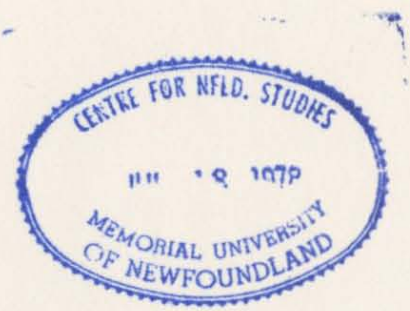
STUDIES ON GUANIDINYL PYRROLIDINE CATALYZED CONJUGATE ADDITIONS AND SYNTHESIS OF (-)-PANCRACINE AND (+)-IPALBIDINE

RAJINIKANTH LINGAMPALLY


CENTRE FOR NFLD. STUDIES
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Studies on guanidinyl pyrrolidine catalyzed conjugate additions and synthesis of (-)-pancracine and (+)-ipalbidine

by

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To my family

Abstract

The organocatalytic, asymmetric conjugate addition of carbon nucleophiles and heteroatom nucleophiles to enones is of interest because the products are useful synthetic intermediates. We have observed that these reactions are catalyzed by proline-derived guanidines. The present study examines the enantioselective addition of malonates, nitroalkanes and heteroatom nucleophiles to a variety of enones in order to provide the corresponding Michael adducts. The observations from this study provide some insight into the reactivity of amine-guanidine bifunctional catalyst motifs and lay the foundation for designing second generation catalysts having modulated nucleophilic and basic character.

Enantiomerically pure γ–nitroketones and their derivatives are an important class of organic compounds due to their utility as building blocks for the asymmetric synthesis of natural products and biologically active molecules. In the present study, the organocatalytic Michael addition of a monoprotected cyclohexane 1,3-dione and selected β-nitro styrenes in the presence of a proline-derived triamine catalyst provided the conjugate addition products in good yield (83-90%), with high enantiomeric excess (89-99%) and high diastereoselectivity ($\geq$19/1). These Michael adducts were utilized in a stereoselective synthesis of *cis* and *trans*-3-aryloctahydroindoles. Application of this methodology is presented in a short formal total synthesis of the methanomorphanthridine alkaloid (-)-pancracine.

Enantiomerically enriched γ–nitroketones obtained from the triamine catalyzed organocatalytic Michael addition were also utilized as starting materials in an efficient synthesis of indolizidines. The utility of this methodology is highlighted by its application in a short total synthesis of the arylindolizidine alkaloid (+)-ipalbidine. The synthetic strategy has potential applications in the preparation of congeners and analogs of several arylindolizidine alkaloids.

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List of Abbreviations

ACE	angiotensin-converting enzyme
APCI	atmospheric pressure chemical ionization
AIBN	azobisisobutyronitrile
aq.	aqueous
Boc	*tert*-butoxycarbonyl
br	broad
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
CSA	camphor-10-sulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisoproyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine

DME	1,2-dimethoxyethane
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
DMDO	dimethyldioxirane
DMSO	dimethyl sulfoxide
ds	diastereoselectivity
ee	enantiomeric excess
EI	electrospray ionization
eq.	equivalent(s)
Et	ethyl
g	gram
h	hour
HOMO	highest occupied molecular orbital
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
i-Bu	isobutyl
i-Pr	isopropyl
J	coupling constant

LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molar
M+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MsCl	methanesulfonyl chloride
mp	melting point
MS	mass spectrum
MVK	methyl vinyl ketone
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
PCC	pyridinium chlorochromate

Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNBA	*para*-nitrobenzoic acid
Pr	propyl
psi	pounds per square inch
PTSA	*para*-toluenesulphonic acid
pyr	pyridine
rt	room temperature
S_N2	bimolecular nucleophilic substitution
t-Bu	tertiary butyl
TBAF	tetra-*N*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Tosyl	*p*-toluenesulfonyl
TPS	triphenylsilyl

TPAP	tetrapropylammonium perruthenate

List of Appendices

Chapter 1

Guanidinyl pyrrolidine mediated organocatalytic conjugate addition reactions

Part of the work described in this chapter has been published in

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Chapter 1

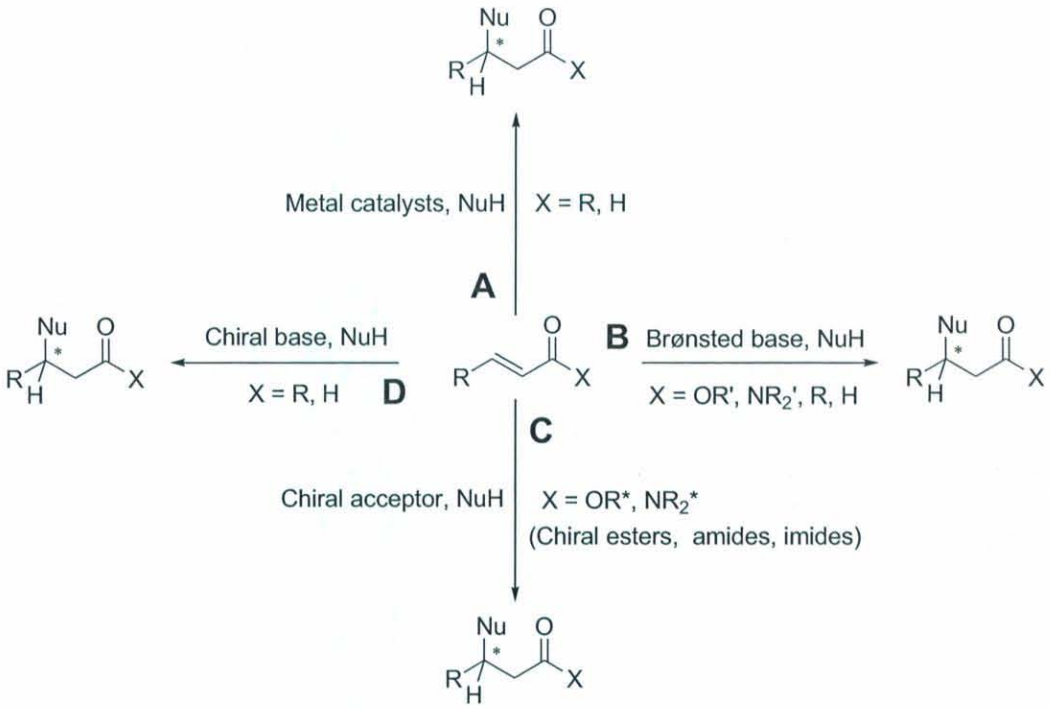
Guanidinyl pyrrolidine mediated organocatalytic conjugate addition reactions

Introduction

The conjugate addition of malonates and nitroalkanes to cyclic and acyclic α,β-unsaturated aldehydes and ketones as well as esters and amides is one of the fundamental C-C bond forming reactions in organic chemistry.[1] The products obtained from these reactions have applications in the synthesis of new medicinal agents and pharmacophores.[2] Consequently, the development of new methods to achieve asymmetric conjugate addition of malonates and nitroalkanes to enones in the presence of catalytic amounts of chiral bases continues to be a subject of active interest with emphasis on stereocontrol of the C-C bond forming reactions.[3]

Several synthetic strategies are available for the asymmetric conjugate addition of carbon and hetero atom nucleophiles to α,β–unsaturated enones. [1,4] The use of a Brønsted base for the activation of a chiral nucleophile is one of the classical approaches (Scheme 1, B). [5-10] A complimentary strategy involving the use of a chrially modified Michael acceptor has also been extensively investigated (Scheme 1, C). Metal based catalytic approaches have also been examined (Scheme 1, A), and all of the above mentioned methods have been reviewed.[3] A conceptually different "metal free" strategy has also

been known for several years but was more recently formalized by MacMillan (Scheme 1, D).[11] In this approach, the Michael acceptor is converted to an iminium ion with a catalytic amount of a chiral amine. Details of this approach will be the focus of the following discussion.



Scheme 1

Conjugate addition reactions of malonates and nitroalkanes via iminium catalysis

More recently, the activation of unsaturated aldehydes and ketones for conjugate addition, by reversible iminium ion formation with chiral amines, was reported as a

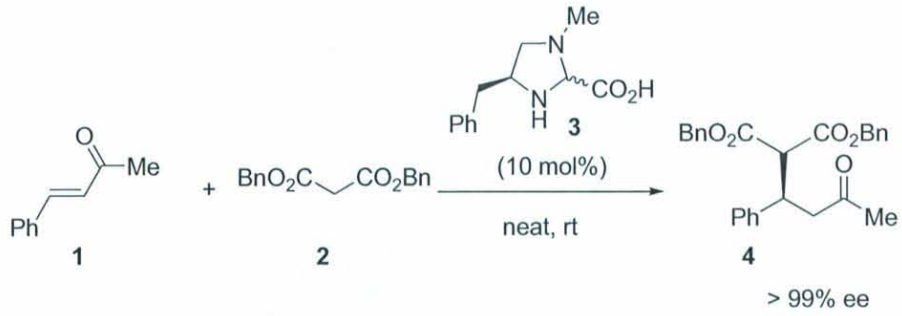
highly generalized strategy by MacMillan.[12,13] The formation of the iminium ion activates the substrate to enhance π-facial addition by lowering the LUMO energy of the electrophile with respect to the HOMO of the nucleophile. This activation effect is similar to that associated with reactions involving metal-based Lewis acids.[14]

Iminium catalysis forms the basis for several conjugate addition reactions of various Michael donors such as malonates,[15,16] nitroalkanes[17,18] and thiols[19] to enones as well as for Mukaiyama-Michael reactions of silyloxyfurans with enals.[12,13] The organocatalytic conjugate addition of malonates and nitroalkanes to cyclic and acyclic enones is an enduring challenge and the search for new and efficient catalysts for these reactions continues.[15-21]

Studies on the iminium ion-mediated organocatalytic conjugate addition of malonates to enones have employed catalysts based on functionalized imidazolidinones[15] and modified prolines.[16,22] The first iminium-catalyzed conjugate addition of malonates to enones was reported by Yamaguchi and co-workers[23] using the rubidium salt of *S*-proline to obtain moderate-to-good enantioselectivities. Since reactions using metal based catalysts are beyond the scope of this thesis, the following presentation will be limited only to reactions catalyzed by organic molecules (organocatalytic reactions).

Kawara and Taguchi[22] reported the first organocatalytic Michael addition using chiral proline-derived ammonium hydroxides. Moderate yields and low-to-good enantioselectivities (3.9-69% ee) were obtained with cyclic and acyclic enones.

Jorgensen developed the first highly enantioselective organocatalytic Michael addition[15] of malonates to α,β-unsaturated enones using an imidazolidine catalyst **3**, which was readily prepared from phenylalanine (Scheme 2).



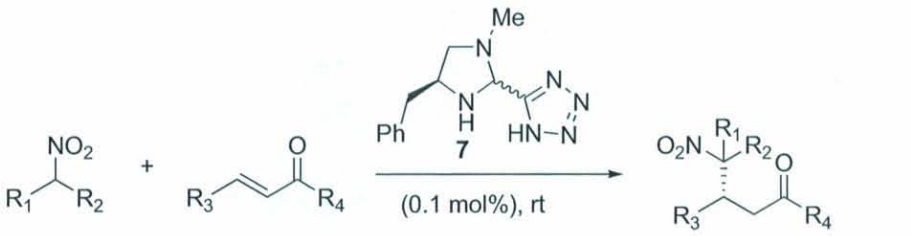
Scheme 2

A number of malonates were tested, and it was observed that the nature of the alkyl group has a large effect on the asymmetric induction of the reaction. The use of dimethyl malonate afforded only 73% ee, which is substantially lower than the 91% ee obtained in the reaction with diethyl malonate. For the sterically more hindered malonates, (*iso*-propyl and *tert*-butyl) the reaction rate however, was decreased considerably and only low yields were obtained (26% and <5% respectively). The reaction with dibenzyl malonate on the other hand, afforded the Michael adduct in 93% yield and greater than 99% ee.

Jorgensen has also used the imidazolidine catalyst **3** for the conjugate addition of nitroalkanes to acyclic α,β-unsaturated enones.[24] These reactions proceeded with moderate to good enantioselectivities (34–86%). However, only moderate enantioselectivity (49%) was obtained using cyclohexenone as the acceptor. Reaction

times were typically between 4.5 to 12.5 days. In addition, the nitroalkane nucleophiles were employed as the reaction solvent in these earlier studies.

Three years later, the same group reported the use of imidazolidine-2-yltetrazole[25] as an organocatalyst for the conjugate addition of nitroalkanes with improved enantioselectivities (up to 92%) and the reaction times were halved in most cases (3–8 days, Scheme 3).



5 **6** **8a** up to 92% ee

Scheme 3

In this study, nitroalkanes were employed as the solvent, and the catalyst performed best with acyclic enones (92% ee) relative to cyclic precursors (77% ee). The reason for improved reaction rates by using catalysts **7** over **3** was suggested to be the better solubility of **7**. It was also proposed that a more sterically well-defined iminium ion intermediate is obtained from **7** as compared with **3**. The observed stereochemistry of the products was explained in terms of formation of the catalyst-substrate iminium ion intermediate, in which the benzyl group of the catalyst stacks on the side of the enone side-chain in **9a** and shields the *re* face of the enone from nucleophilic addition (Figure 1).

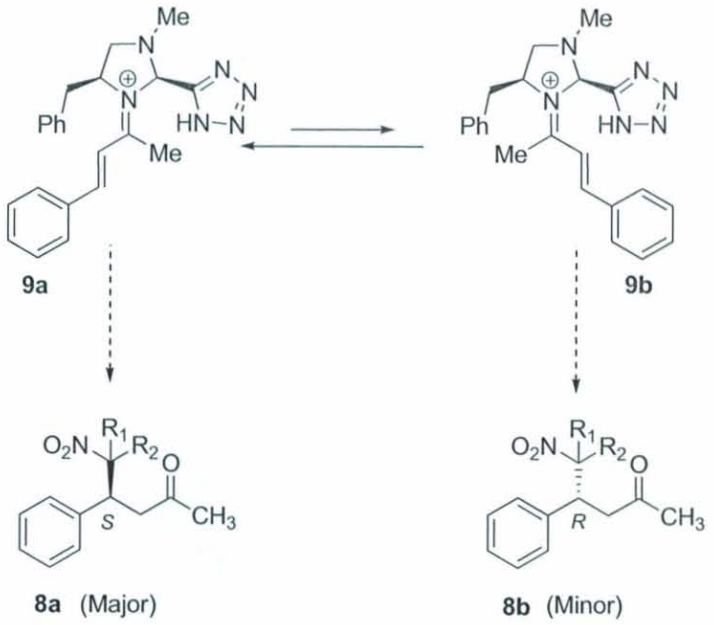
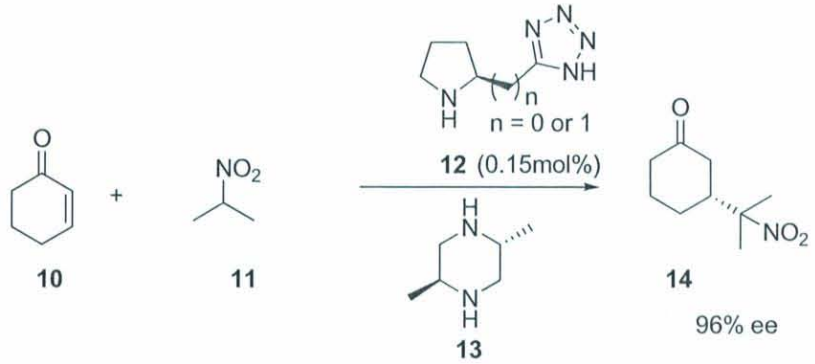


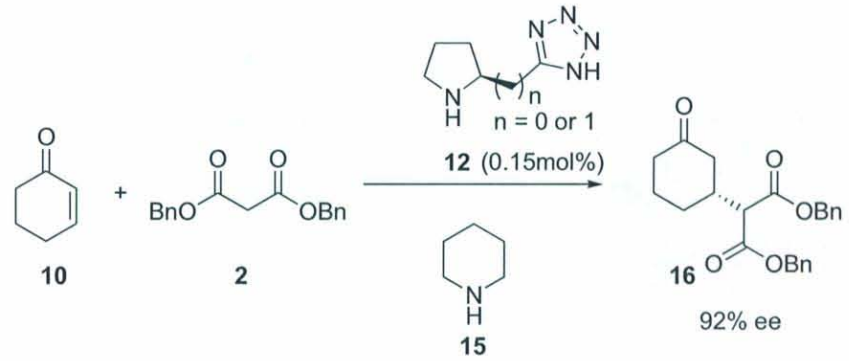
Figure 1. Proposed iminium intermediate obtained from Jorgensen's catalyst **7**

Ley and co-workers developed an improved organocatalytic conjugate addition of malonates and nitroalkanes to enones by using prolyltetrazole **12** as a catalyst.[16] The reaction works well for a range of substrates and furnishes the products in good yield and with good to high enantioselectivities. The *meso* base *trans*-2,5-dimethylpiperazine (**13**), was used as an additive for conjugate addition of nitroalkanes to cyclic and acyclic enones. These reactions (Scheme 4) afford moderate yields (47-84%) and excellent enantioselectivities (94-98% ee) for cyclohexenone adducts and moderate to good enantioselectivities for phenylbutenone adducts (53-84% ee).[26]



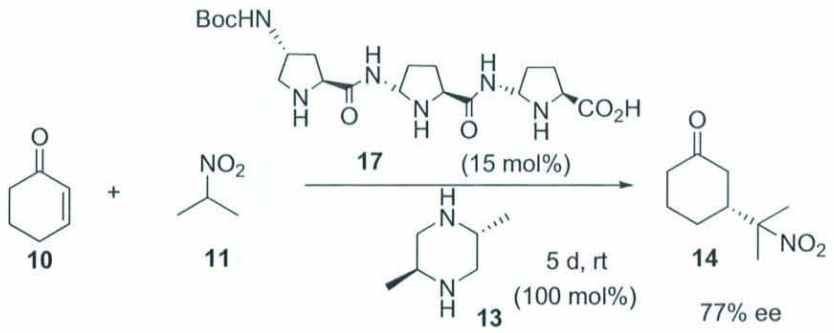
Scheme 4

Since malonates (pK_a diethyl malonate = 13) are less acidic than nitroalkanes (pK_a nitromethane = 10), a stronger base, piperidine, was examined instead of piperazine. The reaction of dibenzyl malonate with acyclic enones such as 4-phenyl-3-buten-2-one, which is a less reactive acceptor, provided the Michael adduct in 59% conversion and 83% ee over 3 days. Also, the addition of dibenzyl malonate to cyclohexenone in CH_2Cl_2 in the presence of piperidine as base afforded the Michael adduct in 89% conversion and 92% ee after 2 days (Scheme 5).



Scheme 5

Tsogoeva and co-workers demonstrated the utility of *trans*-4-amino-proline based di-, tri-, and tetrapeptides as chiral catalysts in combination with *trans*-2,5-dimethylpiperazine **13** as an additive for asymmetric conjugate addition of nitroalkanes to prochiral acceptors. Proline-derived tripeptide **17**[27] catalyzed the reaction between 2-nitropropane and cyclohexenone in $CHCl_3$ to form **14** in 77% ee and 80% yield (Scheme 6).



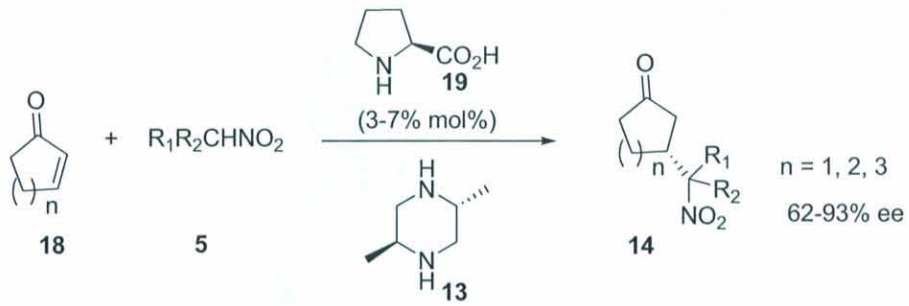
Scheme 6

Similar results were obtained with four other cyclic and acyclic nitroalkanes. In the same year, Tsogoeva and Jagtap introduced two histidine-based dipeptides as catalysts[28] for the same transformation. These catalysts exhibited only moderate stereoselectivities (up to 60% ee) in conjunction with several chiral and achiral amine additives.

In addition to the tripeptide, proline-derived dipeptides and tetrapeptides[29] were also studied as catalysts for conjugate addition reactions. It was observed that steric bulkiness of the nitroalkane was important for asymmetric induction in these reactions. The large nucleophile does react slowly, but is more selective with activated enones. The highest enantioselectivity (88% ee) was therefore observed for nitrocyclopentane, while the lowest ee was observed for nitromethane (57% ee). Additionally, the ring size of the

enones also affected the enantioselectivity. Higher levels of asymmetric induction were observed with cyclohexenone (66–88% ee) compared with cyclopentenone (54–77% ee).

Hanessian and Pham[17] have studied the conjugate addition of nitroalkanes to cyclic enones in the presence of *S*-proline **19** with the achiral base *trans*-2,5-dimethylpiperazine (**13**) (Scheme 7).



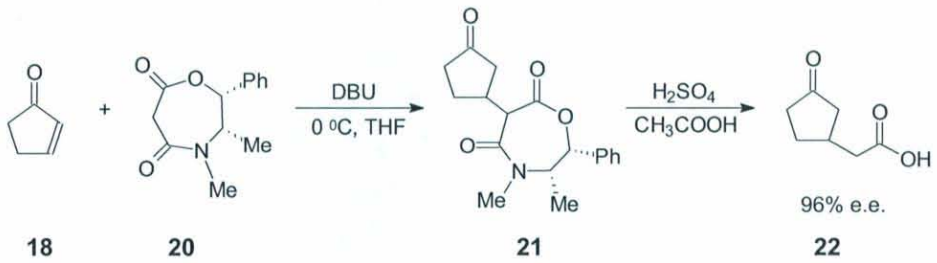
Scheme 7

In this study, the organocatalytic asymmetric conjugate addition of various nitroalkanes to cyclic enones such as cyclopentenone, cyclohexenone, and cycloheptenone proceeded with moderate to high enantioselectivity (62-93% ee). Promising results were also observed with some acyclic α,β-unsaturated ketones. Addition of 2-nitropropane to chalcone (acyclic enone), was reported to afford the adduct in 68% ee. Later, Hanessian and co-workers investigated the effect of *trans*-2,5-dialkylpiperazines[30] as basic additives in the organocatalytic asymmetric conjugate addition of 2-nitropropane to cyclohexenone in the presence of *trans*-4,5-methano-L-proline as catalyst. The chirality or steric bulk of the constituents on the piperazine does not affect the enantioselectivity. Proline hydroxamic acid[31] was also found to be an

effective catalyst, albeit with modest enantioselectivity (75% ee), and a slower reaction rate as compared with *S*-proline itself.

Brønsted base-catalyzed reactions

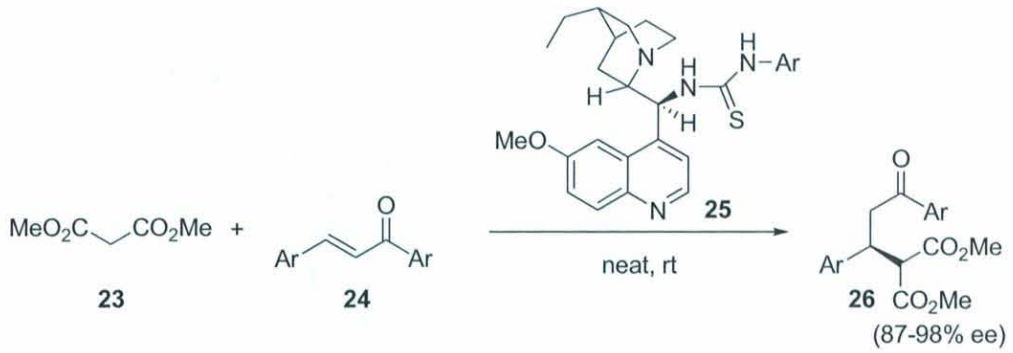
A few organocatalysts that do not rely on iminium ion formation have also been examined for malonate conjugate addition reactions. Mukaiyama and co-workers have described the asymmetric synthesis of δ-oxocarboxylic acids by the Michael addition reaction involving a chiral malonic acid derivative. The reaction of (2*R*, 3*S*)-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (**20**) (synthesized from methyl hydrogen malonate and (1*R*, 2*S*)-ephedrine hydrochloride) and 2-cyclopenten-1-one (**18**) in the presence of DBU, followed by hydrolysis and decarboxylation of the resulting adduct generates 3-oxocyclopentane acetic acid (**22**) in 96% e.e. (Scheme 8). Low enantioselectivity (55%) was however observed with 1-phenyl-2-buten-1-one as the Michael acceptor.



18 **20** **21** **22**

Scheme 8

Wang and co-workers[32] developed the cinchona-based thiourea catalyst **25** for asymmetric conjugate addition of various nucleophiles (nitroalkanes, malonate esters, ketoesters, 1,3-diketones, nitroesters and 1,1-dinitriles) to enones, providing versatile, highly enantiomerically-enriched adducts (Scheme 9).



Scheme 9

The adducts **26** were obtained in high yields (85-97%) and good to excellent enantioselectivities (87-98% ee). The nature of the substituent on the aromatic ring in chalcone **(24)** had a very limited effect on the reaction. In comparison, the imidazolidinone catalysts provide better stereoselectivities in these reactions but they often require a large excess of malonate, whereas proline-based catalysts usually require amine additives for optimum performance.

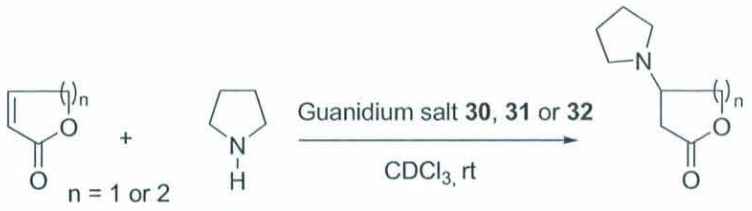
Chiral guanidine-catalyzed conjugate addition reactions

Guanidine is one of the most basic forms of neutral nitrogen compounds and guanidine derivatives are used as strong bases in synthetic chemistry.[33] In peptides, the guanidine residue of arginine exists in protonated form as a guanidinium ion, which

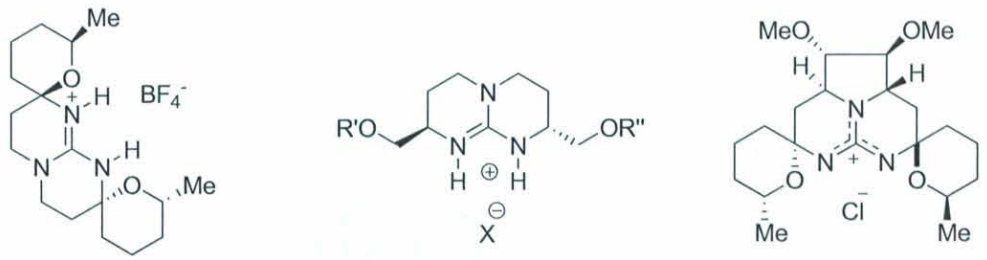
functions as an efficient recognition moiety of anionic functionalities, such as carboxylates, phosphate, and nitronate through double hydrogen bond,[34] It is therefore reasonable to expect that the strong basic character of guanidine derivatives coupled with their ability to act as recognition elements would make them particularly useful asymmetric base catalysts. However, enantioselective catalysis using chiral guanidine bases has attracted attention only recently.[35,36] One problem in the development of guanidines as efficient chiral catalysts is their planar and highly symmetric structure. This has been overcome by constructing chiral guanidines composed of five-, or six-membered rings having chirality in the ring. Another approach involves the use of chiral amines to prepare acyclic guanidines.[6,8]

The conjugate addition of amines to α,β-unsaturated lactones yielding β-aminolactones is of considerable interest, allowing flexible and enantioselective routes to β-aminoesters, β-aminoalcohols and β-lactams. In this context, a chiral guanidine-mediated conjugate addition of pyrrolidine to lactones was reported independently by Mendoza,[37] Murphy,[38] and Nagasawa.[39]

Mendoza and co-workers[37] observed more than eight-fold reaction rate enhancement for conjugate additions of pyrrolidine to α,β-unsaturated lactones in the presence of catalytic amounts of bicyclic chiral guanidinium salts **31**. Unfortunately they did not observe any asymmetric induction during the process. Murphy and co-workers[38] investigated the application of the C_2-symmetric chiral guanidine catalyst **30**, in the conjugate addition of pyrrolidine **28** to the unsaturated lactone such as **27** (Scheme 10).



27 28 29

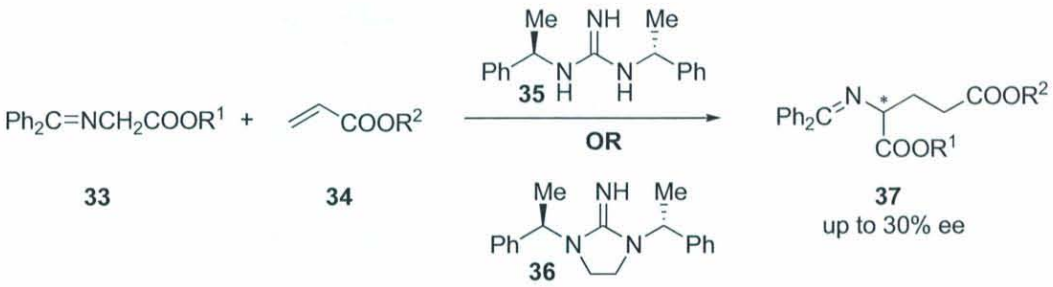


30 31 32

Scheme 10

Murphy and co-workers carried out the reaction under identical conditions to those reported by Mendoza an observed that a 4.3-fold increase in reaction rate was obtained when guanidine.HBF_4 salt was employed as a catalyst. In line with the report of Mendoza, changing the counterion in **30** from tetrafluoroborate to tetraphenylborate led to a 16.3-fold increase in reaction rate over the uncatalyzed process. Unfortunately, no asymmetric induction was observed in this reaction. Nagasawa and co-workers[39] used symmetrical pentacyclic guanidine **32** for the asymmetric hetero-Michael reaction between pyrrolidine and these α,β-unsaturated lactones **27** and observed the similar reaction rate enhancement as Mendoza (8.3 fold increase) and concluded that reaction rate is more dependent on the size and nature of the catalyst cavity.

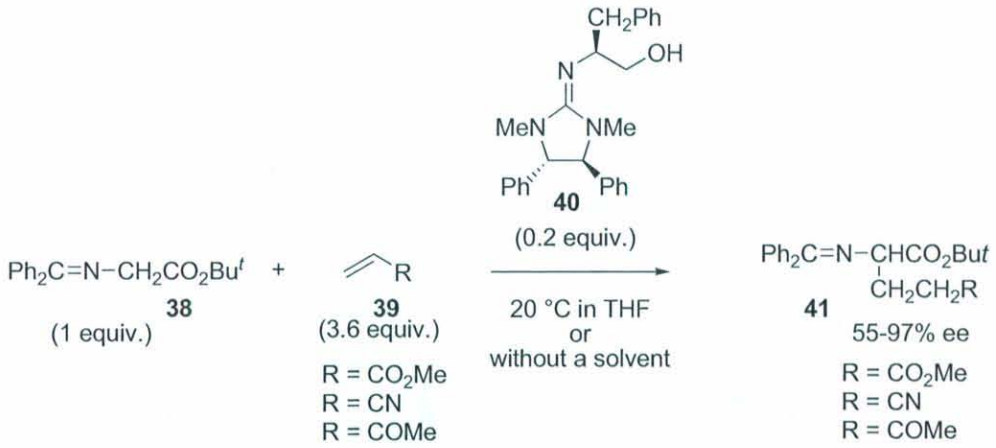
An asymmetric Michael addition reaction catalyzed by chiral guanidines was reported by Ma[6] in 1999. Several chiral guanidines were evaluated as catalysts for the Michael reaction of glycine derivatives with acrylic esters. The success of this reaction led to a new methodology for preparing synthetically useful α-aminoacid derivatives. The reaction was carried out by simply stirring a mixture of the imine, excess acrylic ester and a catalytic amount of chiral guanidine in a suitable solvent at room temperature (Scheme 11).



Scheme 11

The reaction proceeded with high yield (85-99%) and modest enantioselectivity (up to 30% ee). As in many other asymmetric catalytic reactions, the enantioselectivity of the reaction was highly dependent on the nature of solvent. Although the enantioselectivity was poor, these results demonstrated the utility of chiral guanidines as asymmetric catalysts in the Michael addition reaction.

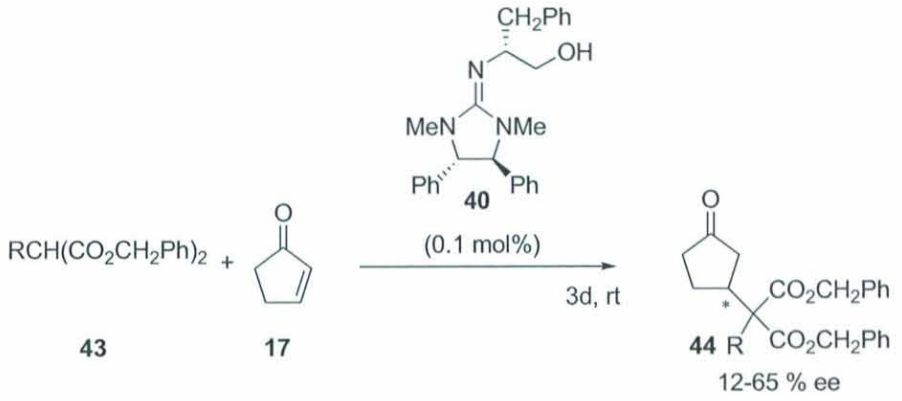
Ishikawa and co-workers[35] attempted a conjugate addition of glycine imine **38** with acrylic acid derivatives **39** in the presence of modified guanidines. Exploration of various conditions led to effective asymmetric induction (55-97% ee) when guanidine **40** was used as a catalyst either in solution or without a solvent (Scheme 12).



Scheme 12

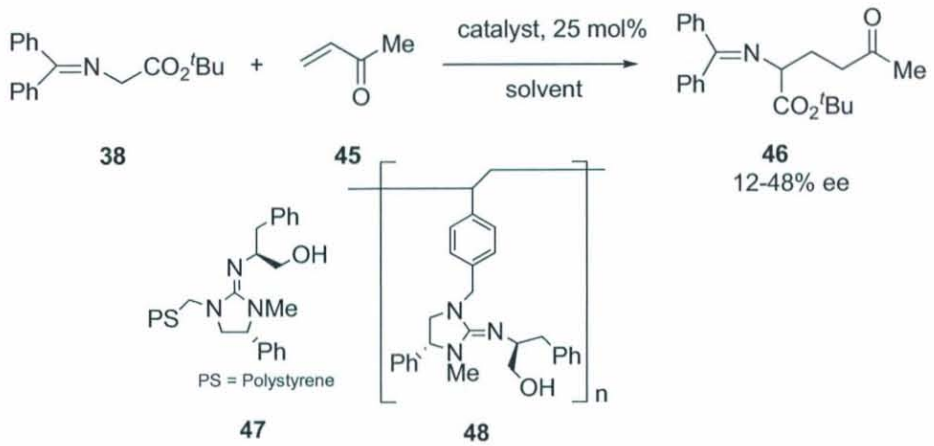
The same group reported the Michael reaction of cyclopentenone with dibenzyl malonate and epoxidation of chalcones with hydroperoxides with various chiral guanidines.[33]A total of twenty-six acyclic and cyclic guanidines were screened for the epoxidation reaction and epoxides were obtained in 15-65% ee.

The reaction between cyclopentenone **17** and dibenzyl malonate **43** was carried out in the presence of stoichiometric amount of acyclic guanidines, under refluxing conditions in chloroform to give the Michael adduct in 80% yield with only 12% ee. When the cyclic guanidine such as **40**, with diphenyl substituents on the imidazolidine ring were used, moderate asymmetric induction (43% ee, 65% yield) was observed under reflux conditions. Enantioselectivity was improved to 62% when the reaction was carried out in chloroform at room temperature, but the yield was low 11% (Scheme 13).



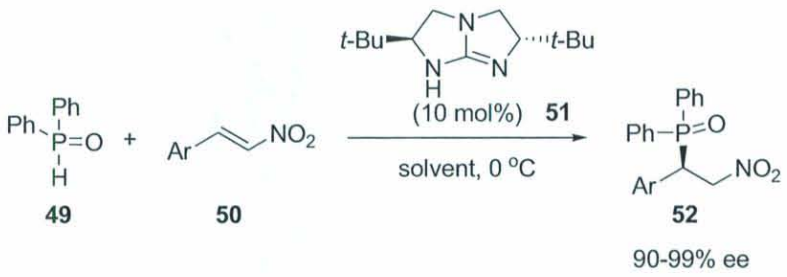
Scheme 13

A polymer-supported guanidine and a polymeric chiral guanidine were examined as catalysts for the Michael reaction of *t*-butyl diphenyliminoacetate with methyl vinyl ketone by Ishikawa and co-workers.[9] Catalytic activity was observed only with **48**. The expected adduct was produced with moderate asymmetric induction (12-48% ee). The lack of reactivity in the case of polymer-supported guanidine **47** may be due to steric hindrance by the polymer backbone near the reaction site (Scheme 14).



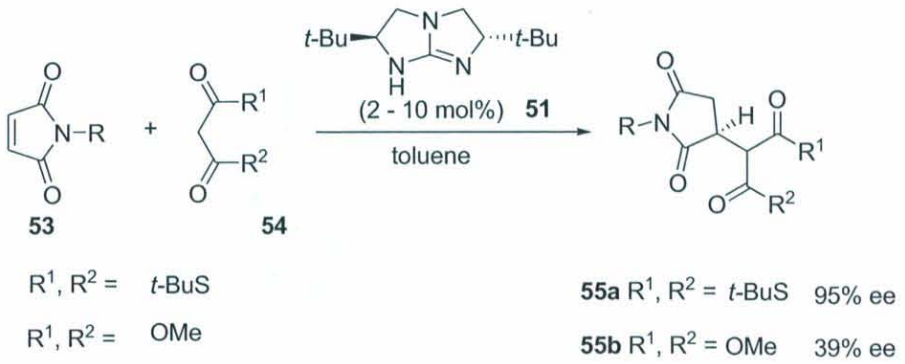
Scheme 14

Tan and co-workers[5] reported the first Michael reaction between diaryl phosphine oxide **49** and nitroalkenes **50** by using the chiral bicyclic guanidine catalyst **51** (Scheme 15). This is a direct and atom-economical method to synthesize chiral *β*–nitrophosphine oxides **52** which can be converted to *β*-aminophosphines by reduction of the nitro group. Adducts **52** were obtained in moderate to high yields (75-99%) and high enantioselectivities (90-99% ee).



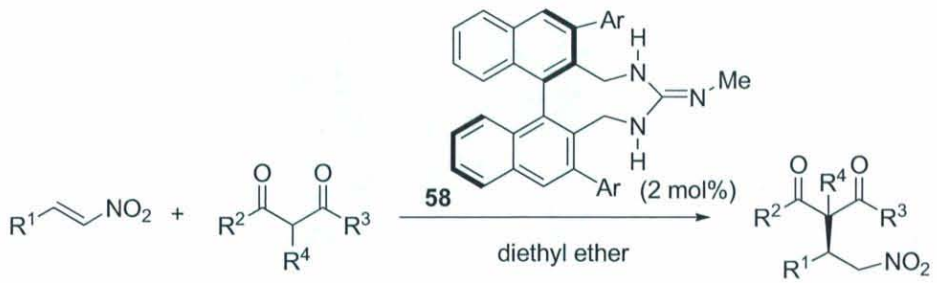
Scheme 15

Guanidine **51** also catalyzes reactions of dithiomalonates **54** and *β*-keto esters and thioesters with a wide range of acceptors including maleimides **53**, cyclic enones and furanones. The reactions with thiomalonates proceed with good enantioselectivity (Scheme 16).[10]



Scheme 16

Terada and coworkers[8] developed a new class of chiral guanidines with an axially chiral binaphthyl backbone. The substitutents at the 3,3′ positions of the binaphthyl ring create an efficient chiral environment for asymmetric organic transformations. The axially chiral guanidine catalyst **58** was used as a catalyst for the conjugate addition of 1,3-dicarbonyl compounds **57** with a broad range of nitroalkenes **56**. Various types of optically active nitroalkane derivatives **59**, have been produced by this method in 86-96% ee (Scheme 17).



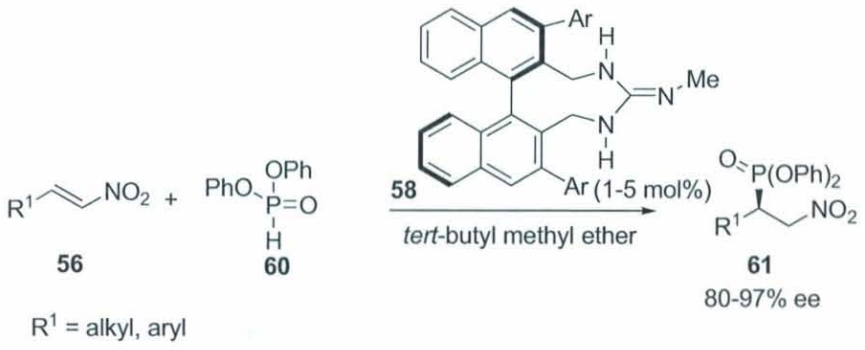
56 **57** **59**

86-96% ee

Scheme 17

Terada also reported the asymmetric 1,4-addition reaction of diphenyl phosphite **60**[7] to nitroalkenes **56**, catalyzed by axially chiral guanidines **58**. The *β*-nitro phosphonates **61**, produced in these reactions can be transformed into *β*-amino phosphonates by simple reduction of the nitro group. The enantioselectivities obtained in these reactions are good to excellent (80-97% ee). Nitroalkenes with aliphatic substituents

gave lower enantioselectivities compared to those with aromatic substituents (Scheme 18).



Scheme 18

Objective

The objective of the study being presented in this thesis was to examine the utility of bifunctional organocatalysts containing both iminium-ion forming functionality, and basic functionality, in asymmetric conjugate addition reactions. The concept is summarized in Figure **2**.

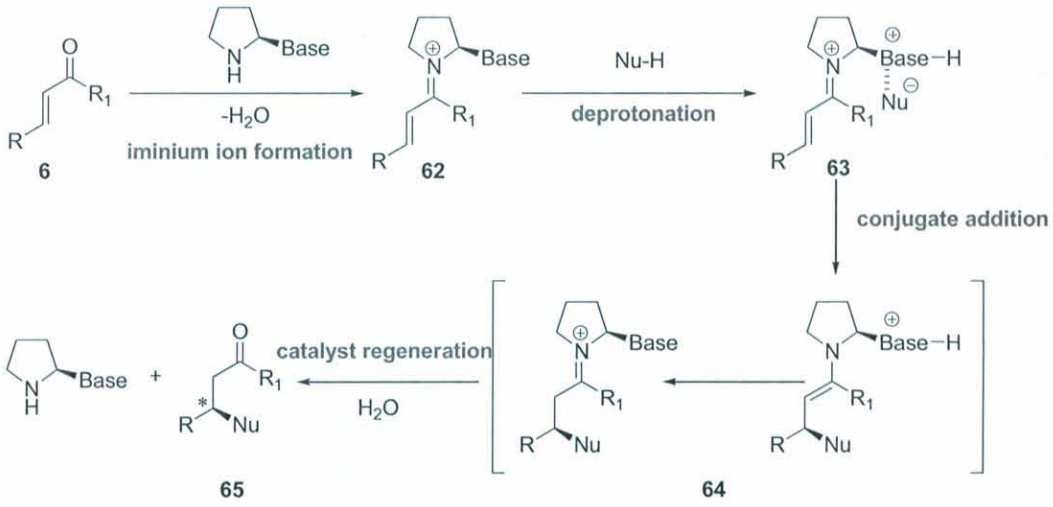


Figure 2. Conjugate additions mediated by bifunctional organocatalysts

It was reasoned that initial iminium formation, followed by deprotonation of the nucleophile would give an intermediate such as **63** (Figure 2) in which the deprotonated nucleophile is associated with the basic side-chain in the catalyst. An "internal" delivery of the nucleophile from one face of the enone would result in an enantioselective conjugate addition reaction to provide the enamine **64**, which after hydrolysis would regenerate the catalyst and give the required conjugate addition product **65**.

A cursory examination of the acidity of carbon nucleophiles suggested that a guanidine moiety would be well-suited as the base for deprotonation of malonate and nitroalkane nucleophiles. Hence, the synthesis of guanidinyl pyrrolidines **66, 67** and **68** (Figure 3) were chosen as catalyst candidates for this study.

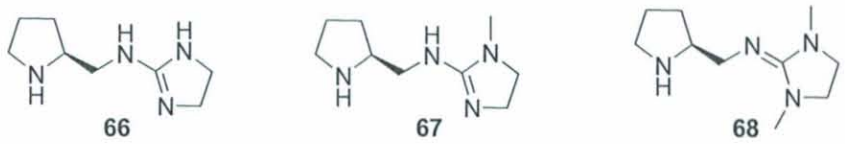
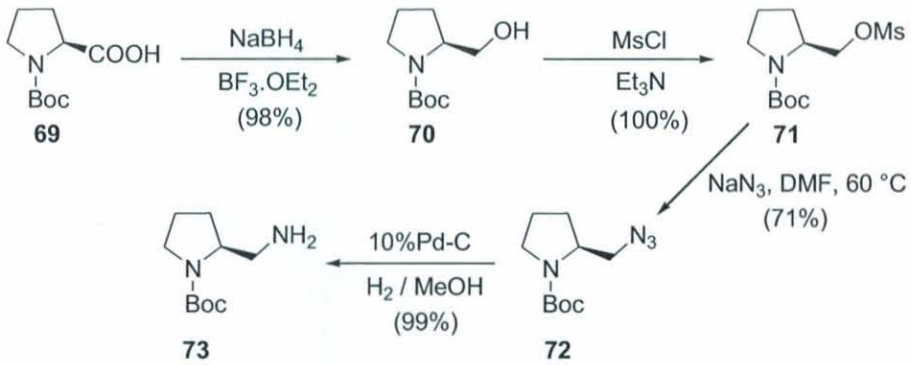


Figure 3. Guanidinyl pyrrolidines designed for this study

Results and discussion

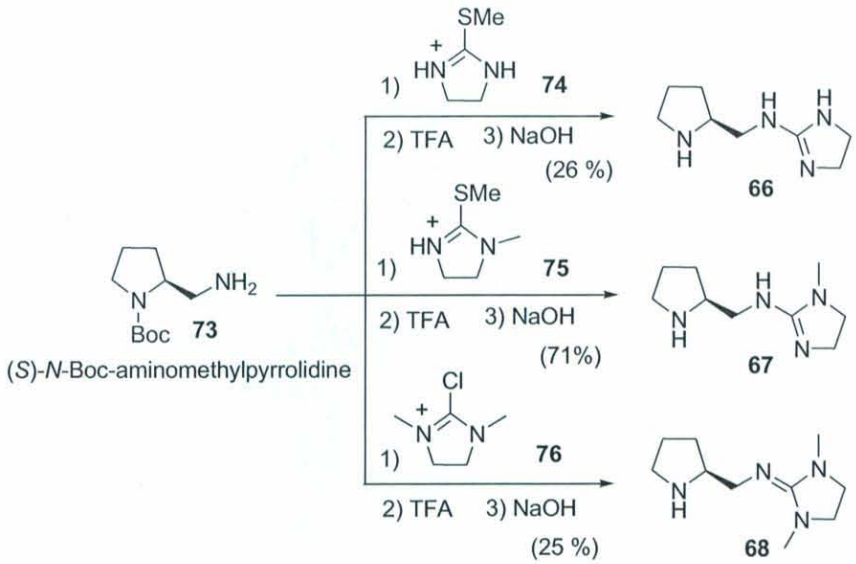
The synthesis of **66**, **67** and **68** began with Boc-*S*-Proline (**69**).[40] Borane reduction ($NaBH_4/BF_3.OEt_2$) of **69** in isopropyl acetate provided *N*-Boc prolinol **70** in 98% yield (Scheme 17).



Scheme 17

Treatment of **70** with methanesulfonyl chloride and triethylamine in dichloromethane at -78 °C gave the mesylate **71** in quantitative yield. The mesylate was converted with sodium azide in DMF at 60 °C to form azide **72** in 71% yield. Finally, azide **72** was reduced to provide (*S*)-*N*-Boc-aminomethylpyrrolidine (**73**) as a colorless gum in near quantitative yield.

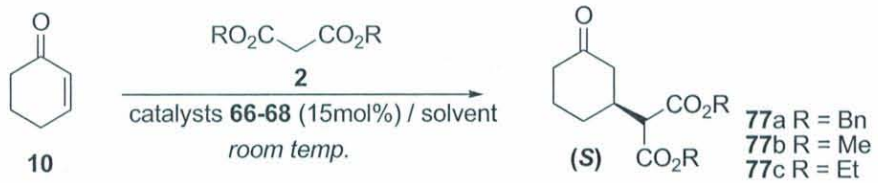
With the amine **73** in hand, the synthesis of guanidinyl pyrrolidines **66, 67** and **68** was readily achieved by reaction of **73** by heating with isopropyl alcohol at reflux with an appropriate imidazolium species **74**, **75** and **76** respectively in refluxing isopropyl alcohol followed by deprotection of the pyrrolidine ring using TFA. These reactions are shown in Scheme 18.



Scheme 18

Having developed an efficient synthesis of the chiral guanidinyl pyrrolidines, a study of the Michael addition between 2-cyclohexene-1-one and dibenzyl malonate was embarked. Initial experiments involved the screening of the guanidinyl pyrrolidines **66-68** in various solvents to provide the Michael adduct (*S*)-**77a** and the results are summarized in Table 1. Although reasonable yields were obtained with catalysts **66** and **68** the enantiomeric excess was negligible (0–12%, Table 1, entries 1–6). Results with catalyst **67** however, were more promising.

Table 1: Catalyst and solvent screening for the asymmetric Michael reaction



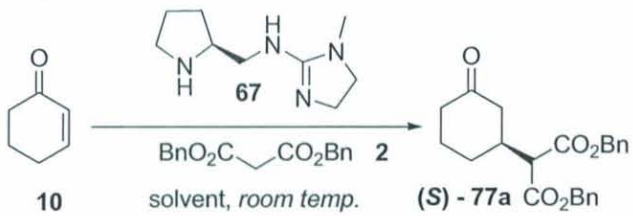
Entry[a]	Cat.	Solvent	Time (h)	R	Yield	ee (%)[b]
1	**66**	Toluene	168	Bn	94	4
2	**66**	CH_2Cl_2	92	Bn	91	12
3	**66**	DMF	168	Bn	82	6
4	**68**	Toluene	36	Bn	41	5
5	**68**	$CHCl_3$	36	Bn	35	3
6	**68**	DMF	36	Bn	75	<1
7	**67**	-	20	Bn	99	4
8	**67**	DMF	48	Bn	56	21
9	**67**	Toluene	48	Bn	68	36
10	**67**	CH_2Cl_2	48	Bn	41	61
11	**67**	CH_2Cl_2	92	Me	94	59
12	**67**	CH_2Cl_2	92	Et	90	52
13	**67**	CH_2Cl_2	168	*t*-Bu	-	-

a: 1.2 eq. malonate b: chiral HPLC analysis

Also, with **67** as the catalyst, dibenzyl malonate provided higher enantioselectivity (Table 1, entry 10) compared to its dimethyl (**77b**, 59% ee) and diethyl (**77c**, 52% ee) (Table 1, entries 11, 12) congeners, whereas di-*t*-butyl malonate (Table 1, entry 13) failed to react. Interestingly, the enantioselectivity was negligible (4%, entry 7, Table 1) when dibenzyl malonate was used as the solvent. These observations clearly indicated an important role of the solvent and we therefore conducted an optimization study with

dibenzyl malonate, cyclohexenone and catalyst **67** in various solvents. The results are summarized in Table 2.

Table 2: Solvent screening for the asymmetric Michael reaction with catalyst 67



Entry[a]	Solvent	Time (h)	Yield (%)	Ee (%)[b]
1	toluene	48	68	36
2	dioxane	48	-	-
3	THF	48	84	50
4	ethylacetate	48	75	43
5	$CHCl_3$	48	46	49
6	**DCE**	**48**	**70**	**58**
7	**CH_2Cl_2**	**48**	**41**	**61**
8	***t*-BuOH**	**48**	**45**	**63**
9	DMF	48	56	21
10	DMSO	48	75	43
11	acetonitrile	48	48	39
12	IPA	48	91	8

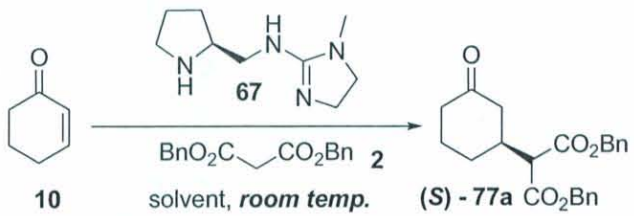
a: 1.2 eq. malonate b: chiral HPLC analysis

Catalyst **67** was functional in almost all of the conventional organic solvents except dioxane. This is probably due to the poor solubility of **67** in dioxane. Halogenated solvents provided better enantioselectivity (Table 2, entries 6, 7), than most of the polar

solvents except *t*-BuOH which was the best solvent in this study (Table 2, entry 8, 63% ee).

After completion of the solvent survey, we next examined the effect of catalyst loading and reaction concentration. These studies are summarized in Table 3.

Table 3: Optimization studies with catalyst 67.



Entry[a]	Cat. (mol%)	Solvent	Vol. (mL)	Malonate (M)	Time (h)	Yield (%)	Ee(%)[b]
1	15	*t*-BuOH	2	0.30	48	88	31
2	15	CH_2Cl_2	1	0.60	48	41	61
3	5	CH_2Cl_2	2	0.30	90	16	74
4	10	CH_2Cl_2	2	0.30	120	50	82
5	15	CH_2Cl_2	2	0.30	90	61	82
6	**10**	**CH_2Cl_2**	**4**	**0.15**	**156**	**27**	**86**
7	15	DCE	2	0.30	48	92	73
8	20	DCE	5	0.12	164	99	79
9	20	DCE	7	0.090	185	87	81
10	10	DCE	2	0.30	140	78	84
11	10	DCE	4	0.15	156	47	86
12	**10**	**DCE**	**3**	**0.20**	**140**	**64**	**86**

a: 0.5 mmol cyclohexenone, 1.2 eq. malonate b: by chiral HPLC

Although *tert*-butyl alcohol had provided the highest enantioselectivity in the solvent screening study, it was immediately apparent that dilution was not an option with this solvent (Table 3, entry 1, 31% ee). Experiments in dichloromethane and 1,2-dichloroethane (DCE) were more fruitful, and diluting the reaction mixture had a significant, positive effect on enantioselection in these solvents. For example, doubling the dilution in dichloromethane with 15 mol% of **67**, increased the enantioselectivity from 61% to 82% (entries 2 and 5, Table 3). Further dilution and a concomitant decrease in catalyst loading improved the enantioselectivity to 86% (Table 3, entry 6) but at the expense of the yield.

A similar effect of dilution was also observed in 1,2-dichloroethane but, in this case, decreasing the catalyst loading was less detrimental to the overall yield. Consequently, 1,2-dichloroethane was the solvent of choice, and under the optimized conditions **77a** was obtained in 64% yield and 86% ee (Table 3, entry 12). The precise reasons for the effect of dilution on the enantioselection are not clear at this time. It is hypothesized that at higher reaction concentrations, deprotonation of the malonate by **67** is faster than iminium ion formation (direct deprotonation, Figure 4) and this results in a direct conjugate addition of malonate anion to cyclohexenone with low enantioselectivity. The poor enantioselectivity observed in malonate as the reaction medium provides some support for this hypothesis.

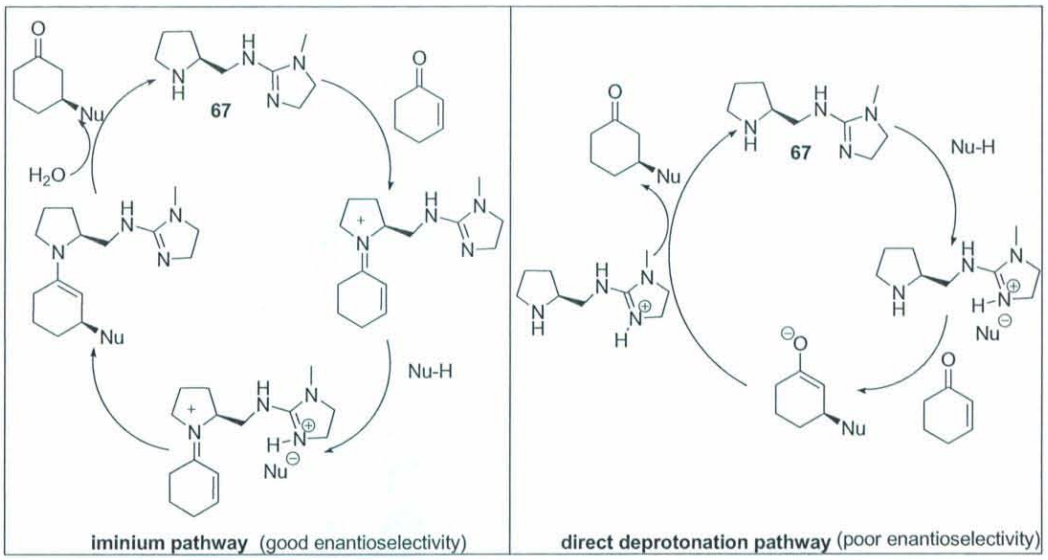
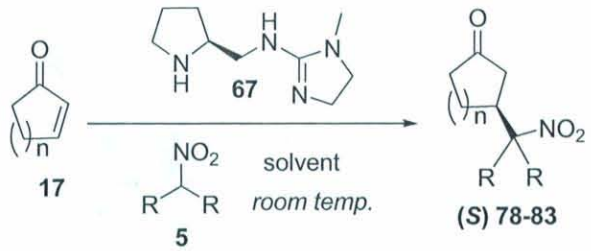


Figure 4. Iminium and direct deprotonation pathway

As the effective concentration of malonate is lowered however, the rate of malonate deprotonation by free catalyst **67** is sufficiently reduced to allow iminium ion formation, and conjugate addition to an iminium species involving **67** proceeds with higher enantioselectivity (iminium ion pathway, Figure 4). These observations suggest a bifunctional role for guanidinyl pyrrolidine **67**, namely, iminium ion formation and malonate deprotonation. It is also plausible that as the dilution increases, self-association of the malonate (e.g. enolate-enol association) decreases sufficiently to permit association with the guanidinium species in the iminium ion via hydrogen bonding. This results in a 'directed' or 'intramolecular type' addition of the malonate that is face selective.

With an optimized protocol for the malonate conjugate addition in hand, the conjugate addition of nitroalkanes to cyclohexenone and cyclopentenone was investigated next. These results are summarized in Table 4.

Table 4: Asymmetric conjugate addition of nitroalkanes to cycloalkenones.

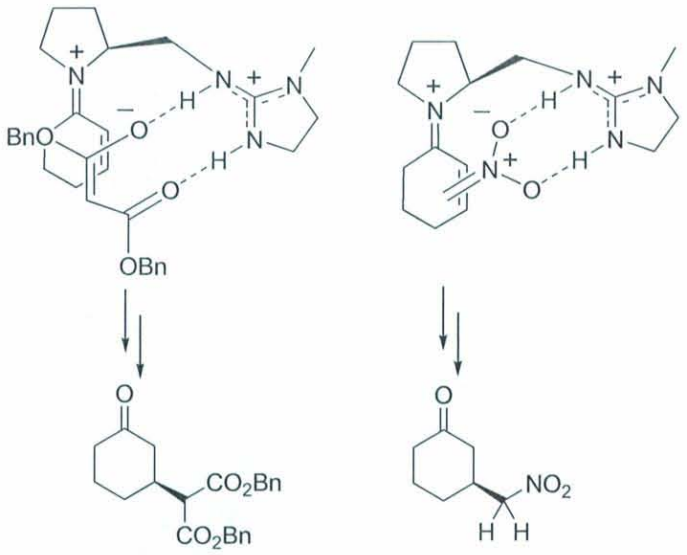


Entry[a]	78[b]	n	R	Cat. (mol%)	Vol. (mL)	Nitro-alkane (M)	Time (h)	Yield (%)	Ee(%)[c]
1	**78**	**2**	**H**	**15**	**2**	**1.2**	**120**	**31**	**72**
2			H	5	1	2.5	192	15	72
3			H	15	3	0.80	168	97	56
4			H	10	3	0.80	164	54	66
5	**79**	**2**	**CH_3**	**10**	**4**	**0.25**	**156**	**43**	**65**
6			CH_3	15	2	0.50	120	52	58
7	80	2	$(CH_2)_4$	10	4	0.60	240	44	41
8	81	2	$(CH_2)_5$	10	4	0.25	192	42	45
9	82	1	H	15	2	1.5	96	50	50[d]
10	83	1	CH_3	10	4	0.30	96	88	26

a: CH_2Cl_2 as solvent, DCE for entries 4, 5 and 9. b: 5 eq. of nitroalkane 2 eq. for entries 5, 6 and 8. c: chiral HPLC. d: ^{13}C NMR of ketal with (2*R*,3*R*)-2,3-butanediol.

The guanidinyl pyrrolidine **67** was again the catalyst of choice in these reactions and a small excess (2–5 eq.) of the nitroalkane was beneficial for enantioselectivity. Compared

with the malonate study, the trend in stereoselection was less predictable and lowering catalyst loading and increasing dilution did not always increase enantioselectivity. (**78**, entries 1, 3 and 4, Table 4). Interestingly, increasing the size of the nitroalkane did not result in an increase in enantioselectivity as has been observed in some studies and the enantioselectivity with nitrocyclopentane and nitrocyclohexane is lower than the acyclic nitroalkanes.[26,27] It is also noteworthy that an increase in catalyst loading and reaction time for the nitromethane/cyclohexenone reaction provided **78** in excellent yield (97%, Table 4, entry 3). This suggests that **78** is stable under the reaction conditions and may not be reacting further as indicated in studies with the tetrazolyl proline catalyst.[26] Significantly, all of the malonate and the nitroalkane addition products have the '*S*' configuration whereas the earlier proline-derived catalysts[15,16,25,30] provide the '*R*' products in the majority of cases. A possible explanation of this observation is that initial iminium ion formation is followed by addition of malonate or nitronate that is doubly hydrogen-bonded to the protonated guanidine, as shown in Figure 5.



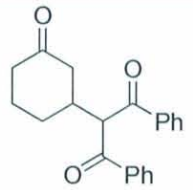
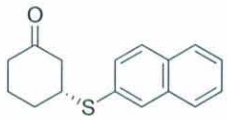
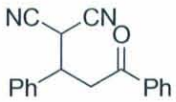
(*S*)-77a **(*S*)-78**

Figure 5. Proposed model for the origin of stereoselectivity with amino guanidine catalyst 67

This model may also explain the lower enantioselectivity for the substituted (larger) nitroalkanes as compared to nitromethane. Steric interactions of the nitroalkane substitutents with the cyclohexenone ring may disfavour the assembly shown in Figure 5, and consequently result in lower enantioselectivity.

The conjugate addition of other carbon and heteroatom nucleophiles such as dibenzoylmethane, malononitrile, and naphthalene-2-thiol was also effectively catalyzed with amino guanidine **67** to provide the conjugate addition products respectively (Table 5, entries 1-3).

Table 5: Asymmetric conjugate additions of other nucleophiles to enones.

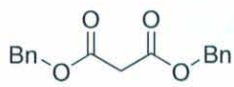
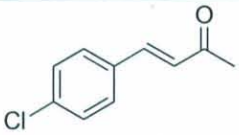
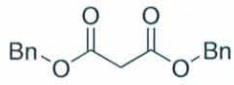
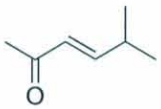
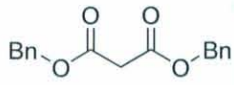
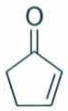
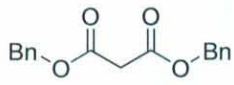
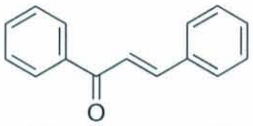
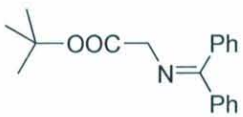
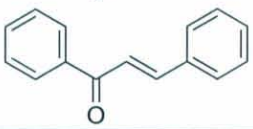
Entry	Michael adduct	Catalyst mol %	Solvent	Time (h)	Yield (%)	Ee (%)
1	 **84**	15	CH_2Cl_2	48	99	39
2		1	CH_2Cl_2	48	12	80
3	 **85**	1	CH_2Cl_2	48	95	20
4	 **86**	1	CH_2Cl_2	20	99	1

The stereoselectivities for these reactions were strongly dependant on the amount of catalyst employed, and low catalyst loading was necessary for appreciable enantioselection. This observation highlights the basicity of the guanidine pendant in catalyst **67**. Presumably, these nucleophiles are rapidly deprotonated due to their higher acidity, and the direct-deprotonation conjugate addition pathway (Figure 4, page 28) predominates as the catalyst loading increases. Low catalyst loading increases enantioselection but reduces the product yield. For example, **84** (product of dibenzoylmethane addition to cyclohexenone) was obtained in 99% yield and 39% ee when 15 mol% of catalyst **67** were employed (Table 5, entry1). However, a similar

reaction with 1 mol% of **67** provided **84** with 80% ee (Table 5, entry 2) but reduced yield (12%). While this highlights the inherent potential in **67** for asymmetric induction, a balance between iminium ion forming ability and basicity seems necessary, especially when nucleophiles with low pK_a values are employed.

Asymmetric conjugate addition of malonate and other nucleophiles to other cyclic and acyclic enones was also examined with guanidine catalyst **67**. The results of these studies are summarized in Table 6.

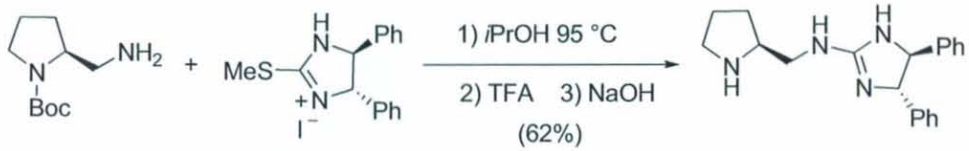
Table 6: Asymmetric conjugate additions of nucleophiles to other enones.

Entry	Michael donor	Michael acceptor	Time (h)	Yield (%)	Ee (%)
1			48	-	-
2			48	-	-
3			168	-	-
4			168	-	-
5			20	98	2
6			72	-	-

Surprisingly the reactions of dibenzyl malonate with cyclopentenone and cycloheptenone in the presence of **67** were unsuccessful as were the reactions with acyclic enones (Table 6, entries 1, 2 and 6). The reasons for the failure of these reactions are not clear at present. However, the more acidic nucleophile, malononitrile, (pK_a = 11) provided the Michael adduct with chalcone in quantitative yield. Unfortunately, this reaction was completely non-enantioselective (2% ee).

Reactions with other amino guanidines

Modifications to the 'secondary amine-guanidine' structural features in **67** were also examined. Additional chirality was introduced into **67**, by employing the C_2-symmetric 1,2-diphenyl ethylene diamine salt **73** for constructing the guanidine portion. Thus, reaction of (*S*)-*N*-Boc-aminomethylpyrrolidine (**73**) with the salt **87** (as described for the synthesis of **67**) provided the guanidinyl pyrrolidine **88** in 62% overall yield (Scheme 20).

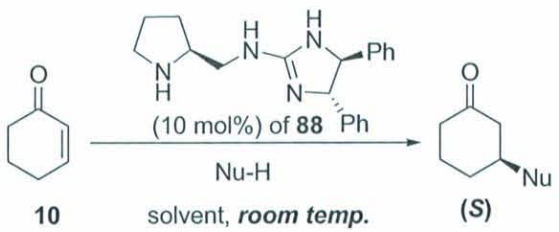


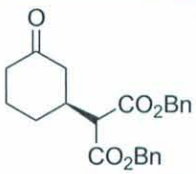
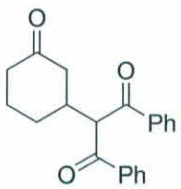
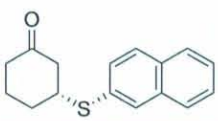
73 **87** **88**

Scheme 20

Asymmetric conjugate addition of malonate and other nucleophiles (naphthalene thiol and dibenzoylmethane) to cyclohexenone was then examined with guanidine **88** and the results of these studies are summarized in Table 7.

Table 7: Asymmetric conjugate addition reactions with catalyst 88.

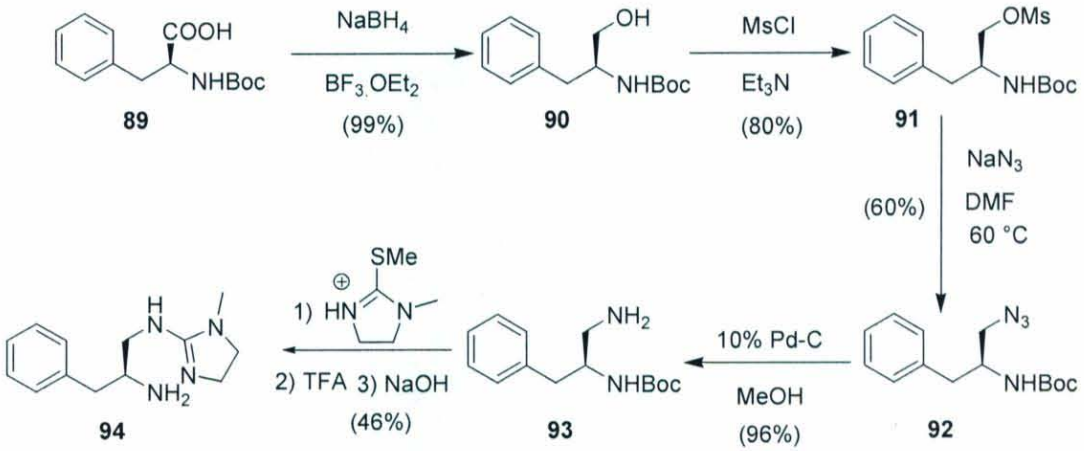


Entry	Michael adduct	Solvent	Time (h)	Yield (%)	Ee (%)
1		DCE	168	97	26
2		CH_2Cl_2	168	67	66
3		DCE	168	56	28
4		DCE	48	91	0

The Michael adduct of dibenzyl malonate with cyclohexenone was obtained in good to excellent yields (Table 7, entries 1 and 2). Unfortunately the enantioselectivity observed with **88** is lower than that observed with **67**. Enantioselection was also low for

reactions of cyclohexenone with dibenzoylmethane and naphthalene thiol. These observations suggest that chirality in the guanidine portion of these catalysts might not be beneficial for stereoselection.

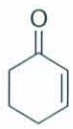
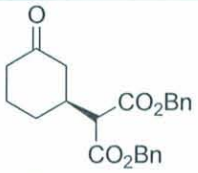
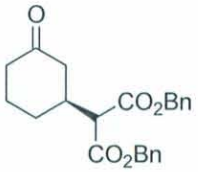
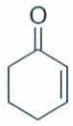
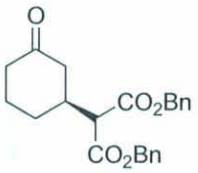
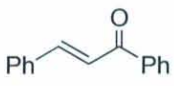
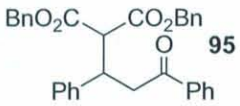
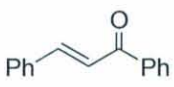
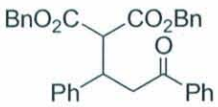
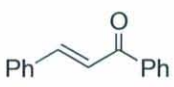
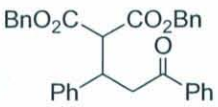
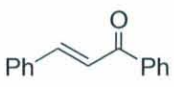
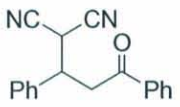
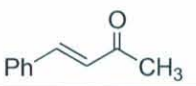
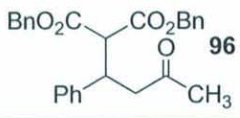
The effect of replacing one of the secondary amines in **67** with a primary amino group was also investigated. The aminoguanidine **94,** which is readily prepared from phenylalanine, was chosen as the candidate for this study. The synthesis of catalyst **94** is similar to that of catalysts **66-68**, and is summarized in Scheme 21.



Scheme 21

Interestingly the reactions which did not proceed with the guanidinyl-pyrrolidine catalyst **67** did, with catalyst **94**, and Michael adducts of dibenzyl malonate with acyclic enones were obtained in good to excellent yields in short reaction times. However, the enantiomeric excess of all the products is negligible. These results are summarized in Table 8.

Table 8: Asymmetric conjugate addition reactions with catalyst 94.

Entry[b]	Michael acceptor	Michael adduct	Solvent	Time (h)	Yield (%)	Ee (%)
1			CH_2Cl_2	48	100[a]	1
2			DMF	2	89[a]	2
3			Toluene	24	92[a]	3
4		 **95**	THF	48	87	1
5			CH_2Cl_2	48	100[a]	0
6			*t*-BuOH	24	70	1
7			CH_2Cl_2	48	83	4
8		 **96**	CH_2Cl_2	48	100[a]	2

[a] crude yield, [b] 5 mol% catalyst

The successful nucleophilic conjugate addition to acyclic enones with **94** are of note and futher studies with **94** and related catalysts are warranted. It is plausible that

iminium ion formation with the primary amine functionality in **94** is easier than with the secondary amine in **67**. However, the primary amine-derived iminium ion is probably not conformationally rigid, and consequently, the enantioselectivity is low.

Conclusion

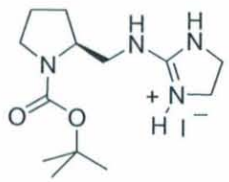
In conclusion, new organocatalysts incorporating iminium ion forming (pyrrolidine) and strongly basic (guanidine) functionalities were prepared and examined in the conjugate addition reactions of cyclohexenone and cyclopentenone with a variety of nucleophiles. The enantioselectivity for the Michael addition of dibenzyl malonate to cyclohexenone (86% ee) observed is, to the best of our knowledge, the highest reported for an organocatalytic variant of this reaction in the absence of an externally added base. It is also noteworthy that the malonate conjugate additions do not require a large excess of the malonate and good yields of the products with cyclohexenone are obtained in a reasonable time (Table 3, 1.2 eq. of malonate, average time 115 h, average yield 63%). Qualitatively, this implies an increased reaction rate compared to the functionalized imidazolidinone catalysts[15] used for this reaction (malonate as reaction medium (8 eq.), 78% yield, 150 h). The observations from this study provide some insight into the reactivity of amine-guanidine bifunctional catalyst motifs and lay the foundation for designing second-generation catalysts with modulated nucleophilic and basic character.

Experimental section

General

All commercially available reagents and solvents were used without purification. Commercial precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. IR spectra were recorded on a Bruker TENSOR 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 instrument. Coupling constants (*J*) are given in Hz. Mass spectra were obtained on an Agilent 1100 series LC/MSD chromatographic system. High-resolution mass spectra (EI or ESI) were obtained on a Waters GCT Premier Micromass mass spectrometer. Optical rotations were measured at the sodium D line on a JASCO-DIP 370 digital polarimeter at ambient temperature.

(*S*)-*Tert*-butyl-2-[(4,5-dihydro-1H-imidazol-2-ylamino)methyl)]pyrrolidine-1-carboxylate hydroiodide (66a):

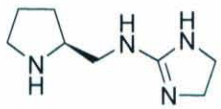


To a solution of (*S*)-*N*-Boc-2-aminomethylpyrrolidine (**73**)[13] (1.25 g, 6.25 mmol) in isopropanol (50.0 mL) was added 2-methylthio-2-imidazolinehydroiodide which was prepared from ethylenediamine by conversion to imidazolidine-2-thione and subsequent reaction with iodomethane), (1.53 g, 6.25 mmol), at room temperature.

The resulting solution was heated to reflux at 95 °C for 2 days. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (dichloromethane/methanol 98/2) to provide 1.40 g, (57%) of (*S*)-*tert*-butyl 2-[(4,5-dihydro-1H-imidazol-2-ylamino)methy]pyrrolidine-1-carboxylate hydroiodide (**66a**) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H, N*H*), 8.36 (s, 1H, N*H*), 7.59 (s, 1H, N*H*), 3.77 (s, 4H, NCH_2CH_2N), 3.68-3.65 (br m, 1H, C*H*N), 3.39-3.34 (m, 1H, CH_2NCO), 3.34-3.29 (dd, 1H, *J* = 6, 15, CHCH_2N), 3.23-3.12 (m, 2H, CH_2NCO, CHCH_2N), 2.02-1.87 (m, 4H, CH_2CH_2), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.1 (N*C*O), 156.3 (N*C*N), 81.4 (*C*(CH$_3$)$_3$), 57.6 (*C*HN), 47.2 (*C*H$_2$NCO), 46.5 (*C*H$_2$N), 43.6 (*C*H$_2$N), 43.3 (*C*H$_2$N), 30.4 (*C*H$_2$CH$_2$), 28.8 (C(*C*H$_3$)$_3$), 23.8 (CH$_2$*C*H$_2$); MS (APCI, Positive): m/z 269.2 ((M-I)$^+$, 100); IR: (neat) 2960, 1663, 1291, 1199, 1175, 1127 cm^{-1}; HRMS (CI): m/z 268.1897 (268.1899 calc. for $C_{13}H_{24}N_4O_2$ (M-I)).

4,5-Dihydro-*N*-[[(*S*)-pyrrolidin-2-yl]methyl]-1H-imidazol-2-amine (66):

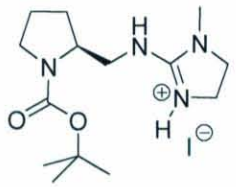


Hydroiodide **66a** (0.25 g, 0.63 mmol) was dissolved in dry CH_2Cl_2 (3.0 mL), and trifluoroacetic acid (1.5 mL) was added at 0 °C. After 30 min of stirring, the solution was brought to room temperature, stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5.0 mL) and the solution was extracted with water (2.0 mL). The aqueous phase was cooled (<5 °C), basified with

NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 0.050 g (47%) of **66** as a colourless oil. This material was used directly without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.50 (s, 4H, NC*H*$_2$C*H*$_2$N), 3.28-3.23 (m, 1H, C*H*N), 3.20-3.16 (dd, 1H, *J* = 3.5, 13.5 CHC*H*$_2$N), 2.98-2.93 (dd, 1H, *J* = 8.2, 13.5 CHC*H*$_2$N), 2.88-2.83 (m, 1H, C*H*$_2$N), 2.77-2.72 (m, 1H, C*H*$_2$N), 1.84-1.71 (m, 2H, C*H*$_2$CH$_2$, 1 x N*H*), 1.63-1.56 (m, 1H, C*H*$_2$C*H*$_2$), 1.63-1.56 (m, 1H, C*H*$_2$C*H*$_2$), 1.40-1.31 (m, 1H, C*H*$_2$CH$_2$, N*H*); visible peaks for tautomer: 3.73-3.7 (m); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 163.4 (NCN), 59.0 (NC*H*$_2$C*H*$_2$N), 48.5 (br, NCH), 46.8 (br, 2 x NC*H*$_2$), 29.4 (br, C*H*$_2$CH$_2$), 26.4 (br, CH$_2$C*H*$_2$); visible peaks for minor tautomer: δ 63.9, 49.5, 46.5, 41.9, 31.9; MS (APCI, Positive): m/z 169.2 (M+H)+, 100); IR: (neat): 3261, 2960, 1608, 1559, 1456, 1263, 1199 cm^{-1}; HRMS (CI): m/z 169.1454 (169.1453 calc. for $C_8H_{17}N_4$ (M+H)+). $[\alpha]_D^{23}$ = - 33.2 (*c* 1, $CHCl_3$).

(*S*)-*Tert*-butyl-2-[(4,5-dihydro-1-methyl-1H-imidazol-2-ylamino)methyl]pyrrolidine-1-carboxylate hydroiodide (67a):

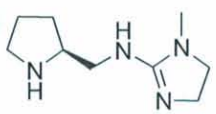


To a solution of (*S*)-*N*-Boc-2-aminomethylpyrrolidine (**73**) (3.00 g, 15.0 mmol) in isopropanol (50.0 mL) was added 4,5-dihydro-1-methyl-2-(methylthio)-1H-imidazole

hydroiodide previously prepared from *N*-methyl ethylenediamine by conversion to 1-methyl imidazolidin-2-thione and subsequent reaction with iodomethane, (3.87 g, 15.0 mmol) at room temperature and the solution was heated to reflux at 95 °C for 2 days. The solution was concentrated under reduced pressure to provide 6.13 g (99%) of (*S*)-*tert*-butyl-2-{(4,5-dihydro-1-methyl-1H-imidazol-2-ylamino)methyl}pyrrolidine-1 carboxylate hydroiodide (**67a**) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H, N*H*), 8.54 (s, 1H, N*H*), 3.84-3.83 (m, 1H, C*H*N), 3.80-3.76 (m, 2H, CH_2NCO), 3.68-3.59 (m, 3H, NCH_2CH_2N, CHCH_2N), 3.42-3.35 (m, 2H, NCH_2CH_2N), 3.27-3.24 (m, 1H, CHCH_2N), 3.14 (s, 3H, NCH_3), 2.26 (m, 1H, CH_2CH_2), 2.04-1.89 (m, 2H, CH_2CH_2), 1.89-1.85 (m, 1H, CH_2CH_2), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.5 (N*C*O), 156.9 (N*C*N), 81.0 (O*C*(CH$_3$)$_3$, 56.9 (*C*HN), 50.3 (*C*H$_2$NCO), 48.2 (CH*C*H$_2$N), 47.1 (*C*H$_2$N), 41.4 (N*C*H$_3$), 33.2 (*C*H$_2$N), 29.7 (*C*H$_2$CH$_2$), 28.4 (C(*C*H$_3$)$_3$), 23.7 (CH$_2$*C*H$_2$); MS (APCI, Positive): m/z 283.3 ((M+H)+, 100); IR (neat): 3199, 2967, 2228, 2024, 1669, 1405 cm^{-1}; HRMS (CI): m/z 282.2054 (282.2056 calc. for $C_{14}H_{26}N_4O_2$ (M-I)+).

4,5-Dihydro-1-methyl-*N*-[[(*S*)-pyrrolidin-2-yl]methyl]-1H-imidazol-2-amine (67):

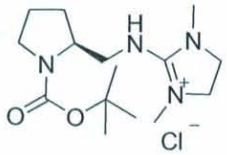


The hydroiodide salt **67a** (1.50 g, 3.61 mmol) was dissolved in dry CH_2Cl_2 (5.00 mL), and trifluoroacetic acid (5.00 mL) was added at 0 °C. After 30 min of stirring, the solution was brought to room temperature, stirred for 3 h and concentrated under reduced

pressure. The residue was dissolved in ethyl acetate (5.00 mL) and the solution was extracted with water (2.00 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 x 10.00 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 624 mg (93%) of **67** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45-3.41 (m, 2H, NCH_2CH_2N), 3.33-3.28 (m, 1H, C*H*N), 3.27-3.21 (m, 3H, CHCH_2N, NCH_2CH_2N), 3.04-3.00 (dd, 1H, J = 8.3, 12.7, CHCH_2N), 2.93-2.85 (m, 2H, CH_2N), 2.73 (m, 3H, CH_3N), 1.87-1.79 (m, 1H, CH_2CH_2), 1.77-1.73 (m, 1H, CH_2CH_2), 1.70-1.62 (m, 1H, CH_2CH_2), 1.45-1.38 (m, 1H, CH_2CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.8 (N*C*N), 59.5 (*C*HN), 51.4 (NCH_3), 48.1 (CH*C*H_2N), 46.5 (NCH$_2$*C*H_2N), 41.7 (N*C*H_2CH_2N), 33.7 (*C*H_2N), 29.2 (*C*H_2CH_2), 26.8 (CH_2*C*H_2); MS (APCI, Positive): m/z 183.1 ((M+H)+, 100); IR (neat): 2958, 2024, 1655, 1409, 1262, 1031 cm^{-1}; HRMS (CI): m/z 183.1605 (183.1610 calc. for $C_9H_{19}N_4$ (M+H)+). $[\alpha]_D^{23}$ = - 50.4 (*c* 1, $CHCl_3$).

(*S*)-*Tert*-butyl-2-[(1,3-dimethylimidazolidin-2-ylideneamino)methyl]pyrrolidine-1-carboxylate hydro chloride (68a):

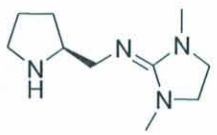


To a solution of (*S*)-*N*-Boc-2-aminomethylpyrrolidine (**73**) (1.38 g, 6.90 mmol) in acetonitrile (25.0 mL) was added commercially-available 2-chloro-1,3-

dimethylimidazolinium chloride (1.17 g, 6.90 mmol), potassium carbonate (2.86 g, 21.0 mmol) at room temperature and the solution was stirred at room temperature for 2 days. The undissolved solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (dichloromethane/methanol 90/10) to provide 0.780 g (34%) of (*S*)-*tert*-butyl-2-((1,3-dimethylimidazolidin-2ylideneamino)methyl)pyrrolidine-1-carboxylate hydrochloride (**68a**) as a white, gummy foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.6 (s,1H, N*H*), 3.94-3.93 (br m, 1H, C*H*N), 3.75-3.72 (m, 1H, CHCH_2N), 3.64 (s, 4H, NCH_2CH_2N), 3.52-3.48 (m, 1H, CHCH_2N), 3.37-3.32 (m, 2H, CH_2NCO), 3.28 (s, 6H, NCH_3), 2.33-2.29 (m, 1H, CH_2CH_2), 2.11-2.09 (1H, m, CH_2CH_2), 1.93-1.83 (m, 2H, CH_2CH_2), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.9 (N*C*O), 156.1 (N=*C*N), 80.2 (O*C*(CH$_3$)$_3$), 57.1 (*C*HN), 49.7 (CH*C*H$_2$N, NCH_2*C*H$_2$N), 47.3 (N*C*H$_3$), 46.1 (N*C*H$_3$), 35.3 (*C*H$_2$NC(O)), 29.5 (C(*C*H$_3$)$_3$), 28.4 (NCH$_2$CH$_2$(pyrrolidine)), 23.7 (NCH$_2$ (pyrrolidine)). Visible peaks for isomeric salt: δ 157.3, 81.1, 56.1, 53.6, 47.8, 45.6, 30.9; MS (APCI, Positive): m/z 297.2 ((M-I)+, 100); IR (neat): 2972, 1684, 1632, 1392, 1166, 1109 cm^{-1}; HRMS (CI): m/z 296.2203 (296.2212 calc. for $C_{15}H_{28}N_4O_2$ (M-I)+).

***N*-(1,3-Dimethylimidazolidin-2-ylidene)[(*S*)-pyrrolidin-2-yl]methanamine (68):**



Hydrochloride **68a**, (0.320 g, 0.960 mmol) was dissolved in dry CH_2Cl_2 (3.00 mL), and trifluoroacetic acid (1.50 mL) was added at 0 °C. After 30 min of stirring, the solution was brought to room temperature and stirred for 3h. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5.00 mL) and the solution was extracted with water (2.00 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give 138 mg (73%) of **68** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96-3.92 (m, 1H, C*H*N), 3.84-3.8 (dd, 1H, J = 9.2 Hz, 13.0 Hz, CHCH_2N), 3.5-3.45 (m, 1H, CH_2N), 3.4-3.37 (dd, 1H, J = 5.7, 13.0 Hz, CHCH_2N), 3.24-3.14 (m, 3H, CH_2N, NCH_2CH_2N), 2.87 (s, 3H, CH_3N), 2.82 (br s, 1H, N*H*), 2.81-2.76 (m, 3H, N*H*), 2.45(s, 3H, CH_3N), 1.96-1.9 (m, 1H, CH_2CH_2), 1.82-1.74 (m, 2H, CH_2CH_2), 1.54-1.47 (m, 1H, CH_2CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 167.7 (N*C*N), 64.2 (*C*HN), 58.6 (CH*C*H$_2$N), 51.3 (*C*H$_2$N), 51.1 (NCH$_2$*C*H$_2$N), 49.4 (NCH$_2$CH$_2$N), 36.9 (N*C*H$_3$), 36.7 (N*C*H$_3$) 32.4 (*C*H$_2$CH$_2$), 26.1 (CH$_2$*C*H$_2$); MS (APCI, Positive): m/z 197.1 (M+1, 100); IR (neat): 2937, 2231, 2024, 1652, 1603, 1447, 1403, 1288, 1263, 1114 cm^{-1}; HRMS (CI): m/z 197.1774 (197.1766 calc. for $C_{10}H_{21}N_4$ (M+H)+). $[\alpha]_D^{23}$ = - 54.6 (*c* 1, $CHCl_3$).

General procedure for the guanidine-catalyzed conjugate addition reactions:

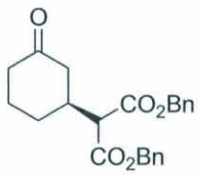
All reactions were performed in closed vials without the exclusion of air or moisture. To a solution of the catalyst in an appropriate solvent was added the enone followed by

the nucleophile. The solution was stirred at ambient temperature for the specified time and the reaction was monitored by TLC. The mixture was diluted with solvent and the resulting solution was washed once with aqueous HCl (0.5 *N*), dried with Na_2SO_4 and concentrated under reduced pressure to provide the crude product which was purified by flash chromatography on silica gel.

All conjugate addition products displayed spectral data in agreement with those reported in the literature.

The enantiomeric excess and absolute configuration of **77a** and **77b** were assigned by comparison of the HPLC retention times with those reported in the literature.[41] The configuration of **77c** was assigned by analogy to the retention times for **77a** and **77b**. The enantiomeric excess of nitroketones **78a-d** and **78f** were determined by chiral HPLC comparison with racemic samples. The enantiomeric excess of **78e** was determined by converison to diastereomeric ketals with (2*R*,3*R*)-2,3-butanediol. The absolute configurations of **78a-f** were determined by comparison of the sign of the observed optical rotations with those reported in the literature.[17]

Dibenzyl 2-[(*S*)-3-oxocyclohexyl]malonate (77a):[15,41]



The reaction of cyclohexenone (50.0 μL, 0.500 mmol)), dibenzyl malonate (152 μL, 0.600 mmol) and **67** (9.50 mg, 10.0 mol%), according to the general procedure, in 1,2-

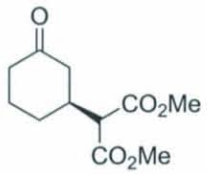
dichloroethane (3.00 mL) for 139 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 125 mg (64%) of **67a** as a colourless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.34 (m, 6H, Ar*H*), 7.30-7.27 (m, 4H, Ar*H*), 5.16 (AB system, 4H, OCH_2), 3.42 (d, 1H, J = 8.3, C*H*($CO_2Bn)_2$), 2.62-2.52 (m, 1H, C*H*CH_2), 2.47-2.41 (m, 1H, CH_2), 2.41-2.36 (m, 1H, CH_2), 2.28-2.18 (m, 2H, CH_2), 2.16-2.00 (m, 1H, CH_2), 1.95-1.88 (m, 1H, CH_2), 1.7-1.6 (m, 1H, CH_2), 1.52-1.44 (m, 1H, CH_2); MS (APCI): m/z 381.1 (M+1); IR (neat): 2928, 1729, 1712, 1257, 1226, 1148 cm^{-1}.

Enantiomeric excess: 86.3%

t_{major}: 49.1 min; t_{minor}: 41.6 min (Chiralpak AS-H, 230 nm, hexanes/*i*PrOH, 95/5, 1 mL/min).

Dimethyl 2-[(*S*)-3-oxocyclohexyl]malonate (77b):[16,41]



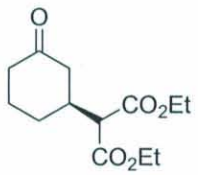
The reaction of cyclohexenone (0.050 mL, 0.50 mmol), dimethyl malonate (71 μL, 0.60 mmol) and **67** (14 mg, 15 mol%), according to the general procedure, in dichloromethane (1.0 mL) for 92 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 110 mg (94%) of **77b** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.47 (d, 1H, J = 8.5, $CH(CO_2Me)_2$), 2.59-2.50 (m, 1H, $CHCH_2$), 2.47-2.41 (m, 1H, CH_2), 2.41-2.36 (m, 1H, CH_2), 2.28-2.18 (m, 2H, CH_2), 2.16-2.00 (m, 1H, CH_2), 1.95-1.88 (m, 1H, CH_2), 1.7-1.6 (m, 1H, CH_2), 1.52-1.44 (m, 1H, CH_2); MS (APCI): m/z 229.1 (M+1); IR (neat): 2923, 1732, 1711, 1436, 1257, 1228, 1153 cm^{-1}.

Enantiomeric excess: 59%

t_{major}: 26.2 min; t_{minor}: 21.6 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

Diethyl 2-[(S)-3-oxocyclohexyl]malonate (77c):[16,41]



The reaction of cyclohexenone (50.0 μL, 0.500 mmol), diethyl malonate (94.0 μL, 0.600 mmol) and **67** (14.0 mg, 15.0 mol%), according to the general procedure, in dichloromethane (1.00 mL) for 92 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 111 mg (90%) of **77c** as white solid.

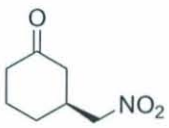
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24-4.18 (2 q, 4H, CH_2CH_3), 3.29 (d, 1H, J = 7.4, $CH(CO_2Et)_2$), 2.59-2.50 (m, 1H, $CHCH_2$), 2.49-2.38 (m, 2H, CH_2), 2.31-2.22 (m, 2H, CH_2), 2.11-2.03 (m, 1H, CH_2), 1.99-1.94 (m, 1H, CH_2), 1.73-1.64 (m, 1H, CH_2), 1.56-

1.47 (m, 1H, CH_2), 1.29-1.26 (2 t, 6H, CH_3); MS (APCI): m/z 257.1 (M+1); IR (neat): 2936, 1727, 1713, 1255, 1227, 1152, 1096, 1028 cm^{-1}.

Enantiomeric excess: 52%

t_{major}: 13.5 min; t_{minor}: 11.9 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

(*S*)-3-(Nitromethyl)cyclohexanone (78):[26]



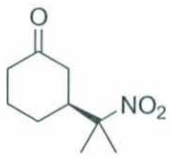
The reaction of cyclohexenone (0.050 mL, 0.50 mmol), nitromethane (140 μL, 2.5 mmol) and **67** (14 mg, 15 mol%), according to the general procedure, in dichloromethane (2.0 mL) for 120 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 25 mg (31%) of **78** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41-4.35 (d of AB, 2H, J = 7.4, 12.1, CH_2NO_2), 2.71-2.61 (m, 1H, CHCH_2), 2.54-2.44 (m, 2H, CH_2), 2.84-2.27 (m, 1H, CH_2), 2.21-2.10 (m, 2H, CH_2), 2.03-1.96 (m, 1H, CH_2), 1.80-1.70 (m, 1H, CH_2), 1.59-1.48 (m, 1H, CH_2); MS (EI, 70 eV): m/z 157 (M^+); IR (neat): 2923, 2853, 1710, 1544, 1383, 1229 cm^{-1}.

Enantiomeric excess: 72%

t_{major}: 36.1 min; t_{minor}: 64.1 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

(*S*)-3-(2-Nitropropan-2-yl)cyclohexanone (79):[28]



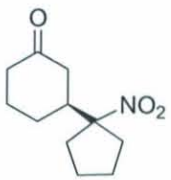
The reaction of cyclohexenone (0.050 mL, 0.50 mmol), 2-nitropropane (93 μL, 1.0 mmol) and **67** (9.5 mg, 10 mol%), according to the general procedure, in 1,2-dichloroethane (4.0 mL) for 156 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 42 mg (43%) of **79** as a colourless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.47-2.35 (m, 3H, C*H*CH_2, C*H*$_2$), 2.28-2.20 (m, 1H, C*H*$_2$), 2.16-2.08 (m, 2H, C*H*$_2$), 1.83-1.77 (m, 1H, C*H*$_2$), 1.67-1.6 (m, 1H, C*H*$_2$), 1.57 (s, 3H, C*H*$_3$), 1.55 (s, 3H, C*H*$_3$), 1.47-1.38 (m, 1H, C*H*$_2$); MS (EI, 70 eV): m/z 185 (M^+); IR (neat): 2924, 1711, 1531, 1401, 1314, 1234, 1140 cm^{-1}; $[\alpha]_D^{23}$ = - 27 (*c* 1, $CHCl_3$).

Enantiomeric excess: 65%

t_{major}: 43.3 min; t_{minor}: 40.5 min (Chiralpak AS-H, 230 nm, hexanes/*i*PrOH, 95/5, 1 mL/min).

(*S*)-3-(1-Nitrocyclopentyl)cyclohexanone (80):[16]



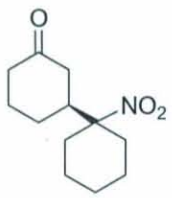
The reaction of cyclohexenone (50.0 μL, 0.500 mmol)), nitrocyclopentane (274 μL, 2.50 mmol) and **67** (9.50 mg, 10.0 mol%), according to the general procedure, in 1,2-dichloroethane (4.00 mL) for 240 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 47.0 mg (44%) of **80** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.74-2.64 (m, 2H, C*H*CH_2, CH_2), 2.49-2.46 (m, 1H, CH_2), 2.42-2.35 (m, 1H, CH_2), 2.32-2.16 (m, 3H, CH_2), 2.15-2.08 (m, 1H, CH_2), 1.97-1.91 (m, 1H, CH_2), 1.83-1.66 (m, 6H, CH_2), 1.65-1.55 (m, 1H, CH_2), 1.45-1.36 (m, 1H, CH_2); MS (EI, 70 eV): m/z 211 (M^+); IR (neat): 2957, 1713, 1530, 1449, 1434, 1351 cm^{-1}; $[\alpha]_D^{23}$ = + 6.1 (c 1, $CHCl_3$).

Enantiomeric excess: 41%

t_{major}: 28.7 min; t_{minor}: 14.6 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

(*S*)-3-(1-Nitrocyclohexyl)cyclohexanone (81):[16]



The reaction of cyclohexenone (50.0 μL, 0.500 mmol), nitrocyclohexane (126 μL, 1.00 mmol) and **67** (9.50 mg, 10.0 mol%), according to the general procedure, in 1,2-dichloroethane (4.00 mL) for 192 h gave after purification by flash column

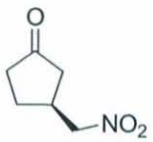
chromatography on silica gel (hexanes/ethylacetate 60/40) 49.0 mg (42%) of **81** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54-2.45 (m, 3H, C*H*CH_2, C*H*$_2$), 2.43-2.38 (m, 1H, C*H*$_2$), 2.25-2.14 (m, 1H, C*H*$_2$), 2.14-2.02 (m, 2H, C*H*$_2$), 1.96-1.91 (m, 1H, C*H*$_2$), 1.73-1.62 (m, 3H, C*H*$_2$), 1.53-1.49 (m, 2H, C*H*$_2$), 1.40-1.18 (m, 6H, C*H*$_2$); MS (EI, 70 eV): m/z 225 (M^+); IR (neat): 2925, 2856, 1711, 1677, 1546, 1530, 1346, 1149 cm^{-1}; $[\alpha]_D^{23}$ = - 0.3 (*c* 1, $CHCl_3$).

Enantiomeric excess: 45%

t_{major}: 25.6 min; t_{minor}: 13.1 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

(*S*)-3-(Nitromethyl)cyclopentanone (82):[17]

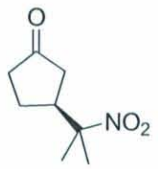


The reaction of cyclopentenone (50.0 μL, 0.600 mmol)), nitromethane (161 μL, 3.00 mmol) and **67** (16.0 mg, 15.0 mol%), according to the general procedure, in dichloromethane (2.00 mL) for 96 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 40.0 mg (49%) of **82** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56-4.45 (m, 2H, CH_2NO_2), 3.06-2.97 (m, 1H, $CHCH_2$), 2.54 (dd, 1H, J = 7.3, 18.2, CH_2), 2.44-2.35 (m, 1H, CH_2), 2.33-2.21 (m, 2H, CH_2), 2.02 (dd, 1H, J = 9.6, 18.2, CH_2) 1.76-1.67 (m, 1H, CH_2); MS (APCI): m/z 142.1 (M-1); IR (neat): 1738, 1544, 1403, 1383, 1161 cm^{-1}.

Enantiomeric excess: 50% (based on ^{13}C spectra of ketal with (2*R*,3*R*)-2,3-butanediol).

(*S*)-3-(2-Nitropropan-2-yl)cyclopentanone (83):[17]



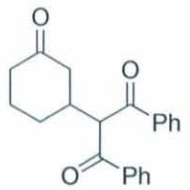
The reaction of cyclopentenone (50.0 μL, 0.600 mmol)), 2-nitropropane (276 μL, 1.20 mmol) and **67** (11.0 mg, 10.0 mol%), according to the general procedure, in 1,2-dichloroethane (4.00 mL) for 96 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 85.0 mg (88%) of **83** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.89-2.81 (m, 1H, $CHCH_2$), 2.45-2.32 (m, 2H, CH_2), 2.28-2.20 (m, 1H, CH_2), 2.14-2.03 (m, 2H, CH_2), 1.73-1.65 (m, 1H, CH_2), 1.64 (s, 3H, CH_3), 1.62 (s, 3H, CH_3); MS (EI, 70 eV): m/z 171 (M^+); IR (neat): 2926, 1743, 1533, 1375, 1348, 1278, 1164, 1148 cm^{-1}; $[\alpha]_D^{23}$ = - 13.3 (*c* 1, $CHCl_3$).

Enantiomeric excess: 26%

t_{major}: 39.3 min; t_{minor}: 58.8 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)cyclohexanone (84):[42]



The reaction of cyclohexenone (50.0 μL, 0.500 mmol)), dibenzoylmethane (127 mg, 0.60 mmol) and **67** (1.00 mg, ~1.00 mol%), according to the general procedure, in 1,2-dichloroethane (3.00 mL) for 120 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 75/25) 20.0 mg (12%) of **84** as a white solid.

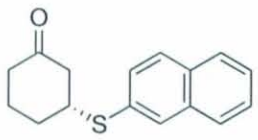
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0-7.96 (m, 4H, Ar*H*), 7.59-7.55 (m, 2H, Ar*H*), 7.47-7.43 (m, 4H, Ar*H*), 5.25 (d, 1H, J = 8.1, C*H*(COPh)$_2$), 3.08-3.00 (m, 1H, C*H*CH$_2$), 2.46-2.40 (m, 2H, C*H*$_2$), 2.31-2.24 (m, 2H, C*H*$_2$), 2.07-2.02 (m, 1H, C*H*$_2$), 1.98-1.93 (m, 1H, C*H*$_2$), 1.75-1.66 (m, 1H, C*H*$_2$), 1.61-1.52 (m, 1H, C*H*$_2$); MS (APCI): m/z 319.2 (M-1) ; IR (neat): 2926, 1693, 1664, 1447, 1258, 1229, 1179 cm^{-1}.

Enantiomeric excess: 80%

t_{major}: 36.1 min; t_{minor}: 31.9 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

A similar reaction of cyclohexenone (50.0 μL, 0.500 mmol)), dibenzoylmethane (244 mg, 1.00 mmol) and **67** (14.0 mg, 15.0 mol%) in dichloromethane (2.00 mL) for 48 h gave 167 mg (99%) of **84** with 39% ee.

(*R*)-3-(Naphthalen-2-ylthio)cyclohexanone (85):[19,43]



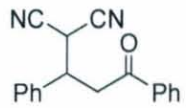
The reaction of cyclohexenone (0.050 mL, 0.50 mmol), naphthalene-2-thiol (83 mg, 0.50 mmol) and **67** (1.0 mg, 1.0 mol%), according to the general procedure, in 1,2-dichloroethane (3.0 mL) at -20 °C for 48 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 88 mg (66%) of **85** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (br s, 1H, Ar*H*), 7.83-7.78 (m, 3H, Ar*H*), 7.52-7.48 (m, 3H, Ar*H*), 3.58-3.52 (m, 1H, C*H*CH_2), 2.76-2.72 (m, 1H, CH_2), 2.46-2.29 (m, 3H, CH_2), 2.22-2.13 (m, 2H, CH_2), 1.83-1.68 (m, 2H, CH_2); MS (EI, 70eV): m/z 256 (M^+); IR (neat): 2929, 1709, 1418, 1220 cm^{-1}.

Enantiomeric excess: 20%

t_{major}: 16.9 min; t_{minor}: 10.9 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

2-(3-Oxo-1,3-diphenylpropyl)malononitrile (86):[44]



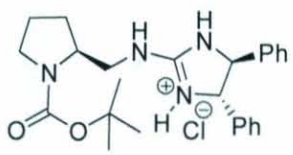
The reaction of *trans*-chalcone (0.100 g, 0.500 mmol)), malononitrile (38.0 mg, 0.60 mmol) and **67** (4.50 mg, 5.00 mol%), according to the general procedure, in dichloromethane (1.00 mL) for 20 h gave 132 mg (quant.) of **86** as a solid that was pure by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H, Ar*H*), 7.66-7.62 (m, 1H, Ar*H*), 7.52-7.41 (m, 7H, Ar*H*), 4.66 (d, 1H, C*H*$(CN)_2$), 3.98-3.96 (m, 1H, C*H*CH_2), 3.75-3.67 (m, 2H, CH_2); MS (APCI): m/z 273.1 (M-1); IR (neat): 2257, 1681, 1450, 1313, 1235 cm^{-1}.

Enantiomeric excess: 2%

t_{major}: 20.9 min; t_{minor}: 18.9 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 70/30, 1 mL/min).

(*S*)-*Tert*-butyl2-(4,5-dihydro-4,5-diphenyl-1H-imidazol-2-ylamino)methyl)pyrrolidine -1-carboxylate (88a):

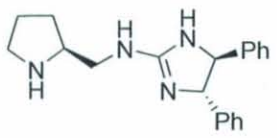


To a solution of (*S*)-*N*-Boc-2-aminomethyl pyrrolidine (**73**)[13] (0.405 g, 2.02 mmol) in isopropanol (20.0 mL) was added (4*S*,5*S*)-4,5-dihydro-2-(methylthio)-4,5-diphenyl-

1H-imidazole hydroiodide ((prepared from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine by conversion to diphenylimidazolidine-2-thione and subsequent reaction with iodomethane, (0.802 g, 2.02 mmol)) at room temperature and the solution was heated to reflux at 95 °C for 24 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (dichloromethane/methanol 98/2) to provide 0.500 g, (45%) of (*S*)-*Tert*-butyl2-{(4,5-dihydro-4,5-diphenyl-1H-imidazol-2-ylamino)methyl}pyrrolidine-1-carboxylate (**88a**) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.1-9 (t, 1H, *J* = 6.7, N*H*), 8.9 (s, 1H, N*H*), 7.96 (s, 1H, N*H*), 7.41-7.39 (m, 5H, Ar*H*), 7.29-7.22 (m, 5H, Ar*H*), 4.91-4.90 (d, 1H, *J* = 7.6, NC*H*CHN), 4.84-4.83 (d, 1H, *J* = 7.6, NCHC*H*N), 3.82-3.78 (br m, 1H, C*H*N), 3.51-3.46 (dd, 1H, *J* = 6.74, 14.6, CHCH_2N), 3.42-3.39 (dd, 1H, *J* = 5.47, 10.85, CHCH_2N), 3.38-3.31 (m, 1H, CH_2NCO), 3.28-3.23 (m, 1H, CH_2NCO), 2.14-2 (m, 2H, CH_2CH$_2$), 1.95-1.93 (m, 2H, CH$_2$CH_2), 1.27 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.3 (N*C*N), 129.3 (2 x Ar*C*), 129.2 (4 x Ar*C*), 128.7 (4 x Ar*C*), 126.4 (2 x Ar*C*), 81.1 (*C*(CH$_3$)$_3$, 68.3 (N*C*HCHN), 67.8 (NCH*C*HN), 57.6 (*C*HN), 46.9 (*C*H$_2$NCO), 46 (*C*H$_2$N), 30.3 (*C*H$_2$CH$_2$), 28.2 (C(*C*H$_3$)$_3$), 23.5 (CH$_2$*C*H$_2$); MS (APCI, Positive): m/z 421.3 (M+H, 100); IR: (neat) 2960, 1663, 1291, 1199, 1175, 1127 cm^{-1}; HRMS (EI): m/z 420.2527 (420.2525 calc. for $C_{25}H_{32}N_4O_2$ (M+).

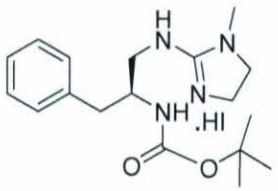
4,5-dihydro-4,5-diphenyl-*N*-(((*S*)-pyrrolidin-2-yl)methyl)-1H-imidazol-2-amine (88):



The above hydroiodide (0.250 g, 0.457 mmol) was dissolved in dry CH_2Cl_2 (1.50 mL), and trifluoroacetic acid (1.50 mL) was added at 0 °C. After 30 min of stirring, the solution was brought to room temperature, stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5.00 mL) and the solution was extracted with water (2.00 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 0.145 g (99%) of **88** as a colourless oil. This material was used without further purification.

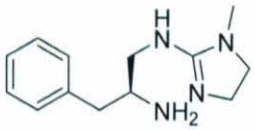
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.11 (m, 10H, ArC*H*), 4.57-4.5 (s, 2H, NC*H*C*H*N), 3.38-3.34 (dd, 1H, *J* = 3.67, 13.2, CHC*H*$_2$N), 3.32-3.3 (m, 1H, C*H*N), 3.12-3.08 (dd, 1H, *J* = 7.5, 13.2, CHC*H*$_2$N), 2.84-2.81 (m, 2H, C*H*$_2$N), 1.85-1.74 (m, 2H, C*H*$_2$CH$_2$), 1.66-1.62 (m, 1H, C*H*$_2$C*H*$_2$), 1.45-1.40 (m, 1H, C*H*$_2$C*H*$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.7 (NCN), 128.6 (2 x Ar*C*), 128.4 (4 x Ar*C*), 127.3 (2 x Ar*C*), 126.4 (4 x Ar*C*), 77.25 (NC*H*C*H*N), 61.3 (N*C*H), 46.4 (CH*C*H$_2$), 28.9 (*C*H$_2$CH$_2$), 26.2 (CH$_2$*C*H$_2$); visible peaks for minor tautomer: δ 163.8, 61.3, 46.3, 29.5, 24, 13.8; MS (APCI, Positive): m/z 321.2 (M+1, 100); IR: (neat): 2961, 2358, 2230, 2023, 1772, 1652, 1452, 1263, 1197 cm^{-1}; HRMS (EI): m/z 320.2004 (320.2001 calc. for $C_{20}H_{24}N_4$ (M+)).

(*S*)-*Tert*-butyl-3-(4,5-dihydro-1-methyl-1H-imidazol-2-ylamino)-1-phenylpropan-2 ylcarbamate (94a):



To a solution of (*S*)-*tert*-butyl1-amino-3-phenylpropan-2-ylcarbamate (0.400 g, 1.60 mmol) in isopropanol (20.0 mL) was added 4,5-dihydro-1-methyl-2-(methylthio)-1H-imidazole hydroiodide (**75**) (prepared from *N*-methyl ethylenediamine by conversion to 1-methyl imidazolidin-2-thione and subsequent reaction with iodomethane), 0.413 g, 1.60 mmol) at room temperature and the solution was heated to reflux at 95 °C for 2 days. The solution was concentrated under reduced pressure to provide 0.168 g (32%) of (*S*)-*Tert*-butyl3-(4,5-dihydro-1-methyl-1H-imidazol-2-ylamino)-1-phenylpropan-2-ylcarbamate hydroiodide (**94a**) as a pale yellow solid.

***N*-((*S*)-2-amino-3-phenylpropyl)-4,5-dihydro-1-methyl-1H-imidazol-2-amine (94):**

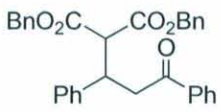


Hydroiodide (0.140 g, 0.421 mmol) was dissolved in dry CH_2Cl_2 (2.00 mL), and trifluoroacetic acid (2.00 mL) was added at 0 °C. After 30 min of stirring, the solution was brought to room temperature, stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5.00 mL) and the solution was

extracted with water (2.00 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 45.0 mg (46%) of **94** as a colourless oil. This was directly used further.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.23 (m, 5H, ArC*H*), 4.14-4.1 (m, 1H, C*H*NH_2), 3.64-3.6 (t, 1H, *J* = 9.9, CHCH_2Ar), 3.44-3.36 (m, 4H, NCH_2CH_2N), 3.33-3.28 (m, 1H, CHCH_2Ar), 3.18-3.13 (m, 2H, CH_2NH), 2.74 (s, 3H, NCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 140 (NCN), 129.4 (2 x Ar*C*), 129.2 (Ar*C*), 128.3 (2 x Ar*C*), 126 (Ar*C*), 47.8 (NCH_3), 42.8 (NH_2*C*H), 38.5 (NCH_3*C*H_2), 33.5 (N*C*H_2), 30.8 (Ar*C*H_2,CH*C*H_2); MS (APCI, Positive): m/z 233.1 (M+1, 100); HRMS (CI): m/z 233.1774 (233.1766 calc. for $C_{13}H_{21}N_4$ (M+H)).

Dibenzyl 2-(3-oxo-1,3-diphenylpropyl)malonate (95):[32]



The reaction of *trans*-chalcone (107 mg, 0.500 mmol)), dibenzylmalonate (0.152µl, 0.619 mmol) and **94** (6.00 mg, 0.050 mol%), according to the general procedure, in dichloromethane (1.00 mL) for 48 h gave 279 mg (quant) of **95** as a colourless solid.

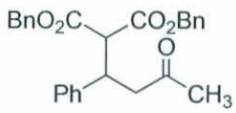
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, 2H, *J* = 7.5, Ar*H*), 7.54-7.47 (m, 1H, Ar*H*), 7.42-7.35 (m, 2H, Ar*H*), 7.32-7.12 (m, 13H, Ar*H*), 7.09-7 (m, 2H, Ar*H*), 5.17 (d, 1H, *J* = 7,

OCH_2), 5.13 (d, 1H, J = 7, OCH_2), 4.9 (s, 2H, OCH_2), 4.27-4.15 (m, 1H, CH), 3.95 (d, 1H, J = 9.5, CH), 3.59-3.42 (d, 2H, J = 6.5, CH_2).

Enantiomeric excess: 1 %

t_{major}: 17.4 min; t_{minor}: 16.4 min (Chiralpak OD-H, 254 nm, hexanes/*i*PrOH, 70/30, 0.5 mL/min).

Dibenzyl 2-(3-oxo-1-phenylbutyl)malonate (96)[15]



The reaction of *trans*-4-phenyl-3-butene-2-one (50.0 mg, 0.340 mmol)), dibenzylmalonate (0.100 mL, 0.41 mmol) and **94** (4.00 mg, 50.0 mmol%), according to the general procedure, in 1,2-dichloroethane (1.00 mL) for 48 h gave 156 mg of **96** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.3-6.97 (m, 15H, ArH), 5.06 (d, 2H, J = 2.7, OCH_2), 4.81 (s, 2H, OCH_2), 3.9-3.96 (m, 1H, CH), 3.75 (d, 1H, J = 9.8, CO_2CHCO_2), 2.8 (d, 2H, J = 6.6, COCH_2), 1.88 (s, 3H, CH_3CO).

Enantiomeric excess: 2 %

t_{major}: 20.7 min; t_{minor}: 18.9 min (Chiralpak AS-H, 230 nm, hexanes/*i*PrOH, 95/5, 1 mL/min).

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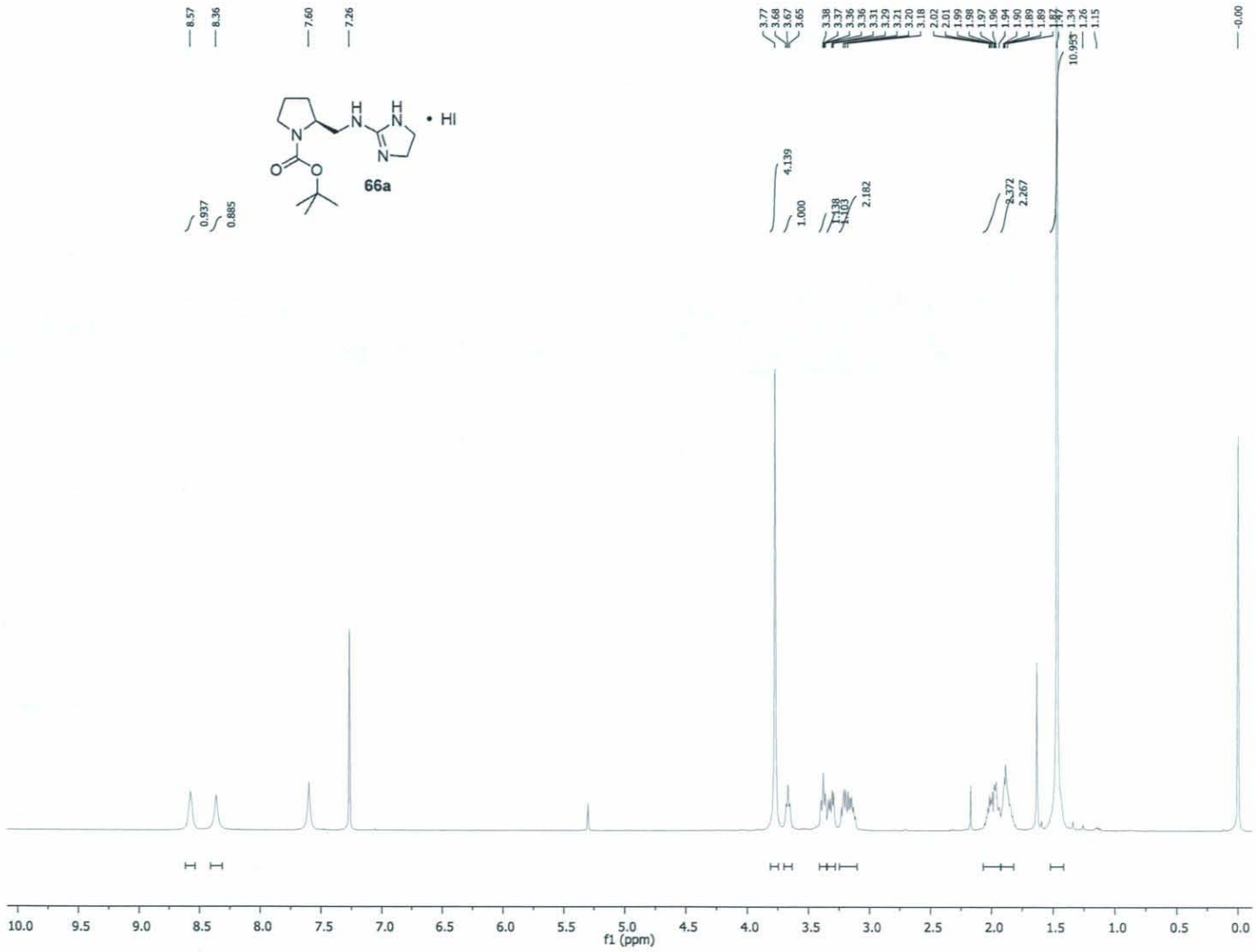
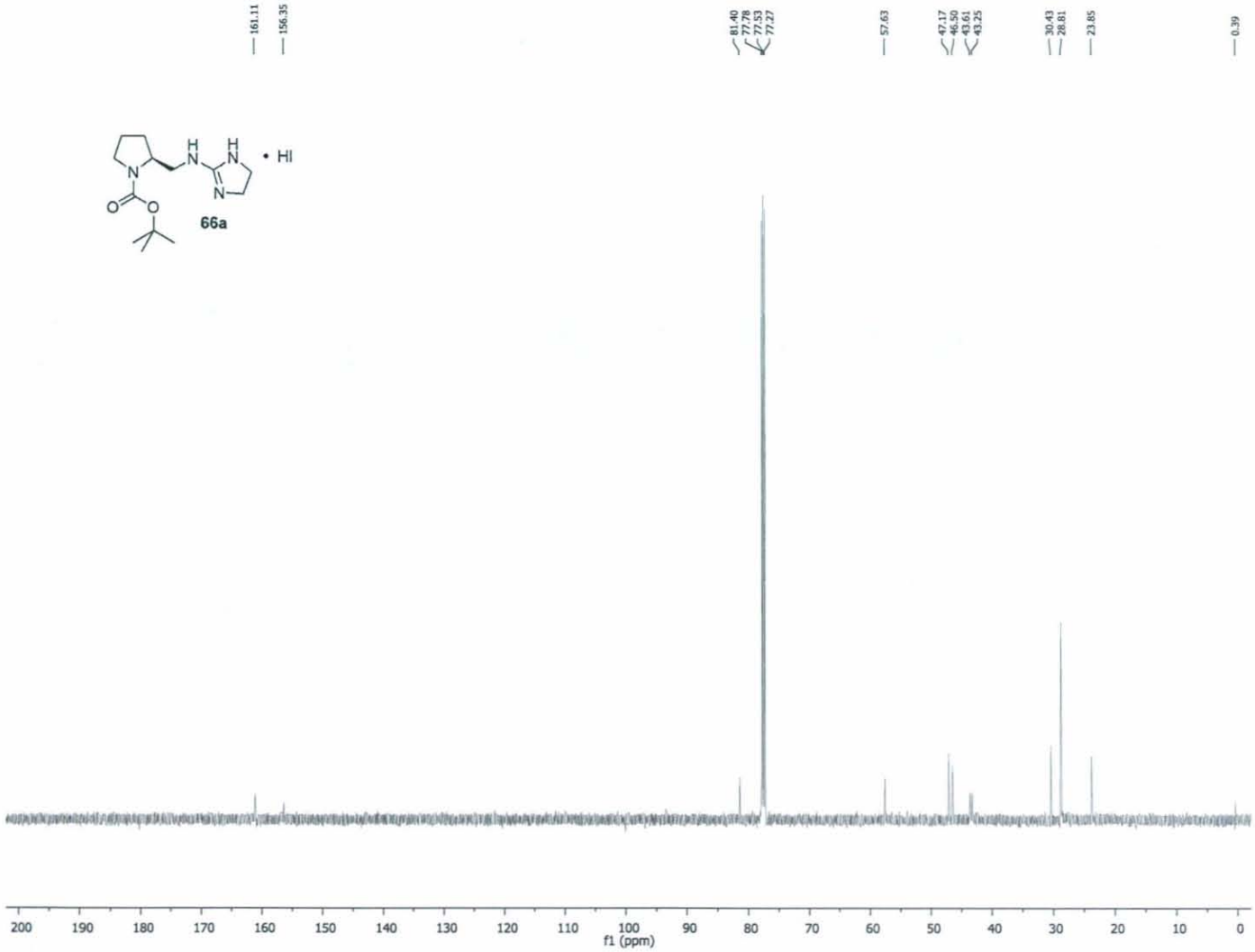
Appendix 1:

^{1}H and ^{13}C NMR Spectra for Chapter 1


8.57
8.36
7.60
7.26
3.77
3.68
3.67
3.65
3.38
3.37
3.36
3.31
3.29
3.21
3.20
3.18
2.02
2.01
1.99
1.98
1.97
1.96
1.94
1.90
1.89
1.89
1.34
1.26
1.15
10.955
-0.00
4.139
1.000
2.182
2.372
2.267
0.937
0.885
66a
f1 (ppm)


161.11
156.35
81.40
77.78
77.53
77.27
57.63
47.17
46.50
43.61
43.25
30.43
28.81
23.85
0.39
• HI
66a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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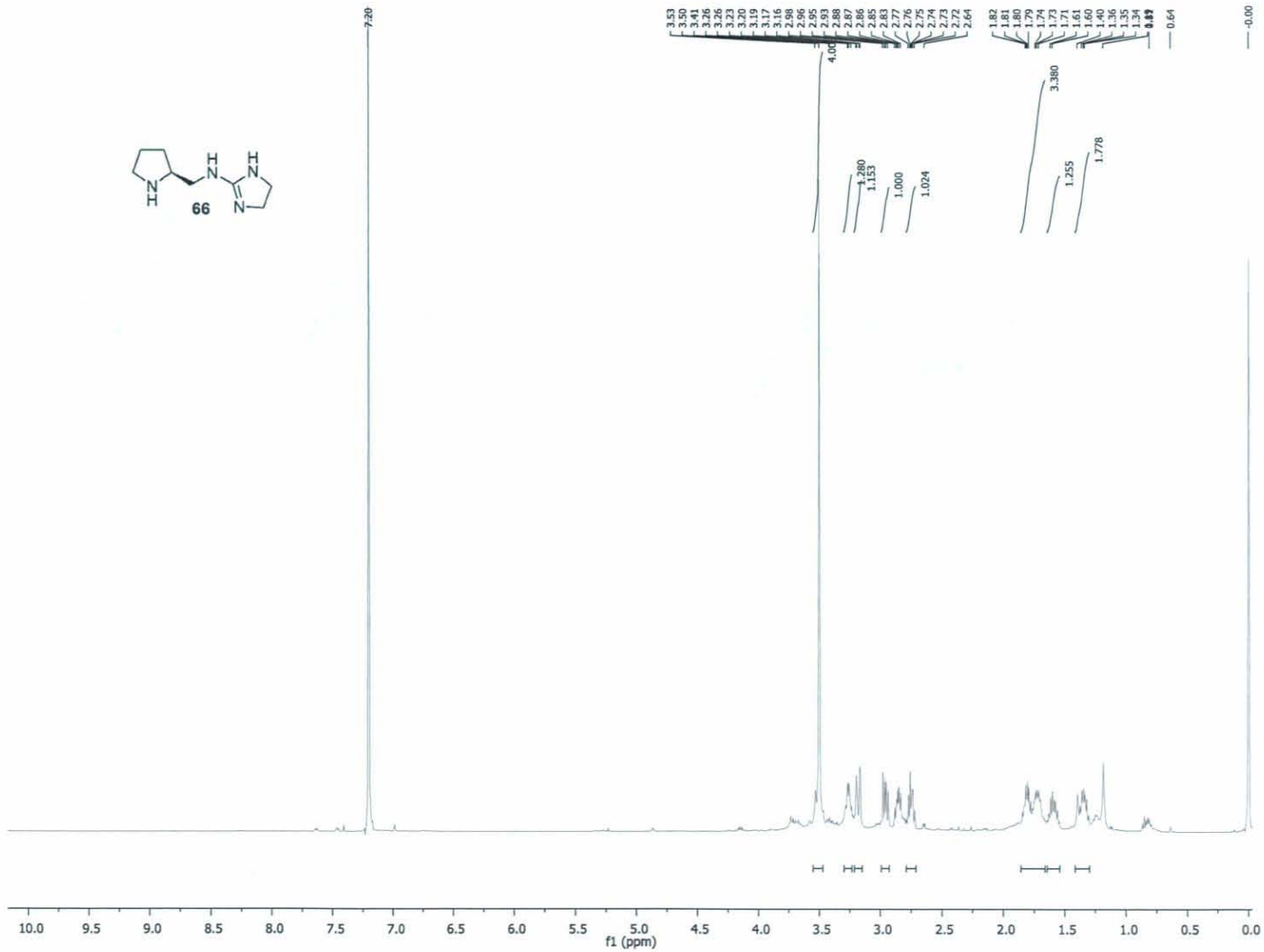
f1 (ppm)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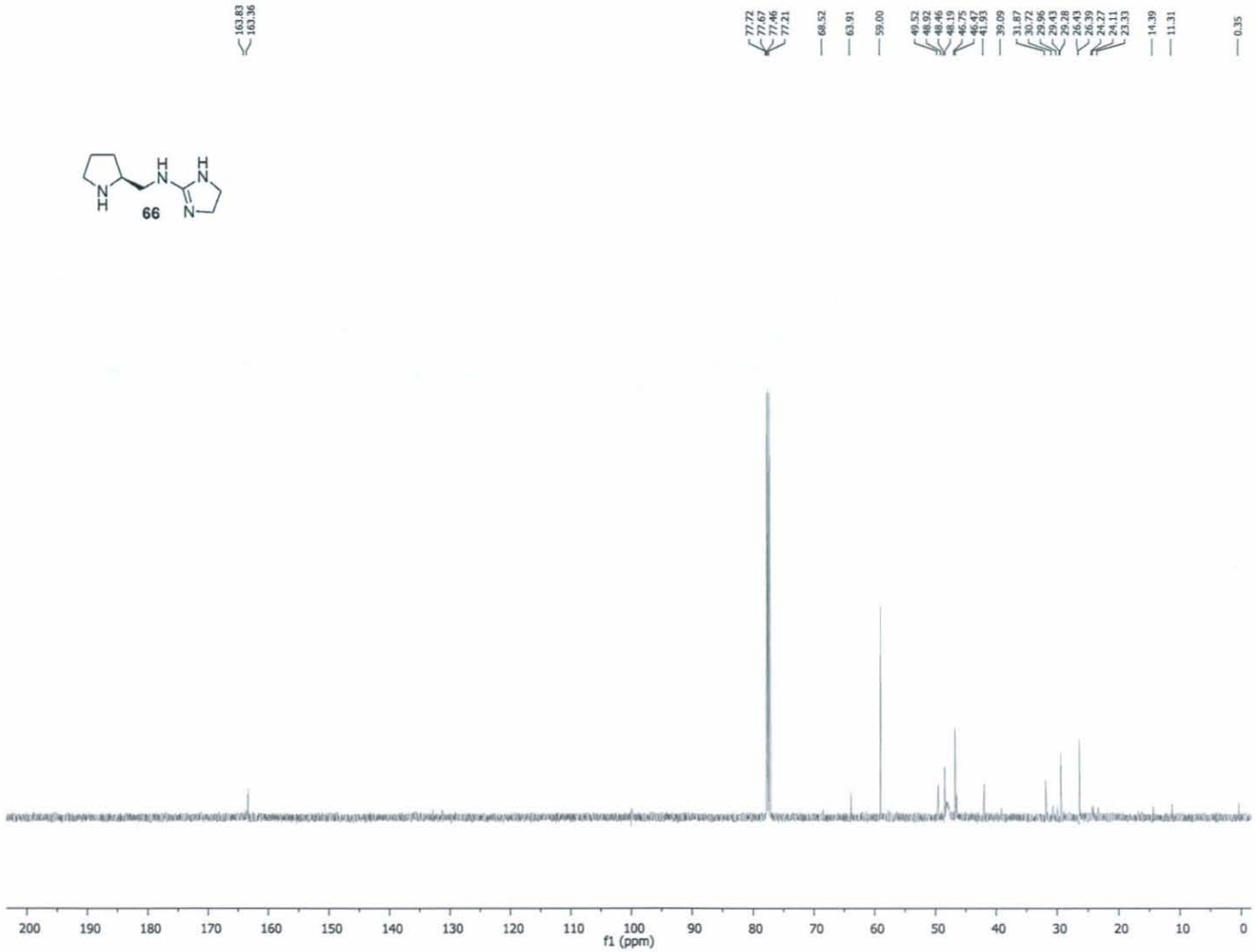
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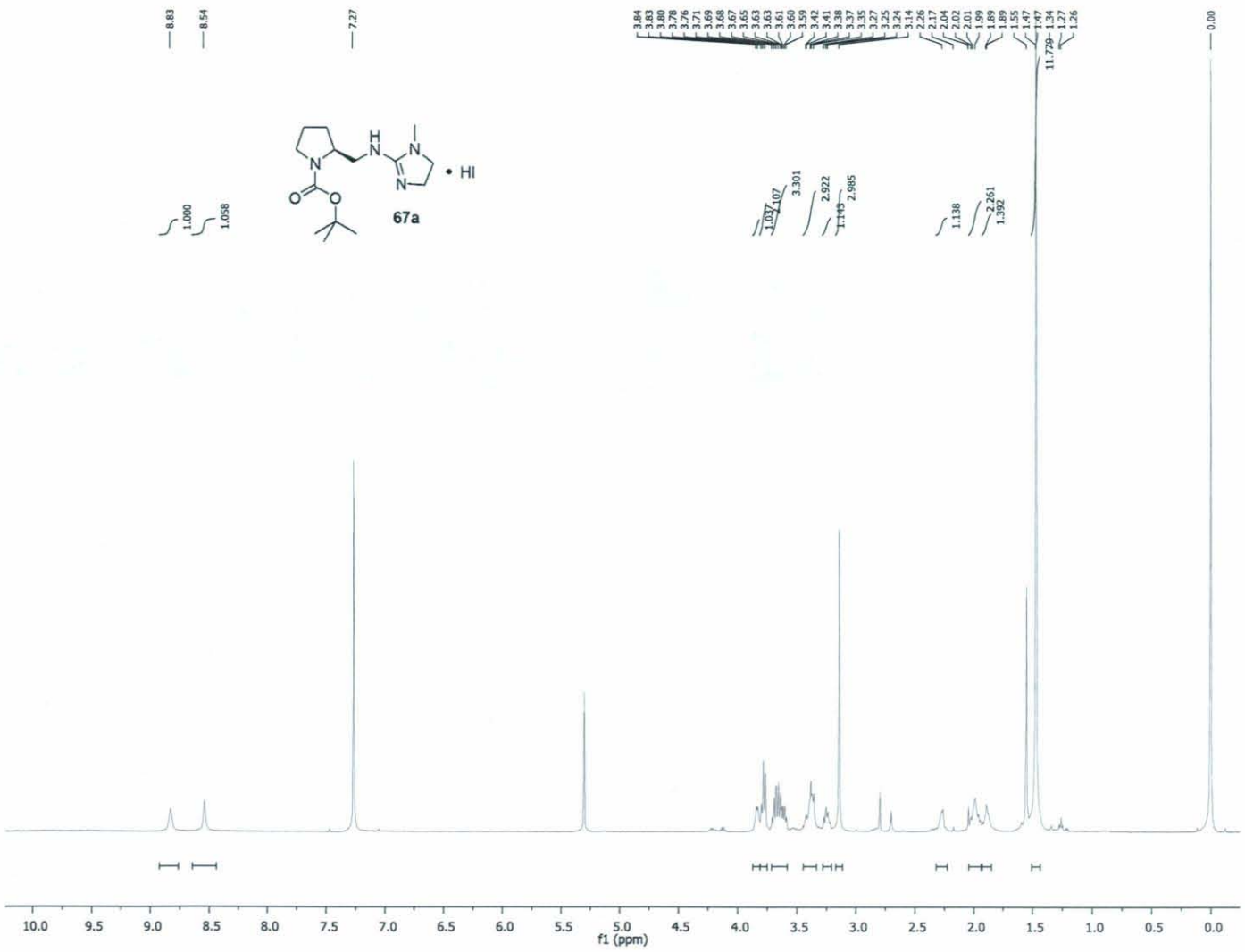
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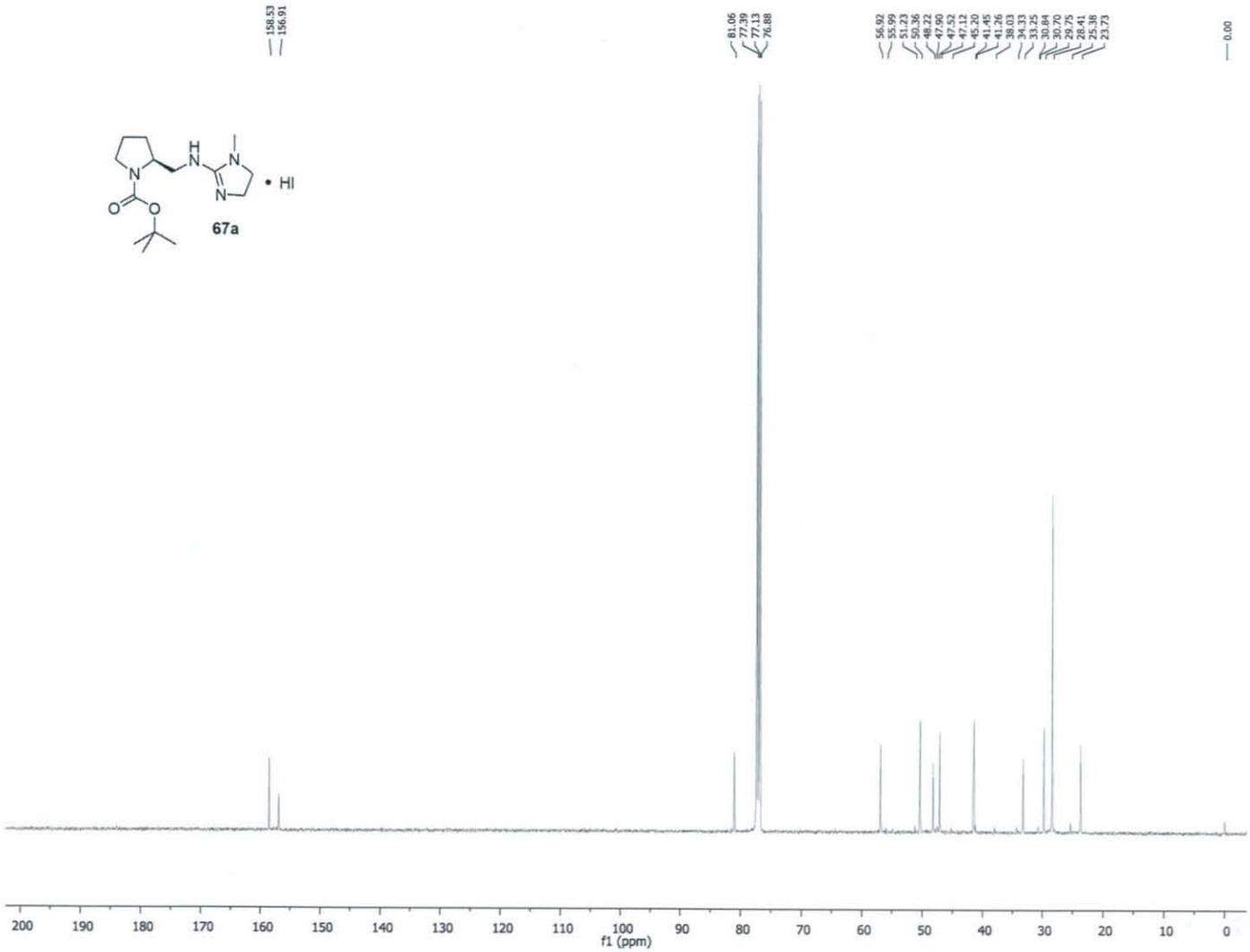
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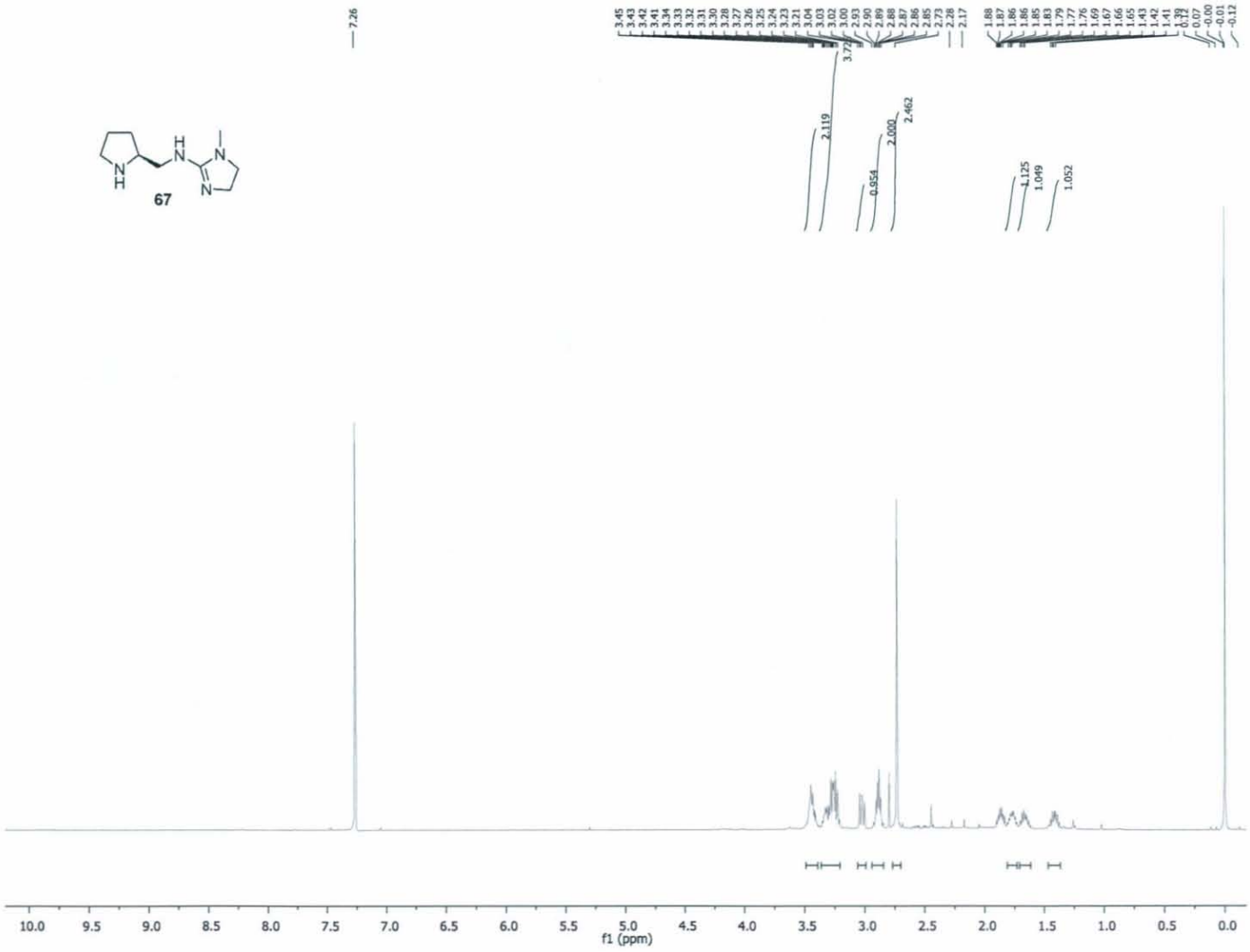
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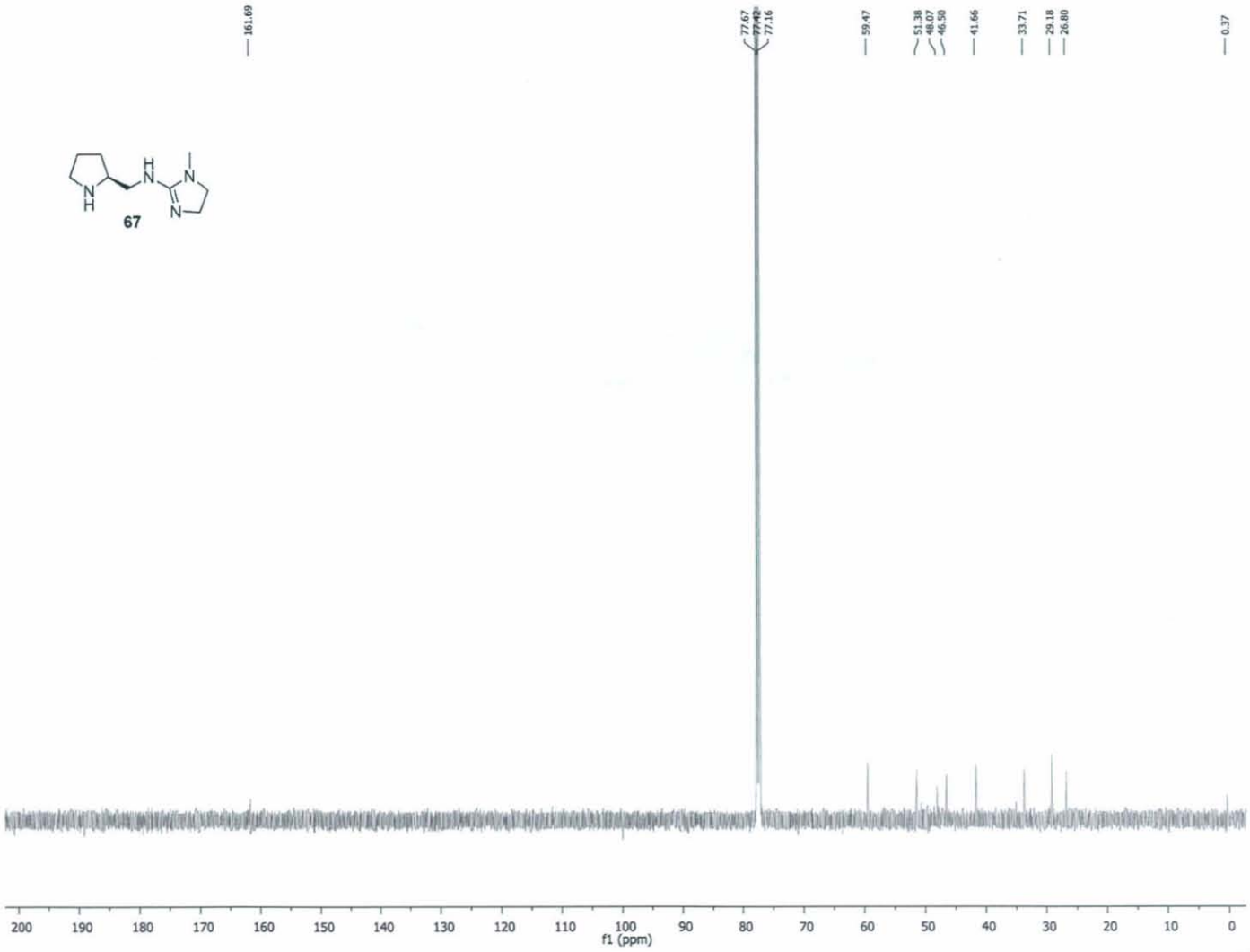
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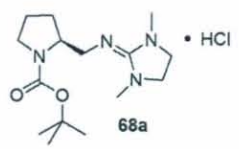
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2.77
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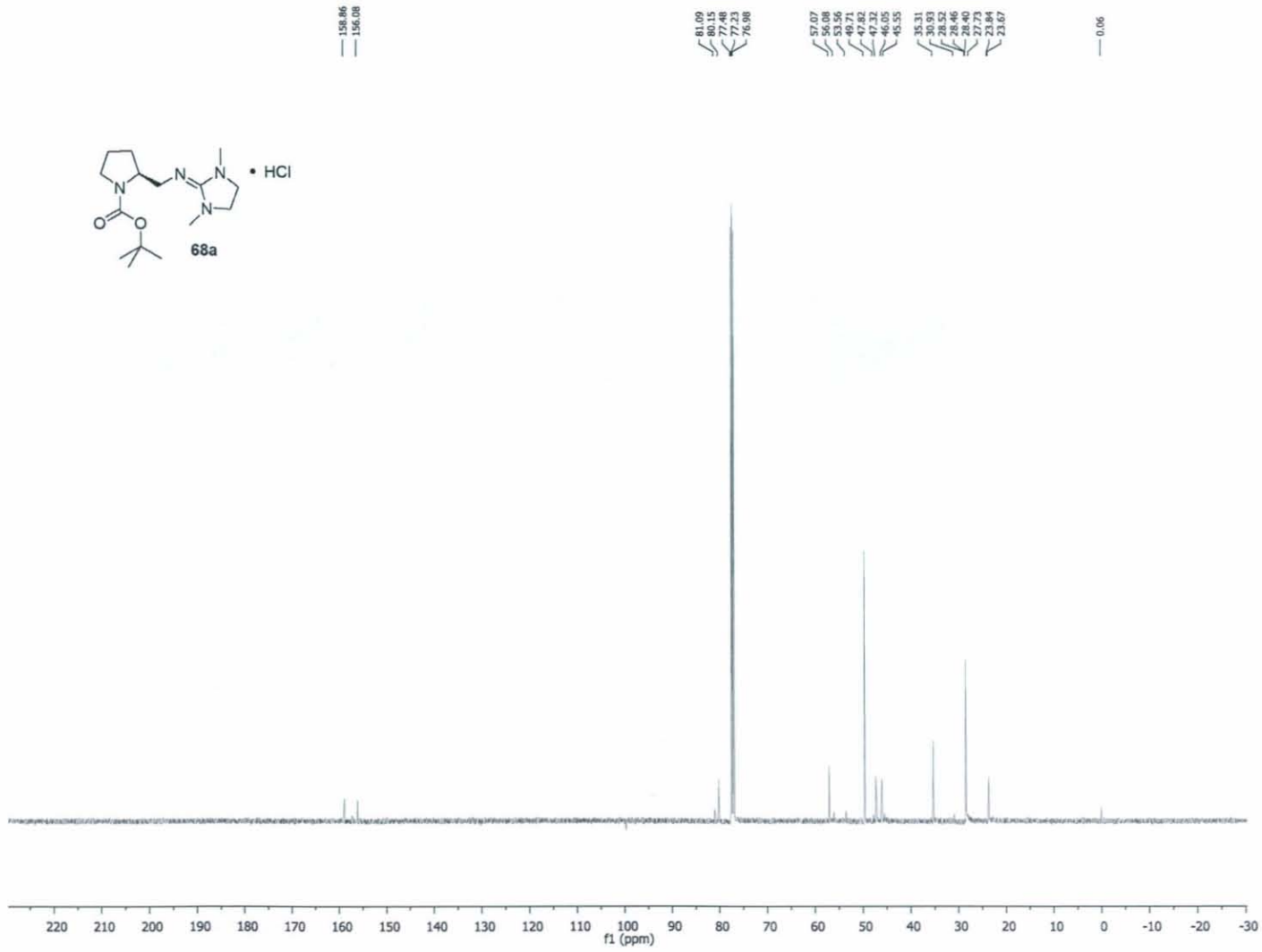
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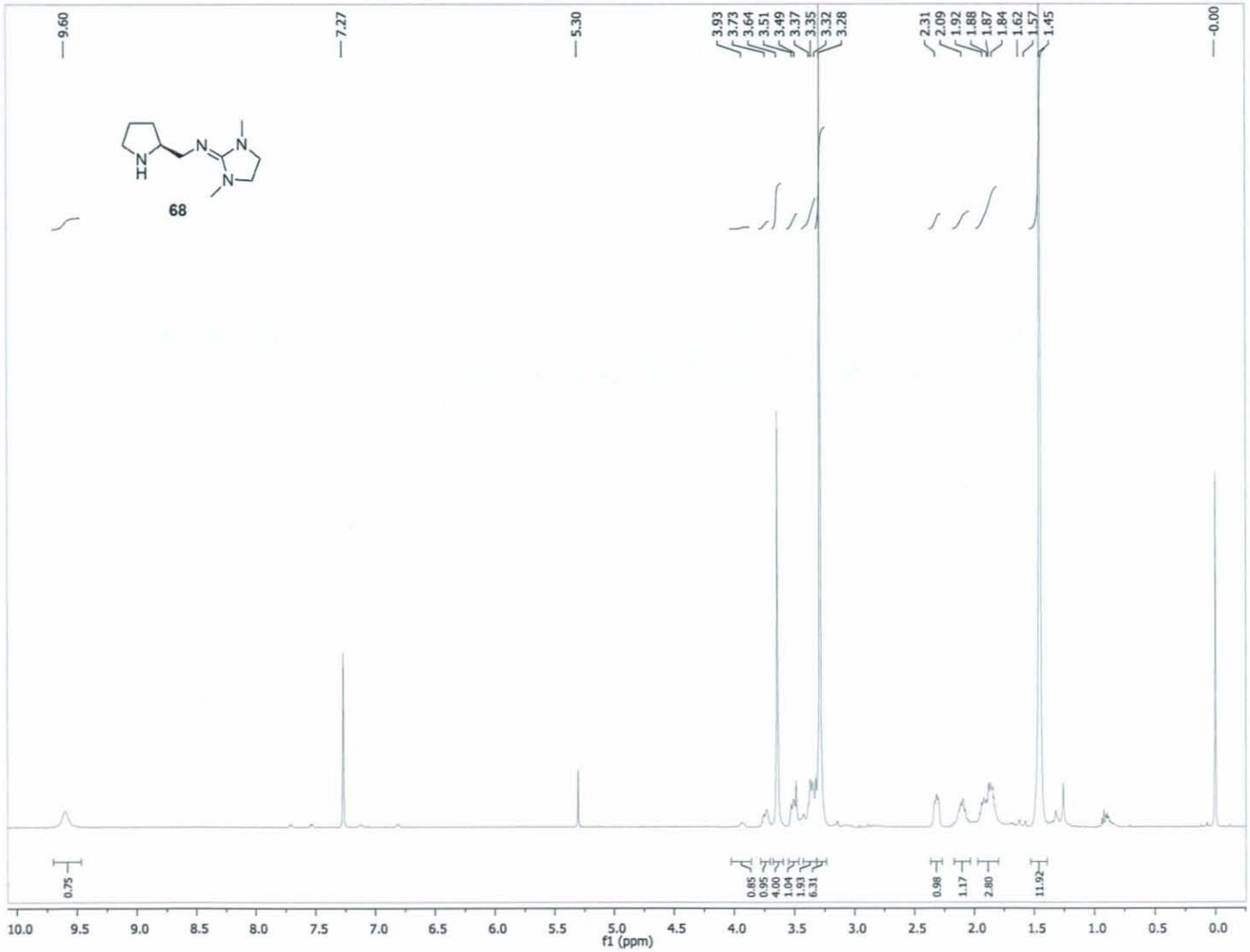
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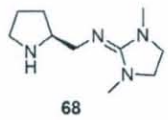

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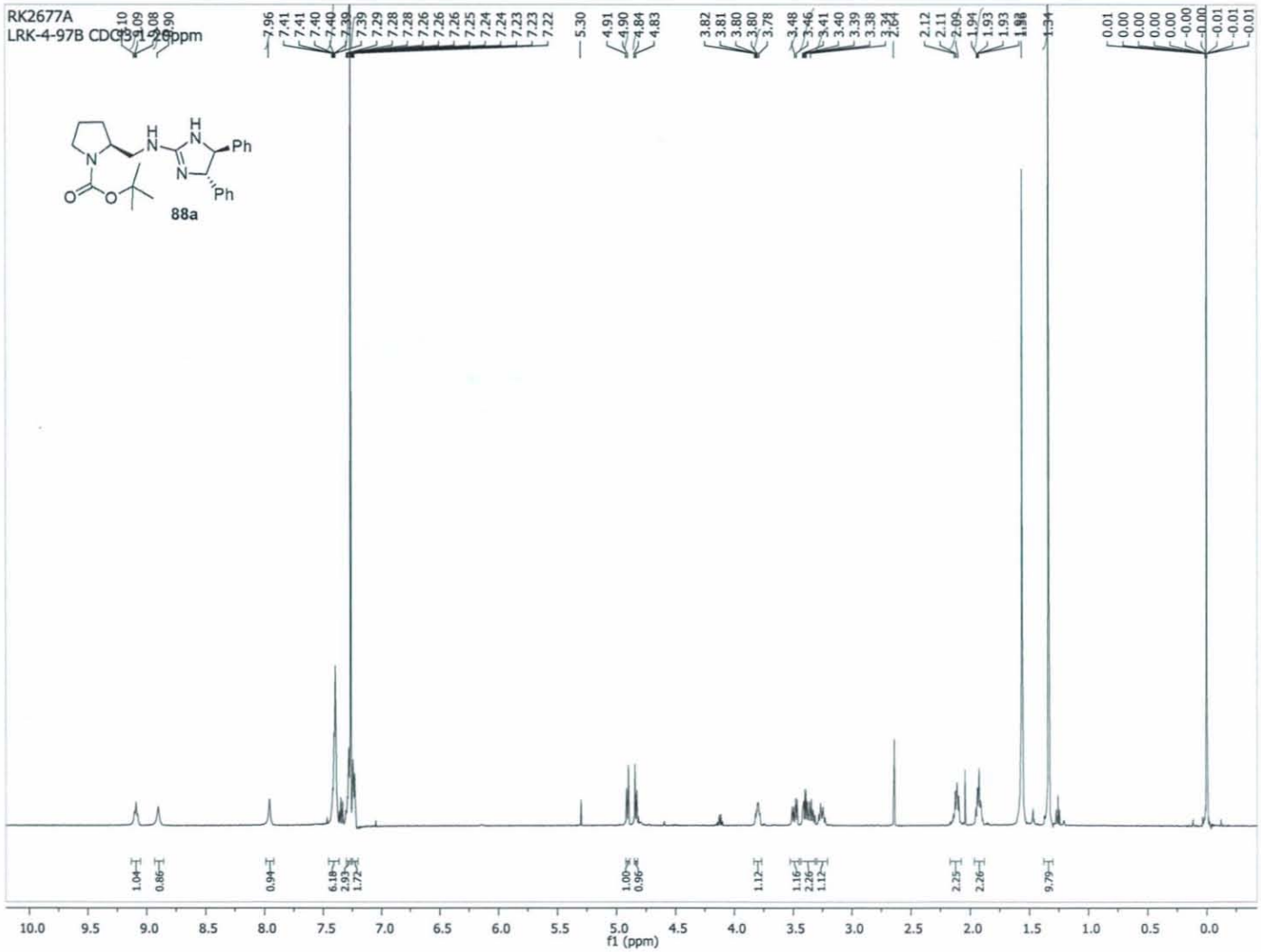
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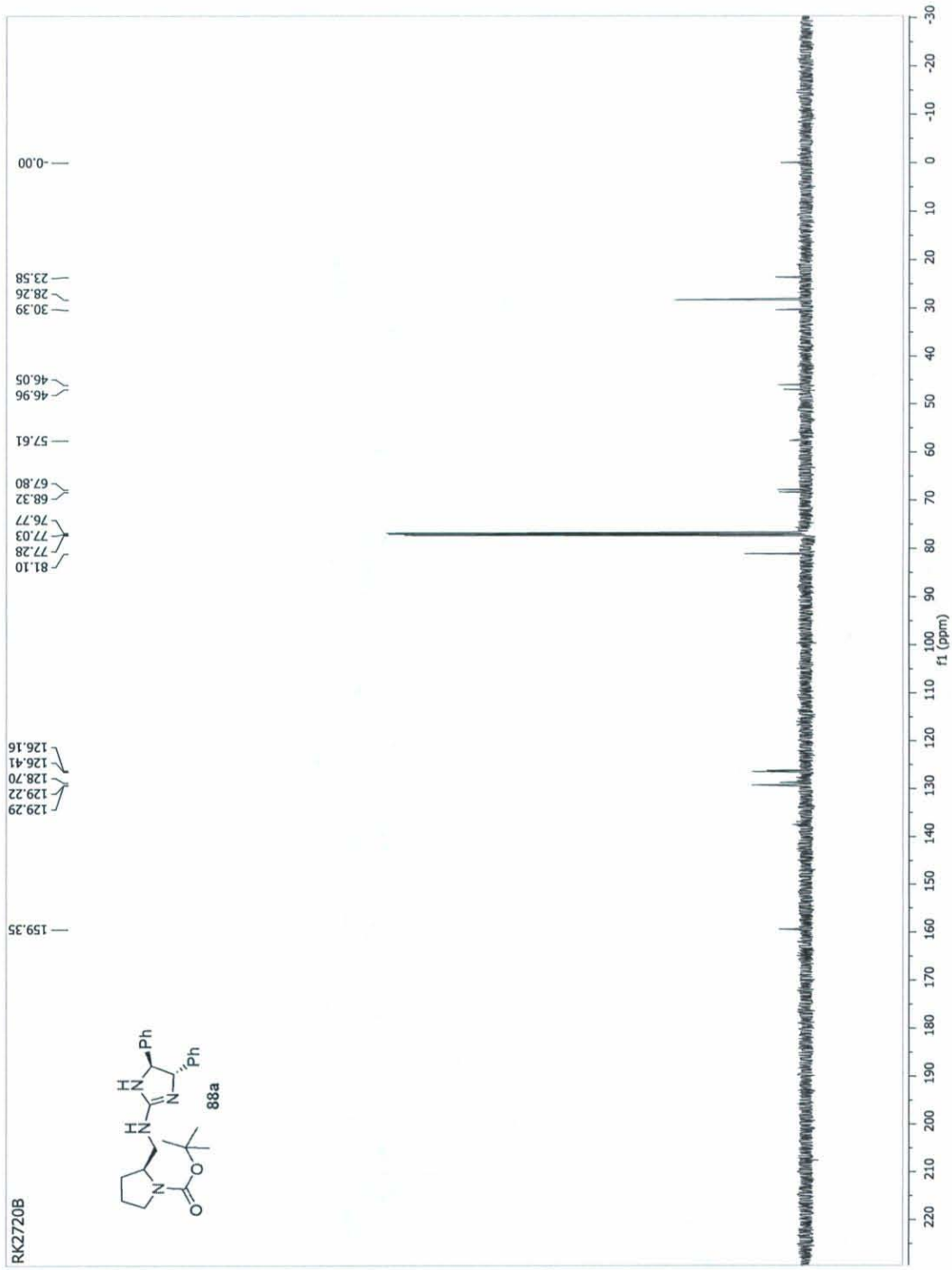
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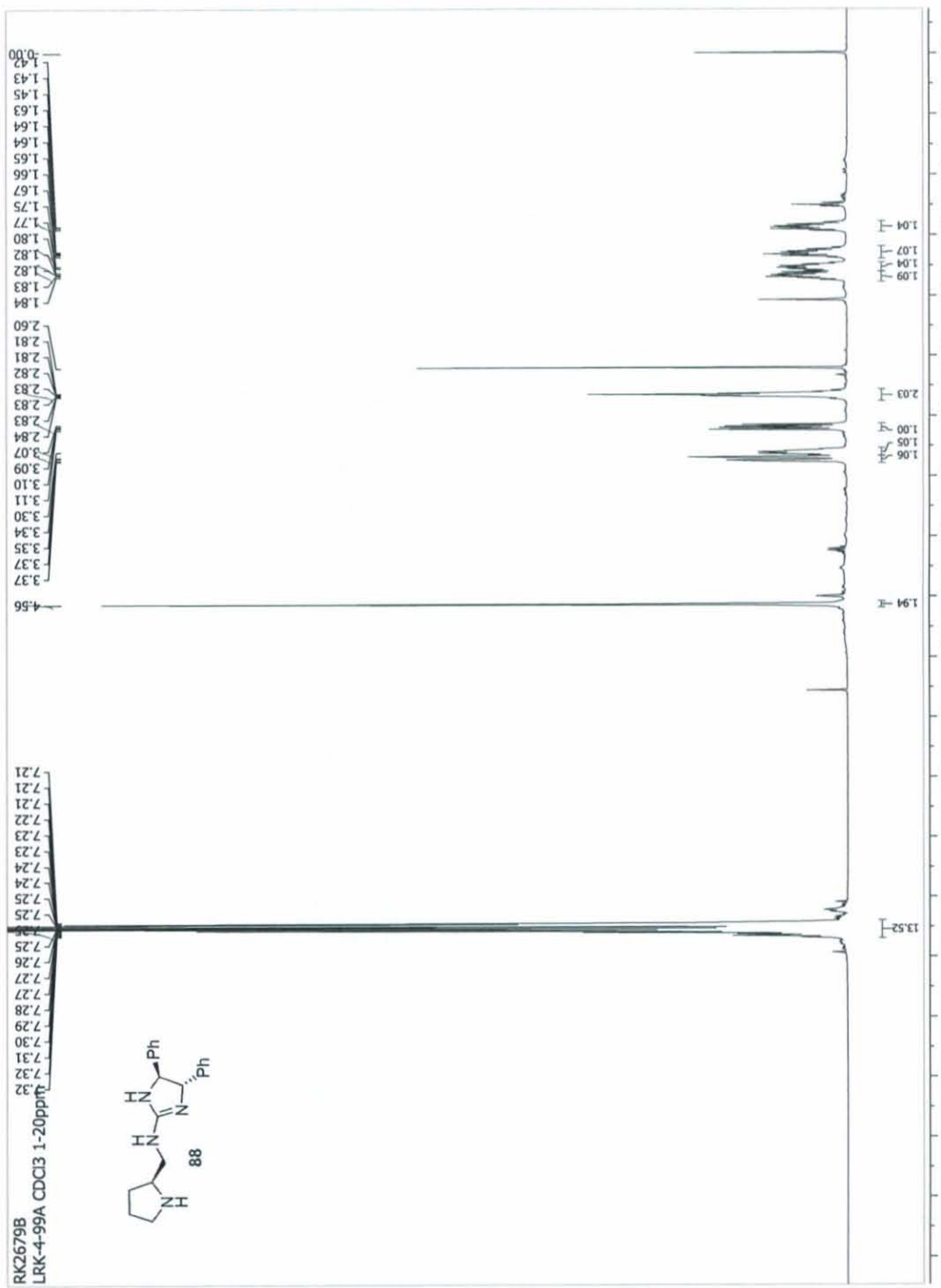
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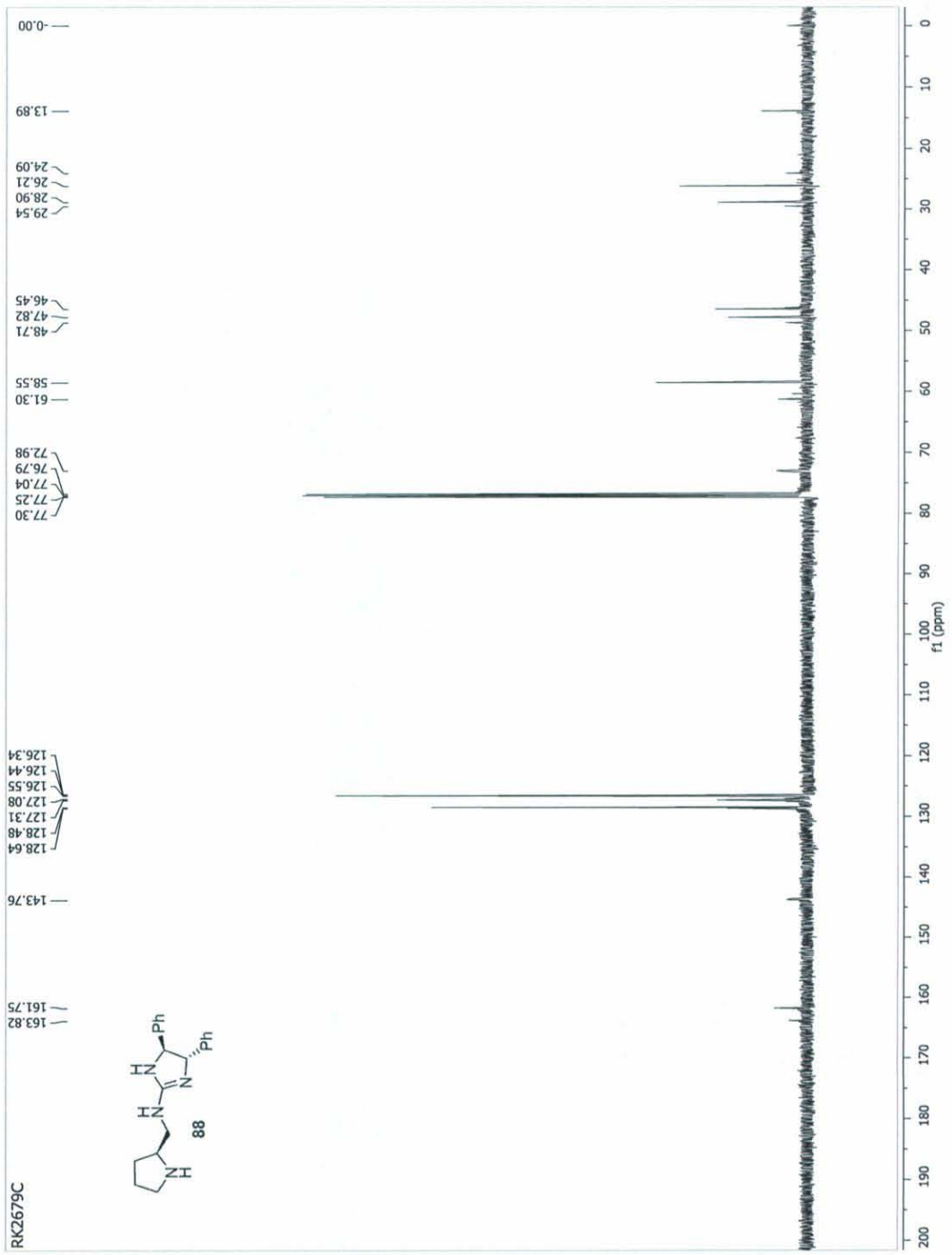
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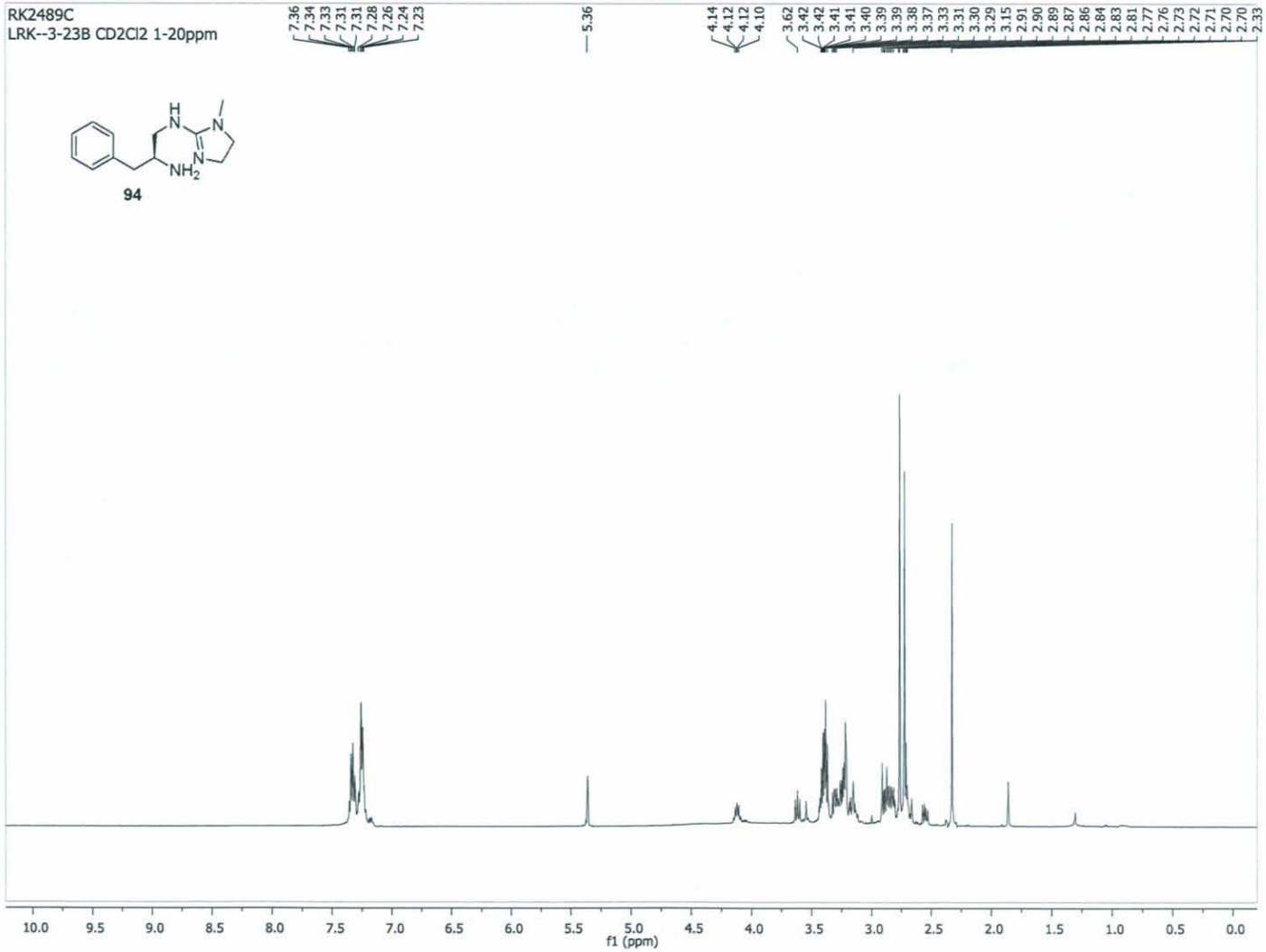
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N
N
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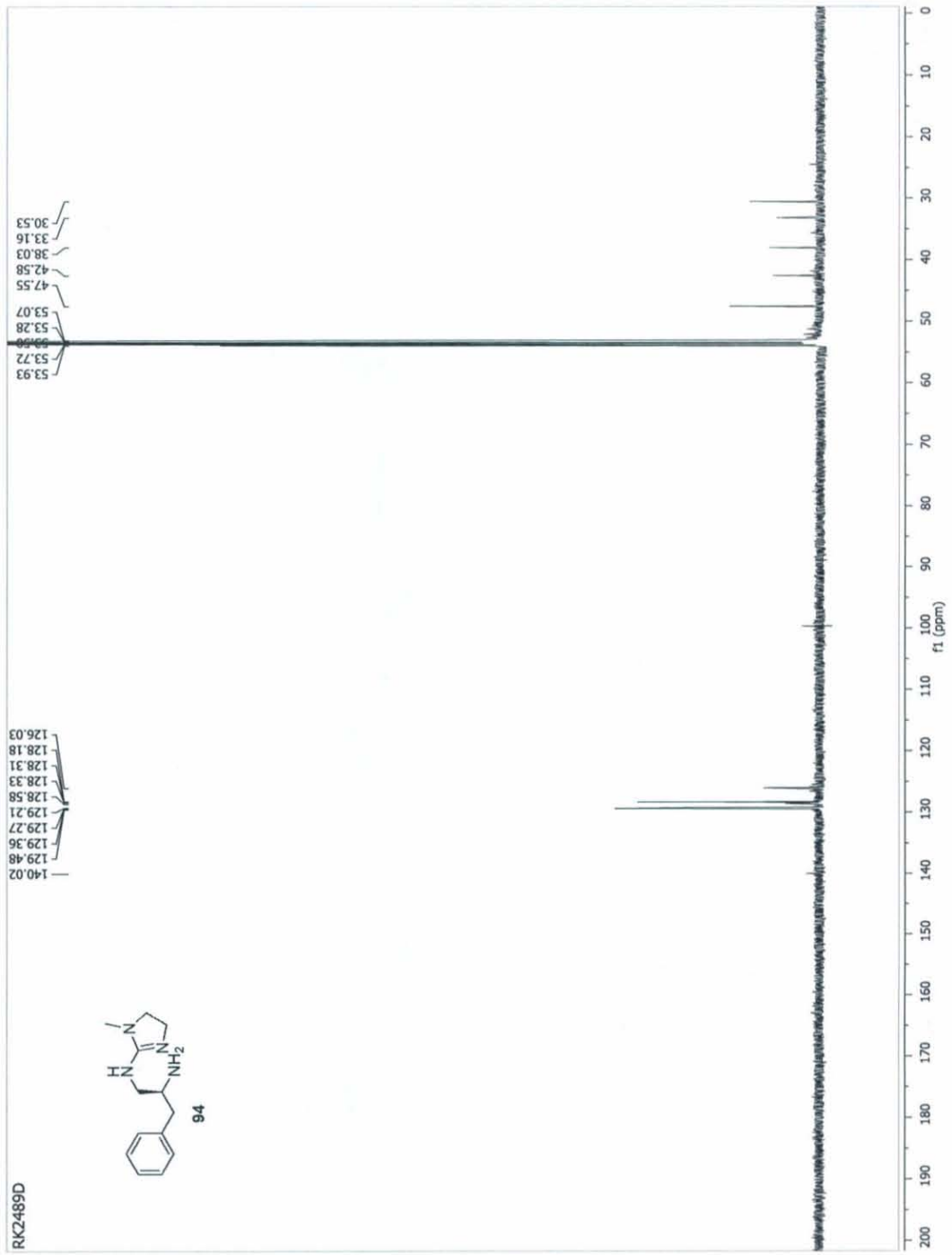
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f1 (ppm)

Chapter 2

Stereoselective Synthesis of 3-Aryloctahydroindoles and a Formal Total Synthesis of (-)-Pancracine

Part of the work described in this chapter has been published in

Organic Letters **2010**, *12*, 556-559

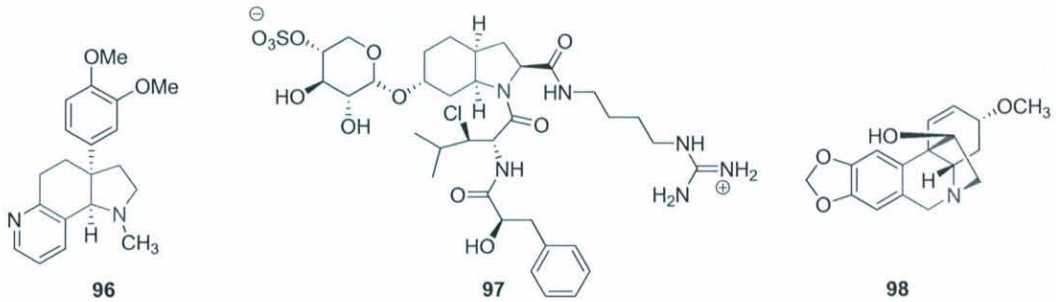
Chapter 2

General Introduction

Chapter 2 is divided into two parts. In the first part, the importance of octahydroindoles and the synthesis of *cis* and *trans*-3-aryloctahydroindoles will be presented. The second part deals with a formal total synthesis of (-)-pancracine along with a literature overview of the known approaches towards this target.

Part I: Stereoselective Synthesis of 3-Aryloctahydroindoles

Introduction



96
(+)-sceletium A4

97
aeruginosin 205B

98
crinamine

Figure 1. Selected natural products having the *cis*-hydroindole moiety

The hydroindole ring system has attracted considerable attention due to its importance in natural product chemistry and medicine. For example, the hydroindole motif is found in several bioactive natural products including the *Amaryllidaceae*

alkaloids such as e.g. crinamine (**98**),[1-3] and sceletium (**96**)[4,5] and also the aeruginosins such as **97** (Figure 1).[6-9] Recently, applications of octahydroindole scaffolds in the diversity-oriented synthesis of *Amaryllidaceae* alkaloid-type structures,[10] glycomimetics[11] and glycosidase inhibitors[12] have been reported.

The stereochemistry of the ring junction in the octahydroindole influences its biological profile. Thus, certain *cis*-octahydroindoles have been utilized in peptide β-turn mimics[13] and have also been known to have noradrenaline uptake inhibitor activity[14] whereas the *trans*-octahydroindole motif has been employed in preparing ACE inhibitors.[15] The synthesis of octahydroindoles therefore continues to be actively investigated[16-20] and selective access to either the *cis* or the *trans*-octahydroindole motif is of particular interest.

Our interest in octahydroindoles stems from our studies on the enantioselective organocatalytic synthesis of γ-nitroketones **99** from cyclic ketones **103** and 2-nitrovinyl arenes **50** via an enamine-based, organocatalytic conjugate addition reaction (Figure 2).[21,22]

Figure 2. Organocatalytic conjugate addition reaction of cyclic ketones to nitroalkenes

A large number of studies[23] have demonstrated the utility of this reaction and the development of new catalysts for this reaction continues at a remarkable pace. Clearly, the full potential of the organocatalytic ketone-nitroalkene conjugate addition reaction will be realized when the enantiomerically-enriched γ-nitroketone products find applications in other synthetic endeavours.[24-27]

Generally, γ-nitrocarbonyl compounds can be converted to the corresponding nitrones[28] or pyrrolines[29] selectively and these can serve as precursors to pyrrolidines.[27,30] Hence, at the outset, a stereoselective synthesis of octahydroindoles from cyclohexanone-derived γ-nitroketones, by reduction of the derived nitrones or imines,[31-33] appeared attractive. Stereocontrol in the reduction step may be anticipated to be a function of the stereocenters which are α-and/or β' to the carbonyl group. These stereocenters, in turn, are readily set by the organocatalytic Michael addition reaction. While a few reports describe the reduction of tetrahydrobenzo[*e*]indole (Figure 3, compound **E**) and tetrahydropyrrolo[*f*]quinoline (Figure 3, compound **G**) ring systems (embedded imine functionality) to the corresponding *cis*-fused hexahydro products,[29,34,35] reduction of a hexahydro[2H]indole (Figure 3, compound **I**) to a mixture of *cis* and *trans* octahydroindoles has also been reported.[36]

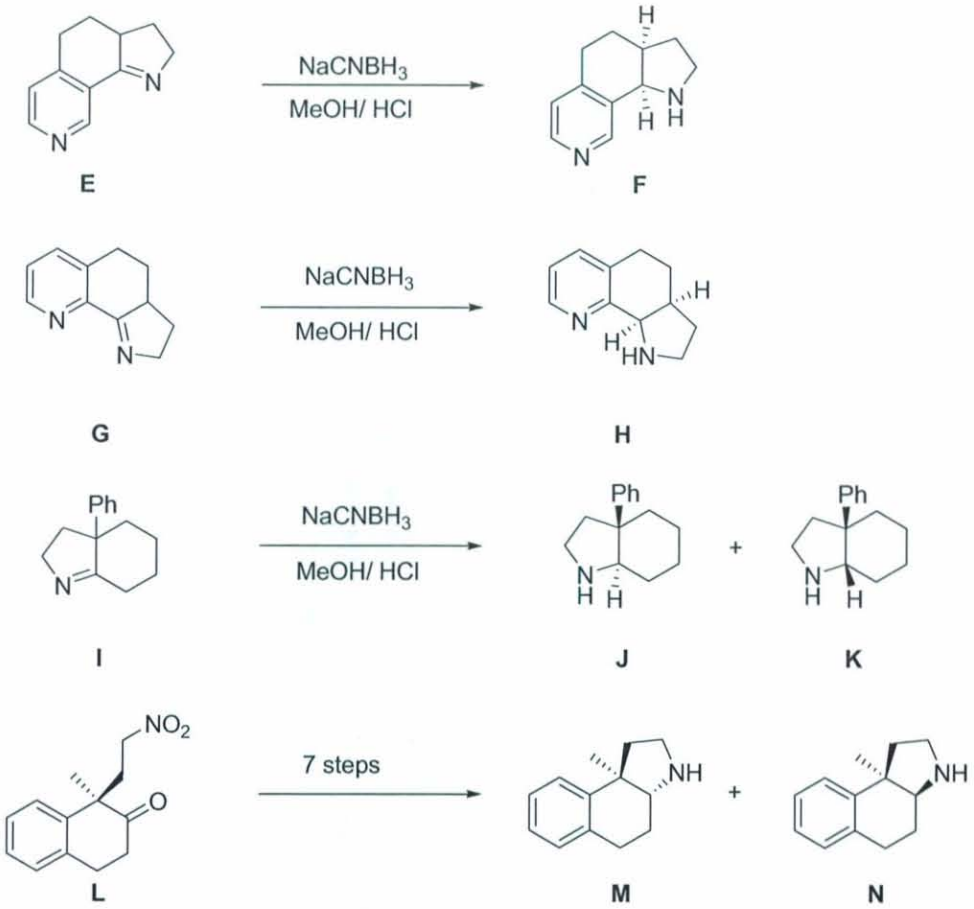


Figure 3. Selected examples of stereoselective synthesis of octahydroindoles

The challenges associated with the conversion of tetralin-based γ-nitroketones (Figure 3, compound **L**) into *cis* or *trans* octahydrobenz[*e*]indoles (M or N) have been addressed in a recent study.[37] Evidently, methodology that provides stereocontrolled access to octahydroindoles would be useful.

Objective

The goal of this study was to utilize the enantiomerically-enriched γ-nitroketones such as **99**, obtained from organocatalytic Michael addition reactions, for the synthesis of *cis* and *trans*-3-aryloctahydroindoles. The synthesis of an appropriately substituted *cis*-3-aryloctahydroindole that could be utilized in a formal synthesis of (-)-pancracine was also targeted (Figure 4).

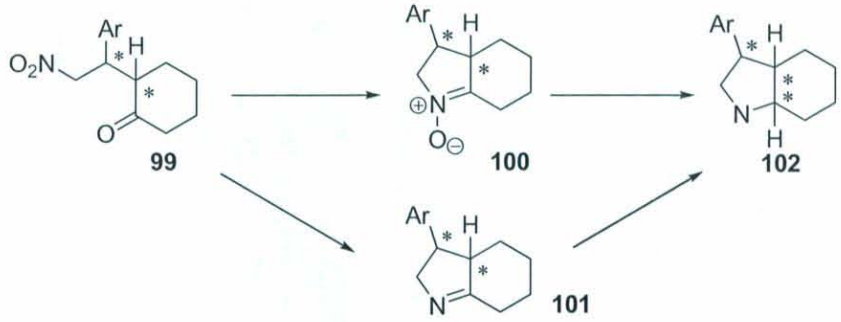
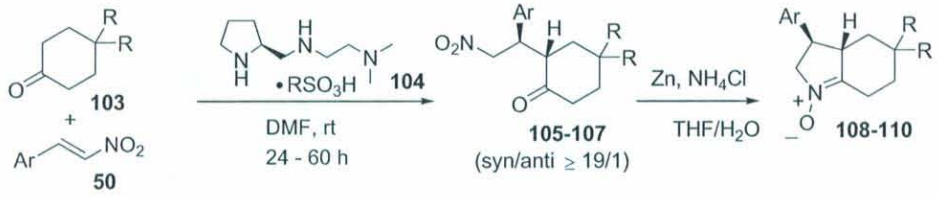


Figure 4. Strategy for synthesis of 3-aryloctahydroindoles

Results and discussion

At the outset, γ-nitroketones **105**[38]**-107** were prepared by employing the Michael addition protocol developed in the Pansare group using a secondary-secondary triamine salt as the catalyst.[21,22] The nitroketones were obtained in good yield and high diastereomeric and enantiomeric excess. Partial reduction of the nitro group[33] in **105**, **106** and **107** to the corresponding hydroxylamines with Zn/aq. NH_4Cl, provided the cyclic nitrones **108**, **109** and **110** respectively in good yields. These results are summarized in Table 1.

Table 1: Synthesis of 3-arylhexahydroindole 1-oxides

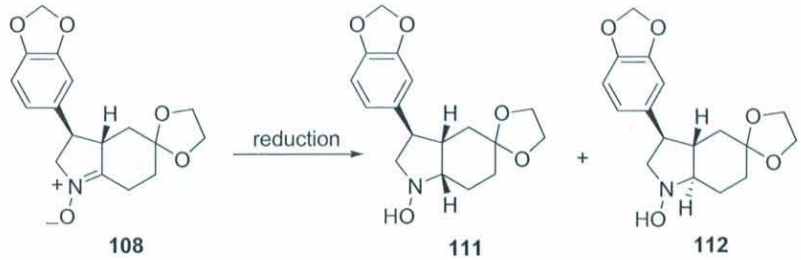


Compound	Ar	R	Yield (%)	ee (%)[a]
105	3,4-(OCH_2O)-Ph	$O(CH_2)_2O$	90	89
106	4-OMe-Ph	H	83	99
107	2-naphthyl	H	90	99
108	3,4-(OCH_2O)-Ph	$O(CH_2)_2O$	70	B
109	4-OMe-Ph	H	74	B
110	2-naphthyl	H	63	B

[a] Chiral HPLC [b] same as precursor

The nitrone **108** was chosen as a candidate for developing suitable reduction methods toward the octahydroindole system. Treatment of **108** with $NaBH_4$ in methanol provided a 2/1 mixture of the *cis* and *trans* hydroxylamines **111** and **112** respectively. A brief survey of reducing conditions was conducted with the objective of improving the *cis*/*trans* ratio. The results of this study are summarized in Table 2.

Table 2: Reduction of nitrone **108**



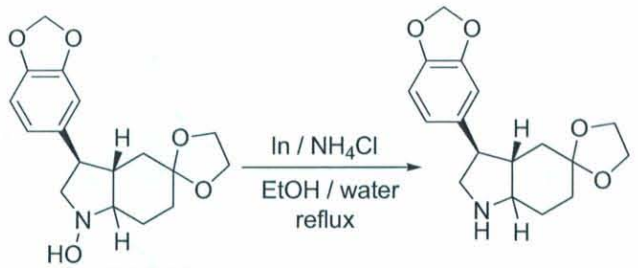
Entry	Reducing agent/conditions	111/112	Yield 111+112 (%)
1	$NaBH_4$/MeOH, rt	1.5/1	50
2	$NaBH(OAc)_3$, rt	1/1	76
3	$NaBH_3CN$/AcOH, -10 °C	2/1	44
4	$NaBH_3CN$/pivalic acid, 0 °C	2.5/1	67
5	L-Selectride®	1/1	89
6	$LiAlH_4$	1/1	90
7	H_2, Pd/C, 1 atm	-	-
8	Pd/C, HCO_2NH_4	A	50

[a] *trans*-octahydroindole **114** was obtained

Unfortunately, selective reduction of **108** to **111** or **112** was not observed in any of these experiments, and the best result was obtained using sodium cyanoborohydride/pivalic acid (**111**/**112** = 2.5/1). Surprisingly, the catalytic hydrogenation of **108** (H_2, Pd/C, 1 or 3 atm. H_2, PtO_2, H_2, 1 atm) in ethanol generated a complex mixture which did not contain any of the anticipated hydroxylamine or the octahydroindole products.[39] In contrast, transfer hydrogenation of **108** provided the *trans*-octahydroindole product **112** in a modest yield. This stereochemical result is comparable to earlier observations made by Sanchez on the catalytic hydrogenation (H_2, RaNi, 50 psi, 55 °C) of an analog of nitroketone **105**, lacking the dioxolane functionality, which

provided only the corresponding *trans* octahydroindole (presumably by reduction of the nitrone formed *in situ*).[32] In our studies, hydrogenation of **105** under less forcing conditions (RaNi, H_2, 45 psi, EtOH, ambient temperature) provided the pyrroline analog (imine) of nitrone **108**.

Now the hydroxylamines **111** and **112** were separated by flash column chromatography and reduced with indium metal[40] to the *cis* octahydrindole **113** and its *trans* isomer **114** respectively (Scheme 1).



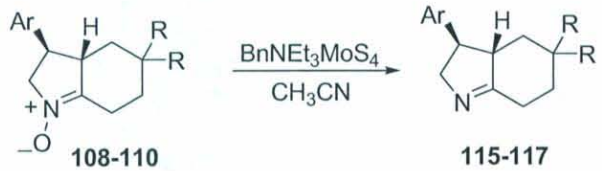
Scheme 1

The stereochemical assignments for **113** and **114** (and consequently for **111** and **112**) are based on ^{1}H NMR data for the *N*-Cbz derivative of **113** which is in agreement with that reported in the literature for the corresponding racemate.[41] It is noteworthy that **113** is a known intermediate to the montanine-type *Amaryllidaceae* alkaloids, particularly (-) pancracine.[41]

Given the lack of stereoselectivity in the reduction of nitrone **108**, and the known *cis* selectivity in the reduction of a tetrahydrobenzo[*e*]indole system (Figure 3, pg 88),[34,35] we turned our attention to the reduction of the imine analog of **108** as an alternative approach to the corresponding *cis* octahydroindole. Although the required imine **115** can

be obtained (along with nitrone **108**) by reduction of the nitroketone **105** with Zn/acetic acid, a route involving deoxygenation of the nitrone **108** with benzyltriethylammonium tetrathiomolybdate is more efficient.[42] This method is also applicable to the nitrones **109** and **110** to provide the imines **116** and **117** respectively in reasonable yields (Table 3).

Table 3: Conversion of nitrones **108-110** to imines **115-117**

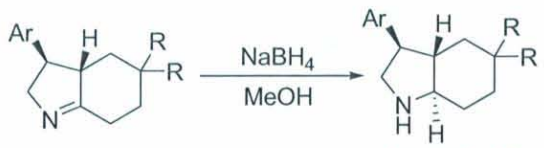


108-110 **115-117**

Entry	Ar	R	Yield (%)
115	3,4-(OCH_2O)-Ph	$O(CH_2)_2O$	70
116	4-OMe-Ph	H	62
117	2-naphthyl	H	64

Curiously, reduction of the imines with $NaBH_4$ provided the *trans* octahydroindoles as the major products (Table 4) with some of the *cis* product being observed (^{1}H NMR) only in the reduction of **115** and **117** (*trans/cis* ratio of 10/1 and 6/1, respectively). The reasons for the marked difference in stereoselectivity of reduction of the nitrone **108** and the imine **115** as well as the imines **116** and **117** are not apparent. Also, the dependance of *trans/cis* ratios on the nature of the relatively similar 3-aryl substituents in **115-117** is intriguing.

Table 4: Conversion of imines to *trans*-octahydroindoles



115-117 **114, 118, 119**

Entry	Ar	R	Yield (%)	*trans*/*cis*
114	3,4-(OCH_2O)-Ph	$O(CH_2)_2O$	75	10/1
118	4-OMe-Ph	H	75	>19/1[a]
119	2-naphthyl	H	72	6/1

[a] Single diastereomer by ^{1}H NMR

1.4 Conclusion

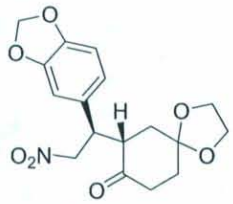
In conclusion, the imine reduction method provides access to the *trans* 3-aryl octahydroindoles as the major products. However, the *cis* isomers cannot be produced in good yield from either the nitrone or the imine intermediates. Therefore, an alternative approach has been examined, in which the octahydroindole **113** was chosen as the representative target. This particular octahydroindole is a key intermediate in the synthesis of (-)-pancracine. These studies and the synthesis of an advanced intermediate to (-)-pancracine from the octahydroindole **113** are described in Section 2 of this Chapter.

Experimental section

General procedure for the preparation of γ-nitroketones 105-107:

The literature procedure[22] was adapted. To a solution of the amine catalyst in DMF was added the protic acid, ketone and nitrostyrene. The resulting solution was stirred at ambient temperature for 24-60 h. Ethyl acetate was added and the solution was washed with water, HCl (aq) (3 *N*), the layers separated dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel to provide the pure γ-nitroketones.

(7*S*)-7-[(1*R*)-1-(1,3-Benzodioxol-5-yl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-one (105):[38]

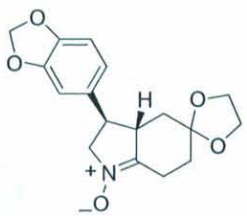


The reaction of 1,4-cyclohexanedione mono ethylene ketal (3.90 g, 25.0 mmol), 3,4-methylenedioxy-β-nitrostyrene (965 mg, 5.00 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine[22] (171 mg, 1.00 mmol) and methane sulfonic acid (65.0 μL, 1.00 mmol) in DMF (10.0 mL) for 60 h according to the general procedure, followed by purification of the crude product by flash chromatography on silica gel provided 1.57 g (90%) of **105** as a pale brown foam.

IR (neat): 2894, 1711, 1550, 1504, 1488, 1442, 1246, 1118, 1037, 932, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.77 (d, 1H, J = 8, Ar*H*), 6.67 (d, 1H, J = 1.7, Ar*H*) 6.63 (dd, 1H, J = 8, 1.7, Ar*H*), 5.97 (m, 2H, OCH_2O), 4.94-4.89 (dd, 1H, J = 12.4, 4.5, CH_2NO_2), 4.57-4.53 (dd, 1H, J = 12.4, 10.1, CH_2NO_2), 4.02-3.88 (m, 4H, OCH_2CH_2O), 3.79-3.74 (dt, 1H, J = 10.1, 4.7, ArC*H*), 3.02-2.97 (m, 1H, COC*H*), 2.74-2.68 (dt, 1H, J = 13.5, 6.4, COCH_2), 2.49-2.45 (m, 1H, COCH_2), 2.07-2.04 (m, 1H, CHCH_2), 2.0-1.9 (dt, 1H, J = 13.3, 5.2, CH_2), 1.77-1.73 (m, 1H, CH_2CH_2), 1.59 (t, 1H, J = 13.0, 1H, CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.5 (*C*O), 148.4 (Ar*C*H), 147.4 (Ar*C*H), 131.0 (Ar*C*H), 121.9 (Ar*C*H), 108.9 (Ar*C*H), 108.5 (Ar*C*H), 107.3 (O*C*O), 101.5 (O*C*H_2O), 79.3 (*C*H_2NO_2), 65.1 (O*C*H_2CH_2O), 64.8 (OCH_2*C*H_2O), 48.5 (CO*C*H), 43.5 (Ar*C*H), 39.6 (CO*C*H_2), 38.9 (*C*H_2), 35.3 (*C*H_2); HPLC (Chiralpak AS-H, 2-propanol/hexane: 40/60, flow rate 1.0 mL/min, 254 nm): t_{minor} = 16.2 min, t_{major} = 20.9 min, ee = 89%, dr = 20:1 (average values for multiple reactions).

Nitroketones **106**[22] and **107**[22] were prepared in a similar manner.

(3'*R*,3a'*S*)-3'-(1,3-Benzodioxol-5-yl)-2',3',3a',4',6',7'-hexahydrospiro[1,3-dioxolane-2,5'-indole] 1'-oxide (108):

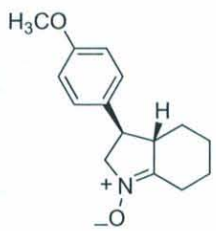


A solution of NH_4Cl (76.5 mg, 1.43 mmol) in water (3.00 mL) was added to a solution of the nitro ketone **105** (0.500 g, 1.43 mmol) in THF (10.0 mL). Activated Zn powder (936 mg, 14.3 mmol) was added and the mixture was stirred vigorously at room

temperature under nitrogen for 1.5 h. The mixture was filtered through a pad of celite® and the filtrate was concentrated under reduced pressure to remove volatiles. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 98/2 to 95/5 as the eluant) to provide 319 mg (70%) of **108** as a pale yellow gum.

IR (neat): 2889, 1619, 1504, 1489, 1243, 1122, 1037, 929 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.81-6.63 (m, 3H, Ar*H*), 5.90 (m, 2H, O*CH*$_2$O), 4.28-4.24 (m, 1H, *CH*$_2$NO), 4.15-4.10 (m, 1H, *CH*$_2$NO), 3.96-3.88 (m, 4H, O*CH*$_2$*CH*$_2$O), 3.24-3.12 (m, 3H, Ar*CH*, CH*CH*$_2$), 2.35-2.26 (br m, 1H, *CH*C=NO), 2.08-2.04 (ddd, 1H, *J* = 8.5, 5.9, 2.5, N=C*CH*$_2$), 1.94-1.90 (m, 1H, N=C*CH*$_2$), 1.73-1.67 (dt, 1H, *J* = 13.4, 5.9, CH$_2$*CH*$_2$), 1.56-1.51 (t, 1H, *J* = 12.2, 1H, CH$_2$*CH*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5 (*C*=NO), 147.3 (Ar*C*), 146.2 (Ar*C*), 133.0 (Ar*C*), 120.9 (Ar*C*), 108.8 (Ar*C*), 108.2 (Ar*C*), 107.6 (O*C*O), 101.5 (O*C*H$_2$O), 69.1 (*C*H$_2$NO), 64.9 (O*C*H$_2$CH$_2$O), 64.8 (OCH$_2$*C*H$_2$O), 48.6 (*C*HC=NO), 46.1 (*C*HCH$_2$NO), 40.3 (N=C*C*H$_2$), 31.9 (*C*H$_2$), 20.6 (*C*H$_2$), MS (APCI, pos.): m/z 318.1 (M+1); HRMS (CI): m/z 318.1343 (318.1341 calc. for $C_{17}H_{19}NO_5$ (M+H)).

(3*R*,3a*S*)-3-(4-Methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indole 1-oxide (109):

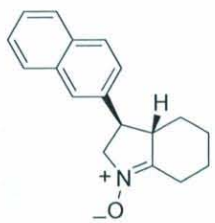


To a solution of the nitroketone **106** (0.300 g, 1.08 mmol) in THF (5.00 mL) was added zinc powder (707 mg, 10.8 mmol) and a solution of NH_4Cl (57.0 mg, 1.08 mmol) in water (2.00 mL). The mixture was stirred vigorously at room temperature for 6 h and

filtered. The residual solids were washed with THF and the combined filtrates were concentrated. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 95/5 as the eluant) to provide 197 mg (74%) of **109** as a colourless, solid foam.

IR (neat): 2934, 2855, 1626, 1612, 1514, 1451, 1244, 1228, 1179, 1033, 831cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.27-4.24 (br m, 1H, NCH_2), 4.15-4.10 (br m, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 3.25-3.15 (m, 2H, ArC*H*, NCCH_2), 2.8-2.7 (m, 1H, ArCHC*H*), 2.12-1.84 (m, 3H, CH_2), 1.85 (br d, 1H, J = 12.8, CH_2), 1.45-1.18 (m, 4H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9 (*C*=NO), 148.6 (ArC_{ipso}), 131.7 (ArC_{ipso}), 128.3 (Ar*C*), 114.4 (Ar*C*), 68.4 (NCH_2), 55.3 (Ar*C*H), 50.6 (ArCH*C*H), 45.3 (OCH_3), 32.3 (*C*H_2), 24.3 (*C*H_2), 23.8 (*C*H_2), 23.5 (*C*H_2); MS (API-ES pos.): *m/z* 246.1 (M+H); HRMS (CI pos.): m/*z* 246.1495 (246.1494 calc. for $C_{15}H_{20}NO_2$ (M+H)).

(3*R*,3a*S*)-3-(Naphthalen-2-yl)-3,3a,4,5,6,7-hexahydro-2*H*-indole 1-oxide (110):



A solution of NH_4Cl (126 mg, 2.36 mmol) in water (4.00 mL) was added to a solution of the nitroketone **107** (0.700 g, 2.36 mmol) in THF (15.0 mL). Activated Zn powder (1.54 g, 23.6 mmol) was added and the mixture was stirred vigourously at room temperature under nitrogen for 5 h. The mixture was filtered through a pad of celite® and the filtrate was concentrated under reduced pressure to remove THF. The residue was

diluted with ethyl acetate (10.0 mL) and the solution was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 95/5 as the eluant) to provide 0.390 g (63%) of **110** as a pale yellow gum.

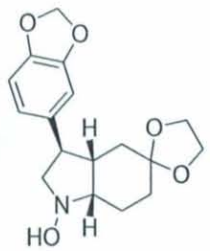
IR (neat) 2934, 2857, 2196, 1617, 1508, 1447, 1381, 1251, 1230, 1183, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.85-7.78 (m, 3H, Ar*H*), 7.67 (s, 1H, Ar*H*), 7.5-7.45 (m, 2H, Ar*H*), 7.35 (d, 1H, J = 8.5, Ar*H*), 4.33-4.08 (m, 2H, CH_2NO), 3.43-3.35 (q, 1H, J = 9, ArC*H*), 3.27-3.23 (dd, 1H, J = 5.9, 4.3, N=CC*H*), 2.91 (br, 1H, N=CCH_2), 2.13-2.02 (m, 2H, CH_2), 1.99-1.96 (m, 1H, CH_2), 1.89-1.80 (m, 1H, CH_2), 1.45-1.35 (m, 1H, CH_2), 1.35-1.22 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2 (*C*=NO), 137.0 (Ar*C*), 133.3 (Ar*C*), 132.5 (Ar*C*), 128.9 (Ar*C*), 127.6 (Ar*C*), 127.5 (Ar*C*), 126.5 (Ar*C*), 126.1 (Ar*C*), 125.9 (Ar*C*), 124.7 (Ar*C*), 68.2 (*C*H_2NO), 50.4 (Ar*C*H), 45.9 (N=*C*CH), 32.4 (N=C*C*H_2), 24.2 (*C*H_2), 23.8 (CH_2), 23.5 (*C*H_2); MS (APCI pos.): *m/z* 266.1 (M+H); HRMS (CI): *m/z* 265.1472 (265.1467 calc. for $C_{18}H_{19}NO$ (M^+)), 266.1539 (266.1545 calc. for $C_{18}H_{20}NO$ (M+H)).

Reduction of 108 to 111 and 112

To a solution of the nitrone **108** (623 mg, 1.97 mmol) in methanol (15.0 mL) was added sodium cyanoborohydride (247 mg, 3.93 mmol) followed by pivalic acid (1.00 mL, 9.83 mmol) at 0°C. The mixture was stirred overnight at ambient temperature and then concentrated under reduced pressure. The residue was basified with aqueous NaOH (5%). The resulting mixture was extracted with ethyl acetate (2 x 10.0 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a colourless foam which was purified by flash column chromatography on silica gel.

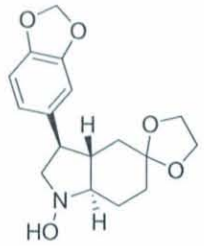
Elution with hexane/ethyl acetate (40/60) provided 0.300 g (48%) of the *cis* hydroxylamine **111**. Further elution with hexane/ethyl acetate (30/70) provided 0.120 g (19%) of the *trans* hydroxylamine **112** as a colourless gum.

(3'*R*,3a'*S*,7a'*S*)-3'-(1,3-Benzodioxol-5-yl)hexahydrospiro[1,3-dioxolane-2,5'-indol]-1'(4'*H*)-ol (111):



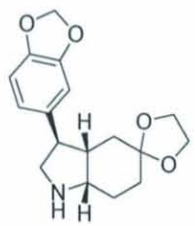
IR (neat) 3330, 2927, 1487, 1247, 1037, 934 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.81 (s, 1H, ArH), 6.74-6.70 (m, 2H, Ar*H*), 5.93 (s, 2H, OCH_2O), 3.96-3.94 (m, 2H, OCH_2CH_2O), 3.91-3.86 (m, 2H, OCH_2CH_2O), 3.76 (t, 1H, J = 8.9, C*H*NO), 3.13-3.11 (m, 1H, CH_2N), 3.05-2.95 (br s, 1H, CH_2N), 2.93-2.89 (m, 1H, $CHCH_2N$), 2.39-2.33 (m, 1H, C*H*CHN), 2.01-1.94 (m, 1H, CH_2), 1.90-1.78 (m, 3H, CH_2), 1.64-1.54 (m, 2H, CH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.9 (Ar*C*), 146.0 (Ar*C*), 138.4 (Ar*C*), 120.5 (Ar*C*), 108.8 (Ar*C*), 108.1 (Ar*C*), 107.9 (O*C*O), 100.9 (OCH_2O), 66.4 (N*C*H), 65.4 (CH_2N), 64.2 (OCH_2CH_2O) , 64.1 (OCH_2CH_2O), 46.9 (NCH*C*H), 43.6 (NCH_2CH), 37.0 (CH_2), 30.6 (CH_2), 23.1 (CH_2); MS (APCI, pos.): m/z 320.2 (M+H); HRMS (CI): m/z 320.1510 (320.1498 calc. for $C_{17}H_{22}NO_5$ (M+H)).

(3'*R*,3a'*S*,7a'*R*)-3'-(1,3-Benzodioxol-5-yl)hexahydrospiro[1,3-dioxolane-2,5'-indol]-1'(4'*H*)-ol (112):



IR (neat) 3400-3000 (br), 2925, 2877, 1734, 1504, 1487, 1441, 1245, 1142, 1099, 1060, 1037, 934 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.76 (s, 1H, Ar*H*), 6.72 (s, 1H, Ar*H*), 6.64 (br s, 1H, Ar*H*), 5.92 (s, 2H, OCH_2O), 3.93-3.75 (br m, 5H, OCH_2CH_2O, C*H*), 3.50-3.25 (br m, 2H), 3.00-2.85 (br m, 1H), 2.65-2.45 (br s, 1H), 2.15-2.00 (br m, 1H), 1.90-1.75 (br m, 3H), 1.65-1.50 (br m, 2H), 1.41-1.26 (br m, 1H); MS (APCI, pos.) *m/z* 320.1 (M+H); HRMS (EI+): *m/z* 319.1419 (319.1420 calc. for $C_{17}H_{21}NO_5$). A satisfactory ^{13}C spectrum could not be obtained due gradual decomposition of the product, in soultion at ambient temperature.

(3'*R*,3a'*S*,7a'*S*)-3'-(1,3-Benzodioxol-5-yl)octahydrospiro[1,3-dioxolane-2,5'-indole] (113):

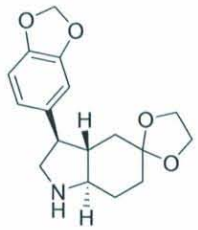


The *cis* hydroxylamine **111** (245 mg, 0.770 mmol) was dissolved in a mixture of EtOH (4.00 mL) and aqueous saturated NH_4Cl (2.00 mL). Indium powder (176 mg, 1.54 mmol) was added and the mixture was heated to reflux for 3 h. The mixture was cooled, filtered through a pad of celite®, and concentrated. Saturated aqueous Na_2CO_3 (15.0 mL) was added to the residue and the mixture was extracted with ethyl acetate (3 x 10.0 mL).

The combined organic phases were dried (Na_2SO_4) and concentrated to provide 218 mg (94%) of the amine **113** as a colorless gum that was pure by ^{1}H NMR (500 MHz).

IR (neat): 3333, 2925, 1505, 1488, 1440, 1247, 1096, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78-6.65 (m, 3H, Ar*H*), 5.92 (s, 2H, OCH_2O), 3.97-3.92 (m, 2H, OCH_2CH_2O), 3.90-3.85 (m, 2H, OCH_2CH_2O), 3.52-3.47 (dd, 1H, J = 8.6, 10.9, NHCH_2), 3.41-3.34 (m, 1H, NC*H*), 3.28-3.25 (q, 1H, J = 8.3), 2.98-2.94 (dd, 1H, J = 8.2, 10.9, NHCH_2), 2.24-2.17 (m, 1H, C*H*CHAr), 2.06-2.04 (br s, 1H, NH), 1.82-1.72 (m, 4H, CH_2), 1.58-1.51 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7 (Ar*C*), 145.9 (Ar*C*), 137.6 (Ar*C*), 120.7 (Ar*C*), 108.8 (Ar*C*), 108.1 (ArC), 107.8 (O*C*O), 100.8 (O*C*H$_2$O), 64.3 (O*C*H$_2$CH$_2$O), 63.9 (OCH$_2$*C*H$_2$O), 56.9 (N*C*H), 53.6 (*C*H$_2$N), 48.3 (NCH$_2$*C*H) , 46.8 (NCH*C*H), 33.9 (*C*H$_2$), 31.5 (*C*H$_2$), 27.1 (*C*H$_2$); MS (APCI, pos.): m/z 304.0 (M+H); HRMS (EI): m/z 303.1471 (303.1471 calc. for $C_{17}H_{21}NO_4$ (M^+)).

(3'*R*,3a'*S*,7a'*R*)-3'-(1,3-Benzodioxol-5-yl)octahydrospiro[1,3-dioxolane-2,5'-indole] (114):

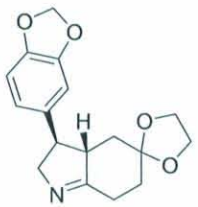


The *trans* hydroxylamine **112** (34.0 mg, 0.106 mmol) was dissolved in a mixture of EtOH (2.00 mL) and aqueous saturated NH_4Cl (1.00 mL). Indium powder (25.0 mg, 0.213 mmol) was added, and the reaction mixture was heated to reflux for 3 h. The mixture was cooled, filtered through a pad of celite®, and concentrated. Aqueous saturated Na_2CO_3 (15.0 mL) was added to the residue and the mixture was extracted with

ethyl acetate (3 x 10.0 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to provide 25.0 mg (78%) of the amine **114** as a colorless gum that was pure by ^{1}H NMR (500 MHz).

IR (neat): 3500-3000 (br), 2938, 2882, 1504, 1487, 1441, 1247, 1061, 1037, 929 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74-6.70 (m, 2H, Ar*H*), 6.66-6.57 (m, 1H, Ar*H*), 5.92 (s, 2H, OCH_2O), 4.13-3.87 (m, 4H, OCH_2CH_2O), 3.51-3.47 (br t, 1H, *J* = 10.3, NC*H*), 3.05-3.01 (m, 1H, NCH_2), 2.84-2.78 (br q, 1H, *J* = 9.5, NCH_2), 2.66-2.62 (m, 1H, ArC*H*), 2.04-1.99 (m, 1H, CH_2), 1.85-1.70 (m, 3H, CH_2, N*H*), 1.65-1.55 (m, 1H, CH_2), 1.55-1.46 (m, 1H, CH_2), 1.36-1.34 (t, 1H, *J* = 12.4, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7 (Ar*C*-O), 146.0 (Ar*C*-O), 136.2 (ArC_{ipso}), 120.5 (Ar*C*), 109.4 (Ar*C*), 108.1 (Ar*C*), 107.4 (O*C*O), 100.8 (OCH_2O), 64.34 (OCH_2CH_2O), 64.30 (OCH_2CH_2O), 64.1 (N*C*H), 54.9 (NCH_2), 51.5 (Ar*C*H), 50.5 (NCH*C*H), 37.4 (*C*H_2), 33.8 (*C*H_2), 28.4 (*C*H_2); MS (APCI, pos.): m/z 304.0 (M+H); HRMS (EI): m/z 303.1471 (303.1471 calc. for $C_{17}H_{21}NO_4$ (M^+)).

(3'*R*,3a'*S*)-3'-(1,3-Benzodioxol-5-yl)-2',3',3a',4',6',7'-hexahydrospiro[1,3-dioxolane-2,5'-indole] (115):

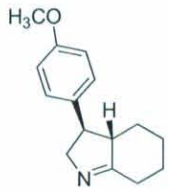


To a solution of the nitrone **108** (50 mg, 0.16 mmol) in acetonitrile (2.0 mL) was added benzyl triethylammonium tetrathiomolybdate (99 mg, 0.19 mmol) and the mixture was stirred at room temperature for 72 h. The mixture was filtered though a pad of celite®

followed by a wash of the celite® with dichloromethane. The combined filtrates were concentrated to provide 33 mg (70%) of **115** as a pale yellow gum.

IR (neat): 2927, 1652, 1504, 1487, 1243, 122, 1037, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, 2H, *J* = 7.9, Ar*H*), 6.69 (br s, 1H, Ar*H*), 6.64 (br d, 1H, *J* = 7.9, Ar*H*), 5.93 (s, 2H, OCH_2O), 4.31-4.26 (br dd, 1H, *J* = 8.5, 15.0, NCH_2), 3.99-3.93 (m, 4H, OCH_2CH_2O), 3.68-3.64 (m, 1H, NCH_2), 3.05-3.00 (q, 1H, J = 8.5, ArC*H*), 2.95-2.90 (br m, 1H, NCC*H*), 2.69-2.65 (br dd, 1H, *J* = 4.0, 14.5, CH_2), 2.60-2.50 (br m, 1H, CH_2), 2.20-2.10 (br m, 1H, CH_2), 2.00-1.94 (br m, 1H, CH_2), 1.85-1.75 (dt, 1H, *J* = 13.5, 5.2, CH_2), 1.75-1.65 (br m, 1H, CH_2), 1.55 (t, 1H, *J* = 12.6, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1 (*C*=N), 147.8 (Ar*C*-O), 146.1 (Ar*C*-O), 136.1 (ArC_{ipso}), 120.3 (Ar*C*), 108.2 (2xAr*C*), 107.3 (O*C*O), 100.9 (OCH_2O), 67.9 (NCH_2), 64.4 (OCH_2CH_2O), 64.5 (OCH_2CH_2O), 51.6 (Ar*C*H), 40.7 (ArCH*C*H), 36.6 (CH_2), 33.8 (CH_2), 28.0 (CH_2); MS (APCI, pos.): *m/z* 302.1 (M+H); HRMS (CI): m/z 301.1313 (301.1314 calc. for $C_{17}H_{19}NO_4$ (M+H)).

(3*R*,3a*S*)-3-(4-Methoxyphenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indole (116):

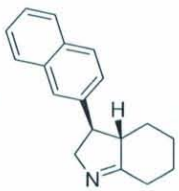


To a solution of the nitrone **109** (0.10 g, 0.43 mmol) in acetonitrile (2.0 mL) was added benzyl triethylammonium tetrathiomolybdate (0.27 g, 0.52 mmol) and the mixture was stirred at room temperature for 96 h. The mixture was filtered though a pad of celite® and the residue on the celite® was washed with dichloromethane. The combined filtrates

were concentrated and the residue was purified by flash column chromatography on silica gel (EtOAc as the eluant) to provide 61 mg (62%) of **116** as a pale yellow gum.

IR (neat): 2931, 2857, 1648, 1612, 1513, 1445, 1244, 1179, 1034, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, 2H, *J* = 8.7, Ar*H*), 6.85 (d, 2H, *J* = 8.7, Ar*H*), 4.26-4.21 (dd, 1H, *J* = 15.2, 9.0, NCH_2), 3.79 (s, 3H, OCH_3), 3.70-3.65 (br m, 1H, NCH_2), 3.05-3.00 (q, 1H, *J* = 9.0, ArC*H*), 2.73 (br m, 1H, ArCHC*H*), 2.65-2.55 (m, 1H, NCCH_2), 2.23-2.17 (m, 2H, CH_2), 2.05-1.98 (m, 1H, CH_2), 1.85-1.83 (m, 1H, CH_2), 1.48-1.37 (m, 2H, CH_2), 1.28-1.20 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.0 (*C*=N), 158.1 (ArC_{ipso}), 135.3 (ArC_{ipso}), 128.1 (Ar*C*), 114.0 (Ar*C*), 67.2 (NCH_2), 56.5 (ArCH*C*H), 55.2 (OCH_3), 50.4 (Ar*C*H), 33.5 (*C*H_2), 31.9 (*C*H_2), 26.3 (*C*H_2), 25.1 (*C*H_2); MS (API, ES, pos.) m/z 230.1 (M+H); HRMS (TOF, EI+): m/z 229.1464 (229.1467 calc. for $C_{15}H_{19}NO$, M^+).

(3*R*,3a*S*)-3-(Naphthalen-2-yl)-3,3a,4,5,6,7-hexahydro-2*H*-indole (117):

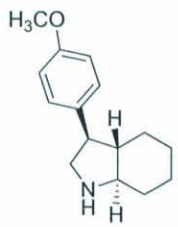


To a solution of the nitrone **110** (0.100 g, 0.380 mmol) in acetonitrile (2.00 mL) was added benzyltriethylammonium tetrathiomolybdate (237 mg, 0.450 mmol) and the mixture was stirred at temperature for 120 h. Additional benzyltriethylammonium tetrathiomolybdate (176 mg, 0.340 mmol) was added and stirring was continued for 192 h. The mixture was filtered though a pad of celite®, the celite® was with dichloromethane (3 x 10.0 mL). The combined filtrates were concentrated and the residue was purified by

flash column chromatography on silica gel (CH_2Cl_2/methanol 98/3) to provide 60.0 mg (64%) of **117** as a gum.

IR (neat): 2928, 2857, 1735, 1648, 1600, 1507, 1446, 1352, 1242, 1041, 1017, 993, 948, 856, 819, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.81-7.74 (m, 4H, Ar*H*), 7.48-7.42 (m, 3H, ArH), 7.35-7.33 (m, 1H, ArH), 4.37-4.32 (dd,1H, J = 15.4, 8.9, NCH_2), 3.86-3.77 (m, 1H, NCH_2), 3.27-3.22 (q, 1H, J = 8.6, ArC*H*), 2.78-2.76 (m, 1H, ArCHC*H*), 2.27-2.20 (m, 2H, CH_2), 2.04-2.00 (m, 1H, CH_2), 2.00-1.75 (m, 2H, CH_2), 1.55-1.40 (m, 2H, CH_2), 1.40-1.25 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9 (*C*=N), 140.9 (Ar*C*), 133.5 (Ar*C*), 132.3 (Ar*C*), 128.4 (Ar*C*), 127.6 (Ar*C*), 127.5 (Ar*C*), 126.2 (Ar*C*), 125.7 (Ar*C*), 125.5 (Ar*C*), 125.4 (Ar*C*), 67.3 (*C*H_2N), 56.6 (Ar*C*H), 51.5 (N=C*C*H), 33.7 (N=CCH_2), 32.0 (*C*H_2), 26.4 (CH_2), 25.2 (*C*H_2); MS (APCI, pos.): m/z 250.1 (M+H); HRMS (TOF, EI+): m/z 249.1521 (249.1517 calc. for $C_{18}H_{19}N$ (M^+)).

(3*R*,3a*S*,7a*R*)-3-(4-Methoxyphenyl)octahydro-1*H*-indole (118):

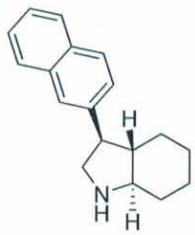


A solution of the imine **116** (0.060 g, 0.26 mmol) in ethanol (3.0 mL) was cooled to 0 °C and $NaBH_4$ (0.020 g, 0.44 mmol) was added. The mixture was stirred at 0 °C for 1 h then acidifed to pH 3 with aq. HCl (1 N). The mixture was then basified to pH 9 with aq. NaOH (5%) and extracted with dichloromethane (2 x 15 mL). The combined extracts were dried and concentrated to provide 58 mg (96%) of the crude amine. Purification by

flash chromatography on silica gel (CH_2Cl_2/methanol, 9/1) provided 45 mg (75%) of **118** as a gum.

IR (neat): 3500-3100 (br), 2925, 2854, 1612, 1583, 1444, 1245, 1178, 1035, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, *J* = 8.5, Ar*H*), 6.85 (d, 2H, *J* = 8.5, Ar*H*), 3.79 (s, 3H, OCH_3), 3.45-3.41 (t, 1H, *J* = 10.3, NC*H*), 3.01-2.97 (dd, 1H, *J* = 8.3, 10.8, NCH_2), 2.82-2.76 (br q, 1H, *J* = 9.3, NCH_2), 2.55-2.51 (dt, 1H, *J* = 3, 10, ArC*H*), 2.10-2.05 (m, 1H, NCHC*H*), 1.81-1.70 (m, 4H, CH_2), 1.35-1.25 (m, 3H, CH_2), 1.10-1.00 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5 ($ArC_{ipso}O$), 132.4 (ArC_{ipso}), 128.6 (2xAr*C*), 114.1 (2xAr*C*), 64.3 (N*C*H), 55.2 (OCH_3), 51.4 (NCH_2), 48.9 (ArCH), 30.0 (CH_2), 28.1 (CH_2), 25.0 (CH_2), 24.6 (CH_2). MS (API, ES, pos.) m/z 232.1 (M+H); HRMS (CI, pos.) m/z 232.1697 (232.1701 calc. for $C_{15}H_{22}NO$, M+H)

(3*R*,3a*S*,7a*R*)-3-(Naphthalen-2-yl)octahydro-1*H*-indole (119):



A solution of the imine **117** (125 mg, 0.500 mmol) in ethanol (5.00 mL) was cooled to 0 °C and $NaBH_4$ (38.0 mg, 1.00 mmol) was added. The mixture was stirred at 0 °C for 1 h then acidifed to pH 3 with aq. HCl (1N). The mixture was then basified to pH 9 with aq. NaOH (5%) and extracted with dichloromethane (2 x 15.0 mL). The combined extracts were dried and concentrated to provide 125 mg (99%) of **119** as a gum which was pure by ^1H NMR.

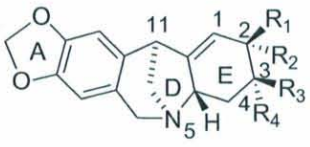
IR (neat): 3500-3100 (br), 2923, 2852, 1632, 1599, 1507, 1445, 896, 856 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85-7.76 (m, 3H, Ar*H*), 7.65 (s, 1H, Ar*H*), 7.47-7.36 (m, 3H, Ar*H*), 3.50 (t, 1H, *J* = 10.4,), 3.15-3.11 (dd, 1H, *J* = 8.0, 11.1,), 3.03-2.97 (q, 1H, *J* = 9.5,), 2.59-2.55 (m, 1H,), 2.11-2.09 (m, 1H, NCHC*H*), 1.86-1.71 (m, 3H, CH_2), 1.5-1.42 (dq, 1H, *J* = 3, 11, CH_2), 1.35-1.25 (m, 2H, CH_2), 1.20-1.15 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1 (ArC_{ipso}), 133.5 (ArC_{ipso}), 132.3 (ArC_{ipso}), 128.2 (Ar*C*), 127.6 (Ar*C*), 127.4 (Ar*C*), 125.9 (Ar*C*), 125.7 (Ar*C*), 125.3 (Ar*C*), 64.9 (N*C*H), 54.1 (NCH2), 52.8 (NCHCH), 50.8 (Ar*C*H), 31.8 (*C*H_2), 28.4 (*C*H_2), 25.7 (*C*H_2), 24.9 (*C*H_2).

MS (APCI, pos.): m/z 252.2 (M+1). HRMS (CI, pos.): m/z 252.1753 (252.1752 calc. for $C_{18}H_{22}N$, M+H).

Part II: Formal Total Synthesis of (-)-Pancracine

Introduction

(-)-Pancracine, (-)-brunsvigine, (-)-montanine, (-)-coccinine and (-)-manthine (Figure 5) are members of the montanine–type *Amaryllidaceae* alkaloids.[43-45] These alkaloids share a characteristic pentacyclic 5,11-methanomorphanthridine as the core skelton with a C-1/C-11a double bond and differ only in the nature and stereochemistry of the oxygen-based substituents at C-2 and C-3 in the E ring (Figure 5).[43,44] Wildman and co-workers isolated these *Amaryllidaceae* alkaloids in 1955 from various plant species.[45] These alkaloids have been shown to display important biological activities including anxiolytic, antidepressant, weak hypotensive, and anticonvulsant-type effects.[46]



Compound	R_1	R_2	R_3	R_4	
120	H	OH	OH	H	(-)-pancracine
121	H	OH	H	OH	(-)-brunsvigine
122	H	OCH_3	OH	H	(-)-montanine
123	OCH_3	H	OH	H	(-)-coccinine
124	H	OCH_3	OCH_3	H	(-)-manthine

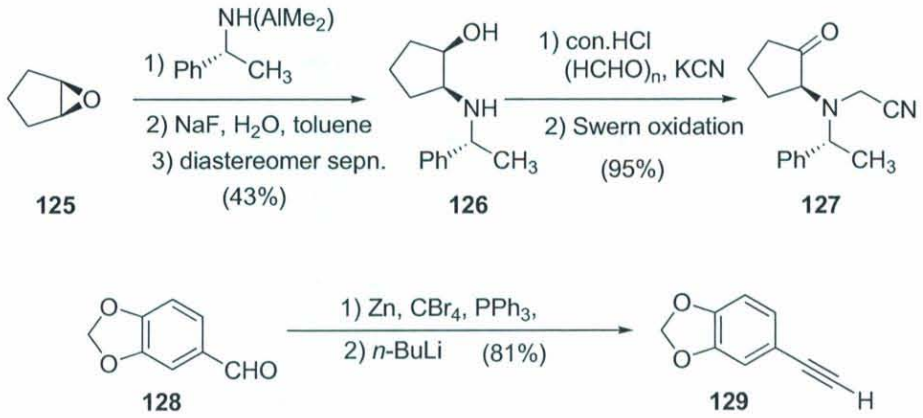
Figure 5. Structures of selected montanine-type *Amaryllidaceae* alkaloids

Known synthetic routes to pancracine

The following summary provides an overview of the syntheses of pancracine in enantiomerically enriched, as well as racemic, form which have been reported to date.

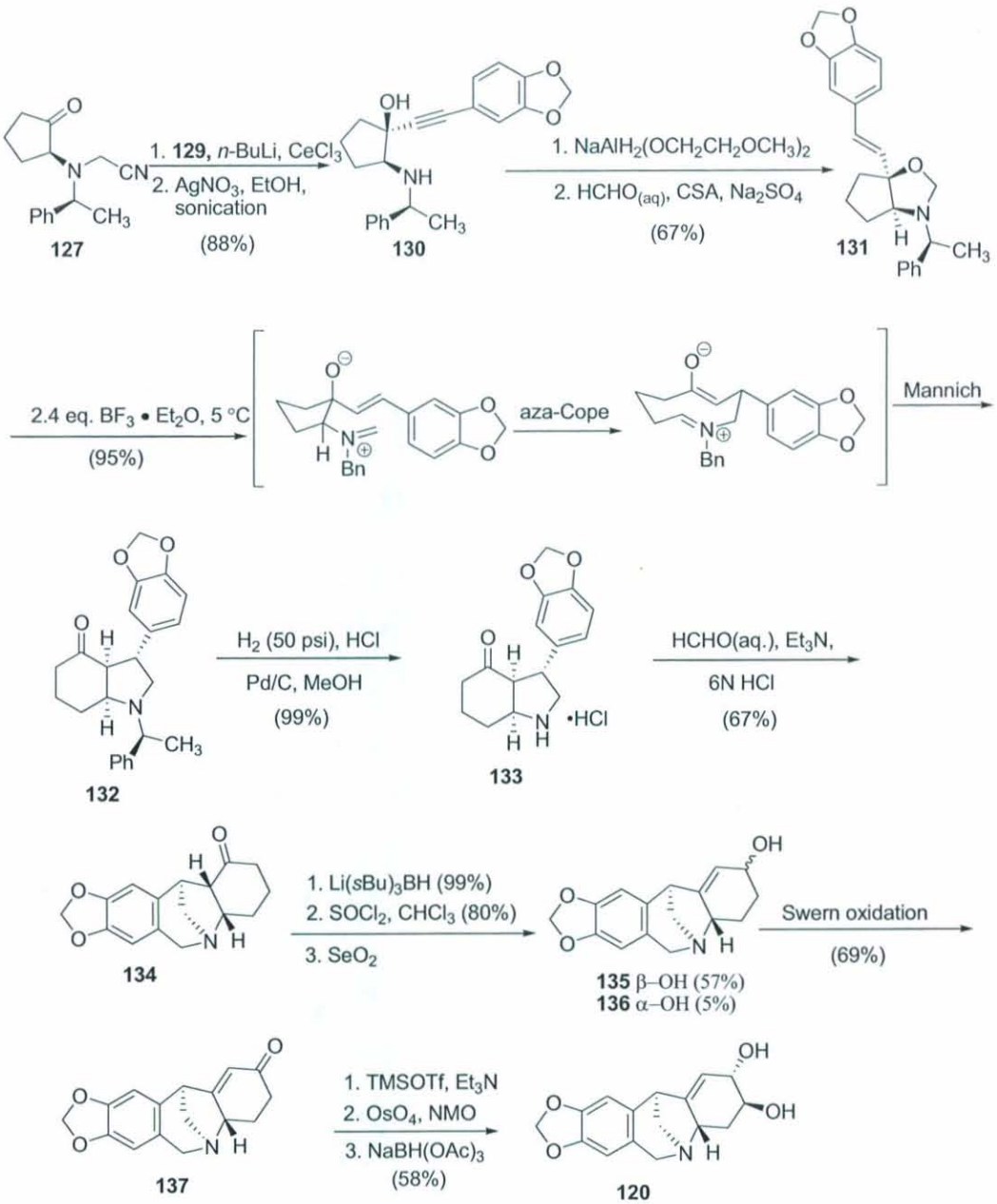
The Overman synthesis of (-)-pancracine

In 1993, Overman and Shim reported an enantioselective total synthesis of (-)-pancracine. The key step was a Lewis acid-mediated aza-Cope rearrangement–Mannich cyclization reaction.[47] The synthesis began with the formation of amino alcohol **126** from a reaction of cyclopentene oxide, (*R*)-α-methyl-benzylamine in the presence of trimethylaluminum. Following the formation of the aminoacetonitrile precursor formed from **126**, a Swern oxidation was conducted to make the ketone **127.**[48] The Corey-Fuchs procedure was used to convert piperonal (**128**) to the acetylene starting material **129** (Scheme 2).



Scheme 2

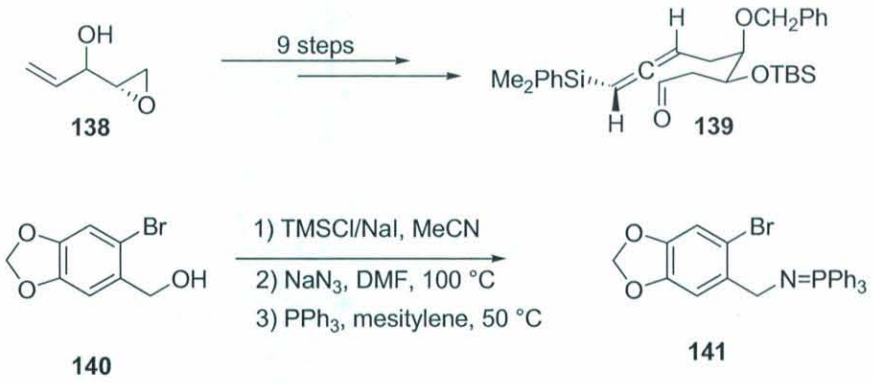
Coupling of (*S*)-amino ketone **127** with the organocerium reagent derived from alkyne **129** proceeded with good yields to give the corresponding protected amino alcohol (Scheme 3). Subsequent removal of the cyanomethyl group gave propargylic alcohol **130**. Reduction of **130** to the *trans*-allylic alcohol followed by oxazolidine formation using formaldehyde and camphorsulfonic acid provided **131** in 75% yield. The key aza-Cope-Mannich rearrangement reaction of **131** was initiated with boron trifluoride etherate and provided hydroindolone **132**. Hydrogenolysis of the α–methyl benzyl group in **132** in the presence of HCl provided the crystalline hydrochloride salt **133**. Compound **133** was then basified in the presence of formaldehyde and the resulting *N*-hydroxymethyl intermediate was treated with 6N HCl to form the Pictet-Spengler cyclization product **134**. Reduction of the ketone in **134** with lithium tri-*sec*-butylborohydride, dehydration of the secondary alcohol to the more substituted alkene and subsequent allylic oxidation provided a mixture of allylic alcohols **135** and **136**. Swern oxidation of this mixture provided the enone **137** which was converted to the dienoxysilane. Dihydroxylation of the silylenol ether (OsO_4, NMO) and subsequent reduction of the β-hydroxy ketone intermediate with sodium triacetoxyborohydride provided the desired (-)-pancracine **120** stereoselectively.


1. 129, n-BuLi, CeCl3
2. AgNO3, EtOH, sonication
(88%)
1. NaAlH2(OCH2CH2OCH3)2
2. HCHO(aq), CSA, Na2SO4
(67%)
127
130
131
2.4 eq. BF3 • Et2O, 5 °C
(95%)
aza-Cope
Mannich
H2 (50 psi), HCl
Pd/C, MeOH
(99%)
HCHO(aq.), Et3N,
6N HCl
(67%)
132
133
1. Li(sBu)3BH (99%)
2. SOCl2, CHCl3 (80%)
3. SeO2
Swern oxidation
(69%)
134
135 β–OH (57%)
136 α–OH (5%)
1. TMSOTf, Et3N
2. OsO4, NMO
3. NaBH(OAc)3
(58%)
137
120

Scheme 3

The Weinreb synthesis of (-)-pancracine

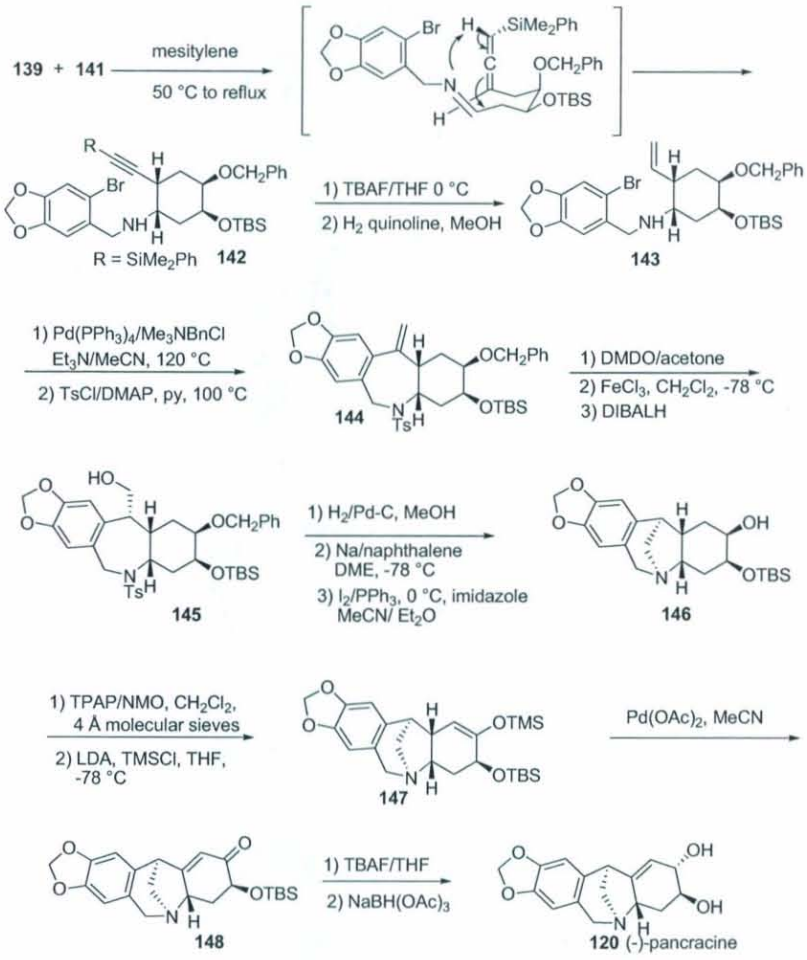
Weinreb and Jin reported an enantioselcetive total synthesis of (-)-pancracine in 1997.[49] Their approach involved the use of an intramolecular concerted pericyclic allenylsilane imino ene cycloaddition as a key step. The synthesis began with conversion of readily available enantiomerically pure epoxy alcohol **138** to the allenyl aldehyde **139** *via* a nine-step sequence. Another starting material, iminophosphorane **141** was obtained from the known piperonyl alcohol **140** (Scheme 4).



Scheme 4

The key ene-cycloaddition was initiated by heating allenylsilane aldehyde **139** and iminophosphorane **141** in mesitylene to afford a single ene-cyclization product, **142** (Scheme 5). Desilylation followed by reduction of alkyne **142** using Lindlar's catalyst gave the terminal alkene **143**. Compound **143** was further transformed by a Heck cyclization to form a seven-membered exocyclic alkene, which was protected as its *N*-tosyl derivative **144**. Epoxidation of **144** followed by Lewis acid-induced rearrangement afforded the aldehyde which was reduced to alcohol **145**. Debenzylation of **145** followed

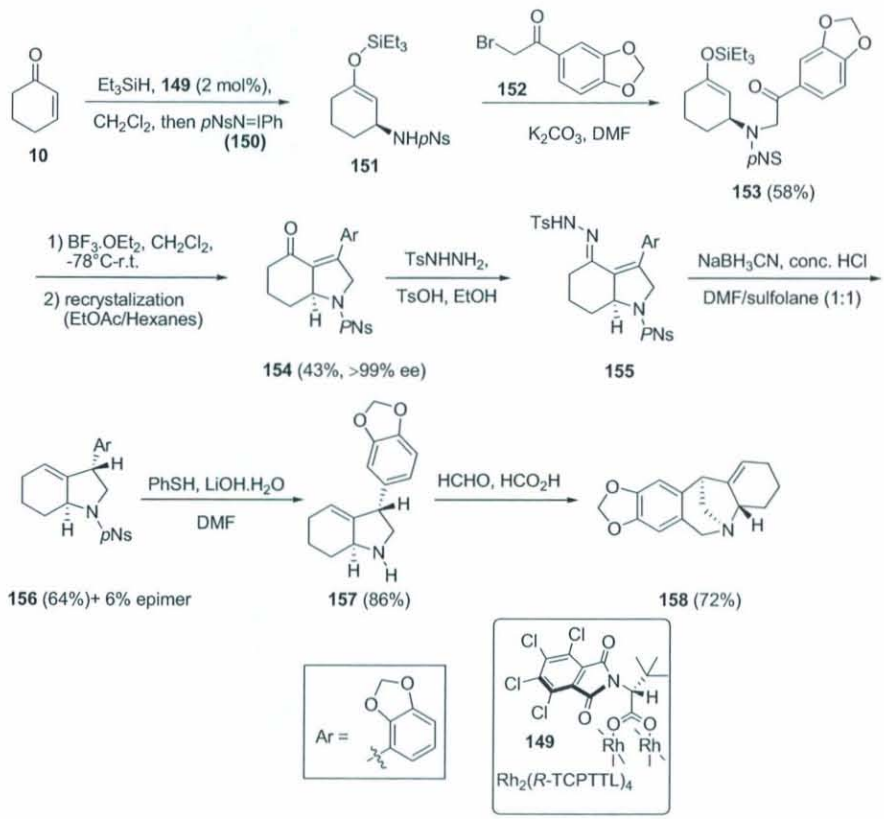
by *N*-tosyl removal gave the corresponding amino alcohol. Cyclization using triphenylphosphine and iodine afforded **146** in 82% yield. Oxidation of **146** using TPAP/NMO gave the corresponding ketone, which was converted to silyl enol ether **147** using LDA/TMSCl. Compound **147** was successfully converted to enone **148** by the Saegusa method ($Pd(OAc)_2$ in acetonitrile).[50] Desilylation of **148** followed by reduction with $NaBH(OAc)_3$ provided (-)-pancracine **120** in enantiomerically pure form.



Scheme 5

The Hashimoto formal synthesis of (-)-pancracine

A recent publication by Hashimoto and co-workers describes an approach to the synthesis of (-)-pancracine using a catalytic enantioselective C-H amination process as the key step.[51] The catalyst used in this approach is the dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*R*)-*tert*-leucinate, Rh_2(*R*-TCPTTL)$_4$ **149**, and successfully represents the first example of the insertion of nitrene species (obtained from compound **150**), and ([(4-nitrophenylsulfonyl)-imino]phenyliodinane, *p*NsN=Ph), into an allylic C-H bond of a silyl enol ether (Scheme 6).



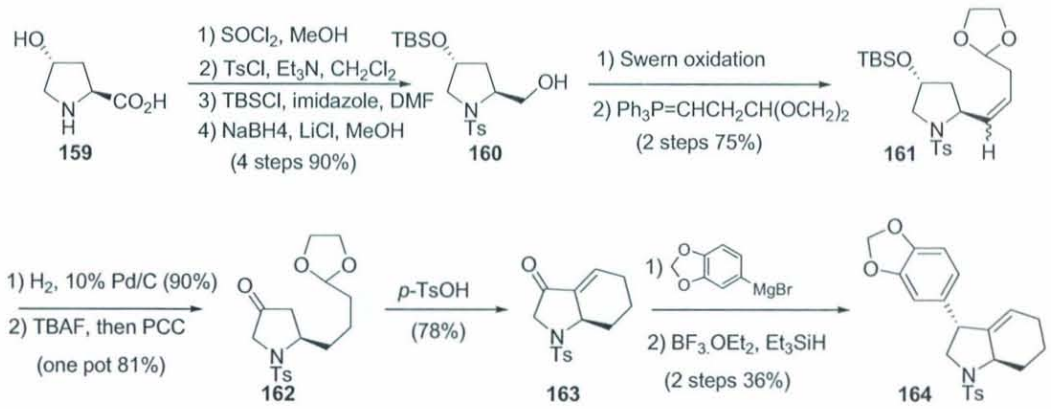
Scheme 6

The synthesis began with a one-pot 1,4-hydrosilyation/C-H amination of enone **10** with **150** using 2 mol % catalyst **149** to produce the *N*-*p*Ns-protected *β*-amino silyl enol ether **151**. This product was relatively unstable, so the *N*-alkylation procedure was carried out without purification of the crude product, to produce *N,N*-disubstituted *β*-amino silyl enol ether **153** in 58% yield (3 steps). Intramolecular Mukaiyama aldol condensation produced the bicyclic enone **154** which was converted to **155** by reaction with tosylhydrazine. Hydrazone **155** was then reduced to give alkene **156** in 64% yield plus 6% of the C11-epimer. Removal of the *p*Ns protecting group followed by a Pictet-Spengler cyclization gave **158** which is an intermediate in the Overman synthesis of (-)-pancracine.

The Chang formal total synthesis of (+)-pancracine

Chang and co-workers reported a formal total synthesis of (+)-pancracine.[52] Their approach involved the synthesis of a hexahydro-1*H*-indol-3-one **163** by intramolecular aldol condensation of ketone **162** (Scheme 7). The synthesis began with *trans*-4-hydroxyproline **159** which was transformed into *trans*-4-hydroxyprolinol **160** in four steps. Alcohol **160** was converted into alkene **161** by Swern oxidation followed by Wittig olefination. Alkene **161** was reduced and the product was transformed to ketone **162** by desilylation with TBAF followed by oxidation of the resulting alcohol with PCC. Intramolecular aldol condensation of ketone **162** under acidic conditions gave the hexahydro-1*H*-indol-3-one **163**. Addition reaction between **163** and a 3,4-methylenedioxyphenylmagnesium bromide, followed by reduction of the resulting

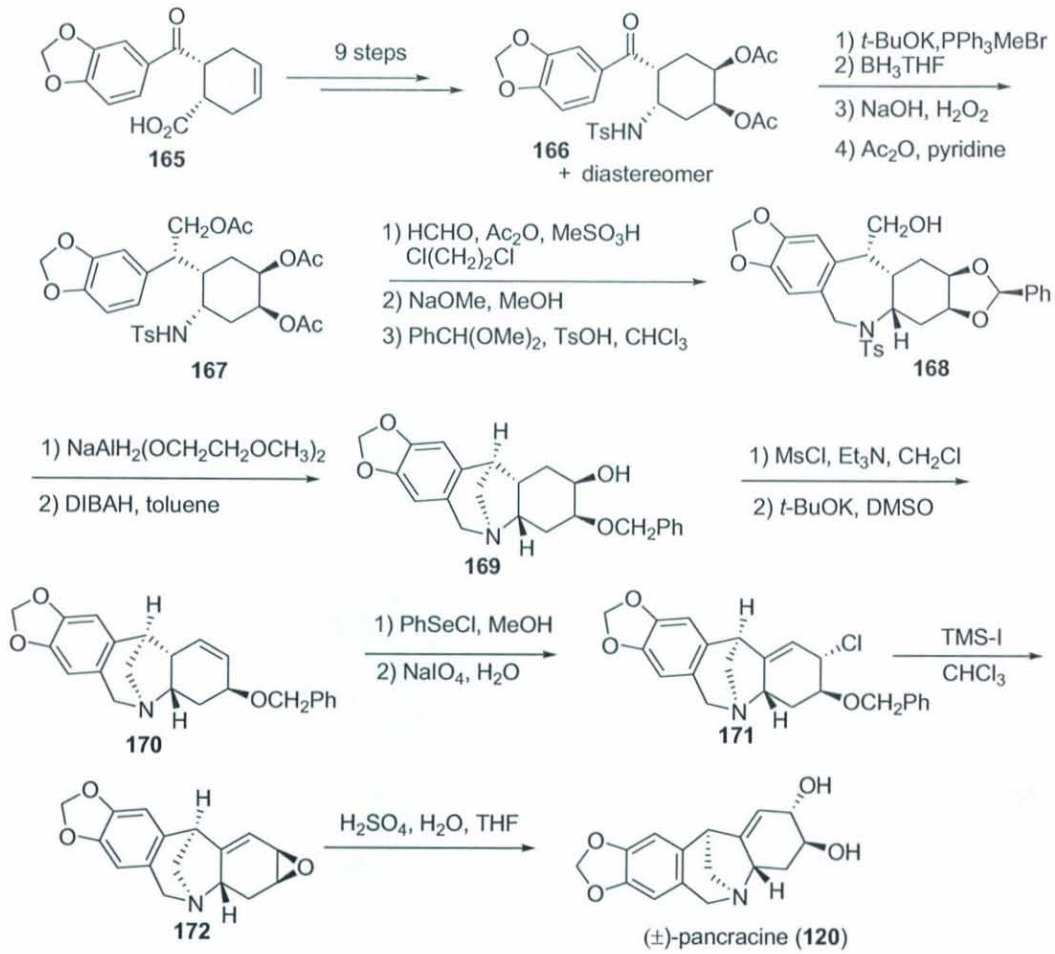
tertiary benzylic alcohol gave **164**, which is an intermediate in the Banwell synthesis of pancracine.[53]



Scheme 7

The Hoshino total synthesis of (±)-pancracine

The total synthesis of (±)-pancracine by Hoshino involves a convenient route to the 5,11-methanomorphanthridine ring system using a reductive cyclization reaction as its key step.[54] The synthesis begins with keto acid **165** which was obtained from the reaction of 1,2-*cis*-cyclohex-4-ene dicarboxylic anhydride and 3,4-methylenedioxyphenylmagnesium bromide. (Scheme 8).



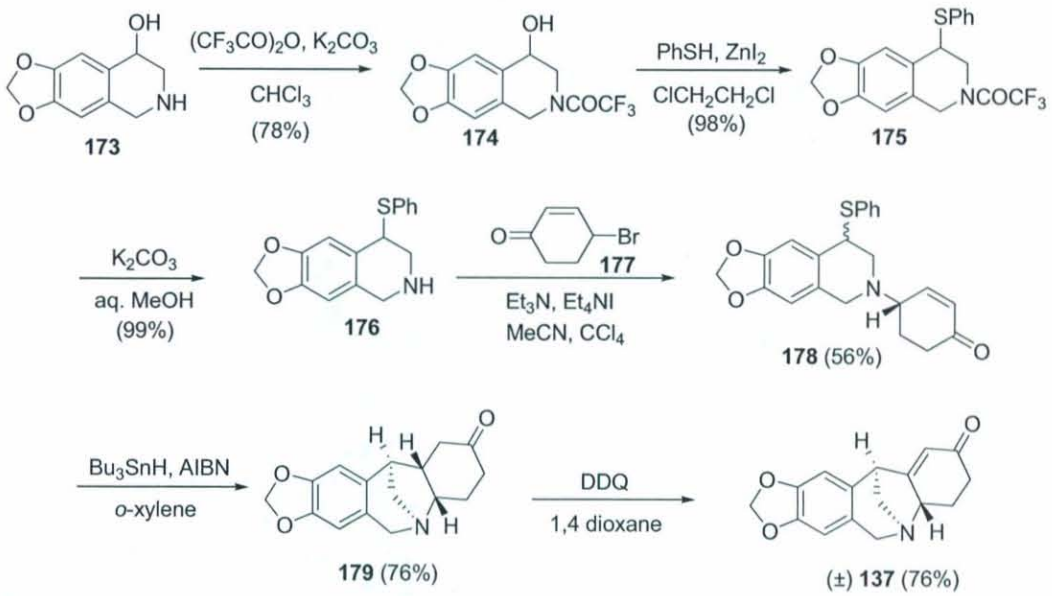
Scheme 8

Compound **165** was converted to a separable mixture of **166** and its diastereomer in nine steps. Wittig reaction of **166** followed by hydroboration and oxidation provided the primary alcohol which was acetylated to give **167**. Hydrolysis of **167** followed by protection of the vicinal diol gave the benzylidene tosylamide **168**. Reductive cyclization with sodium bis(2-methoxyethoxy) aluminium hydride and subsequent deprotection of acetal with DIBAH gave **169**. Alkene **170** was obtained from **169** via mesylation and

elimination. Epoxidation of **170** was unsuccessful; hence it was transformed into the allylic chloride **171** by using phenylselenenyl chloride followed by oxidation. Debenzylation of **171** with trimethylsilyl iodide produced epoxide **172** which upon treatment with aqueous sulfuric acid in THF provided (±)-pancracine.

The Hoshino formal total synthesis of (±)-pancracine

The formal synthesis of (±)-pancracine by Hoshino gives a convenient route to a 5,11-methanomorphanthridine ring system using a radical cyclization reaction as the key step.[55] The synthesis began with trifluoroacetylation of the known tetrahydroisoquinolin-4-ol **173**[56] to produce *N*-(trifluoroacetyl) tetrahydroisoquinolin-4-ol **174** in 78% yield (Scheme 9).



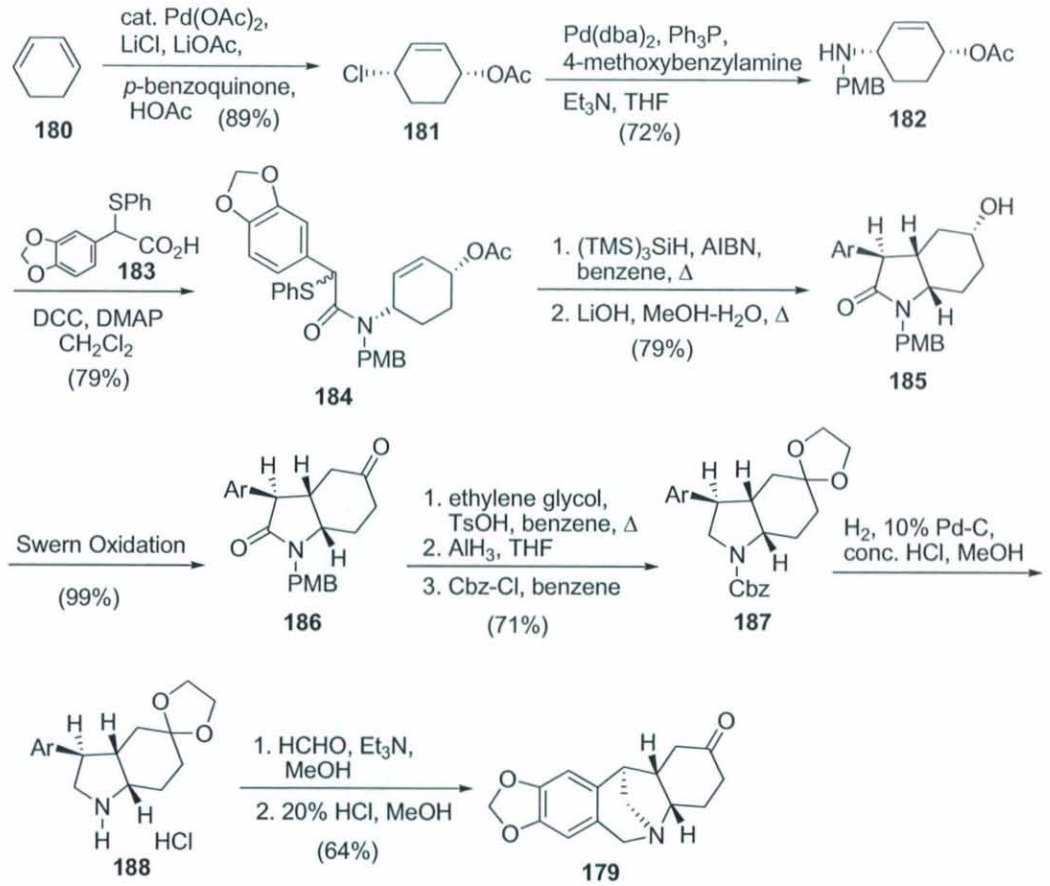
Scheme 9

Compound **174** was subsequently treated with thiophenol in the presence of ZnI_2 in 1,2-dichloroethane to give the corresponding phenyl sulfide **175**. Hydrolysis of **175** provided tetrahydroisoquinoline **176** in near quantitative amounts. Heating a mixture of **176** and 4-bromocyclohex-2-enone **177**[57] in the presence of triethylamine and Et_4NI afforded a 1:1 mixture of inseparable diasteroisomers of **178** in 56% yield. Compound **178** is the precursor for the key radical cyclization reaction using Bu_3SnH and AIBN in *o*-xylene to give 5,11-methanomorphanthridin-2-one **179** in 76% yield. Oxidation of ketone **179** using 2,3-dichloro-5,6-dicyanobenzoquinone in 1,4-dioxane afforded the enone **137** which is a known intermediate in the Overman synthesis[58] of (±)-pancracine.

The Ikeda formal total synthesis of (±)-pancracine

The formal total synthesis of (±)-pancracine developed by Ikeda utilized the 5-*exo-trig* radical cyclization as the key step.[41] The synthesis began with the 1,4-acetoxychlorination of cyclohexa-1,3-diene **180** in the presence of palladium catalyst to give (±)-*cis*-3-acetoxy-6-chlorocyclohexene **181** in 89% yield (Scheme 10).[59] 1,4-Acetoxychloride **181** was converted to PMB protected amine **182** in 72% yield. Acylation of **182** with the thiophenyl acetic acid **183** provided the amide **184**. Amide **184** was treated with $(TMS)_3SiH$ in the presence of AIBN in boiling benzene to give the *cis* isomer of the 5-*exo-trig* radical cyclization product stereoselectively. Removal of the acetoxy group by hydrolysis provided compound **185** as a single stereoisomer in 94% yield. Swern oxidation of **185** gave ketolactam **186** which was protected as ketal with ethylene glycol. Subsequent reduction of the amide and heating the obtained tertiary amine with benzylchloroformate provided the carbamate **187** in 71% yield. Catalytic hydrogenolysis

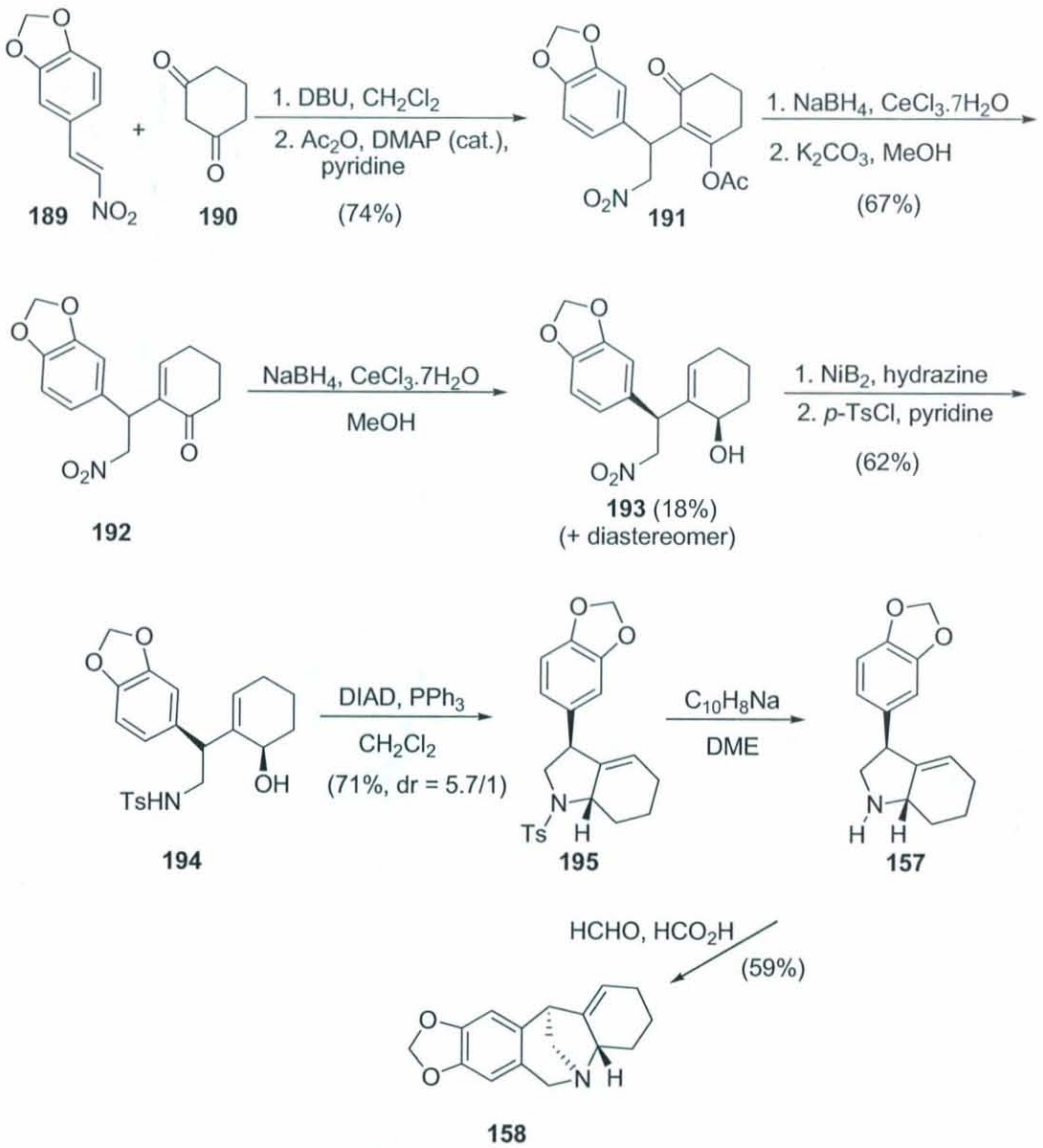
of **187** in the presence of conc. HCl gave amine hydrochloride **188** which was directly subjected to a Pictet-Spengler reaction which proceeded with concomitant deprotection of the ketal to give **179**. The conversion of **179** to the Overman intermediate to (±)-pancracine has been previously described by Hoshino.[55]



Scheme 10

The Banwell formal synthesis of (±)-pancracine

The formal synthesis of (±)-pancracine by Banwell[53] began with the DBU-promoted reaction of 3,4-methylenedioxyphenyl-β-nitrostyrene[60] **189** with cyclohexane-1,3-dione **190** to give the corresponding Michael adduct in quantitative yield (Scheme 11). This adduct was subsequently acetylated to provide the enol-acetate derivative **191**. Luche reduction[61] of **191** followed by treatment with methanolic potassium carbonate provided enone **192** in 67% yield. A second Luche reduction of **192** afforded a 1:1 diastereomeric mixture of allylic alcohols which were separated using chromatography and the desired diastereomer **193** was carried further. Reduction of the nitro group in **193** was achieved with nickel boride and hydrazine and tosylation of the resulting primary amine gave sulfonamide **194**. Ring closure of **194** was achieved by an intramolecular Mitsunobu reaction to provide the 3-arylhexahydroindole **195** as a 5.7/1 mixture of diastereomers. Reductive cleavage of the sulfonamide group in **195** using sodium naphthalenide followed by treatment of the amine **157** with formic acid-paraformaldehyde gave the Pictet-Spengler product **158** in 59% yield. Following the Overman synthesis, 5,11-methano-morphanthinidine **158** can be converted to (±)-pancracine in a series of five simple oxidation and reduction steps.

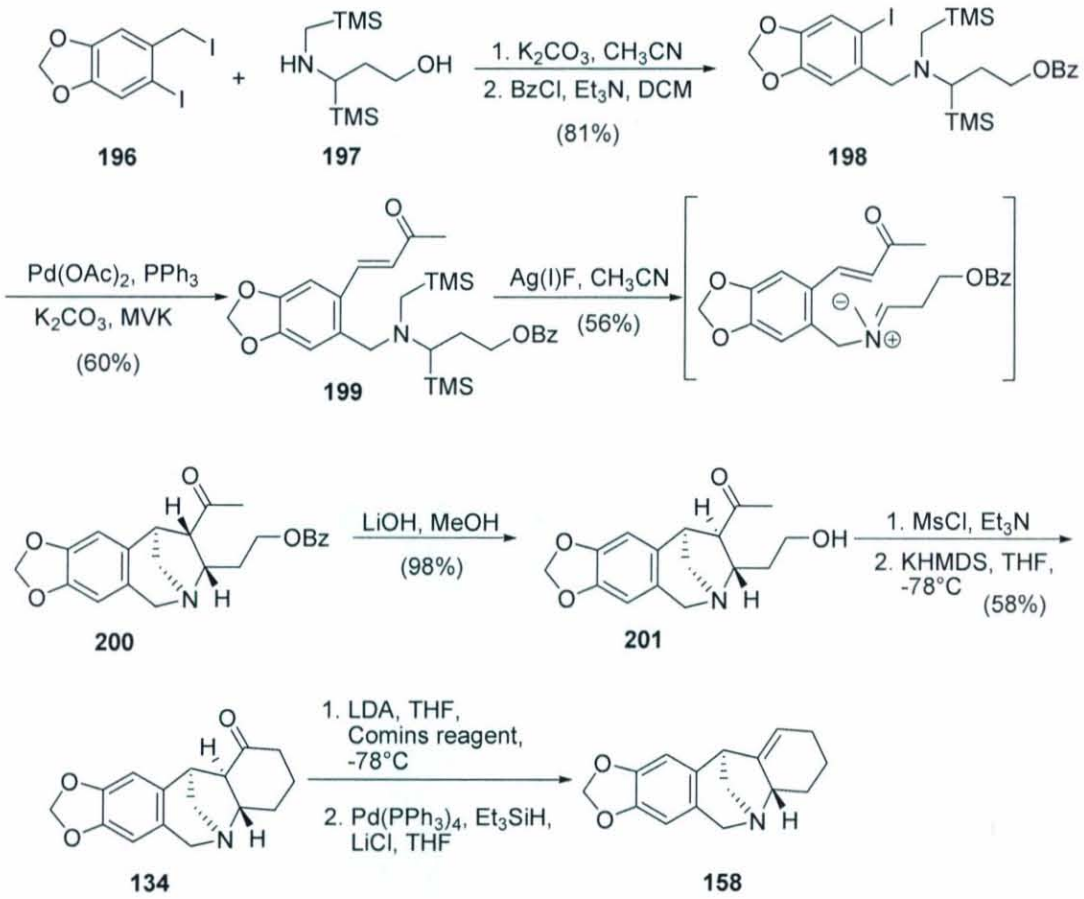


Scheme 11

The Pandey formal total synthesis of (±)-pancracine

Pandey and co-workers reported a formal total synthesis of (±)-pancracine in 2005 using an intramolecular [3+2]-cycloaddition of a nonstabilized azomethine ylide as the

key step to prepare the Overman intermediate to pancracine.[62] The synthesis (Scheme 12) began with the coupling of di-iodo compound **196** and secondary amine **197.** The coupling was followed by benzoylation to produce tertiary amine **198**. Compound **198** was then subjected to a modified Heck reaction using $Pd(OAc)_2$ as the catalyst with methyl vinyl ketone to produce compound **199** in 60% yield. Compound **201** was then produced from **199** by an intramolecular cycloaddition of an azomethine ylide to provide **200**. Removal of the benzoyl group in **200** using LiOH in MeOH provided **201**. The deprotection is accompanied by epimerization of the stereocenter α to the ketone. However, this stereocenter is not relevant to the synthesis and hence the epimerized alcohol **201** was carried further. Mesylation of **201** followed by intramolecular cyclization through the kinetic-enolate provided **134**. Conversion of **134** to the enol triflate followed by reductive elimination provided **158** which is an intermediate in the Overman synthesis of (±)-pancracine.



Scheme 12

Results and Discussion

The work described in this section focuses on studies on the stereoselctive conversion of a γ-nitroketone Michael adduct (**105**) (made by using a proline derived triamine organocatalyst) to a *cis*-3-aryloctahydroindole (**113**), which is an important intermediate to the montanine alkaloid (-)-pancracine (**120**). Considering the lack of

stereoselectivity in the reduction of nitrone or imine intermediates to the *cis*-octahydroindoles (Part I of this Chapter), an alternative approach to **113** was necessary. We reasoned that a strategy involving the direct assembly of the pyrrolidine ring by stereoselective C-N bond formation from an appropriate precursor derived from the nitroketone **105** would be more fruitful. Specifically, an invertive cyclization of the equatorial alcohol **202** derived from **105** should provide the required *cis*-octahydroindole exclusively (Figure 6).

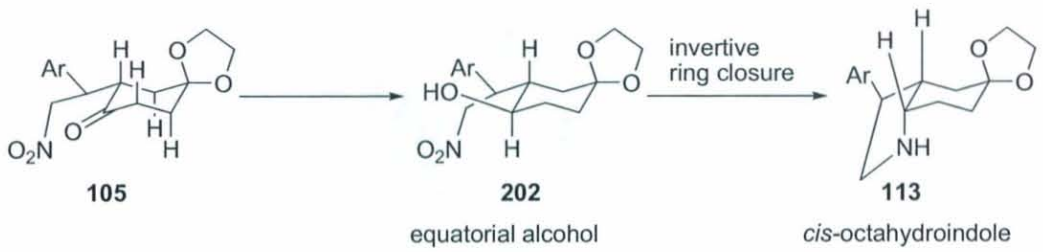
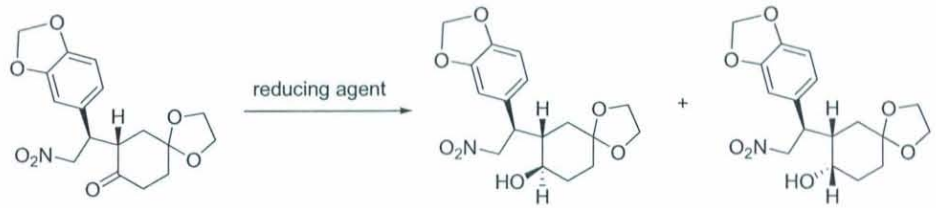


Figure 6. Synthesis of *cis*-octahydroindole **113**

With this objective in mind, a study of the stereoselective reduction of the γ–nitroketone **105** under a variety of conditions was undertaken. These results are summarized in Table **5**.

Table 5: Reduction study of nitroketone **105**



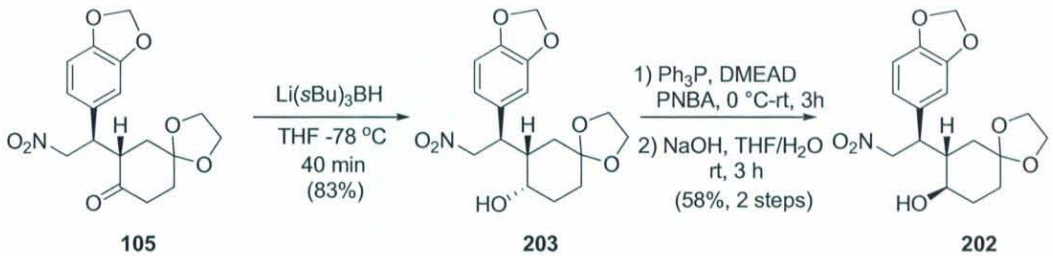
Reducing agent	Yield (%)	Equatorial alcohol (202)	Axial alcohol (203)
i-Bu_2AlOi-Pr, THF	-		NR
Daucus carrota, H_2O, EtOH	-		NR
Baker's yeast, H_2O, Sucrose	-		NR
$NaBH_4$, CH_3COOH, THF	47	1	1
KOH, $NaBH_4$, CH_3OH, H_2O	87	1	1.6
$NaBH_4$, CH_3OH	76	1	2.3
L-Selectride®, -78 °C, THF	83	1	>30

NR = Starting material was recovered

Treatment of nitro ketone **105** with sodium borohydride under a variety of conditions provided a inseparable mixture of equatorial (**202**) and axial (**203**) alcohols. The stereochemical assignments for **202** and **203** are based on the known trend in chemical shifts for the alcohol methine proton in structurally related compounds (C*H* for equatorial alcohol resonates upfield of C*H* for axial alcohol).[63,64] Surprisingly, the ketone was unreactive toward *i*-Bu_2AlOiPr in THF, a reducing agent that is known to selectively generate equatorial alcohols[65,66] from cyclic ketones. Attempted reduction of **105** using

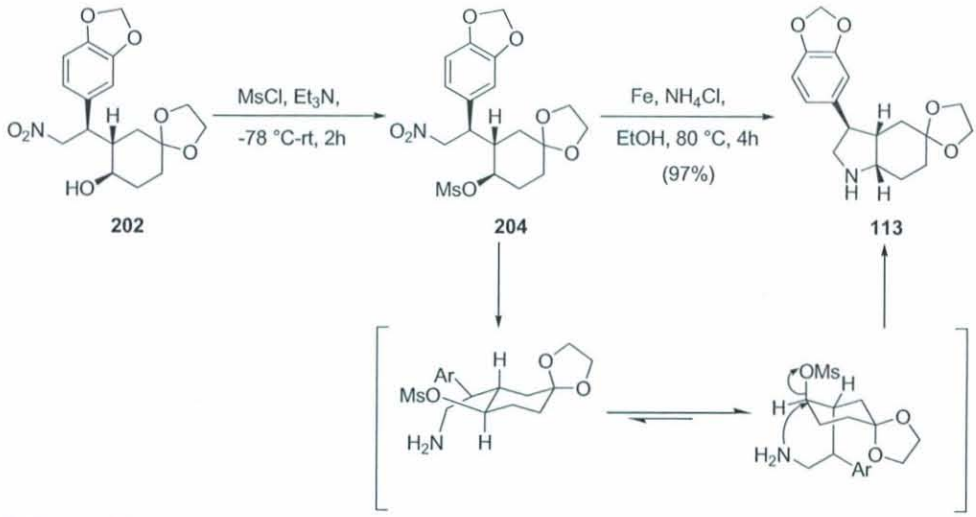
carrot[67] or yeast[68] was unsuccessful and only unreacted starting material was recovered from these reactions.

It thus became apparent that a one-step synthesis of **202** from **105** was not feasible. Therefore, in an alternative approach, the γ-nitroketone **105** was subjected to a stereoselective reduction with L-Selectride® [69] to provide the nitroalcohol **203** (axial alcohol) as a single diastereomer (Scheme 13). A Mitsunobu reaction of alcohol **203** (Ph_3P, di-2-methoxyethylazodicarboxylate (DMEAD),[70] 4-nitrobenzoic acid) followed by hydrolysis of the 4-nitrobenzoate provided the nitroalcohol **202** (equatorial alcohol) as a single diastereomer.[65,66]



Scheme 13

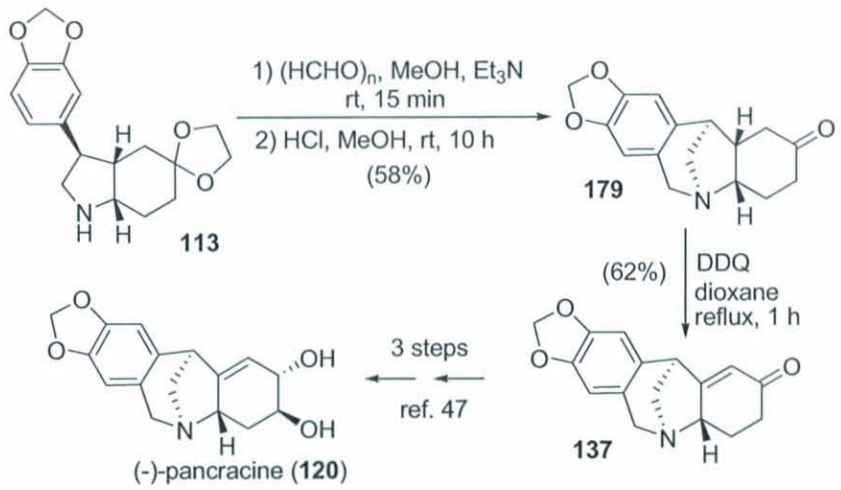
Mesylation of **202** provided the key substrate for the ring closure reaction. Gratifyingly, reduction of the nitro group in the mesylate **204** with Fe/NH_4Cl directly provided the *cis* octahydroindole **113** as a single diastereomer in excellent yield (97%). This result is indicative of a S_N2 type reaction of the intermediate amino mesylate which proceeds with complete inversion at the ring junction (Scheme 14).



Scheme 14

It is reasonable to assume that the overall conversion of **105** to **113** is representative of a general approach to *cis* octahydroindoles from cyclohexanone-derived γ-nitroketones. The efficiency of the intramolecular nucleophilic displacement should render this strategy relatively insensitive to substitution in the γ-nitroketone starting material.

Having established a stereoselective synthesis of the *cis* octahydroindole **113**, we proceeded to utilize **113** in a formal synthesis of (-)-pancracine. Treatment of **113** with aqueous formaldehyde followed by removal of the acetal protecting group, by adaptation of the literature method,[41] provided the methanomorphanthridine **179**. Oxidation of **179** with DDQ, as described by Hoshino,[55] provided **137** which is an advanced intermediate in the Overman synthesis of (-)-pancracine.[47] (Scheme 15)



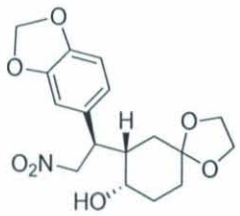
Scheme 15

Conclusion

In conclusion, the stereoselective synthesis of a *cis and trans* 3-aryl octahydroindoles were developed from an enantiomerically enriched γ-nitroketone. The methodolgy was applied in a short formal total synthesis of (-)-pancracine. The synthetic route to pancracine developed in this study is the shortest (12 steps) in comparison to any of the previously reported methods. Overall, these studies provide an efficient synthesis to the octahydroindole motif and also highlight the utility of the organocatalytic synthesis of γ-nitroketones.

Experimental section

(7*S*,8*S*)-7-[(1*R*)-1-(1,3-Benzodioxol-5-yl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-ol (203):

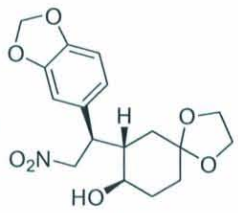


To a solution of the nitroketone **105** (1.0 g, 2.0 mmol) in anhydrous THF (0.010 L) at -78°C under nitrogen was added a solution of L-Selectride® (1 M in THF, 3.5 mL, 3.5 mmol) and the mixture was stirred for 40 min at -78 °C. EtOH (1.5 mL) was added, followed by H_2O (0.50 mL), aqueous NaOH (10%, 1.0 mL) and aqueous H_2O_2 (30%, 1.5 mL). The mixture was then warmed to ambient temperature and saturated aqueous K_2CO_3 (0.020 L) was added. The resulting solution was extracted with ethyl acetate (3 x 0.010 L). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane: 40/60) to afford 830 mg (83%) of **203** as a colourless foam.

IR (neat): 3390, 2902, 1549, 1246, 1128, 1055, 1035, 941 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, 1H, J = 7.9, Ar*H*), 6.68 (d, 1H, J = 1.7, Ar*H*) 6.63 (dd, 1H, J = 7.9, 1.7, Ar*H*), 5.95-5.93 (m, 2H, OCH_2O), 4.83-4.79 (dd, 1H, J = 12.4, 4.5, CH_2NO_2), 4.68-4.64 (dd, 1H, J = 12.4, 10.1, CH_2NO_2), 4.01 (br s, 1H, C*H*OH), 3.89-3.84 (m, 4H, OCH_2CH_2O), 3.84-3.75 (m, 1H), 3.50-3.45, (dt, 1H, J = 10, 4.8), 2.02-2.0 (m, 1H), 1.86-1.76 (m, 3H, CH_2), 1.70-1.60 (t, 1H, CH_2), 1.60-1.50 (m, 1H, CH_2), 1.30-1.25 (m, 1H

CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0 (Ar*C*), 146.9 (Ar*C*), 132.3 (Ar*C*), 121.9 (Ar*C*), 108.9 (2 x Ar*C*), 108.5 (O*C*O),101.5 (OCH_2O), 79.2 (CH_2NO_2), 65.3 (*C*HOH), 64.6 (OCH_2CH_2O), 64.5 (OCH_2CH_2O), 46.4 (Ar*C*HCH), 43.1 (ArCH*C*H), 34.1 (CH_2), 31.6 (CH_2), 28.4 (CH_2); HRMS (EI): m/z 351.1332 (351.1318 calc. for $C_{17}H_{21}NO_7$ (M^+)).

(7*S*,8*R*)-7-[(1*R*)-1-(1,3-Benzodioxol-5-yl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-ol (202):



To a solution of triphenyl phosphine (1.47 g, 5.48 mmol) in anhydrous THF (5.00 mL) at 0 °C, was added dimethoxyethyl azodicarboxylate (1.28 g, 5.48 mmol) and the solution was stirred for 5 min. A solution of the nitroalcohol **203** (962 mg, 2.74 mmol) in THF (5.00 mL) was added, the mixture was stirred for 5 min and *p*-nitrobenzoic acid (916 mg, 3.80 mmol) was added. The mixture was stirred at 0 °C for 30 min and then at ambient temperature for 3 h. The THF was removed under reduced pressure, the residue was dissolved in ethyl acetate (20.0 mL) and the solution was washed with water (2 x 20.0 mL) and aq. saturated $NaHCO_3$ (2 x 10.0 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate: 80/20) to afford 825 mg (60%) of the product *p*-nitrobenzoate as a pale yellow gum.

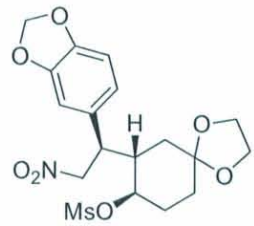
^1H NMR (500 MHz, $CDCl_3$): δ = 8.37-8.35 (d, 2H, *J* = 8.9, Ar*H*), 8.31-8.28 (d, 2H, *J* = 8.9, Ar*H*), 6.71-6.95 (d, 1H, *J* = 8.0, Ar*H*), 6.47 (d, 1H, *J* = 1.4, Ar*H*), 6.38-6.42 (dd,

1H, J = 1.4, 8, Ar*H*), 5.95-5.94 (m, 2H, OCH_2O), 4.75-4.71 (dd, 1H, J = 12.6, 8.2 CH_2NO$_2$), 4.65-4.60 (dd, 1H, J = 12.6, 8.2, CH_2NO$_2$), 4.63-4.60 (m, 1H), 4.0-3.95 (m, 4H, OCH_2CH_2O), 3.92 (m, 1H), 2.43-2.37 (m, 1H, ArCHC*H*CH$_2$), 2.20-2.16 (m, 1H, CHC*H*), 1.85-1.65 (m, 2H, CH_2), 1.60-1.50 (CH_2), 1.45-1.35 (CH_2).

To a cold (0 °C) solution of the above ester (825 mg, 1.65 mmol) in THF (10.0 mL) was added a solution of NaOH (132 mg, 3.30 mmol) in water (6.00 mL) and the solution was stirred at ambient temperature for 24 h. The solution was diluted with ethyl acetate (15.0 mL) and the aqueous layer was separated. The aqueous layer was acidified with aq. HCl (3 M) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined extracts were washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated to give 0.560 g (96%) of the alcohol **202** as a pale yellow gum. This material was pure by ^{1}H NMR (500 MHz) and was directly used in the next step without further purification.

IR (neat): 3337 (br), 1715, 1551, 1503, 1444, 1242, 1035, 926 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, 1H, J = 7.9, Ar*H*), 6.7 (d, 1H, J = 1.6, Ar*H*), 6.64-6.62 (dd, 1H, J = 7.9, 1.6, Ar*H*), 5.95-5.94 (apparent d, 2H, J = 2.3, OCH_2O), 4.86-4.82 (dd, 1H J =12.6, 7.0, CH_2NO$_2$), 4.69-4.64 (dd, 1H J =12.6, 9.5, CH_2NO$_2$) 4.02-3.98 (m, 1H), 3.9 (br s, 4H, OCH_2CH_2O), 3.24-3.21 (m, 1H), 1.95-1.85 (m, 2H, ArCHC*H*, CH_2), 1.72-1.61 (m, 2H, CH_2), 1.58-1.61 (m, 1H, CH_2), 1.46-1.37 (m, 1H, CH_2), 1.25-1.20 (t, 1H, J = 13.1, CH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7 (ArC_{ipso}), 146.9 (ArC_{ipso}), 129.9 (ArC_{ipso}), 121.9 (Ar*C*), 109.0 (Ar*C*), 108.3 (Ar*C*), 108.0 (O*C*O),101.1 (OCH$_2$O), 78.6 70.7 (*C*H$_2$NO$_2$), 64.4 (*C*HOH), 64.3 (OCH$_2$CH$_2$O), 64.5 (OCH$_2$*C*H$_2$O), 44.0 (Ar*C*HCH), 43.7 (ArCH*C*H), 34.7 (*C*H$_2$), 32.8 (*C*H$_2$), 32.6 (*C*H$_2$) HRMS (CI): m/z 351.1325 (351.1318 calc. for $C_{17}H_{21}NO_7$ (M^+)).

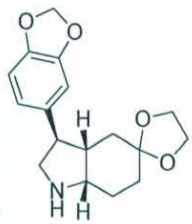
(7*S*,8*R*)-7-[(1*R*)-1-(1,3-Benzodioxol-5-yl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-methanesulfonate (204):



To a solution of the nitroalcohol **203** (0.300 g. 0.850 mmol) in dichloromethane (5.00 mL) at -78 °C was added methanesulfonyl chloride (86.0 μL, 1.11 mmol) followed by triethyl amine (257 μL, 2.20 mmol). The mixture was stirred at -78 °C for 1 h and then at ambient temperature for 2 h. The solution was washed with water (2 x 10.0 mL), dried (Na_2SO_4) and concentrated to provide 366 mg (quant.) of **204** as a pale yellow foam. This material was pure by ^{1}H NMR and was used without further purification.

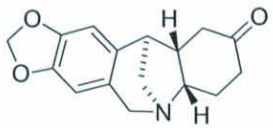
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, 1H, J = 8, Ar*H*), 6.74-6.68 (m, 2H, Ar*H*), 5.97 (m, 2H, OCH_2O), 4.75-4.65 (m, 2H, CH_2NO$_2$), 4.45-4.38 (dt, 1H, J = 4.6, 10.2, C*H*OMs), 3.97-3.90 (m, 5H, OCH_2CH_2O, ArC*H*), 2.35-2.28 (m, 1H, ArCHC*H*), 2.25-2.15 (m, 1H, CH_2), 1.95-1.85 (m, 1H, CH_2), 1.75-1.70 (m, 2H, CH_2), 1.50-1.45 (m, 1H, CH_2), 1.35-1.25 (m, 1H, CH_2).

(3'*R*,3a'*S*,7a'*S*)-3'-(1,3-Benzodioxol-5-yl)octahydrospiro[1,3-dioxolane-2,5'-indole] (113):



A mixture of Fe powder (78.0 mg, 1.39 mmol), aq. NH_4Cl (24.0 mg, 0.460 mmol in 2.00 ml water) and the above nitromesylate (0.100 g, 0.230 mmol) in ethanol (6.00 mL) was heated at 80 °C (bath temp.) for 3 h. The mixture was cooled to room temperature and filtered through a pad of celite®. The filtrate was concentrated and the residue was dissolved in dichloromethane (15.0 mL). The resulting solution was washed with aq. NaOH (5%, 2 x 10.0 mL), dried and concentrated to provide 68.0 mg (97%) of **113** as a pale yellow gum. This material was pure by ^1H NMR (500 MHz) and can be used further without purification. A pure reference sample was obtained by purification using flash column chromatography on silica gel employing CH_2Cl_2/MeOH (9/1) as the eluant (experimental for compound **113** was reported in part I of this Chapter).

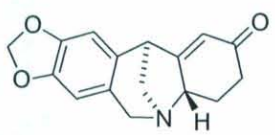
8,9-Methylenedioxy-5,11- methanomorphanthridin-2-one (179):[41]



A mixture of the amine **113** (0.170 g, 0.560 mmol), formalin (37%, 2.30 mL, 28.0 mmol), methanol (2.30 mL) and triethyl amine (156 μL, 1.10 mmol) was stirred at ambient temperature for 15 min. The resulting solution was concentrated, and the residue (176 mg) was treated with aqueous HCl (6 N, 15.0 mL). Methanol (5.00 mL) was added to provide a solution which was stirred at room temperature for 10 h. The solution was cooled (ice bath), and aqueous NH_4Cl (10 mL) was added; the mixture was stirred for a few minutes and then basified with aqueous NaOH (5%, 0.500 mL). The basic solution was extracted with dichloromethane (4 x 10.0 mL) and the combined organic layers were dried (Na_2SO_4) concentrated to provide 87.0 mg (58%) of **179**[41] as a pale yellow oil.

IR (neat): 2923, 2853, 1710, 1481, 1229, 1029, 932, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.48 (s, 1H, Ar*H*), 6.46 (s, 1H, Ar*H*), 5.88 (s, 2H, OCH_2O), 4.35-4.31 (d, 1H, *J* = 17, $ArCH_2N$), 3.81-3.78 (d, 1H, *J* = 17, $ArCH_2N$), 3.34-3.28 (m, 1H, NC*H*), 3.21-3.19 (d, 1H, *J* = 11.1, NCH_2CH), 3.04-3.02 (d, 1H, *J* = 11.1, NCH_2CH), 2.67 (br s, 1H, NCH_2CH), 2.57-2.53 (m, 1H, NCHC*H*), 2.45-2.38 (m, 3H, $CHCH_2CO$, CH_2CH_2CO), 2.25-2.20 (m, 1H, CH_2CO), 2.07-2.0 (m, 1H, CH_2), 1.84-1.76 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9 (*C*O), 146.6 (Ar*C*), 145.9 (Ar*C*), 135.4 (Ar*C*), 125.0 (Ar*C*), 106.9 (Ar*C*), 106.4 (Ar*C*), 100.7 (O*C*O), 64.3 (N*C*H), 60.4 ($ArCHCH_2N$), 51.9 ($ArCH_2N$), 46.9 (NCH_2CH), 46.0 ($CHCH_2CO$), 41.5 (CH_2CO), 36.7 (CH_2CO), 26.1 ($NCHCH_2$); HRMS (EI): m/z 271.1209 (271.1208 calc. for $C_{16}H_{17}NO_3$ (M^+)).

1,11a -Didehydro-8,9-methylenedioxy-5,11- methanomorphanthridin-2-one (137):[47]



The literature procedure[55] was adapted. To a solution of the ketone **179** (18 mg, 0.066 mmol) in dioxane (1.5 mL) was added DDQ (45 mg, 0.20 mmol) and the mixture was heated to reflux for 1 h and cooled to room temperature. The mixture was diluted with CH_2Cl_2 and the solution was washed successively with a saturated, aq. $NaHCO_3$ solution, and brine. Drying (K_2CO_3) and concentration of the organic phase provided 11 mg (62%) of **137**[47,55] as a pale yellow solid. IR (neat): 2922, 2853, 1657, 1481, 1233, 1035, 932, 811 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.57 (s, 1H, Ar*H*), 6.50 (s, 1H, Ar*H*), 5.92 (s, 1H, OCH_2O), 5.90 (br s, 2H, OCH_2O, *C*HC(O)), 4.39 (d, 1H, *J* = 16.8, NCH_2Ar), 3.87 (d, 1H, *J* = 16.8, NCH_2Ar), 3.58-3.55 (br m, 1H, $NCHCH_2$), 3.44 (br s,

1H, ArC*H*), 3.22-3.15 (apparent br q, 2H, NCH_2CH), 2.56-2.52 (br m, 1H, CH_2), 2.34-2.26 (m, 2H, CH_2), 1.90-1.82 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8 (*C*O), 176.3 (*C*=C-C(O), 147.5 (Ar*C*-O), 146.4 (Ar*C*-O), 130.3, 124.5 (Ar*C*, C=*C*-C(O)), 117.4 (Ar*C*), 107.7 (Ar*C*), 106.9 (Ar*C*), 101.0 (O*C*H_2O), 64.7 (N*C*H), 60.9 (Ar*C*H_2N), 54.9 (N*C*H_2CH), 46.3 (Ar*C*H), 37.2 (*C*H_2C(O)), 30.7 (*C*H_2CH_2C(O)); ((MS (API-ES pos.): *m/z* 270 (M+H); HRMS (CI pos.): m/*z* 269.1051 (269.1052 calc. for $C_{16}H_{15}NO_3$ (M+)).

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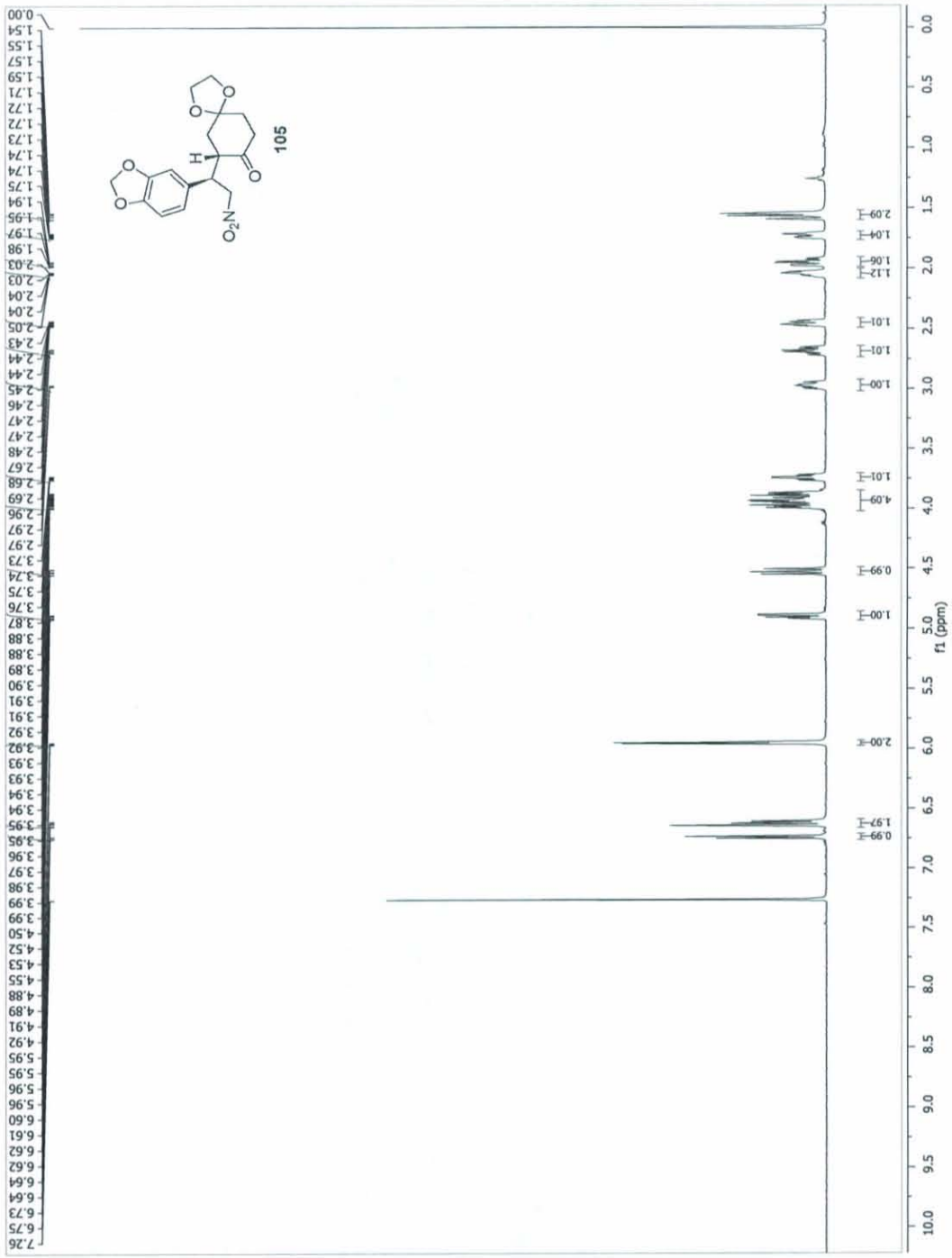
Appendix 2:

^{1}H and ^{13}C NMR Spectra for Chapter 2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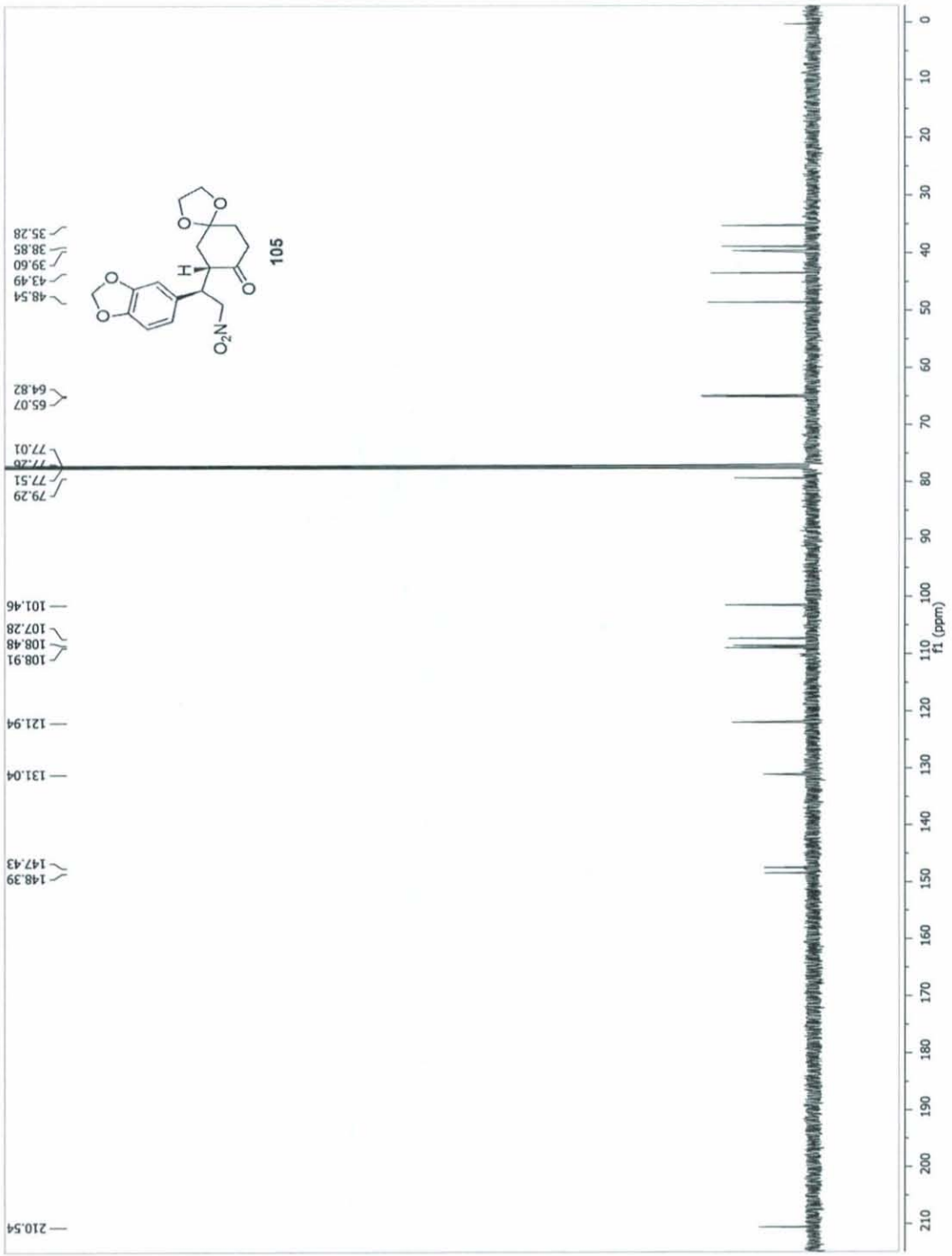
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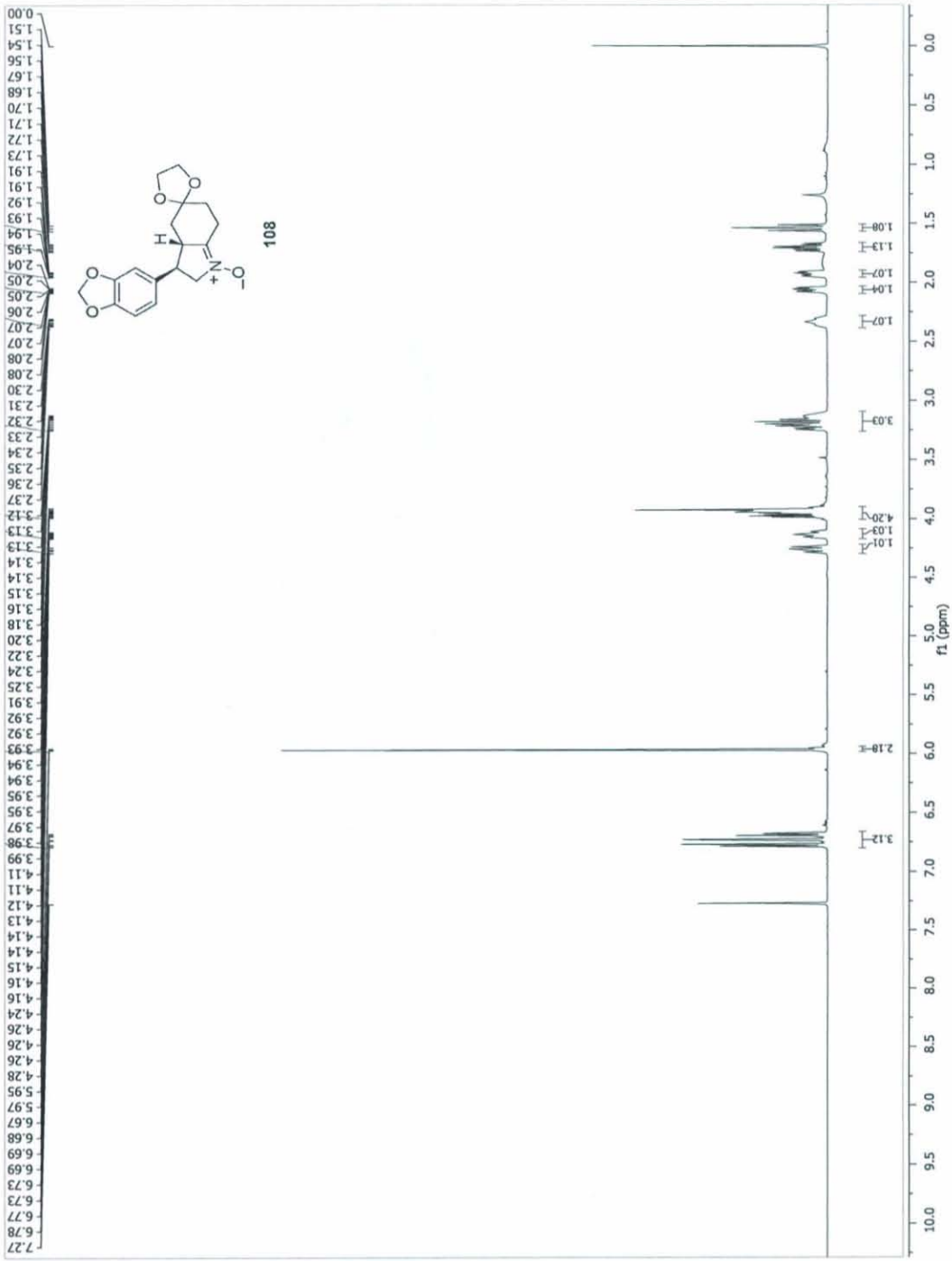
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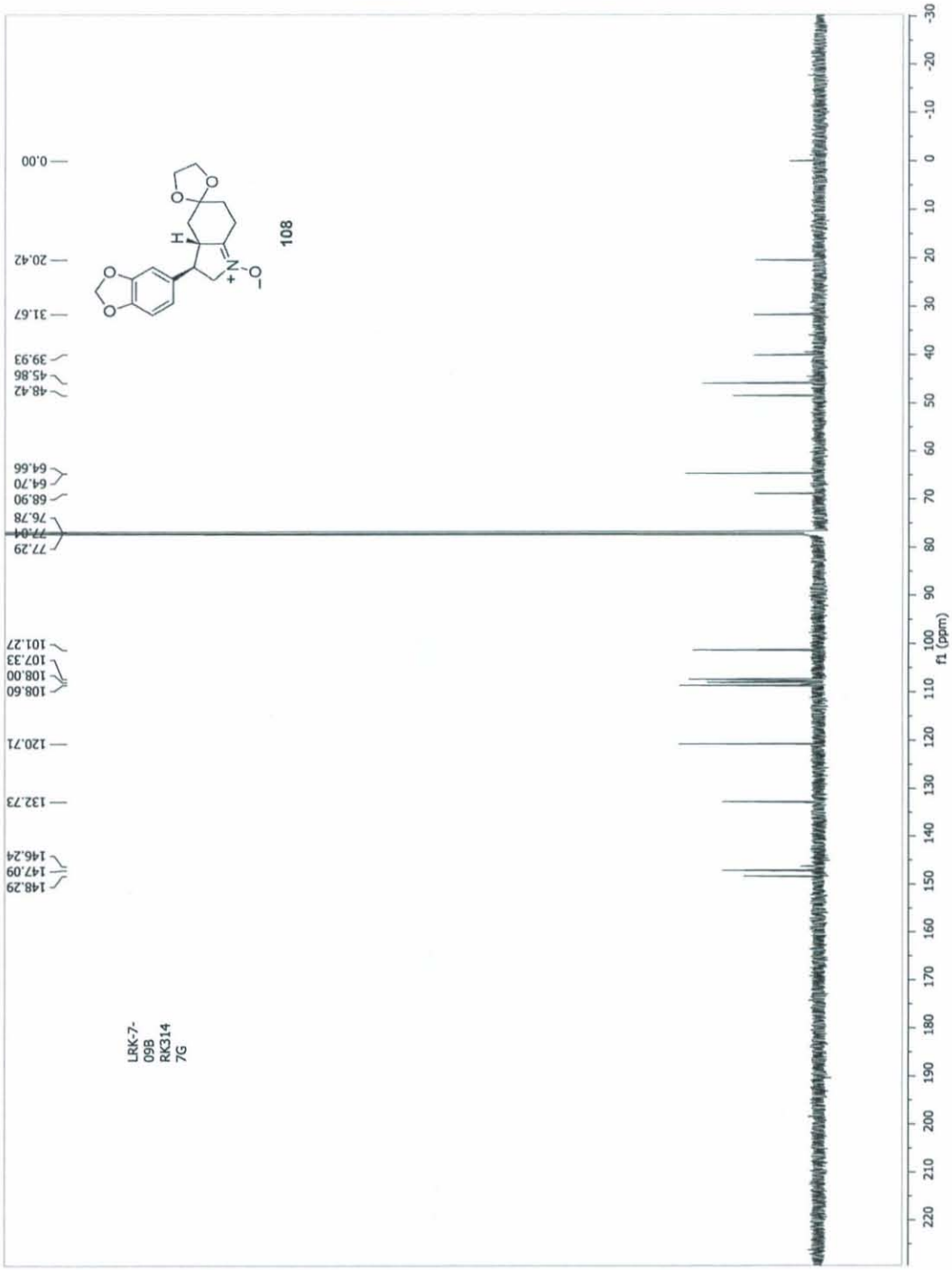
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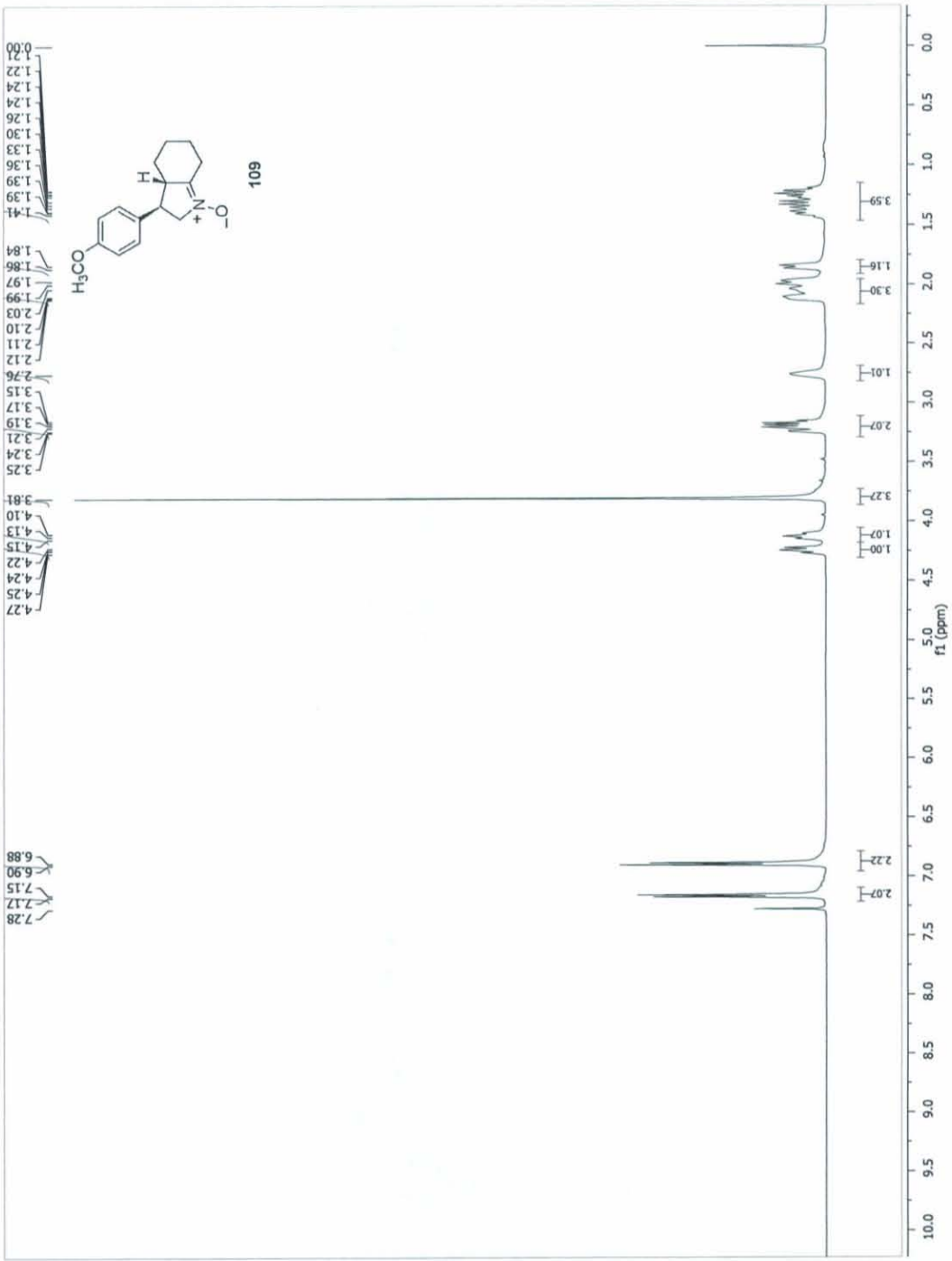
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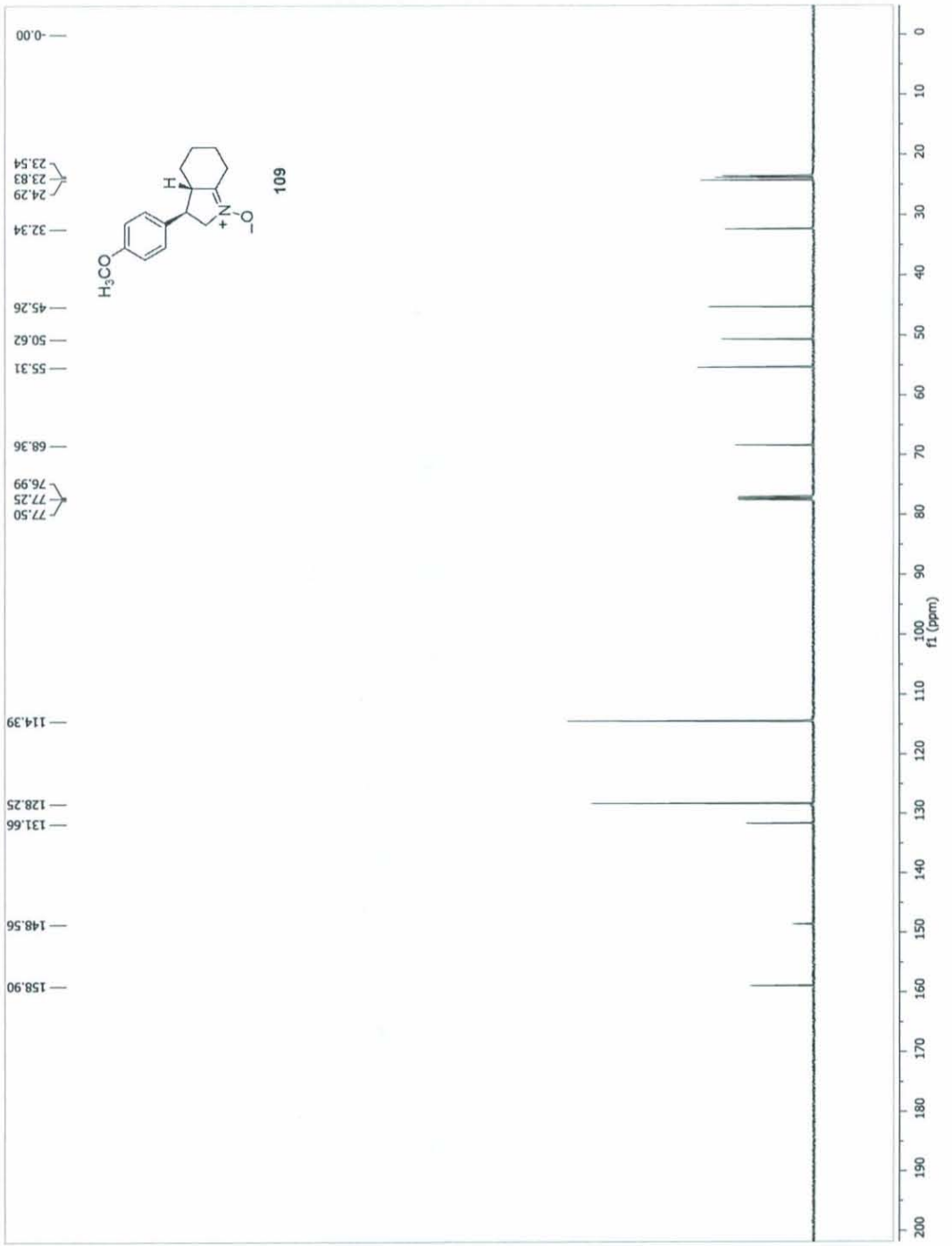
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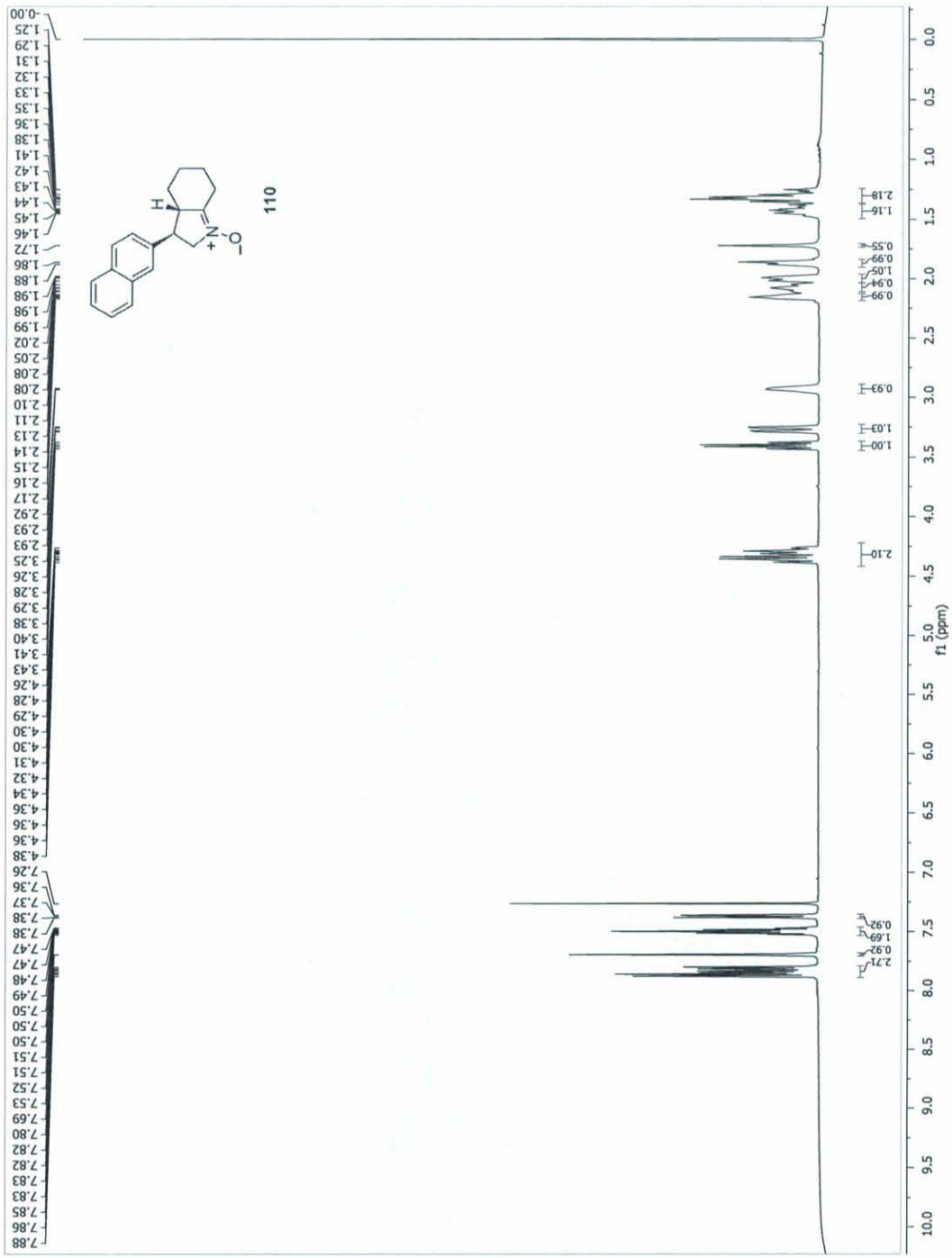
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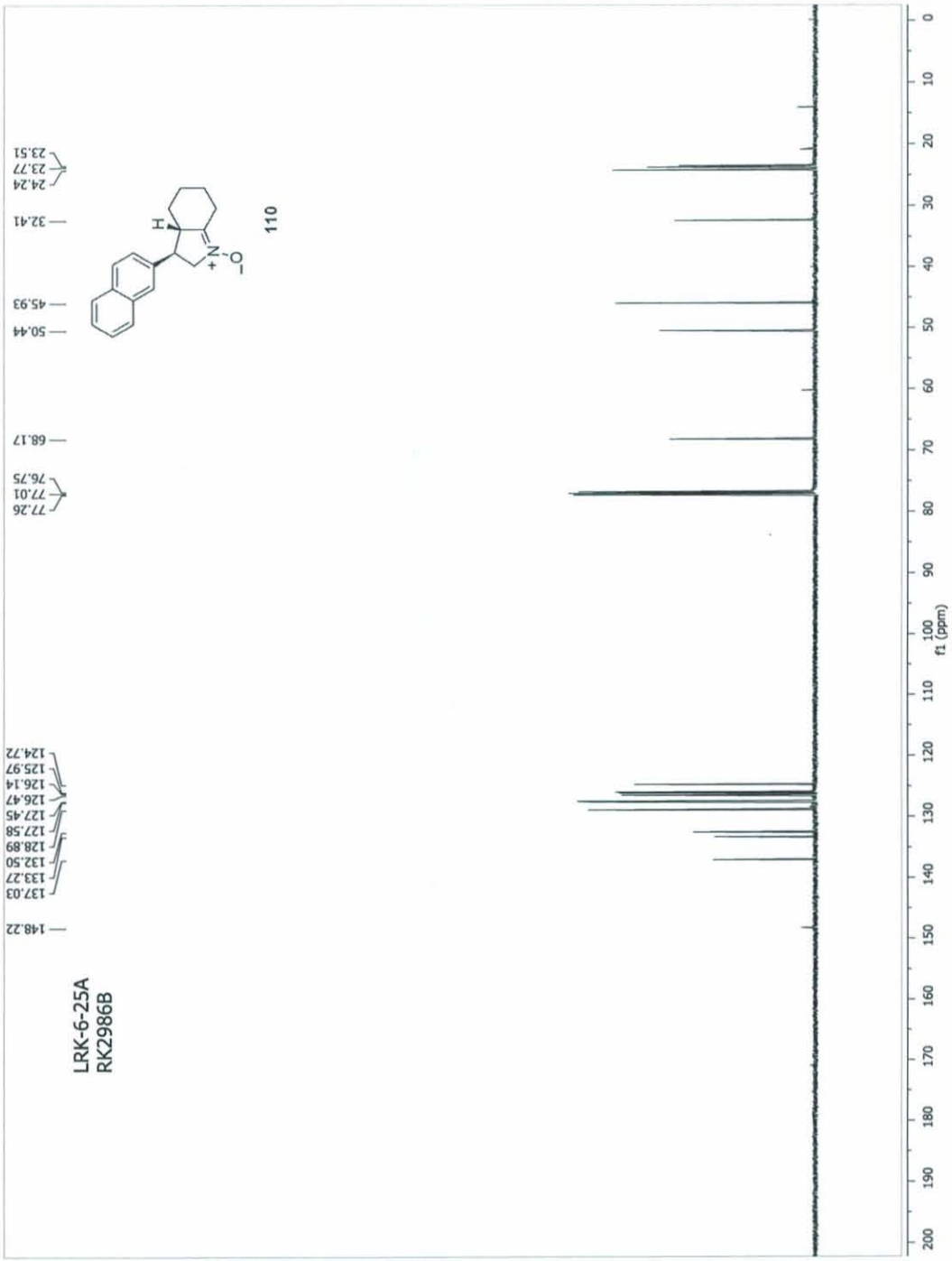
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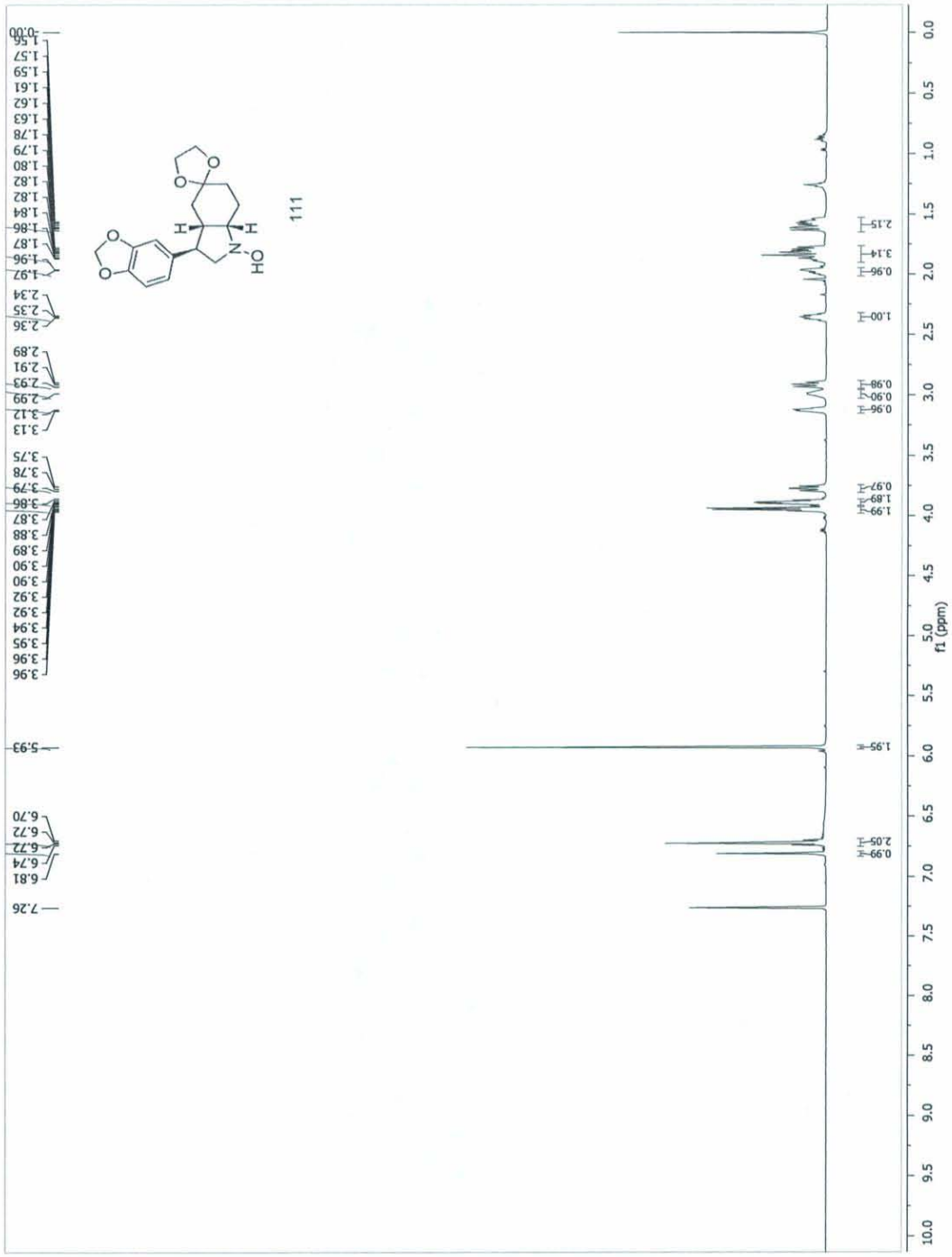
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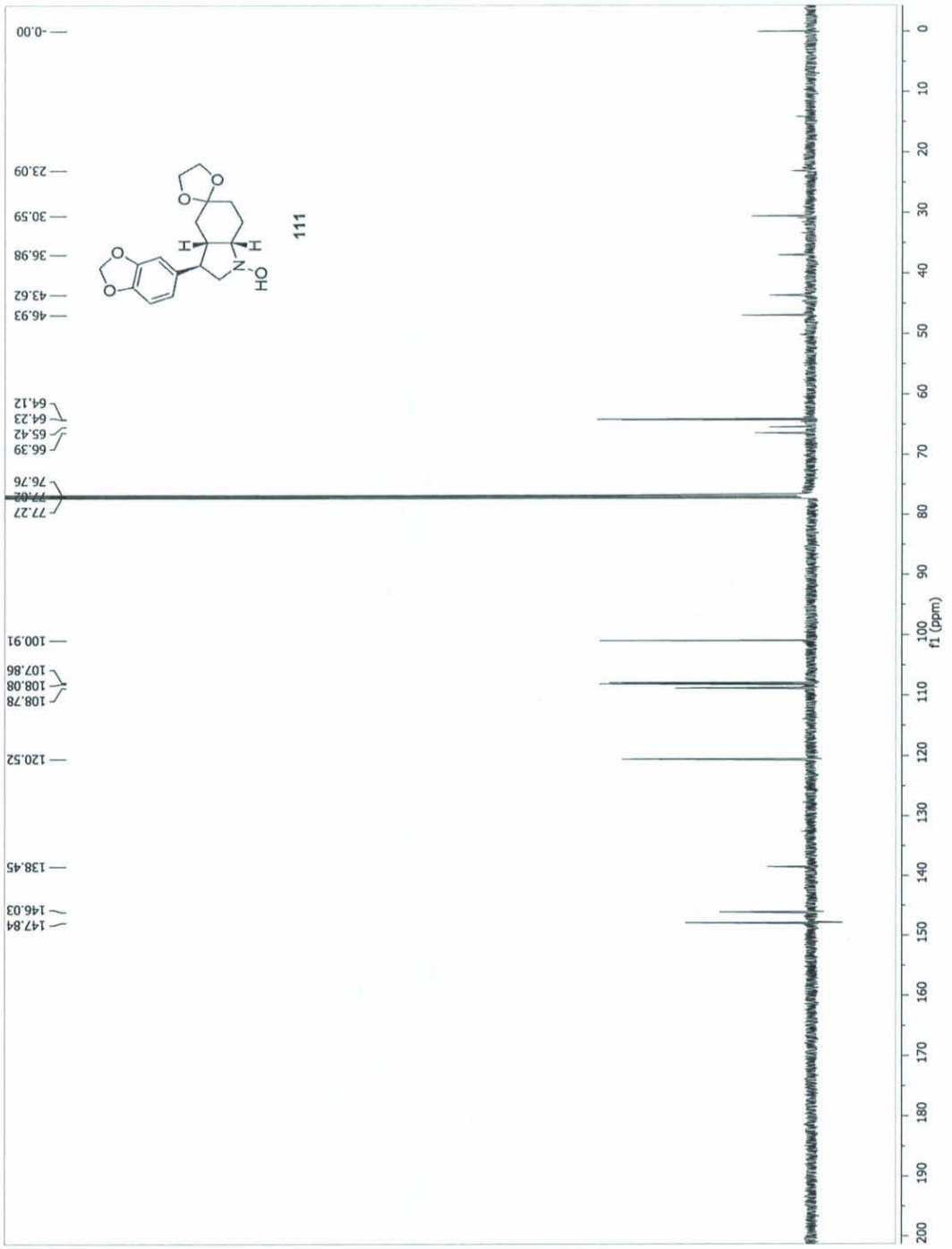
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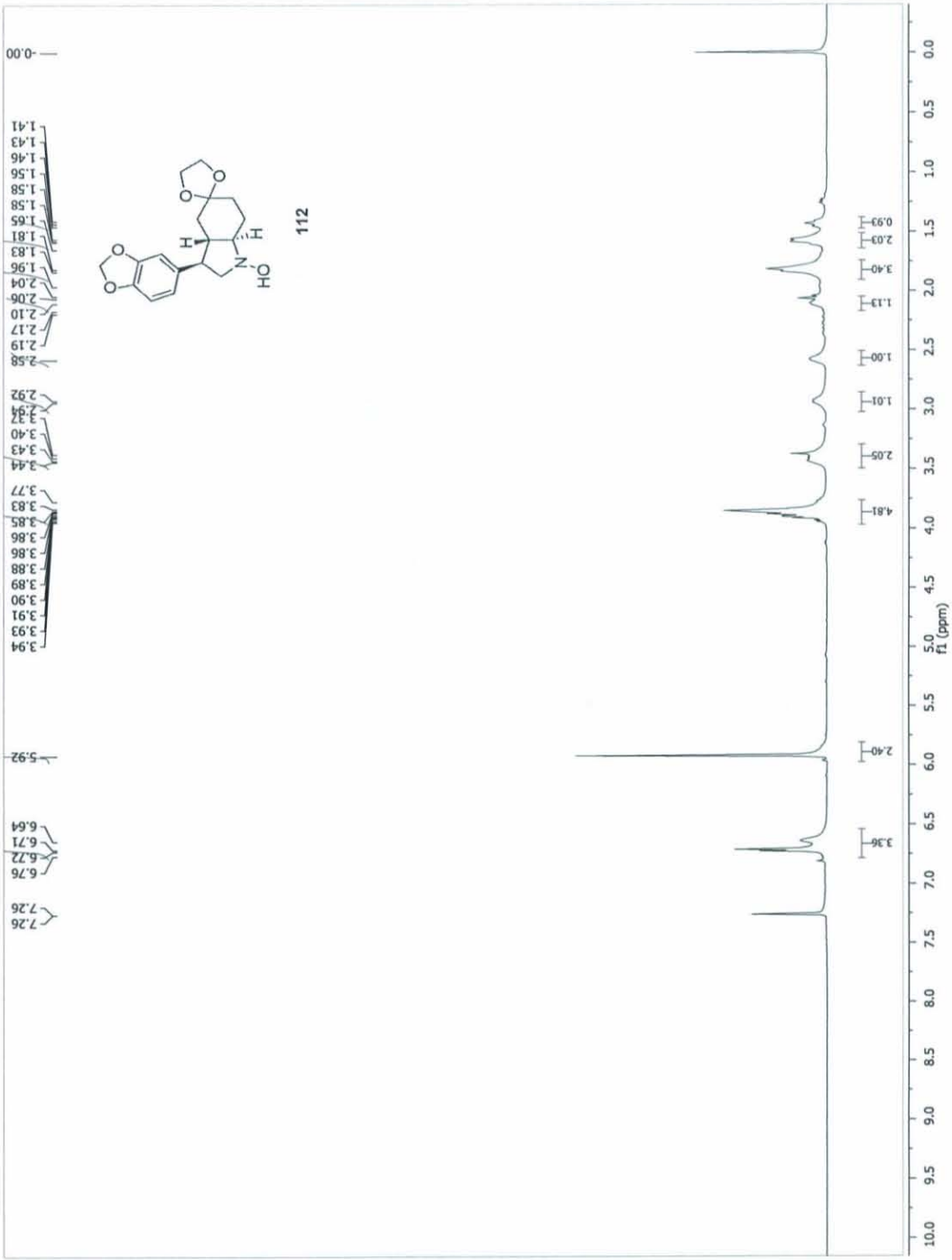
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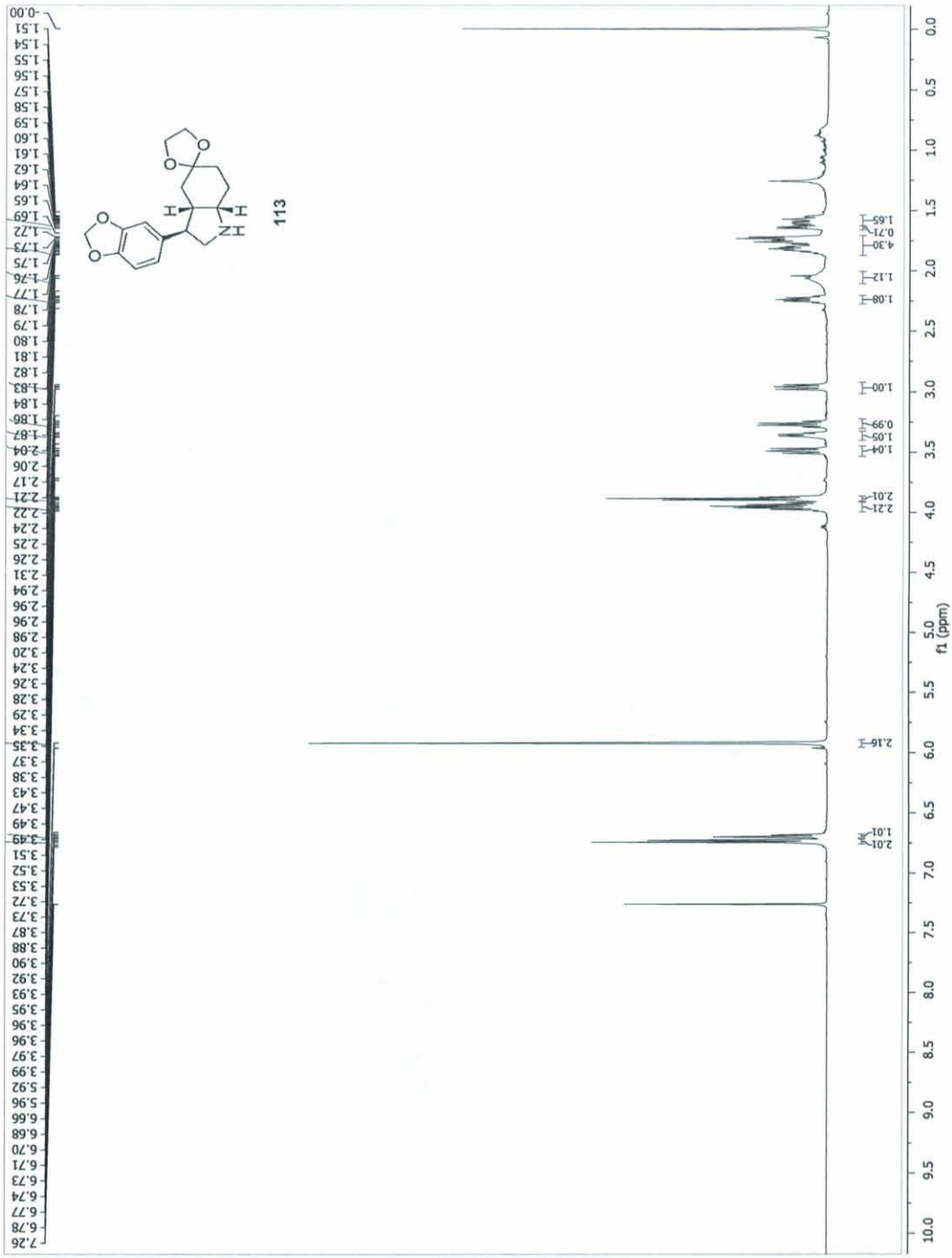
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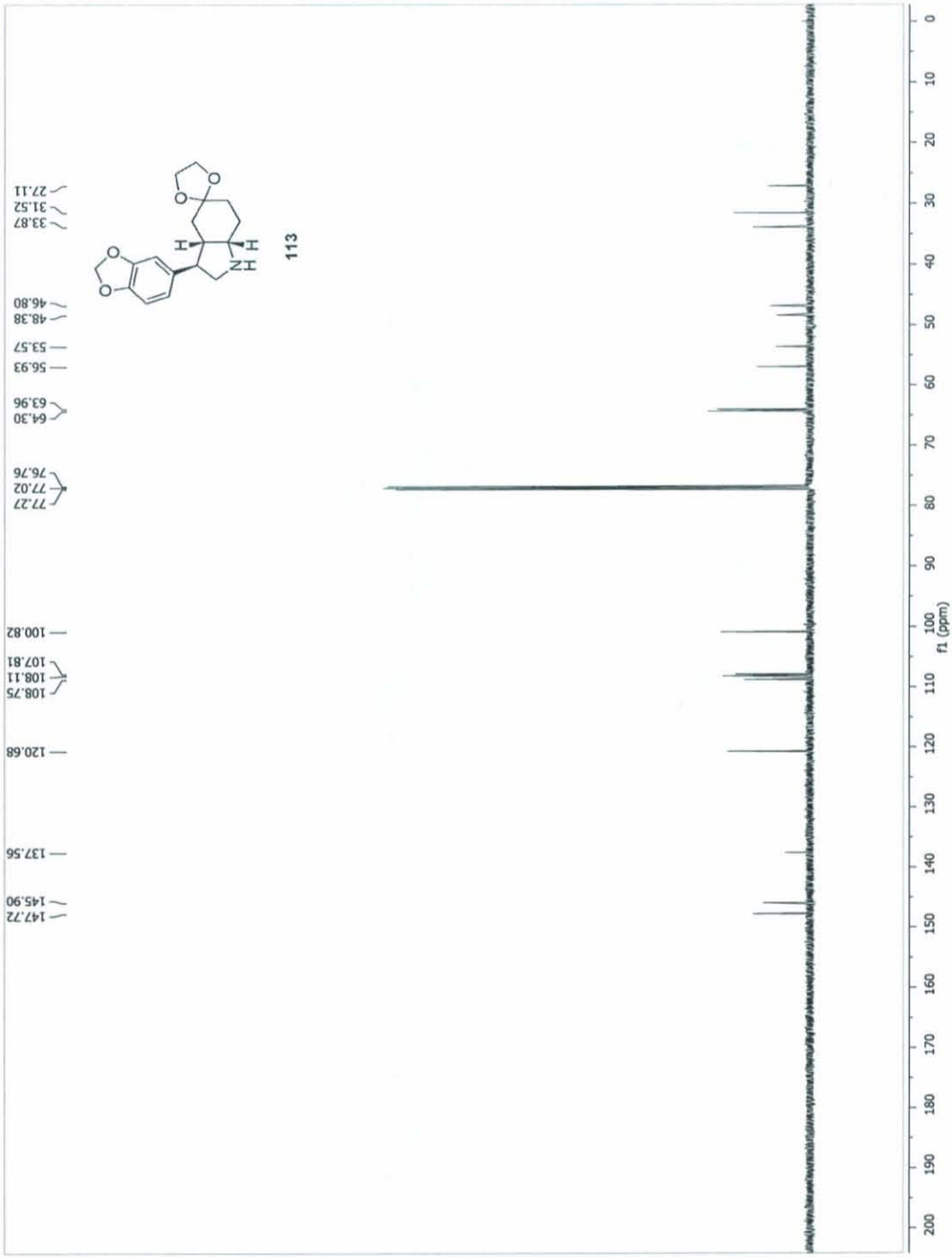
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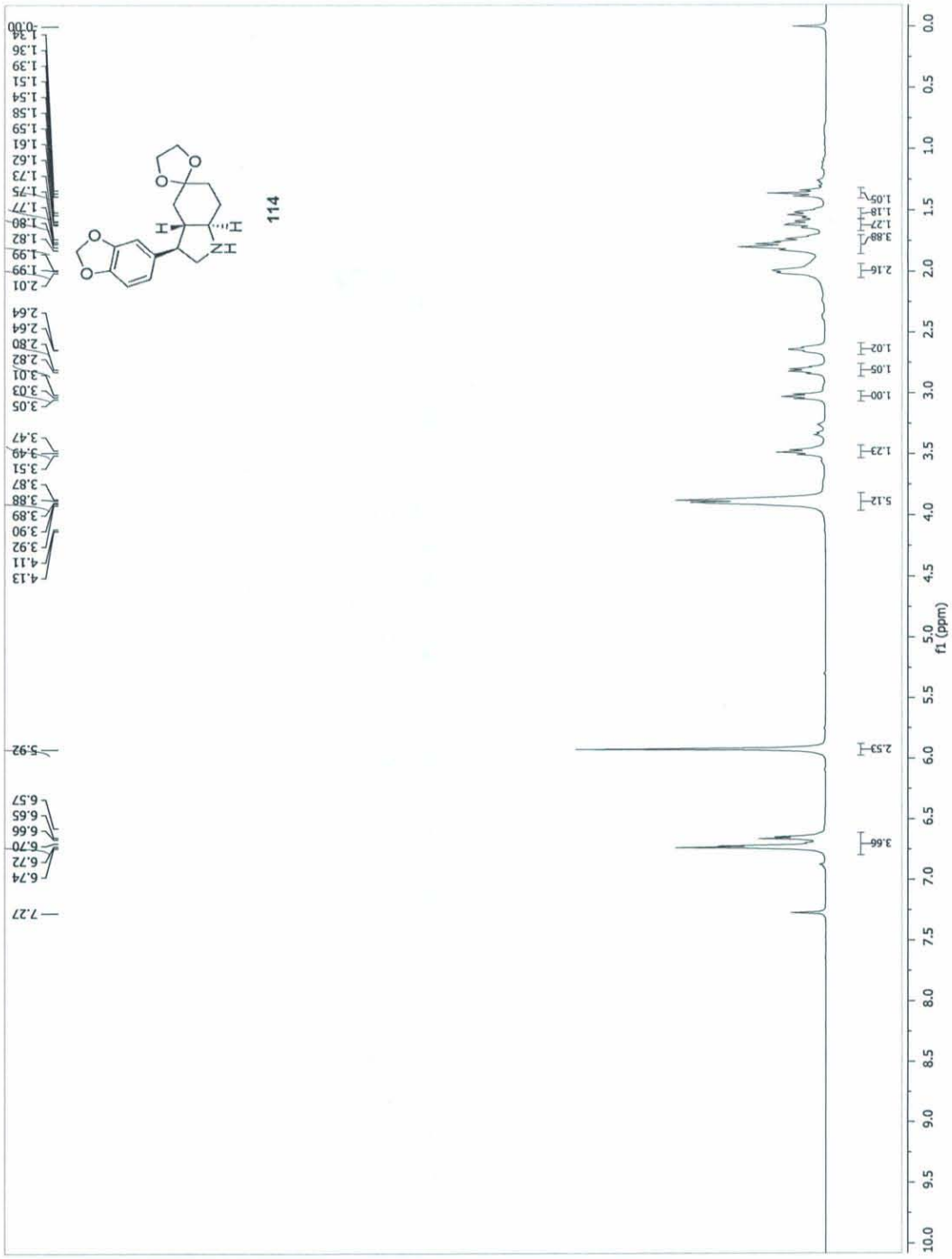
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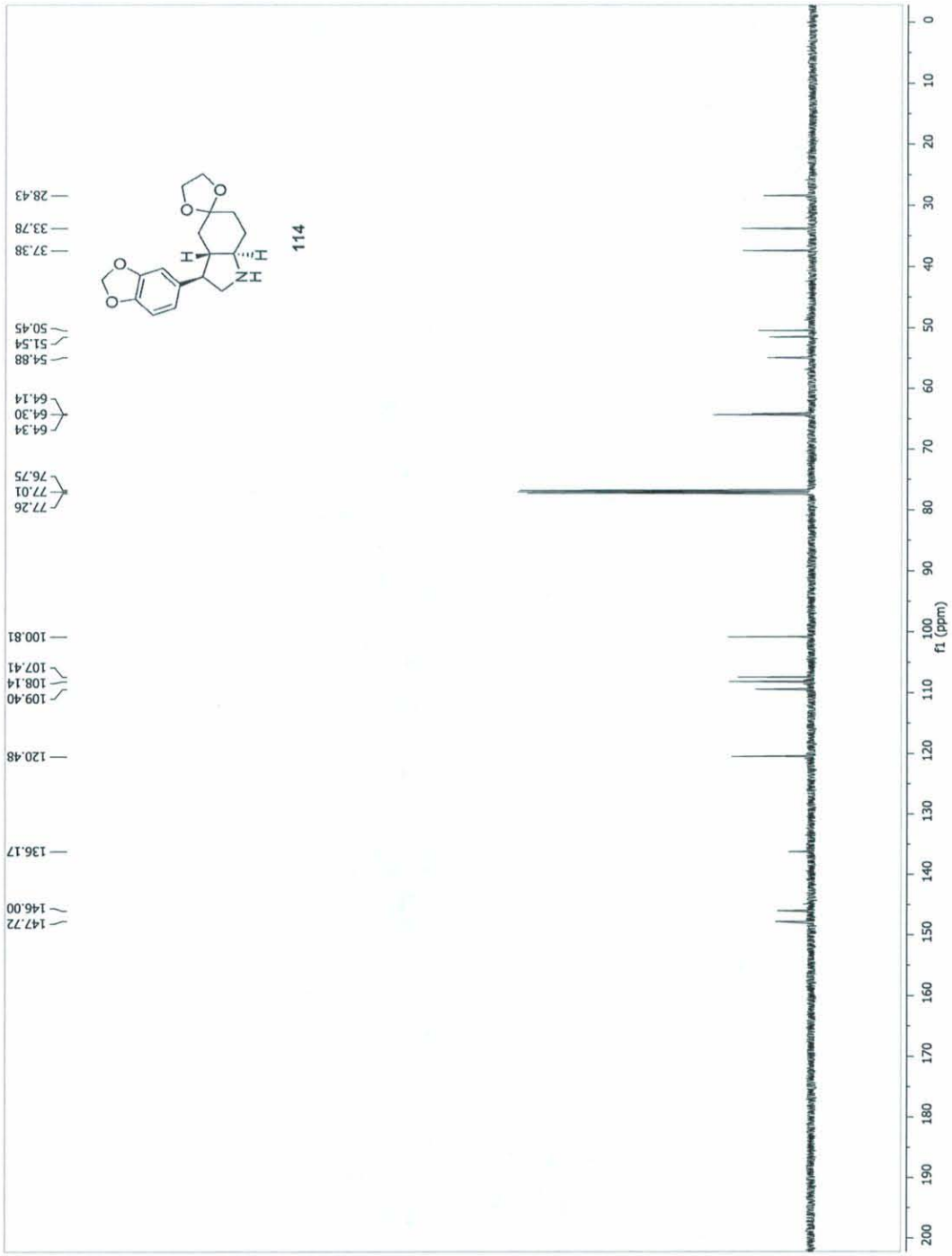
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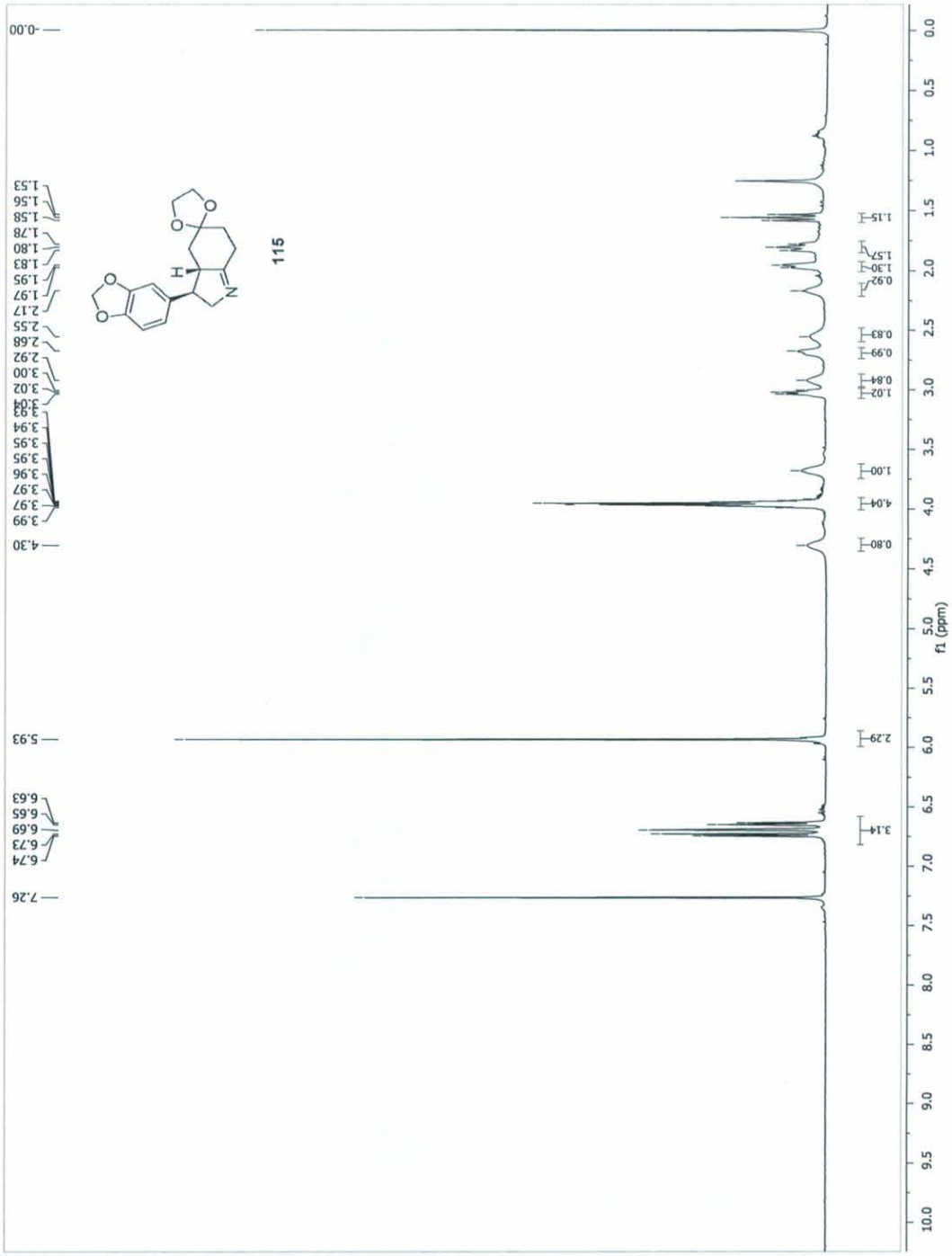
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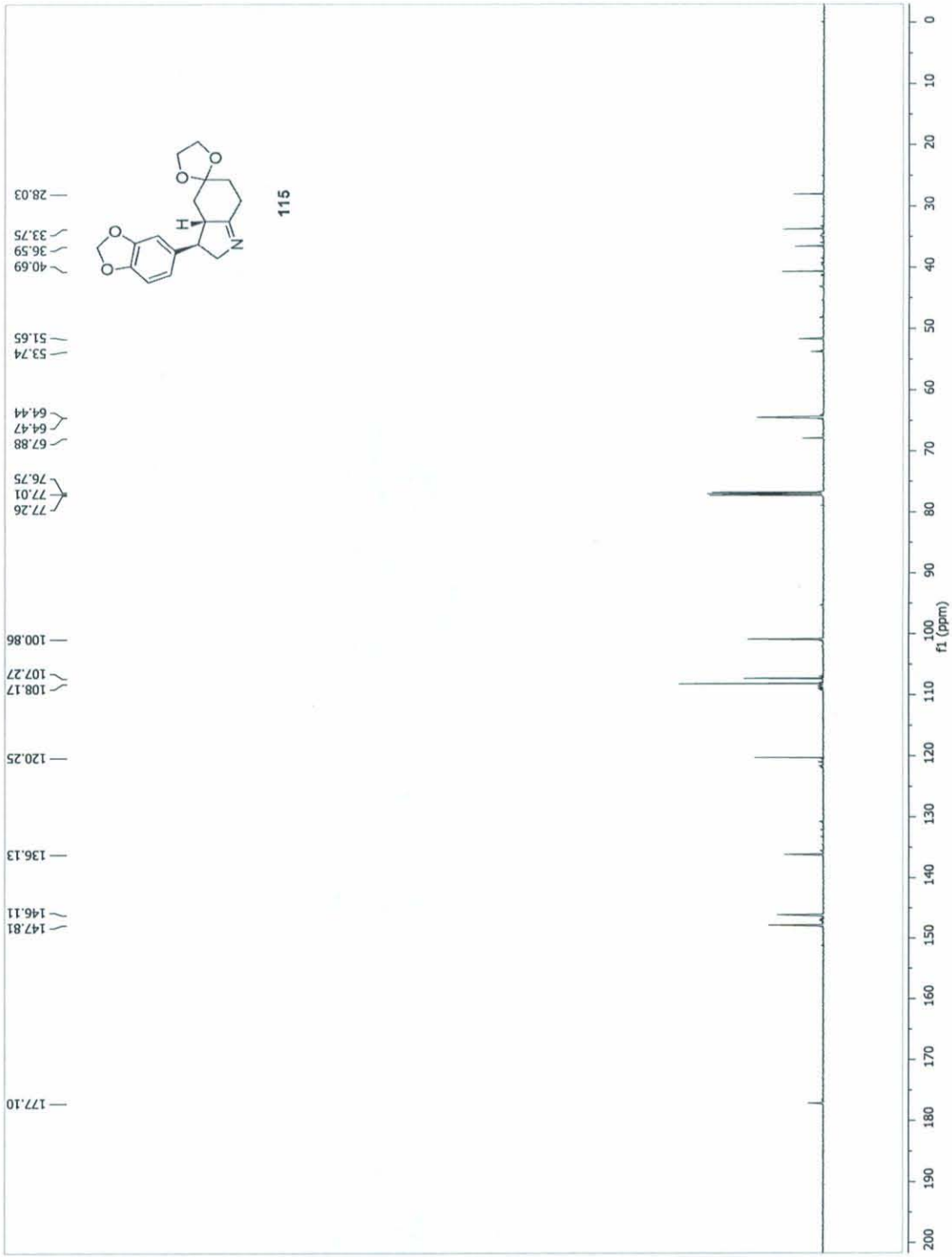
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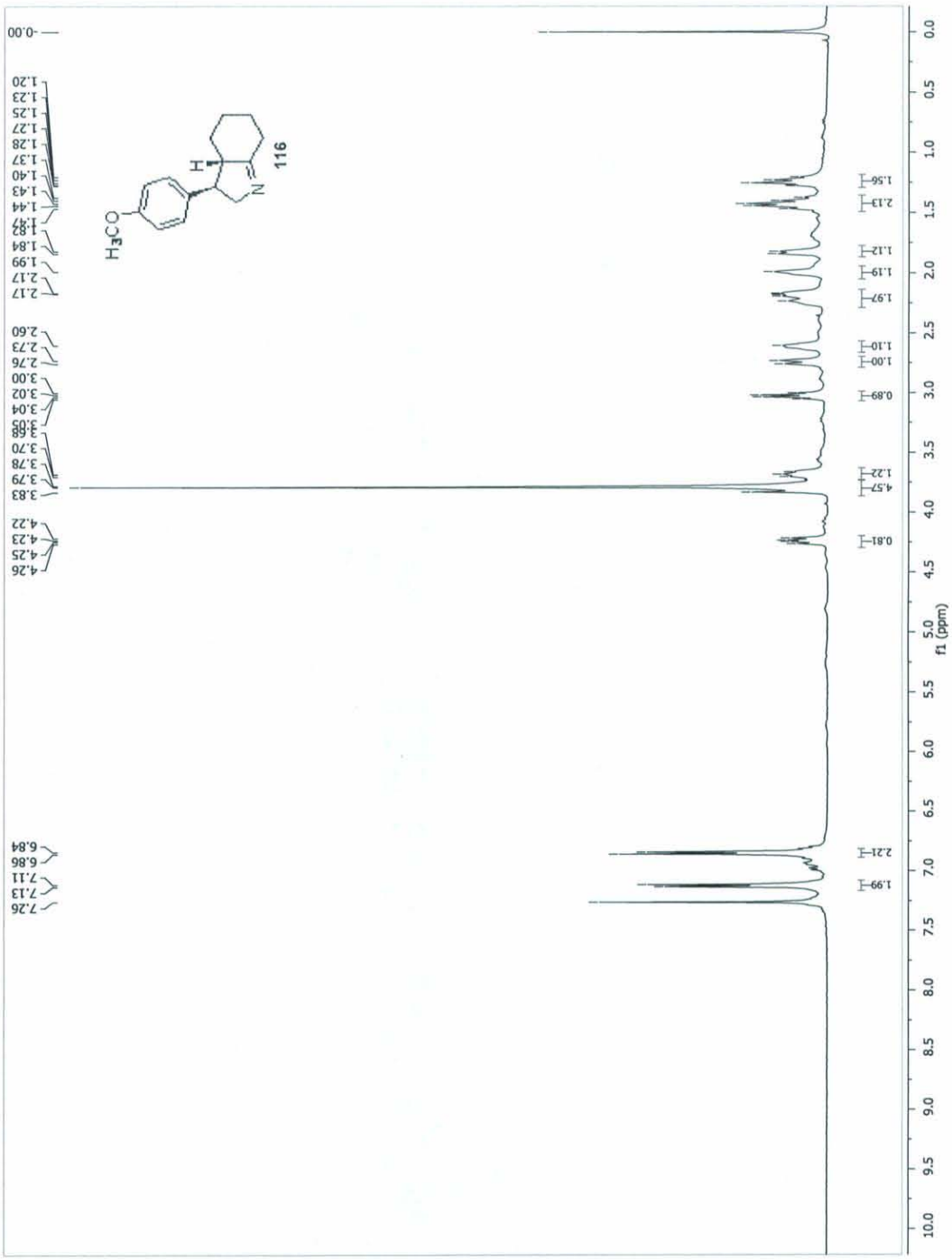
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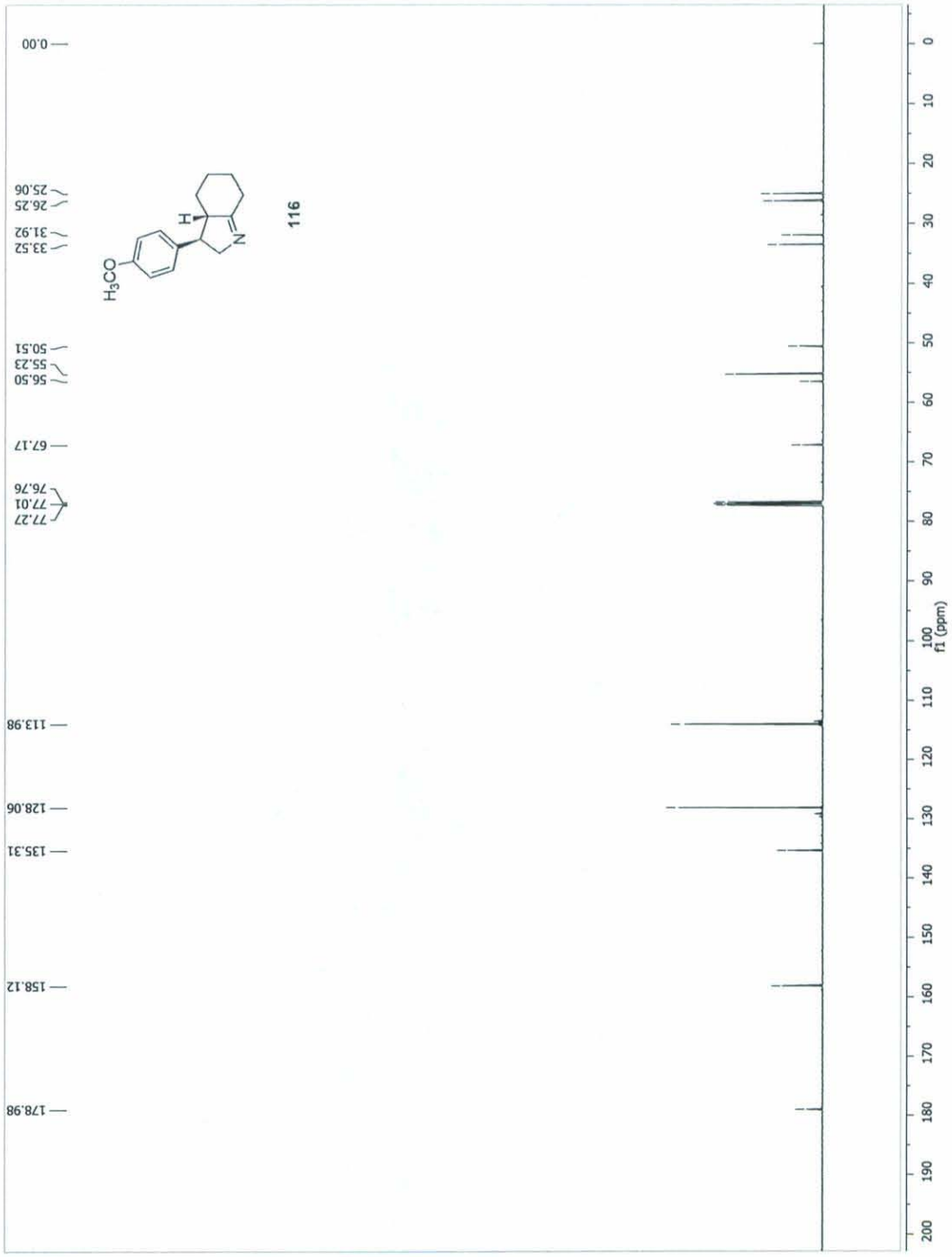
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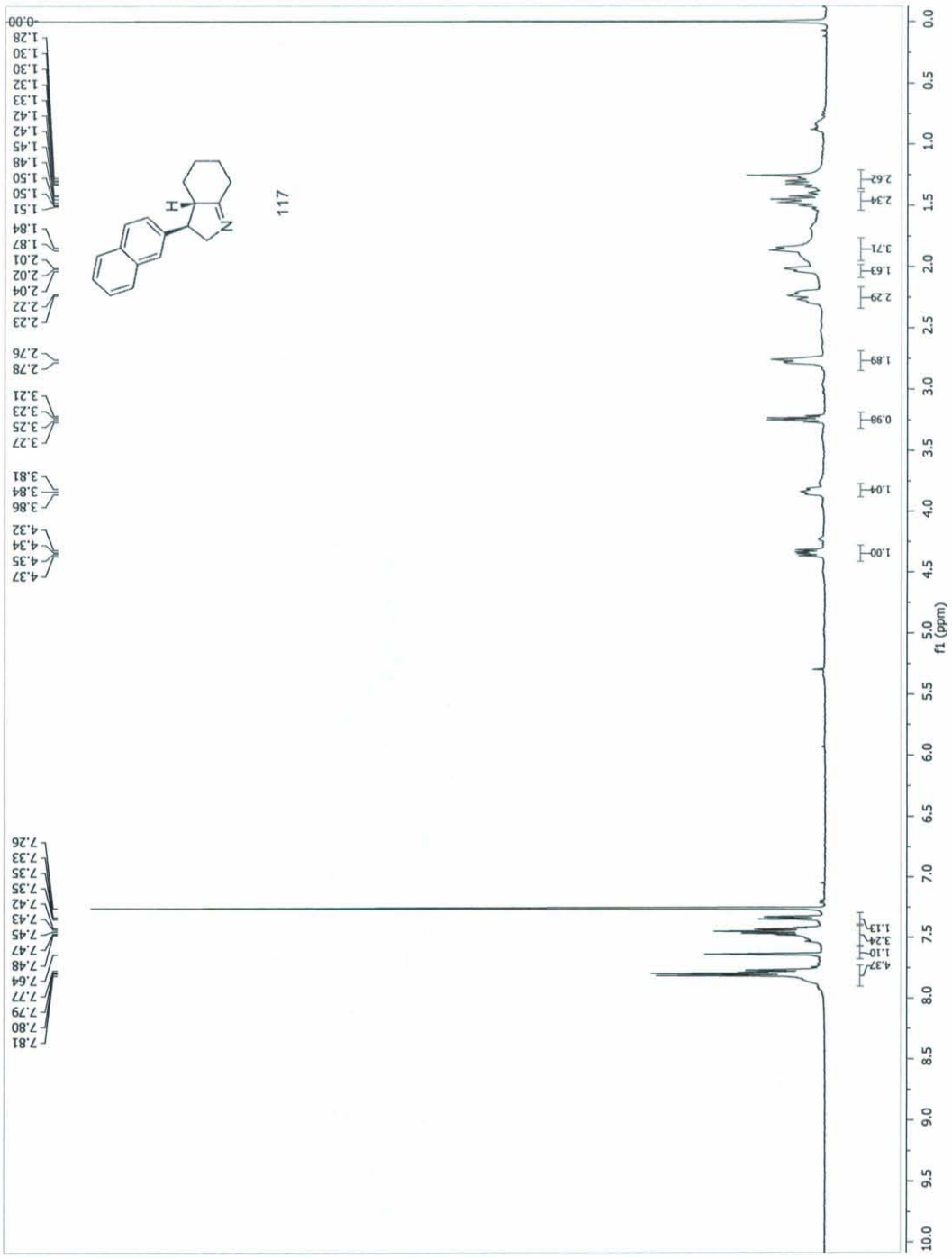
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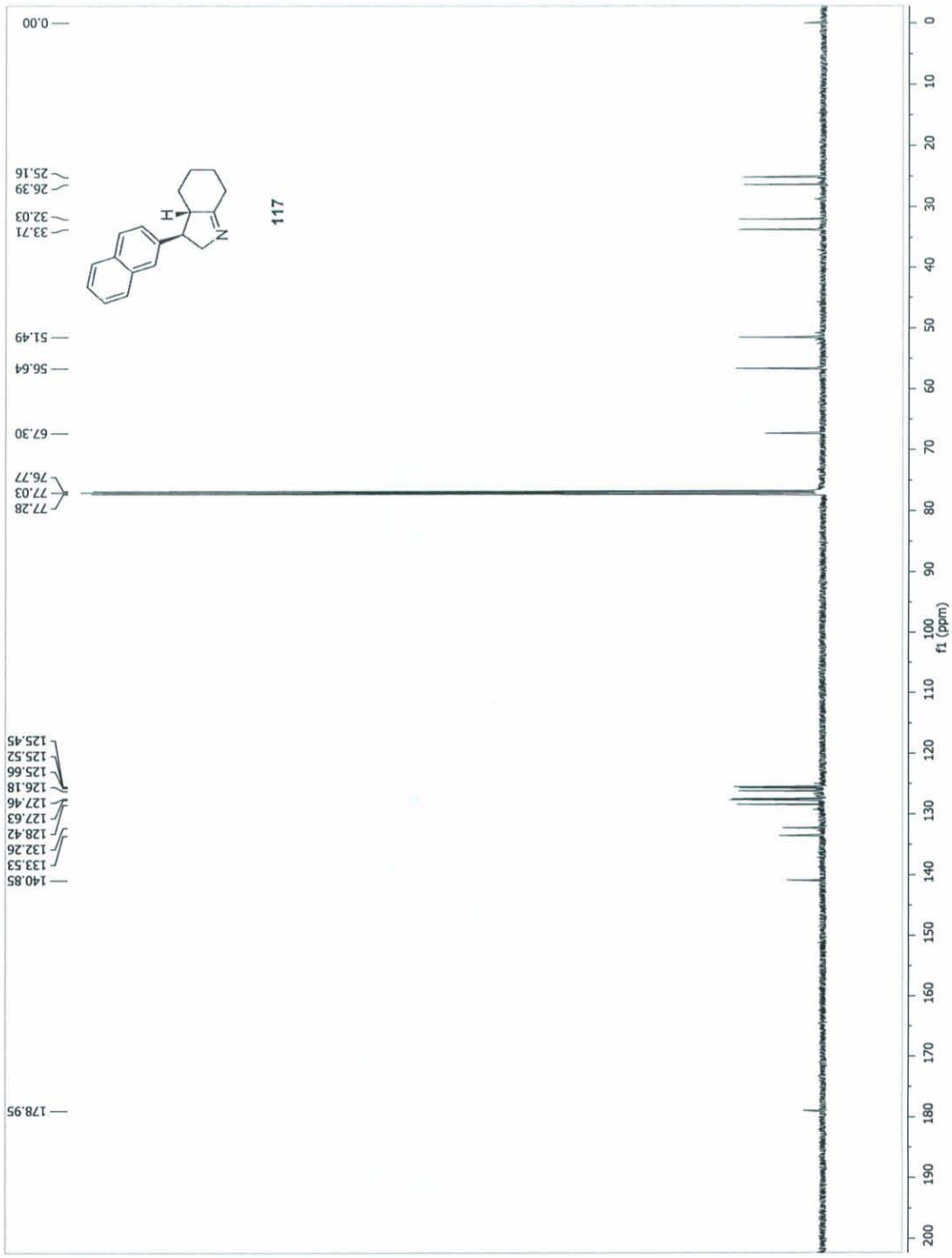
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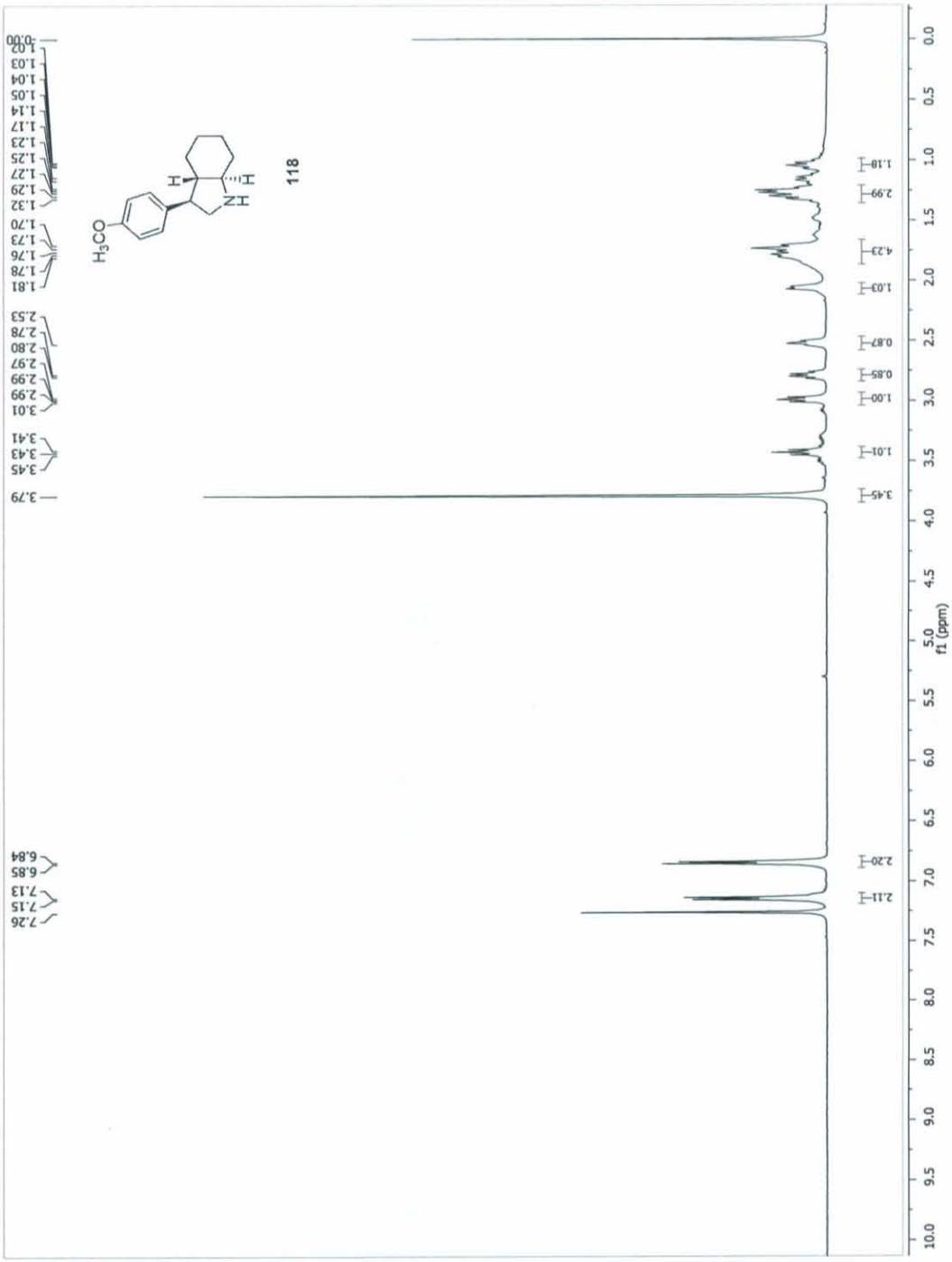
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3.01
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2.97
2.80
2.78
2.53
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1.70
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1.27
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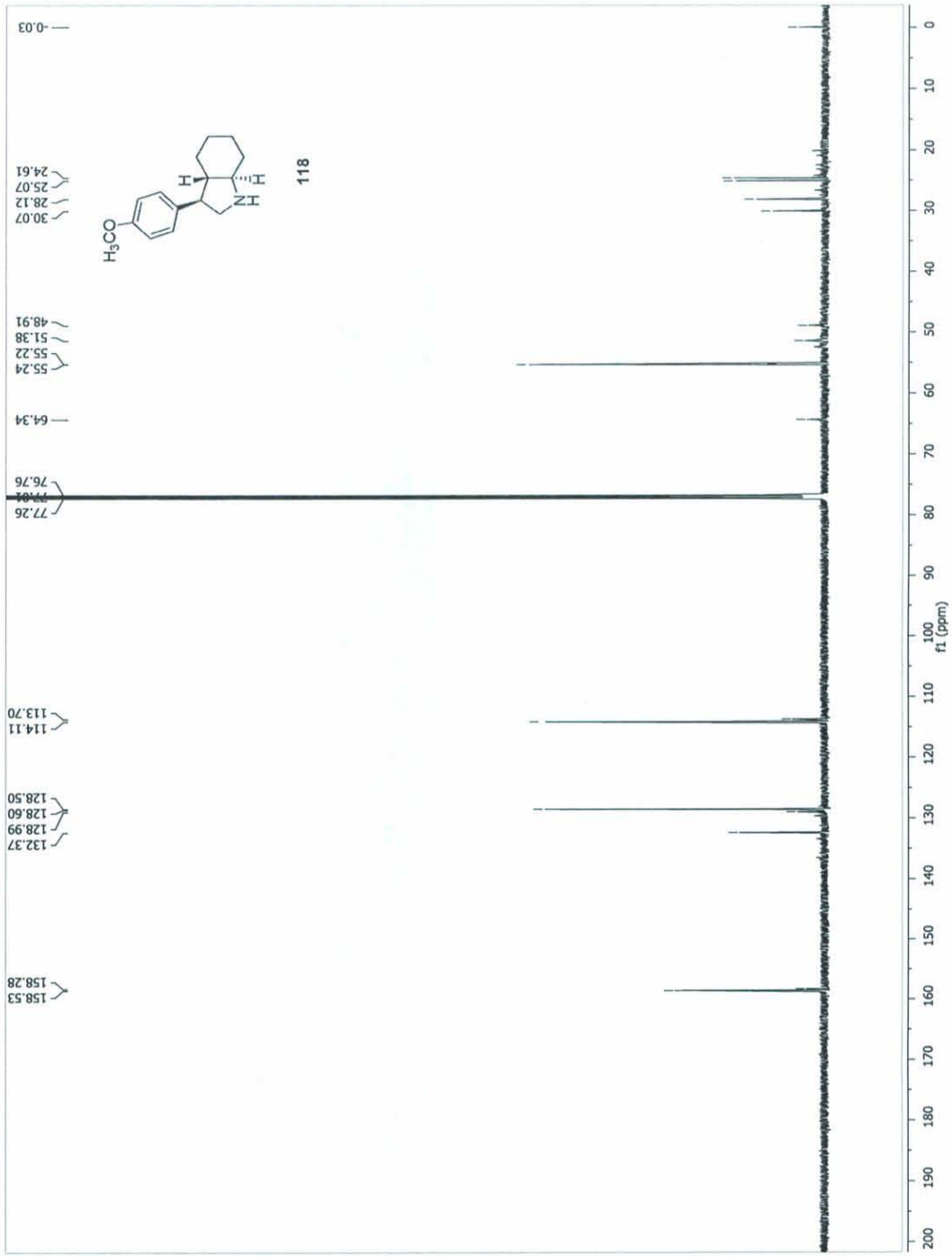
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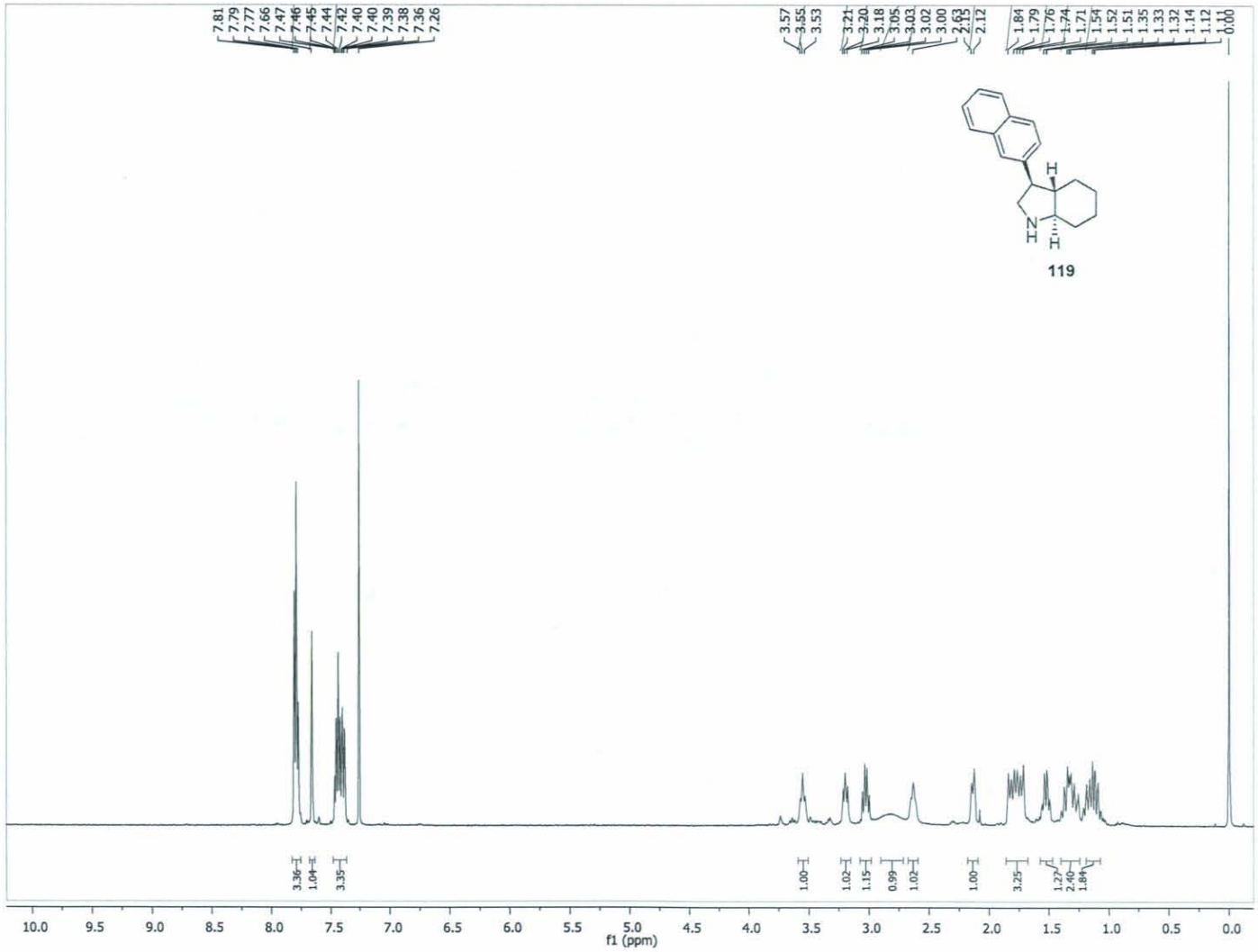
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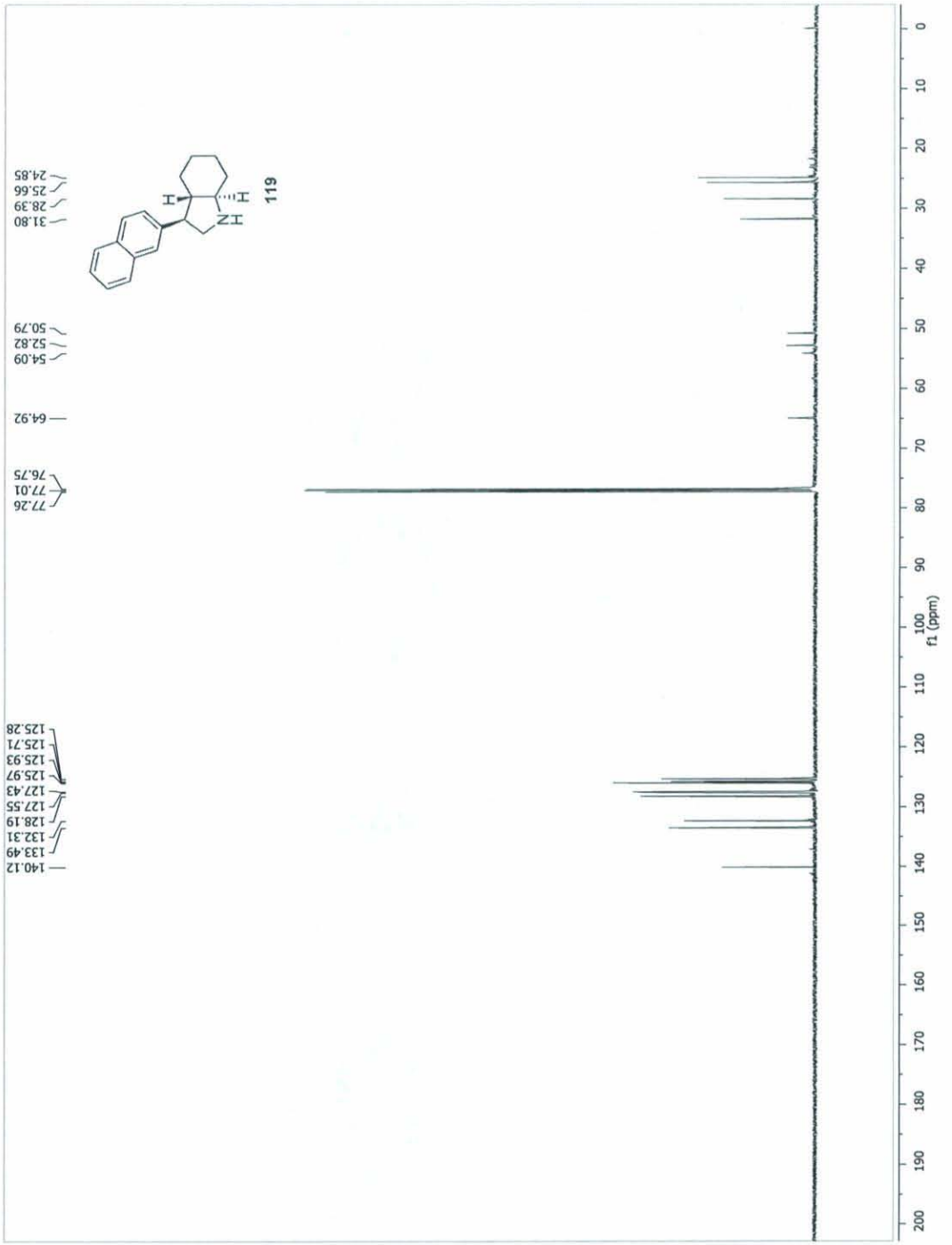
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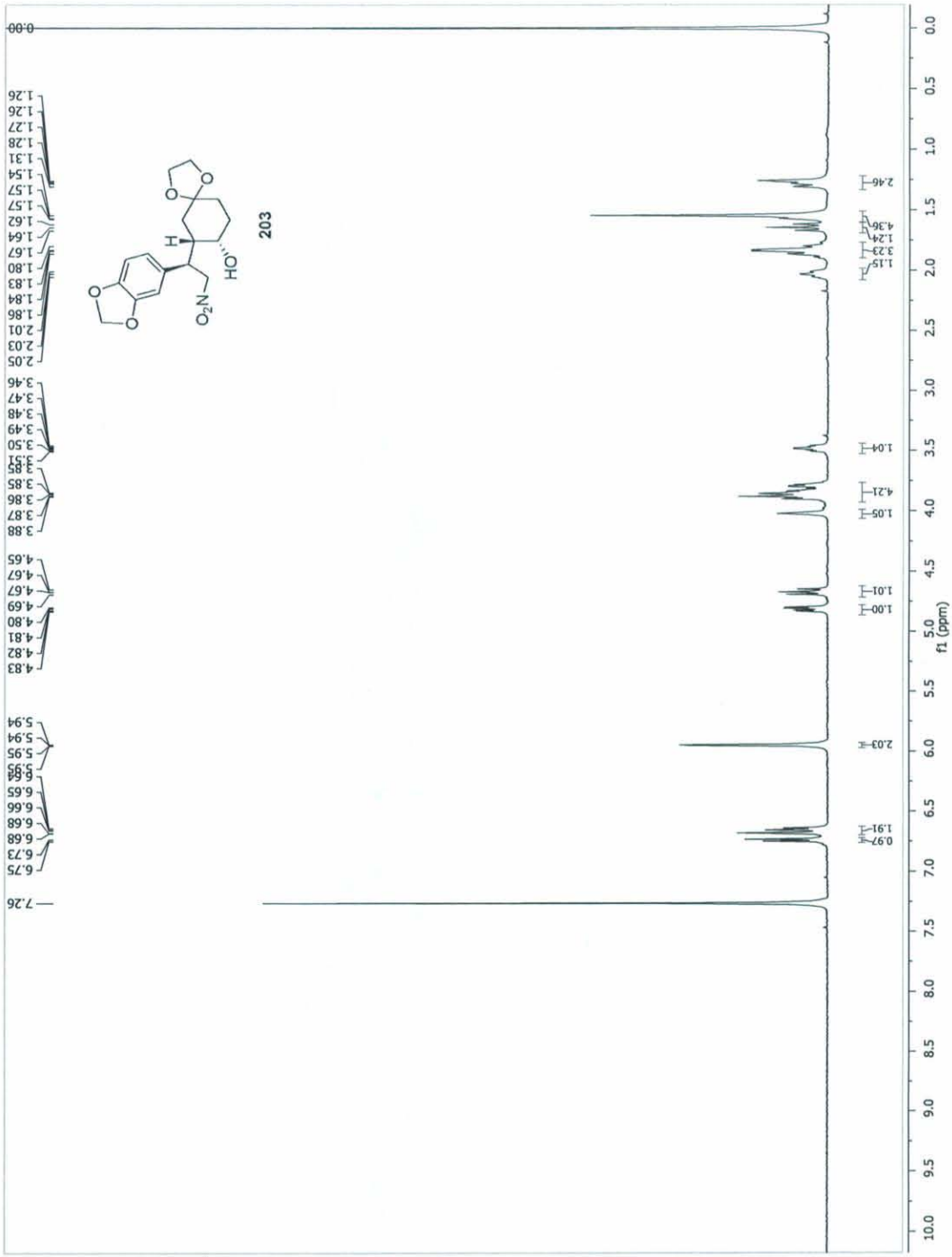
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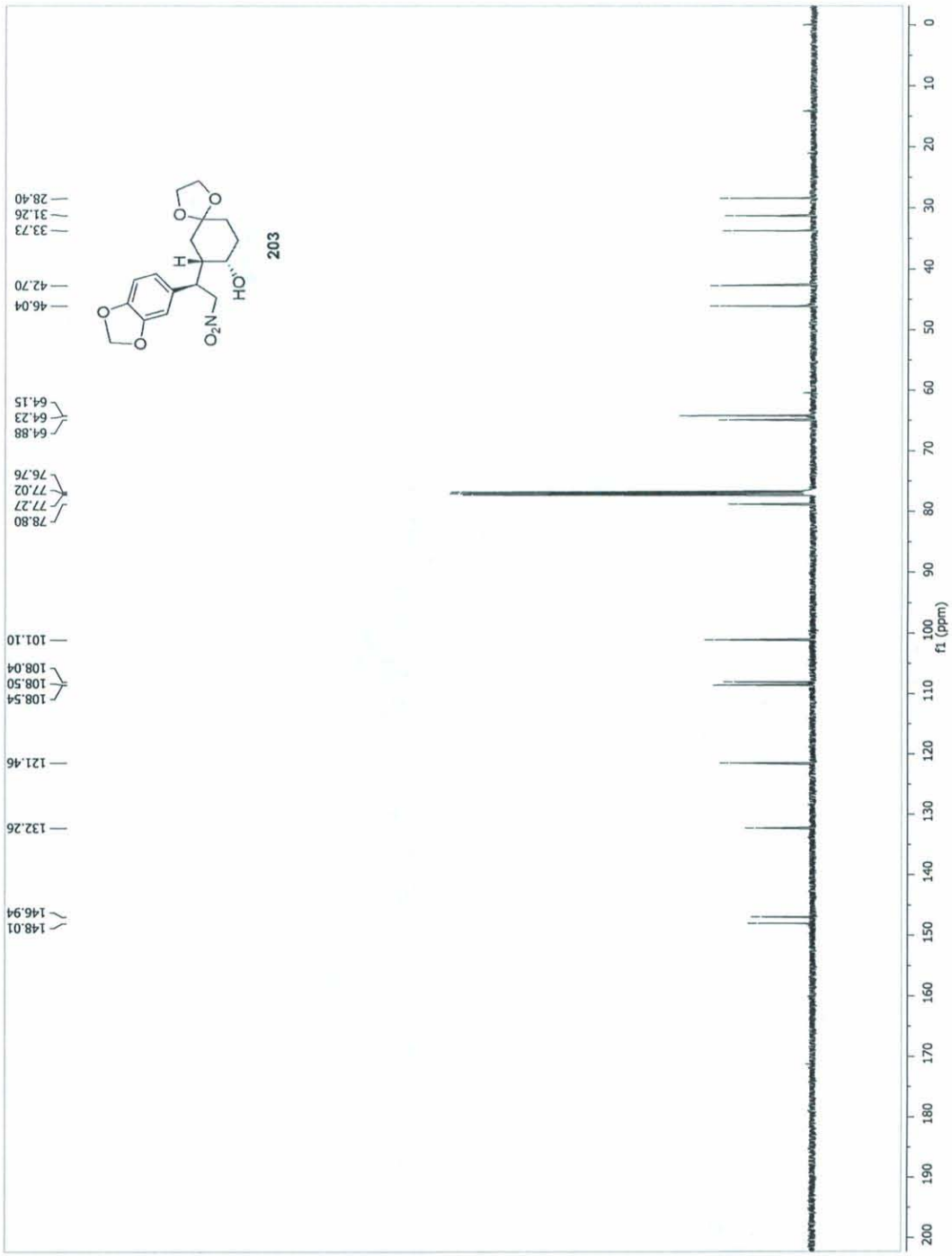
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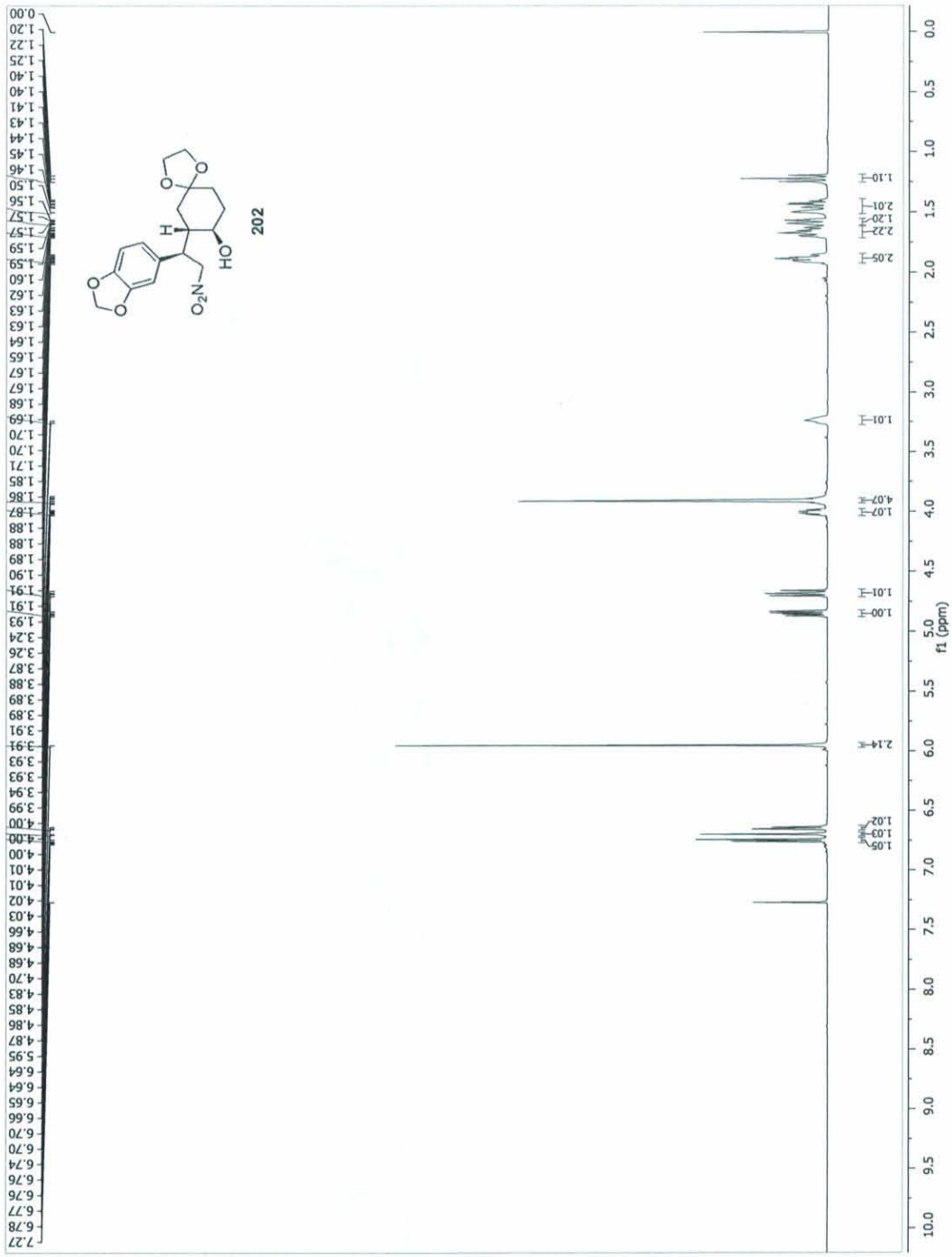
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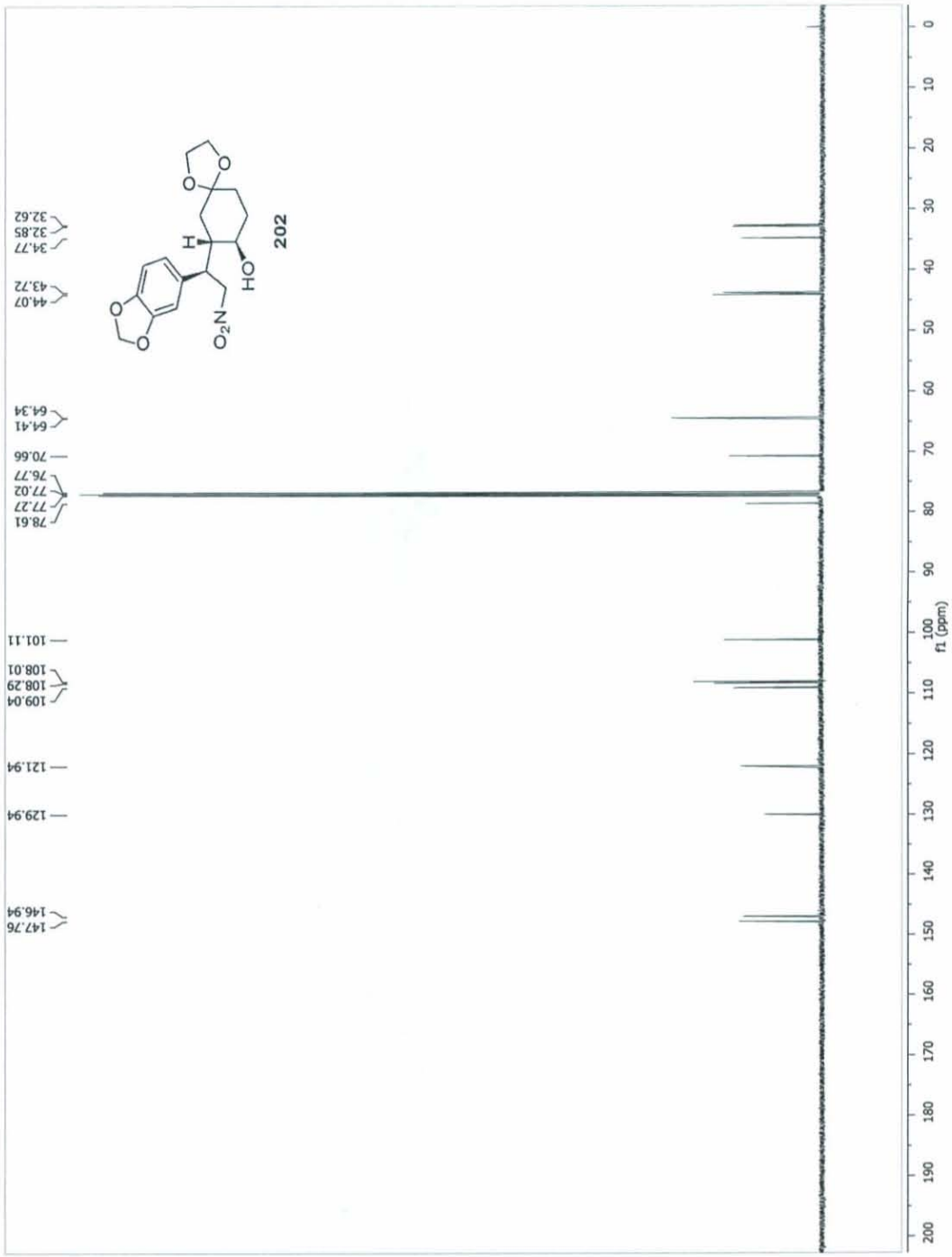
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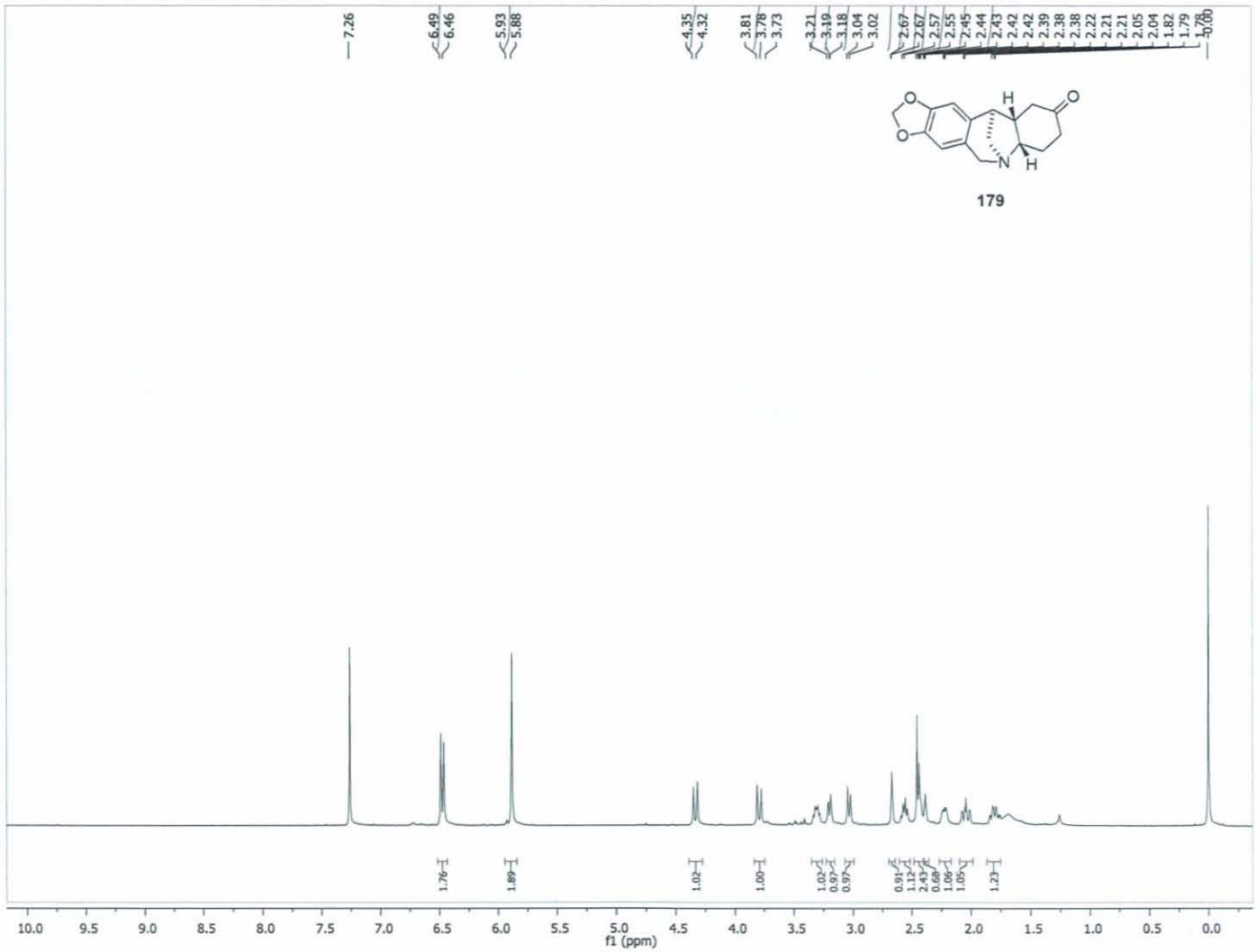
f1 (ppm)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O
O
O
N
H
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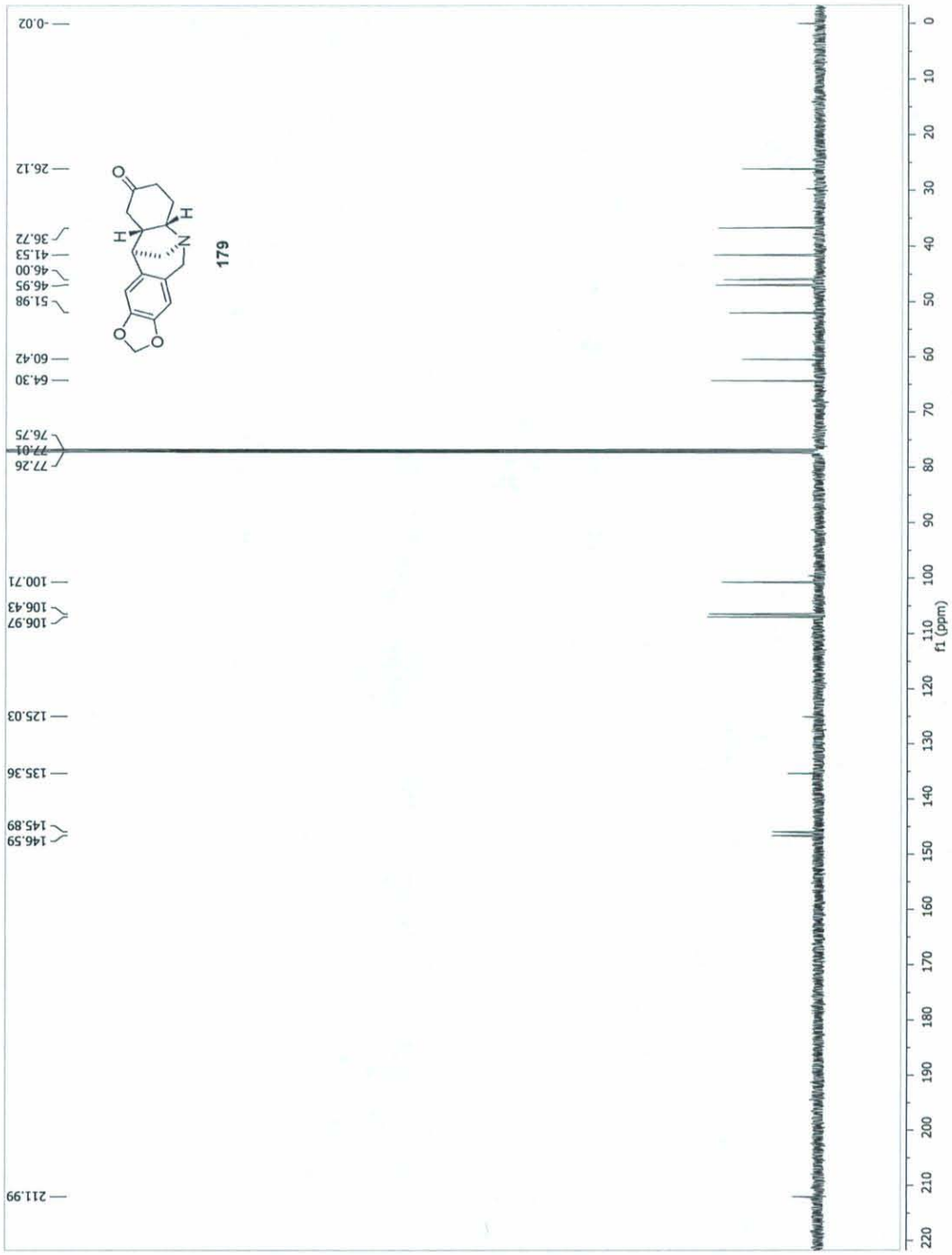
f1 (ppm)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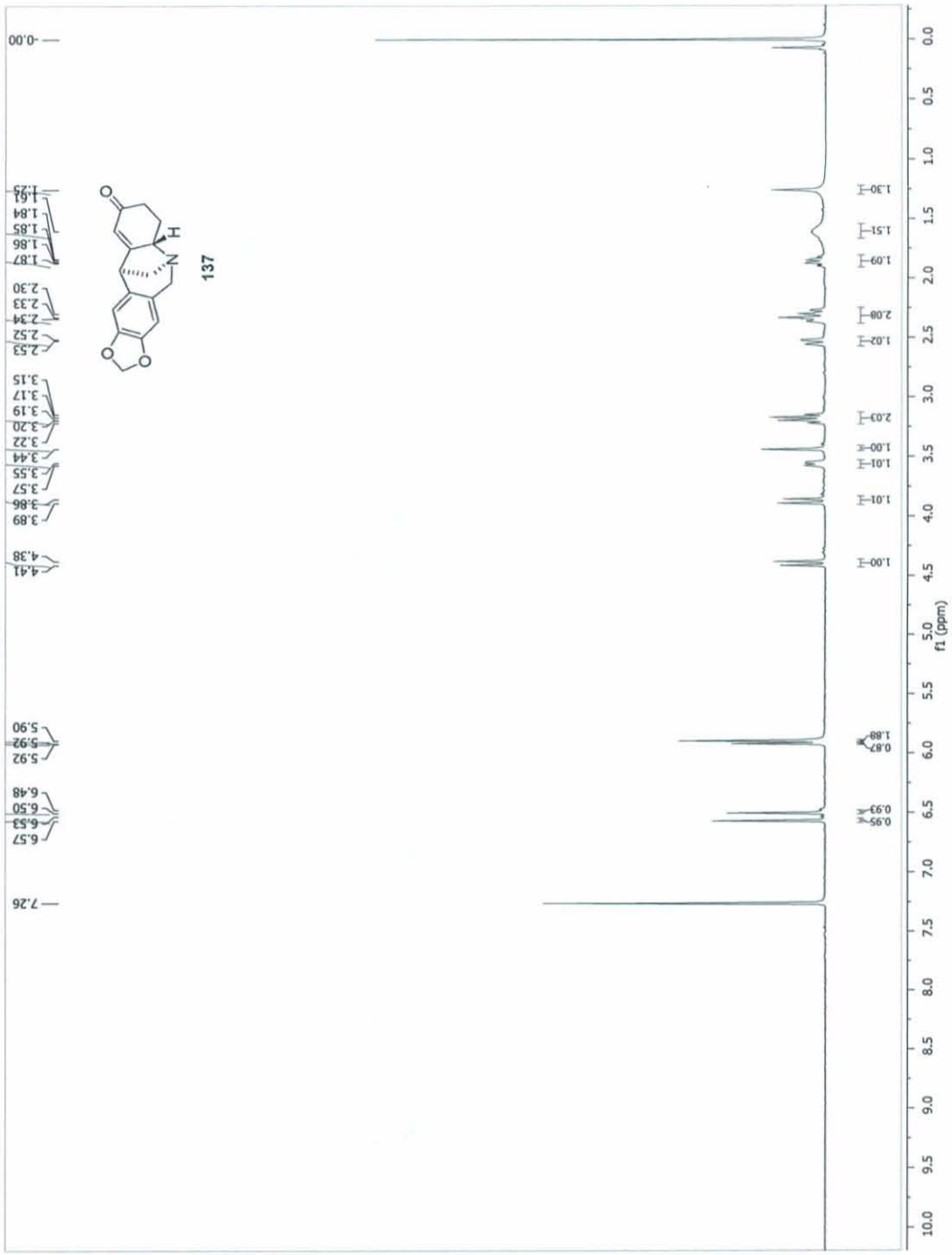
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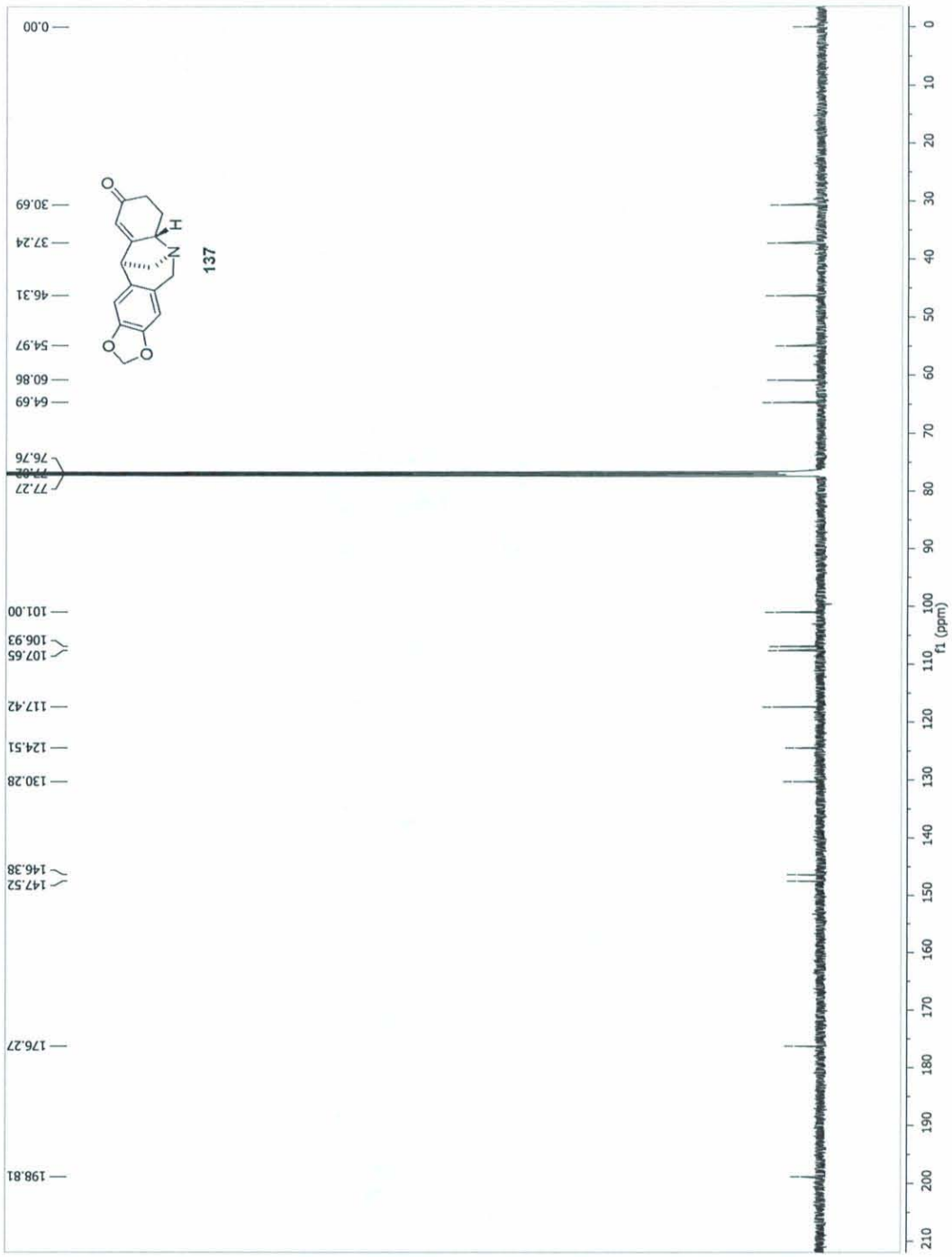
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77.27
101.00
106.93
107.65
117.42
124.51
130.28
146.38
147.52
176.27
198.81
f1 (ppm)

Chapter 3

Total synthesis of (+)-*ipalbidine*

Part of the work described in this chapter has been published in

Eur. J. Org. Chem. **2011**, (DOI: 10.1002/ejoc.201100125)

Chapter 3

Total synthesis of (+)-ipalbidine

Introduction

Ipalbidine is a naturally occurring indolizidine alkaloid, isolated from seeds of *Ipomoea alba* L. The presence of indolizidine alkaloids in *Ipomoea alba* L. was first reported by Gourley *et al.*[1] who isolated the two glycoside alkaloids, ipalbine and ipomine, and their aglycone, ipalbidine (Figure 1).[1-3] A unique structural feature of this class of alkaloids is the location of the *C*-methyl group on the hexahydroindolizidine nucleus.[4]

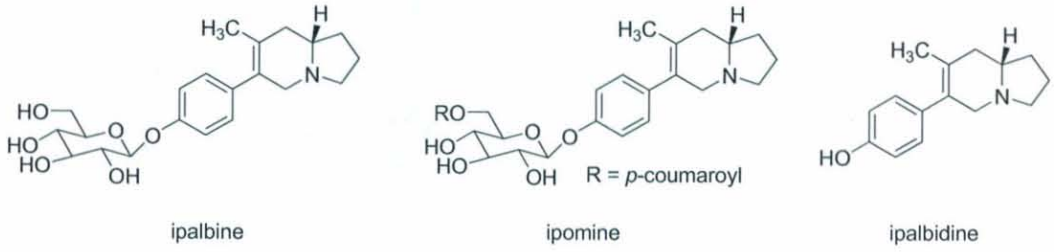


Figure 1. Structures of indolizidine alkaloids

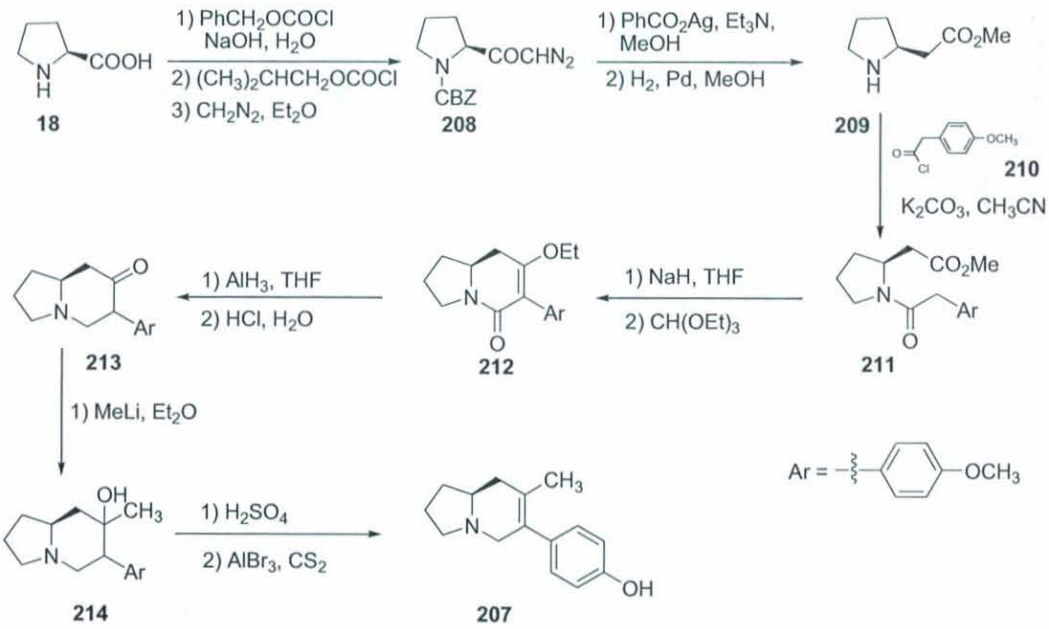
Apart from their prototypical structures these compounds have remarkable biological profiles. (+)-Ipalbidine is a non-addictive analgesic, an oxygen free-radical scavenger, and has demonstrated inhibitory effects on the respiratory burst of leukocytes.[5]

Known synthetic routes to ipalbidine

The following summary provides an overview of the syntheses of ipalbidine in enantiomerically enriched as well as racemic form.

The Jin synthesis of (+)-ipalbidine

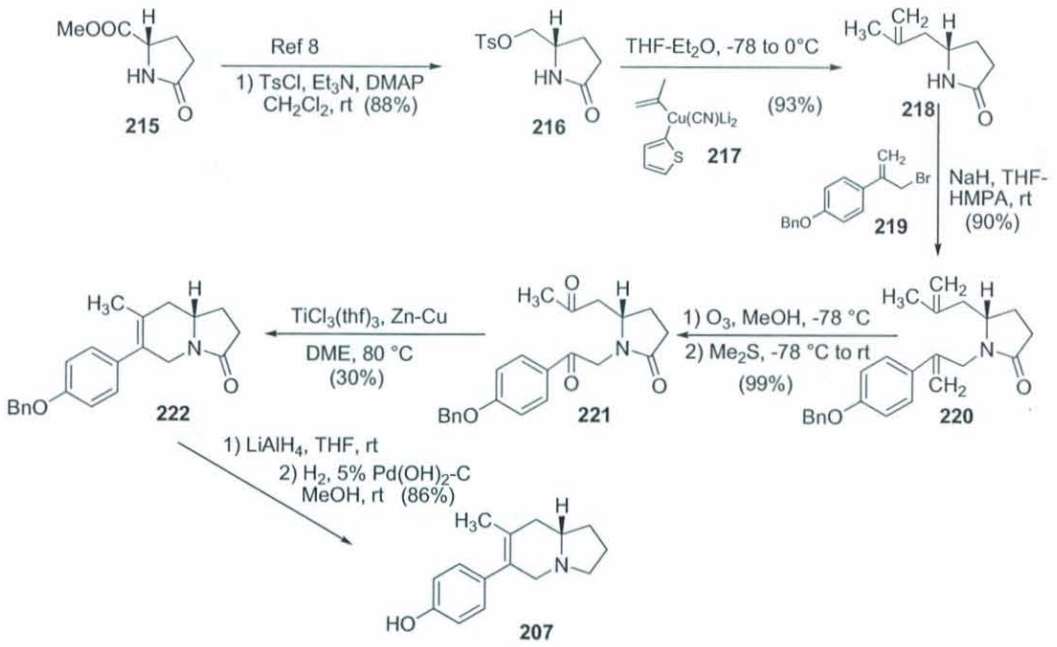
Jin and co-workers reported the first enantioselective total synthesis of (+)-ipalbidine in 1985.[6] The synthesis begins with (*S*)-proline **18** (Scheme 1), which is homologated to **209** in four steps by using Arndt-Eistert reaction conditions. *N*-alkylation of **209** with 2-(4-methoxyphenyl)acetyl chloride provided the amide **211**. Amide **211** was cyclized in the presence of NaH in THF to give the *β*–keto amide, which upon treatment with triethyl orthoformate provided **212**. The amide in **212** was reduced to the amine using AlH_3, and the enol ether was hydrolysed with HCl to generate ketone **213**. The ketone **213** was reacted with methyl lithium to provide tertiary alcohol **214**, which upon dehydration and subsequent demethylation provided the natural product (+)-ipalbidine **207** in a stereoselective fashion.



Scheme 1

The Honda synthesis of (+)-ipalbidine

In 2003, Honda and coworkers reported an enantiospecific total synthesis of (+)-ipalbidine.[7] The key step in this synthesis is an intramolecular McMurray coupling using a low-valent titanium reagent. The synthesis starts with (-)-pyroglutamic acid methyl ester **215** (Scheme 2), which was converted to tosylate **216**.[8]

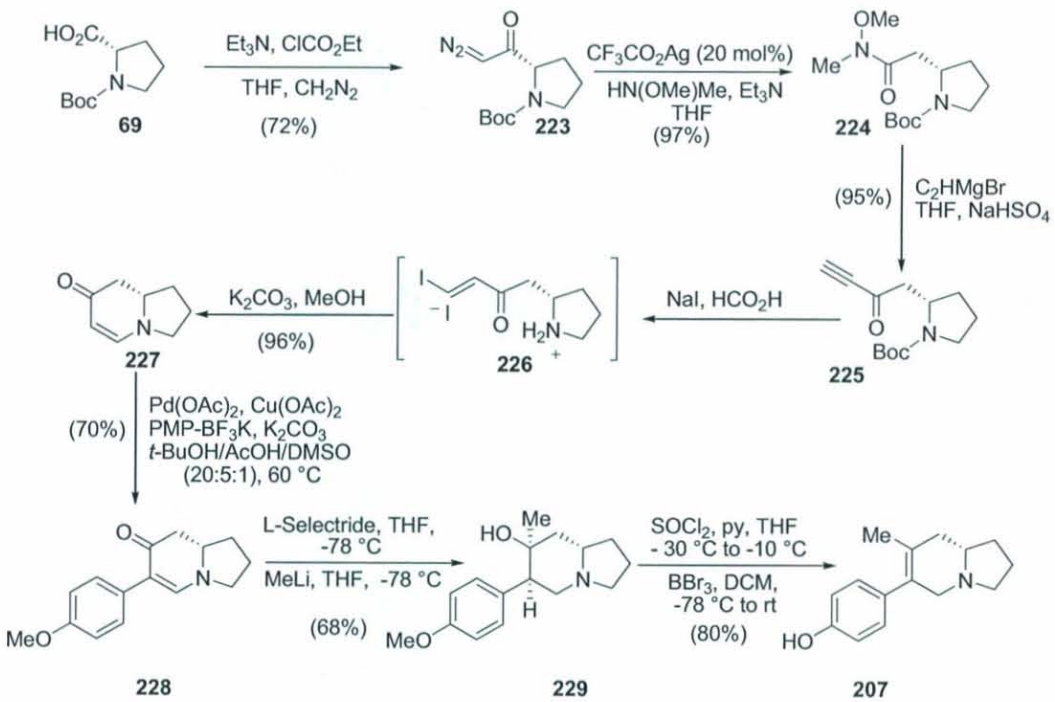


Scheme 2

Treatment of **216** with higher-order cuprate reagent **217** gave the desired olefinic amide **218**. *N*-alkylation of amide **218** with bromide **219** afforded diene **220** in good yield. Ring closing metathesis of the diene **220** in the presence of the Grubbs, Hoveyda or Schrock catalysts was unsuccessful and hence an alternative strategy for constructing the six-membered ring of ipalbidine was followed. Ozonolysis of the diene **220** followed by reductive work-up with dimethyl sulfide provided the diketone **221**, which on treatment with titanium (0), (prepared from $TiCl_3$.THF complex and Zn-Cu couple) in DME furnished the desired product **222** in only 30% yield. Reduction of the amide using LAH followed by hydrogenolysis of the benzyl ether provided (+)-ipalbidine (**207**).

The Georg synthesis of (+)-ipalbidine

Georg and Niphakis reported an enantioselective total synthesis of (+)-ipalbidine.[9] Their synthesis starts with Boc-*S*-proline **69**, which was homologated using standard Arndt-Eistert reaction conditions. The acid was first converted into diazoketone **223** which was then subjected to a Wolff rearrangement with catalytic CF_3CO_2Ag (Scheme 3) in the presence of freshly distilled *N,O*-dimethylhydroxylamine to provide the Weinreb amide **224** (97%). Ynone **225** was prepared by treatment of **224** with ethynylmagnesium bromide.

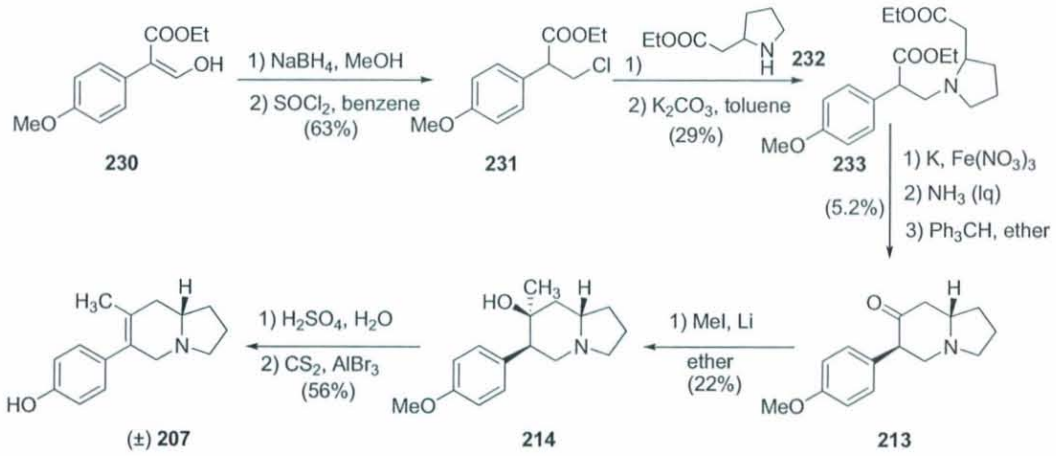


Scheme 3

Initially, enaminone **227** was prepared from the ynone **225** by stepwise treatment with aqueous 4 *N* HCl in dioxane followed by addition of methanolic K_2CO_3. However, this protocol led to racemization of **225**. Alternatively, a milder deprotection protocol (formic acid and NaI) was used to mitigate racemisation at the α–stereocentre. Treatment of the obtained vinyl iodide **226** with K_2CO_3 gave enaminone **227**. A Pd(II)-catalyzed C-H arylation of **227** with an appropriate organotrifluoroborate produced the arylindolizidinone **228**. The enaminone **228** was reduced to the ketone with L-Selectride using the Liu's protocol.[6] Treatment of the ketone with methyllithium furnished the tertiary alcohol **229**. Dehydration of the tertiary alcohol using $SOCl_2$ in pyridine, followed by demethylation with BBr_3 furnished (+)-ipalbidine (**207**) in enantiomerically pure form.

The Govindachari total synthesis of (±)-ipalbidine

The first total synthesis of (±)-ipalbidine by Govindachari describes a convenient route to arylindolizidine alkaloids in general.[10] The synthesis begins with hydroxymethylene derivative **230** which was prepared from ethyl 4-methoxyphenyl acetate by treatment with sodium and ethyl formate (Scheme 4).



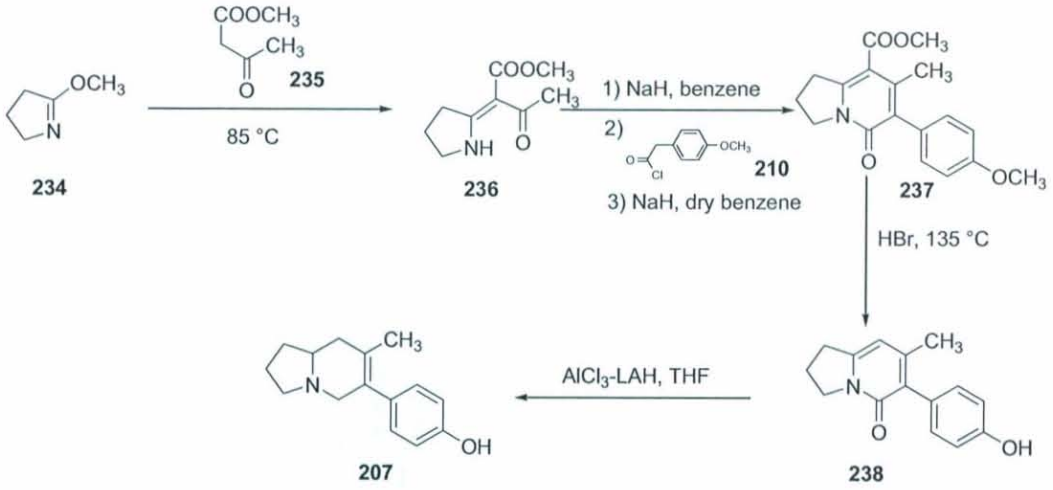
Scheme 4

Compound **230** was subsequently reduced with sodium borohydride to the corresponding *β*-hydroxy ester which was then converted to the β–chloro ester **231** with $SOCl_2$. The chloroester **231** was condensed with ethyl 2-pyrrolidinyl acetate to give diester **233**. Dieckmann cyclization of **233** followed by hydrolysis and decarboxylation afforded the ketone **213**. Ketone **213** was reacted with methyl lithium to yield tertiary alcohol **214**. Dehydration of the tertiary alcohol **214** using sulfuric acid, followed by demethylation of the methyl ether with aluminum bromide, yielded racemic ipalbidine **207**.

The Wick total synthesis of (±)-ipalbidine

In 1971, Wick and co-workers reported the total synthesis of (±)-ipalbidine.[11] The synthesis begins with 2-methoxy pyrrolidine **234**. Compound **234** was condensed with methyl acetoacetate **235** to give keto ester **236**. Keto ester **236** was acylated with *p*-methoxyphenylacetyl chloride **210**. Cyclization of the resulting amide provided the

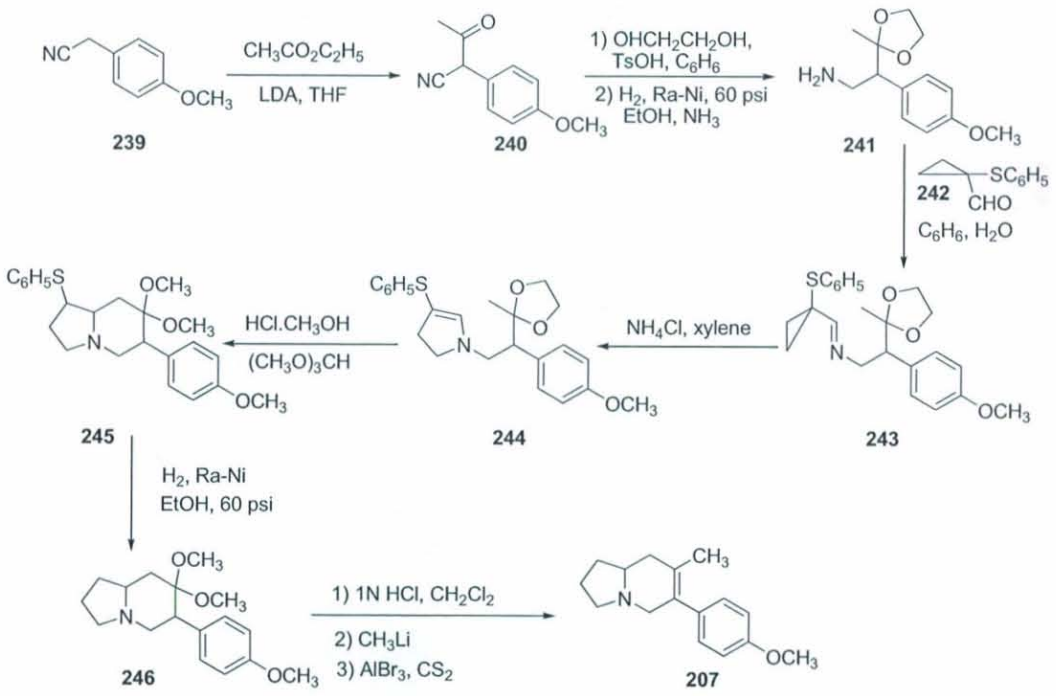
pyridone **237** which was further demethylated and decarboxylated in hot hydrobromic acid to the substituted pyridone **238**. Reduction of **238** with excess alane (made from $AlCl_3$-LAH) in THF provided racemic ipalbidine (**207**) (Scheme 5).



Scheme 5

The Stevens total synthesis of (±)-ipalbidine

Stevens and Luh reported a total synthesis of (±)-ipalbidine in 1977.[12] Their approach uses an acid-catalyzed rearrangement of a cyclopropane to generate a 3-phenylthio-2-pyrroline synthon as a key step (Scheme 6).

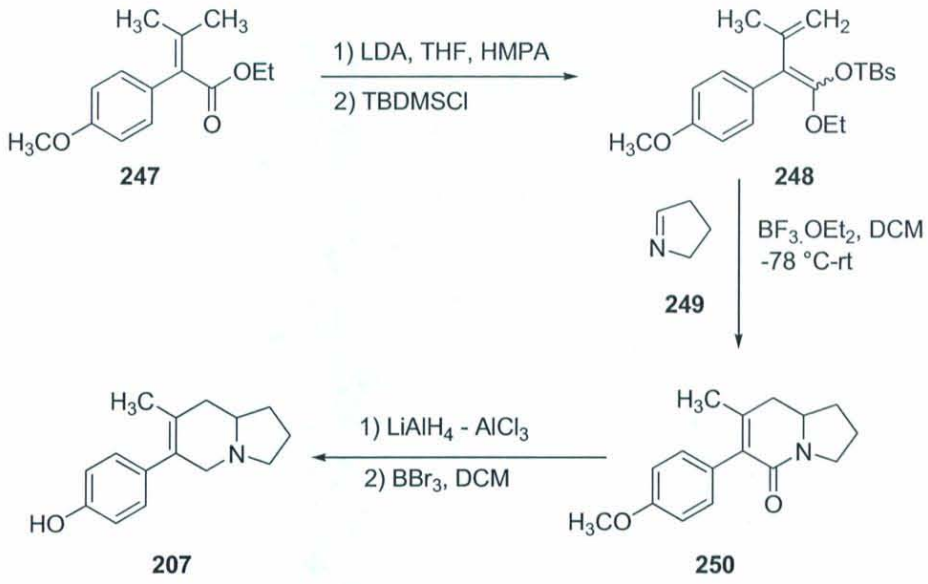


Scheme 6

The synthesis began with readily available *p*-methoxybenzyl cyanide **239**. Compound **239** was acylated (LDA/ethylacetate) to provide **240**. Ketalization of the ketone in **240** followed by reduction of the cyano group afforded the amine **241**. The requisite cyclopropyl imine **243** was prepared by condensation of aldehyde **242** and amine **241**. The key acid-catalyzed rearrangement of **243** took place in the presence of ammonium chloride to form the corresponding 2-pyrroline **244**. Treatment of compound **244** with methanolic HCl and trimethyl orthoformate produced indolizidine **245**. Desulfurization of **245** using Ra-Ni afforded ketal **246** which was hydrolysed to the corresponding ketone. The conversion of this ketone to ipalbidine was previously reported by Govindachari and Wick.[10,11]

The Danishefsky total synthesis of (±)-ipalbidine

Danishefsky and Vogel outlined an approach to (±)-ipalbidine which utilized a Lewis-acid catalyzed cycloaddition of a silyloxydiene with an aldimine as the key step (Scheme 7).[13]

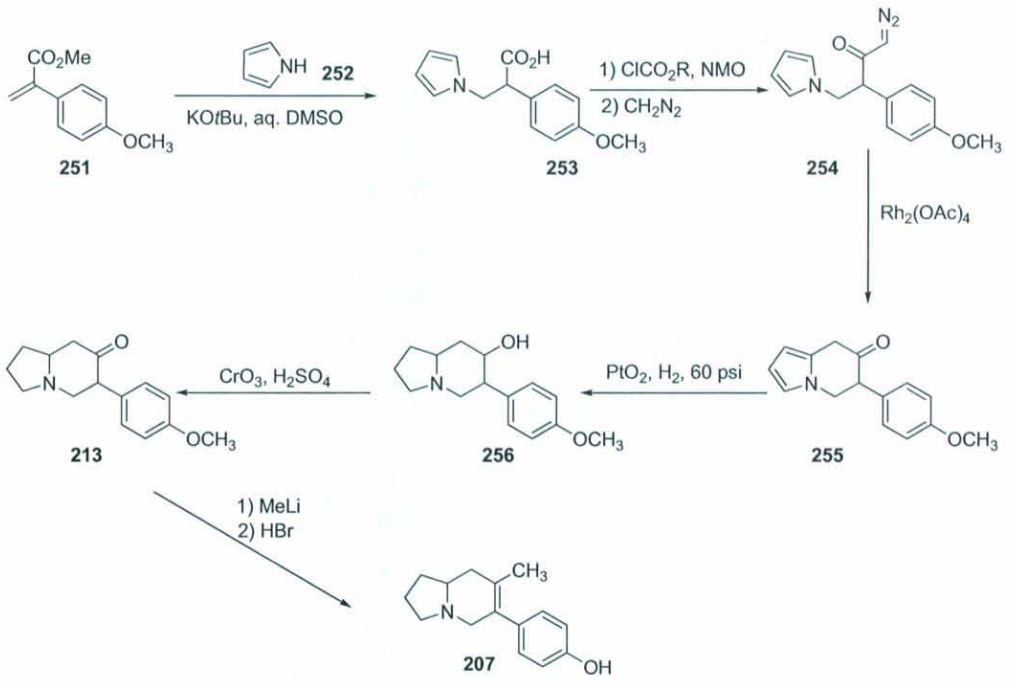


Scheme 7

The synthesis began with the known α-aryl-β-methylcrotonate derivative **247**,[14] which was converted to the silylketene acetal **248** by deprotonation with LDA followed by *O*-silylation with *tert*-butyldimethylsilyl chloride. Reaction of silylketene acetal **248** with the pyrroline **249** in the presence of boron trifluoride etherate at -78 °C afforded the unsaturated lactam **250**. Reduction of the lactam **250** using alane (LAH-$AlCl_3$) followed by demethylation of the resulting hexahydroindolizidine with boron tribromide produced (±)-ipalbidine.

The Jefford total synthesis of (±)-ipalbidine

Jefford and coworkers reported the total synthesis of (±)-ipalbidine.[15] Their strategy involves a rhodium (II) acetate-catalyzed C-H insertion of the diazo ketone **254** to form dihydroindolizidine **255** as key the intermediate (Scheme 8).



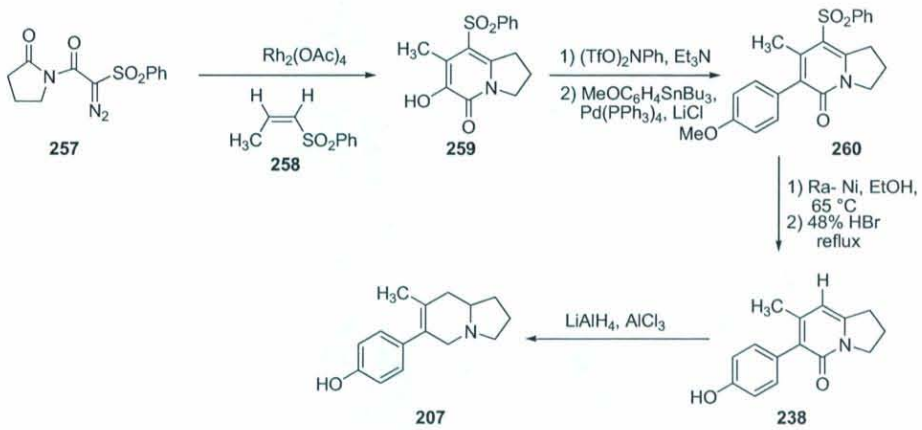
Scheme 8

The synthesis begins with arylpropenoate **251** which was prepared from the corresponding arylacetic acid. Michael addition of pyrrole (**252**) to **251** gave the adduct **253**. The ester in the adduct underwent hydrolysis during the course of the reaction. Conversion of the acid into diazoketone **254** was achieved by conversion to the mixed anhydride followed by reaction with diazomethane. $Rh(OAc)_2$ catalyzed decomposition of diazobutanone **254** yielded the key intermediate dihydroindolizidinone **255** as the

product of an insertion reaction of the diazocarbonyl into the pyrrole C-H bond. Hydrogenation of **255** using PtO_2 afforded the amino alcohol **256** which was oxidised using the Jones reagent to provide the ketone **213**. Reaction of the ketone with excess MeLi resulted in the formation of tertiary alcohol and concomitant demethylation of the methyl ether. Treatment of this product with acetic anhydride yielded the diacetate which upon treatment with hot HBr gave (±)-ipalbidine (**207**).

The Padwa total synthesis of (±)-ipalbidine

The total synthesis of (±)-ipalbidine by Padwa and Sheehan describes a convenient route to indolizidine alkaloids.[16] The synthesis begins with the [3+2] cycloaddition of *α*–diazoimide **257** with *cis*-1-(phenylsulfonyl)-1-propene in the presence of $Rh_2(OAc)_4$ to provide pyridone **259** (Scheme 9). This reaction proceeds via the formation of a carbonyl ylide from **257** which functions as the 1,3 dipole in the cycloaddition.

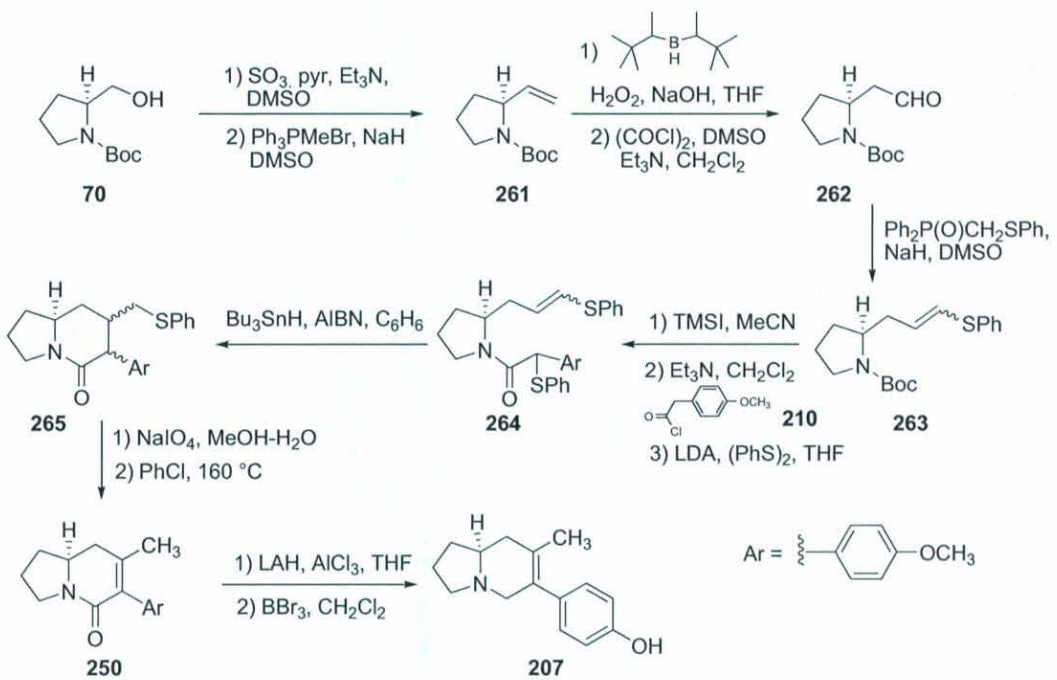


Scheme 9

Conversion of the cycloadduct **259** to the corresponding triflate, followed by a Stille coupling using tributyl(4-methoxyphenyl) tin gave the aryl-substituted 2-pyridone **260**. Desulfonylation of **260** using Ra-Ni followed by demethylation provided 2-pyridone **238**. Complete reduction of the enamide in **238** afforded (±)-ipalbidine.

The Ikeda total synthesis of (±)-ipalbidine

The total synthesis of (±)-ipalbidine by Ikeda utilizes a 6-*exo-trig* radical cyclization as the key reaction.[17] The synthesis begins with the *N*-Boc-(*S*)-prolinol **70**. Oxidation of **70** followed by Wittig olefination provided **261**. Hydroboration of the olefin in **261** followed by oxidation afforded aldehyde **262** (Scheme 10).

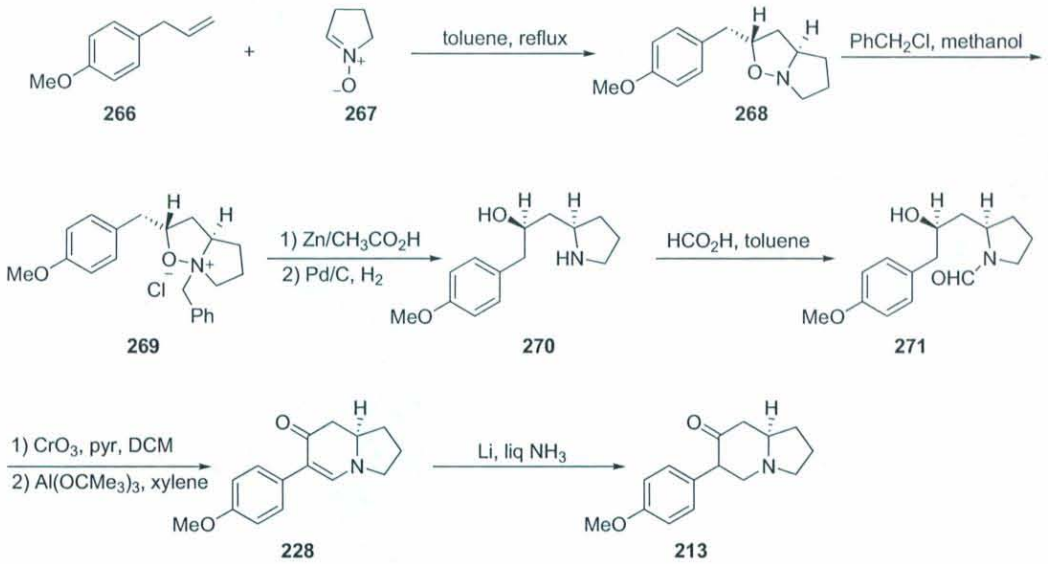


Scheme 10

The aldehyde **262** was treated with diphenyl(phenylthiomethyl)phosphine oxide in the presence of NaH to give vinyl sulfide **263** as a 1:2 mixture of *E*/*Z* isomers. Removal of the Boc group followed by acylation of the amine with *p*-methoxyphenylacetyl chloride (**210**) gave the corresponding amide which was converted to the sulfide **264**. The key 6-*exo*-*trig* radical cyclization of amide **264** was initiated with Bu_3SnH in the presence of AIBN in boiling benzene to provide the lactam **265** as a 1:1 mixture of diastereomers. Treatment of **265** with sodium metaperiodate followed by heating the resulting sulfoxide in chlorobenzene at 160 °C provided the unsaturated lactam **250**. The conversion of **250** to the (±)-ipalbidine was achieved as previously described by Danishefsky and Vogel.[13]

The Kibayashi formal total synthesis of (±)-ipalbidine

Kibayshi and coworkers reported a formal total synthesis of (±)-ipalbidine.[18] They have synthesized bicyclic ketone **213** using a 1,3 dipolar cycloaddition and Dieckmann condensation as the key reactions (Scheme 11). Ketone **213** is an advanced intermediate in the synthesis of (±)-ipalbidine.

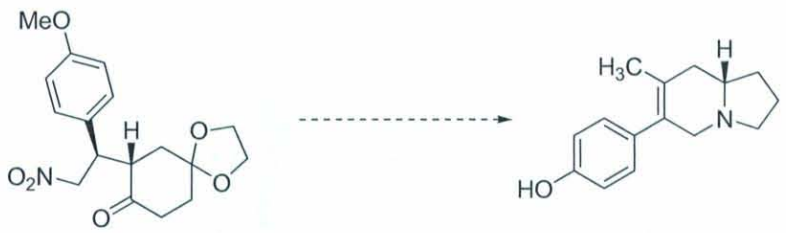


Scheme 11

The synthesis begins with a 1,3-dipolar cycloaddition between nitrone **267** and *p*-methoxy allyl benzene (**266**) to provide the cycloadduct **268** as a single diastereomer. *N*-benzylation of **268** provided the salt **269** which was subjected to N-O bond cleavage with Zn/CH_3COOH and subsequent hydrogenolysis of the benzyl group to provide the amino alcohol **270**. Aminoalcohol **270** was then *N*-formylated to provide **271** by heating in formic acid. Subsequent Collins oxidation followed by an intramolecular aldol condensation (using aluminium *t*-butoxide according to Ban's method[19]) yielded the bicyclic enaminone **228**. Selective reduction of the alkene in **228** using lithium in liq. NH_3 produced amino ketone **213** which is an advanced intermediate in the synthesis of ipalbidine.[6]

Objective

The aim of the present study was to utilize the enantiomerically-enriched γ-nitroketone **274**, obtained from an organocatalytic Michael addition, as a starting material for the stereoselective synthesis of (+)-ipalbidine **207** (Figure 2).

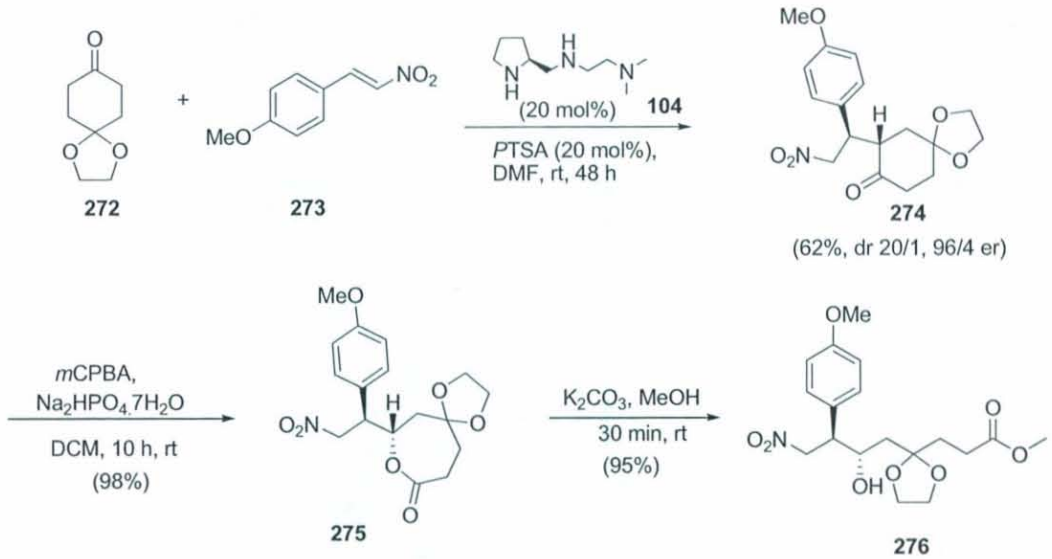


274 **207**

Figure 2. γ–Nitroketone **274** as a starting material for the synthesis of (+)-ipalbidine

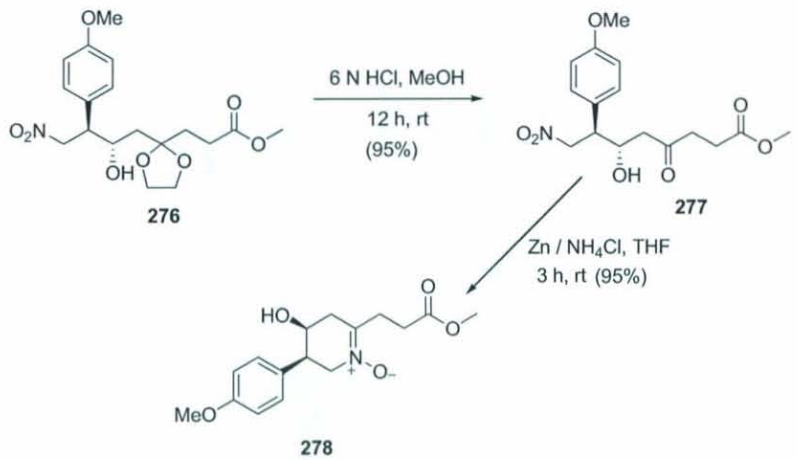
Results and discussion

Initially, γ-nitroketone **274** was prepared from 1,4-cyclohexanedione monoethylene ketal (**272**) and 4-methoxy β–nitrostyrene (**273**) by employing the secondary-secondary diamine salt-catalyzed Michael addition protocol developed in our group (as discussed in Chapter 2).[20,21] The nitroketone **274** was obtained in good yield and high diastereomeric and enantiomeric excess (*dr* > 20/1, 96/4 *er*). Baeyer-Villiger oxidation of **274** with *m*CPBA provided the lactone **275** in 98% yield. Methanolysis of the lactone under basic conditions provided the hydroxy ketal **276** in 95% yield (Scheme 12).



Scheme 12

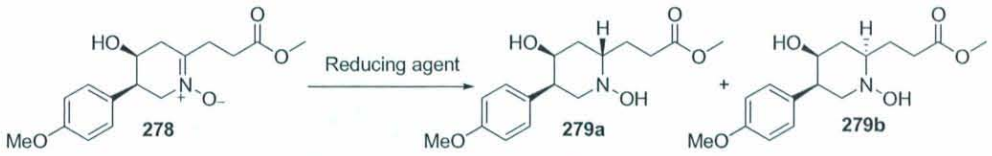
Deprotection of the acetal in **276** (6 *N* HCl, MeOH) furnished the hydroxy ketone **277** in 95% yield. Partial reduction of the nitroketone with Zn/NH_4Cl provided the nitrone **278** in 95% yield. This step constructs the six -membered ring of the required indolizidine moiety (Scheme 13).



Scheme 13

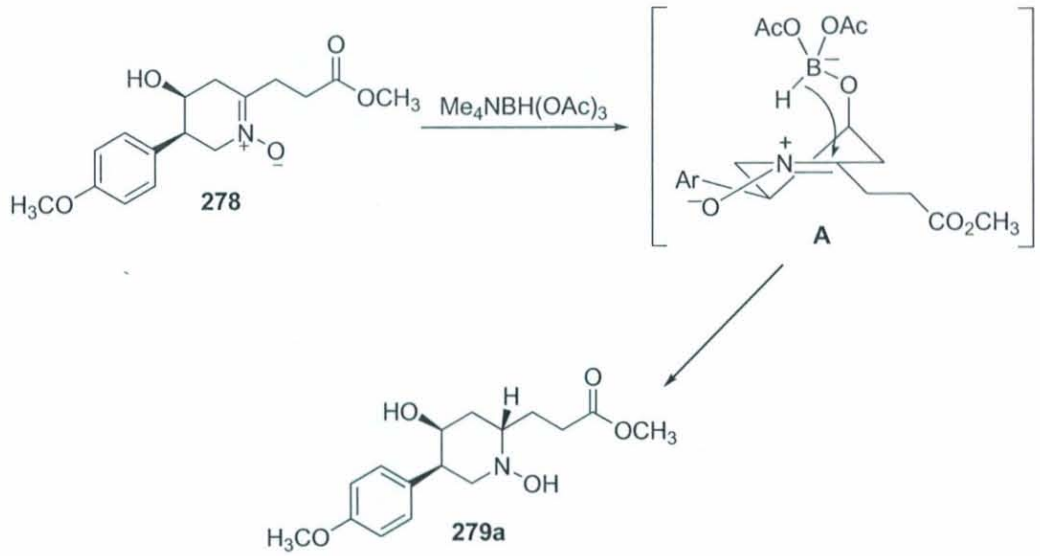
The nitrone **278** was subjected to stereoselective reduction under a variety of conditions and the results are summarized in Table 1.

Table 1. Conversion of nitrone **278** to hydroxylamines



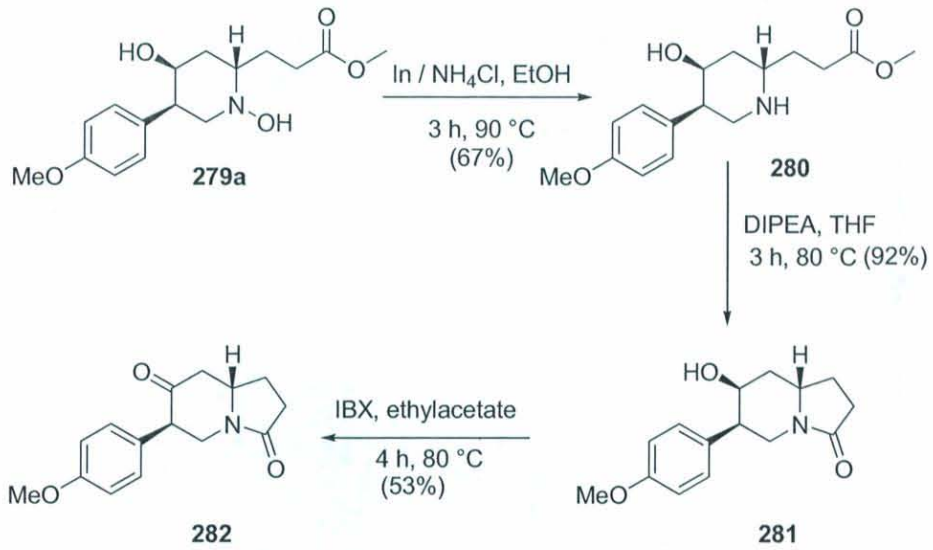
Reducing agent	Yield (%)	Hydroxylamine 279a	Hydroxylamine 279b
$NaBH_4$	47	1	1
LAH, -78 °C	-	reduction of ester	
L-Selectride, -78 °C	-	reduction of ester	
$(CH_3)_4N(CH_3CO_2)_3BH$, 0 °C	83	only hydroxyl amine **279a**	

Treatment of the nitrone with $NaBH_4$ provided a 1:1 mixture of hydroxyl amines **279a** and **279b**. Reaction with LAH or L-Selectride resulted in reduction of the ester functionality. However, the use of $Me_4NBH(OAc)_3$ provided hydroxyl amine **279a** as a single diastereomer in 83% yield. It is presumed that the diastereoselectivity of this reaction may be due to a substrate-directed stereoselective reduction, via ligand exchange of the acetoxy group in the reducing agent with the hydroxy functional group[22] in the substrate (**A**, Scheme 14). This intermediate, in turn, delivers the hydride intramolecularly to reduce the nitrone stereoselectively.



Scheme 14

Deoxygenation of the hydroxylamine **279a** was achieved with In/NH_4Cl to provide the piperidine **280** in 67% yield. During this reaction, some of the amino ester **280** was converted into lactam **281**. Complete conversion of this mixture to lactam **281** was achieved by heating with Hunig's base. Comparison of the ^1H NMR data of **281** with that of the racemate[15] established its relative stereochemistry, thereby confirming the stereochemistry of the reduction of **278** to **279a**. The alcohol in lactam **281** was then oxidized to the ketone with IBX to provide the ketolactam **282** (Scheme 15).



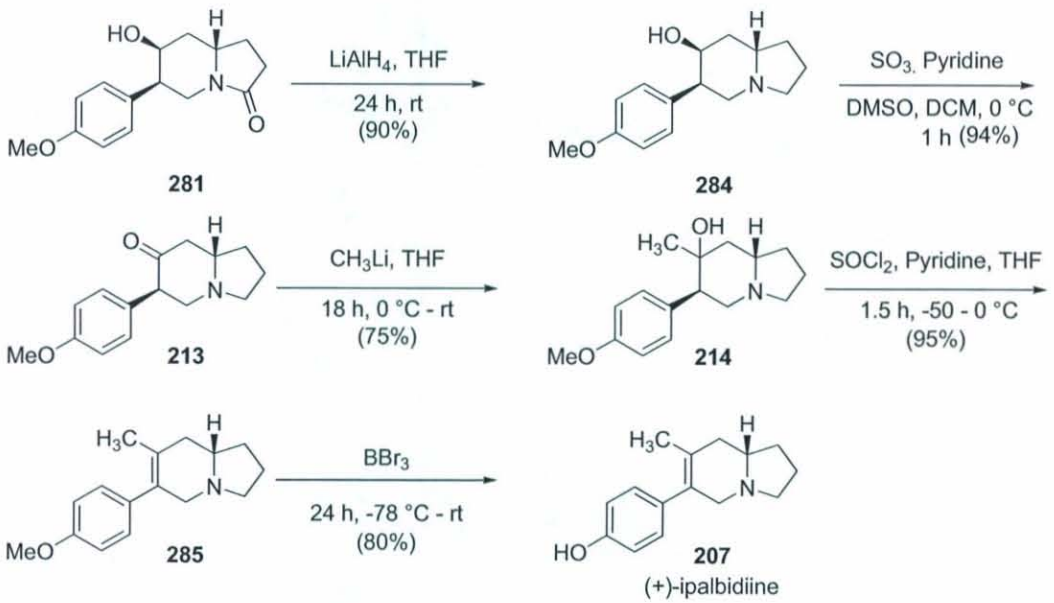
Scheme 15

Our initial attempt to form tertiary alcohol **283** by methylation of the amido ketone **282** was unsuccessful, presumably due to competing addition to the lactam carbonyl (Scheme 16). Hence, an alternative synthetic sequence was examined.

Scheme 16

In this alternative approach, lactam **281** was reduced to the amino alcohol **284** with LAH. Oxidation of **284** (SO_3. pyridine/DMSO) provided the ketone **213**. Conversion of ketone **213** to the tertiary alcohol **214** was now readily possible by reaction with methyllithium. Dehydration of **214** at low temperature (–30 to –10 °C) with only a slight excess of $SOCl_2$

and pyridine provided the indolizidine **285** in 95% yield. Removal of the *O*-methyl group in **285** with BBr_3 provided (+)-ipalbidine (**207**) (Scheme 17). The synthetic ipalbidine exhibited ^1H and ^{13}C spectroscopic data in agreement with that reported for the natural product.[9] The sign of the observed optical rotation confirmed the *S*-stereochemistry ($[\alpha]^{23}_D = +199$ (*c* 1, $CHCl_3$); lit.[11] $[\alpha]^{25}_D = +233$ (*c* 1, $CHCl_3$) for the *S* enantiomer with 98% ee). The enantiomeric ratio for (+)-ipalbidine was 97.2: 2.8 (94.4% ee, Chiralcel OJ-H, 2-propanol, 2-20% in hexanes, 30 min, 1.0 mL/ min, 254 nm; $t_R = 13.9$ min (minor); $t_S = 15.2$ min (major)).



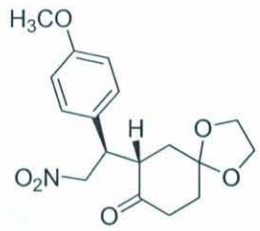
Scheme 17

Conclusion

In conclusion, an organocatalytic Michael addition-based enantioselective synthesis of the indolizidine framework was developed. The utility of this methodology is highlighted by application in a total synthesis of (+)-ipalbidine. A unique feature of our methodology is the creation of the stereocenter in (+)-ipalbidine by using a stereocenter constructed by the enantioselective, organocatalytic Michael addition step. All other enantioselective approaches to ipalbidine begin with *S*-proline (pre-existing stereocenter). Another advantage of our approach is the potential for adaptation for the synthesis of congeners and analogs of the target alkaloids. This may be achieved by a) variation in the ketone and nitrostyrene and b) embellishment of the propanoate side chain in **279a**. The utility of our strategy is augmented by the large number of methods available for the stereoselective synthesis of a variety of γ-nitroketones.[23-25] The overall efficiency of our synthetic protocol coupled with the high enantioselectivity strongly advocates an investigation of the application of these methods in the synthesis of selected, naturally occurring indolizidines and their analogues.

Experimental section

(7*S*)-7-[(1*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-one (274):

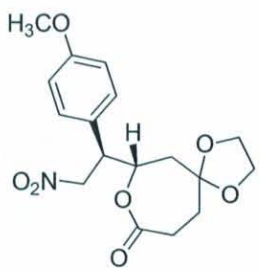


To a solution of 1,4-cyclohexanedione monoethylene ketal (13.0 g, 83.7 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine[20] (572 mg, 3.34 mmol) and *p*-toluene sulfonic acid monohydrate (634 mg, 3.34 mol) in DMF (10 mL) was added a solution of 4-methoxy-*β*-nitrostyrene (3.00 g, 16.7 mmol) in DMF (20 mL) and the resulting solution was stirred at ambient temperature for 48 h. Ethyl acetate (100 mL) was added and the solution washed with water, and aq. HCl (3 N), dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash chromatography on silica gel to provide 4.60 g of a solid. This was dissolved in ethyl acetate (23 mL) and precipitated by addition of hexanes (70 mL). The procedure was repeated once to provide 3.50 g (62%) of **274** with 92% ee. In repeated runs, **274** was obtained in 90-96% ee.

IR (neat): 2897, 2360, 1712, 1548, 1512, 1247, 1132, 1026, 950, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, 2H, *J* = 8.7, Ar*H*), 6.85 (d, 2H, *J* = 8.7, Ar*H*), 4.93-4.89 (dd, 1H, *J* = 12.3, 4.8, CH_2NO_2), 4.58-4.54 (dd, 1H, *J* = 12.3, 9.9, CH_2NO_2), 4.0-3.83 (m, 4H, OCH_2CH_2O), 3.78 (s, 3H, OCH_3), 3.04-2.98 (m, 1H, ArC*H*), 2.72-2.66 (dt, 1H, *J* = 13.8,

6.4, COC*H*), 2.48-2.43 (m, 1H, COCH_2), 2.07-2.01 (m, 1H, COCH_2), 1.98-1.92 (dt, 1H, *J* = 13.3, 5.2, CHCH_2), 1.72-1.68 (m, 1H, CHCH_2), 1.57-1.51 (apparent t, 2H, *J* = 13.4, CH_2CH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.4 (*C*O), 159 (Ar*C*), 129.2 (2xAr*C*), 129.0 (Ar*C*), 114.4 (2xAr*C*), 107.1 (O*C*O), 79.1 (CH_2NO_2), 64.8 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 55.2 (OCH_3), 48.3 (CO*C*H), 42.7 ($CHCH_2NO_2$), 39.3 (COCH_2), 38.6 (CH_2), 35.1 (CH_2); MS (APCI, pos.): m/z 336 (M+1); HRMS (EI): m/z 335.1367 (335.1369 calc. for $C_{17}H_{21}NO_6$ (M^+)); HPLC (Chiralpak AS-H, hexane/2- propanol: 60/40, flow rate 1.0 mL/min, 254 nm): t_{minor} = 9.45 min, t_{major} = 12.97 min, ee = 92%, dr = 20:1 (average values from multiple reactions).

(*S*)-7-((*R*)-1-(4-methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (275):

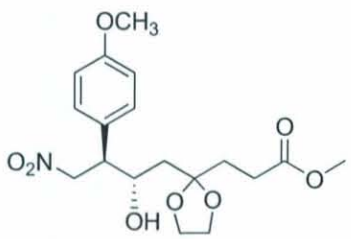


To a solution of the nitroketone **274** (3.10 g, 9.24 mol) in anhydrous dichloromethane (60 mL) at ambient temperature, was added solid sodium phosphate (3.21 g, 12.0 mol) followed by *m*-chloro perbenzoic acid (~77%, 4.94 g, 28.6 mmol). The resulting white slurry was stirred vigorously for 16 h. Dichloromethane (100 mL) was

added and the solution was washed with 5% aq. NaOH (2 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 3.20 g, (98%) of **275** as a white, solid foam. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 2962, 1736, 1550, 1514, 1249, 1154, 1117, 1099, 1029, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, 2H, J = 11.6, Ar*H*), 6.89 (d, 2H, J = 11.6, Ar*H*), 4.95-4.92 (dd, 1H, J = 12.6, 4.7, C*H*$_2$NO$_2$), 4.76-4.69 (m, 2H, C*H*$_2$NO$_2$, (CO)OC*H*)), 3.89-3.85 (m, 2H, OC*H*$_2$CH$_2$O), 3.80 (4H, OC*H*$_3$, OCH$_2$C*H*$_2$O), 3.62-3.58 (dt, 1H, J = 9.3, 4.7, Ar-C*H*), 3.54-3.51 (m, 1H, OCH$_2$C*H*$_2$O), 2.88-2.81 (m, 1H, C*H*$_2$CO), 2.65-2.60 (m, 1H, C*H*$_2$CO), 1.93-1.89 (m, 2H, C*H*$_2$(C)CH$_2$), 1.86-1.79 (m, 2H, CH$_2$(C)C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5 (*C*O), 159.5 (Ar*C*), 129.3 (2xAr*C*), 127.8 (Ar*C*), 114.6 (2xAr*C*), 107.2 (O*C*O), 77.7 (*C*H$_2$NO$_2$), 75.8 (*C*OC(O)), 65.0 (OCH$_2$*C*H$_2$O), 64.3 (O*C*H$_2$CH$_2$O), 55.3 (O*C*H$_3$), 48.1 (OCH*C*H$_2$), 41.5 (*C*HCH$_2$NO$_2$), 33.1 (*C*H$_2$(C)CH$_2$), 29.3 (CH$_2$(C)*C*H$_2$); HRMS (CI): m/z 351.1308 (351.1318 calc. for $C_{17}H_{21}NO_7$ (M+H)).

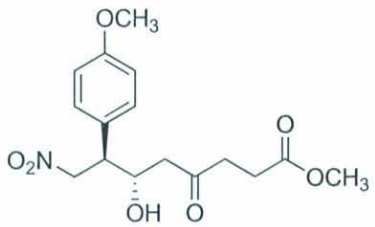
Methyl 3-(2-((2*S*, 3*R*)-2-hydroxy-3-(4-methoxyphenyl)-4-nitrobutyl)-1, 3-dioxolan-2-yl) propanoate (276):



A solution of the lactone **275** (3.40 g, 9.68 mmol) in methanol (70 mL) was cooled to 0 °C and potassium carbonate (2.67 g, 19.4 mmol) was added. The mixture was stirred at room temperature for 30 min. The mixture was cooled to 0 °C, neutralized with aq. HCl (0.5 M) and the solution was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 3.50 g (95%) of the nitroketal **276** as a light brown gum. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3501, 2956, 1732, 1548, 1514, 1249, 1179, 1134, 1030, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J* = 8.6, Ar*H*), 6.85 (d, 2H, *J* = 8.6, Ar*H*), 5.06-5.02 (dd, 1H, *J* = 5.2, 12.7, C*H*$_2$NO$_2$), 4.61-4.56 (dd, 1H, *J* = 9.7, 12.7, C*H*$_2$NO$_2$), 4.05-4.02 (m, 1H, Ar-C*H*) 4.01-3.91 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.86 (s, 1H, CHO*H*), 3.78 (s,3H, ArOC*H*$_3$) 3.64 (s,3H, OC*H*$_3$), 3.42-3.37 (dt, 1H, *J* = 5.3, 9.5, C*H*OH), 2.25-2.16 (m, 2H, CO_2CH_2), 2.02-1.97 (m, 1H, C*H*$_2$(C)CH$_2$), 1.79-1.85 (m, 1H, C*H*$_2$(C)CH$_2$),1.64-1.62 (m, 2H, CH$_2$(C)C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (*C*O$_2$CH$_3$), 159.2 (Ar*C*), 129.2 (Ar*C*), 129.1 (Ar*C*), 114.5 (Ar*C*), 110.9 (O*C*O), 78.5 (*C*H$_2$NO$_2$), 70.0 (*C*HOH), 65.1 (OCH$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 55.2 (ArO*C*H$_3$), 51.7 (CO$_2$*C*H$_3$), 50.3 (HO-C*C*H$_2$), 40.5 (Ar-*C*H), 31.7 (*C*H$_2$CH$_2$CO$_2$CH$_3$), 28.4 (*C*H$_2$CO$_2$CH$_3$); MS (APCI, pos.): m/z 366 (M-OH); HRMS (CI): m/z 384.1647 (384.1658 calc. for $C_{18}H_{26}NO_8$ (M+H).

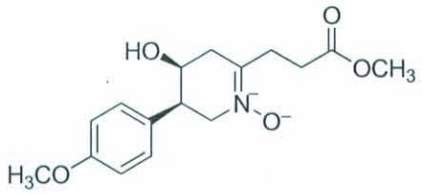
(6*S*,7*R*)-Methyl 6-hydroxy-7-(4-methoxyphenyl)-8-nitro-4-oxooctanoate (277):



To a solution of the nitroketal **276** (3.50 g, 10.3 mmol) in methanol (70 mL) at 0 °C, was added aq. HCl (6 N, 40 mL), and the mixture was stirred at room temperature overnight. The methanol was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (2x50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 2.90 g (95%) of the nitro ketone **277** as a light brown solid. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3436, 2953, 1723, 1710, 1553, 1514, 1380, 1251, 1204, 1179, 1157, 1102, 1032, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J* = 6.6, Ar*H*), 6.87 (d, 2H, *J* = 6.6, Ar*H*), 5.09-5.05 (dd, 1H, *J* = 5.1, 12.8, C*H*$_2$NO$_2$), 4.58-4.63 (dd, 1H, *J* = 9.9, 12.8, C*H*$_2$NO$_2$), 4.24-4.19 (m, 1H, Ar-C*H*), 3.79 (s, 3H, ArOC*H*$_3$) 3.65 (s, 3H, OC*H*$_3$), 3.55 (d, 1H, *J* = 4, CHO*H*) 3.51-3.46 (dt, 1H, *J* = 5.2, 9.8, C*H*OH), 2.57-2.64 (m, 4H, C*H*$_2$COC*H*$_2$), 2.41-2.52 (m, 2H, C*H*$_2$CO$_2$CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.7 (*C*O), 173.1 (*C*O$_2$CH$_3$), 159.3 (Ar*C*) 129.0 (2xAr*C*), 128.6 (Ar*C*), 114.6 (O*C*O), 78.4 (*C*H$_2$NO$_2$), 69.8 (*C*HOH), 55.2 (ArCO*C*H$_3$), 51.9 (CO$_2$*C*H$_3$), 49.2 (HO-C*C*H$_2$CO), 47 (Ar-*C*H), 37.7 (CO*C*H$_2$), 27.4 (*C*H$_2$CO$_2$CH$_3$); MS (APCI, pos.): m/z 322 (M-OH); HRMS (CI): m/z 322.1284 (322.1291 calc. for $C_{16}H_{20}NO_6$ (M-OH)).

(3*R*,4*S*)-4-Hydroxy-6-(3-methoxy-3-oxopropyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-1-oxide (278):

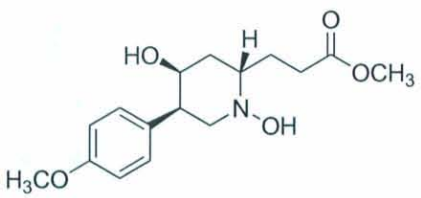


A solution of NH_4Cl (0.368 g, 6.00 mmol) in water (5 mL) was added to a solution of the nitroketone **277** (2.33 g, 6.00 mmol) in THF (20 mL). Activated Zn powder (4.37 g, 60.0 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered (celite), the residue was washed with THF, and the combined filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and the mixture was washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 2.00 g, (95%) of **278** as a brown foam. This material was pure by ^1H NMR (500 MHz) and was directly used further. An analytical sample was obtained by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95/5).

IR (neat): 2953, 1738, 1612, 1512, 1434, 1249, 1175, 1134, 1070, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.6, Ar*H*), 6.88 (d, 2H, J = 8.6, Ar*H*), 4.34-4.29 (br t, 1H, J = 13.3, ArC*H*), 4.18 (br s, 1H, C*H*OH), 3.93-3.86 (dd, 1H, J = 14.9, 5.5, CH_2N), 3.79 (s, 3H, ArOCH_3), 3.68 (s, 3H, CO_2CH_3), 3.22-3.19 (dd, 1H, J = 11.9, 4.8,

CH_2N), 2.94-2.68 (m, 6H, $CH_2C{=}N$, $COCH_2CH_2$, $COCH_2$), ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7 (*C*O), 159.1 (Ar*C*), 144.7 (*C*=NO), 129.7 (Ar*C*), 128.8 (2xAr*C*), 114.3 (2xAr*C*), 65.2 (CH_2NO), 57.8 (Ar-*C*H), 55.3 (OCH_3), 51.8 (CO_2CH_3), 43.7 (*C*HOH), 38.7 ($CH_2CO_2CH_3$), 28.3 ($N{=}CCH_2$), 27.5 ($N{=}CCH_2$); MS (APCI, pos.): m/z 308 (M+1); HRMS (CI): m/z 308.1499 (308.1498 calc. for $C_{16}H_{22}NO_5$ (M+H)).

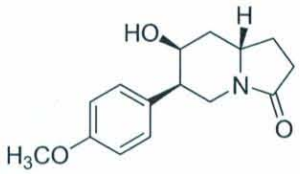
Methyl-3-((2*R*,4*S*,5*S*)-4-hydroxy-5-(4-methoxyphenyl)-*N*-hydroxypiperidin-2-yl)propanoate (279a):



To a solution of tetramethylammonium triacetoxyborohydride (3.25 g, 12.0 mmol) in acetonitrile (10 mL) was added acetic acid (10 mL). The mixture was stirred at 0 °C for 5 min and a solution of the nitrone **278** (1.90 g, 6.00 mmol) in acetonitrile (5 mL) was added. The mixture was stirred at 0 °C for 1 h and the pH of the solution was adjusted (pH 7 to 8) with aqueous NaOH (5% solution). The mixture was extracted with dichloromethane (2 x 50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to give 1.59 g (83%) of **279a** as a white solid. This material was pure by ^1H NMR (500 MHz) and was directly used further.

IR (neat): 3518, 3203, 2920, 1715, 1511, 1437, 1245, 1205, 1175, 1105, 1025, 981, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.7, Ar*H*), 6.88 (d, 2H, J = 8.7, Ar*H*), 3.93 (d, 1H, J = 12.3, 4.8, ArC*H*), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, COCH_3), 3.52-3.44 (t, 1H, J = 10.1, C*H*OH), 3.31-3.13 (m, 1H, ArCHCH_2), 3.07-2.9 (m, 1H, ArCHCH_2), 2.53-2.32 (m, 2H, COCH_2), 2.22-2.14 (m, 1H, NC*H*), 2.04-1.98 (dt, 1H, J = 13.3, 5.2, OHCHCH_2), 1.92-1.84 (m, 1H, OHCHCH_2), 1.74-1.66 (m, 1H, NCHCH_2), 1.54-1.50 (m, 1H, NCHCH_2); MS (APCI, pos.): m/z 272 (M-OCH_3+1), 310 (M+1); HRMS (CI): m/z 310.1636 (310.1654 calc. for $C_{16}H_{24}NO_5$ (M+H)).

(6*R*,7*S*,8a*S*)-Hexahydro-7-hydroxy-6-(4-methoxyphenyl)indolizin-3(5H)-one (281):



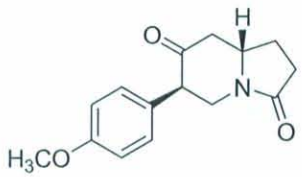
The hydroxylamine **279a** (1.65 g, 5.34 mmol) was dissolved in a mixture of EtOH (20 mL) and saturated aqueous NH_4Cl (10 mL). Indium powder (1.22 g, 10.0 mmol) was added and the mixture was heated to reflux for 4 h. The mixture was cooled, filtered through a pad of celite, and the filtrate was concentrated. The residue was diluted with dichloromethane (40 mL) and the aqueous layer was separated. The organic layer was washed with sataturated aqueous $NaHCO_3$ soln (3 x 10 mL) dried (Na_2SO_4) and concentrated to give 1.04 g of a yellow gum. This material is a mixture of the amino ester

and the cyclization product (lactam **281**, ~30%). The mixture was therefore directly converted to the lactam as follows:

To a solution of the crude amino ester and lactam mixture (1.00 g) in THF (15 mL) was added diisopropylethyl amine (1.49 mL, 8.00 mmol) and the solution was heated to reflux for 5 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 0.820 g (60% from **279a**) of the lactam (**281**) as a pale yellow foam. This material was pure by ^{1}H NMR (500 MHz) and was directly used further.

IR (neat): 3356, 2923, 1652, 1510, 1453, 1242, 1175, 1027, 828 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.13 (br s, 1H, C*H*OH), 4.12 (dd, 1H, J = 4.7, 12.6, NCH_2), 3.97-3.91 (m, 1H, ArC*H*), 3.8 (s, 3H, OCH_3), 3.37-3.32 (t, 1H, J = 12.6, NCH_2), 2.81-2.77 (dt, 1H, J = 4.6, 1.8, NC*H*), 2.44-2.41 (br t, 2H, J = 7.1, COCH_2), 2.29-2.22 (m, 1H, CH_2CHOH), 2.21-2.16 (m, 1H, NCHCH_2), 1.65-1.61 (m, 2H, CHCH_2CH), 1.6-1.52 (dt, 1H, J = 2.4, 9.6, NCHCH_2), ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6 (*C*O), 158.8 (ArC_{ipso}), 131.5 (ArC_{ipso}), 128.6 (Ar*C*), 114.2 (Ar*C*), 69.1 (*C*HOH), 55.3 (OCH_3), 50.8 (N*C*H), 44.8 (NCH_2), 39.6 (Ar*C*H), 38.1 (HOCHCH_2), 30.6 (NCOCH_2), 24.7 (NCHCH_2); MS (APCI, pos.): m/z 262 (M+1); HRMS (EI): m/z 261.1364 (261.1365 calc. for $C_{15}H_{19}NO_3$ (M^+).

(6*R*,8a*S*)-Hexahydro-6-(4-methoxyphenyl)indolizine-3,7-dione (282):

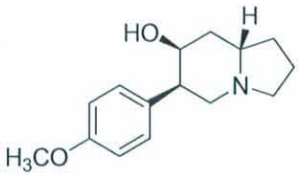


To a stirred solution of the alcohol **281** (0.20 g, 0.77 mmol) in dichloromethane (7 mL) was added DMSO (3.5 mL) followed by DIPEA (1 mL) at 0 °C. Solid SO_3.pyridine (0.36 g, 2.3 mmol) was added portion wise and the mixture was stirred at 0 °C for 1 h. Water (3 mL) was added and the mixture was diluted with dichloromethane (10 mL). The mixture was washed with water (2x15 mL) and the organic layer was dried (Na_2SO_4) and concentrated to provide a brown solid which was purified by flash chromatography on silica gel (EtOAc) to provide 0.14 g (70%) of **282** as a white solid.

IR (neat): 2955, 1714, 1673, 1515, 1455, 1239, 1186, 1036, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, 2H, J = 8.7, Ar*H*), 6.90 (d, 2H, J = 8.7, Ar*H*), 4.61-4.57 (dd, 1H, J = 13.1, 6.9, ArCC*H*), 4.01-3.96 (m, 1H, NC*H*) 3.80 (s, 3H, OCH_3), 3.65-3.61 (dd, 1H, J = 12.0, 6.9, NCH_2), 3.11-3.06 (t, 1H, J = 12.5, NCH_2), 2.76-2.72 (dd, 1H, J = 3.8, 13.6, $COCH_2$), 2.56-2.46 (m, 2H, $COCH_2$, $NCOCH_2$) 2.44-2.40 (m, 2H, $NCOCH_2CH_2$, $COCH_2CH_2$), 1.83-1.79 (m, 1H, $COCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (*C*O), 173.5 (N*C*O), 159.1 (Ar*C*OCH_3), 130.0 (Ar*C*H), 126.4 (Ar*C*), 114.1 (Ar*C*H), 57.2 (N*C*H), 55.3 (OCH_3), 54.9 (ArC*C*H), 48.6 (NCH_2), 45.1 ($COCH_2$), 29.7 ($NCOCH_2$), 24.7

($COCH_2CH_2$); MS (APCI pos.): *m/z* 260.1 (M+1); HRMS (CI+): m/z 259.1214 (259.1208 calc. for $C_{15}H_{17}NO_3$ M^+).

(6*R*,7*S*,8a*S*)-Octahydro-6-(4-methoxyphenyl)indolizin-7-ol (284):

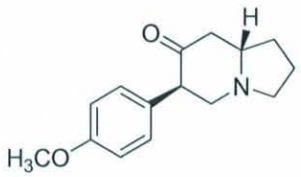


To a suspension of LAH (436 mg, 11.0 mmol) in dry THF (10 mL) at 0 °C was slowly added a solution of the lactam **281** (0.750 g, 2.87 mmol) in THF (10 mL). After stirring for an hour at 0 °C, the mixture was stirred at ambient temperature for 24 h. It was then cooled to 0 °C and water (0.210 mL, 10.0 mmol), 1N NaOH (0.210 mL, 10.0 mmol) and water (0.620 mL, 0.030 mol), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and washed with dichloromethane. The combined filtrates were dried (Na_2SO_4) and concentrated to provide 638 mg, (90%) of **284** as a pale yellow gum. This material was pure by ^1H NMR (500 MHz) and was directly used further.

IR (neat): 3345, 2909, 2831, 1738, 1610, 1511, 1461, 1243, 1177, 1033, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, 2H, *J* = 8.6, Ar*H*), 6.89 (d, 2H, *J* = 8.6, Ar*H*), 4.07 (brm, 1H, C*H*OH), 3.80 (s, 3H, OCH_3), 3.09-3 (m, 3H, ArC*H*, ArCHCH_2, NCH_2), 2.74-2.70 (t, 1H, *J* = 10.8, NCH_2), 2.35-2.31 (m, 1H, NC*H*), 2.27-2.22 (q, 1H, *J* = 8.9,

ArCHCH_2), 2.15-2.11 (ddd, 1H, J = 2.7, 5.6, 13.4, HOCHCH_2), 1.88-1.85 (m, 2H, CH_2CH_2CH), 1.79-1.73 (m, 1H, CHCH_2CH_2), 1.63-1.57 (ddd, 1H, J = 13, 12, 3, CH_2CHOH), 1.43-1.39 (m, 1H, CHCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5 (ArC_{ipso}), 132.9 (ArC_{ipso}), 129.0 (Ar*C*), 114.1 (Ar*C*), 69.4 (*C*HOH), 57.3 (N*C*H), 55.3 (OCH_3), 54.0 (NCH_2CH), 51.1 (NCH_2Ar), 46.4 (Ar*C*H), 37.6 (HO*C*HCH_2), 30.1 (NCH*C*H_2), 21.2 (NCH$_2$*C*H_2); MS (APCI, pos.): m/z 248.1 (M+1); HRMS (CI): m/z 247.1569 (247.1572 calc. for $C_{15}H_{21}NO_2$ (M+)), 248.1653 (248.1651 calc. for $C_{15}H_{22}NO_2$ (M+H).

(6*R*)-Hexahydro-6-(4-methoxyphenyl)indolizin-7(1H)-one (213):

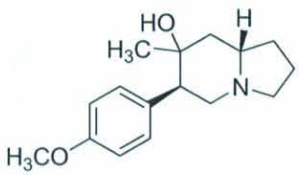


To a stirred solution of the amino alcohol **284** (0.740 g, 2.99 mmol) in dichloromethane (26 mL) was added DMSO (13 mL) followed by diisopropylethylamine (4.0 mL) at 0 °C. Solid SO_3.pyridine (1.43 g, 8.98 mmol) was added in portions and the mixture stirred at 0 °C for 1 h. Water (10 mL) was added and the mixture was diluted with dichloromethane (50 mL). The phases were separated and the organic layer was washed with water (3 x 20 mL), dried (Na_2SO_4) and concentrated to provide 0.690 g (94%) of the aminoketone **213** as a cream-coloured solid. This material was pure by ^{1}H

NMR (500 MHz) and was directly used further. An analytical sample was obtained by flash chromatography on silica gel (ethylacetate).

IR (neat): 2920, 1652, 1510, 1451, 1242, 1173, 1026, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, 2H, *J* = 8.7, Ar*H*), 6.89 (d, 2H, *J* = 8.7, Ar*H*), 3.82-3.75 (m, 1H, ArC*H*), 3.81 (s, 3H, OCH_3), 3.48-3.45 (dd, 1H, *J* = 6.3, 11, ArCHCH_2), 3.2-3.16 (dt, 1H, *J* = 2.1, 8.6, NCH_2), 2.67-2.63 (d, 1H, *J* = 10.7, CH_2CO), 2.58-2.53 (t, 1H, *J* = 11.3, NCH_2), 2.49-2.44 (m, 2H, COCH_2, NC*H*), 2.31-2.25 (q, 1H, *J* = 8.9, NCH_2), 2.04-1.99 (m, 2H, CHCH_2, CHCH$_2$CH_2), 1.88-1.84 (m, 1H, CHCH$_2$CH_2), 1.64-1.58 (m, 1H, CHCH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.9 (*C*O), 158.5 (ArC_{ipso}), 130.0 (Ar*C*), 128.3 (ArC_{ipso}), 113.7 (Ar*C*), 64.7 (N*C*H), 57.9 (CO*C*H), 55.2 (OCH_3), 55.0 (NCH_2), 52.7 (ArCH*C*H$_2$), 47.0 (COCH_2), 31.3 (NCH*C*H$_2$), 22.3 (NCH$_2$*C*H$_2$); MS (APCI, pos.): m/z 246.1 (M+1); HRMS (CI): m/z 245.1413 (245.1416 calcd for $C_{15}H_{19}NO_2$ (M+), 246.1488 (246.1494 calc. for $C_{15}H_{20}NO_2$ (M+H)).

(6*R*,7*S*,8a*S*)-Octahydro-6-(4-methoxyphenyl)-7-methylindolizin-7-ol (214):

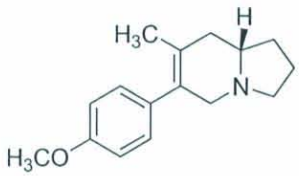


To a stirred solution of the ketone **213** (0.300 g, 1.00 mmol) in dry THF (5 mL) was added methyllithium (1.6 M in diethyl ether, 3.8 mL, 7.00 mmol) at 0 °C and the

mixture was stirred for 30 min. The reaction mixture was then stirred at ambient temperature for 24 h. Saturated, aqueous NH_4Cl (3 mL) was added, the mixture was basified with aqueous NaOH (5%) and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/ethylacetate 4/1, 1% triethylamine)[2] to provide 0.240 g, (75%) of **214** as a white crystalline solid.

IR (neat): 2955, 2807, 1609, 1507, 1452, 1361, 1294, 1168, 1122, 1031, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.2 (d, 2H, J = 8.6, Ar*H*), 6.87 (d, 2H, J = 8.6, Ar*H*), 3.8 (s, 3H, OCH_3), 3.09-3.05 (dt, 1H, J = 1.8, 10.5, ArC*H*), 2.95-2.93 (dd, 1H, J = 3.9, 10.6, NCH_2), 2.84-2.81 (dd, 1H, J = 3.9, 11.9, NCH_2), 2.69-2.65 (t, 1H, J = 9, NCH_2), 2.4-2.34 (m, 1H, NC*H*), 2.25-2.2 (q, 1H, J = 8.9, NCH_2CH_2), 1.98-1.95 (dd, 1H, J = 2.6, 13.3, HOCHCH_2), 1.89-1.85 (m, 2H, NCHCH_2), 1.83-1.75 (m, 1H, OHCHCH_2), 1.49-1.39 (m, 2H, $CH_2CH_2CH_2$), 1.05 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6 (ArC_{ipso}), 131.8 (ArC_{ipso}), 130.3 (Ar*C*), 113.7 (Ar*C*), 70.4, (OH*C*), 59.5 (N*C*H), 55.2 (NCH_2CH_2), 53.7 (OCH_3), 53.6 (NCH_2CH), 51.3 (ArC*H*), 44.2 (HOCCH_2), 30.1 (NCHCH_2), 29.6 (NCH$_2$CH_2), 21.3 (CH_3); MS (APES, pos.): m/z 262.0 (M+1).

(*S*)-1,2,3,5,8,8a-Hexahydro-6-(4-methoxyphenyl)-7-methylindolizine (285):

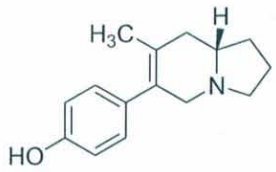


A solution of the amino alcohol **214** (0.135 g, 0.520 mmol) in dry THF (5 ml) was cooled to -50 °C and pyridine (0.210 mL, 2.59 mmol) and thionyl chloride (94.0 μL, 1.29 mmol) were added. The reaction mixture was allowed to warm to 0 °C (30 min) and then maintained at 0 °C for 30 min. Aqueous NaOH (5%) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined oraganic layers were dried (Na_2SO_4) and concentrated to provide 0.120 g (95%) of **285** as a brown oil which was used further without purification.

IR (neat): 2907, 2783, 1606, 1508, 1451, 1285, 1239, 1170, 1034, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, J = 8.7, Ar*H*), 6.87 (d, 2H, J = 8.7, Ar*H*), 3.80 (s, 3H, OCH_3), 3.63 (d, 1H, J = 15.4, $ArCCH_2$), 3.24-3.2 (dt, 1H, J = 2, 10.6, NCH_2), 2.92-2.88 (d, 1H, J = 15.4, $ArCCH_2$), 2.29-2.21 (m, 2H, NC*H*, CH_3CCH_2), 2.19-2.14 (q, 1H, J = 9, CH_3CCH_2), 2.14-2.06 (m, 1H, NCH_2), 2.06-2.0 (m, 1H, $NCHCH_2$), 1.92-1.86 (m, 1H, $NCHCH_2$), 1.81-1.75 (m, 1H, NCH_2CH_2), 1.6 (s, 3H, CH_3), 1.54-1.46 (m, 1H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1 (Ar*C*), 133.8 (CH_3C=CAr), 130.4 (Ar*C*), 129.8 (Ar*C*), 127.9 (CH_3C=*C*Ar), 113.5 (Ar*C*), 60.2 (NCH), 57.9 ($ArCCH_2N$),

55.2 (OCH_3), 54.2 (NCH_2), 38.6 (CH_3CCH_2), 30.9 ($NCHCH_2$), 21.4 (NCH_2CH_2), 20.0 (CH_3); MS (API-ES, pos.): m/z 244.1 (M+1).

4-((*S*)-1,2,3,5,8,8a-Hexahydro-7-methylindolizin-6-yl)phenol (+)-ipalbidine (207)[9]:



To a solution of **285** (0.10 g, 0.41 mmol) in dichloromethane (2 mL) was added BBr_3 (1.0 M in dichloromethane, 0.41 mL, 0.41 mmol) at -78 °C. The reaction mixture was gradually warmed to ambient temperature and stirred for 12 h. Water (2 mL) and saturated, aqueous $NaHCO_3$ (10 mL) were added. The resulting mixture (which contained a dark, gummy material) was diluted with dichloromethane (20 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3x10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to provide a pale yellow gum. This was purified by flash chromatography on silica gel (hexanes/ethylacetate 1/1, 1% triethylamine) to provide 0.076 g (80%) of **207** as a white solid.

IR (neat): 2911, 2791, 1607, 1511, 1440, 1376, 1234, 1165, 998, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.02 (d, 2H, J = 8.7, Ar*H*), 6.78 (d, 2H, J = 8.7, Ar*H*), 3.69 (d, 1H, J = 15.6, ArCCH_2), 3.27-3.23 (dt, 1H, J = 2.1, 10.8, NCH_2), 2.99 (br d, 1H, J = 15.6, ArCCH_2), 2.38-2.33 (m, 1H, NC*H*), 2.28-2.25 (m, 1H, CH_3CCH_2), 2.22-2.15 (m, 2H,

NCH_2, CH_3CCH_2), 2.06-2.03 (m, 1H, $NCHCH_2$), 1.96 (m, 1H, $NCHCH_2$), 1.82-1.80 (m, 1H, NCH_2CH_2), 1.63-1.55 (m, 1H, NCH_2CH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6 (ArC_{ipso}), 132.4 (CH_3C=CAr), 130.0 (ArC_{ipso}), 129.7 (ArC), 128.2 (CH_3C=CAr), 115.4 (ArC), 60.6 (NCH), 57.8 ($ArCCH_2N$), 54.1 (NCH_2), 37.8 (CH_3CCH_2), 30.3 ($NCHCH_2$), 21.2 (NCH_2CH_2), 20.0 (CH_3); MS (APES, pos.): m/z 230.1 (M+1); HRMS (EI): m/z 229.1467 (229.1467 calc. for $C_{15}H_{19}NO$ (M+); $[\alpha]^{23}_D$ = + 199 (*c* 1, $CHCl_3$; Lit.[11] $[\alpha]^{25}_D$ = + 233 (*c* = 1, $CHCl_3$, for the *S* enantiomer)).

The enantiomeric ratio for (+)-ipalbidine was 97.2: 2.8 (94% ee); Chiralcel OJ-H, 2-propanol, 2-20% in hexanes, 30 min, 1.0 mL/ min, 254 nm; t_R = 13.9 min (minor); t_S = 15.2 min (major).

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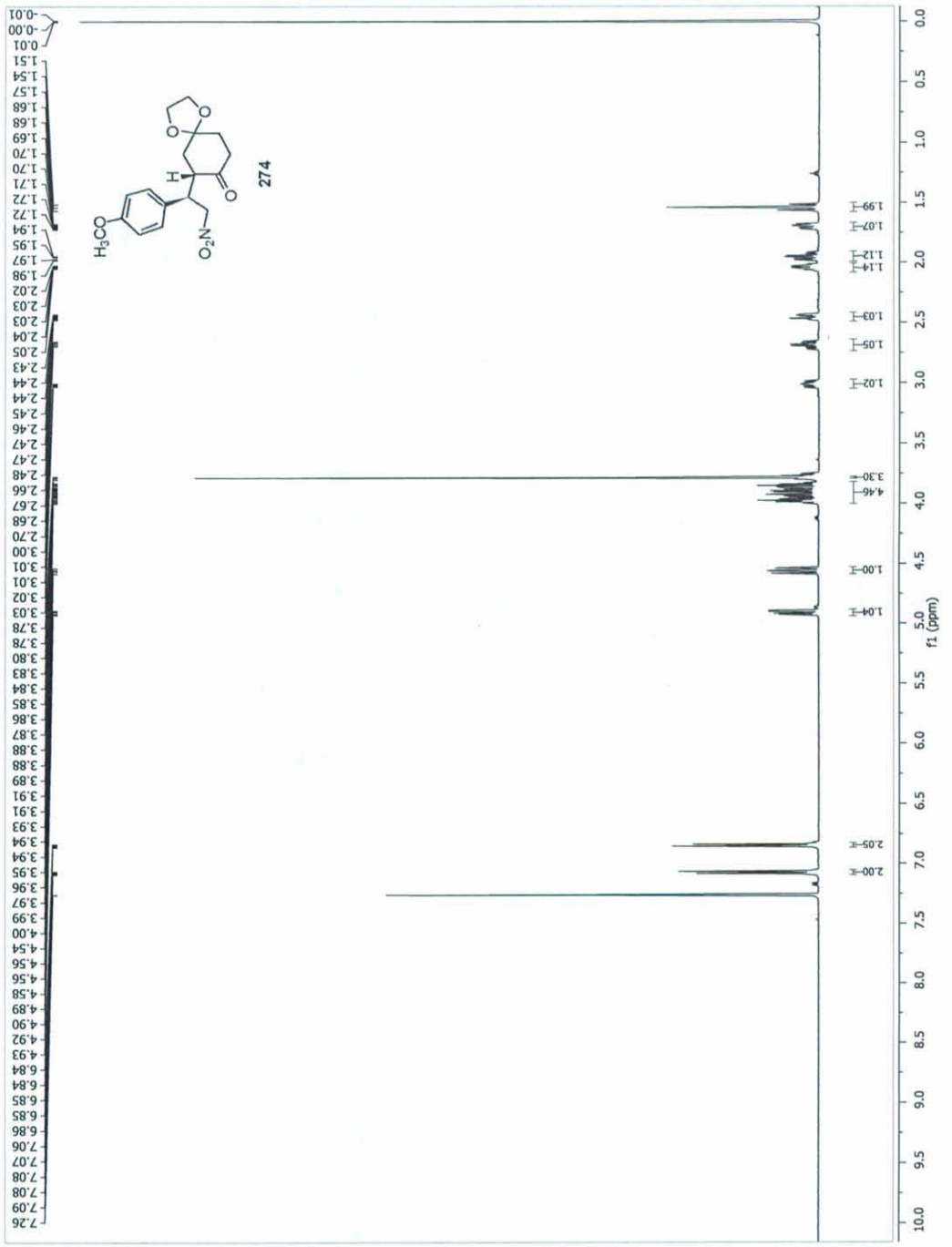
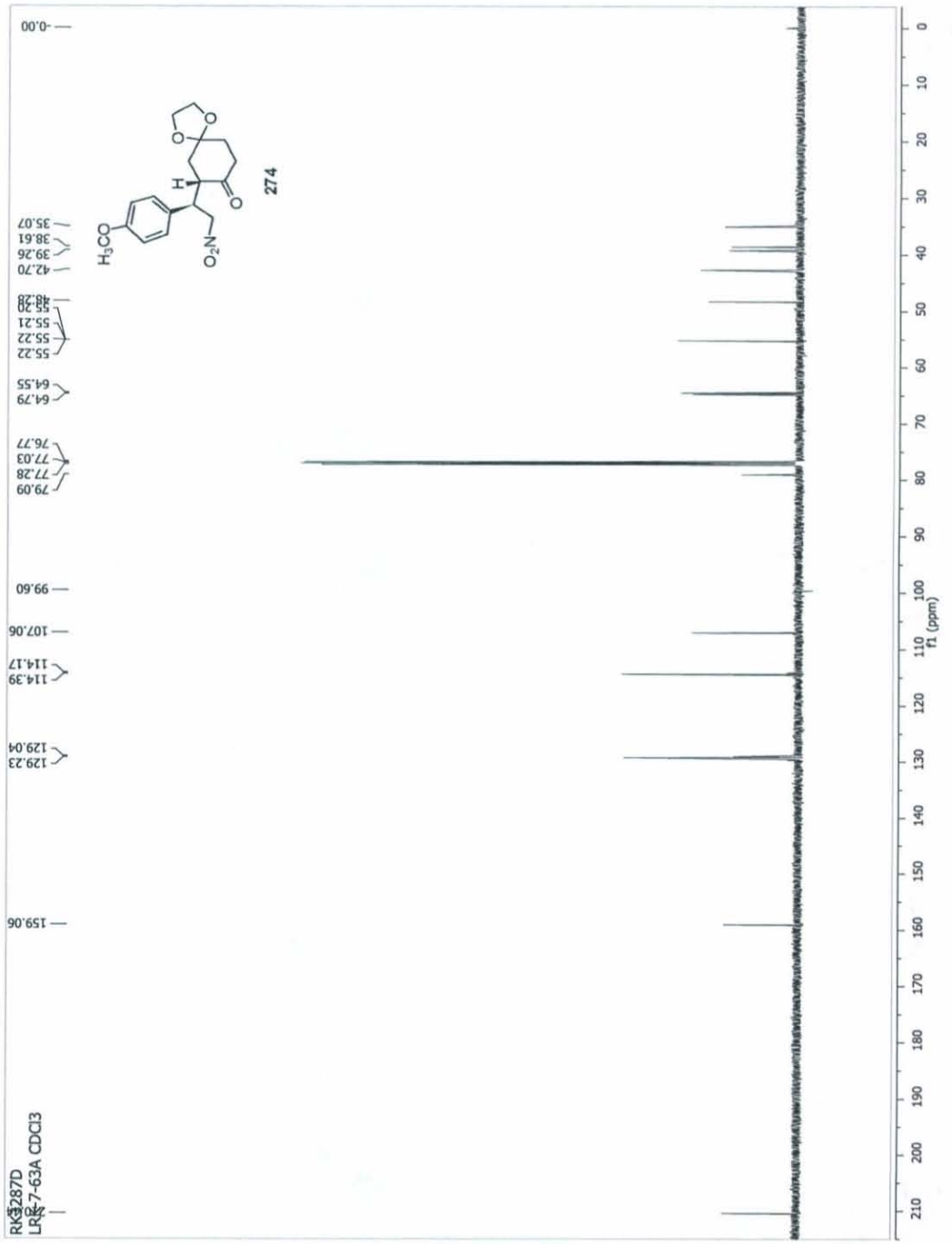
Appendix 3:

^{1}H and ^{13}C NMR Spectra for Chapter 3


H
H3CO
O2N
O
O
O
274
f1 (ppm)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LRK7-63A CDCl3
274
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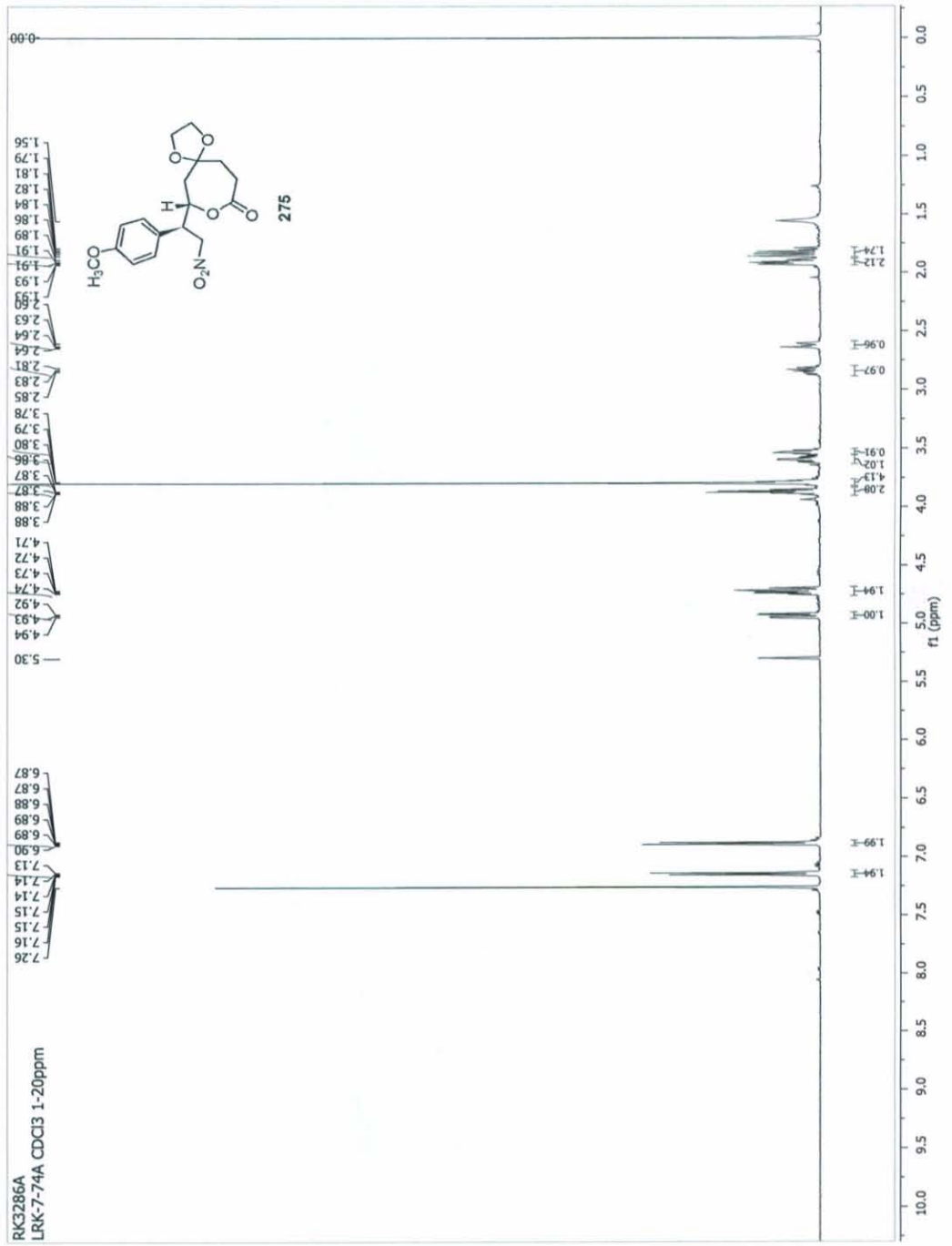
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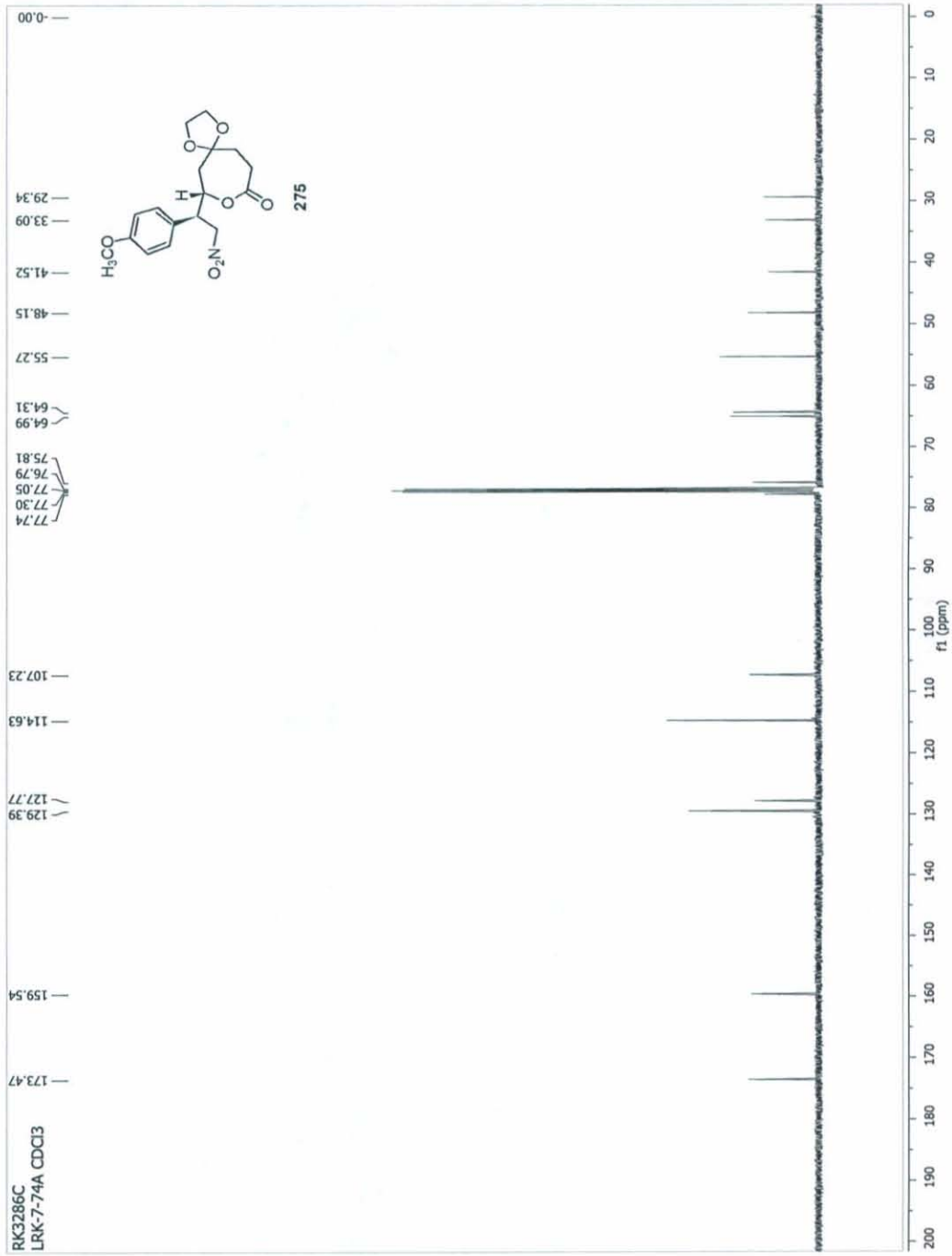
O2N
275
f1 (ppm)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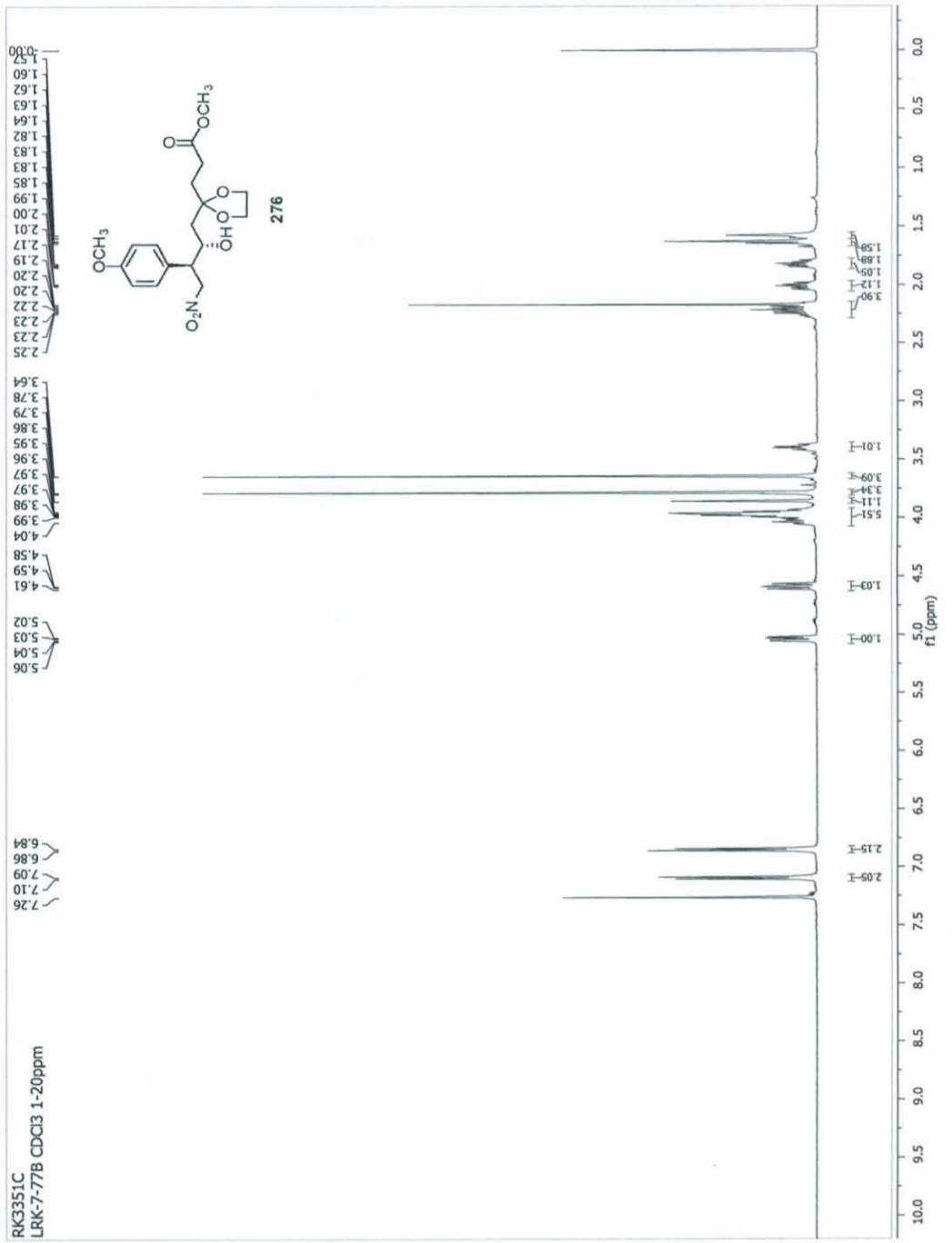
275
f1 (ppm)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276
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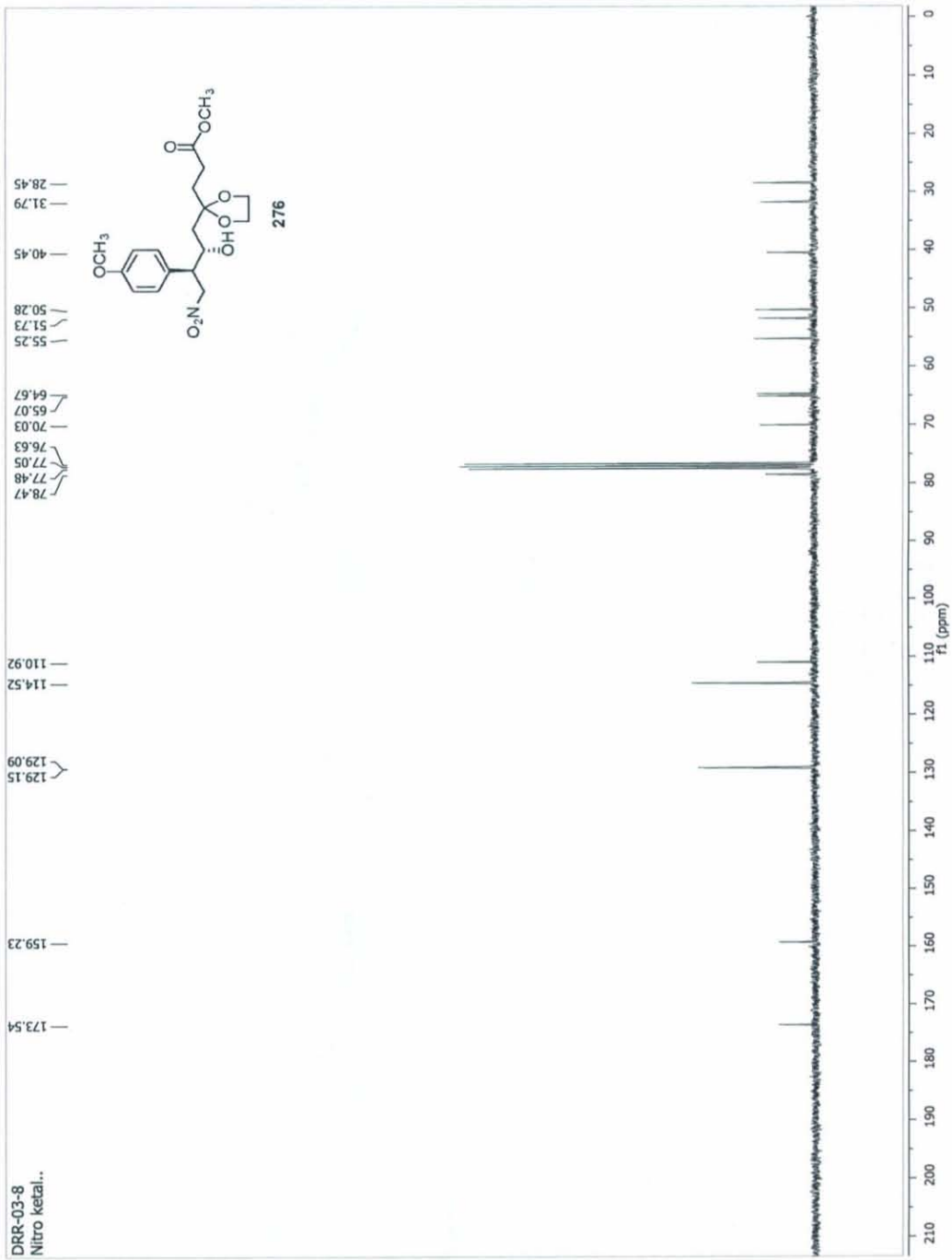
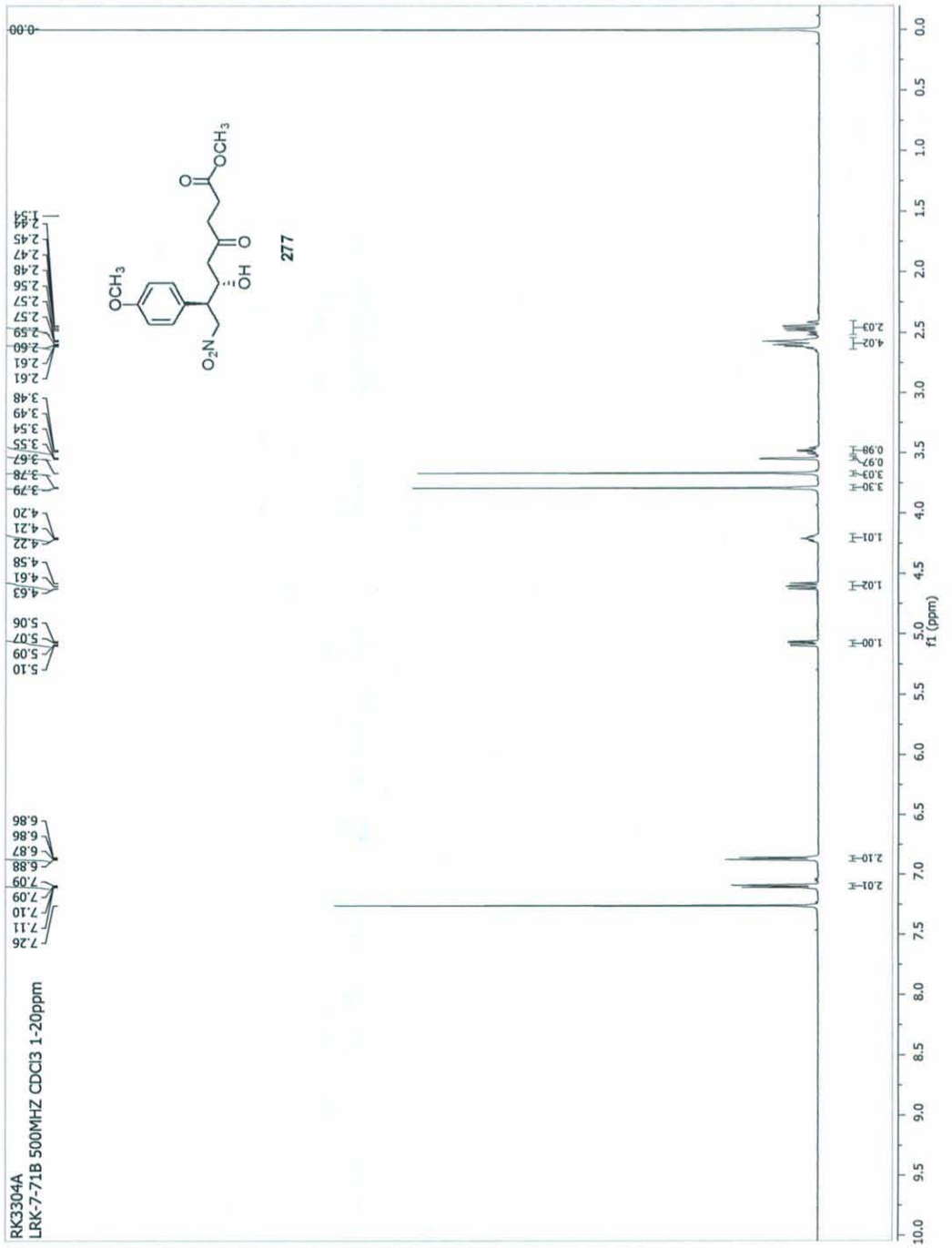

DRR-03-8
Nitro ketal...
173.54
159.23
129.15
129.09
114.52
110.92
78.47
77.48
77.05
76.63
70.03
65.07
64.67
55.25
51.73
50.28
40.45
31.79
28.45
OCH3
OCH3
O2N
OH
276
f1 (ppm)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LRK-7-71B 500MHZ CDCl3 1-20ppm
277
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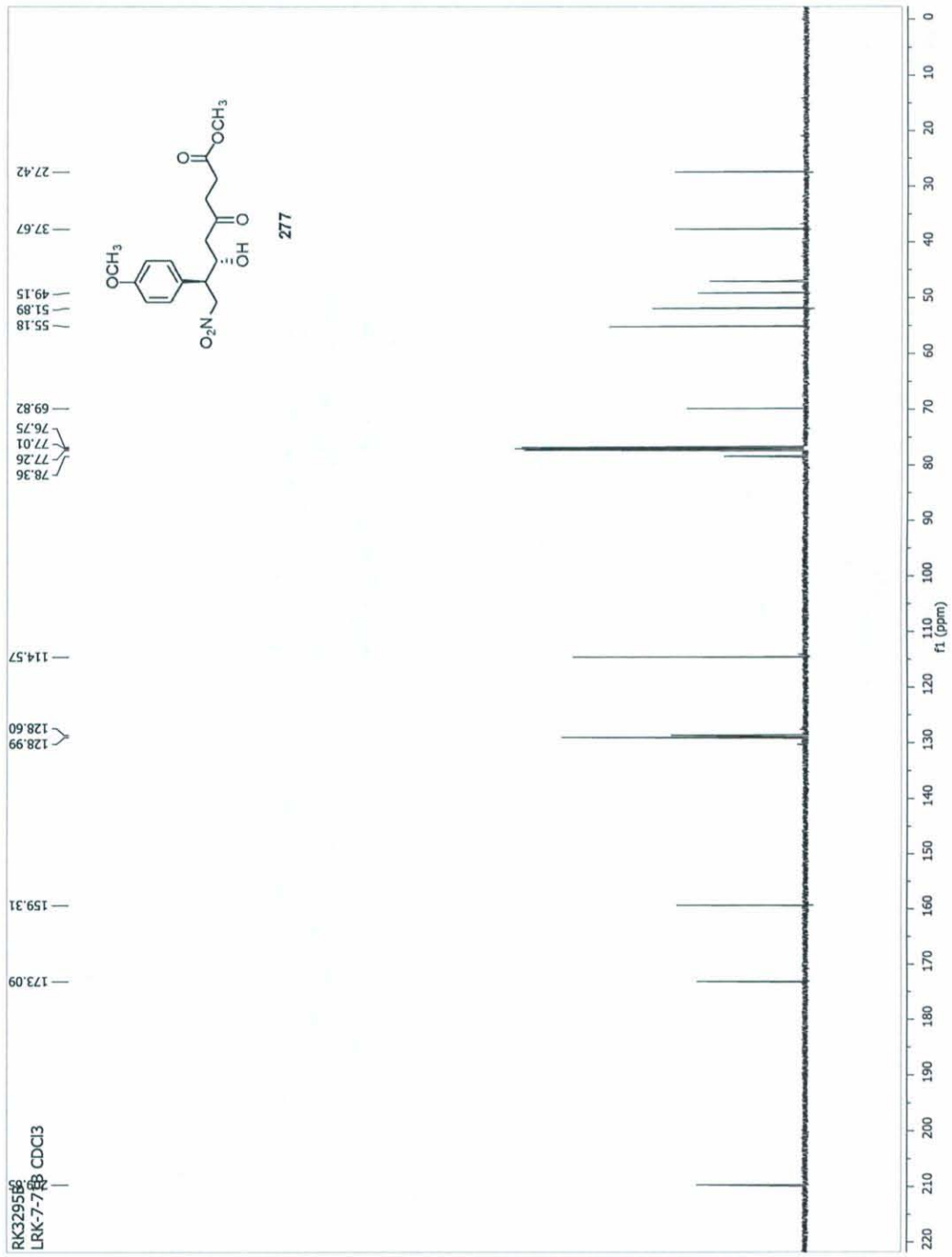
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277
27.42
37.67
49.15
51.89
55.18
69.82
76.75
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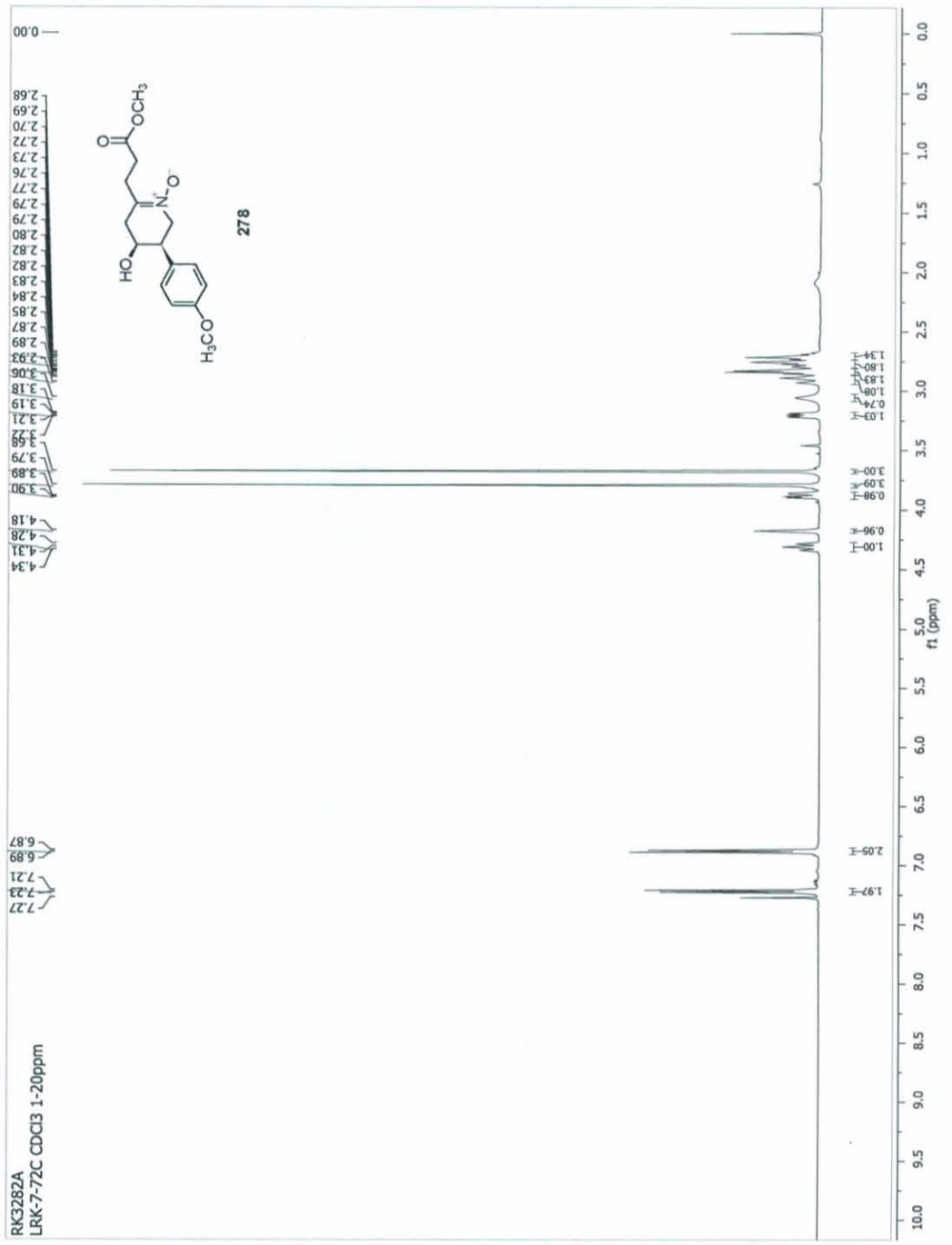
114.57
128.60
128.99
159.31
173.09
f1 (ppm)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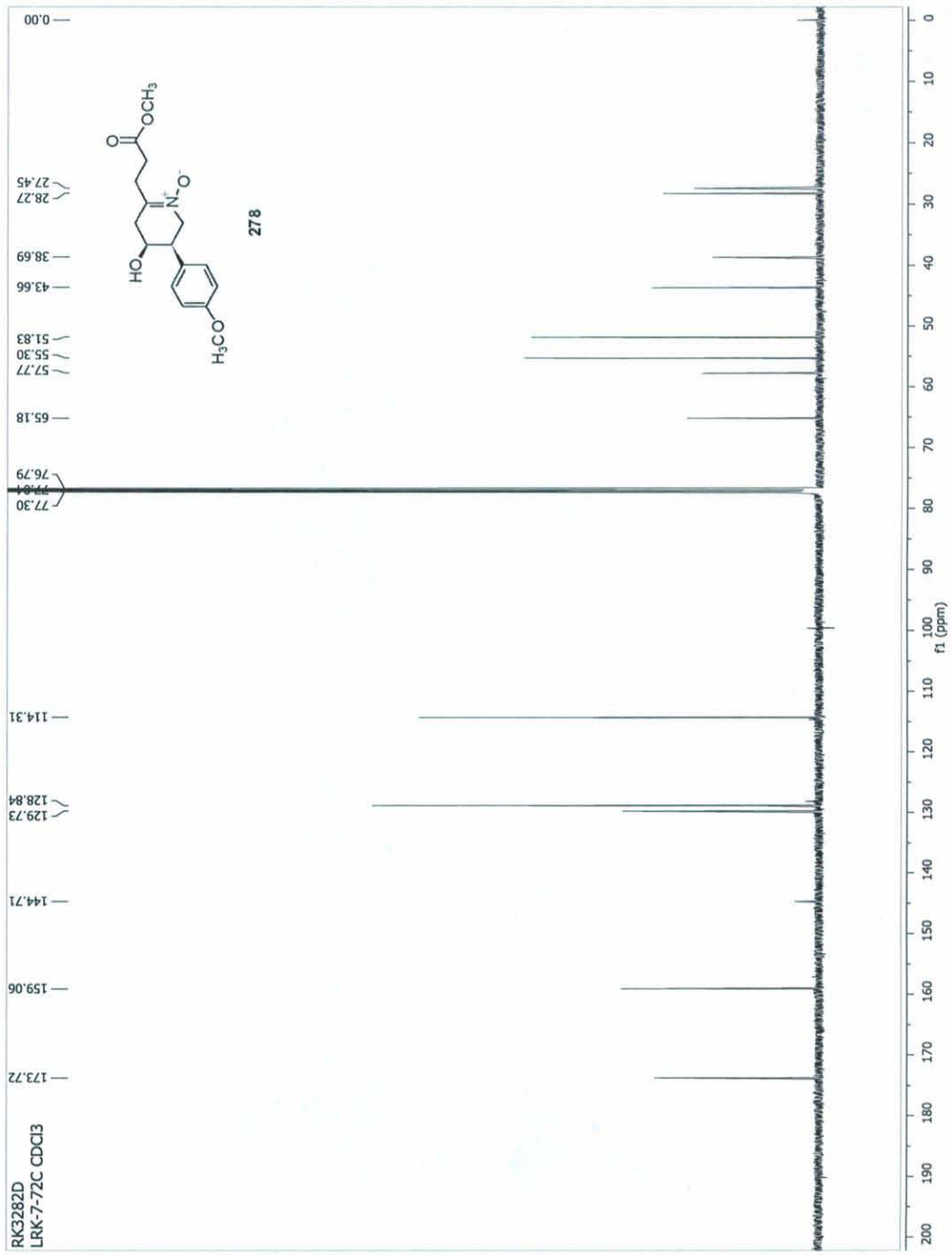
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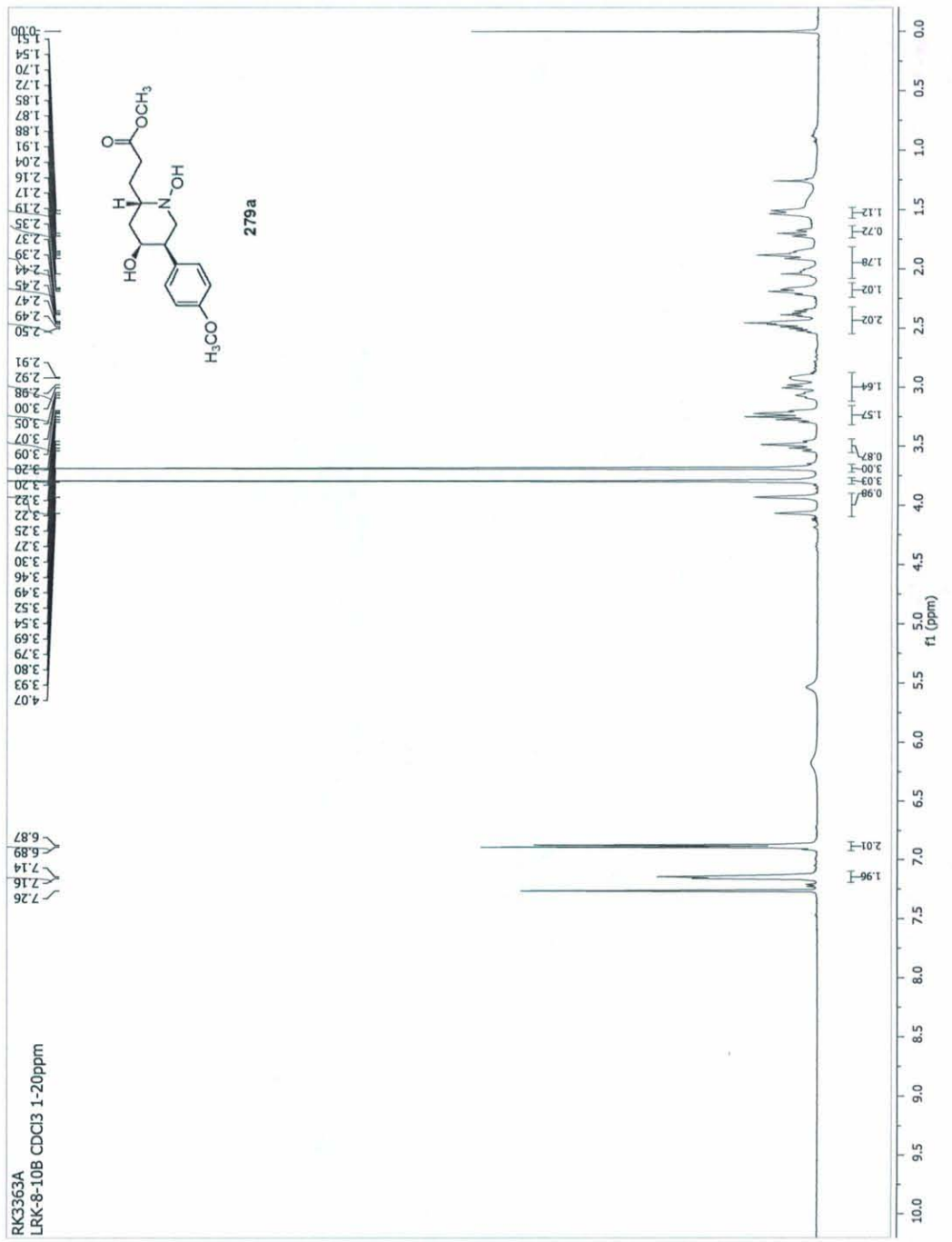
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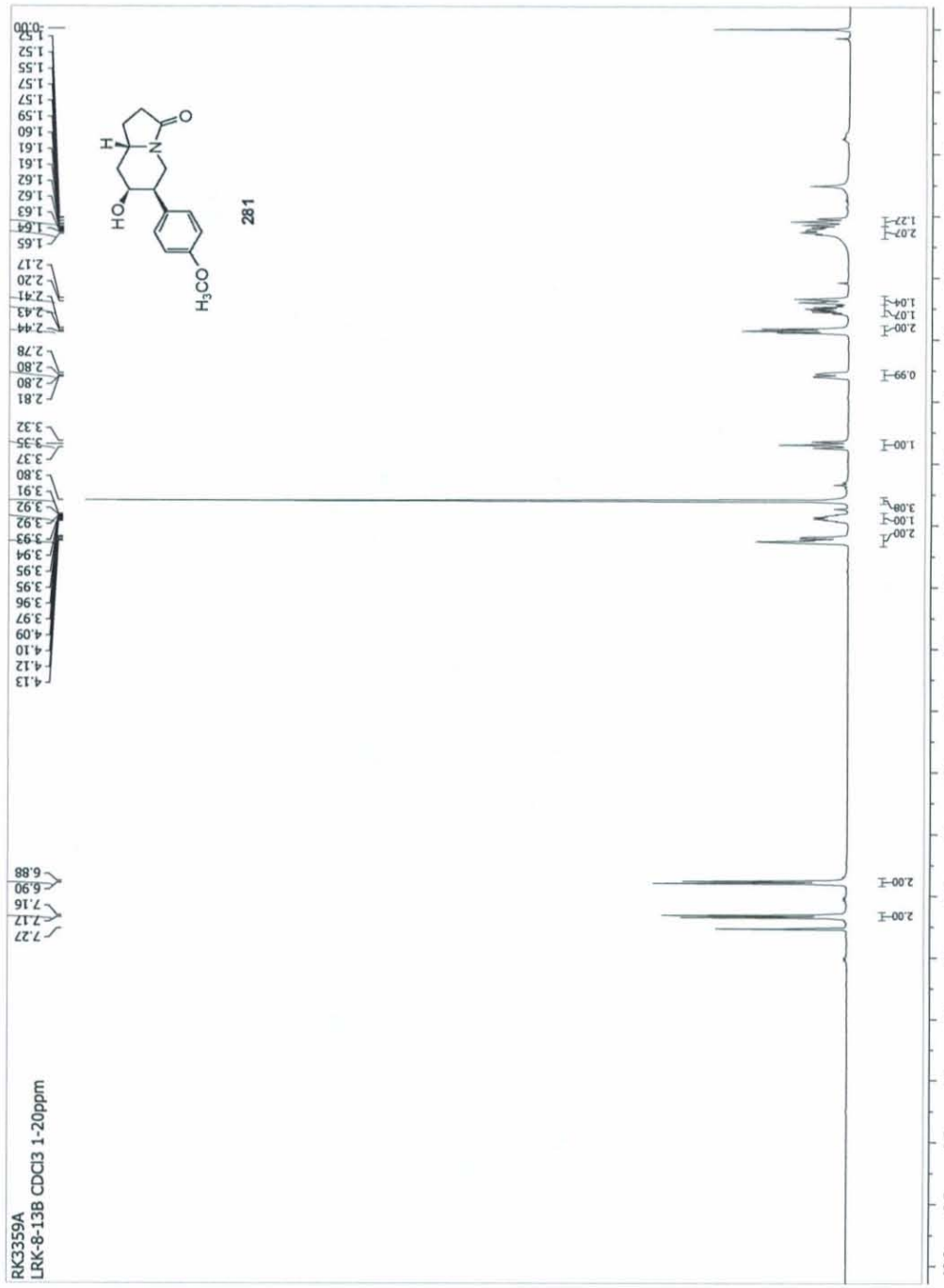
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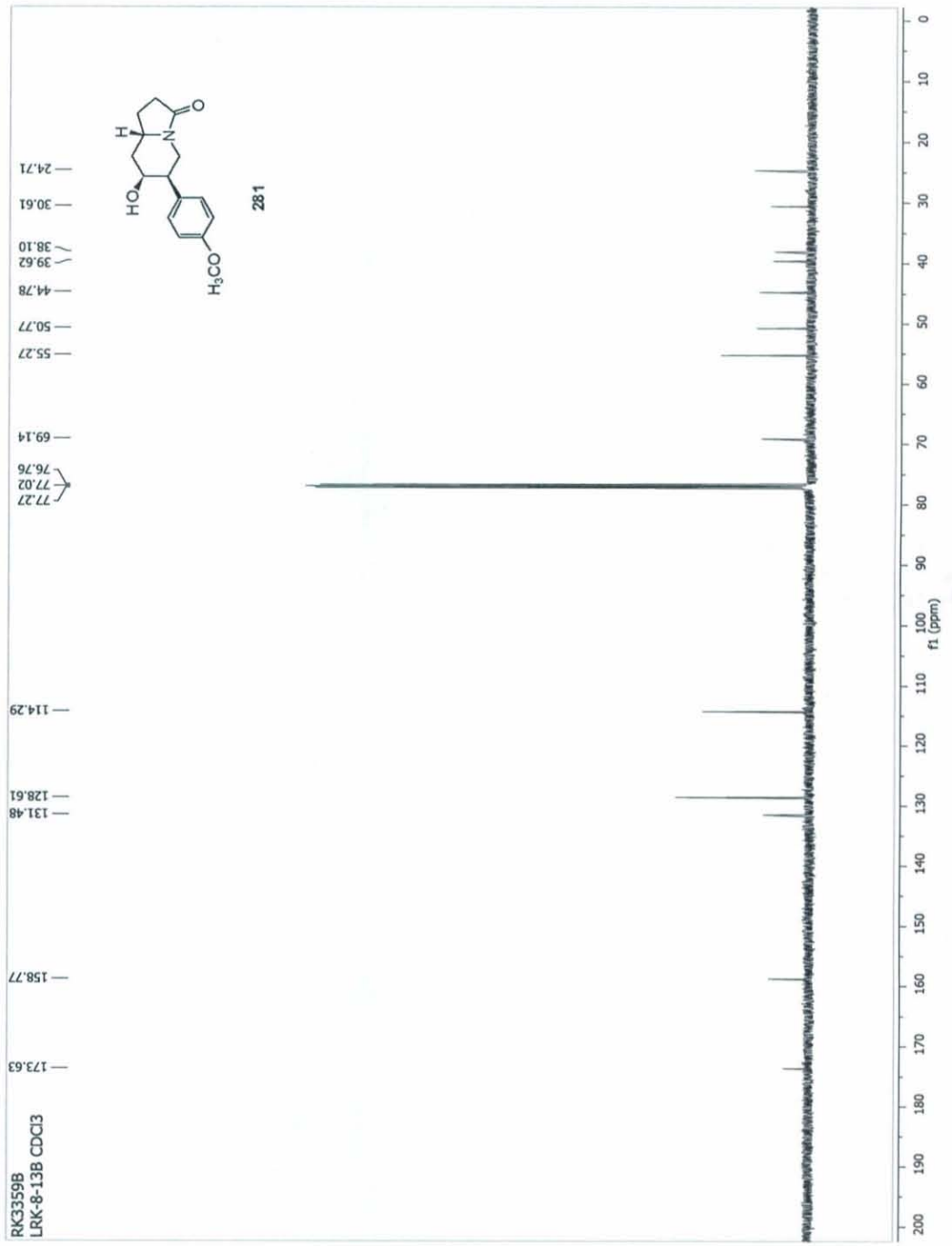
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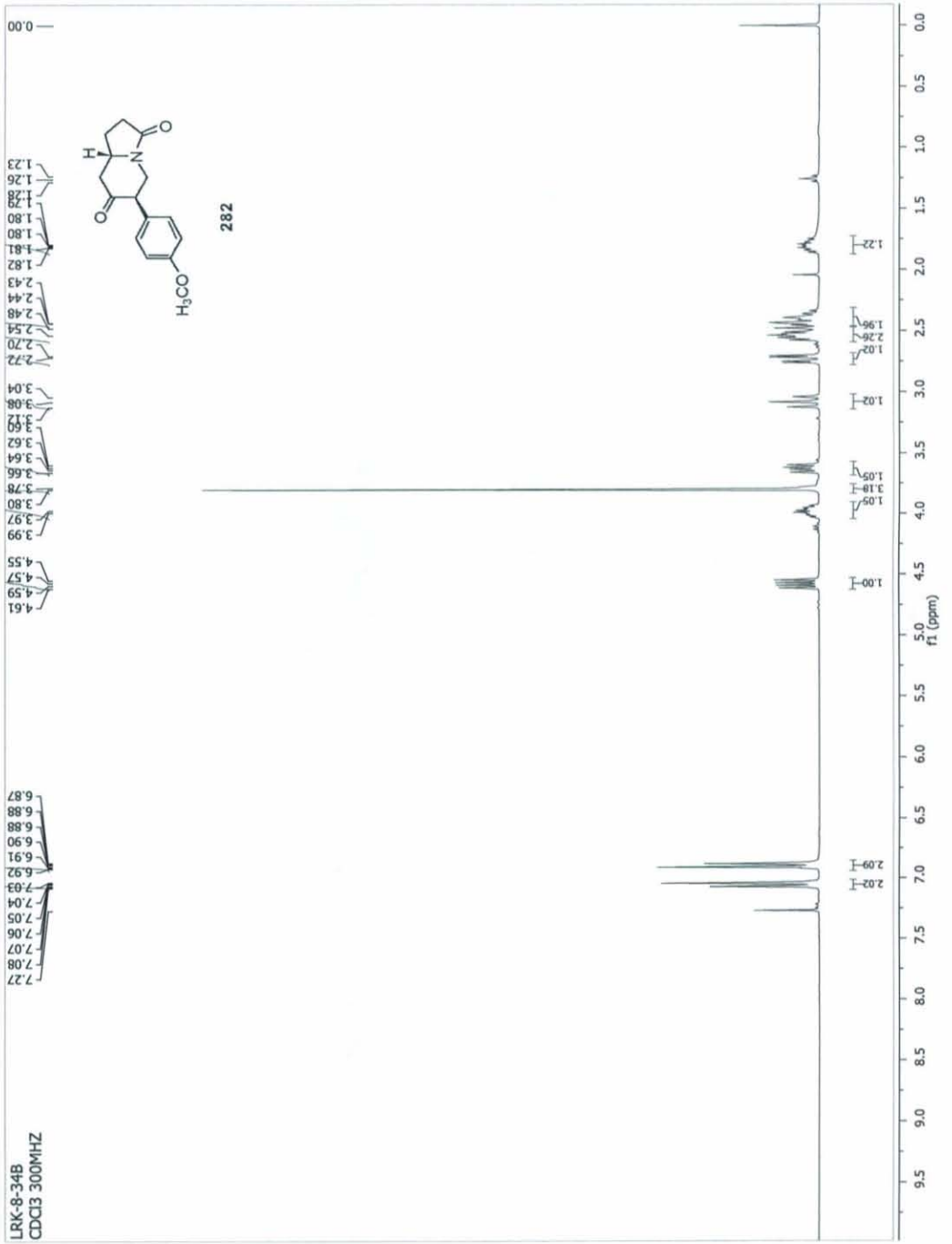
LRK-8-13B CDCl3
281
HO
H
N
O
H3CO
173.63
158.77
131.48
128.61
114.29
77.27
77.02
76.76
69.14
55.27
50.77
44.78
39.62
38.10
30.61
24.71
f1 (ppm)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CDCl3 300MHZ
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H3CO
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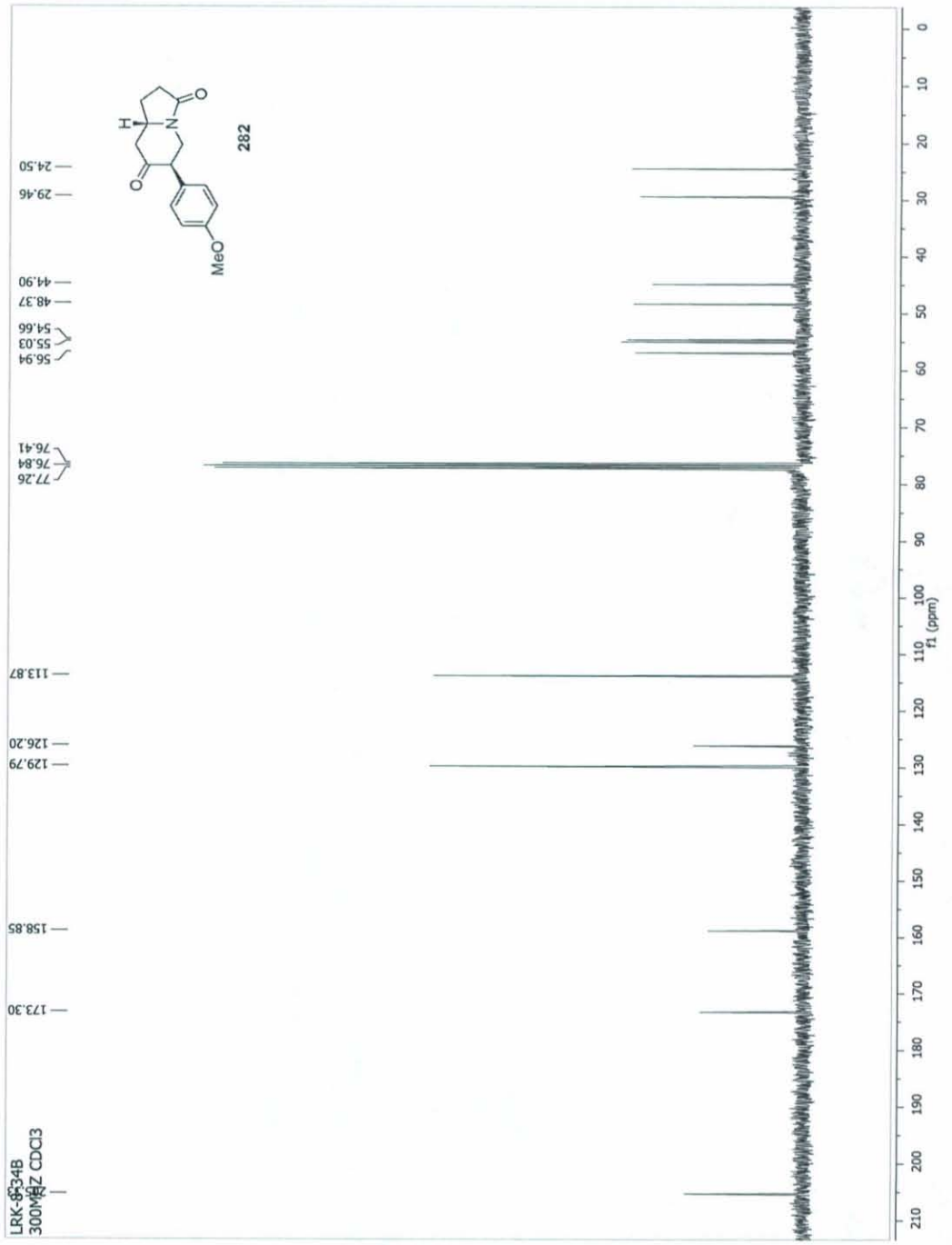
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300MHz CDCl3
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MeO
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76.41
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77.26
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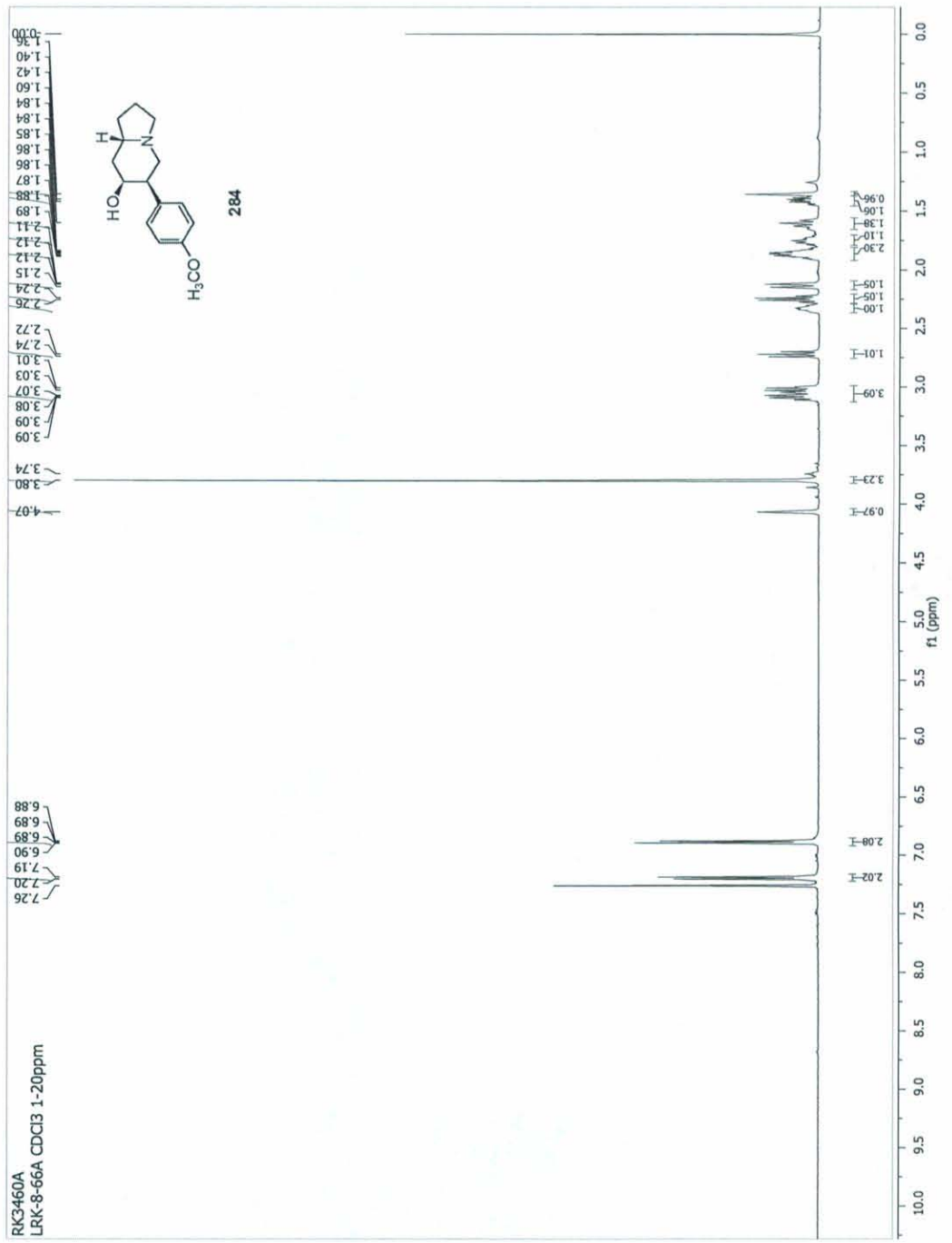
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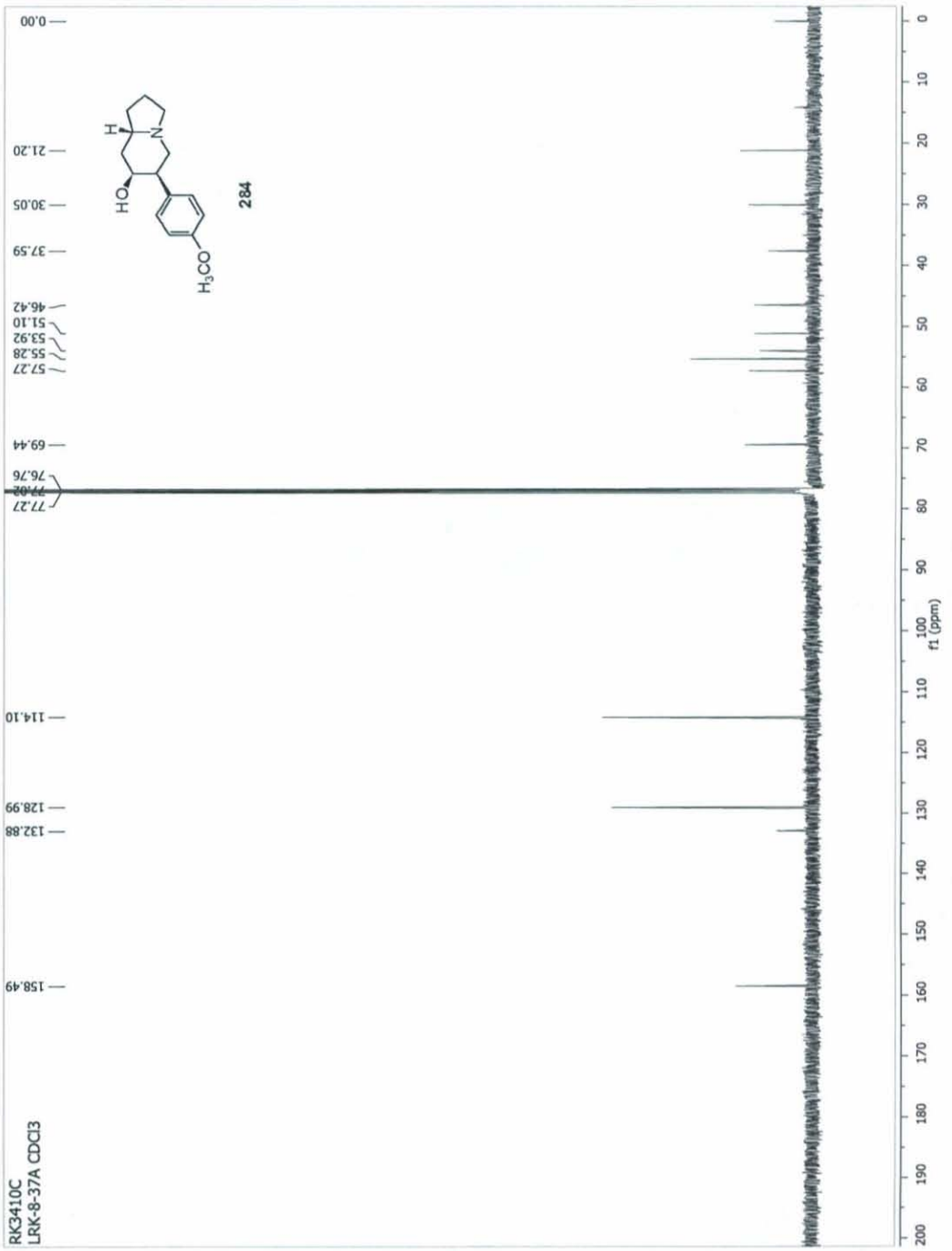
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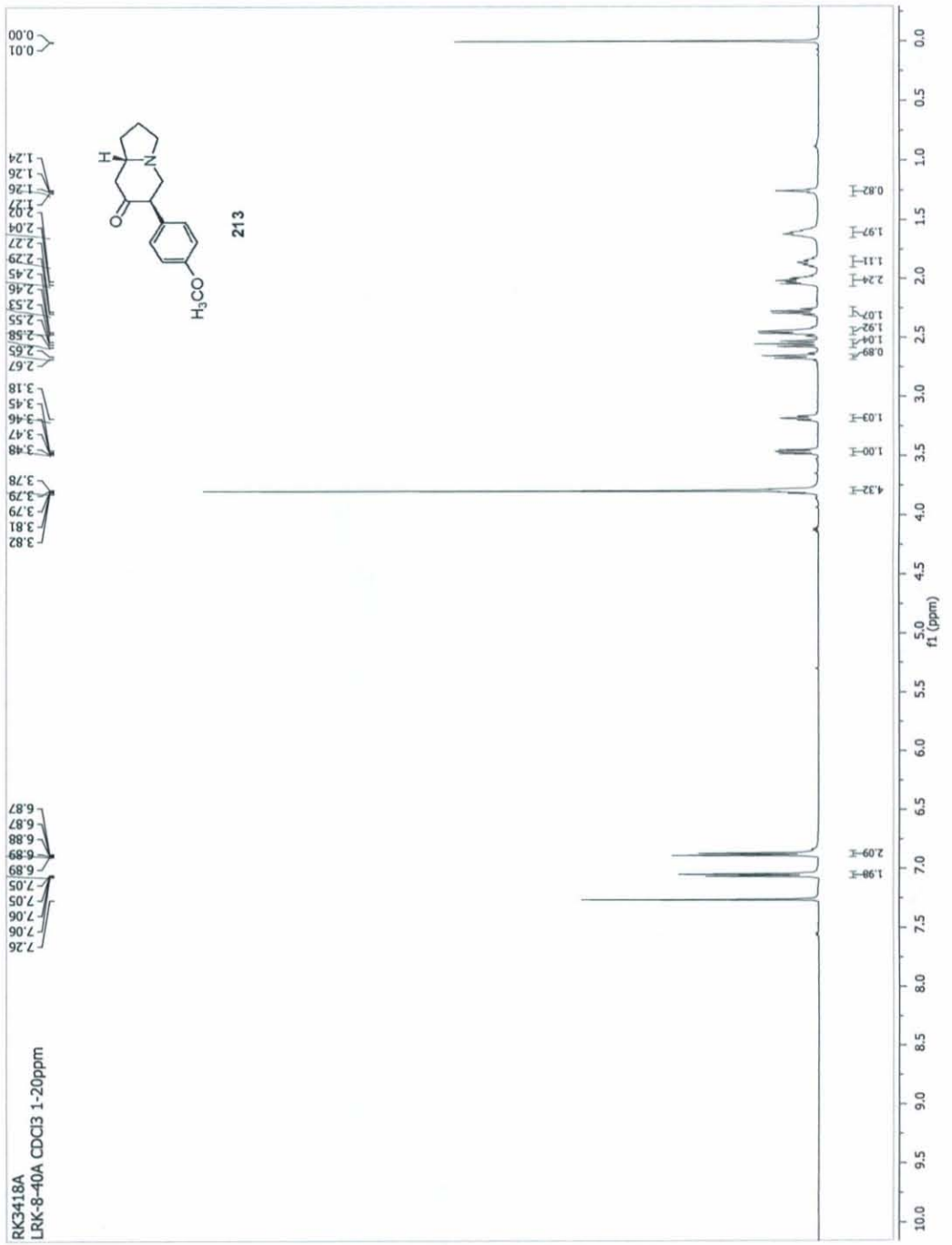
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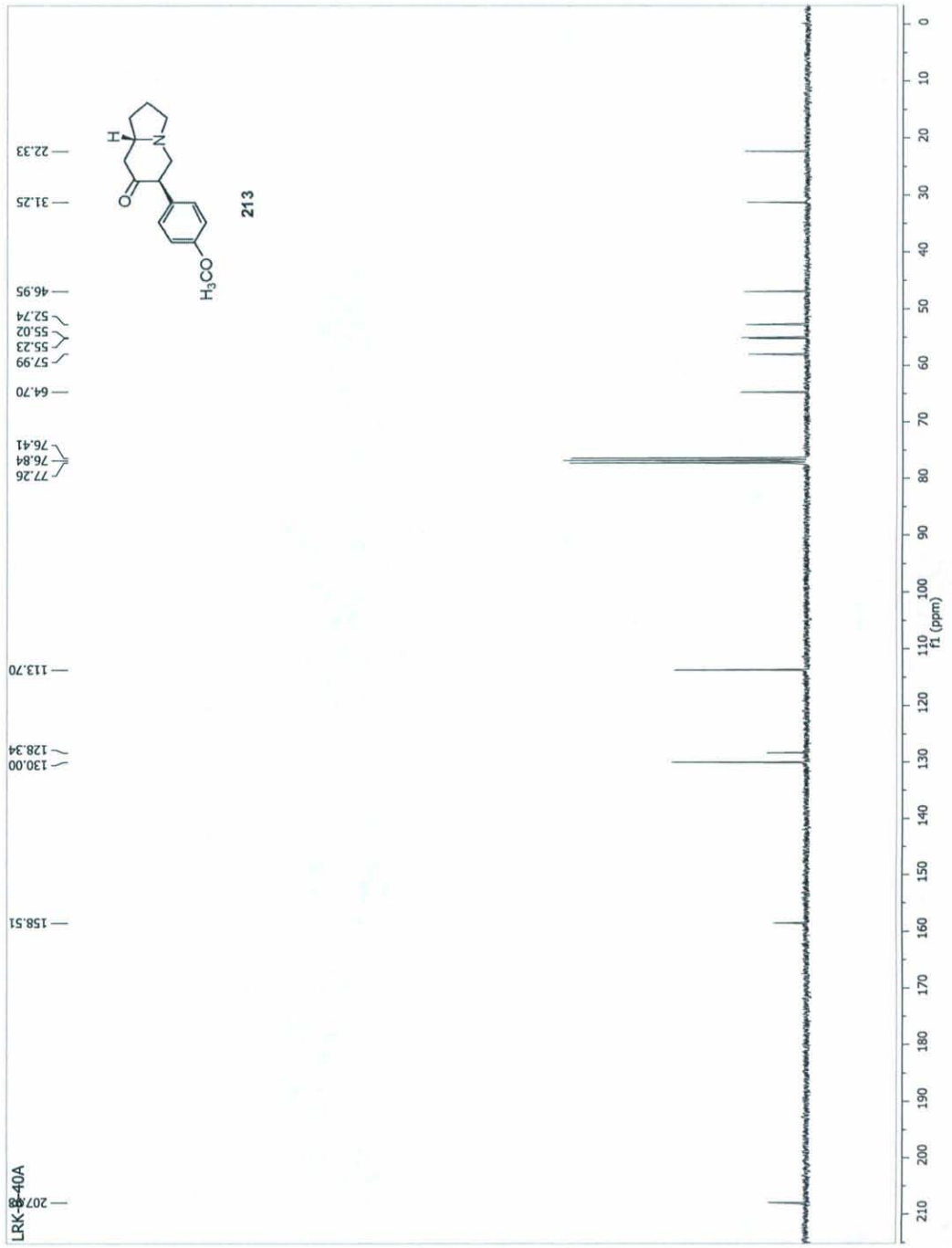
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76.41
64.70
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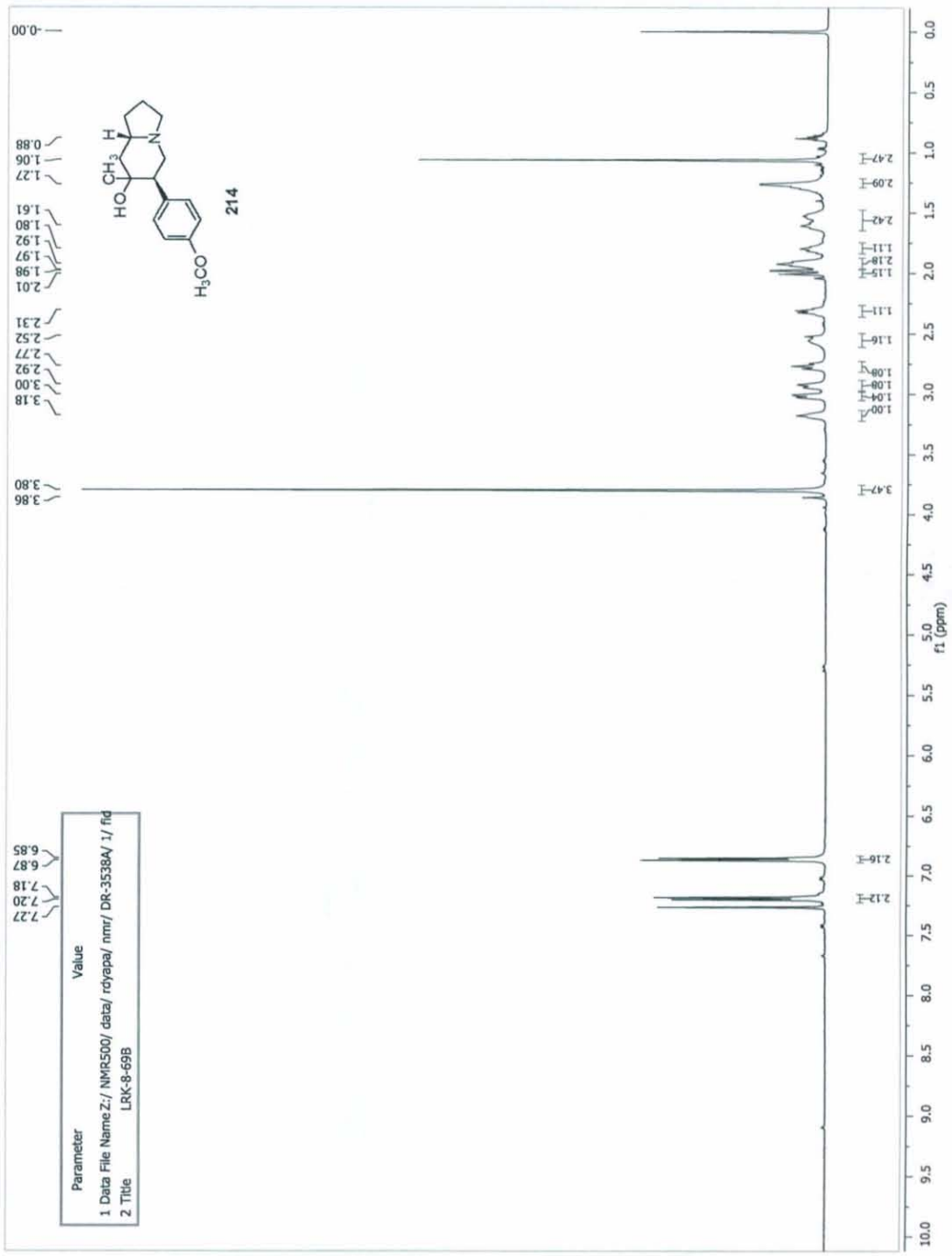
22.33
O
H
N
H3CO
213
f1 (ppm)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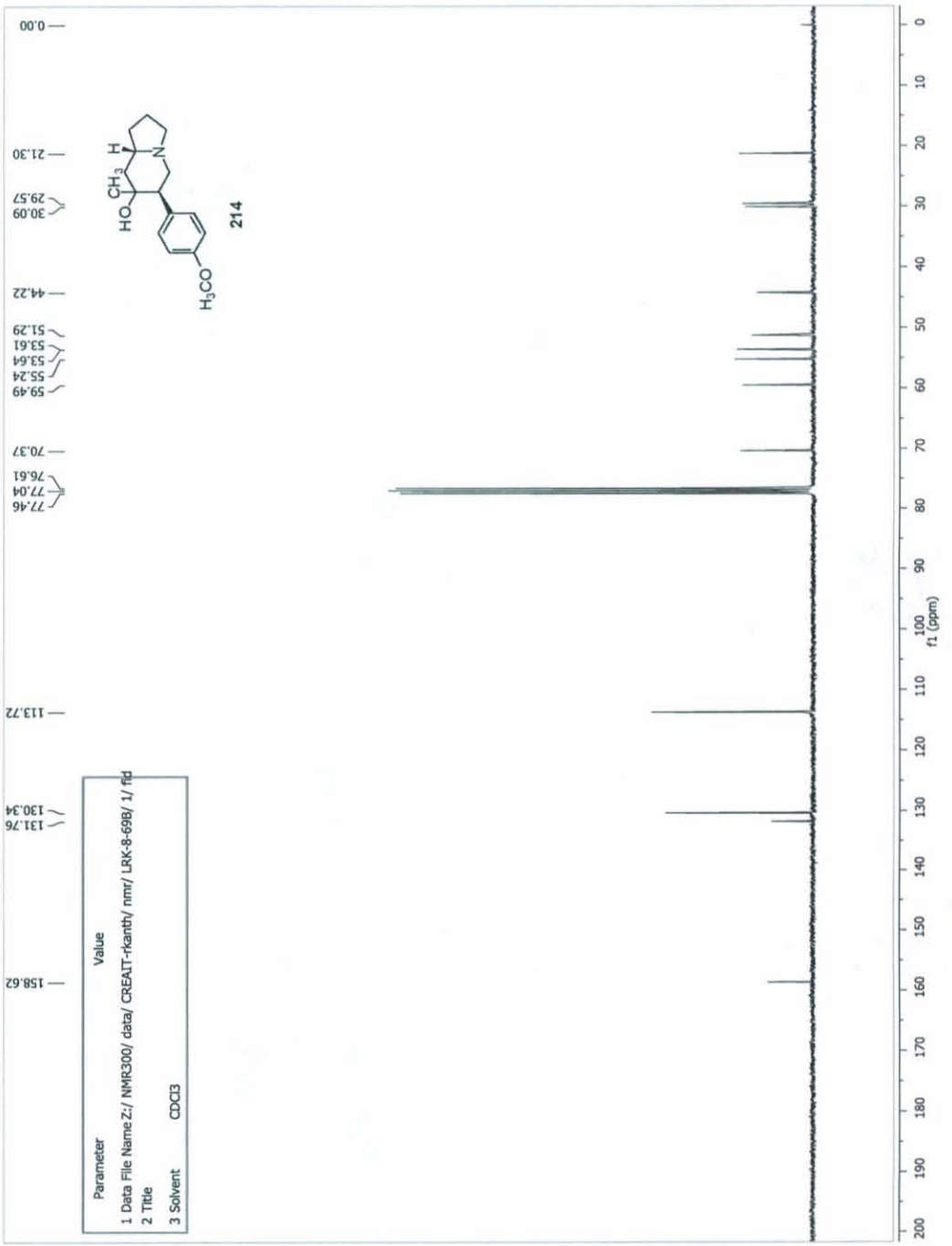
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77.04
76.61
70.37
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55.24
53.64
53.61
51.29
44.22
30.09
29.57
21.30
0.00
HO
CH3
H
N
H3CO
214
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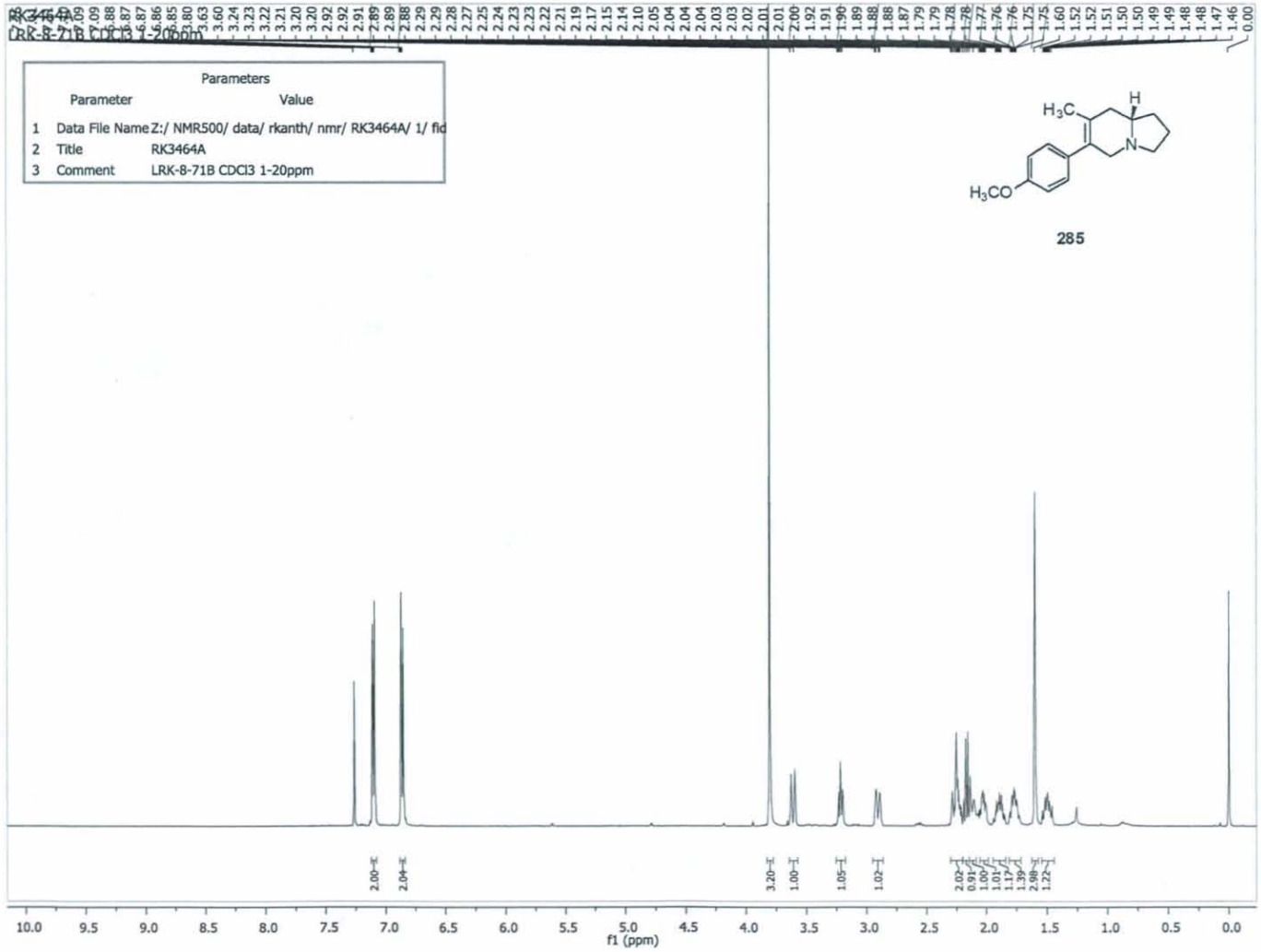
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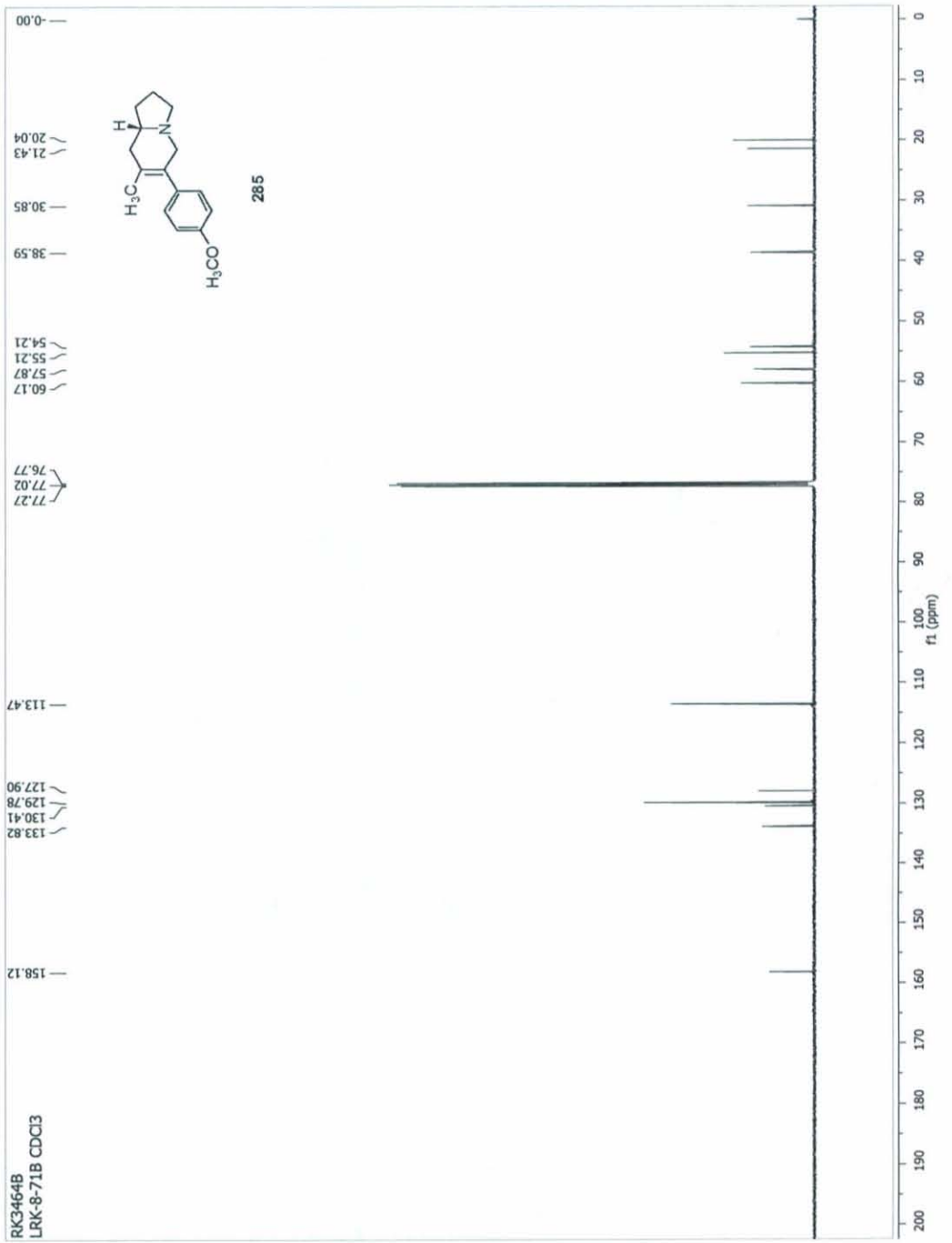
H3C
H
N
H3CO
285
2.00
2.04
3.20
1.00
1.05
1.02
2.02
0.91
1.00
1.01
1.17
1.39
2.98
1.22
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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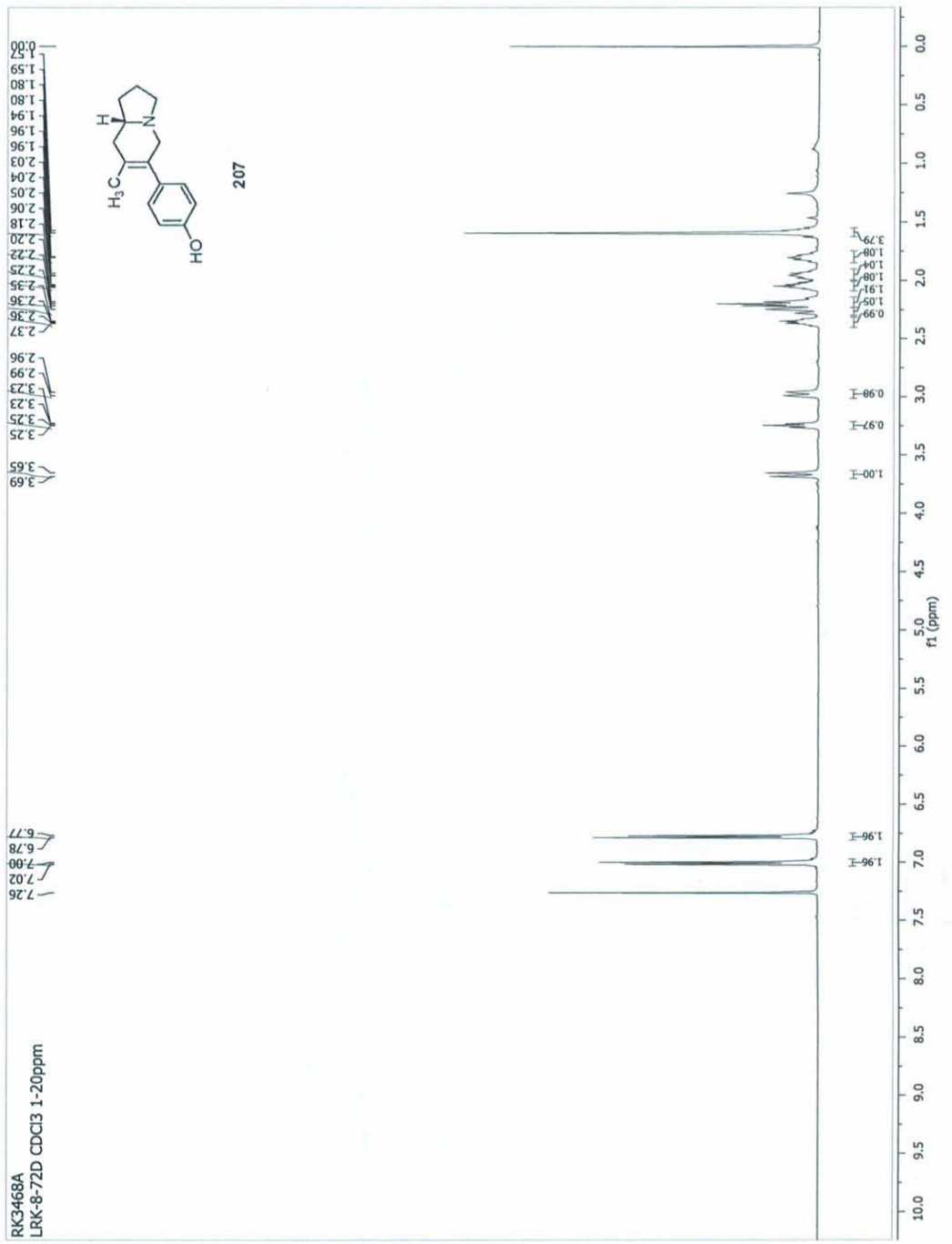
f1 (ppm)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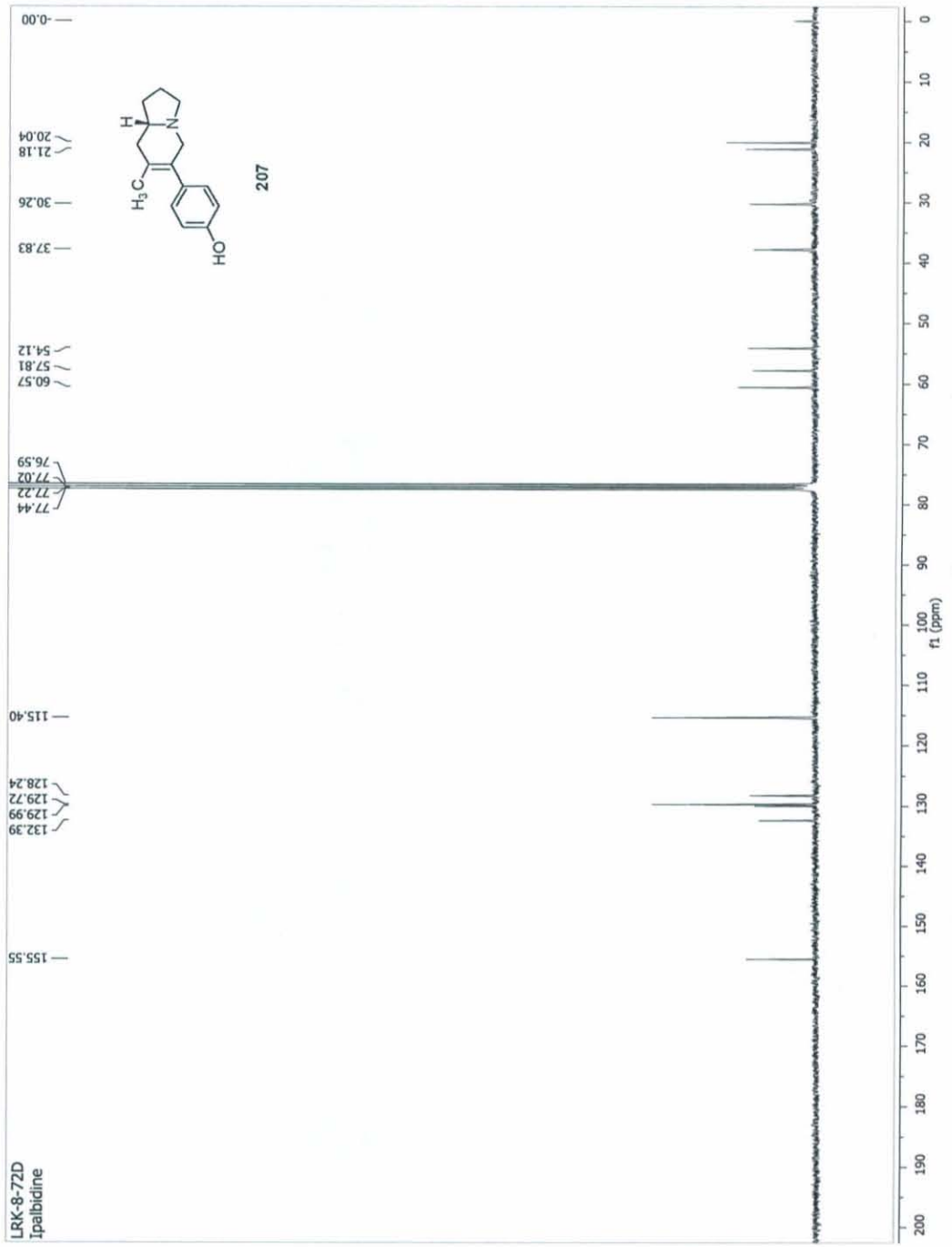
LRK-8-72D
Ipalbidine
207
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20.04
21.18
30.26
37.83
54.12
57.81
60.57
76.59
77.02
77.22
77.44
115.40
128.24
129.72
129.99
132.39
155.55
f1 (ppm)