Organocatalyzed Reactions for Breaking Symmetry and Reduced Protecting Group Drug Synthesis

by

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A Thesis submitted in partial fulfillment
of the requirements for the degree of

Doctor of Philosophy
in Chemistry

Approved Dissertation Committee

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Life Science & Chemistry

Statutory Declaration
(Declaration on Authorship of a Dissertation)

I, Hussein Ali El Damrany Hussein hereby declare, under penalty of perjury, that I am aware of the consequences of a deliberately or negligently wrongly submitted affidavit, in particular the punitive provisions of § 156 and § 161 of the Criminal Code (up to 1 year imprisonment or a fine at delivering a negligent or 3 years or a fine at a knowingly false affidavit).

Furthermore I declare that I have written this PhD cumulative thesis independently upon my contribution, unless where clearly stated otherwise. I have used only the sources, the data and the support that I have clearly mentioned (see summary and contribution).

This PhD thesis has not been submitted for the conferral of a degree elsewhere.

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Contents

Abstract

The first part of my Ph.D. work focused on an ignored reaction, the enantioselective mono-aldolization of diketones. 4-substituted cyclohexanone based diketones were synthesized and it was convincingly shown that the regio-, diastereo- and enantiocontrol could be imparted at the cyclohexanone ketone carbonyl unit while acyclic methyl, aromatic, or benzyl ketones remained unreacted. The mono-aldol products were then converted into diastereomerically pure keto-1,3-diols or keto-lactones with excellent enantioselectivity ee. These advanced building blocks then allowed a variety of Alzheimer γ-secretase inhibitor drug targets to formally be accessed. Beyond those fundamental achievements, but within the same project, I was able to show a catalyst based achievement, the first useful access to previously inaccessible diastereomeric aldol products.

The last third of my research focused on the use of primary amine catalysts, amino acid based, for the first extensive broadening of the Michael substrate scope since its broader introduction decades ago. Here I was able to show that acidic functional groups, e.g., phenolic OH, amide NH, and carboxylic acid moieties are fully tolerated under catalytic enantioselective conditions. This is important because it shows that protecting groups can be avoided and this lead to the shortest and highest yielding route to (R)-Pristiq, (-)-O-desmethylvenlafaxine, a commercially prescribed antidepressant.

Summary and Contribution

I have two other co-authors on the first manuscript, see *Chem. Eur. J*. **2016**, *22*, 14342-14348, and they started that research before I joined our group. That said, my contributions reached a minimum of 40% of the total invested contribution and my key contributions were to: i) synthesize the aromatic diketone and the benzyl-diketone, ii) perform multiple difficult compound purifications that no other author could achieve for several acetonide and lactone products, iii) repeat of the Alzheimer drug synthesis steps to optimize the noted reactions, iv) provide X-ray acceptable crystals allowing the relative stereochemistry of the catalyzed reactions to be established, and v) provide circular dichroism (CD) cpectroscopy studies for assigning the absolute stereochemistry.

Regarding the same project theme as noted in the above paragraph, i.e., highly diastereo- and enantioselective mono-aldolization of diketones, but within the conceptual framework of providing the first useful quantities of a non-accessible epimer, I contributed a minimum of 50% to another manuscript, see: *Adv. Synth. Catal.* **2016**, *358*, 3706-3713. The results were a conceptual triumph, inversion of a remote stereogenic center, and were only possible because we employed an alternative catalyst template the desymmetrization of a 4-substituted cyclohexanone. It is important to note that access to those epimeric products cannot be achieved via alternative pathways in any efficient, step or yield, manner. I was able to keep this project going by providing: i) constant access to pure quantities of the picolylamine catalyst that catalyzed those reactions, ii) repetition of reactions to ensure reproducibility, and iii) endless purifications that allowed the full characterization of these products.

My final project related to a general deficit within the realm of total synthesis, the use of protection/deprotection protocols. Here I made a minimum 60% contribution to this research (see section 3.0 experimental for submitted manuscript). The conceptual significance was to provide the first guidance on how to broaden the common enantioselective Michael reaction to those which allow the Michael nucleophile or electrophile, e.g., β-nitrostyrene or maleimide, to contain an unprotected acidic spectator groups, e.g., phenols, maleimide NH groups, etc. and other co-authors using carboxylic acids, N-phenylamides, phenols, and catechols. I have demonstrated that these reactions proceed even when both the nucleophilic and electrophilic Michael partners simultaneously contain acidic spectator groups. The reactions have excellent starting material stoichiometries (1.0-2.0 equiv.), good yield (63-87%), and excellent ee (90-97%). Application of this method allowed me to actualize the first enantioselective synthesis of (R)-Pristiq, (-)-O-desmethylvenlafaxine, in the highest reported yield to date.

Acknowledgments

Foremost, I would start by thanking God for all the blessings that have been given to me. I thank all who in one way or another contributed in the completion of this thesis.

I would like to express my sincere gratitude and appreciation to my supervisor, Prof. Dr. Thomas C. Nugent, for his constant encouragement, thoughtful discussion, and continuous guidance. His knowledge, motivation, and support have helped me throughout my Ph.D.

Besides my advisor, I would like to thank the rest of my thesis committee: Prof. Dr. Nikolai Kuhnert and Dr. Muhammad Sharif Akbar, for their encouragement and insightful comments.

I am also thankful to all former and present members of the Nugent's group for the collaborative work, helpful discussions, and for all the fun that we have had together in the last three years. In particular, I would like to thank Dr. Foad Tehrani Najafian, Dr. Hussain Ishtiaq, Dr. Shahzad Ahmed for the shared projects. Also, I thank my best friends Khodr Saaifan, Khaleel Assaf, Mohammad Al-Najjar, who were sharing with me an extremely pleasant time here in Bremen.

I would like to thank Mahmoud Khalaf Aljoumhawy, Tony Georgiev, Asmita Manandhar, Jasmina Bier for their help with the different projects outlined in this thesis.

I am thankful to the Deutsche Forschungsgemeinschaft (DFG) for financial support, Jacobs University Bremen for providing the lab facility and consumables. I would like to thank Aswan University for giving me the opportunity and financial support to study abroad.

Last, but certainly not the least; I have to thank my parents and my family. Special thanks for my love, my wife, for her endless support, understanding, and love. Her support and encouragement have always inspired and helped me to overcome difficult moments.

Abbreviations List

aq.	aqueous
Ar	aryl
Bn	benzyl group
Boc	tertiary-butyl carbamates
bs	broad singlet (1H NMR)
*i*Bu	*iso*-butyl
*n*Bu	*n*-butyl
conv	conversion
CD	circular dichrosim
$CDCl_3$	deuterated chloroform
d	doublet (1H NMR)
dd	doublet of doublet (1H NMR)
ddd	doublet of doublet of doublet (1H NMR)
dq	doublet of quartet (1H NMR)
DCM	dichloromethane
de	diastereomeric excess
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylfomamide
DNBSA	2,4-dinitrobenzene sulfonic acid
dr	diastereomeric ratio
ee	enantiomeric excess
δ	chemical shift (1H NMR)
equiv	equivalent
ESI	electrospray ionization (Mass spectroscopy)
Et	ethyl
EtOH	ethanol
EtOAc	ethylacetate
h	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
J	coupling constant (1H NMR)
L-Pro	L-proline
m	multiplate (1H NMR)
M	molarity
Me	methyl
min	minutes
mmol	milimole
MS	mass spectroscopy
MW	molecular weight
m/z	mass/charge
m	*meta*
NMR	nuclear Magnetic Resonance
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate

Pd/C	palladium on carbon
Ph	phenyl
*i*PrOH	*iso*-propyl alcohol
*i*Pr	*iso*-propyl
*n*Pr	*n*-propyl
Pt/C	platinum on carbon
PPTS	pyridinium *p*-toluene sulfonate
Pyr	pyridine
q	quartet (1H NMR)
RT	room temperature
Ru/C	ruthenium on carbon
R	alkyl group
Ref	reference
s	singlet (1H NMR)
t	triplet (1H NMR)
TBDPS	*tert*-butyl diphenyl silyl
TBS	*tert*-butyl dimethyl silyl
t-Bu	*tert*-butyl
tert	tertiary
temp	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TFA	trifluoroacetic acid
TMS	tetramethylsilane

Chapter 1
Introduction

1.0 Introduction

1.1 Brief History on Organocatalysis

Organocatalysis chemistry was started in 1912,[1] when a cyanohydrin has been synthesized first *via* cinchona alkaloids by Bredig and Fiske. But this research area exponentially increased after the 1971 Z. G. Hajos and D. R. Parrish, and simultaneously U. Eder, G. Sauer and R. Wiechert, finding that triketones could undergo very selective intramolecular aldol reactions in the presence of proline.[2-4] In the recent years various examples of different organocatalysts have been reported for asymmetric reactions e.g. aldol, Mannich, and Michael reactions.

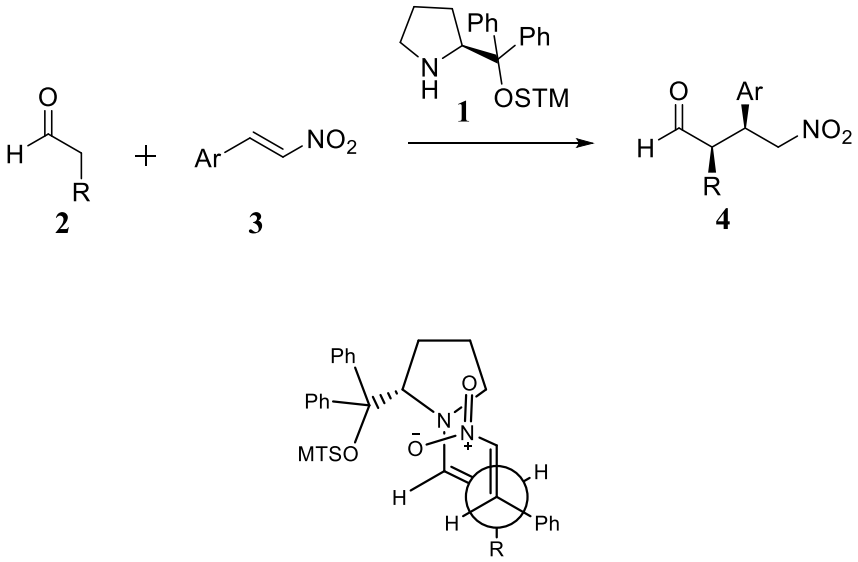
Today, organocatalysis is a rapidly rising field within organic chemistry, which describes the concept of using a sub stoichiometric ratio of organic molecules for accelerating chemical reactions to achieved complex molecular skeletons from simple molecules.[5,6] These methods have either directly competed with or complement the advanced building blocks formed via enzymes and metal complexes based catalysis for applications in the fields of the pharmaceutical and agricultural industry. During the early 2000's proline catalyzed asymmetric aldol reactions were reported by B. List, R. A. Lerner, and C. F. Barbas III.[7] Also in the same year MacMillan reported enantioselective organocatalytic Diels Alder reaction.[8] This very early organocatalyst research showed that chiral amines play an important role in stereoselective organocatalysts and unleashed an enormous number of creative catalytic outlets therefrom. Concerning the use of chiral amines for enamine based organocatalysis, secondary amines are the most common as compared to primary amines, perhaps because they were not thought to tautomerize the initially formed imine to an enamine readily enough for productive reactions to occur. In general organocatalysts can be widely categorized as Brønsted acids or Brønsted bases.

Sections 1.1.1 to 1.2.7.3 follow and the goal here is to present a very general and simplified conceptual overview of how an asymmetric aldol reaction with cyclohexanone substrates can be catalyzed by amine organocatalysts such as proline (1.1.2) based catalyst. This is important because those concepts are in step with the catalysts I used. For perspective, I remind the reader that much of my research focused on the desymmetrization of 4-substituted cyclohexanone based diketones. No one has ever invested those type of substrates, but researcher have investigated the desymmetrization of 4-substituted cyclohexanones. That is cyclohexanones with a 4-positioned substituent but not with an acyclic ketone present. Thus I

now outline those research efforts and accomplishments so that some comparisons can be made with our higher level challenge of also having an acyclic ketone present.

1.1.1 Steric Based Organocatalysts

This category of organocatalysts employs steric hindrance, as opposed to non-covalent attractive forces, to impart diastereo- and enantiocontrol in the products. In the presence of a nucleophilic nitrogen atom, within a steric based organocatalyst, an enamine is produced. A blocking moiety then directs the electrophile to attack the enamine from the opposite, least hindered, face. To our attention, we are unaware of any practical asymmetric aldol reactions that use steric based organocatalysts (Scheme 1), but Michael reactions often use these types of catalysts.[9,10]

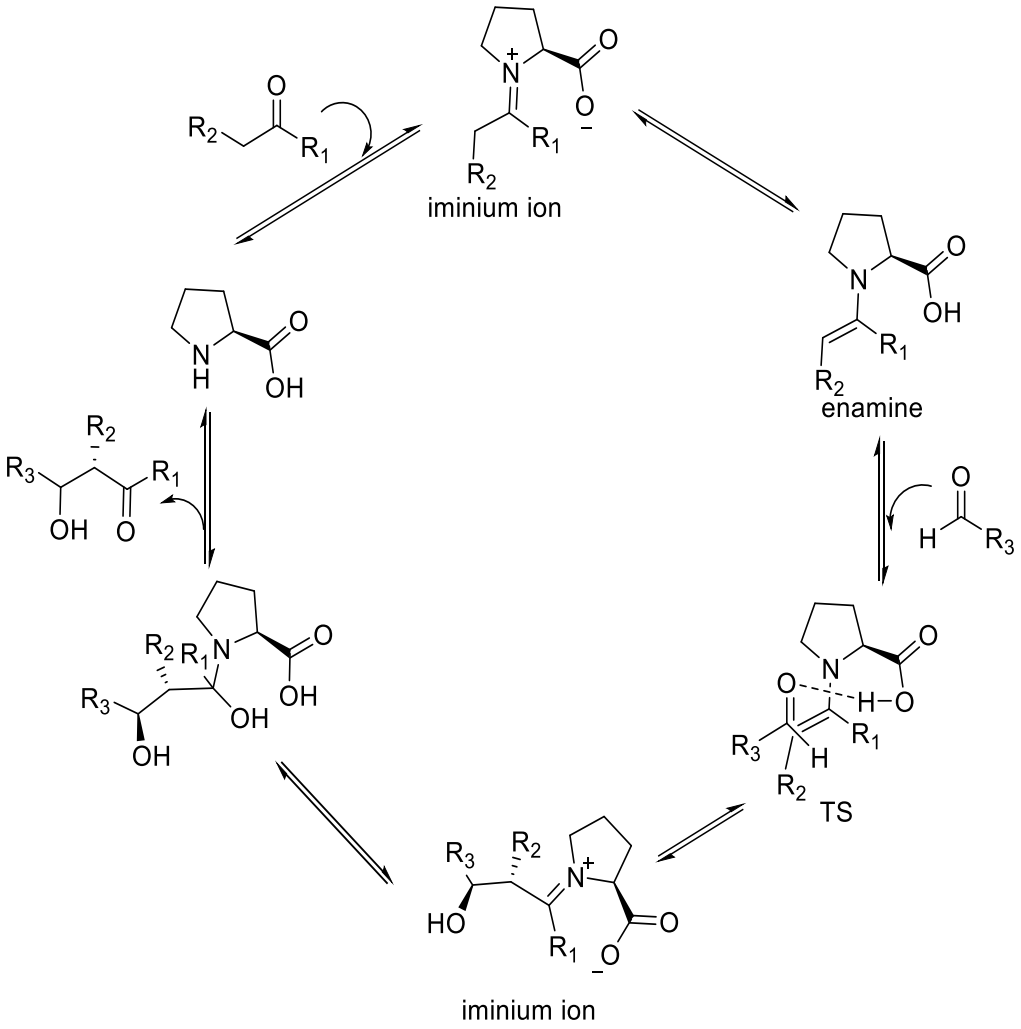


Scheme 1 Steric based organocatalyst.

1.1.2 Bifunctional Organocatalysis and Enamines

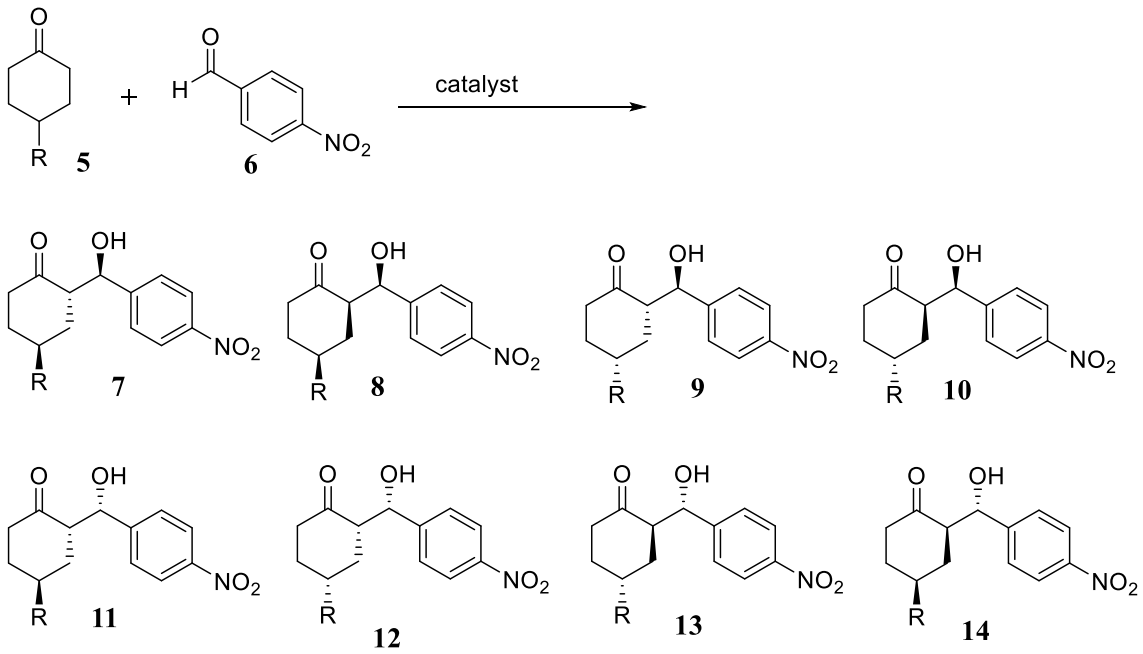
Bifunctional organocatalytic reactions are driven by two functional groups: a hydrogen bond donor and a nucleophilic hetero-atom, for example a primary or secondary amine. The amine activates the nucleophile by converting an aldehyde or ketone into enamine, which is higher in energy than a corresponding enol HOMO.[11] The electrophile is additionally activated by a hydrogen bond donor on the catalyst, this lowers the LUMO energy. When the catalyst is

correctly designed the space proximity of the amine and the hydrogen bond donor on the catalyst will allow the nucleophilic carbon of the enamine to be in close proximity to the electrophilic atom of the electrophile. This is displayed using the most organocatalyst, L-proline (Scheme 2).



Scheme 2 Enamine catalysis cycle of bifunctional organocatalysts.

1.2 A Comprehensive Overview of 4-Substituted-Cyclohexanone Desymmetrization with Aromatic Aldehydes



Scheme 3. These stereoisomers are all potential products for desymmetrization of 4-substituted-cyclohexanones.

The desymmetrization of 4-substituted-cyclohexanones provides a minimum of two stereogenic centers and when the electrophile contains a prochiral face, the most often situation, then three stereogenic centers are formed (Scheme 3). For sections 1.2.1 to 1.2.7.3, a specific 4-substituted-cyclohexanone is shown reacting with an aldehyde, most commonly an aromatic aldehyde. Thus, for all examples shown here, the formation of three stereogenic centers from two achiral starting materials (4-substituted-cyclohexanones and aldehydes) is noted (Scheme 3). These types of transformations are important because they demonstrate the conversion of relatively simple achiral starting materials, in one step, into products of high complexity.

The framework for this historical review section is now briefly described. The most studied 4-substituted-cyclohexanone, 4-methyl-cyclohexanone, is shown first (section 1.2.1) from the perspective of the electrophile that has been most often reacted with it, namely *p*-nitrobenzaldehyde (section 1.2.1.1). This tabularized data is followed by the reaction of 4-methyl-cyclohexanone with all other *para*-substituted benzaldehydes (section 1.2.1.2), then with all *meta*-substituted benzaldehydes (section 1.2.1.3), and finally all *ortho*-substituted

benzaldehydes (section 1.2.1.4). After 4-methylcyclohexanone, the number of alternative 4-substituted cyclohexanones dramatically lessens, but are reviewed here. I start with 4-ethyl-cyclohexanone (section 1.2.2), followed by other simple 4-substituted cyclohexanone substrates. The literature examination ends with a review of the known, but small number, of 4-heteroatom substituted cyclohexanone substrates. In short, the sections begin with the bench mark reaction, 4-methyl-cyclohexanone with *p*-nitrobenzaldehyde, and ends with the least frequently examined 4-substituted-cyclohexanone substrates.

A recurring theme that is immediately noted in the below tabularized data is that the vast majority of the examples require chiral enamine catalysis to afford the products. The few examples that require a transition metal, see Table 1 (entries 10 and 11), Table 3 (entry 2) and Table 4 (entry 5), are not competitive with the best organocatalyzed reactions. Regarding all of that summarized literature, all of the catalyst structures have been placed in Figure 1 and 2. Please additionally note that no racemic products were included in this review.

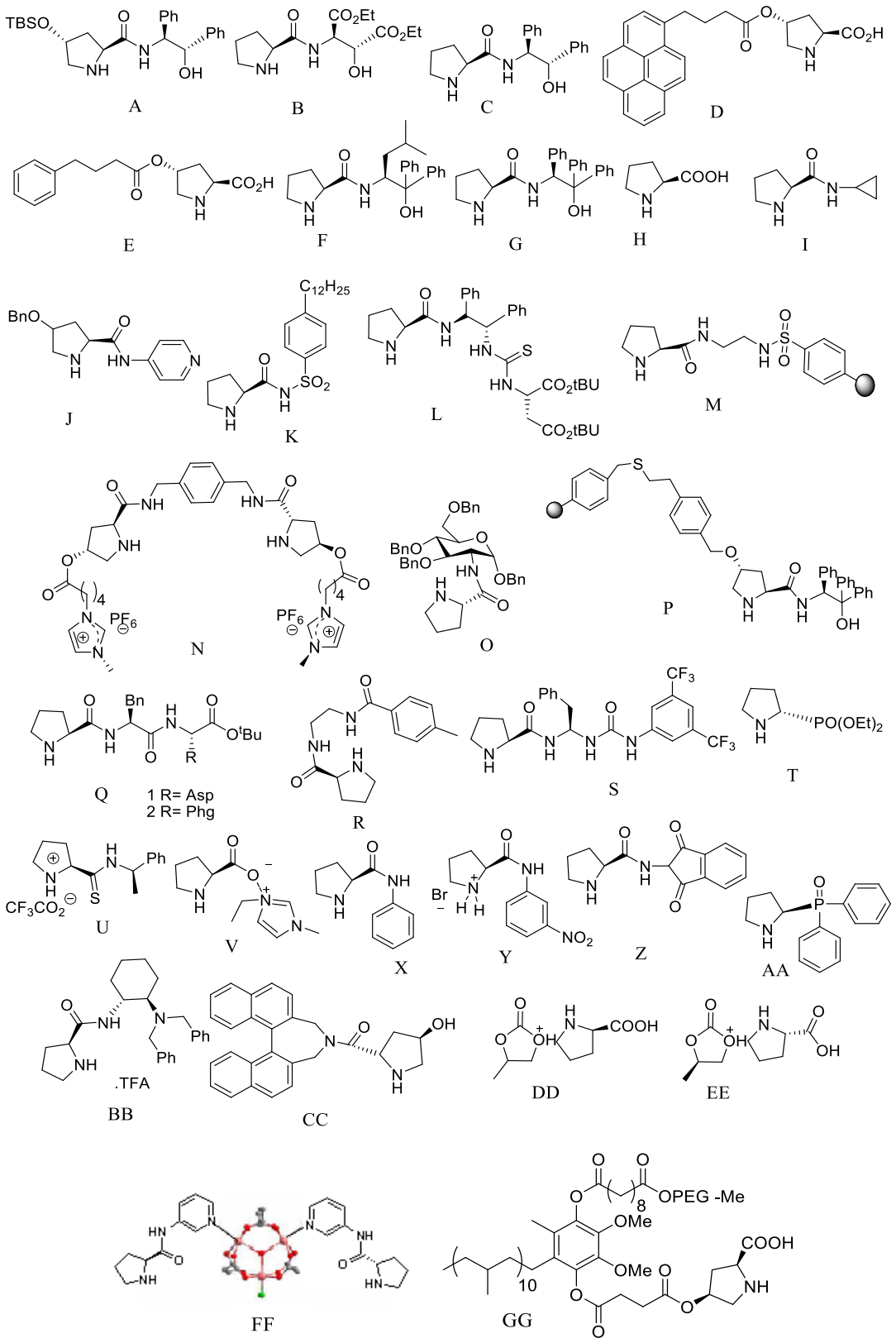


Figure 1. Proline based catalysts for 4-substituted cyclohexanone desymmetrizations.

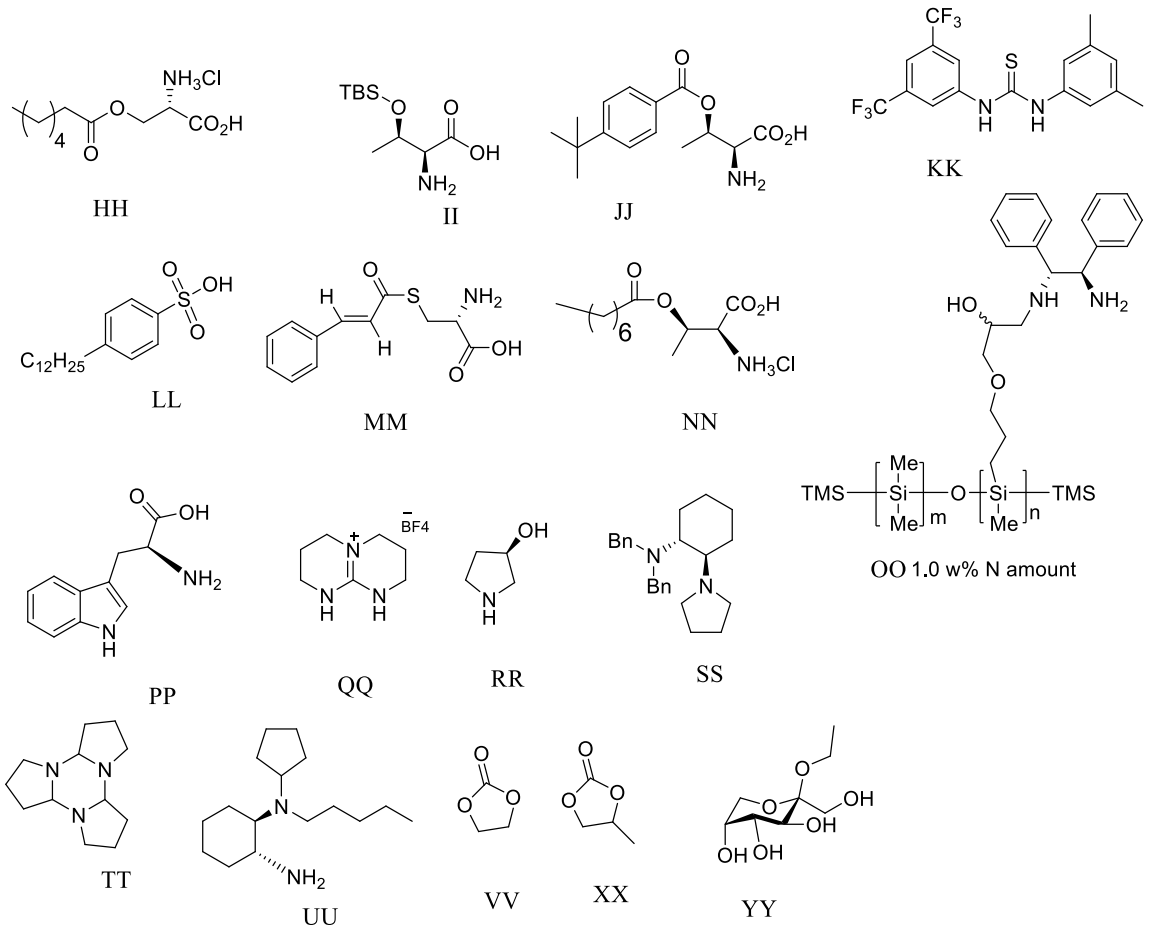


Figure 2. Non-proline based catalysts for 4-substituted cyclohexanone desymmetrizations.

Finally, each section (1.2.3 to 1.2.7.3) will begin with a generic reaction scheme to orient the reader regarding the reaction under discussion, this will be followed by a critical overview of the data in the table soon after the description. Regardless of the type of catalysis under review, the important parameters are always the same. It is obvious that high yield and stereoselectivity are critical, but reference points need to be established and here we arbitrarily refer to yields >85% as excellent, those between 75-84% as good, and those between 60-74% as mediocre. In a very broad sense, we will refer to enantiomeric excess (ee) values of the major product as high (excellent) when >90%, and note that the corresponding diastereomeric ratio (dr) when >15:1 as high, good when >10:1, mediocre when >5:1. High ee and dr are critical, and it must be noted that researchers in this area rarely discuss/note the ratios of all possible eight diastereomers resulting from the three stereogeneric centers formed during these reactions, instead researchers almost unanimously only state the *R*/*S* ratio of the two adjacent stereogenic centers α and β to the cyclohexanone carbonyl carbon, while ignoring comment on the remote stereogenic center. That leaves the 4-substituent, on the cyclohexanone, stereochemically undefined; but a deeper reading of those manuscripts and correlations to others either shows

that the main catalyst type examined, natural proline (L-proline, which is *S*-proline), provides >15:1 dr for the 4-substituent on the cyclohexanone. To be clear, I am referring to the diastereomers in which the alpha and beta stereogenic centers are static, while the 4-substituent is either up or down in reference to the cyclohexanone ring generic, Scheme 3 at the beginning of this section. That said, it was also apparent to us that many researchers have avoided this discussion and just assume that the 4-substituent on the cyclohexanone is in the up (β-face) position as depicted in generic scheme 3. That is unsettling to us, but it reflects the current literature. Thus, in the tables you will only see dr expressed as the ratio of the adjacent alpha and beta stereogenic centers without reference to the stereogenic center where the 4-substituent resides on the cyclohexanone.

Beyond the assumed high yield and stereoselectivity requirements of any methodology (enzymatic based, transition metal based, organocatalysis based), the discussion must focus on and define what the best current stoichiometry for the starting materials are. In this semi-review that means the 4-substituted-cyclohexanone and the aldehyde. Just as importantly, this information must be coupled with the catalyst loading (this is expressed in a mol%). A combination of yield, stereoselectivity, starting material stoichiometry, and catalyst loading are the paramount factors that consequently define the best methodologies. Catalyst cost, catalyst synthesis, reaction times, solvent, molarity, *etc*. are important, but generally secondary to these parameters and are used to differentiate very similar literature results.

The importance of the above noted literature becomes relevant when examining my research on diketone based 4-substituted cyclohexanones (*Chemistry a European Journal* **2016**) which is very briefly summarized in Figure 3 (see next page). For example, using 2.0mol% of the noted proline based catalyst (Figure 3, left panel) I was able to equal, but usually exceed, all previous best indicated diastereomeric and enantiomeric highs for type I products with very good yields. This was accomplished under the extremely practical reaction conditions in which 1.5 equiv. of the diketone were used. Those are important milestones, but here the higher level conceptual achievement was that all of this was possible in the presence of another, non-reactive, ketone carbonyl unit which was located on the 4-substituent of the 4-substituted-cyclohexaone. In total our diketone desymmetrizations (see manuscripts within this thesis) were able to control the carbonyl site-selectivity (regiochemistry), while providing the very good to excellent diastereo- and enantiocontrol.

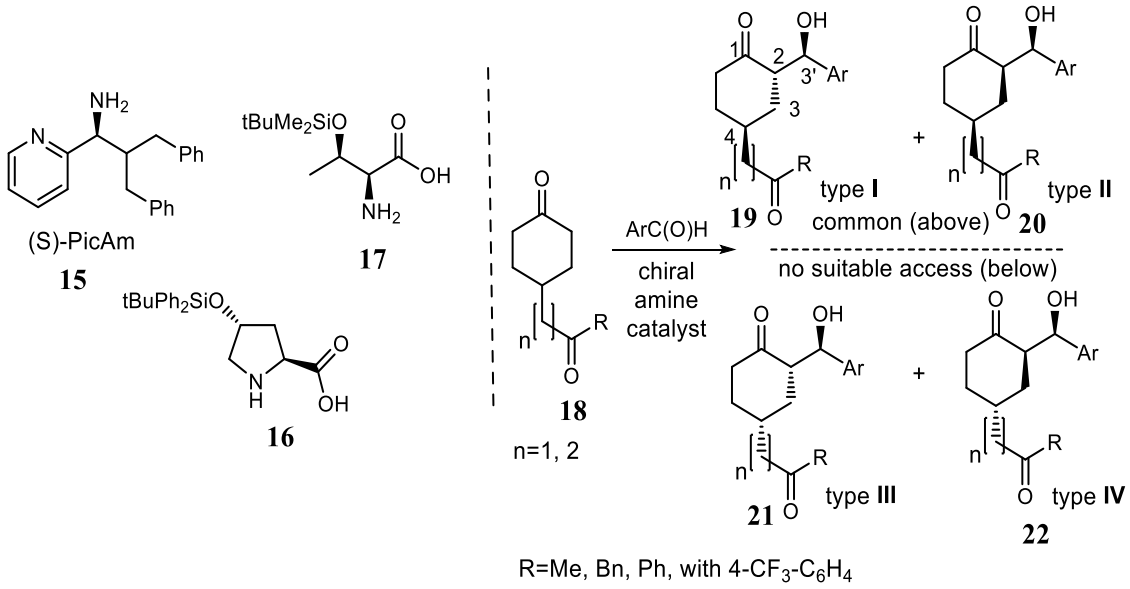
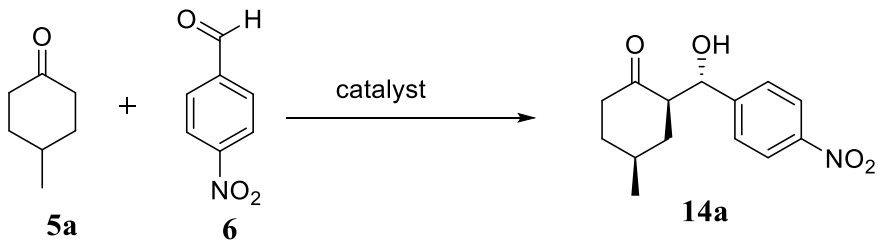


Figure 3 Different catalysts I used to impart desymmetrization on 4-substituted-cyclohexanones based diketones.

It needs to be noted that when desymmetrizing a 4-substituted-cyclohexanone only type I products can currently be accessed with any practical yields. In my second manuscript (*Advanced Synthesis & Catalysis* **2016**) based on diketones I was able to show the first practical access to type III products when using the (S)-PicAm (Figure 3, left panel).

1.2.1 4-Methylcyclohexanones with Aromatic Aldehydes

1.2.1.1 The Reaction of 4-Methylcyclohexanone with p-Nitrobenzaldehyde



Scheme 4 The reaction of 4-methylcyclohexanone with p-nitrobenzaldehyde, the shown product is the major product under L-proline catalysis.

Table 1 summarizes the most popularized desymmetrization, the reaction of 4-methylcyclohexanone reacting with *p*-nitrobenzaldehdye. As noted in the introductory material all Tables have been arranged according to the best stoichiometry of the 4-substituted cyclohexanone starting material as compared to the aldehyde. Entry 2 shows the use of a 1:1

ratio of the starting materials, but it is also noted that the yield is poor (60%) and the catalyst loading is relatively high (10 mol%). From this prospective, entries 1 (1.5 equiv. of 4-methylcyclohexanone) and 6 (2.0 equiv. of 4-methylcyclohexanone), respectively by Gryko[12] and Fu[13], would represent the best current results. Gryko used 5.0mol% of a thioamide proline derivative with an incorporated chiral phenyl ethyl amine moiety U in Figure 1, while Fu employed 5 mol% of an O-tBu-benzoyl protected threonine catalyst (catalyst JJ, Figure 2). For both of these reactions the yields and stereoselectivity are excellent and the reaction times are very good.

Further examination of the data shows similar yield and stereoselectivity was obtained by other researchers, but there was always some associated negative attribute, e.g. significantly higher ketone stoichiometries or catalyst loadings. From those type of results, the most interesting are the research of Singh, entry 17 (0.5mol% loading, 4.0 equiv. of 4-methylcyclohexanone), Luo[14], Liu[15], Concellon[16] and Rios[17] (entries 3, 21, 30, 32) respectively. The former work required the combination of proline based catalysts with co-catalyst, also Reiser[18] and Fu[19] entry 10 and 11 combined proline catalysts with metal catalyst, while Gruttadauria[20], entry 28 (2.0 mol% loading, 5.0 equiv of 4-methylcyclohexanone) took advantage of investigation two very similar 4-OH alkylated proline catalysts to again produce high yield and stereoselectivity smeller by Singh[21] and Kokotos[22] entry 17 and 25. These are interesting results, but from a practical point of view, and especially when the ketone is even slightly expensive, they are less interesting.

Table 1. A summary of 4-methylcyclohexanone reacting with p-nitrobenzaldehdye (Scheme 4).[a]

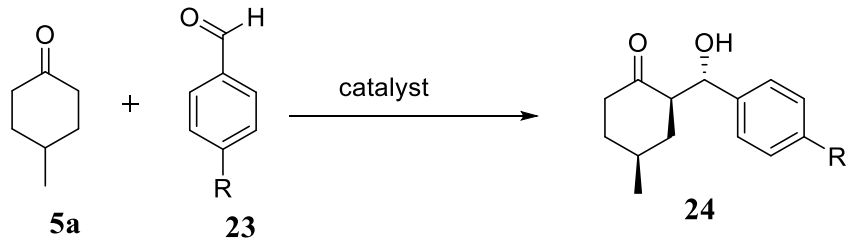
Entry	Equivalent ketone	Catalyst	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee*%[d]	Reaction time
1[12]	1.5	U	5mol%	87	>95 : 5	97	16 h
				97	>95 : 5	92	36 h
2 [23]	1	SS	10mol%	60	99:1	94	24 h
	2			89	98:2	96	
3[14]	2	J with LL	10mol%	90	>16:1	99	12 h
4[24]	2	O	20mol%	93	Not mentioned	92	8 h
5[25]	2	M	20mol%	80	94:6	95:5	48 h
6[13]	2	JJ	5mol %	98	95:5	97	12 h
7[26]	2.5	HH	5mol%	95	93:7	96	24 h

		Et_3N	5mol%				
8[27]	3	UU	10mol%	77	82:1	98	24 h
9[28]	3	N	10mol%	89	88:12	98	24 h
10[18]	3	H&$CoCI_2$	20mol%	83	10:1	77	48 h
		H		50	1.7:1	84	36 h
11[19]	4	BB	10mol %	95	90:10	96	24 h
		$ZnCl_2$	10mol %				
12[29]	4	Z	15mol%	85	93:7	89	18 h
13[30]	4	I	5mol%	95	97:3	96	24 h
14[31]	4	X	5mol%	99	99:1	97	24 h
15[32]	4	MM	5mol%	90	95:5	93	24 h
16[33]	4	HH	10mol%	90	95:5	97	30 h
17[21]	4	F or G	0.5mol%	90	Not mentioned	>99	35 h
18[34]	5	PP	10mol%		1:4	73	36
19[35]	5	Y	20mol%	88	Not mentioned	95	24 h
20[36]	5	K	20mol%	93	49:1	97	72 h
21[15]	5	AA with TT	20mol%	61	64:26	85	48 h
22[37]	5	V	30mol%	85	29:71	97:99	24
23[38]	5	P	10mol%	54	97:3	96	48 h
24[39]	5	K	20mol%	93	49:1	97	72 h
25[22]	5	Q 1	5mol%	91	97:3	99	24 h
		Q 2		43	70:30	82	24 h
26[40]	5	R	10mol%	88	98:2	96	22 h
27[41]	5	S	10mol%	90	99:1	99	24 h
28[20]	5	D	2mol%	87	94:6	99	48 h
		E			98:2	98	
29[42]	10	OO	20mol %	94	>19:1	98	16 h

30[16]	10	H with QQ	15mol% 10mol%	81	86:14	97	36 h
31[43]	10	A B C	5mol%	90 46 90	Not mentioned	>99 74 79	4d 2 d 2 d
32[17]	10	H with KK	20mol%	85	10:1	99	5d
33[44]	10	II	10mol%	90	94.5:5.5	>99 up 97 down	90 h
34[45]	10	L	10mol%	99	93:7	99	24 h

[a]Arranged based on the number of equivalents of the 4-methylcyclohexanone used to react with *p*-nitrobenzaldehyde.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC.

1.2.1.2 The Reaction of 4-Methylcyclohexanone with p-Substituted Benzaldehydes



Scheme 5 The reaction of 4-methylcyclohexanone with p-substituted benzaldehydes.

A review of the literature shows that a handful of alternative functional groups have been studied at the *para* position of 4-substituted benzaldehydes, they are: H, F, Cl, Br, CF_3, and CN and they are now shortly discussed. In general it can be stated that *para*-halogenated benzaldehydes provide mediocre to good yield and good to excellent stereoselectivity, with the results outlined in entry 3 (Table 2) by Gong[43] looking the most appealing because they represent the lowest catalyst loading (5mol%) in this group.

A notable limitation is also apparent. When considering the reaction product when the *para*-substituent is hydrogen (benzaldehyde substrate), the stereoselectivity is excellent but the reactions are not practical. As seen in Table 2, the yields are 41% and 46% (R=H, entries 1 and 4). It is further noted that no weakly donating, e.g. methyl, or strongly donating, e.g. methoxy,

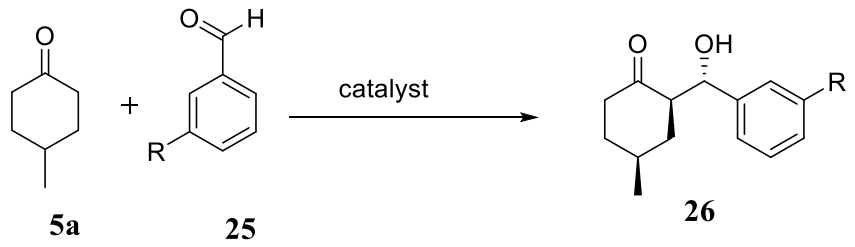
substituents were examined, but it can be expected (based on the benzaldehyde result) that they would be poor substrates.

Table 2. An overview of the remaining *p*-substituted benzaldehydes [a].

Entry	Equivalent ketone	Electrophile	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee%*[d]	Reaction time
1[14]	2	4-CF_3	10mol%	86	>16:1	98	48 h
		4-Cl	J with LL	77	>16:1	91	72 h
		4-H		41	>16:1	98	72 h
2[35]	5	4-Cl	10mol% Y	80	Not mentioned	97	24 h
3[43]	10	4-F	5mol%	76	Not	>99	4 d
		4-CF_3	A	70	mentioned	99	4 d
		4-CN		80		96	4 d
		4-Br		61		96	5d
		4-Cl		70		96	5d
		H		46		94	5d
4[17]	10	4-CN	20mol%	68	7:2	99	120 h
		4-CF_3	H with KK	86	24:3	99	

[a]Arranged based on the number of equivalents of the 4-methylcyclohexanone.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC

1.2.1.3 The Reaction of 4-Methylcyclohexanone with m-Substituted Benzaldehydes



Scheme 6 The reaction of 4-methylcyclohexanone with m-substituted benzaldehydes.

Aromatic aldehydes containing *meta* substituents are much less explored in aldol reactions with 4-substituted cyclohexanones, See Table 3. The reaction of m-nitrobenzaldehyde has been studied by Fu's group (entry1-3) and the stereoselectivity and the yield were excellent. Daniellou and Plusquellec [46], Table 3, entry 4, successfully obtained the product with lower catalyst loading (2mol%) when using (*R*)-3-pyrrolidinol as catalyst with alkyl β-D-

fructopyranosides in aqueous solutions, and obtained higher yield (82%) but without enantioselective differentiation (>5% *ee).*

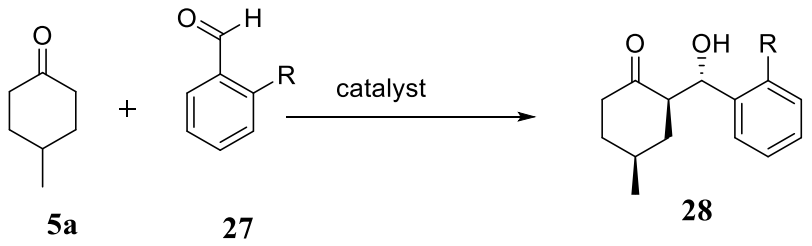
When the CF_3 group was introduced at the *meta* positions, Rios[17] reported an excellent stereoselectivity as well as a good yield (entry 6). While, Gong's[43] reaction, using lowest catalyst loading of 5mol%, provided a lower yield (55%) and comparable stereoselectivity to Rios's reaction. A higher yield was obtained by Gong when he replaced the CF_3 group with a 3,5-dibromobenzaldehyde substitution pattern (entry 5in Table 3).

Table 3. A summary of 4-methylcyclohexanone reacting with *m*-substituted benzaldehydes[a].

Entry	Equivalent ketone	Electrophile	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee*%[d]	Reaction time
1[26]	2.5	m-NO_2	5mol% NN Et_3N 5mol%	97	96:4	95	24 h
2[19]	4	m-NO_2	10mol % BB $ZnCl_2$ 10mol %	97	98:2	92	24 h
3[32]	4	m-NO_2	MM 5mol%	87	88:12	91	25 h
4[46]	5	m-NO_2	2mol% RR with YY	82	1.4 : 1	<5	24 h
5[43]	10	3,5-Br_2	5mol%	82		96	5d
		3,5-$(CF_3)_2$	A	55		98	5d
6[17]	10	3,5-$(CF_3)_2$	20mol% H with KK	74	5:1	95	120 h

[a]Arranged based on the number of equivalents of the 4-methylcyclohexanone.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC

1.2.1.4 The Reaction of 4-Methylcyclohexanone with o-Substituted Benzaldehydes



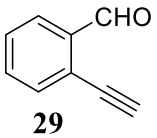
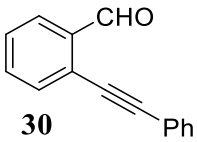
Scheme 7 The reaction of 4-methylcyclohexanone with o-substituted benzaldehydes.

This reaction has been studied with three different functional groups (NO_2, F, and Cl) at *ortho* position of 2-substituted benzaldehydes. The most common reaction was conducted with 2-nitro-benzaldehyde, which has been reported by many research groups. Reactions in Table 4 are summarized based on the cyclohexanone equivalent, catalyst loading, yield and stereoselectivity. Fu and Gong reported lowest catalyst loading 5mol% with good yield except the reaction with 2,6-dichlorobenzaldehyde, that provided less than 50% yield with Hyashi catalyst. When Rios used L-proline as a catalyst with a co-catalyst in case of 2,6-dichlorobenzaldehyde, he obtained 87% yield.

Ramachary achieved a high yield, good diastereoselectivities, and enantioselectivities by using Barbas-List aldol reaction of 2-alkynylbenzaldehydes with 4-methyl-cyclohexanones in presence of L-prolinamide derivatives as catalyst and benzoic acid as co-catalyst.

Table 4. A summary of 4-methylcyclohexanone reacting with *o*-substituted benzaldehydes [a.]

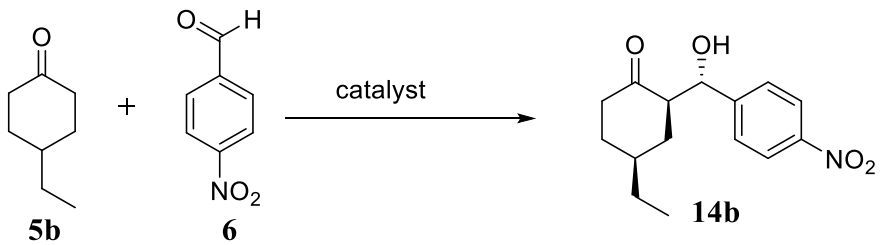
Entry	Equivalent of ketone	Electrophile	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee*%[d]	Reaction time
1[24]	2	2-NO_2	O 20mol%	97	Not mentioned	95	8 h
2[14]	2	2-NO_2	10mol% Q and R	85	>16:1	98	16 h
3[26]	2.5	2-NO_2	NN 5mol% Et_3N (5mol%)	98	99:1	99	24 h

4[47]	3	 **29**	10mol% F and Benzoic acid	85 90 92	>99:1 1.4:1 >99:1	96 77 86	24 h 72 h 24 h
		 **30**					
5[19]	4	2-NO_2	BB 10mol % $ZnCl_2$ 10mol %	92	92:8	95	24 h
6[32]	4	2-NO_2	MM 5mol%	91	83:17	89	27 h
7[35]	5	2-NO_2	Y 10mol%	85	Not mentio ned	95	24 h
8[42]	10	2-NO_2	OO 20mol %	65	>19:1	94	60 h
9[43]	10	2-F 2-NO_2 2,6-Cl_2	A 5mol%	90 84 45	Not mentio ned	>99 99 >99	3 d 4 d 3d
10[17]	10	2-NO_2 2,6-Cl_2	20mol% H with KK	86 87	12:1	97 96	120 h

[a]Arranged based on the number of equivalents of the 4-methylcyclohexanone.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC

1.2.2 The Reaction of 4-Ethylcyclohexanone with Aromatic Aldehydes

1.2.2.1 The Reaction 4-Ethylcyclohexanone and p-Nitrobenaldehyde.



Scheme 8 The reaction 4-ethylcyclohexanones and p-nitrobenaldehyde.

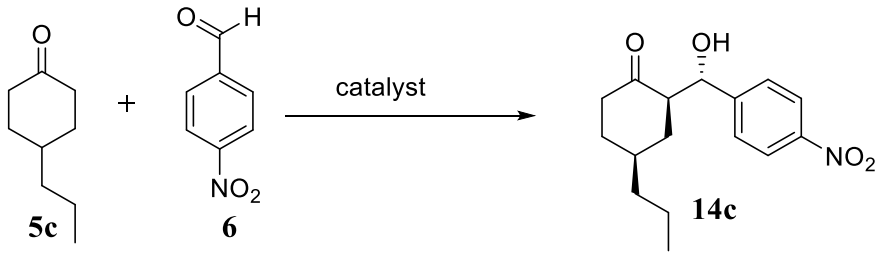
Table 5 summarizes the four reports found in the literature for the reaction of the benchmark aldehyde, 4-nitrobenzaldehyde with 4-ethylcyclohexanone. Luo[14] used a mixture of proline and a Brønsted acid (*p*-dodecylbenzenesulfonic acid, DBSA) to achieve an 86% yield, >16:1 dr, and>98% *ee* with water in the micelle media. Agarwal[24] reported high enantioselectivities and good yield (90%) by using 2.0 equivalent of 4-ethylcyclohexanone and sugar based prolinamide as a catalyst(20mol%). He also gave an example with *o*-nitrobenzaldehyde, shown in entry 2 of Table 5. In addition, Gong provided a lowest catalyst loading of 5mol% with 90% yield and 99% *ee*, see entry 3. Rios stated a highly enantioselective (94% *ee)* and diastereoselective desymmetrization (11:2 *dr*) reaction of 4-ethylcyclohexanone (10 equiv.) using L-proline as catalyst and a simple hydrogen bond donor as a co-catalyst to increase the efficiency of the process dramatically, resulted in 65% yield.

Table 5. A summary of 4-ethylcyclohexanone reacting with *p*-nitrobenzaldehydes.

Entry	Equivalent ketone	Catalyst loading	Yield	*dr* *anti/syn*	*ee*%	Reaction time
1[14]	2	10mol% J with LL	86	>16:1	98	31 h
2[24]	2 with 4-NO_2, 2-NO_2	O 20mol%	90 92	Not mentioned	90 98	9 h 8 h
3[43]	10	A 5mol%	90	Not mentioned	99	3 d
4[17]	10	H with KK 20mol%	65	11:2	94	120 h

1.2.3 The Reaction of 4-Propylcyclohexanone with Aromatic Aldehydes.

1.2.3.1 The Reaction of 4-Propylcyclohexanone and p-Nitrobenaldehyde.



Scheme 9 The reaction of 4-propylcyclohexanones and p-nitrobenaldehyde.

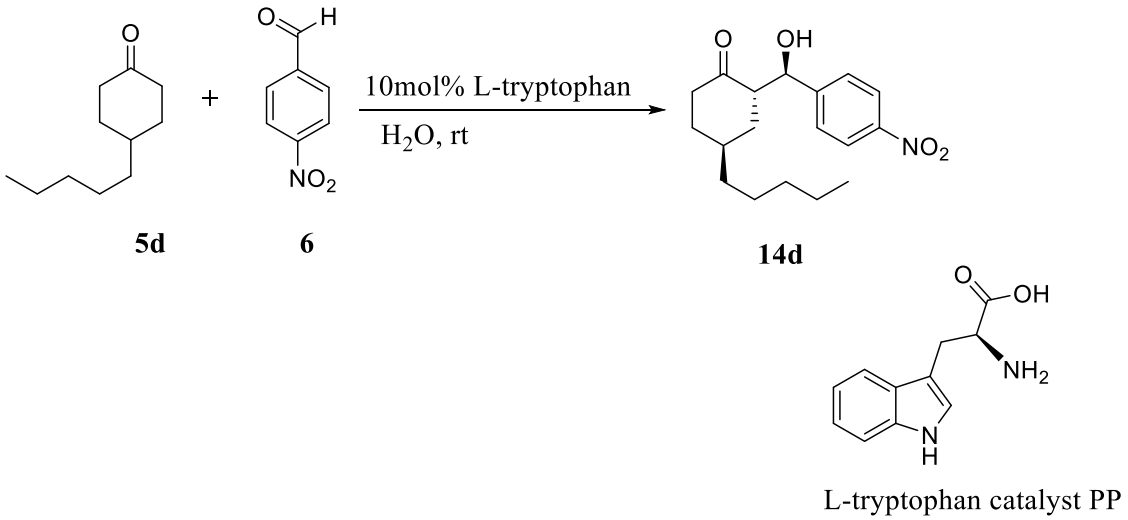
The desymmetrization of 4-propylcyclohexanone with *p*-nitrobenzaldehyde in the presence of 5mol% catalyst loading was investigated by Gong[43] using proline amides catalyst (A, Figure 1) to achieve strong ability to control enantioselectivities ratios of 4-methyl, 4-ethyl and 4-propylcyclohexenones ranged from 98 to 99% with 90% yield, Table 7 (entry 1). The second example in the literature reported by Rios[17] using L-proline as catalyst with a hydrogen bond donor co-catalyst (KK), in order to increase the efficiency of the enantioselectivity.

Table 6. A summary of 4-propylcyclohexanone reacting with *p*-nitrobenzaldehydes.

Entry	Equivalent ketone	Catalyst loading	Yield	*dr anti/syn*	*ee*%	Reaction time
1[43]	10	A 5mol%	90	Not mentioned	98	1.5 d
2[17]	10	H with KK 20mol%	80	4:1	96	120 h

1.2.4 The Reaction of 4-Pentylcyclohexanone with Aromatic Aldehydes.

1.2.4.1 The Reaction of 4-Pentylcyclohexanone and p-Nitrobenzaldehyde.



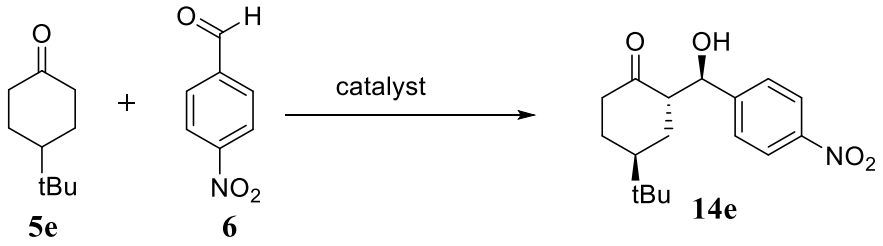
Scheme 10 The reaction of 4-pentylcyclohexanones and p-nitrobenzaldehyde.

There is only one example reported in the literature for the reaction of pentylcyclohexanone by Wong[34] in 2010, using primary amino acid such as L-tryptophan as catalysts for asymmetric aldol reaction in water. The reaction conditions were 41 hours at room temperature, with catalyst

loading 10mol%. This reaction performed well and gives a good yield 90%, 2:1 *dr*, and 86% *ee.*

1.2.5 The Reaction of 4-Tertiarybutylcyclohexanone with Aromatic Aldehydes

1.2.5.1 The Reaction of 4-Tertiarybutylcyclohexanone and p-Nitrobenaldehyde



Scheme 11 The reaction of 4-tertiarybutylcyclohexanones and p-nitrobenaldehyde.

Table 7 summarizes the most popular desymmetrization reaction of 4-tertiary-butylcyclohexanones, that with *p*-nitrobenzaldehyde. Entry 1 shows the use of a 1:1 ratio of the starting materials, but provided less than a 50% yield with a relatively high catalyst loading of proline (10mol%), in 300mol% of water.[48] Bolm[49]used 1.1 equiv. of the ketone catalyzed by proline under ball milling technique and solvent-free conditions, and there he obtained higher yield compared to Pihko[48](entry 1), with excellent stereoselectivity.

Amedjkouh[50] used 5.0mol% catalyst loading of chiral α-aminophosphonates as organocatalysts (entry 5). While North[51] employed 10mol% of two very similar proline based catalysts combined with co-catalyst entries (3 and 6). In addition, Rios applied 20mol% proline as catalyst and a simple hydrogen bond donor as co-catalyst. All these reactions gave good yields, excellent stereoselectivities, and good reaction times. Further examination of the data shows similar yields and stereoselectivities, which were obtained by other researchers.

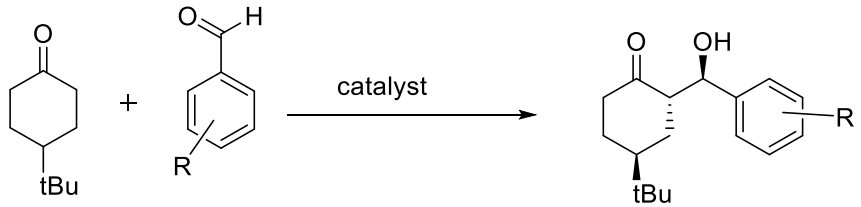
Table 7. A summary of 4-tertiarybutylcyclohexanones reacting with *p*-nitrobenzaldehyde [a].

Entry	Equivalent ketone	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee*%[d]	Reaction time
1[48]	1	H 10mol%	45	2.5:1	74	8 d
2[49]	1.1	H 10mol%	85	91:9	91	1.4d
		under ball-milling conditions	58	93:7	89	5d
3[51]	2	DD	58	1.7:1	99	24 h

		EE 10mol% in 1ml propylene carbonate	72	3.9:1	99	
4[24]	2	O 20mol%	88	Not mentioned	87	48 h
5[50]	2	T 5mol%	52	Not mentioned	96	44 h
6[52]	2	H with XX	58	1.7:1	90	24 h
		H with VV 10mol%	89	8.4:1	95	24h
7[36]	5	K 20mol%	97	15:1	98	48 h
8[53]	5	GG 10mol%	85	85:15	79	18 h
9[35]	5	10mol% Y	90	Not mentioned	92	24 h
10[54]	5	CC 10mol%	95	98:2	>99	3 d
11[43]	10	A 5mol%	52	Not mentioned	93	5 d
12[17]	10	H with KK 20mol%	69	7:2	97	120 h
13[55]	10	FF 10mol%	49	Not mentioned	81	36 h

[a]Arranged based on the number of equivalents of the 4-tertiarybutylcyclohexanones.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC.

1.2.5.2 The Reaction of 4-Tertiarybutylcyclohexanone with Substituted Benzaldehyde



Scheme 12 The reaction of 4-tertiarybutylcyclohexanones with substituted benzaldehyde.

This aldol reaction of 4-tertiarybutylcyclohexanones has been studied using *ortho, para* and *meta* substitution for only a couple of functional groups (H, NO_2, Cl and Br). When the *para*-substituent is hydrogen (benzaldehyde substrate), the stereoselectivity is excellent but as noted earlier for other reactions with benzaldehyde, the reactions are not practical, both provide less than 50% yield (Table 8, entries 1, 2, and 4). While with NO_2 substituent of benzaldehyde at

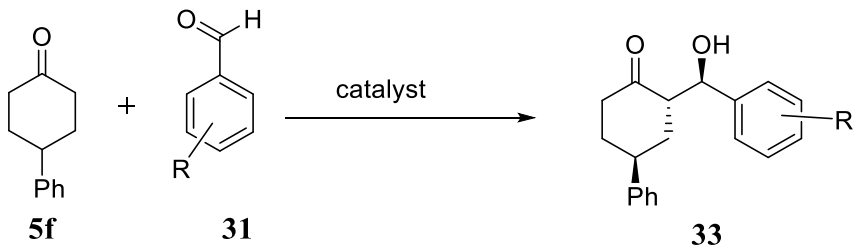
ortho or *meta* positions, the reactions provided excellent yields and high stereoselectivities (entries 3 and 5). Further examination of Cl and Br shows excellent yields and stereoselectivities as well (entries 3 and 6).

Table 8. A summary of 4-tertiarybutylcyclohexanones reacting with various substituted benzaldehyde [a].

Entry	Equivalent ketone	Electrophile R=	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee*%[d]	Reaction time
1[48]	1	4-H	H 10mol%	45	2.5:1	74	8 d
2[56]	1	4-H	H 10mol% 300mol% H_2O	45	2:1	74	8 d
3[49]	1.1	4-Cl	H10mol%	75	92:8	93	1.6 d
		2-NO_2	under ball-	66	81:19	88	1 d
		3-NO_2	milling conditions	80	78:22	92	1 d
4[14]	2	4-H	10mol% J with LL	58	>16:1	96	72 h
5[24]	2	2-NO_2	O 20mol%	90	Not mentioned	97	48 h
6[53]	5	R=m-Br	GG	80	83:17	91	36 h
		pyridine	10mol%	85	89:11	75	18 h

[a]Arranged based on the number of equivalents of the 4-tertiarybutylcyclohexanones.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC.

1.2.6 The Reaction of 4-Phenylcyclohexanones with Aromatic Aldehydes



Scheme 13 The reaction of 4-phenylcyclohexanones with aromatic aldehyde.

Table 9 summarizes results from the literature for aldol reactions of 4-phenylclohexanone with *p*-nitrobenzaldehyde and *m*-bromobenzaldehyde. Bolm[49] obtained *anti*-aldol products with enantioselectivity up to 84% *ee* by using a 1.1 equiv. of the ketone. Although providing less than 50% yield (entries 1) by proline catalyst under ball milling mechanochemical technique and solvent-free conditions. Gong provided a lowest catalyst loading 5 mol% with 74% yield and 94% *ee* (entry 2). Rios stated a highly enantioselective (97% *ee)* and diastereoselective (11:2 *dr*) of 4-phenylcyclohexanone (10 equiv.) using L-proline as catalyst and simple hydrogen bond donor as co-catalyst to improve efficiency of process in 83% yield (entry 3). Lipshutz[53] designed a new catalyst contain a covalent bound organocatalysts proline catalyzed aldol reaction of 4-phenylcyclohexanone with *meta*- bromobenzaldehyde to obtain 82% yield, 68:32 *dr* and 86% *ee* (entry 4).

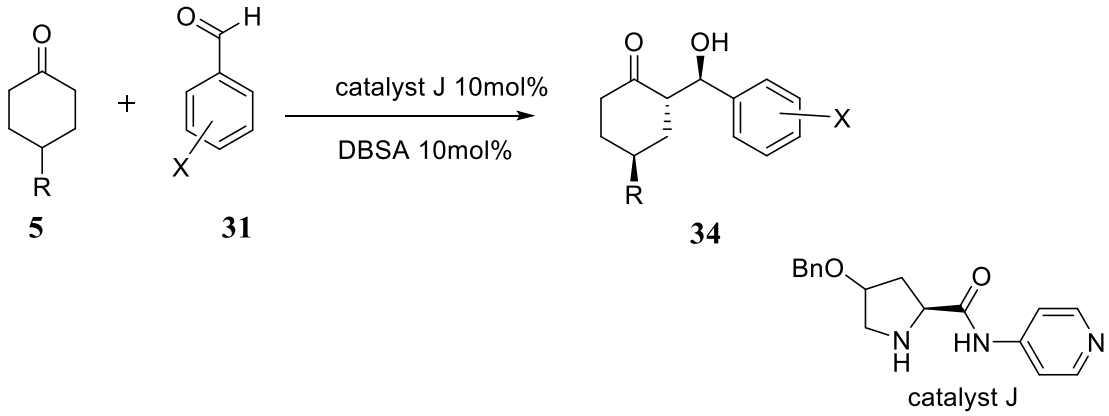
Table 9. A summary of 4-phenyl-cyclohexanones reacting with aromatic aldehyde [a].

Entry	Equivalent ketone	R	Catalyst loading	Yield[b]	*dr*[c] *anti/syn*	*ee*%[d]	Reaction time
1[49]	1.1	*p*-NO_2	H 10mol% under ball-milling conditions	42	69:31	84	2 d
				42	45:55	Rac.	8 d
2[43]	10	*p*-NO_2	A 5mol%	74		94	5 d
3[17]	10	*p*-NO_2	H with KK 20mol%	83	11:2	97	120 h
4[53]	5	*m*-Br	GG 10mol%	82	68:32	86	36 h

[a]Arranged based on substituted aromatic aldehyde *para* to *meta*.
[b] Yields determined after chromatographic purification (Isolated yield).
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC.

1.2.7 Miscellaneous Examples

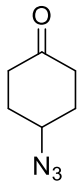
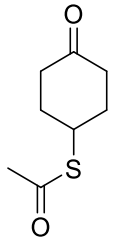
1.2.7.1 The Reaction of 4-Heteroatom Substituted Cyclohexanone Substrates with Aromatic Aldehydes

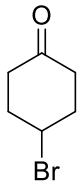


Scheme 14 4-Heteroatom Substituted Cyclohexanone Substrates with Aromatic Aldehydes.

Luo[14] modified asymmetric catalyst by using a mixture of proline and Brønsted acids as p-dodecyl benzenesulfonic acid (DBSA) which containing hydrophobic part to achieved active and selective organocatalysts in water with micelle as media to afford high yields, excellent diastereoselectivity up to >16:1 *dr* and enantioselectivity in rang 94% to 99% *ee* table 10. In addition, he applied this strategy with asymmetric Michael addition in water.

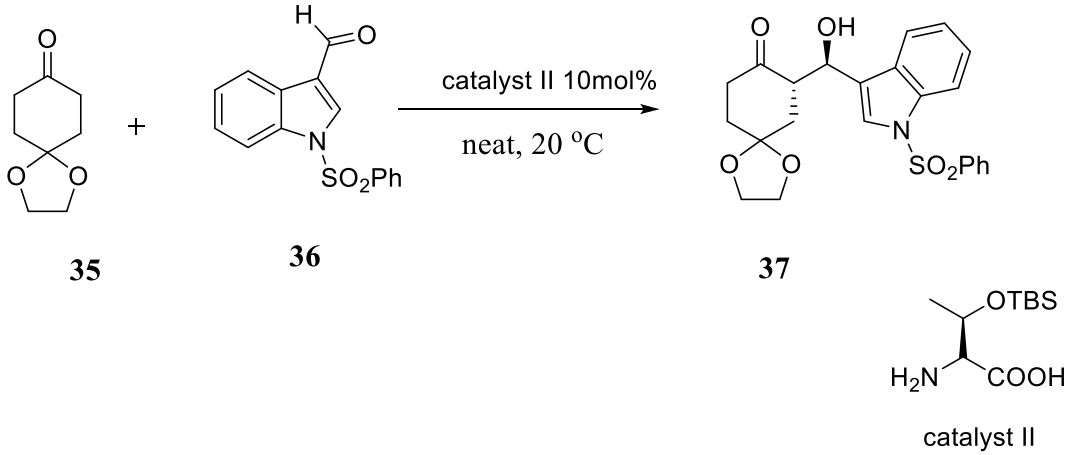
Table 10. A summary of 4-heteroatom substituted cyclohexanone reacting with *p*-substituted benzaldehyde .

Entry	Equivalent ketone	Electrophile	Catalyst loading	Yield[a]	*Dr*[b] *anti/syn*	*ee%*[c]	Reaction time
1	 **5g** 2 equiv.	p-NO_2	10mol%	69	>10:1	97	40 h
		p-Cl		52	>16:1	94	72 h
2	 **5h** 2 equiv.	p-NO_2	10mol%	97	>16:1	99	36 h
		p-CF_3		99	>16:1	>99	60 h

3	 **5i** 2 equiv.	p-NO_2	10mol%	74	>16:1	96	40 h

[a] Yields determined after chromatographic purification (Isolated yield).
[b] Diastereomeric excess determined by NMR of crude reaction mixture.
[c] Enantiomeric excess determined by chiral HPLC.

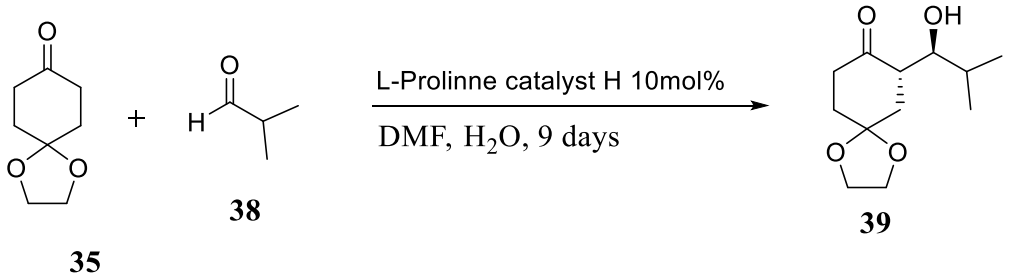
1.2.7.2 The Reaction of 4-Heteroatom Substituted Cyclohexanone Substrates with Different Aldehydes



35 **36** **37**

Scheme 15 Reaction of 1,4-Cyclohexanedione monoethylene ketal with indole-3-carbaldehyde

Qi-Xiang Guo[57] performed aldol addition of 1,4-Cyclohexanedione monoethylene ketal to indole-3-carbaldehyde using O-TBS-protected L-threonine catalyst, 20 equiv. of ketone and 15mol% catalyst loading to afford 3-indolylmethanols with good yields, excellent diastereoselectivities, and enantioselectivities (86% yield, 97:3 *dr*, 98% *ee*).

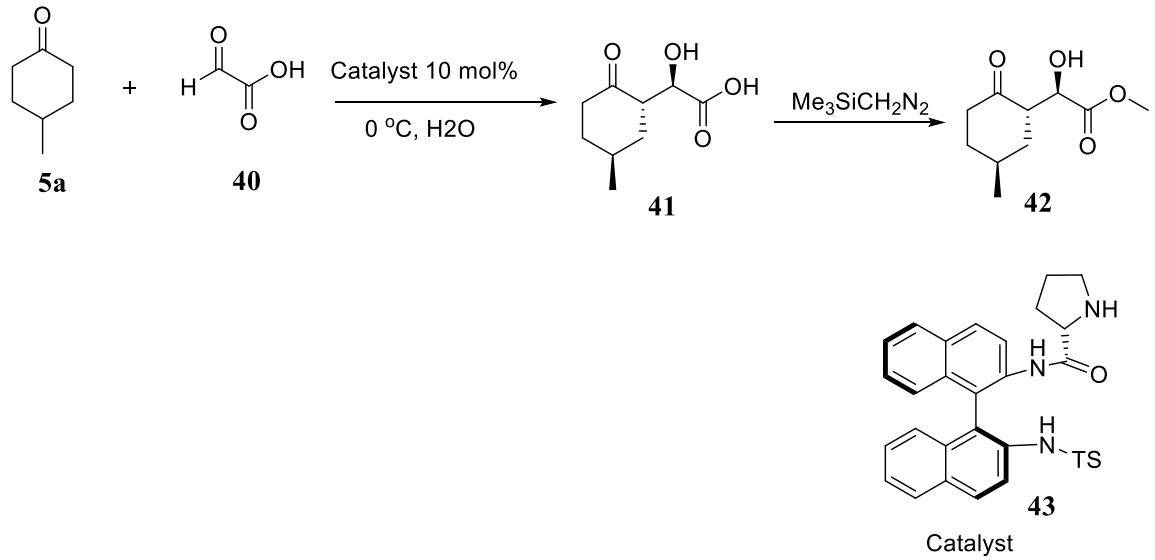


35 **38** **39**

Scheme 16 Reaction of 1,4-Cyclohexanedionemonoethylene ketal and Isobutyraldehyde.

Pihko[48] studied aldol reaction between ketone and aldehyde in different conditions: bases, acids, and water in presence of proline catalyst. The reaction smoothly work with small amounts of tertiary amine base or weak acids but not with strong acids it completely stops.in case of water addition distinguishes a highly beneficial effect on this reaction. The aldol reaction of 1,4-Cyclohexanedionemonoethylene ketal and Isobutyraldehyde with proline in 300mol% of water afford 89% *ee*, 2.4:1 *dr* and lowest yield 31%.

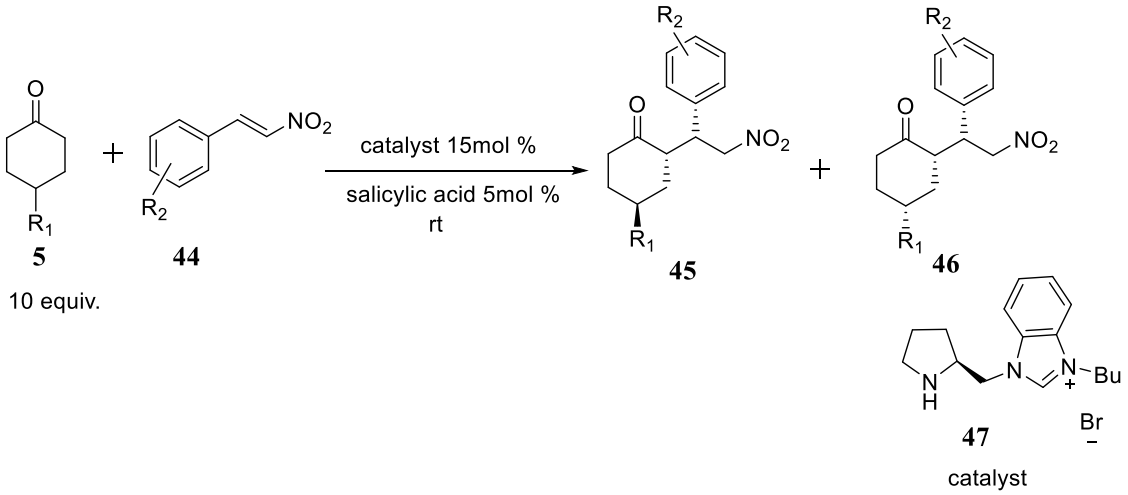
1.2.7.3 4-Methyl-Cyclohexanone Substrates with Different Aldehydes



Scheme 17 Reaction of 4-methylcyclohexanone with glyoxylic acid monohydrate.

In 2014, Najera[58] used an N-Tosyl-(S)-binam-L-prolinamide as efficient catalyst for attack of 4-methylcyclohexanone on a novel electrophile, glyoxylic acid in 2:1 stoichiometric ratio. This formed a chiral α-hydroxy-γ-ketocarboxylic acid with high diastereo- and enantioselectivity. When glyoxylic acid was used as the monohydrate with a catalyst loading of 10mol%, the product was noted in 80% yield, 95% *ee*, 84:12 *dr* but in case of using glyoxylic acid as 50% aqueous solution gives 90% yield, 91% *ee*, 76:15 *dr*.

1.3 Michael Addition



Scheme 18 Addition of 4-substututied cyclohexanones to β−nitrostyrene derivatives.

The Michael reaction of 4-substututied cyclohexanones with nitrostyrene derivatives has been reported by 25 research groups. One article has been selected here because our research did not examine this reaction, but I felt it important to show that these reactions are possible. The chosen article, by Cheng[59] in 2007, is the broadest such examination as seen by the great variety of 4-substituted cyclohexanones added to nitroalkenes with 10:1 stoichiometric ratio, using a functionalized chiral ionic catalyst (15mol%) with salicylic acid (5mol%) co-catalyst. Excellent enantioselectivities (93-99% *ee*) and diastereoselectivities in the range of 4:1 to 10:1*dr* were noted (Table 12, entries 1-19). In addition, alternative 4-positioned functional groups (OH, Br, and CN) on the cyclohexanones were studied, but oddly they provided only trace quantities of the desired products (entries 20-22).

Table 11. A summary of 4-substituted cyclohexanone reacting with nitroalkenes.

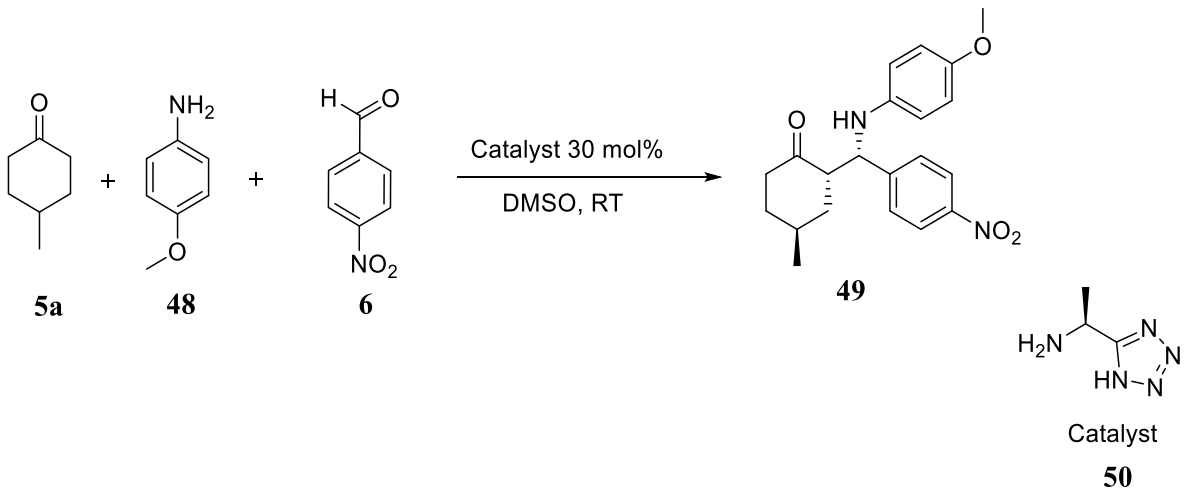
Entry	R_1	R_2	Yield%[a]	*dr*[b] *anti/syn*	*ee*%[c]	Time(h)
1	Me	H	89	6.2:1	97	10
2	Me	4-Cl	89	6.1:1	99	10
3	Me	2-Cl	99	>10:1	97	10
4	Me	4-Me	89	7.0:1	98	16
5	Me	4-Ph	92	6.0:1	94	12
6	Me	4-MeO	94	7.6:1	97	21
7	Me	4-NO2	88	5.0:1	98	3

8	Me	2-NO2	93	4.4:1	97	3
9	Me	2-NO2	99	4.8:1	97	4
10	Me	2-NO2	94	5.1:1	93	12
11	Me	2-NO2	78	6.3:1	96	24
12	Me	3-NO2	80	4.0:1	98	12
13	Me	1-Naph	99	8.1:1	97	24
14	Me	Piperal	95	6.8:1	96	24
15	Et	H	81	6.5:1	97	10
16	*t*-Bu	H	88	7.9:1	98	12
17	Ph	H	63	12:1	96	10
18	N3	H	61	>5:1	93	20
19	SAc	H	65	>5:1	93	24
20	OH	H	trace			24
21	Br	H	trace			24
22	CN	H	NR			24

[a] Yields determined after chromatographic purification (Isolated yield).
[b] Diastereomeric excess determined by NMR of crude reaction mixture.
[c] Enantiomeric excess determined by chiral HPLC.

1.4 Enantioselective Mannich Reaction

The Mannich reaction is one of historical significance because it allows carbon-carbon bond formation while producing a nitrogenous product. Here I show the only literature example of an organocatalized Mannich reaction with a 4-substituted-cyclohexanone, specifically 4-mthylcyclohexanone. Cordova[60] provided this unprecedented work and showed that chiral amines or amino acids catalyze the three component asymmetric Mannich reaction, with the shown product (Scheme 19) found in 87% yield, 96% enantioselectivity and with good diastereoselectivity (4:1). The reaction has relatively fast, 13 h, but required 3.0 equiv. of 4-methyl-cyclohexanones with a high catalyst loading (30mol%) in DMSO.

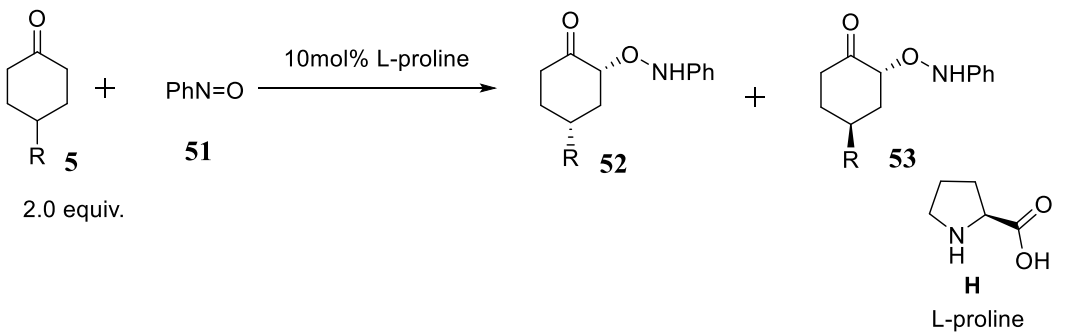


Scheme 19 Mannich reaction.

1.5 Enantioselective α-Oxygenation of Ketones

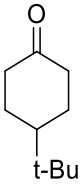
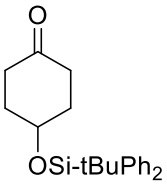
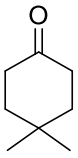
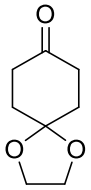
The enantioselective α-oxygenation of ketones has challenged organic chemists for a long time. Indirect proof of this, until recently, was the need to use stoichiometric quantities of the Davis' chiral oxaziridine.[61,62] Organocatalytic methods have made excellent, albeit not broad, inroads to this problem.

In 2004 Hayashi[63] and co-workers published the first work describing an enantioselective α-aminoxylation of a 4-substituted cyclohexanone with nitrosobenzene. The reactions were catalyzed by L-proline (10mol% catalyst loading) in DMF at 0 ^{o}C with 2.0 equiv. of various cyclohexanones (Table 12). From those, the first two entries of Table 12 are the most relevant. It is interesting to note that even though nitrosobenzene exactly mimics the atom space filling of an aldehyde, the diastereoselectivity is strikingly different and poor at essentially a 1:1 ratio.



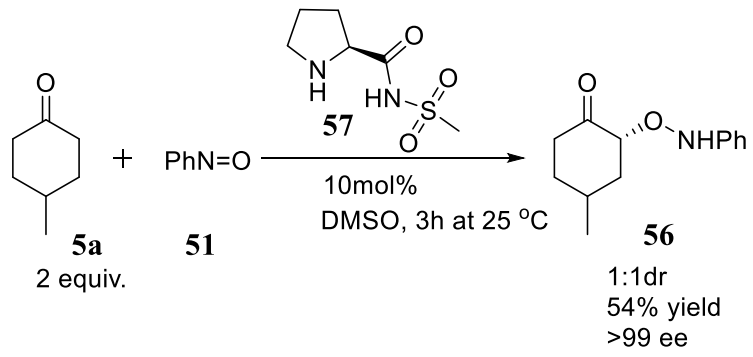
Scheme 20 α-aminoxylation of a 4-substituted cyclohexanone with nitrosobenzene.

Table 12. A summary of 4-substituted cyclohexanone reacting with nitrosobenzene.

Entry	Ketones	Catalyst loading	Yield[a]	*ee*% [c]	Reaction time
1	 **5e**	10mol%	31 (53), 31 (52)[b]	>99 (53), 94 (52)	24 h
2	 **54**	10mol%	46 (53), 23 (52) [b]	>99(53), 96(52),	24 h
3	 **55**	10mol%	84	99	24 h
4	 **35**	30mol% 10mol% 5mol%	96 93 86	>99 >99 >99	12 h 24 h 60 h

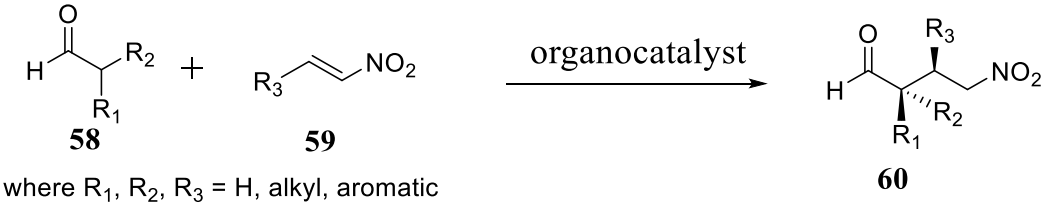
[a] Yields determined after chromatographic purification (Isolated yield).
[b] Diastereomeric excess determined by NMR of crude reaction mixture dr =1:1.
[c] Enantiomeric excess determined by chiral HPLC.

In 2005 Córdova[64] and co-workers published their work on the asymmetric α-aminoxylation of 4-substituted cyclohexanones via the slow addition of nitrosobenzene. The reactions were catalyzed by L-proline derivatives (10 mol%) in DMSO at room temperature with 2.0 equiv. of 4-methylcyclohexanone. The results, see Scheme 21, were inferior to Hayashi's.



Scheme 21

1.6 A Brief Overview of Enantioselective Aldehyde Addition to β-Nitrostyrene Derivatives



Scheme 22

The Michael reaction is a common reaction and a greatly relied on reaction because it allows the most fundamental of all bonds to be formed from the perspective of the carbon framework, the carbon-carbon bond.[65,66] Within the last fifteen years the enantioselective organocatalyzed Michael reaction has undergone tremendous progress such that these reactions are now within the practical reach of industrial usefulness.[67-71] In this section, I will briefly outline only the most popular Michael reaction, that of aldehyde addition to an unsaturated nitro-compound as depicted in Scheme 22. Importantly, most of those reaction outcomes provide Michael products with two adjacent stereogenic centers.

While there are many variations on the noted Michael reaction (where R, R', and R'' can be any combination of H, alkyl, or aromatic, see Scheme 22), the fact is that the most often expressed version of this reaction is the addition of a linear aldehyde (Scheme 22, R= H, R'=alkyl) to β-nitrostyrene (R''= phenyl). Furthermore, it can be stated that β-nitrostyrene is the common denominator for all benchmark reactions regardless of the used aldehyde. After the addition of linear aldehydes to β-nitrostyrene, and its analogs, the addition of α-branched aldehydes, while significantly lower in number, are covered. What is special about the latter is that a quaternary carbon is formed and organic chemists still do not have comprehensive broad

methods to do so. Therefore, these reactions are of higher importance and they are the focus of my last research efforts. The associated manuscript will soon be submitted but a draft version of it has been provided within this thesis. In this context, during Section 2.3 of this thesis you will note that I have focused on this particular reaction, in large part because many deficiencies remain within this reaction and we have made significant progress in that regard.

Thus, the intention of this brief overview is to inform the reader of the current progress within the noted reaction (Scheme 22). It is also useful to know that no current transition metal or enzymatic catalyzed reactions could surpass the reaction product profiles that these organocatalyzed reactions can. This is relevant because of the high application potential of these highly enantio-enriched products for natural product or pharmaceutical drug synthesis. During my research, within Section 2.3, I show a significant broadening of the Michael reaction substrate scope and this has allowed me to show the first step-efficient synthesis of a commonly prescribed drug, Pristiq.

The summaries that follow discuss what organocatalysts are the best and for the shown Michael nucleophile and electrophiles. The current best template catalyst is proline based, e.g. XXIII and XXIV for linear aldehyde addition and for α-branched additions primary amine are currently the best as exemplified by O-tert-butyl-l-threonine. All of the catalysts used within the tabularized summary are noted in Figure 4.

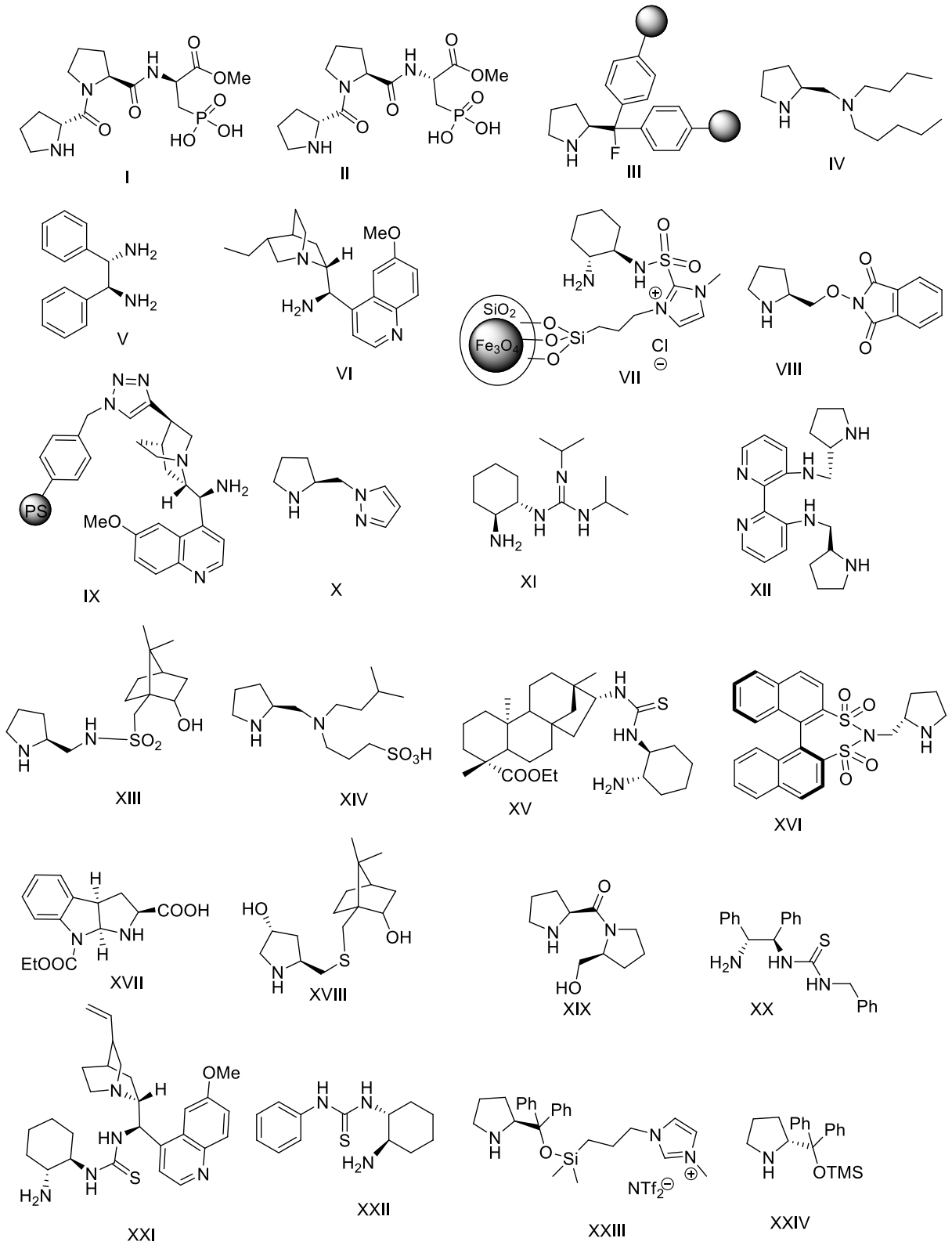
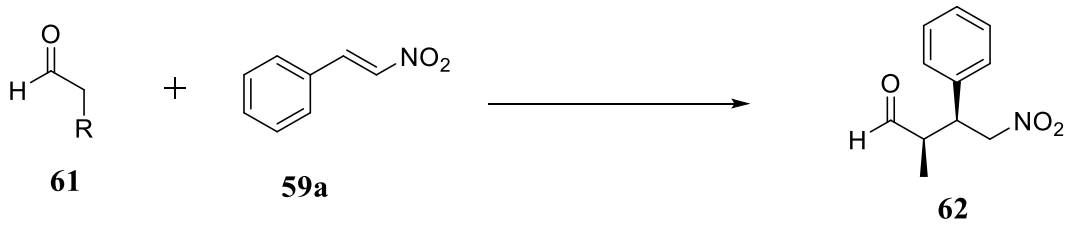


Figure 4. All types of catalysts used for Michael addition of liner and branched aldehyde to β-nitrostyrene as noted in Tables 13 and 14.

1.6.1 Linear Aldehyde Additions to β-Nitrostyrene



61 **59a** **62**

Scheme 23

There are a large variety of linear aldehydes that have been added to β-nitrostyrene. From those the most commonly examined are: propionaldehyde, butyraldehyde, valeraldehyde, and hydrocinnamaldehyde. Here I provide an overview for the addition of propanal to β-nitrostyrene (Table 13), which is the benchmark reaction. Since it is the most commonly used reaction clear parallels can be drawn between the literature examined catalysts. Note that in one instance propanal was not used and then a related aldehyde, e.g. pentanal, is shown in my tabular summary (Table 13, entry 11).

Based on a review of the top literature findings, I will now summarize only the best reactions found within Table 13. Here we define practical reactions as those which employ no greater than a 5:1 stoichiometry for the starting aldehyde and nitroalkene. Some of the reactions which employ a higher stoichiometry than 5:1 can be pursued by the reader desires to do so.[67-71] Within this set of "practical reactions" that I have just defined, one will find that the catalyst loading can vary from 0.50 to 30mol%. Before going into the nuances of which catalysts are actually the most efficient, I note for you the underlying structural templates within Figure 4. Of the 24 shown catalysts, it is seen that the proline based ones are the most frequently employed with 14 representatives (Figure 4, I, II, III, IV, VIII, X, XII, XIII, XIV, XVI, XVIII, XIX, XXIII, XXIV). The remaining catalyst are primary amines and can be conveniently divided into three different template types, *i.e.*, trans-1,2-diaminocyclohexane derivatives (Figure 4, VII, XI, XV, XXII), 1,2-diaminostilbene derivatives (V), and those based on cinchona alkaloids (VI, IX, XXI).

From all of the Table 13 examples, entries 1 and 10, by corresponding authors Lecouvey and Lombardo demonstrate the highest achievements to date. Lecouvey in 2016, used a 3:1 ratio of propanal to β-nitrostyrene and under catalysis with 1.0 mol% of a proline based tripeptide with a phosphinic acid residue (Figure 4, catalyst I). While this constitutes an excellent catalyst

loading the stoichiometry is still a bit high for the starting materials and more importantly with a 78% yield and ~1:9 dr with 78% ee the result is not practical in nature, meaning chemists will not rely on it for target based syntheses. Thus, the work of Lombardo (Table 13, entry 10) in 2009 remains the highest-level achievement when he produced a 99% yield of the desired product in 93:7 dr with 99% ee for the major diastereomer using 1.0mol% of proline based ionic liquid catalyst which he stated was recoverable. Those Lombardo results used a 1.2:1 ratio of propanal to β-nitrostyrene the starting materials. Furthermore, in 2008 Ma used a commercially available Hayashi catalyst (Figure 4, catalyst XXIV) for this Michael reaction, using 1mol% catalyst loading with 2:1 stoichiometric ratio of pentanal to β-nitrostyrene to afford higher yield 96 and excellent ee >99% with 2:98 dr entry 11.

Within all of these 11 reactions that are shown in Table 13, are few interesting points can be noted beyond the most practical reaction outline above. For example, entry 4 relies on a carboxylic salt and consequently represents the only example in which basic conditions are employed. Be that as it may, there currently appears to be no advantage when using this mode of catalysis as compared to the results noted in entries 1 and 10 which do not have carboxylic acid salts.

It would of course be dangerous to make generalized conclusions based on one benchmark reaction, but in a qualitative manner it can be stated that when the aldehyde is of greater steric bulk than propanal (has a longer alkyl chain), then the reactions are slower, the catalyst quantities must, in general, be twice as high.[67-71] When the α-aldehyde substituent is greater in size than the methyl group, which is noted in propanal, e.g. in pentanal there would be a n-propyl group, then the reactions are without exception much slower. This strongly implies that the Ma results are more significant than those reported by Lombardo.

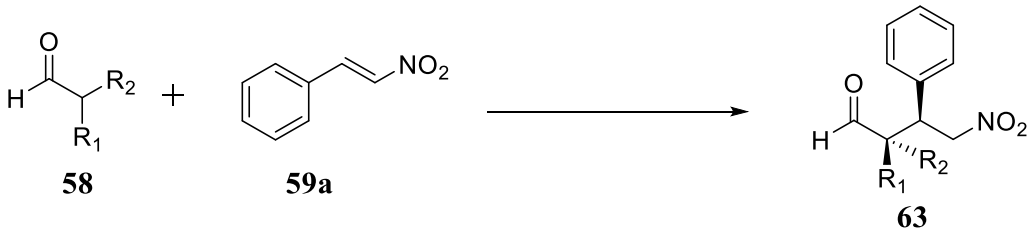
In conclusion, the practical results of Ma and Lombardo, both use 1.0mol% catalyst loadings, mean that these enantioselective Michael reactions can be employed for natural product and pharmaceutical drug synthesis. Importantly, the catalyst of Ma is commercially available.

Table 13. An overview of Michael addition of liner aldehyde to β-nitrostyrene.

Entry	Equivalent Aldehyde	R	Catalyst loading	Yield[a]	*dr*[b] *anti/syn*	*ee*[c] %	Reaction time
1[72]	3	Me	I (1mol%)	60	12:88	78	3.5h
		Me	II (1mol%)	96	9:91	86	20h at 0°C
2[73]	3	Me	III (10mol%) 4-nitrophenol (10mol%)	99	5:95	95	1.5h
3[74]	1.9	Me	XII (10mol%)	95	14:86	62	16h
4[75]	3	Me	L-Proline (10mol%) LiOH (10mol%)	85	1:20	95	48h
5[76]	5	Me	XIII (20mol%)	91	12:88	94	23h
6[77]	5	Me	X (10mol%)	82	7:93	78	18h
7[78]	2	Me	XVII (5mol%)	96	9:91	>99	8h
8[79]	3	Me	L-Proline (10mol%)	96	30:70	94	17h
9[80]	3	Me	Thiourea (10mol%)	90 80	9:91 4:96	88 96	36h
10[81]	1.2	Me	XIX (1.5 mol%)	99	7:93	99	6h,0C
	2		(5 mol%)	99	5:95	99	1.5h
	2			94	10:90	99	4h, ,0C
	2		XXIII (1 mol%) XXIII (0.5 mol%)	97	10:90	99	3h, ,0C
11[82]	2	n-Pr	XXIII (1 mol%) XXIII (5 mol%) XXIV (1 mol%)	96	2:98	>99	6h

[a] Yields determined after chromatographic purification (Isolated yield).
[b] Diastereomeric excess determined by NMR of crude reaction mixture.
[c] Enantiomeric excess determined by chiral HPLC.

1.6.2 α-Branched Aldehyde Addition to β-Nitrostyrene

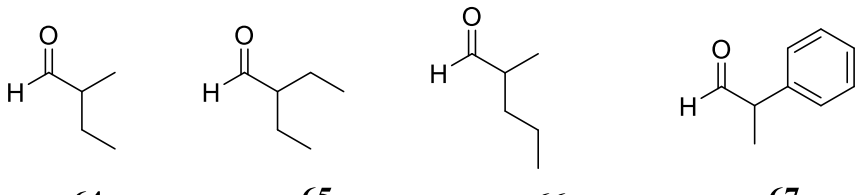


58 **59a** **63**

Scheme 24

The addition of α-branched aldehydes to nitroalkenes is less advanced, regarding practical reaction conditions, than the findings noted for linear aldehyde additions. This is immediately noted by the greater stoichiometry of the aldehyde and the simultaneous need for higher catalyst loadings. In short this reaction type remains as an open challenge to continue to investigate. These less than desirable results inevitably trace back to the difficulty of forming a quaternary carbon in the product. As a consequence, the most commonly examined α-branched aldehyde is isobutyraldehyde because it represents the least steric congestion during the carbon-carbon bond forming process. Here we consequently detail the reaction conditions and product profile for the benchmark reaction, i.e., isobutyraldehyde with β-nitrostyrene (Table 14).

Before doing so, we make the reader aware that, while not comprehensive, Figure 5 shows other infrequently examined α-branched aldehydes. Note that these type of unsymmetrical α-branched aldehydes generate products with a stereogenic quaternary center. This expresses yet another level of complexity which is important, and although not further discussed here, this challenge was addressed during my research where I show an example of one stereogenic quaternary carbon being formed.



64 **65** **66** **67**

Figure 5. Other α-branched aldehydes examined in literature.

For the benchmark reaction, we define a 5:1 stoichiometry for the starting aldehyde and nitroalkene as the cut off mark for inclusion in the tabularized data. We arbitrarily made this limit to reduce the discussion to only the most useful and relevant results.

Within Table 14 the most interesting reactions from the point of application potential would be those which use a ≤ 2:1 ratio of isobutyraldehyde to β-nitrostyrene. Those results are noted in entries 2, 9, 12, 13, 16, and 21 of Table 14. From those results, entries 2 and 9 can be discarded because of the low yields (≤ 50%) noted for those methods. From the remaining entries, 12, 13, 16, and 21, the highest achievement is represented by Nugent and coworkers in 2011, see entry 12. They used a 1.2:1 ratio of isobutyraldehyde to β-nitrostyrene with a 5mol% catalyst loading of OtBu-L-threonine (commercially available) in the presence of a hydrogen bond donor (sulfamide) and amine base (DMAP) or alternatively with only an equal catalytic quantity of LiOH. [83] This constitutes the lowest catalyst loading and stoichiometry when compared to all other examples and the product was noted in high yield and excellent ee (98%).
Regarding the other useful examples, entries 13, 16, and 21, are now discussed. Significant progress has been made by Ma using a commercially available Hayashi catalyst (Figure 4, catalyst XXIV), using 10mol% catalyst loading with 2:1 stoichiometric ratio of isobutyraldehyde to β-nitrostyrene to afford good yield 97 and ee 92% entry 21.[82] In 2011, Tao and Tang[84] reported asymmetric Michael addition between isobutyraldehyde and β-nitrostyrene 2:1 ratio entry 13, using different catalyst loading 10mol% and 20mol% of XV to gives same yield but slightly greater ee 97 with 20 mol %. While they used 5 mol% catalyst loading the yield goes down but the ee is still high. On the other side in 2013, Hong-Wu Zhao tried to test his catalyst and reduced the stoichiometric ratio to 1.9:1 for isobutyraldehyde and β-nitrostyrene, but delivered the desired products in low yield and moderate enantioselectivity (Table 14, entry 9). In 2010 Teck-Peng Loh designed a new chiral catalyst based on the hexahydropyrrolo[2,3-b] indole template. This new type of chemzyme catalyst provides the Michael addition between isobutyraldehyde and β-nitrostyrene (2:1 ratio) entry 16, using a 10mol% catalyst loading to gives good yield but with excellent enantioselectivity (95%).

Table 14 An overview of Michael addition of α-branched aldehyde to β-nitrostyrene

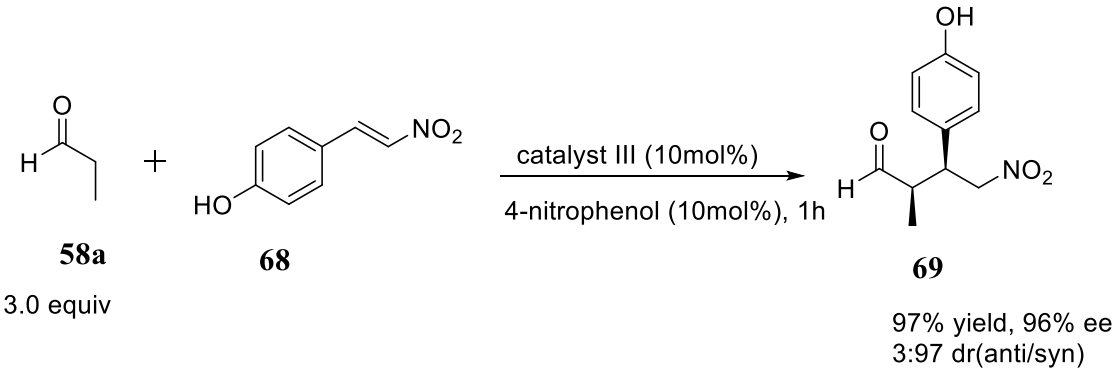
Entry	Equivalent Aldehyde	R_1	R_2	Catalyst loading	Yield[a]	*ee%*[b]	Time
1[85]	4	Me	Me	IV (10mol%)	90	88	24h
2[86]	2	Me	Me	V (20mol%) Benzoic acid (40mol%)	53	96	2d
3[87]	5	Me	Me	VI (10mol%) Benzoic acid (10mol%)	93	88	1.8d
4[88]	5	Me	Me	VII (20mol%)	87	97	4h
5[89]	4	Me	Me	VIII (15mol%)	87	89	48h
6[90]	5	Me	Me	IX (30mol%)	78	94	48h
7[91]	4	Me	Me	X (20mol%) Benzoic acid (10mol%)	93	92	36h
8[92]	5	Me	Me	XI (20mol%) Imidazole (10mol%)	90	80	2d
9[74]	1.9	Me	Me	XII (10mol%)	47	89	60h
10[75]	3	Me	Me	L-Proline (10mol%) LiOH (10mol%)	69	88	48h
11[93]	4	Me	Me	XIV (20mol%)	96	79	30h
12[83]	1.2	Me	Me	O-tert-butyl-l-threonine (5mol%) DMAP Sulfamide	97	98	7h
13[84]	2	Me	Me	XV (20mol%) XV (10mol%) XV (5mol%)	89 88 50	97 93 93	3h 5h 5h
14[94]	5	Me	Me	XVI (10mol%)	80	83	72h

15[77]	5	Me	Me	X (10mol%)	85	82	18h
16[78]	2	Me	Me	XVII (10mol%)	86	95	96h
17[95]	4	Me	Me	XIX (20mol%)	90	93	1d
18[96]	3	Me	Me	XX (15mol%) XX (30mol%)	47 77	99 99	3h 2h
19[97]	3	Me	Me	XXI (10mol%)	88	97	48h
20[98]	2.75	Me	Me	XXII (20mol%) DMAP	92	98	2h
21[82]	2	Me	Me	XXIV (10mol%)	97	92	60h

[a] Yields determined after chromatographic purification (Isolated yield).
[b] Enantiomeric excess determined by chiral HPLC.

In conclusion, α-branched aldehyde addition is very likely to be more important for natural product or pharmaceutical drug formation than examples with linear-aldehydes because of the greater substitution afforded in those products. Unfortunately, α-branched aldehyde additions remain underdeveloped and while not discussed here specifically regarding the generation of stereogenic quaternary centers.

1.6.3 Substituent Limitations



58a
3.0 equiv

68

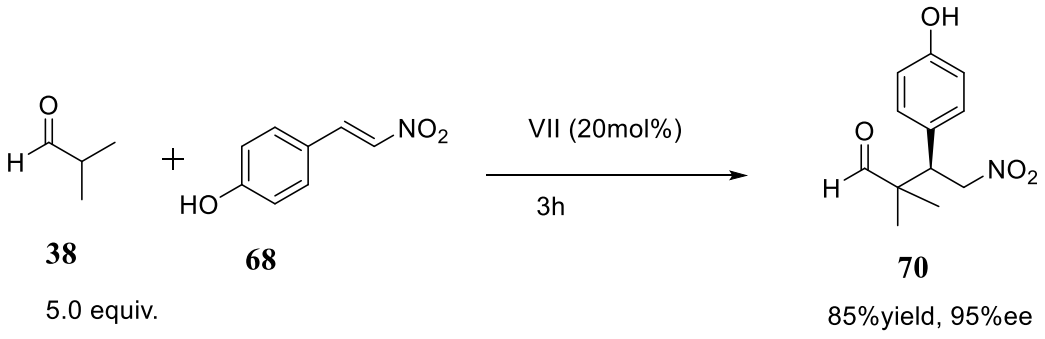
69
97% yield, 96% ee
3:97 dr(anti/syn)

Scheme 25 Michael addition of liner aldehyde to 4-OH β-nitrostyrene.

In Scheme 25 and 26, I detail intermittent discoveries within the research area of organocatalyzed additions of linear or α-branched aldehydes to variously substituted β-nitrostyrenes with acidic spectator groups. Why do I mention this? The point is that why well over 200 publications are noted for aldehyde addition to β-nitrostyrene, at no point has anyone shown that acidic moieties can be present, it is a glaring omission and points to the difficulty of performing reactions with acidic functional groups present. I now show all the known examples, none of which are comprehensive or discuss this problem.

In 2015 Gilmour and Pericàs[73] reported the Michael addition of linear aldehydes to nitroalkenes in the presence of an acidic group. For this purpose, they prepared a polymer based fluorinated organocatalyst (10mol%, see Figure 4, III) that allowed the Michael addition of propionaldehyde and β-nitrostyrene (3:1 ratio) in the presence of 10mol % 4-nitrophenol. Excellent yield and ee (96%) with 3:97 dr were noted Scheme 25.

In 2016, Ying and Songlin Xu[88] prepared magnetic nanoparticles with a tethered chiral aminocyclohexane sulfamide see Figure 4, VII). They applied this catalyst in Michael addition between isobutyraldehyde and β-nitrostyrene (5:1 ratio), using a high catalyst loading (20mol%) providing excellent yield 85 and ee (95%) Scheme 26**.** This catalyst is recoverable and easily separated using an external magnetic force



Scheme 26 Michael addition of branched aldehyde to 4-OH β-nitrostyrene.

1.7 References

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Chapter 2

2.0 Published and Submitted Manuscripts

Doctoral Cumulative thesis is presented in the following three manuscripts:

Published manuscript

2.1 Beyond Chemoselectivity: Catalytic Site-Selective Aldolization of Diketones and Exploitation for Enantioselective Alzheimer Drug Candidate Synthesis

Thomas C. Nugent, Foad Tehrani Najafian, Hussein Ali El Damrany Hussein, and Ishtiaq Hussain, *Chem. Eur. J.* 2016, 22, 14342

The Supporting Information for this manuscript is 198 pages long and therefore its inclusion here is not realistic. Instead I have provided the following internet link where the experimental details can be found in a pdf format.

2.2 A Catalyst Directed Remote StereogenicCenterSwitch During the Site-Selective Aldol Desymmetrization of Cyclohexanone Based Diketones

Thomas C. Nugent, Peter Spiteller, Ishtiaq Hussain, Hussein Ali El Damrany Hussein, and Foad Tehrani Najafian, *Adv.Synth. Catal.* 2016, 358,3706

The Supporting Information for this manuscript is 111 pages long and therefore its inclusion here is not realistic. Instead I have provided the following internet link where the experimental details can be found in a pdf format.

Manuscript under Submission (It will be submitted in the very near future)

2.3 Catalytic Enantioselective Michael Reactions in the Presence of a Diverse Array of Acidic Spectator Functional Groups. Expedient Synthesis of Antidepressant (R)-Pristiq

Thomas C. Nugent, Hussein Ali El Damrany Hussein, Shahzad Ahmed, Foad Tehrani Najafian, Tony Georgiev, Ishtiaq Hussain, Mahmoud Khalaf Aljoumhawy

2.1 Beyond Chemoselectivity: Catalytic Site-Selective Aldolization of Diketones and Exploitation for Enantioselective Alzheimer Drug Candidate Synthesis

Thomas C. Nugent, Foad Tehrani Najafian, Hussein Ali El Damrany Hussein, and Ishtiaq Hussain

Note: the numbering correlates to those found in this published manuscript

Abstract: Site-selectivity, differentiating members of the same functional group type on one substrate, represents a forward-looking theme within chemistry: reduced dependence on protection/deprotection protocols for increased overall yield and step-efficiency. Despite these potential benefits and the expanded tactical advantages afforded to synthetic design, site-selectivity remains elusive and especially so for ketone-based substrates. Here we report on the site-selective intermolecular mono-aldolization of an array of prochiral 4-ketosubstituted cyclohexanones with concomitant regio-, diastereo-, and enantiocontrol. Importantly, the aldol products allow rapid access to molecularly complex keto-lactones or keto-1,3-diols respectively containing three and four stereogenic centers. The reaction conditions are of immediate practical value and general enough to be applicable to other reaction types. These findings are encapsulated by the first enantioselective formal synthesis of a leading Alzheimer research drug, a γ-secretase modulator (GSM), in the highest known yield.

2.1.1 Introduction

Differentiation of the same functional group type on one molecule is the unmet challenge of site-selective transformations,[1] a subcategory of regioselectivity. Mild reagents sometimes achieve site-selectivity when recognizable steric or electronic dissimilarities prevail, but when subtle differences exist the product outcome is non-selective. The latter is the focus here, and catalyst design can be pivotal to addressing this challenge. In this light, the most successful applications of site-selectivity have been demonstrated for polyol substrates, and elegant natural product examples have been demonstrated in the name of expedited drug discovery.[2,3] In parallel, a smaller subset of polyols, *e.g. meso*-diols, require desymmetrization to differentiate their alcohol moieties.[4,5]

In contrast to those polyol achievements, little is known about controlling the reaction outcome at one of two electronically disconnected ketone functional groups within a 1,n-diketone where $n \geq 4$. These substrates are the focus of this manuscript, and to the best of our knowledge only

four systematic studies detail site-selectivity or desymmetrization with high enantioselectivity (Figure 1). It is informative that half of those investigations resulted in tactical advantages that permitted the shortest known syntheses of two natural products (Figure 1, right panel). Two of those four studies employ enzymes and intimate how to reduce (Niemeyer)[6] or reductively aminate (Kroutil)[7] one carbonyl unit, specifically a methyl ketone.

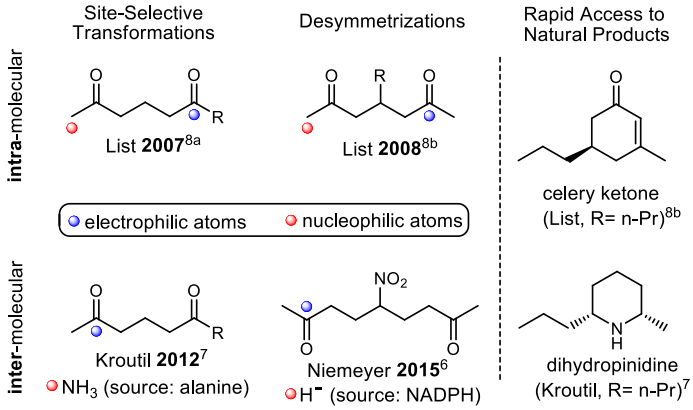


Figure 1. Left panel: Diketone starting materials of prior site-selectivity or desymmetrization studies. Right panel: Natural product applications. Blue labeled atoms are electrophilic, red nucleophilic.

The remaining two studies (List)[8] are chemical based and demonstrate how to perform intramolecular reactions, again with methyl ketones (Figure 1). All four of those studies show exquisite selectivities. We are additionally aware of a single example of double intermolecular site-selective aldolization of a methyl ketone within a diketone (not shown).[9] Finally, it is important to note the intramolecular aldol studies of the Hajos–Parrish–Eder–Sauer–Wiechert triketones. These triketones (not shown) and analogs thereof have been studied and reviewed elsewhere,[10,11,12] and all conclusions made here take those findings into account.

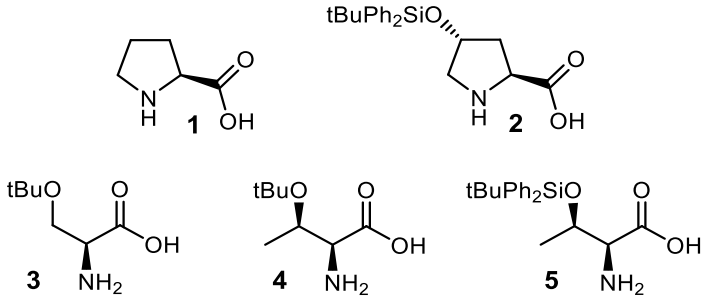


Figure 2. Catalysts examined during this study.

General guidance on how to broaden or improve ketone site-selectivity is not apparent from the small number of publications within this emerging field of study; and catalyst loadings can be prohibitively high. Furthermore, many challenges remain open to investigation, *e.g.,* can methyl ketones be preserved (remain unreacted) while another ketone carbonyl undergoes a transformation. A useful entry point to that question is Stork's 1963 observation that stoichiometric pyrrolidine enamine formation is more rapid for cyclohexanone than for acyclic ketones.[13] Those results are in general agreement with the last fifteen years of modern enamine-based organocatalysis observations.[10,11,14,15] For example, List demonstrated rather early that L-proline (**1**) (Figure 2) produced the aldol products of cyclohexanone faster than for acetone.[16] But these trends can also be interrupted, *e.g.,* it has been repeatedly shown that 2-butanone and cyclohexanone react with *p*-nitrobenzaldehyde by way of L-proline[17] or prolinamide[18] catalysis under the same reaction conditions and reaction times to produce remarkably similar aldol product yields of each. However, when starting materials are not used in excess, clearer reactivity trends can sometimes be noted for particular amine catalysts. For example, Hayashi's aldol studies of TBDPSO-4-hydroxyproline catalyst **2** (Figure 2) revealed a large difference in reactivity for 2-butanone and cyclohexanone.[19] In summary, despite long held knowledge of cyclohexanone enamine reactivity trends, it is remarkable that those differences have never been demonstrated within a multi-ketonic substrate, let alone exploited for synthetic advantage. This manuscript details the first inroads toward that goal.

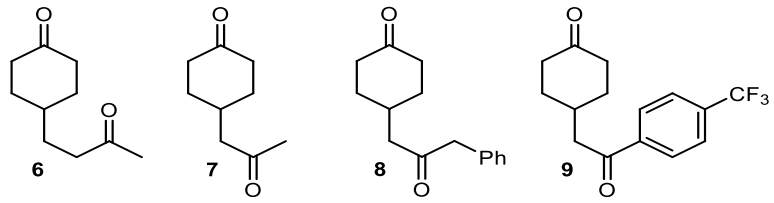


Figure 3. Diketones investigated.

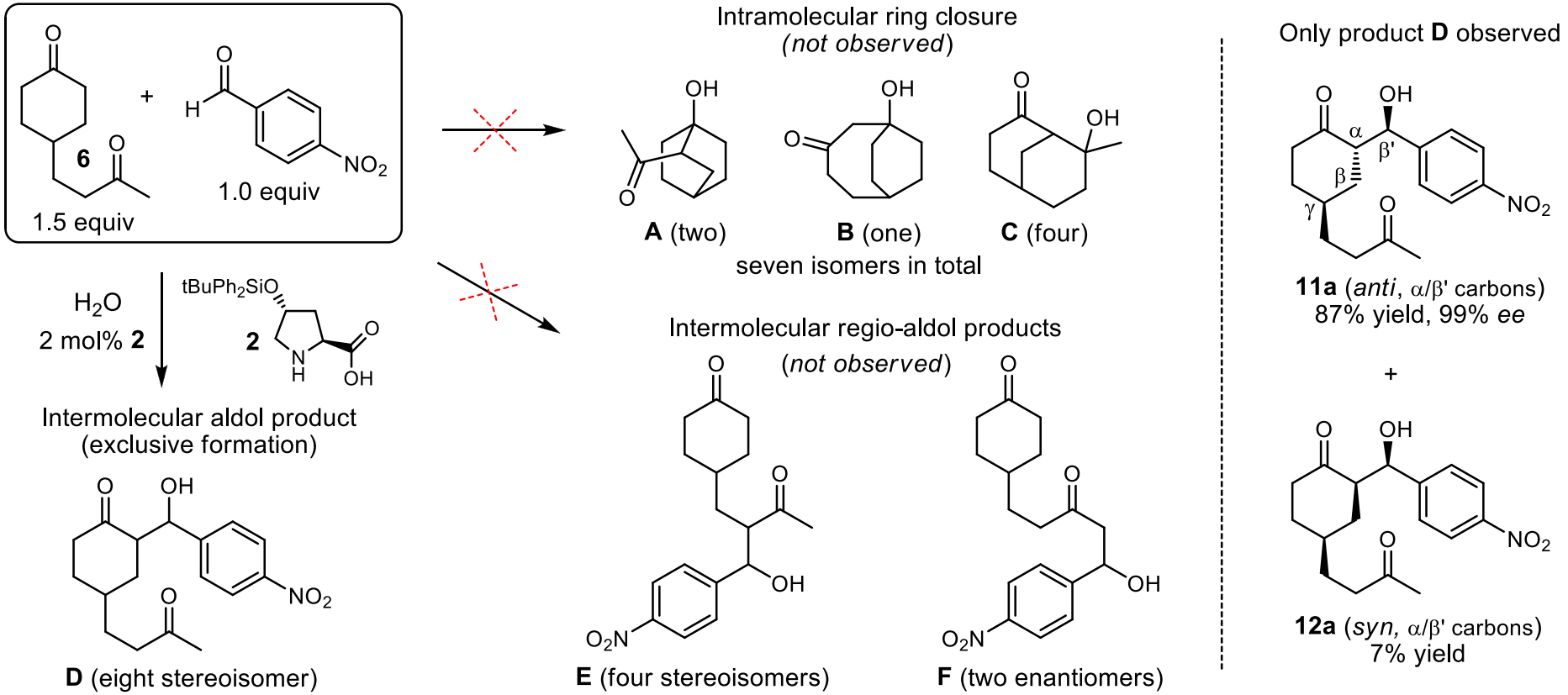


Figure 4. Left panel: Twenty-one possible first generation products. Right panel: Only two stereoisomers of product type D are noted (11a and 12a).

2.1.2 Results and Discussion

We speculated that 4-ketosubstituted cyclohexanones **6**-**9** (Figure 3) could serve as prototypes to establish broader knowledge in this area, and envisioned that high aldol site-selectivity could be achieved via amine catalysis if the catalyst was capable of dramatically differentiating the enamine equilibriums of the available (competing) carbonyl carbons.[20] Over the course of this manuscript we will show that this was possible and demonstrate: i) the first reaction examples in which unhindered methyl ketone remain unreacted, ii) the first comprehensive chemical study demonstrating that intermolecular ketone site-selectivity is possible, and iii) the beneficial use of this methodology to demonstrate the highest yielding synthesis of a recently described frontline Alzheimer drug candidate GSM-1 (Scheme 2).[21,22,23]

Diketone **6** is a compelling starting point because it merges 2-butanone and cyclohexanone into one diketone substrate. Its reaction with *p*-nitrobenzaldehyde under TBDPSO-4-hydroxyproline (**2**) catalysis can yield up to twenty-one possible products (Figure 4, left panel), but provided only two products of type **D** from cyclohexanone carbonyl attack: aldol **11a** (major) and **12a** (minor), Figure 4 right panel. Two regioisomeric intermolecular aldol products of the methyl ketone are additionally possible: **E** and **F** (Figure 4, left panel), but no evidence of their formation was noted. Although intramolecular aldol cyclization may occur, *e.g.*, **A** and **C** are Baldwin favored,[24,25] control experiments, without the aldehyde, ruled out this possibility by returning only the starting diketone (**6**). In that light, it is interesting to note that intramolecular cyclization of the corresponding aldehydic cyclohexanone (not shown), replace the methyl ketone of **6** with an aldehyde moiety, occurs in the presence of catalyst **2**.[26] Formation of **11a** (87% yield, 99% ee) consequently represents a highly site-selective differentiation of diketone **6** with concomitant diastereo- and enantiocontrol.

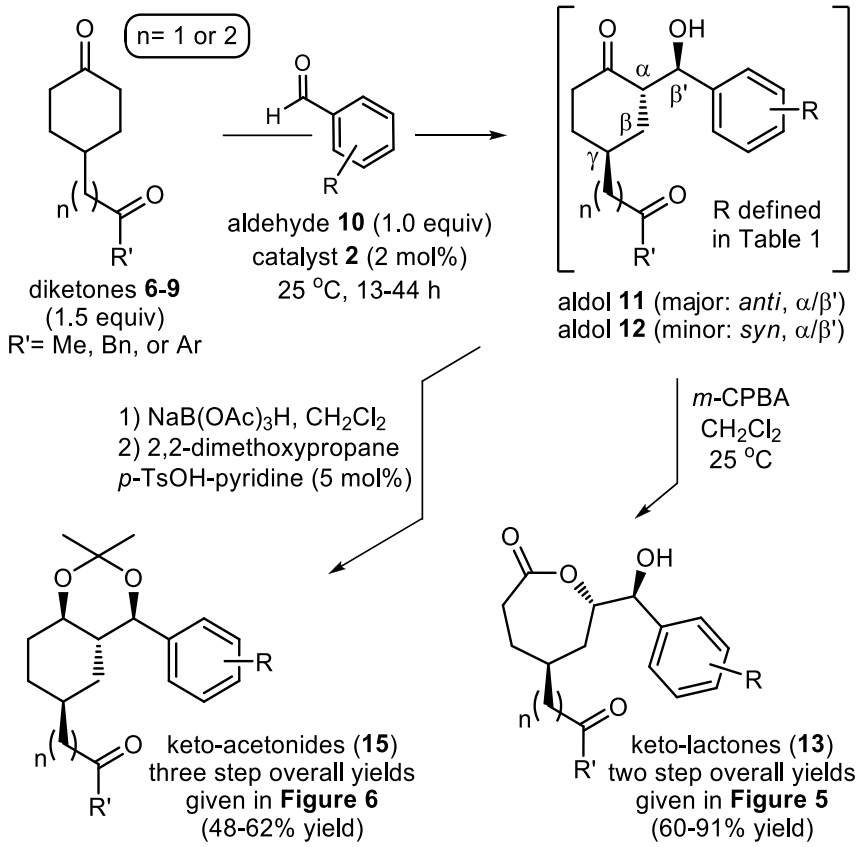
To preserve the α-keto labile stereogenic center of the aldol products **11**,[27] they were worked-up by organic solvent extraction from water, and dried under high vacuum. Their diastereomeric ratios were assessed by ^{1}H NMR, and the crude aldol products oxidized or reduced to respectively give previously unknown, but stable and fully characterizable, keto-lactones (**13**, three stereogenic centers) or keto-1,3-diols (**14**, not shown) that were identified as their keto-acetonides (**15**, four stereogenic centers) (Scheme 1). These densely functionalized keto-lactones (**13**) and keto-acetonides (**15**) were isolated after chromatography as single diastereomers;

Table 1. Aldol (**11**/**12**) Data for Scheme 1.[a]

Entry	Diketone	Aldehyde $RC_6H_4C(O)H$	t (h)[b]	Aldol Product, **11**/**12**, dr[c]
1	**6**	4-NO_2	30	**11a**/**12a**, 12:1
2[d]	**6**	4-NO_2	80	**11a**/**12a**, 6:1
3[e]	**6**	3-NO_2	30	**11b**/**12b**, 19:1
4	**6**	2-NO_2	38	**11c**/**12c**, >24:1
5	**6**	2,6-Cl_2	30	**11d**/**12d**, >24:1
6	**6**	4-CN	36	**11e**/**12e**, 13:1
7[e]	**6**	4-Br	28	**11f**/**12f**, 3.3:1
8	**6**	4-CF_3	30	**11g**/**12g**, 10:1
9	**7**	4-NO_2	34	**11h**/**12h**, 17:1
10[f,g,h]	**8**	4-NO_2	13	**11j**/**12j**, 6.3:1
11[f,g,i]	**8**	4-NO_2	23	**11j**/**12j**, 8.2:1
12[h,j]	**9**	4-CF_3	44	**11i**/**12i**, >24:1

(a) Aldehyde (0.50 or 0.75 mmol), diketone (1.5 equiv.), water (3.0 equiv), catalysts **2** (2.0mol%), 25 ^oC. The aldol products are stereochemically labile and further reacted without purification, no yield data; (b) Reaction time corresponds to aldehyde consumption (^1H NMR) of 95 ± 2%; (c) ^1H NMR (crude) of *anti*-**11**/*syn*-**12** (α and β' carbons); (d) 50mol% L-proline used; (e) Reaction time corresponds to aldehyde consumption of 91 ± 2%;

(f) 35 ^oC; (g) 8.0 equiv of H_2O; (h) Catalyst **2** (4.0 mol%); (i) Catalyst **2**, 2.0 mol% added at t= 0 and 9 h, total catalyst loading 4 mol%; (j) Diketone **9** is the limiting reagent, aldehyde (2.0 equiv), 4.5 equiv. H_2O, 25 ^oC.



Scheme 1. Ketone site-selectivity and aldol, keto-lactone, and keto-acetonide product overview

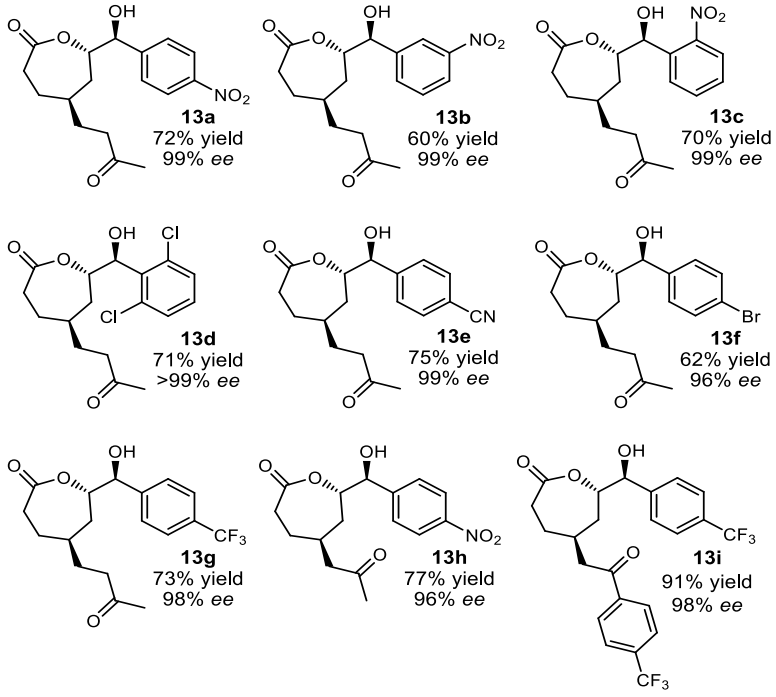


Figure 5. Keto-lactone products from Scheme 1. Two step overall yields from the corresponding diketones (**6**, **7**, or **9**). Each product represents a single diastereomerically pure compound after column chromatography.

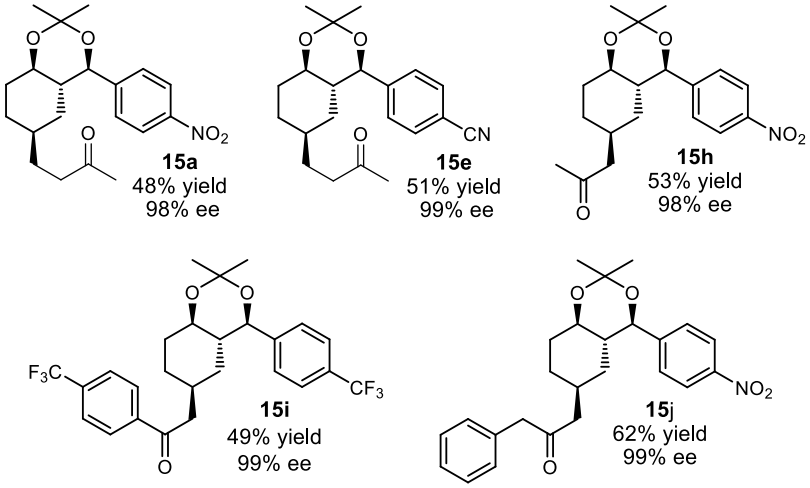


Figure 6. Keto-acetonide products from Scheme 1. Three step overall yields from the corresponding diketones (6-9). Each product represents a single diastereomerically pure compound after column chromatography.

and the overall yield of each diastereomer, calculated from the corresponding diketone (**6**-**9**), is good to excellent considering that these yields respectively reflect two or three reaction steps (Scheme 1 and Figures 5 & 6). Conversion of aldol products **11** to **13** or **15** constituted a second, but predictable, level of site-selectivity based, respectively, on well-established Baeyer-Villiger migratory aptitudes[28] and the known proclivity of $NaB(OAc)_3H$ to chemoselectively reduce β-hydroxyketones selectively over ketones.[29,30,31]

Screening and catalyst optimization of the aldol reactions were guided by the fact that the *O*-protected: serine,[32] threonine,[33] and 4-hydroxyproline[34] catalyst frameworks have been previously used for the aldol desymmetrization of 4-methylcyclohexanone.[35] Reaction of 5.0 mol% of catalysts **3**-**5** (Figure 2) with diketone **6** and *p*-nitrobenzaldehyde resulted in sluggish reactions and mediocre diastereoselectivity, 2:1 to 3.5:1, at the remote, γ carbon, stereogenic center. To our knowledge a silyl protected 4-hydroxyproline,[34a] *e.g.*, the TBDPSO-4-hydroxyproline catalyst (**2**) used here (Figure 2), has never been examined for the desymmetrization of 4-substituted cyclohexanones; so it was consequently gratifying to find that catalyst **2** provided aldol product **11a** with greater than 20 to 1 diastereoselectivity at the remote stereogenic center. This high remote center diastereoselectivity was noted for all products formed here. The use of L-proline provides the same high remote center diastereoselectivity, but required a 50 mol% catalyst loading and an 80 h reaction time (Table 1, entry 2). This proline result offers the possibility of improvement by the ball-mill technique exploited by Bolm,[35a] albeit not pursued here. Generation of this remote stereogenic center, in

high dr, was the pivotal stereochemical element allowing access to the later discussed Alzheimer research drugs (Scheme 2).

Further pursuit of these findings demonstrated that aromatic aldehydes, present as the limiting reagents and under chiral amine catalysis (2.0 mol% of **2**), can site-selectively desymmetrize a diverse set of achiral 4-ketosubstituted-cyclohexanones **6**-**8** (1.5 equiv). In doing so cyclohexanone substituted aldol products **11** and **12** are produced (Scheme 1, Table 1), and most often in diastereomeric ratios (*anti*-**11**/*syn*-**12**, α and β' carbons) of greater than ten to one, and in high ee (96-99%) as noted in the final products **13** and **15**. Diketone **9** is discussed at the outset of the Alzheimer drug synthesis.

Regarding the structural breadth of the aldehyde electrophiles, steric effects can restrict the addition of *ortho*-substituted benzaldehydes but here they are well tolerated as shown by the addition of 2-nitrobenzaldehyde and 2,6-dichlorobenzaldehyde, respectively forming keto-lactones **13c** and **13d** (Figure 5). Finally, from an electronic point of view, high yielding substrates are those with aromatic substituents capable of either an inductive or a resonance-based electron withdrawing effect. Benzaldehyde itself provided a low aldol yield under extended reaction times of four days, even with elevated catalyst loadings (10 mol%). Trials examining this aldehyde were not further pursued.

Our attention then turned to diketone substrates **7** and **9**, which may be more prone than diketone **6** to undergo intramolecular aldol reactions. The former because three, as opposed to two for diketone **6**, Baldwin intramolecular aldol ring closures are favored, and the latter because of the greater electrophilicity of a *p*-CF_3-phenylketone carbonyl unit as compared to a methyl ketone; yet both fully maintain high selectivity for the cyclohexanone carbonyl (Table 1, entries 9 and 12; Figure 5, **13h** and **13i**; Figure 6, **15h** and **15i**). Finally we studied benzyl diketone **8** because a related proline catalyst was shown to have a very similar propensity for enamine formation with either cyclohexanone or benzyl methyl ketone; [20] again the cyclohexanone carbonyl was the only site of attack (see Table 1, entries 10 and 11; Figure 6, keto-acetonide **15j**), presumably due to steric congestion. Attempts to convert the aldol product **11j** of benzyl-diketone **8** into a keto-lactone resulted in low yields due to competitive, but non-selective, Baeyer-Villiger migration of the benzylic carbonyl substituent versus the desired secondary-carbon carbonyl substituent.

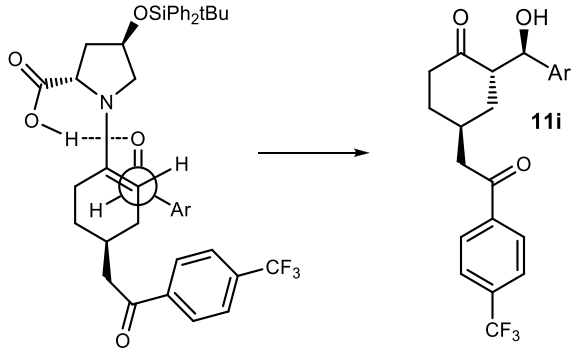


Figure 7. Plausible transition state for aldol 11i.

X-ray crystallographic analysis and CD spectroscopy (Supplementary Information – Section 5) of keto-acetonide **15i** (Figure 6) provided the relative and absolute stereochemistry, and by extension, for all shown aldol products. The Figure 7 transition state depicts a likely scenario for the formation of aldol **11i** *via* the reaction of diketone **9** with *p*-CF_3-benzaldehyde, which in turn was elaborated into keto-acetonide **15i**.

In brief summary, most of the aldol reactions were performed with diketone **6** to unequivocally demonstrate that a non-hindered methyl-ketone repeatedly showed no reactivity. In short, methyl-ketones act as if they are protected under these mild reaction conditions. These results complement the earlier findings that required methyl ketone based substrates (Figure 1).

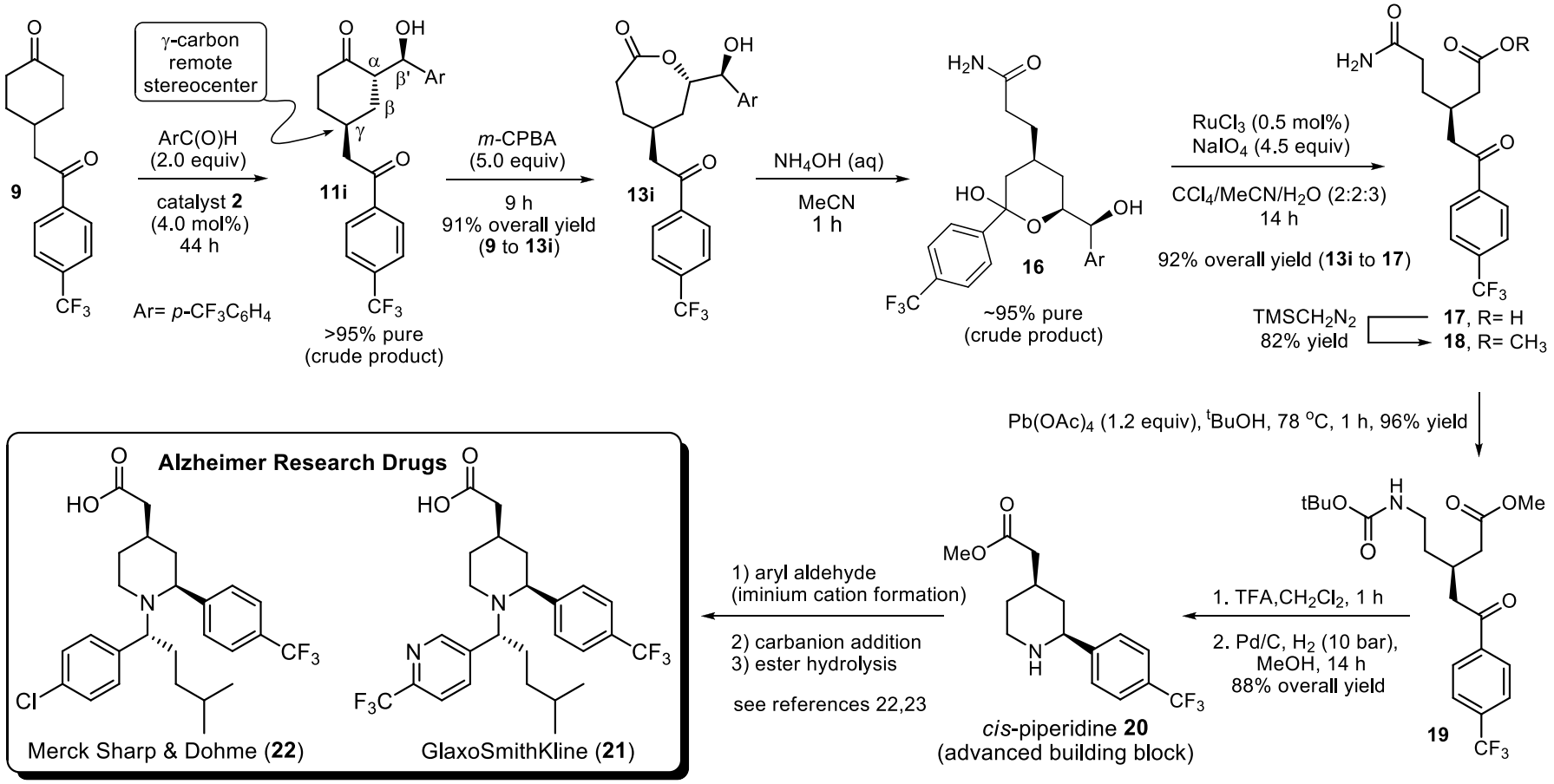
Early onset Alzheimer's disease is marked by proteolysis events initiated by β-secretase but refined multiple times by γ-secretase.[36] The most frequent outcome is amyloid beta (Aβ) peptide formation in the range of 37-43 amino acid residues.[37] In the Alzheimer patient this manifests itself as neurotoxic $A\beta_{42}$ peptide brain deposition, otherwise known, in one typical form, as extracellular senile plaque. Currently, no drugs exist for the treatment of Alzheimer disease, but at present leading investigational drugs are γ-secretase modulators (GSMs).[21] GSMs were explicitly developed for reducing $A\beta_{42}$ peptide formation, and include examples synthesized by GlaxoSmithKline (**21**)[23,38] and Merck Sharp & Dohme (**22**)[22] (Scheme 2). Both companies leveraged one advanced enantiopure piperidine building block (**20**) to produce well over one hundred drug candidates.[22,23,39] Of those, the most often and very recently cited representative with potent $A\beta_{42}$ peptide lowering effects is the piperidine-based amino acid **22**.[21,37,40,41]

All syntheses of these Alzheimer drugs proceed through enantiopure *cis*-piperidine **20**. Our entry to **20** was envisioned through lactone **13i** because we could repeatedly produce an exceptionally high overall yield (91%) and *ee* (98%) from diketone **9** and *p*-CF_3-benzaldehyde (Scheme 2). The reaction is robust, regardless of the scale of the reaction which varied from 1

to 15 mmol. To obtain those results, we modified our general procedure as follows. Diketone **9** became the limiting reagent (1.0 equiv) in the presence of excess *p*-CF_3-benzaldehyde (2.0 equiv), and water (4.5 equiv). After 44 h the ring substituted aldol products **11i** and **12i** formed in an *anti*-(α,β') to *syn*-(α,β') ratio of greater than 24:1 (Scheme 2, **12i** not shown). Extractive work-up gave **11i**/**12i** in high crude yield and purity (≥95%). This material could be used without further purification in the next reaction step.

Transformation of aldol **11i** to lactone **13i** requires the cyclic ketone's secondary-carbon substituent to undergo Baeyer-Villiger migration, while the acyclic ketone's aromatic substituent must remain unreacted. These two types of substituents have similar migratory aptitudes, but we were confident that this aromatic ring would not migrate because Baeyer-Villiger rearrangements with strongly electron withdrawing substituents on the aromatic ring, to our knowledge, have no published precedent when using *m*CPBA. Our results bear out that conclusion, with a 91% overall yield, from diketone **9**, of lactone **13i** as one diastereomerically pure compound after column chromatography. This is an uncommon demonstration of an electronic effect dictating Baeyer-Villiger migratory aptitude.[28]

Ammonolysis of **13i** quantitatively provided the ring opened primary amide, whose concomitantly liberated diol preferred to collapse onto the aromatic ketone resulting in a six-membered lactol **16**. Lactol **16** resisted further purification (Supplementary Info – Section 6), which prompted us to use this nearly pure crude product as such. The next reaction, a catalytic ruthenium (0.5 mol%) based oxidative cleavage, occurs under mildly acidic aqueous biphasic conditions. Those conditions advantageously promoted *in situ* lactol hydrolysis, freeing the vicinal diol whose oxidative cleavage produced an aldehyde that readily oxidized to the desired carboxylic acid (**17**) in the presence of perruthenate. Thus in one-pot, lactol **16** furnished carboxylic acid **17**. The isolated overall yield of **17**, from lactone **13i**, was 92%. Treatment of the carboxylic acidic (**17**) with ethereal TMS-diazomethane uneventfully formed the methyl ester (**18**) in 82% yield.



Scheme 2. The First, Formal, Enantioselective Synthesis of Frontline. [21] Alzheimer Drug Candidates 21 and 22.

We initially sought to elaborate methyl ester **18** to piperidine **20** *via* a Hofmann rearrangement, but otherwise reliable modern reagents for doing so, $PhI(CF_3CO_2)_2$[42] or $PhI(OAc)_2$[43], provided intractable product mixtures. This is perhaps unsurprising due to the number, type, and proximity of the spectator functional groups. By contrast, the combination of 1.2 equiv of lead tetraacetate in near boiling *tert*-butanol proved to be efficient for isocyanate formation,[44] affording the t-butoxycarbonyl (BOC) protected amine (**19**) in high yield after *in situ* solvent trapping. Deprotection of carbamate **19** proceeded satisfactorily in a one-spot to one-spot transformation (TLC) with trifluoroacetic acid (25 equiv); and exclusive hydrogenation (Pd/C 2.0 mol %, 10 bar H_2) from the less hindered face of the resulting crude cyclic imine (not shown) provided the desired *cis*-piperidine **20** at the expense of the undesired *trans*-diastereomer. This synthesis constitutes the first enantioselective synthesis of *cis*-piperidine **20**, and consequently the first (formal) enantioselective synthesis of γ-secretase modulators **21** and **22** (Scheme 2), the latter is sometimes referred to in the neuroscience literature as GSM-1.[40]

The present synthesis constitutes a seven step high yielding transformation of diketone **9** into *cis*-piperidine **20**, occurring in an overall yield of 58%. A 36% overall yield of *cis*-piperidine **20** is noted when starting from 1,1-ethylenedioxy-4-cyclohexanone, the commercial starting material required for the synthesis of diketone **9** (see Supplementary Information, Section 2). This overall yield improves the best known synthesis of *cis*-piperidine **20**,[22,23] which requires an L-(+)-mandelic acid resolution step and occurs in 25% overall yield.[23]

2.1.3 Conclusions

In summary, mild amine catalysis has permitted the site-, regio-, diastereo-, and enantioselective differentiation of a diverse set of cyclohexanone-based diketones (**6**-**9**) during aldol reactions. The present method has accordingly established new chemical territory for further exploration by offering previously unrealized site-selectivity for diketone substrates. Importantly, the aldol products shown here allow fast entry to high-density chiral compounds like keto-lactones (**13**) or keto-acetonides (**15**) under practical reaction conditions. These achievements embody a forward looking theme within chemistry, reduced dependence on protection/deprotection protocols, and the method should extend to other electrophiles, *e.g.*, nitroso compounds, and other diketones, *e.g.*, 3-ketosubstituted cyclobutanones, potentially with reversal of site-selectivity. Of further significance, the product features of rich functional group density combined with a remote stereogenic center may expand tactical application possibilities for more step-efficient approaches to other complex biomolecules. A first

generation encapsulation of this is our formal synthesis of Alzheimer γ-secretase modulator drug candidates in the highest yielding synthesis known to date. It is also clear that new doors have been opened for drug discovery opportunities within Alzheimer drug discovery research. On a different note, we imagine that unraveling keto-lactones **13** into intermediates based on a central chiral methine unit, like that found in keto ester amide **18**, may be a logical starting point for preparing artificial chiral cavities as used in supramolecular host-guest chemistry[45] or for generating, via dendritic extension, chiral tertiary macromolecules reminiscent of protein environments.[46]

2.1.4 Experimental Section

General procedure for aldol products **11**: TBDPSO-4-hydroxyproline (MW= 369.5 g/mol, 0.015 mmol, 2.0 mol%, 5.54 mg) was added to a gently stirred solution of the diketone (**6**-**8**) (1.12 mmol, 1.5 equiv) and the aldehyde (0.75 mmol, 1.0 equiv). Once the catalyst was fully dissolved, water (40.5µL, 3.0 equiv) was added. This mixture was stirred at room temperature in a closed reaction vessel until a starting material conversion of ≥95% could be confirmed by ^{1}H NMR. See the individual compounds (Supplementary Information) for the exact reaction times. [Note: Extension of the indicated reaction times is often detrimental due to decreased diastereoselectivity from α-keto epimerization.] The reaction was worked up by repetitively adding CH_2Cl_2 or EtOAc (6 x 10 mL) to the reaction vessel and combining those fractions. The combined extracts were dried (Na_2SO_4), filtered, and concentrated (rotary evaporator - bath temperature < 28 ^oC). The crude aldol product was then briefly (2-4 h) exposed to high vacuum before treatment in the next reaction step to form **13** or **15**. Full experimental details are provided in the Supplementary Infomation.

The X-ray crystallographic coordinate for keto-acetonide **15i** is deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 1427190. These data can be obtained free of charge (http://www.ccdc.cam.ac.uk/data_request/cif).

Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft (German Science Foundation) under award no. NU 235/6-1, and Jacobs University Bremen. We are very thankful for low and high resolution MS measurements provided by Professor Dr. Nikolai Kuhnert. The authors thank Professor Dr. Jens Beckmann (University of Bremen) for X-ray analysis of keto-acetonide **15i**. We thank Professor Dr. Heiko Ihmels (University Siegen) for initial CD discussions. We thank Dr. Richard Friary for insightful comments regarding style and conciseness.

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2.2 A Catalyst Directed Remote Stereogenic Center Switch During the Site-Selective Aldol Desymmetrization of Cyclohexanone Based Diketones

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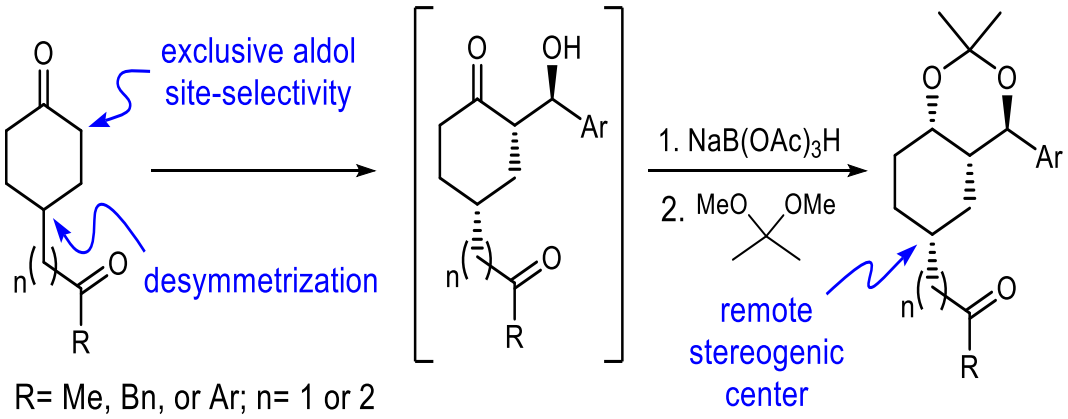
Note: the numbering correlates to those found in this published manuscript

Site-selectivity, differentiating members of the same functional group type on one substrate, is an emerging tactic for shortened advanced building block and biomolecule synthesis. Despite its potential, site-selectivity remains less studied and especially so for ketone-based substrates. During this work ketone site-selectivity has been coupled with the chiral amine catalyzed aldol desymmetrization of 4-ketosubstituted cyclohexanones, allowing three stereogenic centers to form in the aldol product while leaving the acyclic ketone unreacted. Unique here, compared to all previous 4-substituted cyclohexanone desymmetrizations, the first synthetically useful quantities of an epimeric aldol product, at the remote stereogenic center, is formed. To demonstrate the value of those aldol products, we show their elaboration into eight keto-acetonide and one keto-lactone products. All compounds were isolated as single diastereomers and in high ee (≥96%). These efforts represent the first full characterization of aldol products with type III relative stereochemistry (Figure 2), regardless of the enantiomer formed.



2.2.1 Introduction

Ketone transformations are common, reliable, and represented by a large variety of reactions.[1] Nevertheless, the use of prochiraldiketones for enantioselective synthesis is limited due to the difficulty of differentiating: i) non-equivalent ketone carbonyl moieties, a topic of site-selectivity,[2,3a,c,e,4] or ii) equivalent ketone carbonyl units, a topic of desymmetrization (Figure 1).[3a,b,d] Among diketone substrates, 1,2- and 1,3-diketones possess electronically interconnected carbonyl moieties making them susceptible to intramolecular hydrogen bonding (enol-ketone), metal chelation control opportunities, and so forth. By contrast, 1,4- and higher diketones would generally lack those attributes, represent good prototypes for examining ketone carbonyl differentiation, and are the focus of this manuscript. From those diketones, we are aware of only five studies that demonstrate highly enantioselective reactions while concomitantly illustrating site-selectivity or desymmetrization (Figure 1).[5,6]

The Figure 1 examples show that inroads have been made for targeting methyl ketones in the presence of internal acyclic ketones, and the enamine based catalysis achievements among them likely reflect the early observations of Barbas who revealed in 2001 that 2-butanone has good reactivity under (S)-proline catalysis while a complete lack of reactivity was noted for an internal ketone, *e.g.*, 3-pentanone.[7] In an effort to expand beyond methyl ketone site-selectivity, we recently demonstrated that cyclohexanone carbonyls can be targeted over methyl ketone carbonyl moieties (Figure 1, Nugent, R= Me, n= 2) in diketone substrates, namely, 4-ketosubstituted cyclohexanones.[3e] In doing so, we demonstrated the first examples in which a non-hindered methyl ketone remains unreacted. Here we detail an extension of that study in which an alternative amine catalyst, picolyl amine (PicAm) **1** (Figure 2, left panel),[8] is used to form the first realistic quantities of a non-accessibleepimericaldol product (Figure 2, middle panel,type **III**).

All enantioselective transformations performed on 4-substituted cyclohexanones must concomitantly entail a desymmetrization (Figure 2, middle panel), and in 2007 Gong disclosed a highly selective aldol variant.[9] He did so with an efficient prolinamide catalyst **2** (Figure 2), and fifty eight organocatalyst based publications have followed in which the products, typically from 4-methyl,[10] 4-*t*-butyl,[10b,d,11] or 4-phenylcyclohexanone[9,10b,11b,12] starting materials, have been benchmarked against each other under the use of alternative catalysts and reaction conditions. As such, our recent investigation of 4-ketosubstituted cyclohexanone substrates **5-8** (Figure 2, right panel), under TBDPSO-4-hydroxyproline (**3**) catalysis (Figure 2, left panel),[3e]was unique because it was the first to show that diketones, based on 4-substituted

cyclohexanones, can be site-selectively desymmetrized, but the product stereochemistry followed the same well-defined relative and absolute stereo-pattern as noted for all previous aldol desymmetrizations of 4-substituted cyclohexanones.[9]Common to all of those prior studies, two dominant stereochemical outcomes were always noted as the relative stereochemistries of type **I** (major, often greater than 80% yield) and **II** (minor) aldol products,[13] see Figure 2 (middle panel). A small subset of those publications quantitatively describe other stereochemical outcomes as minor products, see aldol products **III** and **IV** of Figure 2.[10b,12b,14]From those studies, two reveal >5% yield for aldol products of type **III**,[14b,c]and the study by Plusquellec is the only study to indicate the formation of an aldol product of type **IV** (8% yield).[14c] Specifically, in 2011 Córdova noted a 3:1 ratio of aldol **I** (68% yield) to aldol**III** (23%) products when examining the desymmetrization of 4-methylcyclohexanone (10 equiv) with 4-nitrobenzaldehyde under 10 mol% TBSO-threonine catalysis (Figure 2, catalyst **4**).[14b] One year later, Plusquellec noted that 4-methylcyclohexanone (5 equiv) could be desymmetrized with 3-nitrobenzaldehyde under 2 mol% (*R*)-3-pyrrolidinol (not shown) catalysis in a 1.0 M aqueous solution of a sugar derivative. During that study, the greatest yield of aldol type **III** was 22%, while aldol **IV** was noted for the first time albeit in 8% yield. Both of Plusquellec's products were racemic.[15] Perhaps unsurprisingly, the low yields of these compounds precluded their isolation in pure form by Córdova or Plusquellec. As such, no aldol products of type **III** or **IV**, or analogs thereof, have ever been fully characterized.

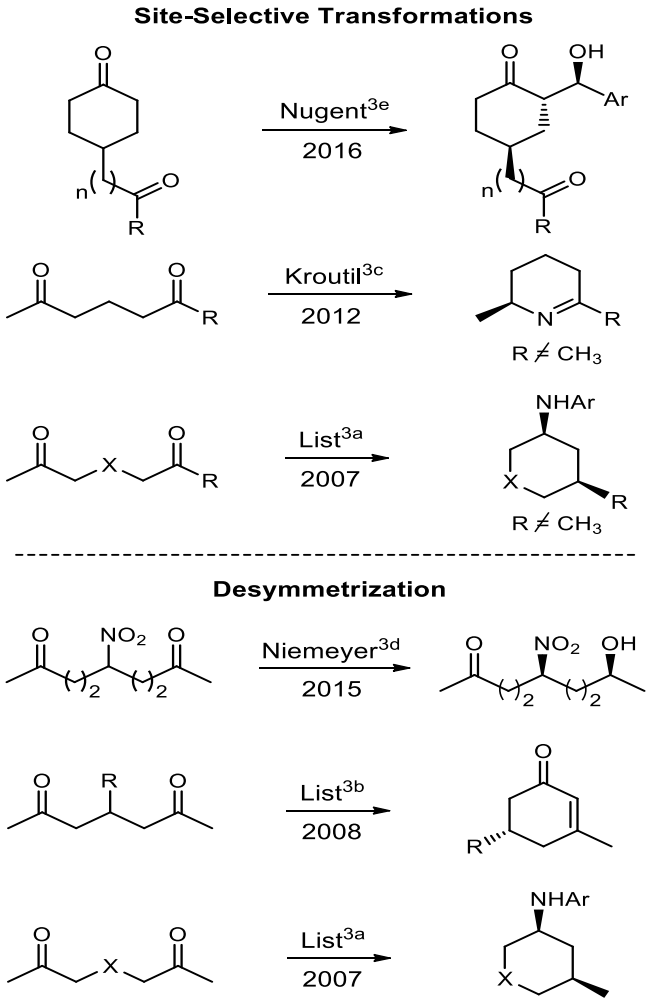


Figure 1. Prior examples of highly enantioselective diketone differentiation.[3]

In summary, regardless of the R substituent on a mono-4-substituted cyclohexanone (Figure 2, middle panel), their desymmetrization only infrequently provides aldol products **III** or **IV**, and then only in minor quantities. Furthermore, only when 4-methylcyclohexanone was used, were yields of up to 23% for aldol product **III** observed. There are no current examples with larger substituents, located at the 4-position, that provide >5% yield of type **III** relative stereochemistry products. In particular we stress here that gaining access to these remote stereogeneric center epimeric products (**III** or **IV**) would be laboriously inefficient *via*:(i) any other synthetic approach; (ii) post modification of aldol products **I** or **II**; or (iii) the application of an enantiomeric catalyst coupled with post modification.[16] With this communication, we change that dynamic by showing that useful, albeit modest, yields of pure type **III** relative stereochemistry compounds can now be accessed.

2.2.2 Results and discussion

With that perspective, we have found that picolyl amine (PicAm) catalyst **1** provides nearly equal quantities of two major aldol products, **9** and **10**, in combined yields of approximately 90% (^{1}H NMR analysis) during the enantioselective desymmetrization of diketones **5-8** (Scheme 1).[17]Aldol products**10a-h** contain the relative stereochemistry as found in all previous studies, *i.e.* type **I**, and have been previously synthesized.[3e] They are not a focus of this manuscript and are not further discussed. On the other hand, structures **9a-h** possess the difficult to access type **III** aldol stereochemistry and were readily isolated and characterized, albeit as their corresponding keto-acetonide (**11a-h**) and keto-lactone (**12**) products and are shortly discussed (Table 1). These PicAm **1** catalyzed reactions consequently permit an epimer switch, albeit non-selective, at the remote stereogenic center of the aldol product (Scheme 1).

Cyclohexanone based aldol products, like aldol**9** and **10**, often undergo non-selective epimerization at their α-carbon (Scheme 1, carbon 2) upon exposure to silica gel.[18,19] Adding to this challenge, a majority of our *anti* and *syn* aldol products had similar R_f values (TLC).As such, we found it practical to lock in the aldol stereochemical information by simply using the worked-up, crude, aldol products for our next reactions. In this manner, we showed that these aldol products can be elaborated into useful keto-acetonide building blocks as single diastereomeric products and in high ee (Table 1).[20] To gain access to the keto-acetonide products, we took advantage of the well-known fact that β-hydroxy ketones are selectively reduced over simple ketones when employing $NaB(OAc)_3H$.[21] The stereochemical outcome of these type of reductions has been discussed elsewhere,[22]but interestingly, carbonyl hydride delivery occurred, predominately, from the opposite face of the cyclohexanone ring for **9** versus **10**. The resultant keto-1,3-diols (not shown), were chromatographically not obtainable as pure diastereomers using EtOAc/petrol ether eluent systems, nonetheless, collection of all diastereomers, with mediocre chemical purity, ~85-90% after chromatography, did allow their conversion to keto-acetonides when treated with 2,2-dimethoxypropane (20-30 equiv) under the mildly acidic conditions of catalytic pyridinium *p*-toluenesulfonate (5.0 to 7.5 mol%) in CH_2Cl_2.[23] The keto-acetonides were focused on because those structures always permitted the chromatographic isolation of a single diastereomer that could be fully characterized.

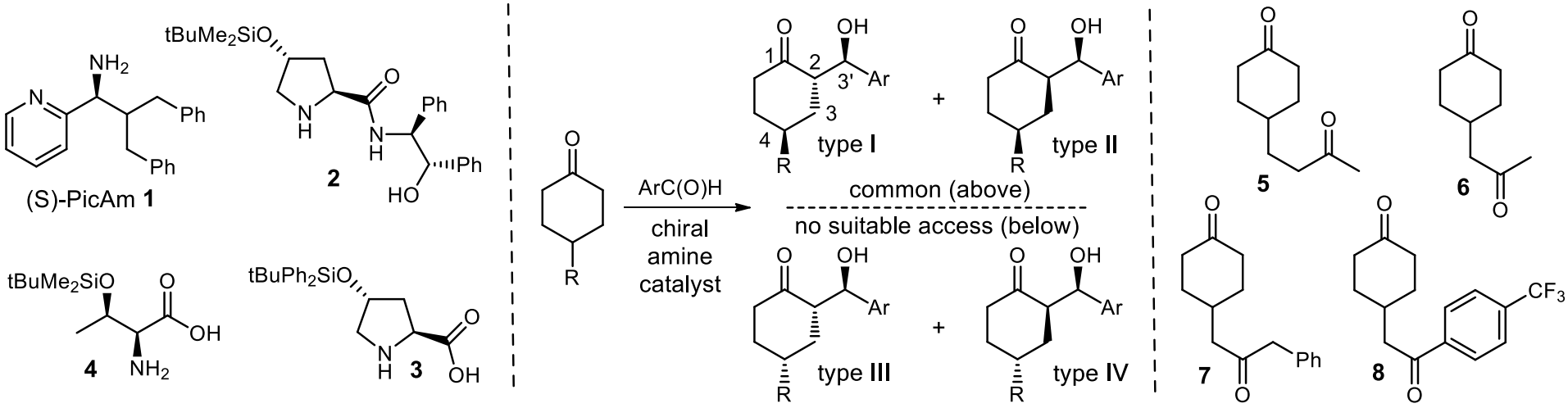
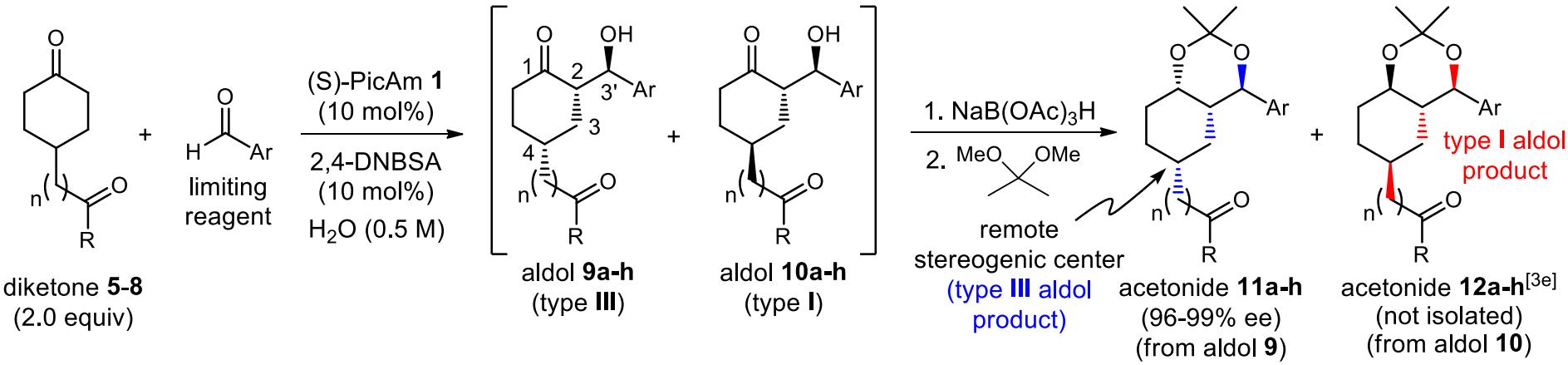


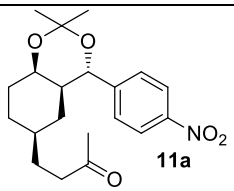
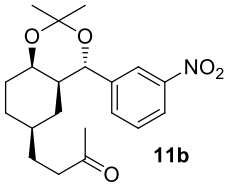
Figure 2. Left to right panels: catalysts (**1**-**4**), generic relative stereochemical outcomes for 4-substituted cyclohexanone desymmetrization (types**I**-**IV**), and diketones examined during this study (**5**-**8**).

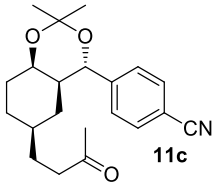
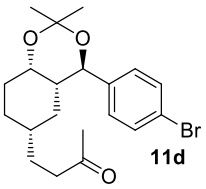
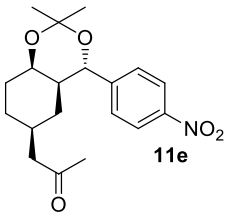
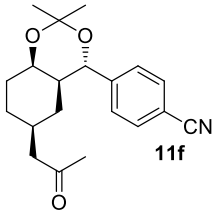
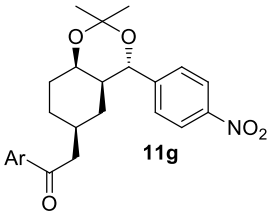
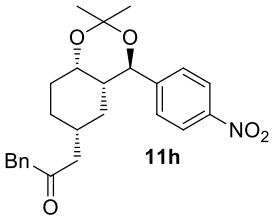
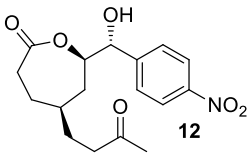


Scheme 1. Aldol products**9** and **10** are formed in near equal quantities as the major reaction products under PicAm**1** catalysis. Keto-acetonides **11**were isolated and characterized, see Table 1.Note: 2,4-DNBSA = 2,4-dinitrobenzenesulfonic acid.

As shown in Table 1, an array of 4-substituted cyclohexanone based diketones (2.0 equiv) has been successfully reacted with a handful of aromatic aldehydes (1.0 equiv) in the presence of 10 mol% of either (R)- or (S)-PicAm **1**.Note that most of the keto-acetonide products were synthesized with (R)-PicAm **1**, which produces the same relative stereochemistry as aldol type **III**, albeit for the opposite enantiomeric form. The overall yields, for the three step diketone to keto-acetonide transformations (Scheme 1), are noted in a range of 25-34% (Table 1). At the low end, a 25% overall yield represents, on average, a 63% yield for each of the three reaction steps: aldol, reduction, and keto-acetonide formation. On the high end, a 34% overall yield represents a 70% yield for each reaction step. By any measure those numbers represent mediocre yield data, but placed in the context of having the first demonstrated access to these highly enantio enriched compounds, with four stereogenic centers and in pure form, the current yields may be considered, if not yet practical, then perhaps as enabling the first speculative applications for otherwise difficult to access natural products or for medicinal chemistry goals. Of equal or higher significance, these examples of epimeric product formation standout as a convincing proof of concept that will drive future catalyst design toward more selective epimer switches.

Table 1.Type **III** keto-acetonide and lactone products from (R)- or (S)-PicAm catalysis.[a]

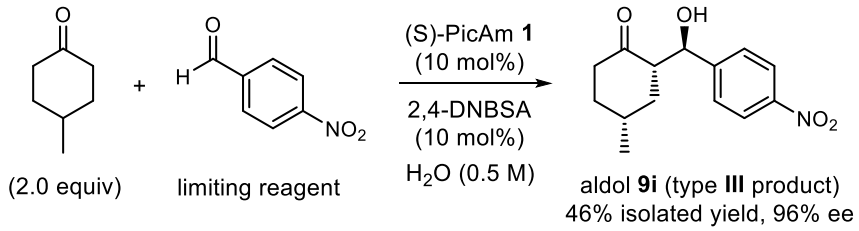
Entry	Keto-acetonides (**11**)	Aldol product data[a]				Keto-acetonide product data	
		Reaction Time (h)	Conversion (^{1}H NMR)[b]	Aldol **9**/**10** (type **III** to **I**)[c,d]	*anti*/*syn* (type **I** &**III** to **II**&**IV**)[c]	Overall yield of **11** (from aldehyde)[e]	*ee*
1	 **11a**	28	96	1.00:1.20	>24:1	28	97
2	 **11b**	40	95	1.00:1.17	>24:1	27	>99

3	 **11c**	30	95	1.00:1.23	>24:1	32	97
4[f]	 **11d**	48	72	1.17:1.00	8:1	25	97
5	 **11e**	25	94	1.00:1.30	>24:1	30	>99
6	 **11f**	40	95	1.00:1.32	>24:1	32	96
7[g]	 **11g**	69	94	1.13:1.00	>24:1	34	96
8[f]	 **11h**	33	94	1.22:1.00	9:1	30	98
9[h]	 **12**	28	96	1.00:1.20	>24:1	31	98

[a] The aldol reactions were performed with (R)-PicAm **1**, entries 4 and 8 used (S)-PicAm **1**. For reaction details, see Scheme 1 and the Supporting Information.
[b] ^{1}H NMR reaction aliquot, integration of aldehydic (limiting reagent) resonance versus the combined integration for the benzylic resonance of the *anti*- and *syn*-aldol products.
[c]See Figure 2 for relative stereochemistry. Crude ^{1}H NMR data: ratioof the two major 2,3'-*anti* products**9** and **10**.
[d] Section 4 of the Supporting Information is dedicated to verifying the **9**/**10** ratios (^{1}H NMR expansions).

[e]The yield is the overall yield from three reaction steps: aldol, reduction, and keto-acetonide formation. Thus the mmol of pure keto-acetonideproduct **11**versus themmol of the aldol limiting reagent (aldehyde)x 100%.
[f](S)-PicAm **1** catalyzed the aldol reaction for this keto-acetonide. Note that the (S)-PicAm **1** catalyst provides the same enantiomer of **10**, a type **I**aldol product, as when the (2S,4R)-TBDPSO-4-hydroxyprolinecatalyst (Figure 2, catalyst **3**) is used.[3e]
[g]Ar equals *p*-trifluoromethylphenyl.
[h] Lactone formation occurred after treatment of aldol product **9a** with*m*CPBA(5 equiv) in CH_2Cl_2, see Section 3 of the Supporting Information.

To establish that PicAm **1** can catalyze useful yields of type **III** aldol products, beyond those studied here: **5**-**8**, we additionally investigated the benchmark substrate 4-methylcyclohexanone.[24] Under unchanged reaction conditions an isolated yield of 46% was found for **9i** (Scheme 2), which doubles the best previously reported yield,[14b] and we have fully characterized this compound for the first time (Section 5, Supp Info). This result firmly establishes that the noted epimer switch is a general phenomenon for 4-substituted cyclohexanones.



Scheme 2.Benchmark substrate (4-methylcyclohexanone) examination.

Finally, the syntheses of the diketone starting materials (**5**-**8**) are straight forward and proceed in good overall yields. In particular, it is noted that diketones **5** and **6** are synthesized after two reaction steps from commercially available phenols.[25]

As discussed earlier, aldol products of type **III** have been previously reported, but we are unaware of any proof of structure in terms of their relative or absolute stereochemistry. We now rigorously address this point.

To define the stereochemical attributes, we examined the crystallization of several keto-acetonide products (**11**) for potential X-ray crystallographic analysis but were unsuccessful. We then took a stepwise approach, first confirming the relative stereochemistry by extensive NMR experiments (see Supp Info, Sections 6 & 7) and then establishing the absolute stereochemistry based on circular dichroism studies (see Supp Info, Section 8).

The short tether at the 4-position of keto-acetonide**11e** (Table 1, entry 5), in combination with the conformational rigidity imposed by the interlocked cyclohexane and acetonide rings of these compounds, made it a good candidate for determination of its relative stereochemistry via NMR measurements.To do so, first the proton and the carbon chemical shifts were assigned to the corresponding atom numbers of **11e** with the aid of the correlations in the COSY and the HSQC and by taking the measured shift values into account (see Supporting Information, Sections 6 and 7).

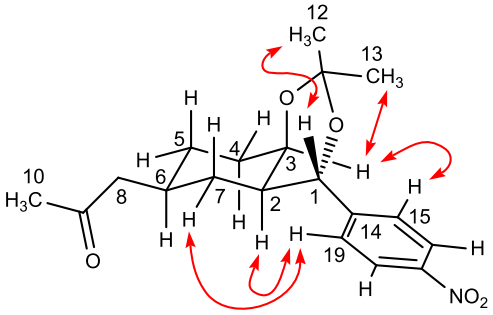


Figure 3. Selected NOE correlations and numbering of **11e**.

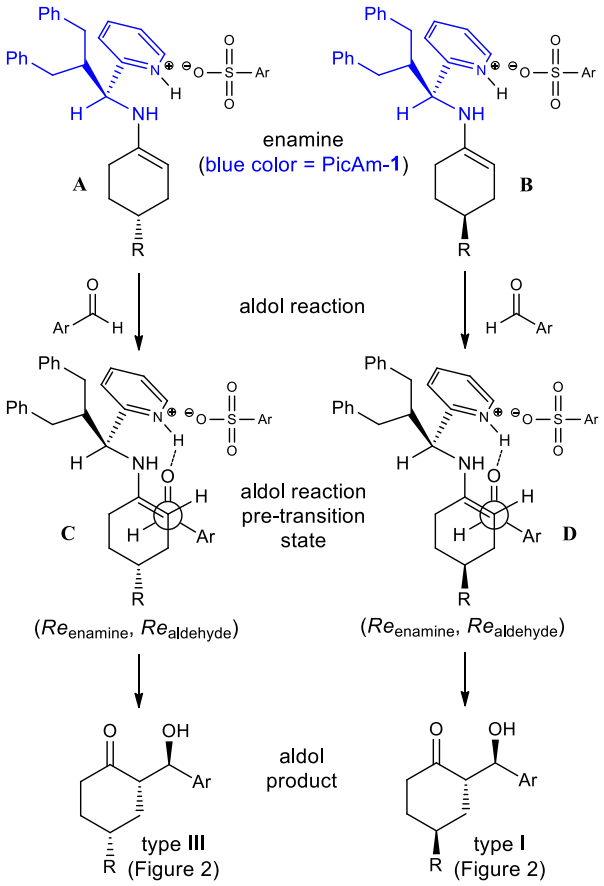
The two dimensional structure of **11e** was then confirmed by analysis of the HMBC correlations. The relative stereochemistry of **11e** was elaborated by analysis of the J_{HH} coupling constants in the ^{1}H NMR and the COSY spectra and analysis of the NOE correlations obtained from the NOESY experiment (see Supporting Information, Section 5). The protons at carbons C-2 to C-7 of the cyclohexane ring show coupling constants typical of a chair conformation (Figure 3), since the protons are either axially or equatorially oriented on account of their coupling constants. Proton H-1 couples to the axial proton H-2 with a coupling constant of $^{3}J_{HH}$ = 6.2 Hz, indicating that these protons are gauche oriented to each other. A characteristic NOE from H-1 to the methyl protons at C-12 and the absence of a NOE correlation between H-1 and H-3 show that H-1 is not oriented in the same direction as H-3. Since there are key correlations between the protons H-15/19 of the aromatic ring and H-3$_{eq}$, H-2$_{ax}$ and H-7$_{eq}$ the six membered ring containing the acetal moiety is most likely present in a boat like conformation and the aromatic ring is oriented as shown in Figure 3. This assignment is further supported by a key NOE correlation between the proton H-3$_{eq}$ and those of the methyl group at C-13. Finally, the relative stereochemistry at C-6 is confirmed by the coupling pattern of H-6 which shows it to be axial.

The absolute stereochemistry was established by two different approaches that supported the same conclusion. First, we generated the theoretical circular dichroism spectrum for the enantiomer represented by keto-acetonide**11e**. This was compared to the experimentally obtained circular dichroism spectrum, in *n*-pentane, and the two were found to have general agreement regarding their: shift, intensity, and positive or negative attributes about the x-axis, which displayed a typical Cotton effect. This result supports the indicated absolute stereochemistry as shown in Figure 3 and Table 1 (entry 4). Section 7 of the Supporting Information is dedicated to a description of the CD study and the conclusions drawn here. To gain a more comprehensive overview, we also generated the theoretical CD spectrums of related diastereomers for the sake of thoroughness (see Section 8 of the Supp Info).

The second piece of supportive evidence for this absolute stereochemistry is that (S)-PicAm **1** has been previously used to catalyze the reaction of cyclohexanone and 4-nitrobenzaldehyde. The aldol product therefore was unequivocally established as having therelative and absolute stereochemistry ofent-**11e**, albeit without the 4-substitutent and its remote stereogeniccenter. During this work,**11e** was formed with (R)-PicAm, thus the C-1 and C-2 stereogeniccentersof the initial aldol products **9e** and **10e** would be expected to have the stereogenicity as depicted in Figure 3.

With the type III aldol products established, the next question is why does PicAm-**1** catalyze a significant increase in their formation. Scheme 3 depicts the expected enamine and aldol transition states that would provide the type I and III aldol products. Because each is formed in essentially equal quantities, it seems logical that transition states C and D are rather similar in energy which results in the non-selective product profile. Why this is true for PicAm-**1**, while proline based catalysts overwhelmingly favorthe analogous transition states D over C will be the focus of a future computational study.

In conclusion, a large number of publications have been devoted to the study of aldol desymmetrizations of 4-substituted cyclohexanones under chiral amine catalysis. These substrates have attracted interest because their desymmetrization provides rapid access to high value building blocks with three stereogenic centers. Furthermore, no other approaches, e.g., transition metal mediated or enzymatic based, can currently surpass the organocatalyzed reaction results.



Scheme 3. Possible transition states for type **I** and **III** aldol products from 4-substituted cyclohexanones.

Here we have successfully expanded the functional group diversity, of these aldol products, by demonstrating that 4-substituted, keto-carbonyl containing, cyclohexanones (**5**-**8**) can be used as starting materials. As important, we have shown a non-selective epimer switch occurs, providing the first reasonable access to either enantiomeric form of a new relative stereochemistry for these aldol products. Their conversion to the corresponding acetonide (four stereogenic centers) and lactone (three stereogenic centers) products represents the first realistic starting point for their planned use to reach a synthetic target.

From a catalysis perspective, we have taken an obscure chemical observation, low yields of type **III** aldol product formation,[14b]to a level where it can now be imagined that a highly selective epimer switch at the remote stereogenic center of these aldol products, is possible via rational

catalyst design. This is significant because there are no known step efficient replacements for the formation of these epimeric products, regardless of the strategy employed.

2.2.3 Experimental Section

Experimental Details – 112 pages of detailed Supporting Information are associated with this manuscript.

General procedure for aldol products (**9** and **10**):To a dry 2.0 mL screw cap reaction vial was added diketone (1.0 mmol, 2.0 equiv), aldehyde (0.5 mmol, 1.0 equiv) and (S)- or (R)-PicAm**1** as a 2,4-dinitrobenzenesulfonic acid 1:1 salt (MW= 550.58g/mol, 0.05 mmol, 10.0 mol %, 27.5 mg). After stirring for 5 min distilled water (0.50 mL) was added. This reaction was then stirred and heated at 45 ^{o}C until a starting material conversion of ≥95% conversion was noted unless otherwise stated. Reaction progress was monitored by aliquot (^{1}H NMR). Reaction conversion was determined by integrating the aldehydic resonance (singlet, ~10.0 ppm) versus the combined integration of the benzylic proton resonance (doublets, both found between 4.50-5.50ppm) of the *syn*- and *anti*-aldol products. Reaction times ranged from 25-69 h, see the individual descriptions for the specific reaction time.Note: Extending the reaction time often results in decreased diastereoselectivity through α-keto epimerization.Reaction work-up. The reaction mixture was transferred to a separatory funnel containing distilled water (25-35 mL) by excessive extractive addition of CH_2Cl_2 (9 x 1.5 mL) to the reaction vessel. After this initial extraction from water, the water was further extracted with CH_2Cl_2 (6 x 20 mL). Combined organic extract was dried (Na_2SO_4), filteredand concentrated (rotary evaporator bath temperature should not exceed 28 ^{o}C to minimize the risk of α-keto epimerization). The crude aldol product was then exposed to high vacuum drying and after 2-3 h the *dr*, *anti*/*syn* ratio (^{1}H NMR), was recorded. The aldol product was used in the next reaction step without further purification. Note: Exposure to silica gel chromatography often results in reduce diastereoselectivity and aldol product yield and is discouraged.

Acknowledgements

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2.2.4 References

[1] a) T. C. Nugent, M. El-Shazly, *Adv. Synth.Catal*. **2010**, *352*, 753-819; b) M. R. Monaco, G. Pupo, B. List, Synlett **2016**, *27*, 1027-1040; c) F. Huang, Z. Liu, Z. Yu, *AngewandteChemie, Int. Ed.* **2016**, *55*, 862-875.

[2] For a broader discussion of site-selectivity, see: P. M. Tadross, E. N. Jacobsen, *Nature Chem.***2012**, *4*, 963-965.

[3] a) J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 7498-7499; b) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem. Int. Ed.***2008**, *47*, 7656–7658; c) R. C. Simon, B. Grischek, F. Zepeck, A. Steinreiber, F. Belaj, W. Kroutil *Angew. Chem. Int. Ed.* **2012**, *51*, 6713-6716; d) M. Skoupi, C. Vaxelaire, C. Strohmann, M. Christmann, C. M. Niemeyer, *Chem. Eur. J.***2015**, *21*, 8701–8705; e) T. C. Nugent, F. T. Najafian, H. A. E. D. Hussein, I. Hussain, *Chem Eur. J.***2016**, *22*, 14342-14348 .

[4] A single example of double aldol site-selectivity has been demonstrated, see Table 2, entry 8, compound **3h** (10 mol% catalyst loading, 67% yield, 9:1 dr, 81% ee) within: Y. Shimoda, T. Kubo, M. Sugiura, S. Kotani, M. Nakajima, *Angew. Chem. Int. Ed.* **2013**, *52*, 3461-3464.

[5] Triketonesite-selectivity coincidentally represents the foundation of modern amine catalysis, namely the Hajos–Parrish–Eder–Sauer–Wiechert intramolecular aldolcyclizationsunder proline catalysis, see: a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.***1971**, *83*, 492; *Angew. Chem. Int. Ed.***1971**, *10*, 496; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

[6]For literature overviews oftriketones, see:a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List,*Chem. Rev.***2007**,*107*, 5471-5569; b) B. Bradshaw, J. Bonjoch, *Synlett***2012**, *23*, 337-356.

[7] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III,*J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.

[8] For the synthesis of the picolyl amine (PicAm)**1**, see: T. C. Nugent, A. Bibi, A. Sadiq, M. Shoaib, M. Umar, F. T. Najafian, *Org. Biomol. Chem.* **2012**, *10*, 9287-9294.

[9]Gong initially reported, ref. 9a, a type III aldolstructure, but corrected it to a type I relative stereochemistry in a corrigendum (Additions and Corrections at *Chem. Commun.*) which is ref. 9b. Later, Singh, ref. 9c, incorrectly used Gong's type III relative stereochemistry for his product: a) J.

Jiang, L. He, S. W. Luo, L.-F. Cun, L.-Z.Gong, *Chem. Commun.***2007**, 736-738; b) J. Jiang, L.He, S. W. Luo, L.-F.Cun, L.-Z.Gong, *Chem. Commun.***2008**, 6609-6014; c) M. R. Vishnumaya, V. K. Singh *J. Org. Chem.* **2009**, *74*, 4289–4297.

[10] For representative examples, see: a) D. Gryko, W. J. Saletra, *Org. Biomol. Chem.* **2007**, *5*, 2148-2153; b) X. Companyó, G. Valero, L. Crovetto, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 6564-6568; c) C. Wu, X. Fu, S. Li, *Eur. J. Org. Chem.* **2011**,1291-1299; d) S. Li, C. Wu, X. Fu, Q. Miao, *Ind. Eng. Chem. Res.* **2011**, *50*, 13711-13716; e) S. Li, C. Wu, X. Long, X. Fu, G. Chen, Z. Liu, *Catal. Sci. Technol.* **2012**, *2*, 1068-1071.

[11] For representative examples, see: a) P. Dinér, M. Amedjkouh, *Org. Biomol. Chem.* **2006**, *4*, 2091-2096; b) B. Rodríguez, A. Bruckmann, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 4710-4722; c) W. Clegg, R. W. Harrington, M. North, F. Pizzato, P. Villuendas, *Tetrahedron: Asymmetry* **2010**, *21*, 1262-1271; d) M. North, P. Villuendas, *Org. Lett.* **2010**, *12*, 2378-2381.

[12] For representative examples, see: a) Q. Zhang, X. Cui, L. Zhang, S. Luo, H. Wang, Y. Wu, *Angew. Chem. Int. Ed.* **2015**, *54*, 5210-5213; b) F. J. N. Moles, G. Guillena, C. Nájera, E. Gómez-Bengoa, *Synthesis* **2015**, *47*, 549-561.

[13]See Table 2, entry 19 for a rare example of high type **II** product selectivity. We are unaware of any other example like this, see: Y. Qian, X. Zheng, Y. Wang *Eur. J. Org. Chem.* **2010**, 3672–3677.

[14] a) M. Majewski, I. Niewczas, N. Palyam, Synlett2006, 2387-2390; b) G. Ma, A. Bartoszewicz, I. Ibrahem, A. Córdova, Adv. Synth. Catal.2011, 353, 3114-3122; c) A. Bellomo, R. Daniellou, D. Plusquellec, Green Chem. 2012, 14, 281-284; d) F. J. N. Moles, A. Bañón-Caballero, G. Guillena, C. Nájera, Tetrahedron: Asymmetry 2014, 25, 1323-1330.

[15] SeeTable 3, entry 4 of reference 14c.

[16] Related to this discussion, selective conversion of an *anti*-aldol product of type **I** to the corresponding *syn*-aldol product **II** or *vice versa* has never been demonstrated. See reference 13 for further information.

[17] The remaining product balance in these aldol reactions is aldol products **II** and **IV**, generally in a combined yield of $\leq$5% with approximately the same quantities of the limiting reagent (the aldehyde).

[18] It is more often than not that cyclohexanone-based aldol products undergo partial, non-selective epimerization upon exposure to silica gel. See page 4 within the Supporting Information of reference 20.

[19] T. C. Nugent, M. N. Umar, A. Bibi, *Org. Biomol. Chem.***2010**, *8*, 4085-4089.

[20] Only one lactone product is noted here (Table 1, entry 9). In fact we synthesized at least five more lactone products, but their isolation in greater than 90% chemical purity was not possible in our hands. We abandoned the further pursuit of these lactones because of these purification problems.We speculate that the analogous ring opened forms may allow this problem to be circumvented, see reference 3e for a possible example.

[21] It is appropriate to mention that *ortho*-substituted aromatic aldehydes, e.g. *o*-nitrobenzaldehyde, smoothly formed the corresponding aldol products, but resisted reduction under our standard conditions with $NaB(OAc)_3H$.

[22] a) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.***1988**, *110*, 3560-3578; b) S. H. J. Thompson, M. F. Mahon, K. C. Molloy, M. S. Hadley, T. Gallagher, *J. Chem. Soc. Perkin. Trans. 1***1995**, 379-383.

[23] K. Mori, S.Maemoto, *Liebigs Ann. Chem.***1987**, 863- 869.

[24]Since Gong's 2007 disclosure of enantioselective organocatalytic aldol desymmetrization of mono-4-substituted cyclohexanone substrates, fifty eight manuscripts based on the same subject have been published. From those, forty eight describe the aldol desymmetrization of 4-methylcyclohexanone, making it the benchmark substrate.

[25] See the Supporting Information of reference 3e.

2. Catalytic Enantioselective Michael Reactions in the Presence of a Diverse Array of Acidic Spectator Functional Groups. Expedient Synthesis of Antidepressant (R)-Pristiq.

Thomas C. Nugent, Hussein Ali El Damrany Hussein, Shahzad Ahmed, Foad Tehrani Najafian, Tony Georgiev, Ishtiaq Hussain, Mahmoud Khalaf Aljoumhawy

Note: the numbering correlates to those found in this published manuscript

Abstract: An undeniable crutch of total synthesis is the use of protection/deprotection protocols. Here we make inroads toward this problem with the first broad guidance on how to catalytically promote aldehyde addition to β-nitrostyrene or maleimide electrophiles in the presence of unprotected acidic spectator groups, *e.g*., carboxylic acids, N-phenylamides, catechols, phenols, and maleimide NH groups. Remarkably, these reactions readily proceed when both the nucleophilic and electrophilic Michael partners simultaneously contain acidic spectator groups. No chemical reactions resemble this type of complexity, regarding the tolerance of acidic functional groups, instead these reactions rival those that are restricted to cellular environments. The reactions are additionally noteworthy for their excellent starting material stoichiometries (1.0-2.0 equiv), good yield (63-87%), and excellent *ee* (90-97%). Adding to the practicality, the employed amino acid catalysts are commercial available. Finally, this new method has permitted the enantioselective synthesis of (R)-Pristiq, (-)-O-desmethylvenlafaxine, a commercially prescribed antidepressant, is in the highest reported yield to date.

2.3.1 Introduction:

Michael reactions embody many different electrophile-nucleophile pairings making them good proving grounds for probing and applying new catalytic methods. An exhaustively examined example is the enantioselective addition of aldehydes to *ortho*-, *meta*-, or *para*-substituted-β-nitrostyrenes (Scheme 1).[1] A large array of electron rich and poor aromatic substituents are compatible and excellent yield and *ee* are noted. However, when weakly acidic functional groups (pKa= 0 to 12) are present, high level achievement is restricted to β-nitrostyrene substrates containing an *ortho*-OH or *ortho*-NHAc substituent.[2,3] An *ortho*-directing effect has been offered as a possible reason.[4] In short, despite the exhaustive study of aldehydic Michael additions to β-nitrostyrenes, only a handful of sporadic phenol based examples are known when an *ortho*-OH or *ortho*-NHAc substituent is lacking (Figure 1).[5,6,7] Here we show that threonine and serine

potassium salt catalysis: (i) far surpass the earlier noted lone examples with 3- or 4-hydroxy based β-nitrostyrenes;[5-7] (ii) is applicable to more acidic, unreported spectator groups, *e.g.*, 3,4-catechols, and 3- or 4-positioned acetamide and carboxylic acid moieties; (iii) and additionally allows both the Michael electrophile and nucleophile to simultaneously contain an acidic spectator group.

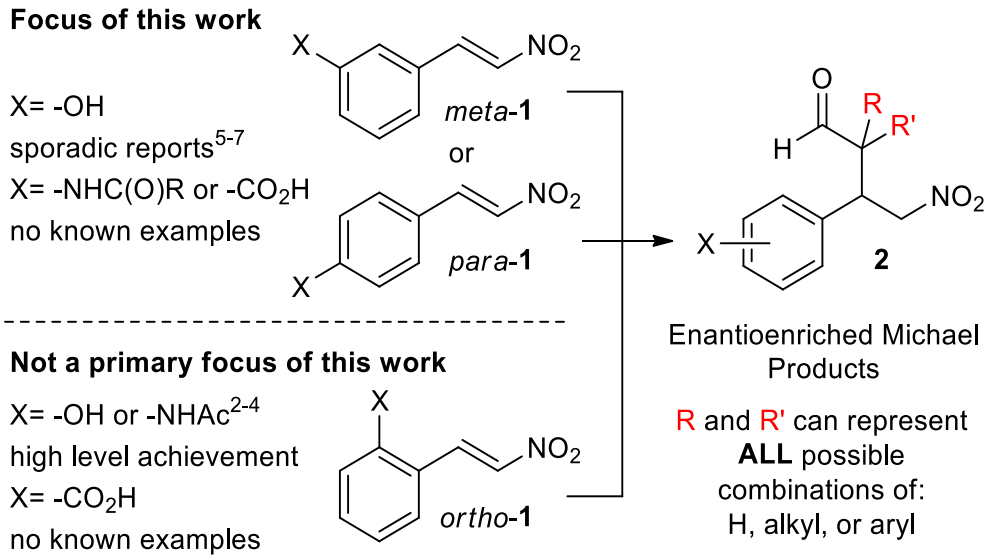


Figure 1. Enantioselective Aldehyde Additions to β-Nitrostyrenes Containing Acidic Moieties.

2.3.2 Results and Discussion

In this study we provide the first clear guidance for the enantioselective addition of aldehydes to *meta*- and *para*-substituted β-nitrostyrenes having a variety of weakly acidic moieties. Ignoring, temporarily, the challenge of coexisting acidic spectator groups, a smaller number of reports show the addition of α-branched aldehydes,[8,9] as opposed to linear aldehydes, to β-nitrostyrenes.[1] We have consequently focused on the more demanding α-branched aldehyde additions which lead to quaternary carbon based products and note that this method tolerates sterically demanding α-branched aldehydes, e.g., cyclohexanecarboxaldehyde.[10]

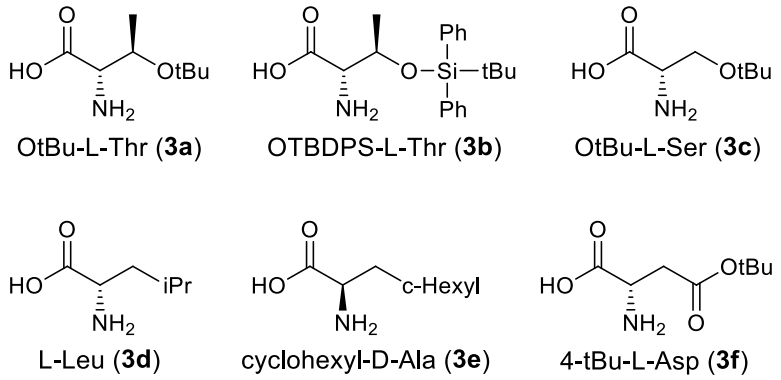
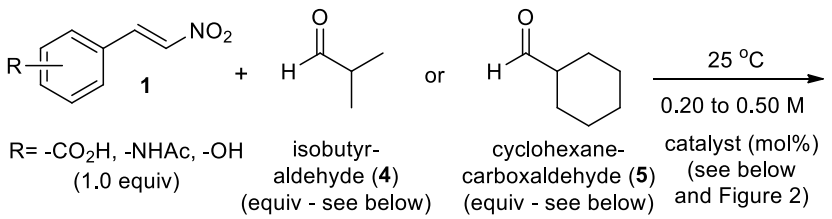
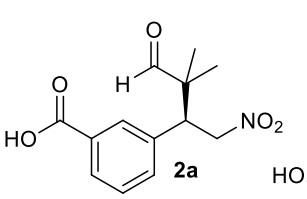


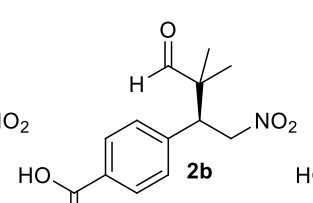
Figure 2. The potassium salts of these threonine, serine, leucine, alanine, and aspartic acid derivatives were screened.

We have previously shown that OtBu-L-Thr (Figure 2) is capable of adding isobutyraldehyde (**4**) to β-nitrostyrenes,[8g,11] and modified conditions there from have now permitted us to readily add isobutyraldehyde to β-nitrostyrenes with *meta*- or *para*-positioned carboxylic acids, analine acetamides, catechol units, or OH moieties in good yield (70-86%) and excellent ee (94-97%), see Scheme 1. For cyclohexanecarboxaldehyde additions, an OtBu-L-Ser catalyst was required. For example when a carboxylic acid, aniline acetamide NH, catechol, or phenolic OH spectator group was present (Scheme 1, see products **2c**, **2e**, **2j**, **2l**), both the yields (62-87%) and *ees* (90-95%) were dramatically higher than under OtBu-L-Thr catalysis. For perspective, cyclohexanecarboxaldehyde (**5**) has never been added in the presence of an acidic spectator group, but before our studies,[12] its addition to simple β-nitrostyrene (no acid groups present) always required a ≥20 mol%[8a-f,h] catalyst loading and, in the best outcome, resulted in 51% yield (80% ee) for the Michael product.[8e] These initial results were rounded out by showing that cyclopentanecarboxaldehyde can also be added, Scheme 1 product **2h**, albeit optimally with a silyl protected threonine catalyst: OTBDPS-L-Thr (Figure 2).[13] With the exception of compounds **2f**[2] and **2i**[6,7], all Scheme 1 products are new and have been fully characterized (Supp Info). Our findings supersede the previous findings for **2f** and **2i**.[6,7]

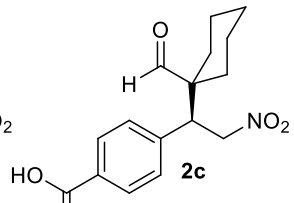




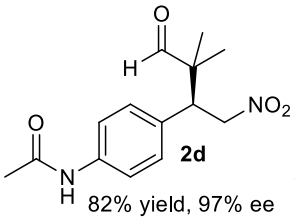
73% yield, 94% ee
2.0 equiv of **4**, 30 h
OtBu-L-Thr (10 mol%)



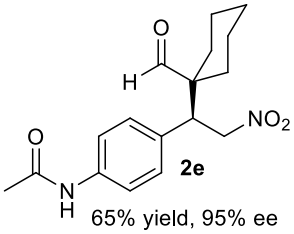
70% yield, 95% ee
2.0 equiv of **4**, 29 h
OtBu-L-Thr (15 mol%)



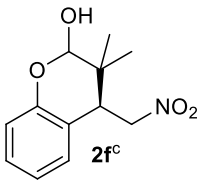
63% yield, 90% ee
2.0 equiv of **5**, 96 h
OtBu-L-Ser (20 mol%)



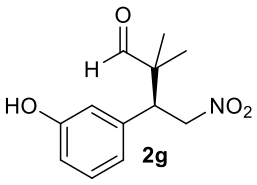
82% yield, 97% ee
3.0 equiv. of **4**, 20 h
OtBu-L-Thr (10 mol%)



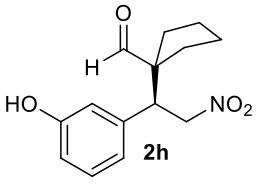
65% yield, 95% ee
2.0 equiv of **5**, 42 h
OtBu-L-Ser (20 mol%)



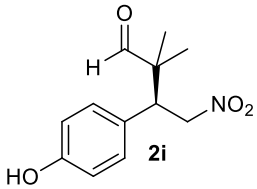
78% yield, 90% ee
1.3 equiv of **4**, 18 h
OtBu-L-Thr (10 mol%)



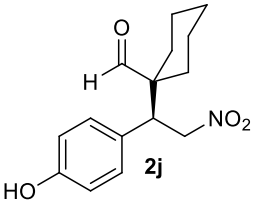
84% yield, 95% ee
1.3 equiv of **4**, 4 h
OtBu-L-Thr (7.5 mol%)



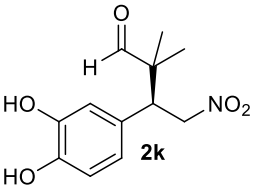
76% yield, 93% ee
1.3 equiv of **6**[a], 7 h
OTBDPS-L-Thr (7.5 mol%)
and
62% yield, 88% ee
1.3 equiv of **6**[a], 24 h
OtBu-L-Thr (7.5 mol%)



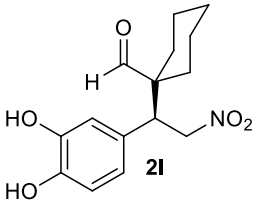
87% yield, 95% ee
1.3 equiv of **4**, 4 h
OtBu-L-Thr (7.5 mol%)
and
93% yield, 91% ee
1.3 equiv of **4**, 6 h
OTBDPS-L-Thr (5.0 mol%)



86% yield, 94% ee
1.5 equiv of **5**, 26 h
OtBu-L-Ser (10 mol%)



83% yield, 94% ee
1.3 equiv of **4**, 8 h
OtBu-L-Thr (7.5 mol%)



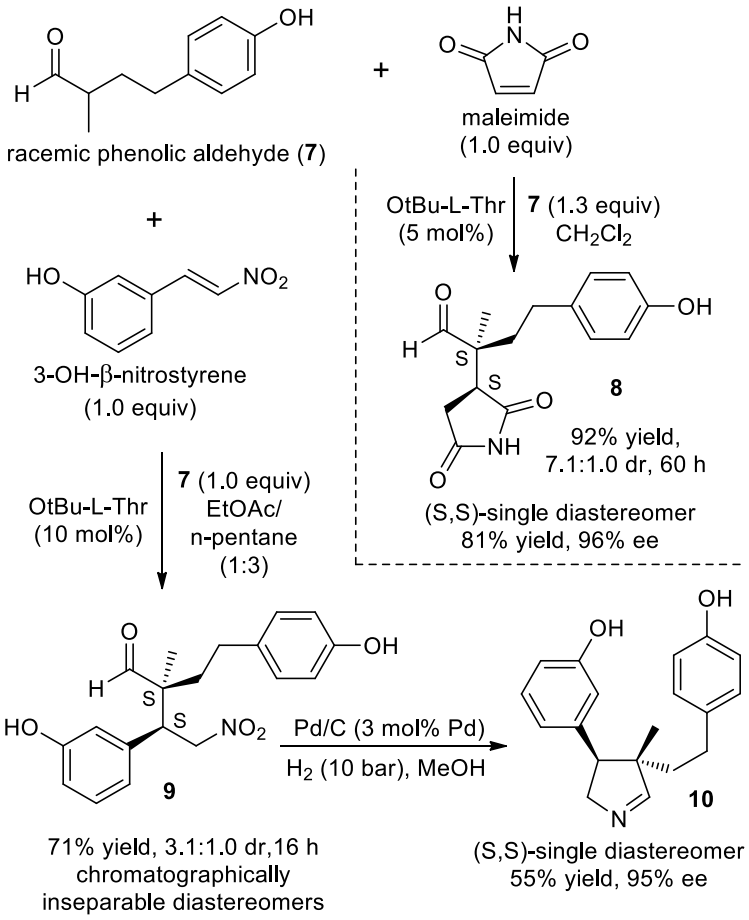
62% yield, 94% ee
2.0 equiv of **5**, 26 h
OtBu-L-Ser (15 mol%)

[a] Cyclopentanecarboxaldehyde (**6**) used. [b] The potassium salt of the stated amino acid was used. [c] The ee was determined for the corresponding lactone. [d] For typical solvents, see the Supp Info.

Scheme 1. Quaternary carbon Michael product formation in the presence of acidic spectator functionality.[b,c]

The Scheme 1 Michael products (**2**) convincingly establish that enantioselective aldehyde addition to β-nitrostyrenes in the presence of mildly acidic functional groups is broadly applicable. They also represent the first examples of aldehyde addition to a β-nitrostyrene when a carboxylic acid (ortho-, meta-, or para-positioned) is present, see products **2a-c**. This holds true whether the reaction is racemic or enantioselective.

Those promising results were the driving force to test a higher level challenge: the first Michael reaction in which both the electrophile and the nucleophile contain an acidic moiety. To test this possibility and simultaneously examine stereogenic quaternary carbon formation, we added a phenol containing nonsymmetrical α-branched aldehyde (**6**) to 3-OH-β-nitrostyrene and separately to maleimide[14,15] (Scheme 2). The produced vicinal quaternary-tertiary stereogenic center based Michael products (**FF** and **ZZ**) were obtained in high *ee* and good yield under remarkably practical starting material stoichiometries and catalyst loadings. No other reported chemical reactions remotely resemble this type of complexity regarding the presence of acidic functional groups; instead the results are reminiscent of the selectivities found only in cellular environments. The absolute configurations of these products were established by earlier DFT calculations on related reactions[11] while the relative configuration was confirmed via in-depth COSY and NOESY NMR experiments of **KK** (Supp Info).

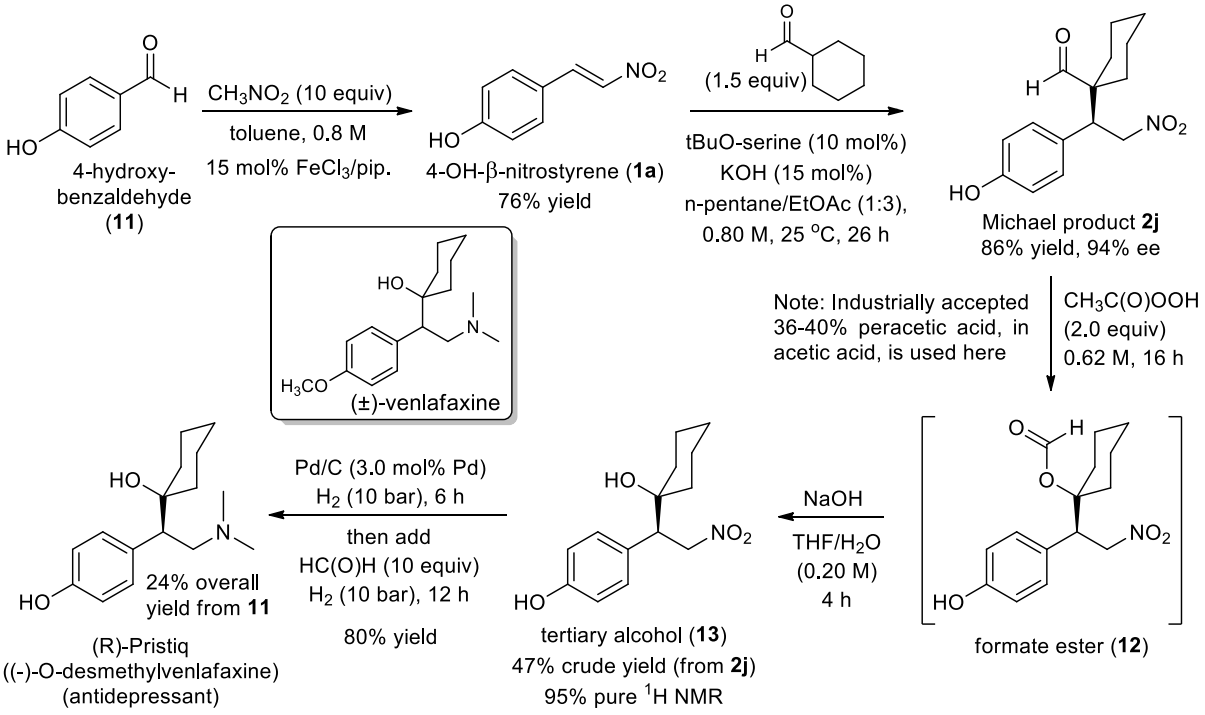


Scheme 2. Nucleophile and Electrophile contain an acidic moiety, formation of two stereogenic centers.

(±)-Venlafaxine (Scheme 4) is a widely prescribed anti-depressant whose HCl salt is marketed as Effexor. The cytochrome P-450 metabolite thereof, (±)-O-desmethylvenlafaxine or Pristiq, has largely replaced the sale of venlafaxine because of its improved half-life and inhibitor potency (norepinephrine and dopamine uptake).[16] (R)-Pristiq is known to be a more active antidepressant than racemic pristiq and is patent protected.[17] While enantioselective syntheses of venlafaxine are known,[18] the best in 25% overall yield,[18a] none are industrially used. O-demethylation[19] of venlafaxine forms pristiq, but all demonstrated procedures require the use of high energy reagents, *e.g.* nBuLi/diphenylphosphine,[17] or use thiolates, *e.g.* anhydrous sodium sulfide, at very high temperatures (≥145 ^{o}C).[20] Importantly, all known syntheses to (R)-pristiq proceed through the resolution of (±)-venlafaxine followed by O-demethylation of (R)-venlafaxine. A resolution allows a maximum 50% yield and the best resolution of (±)-venlafaxine employs di-*p*-toluoyl-D-

tartaric acid to give (R)-venlafaxine in 24% yield.[16c,17] In short, all of these approaches are either far too costly and/or suffer from unacceptably low overall yields (<13%). Finally, in 2009 a three step racemic synthesis of pristiq from 4-methoxyphenylacetonitrile was reported in 26% overall yield,[21] yet to this date no resolutions of racemic pristiq to (R)- or (S)-pristiq are known.

Here we have developed an enantioselective synthesis of (R)-pristiq from inexpensive 4-hydroxybenzaldehyde in the best overall yield, 24% (94% ee), known to date. This was possible because no protecting groups were required. Furthermore, the employed reagents were carefully chosen to provide a good starting point for potential industrial applications.



Scheme 3. Enantioselective synthesis of (R)-pristiq.

Cyclohexanecarboxaldehyde (**3**) additions initially presented a major problem, e.g., under OtBu-L-Thr catalysis pristiq intermediate **2j** was isolated in 71% yield (79% ee) compared to 86% yield (94% ee) for OtBu-L-Ser. From a qualitative perspective, the increased transition state congestion encountered from cyclohexanecarboxaldehyde additions could be relieved by reducing the steric bulk of the amino acid catalyst. After considering the likely enamine and transition state factors, see Figure 3, we noted that OtBu-L-Ser would have increased rotational freedom about the C2-C3 bond *vs* OtBu-L-Thr (Figure 3, right panel). In short, OtBu-L-Ser has a reduced energetic penalty

for C2-C3 rotation and this in turn likely reduces the -OtBu group steric interaction with the cyclohexane ring of cyclohexanecarboxaldehyde,while still maintaining the steric bulk required for enamine facial selectivity. The indicated transition state conformation of the catalyst and the assembled salt-bridge, via the potassium cation, has been previously elaborated on via earlier DFT studies within our laboratory, albeit for a maleimide electrophile.[11] Among other cations, e.g., lithium, sodium, and cesium, the potassium cation is critical for high yield and selectivity; its importance was further underscored when the addition of equal molar quantities (10 mol%) of 18-C-6 had deleterious yield and ee ramifications. All cyclohexanecarboxaldehyde additions required use of the OtBu-L-Ser and alternative amino acids, see Figure 2, were non-competive.

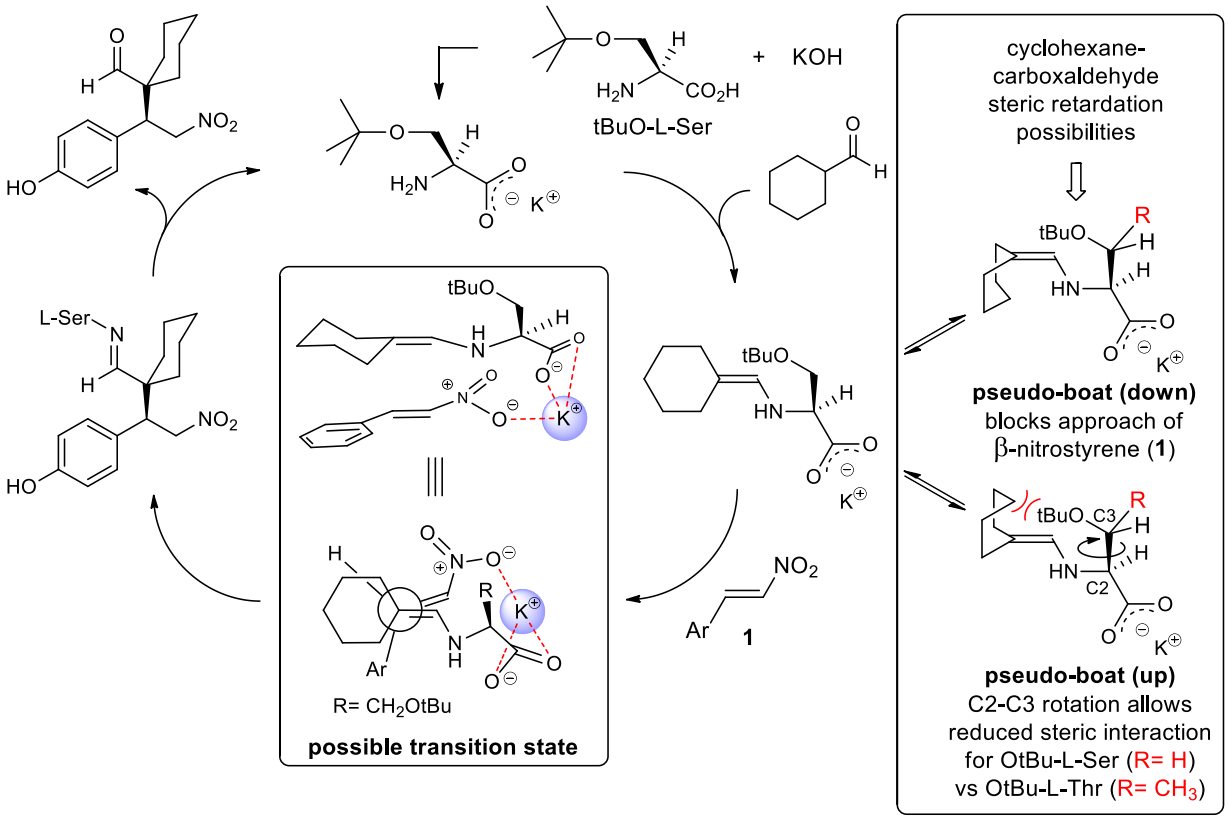


Figure 3. Possible OtBu-L-Ser catalytic cycle for cyclohexanecarboxaldehyde additions. Right panel: steric consideration for OtBu-L-Ser *versus* OtBu-L-Thr enamines of cyclohexanecarboxaldehyde.

2.3.3 Conclusion:

The outlined research directly addresses a modern goal within chemistry: step-efficient synthesis. It does so by providing the first clear guidance regarding an area of previously unknown potential, the common Michael reaction in the presence of acidic spectator functionality. To demonstrate the broad applicability of the method, we have targeted the most challenging aldehydes for addition, those with α-branching.

The products therefrom contain quaternary carbons and two products contain stereogenic quaternary carbons. Keeping the previous literature precedent in mind for α-branched aldehyde additions to β-nitrostyrene derivatives, albeit without any acidic moieties present, the results demonstrated here will be considered excellent regarding: starting material ratios, catalyst loading, yield, and ee. It is also clear that these reactions will be extendable to the less demanding linear aldehyde additions to Michael acceptors. Finally, this opening report will spur future investigation of a much broader number of amino acids, e.g., cysteine analogs, and perhaps more importantly, optimization of the amino acid protecting groups, e.g., pivaloyl esters vs t-Bu groups.

Acknowledgements: We thank Panyapon Sudkaow and Vishal S. Dodke for their preliminary contributions to the project.

2.3.4 References:

[1] a) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135; b) N. Mase, *Enamine catalysis of Michael reactions*, in *Science of Synthesis, Asymmetric Organocatalysis* (Eds.: B. List, K. Maruoka), Georg Thieme Verlag, Stuttgart, Germany, **2012**, vol. 1, 135-216.

[2] For *ortho*-OH examples, see: a) B.-C. Hong, P. Kotame, C.-W. Tsai, J.-H. Liao, *Org. Lett.* ***2010***, *12*, 776-779; b) D. Enders, C. Wang, X. Yang, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 2869–2874; c) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.*, **2010**, *8*, 4259–4265; d) D. Lu, Y. Li, Y. Gong, *J. Org. Chem.* **2010**, *75*, 6900–6907; e) B.-C. Hong, P. Kotame, J.-H. Liao, *Org. Biomol. Chem.*, **2011**, 9, 382–386; f) D. B. Ramachary, M. S. Prasad, R. Madhavachary, *Org. Biomol. Chem.* **2011**, *9*, 2715–2721.

[3] For *ortho*-NHAc examples, see: (a) S. Heo, S. Kim, S.-G. Kim, *Tetrahedron Lett.* **2013**, *54*, 4978-4981; (b) Y. Lee, S. G. Kim, *J. Org. Chem.* **2014**, *79*, 8234-8243; (c) M. Yu, S.-G. Kim,

Tetrahedron Lett. **2015**, *56*, 4159-4162; A.-B. Xia, X.L. Zhang, T. Wang, X.-H. Du, D.-Q. Xu, Z-Y. Xu, *New J. Chem.* **2015**, *39*, 5088-5091.

[4] D. B. Ramachary, R. Sakthidevi, K. S. Shruthi *Chem. Eur. J.* **2012**, *18*, 8008–8012.

[5] For the enzymatic addition of formaldehyde to 3-OH or 4-OH-β-nitrostyrene, respectively in a 74% yield (49% *ee*) and 59% yield (51% *ee*), see: (a) E. Zandvoort, E. M. Geertsema, B.-J. Baas, W. J. Quax, G. J. Poelarends, *Angew. Chem., Int. Ed.* **2012**, *51*, 1240–1243; (b) E. M. Geertsema, Y. Miao, P. G. Tepper, P. de Haan, E. Zandvoort, G. J. Poelarends *Chem. Eur. J.* **2013**, *19*, 14407–14410.

[6] For the aminocyclohexane (20 mol%) catalyzed addition of isobutyraldehyde (5.0 equiv) to 4-OH- or 4-OH,3-MeO-β-nitrostyrene in high yield and ee, see Table 3 of: A. Ying, S. Liu, Z. Li, G. Chen, J. Yang, H. Yan, S. Xu Adv. Synth. Catal. 2016, 358, 2116 – 2125.

[7] For a proline analog (10 mol%) catalyzed addition of propanal (3.0 equiv) to 4-OH-β-nitrostyrene in high yield and ee, see Scheme 5 of: a amano a odr ue - s ri oln r a alero ilmour A eri s *ACS Catal.* **2015**, *5*, 6241−6248.

[8] (a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III *Org. Lett.*, **2004**, *6*, 2527-2530; (b) J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang *Chem. Eur. J.* **2006**, *12*, 4321 – 4332, (c) A. Sato, M. Yoshida and S. Hara, *Chem. Commun*., **2008**, 6242–6244; (d) M. Yoshida, A. Sato and S. Hara, *Org. Biomol. Chem*., **2010**, *8*, 3031–3036; (e) J.-F. Bai, X.-Y. Xu, Q.-C. Huang, L. Peng, L.-X. Wang *Tetrahedron Lett.* **2010**, *51*, 2803–2805; (f) Y. Qiao, L. Zhang, S. Luo, J.-P. Cheng *Synlett* **2011**, 495–498; (g) Nugent, T. C.; Shoaib, M.; Shoaib, A. *Org. Biomol. Chem.* **2011**, *9*, 52-56; (h) L. Tuchman-Shukron, S. J. Miller, M. Portnoy *Chem. Eur. J.* **2012**, *18*, 2290–2296.

[9] For some important early examples, see: (a) N. Mase, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Org. Lett.*, **2004**, *6*, 2527–2530; (b) M. P. Lalonde, Y. Chen and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, **2006**, *45*, 6366–6370; (c) S. H. McCooey and S. J. Connon, *Org. Lett.*, **2007**, *9*, 599–602.

[10] While 187 additions of isobutyraldehyde to simple β-nitrostyrene have been reported, only 8 examples of cyclohexanecarboxaldehyde addition are known (see reference 7).

11 Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk L. L.; Vankova, N.; Bassil, B.S. *Chem. Eur. J.* **2012**, *18*, 4088-4098.

12 This study and an earlier publication of ours: ref. 7g.

13 Among the tested catalysts, OTBDPS-L-Thr was not commercially available. For its synthesizes, see: C. Palomo, M. Oiarbide, A. Landa *J. Org. Chem.* **2000,** *65*, 41-46.

[14] Maleimide Michael reactions have been previously examined, see: a) J. Flores-Ferrándiz, B. Fiser, E. Gómez-Bengoa, R. Chinchilla, *Eur. J. Org. Chem.* 2015, 1218–1225; b) P. Vízcaíno-Milla, J. M. Sansano, C. Nájera, B. Fiser, E. Gómez-Bengoa *Synthesis* 2015, *47*, 2199–2206; c) A. Avila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera *Eur. J. Org. Chem.* 2013, 5085–5092.

[15] An excellent advancement with maleimide Michael reaction has recently been reported, see: C. E. Grînenfelder, J. K. Kisunzu, H. Wennemers, Angew. Chem. Int. Ed. 2016, 55, 8571 –8574;

[16] a) E. A. Muth, J. A. Moyer, J. T. Haskins, T. H. Andree, G.E. M. Husbands Drug Dev. Res. 1991, 23, 191-199; b) K. J. Klamerus, K. Maloney, R. L. Rudolph, S. F. Sisenwine, W. J. Jusko, S. T. Chiang, *J. Clin. Pharmacol.* **1992**, *32*, 716-724; c) T. P. Jerussi, C. H. Senanayake, N. N. Bhongle (Sepracor Inc.), Patent No. US 20040180952 A1, Sep. 16, 2004.

[17] T. P. Jerussi, C. H. Senanayake, N. N. Bhongle (Sunovion Pharmaceuticals Inc.), Patent No. US 9072700 B2, July 7, 2015.

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[20] K. Pospisilik, L. Thijs (Synthon IP Inc.), US 7491848 B2, 17 February 2009.

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Chapter 3

Experimental Section for Submitted Manuscript

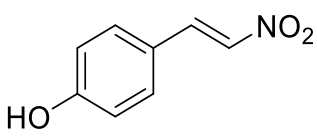
3.0 Experimental for Submitted Manuscript

General procedure for the synthesis of hydroxy-β-nitrostyrenes

The following description represents a small deviation from Dr. Jana's original procedure.[1]

The aldehyde (1.00 equiv), nitromethane (10.0 equiv), and piperidine (0.15 equiv, 15 mol%) were sequentially added to an oven-dried round bottom flask containing toluene which was purchased as anhydrous. $FeCl_3$ (0.15 equiv, 15 mol%, Alfa Aesar anhydrous, 98%, product number 12357) was then added. Note that the bottle of $FeCl_3$ was routinely opened and not stored under nitrogen, and we did not encounter any reaction problems when treating the $FeCl_3$ in this manner over several months of use. Under rigorous stirring the reaction was gently refluxed under a positive nitrogen atmosphere. The reactions were monitored by TLC until complete disappearance of the starting phenolic aldehyde. Note that pushing these reactions to ~95% conversion was vital because removal of the starting aldehyde from the product is generally tedious. Work-up required cooling to room temperature, removal of the toluene and excess nitromethane under rotary evaporation, followed by brief high vacuum drying (2 h). The black-brown crude product was then passed through a plug of silica (60–120 mesh) using ethyl acetate in petroleum ether. This is done to remove very non-polar impurities and very polar impurities. In general it can be said that one is collecting the product and the remaining starting aldehyde when passing through the plug of silica gel. When starting with 4.0 grams of aldehyde, a silica plug of 6.5 cm (diameter) by 8.0 cm (height) was used. The product fractions were collected, concentrated and treated briefly under high vacuum (2 h). Note that even though one spot appears by TLC (UV light and CAM stain), the material usually contains from 5-15% of impurities. When this material is digested (stirred in an unstoppered round bottom flask) in a solvent (see a specific example for the required solvent), the impurities are preferentially dissolved. Simple Büchner funnel filtration and air drying provides the solid product in high purity (≥ 95% by ^{1}H NMR).

4-hydroxy-β-nitrostyrene (1a) :[1]

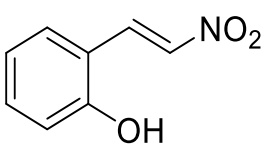


4-hydroxybenzaldehyde (MW= 122.12 g/mol, 4.00 g, 32.8 mmol), nitromethane (MW= 61.04 g/mol, 20.0 g, 17.5 mL, 328 mmol, 10.0 equiv, density=1.14), piperidine (MW= 85.15 g/mol, 419 mg, 487µL, 4.92 mmol, 15 mol%, density= 0.86), $FeCl_3$ (MW= 162.20 g/mol, 798 mg, 4.92 mmol, 15 mol%); Reaction solvent: toluene (20 mL, 1.5 M); Reaction time: 8 h; Silica plug used EtOAc/petroleum

ether (30:70); Digestion solvent: stir with $CHCl_3$/n-pentane (1:1, 200 mL in total) for ~12 h (overnight), then filter to give a yellow solid. Yield: 76% (4.15 g); R_f= 0.32 in EtOAc/petroleum ether (30:70). Note that using dichloromethane as the TLC eluent allows one to see both the product (R_f= 0.29) and the starting 4-hydroxybenzaldehyde (R_f= 0.22). This compound has been previously reported using a different procedure.[2]

^{1}H NMR (acetone-d_6, 400 MHz) δ 6.96 (dt, *J* = 8.7 Hz, 2 H), 7.71 (dt, *J* = 8.5 Hz, 2 H), 7.83 (d, J = 13.6 Hz, 1H), 8.03 (d, J = 13.6 Hz, 1H), 9.24 (bs, 1H) ppm

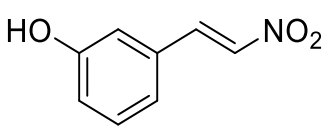
2-hydroxy-β-nitrostyrene (1b): [1]



salicylaldehyde (1.60 g, 13.1 mmol), nitromethane (7.99 g, 7.0 mL, 131 mmol, 10.0 equiv), piperidine (167 mg, 194 µL,1.96 mmol, 15 mol%), $FeCl_3$ (318 mg, 1.96 mmol, 15 mol%); Reaction solvent: toluene (20 mL, M = 0.67); Reaction time: 5 h; Silica plug used solventEtOAc/pet. ether (15:85); Digestion solvent: stir with $CHCl_3$/cyclohexane (3:7, 100 mL in total) for 5 h, then filter to give a brown-yellow solid. Yield: 69% (1.55 g); R_f= 0.34 in EtOAc/pet. ether (15:85).

^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 5.78 (brs, 1 H), 6.85 (d, *J* = 9.1 Hz, 1 H), 7.0 (td, *J* = 7.7, 0.9 Hz, 1 H), 7.35 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.45 (dd, *J*= 7.9,1.9 Hz, 1 H), 7.95 (d, *J* = 13.7 Hz, 1 H), 8.14 (d, *J* = 13.8 Hz, 1 H) ppm.

3-hydroxy-β-nitrostyrene (1e):



3-hydroxybenzaldehyde (4.00 g, 32.8 mmol), nitromethane (20.0 g, 17.5 mL, 328 mmol, 10.0 equiv), piperidine (419 mg, 487µL, 4.92 mmol, 15 mol%), $FeCl_3$ (798 mg, 4.92 mmol, 15 mol%); Reaction solvent: toluene (20 mL, M = 1.5 M); Reaction time: 10 h; Silica plug used EtOAc/pet. ether (20:80); Digestion solvent: stir with $CHCl_3$/pentane (3:7, 200 mL in total) for 5 h, then filter to give a pale-yellow solid. Yield: 72% (3.88 g); R_f= 0.36 in EtOAc/pet. ether (20:80). This compound has been previously reported using a different procedure.[3]

^{1}H-NMR (acetone-d_6, 400 MHz) δ 7.03 (ddd, *J* = 7.8, 2.4, 1.3 Hz, 1H), 7.22-7.25 (m, 1H), 7.28-7.35 (m, 2H), 7.87 (d, *J* = 13.7 Hz, 1H),7.99 (d, *J* = 12.7Hz, 1H),8.74 (s, 1H), ppm.

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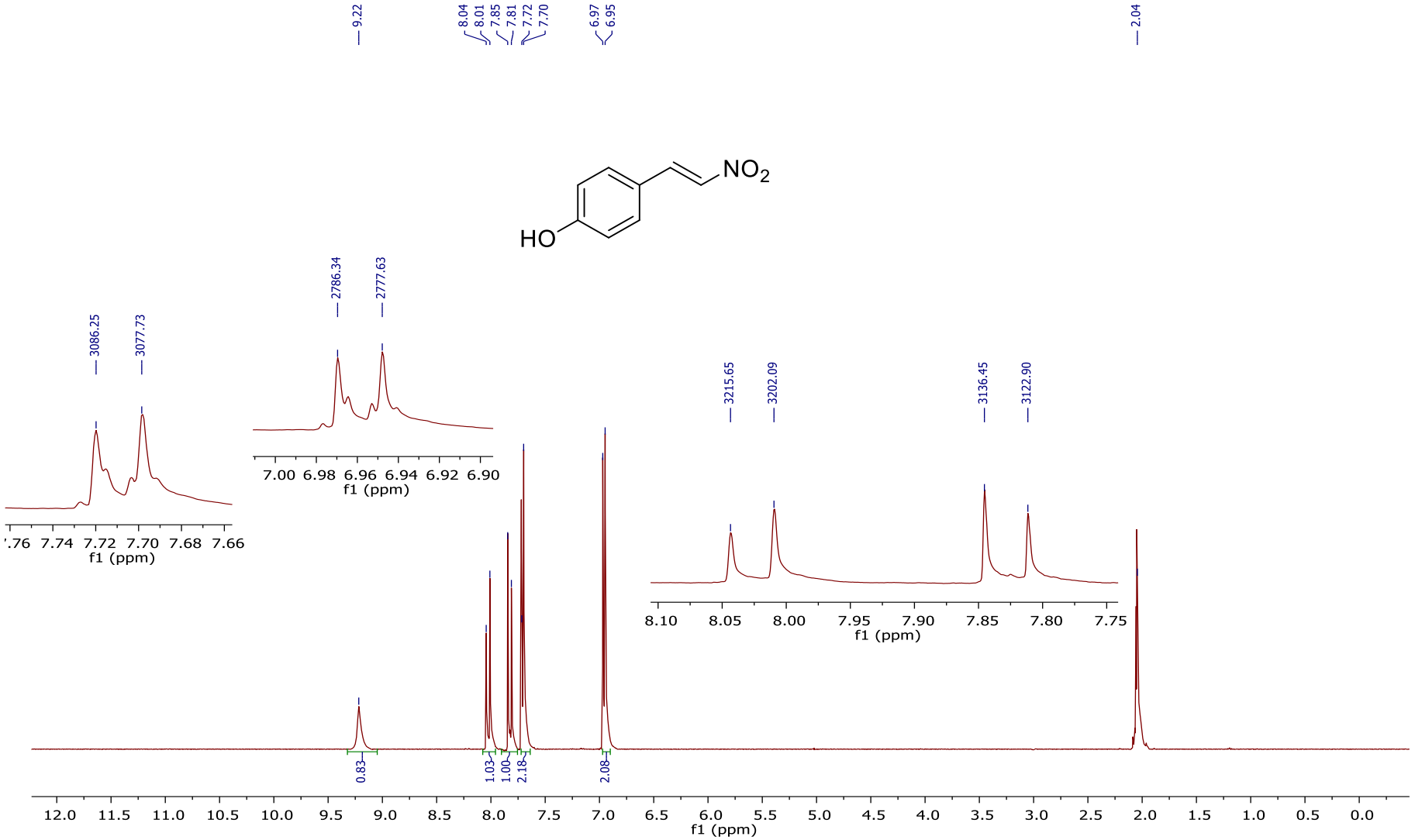
[2] J. Yang, J. Dong, X. Lü, Q. Zhang, W. Ding, X. Shi, *Chin. J. Chem.* **2012**, *30*, 2827–2833.
[3] H. S. Toogood, A. Fryszkowska, M. Hulley, M. Sakuma,D. Mansell,G. M. Stephens, J. M. Gardiner,N. S. Scrutton, *ChemBioChem.***2011**,*12*, 738–749.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8.01
7.85
7.81
7.72
7.70
6.97
6.95
2.04
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HO
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3077.73
2786.34
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3215.65
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f1 (ppm)
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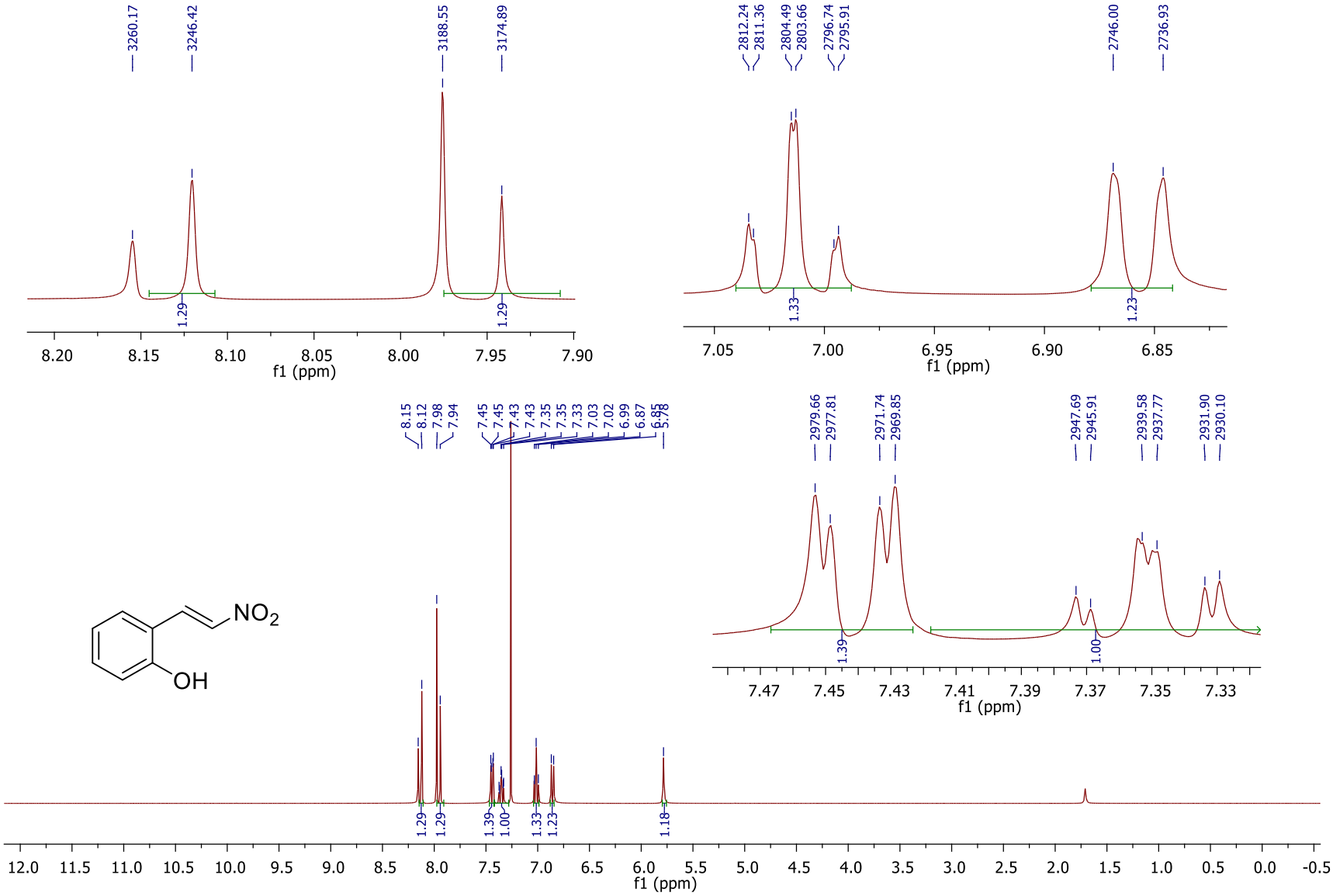
1.03
1.00
2.18
2.08


3260.17
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1.29
1.29
8.20
8.15
8.10
8.05
8.00
7.95
7.90
f1 (ppm)
2812.24
2811.36
2804.49
2803.66
2796.74
2795.91
2746.00
2736.93
1.33
1.23
7.05
7.00
6.95
6.90
6.85
f1 (ppm)
8.15
8.12
7.98
7.94
7.45
7.45
7.43
7.43
7.35
7.35
7.33
7.03
7.02
6.99
6.87
6.85
5.78
NO2
OH
2979.66
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2971.74
2969.85
2947.69
2945.91
2939.58
2937.77
2931.90
2930.10
1.39
1.00
7.47
7.45
7.43
7.41
7.39
7.37
7.35
7.33
f1 (ppm)
1.29
1.29
1.39
1.00
1.33
1.23
1.18
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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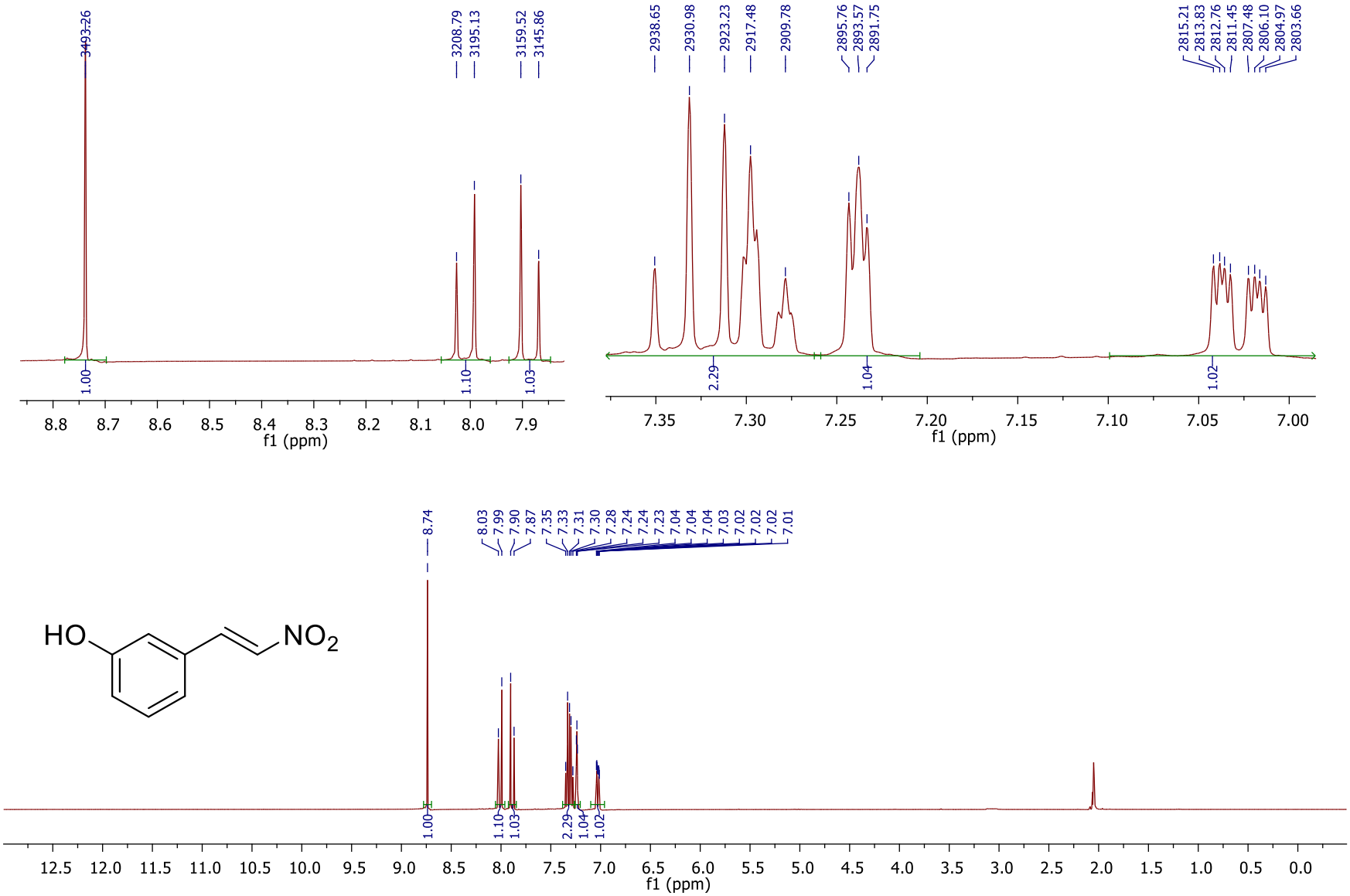
0.5
0.0
-0.5
f1 (ppm)


3493.26
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3145.86
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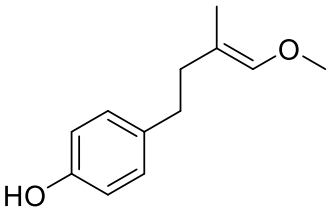
2930.98
2923.23
2917.48
2909.78
2895.76
2893.57
2891.75
2815.21
2813.83
2812.76
2811.45
2807.48
2806.10
2804.97
2803.66
1.00
1.10
1.03
2.29
1.04
1.02
8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9
f1 (ppm)
7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00
f1 (ppm)
8.74
8.03
7.99
7.90
7.87
7.35
7.33
7.31
7.30
7.28
7.24
7.24
7.23
7.04
7.04
7.04
7.03
7.02
7.02
7.02
7.01
HO
NO2
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

(E)-4-(4-methoxy-3-methylbut-3-enyl)phenol



To a solution of (methoxymethyl)triphenylphosphonium chloride (MW=342.80, 1.6 equiv, 29.232 mmol, 10.0 g) in a two-neck round-bottom flask containing dry THF (40 mL) cooled in an ice-bath under a nitrogen atmosphere a 60% dispersion of sodium hydride in mineral oil (MW=24.0, 2.5 equiv, 45.676 mmol, 1.827 g) was slowly added via a wide mouthed funnel. The resulting mixture was stirred for 30 min in an ice-bath.a solution of 4-(4-hydroxyphenyl)-2-butanone (MW=164.2, 1.0 equiv, 18.270 mmol, 3.0 g) in dry THF (20 mL) was added dropwise via syringe. The resulting mixture was stirred for 10 min, and then allowed to warm up to room temperature over the course of 1 hour. The reaction flask was then moved to an oil bath and placed under gentle reflux, with stirring, at 60 °C for 3 h. The reaction was quenched once 100% consumption of the ketone, R_f= 0.32, EtOAc/Pet Ether (1:4), was noted by TLC. Work-up: add water (50 mL) and remove THF (rotary evaporation). The aqueous phase was extracted with DCM (5 x 100 mL), and combined organic extracts were dried over Na_2SO_4. Purification of the crude compound by column chromatography using EtOAc/petroleum ether (1:9) was provided the product as yellow oil (3.074g, 87%, MW=192.25, 15.989 mmol).

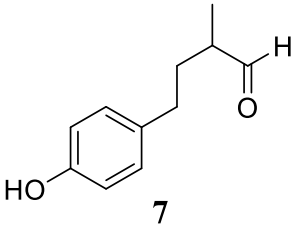
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 5.75-5.72 (m, 1H), 4.68 and 4.66 (s, 1H), 3.52 and 3.46 (s, 3H), 2.65-2.57 (m, 2H), 2.33 (dd, *J* = 9.2, 6.7 Hz, 1H), 2.15-2.10 (m, 1H), 1.64 and 1.53 (d, *J* = 1.3 Hz, 3H),

^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 153.5, 142.4, 142, 134.9, 134.6, 129.6, 115.1, 115, 114, 113.5, 59.3, 44.9, 36.5, 34.1, 32.9, 31, 28.4, 17.4, 13.

IR (ATR, cm^{-1}): ν= 2932.43, 2837.43, 1682.71, 1613.18, 1513.03, 1449.18, 1202.11, 1124.46, 1097.48

MS (EI), *m/z* (relative intensity, negative mode): 190.83, 105.99

4-(4-hydroxyphenyl)-2-methylbutanal (7)



7

The methyl-vinyl-ether (MW = 192.25 g/mol, 493 mg, 2.56 mmol) was dissolved in 7 mL of THF in a 100 mL round-bottom flask. 7 mL of 1M HCl solution (MW = 36.46 g/mol, 2.7 equiv, 7mmol) were added portion-wise to the mixture under stirring at room temperature. The reaction reached completion after 4h as determined by TLC. Then quenched by adding $NaHCO_3$ for the work up: 20 mL of water were added to the mixture, which was then transferred to a separatory funnel and washed 3 times with 30 mL of Ethyl acetate.The organic phase extracts were combined and dried with anhydrous Sodium Sulfate. The solvent was evaporated under vacuum at the Rotary Evaporator and later under high vacuum. The crude mixture was then purified by column chromatography to yield a transparent oil (365 mg, 80% yield, MW = 178.23 g/mol, 2 mmol), R_f = 0.22 (1:9 EtOAc / Petroleum ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.59 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.39 (s, 1H), 2.62-2.53 (m, 2H), 2.38 (qd, *J* = 6.9, 1.8 Hz, 1H), 2.02 (ddd, *J* = 13.5, 9.1, 6.7 Hz, 1H), 1.63 (ddd, *J* = 13.5, 9.0, 6.7 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H).

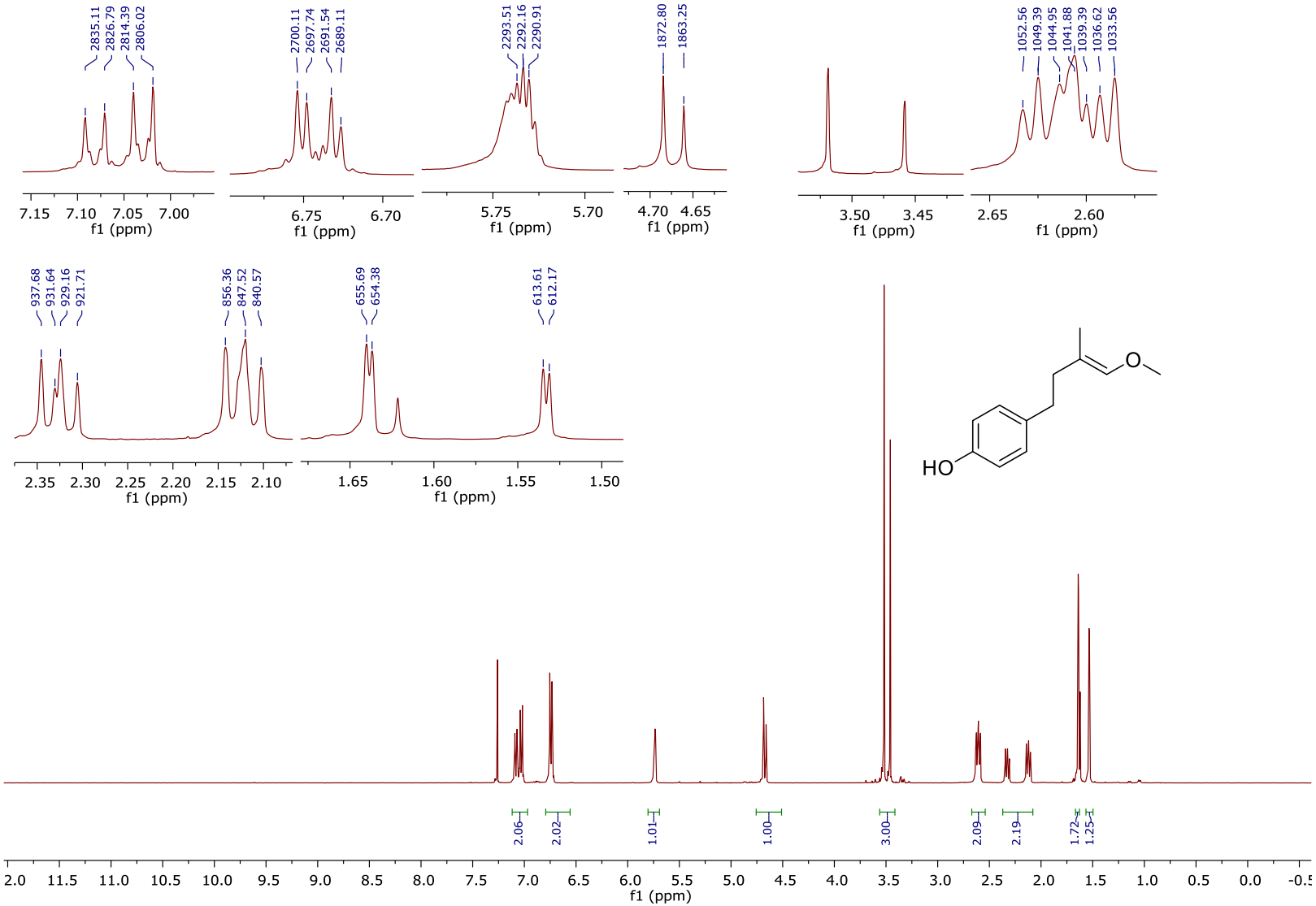
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 206.3, 154.2, 133.2, 129.5, 115.5, 45.7, 32.4, 32.15,13.3.

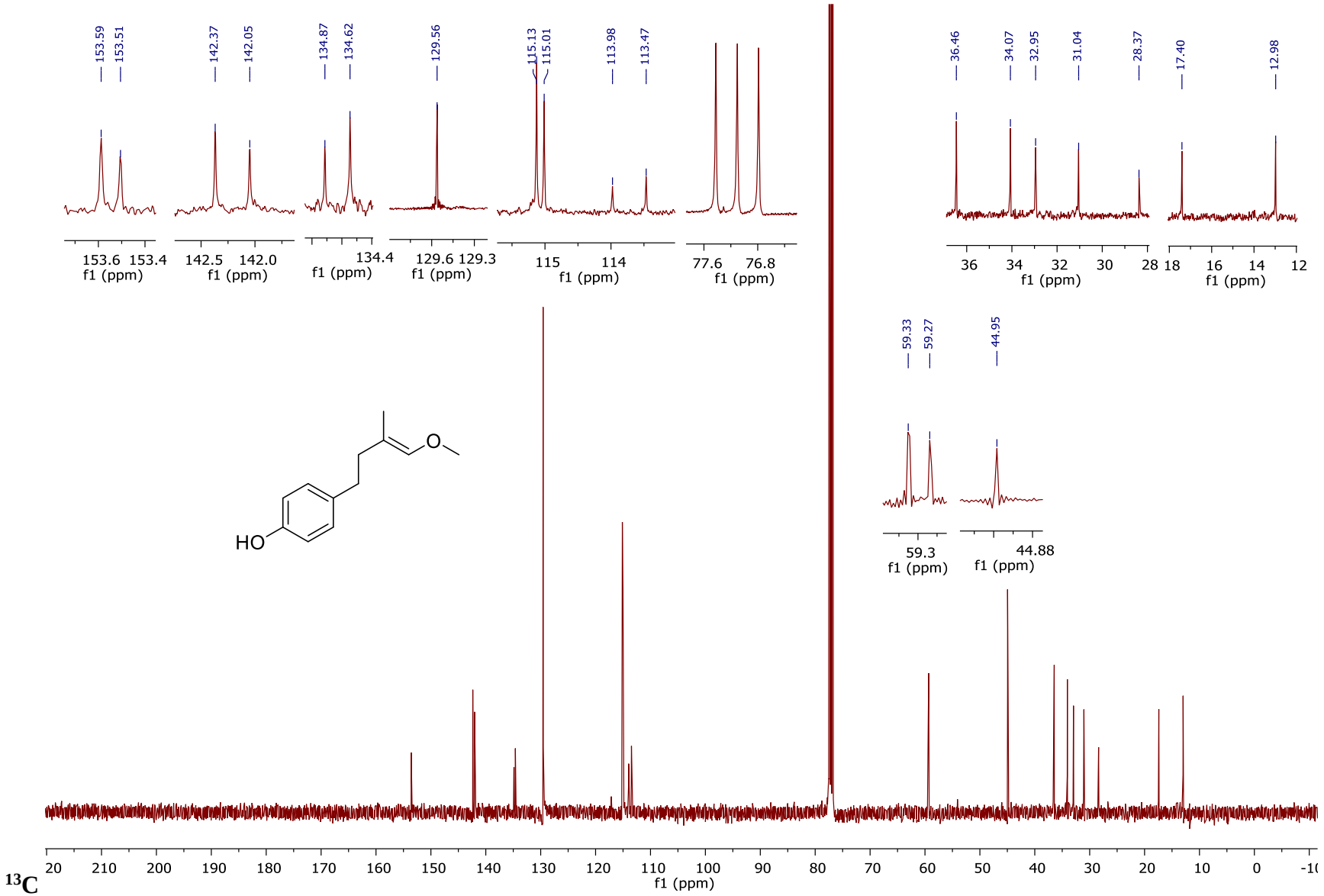
IR (ATR, cm^{-1}): ν= 2931.11, 2857.75, 1710.34, 1613.40, 1513.93, 1219.46, 823.92

MS (EI), *m/z* (relative intensity, negative mode): 176.82, 106.9

HRMS (ESI-TOF) m/z: $[M]^-$ Calculated for $C_{11}H_{13}O_2$: 177.0921; Found: 177.0919

Melting Point: 44.5 °C (45 °C)


2835.11
2826.79
2814.39
2806.02
7.15 7.10 7.05 7.00
f1 (ppm)
2700.11
2697.74
2691.54
2689.11
6.75 6.70
f1 (ppm)
2293.51
2292.16
2290.91
5.75 5.70
f1 (ppm)
1872.80
1863.25
4.70 4.65
f1 (ppm)
1052.56
1049.39
1044.95
1041.88
1039.39
1036.62
1033.56
3.50 3.45
f1 (ppm)
2.65 2.60
f1 (ppm)
937.68
931.64
929.16
921.71
2.35 2.30 2.25 2.20 2.15 2.10
f1 (ppm)
856.36
847.52
840.57
655.69
654.38
1.65 1.60 1.55 1.50
f1 (ppm)
613.61
612.17
HO
O
2.06
2.02
1.01
1.00
3.00
2.09
2.19
1.72
1.25
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


153.59
153.51
142.37
142.05
134.87
134.62
129.56
115.13
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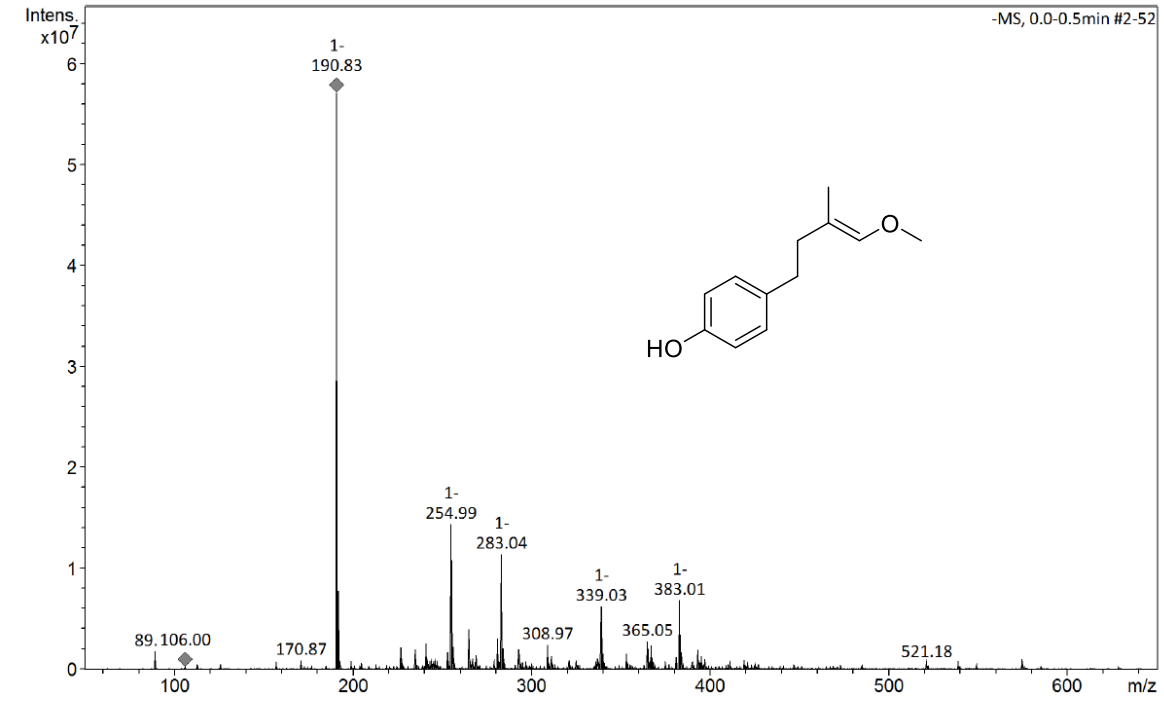
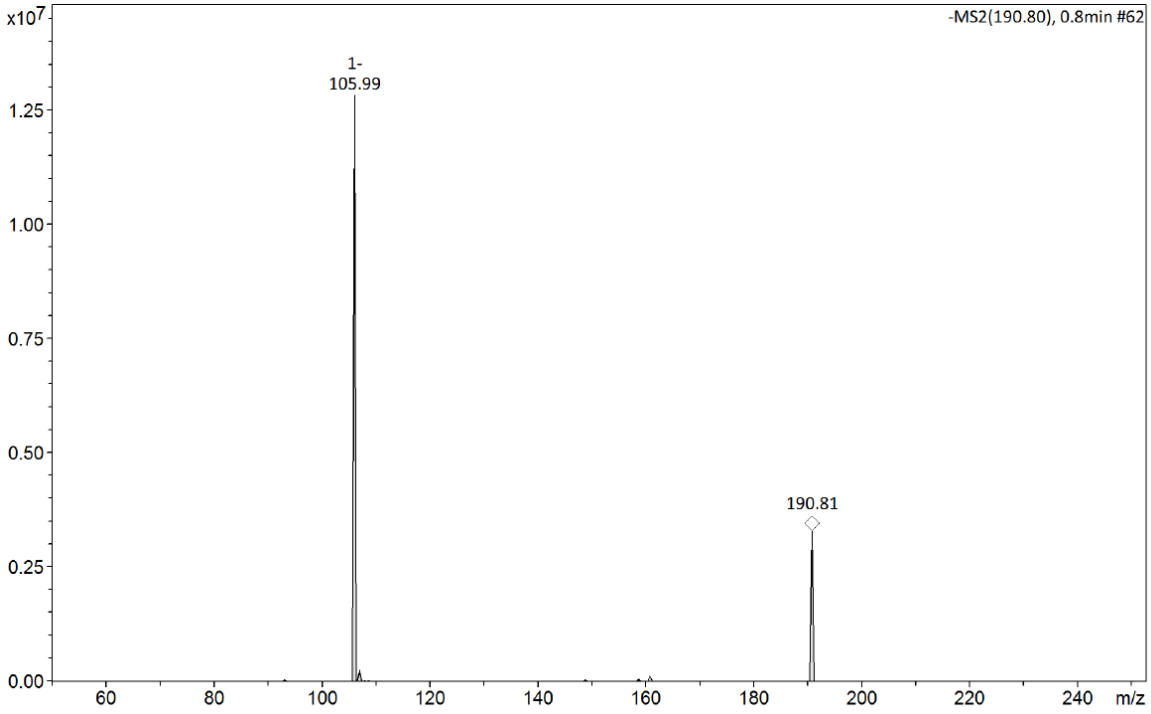
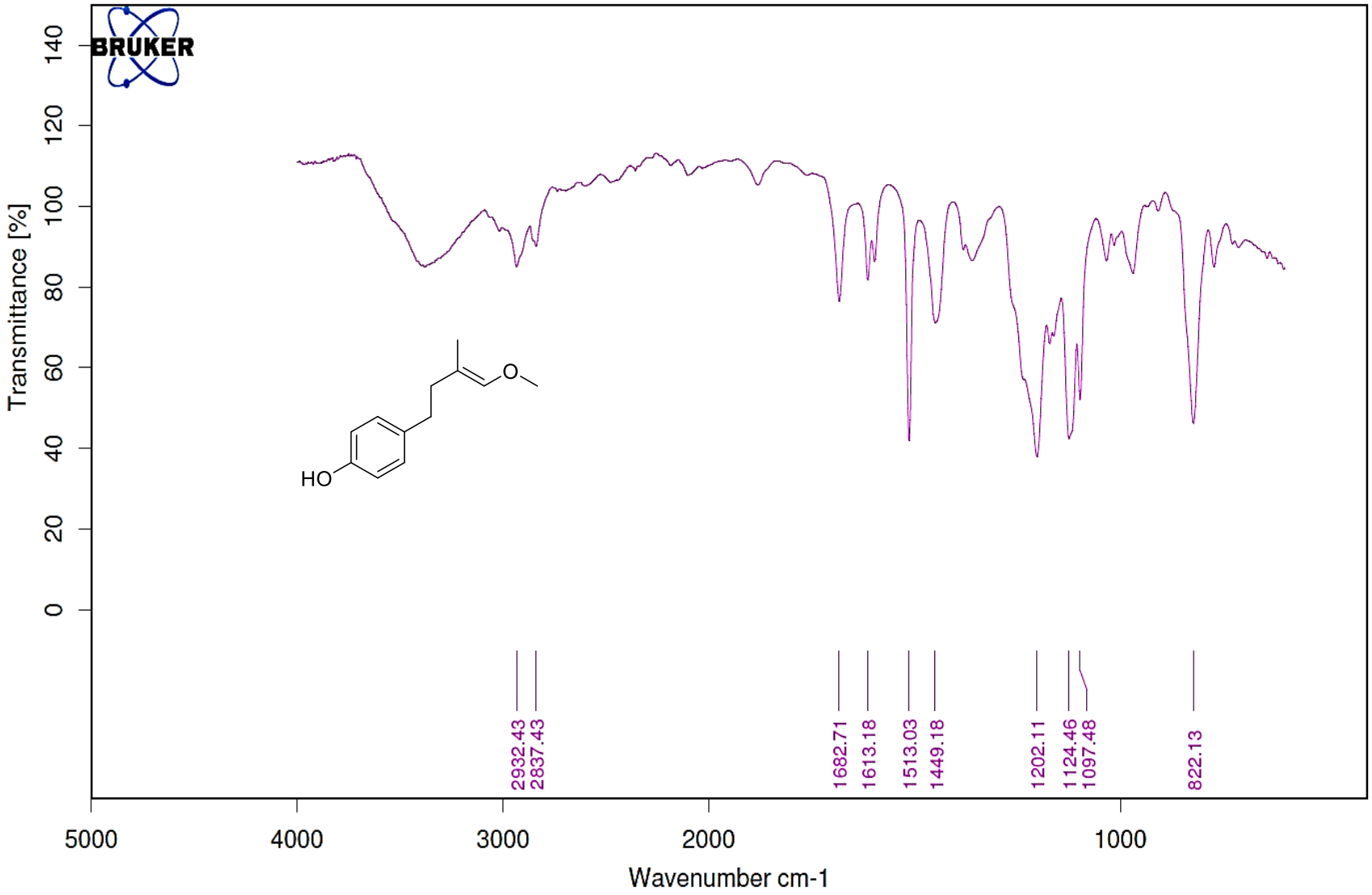
113.98
113.47
36.46
34.07
32.95
31.04
28.37
17.40
12.98
59.33
59.27
44.95
HO
O
153.6 153.4
142.5 142.0
134.4
129.6 129.3
115 114
77.6 76.8
36 34 32 30 28
18 16 14 12
59.3
44.88
f1 (ppm)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
13C

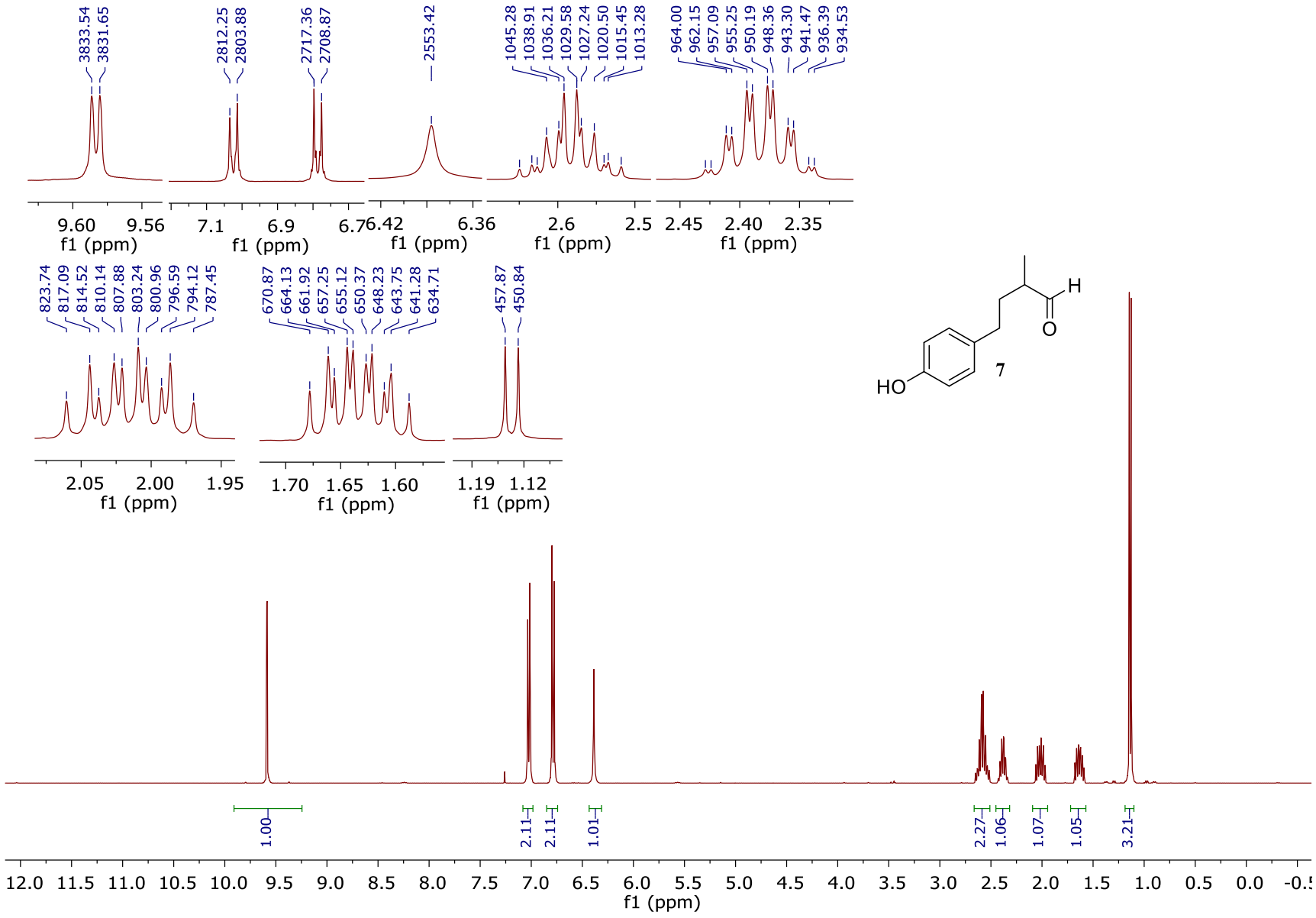
Analysis Info

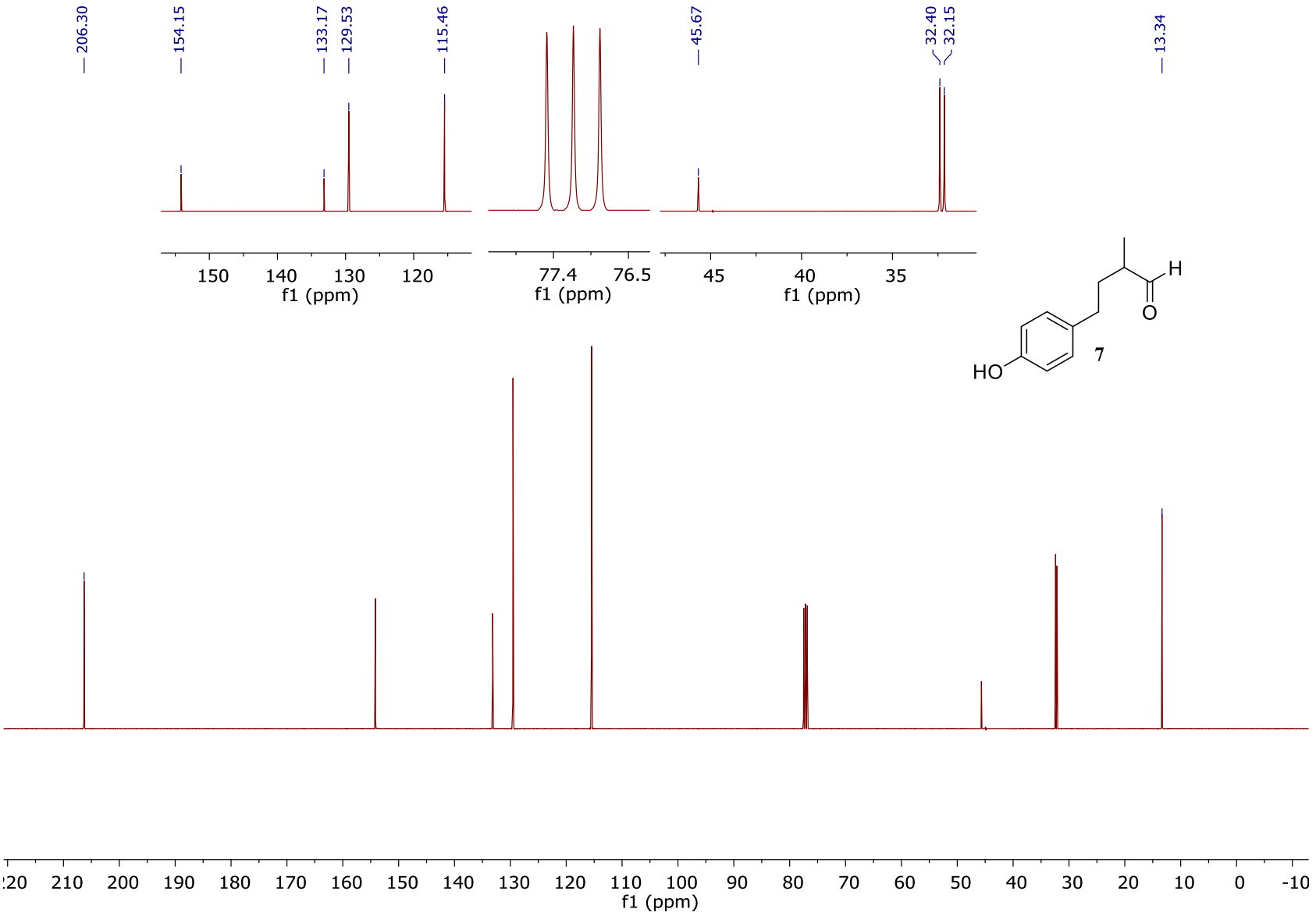
Analysis Name	E:\Methyl-Vinyl- Ether_11022016.d	Acquisition Date	11.02.2016 15:19:39
Method	DEF_MS.M	Operator	Rakesh
Sample Name	20160205_KA_CB7-OH_solid	Instrument	HCTultra
Comment			





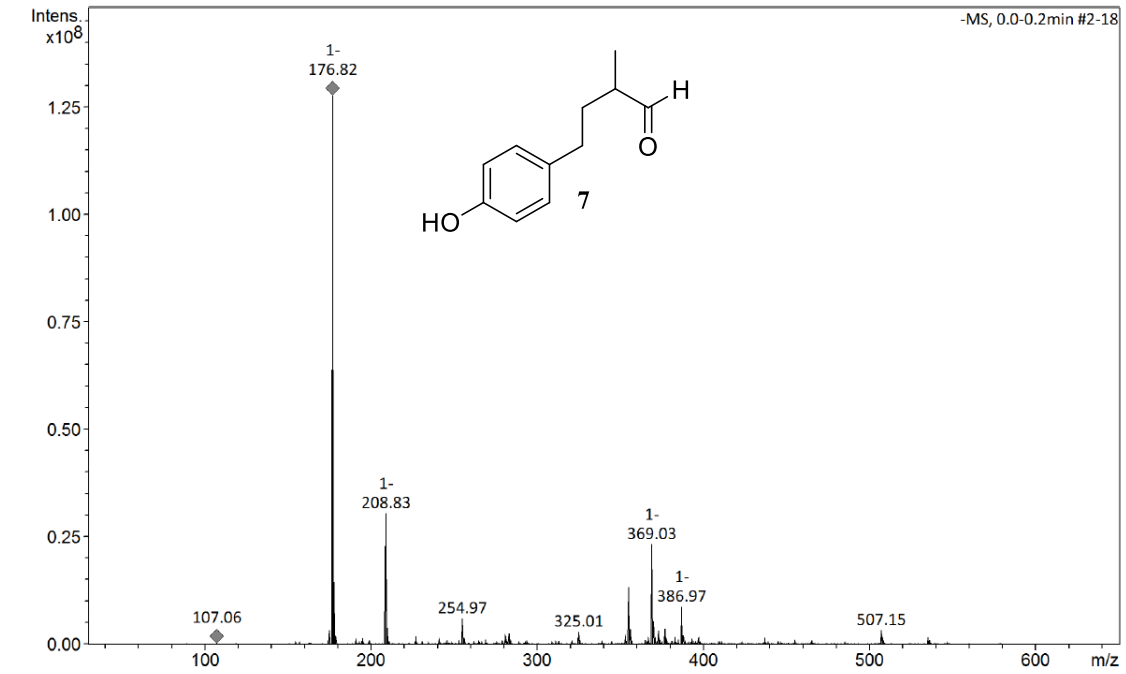

BRUKER
Transmittance [%]
0
20
40
60
80
100
120
140
HO
O
2932.43
2837.43
1682.71
1613.18
1513.03
1449.18
1202.11
1124.46
1097.48
822.13
5000
4000
3000
2000
1000
Wavenumber cm-1

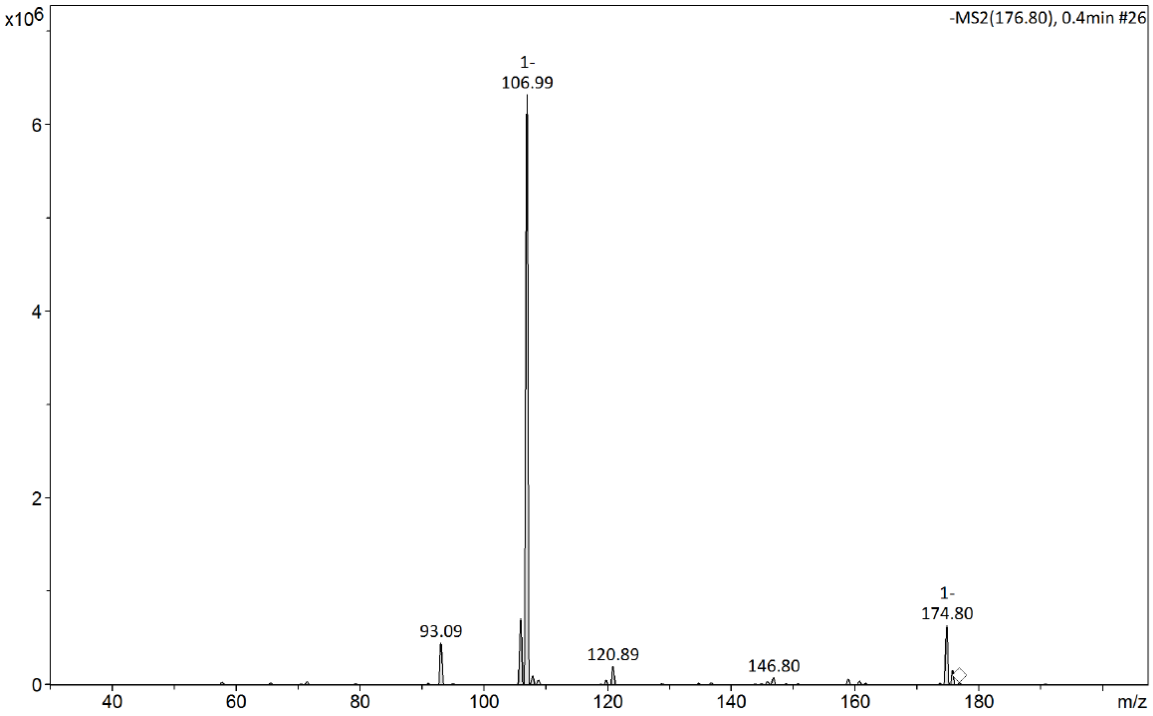

3833.54
3831.65
2812.25
2803.88
2717.36
2708.87
2553.42
1045.28
1038.91
1036.21
1029.58
1027.24
1020.50
1015.45
1013.28
964.00
962.15
957.09
955.25
950.19
948.36
943.30
941.47
936.39
934.53
9.60 9.56
7.1 6.9 6.7
6.42 6.36
2.6 2.5
2.45 2.40 2.35
f1 (ppm)
823.74
817.09
814.52
810.14
807.88
803.24
800.96
796.59
794.12
787.45
670.87
664.13
661.92
657.25
655.12
650.37
648.23
643.75
641.28
634.71
457.87
450.84
2.05 2.00 1.95
1.70 1.65 1.60
1.19 1.12
H
O
HO
7
1.00
2.11
2.11
1.01
2.27
1.06
1.07
1.05
3.21
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

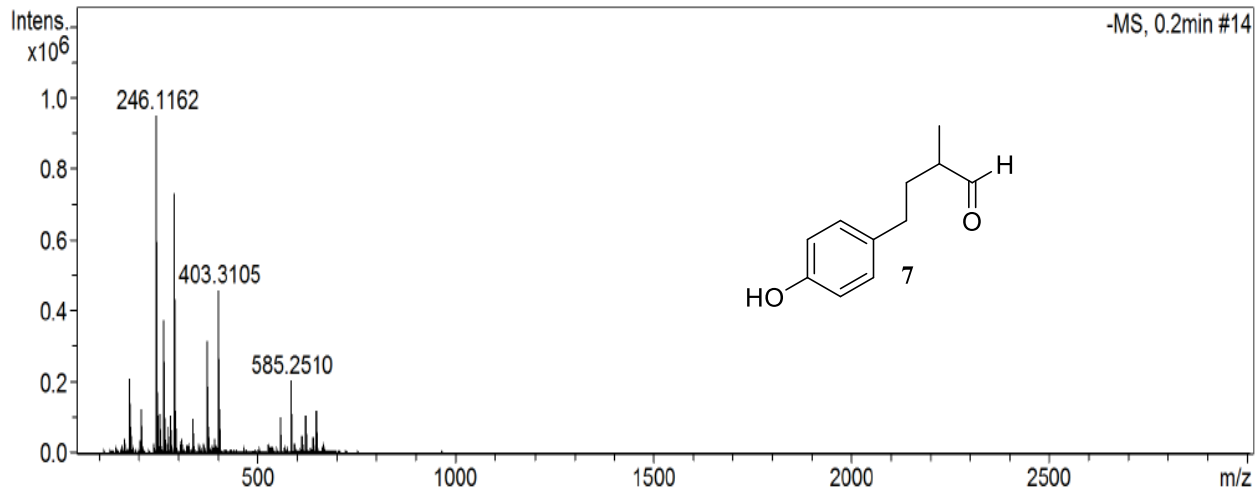

206.30
154.15
133.17
129.53
115.46
45.67
32.40
32.15
13.34
150
140
130
120
f1 (ppm)
77.4
76.5
f1 (ppm)
45
40
35
f1 (ppm)
H
O
HO
7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Analysis Info

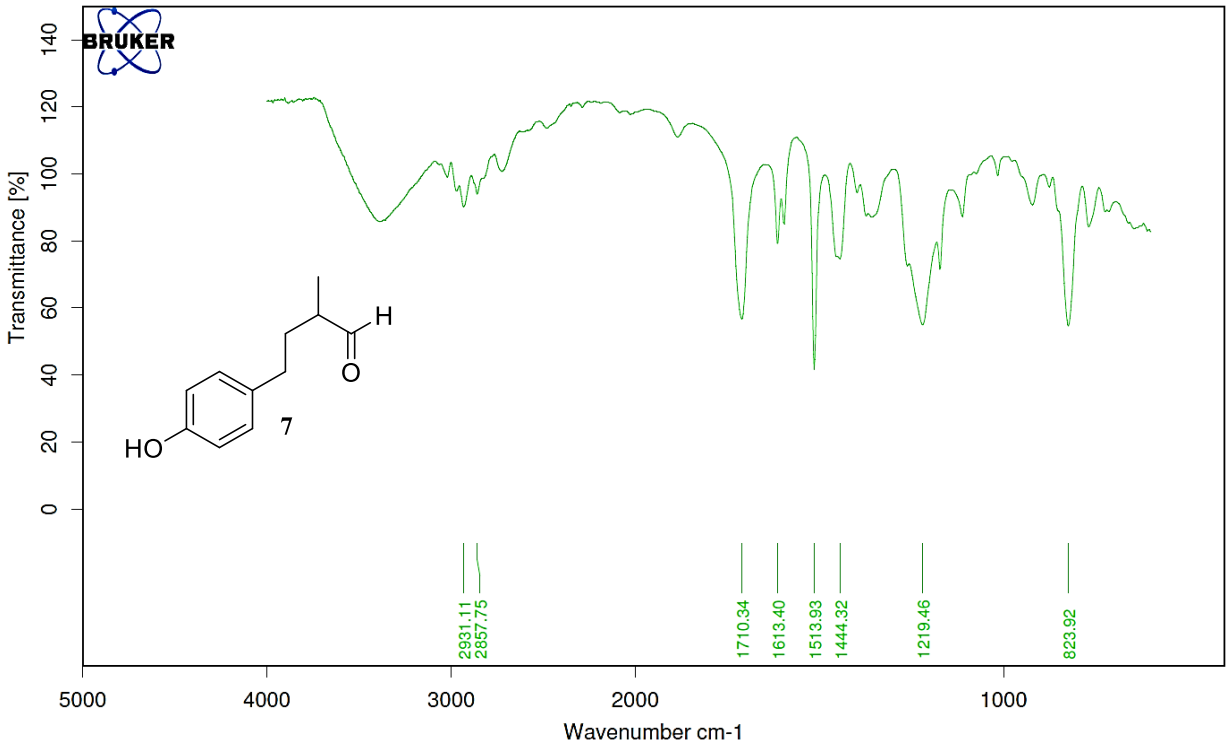
Analysis Name	E:\Long- Phenolic-Aldehyde_11022016.d	Acquisition Date	11.02.2016 15:22:54
Method	DEF_MS.M	Operator	Rakesh
Sample Name	20160205_KA_CB7-OH_solid	Instrument	HCTultra
Comment			



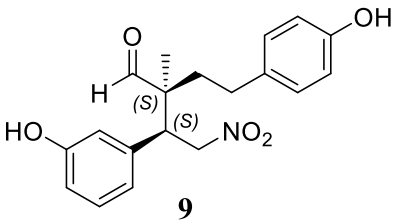




Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
177.0919	1	C11H13O2	177.0921	1.4	6.6	1	100.00	5.5	even	ok



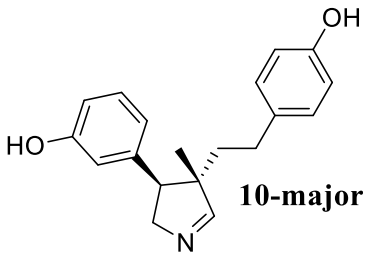
(2R, 3S)-2-(4-hydroxyphenethyl)-3-(3-hydroxyphenyl)-2-methyl-4-nitrobutanal



9

To reaction vial 5 mL, *O*-tert-Butyl-L-threonine (MW= 175.23 g/mol, 0.10 equiv, 0.3028 mmol, 53 mg) was mixed with KOH (MW= 56.1 g/mol, 0.15 equiv, 0.454 mmol, 35 mg) in (3:1) EtOAc/ n-pentane (3.8 mL, 0.8 M). The mixture was stirred for 2.0 min at room temperature to become homogenous then 4-(4-hydroxyphenyl)-2-methylbutanal (MW= 178.23 g/mol, 1.0 equiv, 3.028 mmol, 540 mg) was added to the mixture with stirring for 1 min at room temperature. 3-hydroxy-β-nitrostyrene (MW= 165.15 g/mol, 1.0 equiv, 3.028 mmol, 500 mg) was added to the mixture to give dark red solution. The reaction mixture was stirred at room temperature for 16-18 hour, and followed by TLC until consumption of the starting material (≥95% by stain, CAN staining solution was used). The reaction mixture was directly loaded on to a silica gel column for purification (2.5 x 17 cm, diameter by height) and eluted using the following solvents: EtOAc/pet ether (15:85, 100 mL; then 25:75, 300 mL; 30:70, 500 mL). The desired product (MW= 343.14 g/mol, 2.185 mmol, 750 mg, 72% yield, 1:2.3 dr) was obtained as light yellow oil and become white solid with time. R_f= 0.22 (30%EtOAc/pet ether).

3-((3S, 4S)-4-(4-hydroxyphenethyl)-4-methyl-3,4-dihydro-2H-pyrrol-3-yl)phenol



10-major

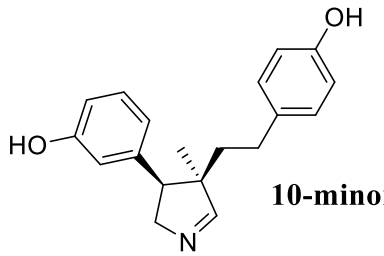
Michael Product (MW= 343.14 g/mol, 1.0 equiv, 0.2914 mmol, 100 mg) was dissolved in methanol (3 mL) then 5% Pd/C (18.6 mg Pd/C no moisture added (Pd: MW= 106.4 g/mol, 0.0087 mmol, 0.93 mg, 3.0 mol% effective Pd added)). Under pressurized hydrogen (10.0 bar) the reaction mixture was stirred at room temperature and monitored by TLC. After 16h the TLC showed a full conversion of the starting material to the corresponding amine. The reaction solution was filtered through a plug of celite to remove the Pd/C. The celite plug was washed with methanol until the TLC plat showed no more compounds coming out of the washing. The reaction mixture was concentrated and added to Silica gel column chromatography (2.5 x 17 cm, diameter by height) and eluted using the following solvents: EtOAc (100 mL) then EtOAc/MeOH/NH_4OH (95:4:1, 300 mL; then 90:9:1, 600 mL).. The product was

obtained as a white solid compound (MW= 295.38 g/mol, 0. 162 mmol, 48 mg, 55% yield). The total yield from 3-hydroxy-β-nitrostyrene to the final desired product was 40%.R_f= 0.27 (90:9:1 EtOAc/MeOH/NH_4OH).

Chiral HPLC (IA column, MeCN/EtOAc (45:55), flow rate = 0.8 mL/min, λ = 254 nm), t_{minor}= 63.5 min and t_{major} = 42.3 min, 90% ee = 95:5 enantiomeric ratio.

^{1}H NMR (400 MHz, Methanol-*D*$_4$) δ 0.85 (s, 3H), 1.89 (t, *J* = 8.4 Hz, 2H), 2.77 – 2.51 (m, 2H), 3.70 (t, *J* = 8.5 Hz, 1H), 4.28 (ddd, *J* = 14.1, 8.7, 1.5 Hz, 1H), 4.36 (ddd, *J* = 14.2, 8.3, 1.6 Hz, 1H), 6.78 – 6.63 (m, 5H), 7.05 (s, 1H), 7.08- 7.02 (m, 2H), 7.17 (t, *J* = 7.9 Hz, 1H).
^{13}C NMR (100 MHz, Methanol-*D*$_4$) δ 20.3, *3*1.4, 42.4, 49.3, 51.5, 66.8, 115.6, 116.4, 116.4, 120.6, 130.3, 130.7, 133.6, 139.5, 147.7, 156.8, 158.8.
(ESI-TOF)-MS m/z: $[M+K]^+$Calcd for $C_{19}H_{21}KNO_2$ 334.1204; Found 334.1208.

3-((3S, 4R)-4-(4-hydroxyphenethyl)-4-methyl-3, 4-dihydro-2H-pyrrol-3-yl) phenol



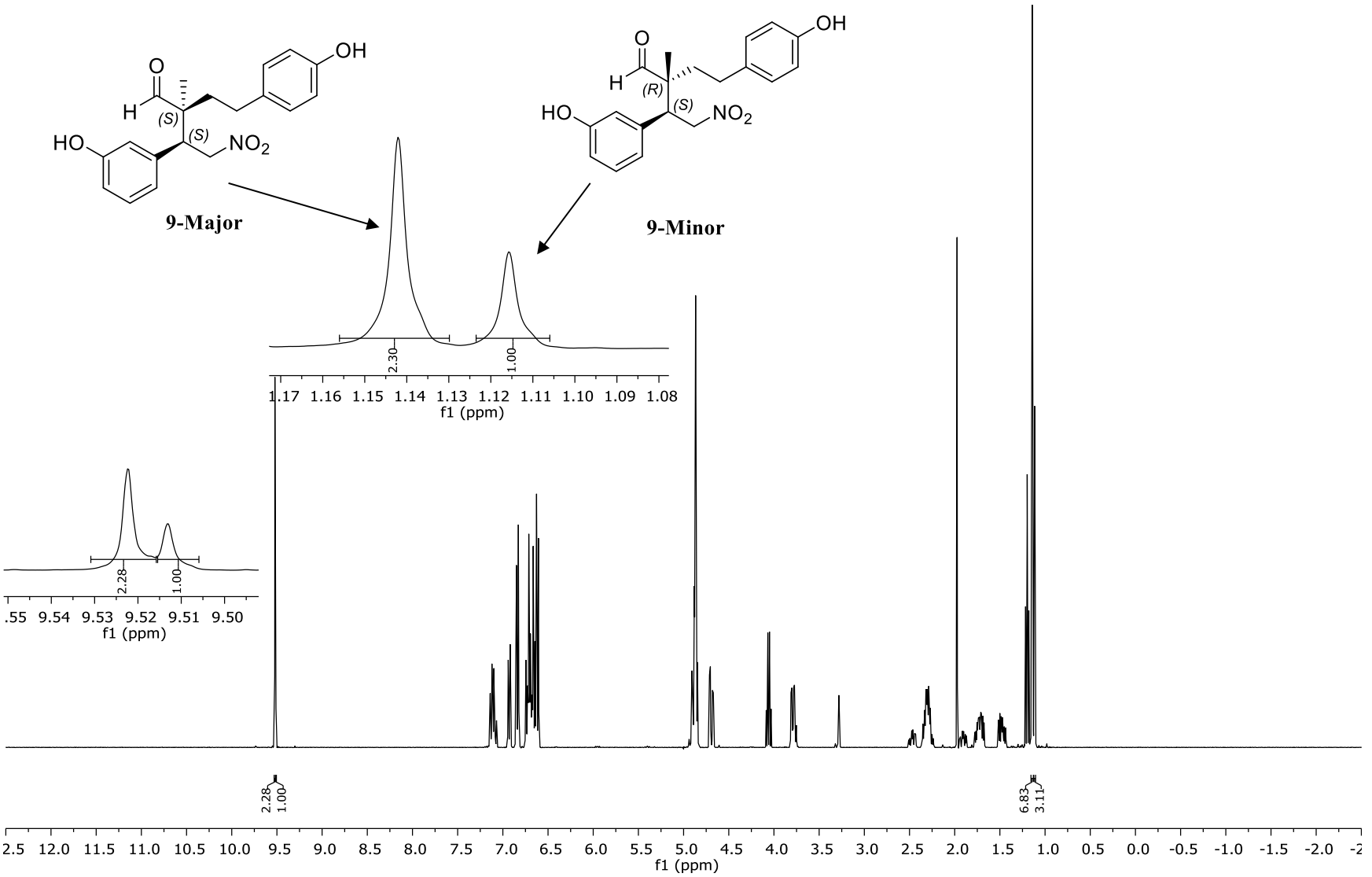
10-minor

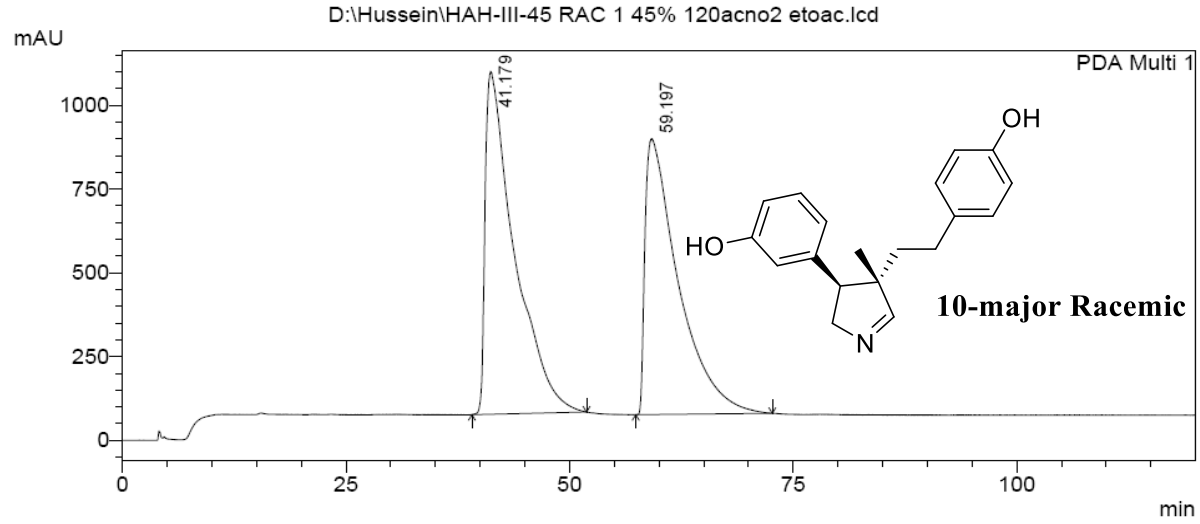
The product was obtained as a white solid compound (MW= 295.38 g/mol, 0. 081 mmol, 24 mg, 27% yield). The total yield from 3-hydroxy-β-nitrostyrene to the final desired product was 20%.R_f= 0.25 (90:9:1 EtOAc/MeOH/NH_4OH).

Chiral HPLC (IA column, MeCN/EtOAc (45:55), flow rate = 0.8 mL/min, λ = 254 nm), t_{minor}= 40.1 min and t_{major} = 76.7 min, 82% ee = 91:9 enantiomeric ratio.

^{1}H NMR (400 MHz, Methanol-*D*$_4$) δ 1.29 (ddd, *J* = 13.9, 11.8, 5.0 Hz, 1H), 1.43 (s, 3H), 1.63 (ddd, *J* = 13.7, 11.7, 5.9 Hz, 1H), 2.40 – 2.23 (m, 2H), 3.61 (t, *J* = 8.6 Hz, 1H), 4.28 (ddd, *J* = 14.0, 8.6, 1.3 Hz, 1H), 4.41 (ddd, *J* = 14.0, 8.6, 1.7 Hz, 1H), 6.63 – 6.56 (m, 1H), 6.81 – 6.70 (m, 6H), 7.11 (s, 1H), 7.19 (t, *J* = 7.7 Hz, 1H).
^{13}C NMR (100 MHz, Methanol-*D*$_4$) δ 23.5, 30.9, 38.9, 51.0, 52.7, 66.7, 115.8, 116.1, 116.3, 120.7, 130.1, 130.8, 133.8, 139.1, 147.9, 156.6, 158.9.
(ESI-TOF)-MS m/z: $[M+K]^+$Calcd for $C_{19}H_{21}KNO_2$ 334.1209; Found 334.1214.

C:\Users\NMR/Documents/files/data/Nugent/Hussein/HAH-III-037 crude





1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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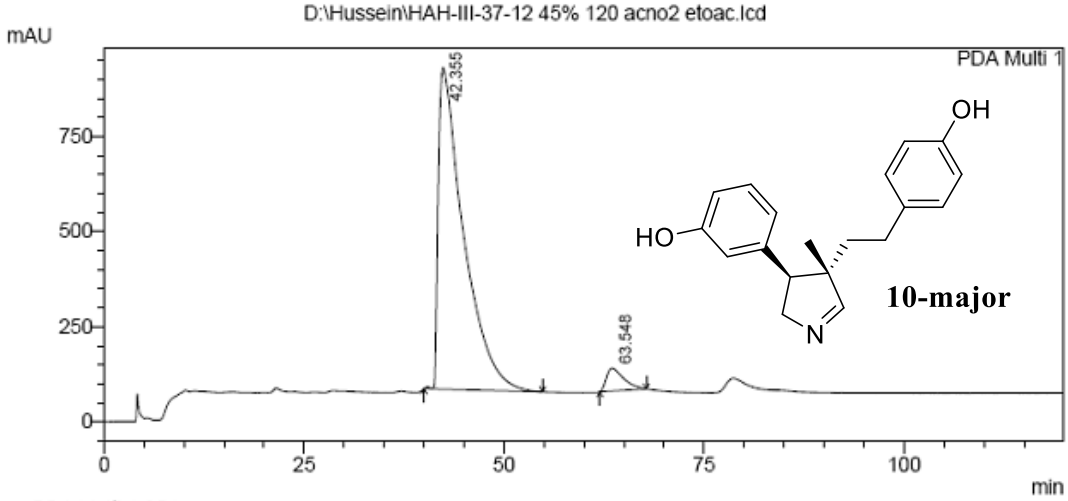

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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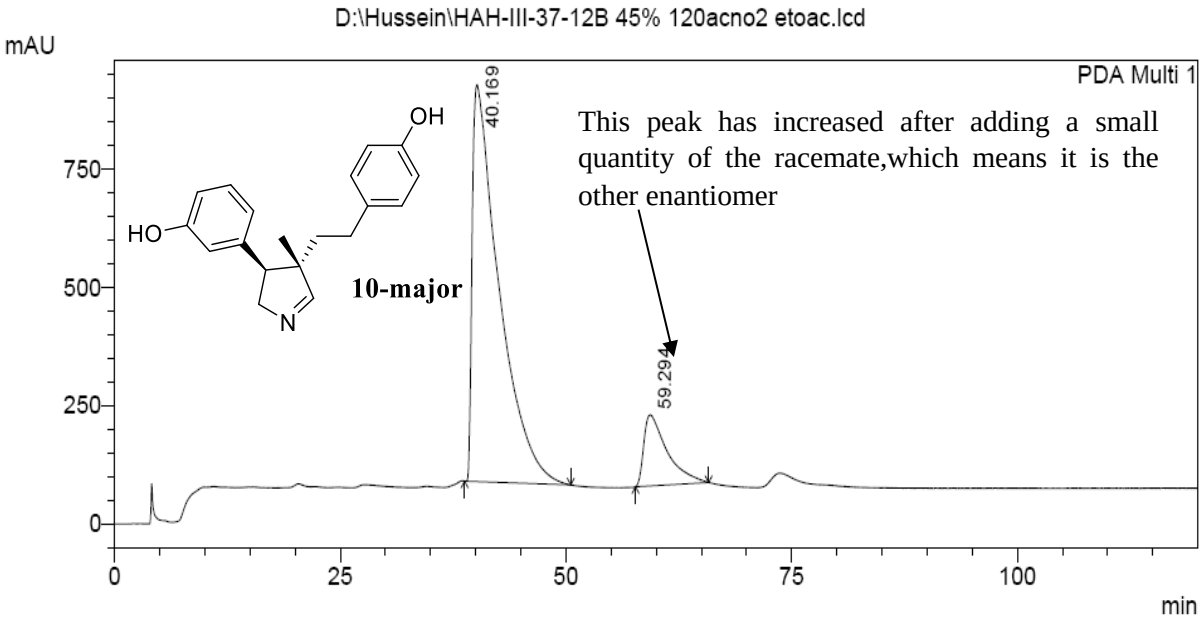

PeakTable

PDA Ch1 254nm 4nm

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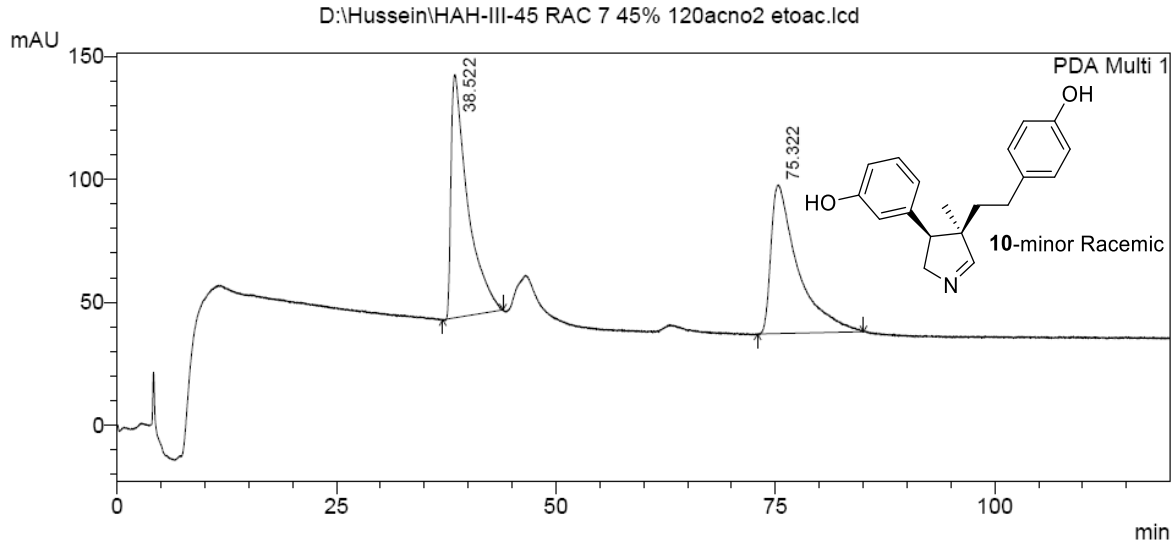

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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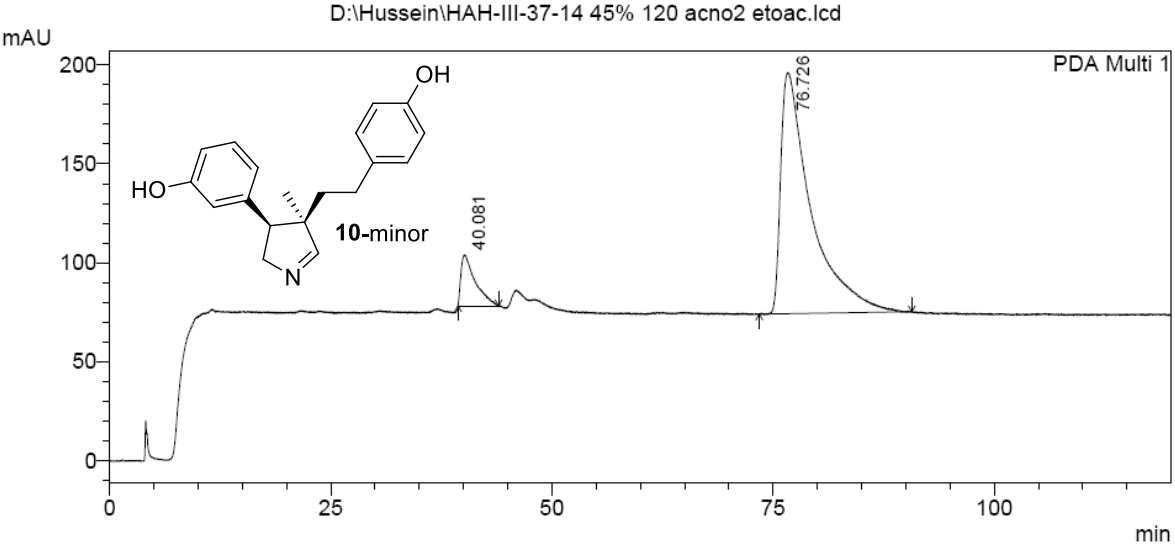

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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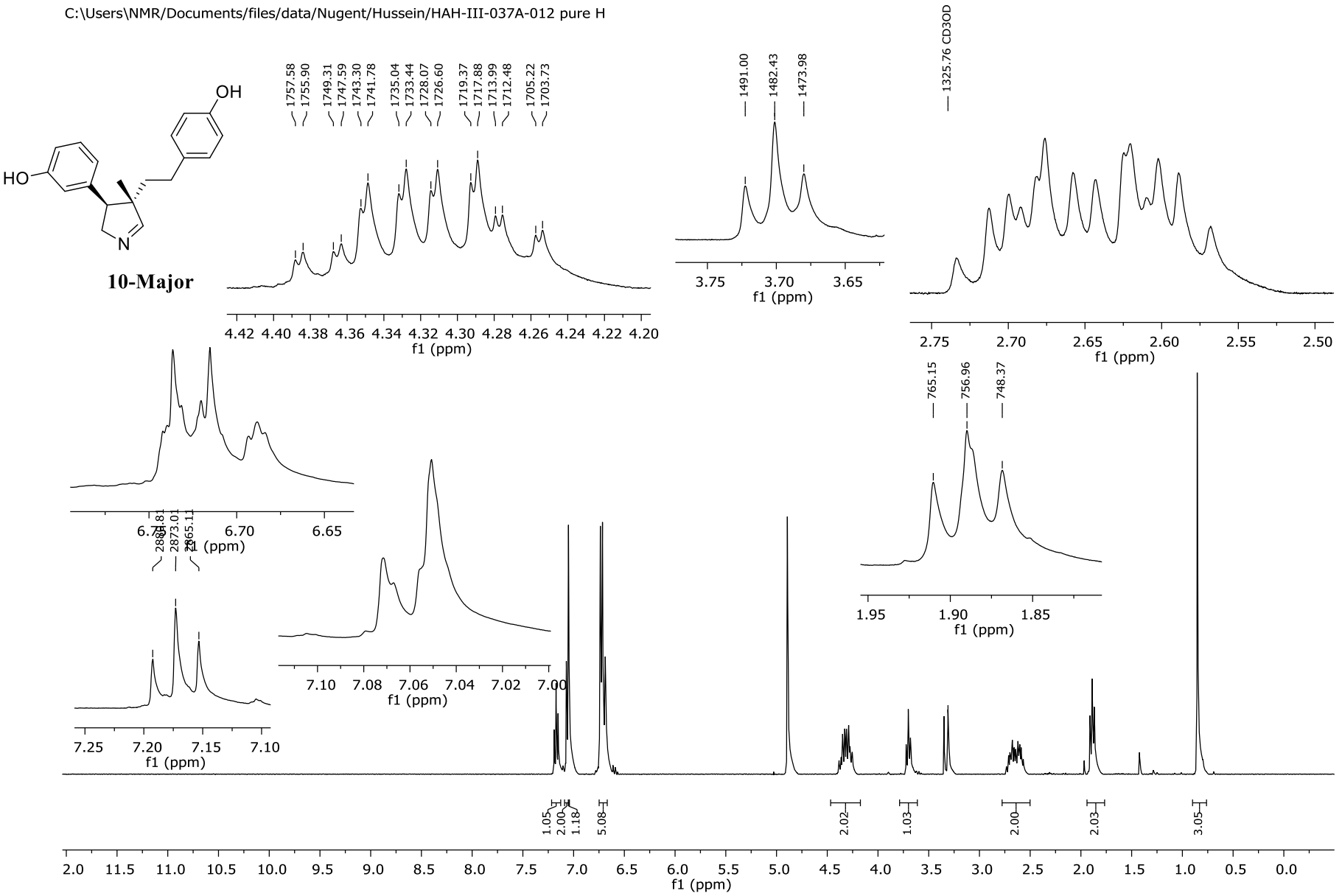
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HO
N
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1747.59
1743.30
1741.78
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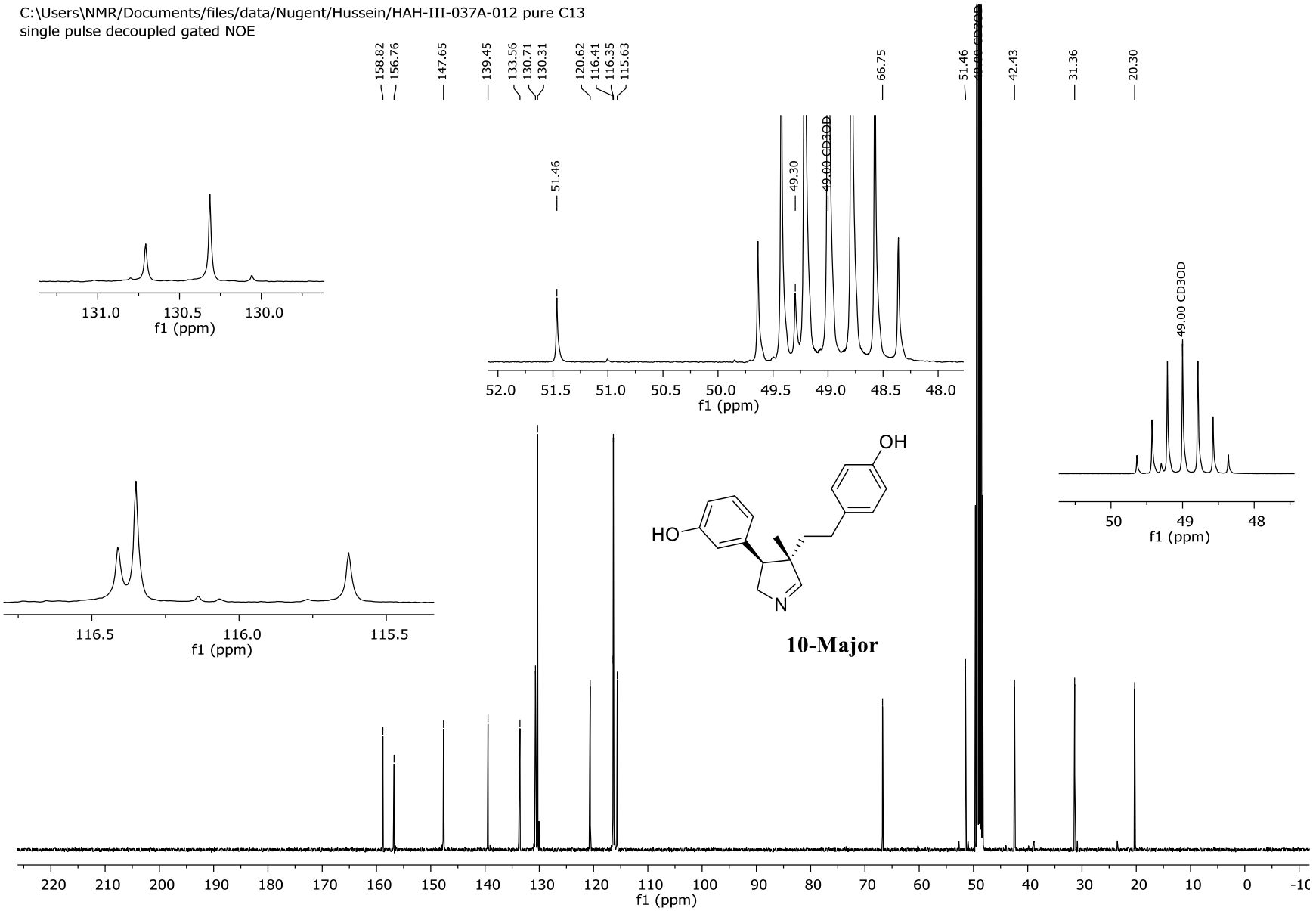
1733.44
1728.07
1726.60
1719.37
1717.88
1713.99
1712.48
1705.22
1703.73
4.42 4.40 4.38 4.36 4.34 4.32 4.30 4.28 4.26 4.24 4.22 4.20
f1 (ppm)
1491.00
1482.43
1473.98
3.75 3.70 3.65
f1 (ppm)
1325.76 CD3OD
2.75 2.70 2.65 2.60 2.55 2.50
f1 (ppm)
6.75 6.70 6.65
f1 (ppm)
2884.81
2873.01
2865.11
7.25 7.20 7.15 7.10
f1 (ppm)
7.10 7.08 7.06 7.04 7.02 7.00
f1 (ppm)
765.15
756.96
748.37
1.95 1.90 1.85
f1 (ppm)
1.05
2.00
1.18
5.08
2.02
1.03
2.00
2.03
3.05
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


C:\Users\NMR/Documents/files/data/Nugent/Hussein/HAH-III-037A-012 pure C13
single pulse decoupled gated NOE
158.82
156.76
147.65
139.45
133.56
130.71
130.31
120.62
116.41
116.35
115.63
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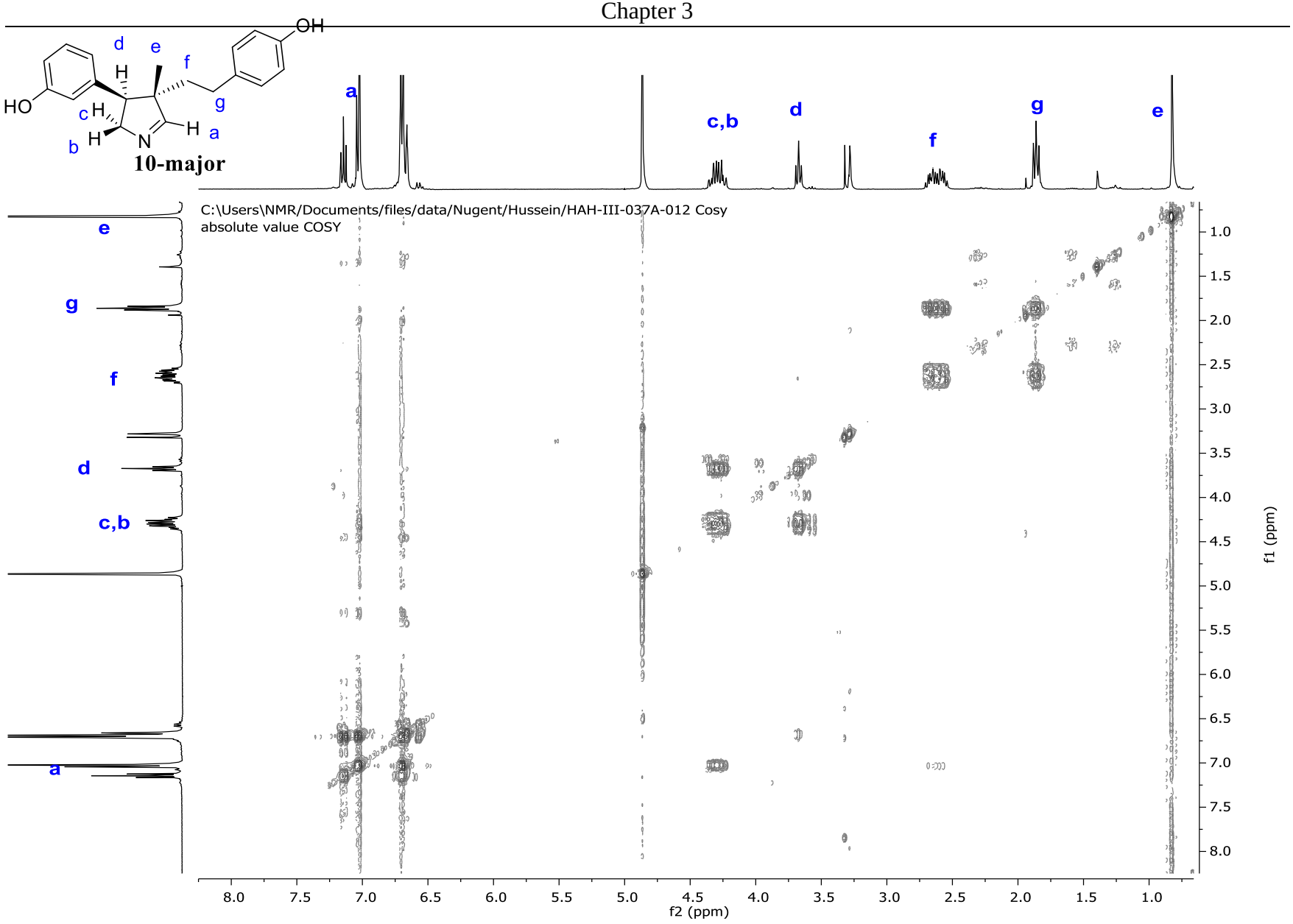
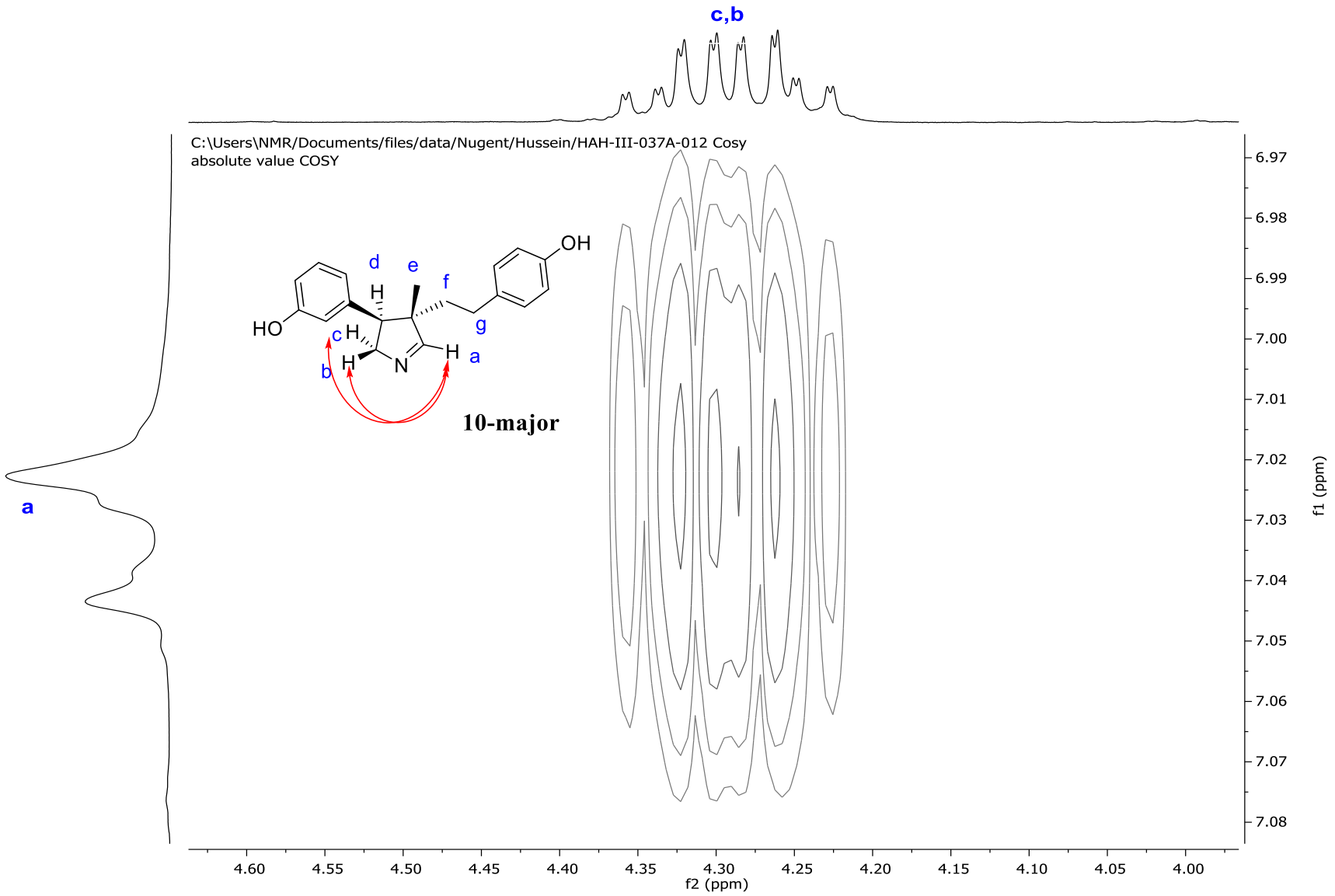
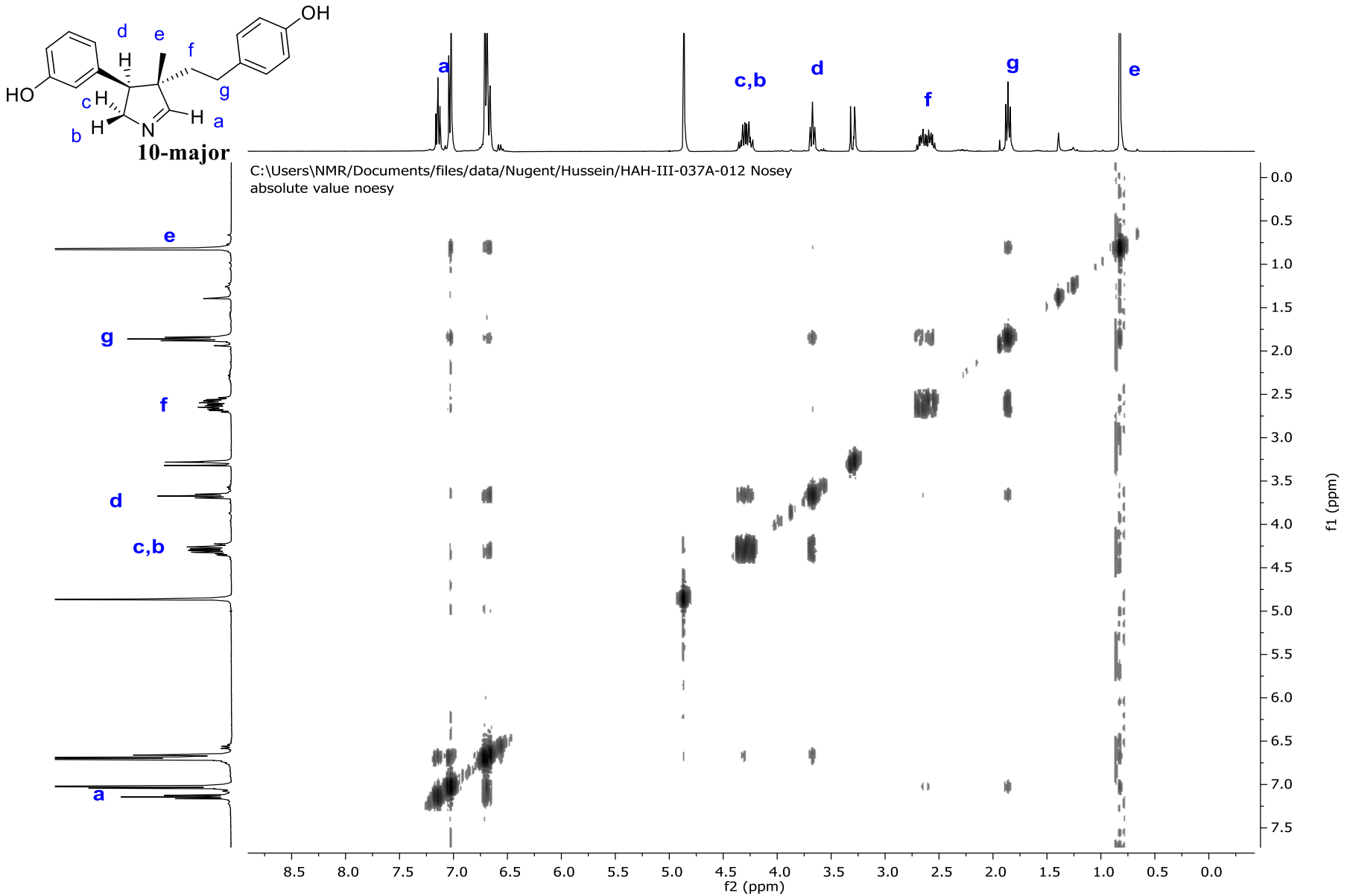
OH
HO
N
10-Major
f1 (ppm)



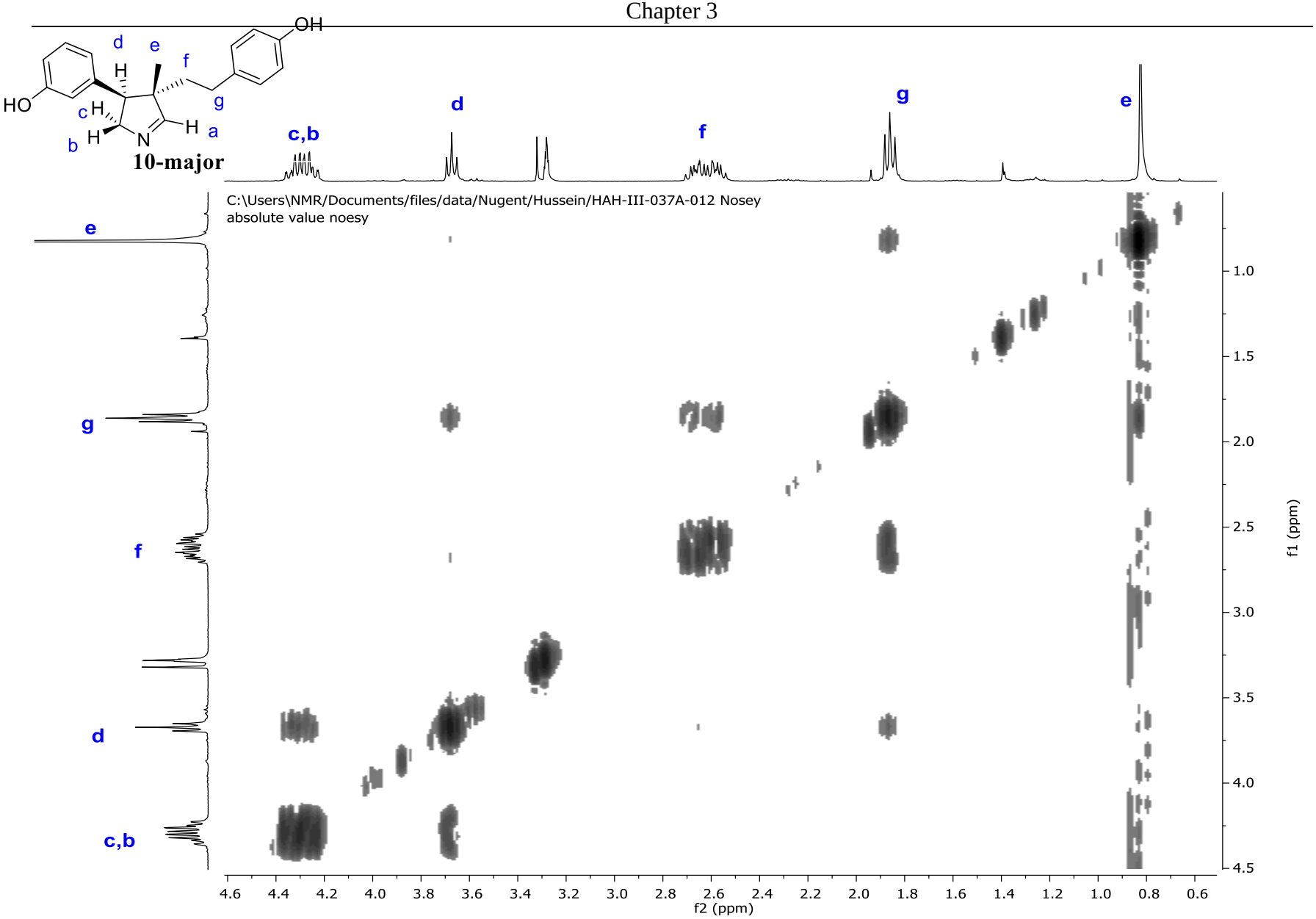
COSY (400 MHz, Methanol-*d*$_4$) of Major



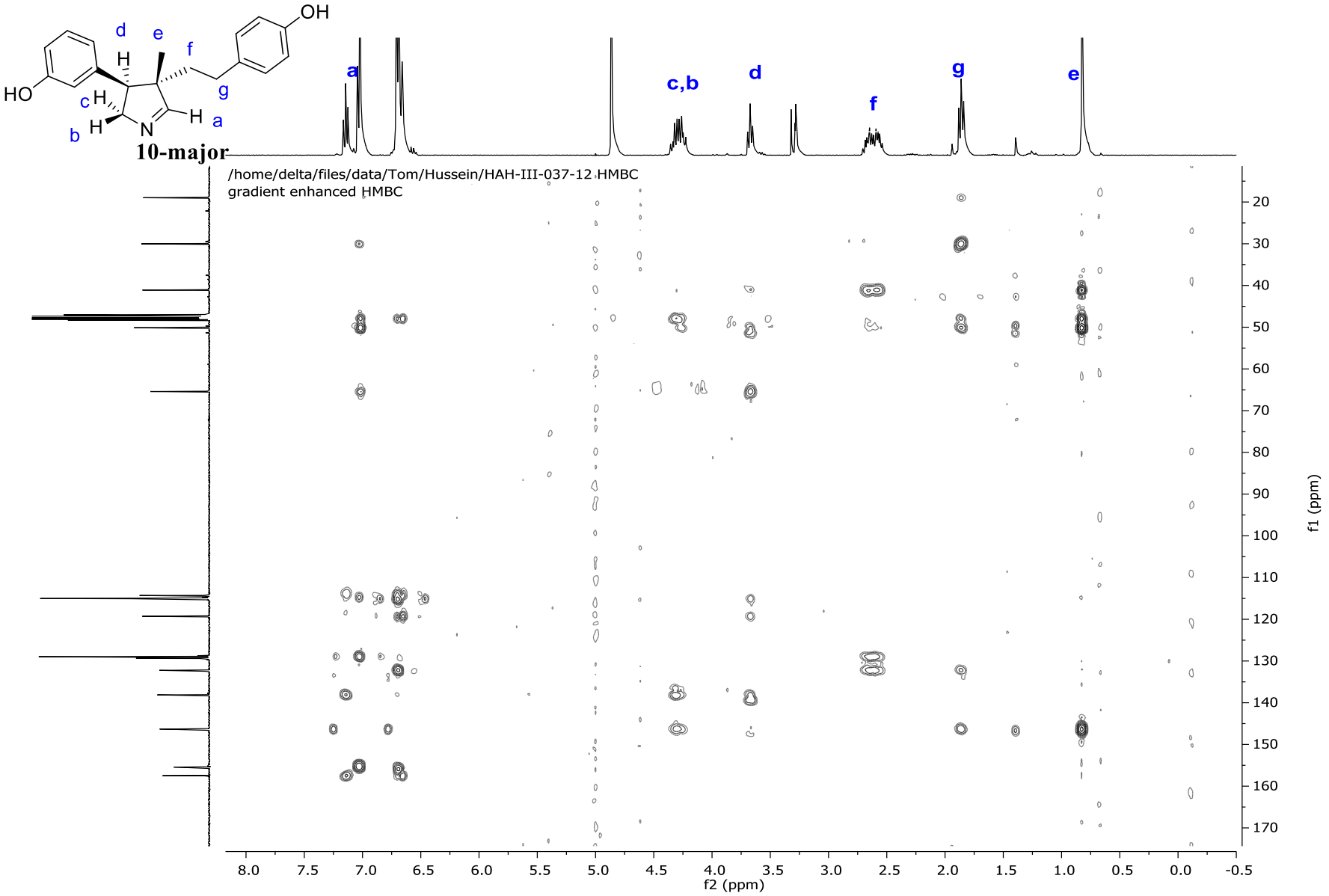
Expansion of COSY (400 MHz, Methanol-d_4) of Major



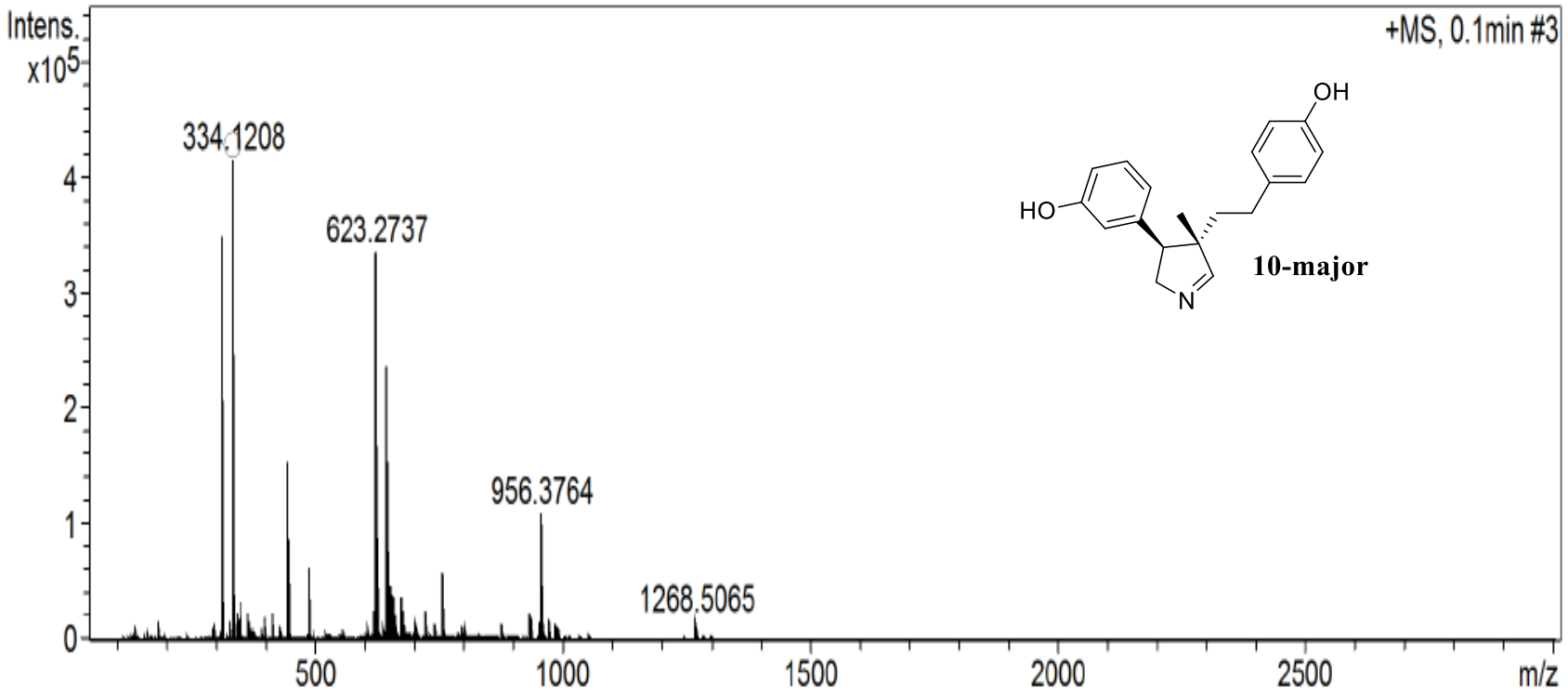
NOESY (400 MHz, Methanol-*d*$_4$) of Major



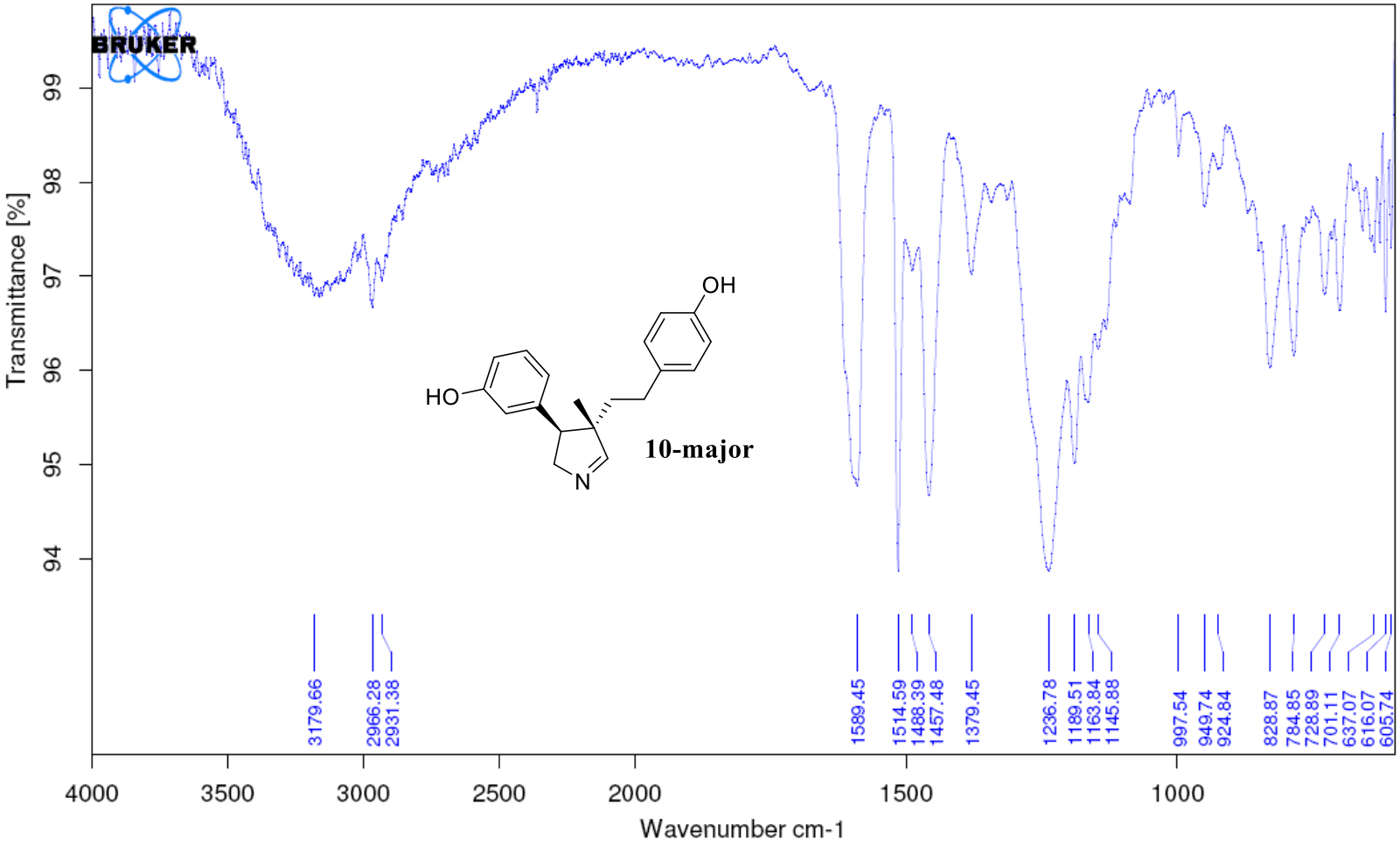
Expansion of NOESY (400 MHz, Methanol-d_4) of Major



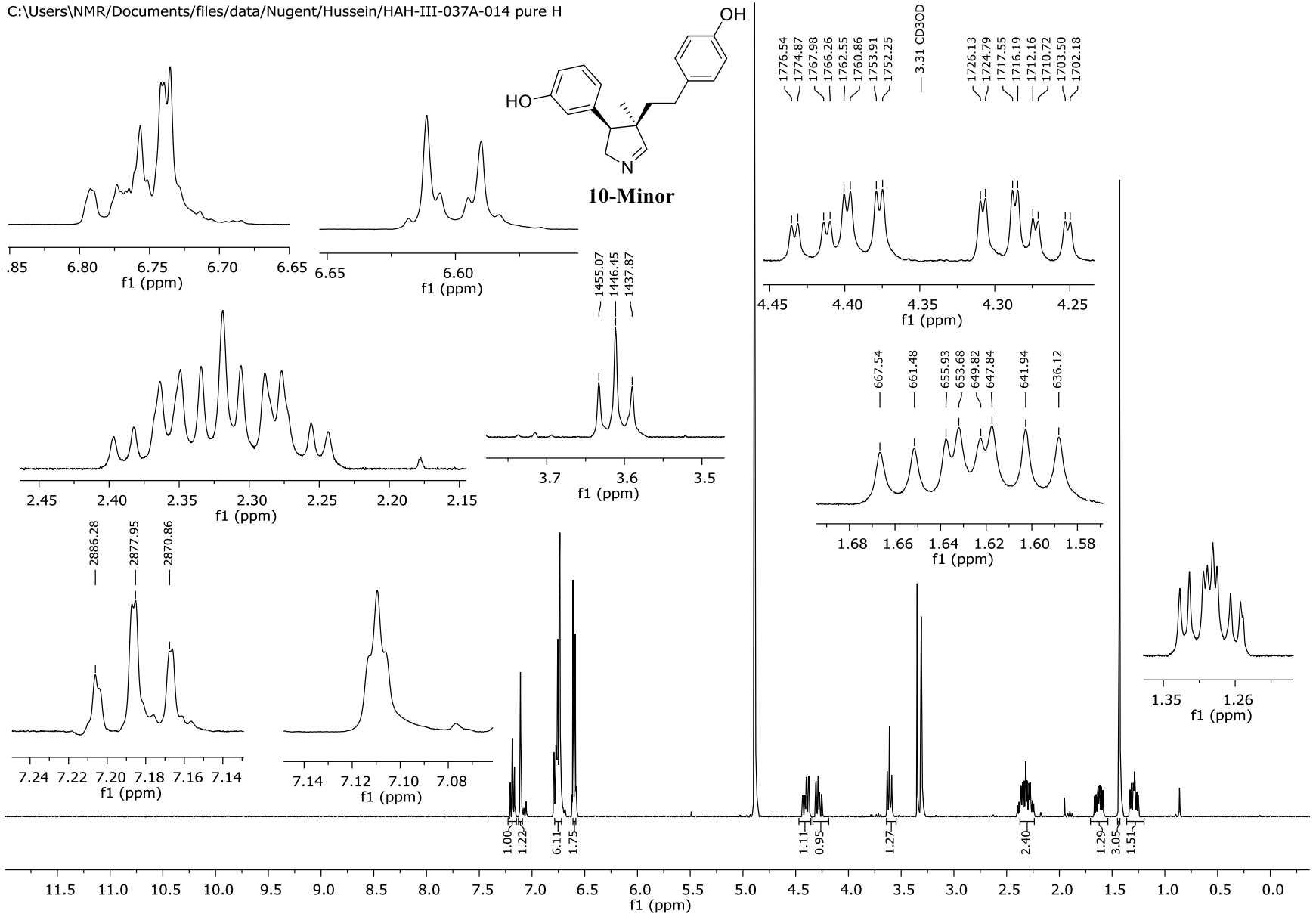
HMBC (400 MHz, Methanol-*d*$_4$) of Major

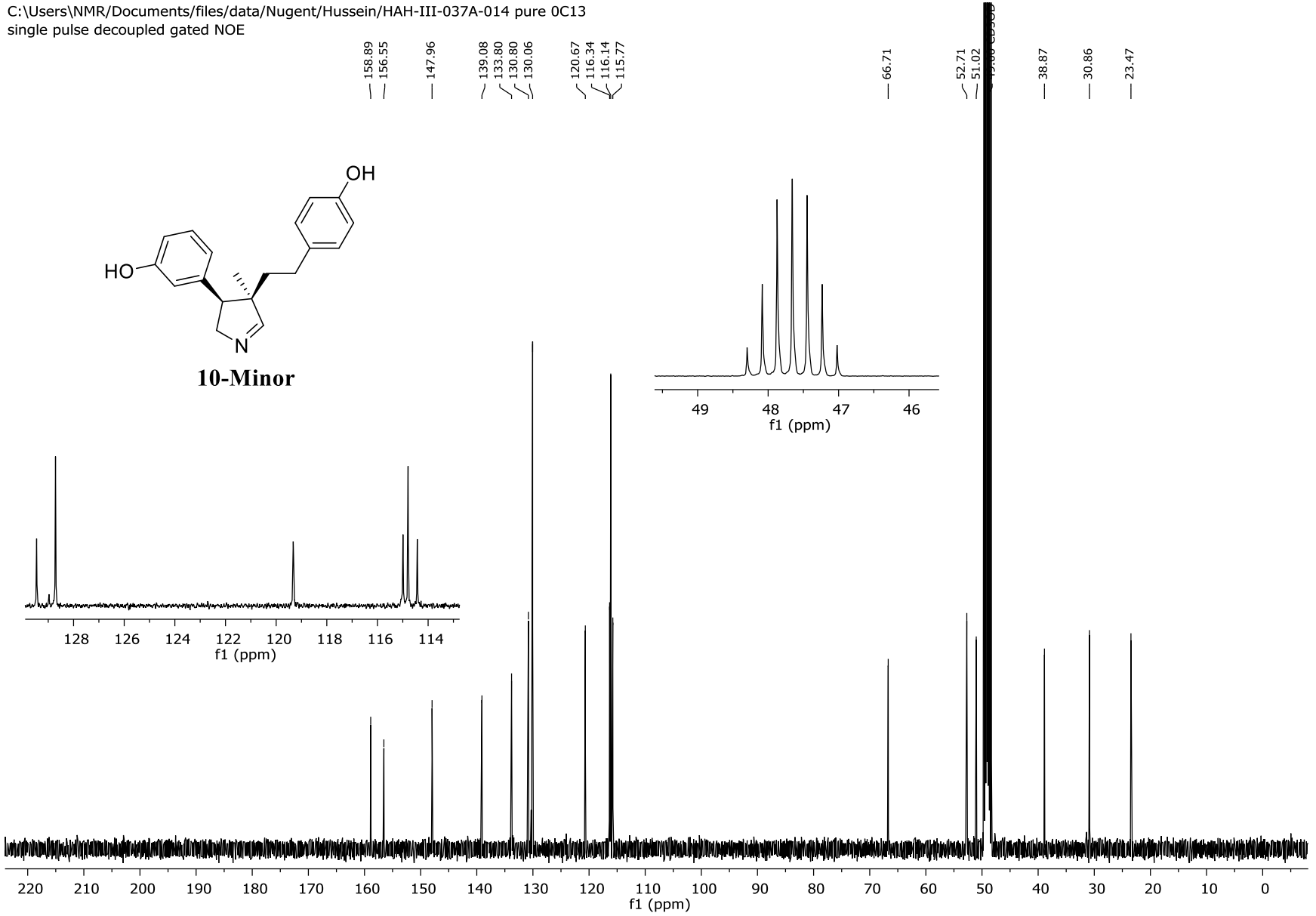


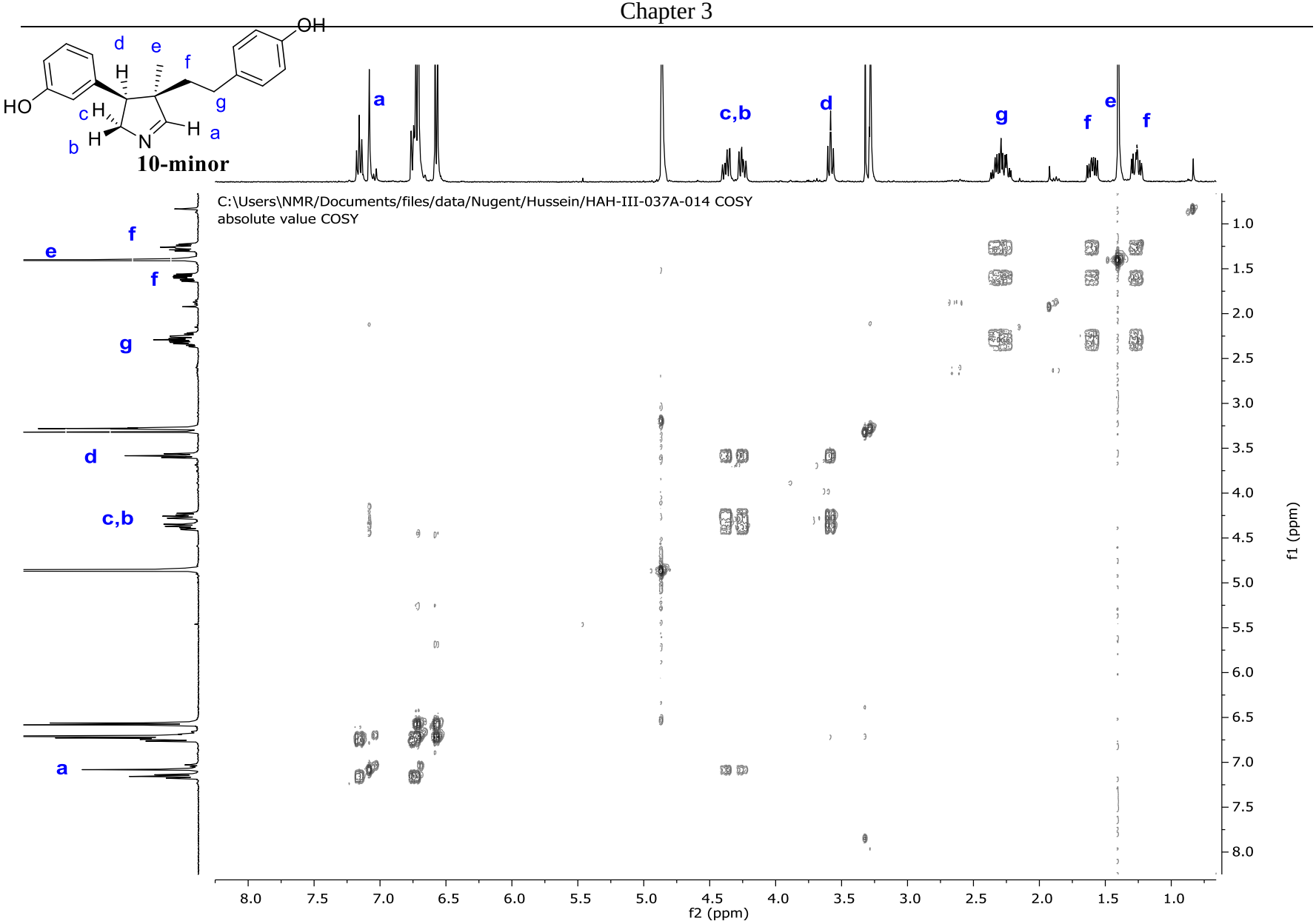
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule	err [mDa]
334.1208	1	C19H21KNO2	334.1204	-1.2	63.9	1	100.00	9.5	even	ok	-0.4



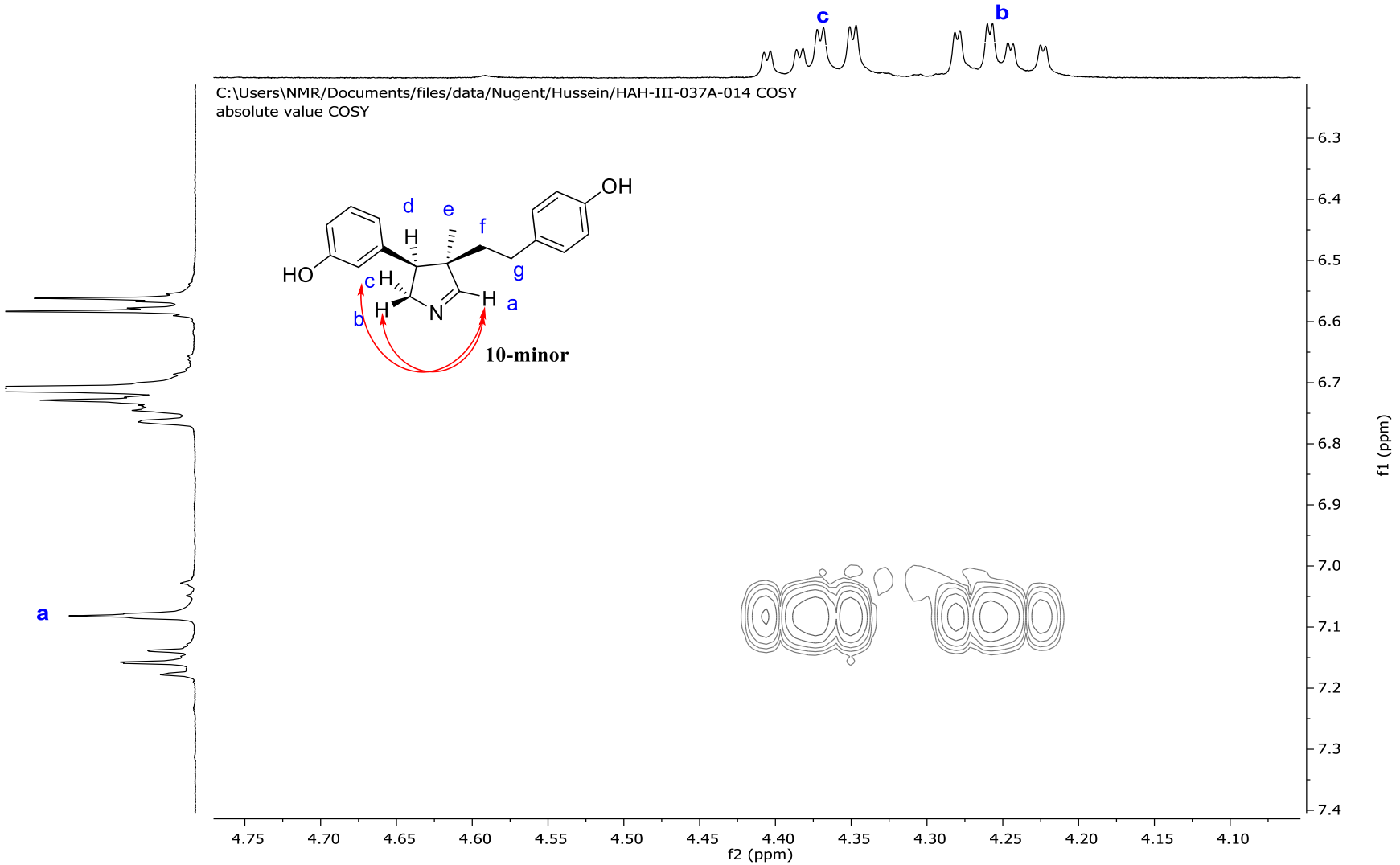
D:\DATA\Hussein\2017\HAH-III-37-12.0	HAH-III-37-12	Solid	12.04.2017


C:\Users\NMR/Documents/files/data/Nugent/Hussein/HAH-III-037A-014 pure H
OH
HO
N
10-Minor
1776.54
1774.87
1767.98
1766.26
1762.55
1760.86
1753.91
1752.25
3.31 CD3OD
1726.13
1724.79
1717.55
1716.19
1712.16
1710.72
1703.50
1702.18
1455.07
1446.45
1437.87
667.54
661.48
655.93
653.68
649.82
647.84
641.94
636.12
2886.28
2877.95
2870.86
f1 (ppm)

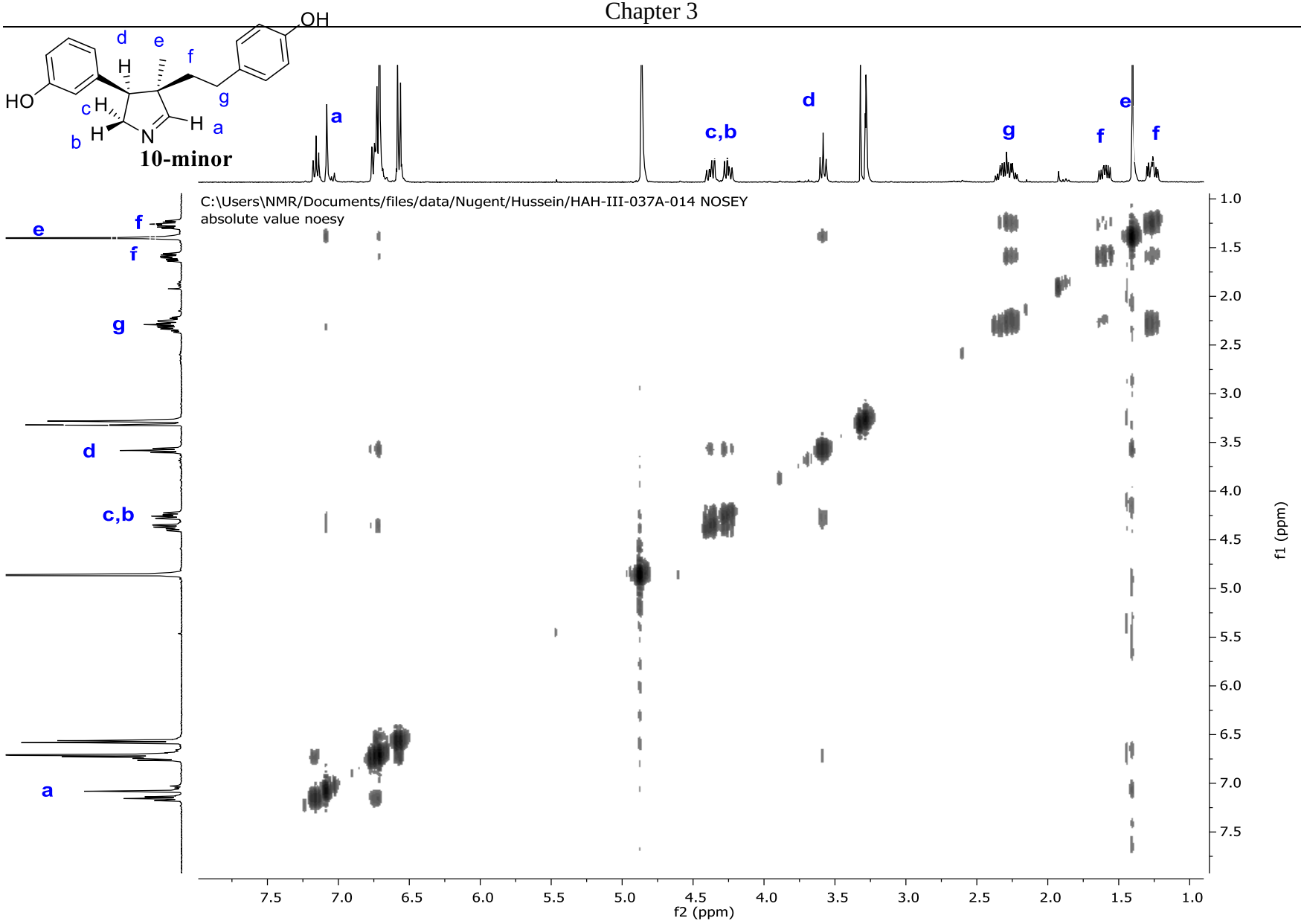

C:\Users\NMR/Documents/files/data/Nugent/Hussein/HAH-III-037A-014 pure 0C13
single pulse decoupled gated NOE
158.89
156.55
147.96
139.08
133.80
130.80
130.06
120.67
116.34
116.14
115.77
66.71
52.71
51.02
38.87
30.86
23.47
OH
HO
N
10-Minor
f1 (ppm)



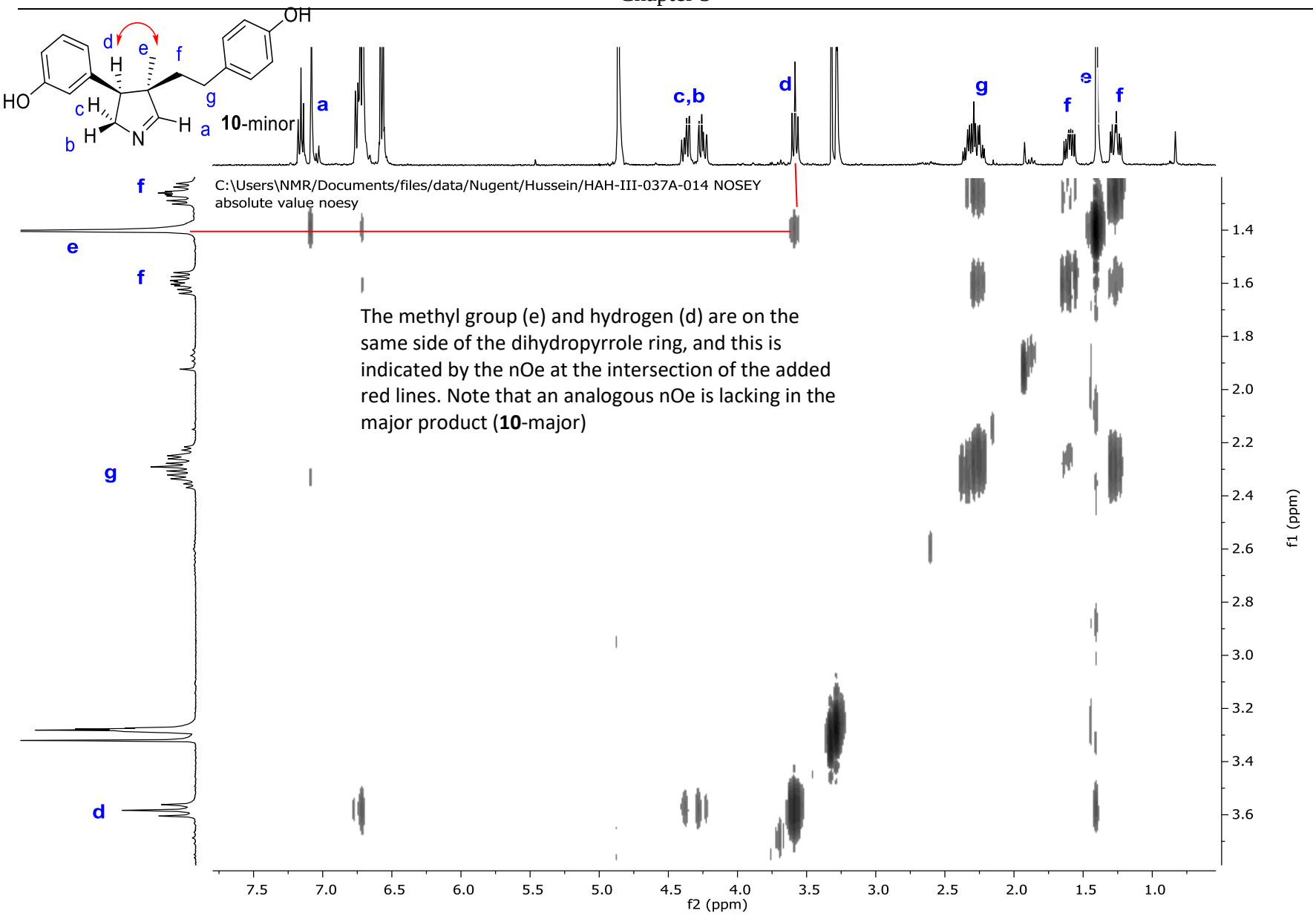
COSY (400 MHz, Methanol-*d*$_4$) of Minor



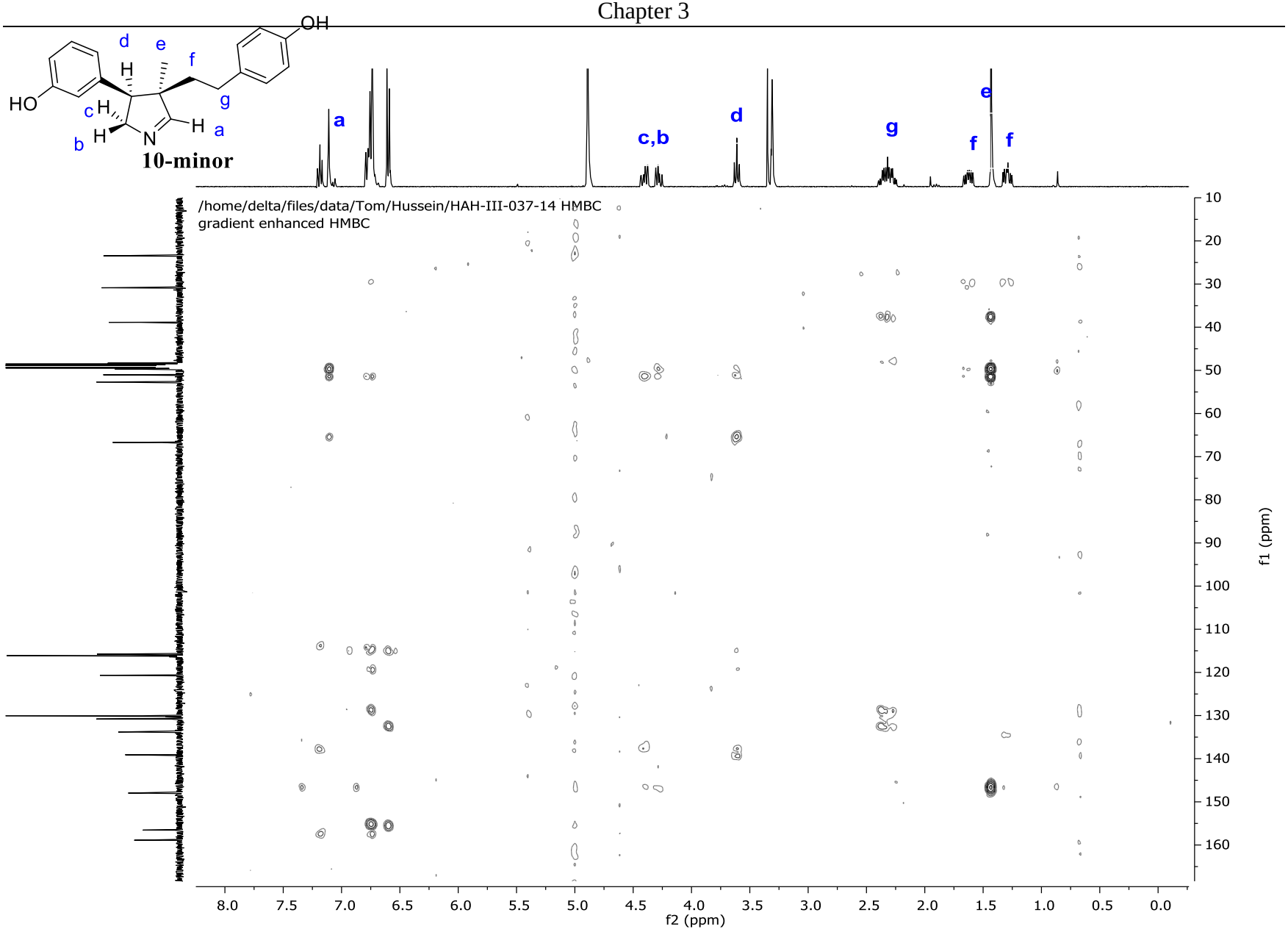
Expansion of COSY (400 MHz, Methanol-d_4) of Minor



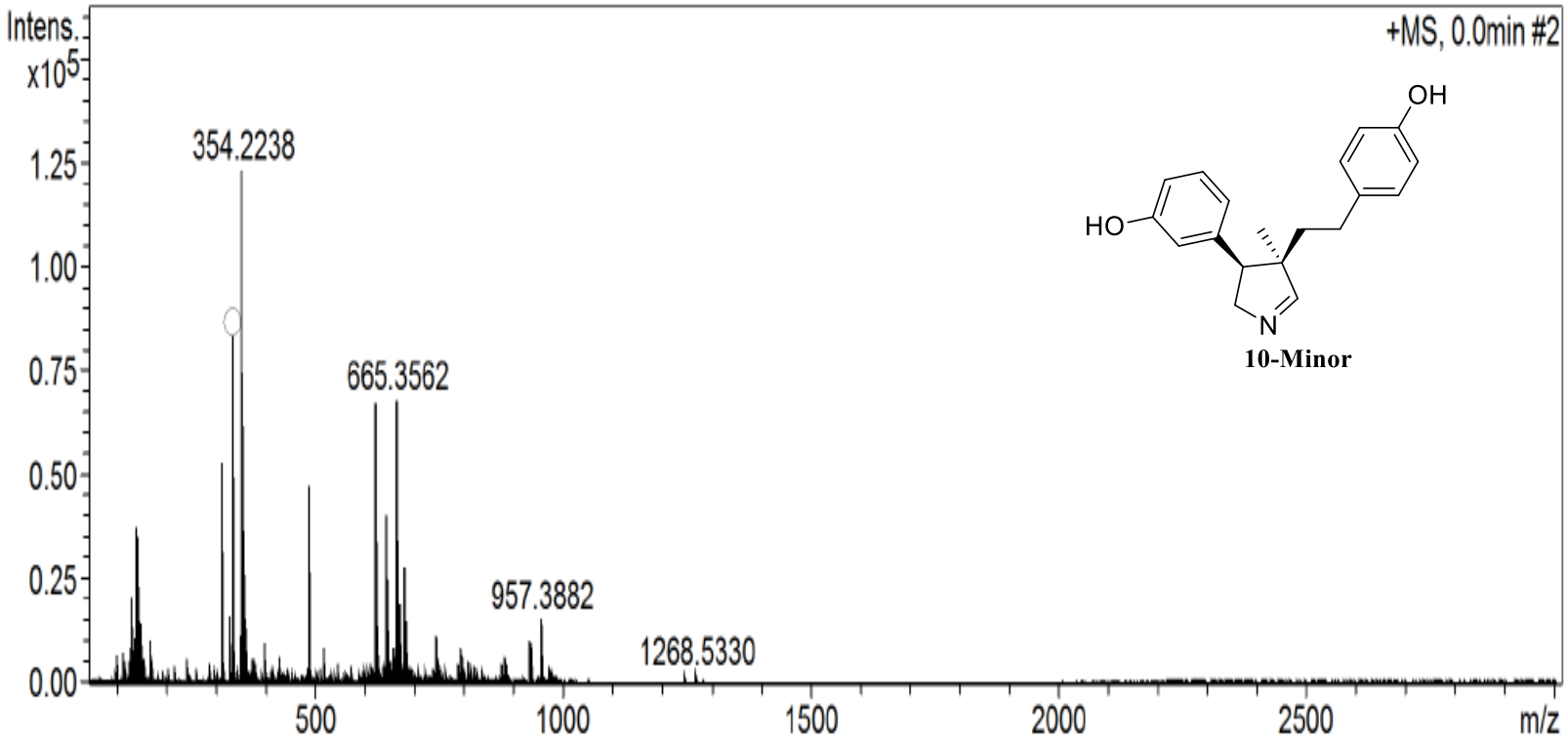
NOESY (400 MHz, Methanol-*d*$_4$) of Minor



Expansion of NOESY (400 MHz, Methanol-d_4) of Minor



HMBC (400 MHz, Methanol-*d*$_4$) of Minor

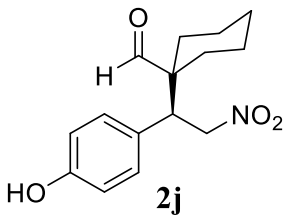


Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule	err [mDa]
334.1214	1	C19H21KNO2	334.1209	-1.4	62.9	2	100.00	9.5	even	ok	-0.5

What follows are two descriptions (**Methods A** and **B**) of how to arrive at the tertiary alcohol intermediate after three reaction steps. The difference between **Methods A** & **B** is when the single chromatography purification is performed. In **Method A** it is performed after step 1. In Method B it is performed after the tertiary alcohol is formed.

Method A: Michael product - reaction step 1

(S)-1-(1-(4-hydroxyphenyl)-2-nitroethyl)cyclohexanecarbaldehyde (2j)



2j

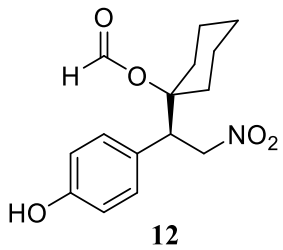
Starting material purification note: Cyclohexanecarboxaldehyde is a liquid aldehyde which readily oxidizes to the corresponding carboxylic acid (white precipitate). Therefore, the aldehyde is always freshly purified before its use. To do this, cyclohexanecarboxaldehyde (2.5 mL) is added to an aqueous solution of NaOH (10 mL, 0.5 M) in a test tube (15 mL). Gentle (no vortex) stirring is applied for 2 minutes. Most of the organic layer is then removed using a standard glass pipette and then passed through another glass pipette containing a cotton plug with 2 cm (height) of neutral alumina (no pre-drying required). ^{13}C NMR of the filtrate shows no carboxylic acid remains. This 'purified' cyclohexanecarboxaldehyde is used within 30 minutes.

To a reaction vial (5 mL) containing EtOAc/n-pentane (3:1 volume ratio, 4.5 mL, 0.8 M) is then added *O*-tert-Butyl-L-serine (MW= 161.20 g/mol, 0.10 equiv, 0.363 mmol, 58.6 mg) and KOH (MW= 56.1 g/mol, 0.15 equiv, 0.545 mmol, 30.6 mg). Within 3-5 min of stirring at room temperature a homogenous solution is noted. Cyclohexanecarboxaldehyde (MW= 112.17 g/mol, 1.50 equiv, 5.45 mmol, 611 mg) was then added. After 1 min of stirring, 4-hydroxy-β-nitrostyrene (MW= 165.15 g/mol, 1.00 equiv, 3.63 mmol, 600 mg) was added and immediately resulted in a dark red solution which was fully dissolved and transparent. It is typical that within 1-2 h a precipitate is noted. After 22-26 h TLC shows ≥95% conversion (CAM staining solution was used). Note the TLC aliquot should include some of the non-dissolved material and this aliquot needs to be further diluted with EtOAc to fully dissolve the sample before the TLC is taken. Work-up: The reaction was diluted with ethyl acetate (50 mL) and water (50 mL) was added. The organic layer is removed and the aqueous layer is further extracted (4x50 mL). The combined organic layer extracts were then washed with water (3x50ml). The organic layer was then concentrated (rotary evaporator) and then high vacuum dried (3 h). This crude Michael product was then used without any further purification for the next step.

Method A: Baeyer-Villiger oxidation - reaction step 2

Please note that peracids present a potential scale-up danger, this is why we have performed the below noted Baeyer-Villiger oxidation with the industrially preferred peracid reagent, *i.e.*, a 36-40% solution of peracetic acid in acetic acid. For a pharmaceutical example, see: L. T. Boulton, D. Brick, M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, N. Parkin, D. Rhodes, G. Ruecroft, *Org. Process Res. & Dev.* **2002**, *6*, 138-145.

(S)-1-(1-(4-hydroxyphenyl)-2-nitroethyl)cyclohexyl formate (12)



12

The crude Michael product (see the procedure above) (MW= 277.32 g/mol, 1.00 equiv, 3.63 mmol, note the number of mmol is taken from the 4-hydroxy-β-nitrostyrene starting material used in the prior step) and sodium acetate (MW= 82.03 g/mol, 2.5 equiv, 9.08 mmol, 745 mg) were added to THF/ acetic acid (3:1 volume ratio, 4.5 mL = 3.37 mL of THF and 1.13 mL of AcOH). Upon addition of peracetic acid (36-40% in acetic acid, MW= 76.05 g/mol, 2.0 equiv, 7.266 mmol, 1.47 mL, we assumed a 36% volume content for our calculation, density= 1.04 g/mL) the solution becomes homogenous within 10 min. *It is important to slowly add the peracetic acid to the reaction mixture over 5 min, without this an exotherm is noted*. The reaction solution is 0.62 M. After stirring for 16 h at room temperature full conversion is noted by TLC, no more starting material is noted. Work-up: The reaction mixture is diluted with EtOAc (5 mL) and then a saturated solution of sodium sulfite (Na_2SO_3, 25 mL) was added slowly over 2 minutes to quench the excess peracetic acid. Note: Without slow addition a large exothermic is observed. This solution was rigorously stirred for 15 min and added to a separatory funnel containing EtOAc (50 mL). The EtOAc was removed and the aqueous layer was further extracted using EtOAc (4 x 50 mL). The combined organic extracts were concentrated (rotary evaporator, water bath temperature = 35 ^{0}C) and then high vacuum dried, with stirring, to evaporate the vast majority of the acetic acid, generally 6 h of high vacuum treatment. This crude formate ester product was used for the next reaction step without any further purification. Note that during formate ester formation, hydrolysis of the formate ester was always observed in ~7-10% yield. The just described extractive work-up allowed the tertiary alcohol hydrolysis product to be fully extracted. Formate ester: R_f= 0.31 (EtOAc/pet ether 20:80), alcohol: R_f= 0.26 (EtOAc/pet ether 20:80)

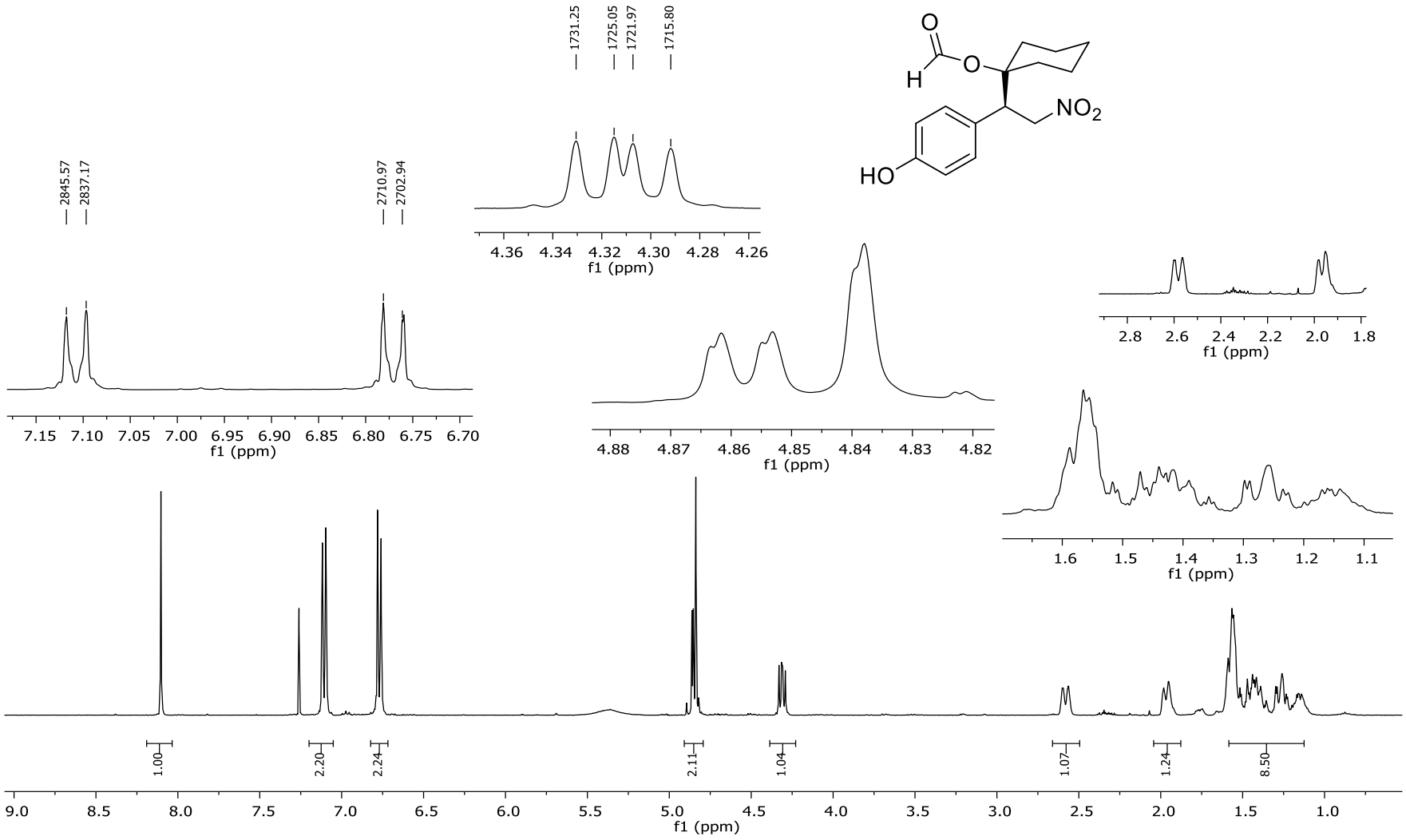
Note: this reaction was repeated to confirm structure of formate ester by spectroscopy. The crude material was directly loaded to a silica gel column for purification (2.5 x 10 cm, diameter by height) and eluted using the following solvents: pet ether (100 mL); then EtOAc/pet ether (10:90, 250 mL; then 25:75, 500 mL). The desired product (MW= 293.32 g/mol, 1.20 mmol, 352 mg, 74% yield) was obtained as yellow oil. Formate ester: Rf= 0.31 (20:80 EtOAc/pet ether), Alcohol: R_f= 0.26 (20:80 EtOAc/pet ether)

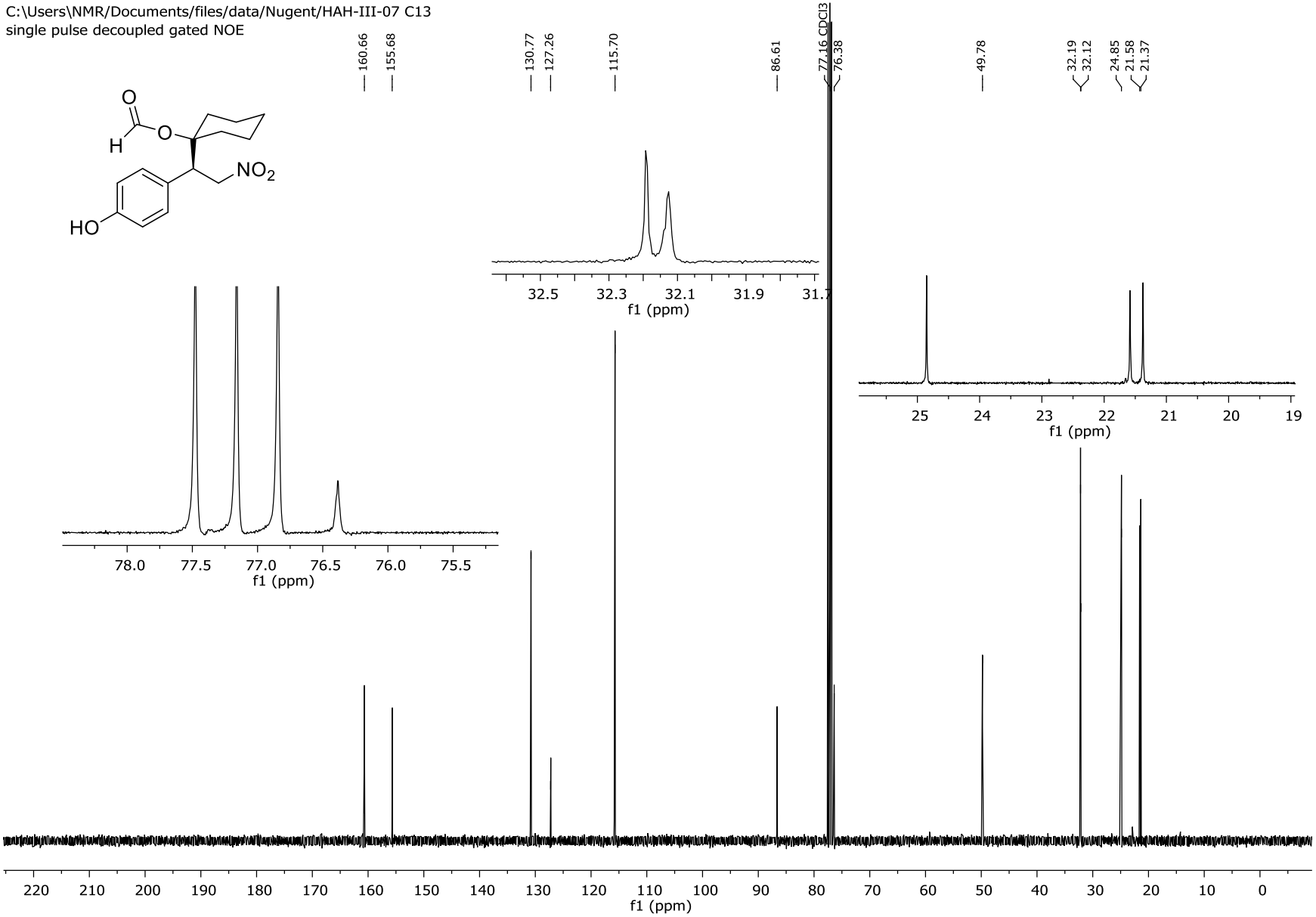
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): δ 1.38 (m, 8H), 1.97 (m, 1H), 2.58 (m, 1H), 4.31 (dd, J = 9.3, 6.2 Hz, 1H), 4.86 (m, 2H), 6.77 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 8.10 (s, 1H).

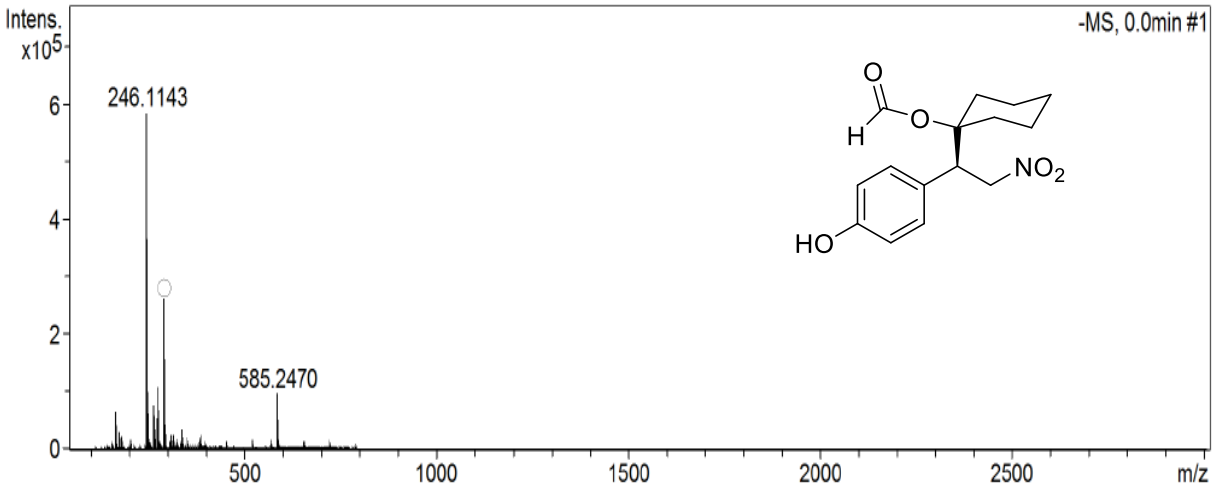
^{13}C NMR (100 MHz, CDCl3) (ppm): δ 21.4, 21.6, 24.8, 32.1, 32.2, 49.8, 76.4, 77.2, 86.6, 115.7, 127.3, 130.8, 155.7, 160.7.

(ESI-TOF)-MS m/z: $[M-H^+]^-$Calcd for $C_{15}H_{19}NO_5$ 292.1187; Found 292.1190.

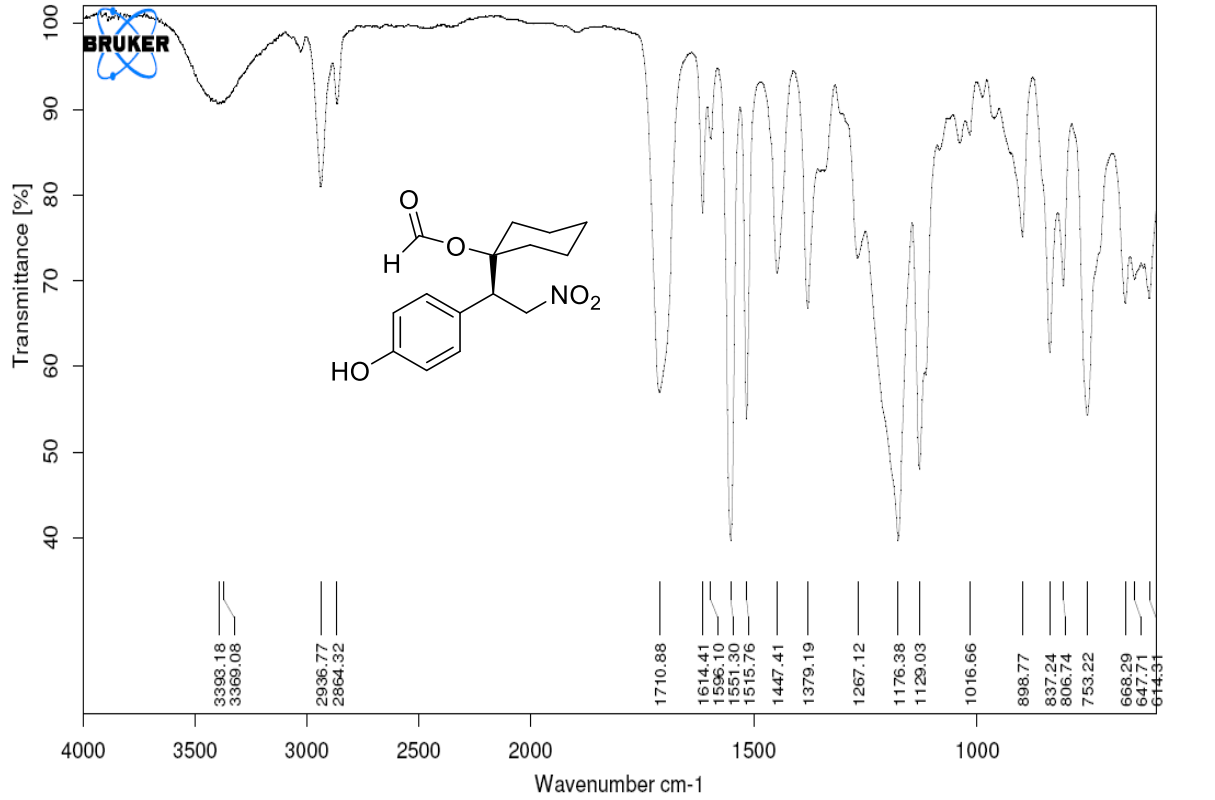
MS (EI), *m/z* (relative intensity): 120.94, 147.88, 245.88, 291.92.

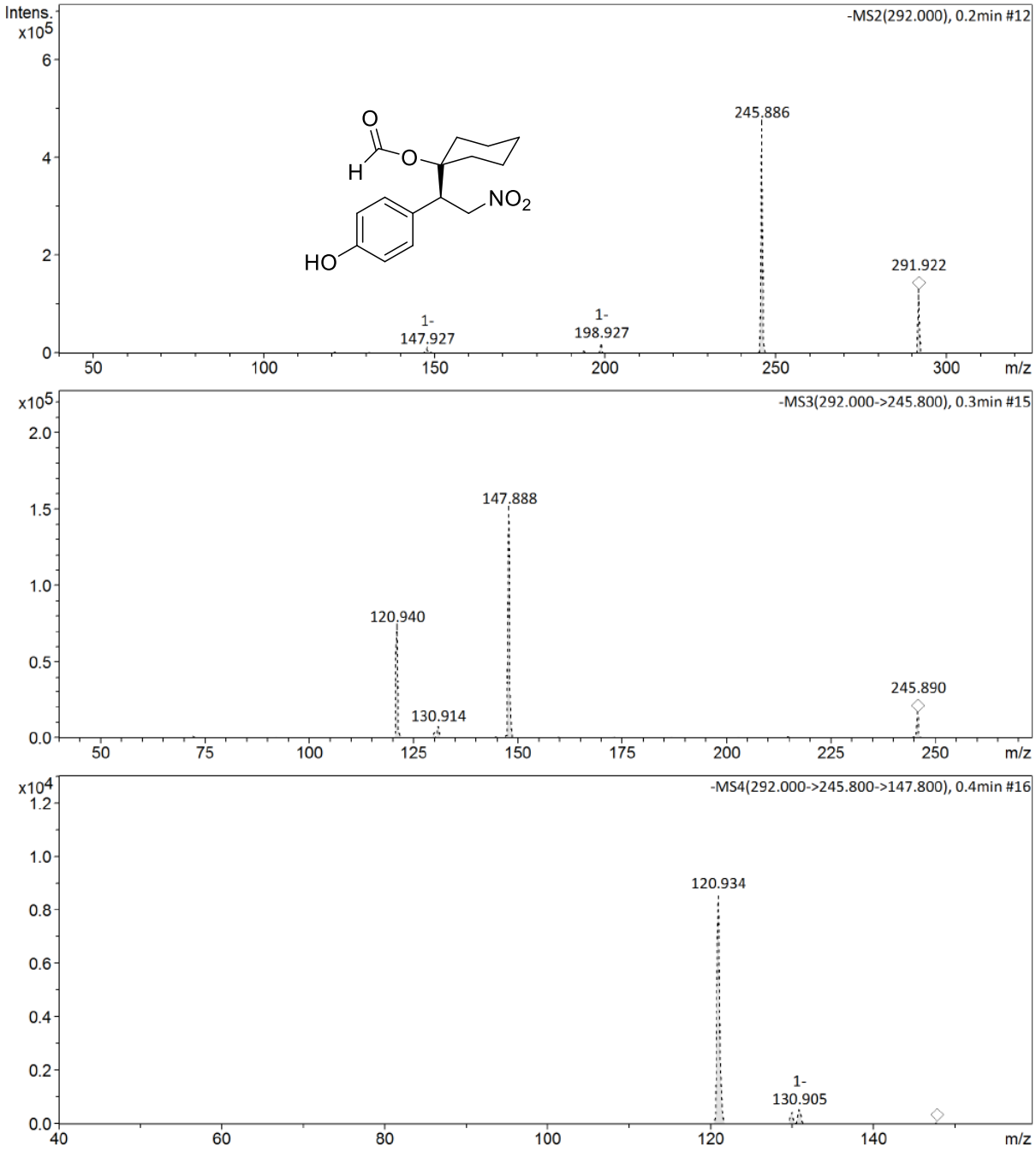

/home/delta/files/data/Tom/Hussein/HAH-III-04-11B
1H
2845.57
2837.17
2710.97
2702.94
1731.25
1725.05
1721.97
1715.80
O
H
O
NO2
HO
7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75 6.70
f1 (ppm)
4.36 4.34 4.32 4.30 4.28 4.26
f1 (ppm)
4.88 4.87 4.86 4.85 4.84 4.83 4.82
f1 (ppm)
2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)
1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)
1.00
2.20
2.24
2.11
1.04
1.07
1.24
8.50
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)


C:\Users\NMR/Documents/files/data/Nugent/HAH-III-07 C13
single pulse decoupled gated NOE
160.66
155.68
130.77
127.26
115.70
86.61
77.16 CDCl3
76.38
49.78
32.19
32.12
24.85
21.58
21.37
O
H
O
NO2
HO
f1 (ppm)



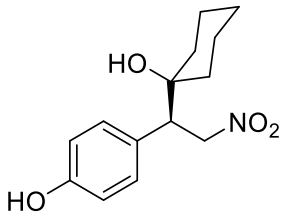
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule	err [mDa]
292.1187	1	C15H18NO5	292.1190	1.1	4.5	1	100.00	7.5	even	ok	0.3




Intens.
x10^5
-MS2(292.000), 0.2min #12
245.886
291.922
1-
147.927
1-
198.927
m/z
x10^5
-MS3(292.000->245.800), 0.3min #15
147.888
120.940
130.914
245.890
m/z
x10^4
-MS4(292.000->245.800->147.800), 0.4min #16
120.934
1-
130.905
m/z

Method A: Hydrolysis (tertiary alcohol formation) – reaction step 3

(S)-4-(1-(1-hydroxycyclohexyl)-2-nitroethyl) phenol (13)



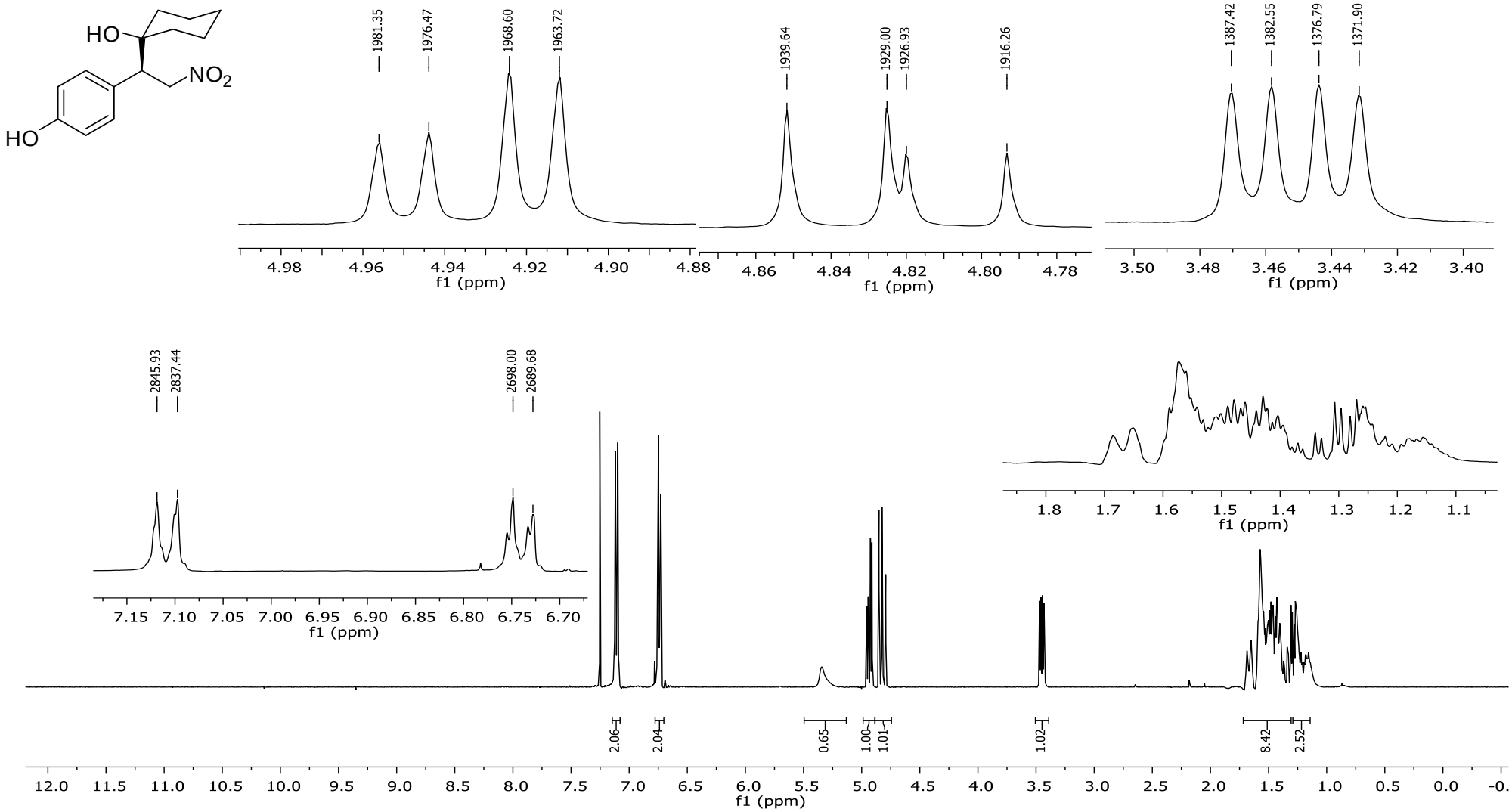
The crude formate ester (MW= 293.32 g/mol, 1.00 equiv, 3.63 mmol, note the number of mmol is taken from the 4-hydroxy-β-nitrostyrene starting material used in the step 1), see the reaction procedure before this one, was dissolved in a mixture of THF/ water (3:1 volume ratio, 18 mL = 13.5 mL of THF and 4.5 mL of water, 0.2 M). Note that this crude formate ester starting material already contains a small quantity of the desired alcohol product. Sodium hydroxide (MW= 40.0 g/mol, 5.0 equiv, 18.16 mmol, 726 mg) addition resulted in dark red reaction mixture. 4 h of stirring at room temperature showed no more starting material (TLC). Work-up: The reaction was quenched by adding aqueous HCl (2.0 M, 10 mL) and the aqueous layer was immediately extracted with dichloromethane (5×50 mL). The combined solvent extracts were concentrated by rotary evaporator and the resulting oil was purified. Silica gel chromatography (2.5 cm x 10 cm, diameter by height) allowed isolation of the pure alcohol using the following solvents: EtOAc/petroleum ether (20:80, 250 mL; then 25:75, 200 mL; then 35:65, 400 mL). The overall yield of the tertiary alcohol (MW= 265.32 g/mol, 1.458 mmol, 387 mg) is 40% yield based on the 4-hydroxy-β-nitrostyrene (3.63 mmol, limiting reagent used in step 1, Method A) was obtained as light yellow oil. R_f= 0.26 (EtOAc/petroleum ether 20:80).

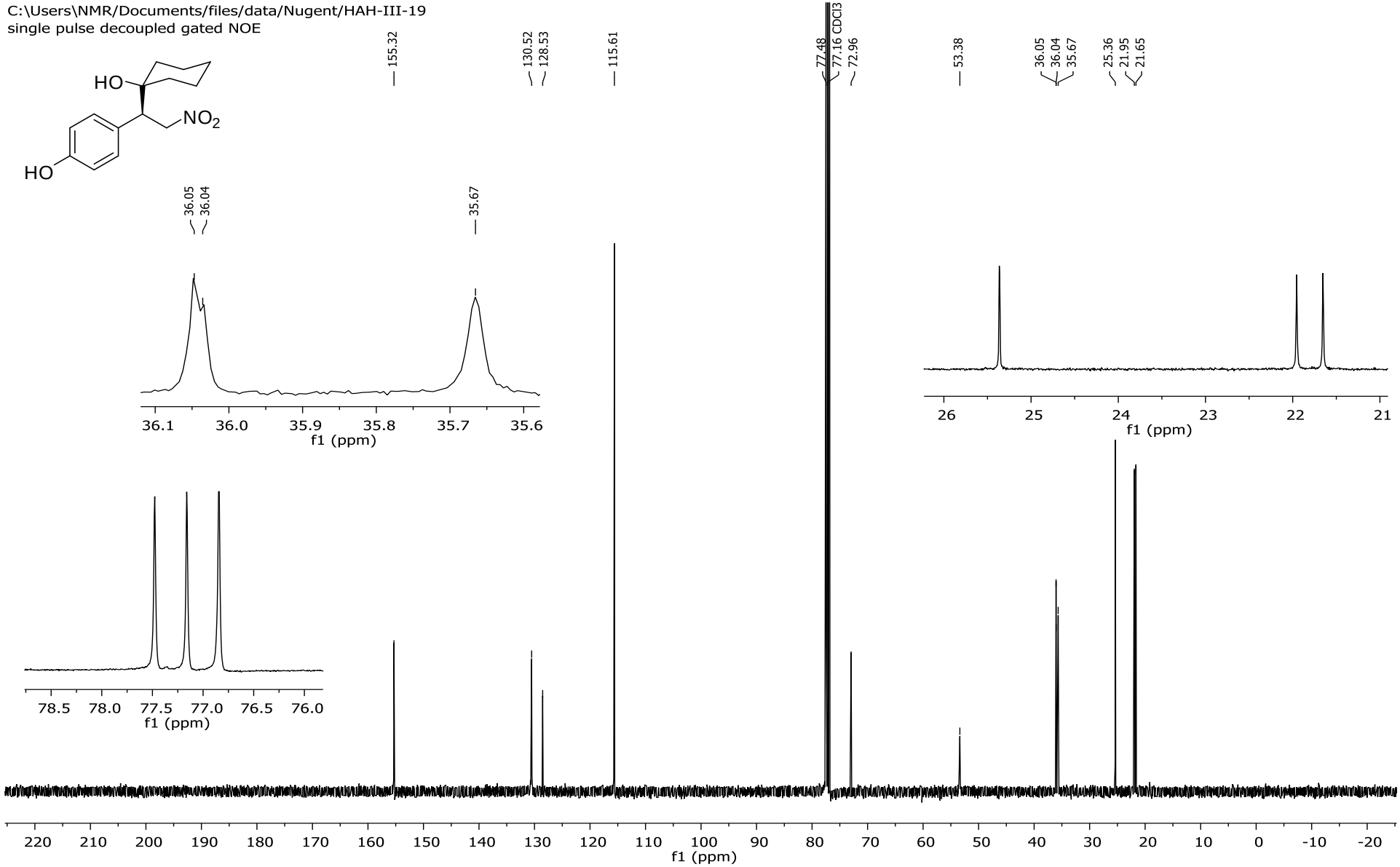
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): δ 1.10-1.70 (m, 10H), 3.45 (dd, J= 10.6, 4.9 Hz, 1H), 4.82 (dd, J= 12.7, 10.6 Hz, 1H), 4.93 (dd, J = 12.8, 4.9 Hz, 1H), 5.34 (bs, 1H, OH), 6.74 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H).

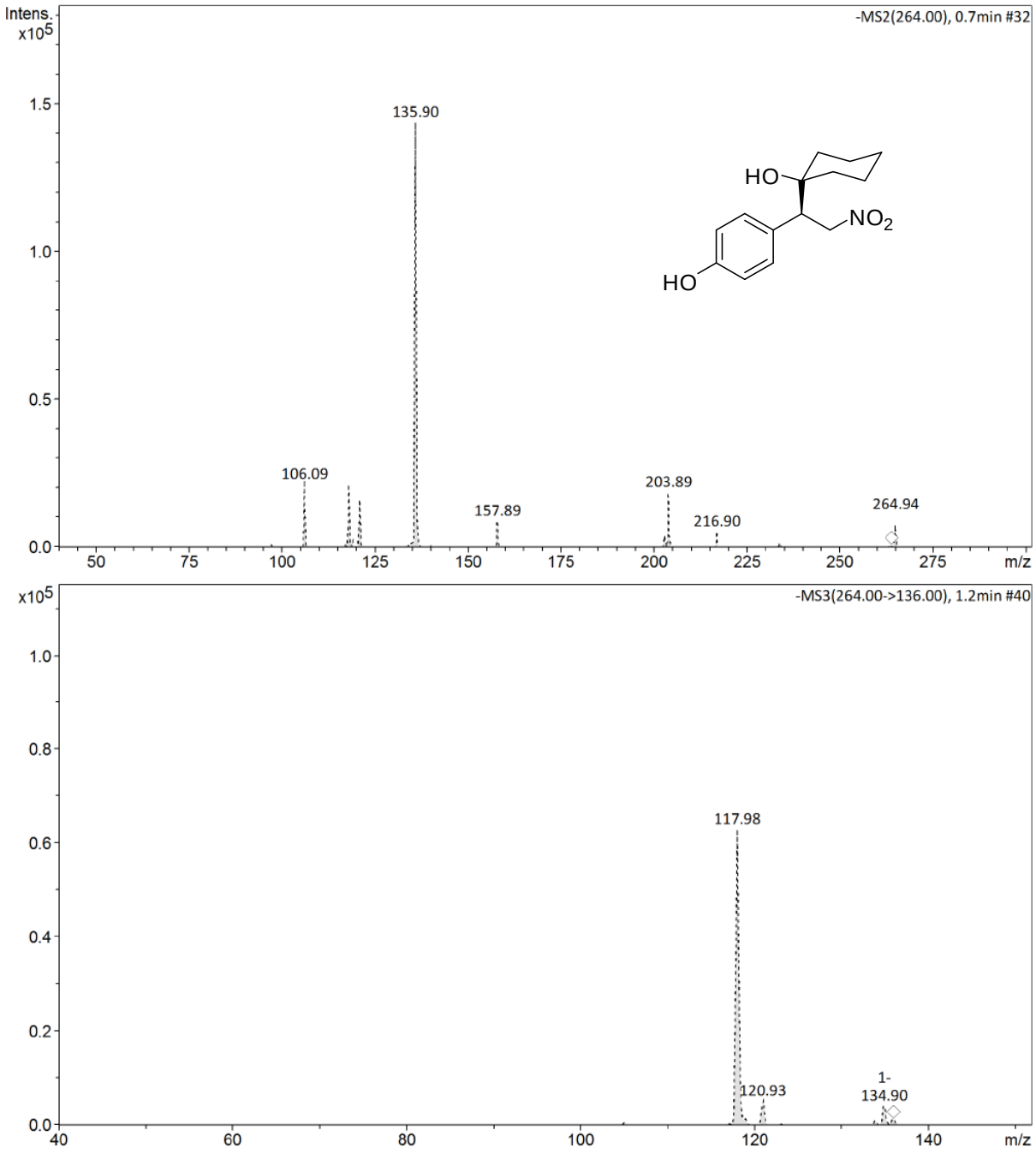
^{13}C NMR (100 MHz, $CDCl_3$) (ppm): δ 21.7, 22.0, 25.4, 35.7, 36.0, 36.1, 53.4, 73.0, 115.6, 128.5, 130.5, 155.3.

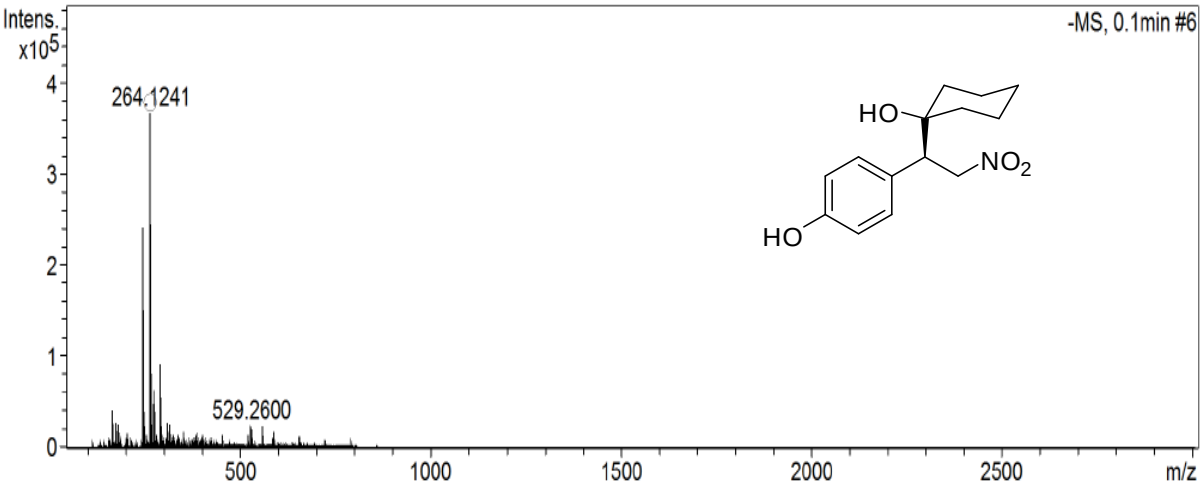
(ESI-TOF)-MS m/z: $[M-H^+]^-$ Calcd for $C_{14}H_{19}NO_4$ 264.1241; Found 264.1241.

MS (EI), *m/z* (relative intensity): 106.09, 117.98, 135.90, 203.89.

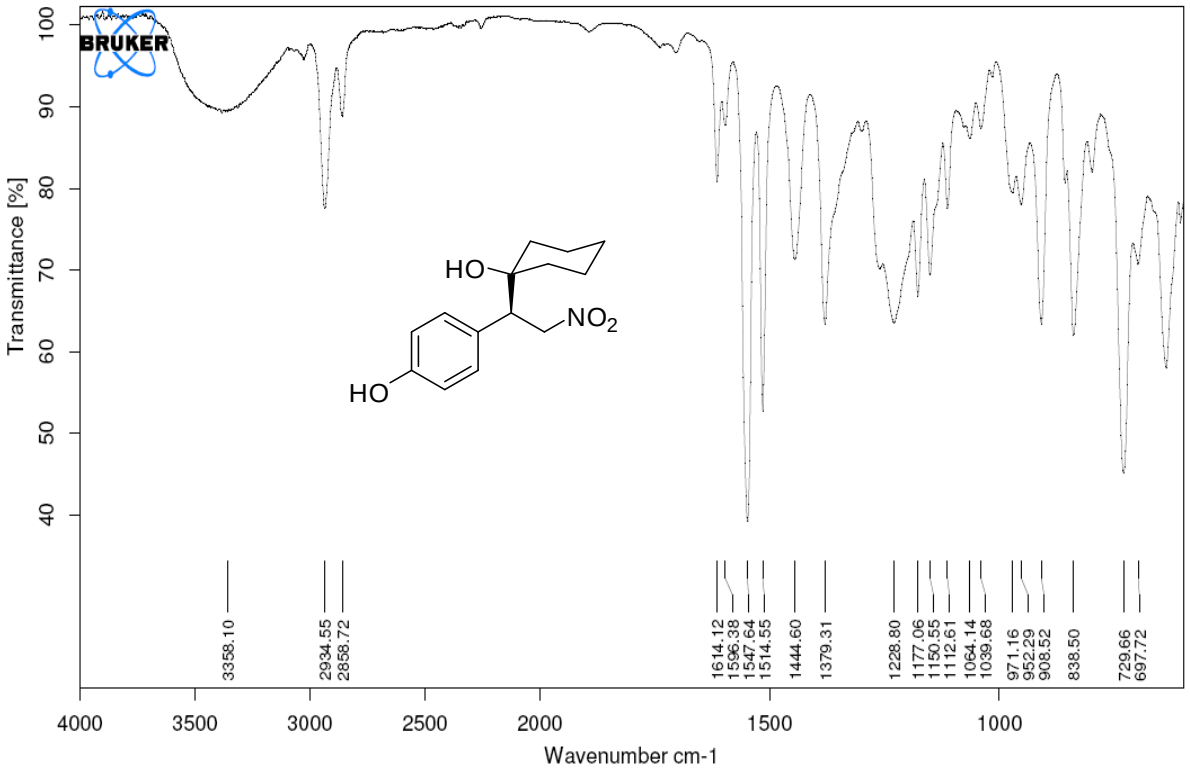

/home/delta/files/data/Tom/Hussein/HAH-III-019
1H
HO
NO2
HO
1981.35
1976.47
1968.60
1963.72
1939.64
1929.00
1926.93
1916.26
1387.42
1382.55
1376.79
1371.90
2845.93
2837.44
2698.00
2689.68
f1 (ppm)
2.06
2.04
0.65
1.00
1.01
1.02
8.42
2.52


C:\Users\NMR/Documents/files/data/Nugent/HAH-III-19
single pulse decoupled gated NOE
HO
NO2
HO
155.32
130.52
128.53
115.61
77.48
77.16 CDCl3
72.96
53.38
36.05
36.04
35.67
25.36
21.95
21.65
f1 (ppm)


Intens.
x10^5
-MS2(264.00), 0.7min #32
135.90
106.09
157.89
203.89
216.90
264.94
HO
NO2
HO
m/z
x10^5
-MS3(264.00->136.00), 1.2min #40
117.98
120.93
1-
134.90
m/z

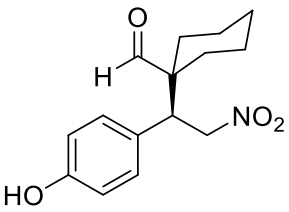


Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
264.1241	1	C14H18NO4	264.1241	-0.0	94.8	2	11.41	6.5	even	ok



Method B: Michael product - reaction step 1

(S)-1-(1-(4-hydroxyphenyl)-2-nitroethyl)cyclohexanecarbaldehyde (2j)



Follow exactly the same procedure as noted in Method A (step 1). Note this reaction was also performed on the same exact reaction scale as noted in Method A, thus it was performed with 600 mg of 4-hydroxy-β-nitrostyrene (MW= 165.15 g/mol, 1.00 equiv, 3.63 mmol). Deviation from Method A follows. Once the reaction was complete, *aqueous work-up was **not** performed.* Instead, the reaction mixture was directly loaded onto a silica gel column for purification (2.5 x 17 cm, diameter by height) and eluted using the following solvents: petroleum ether (100 mL); then EtOAc/ petroleum ether (10:90, 250 mL; then 25:75, 500 mL). The desired product (MW= 277.32 g/mol, 3.14 mmol, 871 mg, 86% yield) was obtained as a light yellow viscous oil. Note our experience shows that this compound is actually a solid, but is more often noted as a viscous oil. R_f= 0.27 (EtOAc/petroleum ether, 15:85). Chiral HPLC (OD-H column, *i*-PrOH/Heptane (15:85), flow rate = 0.8 mL/min, λ = 254 nm), t_{minor}= 15.6 min and t_{major} = 29.8 min, 94% ee = 97:3 enantiomeric ratio.

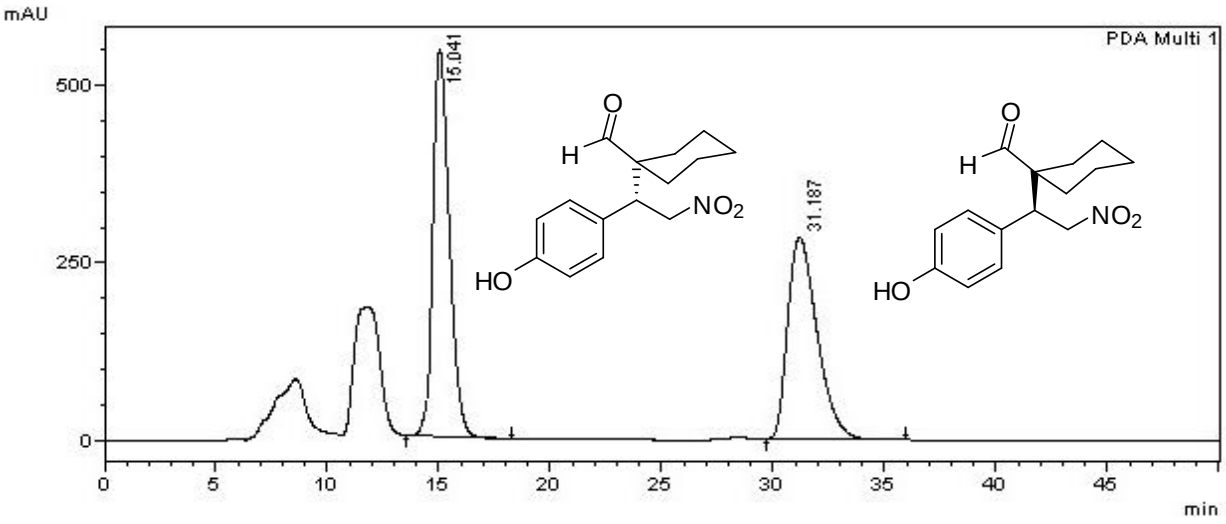
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): δ 1.05-1.27 (m, 4H), 1.37 (dt, J= 12.6, 3.7, 1H), 1.55-1.71 (m, 3H), 1.88 (m, 1H), 2.06 (m, 1H), 3.48 (dd, J= 11.0, 4.8 Hz, 1H), 4.70 (dd, J= 13.0, 4.8 Hz, 1H), 4.76 (dd, J= 12.9, 11.1 Hz, 1H), 5.29 (bs, 1H), 6.74 (d, J= 8.6 Hz, 2H), 6.98 (d, J= 8.6 Hz, 2H), 9.53 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) (ppm): δ 22.7, 22.8, 25.2, 29.9, 31.1, 49.9, 51.6, 76.4, 115.7, 126.8, 130.4, 155.6, 207.9.

(ESI-TOF)-MS m/z: $[M-H^+]^-$ Calcd for $C_{15}H_{19}NO_4$ 276.1235; Found 276.1241.

MS (EI), *m/z* (relative intensity): 107.96, 133.93, 121.01, 163.84, 169.88.

Racemic Michael Product



Peak Table

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.041	28167563	545727	51.981	65.767
2	31.187	26020930	284058	48.019	34.233
Total		54188493	829785	100.000	100.000

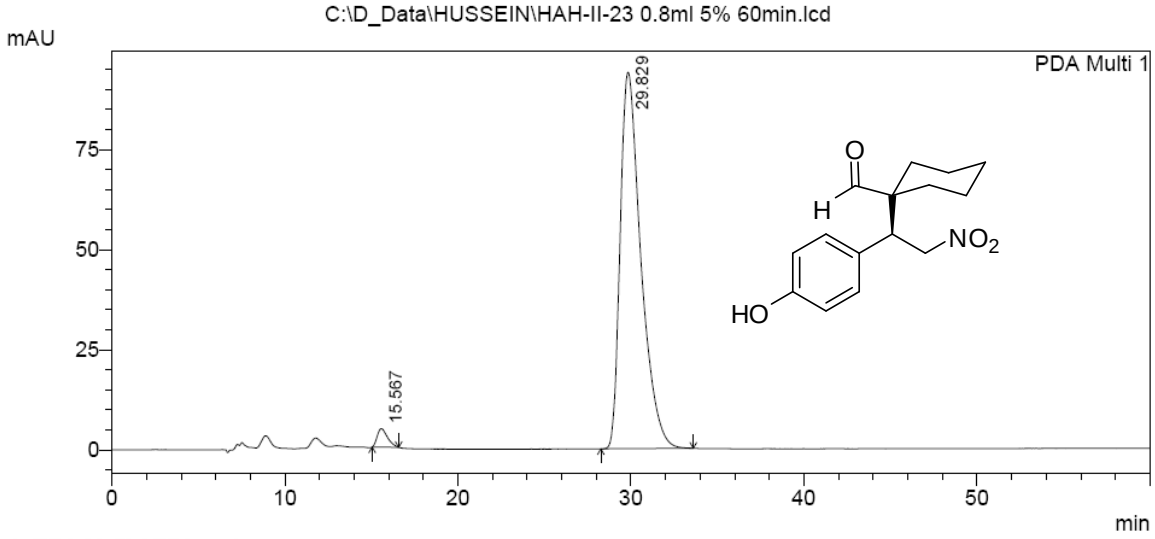
Enantioenriched Michael Product

==== Shimadzu LCsolution Analysis Report ====

C:\D_Data\HUSSEIN\HAH-II-23 0.8ml 5% 60min.lcd

Acquired by	: Admin
Sample Name	: HAH-II-23
Sample ID	:
Vail #	: 1
Injection Volume	: 50 uL
Data File Name	: HAH-II-23 0.8ml 5% 60min.lcd
Method File Name	: 15% 0.8 ml, 60 min.lcm
Batch File Name	: batch13.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/8/2016 5:49:07 PM
Data Processed	: 4/8/2016 6:49:11 PM

<Chromatogram>

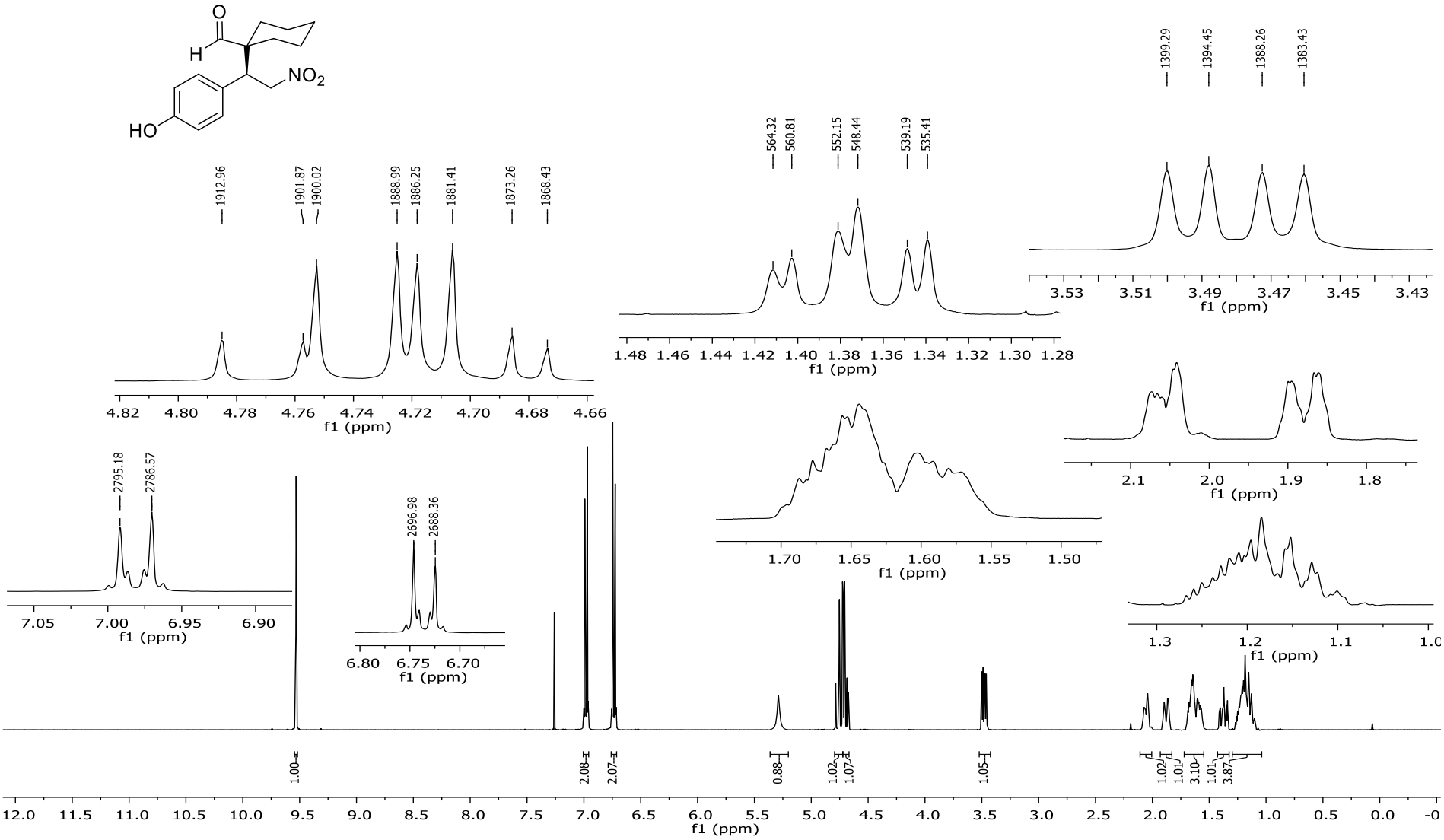


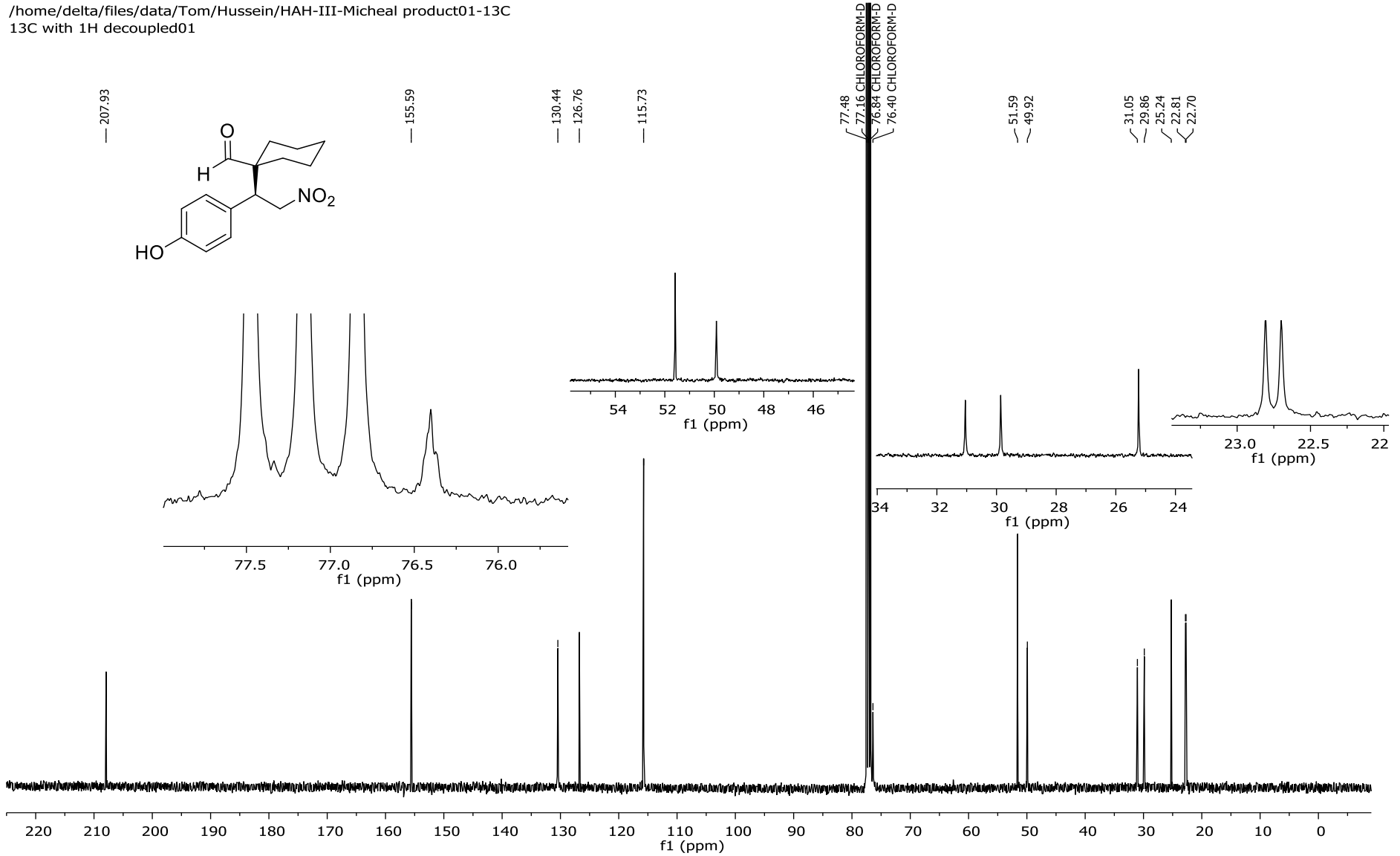
1 PDA Multi 1/254nm 4nm

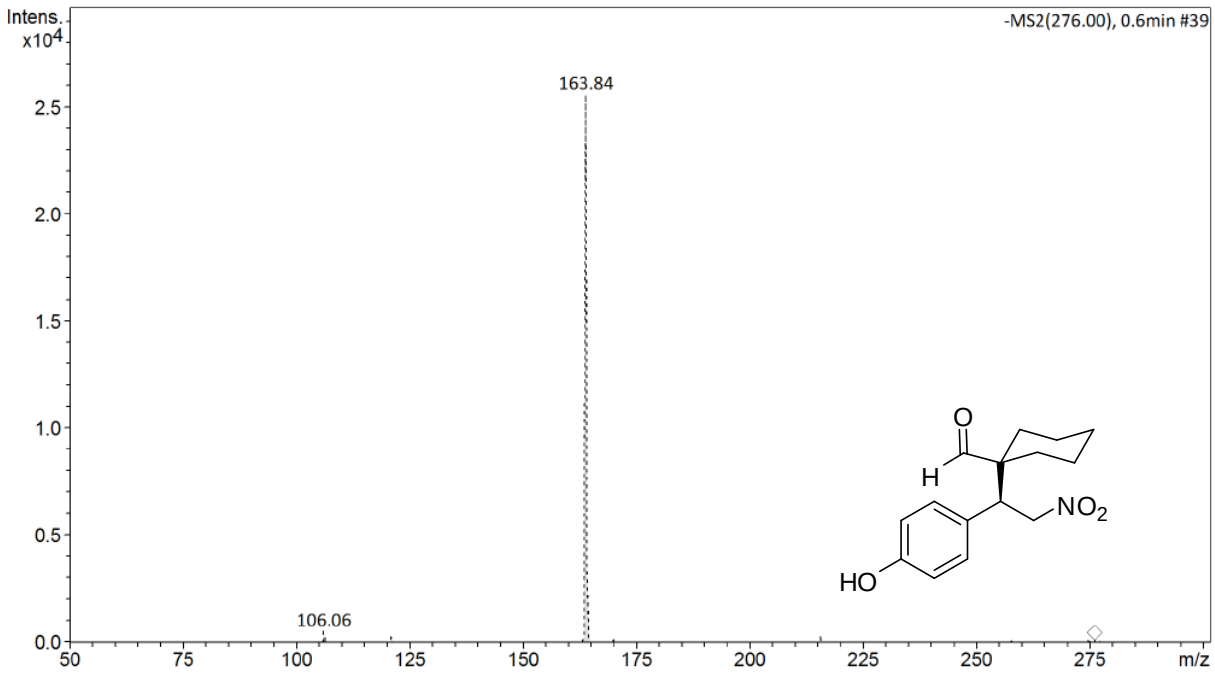
PeakTable

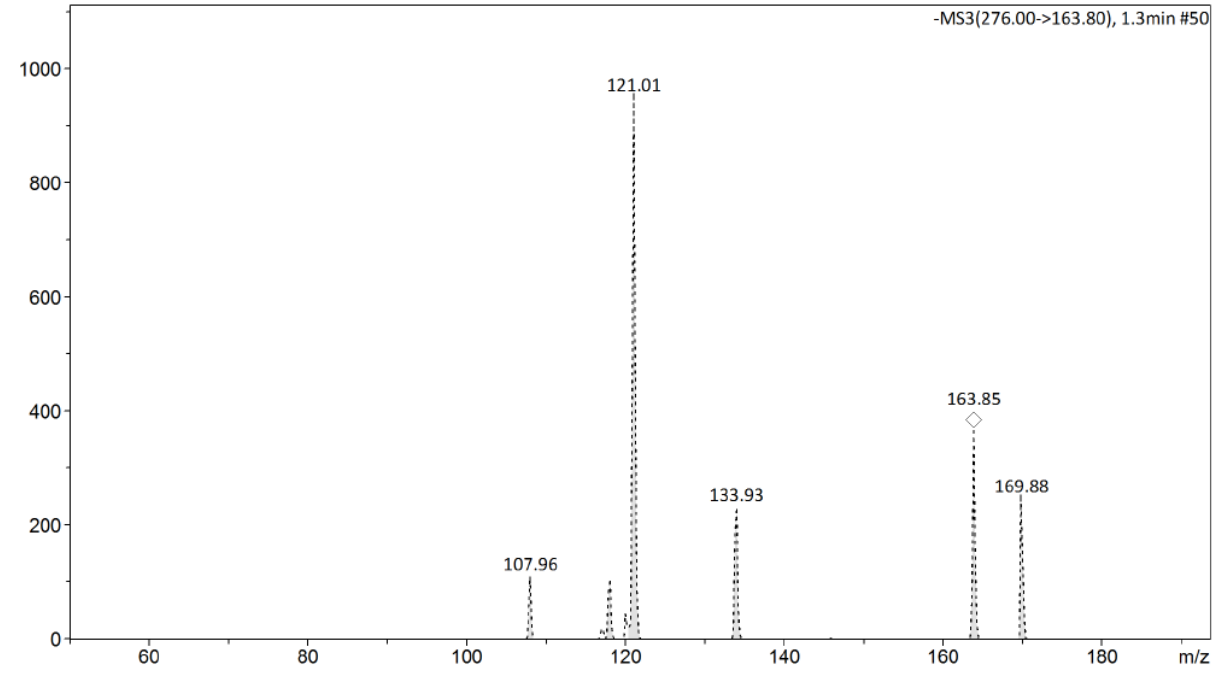
PDA Ch1 254nm 4nm

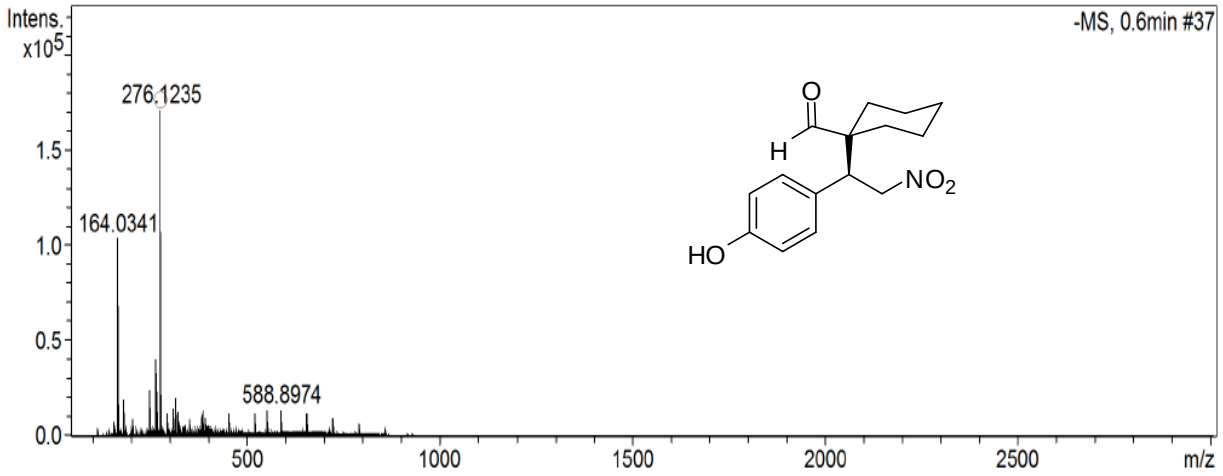
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.567	191636	4637	2.392	4.699
2	29.829	7819947	94046	97.608	95.301
Total		8011583	98683	100.000	100.000


O
H
NO2
HO
1912.96
1901.87
1900.02
1888.99
1886.25
1881.41
1873.26
1868.43
564.32
560.81
552.15
548.44
539.19
535.41
1399.29
1394.45
1388.26
1383.43
2795.18
2786.57
2696.98
2688.36
f1 (ppm)
1.00
2.08
2.07
0.88
1.02
1.07
1.05
1.02
1.01
3.10
1.01
3.87

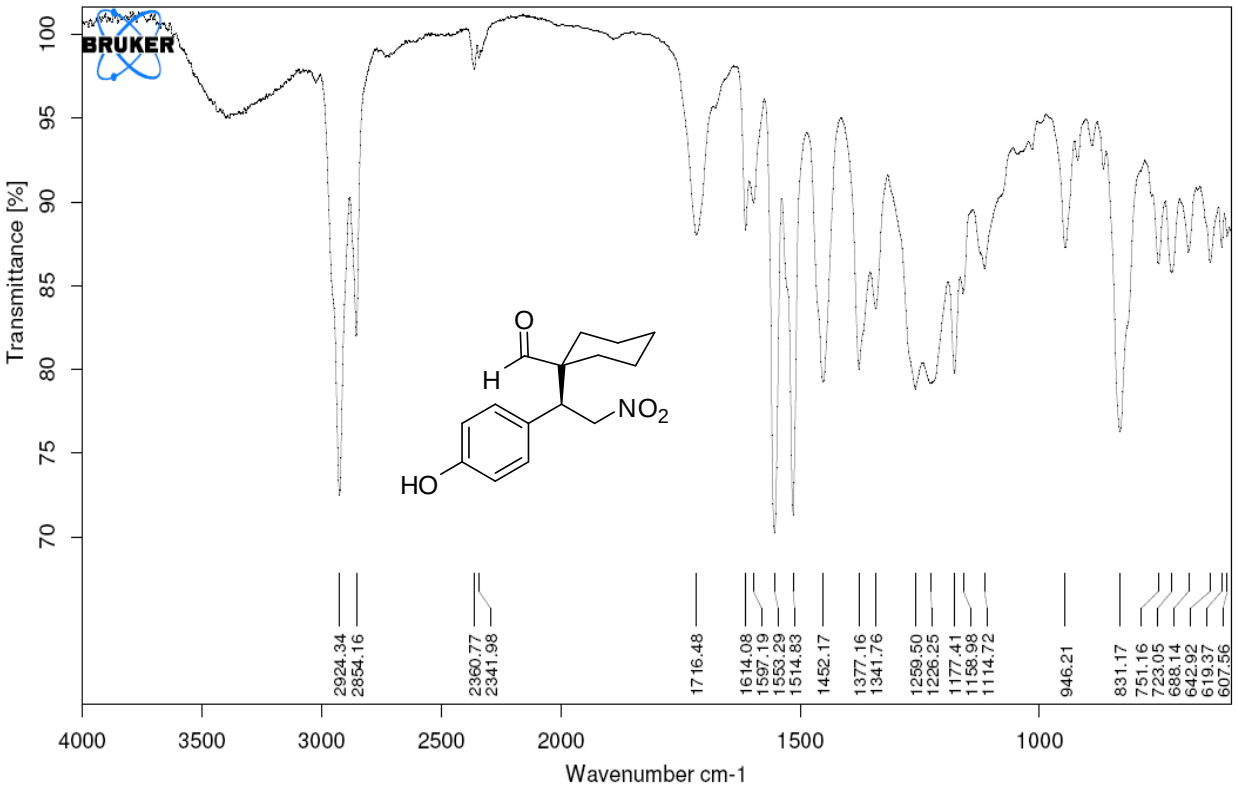

/home/delta/files/data/Tom/Hussein/HAH-III-Micheal product01-13C
13C with 1H decoupled01
207.93
155.59
130.44
126.76
115.73
77.48
77.16 CHLOROFORM-D
76.84 CHLOROFORM-D
76.40 CHLOROFORM-D
51.59
49.92
31.05
29.86
25.24
22.81
22.70
O
H
NO2
HO
f1 (ppm)


Intens.
x10^4
-MS2(276.00), 0.6min #39
163.84
106.06
O
H
NO2
HO
m/z


-MS3(276.00->163.80), 1.3min #50
121.01
163.85
169.88
133.93
107.96
m/z



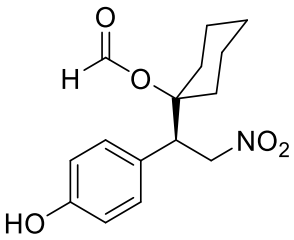
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e¯ Conf	N-Rule
276.1235	1	C15H18NO4	276.1241	2.3	16.2	1	100.00	7.5	even	ok



Method B: Baeyer-Villiger oxidation – reaction step 2

Please note that peracids present a potential scale-up danger, this is why we have performed the below noted Baeyer-Villiger oxidation with the industrially used reagent, i.e., a 36-40% solution of peracetic acid in acetic acid. For a pharmaceutical example, see: L. T. Boulton, D. Brick, M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, N. Parkin, D. Rhodes, G. Ruecroft, *Org. Process Res. & Dev.* **2002**, *6*, 138-145.

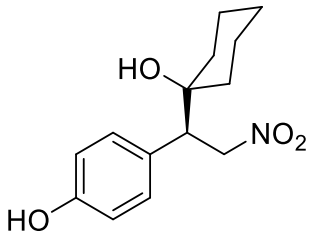
(R)-1-(1-(4-hydroxyphenyl)-2-nitroethyl)cyclohexyl formate (12)



The pure Michael product (MW= 277.32 g/mol, 1.0 equiv, 3.14 mmol, 871 mg) and sodium acetate (MW= 82.03 g/mol, 2.5 equiv, 7.851 mmol, 644 mg) were added to THF/acetic acid (4.0 mL, 3:1 ratio, 3.0 mL of THF and 1.0 mL of AcOH). Peracetic acid (36-40% in acetic acid, MW= 76.05 g/mol, 2.0 equiv, 6.281 mmol, 1.27 mL, assumed a 36% volume content for calculation, density= 1.04 g/mL) was then added. All monitoring of the reaction, the reaction time, and the work-up are exactly the same as noted in Method A: Baeyer-Villiger oxidation - reaction step 2.

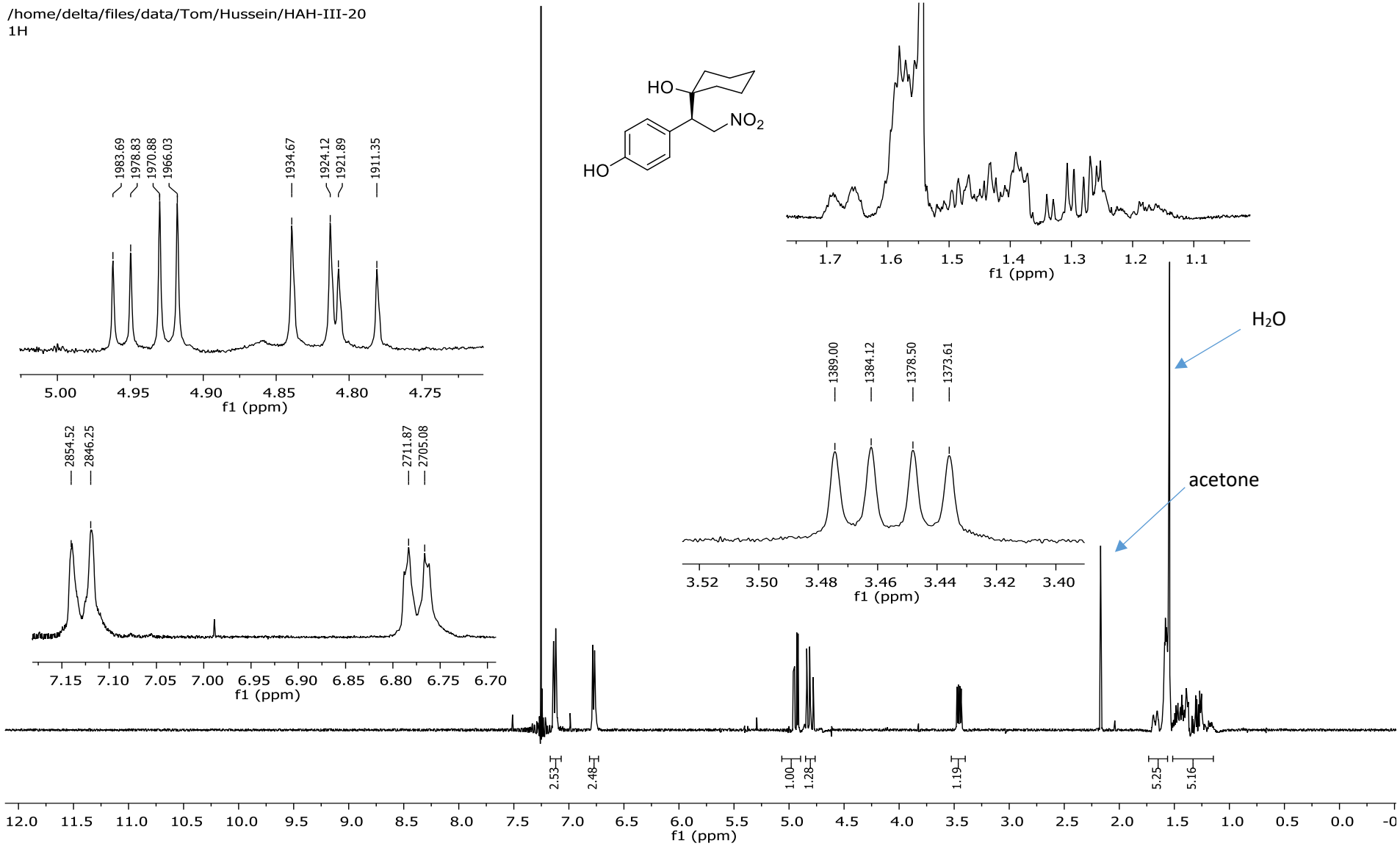
Method B: Hydrolysis (tertiary alcohol formation) – reaction step 3

(S)-4-(1-(1-hydroxycyclohexyl)-2-nitroethyl)phenol (13)



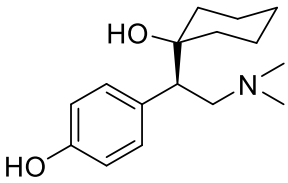
The crude formate ester (MW= 293.32 g/mol, 1.0 equiv, 3.14 mmol, this number of mmol is for the limiting reagent, the Michael product, used during the Baeyer-Villiger reaction step 2 (Method B)), plus small quantities of the corresponding alcohol, from the directly above reaction, was dissolved in a mixture of THF/ water (16 mL, 3:1 ratio, 12.0 mL of THF and 4.0 mL of water, 0.2 M). Sodium hydroxide (MW= 40.0 g/mol, 5.0 equiv, 15.70 mmol, 628 mg) was then added. The resulting dark red reaction mixture was stirred at room temperature for 4 hour (TLC). Work-up: The reaction was quenched by adding HCl (2.0 M, 7.0 mL) and the aqueous layer was immediately extracted with dichloromethane (5×50 mL). The combined organic extracts were concentrated (rotary evaporator, water bath temperature = 35 ^{o}C) and high vacuum dried until a constant weight was obtained. The overall yield of this crude tertiary alcohol (MW= 265.32 g/mol, 1.420 mmol, 377 mg) is 39% based on the 4-hydroxy-β-nitrostyrene starting material (3.63 mmol, limiting

reagent, see step 1 of Method B). The chemical purity is assessed at ~95% based on ^{1}H NMR analysis, see spectrum on the next page and compare to the column chromatography purified tertiary alcohol spectrum noted in Method A. This material is a yellow viscous oil, which we know to be a low melting solid. R_f= 0.26 (EtOAc/petroleum ether 20:80).


/home/delta/files/data/Tom/Hussein/HAH-III-20
1H
HO
NO2
HO
1983.69
1978.83
1970.88
1966.03
1934.67
1924.12
1921.89
1911.35
5.00 4.95 4.90 4.85 4.80 4.75
f1 (ppm)
1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)
H2O
1389.00
1384.12
1378.50
1373.61
3.52 3.50 3.48 3.46 3.44 3.42 3.40
f1 (ppm)
acetone
2854.52
2846.25
2711.87
2705.08
7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75 6.70
f1 (ppm)
2.53
2.48
1.00
1.28
1.19
5.25
5.16
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

(R)-Pristiq [(R)-(-)-O-desmethylvenlafaxine] Drug Formation

(R)-4-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl)phenol



The tertiary alcohol product (MW= 265.30 g/mol, 1.00 equiv, 1.13 mmol, 300 mg) from Method A was dissolved in methanol (5.0 mL). Pd/C was then added (72.0 mg 5 wt% Pd/C no moisture content (Pd: MW= 106.4 g/mol, 0.034 mmol, 3.6 mg, 3.0 mol% effective Pd added)). Under pressurized hydrogen (10.0 bar) the reaction mixture was stirred at room temperature and monitored by TLC. After 6 h the nitro group was fully reduced providing the corresponding primary amine. To the reaction was added formaldehyde (37% aqueous solution, MW= 30.03 g/mol, 10.0 equiv, 11.3 mmol, 0.41 mL, which equals 339 mg of pure formaldehyde) and acetic acid (99% purity, MW= 60.30 g/mol, 0.5 equiv, 0.565 mmol, 32 µL, 34 mg) was added. The reaction was returned to the hydrogenator and again pressurized with H_2 (10 bar). After 12 h full conversion of the intermediary primary amine to Pristiq was noted (TLC). Work-up: The reaction solution was filtered through a plug of celite to remove the Pd/C. The celite plug was washed with methanol until the TLC examination of the filtrate showed no more crude Pristiq product. The reaction filtrates were concentrated (rotary evaporator) and silica gel column chromatography (2.5 x 10 cm, diameter by height) purified. The product was obtained as a white solid compound (MW= 263.38 g/mol, 0.911 mmol, 240 mg, 80% yield). R_f= 0.29 (90:9:1 EtOAc/MeOH/NH_4OH).

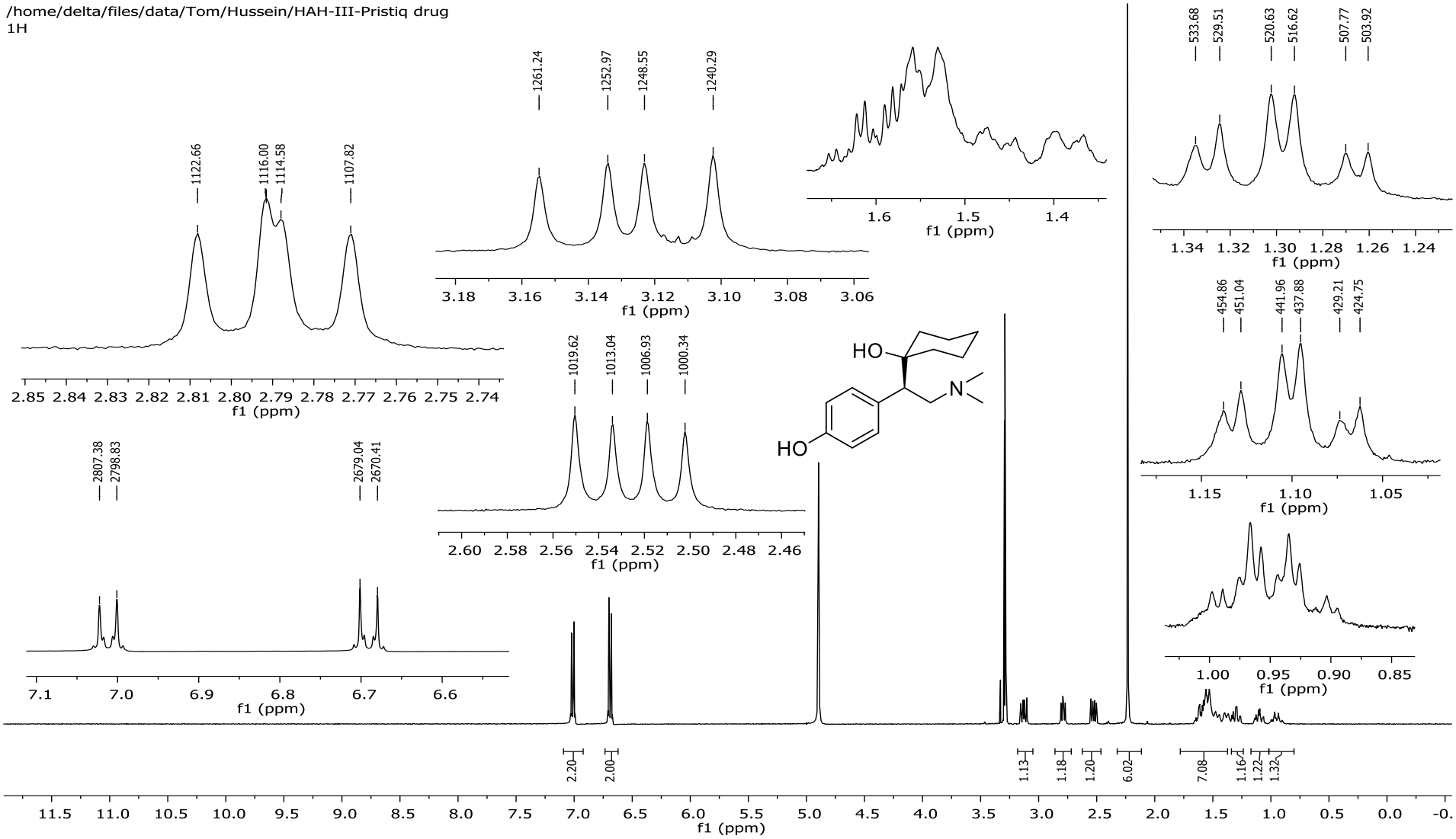
The overall yield of Pristiq (via Method A or B) from 4-hydroxybenzaldehyde is 24%.

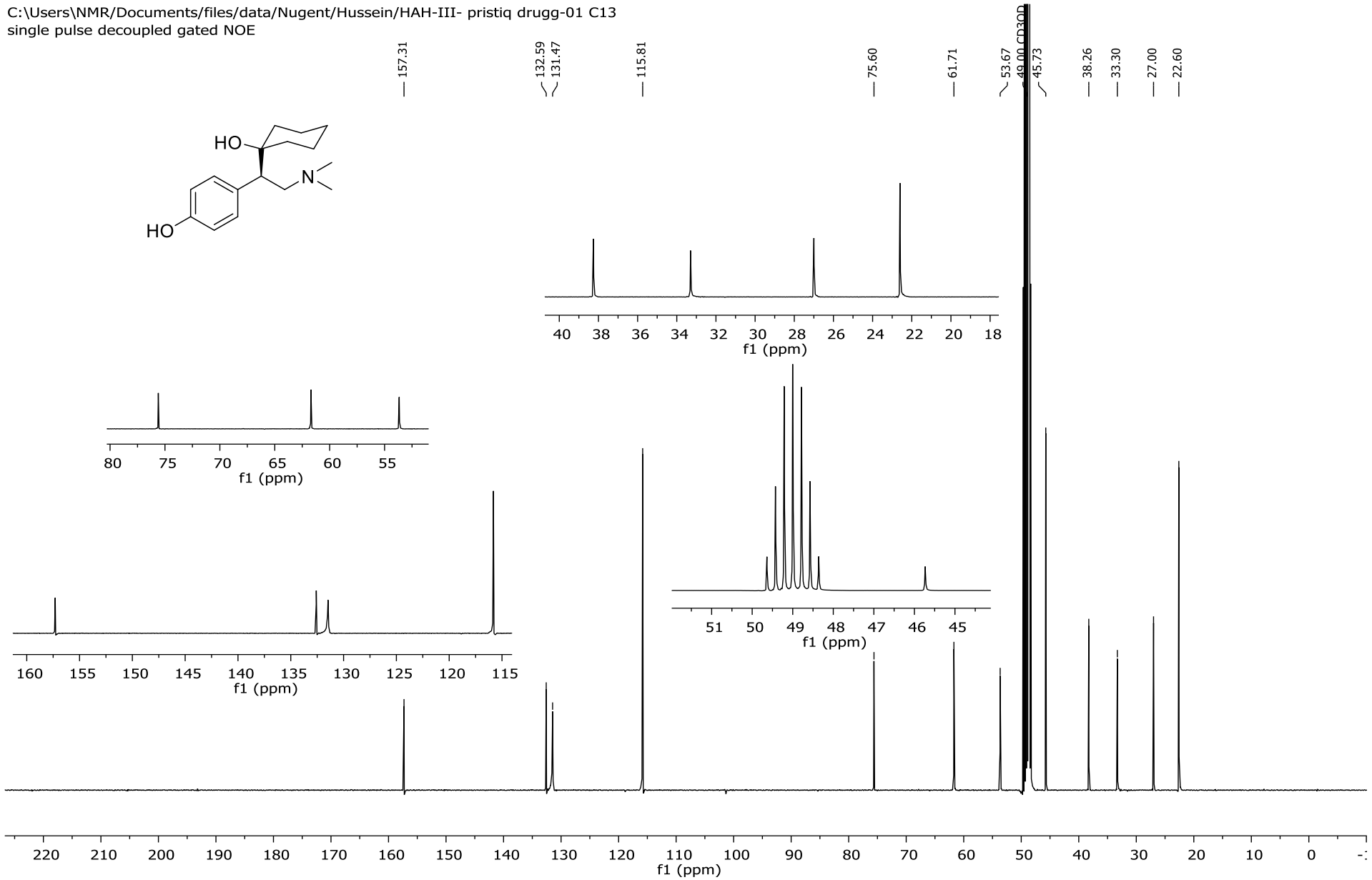
^{1}H NMR (400 MHz, MeOD) (ppm): δ 0.95 (m, 1H), 1.10 (dt, J= 13.0, 4.1, 1H), 1.30 (dt, J= 12.9, 4.0, 1H), 1.33-1.68 (m, 7H), 2.23 (s, 6H), 2.53 (dd, J = 12.7, 6.6 Hz, 1H), 2.79 (dd, J = 8.1, 6.7 Hz, 1H), 3.13 (dd, J = 12.7, 8.3 Hz, 1H), 6.69 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H).

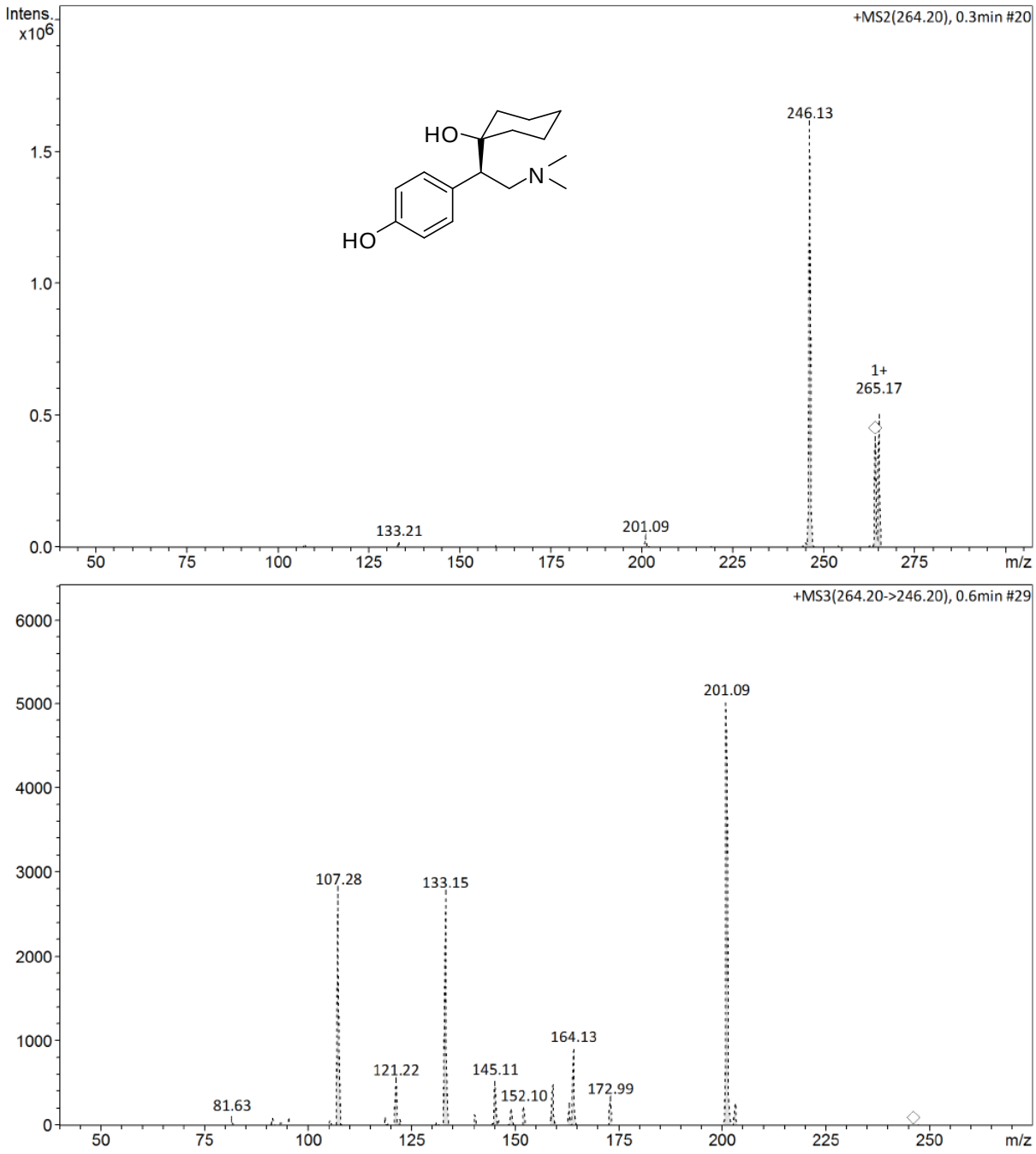
^{13}C NMR (100 MHz, **MeOD) (ppm)**: δ 22.6, 27.0, 33.3, 38.3, 45.7, 53.7, 61.7, 75.6, 115.8, 131.5, 132.6, 157.3.

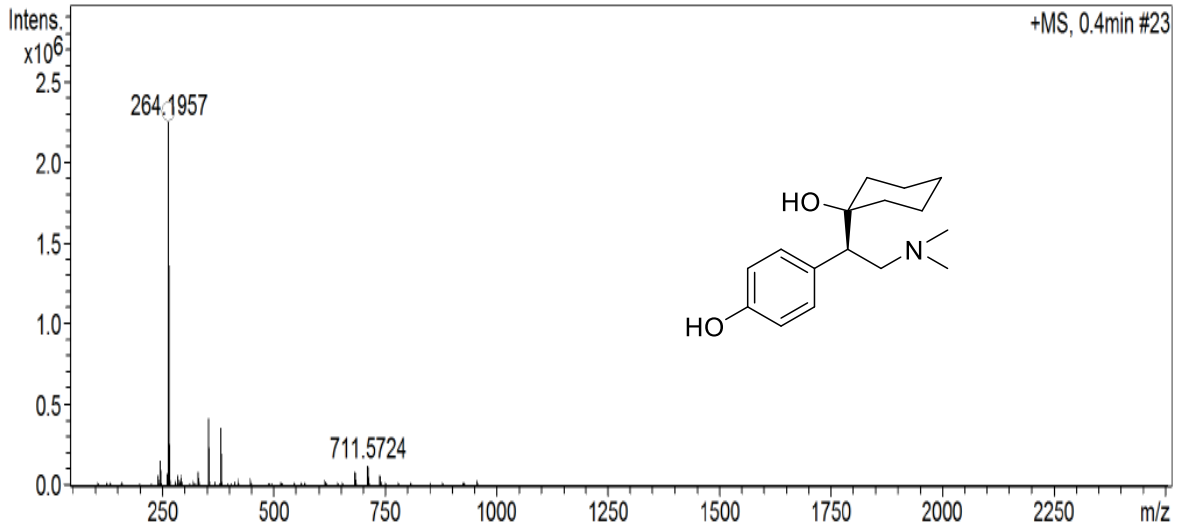
(ESI-TOF)-MS m/z: $[M+H^+]^-$ Calcd for $C_{16}H_{25}NO_2$ 264.1957; Found 264.1958.

MS (EI), *m/z* (relative intensity): 107.28, 164.13, 133.15, 201.09, 246.13, 265.17


/home/delta/files/data/Tom/Hussein/HAH-III-Pristiq drug
1H
HO
HO
N
f1 (ppm)


C:\Users\NMR/Documents/files/data/Nugent/Hussein/HAH-III- pristiq drugg-01 C13
single pulse decoupled gated NOE
157.31
132.59
131.47
115.81
75.60
61.71
53.67
49.00 CD3OD
45.73
38.26
33.30
27.00
22.60
HO
N
HO
f1 (ppm)


Intens.
x10^6
+MS2(264.20), 0.3min #20
246.13
1+
265.17
133.21
201.09
HO
HO
N
m/z
+MS3(264.20->246.20), 0.6min #29
201.09
107.28
133.15
164.13
121.22
145.11
152.10
172.99
81.63
m/z



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e¯ Conf	N-Rule
264.1957	1	C16H26NO2	264.1958	0.4	360.0	1	100.00	4.5	even	ok