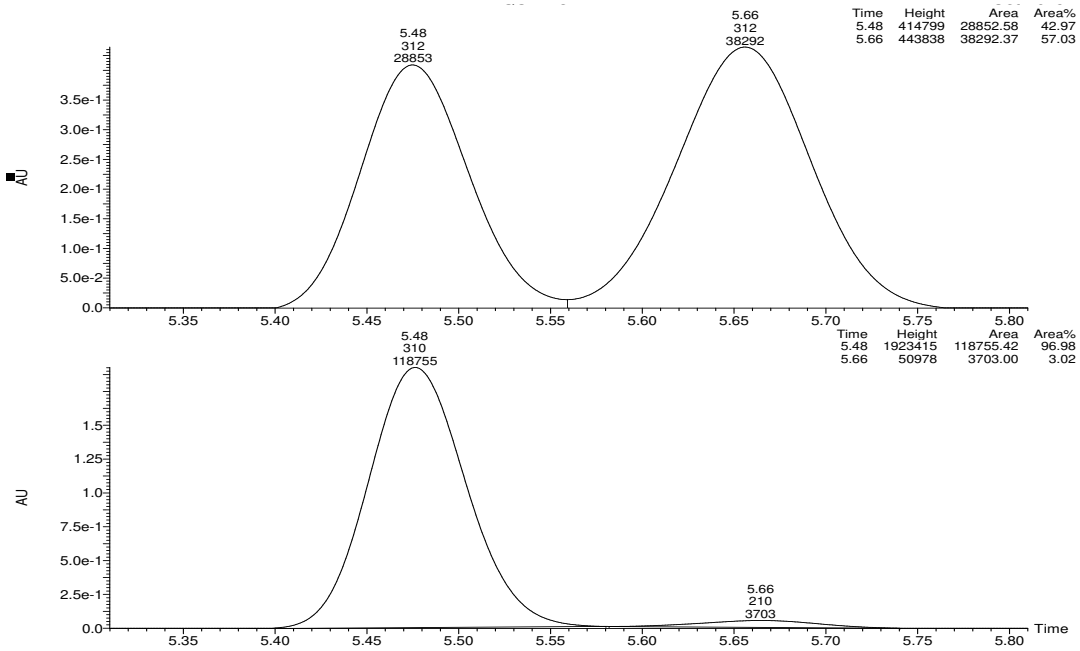


FIGURE 7.91 Chromatograms of compound **2p**.

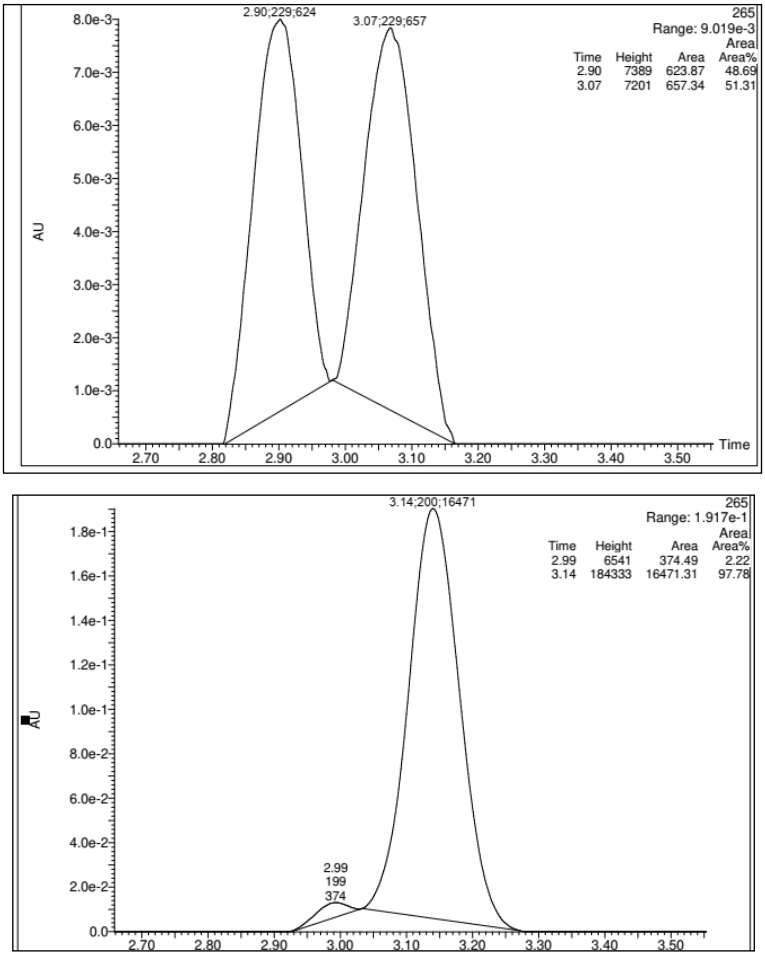


FIGURE 7.92 Chromatograms of compound **2q**.

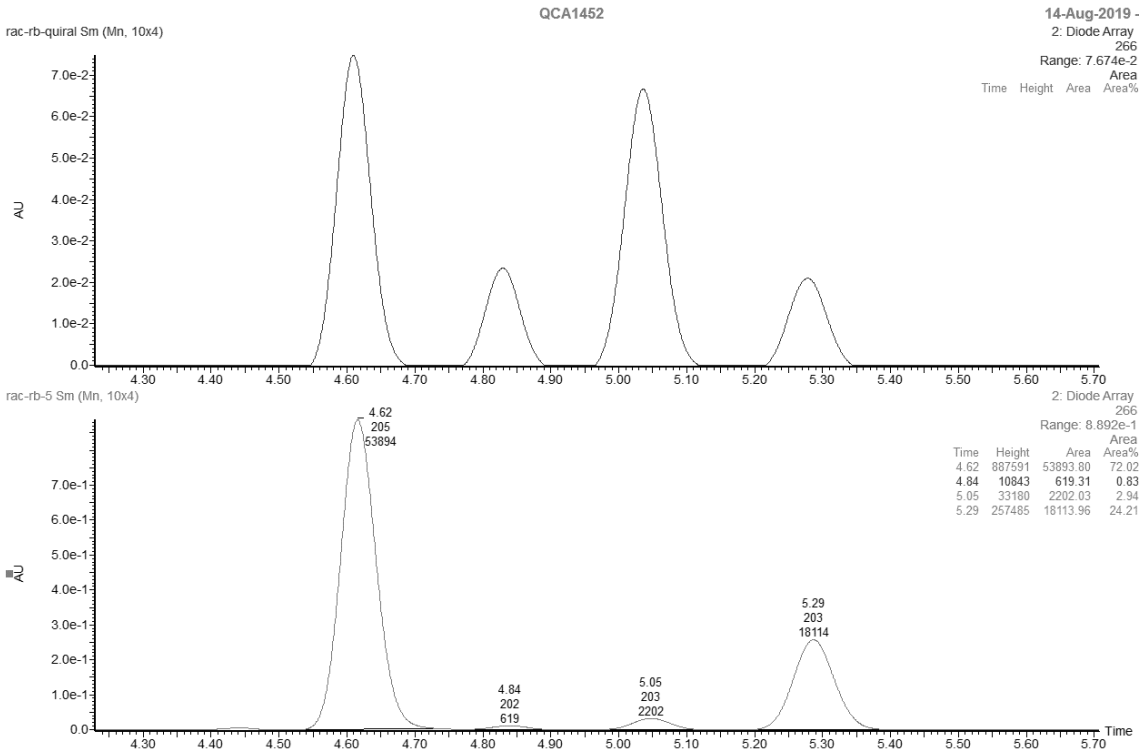


FIGURE 7.93 Chromatograms of compound **2s**.

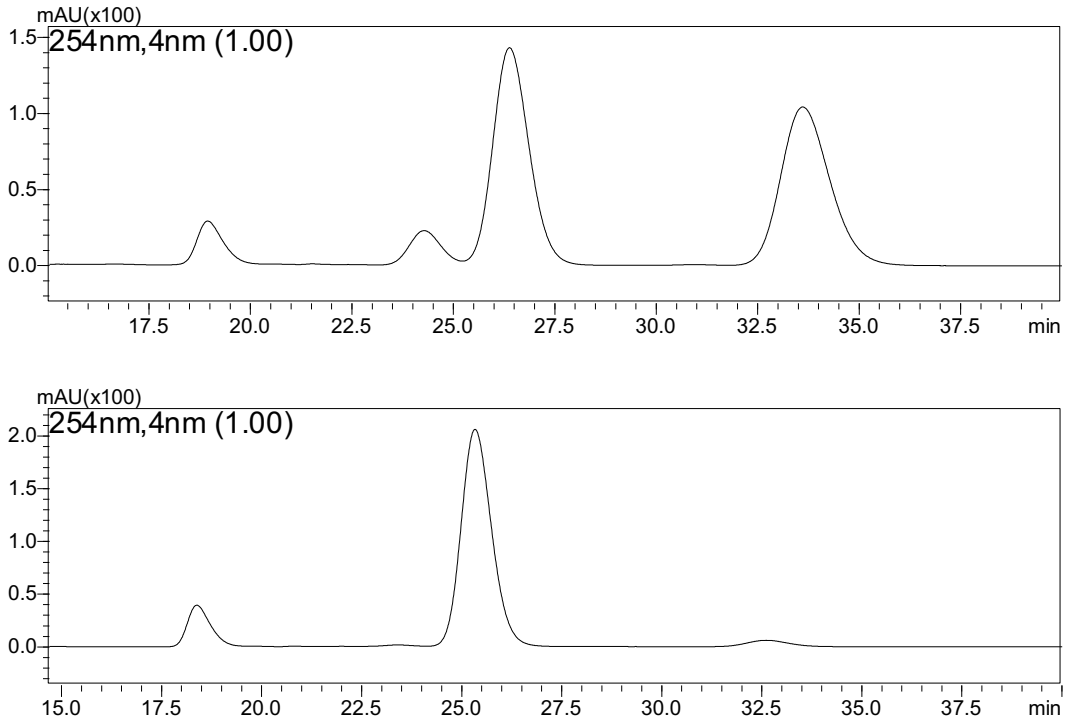


FIGURE 7.94 Chromatograms of compound **2t**.

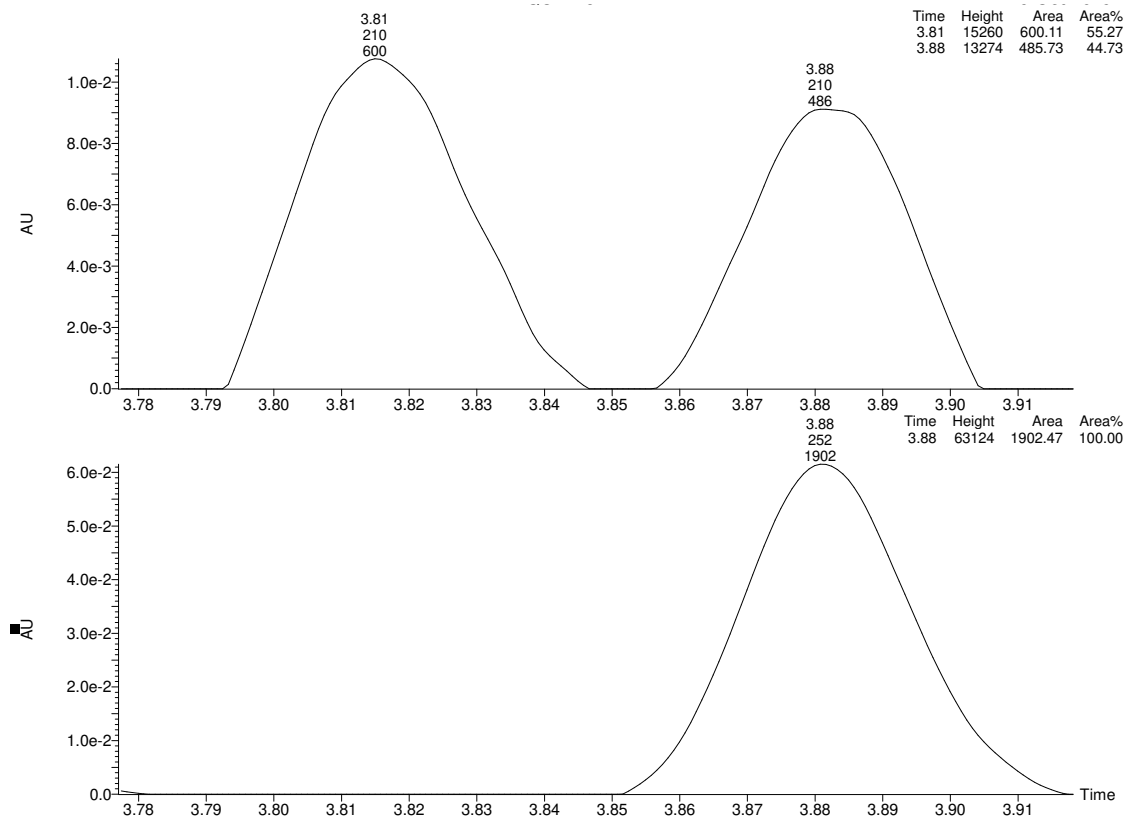


FIGURE 7.95 Chromatograms of compound **2u**.

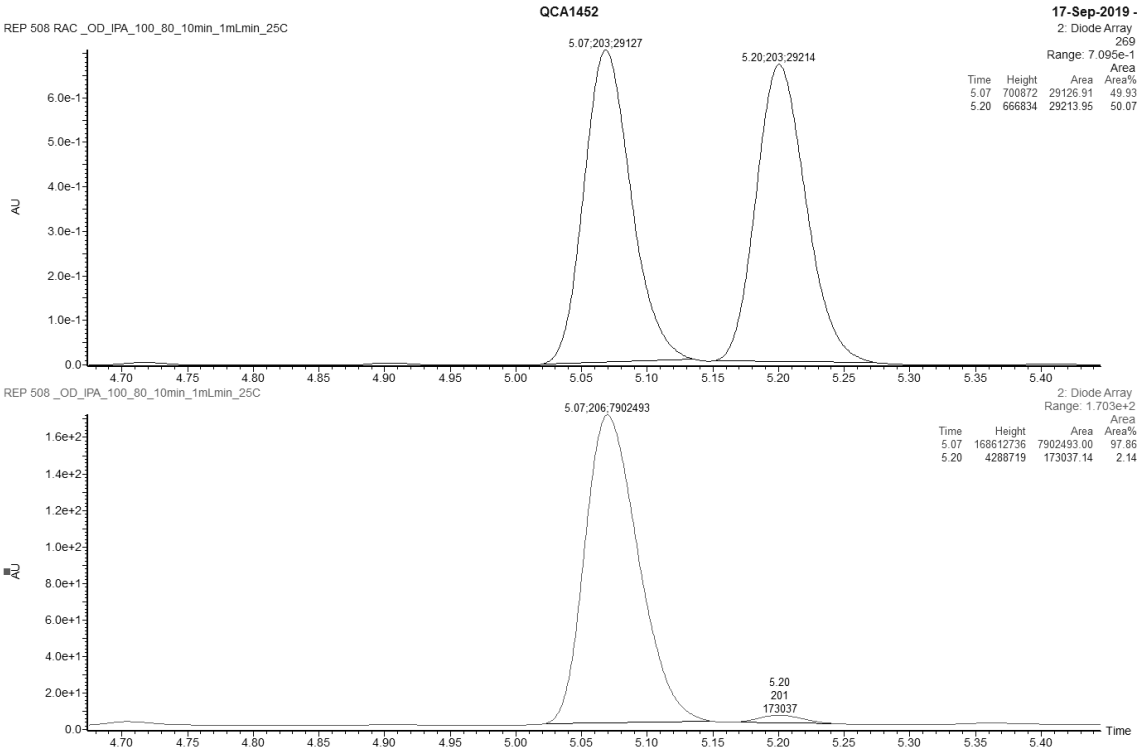


FIGURE 7.96 Chromatograms of compound **2w**.

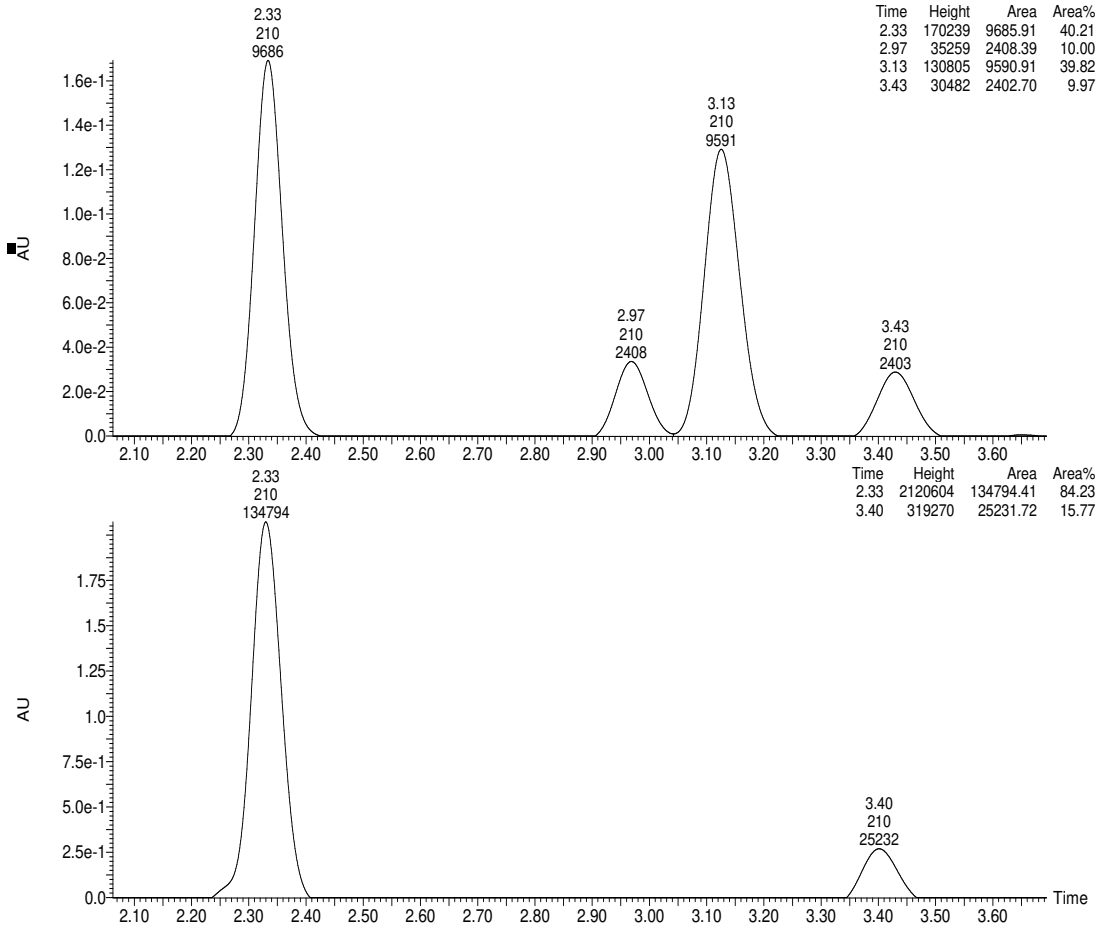


FIGURE 7.97 Chromatograms of compound **2x.**

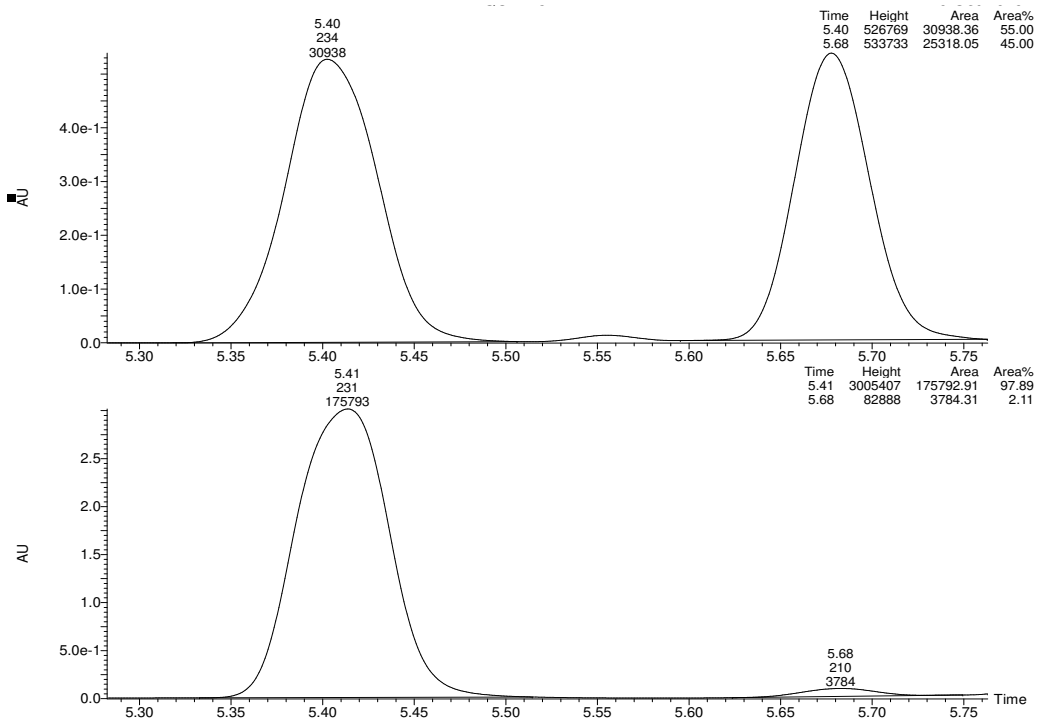


FIGURE 7.98 Chromatograms of compound **2y**.

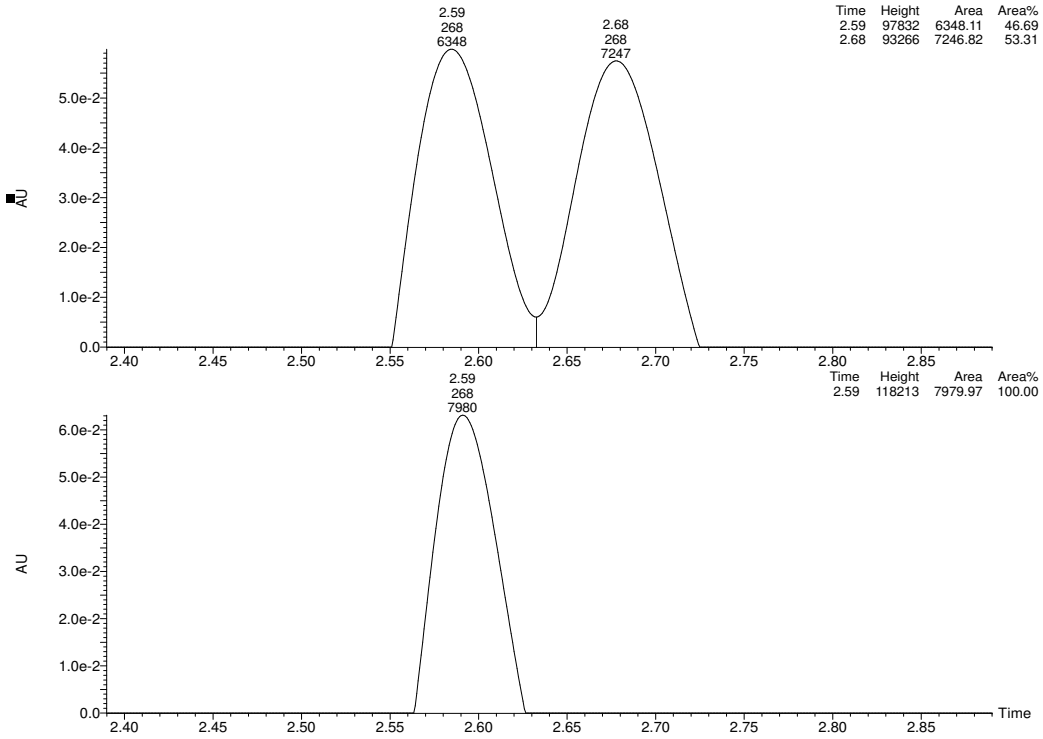


FIGURE 7.99 Chromatograms of compound **2z**.

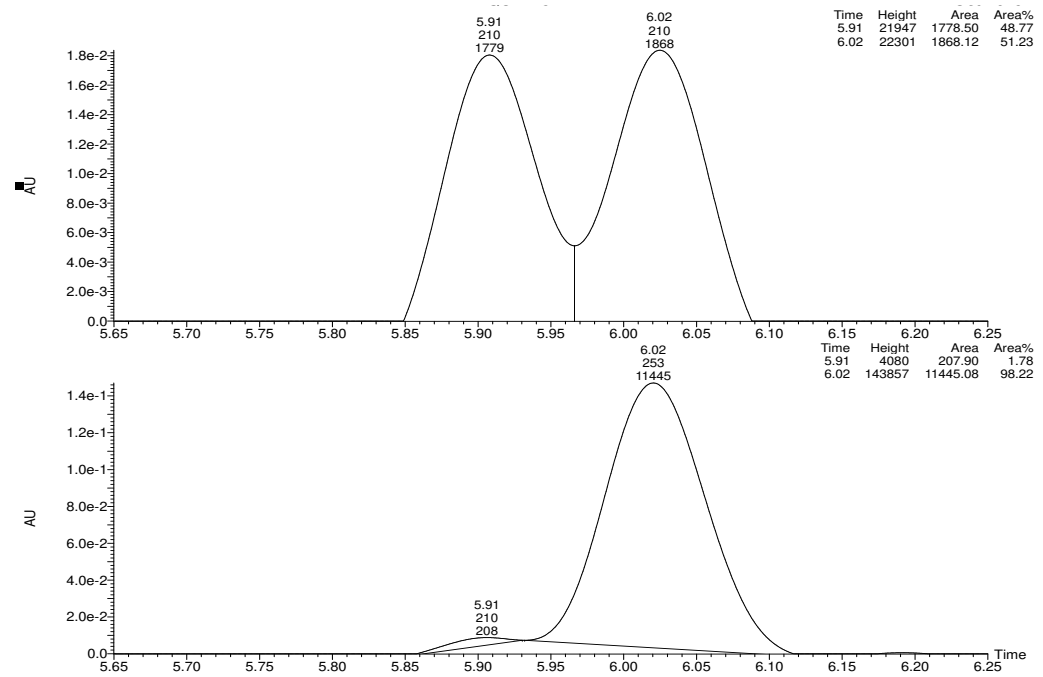


FIGURE 7.100 Chromatograms of compound **2aa**.

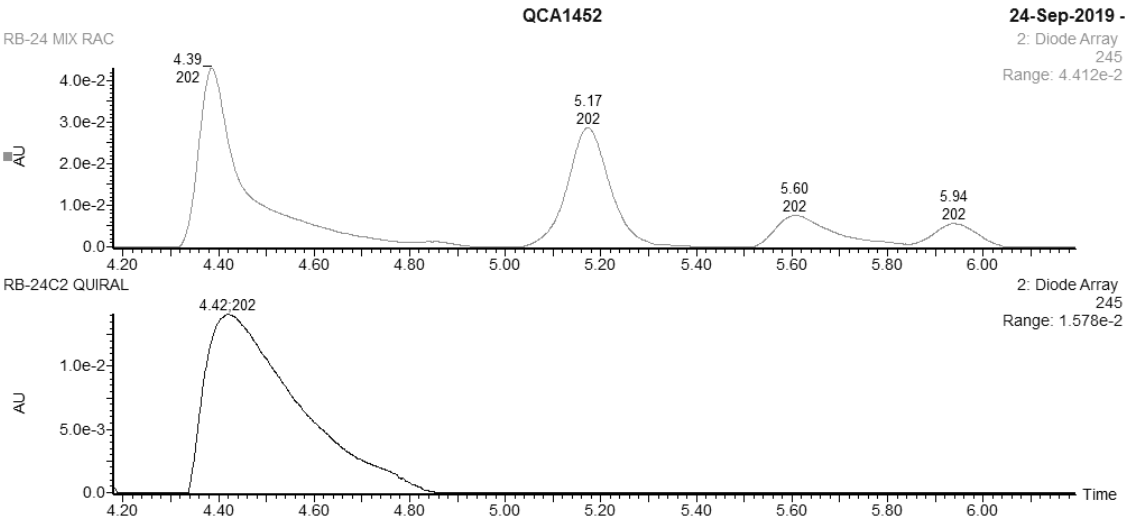


FIGURE 7.101 Chromatograms of compound **2ab**.

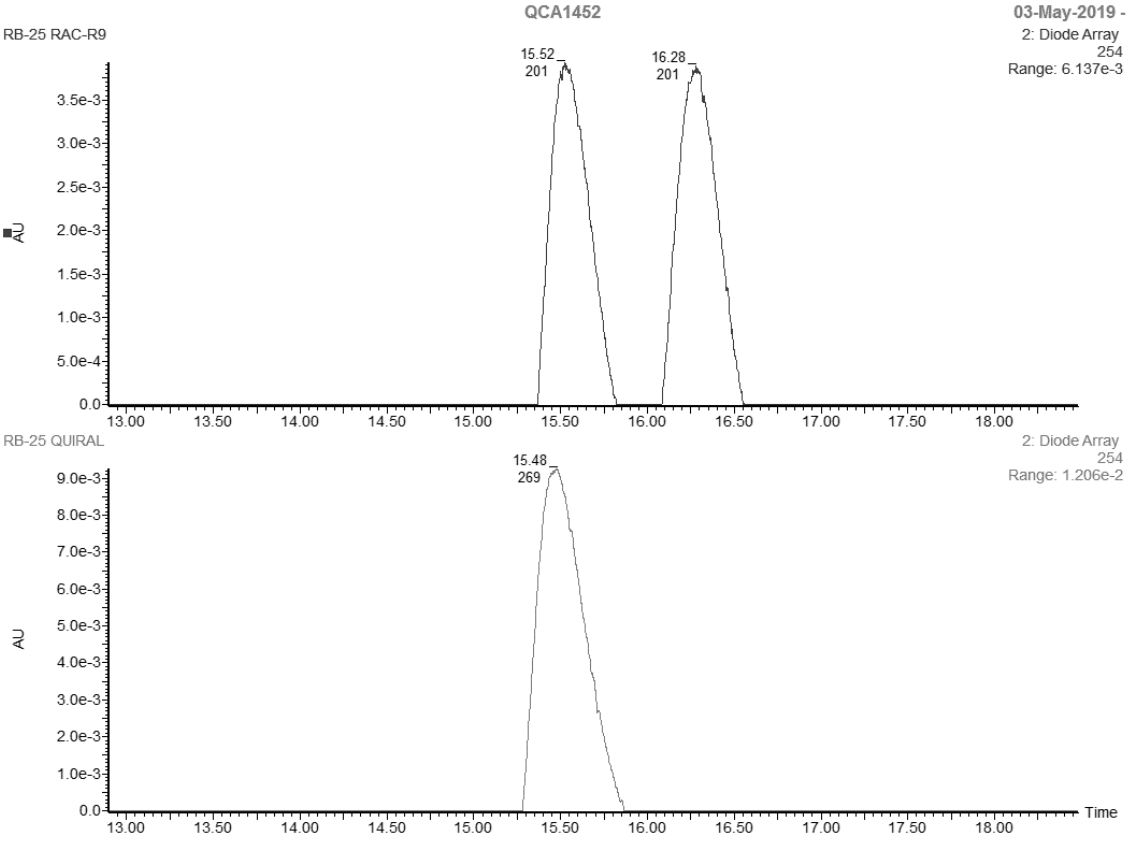


FIGURE 7.102 Chromatograms of compound **2ac**.

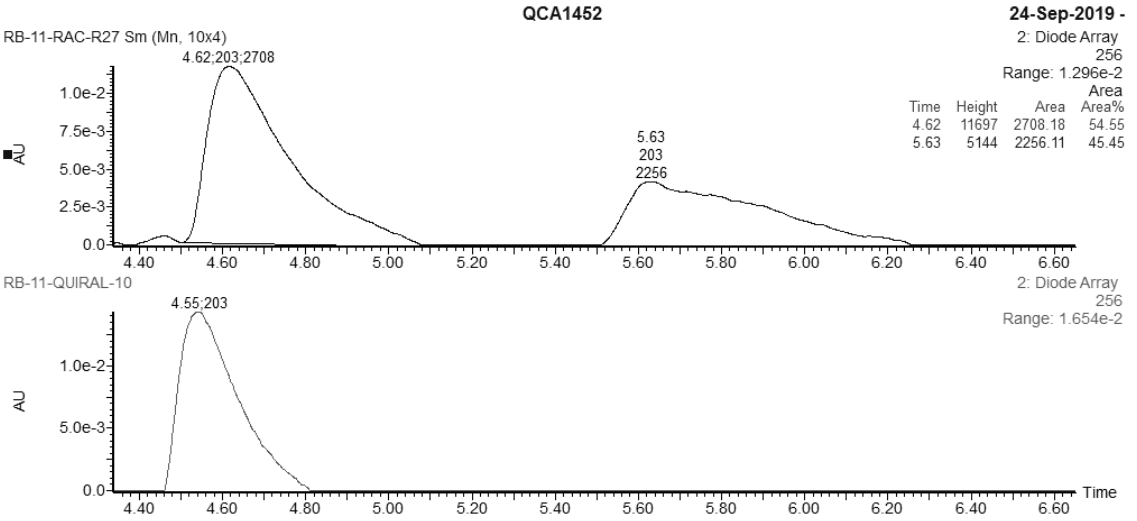


FIGURE 7.103 Chromatograms of compound **2ad**.

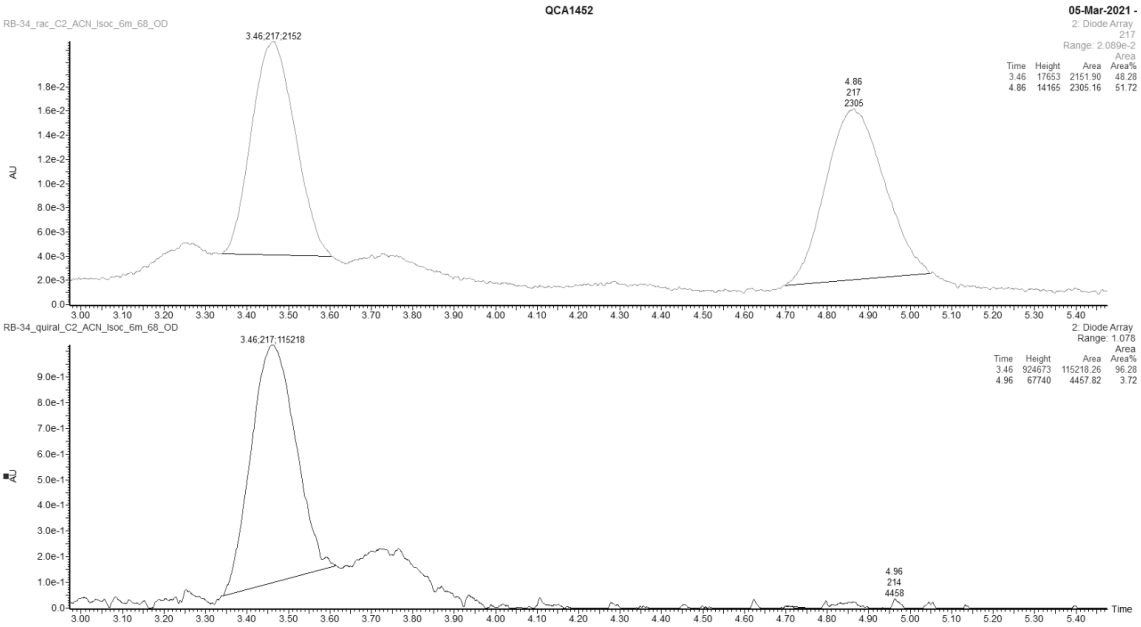


FIGURE 7.104 Chromatograms of compound **2ae**.

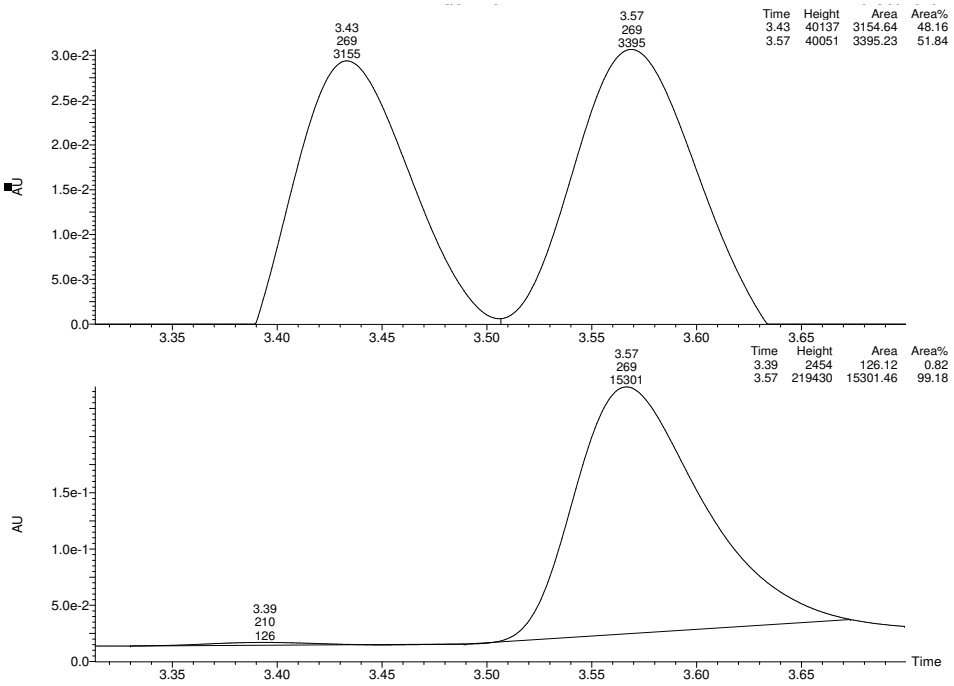


FIGURE 7.105 Chromatograms of compound **2af**.

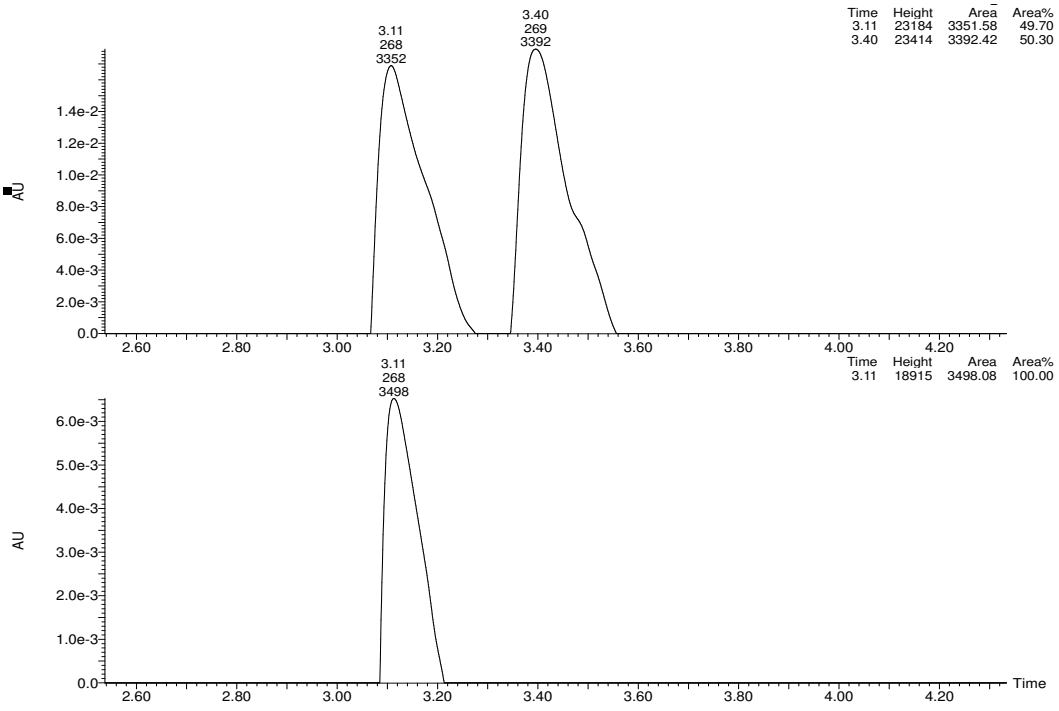


FIGURE 7.106 Chromatograms of compound **2ag**.

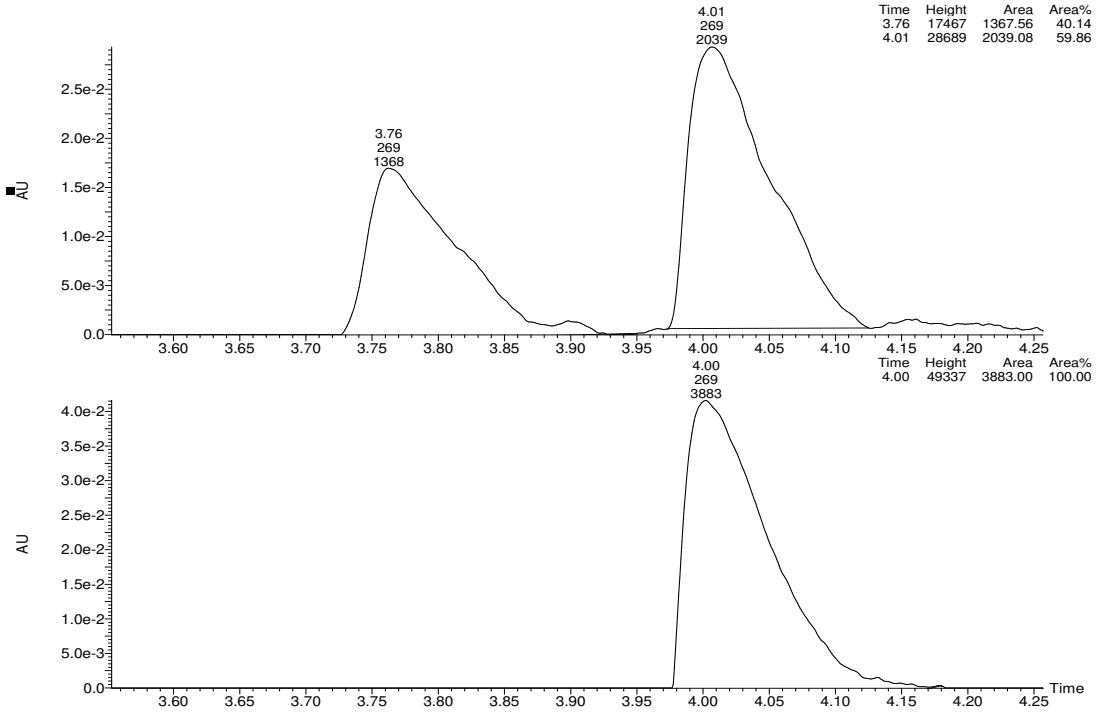


FIGURE 7.107 Chromatograms of compound **2ah**.

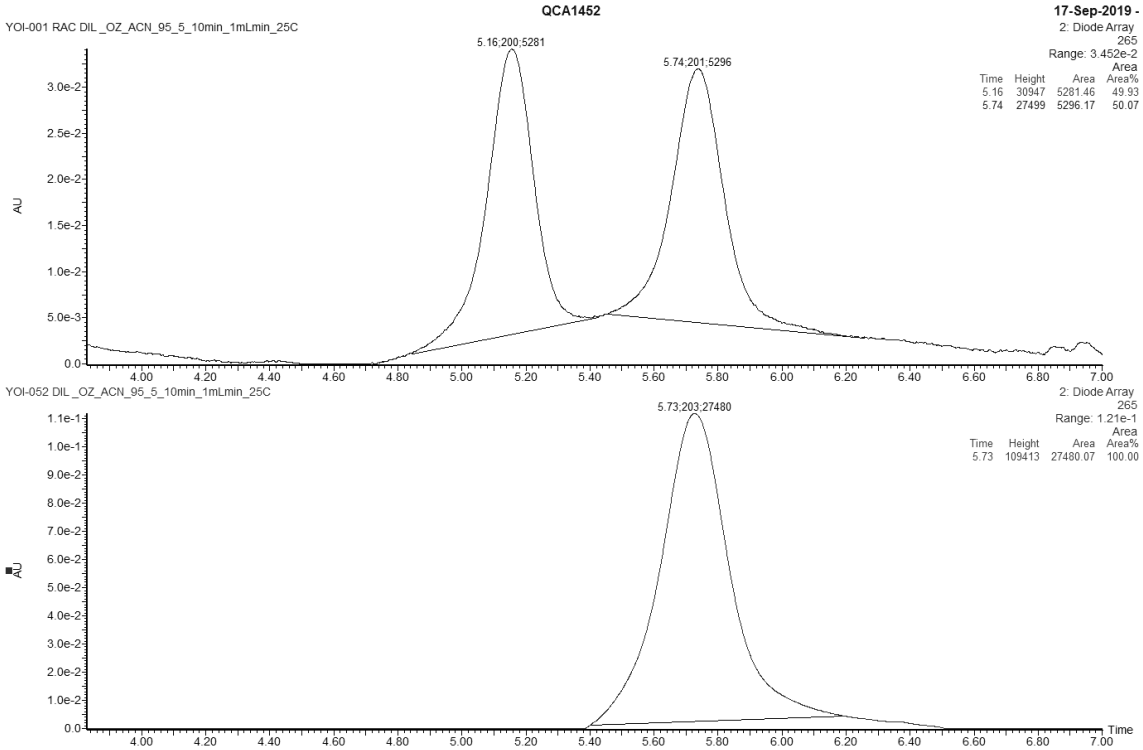


FIGURE 7.108 Chromatograms of compound **2ai**.

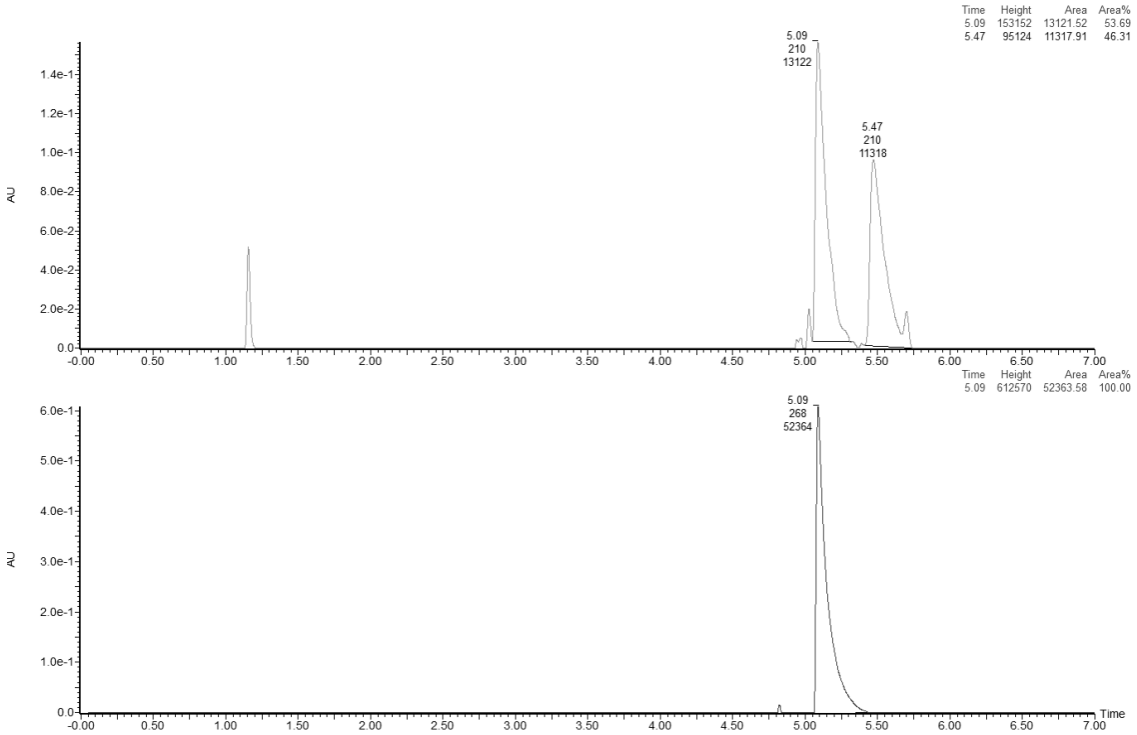


FIGURE 7.109 Chromatograms of compound **2aj**.

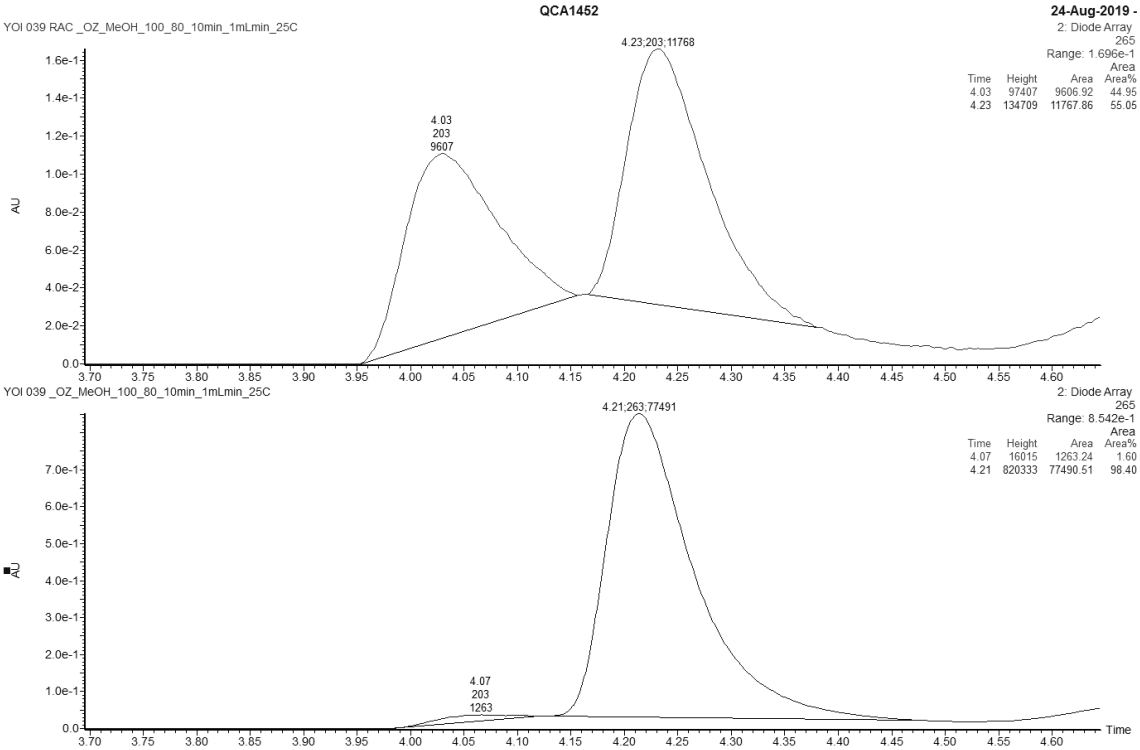


FIGURE 7.110 Chromatograms of compound **2ak**.

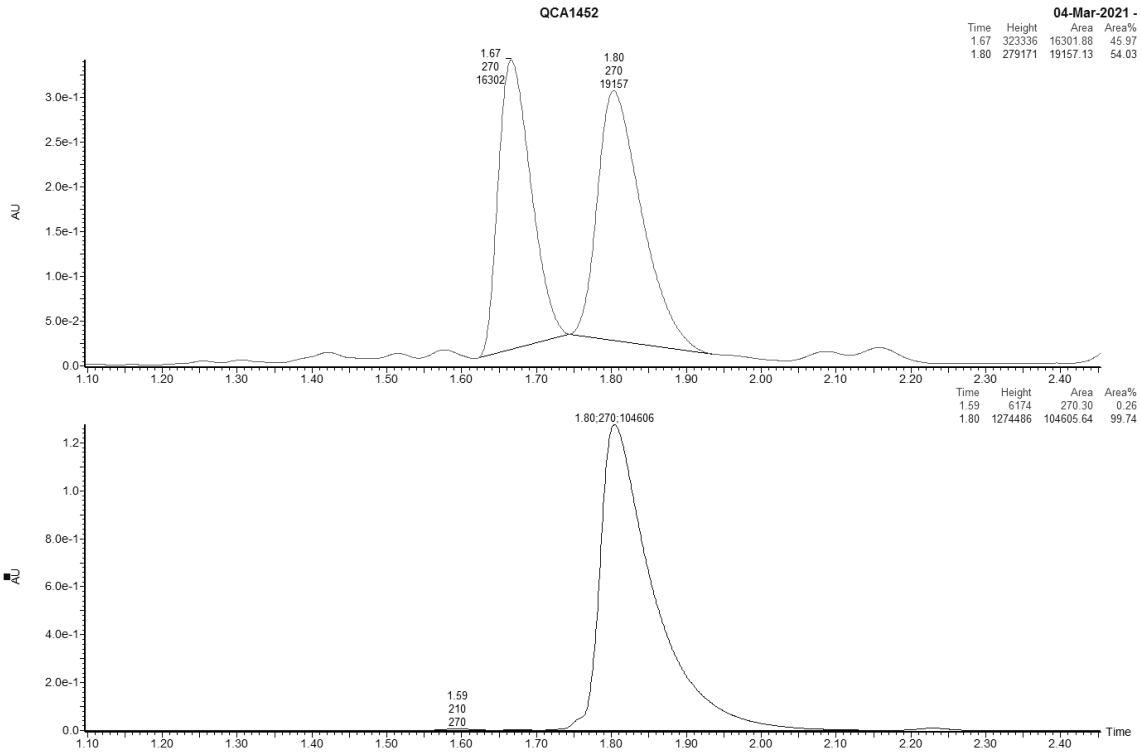


FIGURE 7.111 Chromatograms of compound **2al**.

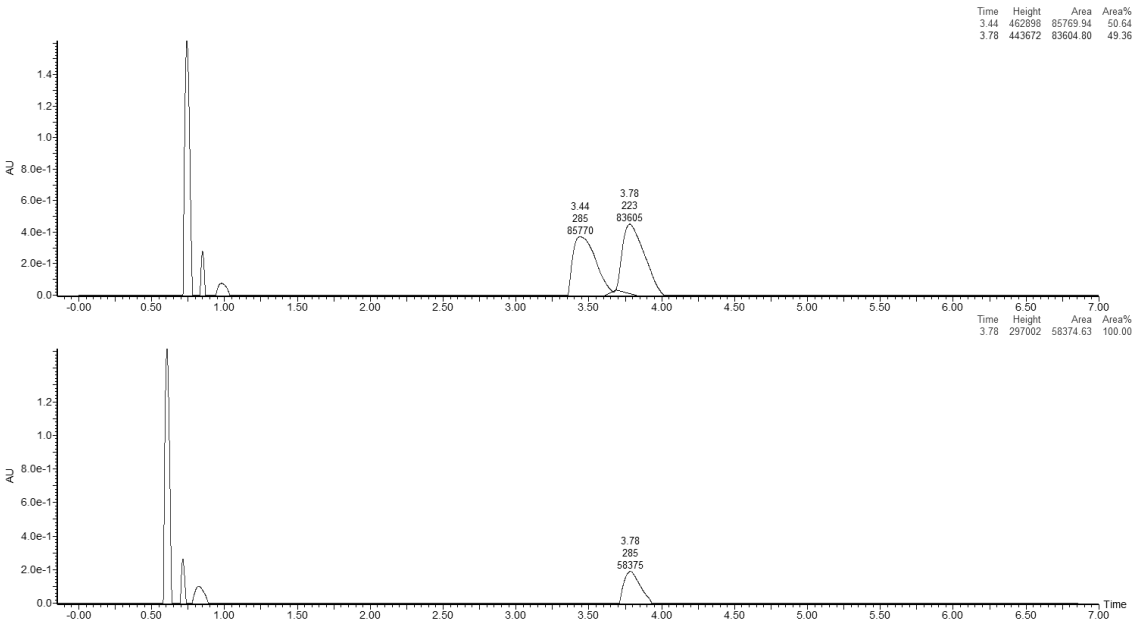


FIGURE 7.112 Chromatograms of compound **2am**.

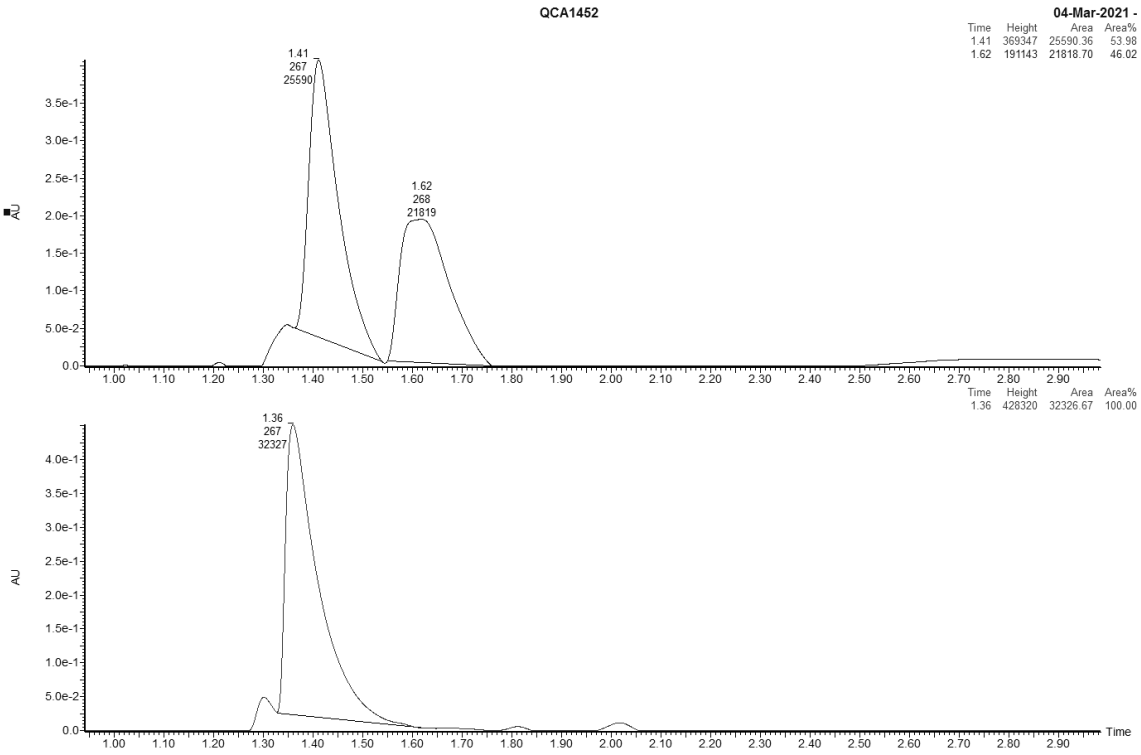


FIGURE 7.113 Chromatograms of compound **2an**.

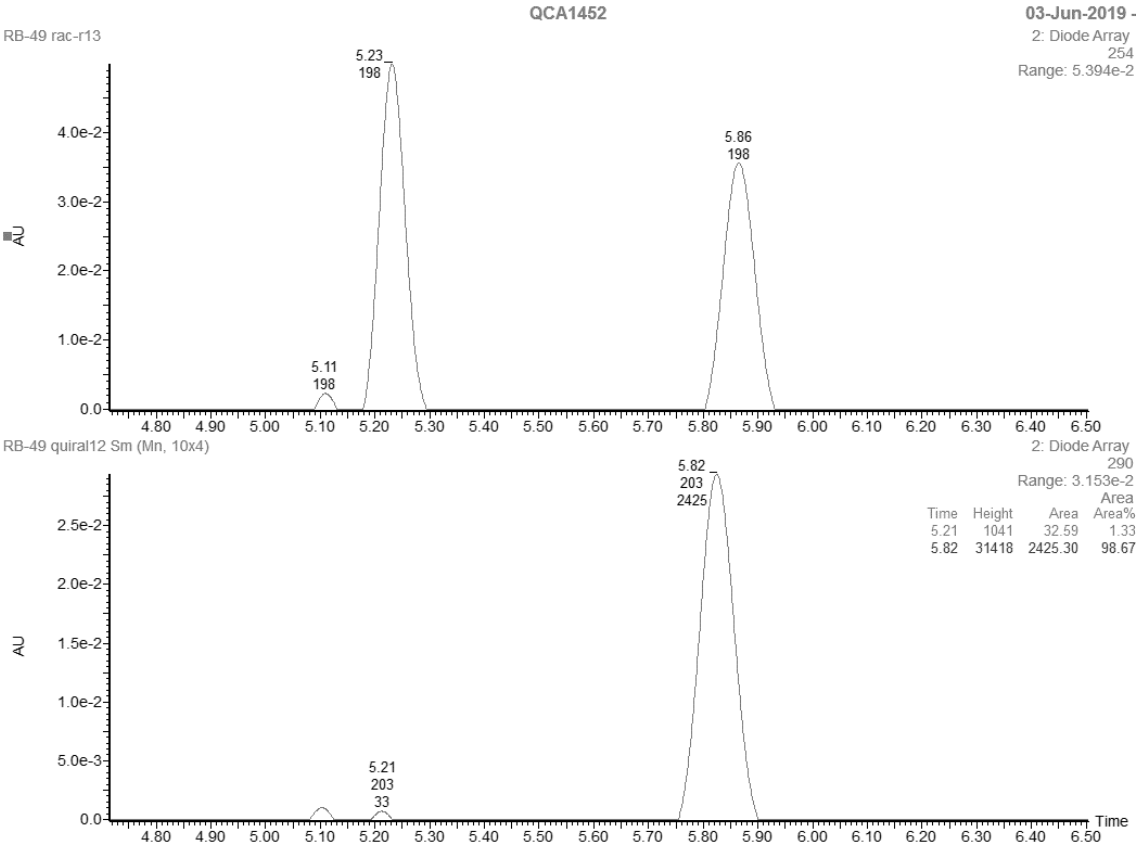


FIGURE 7.114 Chromatograms of compound **3a**.

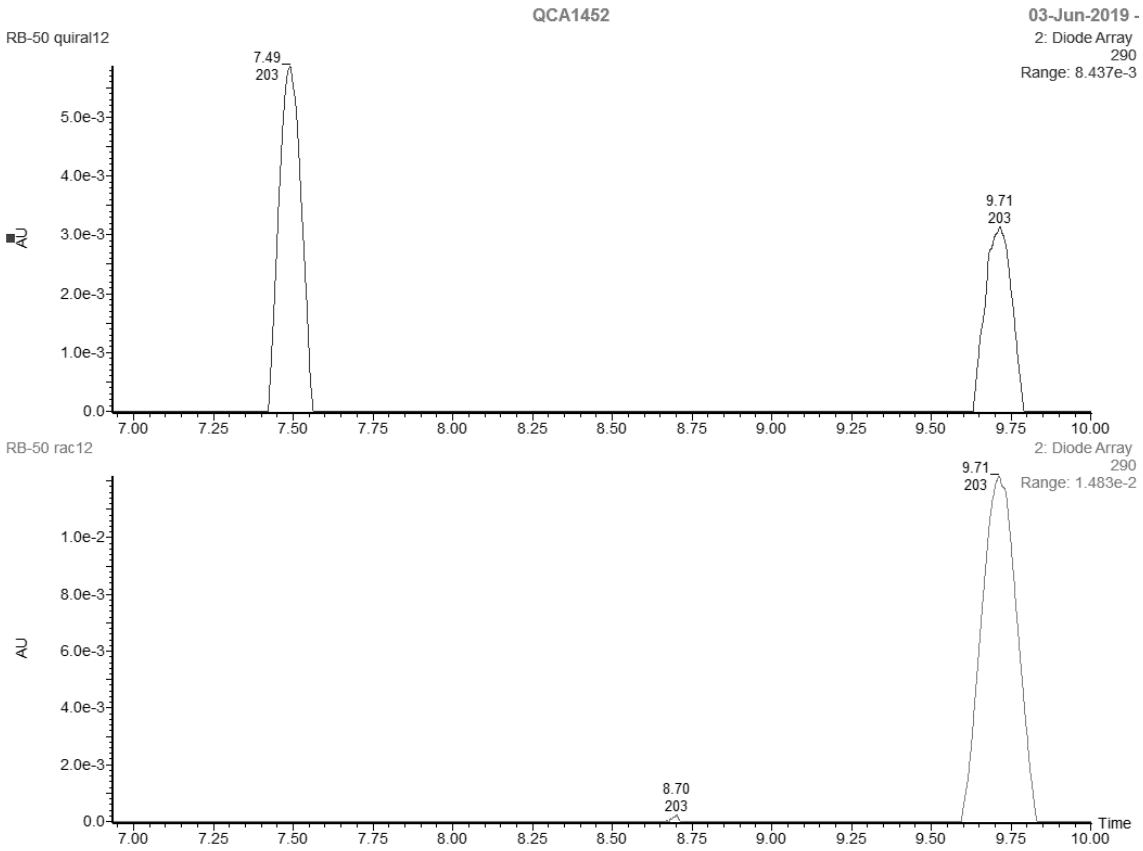


FIGURE 7.115 Chromatograms of compound **3b**.

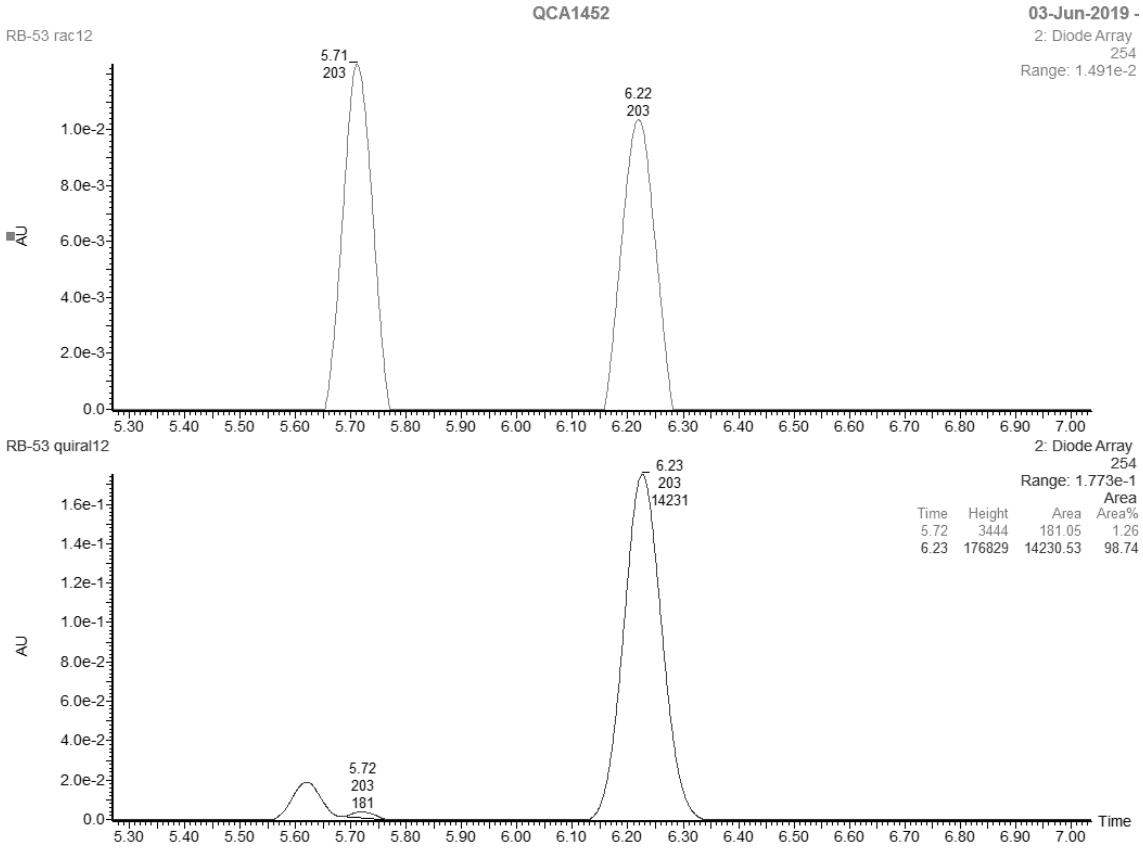


FIGURE 7.116 Chromatograms of compound **3c**.

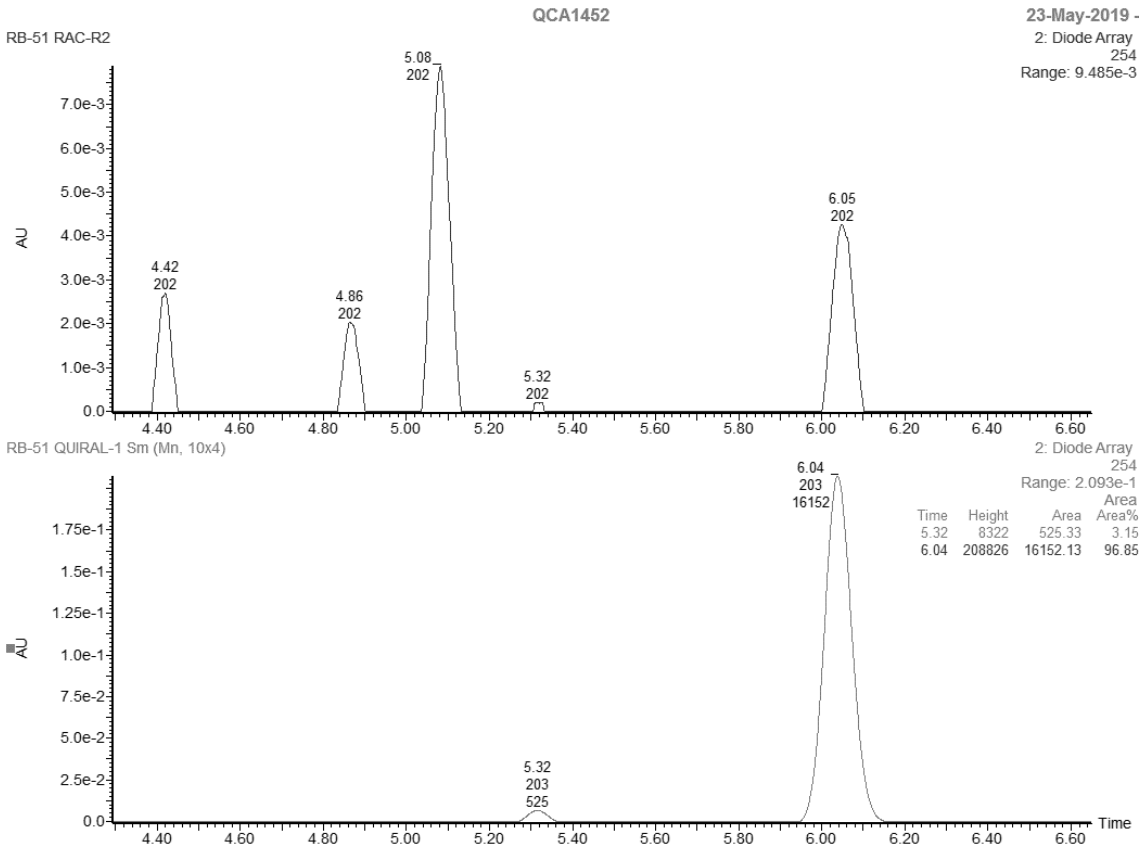


FIGURE 7.117 Chromatograms of compound **3d**.

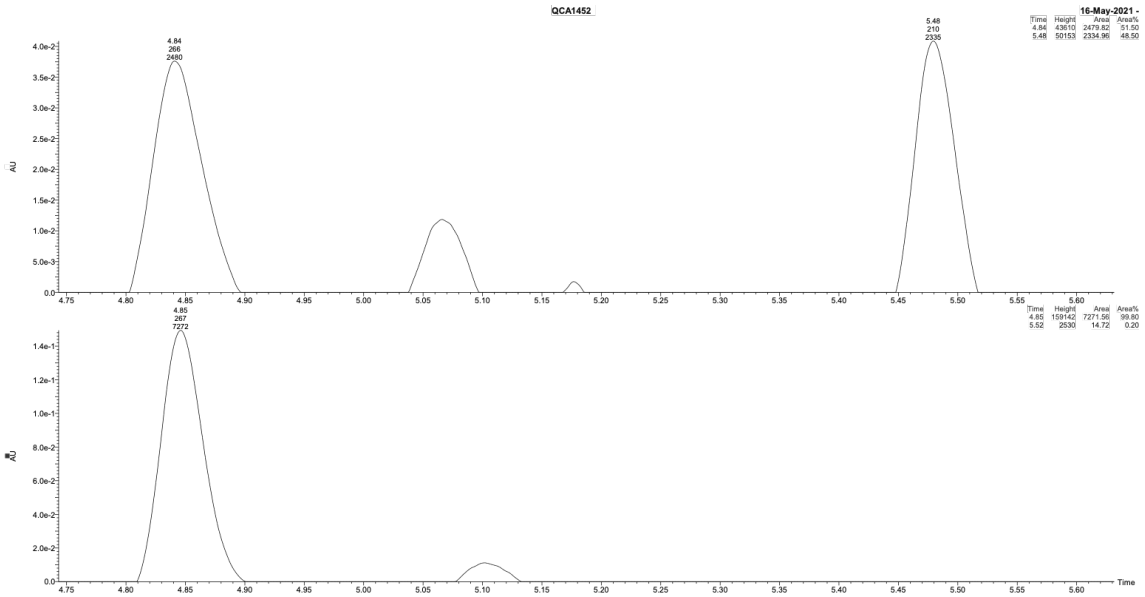


FIGURE 7.118 Chromatograms of compound **4**.