Preface

¨The purpose of this laboratory is to advance the knowledge and apply chemical science for good of the people¨ this motto of National Chemical Laboratory, Pune (India), reflects the impact of chemical sciences on the life of mankind. Although fundamental science may be considered as only of academic interest, it has a great impact on social as well as daily life of the ordinary human being. The purpose of this thesis, along with obtaining Ph. D., was also to make a little contribution to the advances of chemical sciences by applying my creative and tenacious skills in synthetic organic chemistry that could benefit the human race.

The stay in Spain and occasional visits to other European countries like Germany, France and Austria helped me to gain knowledge about the scientific, social and cultural systems being implemented for better living standards of European people. I wish to convey this information to my people in India, at least in my area, so that the ordinary people will be benefited.

This thesis serves as documentation of my research work during the doctoral study, which has been made from October 2002 to January 2006 under the supervision of Professor Claudio Palomo and Professor Mikel Oiarbide in the Departamento de Química Orgánica–I of Universidad del Pais Vasco, San Sebastián, Spain (Europe). The study has been co-funded by Ministerio de Educacion y Ciencia (MEC), and Universidad del Pais Vasco, Spain.

The thesis is divided into six main parts. First part is a literature review of the chirality and impact of chirality on human life and consequent developments in research of academia and pharmaceutical industry. The second part includes a brief discussion of the hypothesis and the objectives of this work. The third part deals with (a) earlier work and importance of Friedel–Crafts (F–C) reaction in organic synthesis, (b) catalytic asymmetric F–C alkylation reactions of pyrrole and indole derivatives including the most important synthetic and mechanistic aspects, and (c) results and discussions of F–C alkylation of pyrrole and indole derivatives with α'–hydroxy enones under Cu(II)–bis(oxazoline) catalysis. Some of the results presented herein were published as a *communication* in *Journal of the American Chemical Society* (Apendix IV). The fourth part deals with the preliminary results obtained in Cu–catalysed conjugate additions of diethyl zinc to α'–hydroxy enones. The general conclusions are presented in the fifth part. The sixth part includes experimental procedures and characterization data for new compounds. Four appendices include crystallographic data for three compounds, several NMR spectra, several HPLC chromatograms and a

publication. Bibliographic references are given at the end of each page and are numbered collectively.

Acknowledgments

I wish to take this opportunity to express my deep sense of gratitude towards my leading supervisor Prof. Dr. Claudio Palomo, for giving opportunity to work in the most competitive field of asymmetric synthesis, although he allowed me the freedom to wander off. Further I would like to thank my co-supervisor Prof. Dr. Mikel Oiarbide for his great co-operation and help, without his advice and unique support this thesis would never had become a reality. I thank to a number of colleagues, although some of them have left the department, who have greatly contributed to good inspiring working and social environment. Special thanks for always helping out goes to the staff at the Department, laboratory assistants and librarians. I would like to thank Dr. Enrique Gómez-Bengoa (UPV, Spain) and Dr. Michael Kelso (University of Wollongong, Australia) for support and discussions.

I remain greatful to Mr. Sanjay Mhaske, Dr. P. Satish Goud, and Mr. Manohar Surve for always encouraging me for pursueing higher education. Thanks for good support, advice and encouragement through ups and downs all those years.

My sincere thanks go to my father, family and friends who have supported me during these most isolated and lonely years of my life. My apologies go to my grandparents for not being with them in their final time.

Finally, I dedicate this thesis to my beloved mother.

Bharat Kardak
San Sebastian
April 2006

List of Abbreviations

aq.	Aqueous
app.	Approximately
cat.	Catalyst
h	Hour(s)
min.	Minute(s)
d	Day(s)
Rt	Retention time (HPLC)
ESI	Electro Spray Ionization (Mass spectrometry)
Rf	Rate of flow (TLC)
Equi.	Equivalent
TES-Cl	Triethly silyl chloride
Ts	*p*-toluenesulfonyl
Tol-binap	bis[2,2'-(di-p-tolylphosphanyl)-1,1'-naphthyl]
Tc	Thiophene carboxylate
BOX/box	bis(oxazoline)
CAN	Cerium (IV) ammonium nitrate
TEA	Triethyl amine
DIPA	*N*,*N*-Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
TMEDA	*N,N,N,N*–tetramethly ethylenediamine
HFIP	Hexafluoro isopropanol
DNA	Deoxyribonucleic acid
GNP	Gross national product
COX–2	Cyclooxygenase-2 enzyme
LUMO	Lowest unoccupied molecular orbital
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PM3	Parametric Model 3

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¨*Highly Enantioselective Friedel–Crafts Alkylations of Pyrroles and Indoles with α'–Hydroxy Enones under Cu(II)–Simple Bis(oxazoline) Catalysis*¨
Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A.
J. Am. Chem. Soc. **2005**, *127*, 4154—4155.

I. Introduction

Origin of chirality at the molecular level

The sequencing of the human genome provides exciting possibilities to explain the complexities of life. But some more basic questions remain unanswered - such as - why the double-helix structure of DNA spirals in a clockwise (right-handed) direction? rather than a left-handed one! And answer lies in the concept of Chirality. Chirality (Greek word for ¨*Handedness*¨) is widespread in nature and is fundamental to life. Chirality of a molecule was first reported in 1815 by the French physicist Jean-Baptiste Biot.[1] However, the first chiral separation, which laid the foundation for stereochemistry, was reported in 1848 by Louis Pasteur.[2] In 1874, Dutch physical chemist Jacobus Hendricus van't Hoff[3] and French chemist Achille Le Bel[4] independently theorised that the molecular basis of chirality, that was first observed by Pasteur, was an asymmetrically substituted tetra-coordinated carbon. Since the discovery, chirality has been the cornerstone of several scientific advances, and is behind the realisation that terrestrial life-forms have evolved to make use of right-handed sugars and left-handed amino acids.

Chirality arises from straightforward geometry−any object that lacks inverse symmetry can exist in two distinguishable mirror images, called enantiomers. Enantiomers belong to the broader class of isomers known as stereoisomers. A pair of chiral molecules that are mirror images of one another and are not superimposable by rotation and translation are enantiomers.

Chirality and life

Although chirality at molecular level might seem to be only of academic interest, it has in fact, a large impact on our daily life. The inherent chirality of living systems dictates extraordinary specificity in the recognition of chiral molecules. Humans and all other living organisms have single enantiomer molecular components.[5] Hence the bioactivity of the two enantiomers of a food ingredient or drug can be totally different.[6]

---

[1] Biot, J. B. *Bull. Soc. Philomath*. Paris, **1815**, 190.
[2] Pasteur, L. *Am. Chim. Phys*. **1848**, *24*, 442.
[3] Van't Hoff, J. H. *Arch. Neerl. Sci. Exactes Nat.***1874**, *9*, 445.
[4] Le Bel, J. A. *Bull.Soc. Chim. Fr.* **1874**, *22*, 337.
[5] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley, New York, 1994.
[6] Sheldon, R. A. *Chirotechnology*; Marcel Dekker, New York, 1993.

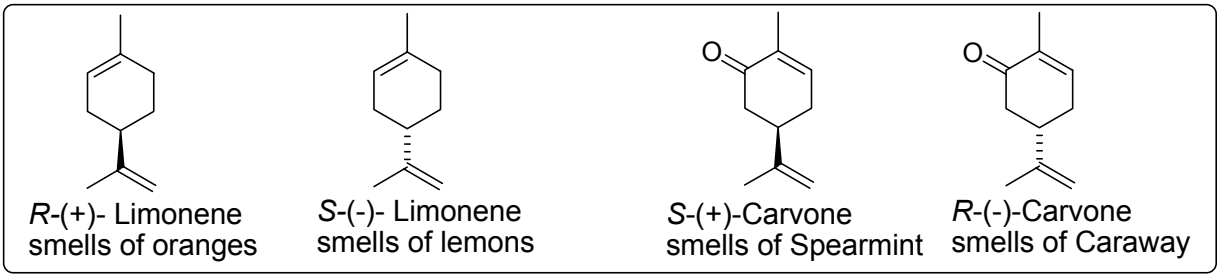


Figure 1: *Enantiomers in daily life.*

The smells of orange and lemon differ in being the right- and left- handed versions of the same molecule, Limonene. Similarly, spearmint and caraway seeds smell quite different (Figure 1). These examples are just the tip of the iceberg. The natural amino acids are all left-handed (L−amino acids). Our enzymes and nucleic acids are predominantly composed of L–amino acids and D–sugars. When interacting, chiral molecules recognise each other just as your right hand distinguishes another right hand from a left when you shake hands. This is why mirror image molecules have radically different fates in our bodies. A simplest example is, our hands are chiral! The right hand is an enantiomer of the left hand, and neither can be superimposed on the other by translation or rotation.

The most famous example of the importance of chirality in pharmaceuticals is probably also the most tragic. *Thalidomide,* a sedative which was prescribed to quell morning sickness in pregnant women in the 1960s affected approximately 10,000 babies due to adverse effect of its *R*–enantiomer. The pharmaceutical industry will not forget the black history of chiral drugs like *Seldane*, *Albuterol*, *Ketamine* either. As a consequence, issues related to chirality have gradually pervaded pharmaceutical chemistry research. It resulted in the FDA (Food and Drug Administration, USA) regulations governing chiral active pharmaceutical ingredients (APIs) (with >30% market share)[7] and consequently the demand from the pharmaceutical industry for optically pure compounds.

Routes to enantiomerically pure compounds

Among several, the most straightforward route to an enantiopure compound is to make use of the chiral pool, i.e. the collection of chiral non racemic compounds which *Mother* nature produces. Natural sources (such as Carbohydrates, Amino acids, Lipids, etc) provide large quantities of enantiopure building blocks, which serve as starting material for synthesis of more complex molecules. This natural homochirality can be a disadvantage

[7] For a review, see: Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788—824.

because the available compound might be the unwanted enantiomer.[8] However, even before Van´t Hoff´s theory about chirality, isolation of single enantiomeric compounds have been developed. In 1848, Pasteur managed to resolve both enantiomers of a salt of racemic tartaric acid by crystallisation.[9] After this pioneering experiment, separation of racemic compounds into their single enantiomers, called resolution,[10] has emerged as one of the most important techniques for obtaining the enantiopure compounds.[11]

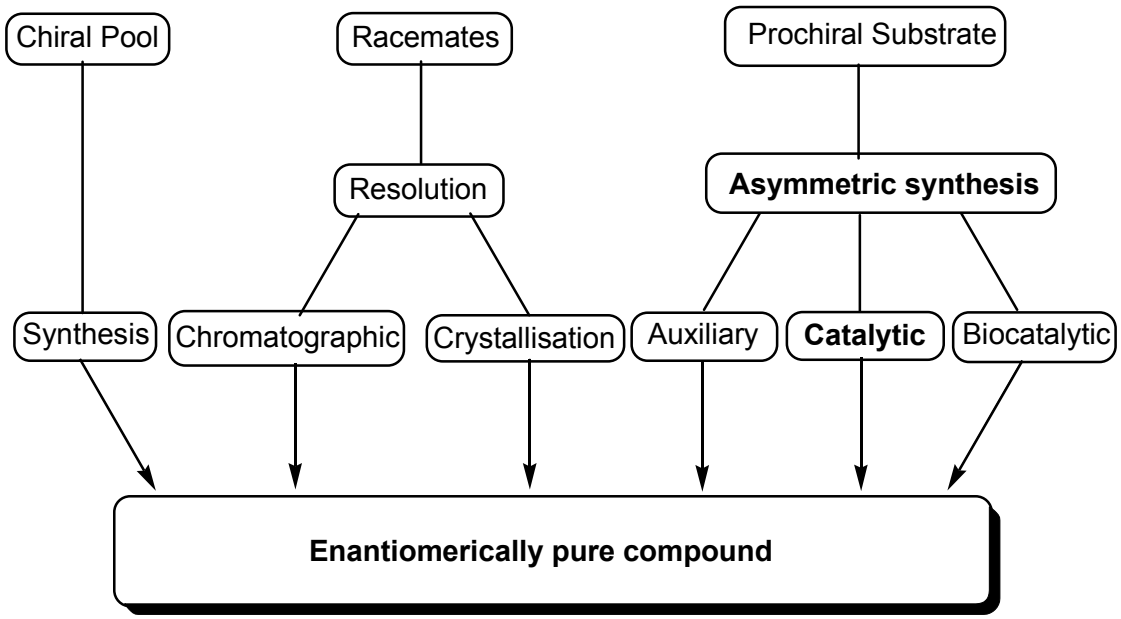


Figure 2: *Routes to enantiomerically pure compounds.*

Chiral chromatographic separations, developed in late 1930s[12,13] is a technique appreciated by chiral drug manufacturers, but only for obtaining gram scale quantities for the preliminary clinical trials. A drawback of crystallisation and chromatographic methods is the maximum yield of only 50%, if the other enantiomer is considered useless. This can be overcome in certain special cases by a (dynamic) kinetic resolution where (*in situ*) racemisation of the starting material can lead to a yield of 100%.[14] In the case of asymmetric synthesis, a prochiral molecule serves as the starting point. In chiral auxiliary approach, a stoichiometric amount of an enantiopure compound is attached to the achiral substrate,

[8] Hanessian, S. *Total Synthesis of Natural Products:The ¨Chiron¨ Approach*; Pergamon Press, Oxford, 1983.
[9] Pasteur, L. *Comp. Rend. Acad. Sci.* **1848**, *26*, 535.
[10] Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley, New York, 1981.
[11] Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2349—2354.
[12] Henderson, G. M.; Rule, H. G. *J. Chem. Soc*. **1939**, 1568—1573.
[13] Klemm, H. L.; Reed, D. *J. Chromatogr*. **1960**, *3*, 364.
[14] van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801—3803.

making the process diastereoselective.[15] However, the drawback is, attachement of the auxiliary and its removal after the reaction adds two extra steps in the synthesis. In a similar fashion stoichiometric amount of chiral reagents can also be employed which will be released from attachement/detachement steps.

In an asymmetric catalytic method, only small amounts of a chiral catalyst is needed to produce a large quantity of chiral product in enantioenriched form from a prochiral precursor. Such reactions are highly productive and economical. The significance of the later approach justified the Nobel Prize in chemistry for year 2001[16] to be awarded to Prof. Sharpless ("for his work on chirally catalysed oxidation reactions¨), Prof. Noyori and Prof. Knowles ("for their work on chirally catalysed hydrogenation reactions"). Biocatalytic methods make use of enzymes and antibodies as catalysts,[17,18] which can be highly selective for specific substrates, but their natural homochirality is an issue when one wants to obtain the non-natural enantiomer. On the other hand, chemical catalysts often accept a broad scope of substrates. In addition, since they are commonly based on (transition) metals modified with enantiopure organic ligands, both enantiomers of a product can be obtained by inverting the configuration of the ligands.

Homogeneous asymmetric catalysis

Catalysis remains a strategic field of chemistry because of its implication in many fields, which include industry, energy, environment, and life sciences. Catalytic technologies have played a vital role in the economic development of the chemical industry in the 20th century, with a total contribution of 20% of world GNP. In the 21st century, we can expect new and exciting opportunities for catalysis and catalytic processes.[19] Homogeneous catalysis is the success story that began with organometallic chemistry initiated by Osborn and Wilkinson[20,21] with the discovery of a rhodium complex, [$(PPh_3)_3$RhCl], as a soluble hydrogenation catalyst for unhindered olefins, and ends with the recent irruption of organocatalysis.[22, 23] With the advent of first powerful ligands (4,5 bis[(diphenylphosphanyl)

[15] Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Catalysis*; Wiley, New York, 1995.
[16] *Current Science*, **December 2001,** *81*, 1519.
[17] Klibanov, A. M. *Nature* **2001**, *409*, 241—246.
[18] Wagner, J.; Lerner, R. A.; Barbas, C. F. *Science* **1995**, *270*, 1797—1800.
[19] Clark, J. H. *Acc. Chem. Res*. **2002**, *35,* 791—797.
[20] Osborn, J. A.; Jardine F.H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A*, **1966**, 1711—1730.
[21] Review: Copéret, C.; Chabanas, M.; Saint-Arroman, R. P.; Basset, J. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 156—181.
[22] Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108—4109.
[23] Review: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2001**, *40*, 3726—3748. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719—724. (c) List, B. *Chem. Commun*. **2006**, 819—824. (d) Berkesel, A.; Gröger, H. In *Asymmetric Organocatalysis*; Wiley–VCH, 2005.

methyl]-2,2-dimethyl 1,3-dioxolane-4,5-diol, DIOP), rhodium complexes served as the basis for development of enantioselective homogeneous catalysis.[24, 25, 26]

To achieve the highest efficiency in catalytic processes, first concern is the design of optimum catalysts, either metallic or purely organic molecules. However, there are two additional directions for research: (a) finding the most appropriate reaction condition (including additives) and (b) finding appropriate achiral templates as reaction substrates. Among the privileged catalysts[27] so far developed are those bearing the chiral ligands depicted below in Figure 3.

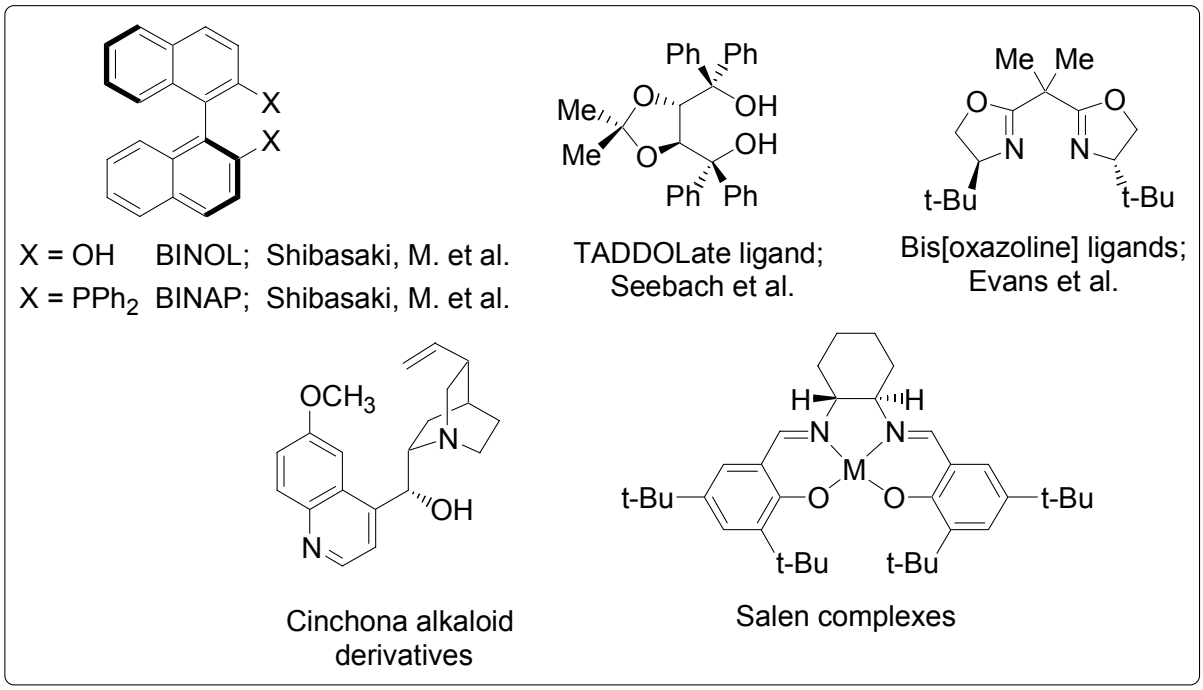


Figure 3: *Privileged ligands in asymmetric synthesis*.

Many carbon-carbon bond-forming reactions employed in organic synthesis are subject to Lewis acid-promoted rate acceleration.[28] Cycloadditions, conjugate additions, and aldol additions are examples of important processes that strongly respond to Lewis acid activation. When the Lewis acid complex is chiral, the stereochemical course of these catalysed processes may be strongly influenced. The `Holy Grail´ in this area is a chiral Lewis acid that exhibits broad generality for more than one reaction family. Since the demands for each reaction family are quite variable, this realisation is not the sole but the exception. The use of previously known chiral catalysts in combination with advanced achiral

[24] Knowles, W. S.; Sabacky, M. J. *Chem. Commun*. **1968**, 1445—1446.
[25] Horner, L.; Winkler, H.; Rapp, A.; Mentrup, A.; Hoffman, H.; Beck, P. *Tetrahedron Lett.* **1961**, *2*, 161—166.
[26] Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4784—4786.
[27] Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691—1693.
[28] Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press, New York, 1996.

templates/substrates is another possibility in this respect. The stereoselectivity in these reactions will be established by manipulating the geometry of the reactive complex by judicious choice of simple, readily available, and easily removable achiral templates, in combination with known chiral ligands and Lewis acids. Some widely employed templates are shown in Figure 4. The bi–dentate templates include α,β–unsaturated N–acyloxazolidinones,[29,30] α,β–unsaturated malonates (alkylidene malonates),[31] β,γ–unsaturated α–ketoesters,[32] α,β–unsaturated acyl phosphonates,[33] α,β–unsaturated imides,[34] α,β–unsaturated heteroaromatic thioesters,[35] and glyoxalates.[36] The monodentate activated carbonyl compounds are aldehydes[37], chlorals,[38] fluorals,[39] α,β–unsaturated aldehydes,[40] α,β–unsaturated ketones.[41] It appears that these substrates have become the

[29] For Cycloaddition reactions, see: (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc*. **1993**, *115*, 6460—6461. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559—7573.

[30] For Cycloaddition reactions, see: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238—1256 and references therein.

[31] For Cycloaddition, Aldol, Michael, and Carbonyl Ene reactions, see: Johnson, J. S.; Evans, D. A. *Acc*. *Chem. Res*. **2000**, *33*, 325—335.

[32] (a) For Domino Michael–Aldol reaction, see: Halland, N.; Aburel, P. S.; Jøergensen, K. A. *Angew. Chem. Int. Ed.* **2004***, 43,*1292—1297. (b) For Friedel–Crafts alkylation, see: Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen. K. A. *Angew. Chem. Int. Ed*. **2001**, *40*, 160—163.

[33] (a) For Diels–Alder reactions, see: Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635—1636. (b) For Friedel–Crafts alkylation, see: Evans, D. A.; Scheidt, K. A.; Frandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10780—10781.

[34] (a) For conjugate addition of cyanide, see: Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442—4443. (b) For Michael additions, see: Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *117*, 4100—4103. (c) For formal Hydration reaction, see: Jacobsen, E.; Vanderwal, C. D. *J. Am. Chem. Soc***. 2004**, *126*, 14724—14725. (d) For radical trapping, see: Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc***. 2005**, *127*, 2390—2391.

[35] For Friedel–Crafts alkylation, see: Bandini, M.; Melloni, A.; Tommasi, S.; Umani–Ronchi, A. *Helv. Chim. Acta* **2003**, *86*, 3753—3763.

[36] For Friedel–Crafts alkylation, see: Jørgensen, K. A.; Zuang, W.; Gathergood, N. *J. Am. Chem. Soc.* **2000,** *122,* 12517—12522.

[37] Reactions for benzaldehyde, see: (a) Adams, S. R.; Kao, J. P. Y.; Grynkeiwicz, G.; Minta, A.; Tsien, R. Y. *J. Am. Chem. Soc.* **1988**, *110*, 3212—3220. (b) Sasakura, K.; Terui, Y.; Sugasawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 1836—1842. (c) Albrecht, K. *Chem. Ber.* **1888**, *21*, 3292.

[38] Reactions for chloral, see: (a) Menegheli, P.; Rezende, M. C.; Zucco, C. *Synth. Commun.* **1987**, *17*, 457—464. (b) Hebert, P. *Bull. Soc. Chim. Fr.* **1920**, *27*, 45—55. (c) Casiraghi, G.; Casnati, G.; Sartori, G.; Catellani, M. *Synthesis* **1979**, 824—825. (d) Fritsch, P. *Lieb. Ann. Chem.* **1897**, *296*, 344. (e) Dinesmann, A. *C. R. Hebd. Seances Acad. Sci.* **1905**, *141*, 201. (f) For Aldol additions see: Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.***1997**, *119*, 10859—10860.

[39] Friedel–Crafts alkylation, see: Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000,** *65,* 1597—1599.

[40] (a) For epoxidation, see: Marigo, M.; Franzen, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6284—6289. (b) For cyclopropanation, see: Kunz. R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240—3241. (c) Friedel–Crafts alkylation, see: Huang, Y.; Walji, A. M.; Larsen, C. H.; Macmillan, D. W. C. *J. Am. Chem. Soc*. **2005**,*127*, 15051—15053.

[41] (a) For Michael addition, see: Shi, M.; Duan, W. L.; Rong, G. B. *Chirality* **2004**,*16*, 642—651. (b) Friedel–Crafts alkylation, see: Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, M.; Trigari, V.; Umani–Ronchi, A. *J. Org. Chem.* **2004,** *69,* 7511—7518.

standard test for new catalyst development, while other achiral templates have been much less investigated.[42]

In this context, α,β–unsaturated carboxylic acids and their surrogates constitute and important type of substrates, given the extreme range of reactions that are susceptible to provide. These achiral templates usually demonstrate good attitudes for catalytic activation and tend to produce well ordered substrate–catalyst complexes. In case of α,β–unsaturated carbonyl compound surrogates, the properties of an ideal ancillary framework are well known: (a) it must enhance the electrophilicity at β–position, (b) it must include suitable functional groups capable of coordinating to the metal center of a Lewis acid, usually through 5–, 6–membered rings, which are highly effective in obtaining rigid complex conformations, and (c) it must be easy to introduce into the starting material and easy to remove from the product, and possibly recyclable. That is why a whole band of templates such as shown in the Figure 4 have been described as equivalents of α,β–unsaturated carboxylic acids, some of them monodentate and some bidentate.

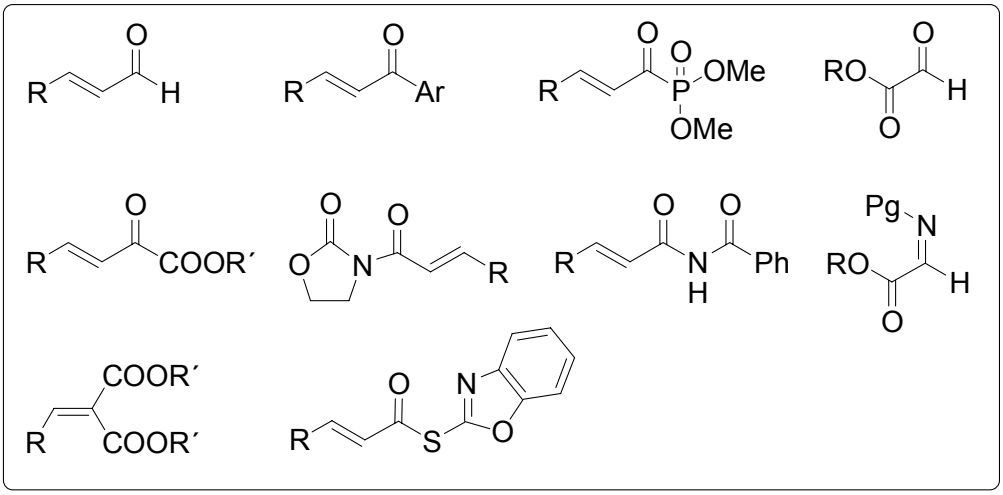


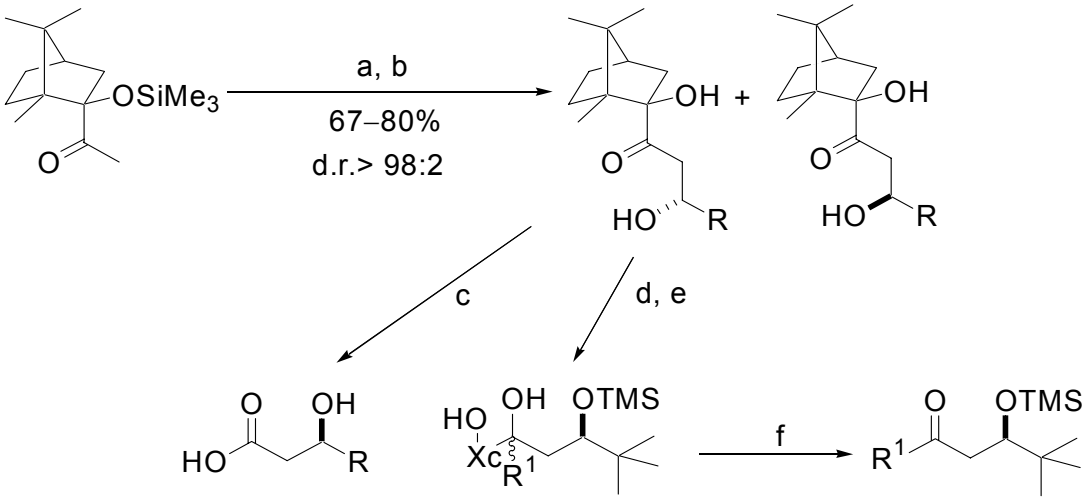
Figure 4: *Available templates for asymmetric catalysis.*

Despite the remarkable templates available, due to diverse needs of each individual reaction family, quest for new, better performing templates/substrates is still providing a driving force to chemists for innovation.

[42] For the use of acrylic acid-derived hydroxamates in enantioselective Diels–Alder reactions, see: (a) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731—1733. (b) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735—1738.

α'–Hydroxy enones as templates in catalysis

Three years before this thesis was initiated, our group reported the design and evaluation of a practical camphor based methyl ketone enolate for highly stereoselective ¨acetate¨ aldol reactions[43] (Scheme 1), inspired in part, in previous work by Heathcock in the area of α–hydroxy ketones in aldol transformation.[44] In this instance, the aldol products, upon oxidative cleavage of the ketol moiety, give the desired β–hydroxy carbonyl system, along with recovery of starting camphor, the source of chiral information.



Scheme 1

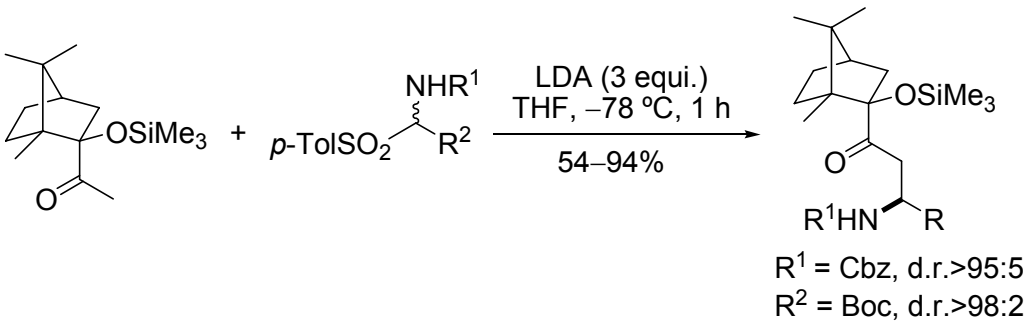
Diastereoselective synthesis of α–unsubstituted β–hydroxy carboxylic acids and ketones: (a) LDA (1.2 equi.), THF, –78 ºC, 0.5 h, then RCHO, 3–7 h. (b) 1 M HCl, MeOH or TBAF (2 equi.), THF, RT, 5 min. (c) $NaIO_4$, MeOH/H_2O (2/1), RT or reflux, 12–48 h. (d) $ClSiMe_2tBu$, imidazole, DMF, RT, 3 days, 86%. (e) R_1MgBr, $CeCl_3$, THF or Et_2O, 0 ºC, 2 h. (f) $Pb(OAc)_4$ (2 equi.), C_6H_6, 5 ºC, 2 h.

In further development from our laboratory,[45] the Mannich reaction (Scheme 2) of lithium enolate of camphor derived methyl ketone with α–amido alkyl sulfones to generate the corresponding β–amino ketones under an analogous stereochemically controlled event, was disclosed.

[43] (a) Palomo, C.; González, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 180—182. (b) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem. Int. Ed.* **2000**, *39,* 1063—1065.

[44] (a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077—7079. (b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290—2300. (c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *ibid.* **1991**, *56*, 2499.

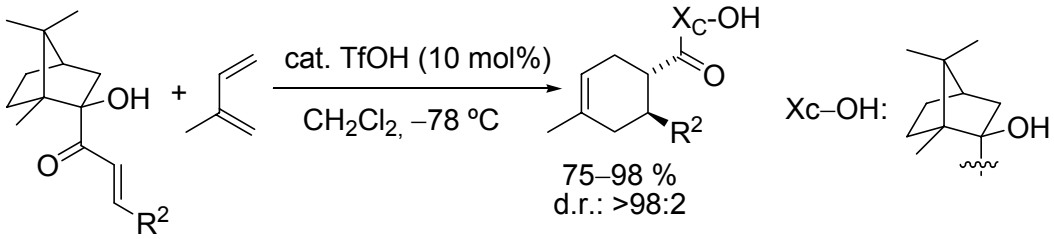
[45] Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem. Int. Ed.* **2000**, *39,* 1063—1065.



Scheme 2: Mannich reaction of lithium enolate of a camphor derived α'–hydroxy ketone.

The idea was further elaborated to the design and synthesis of a novel class of sugar-peptide hybrids by virtue of preparing *C*–linked glyco β–amino acids through a stereoselective "acetate" Mannich reaction.[46] A strategic combination of asymmetric Mannich reaction with a peptide coupling process leading to either β–peptides or α,β–peptides was demonstrated.

Next to this, the idea was extended to the use of α'–hydroxy enones as equivalents of acrylate in organocatalytic Brønsted acid catalysed Diels–Alder reactions (Scheme 3).[47] The remarkable efficiency of these α'–hydroxy enones, even against less reactive dienes, was interpreted on the basis of intermolecular hydrogen bond activation[48] (Figure 5).



Scheme 3: Diels–Alder reaction of α'–hydroxy enones catalysed by TfOH.

However, these earlier developments from our laboratory are dependent on stoichiometric amount of camphor based substrates.

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[46] Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637—8643.

[47] Palomo, C.; Oiarbide, M.; García, J. M.; Gonzalez, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc*. **2002**, *124*, 10288—10289.

[48] For Diels–Alder reactions involving hydrogen-bond complexes, see: (a) Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403—7406. (b) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381—3384. (c) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920—6930. (d) Schuster, T.; Kurz, M.; Gobel, M. W. *J. Org. Chem.* **2000**, *65*, 1697—1701. (e) Atherton, J. C. C.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 8239—8241. (f) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217—220. (g) Corey, E. J.; Shibata, T.; Lee, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 3808—3809.

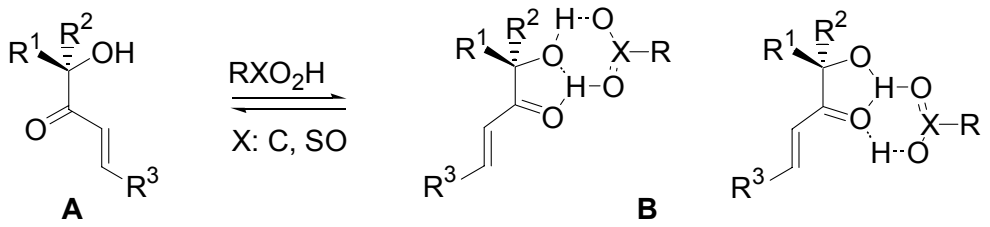
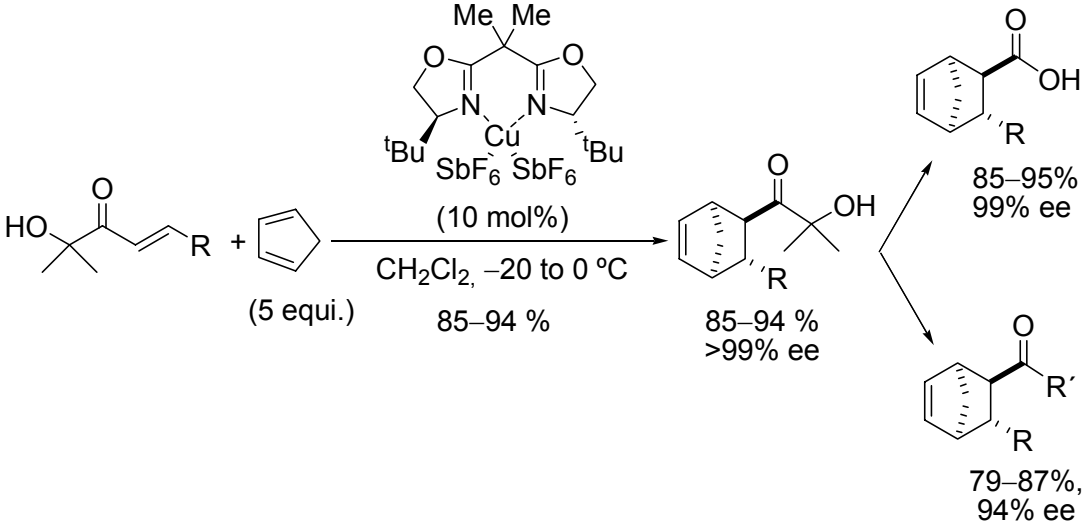


Figure 5: *Working hypothesis that may account for the simultaneous electrophilic activation and rigidification of α'–hydroxy enones by Brønsted acids.*

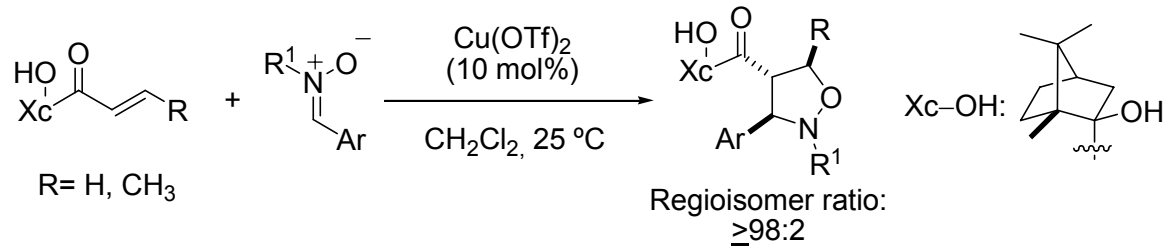
As a further step in the same research direction, our group developed an enantioselective variant of the Diels–Alder reaction that uses achiral α'–hydroxy enone templates and Cu(II)–bis(oxazoline) complexes as chiral catalysts[49] for both β–alkyl and β–aryl substituted enones. The Diels–Alder adducts were further transformed into enantioenriched carboxylic acid and ketone derivatives which is an important aspect of this approach that is of practical interest (Scheme 4). Metal catalysed Diels–Alder reaction using chiral α'–hydroxy enones had been previously described by Masamune,[50] but in his development, the final scission of the ketol moiety led to destruction of the chiral information source.



Scheme 4: Diels–Alder reactions of β–substituted α'–hydroxy enones with cyclopentadiene.

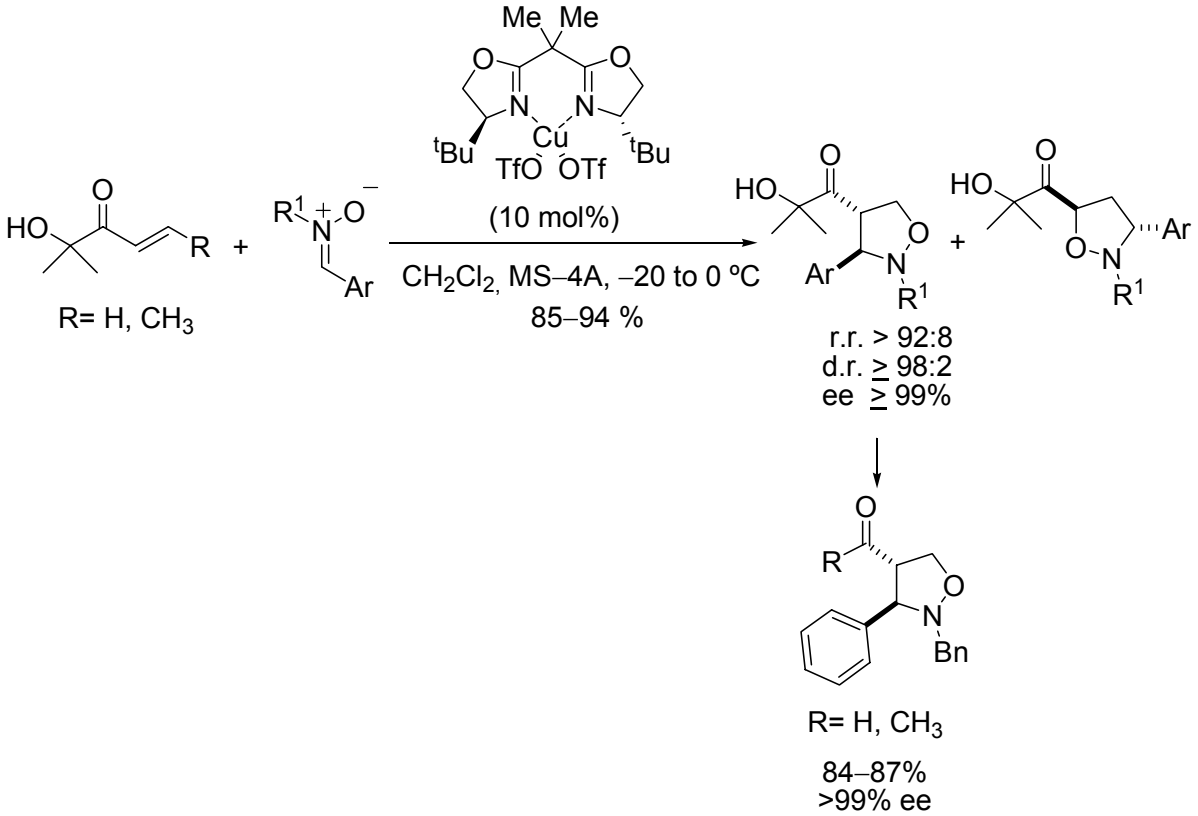
[49] Palomo, C.; Oiarbide, M.; Garcia, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942—13943.
[50] (a) Choy, W.; Reed, L. A. III.; Masamune, *S. J. Org. Chem*. **1983**, *48*, 1137—1139. (b) Masamune, S.; Reed, L. A. III.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441—4444.

In the same research direction, during the time of this thesis work, our group developed an asymmetric variant of the 1,3–dipolar cycloaddition reaction[51] of nitrones and α'–hydroxy enone templates. One method lies on stoichiometric use of camphor derived enones in combination with $Cu(OTf)_2$ (Scheme 5).



Scheme 5: Camphor based α'–hydroxy enone templates in 1,3–dipolar cycloadditions.

The second method is based on the use of achiral α'–hydroxy enone templates and Cu(II)–bis(oxazoline) complexes as chiral catalysts. Excellent diastereoselectivity and enantioselectivity along with regioselectivity were achieved, particularly in the problematic case of β–unsubstituted enoyl systems. The cycloaddition adducts were further transformed into enantioenriched carboxylic acid, aldehyde and ketone derivatives (Scheme 6).



Scheme 6: Regio– and stereoselective cycloadditions of nitrones and α'–hydroxy enones.

[51] Palomo, C.; Oiarbide, M.; Arceo, E.; Garcia, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6187—6190.

The work presented in this thesis is a continuation of previous work by our group as shown in Schemes 1–6, and the aim was to demonstrate the great value of the α'–hydroxy enone motif as a surrogate of α,β–unsaturated carboxylic acids, as Michael acceptors in metal catalysed asymmetric transformations.

2. Hypothesis and Objectives

2.1 Hypothesis

In the pursuit of this plan, we proposed that α'–hydroxy enones can be good bidentate substrates for chelation with Lewis acid metal centers through 1,4–coordination. Previously, work from this laboratory in the context of Cu(II)−bis(oxazoline) catalysed Diels–Alder reaction, as mentioned above, had supported that idea. The general design plan illustrated in Figure 6 highlights the unifying feature of these studies i.e. the substrates undergoing activation must be capable of chelating to the chiral Lewis acid.[52,53] An important outcome of the chelation criterion is that the analysis of the catalyst-substrate complex usually leads to an unambiguous prediction of the sense of asymmetric induction.

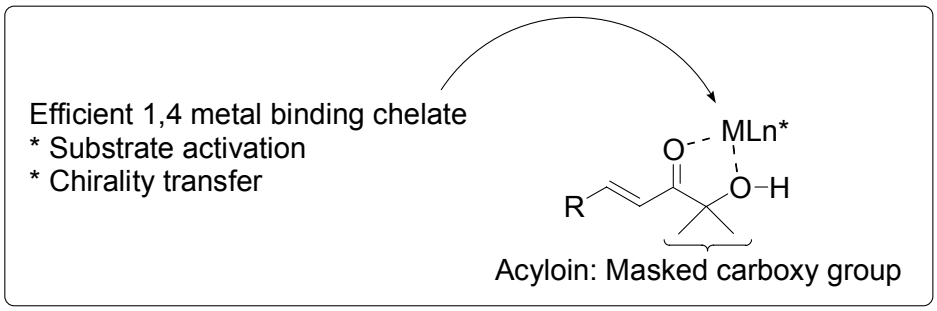


Figure 6: *1,4–Metal binding hypothesis.*

We pursued to validate this 1,4–metal binding hypothesis and, hence, increase the pool of available templates for catalytic, asymmetric reactions. In particular, the aim of the present thesis was to test the above hypothesis in the context of conjugate additions of nucleophilic arenes (Friedel–Crafts alkylation), and of organometallic reagents.

2.2 Objectives

Based on the previous observations from our laboratory and the working hypothesis above, the evaluation of α'–hydroxy enones as Michael acceptors in *C—C* bond forming reactions, viz. Friedel–Crafts alkylations and conjugate additions of organometalic reagents was the general objective. The specific goals at the moment this thesis was initiated were as follows:

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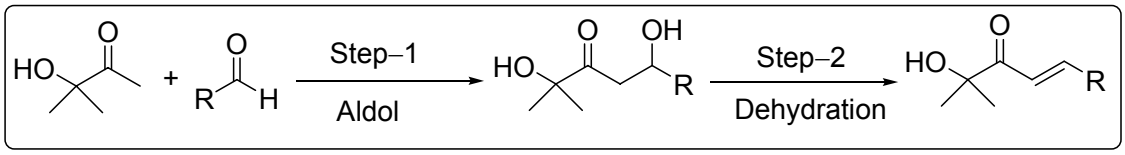
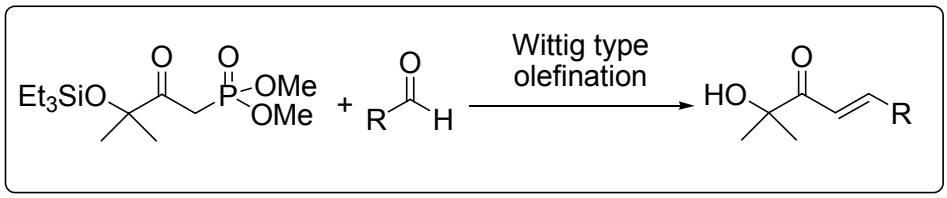
[52] Evans, D. A.; Johnson, J. S. *Acc. Chem. Res*. **2000**, *33*, 325—335 and references therein.
[53] (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26,* 339—345. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1—45.

1) To establish practical conditions for the convenient synthesis of α'–hydroxy enones.

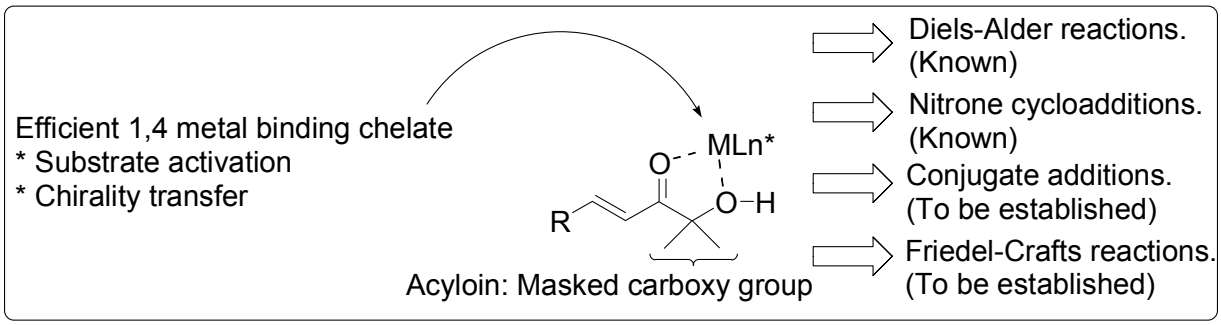
a) An aldol approach from commercially available 3-hydroxy-3-methyl-2-butanone.



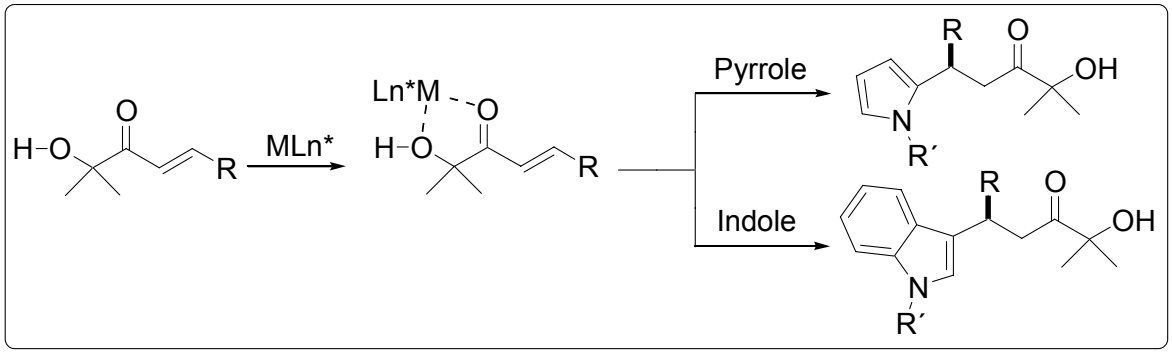
b) A Wittig-type olefination approach starting from (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester.



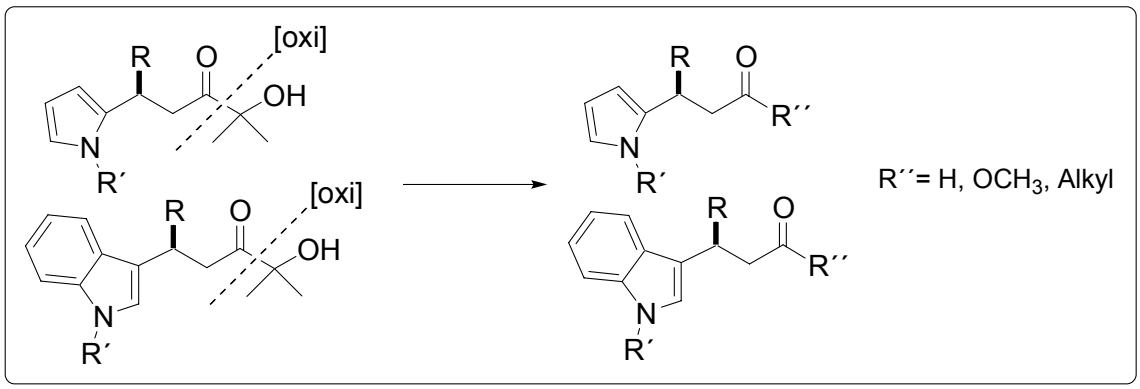
2) To expand the validity of α'–hydroxy enones as achiral templates to different families of catalytic asymmetric reactions.



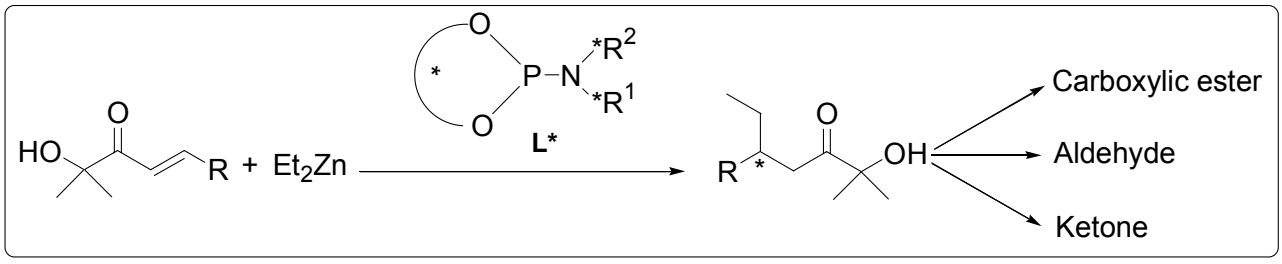
3) To develop an efficient and mild procedure for the catalytic asymmetric Friedel–Crafts reaction of α'–hydroxy enones, setting the best catalytic conditions and the reaction scope.



4) To find suitable oxidation procedures for the scission of the ketol moiety in the F–C adducts as to be capable of synthesising pyrrole and indole containing enantioenriched carboxylic acids, esters, aldehydes and ketones.



5) To find the best chiral ligand for the Cu–catalysed conjugate additions of diethyl zinc to α'–hydroxy enones. Based on previous developments in the area, ligands of general structure **L*** will be tested.



3. Friedel–Crafts Reaction

3.1 General

The catenation power of carbon has empowered the organic chemists with a great tool for construction of organic molecules. The Aldol, Diels–Alder, Michael, and Friedel–Crafts reactions are among the most important atom economic reactions. The Friedel–Crafts (F–C) reaction, since more than 125 years after the pioneering study by Charles Friedel and James M. Crafts,[54] is still one of the most studied and most utilised reactions in organic synthesis.[55] It is one of the oldest organic transformations to employ Lewis acids as promoters. The great versatility in scope and applicability continues to justify its crucial role in the synthesis of more and more complex molecules.[56] Aside from its commercial importance, some of the most interesting aspects are: (a) electrophilic aromatic substitution, (b) carbocation formation, and (c) rearrangement. The alkylation of arenes by alkyl halides, alcohols, cycloalcohols, ethers, esters, alkenes, cycloalkenes, dienes, heterocyclic derivatives (like epoxides, cyclic ethers, aziridines, and lactones), were the early developments in this field.[57] In the last few years, several Lewis acid mediated F–C type additions of electron rich aromatics to electron deficient olefins, in the presence of catalytic or stoichiometric amount of Lewis acid have been published.[58]

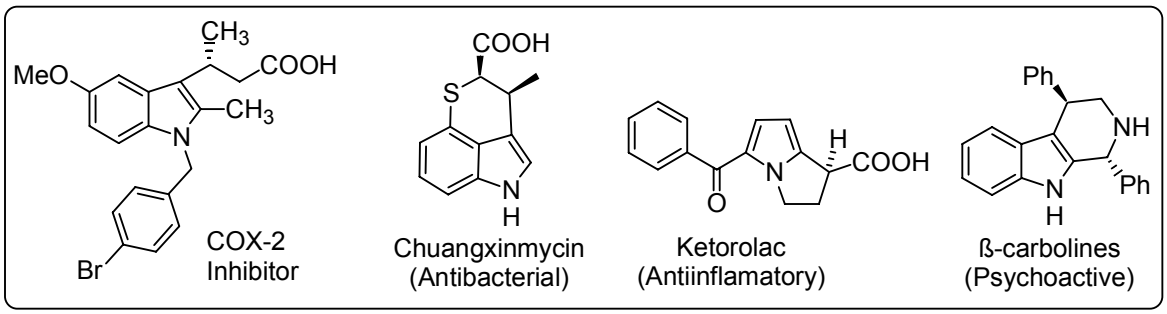
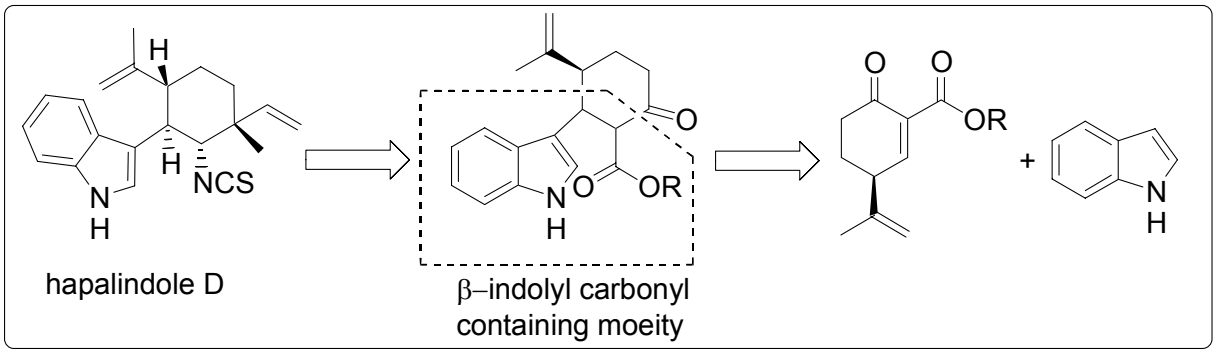


Figure 7: *Important biologicaly active molecules containing pyrrole and indole skeleton.*

[54] (a) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.
[55] Olah G. A. In *Friedel–Crafts and Related Reactions*, Wiley, New York, 1963. (b) Olah G. A. In *Friedel–Crafts Chemistry*; Wiley, New York, 1973.
[56] Review: (a) Bandini, M.; Melloni, A.; Umani–Ronchi, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 550—556. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani–Ronchi, A. *Synlett* **2005**, 1199—1222.
[57] Roberts, R. M., Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry: A Century of Discovery*; Marcel Dekker, New York, 1984.
[58] (a) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani–Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700—3704. (b) Ji, S.– J.; Wang, S.– Y. *Synlett* **2003**, 2074—2076 and references therein.

Among all the aromatic systems suitable for F–C alkylations, nitrogen containing heterocycles play a central role due to their widespread applications in a plethora of research such as material science, agrochemicals, and pharmaceuticals (Figure 7). The synthetic manipulation of N–containing cores is increasing constantly and a great deal of interest is devoted towards the design and development of more efficient alkylations of these heterocycles. In this regard, the indole framework has become widely identified as ¨privileged¨ structure of pharmacophore, with representation in over 3000 natural isolates[59] and 40 medicinal agents for diverse therapeutic action.[60] In this regard, the pioneering work by Kerr et al[61] and later studies by Kobayashi et al[62] underlined the synthetic relevance of the β–indolyl ketone framework in the construction of indolyl alkaloids[63] (Scheme 7).



Scheme 7: Retrosynthetic analysis of hapalindole D leads to the indole and α,β–unsaturated carboxylic acid surrogate moieties.

Since then, the F–C reactions of indoles with electron deficient olefins giving 3–alkylated indoles have been attracting much attention as one important *C—C* bond forming reaction in organic synthesis. However, the coordinating properties of electron rich nitrogen atom center of the heterocycle with the Lewis acidic metal atom needed as reaction promoter, and a natural predisposition of these heterocycles towards oligomerisation in the strong acidic conditions and organic electrophiles, are among the fundamental issues which must be addressed in order to develop mild and more efficient alkylation strategies. Several addition reactions of indoles to electron deficient olefins using Lewis acid and Brønsted acids have been published.[64] Among others, the clay mediated triindolyl compound synthesis,[65]

[59] Based on survey of Beilstein database.
[60] Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*; 4th Ed.; Thieme, New York, 2001.
[61] Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047—1048.
[62] Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174—176.
[63] (a) Moore, R.E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc*. **1984**, *106*, 6456—6457. (b) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331—6342. (c) Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351—6360. (d) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450—7451.
[64] (a) Banik, B. K.; Srivastava, N. *J. Org. Chem.* **2003**, *68*, 2109—2114 and references therein. (b) Venkateshwaralu, Y. *Tetrahedron Lett*. **2003**, *44*, 6257—6260 and references therein.

F–C alkylations in ionic liquid for bis-indolyl compound synthesis,[66] intramolecular F–C cycloalkylations[67] and Michael addition to nitroolefins have been well studied.[68] Hence, the investigation of the chemistry of indoles has been and continues to be one of the most active area of heterocyclic chemistry. Despite the electronic and structural similarity with indoles, pyrroles are not widely investigated for the F–C reaction, probably because of (a) higher reactivity for electrophilic substitution reactions leading to side reactions and (b) polymerisation in acidic conditions.

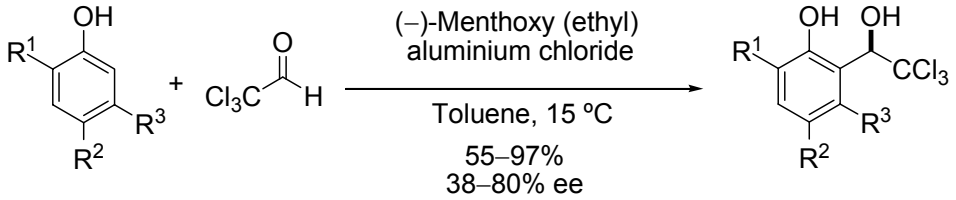
[65] Chakrabarty, M.; Sarkar, S. *Tetrahedron Lett.* **2002**, *43*, 1351—1353.
[66] Zhou, M. F.; Gu, D. G.; Jiang, Z. Q.; Loh, T. P; Ji, S.– J. *Eur. J. Org. Chem.* **2004**, 1584—1587.
[67] (a) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani–Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126—7129. (b) Taylor, S. K.; May, S. A.; Stansby, E. S. *J. Org. Chem.* **1996**, *61*, 2075—2080. (c) Nagumo, S.; Miyoshi, I.; Akita, H.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 2223—2225.
[68] Chakrabarty, M.; Basak, R.; Ghosh, N.; Harigaya, Y. *Tetrahedron* **2004**, *60*,1941—1949 and references therein as: (a) Noland, W. E.; Hartman, P. J. *J. Chem. Soc*. **1954**, *76*, 3227—3228. (b) Noland, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. *J. Chem. Soc*. **1955**, *77*, 456—457. (c) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani–Ronchi, A. *Synthesis* **2002**, 1110—1114.

3.2 Asymmetric Friedel–Crafts reaction

Introduction

Despite its great versatility in scope and applicability to the synthesis of interesting molecules, it has taken more than a century for asymmetric catalytic versions of the F–C reaction to be developed and subsequently extended to a range of aromatic compounds and alkylating agents.[56] Recent developments in the design and use of catalytic and stereoselective strategies for the alkylation of aromatic systems and synthesis of a wide range of polyfunctionalised enantiomerically enriched compounds can be summarised as follows:

In the mid-1980s the first examples of the asymmetric addition of aromatic C—H bonds to carbonyl compounds appeared in the literature[69] (Scheme 8). For the first time, it was hypothesised that, for *C–ortho* regiospecific elaboration of a variety of aromatic molecules, the essence lies in the metal ion which, acting as localised Lewis acid, serves as an activator of the electrophile as well as a stereo-steering group. The hydroxyl alkylation was carried out in the presence of chiral alcohols like (-)-menthyl, (+)-neomenthyl, (-)-borneyl, (+)-sec-butyl, (-)-8-phenylmenthyl, (+)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol, in which (-)-menthyl alcohol was the most effective in terms of stereoselectivity.



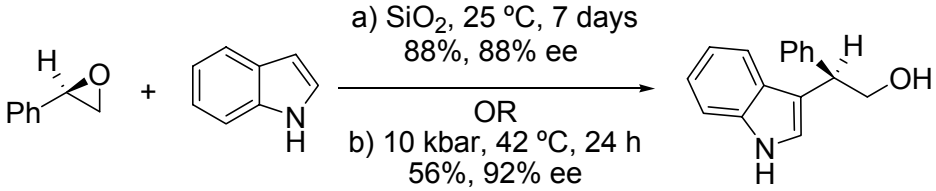
Scheme 8: Asymmetric hydroxyl alkylations of phenols with chloral, assisted by (–)-menthoxy (ethyl) aluminium chloride.

Since this pioneering work, the synthetic relevance of the formation of benzylic carbon stereocenters became an active field of research. The three main cases are: (a) oxirane ring–opening reactions by aromatic compounds, (b) 1,2–additions of aromatic systems to C=O and C=NR groups, and (c) 1,4–conjugate additions of aromatic systems to electron deficient alkenes.

[69] (a) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *J. Org. Chem.* **1985**, *50*, 5018—5022. (b) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem. Int. Ed.* **1990**, *29*, 512—514.

Catalytic stereocontrolled ring-opening of epoxides by aromatic compounds

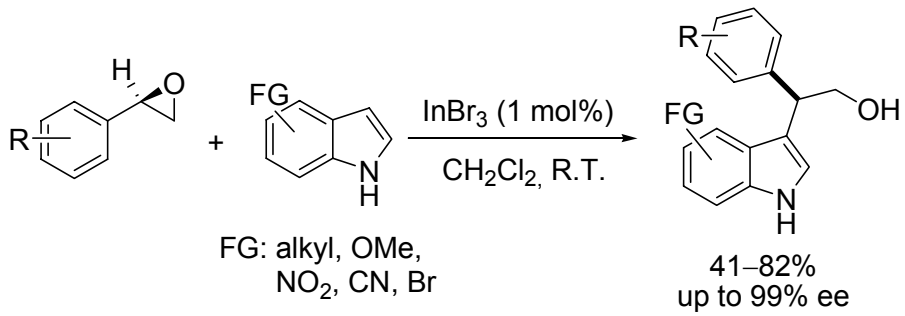
The ring-opening of readily available enantioenriched *cis*- and *trans*- epoxides by aromatic compounds in the presence of Lewis acids, bases, and solid acids is widely recogni¡sed as an effective step in the synthesis of polyfunctionalised compounds.[70] However, only a few examples have been described because of main drawbacks like occurrence of polyalkylation and the frequent absence of regioselectivity. In particular, Kotsuki and co-workers[71] reported the regio– and stereoselective alkylation of indole with (*R*)-(+)-styrene oxide promoted by high pressure or catalysed by silica gel (Scheme 9). Although both approaches guaranteed satisfactory yields, partial racemisation of the enantiomerically pure starting epoxide was observed.



Scheme 9: High pressure and silica-gel-catalysed stereoselective ring opening of epoxide.

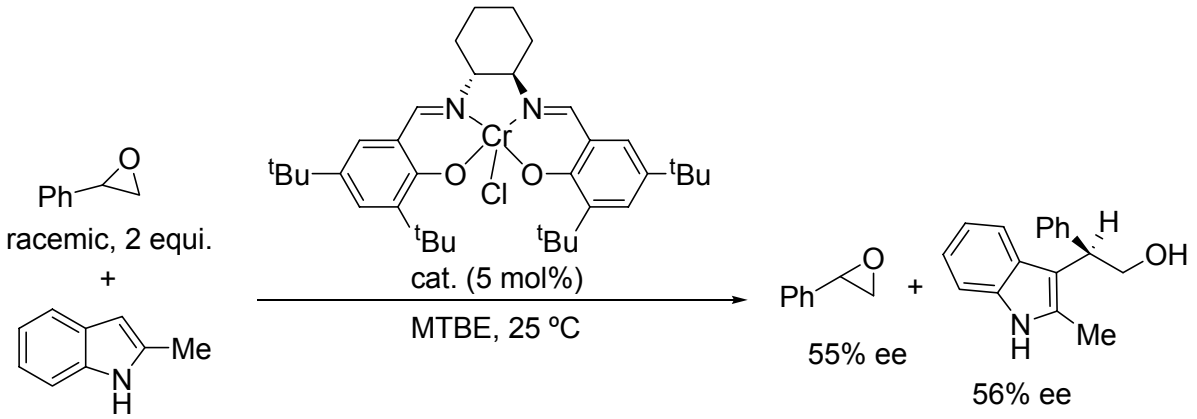
In another example, Bandini[72] and co-workers reported a highly stereoselective alkylation of functionalised indoles with enantiomerically pure aryl epoxides in the presence of anhydrous $InBr_3$ (Scheme 10). The reaction, which proceeds exclusively through a regio− and stereoselective S_N2–type pathway at the benzylic position of the epoxide, allows a number of β–3–indolyl alcohols to be isolated in high yields and with up to 99% ee.

[70] For representative examples of Lewis acid catalyzed ring-openings, see: (a) Taylor S. K.; May, S. A.; Stansby, E. S. *J. Org. Chem*. **1996**, *61*, 2075—2080. (b) Reddy, R.; Jaquith, J. B.; Neelagiri, V. R.; Saleh-Hanna, S.; Durst, T. *Org. Lett*. **2002**, *4*, 695—697. (c) Nagumo, S.; Miyoshi, I.; Akita, H.; Kawahara, N. *Tetrahedron Lett*. **2002**, *43*, 2223—2226.
[71] Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, H. *J. Org. Chem.* **1996**, *61*, 984—990.
[72] Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani–Ronchi, A. *J. Org. Chem*. **2002**, *67*, 5386—5389.



Scheme 10: $InBr_3$ catalysed regio− and stereoselective ring-opening of optically active epoxides.

More advanced is the use of achiral substrates or meso forms in combination with a chiral catalyst. In this context, Bandini and co-workers further developed[73] the first catalytic asymmetric resolution of racemic internal aromatic oxiranes through a carbon–carbon bond forming reaction. It was found that 2-methyl indole reacts smoothly and regioselectively with (±)-styrene oxide in the presence of a catalytic amount (5 mol%) of the commercially available [Cr(salen)Cl] complex (salen=N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine) to afford both the unreacted styrene oxide and the indolyl derivative with moderate enantiomeric excess (55% and 56% ee, respectively) (Scheme 11).

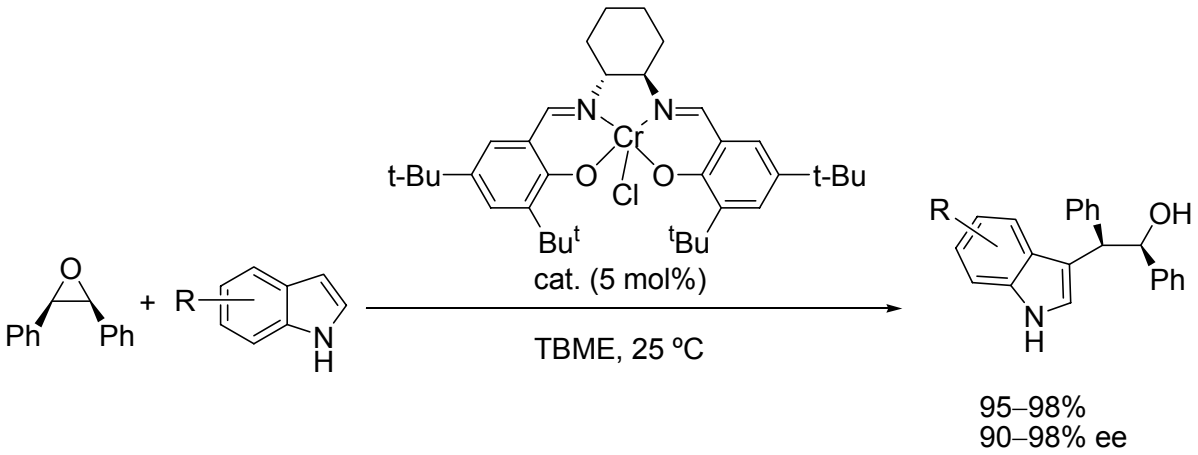


Scheme 11: Kinetic resolution of racemic epoxides catalysed by [Cr(salen)X] complexes.

By careful tuning of the conversion of the kinetically controlled step, the protocol allowed functionalised internal *cis*- and *trans*- epoxides to be prepared in enantiomerically pure form (up to 99% ee) and in moderate yields. Moreover, the [Cr(salen)Cl] was also found able to promote the desymmetrisation of meso stilbene oxide in the presence of variously

[73] Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani–Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 84—87.

substituted indoles. The desired β-indolyl alcohols were isolated in excellent chemical yields and optical purities (up to 98% yield, up to 98% ee) (Scheme 12).

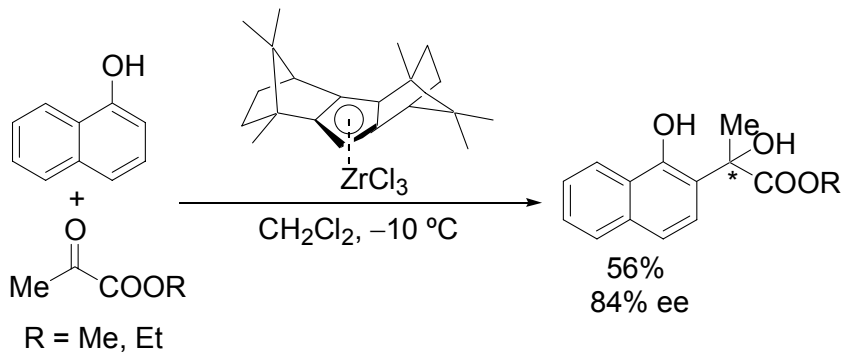


Scheme 12: Enantioselective desymmetrisation of meso stilbene oxide catalysed by [Cr(salen)X] complexes.

Catalytic asymmetric addition of aromatic compounds to C=O and C=NR groups

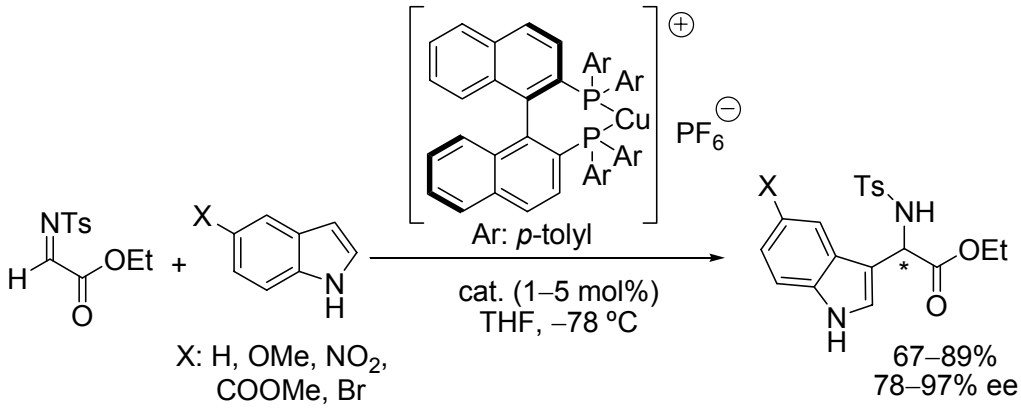
The addition of electron-rich aromatic compounds to aldehydes, ketones, and imines leads to the formation of versatile functionalised compounds.[74] However, because of the intrinsic instability of many aminomethyl and hydroxymethyl aromatic systems, polysubstitution reactions to give bis-aryl compounds are commonly encountered both under homogeneous and heterogeneous catalysis.[75] A first entry in this challenging area was the catalytic asymmetric addition of 1-naphthol to pyruvic esters mediated by the chiral zirconocene complex[76] (Scheme 13).

[74] Olah, G. A.; Kishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp. 293—339.
[75] For homogeneous catalysis, see: (a) Yadav, J. S.; Reddy, B. V. S.; Murthy, Ch. V. S. R.; Kumar, G. M.; Madan, Ch. *Synthesis* **2001**, 783—787. (b) Hao, J.; Taktak, S.; Aikawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. *Synlett* **2001**, 1443—1445. (c) For heterogeneous catalysis, see: Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal*. **2003**, *345*, 557—559.
[76] Erker, G.; der Zeijden, A. A. H. *Angew. Chem. Int. Ed*. **1990**, *29*, 512—514.



Scheme 13: Addition of 1-hydroxy naphthalene to pyruvic esters mediated by chiral zirconocene complexes.

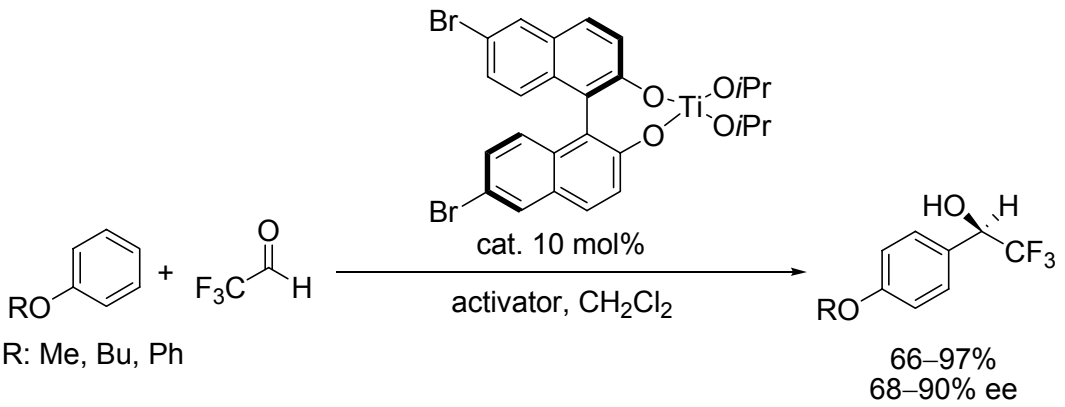
A considerable breakthrough in this area was made independently by Johannsen,[77] and Mikami.[78] Johansen and co-workers described the synthesis of heteroaromatic N-tosyl-α–amino acids catalysed by *p*-tol-binap/$CuPF_6$ (Lectka´s catalyst) (Scheme 14).



Scheme 14: Enantioselective Friedel–Crafts amino alkylation of indoles catalysed by the Cu(I)–tol-binap complex.

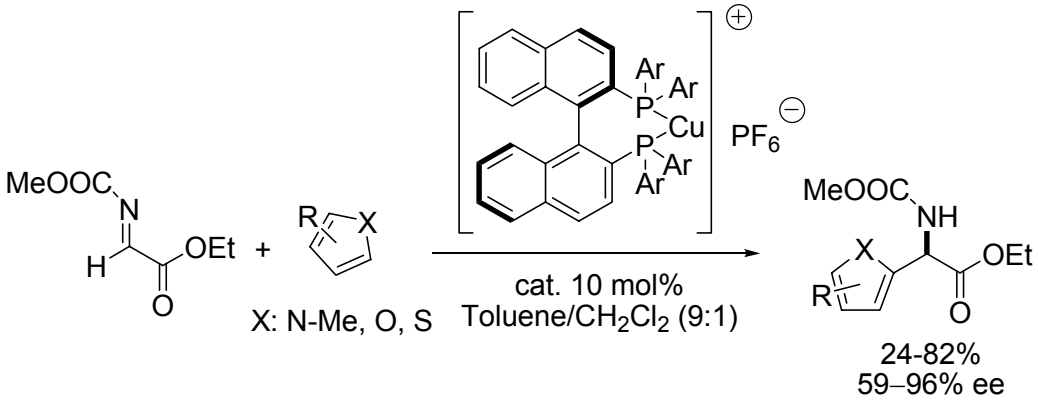
Mikami and co-workers described the preparation of organofluoro compounds by the addition of electron-rich arenes to fluoral in the presence of a chiral substituted BINOL–titanium complex. In this case, a notable improvement in the catalytic effectiveness was observed when biphenols were added as activators (asymmetric activation) to the chiral titanium-based Lewis acid[79] (Scheme 15).

[77] Johannsen, M. *Chem. Commun*. **1999**, 2233—2234.
[78] Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem*. **2000**, *65*, 1597—1599.
[79] Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613—615.



Scheme 15: Use of a BINOL–titanium complex as the catalyst for the asymmetric addition of electron-rich arenes to fluoral.

The range of accessible enantioenriched α–heteroarene α–amino acids, starting from a variety of substituted benzenes and furans, was increased remarkably by utilising the Lectka´s catalytic system and α–glyoxylate imines as electrophiles.[80] In this study, several N-protecting groups were tested, and the highest chemical yields and ee values were observed when a readily removable N-methoxycarbonyl group was used (Scheme 16).

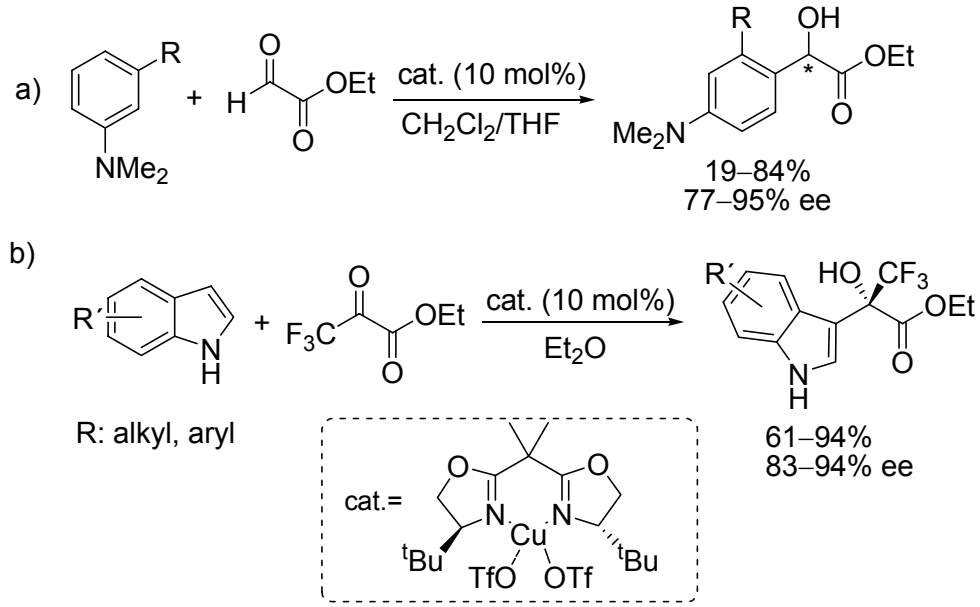


Scheme 16: Enantioselective addition of electron-rich aromatic compounds to imines catalysed by Lectka´s catalyst.

The synthetic versatility of the catalytic F–C alkylation was further emphasised by Jørgensen and co-workers, who were able to obtain aromatic mandelic esters[81] and heteroaromatic hydroxytrifluoromethyl esters[82] by asymmetric F–C reactions of aromatic compounds to ethyl glyoxylate and ethyl trifluoropyruvate respectively (Scheme 17). The cationic t-Bu-box-Cu$(OTf)_2$ complex and chelating substrates were used in these catalytic approaches to give high stereoselectivity. Under these conditions aromatic amines, anisoles,

[80] (a) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2000**, *39*, 4114—4116. (b) Saaby, S.; Bayln, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem*. **2002**, *67*, 4352—4361.
[81] (a) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517—12522.
[82] Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem*. **2001**, *66*, 1009—1013.

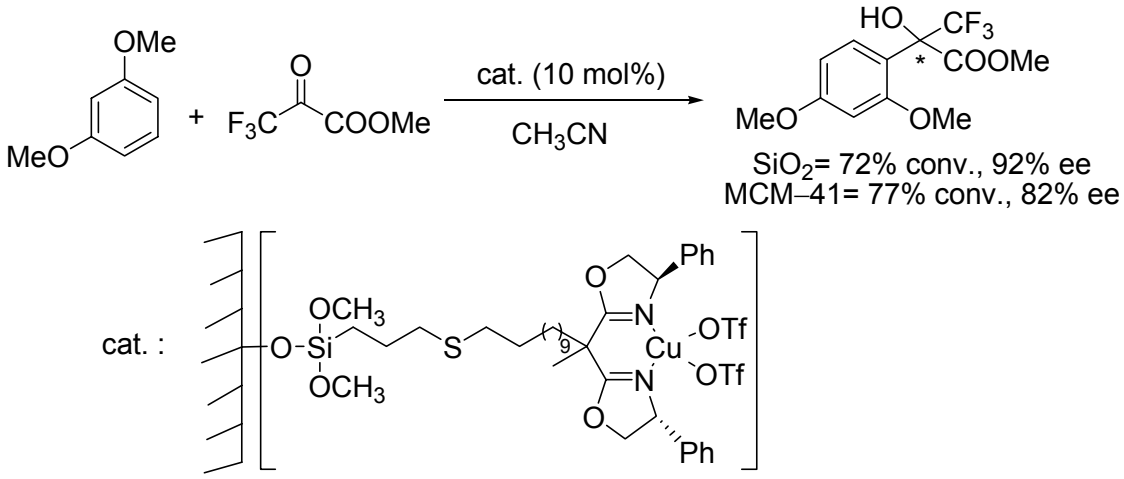
and heteroaromatic compounds were all found to undergo highly enantioselective F–C reactions, thus showing the wide applicability of the catalytic system. However, less reactive substituted furans required a higher catalyst loading (40 mol%) for satisfactory chemical yields.[83]



Scheme 17: Stereoselective synthesis of substituted mandelic esters and heteroaromatic trifluoromethyl-substituted esters through F–C alkylations catalysed by Cu(II)−box complexes.

Corma et al[84] recently studied the first example of heterogeneous catalytic asymmetric F–C alkylation, in the reaction of 1,3–dimethoxybenzene with methyl 3,3,3–trifluoropyruvate in the presence of a chiral copper(II)–Ph-bis(oxazoline) complex covalently anchored to silica or mesoporous MCM–41 (Scheme 18). The use of supported catalysts furnished the same levels of stereoselectivity (82–92% ee, 72–77% conversion) as observed in the homogeneous process (86% ee, by Jørgensen and co-workers), but the heterogeneous catalysts could be recovered easily by filtration. The reusability of the chiral catalyst MCM–41 was also investigated, and the second catalytic reaction afforded the same level of enantioselectivity (84% ee) and only a slight decrease in conversion (73%).

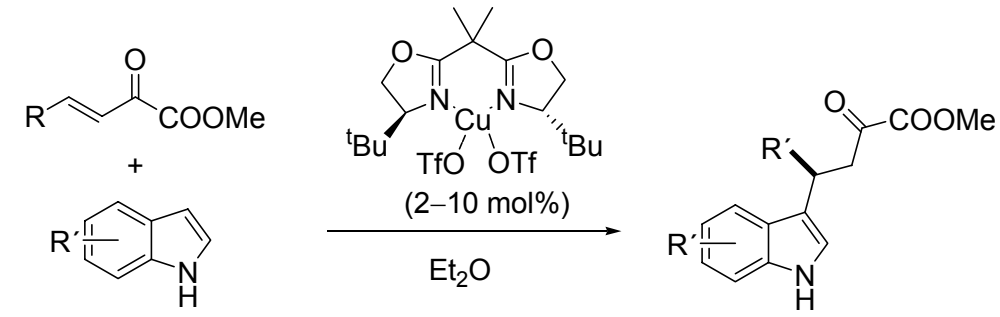
[83] van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953—1958.
[84] Corma, A.; GarcMa, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. *Chem. Commun.* **2002**, 1058—1059.



Scheme 18: Solid supported (Silica, MCM–41) asymmetric catalysis by Cu–bis(oxazoline).

Catalytic asymmetric Michael-type addition of aromatic compounds to electron deficient alkenes

α,β–Unsaturated carbonyl compounds are suitable substrates for F–C alkylations and in fact numerous acid catalysed Michael-type additions of aromatic compounds have been described.[85] Nevertheless, stereoselective variants have been less explored. The first example of highly enantioselective catalytic 1,4–addition of electron-rich aromatic compounds to β,γ–unsaturated-α-keto esters, in the presence of the chiral Cu(II)−bis(oxazoline) complex, was described by Jørgensen and co-workers[86] (Scheme 19).



R= alkyl, aryl
R´= alkyl, aryl, OMe, Cl, COOMe

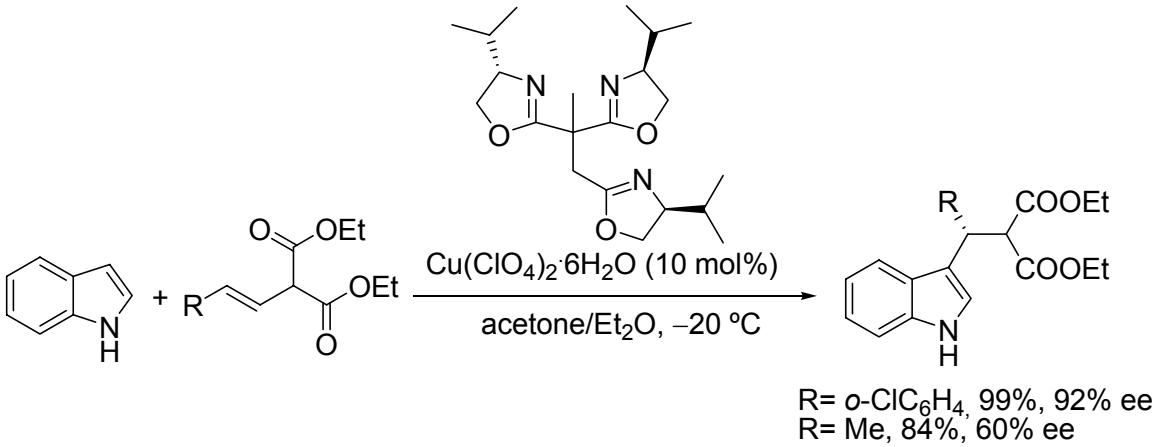
69–99%
60–99.5% ee

Scheme 19: Enantioselective conjugate addition of indoles to α, β–unsaturated γ–ketoesters in the presence of the cationic Cu(II)−bis(oxazoline) complex.

[85] For examples, see: (a) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047—1048. (b) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal*. **2001**, *343*, 174—176. (c) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre. P.; Selva, S.; Umani–Ronchi, A. *J. Org. Chem*. **2002**, *67*, 3700—3704. (d) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani–Ronchi, A. *Synthesis* **2002**, 1110—1114. (e) Bandini, M.; Fagioli, M.; Melloni, A.; Umani–Ronchi, A. *Synthesis* **2003**, 397—402. (f) Srivastava, N.; Banik, B. K. *J. Org. Chem*. **2003**, *68*, 2109—2114.

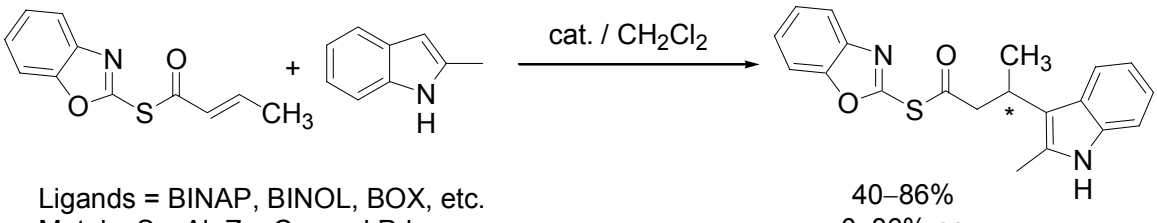
[86] Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2001**, *40*, 160—163.

Later, Zhou and Tang demonstrated[87] the effectiveness of the pseudo C_3–symmetric tris(oxazoline)–$Cu(ClO_4)_2 \cdot 6H_2O$ complex in promoting (both under anhydrous and non-anhydrous conditions), the enantioselective addition of indole to arylmethylidene malonates (R=Ar) at –20 ºC (Scheme 20). The data collected by the authors show that the presence of an aromatic group bounded to the malonate carbon-carbon double bond is crucial for high enantioselectivity to be observed. When the F–C reaction was carried out with an alkylidene malonate (R= Me), the enantioselectivity dropped to 60% ee. Comparison of the results obtained in the analogous reaction by Jørgensen and co-workers with the classic bidentate C_2–symmetric t-Bu-box ligand (maximum ee value 69%)[88] shows the influence of the sidearm present in the tridentate ligand.



Scheme 20: The sidearm effect: Versatility of chiral tris(oxazoline) ligands in the Michael addition of indole to alkylidene malonates.

Furthermore Bandini[89] and co-workers described a method by introduction of a sulfanyl 1,3–benzoxazole unit in α,β–unsaturated carboxylic compounds making them suitable electrophiles for stereoselective F–C reactions of Indoles (Scheme 21).

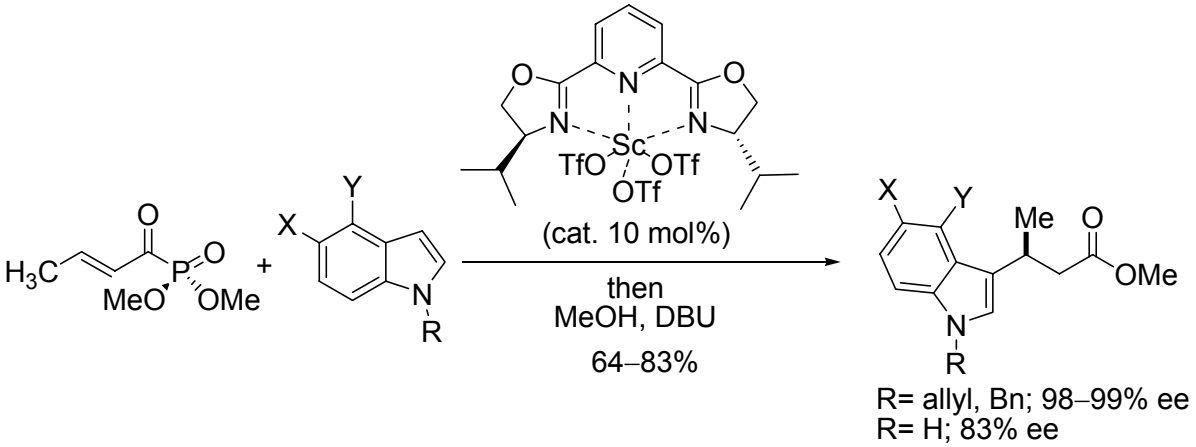


Scheme 21: F–C alkylations by α,β–unsaturated thioesters with various BOX and BINAP derived catalysts.

[87] Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030—9031.
[88] Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun*. **2001**, 347—348.
[89] Bandini, M.; Melloni, A.; Tommasi, S.; Umani–Ronchi, A. *Helv. Chim. Acta* **2003**, *86*, 3753—3763.

Although various BOX and BINAP derived catalysts were tested, the highest of 86% ee was achieved by employing 20 mol% [Pd (II) (Tol- binap)] complex as the catalyst.

Recently Evans[90] and co-workers described the utility of bis(oxazolinyl) pyridine (pybox)–scandium(III)triflate complexes in the additions of electron-rich aromatic substrates to α,β–unsaturated acylphosphonates.[91] The acyl phosphonates are effective active esters that may be employed in subsequent acyl transfer reactions. Accordingly, these intermediates may be further transformed without isolation into esters or amides.[92] Although the ee´s in case of substituted indoles were impressive, the parent N-unsubstituted indole showed limited success (83% ee) (Scheme 22).

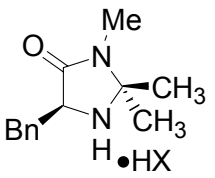


Scheme 22: $Sc(OTf)_2$-Py-BOX catalysed F–C alkylations of indoles.

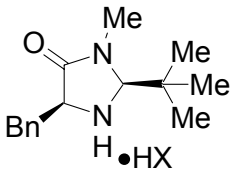
The use of chelating substrates in combination with chiral cationic Lewis acids is an effective strategy to ensure high levels of stereoselectivity. However, it also represents a significant restriction in applicability. A Michael-type reaction between aromatic compounds and non chelating α,β–unsaturated carbonyl compounds was first reported by the research group of MacMillan,[93] and more recently by Bandini.[94] MacMillan and co-workers elegantly designed and employed the chiral tailored benzyl imidazolidinone·HX salts **Ma, Mb** derived from (L)-phenylalanine as organic catalysts for the 1,4–addition of pyrroles, indoles, and aniline derivatives to α,β–unsaturated aldehydes (Scheme 23). The LUMO–lowering

[90] Evans, D. A.; Scheidt, K. A.; Frandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10780—10781.
[91] For the use of α,β–unsaturated acyl phosphonates in Lewis acid-catalyzed reactions, see: (a) Telan, L. A.; Poon, C. −D.; Evans, S. A. Jr. *J. Org. Chem.* **1996**, *61*, 7455—7462. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635—1649.
[92] For dialkyl acyl phosphonates are highly effective acylating agents, see: Sekine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 3617—3620.
[93] (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370—4371. (b) Austin, J. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172—1173. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 7894—7895.
[94] Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani–Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843—5846.

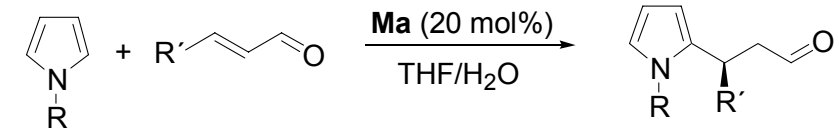
activation of aldehydes by reversible formation of chiral intermediate iminium salts is responsible for the modulation of both reactivity and stereoselectivity in these F–C reactions. This new metal-free approach for the catalytic and stereoselective alkylation of electron-rich arenes proved to be general in scope, and polyalkylation, which is the main type of side reaction in the metallocatalyzed addition of arenes to aldehydes, was not observed. The important limitations of aforementioned organocatalysis protocol are: (1) the highest ever catalyst percentage (20 mol%) used among all reported cases, (2) the method is not applicable to α,β–unsaturated ketones which are less reactive than the corresponding aldehydes and pose the problem of formation of a mixture of E/Z iminium catalytic active intermediates.



Ma

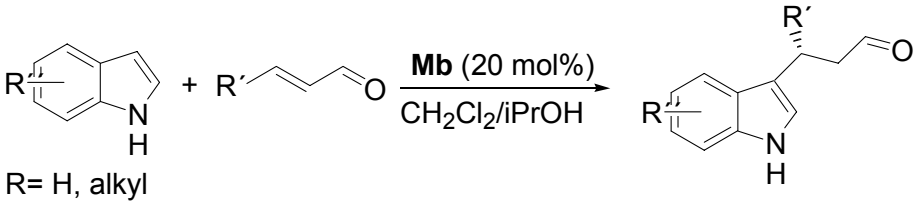


Mb



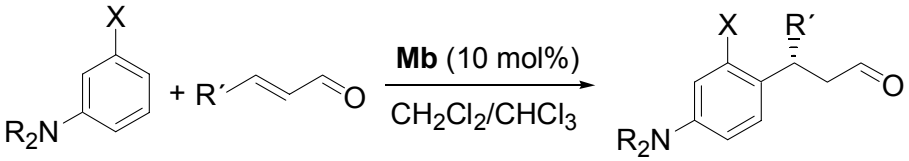
R= Me, Bn, allyl
R´= alkyl, aryl, CH_2OBn, COOMe

> 70%
72–97% ee



R= H, alkyl
R´= alkyl, aryl, COOMe, CH_2OBn
R´´= Me, Cl, MeO

> 80%
89–97% ee

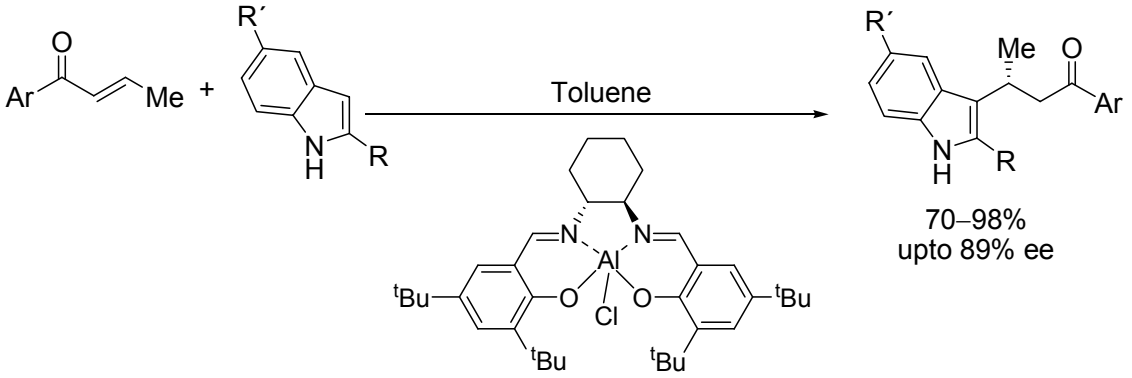


X= OMe, H, Cl, SMe,
R= Alkyl
R´= alkyl, aryl, COOMe, CH_2OBn

> 73%
86–99% ee

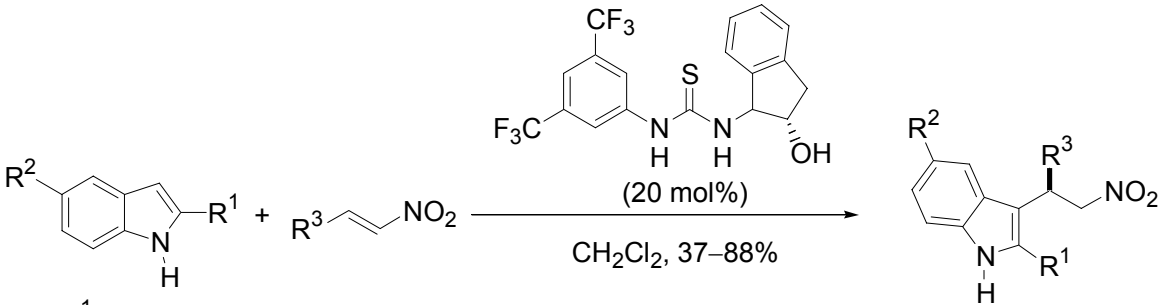
Scheme 23: Enantioselective organocatalysed Friedel–Crafts alkylations of pyrroles, indoles, and anilines with α,β–unsaturated aldehydes.

Recently, Bandini and co-workers[95] investigated the use of the chiral [Al(salen)Cl] complex in the presence of 2,6–lutidine as the catalyst for the first enantioselective addition of indoles to α,β–unsaturated aryl ketones (Scheme 24). Unfortunately, the ee values obtained are considerably lower (55%–89% ee) than those usually attained with bidentate substrates.



Scheme 24: Enantioselective Michael-type addition of indoles to α,β–unsaturated aryl ketones catalysed by an [Al(salen)Cl]/2,6-lutidine complex.

Using thiourea derivatives as organocatalysts, F–C alkylations of indoles with nitroalkenes were recently reported by Ricci and co-workers[96] (Scheme 25). However, ee´s attained were limited up to 85% by employing 20 mol% catalyst.



Scheme 25: Enantioselective F–C alkylations of indoles with nitroalkenes catalyzed by thiourea organocatalyst.

[95] (a) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani–Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843—5846. (b) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani–Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511—7518.
[96] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 6576—6579.

Despite above mentioned impressive progress, many challenges remain unaddressed for the catalytic asymmetric Friedel–Crafts reactions, notably with regard to extension of substrate scope, selectivity and reactivity.

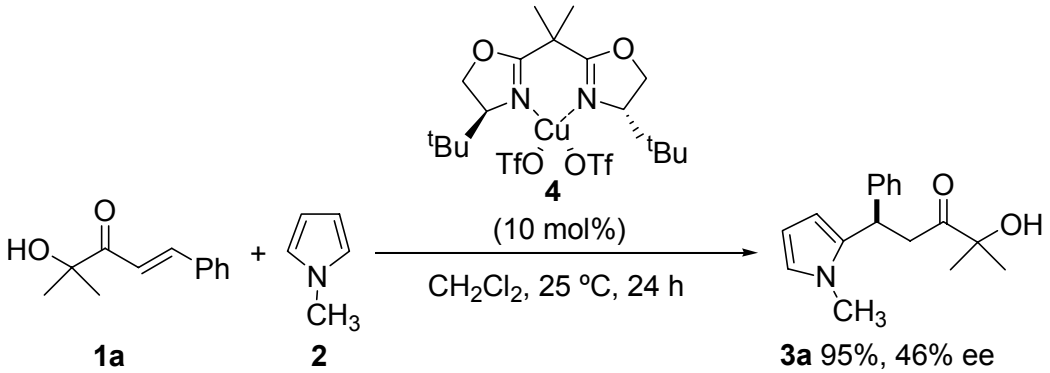
3.3 Results and Discussion: Pyrrole derivatives

3.3.1 Introduction

Since the pyrrole and indole skeletons are important substructures within natural product isolates and medicinal agents, as mentioned before, these heteroarenes were selected for the study. Initial screening reactions were carried out using pyrrole and N-substituted pyrrole derivative with β–phenyl α'–hydroxy enone **1a** under the catalytic conditions that showed good performance in the Diels–Alder reaction of this type of enones carried out previously in our laboratory.

3.3.2 Preliminary results with β–aryl enones

We started initial exploration with easily accessible β–phenyl α'–hydroxy enone **1a** and N-methyl pyrrole **2** (Scheme 26). The reaction protocol consisted of *in situ* pre-formation of the catalyst **4** by admixing $Cu(OTf)_2$ and chiral ligand **L–1** (2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline) (Figure 10) in CH_2Cl_2 for 3 h at room temperature, later subjecting it to specified temperature for sequential addition of β–phenyl α'–hydroxy enone **1a** and N-methyl pyrrole **2** at the interval of 5–10 minutes. The estimation of reaction progress was easily monitored by TLC analysis, while purification of crude product (NMR shown in Fig. 8) by flash column chromatography and enantiomeric excess (ee) determination by using chiralpak AD column on chiral HPLC (as shown in Fig. 9), provided assessment of the efficiency of the reaction.



Scheme 26: Preliminary experiment: F–C alkylation of N-methyl pyrrole **2** with enone **1a** promoted by catalyst **4**.

In the first run, at 25 ºC for 24 h, F–C adduct **3a** was obtained in 95% isolated yield with 46% ee. Varying the molar ratio of N-methyl pyrrole **2** to enone **1a** from 2.0 equivalents (46% ee, Table 1, entry 1) to 1.1 equivalents (37% ee) and 1.5 equivalents (45% ee) did not

showed any considerable change in selectivity. Lowering the reaction temperature to 0 ºC, reaction conversion was lowered (23% in 24 h) with slightly higher selectivity, 57% ee (entry 2).

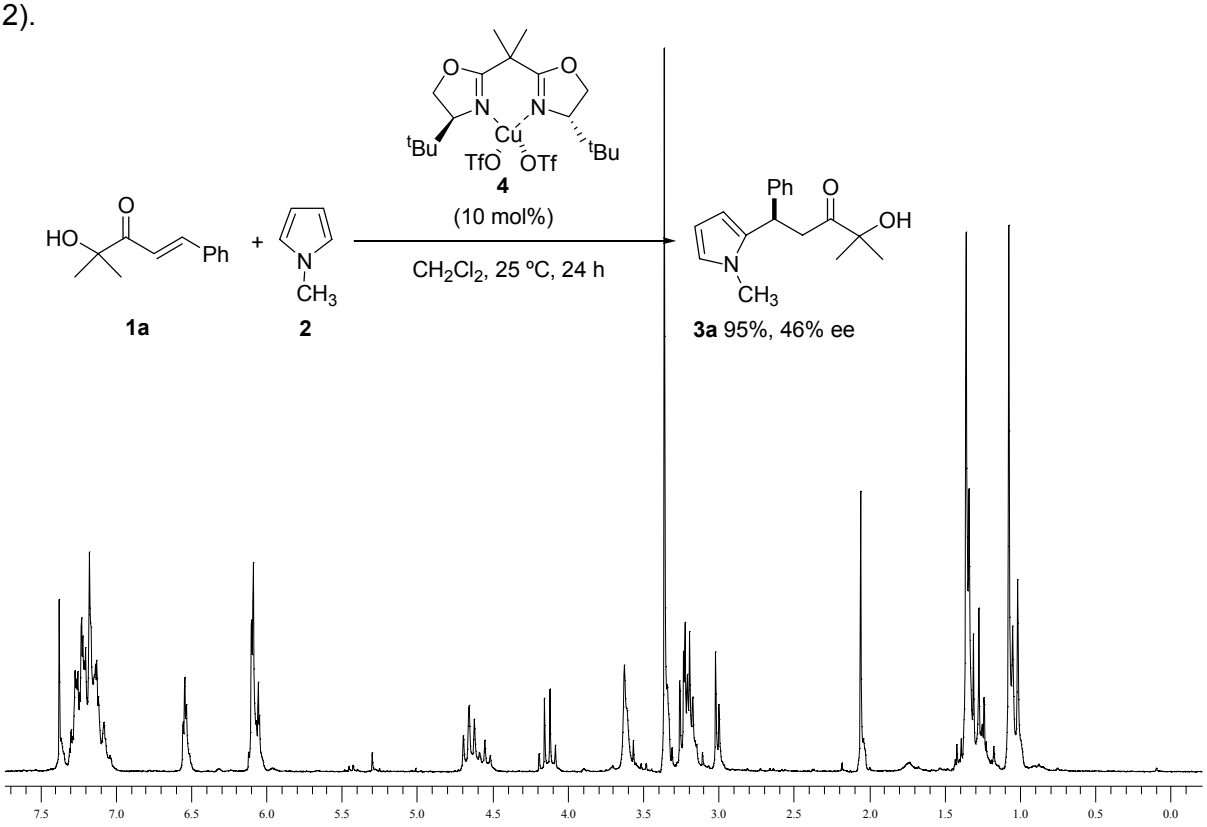


Figure 8: *^{1}H Spectrum of crude product of F–C reaction of N-methyl pyrrole* **2** *and enone* **1a** *under stated conditions*.

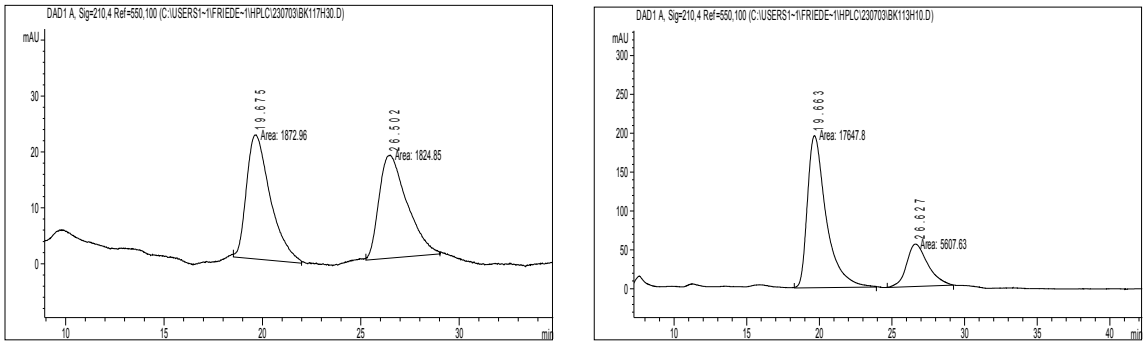


Figure 9: *Determination of ee: HPLC chromatograph of F–C adduct* **3a** *(a) racemic product, (b) asymmetric product. (Column: Chiralpak AD, 94:06 Hexane: Ethanol) (46% ee).*

Based on these preliminary experiments with catalyst **4**, other catalysts and reaction conditions were screened. Subsequently, we decided to evaluate few more members of bis(oxazoline) ligand category as well as other metals like Mg, Zn, and Sc. In this regard, many structural variants are available for the BOX ligand category. In particular, It is well

reported that the bis(oxazoline) ligands can be modified by changing the substituents on bridging methylene (2, 2´–position) and oxazoline ring (4, 4´–position) (Figure 10).

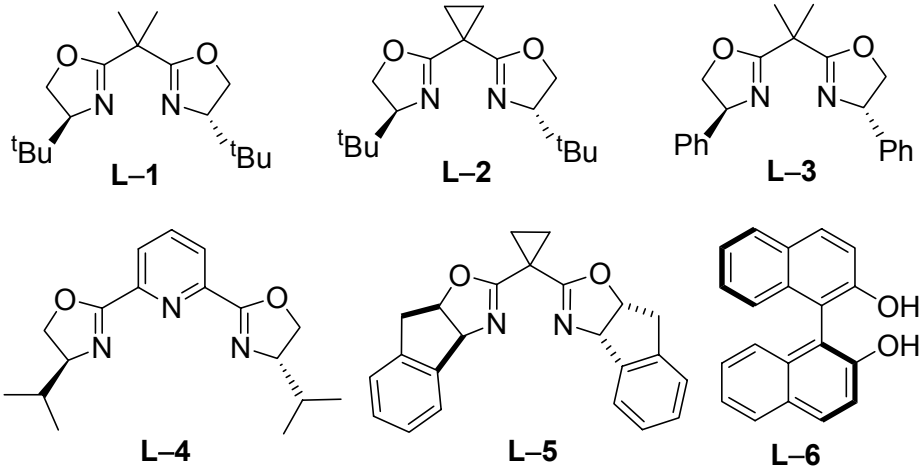
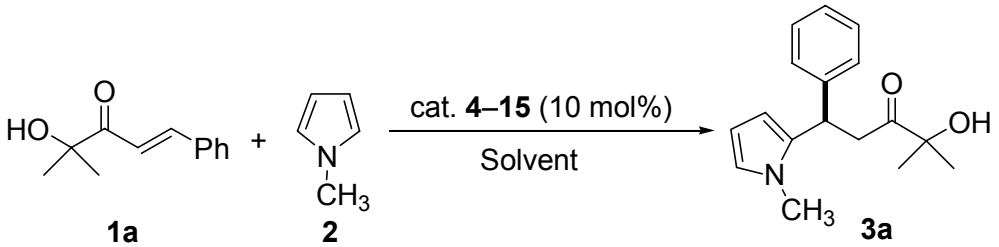


Figure 10: *Various ligands used for preparation of catalysts for F–C alkylation.*

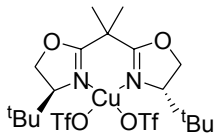
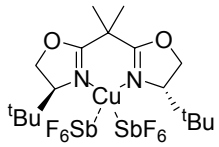
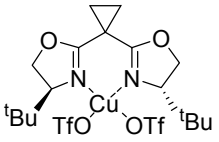
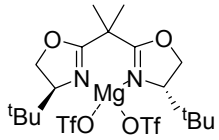
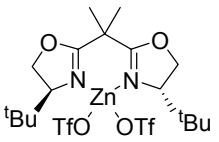
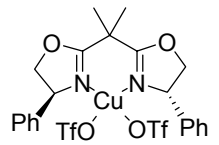
First we chose to examine the effect of substituents at 4, 4´–position. Thus, catalysts **9** and **11** were examined. Catalyst **9**, which was prepared using chiral ligand (*S*)-(-)-2,2'-isopropylidene bis(4-phenyl-2-oxazoline) (**L–3**) and $Cu(OTf)_2$, resulted in poor selectivity i.e. 13% ee (entry 14). Catalyst **11**, which was prepared using chiral ligand **L–5** (prepared according to Sibi[97]) and $Cu(OTf)_2$, also showed poor result (40% ee, entry 16).

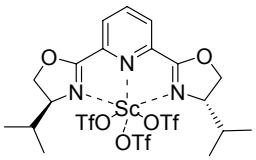
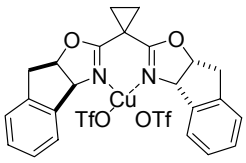
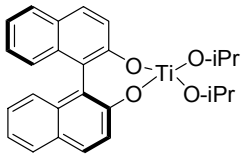
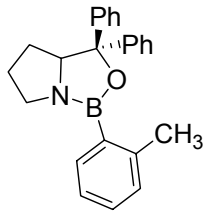
[97] Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615—6616.

Table 1: *Asymmetric Friedel–Crafts reaction of N-methyl pyrrole* **2** *with α'–hydroxy enone* **1a** *promoted by catalysts* **4–15**[a]:



1a **2** **3a**

Entry	Catalyst	Solvent	T, ºC	Yield % [b]	ee % [c]
1		CH_2Cl_2	25	95	46
2		CH_2Cl_2	0	23[d]	57
3		CH_2Cl_2	25	50[d]	33[f]
4		THF	25	37[d]	0
5	**4**	Et_2O	0	9[d]	0
6		CH_3CN	25	0	--
7	 **5**	CH_2Cl_2	25	95	29
8		**CH_2Cl_2**	**25**	**96**	**68**
9		CH_2Cl_2	0	41[d]	70
10		CH_2Cl_2	25	95	60[h]
11	**6**	Toluene	25	39[d]	67
12	 **7**	CH_2Cl_2	25	0	--
13	 **8**	CH_2Cl_2	25	28[d]	11
14	 **9**	CH_2Cl_2	25	95	13

15	 **10**	CH_2Cl_2	25	33[d]	0
16	 **11**	CH_2Cl_2	25	95	40
17	 **12**	CH_2Cl_2	25	95	11
18		CH_2Cl_2	25	95	27[e,g]
19	 **13**	CH_2Cl_2	–50	95	0

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale, reaction time 24 h, with mole ratio of enone (**1a**):N-methyl pyrrole (**2**):catalyst =1:2:0.1. [b] After column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on NMR of crude product after specified time. [e] Reversal of enantiomeric pattern, observed by HPLC chromatograms. [f] Hexafluoro isopropanol (25 mol%) used as additive. [g] Molecular sieves MS–4Å used as additives.

Then we eyed to second possibility, to modify the bis(oxazoline) ligand structure at bridging methylene. Hence, catalyst **10** was prepared by using commercially available tridentate chiral ligand 2,6-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-pyridine (**L–4**) and $Sc(OTf)_3$. The F–C reaction using catalyst **10** was much slower (33% conversion in 24 h) with no selectivity (entry 15). Further, owing to the beneficial effect of modifying the ligand bite angle in bis(oxazoline) ligands by substituting bridging dimethyl moiety of ligand **L–1** by a cyclopropyl ring, as reported by Denmark, Sibi, Pfaltz and Davies independently,[98] the cyclic bridged bis(oxazoline) ligand (spiro-box) (**L–2**) was prepared starting from the commercially available 2,2´–methylene bis(oxazoline) and 1,2–dibromoethane (see

[98] (a) Denmark, S. E.; Stiff, C. M. *J. Org. Chem*. **2000**, *65*, 5875—5878. (b) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615—6616. (c) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232—240. (d) Davies, I. W; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753—1754.

Experimental section). Hence, catalyst **6** was prepared using this chiral ligand 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)] cyclopropane (**L–2**) and $Cu(OTf)_2$. The reaction carried out by using catalyst **6** resulted in limited enantioselectivity i.e. 68% ee at 25 ºC (entry 8). Lowering reaction temperature to 0 ºC led to 70% ee with diminished reactivity (41% reaction conversion in 24 h) (entry 9).

Use of additives is another possibliltiy to enhance the selectivity. In this regard, we examined the influence of hexafluoro isopropanol (HFIP) as additive based on previous reports by Tang and co-workers.[99] But the attempt was unsuccessful to attain satisfactory selectivity (entry 3). Secondly, employing molecular sieves MS–4Å as additive resulted in unsatisfactory results too (entry 10).

Although we chose copper metal, based on previously reported results, the initial poor results forced us to consider other metals too. Hence catalyst **7** was prepared using chiral ligand **L–1** and $Mg(OTf)_2$. The F–C reaction using catalyst **7** in dichloromethane did not proceed at all (entry 12). Catalyst **8** was prepared using chiral ligand **L–1** and $Zn(OTf)_2$. The F–C reaction using catalyst **8** in dichloromethane resulted in 28% reaction conversion and only 11% ee (entry 13).

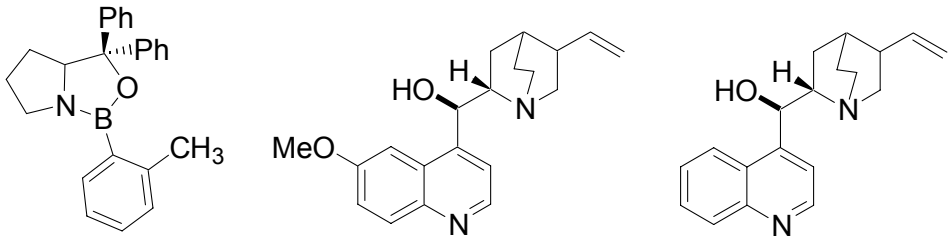
Another possibility was to change the counter ions of Cu(II) from triflate to hexafluoro antimoniate. Hence catalyst **5** was prepared using chiral ligand **L–1** and $Cu(SbF_6)_2$. However, by carring out the reaction at 0 ºC in dichloromethane with catalyst **5** resulted in only 29% ee (entry 7).

By changing the solvent to ethereal solvents like THF, the chemical reactivity and enantioselectivity were affected. NMR analysis showed reaction conversion of only 16% in 24 h at 0 ºC, while increasing temperature to 25 ºC reaction conversion increased to 37%, but with 0% ee in both cases (entry 4). In diethyl ether, after 24 h at 0 ºC, only 9% conversion and 0% ee was obtained (entry 5). Using non polar solvents like toluene similar result was obtained. At 25 ºC, after 24 h, 39% reaction conversions and 67% ee was obtained (entry 11). The reaction did not proceed at all in the highly coordinating solvents like acetonitrile (entry 6).

While bis(oxazoline) ligands were showing somewhat limited results in the initial screening attempts, we thought about switching to BINOL ligands, which had been used successfully by Mikami[100] and Keck [101] independently. Hence, catalyst **12** was prepared using chiral ligand **L–6** (*S*-BINOL) (Figure 10) in combination with $Ti(O\text{-}^{i}Pr)_4$). However, only 11% ee was achieved by employing catalyst **12** (entry 17). Further use of molecular sieves MS–4Å as additive provided 27% ee with the reversal of enantiomer pattern (entry 18).

---

[99] Zhou, J.; Ye, M. C.; Huang, Z. −Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309—1320.
[100] Mikami, K.; Terada, M.; Nakali, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949—3954.
[101] Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363—2364.



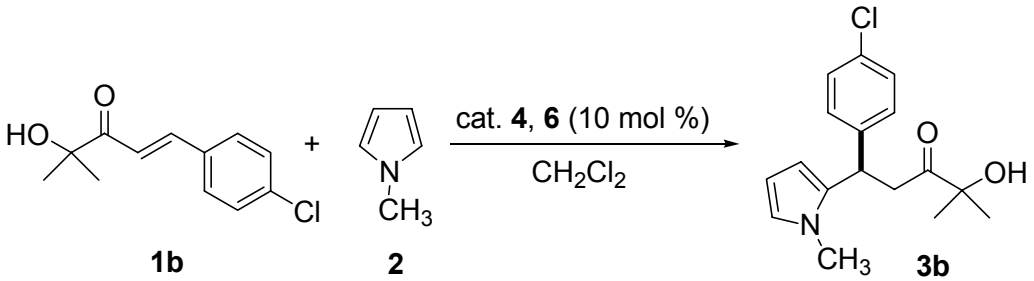
Oxazaborolidine **13** | Quinine **14** | Cinchonidine **15**

Figure 11: *Other catalytic systems employed in F–C alkylation of N-methly pyrrole* **2** *with α'–hydroxy enone* **1a***.*

Furthermore, we employed commercially available oxazaborolidine catalyst **13** reported by Corey and co-workers.[102] The reactions carried out in CH_2Cl_2 and toluene, resulted in no reactivity, while catalyst **13** in combination with triflic acid (equimolar ratio of **13** and triflic acid are stirred at –50 ºC for 15 minutes prior to addition of enone **1a** and N-methyl pyrrole **2**), produced racemic products in both CH_2Cl_2 (entry 19) and toluene. Next to this, we unsuccessfully attempted organocatalytic approach for this F–C reaction using catalyst **14** (quinine) and catalyst **15** (cinchonidine) (Figure 11).

At this point, it seemed that we got a non surmountable 68% ee for the F–C reaction of enone **1a**. In order to establish whether this limit is general for other β–aryl α'–hydroxy enones, a new study was undertaken with the corresponding β–*p*-chlorophenyl substituted enone **1b**. By carrying out the reaction using catalyst **4** in CH_2Cl_2, almost similar results were obtained (Scheme 27, Table 2).

Lowering the temperature did not help either to enhance the selectivity (entry 1). Increasing the molar ratio of N-methyl pyrrole from 2 equivalents to 6 equivalents enhanced only reactivity (reaction time reduced to 3 h as compared to 24 h in earlier case) but not the selectivity (entry 3). Employing the tailored catalyst **6**, unrewarding results were obtained (entries 4 and 5).

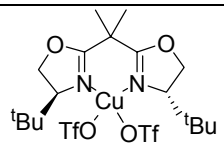
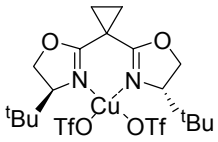


1b **2** **3b**

Scheme 27: F–C alkylation of N-methly pyrrole **2** with β–aryl enone **1b**.

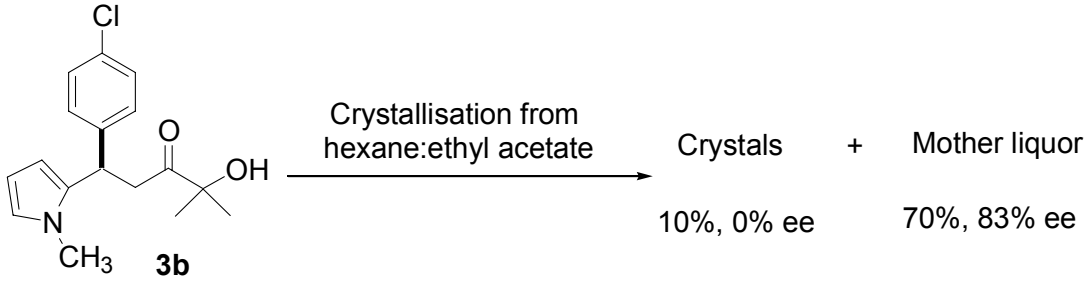
[102] Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151—3152.

Table 2: *Asymmetric Friedel–Crafts reaction of N-methyl pyrrole* **2** *with α'–hydroxy enone* **1b** *promoted by catalysts* **4**, **6**[a]:

Entry	Catalyst	T, ºC	Yield %[b]	ee % [c]
1		0	41[d]	24
2		25	95	49
3		25	95	60[e]
	4			
4		**25**	**95**	**64**
5		0	50[d]	73
	6			

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale, reaction time 24 h. Mole ratio of enone (**1b**):N-methyl pyrrole (**2**):catalyst is 1:2:0.1. [b] After column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on NMR of crude product after specified time. [e] 6 equi. of N-methyl pyrrole **2** was used.

After these trials, we thought about the enantioenrichment of product by crystallisation.

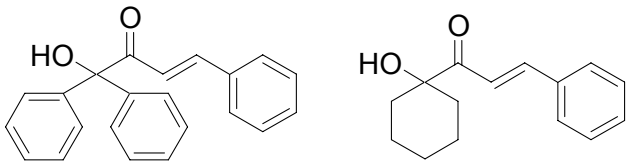


Scheme 28: Enantioenrichment of **3b** through crystallisation.

Hence, F–C adduct **3b** was crystallised from hexane and ethyl acetate (90:10 mixture). Surprisingly, the crystals obtained showed 0% ee, while residual product in the mother liquor showed 83% ee (Scheme 28). We thought that, heat used during crystallisation process might have caused isomerisation. So we subjected a little sample of **3b** in hexane and ethyl acetate (90:10 mixture) for boiling, as like crystallisation. However, instead of allowing it to crystallise, we removed the solvent by rotatory evaporator. We observed no change in the ee of sample (64% ee was retained), thus discarding heat induced isomerisation.

3.3.3 Modification of the ketol motif

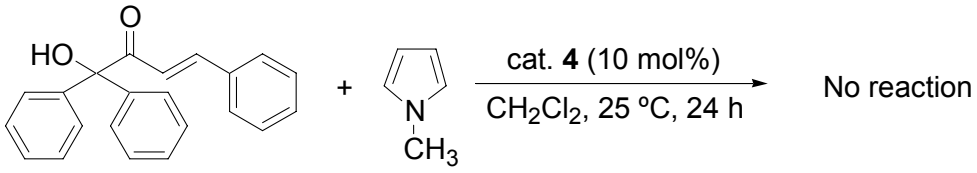
In a last attempt to improve the performance of β–aryl enones, we decided to test the influence of the ketol architecture on the reaction efficiency.



16 **17**

Figure 12: *Modified ketol motif in β–phenyl enone.*

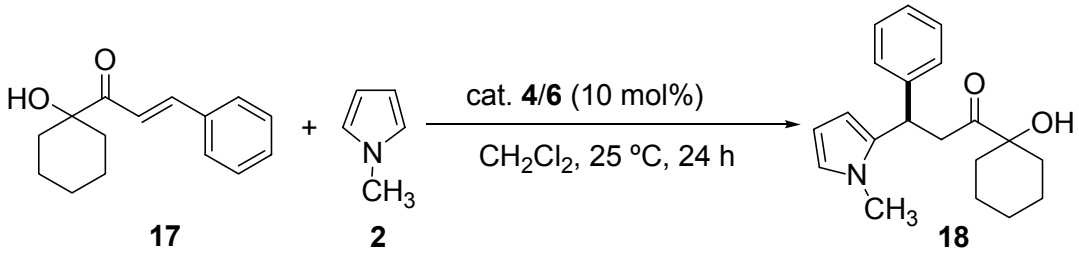
In this regard, we replaced the dimethly group of enone **1a** by two phenyl groups (enone **16**) and cyclohexyl ring (enone **17**), respectively. (For the preparation of modified ketol units from benzophenone and cyclohexanone, respectively, see the Experimental section). When we attempted the F–C alkylation reaction of N-methyl pyrrole **2** with enone **16** under optimised reaction, we observed that reaction did not proceed at all, and starting material was recovered (Scheme 29).



16 **2**

Scheme 29: Enantioselective F–C alkylation of N-methyl pyrrole (**2**) with modified α'–hydroxy enone (**16**) promoted by catalyst **4**.

Fortunately, the F–C reaction of N-methyl pyrrole **2** with enone **17**, under same optimised conditions, in presence of catalyst **4** resulted in 65% ee. The tailored catalyst **6** led to selectivity enhancement up to 78% ee (Scheme 30).



17 **2** **18**

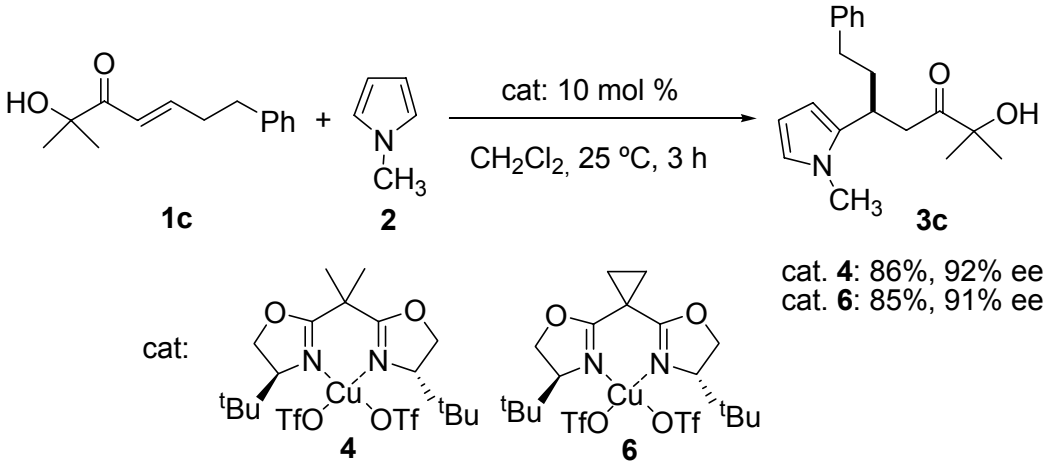
cat. **4**: 95%, 65% ee
cat. **6**: 90%, 78% ee

Scheme 30: Enantioselective F–C alkylation of N-methyl pyrrole **2** with modified α'–hydroxy enone **17** promoted by catalysts **4** and **6**.

Thus, in the F–C reactions of N-methyl pyrrole **2** with β–aryl α'–hydroxy enones, combinations of several bis(oxazoline) ligands, BINOL based catalysts, and Lewis acid metals and also organocatalysts, in various solvents at different temperatures provided up to 68% ee. Finally, modification of ketol motif enhanced the selectivity up to 78% ee.

3.3.4 Preliminary results with β–alkyl enones

After some discouraging results with β–aryl substituted α'–hydroxy enones, we turned to the β–alkyl substituted enones with the hope that improved results may be attainable. We started with phenylethyl enone **1c** as test template, due to easy appraisal of the reaction by TLC monitoring. Gratifyingly, the reaction between this enone and N-methyl pyrrole provided better results.

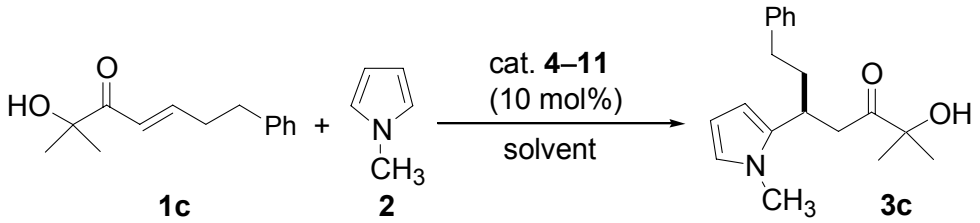


Scheme 31: Preliminary experiments with β–aliphatic enone **1c**.

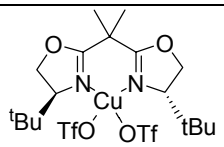
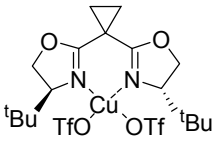
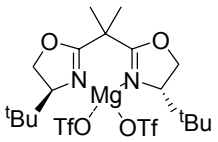
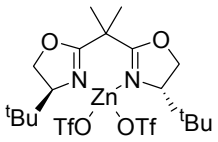
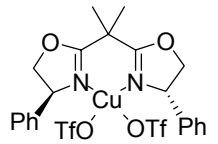
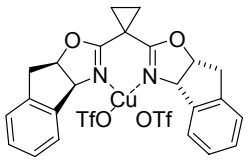
The assessment of the efficiency of the reaction was provided through purification of crude product by flash column chromatography, and ee determination by using chiral HPLC (chiralcel OD column). Thus, the F–C reaction between N-methyl pyrrole **2** and α'–hydroxy enone **1c** in the presence of 10 mol% of chiral Cu(II)–bis(oxazoline) complexes **4** and **6** resulted in 86% and 85% isolated yields and most notably, 92% and 91% ee, respectively (Scheme 31). Based on these encouraging preliminary results, several screening reactions were designed to establish the experimental conditions varying in metal, ligand, solvent, and temperature combinations (Table 3).

In this regard, at the first instance, the F–C alkylation of N-methyl pyrrole **2** with enone **1c** in the presence catalysts prepared from various bis(oxazoline) ligands and different Lewis acid metals were tested. Catalyst **7** prepared by using chiral ligand **L–1** and $Mg(OTf)_2$ did not work at all (entry 7), while catalyst **8** prepared by using chiral ligand **L–1** and $Zn(OTf)_2$ proved less efficient (entry 8). Thus, catalyst **4** provided the best results (entry 1).

Table 3: *Enantioselective Friedel–Crafts alkylation of N-methyl pyrrole* **2** *with α'–hydroxy enone* **1c** *promoted by catalysts* **4–11**[a]:



1c **2** **3c**

Entry	Catalyst	Solvent	T, ºC	Time, h	Yield % [b]	ee % [c]
1		**CH_2Cl_2**	**25**	**3**	**86**	**92**
2		THF	25	2	83	89
3		Et_2O	25	2	82	85
4	**4**	Toluene	25	20	80	88
5		CH_3CN	25	24	0	--
6		**CH_2Cl_2**	**25**	**2**	**86**	**91**
	6					
7		CH_2Cl_2	25	24	0	--
	7					
8		CH_2Cl_2	25	22	100[d]	17
	8					
9		CH_2Cl_2	25	2	78	7
	9					
10		CH_2Cl_2	25	2	76	62
	11					

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale. Mole ratio of enone (**1c**):N-methyl pyrrole (**2**):catalyst is 1:2:0.1. [b] After column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on NMR of crude product after specified time.

Afterwards to establish the structural effects of bis(oxazoline) ligands on the selectivity of the reaction, catalysts **9** and **11** were examined. The reaction carried out using catalyst **9** (prepared by using chiral ligand **L–3** and $Cu(OTf)_2$), in dichloromethane, at 25 ºC, proved almost ineffective providing only 7% ee (entry 9). Catalyst **11** (prepared by using chiral ligand **L–5** and $Cu(OTf)_2$, resulted in diminished selectivity (62% ee) (entry 10).

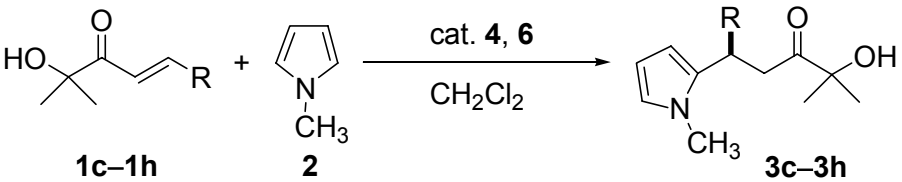
On the other hand, slightly lower enantioselectivity was observed when the reaction was carried out in donor solvents such as THF or diethyl ether (entries 2, 3). Non-polar solvents like toluene showed slightly lower enantioselectivity (entry 4). The reaction did not proceed at all in coordinating solvents like acetonitrile (entry 5). Thus, reaction showed the best enantioselectivity in dichloromethane (92% ee) (entry 1).

3.3.5 Scope of the reaction

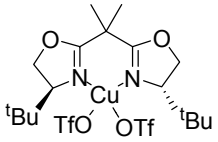
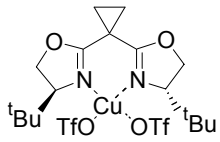
Once the best combination of the metal-ligand complex and optimum reaction conditions were set, different enones with variation in the β–alkyl substituents were examined. This would give us information about the effect of different substituents on reactivity and enantioselectivity (Table 4).

As shown in Table 4, high enantioselectivity (90–97% ee), and good yields (80–88%) were obtained with a series of enones (**1c—1h**) which vary in the identity of the β–alkyl substituent. The reactions are temperature tolerant within the range of –20 ºC to 25 ºC. For example, in case of enone **1d** [R= $CH_3(CH_2)_5$], the temperature variation from –20 ºC to 25 ºC results almost in same enantioselectivity, 96% and 93% ee (entries 3 and 4). In case of enone **1h**, with branched alkyl substituent, reaction rate was sluggish at low temperature (at –20 ºC, only 23% conversion after 20 h and at 0 ºC, 62% conversion after 72 h), but increasing temperature to 25 ºC (entry 12) and further increasing the molar ratio of N-methyl pyrrole **2**, enhanced the rate of reaction (entry 13). On the same line, for enone **1f**, increasing temperature from –20 ºC to 0 ºC enhances the reaction rate (entries 8 and 9) and further increasing the molar ratio of N-methyl pyrrole **2**, enhanced the rate of reaction along with the selectivity (entry 10).

Table 4: *Friedel–Crafts alkylation of N-methyl pyrrole* **2** *with various α'–hydroxy enones* **1c—1h** *promoted by catalysts* **4** *and* **6**[a]**:**



1c–1h **2** **3c–3h**

Entry	Enone	R	Catalyst	T, ºC	Time, h	Product	Yield, %[b]	ee, %[c]
1	**1c**	$PhCH_2CH_2$	 **4**	25	2	**3c**	86	92
2			 **6**	25	2		85	91
3	**1d**	$CH_3(CH_2)_5$	**4**	–20	6	**3d**	82[f]	96
4				25	2		88	93[e]
5	**1e**	CH_3CH_2	**4**	–20	3	**3e**	86	94
6				25	2		88	90
7			**6**	0	2		86	90
8	**1f**	$(CH_3)_2CHCH_2$	**4**	–20	23	**3f**	68[d,f]	93
9				0	12		68[f]	89
10				–20	12		88	94[e]
11	**1g**	$(CH_3)_2CH$	**4**	0	20	**3g**	86	95
12	**1h**	*c*-C_6H_{11}	**4**	25	12	**3h**	65[f]	93
13				25	12		84	97[e]

[a] Unless otherwise stated, all reactions conducted at 0.5 mmol scale and 0.25 M substrate concentration. Mole ratio of arene **2**:enone **1c—1h**:cat is 2:1:0.1. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on NMR of crude product after specified time. [e] Using 6 mole equi. of N-methyl pyrrole. [f] Dialkylation products observed (entry 3= 4.1%; entry 8= 14%; entry 9= 5%,; and entry 12= 8.5%; while in entries 4, 10 and 13, no dialkylation product is detected).

In some instances, dialkylation products were formed. In case of enone **1d** [R=$CH_3(CH_2)_5$], enone **1h** [R= *c*-C_6H_{11}] and enone **1f** [R= $(CH_3)_2CHCH_2$], dialkylation products (4–14%) were isolated, which could be partially or totally suppressed by lowering the temperature and increasing the mole equivalents of N-methyl pyrrole **2**, respectively. Hence, as shown in Table 4 [entries 3 and 4 (enone **1d**), entries 8, 9 and 10 (enone **1f**),

entries 12 and 13 (enone **1h**)], increase in molar ratio of N-methyl pyrrole **2** along with reduction in temperature, serves to suppress the dialkylation product and enhance the reaction rate.

The amount of dialkylated product could be easily measured by carefully integrating the ^{1}H NMR signals of crude product as shown below in Figure 13.

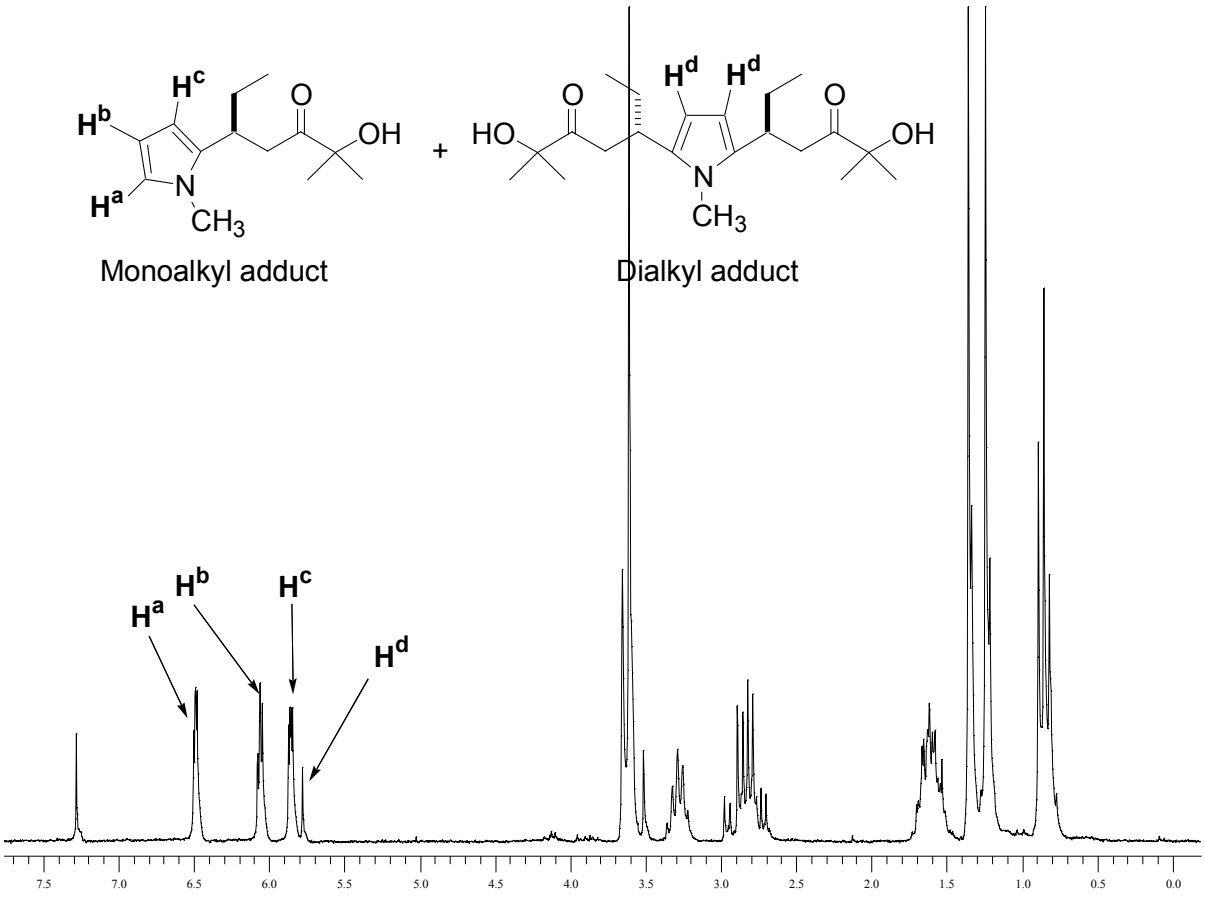
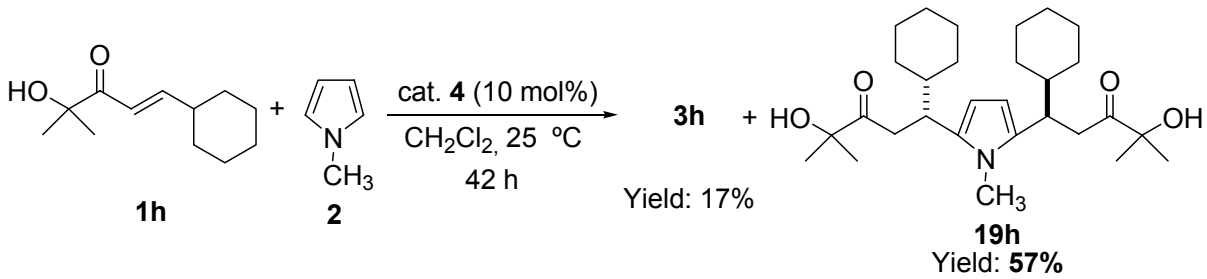


Figure 13: *^{1}H NMR spectrum of crude product corresponding to entry 7 showing presence of dialkylation product.*

3.3.6 Study of dialkylation product

On the other hand, for the study of reactivity and stereoselectivity of dialkylation adduct, a specially designed experiment was carried out (Scheme 32). By employing 2 moles of enone **1h** (R= *c*-C_6H_{11}) with respect to 1 mole of N-methyl pyrrole **2**, and using catalyst **4**, in dichloromethane at room temperature, dialkylated adduct **19h** was obtained as major product in an isolated 57% yield (Figure 14). Monoalkylation adduct was also obtained (17%) and 13% starting enone was recovered after column chromatography.



Scheme 32: Designed F–C reaction for dialkylation product **19h**.

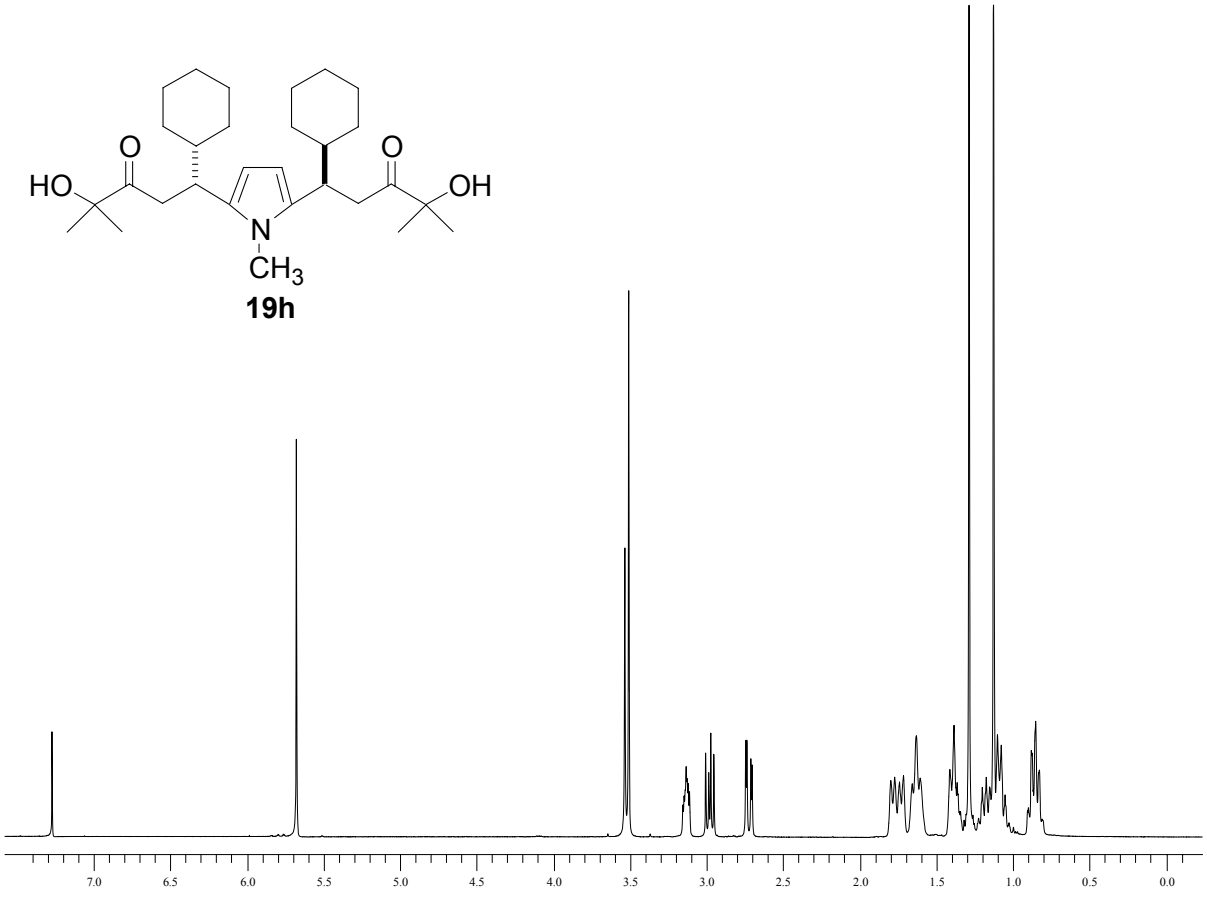


Figure 14: *^{1}H NMR spectrum of pure dialkylation product* **19h.**

Dialkyl product **19h** was subjected to crystallisation in n-hexane and crystallographic analysis was carried out for unambiguous confirmation of its ¨dimeric ¨ structure as well as determination of its relative configuration. As the ORTEP diagram in Figure 15 shows dialkylation product of C_2–symmetry was obtained, which demonstrates that new chiral products are accessible in highly enantioselective and diastereoselective way. The configuration of the rest of dialkylated adducts was assigned by analogy.

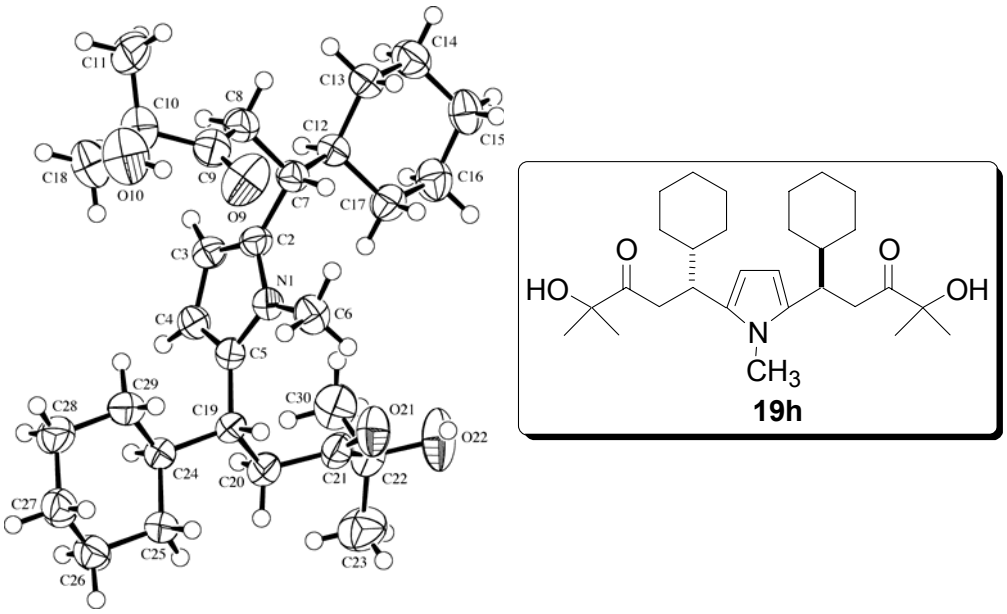
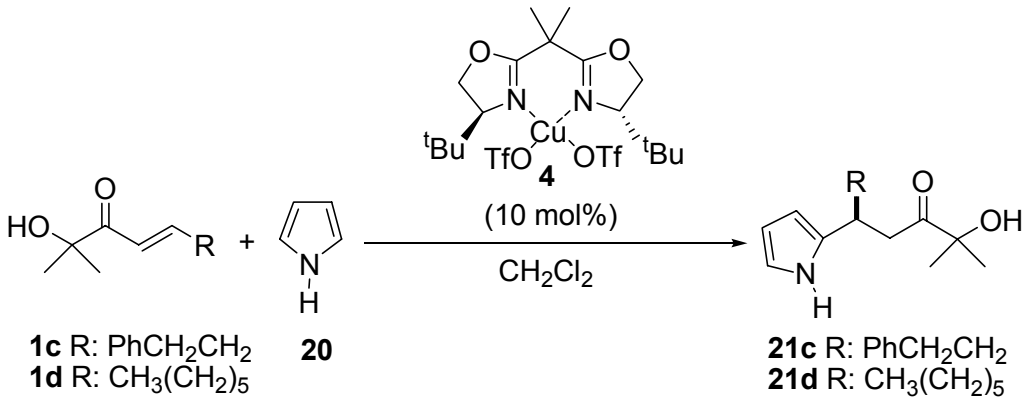


Figure 15: *Dialkylated adduct* **19h** *and its crystal structure.*

As a final issue of the scope of this F–C alkylation methodology with β–alkyl substituted α'–hydroxy enones, the behaviour against *N–H* unsubstituted pyrrole was studied. There are very few reports of F–C reaction with *N–H* unsubstituted pyrrole as it is prone to polymerisation in the presence of acidic conditions. Not surprisingly, when *N–H* pyrrole **20** and enone **1c** and **1d** were subjected to F–C reaction under the optimised conditions, reaction mass became black, fortunately though products **21c** and **21d** were isolated in good yields (70–87%) and 89–91% ee (Table 5). Minor quantities of dialkylation products were also obtained (4–8%) as in the case of F−C alkylation of N-methyl pyrrole. Again, by using excess of pyrrole **20**, formation of dialkylation product was suppressed (Table 5, entry 4).

Table 5: *Friedel–Crafts alkylation of N-H pyrrole* **20** *with α'–hydroxy enones* **1c** *and* **1d** *promoted by catalyst* **4** [a]:



1c R: $PhCH_2CH_2$
1d R: $CH_3(CH_2)_5$

20

21c R: $PhCH_2CH_2$
21d R: $CH_3(CH_2)_5$

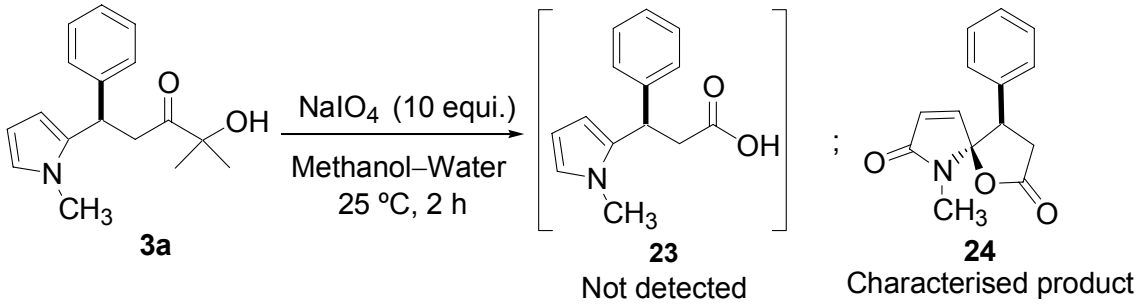
Entry	R	T, ºC	Time, h	Product	Yield, %[b]	ee, %[c]
1	$PhCH_2CH_2$	–20	6	**21c**	83	90
2		0	2		82[d]	89
3	$CH_3(CH_2)_5$	–20	4	**21d**	82[d]	89
4		–20	2		87	91[e]

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale and 0.25 M substrate concentration. Mole ratio of arene:**1c/1d**:cat is 2:1:0.1. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC. [d] Dialkylation products **22c**, **22d** observed (entry 2 = 8%; entry 3= 4%). [e] Molar ratio of enone:pyrrole is 1:6, to suppress the formation of dialkylation product.

3.3.7 Elaboration of the F–C adducts

A synthetically useful aspect of the present reaction is that the Friedel–Crafts alkylation adducts can be easily transformed into the corresponding carboxylic acid derivatives, by means of smooth oxidative scission of the α'–hydroxy carbonyl (ketol) moiety. Based on previous experience of our group on the matter, we decided to elaborate the ketol moiety in three different ways: transformation into carboxylic acids, aldehydes and ketones.

We first subjected F–C adduct **3a** (obtained from F–C alkylation of N-methyl pyrrole **2** with phenyl enone **1a**) to oxidation with $NaIO_4$ in methanol-water system. The reaction mass was turning dark red and after the work up, we were obtaining dark red mass which was observed near baseline in TLC analysis. First we thought that it was acid derivative as it had lower R_f value. So we subjected this crude mass for esterification with TMS-diazomethane in benzene. Neither new spot was observed in TLC analysis nor significant peaks were detected in NMR analysis, so we concluded that reaction product was not the desired compound (Scheme 33).



Scheme 33: Desired acid was not obtained.

Fortunately, we were able to develop satisfactory crystallisation of this undesired product from hexane:ethyl acetate (yield: 40%) and were able to obtain nice crystals for X–ray analysis. The single crystal analysis revealed that it is the spiro compound **24** as shown in Figure 16.

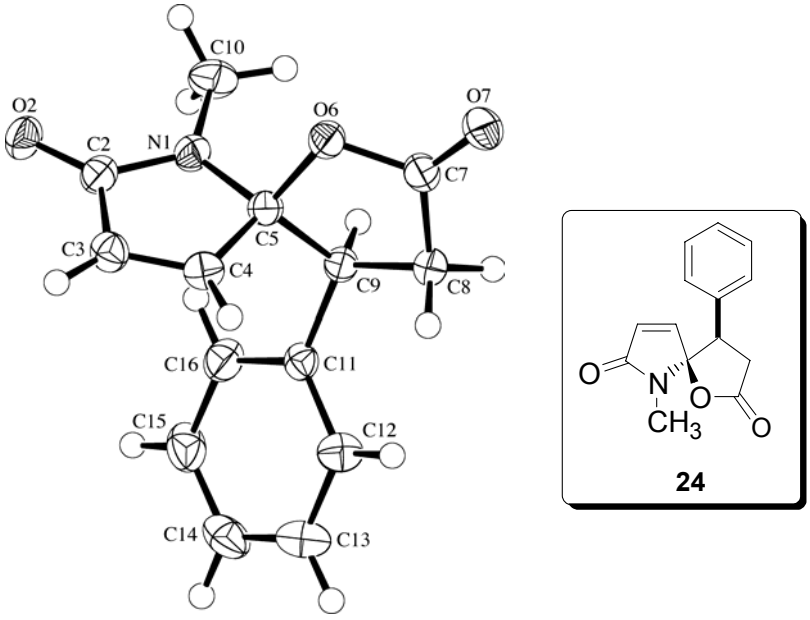
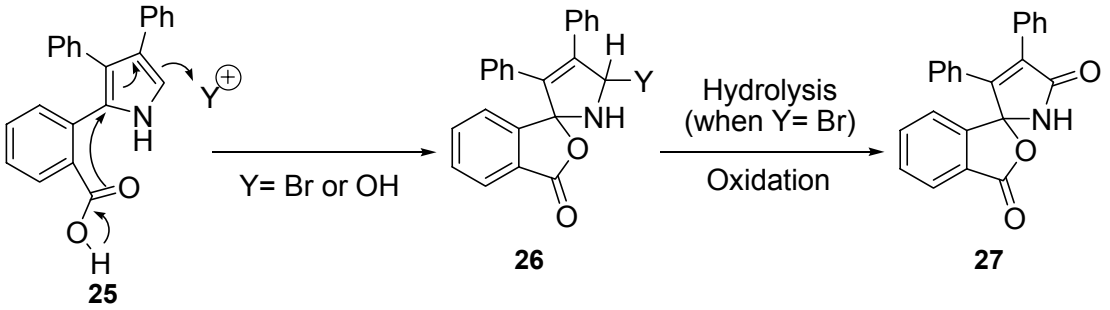


Figure 16: *Crystal structure of spiro compound* **24***.*

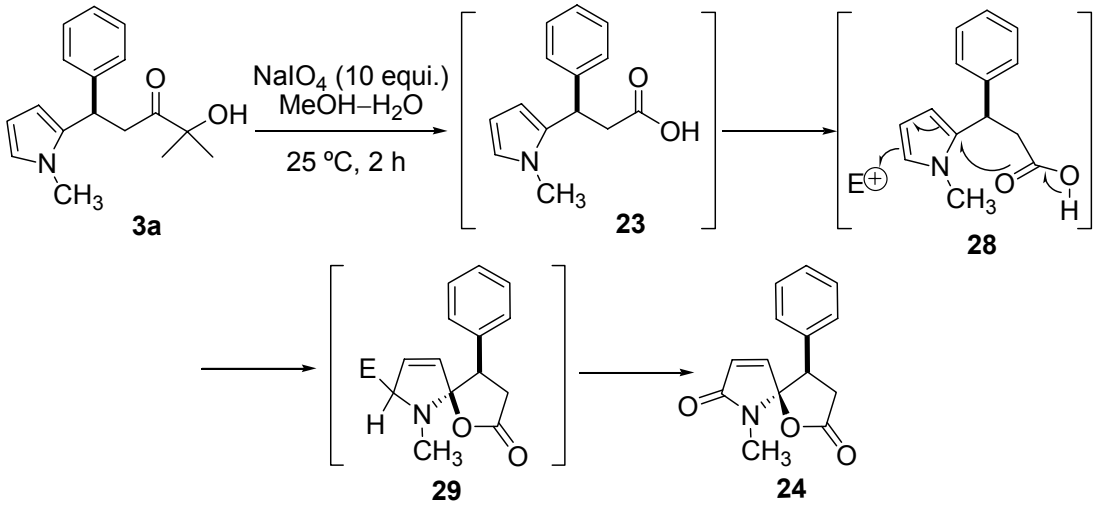
While searching for more information about the spiro compound **24**, we found that only once these type of compounds were reported in the literature,[103] during the rearrangement of phthalimidine derivatives **25** (Scheme 34). The concerted mechanism may well operate here for the conversion of free carboxylic acid to the cyclic compound **27**.

[103] Scartoni, V.; Marsili, A. *Tetrahedron Lett.* **1969**, *11*, 887—890.



Scheme 34: Literature reported mechanism for formation of spiro compounds of similar type.

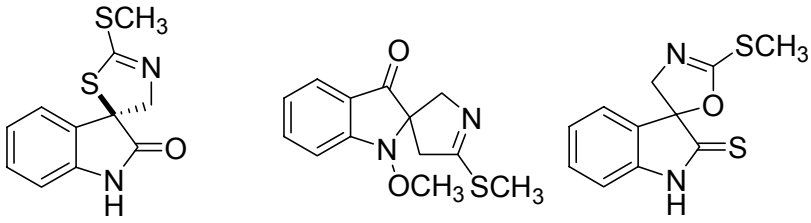
On the basis of above rationale, we propose the following reaction path (Scheme 35) which could explain formation of the isolated spiro compound **24** under the oxidising conditions employed by us.



Scheme 35: Proposed mechanism for formation of spiro compound **24**.

While this type of spiro compounds are apparently not documented, some related spiro compounds derived from indole have been recently disclosed by Pedras and co-workers[104] during total synthesis of a novel anti-fungal Erucalexins of Phytoalexins category (Figure 17).

[104] Pedras, M. S. C.; Suchy, M.; Ahiahonu, P. W. K. *Org. Biomol. Chem.* **2006**, *4*, 691—701.

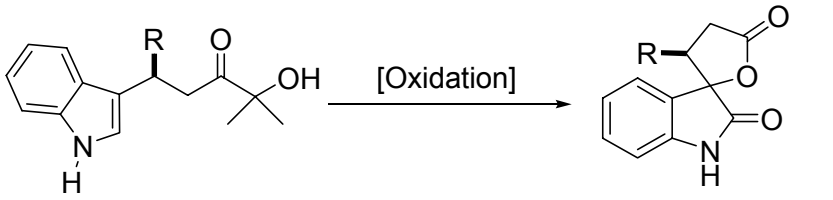


30 Phytoalexin

31 **32** Erucalexin: Possible structures

Figure 17: *Anti-fungal Erucalexins of Phytoalexins category.*

Based on the isolation of products like **24** under the oxidation conditions we used, and assuming a similar behaviour for our F–C adducts of indole, one may anticipate that structures **34** could be afforded (Scheme 36).



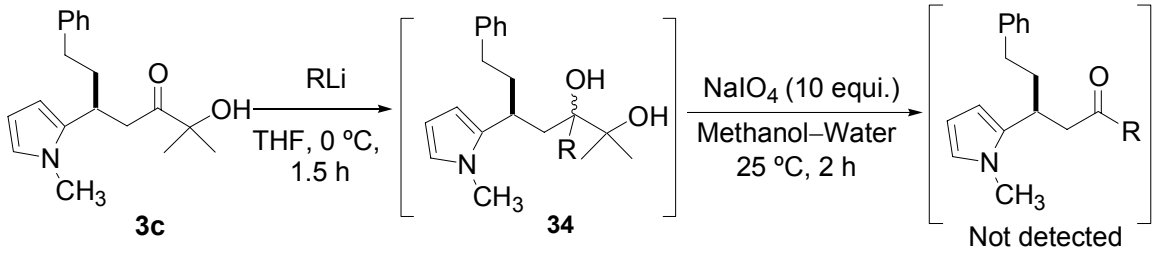
33 F–C adducts of indole

34 Anticipated product

Scheme 36: Anticipated product of oxidation.

Then we attempted oxidation of the F–C adduct **3a** by using cerium ammonium nitrate (CAN) in acetonitrile, but we failed to obtain the desired acid derivative again. So we subjected phenylethyl enone derived F–C adduct **3c** to the treatment with $NaIO_4$/methanol-water system to see whether the β–alkyl derivatives were less prone to heterocyclic ring oxidation. However, the ^1H NMR study revealed again that we were obtaining similar spiro compound only. These observations indicated clearly that under the oxidation conditions being used the pyrrole ring is too prone to be oxidise, and apparently no selective oxidative scission of the ketol side-chain is feasible without affecting the electron-rich ring. Optionally, the protection of the *N–H* group of pyrrole moiety with electron withdrawing groups like Boc- would likely deactivate the ring against side reactions. However, it would increase the number of steps, so at that point, we preferred to explore other alternatives.

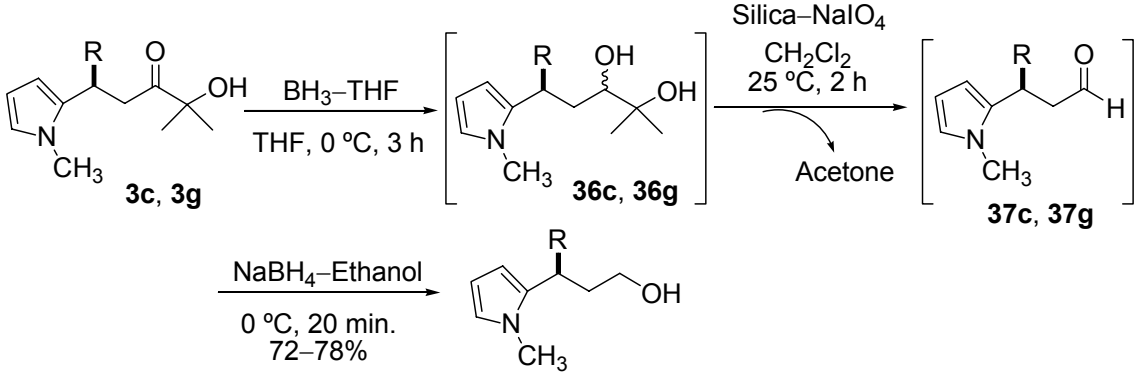
A second option for elaboration of F–C adduct consists of nucleophilic addition of alkyl and aryl lithium reagents to the ketone carbonyl and subsequent diol cleavage (Scheme 37). Unfortunately, the treatment with $NaIO_4$/MeOH-H_2O of the intermediate diol **34** led to formation of undesired product. Thus, the electron rich pyrrole ring did not permit the selective oxidation of diol moiety.



Scheme 37: Attempt to obtain ketone derivative was failed.

The third option was to transform ketol into aldehyde. We reduced the ketol moiety of **3c**, **3g** to diol by simple treatment with borane–THF in 3 h at 0 ºC. The subsequent oxidation with $NaIO_4$ in methanol-water failed again. So we turned our attention to other oxidation systems.

Recently our laboratory had utilised silica gel supported sodium metaperiodate as mild oxidising agent for diol cleavage.[105,106] The idea worked nicely as we were able to oxidise the unisolated crude diols **36c**, **36g** to the corresponding aldehydes **37c** and **37g** using the latter procedure in dichloromethane at room temperature. As aldehydes are prone to air oxidation, their isolation was difficult, a problem that MacMillan[107] had observed for related aldehydes. Therefore, crude aldehydes (**37c** and **37g**) were transformed into the corresponding alcohols (**38c** and **38g**) by reduction with $NaBH_4$ in good yields (72–78% overall three step yield), and most importantly, without appreciable racemisation of the product (Scheme 39).



38c R= $PhCH_2CH_2$, 90% ee
38g R= i-Pr, 95% ee
Observed $[\alpha]_D$= + 31.1º (*c*= 1, MeOH)
Reported $[\alpha]_D$ (for *S*–adduct)= – 20º (*c*= 1, MeOH) (91% ee)[107]

Scheme 38: Elaboration of F–C adducts into aldehydes.

[105] Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem*. **1999**, *64*, 8193—8200.
[106] Zhong, Y. −L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622—2624.
[107] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370—4371.

Thus, the potential of this catalytic approach is demonstrated by the elaboration of adducts through oxidative cleavage of the ketol moiety to aldehydes in good yields and excellent enantioselectivities. Moreover, in these transformations, acetone is the only by-product formed which is an additional aspect of the approach that is of practical interest.

3.3.8 Assignment of the configuration

The absolute configuration (*R*) of adduct **3g** was determined by transforming it into the corresponding aldehyde **37g** and comparison of the optical rotation of its alcohol derivative **38g** with published values (Scheme 38). The same configuration (*R*) for adducts **3a, 3b, 3h, 18** and the opposite (*S*) configuration for adducts **3c–3f** was assumed based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

3.4 Results and Discussion: Indole

Having established the capability of Cu(II)–bis(oxazoline) complexes in promoting enantioselective F–C alkylations of pyrroles, we sought to extend this Friedel–Crafts strategy to indole nucleophiles because of its presence in large plethora of naturally occuring compounds. Despite structural similarities, it has long been established[108] that the pyrrole *π*–system is significantly more active towards electrophilic substitution than the indole framework. Indeed, poor reaction rates and enantioselectivities were observed in the F–C alkylation of indole under conditions that work nicely with pyrrole in the previously reported cases.[109] Recently Evans[110] reported a catalytic method that provides high enantisoselectivity with N–substituted indoles, but the parent *N–H* indole showed less enantioselectivity, proving parent *N–H* indole as a challenging substrate for obtaining high selectivity. As described above, the F–C alkylation reactions of α'–hydroxy enones under the optimised conditions with *N-H* pyrrole resulted in comparatively lower selectivity and yields, along with difficulties in reaction treatment. However, it would be convenient to have a Friedel–Crafts method available for indoles, in particular for indole with no substitution on the nitrogen atom. For that reason, we selected indole itself as the test substrate and a brief search of best conditions for the catalytic reaction with α'–hydroxy enones was undertaken.

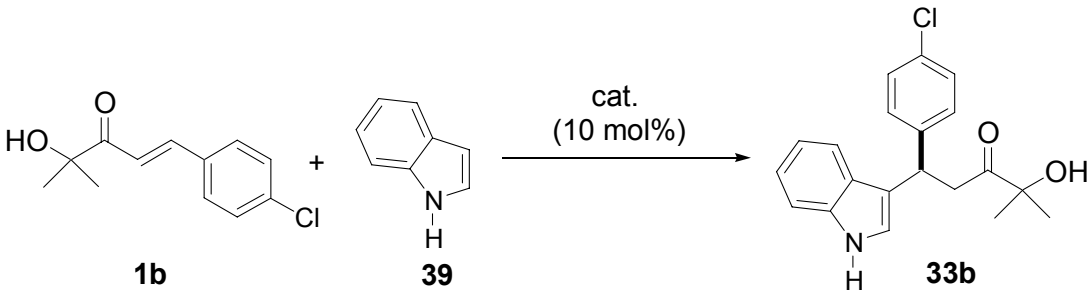
3.4.1 Reaction optimisation with β–aryl enones

The F–C reaction of indole with β–aryl substituted α'–hydroxy enones led to somewhat limited results. For instance, F–C reaction of indole **39** with *p*-Cl-phenyl enone **1b** was tested in combination of various catalysts and varying conditions (Table 6).

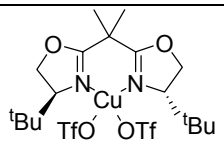
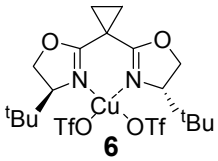
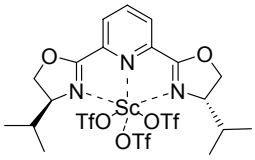
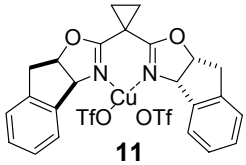
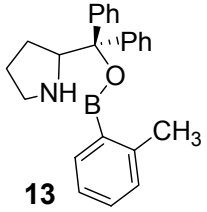
As seen in Table 6, extention of F–C alkylation methodology to β–aryl enones resulted in generally very good yields but modest level of enantioselectivity. In the first run, at 25 ºC, the F–C reaction of enone **1b** and indole **39** using catalyst **4** afforded only 53% ee (entry 1). Increasing catalyst loading to 30% had a little effect on selelectivity (entry 2). Shifting copper source from Cu(II) to Cu(I) went unrewarding, as catalyst prepared by combination of **L−1** and CuOTf showed poor results (entry 3). Employing tailored catalyst **6** led to 69% ee (entry 4). Increasing catalyst loading to 30% and 50% could enhance up to 80% ee (entries 5, 8). Employing additives like molecular sieves MS–4Å proved unefficient

[108] Cipiciani, A.; Clementi, S.; Linda, P.; Marino, G.; Savelli, G. *J. Chem. Soc.*, *Perkin Trans. 2,* **1977**, 1284—1287.
[109] MacMillan, D. W. C.; Austin, J. F. *J. Am. Chem. Soc*. **2002**, *124*, 1172—1173.
[110] Evans, D. A. ; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10780—10781.

Table 6: *Enantioselective Friedel–Crafts alkylation of indole* **39** *with α'–hydroxy enone* **1b** *promoted by catalysts* **4, 6, 10, 11** and **13**[a]:



1b **39** **33b**

Entry	Catalyst	T, ºC	Time, h	Yield, %[b]	ee, %[c]
1		25	24	95	53
2	**4**	0	48	92	75[f]
3	**L-1** + CuOTf	25	6	90	67
4		25	48	97	69
5		**0**	**48**	**95**	**80**[f]
6		25	36	94	71[h]
7	**6**	reflux	5	95	75
8		0	24	90	80[g]
9	**L-2** + $Cu(SbF_6)_2$	0	5	92	53
10	 **10**	25	24	90	11
11		25	24	92	60
12	**11**	25	24	95	55[e]
13	 **13**	25	24	0[d]	0

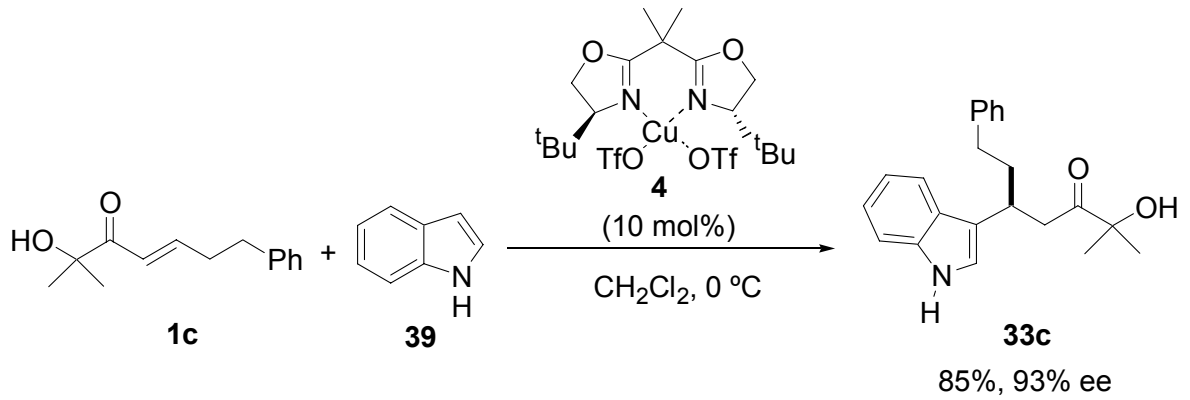
[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale and 0.25 M substrate concentration. Mole ratio of arene:**1b**:cat is 2:1:0.1. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on NMR of crude

product after specified time. [e] Mole ratio of arene:**1b**:cat is 3:1:0.1. [f] 30% catalyst. [g] 50% catalyst. [h] Molecular sieves MS–4Å as additives.

(entry 6). On the other hand, the reaction at reflux temperature was unsuccessful in enhancing selectivity in this particular case (entry 7) (See below for temperature tolerance of F–C reactions of β–alkyl enones). Switching the counter ions from triflate (OTf) to hexafluoro antimonate (SbF_6) lowered selectivity further (entry 9). Use of catalyst **10** (entry 10), and catalyst **11** (entries 11, 12), did not help either to enhance the ee. The reaction did not proceed at all with catalyst **13** (entry 13).

3.4.2 Reaction optimisation with β–alkyl enones

A brief search of best conditions for the F–C reaction with enone **1c** was undertaken. In an initial reaction using the conditions optimised for N-methyl pyrrole **2**, the reaction of enone **1c** and indole **39** gave adduct **33c** in 85% isolated yield and most notably with 93% ee (Scheme 39).

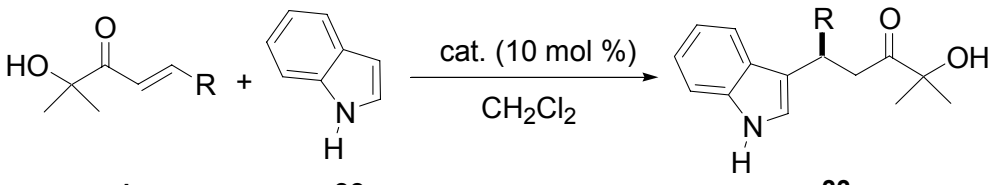


Scheme 39: Groundwork trial for F–C alkylation of indole **39** with α'–hydroxy enone **1c**

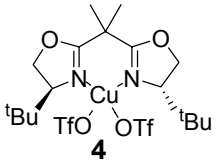
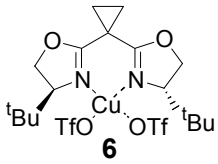
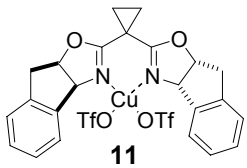
Immediately thereafter, the scope of the reaction with several enones was explored using alternative catalysts **4**, **6** and **11**. Hence, as Table 7 shows, adducts **33c**, **33d**, **33g—33i** were formed with 90–97% ee in 80–88% yields. Excellent enantiomeric excesses and good yields were obtained with a series of enones (**1c**, **1d**, **1g—1i**) which vary in the identity of the β–alkyl substituent.

By changing copper source from Cu(II) to Cu(I) resulted in diminished selectivity (Table 7, entry 1). Enones bearing branched chains at the β–position showed attenuated

Table 7: *Friedel–Crafts alkylation of indole* **39** *with various α'–hydroxy enones* **1c, 1d, 1g—1i** *promoted by catalysts* **4, 6** *and* **11**[a]**:**



1 **39** **33**

Entry	Enone	R	Catalyst	T, ºC	Time, h	Product	Yield, % [b,c]	ee, %[f]
1	**1c**	$PhCH_2CH_2$	**L-1** + CuOTf	0	5	**33c**	66	87
2				0	3		85	98[i]
3				0	3		85	93
4				reflux	0.5		83	98
5				25	3		87	94[j]
6	**1d**	$CH_3(CH_2)_5$		0	12	**33d**	84	96
7				25	12		80	90
8				0	12		88	96[j]
9				0	12		85	96[k]
10	**1g**	$(CH_3)_2CH$		0	48	**33g**	14[d]	71
11				25	24		68	93
12				reflux	4		81	95
13	**1h**	*c*-C_6H_{11}	**4**	25	36	**33h**	44[d,e]	92[g]
14			**6**	25	24		80	96
15				25	24		73	58
16	**1i**	CH_3	**4**	0	3	**33i**	65[h]	98

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale and 0.25 M substrate concentration, Mole ratio of arene:enone:cat is 2:1:0.1. [b] Yield of isolated product after column chromatography. [c] By-products **40d**, **40g**, **40h** were observed and were isolated by column purification (entry 7 = 10%, entry 11 = 29%, entry 15 = 18%). [d] Reaction conversion based on NMR of crude product after specified time. [e] Using 3 molar equi. of Indole **39**. [f] Determined by chiral HPLC. [g] Mol ratio of arene:enone:cat is 3:1:0.1. [h] Impurities were associated with starting enone. [i] Reaction carried out at 10 mmol scale. [j] Catalyst used is 5 mol%. [k] Catalyst used is 2 mol%.

reactivity and lower selectivity using catalyst **4**, but using catalyst **6**,[111] high enantiomeric excesses could be attained (entries 10 & 11, from 71 to 93% ee; entry 14: 96% ee, whereas with cat **4**: 85% ee). However, with enone **1g**, only moderate chemical yield was obtained (entry 11). To achieve higher reactivity, we attempted the reaction at higher temperature i.e. reflux temperature and surprisingly, we obtained the F–C adduct **33g** in 81% isolated yield and 95% ee (entry 12). Based on this result, we attempted to evaluate the generality of temperature tolerance. What was really surprising is the tolerance to considerably high temperatures. As seen for enone **1c** (R= $PhCH_2CH_2$) reaction carried out at reflux temperature resulted in 98% ee and 83% isolated yield (entry 4). Hence, while the typical reaction temperature was either 0 or 25 °C, the catalytic system showed remarkable performance even at reflux temperature (40 °C). Importantly, increasing the scale to 10 mmol (entry 2) and lowering the catalyst loading to 5 and 2 mol% (entries 5, 8 and 9), resulted in no significant loss of enantioselectivity and yield, which represents the lowest catalyst/substrate ratio employed in the asymmetric Friedel–Crafts reaction.[112] However, lowering the catalyst loading below 2 mol% proved adverse for the selectivity. This aspect along with the suitability of temperatures in the 0 to 40 ºC range is of very much importance from a practical point of view. Thus, apart from obvious economic and environmental benefits, this temperature tolerance opens the way to implementation of microwave assisted reaction technology.[113]

3.4.3 Scope of the reaction

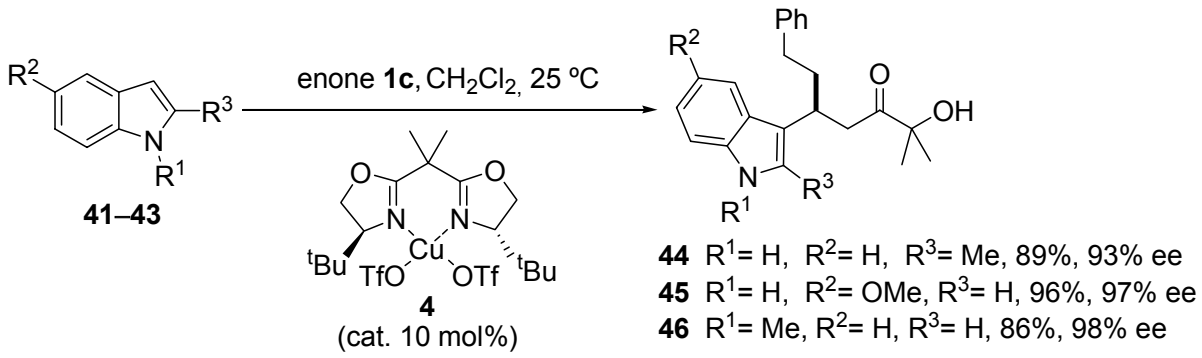
To ensure the generality of indole skeleton, the reactions with differently substituted indoles were tested under optimised conditions. Hence, the F–C reactions of enone **1c** with differently substituted indoles **41—43** worked efficiently and provided adducts **44—46** in good to excellent yields and enantiomeric excesses (Scheme 40). It is noteworthy that substituents on the indole ring did not influence the enantiofacial selectivity with catalyst **4**. The by-products were detected in trace amounts by TLC analysis and were not isolated. However 5–cyano indole failed to give the reaction, demonstrating limitation of this methodology towards less reactive indole frameworks.

---

[111] For enhancement of enantiomeric excess by ligand distortion, see: (a) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875—5878. (b) Lipkowitz, K. B.; Schefzick, S.; Avnir, D. *J. Am. Chem. Soc.* **2001**, *123*, 6710—6711.

[112] Jensen, K. B.; Thorhauge, J.; Mazell, R.-G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 160—163.

[113] Kappe, O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250—6284.



Scheme 40: Enantioselective Friedel–Crafts alkylation of differently substituted indoles with α'–hydroxy enone **1c** catalysed by **4**.

3.4.4 Study of by-products

In some of the reactions included in Table 7 (enone **1d**, **1g** and **1h**), minor to considerable amount of a by-products (10–29%) were observed. Identification of the by-product structure **40g** (isolated in 29% yield from the reaction of enone **1g** and indole **39** using cat. **6** at 25 ºC; Table 7, entry 11) was made by X–ray analysis after chromatographic separation and subsequent crystallisation from hexane-ethyl acetate mixture (Figure 18).

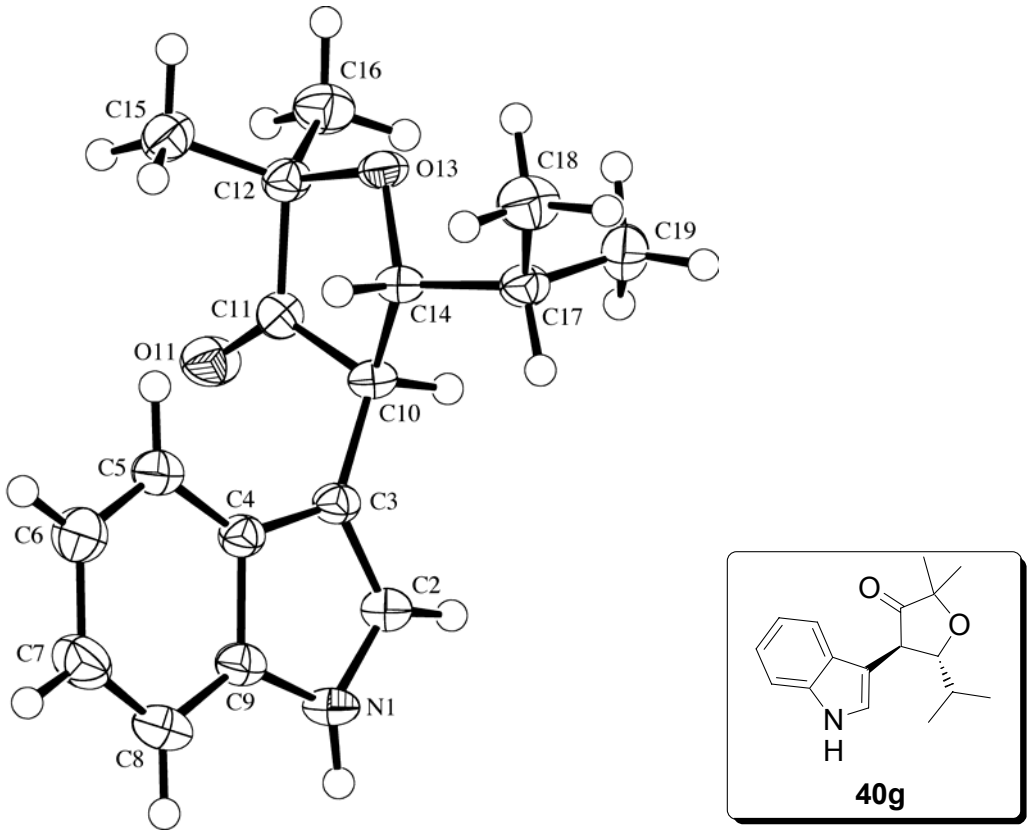
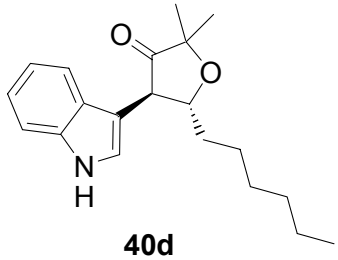
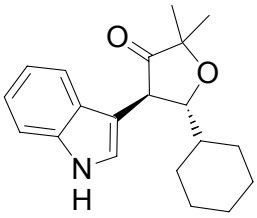


Figure 18: *Crystal structure of by-product* **40g**.

By analogy of the ^{1}H NMR spectra of the other by-products obtained (**40d**, **40h**), similar structure assignments were made (Figure 19). The assignment of the relative configuration for the adduct **40g** from enone **1g** was determined by X–ray diffraction analysis. The configuration of the other isolated by-products was assigned by analogy (Figure 18 and 19).



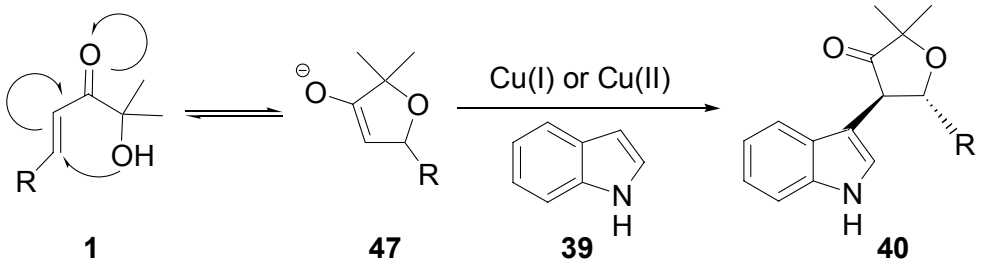
40d
(10%, Table 7, entry 7)



40h
(18%, Table 7, entry 15)

Figure 19: *Other isolated by-products.*

A plausible route to these by-products is depicted in Scheme 41. As illustrated, we propose that an intramolecular conjugate addition of hydroxyl to the enone could generate a enolate like species **47** which subsequently could be coupled with indole in the presence of Cu−species.



1 **47** **39** **40**

Scheme 41: Proposed mechanism for the by-product formation.

Recently, Baran[114] and Chao-Jun Li,[115] independently reported similar copper mediated free radical coupling reactions of indole and enolates en route to the synthesis of Hapalindole derivatives. According to them, while oxidative dimerisation of enolates is known, the analogous process with indoles (or metallo-enamines) is not. In fact, the heterocoupling of enolates has seen little use in synthesis since the process is plagued by low yields, the use of equimolar quantities of metal salts relative to those of all enolate species present, and the requirement of a large excess (3–10 equi.) of one of the partners to avoid homocoupling. While a potential utility of the above proposal, if correct (Scheme 41),

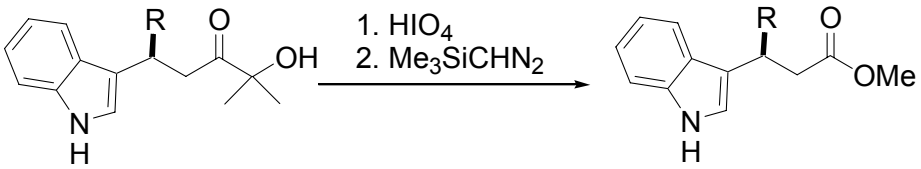
[114] Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 7450—7451.
[115] Li, C. J.; Li, Z. *J. Am. Chem. Soc*. **2005**, *127*, 6968—6969.

would be the implementation of a catalytic tandem alkoxy conjugate addition and subsequent enolate trapping via indole coupling, this aspect remains unexplored yet.

3.4.5 Elaboration of the F–C adducts

The potential of this catalytic approach for indole derivatives is best demonstrated by the versatile elaboration of adducts through oxidative cleavage of the ketol moiety. As for the pyrrole adducts, initially adduct **33c** was subjected to treatment with $NaIO_4$ (10 equi.) in methanol-water, but we were unsuccessful to get the desired carboxylic acid derivative and instead uncharacterised dark red mass was obtained. As in the case of electron rich pyrrole rings, indole framework may be too susceptible against oxidising reagents present in excess. Unfortunately, by decreasing the mole equivalents of $NaIO_4$ from 10 equivalents to 6 equivalents and 3 equivalents, no improvement was observed. We tried by changing the solvent to THF at 0 ºC which again was a failure. Next we tried the ketol cleavage by using varying amounts (10, 5 and 3 mol equivalents) of cerium ammonium nitrate (CAN) in acetonitrile, still we were unsuccessful to get the desired acid.

Our third attempt was successful (Scheme 42). Addition of 1.2 mole equivalents of H_5IO_6 to F–C adducts **33c** and **33i** in diethyl ether at 0 ºC, subsequent stirring at same temperature for 10–11 h, and quenching by 5% aq. sodium sulphite (Na_2SO_3), effected a smooth oxidative cleavage of ketols to the corresponding crude carboxylic acid products in quantitative yields. These carboxylic acids were characterised as methyl esters **48c** and **48i** after purification by column chromatography to give 60% and 67% chemical yield and 98% and 94% ee, respectively.



33c, 33i

48c R= Ph $(CH_2)_2$ (60%, 98% ee)

48i R= Me (67%, 94% ee)

Observed $[\alpha]_D$= + 4.1º (*c*= 1, CH_2Cl_2)

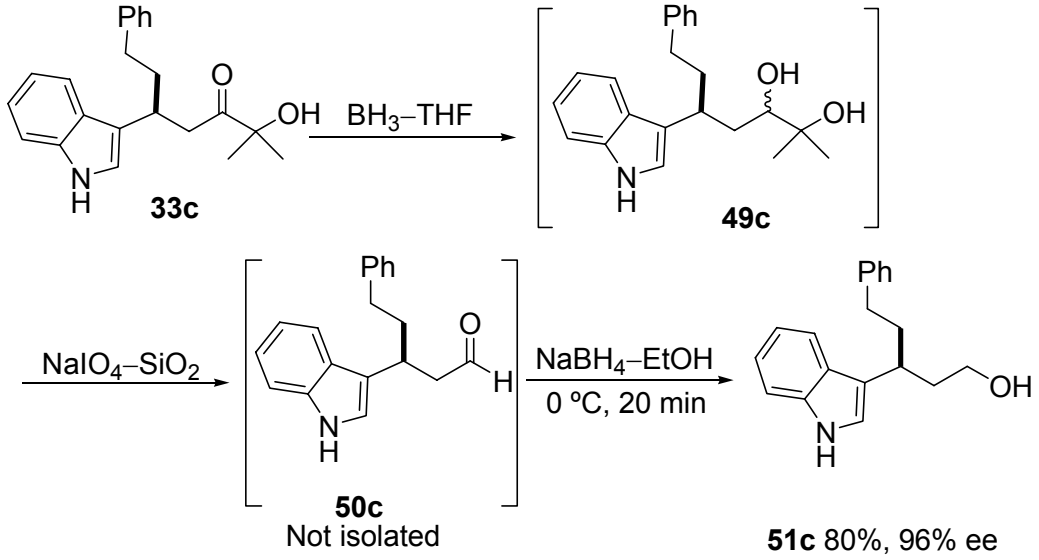
Reported $[\alpha]_D$= + 2.7º (*c*= 1.10, CH_2Cl_2) (83% ee)[116]

Scheme 42: Preparation of carboxylic acid derivatives **48c, 48i**.

3.4.6 Assignment of the configuration

The absolute configuration (*S*) of adduct **33i** was determined by comparison of optical rotation of the methyl ester derivative **48i** with published values[116] (Scheme 42). The same configuration (*S*) for adducts **33c, 33d, 44–46** and the opposite (*R*) configuration for adducts **33b, 33g, 33h** was assumed based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

Alternatively, we were able to get the aldehyde derivative **50c** which was transformed into its corresponding alcohol **51c** by applying the same method we used in case of N-methyl pyrrole derivatives. Reduction of ketol **33c** to the corresponding diol **49c** with borane–THF at 0 ºC in 3 h and subsequent oxidation by silica gel supported sodium metaperiodate as mild oxidizing agent[117] in dichloromethane at room temperature yielded the corresponding aldehyde (Scheme 43). Crude aldehyde product **50c** was subjected to reduction with $NaBH_4$ in ethanol to the corresponding alcohol, as it was prone to oxidation.[118] Alcohol **51c** was obtained in good yield (80% overall three step yield), and most importantly, without appreciable racemisation of the product.

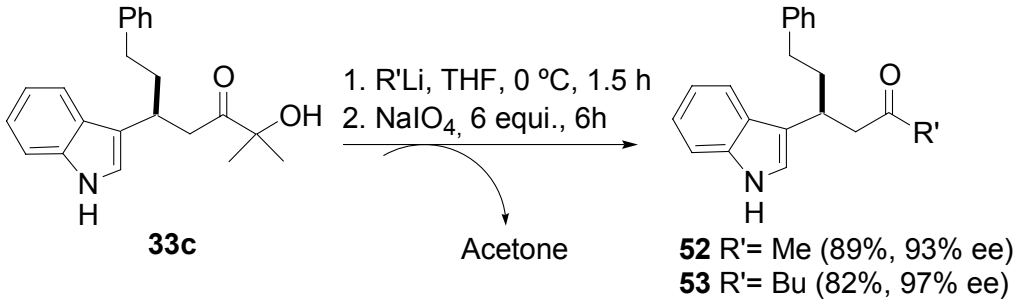


Scheme 43: Preparation of aldehyde derivative **50c**.

In general, obtaining β–indolyl ketone derivatives is more challenging due to the difficulties in achieving higher stereoselectivity in F–C methodology starting from simple

[116] Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10780—10781.
[117] Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem*. **1999**, *64*, 8193—8200.
[118] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370—4371.

monodentate α,β–unsaturated ketone templates.[119] In our case however, addition of available alkyl lithium reagents like MeLi or n-BuLi in THF, and subsequent oxidation of crude diol by using 6 equivalents $NaIO_4$ (added in two lots of 3 equivalents) in methanol-water system provided the desired ketones in high enantiomeric purity (Scheme 44). Ketones **52** and **53** were obtained in 89% and 82% isolated yields and 93% and 97% ee respectively. Again, in these transformations, acetone is the only by-product formed.



Scheme 44: Preparation of ketone derivatives **52** and **53**.

3.4.7 Activation mechanism and stereochemical model

A rationale that would explain the catalytic activation of the reaction as well as the configuration of adducts was seeked. The catalytic cycle we propose is depicted in Figure 20. Chelation of α'–hydroxy enone substrates **1** to the Cu(II) center produces the activated substrate-catalyst complex **54**, which undergoes nucleophilic addition of indole **39** to provide the complexed F–C alkylated indole **55** with chiral catalyst. Subsequent decomplexation affords the product **33** and concomitantly regenerates the catalyst **4**. Hence, the sense of asymmetric induction observed in the F–C alkylation reactions is consistent with the model **54** which considers a Cu(II) metal center adopting a distorted square planar geometry, as previously disclosed in the literature for similar bidentate substrates.[120]

[119] Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani–Ronchi, A. *J. Org. Chem.* **2004***, 69*, 7511—7518.
[120] (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325—335 and references therein. (b) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888—1898.

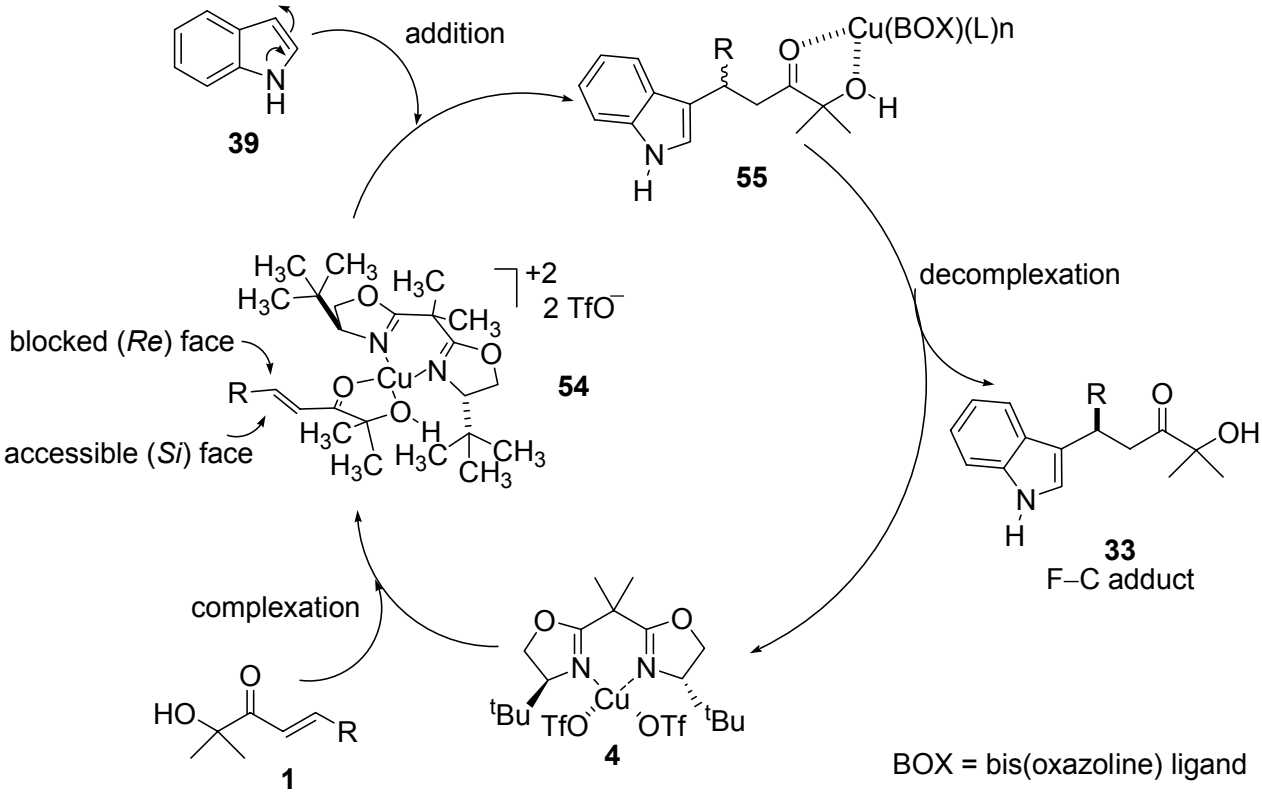
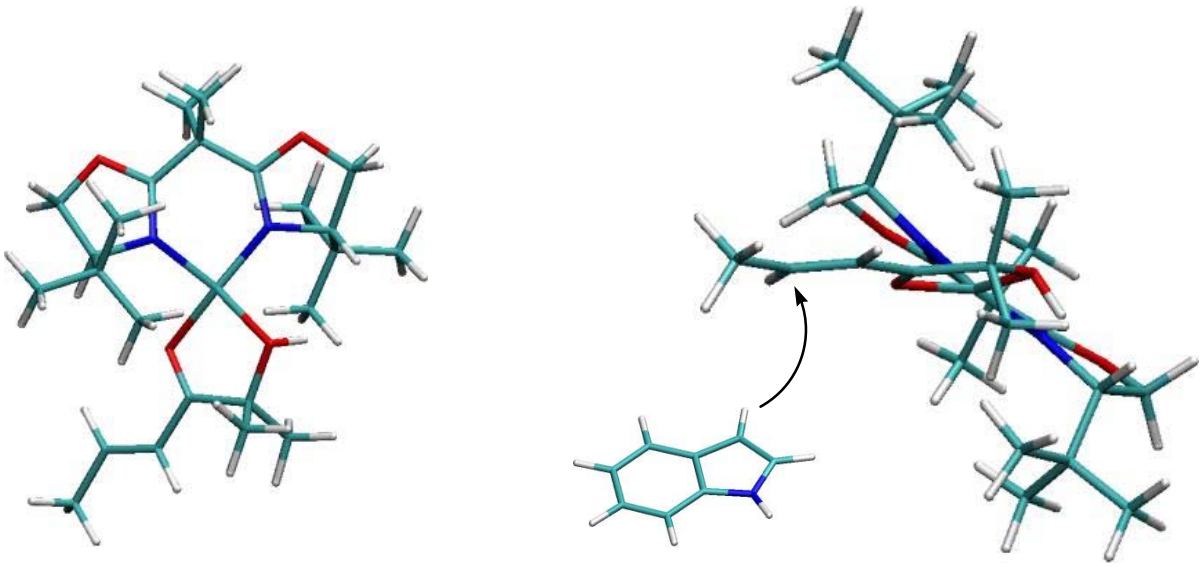


Figure 20: *Activation mechanism and stereochemical model.*

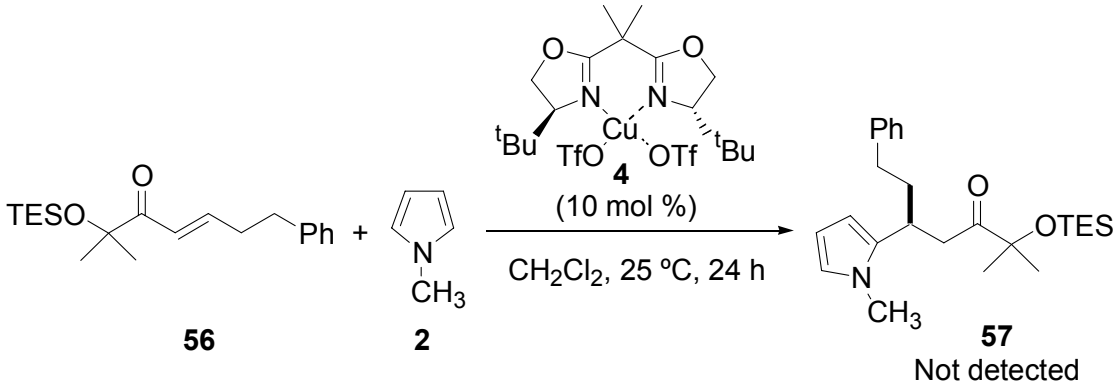
A PM3 geometry optimisation for such a complexes provides a nice explaination of the preferred attack of the indole ring to less shielded *Si*– face of α'–hydroxy enone (Figure 21).



View A **View B**

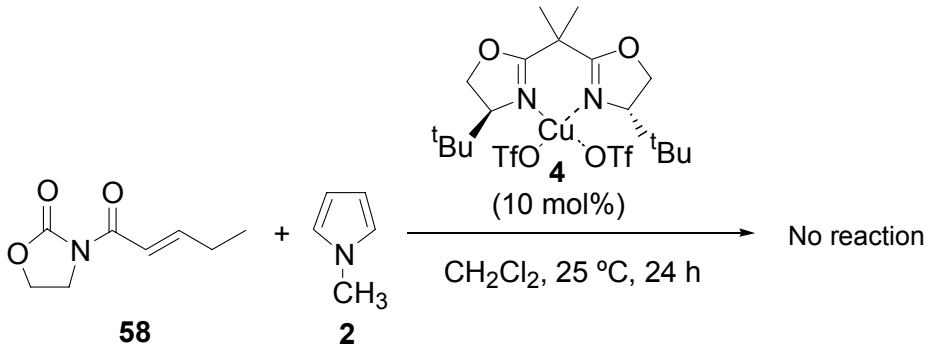
Figure 21: *Two stereoviews of the PM3 minimised structure of the enone-chiral catalyst complex (R=CH_3) showing the more accessible Si- face for indole attack.*

Further evidence of the effective 1,4–metal binding chelated structure that α'–hydroxy enones adopt, was obtained from the control experiments carried out with the corresponding O–silylated hydroxy enones.[121] Thus, the reaction of triethylsilyloxy enone **56** with N-methyl pyrrole under the optimised conditions did not proceed at all, and unreacted starting materials were recovered (Scheme 45). Apparently, the greatly diminished capability of the triethylsilyloxy group for metal chelation affects adversely to the substrate activation, and indirectly proves the need for substrate chelation as a key element of the present methodology.



Scheme 45: Effects of –OH protection of α'–hydroxy enone in F–C reaction of N-methyl pyrrole.

On the other hand, the unique properties of α'–hydroxy enone templates can be reflected by failure of F–C alkylation reaction where N–enoyl oxazolidinone[122] **58** was employed instead of α'–hydroxy enone (Scheme 46).



Scheme 46: F–C alkylation reaction where N–enoyl oxazolidinone **58** was employed.

[121] O–silylated hydroxy enone is easily prepared from the corresponding –OH enone through TEA/DMAP promoted silylation (see Experimental section for details).

[122] (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325—335. (b) Chaozhong, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339—1350.

4. Conjugate Additions of Diethyl Zinc

4.1 Introduction

The conjugate addition of various organometallic reagents to α,β–unsaturated carbonyl compounds is an important process for *C—C* bond formation in organic synthesis. The potential of conjugate addition reactions in synthesis is partly due to the large variety of organometallic reagents and substrates that can be employed and these features have been a strong impetus in the search for enantioselective conjugate additions. Enantioselective Michael addition of a chiral organometallic reagent to a prochiral substrate is an attractive method for creating a center of chirality in an organic molecule.[123]

Most of the enantioselective catalytic approaches were based on use of Grignard reagents as primary organometallics. Michael additions of organolithium, Grignard, and diorganozinc reagents to α,β–unsaturated carbonyl compounds are catalysed inter alia by copper, nickel, and cobalt salts.[124] Although several soft carbon nucleophiles (such as malonates) undergo Michael addition reaction, harder carbon nucleophiles such as organometallic reagents need the presence of transition metals to avoid direct attack on the carbonyl group of the Michael acceptor. In this regard, traditionally copper has found the broadest application in, and various organocopper species have been widely used.[125] Until mid 1990s, the stoichiometric approach with covalent auxiliaries was most successful.[126]

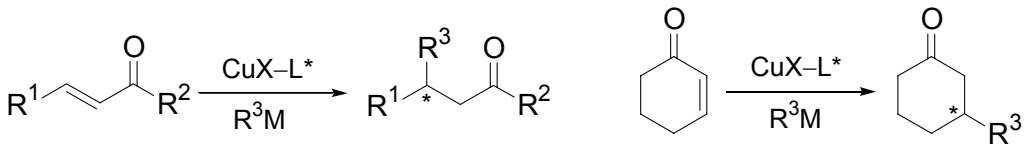


Figure 22: *Addition of organometallic reagent (R^3M) to cyclic and acyclic acceptors.*

[123] Reviews: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev*. **1992**, *92*, 771—806. (b) Krause, N.; Kontakte (Darmstadt) **1993**, *1*, 3—13. (c) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed*. **1997**, *36*, 186—204. (d) Krause, N. *Angew. Chem. Int. Ed*. **1998**, *37*, 283—285.

[124] (a) Zhou, Q. –L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467—4478. (b) Van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135—6138. (c) Spescha, M.; Rihs, G. *Helv. Chim. Acta* **1993**, *76*, 1219—1230. (d) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275—4278. (e) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571—1572. (f) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011—5012. (g) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479—4491. (h) de Vries, A. H. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1377—1378.

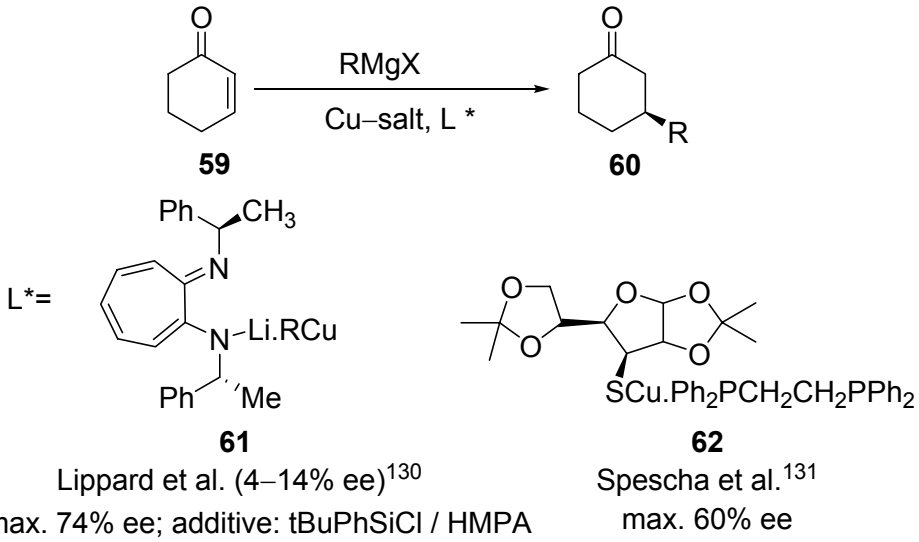
[125] Kozlowaski, J. A. In *Comprehensive Organic Synthesis*; Ed.: Trost, B. M.; Fleming, I.; Oxford, Pergamon Press, 1991, Vol. 4, 169—198.

[126] (a) Alexakis, A. In *Organocopper Reagents*, *a Practical Approach*; Ed.: Taylor, R. J. K., Chapt. 8. Oxford University Press, 1994, pp. 159—183. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley, New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; Weinheim, VCH, 1993. (d) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed.* **1997**, *36*, 186—204.

For high enantioselectivites, chirally modified organocopper compounds of composition RCu(L*)Li were used. The chiral nontransferable ligand L* controls the stereochemical course of the transfer of group `R´ to the substrate.

By using stoichiometric amounts of these ¨chiral cuprates¨, the groups of Bertz, Corey, Dieter, Rossiter, and Tanaka obtained the 1,4–adducts with good enantioselectivities (over 90% ee in some cases), being the naturally occuring chiral alcohols and amines the most often used chiral ligands L* (e.g. ephedrine and proline derivatives).[127]

In 1941, Kharash et al[128] first reported copper catalysed conjugate addition. Currently, a number of organocopper reagents with chiral non-transferable ligands and organocuprates modified with additional chiral ligands are known that provide variable levels of ee's.[129] Lippard et al[130] in 1988 reported the reaction of 2-cyclohexenone **59** with Grignard reagents in the presence of the chiral aminotroponeimine copper complex **61** as catalyst which gave the 1,4–adducts **60** with 4–14% ee (Scheme 47). The selectivity was increased to 74% ee by addition of hexamethylphosphoric triamide (HMPA) and silyl halides. Spescha and co-workers[131] used the copper complex **62**, obtained from a thioglucofuranose derivative, as catalyst for 1,4–additions of Grignard reagents to **59**, and observed enantioselectivities of up to 60% ee.

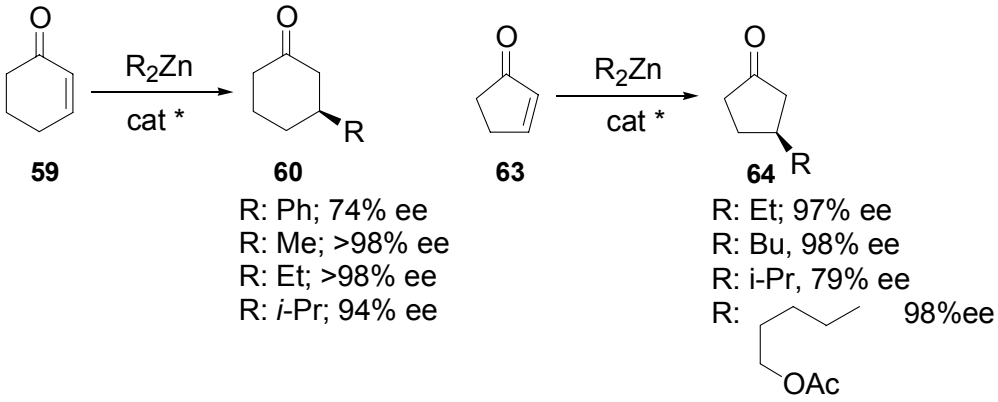


Scheme 47: Organometallic conjugate additions using Grignard reagents.

[127] Krause, N. *Angew. Chem. Int. Ed*. **1998**, *37*, 283—285.
[128] Kharash, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308—2315.
[129] (a) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed.* **1997**, *36*, 186—204. (b) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114—7116. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev*. **1992**, *92*, 771—806. (d) Krause, N.; Roder, H. A., *Synthesis* **2001**, 171—196.
[130] (a) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc*. **1988**, *110*, 3175—3182. (b) Ahn, K. H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178—3181.
[131] Spescha, M.; Rihs, G. *Helv. Chim. Acta* **1993**, *76*, 1219—1230.

Dialkyl zinc reagents

Although the use of Grignard reagents was the first to be applied to enantioselective conjugate addition, dialkylzinc reagents[132] have dominated the field since their first applicationin the mid-1990s. One of the major advantage of dialkyl zinc reagents is their functional compatibility. Dialkyl zinc reagents eliminates background reactions such as 1,2–addition which is problematic with organomagnesium nucleophiles. Dialkyl zinc reagents may be prepared by alkyl iodide/Et_2Zn exchange or by a hydroboration/transmetallation sequence.[133] This allows high synthetic versatility of the diorganozinc reagents. Only a few dialkylzinc reagents (Me_2Zn, Et_2Zn, Bu_2Zn, Ph_2Zn) are commercially available, but most widely used is diethylzinc. Dibutylzinc usually affords similar results to that of diethyl zinc. Dimethylzinc is 10 times less reactive and needs longer reaction times and higher temperatures. Although dialkylzinc reagents react extremely sluggish with carbonyl compounds, effective catalysis has been achieved by several ligands and transition metal complexes. The diisopropyl zinc and reagents bearing ester or acetal functionality have also been reported in conjugate addition reactions with good to excellent enantioselectivity (Scheme 48).



Scheme 48: Various dialkyl zinc reagents used in conjugate addition.

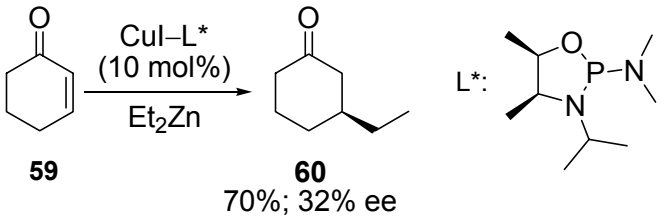
Enantioselective copper catalysed diethylzinc additions

In 1966 the first[134] use of lithium dimethylcuprates for conjugate addition was reported. The utility of organocuprates has been enhanced by the development of heterocuprates, LiCuRX (commonly X=PhS, *t*-BuO), whose advantages include greater thermal stability and atom efficiency.[135] Enantioselective conjugate additions can be

[132] Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993,** *4,* 2427—2430.
[133] Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117—2188.
[134] House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966,** *31,* 3128—3144.
[135] Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973,** *95,* 7788—7780.

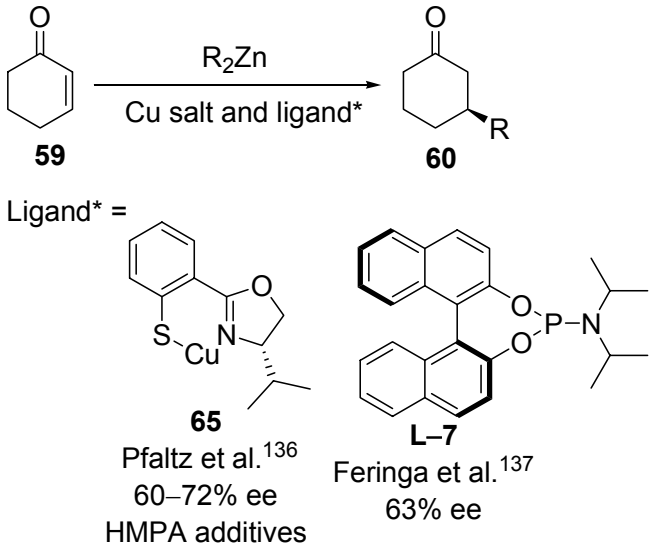
accomplished through the use of cuprates. Two main methods have been employed in enantioselective conjugate additions. The acceptor can be modified with a chiral auxiliary and thus induce diastereoselective conjugate addition. Cuprates can also be chirally modified to perform enantioselective conjugate additions. Both methods have the same disadvantage: they require either stoichiometric amounts of copper or of chiral ligand or both.

In 1993, the first application of a dialkylzinc reagent in copper-catalysed conjugate addition was reported by Alexakis. The substrate used was 2-cyclohexenone (Scheme 49).



Scheme 49: First example of copper catalysed conjugate addition of diethyl zinc.

The dihydrooxazolylthiophenolate copper complex **65** was employed by Pfaltz and co-workers[136] for the enantioselective catalytic diethyl zinc addition to cyclic enones (Scheme 50). The best results were obtained with THF as solvent and HMPA as additive. There was a pronounced dependence of the stereoselectivity on the ring size of the



Scheme 50: Conjugate additions of diethyl zinc.

[136] (a) Zhou, Q. −L.; Pfaltz, A. *Tetrahedron Lett*. **1993**, *34*, 7725—7728. (b) Zhou, Q. −L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467—4478.

substrate: 16–37% ee (for 2-cyclopentenone), 60–72% ee (for 2-cyclohexenone), and 83–87%ee (for 2-cycloheptenone). In all these cases, the regioselectivities (1,4– vs. 1,2–addition) and chemical yields are acceptable or good.

In 1996 Feringa first reported[137] the application of phosphoramidite ligands **L–7** in copper-catalysed asymmetric conjugate addition (ACA) of diethylzinc to cyclohexenone. These reactions are catalysed by copper(I) and copper(II) salts. When 2-cyclohexenone was used as substrate, stereoselectivities of 60% ee (with CuOTf) and 63% ee (with $Cu(OTf)_2$) were obtained (Scheme 50).

This led to the development of chiral monodentate phosphoramidite ligands as highly successful novel class of ligands for various catalytic reactions in future. Phosphoramidites $[P(NR_2)(OR)_2]$ represent a class of trivalent phosphorus compounds hardly recognised as ligands for catalytic transformation despite the prominent role that organophosphorus ligands, especially trivalent phosphines and phosphites, have played in asymmetric catalysis.[138,139] Among the first and best known applications of phosphoramidites is their role as activated monomers for the solid phase oligonucleotide synthesis.[140]

In case of copper–phosphoramidite catalysis employed in the ACA, two coordination sites are occupied by one bidentate or two monodentate phosphoramidite ligands, whereas the other two coordination sites remain available for the substrate and reagents (Figure 23).

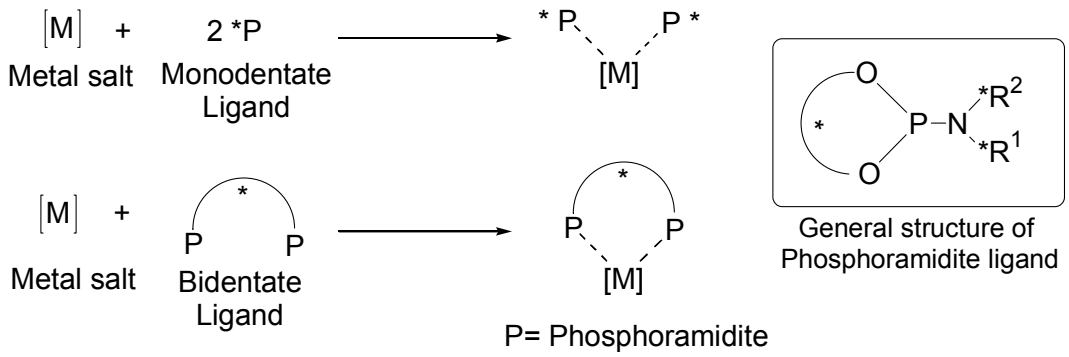


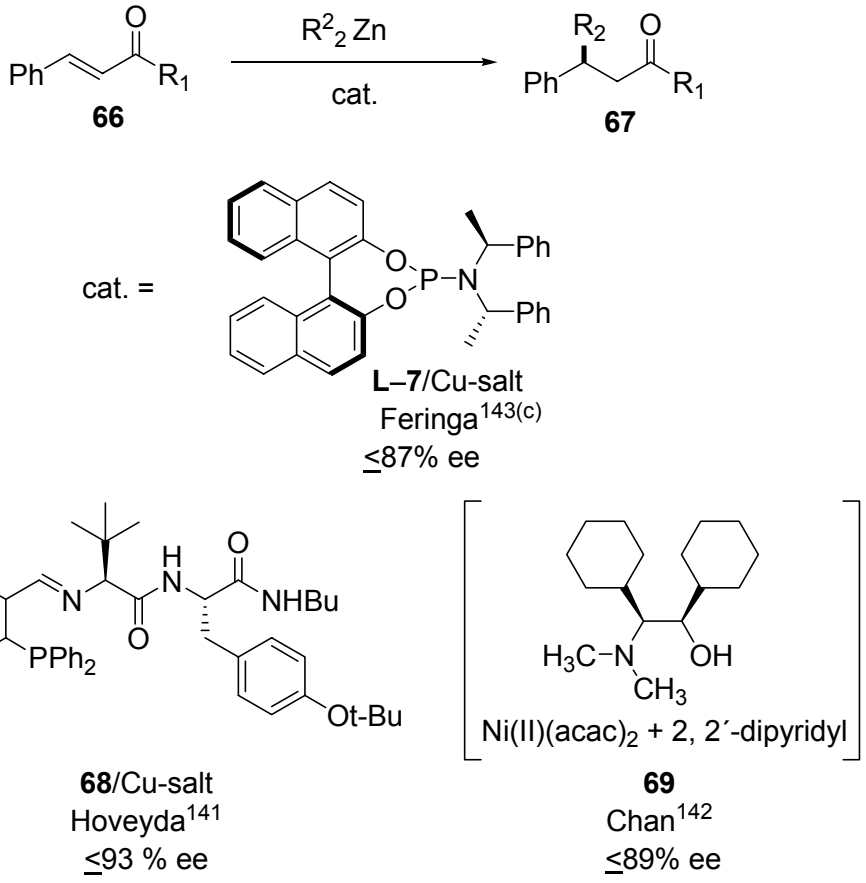
Figure 23: *Catalyst formation with bi– and monodentate phopsphoramidite ligands.*

These investigations also revealed two fundamental problems of Cu–catalysed enantioselective organometallic conjugate additions: (1) In solution, organocopper compounds show dynamic behavior with equilibria between several species. If this leads to the formation of achiral, but more reactive cuprates, a loss of enantioselectivity is

[137] de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 2374—2378.
[138] Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; 1993, Wiley-VCH: New York.
[139] (a) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427—2430. (b) Kanai, M.; Tomioka, M. *Tetrahedron Lett*. **1995**, *36*, 4275—4278.
[140] Stryer, L. *Biochemistry*; 4th Ed.; Freeman, New York, 1995, 124.

unavoidable. Therefore, it is crucial to develop chiral reagents which react so rapidly with the substrate that undesired competing reactions are suppressed. (2) Many chiral organocopper reagents exhibit high substrate specificity, that is, they give good stereoselectivities with only one or very few Michael acceptors.

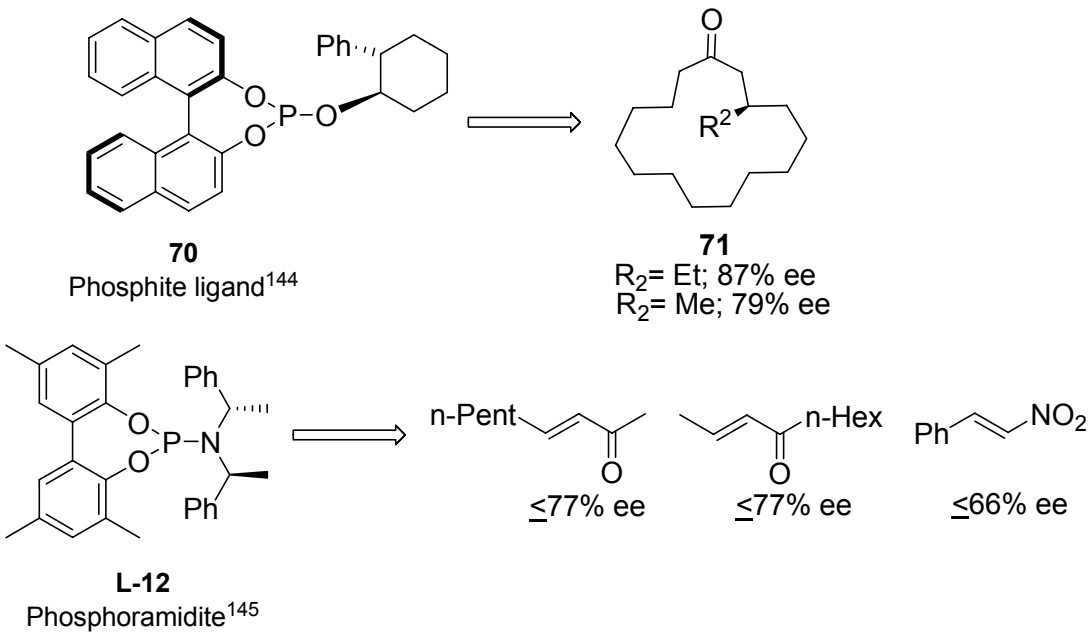
On the other hand, despite significant progress made in the area of Cu–catalysed conjugate additions to cyclic enones, extension of such protocols to include highly enantioselective reactions of aliphatic acyclic enones has proved to be far from routine. Because of *s–cis* and *s–trans* conformational interconversion, acyclic enones are more challenging substrates. Promising data have been reported in certain cases, however, Et_2Zn is nearly always the alkylating agent probed. The most widely studied structural type of acceptor is chalcone and its related cogeners. In some cases, however, good stereoselectivities were also attained with acyclic enones of type **66** (Scheme 51).



Scheme 51: Acyclic enones as substrates.

Progress with regard to this undesired substrate specificity was achieved with the phosphorous amidite **L–7**, which catalyzes not only conjugate additions of organozinc reagents to cyclic enones but also to chalcone (**66**, R^1=Ph) and related acyclic substrates. In the case of the addition of diethylzinc to chalcone, a good stereoselectivity of 87% ee was

observed. Recently, Hoveyda[141] reported Cu–catalysed diethyl zinc conjugate additions to acyclic aliphatic enones in up to 93% ee by using P,N–bidentate peptidyl ligand **68**. The majority of studies has involved aromatic enones, and selectivities are rarely >90% ee when aliphatic substrates are used. The best results (96% ee) for chalcone is reported by Chan[142] by using N,N-dimethyl-2-amino-1,2-cyclohexylethanol **69** as chiral ligand. Nickel catalysed reactions are also efficient for chalcone derivatives.[143] More generally, alkyl substituted acyclic enones have been studied much less, although they provide wider structural variation. Good to excellent enantioselectivities were obtained with phosphite,[144] phosphoramidite[145] ligands (Scheme 52). A particular case of cyclopentadecenone, a large ring, behaves like acyclic enones to give up to 87% ee with phosphite ligands.



70
Phosphite ligand[144]

71
R_2= Et; 87% ee
R_2= Me; 79% ee

L-12
Phosphoramidite[145]

Scheme 52: Acyclic enones as substates.

Among the most studied Michael acceptors,[146] in diethyl zinc conjugate additions are nitro-olefins[147] and alkylidene malonates,[148] lactones[149] (six membered ethylenic lactone,

[141] Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2005**, *127*, 779—780.
[142] Zhang, F. –Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179—1182.
[143] (a) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokohama, S. *Chem. Lett*. **1988**, 1571—72. (b) Bolm, C.; Ewald, M.; Felder, M.; *Chem. Ber.* **1992**, *125,* 1205—1215. (c) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479—4491. (d) Tong, P. –E.; Li, P.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2301—2304. (e) Luliano, A.; Scafato, P. *Tetrahedron: Asymmetry* **2003**, *14*, 611—618.
[144] Alexakis, A.; Benhaïm, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J. –M.; March, S.; Rosset, S. *Synlett* **1999**, 1811—1813.
[145] Alexakis, A.; Benhaim, C.; Rosset, S.; Humama, M. *J. Am. Chem. Soc*. **2002**, *124*, 5262—5263.
[146] Microrewiew: Alexakis, A.; Benhaim, C. *Eur. J. Org. chem*, **2002**, 3221—3226.
[147] (a) Alexakis, A.; Benhaim, C. *Org. Lett*. **2000**, *2*, 2579—2581. (b) Wendisch, V.; Sewald, N. *Tetrahedron: Asymmetry* **1997**, *8*, 12531—257.

and five membered lactones), seven membered rings[150]. Acyclic substrates are less studied[151] (Figure 24).

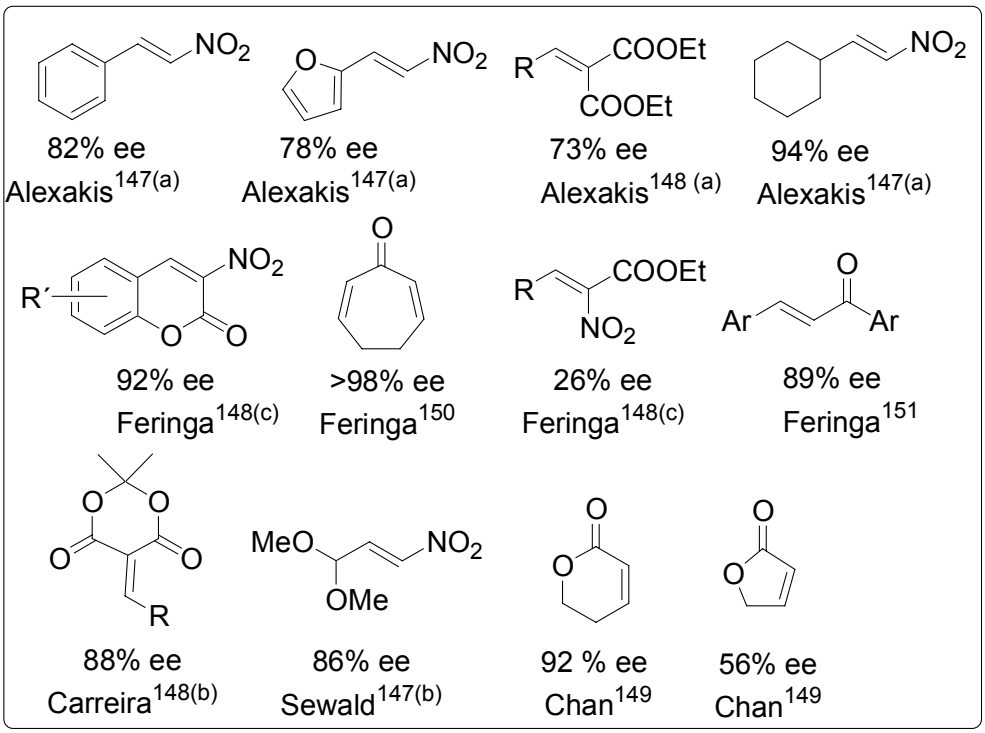


Figure 24: *Various substrates studied for conjugate additions of dialkyl zinc reagents.*

Hence, because of *s*–cis and *s*–trans conformational interconversions, acyclic enones are more demanding substrates. As there is yet no ligand of general acceptability, new chiral ligands to improve enantioselectivities with specific classes of substrates are continuously being designed. Being known from the previous work of our laboratory, about bidentate chelating properties of α'–hydroxy enones in Diels–Alder reactions, Friedel–Crafts alkylations and conjugate additions of carbamates,[152] we were eager to expand the scope of α'–hydroxy enones to asymmetric conjugate additions of diethyl zinc reagent.

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[148] (a) Alexakis, A.; Benhaim, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1151—1157. (b) Watanabe, T.; Knopfel, T.; Carreira, E. *Org. Lett*. **2003**, *5*, 4557—4558. (c) Versleijen, J. P. G.; Van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett*. **1999**, *40*, 5803—5806.

[149] (a) Yang, M.; Zhou, Z.– Y.; Chan, A. S. C. *Chem. Commun*. **2000**, 115—116. (b) Yan, M.; Yang, L. –W.; Wong, K. –Y. Chan, A. S. C. *Chem. Commun*. **1999**, 11—12. (c) Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645—6648.

[150] Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346—353.

[151] Arnold, L. A.; Imbos, R.; Mandoli, A.; De Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865—2878.

[152] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García. J. M. *J. Am. Chem. Soc.* **2004**, *126*,9188—9189.

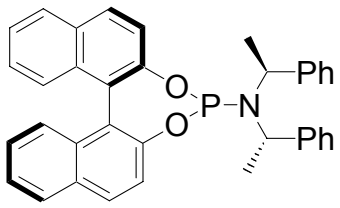
4.2 Results and Discussion

4.2.1 Introduction

We chose phosphoramidite ligands for the initial trials because of their best results reported by Feringa[153] in catalytic 1,4–addition reactions. Also a particularly attractive feature of the phosphoramidite ligands is the convenience with which its structure can be tailored to tune the catalytic activity for the reaction under scrutiny. At first instance, we prepared ligand **L–7** by using *R*–BINOL and (*S,S*)-bis-(1-phenylethyl) amine by following the reported procedures of Feringa and co-workers.

4.2.2 Preliminary results

As the initial trial experiments, conjugate addition of diethyl zinc to α'–hydroxy enone **1c** (R= $PhCH_2CH_2$) using catalysts **73a–73c**, which were prepared by using Feringa´s phosphoramidite ligand **L–7** (10 mol%) and corresponding Cu–salt (5 mol%), was carried out under varying conditions of temperature, solvent, co-catalyst, Lewis acidic metal salts, etc (Table 8).



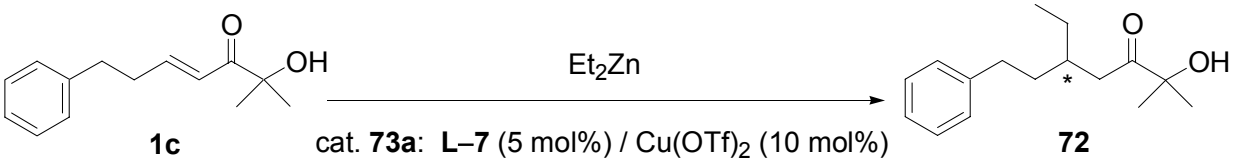
L–7

Figure 25: *Feringa´s phosphoramidite ligand for preparation of catalysts* **73a–73c**.

As seen from the initial experiments with catalysts **73a–73c** (Table 8), it was clear that the enantioselectivity in these reactions is changing dramatically by two parameters viz. solvent and temperature. The general sentiment of achieving good enantioselectivity at lower temperatures is not observed here. Room temperature proved to be the best temperature for obtaining up to 77% ee (entry 5). By increasing the percentage of catalyst loading from 5 mol% to 10 mol%, selectivity does not improve (entries 5 and 6).

[153] (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed*. **1996**, *35*, 2374—2376. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem. Int. Ed.* **1997**, *36*, 2620—2623.

Table 8: *Enantioselective diethyl zinc additions to α'–hydroxy enone* **1c** *catalysed by* **73**[a]**:**



1c **72**

cat. **73a**: **L–7** (5 mol%) / $Cu(OTf)_2$ (10 mol%)
cat. **73b**: **L–7** (5 mol%) / CuOTf (10 mol%)
cat. **73c**: **L–7** (5 mol%) / CuTc (10 mol%)

Entry	Solvent	Catalyst	T, ºC	Time, h	Yield [b]	ee % [c]
1	Et_2O	**73a**	–78	24	76	40
2			–40	24	90	60
3			–20	12	92	65
4			0	2	94	72
5			**25**	**2**	**95**	**77**
6			25	2	95	77[j]
7	CH_2Cl_2	**73a**	–78	48	84	32
8			0	6	86	46
9	THF	**73a**	25	72	90	0
10	Toluene	**73a**	–40	30	100 [d]	36
11			0	6	90	67
12			reflux	0.5	100 [d]	40
13	Et_2O	**73a**	25	2	100 [d]	65[h]
14	Et_2O	**73a**	25	2	100 [d]	75[e]
15	Et_2O	**73a**	25	24	0[i]	--
16	MTBE	**73a**	25	6	100 [d]	60
17	Et_2O	**73b**	25	24	100 [d]	60
18	Et_2O	**73a**	25	8	100 [d]	0[g,h]
19	Et_2O	**73c**[f]	–78	78	100 [d]	0
20	Et_2O	**73c**[f]	–30	48	100 [d]	47
21	Et_2O	**73c**[f]	25	12	100 [d]	20

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale with mole ratio of enone **1c** :Et_2Zn:catalyst is 1:3:0.05 (For preparation of catalyst, 1:2 ratio of Cu−salt and ligand were mixed and stirred under nitrogen for 1 h at room temperature). [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Reaction conversion based on NMR of crude product after specified time. [e] For preparation of catalyst = 1:3 ratio of metal salt and ligand. [f] CuTc = Copper Thiophene carboxylate. [g] t-Bu-bis(oxazoline) ligand (10 mol%) was added in combination with **L–7**. [h] $Zn(OTf)_2$ (5 mol%) was added in combination with **73a**. [i] Additive: Molecular sieves MS–4Å. [j] 10% catalyst was used.

By changing the copper salt from Cu(II) to Cu(I) proved detrimental to the reaction, hence, catalyst **73b** afforded lower selectivity (60% ee) as compared to catalyst **73a** (77%

ee) (entries 5 and 17). Changing ethereal solvent from diethyl ether to methyl ter-butyl ether (MTBE) did not enhance the enantioselectivity (entries 5 and 16). As shown in Table 8, the solvent study shows that the best reactivity and selectivity profiles are obtained in diethyl ether. Surprisingly, cyclic ether like THF proved completely ineffective and resulted in racemic product. Apart from temperature and solvent screening, use of additives and use of in situ co-catalyst, were also studied with the hope of improvement in enantioselectivity. By giving a chance to bimetallic catalysis hypothesis, we added $Zn(OTf)_2$ in addition to $Cu(OTf)_2$, but we did not succeed (entry 13). By adding additive like molecular sieves MS–4Å, the reaction did not proceed at all (entry 15). By combining t-Bu-box ligand **L–1**, we tried to enhance the ee but failed (entry 18). As reported by Alexakis,[154] Sewald,[155] and Woodward[156] during optimization of the asymmetric conjugate addition reaction, the solvent and the nature of the copper salt appear to be crucial to attain good enantiomeric excess. We sought to examine copper thiophenecarboxylate (CuTc) as copper source. Hence, the reaction carried out using catalyst **73c** (incorporating ligand **L–7** and CuTc) in diethyl ether at different temperatures resulted in only 47% ee (entries 19–21).

4.2.3 Synthesis of novel phosphoramidite ligands

Once it seemed that we had reached some maximum limit for reaction optimisation using ligand **L–7**, we decided to explore other phosphoramidite ligands which showed structural modifications with respect to **L–7**.

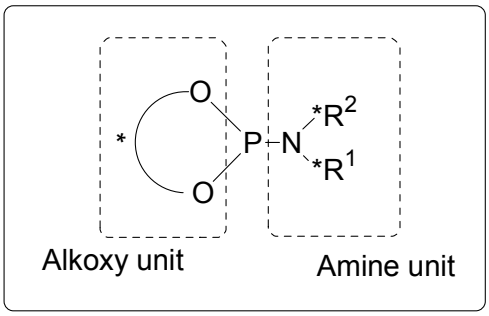


Figure 26: *Tunable units within phosphoramidite ligands.*

As seen in Figure 26, there are two structural units (alkoxy– and secondary amine–) within phosphoramidite ligand, which can be modified easily to obtain structural variants of these ligands. Consequently we prepared (by following reported procedures[157]) and

[154] Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262—5263.
[155] Wendisch, V.; Sewald, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1253—1257.
[156] Bórner, C.; Denis, M. R.; Sinn, E.; Woodward, S. *Eur. J. Org. Chem.* **2001**, 2435—2446.
[157] (a) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000,** *56*, 2865—2878. (b) d´ Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1376—1378.

screened a number of phosphoramidites with the aim of identifying a ligand that would improve the enantioselectivity.

Starting from phosphoryl chloride, phosphoramidite ligands were synthesised by nucleophilic substitution with a wide variety of secondary amines. Beside the amine unit, substituents at 3– and 3´–positions of the binaphthyl part (alkoxy unit) affect the binding mode of the reagent´s alkyl group and substrate enone on the copper and are crucial for ligand modification. We adopted the methodology to synthesize 3,3´–substituted binaphthols which included use of 2,2´–bis-MOM-substituted binaphthol.[158,159] Finally, the phosphoramidite ligands were remarkably stable to air and moisture.

4.2.4 Ligand modification I

As stated above, we then tried to mutate the ligand **L–7** by varying alkoxy unit (BINOL moiety) as our first attempt to enhance selectivity (Figure 27).

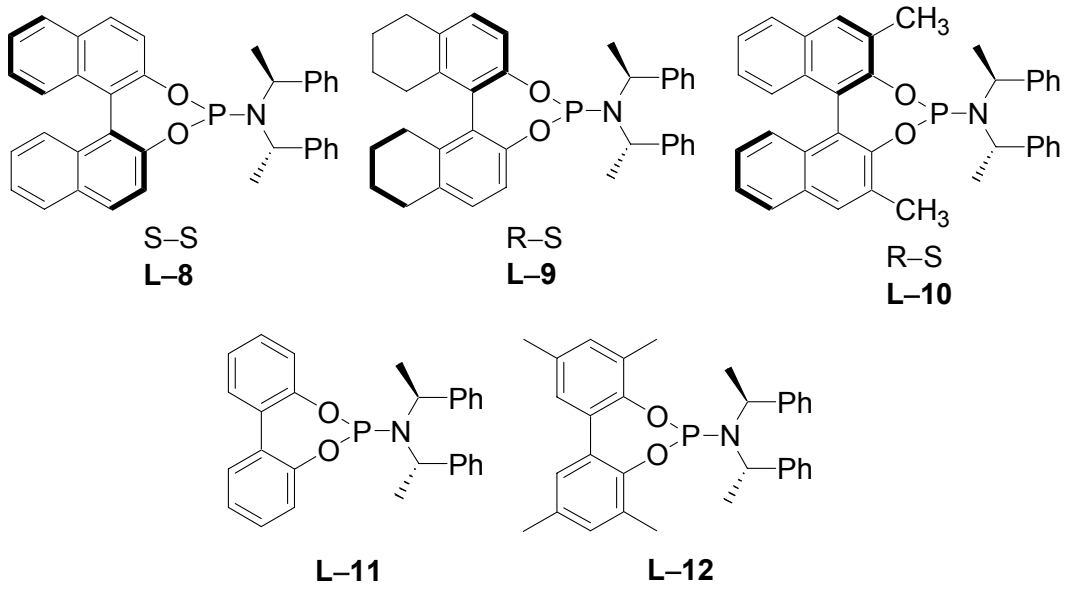


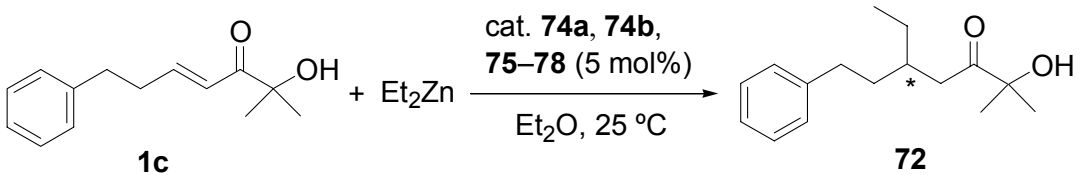
Figure 27: *Ligands prepared by varying alkoxy unit (BINOL moiety).*

We switched from *R*–BINOL to *S*–BINOL for studying the effect of matched and mismatched complexes. Ligand **L–8** was prepared by using *S*–BINOL and corresponding *S*–amine. Catalysts **74a** and **74b** were prepared using lignad **L–8** (10%) in combination with $Cu(OTf)_2$ (5%) and CuOTf (5%), respectively. We observed complete mismatch effect of this

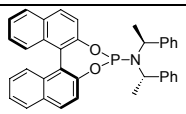
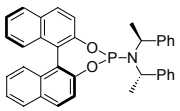
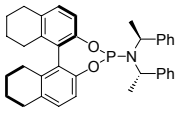
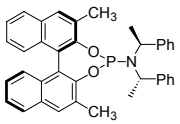
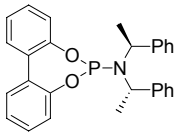
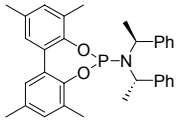
[158] (a) Knoebel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429—1432. (b) Review*:* Narasaka, K. *Synthesis* **1991**, 1—11.
[159] Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett*. **1992**, *33*, 2253—2256.

S–S ligand as conjugate addition of diethyl zinc to eone **1c** did not proceed using catalysts **74a** and **74b** (entries 1 and 2).

Table 9: *Enantioselective conjugate additions of diethyl zinc to α'–hydroxy enone* **1c** *promoted by catalysts* **74a**, **74b**, **75–78**[a]**:**



1c **72**

Entry	Catalyst	Ligand	Metal salt	Time, h	Convs. % [b]	ee % [c]
1	**74a**	 **L–8**	$Cu(OTf)_2$	24	0	--
2	**74b**	 **L–8**	CuOTf	24	0[d]	--
3	**75**	 **L–9**	$Cu(OTf)_2$	12	100	60
4	**76**	 **L–10**	$Cu(OTf)_2$	20	100	65
5	**77**	 **L–11**	$Cu(OTf)_2$	24	0	--
6	**78**	 **L–12**	$Cu(OTf)_2$	24	0	--

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale. Mole ratio of enone: Et_2Zn:catalyst =1: 3: 0.05 (For preparation of catalyst 1:2 ratio of metal salt and ligand was used). [b] Reaction conversion based on NMR of crude product after specified time. [c] Determined by chiral HPLC.

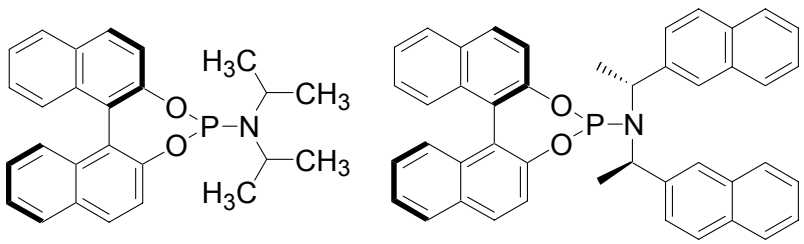
To modify the phosphoramidite ligand further, we employed partially hydrogenated *R*-BINOL as alkoxy unit. Our idea was based on previous reports[160] that demonstrate the

[160] (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed*. **1996**, *35*, 2374—2376. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron*

planar geometry of (*R*)-BINOL will change to some extent to more crowded by partial hydrogenation, which will give effective shielding and will enhance the enantioselectivity. But in reality, the result of catalyst **75** which was prepared by using ligand **L–9** and $Cu(OTf)_2$ showed decrease in the ee (entry 3). By substituting 3,3´–positions in BINOL moiety, we thought we could make the chiral catalyst more bulky and will make the facial discrimination more prominent. So we prepared the 3,3´–bis-methyl substituted BINOL derivative and subsequently the phosphoramidite ligand **L–10**. In contrast to our idea, catalyst **76** prepared using this ligand **L–10** and $Cu(OTf)_2$, we got only 65% ee (entry 4), which is lower than the obtained with parent catalyst **73** (involving ligand **L–7**). Recently, Alexakis[161] reported biphenol derived phosphoramidite ligands **L–11** and **L–12** for Grignard reagents additions. Impressed by those results, we sought to implement this modification for our transformation and prepared catalysts **77** and **78** incorporating ligands **L–11** and **L–12** repectively, but failed to enhance the selectivity (entries 5 and 6).

4.2.5 Ligand modification II

With these unrewarding results from modification of alkoxy unit (BINOL part) of phosphoramidite ligand structure, we switched to scrutinise changes in the secondary amine unit of the ligand and consequently prepared **L–13** and **L–14** using (*R*)-BINOL in combination with diisopropylamine and (*S,S*)-bis-(1-naphthalen-2-yl-ethyl)-amine, respectively.



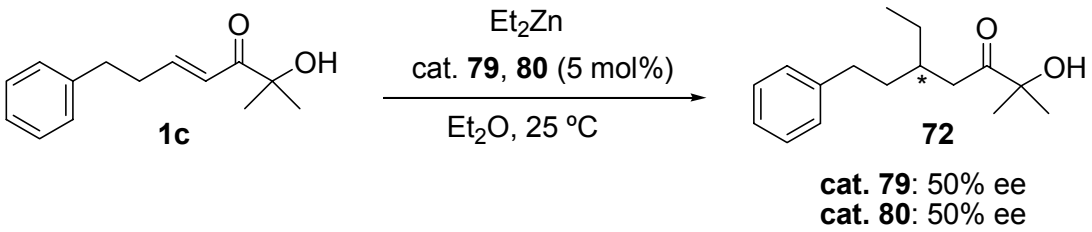
R–BINOL & *i*-Pr amine **L–13**

R–BINOL & *S*-amine **L–14**

Figure 28: *Ligands prepared by varying secondary amine unit.*

2000, *56*, 2865—2878. (c) Schuppan, J.; Minnard, A. J.; Feringa, B. L. *Chem. Comm.* **2004**, 792—793.

[161] d´Augustin, M.; Palais, L.; Alexakis, A. *Angew Chem. Int. Ed*. **2005**, *44*, 1376—1378.



Scheme 53: Enantioselective diethyl zinc additions to α'–hydroxy enone **1c** promoted by catalysts **79** and **80** (modification in amine unit).

Hence, catalysts **79** and **80** were prepared using ligands **L–13** and **L–14** respectively, in combination with $Cu(OTf)_2$. Employing these catalysts to conjugate addition resulted in full reaction conversions but limited selectivity, 50% ee (Scheme 53).

4.2.6 Ligand switch

These experiments proved that surpassing the 77% ee by using Feringa´s phosphoramidite type catalyst is apparently difficult. So we decided to make a wider screening of other ligand families for the conjugate addition of Et_2Zn to α'–hydroxy enone **1c** (Table 10).

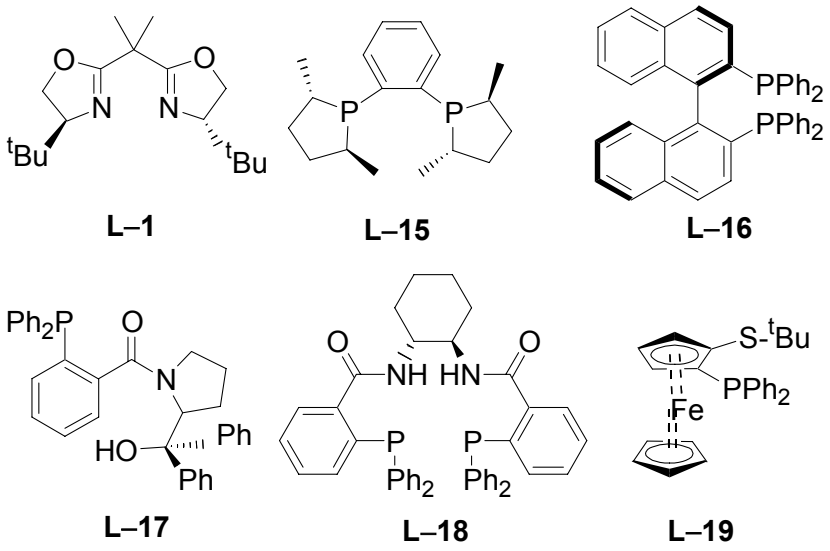
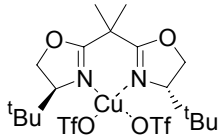
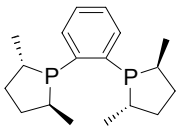
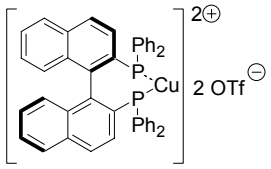
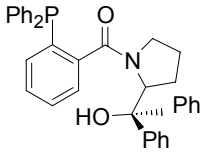
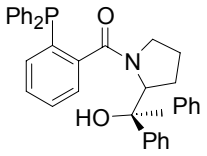
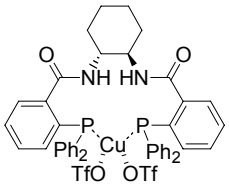
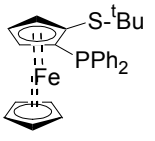


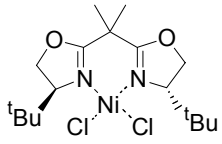
Figure 29: *Ligands used for wider screening.*

By employing catalyst **4** (incorporating ligand **L–1** with $Cu(OTf)_2$) and further under bimetallic conditions in combination with $Zn(OTf)_2$ in different solvents like dichloromethane, and diethyl ether yielded in no selectivity (Table 10, entries 1–3). Cu–Phosphine[162] complexes have been used extensively in asymmetric catalysis. Catalyst **81** was prepared

[162] Côté, A.; Boezio, A. B.; Charrette, A. B. *Angew Chem. Int. Ed*. **2004**, *43*, 6525—6528.

Table 10: *Enantioselective diethyl zinc addition to α'–hydroxy enone* (**1c**) *promoted by catalysts* **4***,* **81**–**86**[a]:

Entry	Catalyst	Solvent	Time, h	Convs. % [b]	ee % [c]
1		Et_2O	24	100	0
2		CH_2Cl_2	24	100	0
3		Et_2O	24	100	0[d]
	4				
4		Toluene	40	100	5
5	$Cu(OTf)_2$ / Me-DUPHOS	CH_2Cl_2	6	100	10
	81				
6		Et_2O	24	100	0
	82				
7	 / $Cu(OTf)_2$	Et_2O	48	0	--
	83a				
8	 / CuOTf	Toluene	48	100	0
	83b				
9		Et_2O	24	0	--
10		Toluene	24	100	0
	84				
11	 / CuOTf	Et_2O	6	100	0
	85				

12	 **86**	CH_3CN	24	0	--

[a] Unless otherwise stated, all reactions were conducted at 0.5 mmol scale at 25 ºC. Mole ratio of enone:diethyl zinc:catalyst =1:3:0.05; (For preparation of catalyst, 1:2 ratio of metal salt and ligand was used). [b] Reaction conversion based on NMR of crude product after specified time. [c] Determined by chiral HPLC. [d] $Zn(OTf)_2$ (5 mol%) was added in combination with $Cu(OTf)_2$.

employing commercially available methyl DUPhos (ligand **L–15)** with $Cu(OTf)_2$. Conjugate addition carried out using **81** in solvents like toluene and dichloromethane resulted in only 5% and 10% ee, respectively (entries 4, 5).

Catalyst **82**, prepared by admixing BINAP (ligand **L–16**) with $Cu(OTf)_2$, was examined in diethyl ether and showed full reaction conversion with no enantioslectivity (entry 6). Furthermore, reactions with catalysts **83a**, **83b** and **84** which incorporated ligands **L–17** and **L–18** (Trost Ligand[163]) were unsuccessfull in either reactivity or selectivity in different solvents (entries 7–11). Sandwitch type compounds of ferrocene as TaniaPhos and JosiPhos ligands reported by Feringa[164] and their thio analogues like ligand **L–19** reported by Carretero[165] prompted us to examine catalyst **85** (incorporating ligand **L–19** with CuOTf), but resulted in no enantioselectivity (entry 11), while reaction with catalyst **86**, prepared by using ligand **L–1** and anhydrous $NiCl_2$ in acetonitrile, did not proceed at all (entry 12).

Thus, the quest for the best combination of correct chiral ligand and corresponding metal salt is still going on.

[163] Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186—14187.
[164] López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784—12785.
[165] Rivero, M. R.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456—457.

5. Conclusions

1) Highly enantioselective Friedel–Crafts alkylations of indole and pyrrole derivatives with α'–hydroxy enones under simple Cu(II)–bis(oxazoline) catalysis is demonstrated. An efficient method for preparation of 3–indolyl and 2–pyrrolyl frameworks, which are ¨priviledged¨ structures within the natural product isolates and medicinal agents, is accomplished. Hence, the efficiency of the ketol moiety of α'–hydroxy enone template, for efficient metal substrate coordination for optimum selectivity is demonstrated. Furthermore, the ketol moiety is transformed into aldehyde, ketone and ester functionalities.

2) Under controlled conditions, C_2–symmetric dialkylated products of pyrrole derivatives are accessible in highly enantioselective and diastereoselective way.

3) β–Aryl substituted enones give more limited selectivity (up to 78% ee). Efficient F–C alkylation methodology with β–aryl substituted α'–hydroxy enones is desired.

4) Treatment of F–C adducts of N-methyl pyrrole with $NaIO_4$/methanol-water led to a new spiranic compound with almost no precedents in literature.

5) Preliminary study of the conjugate addition of diethyl zinc to α'–hydroxy enone **1c** promoted by Feringa´s chiral phosphoramidites-Cu(II) catalyst complexes affords adduct in 77% ee and 95% yield.

6. Experimental section

6.1 Preparation of α'–hydroxy enones

Various α'–hydroxy enone derivatives, varying in their β–substituents, were prepared by two alternative routes using commercially available starting materials. β–Alkyl α'–hydroxy enones **1c**—**1h** were prepared by two step methodology involving aldol reaction of commercially available 3-hydroxy-3-methyl-2-butanone (**87**) with corresponding aliphatic aldehyde and subsequent dehydration of aldol adduct by cerium(III)chloride. β–Aryl α'–hydroxy enones **1a**—**1b** were prepared in one step procedure from commercially available 3-hydroxy-3-methyl-2-butanone (**87**) and corresponding aromatic aldehyde using LiOH/methanol-water system. Synthesis of β–isopropyl α'–hydroxy enone **1g** and β–methyl α'–hydroxy enone **1i** was found problematic by aldol methodology, hence, the Horner-Eadsworth-Emmons reaction using (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester[166] (**91**) was employed according to reported procedure. Structurally modified enones **16** and **17** were prepared starting from 1-hydroxy-1,1-diphenyl-propan-2-one (**95**) and hydroxy-cyclohexyl phenyl-propenone (**98**) respectively,[167] via condensation with benzaldehyde according to the same procedure used for the synthesis of β–aryl enones **1a** and **1b**.

6.1.1 General

All reactions were carried out under an atmosphere of nitrogen in flame/oven dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2), acetonitrile were dried by distilling over CaH_2. THF and diethly ether were dried by distilling over sodium metal. Commercially available HPLC grade ethanol, isopropyl alcohol, and hexane were used without distillation. Diisopropylamine was dried by refluxing over KOH and after distillation, stored with MS–4Å (1.6 mm pellets). LiCl was dried by heating at 150 ºC for 24 h under vacuum. Aliphatic aldehydes were distilled prior to use. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization

[166] Prepared in two steps (92% overall yield) from commercially available methyl 2-hydroxyisobutyrate, according to: (a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525—2529. (b) McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3667—3675.

[167] (a) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; Gonzalez, A.; Garcia, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem*. **1999**, *64*, 8193—8200. (b) *Organic Synthesis*; Coll. Vol. 4, p. 13; Vol. *35*, p. 1. (c) Palomo, C.; Oiarbide, M.; García, J. M.; Gonzalez, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942—13943.

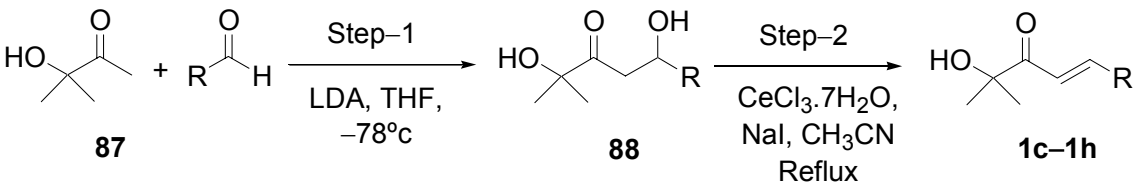
was accomplished with UV light and a solution obtained by admixing in 470 mL of water, ammonium molibdate (21 g), cerium sulphate (1 g) and concentrated sulphuric acid (31 mL), followed by heating. Melting points were measured with a Büchi SMP–20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-200, Bruker Avance-DPX-300, and Bruker Avance-500 spectrometers and are reported in ppm from internal tetramethylsilane (TMS) and chloroform.

6.1.2 Route I: From 3-hydroxy-3-methyl-2-butanone 87

6.1.2.1 General procedure A: For β–Alkyl substituted α'–hydroxy enones 1c–1h

Step 1: Aldol reaction

Under nitrogen atmosphere, to a flame dried three neck round bottom flask fitted with liquid addition funnel and low temperature thermometer, was charged 250 mL dry THF. Then diisopropylamine (35 mL, 250 mmol) (previously dried) was added. The mixture was cooled to –78 ºC using dry ice-acetone bath. To this cooled solution, n-BuLi (2.5 M, 100 mL, 250 mmol), was added keeping temperature at –78 ºC. The resultant solution was stirred at same temperature for 1 h. Then 3-hydroxy-3-methyl-2-butanone **87** (11.1 mL, 100 mmol) was diluted with dry THF (45 mL) and the solution was added dropwise while keeping the temperature at about –78 ºC. The reaction mixture was stirred for one hour at the same temperature before addition of corresponding aldehyde (300 mmol, diluted with 45 mL of dry THF) at –78 ºC. The reaction mixture was stirred at –78 ºC for further 3 h, till TLC analysis (7:3 hexane:ethyl acetate) indicates disappearance of starting ketone. The reaction was quenched with sat. NH_4Cl (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with water (2 x 75 mL), dried over $MgSO_4$ and was evaporated under reduced pressure. Subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) as eluents yielded the corresponding pure aldol products **88**.



87 **88** **1c–1h**

Step 2: Dehydration of aldol adduct[168]

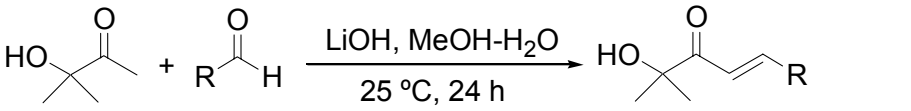
To a suspension of corresponding aldol adduct **88** (10 mmol) in acetonitrile (500 mL) was added $CeCl_3.7H_20$ (8.22 g, 15 mmol) and sodium iodide (2.24 g, 15 mmol). The mixture was heated to reflux until TLC analysis (7:3 hexane:ethyl acetate) indicated disappearance of starting aldol adduct (about 3 h). The reaction mixture was cooled to room temperature and diluted with diethyl ether (500 mL). Organic layer was then washed with 0.5 M HCl soln (3 x 100 mL), sat. $NaHCO_3$ (3 x 100 mL), 20% $NaHSO_3$ (3 x 100 mL), brine (2 x 100 mL) and dried over $MgSO_4$. Evaporation of solvent under reduced pressure and subsequent purification by flash column chromatography using hexane:ethyl acetate eluents (95:5) yielded the corresponding pure enone.

Table 11: Yields of α'–hydroxy enones **1c–1h** after two steps**.**

Enone	R	Yield (%)[a]
1c	Ph-CH_2-CH_2-	74
1d	CH_3-$(CH_2)_5$-	77.5
1e	CH_3-CH_2-	37
1f	$(CH_3)_2$-CH_2-	81
1g	$(CH_3)_2$-CH-	36
1h	Cyclohexyl-	55

[a] Isolated yields after column chromatography

6.1.2.2 General procedure B: For β–aryl α'–hydroxy enones



87

1a R: Ph; 84% yield
1b R: *p*Cl-Ph; 73% yield

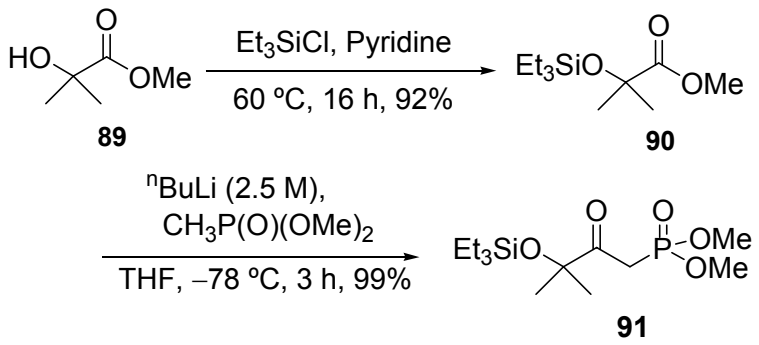
3-Hydroxy-3-methyl-2-butanone **87** (11.1 mL, 100 mmol) was dissolved in methanol-water (3:1 ratio, 400 mL) and the corresponding undistilled aromatic aldehyde (110 mmol), $LiOH.H_20$ (842 mg, 20 mmol) were added successively. The reaction mixture was stirred at room temperature for around 24 h until TLC analysis (7:3 hexane:ethyl acetate) or NMR analysis (if needed) indicated disappearance of starting ketone. (Reaction time can be reduced to 5 hrs by using 9.24 g (220 mmol) of $LiOH.H_2O$ instead of 20 mmol). After

[168] Adapted from: Bartoli, G.; Bellucci, M. C.; Petrini, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Org. Lett*, **2000,** *2*, 1791—1793.

completion of reaction, methanol was removed *in vacuo.* The residue was diluted with water (250 mL) and extracted by dichloromethane (3 x 125 mL). Organic layer was washed with water (3 x 75 mL) and dried over $MgSO_4$. Evaporation of solvent under reduced pressure and subsequent purification of crude product by flash column chromatography using hexane:ethyl acetate (95:5) as eluent yielded the corresponding pure enones.

6.1.3 Route II: For β–methyl and β–isopropyl α'–hydroxy enones [From (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester][169]

Step 1: Preparation of (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester **91**.



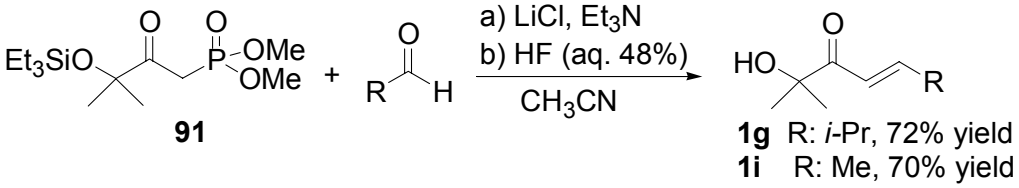
Methyl 2-hydroxyisobutyrate **89** (6.9 mL, 60 mmol) was added under a nitrogen atmosphere to a solution of *N,N*–dimethylamino pyridine (DMAP) (1.22 g, 10 mmol), triethylamine (10 mL, 50 mmol) and triethylchlorosilane (8.5 mL, 50 mmol) in 50 mL dichloromethane. The reaction mass was stirred at room temperature for 24 h. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1 x 50 mL) and water (1 x 50 mL). Evaporation of solvent under reduced pressure yielded compound **90**. Yield: 12.6 g (92%). No further purification is needed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H, OC$\underline{H}_3$), 1.45 (s, 6H, C(C$\underline{H}_3$)$_2$), 0.95 (q, 6H, CH_3-C$\underline{H}_2$, *J*= 4.0 Hz), 0.59 (m, 9H, C$\underline{H}_3$-CH_2).

Commercially available dimethyl methyl phosphonate (13.8 mL, 130 mmol) in dry THF (40 mL) was added dropwise to a cold solution of n-BuLi (1.6 M in hexanes, 79 mL, 130 mmol) in dry THF (80 mL) at –78 °C under nitrogen atmosphere. After stirring the resulting solution for 30 min, a solution of the crude triethylsilyl ether **90** (12 g, 51 mmol) in dry THF (100 mL) was added dropwise at –78 °C. The mixture was stirred at the same temperature

[169] Prepared in two steps (92% overall yield) from commercially available methyl 2-hydroxyisobutyrate, according to: (a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525—2529. (b) McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3667—3675.

(–78 ºC) for 3 h and then quenched at this temperature with sat. NH_4Cl (200 mL). Reaction mass was extracted with diethyl ether (3 x 250 mL), dried over $MgSO_4$. Evaporation of solvent under reduced pressure yielded the title compound **91**. Yield: 17 g (99%). It was used for the next step without purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79 (s, $OC\underline{H}_3$), 3.77 (s, 3H, $OC\underline{H}_3$), 3.39 (d, 2H, $C\underline{H}_2$-PO, *J*= 11.0 Hz), 1.35 (s, 6H, $C(C\underline{H}_3)_2$), 0.96 (t, 9H, $C\underline{H}_3$-CH_2, *J*= 8.0 Hz), 0.63 (q, 6H, CH_3-$C\underline{H}_2$, *J*= 8.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 207.2, 80.1, 52.87, 34.3, 33.2, 26.9, 7.0, 6.5).

Step 2: Preparation of enones **1g** and **1i** by Horner-Eadsworth-Emmons reaction[170]



91

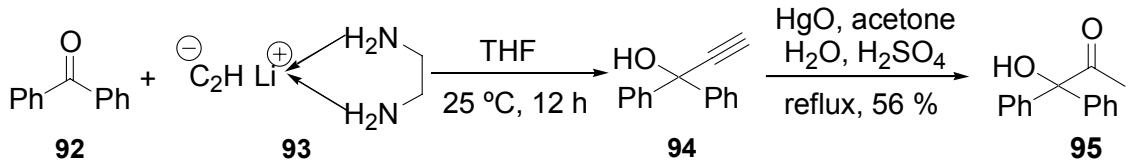
1g R: *i*-Pr, 72% yield
1i R: Me, 70% yield

Dried LiCl (1.05 g, 23.75 mmol) and triethylamine (3.3 mL, 22.85 mmol) were added successively to a solution of (3-hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester **91** (7.0 g, 21.6 mmol) in dry acetonitrile (50 mL). The resulting milky suspension was stirred for 15 min at room temperature and the corresponding aldehyde (21.5 mmol) was added dropwise. The mixture was stirred for 48 h, diluted with water (150 mL) and extracted with diethyl ether (3 x 75 mL). Evaporation of the solvent gave an oil which was dissolved in acetonitrile (120 mL) and HF acid (48% aqueous, 1.2 mL) was added dropwise. The mixture was stirred at 25 ºC for 3 h, diluted with dichloromethane (250 mL), washed with brine (3 x 75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column cromatography (hexane:ethyl acetate, 90:10) of the crude residue gave corresponding pure title α'–hydroxy enone.

6.1.4 Preparation of modified enone 16

Step 1: Synthesis of 1-hydroxy-1,1-diphenyl-propan-2-one[171] 95

[170] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183—2186.
[171] (a) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; Gonzalez, A.; Garcia, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem*. **1999**, *64*, 8193—8200. (b) *Organic Synthesis*; Coll. Vol. 4, p. 13; Vol. *35*, p. 1. (c) Palomo, C.; Oiarbide, M.; García, J. M.; Gonzalez, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942—13943.

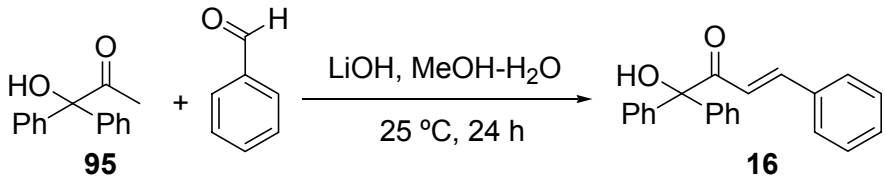


92 **93** **94** **95**

Under nitrogen atmosphere, benzophenone **92** (9.11 g, 50 mmol) was added to a solution of litium acetylide ethylenediamine complex **93** (9.2 g, 100 mmol) in THF (50 mL) at 0 ºC. The reaction mixture was stirred overnight at 25 ºC. The resulting solution was quenched by slow addition of 1N HCl soln (50 mL) at 0 ºC. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over $MgSO_4$. Evaporation of solvent under reduced pressure afforded the compound **94** in 56% yield. The crude compound was used in the next step without purification.

In a three-neck round bottom flask, equipped with a reflux condenser, a magnetic stirrer bar and a dropping funnel, red mercuric oxide (262 mg, 1.22 mmol) was dissolved in a solution of concentrated sulfuric acid (0.39 mL), water (10.5 mL), and acetone (52 mL). Then crude compound **94** was dissolved in acetone (130 mL) and was added dropwise to above warmed (60 ºC) mixture over a period of 1.5 h. The resulting mixture was stirred at 60 ºC for an additional 30 min. and then allowed to cool to room temperature. Sat. $NaHCO_3$ (50 mL) was added to the reaction mixture, the solvent was removed under reduced pressure and CH_2Cl_2 (50 mL) was added. The aqueous layer was separated, and the organic layer was washed with sat. $NaHCO_3$ (2 x 30 mL). Combined aqueous layers were extracted with CH_2Cl_2 (3 x 50 mL) and the organic extracts were combined, dried over $MgSO_4$. Evaporation of solvent under reduced pressure afforded the crude, which subsequently was purified by Kugelrohr distillation under reduced pressure. The 1-hydroxy-1,1-diphenyl-propan-2-one **95** was collected as a colorless liquid in 76% yield (8.6 gm), which becomes solid after cooling, m. p. 66–68 ºC.

Step 2:

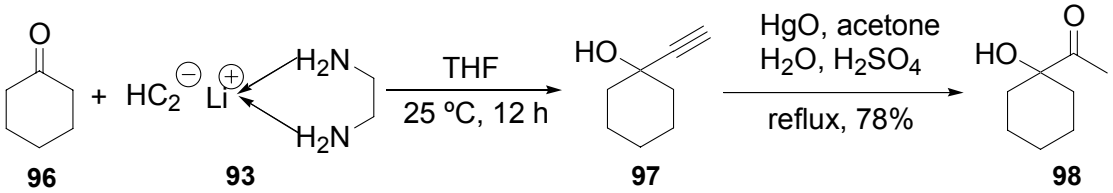


95 **16**

The title enone **16** was prepared in 96% yield (3.0 g) by following the general procedure B of route I (for β–aryl α'–hydroxy enones) using **95** (2.2 g, 10 mmol) and benzaldehyde (1.1 mL, 11 mmol).

6.1.5 Preparation of modified enone 17

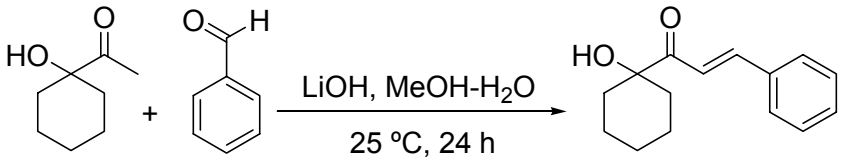
Step 1: Synthesis of Hydroxy-cyclohexyl phenyl-propenone 98



96 **93** **97** **98**

By following the procedure for preparation of **95**, using cyclohexanone **96** (5.16 mL, 50 mmol), title compound 1-acetylcyclohexanol **98** (purified by Kugelrohr distillation under 15 mm of Hg pressure, at 92–94 ºC), was prepared as a colorless liquid in 78% yield (5.5 g).

Step 2:

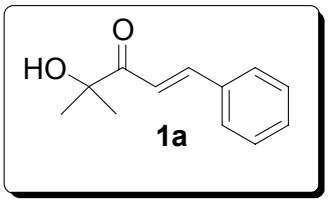


98 **17**

The title compound **17** was prepared in 93% yield (2.1 g) by following the general procedure B of route I (for β–aryl α'–hydroxy enones) using 1-acetylcyclohexanol **98** (1.4 g, 10 mmol) and benzaldehyde (1.1 mL, 11 mmol).

6.1.6 Characterisation data

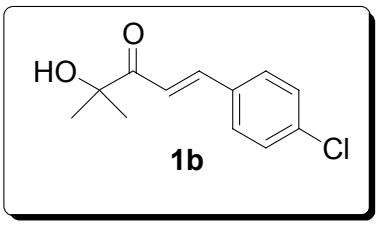
4-Hydroxy-4-methyl-1-phenyl-pent-1-en-3-one 1a



1a

The general procedure B (Route I) was followed using benzaldehyde (2.24 mL, 22 mmol). Yield 3.2 g (84%). IR ($CHCl_3$, cm^{-1}) 3464, 2976, 1690, 1607, 1076; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, C<u>H</u>-Ph, *J*= 15.0 Hz), 7.60–7.41 (m, 5H, <u>Ph</u>), 7.10 (d, 1H, C<u>H</u>-CO, *J*= 15.3 Hz), 4.06 (bs, 1H, O<u>H</u>), 1.47 (s, 6H, C(C<u>H</u>$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 145.4, 134.3, 130.9, 128.9, 128.6, 118.5, 75.6, 26.4.

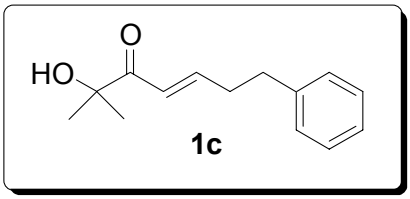
1-(4-Chloro-phenyl)-4-hydroxy-4-methyl-pent-1-en-3-one 1b



1b

The general procedure B (Route I) was followed using *p*Cl-benzaldehyde (3.1g, 22 mmol). Yield 3.2 g (73%). White solid, m. p. = 55–57 ºC (from EtOAc). IR (neat, cm^{-1}) 3416, 2930, 1678, 1595, 1086; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, 2H, C<u>H</u>-*p*Cl-Ph, *J*= 14.0 Hz), 7.48 (d, 2H, C<u>H</u>-CO, *J*= 8.0 Hz), 7.28 (d, 1H, *p*Cl-<u>Ph</u>, *J*= 8.8 Hz), 7.03 (d, 1H, *p*Cl-<u>Ph</u>, *J*= 16.0 Hz), 3.94 (bs, 1H, O<u>H</u>), 1.48 (s, 6H, C($C\underline{H}_3$)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.4, 144.2, 137.0, 132.8, 129.8, 129.4, 118.8, 75.6, 26.5.

2-Hydroxy-2-methyl-7-phenyl-hept-4-en-3-one 1c

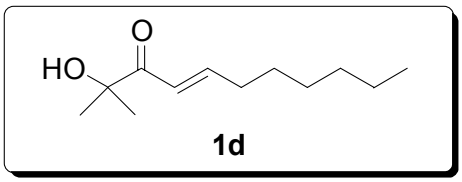


1c

The general procedure A (Route I) was followed using hydrocinnamaldehyde (31.6 mL, 240 mmol). Yield 7.7 g (42%). IR ($CHCl_3$, cm^{-1}) 3446, 2973, 1677, 1630; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.21 (m, 5H, <u>Ph</u> and 1H, C<u>H</u>=CH-CO), 6.41 (d, 1H, CH=C<u>H</u>-CO, *J*=15.5 Hz), 3.98 (bs, 1H, O<u>H</u>), 2.8 (t, 2H, $C\underline{H}_2$, *J*= 8.0 Hz), 2.59 (m, 2H, $C\underline{H}_2$), 1.34 (s, 6H, C($C\underline{H}_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 149.4, 140.6, 128.6, 128.5, 126.3, 123.1, 75.3, 34.5, 34.3, 26.3.

Using General Procedure (Route II) from hydrocinnamaldehyde (0.221 g, 1.65 mmol), 0.270 g (74%) of the title compound was obtained.

2-Hydroxy-2-methyl-undec-4-en-3-one 1d

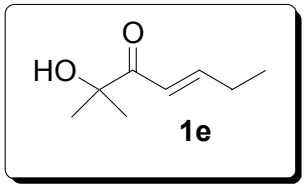


1d

The general procedure A (Route I) was followed using n-heptanal (33.5 mL, 240 mmol). Yield 10.6 g (77.5%). IR ($CHCl_3$, cm^{-1}) 3465, 2959, 1677, 1630, 1475; ^1H NMR (200 MHz, $CDCl_3$) δ 7.0 (m,1H, CH=C<u>H</u>-CH_2), 6.35 (d,1H, CO-C<u>H</u>, *J*= 16.2Hz), 4.04 (bs, 1H, O<u>H</u>), 2.13 (q, 2H, $C\underline{H}_2$, *J*=7.2 Hz), 1.36–1.32 (m, 2H, $C\underline{H}_2$), 1.25 (s, 6H, C($C\underline{H}_3$)$_2$), 1.17 (m, 6H, 3 $C\underline{H}_2$),

0.76 (t, 3H, CH_2-C<u>H</u>$_3$, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.3, 150.8, 122.3, 75.2, 32.7, 31.5, 28.8, 27.9, 26.3, 22.5, 14.0.

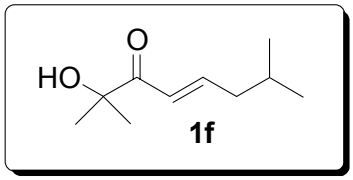
2-Hydroxy-2-methyl-hept-4-en-3-one 1e



1e

The general procedure A (Route I) was followed using n-propanaldehyde (17.5 mL, 240 mmol). Yield 4.2 g (37%). IR ($CHCl_3$, cm^{-1}) 3390, 2950, 1635, 1169, 974; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (m, 1H, CH=C<u>H</u>-CH_2), 6.38 (d, 1H, CO-C<u>H</u>=CH, *J*=15.0 Hz), 4.0 (bs, 1H, O<u>H</u>), 2.27 (m, 2H, C<u>H</u>$_2$), 1.36 (s, 6H, C(C<u>H</u>$_3$)$_2$), 1.08 (t, 3H, C<u>H</u>$_3$-CH_2, *J*= 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 152.3, 121.4, 75.2, 26.4, 25.9, 12.2.

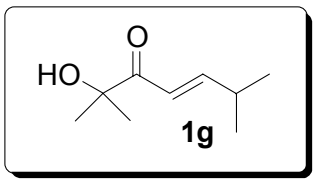
2-Hydroxy-2,7-dimethyl-oct-4-en-3-one 1f



1f

The general procedure A (Route I) was followed using isopentanaldehyde (25.7 mL, 240 mmol). Yield 12.4 g (81%). IR ($CHCl_3$, cm^{-1}) 3465, 2940, 1696, 1621, 1456; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.93 (m, 1H, CH=C<u>H</u>-CH_2), 6.32 (d,1H, CO-<u>CH</u>=CH, *J*=15.2 Hz), 3.98 (bs, 1H, O<u>H</u>), 1.98 (t, 2H, CH-C<u>H</u>$_2$, *J*= 8.5 Hz), 1.61 (m, 1H, C<u>H</u>-$(CH_3)_2$), 1.20 (s, 6H, C(C<u>H</u>$_3$)$_2$), 0.75 (d, 6H, *J*= 6.6 Hz, CH-(<u>CH</u>$_3$)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2, 149.9, 123.5, 75.1, 41.9, 27.8, 26.2, 22.3.

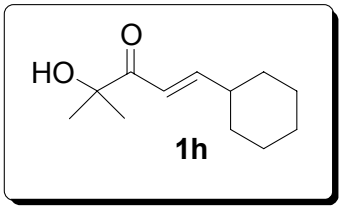
2-Hydroxy-2,6-dimethyl-hept-4-en-3-one 1g



1g

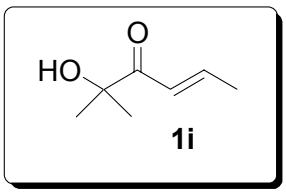
The general procedure (Route II) was followed using isobutyraldehyde (1.65 mL, 18.2 mmol). Yield 2.0 g (72 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, 1H, C<u>H</u>-CH, *J*= 15.3 Hz), 6.35 (d, 1H, CO-C<u>H</u>=CH, *J*= 15.4 Hz), 4.00 (bs, 1H, O<u>H</u>), 2.50 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.40 (s, 6H, C(C<u>H</u>$_3$)$_2$), 1.10 (d, 6H, CH(C<u>H</u>$_3$)$_2$, *J*= 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 157.0, 119.2, 75.1, 31.4, 26.3, 21.2.

1-Cyclohexyl-4-hydroxy-4-methyl-pent-1-en-3-one 1h



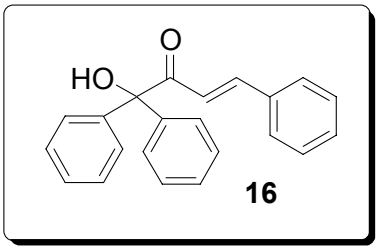
The general procedure A (Route I) was followed using cyclohexylcarbaldehyde (29 mL, 240 mmol). Yield 8.9 g (55%). IR ($CHCl_3$, cm^{-1}) 3456, 2940, 2846, 1696, 1621, 1475; ^1H NMR (200 MHz, $CDCl_3$) δ 6.86 (dd, 1H, CH=C<u>H</u>-*cyclo*, *J*=15.4 Hz), 6.27 (d, 1H, CO-C<u>H</u>, *J*= 15.4 Hz), 4.04 (bs, 1H, O<u>H</u>), 2.00 (m, 1H, C<u>H</u>), 1.60 (m, 4H, 2 C<u>H_2</u>), 1.17 (s, 6H, C(C<u>H_3</u>)$_2$), 1.10 (m, 6H, <u>cyclo</u>); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.6, 155.2, 119.9, 75.2, 40.8, 31.6, 26.2, 25.8, 25.6.

2-Hydroxy-2-methyl-hex-4-en-3-one 1i



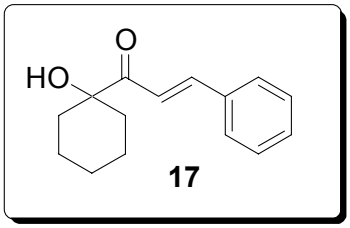
(Procedure not optimized) The general procedure (Route II) was followed using acetaldehyde (1.5 mL, 27 mmol). Yield 2.5 g (70%). IR ($CHCl_3$, cm^{-1}) 3421, 2968, 1646; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 1H, =C<u>H</u>-CH_3), 6.46 (d, 1H, C<u>H</u>-CO, *J*=15.3 Hz), 3.98 (bs, 1H, O<u>H</u>), 1.96 (d, 3H, CH-C<u>H_3</u>, *J*= 6.6 Hz), 1.39 (s, 6H, C(C<u>H_3</u>)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 146.0, 123.9, 75.0, 26.2, 18.4.

1-Hydroxy-1,1,4-triphenyl-but-3-en-2-one 16



The compound was prepared using procedure for modified enone. Yellow solids; m.p.= 104–106 ºC; Yield: 3.0 g (96%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, 1H, C<u>H</u>Ph, *J*= 16.0 Hz), 7.48–7.35 (m, 3H, <u>Ph</u>), 7.02 (d, 1H, C<u>H</u>CO, *J*= 20.0 Hz), 5.23 (bs, 1H, O<u>H</u>); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.3, 144.9, 141.7, 134.3, 131.1, 129.0, 128.8, 128.5, 128.3, 128.2, 121.0.

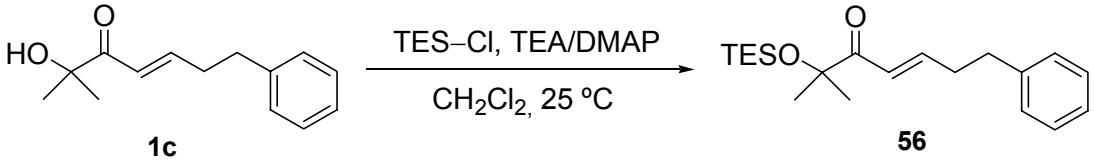
1-(1-Hydroxy-cyclohexyl)-3-phenyl-propenone 17



17

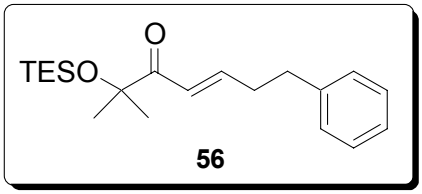
The compound was prepared using procedure for modified enone. Yellow solid; m. p.= 57–59 ºC; Yield: 2.1 g (93%). ^{1}H NMR ((300 MHz, $CDCl_3$) δ 7.84 (d, 1H, C<u>H</u>Ph, *J*= 15.7 Hz), 7.63–7.60 (m, 2H, <u>Ph</u>), 7.44–7.40 (m, 3H, <u>Ph</u>), 7.14 (d, 2H, C<u>H</u>-CO, *J*= 15.7 Hz), 3.75 (bs, 1H, O<u>H</u>), 1.85–1.65 (m, 7H, <u>cyclo</u>), 1.59–1.52 (m, 2H, <u>cyclo</u>), 1.39–1.25 (m, 1H, <u>cyclo</u>); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.7, 145.3, 134.5,130.9, 129.0, 128.7, 119.0, 77.4, 33.8, 25.4, 21.2.

6.1.7 Preparation of TES–protected enone 56



1c **56**

Under N_2 atmosphere, α'–Hydroxy enone **1c** (218 mg, 1 mmol) was dissolved in 10 mL dichloromethane. To this solution *N,N*–dimethylamino pyridine (DMAP) (24 mg, 0.2 mmol), triethylamine (208 µL, 1.5 mmol) were added. Reaction mass was cooled to 0 ºC and triethylchlorosilane (252 µL, 1.5 mmol) was added dropwise over a period of 5 min. The reaction mass was warmed to toom temperature and stirred until TLC analysis indicated the reaction completion (about 12 h). Reaction was quenced with sat. NH_4Cl (25 mL), and extracted in dichloromethane (3 x 30 mL). Organic layer was washed with brine (1 x 30 mL) and water (1 x 30 mL). Evaporation of solvent under reduced pressure and subsequent purification by flash column chromatography using hexane:EtOAc (95:5) as eluents yielded the pure product **56** as colourless oil. Yield: 310 g (95%).



56

Coluorless oil; Yield 310 mg (95%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H, <u>Ph</u>), 7.00 (q, 1H, =C<u>H</u>-CH_2, *J*=7.0 Hz), 6.80 (d, 1H, C<u>H</u>-CO, *J*=16.0 Hz), 2.80 (t, 2H, C<u>H_2</u>, *J*=7.5

Hz), 2.56 (dd, 2H, C<u>H</u>$_2$, *J*= 7.5 Hz), 1.34 (s, 6H, C(C<u>H</u>$_3$)$_2$), 0.96 (t, 9H, 3 C<u>H</u>$_3$-CH$_2$-Si, *J*=8.0 Hz), 0.60 (q, 6H, C<u>H</u>$_2$-Si, *J*=8.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.7, 146.9, 141.0, 128.4, 128.3, 126.1, 124.5, 78.8, 34.48, 34.40, 27.2, 7.0, 6.6.

6.2 Friedel–Crafts reactions of pyrrole derivatives

6.2.1 General

All reactions were carried out under an atmosphere of nitrogen in flame/oven dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2), acetonitrile were dried by distilling over CaH_2. THF and diethly ether were dried by distilling over sodium metal. Commercially available HPLC grade ethanol, isopropyl alcohol, and hexane were used without distillation. Diisopropylamine was dried by refluxing over KOH and after distillation stored with MS–4Å (1.6 mm pellets). Commercial $Cu(OTf)_2$, $Sc(OTf)_3$, $Mg(OTf)_2$, and $Zn(OTf)_2$ were dried by heating at 150 ºC for 24 h under vaccum. Poweder molecular sieves MS-4Å were activated by heating at 150 ºC under vaccum for 24 h and were stored in anhydrous condition. Again, they were heated at 150 ºC under vaccum for 1 h before using for the reaction. Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Hexane, ethyl acetate, dichloromethane and diethyl ether used for flash column chromatography were of commercial grade and were distilled before use. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and a solution obtained by admixing in 470 mL of water ammonium molibdate (21 g), cerium sulphate (1 g) and concentrated sulphuric acid (31 mL), followed by heating. Melting points were measured with a Büchi SMP–20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-200, Bruker Avance-DPX-300, and Bruker Avance-500 spectrometers and are reported in ppm from internal tetramethylsilane (TMS) and chloroform. Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on Waters 600E and Hewlett Packard series 1050 chromatographs, equipped with a diode array UV detector, using Daicel Chiralpak AD, AS, OJ, IA and Chiralcel OD columns.

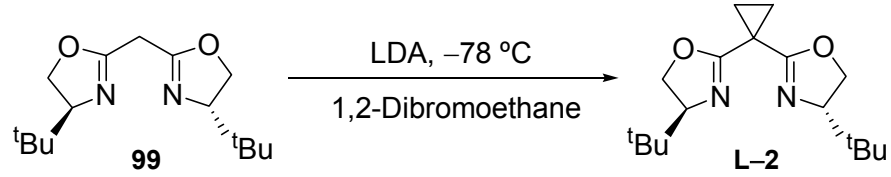
6.2.2 Preparation of chiral ligands and catalysts

Chiral ligands 2,2'-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline (**L–1**), (S)-(-)-2,2'-isopropylidene bis(4-phenyl-2-oxazoline) (**L–3**), 2,6-Bis-(4-isopropyl-4,5-dihydro-oxazol-2-yl)-pyridine (**L–4**) were purchased from Aldrich chemical. Chiral ligand 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)] cyclopropane (**L–2**) was prepared according to procedure reported by Denmark (see below). Chiral ligand {3aS-[2(3'aR*, 8'aα), 3aα, 8aα]}-2,2´-(cyclopropylidene)-bis{3a, 8a-dihydro-8H-indeno[1,2-*d*]-oxazole} (**L–5**) was synthesized

according to Sibi (see below). Catalyst **12** was prepared according to reported proeudures by Mikami using ligand **L–6** (see below). Catalysts **13** (3,3-Diphenyl-1-o-tolyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole), **14** and **15** were purchased from Aldrich chemical.

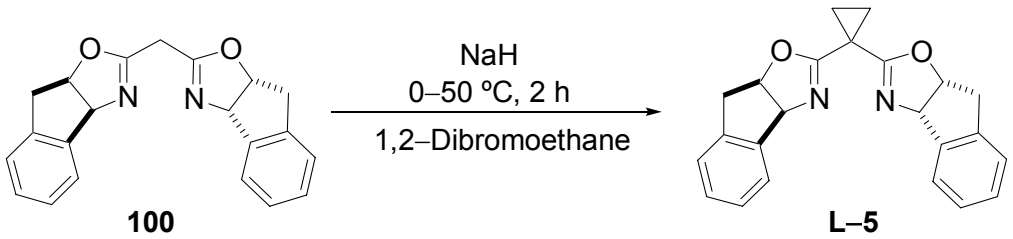
Preparation of chiral ligands

Preparation of chiral ligand L–2[172]



Chiral ligand **L–2** i.e. 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)] cyclopropane was prepared according to the procedure repoted by Denmark and co-workers as follows: Under N_2 atmosphere, to a solution of commercially available 2,2'-methylenebis [(4S)-4-ter-butyl-2-oxazoline)] **99** (1.0 g, 3.75 mmol) in dry THF (100 mL), was added *N,N*-tetramethly ethylene diamine (TMED) (1.13 mL, 7.5 mmol) and diisopropyl amine (DIPA) (533 µL, 3.75 mmol). Reaction mass was cooled to –75 ºC and n-BuLi (5.0 mL, 1.5 M soln in n-hexane, 7.5 mmol) was added keeping temperature at –75 ºC. Reaction mass was warmed to –20 ºC and stirred for 30 min. and again cooled to –75 ºC. 1,2–Dibromoethane (324 µL, 3.75 mmol) was added slowly to the reaction in about 10 min. Then reaction mass was allowed to warm to room temperature and stirred at the same temperature for 16 h. The yellow reaction mass was quenched with sat. NH_4Cl (40 mL) and extracted with diethyl ether (3 x 100 mL). Combined organic layers were washed with water (3 x 75 mL), dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using ethyl acetate:methanol (98:2) eluents and further crystallisation using hexane/ethyl acetate yielded white solid with yellow tinch as pure product **L–2** in 30% yield (330 mg).

Preparation of chiral ligand L–5[173]



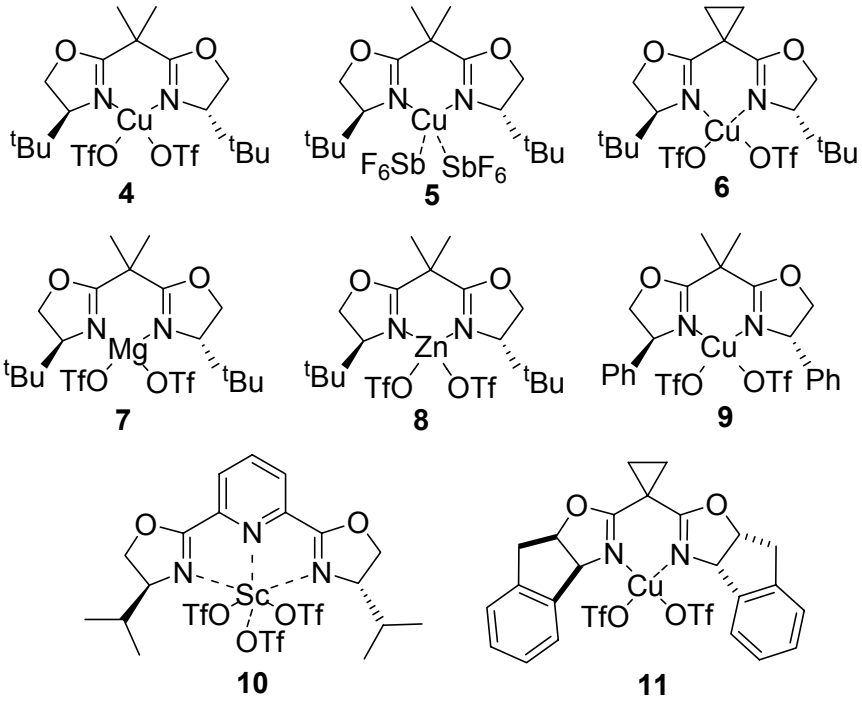
[172] Denmark, S. E.; Stiff, C. M. *J. Org. Chem*. **2000**, *65*, 5875—5878.
[173] Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615—6616.

The title compound was prepared according to process repoted by Sibi and co-workers as follows: Under N_2, to a solution of commercially available dihydro bisoxazoline **100** (400 mg, 1.2 mmol) in dry THF (6 mL), at 0 ºC, was added sodium hydride (145 mg, 3.6 mmol, 60% in mineral oil) in 3 lots at 10 min interval between each. Reaction mass was stirred for 30 min at 0 ºC. 1,2–Dibromoethane (125 µL, 1.4 mmol) was added slowly to the reaction. Then reaction mass was then warmed to 50 ºC till reaction completion indicated by TLC analysis (around 2 h). The reaction was quenched with sat. NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 x 100 mL). Combined organic layers were washed with water (3 x 75 mL), dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using ethyl acetate:methanol (98:2) eluents and further crystallisation using hexane:ethyl acetate (90:10) yielded white solids as pure product **L–5** in 80% yield (340 mg).

Preparation of catalyst complexes

All the catalysts were prepared in situ, during the reaction.

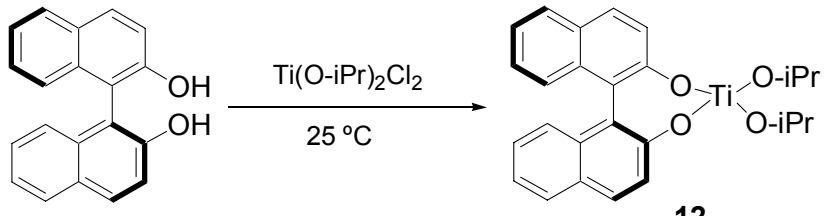
General procedure for preparation of catalyst complexes 4-11



At room temperature, under an N_2 atmosphere, corresponding bis(oxazoline) ligand **L–1—L–5** (0.075 mmol) and corresponding metal salt (0.05 mmol) were admixed in stated

solvent and stirred for 3 h. Then this solution was subjected to the specified condition for F–C alkylation reaction.

Preparation of catalyst 12[174]

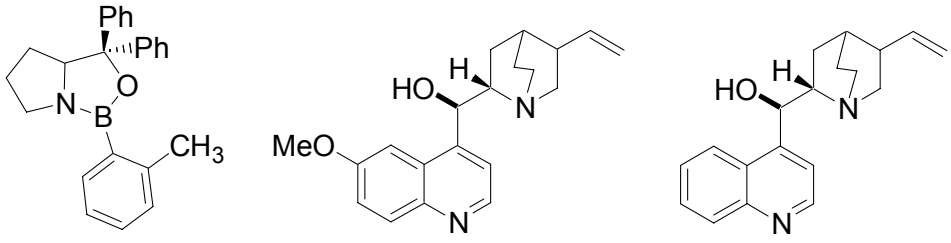


L–6 **12**

At room temperature, under an N_2 atmosphere, 0.3 M toluene solution of diisopropoxytitanium dichloride (0.33 mL, 0.10 mmol) and (S)-[1,1']Binaphthalenyl-2,2'-diol **L–6** (28.6 mg**,** 0.10 mmol) were added in CH_2Cl_2 (5 mL). After stirring for 1 h at room temperature, the mixture was subjected to specified condition for F–C alkylation reaction.

When reaction is carried out in presence of MS–4Å: At room temperature, under N_2 atmosphere, to a suspension of activated powdered molecular sieves–4Å (500 mg) in CH_2Cl_2 (5 mL) was added a 0.3 M toluene solution of diisopropoxytitanium dichloride (0.33 mL, 0.10 mmol) and (S)- [1,1']Binaphthalenyl-2,2'-diol **L–6** (28.6 mg**,** 0.10 mmol). After stirring for 1 h at room temperature, the mixture was subjected to specified condition for F–C alkylation reaction.

For catalysts 13, 14, 15

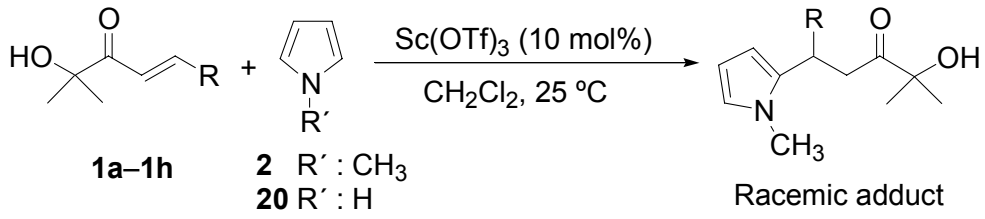


Oxazaborolidine **13** Quinine **14** Cinchonidine **15**

Under an N_2 atmosphere, at stated reaction conditions of solvent and temperature, corresponding catalysts **13, 14** or **15** were added to the previously prepared solution of corresponding α'–hydroxy enone in stated solvent.

[174] (a) Mikami, K.; Terada, M.; Nakali, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949—3954. (b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363—2364.

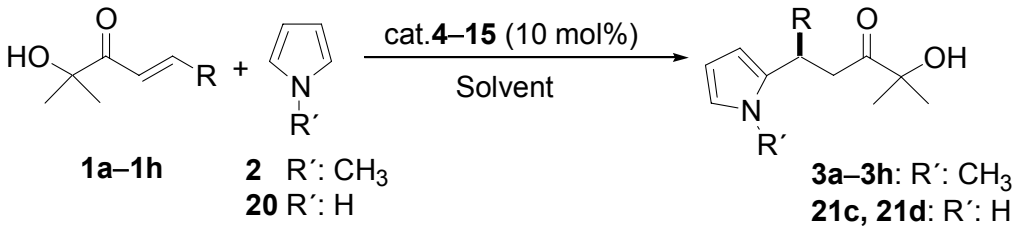
6.2.3 Preparation of racemic adducts



1a–1h **2** R´ : CH_3 **20** R´ : H Racemic adduct

The corresponding α'–hydroxy enone **1a–1h** or modified enone **17** (0.5 mmol) was weighed into an oven or flame-dried flask and placed under nitrogen. It was dissolved in 1.0 mL dry CH_2Cl_2. $Sc(OTf)_3$ (0.024 g, 0.05 mmol) was then added by rinsing with dry CH_2Cl_2 (1.0 mL) from a weighing boat directly into the reaction flask. Then N-methyl pyrrole **2** (89 µL, 1 mmol) or N–H pyrrole **20** (69.5 µL, 1 mmol) was added drop wise by syringe directly into the reaction flask. The resulting solution was stirred at room temperature until disappearance of starting material as monitored by TLC. The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10mL). The combined organic layer was washed with water (2 x 10 mL) and dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) eluents yielded the corresponding pure racemic products.

6.2.4 General procedure for the asymmetric F–C reaction of N-methyl pyrrole 2 and N–H pyrrole 20 with α'–hydroxy enones 1a–1h, 17 catalysed by 4–15



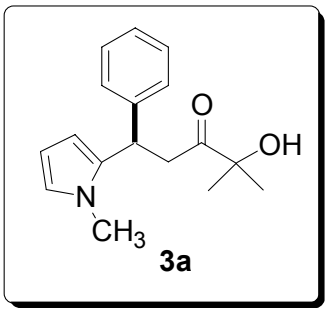
1a–1h **2** R´: CH_3 **20** R´: H **3a–3h**: R´: CH_3 **21c, 21d**: R´: H

Under nitrogen atmosphere, at stated temperature conditions, solution of the corresponding α'–hydroxy enone **1a–1h**, **17** (0.5 mmol) in stated dry solvent (0.5 mL) was cannulated to the previously in situ prepared catalyst solution according to above mentioned procedures, followed by a 0.5 mL rinse, and the resulting mixture was stirred for a further 10 min. at the same temperature. Then N-methyl pyrrole **2** (89µL, 1 mmol) or N–H pyrrole **20** (69.5 µL, 1 mmol) was added dropwise by syringe directly into the reaction, and the mixture was stirred at stated temperature for the stated time. Reaction progress was monitored by TLC analysis. After completion, the reaction was quenched with sat. NH_4Cl (5 mL) and

extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with water (2 x 10 mL) and dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) eluents yielded the corresponding pure product.

6.2.5 Characterisation data

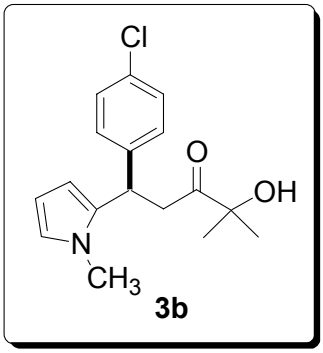
(*R*)-4-Hydroxy-4-methyl-1-(1-methyl-1H-pyrrol-2-yl)-1-phenyl-pentan-3-one 3a



3a

The title compound was prepared according to the general procedure starting from enone **1a** (95.12 mg, 0.5 mmol) and using catalyst **6** at 25 ºC. Yield 128 mg (95%); Yellow oil; $[\alpha]_D^{25}$ = – 3.30º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3456, 3071, 1707, 1489; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20−7.28 (m, 5H, Ph), 6.56 (dd, 1H, Pyrrole, *J*=0 Hz), 6.11 (m, 2H, Pyrrole), 4.68 (t, 1H, Ph-CH, *J*=7.0 Hz), 3.56 (bs,1H, OH), 3.38 (s, 3H, N-CH_3), 3.26 (dd, 1H, CH_{2b}-C=O, *J*=7.5 Hz), 3.17 (dd, 1H, CH_{2a}-C=O, *J*=8.5 Hz), 1.38 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 142.6, 133.9, 128.6, 127.8, 126.7, 122.1, 106.4, 105.4, 76.3, 43.0, 38.1, 33.8, 26.2, 25.7; MS (ESI): *m/z* 271; Elemental analysis calcd (%) for $C_{17}H_{21}NO_2$ (271.35): C 75.25, H 7.80, N 5.16; found: C 74.96, H 8.10, N 4.93; Chiral HPLC was performed on Waters 600E (Chiralpak AD column, hexane:EtOH 94:06, 0.5 mL/min., 254 nm), Rt_{major}: 16.26 min., Rt_{minor}: 20.13 min., 68.0% ee.

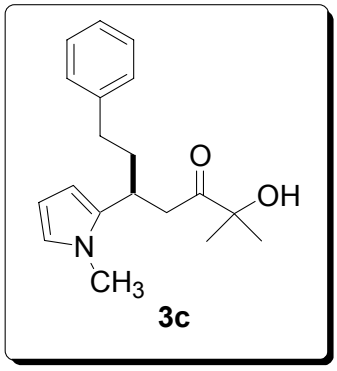
(*R*)-1-(4-Chloro-phenyl)-4-hydroxy-4-methyl-1-(1-methyl-1H-pyrrol-2-yl)-pentan-3-one 3b



3b

The title compound was prepared according to the general procedure starting from enone **1b** (112 mg, 0.5 mmol) and using catalyst **6** at 25 ºC. Yield 290 mg (95%); Yellow oil; $[\alpha]_D^{25}$ = – 13.20º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3522, 3050, 1715, 1487; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 2H, Ph, *J*=8.0 Hz), 7.09 (d, 2H, Ph, *J*=8.5 Hz), 6.54 (d, 1H, Pyrrole, *J*=2.0 Hz), 6.09 (dd, 1H, Pyrrole, *J*=3.5 Hz), 6.07 (d, 1H, Pyrrole, *J*=0 Hz), 4.63 (t, 1H, Ar-CH, *J*=7.0 Hz), 3.47 (bs, 1H, OH), 3.35 (s, 3H, N-CH_3), 3.25 (dd, 1H, CH_{2b}-C=O, *J*=6.5 Hz), 3.15 (dd, 1H, CH_{2a}-C=O, *J*=8.0 Hz), 1.35 (s, 3H, CH_3), 1.11(s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 141.2, 133.4, 132.5, 129.3, 128.8, 122.4, 106.5, 105.6, 42.9, 37.4, 33.9, 26.3, 25.9. (ESI): *m/z* 305; Elemental analysis calcd (%) for $C_{17}H_{20}NO_2Cl$ (305.80): C 66.77, H 6.59, N 4.85; found: C 66.80, H 6.25, N 4.53; Chiral HPLC was performed on HP series 1050 (Chiralpak AS column, hexane:iPrOH 95:05, 0.5 mL/min., 210 nm), Rt_{major}: 18.43 min., Rt_{minor}: 15.83 min., 83.1% ee.

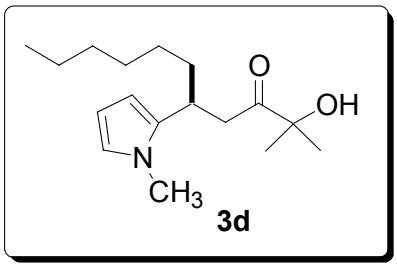
(*S*)-2-Hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-7-phenyl-heptan-3-one 3c



3c

The title compound was prepared according to the general procedure starting from enone **1c** (109 mg, 0.5 mmol) and using catalyst **4** at 25 ºC. Yield 137 mg (92 %); Yellow thick oil; $[\alpha]_D^{25}$ = +10.80º (*c*= 1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3475, 2959, 1710, 1480; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, 2H, Ph, *J*= 7.5 Hz), 7.19 (dd, 1H, Ph, *J*= 7.0 Hz), 7.12 (d, 2H, Ph, *J*= 6.5 Hz), 6.49 (d, 1H, Pyrrole, *J*=0.0 Hz), 6.09 (dd, 1H, Pyrrole, *J*=3.0 Hz), 5.94 (d, 1H, Pyrrole, *J*=0.0 Hz), 3.54 (bs, 1H, OH), 3.51 (s, 3H, N-CH_3), 3.37 (m, 1H, CH), 2.92 (dd, 1H, CH_{2b}-CO, *J*= 7.5 Hz), 2.77 (dd, 1H, CH_{2a}-CO, *J*= 6.5 Hz), 2.57 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 1.32 (s, 3H, CH_3), 1.21 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 141.7, 135.4, 128.3, 128.3, 125.9, 121.0, 106.9, 104.2, 76.2, 42.8, 37.7, 33.6, 33.4, 31.1, 26.2, 26.0; MS (ESI): *m/z*: 299, 108; Elemental analysis calcd (%) for $C_{19}H_{25}NO_2$ (299.41): C 76.22, H 8.42, N 4.68; found: C 75.90, H 8.78, N 4.79; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 254 nm), Rt_{major}: 32.54 min., Rt_{minor}: 23.42 min., 91.7% ee.

(*S*)-2-Hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-undecan-3-one 3d

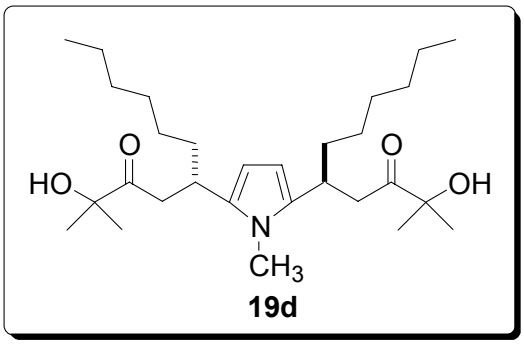


3d

The title compound was prepared according to the general procedure starting from enone **1d** (85 mg, 0.5 mmol) and using catalyst **4** at –20 ºC. Yield 85 mg (88 %); Yellow thick oil; $[\alpha]_D^{25}$ = +11.50º (*c*=1, CH_2Cl_2). IR (CH_2Cl_2, cm^{-1}) 3500, 2950, 1700, 1487; ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, 1H, Pyrrole, *J*=0.0 Hz), 6.04 (dd, 1H, Pyrrole, *J*=3.0 Hz), 5.85 (d, 1H, Pyrrole, *J*=2.0 Hz), 3.59 (s, 3H, N-CH_3), 3.58 (bs, 1H, OH), 3.32 (m, 1H, Ar-CH), 2.88 (dd, 1H, CH_{2b}-CO, *J*=8.0 Hz), 2.74 (dd, 1H, CH_{2a}-CO, *J*=6.0 Hz), 1.58 (q, 2H, CH_2), 1.34 (s, 3H, CH_3), 1.23 (m, 8H, 4 CH_2), 1.22 (s, 3H, CH_3), 0.86 (t, 3H, CH_3, *J*=7.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 213.6, 136.3, 120.9, 106.7, 103.9, 76.3, 42.8, 36.5, 33.7, 31.7, 31.5, 29.3, 27.6, 26.3, 26.1, 22.6, 14.1; MS (ESI): *m/z*: 279, 94; Elemental analysis calcd (%) for $C_{17}H_{29}NO_2$ (279.42): C 73.09, H 10.46, N 5.01; found: C 72.46, H 9.86, N 5.23; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 210 nm), Rt_{major}: 21.68 min., Rt_{minor}: 14.26 min., 95.8% ee.

A 10 mg (4%) fraction of the dialkylated adduct (2-Hydroxy-5-{5-[1-(3-hydroxy-3- methyl-2-oxo-butyl)-heptyl]-1-methyl-1H-pyrrol-2-yl}-2-methyl-undecan-3-one, **19d**) was also obtained from column.

(*S,S*)-Bis-2,5-(2-hydroxy-2-methyl-undecan-3-one-5-yl)-1-methyl pyrrole 19d

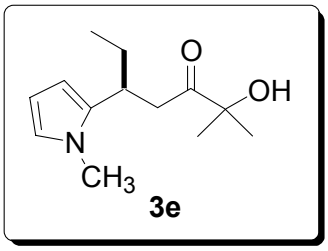


19d

The title compound was prepared according to the general procedure starting from enone **1d** (85 mg, 0.5 mmol) and using catalyst **4** at –20 ºC. Yield 10 mg (4%); Yellow oil; $[\alpha]_D^{25}$ = –30.60º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3503, 2922, 1706, 1452; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (d, 2H, Pyrrole), 3.58 (s, 2H, OH), 3.51(s, 3H, N-CH_3), 3.34 (m, 2H, Ar-CH), 2.89 (dd, 2H, CH_{2b}-CO, *J*= 7.2 Hz), 2.73 (dd, 2H, CH_{2a}-CO, *J*= 6.0 Hz), 1.57 (m, 4H, 2 CH_2), 1.34 (s,

6H, C(C<u>H</u>$_3$)$_2$), 1.24 (m, 16H, 8 C<u>H</u>$_2$), 1.21 (s, 6H, C(C<u>H</u>$_3$)$_2$), 0.89 (t, 6H, 2 C<u>H</u>$_3$, *J*= 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 135.2, 103.0, 76.2, 42.7, 36.3, 31.8, 31.7, 30.1, 29.2, 27.2, 26.1, 26.0, 22.5, 14.0; MS (ESI): *m/z* 476, 49.

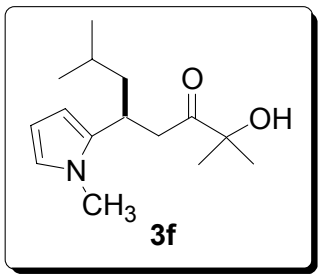
(*S*)-2-Hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-heptan-3-one 3e



3e

The title compound was prepared according to the general procedure starting from enone **1e** (71 mg, 0.5 mmol) and using catalyst **4** at –20 ºC. Yield 98 mg (88 %); Yellow thick oil; $[\alpha]_D^{25}$ = –6.30º (*c*=1, CH_2Cl_2); IR (cm$^{-1,}$ CH_2Cl_2) 3484, 2968, 1715, 1487; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (dd, 1H, <u>Pyrrole</u>, *J*=3.5 Hz), 6.47 (d, 1H, <u>Pyrrole</u>, *J*= 0.0 Hz), 5.84 (d,1H, <u>Pyrrole</u>, *J*= 2.0 Hz), 3.61 (bs, 1H, O<u>H</u>), 3.60 (s, 3H, N-C<u>H</u>$_3$), 3.27 (m, 1H, -C<u>H</u>-CH$_2$-C=O), 2.90 (dd, 1H, C<u>H</u>$_{2b}$-CO, *J*=7.5 Hz), 2.76 (dd, 1H, C<u>H</u>$_{2a}$-CO, *J*= 6.5 Hz), 1.61 (m, 2H, C<u>H</u>$_2$-CH$_3$), 1.34 (s, 3H, C<u>H</u>$_3$), 1.23 (s, 3H, C<u>H</u>$_3$), 0.85 (t, 3H, CH$_2$-C<u>H</u>$_3$, *J*= 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 136.0, 120.9, 106.7, 104.0, 76.3, 42.3, 33.7, 32.9, 29.2, 26.3, 26.1, 11.8; MS (ESI): *m/z* 223, 122; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 210 nm), Rt_{major}: 16.86 min., Rt_{minor}: 12.45 min., 93.7% ee.

(*S*)-2-Hydroxy-2,7-dimethyl-5-(1-methyl-1H-pyrrol-2-yl)-octan-3-one 3f



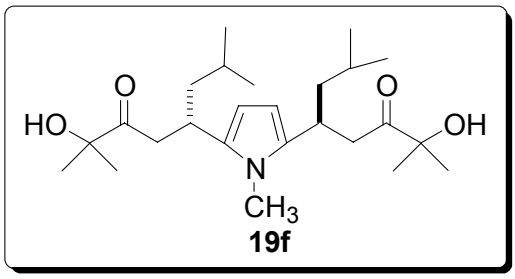
3f

The title compound was prepared according to the general procedure starting from enone **1f** (85 mg, 0.5 mmol) and using catalyst **4** at –20 ºC. Yield 85 mg (68 %); Yellow thick oil; $[\alpha]_D^{25}$ = +11.50º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3475, 2959, 1710, 1470; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, 1H, <u>Pyrrole,</u> *J*= 2.5 Hz), 6.04 (dd, 1H, <u>Pyrrole</u>, *J*= 3.5 Hz), 5.86 (d, 1H, <u>Pyrrole</u>, *J*= 2.0 Hz), 3.60 (s, 3H, N-C<u>H</u>$_3$), 3.56 (s, 1H, O<u>H</u>), 3.40 (m, 1H, C<u>H</u>), 2.86 (dd, 1H, C<u>H</u>$_{2b}$-CO, *J*= 7.5 Hz), 2.68 (dd, 1H, -C<u>H</u>$_{2a}$-CO, *J*= 6.5 Hz), 1.55 (m, 1H, C<u>H</u>), 1.47 (m, 1H, C<u>H</u>), 1.39 (m, 1H, C<u>H</u>(CH$_3$)$_2$), 1.32 (s, 3H, C<u>H</u>$_3$), 1.18 (s, 3H, C<u>H</u>$_3$), 0.90 (d, 3H, C<u>H</u>$_3$, *J*= 6.0

Hz), 0.87 (d, 3H, C<u>H</u>$_3$, *J*= 6.5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 213.5, 136.3, 120.8, 106.8, 104.0, 76.3, 45.7, 43.3, 33.7, 29.5, 26.2, 25.9, 25.7, 23.1, 22.2; MS (ESI): *m/z* 251, 94; Chiral HPLC (Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 210 nm), Rt_{major}: 21.44 min., Rt_{minor}: 12.93 min., 94.0% ee.

A 18 mg (8%) fraction of the dialkylated adduct (2-Hydroxy-5-[5-(4-hydroxy-1- isobutyl-4-methyl-3-oxo-pentyl)-1-methyl-1H-pyrrol-2-yl]-2,7-dimethyl-octan-3-one, **19f**) was also obtained from the column.

(*S,S*)-Bis-2,5-(2,7-dimethyl-2-hydroxy-octan-3-one-5-yl)-1-methyl pyrrole 19f

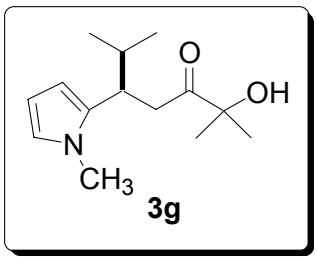


19f

The title compound was prepared according to the general procedure starting from enone **1f** (85 mg, 0.5 mmol) and using catalyst **4** at 0 ºC. Yield 18 mg (8%); Yellow waxy solid; $[\alpha]_D^{25}$ = –10.6º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3484, 1712, 1665; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (s, 2H, <u>Pyrrole</u>), 3.55 (bs, 2H, O<u>H</u>), 3.49 (s, 3H, N-C<u>H</u>$_3$), 3.39 (m, 2H, C<u>H</u>), 2.82 (dd, 2H, C<u>H</u>$_{2b}$-CO, *J*= 7.5 Hz), 2.64 (dd, 2H, C<u>H</u>$_{2a}$-CO, *J*= 6.5 Hz), 1.51 (m, 2H, C<u>H</u>), 1.46–1.32 (m, 4H, C<u>H</u>$_2$-CH(CH$_3$)$_2$), 1.28 (s, 6H, C(C<u>H</u>$_3$)$_2$), 1.14 (s, 6H, C(C<u>H</u>$_3$)$_2$), 0.86 (d, 6H, CH(C<u>H</u>$_3$)$_2$, *J*= 6.0 Hz), 0.83 (d, 6H, CH(C<u>H</u>$_3$)$_2$, *J*= 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 135.1, 103.2, 76.2, 75.3, 69.0, 45.6, 43.4, 30.1, 29.9, 26.0, 25.9, 25.6, 24.4, 23.1, 22.2.

By following the General Procedure, but using 6 mol equivalents of **2** at –20 ºC, the title compound **3f** was obtained in 86% yield and 94% ee, without traces of dialkylation adduct **19f**.

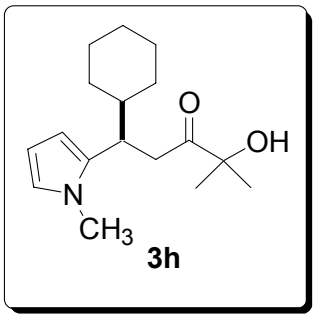
(*R*)-2-Hydroxy-2,6-dimethyl-5-(1-methyl-1H-pyrrol-2-yl)-heptan-3-one 3g



3g

The title compound was prepared according to the general procedure starting from enone **1g** (78 mg, 0.5 mmol) and using catalyst **4** at 0 ºC. Yield 102 mg (86%); Yellow thick oil. $[\alpha]_D^{25}$ = +13.40º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3437, 2931, 1710, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (d, 1H, Pyrrole, *J*= 1.8 Hz), 6.04 (dd, 1H, Pyrrole, *J*= 2.7 Hz), 5.82 (dd, 1H, Pyrrole, *J*= 1.8 Hz), 3.64 (s, 3H, N-CH_3), 3.61 (bs, 1H, OH), 3.17 (m, 1H, CH), 3.05 (dd, 1H, CH_{2b}-CO, *J*= 10.5 Hz), 2.76 (dd, 1H, CH_{2a}-CO, *J*= 4.2 Hz), 1.83 (m, 1H, CH$(CH_3)_2$), 1.36 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 0.95 (d, 3H, CH_3, *J*= 6.6 Hz), 0.87 (d, 3H, CH_3, *J*= 6.9 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 213.8, 135.2, 120.7, 106.4, 104.7, 76.3, 39.8, 37.7, 33.9, 33.5, 26.25, 26.25, 20.3, 20.1; MS (ESI): *m/z*: 237, 108; Elemental analysis calcd (%) for $C_{14}H_{23}NO_2$ (237.34): C 70.89, H 9.77, N 5.90; found: C 71.54, H 9.83, N 5.85; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 97:3, 0.5 mL/min., 254 nm), Rt_{major}: 15.40 min., Rt_{minor}: 12.53 min., 94.7% ee.

(*R*)-1-Cyclohexyl-4-hydroxy-4-methyl-1-(1-methyl-1H-pyrrol-2-yl)-pentan-3-one 3h

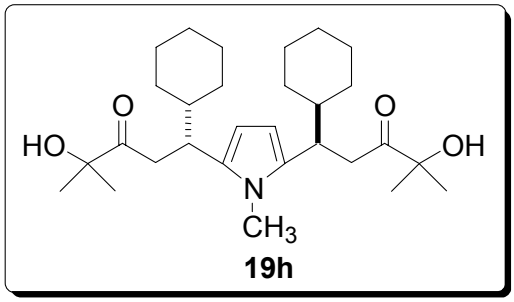


3h

The title compound was prepared according to the general procedure starting from enone **1h** (98 mg, 0.5 mmol) and using catalyst **4** at 25 ºC. Yield 90 mg (65%); Yellow solid; m. p. 146–148 ºC (from hexane); $[\alpha]_D^{25}$ = –22.10º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3492, 2950, 1712, 1492; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, 1H, Pyrrole, *J*= 2.1 Hz), 6.04 (dd, 1H, Pyrrole, *J*= 3.3 Hz), 5.80 (dd, 1H, Pyrrole, *J*=1.8 Hz), 3.65 (s, 3H, N-CH_3), 3.63 (bs, 1H, OH), 3.18 (m, 1H, Ar-CH), 3.04 (dd, 1H, CH_{2b}-CO, *J*= 9.9 Hz), 2.79 (dd, 1H, CH_{2a}-CO, *J*= 3.6 Hz), 1.34 (s, 3H, CH_3), 1.44–1.86 (m, 5H, cyclo), 1.20 (s, 3H, CH_3), 1.17 (m, 2H, cyclo), 0.95 (m, 4H, cyclo); ^{13}C NMR (300 MHz, $CDCl_3$) δ 214.0, 135.4, 120.6, 106.4, 104.5, 76.3, 43.6, 39.7, 37.0, 33.9, 31.0, 30.6, 26.4, 26.4, 26.3, 26.20, 26.25; MS (ESI): *m/z*: 277, 108; Chiral HPLC was performed on Waters 600E (Chiralpak AS column, hexane:iPrOH 98:2, 0.5 mL/min., 254 nm), Rt_{major}: 18.41 min., Rt_{minor}: 13.70 min., 92.8% ee.

A 34 mg (14%) fraction of dialkylated adduct **19h** was also obtained from column.

(*R,R*)-Bis-2,5-(5-cyclohexyl-2-hydroxy-2-methyl-pentan-3-one-5-yl)-1-methyl pyrrole 19h

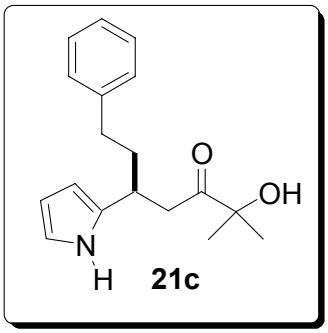


19h

The title compound was prepared according to the general procedure starting from enone **1h** (98 mg, 0.5 mmol) and using catalyst **4** at 25 ºC. Yield 34 mg (14%); Yellow solid; m.p. 94–95 ºC (from hexane); $[\alpha]_D^{25}$ = +70.60º (*c*=1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3492, 2931, 1712, 1454; ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (s, 2H, Pyrrole), 3.53 (s, 2H, OH), 3.50 (s, 1H, N-CH_3), 3.13 (m, 2H, CH-Pyrrole), 2.97 (dd, 2H, CH_{2b}-C=O, *J*=10.5 Hz), 2.72 (dd, 2H, CH_{2a}-C=O, *J*= 4.0 Hz), 1.75 (q, 1H, CH, *J*= 12.5 Hz), 1.63 (t, 1H, CH, *J*= 12.0 Hz), 1.38 (t, 2H, CH_2, *J*=10.0 Hz), 1.128 (s, 6H, $C(CH_3)_2$), 1.127 (s, 6H, $C(CH_3)_2$), 1.126 (m, 4H, cyclo), 0.86 (m, 4H, cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 134.1, 103.6, 76.23, 43.7, 39.9, 37.6, 31.1, 30.6, 30.4, 26.4, 26.2, 26.1; Elemental analysis calcd (%) for $C_{29}H_{47}NO_4$ (473.69): C 73.53, H 10.00, N 2.96; found: C 73.75, H 10.25, N 3.00. (See the ORTEP diagram in the Apendix I).

By following the General Procedure, but using 6 mol equivalents of **2**, the title monoalkyl adduct **3h** was obtained in 84% yield and 97% ee, without traces of dialkylated byproduct **19h**.

(*S*)-2-Hydroxy-2-methyl-7-phenyl-5-(1H-pyrrol-2-yl)-heptan-3-one 21c



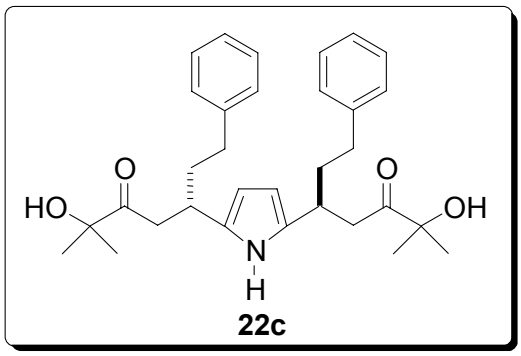
21c

The title compound was prepared according to the general procedure starting from enone **1c** (109 mg, 0.5 mmol), pyrrole **20** and using catalyst **4** at 0 ºC. Yield 118 mg (83 %); Yellowish red oil; $[\alpha]_D^{25}$ = +12.0º (*c*= 1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3384, 2974, 1709, 1455, 966, 701; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (bs, 1H, NH), 7.16–7.34 (m, 5H, Ph), 6.68 (d, 1H, Pyrrole,

J=1.8 Hz), 6.17 (dd, 1H, Pyrrole, *J*= 2.7 Hz), 5.99 (d, 1H, Pyrrole, *J*= 3.9 Hz), 3.32 (m, 1H, CH), 2.96 (dd, 1H, CH_{2b}-CO, *J*= 7.5 Hz), 2.80 (dd, 1H, CH_{2a}-CO, *J*= 4.8 Hz), 2.63 (m, 2H, CH_2), 2.06 (m, 2H, CH_2), 1.34 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 141.8, 134.2, 128.4, 125.9, 116.3, 108.2, 104.0, 43.1, 36.4, 33.7, 33.5, 26.1, 25.9; Chiral HPLC was performed on HP 1050 series (Chiralcel OD column, hexane:iPrOH 95:5; 0.5 mL/min., 210 nm), Rt_{major}: 38.58 min., Rt_{minor}: 47.62 min., 90.2% ee.

A 20 mg (8%) fraction of the dialkylated adduct (2-Hydroxy-5-[5-(4-hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-1H-pyrrol-2-yl]-2-methyl-7-phenyl-heptan-3-one, **22c**) was also obtained from the column.

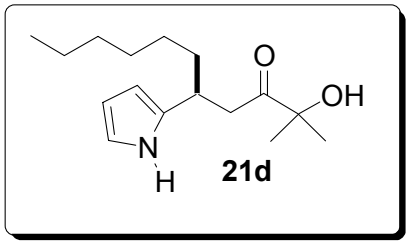
(*S,S*)-Bis-2,5-(2-hydroxy-2-methyl-7-phenyl--heptan-3-one-5-yl)-1H-pyrrole 22c



22c

The title compound was prepared according to the general procedure starting from enone **1c** (109 mg, 0.5 mmol), pyrrole **20** and using catalyst **4** at 0 ºC. Yield: 20 mg (8%); Yellow red oil; $[\alpha]_D^{25}$ = –3.9º (*c*= 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (bs, 1H, NH), 7.27–7.10 (m, 10H, Ph), 5.80 (d, 2H, Pyrrole, *J*= 2.5 Hz), 3.19 (m, 2H, CH), 2.86 (dd, 2H, CH_{2b}-CO, *J*= 9.0 Hz), 2.71 (dd, 2H, CH_{2a}-CO, *J*= 5.0 Hz), 2.55 (m, 4H, CH_2), 1.94 (m, 4H, CH_2), 1.29 (s, 6H, CH_3), 1.16 (s, 6H, CH_3).

(*S*)-2-Hydroxy-2-methyl-5-(1H-pyrrol-2-yl)-heptan-3-one 21d



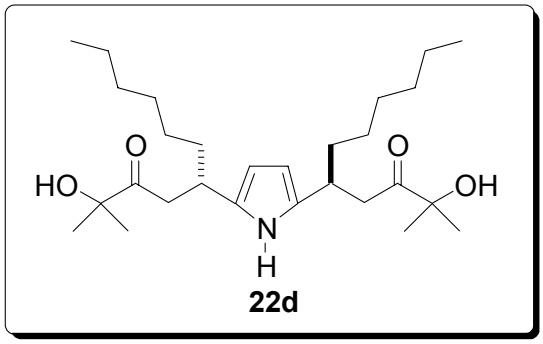
21d

The title compound was prepared according to the general procedure starting from enone **1d** (99 mg, 0.5 mmol) and pyrrole **20** and using catalyst **4** at –20 ºC. Yield 108 mg (82 %); Yellowish red oil; $[\alpha]_D^{25}$ = +23.4º (*c*= 1, CH_2Cl_2); IR (CH_2Cl_2, cm-1) 3411, 2940, 1707, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (bs, 1H, NH), 6.62 (d, 1H, Pyrrole, *J*= 0.0 Hz), 6.10 (dd, 1H,

Pyrrole, *J*= 3.0 Hz), 5.88 (d, 1H, Pyrrole, *J*= 0.0 Hz), 3.57 (bs, 1H, OH), 3.24 (m, 1H, Ar-CH), 2.86 (dd, 1H, CH_{2b}-CO, *J*= 8.5 Hz), 2.75 (dd, 1H, CH_{2a}-CO, *J*= 5.0 Hz), 1.70 (m, 1H, CH_2), 1.58 (m, 1H, CH_2), 1.33 (s, 3H, CH_3), 1.28 (m, 8H, 4 CH_2), 1.17 (s, 3H, CH_3), 0.87 (t, 3H, CH_3, *J*= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 135.0, 116.1, 108.1, 103.8, 76.5, 43.0, 34.8, 33.9, 31.7, 29.3, 27.6, 26.2, 26.0, 22.6, 14.1; Chiral HPLC was performed on Waters 600E (Chiralpak IA column, hexane:iPrOH 95:5, 0.5 mL/min., 254 nm), Rt_{major}:19.62 min., Rt_{minor}: 23.12 min., 89.0% ee.

A 10 mg (4%) fraction of the dialkylated adduct (2-Hydroxy-5-{5-[1-(3-hydroxy-3- methyl-2-oxo-butyl)-heptyl]-1H-pyrrol-2-yl}-2-methyl-undecan-3-one, **22d**) was also obtained from the column.

(*S,S*)-Bis-2,5-(2-hydroxy-2-methyl-undecan-3-one-5-yl)-1H-pyrrole 22d

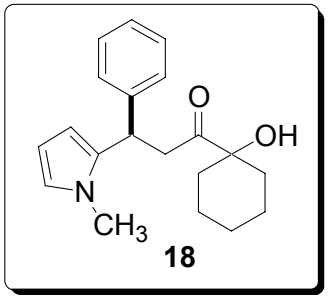


22d

The title compound was prepared according to the general procedure starting from enone **1d** (99 mg, 0.5 mmol) and pyrrole **20** and using catalyst **4** at –20 ºC. Yield 10 mg (4%); Yellowish red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (bs,1H, NH), 5.70 (d, 2H, Pyrrole, *J*= 2.0 Hz), 3.59 (bs, 2H, OH), 3.14 (m, 2H, Ar-CH), 2.83 (dd, 2H, CH_{2b}-CO, *J*= 9.0 Hz), 2.68 (dd, 2H, CH_{2a}-CO, *J*= 5.0 Hz), 1.61 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 1.31 (s, 6H, $C(CH_3)_2$), 1.22 (m, 16H, 8 CH_2), 1.15 (s, 6H, $C(CH_3)_2$), 0.85 (t, 6H, 2 CH_3, *J*= 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6, 133.4, 103.6, 76.4, 42.9, 34.9, 33.9, 31.7, 29.2, 27.5, 26.2, 26.0, 22.6, 14.1.

By following the General Procedure, but using 6 mol equivalents of **20** and running the reaction at –20ºC, the monoalkyl compound **21d** was obtained in 87% yield and 91.4% ee, without traces of dialkylated by-product **22d**.

(*R*)-1-(1-Hydroxy-cyclohexyl)-3-(1-methyl-1H-pyrrol-2-yl)-3-phenyl-propan-1-one 18

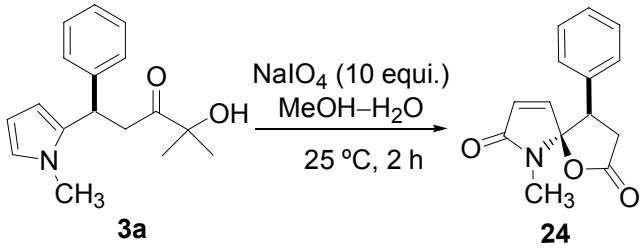


18

The title compound was prepared according to the general procedure starting from enone **17** (112 mg, 0.5 mmol) and using catalyst **6** at 25 ºC. Yield 140 mg (90 %); Yellowish red oil; $[\alpha]_D^{25}$ = –82.0º (*c*= 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H, Ph), 6.56 (dd, 1H, Pyrrole, *J*= 2.1 Hz), 6.11 (dd, 2H, Pyrrole, *J*= 2.7 Hz), 4.68 (t, 1H, Ar-CH, *J*= 6.9 Hz), 3.38 (s, 3H, N-CH_3), 3.30 (dd, 1H, CH_{2a}-CO, *J*= 6.6 Hz), 3.26 (dd, 1H, CH_{2b}-CO, *J*= 7.5 Hz), 1.75–1.45 (m, 10H, Cyclo); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 142.8, 134.0, 128.6, 127.8, 126.6, 122.0, 106.3, 105.4, 78.0, 43.2, 38.0, 33.6, 33.1, 25.2, 20.99, 20.94; Chiral HPLC was performed on HP series 1050 (Chiralpak IA column, hexane:iPrOH 95:05, 0.5 mL/min., 210 nm), Rt_{major} : 20.94 min., Rt_{minor}: 30.50 min., 78.0% ee.

6.2.6 Elaboration of adducts

6.2.6.1 Elaboration to obtain spiro compound 24

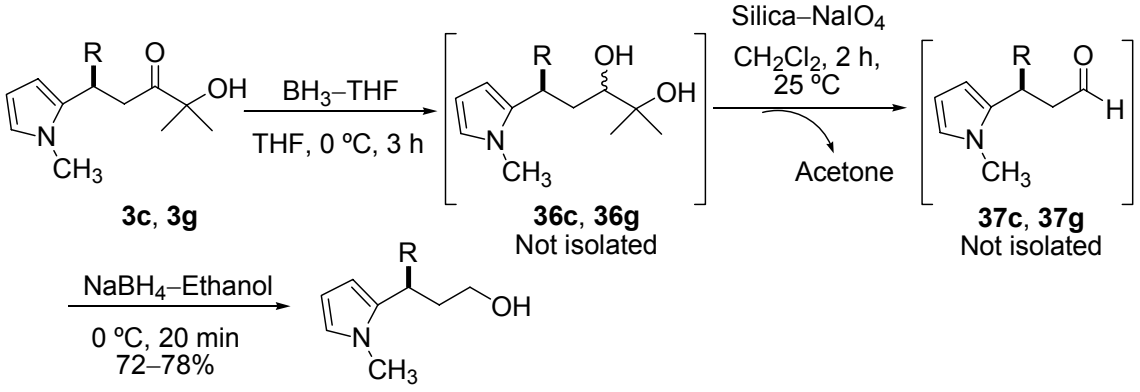


3a **24**

In a round bottom flask, Friedel–Crafts adduct **3a** (1 mmol) was dissolved in a mixture of methanol (6 mL) and water (3 mL), cooled to 0 ºC (ice bath). To this solution, $NaIO_4$ (2.10 g, 10 mmol) was added in 2 portions with 10 min. of interval between each. The reaction mass is allowed to stir at room temperature. After completion of the reaction as monitored by TLC analysis (around 2 h), the reaction mass was diluted with dichloromethane (2 x 30 mL). The reaction mass was washed with 5% aq. sodium sulfite solution (2 x 10 mL) and water (2 x 10 mL), dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) as eluent yielded pure product **24**.

Data of **24**: Yield 49 mg (40%); Red solid; m.p.=147–149 ºC (from EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.29 (m, 3H, Ph), 7.07–7.04 (m, 2H, Ph), 6.66 (d, 1H, CO-CH=C-, *J*=6.0 Hz), 5.93 (d, 1H, CH=CH, *J*=6.0 Hz), 3.98 (t, 1H, CH-Ph, *J*=10.0 Hz), 3.16 (dd, 2H, CH_2-C=O, *J*=10.0 Hz), 3.05 (s, 3H N-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 169.6, 143.3, 133.9, 129.5, 128.9, 128.5, 127.2, 101.5, 44.7, 33.9, 24.1; Elemental analysis: Calcd for $C_{14}H_{13}NO_3$ (243.26): C 69.12, H 5.39, N 5.67; found: C 68.92, H 5.18, N 5.75; crystal data obtained (See appendix: I).

6.2.6.2 Elaboration of adducts into aldehydes (General Procedure)



38c R= $PhCH_2CH_2$, 90% ee
38g R= i-Pr, 95% ee
Observed $[\alpha]_D$= + 31.1º (*c*= 1, MeOH) and
Reported $[\alpha]_D$= – 20º (*c*= 1, MeOH) (91% ee)[176]

In a round bottom flask, under nitrogen atmosphere, to a solution of corresponding Friedel–Crafts adduct **3c** or **3g** (1 mmol) in THF (3 mL), at 0 ºC (ice bath), was added drop wise a solution of borane in THF (1 M soln, 2.24 mL, 2 mmol) keeping temperature at 0 ºC. The reaction was stirred at the same temperature until TLC analysis indicates completion of the reaction (around 3 h). While keeping reaction at 0 ºC, methanol (3 mL) was added and then the mixture was allowed to come to room temperature and stirred for additional 30 minutes. Evaporation of solvent afforded the crude diol compound **36c** or **36g**, used as is for the next step.

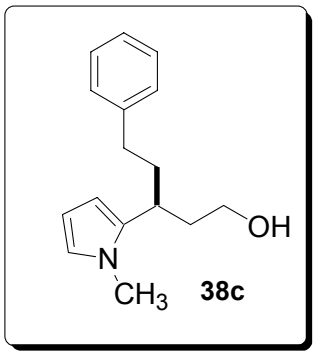
In a round bottom flask, under nitrogen atmosphere at 0 ºC, the crude diol was dissolved in dry dichloromethane (25 mL) and a previously prepared mixture of $NaIO_4$-SiO_2[175] (2 g, 2 mmol of oxidant) was added in portions over a period of 5–10 min. The

[175] Adsorbed sodium meta periodate on silica was prepared according to Zhong, Y. –L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622—2624, as follows: $NaIO_4$ (25 g) and water (50 mL) are mixed with

reaction mass was allowed to warm to room temperature and stirred until TLC analysis indicated reaction completion (around 3 h). If necessary, additional excess of pre-adsorbed $NaIO_4$-silica might be added for reaction completion. The mixture was filtered and the silica was washed with dichloromethane (20 mL). The combined organic layer was evaporated under reduced pressure to give the crude aldehyde compound **37c** or **37g**, which was characterised as the corresponding alcohol **38c** or **38g** after reduction with $NaBH_4$, as follows:

In a round bottom flask, under nitrogen atmosphere, the crude aldehyde **37c** or **37g** was dissolved in dry ethanol (3 mL) and, after cooling to 0 ºC, $NaBH_4$ (38 mg, 1 mmol) was added in 3 portions over a period of about 5 minutes. The reaction was stirred at the same temperature until TLC analysis indicated completion of the reaction (around 20 minutes). Then, the reaction was quenched with sat. $NaHCO_3$ (5 mL), extracted with dichloromethane (3 x 10 mL). The combined organic layer was washed with water (2 x 10 mL), dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) as eluents yielded corresponding pure alcohol product **38c** or **38g**.

(*S*)-3-(1-Methyl-1H-pyrrol-2-yl)-5-phenyl-pentan-1-ol 38c



38c

The title compound was prepared according to the general procedure starting from **3c** (237 mg, 1.0 mmol). Yield and data of the alcohol **38c** (over the three steps): 120 mg (72%); Red thick oil ; $[\alpha]_D^{25}$ = +31.10º (c= 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (m, 5H, Pyrrole), 6.08 (dd, 1H, Pyrrole), 5.86 (m, 2H, Pyrrole), 3.55 (s, 1H, N-CH_3), 3.46 (m, 1H, CH-Pyrrole), 2.65 (m, 2H, CH_2-OH), 1.98 (m, 2H, CH_2), 1.78 (m, 1H, CH(CH_3)$_2$, 0.89 (q, 6H, *J*= 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.43, 120.87, 106.49, 105.21, 61.70, 39.60, 35.06, 33.49, 20.40, 19.94. Chiral HPLC was performed on HP series 1050 (Chiralpak OD column, hexane:iPrOH 90:10, 0.5 mL/min., 220 nm), Rt_{major}: 27.42 min., Rt_{minor}: 17.14 min., 90.13% ee.

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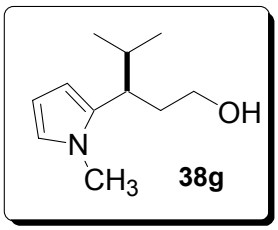
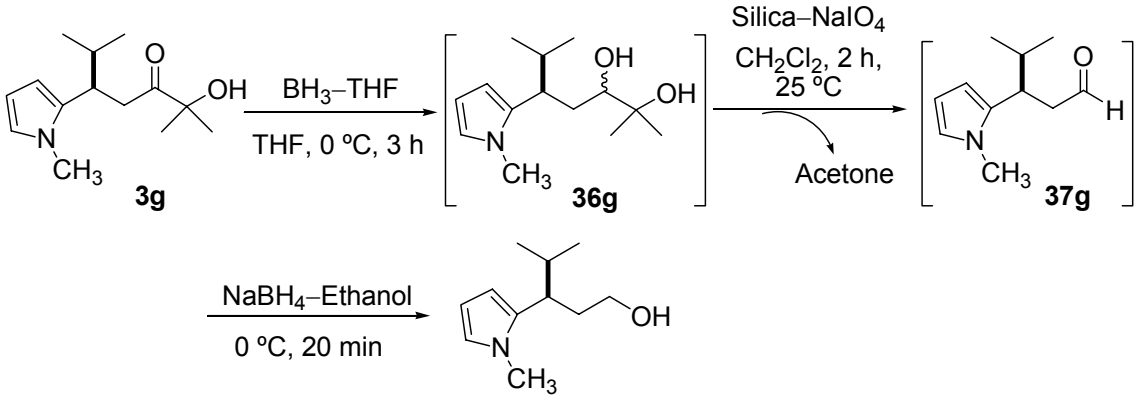
stirring at 70 ºC, and then silica gel (60 mesh, 100 g) is added and the mixture vigorously stirred for 1 h. The resulting powder can be stored for weeks and used as it is.

(*R*)-4-Methyl-3-(1-methyl-1H-pyrrol-2-yl)-pentan-1-ol 38g



The title compound was prepared according to the general procedure starting from **3g** (237 mg, 1.0 mmol). Yield and data of the alcohol **38g** (over the three steps): 141 g (78%); $[\alpha]_D^{25}$ = +31.1º (*c*=1.0, CH_3OH); Literature data[176] for (*S*)-enatiomer $[\alpha]_D^{25}$ = –20º (*c*=1.0, CH_3OH); All other spectroscopic and physical data were identical to those previously reported. Chiral HPLC was performed on Waters 600E (Chiralpak OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm), Rt_{major}: 15.67 min., Rt_{minor}: 11.97 min., 95.04% ee.

6.2.6.3 Assignment of the configuration for the adducts



38g R= i-Pr, 78%, 95% ee
Observed $[\alpha]_D = +31.1º$ (*c*= 1, MeOH) and
Reported $[\alpha]_D = -20º$ (*c*= 1, MeOH) (91% ee)[176]

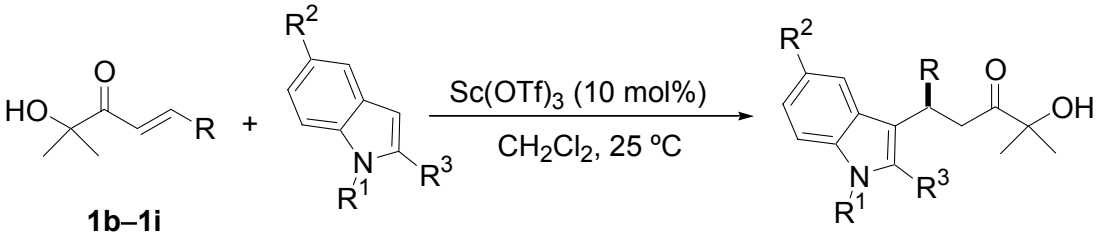
The absolute configuration (*R*) of adduct **3g** was determined by transforming it into aldehyde **37g** and comparison of the optical rotation of its alcohol **38g** derivative with published values. The same configuration (*R*) for adducts **3a, 3b, 3h** and **18** and the opposite (*S*) configuration for the rest of adducts **3c–3f** was assumed based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

[176] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370—4371.

The assignment of the relative configuration for the dialkylated adduct **19h** was determined by X−ray diffraction analysis (see Apendix I). The configuration of the rest of dialkylated adducts was assigned by analogy.

6.3 Friedel–Crafts reactions of indole derivatives

6.3.1 Preparation of racemic adducts

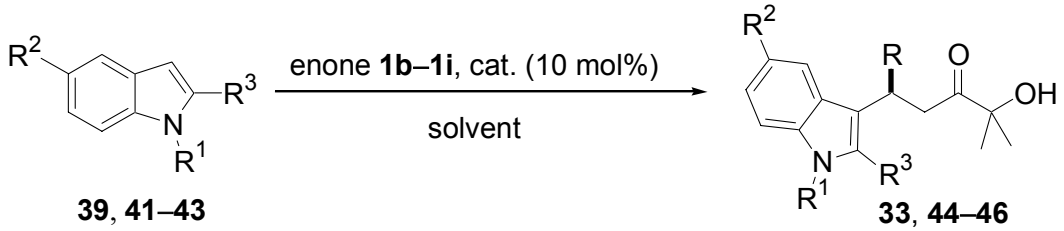


1b–1i

Racemic adduct

The corresponding enone **1b–1i** (0.5 mmol) was weighed into an oven or flame-dried flask and placed under nitrogen. It was dissolved in 1.0 mL dry CH_2Cl_2. $Sc(OTf)_3$ (0.024 g, 0.05 mmol) was then added by rinsing with dry CH_2Cl_2 (1.0 mL) from a weighing boat directly into the reaction flask. Then corresponding indole derivative **39, 41–43** (1 mmol) was dissolved in 0.25 mL CH_2Cl_2 and added dropwise by syringe into the reaction flask followed by 0.25 mL rinse, and the mixture was stirred at room (or otherwise stated) temperature until the disappearance of starting enone (TLC monitoring). The reaction was quenched with sat. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with water (2 x 10 mL), dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) as eluent yielded corresponding pure products.

6.3.2 General procedure for asymmetric Friedel–Crafts reaction of indoles 39, 41–43 with α'–hydroxy enones 1b–1i catalysed by various catalysts



39, **41–43**

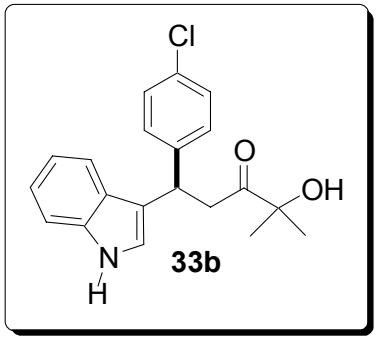
33, **44–46**

Under nitrogen atmosphere, at stated temperature conditions, solution of the corresponding α'–hydroxy enone **1b–1i** (0.5 mmol) in stated dry solvent (0.5 mL) was cannulated to the previously in situ prepared catalyst solution according to above mentioned procedures, followed by a 0.5 mL rinse, and the resulting mixture was stirred for a further 10 min. at the same temperature. Then corresponding indole derivative **39, 41–43** (1 mmol) by dissolving in 0.5 mL corresponding solvent was added dropwise to the reaction, and the mixture was stirred at stated temperature for the stated time. Reaction progress was

monitored by TLC analysis. After completion, the reaction was quenched with sat. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with water (2 x 10 mL) and dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:05) eluents yielded the corresponding pure products.

6.3.3 Chracterisation data

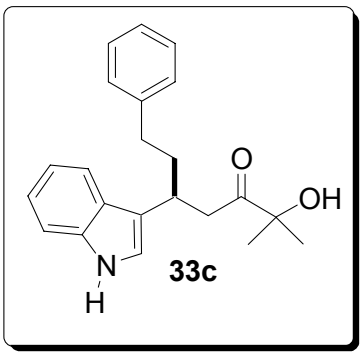
(*R*)-1-(4-Chloro-phenyl)-4-hydroxy-1-(1H-indol-3-yl)-4-methyl-pentan-3-one 33b



33b

The title compound was prepared according to the general procedure starting from enone **1b** (112.5 mg, 0.5 mmol) and using catalyst **6** at 25 ºC. Yield 162 mg (95%); White solid; m.p.= 140–142 ºC (Hexane); $[\alpha]_D^{25}$ = –12.3º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3428, 1711, 1494, 1461; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (bs, 1H, NH), 7.39 (d, 1H, Indole, *J*= 8.0 Hz), 7.35 (d, 1H, Indole, *J*= 7.5 Hz), 7.26–7.22 (m, 4H, Ph), 7.18 (dd, 1H, Indole, *J*= 7.5 Hz), 7.05 (dd, 1H, Indole, *J*= 7.0 Hz), 6.99 (s, 1H, Indole), 4.93 (t, 1H, CH, *J*= 7.5 Hz), 3.52 (bs, 1H, OH), 3.34 (dd, 2H, CH_2, *J*= 3.5 Hz), 1.27 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 142.3, 136.7, 132.3, 129.3, 128.6, 126.3, 122.5, 121.2, 119.8, 119.4, 118.6, 111.3, 76.4, 42.3, 37.3, 26.2, 26.1; Elemental analysis: Calcd for $C_{20}H_{20}ClNO_2$ (341.83): C 70.27, H 5.90, N 4.10; found C 69.70, H 5.83, N 3.92. Chiral HPLC was performed on HP series 1050 (Chiralpak AD column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm), Rt_{major}: 53.80 min., Rt_{minor}: 74.0 min., 82.8% ee (ee of mother liquor of crystallisation process).

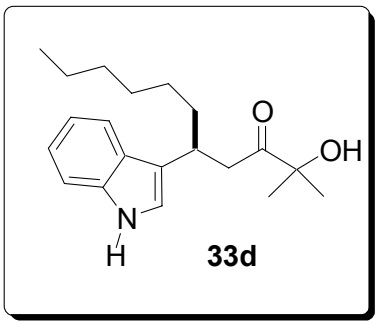
(*S*)-2-Hydroxy-5-(1H-indol-3-yl)-2-methyl-7-phenyl-heptan-3-one 33c



33c

The title compound was prepared according to the general procedure starting from enone **1c** (1.0 g, 10 mmol) and using catalyst **4** at 0 ºC. Yield 1.4 g (85%); Brown thick oil; $[\alpha]_D^{25}$ = +27.2º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3428, 1706, 1499, 1456, 742, 702; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (bs, 1H, NH), 7.69 (d, 1H, Indole, *J*= 7.8 Hz), 7.41 (d, 1H, Indole, *J*= 7.8 Hz), 7.14–7.29 (m, 7H, Indole, Ph), 7.06 (d, 1H, Ph, *J*= 2.1 Hz), 3.65 (m, 1H, CH), 3.12 (dd, 1H, CH_{2b}-CO, *J*= 7.2 Hz), 2.92 (dd, 1H, CH_{2a}-CO, *J*=8.1 Hz), 2.59 (m, 2H, CH_2-Ph), 2.13 (m, 2H, CH_2), 1.33 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 142.2, 136.6, 128.3, 128.3, 126.3, 125.7, 122.0, 121.6, 119.4, 119.3, 118.2, 111.4, 76.3, 42.5, 36.9, 34.1, 32.5, 26.2, 25.8; Elemental analysis: Calcd for $C_{22}H_{25}NO_2$ (335.44): C 78.77, H 7.51, N 4.18; found: C 78.23, H 7.87, N 4.15; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm), Rt_{major}: 54.47 min., Rt_{minor}: 40.05 min., 98.0% ee.

(*S*)-2-Hydroxy-5-(1H-indol-3-yl)-2-methyl-undecan-3-one 33d

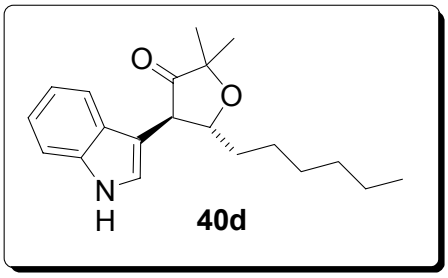


33d

The title compound was prepared according to the general procedure starting from enone **1d** (99 mg, 0.5 mmol) and using catalyst **4** at 0 ºC. Yield 132 mg (85%); Off white solid; m.p.= 88–90 ºC (from hexane); $[\alpha]_D^{25}$ = +19.4º (*c*= 1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3418, 2922, 1708, 732. ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (bs, 1H, NH), 7.67 (d, 1H, Indole, *J*= 8.0 Hz), 7.34 (d, 1H, Indole, *J*= 8.0 Hz), 7.20 (t, 1H, Indole, *J*=7.0 Hz), 7.13 (t, 1H, Indole, *J*= 7.5 Hz), 6.96 (d, 1H, Indole, *J*= 3.0 Hz), 3.83 (s, 1H, OH), 3.60 (m, 1H, CH), 3.06 (dd, 1H, CH_{2b}-CO, *J*= 7.0 Hz), 2.89 (dd, 1H, CH_{2a}-CO, *J*= 7.0 Hz), 1.84 (m, 1H), 1.74 (m, 1H), 1.35 (s, 3H, CH_3), 1.25

(m, 8H, 4 C$\underline{H}_2$), 1.08 (s, 3H, C$\underline{H}_3$), 0.86 (t, 3H, C$\underline{H}_3$, *J*= 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.0, 136.6, 126.5, 122.0, 121.9, 121.5, 121.4, 119.4, 119.3, 119.2, 118.8, 111.6, 76.4, 42.7, 35.4, 32.7, 31.8, 29.3, 27.8, 26.3, 25.9, 25.8, 22.7; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min, 254 nm), Rt_{major}: 33.26 min., Rt_{minor}: 24.75 min., 95.5% ee.

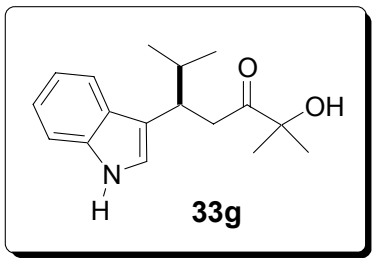
(*4S,5R*)-5-Hexyl-4-(1H-indol-3-yl)-2,2-dimethyl-dihydro-furan-3-one 40d



40d

The title compound was prepared according to the general procedure starting from enone **1d** (99 mg, 0.5 mmol) and using catalyst **4** at 0 ºC. Yield 5 mg (3 %); Red-white solid; IR (CH_2Cl_2, cm^{-1}) 3410, 2848, 1755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (bs, 1H, N$\underline{H}$), 7.48 (d, 1H, indole, *J*= 7.5 Hz), 7.37 (d, 1H, indole, *J*= 8.5 Hz), 7.22 (t, 1H, indole, *J*= 7.5 Hz), 7.13 (t, 1H, indole, *J*= 7.5 Hz), 6.98 (d, 1H, indole, *J*= 2.0 Hz), 4.25 (m, 1H, C$\underline{H}$-O), 3.68 (d, 1H, C$\underline{H}$-CO, *J*= 10.5 Hz), 1.76 (m, 4H, 2 C$\underline{H}_2$), 1.55 (m, 4H, 2 C$\underline{H}_2$), 1.43 (s, 6H, C(C$\underline{H}_3$)$_2$), 1.24 (m, 2H, C$\underline{H}_2$), 0.85 (t, 3H, C$\underline{H}_3$, *J*= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 136.5, 126.7, 122.9, 122.4, 119.9, 118.9, 111.5, 109.5, 81.0, 79.1, 51.1, 34.8, 31.7, 29.3, 25.3, 25.2, 22.5, 22.4, 14.0.

(*R*)-2-Hydroxy-5-(1H-indol-3-yl)-2,6-dimethyl-heptan-3-one 33g

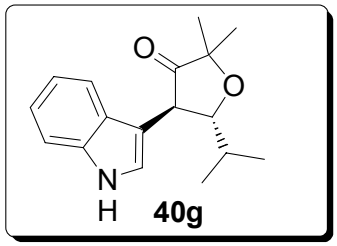


33g

The title compound was prepared according to the general procedure starting from enone **1g** (78 mg, 0.5 mmol) and using catalyst **6** at 41 ºC (reflux). Yield 110 mg (81%); Off white waxy solid; m.p.= 112–114 ºC; $[\alpha]_D^{25}$ = +45.6º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3415, 2962, 1709, 750; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (bs, 1H, N$\underline{H}$), 7.71 (d, 1H, Indole, *J*= 7.5 Hz), 7.35 (d, 1H, Indole, *J*= 7.8 Hz), 7.11–7.23 (m, 2H, Indole), 6.94 (d, 1H, Indole, *J*= 2.1 Hz), 3.78 (bs, 1H, O$\underline{H}$), 3.45 (m, 1H, C$\underline{H}$), 3.17 (dd, 1H, C$\underline{H}_{2b}$-CO, *J*= 9.0 Hz), 2.95 (dd, 1H, C$\underline{H}_{2a}$-CO, *J*= 4.5 Hz), 2.16 (m, 1H, C$\underline{H}$(CH_3)$_2$), 1.33 (s, 3H, C$\underline{H}_3$), 1.04 (s, 3H, C$\underline{H}_3$), 1.03 (d, 3H, (C$\underline{H}_3$)$_2$, *J*=

6.6 Hz), 0.89 (d, 3H, (C<u>H</u>$_3$)$_2$, *J*= 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 136.3, 126.9, 121.89, 121.83, 119.5, 119.2, 117.7, 111.2, 76.4, 39.5, 39.1, 32.1, 26.2, 25.9, 21.1, 20.6; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm), Rt_{major}: 34.07 min., Rt_{minor}: 21.51 min., 95% ee.

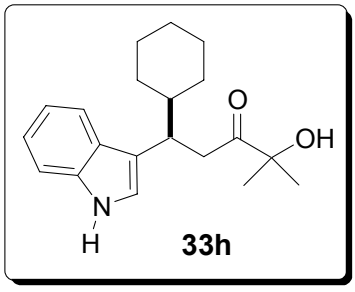
(*4S,5R*)-4-(1H-Indol-3-yl)-5-isopropyl-2,2-dimethyl-dihydro-furan-3-one 40g



40g

The title compound was prepared according to the general procedure starting from enone **1g** (78 mg, 0.5 mmol) and using catalyst **4** at 25 ºC. Yield 40 mg (29%); Off white solid; m.p.=132–133 ºC (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (bs, 1H, N<u>H</u>), 7.53 (d, 1H, *J*= 7.4 Hz, <u>Indole</u>), 7.39 (d, 1H, <u>Indole</u>, *J*= 8.0 Hz), 7.28–7.11 (m, 2H, <u>Indole</u>), 7.01 (s, 1H, <u>Indole</u>), 4.22 (dd, 1H, C<u>H</u>-O, *J*= 5.6 Hz), 3.80 (d, 1H, C<u>H</u>-CO, *J*= 10.0 Hz), 1.97 (m, 1H, C<u>H</u>(CH$_3$)$_2$), 1.43 (s, 6H, C(C<u>H</u>$_3$)$_2$), 1.00 (dd, 6H, CH(C<u>H</u>$_3$)$_2$, *J*= 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.8, 136.4, 126.6, 122.9, 122.4, 119.8, 118.8, 111.6, 110.2, 83.2, 80.7, 48.2, 31.2, 25.2, 22.8, 18.9, 16.8.

(*R*)-1-Cyclohexyl-4-hydroxy-1-(1H-indol-3-yl)-4-methyl-pentan-3-one 33h

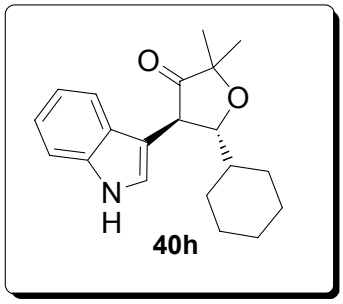


33h

The title compound was prepared according to the general procedure starting from enone **1h** (98 mg, 0.5 mmol) and using catalyst **6** at 25 ºC. Yield 125 mg (80%); Off white solid; m. p.= 114–115 ºC (from hexane); $[\alpha]_D^{25}$= +51.4º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2,cm^{-1}) 3420, 2850, 1705, 738; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (bs, 1H, N<u>H</u>), 7.33 (d, 1H, <u>Indole</u>, *J*= 8.5 Hz), 7.17 (dd, 1H, <u>Indole</u>, *J*= 8.0 Hz), 7.11 (dd, 1H, <u>Indole</u>, *J*= 7.0 Hz), 6.92 (d, 1H, <u>Indole</u>, *J*= 0.0 Hz), 3.66 (bs, 1H, O<u>H</u>), 3.42 (m, 1H, C<u>H</u>), 3.11 (dd, 1H, C<u>H</u>$_{2b}$-CO, *J*= 9.5 Hz), 2.94 (dd, 1H, C<u>H</u>$_{2a}$-CO, *J*= 5.0 Hz), 0. 1.31 (s, 3H, C<u>H</u>$_3$), 1.89–0.88 (m, 11H, <u>Cyclo</u>), 0.98 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 136.4, 127.0, 122.0, 121.8, 119.6, 119.3, 117.8, 111.3, 76.4, 41.9, 39.3, 38.4, 31.7, 31.0, 26.59, 26.51, 26.4, 26.3, 25.9; Elemental analysis: Calcd for

$C_{20}H_{27}NO_2$ (313.43) : C 76.64, H 8.68, N 4.47; found: C 76.87, H 8.84, N 4.54; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm), Rt_{major}: 36.80 min., Rt_{minor}: 21.22 min., 95.6% ee.

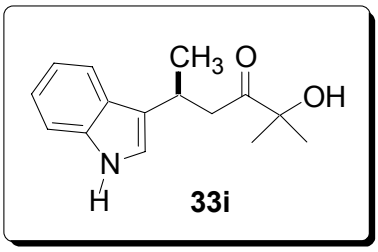
(*4S,5R*)-5-Cyclohexyl-4-(1H-indol-3-yl)-2,2-dimethyl-dihydro-furan-3-one 40h



40h

The title compound was obtained as side product, according to the general procedure starting from enone **1h** (98 mg, 0.5 mmol) and using catalyst **4** at 25 ºC. Yield 10 mg (7.3 %); Off white solid; m.p.= 114−115 ºC (from hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (bs, 1H, NH), 7.55–6.92 (m, 5H, Indole), 4.23 (dd, 1H, CH-O, *J*= 5.6 Hz), 3.86 (d, 1H, CH-CO, *J*= 11.2 Hz), 1.43 (s, 6H, $(CH_3)_2$), 1.96–1.19 (m, 11H, Cyclo); ^{13}C NMR (50 MHz, $CDCl_3$) δ 218.5, 136.2, 126.5, 122.7, 122.2, 119.7, 118.8, 111.4, 110.1, 82.4, 80.5, 47.7, 41.0, 29.3, 27.2, 26.4, 26.2, 26.1, 25.1, 22.6.

(*S*)-2-Hydroxy-5-(1H-indol-3-yl)-2-methyl-hexan-3-one 33i

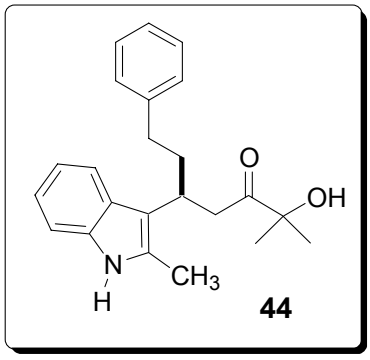


33i

The title compound was prepared according to the general procedure starting from enone **1i** (69 mg, 0.5 mmol) and using catalyst **4** at 0 ºC. Yield 80 mg (65%); Reddish white solid; m. p.= 89–91 °C (from hexane); $[\alpha]_D^{25}$= –8.6º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2,cm^{-1}) 3420, 2969, 1714, 732; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (bs, 1H, NH), 7.65 (d, 1H, Indole, *J*= 7.0 Hz), 7.37 (d,1H, Indole, *J*= 8.0 Hz), 7.21 (dd, 1H, Indole, *J*= 7.5 Hz), 7.13 (dd, 1H, Indole, *J*= 7.5 Hz), 7.00 (s, 1H, Indole), 3.82 (bs, 1H, OH), 3.76 (m, 1H, CH-Indole), 3.06 (dd, 1H, CH_{2b}-CO, *J*= 3.5 Hz), 2.83 (dd, 1H, CH_{2a}-CO, *J*= 9.0 Hz), 1.41 (d, 3H, CH_3 , *J*= 5.5 Hz), 1.33 (s, 3H, CH_3), 1.22 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 136.6, 126.2, 122.1, 120.8, 120.4, 119.4, 119.2, 111.5, 76.5, 43.9, 26.8, 26.4, 26.1, 20.9; Elemental analysis: Calcd for $C_{15}H_{19}NO_2$ (245.14): C 73.44, H 7.81, N 5.71; found: C 73.23, H 7.46, N 5.65; Chiral HPLC

was performed on HP series 1050 (Chiralpak OJ column, hexane:iPrOH 80:20, 0.5 mL/min., 254 nm), Rt_{major}: 52.03 min., Rt_{minor}: 46.70 min., 97.6% ee.

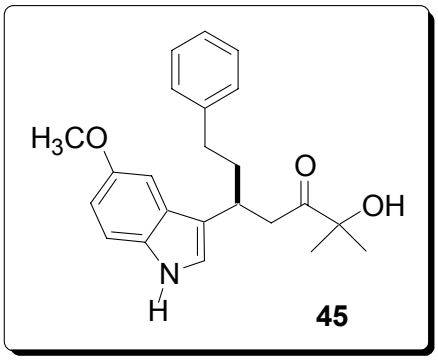
(*S*)-2-Hydroxy-2-methyl-5-(2-methyl-1H-indol-3-yl)-7-phenyl-heptan-3-one 44



44

The title compound was prepared according to general procedure starting from enone **1c** (109 mg, 0.5 mmol), substituted indole **41** (131 mg) and using catalyst **4** at 25 ºC. Yield 155 mg (89%); Yellow waxy solid; $[\alpha]_D^{25}$ = +52.2º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3411, 2973, 1709, 1458, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H, NH), 7.66 (d, 1H, Indole, *J*= 7.2 Hz), 7.31–7.09 (m, 8H, Indole, Ph), 3.58 (m, 1H, CH-Indole), 3.31 (dd, 1H, CH_{2b}-CO, *J*= 8.7 Hz), 2.90 (dd, 1H, CH_{2a}-CO, *J*= 5.4 Hz), 2.54 (m, 2H, CH_2-Ph), 2.35 (s, 3H, Indole-CH_3), 2.14 (m, 2H, CH_2), 1.33 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 142.2, 135.7, 132.0, 128.4, 128.2, 126.9, 125.7, 120.8, 119.1, 118.7, 112.3, 110.6, 76.4, 41.6, 36.3, 34.2, 32.4, 26.1, 25.5, 11.9; Elemental analysis: Calcd for $C_{23}H_{27}NO_2$ (349.47): C 79.05, H 7.79, N 4.01; found: C 79.42, H 7.54, N 4.02; Chiral HPLC was performed on Waters 600E (Chiralpak AD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm), Rt_{major}:41.35 min., Rt_{minor}: 30.06 min., 93.0% ee.

(*S*)-2-Hydroxy-5-(5-methoxy-1H-indol-3-yl)-2-methyl-7-phenyl-heptan-3-one 45

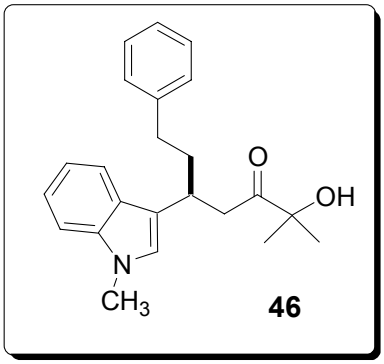


45

The title compound was prepared according to the general procedure starting from enone **1c** (109 mg, 0.5 mmol), 5-methoxy indole **42** (147 mg) and using catalyst **4** at 25 ºC. Yield 175 mg (96%); Yellow waxy solid; $[\alpha]_D^{25}$ = +43.2º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3415, 2933,

1709, 1483, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (bs,1H, NH), 7.32–6.90 (m, 9H, Indole, Ph), 3.91 (s, 3H, OCH_3), 3.74 (bs, 1H, OH), 3.65 (m, 1H, CH), 3.10 (dd,1H, CH_{2b}-CO, *J*= 6.6 Hz), 2.91 (dd, 1H, CH_{2a}-CO, *J*= 7.2 Hz), 2.62 (m, 2H, CH_2-Ph), 2.14 (m, 2H, CH_2), 1.35 (s, 3H, CH_3), 1.13 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 153.9, 142.2, 131.8, 128.4, 128.3, 126.9, 125.7, 122.3, 118.1, 112.0, 101.5, 76.3, 56.0, 42.6, 37.0, 34.0, 32.2, 26.2, 25.9; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 90:10; 0.5 mL/min., 210 nm), Rt_{major}: 78.85 min., Rt_{minor}: 61.85 min., 97.1% ee.

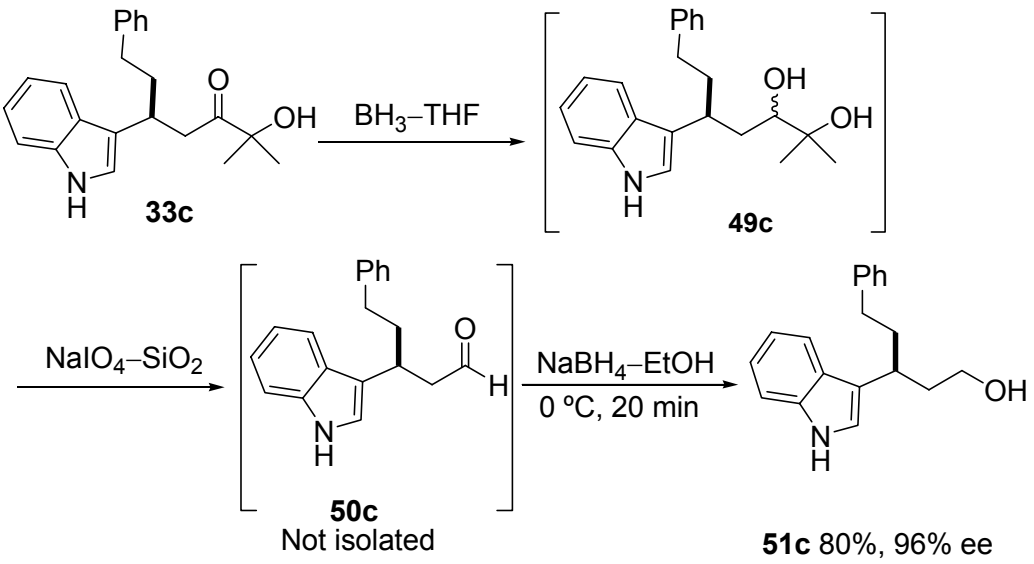
(*S*)-2-Hydroxy-2-methyl-5-(1-methyl-1H-indol-3-yl)-7-phenyl-heptan-3-one 46



46

The title compound was prepared according to the general procedure starting from enone **1c** (109 mg, 0.5 mmol), N-methyl indole **43** (131 mg) and using catalyst **4** at 25 ºC. Yield 150 mg (86 %); Yellow waxy solid; $[\alpha]_D^{25}$ = +28.4º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3457, 2931, 1709, 1468, 966, 740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.12 (m, 8H, Indole, Ph), 6.91 (*s*, 1H, Indole), 6.68 (d, 1H, Indole, *J*= 6.9 Hz), 3.79 (*s*, 3H, N-CH_3), 3.65 (m, 1H, CH), 3.10 (dd, 1H, CH_{2b}-CO, *J*= 6.3 Hz), 2.93 (dd, 1H, CH_{2a}-CO, *J*= 6.9 Hz), 2.62 (m, 2H, CH_2-Ph), 2.18 (m, 2H, CH_2), 1.34 (*s*, 3H, CH_3), 1.11 (*s*, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 142.3, 137.3, 128.4, 128.2, 126.8, 126.4, 125.7, 121.6, 119.4, 118.8, 116.7, 109.4, 76.2, 42.8, 37.1, 34.1, 32.6, 32.4, 26.3, 25.9; Elemental analysis: Calcd for $C_{23}H_{27}NO_2$ (349.47): C 79.05, H 7.79, N 4.01; found: C 79.10, H 7.63, N 4.05; Chiral HPLC was performed on Waters 600E (Chiralpak AD column, hexane:iPrOH 90:10; 0.5 mL/min., 254 nm), Rt_{major}: 18.61 min., Rt_{minor}: 22.67 min., 98.10% ee.

6.3.4 Elaboration of adducts into aldehydes. General Procedure



In a round bottom flask, under nitrogen atmosphere, to a solution of the Friedel–Crafts adduct **33c** (335 mg, 1 mmol) in THF (3 mL), cooled to 0 ºC (ice bath), was added dropwise a solution of borane in THF (1 M soln, 2.24 mL, 2 mmol) keeping temperature at 0 ºC. The reaction was stirred at the same temperature until TLC analysis indicates completion of the reaction (around 3 h). While keeping temperature at 0 ºC, methanol (3 mL) was added and then the mixture was allowed to come to room temperature and stirred for additional 30 minutes. Evaporation of solvent afforded the crude diol compound **49c**, used as is for the next step.

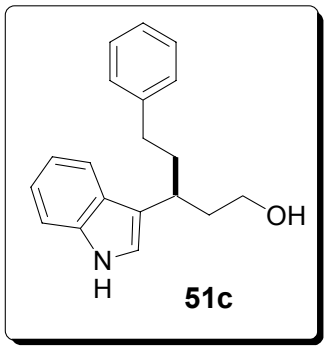
In a round bottom flask, under nitrogen atmosphere at 0 ºC, the crude diol **49c** was dissolved in dry dichloromethane (25 mL) and a previously prepared mixture of $NaIO_4$-SiO_2[177] (2 g, 2 mmol of oxidant) was added in portions over a period of 5–10 min. The reaction mass was allowed to come to room temperature and stirred until TLC analysis indicated reaction completion (around 3 h). If necessary, additional excess of pre-adsorbed $NaIO_4$ on Silica might be added for reaction completion. The mixture was filtered and the silica was washed with dichloromethane (20 mL). The combined organic layer was evaporated under reduced pressure to give the crude aldehyde compound **50c**, which was characterised as the corresponding alcohol **51c** after reduction with $NaBH_4$, as follows:

In a round bottom flask, under nitrogen atmosphere, the crude aldehyde **50c** was dissolved in dry ethanol (3 mL) and, at to 0 ºC, $NaBH_4$ (38 mg, 1 mmol) was added in 3

[177] Adsorbed sodium meta periodate on silica was prepared according to Zhong, Y. –L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622—2624, as follows: $NaIO_4$ (25 g) and water (50 mL) are mixed with stirring at 70 ºC, and then silica gel (60 mesh, 100 g) is added and the mixture vigorously stirred for 1 h. The resulting powder can be stored for weeks and used as it is.

portions over a period of about 5 minutes. The reaction was stirred at the same temperature until TLC analysis indicated completion of the reaction (around 20 minutes). Then, the reaction was quenched with sat. $NaHCO_3$ (5 mL), extracted with dichloromethane (3 x 10 mL). The combined organic layer was washed with water (2 x 10 mL) and dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) as eluent yielded pure product **51c**.

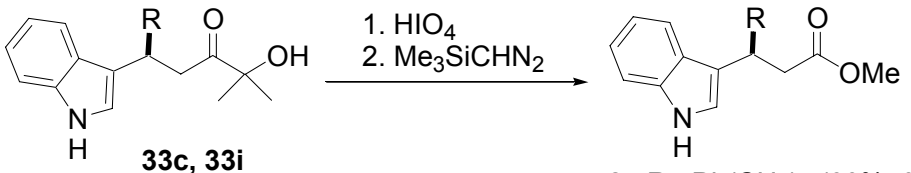
(*S*)-3-(1H-Indol-3-yl)-5-phenyl-pentan-1-ol 51c



51c

The title compound was prepared according to the general procedure starting from **33c** (335 mg, 1.0 mmol). Yield and data of the alcohol **51c** (over the three steps): 225 mg (80%); Yellow waxy solids, $[\alpha]_D^{25}$ = +7.8º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3417, 3314, 2928, 2857, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (bs, 1H, NH), 7.69 (d, 1H, Indole, *J*= 7.8 Hz), 7.41 (d, 1H, Indole, *J*= 8.1 Hz), 7.31–7.12 (m, 7H, Indole, Ph), 7.05 (d, 1H, Indole, *J*= 2.1 Hz), 3.63 (m, 2H, CH_2-OH), 3.13 (m, 1H, CH), 2.60 (m, 2H, CH_2-Ph), 2.12 (m, 4H, 2 CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 136.7, 128.4, 128.2, 126.8, 125.6, 122.0, 121.2, 119.5, 119.2, 119.0,111.2, 61.5, 38.9, 38.0, 33.9, 33.4; Elemental analysis : Calcd for $C_{19}H_{21}NO$ (279.38): C 81.68, H 7.58, N 5.01; found : C 81.79, H 8.10, N 4.81; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 80:20, 0.5 mL/min., 210 nm), Rt_{major}: 22.06 min., Rt_{minor}: 16.92 min., 95.7% ee.

6.3.5 Elaboration of adducts into carboxylic acid esters. General Procedure

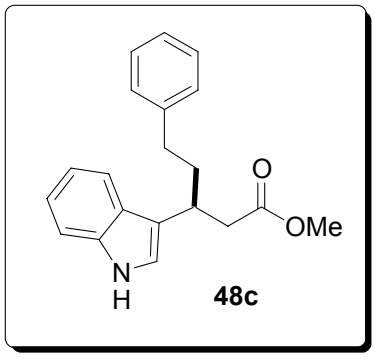


33c, 33i

48c R= $Ph(CH_2)_2$ (60%, 98% ee)
48i R =Me (67%, 94% ee)

In an oven-dried flask, the corresponding F–C adduct (1mmol) was dissolved in 4 mL of dry diethyl ether. The solution was cooled to 0 ºC using ice bath and periodic acid (274 mg, 1.2 mmol) was added slowly in 3 portions over a period of 10 min. During the course of the reaction, black coloured solids are generated which stick to the walls of reaction flask. The reaction was stirred at 0 ºC until completion (TLC analysis, around 9–10 h). After completion, reaction was quenched with 5% aqueous sodium sulfite (5 mL) and the mixture was extracted with diethyl ether (3 x 20 mL). Organic layers were combined and washed with water (2 x 10 mL) and dried over $MgSO_4$. Evaporation of solvent under reduced pressure yielded the crude carboxylic acids which were directly submitted to methylation. Trimethylsilyl diazomethane (2 M solution in hexanes, 0.548 mL, 1.1 mmol) (**Caution**: Diazo derivatives are explosive under certain conditions and should be handled with care!) was added dropwise to a solution of crude carboxylic acid (1 mmol) in benzene (20 mL) and methanol (2 mL) at room temperature. After 20 min of stirring, solvents were removed under reduced pressure to afford the corresponding crude ester which was purified by flash column chromatography (eluent: ethyl acetate/hexane).

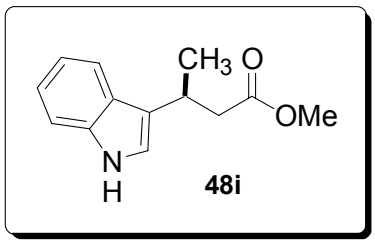
(*S*)-3-(1H-Indol-3-yl)-5-phenyl-pentanoic acid methyl ester 48c



48c

The title compound was prepared according to the general procedure starting from **33c** (335 mg, 1.0 mmol). Yield 185 mg (60%); Brown thick oil; $[\alpha]_D^{25}$ = + 7.0º (*c*=1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (bs, 1H, NH), 7.69 (d, 1H, Indole, *J*= 7.5 Hz), 7.41 (d, 1H, Indole, *J*=7.5 Hz), 7.29 (t, 1H, Indole, *J*= 8.0 Hz), 7.16 (t, 1H, Indole, *J*= 6.5 Hz), 7.07 (s, 1H, Indole), 3.62 (s, 3H, OCH_3), 3.56 (m, 1H, CH), 2.81 (d, 1H, *J*= 7.2 Hz), 2.61 (m, 2H, CH_2), 2.16 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 142.2, 128.4, 128.2, 125.7, 121.9, 121.3, 119.3, 119.2, 111.2, 51.5, 41.1, 37.1, 33.8, 33.3. Elemental analysis: Calcd for $C_{20}H_{21}NO_2$ (307.16): C 78.15, H 6.89, N 4.45; found: C 77.75, H 6.94, N 4.68; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm), Rt_{major}: 42.91 min., Rt_{minor}: 31.45 min., 98.5% ee.

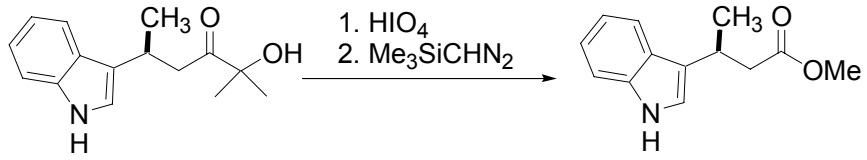
(*S*)-3-(1H-Indol-3-yl)-butyric acid methyl ester 48i



48i

The title compound was prepared according to the general procedure starting from **33i** (245 mg, 1.0 mmol). Yield 145 mg (67%); Brown thick oil, $[\alpha]_D^{25}$ = + 4.0º (*c*=1.10, CH_2Cl_2); Lit [178] $[\alpha]_D^{25}$ = +2.7º (*c*=1.10, CH_2Cl_2); All other spectroscopic and physical data were identical to those previously reported. Elemental analysis: Calcd for $C_{13}H_{15}NO_2$ (217.11): C 71.87, H 6.96, N 6.45; found: C 71.36, H 6.87, N 6.41; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm), Rt_{major}: 36.05 min., Rt_{minor}: 25.33 min., 93.6% ee.

6.3.6 Assignment of the configuration



33i

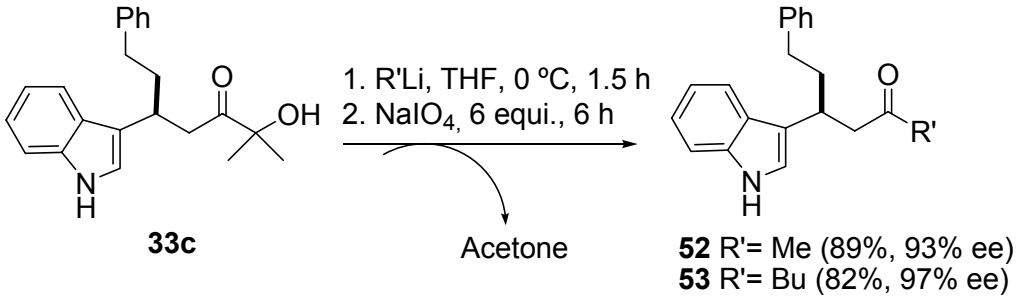
48i R = Me (67%, 94% ee)
Observed $[\alpha]_D$= + 4.1º (*c*= 1, CH_2Cl_2) and
Reported $[\alpha]_D$= + 2.7º (*c*= 1.10, CH_2Cl_2) (83% ee)[178]

The absolute configuration (*S*) of adduct **33i** was determined by transforming it into methyl ester **48i** and comparison of its optical rotation with published values. The same configuration (*S*) for adducts **33c, 33d** and **44–46** and the opposite (*R*) configuration for adducts **33b, 33g, 33h** was assumed based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

The assignment of the relative configuration for the by-product **40g** was determined by X−ray diffraction analysis (see Apendix I). The configuration of the rest of by-products were assigned by analogy.

[178] Evans, D. A.; Scheidt, K. A.; Frandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc*. **2003**, *125*, 10780—10781.

6.3.7 Elaboration of adducts into ketones. General Procedure

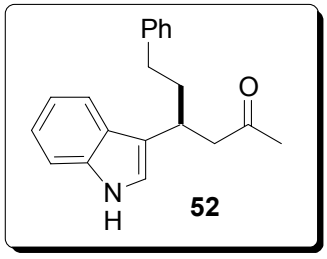


33c

52 R'= Me (89%, 93% ee)
53 R'= Bu (82%, 97% ee)

n-BuLi (2.5 M in hexanes, 1.2 mL, 3 mmol) or MeLi (1.4 M in Et_2O, 2.14 mL, 3 mmol) was added to a solution of corresponding F–C adduct (1 mmol) in THF (3 mL) at –78 °C and the solution was stirred at 0 °C for 1.5 h. The reaction mixture was quenched with sat. NH_4Cl soln (5 mL), and the resulting mixture was allowed to warm to room temperature, after which the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, under the following conditions. The crude residue from the previous reaction was dissolved in a mixture of methanol (6 mL) and water (3 mL). To this solution, $NaIO_4$ (1.25 g, 6 mmol) was added at room temperature in 2 portions with 3 hours of interval between each. During stirring of the mixture at room temperature, brown coloured precipitates are developed. After completion of the reaction as monitored by TLC analysis (around 6 h), the reaction was quenched with 5% aq. sodium sulfite solution (10 mL) and extracted with dichloromethane (3 x 10 mL). Organic layer was washed with water (1 x 10 mL) and dried over $MgSO_4$. Evaporation of solvent and subsequent purification by flash column chromatography using hexane:ethyl acetate (95:5) as eluents yielded corresponding pure products.

(*S*)-4-(1H-Indol-3-yl)-6-phenyl-hexan-2-one 52

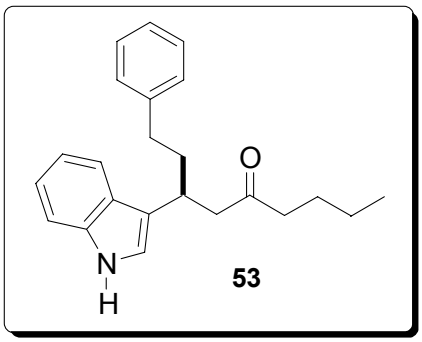


52

The title compound was prepared according to the general procedure starting from **33c** (335 mg, 1.0 mmol) and methyllithium (3.0 mmol). Yield 247 mg (89 %); Yellow waxy solids, $[\alpha]_D^{25}$ = +12.6º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3416, 2923, 1706, 1455, 742, 701; ^1H NMR (300

MHz, $CDCl_3$) δ 8.19 (bs, 1H, NH), 7.72 (d, 1H, Indole, *J*= 7.8 Hz), 7.42 (d, 1H, Indole, *J*= 7.8 Hz), 7.34–7.06 (m, 7H, Indole, Ph), 7.03 (d, 1H, Indole , *J*= 2.1 Hz), 3.60 (m, 1H, CH), 3.00 (dd, 1H, CH_{2b}-CO, *J*= 6.9 Hz), 2.89 (dd, 1H, CH_{2a}-CO, *J*= 6.6 Hz), 2.62 (t, 2H, CH_2-Ph, *J*= 7.5 Hz), 2.17 (m, 2H, CH_2), 2.06 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 142.3, 136.6, 128.5, 128.3, 126.5, 125.8, 122.0, 121.6, 119.3, 118.2, 111.5, 50.2, 37.5, 33.9, 32.7, 30.5; Elemental analysis: Calcd for $C_{20}H_{21}NO$(291.39): C 82.44, H 7.26, N 4.81; found: C 84.22, H 6.90, N 4.50; Chiral HPLC was performed on Waters 600E (Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm), Rt_{major}:34.48 min., Rt_{minor}: 31.38 min., 94.5% ee.

(*S*)-3-(1H-Indol-3-yl)-1-phenyl-nonan-5-one 53



53

The title compound was prepared according to the general procedure starting from **33c** (335 mg, 1.0 mmol) and n-BuLi (3.0 mmol). Yield 273 mg (82%); Yellow waxy solid; $[\alpha]_D^{25}$ = + 20.0º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3414, 2934, 1708, 739; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (bs, 1H, NH), 7.72 (d, 1H, Indole, *J*= 7.8 Hz), 7.41 (d, 1H, Indole, *J*= 8.1 Hz), 7.33–7.15 (m, 7H, Indole, Ph), 7.03 (d, 1H, Indole, *J*= 2.1 Hz), 3.61 (m, 1H, CH), 2.99 (dd, 1H, CH_{2b}-CO, *J*= 6.9 Hz), 2.86 (dd, 1H, CH_{2b}-CO, *J*= 6.6 Hz), 2.61 (t, 2H, CH_2CO, *J*= 6.9 Hz), 2.32 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.24 (m, 2H, CH_2), 0.86 (t, 3H, CH_3, *J*= 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 142.4, 136.7, 128.4, 128.3, 126.5, 125.7, 121.9, 121.6, 119.4, 119.2, 118.4, 111.4, 149.4, 43.1, 37.4, 34.0, 32.7, 25.7, 22.2, 13.8; Elemental analysis: Calcd for $C_{23}H_{27}NO$ (333.21): C 82.84, H 8.16, N 4.20; found: C 82.24, H 9.48, N 3.95; Chiral HPLC was performed on HP series 1050 (Chiralcel OD column, hexane:iPrOH 95:05, 0.5 mL/min., 254 nm), Rt_{major}: 22.11 min., Rt_{minor}: 20.49 min., 97.0% ee.

6.4 Conjugate additions of diethyl zinc

6.4.1 General

All reactions were carried out under an atmosphere of nitrogen in flame/oven dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. Commercially available HPLC grade ethanol, isopropyl alcohol, and n-hexane were used without distillation. Diisopropylamine was dried by refluxing over KOH and after distillation, stored with MS–4Å (1.6 mm pellets). Commercial $Cu(OTf)_2$, $Sc(OTf)_3$, $Mg(OTf)_2$, and $Zn(OTf)_2$ were dried by heating at 150 ºC for 24 h under vaccum. Powedered molecular sieves MS–4Å were activated by heating at 150 ºC under vaccum for 24 h and were stored in anhydrous condition. Again, they were heated at 150 ºC under vaccum for 1 h before using for the reaction. Copper thiophenecarboxylate (CuTc) was purchsed from Frontier scientific and was used without purification. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230–400 mesh). Solvents used for column chromatography were of commercial grade and were distilled before use. Analytical thin layer chromatography was performed on 0,25 mm silica gel 60-F plates. Visualization was accomplished with UV light and a solution obtained by admixing in 470 mL of water ammonium molibdate (21 g), cerium sulphate (1 g) and concentrated sulphuric acid (31 mL), followed by heating. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-200, Bruker Avance-DPX-300, and Bruker Avance-500 spectrometers and are reported in ppm from internal tetramethylsilane (TMS) and chloroform. Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on Hewlett Packard series 1050 instrument, equipped with a diode array UV detector, using Daicel Chiralpak OJ column.

6.4.2 Preparation of chiral ligands and catalysts

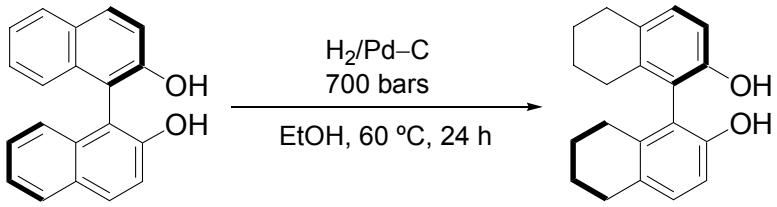
Chiral secondary amines (*S,S*)-bis-(1-phenylethyl) amine and (*S,S*)-bis-(1-naphthalen-2-yl-ethyl)-amine were purchased from Aldrich Chemical and were used without further purification. Diisopropylamine was dried by refluxing over KOH and after distillation, stored with MS–4Å (1.6 mm pellets). Chiral ligands 2,2'-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline (**L–1**), methyl Duphos (**L–15**), 2,2'-Bis-diphenylphosphanyl-[1,1']-binaphthalenyl (**L–16**) were purchased from Aldrich Chemical, and used without further purification. Chiral ligands **L–7—L–14** were synthesised according to Feringa, Chong and Alexakis (see below).

Chiral ligands **L–17**, **L–18** were synthesised according to reported procedure (see below). Chiral ligand **L–19** was generously donated by Prof. Carretero.[179] The precursor, 3,5,3',5'-Tetramethyl-biphenyl-2,2'-diol (for **L–12**) was purchased from Strem chemical Inc.

Preparation of Phosphoramidite ligands

Preparation of precursors

Preparation of (*R*)-5,6,7,8,5',6',7',8'-Octahydro-[1,1']binaphthalenyl-2,2'-diol (Partial hydrogenation of *R*–BINOL) (Precursor of **L–9**) [180]

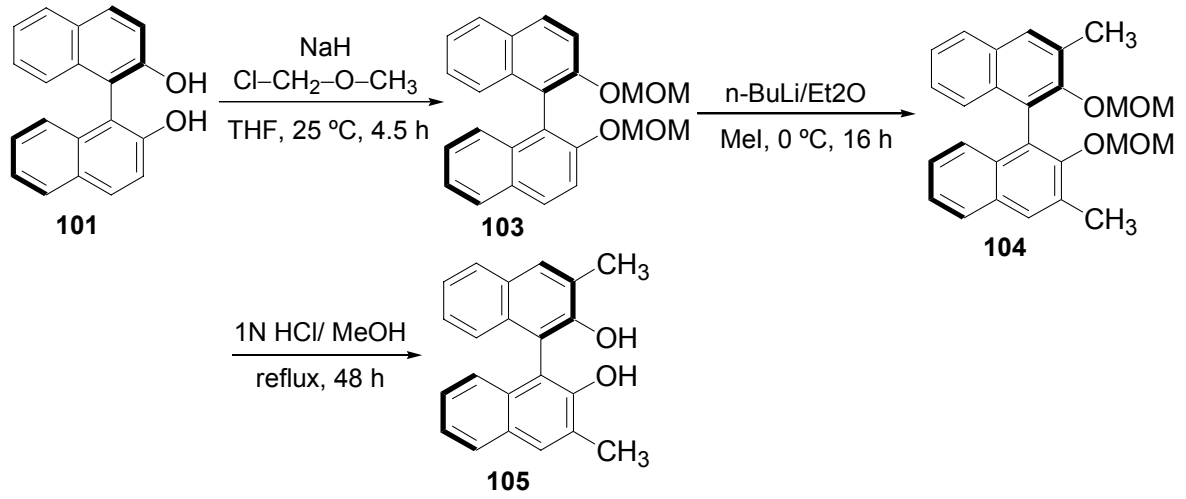


101 **102**

Under N_2 atmosphere, (*R*)-2,2'-dihydroxy-1,1'-binaphthyl **101** (2.9 g, 10 mmol) was dissolved in ethanol (500 mL) in a hydrogenator. To this solution, Pd (1.5 g, 5% w/w, 10% on carbon) was added. After the addition, the mixture was heated at 60 ºC under 700 bars pressure until TLC analysis indicated the completion of reaction (about 24 h). After completion, filteration over celite and evaporation under reduced pressure yielded pure partial hydrogenated binaphthol **102** (2.9 g, 100% yield).

[179] Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126,* 456—457.
[180] Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Börner, A. *J. Org. Chem.* **2004**, *69*, 3220—3221.

Preparation of (*R*)-3,3'-dimethyl-[1,1']binaphthalenyl-2,2'-diol (Precursor of **L–10**)[181]



A) Preparation of (*R*)-2,2'-bis-methoxymethoxy-[1,1']binaphthalenyl **103** (MOM protected BINOL)

Under N_2 atmosphere, sodium hydride (2.92 g, 73.0 mmol, 60% in mineral oil) was suspended in dry THF (150 mL) in a 500 mL round bottom flask at 0 ºC. To the mixture with stirring, was added a solution of (*R*)-2,2'-dihydroxy- 1,1'-binaphthyl **101** (9.50 g, 33.2 mmol) in THF (50 mL) by dropping funnel. After the addition, the mixture was stirred at 0 ºC for 1 h, then allowed to warm up to room temperature for 15 min. After the mixture was re-cooled to 0 ºC, chloromethyl methyl ether (5.54 mL, 73.0 mmol) was slowly added from the dropping funnel. After the addition, the reaction mixture was warmed to room temperature and stirred for 4.5 h. Sat. NH_4Cl (50 mL) was added to the flask, then the solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated. Crude product was purified by flash column chromatography using hexane:EtOAc (90:10) as eluents and crystallised from CH_2Cl_2/hexane to give title compound **103** as white crystalline solid in 95% yield (11.8 g).

[181] (a) Adapted (with some modifications), from: Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett*. **2004**, *6*, 2701—2704. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000,** *56*, 2865—2878. (c) Sigimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 649—655.

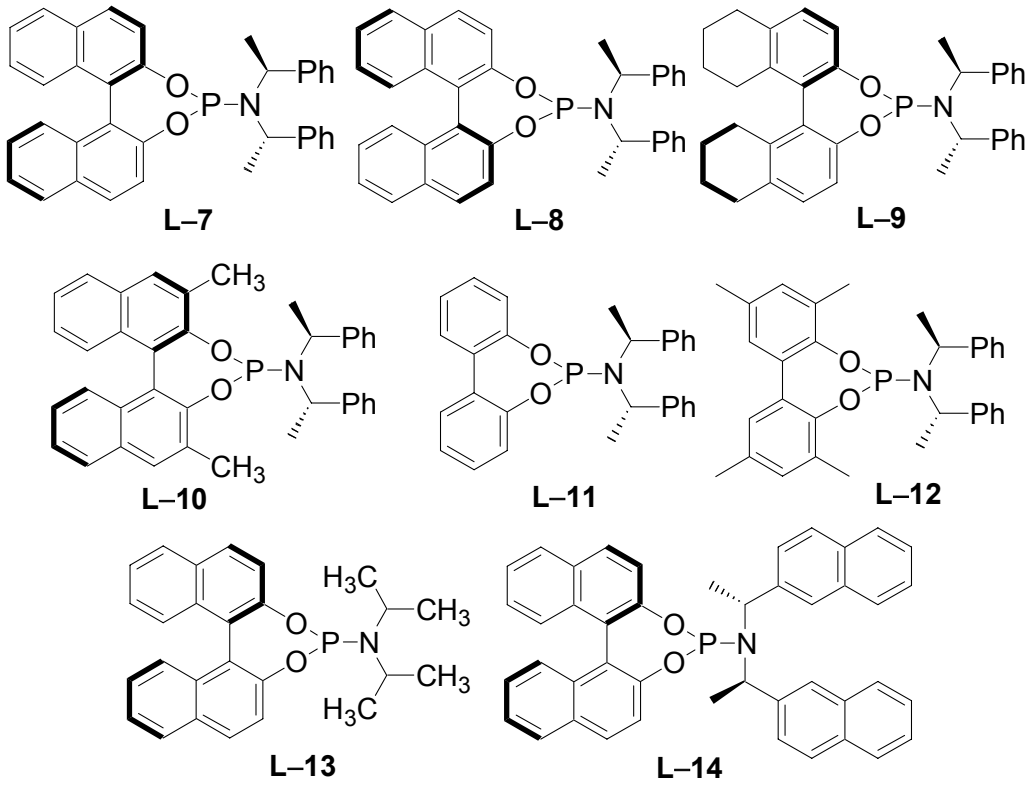
B) Preparation of (*R*)-2,2'-Bis-methoxymethoxy-3,3'-dimethyl-[1,1']binaphthalenyl **104**

A solution of (R)-MOM-protected BINOL **103** (0.72 g, 2.29 mmol) and TMEDA (1.81 mL, 12.0 mmol) in 40 mL of diethyl ether was cooled 0 ºC with ice/water. Then n-BuLi (4.9 mL, 9.8 mmol, 2.0 M in hexane) was added dropwise over a period of 25 min. The mixture was stirred at 0 ºC for 30 min and was then slowly warmed to reflux. After refluxing for 20 h the resulting orange suspension was cooled to 0 ºC and methyl iodide (1.56 mL, 25 mmol) was added dropwise over a period of 45 min resulting in a white suspension. After stirring for 16 h at room temperature the white mixture was poured into 200 mL of aqueous 1 N HCl. The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the organic layer was washed with sat. $NaHCO_3$ (2 x 100 mL), brine (2 x 100 mL), dried over $MgSO_4$. Evaporation of solvent yielded the crude product as a yellow solid (0.94 g). Subsequnt purification by flash column chromatography using hexane:EtOAc (90:10) as eluents and recrystallisation from hexane:EtOAc (10:1, 35 mL) yielded title compound **104** as colourless crystals in 63% yield (0.46 g).

C) Preperation of **105** (Deprotection of MOM group)

(*R*)-3,3'-disubstituted-2,2'-bis(methoxymethoxy)-1,1'-binaphthalenyl **104** (1.8 g, 5.0 mmol) and 1 M HCl (100 mL) in THF/MeOH (1:1 ratio, 250 mL) were stirred and heated to reflux for 15 h, then cooled to room temperature. The concentrated mass obtained by evaporation of solvent by rotary evaporation, is dissolved in CH_2Cl_2 (250 mL). Subsequently it was washed by sat. $NaHCO_3$ (2 x 100 mL), water (2 x 100 mL) and dried over $MgSO_4$. Evaporation of solvent and purification of crdue by flash column chromatography using hexane:EtOAc (90:10) as eluents yielded pure product **105** in 90% yield (1.4 g).

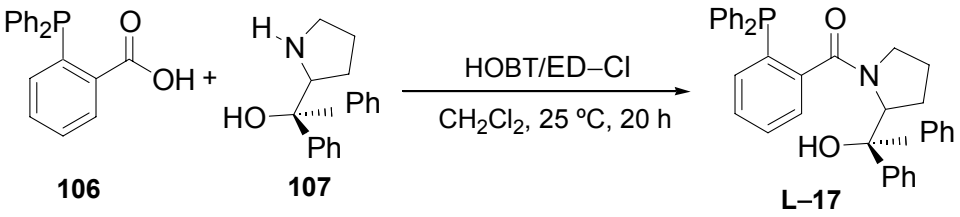
General procedure for preparation of phosphoramidite ligands (L–7 to L–14)[182]



Under N_2 atmosphere, to a cooled solution (0 ºC) of PCl_3 (270 mL, 3.0 mmol), Et_3N (860 mL, 6.0 mmol), and toluene (5 mL), was added a warm solution (60 ºC) of the corresponding binaphthol or biphenol derivative (3.0 mmol) in toluene (25 mL) over a period of 5 min. After stirring at 0 ºC for 2 h, the reaction mixture was warmed to room temperature and filtered under N_2 atmosphere. The filtrate was cooled to –40 ºC. Triethyl amine (410 mL, 3 mmol) and 3 mmol of the corresponding secondary amine were successively added to reaction flask keeping temperature –40 ºC and then it was warmed to room temperature and stirred for 16 h. Afterwards, the reaction mixture was filtered and the solids obtained were purified by flash column chromatography using hexane:CH_2Cl_2 (90:10) as eluents to give the pure phosphoramidite compound as colorless solids. Crystallisation from diethyl ether/CH_2Cl_2 mixtures gave crystalline products in quantitative yields.

[182] (a) For **L–7**—**L–10**, **L–13**, **L–14**: Adapted from: Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000,** *56*, 2865—2878. (b) For **L–11**—**L–12**: (i) d´ Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1376—1378. (ii) Polet, D.; Alexakis, A. *Org. Lett*. **2005**, *7*,1621—1624.

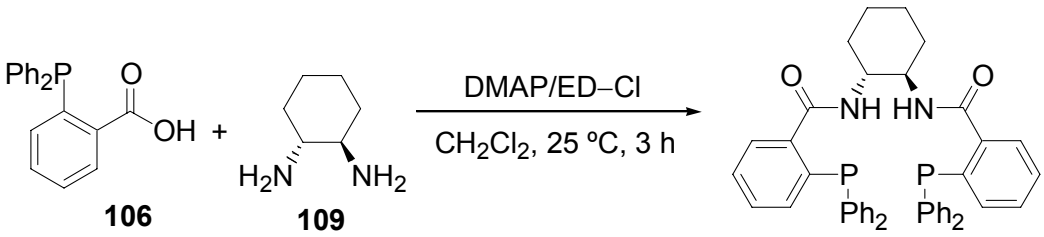
Preparation of chiral ligand L–17[183]



106 **107** **L–17**

Under N_2 atmosphere, at 0 ºC, to a solution of (S)-(-)diphenyl-pyrrolidin-2-yl-methanol **107** (253 mg, 1 mmol) in CH_2Cl_2 (10 mL), 3-diphenylphosphanyl-benzoic acid **106** (306 mg, 1 mmol), HOBT (135 mg, 1 mmol), ED-Cl (213 mg, 1 mmol) were added and allowed to stirr for 20 h at room temperature. Then reaction was diluted with CH_2Cl_2 (100 mL) and washed with 1 M HCl (2 x 30 mL), sat. $NaHCO_3$ (2 x 30 mL), brine (2 x 30 mL), water (2 x 30 mL). Drying of organic layer and evaporation of solvent afforded the crude compound which was purified by flash column chromatography to obtain pure product as yellowish white solid in 40% yield (220 mg).

Preparation of chiral ligand L–18



106 **109** **L-18**

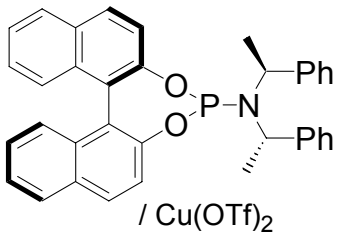
Solution of (*1R,2R*)-trans-1.2-diaminocyclohexane **109** (400 mg, 3.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of 3-diphenylphosphanyl benzoic acid **106** (2.25 g, 7.35 mmol) and DMAP (4.9 mg, 0.04 mmol) in CH_2Cl_2 (40 mL). After addition of ED-Cl (1.75 g, 8.21 mmol) the slightly cloudy yellow solution was stirred at 25 ºC for 3 h. Then reaction was diluted with diethyl ether (200 mL) and washed with 1 M HCl (2 x 50 mL), sat. $NaHCO_3$ (2 x 50 mL), brine (2 x 50 mL), water (2 x 50 mL). Drying of organic layer and evaporation of solvent afforded the crude compound which was crystallised from acetonitrile. The pure product was obtained as white solid in 55% yield (2.8 g).

[183] For **L–17**/**L–18**: (a) Lloyd–Jones, G. C.; Stephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539—2549. (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114,* 9327—9343.

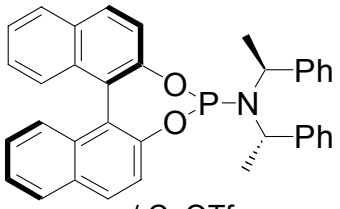
Preparation of catalysts

All the catalysts were prepared in situ, during the reaction.

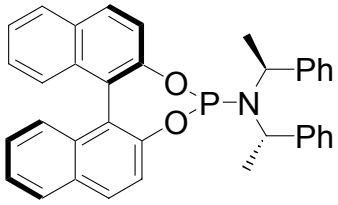
Preparation of catalysts 73–80



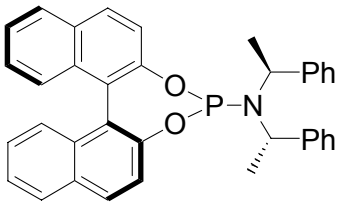
/ $Cu(OTf)_2$
73a



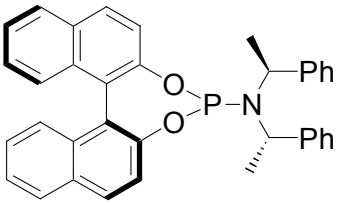
/ CuOTf
73b



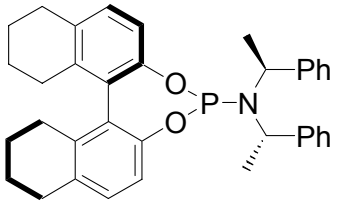
/ CuTc
73c



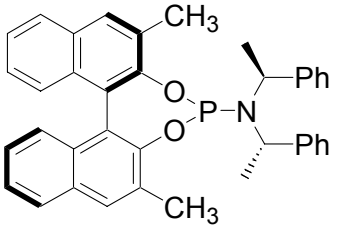
/ $Cu(OTf)_2$
74a



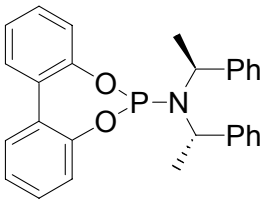
/ CuOTf
74b



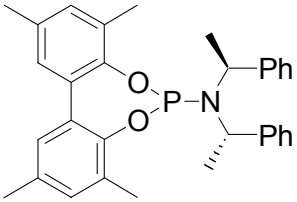
/ $Cu(OTf)_2$
75



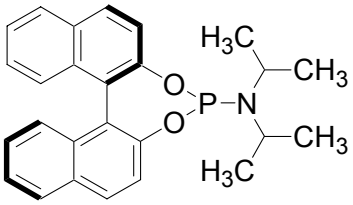
/ $Cu(OTf)_2$
76



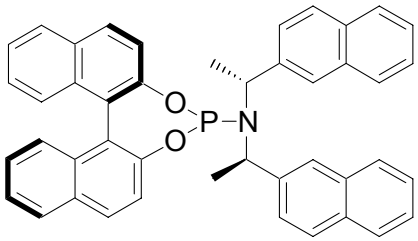
/ $Cu(OTf)_2$
77



/ $Cu(OTf)_2$
78



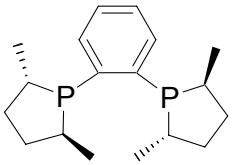
/ $Cu(OTf)_2$
79



/ $Cu(OTf)_2$
80

Under N_2 atmosphere, corresponding phosphoramidite ligand (0.05 mmol) and corresponding metal-salt (0.025 mmol) were admixed in stated solvent and stirred for 1 h at room temperature. Then this solution was subjected to stated reaction condition.

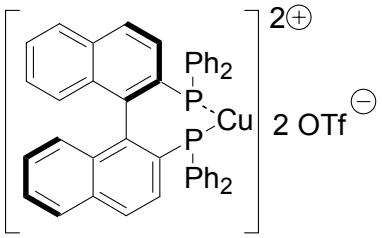
Preparation of catalyst 81



$Cu(OTf)_2$ / Me-DUPHOS
81

Under N_2 atmosphere, commercially available methyl Duphos **L–15** (30 mg, 0.05 mmol) and $Cu(OTf)_2$ (9 mg, 0.025 mmol) were admixed in stated solvent and stirred for 3 h at room temperature. Then this solution was subjected to stated reaction condition.

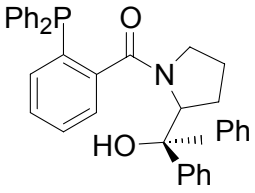
Preparation of catalyst 82



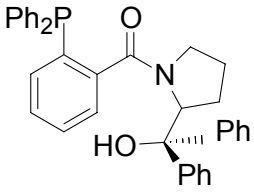
82

Under N_2 atmosphere, commercially available (*R*)-2,2'-Bis-diphenylphosphanyl-[1,1']binaphthalenyl **L–16** (22 mg, 0.037 mmol) and $Cu(OTf)_2$ (0.025 mmol) were admixed in stated solvent and stirred for 3 h at room temperature. Then this solution was subjected to stated reaction condition.

Preparation of catalyst 83a and 83b



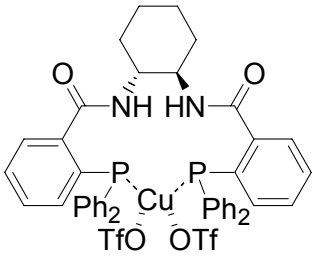
/ $Cu(OTf)_2$
83a



/ CuOTf
83b

Under N_2 atmosphere, chiral ligand **L–17** (prepared as above) (30 mg, 0.055 mmol) and Cu-salt (0.025 mmol) were admixed in stated solvent and stirred for 3 h at 25 ºC. Then this solution was subjected to stated reaction condition.

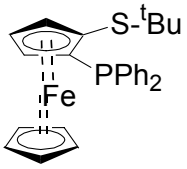
Preparation of catalyst 84



84

Under N_2 atmosphere, chiral ligand **L–18** (prepared as above) (38 mg, 0.055 mmol) and $Cu(OTf)_2$ (9 mg, 0.025 mmol) were admixed in stated solvent and stirred for 3 h at 25 ºC. Then this solution was subjected to stated reaction condition.

Preparation of catalyst 85

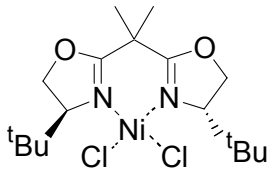


/ CuIOTf

85

Chiral ligand **L–18** (12 mg, 0.025 mmol) and CuOTf (0.025 mmol) were admixed in stated solvent and stirred for 3 h at 25 ºC. Then this solution was subjected to stated reaction condition.

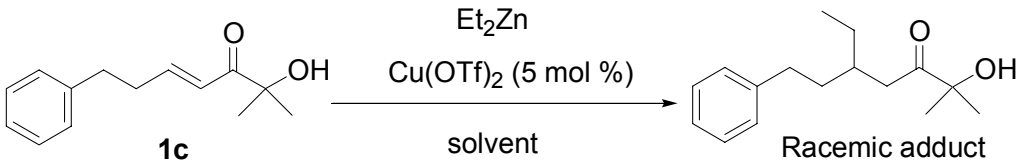
Preparation of catalyst 86



86

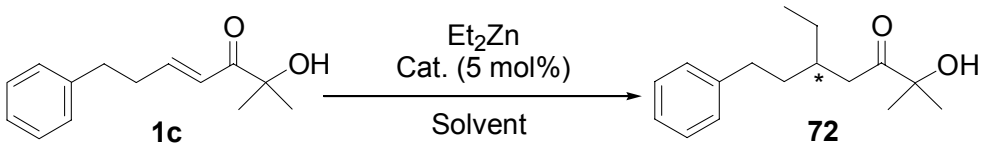
Commercially available 2,2'-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline **L–1** (22 mg, 0.05 mmol) and anhydrous $NiCl_2$ (7 mg, 0.05 mmol) were admixed in stated solvent and stirred for 12 h at reflux temperature. Then this solution was subjected to stated reaction condition.

6.4.3 Preparation of racemic adduct



The enone **1c** (0.5 mmol) was weighed into an oven or flame-dried flask and placed under nitrogen. It was dissolved in 1.0 mL dry CH_2Cl_2. Then $Cu(OTf)_2$ (0.016 g, 0.05 mmol) and 2,2´–bipyridyl (8 mg, 0.05 mmol) were successively added from weighing boat directly into the reaction flask, rinsing the weighing boat with dry CH_2Cl_2 (0.5 mL each). Then diethyl zinc (1.5 mmol, 1M in n-hexane) was added drop wise by syringe directly into the reaction flask. The resulting solution was stirred at room temperature until disappearance of starting material as monitored by NMR. The reaction was quenched with 0.1 M HCl soln. (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 layers were combined, washed with sat. $NaHCO_3$ soln. (1 x 1o mL), and water (1 x 10 mL), dried over $MgSO_4$ and concentrated to give crude product. Subsequent purification by flash column chromatography using gradient mixture of hexane:ethyl acetate (95:5) as eluent yielded pure product.

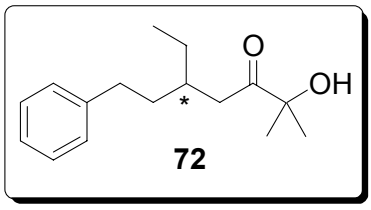
6.4.4 General procedure for the 1,4–conjugate addition of diethyl zinc to α'–hydroxy enone 1c promoted by catalysts 72–86



To the catalyst solution prepared as described before, diethyl zinc soln (1 M in n-hexane) (1.5 mL, 1.5 mmol) was added to the reaction flask and the solution was stirred at room temperature for another 1 h. The resulting slightly cloudy black solution was cooled to specified temperature. A solution of α'–hydroxy enone **1c** (109 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added drop wise. The reaction was stirred at the same temperature until NMR analysis indicated the reaction completion. After completion, the reaction was quenched with 0.1 M HCl (10 mL) and extracted with dichloromethane (3 x 15 mL). Organic layer was washed with sat. $NaHCO_3$ (2 x 10 mL) and water (2 x 10 mL). Drying of organic layer over $MgSO_4$ and concentration afforded the unpurified product. Subsequent purification by flash column chromatography using gradient mixture of n-hexane:ethyl acetate (95:5) as eluents yielded pure product.

6.4.5 Characterisation data

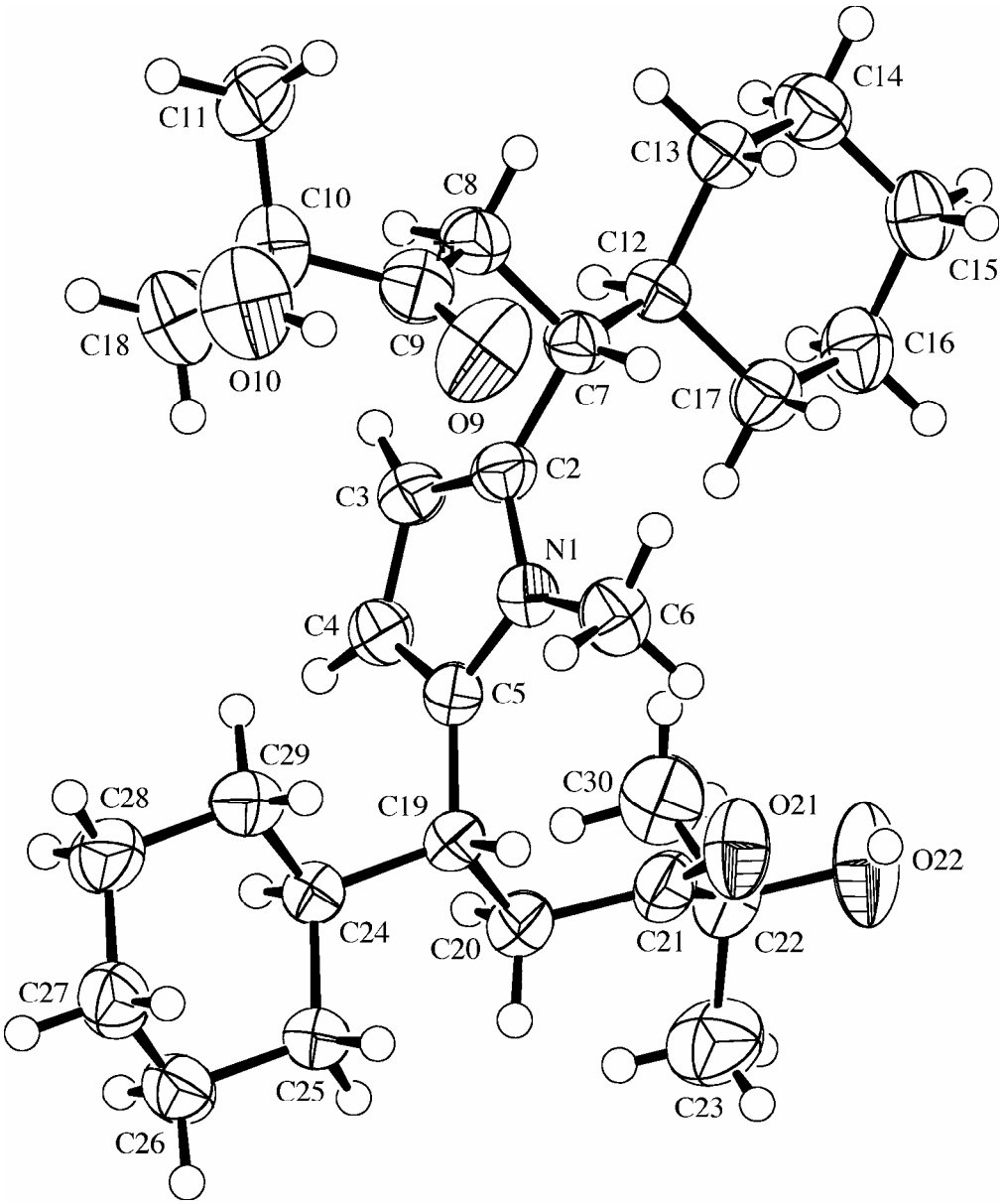
5-Ethyl-2-hydroxy-2-methyl-7-phenyl-heptan-3-one 72

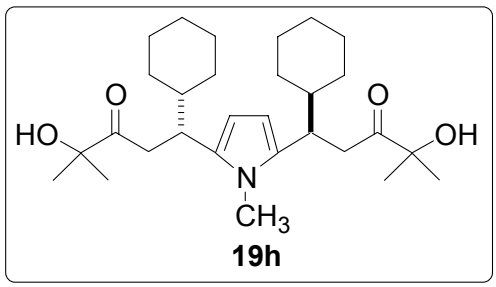


72

The title compound was prepared according to the general procedure starting from **1c** (109 mg, 0.5 mmol) and catalyst **73a** at 25 ºC. Yield 120 mg (96%); Yellowish red oil; $[\alpha]_D^{25}$ = +1.5º (*c*=1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 3482, 2962, 2931, 1706, 1457, 699; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 1H, Ph, *J*= 7.5 Hz), 7.31 (dd, 2H, Ph, *J*= 7.5 Hz), 7.21 (dd, 2H, Ph, *J*= 8.5 Hz), 3.77 (bs, 1H, OH), 2.63 (m, 2H, CH_2), 2.56 (dd, 2H, CH_2-CO, *J*= 6.0 Hz), 2.10 (m, 2H, CH_2), 1.64 (m, 3H, CH_2-CH), 1.41 (s, 6H, $(CH_3)_2$), 0.93 (t, 3H, CH_3, *J*= 12.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 142.3, 128.3, 128.2, 125.7, 76.2, 39.9, 35.2, 34.5, 33.2, 26.5, 26.1, 10.7; Chiral HPLC was performed on HP series 1050. (Chiralpak OJ column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm), Rt_{major} : 34.07 min., Rt_{minor}: 21.51 min., 77.0% ee.

Apendix: I





19h

Table 1: Crystallographic Data

Crystallised from	*n*-hexane / EtOAc
Empirical formula	$C_{29}H_{47}NO_4$
Formula weight [g mol^{-1}]	473.69
Crystal colour, habit	yellow, prism

Crystal dimensions [mm]	0.25 x 0.25 x 0.25
Temperature [K]	160 (1)
Crystal system	monoclinic
Space group	*C*2 (#5)
Z	4
Reflections for cell determination	2629
2 θ range for cell determination [°]	4 – 50
Unit cell parameters *a* [Å]	15.856(1)
b [Å]	9.4706(8)
c [Å]	20.292(1)
α [°]	90
β [°]	112.441(4)
γ [°]	90
V [Å^3]	2816.4(4)
F (000)	1040
D_X [g cm^{-3}]	1.117
μ (Mo *K*α) [mm^{-1}]	0.0727
Scan type	ω
2θ(max) [°]	50
Total reflections measured	19564
Symmetry independent reflections	2636
R_{int}	0.096
Reflections with $I > 2\sigma(I)$	1768
Reflections used in refinement	2632
Parameters refined; restraints	315; 1
Final *R (F)* [$I>2\ \sigma(I)$ reflections]	0.0518
wR (F^2) (all data)	0.1373
Weights:	$w = [\sigma^2(F_o^2) + (0.0698P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.040
Secondary extinction coefficient	0.007(1)
Final Δ_{max}/σ	0.001
Δ (max; min) [e Å^{-3}]	0.19; -0.17
$\sigma(d_{(C-C)})$ [Å]	0.005 – 0.007

Table 2: Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) with standard uncertainties in parentheses.

- U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

ATOM	x	y	z	U_{eq}*
O(9)	0.9098(2)	0.1939(4)	0.4319(2)	0.085(1)
O(10)	0.8323(2)	0.0632(4)	0.5039(2)	0.088(1)
O(21)	0.8053(2)	0.2691(4)	0.0994(2)	0.0678(9)
O(22)	0.7857(2)	0.4880(4)	0.0220(2)	0.092(1)
N(1)	0.7838(2)	0.2779(4)	0.2560(2)	0.0424(8)
C(2)	0.7774(3)	0.3882(4)	0.2990(2)	0.043(1)
C(3)	0.6881(2)	0.4272(5)	0.2759(2)	0.046(1)
C(4)	0.6390(3)	0.3426(5)	0.2170(2)	0.047(1)
C(5)	0.6979(2)	0.2521(5)	0.2047(2)	0.043(1)
C(6)	0.8664(3)	0.1994(5)	0.2644(2)	0.053(1)
C(7)	0.8594(3)	0.4530(4)	0.3577(2)	0.045(1)
C(8)	0.8525(3)	0.4258(5)	0.4300(2)	0.054(1)
C(9)	0.8606(3)	0.2720(6)	0.4487(2)	0.056(1)
C(10)	0.8097(3)	0.2113(5)	0.4924(3)	0.062(1)
C(11)	0.8370(3)	0.2870(7)	0.5627(2)	0.089(2)
C(12)	0.8679(3)	0.6105(4)	0.3409(2)	0.046(1)
C(13)	0.9432(3)	0.6867(5)	0.4010(2)	0.057(1)
C(14)	0.9559(3)	0.8379(5)	0.3809(2)	0.064(1)
C(15)	0.9752(3)	0.8437(5)	0.3133(2)	0.060(1)
C(16)	0.8994(3)	0.7732(5)	0.2526(2)	0.063(1)
C(17)	0.8849(3)	0.6221(5)	0.2719(2)	0.055(1)
C(18)	0.7079(3)	0.2200(6)	0.4494(3)	0.072(2)
C(19)	0.6790(2)	0.1388(5)	0.1484(2)	0.042(1)
C(20)	0.6507(3)	0.2110(5)	0.0751(2)	0.049(1)
C(21)	0.7252(3)	0.3005(5)	0.0684(2)	0.050(1)
C(22)	0.7030(3)	0.4304(5)	0.0217(2)	0.055(1)
C(23)	0.6428(4)	0.3918(7)	-0.0549(3)	0.087(2)
C(24)	0.6079(2)	0.0315(4)	0.1511(2)	0.043(1)
C(25)	0.5939(3)	-0.0898(5)	0.0976(2)	0.051(1)
C(26)	0.5261(3)	-0.1975(5)	0.1013(2)	0.058(1)
C(27)	0.5531(3)	-0.2587(5)	0.1753(2)	0.060(1)
C(28)	0.5652(3)	-0.1413(5)	0.2290(2)	0.065(1)

C(29)	0.6339(3)	-0.0302(5)	0.2255(2)	0.059(1)
C(30)	0.6574(3)	0.5405(6)	0.0507(3)	0.075(2)

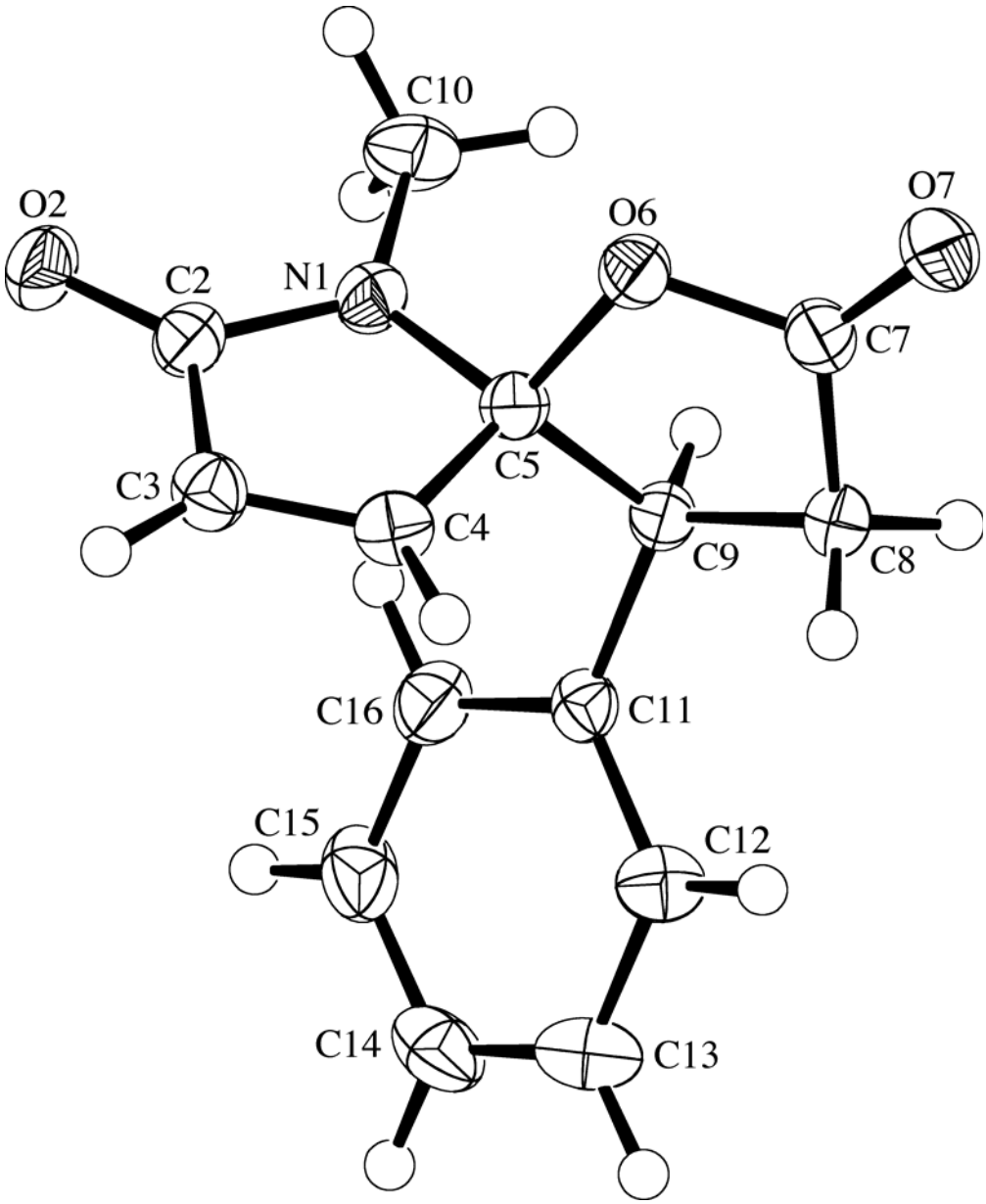
Table 3: Bond lengths (Å) with standard uncertainties in parentheses.

O(9) -C(9)	1.214(5)	C(12) -C(13)	1.523(5)
O(10) -C(10)	1.444(6)	C(12) -C(17)	1.529(5)
O(21) -C(21)	1.220(4)	C(13) -C(14)	1.523(7)
O(22) -C(22)	1.416(5)	C(14) -C(15)	1.517(6)
N(1) -C(5)	1.383(4)	C(15) -C(16)	1.509(6)
N(1) -C(2)	1.391(5)	C(16) -C(17)	1.525(7)
N(1) -C(6)	1.458(5)	C(19) -C(24)	1.535(5)
C(2) -C(3)	1.362(5)	C(19) -C(20)	1.540(5)
C(2) -C(7)	1.518(5)	C(20) -C(21)	1.500(6)
C(3) -C(4)	1.402(5)	C(21) -C(22)	1.511(6)
C(4) -C(5)	1.360(5)	C(22) -C(30)	1.511(6)
C(5) -C(19)	1.511(6)	C(22) -C(23)	1.526(7)
C(7) -C(8)	1.534(5)	C(24) -C(29)	1.522(6)
C(7) -C(12)	1.547(6)	C(24) -C(25)	1.537(6)
C(8) -C(9)	1.498(7)	C(25) -C(26)	1.505(5)
C(9) -C(10)	1.522(6)	C(26) -C(27)	1.511(6)
C(10) -C(11)	1.505(7)	C(27) -C(28)	1.517(6)
C(10) -C(18)	1.517(6)	C(28) -C(29)	1.535(6)

Table 4: Bond angles (°) with standard uncertainties in parentheses.

C(5) -N(1) -C(2)	108.6(3)	C(14) -C(13) -C(12)	112.0(4)
C(5) -N(1) -C(6)	125.5(3)	C(15) -C(14) -C(13)	111.7(4)
C(2) -N(1) -C(6)	125.9(3)	C(16) -C(15) -C(14)	110.4(3)
C(3) -C(2) -N(1)	107.6(3)	C(15) -C(16) -C(17)	110.9(4)
C(3) -C(2) -C(7)	128.9(4)	C(16) -C(17) -C(12)	113.5(4)
N(1) -C(2) -C(7)	123.4(3)	C(5) -C(19) -C(24)	112.3(3)
C(2) -C(3) -C(4)	107.8(4)	C(5) -C(19) -C(20)	108.4(3)
C(5) -C(4) -C(3)	108.6(3)	C(24) -C(19) -C(20)	112.4(3)
C(4) -C(5) -N(1)	107.4(3)	C(21) -C(20) -C(19)	112.9(3)
C(4) -C(5) -C(19)	129.3(3)	O(21) -C(21) -C(20)	121.0(4)
N(1) -C(5) -C(19)	123.2(3)	O(21) -C(21) -C(22)	118.0(4)

C(2) -C(7) -C(8)	109.2(3)	C(20) -C(21) -C(22)	121.0(4)
C(2) -C(7) -C(12)	109.7(3)	O(22) -C(22) -C(30)	108.2(4)
C(8) -C(7) -C(12)	114.6(3)	O(22) -C(22) -C(21)	108.5(3)
C(9) -C(8) -C(7)	112.0(4)	C(30) -C(22) -C(21)	110.4(3)
O(9) -C(9) -C(8)	121.6(4)	O(22) -C(22) -C(23)	108.4(4)
O(9) -C(9) -C(10)	118.3(5)	C(30) -C(22) -C(23)	110.8(4)
C(8) -C(9) -C(10)	120.1(4)	C(21) -C(22) -C(23)	110.4(4)
O(10) -C(10) -C(11)	110.3(4)	C(29) -C(24) -C(19)	111.4(3)
O(10) -C(10) -C(18)	106.9(4)	C(29) -C(24) -C(25)	109.0(4)
C(11) -C(10) -C(18)	112.1(4)	C(19) -C(24) -C(25)	112.3(3)
O(10) -C(10) -C(9)	107.9(4)	C(26) -C(25) -C(24)	112.6(3)
C(11) -C(10) -C(9)	110.4(4)	C(25) -C(26) -C(27)	111.9(4)
C(18) -C(10) -C(9)	109.3(4)	C(26) -C(27) -C(28)	110.0(4)
C(13) -C(12) -C(17)	109.9(3)	C(27) -C(28) -C(29)	111.5(3)
C(13) -C(12) -C(7)	112.8(3)	C(24) -C(29) -C(28)	112.4(3)
C(17) -C(12) -C(7)	109.4(3)		



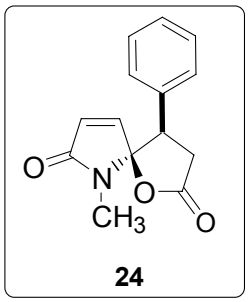


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Table 1: Crystallographic Data

Crystallised from	EtOAc
Empirical formula	$C_{14}H_{13}NO_3$
Formula weight [g mol^{-1}]	243.26
Crystal colour, habit	colourless, prism

Crystal dimensions [mm]	0.20 x 0.22 x 0.30
Temperature [K]	160 (1)
Crystal system	monoclinic
Space group	$P2_1/c$ (#14)
Z	4
Reflections for cell determination	3760
2θ range for cell determination [°]	4 – 60
Unit cell parameters a [Å]	13.2811(3)
b [Å]	7.0574(2)
c [Å]	13.1264(3)
α [°]	90
β [°]	102.890(2)
γ [°]	90
V [Å^3]	1199.33(5)
F(000)	512
D_X [g cm^{-3}]	1.347
μ(Mo $K\alpha$) [mm^{-1}]	0.0953
Scan type	ø and ω
2θ(max) [°]	60
Total reflections measured	30628
Symmetry independent reflections	3505
R_{int}	0.050
Reflections with $I > 2\sigma(I)$	2607
Reflections used in refinement	3503
Parameters refined	165
Final $R(F)$ [$I>2\sigma(I)$ reflections]	0.0509
$wR(F^2)$ (all data)	0.1415
Weights:	$w = [\sigma^2(F_o^2) + (0.0665P)^2 + 0.3492P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.045
Secondary extinction coefficient	0.015(4)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.34; -0.24
$\sigma(d_{(C-C)})$ [Å]	0.002

Table 2: Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) with standard uncertainties in parentheses.

* U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

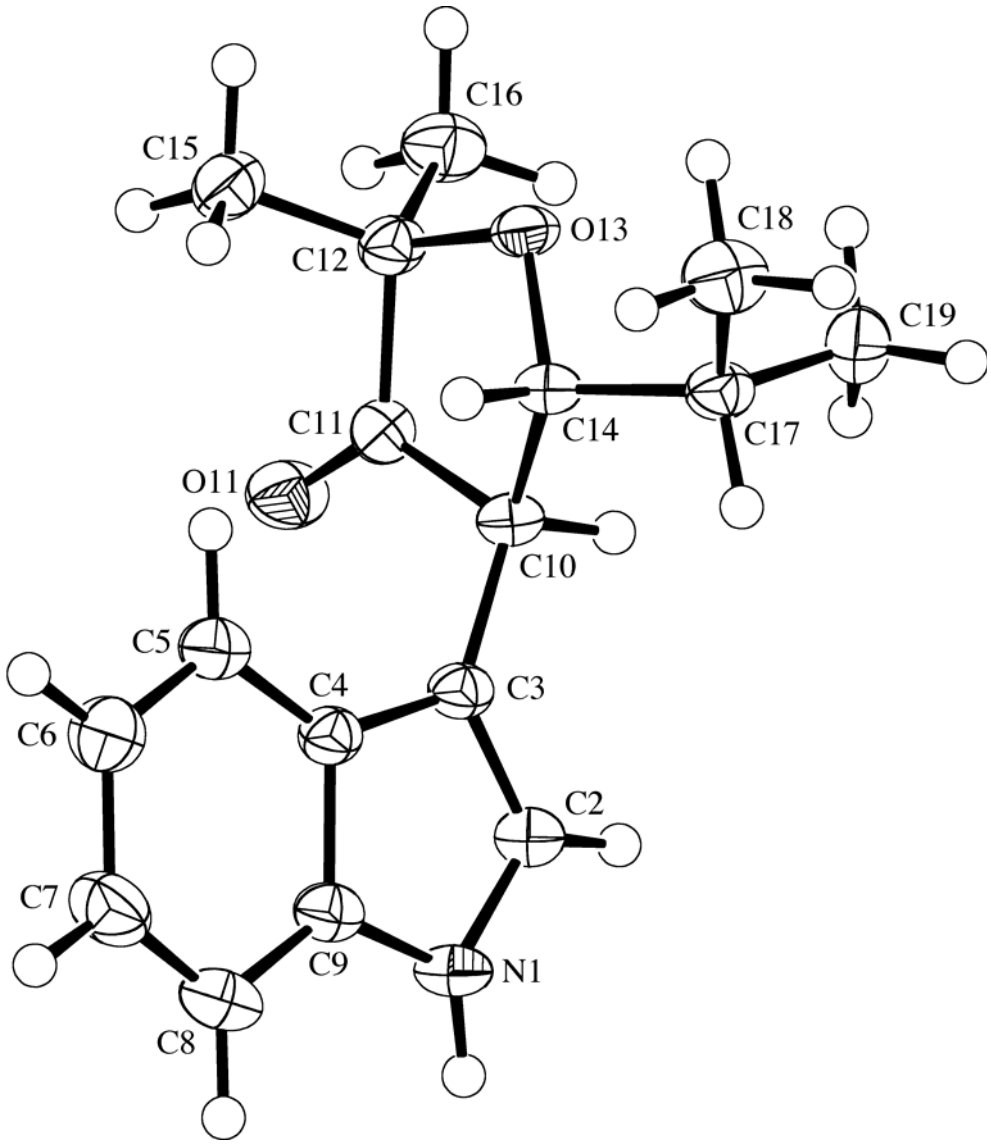
ATOM	x	y	z	U_{eq}*
O(2)	0.76814(8)	0.3609(2)	0.52802(7)	0.0350(3)
O(6)	0.56287(7)	0.1665(1)	0.23867(7)	0.0304(3)
O(7)	0.44863(8)	0.0637(2)	0.09917(8)	0.0373(3)
N(1)	0.67642(9)	0.1598(2)	0.40450(8)	0.0272(3)
C(2)	0.7462(1)	0.2993(2)	0.4391(1)	0.0283(3)
C(3)	0.7900(1)	0.3538(2)	0.3482(1)	0.0299(3)
C(4)	0.7450(1)	0.2518(2)	0.2670(1)	0.0270(3)
C(5)	0.6675(1)	0.1177(2)	0.2965(1)	0.0245(3)
C(7)	0.5309(1)	0.0431(2)	0.1582(1)	0.0281(3)
C(8)	0.6137(1)	-0.1013(2)	0.1579(1)	0.0277(3)
C(9)	0.6790(1)	-0.0935(2)	0.2693(1)	0.0237(3)
C(10)	0.6154(1)	0.0718(2)	0.4700(1)	0.0373(4)
C(11)	0.7903(1)	-0.1580(2)	0.2892(1)	0.0245(3)
C(12)	0.8367(1)	-0.2156(2)	0.2094(1)	0.0328(3)
C(13)	0.9384(1)	-0.2801(2)	0.2319(1)	0.0408(4)
C(14)	0.9955(1)	-0.2844(2)	0.3334(1)	0.0403(4)
C(15)	0.9511(1)	-0.2247(2)	0.4128(1)	0.0408(4)
C(16)	0.8491(1)	-0.1635(2)	0.3915(1)	0.0350(3)

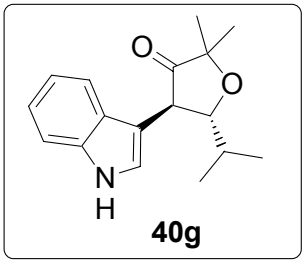
Table 3: Bond lengths (Å) with standard uncertainties in parentheses.

O(2) -C(2)	1.218(2)	C(5) -C(9)	1.548(2)
O(6) -C(7)	1.362(2)	C(7) -C(8)	1.501(2)
O(6) -C(5)	1.468(2)	C(8) -C(9)	1.526(2)
O(7) -C(7)	1.199(2)	C(9) -C(11)	1.513(2)
N(1) -C(2)	1.359(2)	C(11) -C(12)	1.390(2)
N(1) -C(5)	1.427(2)	C(11) -C(16)	1.395(2)
N(1) -C(10)	1.447(2)	C(12) -C(13)	1.392(2)
C(2) -C(3)	1.491(2)	C(13) -C(14)	1.378(2)
C(3) -C(4)	1.315(2)	C(14) -C(15)	1.374(2)
C(4) -C(5)	1.510(2)	C(15) -C(16)	1.390(2)

Table 4: Bond angles (°) with standard uncertainties in parentheses.

C(7) -O(6) -C(5)	110.3(1)	O(7) -C(7) -O(6)	120.4(1)
C(2) -N(1) -C(5)	112.5(1)	O(7) -C(7) -C(8)	130.1(1)
C(2) -N(1) -C(10)	122.9(1)	O(6) -C(7) -C(8)	109.5(1)
C(5) -N(1) -C(10)	124.6(1)	C(7) -C(8) -C(9)	103.5(1)
O(2) -C(2) -N(1)	125.4(1)	C(11) -C(9) -C(8)	118.6(1)
O(2) -C(2) -C(3)	128.5(1)	C(11) -C(9) -C(5)	113.1(1)
N(1) -C(2) -C(3)	106.2(1)	C(8) -C(9) -C(5)	101.0(1)
C(4) -C(3) -C(2)	108.6(1)	C(12) -C(11) -C(16)	118.1(1)
C(3) -C(4) -C(5)	110.4(1)	C(12) -C(11) -C(9)	122.6(1)
N(1) -C(5) -O(6)	108.9(1)	C(16) -C(11) -C(9)	119.4(1)
N(1) -C(5) -C(4)	102.4(1)	C(11) -C(12) -C(13)	120.5(1)
O(6) -C(5) -C(4)	109.9(1)	C(14) -C(13) -C(12)	120.7(2)
N(1) -C(5) -C(9)	116.0(1)	C(15) -C(14) -C(13)	119.3(1)
O(6) -C(5) -C(9)	103.7(1)	C(14) -C(15) -C(16)	120.4(2)
C(4) -C(5) -C(9)	115.9(1)	C(15) -C(16) -C(11)	120.9(1)





40g

Table 1: Crystallographic Data

Crystallised from	hexane / EtOAc
Empirical formula	$C_{17}H_{21}NO_2$
Formula weight [g mol^{-1}]	271.36
Crystal colour, habit	colourless, prism
Crystal dimensions [mm]	0.22 x 0.25 x 0.25
Temperature [K]	160 (1)

Crystal system	orthorhombic
Space group	$P2_12_12_1$ (#19)
Z	4
Reflections for cell determination	2029
2θ range for cell determination [°]	4 – 55
Unit cell parameters a [Å]	7.6114(2)
b [Å]	8.6909(2)
c [Å]	22.8781(6)
α [°]	90
β [°]	90
γ [°]	90
V [Å^3]	1513.38(7)
F(000)	584
D_X [g cm^{-3}]	1.191
μ(Mo $K\alpha$) [mm^{-1}]	0.0774
Scan type	ø and ω
2θ(max) [°]	55
Total reflections measured	20593
Symmetry independent reflections	2006
R_{int}	0.068
Reflections with $I > 2\sigma(I)$	1622
Reflections used in refinement	2005
Parameters refined	190
Final $R(F)$ [$I>2\sigma(I)$ reflections]	0.0405
$wR(F^2)$ (all data)	0.0970
Weights:	$w = [\sigma^2(F_o^2) + (0.0533P)^2 + 0.0182P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.048
Secondary extinction coefficient	0.018(3)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.17; -0.18
$\sigma(d_{(C-C)})$ [Å]	0.002 – 0.003

Table 2: Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) with standard uncertainties in parentheses.

* U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

ATOM	x	y	z	U_{eq}*
O(11)	0.3005(2)	0.2720(2)	0.50158(7)	0.0403(4)
O(13)	0.4299(2)	-0.0073(1)	0.39984(5)	0.0283(4)
N(1)	0.3938(2)	0.6734(2)	0.37180(8)	0.0322(5)
C(2)	0.4871(3)	0.5500(2)	0.39196(8)	0.0287(5)
C(3)	0.3914(3)	0.4180(2)	0.38801(8)	0.0255(5)
C(4)	0.2244(3)	0.4614(2)	0.36368(8)	0.0266(5)
C(5)	0.0699(3)	0.3841(3)	0.34804(9)	0.0349(5)
C(6)	-0.0674(3)	0.4643(3)	0.3239(1)	0.0433(6)
C(7)	-0.0567(3)	0.6235(3)	0.3143(1)	0.0439(6)
C(8)	0.0918(3)	0.7040(3)	0.32924(9)	0.0383(6)
C(9)	0.2303(3)	0.6226(2)	0.35411(8)	0.0289(5)
C(10)	0.4509(3)	0.2616(2)	0.40754(7)	0.0253(5)
C(11)	0.3570(3)	0.1992(2)	0.46071(8)	0.0278(5)
C(12)	0.3420(3)	0.0254(2)	0.45470(8)	0.0284(5)
C(14)	0.4326(3)	0.1292(2)	0.36379(8)	0.0245(4)
C(15)	0.1500(3)	-0.0211(3)	0.45133(9)	0.0360(5)
C(16)	0.4414(3)	-0.0576(3)	0.50291(9)	0.0398(6)
C(17)	0.5750(3)	0.1111(2)	0.31801(8)	0.0286(5)
C(18)	0.5193(3)	-0.0043(3)	0.27132(9)	0.0414(6)
C(19)	0.7522(3)	0.0667(3)	0.3437(1)	0.0404(6)

Table 3: Bond lengths (Å) with standard uncertainties in parentheses.

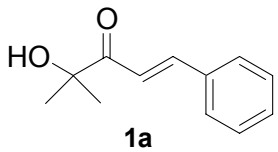
O(11) -C(11)	1.208(2)	C(6) -C(7)	1.403(3)
O(13) -C(14)	1.444(2)	C(7) -C(8)	1.373(3)
O(13) -C(12)	1.450(2)	C(8) -C(9)	1.391(3)
N(1) -C(2)	1.367(3)	C(10) -C(11)	1.511(3)
N(1) -C(9)	1.381(3)	C(10) -C(14)	1.532(2)
C(2) -C(3)	1.362(3)	C(11) -C(12)	1.522(3)
C(3) -C(4)	1.438(3)	C(12) -C(15)	1.518(3)
C(3) -C(10)	1.501(3)	C(12) -C(16)	1.520(3)

C(4) -C(5)	1.401(3)	C(14) -C(17)	1.516(3)
C(4) -C(9)	1.419(3)	C(17) -C(19)	1.521(3)
C(5) -C(6)	1.372(3)	C(17) -C(18)	1.526(3)

Table 4: Bond angles (°) with standard uncertainties in parentheses.

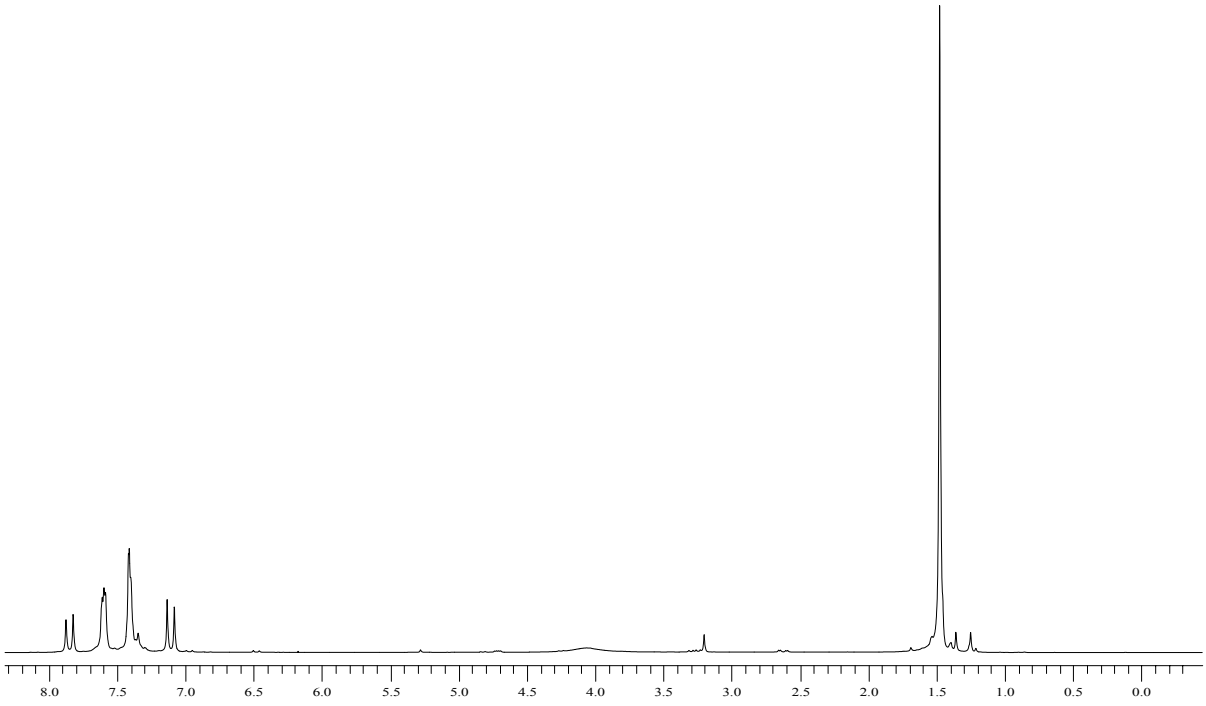
C(14) -O(13) -C(12)	109.9(1)	C(3) -C(10) -C(14)	117.3(2)
C(2) -N(1) -C(9)	108.5(2)	C(11) -C(10) -C(14)	102.3(2)
C(3) -C(2) -N(1)	111.1(2)	O(11) -C(11) -C(10)	127.1(2)
C(2) -C(3) -C(4)	106.1(2)	O(11) -C(11) -C(12)	124.3(2)
C(2) -C(3) -C(10)	125.6(2)	C(10) -C(11) -C(12)	108.6(2)
C(4) -C(3) -C(10)	128.3(2)	O(13) -C(12) -C(15)	110.4(2)
C(5) -C(4) -C(9)	117.4(2)	O(13) -C(12) -C(16)	107.8(2)
C(5) -C(4) -C(3)	135.7(2)	C(15) -C(12) -C(16)	113.0(2)
C(9) -C(4) -C(3)	106.9(2)	O(13) -C(12) -C(11)	103.8(2)
C(6) -C(5) -C(4)	119.9(2)	C(15) -C(12) -C(11)	109.9(2)
C(5) -C(6) -C(7)	121.3(2)	C(16) -C(12) -C(11)	111.6(2)
C(8) -C(7) -C(6)	120.8(2)	O(13) -C(14) -C(17)	108.6(2)
C(7) -C(8) -C(9)	117.8(2)	O(13) -C(14) -C(10)	104.2(1)
N(1) -C(9) -C(8)	129.8(2)	C(17) -C(14) -C(10)	117.7(2)
N(1) -C(9) -C(4)	107.4(2)	C(14) -C(17) -C(19)	113.2(2)
C(8) -C(9) -C(4)	122.8(2)	C(14) -C(17) -C(18)	110.7(2)
C(3) -C(10) -C(11)	115.0(2)	C(19) -C(17) -C(18)	110.5(2)

Apendix: II

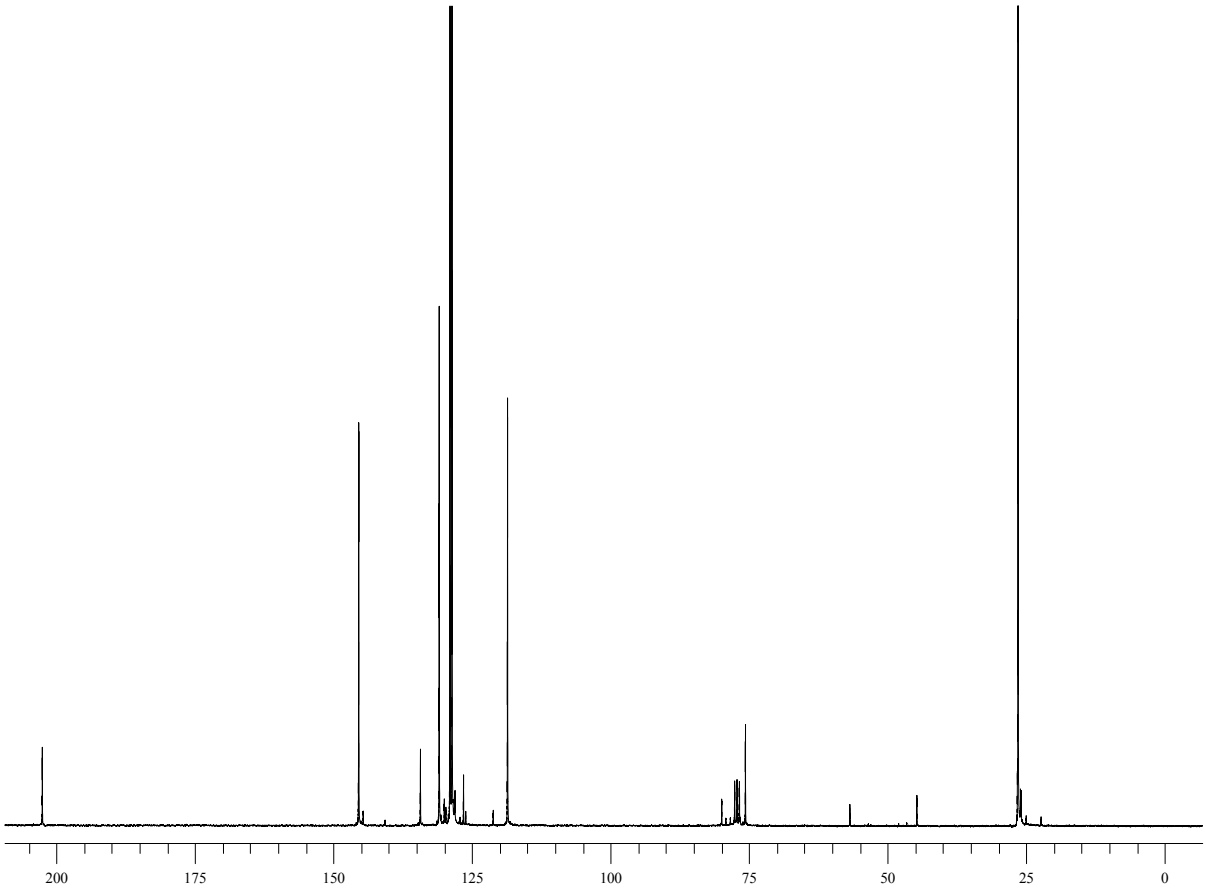


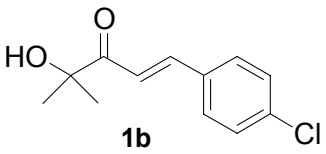
1a

^{1}H NMR



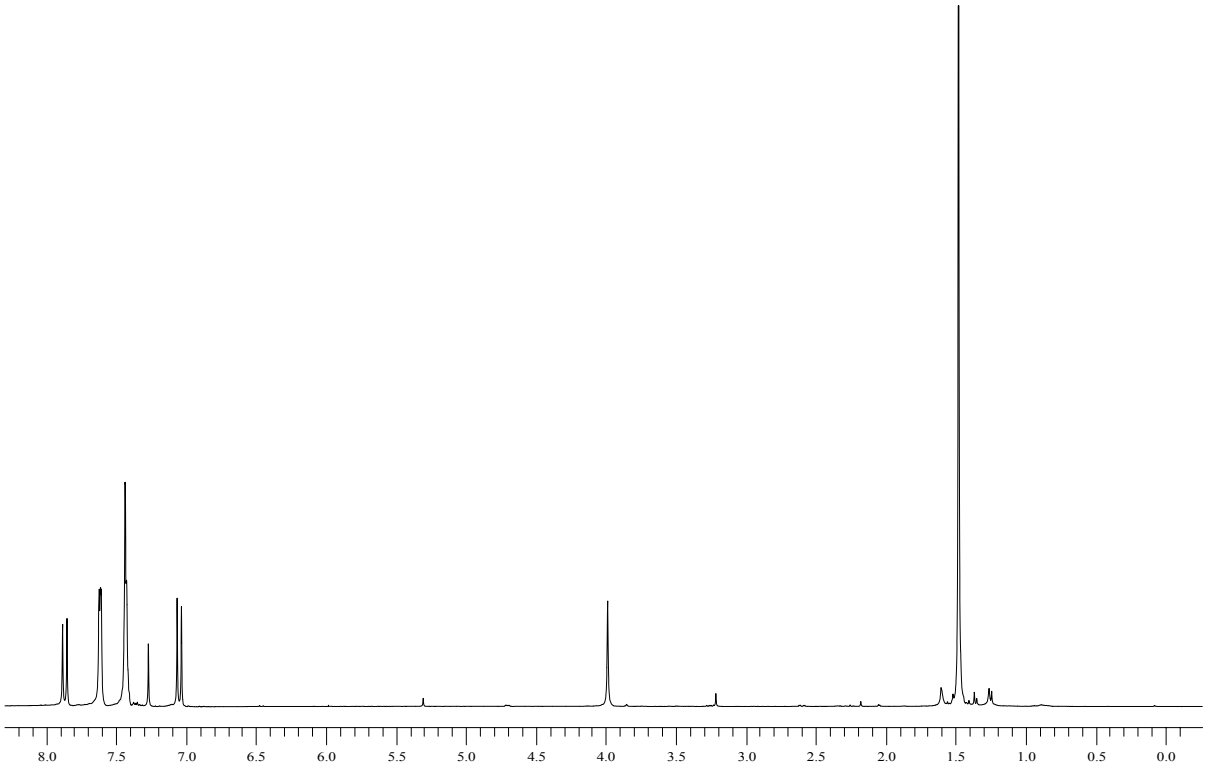
^{13}C NMR



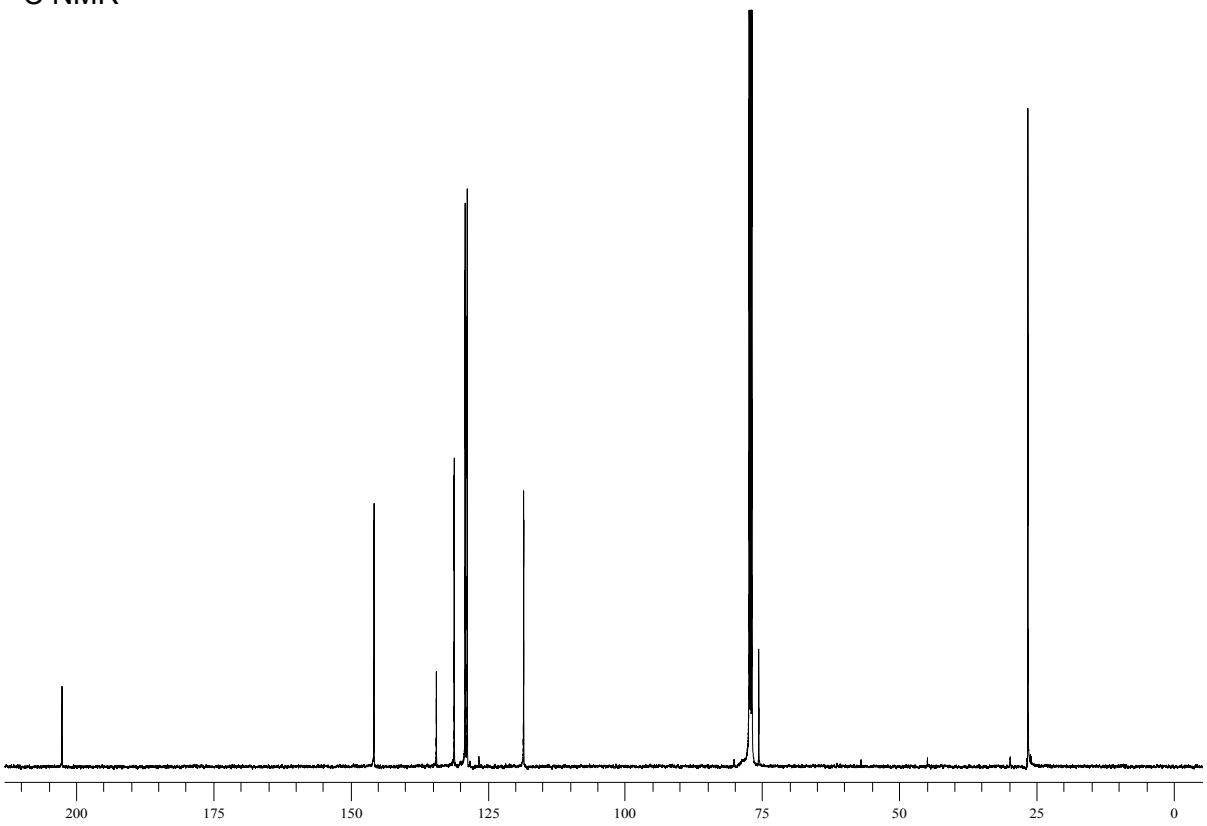


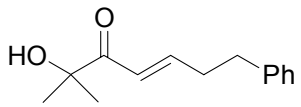
1b

^{1}H NMR



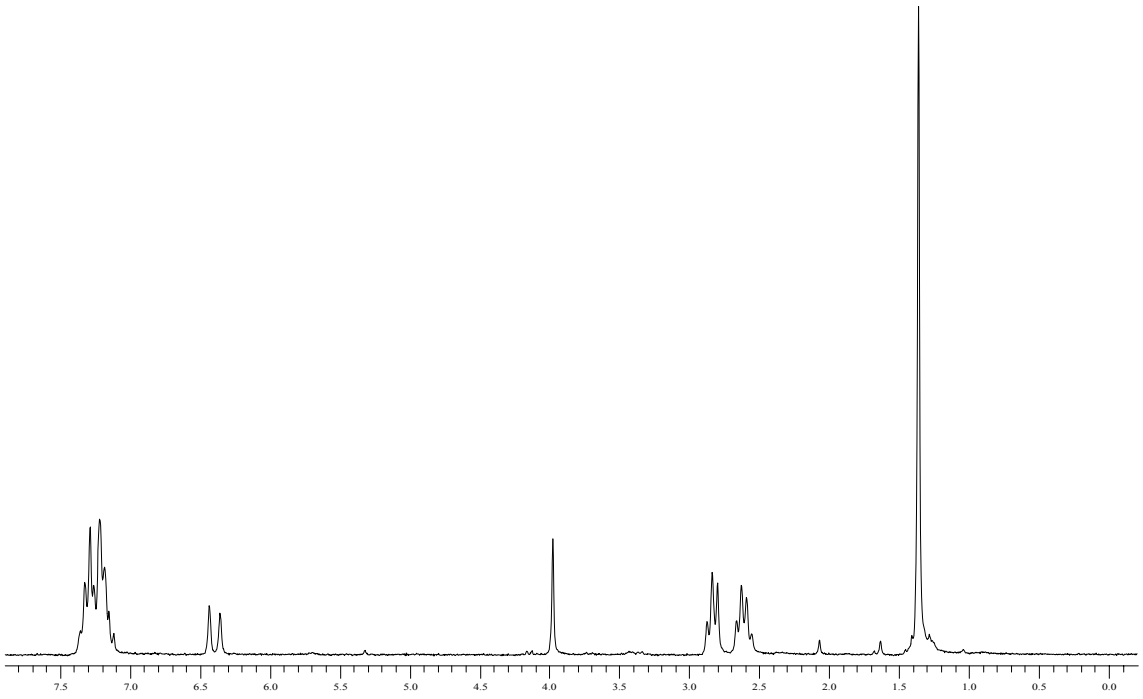
^{13}C NMR



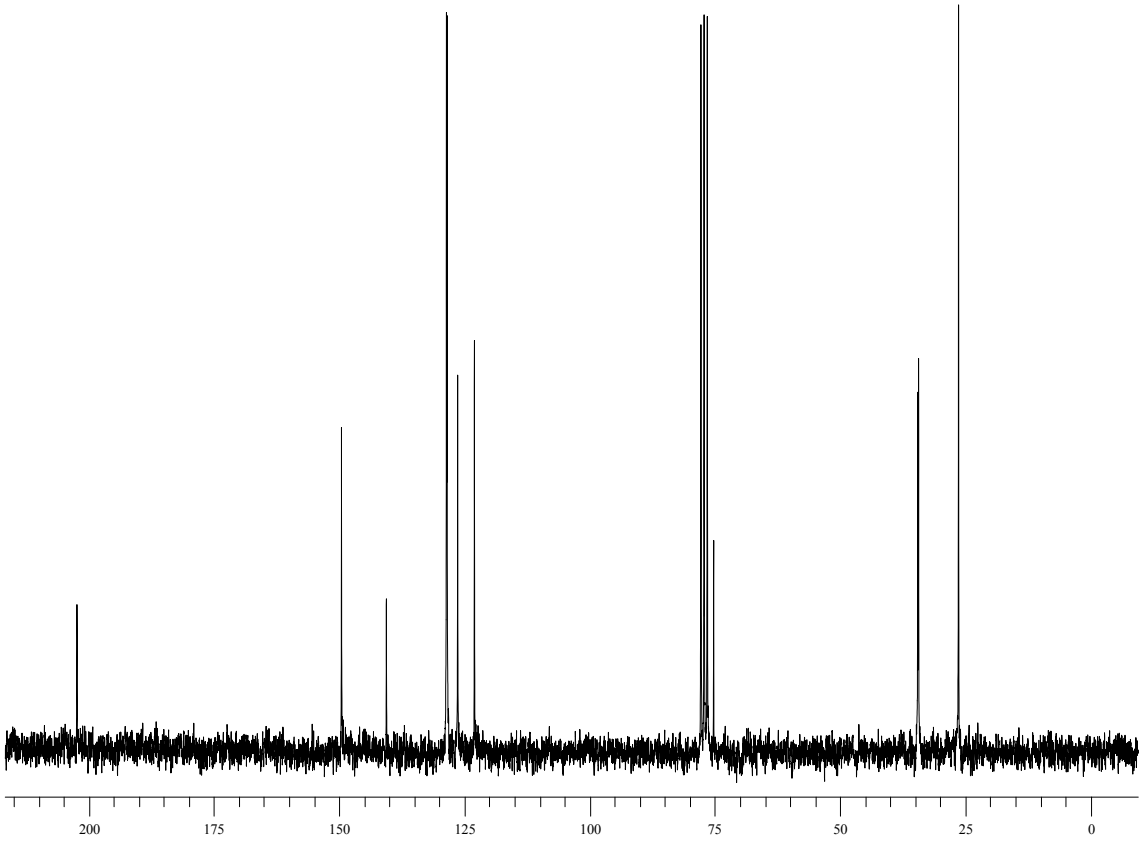


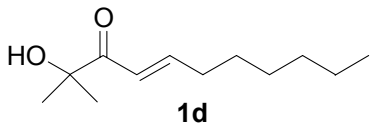
1c

^{1}H NMR



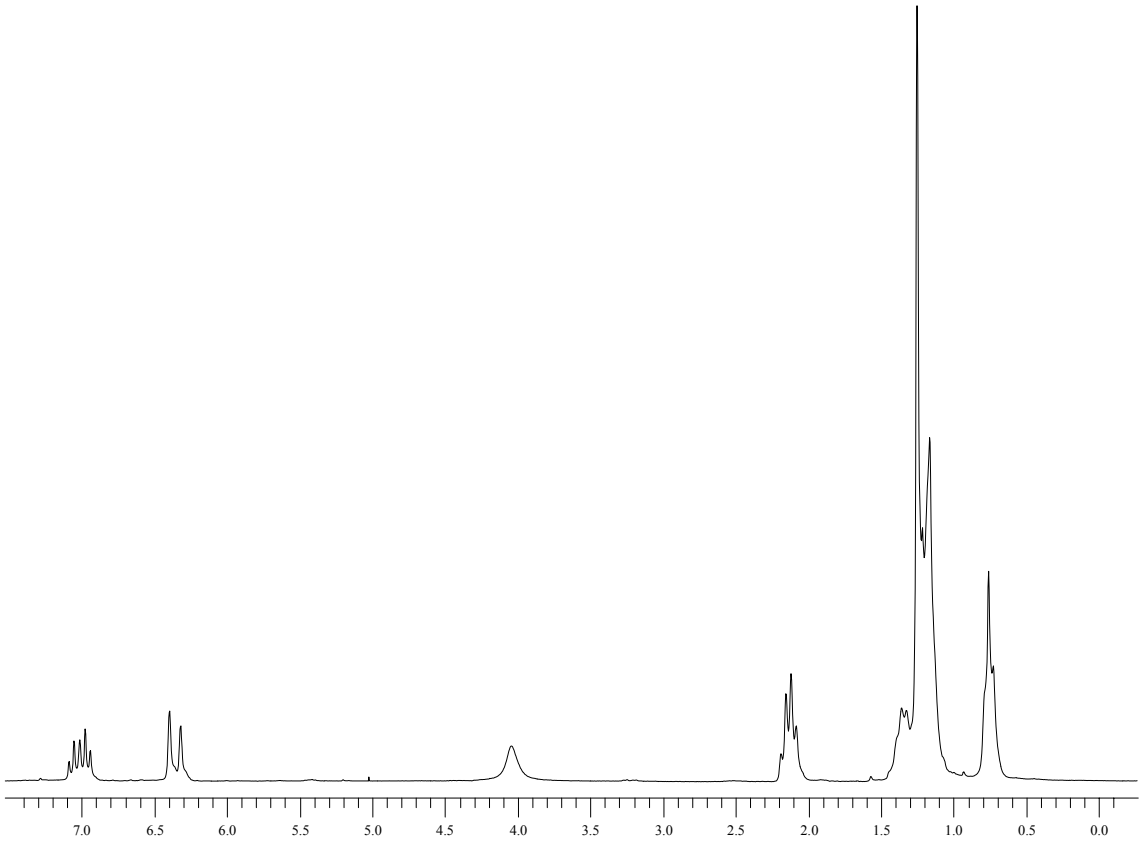
^{13}C NMR



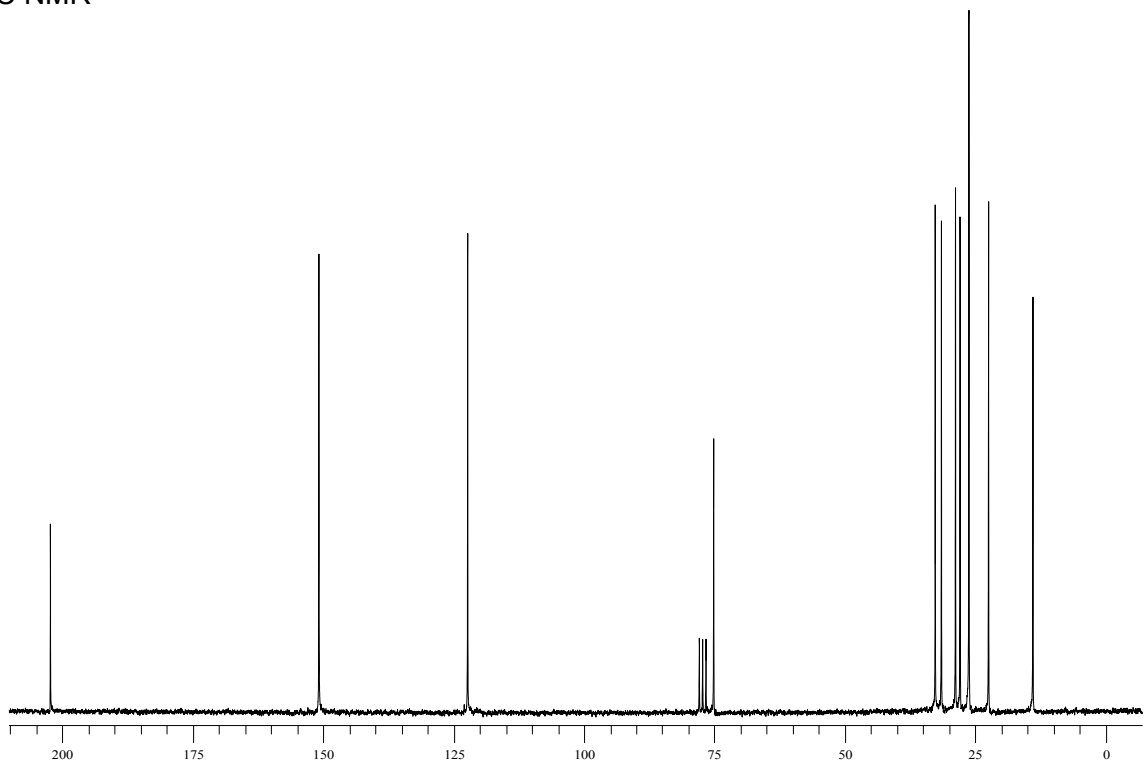


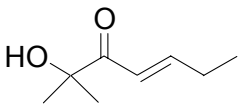
1d

^{1}H NMR



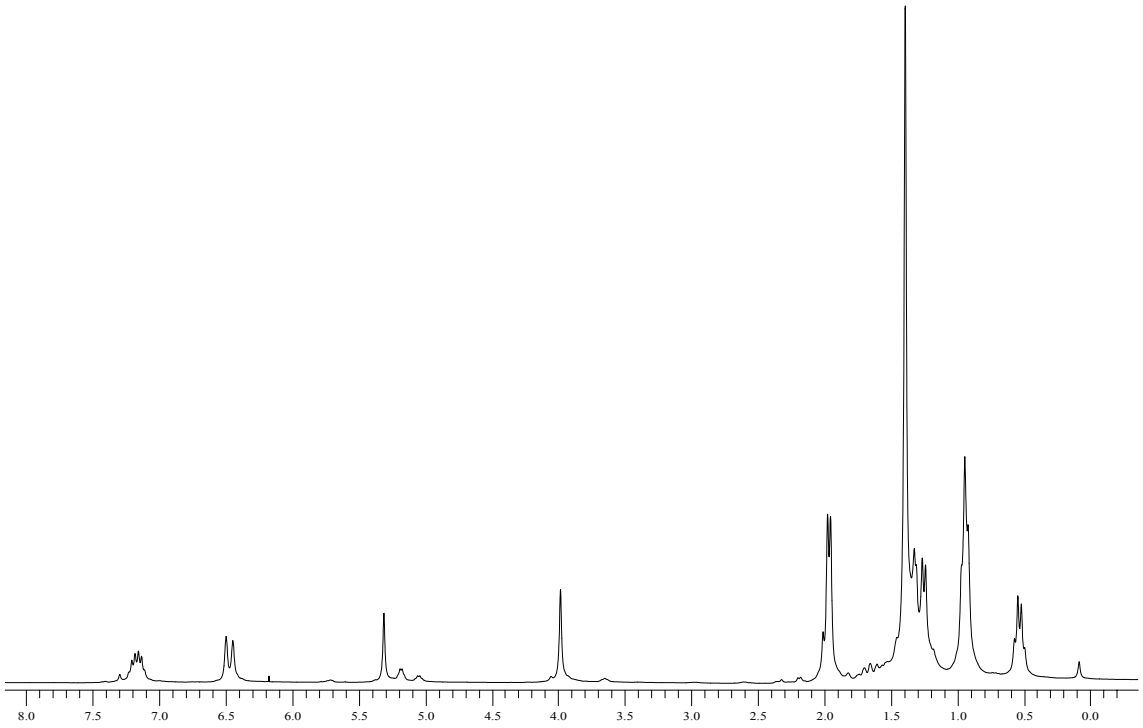
^{13}C NMR



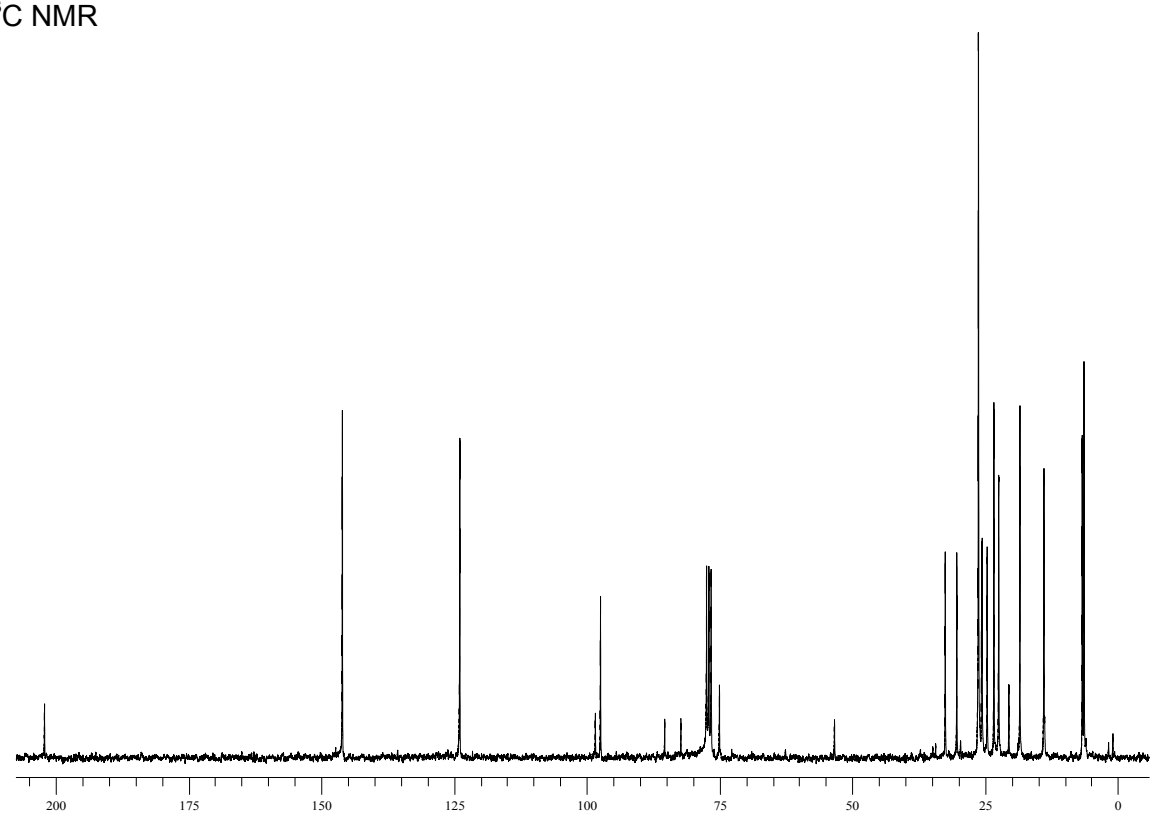


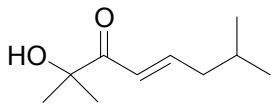
1e

^{1}H NMR



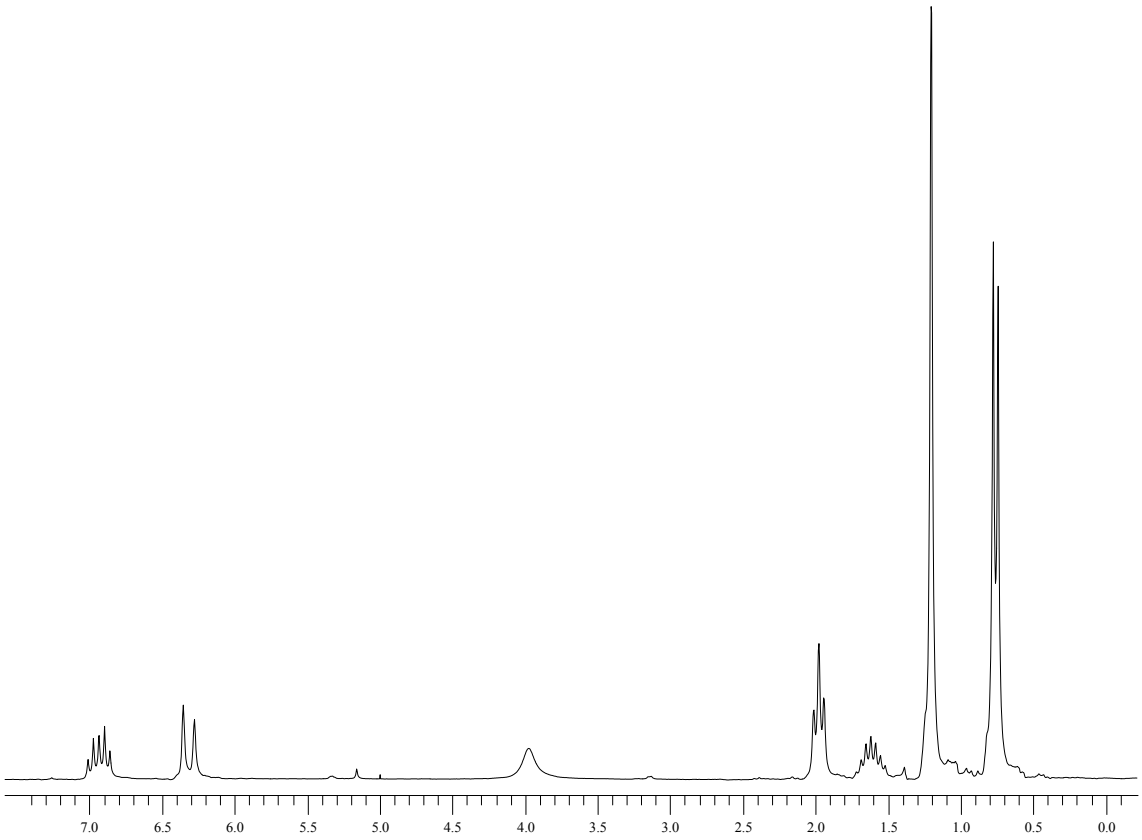
^{13}C NMR



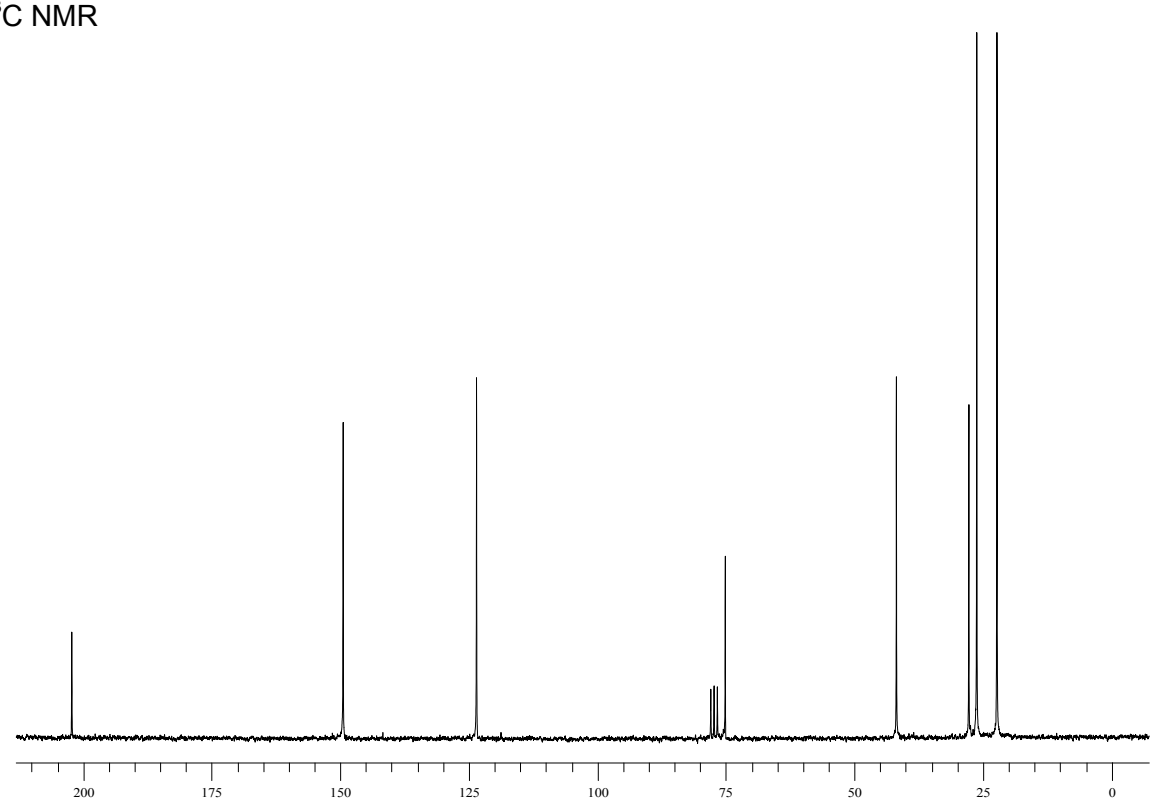


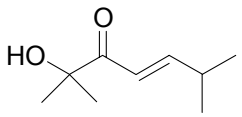
1f

^{1}H NMR



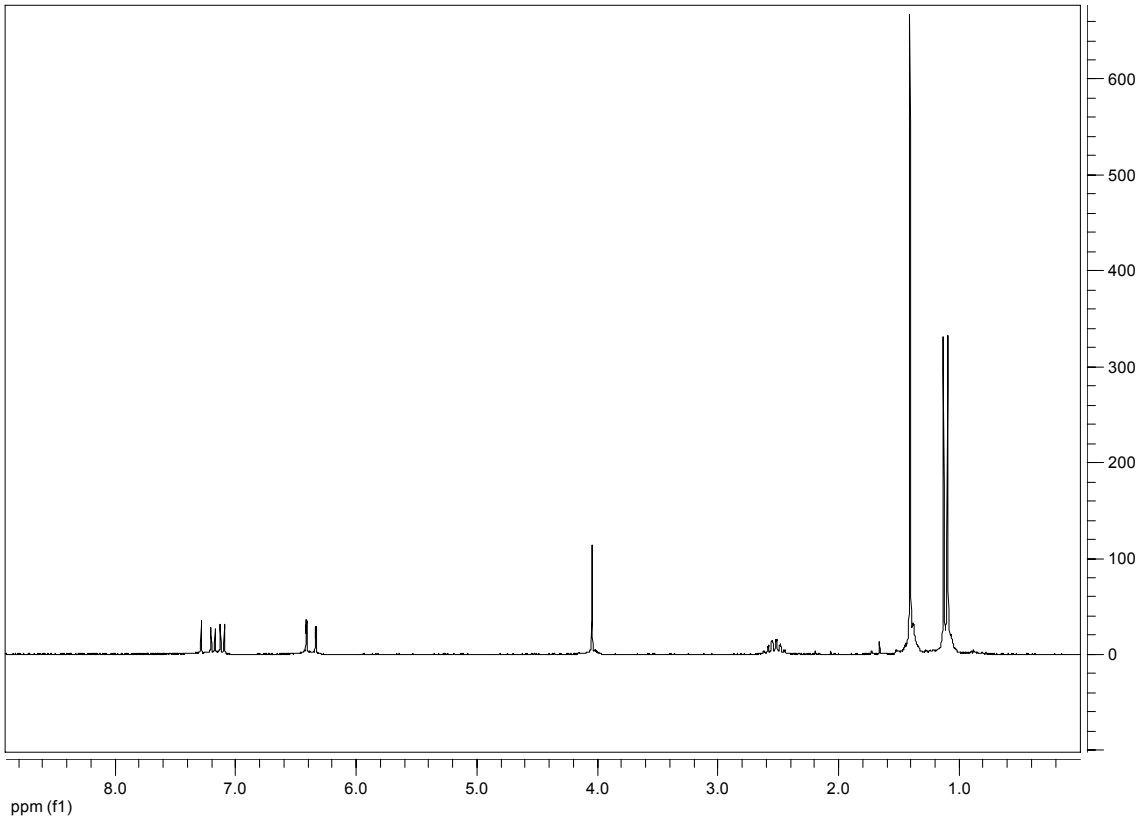
^{13}C NMR



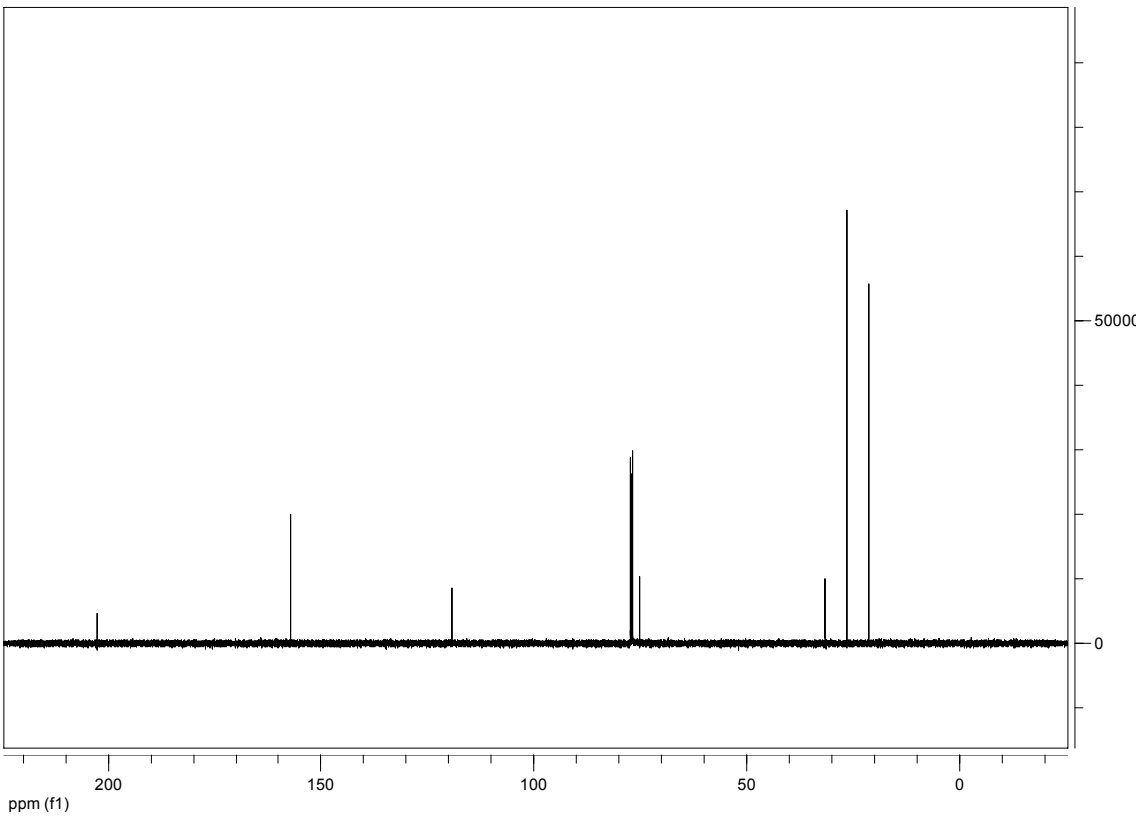


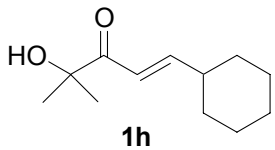
1g

^{1}H NMR



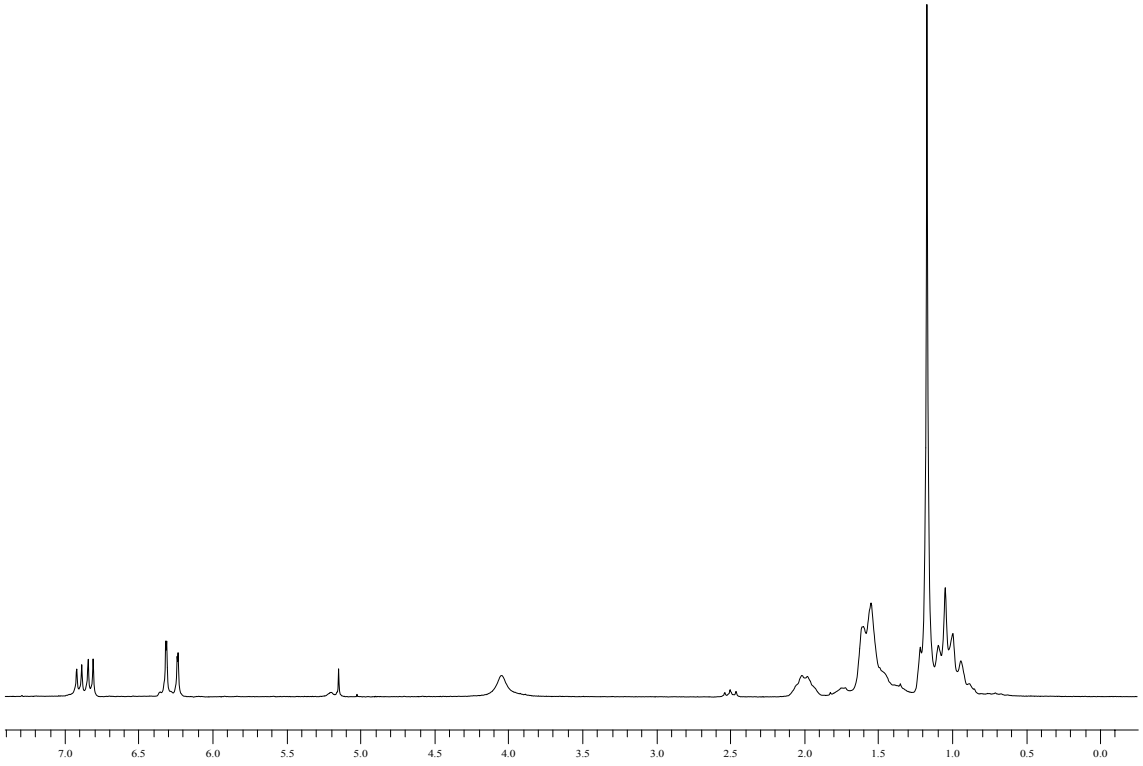
^{13}C NMR



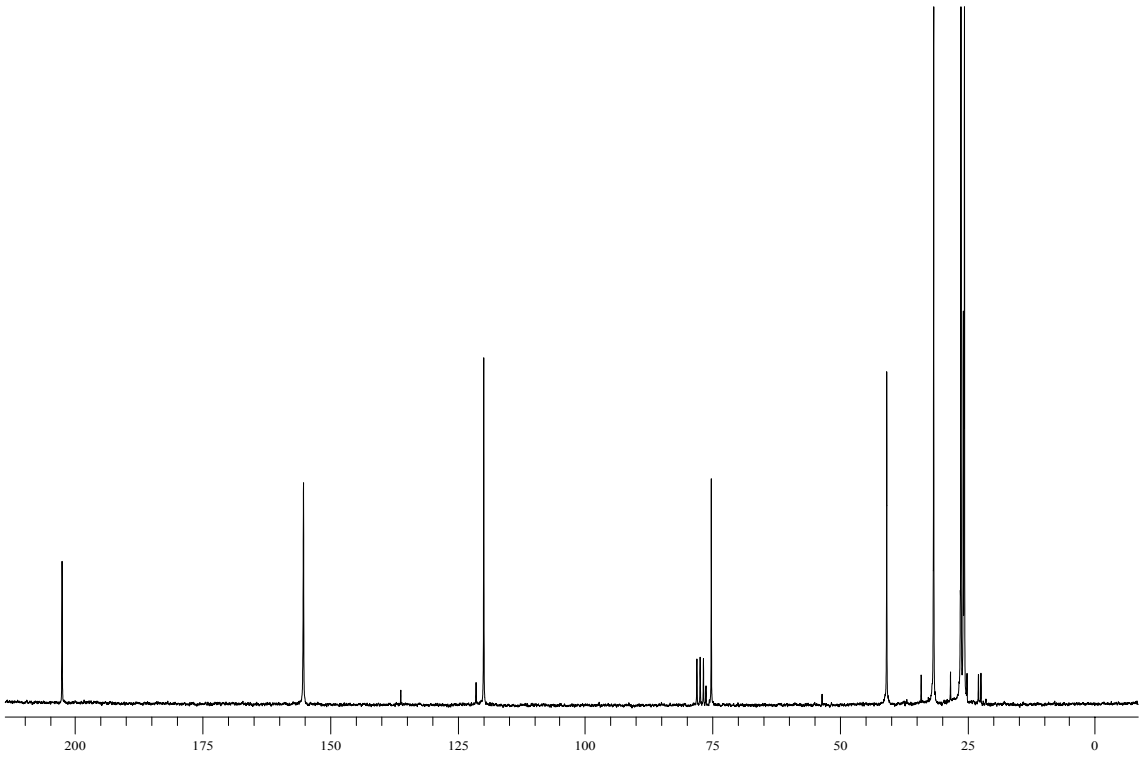


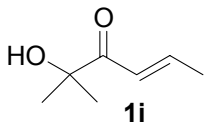
1h

^{1}H NMR



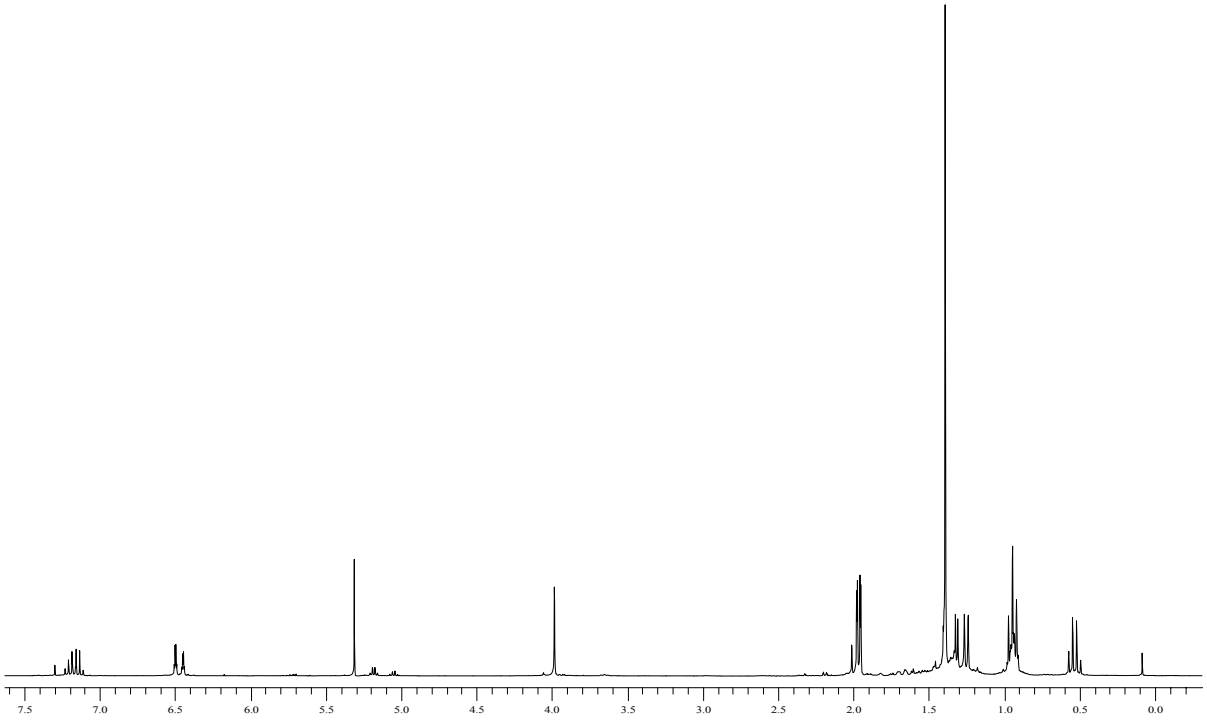
^{13}C NMR



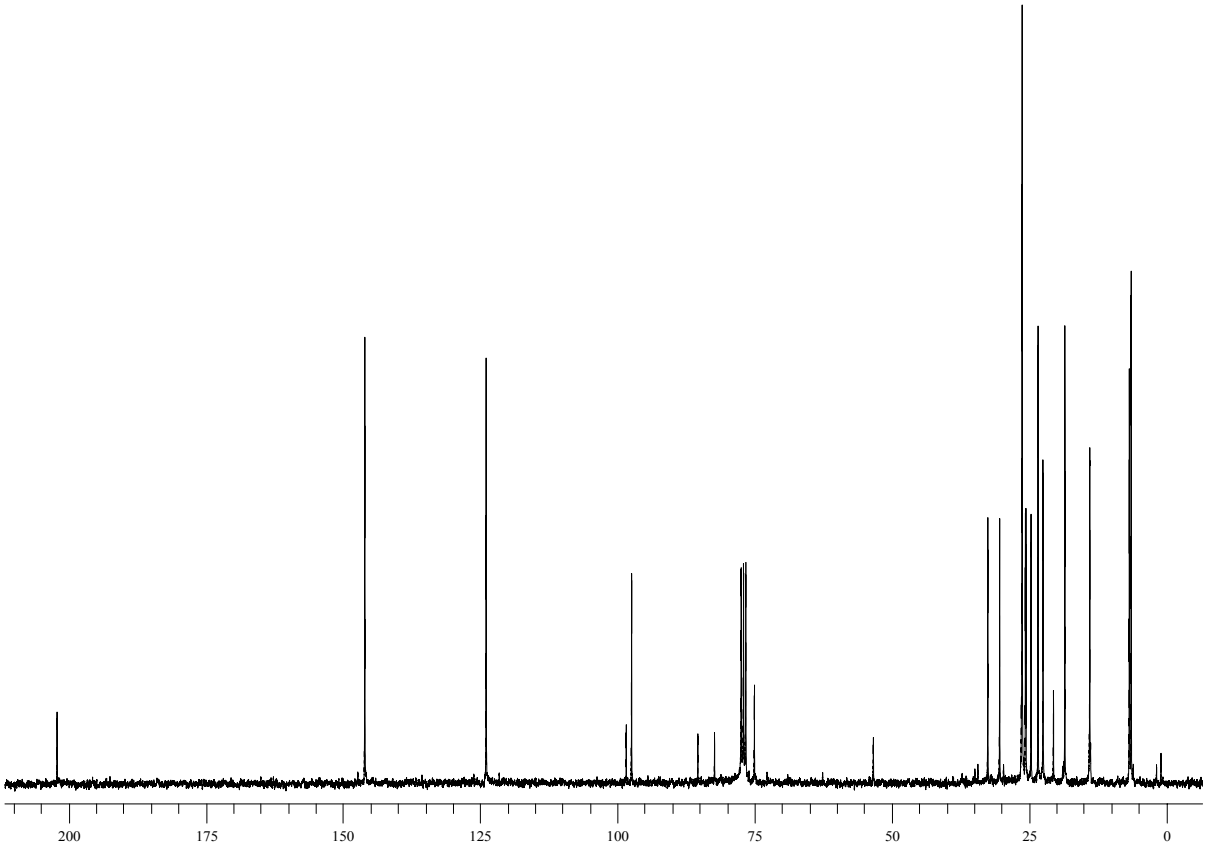


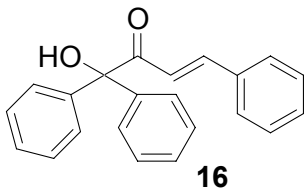
1i

^{1}H NMR



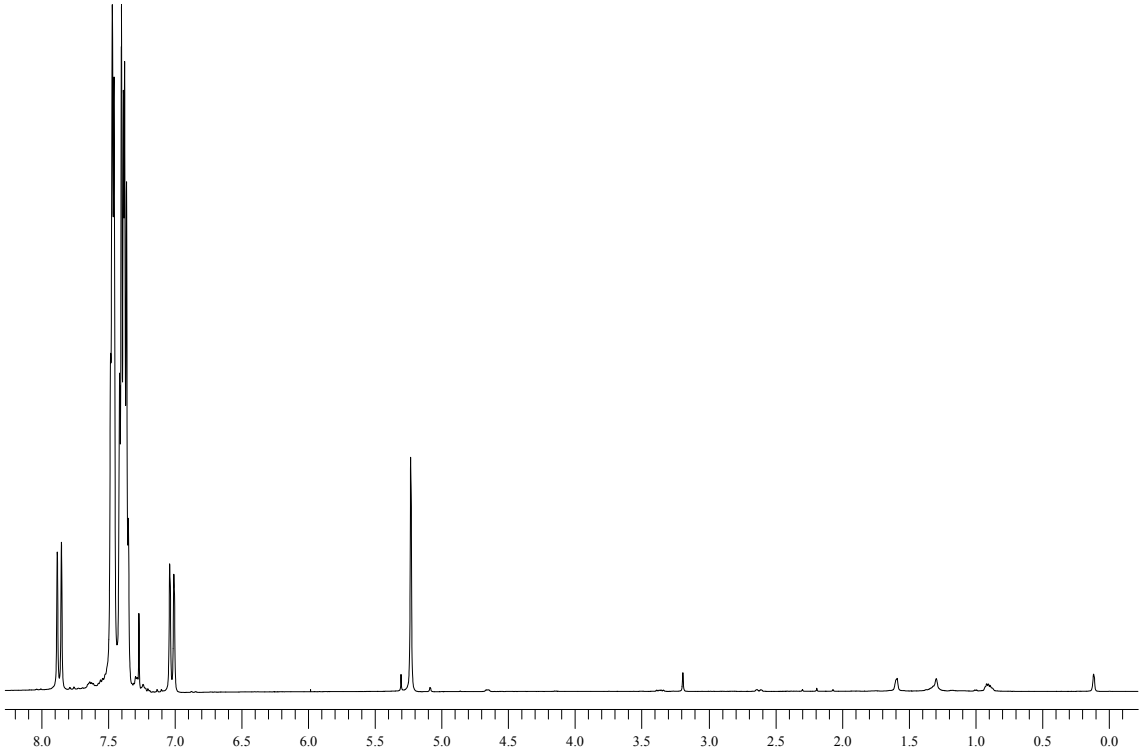
^{13}C NMR





16

^{1}H NMR



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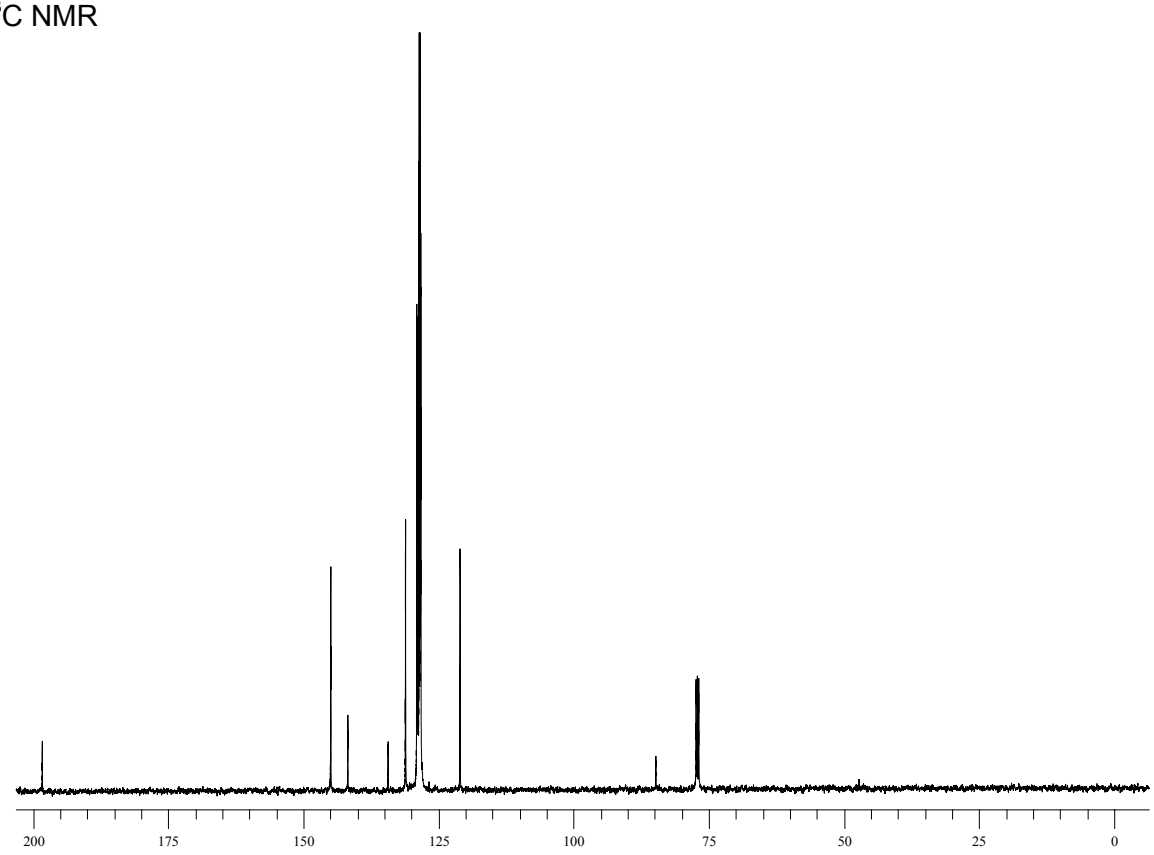
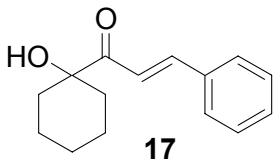
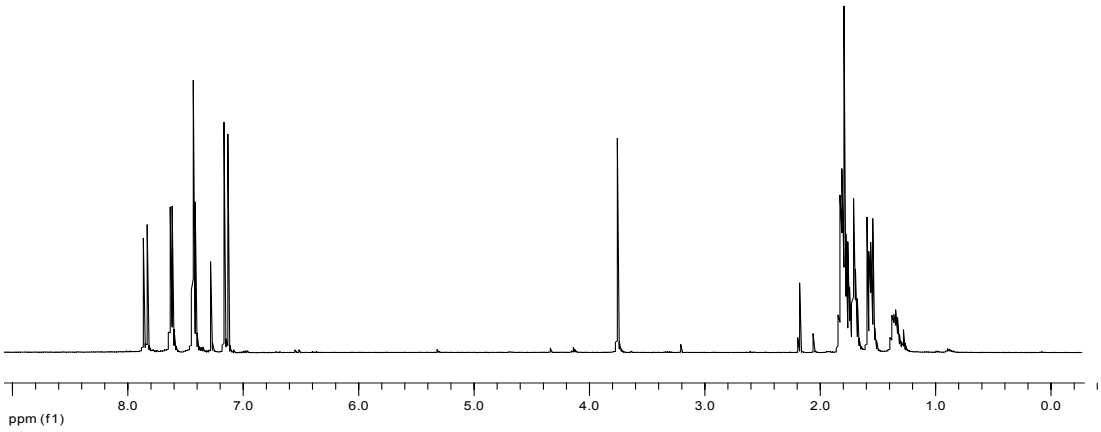




17

^{13}C NMR



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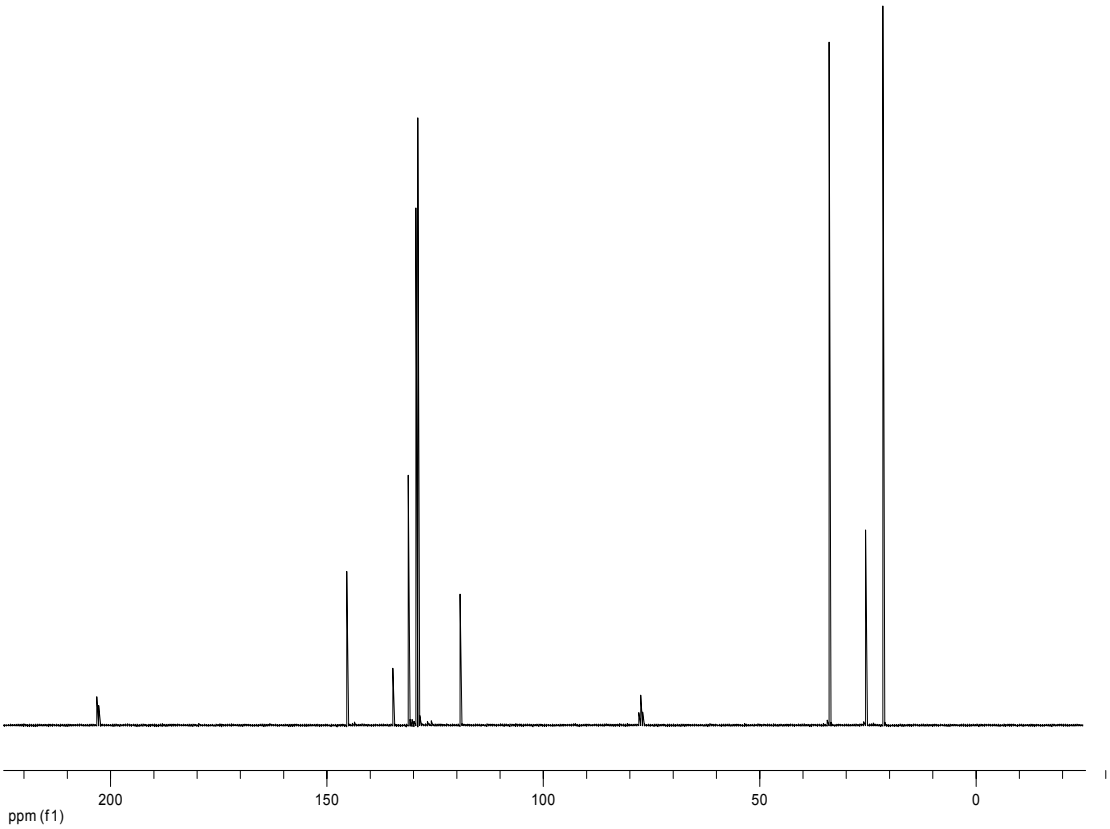
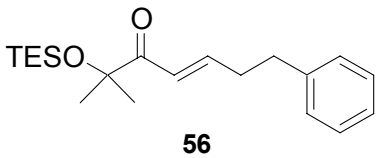
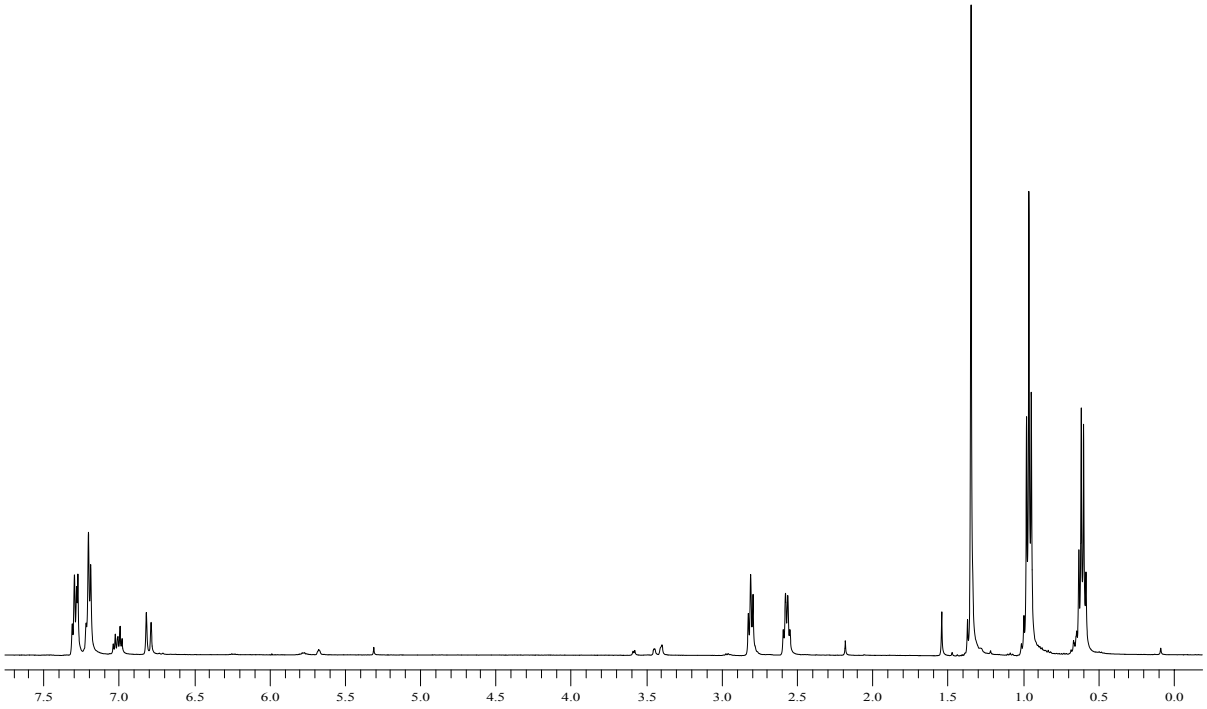




56

^{1}H NMR



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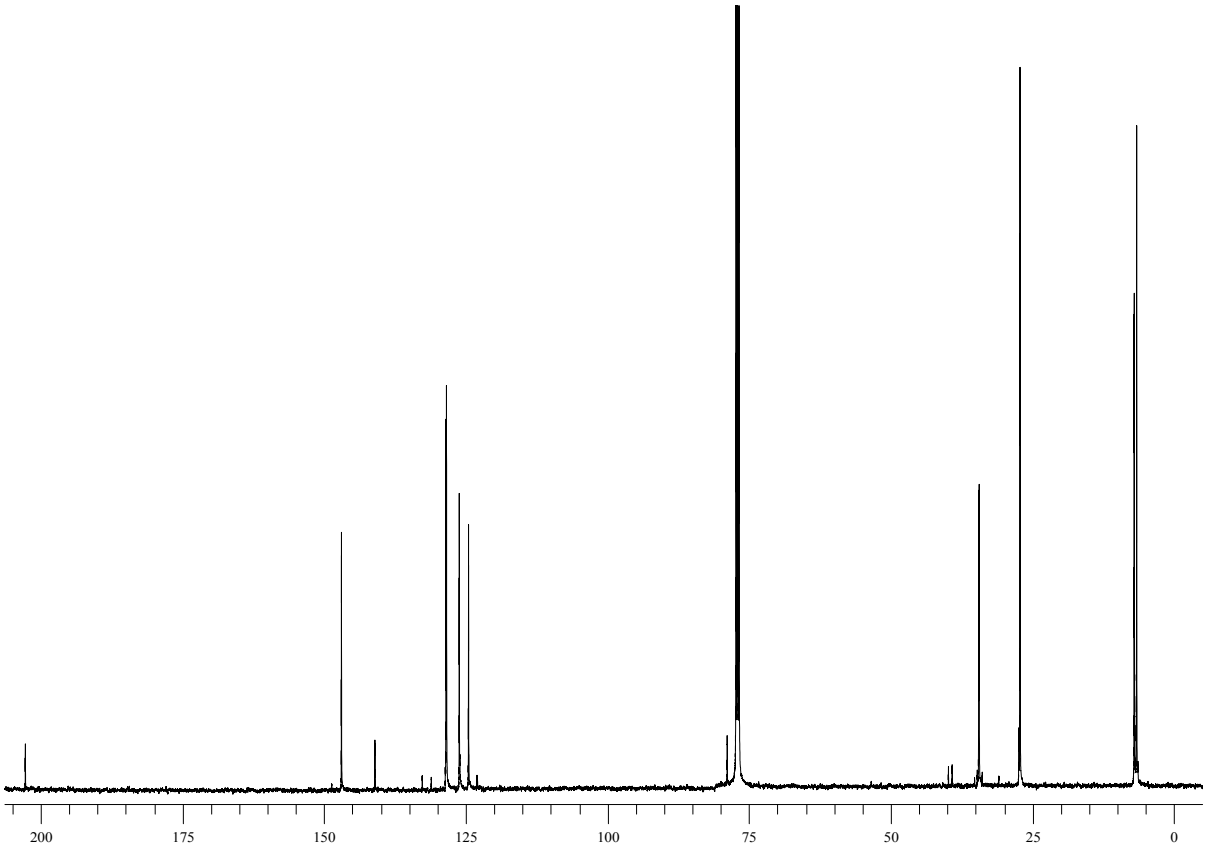
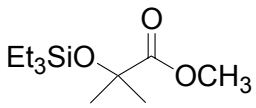
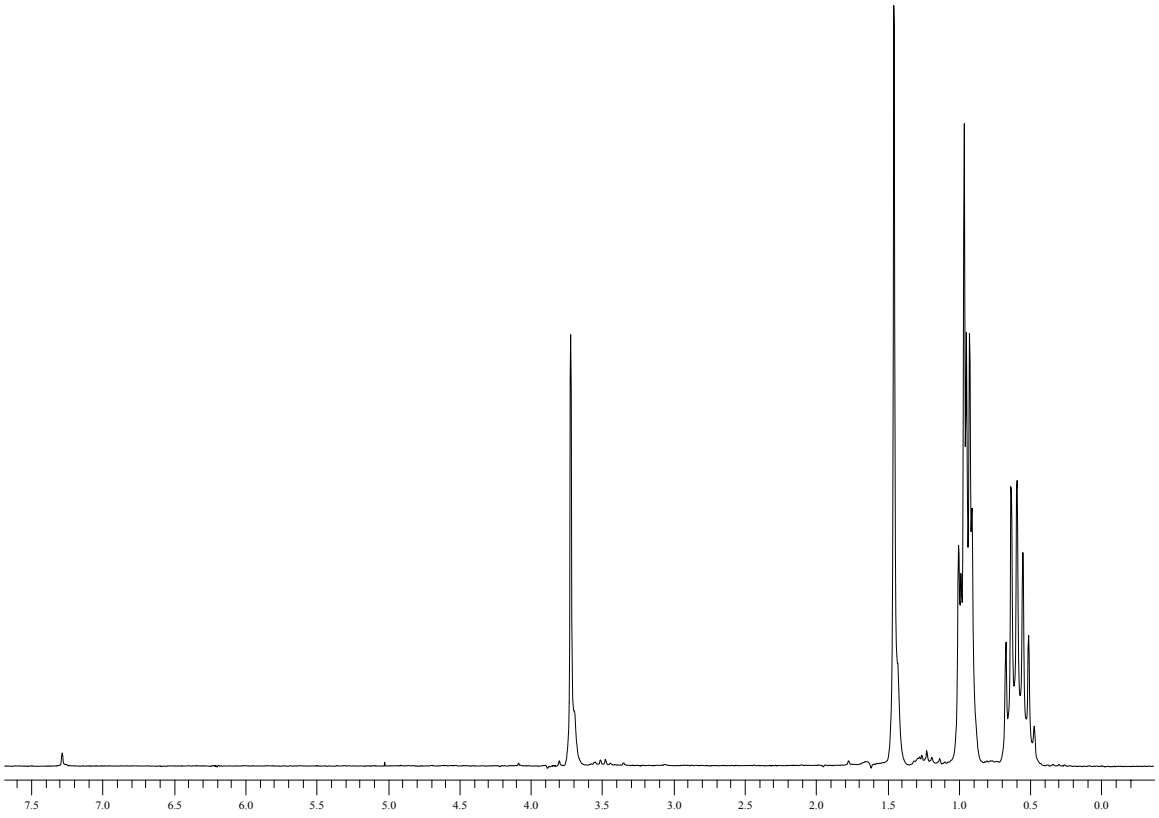
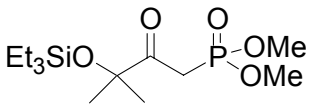




90

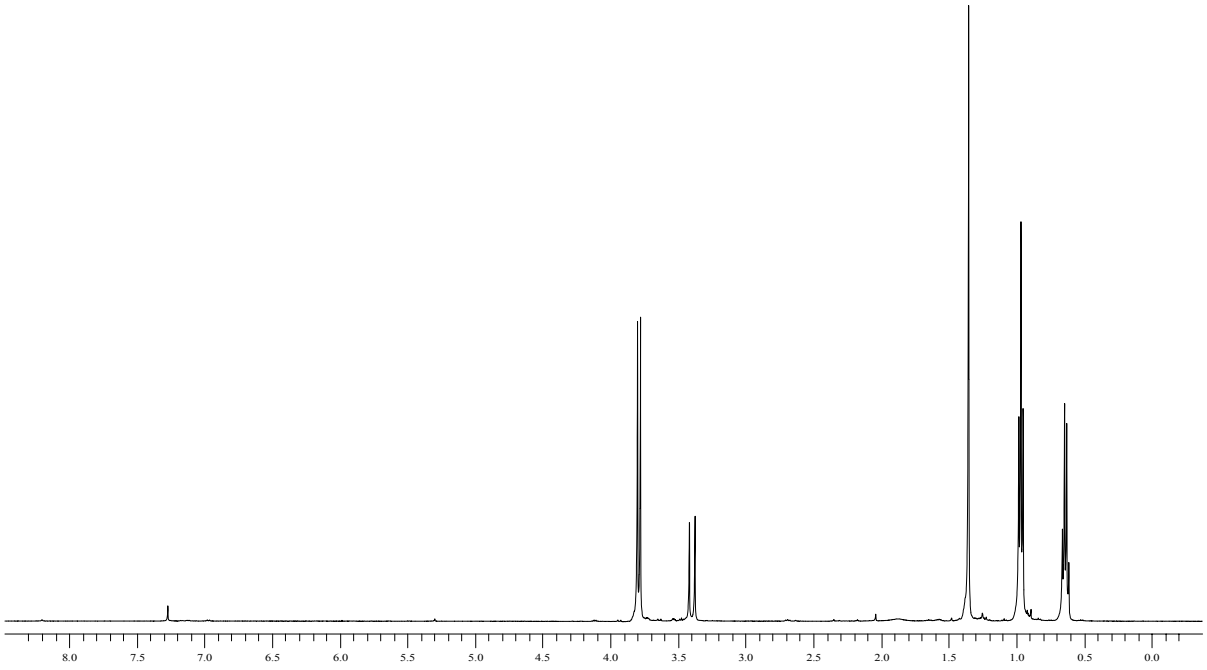
^{1}H NMR





91

^{1}H NMR



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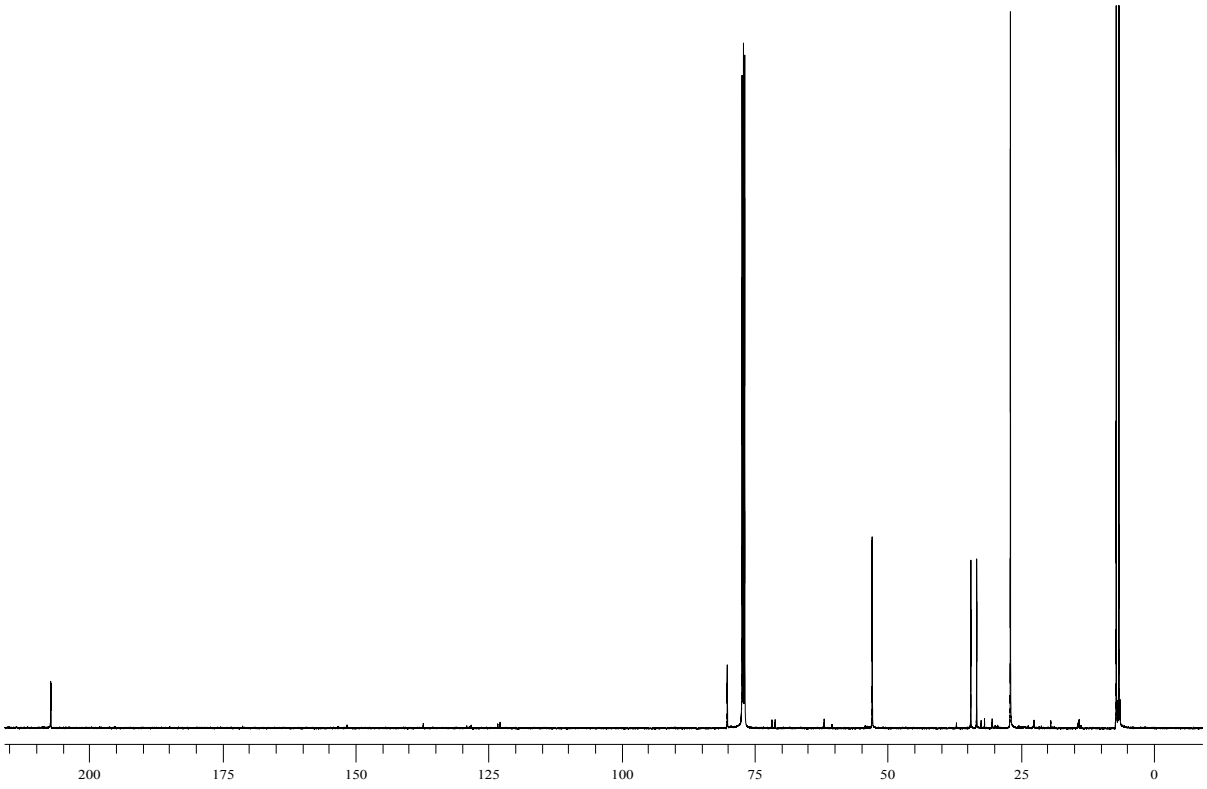
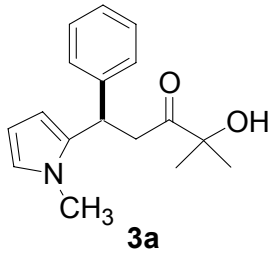
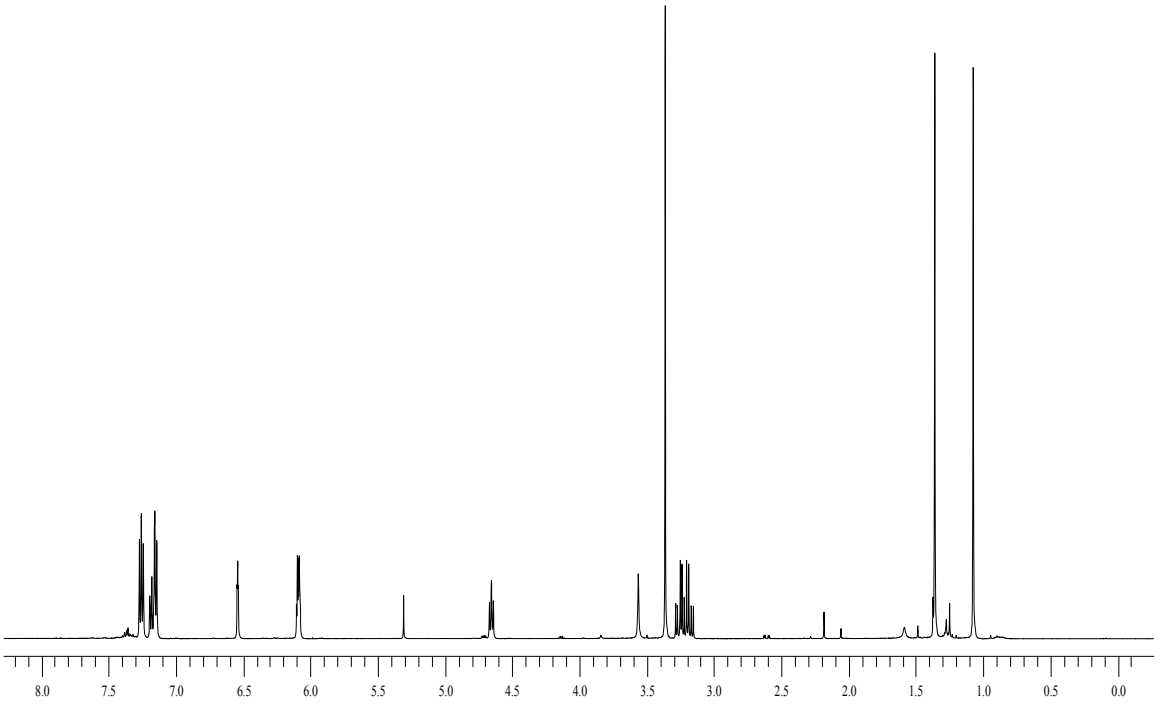


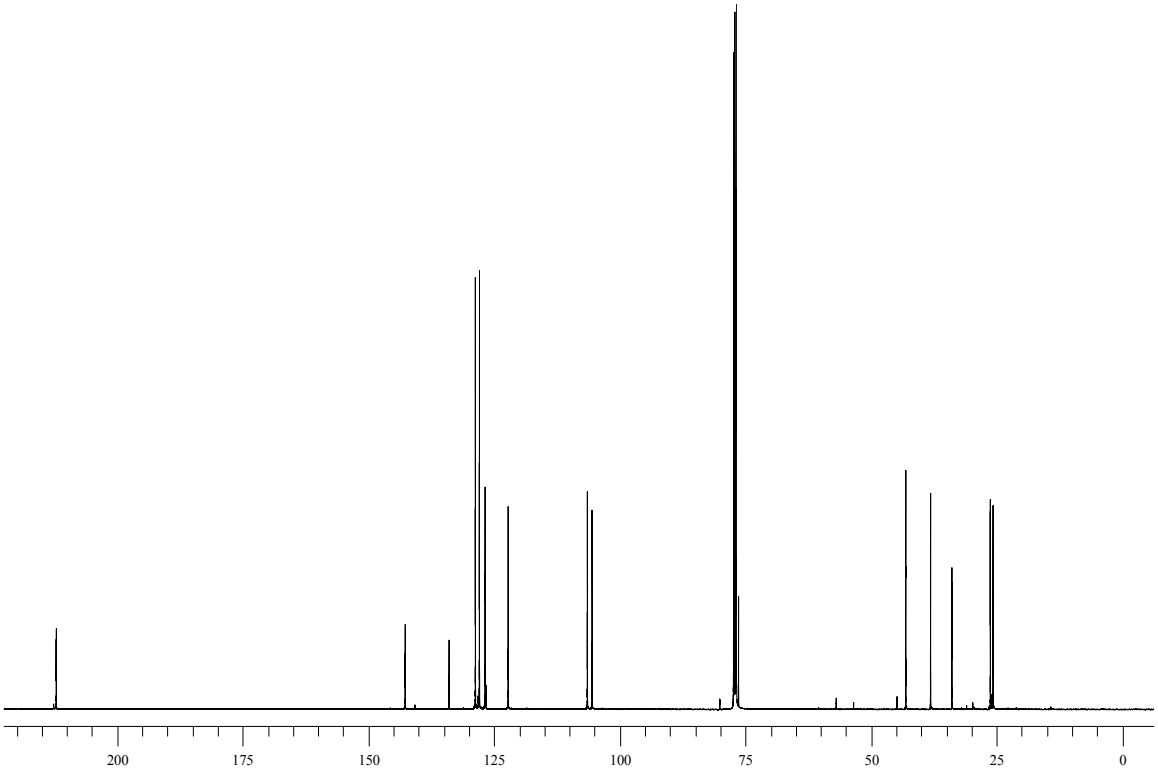


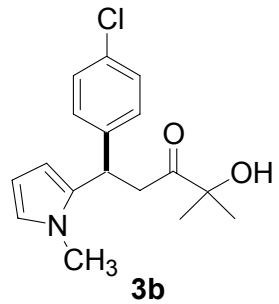
3a

^{1}H NMR



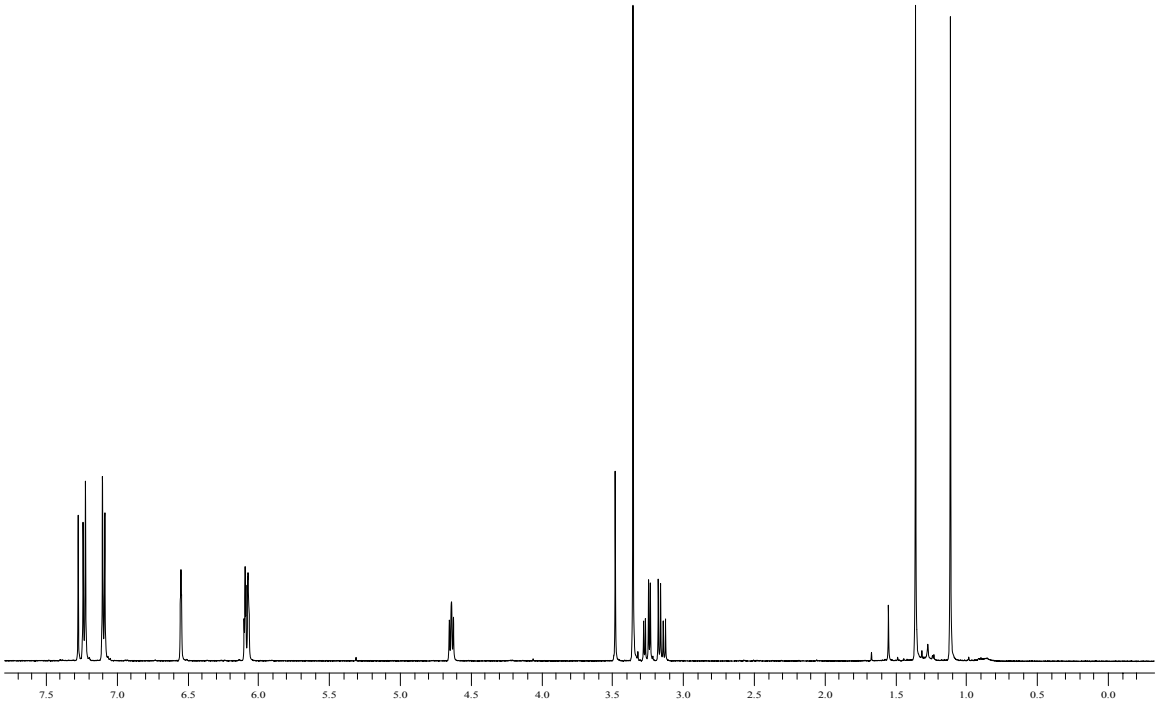
^{13}C NMR





3b

^{1}H NMR



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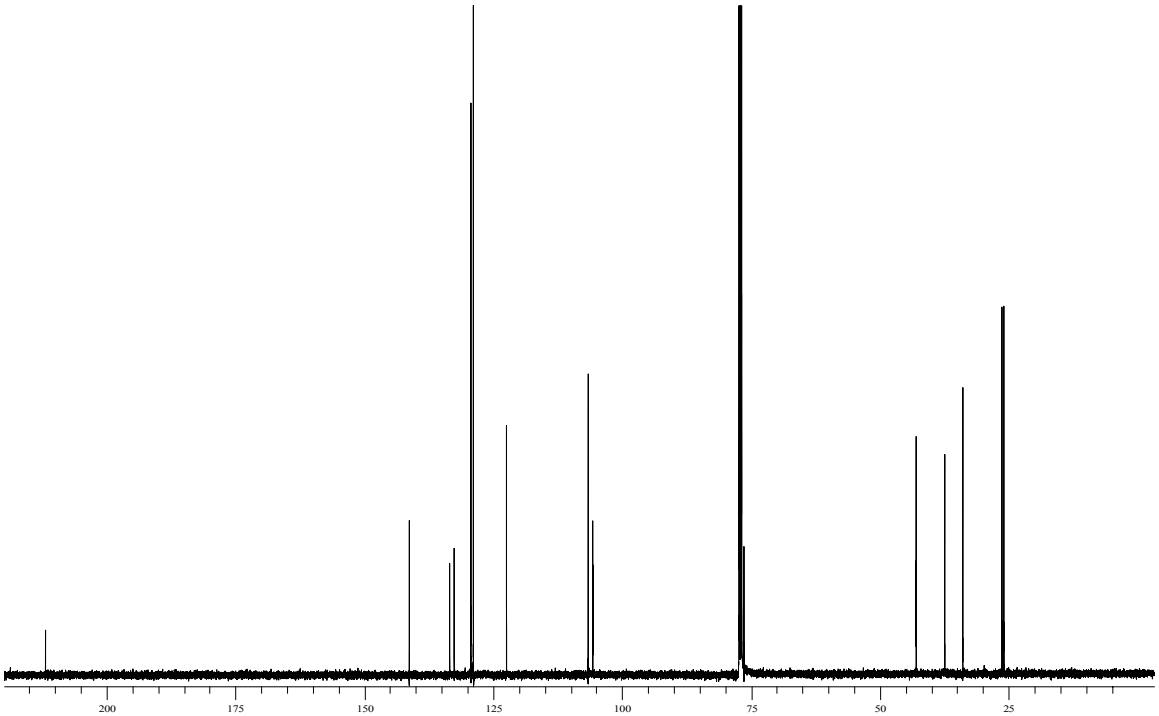
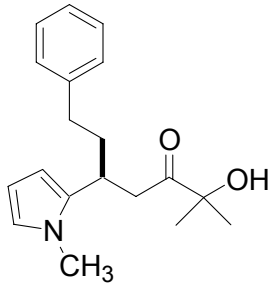
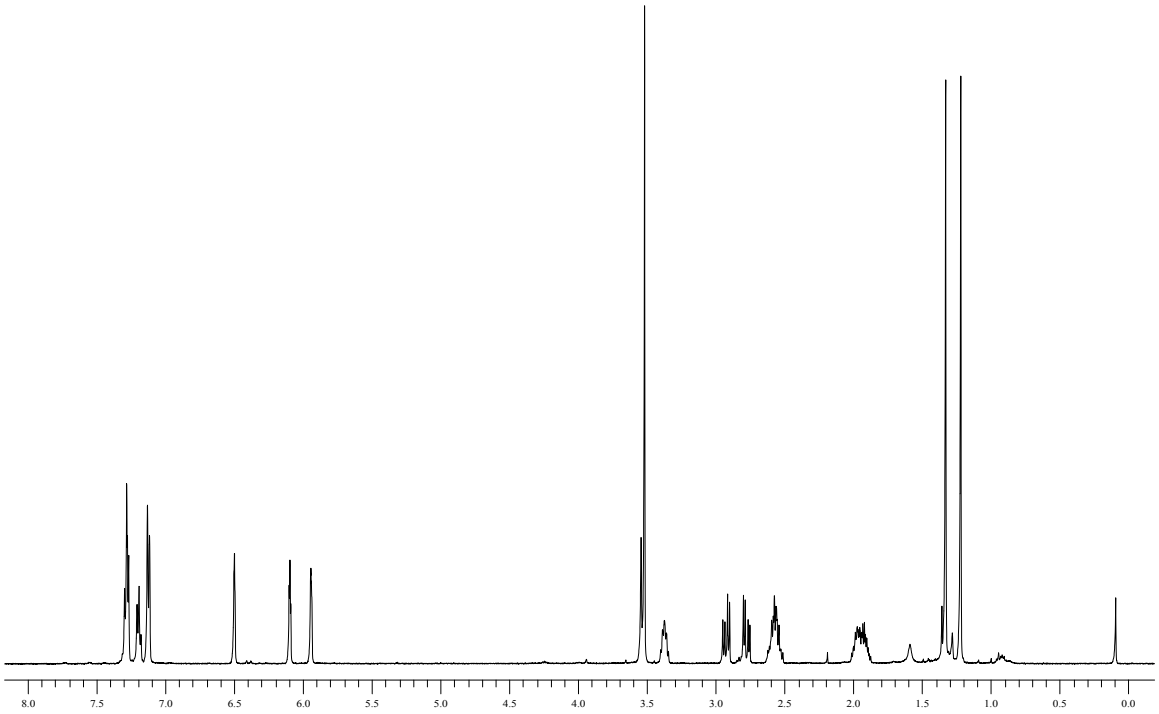


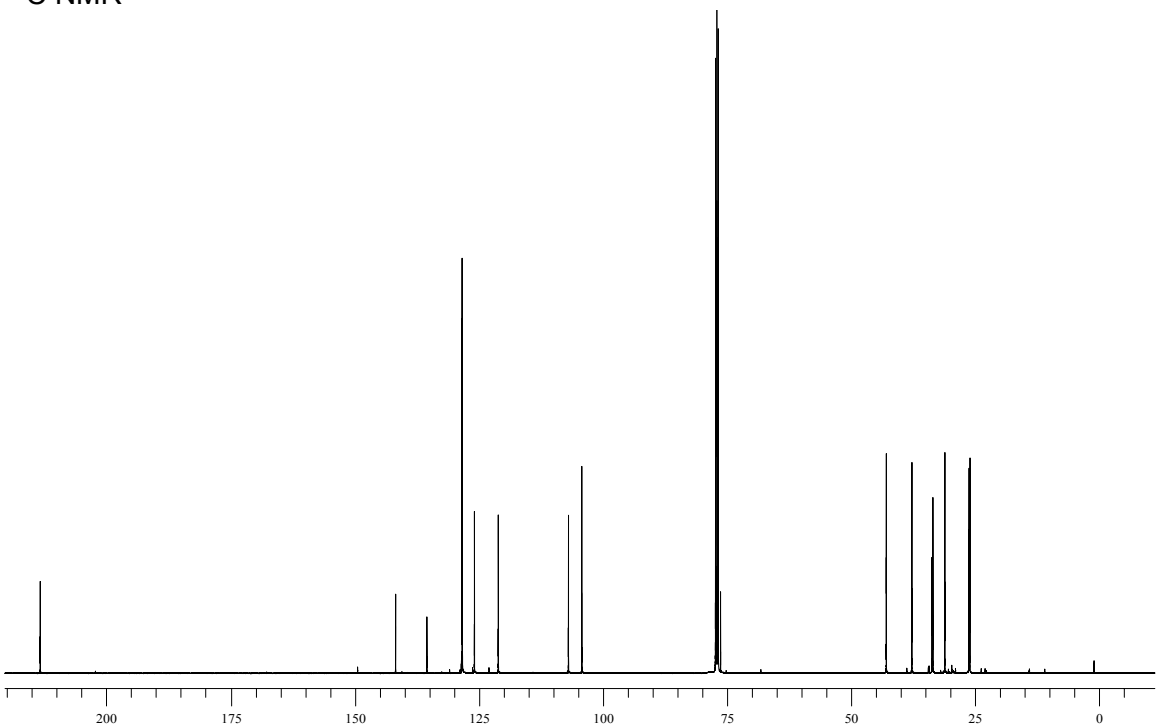


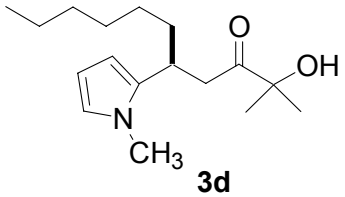
3c

^{1}H NMR



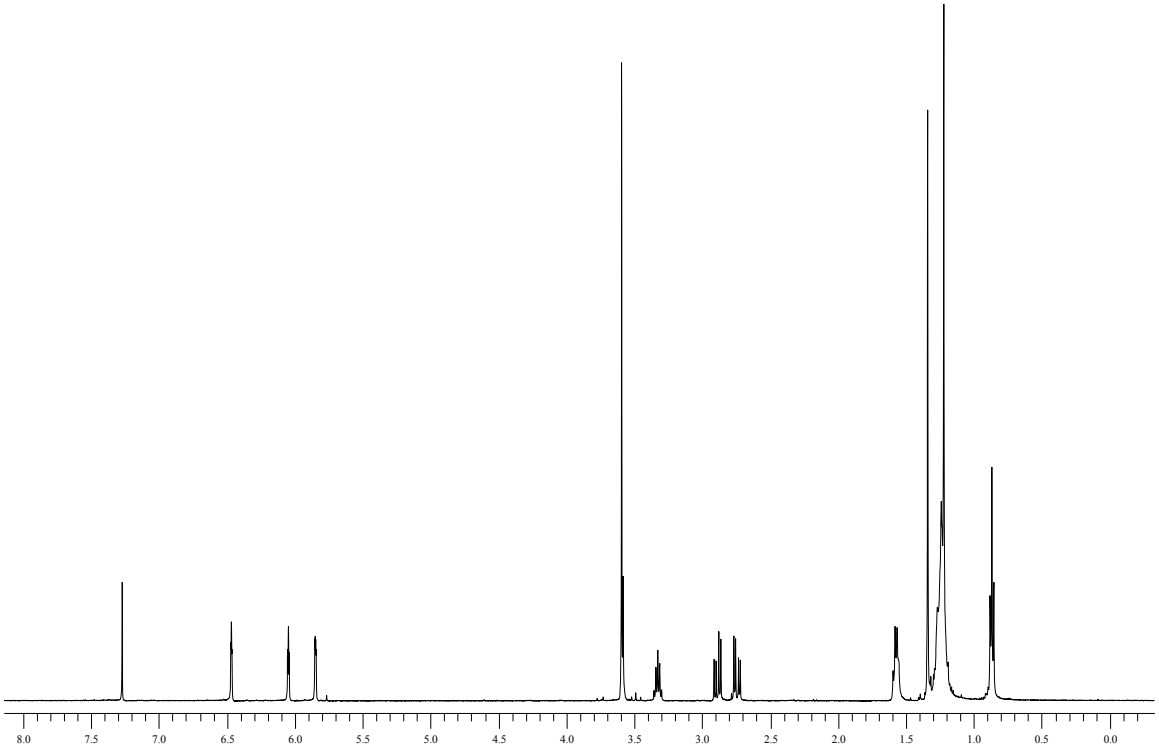
^{13}C NMR



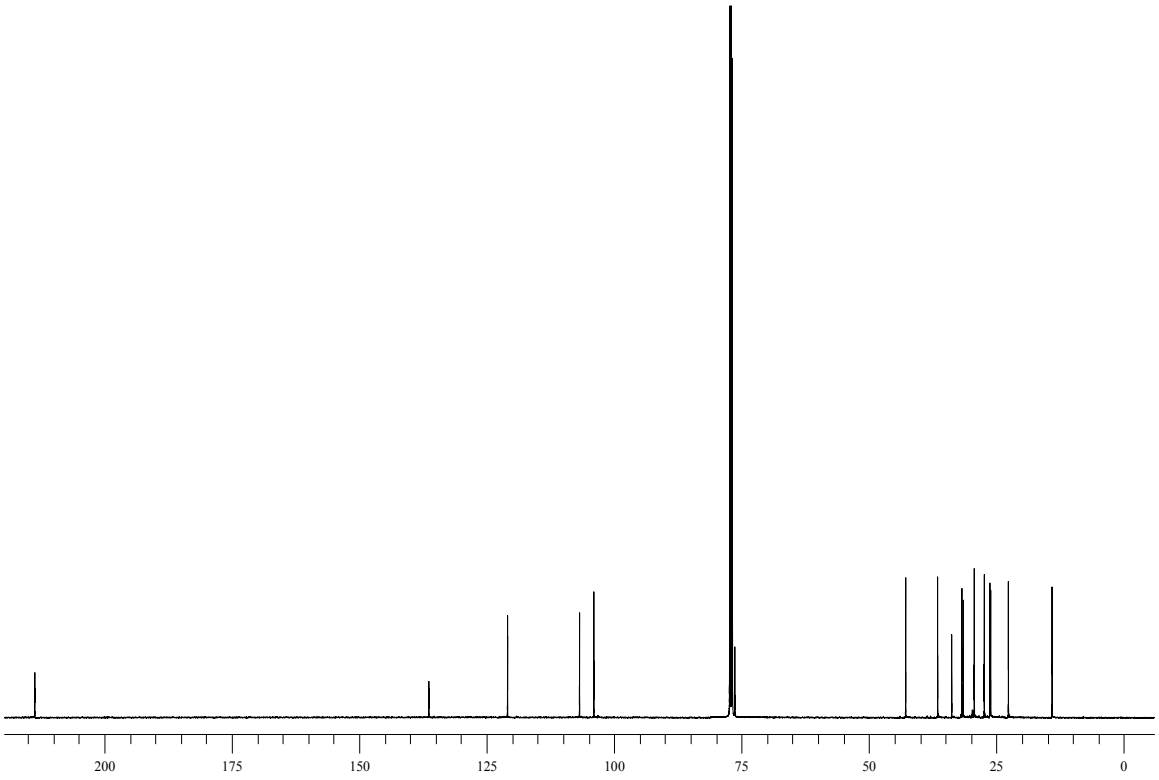


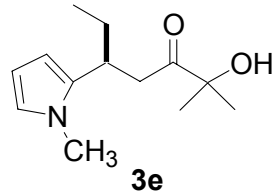
3d

^{1}H NMR



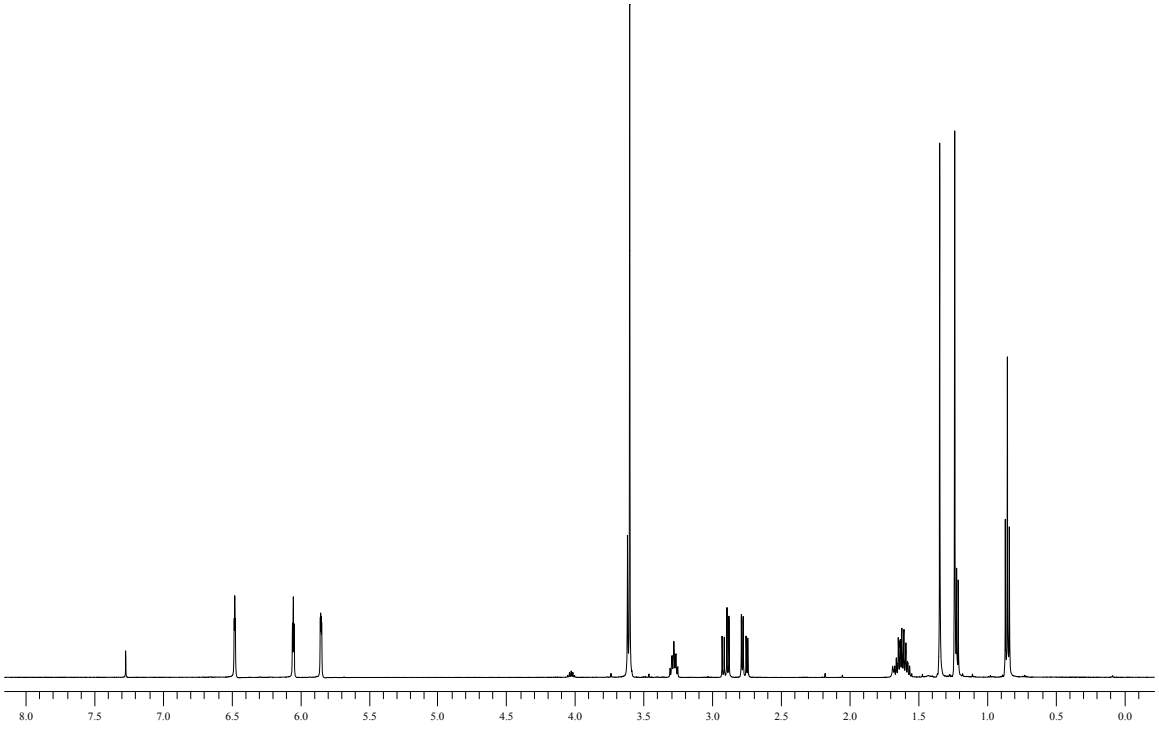
^{13}C NMR



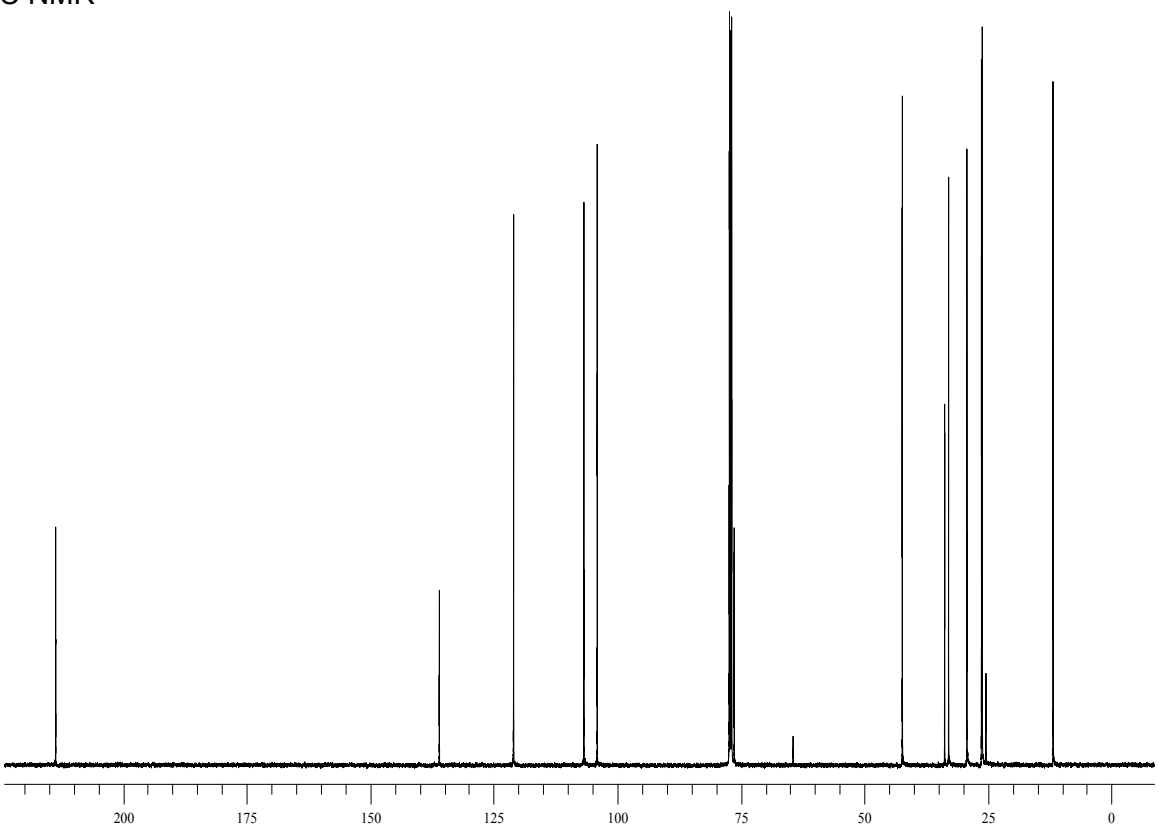


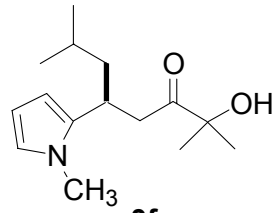
3e

^{1}H NMR



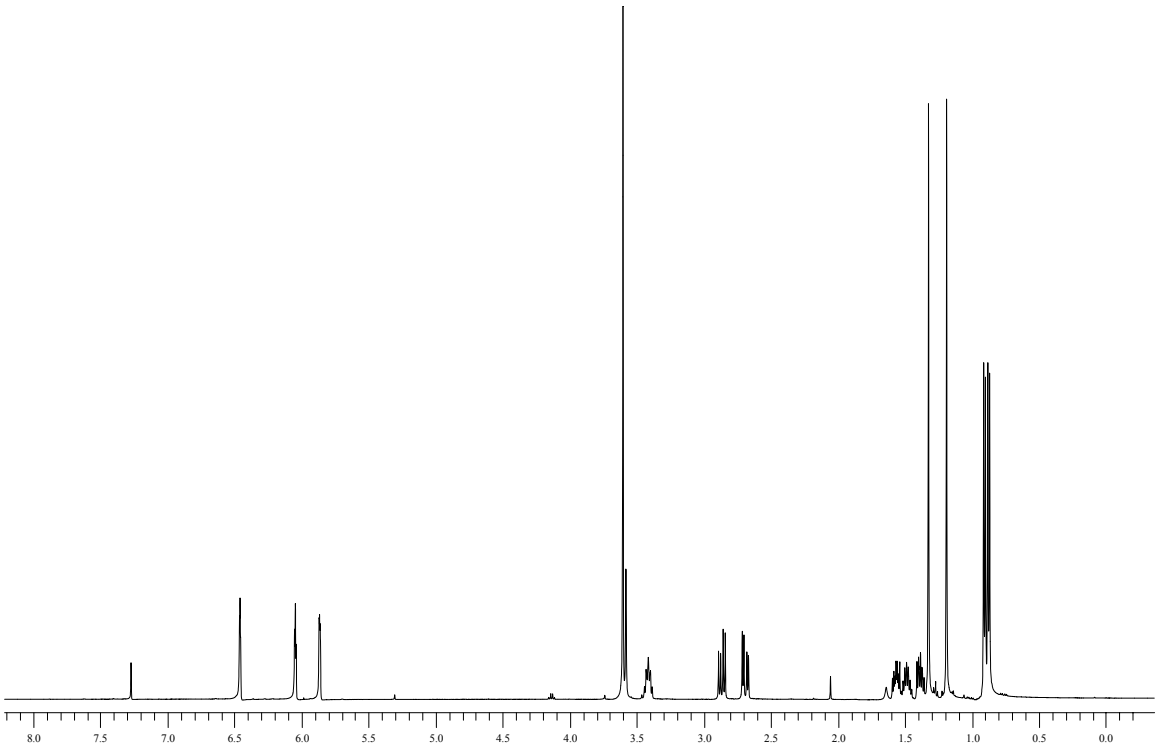
^{13}C NMR



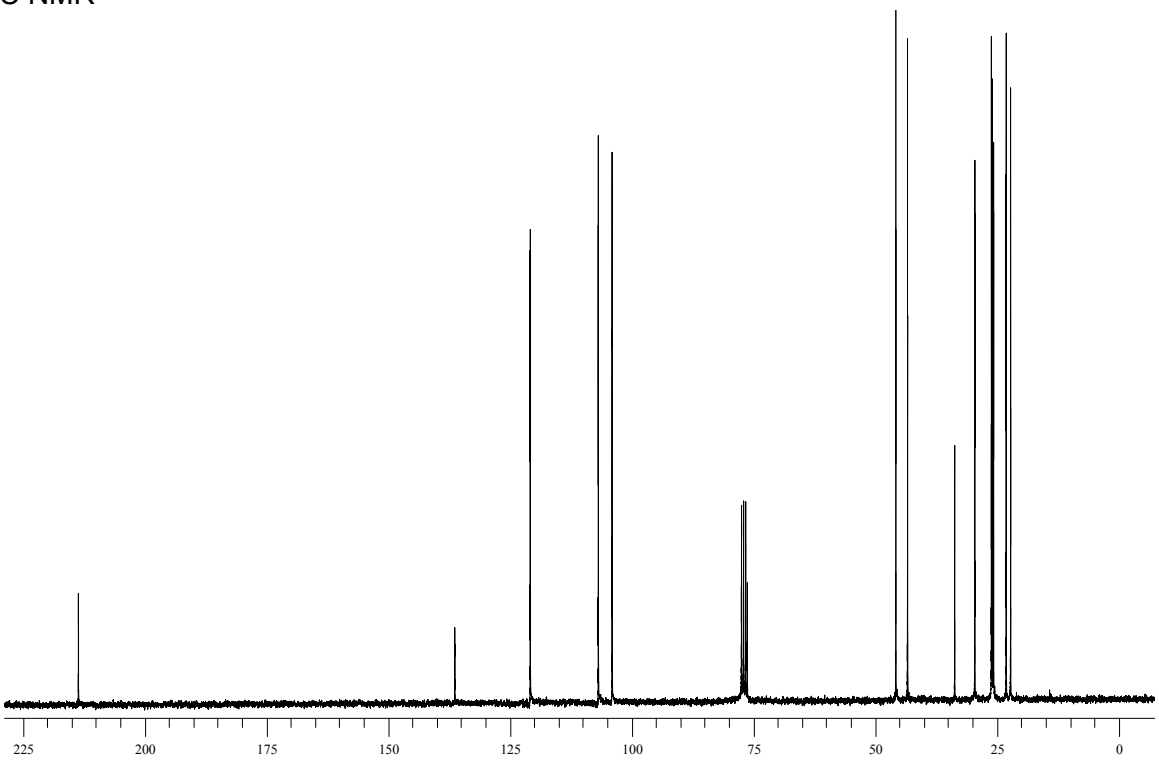


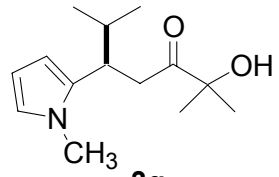
3f

^{1}H NMR



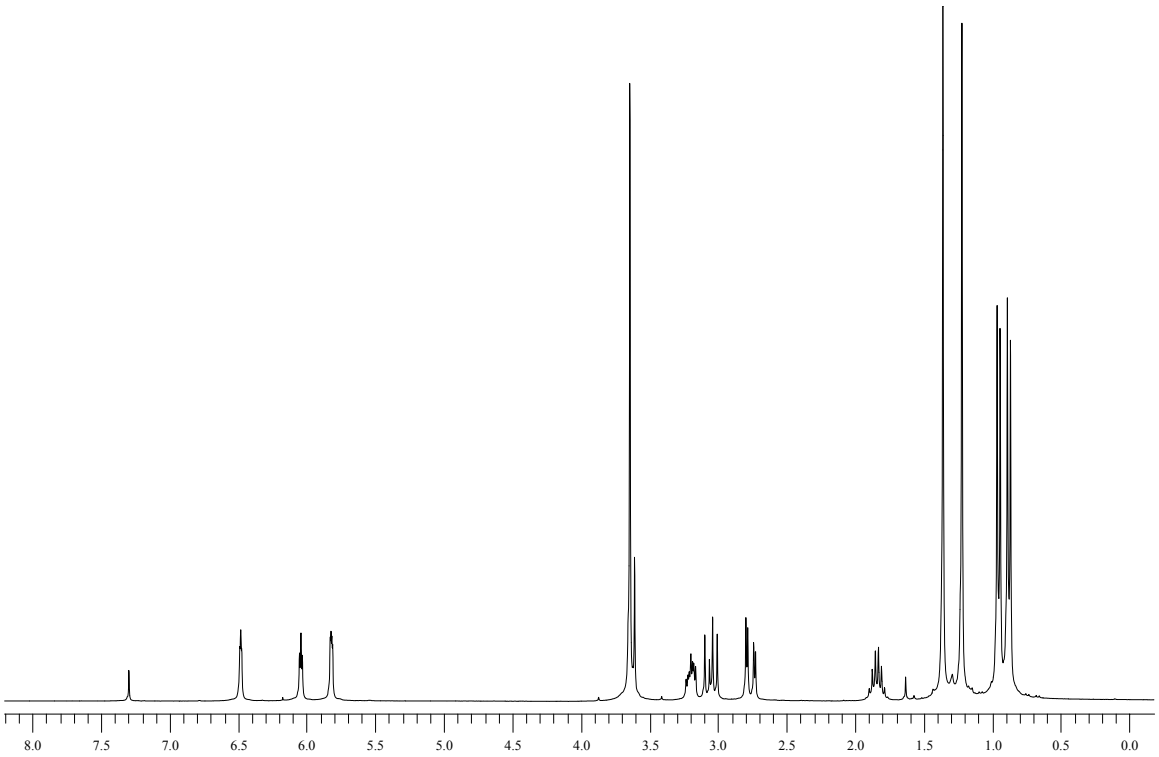
^{13}C NMR



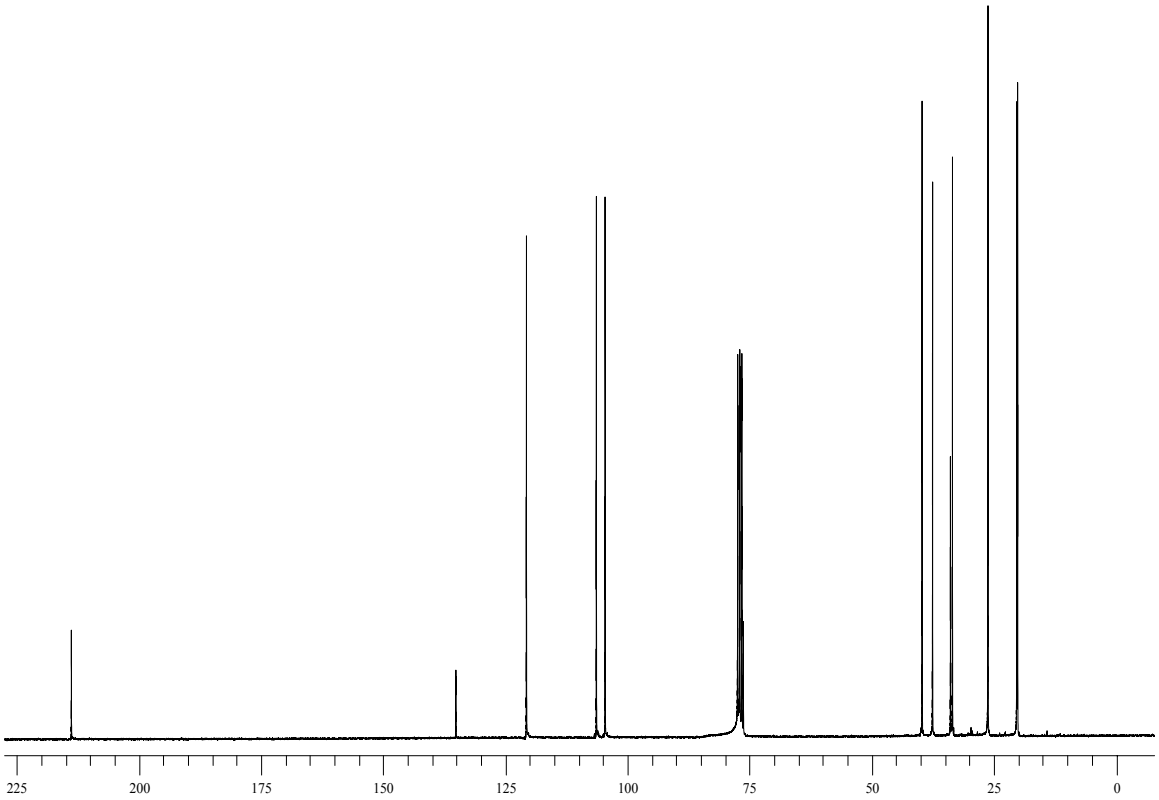


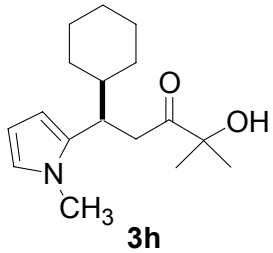
3g

^{1}H NMR



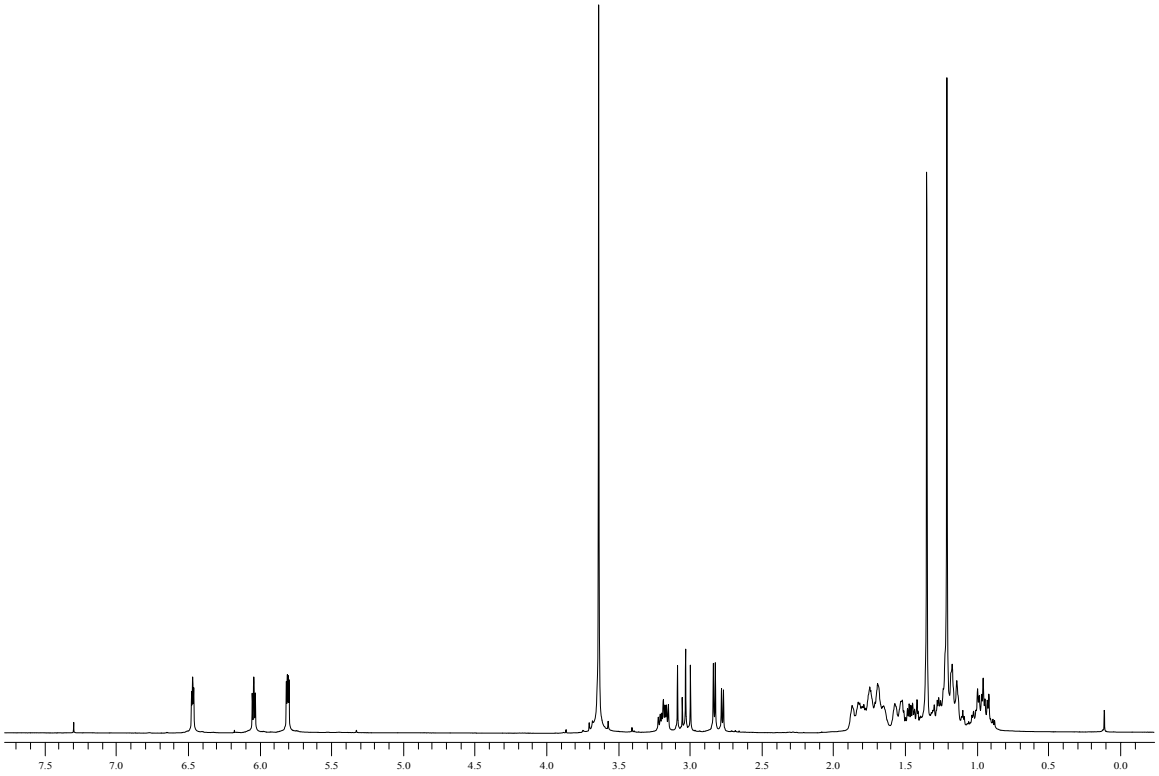
^{13}C NMR



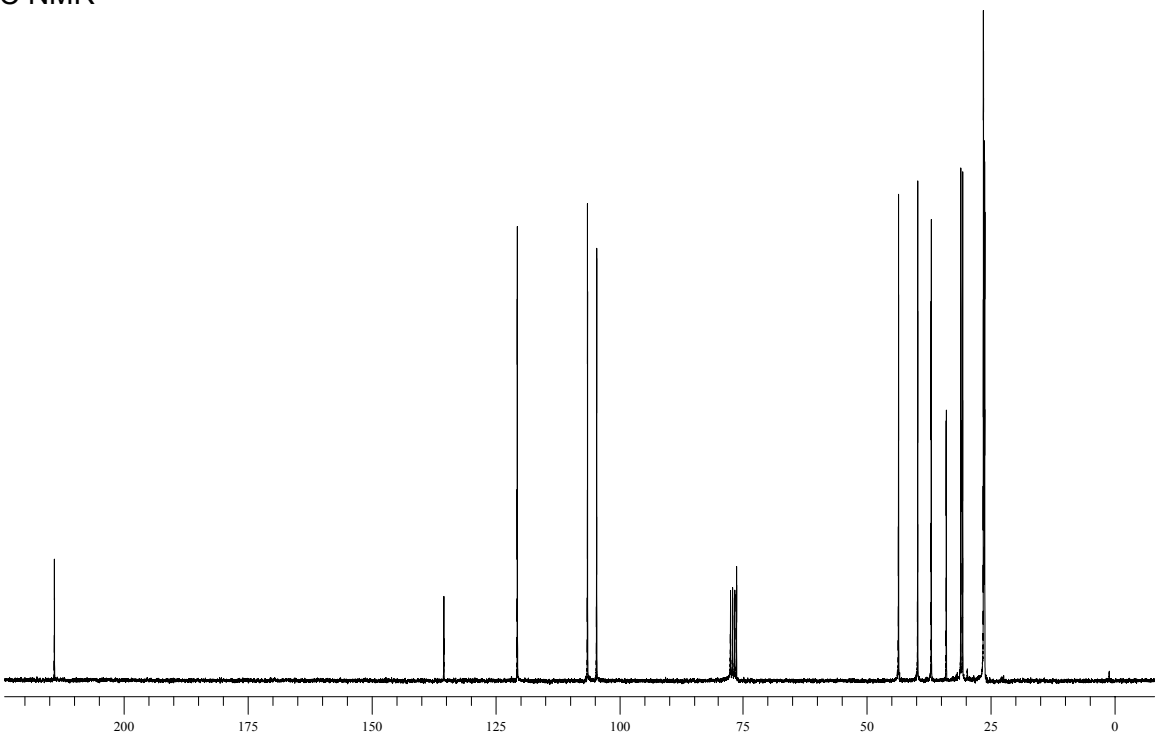


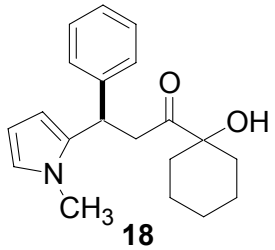
3h

^{1}H NMR



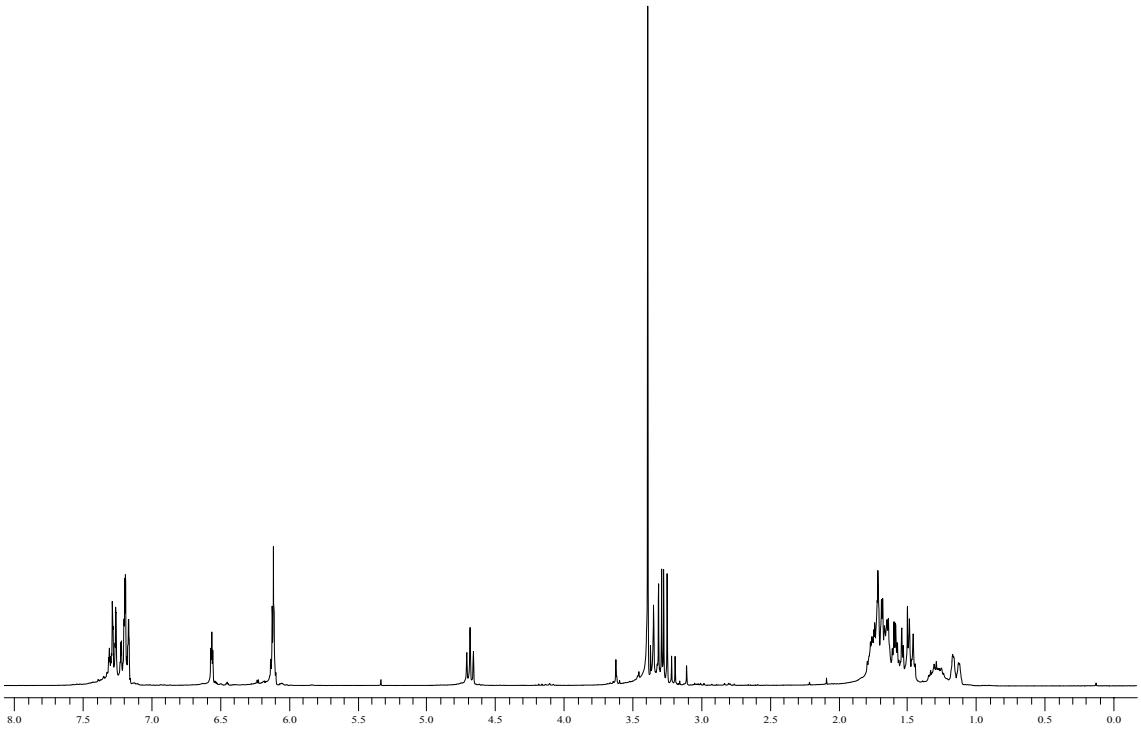
^{13}C NMR



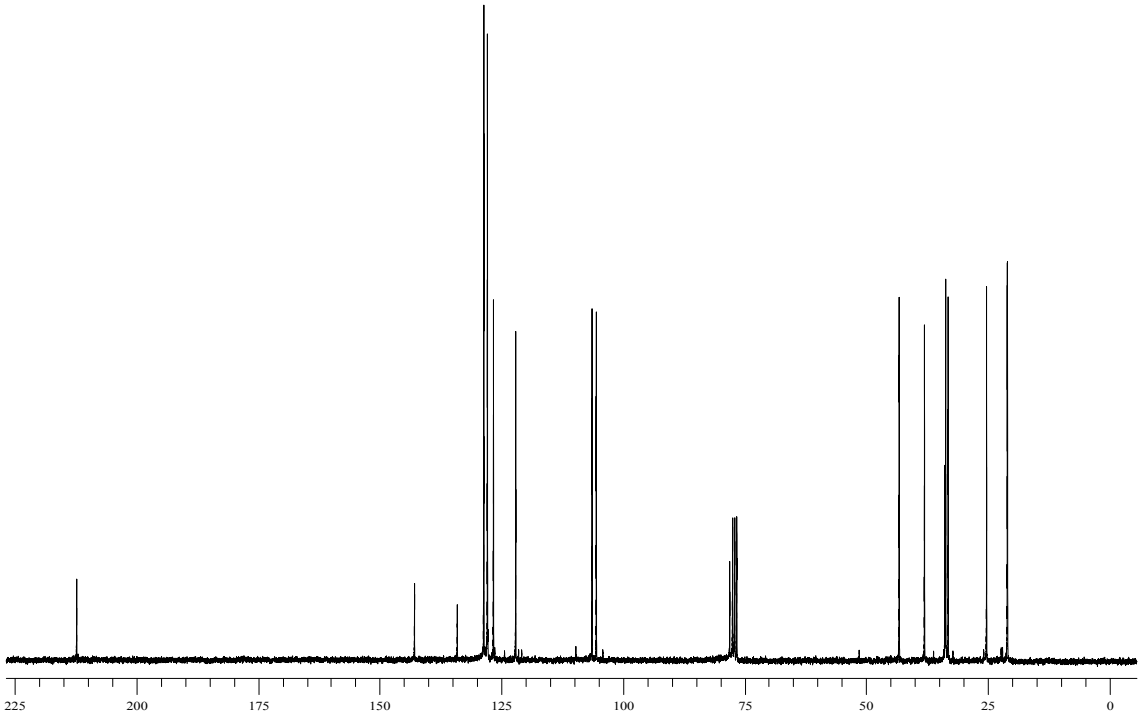


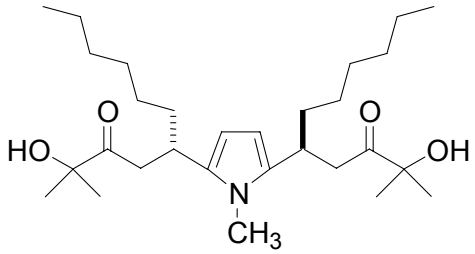
18

^{1}H NMR



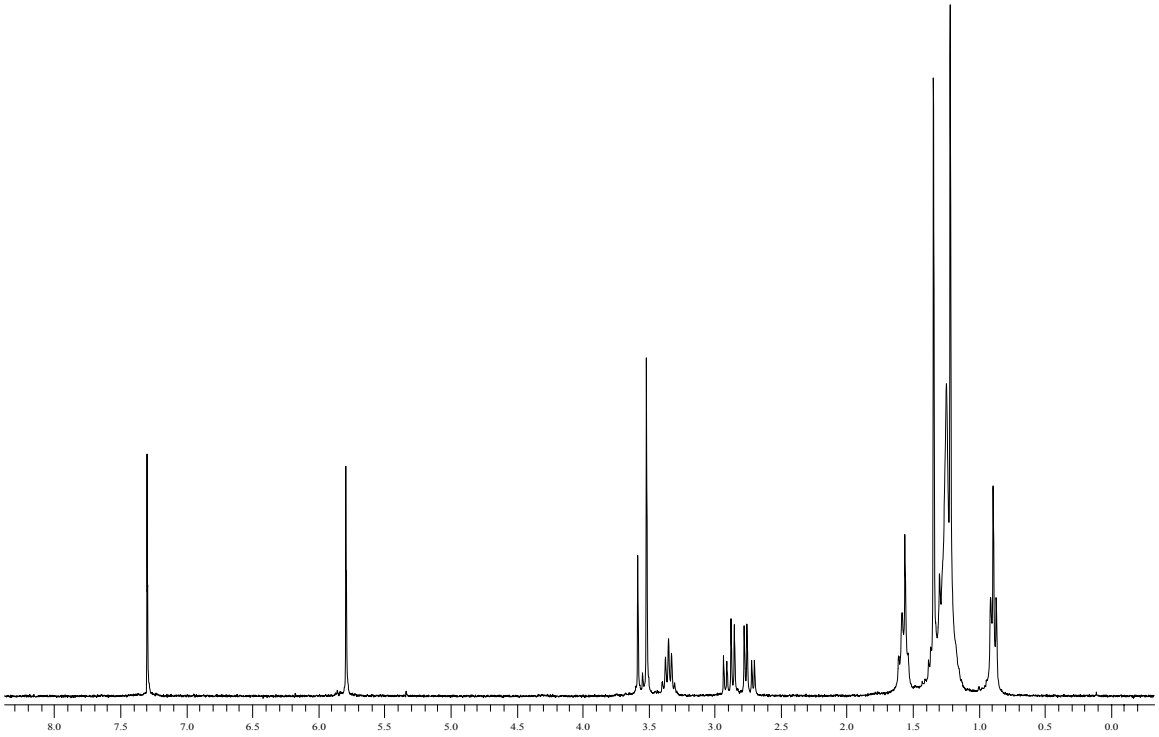
^{13}C NMR



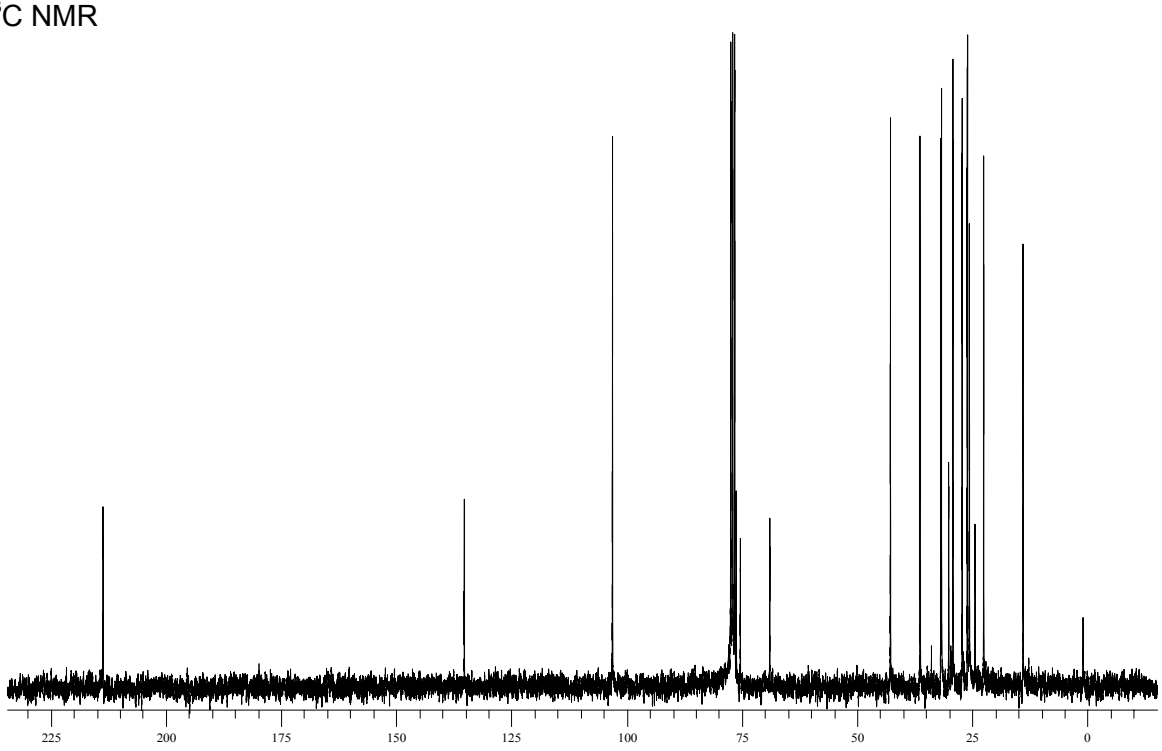


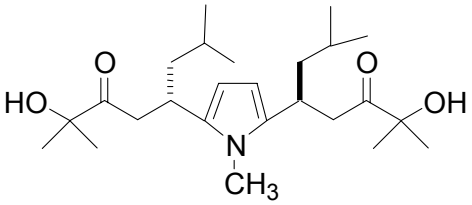
19d

^{1}H NMR



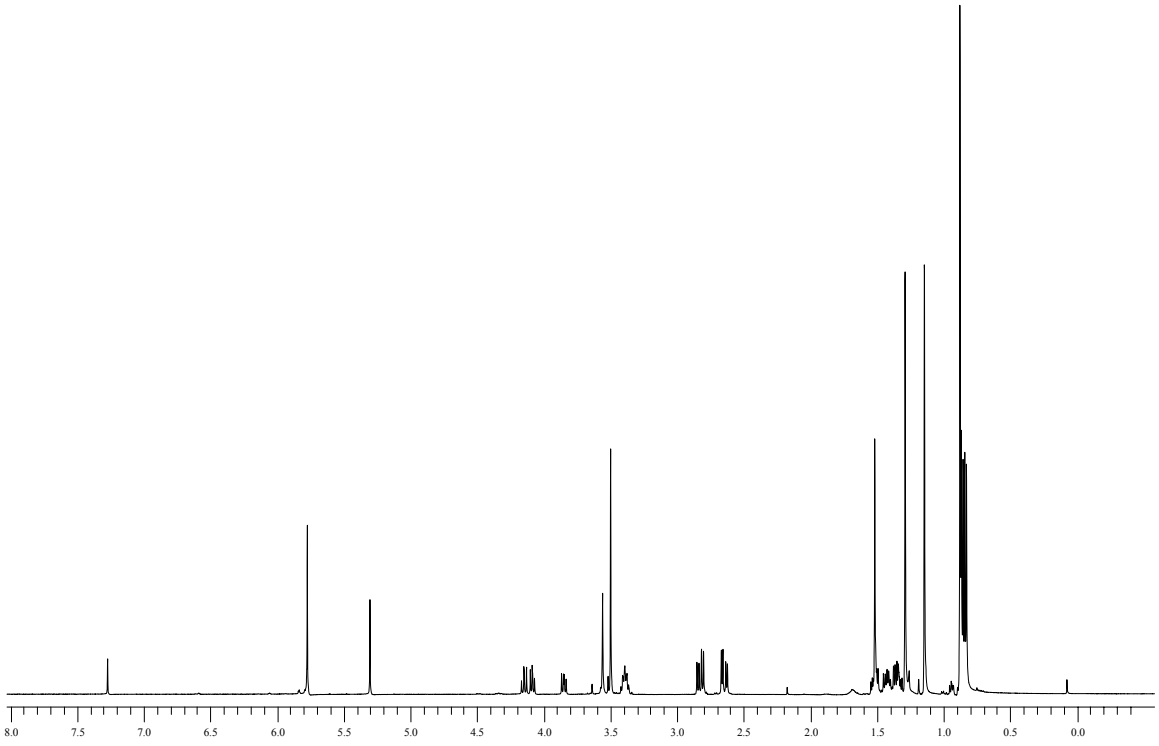
^{13}C NMR



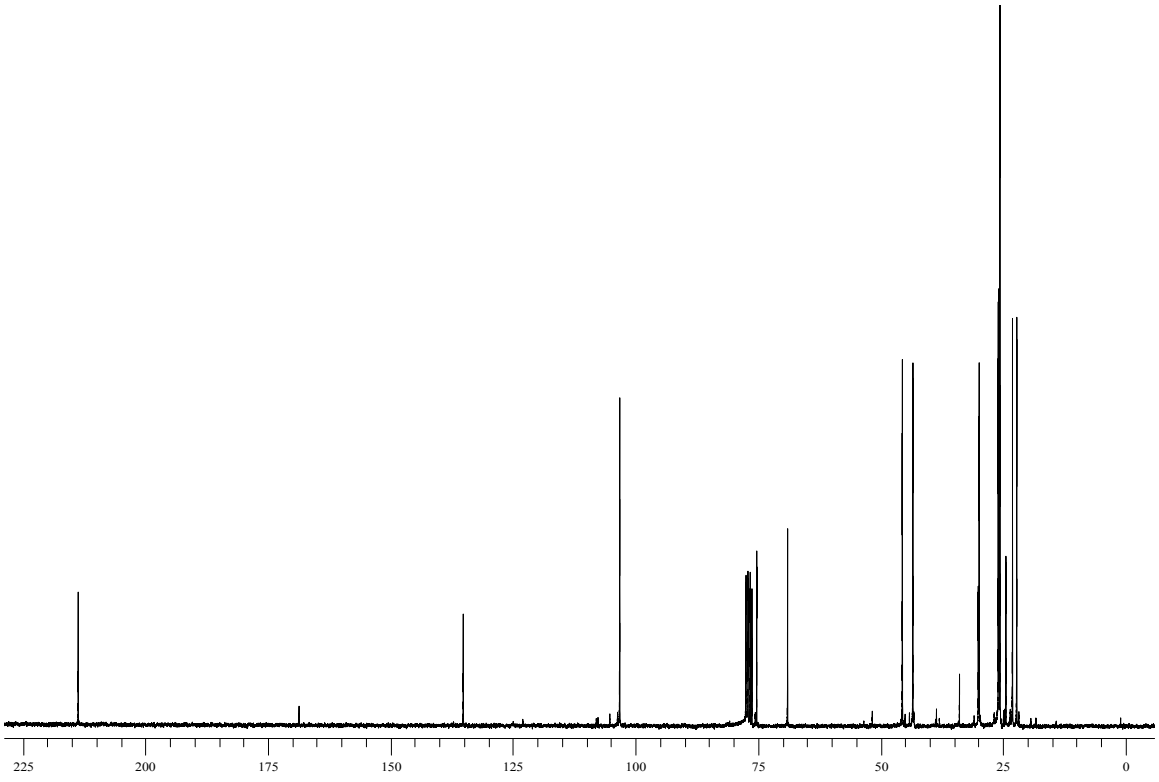


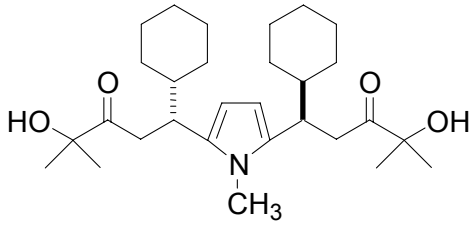
19f

^{1}H NMR



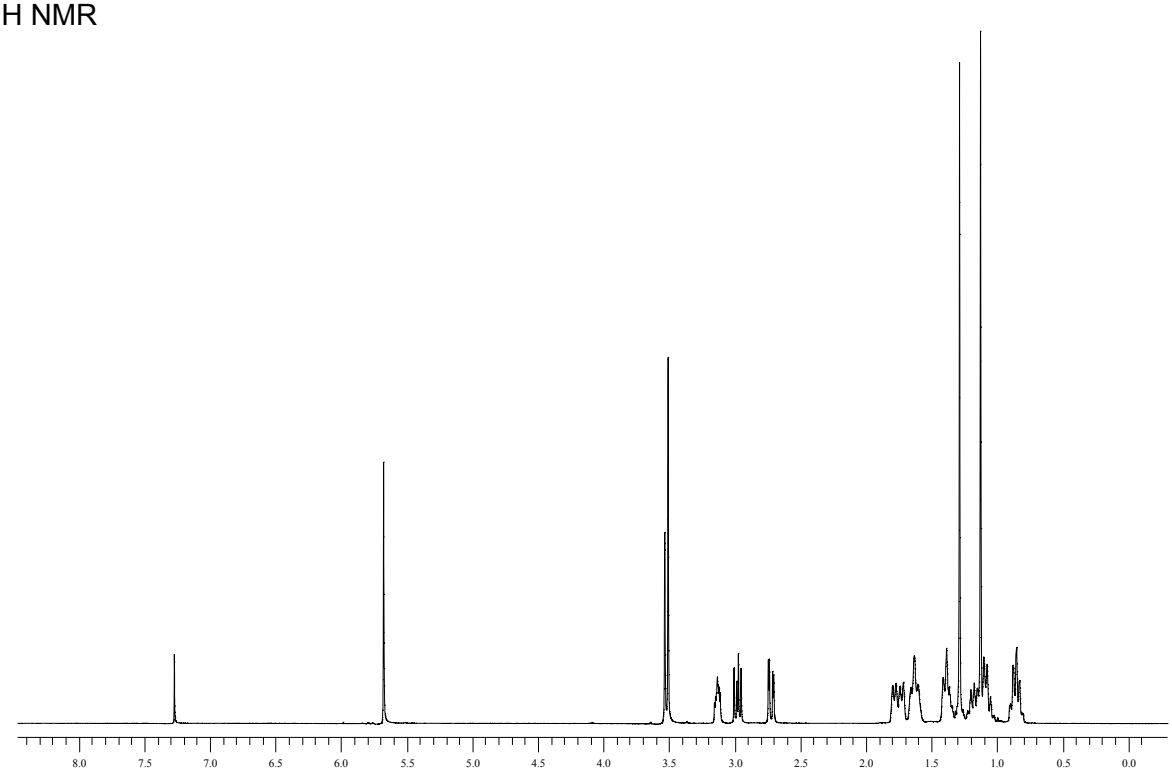
^{13}C NMR



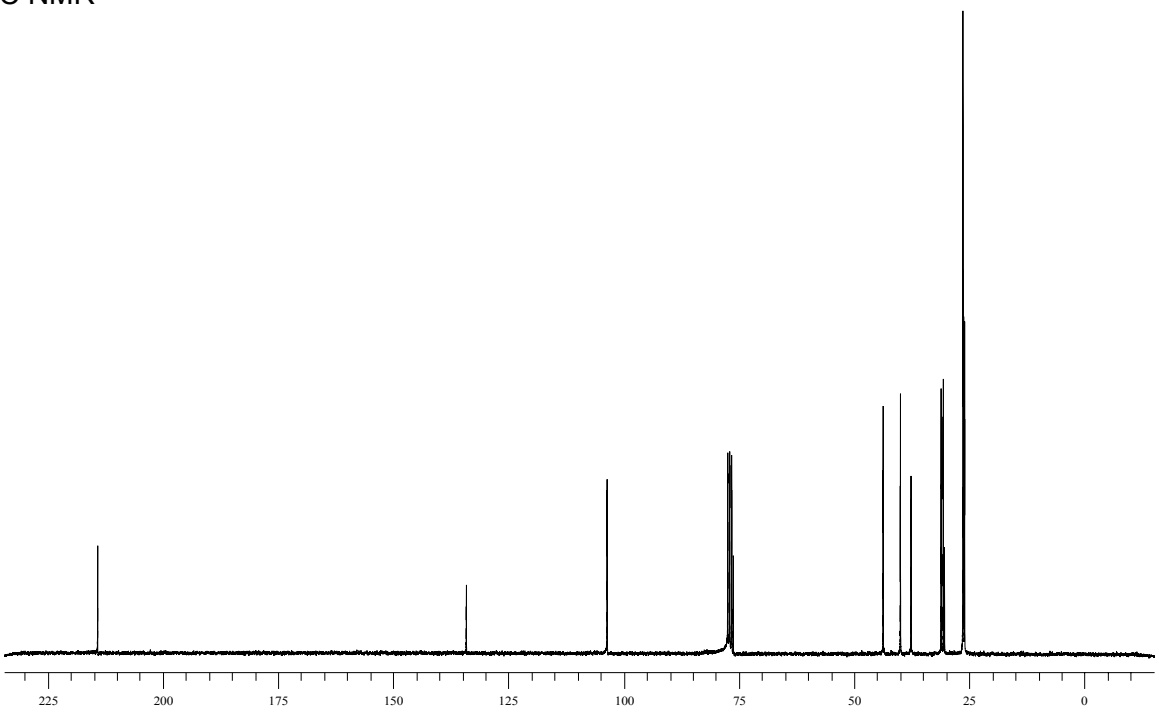


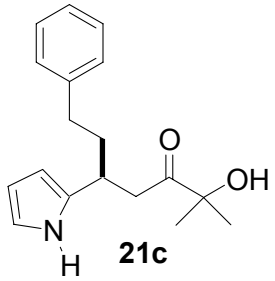
19h

^{1}H NMR



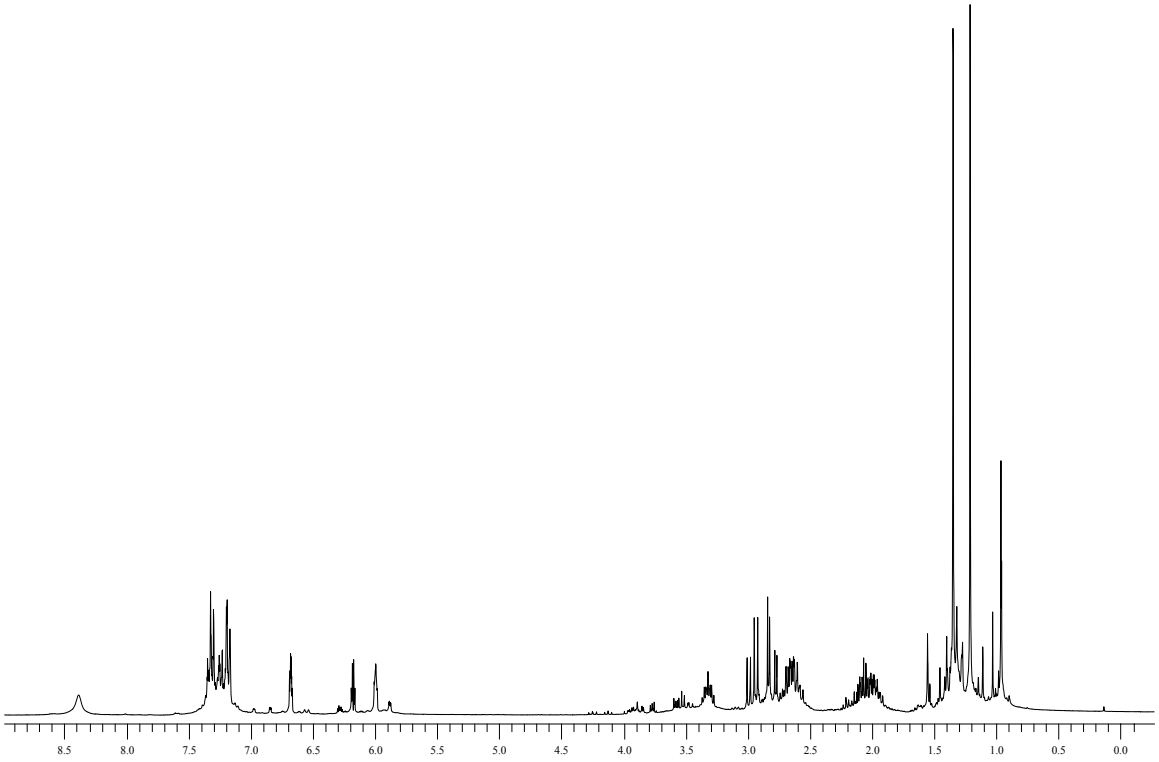
^{13}C NMR



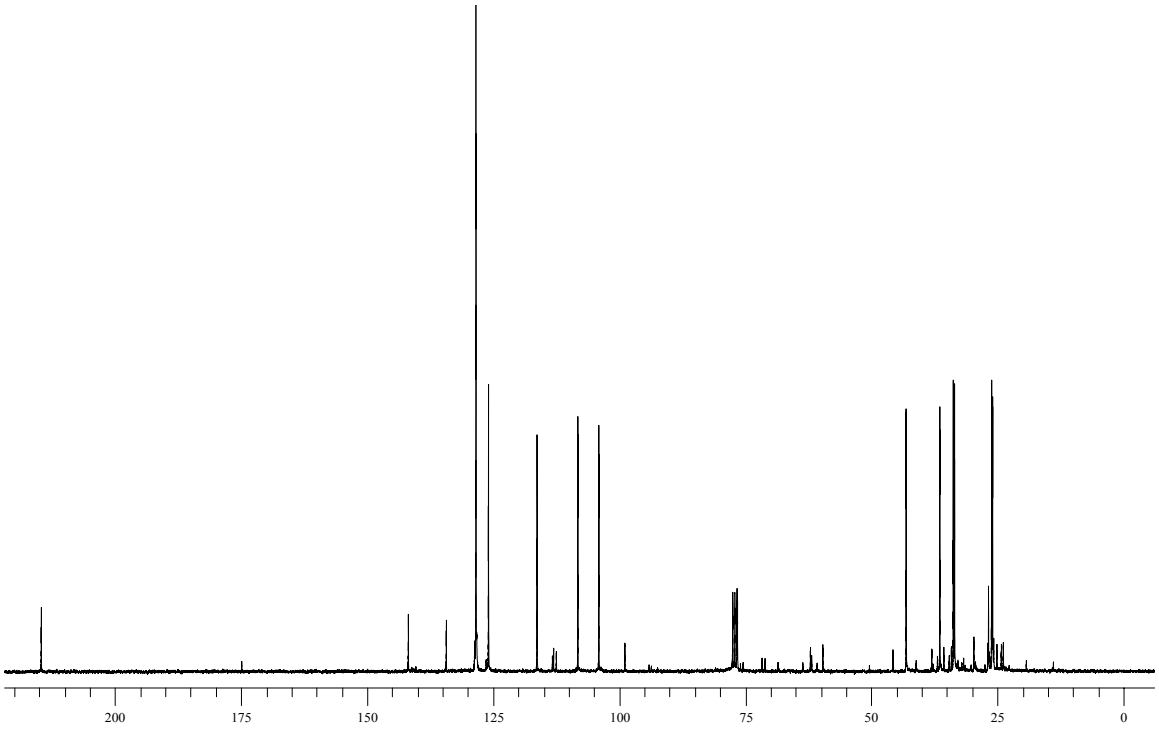


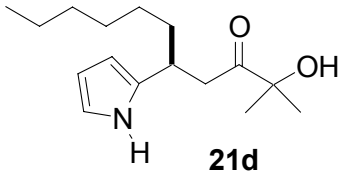
21c

^{1}H NMR



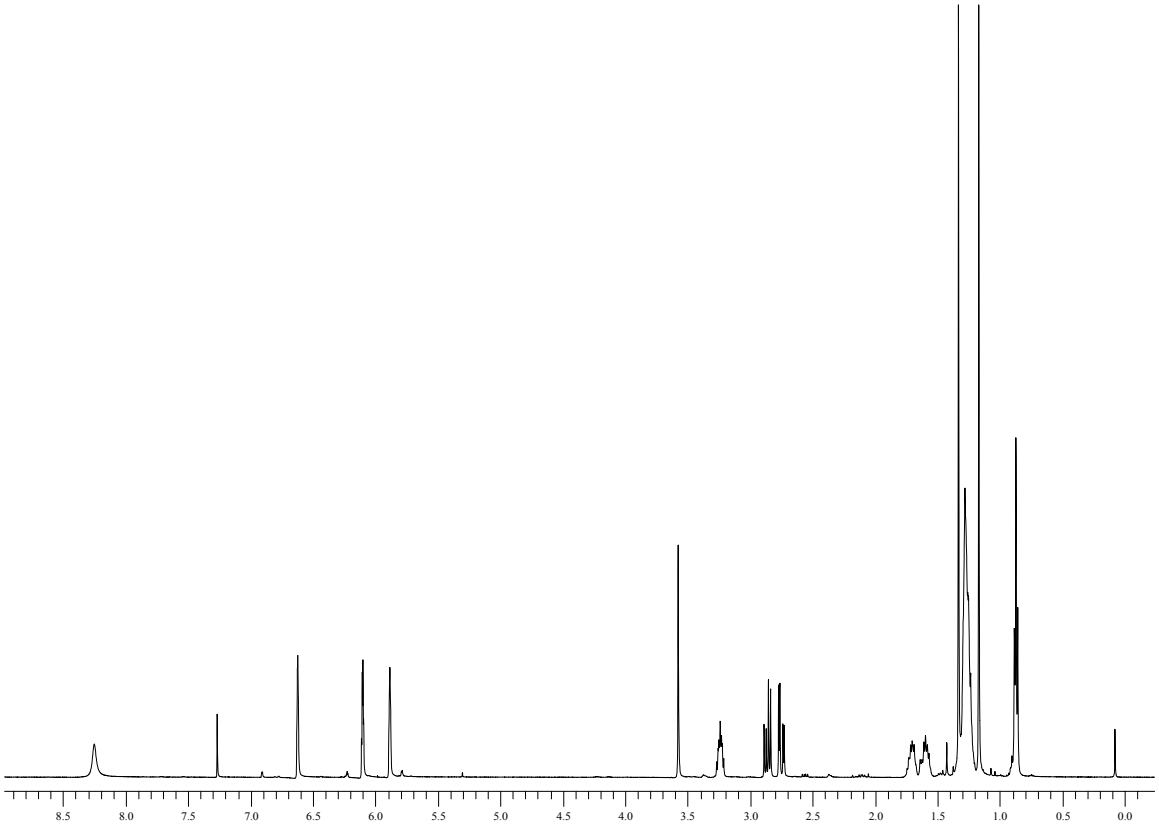
^{13}C NMR



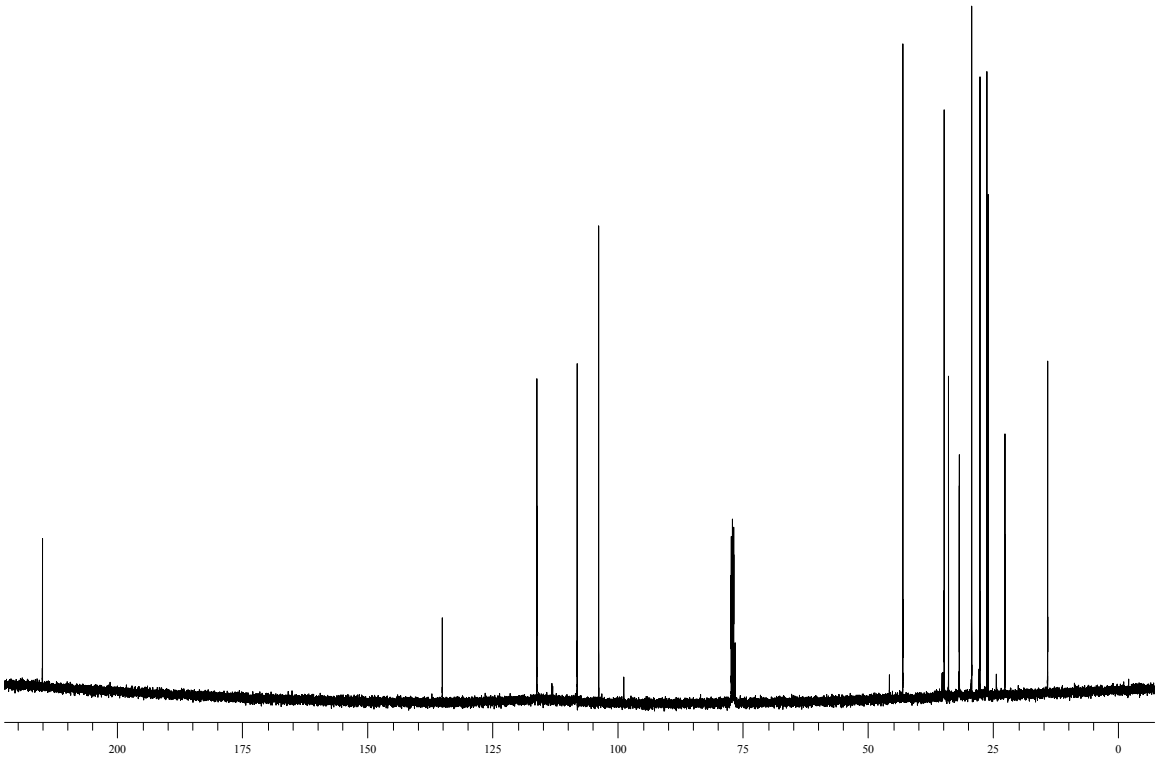


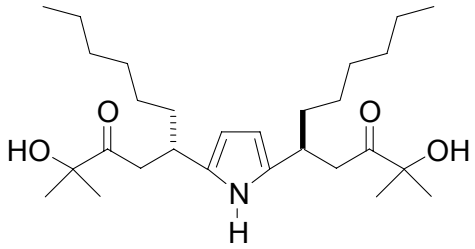
21d

^{1}H NMR



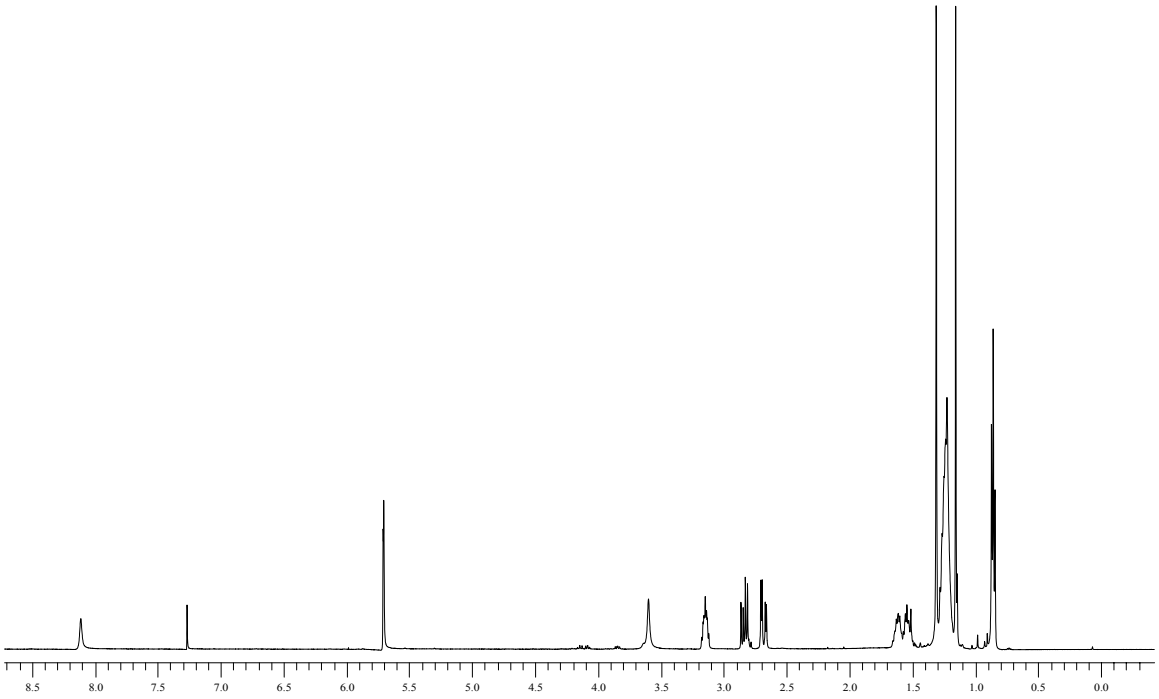
^{13}C NMR



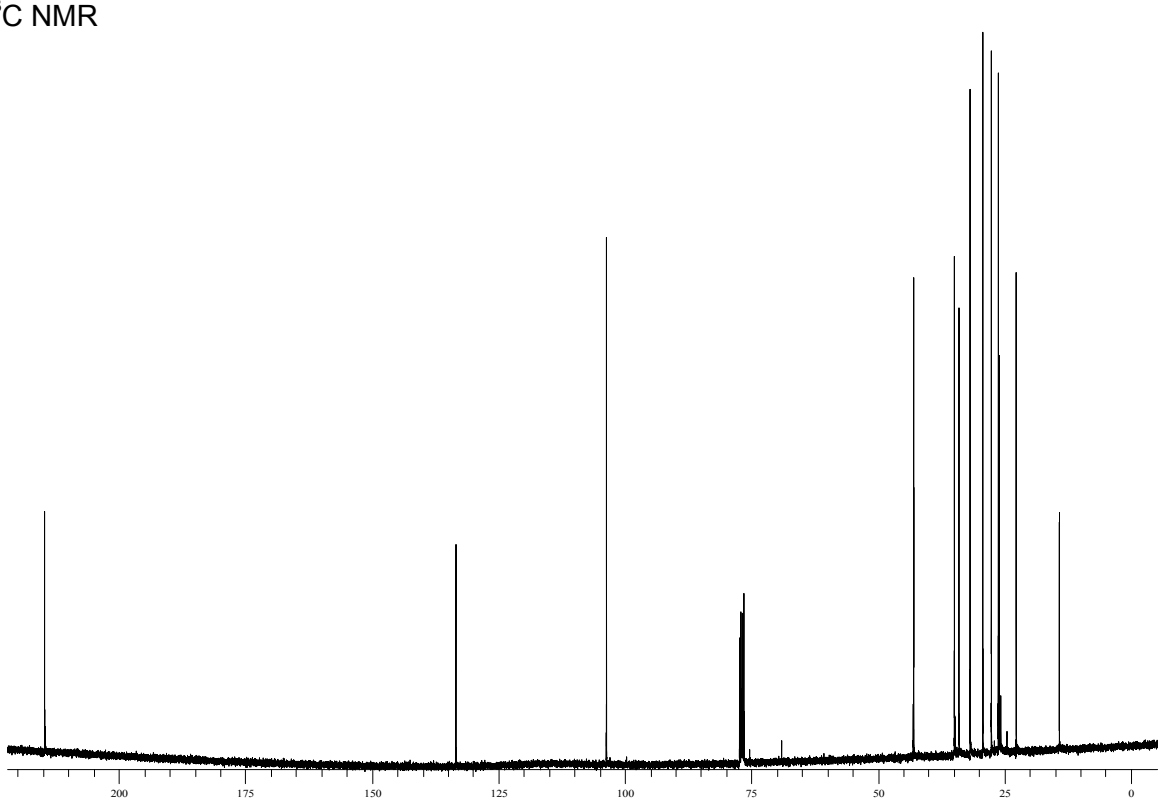


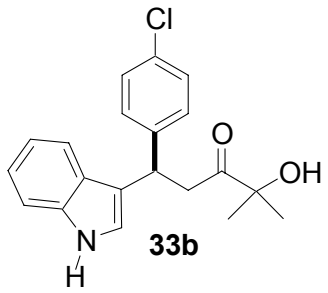
22d

^{1}H NMR



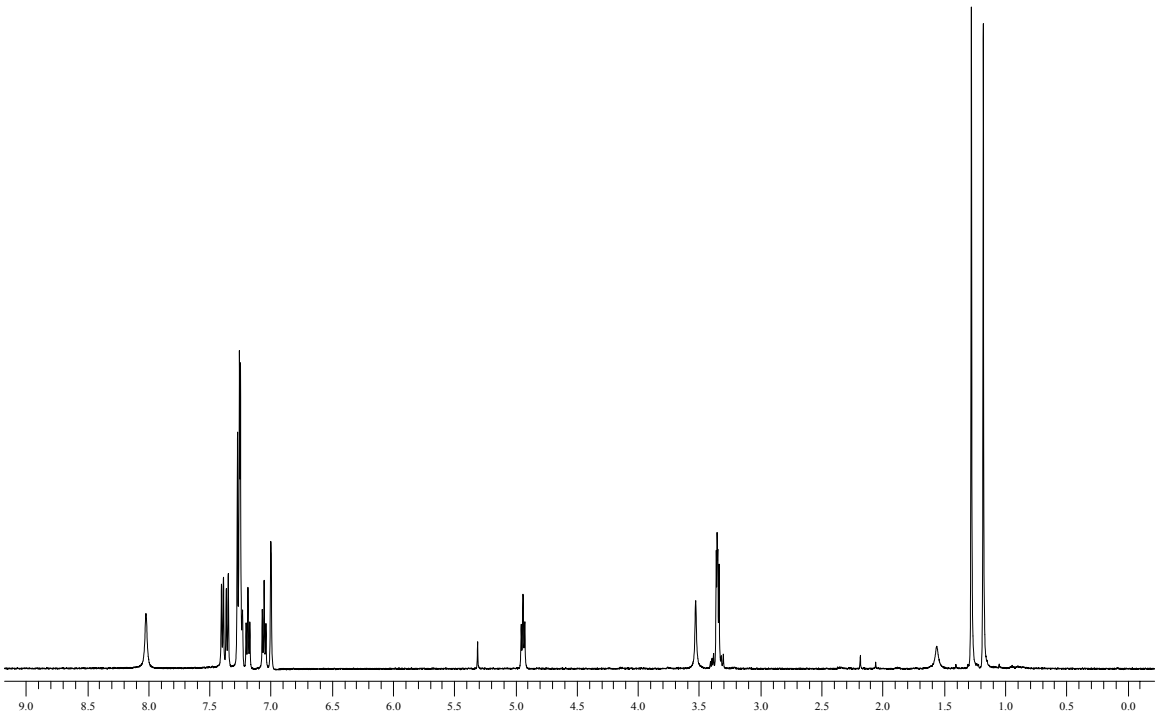
^{13}C NMR



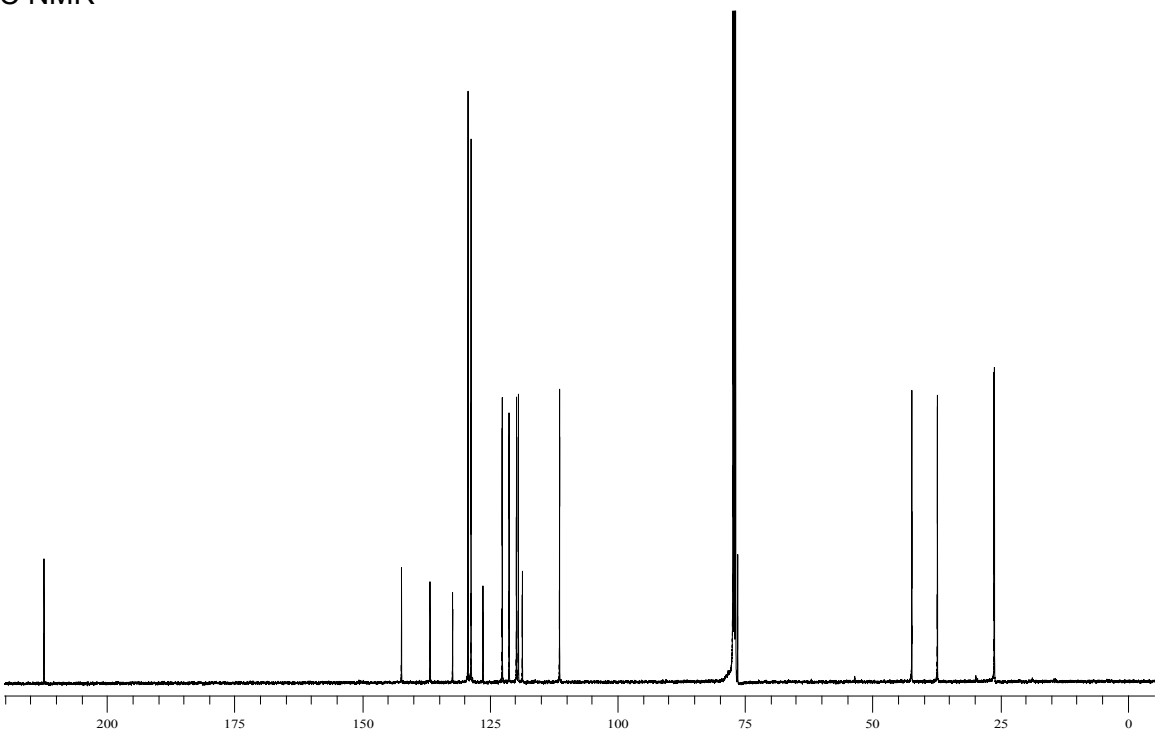


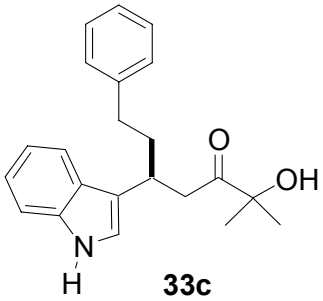
33b

^{1}H NMR



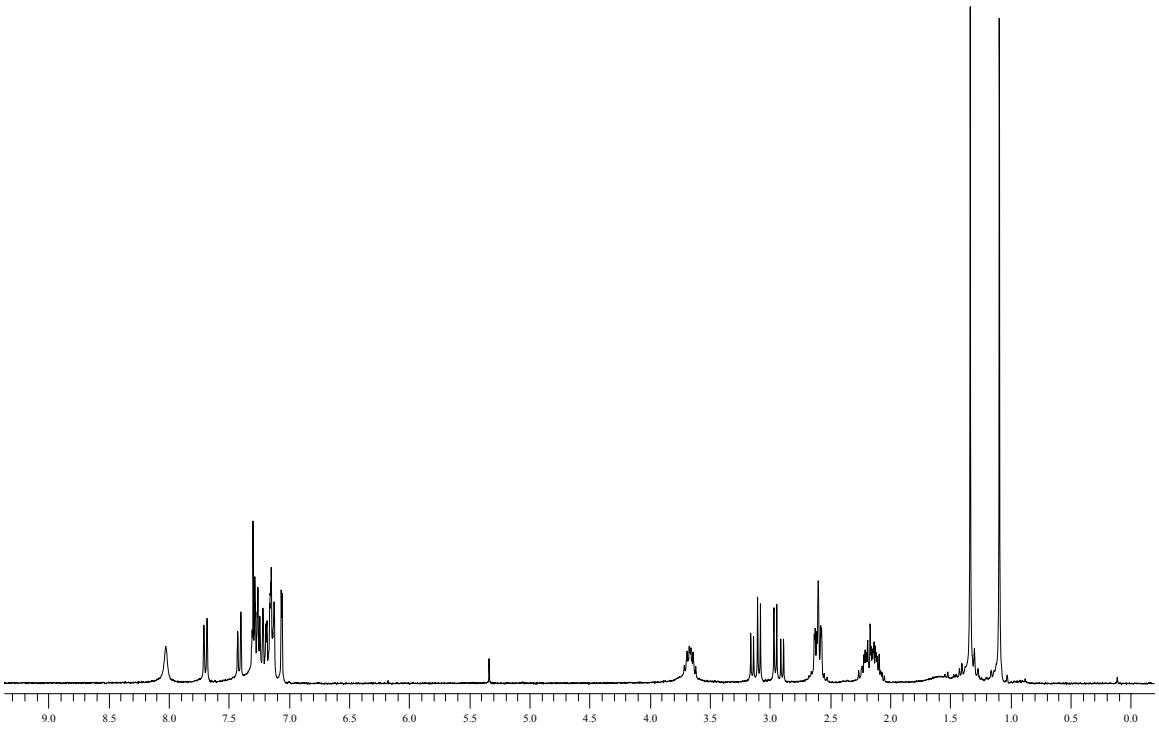
^{13}C NMR



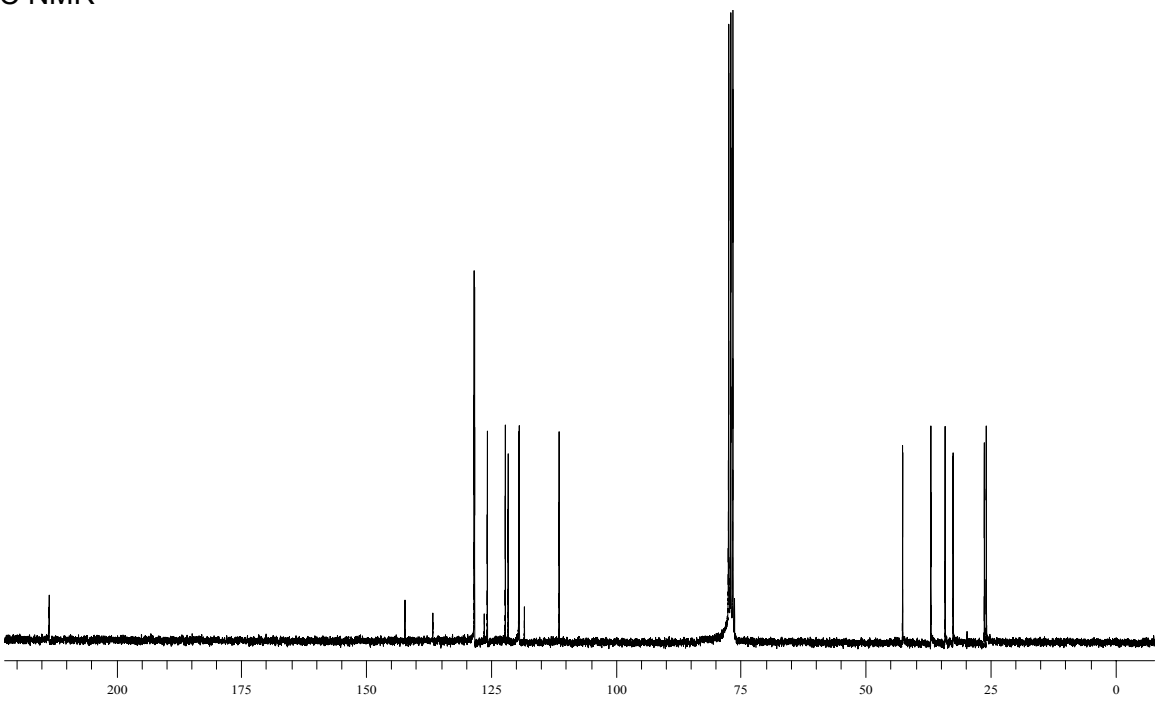


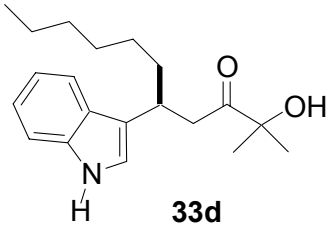
33c

^{1}H NMR



^{13}C NMR





33d

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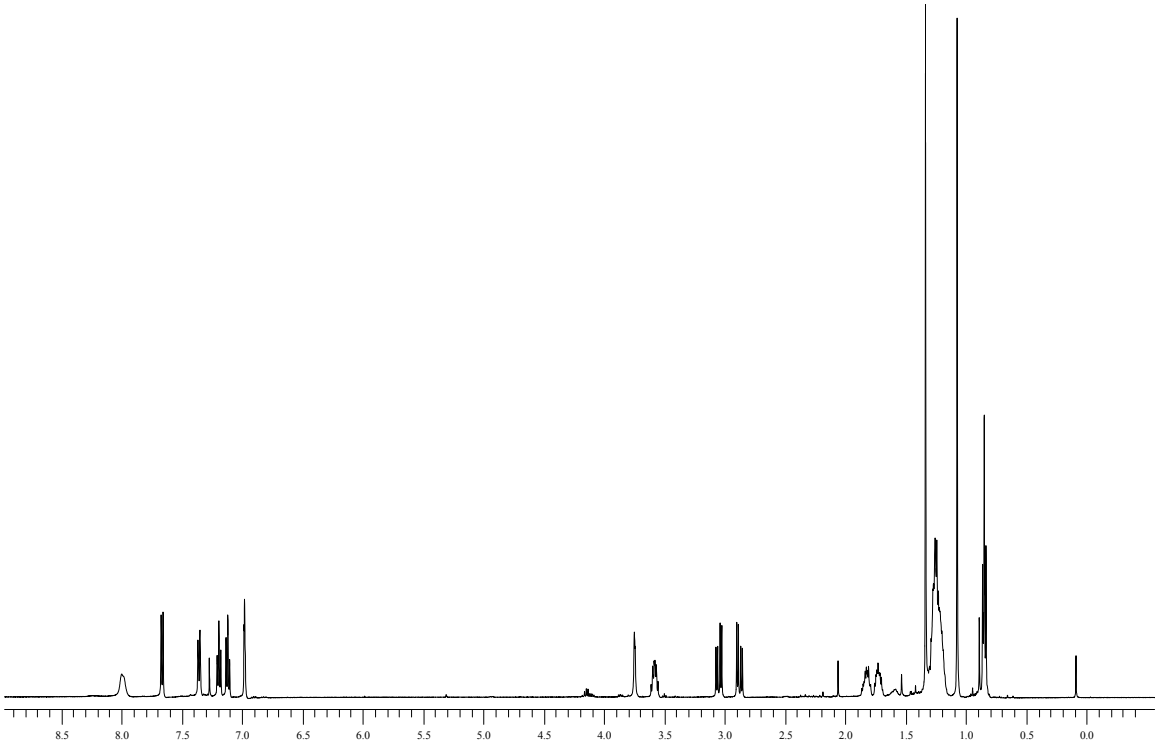
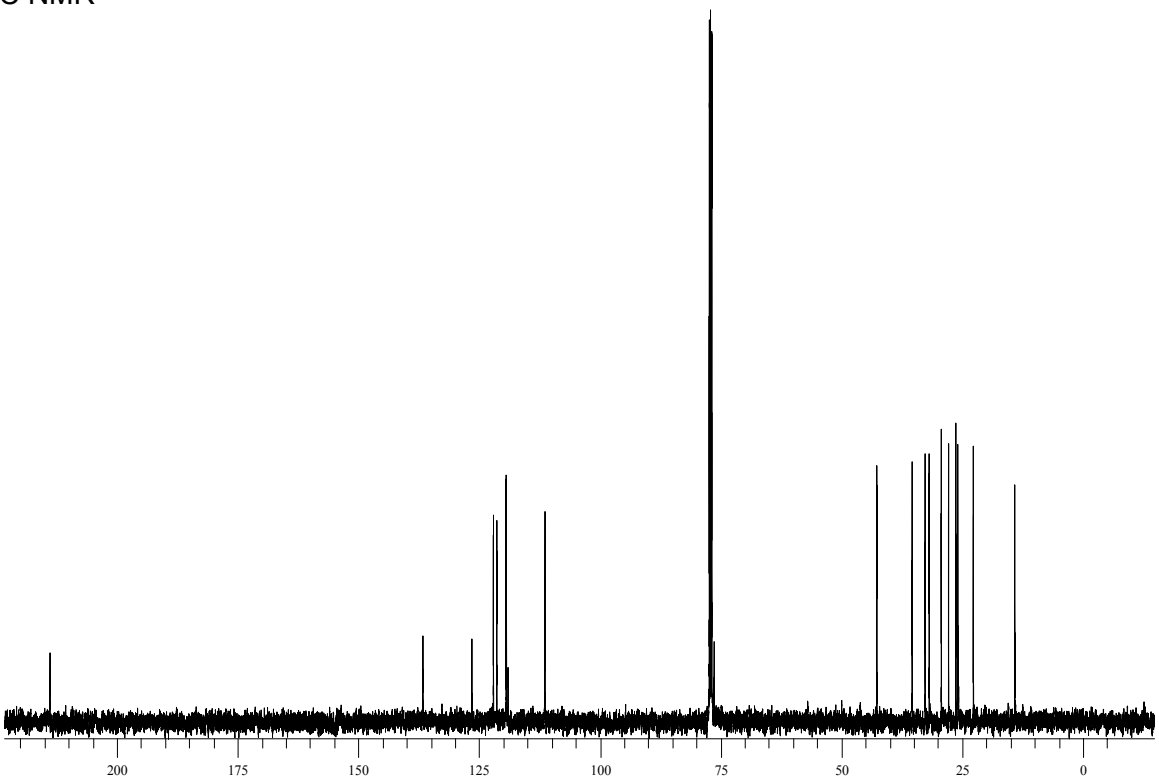
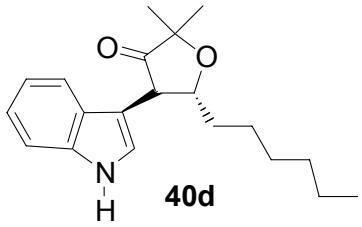


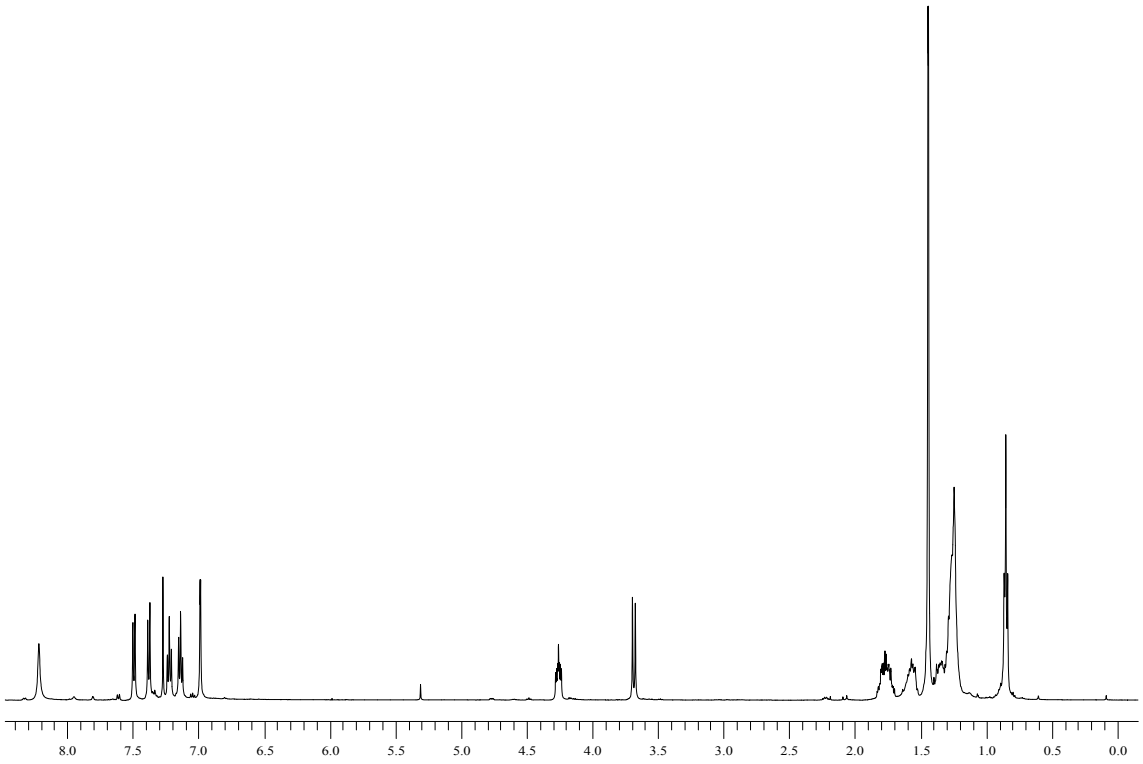
^{13}C NMR



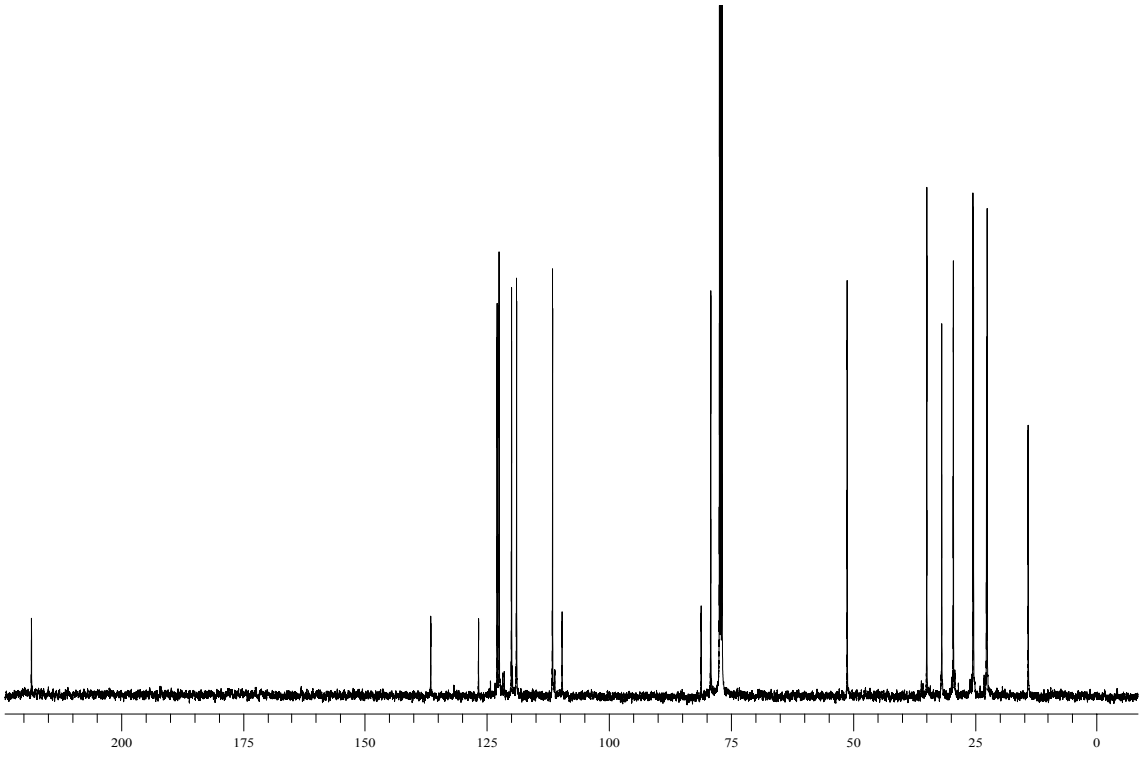


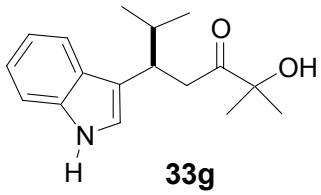
40d

^{1}H NMR



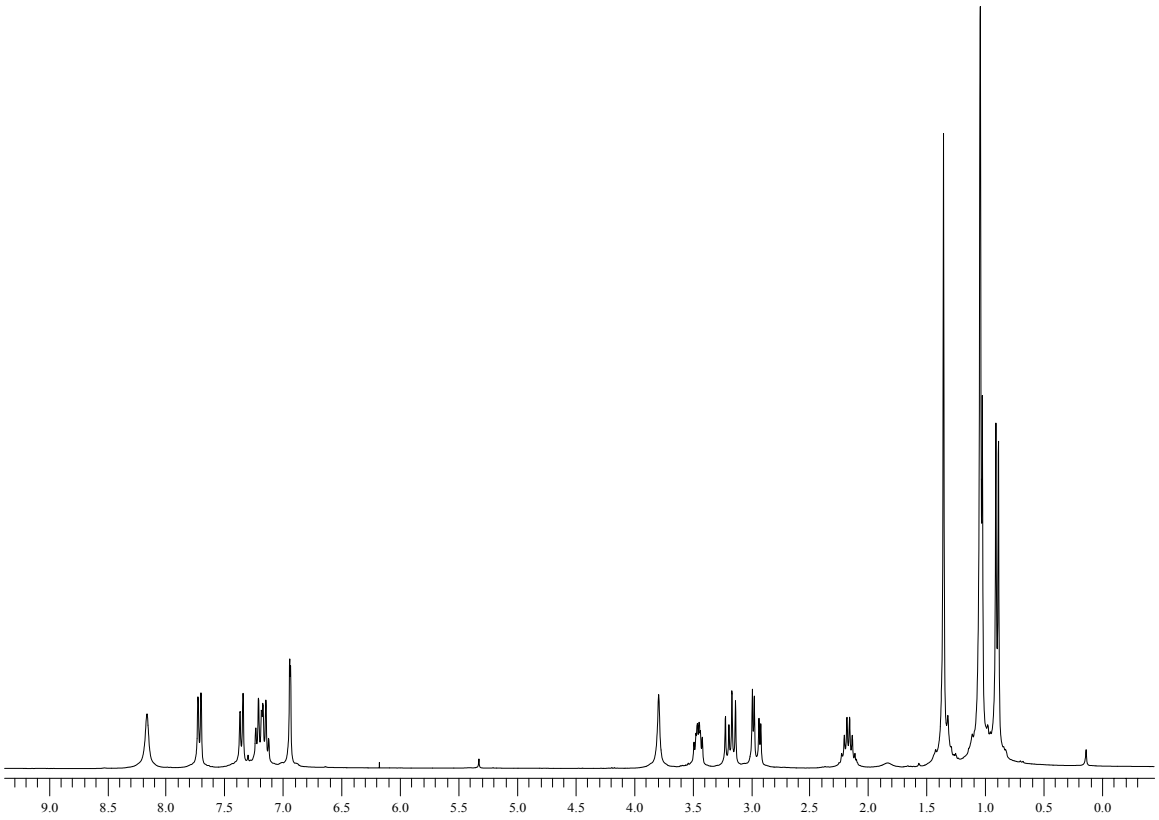
^{13}C NMR





33g

^{1}H NMR



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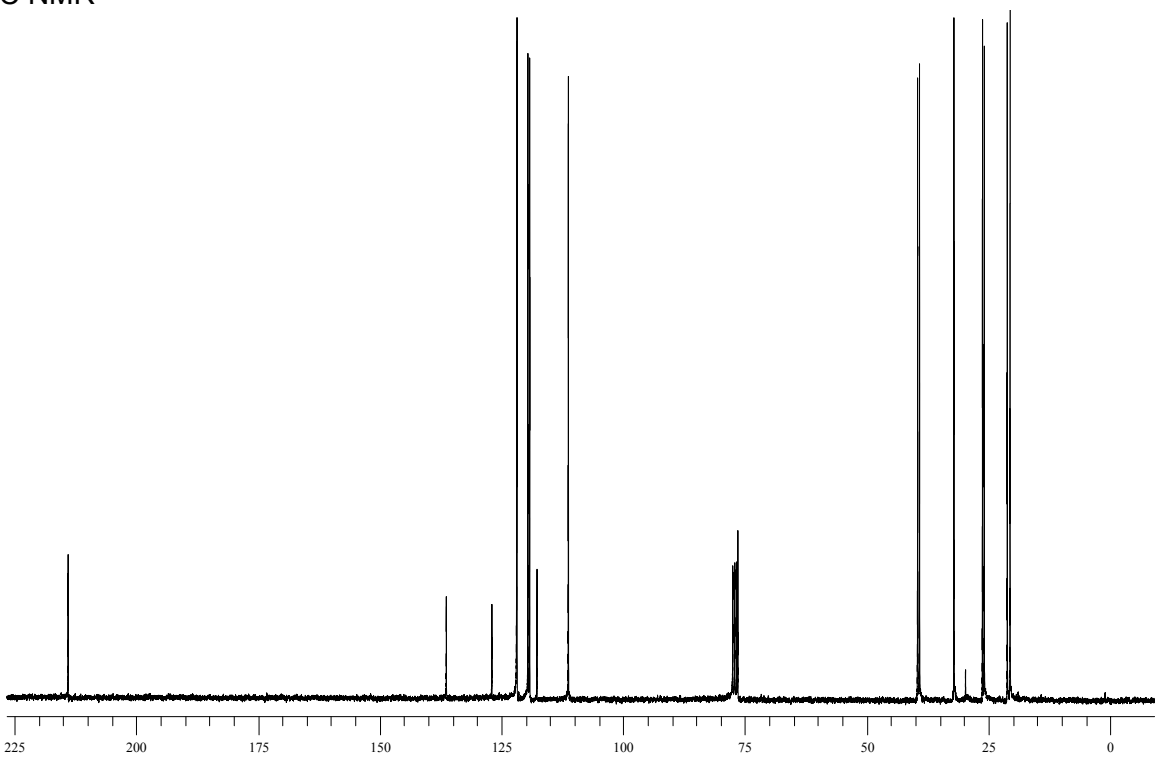
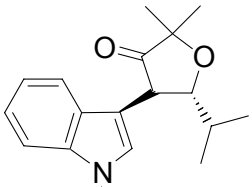
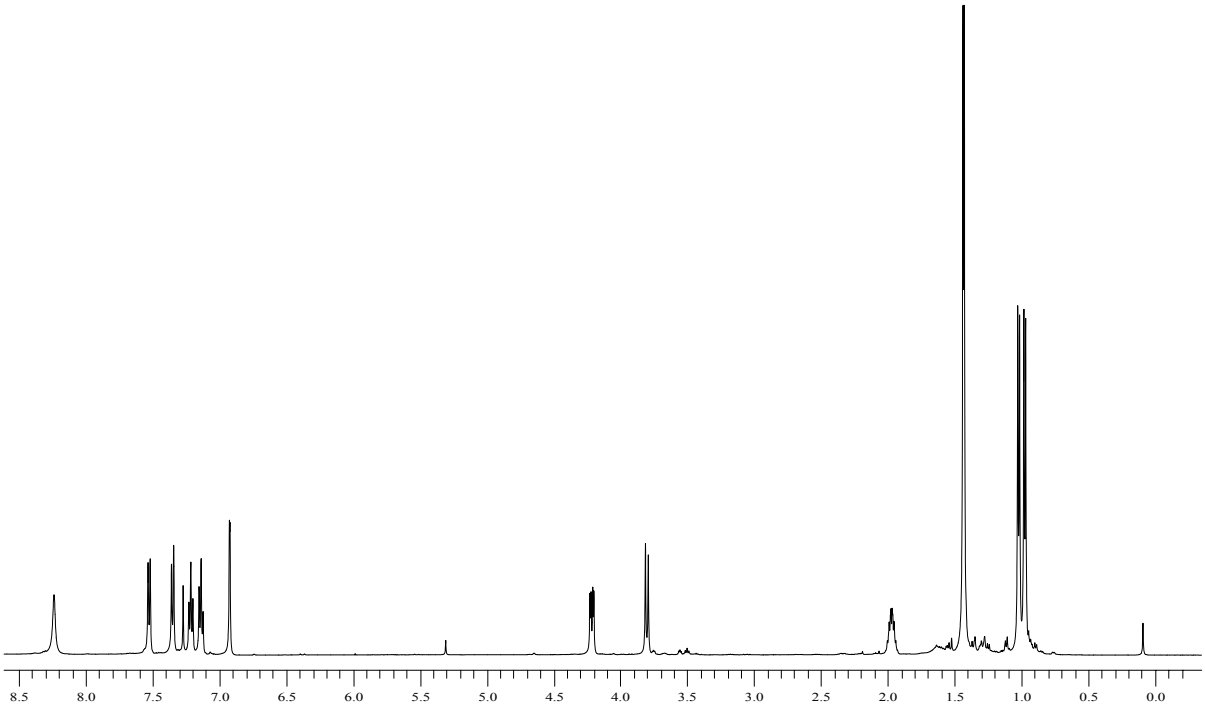


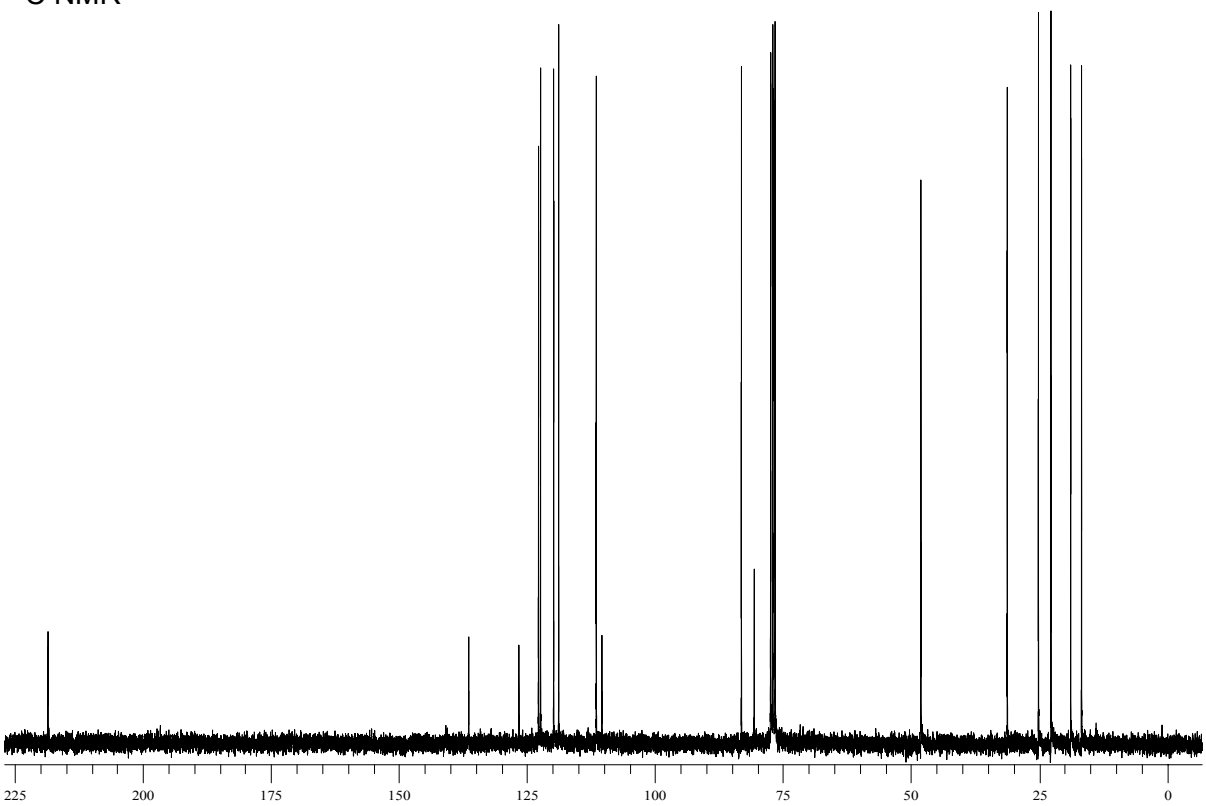


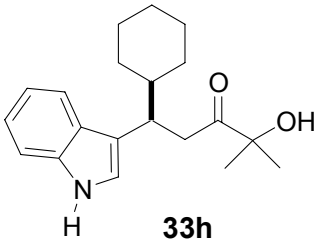
40g

^{1}H NMR



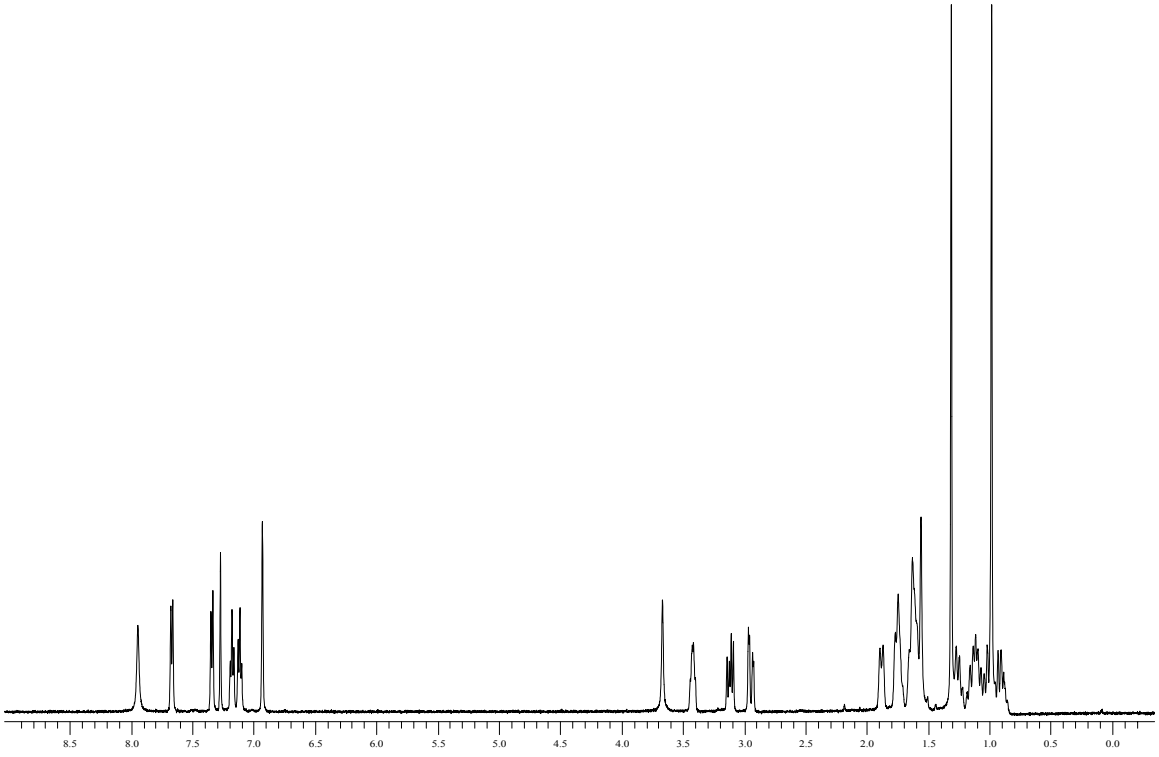
^{13}C NMR



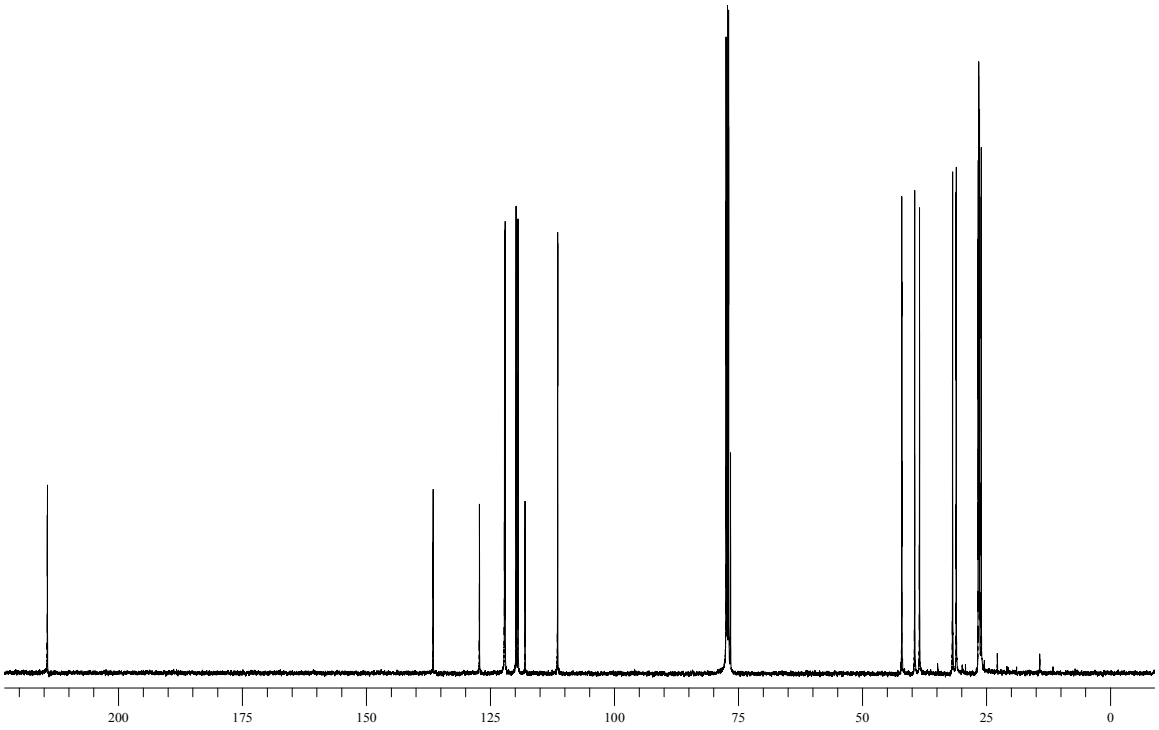


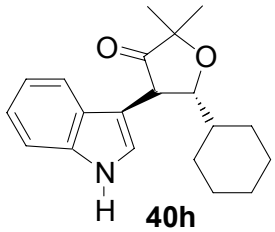
33h

^{1}H NMR



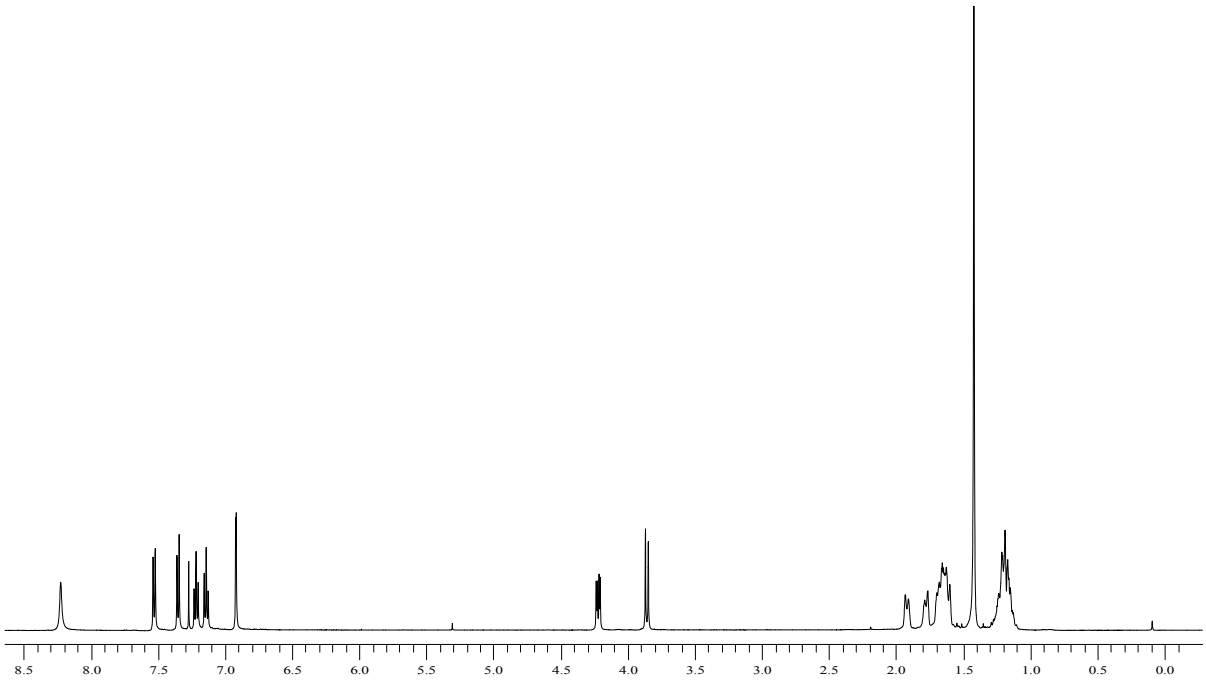
^{13}C NMR



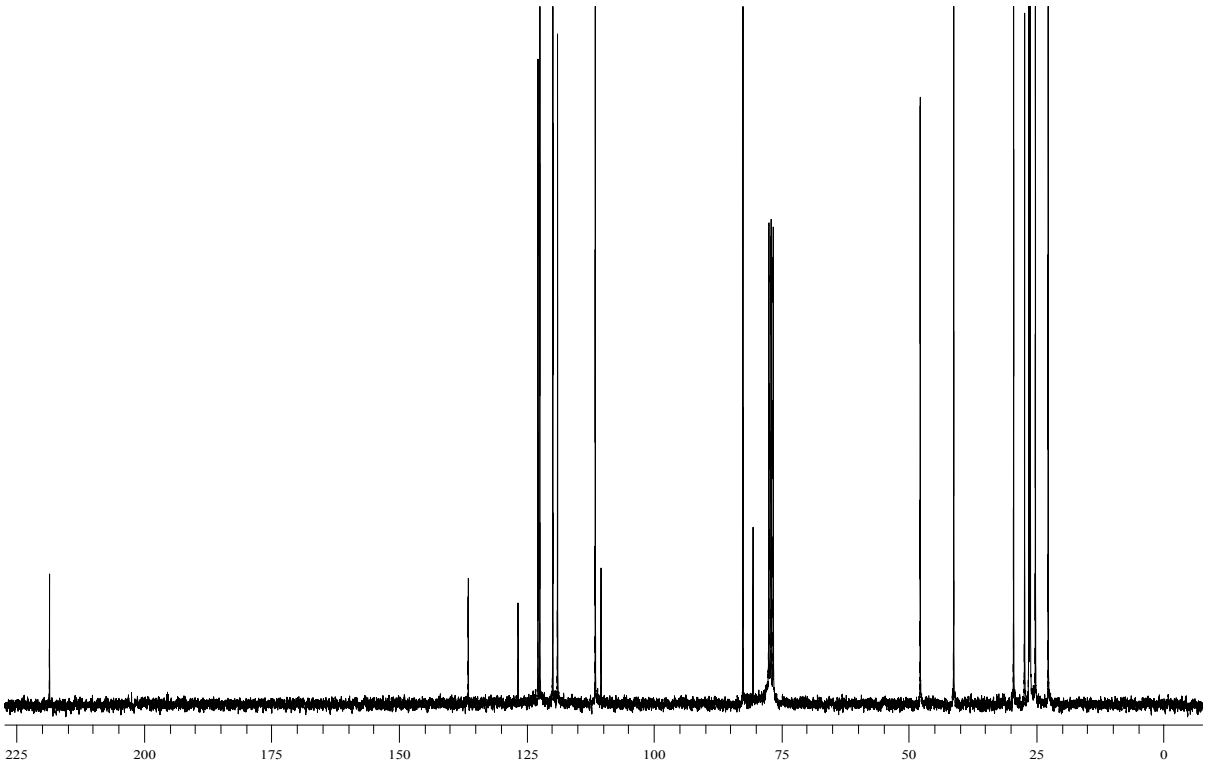


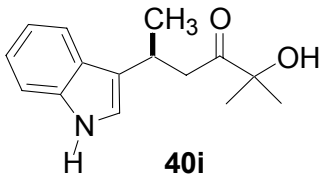
40h

^{1}H NMR



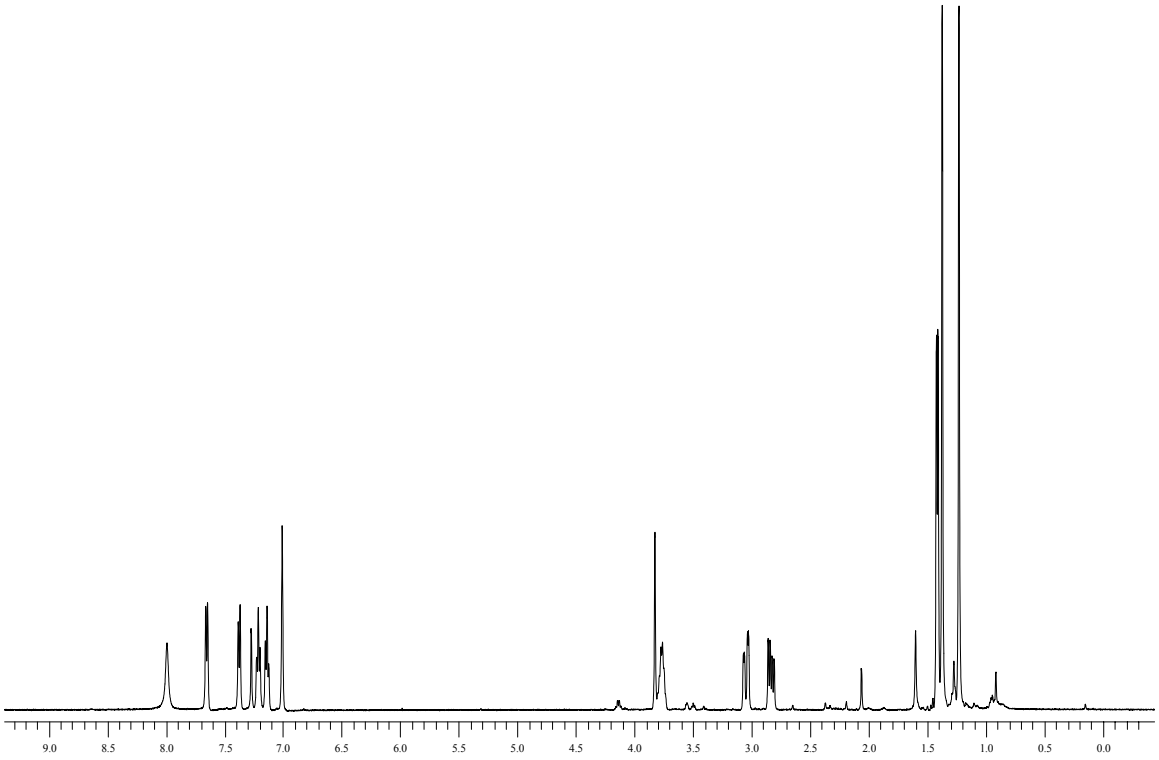
^{13}C NMR



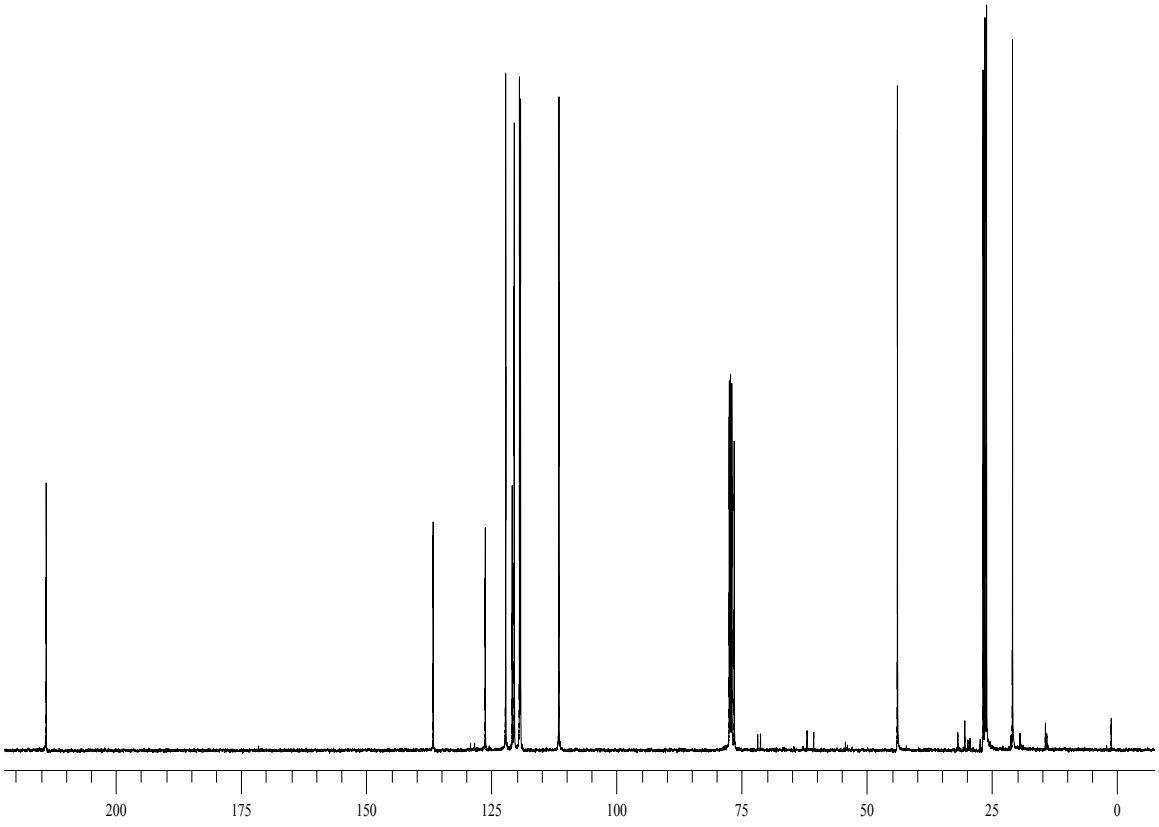


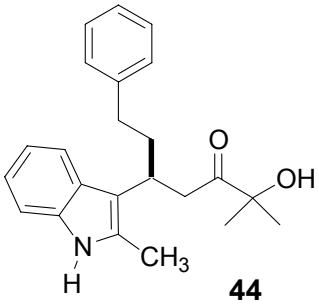
40i

^{1}H NMR



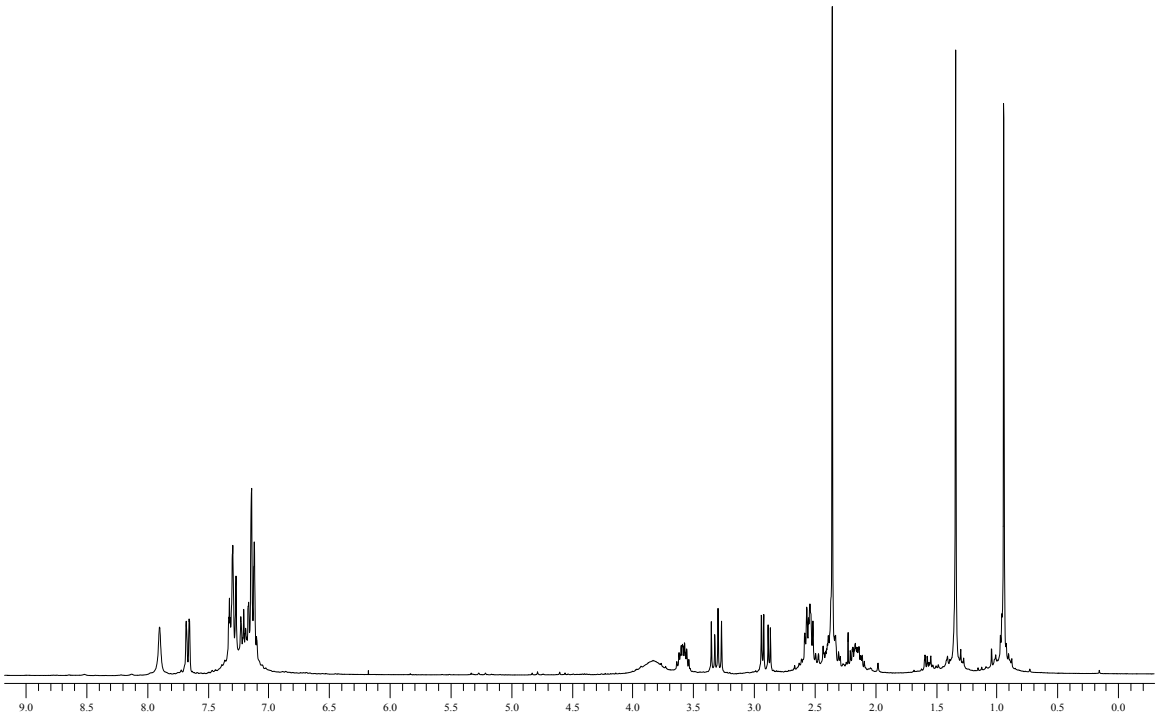
^{13}C NMR



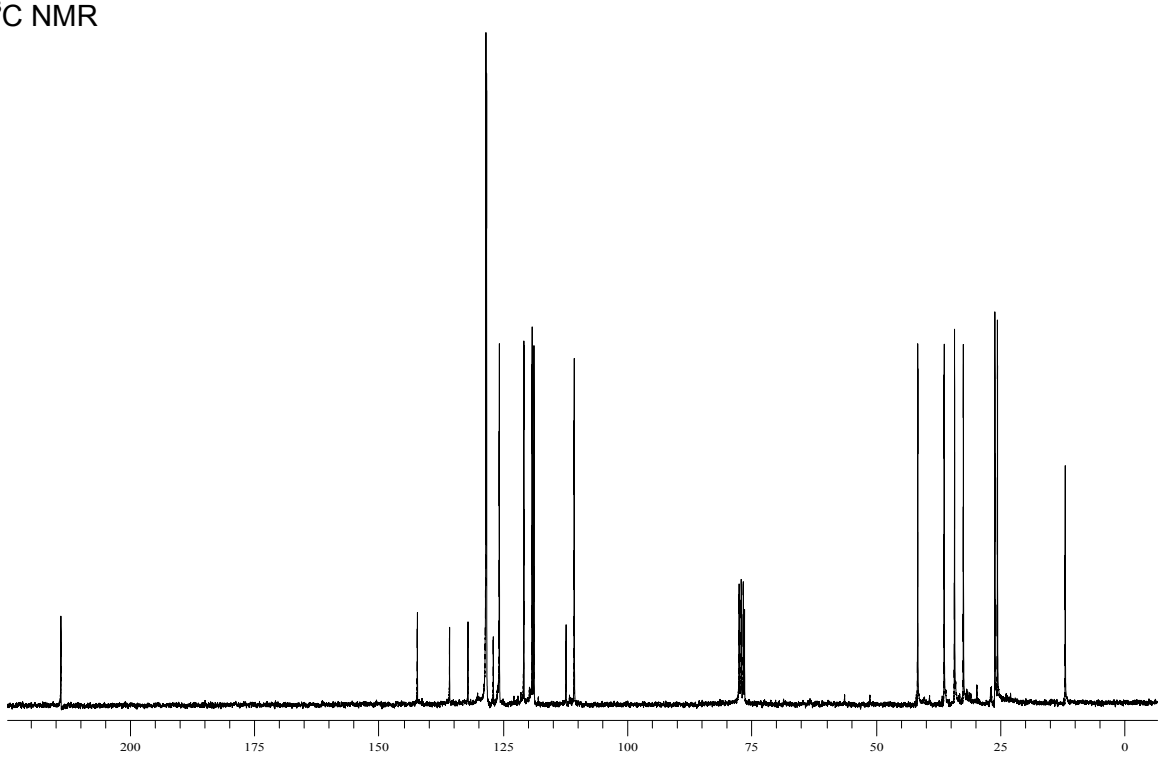


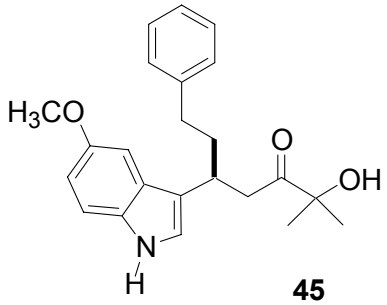
44

^{1}H NMR



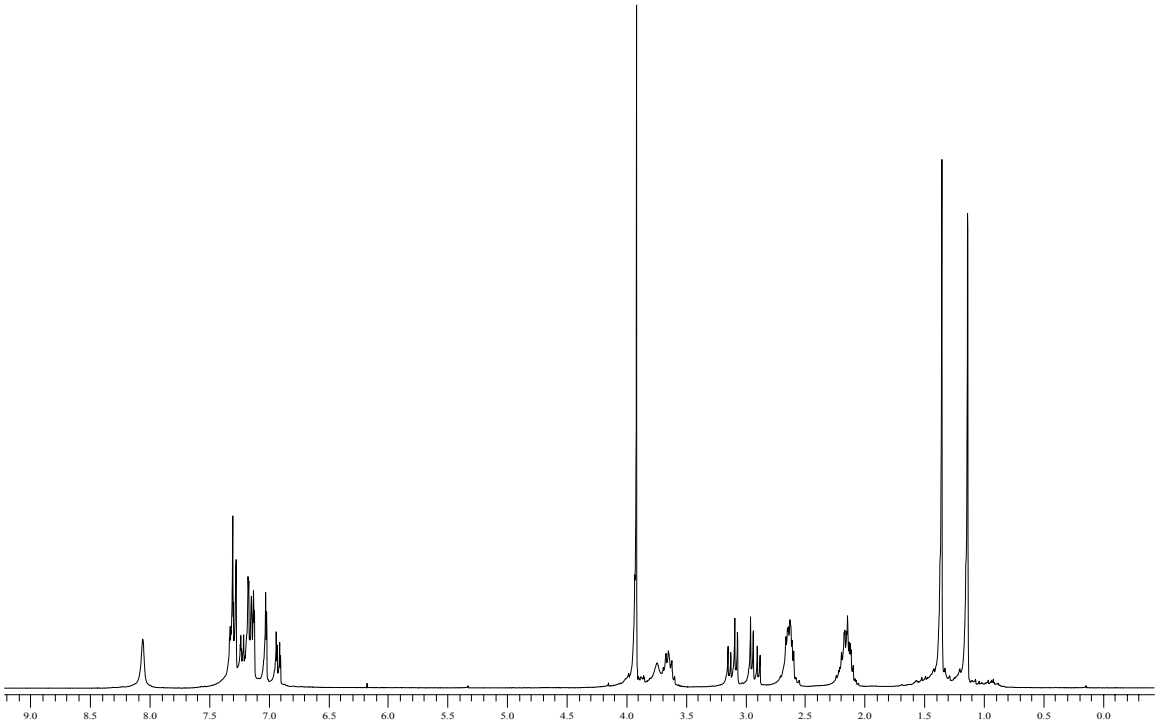
^{13}C NMR



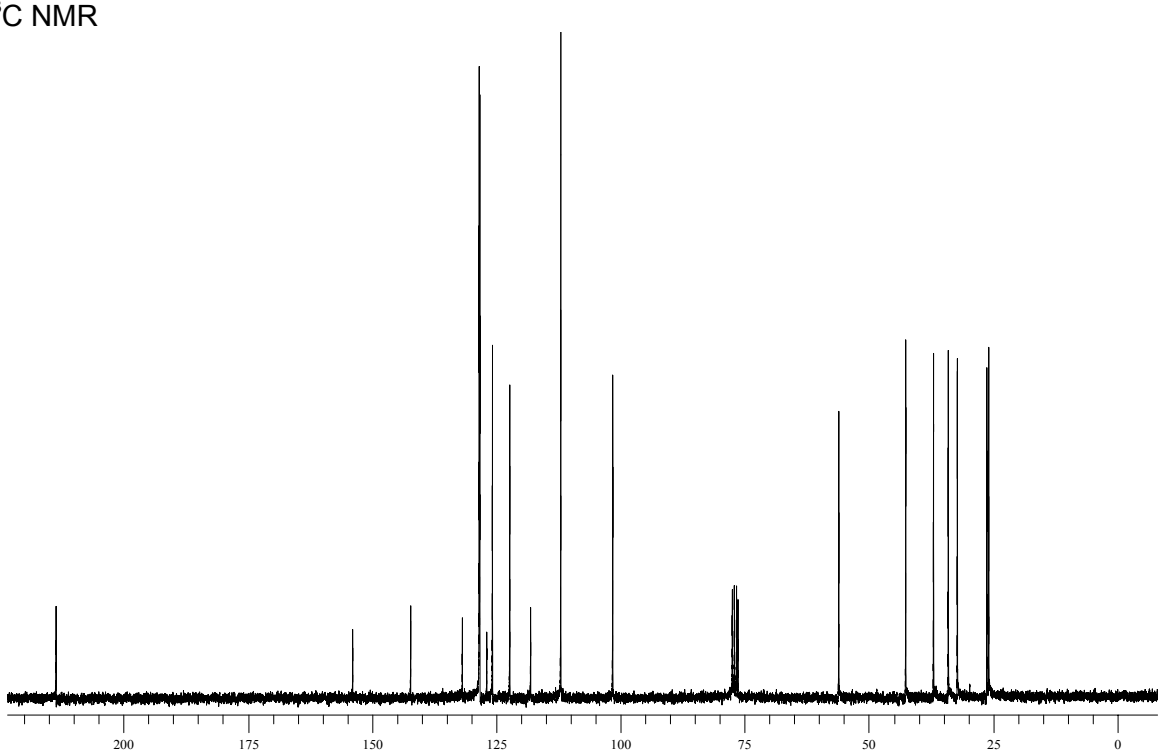


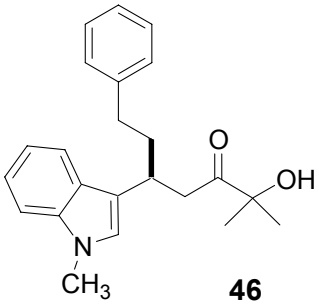
45

^{1}H NMR



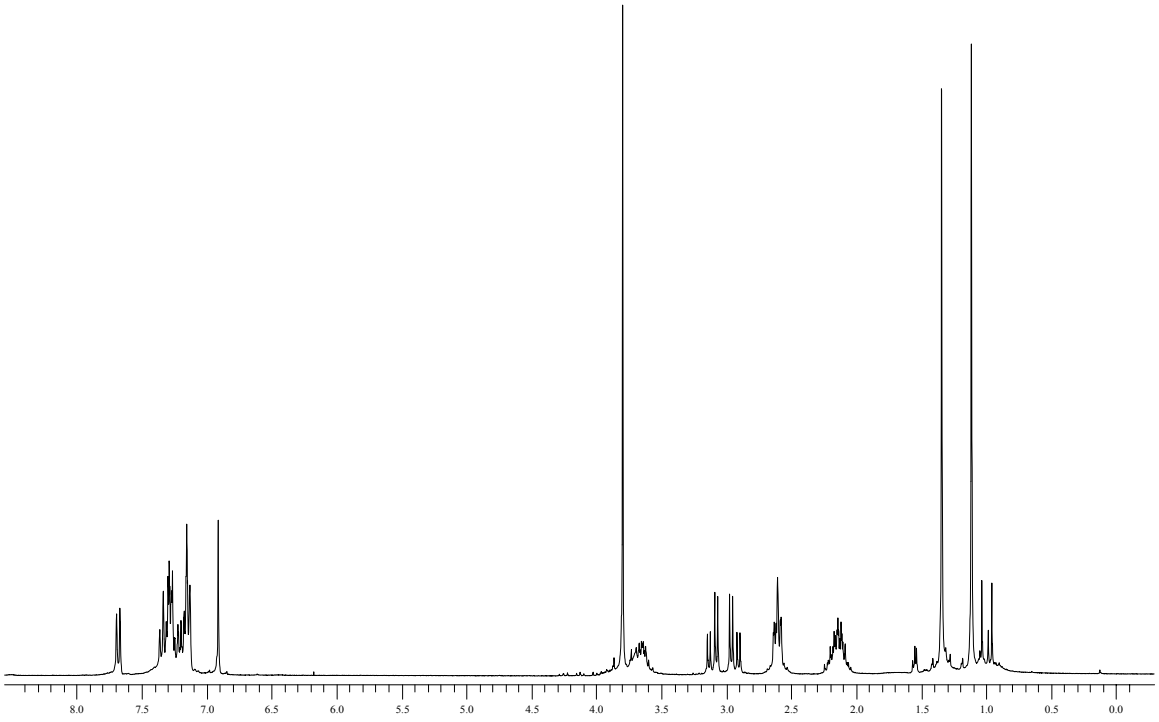
^{13}C NMR



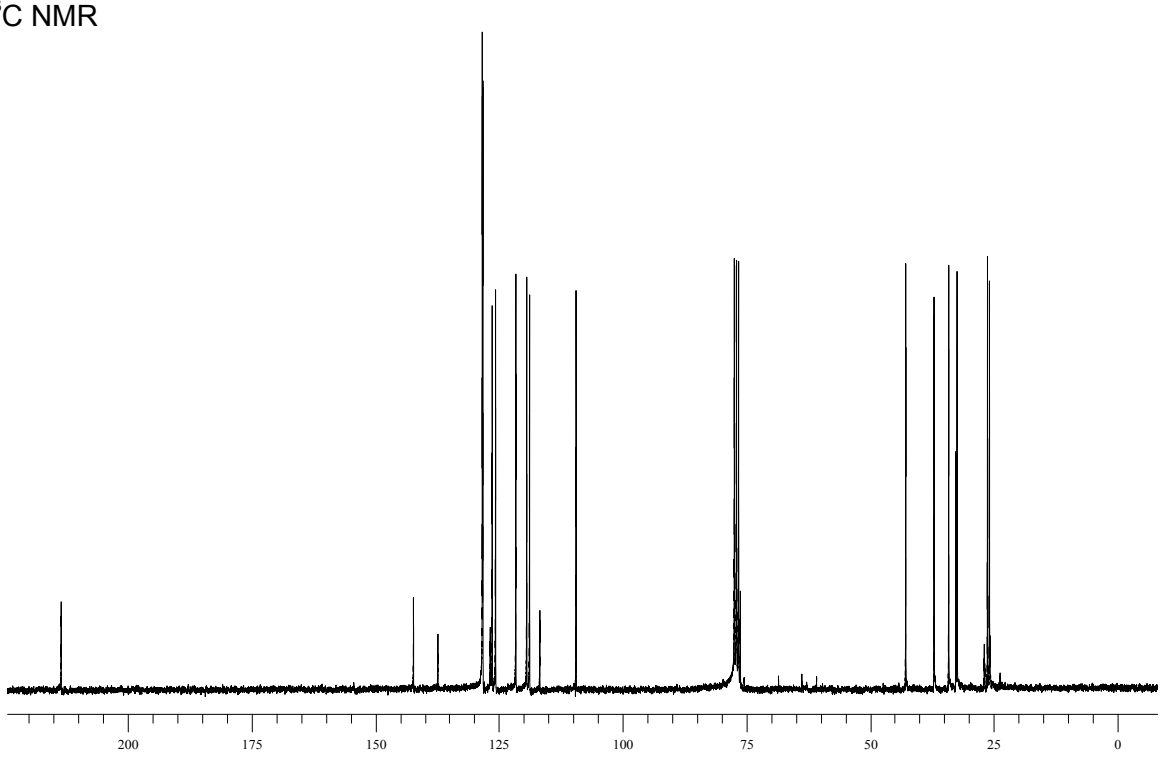


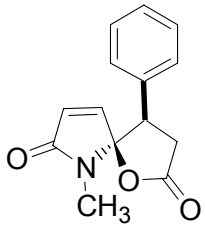
46

^{1}H NMR



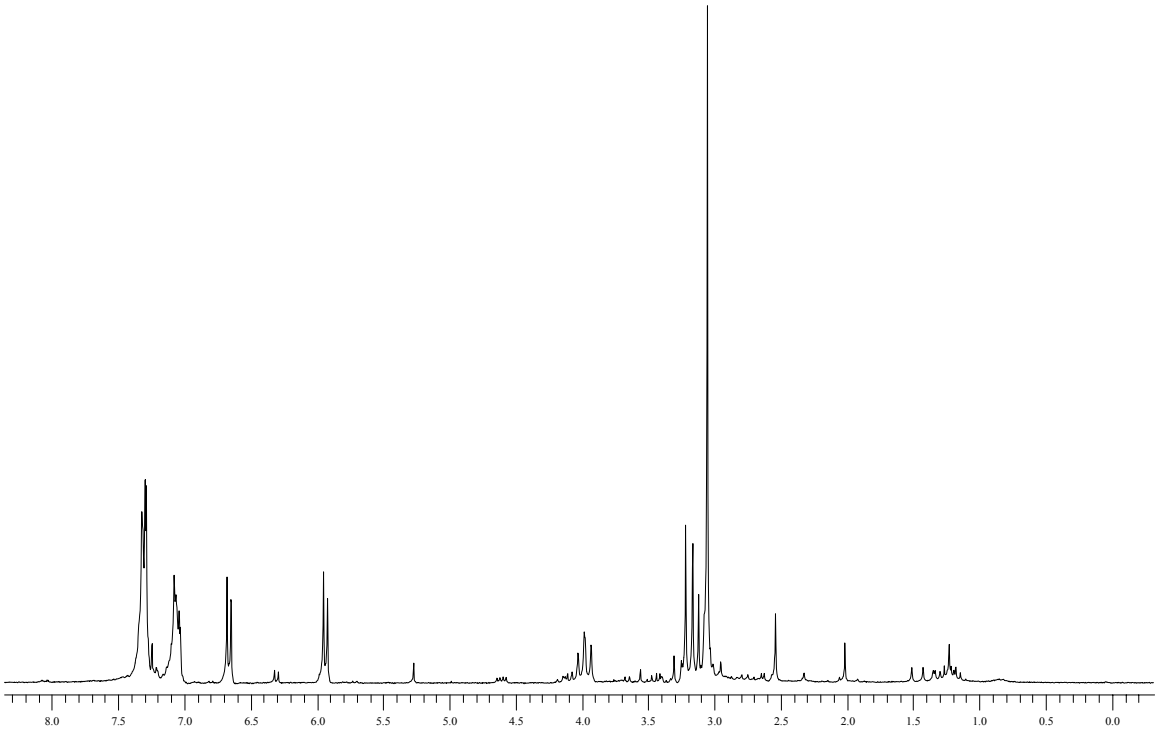
^{13}C NMR



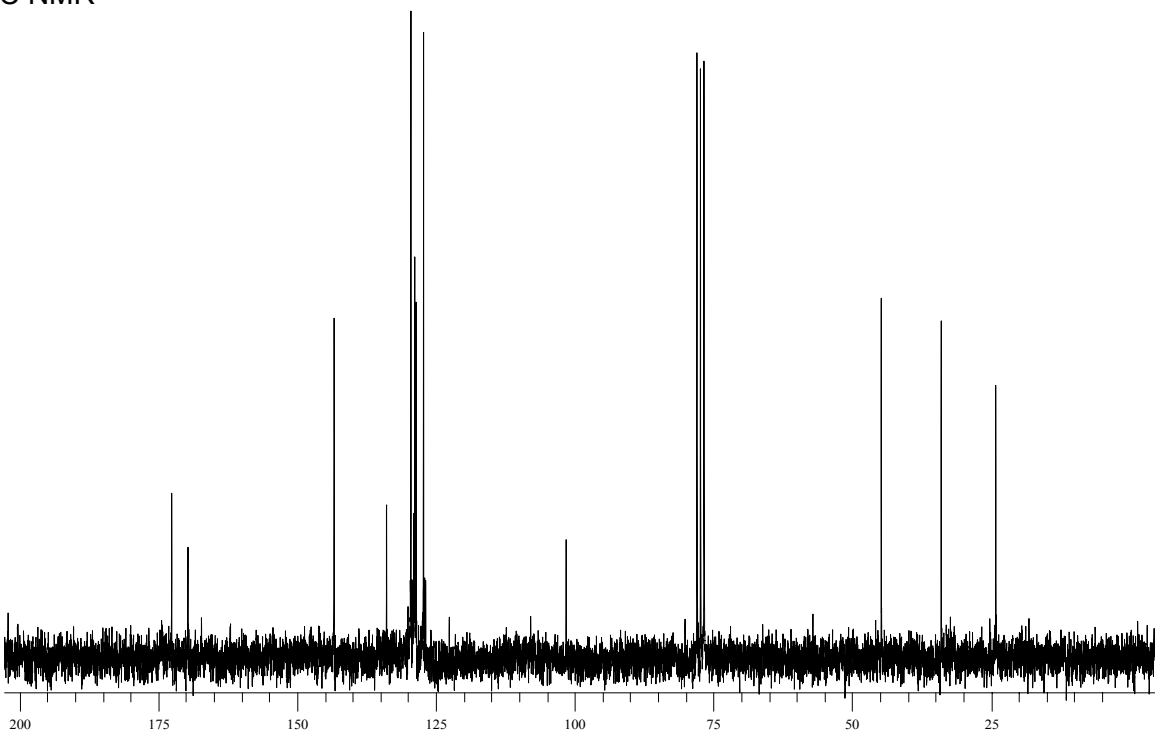


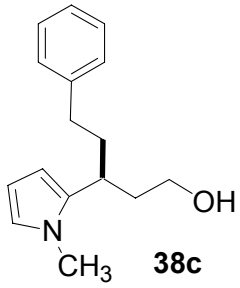
24

^{1}H NMR



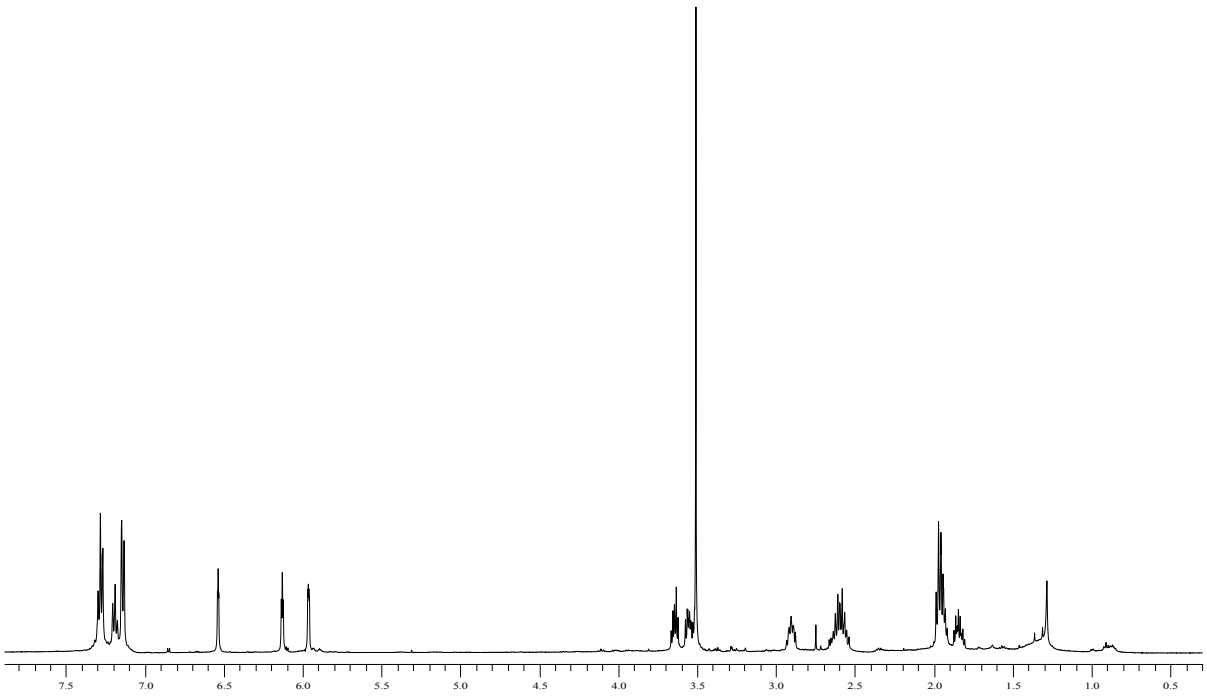
^{13}C NMR



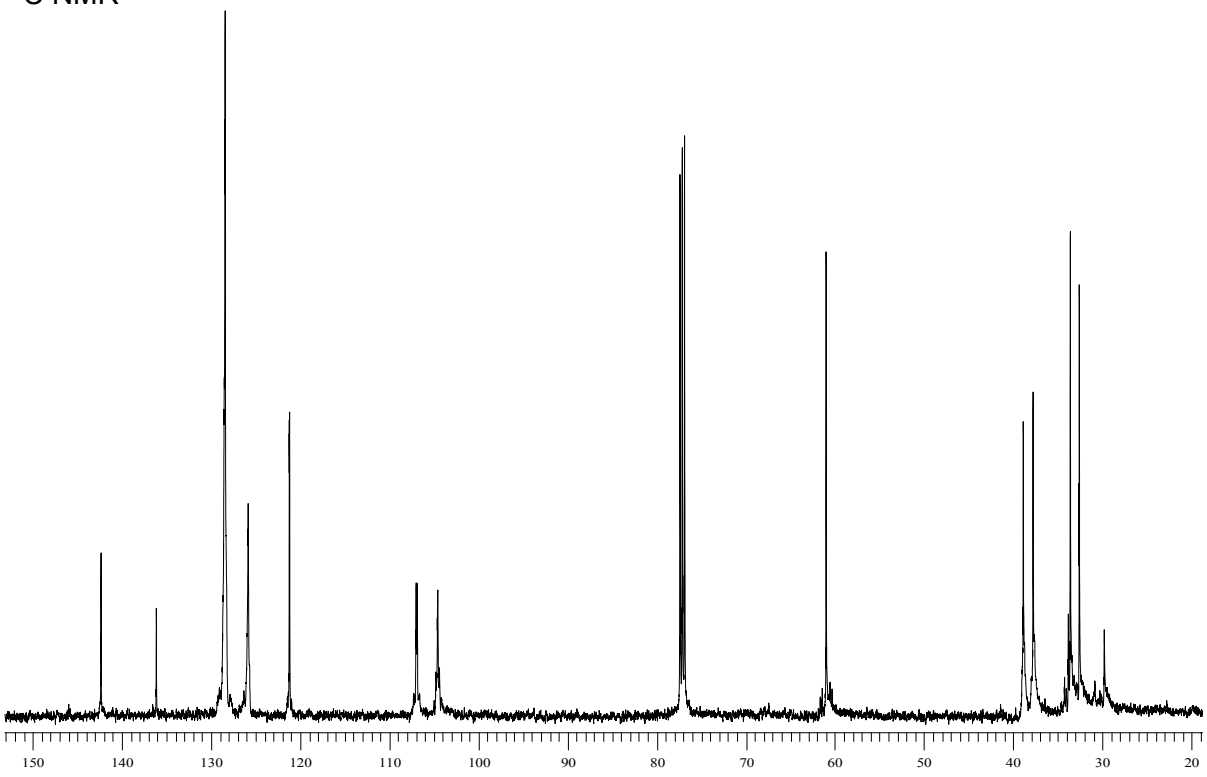


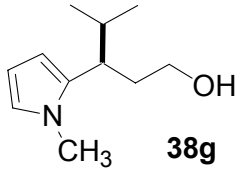
38c

^{1}H NMR



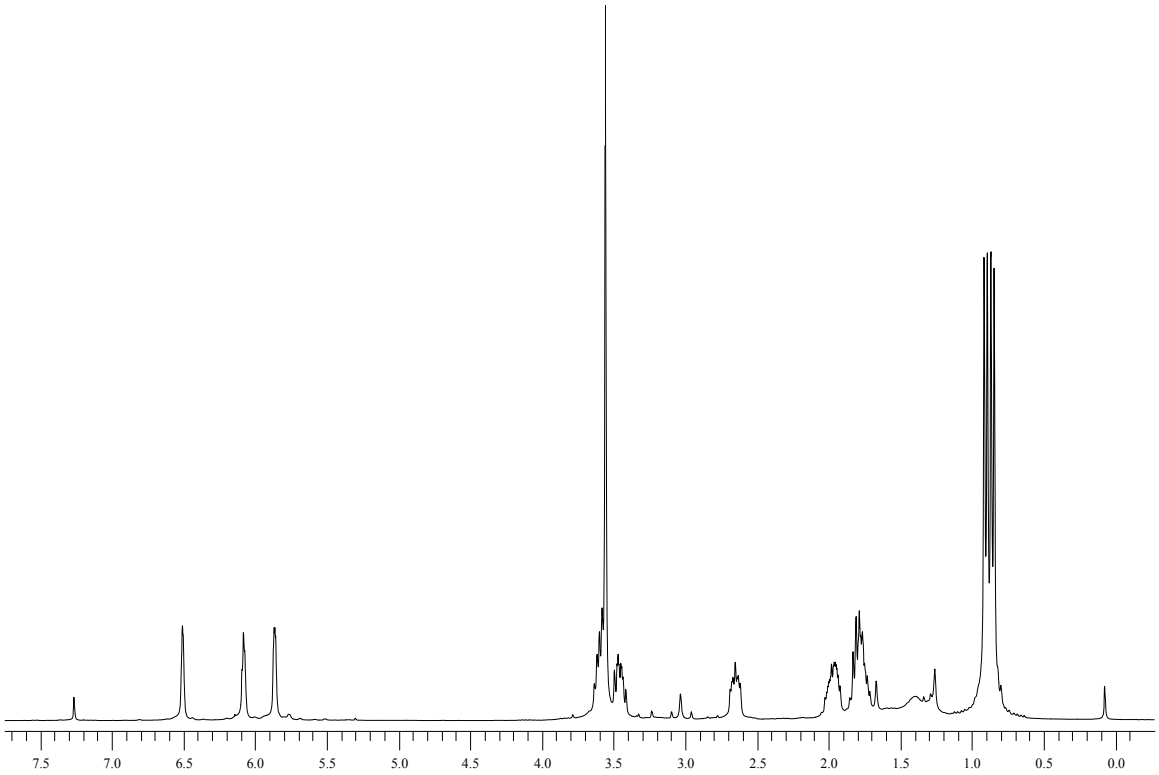
^{13}C NMR



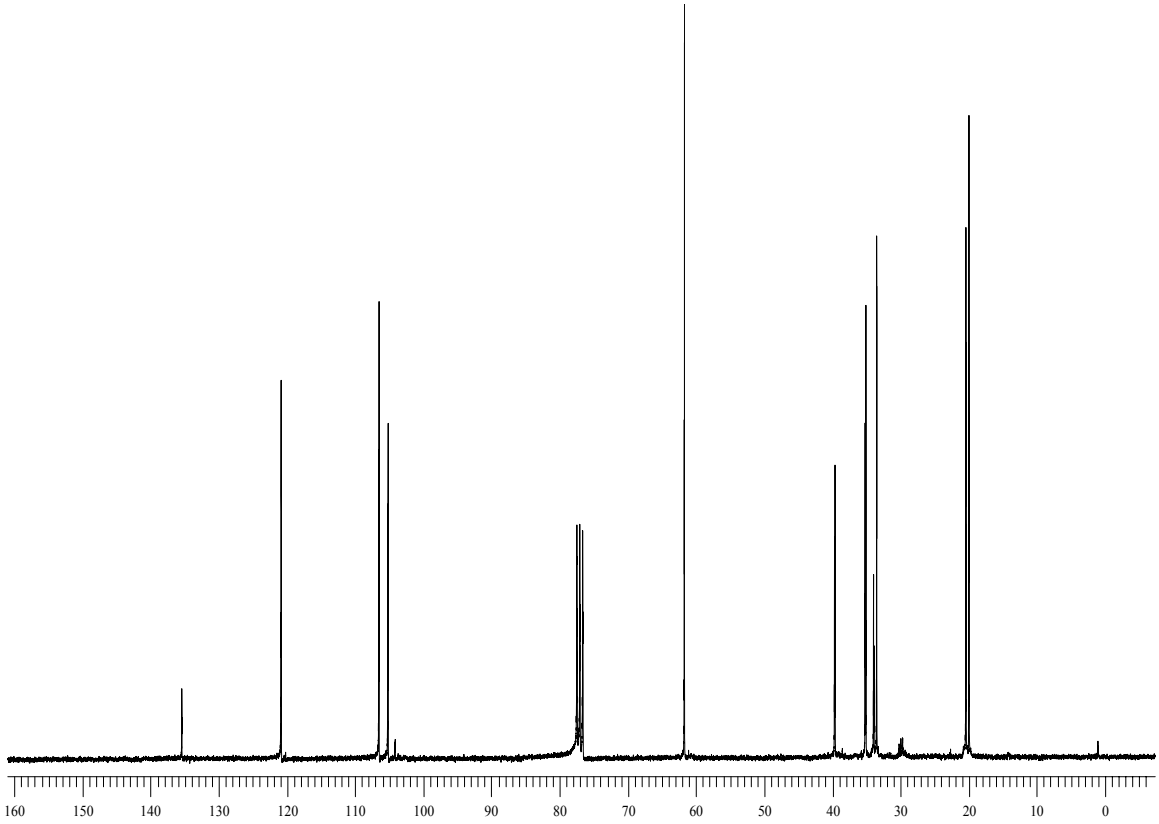


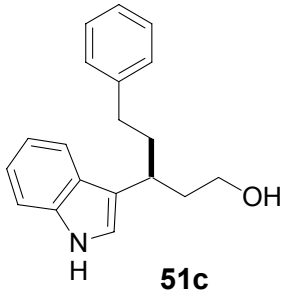
38g

^{1}H NMR



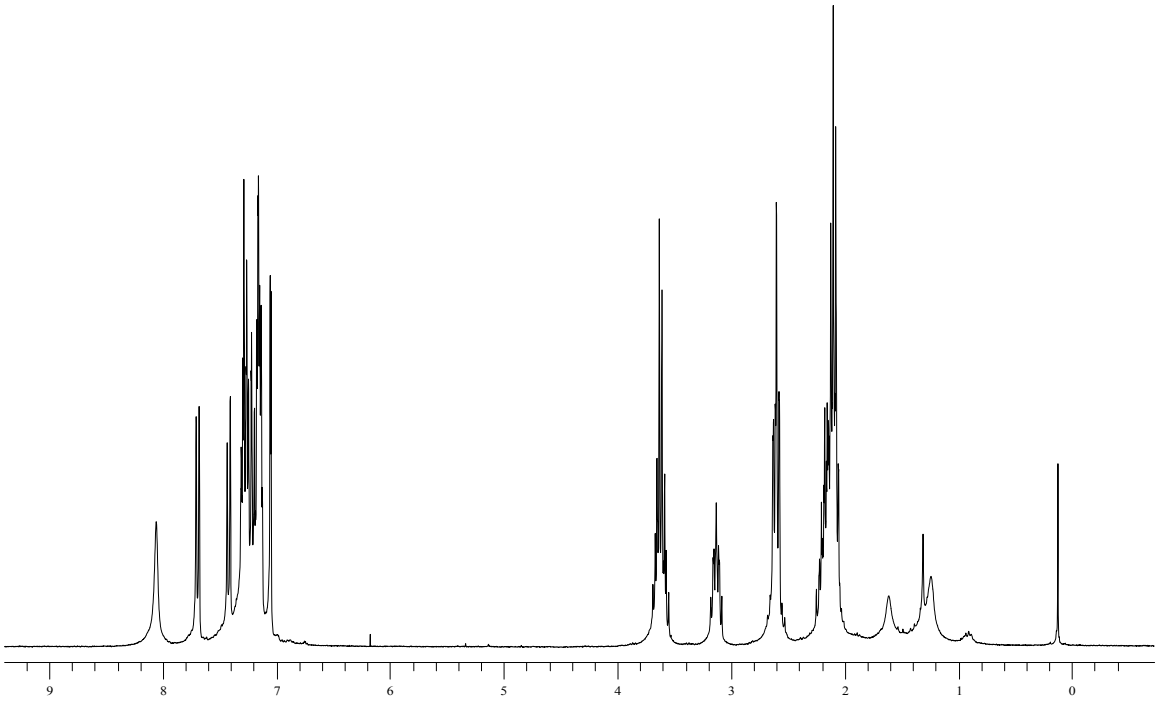
^{13}C NMR



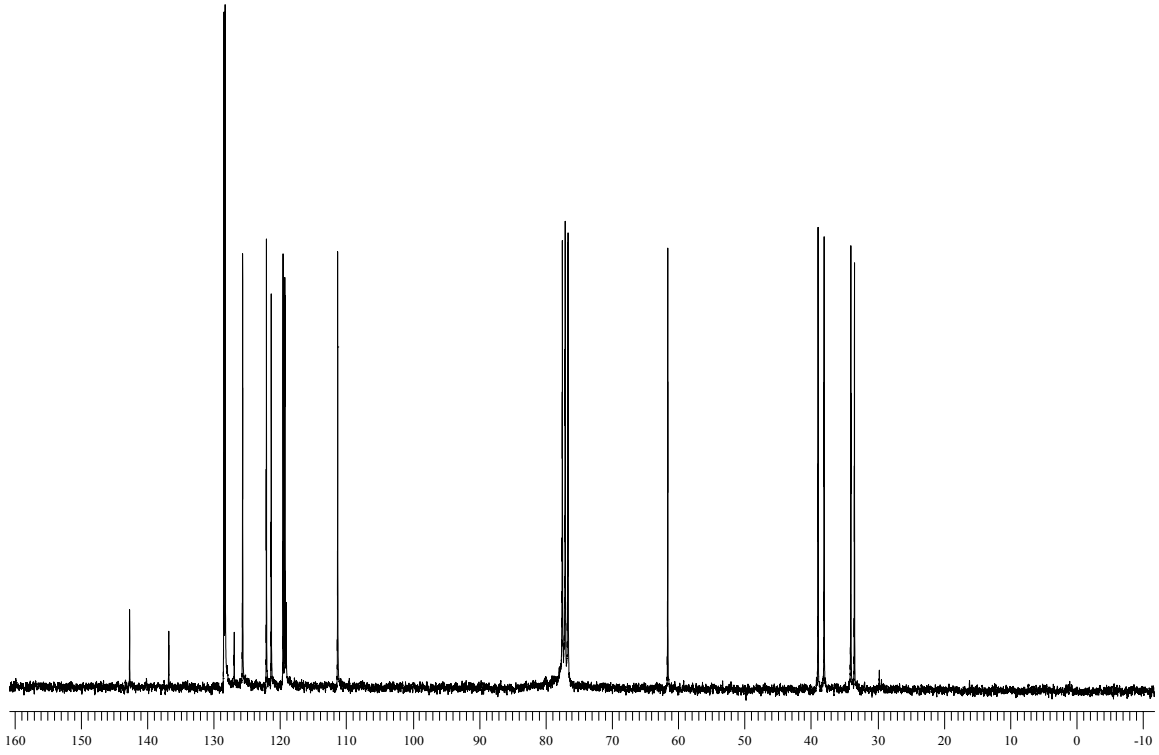


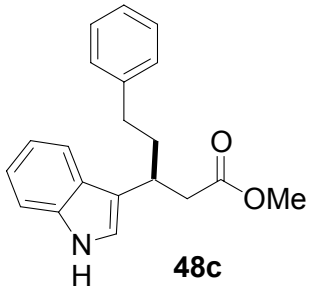
51c

^{1}H NMR



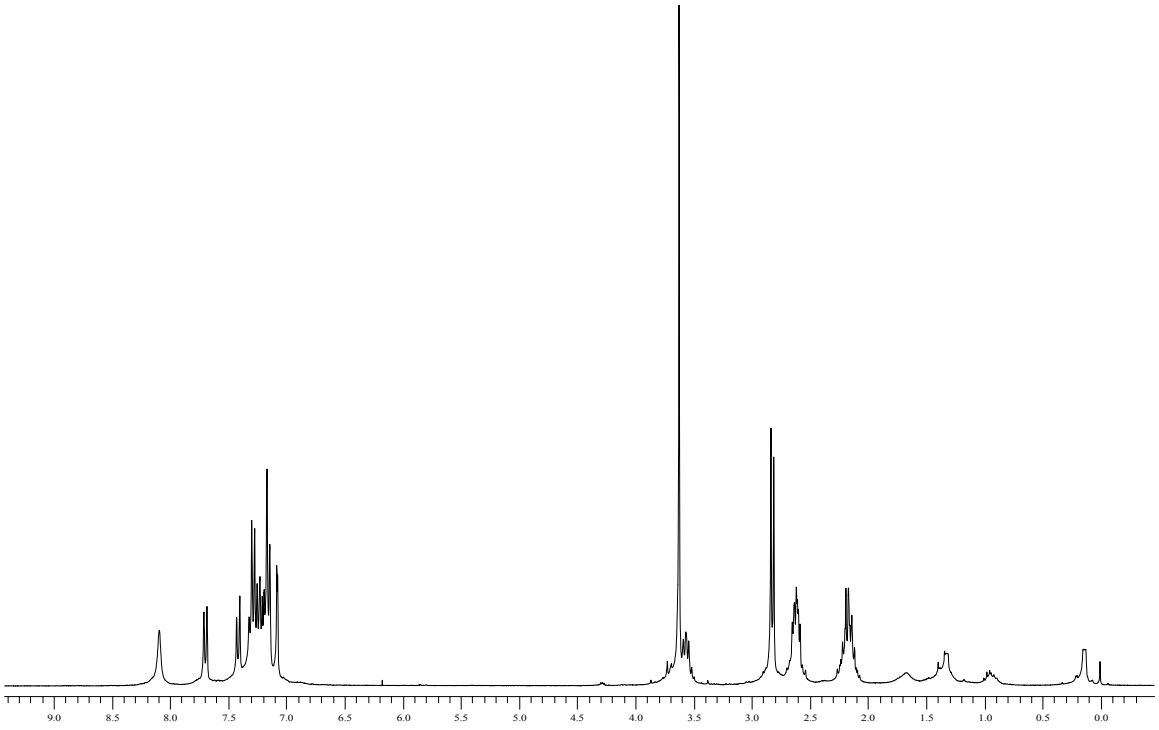
^{13}C NMR



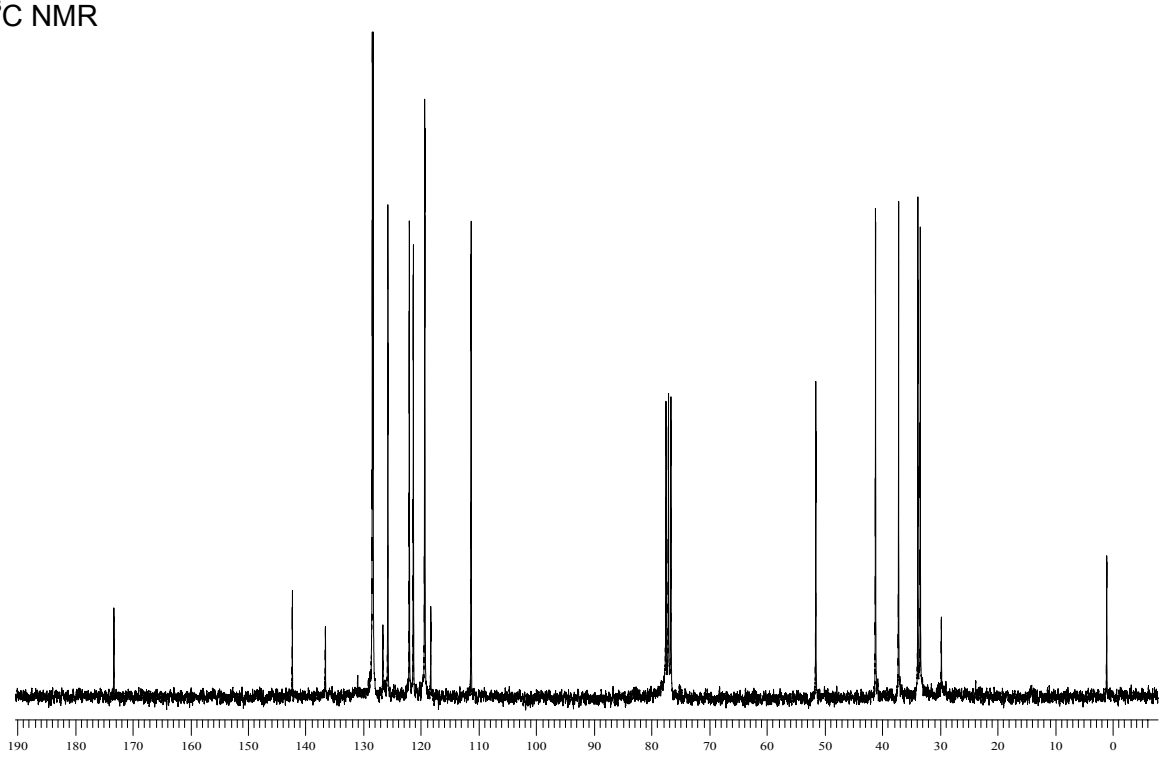


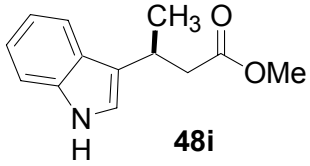
48c

^{1}H NMR



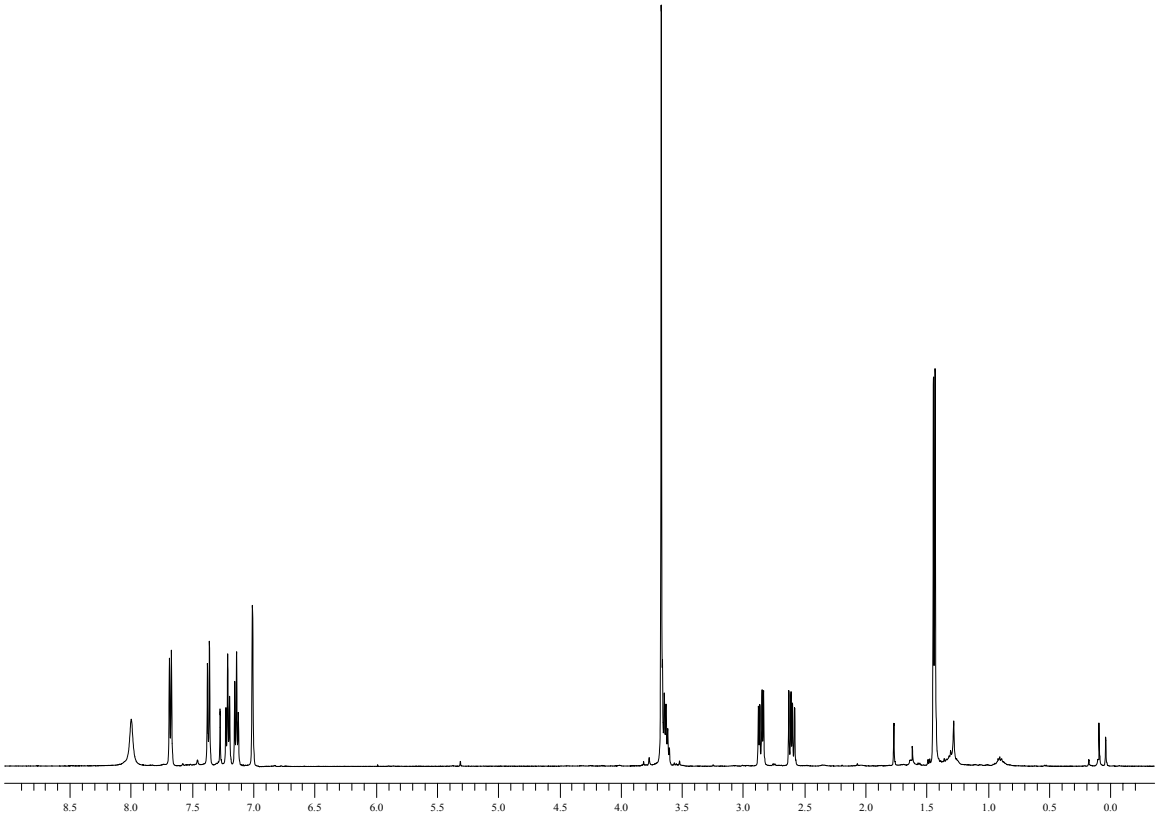
^{13}C NMR



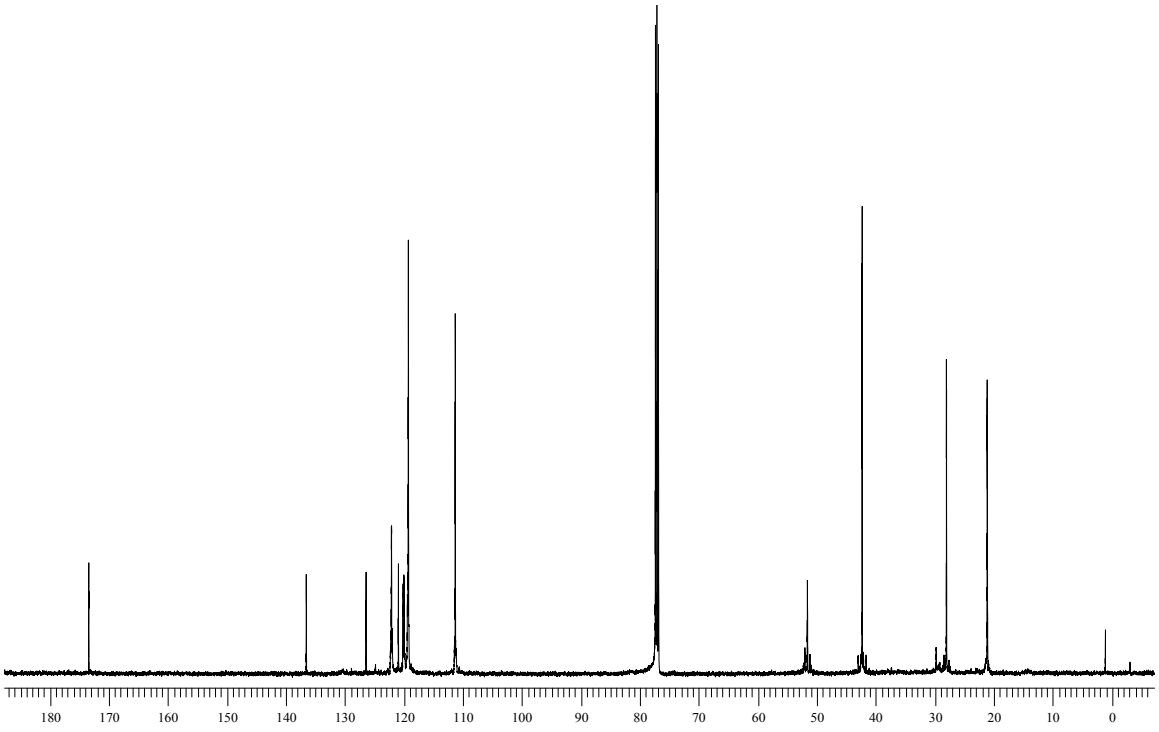


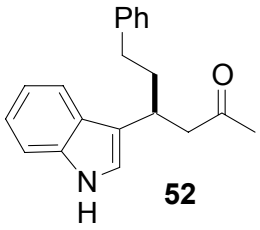
48i

^{1}H NMR



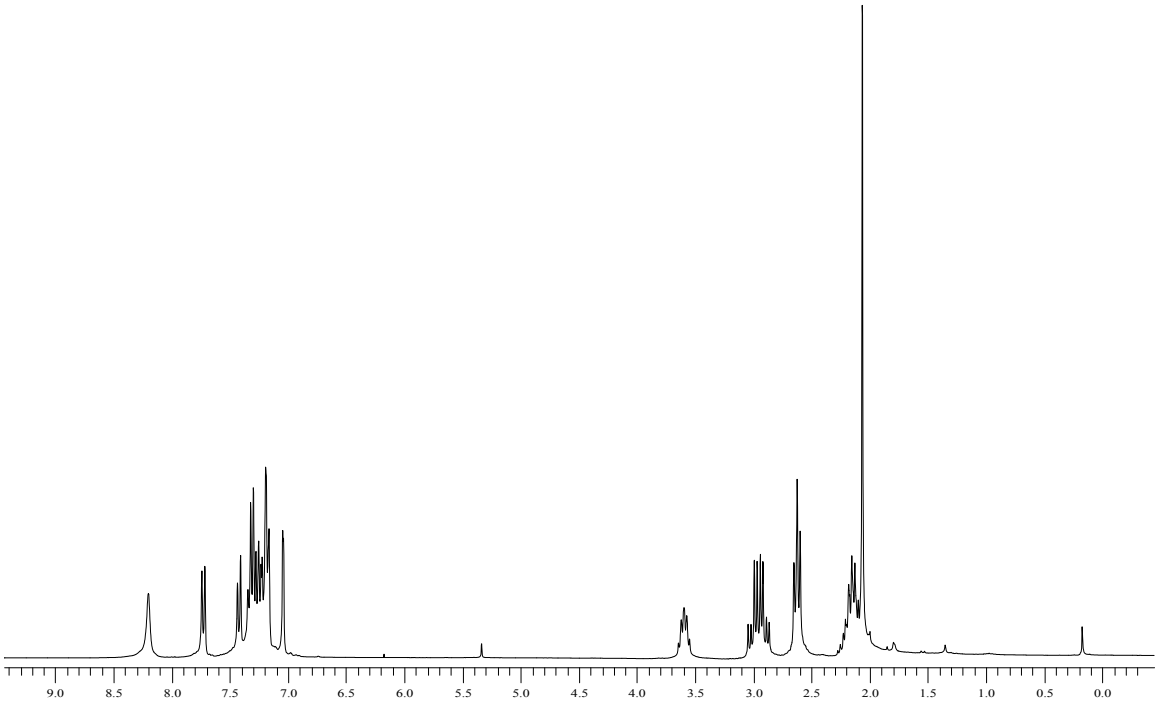
^{13}C NMR



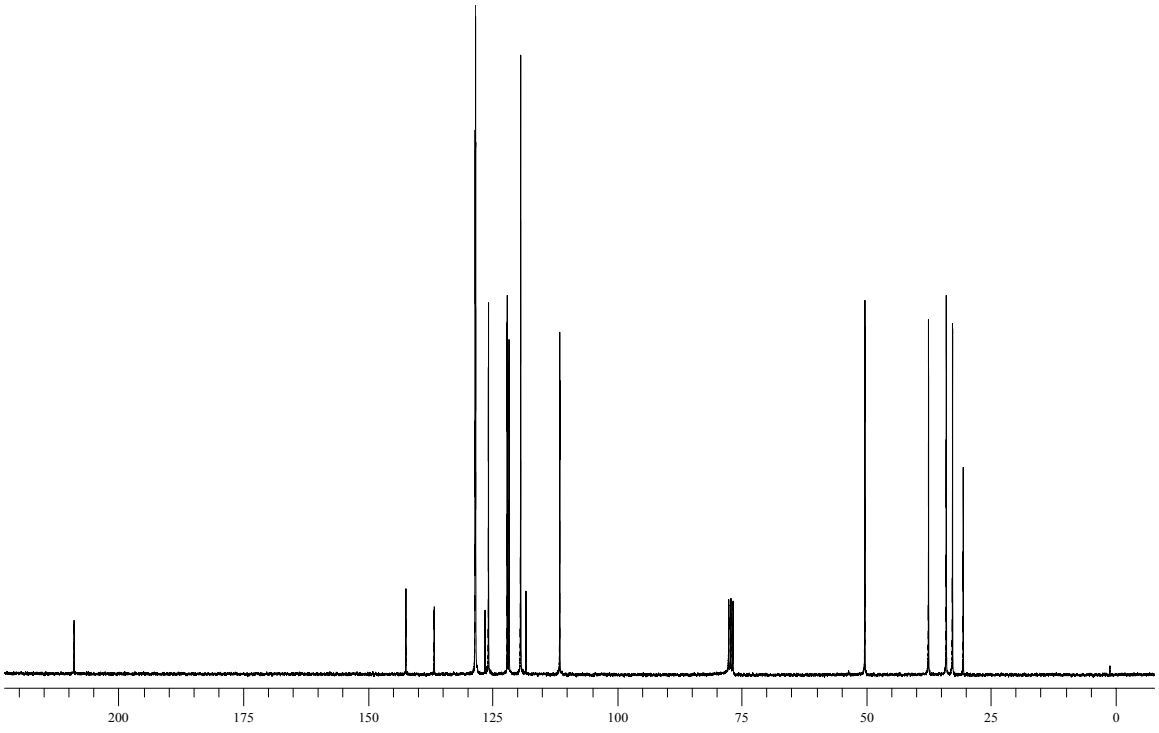


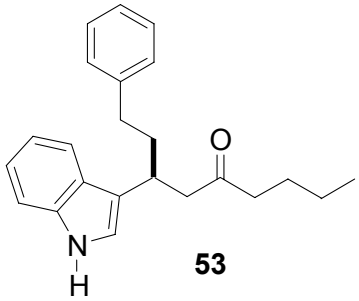
52

^{1}H NMR



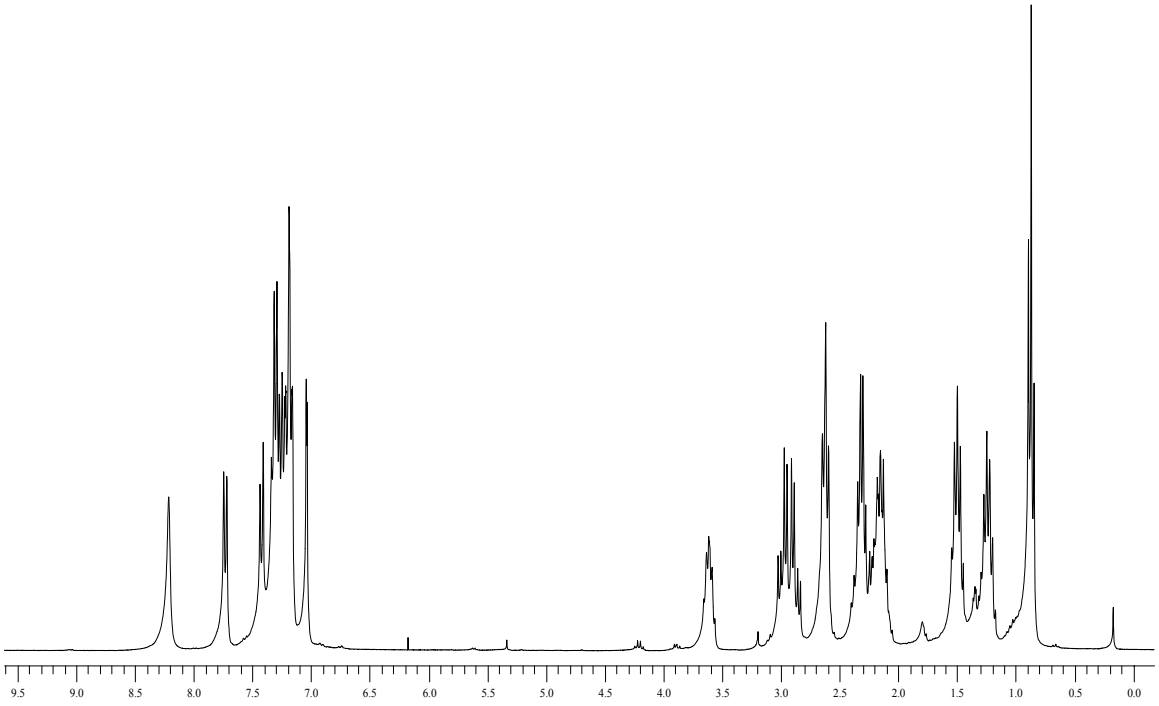
^{13}C NMR



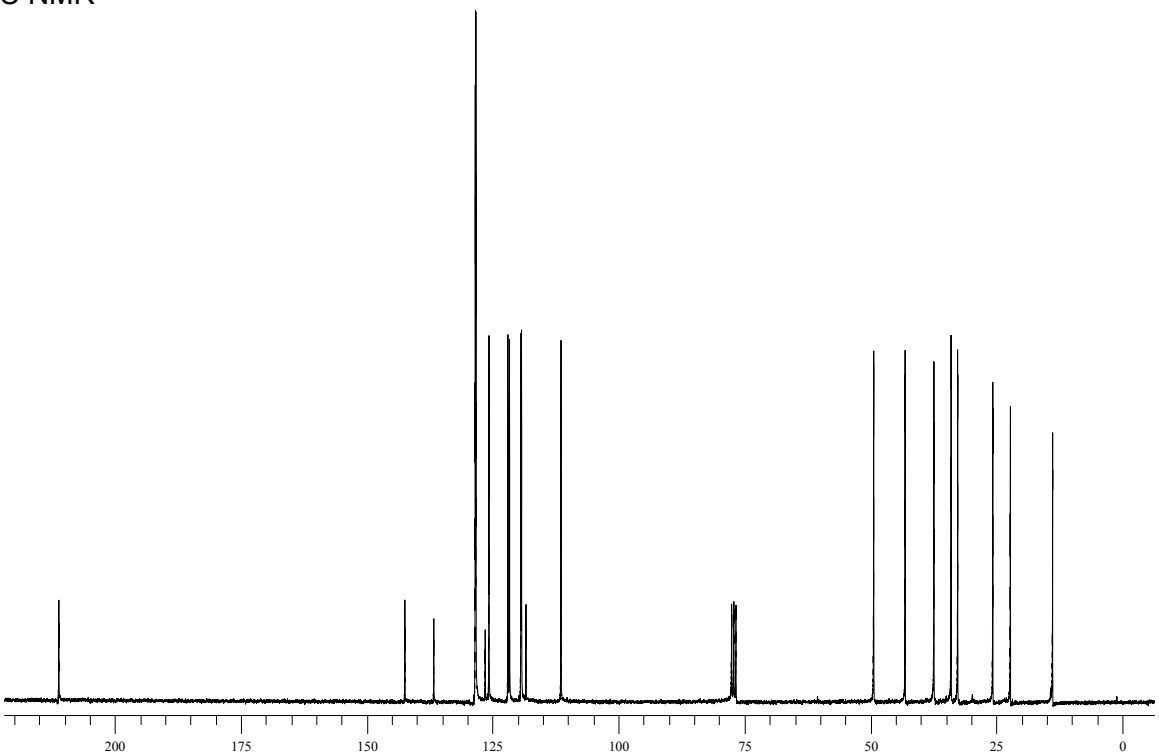


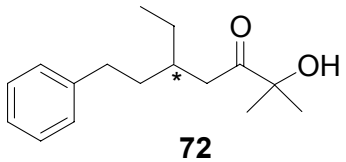
53

^{1}H NMR



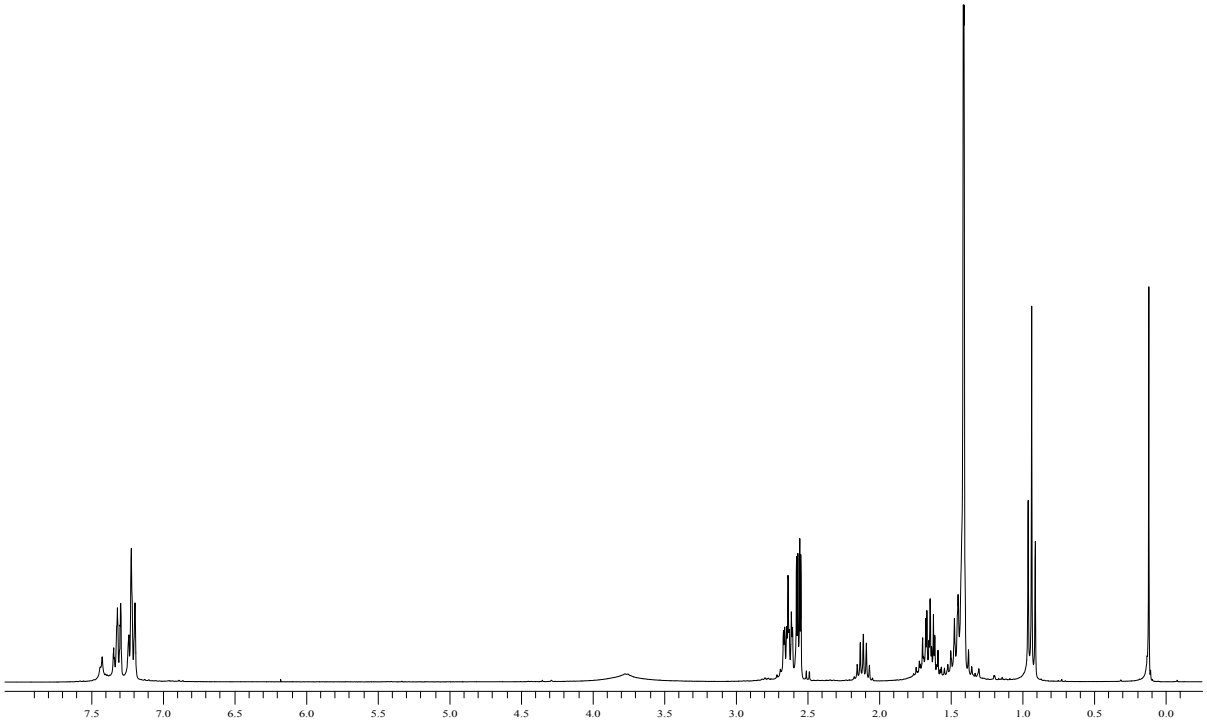
^{13}C NMR



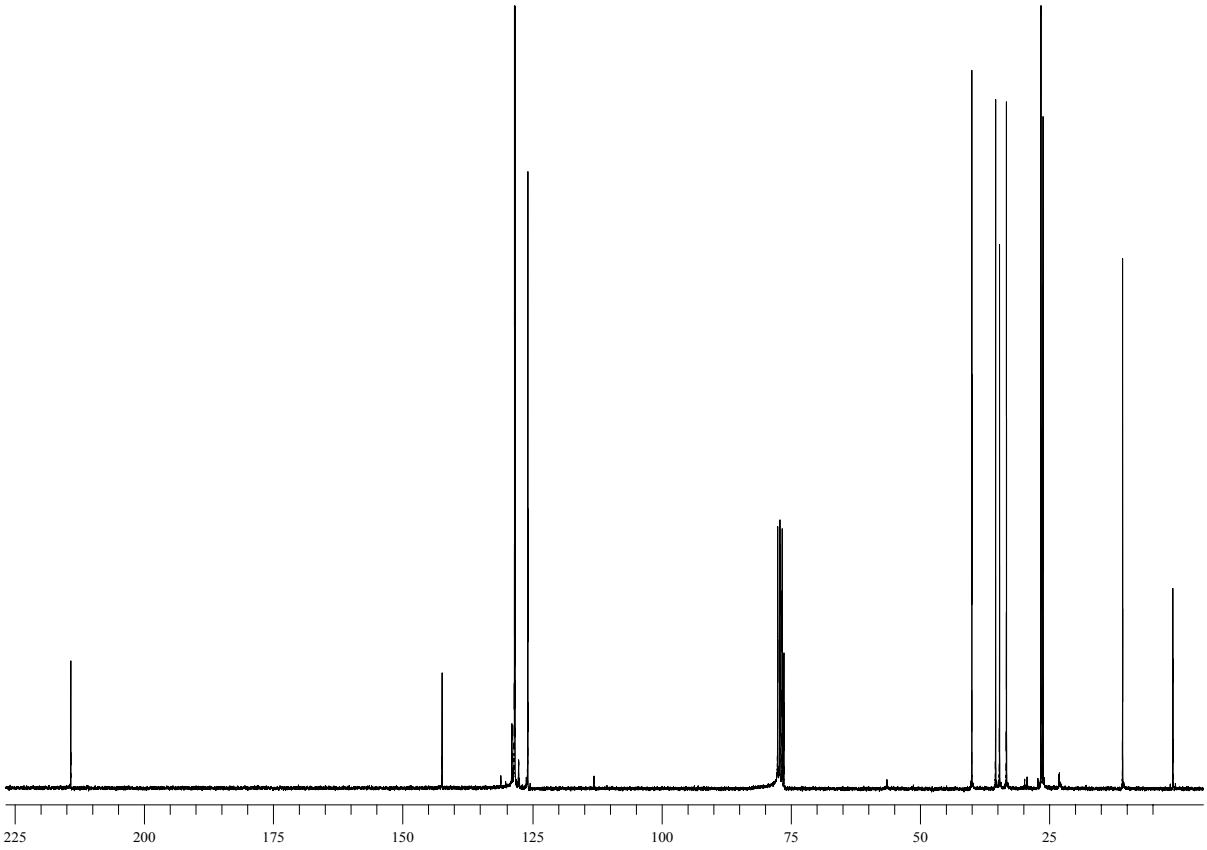


72

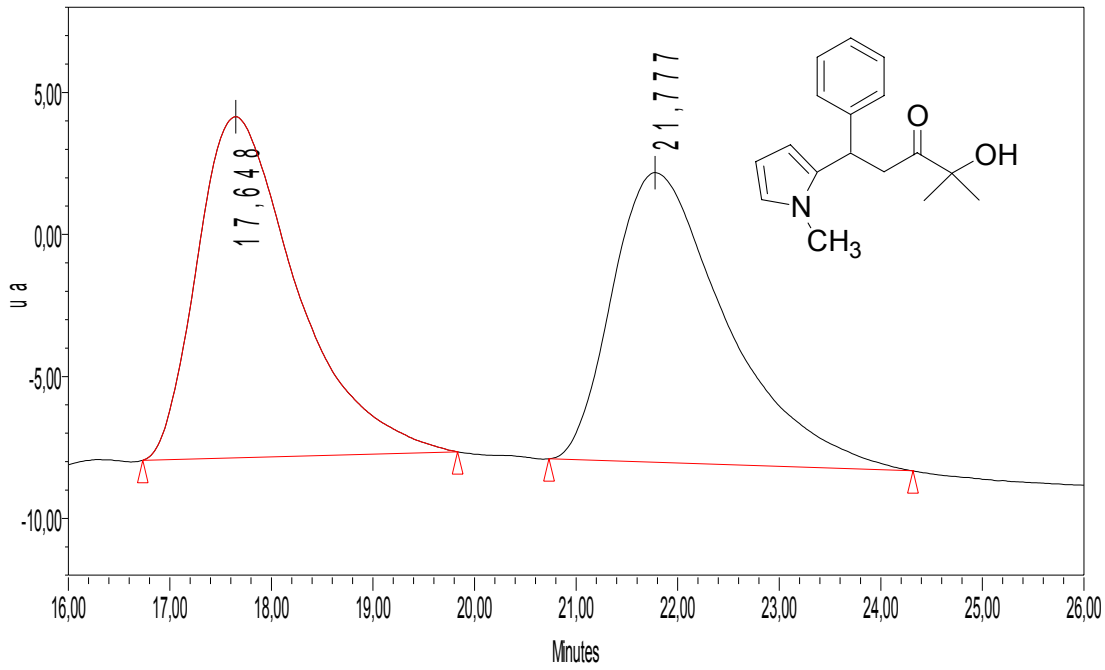
^{1}H NMR

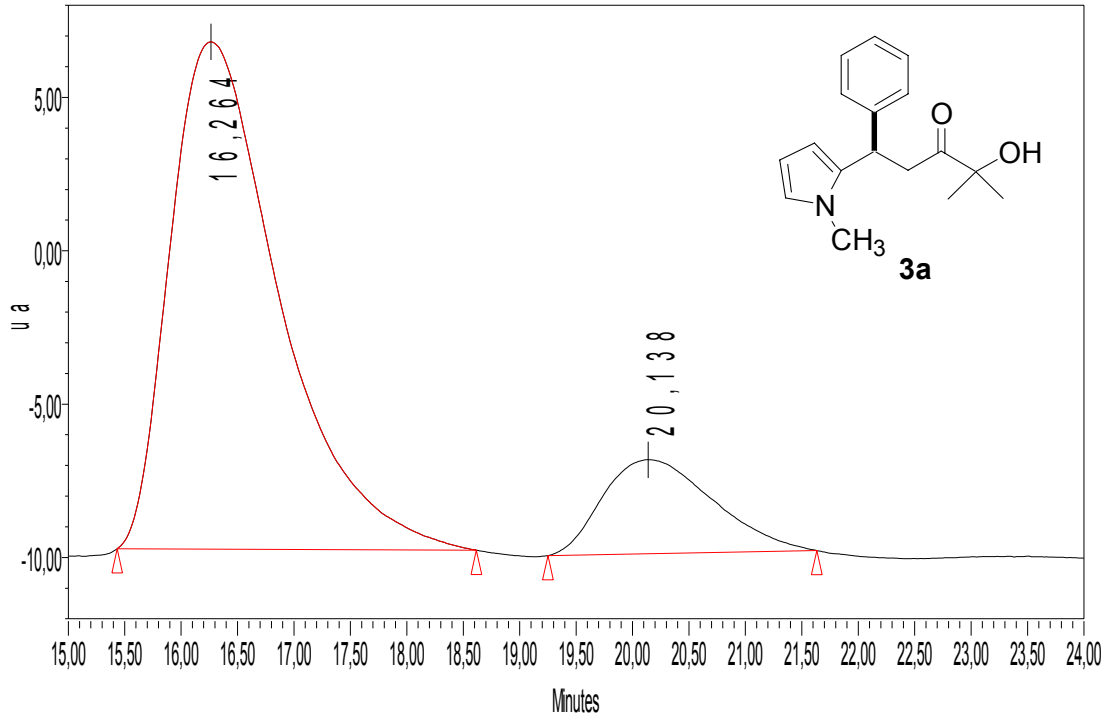


^{13}C NMR



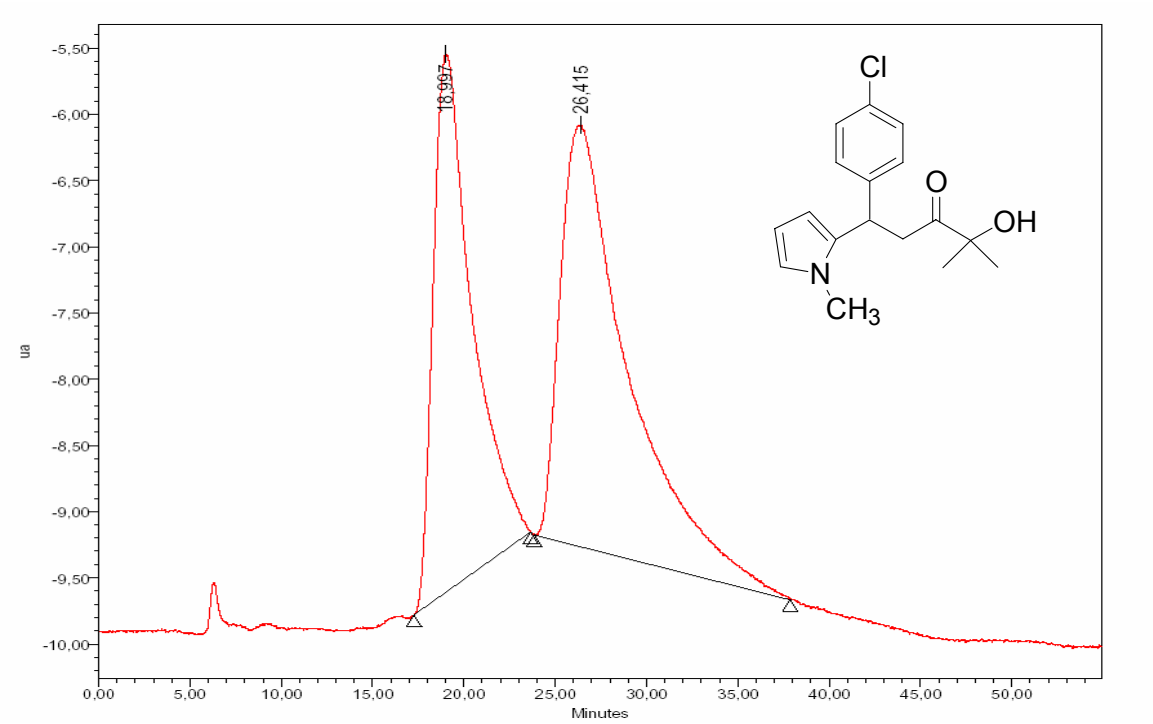
Apendix: III

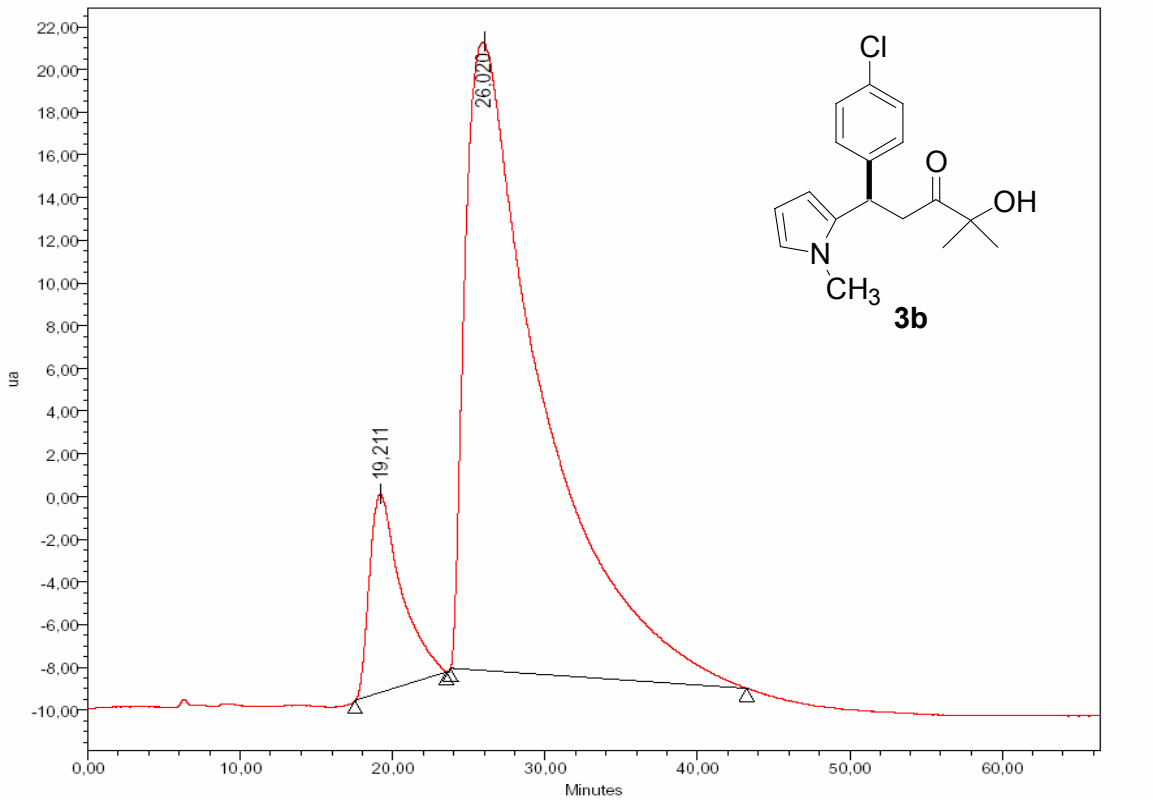




Retention Time (min)	Area	% Area
16,264	1112660	84,23
20,138	208337	15,77

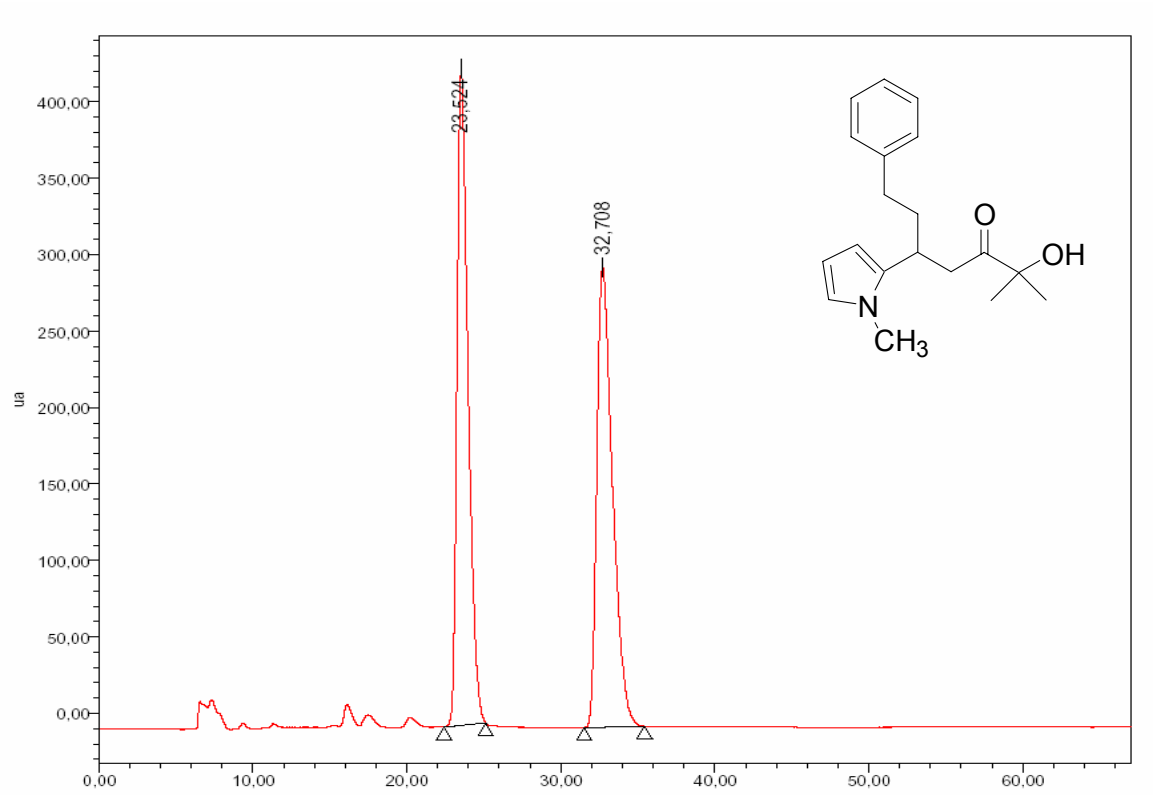
(Chiralpak AD column, hexane:EtOH 94:06, 0.5 mL/min., 254nm)

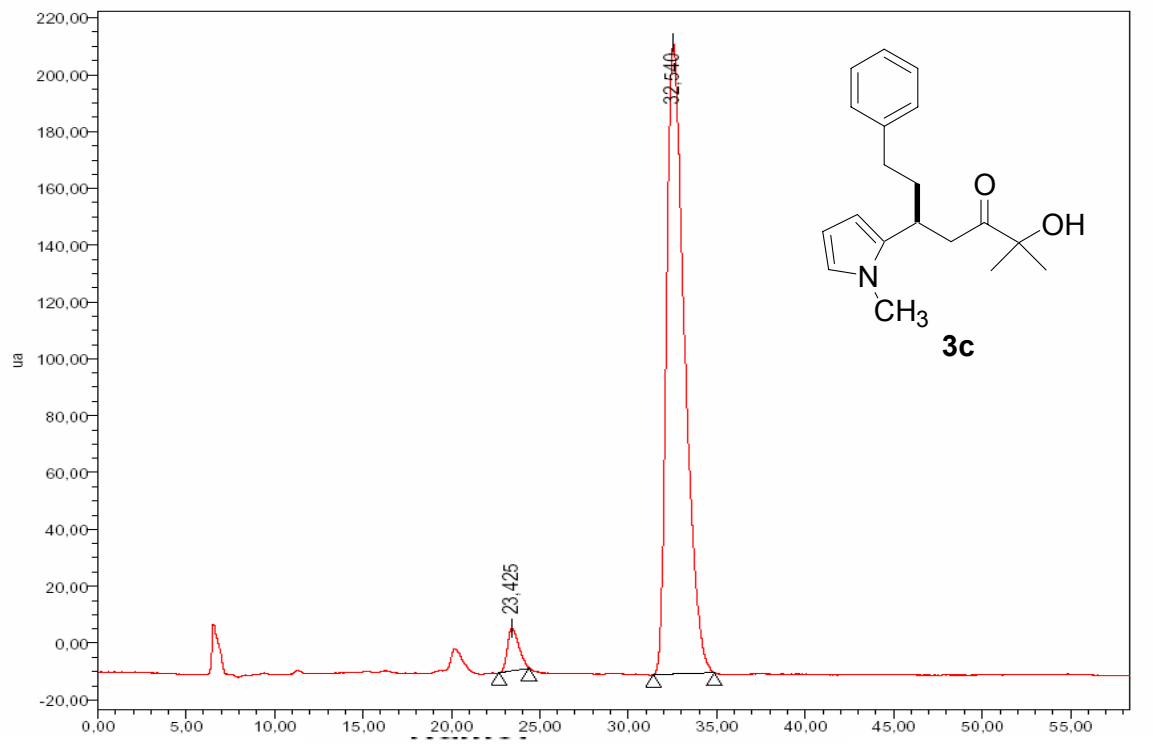




Retention Time (min)	Area	% Area
19,211	1356730	11,60
26,020	10342540	88,40

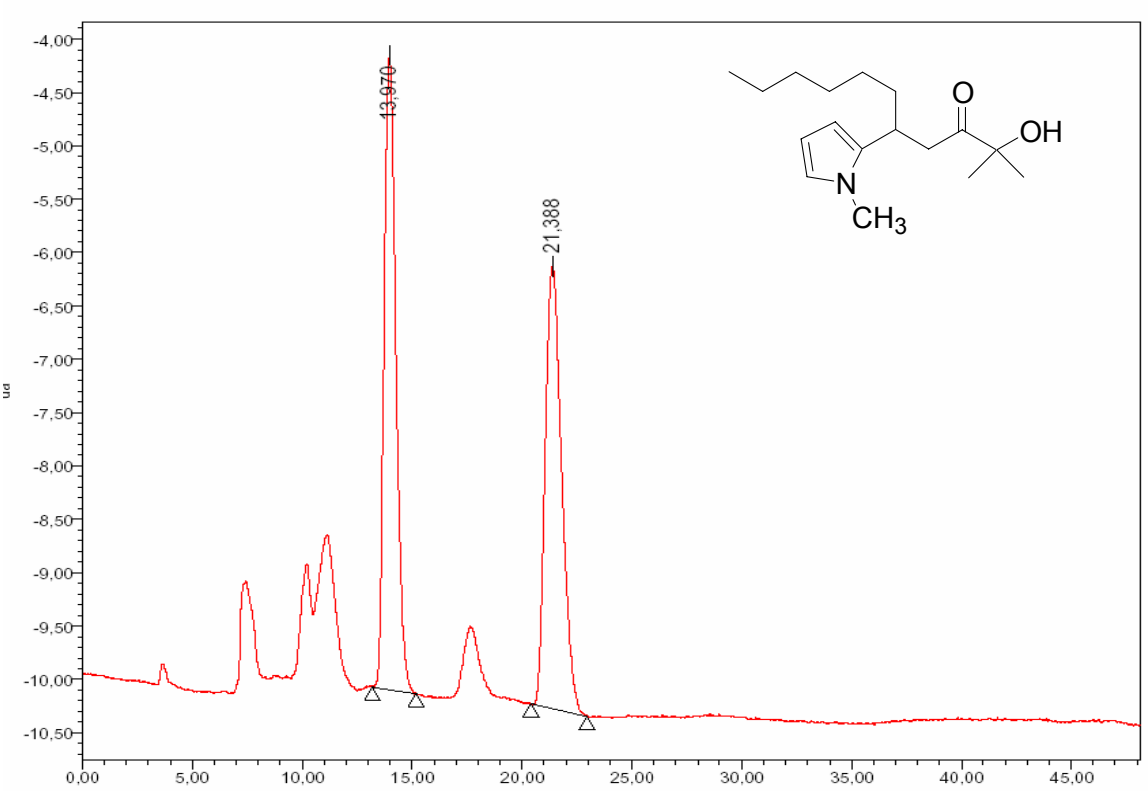
(Chiralpak AS column, hexane:iPrOH 95:05, 0.5 mL/min., 210 nm)

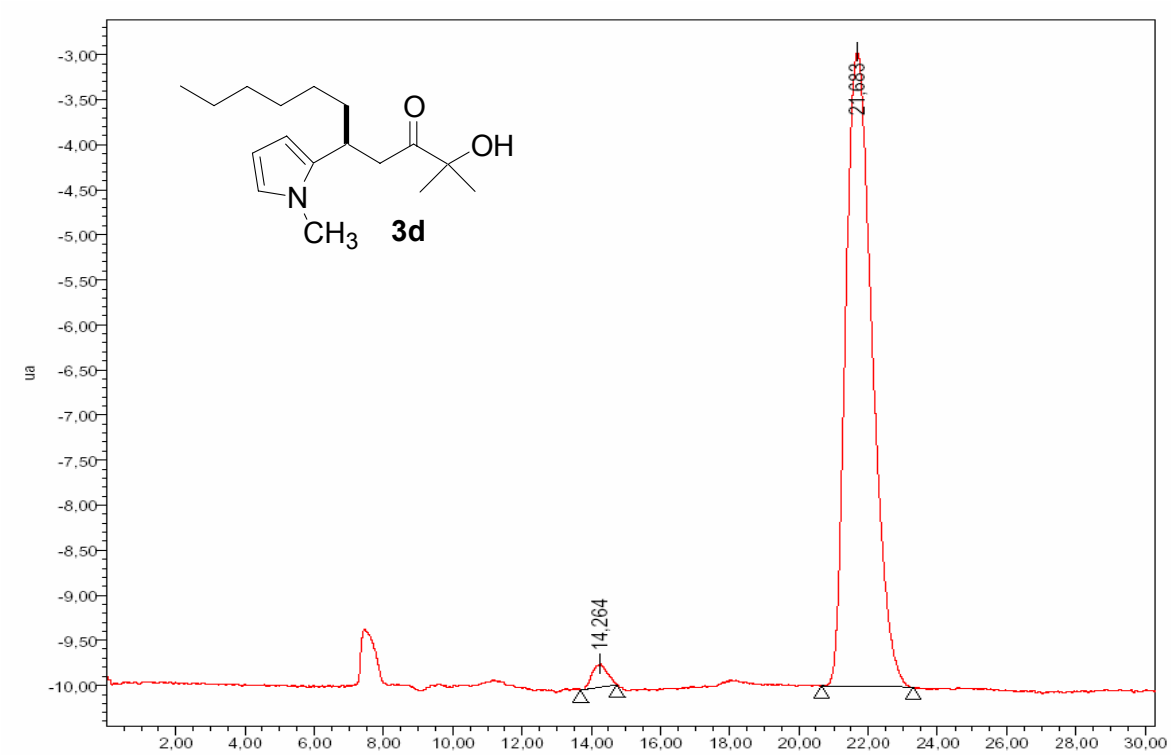




Retention Time (min)	Area	% Area	Height
23,425	677701	4,13	15100
32,540	15720492	95,87	222085

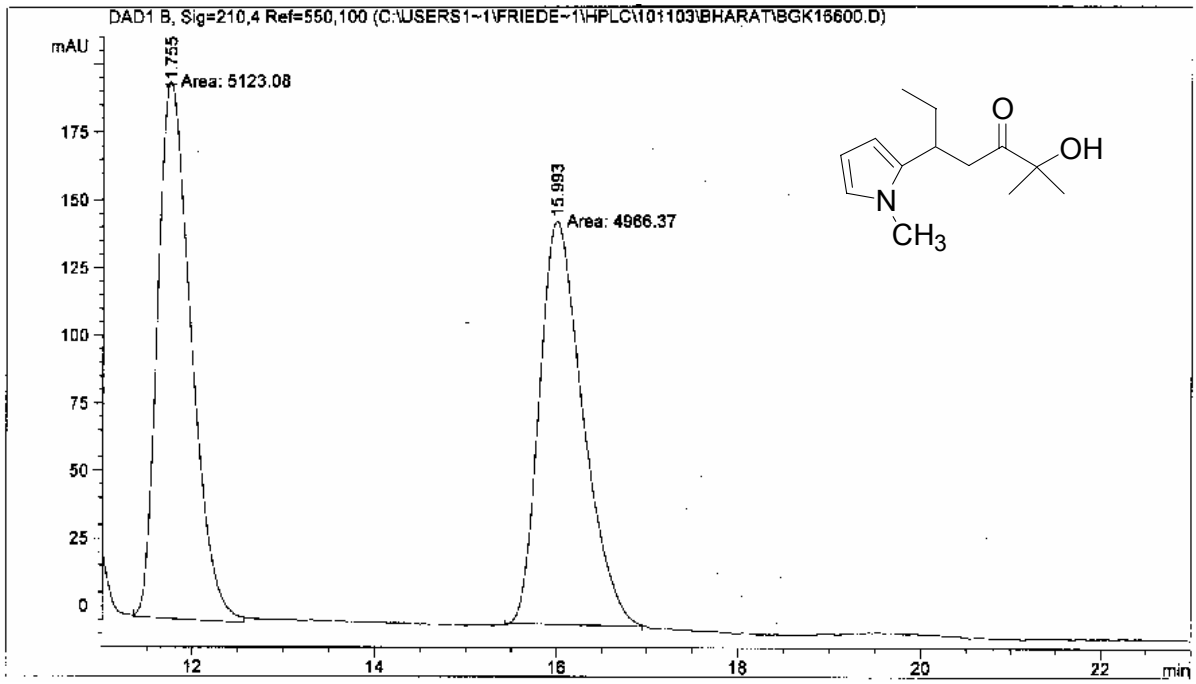
(Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 254 nm)

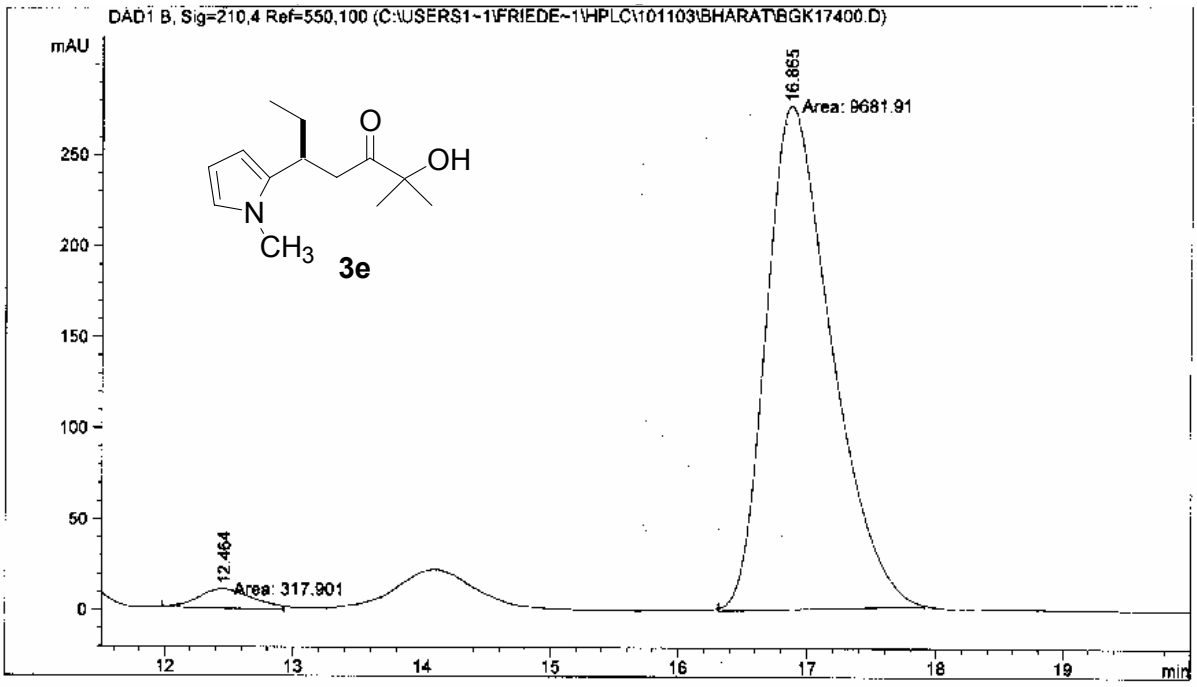




Retention Time (min)	Area	% Area
14,264	7949	2,08
21,683	373367	97,92

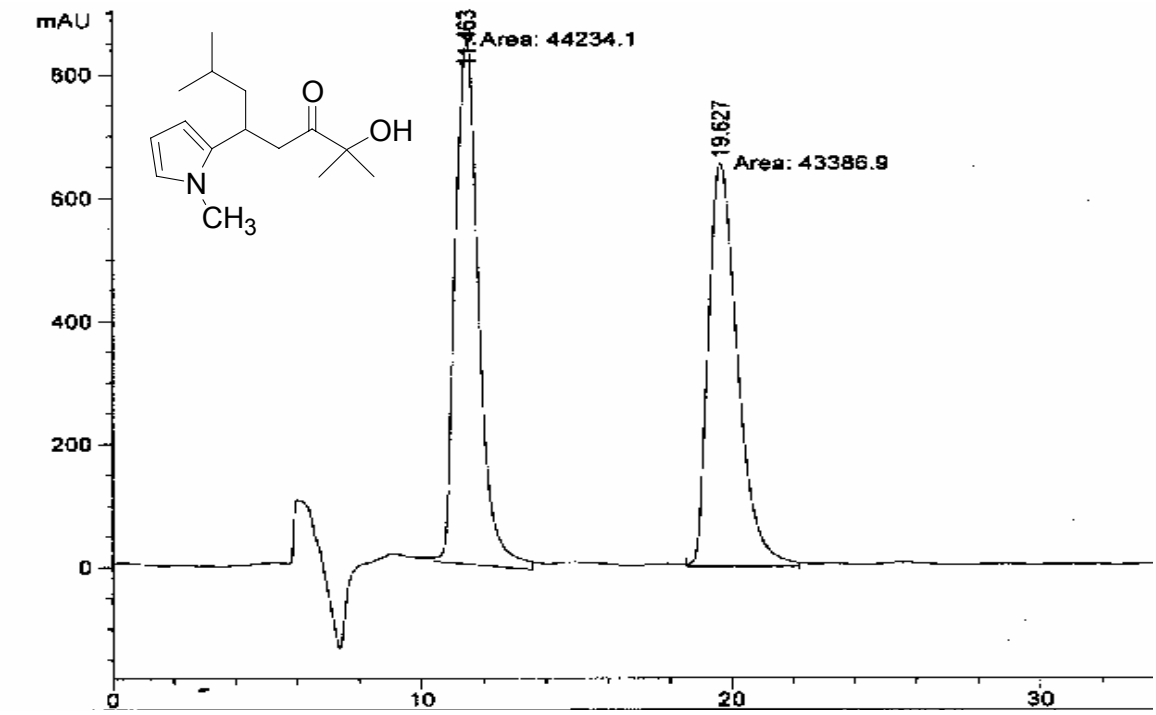
(Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 210 nm)

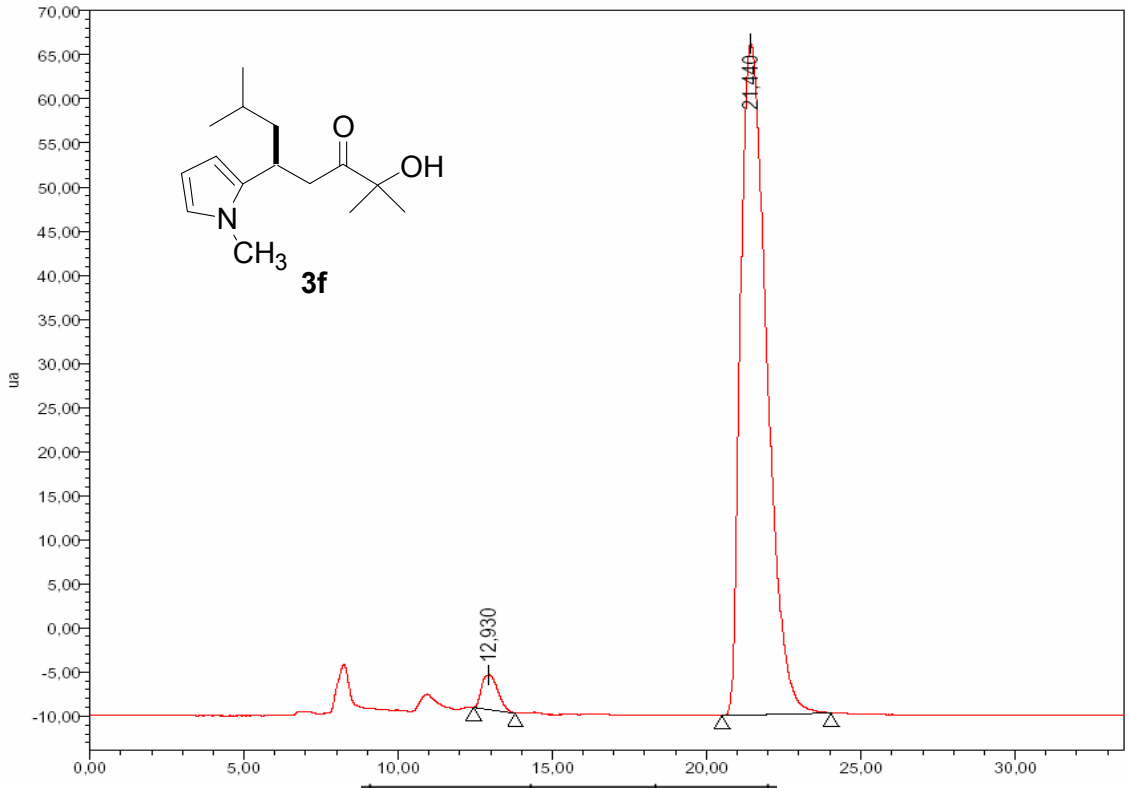




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
12.464	MM	0.4909	317.90097	10.79419	3.1791
16.865	MM	0.5864	9681.91113	275.18427	96.8209

(Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 210 nm)

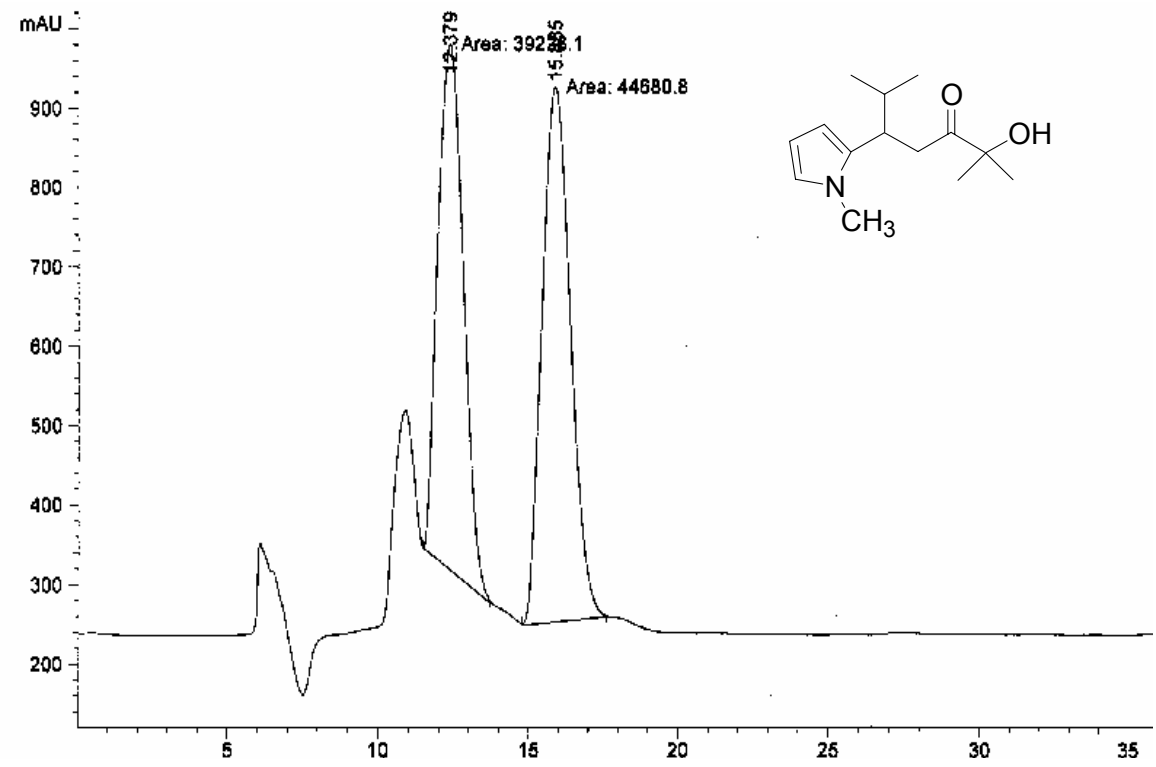


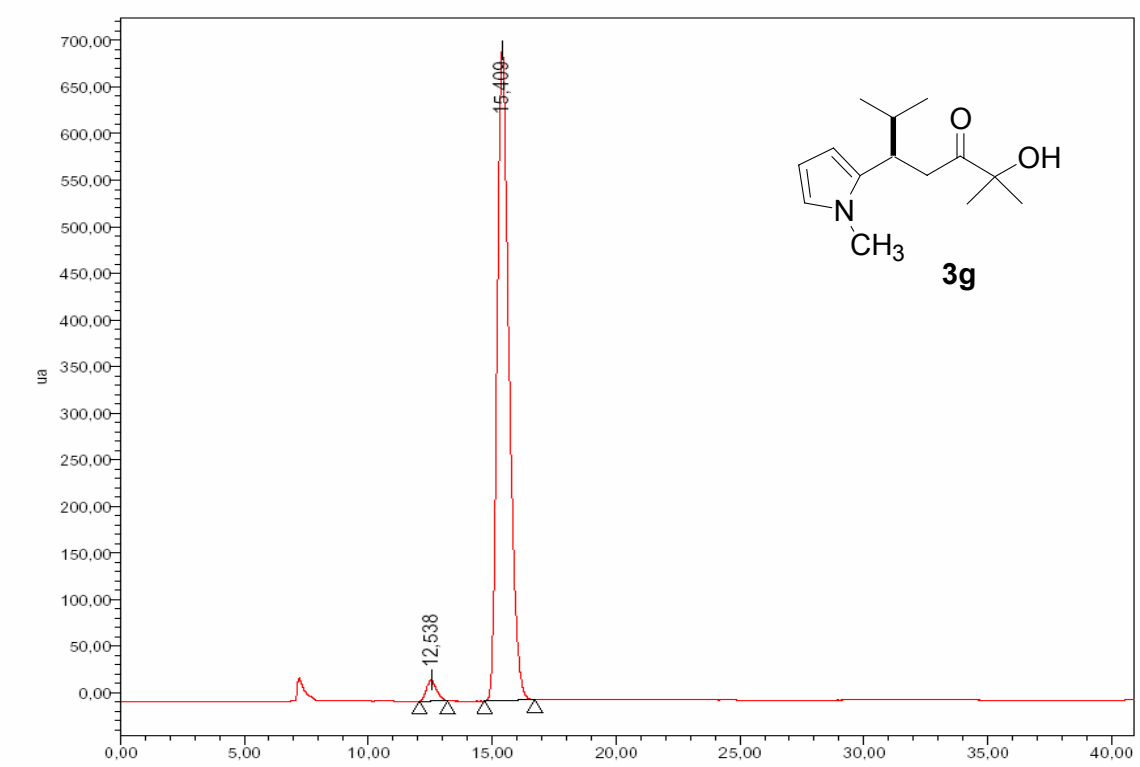


3f

Retention Time (min)	Area	% Area
12,930	143622	3,09
21,440	4500758	96,91

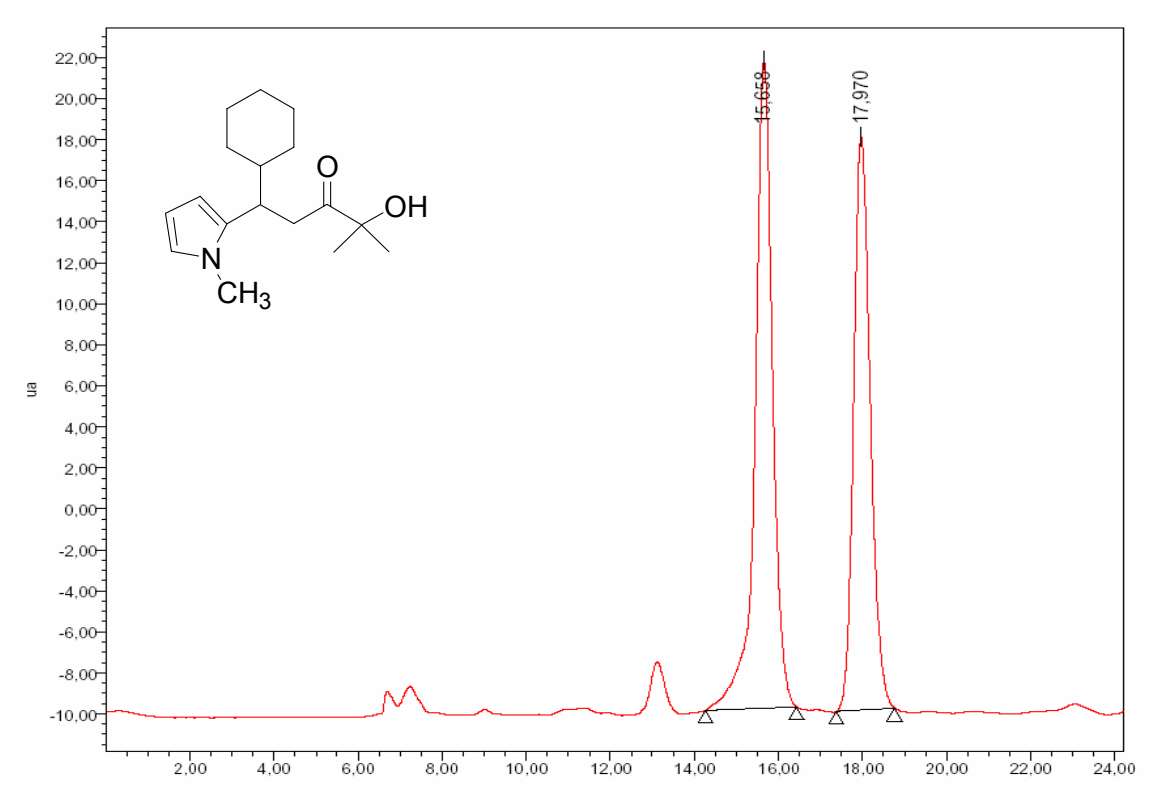
(Chiralcel OD column, hexane:iPrOH 95:5, 0.5 mL/min., 210 nm)

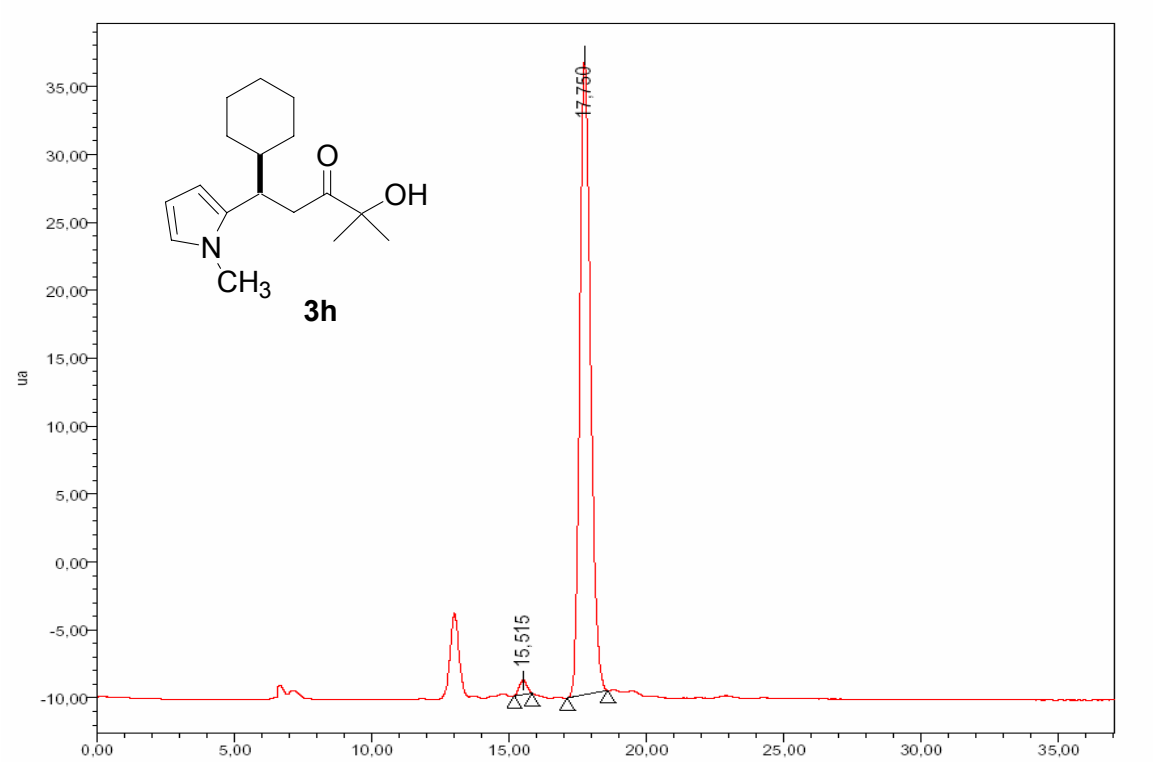




Retention Time (min)	Area	% Area	Height
12,538	630355	2,64	22768
15,409	23204920	97,36	698598

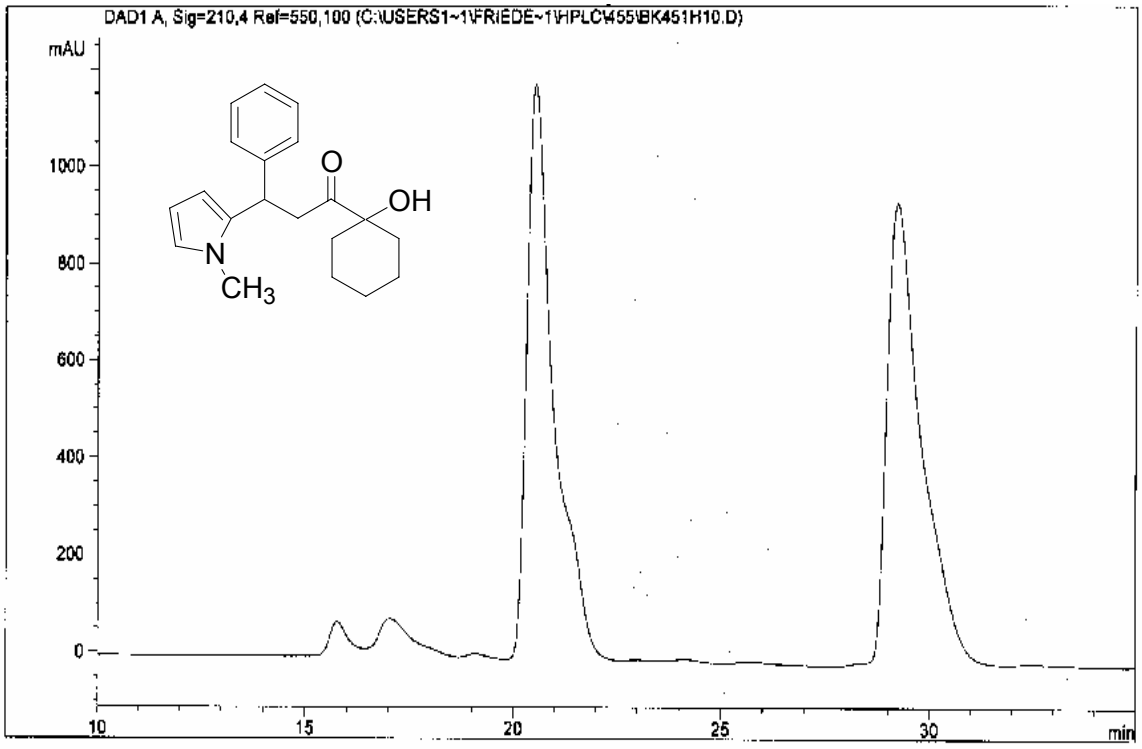
(Chiralcel OD column, hexane:iPrOH 97:3, 0.5 mL/min., 254 nm)

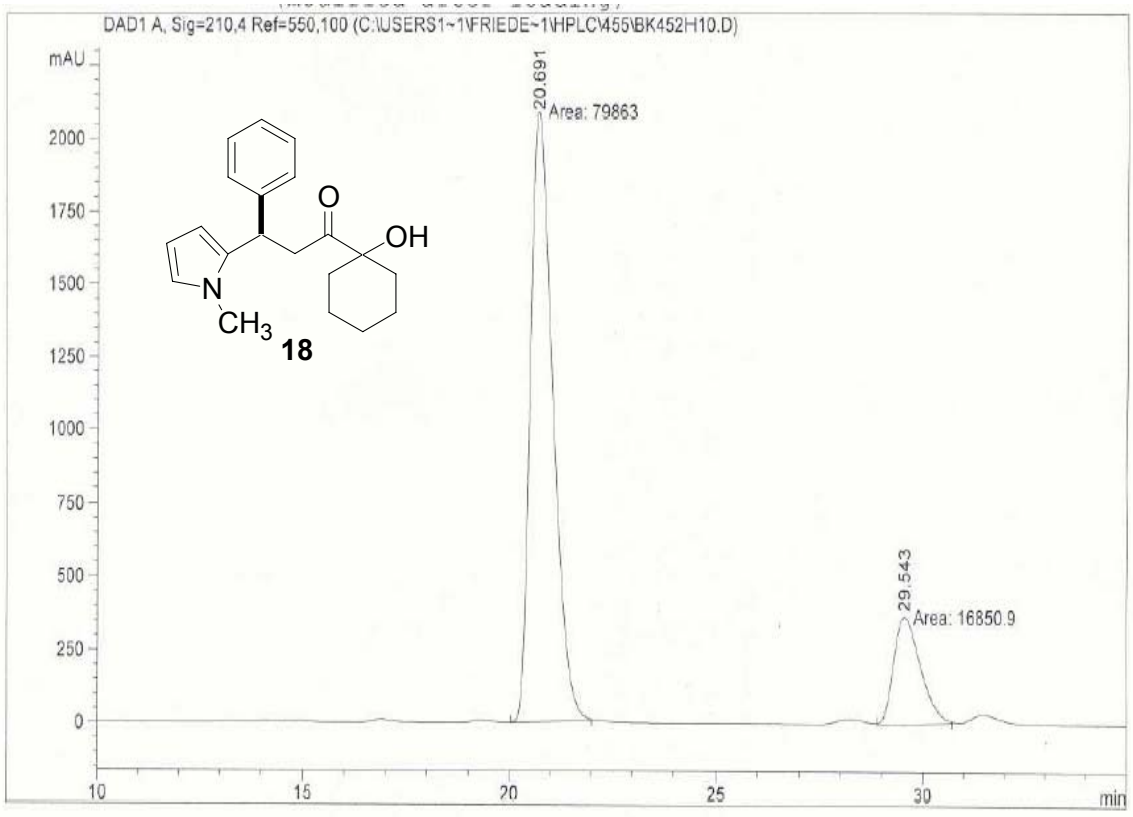




Retention Time (min)	Area	% Area
15,515	21269	1,64
17,750	1276155	98,36

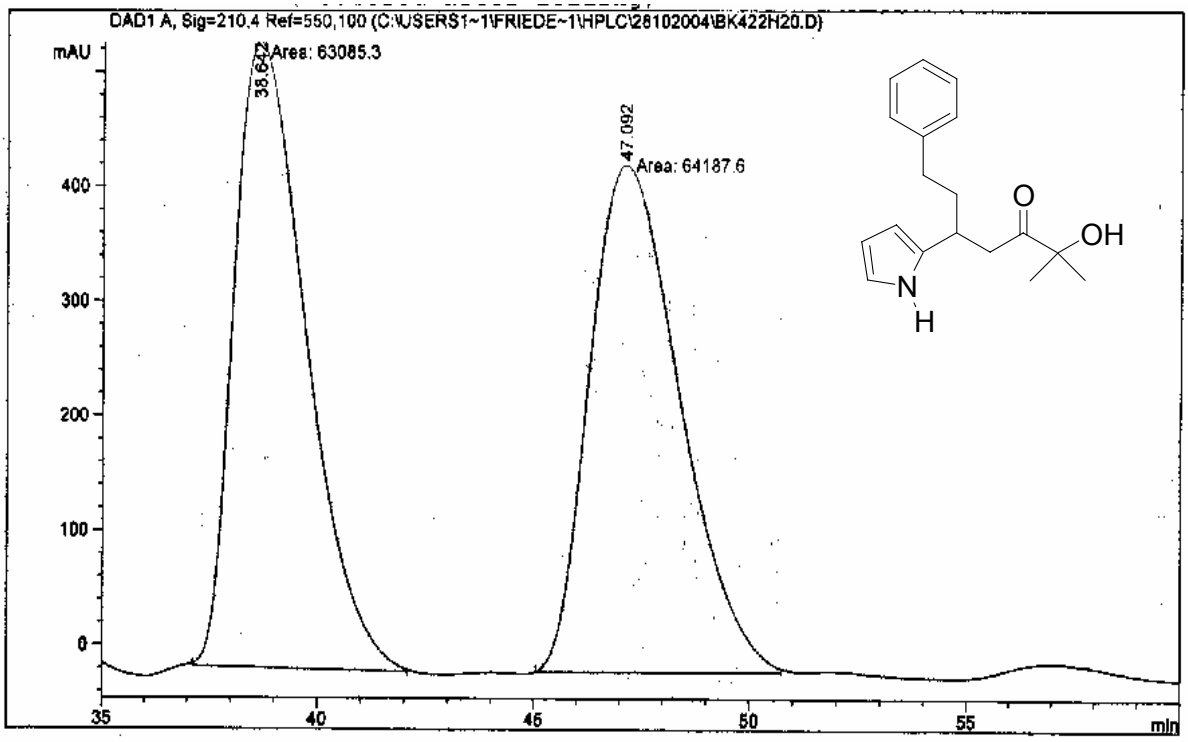
(Chiralpak AS column, hexane:iPrOH 98:2, 0.5 mL/min., 254 nm)

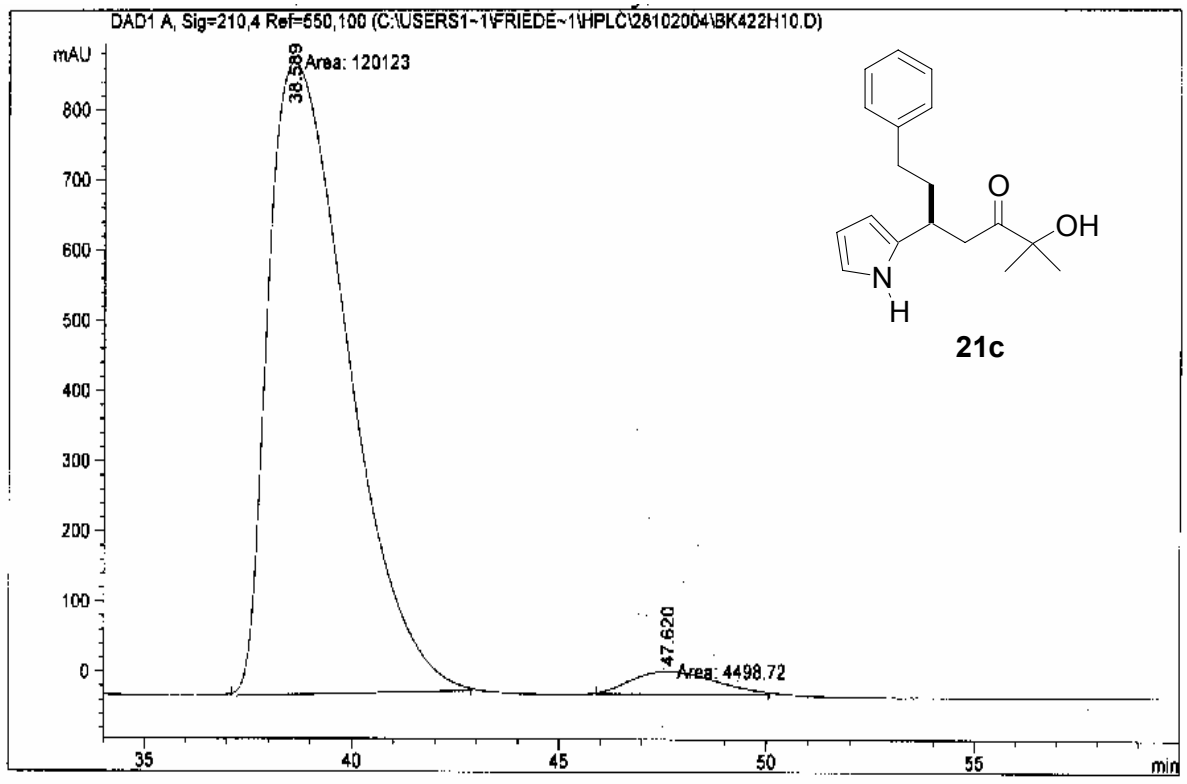




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
20.691	MM	0.6378	7.98630e4	2086.79517	82.5766
29.543	MM	0.7666	1.68509e4	366.33920	17.4234

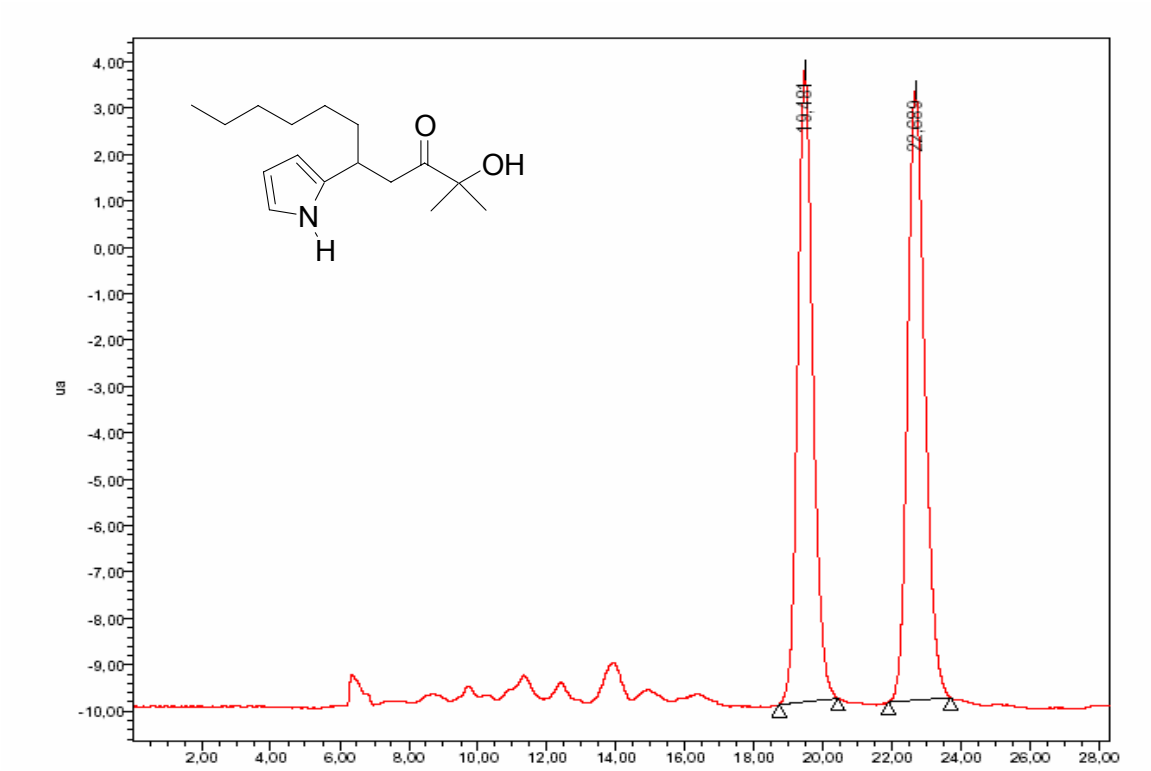
(Chiralpak IA column, hexane:iPrOH 95:05, 0.5 mL/min., 210 nm)

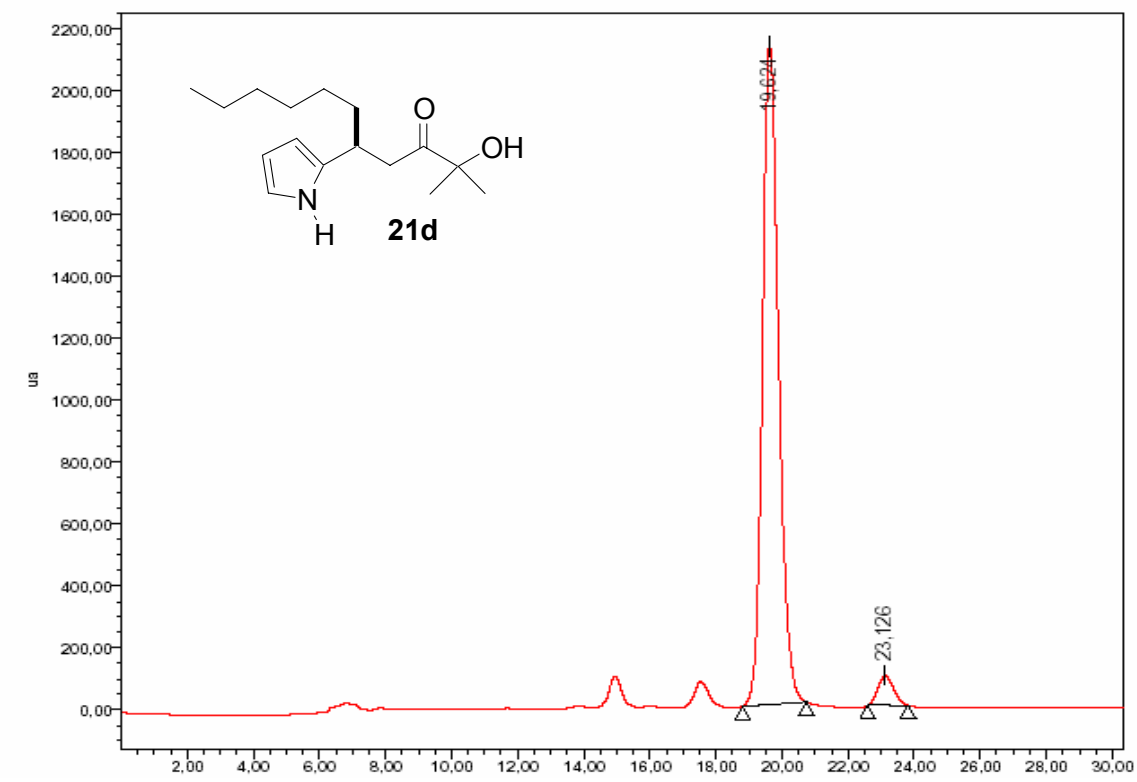




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
38.589	MM	2.2455	1.21590e5	902.49377	95.2475
47.620	MM	2.7191	6066.97607	37.18782	4.7525

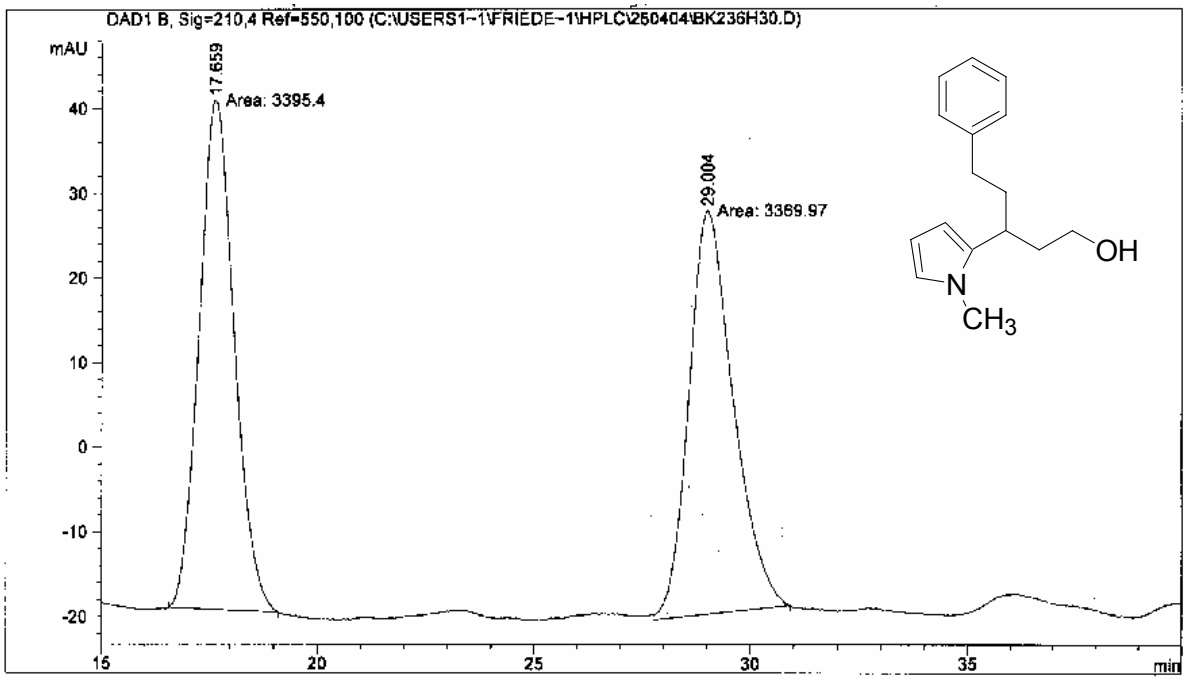
(Chiralcel OD column, hexane:iPrOH 95:5; 0.5 mL/min., 210 nm)

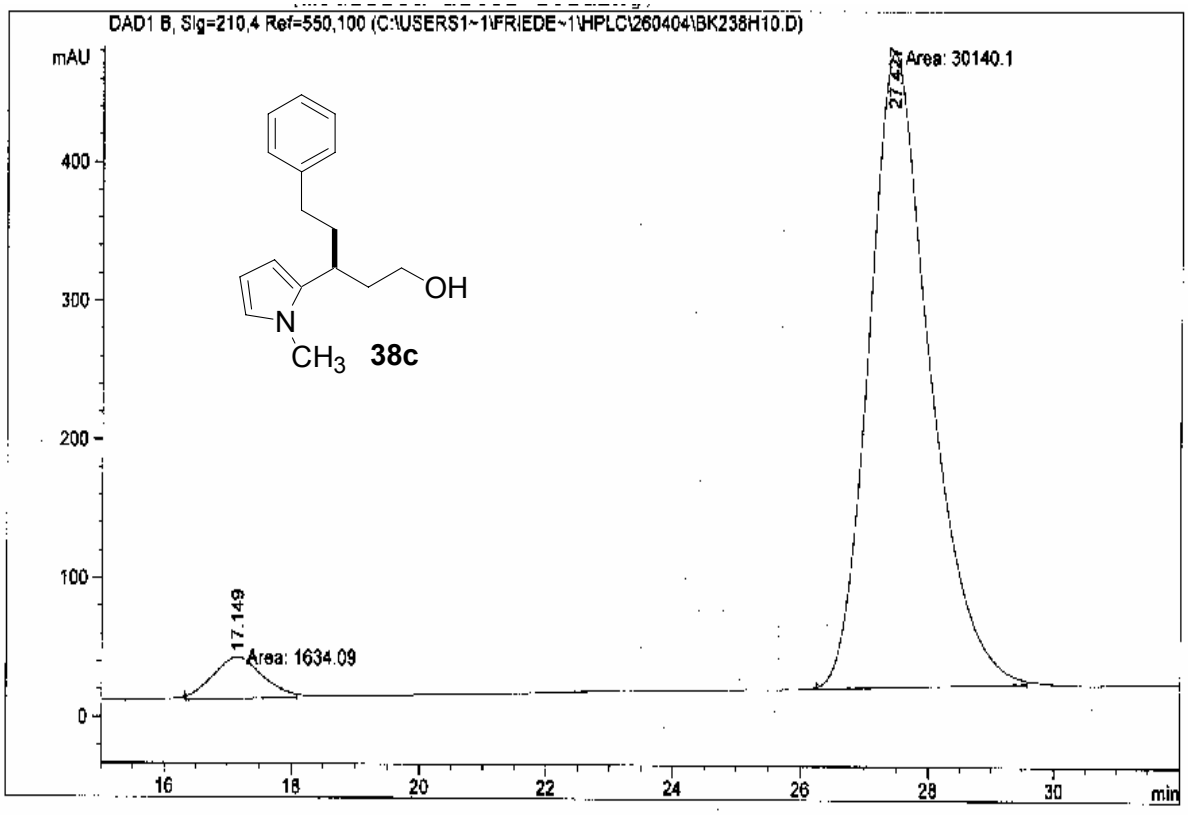




Retention Time (min)	Area	% Area
19,624	72289534	95,73
23,126	3223409	4,27

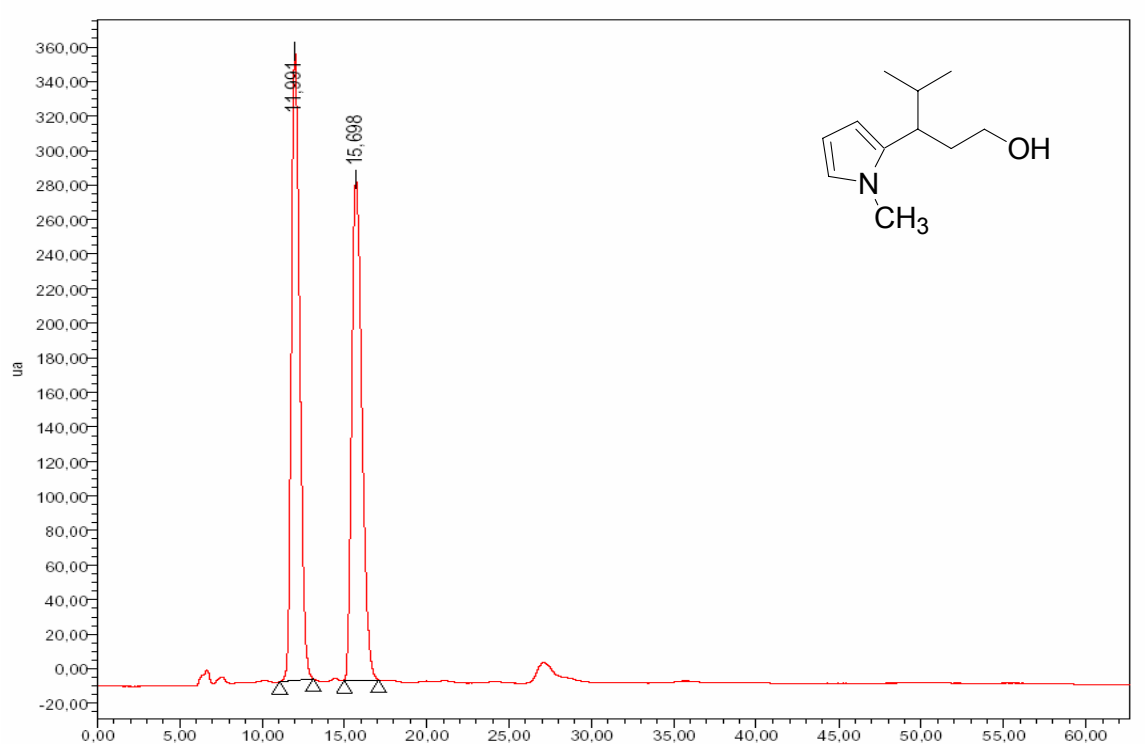
(Chiralpak IA column, hexane:iPrOH 95:5, 0.5 mL/min., 254 nm)

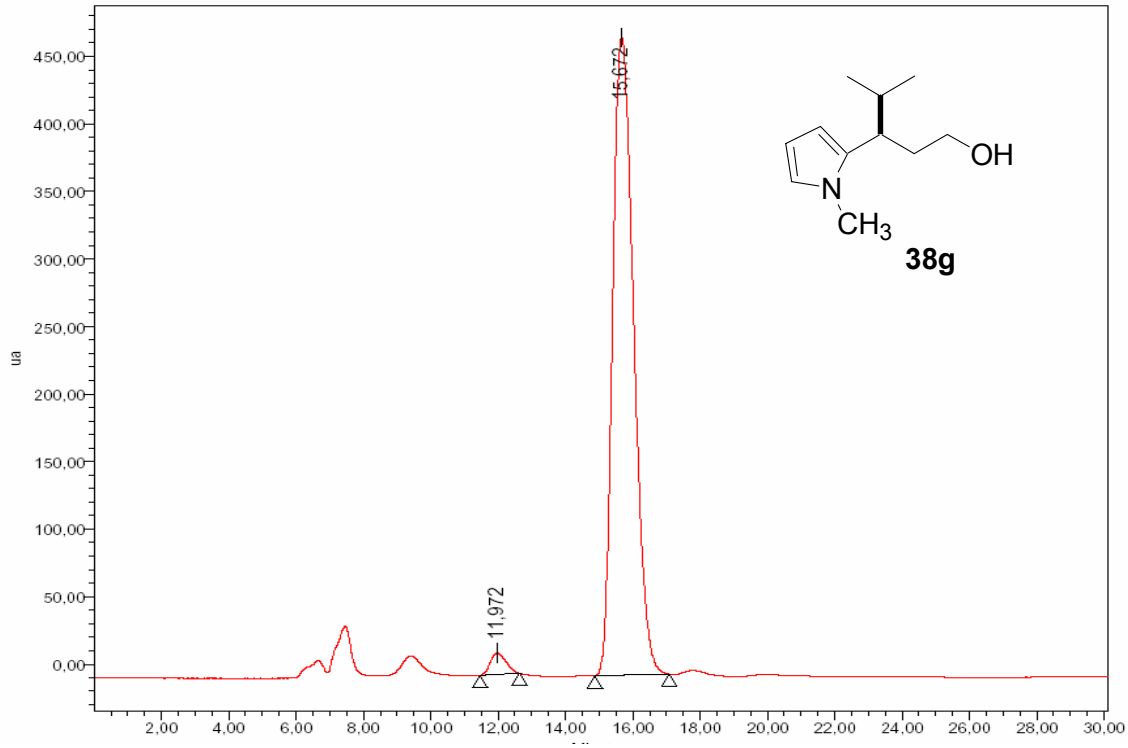




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
17.149	MM	0.9905	1888.89844	31.78224	5.7470
27.427	MM	1.1280	3.09788e4	457.70676	94.2530

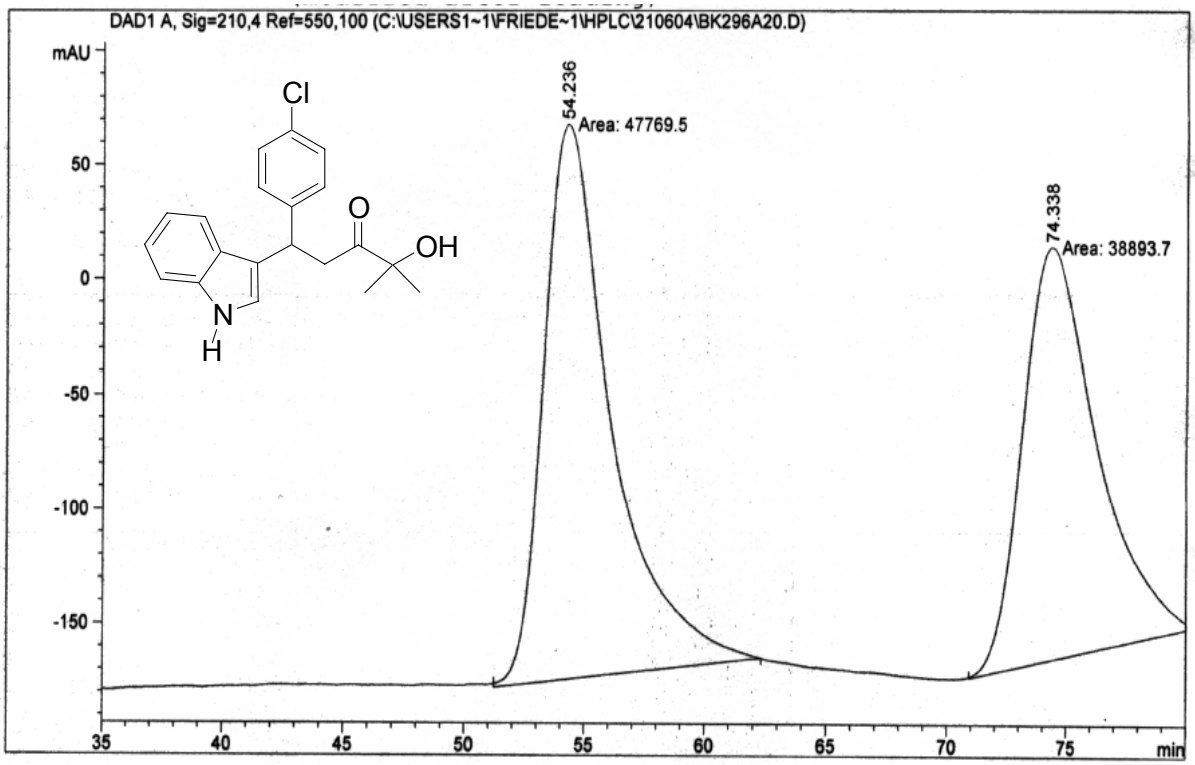
(Chiralpak OD column, hexane:iPrOH 90:10, 0.5 mL/min., 220 nm)

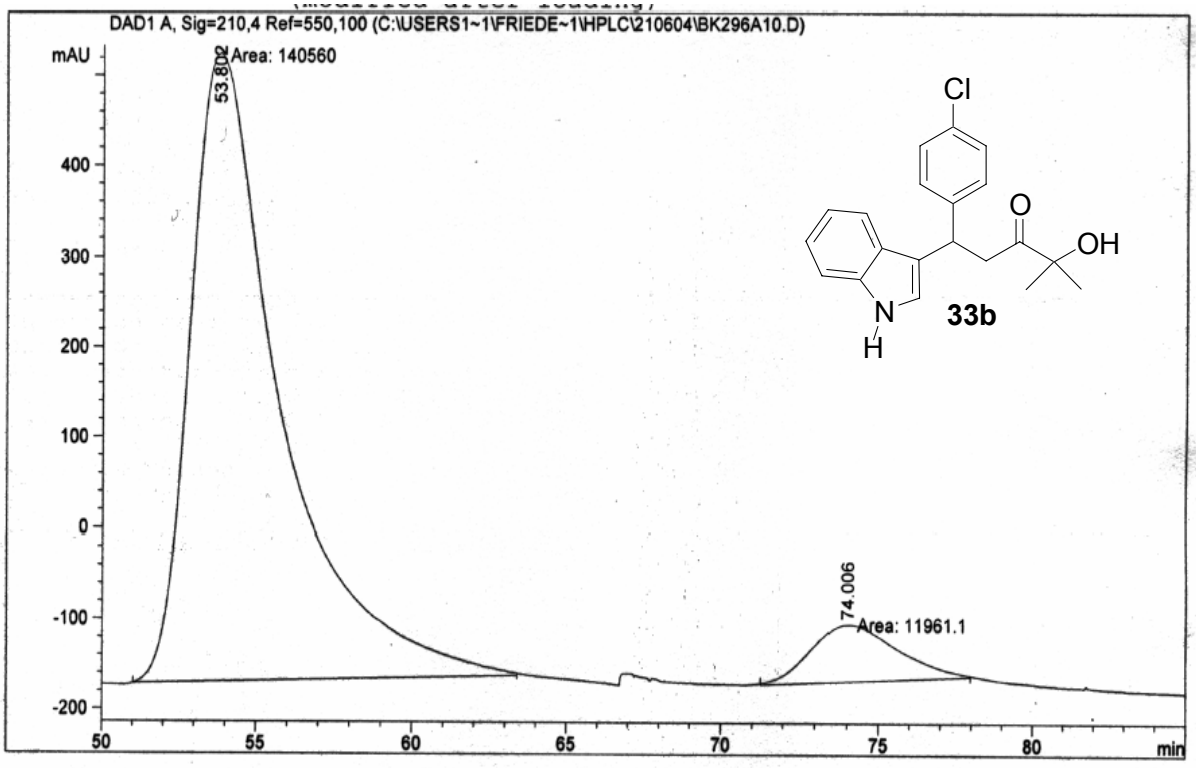




Retention Time (min)	Area	% Area
11,972	517352	2,48
15,672	20360172	97,52

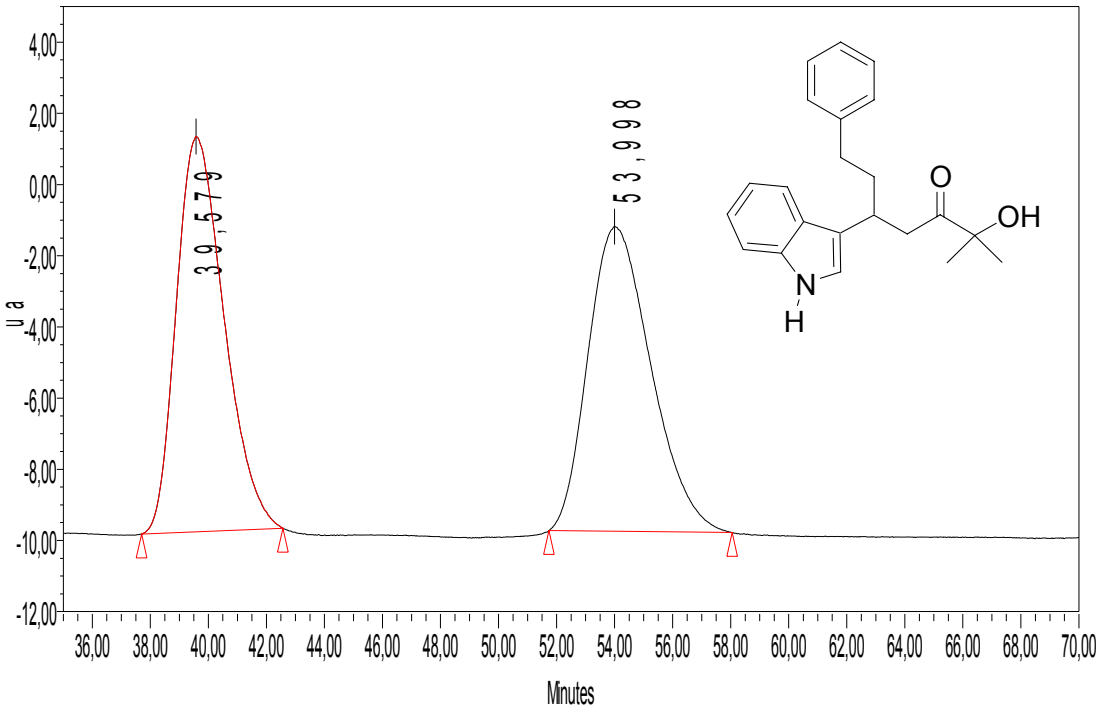
(Chiralpak OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm)

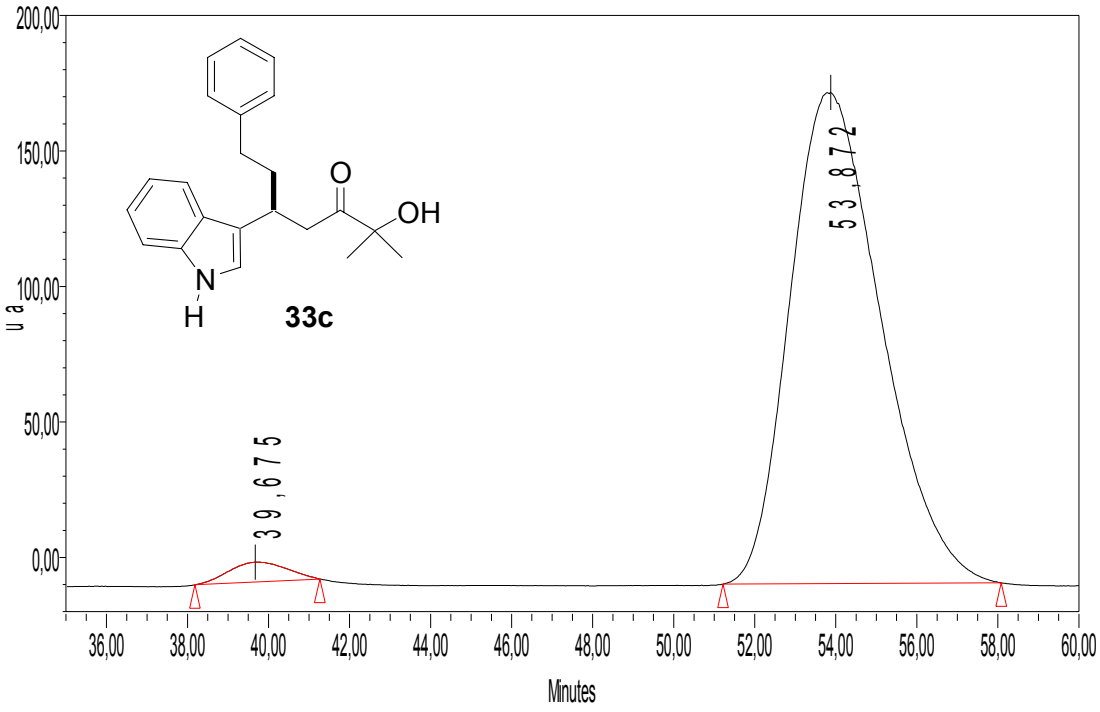




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
53.802	MM	3.3733	1.40560e5	694.46564	92.1577
74.006	MM	3.1658	1.19611e4	62.97143	7.8423

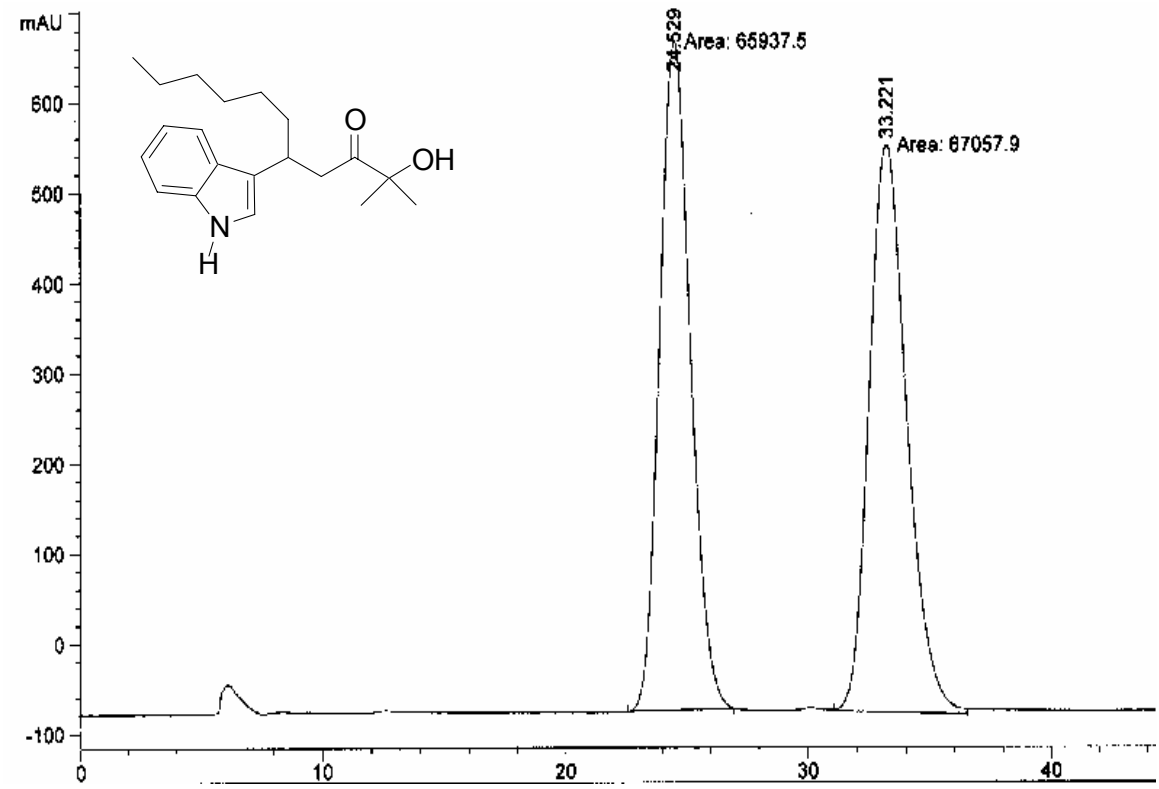
(Chiralpak AD column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm)

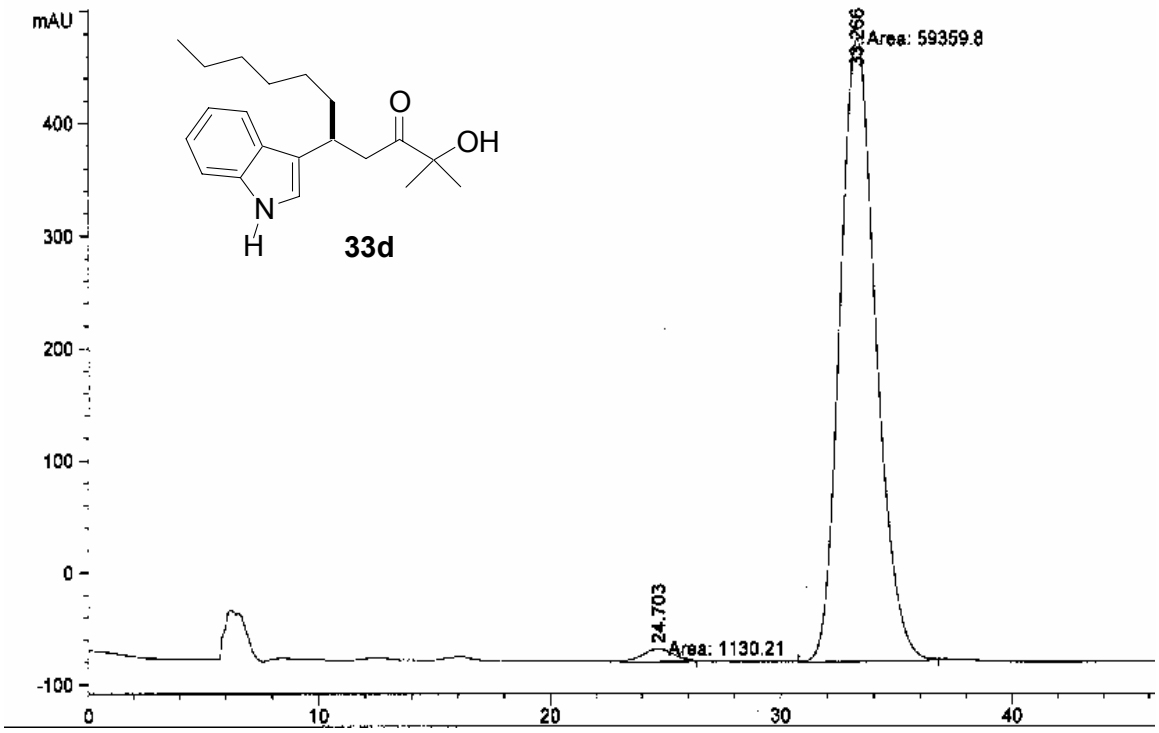




Retention Time (min)	Area	% Area
40,050	2492334	1,21
54,476	202894248	98,79

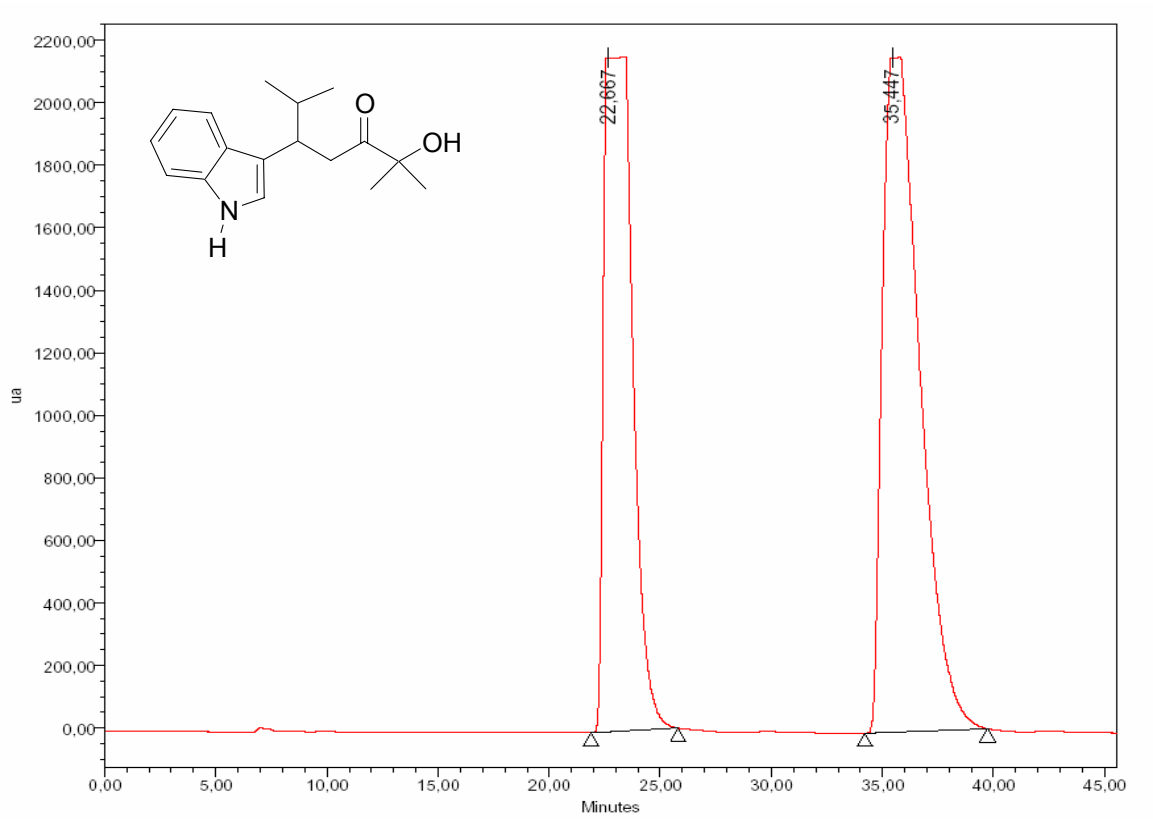
(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm)

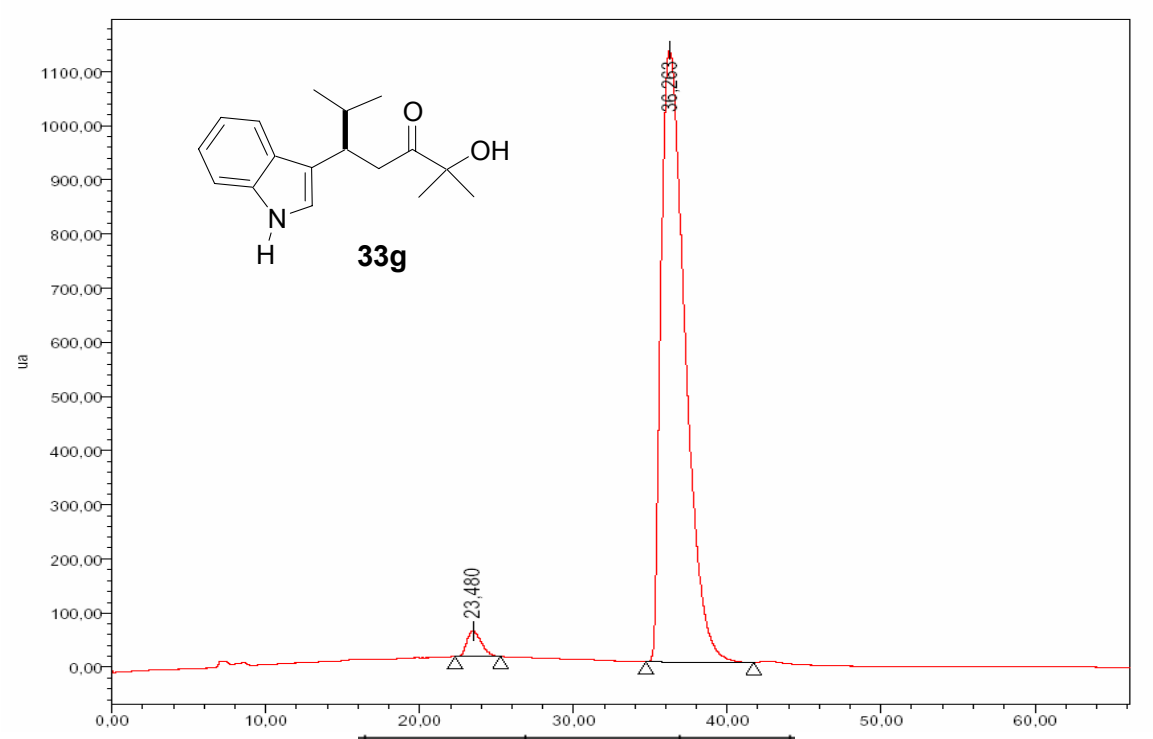




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
24.703	MM	1.5823	1130.21045	11.90457	1.8684
33.266	MM	1.7848	5.93598e4	554.30847	98.1316

(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min, 254 nm)

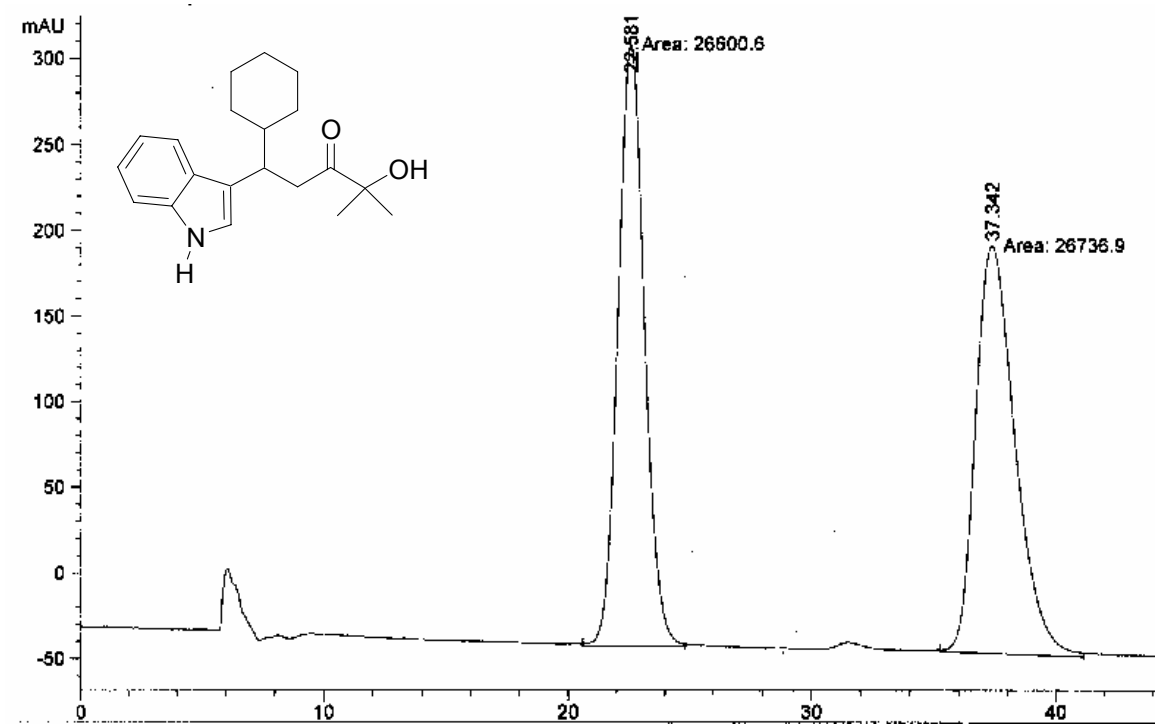


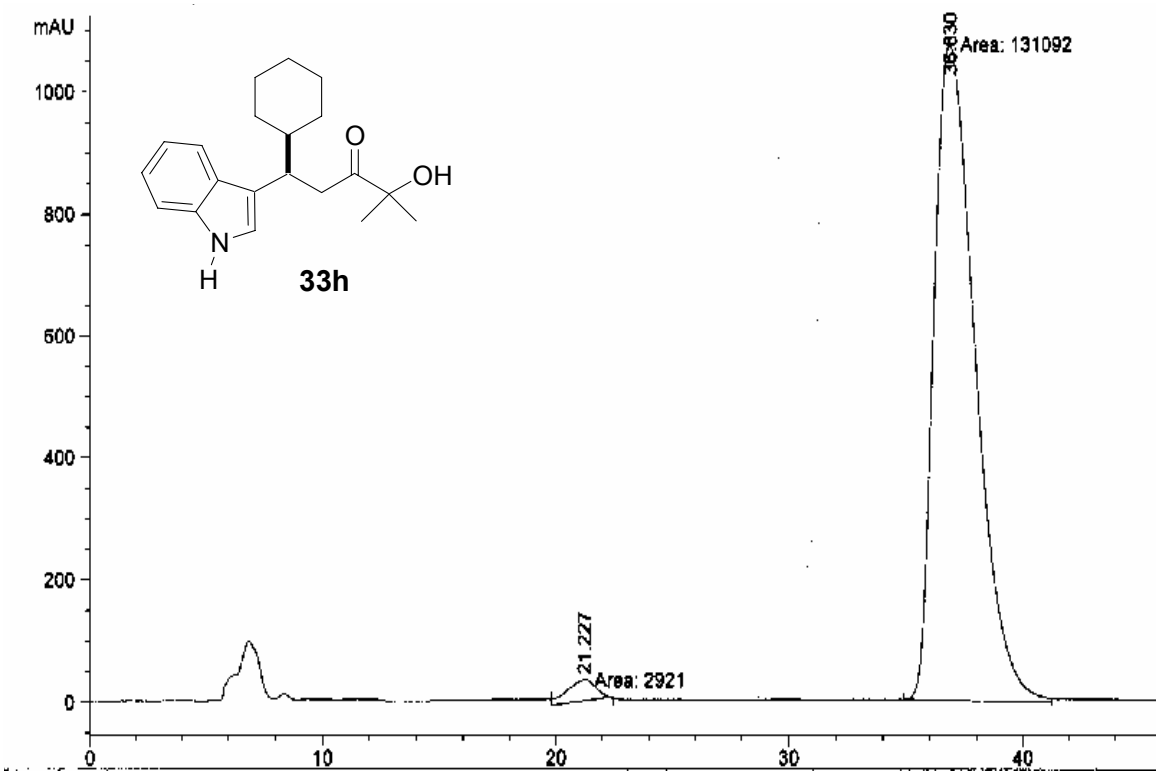


33g

Retention Time (min)	Area	% Area
23,480	3112839	2,47
36,263	122884604	97,53

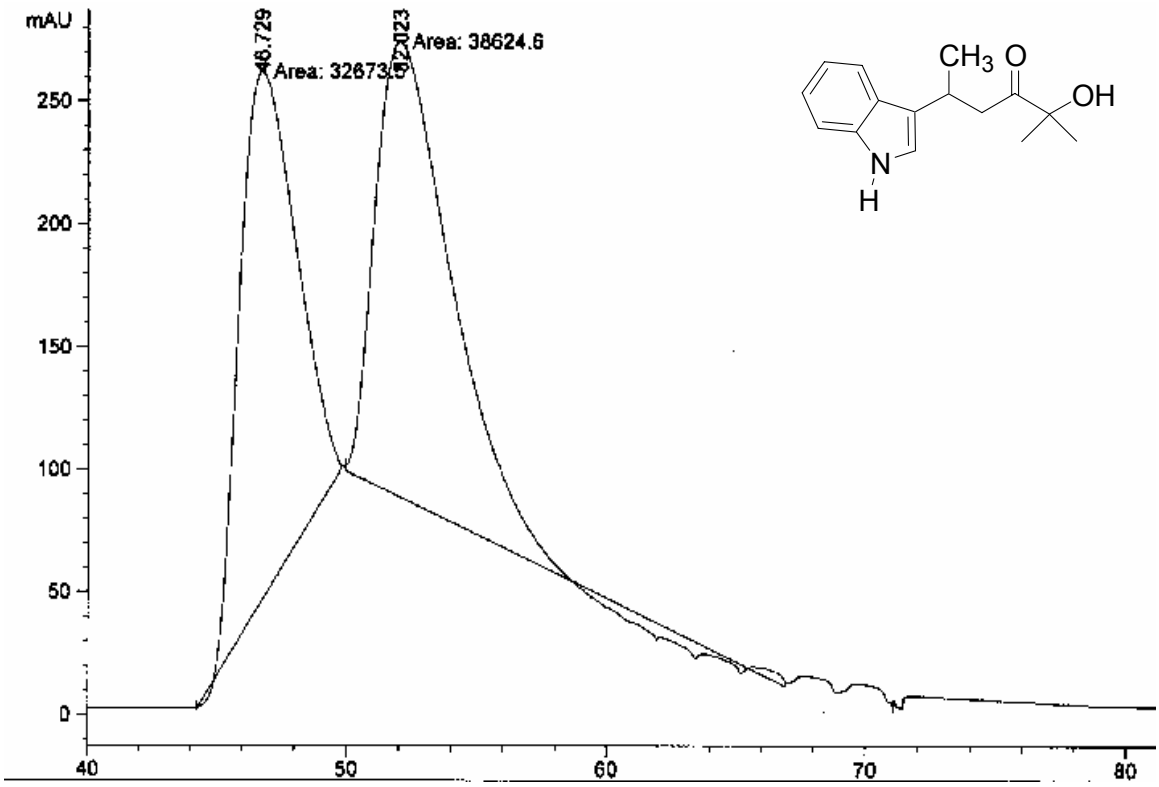
(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm)

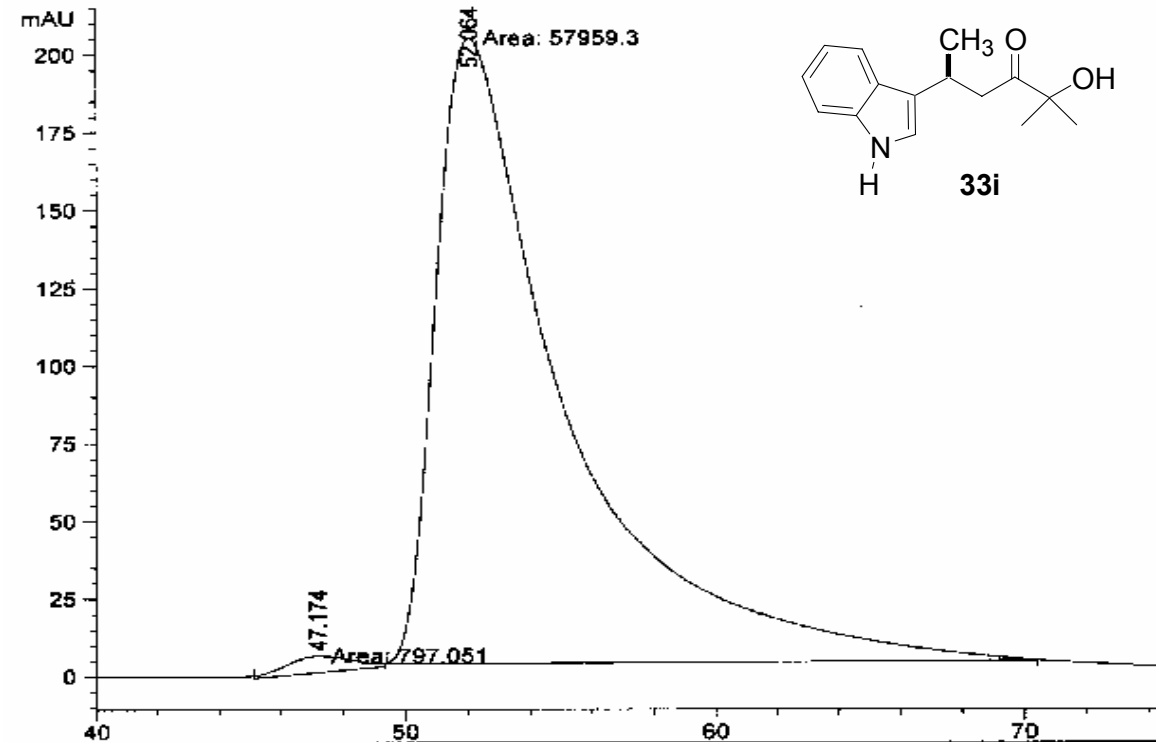




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
21.227	MM	1.0373	2920.99927	33.54160	2.1796
36.830	MM	2.0417	1.31092e5	1070.13342	97.8204

(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm)

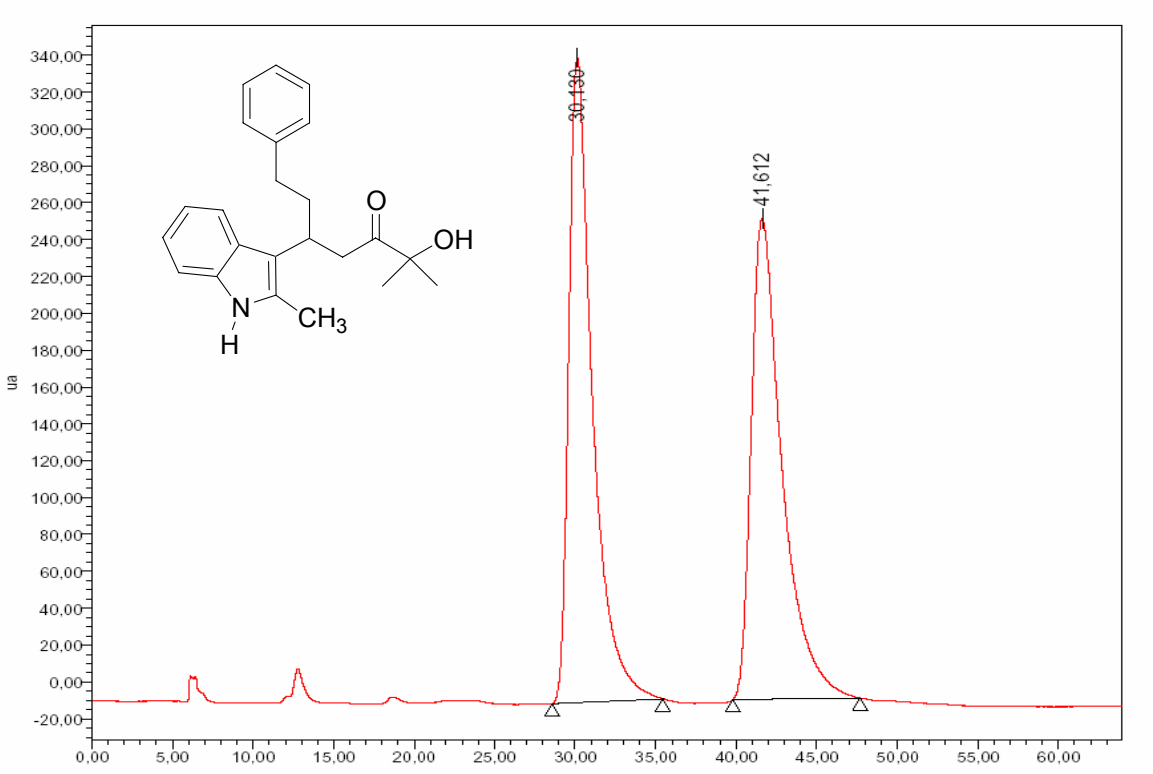


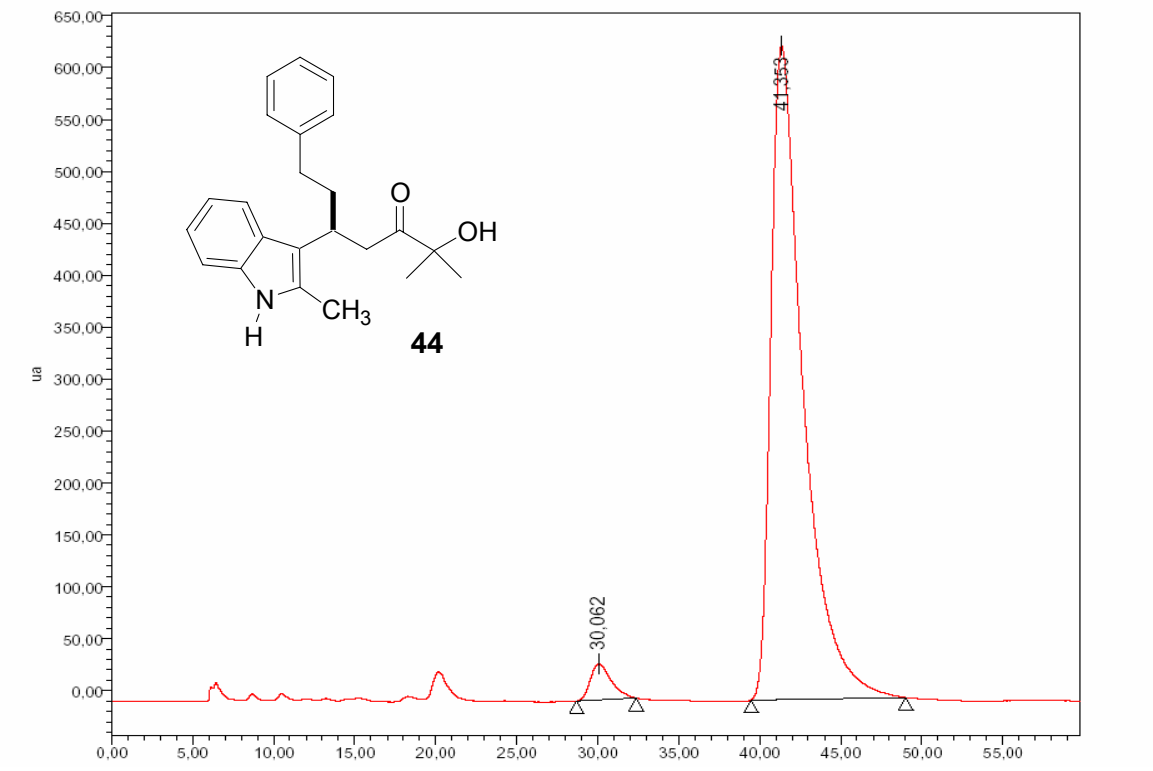


33i

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
47.174	MM	2.4482	797.05127	5.42600	1.3565
52.064	MM	4.8097	5.79593e4	200.84288	98.6435

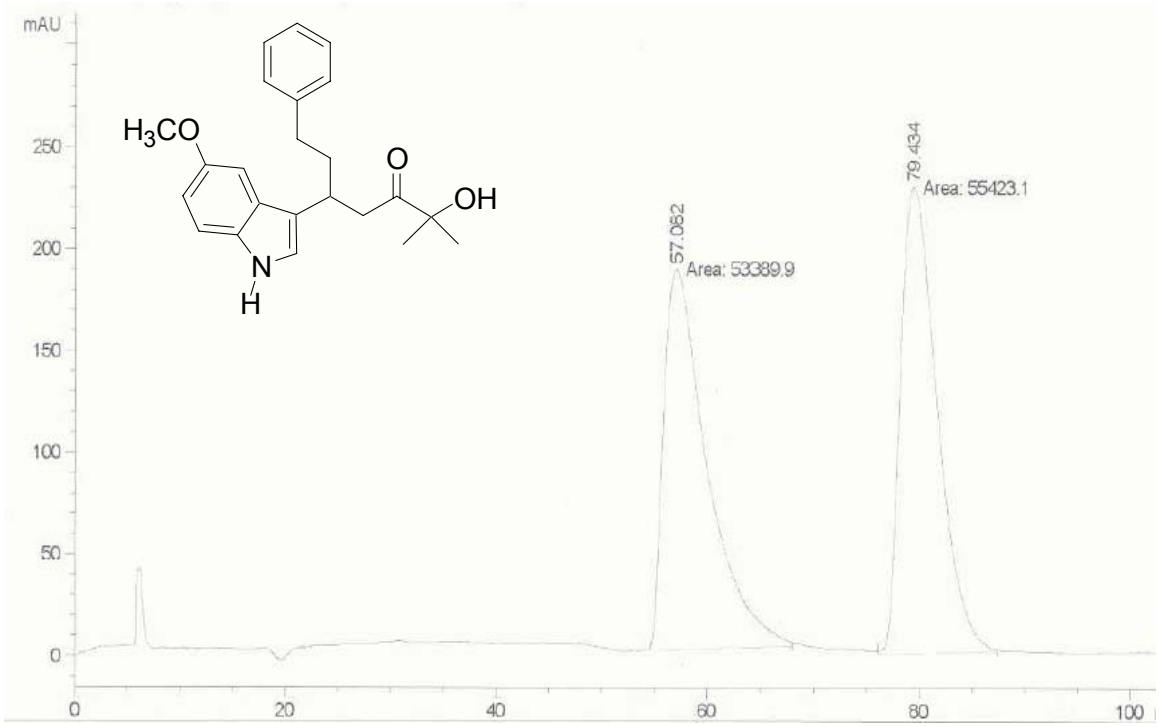
(Chiralpak OJ column, hexane:iPrOH 80:20, 0.5 mL/min., 254 nm)

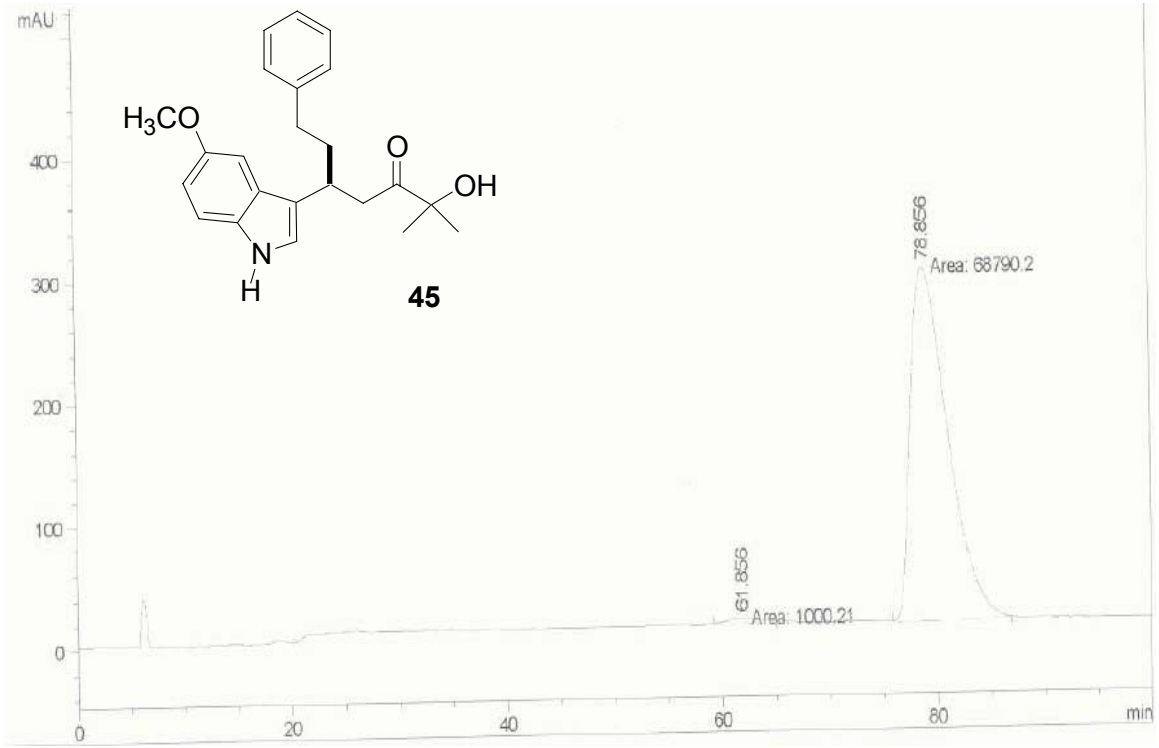




Retention Time (min)	Area	% Area
30,062	3100764	3,42
41,353	87523558	96,58

(Chiralpak AD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm)





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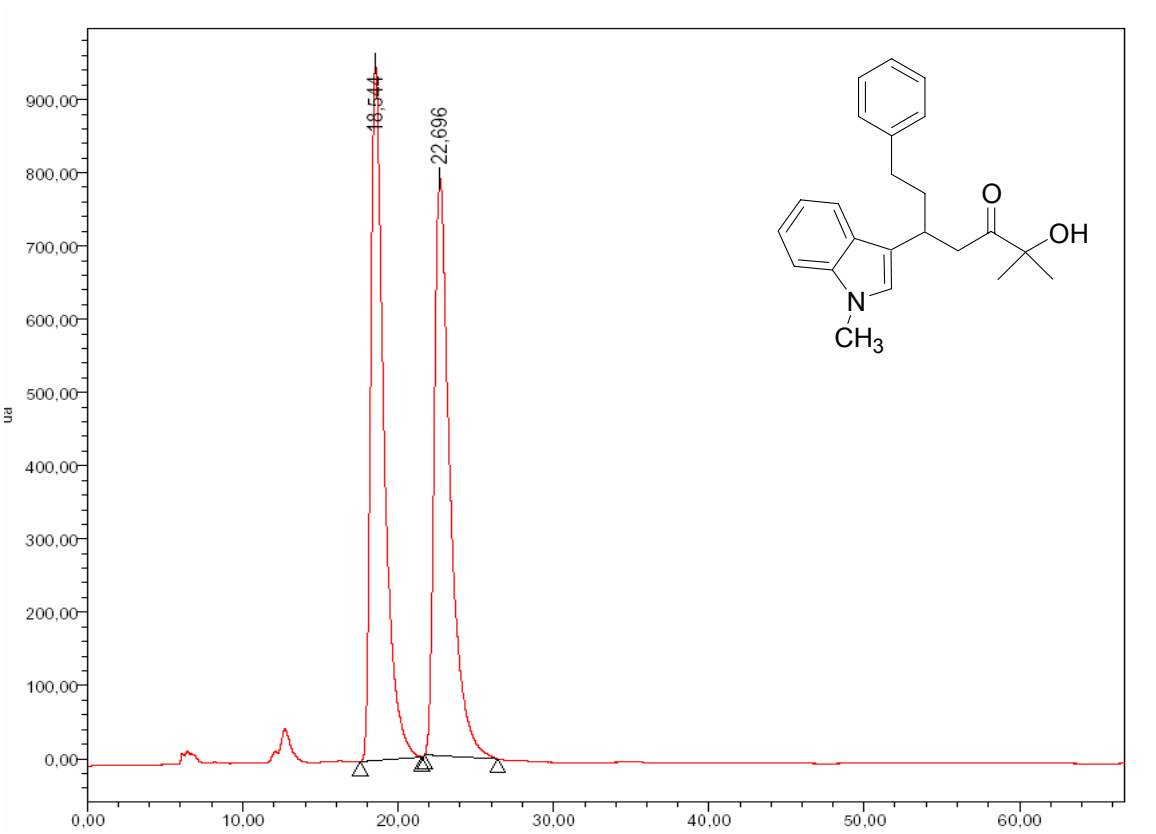
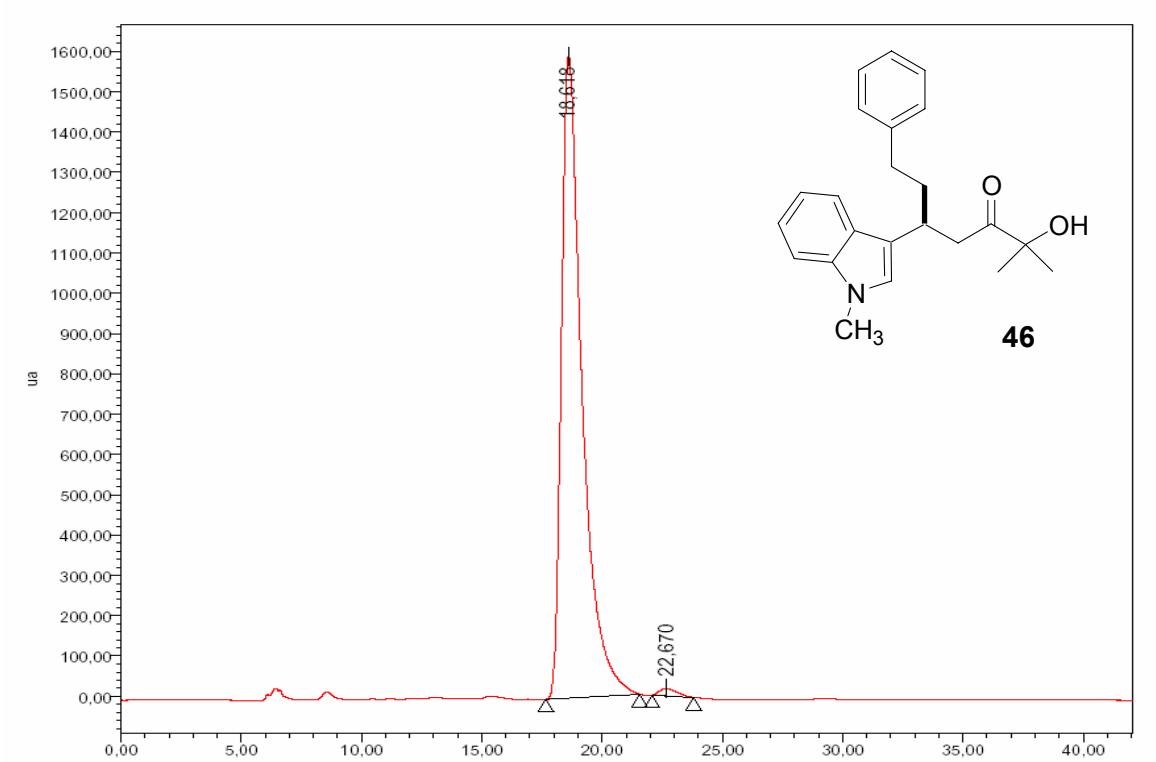
RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
61.856	MM	3.8355	1000.21326	4.34627	1.4332
78.856	MM	3.9796	6.87902e4	288.09320	98.5668

(Chiralcel OD column, hexane:iPrOH 90:10; 0.5 mL/min., 210 nm)





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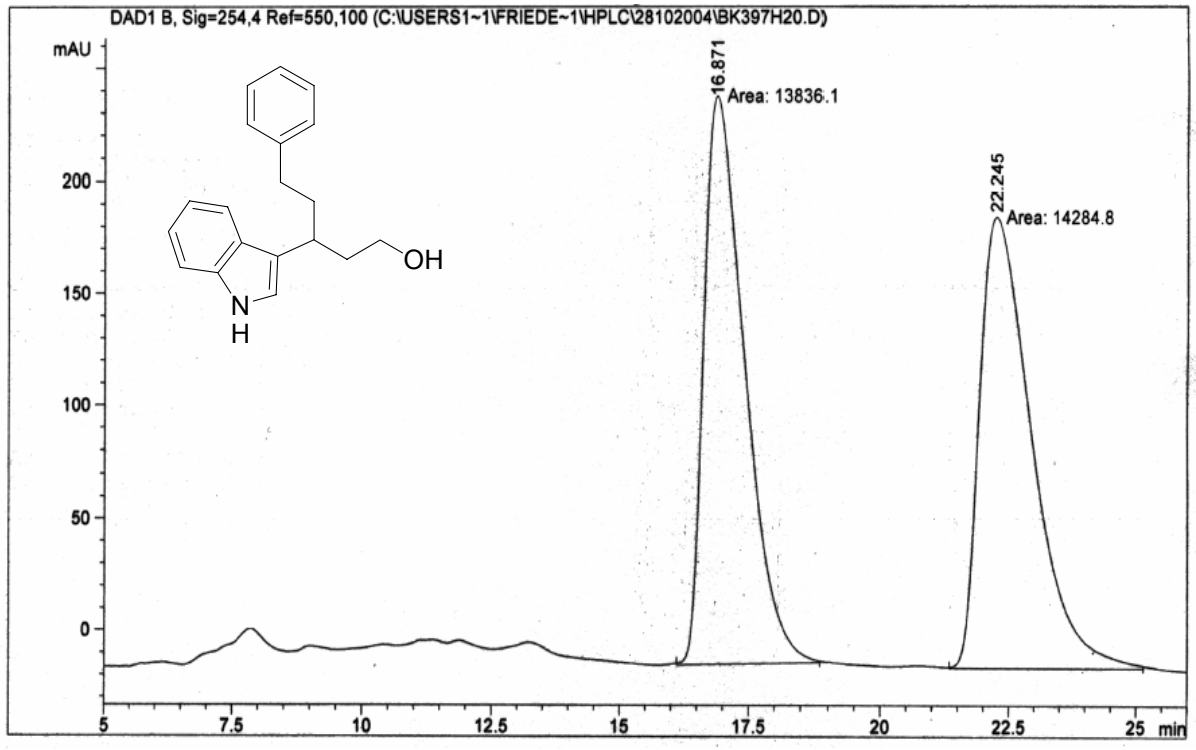
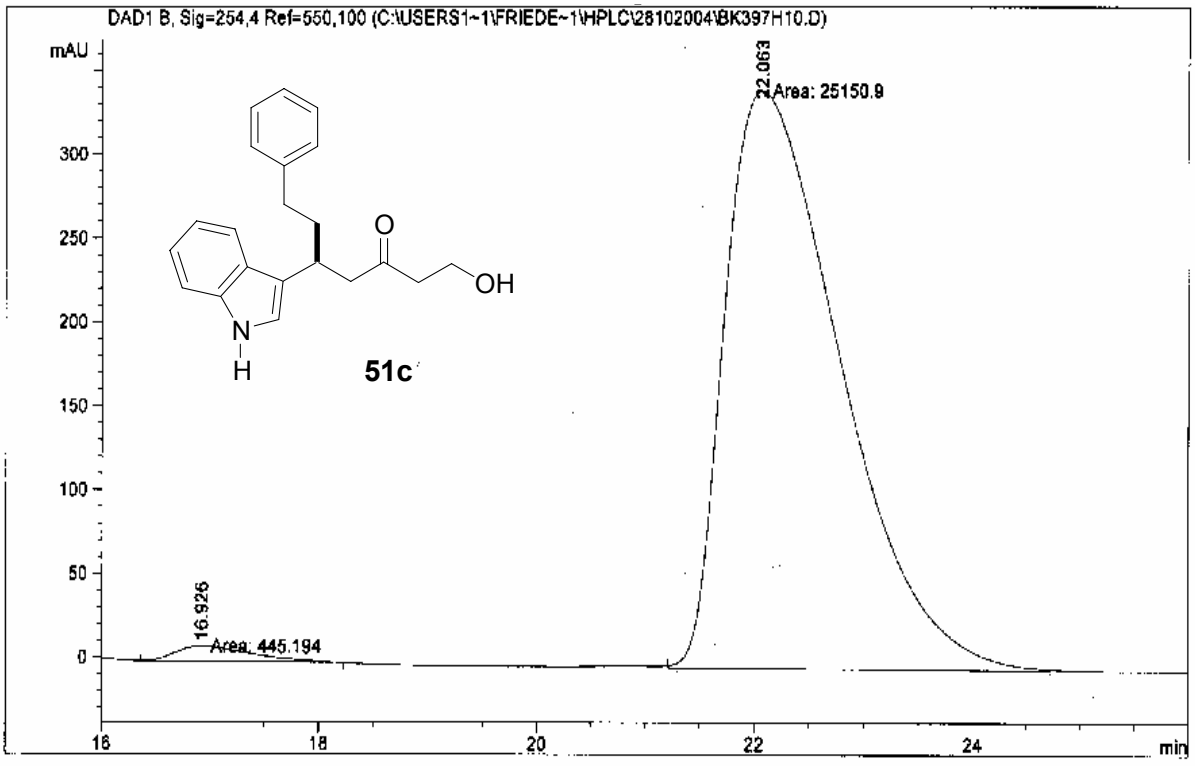
Retention Time (min)	Area	% Area
18,618	95499357	99,05
22,670	918619	0,95

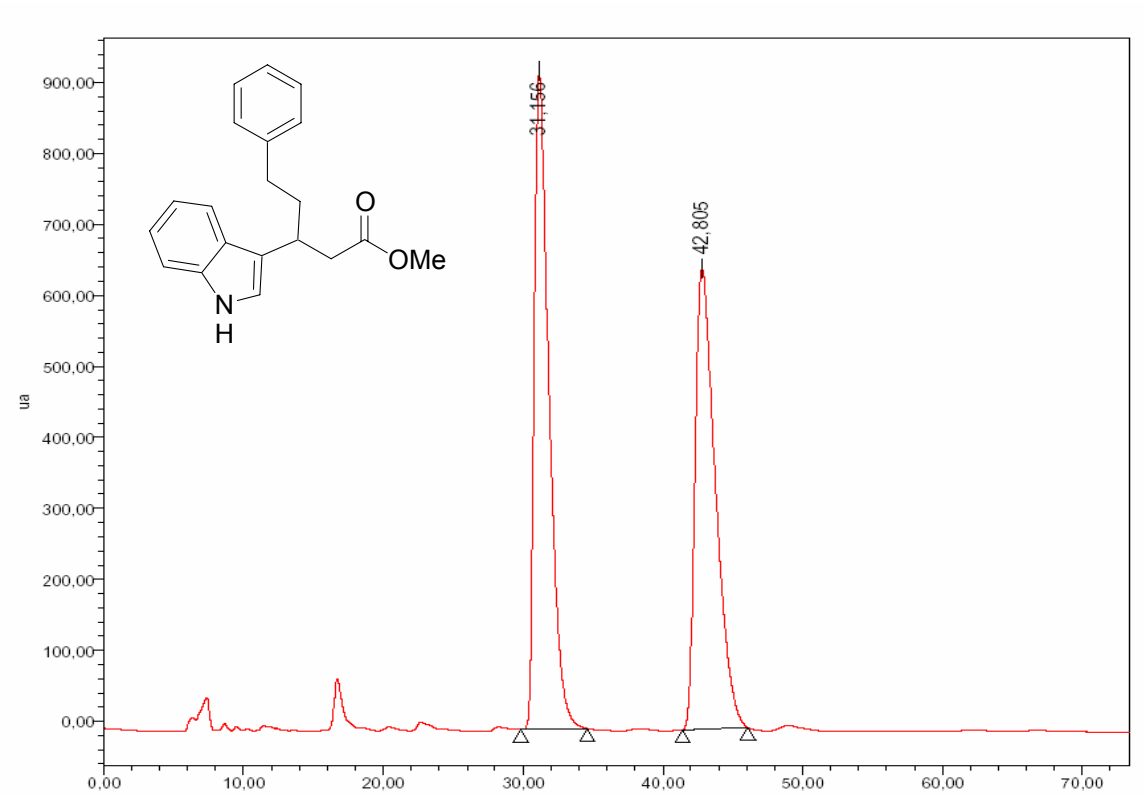
(Chiralpak AD column, hexane:iPrOH 90:10; 0.5 mL/min., 254 nm)

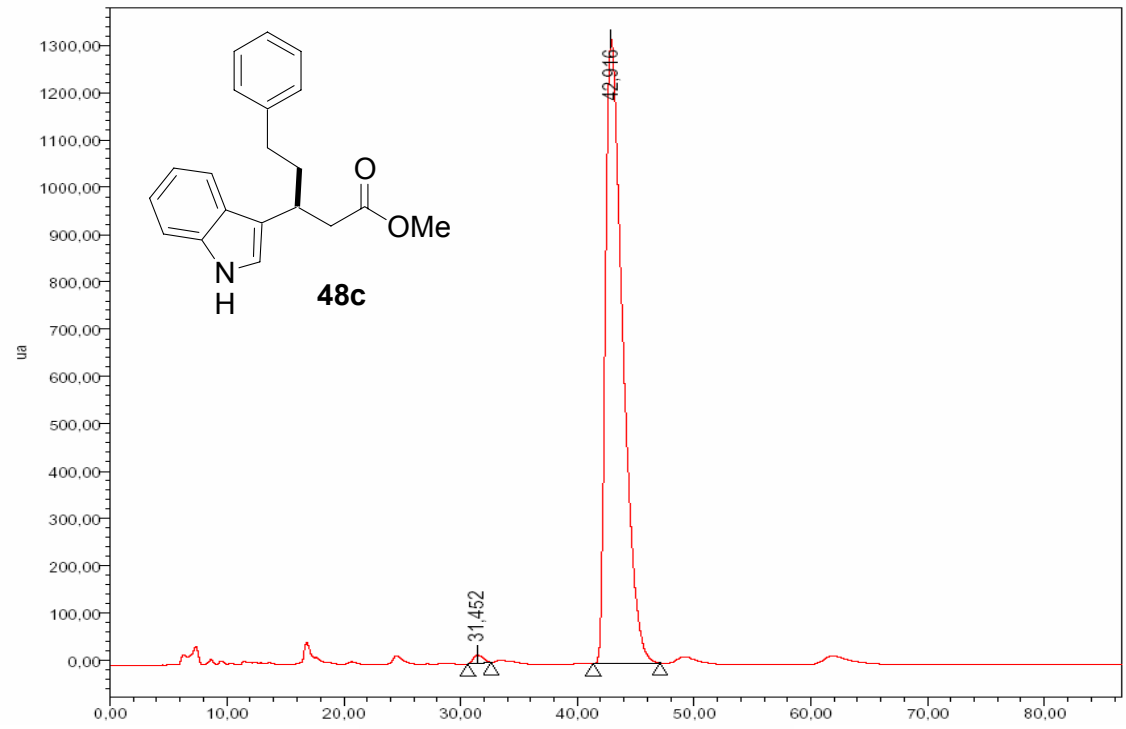




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
16.926	MM	0.7938	445.19449	9.34757	1.7393
22.063	MM	1.2195	2.51509e4	343.71844	98.2607

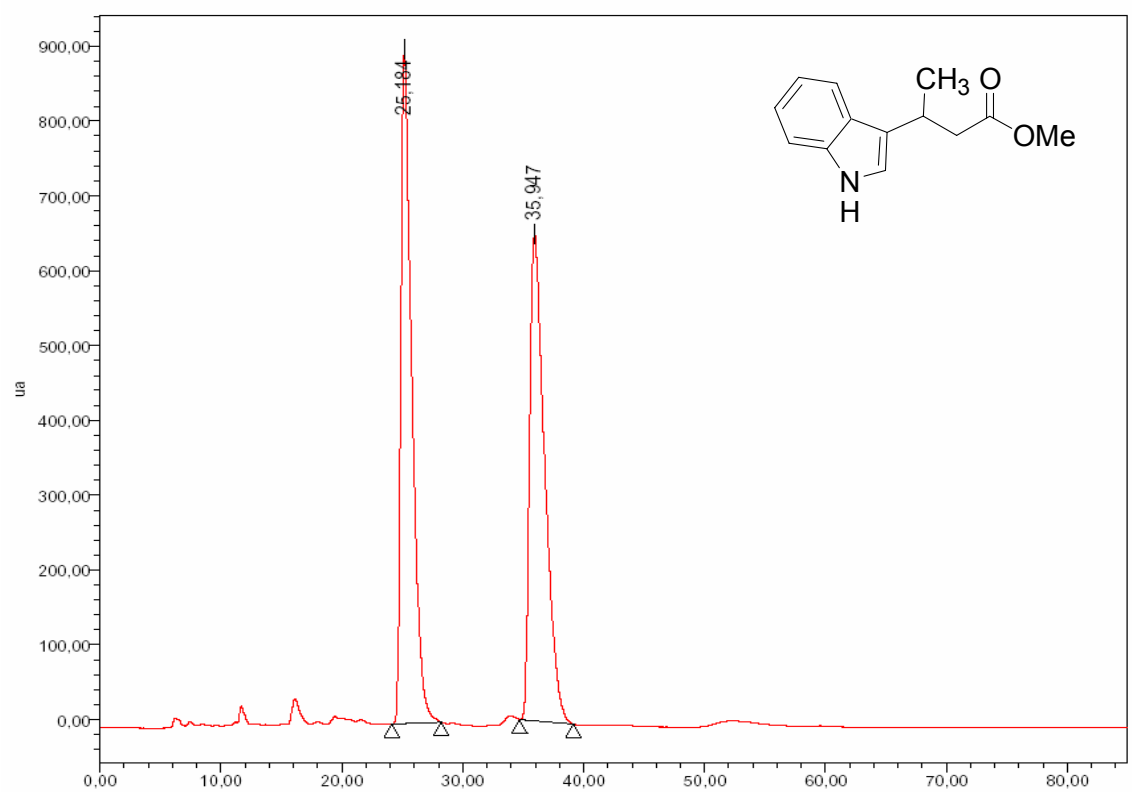
(Chiralcel OD column, hexane:iPrOH 80:20, 0.5 mL/min., 210 nm)

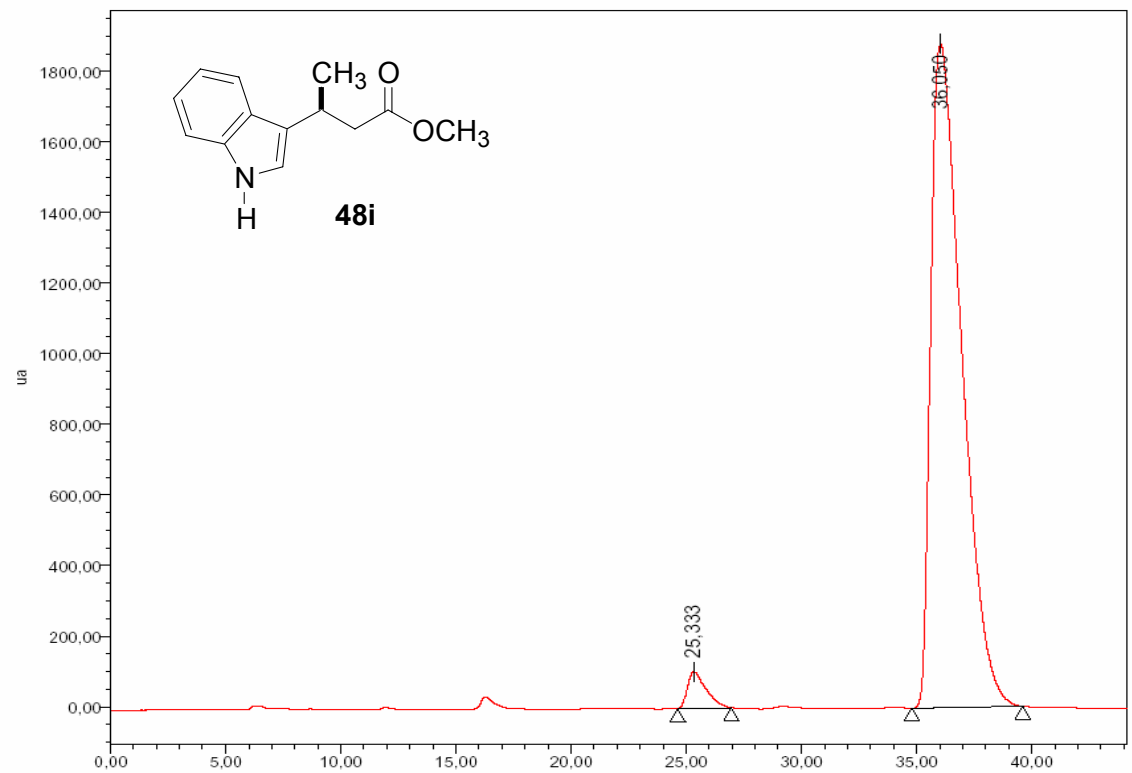




Retention Time (min)	Area	% Area
31,452	1021043	0,75
42,916	135317513	99,25

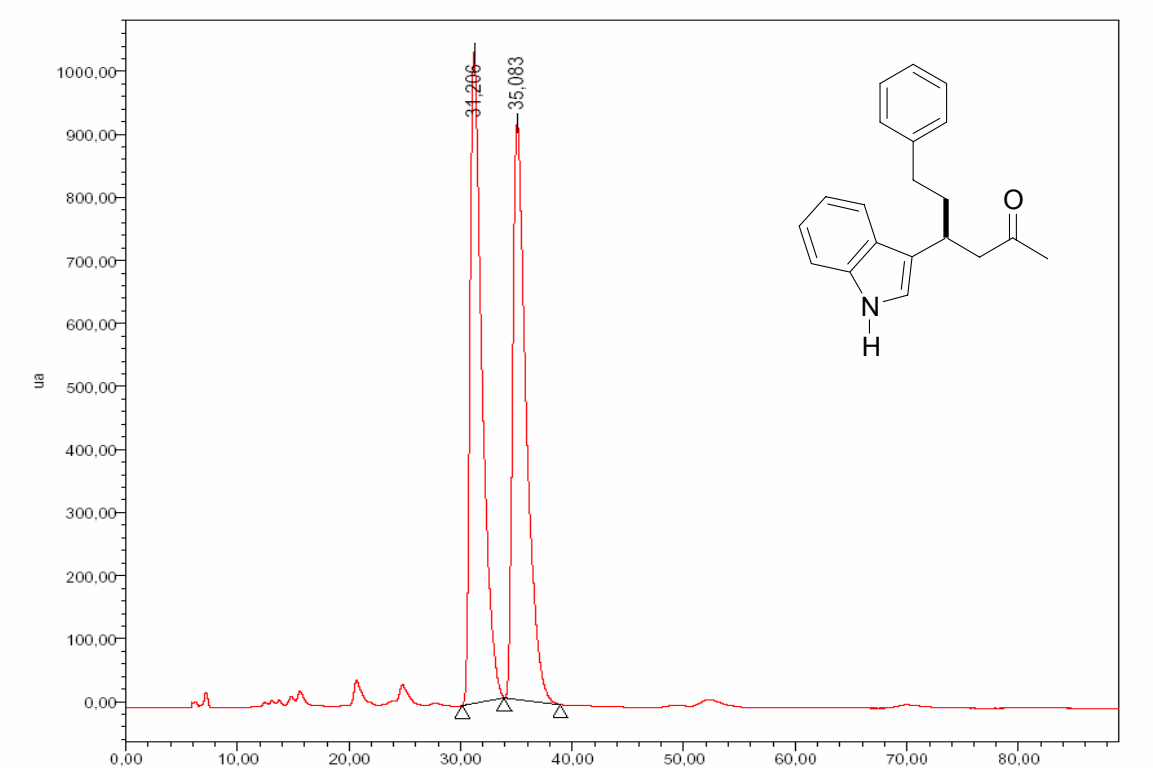
(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm)

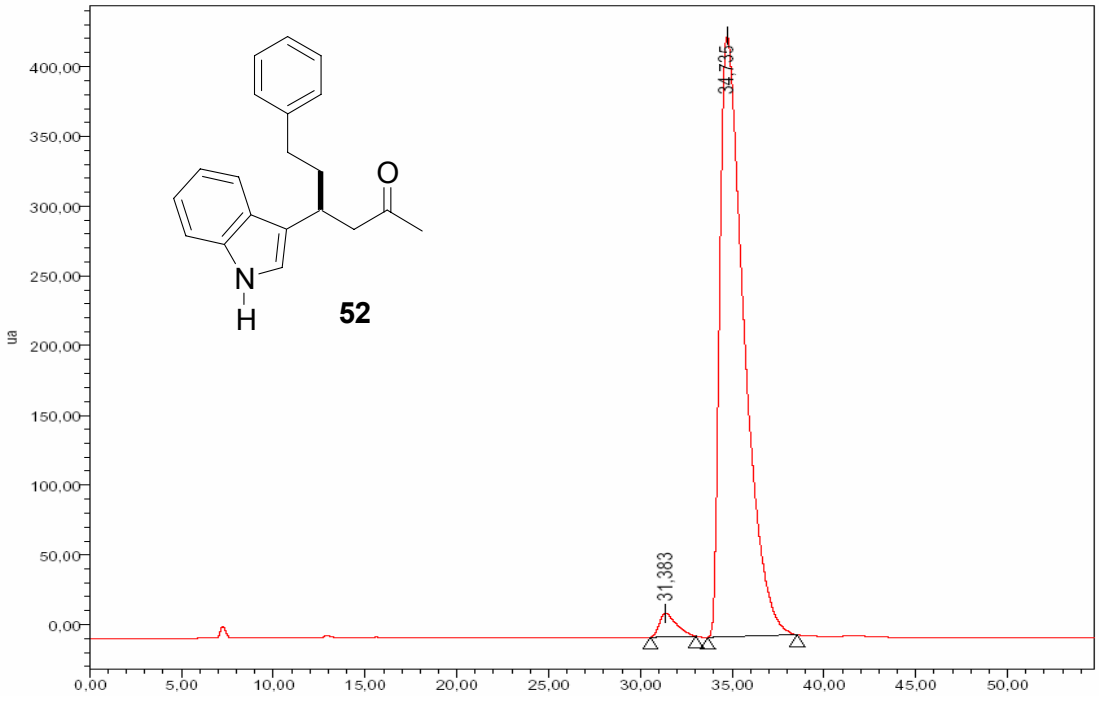




Retention Time (min)	Area	% Area
25,333	5780738	3,18
36,050	176050587	96,82

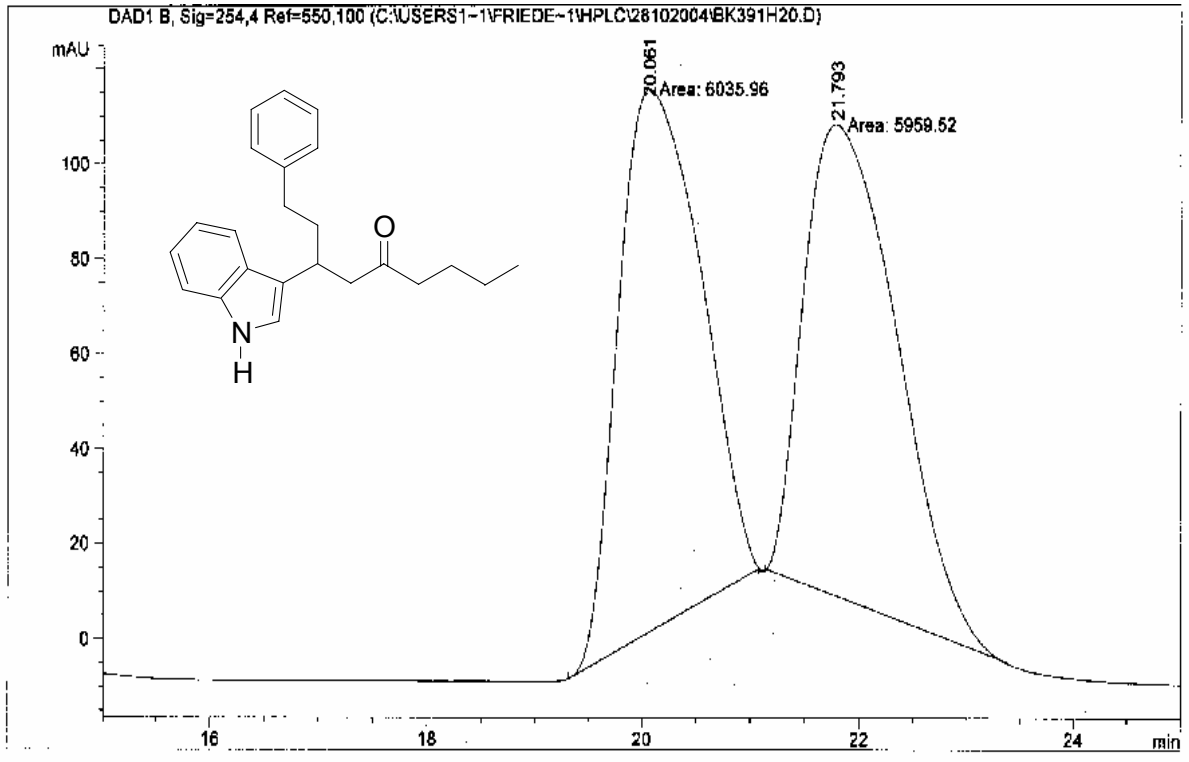
(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 254 nm)

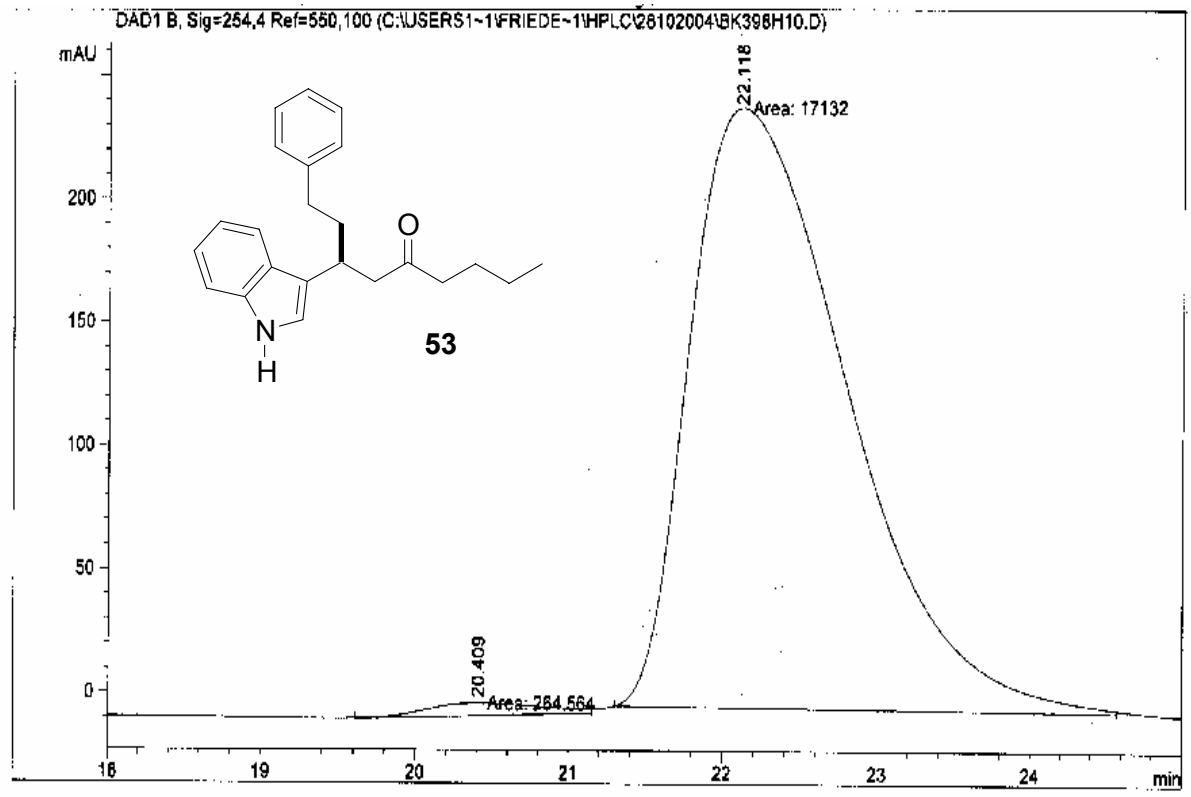




Retention Time (min)	Area	% Area
31,383	1119397	2,76
34,735	39504355	97,24

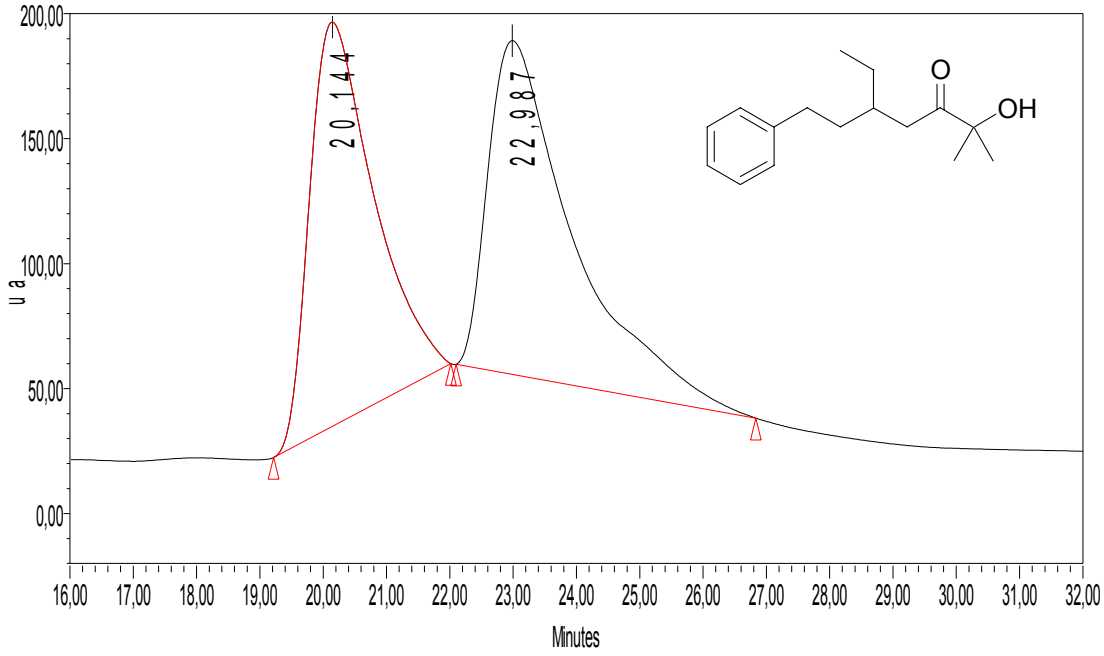
(Chiralcel OD column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm)

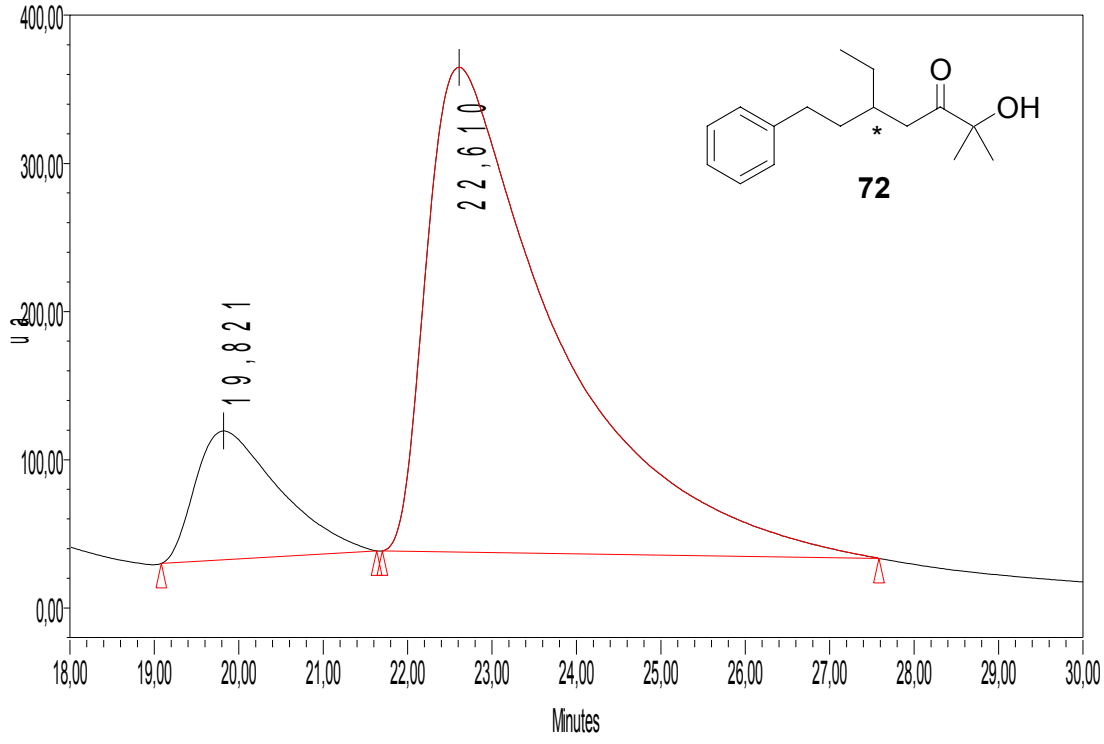




RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
20.409	MM	0.6174	249.96851	4.89606	1.4211
22.118	MM	1.1920	1.73393e4	242.43062	98.5789

(Chiralcel OD column, hexane:iPrOH 95:05, 0.5 mL/min., 254 nm)





Retention Time (min)	Area	% Area
19,067	0	0,00
19,821	6040991	14,11
22,610	36775347	85,89

(Chiralpak OJ column, hexane:iPrOH 90:10, 0.5 mL/min., 210 nm)

Apendix: IV