ONE-POT SYNTHESIS OF CHLOROALCOHOLS AND THEIR LIPASE MEDIATED KINETIC RESOLUTION

FERROCENYL AZIRIDINYLMETHANOLS AS CHIRAL LIGANDS IN ENANTIOSELECTIVE CONJUGATE DIETHYLZINC ADDITION TO ENONES

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ALPER İŞLEYEN

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Approval of the thesis:

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ABSTRACT

ONE-POT SYNTHESIS OF CHLOROALCOHOLS AND THEIR LIPASE MEDIATED KINETIC RESOLUTION

FERROCENYL AZIRIDINYLMETHANOLS AS CHIRAL LIGANDS IN ENANTIOSELECTIVE CONJUGATE DIETHYLZINC ADDITION TO ENONES

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An unexpected tricyclic ether formation instead of acetate addition to the double bond of a norbornene derivative aroused our interest to explore the mechanism of this reaction. Mechanistic studies showed that methylene diacetate (MDA) was formed in the stock solution (NBu_4OAc + dichloromethane) and decomposed to formaldehyde under Lewis or Brønsted acid conditions. Formaldehyde and olefin condensation (Prins reaction) clearly explains the formation of the unexpected product. Same methodology was then successfully applied to develop a one-step procedure for the synthesis of 3-chloro-3-arylpropanols, which are important starting materials for the synthesis of biologically active benzanilide derivatives. Styrenes

were reacted with MDA in the presence of boron trifluoride to give the corresponding 3-chloro-3-arylpropanols in 36–84% yield.

The second part of the thesis involves kinetic resolution of 3-chloro-3-arylpropanols by lipase mediated acylation which are described for the first time. Acylation with the CCL provided the best enantioselectivity amongst the enzymes used. Enantiomerically enriched products with up to 78% ee were obtained after two successive lipase-mediated acylations. Different substituents on the aromatic ring and bromide, instead of chloride, at the benzylic position of the substrates were found to have no drastic influence on the enantioselectivity of the reaction.

In the last part, easily available ferrocenyl substituted aziridinylmethanols (FAM) were complexed with nickel to catalyze the enantioselective diethylzinc addition to various enones with ee's reaching 82%. The ligands can be recovered and used without losing their activity. The sense of asymmetric induction was found to be dependent on the configuration of the aziridine ring.

Key words: Prins reaction, arylpropanols, enzymatic kinetic resolution, asymmetric catalysis, conjugate diethylzinc addition.

ÖZ

KLORALKOLLERİN TEK-KAPTA SENTEZİ VE
LİPAZLI ORTAMDA KİNETİK AYRIŞTIRILMASI

ENONLARA ENANTİOSEÇİCİ KONJUGE DİETİLÇİNKO KATILMASINDA
KİRAL LİGAND OLARAK FERROSENİL AZİRİDİNİLMETANOLLER

İşleyen, Alper

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Eylül 2007, 194 sayfa

Bir norbornen türevinin çifte bağına asetat katılması yerine beklenmedik bir trisiklik eter oluşması, tepkimenin mekanizmasının araştırılması için ilgimizi uyandırdı. Mekanistik çalışmalar, stok çözeltide (NBu_4OAc + dichloromethane) metilen diasetat (MDA) oluştuğunu ve Lewis veya Brønsted asitli ortamda formaldehite bozunduğunu gösterdi. Formaldehit ve olefin yoğunlaşması (Prins tepkimesi) net bir şekilde beklenmedik ürünün oluşumunu açıklamaktadır. Aynı metodoloji daha sonra biyolojik açıdan aktif benzanilid türevlerinin önemli çıkış maddesi olan 3-klor-3-arilpropanollerin tek basamakta sentezine yönelik prosedür geliştirilmesinde başarıyla uygulanmıştır. Stirenler boron triflorürlü ortamda MDA ile tepkimeye sokulmuş ve 3-klor-3-arilpropanoller %36-84 verimlerle elde edilmiştir.

Tezin ikinci kısmı 3-klor-3-arilpropanollerin lipazlı ortamda ilk kez gerçekleştirilen açillenmesini içermektedir. CCL ile açilleme, denenen enzimler içinde en iyi enantioseçiciliği sağlamıştır. Enantiozenginleştirilmiş ürünler iki kez tekrarlanan lipazlı ortam açillemesi ile %78 ee'ye kadar elde edilmiştir. Sübstratların aromatik halkasındaki değişik sübstitüentlerin ve benzilik pozisyondaki klor yerine bromun tepkimenin enentioseçiciliğine çok önemli etkisinin olmadığı görülmüştür.

Son kısımda kolayca elde edilebilen ferrosenil sübstitüe aziridinil metanoller (FAM) çeşitli enonlara enantioseçici dietilçinko katılmasını katalizlemek için nikelle kompleksleştirilmiş ve %82'ye varan ee'ler elde edilmiştir. Ligandlar geri kazanılabilmekte ve aktivitelerini kaybetmeden kullanılabilmektedir. Asimetrik indüksiyonun aziridin halkasının kofigürasyonuna bağlı olduğu tespit edilmiştir.

Anahtar kelimeler: Prins tepkimesi, arilpropanoller, enzimatik kinetik ayrıştırma, asimetrik katalizleme, konjuge dietilçinko katılması.

Ailem’e

To My Family

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LIST OF ABBREVIATIONS

Ac	acyl
acac	acetyl acetonate
Bu	butyl
br s	broad singlet (spectral)
°C	degrees Celcius
Calcd.	calculated
CCL	Candida cylindracea lipase
CIP	Cahn Ingold Prelog system (*R-S* system)
COSY	correlation spectroscopy
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
dd	doublet of doublets(spectral)
ddd	doublet of doublet of doublets(spectral)
Diac-*e*	diacetate erythro
Diac-*t*	diacetate threo
Diox-*c*	dioxane cis
Diox-*t*	dioxane trans
dt	doublet of triplets(spectral)
E_a	activation energy
ee	enantiomeric excess
EI	electron impact (mass spectrometry)

Et	ethyl
EWG	electron withdrawing group
FAM	ferrocenyl substituted aziridinylmethanol
FT	fourier transform
FDA	food and drug administration
GC	gas chromatography
g	gram(s)
h	hour(s)
HMBC	heteronuclear multi bond coherence
HLE	horse liver esterase
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
i-Pr	isopropyl
LA	Lewis acid
L-Selectride	lithium tri-sec-butylborohydride
m	multiplet (spectral)
MDA	methylene diacetate
Me	methyl
MHz	megahertz
min	minutes
mL	millilitre(s)
mmol	millimole(s)
MS	mass spectrometry
M.p.	melting point
MPEG	methoxy polyethylene glycol
nd	not determined
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PLE	pig liver esterase

ppm	parts per million (in NMR)
PPL	porcine pancreatic lipase
PS	Pseudomonas cepacia
PTSA	*para*-toluene sulfonic acid
q	quartet (spectral)
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
t-Bu	*tert*-butyl
TBVE	*tert*-butyl vinyl ether
Tf	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time (in HPLC)
Trt	trityl
UV	ultraviolet

PART I

EXPLORATION OF AN UNEXPECTED PRINS REACTION LEADING TO TRICYCLIC ETHERS AND CHLOROALCOHOLS

CHAPTER I

INTRODUCTION

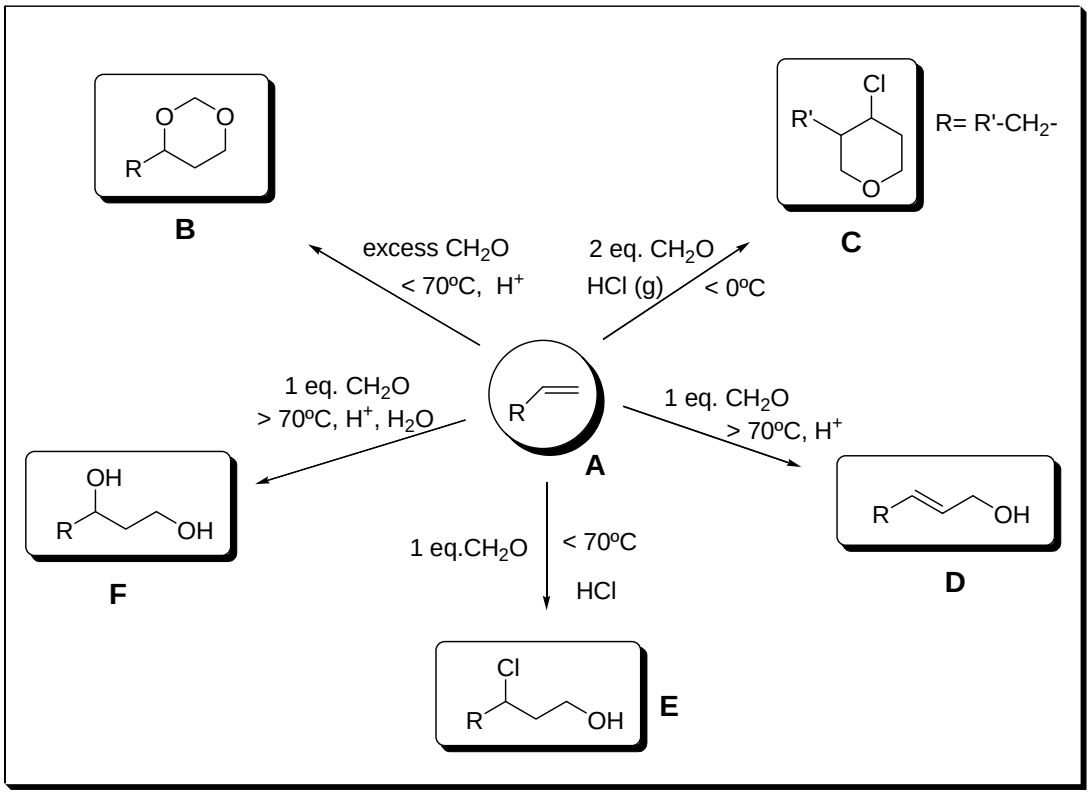
1.1.1. Prins Reaction

The first work on the condensation of olefins with aldehydes was done by Kriewitz**,** who, in 1899, found that unsaturated alcohols were produced when pinene or dipentene was heated with paraformaldehyde in a sealed tube [1]. It was not until 1917, however, that Prins carried out the first, rather comprehensive study of the reactions of formaldehyde with ethylenic hydrocarbons [2]. Because of this early work, the condensation of olefins with aldehydes is sometimes called the Prins reaction. The reaction did not receive much attention until about 1937. At that time the olefin-aldehyde condensation was actively investigated both in the United States and other countries for producing diolefins which were required for the manufacture of synthetic rubber. Even though this reaction proved to be less attractive than dehydrogenation or cracking processes for the production of butadiene and isoprene, numerous new chemical products were produced in the course of these studies. These compounds were identified and their uses and conversion to other organic chemicals were investigated. The development of improved petroleum-cracking processes in the late 1930's increased the production of unsaturated hydrocarbons and greatly stimulated the preparation of synthetic organic chemicals. The commercial availability of the lower olefins, coupled with the production of aldehydes by the direct oxidation of the low-boiling paraffins, provided an added incentive for the

further investigation of the olefin-aldehyde condensation.

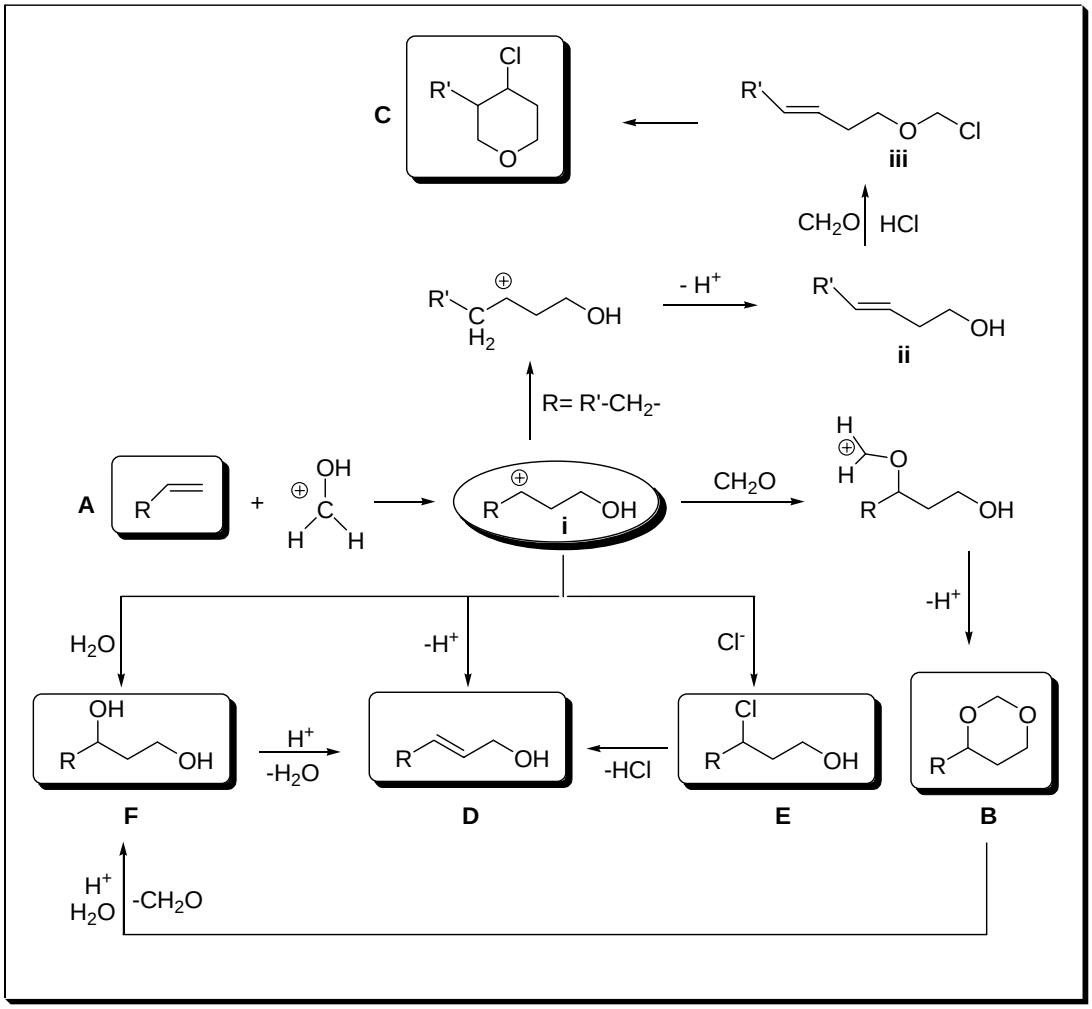
Up to now, two reviews have been published on the subject [3]. The Prins reaction is a fundamental reaction for carbon–carbon bond formation and is one of the most effective reactions for the synthesis of tetrahydropyrans and dioxanes [4].

The Prins reaction of alkenes **A** and formaldehyde can proceed to a variety of synthetically useful products depending on the reaction conditions (Scheme 1). Major products commonly observed include 1,3-dioxanes **B**, tetrahydropyrans **C,** allylic alcohols **D**, chloro alcohols **E** and 1,3-diols **F**. In the considerable volume of literature on the Prins reaction it is readily apparent, with certain exceptions, that the use of aqueous systems and mineral acid catalysts for the condensation of olefins with formaldehyde leads to complex mixtures of products. Additional side reactions may further complicate the outcome of the reaction. In particular, a polymerization of the olefin which is induced by Lewis or Brønsted acids can severely interfere with the desired C–C-bond formation.



Scheme 1. Possible products of the Prins reaction

Numerous investigations into the mechanism of the Prins reaction have been carried out, and various mechanisms have been postulated, including the intermediacy of oxetanes [5] and non-classical carbenium ions [6, 7]. It is generally accepted that the reaction, in simple terms, be considered to proceed stepwise involving the initially formed ion **i** which is formed with the electrophilic addition of a protonated aldehyde to an olefin (Scheme 2). The ion **i** may react further with any number of species present in the reaction mixture e.g. with water to form the 1,3-diol **F**, with chloride to afford a chloroalcohol **E**; alternatively **i** may lose a proton to afford an allylic alcohol **D** or react with excess carbonyl compound to to give the dioxane **B**.



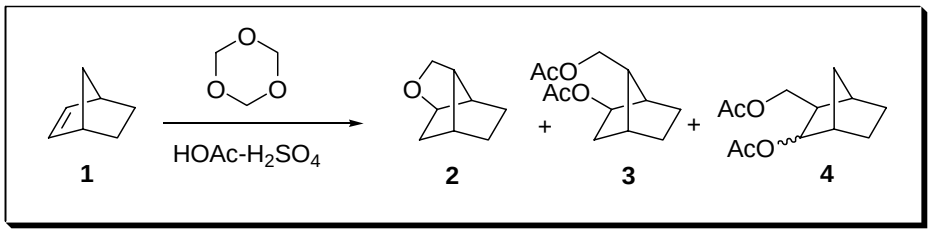
Scheme 2. Accepted mechanism of the Prins reaction

Each of the reaction products may in addition react further to give the indicated final products. Alternatively, if an α-proton which can be eliminated by the intermolecular hydroxyl attack is available, then an intermediate **ii** can form. This intermediate can further attack a second mole of formaldehyde to give **iii** after replacement of protonated hydroxyl with chloride. Finally a ring closure can lead to tetrahydropyrans, **C**.

Although Prins reaction can be fine tuned to prepare a variety of products as mentioned in Scheme 1, we will mainly focus on the synthesis of chloro alcohols and tricyclic ethers that can be obtained from bicyclic olefins. Besides, we will also give brief information on applications of the Prins reaction for the selective synthesis of 1,3-dioxanes.

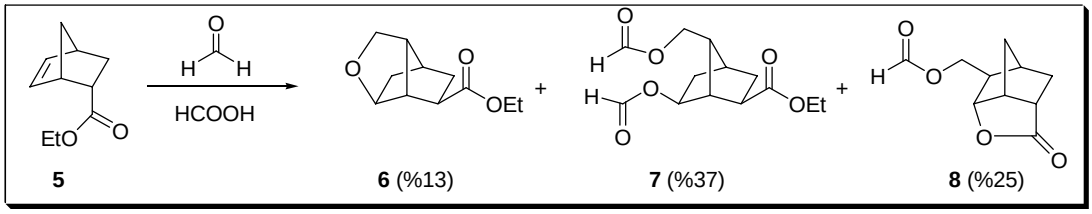
1.1.1.1. Prins Reaction of Bicyclic Olefins

When bicyclic olefins were used in the Prins reaction, besides the expected products, unexpected tricyclic ethers **2** and **6** in Schemes 3 and 4, respectively were also obtained. Sauers group reported that the treatment of norbornene **1** with trioxane in acetic-sulfuric acids resulted in formation of tricyclic ether **2** in 16% yield from a complex mixture of products (Scheme 3) [8].



Scheme 3. Prins reaction of norbornene with trioxane

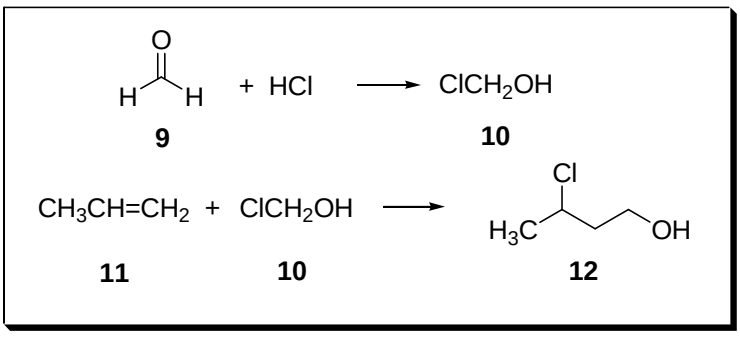
Similarly, Prins reaction of the *endo*-ester **5** was reported to yield tricyclic ether **6**, diformate **7**, and lactone **8** (Scheme 4) [9].



Scheme 4. Prins reaction of *endo*-ester **5**

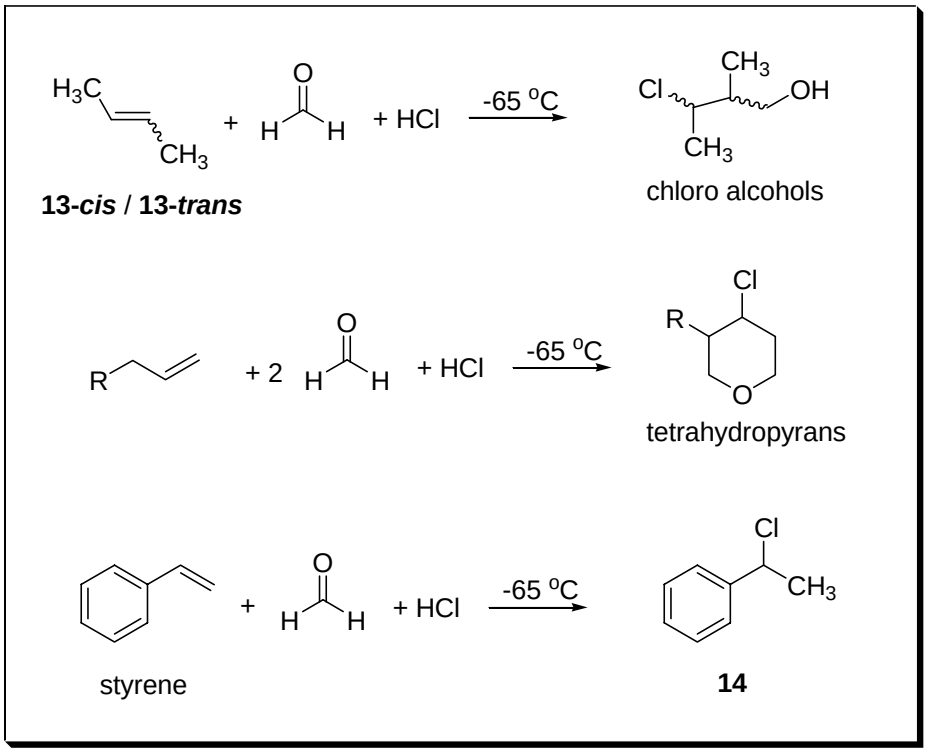
1.1.1.2. Synthesis of chloro alcohols via Prins Reaction

Hydrochloric acid, like sulfuric acid, is a very active catalyst for the condensation of olefins and other unsaturated compounds with formaldehyde, acetaldehyde, and the like. However, such halogenated acids enter into the reaction, with the result that halohydrins, dihalides, or both are formed depending on the reaction conditions. Fitzky produced 7-chloro-substituted alcohols when he condensed propylene, ethylene, or vinyl chloride at about 50 °C with formaldehyde (**9**) solution which had been saturated with hydrogen chloride [10]. The halides of elements in the second group of the periodic table (e.g., zinc chloride, calcium chloride) could also be added as auxiliary catalysts. The reaction apparently took place through the formation of an unstable intermediate **10** (chloromethyl alcohol) which subsequently added to the olefin. The condensation taking place with propylene (**11**) is shown in Scheme 5.



Scheme 5. Prins reaction of propylene (**11**)

Stapp et al. have reported that the Prins reaction of 2-butenes with formaldehyde and hydrogen chloride at –65 °C gave of chloroalcohols in 45–60% yield as shown in Scheme 6 [11]. However, 1-alkenes under the same reaction conditions yielded 3-alkyl-4-chlorotetrahydropyrans, while styrene, on the other hand, gave the simple hydrogen chloride addition product **14** (Scheme 6).



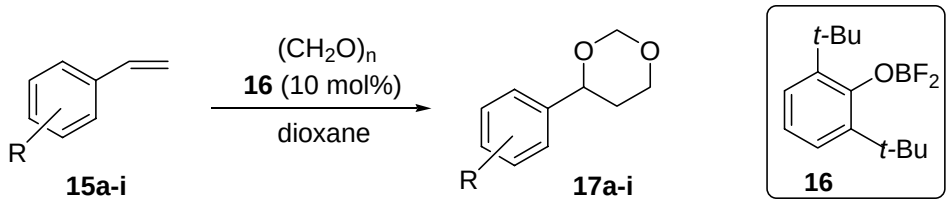
Scheme 6. Condensation of internal and terminal olefins with formaldehyde and HCl

1.1.1.3. Synthesis of 1,3-Dioxanes via the Prins reaction

Tateiwa et al. reported that the reaction of styrenes with paraformaldehyde or trioxane in the presence of cation-exchanged montnorillonite (clay), which worked as a Brønsted acid catalyst produced 4-aryl-1,3-dioxanes selectively in up to 99% yield [4b].

In a similar study, Bach and Lobel studied with substituted styrene derivatives and formaldehyde, in the presence of aryloxyboron difluoride as a Lewis acid catalyst to yield 1,3-dioxanes, exclusively (Table 1) [4c].

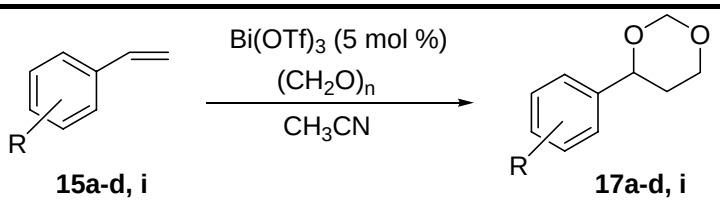
Table 1. Selective synthesis of 1,3-dioxanes catalyzed by 2,6-di-*tert*- butylphenoxy(difluoro)borane (**16**)



Substrate	R	Temp. (°C)	Time (h.)	Yield (%)
15a	H	80	12	95
15b	*p*-Me	80	12	97
15c	*p*-MeO	70	8	65
15d	*p*-Cl	100	24	88
15e	*m*-Cl	110	48	55
15f	*o*-Cl	110	48	81
15g	*p*-NHCOMe	80	12	56
15h	*m*-NHCOMe	110	24	35
15i	*p*-OCOMe	100	12	99

In a recent study, bismuth triflate was shown to be an efficient Lewis acid catalyst for the transformation of styrenes to the corresponding 1,3-dioxanes (Table 2) [12].

Table 2. Prins reaction of styrenes with paraformaldehyde using $Bi(OTf)_3$ as catalyst



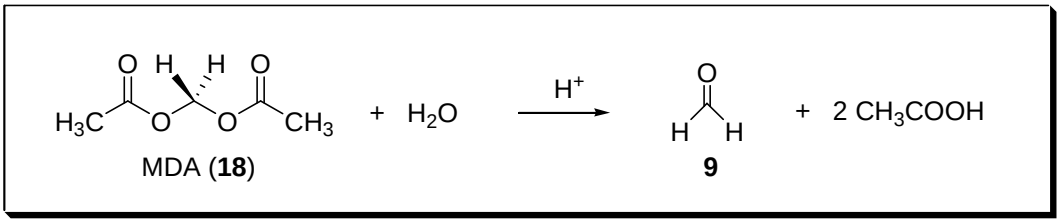
15a-d, i **17a-d, i**

Substrate	R	Time (h)	Yield (%)
15a	H	4	90
15b	*p*-Me	6	88
15c	*p*-MeO	7	87
15d	*p*-Cl	10	82
15i	*p*-OCOMe	10	77

1.1.2. Use of methylene diacetate as formaldehyde source in Prins reaction

Several different formaldehyde sources such as paraformaldehyde, trioxane, and methylene diacetate were used along with the aqueous solution of formaldehyde in Prins reactions.

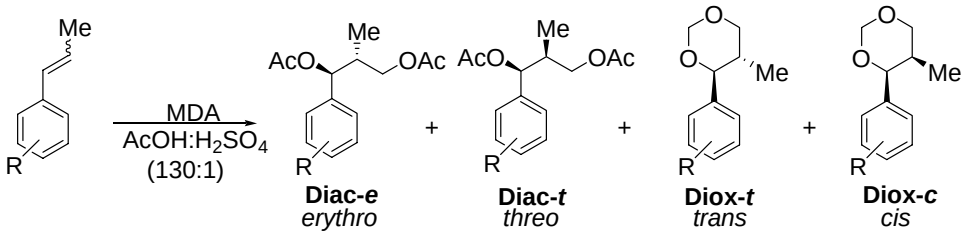
Hydrolysis of methylene diacetate (MDA, **18**) to give formaldehyde (**9**) (Scheme 7) under acidic conditions is known in the literature and kinetics of this reaction was studied extensively by Salomaa [13].



Scheme 7. Hydrolysis of MDA giving formaldehyde under acidic conditions

Use of MDA in the Prins reaction of several olefins including *trans*- and *cis*-*β*-methyl-styrenes [14a], substituted 1-phenyl-1-propenes [14b], 4-octene and cyclohexene [14c], *E*- and *Z*-stilbenes [14d] were studied by Ferrand and Huet. Results of the *β*-methyl-styrenes are summarized on Table 3.

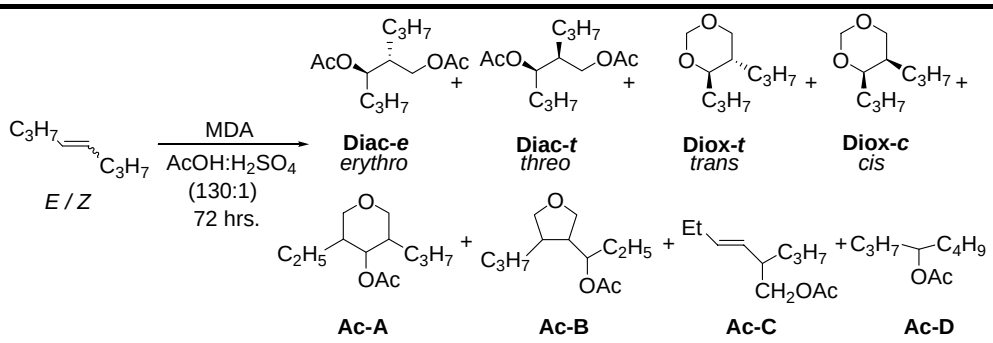
Table 3. Prins reaction of *trans*- and *cis*-*β*-methyl- styrenes with MDA



alkene	R	Rxn. Time (h)	Temp. (°C)	**Diac**. Ratio *e:t* -Yield (%)	**Diox**.Ratio *t:c*- Yield (%)	Tot. Yield (%)
E	H	72	25	*62:38* - 70	*59:41* - 16	86
Z	H	72	25	*55:45* - 42	*66:34* - 14	56
E	*m*-NO_2	72	60	*70:30* - 9	*61:39* - 6	15
E	*p*-Me	24	25	*52:48* - 85	*58:42* - 5	90

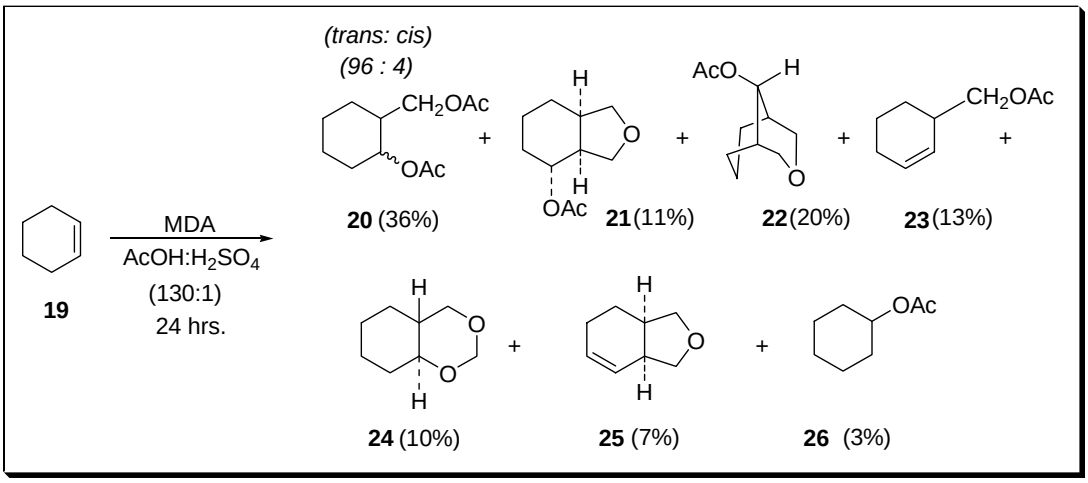
When MDA was added to 4-octene, complex mixture of products were obtained as shown on Table 4.

Table 4. Prins reaction of *4*-octene with MDA



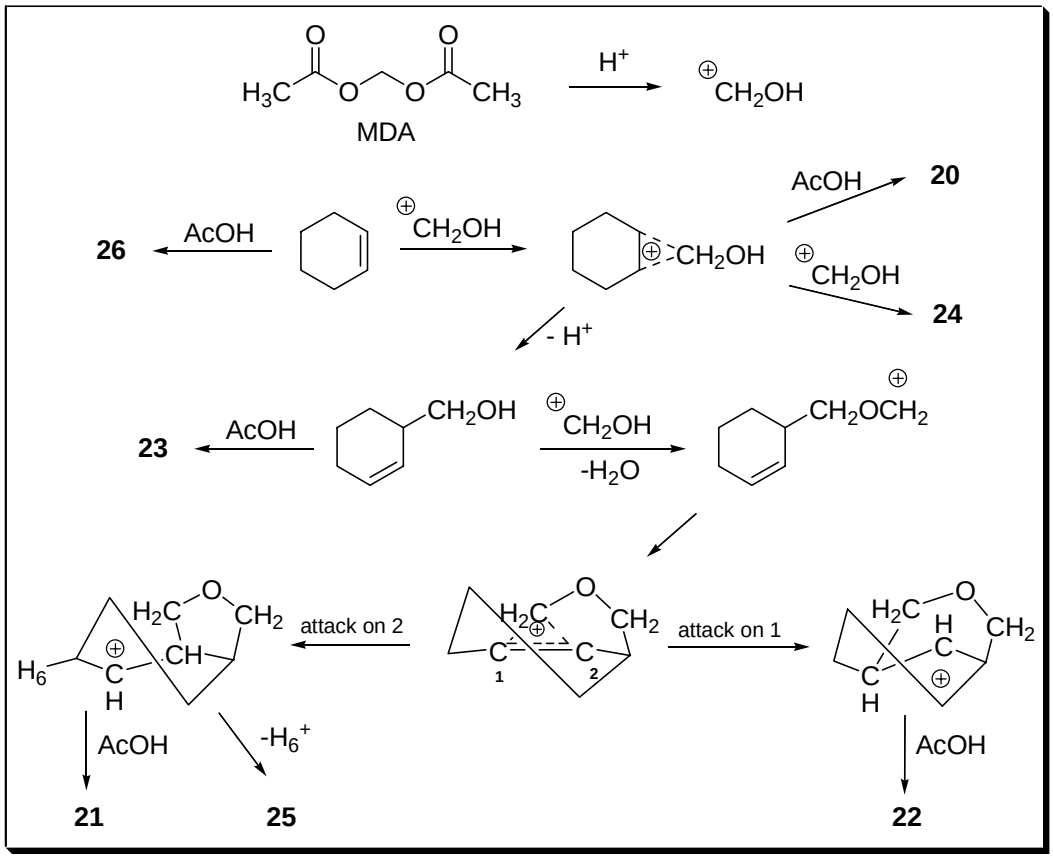
alkene	Temp (°C)	**Diac**.Ratio *e:t*- Yield (%)	**Diox**. Ratio *t:c*- Yield (%)	**Ac-A** Yield (%)	**Ac-B** Yield (%)	**Ac-C** Yield (%)	**Ac-D** Yield (%)	Total Yield (%)
E	25	*89:11* -14	*44:56* - 5	44	34	4	< 0.5	82
Z	25	*7:93* – 38	*86:14* - 9	34	17	2	< 0.5	53
E	70	*65:35* -14	- ~1	33	27	9	16	85
Z	70	*33:67* - 32	*93:7* - 4	30	12	7	16	65

When cyclohexene was chosen as the olefin, again a complex mixture of products were obtained (Scheme 8).



Scheme 8. Reaction of cylohexene and MDA.

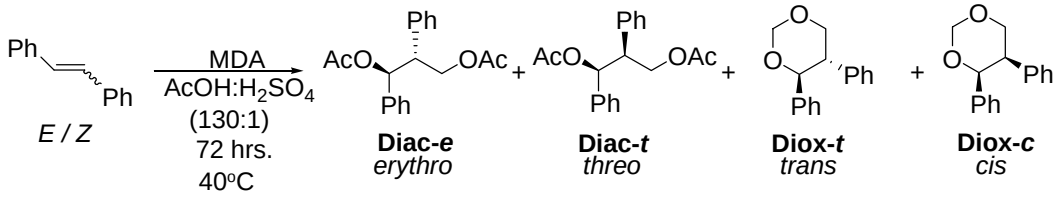
Formation of the products **20**-**26** were rationalized with the proposed mechanism given in Scheme 9.



Scheme 9. Proposed mechanism for the formation of products in the reaction of cyclohexene with MDA

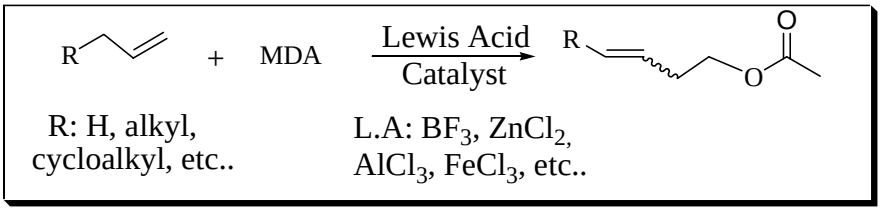
E- and *Z*-stilbenes were reported to yield the following products shown on Table 5.

Table 5. Prins reaction of stilbenes with MDA



alkene	**Diac**.Ratio *e:t*-Yield (%)	**Diox**.Ratio *t:c*-Yield (%)	Total Yield (%)
E	*56:44* - 9	*86:14* - 6	15
Z	*49:51*- 9	*80:20* - 8	17

MDA was also used in the commercial synthesis of alkenyl acetates by treating with 1-alkenes in the presence of a Lewis acid (Scheme 10) [15].



Scheme 10. Commercial synthesis of alkenyl acetates with MDA

1.1.3. 1,3-Chloro alcohols as key intermediates for the synthesis of biologically important compounds

Benzanalide derivatives (Figure 1) are dual-acting agents which have both α-1-adrenoceptor antagonistic action and steroid 5α-reductase inhibitory activity. From this standpoint it was speculated that they would be effective therapeutic agents for urethral obstruction caused by benign prostatic hyperplasia which is a common disease in aging men [16].

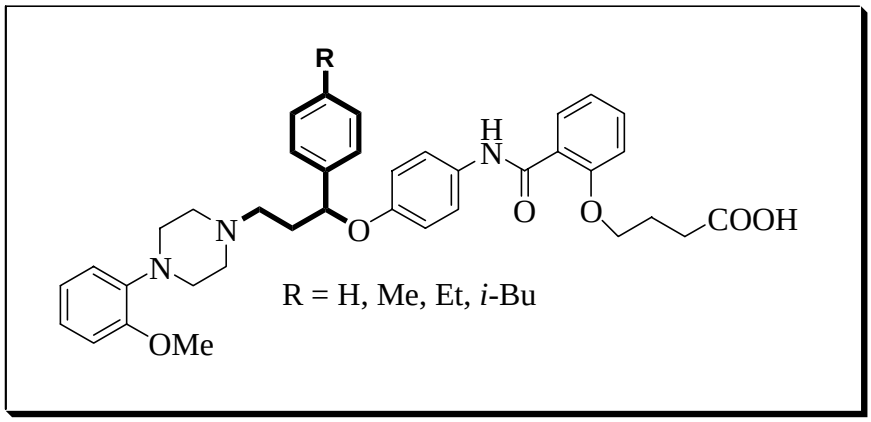
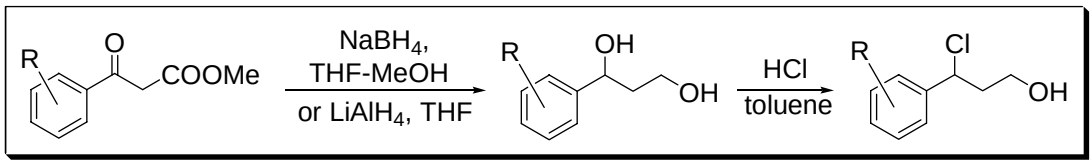


Figure 1. Benzanilide derivatives

Yoshida et al. claimed that different R groups on aromatic ring (shown in bold on the skeleton) were reported to affect the bioactivity of the whole molecule significantly (Figure 1). In the same article, aryl substituted chloroalcohols were used as the key intermediates for the synthesis of the benzanalide derivatives. These chloroalcohols were reported to be synthesized from the corresponding oxo esters as depicted in Scheme 11.

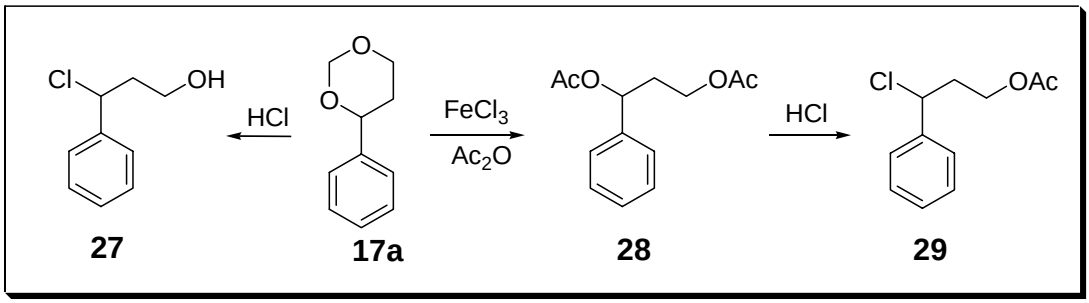


Scheme 11. Two step synthesis of aryl substituted chloroalcohols.

A literature survey on chloroalcohol **27** and chloroacetyl **29** revealed that these compounds were also reported to be used as odorant and fixative in perfumes [17]. Alternatively, 4-phenyl-1,3-dioxane (**17a**) was used as the starting material for the synthesis of these compounds (Scheme 12).

4-Phenyl-1,3-dioxane (**17a**), used in these transformations, was obtained from the Prins reaction of styrene and formaldehyde [4]. Hydrochloric acid treatment of

dioxane **17a** was reported to yield the desired chloroalcohol **27** in 23% yield.



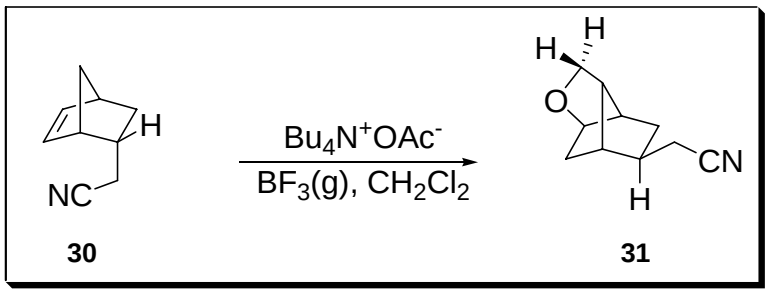
Scheme 12. Alternative routes to chloroalcohols and chloroacetyls in the literature

CHAPTER II

RESULTS & DISCUSSION

1.2.1. Aim of the work

In our previous nucleophilic addition studies to *endo* and *exo*-2-substituted norbornene derivatives; iodide, bromide, cyanide, and acetate were used as nucleophiles [18]. While expected products were isolated in the case of halogens [19], an unexpected tricyclic ether was isolated in the case of acetate from the reaction as shown in Scheme 13.

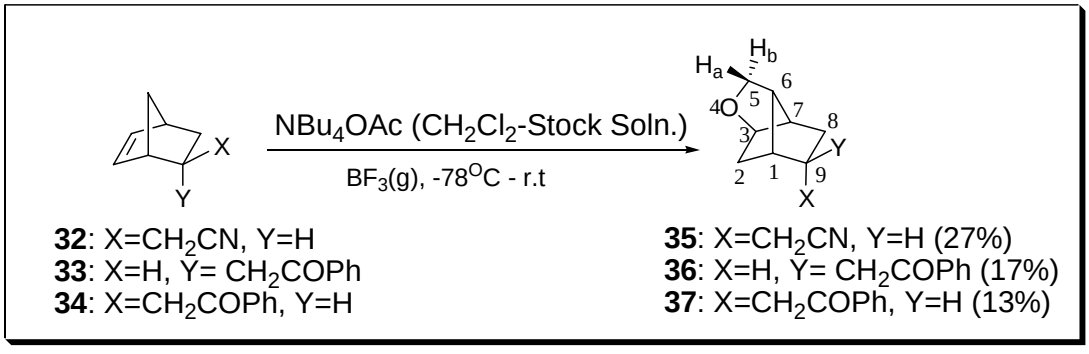


Scheme 13. Unexpected tricyclic ether formation

Our aim in this study was to clarify the reaction mechanism of the unexpected tricyclic ether formation. In addition, the scope and limitations of this reaction were also explored by testing the reaction on styrenes.

1.2.2. Reaction with norbornene derivatives

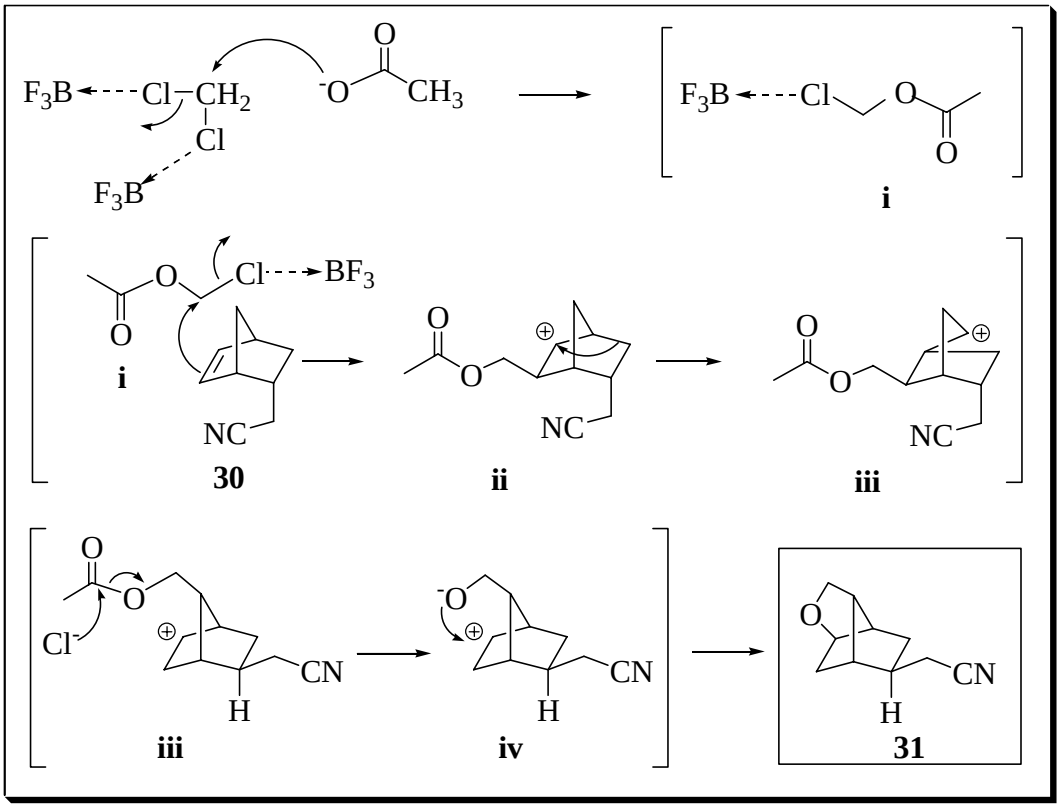
After obtaining such a surprising result with *endo*-nitrile **30**, we anticipated to test our reaction with other available norbornene derivatives. Results of these studies are summarized in Scheme 14. Tricyclic ethers **35**, **36** and **37** were obtained from the corresponding norbornenes **32**, **33** and **34**, respectively. Structural assignments of the tricyclic ethers were based on ^{1}H, ^{13}C NMR, 2-D NMR (COSY, HMBC), and mass spectrometry. W-coupling seen on COSY spectra between H_{2endo} and H_6 for compounds **31** and **37** helped us to assign the signal of H_{2endo} on ^{1}H NMR spectra. Correlation between C_3-$H_{8endo,exo}$ and C_2-H_9 on HMBC spectra of compounds **31** and **37** helped us to determine the exact regiochemistry of these compounds. Absence of correlation signals between C_3-H_9 and C_2- $H_{8endo,exo}$ on HMBC spectra of compounds **31** and **37** clearly excluded the formation of the regioisomer (oxygen attached to C_2).



Scheme 14. Tricyclic ethers obtained with both *endo* and *exo*-2-substituted norbornene derivatives

We proposed a mechanism in which BF_3 activated dichloromethane was attacked by acetate ion and formed chloromethyl acetate **i** which was then attacked

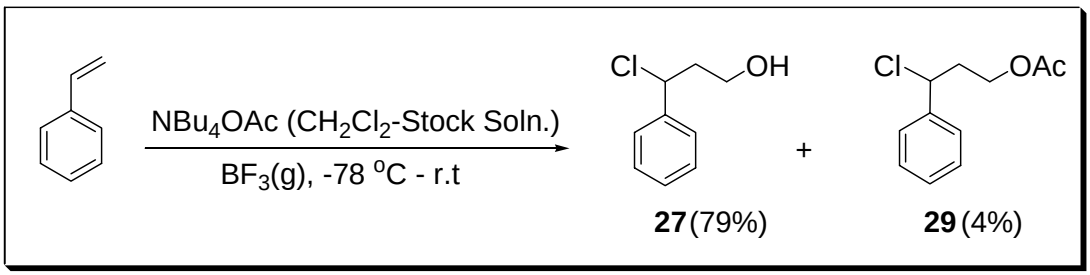
by the norbornene **30** regio and stereoselectively to give cationic intermediate **ii** [19]. This mechanism resembles the addition of olefins to halo-ethers [20]. Wagner-Meerwein rearrangement of the intermediate **ii** gave carbocation **iii**. Cleavage of the acetyl group with chloride ion yields an alkoxide **iv** which cyclizes by the attack of oxygen to the cationic center to give product **31** (Scheme 15).



Scheme 15. Proposed mechanism for the formation of tricyclic ether **31**

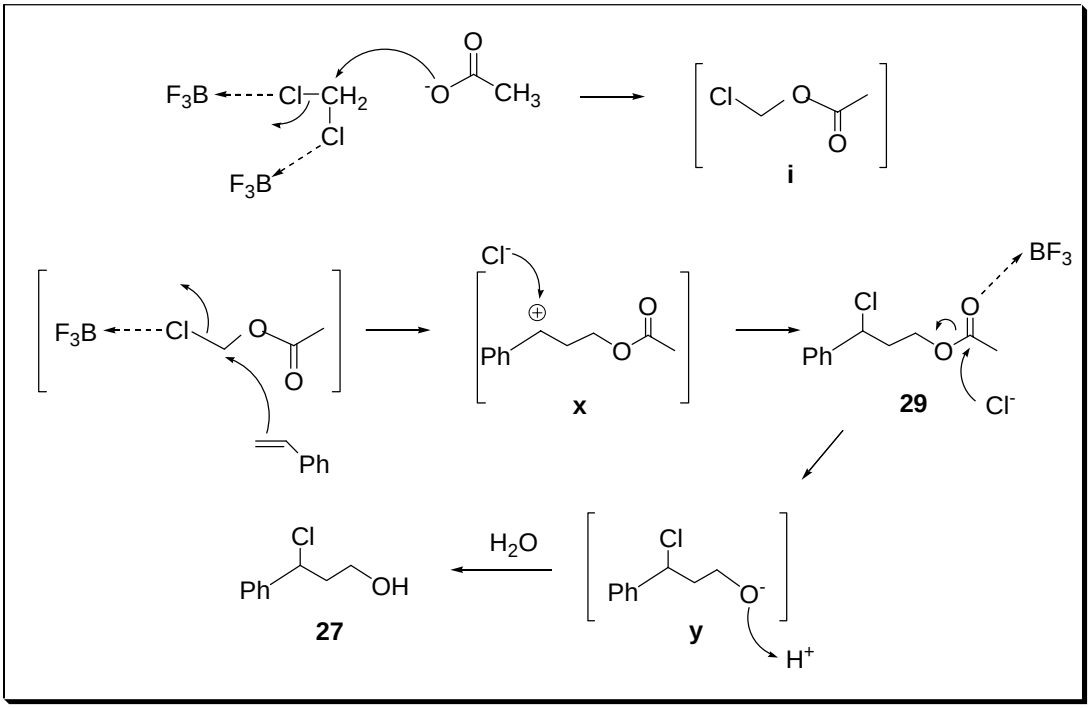
1.2.3. Reaction with styrene

When the same reaction conditions were applied to an acyclic olefin such as styrene, 3-chloro-3-phenylpropan-1-ol (**27**) was obtained with good yield along with minor amount of the acetylated form **29** (Scheme 16).



Scheme 16. Reaction of styrene gave chloro alcohol **27** in good yield

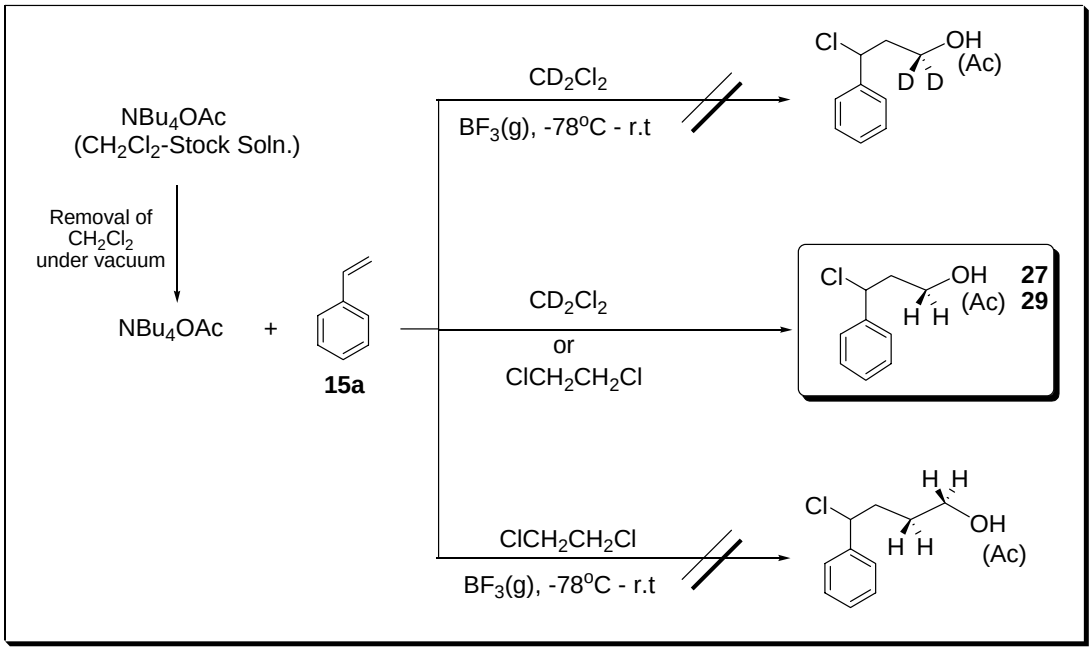
We proposed a similar mechanism for the tricyclic ether formation. Again BF_3 activated dichloromethane is attacked by acetate ion to form chloromethyl acetate (**i**) which is then attacked by the styrene and cationic intermediate **x** is formed. With the addition of the chloride ion to cationic intermediate **x**, product **29** is formed. BF_3 catalyzed cleavage of the acetyl group with chloride ion forms an alkoxide **y** which can be protonated to form product **27** after hydrolysis (Scheme 17).



Scheme 17. Proposed mechanism for the reaction of styrene

1.2.4. Studies done to clarify the proposed mechanism

For the proof of this mechanism we designed two experiments in which deutorated dichloromethane and 1,2-dichloroethane was used as solvent instead of dichloromethane. If our proposed mechanism was correct then, we should expect to see deuterium labeled product in the case of CD_2Cl_2 and one carbon extended product in the case of $ClCH_2CH_2Cl$. However, the isolated product was the same with that of CH_2Cl_2 in both cases (Scheme 18).

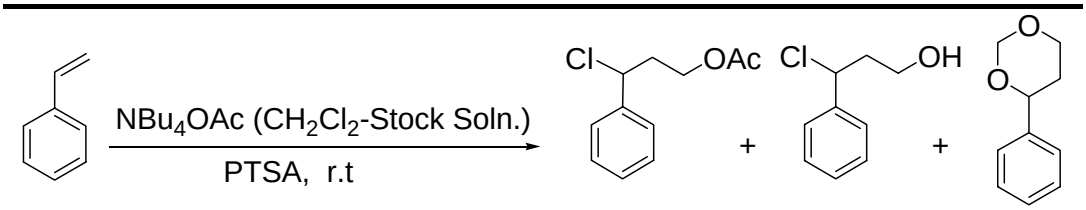


Scheme 18. Experiments designed for the proof of the mechanism

1.2.5. Parallel studies done with a Brønsted acid instead of BF_3

When *para*-toluene sulfonic acid was used instead of BF_3, styrene (**15a**) yielded 4-phenyl-1,3-dioxane (**17a**) as an additional product to chloro alcohol **27** and its acetate derivative **29** (Table 6). Results of our optimization studies revealed that increase in the amount of PTSA increases the yield of **29** and **17a** considerably, even at much shorter reaction times (Table 6).

Table 6. Reactions conducted with a Brønsted acid: PTSA



15a **29** **27** **17a**

Entry	Amount of PTSA	Time (h)	Yield **29** (%)	Yield **27** (%)	Yield **17a** (%)	Total Yield (%)
1	1.5 eq	120	7	15	5	27
2	3.0 eq	28	17	21	11	49
3	6.0 eq	23	47	21	18	86

As mentioned before, it is known in the literature [4b,c,12] that the acid catalyzed Prins reaction of styrene derivatives (**15**) with formaldehyde yields 4-aryl-1,3-dioxanes (**17**). The question that has to be asked is the source of -CH_2O- in our reactions.

1.2.6. ^{1}H NMR studies on NBu_4OAc-CH_2Cl_2 stock solution

Since our deuterium labeling and carbon extension studies were unsuccessful (Scheme 18), we focused our attention on the NBu_4OAc-CH_2Cl_2 stock solution used in our reactions. ^{1}H NMR studies done with the stock solution clearly showed the formation of MDA even just after the addition of CH_2Cl_2 to NBu_4OAc (Figure 4). Reaction was observed to be completed (checked by the disappearance of the methyl signal of the acetate ion on ^{1}H NMR) in one week time even the stock solution was refrigerated at +4 °C.

Figure 2. ^{1}H NMR Spectra of NBu_4OAc and NBu_4OAc-CH_2Cl_2 stock solution

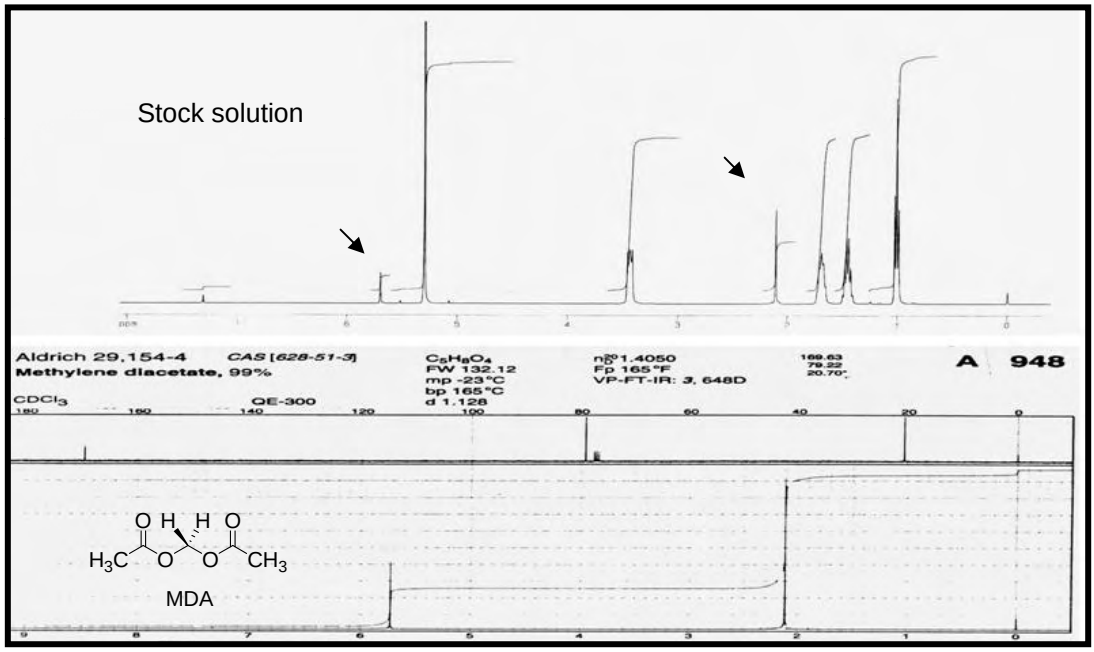


Figure 3. Comparison of the ^{1}H NMR spectra of our stock solution and MDA (taken from the Aldrich NMR catalogue)

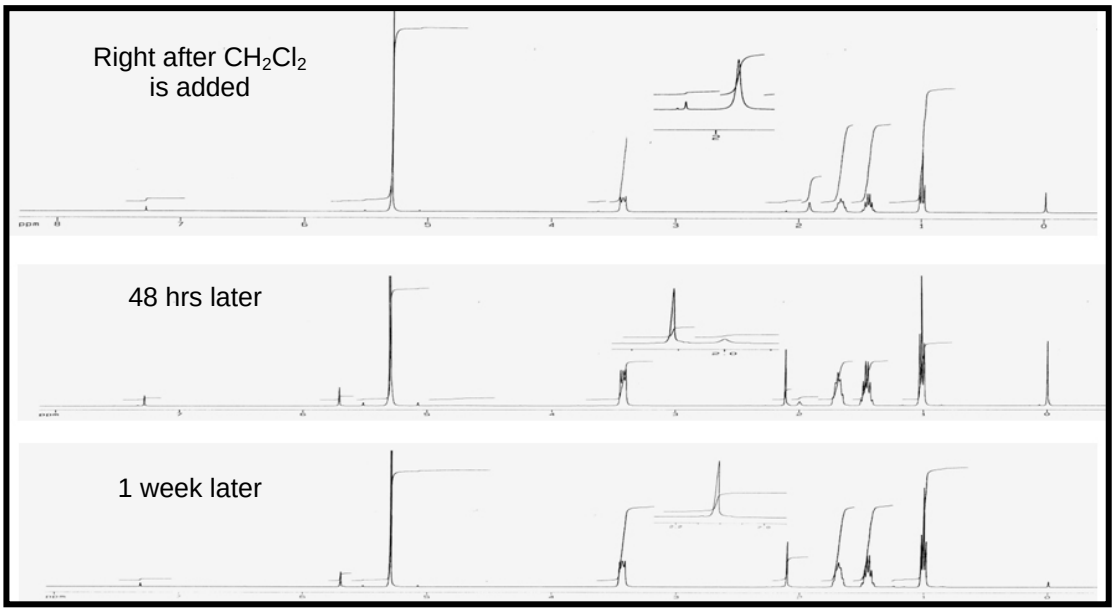
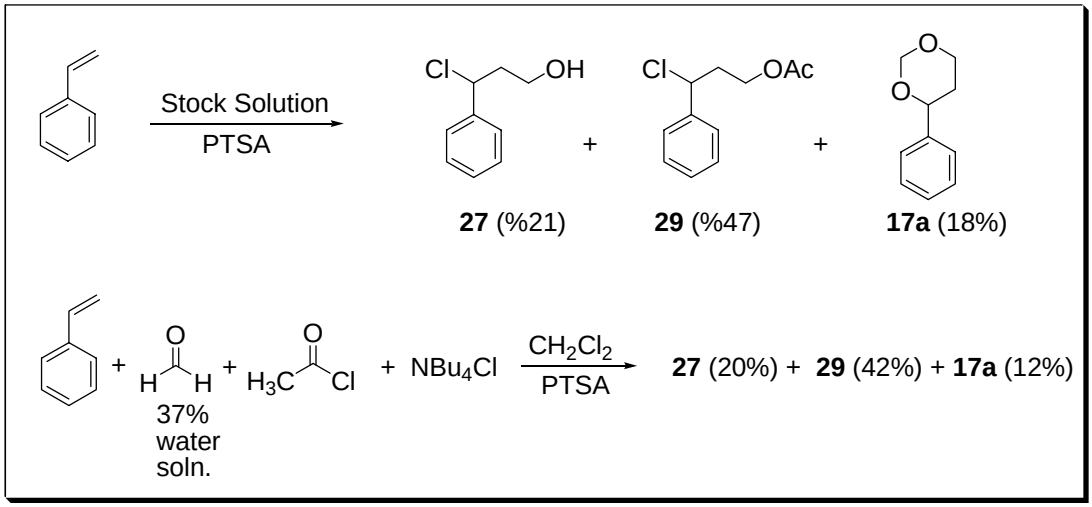


Figure 4. Monitoring the formation of MDA in the stock solution by ^{1}H NMR

Although the synthesis of different methylene diesters was reported by refluxing tetrabutylammonium salts of carboxylic acids in dichloromethane for four days [21], there is no report on the synthesis of MDA [22] from tetrabutylammonium acetate in dichloromethane at high or low temperature.

1.2.7. Experiment designed to explain the mechanism of the reaction

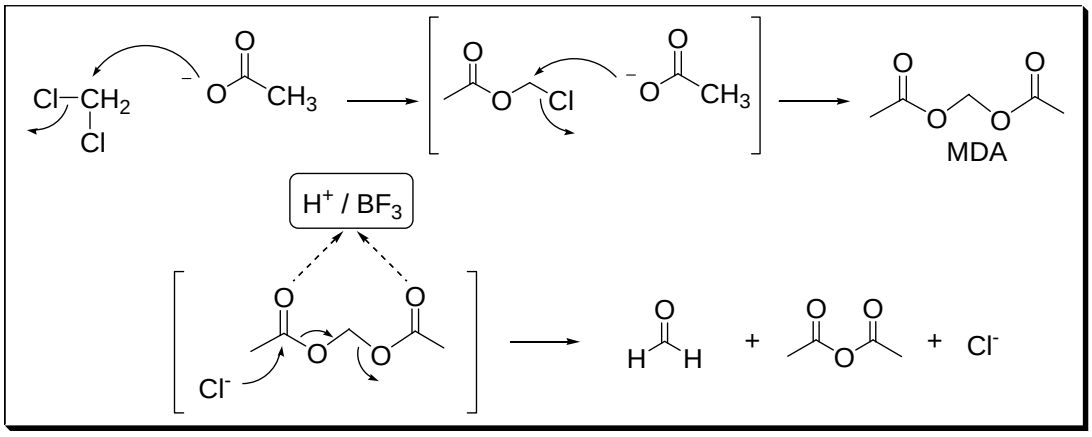
After the discovery of the presence of MDA in our stock solution, we conducted an experiment in which all possible reactive species were added directly to the reaction flask (Scheme 19). As indicated in the introduction part, decomposition of MDA to formaldehyde under Brønsted or Lewis acid conditions is a well known process. Acetyl chloride and formaldehyde were added to the reaction as possible decomposition products of MDA. Result of this experiment revealed that product yields and distributions were almost same compared to the one conducted with the stock solution.



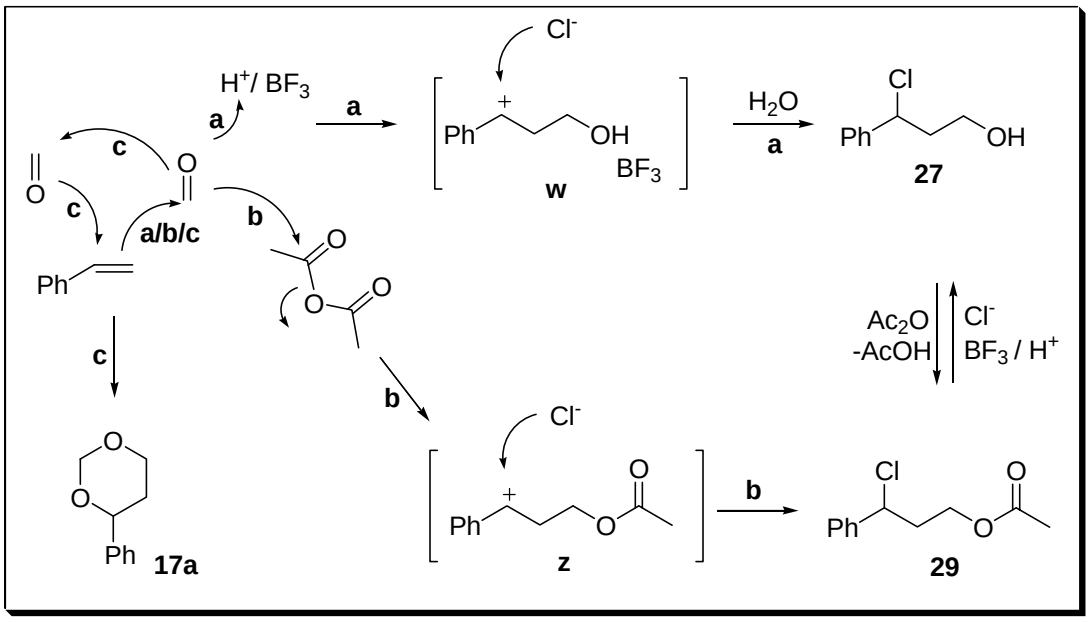
Scheme 19. Comparison of the stock solution result with the experiment done with possible decomposition products of MDA

1.2.8. Proposed mechanism

Key step in understanding the mechanism was the discovery of MDA formation in our stock solution. In the light of our results and the studies done in the literature, it is reasonable to propose the following reaction mechanism. Acetate ion reacts with dichloromethane to form chloromethyl acetate (which is even more reactive than dichloromethane) which is reacted with another acetate ion to form MDA. With the help of chloride ion and the Brønsted or Lewis acid found in the medium, MDA decomposes to formaldehyde and acetic anhydride (Scheme 20). Then the reaction of olefin with formaldehyde can follow three different routes (Scheme 21). In route **a**, formed alkoxide is protonated/BF_3 coordinated to give carbocationic intermediate **w** which is attacked by chloride ion to give chloroalcohol **27**. In route **b**, formed alkoxide is reacted with acetic anhydride to form carbocationic intermediate **z**, which is attacked by the chloride ion to yield chloroacetate **29**. If two formaldehyde molecules react with the olefin (route ***c***), then dioxane **17a** can be formed. Product **27** can alternatively be formed via hydrolysis of the ester group of product **29** with the help of chloride and the Brønsted or Lewis acid found in the medium.



Scheme 20. Formation of MDA and its decomposition to formaldehyde



Scheme 21. Proposed mechanism leading to three different products

When BF_3 was used as the acid source, chloroalcohol **27** is obtained as the major product with 4% of the acetylated derivative **29**, and without 1,3-dioxane or 1,3-diol formation. This can be explained by the strong complexation of the intermediate alkoxide to boron trifluoride. As a result, this alkoxide is not nucleophilic enough to react with a second molecule of formaldehyde to give 1,3-

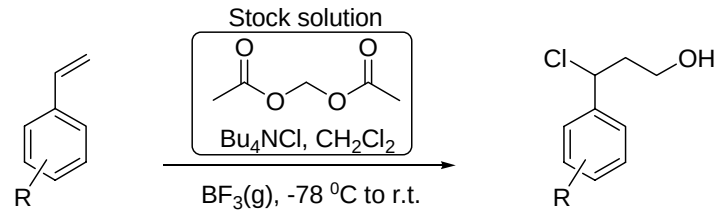
dioxanes. Also, in our case, the reactions take place under anhydrous conditions which prevents 1,3-diol formation.

1.2.9. Application of the developed method for the one-pot synthesis of 3-chloro-3-arylpropanols

As mentioned before (Part 1.1.3, page 13), 3-chloro-3-arylpropanols are important as the starting materials in the synthesis of benzanilide derivatives which have important biological activity. Therefore we were interested in synthesizing 3-chloro-3-arylpropanols by our method. Our method has several advantages over the methodologies used in the literature. Starting materials of Yoshida et al. were *β*-dicarbonyl compounds which are complicated and commercially unavailable (Scheme 11, page 14). Synthesis requires two steps: a reduction and HCl treatment to obtain the desired chloro alcohols. Another reported synthesis to reach the desired compounds was through dioxanes (Scheme 12, page 15). First dioxanes should be synthesized and then HCl treatment is required for the completion of the synthesis. However the yield of the acid treatment step was reported to be 23%. In another study, Stapp et al. planned a direct synthesis starting with styrenes (Scheme 6, page 7). However, simple HCl addition to the double bond of styrene was observed. Because of this problem, they could not achieved the synthesis of the desired chloroalcohols.

We reported a one-pot procedure for the synthesis of 3-chloro-3-arylpropanols starting from commercially available styrenes [23]. Styrenes having a range of substituents at different positions of the aromatic ring (Table 7) were subjected to our reaction conditions. Results of this study are summarized on Table 7. From these reactions we also hoped to determine if there were substituent effects operating. All the styrenes except *p*- and *m*-methoxystyrenes gave the corresponding 3-chloro-3-arylpropanols **27, 49a-p**.

Table 7. Reaction of MDA with styrenes in the presence of BF_3



Entry	Substrate	R	Product	Yield (%)
1	**15a**	H	**27**	79
2	**38**	*p*-F	**49a**	79
3	**15d**	*p*-Cl	**49b**	84
4	**39**	*p*-Br	**49c**	79
5	**15b**	*p*-Me	**49d**	71
6	**15c**	*p*-MeO	**49e**	–[a]
7	**40**	*p*-NO_2	**49f**	5
8	**41**	*m*-F	**49g**	76
9	**15e**	*m*-Cl	**49h**	62
10	**42**	*m*-Br	**49i**	59
11	**43**	*m*-Me	**49j**	63
12	**44**	*m*-MeO	**49k**	36
13	**45**	*o*-F	**49l**	45
14	**15f**	*o*-Cl	**49m**	44
15	**46**	*o*-Br	**49n**	47
16	**47**	*o*-Me	**49o**	41
17	**48**	*o*-MeO	**49p**	–[a]

[a] Product was not isolated due to polymerization.

It can be concluded from Table 7 that the highest yields were observed for *para*-substituted styrenes, except *p*-methoxystyrene which polymerizes under these conditions. It is also true that halides at the *para* position of the styrene have a very similar effect on the yield as a methyl group. For the *meta*-substituted styrenes, yields decrease slightly as the electronegativity of the halide decreases. In the case of

the *ortho*-substituted styrenes yields were lower than both *para*- and *meta*-substituted styrenes but there was not much variance with respect to the type of the substituent. Again no chloroalcohol formation was observed for *o*-methoxystyrene due to polymerization. We believe that both electronic and steric effects are involved in the lower yields of *ortho*-substituted styrenes. In a similar study where the Prins reaction was studied systematically with substituted styrene derivatives and formaldehyde, in the presence of aryloxyboron difluoride as a Lewis acid catalyst, 1,3-dioxanes were formed exclusively [4c]. The highest yields were reported for the methyl-substituted styrene derivatives and no product formation was observed for styrenes having strong electron-withdrawing substituents (CN, CO_2Me). In our case, methyl-substituted styrenes gave very similar results to the halogen-substituted styrenes and a very low yield was seen in the case of *p*-nitrostyrene, where most of the starting material was recovered (Table 7, entry 7).

It can also be concluded from Table 7 that the substituents with a highly negative (like methoxy, $\sigma_p = -0.28$) or highly positive (like nitro, $\sigma_p = 0.81$) Hammett constant do not form 3-chloro-3-arylpropanols with ease under our experimental conditions. It is also important to note that *m*-methoxystyrene having as positive a Hammet constant [24] as the halides (MeO: $\sigma_m = 0.10$, F: $\sigma_m = 0.34$, Cl: $\sigma_m = 0.37$, Br: $\sigma_m = 0.37$) gave the 3-chloroalcohol in a poor 36% yield (Table 7, entry l2).

Although the reactions take place via the Prins reaction, the products are different than the products of the classical Prins reaction. 3-Chloro-3-arylpropanols are obtained as the major products with 2–4% of the acetylated derivatives, and without 1,3-dioxane or 1,3-diol formation. This can be explained by the strong complexation of the intermediate alkoxide to boron trifluoride. As a result, this alkoxide is not nucleophilic enough to react with the second molecule of formaldehyde to give 1,3-dioxanes. Also, in our case, the reactions take place under anhydrous conditions which prevents 1,3-diol formation.

CHAPTER III

CONCLUSION

Hygroscopic nature of NBu_4OAc forced us to use it as a stock solution in our reactions. NBu_4OAc was dried and mixed with CH_2Cl_2 to prepare a stock solution. Reacting this stock solution with norbornene derivative **30** in the presence of BF_3 yielded an unexpected tricyclic ether **31**. An acyclic olefin, styrene (**15a**) yielded 3-chloro-3-phenylpropanol (**27**) under the same reaction conditions. Mechanistic studies showed that methylene diacetate (MDA) was formed in the stock solution and decomposed to formaldehyde under Lewis or Brønsted acid conditions. Reaction of formaldehyde with olefins under acidic conditions is a well known reaction called Prins reaction.

3-Chloro-3-arylpropanols are key intermediates in the synthesis of biologically important benzanilide derivatives. Using our method these compounds were synthesized in high yields in a single step. In other words we have discovered a new method for the one-pot synthesis of 3-chloro-3-arylpropanols starting from styrene and its derivatives.

CHAPTER IV

EXPERIMENTAL

1.4.1. General Consideration

All reactions were carried out in oven- or flame-dried glassware under an argon atmosphere unless otherwise stated. CH_2Cl_2 was distilled from CaH_2 under argon. Analytical TLC was performed on precoated silica gel 60 F-254. Flash chromatography was performed using silica gel 60 (230–400 mesh). Nuclear Magnetic Resonance (^1H, ^{13}C and 2-D) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer. NMR samples were prepared in CCl_4-$CDCl_3$ (2/3) solvent system. ^1H NMR spectra were measured at 400 MHz and reported in ppm using TMS as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz and are reported in ppm with the residual solvent peak as internal standard ($CDCl_3$ at 76.9 ppm). IR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer in $CHCl_3$. HRMS were recorded on a Kratos MS25RFA mass spectrometer. GC was performed by Thermo Quest Trace 2000 Series GC instrument using 30m x 0.25mm i.d. x 0.25um ft Phenomenex Zebron ZB-5 5% Phenyl Polysiloxane column. Mass data obtained by Thermo Quest Finnigan Automass Multi instrument were reported for M^+ and high mass fragments derived from M^+ in electron impact (EI) mode. Flash column chromatography was performed using thick-walled glass columns and “flash grade” silica (Merck 60 230-400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm

silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio.

1.4.2. Preparation of the methylene diacetate stock solution

Bu_4NOAc (11.4 g, 37.8 mmol) and anhydrous benzene (60 mL) were placed in a round-bottomed flask equipped with a Dean–Stark apparatus. This solution was refluxed under an argon atmosphere with continuous removal of the azeotrope over a period of 1 h. Then the flask was connected to a vacuum line to remove the rest of the benzene. Finally, anhydrous CH_2Cl_2 (37 mL) was added to the flask containing Bu_4NOAc (11.2 g, 37.1 mmol) under an argon atmosphere. This stock solution was allowed to stand at rt for 3 days before use and then kept at 4 °C.

1.4.3. Synthesis of tricyclic ethers and 3-chloro-3-arylpropanols; General Procedure

Methylene diacetate stock solution (2.5 mL), and alkene (0.39 mmol) were added to a 10-mL flask under an argon atmosphere. The flask was then cooled to –78 °C and BF_3 gas was slowly bubbled through the solution (30 min for norbornene derivatives and 10 min for styrenes) to give a cloudy solution. At this point, the flow of BF_3 was stopped, the reaction flask was allowed to warm to rt, and the solution was left stirring overnight at this temperature. In the morning, H_2O (5 mL) was added to the reaction flask, followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Finally, flash column chromatography (hexanes–EtOAc, 5:1) gave the desired pure product.

1.4.3.1. 9-*exo*-(4-Oxatricyclo[4.3.0.03,7]non-9yl)acetonitrile (31). 12.7 mg (20% yield); white waxy oil; R_f = 0.21 (hexanes–EtOAc, 2:1); ^{1}H NMR: δ 4.06 (t, *J* = 2.7 Hz, 1 H, H3), 3.83 (dd, *J* = 8.1, 3.9 Hz, 1 H, H_{5b}), 3.64 (d, *J* = 8.1 Hz, 1 H, H_{5a}), 2.36 (br s, 1 H, H_7), 2.29–2.25 (m, 3 H, H_1, CH_2CN), 2.19 (d, *J* = 6.0 Hz, 1 H, H_6), 1.91 (q, *J* = 7.9 Hz, 1 H, H_9), 1.73 (dd, *J* = 14.1, 8.2 Hz, 1 H, H_{8endo}), 1.67 (dd, *J* = 13.3,

6.0 Hz, 1 H, H_{2endo}), 1.32 (dd, *J* = 14.1, 4.1 Hz, 1 H, H_{8exo}), 1.15 (d, *J* = 13.3 Hz, 1 H, H_{2exo}); ^{13}C NMR: δ 118.8 (CN), 78.5 (C_3), 66.3 (C5), 45.1 (C_7), 45.0 (C_1), 42.5 (C_6), 41.4 (C_9), 35.8 (C_2), 26.9 (C_8), 23.1 ($\underline{C}H_2CN$); IR: 2966, 2249, 1454, 1424, 1360, 1308, 1223, 1038, 972, 926, 894, 855, 760, 640 cm^{-1}; MS e/z: 163 (M^+, 20), 134 (5), 121(8), 119 (13), 103 (16), 94 (70), 78 (96), 66 (52), 52 (76), 40 (100); HRMS (EI, 70 eV): *m*/*z* calcd for $C_{10}H_{13}NO$ (M^+): 163.0997; found:163.0997.

1.4.3.2. 9-*endo*-(4-Oxatricyclo[4.3.0.0^{3,7}]non-9yl)-acetonitrile (35). 17.1 mg (27% yield); white solid; R_f = 0.20 (2:1 hexanes-EtOAc); Mp: 55-56°C; ^{1}H NMR: δ 4.04 (t, *J* = 2.7 Hz, H_3), 3.77 (dd, *J* = 3.7, 8.2 Hz, H_{5b}), 3.68 (d, *J* = 8.2 Hz, H_{5a}), 2.40-2.17 (6H overlapped, H_6, H_7, H_1, $C\underline{H}_2CN$, H_9), 1.93 (ddd, *J* = 5.1, 9.1, 13.3 Hz, H_{8exo}), 1.43 (dd, *J* = 5.4, 13.9 Hz, H_{2exo}), 1.36 (d, *J* = 13.9 Hz, H_{2endo}), 0.85 (dd, *J* = 7.5, 13.3 Hz, H_{8endo}); ^{13}C NMR: δ 118.7 (CN), 79.6 (C_3), 66.8 (C_5), 49.6, 45.7, 41.8 , 39.0, 27.7, 25.7, 18.4; IR 2973, 2253, 1451, 1392, 1258, 1214, 1046, 972, 879, 780, 764, 667 cm^{-1}; MS e/z 163 (M^+, 75), 134 (35), 122 (50), 120 (45), 105 (43), 95 (83), 79 (95), 66 (76), 53 (83), 40 (100).

1.4.3.3. 9-*exo*-(4-Oxatricyclo[4.3.0.0^{3,7}]non-9yl)-1-phenyl-ethanone (36). 16.1 mg (17% yield); pale yellow solid; R_f = 0.34 (2:1 Hexanes/EtOAc); Mp: 38-39 °C; ^{1}H NMR: δ 7.91 (d, *J* = 7.3 Hz, 2H, Ph), 7.54 (t, *J* = 7.3 Hz, 1H, Ph), 7.44 (t, *J* = 7.4 Hz, 2H, Ph), 4.05 (t, *J* = 2.7 Hz, H_3), 3.82 (dd, *J* = 3.9, 7.9 Hz, H_{5b}), 3.63 (d, *J* = 7.9 Hz, H_{5a}), 2.97 (dd, *J* = 7.4, 16.3 Hz, 1H $C\underline{H}_2COPh$), 2.88 (dd, *J* = 7.4, 16.3 Hz, 1H $C\underline{H}_2COPh$), 2.42 (br s, H_6), 2.23 (br s, H_7), 2.15 (q, *J* = 7.2 Hz, H_9), 2.05 (d, *J* = 5.8 Hz, H_1); 1.74 (dd, *J* = 8.2, 13.9 Hz, H_{8exo}), 1.61 (dd, *J* = 5.8, 13.2 Hz, H_{2exo}), 1.29 (ddd, *J* = 2.0, 5.2, 13.9 Hz, H_{8endo}), 1.20 (dt, *J* = 2.7, 13.2 Hz, H_{2endo}); ^{13}C NMR: δ 198.5 (CO), 137.2 (C_q, Ph), 132.8 (CH, Ph), 128.5 (2x CH, Ph), 128.0 (2x CH, Ph), 78.6 (C_3), 66.3 (C_5), 45.3 (CH), 44.9 (CH), 44.2 (CH_2), 42.6 (CH), 40.3 (CH), 35.9 (CH_2), 27.1 (CH_2); IR 2961, 1678, 1594, 1450, 1409, 1373, 1277, 1223, 1027, 997, 967, 925, 895, 853, 779, 763, 749, 734, 689 cm^{-1}.

1.4.3.4. 9-*endo*-(4-Oxatricyclo[4.3.0.0^{3,7}]non-9yl)-1-phenyl-ethanone (37). 12.3 mg (13% yield); pale yellow solid; R_f = 0.36 (2:1 Hexanes/EtOAc); Mp: 79-80 °C;

^{1}H NMR: δ 7.91 (d, *J* = 7.4 Hz, 2H, Ph), 7.54 (t, *J* = 7.3 Hz, 1H, Ph, 7.45 (t, *J* = 7.3 Hz, 2H, Ph), 4.04 (t, *J* = 2.8 Hz, H_3), 3.78 (dd, *J* = 3.7, 8.0 Hz, H_{5b}), 3.68 (d, *J* = 8.0 Hz, H_{5a}), 3.01 (dd, *J* = 7.2, 16.6 Hz, 1H C$\underline{H_2}$COPh), 2.91 (dd, *J* = 7.2, 16.6 Hz, 1H C$\underline{H_2}$COPh), 2.56 (m, H_9) 2.37 (br s, H_6), 2.21 (br s, H_7), 2.14 (br s, H_1), 1.95 (ddd, *J* = 5.6, 10.1, 13.2 Hz, H_{8exo}), 1.51 (dq, *J* = 1.9, 13.5 Hz, H_{2endo}), 1.38 (dd, *J* = 5.7, 13.5 Hz, H_{2exo}), 0.85 (dd, *J* = 8.1, 13.2 Hz, H_{8endo}); ^{13}C NMR: δ 199.5 (CO), 137.5 (C_q, Ph), 133.3 (CH, Ph), 128.9 (2x CH, Ph), 128.4 (2x CH, Ph), 79.9 (C_3), 67.1 (C_5), 49.6 (C_6), 45.8 (C_5), 42.2 (C_1), 39.7 ($\underline{C}H_2$COPh), 37.9 (C_9), 28.5 (C_2), 26.2 (C_8); IR 2972, 1680, 1601, 1449, 1376, 1224,1045, 972, 879, 853, 779, 763, 749, 734, 689 cm^{-1}; MS e/z 242 (M^+, 5), 214 (8), 198 (5), 157 (7), 122 (40), 120 (55), 105 (100), 93 (23), 77 (95), 66 (10), 51 (29), 41 (27).

1.4.3.5. 3-Chloro-3-phenylpropan-1-ol (27). 52.4 mg (79% yield); light-yellow oil; R_f = 0.34 (hexanes–EtOAc, 2:1); ^{1}H NMR: δ 7.39–7.28 (m, 5 H, Ph), 5.10 (dd, *J* = 9.0, 5.5 Hz, 1 H, H_3), 3.86 (m, 1 H, H_1), 3.71 (m, 1 H, $H_{1'}$), 2.33–2.16 (m, 2 H, H_2, $H_{2'}$), 1.40 (br s, 1 H, OH); ^{13}C NMR: δ 141.5 (Cq, Ph), 128.6 (2 × CH, Ph), 128.3 (CH, Ph), 126.9 (2 × CH, Ph), 60.1 (C_3), 59.7 (C_1), 42.3 (C_2); IR: 3629, 3465, 3016, 2955, 2885, 1495, 1453, 1233, 1042, 897, 865, 822, 699, 616 cm^{-1}; HRMS (EI, 70 eV): *m*/*z* calcd for C_9H_9Cl ($M^+ - H_2O$): 152.0393; found: 152.0394.

1.4.3.6 3-Chloro-3-(4-fluorophenyl)propan-1-ol (49a). 57.9 mg (79% yield); colorless oil; R_f = 0.30 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.36 (dd, *J*= 5.3, 8.6 Hz, 2H, Ph), 7.02 (t, *J*= 8.6 Hz, 2H, Ph), 5.09 (dd, *J* = 5.5, 9.1 Hz, 1H, H_3), 3.85 (m, 1H, H_1), 3.69 (m, 1H, $H_{1'}$), 2.33-2.15 (m, 2H, H_2 and $H_{2'}$) 1.58 (br s, 1H, O$\underline{H}$); ^{13}C NMR: δ 162.5 (d, *J*= 246.5 Hz, CF, Ph), 137.4 (d, *J*= 3.5 Hz, C_q, Ph), 128.7 (d, *J*= 8.5 Hz, 2 x CH, Ph), 115.6 (d, *J*= 4.5 Hz, 2 x CH, Ph), 59.5 (C_1), 59.2 (C_3), 42.5 (C_2). IR: 3621, 3423, 3013, 2955, 2891, 1894, 1606, 1512, 1473, 1422, 1296, 1228, 1160, 1044, 836, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 188.0404, found: 188.0402.

1.4.3.7. 3-Chloro-3-(4-chlorophenyl)propan-1-ol (49b). 66.8 mg (84% yield); colorless oil; R_f = 0.31 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.32 (br s, 4H, Ph), 5.07

(dd, *J* = 5.5, 9.1 Hz, 1H, H_3), 3.85 (m, 1H, H_1), 3.68 (m, 1H, $H_{1'}$), 2.31-2.14 (m, 2H, H_2 and $H_{2'}$) 1.54 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 140.0 (C_q, Ph), 134.2 (C_q, Ph), 128.9 (2 x CH, Ph), 128.3 (2 x CH, Ph), 59.5 (C_1), 59.1 (C_3), 42.3 (C_2); IR: 3622, 3442, 3018, 2962, 2881, 1901, 1602, 1495, 1410, 1244, 1090, 1049, 1020, 835, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+-H_2O): 186.0003, found: 186.0005.

1.4.3.8. 3-(4-Bromophenyl)-3-chloropropan-1-ol (49c). 76.4 mg (79% yield); white wax; R_f = 0.31 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.48 (d, *J* = 8.4 Hz, 2H, Ph), 7.27 (d, *J* = 8.4 Hz, 2H, Ph), 5.07 (dd, *J* = 5.5, 9.1 Hz, 1H, H_3), 3.86 (m, 1H, H_1), 3.70 (m, 1H, $H_{1'}$), 2.32-2.14 (m, 2H, H_2 and $H_{2'}$) 1.34 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 140.6 (C_q, Ph), 131.8 (CH, Ph), 128.6 (CH, Ph), 122.3 (C_q, Ph), 59.4 (C_1), 59.1 (C_3), 42.3 (C_2); IR: 3629, 3437, 3008, 2958, 2883, 1587, 1491, 1402, 1242, 1075, 1004, 834, 809, 668 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 247.9604, found: 247.9597.

1.4.3.9. 3-Chloro-3-*p*-tolylpropan-1-ol (49d). 51.0 mg (71% yield); light green oil; R_f = 0.38 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.27 (d, *J*= 8.0 Hz, 2H, Ph), 7.14 (d, *J*= 8.0 Hz, 2H, Ph), 5.08 (dd, *J* = 5.6, 9.0 Hz, 1H, H_3), 3.86 (m, 1H, H_1), 3.71 (m, 1H, $H_{1'}$), 2.35 (s, 3H, CH_3), 2.35-2.19 (m, 2H, H_2 and $H_{2'}$) 1.43 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 138.6 (C_q, Ph), 138.0 (C_q, Ph), 129.3 (2 x CH, Ph), 126.9 (2 x CH, Ph), 60.2 (C_3), 59.8 (C_1), 42.4 (C_2), 21.2 (CH_3); IR: 3620, 3450, 3009, 2956, 2881, 1710, 1612, 1511, 1440, 1417, 1380, 1241, 1181, 1049, 899, 869, 817, 669, 626 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 184.0655, found: 184.0659.

1.4.3.10. 3-Chloro-3-(3-nitrophenyl)propan-1-ol (49f). 4.2 mg (5% yield); light yellow oil; R_f = 0.20 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 8.22 (d, *J*= 8.7 Hz, 2H, Ph), 7.59 (d, *J*= 8.7 Hz, 2H, Ph), 5.20 (dd, *J* = 5.4, 9.1 Hz, 1H, H_3), 3.91 (m, 1H, H_1), 3.71 (m, 1H, $H_{1'}$), 2.31-2.17 (m, 2H, H_2 and $H_{2'}$) 1.46 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 148.4 (C-NO_2, Ph), 147.8 (C_q, Ph), 127.9 (2 x CH, Ph), 123.9 (2 x CH, Ph), 59.0 (C_1), 58.2 (C_3), 42.2 (C_2); IR: 3626, 3470, 3027, 2957, 2890, 1736, 1608, 1528, 1350, 1221, 1045, 1015, 850, 667 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+-H_2O): 197.0244, found: 197.0246.

1.4.3.11. 3-Chloro-3-(3-fluorophenyl)propan-1-ol (49g) 55.7 mg (76% yield); colorless oil; R_f = 0.31 (Hexanes/EtOAc, 2:1); ^{1}H NMR: 7.35 (dd, *J*= 4.7, 8.1 Hz, 1H, Ph), 7.16 (dd, *J*= 4.7, 8.1 Hz, 2H, Ph), 6.99 (t, *J*= 4.7 Hz, 1H, Ph), 5.08 (dd, *J* = 5.5, 9.0 Hz, 1H, H_3), 3.87 (m, 1H, H_1), 3.70 (m, 1H, $H_{1'}$), 2.32-2.16 (m, 2H, H_2 and $H_{2'}$) 1.46 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 162.8 (d, *J*= 245.6 Hz, CF, Ph), 144.0 (d, *J*= 7.3 Hz, C_q, Ph), 130.1 (d, *J*= 8.3 Hz, CH, Ph), 122.6 (d, *J*= 2.7 Hz, CH, Ph), 115.2 (d, *J*= 20.9 Hz, CH, Ph), 114.1 (d, *J*= 22.1 Hz, CH, Ph), 59.4 (C_1), 59.0 (C_3), 42.3 (C_2); IR: 3627, 3448, 3015, 2954, 2882, 1614, 1593, 1489, 1446, 1263, 1235, 1138, 1038, 959, 945, 869, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 188.0404, found: 188.0408.

1.4.3.12. 3-Chloro-3-(3-chlorophenyl)propan-1-ol (49h). 49.3 mg (62% yield); light yellow oil; R_f = 0.33 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.40 (br s, 1H, Ph), 7.27 (br s, 3H, Ph), 5.07 (dd, *J*= 5.5, 9.0 Hz, 1H, H_3), 3.88 (m, 1H, H_1), 3.71 (m, 1H, $H_{1'}$), 2.33-2.17 (m, 2H, H_2 and $H_{2'}$) 1.32 (t, *J*= 4.8 Hz, 1H, O<u>H</u>); ^{13}C NMR: δ 143.5 (C_q, Ph), 134.6 (C_q, Ph), 129.9 (CH, Ph), 128.5 (CH, Ph), 127.3 (CH, Ph), 125.1 (CH, Ph), 59.4 (C_1), 59.0 (C_3), 42.3 (C_2); IR: 3622, 3425, 3017, 2963, 2881, 1599, 1571, 1481, 1435, 1249, 1080, 1045, 887, 668 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 204.0109, found: 204.0111.

1.4.3.13. 3-(3-Bromophenyl)-3-chloropropan-1-ol (49i). 57.1 mg (59% yield); light yellow oil; R_f = 0.33 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.54 (s, 1H, Ph), 7.42 (d, *J* = 7.9 Hz, 1H, Ph), 7.32 (d, *J* = 7.8 Hz, 1H, Ph), 7.22 (t, *J*= 7.8 Hz, 1H, Ph), 5.05 (dd, *J*= 5.5, 9.0 Hz, 1H, H_3), 3.87 (m, 1H, H_1), 3.70 (m, 1H, $H_{1'}$), 2.32-2.16 (m, 2H, H_2 and $H_{2'}$) 1.31 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 143.8 (C_q, Ph), 131.4 (CH, Ph), 130.2 (CH, Ph), 130.1(CH, Ph), 125.6 (CH, Ph), 122.7 (C_q, Ph), 59.4 (C_1), 58.9 (C_3), 42.3 (C_2); IR: 3632, 3460, 3017, 2957, 2886, 1593, 1570, 1476, 1428, 1236, 1075, 884, 835, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 247.9604, found: 247.9610.

1.4.3.14. 3-Chloro-3-*m*-tolylpropan-1-ol (49j). 45.2 mg (63% yield); light yellow oil; R_f = 0.36 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.24-7.16 (m, 3H, Ph), 7.08 (d, *J*= 7.1 Hz,1H, Ph), 5.05 (dd, *J*= 5.6, 9.0 Hz,1H, H_3), 3.83 (m,1H, H_1), 3.70 (m, 1H, $H_{1'}$),

2.36 (s, 3H, CH_3), 2.34-2.18 (m, 2H, H_2 and $H_{2'}$) 1.51 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 141.5 (C_q, Ph), 138.2 (C_q, Ph), 129.1 (CH, Ph), 128.5 (CH, Ph), 127.6 (CH, Ph), 124.0 (CH, Ph), 60.2 (C_3), 59.8 (C_1), 42.4 (C_2), 21.4 (CH_3); IR: 3626, 3447, 3009, 2962, 2883, 1604, 1485, 1471, 1381, 1259, 1234, 1166, 1040, 878, 850, 667 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 184.0655, found: 184.0653.

1.4.3.15. 3-Chloro-3-(3-methoxyphenyl)propan-1-ol (49k). 28.1 mg (36% yield); light yellow oil; R_f = 0.26 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.23 (t, *J*= 7.9 Hz,1H, Ph), 6.95 (d, *J*= 7.7 Hz, 1H, Ph), 6.92 (t, *J*= 2.0 Hz, 1H, Ph), 6.81(dd, *J*= 2.5, 8.3 Hz, 1H, Ph), 5.05 (dd, *J*= 5.6, 8.9 Hz, 1H, H_3), 3.84 (m, 1H, H_1), 3.80 (s, 3H, OCH_3), 3.70 (m, 1H, $H_{1'}$), 2.32-2.19 (m, 2H, H_2 and $H_{2'}$) 1.46 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 159.8 (C_q, Ph), 143.0 (C_q, Ph), 129.6 (CH, Ph), 119.2 (CH, Ph), 113.8 (CH, Ph), 112.7 (CH, Ph), 60.0 (C_3), 59.7 (C_1), 55.1 (O<u>C</u>H_3), 42.4 (C_2); IR: 3621, 3454, 3011, 2964, 2886, 2829, 1597, 1583, 1484, 1459, 1434, 1264, 1157, 1036, 880, 841, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 200.0604, found: 200.0602.

1.4.3.16. 3-Chloro-3-(2-fluorophenyl)propan-1-ol (49l). 33.0 mg (45% yield); orange oil; R_f = 0.41 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.49 (td, *J*= 1.6, 8.0 Hz, 1H, Ph), 7.29 (m, 1H, Ph), 7.15 (td, *J*= 1.0, 8.0 Hz, 1H, Ph), 7.04 (d, *J*= 1.3, 8.0 Hz, 1H, Ph), 5.43 (dd, *J* = 5.3, 9.2 Hz, 1H, H_3), 3.87 (m, 1H, H_1), 3.76 (m, 1H, $H_{1'}$), 2.37-2.21 (m, 2H, H_2 and $H_{2'}$) 1.34 (t, *J*=4.9 Hz, 1H, O<u>H</u>); ^{13}C NMR: δ 159.6 (d, *J*= 247.4 Hz, CF, Ph), 129.8 (d, *J*= 8.2 Hz, CH, Ph), 128.7 (d, *J*= 12.7 Hz, C_q, Ph), 128.6 (d, *J*= 3.3 Hz, CH, Ph), 124.4 (d, *J*= 3.5 Hz, CH, Ph), 115.7 (d, *J*= 21.9 Hz, CH, Ph), 59.6 (C_1), 52.8 (d, *J*= 3.8 Hz, C_3), 41.3 (C_2); IR: 3626, 3449, 3010, 2956, 2887, 1470, 1437, 1234, 1046, 1027, 875, 824, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 188.0404, found: 184.0406.

1.4.3.17. 3-Chloro-3-(2-chlorophenyl)propan-1-ol (49m). 35.0 mg (44% yield); light yellow oil; R_f = 0.38 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.59 (dd, *J*= 1.6, 8.0 Hz, 1H, Ph), 7.35 (dd, *J*= 1.4, 7.9 Hz, 1H, Ph), 7.29 (td, *J*=1.4, 7.5 Hz, 1H, Ph), 7.22 (td, *J*=1.7, 7.7 Hz, 1H, Ph) 5.61 (t, *J*= 7.1, 1H, H_3), 3.88 (m, 1H, H_1), 3.78 (m, 1H, $H_{1'}$), 2.25 (q, *J*=6.7 Hz, 2H, H_2 and $H_{2'}$) 1.49 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 139.0 (C_q,

Ph), 132.5 (C_q, Ph), 129.6 (CH, Ph), 129.2 (CH, Ph), 128.6 (CH, Ph), 127.3 (CH, Ph), 59.7 (C_1), 55.8 (C_3), 41.6 (C_2); IR: 3615, 3433, 3017, 2955, 2886, 1593, 1572, 1472, 1443, 1246, 1129, 1035, 823, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 204.0109, found: 204.0107.

1.4.3.18. 3-(2-Bromophenyl)-3-chloropropan-1-ol (49n). 45.5 mg (47% yield); light yellow oil; R_f = 0.38 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.62 (dd, *J*= 1.6, 8.0 Hz, 1H, Ph), 7.54 (dd, *J*= 1.1, 8.0 Hz, 1H, Ph), 7.35 (t, *J*=7.3 Hz, 1H, Ph), 7.15 (td, *J*=1.6, 7.6 Hz, 1H, Ph) 5.58 (dd, *J*= 5.6, 8.6 Hz, 1H, H_3), 3.89 (m, 1H, H_1), 3.80 (m, 1H, $H_{1'}$), 2.31-2.18 (m, 2H, H_2 and $H_{2'}$) 1.37 (t, *J*= 5.4 Hz, 1H, O<u>H</u>); ^{13}C NMR: δ 140.6 (C_q, Ph), 132.9 (CH, Ph), 129.5 (CH, Ph), 128.8 (CH, Ph), 128.0(CH, Ph), 122.8 (C_q, Ph), 59.7 (C_1), 58.5 (C_3), 41.8 (C_2); IR: 3621, 3452, 3016, 2954, 2886, 1614, 1582, 1488, 1452, 1236, 1045, 833, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 247.9604, found: 247.9601.

1.4.3.19. 3-Chloro-3-o-tolylpropan-1-ol (49o) 29.4 mg (41% yield); light yellow oil; R_f = 0.37 (Hexanes/EtOAc, 2:1); ^{1}H NMR: δ 7.45 (d, *J*= 8.1 Hz, 1H, Ph), 7.23-7.12 (m, 3H, Ph), 5.39 (dd, *J*= 5.0, 9.4 Hz, 1H, H_3), 3.90 (m, 1H, H_1), 3.75 (m, 1H, $H_{1'}$), 2.42 (s, 3H, CH_3), 2.39-2.19 (m, 2H, H_2 and $H_{2'}$) 1.43 (br s, 1H, O<u>H</u>); ^{13}C NMR: δ 139.4 (C_q, Ph), 135.2 (C_q, Ph), 130.6 (CH, Ph), 128.1 (CH, Ph), 126.6 (CH, Ph), 126.5 (CH, Ph), 59.8 (C_1), 56.2 (C_3), 41.3 (C_2), 19.1 (CH_3); IR: 3626, 3462, 3013, 2956, 2884, 1492, 1461, 1382, 1226, 1051, 669 cm^{-1}; HRMS (EI, 70 eV): *m/z* calcd (M^+): 184.0655, found: 184.0652.

1.4.4. Reaction of the stock solution and styrene with Brønsted acid Methylene diacetate stock solution (2.5 mL), and styrene (41 mg, 0.39 mmol) were added to a 10-mL flask and allowed to mix for 5 min. Then at rt, PTSA (549 mg, 2.88 mmol) was added to give a cloudy solution. After 23 h. mixing at rt, H_2O (5 mL) was added to the reaction flask, followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Finally, flash column chromatography (hexanes–EtOAc, 10:1) gave the acetyl **29** (39.1 mg, 47% yield), dioxane **17a** (11.5 mg, 18% yield) and alcohol **27** (14.0 mg, 21% yield).

1.4.5. Reaction done for the proof of the proposed mechanism Styrene (50 mg, 0.48 mmol), formaldeyhyde (57.7 mg, 0.72 mmol, 37% aq. solution), acetylchloride (56.5 mg, 0.72 mmol) and NBu_4Cl (399 mg, 1.44 mmol) were all dissolved in 3 mL CH_2Cl_2. Then at rt, PTSA (549 mg, 2.88 mmol) was added to give a cloudy solution. After 24 h. mixing at rt, H_2O (5 mL) was added to the reaction flask, followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Finally, flash column chromatography (hexanes–EtOAc, 10:1) gave the acetyl **29** (43.0 mg, 42% yield), dioxane **17a** (9.5 mg, 12% yield) and alcohol **27** (16.4 mg, 20% yield).

PART II

LIPASE MEDIATED KINETIC RESOLUTION OF 3-CHLORO-3-ARYLPROPANOLS

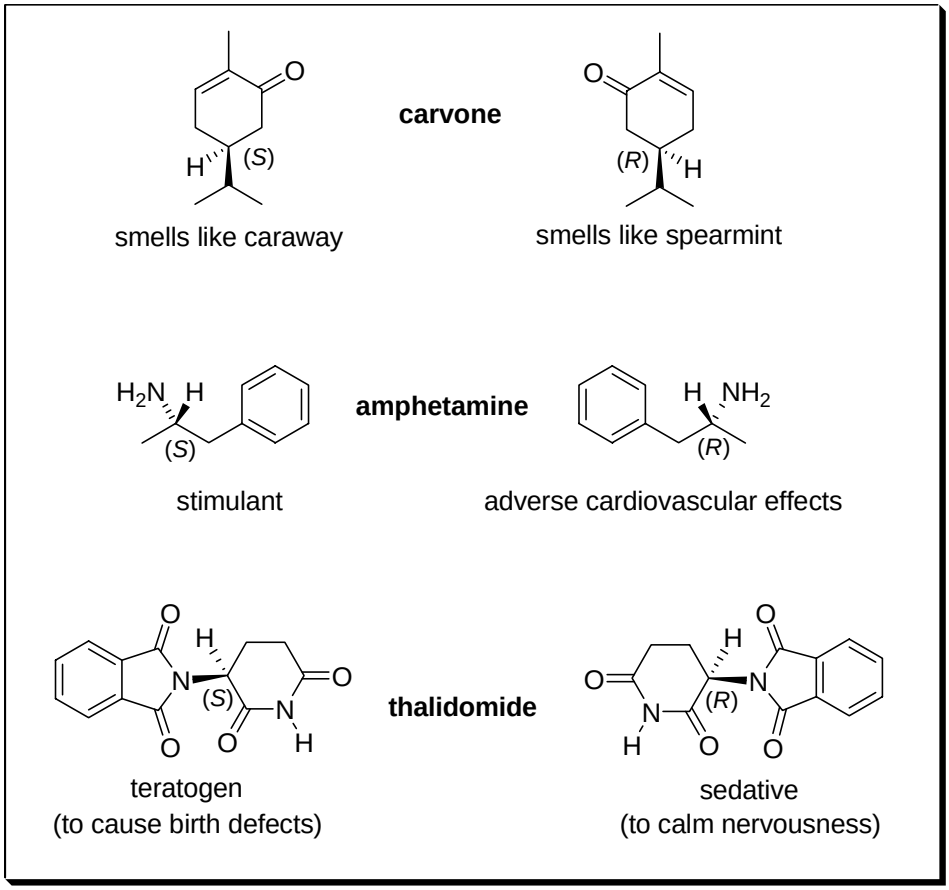
CHAPTER I

INTRODUCTION

2.1.1. Biological significance of chiral compounds

All the major biochemical events taking place in an organism are governed by enzymes. Since the majority of these events are highly selective with respect to the chirality of a substrate, it is obvious that the enantiomers of a given bioactive compound such as a pharmaceutical or an agrochemical cause different biological effects [25]. Consequently, they must be regarded as two distinct species. The isomer with the highest activity is denoted as the 'eutomer' whereas its enantiomeric counterpart possessing less or even undesired activities is termed as the 'distomer'. The range of effects derived from the distomer can extend from lower (although positive) activity, no response or toxic events. Some representative examples of different biological effects are given in Scheme 22.

Probably the most well-known and tragic example of a drug where the distomer causes serious side-effects is 'Thalidomide', which was administrated in 1960s. At that time it was not known that the sedative effect resides in the (*R*)-enantiomer but the (*S*)-counterpart is highly teratogenic [26].



Scheme 22. Biological effects of enantiomers

As a consequence, racemates of pharmaceuticals and agrochemicals should be regarded with suspicion. Chiral purity of drug molecules is therefore warranted essential. The FDA has issued guidelines concerning the development of drugs having chiral centers [27]. The FDA does not prohibit the marketing of racemates, but the choice of a racemic synthesis over the development of a chirally pure drug must be justified. It also requires investigations on the bioavailability and pharmacological data of the chiral drug and the final approval is based on complete background information on each enantiomer and the racemic mixture.

Quite astonishingly, 88% of the 480 chiral synthetic drugs on the market were sold in racemic form in 1982 [28].

In last years, worldwide sales of chiral drugs in single-enantiomer forms increased considerably. The market share of single enantiomer dosage form drugs

increased from 27% (US $74.4 billion) in 1996 to 38% in 2001 [29]. In the year 2003, active ingredients of nine out of ten top-selling drugs on the market were reported to be chiral [30]. Consequently, the majority of drug companies are now developing single enantiomers in preference to racemates. This has led to an increased need for enantiopure compounds.

The principle of asymmetric synthesis [31] makes use of enantiomerically pure auxilary reagents which are used in catalytic or sometimes in stoichometric amounts. They are often expensive and cannot be recovered in many cases.

Likewise, starting a synthesis with an enantiomerically pure compound which has been selected from the large stock of enantiomerically pure natural compounds [32] such as carbohydrates, amino acids, terpenes or steroids (the so-called 'chiral pool') has its limitations. According to a survey [33] only about 10 - 20% of compounds are available from the chiral pool at an affordable price (in the range of 100 – 250 US $ per kg). Considering the above mentioned problems with the alternative ways of obtaining enantiomerically pure compounds, it is obvious that enzymatic methods represent a valuable extra kit for the preexisting toolbox available for the asymmetric synthesis of fine chemicals [34].

2.1.2. Use of enzymes as catalysts

The development of synthetic organic chemistry has made possible the stereocontrolled synthesis of a very large number of complex molecules. As the field has developed, its targets and constraints have changed. Two problems now facing organic synthesis are the development of techniques for preparing complex, water-soluble biochemicals, and the development of environmentally acceptable synthetic processes that are also economically acceptable. Enzymes are able to contribute to the resolution of both of the issues, and they should be considered as one useful class of catalysts to be used, when appropriate, for organic synthesis.

Enzymes are proteins; they catalyze most biological reactions *in vivo* [35]. They also catalyze reactions involving both natural and unnatural substrates *in vitro* [36]. As catalysts, enzymes have the following characteristics:

Advantages:

- They accelerate the rate of reactions, and operate under mild conditions.
- Enzymes can catalyze a broad spectrum of reactions. They only accelerate a reaction, but they have no impact on the position of the thermodynamic equilibrium of the reaction. Thus, in principle, some enzyme-catalyzed reactions can be run in both directions.
- Enzymes display three major types of selectivities in the reactions that they involve:

1. Chemoselectivity:

   Since the purpose of an enzyme is to act on a single type of functional group, other sensitive functionalities, which would normally react to a certain extent under chemical catalysis, survive. As a result, reactions generally tend to be cleaner and purification of product(s) from impurities emerging through side-reactions can largely be omitted. For instance, enzymatic ester hydrolysis does not show any propensity for acetal cleavage.

2. Regioselectivity and Diastereoselectivity:

   Due to their complex three-dimensional structure, enzymes may distinguish between functional groups which are chemically situated in different regions of the same substrate molecule [37].

3. Enantioselectivity:

   Almost all enzymes are made from L-amino acids and thus are chiral catalysts [38]. As a consequence, any type of chirality present in the substrate molecule is recognized upon the formation of the enzyme-substrate complex. Thus a prochiral substrate may be transformed into an optically active product and both enantiomers of a racemic substrate may react at different rates, affording a kinetic resolution. These properties collectively constitute the specificity of an enzyme and represent its most important feature for selective and asymmetric exploitation [39]. This key feature was recognized by E. Fischer as long ago as 1898 [40].

- Enzymes are environmentally acceptable. Unlike heavy metals, they are completely degraded in the environment.
- Enzymes are not bound to their natural role. They exhibit a high substrate tolerance by accepting a large variety of man-made unnatural substances and often they are not required to work in water.

Disadvantages:

- Enzymes are provided by nature in only one enantiomeric form. Since there is no general way of creating mirror-image enzymes, it is impossible to invert the chiral induction of a given enzymatic reaction by choosing the other enantiomer of the biocatalyst, a strategy which is possible if chiral chemical catalysts are involved. To gain access to the other enantiomeric product, one has to follow a longer path in search of an enzyme with exactly the opposite stereochemical selectivity. However, this is sometimes possible.
- Enzymes require narrow operation parameters. The obvious advantage of working under mild reaction conditions sometimes turn into a drawback. If a reaction proceeds only slowly under given parameters of temperature or pH, there is only a narrow scope for alteration. Elevated temperatures as well as extreme pH lead to deactivation of the protein, as do high salt concentrations. The usual technique of lowering the reaction temperature in order to gain an increase in selectivity is of limited use with enzymatic transformations.
- Enzymes display their highest catalytic activity in water. Due to its high boiling point and high heat of vaporization, water is usually the least desired solvent of choice for most organic reactions. Furthermore, the majority of organic compounds are only poorly soluble in aqueous media. Thus shifting enzymatic reactions from an aqueous to an organic medium would be highly desired, but usually some loss of activity happens, which is often in the order of one magnitude [41].
- Enzymes are prone to inhibition phenomena. Many enzymatic reactions are prone to substrate or product inhibition, which causes the enzyme to cease to work at higher substrate and/or product concentrations, a factor which limits the efficiency of the process. Whereas substrate inhibition can be circumvented

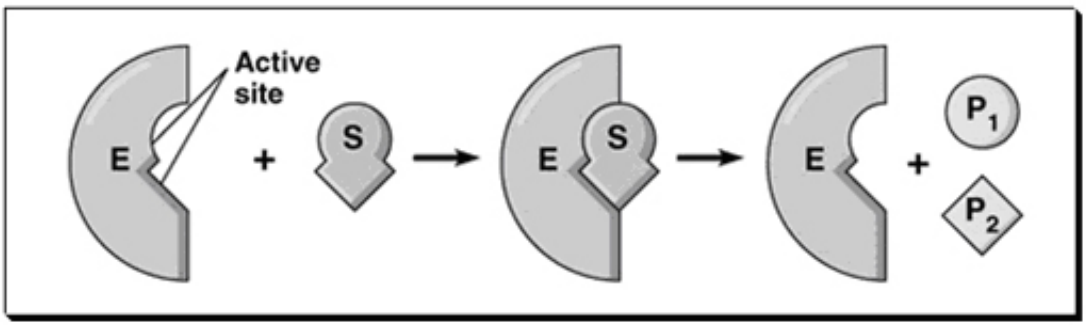
comparatively easily by keeping the substrate concentration at a low level through continuous addition, product inhibition is a more complicated problem. The gradual removal of product by physical means is usually difficult as is the engagement of another step to the reaction sequence in order to effect chemical removal of the product.

2.1.3. Mechanistic aspects

Among the numerous theories and rationales which have been developed in order to understand enzyme catalysis, the most illustrative models for the organic chemist will be briefly discussed.

2.1.3.1. Lock and key mechanism

The first proposal for a general mechanism of enzymatic action was developed by E. Fischer in 1894 [42]. It assumes that an enzyme and its substrate mechanistically interact like a lock and a key, respectively (Scheme 23). Although this assumption was quite sophisticated at that time, it assumes a completely rigid enzyme structure.

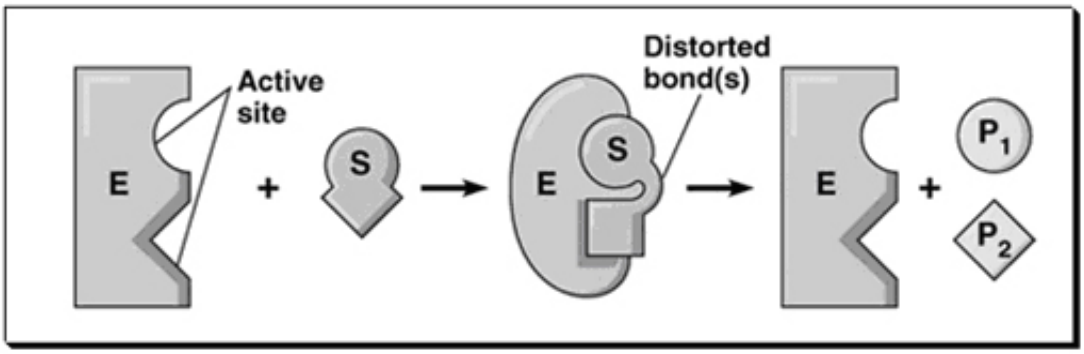


Scheme 23. Representation of the Lock and Key mechanism

Thus, it cannot explain why many enzymes do act on large substrates, while they are inactive on smaller, similar counterparts. Given Fischer's rationale, small substrates should be transformed at even higher rates than larger substrates since the access to the active site would be easier. Furthermore, the hypothesis cannot explain why many enzymes can convert not only their natural substrates but also numerous non-natural compounds possessing different structural features. Thus, a more sophisticated model had to be developed.

2.1.3.2. Induced-fit mechanism

This rationale, which takes into account that enzymes are not entirely rigid but rather represent delicate and soft structures, was developed by Koshland Jr. in the late 1960s [43]. It assumes that upon approach of a substrate during the formation of the enzyme-substrate complex, the enzyme can change its conformation under the influence of the substrate structure so as to wrap around its guest (Scheme 24). A similar picture is given by the interaction of a hand (the substrate) and a glove (the enzyme).



Scheme 24. Representation of the induced-fit mechanism

This model can indeed explain why in many cases several structural features on a substrate are required. These structural features may be located quite a distance from the actual site of the reaction. The most typical 'induced-fit' enzymes are the

lipases. They can convert an amazing large variety of artificial substrates which possess structures which do not have much in common with the natural substrates, triglycerides.

2.1.3.3. Desolvation and solvation-substitution theory

Quite recently, Dewar developed a different rationale [44] in attempting to explain the high conversion rates of enzymatic reactions, which are often faster than the chemically-catalyzed equivalent processes [45]. The theory (called the 'desolvation-theory') assumes that the kinetics of enzyme reactions have much incommon with those of gas-phase reactions. If a substrate enters the active site of the enzyme, it replaces all of the water molecules from the active site of the enzyme. Then, a formal gas phase reaction can take place which mimics two reaction partners interacting without disturbing solvent. In a solution, the water molecules impede the approach of the partners, hence the reaction rate is reduced. This theory would explain why small substrate molecules are often more slowly converted than larger analogues, since the former are unable to replace all the water molecules from the active site. However, there is still much debate about this theory.

This desolvation theory has recently been extended by a solvation substitution theory [46]. It is based on the assumption that the enzyme would not be able to strip off the water which is surrounding the substrate to effect a desolvation, because this would be energetically unfavored. Instead, the solvent is displaced by another environment (provided by the active site of the enzyme) by a so-called 'solvation substitution'. Thus the (often) hydrophobic substrates replace the water with the (often) hydrophobic site of the enzyme.

In any case it is clear that a maximum change in entropy is only obtained upon a tight and close fit of a substrate into the pocket of an active site of an enzyme [47].

2.1.3.4. Three-point attachment rule

This widely used rationale to explain the enantioselectivity of enzymes was suggested by Ogston [48]. To get a high degree of enantioselection, a substrate must be held firmly in a three dimensional space. As a consequence, there must be at least three different points of attachment of the substrate onto the active site [49].

This is exemplified for the discrimination of the enantiomers of a racemic substrate (A and B, Figure 5) with its chirality located on a sp^3-carbon atom.

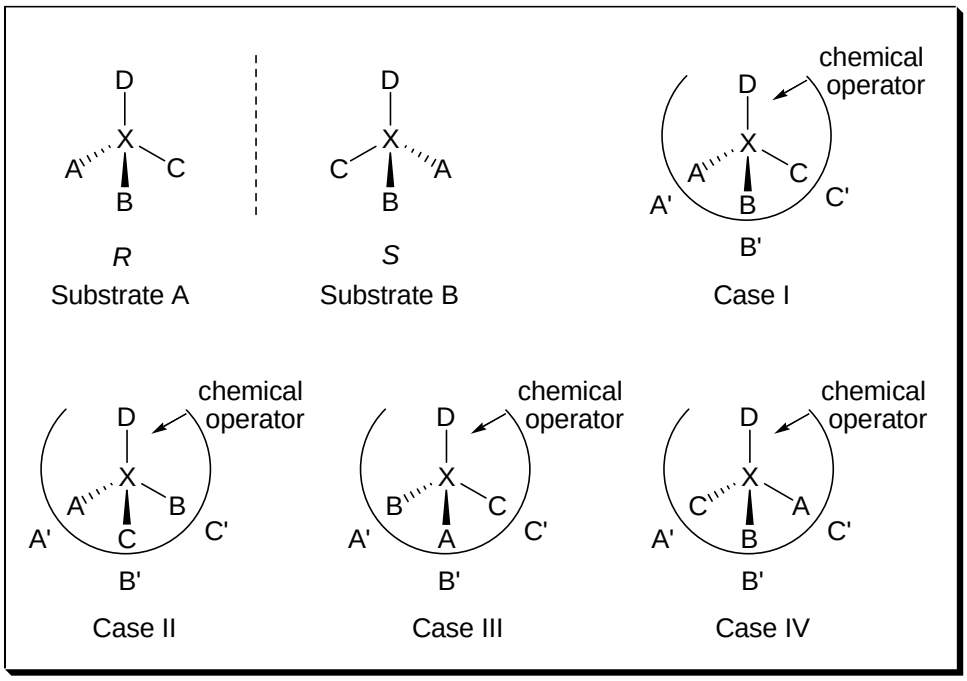


Figure 5. Enzymatic enantiomer discrimination

Case I: Enantiomer A is a good substrate by allowing an optimal interaction of its groups (A, B, C) with their complementary binding site areas of the enzyme (A´, B´, C´). It ensures an optimal orientation of the reactive group (D) towards the chemical operator which is required for a successful transformation.

Cases II through IV: Regardless of its orientation in the active site, enantiomer B is a poor substrate because optimal binding and orientation of the

reactive group D is not possible. Thus poor catalysis will be observed.

2.1.3.5. Kinetic reasons for selectivity

As in every other catalytic reaction, an enzyme (E) accelerates the reaction by lowering the energy barrier, the activation energy (Ea), between substrate (S) and product (P) [50]. The origin of this catalytic power (the rate acceleration) has generally been attributed to transition-state stabilization of the reaction by the enzyme [51], assuming that the catalyst binds more strongly to the transition state than to the ground state of the substrate, by a factor approximately equal to the rate acceleration (Figure 6) [52].

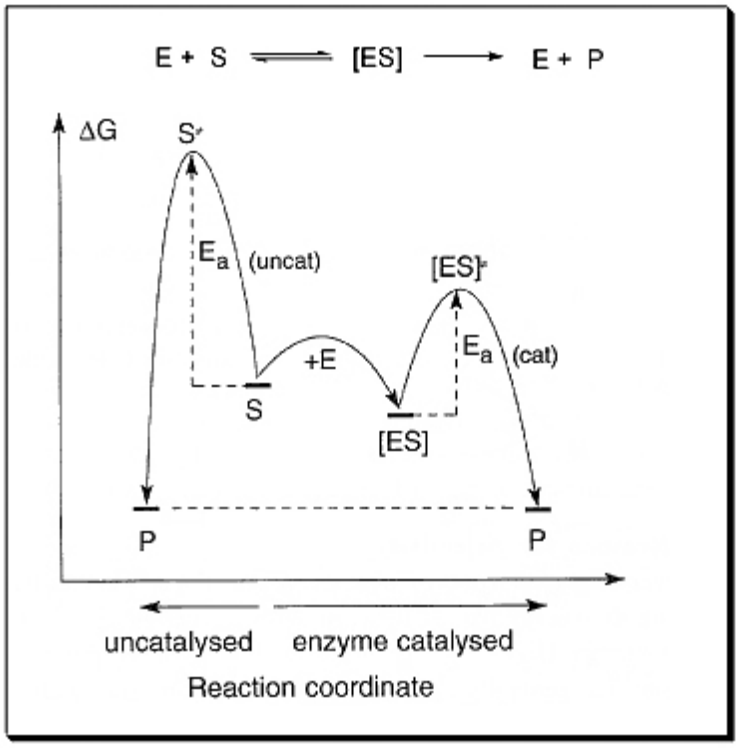


Figure 6. Energy diagram of catalyzed versus uncatalyzed reaction

Virtually all stereoselectivities of enzymes originate from the energy difference in the enzyme-transition state complex $[ES]^{\neq}$. For instance, in an enantioselective reaction both of the enantiomeric substrates (A and B, Figure 5, page 48) compete for the active site of the enzyme. Due to the chiral environment of the active site, diastereomeric enzyme-substrate complexes [EA] and [EB] are formed, which possess different values of free energy (ΔG) for their respective transition states $[EA]^{\neq}$ and $[EB]^{\neq}$ (Figure 7). The result is a difference in activation energy ($\Delta\Delta G^{\neq}$) for both of the enantiomeric substrates. As a result, one enantiomer will be transformed faster than the other. This process is generally refererred to as 'chiral recognition'.

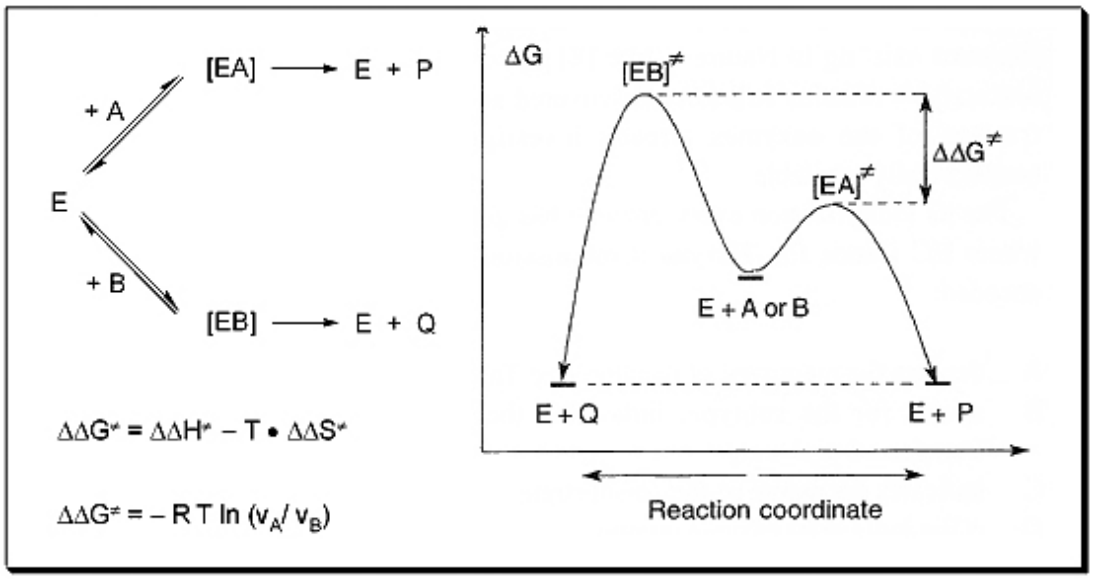


Figure 7. Energy diagram for an enzyme-catalyzed enantioselective reaction

The value of this difference in free energy, expressed as $\Delta\Delta G^{\neq}$, is a direct measure for the selectivity of the reaction which in turn depends on the ratio of the individual reaction rates (v_A, v_B) of enantiomeric substrates A and B competing for the active site of the enzyme (Figure 7). These values are of great importance since they determine the optical purity of the product. $\Delta\Delta G^{\neq}$ is composed of an enthalpy

($\Delta\Delta H^{\neq}$) and an entropy term ($\Delta\Delta S^{\neq}$). The enthalpy of activation is usually dominated by changes in bonds when the substrate is transformed into the product. The entropy contribution includes the energy balance which is needed for orienting the reactants or from changes in conformational flexibility during the induced fit and various concentration and salvation effects. Some representative values of enantiomeric excess (ee) of product corresponding to a given $\Delta\Delta G^{\neq}$ of the reaction are presented in Table 8.

Table 8. Free energy values $\Delta\Delta G^{\neq}$ for optical purities of product and the corresponding ratio of reaction rates of enantiomers

$\Delta\Delta G^{\neq}$ (kcal/mol)	v_A / v_B	ee (%)
0.118	1.2	10
0.651	3	50
1.74	19	90
2.17	39	95
3.14	199	99
4.50	1999	99.9

From Table 8 it can be seen that even a remarkable small difference in free energy (such as 2.17 kcal/mol) already leads to a considerable enantiomeric excess of the product (95%). However, if highly enantiopure material is desired, $\Delta\Delta G^{\neq}$ has to be considerably higher ($\geq$ 4.50 kcal/mol) [28].

2.1.4. Enzyme catalyzed reactions

There is an enzyme-catalyzed process equivalent to almost every type of organic reaction [53]: for example;

- Hydrolysis-synthesis of esters [54], amides [55], lactones [56], lactams [57], ethers [58], acid anhydrides [59], epoxides [60], and nitriles [61].
- Oxidation-reduction of alkanes [62], alkenes [63], aromatics [64], alcohols [65], aldehydes and ketones [66, 67], sulfides and sulfoxides [68].
- Addition-elimination of water [69], ammonia [70], hydrogen cyanide [71].
- Halogenetion and dehalogenation [72], alkylation and dealkylation [73], isomerization [74], acyloin- [75] and aldol reactions [76]. Even Michael-additions have been reported [77].

Some major exceptions, where equivalent reaction types cannot be found in nature are the Diels-Alder reaction [78, 79], and the Cope rearrangement, although [3,3]-sigmatropic rearrangements such as Claisen-rearrangement are known [80, 81]. On the other hand, some biocatalysts can accomplish reactions impossible to emulate in organic chemistry e.g. the selective functionalization of non-activated positions in organic molecules, such as hydroxylation of aliphatics.

Among the mentioned broad range of useful reactions, we will only give further information on hydrolytic reactions due to the scope of our studies.

2.1.4.1. Hydrolytic reactions

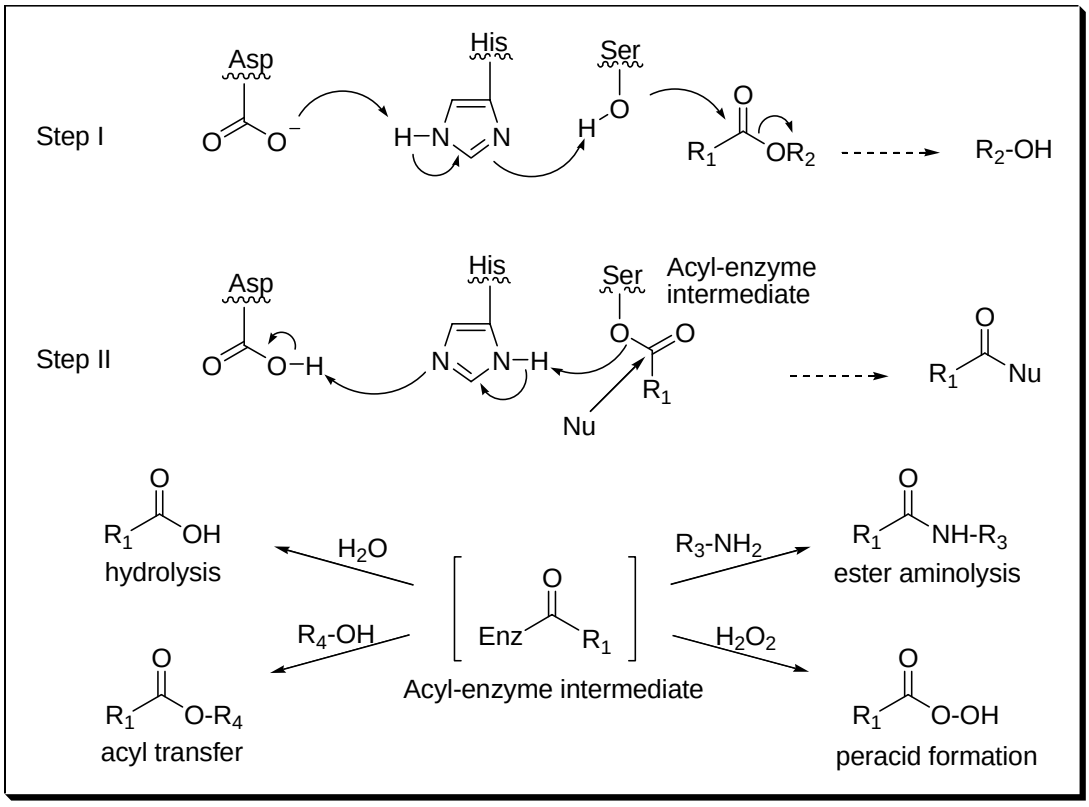
Of all the types of enzyme-catalyzed reactions, hydrolytic transformations involving amide and ester bonds are the easiest to perform using proteases, esterases or lipases. No need for cofactors and a large number of readily available enzymes to choose for the substrate specificity have made hydrolases the favorite class of enzyme for organic chemists during the past decade. About two thirds of the total research in the field of biotransformations has been performed using hydrolytic enzymes of this type [82]. The reversal of the reaction, giving rise to ester or amide

synthesis, has been particularly well investigated using enzymes in solvent systems of low water activity.

2.1.4.1.1. Mechanistic aspects

The mechanism of ester-hydrolysing enzymes is very similar to that describing chemical hydrolysis by base. A nucleophilic group from the active site of the enzyme attacks the carbonyl group of the substrate ester. This nucleophilic chemical operator can be either the hydroxyl group of a serine, a carboxy group of an aspartic acid or a thiol-functionality of a cysteine [83].

The mechanism that has been elucidated in detail is that of the serine hydrolases (Scheme 25) [84]. Two additional groups (Aspartine and Histidine) located together with the serine residue (which is the actual reacting chemical operator in the active site) form the so called catalytic triad [85]. The special



Scheme 25. The serine hydrolase mechanism

arrangement of these three groups affects a decrease of the pK-value of the serine hydroxy group thus enabling it to perform a nucleophilic attack on the carbonyl group of the substrate R_1-CO-OR_2 (Step I). Thus the acyl moiety of the substrate is covalently linked onto the enzyme, forming the 'acyl-enzyme intermediate' by liberating the leaving group (R_2-OH). Then a nucleophile (Nu), usually water can attack the acyl-enzyme intermediate, regenerating the enzyme an releasing a carboxylic acid R_1-CO-OH (Step II).

When the enzyme is operating in an environment of low water concentrations, any other nucleophile can compete with the water for the acyl-enzyme intermediate thus leading to a number of synthetically useful transformations:

- attack of another alcohol R_4-OH leads to another ester R_1CO-OR_4. This is an interesterification reaction, called enzymatic acyl transfer [86],
- an incoming amine R_3-NH_2 results in the formation of an amide R_1CO-NHR_3, yielding an enzymatic aminolysis of esters [87],
- peracids of type R_1CO-OOH are formed when hydrogen peroxide is acting as the nucleophile [88].

2.1.5. Enzymes in nonaqueous media

Historically, enzymatic catalysis has been carried out primarily in aqueous systems. However, water is a poor solvent for nearly all reactions in preparative organic chemistry. Attempts to place enzymes in systems other than aqueous media date back to the beginning of last century [89]. In the earlier attempts, water-miscible organic solvents (e.g., ethanol or acetone) were added to aqueous solutions of enzymes. As long as a high water content was available, enzymes retained the catalytic activity, although much less so than in water.

The next step was the use of biphasic mixtures in which an aqueous solution of enzyme is emulsified in a water-immiscible solvent (e.g., isooctane or heptane). Substrates are added to the system where they diffuse to the aqueous phase, undergo enzymatic conversion, and the products diffuse back to the organic phase. To

facilitate mass transfer, the size of water droplets may be reduced to result in microemulsions. To stabilize these microemulsions, surfactants may be added to form reverse micelles [90].

A more recent development was to employ nearly nonaqueous solvents as media for enzymatic reactions [91]. Such solvents containing traces of water have been successful in keeping the enzyme activity at high levels. This approach emphasized by Klibanov has stimulated tremendous research efforts in the direction of achieving various kinds of synthetic reactions with high efficiency enzymatically.

A further important step [92] was to use enzymes (both soluble and immobilized) in anhydrous organic solvents. Enzymatic reactions in nonaqueous solvents offer new possibilities for the biotechnological production of many useful chemicals using reactions that are not feasible in aqueous media. The use of enzymes in nonaqueous media has found applications in organic synthesis [91a], chiral synthesis or resolution [41], modification of fats and oils [93], synthesis of sugar-based polymers [94], and gas phase biocatalysis [95]. Hydrolytic enzymes can be employed to usefully carry out synthetic reactions if the equilibrium position of the reaction is shifted sufficiently to give a high product yield [96]. At present, there is considerable interest in the use of enzymes as catalysts in organic synthesis [97]. Among the reactions that are studied are hydrolysis, esterification, and transesterification catalyzed by hydrolytic enzymes such as lipases, esterases, and proteinases.

Lipases have diverse functions in the degradation of food and fat, and are shown to synthesize aliphatic [98], aromatic [99], and other esters [100] in nonaqueous and biphasic systems. They have also qualified as valuable drugs against digestive disorders and diseases of the pancreas, and find applications in biotechnology (mainly as detergent additives) and as catalysts for the manufacture of specialty oleochemicals and for organic synthesis. Lipases, when employed to catalyze esterification and transesterification reactions in organic solvents, have shown pH memory [101], increased enzyme activity and stability at elevated temperatures [102], regiospecificity and stereoselectivity, and may be affected by water activity [103]. Most importantly, lipases do not require cofactors for activity. The advantages mentioned earlier enable their use in the synthesis of certain

specialty chemicals and pharmaceutical intermediates. The use of lipases in esterification reactions to produce industrially important products such as emulsifiers, surfactants, wax esters, chiral molecules, biopolymers, modified fats and oils, structured lipids, and flavor esters is very attractive. Although these reactions can also be carried out using inorganic metal-derived catalysts, the interest in using enzymes as biotechnological vectors for performing various reactions in both macro- and microaqueous systems has picked-up tremendously during the last decade. In fact, about one-third of all biotransformations reported till-date have been performed with lipases [104]. On an average, at least one paper dealing with biocatalysis in organic solvents is published every day.

Among the diversity of reactions that lipases can catalyze in non-aqueous media, acyl-transfer reaction will be further explored for the scope of our studies.

2.1.5.1. Acyl-Transfer

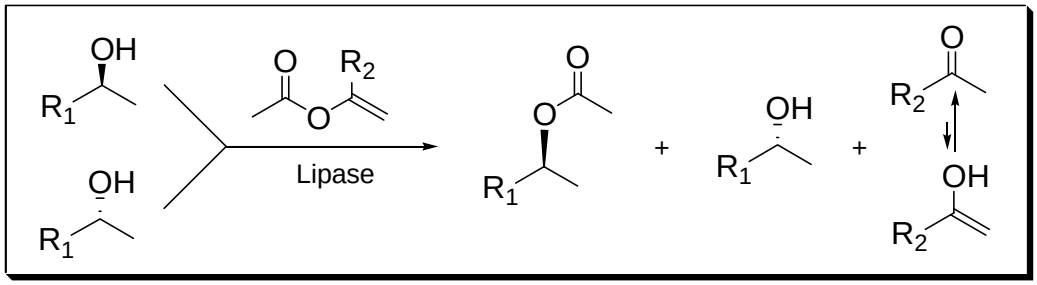
In contrast to hydrolytic reactions, where the nucleophile (water) is always in excess, the concentration of the foreign nucleophile in acyl transfer reactions (usually another alcohol or ester) is always limited. As a result, trans and interestrification reactions involving normal esters are generally reversible in contrast to the irreversible nature of a hydrolytic reaction. This leads to a slow reation rate and can cause a severe depletion of the selectivity of the reaction.

In order to avoid the undesired depletion of the optical purity of the remaining substrate during an enzymatic resolution under reversible reaction conditions, two tricks can be applied to shift the equilibrium of the reaction:

- use of an excess of acyl donor; this may be expensive and not always compatible to retain high enzyme activity,
- a better solution however, is the use of special acyl donors which ensure a more or less irreversible type of reaction.

Irreversible transesterification reagents such as oxime esters may also drive the equilibrium in the desired direction (i.e., ester formation) [105]. The most widely

accepted choice is the use of enol esters (vinyl or isopropenyl ester) and the unstable enols formed during hydrolysis tautomerizes to result in a carbonyl compound, and thus becoming unavailable for the reverse reaction (Scheme 26) [106].



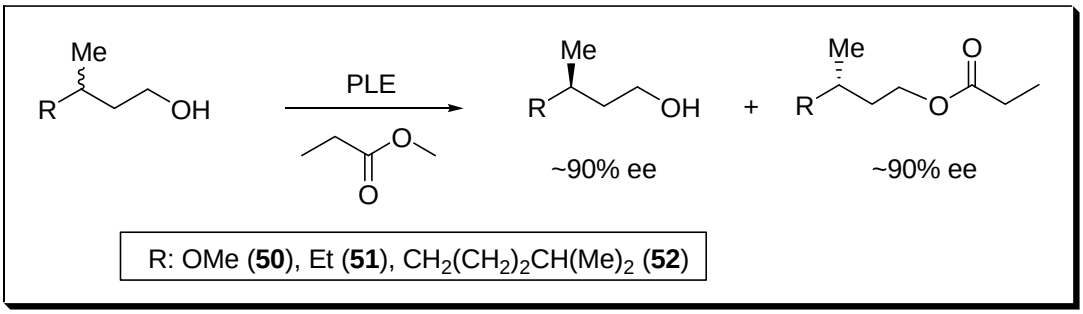
Scheme 26. Irreversible acylation of alcohols with enol esters

2.1.6. Kinetic resolution of substrates having remote stereogenic centers

Lipases are able to catalyze asymmetric hydrolysis [107] and esterification [37a, 101a, 102a, 108] in a wide range of substrates. However, in most cases, the substrates undergoing the enzymatic reaction have the chiral/prochiral center only one or two bonds away from the reacting carbonyl or alcohol group. Very limited examples have been reported in which the chiral/prochiral center is three or more bonds away from the reacting carbonyl/alcohol center [109].

In one of these examples, Cambou and Klibanov [109b] used pig liver esterase (PLE) to esterify alcohols having three bonds between the reacting alcohol and the stereogenic center with ee's generally above 90% (Scheme 27). In their novel approach, they used porous supports (such as Sepharose and Chromosorb) whose pores were initially filled with an aqueous solution of the enzyme. The substrates diffused into the aqueous phase and undergo the enzymatic conversion. Then the products diffused back into the organic phase. The fraction of water in such a biphasic system can be made extremely low that transesterification will be greatly favored over hydrolysis. When alcohol (±)-**50** was subjected to enzymatic esterification under these conditions, optically active (+)-**50** and (–)-3-methoxy-1-

butyl propionate (**53**) were isolated. The former was reported to be totally unreactive in the esterase catalyzed reaction with methyl propionate.

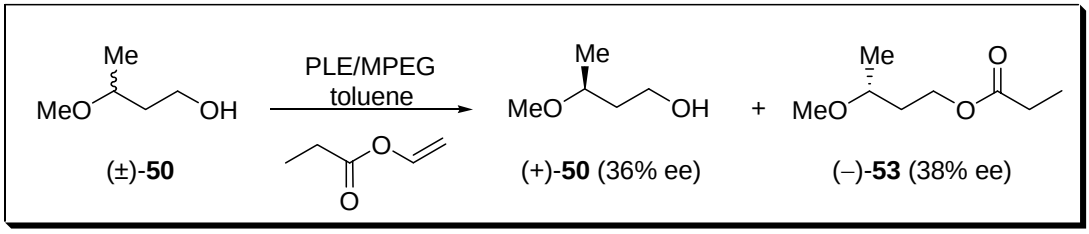


Scheme 27. Esterification of primary alcohols with remote stereogenic centers

Using the same approach, authors reported that only (*S*)-isomers of **51** and **52** can act as nucleophiles in the transesterification reaction shown in Scheme 27. It is quite remarkable that the enzyme recognizes configuration of the chiral carbon which is two methylene groups away from the alcohol's reactive hydroxyl.

Later, Klibanov et al. revealed that the main drawbacks of the approach were tediousness and poor reproducibility of entrapment of enzymes in porous supports and relatively low operational stability of the enzyme [110]. Even minor variations in the water content of the system was reported to have a dramatic effect on the rate and stereospecificity of the enzymatic transesterifications.

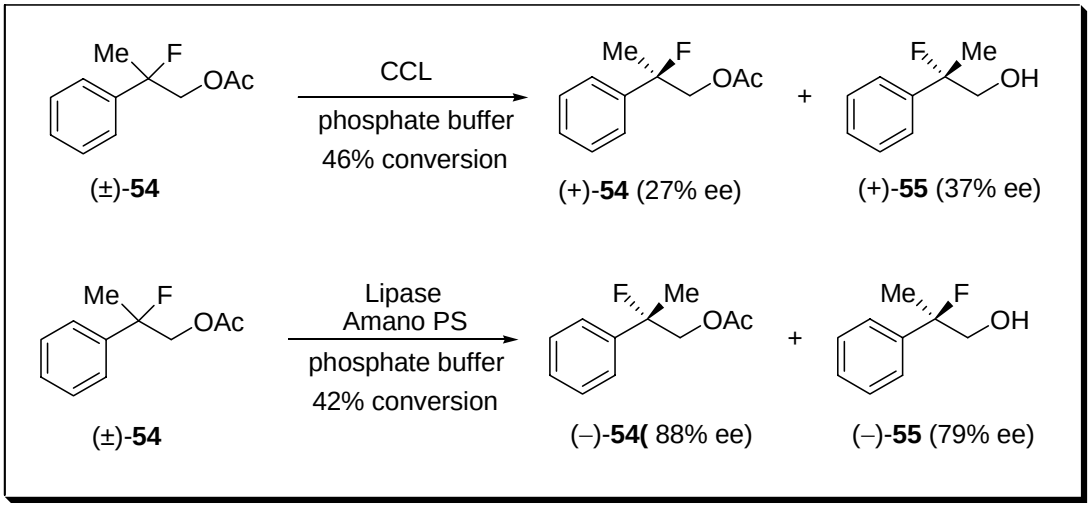
In order to overcome these problems, Ruppert and Gais colyophilized pig liver esterase with methoxypolyethylene glycol (MPEG) to obtain a catalyst (PLE/ MPEG), which showed an enhanced activity in organic solvents but ee's did not exceed 38% for the resolution of alcohol (±)-**50** (Scheme 28) [111].



Scheme 28. PLE/MPEG catalyzed acylation of alcohol (±)-**50**

Goj et al. studied the kinetic resolutions of (±)-1-acetoxy-2-fluoro-2-phenylalkanes by enzymatic hydrolysis and of (±)-1-hydroxy-2-fluoro-2-phenylalkanes by lipase-catalyzed acylation [112]. In this study, the reactive center was two bonds away from the tertiary stereogenic center. Hydrolysis of ester (±)-**54** using CCL gave alcohol (+)-**54** in 37% ee and ester (+)-**55** in 27% ee with 46% conversion (Scheme 29).

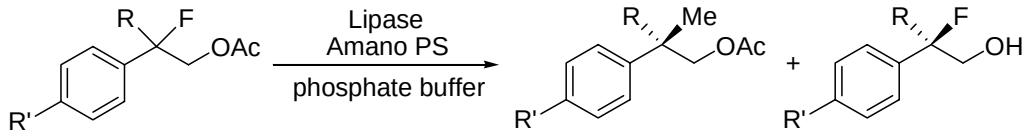
When lipase Amano PS was used as the enzyme in the hydrolysis of the same substrate, an improved selectivity (79% ee for the alcohol and 88% ee for the ester with 42% conversion) was obtained with an opposite specific rotation relative to the CCL catalyzed hydrolysis (Scheme 29).



Scheme 29. CCL and lipase Amano PS catalyzed hydrolysis of ester (±)-**54**

Applying the same reaction conditions to the homologous esters (±)-**56a-d**, good ee values were obtained (Table 9, entries 1, 2, 3). Authors claimed that elongation of the alkyl side chain improves chiral recognition. Moreover, they assumed that the flexible alkyl side chains possess the structural features for good induced fit. However, para-substitution of the phenyl ring by an isobutyl group was shown to decrease the ee-values dramatically (Table 9, entry 4).

Table 9. Kinetic resolution of ester (±)-**56a-d** with lipase Amano PS

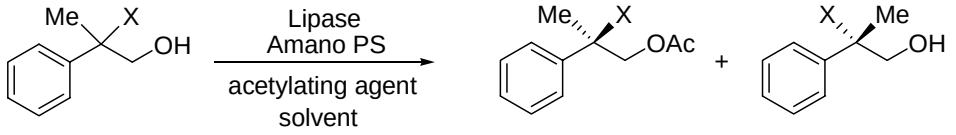


(±)-**56a-d** (–)-**56a-d** (–)-**57a-d**

Entry	R	R´	Time (h)	Conversion (%)	product	Yield (%)	ee (%)
1	C_2H_5	H	4.5	48	(–)-**56a**	27	>98
					(–)-**57a**	35	91
2	*n*-C_3H_7	H	8.0	43	(–)-**56b**	34	92
					(–)-**57b**	29	86
3	*n*-C_4H_9	H	8.5	46	(–)-**56c**	33	96
					(–)-**57c**	31	88
4	CH_3	*i*-C_4H_9	2.5	45	(–)-**56d**	32	39
					(–)-**57d**	27	38

Furthermore, Goj et al. studied enzymatic esterification of the alcohols (±)-**55** and (±)-**58** using both pure and immobilized [113] lipase Amano PS with vinylacetate or acetic anhydride as acylating agents in cyclohexane, toluene or benzene (Table 10). Utilization of immobilized lipase Amano PS and vinylacetate in toluene was reported to give the highest ee for the ester (+)-**54** (95% ee) at 46% conversion (Table 10, entry 3).

Table 10. Esterification of alcohols (±)-**55** and (±)-**58** with lipase Amano PS



X= F (±)-**55** — *R*-(+)-**54** — *S*-(+)-**55**

X= H (±)-**58** — *S*-(–)-**59** — *R*-(+)-**58**

Ent.	subst.	enzyme Amano PS	acylating agent	solvent	time (h)	conv. (%)	product	yield (%)	ee (%)
1	(±)-**55**	pure	vinylacetate	cyclohexane	18	63	*R*-(+)-**54**	33	75
							S-(+)-**55**	12	78
2	(±)-**55**	immob.	vinylacetate	cyclohexane	12	47	*R*-(+)-**54**	24	84
							S-(+)-**55**	26	60
3	(±)-**55**	immob.	vinylacetate	toluene	18	46	*R*-(+)-**54**	26	95
							S-(+)-**55**	31	70
4	(±)-**55**	immob.	Ac_2O	toluene	3	37	*R*-(+)-**54**	12	80
							S-(+)-**55**	38	46
5	(±)-**58**	pure	vinylacetate	cyclohexane	17	53	*S*-(-)-**59**	30	48
							R-(+)-**58**	20	70
6	(±)-**58**	immob.	Ac_2O	benzene	1	60	*S*-(-)-**59**	50	8
							R-(+)-**58**	34	28

Authors assumed the (*R*)-enantiopreference for the lipase Amano PS for esterification of chiral vicinal monofluorinated primary alcohols. This was in good agreement with an emprical rule, proposed by Kazlauskas et al. [114] that predicts (*S*)-selectivity of lipase Amano PS in enzymatic esterifications of nonfluorinated primary alcohols with a tertiary stereocenter. The formal substitution of H with F changes the priority of the substituents determining the (*R*)- or (*S*)- description according to the CIP system.

CHAPTER II

RESULTS AND DISCUSSION

2.2.1. Aim of the work

As mentioned before (part 1.1.3, page 13) benzanilide derivatives are biologically important compounds and 3-chloro-3-arylpropanols are the key intermediates in the synthesis of these compounds. After the development of a new methodology for the one-pot synthesis of racemic 3-chloro-3-arylpropanols, we thought that the synthesis of enantiopure 3-chloro-3-arylpropanols will be a challenge and gateway for the synthesis of the corresponding enantiopure benzanilide derivatives. The advantages of enantiomerically pure drugs over the racemic counterparts were explained in details (Part 2.1.1, pages 40-42). Similarly, one might expect enantiopure benzanilide derivatives to display better biological activities along with reduced side effects.

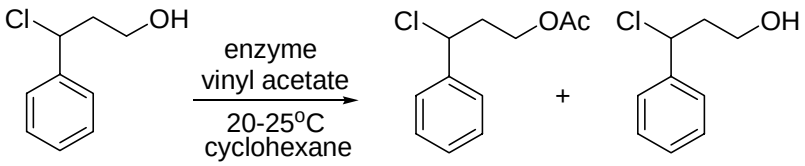
The promising results obtained in the literature [109b, 112] triggered us to study the enzymatic resolution of (±)-1-hydroxy-3-chloro-3-arylpropanes and (±)-1-acetoxy-3-chloro-3-arylpropanes [115].

2.2.2. Optimization studies on the biotransformations

Over the course of our studies on the biotransformations of (±)-3-chloro-3-phenylpropanol **(27**), screening reactions were first examined with CCL, PPL, PLE,

HLE, Amano PS, and Amano PSC-II (Table 11). Among the enzymes studied, CCL mediated esterification of substrate (±)-27 gave the highest enantioselectivity by giving (+)-alcohol **27** in 45% yield with 25% ee and (–)-ester **29** in 35% yield with 28% ee (Table 11, entry 1). HLE mediated esterification of the same substrate, on the other hand, gave the products in slightly lower yields and ee's with an opposite configuration (Table 11, entry 4). We also planned to study the enzymatic hydrolysis of (±)-1-acetoxy-3-chloro-3-phenylpropane **29**, but (±)-**29** was found to decompose almost completely in both phosphate and tris buffer conditions in the absence of enzymes. This was presumably due to the side reactions of the benzylic chloride group, which might undergo elimination and displacement reactions under aqueous conditions. Due to these uncontrolled side reactions, we continued our studies with enantioselective esterification in the organic medium.

Table 11. Enzymatic acylation studies of (±)-**27** with various enzymes



(±)-**27** (–)-**29** (+)-**27**

Entry	Enzyme[a]	Time	Conversion (%)[b]	Alcohol **27** yield (%)[c]	Alcohol **27** ee (%)[d]	Ester **29** yield (%)[c]	Ester **29** ee (%)[d]
1	CCL	3 h	44	47	25	33	28
2	PPL	1 d	43	35	4	20	6
3	PLE	1 d	30	34	2	16	5
4	HLE	1 d	52	31	-21	29	-20
5	Amano PS	2 h	37	57	5	33	8
6	Amano PSC-II	1 d	64	20	4	30	1

[a]175.0 mg of enzyme /mmol (±)-**27** and same equivalent of vinyl acetate as that of (±)-**27** was used in reactions.
[b]Determined by the ^{1}H-NMR analysis.
[c]Yields are isolated yields.
[d]Determined by HPLC using Chiralcel ODH column.

After finding out that CCL is the best enzyme for the acylation of racemic **27**, we searched for the effect of amount of enzyme and acetylating reagent as well as the solvent. The results of these studies are summarized in Table 12. As can be seen in Table 2, stoichiometric amounts of CCL and 0.6 eq of vinyl acetate with respect to the substrate **27** gave the best results. Among the solvents tested, cyclohexane and toluene gave good results. Although the yields are very similar, the reaction in toluene requires longer time and the ee of alcohol **27** is lower compared to cyclohexane (Table 12, entries 4 and 5). When *tert*-butyl vinyl ether was used as the solvent, comparable ee's relative to cyclohexane were obtained but the chemical yields were too low (Table 12, entry 6). In the case of tetrahydrofurane the reaction was sluggish. Six days were required for 49% conversion even with the addition of totally five fold more vinyl acetate. Although the reaction in THF proceded slowly, there was no improvement in the enantioselectivity (Table 12, entry 7). We have also tried the reaction at 14°C in cyclohexane which slowed down the reaction, 30% conversion obtained after 22 h, but had no effect on improving the enantioselectivity.

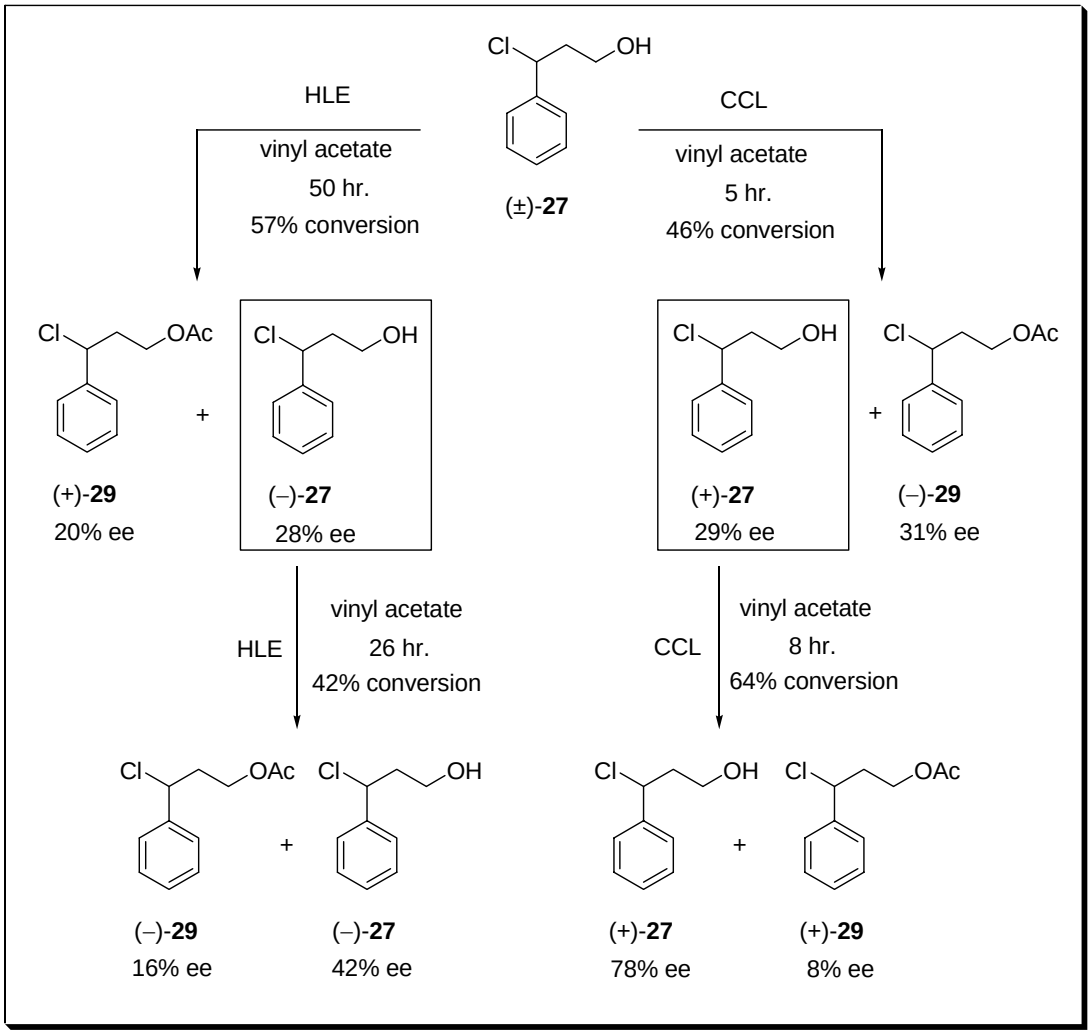
Table 12. Effect of the amount of CCL and vinyl acetate on enzymatic acylation

Ent.	Amount of CCL[a]	Eq. of vinyl acetate	Solvent	Time	Conv. (%)[b]	Alcohol **27**		Ester **29**	
						yield (%)[c]	ee (%)[b]	yield (%)[c]	ee (%)[b]
1	17.5	38	-	3 d	49	29	21	31	22
2	175.0	38	-	35 min	53	44	24	46	21
3	"	1.2	cyclohexane	165 min	61	27	35	54	23
4	"	0.6	cyclohexane	225 min	44	45	29	33	33
5	"	0.6	toluene	455 min	50	41	24	39	24
6	"	0.6	TBVE	22 h	46	5	27	6	30
7[e]	"	0.6	THF	6 d	49	28	14	22	26

[a]In mg CCL/mmol (±)-**27**
[b]Determined by the ^{1}H-NMR analysis.
[c]Yields (%) are given as isolated yields.
[d]Enantiomeric excess values were determined by HPLC using Chiralcel ODH column.
[e]Total of five fold vinyl acetate was added in portions during six days.

2.2.3. Multiple resolution strategy

Due to relatively lower enantioselectivities of the enzymatic acylation of (±)-**27,** we tried multiple resolution strategy. When the substrate (±)-**27** was subjected to CCL mediated double enzymatic resolution, alcohol (+)-**27** was obtained in 78% ee (Scheme 30). However, the same strategy with HLE gave (**–**)-**27** in 42% ee.



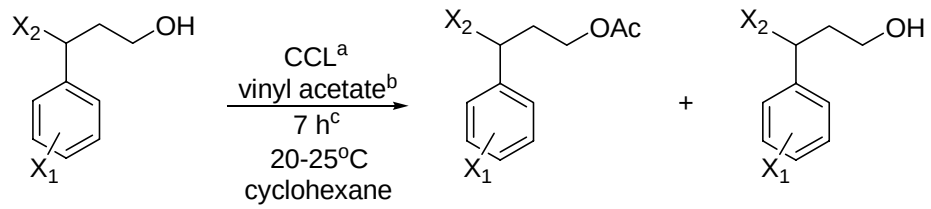
Scheme 30. Double kinetic resolution with enzymes CCL and HLE

In the second kinetic resolution step, for both CCL and HLE, reversal of enantioselectivity for the acetylated product **29** relative to the first kinetic resolution step was observed. This result can be attributed to the increased rate of acyl transfer to less reactive enantiomeric form of alcohol due to increase in its concentration relative to the first kinetic resolution step. We have also tried a third acylation run with CCL (not shown in Scheme 30) which diminished the ee of alcohol (+)-**27** from 78% to 68% after 30% conversion. Ester (+)-29 was isolated in 42% ee in the third run.

2.2.4. Enzymatic acylation of (±)-3-halo-3-aryl-propanols with CCL

In the study of Goj et al. they observed that isobutyl group on the aromatic ring of ester (±)-**56** decreased the ee value dramatically in enzymatic hydrolysis (Table 9, entry 4, page 60). This result clearly demonstrates the importance of substituents on the aromatic ring in chiral recognition of such compounds. In the light of this observation, we thought that it would be interesting to find out the substituent effect on the enzymatic acylation of our substrates. For this reason various racemic 3-chloro-3-arylpropanols, and 3-bromo-3-phenylpropanol (**60**) were subjected to single enzymatic acylation by CCL. Results of this study are summarized in Table 13. Enantiomeric excess values for the unreacted alcohols were ranged between 21-43% and that of acetylated products were ranged between 24-38%. Based on these results, it can be concluded that different substituents at different position of the aromatic ring have no significant effect on the lipase CCL selectivity. Slight increase in ee's were observed in case of bromide at ortho position (Table 13, entry 6). This result might be explained with the better fit into the enzyme's pocket due to much fixed conformation of substrate **49m** caused by the restricted rotation of the aromatic ring because of proximal halides in the molecule. In order to see whether a different halide at the benzylic position has any effect on the selectivity we synthesized compound **60** by adapting our methodology (for details, see: Part 2.4.2, page 70). When this substrate was subjected to CCL mediated acylation under the same reaction conditions as previous substrates, similar results were obtained in terms of yield and enantioselectivity (Table 13, entry 7). This

Table 13. Enzymatic acylation of (±)-3-halo-3-aryl-propanols with CCL



(±)-alcohol (–)-ester (+)-alcohol

Ent.	Subst.	X_1, X_2	Conv. (%)[d]	Alcohol			Ester			
				Yield (%)[e]	Ee (%)[f]	E_s[g]	Product	Yield (%)[e]	Ee (%)[f]	E_p[g]
1	**27**	H, Cl	44	45	29	2.8	**29**	33	33	2.5
2	**49a**	*p*-F, Cl	40	60	21	2.3	**61**	36	32	2.4
3	**49b**	*p*-Cl, Cl	39	51	21	2.4	**62**	29	37	2.7
4	**49c**	*p*-Br, Cl	38	33	23	2.7	**63**	17	30	2.2
5	**49l**	*o*-F, Cl	52	45	27	2.0	**64**	44	24	2.1
6	**49m**	*o*-Br, Cl	52	24	43	3.4	**65**	28	36	3.0
7	**60**	H, Br	38	27	21[h]	2.5	**66**	19	38[h]	2.8

[a]175.0 mg CCL/mmol (±)-alcohol was used in reactions.
[b]0.6 equivalent vinyl acetate was used relative to substrate.
[c]Except substrate **27**, for which reaction time was 225 min.
[d]Determined by the ^{1}H-NMR analysis.
[e]Yields (%) are given as isolated yields.
[f]Enantiomeric excess values were determined by HPLC using Chiralcel ODH column.
[g]Calculated using Sih and coworkers method [116].
[h]Enantiomeric excess values were determined by HPLC using Chiralcel OD column.

experiment showed that bromide having a larger size than chloride had no effect on the enzyme selectivity. Interestingly, enantiomerically enriched substrate **60** racemized completely within few days upon standing in solution (n-hexane:2-propanol, 10:1, v/v) at +4°C. This may be attributed to the better leaving ability of bromide than chloride. Under the same conditions, racemization of substrate **66** (acetylated form of **60**) was not observed. This may indicate that hydroxyl group is playing a role in the racemization process.

CHAPTER III

CONCLUSION

We have studied enzymatic resolution of (±)-3-halo-3-arylpropanols for the first time. Among the enzymes used under the esterification conditions, CCL showed the best enantioselectivity. Even though these substrates have a chiral center three bonds away from the reaction site, they showed enantioselectivities up to 43 % for the alcohols and 38% for the esters. We have also showed that enantiopurity of the alcohol **27** can be raised to 78% by double enzymatic acylation. It was also found that CCL and HLE show opposite stereoselectivity in the products. Substituents on the aromatic ring or bromide instead of chloride at the benzylic position were found to have no drastic influence on the enantioselectivity of the enzyme.

CHAPTER IV

EXPERIMENTAL

2.4.1. General Consideration

The ^{1}H and ^{13}C NMR spectra were recorded in $CCl_4/CDCl_3$ (2:3, v/v) solvent system on a Bruker Spectrospin Avance DPX 400 spectrometer. ^{1}H NMR spectra were reported in parts per million using TMS as an internal standard (TMS at 0.00 ppm). ^{13}C NMR spectra were reported in parts per million using solvent as an internal standard ($CDCl_3$ at 76.9 ppm). Infrared spectra were recorded on a Bruker IFS 66V/S series FT-IR spectrometer using $CHCl_3$ as the solvent. GC-MS spectra were obtained with a Thermo-Quest (TSP) TraceGC-2000 Series instrument equipped with a Phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 lm), MS: Thermo Quest Finnigan multi Mass (EI, 70 eV). High resolution mass spectra (HRMS) were recorded on a Kratos MS25RFA mass spectrometer using electron impact (EI) method. Optical rotations were measured in $CHCl_3$ solutions in a 1 dm cell using a Rudolph Autopol III polarimeter at 25 °C. HPLC measurements were performed with Dionex System instrument. Separations were carried out on Chiralcel OD-H analytical column (250 · 4.60 mm) with hexane/2-propyl alcohol as eluent. Flash column chromatography was performed on silica gel (60 mesh, Merck). Analytical thin layer chromatography (TLC) was performed on precoated silica gel (60 F254, Merck). Commercially available reagents and solvents were used, unless otherwise stated, without further

purification. CCL (lipase, Type VII, from Candida rugosa), PPL (Lipase Type II, from Porcine pancreas), Amano PS, Amano PSC-II and HLE (Horse Liver Esterase-acetone powder) were purchased from Aldrich. PLE (Pig Liver Esterase) was purchased from Sigma as powder.

2.4.2. Synthesis of (±)-3-bromo-3-phenylpropan-1-ol (60). Methylene diacetate (MDA) was isolated from MDA stock solution as follows: MDA stock solution (preparation explained in Part 1.4.2, page 31) was concentrated under reduced pressure and then n-hexane was added to the residue. Solid particles (NBu_4Cl) were separated by filtration and the liquid part was concentrated under reduced pressure to give MDA.

MDA (155 mg, 1.17 mmol), NBu_4Br (754 mg, 2.34 mmol), and styrene (**15a**) (81 mg, 0.78 mmol) were added to a 10 mL flask under an argon atmosphere. The flask was then cooled to −78 °C and BF_3 gas was slowly bubbled through the solution for 20 min to give a cloudy solution. At this point, the BF_3 flow was stopped and the reaction flask was allowed to warm up to rt and left stirring overnight at this temperature. In the morning, water was added (10 mL) to the reaction flask, followed by extraction with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. Final purification was done by flash column chromatography on silica gel using 5:1 hexanes/ethyl acetate as the eluent to give product **60** (138 mg, 82% yield) as a colorless oil. R_f = 0.61 (EtOAc–hexanes, 2:1); IR: 3444, 2926, 1456, 1253, 1093, 1005, 889, 806, 721, 626, 537 cm^{-1}; ^1H NMR: δ 1.60 (br s, 1H, OH), 2.30 (m, 1H, CH_2, H_2), 2.46 (m, 1H, CH_2, $H_{2'}$), 3.72 (m, 1H, CH_2, H_1), 3.81 (m, 1H, CH_2, $H_{1'}$), 5.17 (dd, J = 5.7, 9.1 Hz, 1H, CH, H_3), 7.26 (d, J = 7.3 Hz, 1H, CH, Ph), 7.31 (t, *J* = 7.3 Hz, 2H, CH, Ph), 7.38 (d, *J* = 7.3 Hz, 2H, CH, Ph). ^{13}C NMR: δ 42.31, 51.65, 60.49, 127.33, 128.33, 128.66, 141.88.

2.4.3. General procedure for enzymatic acylation of 3-halo-3-arylpropanols. To a solution of racemic alcohol (0.171 mmol) and vinyl acetate (9.5 μL, 0.103 mmol) in cyclohexane (1 mL), 30 mg CCL (or lipase) was added and the reaction mixture was shaken at 20-25 °C (TLC monitoring). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The products; ester and alcohol

were separated and purified by flash column chromatography (EtOAc–hexanes, 1:5).

2.4.3.1a. (–)-3-Chloro-3-phenylpropyl acetate (29). 12.0 mg (33% yield); pale yellow oil; $[\alpha]_D^{25}$ = –19.9 (*c* 1.2, $CHCl_3$) for 33% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane–2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**29**: 8.6 min; t_R for (+)-**29**: 11.5 min; IR: 2921, 1738, 1490, 1457, 1363, 1248, 1199, 1033, 785, 543 cm^{-1}; ^{1}H NMR: δ 2.02 (s, 3H, $COCH_3$), 2.29-2.43 (m, 2H,CH_2, H_2), 4.12 (m, 1H, CH_2, H_1), 4.21 (m, 1H, CH_2, $H_{1'}$), 4.95 (dd, *J* = 5.9, 8.6 Hz, 1H, CH, H_3), 7.29-7.37 (m, 5H, CH, Ph); ^{13}C NMR: δ 20.61, 38.78, 59.58, 61.31, 126.78, 128.34, 128.59, 140.89, 170.10 (C=O); MS (EI) *m/z* (%) : 153 (55) [M^+ – OAc], 151 (100), 124 (90), 118 (100), 117 (100), 103 (100), 91 (90), 77 (90), 63 (30), 51 (55), 43 (100).

2.4.3.1b. (+)-3-Chloro-3-phenylpropan-1-ol (**27**)**.** 13.1 mg (45% yield); colorless oil; $[\alpha]_D^{25}$ = +12.1 (*c* 1.3, $CHCl_3$) for 29% ee; $[\alpha]_D^{25}$ = +32.3 (*c* 1.0, $CHCl_3$) for 78% ee after double resolution; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (+)-**27**: 34.3 min; t_R for (–)-**27**: 48.1 min. All spectroscopic data agree with those given for racemic **27** (Part 1.4.3.5, page 33).

2.4.3.2a. (–)-3-Chloro-3-(4-fluorophenyl)propyl acetate (**61**). 14.2 mg (36% yield); colorless oil; $[\alpha]_D^{25}$ = –16.3 (*c* 1.4, $CHCl_3$) for 32% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**61**: 8.3 min; t_R for (+)-**61**: 9.3 min; IR: 2925, 1742, 1607, 1505, 1464, 1369, 1250, 1195, 1157, 1029, 724, 548 cm^{-1}; ^{1}H NMR: δ 2.03 (s, 3H, $COCH_3$), 2.26-2.43 (m, 2H,CH_2, H_2), 4.12 (m, 1H, CH_2, H_1), 4.21 (m, 1H, CH_2, $H_{1'}$), 4.94 (dd, *J* = 5.9, 8.7 Hz, 1H, CH, H_3), 7.03 (m, 2H, CH, Ar), 7.35 (m, 2H, CH, Ar); ^{13}C NMR: δ 20.71, 38.99, 58.84, 61.30, 115.68 (d, *J* = 21.6 Hz), 128.64 (d, *J* = 7.7 Hz), 136.90, 162.55 (d, *J* = 247.1 Hz) 170.18 (C=O); MS (EI) *m/z* (%) : 171 (40) [M^+ – OAc], 169 (100), 142 (90), 135 (90), 134 (100), 121 (90), 108 (40), 101 (40), 95 (35), 75 (30), 43 (100).

2.4.3.2b. (+)-3-Chloro-3-(4-fluorophenyl)propan-1-ol (49a). 19.4 mg (60% yield); colorless oil; $[\alpha]_D^{25}$ = +15.4 (*c* 1.9, $CHCl_3$) for 21% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**49a**: 23.9 min; (+)-**49a**: 26.7 min. All spectroscopic data agree with those given for racemic **49a** (Part 1.4.3.6, page 33).

2.4.3.3a. (–)-3-Chloro-3-(4-chlorophenyl)propyl acetate (62). 12.3 mg (29% yield); colorless oil; $[\alpha]_D^{25}$ = –19.7 (*c* 1.2, $CHCl_3$) for 37% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**62**: 9.6 min; t_R for (+)-**62**: 10.8 min; IR: 2925, 1741, 1492, 1458, 1363, 1257, 1201, 1095, 1008, 806, 721, 620, 530 cm^{-1}; ^{1}H NMR: δ 2.03 (s, 3H, $COCH_3$), 2.24-2.41 (m, 2H,CH_2, H_2), 4.11 (m, 1H, CH_2, H_1), 4.21 (m, 1H, CH_2, $H_{1'}$), 4.92 (dd, *J* = 5.9, 8.7 Hz, 1H, CH, H_3), 7.31 (br s, 4H, CH, Ar); ^{13}C NMR: δ 20.71, 38.86, 58.75, 61.22, 128.24, 128.94, 134.43, 139.49, 170.16 (C=O); MS (EI) *m/z* (%): 171 (40) [M^+ – OAc], 186 (15), 185 (20), 158 (10), 150 (45), 137 (10), 115 (30), 103 (20), 89 (10), 77 (15), 75 (10), 43 (100).

2.4.3.3b. (+)-3-Chloro-3-(4-chlorophenyl)propan-1-ol (49b). 17.9 mg (51% yield); colorless oil; $[\alpha]_D^{25}$ = +10.0 (*c* 1.8) for 21% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (+)-**49b**: t_R for 28.7 min; t_R for (–)-**49b**: 30.1 min. All spectroscopic data agree with those given for racemic **49b** (Part 1.4.3.7, page 33).

2.4.3.4a. (–)-3-Chloro-3-(4-bromorophenyl)propyl acetate (63). 8.48 mg (17% yield)**;** light yellow wax; $[\alpha]_D^{25}$ = –11.2 (*c* 0.85, $CHCl_3$) for 30% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**63**: 10.0 min; t_R for (+)-**63**: 11.8 min; IR: 2932, 1738, 1589, 1490, 1363, 1242, 1028, 816, 716, 632, 532 cm^{-1}; ^{1}H NMR: δ 2.02 (s, 3H, $COCH_3$), 2.24-2.40 (m, 2H,CH_2, H-2), 4.11 (m, 1H, CH_2, H-1), 4.20 (m, 1H, CH_2, H-1), 4.90 (dd, *J* = 6.0, 8.5 Hz, 1H, CH, H-3), 7.24 (d, *J* = 8.3 Hz, 2H, CH, Ar), 7.47 (d, *J* = 8.3 Hz, 2H, CH, Ar); ^{13}C NMR: δ 20.71, 38.81, 58.78, 61.21, 122.51,

128.56, 134.43, 131.91,140.01, 170.18 (C=O); MS (EI) *m/z* (%) : 231 (30) [M^+ – OAc], 230 (40), 228 (30), 203 (10), 194 (10), 181 (10), 150 (40), 116 (80), 115 (100), 103 (35), 89 (30), 77 (40), 63 (20), 51 (20), 43 (100).

2.4.3.4b. (+)-3-Chloro-3-(4-bromorophenyl)propan-1-ol (49c). 14.1 mg (33% yield); colorless oil; $[\alpha]_D^{25}$ = +7.6 (*c* 1.4, $CHCl_3$) for 23% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**49c**: 33.1 min; t_R for (+)-**49c**: 34.5 min. All spectroscopic data agree with those given for racemic **49c** (Part 1.4.3.8, page 34).

2.4.3.5a. (–)-3-Chloro-3-(2-fluorophenyl)propyl acetate (64). 17.4 mg (44% yield); colorless oil; $[\alpha]_D^{25}$ = –18.0 (*c* 1.7, $CHCl_3$) for 24% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**64**: 7.7 min; t_R for (+)-**64**: 9.2 min; IR: 2937, 1726, 1620, 1587, 1495, 1368, 1253, 1185, 1157, 1032, 818, 721, 626, 536 cm^{-1}; ^{1}H NMR: δ 2.02 (s, 3H, $COCH_3$), 2.29-2.45 (m, 2H,CH_2, H_2), 4.19 (m, 2H, CH_2, H_1), 5.31 (dd, *J* = 5.9, 8.6 Hz, 1H, CH, H_3), 7.03 (t , *J* = 7.6 Hz, 1H, CH, Ar), 7.15 (t , *J* = 7.6 Hz, 1H, CH, Ar), 7.25-7.30 (m, 1H, CH, Ar) 7.47 (td , *J* = 7.6, 1.4 Hz, 1H, CH, Ar); ^{13}C NMR: δ 20.68, 37.89, 52.22 (d, *J* = 3.7 Hz), 61.20, 115.67 (d, *J* = 22.0), 124.51 (d, *J* = 2.9 Hz), 128.07 (d, *J* = 12.7 Hz), 128.45 (d, *J* = 3.0 Hz), 129.96 (d, *J* = 8.9 Hz), 159.75 (d, *J* = 250.0), 170.25 (C=O); MS (EI) *m/z* (%) : 171 (60) [M^+ – OAc], 169 (100), 142 (80), 135 (75), 134 (100), 121 (90), 108 (40), 101 (50), 96 (40), 95 (35), 75 (30), 43 (100).

2.4.3.5b. (+)-3-Chloro-3-(2-fluorophenyl)propan-1-ol (49l). 14.5 mg (45% yield); colorless oil; $[\alpha]_D^{25}$ = +6.7 (*c* 1.4, $CHCl_3$) for 27% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (+)-**49l**: 24.5 min; t_R for (–)-**49l**: 29.8 min. All spectroscopic data agree with those given for racemic **49l** (Part 1.4.3.16, page 36).

2.4.3.6a. (–)-3-Chloro-3-(2-bromorophenyl)propyl acetate (65). 14.0 mg (28%

yield); colorless oil; $[\alpha]_D^{25}$ = –11.8 (*c* 1.4, $CHCl_3$) for 36% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**65**: 9.0 min; t_R for (+)-**65**: 9.6 min; IR: 2925, 1732, 1471, 1364, 1251, 1036, 809, 702, 623, 543 cm^{-1}; ^1H NMR: δ 2.03 (s, 3H, $COCH_3$), 2.23-2.32 (m, 2H,CH_2, H_2), 4.22 (m, 2H, CH_2, H_1), 5.48 (dd, *J* = 5.2, 8.9 Hz, 1H, CH, H_3), 7.12 (td, *J* = 7.9, 1.4 Hz, 1H, CH, Ar), 7.34 (t, *J* = 7.9 Hz, 1H, CH, Ar), 7.53 (d, *J* = 7.9 Hz, 1H, CH, Ar), 7.59 (dd, *J* = 7.9, 1.4 Hz, 1H, CH, Ar); ^{13}C NMR: δ 20.75, 38.27, 57.99, 61.13, 122.72, 128.01, 128.66, 129.64, 132.92, 140.13, 170.23 (C=O); MS (EI) *m/z* (%) : 231 (40) [M^+ – OAc], 230 (80), 228 (60), 203 (20), 196 (30), 194 (30), 181 (10), 150 (20), 116 (90), 115 (100), 103 (80), 102 (80), 89 (40), 77 (70), 63 (20), 51 (30), 43 (100).

2.4.3.6b. (+)-3-Chloro-3-(2-bromorophenyl)propan-1-ol (49m). 10.2 mg (24% yield); colorless oil; $[\alpha]_D^{25}$ = +4.4 (*c* 1.00, $CHCl_3$) for 43% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (+)-**49m**: 41.3 min; t_R for (–)-**49m**: 48.3 min. All spectroscopic data agree with those given for racemic **49m** (Part 1.4.3.17, page 36).

2.4.3.7a. (–)-3-Bromo-3-phenylpropyl acetate (66). 8.4 mg (19% yield); colorless oil; $[\alpha]_D^{25}$ = –28.7 (*c* 0.84) for 38% ee; HPLC: Chiralcell OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, t_R for (–)-**66**: 10.1 min; t_R for (+)-**66**: 16.5 min; IR: 2926, 1743, 1451, 1363, 1258, 1196, 1088, 1027, 801, 727, 626, 531 cm^{-1}; ^1H NMR: δ 2.07 (s, 3H, $COCH_3$), 2.46 (m, 1H,CH_2, H_2), 2.59 (m, 1H,CH_2, $H_{2'}$), 4.19 (m, 2H, CH_2, H_1), 5.06 (t, *J* = 7.5 Hz, 1H, CH, H_3), 7.28-7.42 (m, 5H, CH, Ph); ^{13}C NMR: δ 20.70, 38.89, 50.62, 62.23, 127.23, 128.50, 128.74, 141.37, 170.08 (C=O); HRMS (EI): M^+–Br, found 177.0916, $C_{11}H_{13}O_2$ requires 177.0916.

2.4.3.7b. (+)-3-Bromo-3-phenylpropan-1-ol (60). 9.9 mg (27% yield); yellow wax; $[\alpha]_D^{25}$ = +8.8 (*c* 0.99) for 21% ee; HPLC: Chiralcell OD column, UV detection at 230 nm, eluent: hexane/2-propanol = 95:5 flow 1.0 Ml min^{-1}, 20 °C, t_R for (+)-**60**:

15.8 min; t_R for (–)-**60**: 21.2 min. All spectroscopic data agree with those given for racemic **60** (Part 2.4.2, page 70). Complete racemization of compound **60** within few days upon standing in n-hexane:2-propanol solution (10:1, v/v) at + 4 °C was observed.

PART III

APPLICATION OF FERROCENYL SUBSTITUTED AZIRIDINYLMETHANOLS (FAM) AS CHIRAL LIGANDS IN ENANTIOSELECTIVE CONJUGATE ADDITION OF DIETHYLZINC TO ENONES

CHAPTER I

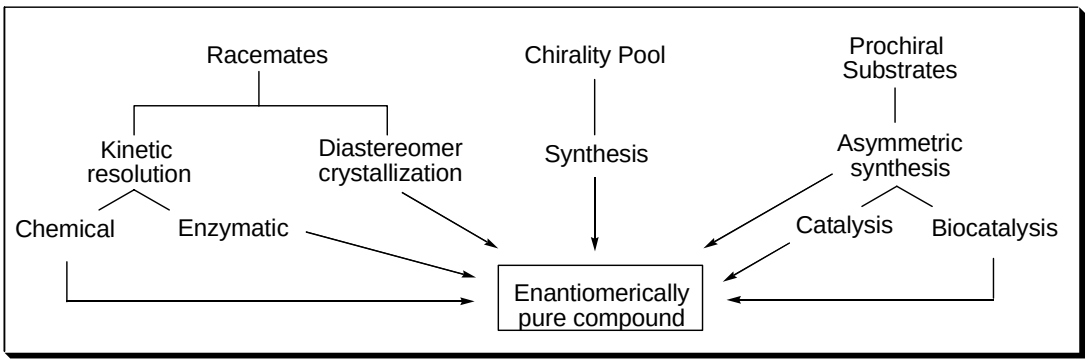
INTRODUCTION

3.1.1. Routes to enantiomerically pure compounds

The synthesis of optically active compounds is a subject that has fascinated chemists for more than a century. Since the pioneering work of Pasteur, van't Hoff and Le Bell [117] the area of stereochemistry began to evolve into the major field of research nowadays [118]. In recent years, the synthesis and isolation of enantiomerically pure compounds has gained new impetus, due to the realization that a chiral compound interacts with enantiomers in different ways as a result of a diastereomeric relationship [119]. A well known example of the dramatic difference in activity of enantiomers of thalidomide was mentioned before (Part 2.1.1, page 40).

The search for efficient syntheses of enantiomerically pure compounds is going on, largely stimulated by the requirements for new bioactive materials. In general there are three main routes to obtain pure enantiomers (Scheme 31):

- resolution of a racemic mixture
- synthesis with compounds from the chirality pool
- asymmetric synthesis



Scheme 31. Routes to enantiomerically pure compounds

Although significant advances in other routes to obtain enantiomerically pure compounds have been reported, the classical resolution of racemates by diastereomeric crystallisation still constitutes the most important method in industry [120]. However, the maximum theoretical yield of one enantiomer is 50%, unless the unwanted enantiomer can be recycled. In a kinetic resolution the two enantiomers of a racemic mixture react at different rates with a chiral entity, preferably used in catalytic amounts [121]. Excellent kinetic resolutions employing enzymes [36, 122] were reported and this subject was discussed in details before (Part 2.1, pages 40-61).

Naturally occurring chiral compounds (referred to as the “chirality pool”) can be used as starting materials for enantiomerically pure compounds or may be employed as enantioselective agents (catalysts or ligands) in organic synthesis [32]. The lack of availability of both enantiomers of most natural compounds often is a limiting factor. Therefore many desired enantiomers have to be obtained by synthesis. In the early days, synthesis to enantiomerically pure compounds from prochiral precursors was considered possible only by using biochemical methods. Although powerful, those methods using enzymes, cell cultures, or (living) microorganisms are in most cases substrate specific.

Organic synthesis, on the other hand, has revealed a variety of versatile stereoselective reactions that complement biological processes [124]. Asymmetric synthesis is “a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The

stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate" [125]. Optically active compounds can be obtained using either a stoichiometric or a catalytic amount of chiral auxiliary. All stereoselective syntheses are based on the principle that the products are formed via diastereomeric transition states that differ in Gibbs free energy of activation. If this energy difference is sufficient (≥ 3 kcal/mol) one enantiomer will be formed, preferentially.

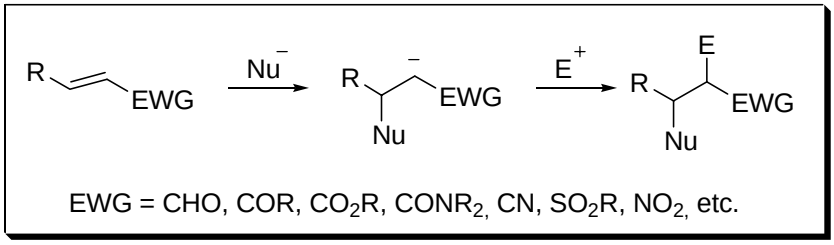
Asymmetric catalysis is the most promising and attractive form of stereoselective synthesis, since a small amount of enantiomerically pure material produces large quantities of enantiomerically enriched, or in the ideal situation, enantiomerically pure material. A wide variety of highly successful reactions with enantiomeric excesses (ee's) > 95% have been reported [126]. In most cases chiral transition metal complexes, often prepared in situ, are employed as the catalysts [127]. The reactions involved are generally asymmetric reduction, asymmetric oxidation and asymmetric carbon-carbon bond formation. Especially the last category has a tremendous synthetic utility and in the next section selected examples of successful catalytic asymmetric carbon-carbon bond formations will be highlighted. It should also be mentioned to present the importance and impact of asymmetric catalysis that in 2001, William S. Knowles, Ryoji Noyori, and K. Barry Sharpless were awarded the Nobel Prize in Chemistry for their contribution to the development of catalytic asymmetric synthesis.

3.1.2. Catalytic asymmetric carbon-carbon bond formations

Among the broad range of asymmetric carbon-carbon bond formation reactions; cyclopropanations [128], Diels-Alder reactions [129], allylic alkylations [130], 1,2- [131] and 1,4-addition of carbon nucleophies have attracted considerable interest and remarkable progress have been made in these reactions. In the next section 1,4- addition of carbon nucleophiles will be further explored for the scope of our studies.

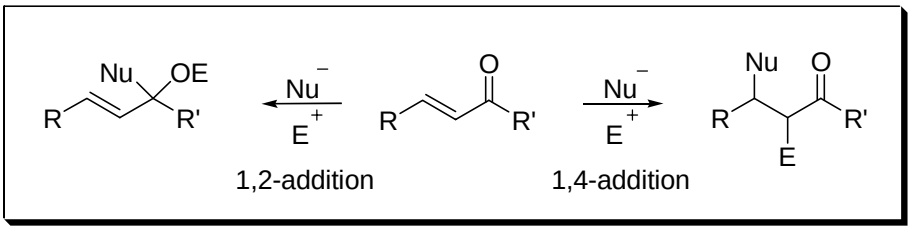
3.1.2.1. Catalytic asymmetric (1,4-) conjugate addition

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are among the most widely used methods for carbon-carbon bond formation in organic synthesis [132]. It is therefore not surprising that major efforts have been devoted to achieve asymmetric conjugate addition despite the often complicated nature of many 1,4-addition reactions [133]. Addition of the nucleophile to the β-position of an electron deficient alkene results in a stabilized carbanion. After protonation of the carbanion ($E^+ = H^+$) a β-substituted product is formed. Quenching of the stabilized carbanion with electrophiles provides α,β-disubstituted products with two newly created stereocenters (Scheme 32).



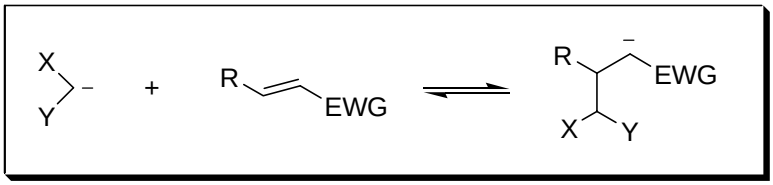
Scheme 32. Conjugate addition of carbon nucleophiles

As carbon nucleophiles, one can use a variety of organometallic reagents, "classical" Michael donors, carbanions derived from nitro alkanes, nitriles or dithianes, and enolates (and derivatives). Common substrates for conjugate addition reactions are α,β-unsaturated aldehydes, ketones, esters, amides, nitriles, sulfones, and nitro compounds. Typical problems associated with conjugate addition are regioselectivity and reversibility [134]. Competition between 1,2- and 1,4-addition to enones is governed by several parameters, but in general the use of soft carbon nucleophiles results in high selectivities for conjugate addition products (Scheme 33).



Scheme 33. 1,2- and 1,4-additions to enones

In Michael additions, which are often executed under thermodynamically controlled conditions employing stabilized carbanions, reversibility is not an uncommon feature (Scheme 34). The stereochemistry might be affected by such reversible processes, whereas the presence of a labile hydrogen at the α-carbon of the product (with respect to EWG) could be another complicating factor which may lead to racemisation or epimerization.



Scheme 34. Reversibility of Michael additions

The enormous utility of conjugate addition reactions in synthesis is partly a result of the large variety of donor and acceptor compounds that can be employed. Another important aspect is the high diastereoselectivity often observed. These features have been a strong driving force for the development of enantioselective conjugate additions. The use of natural product-based Michael type acceptors has been extremely successful, commonly leading to Michael products with high and predictable stereoselectivities [133, 134, 135a].

Stoichiometric asymmetric conjugate additions have been developed along two lines:

1. Using a chiral auxiliary-based Michael acceptor i.e. chiral α,β-unsaturated ester, amide, sulfoxide [133a, 135] or
2. By reaction of a chiral reagent with a prochiral electrondeficient alkene [133a,b].

In the latter case two strategies have been used mainly, namely chiral auxiliary based donors, such as enamines and enol derivatives, and chiral ligand modified organometallic reagents, in particular chiral cuprates, Grignard reagents, organozincates, and organolithium reagents. Natural product-based and synthetic organic ligands and auxiliaries have been successfully employed, but high diastereoselectivities were reached also with organometallic auxiliaries [136]. Asymmetric conjugate addition reactions using stoichiometric chiral auxiliary-based Michael donors and acceptors and chiral organometallic reagents have been extensively covered by reviews [132-135].

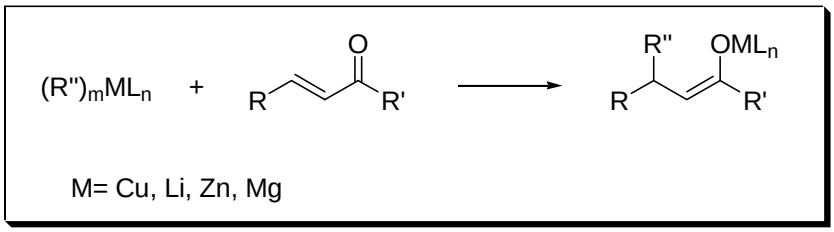
It should be emphasised that several chiral auxiliary-based acyclic and cyclic α,β-unsaturated substrates, enolates, and enamines are now available which give ee's exceeding 95% in a variety of reactions. Furthermore, there are a number of organocopper reagents with chiral non-transferable ligands as well as organocuprates modified by additional chiral ligands known today, that provide 1,4- addition products with ee's > 95%.

However, only for a limited number of prochiral acyclic and cyclic enones, high enantioselectivities are reached [133c]. Major improvements are necessary, in particular with respect to the scope of chiral reagent-based methods. This becomes evident when one considers applications in practical synthesis of enantiomerically pure compounds employing conjugate addition as a key step. Even more challenging is the development of general methodology for enantioselective carbon-carbon bond formation using chiral non-racemic catalysts in combination with readily available organometallic reagents and Michael donors. A literature survey of this area will be given in next section with the emphasis on enantioselective conjugate addition catalysed by chiral transition metal complexes.

3.1.2.2. Asymmetric metal-mediated 1,4-addition

In order to achieve a rational synthesis of new chiral catalysts for enantioselective conjugate addition it is important to consider several factors that might govern the 1,4-addition step. Among these are:

1. the nature of organometallic reagent $(R'')_mM$ (Scheme 35),
2. the ligands L_n associated with it,
3. the fact that most of these reagents are aggregated in solution (solvent dependent),
4. the notion that stereoselectivity (as well as regioselectivity) can be affected by additional ligands, coordinating solvents and salts.



Scheme 35. Metal mediated 1,4-addition

Furthermore, activation of the electron deficient alkene by Lewis acid or cation complexation to the carbonyl moiety is often proposed as a means to tether the reagent, catalyst, and enone in order to increase stereoselectivity and enhance reactivity towards weaker nucleophiles. The coordinating metal can either be from the organometallic reagent, the catalyst, or additional metal ions (i.e. salts). The proposed intermediate **I** in the highly enantioselective (90% ee) conjugate addition of the (1*R*,2*S*)-ephedrine based mixed cuprate, reported by Corey and co-workers [137], nicely illustrates additional lithium ion coordination between the oxygen of the enone and the cuprate ligand (Figure 8).

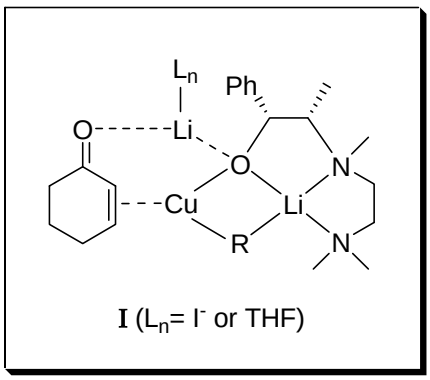
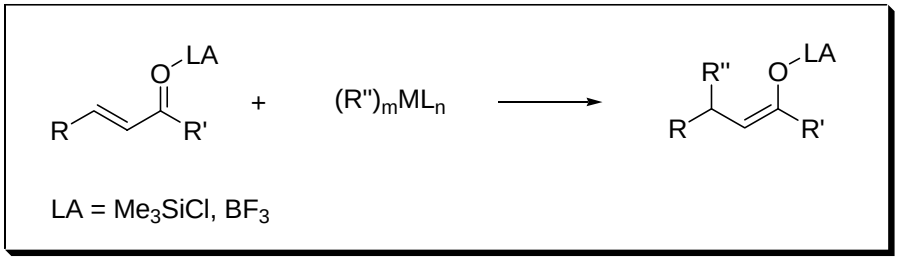


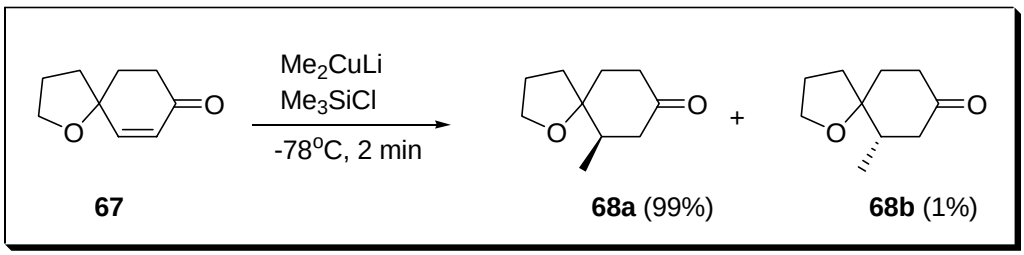
Figure 8. Proposed intermediate **I** in the conjugate addition of a mixed cuprate

The use of Lewis acids, in particular Me_3SiCl or BF_3, often results in a dramatic increase of reaction rates in 1,4-addition reactions of cuprates, presumably by enone activation (Scheme 36) [138].



Scheme 36. Lewis acid activated conjugate additions

Increased stereoselectivity, for instance, almost exclusive formation of **68a** by Me_2CuLi addition to **67** in the presence of Me_3SiCl (Scheme 37), and the formation [139] of enol derivatives, which can subsequently be used in electrophilic additions (tandem 1,4 -addition-enolate processes), are additional important advantages.



Scheme 37. Me_2CuLi addition in the presence of Me_3SiCl

Lewis acid catalysis has been extremely successful in 1,4-additions of enol silyl ethers (and tin-analogues) [140] . The role of the Lewis acid can be an activation of the enone and the silyl-enolate leading, via a cyclic transition state **II** (Figure 9), to Michael adducts with high stereoselectivities.

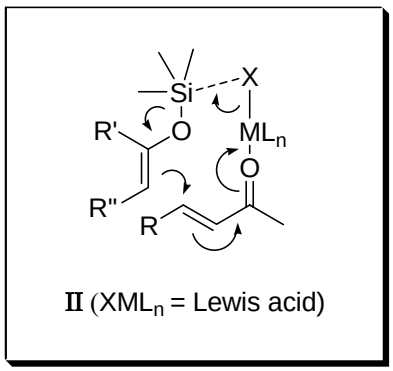


Figure 9. Cyclic transition state **II**

The use of chiral metal catalysts for enantioselective carbon-carbon bond formation using Grignard [141], organolithium [142], and dialkylzinc reagents have been reported. Last one will be explored in details in next section for the scope of our studies.

3.1.2.3. Conjugate addition of dialkylzinc reagents catalysed by chiral metal complexes

Enantioselective carbon-carbon bond formation by 1,2-addition of organozinc reagents to aldehydes has become one of the most successful and active area's of asymmetric synthesis in recent years [143]. Although dialkylzinc reagents react extremely sluggish with carbonyl compounds, effective catalysis has been achieved by several ligands and transition metal complexes. The catalytic effect was explained by changes in geometry and bond energy of the zinc reagents [144]. For example, dimethylzinc has a linear structure and is not reactive towards aldehydes or ketones (Figure 10). Upon coordination of triazine a tetrahedral configuration at the zinc atom and an elongated zinc-carbon bond is found, resulting in enhanced reactivity of the dialkylzinc reagent.

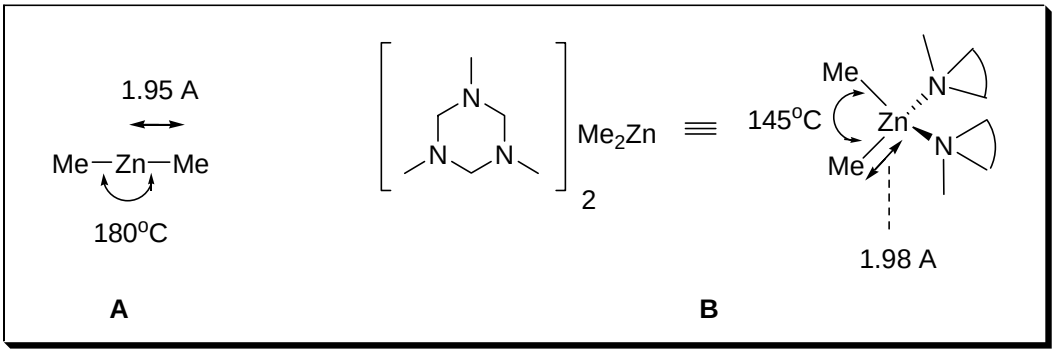


Figure 10. Structures of dimethylzinc (**A**) and its adduct with 1,3,5-trimethylhexahydro-1,3,5-triazine (**B**)

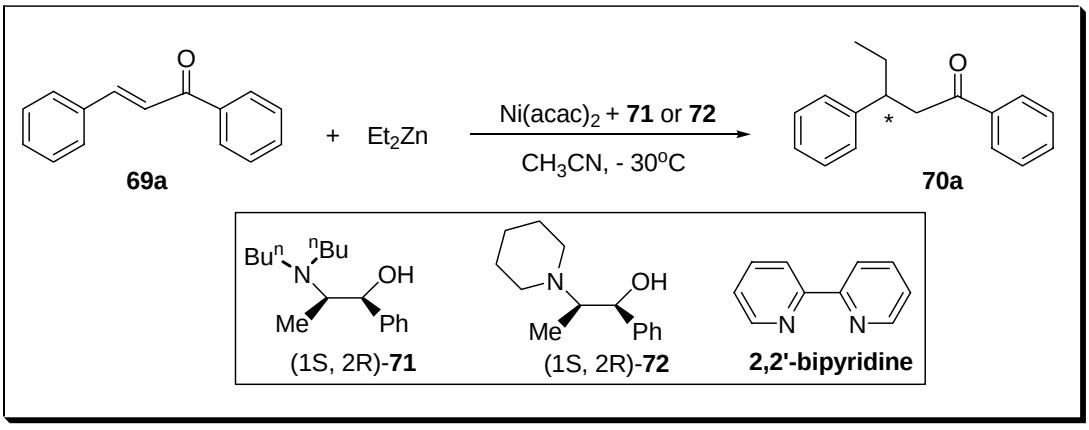
Dialkylzinc addition to enones requires a metal catalyst such as Cu(I) or Ni(II) generally. It is clearly demonstrated in the literature that copper salts work much efficiently with trivalent phosphorus ligands (phosphanes, phosphites, phosphoramidites, phosphonites) [145]. Excellent enantioselectivities in dialkylzinc additions to enones using phosphorus ligans were achieved. Lower catalyst loadings and wider substrate toleration are other advantages of using copper salts with

phosphorus ligands. Ni(II) is the metal salt of choice with amino alcohol type ligands. Nickel catalysed reaction is also efficient for chalcone-type substrates and will be further explored for the scope of our studies.

3.1.2.3.1. Conjugate addition of dialkylzinc to acyclic enones catalysed by chiral nickel-amino alcohol complexes

Several catalytic 1,4-additions of diethylzinc to acyclic enones employing chiral nickel complexes have been developed.

Based on work of Luche and Greene [146], an enantioselective modification of the nickel catalysed alkyl transfer from diethylzinc to chalcone (**69a**) was found by Soai and co-workers [147]. The chiral catalyst, prepared in situ from $NiBr_2$ and (1*S*,2*R*)-N,N-di-*n*-butylnorephedrine (**71**), afforded (*R*)-1,3-diphenylpentan-1-one (**70a**) in 32% yield with 48% enantiomeric excess. Higher yields (> 70%) were achieved with $Ni(acac)_2$ instead of $NiBr_2$, although large amounts [148] of chiral ligand are required (Scheme 38). A remarkable achiral ligand effect was observed . Preparation of the chiral catalyst from 6 mol% of $Ni(acac)_2$, 14 mol% of chiral ligand **72**, and 7 mol% of 2,2'-bipyridine in acetonitrile was reported to rise enantioselectivity up to 90% [149] (Scheme 38).



Scheme 38. Pioneering study of Soai et al. on diethylzinc addition to enones

In an outstanding study, Bolm et al. presented further insight into the important factors which govern activity and stereoselectivity of asymmetric metal-catalyzed conjugate addition reactions. Comparable yields and enantioselectivities were reported with nickel catalysts prepared in situ from C_2-symmetric bipyridine **73** and chiral pyridine **74** [150] (Figure 11). A nice ligand structure-enantioselectivity relation was also demonstrated (Table 14).

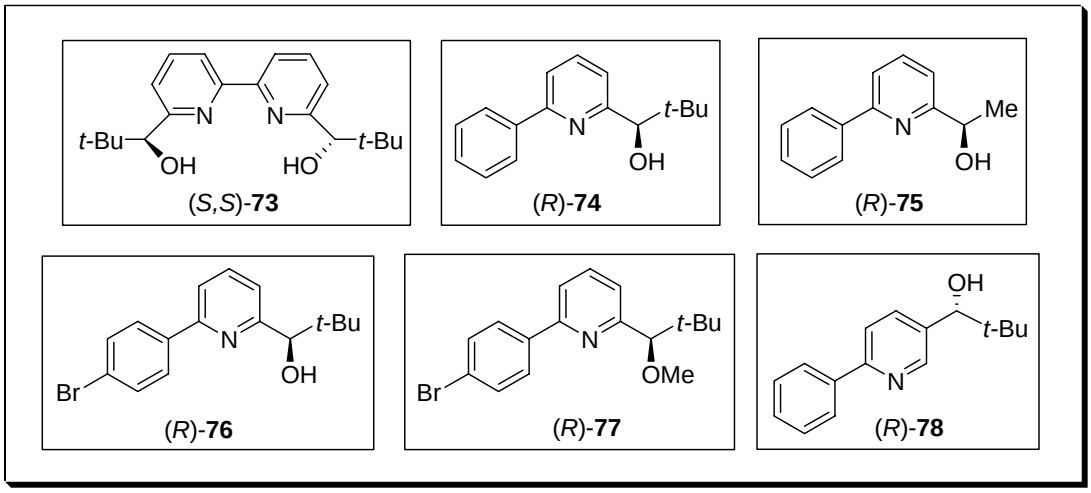
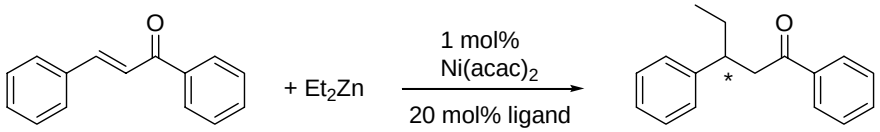


Figure 11. Ligands used in Bolm's study

Table 14. Ligand structure-ee relation in diethylzinc addition to chalcone



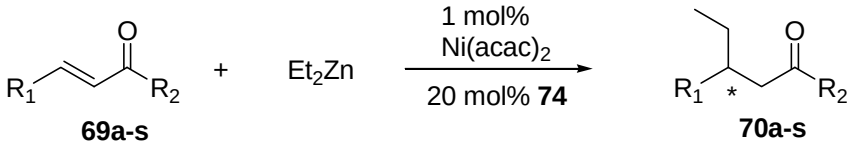
69a **70a**

Entry	Ligand	Yield (%)	ee (%)
1	**73**	75	72
2	**74**	79	82
3	**75**	72	2
4	**76**	75	60
5	**77**	70	0
6	**78**	64	2

The steric bulk of the *tert*-butyl group was found to be essential for high enantioselectivity (Table 14, entries 2 and 3). Methyl ether **77** and 2,5-disubstituted pyridine **78** gave almost racemic product (Table 14, entries 5 and 6), indicating the necessities of direct metal binding at the oxygen atom and of internal chelation with the pyridine nitrogen atom.

In the same study, diethylzinc addition to various enones were performed to demonstrate the effect of substrate variation (Table 15). Chloro and methoxy substituents on aromatic rings of R_1 were tolerated, and ee's of 90 and 80 were achieved, respectively (Table 15, entries 2 and 3). Benzalacetone (**69l**) gave the conjugate addition product **70l** in 76% chemical yield, but ee was reported to be essentially racemic (Table 15, entry 4). Increasing the steric requirements at the carbonyl carbon atom resulted in the reduction of the oxo group and expected product of conjugate addition was not obtained (Table 15, entry 5).

Table 15. Substrate dependency of asymmetric diethylzinc addition



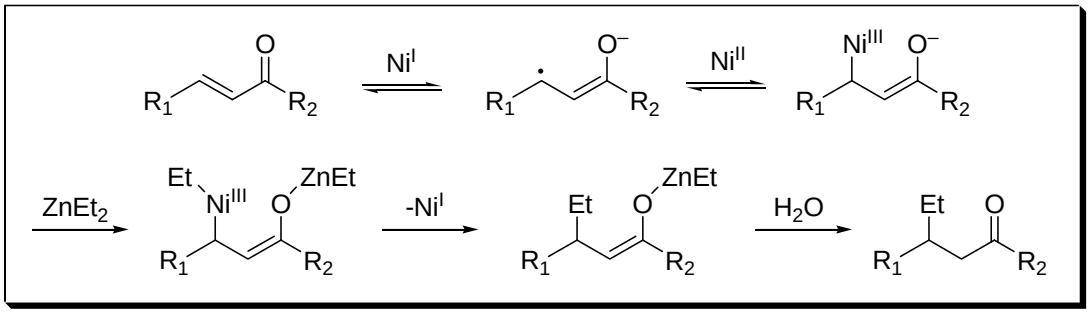
69a-s **70a-s**

Entry	R_1	R_2	Substrate	Yield (%)	ee (%)
1	C_6H_5	C_6H_5	**69a**	79	82
2	*p*-Cl-C_6H_4	C_6H_5	**69d**	78	90
3	*p*-OMe-C_6H_4	C_6H_5	**69e**	75	80
4	C_6H_5	Me	**69l**	76	2
5	C_6H_5	*t*-Bu	**69o**	0	-
6	*t*-Bu	C_6H_5	**69p**	0	-
7	*p*-NO_2-C_6H_4	C_6H_5	**69r**	0	-
8	C_6H_5	OEt	**69s**	0	-

Similarly diethylzinc addition to the structural isomer **69p** gave a product with reduced double bond, no expected conjugate addition product was observed (Table 15, entry 6). Nitrochalcone **69r** and ethyl cinnamate (**69s**) was reported to give either unidentified product mixtures or else no conjugate addition occurred (Table 15, entries 7 and 8).

In order to obtain a product with high optical purity, an appropriate amount of ligand was required, and the optimized nickel to ligand ratio was reported to be 1: 20. The dependence of the asymmetric induction was explained to indicate an equilibrium between ligand-bound and uncomplexed catalytically active nickel species. The former would produce enantiomerically enriched product, whereas the latter would lead to the formation of racemic β-alkylated ketone in a competitive pathway. The use of aceto- or propionitrile was also found to be essential for catalyst activity and high asymmetric induction. The strong solvent dependence in the conjugate addition reaction seems to indicate the necessity to further stabilize catalytically active (chirality transferring) metal species by coordinated solvent molecules [151].

Bolm proposed a mechanism for enantioselective nickel-catalyzed conjugate addition. According to this mechanism, an electron transfer involving changes in the oxidation state from Ni^{II} to Ni^{I} and Ni^{0} could be proposed. In this scenario, the organozinc reagent is used to reduce $Ni(acac)_2$ to a catalytically active nickel(I) species [152]. Electron transfer from Ni^{I} to the substrate generates a ketyl radical which reacts with the resulting nickel(II) species. Transmetallation followed by reductive elimination gives zinc enolate and regenerates the catalytically active nickel(I) species (Scheme 39). According to this mechanism, the asymmetric induction could be dictated by an enantioselective formation of the nickel(III) intermediate followed by a stereoselective reductive elimination. The proposed electron-transfer mechanism in the nickel-catalyzed conjugate addition might also explain the dependence of the enantiomeric excess of the product on reaction time. The change of oxidation state from Ni^{II} to Ni^{I} and finally to Ni^{0}, generates a number of reactive nickel species of which some are highly enantioselective.



Scheme 39. Proposed mechanism of nickel-catalyzed conjugate addition

After a certain time, most of these selective catalysts are transformed into species which are still catalytically active, but which produce racemic product. As a result the overall optical purity of the product will decrease with time.

Another significant contribution to rational chiral catalyst design was achieved by Feringa et al. [153]. They found that aminoisoborneols *cis-exo*-**81a** and *cis-endo*-**81b** were more enantioselective (Table 16) than their *trans*-counterpart **81c** (Figure 12). *Trans*-aminoisoborneol **81c** gave almost racemic product indicating the necessity of *cis*-configuration of the alcohol and the tertiary amine moities (Table 16, entry 8).

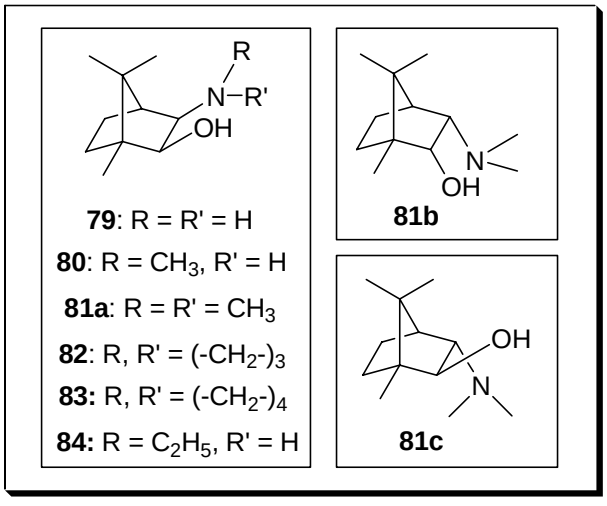
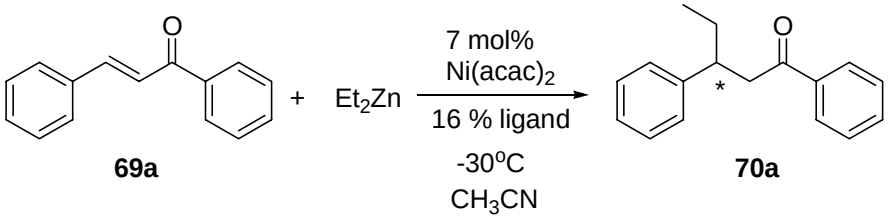


Figure 12. Ligands used in Feringa's study

Table 16. Effect of ligand structure on ee of **70a**



69a **70a**

Entry	Ligand	Yield (%)	ee (%)	Config.
1	**79**	nd	0	-
2	**80**	85	4	*R*
3	**81a**	81	65	*R*
4	**82**	78	33	*R*
5	**83**	nd	35	*R*
6	**84**	84	7	*R*
7	**81b**	82	79	*S*
8	**81c**	82	4	*R*

Another important point that has to be mentioned in Feringa's study was 'asymmetric amplification' phenomena. In order to gain more insight in the nature of the catalytically active species, the relationship between the ee of ligand **81a** and product **70a** was determined. Scalemic **81a** with defined ee was employed in the nickel-catalyzed conjugate addition of diethylzinc to chalcone (**69a**). A 'positive nonlinear' relationship was found. The use of **81a** with low ee resulted in the formation of **70a** with higher ee than expected on the basis of a linear relationship (Table 17).

Nonlinear relationships between ee of chiral auxilaries and products in asymmetric catalysis were described by Kagan and Agami et al. [154]. Extensive investigations of non-linear effects were carried out in the enantioselective alkylation of aldehydes [155].

Table 17. Effect of ee of ligand **81a** on ee of product **70a**

Entry	ee of Ligand **81a**	ee of product **70a**
1	12.5	19
2	25	33
3	37.5	43
4	50	48
5	62.5	53
6	75	56
7	87.5	58
8	100	65

These phenomena have been interpreted in terms of differences in the chemical behavior of diastereomeric dinuclear complexes. In the conjugate addition of diethylzinc to chalcone, Sanchez and co-workers used fully characterized nickel complexes where an acetylacetonate anion has been replaced by one equivalent of *N*-alkylaminocarbonylpyrrolidine [156]. Using this information, Feringa proposed that two equivalents of scalemic aminoisoborneol **81a** replace both acetylacetonate anions from $Ni(acac)_2$ and form diastreomeric mononuclear nickel complex **85** and dinuclear nickel complex **86** (Figure 13).

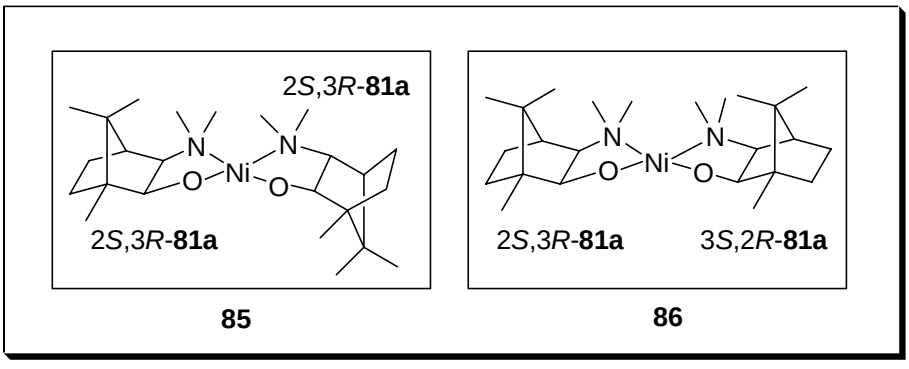
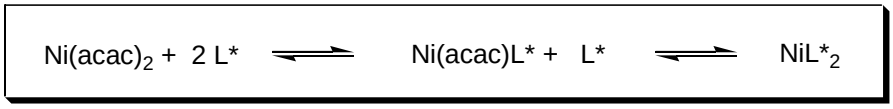


Figure 13. Possible diastereomeric nickel complexes

Predominant reaction of diethylzinc with the less stable optically active complex **85** would lead to the formation of a homochiral catalytically active species. The minor enantiomer of the ligand is trapped in the more stable *meso* complex **86**, and becomes less available for catalyst formation.

In the studies of Soai [147-149], Bolm [150] and Feringa [153], they all observed the importance of ligand to nickel ratio and chiral catalyst concentration. With a low concentration of chiral ligand, the concentration of enantioselective catalyst (NiL_2^*) will be small. The asymmetric induction could well depend on the equilibrium between chiral nickel complexes (NiL_2^*) and catalytically active nickel species ($Ni(acac)_2$, $Ni(acac)L^*$) which will produce racemic material (Scheme 40).



Scheme 40. Equilibrium between catalytically active nickel species

The ability of bispidines to form stable complexes with transition metals and high levels of enantioselectivity induced by spartaine roused Waldmann and his coworkers interest in the synthesis of chiral bispidines (Figure 14) and their investigation as ligands in enantioselective transformations [157].

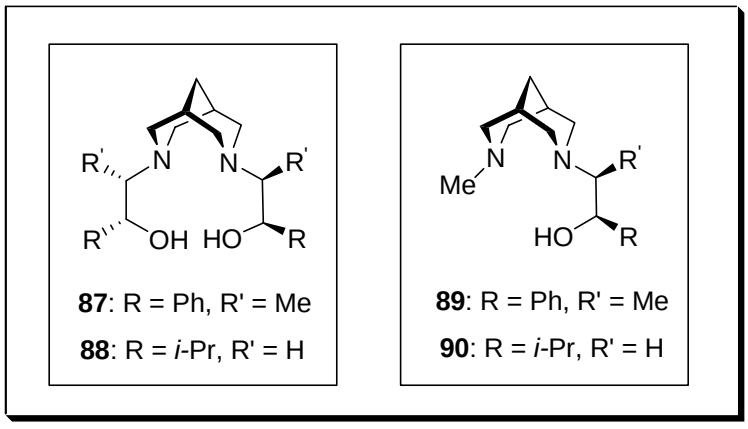
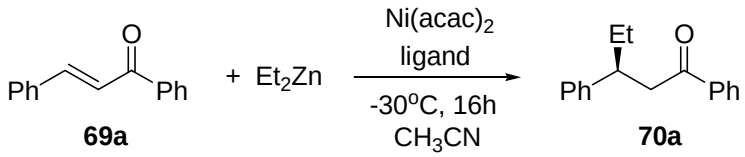


Figure 14. Chiral bispidine ligands used in Waldmann's study

Tridentate ligands **89** and **90** were superior to tetradentate amino alcohols **87** and **88 (**Table 18**)**. Furthermore, ligand **89** was superior to bispidine derivative **90**, with respect to both enantioselectivity and yield. In the presence of ligands **87** or **88**, only racemic product was obtained, indicating that with these bicyclic compounds, no Ni complex that could influence the steric course of the transformation was formed.

Table 18. Conjugate diethylzinc addition to chalcone in the presence of bispidine-derived ligands

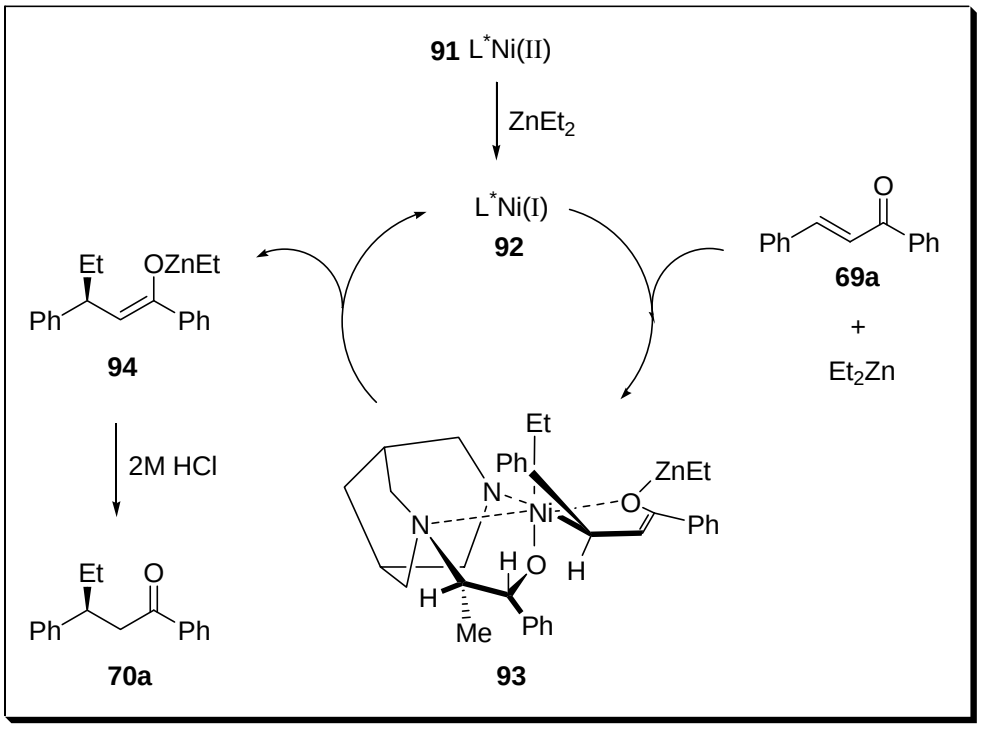


69a **70a**

Entry	Ligand [mol%]	$Ni(acac)_2$ [mol%]	Yield [%]	ee [%]
1	**90** (16)	7	69	53
2	**90** (20)	1	76	70
3	**89** (16)	7	92	79
4	**89** (20)	1	86	85
5	**87** (13)	7	96	0
6	**88** (13)	7	95	0

The reactions of diethylzinc with chalcone in the presence of bispidine Ni complexes delivered predominantly the (*S*) enantiomer of the addition product. This can be rationalized on the basis of a mechanism proposed by Bolm et al. (Scheme 39, page 91). Presumably diethylzinc reacts with the Ni^{II} complex **91** to a catalytically active Ni^{I} species **92**. This complex then undergoes an electron transfer reaction to chalcone and a transmetallation with diethylzinc giving a Ni^{III} enolate complex **93** (Scheme 42). Reductive elimination finally leads to formation of product enolate **94** and regeneration of the Ni^{I} intermediate **92**. The stereoselectivity observed if bispidine **89** is employed as mediator of chirality can be rationalized by the

assumption that **93** is formed as an intermediate in the catalytic cycle (Scheme 41). In complex **93** steric interactions between the substituents of the stereodirecting amino alcohol and the *β*-phenyl group of the enolate are minimized. The involvement of a complex like **93** in the asymmetric transformation would also explain why only racemic product is formed with C_2-symmetric bis(amino alcohols) **87** and **88**. In this case presumably complexes like **93** could not form since direct coordination of the second amino alcohol to the nickel (instead of the enolate) should be preferred.



Scheme 41. Proposed mechanism and of conjugate addition of diethylzinc to chalcone (**69a**) in the presence of **89** as chiral ligand

In a very recent study, Unaleroglu et al. reported synthesis of novel norephedrine-based chiral ligands with multiple stereogenic centers from norephedrine and *N*-substituted pyrrole (Figure 15). These chiral ligands were then tested in conjugate diethylzinc addition to chalcone [158] (Table 19).

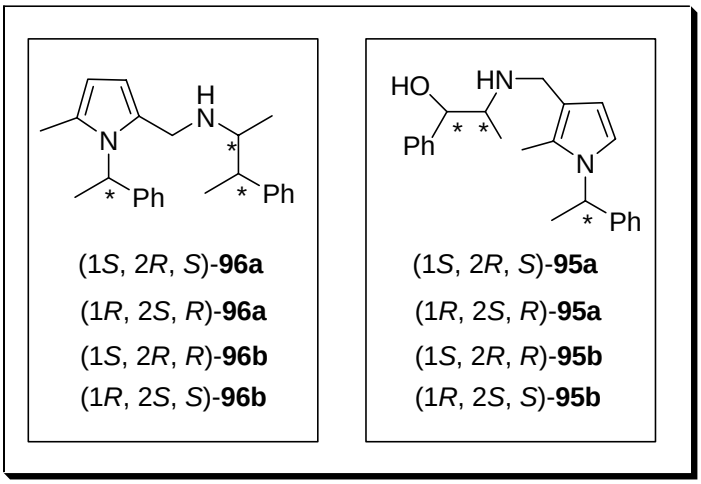
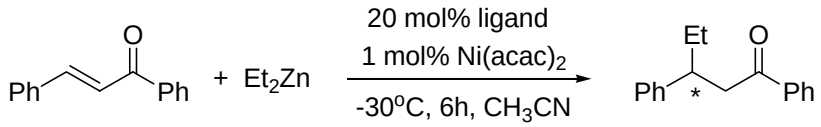


Figure 15. Chiral ligands used in Unaleroglu's study

Table 19. Enantioselective conjugate addition of diethylzinc to chalcone using ligands **95a**,**b** and **96a**,**b**



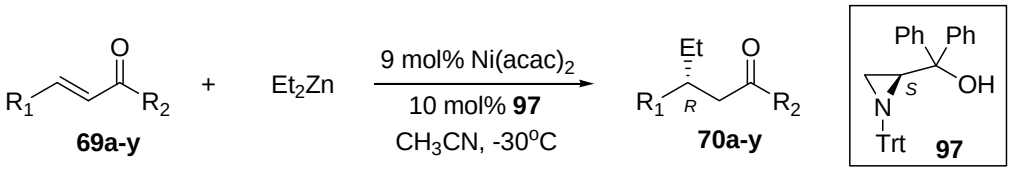
69a **70a**

Entry	Ligand	Yield(%)	ee(%)	Conf.
1	(1*S*,2*R*,*S*)-**95a**	80	32	*R*
2	(1*R*,2*S*,*R*)-**95a**	93	36	*S*
3	(1*R*,2*S*,*S*)-**95b**	80	42	*S*
4	(1*S*,2*R*,*R*)-**95b**	70	53	*R*
5	(1*R*,2*S*,*R*)-**96a**	72	48	*S*
6	(1*R*,2*S*,*S*)-**96b**	81	28	*S*

The best enantioselectivity was moderate and obtained with the use of ligand (1*S*,2*R*,*R*)-**95b** (Table 19, entry 4). Authors concluded that the absolute configuration of the products are mainly controlled by the stereogenic centers of norephedrine on chiral ligands.

Aziridine based ligands have recently gained increasing importance and have been used as catalysts in diethylzinc addition reactions to aldehydes [159]. In a recent study by Nayak et al., *N*-trityl aziridinyl methanol (**97**) was used as the chiral catalyst for the enantioselective diethylzinc addition reaction to chalcones to give the products in good yields and up to 93% ee's (Table 20) [160].

Table 20. Enantioselective conjugate diethylzinc addition to chalcones using $Ni(acac)_2$-**97** as catalyst



Entry	R_1	R_2	Substrate	Yield (%)	ee (%)
1	C_6H_5	C_6H_5	**69a**	75	78
2	*p*-OMe-C_6H_4	C_6H_5	**69e**	55	70
3	*o*-OMe-C_6H_4	C_6H_5	**69g**	69	78
4	*p*-Cl-C_6H_4	C_6H_5	**69d**	50	78
5	*p*-OMe-C_6H_4	*m*-OMe-C_6H_4	**69t**	72	83
6	*p*-Cl-C_6H_4	*m*-OMe-C_6H_4	**69u**	70	71
7	C_6H_5	*o*-OMe-C_6H_4	**69v**	45	12
8	C_6H_5	*m*-OMe-C_6H_4	**69y**	67	93

CHAPTER II

RESULTS AND DISCUSSION

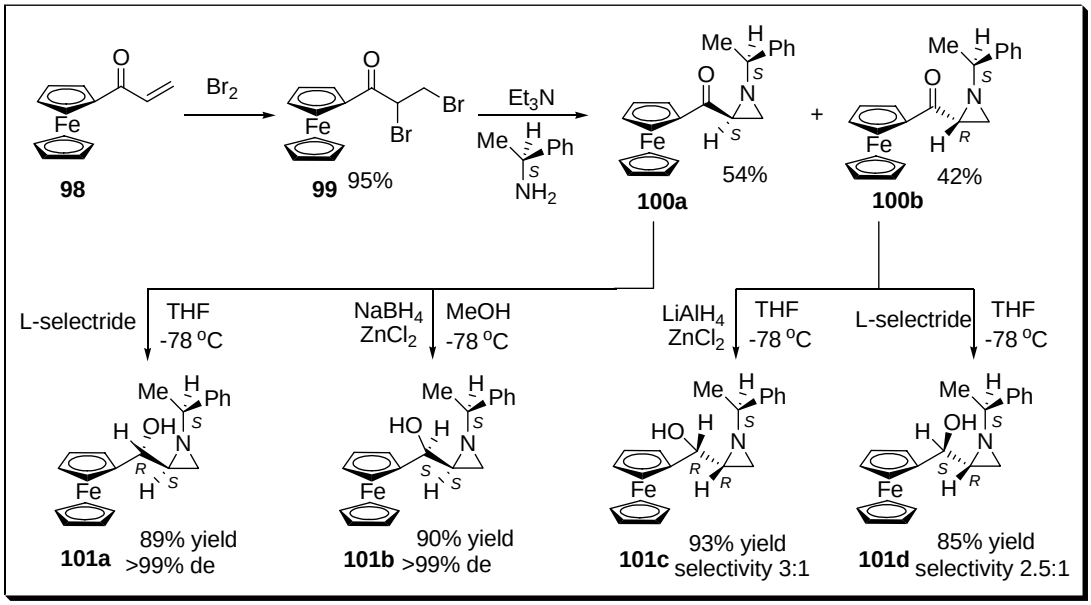
3.2.1. Aim of the work

Our group recently synthesized novel ferrocenyl substituted aziridinyl methanols (Fam) and used them as chiral catalysts for 1,3-dipolar cycloaddition reactions of azomethine ylides to obtain pyrrolidines with ee's up to 95% [161]. The use of these ligands in diethylzinc addition reactions to aldehydes gave the secondary alcohols with ee's up to 96% [162]. These results prompted us to screen these ligands in other asymmetric transformations to demonstrate their catalytic potential. In this study, we used our Fam ligands with $Ni(acac)_2$ as a chiral catalyst to promote enantioselective diethylzinc additions to enones. Although significant advance in this field was achieved, there is yet no general solution to the problem of achieving efficient catalytic enantioselective conjugate addition to a wide range of enones. The details of this study will be presented in the following sections [163].

3.2.2. Synthesis of the chiral ligands

Our chiral ligand design was based on the known attributes of ferrocene-derived ligands [164] and an improved route to acryloylferrocene (**98**) [165]. The synthesis of ligands commenced with Gabriel-Cromwell reaction [166] of the dibromo ketone **99** using (*S*)-methylbenzylamine (Scheme 42). This reaction gave a

mixture of diastereomeric aziridinyl ketones **100a** (54%) and **100b** (42%) that were easily separated by flash chromatography on silica gel [167]. Stereoselective reduction of aziridinyl ketone **100a** with *L*-Selectride gave Fam-**101a** in 89% yield as a single diastereomer (Scheme 42). Stereocontrolled reduction of aziridinyl ketone **100a** with $NaBH_4$ + $ZnCl_2$ (chelation control) [168] according to Lee and co-workers afforded the Fam-**101b** having (*S*)-configuration at alcohol center in 90% yield as a single diastereomer. Reduction of aziridinyl ketone **100b** with $NaBH_4$ was not possible (more likely due to steric reasons) therefore stronger reducing reagent $LiAlH_4$ + $ZnCl_2$ was used. Although the reduction went smoothly with high yield, the selectivity was not as high as in the case of **100a**, diastereomeric products Fam-**101c** and Fam-**101d** were obtained in 93% total yield in a ratio of 3/1, respectively. Reduction of the same ketone **100b** with *L*-Selectride proceded also with low selectivity by giving the products Fam-**101d** and Fam-**101c** in 85% total yield with a ratio of 2.5/1, respectively (Scheme 42). Diastereomers Fam-**101c** and Fam-**101d** can easily be seperated by flash column chromatography on silica gel [167]. We did not try to modify the reaction conditions interms of increasing the selectivity because we needed both diastereomers as chiral ligands.

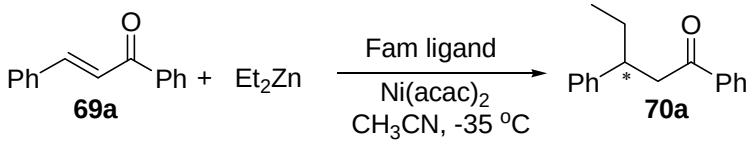


Scheme 42. Synthesis of the chiral ligands **101a-d**

3.2.3. Ligand screening and optimization of diethylzinc addition to chalcone

First the efficiency of the ligands in enantioselective diethylzinc addition to chalcone was tested by adapting the literature procedure [150]. Reaction of chalcone with diethylzinc (1.5 eq) in the presence of 25 mol % of ligand Fam-**101a** and 1 mol % $Ni(acac)_2$ gave the expected product in 82% yield and 80% ee (Table 21, entry 1) at −35 ^oC. Under the same reaction conditions, the other ligands (Fam-**101b-d**) were less efficient (Table 21, entries 2-4). Previous studies carried out with aminoalcohols as ligands on the enantioselective diethylzinc addition to chalcones showed that the suitable solvent is acetonitrile and Co, Cu, and Zn salts are less efficient than $Ni(acac)_2$. We found similar results, the use of toluene as the solvent and $Cu(OTf)_2$ inplace of $Ni(acac)_2$ gave the product in low yield and ee.

Table 21. Diethylzinc addition to chalcone under different conditions



69a **70a**

Entry	Ligand	Ligand mol%	$Ni(acac)_2$ mol%	Yield[a] (%)	ee[b] (%)	Config.[c]
1	**101a**	25	1.0	82	80	*R*
2	**101b**	25	1.0	61	42	*R*
3	**101c**	25	1.0	72	3	*S*
4	**101d**	25	1.0	65	34	*S*
5	**101a**	15	1.0	61	69	*R*
6	**101a**	5	1.0	40	47	*R*
7	**101a**	35	1.0	78	82	*R*
8	**101a**	25	0.5	71	76	*R*
9	**101a**	15	0.5	78	70	*R*
10	**101a**	5	0.2	84	44	*R*

[a] Isolated yield.
[b] Determined by HPLC using a Chiracel AD column.
[c] Determined by comparing the reported optical rotation data.

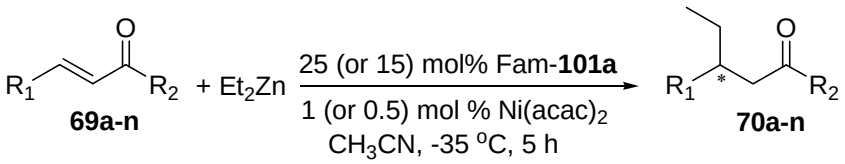
After determining that ligand Fam-**101a** was catalyzing the reaction with highest yield and ee, the effect of ligand and $Ni(acac)_2$ concentrations on the yield and enantioselectivity of the reaction was searched. When the ligand concentration was lowered to 15 mol % or 5 mol %, both the the yield and the ee of the product were low (Table 21, entries 5 and 6). On the other hand, increasing the ligand concentration from 25 mol% to 35 mol% didn't show a significant effect on the yield and ee (Table 21, entry 7). By keeping the ligand concentaration at 25 mol % and reducing $Ni(acac)_2$ concentration from 1 mol % to 0.5 mol % the product was formed in slightly lower yield and ee (Table 21, entry 8). Interestingly, at a concentration of 5 mol % ligand and 0.2 mol % Ni, the product was formed in 84% yield and 44 % ee (Table 21, entry 10). These results are very similar to the findings of previous studies where Bolm et al.[150] and Feringa et al. [153] reported that ligand to nickel ratio is crucial to obtain high enantioselectivity. They also reported that asymmetric induction depends on the equilibrium between the chiral nickel complex and catalytically active nickel species which lead to the racemic product.

3.2.4. Enantioselective diethylzinc addition to various enones

In order to show the catalytic effect of ligand Fam-**101a**, enantioselective diethylzinc addition reaction to various enones were carried out under the optimized conditions (25 mol % ligand, 1 mol % Ni-salt, acetonitrile, and −35 ^{o}C). The results of these reactions are summarized in Table 22.

As can be seen from Table 22, enantioselective diethylzinc addition to enonones where R_1 and R_2 are aromatic took place smoothly to give the β-ethylated ketones in good chemical yields and ee's in the range of 42−80%. Enantioselective diethylzinc addition to enone with R_2 being methyl formed the product in acceptable yield but low ee (Table 22, entry 13). In the study of Bolm and coworkers [150b], the same substrate gave the product in 76% yield as a racemic mixture. Enones with methyl or cyclohexyl group at the β-position gave the products in reasonable yields and ee's (Table 22, entries 14 and 15). However when sterically hindered *tert*-butyl group is introduced at R_1 (R_2=Ph) or R_2 (R_1=Ph) position of the enone, most of the

Table 22. Diethylzinc addition to various enones[a]



69a-n 70a-n

Entry	R_1	R_2	Substrate	Yield (%)[b]	Ee (%)[c]	Config.[d,e]
1[f]	Ph	Ph	**69a**	85	80	*R*
2[g]	*p*-MeC_6H_4	Ph	**69b**	90(95)	76(62)	–
3[g]	*p*-$CF_3C_6H_4$	Ph	**69c**	80(86)	70(52)	+
4	*p*-ClC_6H_4	Ph	**69d**	77(94)	70(60)	*R*
5	*p*-$MeOC_6H_4$	Ph	**69e**	75(96)	76(60)	*R*
6	*m*-$MeOC_6H_4$	Ph	**69f**	85(71)	80(74)	–
7	*o*-$MeOC_6H_4$	Ph	**69g**	60(85)	66(54)	*R*
8	*o*-ClC_6H_4	Ph	**69h**	55(88)	50(40)	+
9	*o*-FC_6H_4	Ph	**69i**	77(94)	76(70)	+
10[f]	*o*-FC_6H_4	Ph	**69i**	82	76	+
11[g]	2-Naphthyl	Ph	**69j**	57(63)	78(72)	+
12[g,h,i]	Fc	Ph	**69k**	71(63)	42(40)	+
13[h]	Ph	Me	**69l**	49(66)	22(16)	*R*
14	Me	Ph	**69m**	57(60)	60(53)	*R*
15	*c*-C_6H_{11}	Ph	**69n**	45(55)	70(57)	*S*

[a] An amount of 1 mol% $Ni(acac)_2$ with 25 mol% of Fam-**101a** or 0.5 mol% $Ni(acac)_2$ with 15 mol% of Fam-**101a** (data in parenthesis) were used.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Absolute configuration was assigned by comparing the reported optical rotation data.
[e] The + or – signs refer to the optical rotation.
[f] The recovered ligand was used.
[g] Enone was dissolved in CH_2Cl_2 because of solubility problem in CH_3CN.
[h] Reaction was conducted at 0 °C.
[i] Yield was 13% and ee was 56% at –35 °C.

starting materials were recovered, no β-ethylated ketone was observed. A similar result was also seen when R_2 (R_1=Ph) was a ferrocenyl group [169]. The numbers in parenthesis in Table 22 obtained by using 15 mol % ligand and 0.5 mol % $Ni(acac)_2$ indicate that at low ligand concentration products are formed in higher yield but lower ee. Once again these results support the hypothesis that at low ligand concentration, less chiral nickel-complex is formed. Interms of substituent effect,

stereoselectivity did not change seriously by the electronic nature of the substituents at the *para*-position of the *β*-phenyl group of the enones (entries 2-5) which is contrary to the findings of the literature where considerably lower stereoselectivities were reported for the *p*-CF_3 substituent [173b,g]. These results show that our catalyst is active enough to react with enones having electron donating and withdrawing *para*-substitents. For the *ortho*-substituted enones (entries 7-9), it looks like that the size of the substituent is more important than its electronic nature because electronegative fluoride on the substrate gives the product in high yield and ee as compared to the less electeronegative chloride. Steric effect can also be seen by the results of the *p*-, *m*-, and *o*-methoxy substituted enones (entries 5-7) where the first two gave the product in about the same yield and ee but the last one gave the product in lower yield and ee.

Based on the assigned configurations, the configuration of the ligands Fam-**101a-d** at aziridine center is important in determining the configuration of the product. Thus ligands with (*S*)-configuration at aziridine center give the product with (*R*)-configuration (Table 22, entries 1, 4, 5, 7, 13, and 14) and vice versa (Table 21, entries 3 and 4). This is also the case in Nayak et al.'s study [160] where aziridine based chiral ligand with (*S*)-stereogenic center was responsible for the products with (*R*)-configuration (Table 20, page 98). *β*-Cyclohexylenone (Table 22, entry 15) is an exception to this observation in our study.

CHAPTER III

CONCLUSION

It was shown that aziridine based chiral ligand Fam-**101a** can be used as a catalyst for enantioselective diethylzinc addition reactions to enones to give *β*-ethylated ketones in up to 82% ee. The sense of induction was found to depend on the configuration of the aziridine ring. The advantage of this ligand is that it can easily be prepared on a gram scale in optically pure form in three easy steps. Our ligand can be recovered in >90 % yield and used without losing its activity. Another advantage of this ligand is that its antipode can be prepared easily starting from (*R*)-methylbenzyamine. Thus one can synthesize *β*-ethylated ketones with desired configuration by choosing the appropriate ligand.

CHAPTER IV

EXPERIMENTAL

3.4.1. General Consideration

The ^{1}H and ^{13}C NMR spectra were recorded in CCl_4–$CDCl_3$ (2/3, v/v) solvent system on a Bruker Spectrospin Avance DPX 400 spectrometer. ^{1}H NMR spectra were reported in ppm using TMS as an internal standard (TMS at 0.00 ppm). ^{13}C NMR spectra were reported in ppm using solvent as an internal standard ($CDCl_3$ at 76.9 ppm). Infrared spectra were recorded on a Perkin Elmer 16 PC FT-IR spectrometer using $CHCl_3$ as the solvent. GC-MS spectra were obtained with a Thermo-Quest (TSP) TraceGC-2000 Series instrument equipped with a Phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 µm), MS: Thermo Quest Finnigan multi Mass (EI, 70 eV). High resolution mass spectra (HRMS) were recorded on a Kratos MS25RFA mass spectrometer using electron impact (EI) method. Optical rotations were measured in a 1 dm cell using a Rudolph Autopol III polarimeter at 25°C. HPLC measurements were performed with Dionex System instrument. Separations were carried out on Chiralcel AD, OD-H or OD analytical columns (250 x 4.60 mm) with hexane/2-propyl alcohol as eluent. Flash column chromatography was performed on silica gel (60 mesh, Merck). Analytical thin layer chromatography (TLC) was performed on precoated silica gel (60 F_{254}, Merck). Solvents CH_3CN and CH_2Cl_2 were distilled from CaH_2 before use. All other reagents were commercially available and used without further purification.

Elemental analysis were determined by C/H/N-Analysator 932 (Leco). Melting points were obtained using an electrothermal digital melting point apparatus (Gallenkamp) and were uncorrected.

3.4.2. Synthesis of chiral Fam ligands

3.4.2.1. Synthesis of aziridino ketones 100a and 100b. Br_2 (17.55 mmol in 28.4 mL CH_2Cl_2) was added to a stirred solution of acryloyl ferrocene **(98)** (3.15 g, 13.14 mmol) in CH_2Cl_2 at –78 °C over 5 minutes, at which point the reaction was judged to be complete by TLC. The crude mixture was filtered through a short plug of silica gel using $CHCl_3$ as the eluent. Evaporation of the solvent gave pure 1,2-dibromopronionylferrocene (**99**) (4.98 g, 95% yield). To a stirred solution of comound **99** (4.98 g, 12.45 mmol) in $CHCl_3$ (150 mL) was added Et_3N (2.95 mL, 21.18 mmol). After 4 h stirring at rt, TLC analysis signified complete conversion to α-bromoacryloylferrocene.To this solution, *L*-(–)-α-methylbenzylamine (2.86 mL, 22.17 mmol) was added and the mixture was stirred at rt overnight. The solvent was removed by rotary evaporation and the crude reaction mixture was flash chromatographed on silica gel (1:3 EtOAc-hexanes) to afford aziridino ketone **100a** (2.43 g, 54% yield) and **100b** (1.89 g, 42% yield).

Aziridino ketone (*S,S*)-**100a**: R_f = 0.17, 3:1 hexanes-EtOAc; Mp 130-132 °C; $[\alpha]_D^{25}$= –90.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.42 (d, *J* = 7.4 Hz, 2H, Ph), 7.34 (t, *J* = 7.4 Hz, 2H, Ph), 7.26 (t, *J* = 7.2 Hz, 1H, Ph), 5.03 (br s, 1H, ferrocene), 4.94 (br s, 1H, ferrocene), 4.52 (br s, 2H, ferrocene), 4.23 (s, 5H, ferrocene), 2.62 (q, *J* = 6.5 Hz, 1H), 2.57 (dd, *J* = 6.5, 3.0 Hz, 1H), 2.26 (br s, 1H), 1.66 (d, *J* = 6.5 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR: δ 199.8, 143.8, 128.4, 127.3, 126.9, 78.07, 72.32, 72.21, 70.36, 69.88, 69.82, 43.50, 35.64, 23.72; IR: (neat) 2939, 1660, 1450, 1251, 818, 796, 701; Anal. Calcd. $C_{21}H_{21}FeNO$: C, 70.21; H, 5.89; N, 3.90. Found: C, 69.45; H, 5.61; N, 3.94.

Aziridino ketone (*R,S*)-**100b**: R_f = 0.10, 3:1 hexanes-EtOAc; Mp: 119-121 °C; $[\alpha]_D^{25}$ = –220.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.37 (d, *J* = 7.3 Hz, 2H, Ph), 7.25 (t, *J* = 7.6 Hz, 2H, Ph), 7.14 (t, *J* = 7.3 Hz, 1H, Ph), 4.59 (br s, 2H, ferrocene), 4.32 (br s,

2H, ferrocene), 3.81 (s, 5H, ferrocene), 2.51 (q, *J* = 6.5 Hz, 1H), 2.44 (dd, *J* = 6.5, 3.1 Hz, 1H), 2.33 (dd, *J* = 2.6 & 1.5 Hz, 1H), 1.74 (dd, *J* = 6.5 & 1.3 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR: δ 199.1, 144.3, 137.3, 128.7, 127.6, 126.9, 78.60, 72.28, 72.11, 71.12, 69.72, 69.49, 69.37, 41.51, 37.07, 23.58; IR: (neat) 2969, 1660, 1455, 1251, 823, 755, 696; Anal. Calcd. $C_{21}H_{21}FeNO$: C, 70.21; H, 5.89; N, 3.90. Found: C, 70.51; H, 5.77; N, 3.85.

3.4.2.2. Synthesis of (*R,S,S*) Fam-101a. Aziridino ketone **100a** (1.42 g, 3.95 mmol) was dissolved in THF (23 mL, distilled over Na-benzophenone) in a reaction flask. The flask was cooled to –78 °C and L-Selectride (6 mL, from 1M THF solution) was added slowly over 30 min. After stirring about 1h, TLC showed no starting material. The reaction flask was added 10% NaOH solution (25 mL) followed by ether (30 mL) and the two layers were separated. The aqueous layer was extracted one more time with ether (30 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash chromatography on silica gel using: 1:15 EtOAc-hexanes. Ligand Fam-**1** was obtained as yellow oil. R_f = 0.29, 1:2 EtOAc-hexanes; $[\alpha]_D^{25}$ = –45.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR: δ 1.34 (d, *J* = 6.4 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.72 (d, *J* = 3.4 Hz, 1H), 1.76-1.79 (m, 1H), 2.49 (q, *J* = 6.5 Hz, 1H), 2.70 (d, *J* = 4.7 Hz, 1H, OH), 4.10-4.13 (m, 4H), 4.18 (s, 5H), 4.30 (br s, 1H), 7.19-7.24 (m, 2H, Ph), 7.27-7.34 (m, 3H, Ph), ^{13}C NMR: δ 23.8, 31.5, 45.5, 65.8, 66.3, 67.7, 67.8, 68.6, 69.2, 70.2, 90.9, 126.7, 127.0, 128.3, 144.4; HRMS (EI) for $C_{21}H_{23}FeNO$ calculated 361.1129, found 361.1133.

3.4.2.3. Synthesis of (*S,S,S*) Fam-101b. Aziridino ketone **100a** (467 mg, 1.30 mmol) was dissolved in MeOH (13 mL) and cooled to –78 °C. To this stirred solution was added $ZnCl_2$ (266 mg, 1.95 mmol). After 1 h, $NaBH_4$ (98 mg, 2.59 mmol) was added and stirring continued at –78 °C for 2 hours when TLC analysis showed the reaction to be complete. The reaction mixture was partitioned between CH_2Cl_2 (2 x 10 mL) and water (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give crude Fam-**101b**. Purification by flash column chromatography on silica gel eluting with 1:4 EtOAc-hexanes gave pure Fam-**101b** (422 mg, 90% yield) as yellow solid. R_f = 0.5, 1:2 EtOAC-hexanes; Mp:

83-85 °C; $[\alpha]_D^{25}$ = –46.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR: δ 1.29 (d, *J* = 7.0 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.80-1.83 (m, 2H), 2.57 (q, *J* = 6.5 Hz, 1H), 2.61 (br s, 1H, OH), 4.13 (br s, 2H), 4.17 (s, 5H), 4.23 (br s, 1H), 4.26 (br s, 1H), 4.47 (d, *J* = 3.8 Hz, 1H), 7.19-7.33 (m, 5H, Ph); ^{13}C NMR: δ 23.5, 30.0, 43.8, 65.7, 67.0, 67.6, 67.8, 68.2, 68.4, 68.8, 89.7, 126.5, 126.9, 128.2, 144.2; IR: (neat) 3431, 3100, 2969, 1494, 1445, 1221, 1100, 812, 759, 691, 481; Anal. Calcd. $C_{21}H_{23}FeNO$: C, 69.82; H, 6.42; N, 3.88. Found: C, 69.15; H, 6.24; N, 3.91.

3.4.2.4. Synthesis of (*R,R,S*) Fam-101c. Aziridino Ketone **100b** (522 mg, 1.45 mmol) was dissolved in THF (15 mL) and then cooled to –78 °C. $ZnCl_2$ (297 mg, 2.18 mmol) was added and the reaction mixture was stirred for 1 h at this temperature. Then $LiAlH_4$ (110 mg, 2.91 mmol) was added and stirring continued for about 2 h at which point TLC showed that no starting material was left. The contents of the reaction flask was hydrolyzed with distilled water and then extracted with CH_2Cl_2 (15 mL). The aqueous layer was extracted one more time with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash chromatograhy on silica gel using 1:4 EtOAc-hexanes. Ligand Fam-**101c** was obtained as yellow oil (318 mg, 61% yield) along with the minor diastereomer Fam-**101d** (127 mg, 24% yield). $[\alpha]_D^{25}$ = –3.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR: δ 1.40 (d, *J* = 6.6 Hz, 1H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.73-1.77 (m, 1H), 2.02 (d, *J* = 3.4 Hz, 1H), 2.55 (br s, 1H, OH), 2.59 (q, *J* = 6.5 Hz, 1H), 4.02-4.03 (m, 2H, ferrocene), 4.04-4.05 (m, 2H, ferrocene), 4.07 (s, 5H, ferrocene), 4.29 (d, *J* = 3.4 Hz, 1H), 7.21-7.25 (m, 2H, Ph), 7.27-7.30 (m, 3H, Ph); ^{13}C NMR: δ 23.0, 30.6, 43.1, 67.0, 67.4, 67.5, 68.3, 68.5, 69.1, 70.1, 90.0, 127.3, 127.9, 129.2, 145.0; Anal. Calcd. $C_{21}H_{23}FeNO$: C, 69.82; H, 6.42; N, 3.88. Found: C, 69.85; H, 6.24; N, 3.95.

3.4.2.5. Synthesis of (*S,R,S*) Fam-101d. Aziridino ketone **100b** (653 mg, 1.82 mmol) was dissolved in dry THF (10 mL) under argon atmosphere and cooled to –78 °C. L-Selectride (2.73 mL, 1 M in THF) was added slowly over 30 min. After stirring about 1h, TLC analysis indicated no starting material. The reaction mixture was added 10% NaOH solution (10 mL) and extracted with ether (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash

chromatography on silica gel (1:5 EtOAc-hexanes). Ligand Fam-**101d** was obtained as a yellow oil (460 mg, 70% yield) along with minor diastereomer Fam-**101c** (151 mg, 23% yield). R_f = 0.29, 1:2 EtOAc-hexanes; $[\alpha]_D^{25}$ = –20.9 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.44 (d, *J* = 6.5 Hz, 3H), 1.50 (d, *J* = 6.5 Hz, 1H), 1.73-1.77 (m, 1H), 1.90 (d, *J* = 3.4 Hz, 1H), 1.98 (br s, 1H, OH), 2.50 (q, *J* = 6.5 Hz, 1H), 3.76 (br s, 1H), 3.94 (br s, 2H, ferrocene), 3.97 (br s, 1H), 4.05 (s, 5H), 7.23-7.34 (m, 5H, Ph); ^{13}C NMR: δ 22.8, 29.8, 32.0, 43.9, 66.1, 66.3, 67.6, 68.5, 69.8, 70.5, 90.0, 127.0, 127.6, 128.7, 144.4; IR: (neat) 3412, 3086, 2960, 1489, 1455, 1378, 1280, 1105, 817, 754, 696, 482; HRMS (EI) for $C_{21}H_{23}FeNO$ calculated 361.1129, found 361.1127.

3.4.3. General Procedure for the synthesis of enones [170]

Aldehyde (43.2mmol) was added gradually to a solution of NaOH (2.2 g) in H_2O (20.0 mL) and ketone (43.3 mmol) in ethanol (12 mL) at 0 ºC. The mixture was then allowed to warm to room temperature and stirred for 4 h. At the end of this period sat. NH_4Cl solution was added to the flask, followed by extraction with ether. The combined organic layers were dried over Na_2SO_4 and concentrated to give a solid which was washed successively with hexane to get pure enones **69a-l**. Enone **69n** was obtained as oil and purified by flash column chromatography using EtOAc-hexanes (1:30). Enone **69m** was synthesized from *trans*-crotonyl chloride and benzene according to the literature procedure [171]. All spectroscopic data of the enones were identical to those reported in the literature [172].

3.4.4. General procedure for the asymmetric addition of diethylzinc to enones

Chiral ligands Fam-**101a-d** and $Ni(acac)_2$ were benzene azeotroped and used from a stock solution in acetonitrile. Method A: Chiral ligand (0.88 mL, 0.079 M, 25 mol%, freshly prepared) and $Ni(acac)_2$ (30 µL, 0.093 M, 1 mol%) or Method B: Chiral ligand (0.53 mL, 0.079 M, 15 mol%, freshly prepared) and $Ni(acac)_2$ (60 µL, 0.023 M, 0.5 mol%) were mixed and refluxed under argon atmosphere for 1h. At the end of this period, the reaction mixture was cooled to room temperature and enone (0.280 mmol) in CH_3CN (0.2 mL) was added. Then diethylzinc (0.42 mL, 0.42 mmol, 1M in hexane) was added slowly over a period of 10 min to the reaction

mixture cooled to –35 °C. The color of the reaction mixture was changed from orange to dark brown. After stirring for 5h at this temperature, the mixture was quenched with sat. NH_4Cl solution followed by extraction with ether (2x10 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (EtOAc / hexanes 1:20) to obtain the pure product.

3.4.4.1. 1,3-Diphenyl-1-pentanone (70a). Using method A, **70a** was obtained as a white solid (54.7 mg, 82% yield), mp: 55-56 °C; $[\alpha]_D^{25}$ = –4.3 (*c* 1.35, EtOH) for 80% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 0.5 mL min^{-1}, 20 °C, t_R (+)-**70a**: 15.0 min; for (*S*), t_R (–)-**70a**: 18.3 min for (*R*). All spectroscopic data are in good agreement with those reported in the literature [173b-e].

3.4.4.2. 1-Phenyl-3-*p*-tolylpentan-1-one (70b). Using method A, **70b** was obtained as a pale yellow oil (63.6 mg, 90% yield), $[\alpha]_D^{25}$ = –9.4 (*c* 2.22, EtOH) for 76% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 1.0 mL min^{-1}, 20 °C, t_R (+)-**70b**: 6.6 min, t_R (–)-**70b**: 9.0. All other spectroscopic data are in good agreement with those reported in the literature [173d]

3.4.4.3. 3-(4-(Trifluoromethyl)phenyl)-1-phenylpentan-1-one (70c). Using method A, **70c** was obtained as a yellow waxy oil (68.6 mg, 80% yield), $[\alpha]_D^{25}$ = +4.2 (*c* 1.92, EtOH) for 70% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 0.5 mL min^{-1}, 20 °C, t_R (–)-**70c**: 13.2 min, t_R (+)-**70c**: 17.2 min. All other spectroscopic data are in good agreement with those reported in the literature [173b].

3.4.4.4. 3-(4-Chlorophenyl)-1-phenylpentan-1-one (70d). Using method A, **70d** was obtained as a colorless oil (58.8 mg, 77% yield), $[\alpha]_D^{25}$ = –1.8 (*c* 1.97, EtOH) for 70% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 1.0 mL min^{-1}, 20 °C, t_R (+)-**70d**: 7.8 min for (*S*), t_R (–)-**70d**: 11.1 min for (*R*). All other spectroscopic data are in good agreement with those reported in the literature [173c,d].

3.4.4.5. 3-(4-Methoxyphenyl)-1-phenylpentan-1-one (70e). Using method A, **70e** was obtained as a pale yellow solid (56.4 mg, 75% yield), mp: 49-50 °C; $[\alpha]_D^{25}$ = –12.4 (*c* 1.49, EtOH) for 76% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 1.0 mL min^{-1}, 20 °C, t_R (+)-**70e**: 9.0 min for (*S*), t_R (–)-**70e**: 13.2 min for (*R*). All other spectroscopic data are in good agreement with those reported in the literature [173c,d].

3.4.4.6. 3-(3-Methoxyphenyl)-1-phenylpentan-1-one (70f). Using method A, **70f** was obtained as a pale yellow waxy oil (63.9 mg, 85% yield), R_f = 0.35, 1:10 EtOAc-hexanes, $[\alpha]_D^{25}$ = –3.4 (*c* 2.06, EtOH) for 80% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 0.5 mL min^{-1}, 20 °C, t_R (+)-**70f**: 17.2 min, t_R (–)-**70f**: 20.2 min; IR: ν 3039, 3008, 2964, 2930, 2878, 2835, 1687, 1604, 1486, 1452, 1363, 1316, 1261, 1155, 1047, 1013, 976, 923 cm^{-1}; ^{1}H NMR: δ 0.82 (t, *J* = 7.3 Hz, 3H), 1.57-1.67 (m, 1H), 1.72-1.82 (m, 1H), 3.17-3.27 (m, 3H), 3.77 (s, 3H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR: δ 12.13, 29.10, 43.04, 45.58, 54.93, 111.32, 113.67, 119.94, 128.05, 128.42, 129.29, 132.69, 137.40, 146.32, 159.68, 198.44; MS (EI) *m/z* (%) : 268 (18) [M^+], 239 (25), 185 (20), 163 (75), 148 (95), 134 (8), 121 (40), 105 (83), 91 (36), 77 (100), 65 (13), 55 (17), 50 (24).

3.4.4.7. 3-(2-Methoxyphenyl)-1-phenylpentan-1-one (70g). Using method A, **70g** was obtained as a pale yellow oil (45.1 mg, 60% yield), $[\alpha]_D^{25}$ = –5.7 (*c* 1.80, EtOH) for 66% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 0.5 mL min^{-1}, 20 °C, t_R (+)-**70g**: 16.1 min for (*S*), t_R (–)-**70g**: 19.8 min for (*R*). All other spectroscopic data are in good agreement with those reported in the literature [160, 173a].

3.4.4.8. 3-(2-Chlorophenyl)-1-phenylpentan-1-one (70h). Using method A, **70h** was obtained as a pale yellow solid (42.0 mg, 55% yield), mp: 61-62°C; $[\alpha]_D^{25}$ = +16.4 (*c* 1.30, EtOH) for 50% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 0.5 mL min^{-1}, 20 °C, t_R (–)-**70h**: 14.3

min, t_R (+)-**70h**: 17.4 min. All other spectroscopic data are in good agreement with those reported in the literature [173a].

3.4.4.9. 3-(2-Fluorophenyl)-1-phenylpentan-1-one (70i). Using method A, **70i** was obtained as a pale yellow solid (55.2 mg, 77% yield), R_f = 0.48, 1:10 EtOAc-hexanes; Mp: 38-39 °C; $[\alpha]_D^{25}$ = +10.0 (*c* 2.19, EtOH) for 76% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 0.5 mL min^{-1}, 20 °C, t_R (–)-**70i**: 14.4 min, t_R (+)-**70i**: 16.6 min**;** IR: ν 3072, 3039, 2967, 2934, 2874, 1685, 1599, 1586, 1490, 1448, 1365, 1289, 1243, 1180, 1117, 1022, 985, 929 cm^{-1}; ^{1}H NMR: δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.65-1.85 (m, 2H), 3.23-3.36 (m, 2H), 3.46-3.54 (m, 1H), 6.95-7.05 (m, 2H), 7.11-7.16 (m, 1H), 7.21 (td, *J* = 7.4, 1.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H),7.50 (t, *J* = 7.3 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR: δ 12.16, 27.82, 37.53, 43.90, 115.60 (d, *J* = 22.9 Hz), 123.94 (d, *J* = 3.7 Hz), 127.66 (d, *J* = 8.9 Hz), 128.04, 128.43, 129.55 (d, *J* = 5.5 Hz), 131.13 (d, *J* = 13.6 Hz), 132.72, 137.23, 161.22 (d, *J* = 243.8 Hz), 198.00 ; MS (EI) *m/z* (%) : 256 (22) [M^+], 227 (94), 137 (7), 135 (39), 120 (59), 105 (100), 76 (65), 50 (41).

3.4.4.10. 3-(Naphthalen-2-yl)-1-phenylpentan-1-one (70j). Using method A, **70j** was obtained as a pale yellow solid (46.03 mg, 57% yield), R_f = 0.42, 1:10 EtOAc-hexanes; Mp: 51-52 °C; $[\alpha]_D^{25}$ = +1.1 (*c* 1.99, EtOH) for 78% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 1.0 mL min^{-1}, 20 °C, t_R (–)-**70j**: 8.7 min, t_R (+)-**70j**: 11.1 min**;** IR: ν 3061, 3004, 2970, 2929, 2868, 1677, 1602, 1582, 1507, 1446, 1385, 1354, 1286, 1235, 1198, 1174, 1099, 1021, 983, 925 cm^{-1}; ^{1}H NMR: δ 0.83 (t, *J* = 7.3 Hz, 3H), 1.54-1.77 (m, 1H), 1.79-1.91 (m, 1H), 3.21-3.32 (m, 2H), 3.35-3.44 (m, 1H), 7.35-7.42 (m, 4H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.62 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 3H), 7.88 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR: δ 12.23, 29.13, 43.06, 45.63, 125.22, 125.84 (2C), 126.24, 127.57, 127.63, 128.06, 128.13, 128.44, 132.42, 132.71, 133.62, 137.38, 142.03, 198.20; MS (EI) *m/z* (%) : 288 (15) [M^+], 259 (15), 241 (5), 182 (21), 168 (61), 152 (22), 140 (35), 127 (14), 114 (10), 104 (91), 76 (100), 54 (10), 50 (27).

3.4.4.11. 3-Ferrocenyl-1-phenylpentan-1-one (70k). Using method A, **70k** was obtained as a yellow oil (12.6 mg, 13% yield), $[\alpha]_D^{25}$ = +42.9 (*c* 0.84, EtOH) for

56% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 95:5 flow 1.0 mL min^{-1}, 20 °C, t_R (+)-**70k**: 9.5 min, t_R (–)-**70k**: 17.1 min. All other spectroscopic data are in good agreement with those reported in the literature [173c].

3.4.4.12. 4-Phenylhexan-2-one (70l). Using method A, **70l** was obtained as a yellow oil (24.2 mg, 49% yield), $[\alpha]_D^{25}$ = –3.5 (*c* 1.61, EtOH) for 22% ee; HPLC: Chiralcel OD-H column, UV detection at 220 nm, eluent: hexane/2-propanol = 99:1 flow 1.0 mL min^{-1}, 20 °C, t_R (+)-**70l**: 9.8 min for (*S*), t_R (–)-**70l**: 10.8 min for (*R*). All other spectroscopic data are in good agreement with those reported in the literature [173c,e,f].

3.4.4.13. 3-Methyl-1-phenylpentan-1-one (70m). Using method A, **70m** was obtained as a colorless oil (28.1 mg, 57% yield), $[\alpha]_D^{25}$ = –10.4 (*c* 1.87, Et_2O) for 60% ee; HPLC: Chiralcel OD column, UV detection at 240 nm, eluent: hexane/2-propanol = 99.8:0.2 flow 0.7 mL min^{-1}, 20 °C, t_R (**–**)-**70m**: 15.2 min for (*R*), t_R (+)-**70m**: 16.0 min for (*S*). All other spectroscopic data are in good agreement with those reported in the literature [148, 173e].

3.4.4.14. 3-Cyclohexyl-1-phenylpentan-1-one (70n). Using method A, **70n** was obtained as a white waxy oil (30.8 mg, 45% yield), $[\alpha]_D^{25}$ = + 0.7 (*c* 1.54, EtOH) for 70% ee; HPLC: Chiralcel AD column, UV detection at 240 nm, eluent: hexane/2-propanol = 99.9:0.1 flow 0.5 mL min^{-1}, 20 °C, t_R (**–**)-**70n**: 37.8 min for (*R*), t_R (+)-**70n**: 41.5 min for (*S*). All other spectroscopic data are in good agreement with those reported in the literature [173c].

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APPENDIX

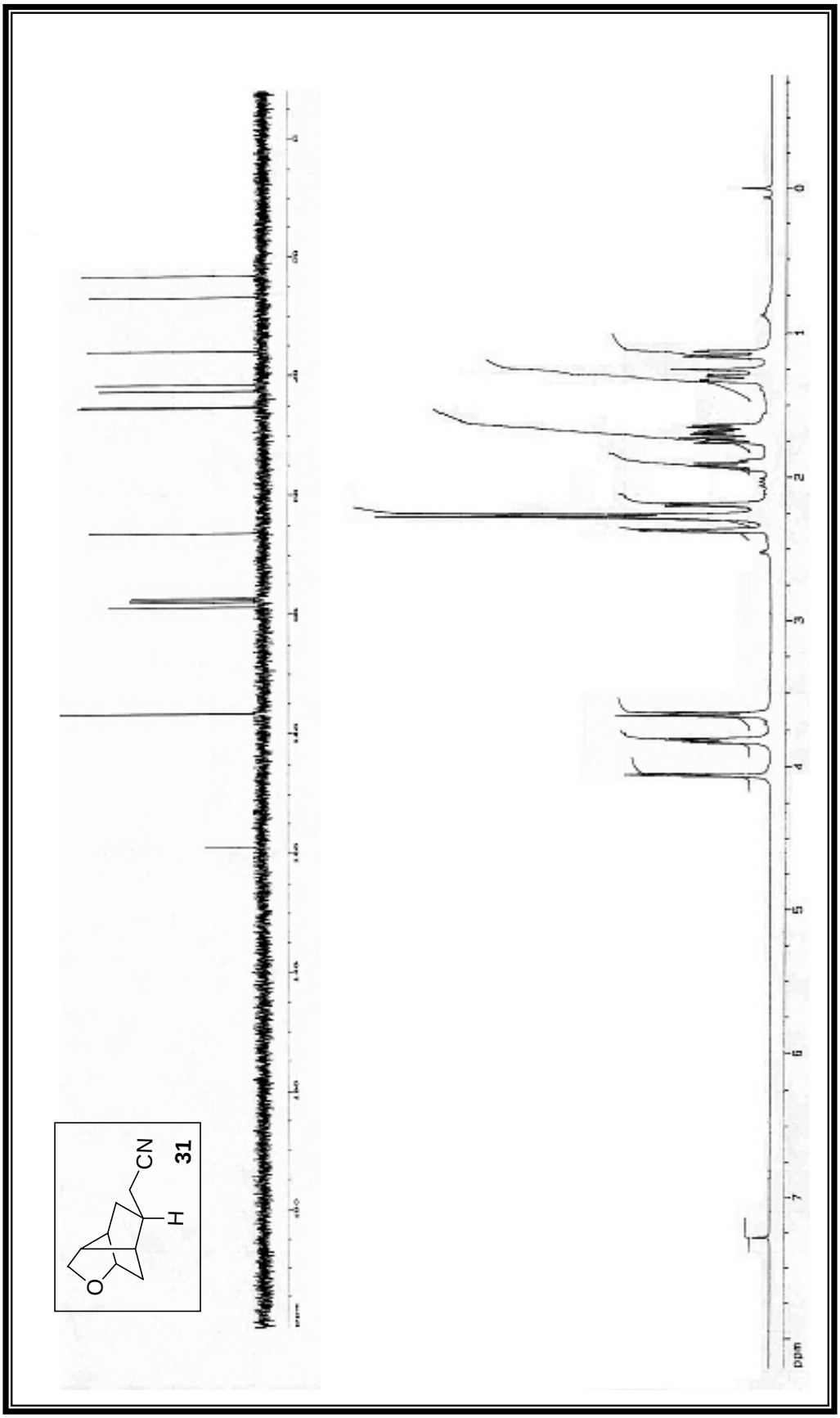

Figure A1. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of tricyclic ether **31**

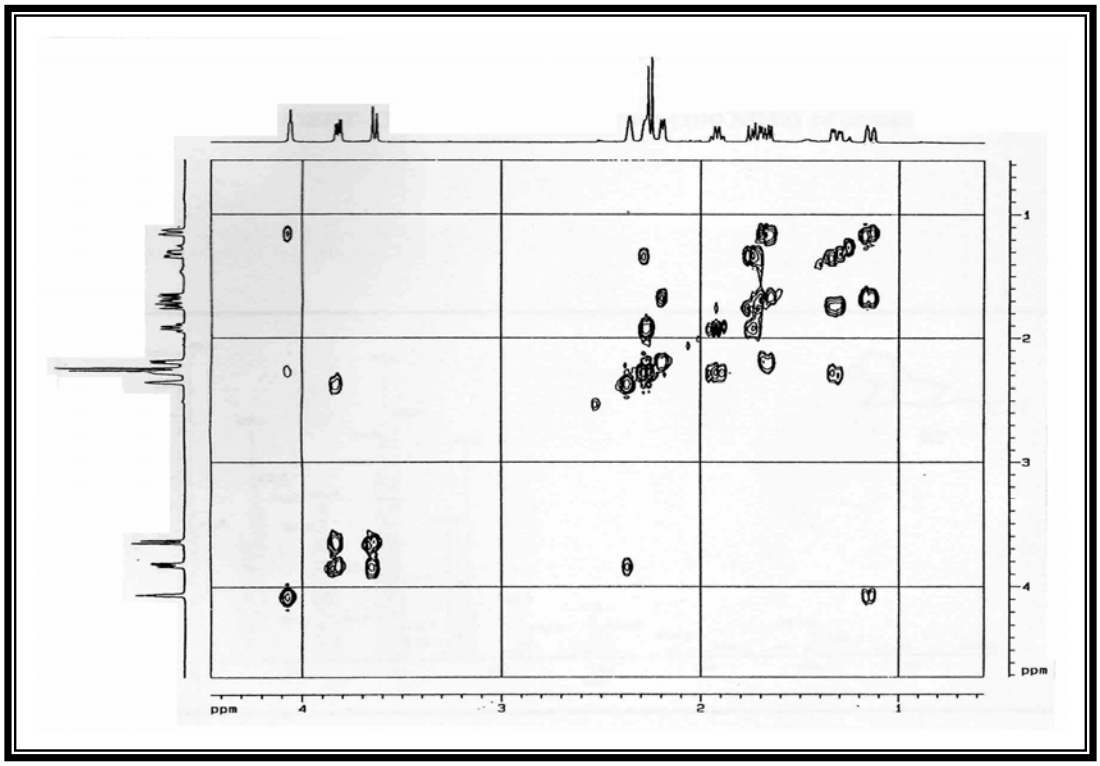

Figure A2. COSY spectrum of tricyclic ether **31**

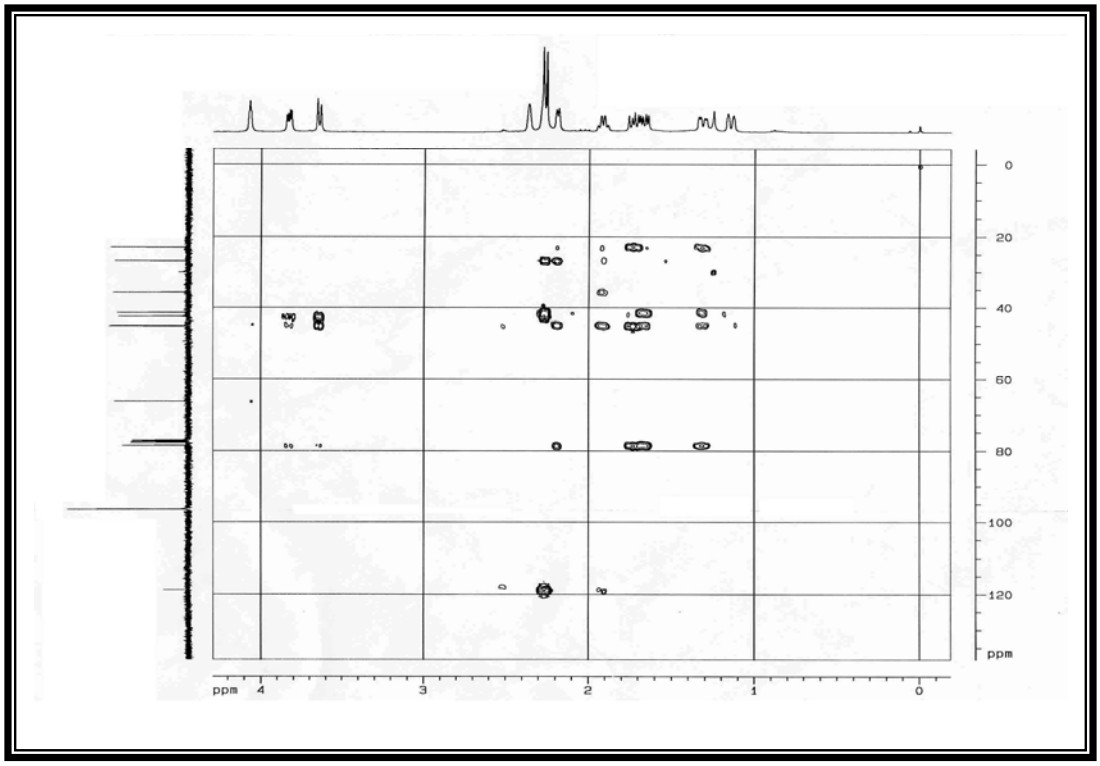

Figure A3. Part of HMBC spectrum of tricyclic ether **31**

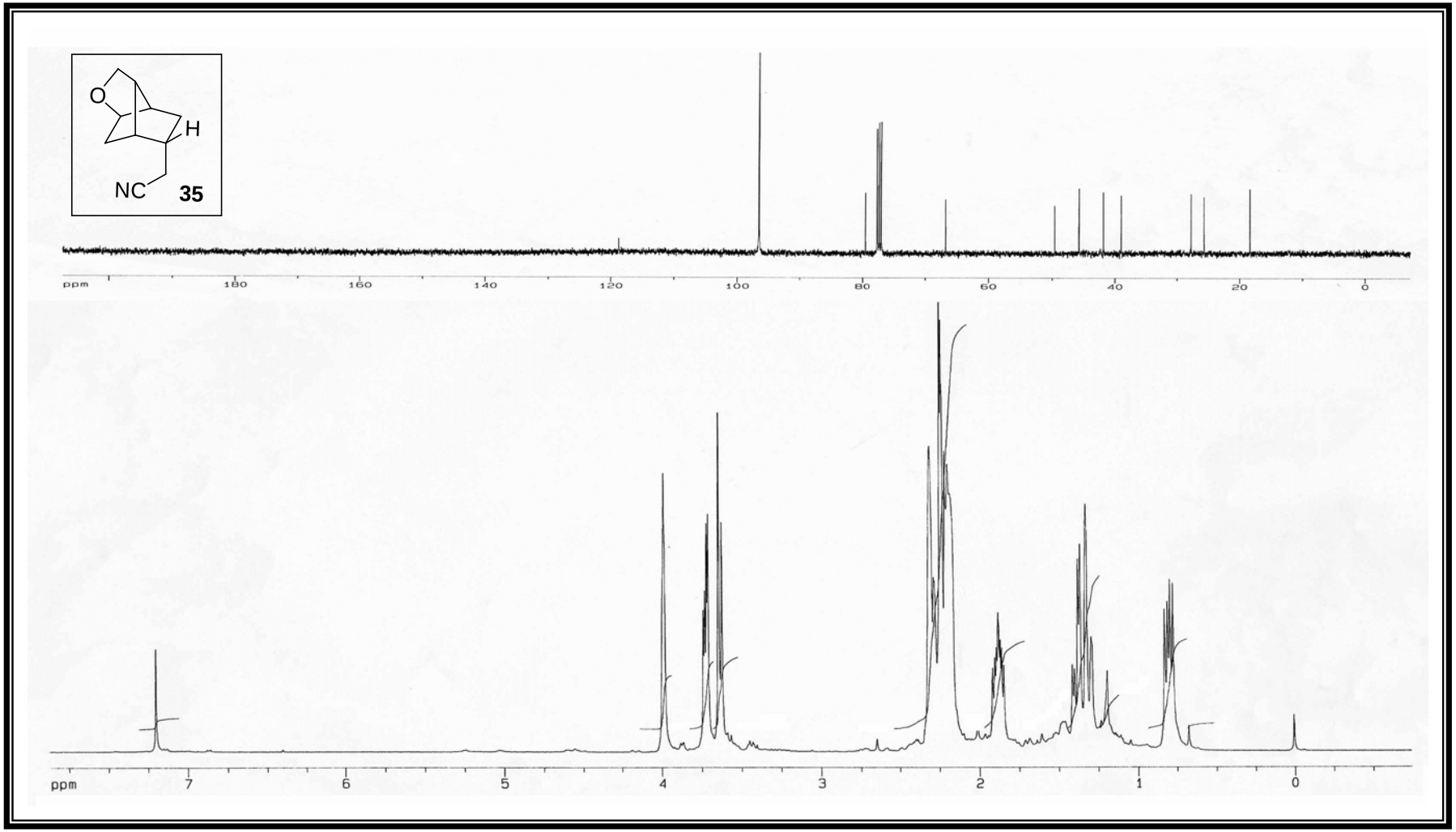

Figure A4. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of tricyclic ether **35**

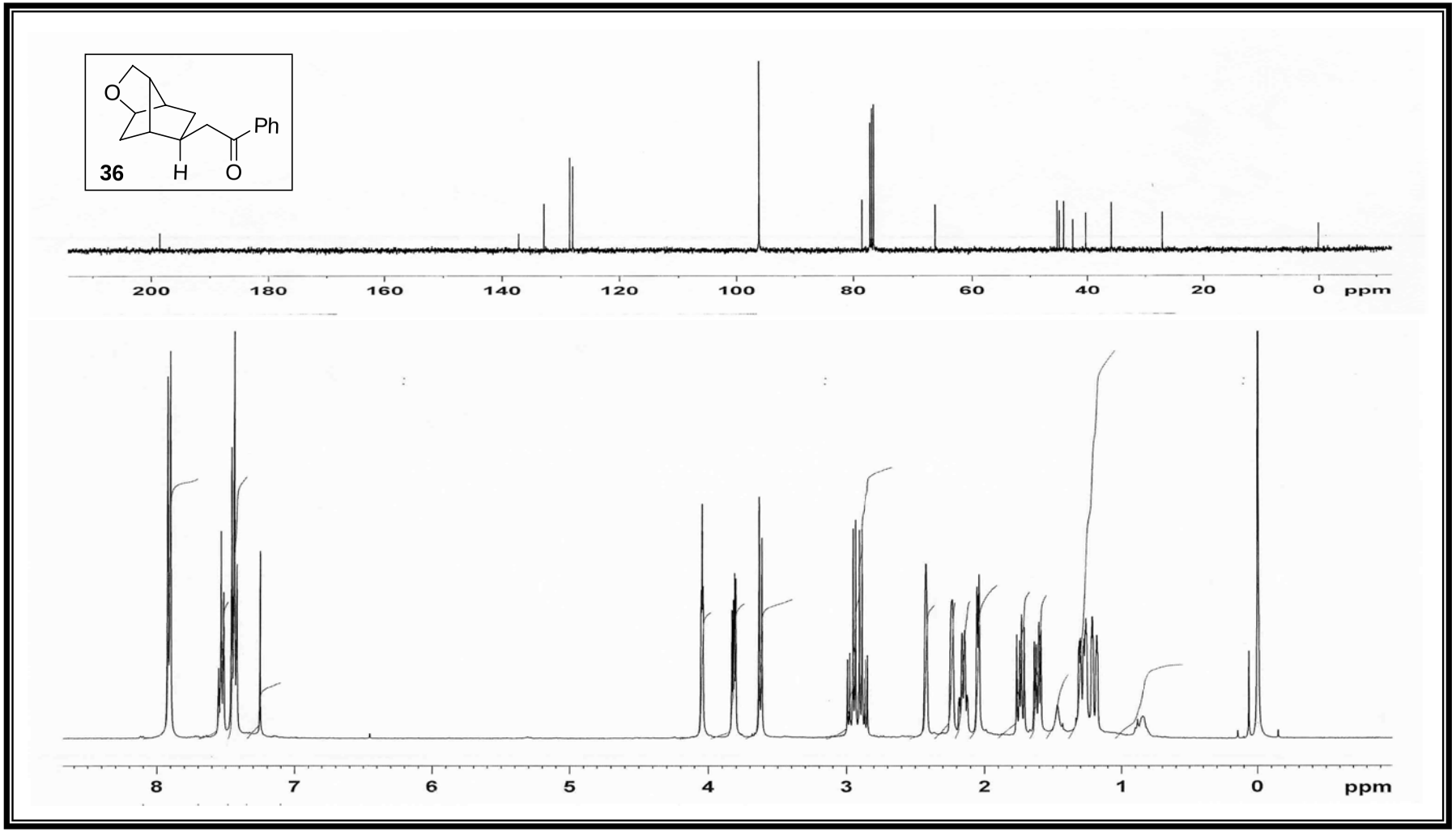

Figure A5. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of tricyclic ether **36**

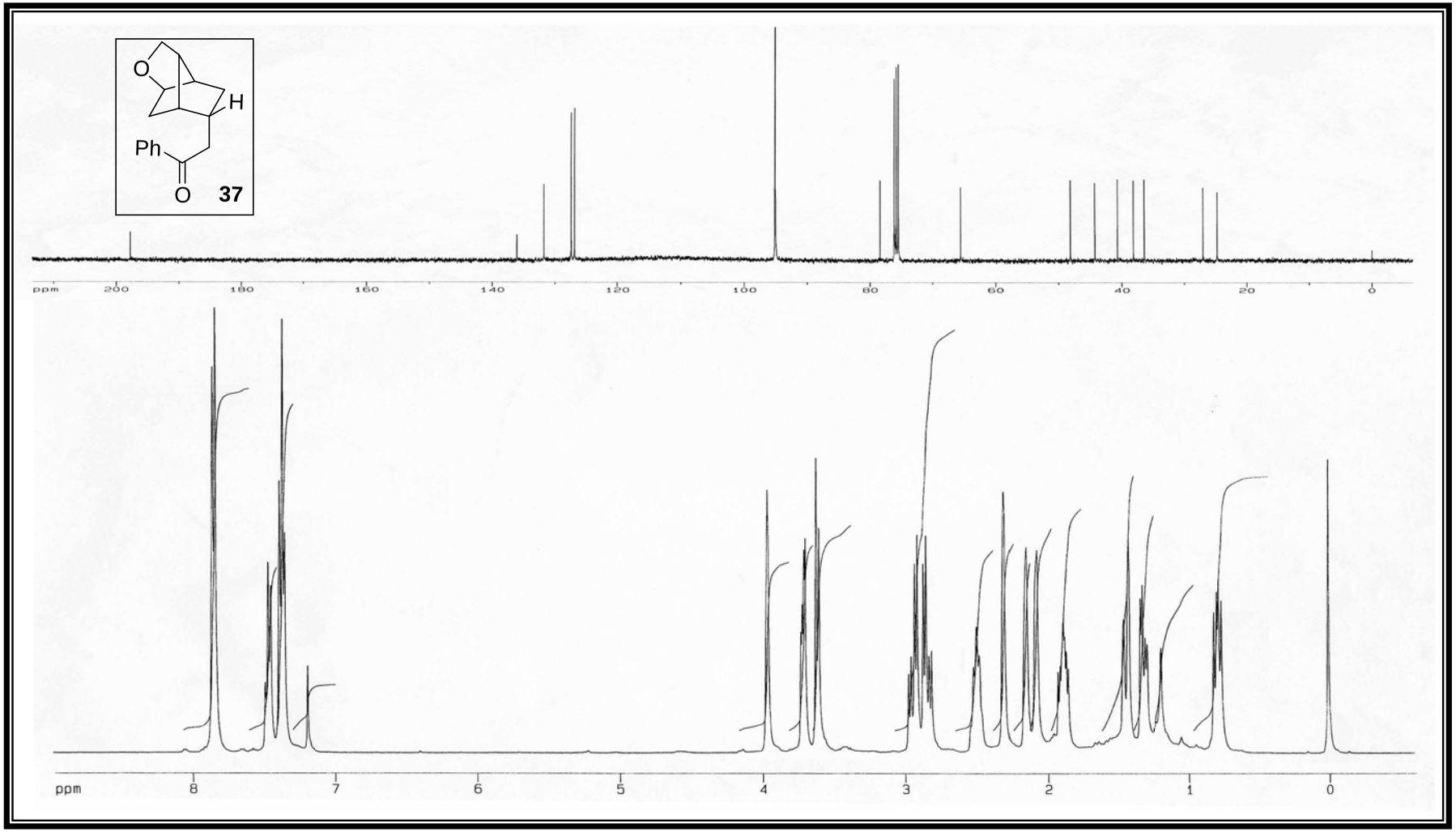

Figure A6. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of tricyclic ether **37**

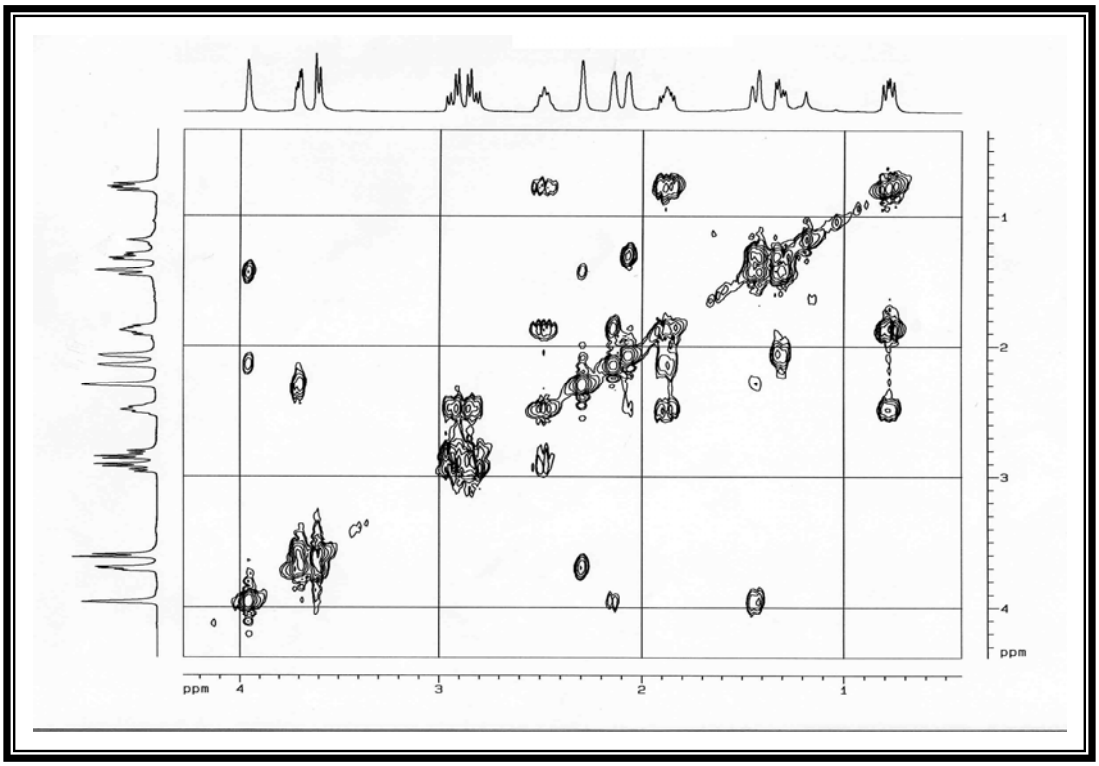

Figure A7. Part of COSY spectrum of tricyclic ether **37**

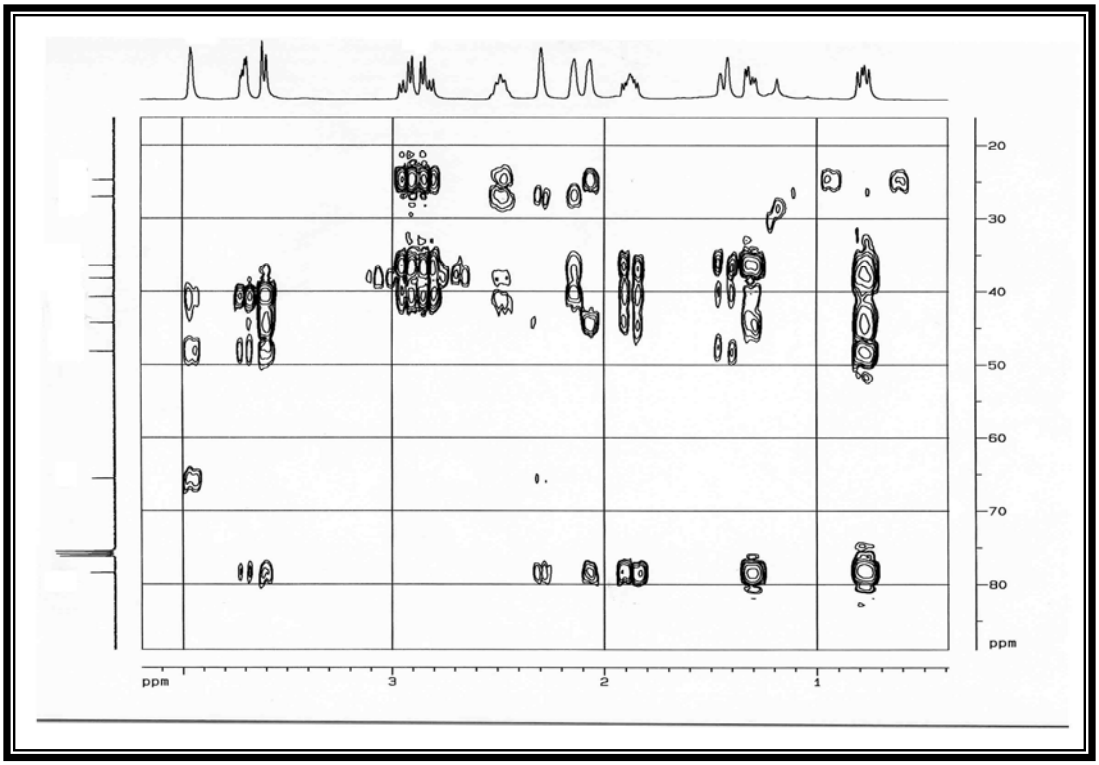

Figure A8. Part of HMBC spectrum of tricyclic ether **37**

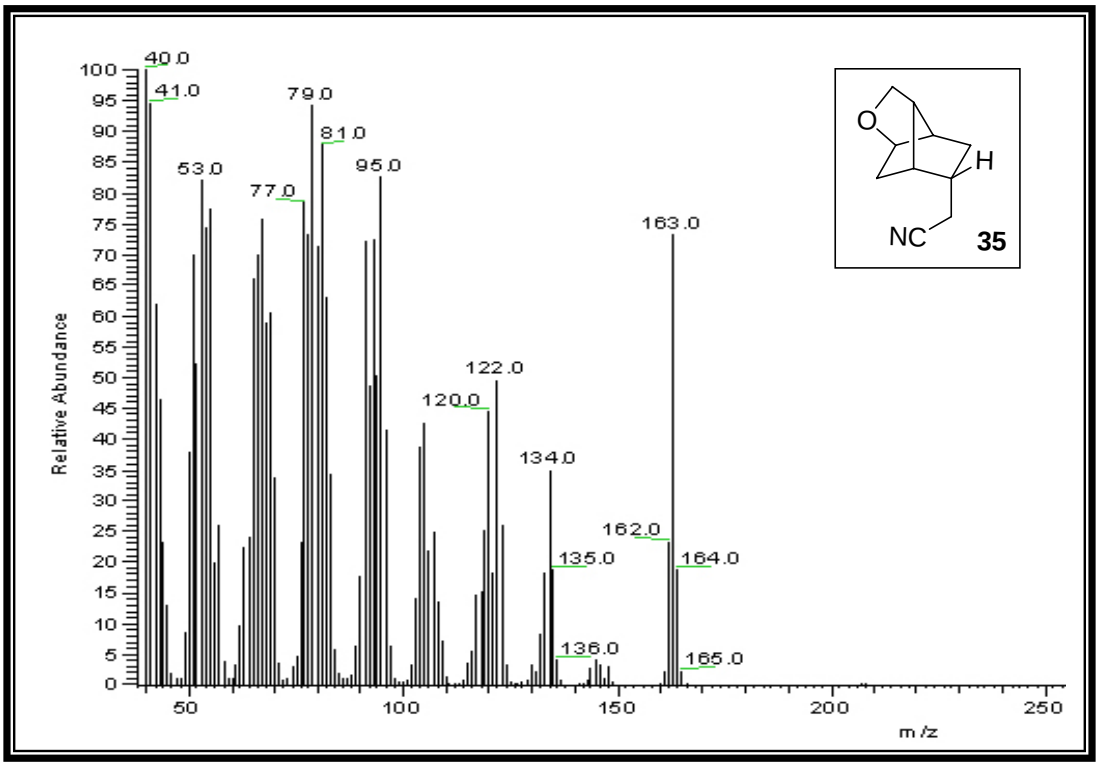

Figure A9. Mass spectrum of tricyclic ether **35**

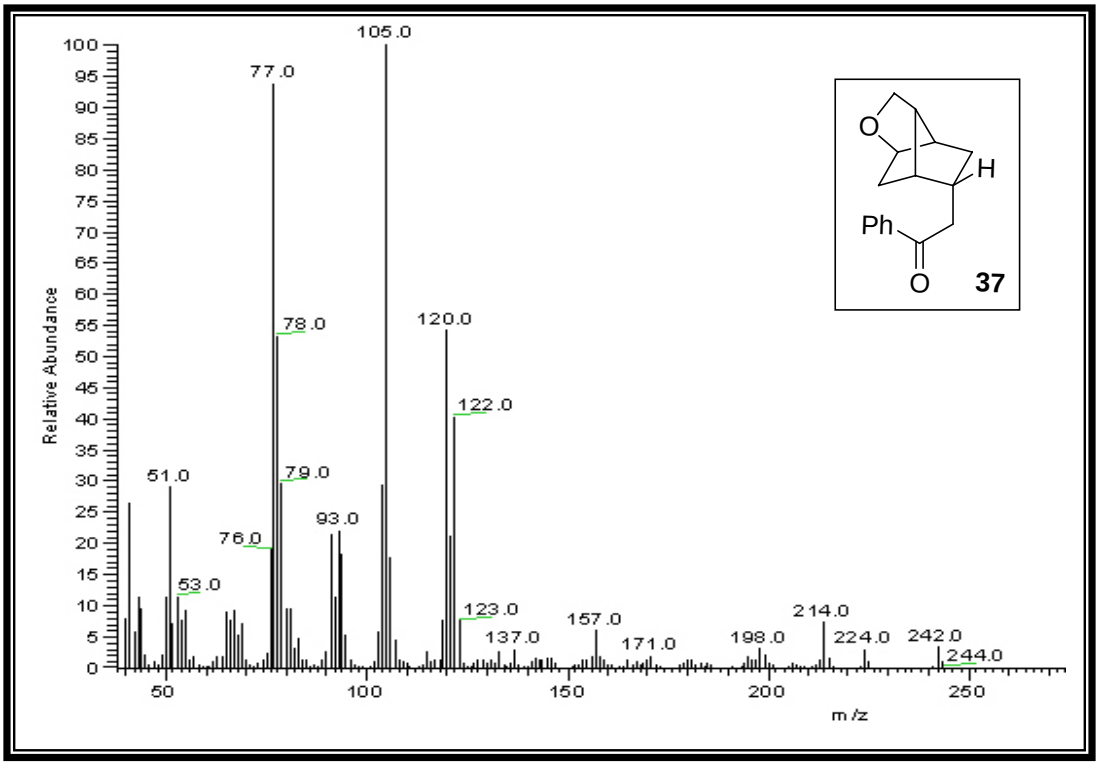

Figure A10. Mass spectrum of tricyclic ether **37**

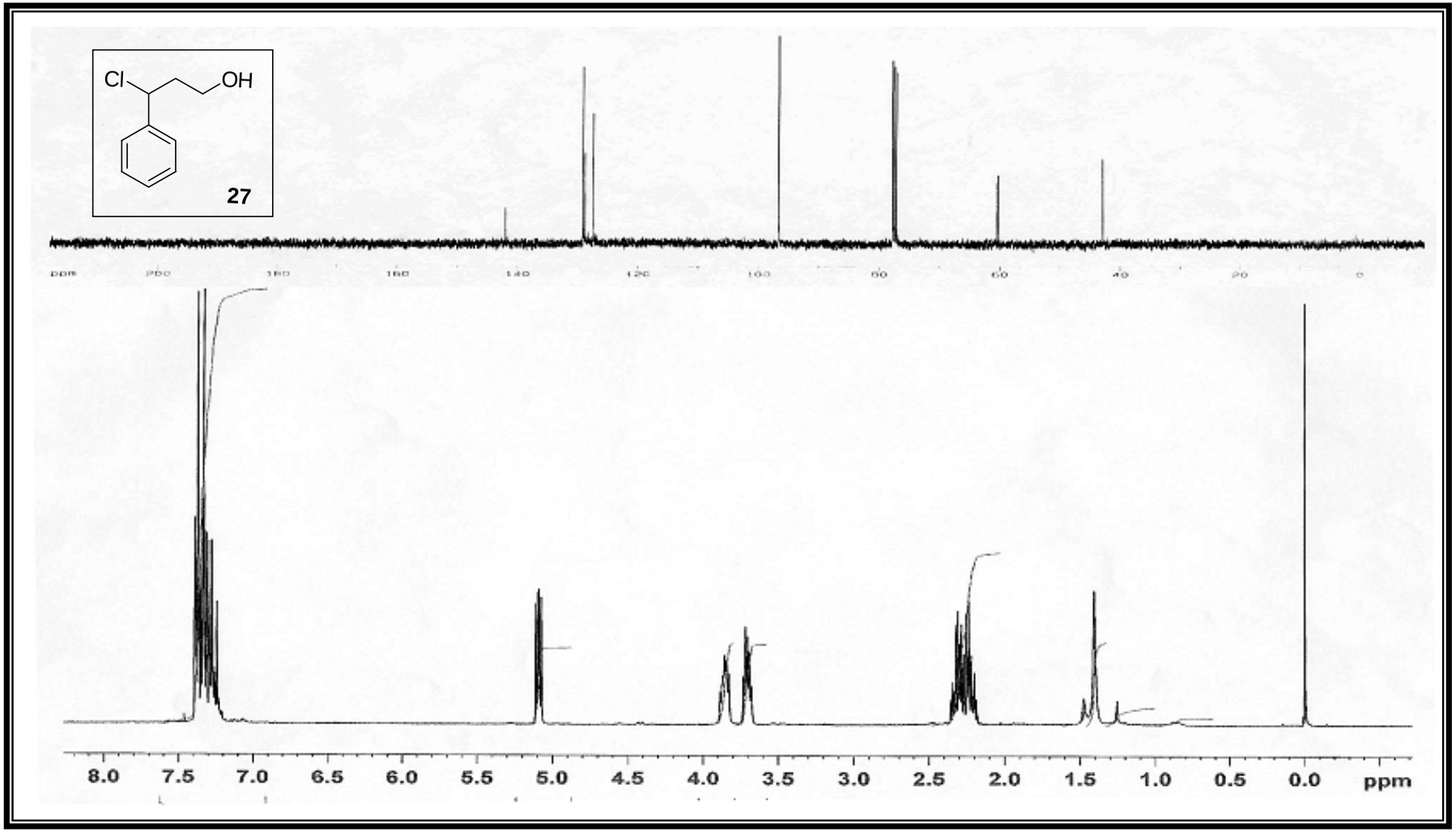

Figure A11. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **27**

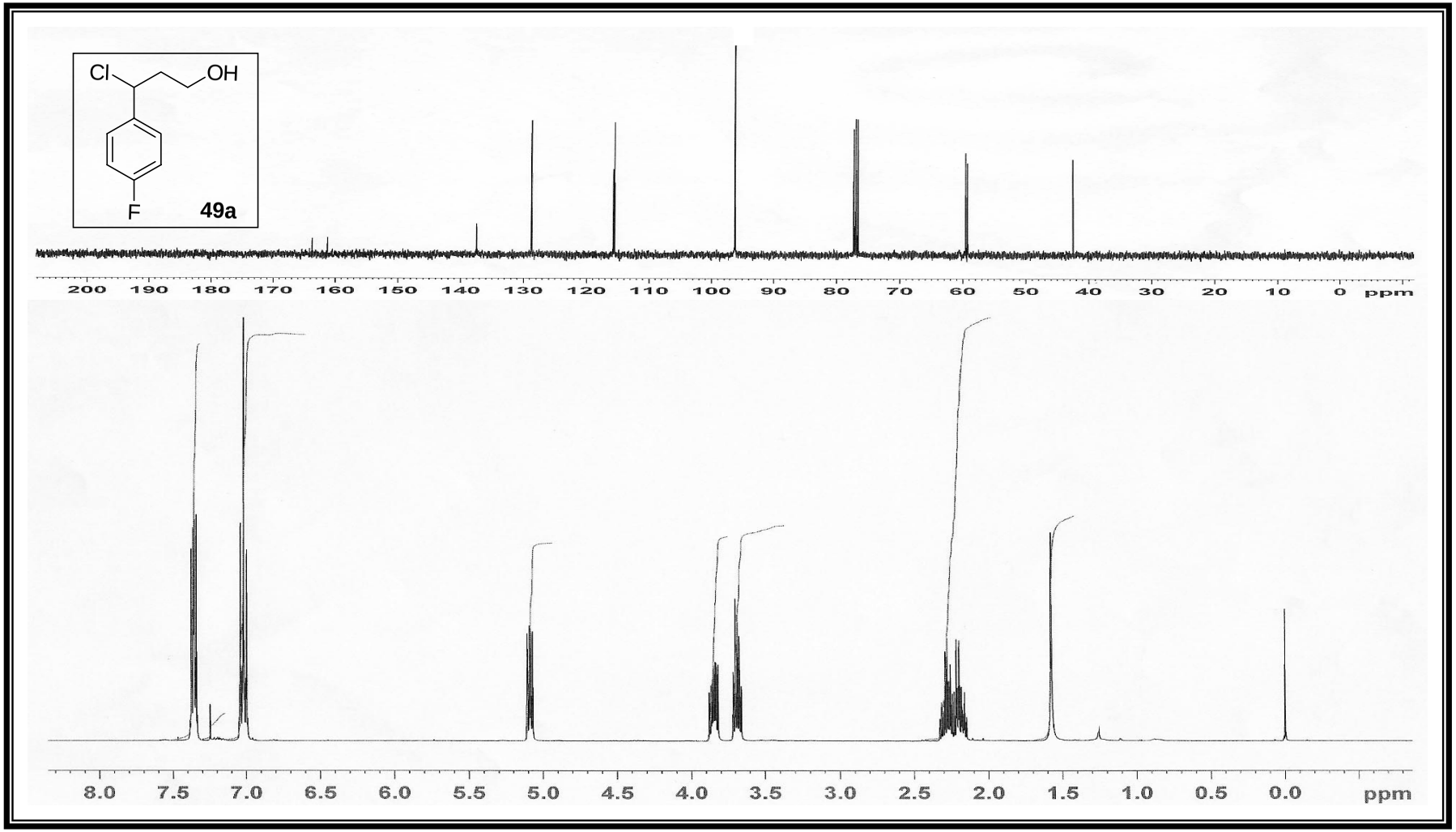

Figure A12. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49a**

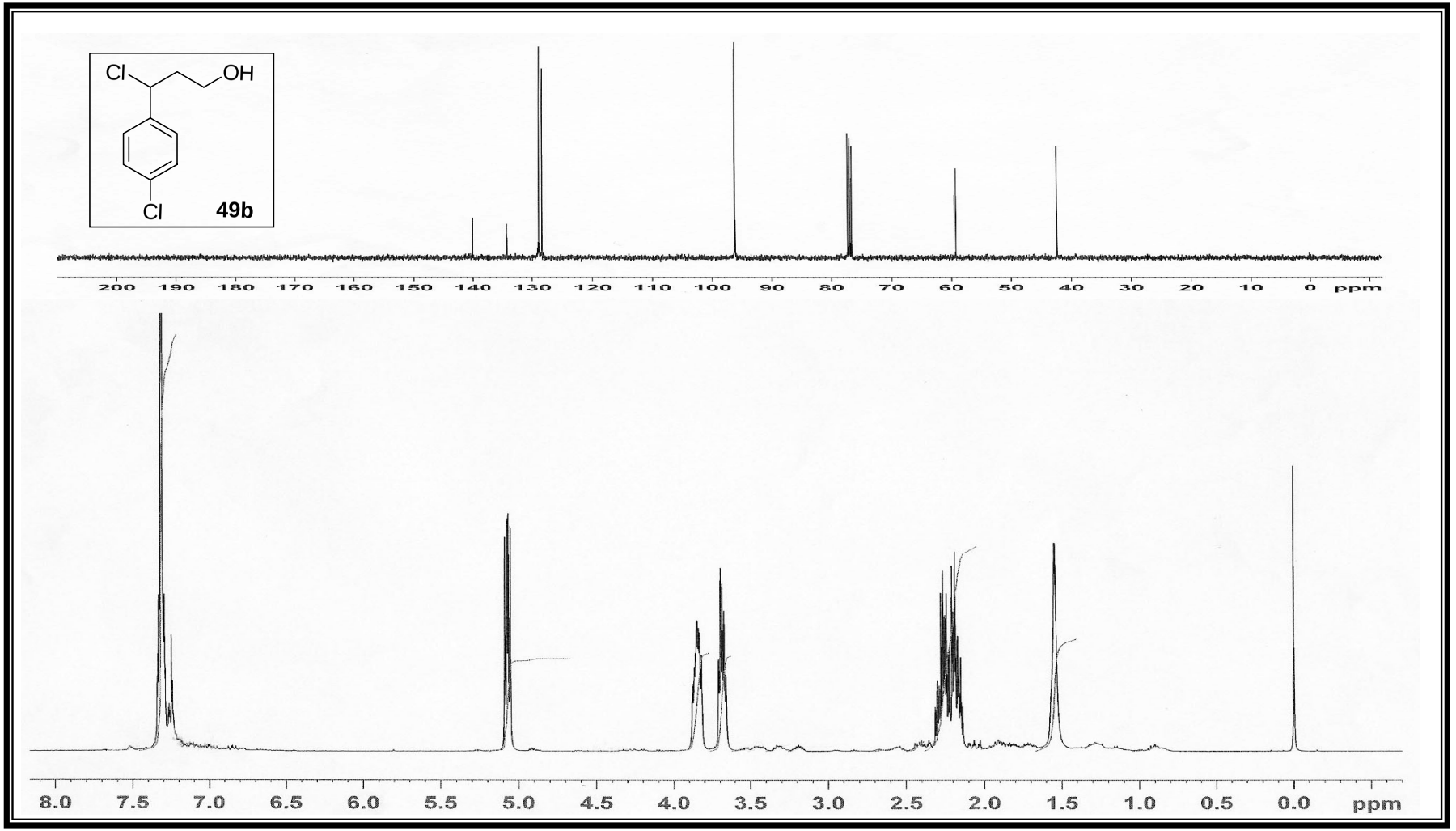

Figure A13. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49b**

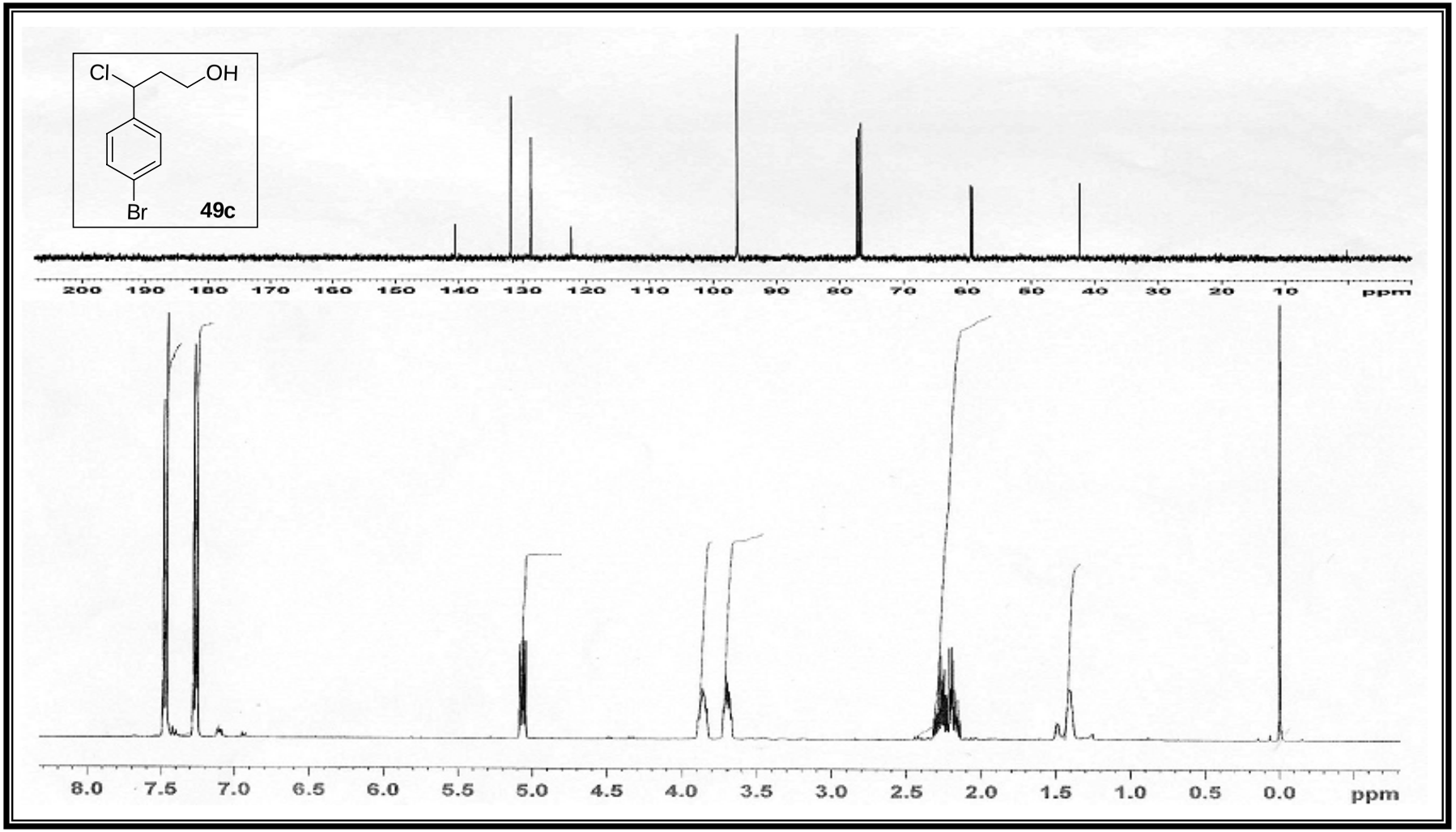

Figure A14. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49c**

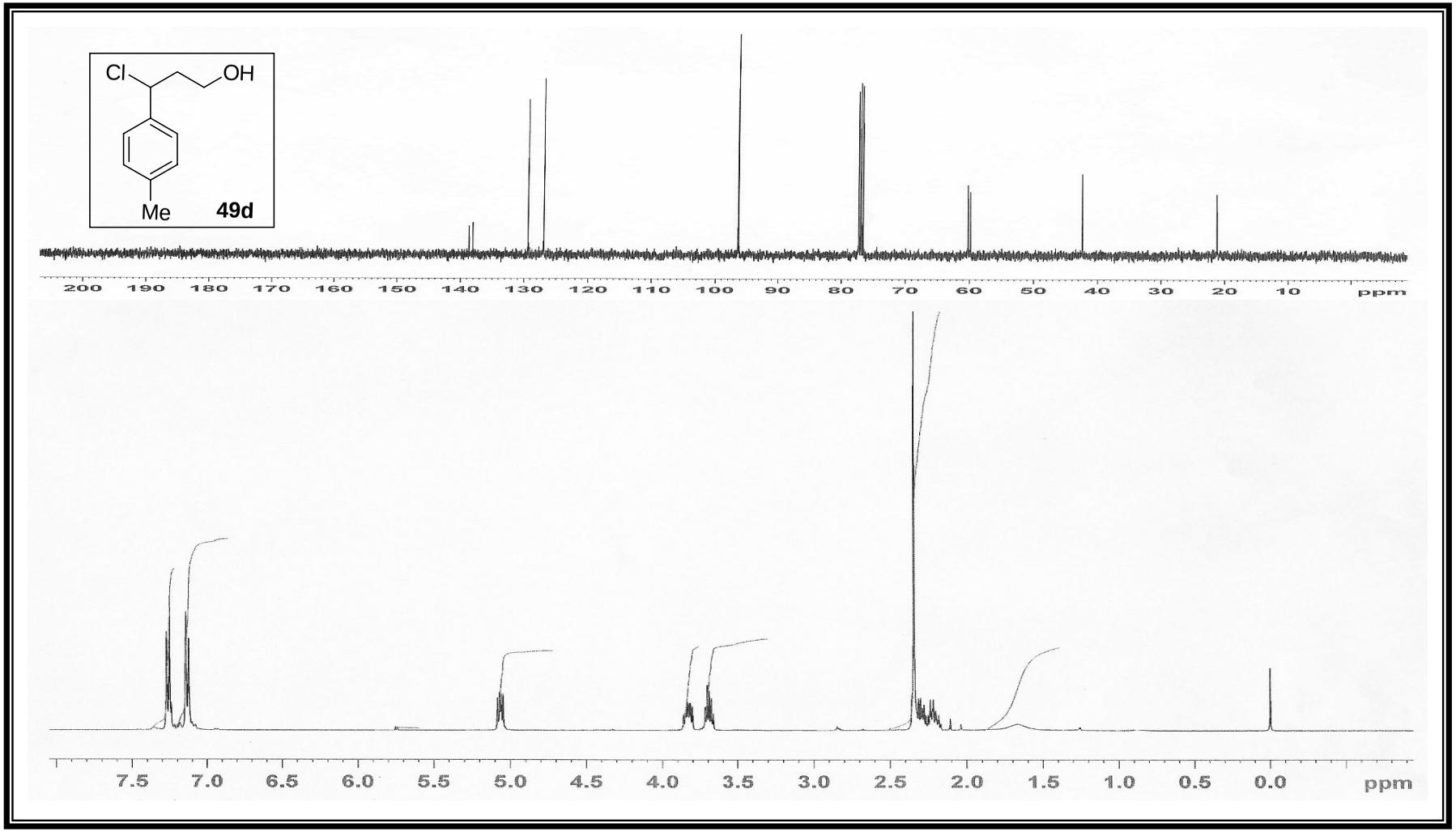

Figure A15. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49d**

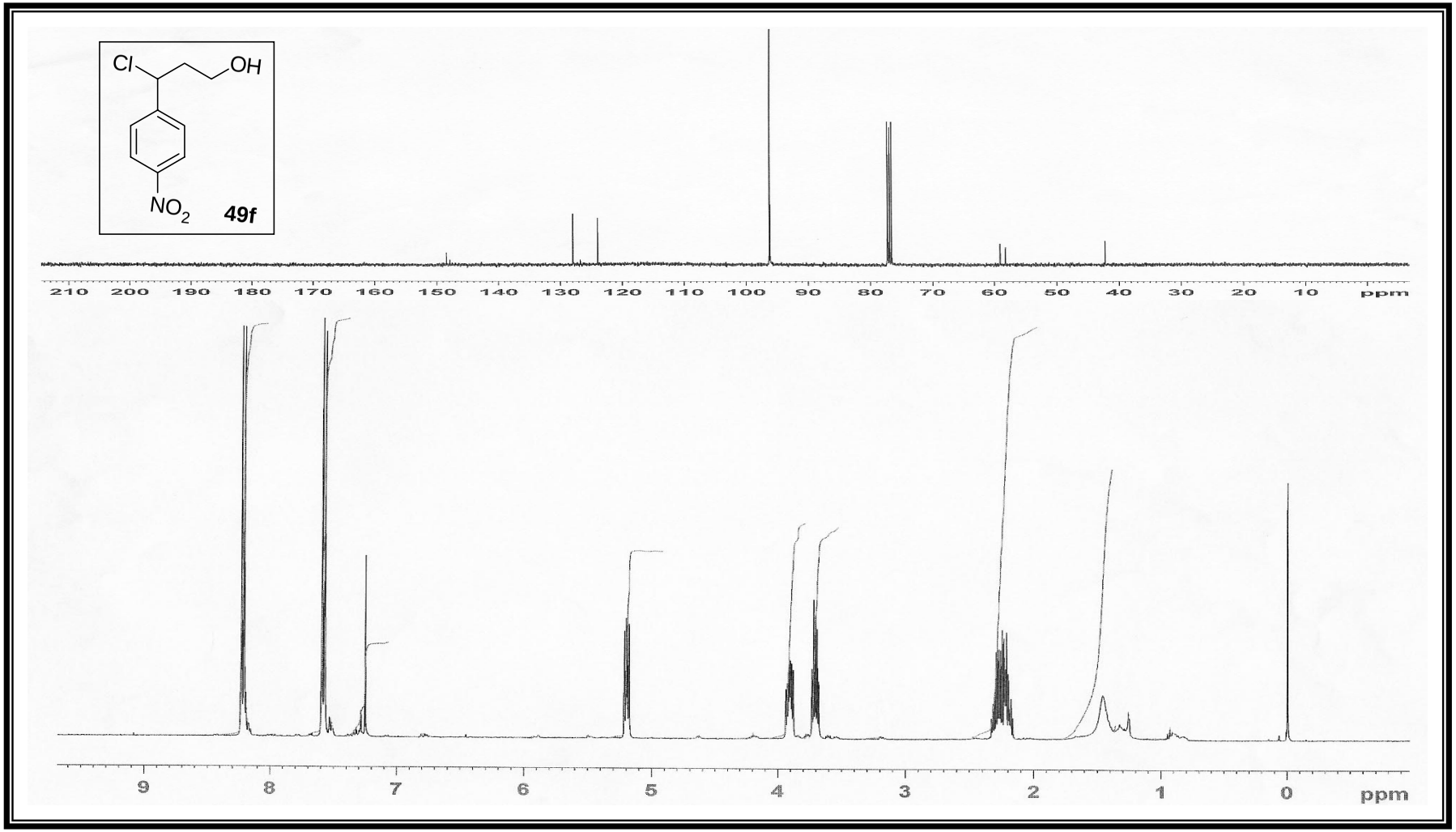

Figure A16. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49f**

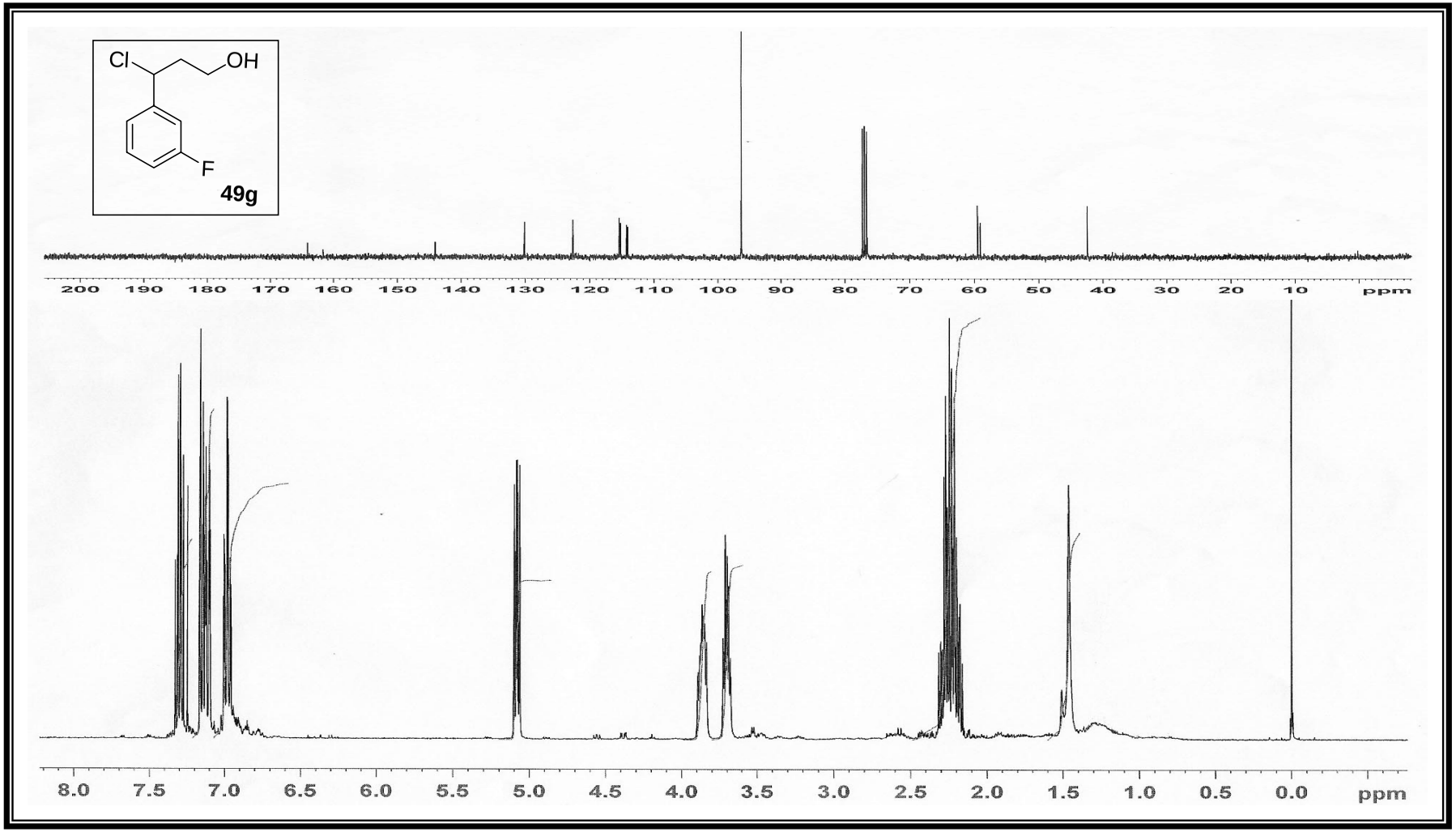

Figure A17. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra compound **49g**

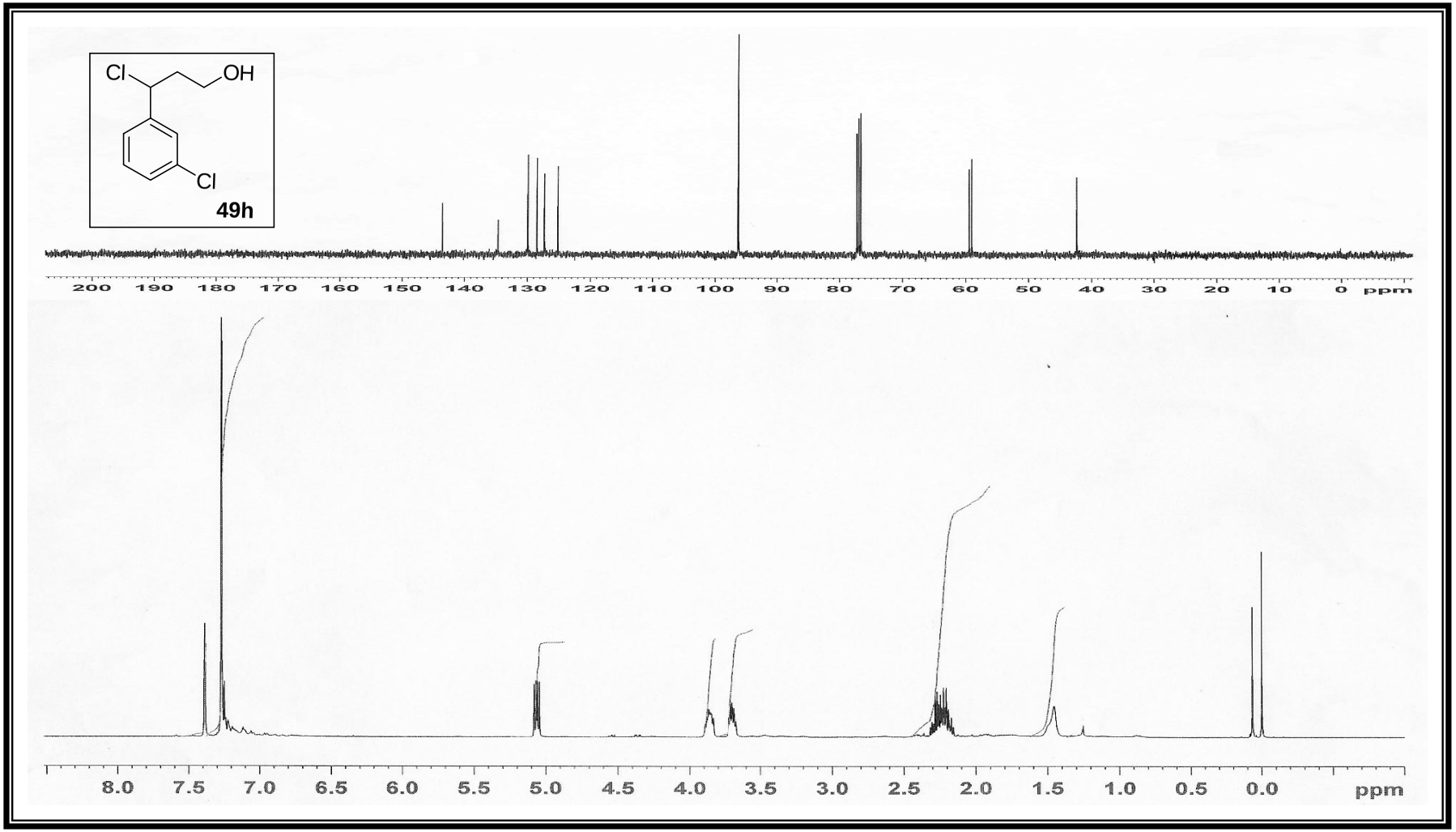

Figure A18. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49h**

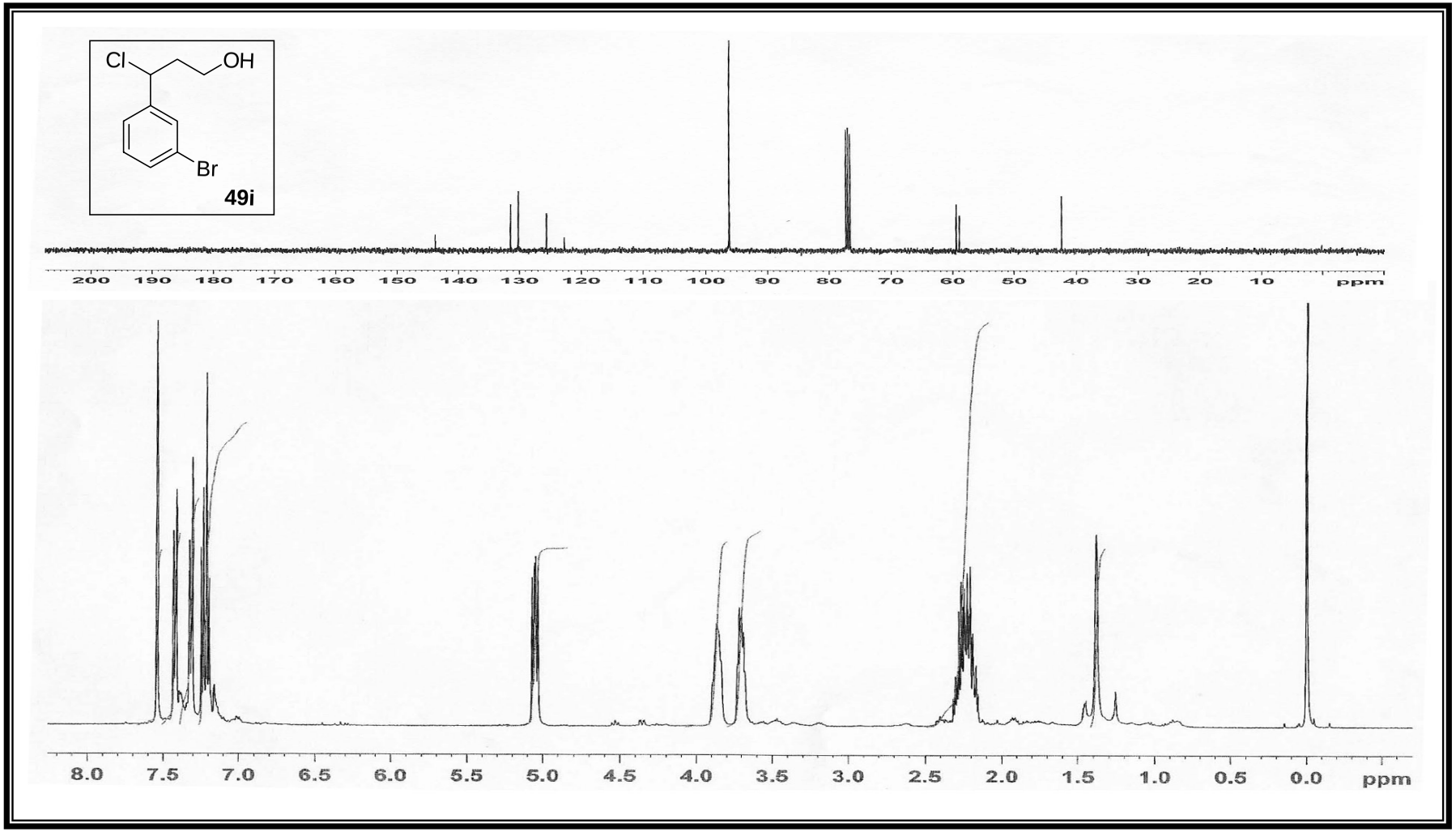

Figure A19. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49i**

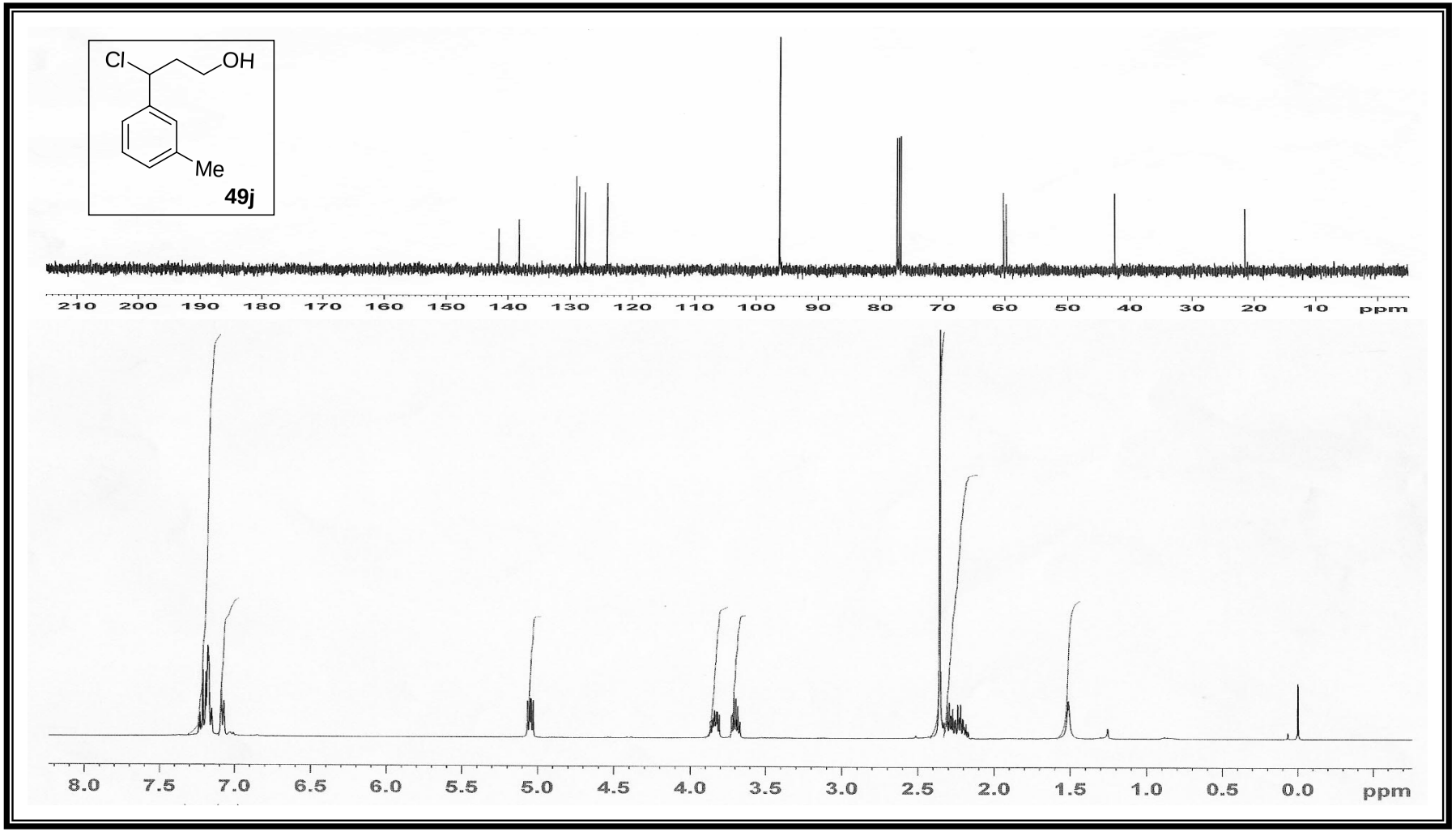

Figure A20. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra compound **49j**

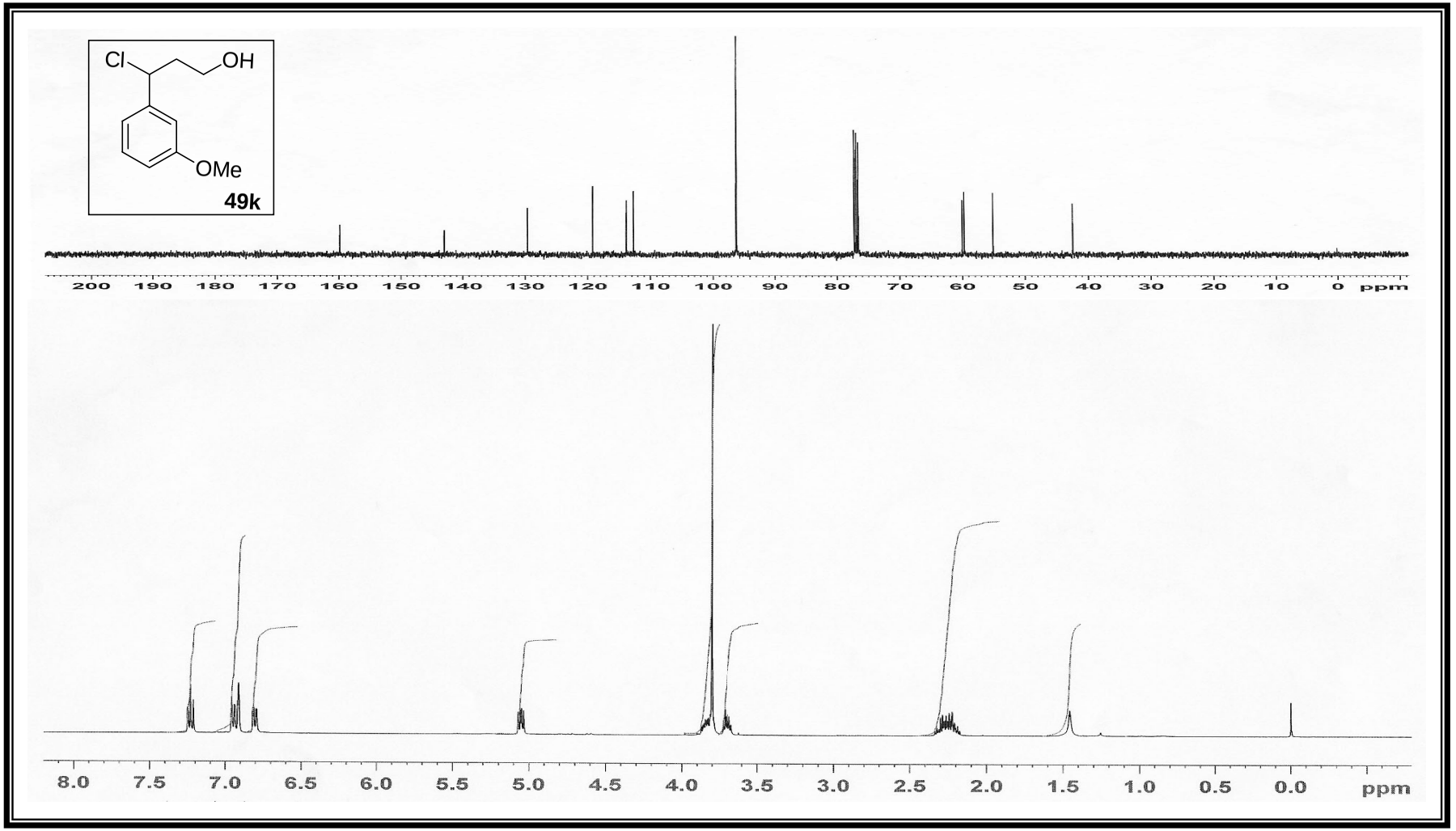

Figure A21. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49k**

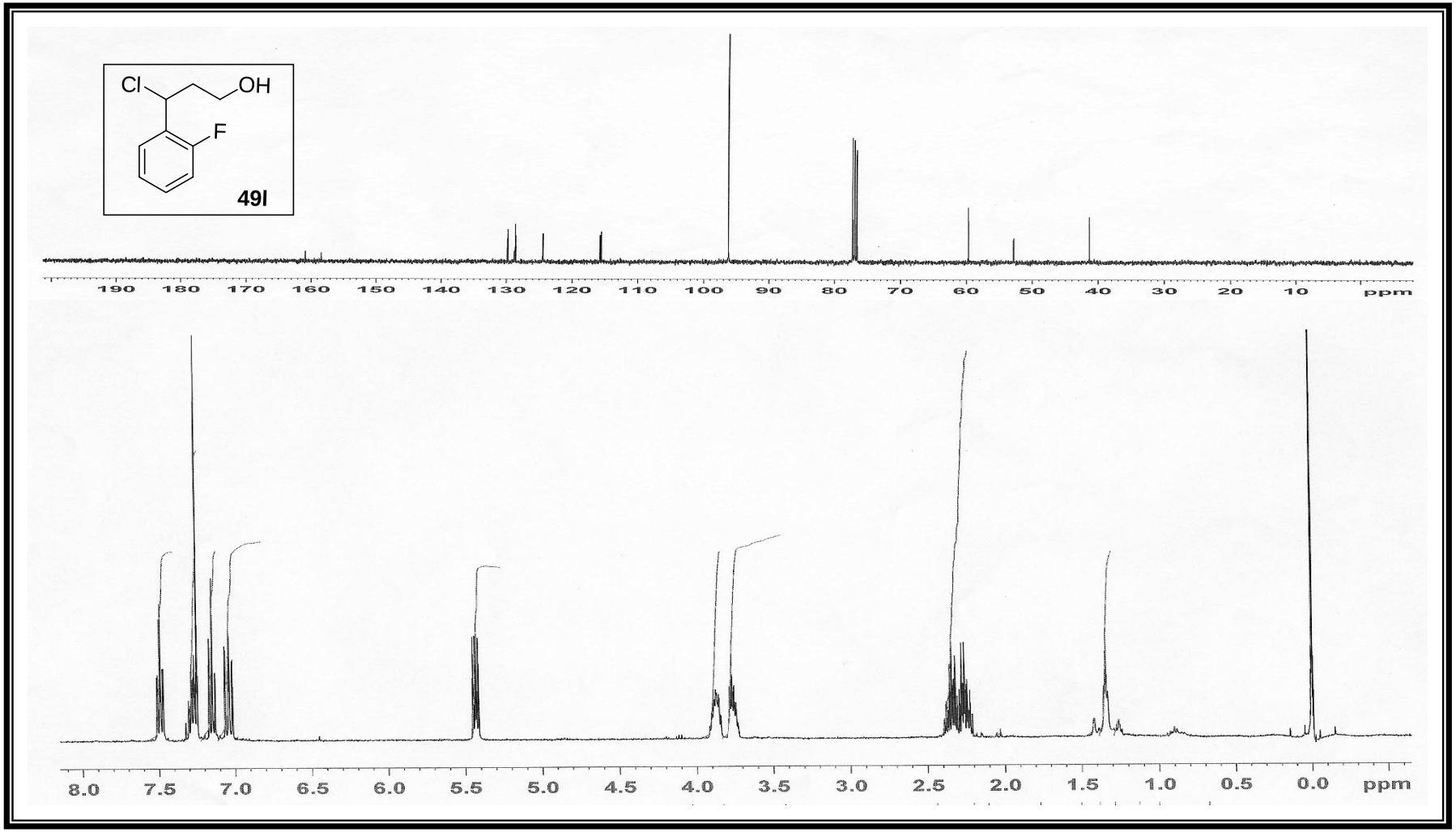

Figure A22. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49l**

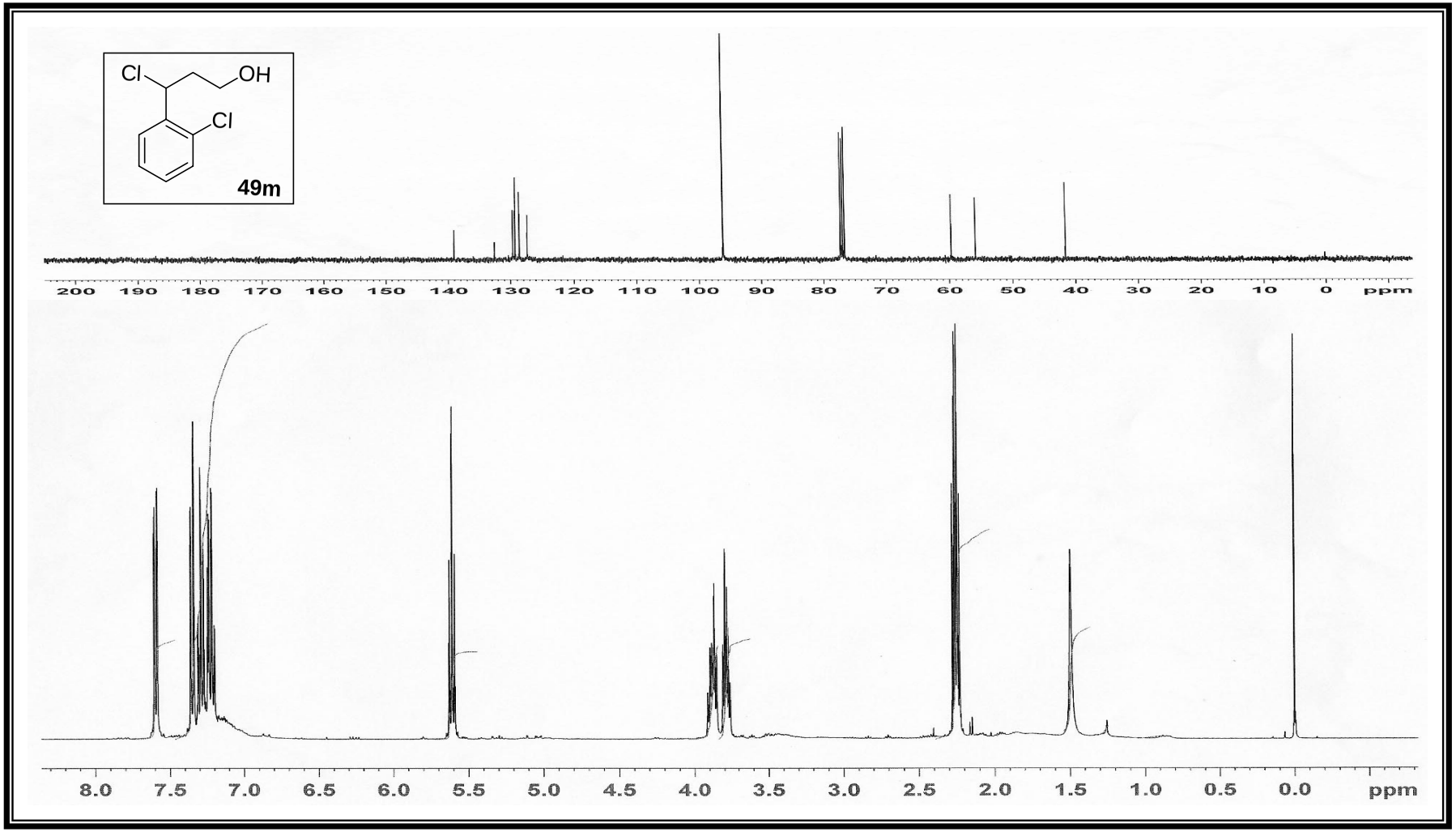

Figure A23. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49m**

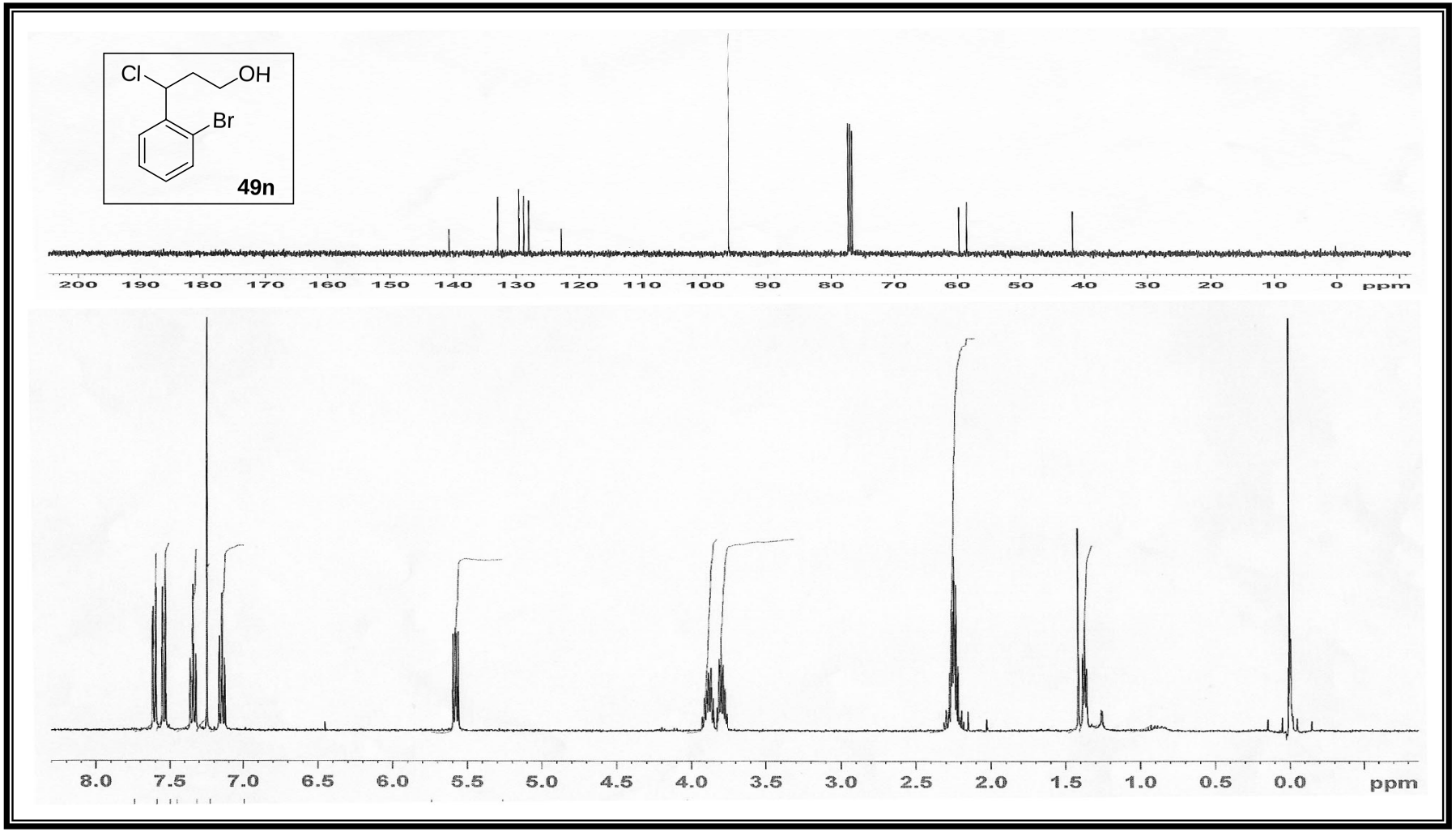

Figure A24. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49n**

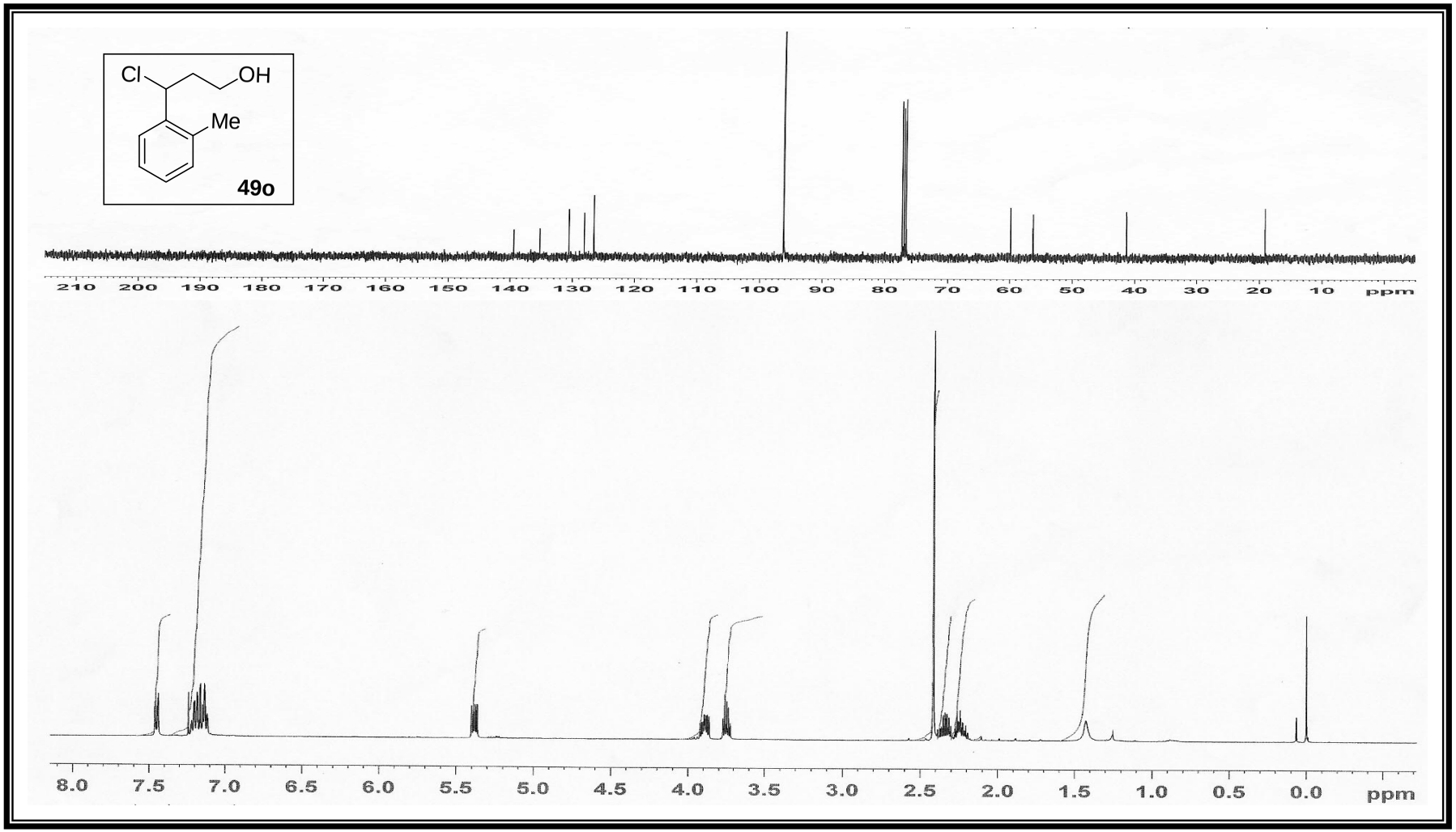

Figure A25. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **49o**

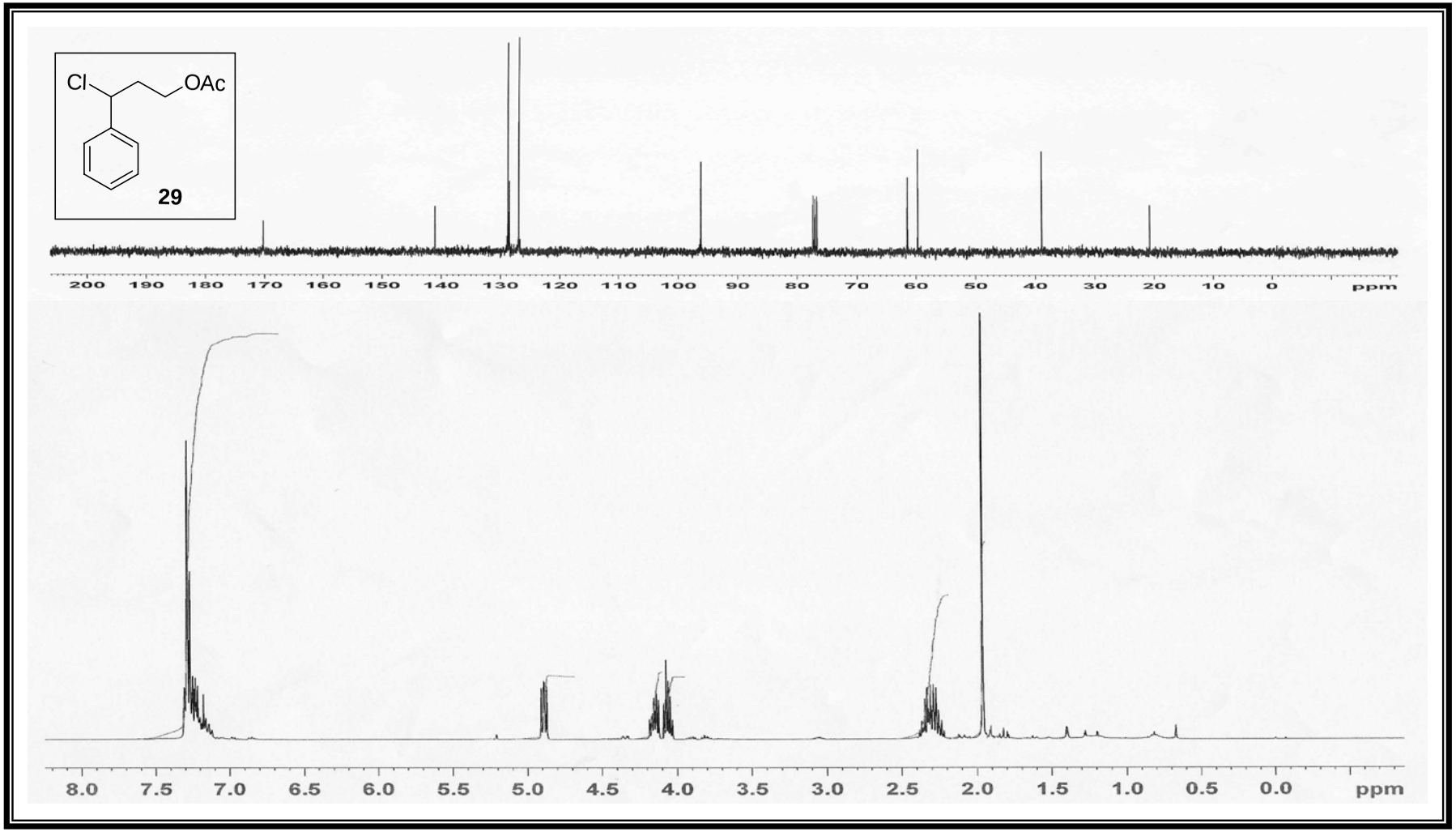

Figure A26. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **29**

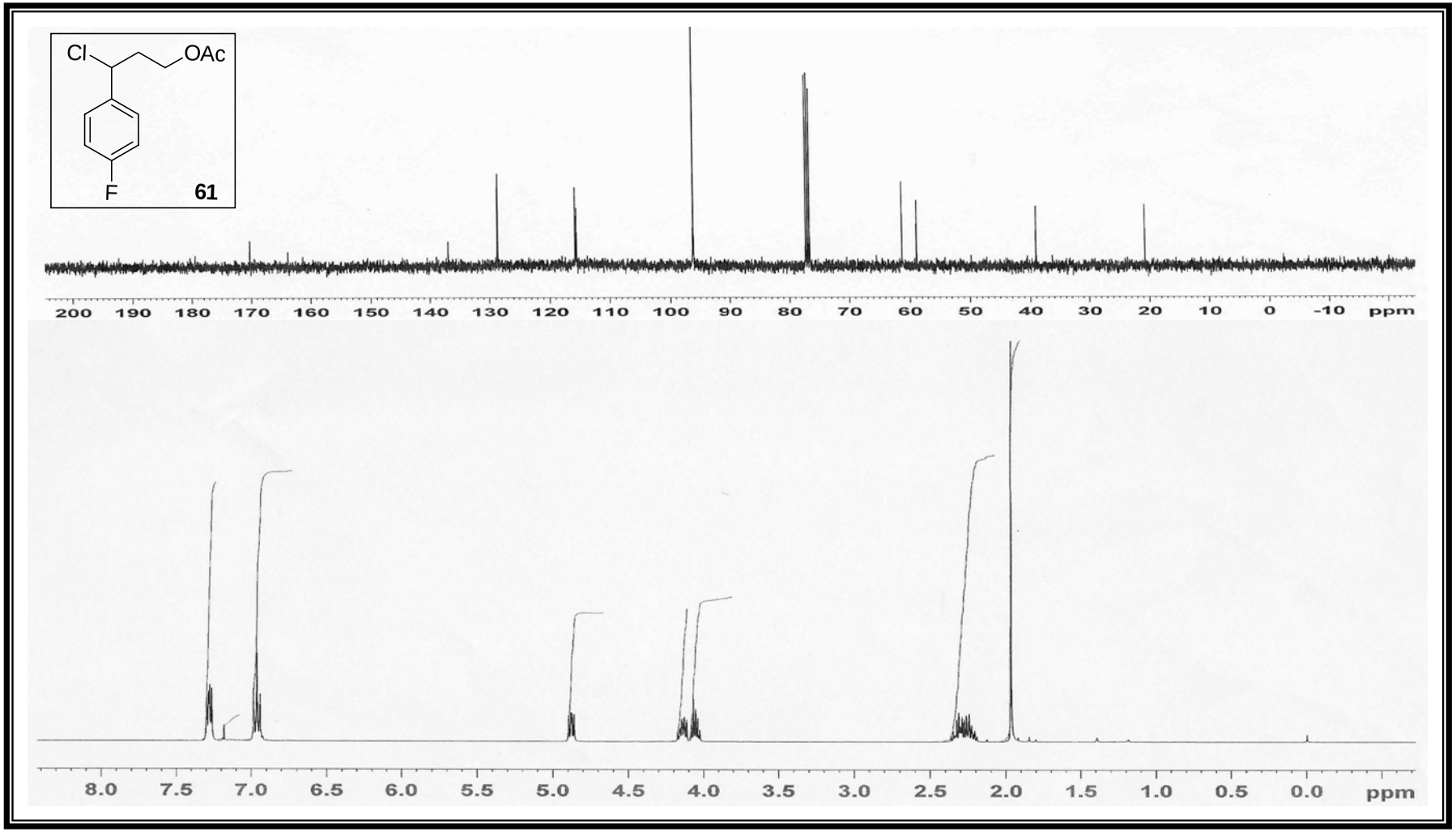

Figure A27. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **61**

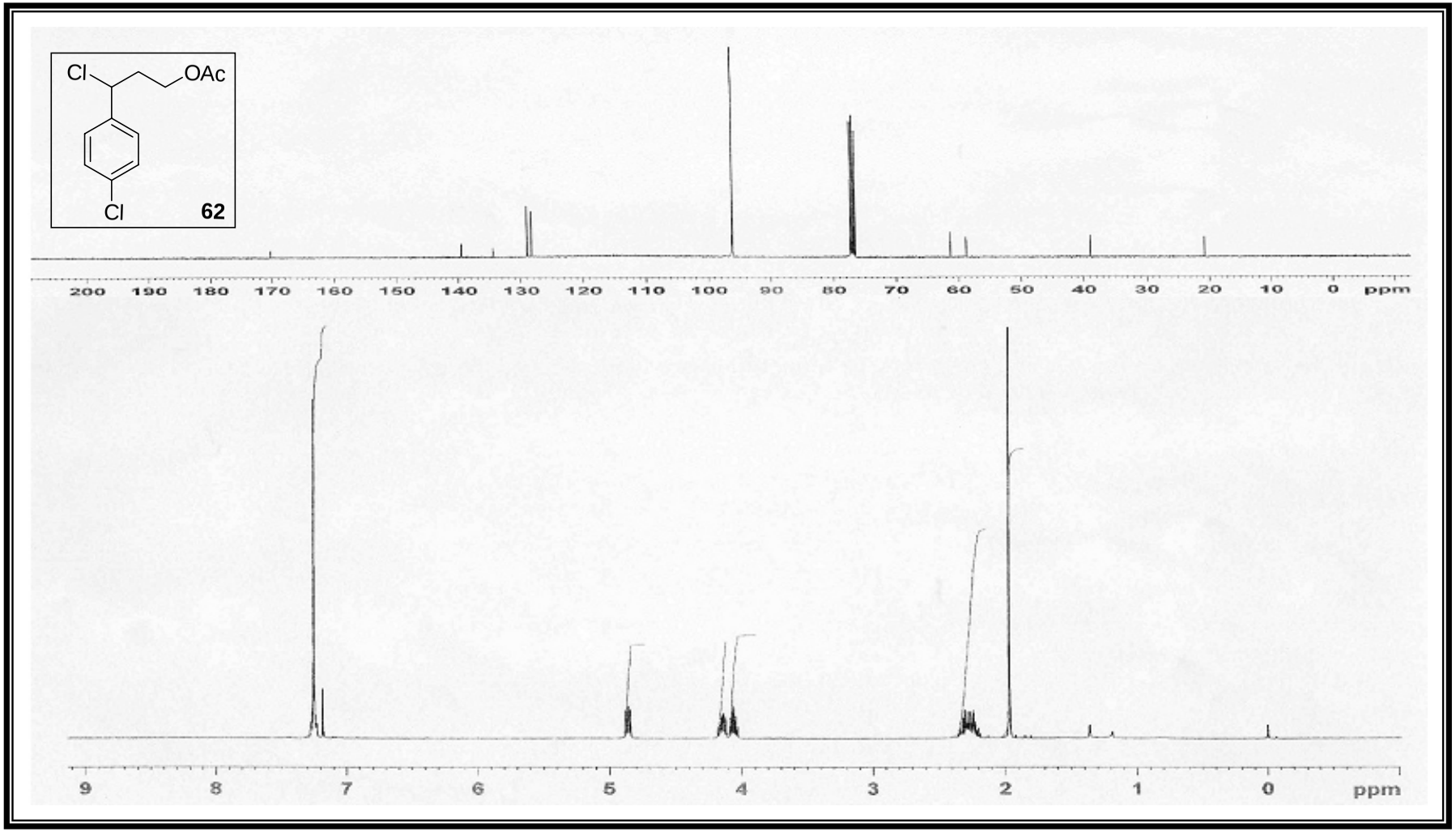

Figure A28. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **62**

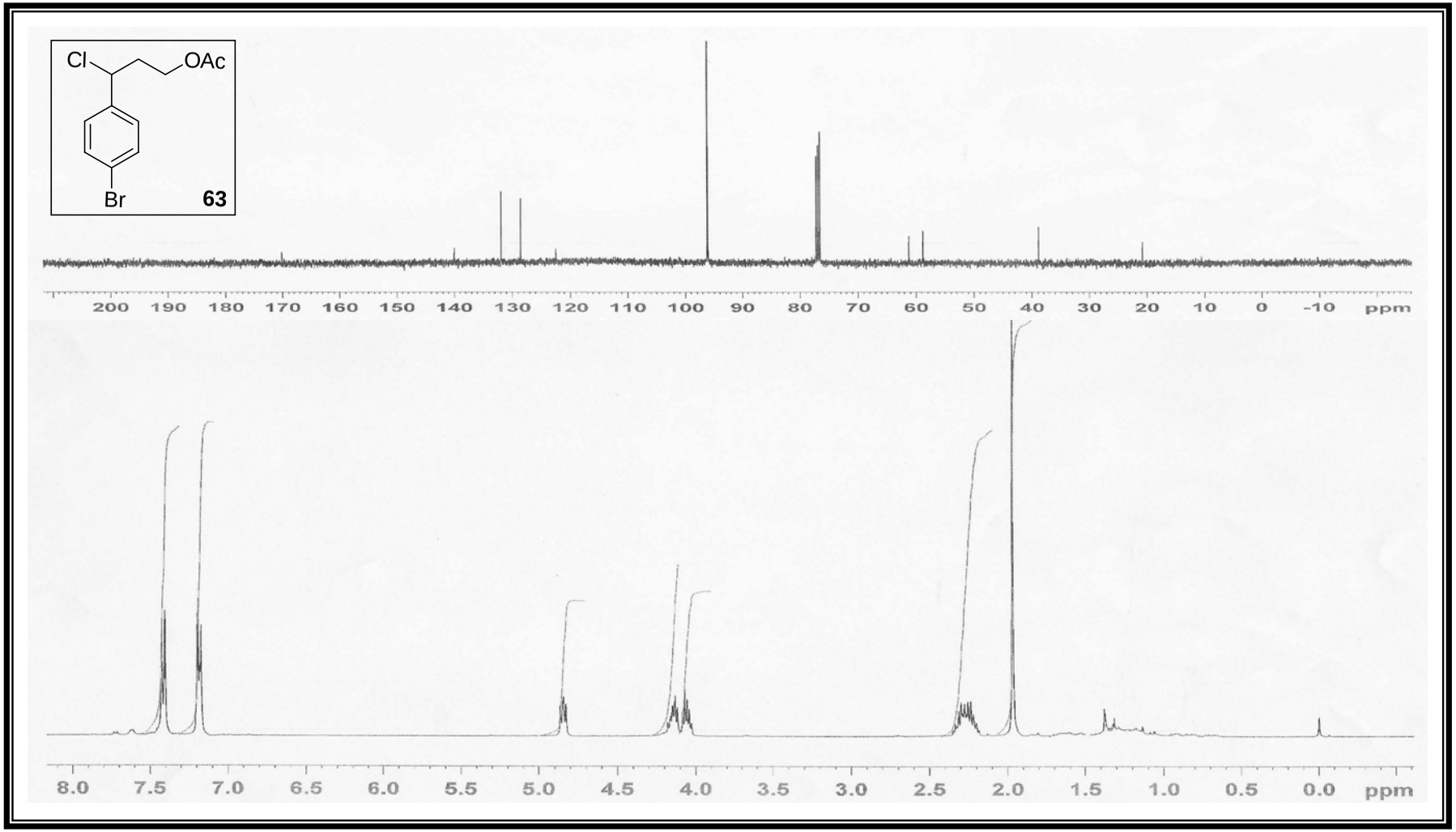

Figure A29. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **63**

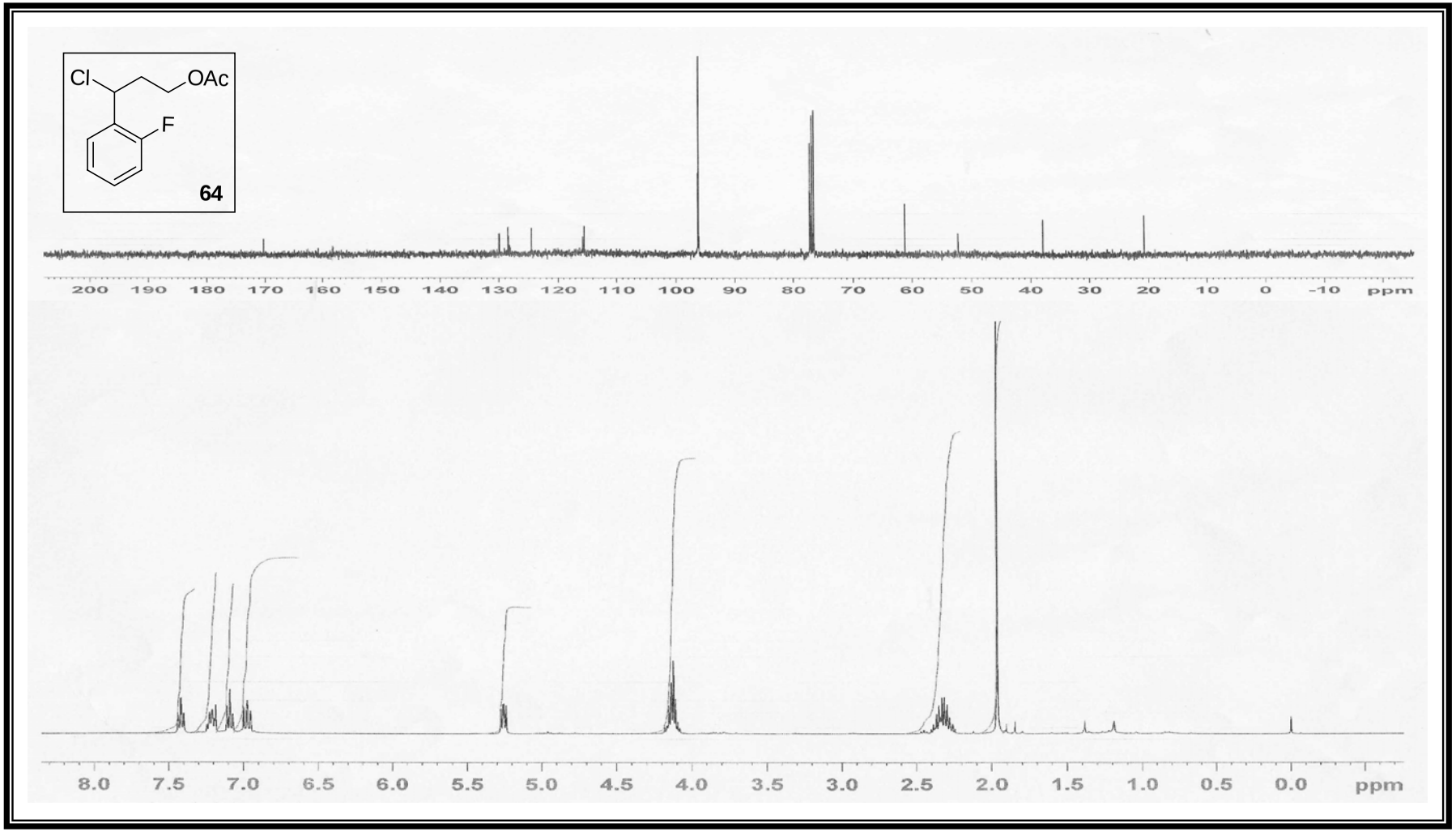

Figure A30. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **64**

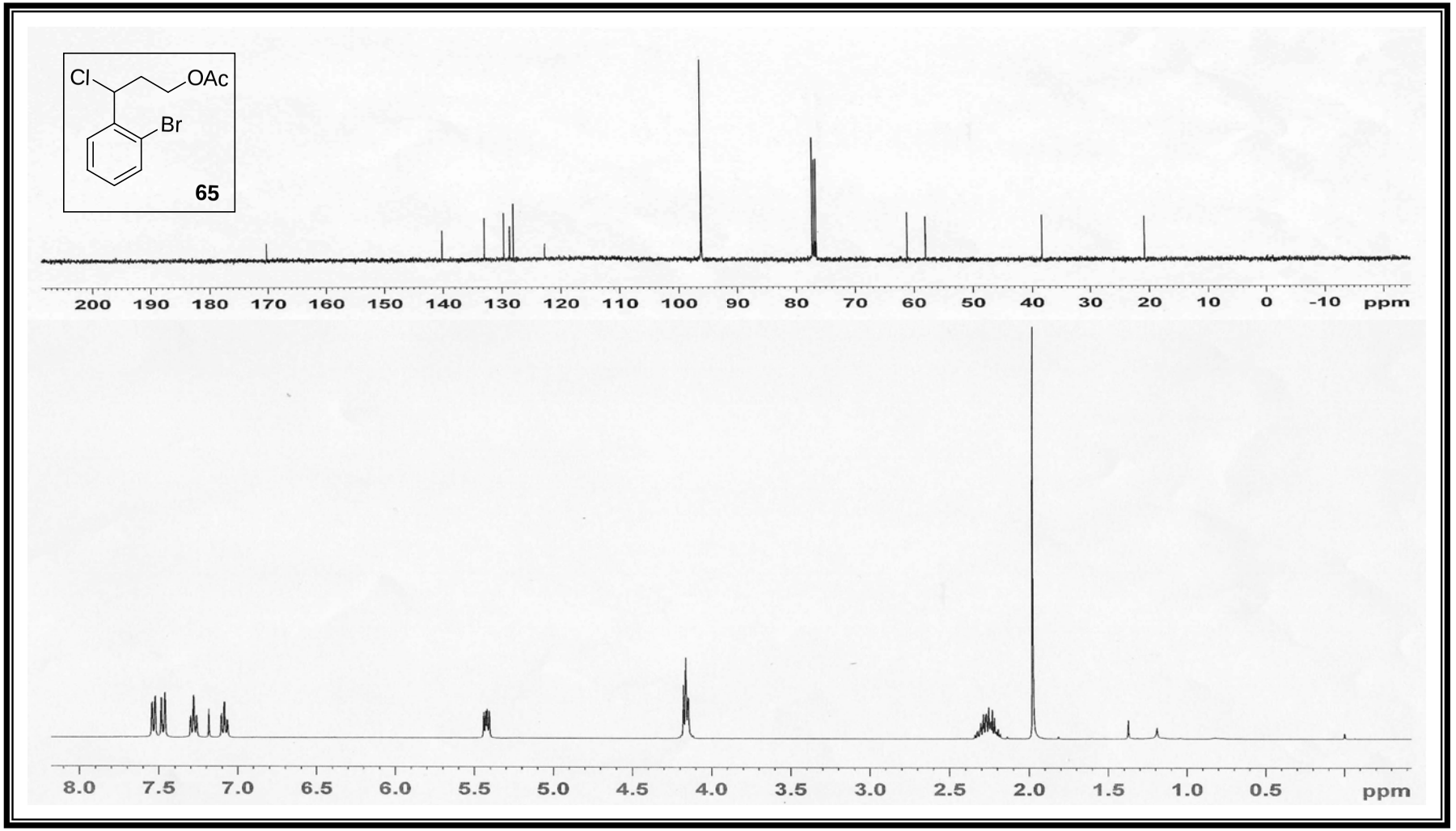

Figure A31. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **65**

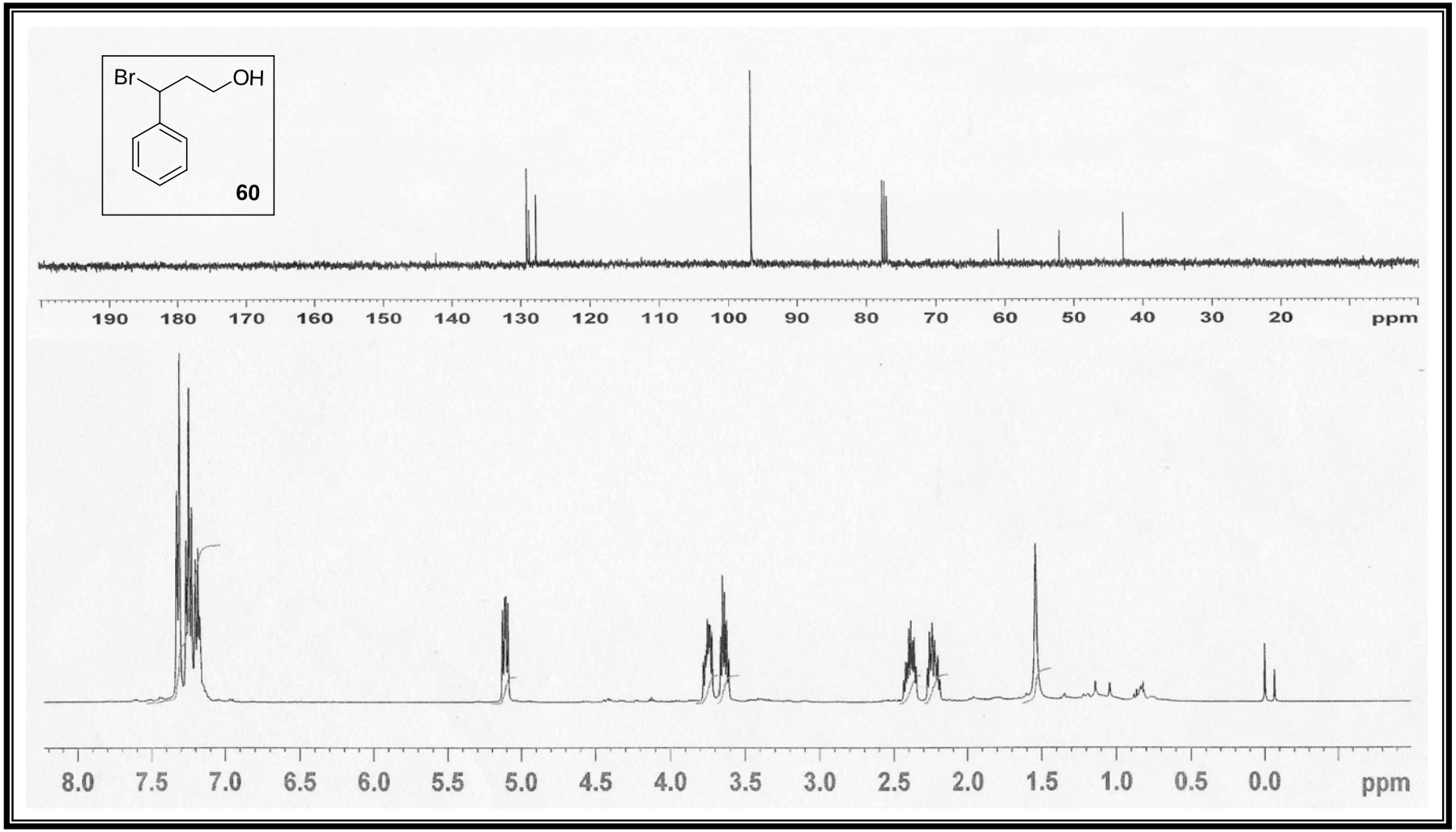

Figure A32. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **60**

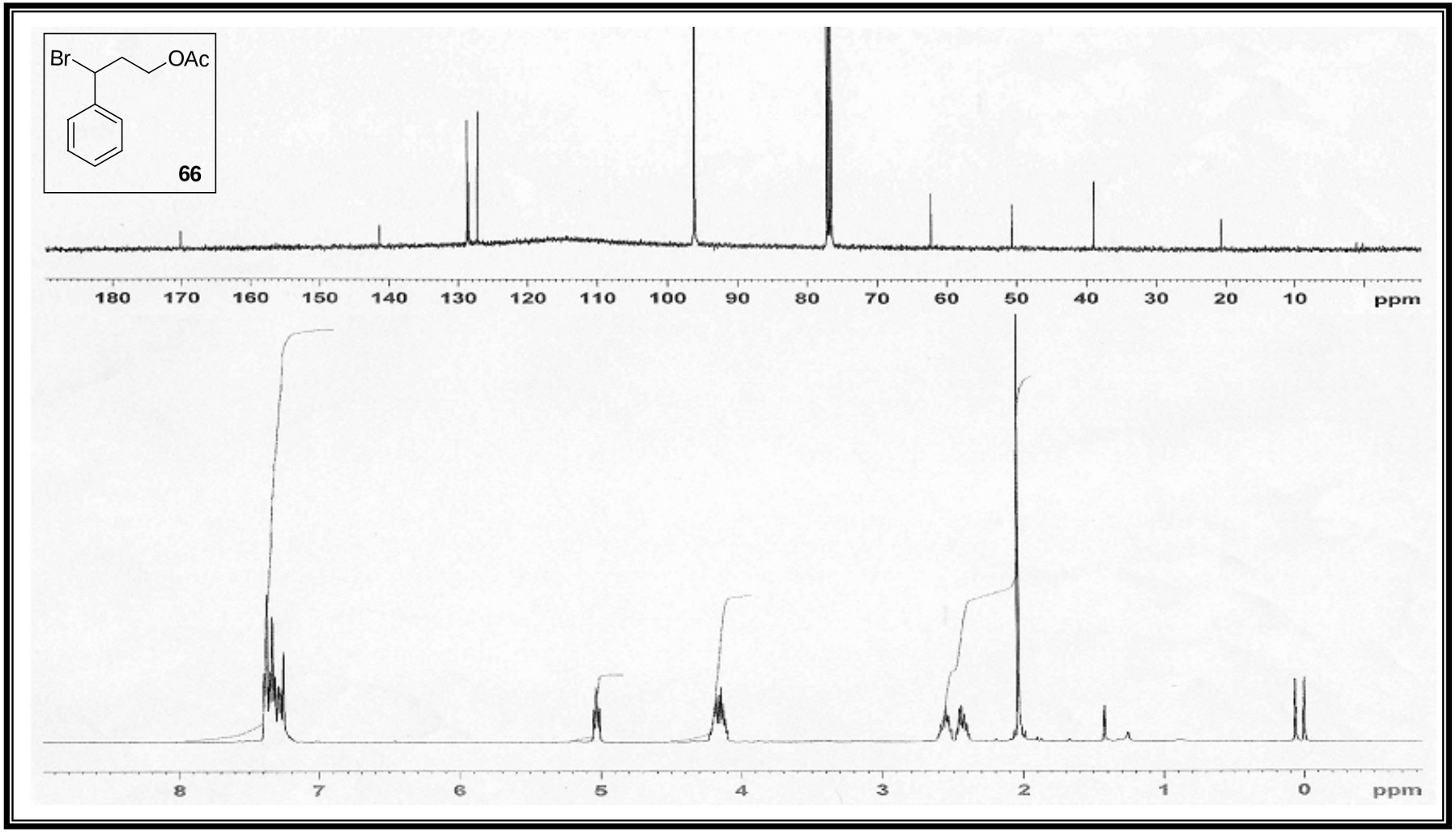

Figure A33. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **66**

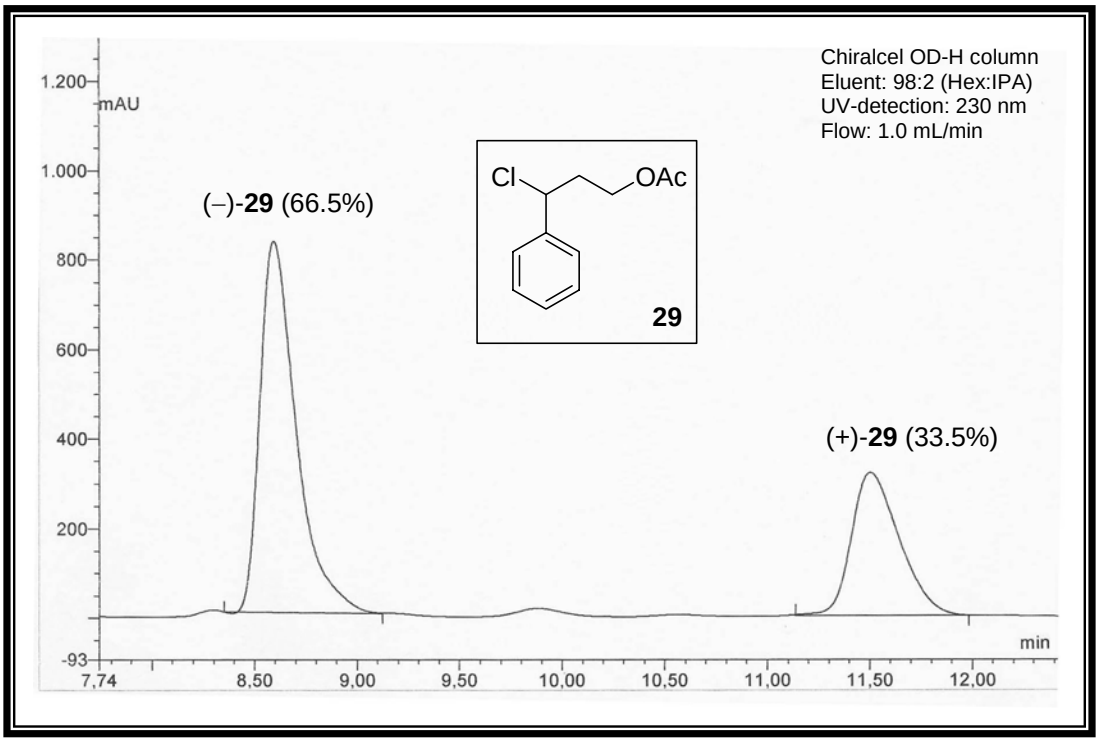

Figure A34. HPLC chromatogram of ester **29** (33% ee)

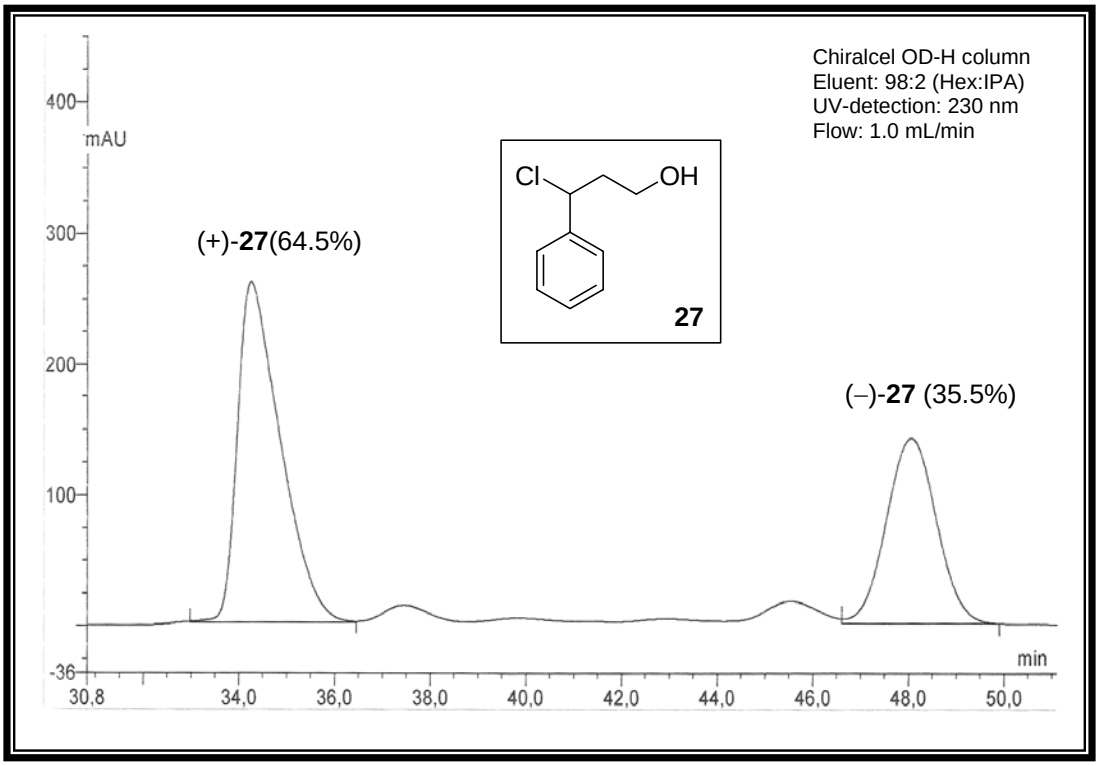

Figure A35. HPLC chromatogram of alcohol **27** (29% ee)

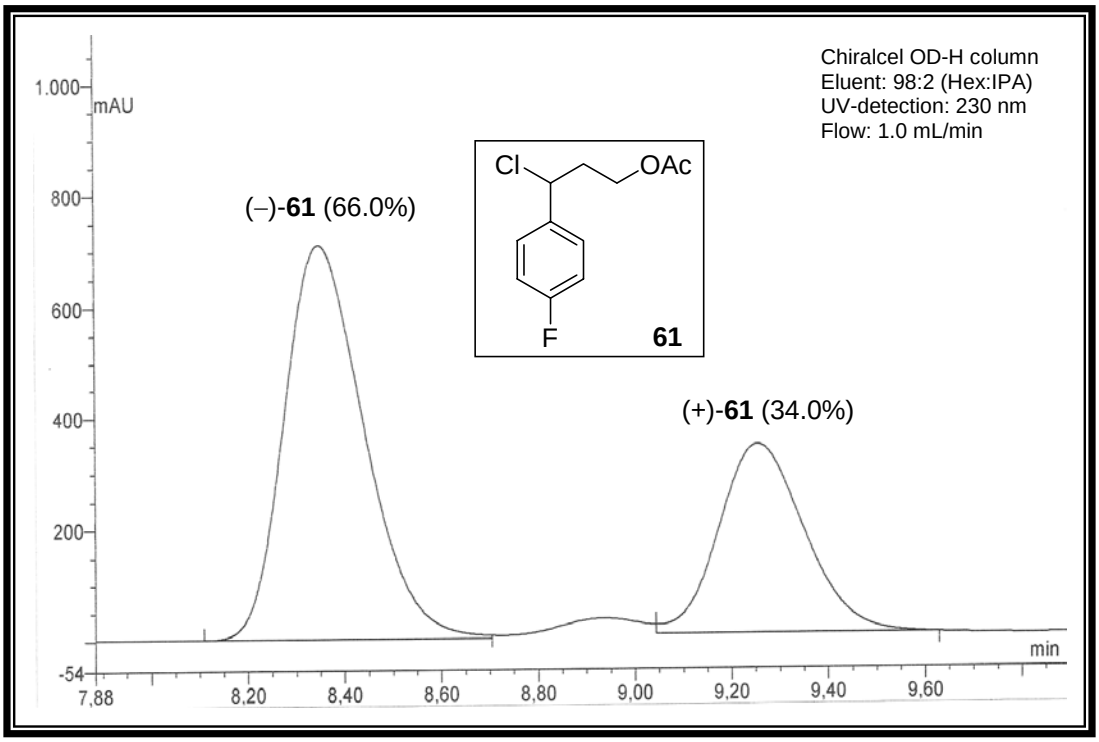

Figure A36. HPLC chromatogram of ester **61** (32% ee)

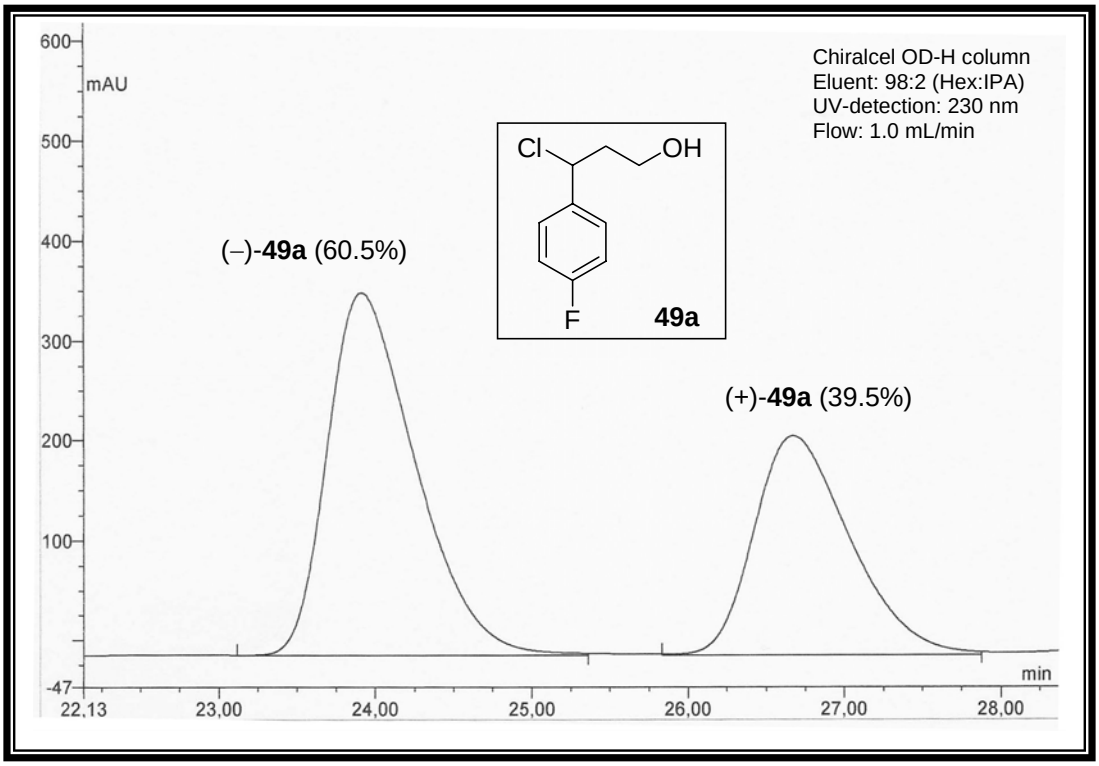

Figure A37. HPLC chromatogram of alcohol **49a** (21% ee)

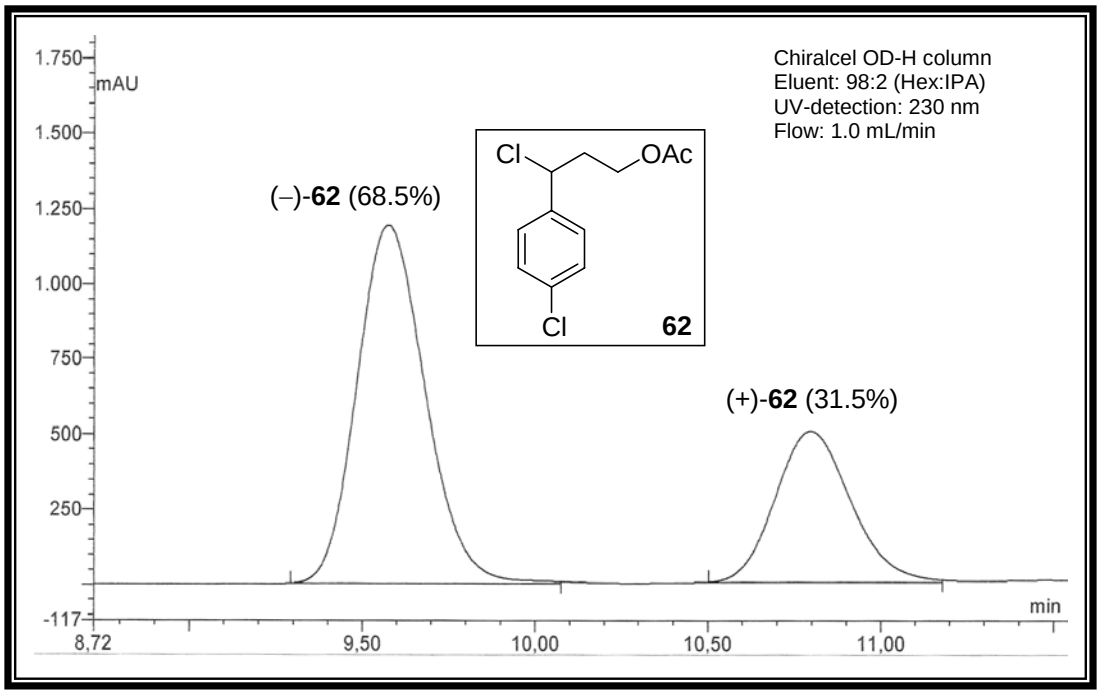

Figure A38. HPLC chromatogram of ester **62** (37% ee)

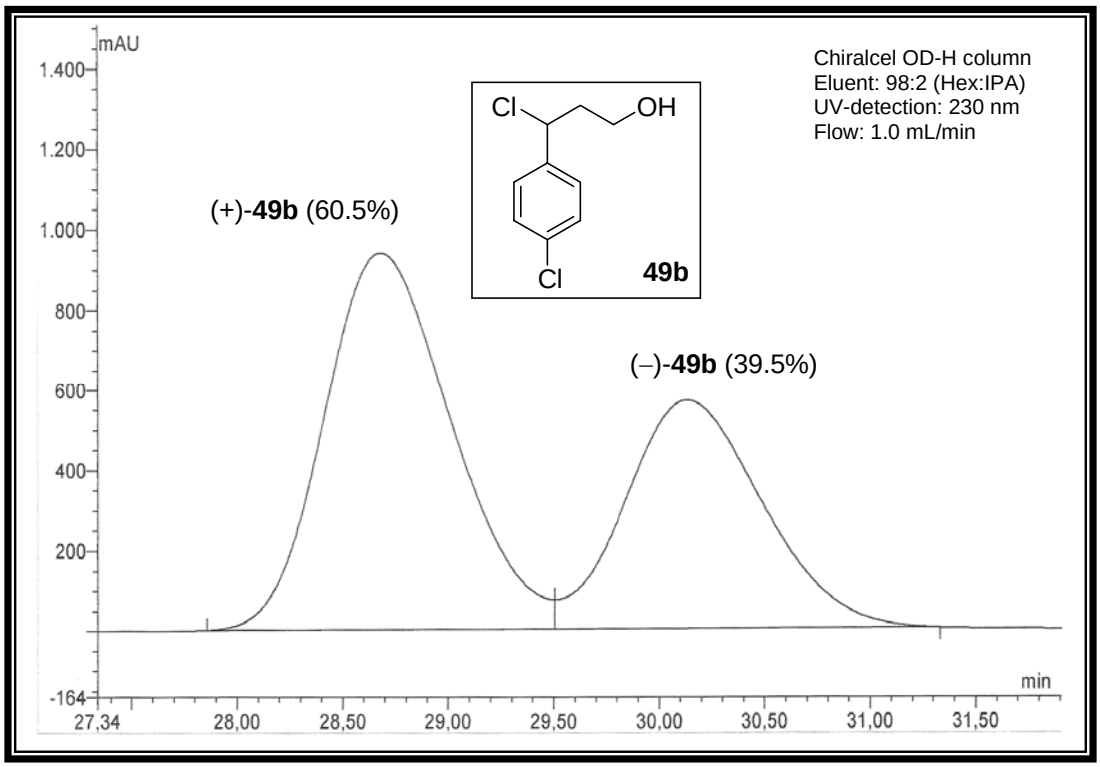

Figure A39. HPLC chromatogram of alcohol **49b** (21% ee)

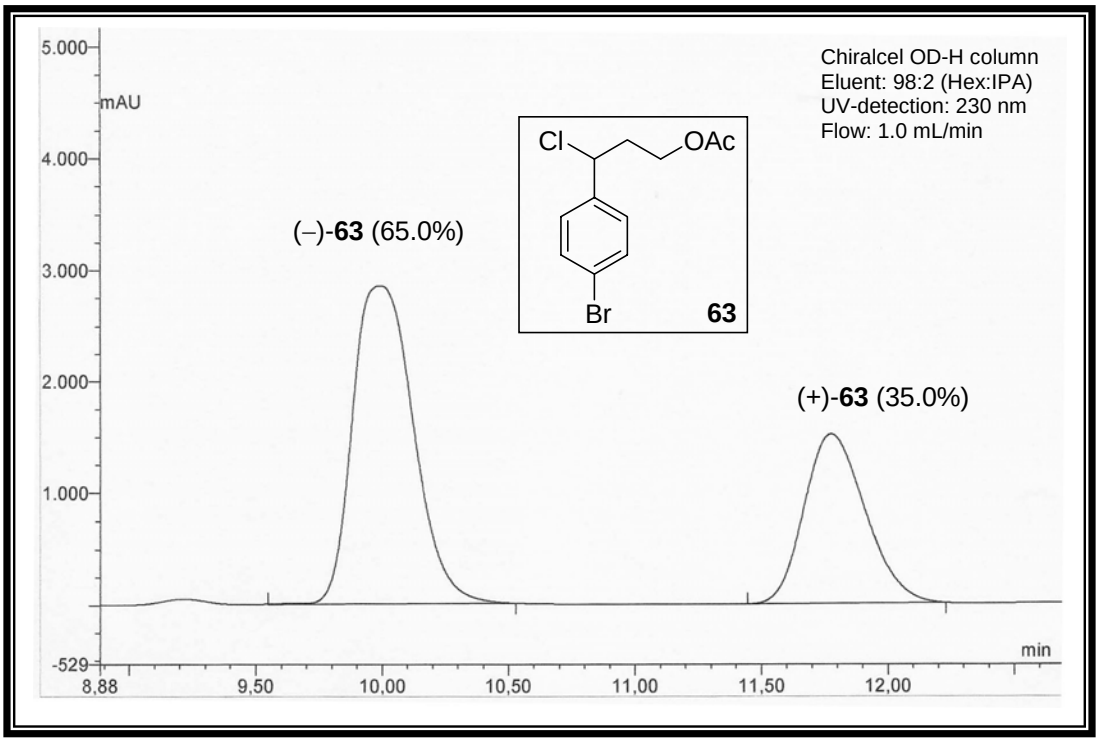

Figure A40. HPLC chromatogram of ester **63** (30% ee)

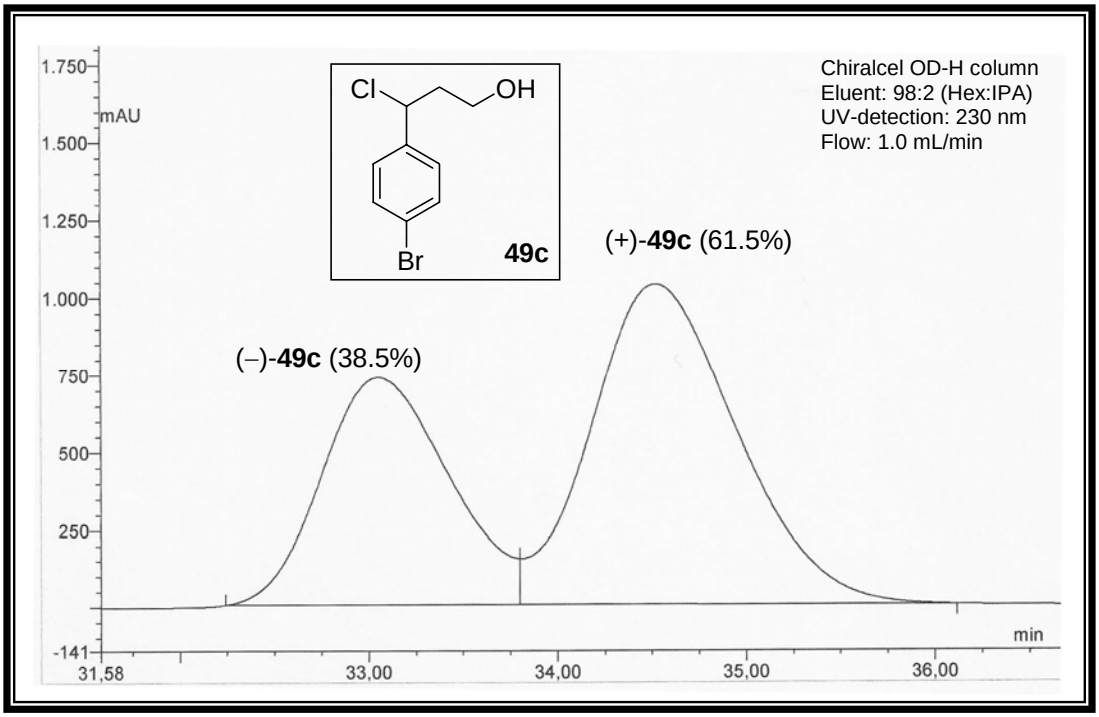

Figure A41. HPLC chromatogram of alcohol **49c** (23% ee)

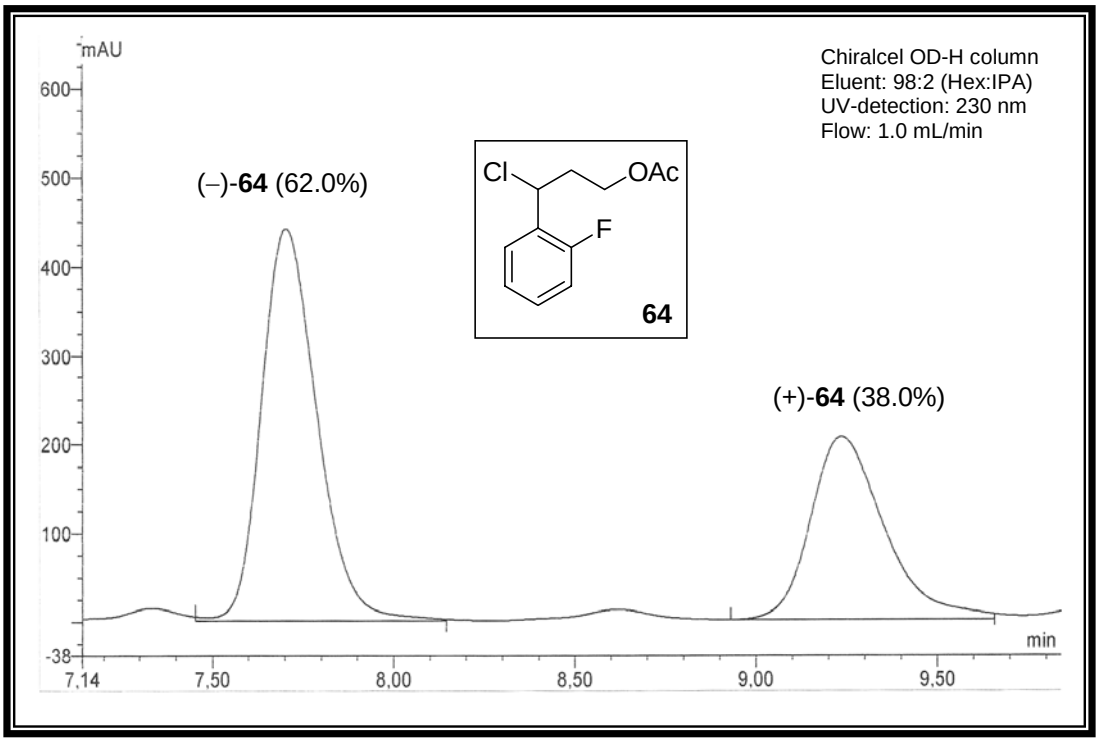

Figure A42. HPLC chromatogram of ester **64** (24% ee)

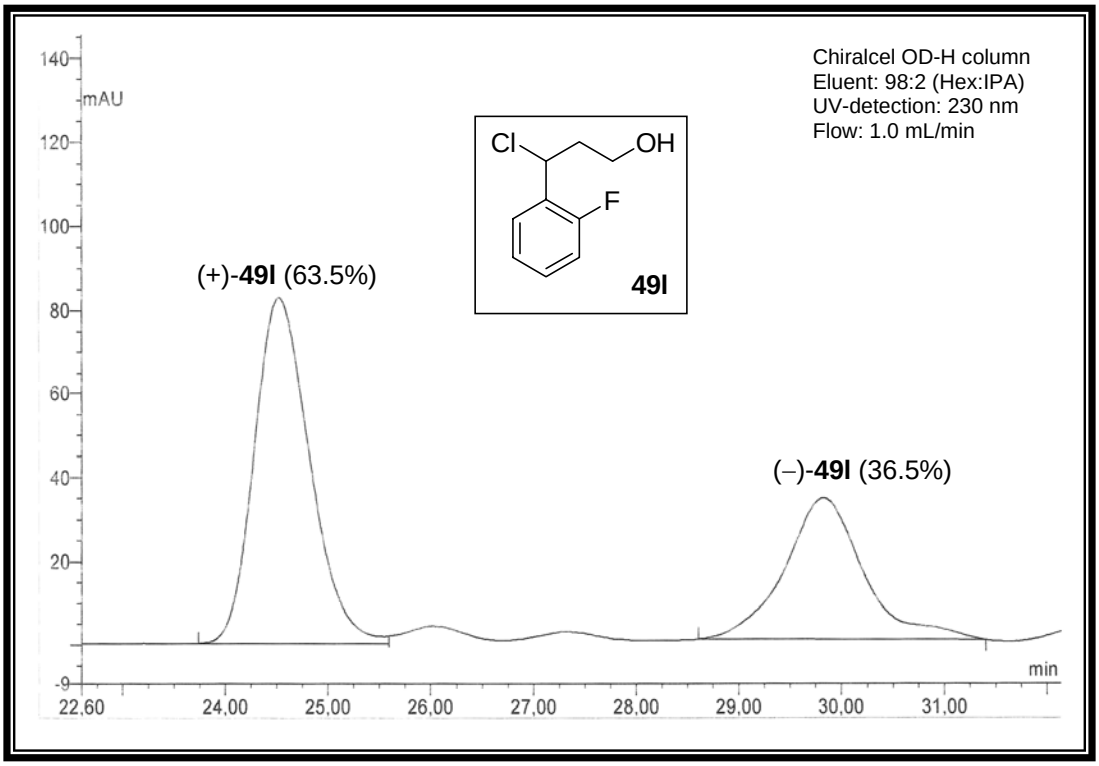

Figure A43. HPLC chromatogram of alcohol **49l** (27% ee)

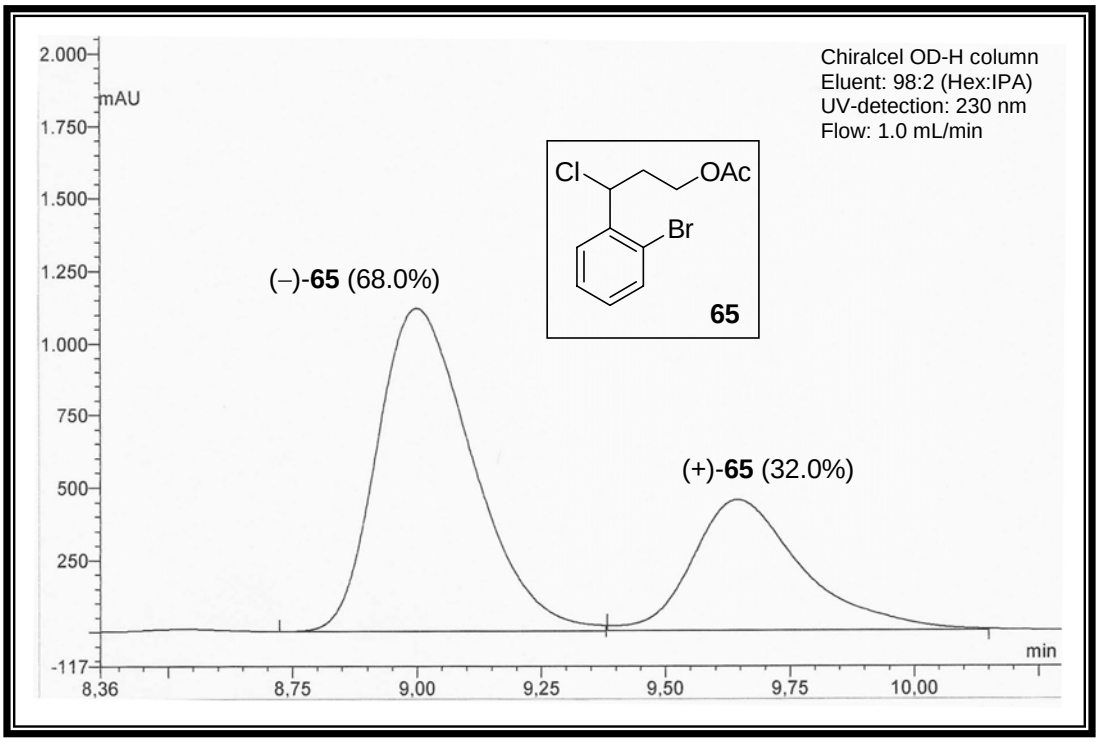

Figure A44. HPLC chromatogram of ester **65** (36% ee)

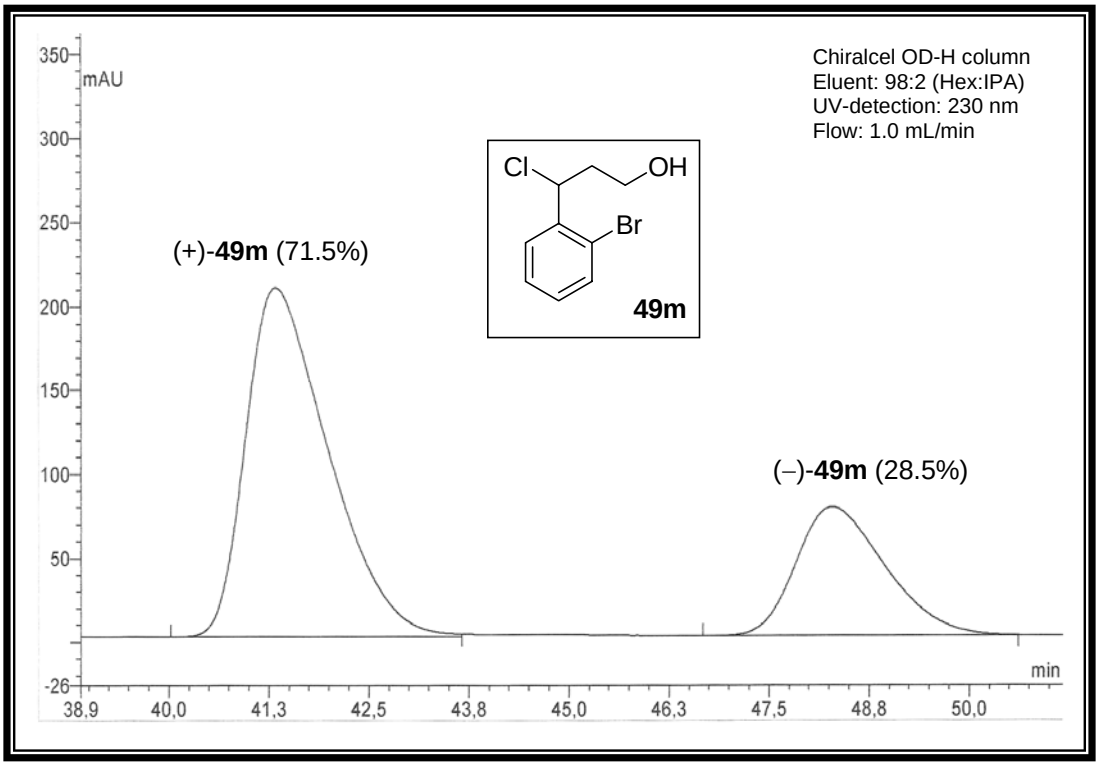

Figure A45. HPLC chromatogram of alcohol **49m** (43% ee)

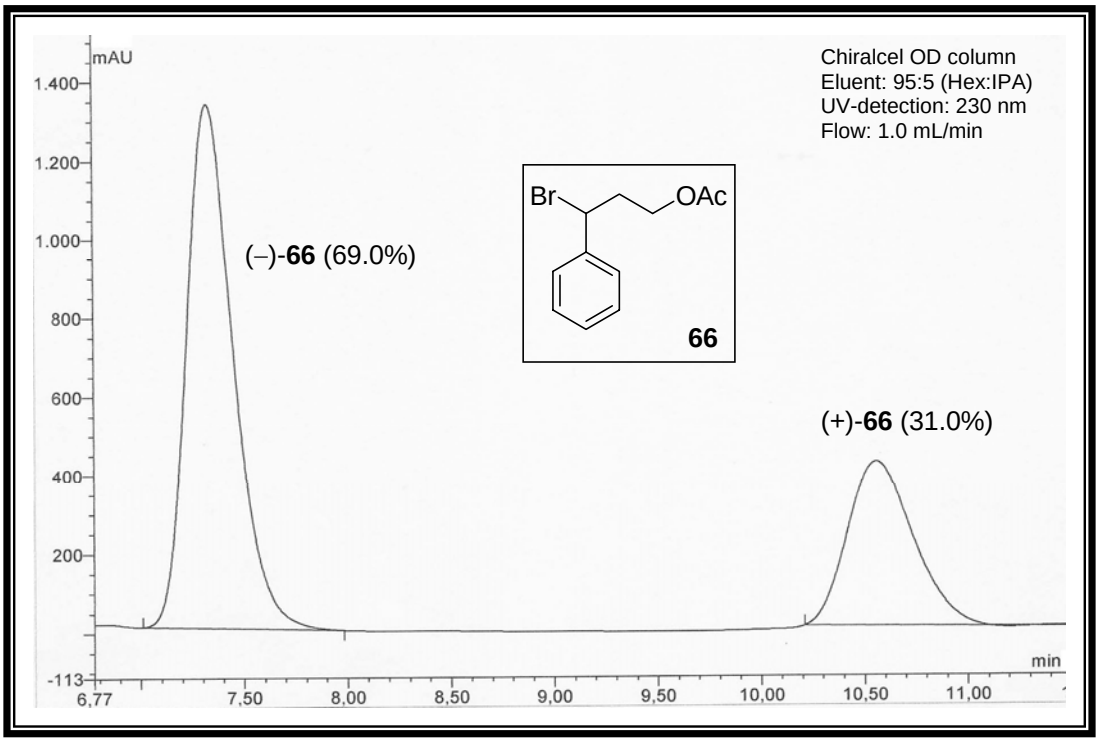

Figure A46. HPLC chromatogram of ester **66** (38% ee)

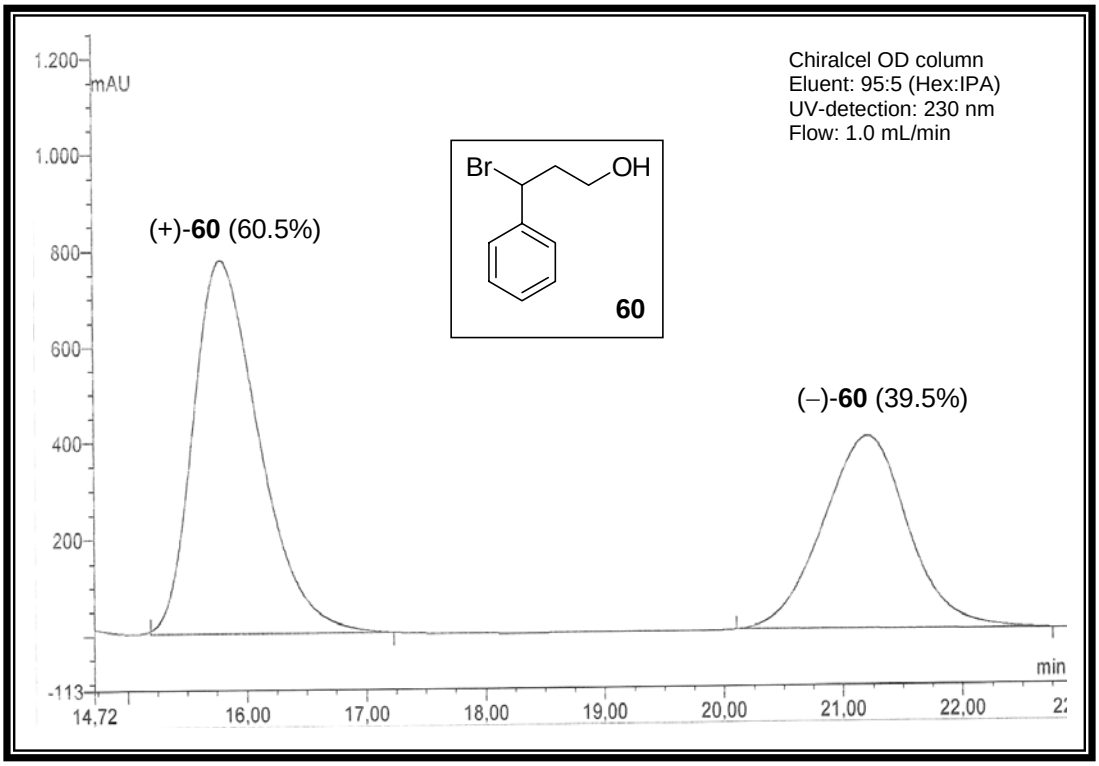

Figure A47. HPLC chromatogram of alcohol **60** (21% ee)

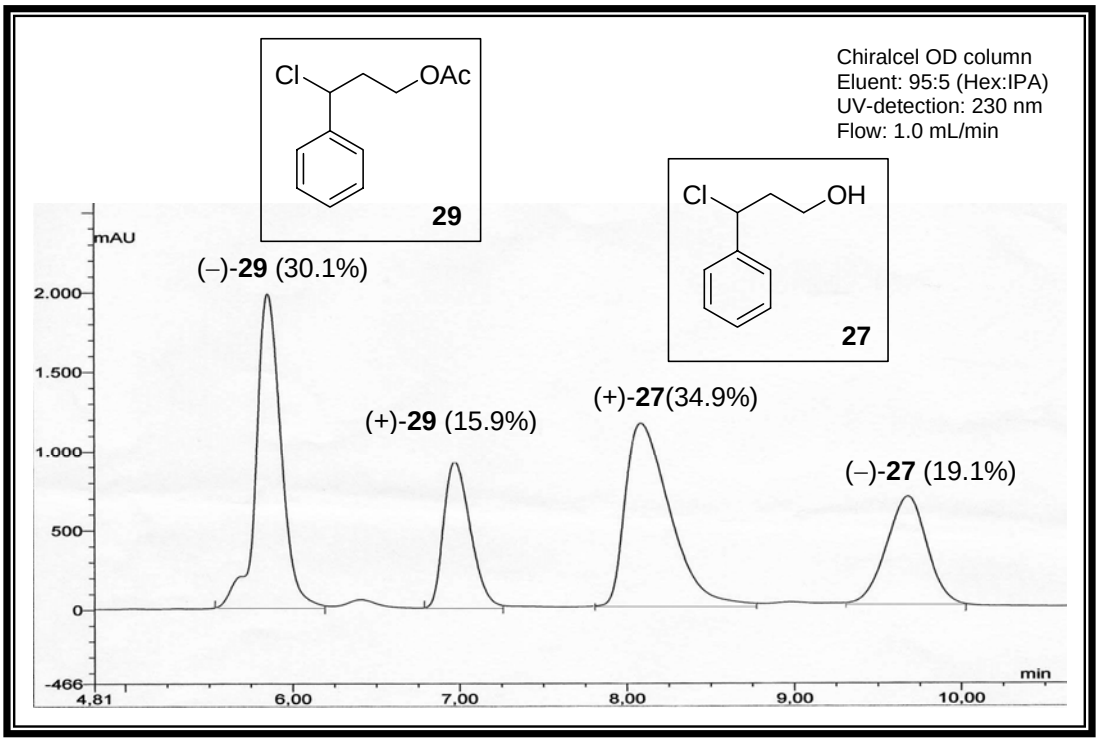

Figure A48. HPLC chromatogram of the first run of double enzymatic resolution

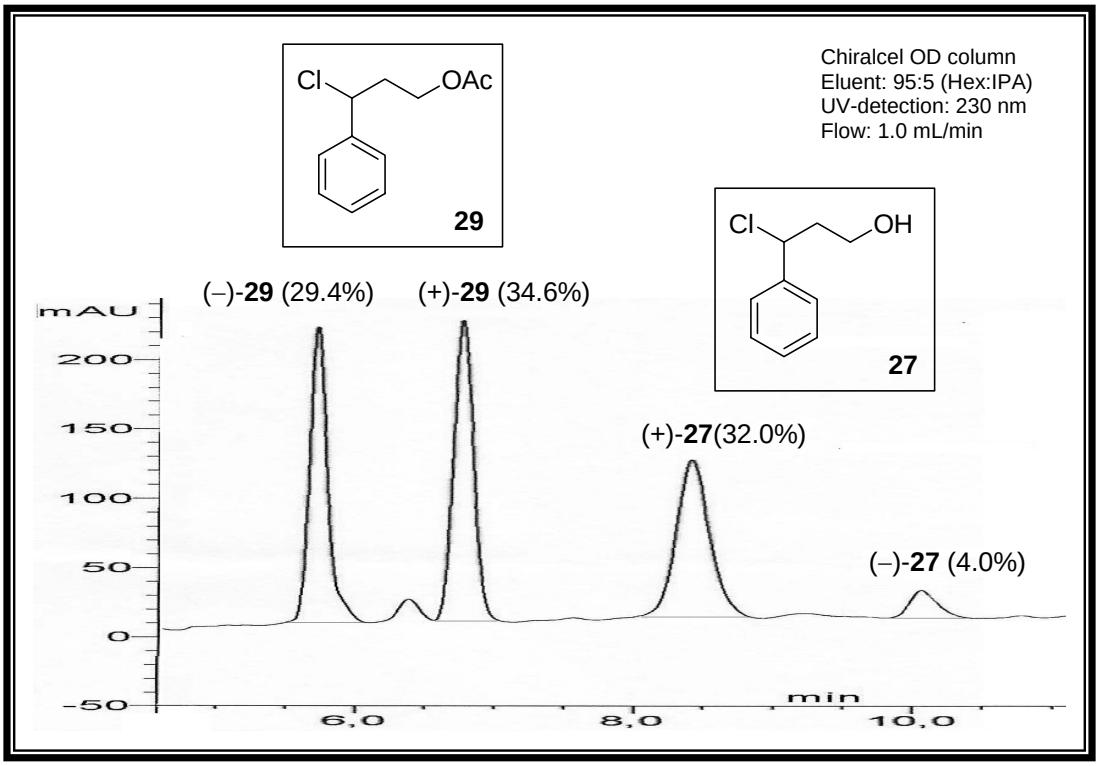

Figure A49. HPLC chromatogram of the second run of double enzymatic resolution

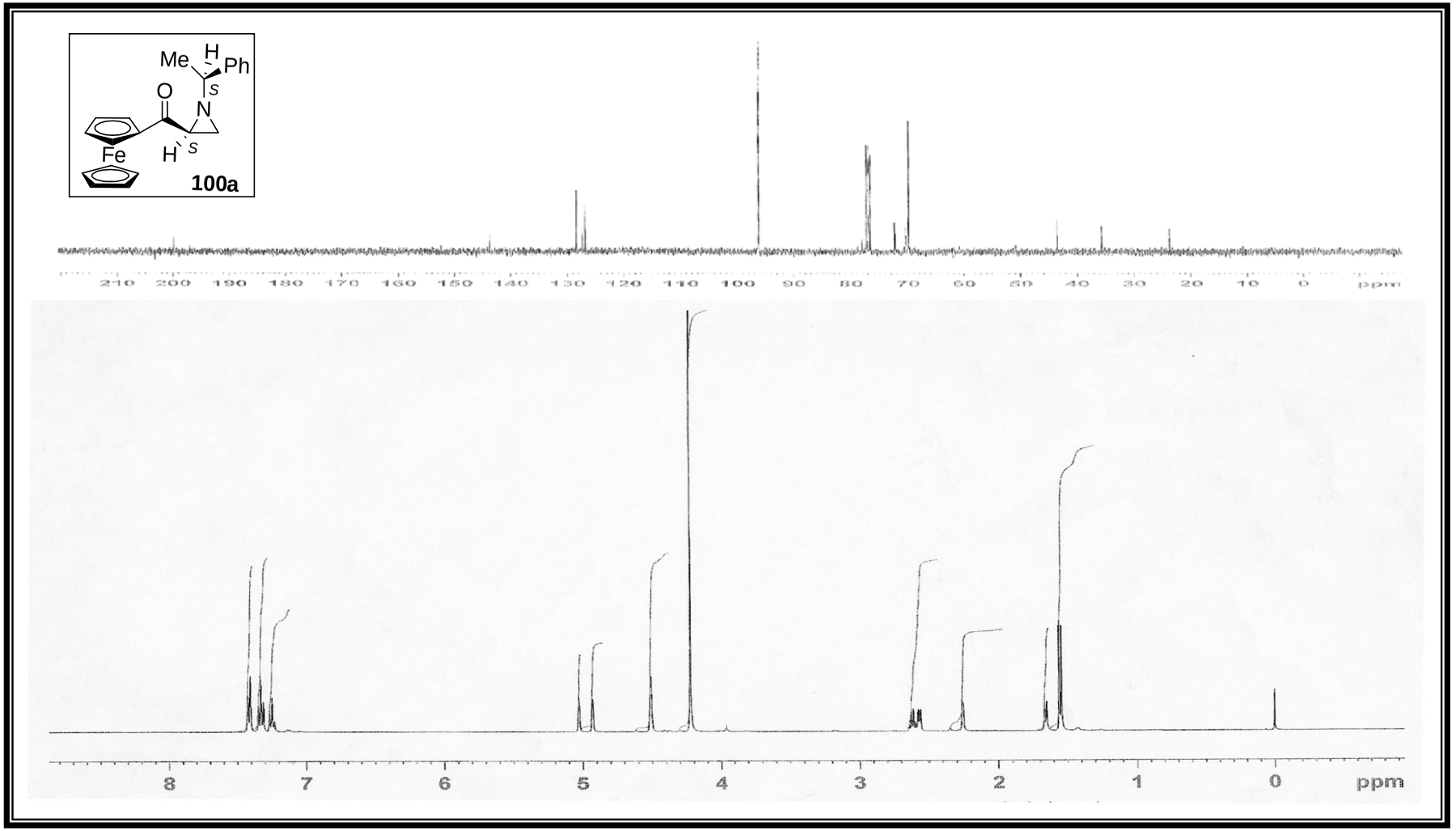

Figure A50. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of chiral ketone **100a**

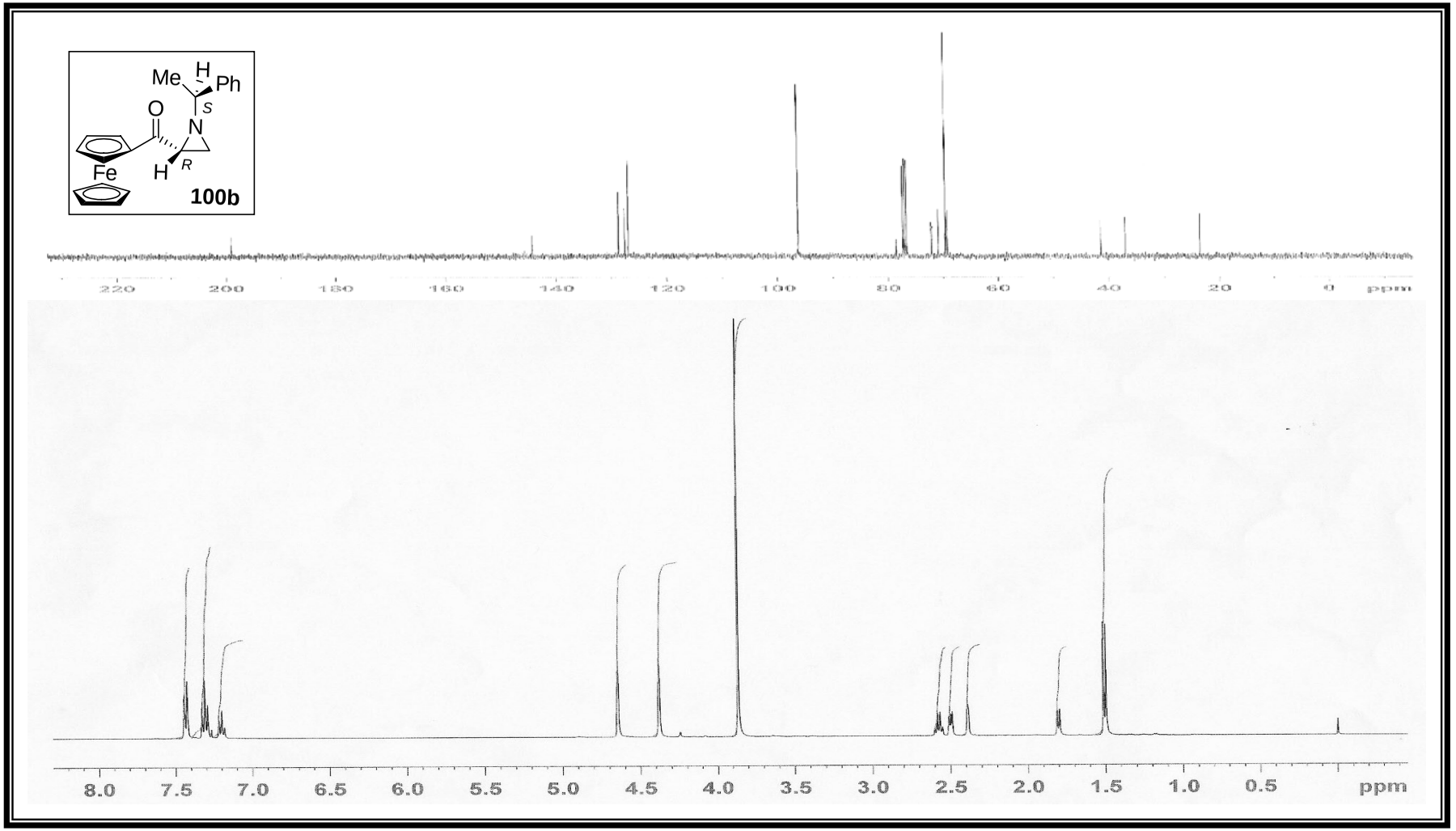

Figure A51. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of ketone **100b**

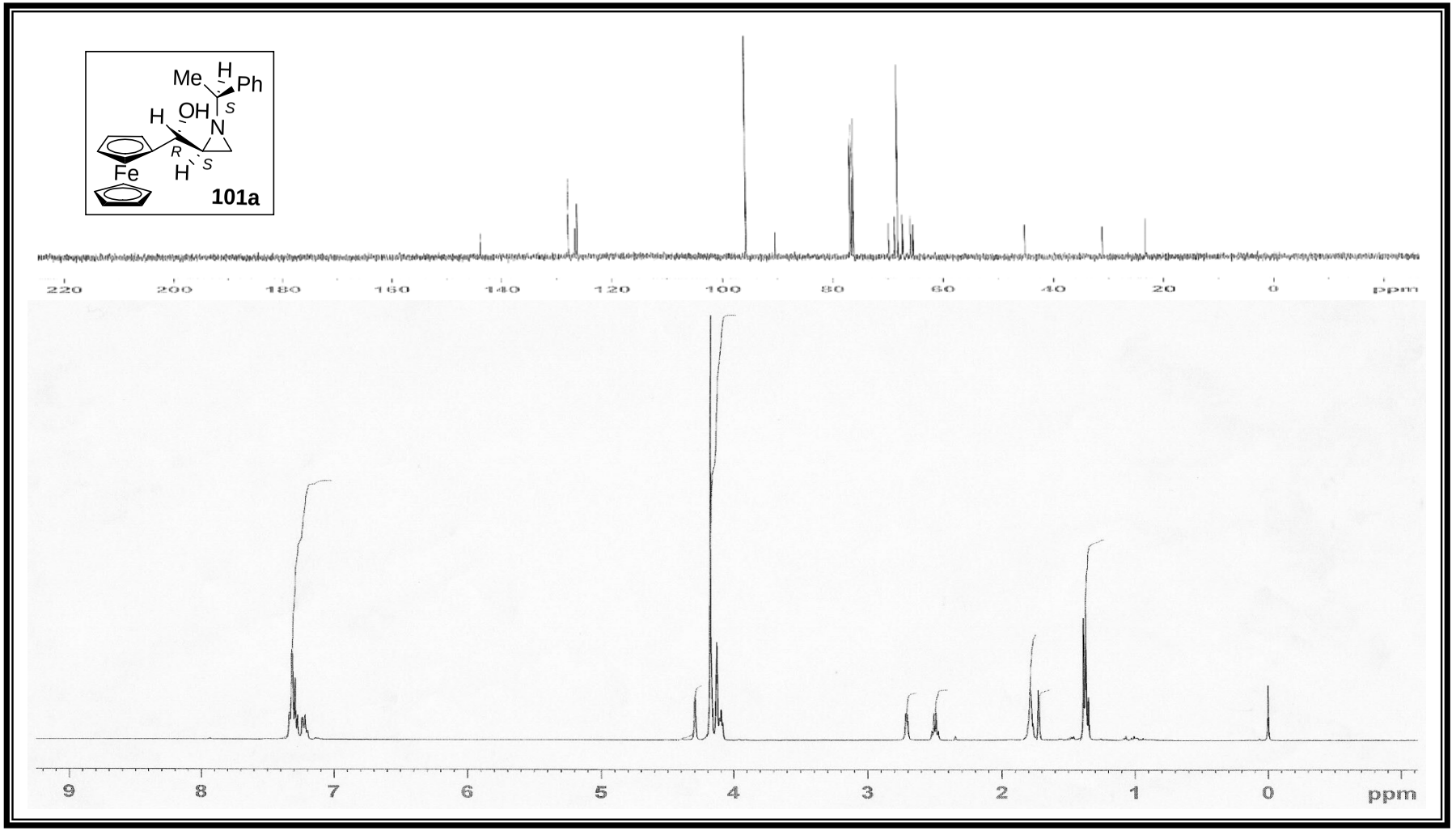

Figure A52. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of ligand (*R*,*S*,*S*)-**101a**

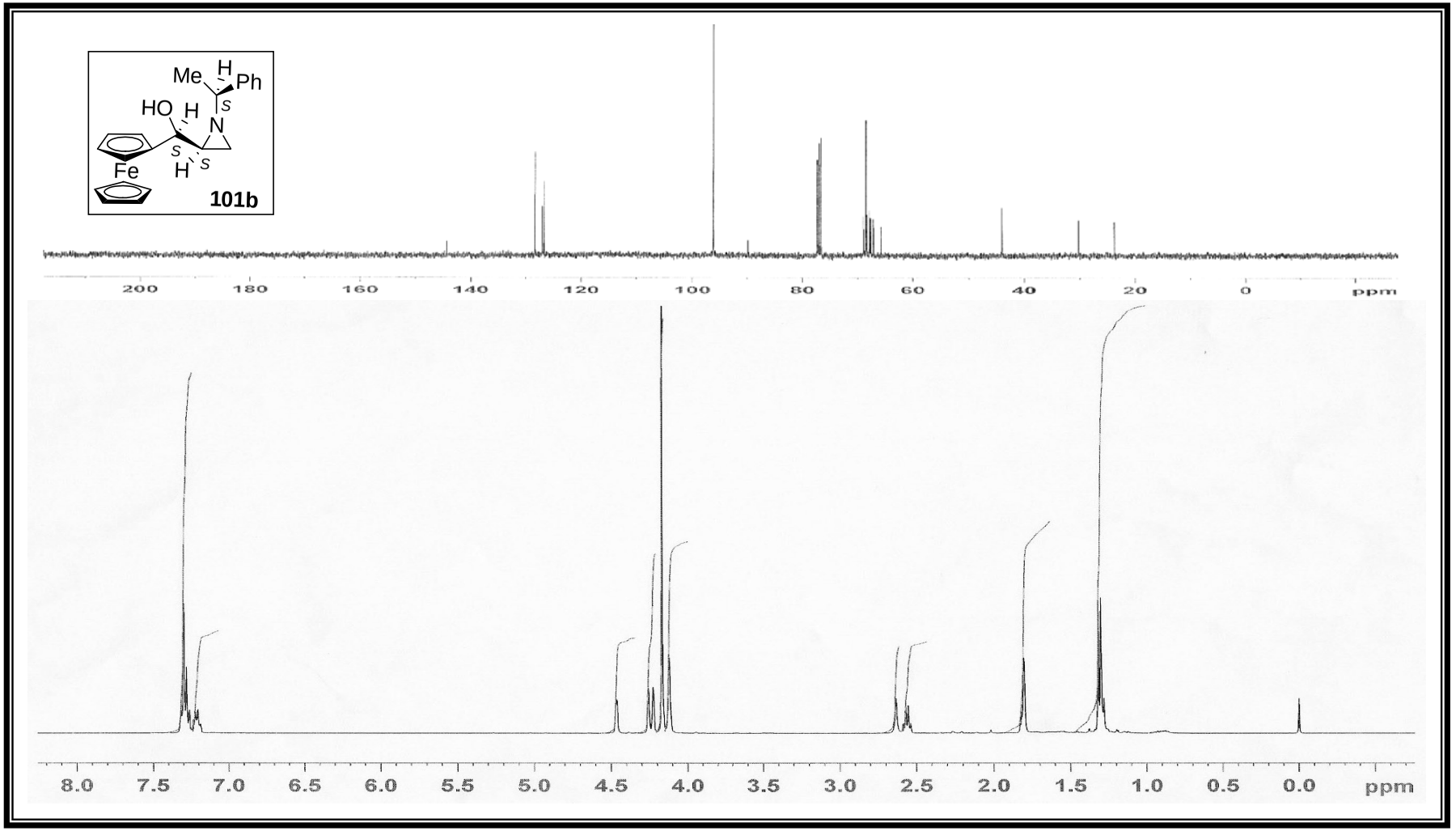

Figure A53. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of ligand (*S*,*S*,*S*)-**101b**

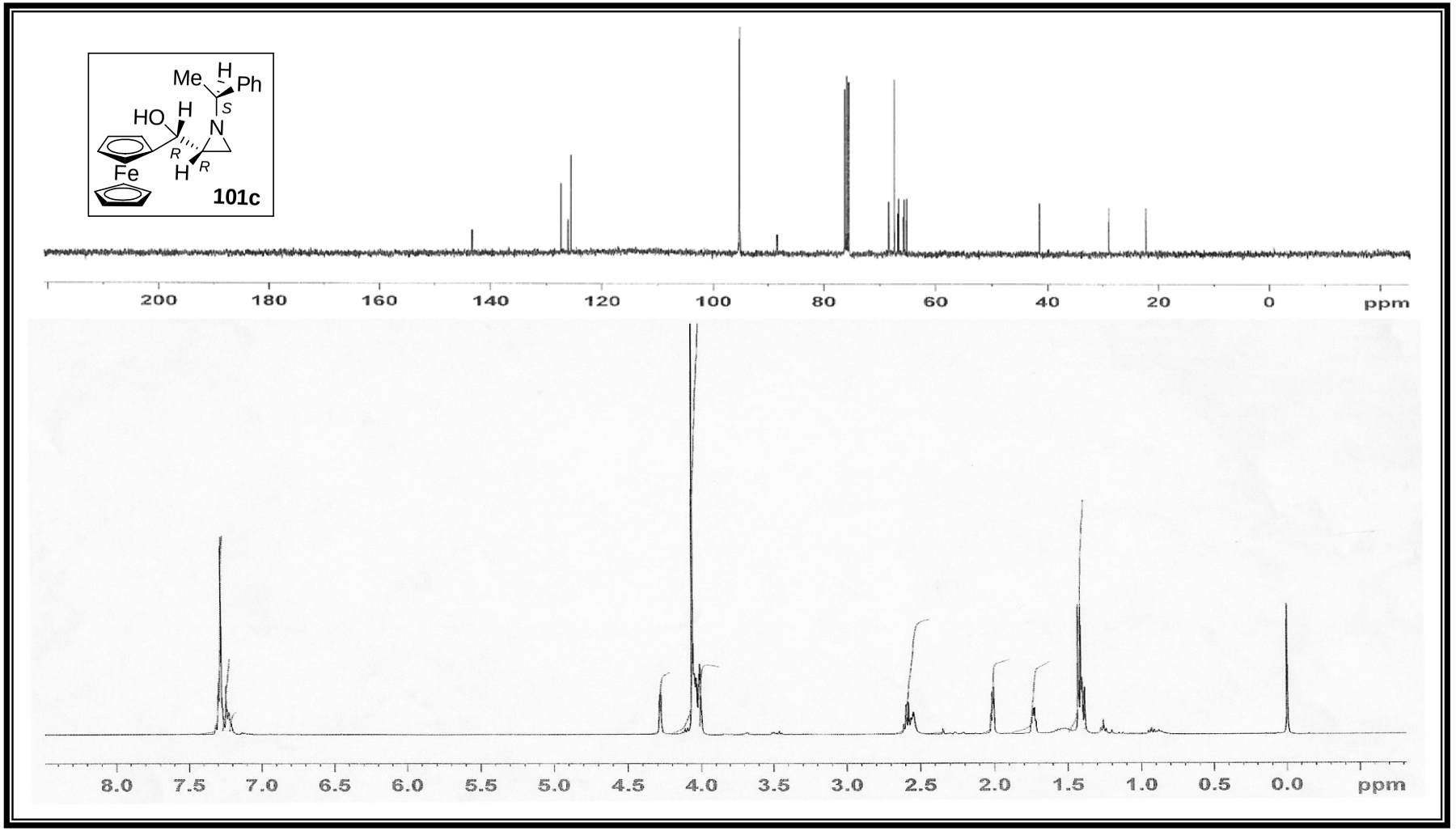

Figure A54. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of ligand (*R*,*R*,*S*)-**101c**

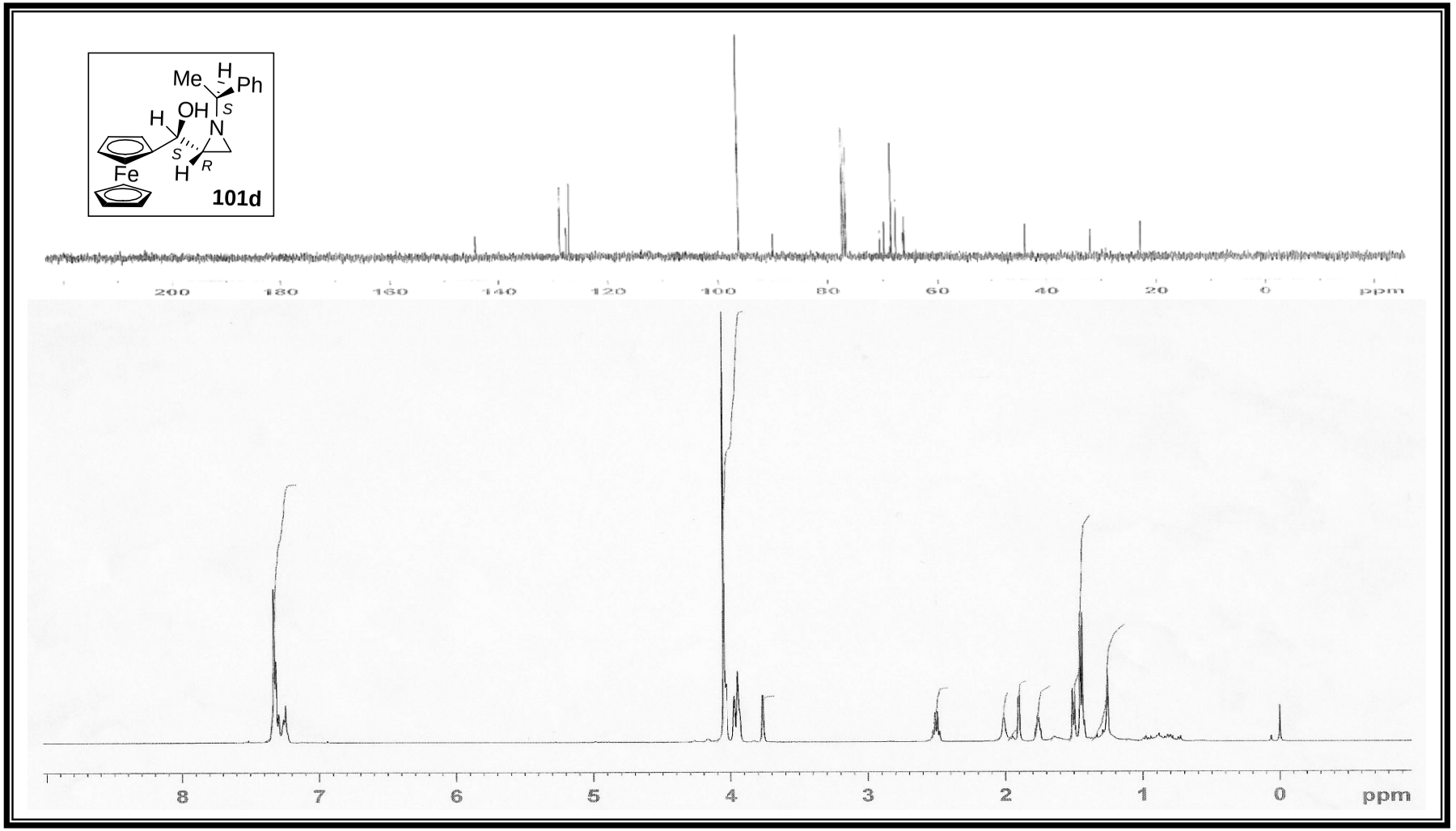

Figure A55. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of ligand (*S*,*R*,*S*)-**101d**

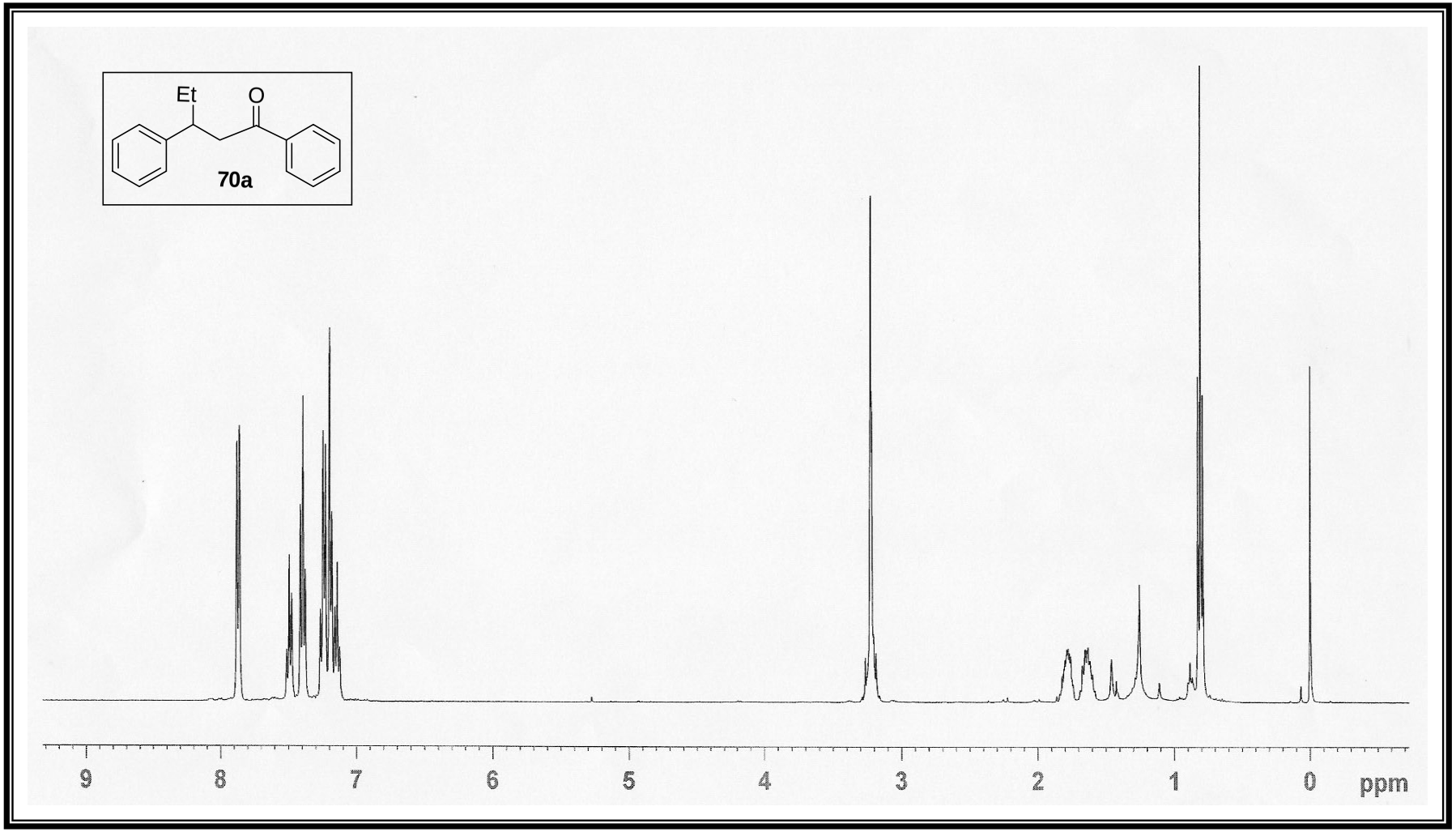

Figure A56. ^{1}H-NMR (400 MHz) spectrum of compound **70a**

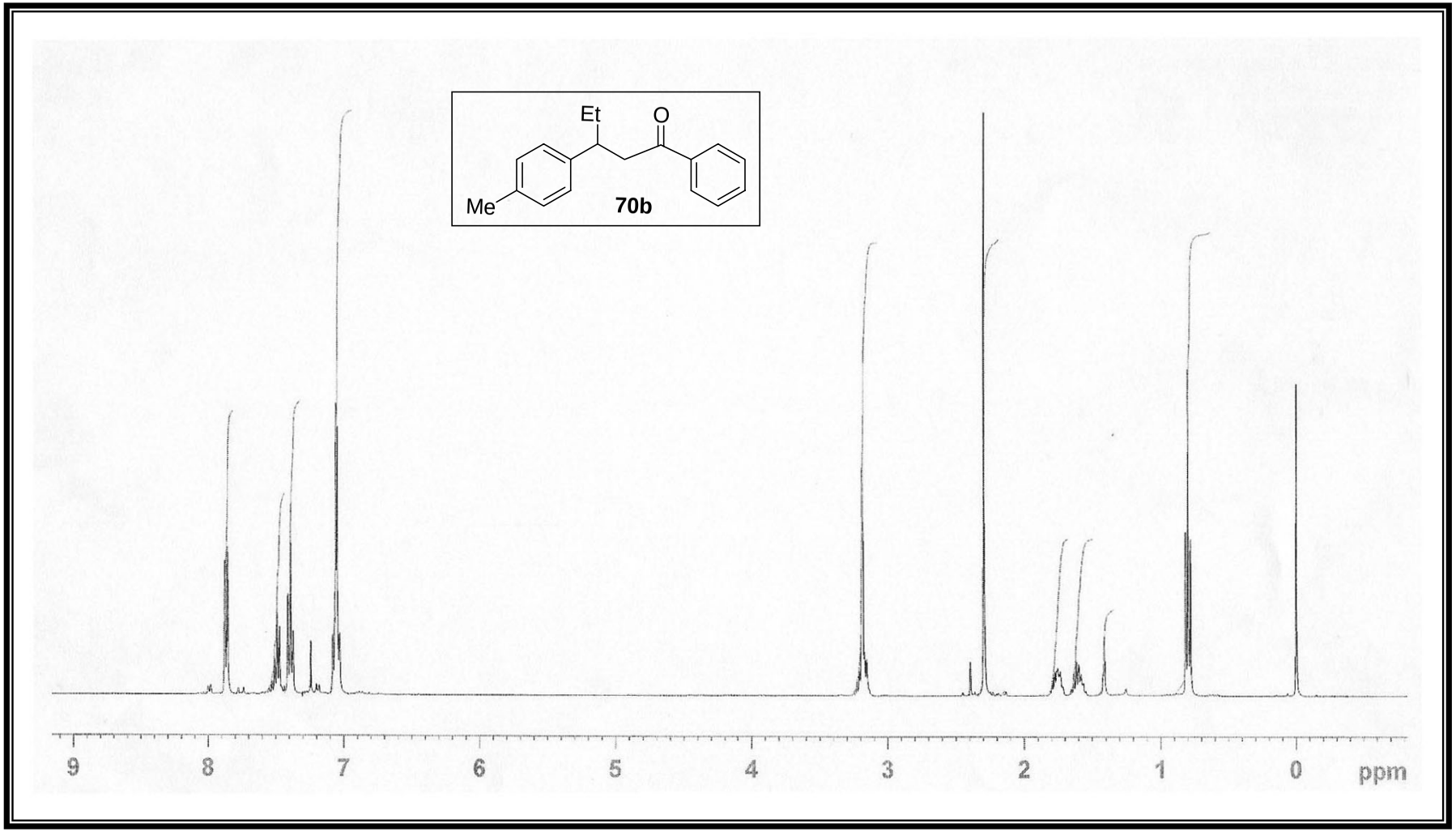

Figure A57. ^{1}H-NMR (400 MHz) spectrum of compound **70b**

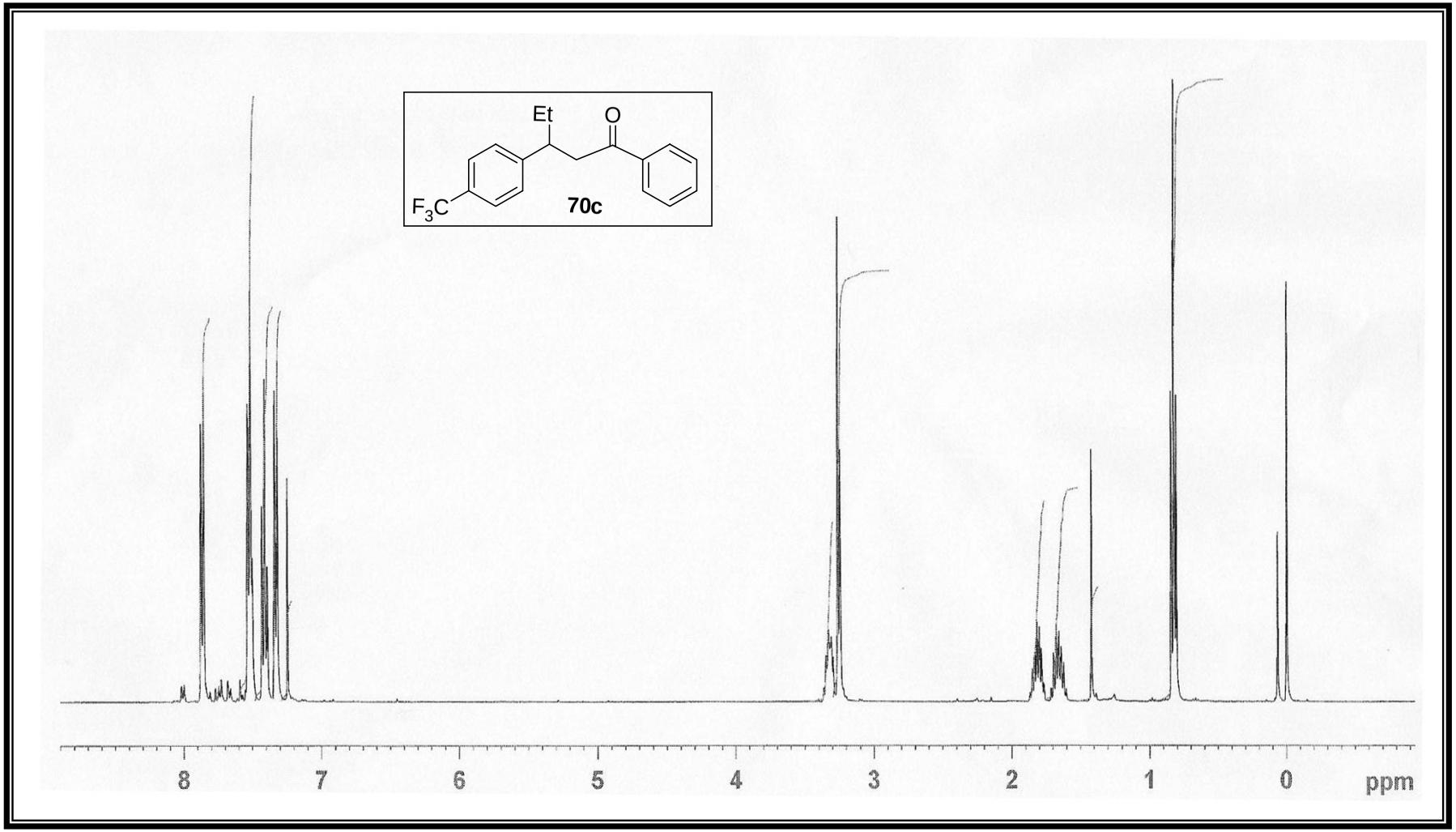

Figure A58. ^{1}H-NMR (400 MHz) spectrum of compound **70c**

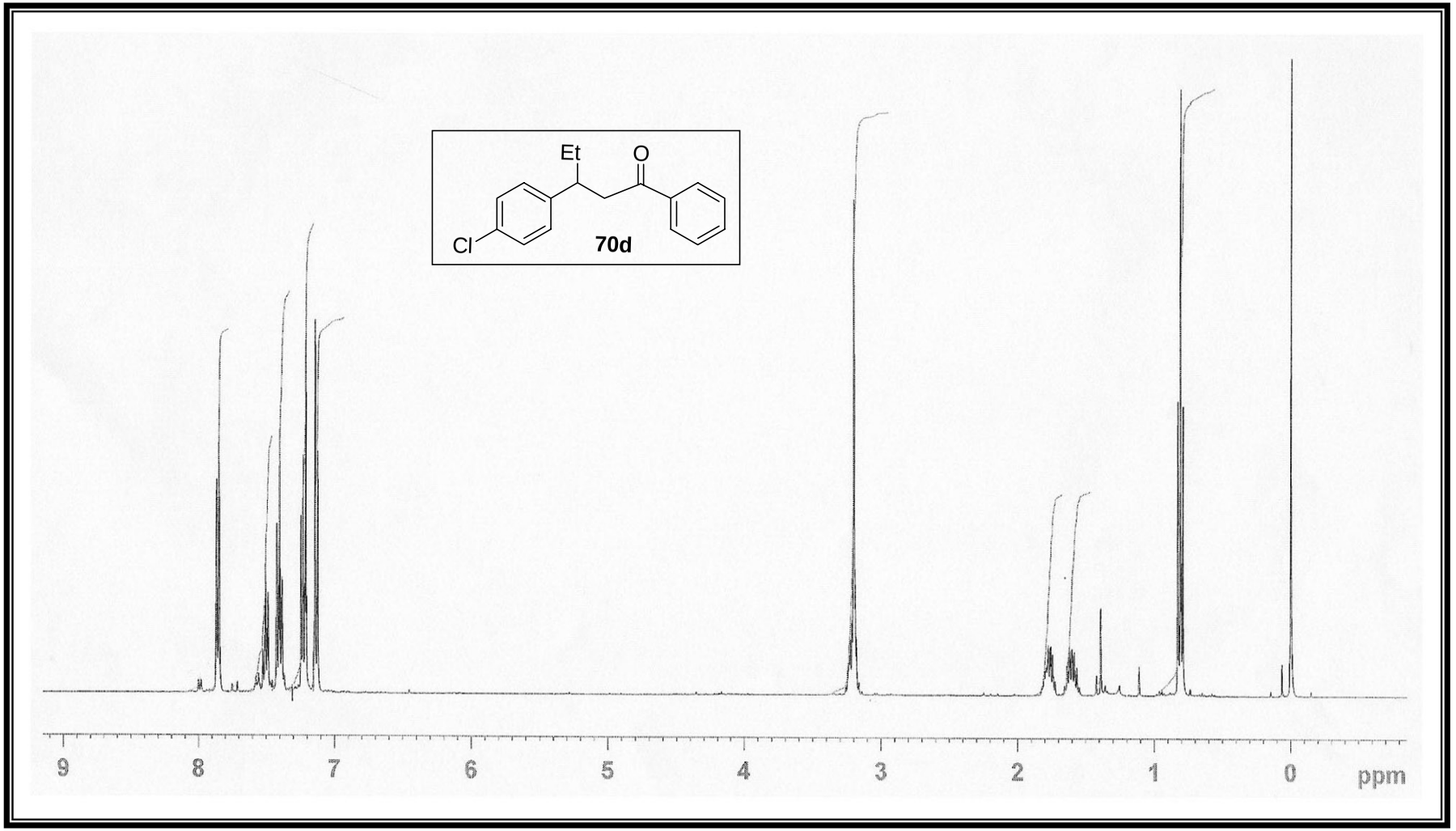

Figure A59. ^{1}H-NMR (400 MHz) spectrum of compound **70d**

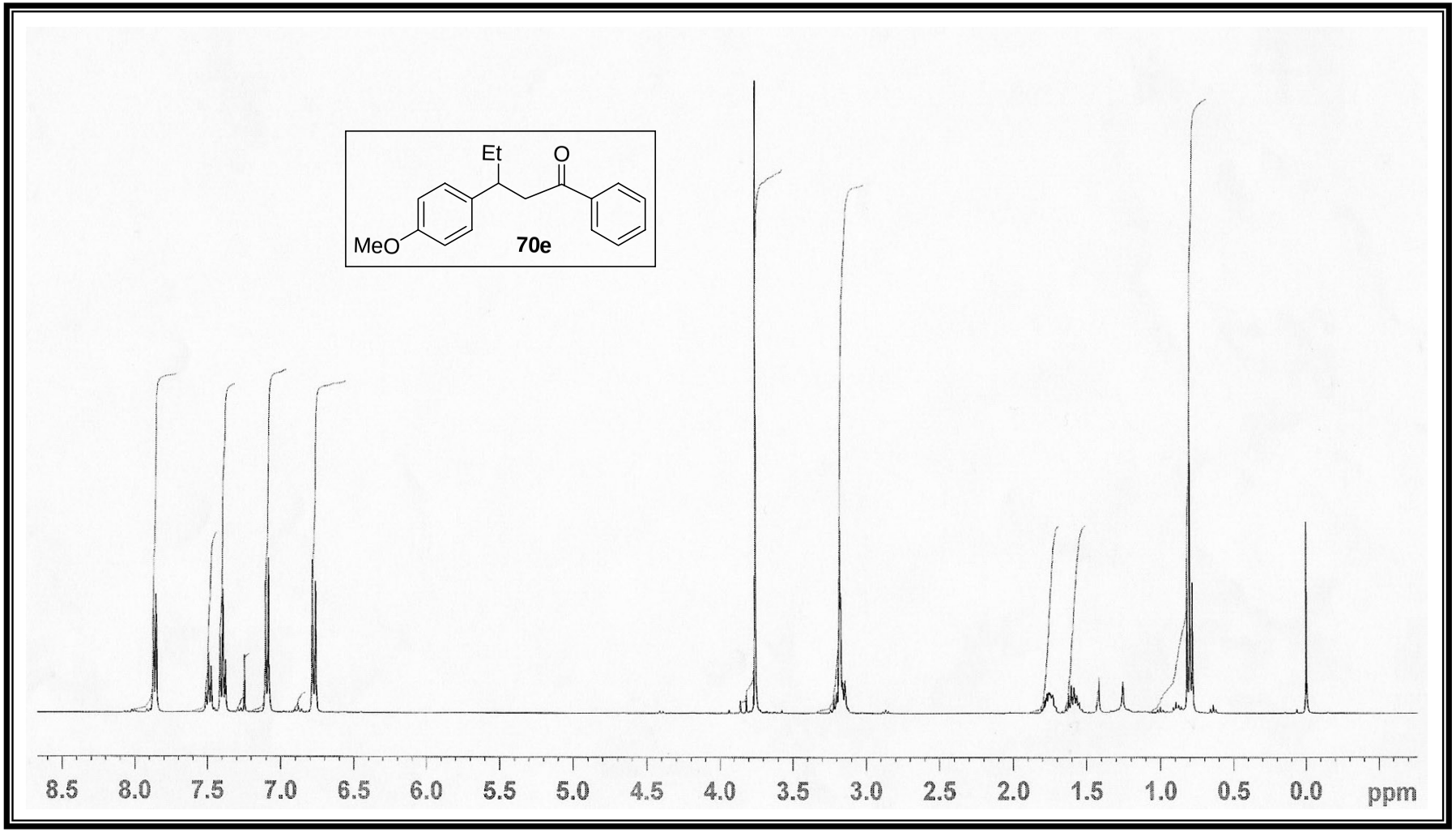

Figure A60. ^{1}H-NMR (400 MHz) spectrum of compound **70e**

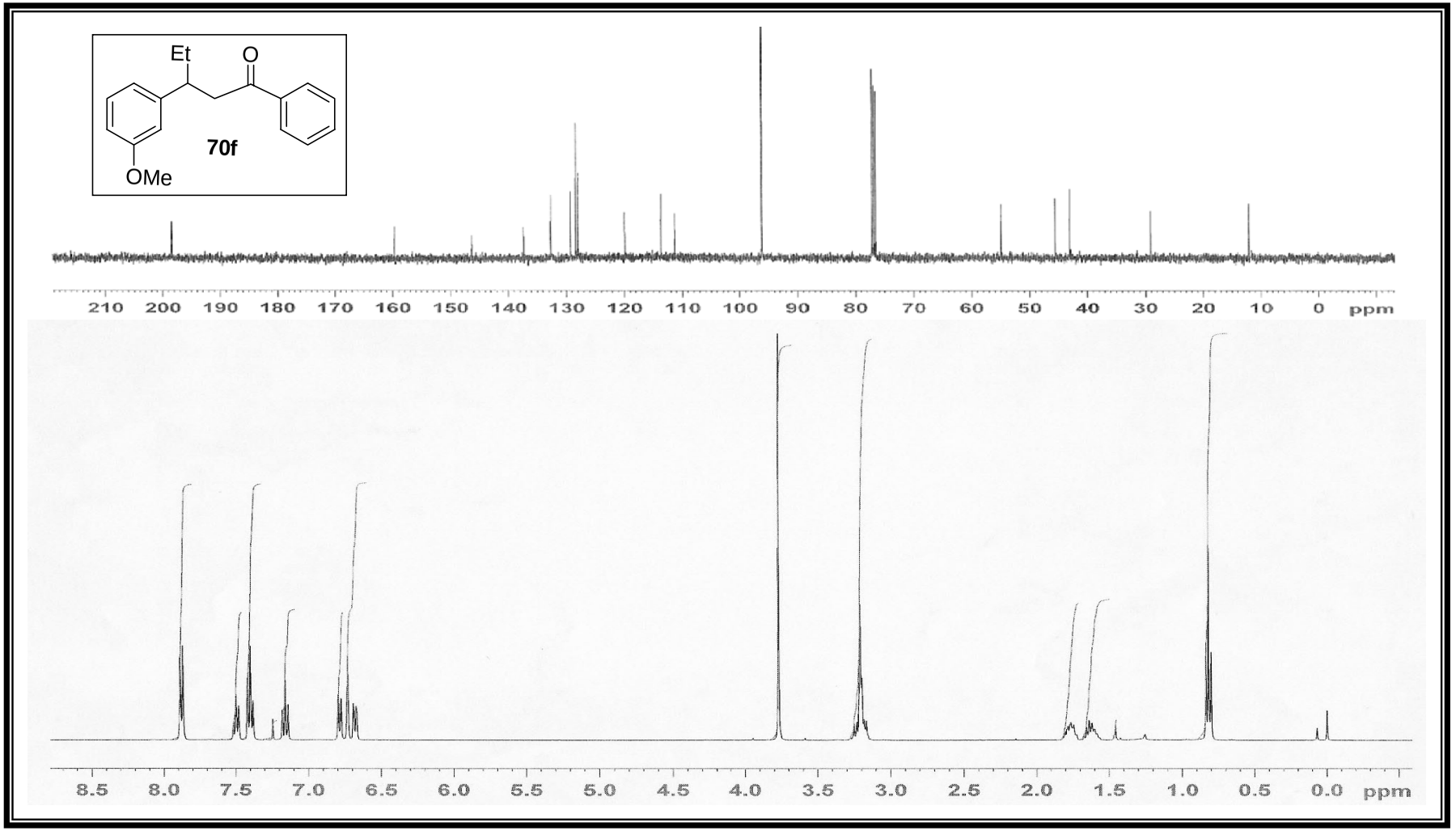

Figure A61. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra of compound **70f**

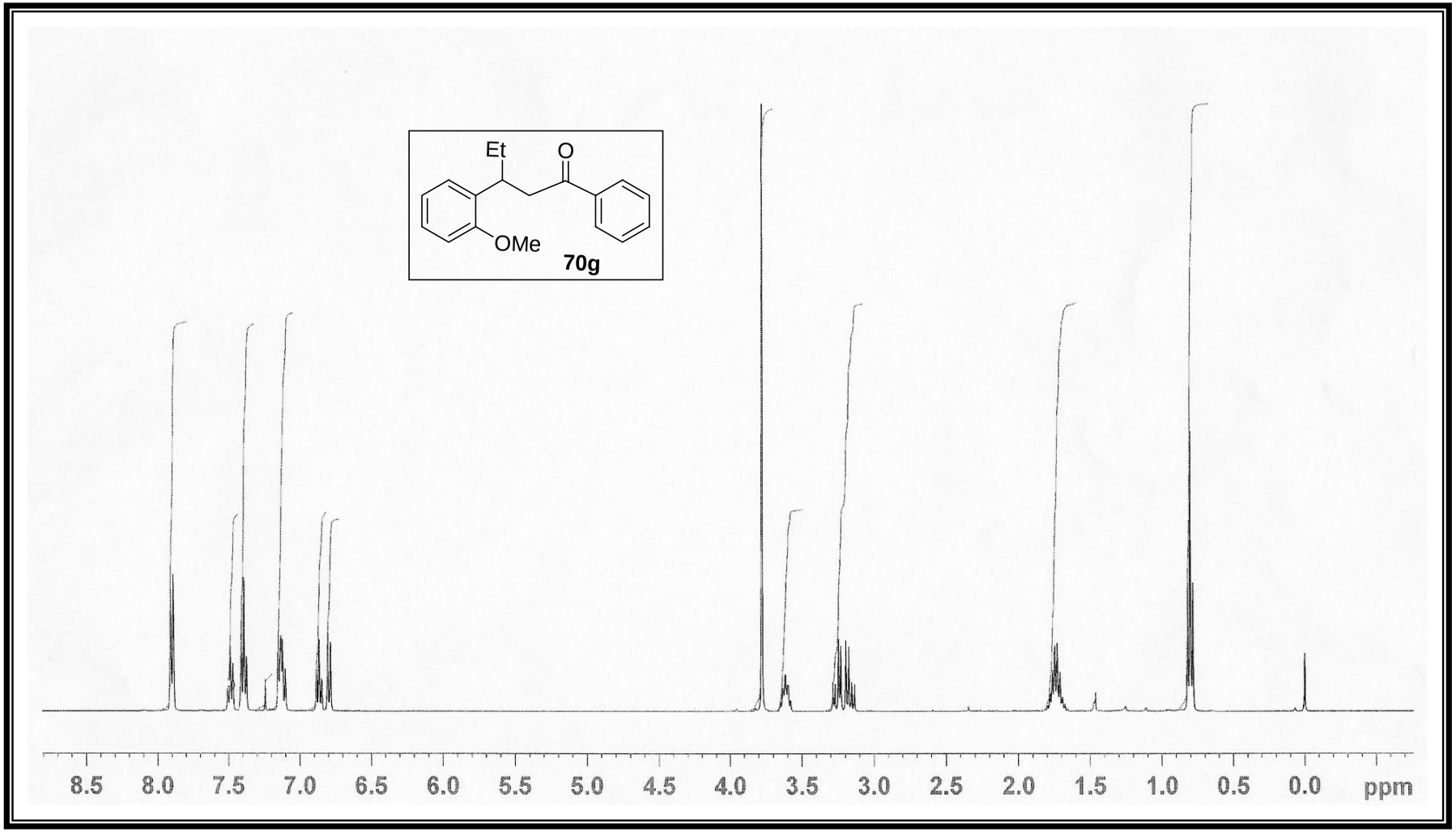

Figure A62. ^{1}H-NMR (400 MHz) spectrum of compound **70g**

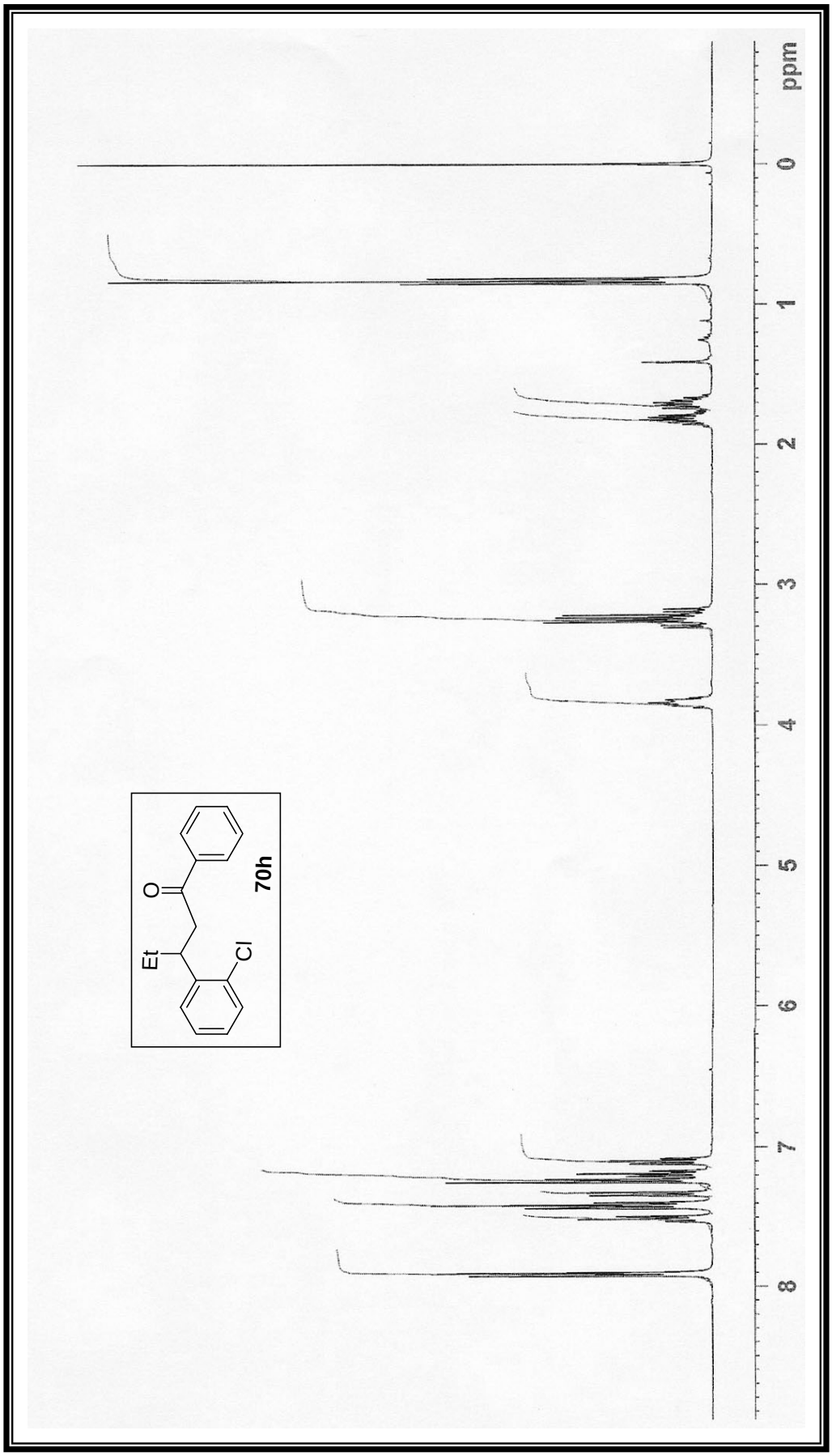

Figure A63. ^{1}H-NMR (400 MHz) spectrum of compound **70h**

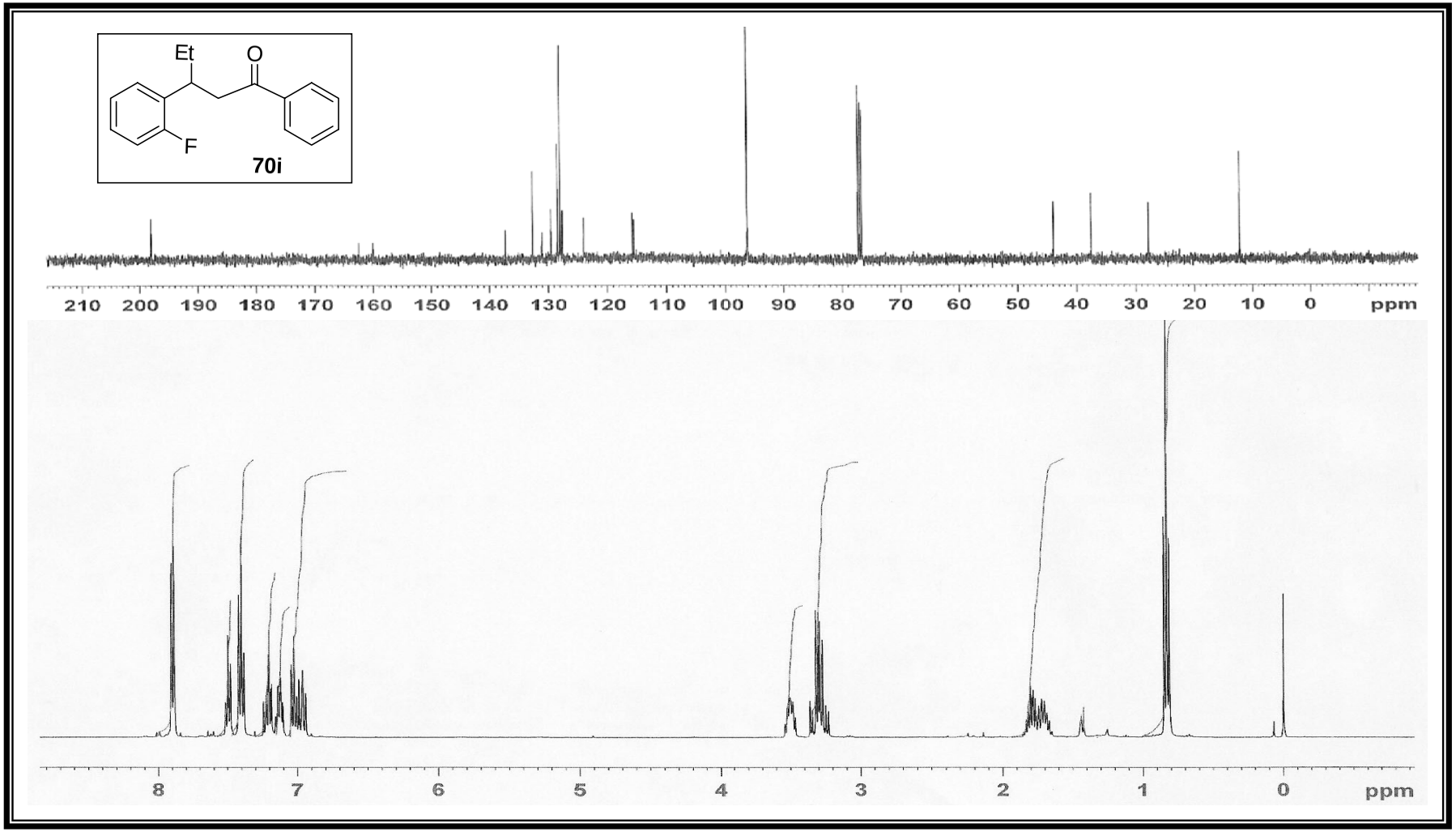

Figure A64. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR Spectra of compound **70i**

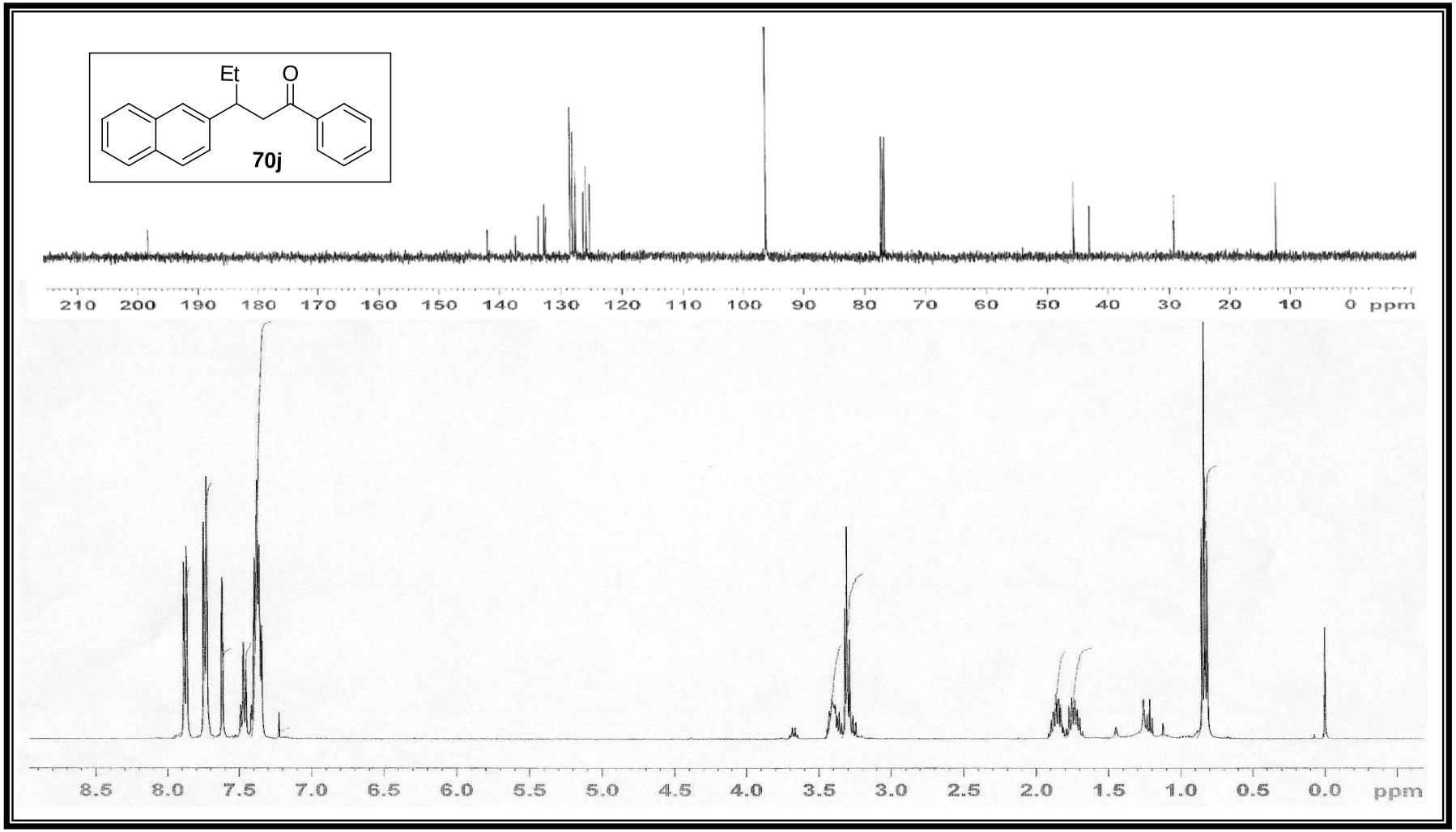

Figure A65. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR Spectra of compound **70j**

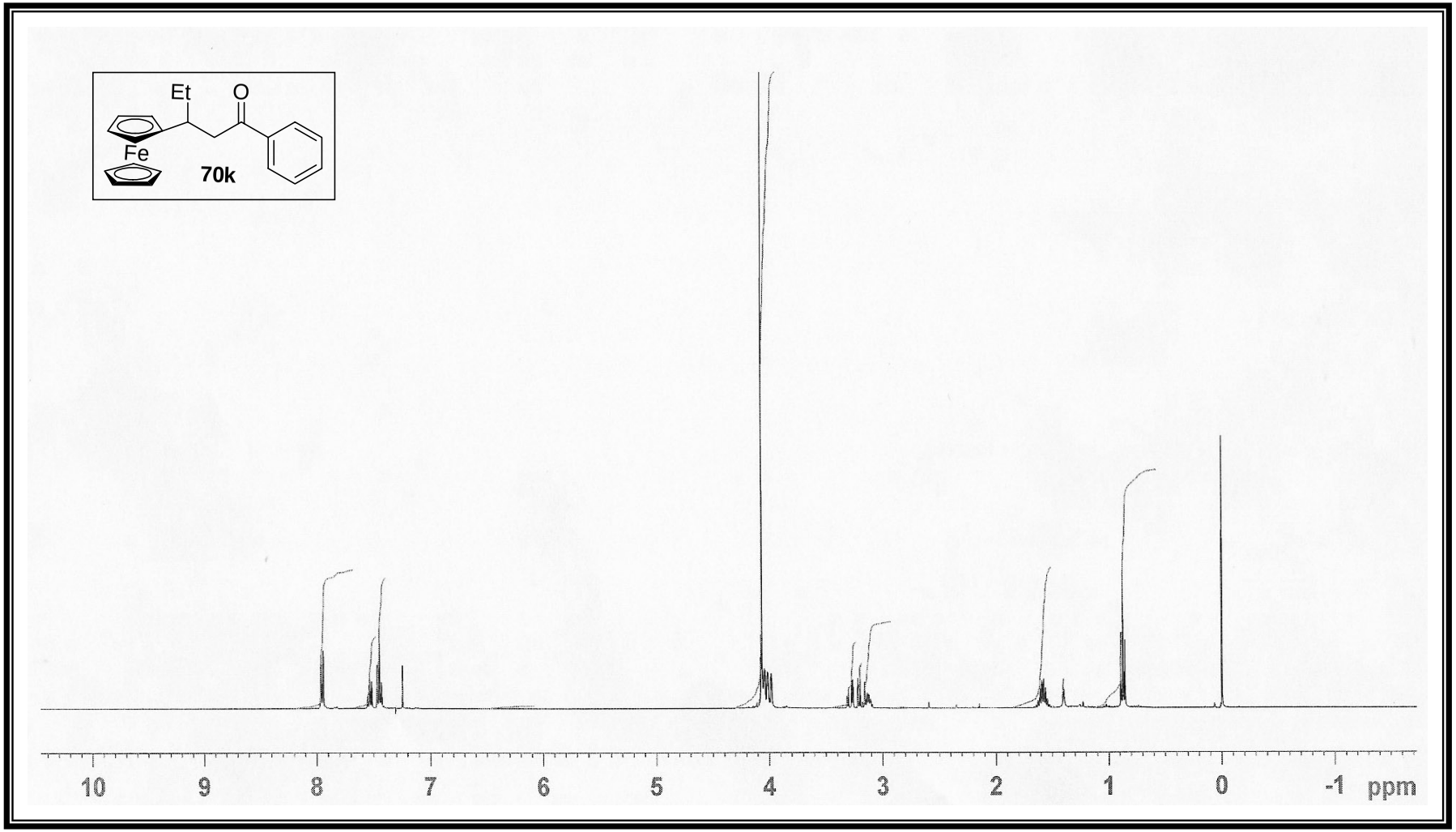

Figure A66. ^{1}H-NMR (400 MHz) Spectrum of compound **70k**

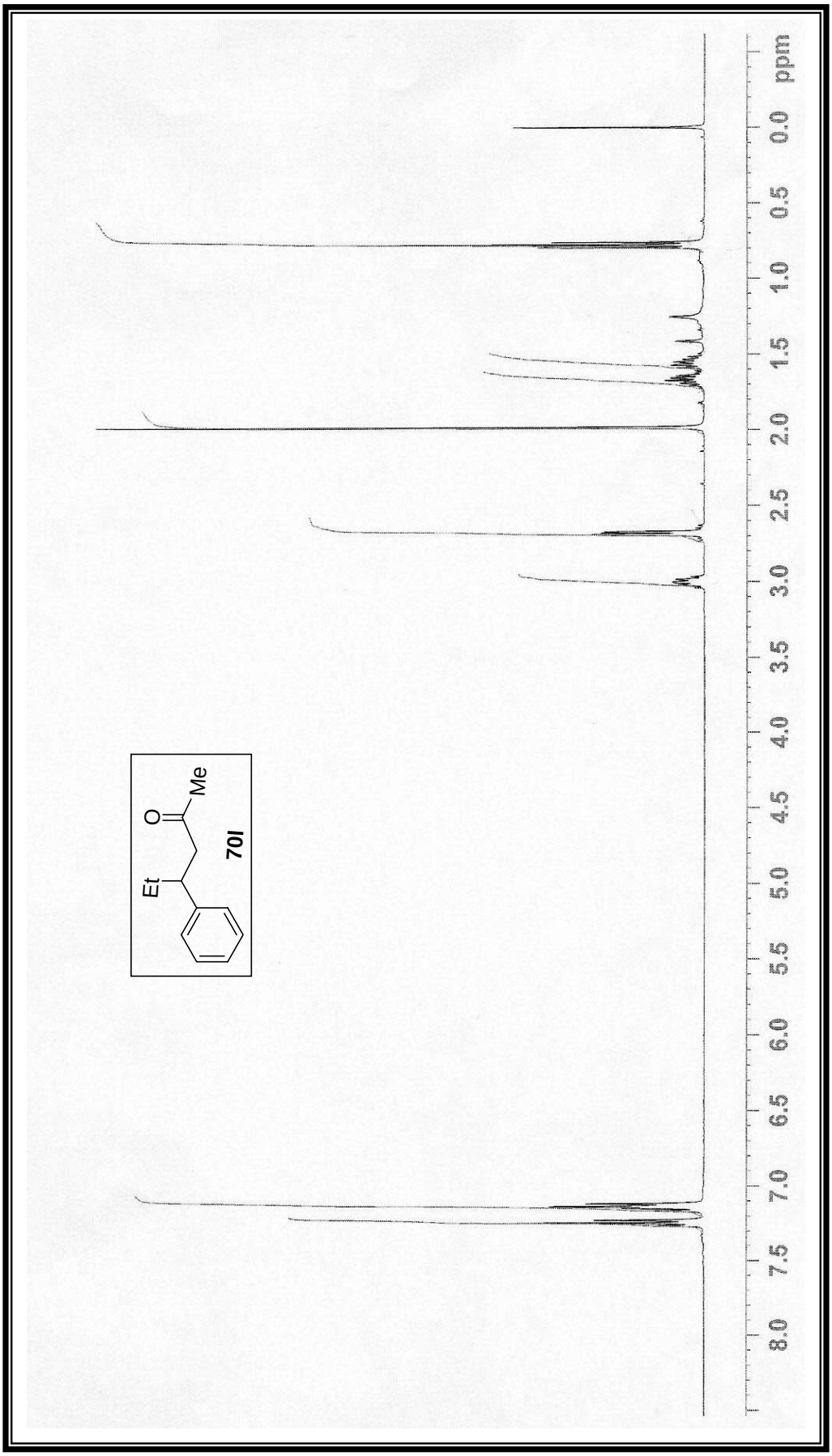

Figure A67. ^{1}H-NMR (400 MHz) Spectrum of compound **70l**

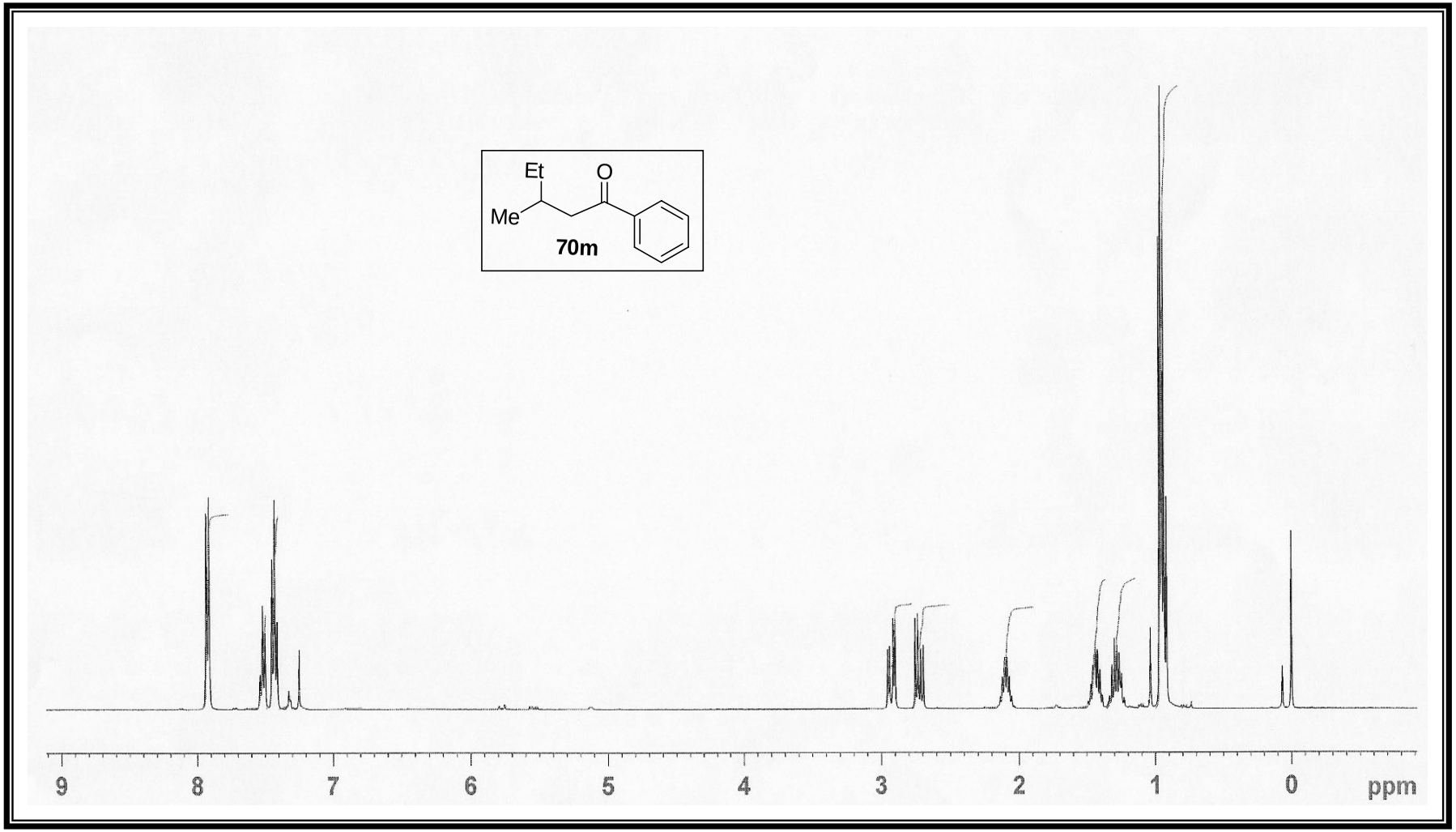

Figure A68. ^{1}H-NMR (400 MHz) Spectrum of compound **70m**

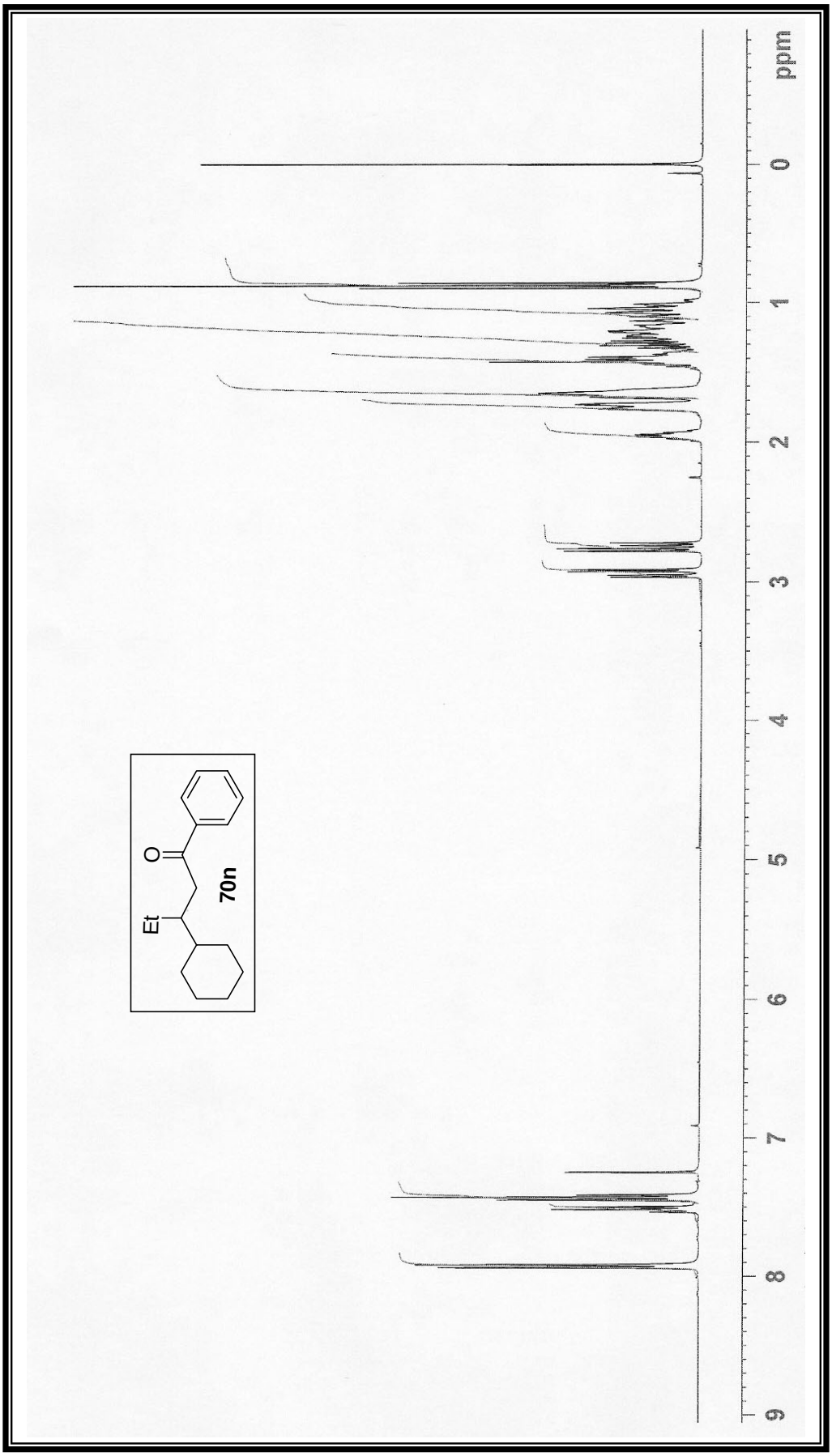

Figure A69. ^{1}H-NMR (400 MHz) Spectrum of compound **70n**

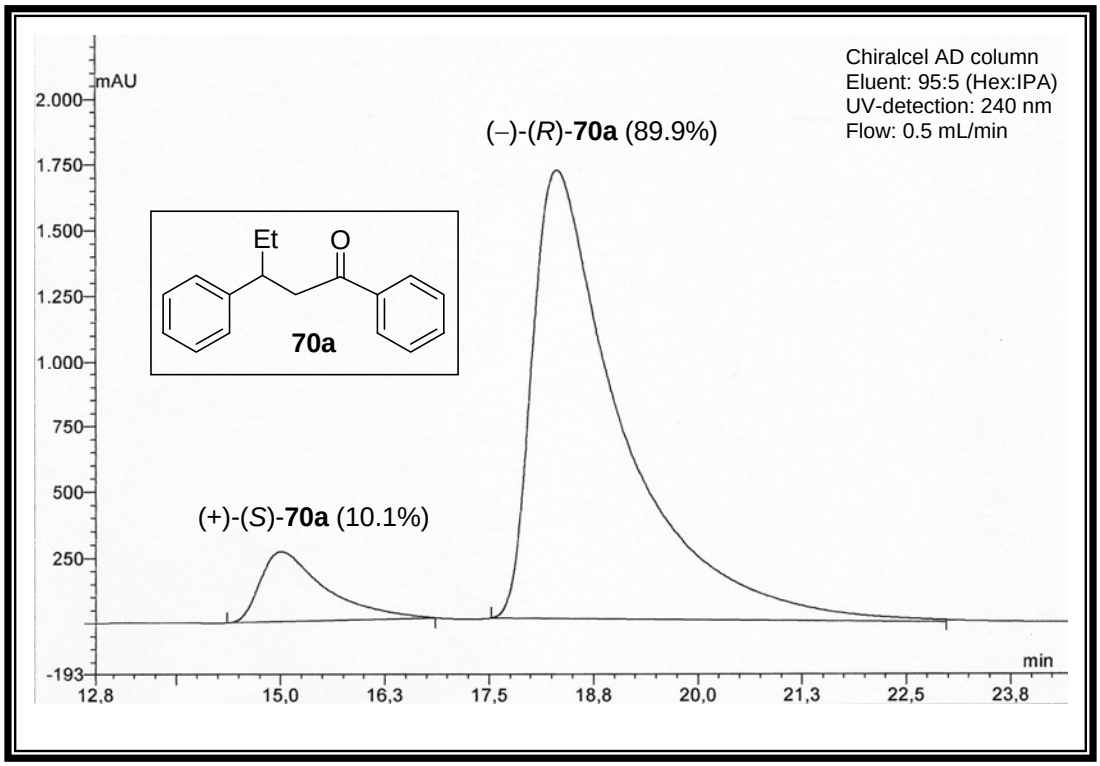

Figure A70. HPLC chromatogram of compound **70a** (80% ee)

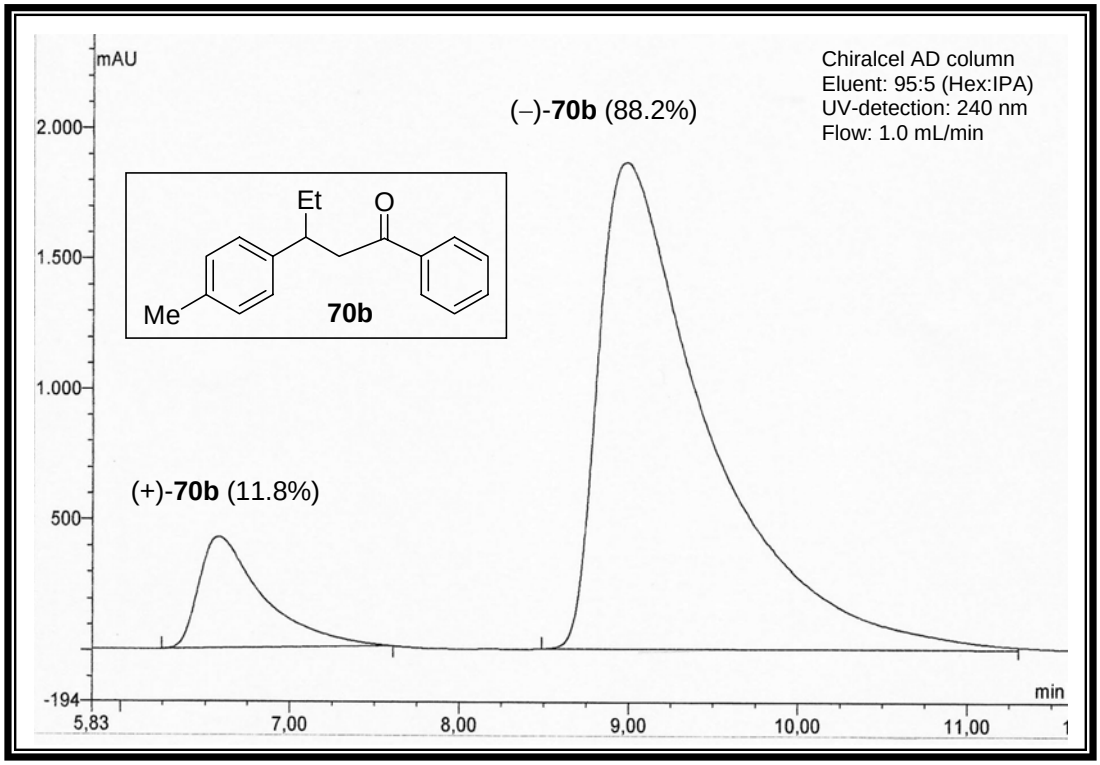

Figure A71. HPLC chromatogram of compound **70b** (76% ee)

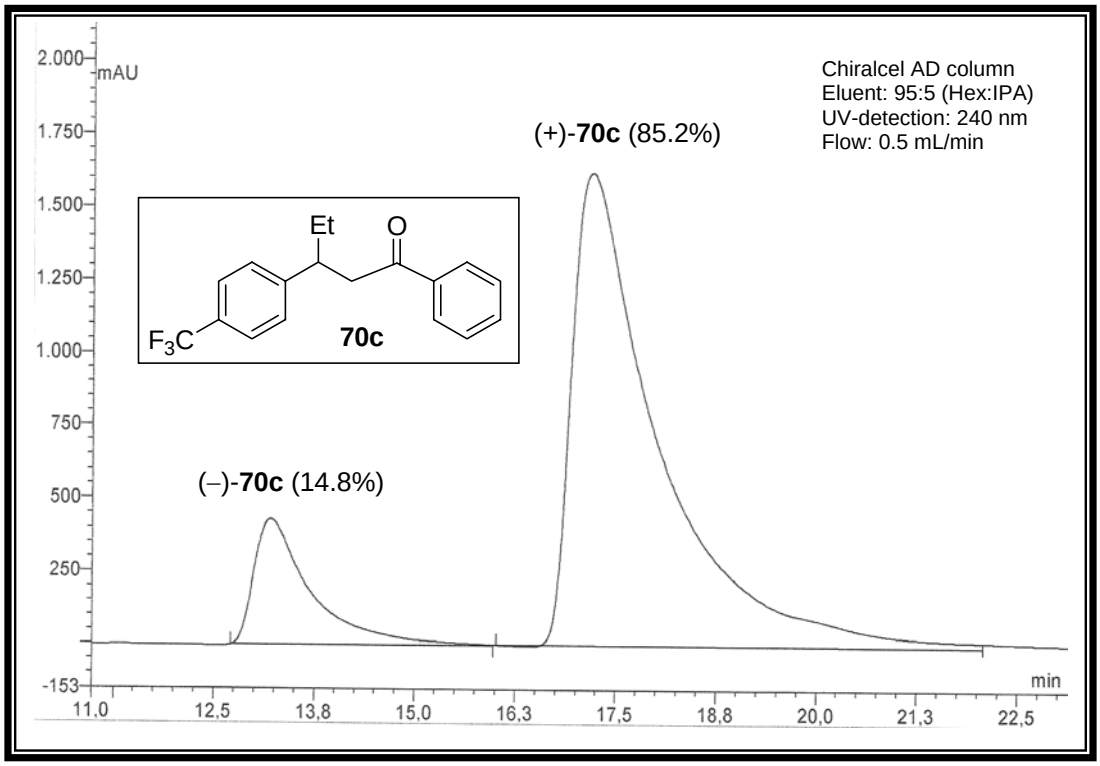

Figure A72. HPLC chromatogram of ester **70c** (70% ee)

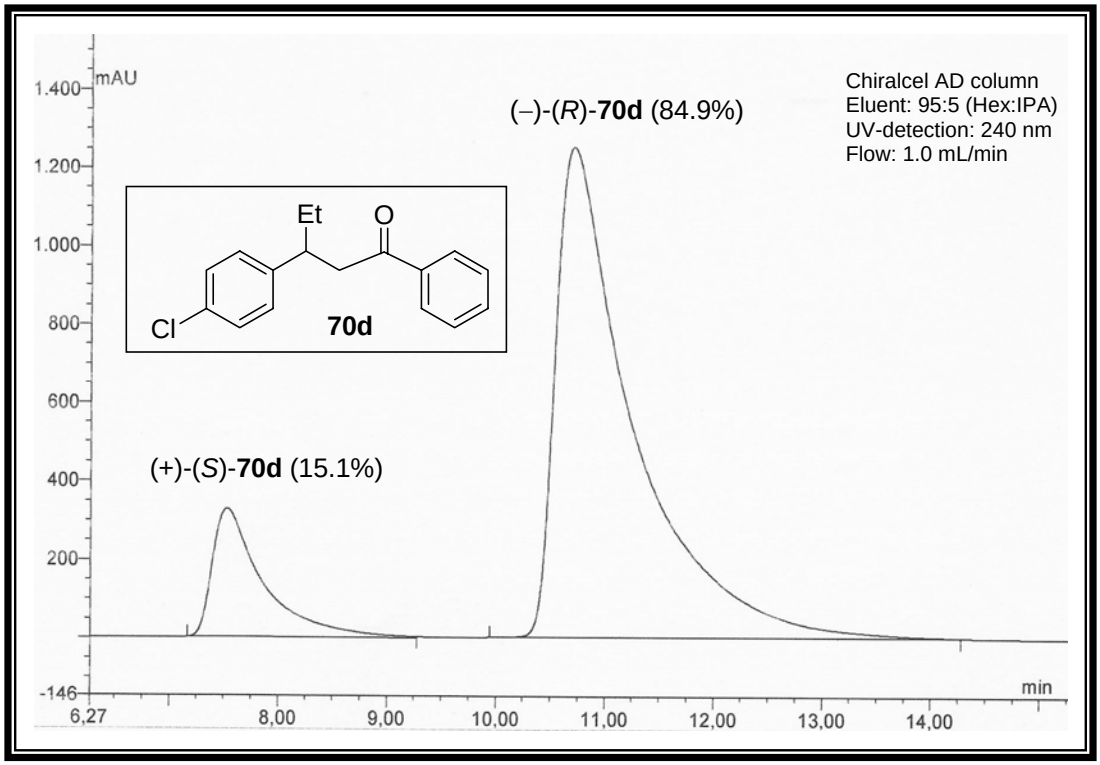

Figure A73. HPLC chromatogram of alcohol **70d** (70% ee)

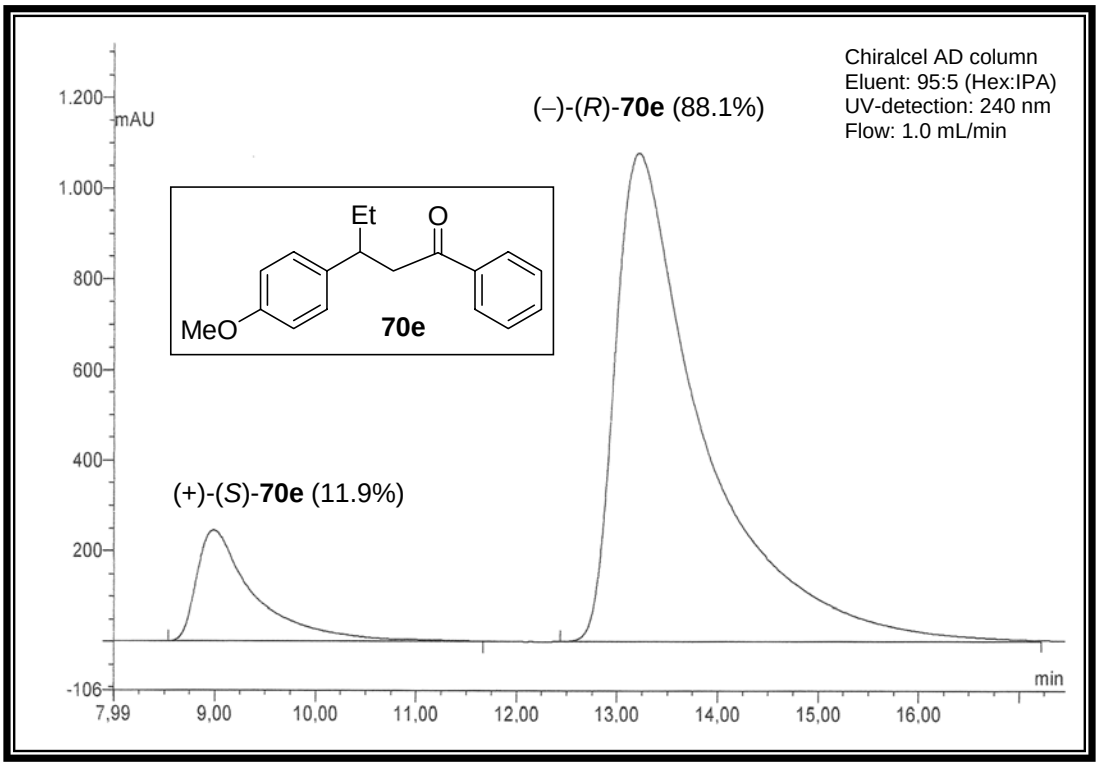

Figure A74. HPLC chromatogram of compound **70e** (76% ee)

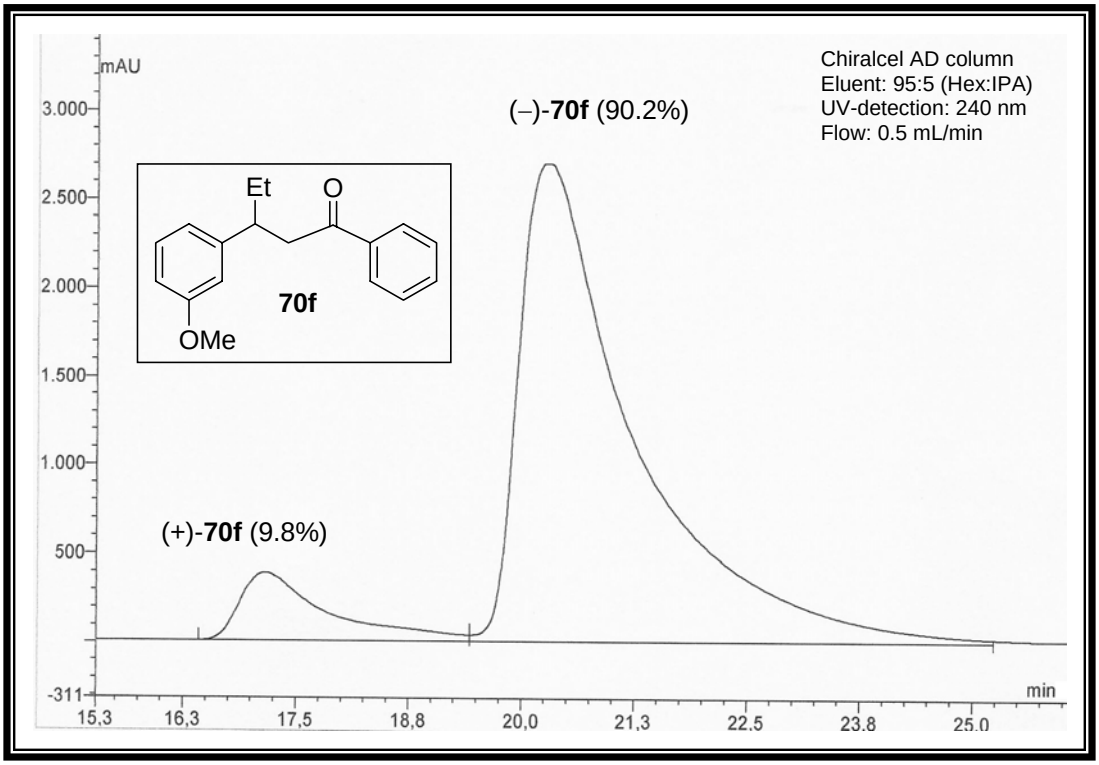

Figure A75. HPLC chromatogram of compound **70f** (80% ee)

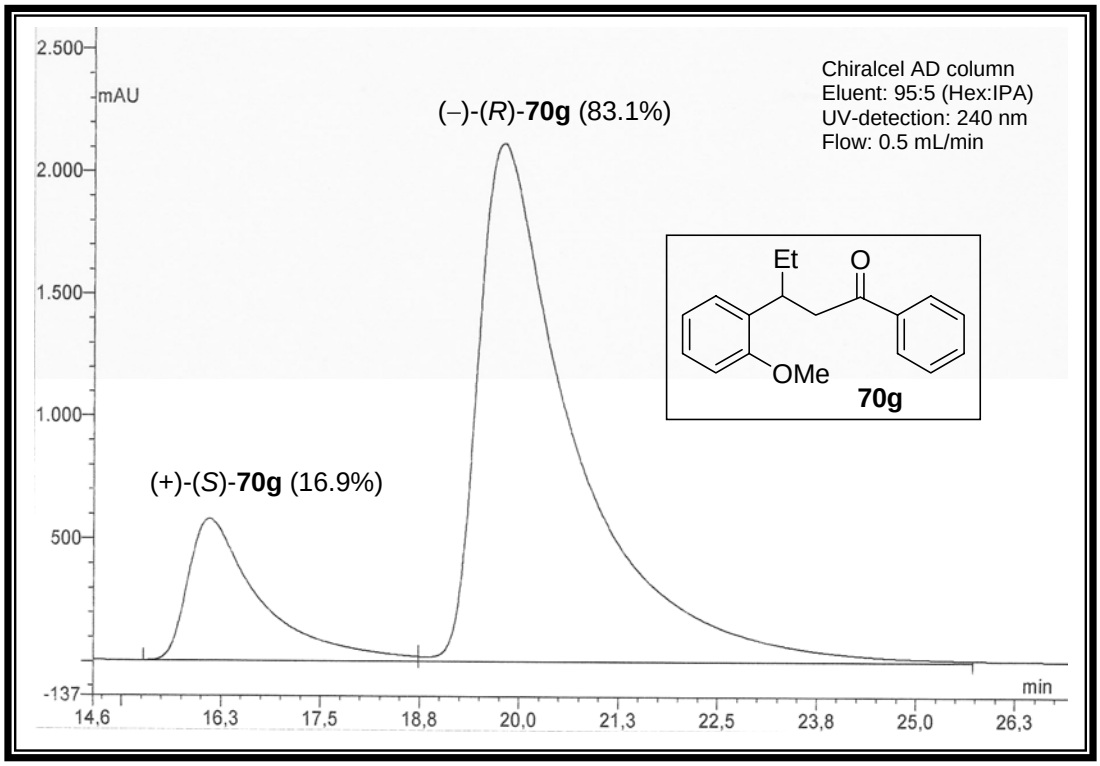

Figure A76. HPLC chromatogram of compound **70g** (66% ee)

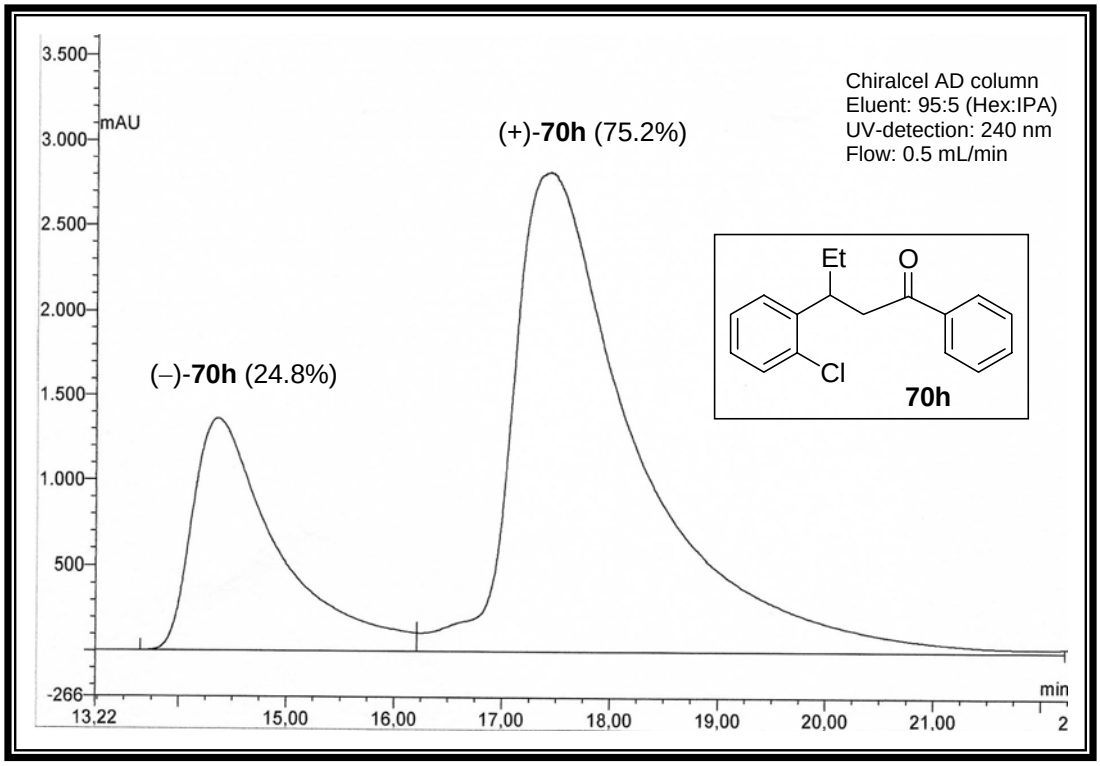

Figure A77. HPLC chromatogram of compound **70h** (50% ee)

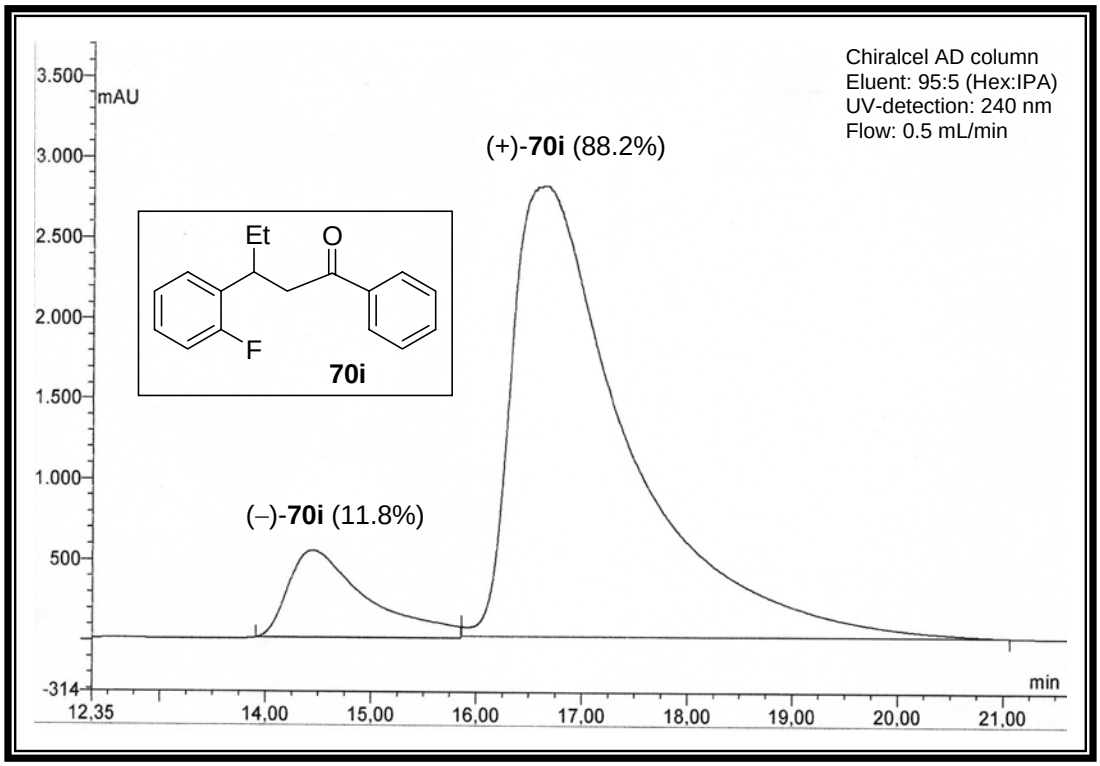

Figure A78. HPLC chromatogram of compound **70i** (76% ee)

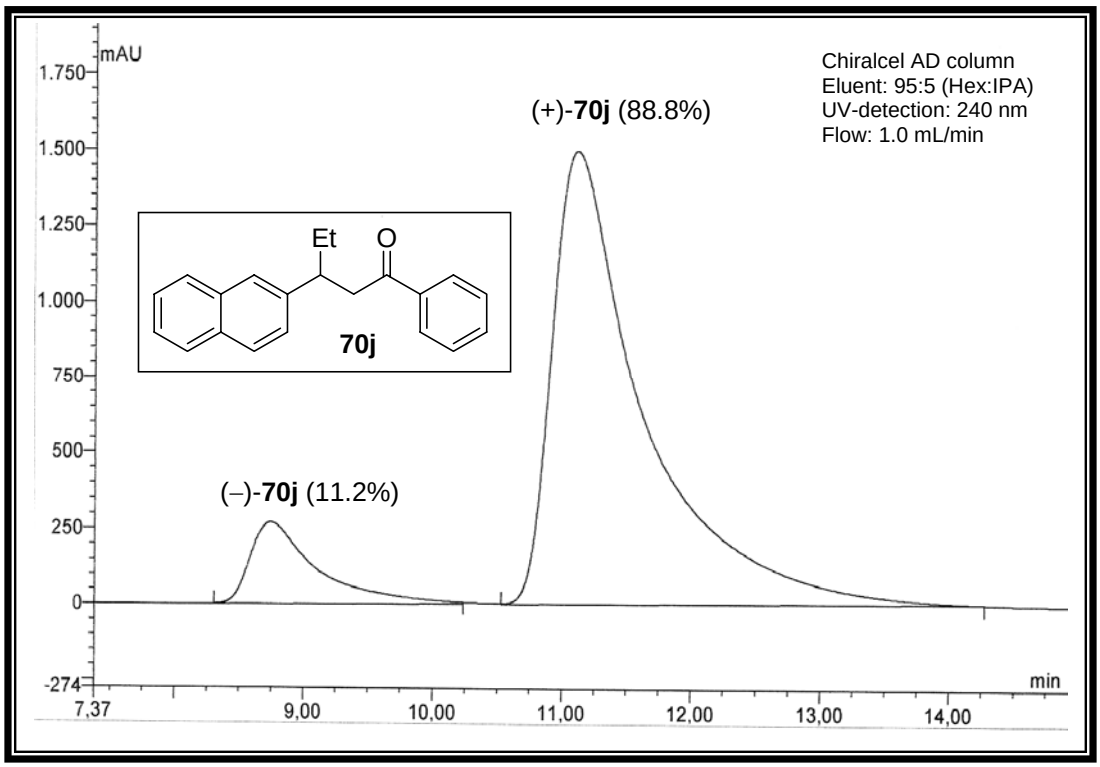

Figure A79. HPLC chromatogram of compound **70j** (78% ee)

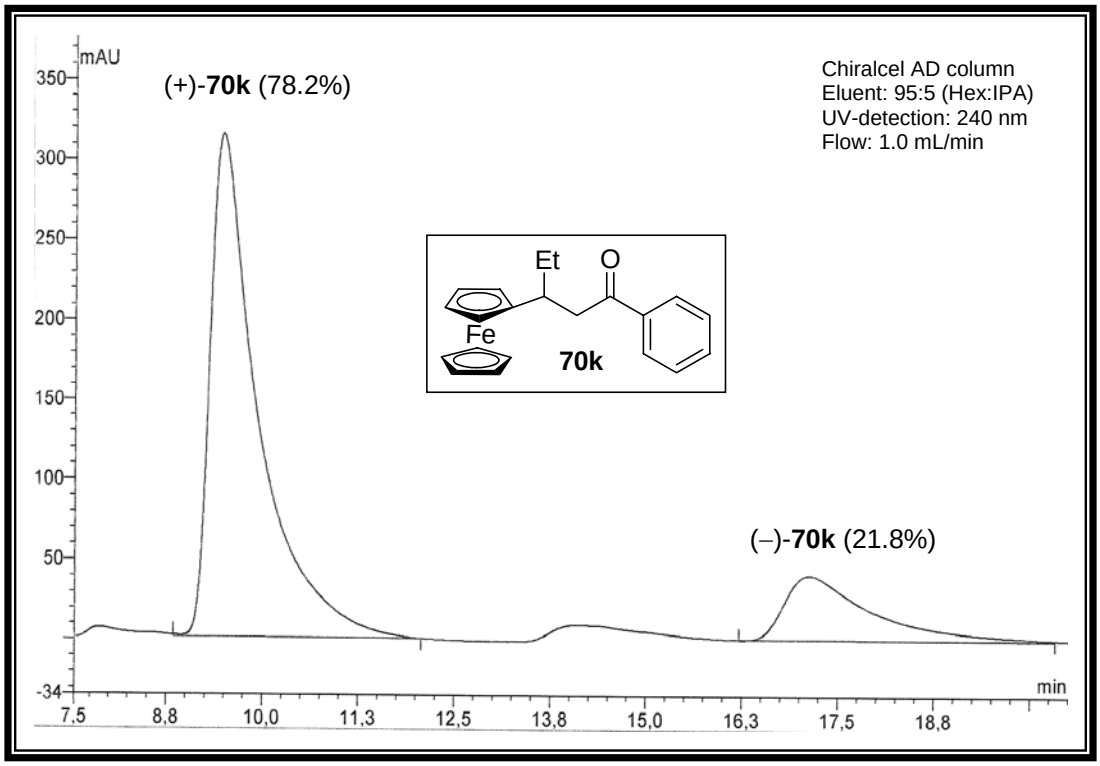

Figure A80. HPLC chromatogram of compound **70k** (56% ee)

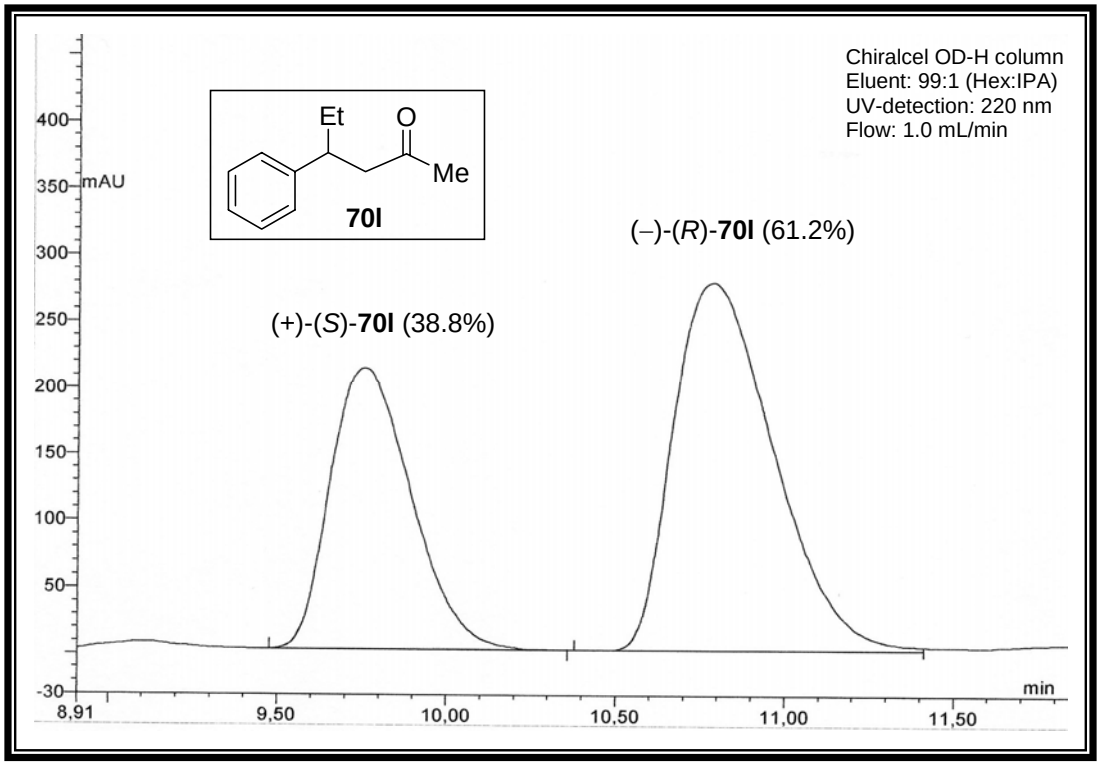

Figure A81. HPLC chromatogram of alcohol **70l** (22% ee)

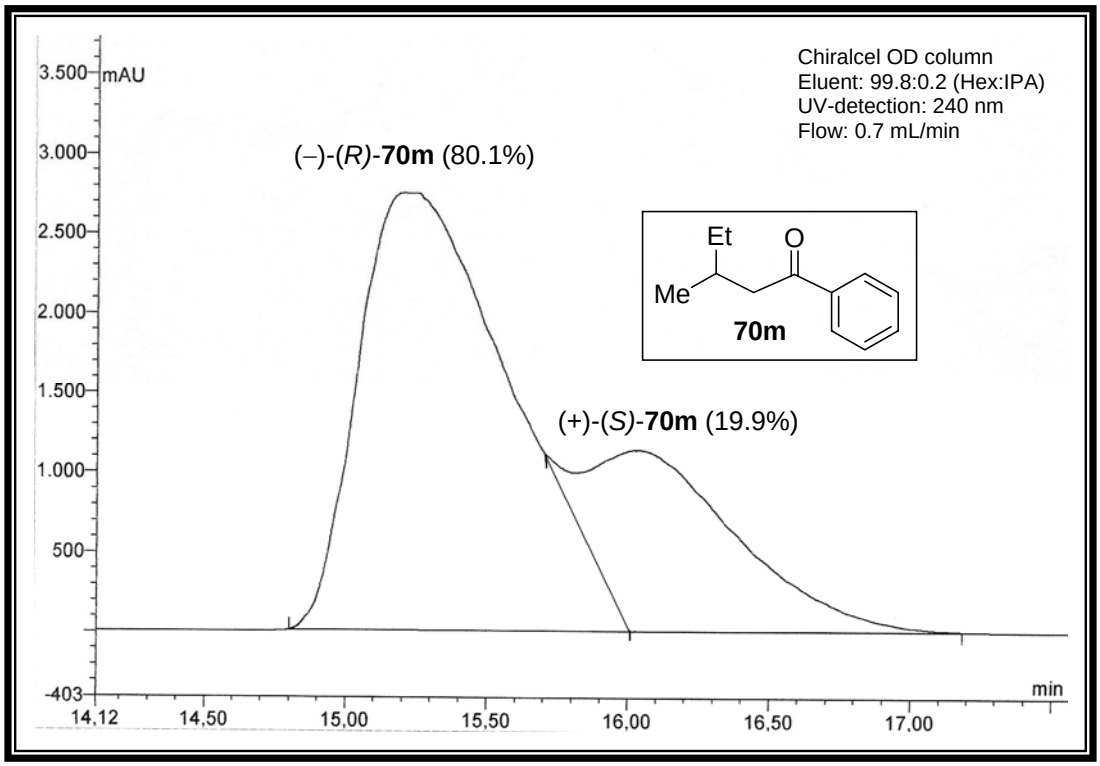

Figure A82. HPLC chromatogram of compound **70m** (60% ee)

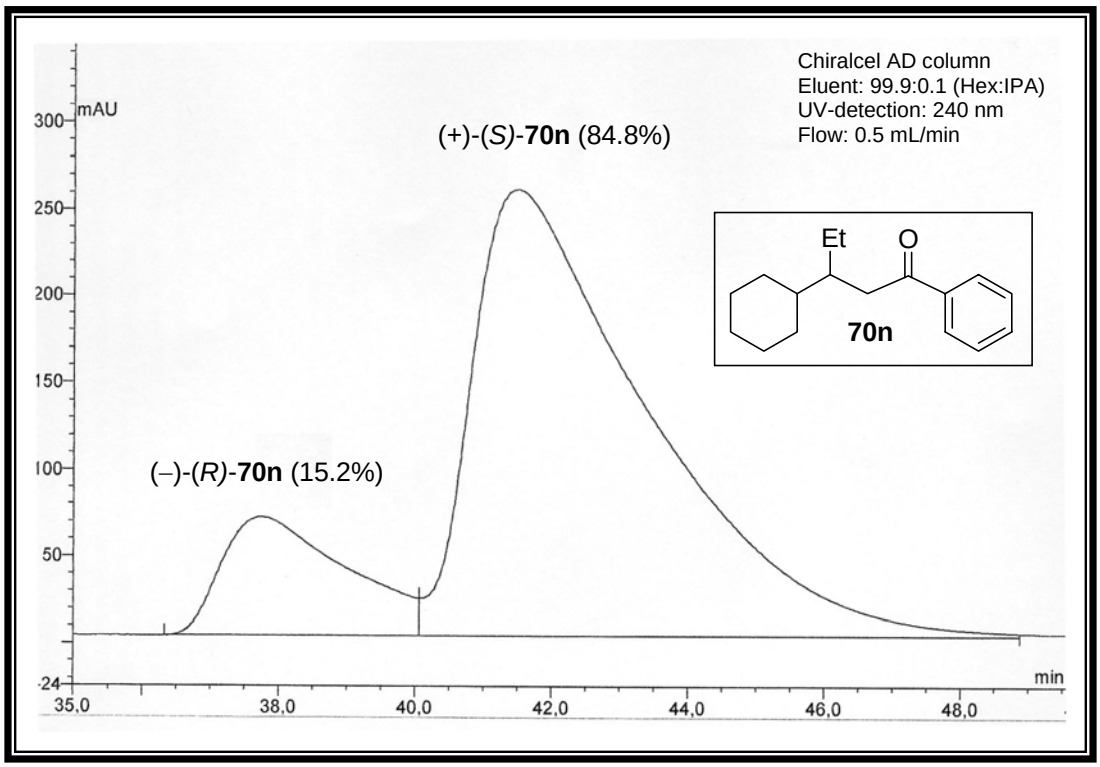

Figure A83. HPLC chromatogram of compound **70n** (70% ee)

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PUBLICATIONS

1. Isleyen, A.; Dogan, Ö. *Tetrahedron: Asymmetry*, **2007**, *18*, 679.
2. Isleyen, A.; Tanyeli, C.; Dogan, Ö. *Tetrahedron: Asymmetry*, **2006**, *17*, 1561.
3. Isleyen, A.; Dogan, Ö. *Synthesis*, **2006,** 1427.
4. İşleyen, A.; Sayraç, T.; Doğan, Ö. *Z. Naturforsch. B*, **2004**, 59, 109.