Synthetic Studies of the Formation of Oxazoles and Isoxazoles from *N*-Acetoacetyl Derivatives: Scope and Limitations

and

Aqueous Rhodium-Catalyzed Heck-Type Coupling Reactions Between Boronic Acids and Olefins

By

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A thesis submitted in conformity with the requirements
For the degree of Master of Science
Graduate Department of Chemistry
University of Toronto

Objectives

This thesis is divided into two different parts.

The first one deals with the preparation of two types of heterocycles, oxazoles and isoxazoles, from *N*-acetoacetyl derivatives. The overall objective of this project was to develop a general method allowing the formation of these two heterocycles in a rapid and simple way by using readily accessible derivatives of oxazolidinones. The possibility of controlling the formation of each heterocycle by reacting an identical precursor under two different sets of reaction conditions was studied.

The first objective was to study the reactivity of *N*-acetoacetyl substrates bearing the chiral oxazolidinone derived from (1*R*,2*S*)-(–)-norephedrine under the two sets of conditions. To this end, substrates with various substituents on the *N*-acetoacetyl skeleton were prepared and tested. The steric and electronic effects caused by the nature of the substituents were investigated.

The second objective was to extend the methodology to substrates with various oxazolidinone auxiliaries.

The second part of this thesis deals with the aqueous rhodium-catalyzed Heck-type coupling reaction between olefins and boronic acids. The overall objective was to investigate the general scope of this coupling reaction as well as the mechanism.

The first objective was to conduct studies on the aqueous rhodium catalyzed Heck-type coupling reaction between styrene and various boronic acids. Initial investigations focused on establishing good reaction conditions that would allow the coupling reaction between styrene and various boronic acids. Mechanistic hypotheses were also investigated.

The second objective was to extend this methodology to various olefins.

The third objective was to investigate the new reactivity showed by a class of olefins, 2- and 4-vinylpyridines.

Abstract

The preparation of two types of heterocycles, oxazoles and isoxazoles, was achieved in good yields in a rapid and simple way by using *N*-acetoacetyl derivatives of oxazolidinones. Steric and electronic effects caused by the nature of the substituents at C1, C2 and C3 were studied. It was shown that, in most cases, the controlled synthesis of oxazoles or isoxazoles from the same precursor was achieved by reacting it under specific reaction conditions. The best results were obtained with a chiral oxazolidinone moiety on C1 derived from (1*R*,2*S*)-(–)-norephedrine.

The aqueous rhodium catalyzed Heck-type coupling reaction between olefins and boronic acids was studied. It was shown that the reaction works only when water is the only solvent and that the presence of an organic solvent in the reaction mixture inhibits the coupling. The coupling products between styrene and various boronic acids were formed in 50-95% yield. A novel mechanism was proposed to rationalize the observed reactivity. 2- and 4-Vinylpyridine, in presence of rhodium, showed a new reactivity giving access to 1,2-diaryl- and 1,1,2-triaryl-ethylderivatives.

Acknowledgements

I would like to thank my supervisor, Mark Lautens, not only for his support, guidance and instruction throughout the last two years, but also for giving me the freedom to work on what interested me most. I am extremely grateful for the tremendous opportunity he has offered me.

A number of people in the Lautens group deserve special thanks: Dr Stéphane Raeppel, who is at the origin of our breakthrough in the oxazoles and isoxazoles chemistry and under whose guidance I developed this project; Keith Fagnou, who discovered the reaction that led to my second project and who introduced me to the organometallic chemistry; Stéphane G. Ouellet for daily discussions about chemistry and an endless supply of helpful advice; and all the others who made daily lab life more stimulating and exciting.

I would also like to thank my family for their support and interest in what I have achieved. Most importantly, I want to thank my fiancé, Stéphane, who provided me with all the love and encouragement I could have ever wanted and who makes me a better chemist and a better person.

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List of Abbreviations

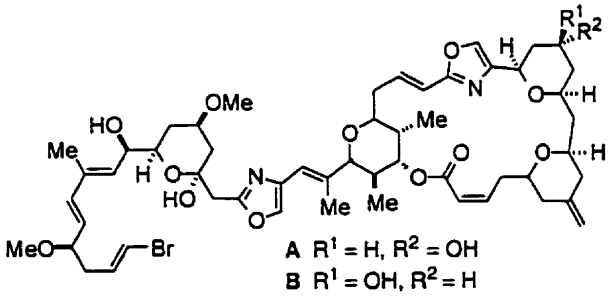
Ac	acetyl
Ar	aryl
de	diastereomeric excess
dr	diastereomeric ratio
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
eq.	equation
Et	ethyl
GC	gas chromatography
HMBC	heteronuclear multi-bonding correlation
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation
i-Pr	isopropyl
IR	infrared
L	ligand
M	generic metal
Me	methyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ph	phenyl
py	pyridine

R	generic alkyl group
r.t.	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatograhy
TMS	tetramethylsilane

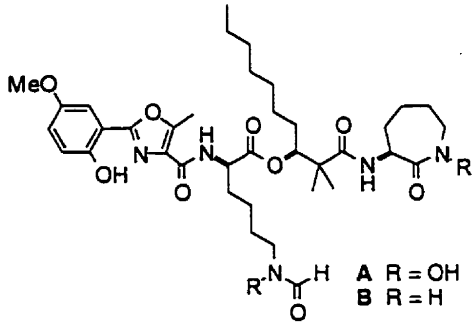
1 Synthetic Studies of the Formation of Oxazoles and Isoxazoles from *N*-Acetoacetyl Derivatives: Scope and Limitations

1.1 General Introduction

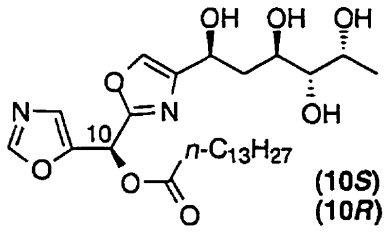
Oxazoles and isoxazoles are important constituents in biologically active natural products as well as synthetic drugs. Naturally occurring oxazoles have been isolated from plants,[1] nudibranch egg masses[2] and microorganisms.[3] These oxazoles as well as many derivatives show a variety of biological activities,[4] including anti-cancer and anti-HIV/AIDS activity. For example, phorboxazoles **I** are marine natural products containing two oxazole rings. They exhibit *in vitro* antifungal activity against *Candida albicans* and extraordinary cytostatic activity.[5] Amamistatins **II** contain one oxazole nucleus and both are novel growth inhibitors of human tumor cell lines isolated from an actinomycete.[6] Also, bengazole A and *epi*bengazole A **III**, isolated from marine sponges of the genus *Jaspis*, are representative members of a small family of bis-oxazole natural products.[7] Like phorboxazoles A and B, bengazole A and *epi*bengazole A exhibit potent *in vitro* antifungal activity against *Candida albicans*.[8]



I: phorboxazoles A and B



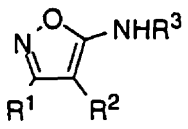
II: Amamistatins A and B



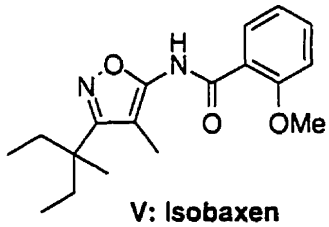
(10*S*) bengazole A
(10*R*) *epi*bengazole A

III

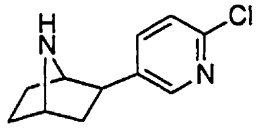
Amino-isoxazoles **IV** and their *N*-substituted derivatives are also interesting heterocyclic compounds with useful biological properties. Indeed, isoxaben **V**[9] is one of the most used herbicides for winter cereals. Likewise, epibatidine **VI**, isolated in 1992,[10] was found to be a member of an entirely new class of alkaloids exhibiting powerful analgesic properties and potent anti-nociceptive activity via activation of central nicotinic receptors. However, due to its high toxicity, epibatidines's therapeutic development has become a major challenge.



IV

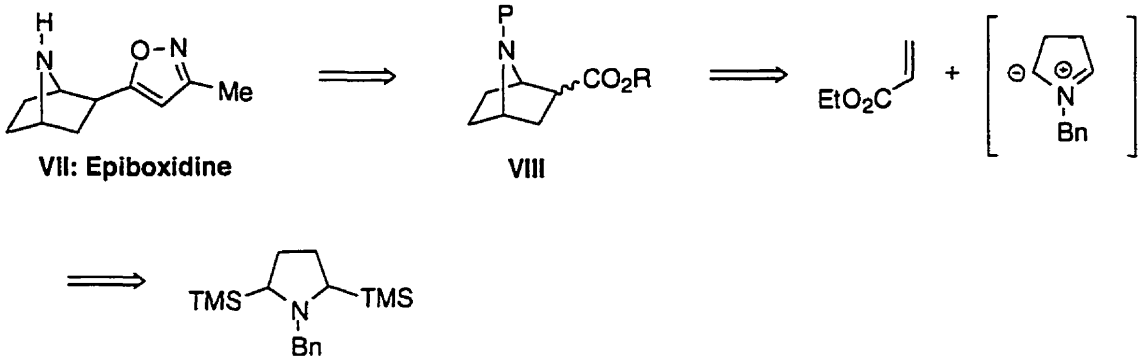


V: Isobaxen



VI: Epibatidine

Epiboxidine **VII** was then designed,[11] combining the structural features of epibatidine **VI** (7-aza-bicyclo[2.2.1]heptane framework) but containing the isoxazole pharmacophore. Epiboxidine **VII** was shown to be a potent nicotinic receptor agonist with 20-fold less toxicity than epibatidine.[11] In 1999, an efficient synthesis of **VII** was reported,[12] utilizing *N*-protected-2-*exo*-(carboxy)-7-azabicyclo[2.2.1]heptane **VIII** as a key precursor (Scheme 1).



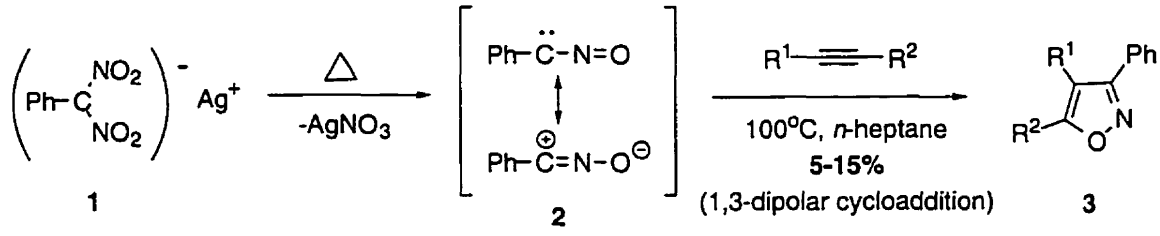
VII: Epiboxidine VIII

Scheme 1

1.2 *Literature Precedents about the Synthesis of Substituted Oxazoles and Isoxazoles*

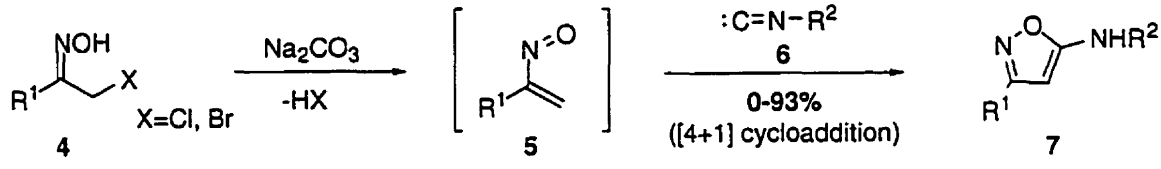
The high activity of the oxazole and isoxazole pharmacophores in therapeutic agents has stimulated substantial interest in developing elegant and effective methods to synthesize these heterocycles and use them as starting materials for the synthesis of more complex molecules.[13] A large number of methods have been published detailing the synthesis of substituted oxazoles and isoxazoles including approaches based on intermolecular cycloadditions,[14] condensations,[15] and intramolecular cyclization of amino acids.[16]

Alexandrou and co-workers reported that thermal decomposition of silver salts of aryldinitromethanes **1** in the presence of several alkynes provides 4,5-disubstituted 3-phenyl-isoxazoles **3** (Scheme 2).[17] It is believed that upon heating of the silver salt, $AgNO_3$ is lost, giving rise to arylnitrocarbene **2**. This species subsequently reacts with an alkyne in a 1,3-dipolar cycloaddition manner. The yields though are low, ranging from 5 to 15%.



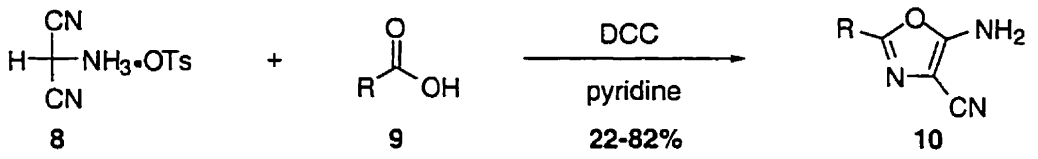
Scheme 2

El Kaïm and co-workers published a method to synthesize amino-isoxazoles **7** from isocyanides **6** (Scheme 3).[14b] The mechanism of this addition relies on a base induced hydrochloric elimination of α-chloro or α-bromoketone oxime **4** to form a reactive nitrosoalkene **5** rapidly attacked by the nucleophile, in this case isocyanide **6**, in a [4+1] cycloaddition fashion. The success of this method is highly dependent on the nature of the substituents on both the oxime and the isocyanide, the yields ranging from 0 to 93%. In order to be successful, the substituent on the oxime has to be strongly electron withdrawing (CF_3, CO_2Et) and the one on the isocyanide has to be bulky (*t*-Bu, CR_3).



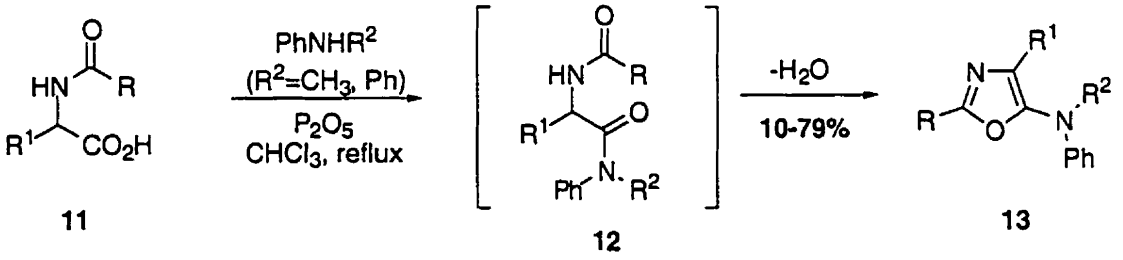
Scheme 3

Freeman and co-workers reported a versatile method for the synthesis of substituted 1,3-oxazoles from aminomalononitrile tosylate (AMNT) and carboxylic acids (Scheme 4).[15] The carboxyl activating reagent, 1,3-dicyclohexylcarbodiimide (DCC), has been used in the presence of pyridine to synthesize 2–substituted 5-amino-4-cyano-1,3-oxazoles. The R groups that were tested are branched alkyl chains.



Scheme 4

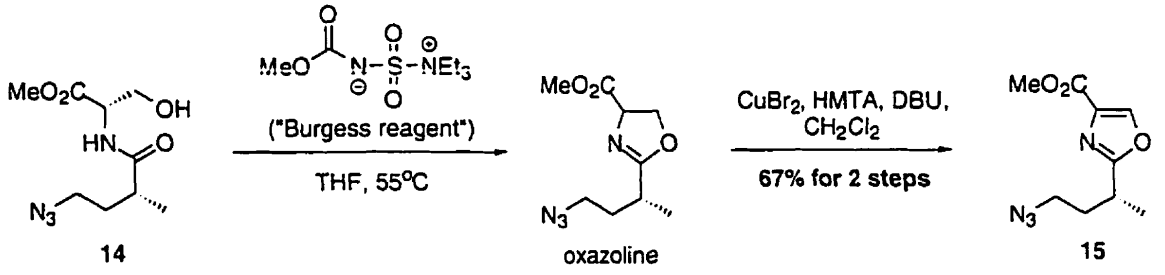
In 1978, a Russian group reported the synthesis of amino-oxazoles **13** from α-acylated amino acids **11** and secondary amines in the presence of a dehydrating reagent, P_2O_5.[16] The condensation was carried out in the presence of an excess of P_2O_5 in boiling chloroform (Scheme 5). Although the dehydration was spontaneous, in many cases **12** was recovered with the 5-R_2N-oxazoles **13** after isolation of the reaction mixture. They attributed this result to the incompleteness of the reaction and/or the hydrolysis of the oxazole ring upon the neutralization of the acidic mixture. Varying the reaction time, the relative amounts of the reactants, the concentration of the base and the neutralization temperature did not significantly improve the yields of oxazoles **13**.



Scheme 5

As another example, Smith and co-workers published a two-step synthesis of a substituted oxazole ring in the course of the total synthesis of (+)-calyculin A and (−)-calyculin B (Scheme 6).[18] The highly functionalyzed β-hydroxyamide **14** was reacted

with the Burgess reagent,[19] as introduced by Wipf et al.[20] to first form the oxazoline. Subsequent oxidation under the Barrish-Singh $CuBr_2$ oxidation[21] furnished the disubstituted oxazole **15** in 67% yield for the two steps.

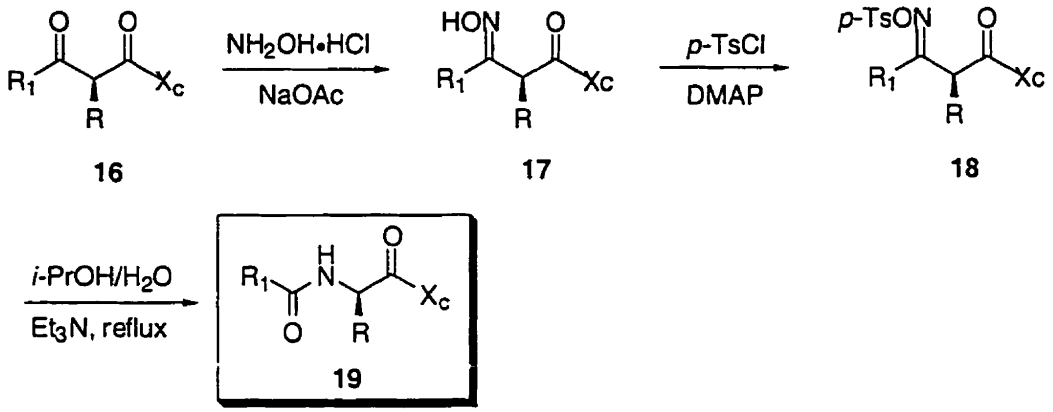


Scheme 6

Despite the significant number of papers that have been published to date about the synthesis of substituted oxazoles and isoxazoles, some of the methods described in the literature suffer in their versatility, convenience, and yield. First having in mind the synthesis of amino acids, we became interested in the study of the synthesis of this class of heterocycles.

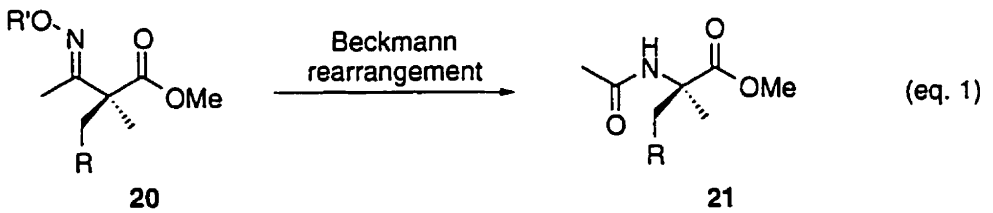
1.3 Synthesis of Non Natural Amino Acids from Chiral β-Ketoesters and β-Ketoimides

This project began with the goal of preparing novel enantiomerically pure fully protected α-monosubstituted amino acids **19** from chiral β-ketoimides **16**. Subsequent transformations of **16** followed by a Beckmann rearrangement (**18**→**19**) would furnish the protected amino acids. (Scheme 7).



Scheme 7

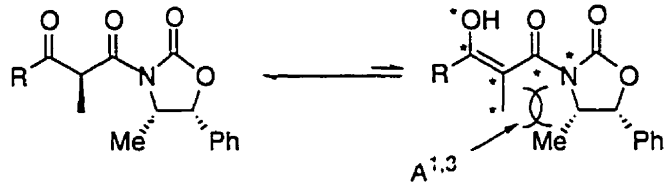
The Beckmann rearrangement is an acid-catalyzed transformation of a ketoxime to an amide.[22a] Acid converts the oxime to a good leaving group and promotes the rearrangement of an adjacent aryl or alkyl group. A base-catalyzed version of this rearrangement is also feasible with the already protected oxime, often with a tosylate or mesylate group. The group *anti* to hydroxy migrates with its bonding electron pair; when that group is chiral, the Beckmann rearrangement occurs with retention of configuration.[22b, 23]



(eq. 1)

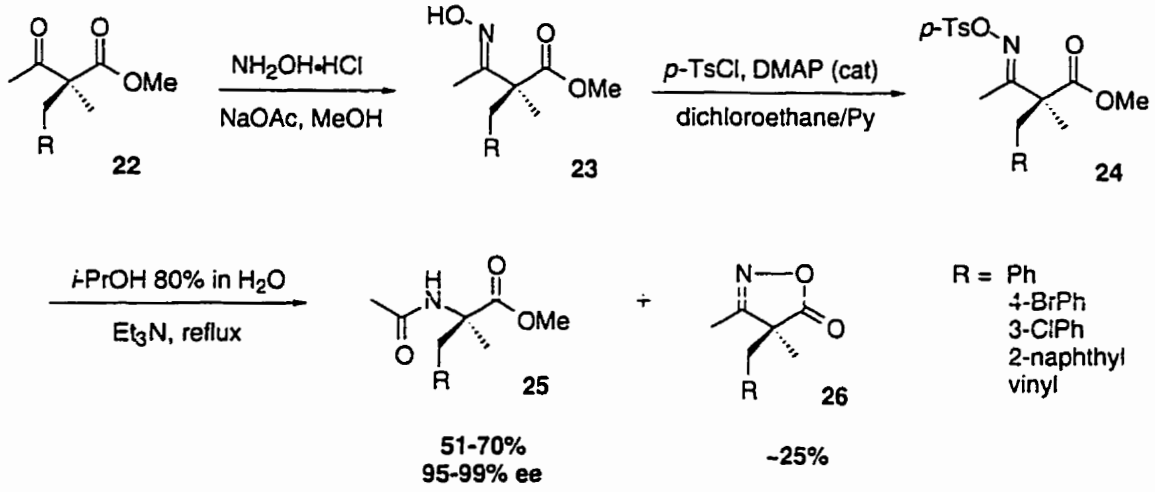
By using the strategy described in Scheme 7, we wanted to take advantage of the fact that β-ketoimide **16** is less prone to enolization than normal β-diketones because of the developing allylic 1,3 strain in the enolate (Scheme 8).[24] Indeed, in order to epimerize, all the marked atoms would have to be in the same plane resulting in

significant allylic 1,3 strain. Since this process requires important amount of energy, it is not favorable and therefore does not occur under mildly basic or acidic conditions.



Scheme 8

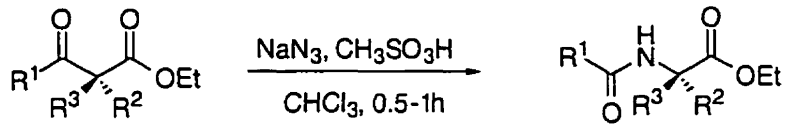
Our strategy toward chiral α-monosubstituted amino acids was based on two reports. Frutos and co-workers reported the synthesis of protected, chiral α,α-disubstituted α-amino acids *via* a Beckmann rearrangement (eq. 1).[25] The synthesis of the protected α,α-disubstituted α-amino acids through the Beckmann rearrangement is illustrated by the preparation of (*R*)-*N*-acetyl-α-methylphenylalanine methyl ester **25** (Scheme 9). β-Ketoesters like **22** were prepared as single enantiomers according to the procedure described by Koga.[26] This procedure consists in diastereoselective alkylation of lithio enamines α-alkylated β-ketoesters utilizing readily L-valine *tert*-butyl ester as the chiral auxiliary. Under these conditions, a substantial amount of the undesired isoxazolone **26** is produced, which arises from the displacement of the tosyl group by the carbonyl oxygen. Different solvents such as ethanol, methanol, butanol, acetic acid, pyridine and THF were used to minimize the formation of **26**, as well as the amount of water in the mixture, but no improvement on the yield was noticed. It was observed that mesylates gave a slightly inferior yield compare to the corresponding tosylates. It was determined that compounds **25** were obtained with 95-99% ee's, which confirms that the Beckmann rearrangement occurs with retention of configuration at the migrating carbon.

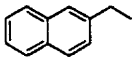
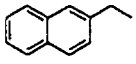


Scheme 9

Georg and co-workers reported the second paper on which our initial plan was based.[27] They used the Schmidt rearrangement of α,α-bisalkylated β-ketoesters to synthesize α-alkylated α-amino acids. This strategy has been previously used by Schmidt to access this class of protected amino-acids in high yields.[28] In the case of the Schmidt rearrangement, an azide is the rearrangement precursor. Several studies have revealed that the Schmidt rearrangement takes place with retention of configuration.[29] Georg and co-workers prepared optically active β-ketoesters of high enantiomeric purity also using the procedure described by Koga.[26, 30] The chiral β-ketoesters were then subjected to the Schmidt rearrangement and the corresponding *N*-acyl amino acids were obtained in excellent yields (Table 1). The ee's, determined by NMR experiments utilizing the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium(III), revealed that no detectable racemization had occurred during the Schmidt rearrangement.

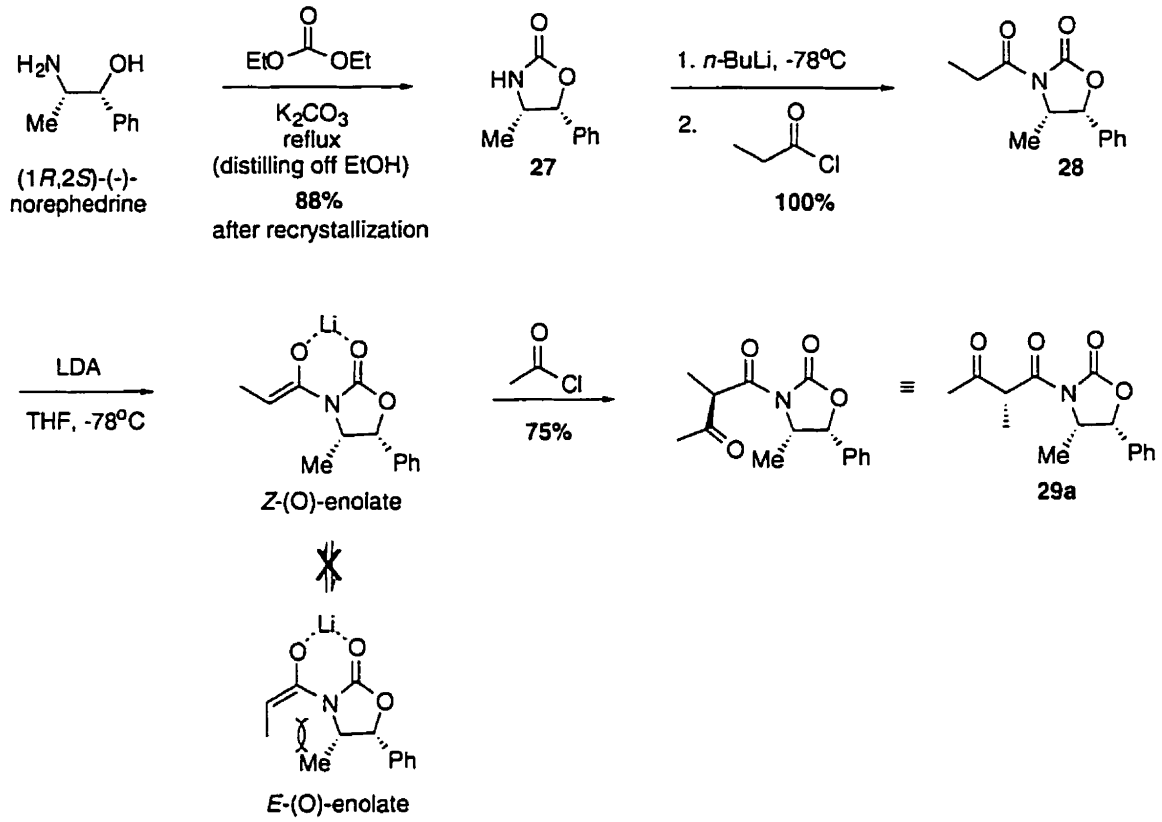
Table 1: Schmidt Reactions of α,α-disubstituted β-ketoesters



entry	R^1	R^2	R^3	yield (%)	ee (%)
1	CH_3	CH_3	$PhCH_2$	95	>95
2	CH_3	CH_3		89	>95
3	$(CH_2)_4$		$PhCH_2$	97	>95
4	$(CH_2)_4$			71	>95
5	CH_3	CH_3	CH_2CO_2Me	88	70

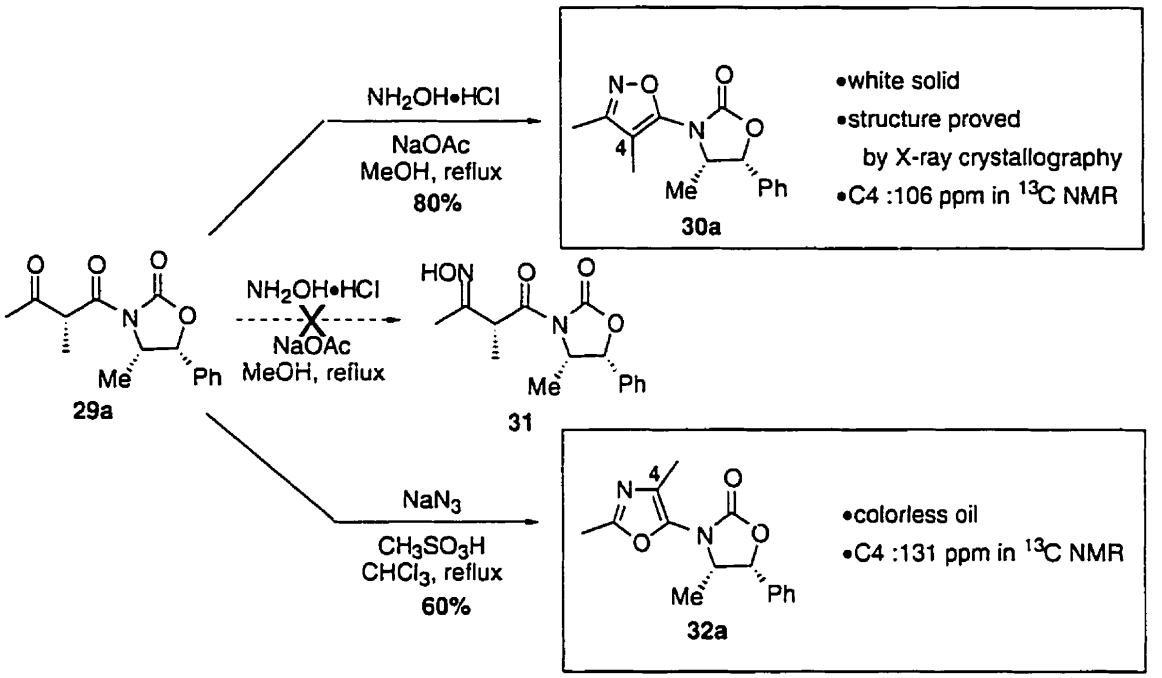
1.4 Preliminary Results

With these literature precedents, we set out to apply these strategies to synthesize α-monosubstituted amino acids from chiral α-monosubstituted β-ketoimides. Starting material **29a** was first prepared according to the methodology developed by Evans and co-workers (Scheme 10).[31] Commercially available (1*R*,2*S*)-(−)-norephedrine was reacted neat with diethyl carbonate in the presence of K_2CO_3 to furnish oxazolidinone **27**, which could be purified by recrystallization. **27** was acylated a first time under standard conditions and the intermediate **28** was used crude in the second acylation step yielding the oxazolidinone derivative **29a** in a non-optimized yield of 75%. Chelation between the two carbonyl oxygens fixes the conformation of the auxiliary and acylation then occurs from the least hindered face, away form the methyl and phenyl groups. The enolate geometry is always *Z*-(O), as shown, because of the 1,3-allylic strain which develops in the *E*-(O)-enolate. Only the diastereomer shown was detected (^{1}H NMR).



Scheme 10

When **29a** was reacted with hydroxylamine hydrochloride (NH_2OH•HCl), the only compound obtained in 80% yield was the isoxazole **30a** (a white solid), instead of the expected corresponding oxime **31** (Scheme 11). Structure **30a** was proved by X-ray crystallography. Extensive nOe, HSQC and HMBC NMR experiments did not allow defenitive structure determination of **30a**.



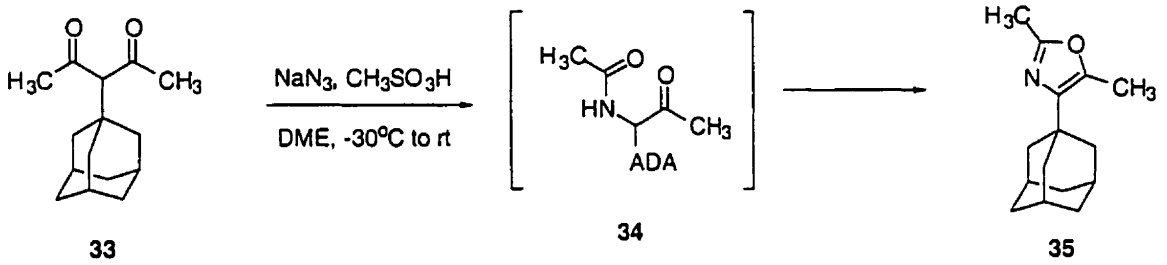
Scheme 11

In an effort to synthesize the amino acid, the same starting material **29a** was reacted with NaN_3 under the Schmidt rearrangement reaction conditions. However, the only product observed was the oxazole **32a**, a colorless oil, which was obtained in 60% yield. Although **30a** and **32a** have similar spectroscopic data, they can be differentiated by the chemical shift of carbon C4. Indeed, carbon C4 of the isoxazole resonates at higher field (106 ppm compare to 131 ppm for carbon C4 of the oxazole).

1.5 Literature Precedents about the Reactivity of β-Ketoimides

Intrigued by these results, we looked in the literature to see if there were precedents relating to the reactivity of β-ketoimides under these conditions. Moreno-

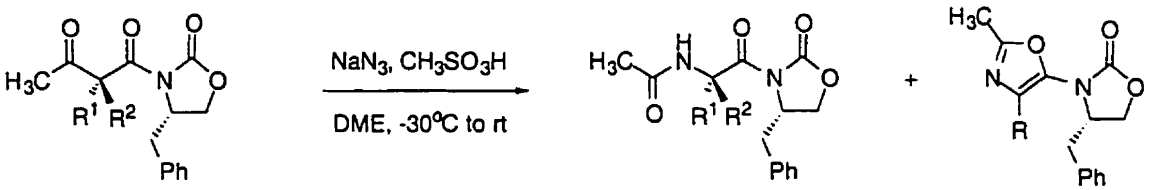
Mañas and co-workers reported in 1986 that when sterically hindered β-diketone **33** was treated with NaN_3, 4-(1-adamantyl)2,5-dimethyloxazole **35** was isolated in 87% yield instead of the amidoketone **34**, which cyclizes under the action of the acid (Scheme 12).[32a,b] However, with groups other than 1-adamantyl between the two carbonyl moieties (e.g. R= CH_3, $PhCH_2CH_2$, $PhCH{=}CHCH_2$ and Ph_2CH) the reaction stops at the amidoketone.[32b] The conversion of amidoketones into oxazoles by strong acids (**34**→**35**) is the Robinson-Gabriel reaction.[33]



Scheme 12

In 1996 the same authors reported a few results with chiral *N*-acetoacetyl derivatives **36**, featuring (4*S*)-4-benzyloxazolidin-2-one as chiral moiety (Table 2).[32b] When **36** was treated in dimethoxyethane with sodium azide and methanesulfonic acid, the nature of the product (protected amino acid **37** or oxazole **38**) as well as the yield varies a lot depending on the nature of R^1 and R^2. At this stage, they did not provide extensive explanations for their results. They only stipulated that steric hindrance is most probably the driving force for cyclization when severely hindered compounds such as **34** and **37** are the primary products of the Schmidt rearrangement.

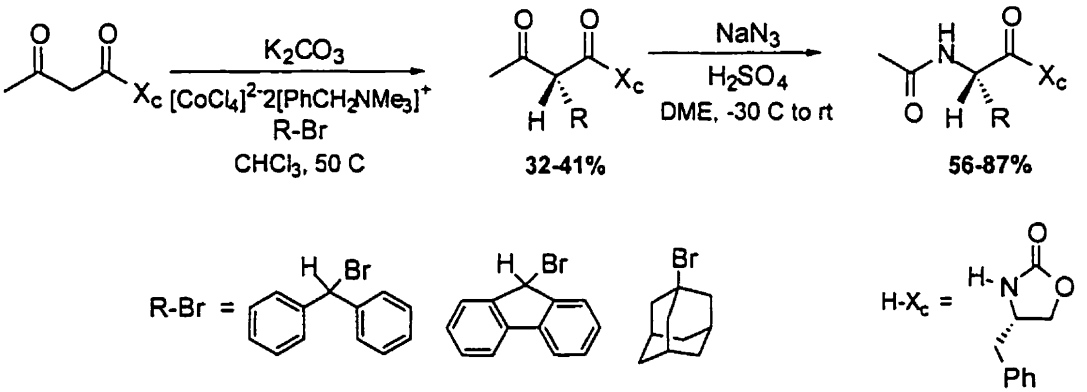
Table 2: Schmidt Reactions of *N*-Acetoacetyl Derivatives of Oxazolidinone



36 37 38

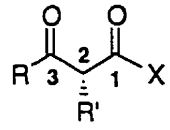
entry	R^1	R^2	yield **37** (%)	yield **38** (%)	R
1	CH_3	H	0	91	CH_3
2	H, CH_3 as a mixture of diast.		14	21	CH_3
3	$PhCH_2$	H	0	27	$PhCH_2$
4	$PhCH_2$, H as a mixture of diast.		54	0	
5	H	H	0	45	H

The same authors published a second paper in 1996 in which they reported that the *N*-acetoacetyl oxazolidinone with the three bulky groups Ph_2CH, fluorenyl and adamantyl, gave the protected amino acid in 85%, 33% and 23% respectively (Scheme 13).[32c]



Scheme 7

1.6 Objectives



In the three papers described in the last two pages, the scope of the reaction of β-ketoimides with sodium azide in the presence of a strong acid was not well established. There was a lack of data, in particular about steric and electronic effects at C1 and C3. Indeed, their study was done exclusively with (4*S*)-4-benzyloxazolidin-2-one at C1 and a methyl group at C3. This lack of data prompted our studies. Also, we wanted to investigate the possibility of favoring the formation of the oxazole or the protected amino acid by changing the substituent at C3 and the auxiliary at C1. What happens when there is no substituent at C2? Another point was intriguing: could the formation of the isoxazole and oxazole be controlled from the same starting material by using the right reaction conditions (NH_2OH•HCl or NaN_3)? Finally, could the oxazoles and isoxazoles thus synthesized be used as building blocks for more complex molecules? Chapter 1 of this thesis reports the results concerning these questions.

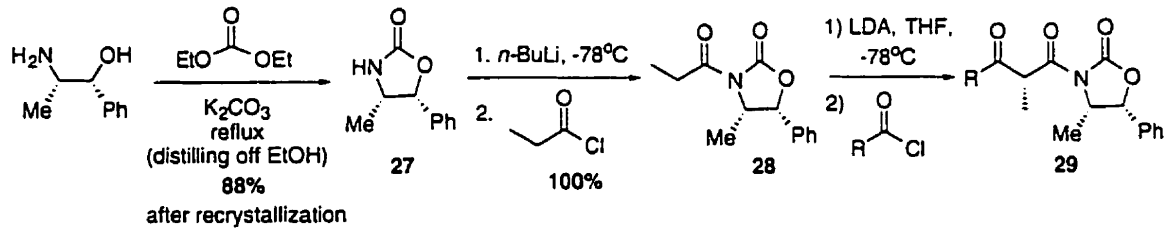
1.7 Synthetic Studies about the Synthesis of Oxazoles and Isoxazoles from β-Ketoimides

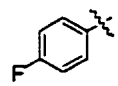
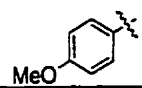
1.7.1 Preparation of Chiral β-Ketoimides

The effect of the nature of the substituent at C3 was first examined. (1*R*,2*S*)-(−)-Norephedrine-derived oxazolidinone β-ketoimides containing different aliphatic and

aromatic R groups were prepared according to the methodology developed by Evans and co-workers (Table 3).[24] Intermediates **27** and **28** (Scheme 10) could be prepared in multi-gram quantity (15 g) without complications. In the case of the aromatic substituents HMPA was added prior to the addition of the acyl chloride, otherwise the yields are diminished. In the cases of **29b-29f**, the presence of the minor diastereomer could be detected in the crude ^{1}H NMR (5-15%), but it was never isolated. The amount of the minor diastereomer increases when R=Ar. In all cases the two diastereomers, when the second was present, could easily be separated by column chromatography on silica gel, and only the pure fractions containing the desired diastereomer were isolated. It was noticed that **29f** was unstable on silica gel, even when pre-treated with Et_3N.

Table 3: Synthesis of the Oxazolidinone Derivatives

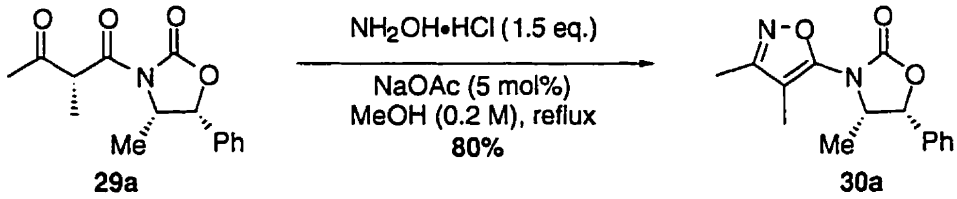


entry	compound	R	yield (%)
1	**29a**	Me	75
2	**29b**	Et	69
3	**29c**	$PhCH_2CH_2$	60
4	**29d**		57[a]
5	**29e**		57[a]
6	**29f**		48[a,b]

[a] HMPA was used
[b] product decomposed on silica gel

1.7.2 Synthesis of Isoxazoles: Effects of the Substituent at C3

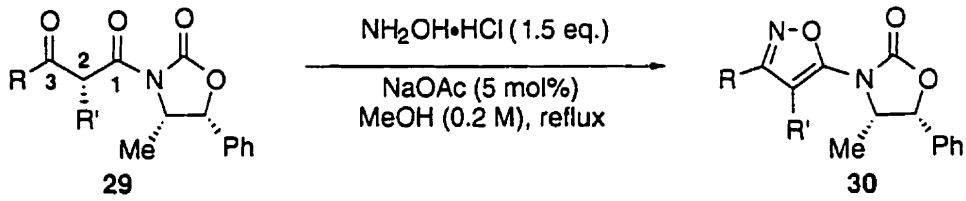
Compounds **29a-29g** were then reacted with $NH_2OH•HCl$ in the presence of NaOAc in refluxing MeOH. Several reaction conditions were surveyed, especially varying the amount of NaOAc and the reaction temperature. Indeed, several conditions are reported in the literature for the formation of an oxime from the corresponding ketone. $NH_2OH•HCl$ is a commonly used reagent to achieve this transformation. However the base used as well as the solvent vary depending on the method: aqueous NaOH in EtOH at 0°C,[34] an excess of NaOAc in MeOH (relative to $NH_2OH•HCl$) at room temperature,[25,35] and one equivalent of Na_2CO_3 relative to $NH_2OH•HCl$ in H_2O or H_2O/MeOH at 0°C.[36] However, none of these methods proved to be successful with substrates **29**. Starting material as well as a substantial amount of the chiral auxiliary was recovered under these conditions. Other polar solvents were also surveyed (THF, DMSO), without success. The pH of the reaction mixture seemed to be very important for the success of the reaction. When the base was in excess, total cleavage of the chiral auxiliary was observed. In an effort to obtain only one reaction product and to minimize the amount of cleavage of the chiral auxiliary, different conditions were tried, varying the relative stoichiometry of NaOAc and $NH_2OH•HCl$, as well as the temperature of the reaction (0°C, r.t. reflux). It was finally found that the best conditions were the ones described below (eq. 2), i.e. using a catalytic amount of NaOAc in refluxing MeOH. Under these optimized conditions, a minimum amount of auxiliary was formed (~5%) and only the isoxazole was produced in 80%.

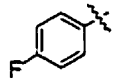
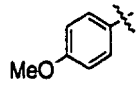


(eq. 2)

Substrates **29b-29f** were then reacted under the optimized conditions. The results are summarized in Table 4.

Table 4: Synthesis of Isoxazoles
(Chiral Auxiliary Derived From (1*R*,2*S*)-(−)-norephedrine)



entry	R	R'	yield **30** (%)
1 (**29a**)	Me	Me	80 (**30a**)
2 (**29b**)	Et	Me	84 (**30b**)
3 (**29c**)	$PhCH_2CH_2$	Me	67 (**30c**)
4 (**29d**)		Me	45 (**30d**) + 15 (**29d**)
5 (**29e**)		Me	30 (**30e**) + 25 (**29e**)
6 (**29f**)		Me	6 (**30f**) + 36 (**29f**)+ 6[a]
7 (**29g**)	Me	H	82 (**30g**)

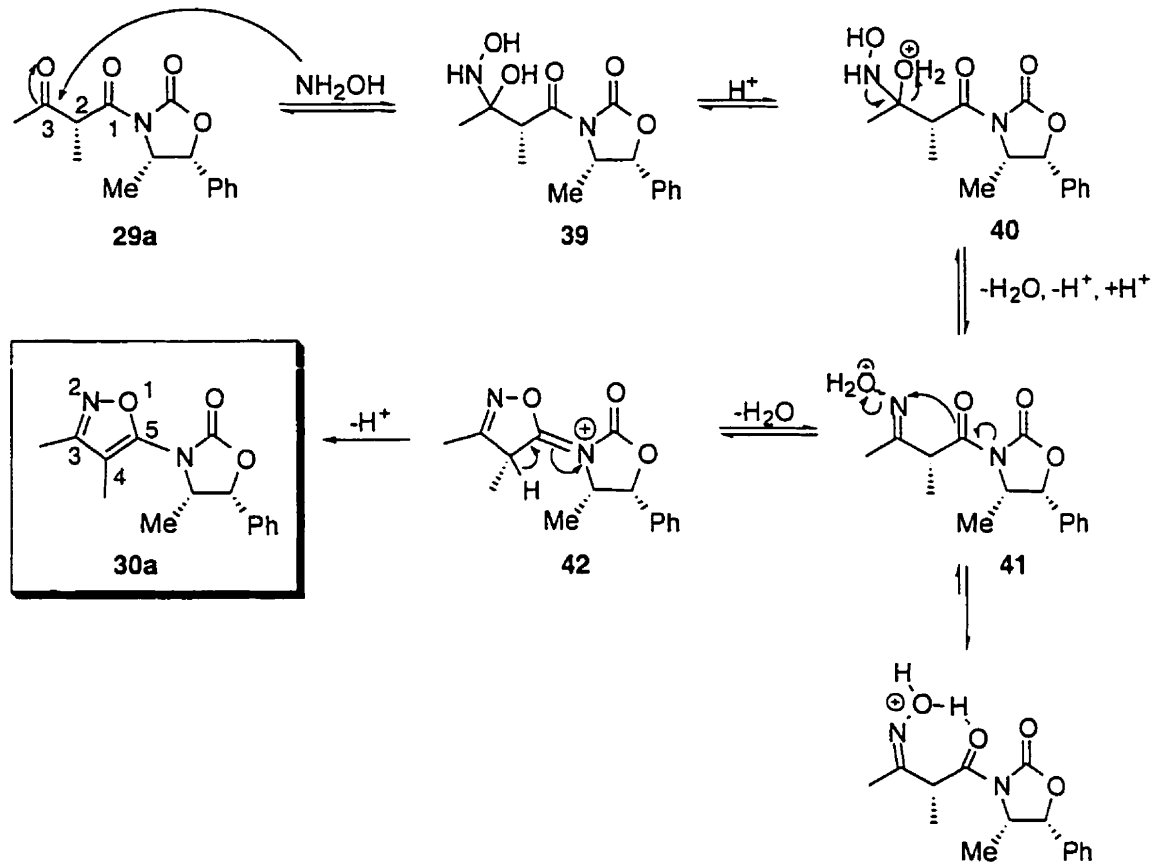
[a] Epimerisation at C2

Upon treatment with $NH_2OH•HCl$, the corresponding isoxazoles were isolated in good yields when aliphatic R groups are present (entries 1-3). Substrates with aromatic substituents proved to be substantially less reactive (entries 4-6). The yields were lower, starting material was recovered, and in one case, epimerization at C2 was observed (entry

6). Two factors may be responsible for this outcome. The carbonyl group undergoing reaction (C3) may be less electrophilic due to conjugation with the aromatic ring. Second, the aromatic ring may disfavor the *trans* oxime **41**, which is necessary for the ring closure to occur (Scheme 12).

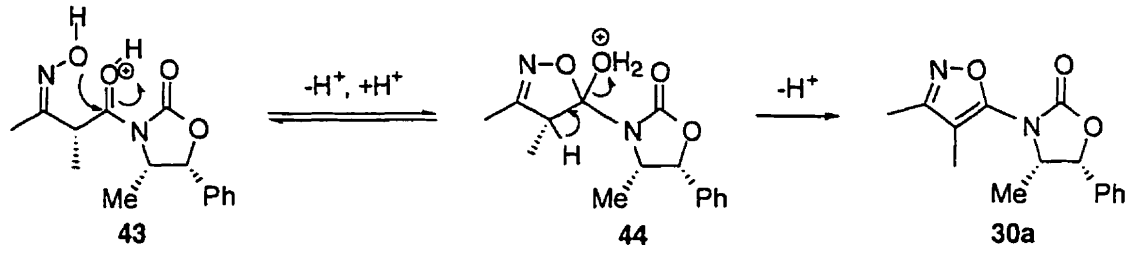
1.7.2.1 Proposed Mechanism

As depicted in Scheme 12, it seems that in our case, the participation of the nitrogen's lone pair to eliminate a molecule of H_2O is faster than the bond migration, which would give the Beckmann rearrangement product. It is also possible that the equilibration between the *cis* oxime, which is more stable because of hydrogen bonding, and the *trans* oxime, which is the reactive species, is very slow. And as soon as the *trans* oxime is formed, water is eliminated to furnish the isoxazole, instead of the migration of the bond.



Scheme 12

Another mechanism could be envisaged to rationalize our results involving nucleophilic attack of the oxime oxygen on carbonyl C2 (Scheme 13). Indeed, the resulting heterocycle would be exactly the same. It might be possible to verify the validity of this hypothesis by utilizing labeled oxygen (e.g. ^{18}O), either on the $NH_2OH \bullet HCl$ or on the oxygen carbonyl C2. The characterization of the product by mass spectrometry would indicate if one labeled oxygen is present.

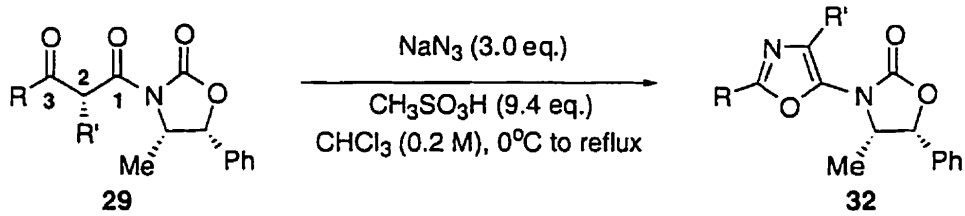


Scheme 13

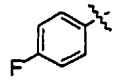
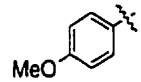
1.7.3 Synthesis of Oxazoles: Effect of the Substituent at C3

In an effort to form the α-amino acids, the same substrates **29a-29g** were reacted with sodium azide in the presence of methanesulfonic acid in refluxing chloroform according to the procedure published by Georg and co-workers.[27] Consistent with the observations of Moreno-Mañas and co-workers,[32b] oxazoles were obtained under these conditions (Table 5). Again, the same trend was observed, i.e. substrates with aliphatic groups furnished the desired oxazoles, this time in moderate yields, whereas substrates with aromatic groups seem less reactive and more prone to epimerization at C2.

Table 5: Synthesis of Oxazoles Using the Schmidt Rearrangement (Chiral Auxiliary Derived From (1*R*,2*S*)-(−)-norephedrine)



29 32

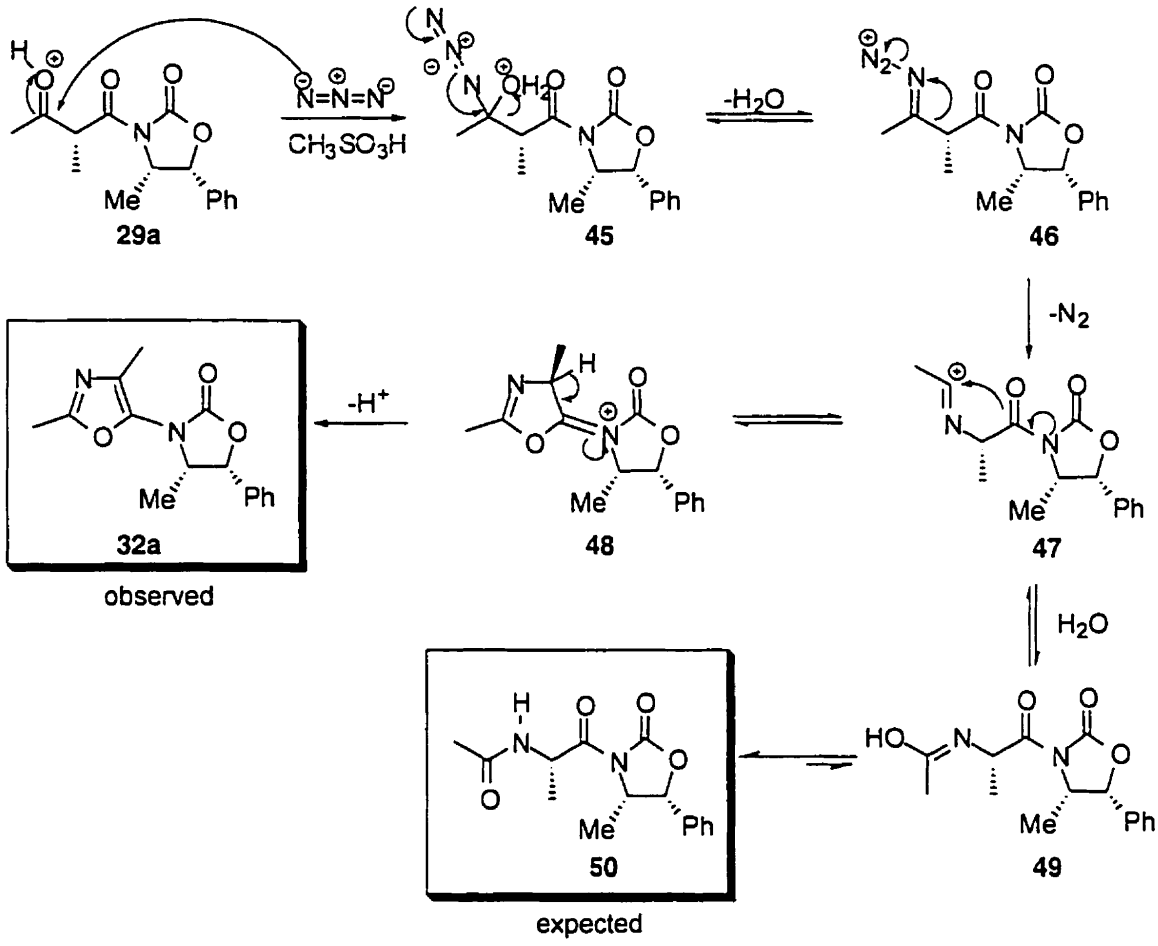
entry	R	R'	yield **32** (%)
1 (**29a**)	Me	Me	60 (**32a**)
2 (**29b**)	Et	Me	64 (**32b**)
3 (**29c**)	$PhCH_2CH_2$	Me	58 (**32c**)
4 (**29d**)		Me	50 (**29d**) + 28[a]
5 (**29e**)		Me	50 (**29e**) + 36[a]
6 (**29f**)		Me	degradation
7 (**29g**)	Me	H	50 (**32g**)

[a] Epimerisation at C2

1.7.3.1 Proposed Mechanism

Oxazoles are formed upon loss of N_2 to form **47**, which is trapped by the carbonyl oxygen faster than an external nucleophile (Scheme 14). Subsequent loss of the α-proton provides the oxazole. In our case, it is doubtful that the mechanism involves the cyclization of **50** to give oxazole **32a**, as was previously proposed by Moreno-Mañas and co-workers.[32a] First, **50** has never been detected as a intermediate in the course of the reaction either by TLC or ^{1}H NMR, even when the reaction was done at lower temperature or stopped very quickly, long before completion. Also, the presence of the auxiliary influences the conformation of intermediate **47**, making the trapping of the

carbocation by the carbonyl oxygen more likely to occur (in Moreno-Mañas's case, they deal with β-ketoesters).



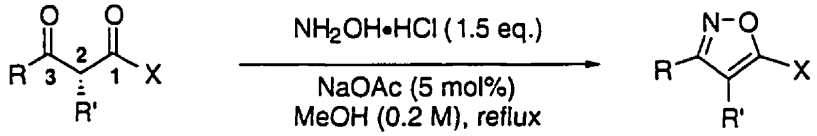
Scheme 14

1.7.4 Effect of the Substituent at C1

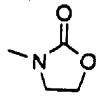
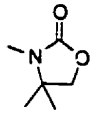
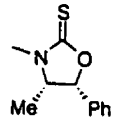
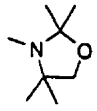
Investigations were then focused on the steric and electronic effects of the nature of the auxiliary at C1. Since neither product retained the stereochemical information at C2, it seemed obvious to continue the investigation in the absence of the chiral oxazolidinone. Also, since there seemed to be a nucleophilic partcipation of the

nitrogen's lone pair during the ring closure step in both cases (oxazole and isoxazole), we could envisage that a more nucleophilic nitrogen at C1 would increase the rate of the reaction and hopefully increase the yield as well.

Table 6: Synthesis of Isoxazoles (Achiral Auxiliaries)



51 **52**

entry	R	R'	X	Yield **52** (%)
1[c] (**51a**)	Me	Me	$N(Me)_2$	degradation
2[c] (**51b**)	Me	Me	$N(Et)_2$	degradation
3[c] (**51c**)	Me	Me	$N(i\text{-}Pr)_2$	60 (**52c**)
4[c] (**51d**)	Me	Me		95 (**52d**)
5[c] (**51e**)	Et	Me	"	72 (**52e**)
6[c] (**51f**)	$PhCH_2CH_2$	Me	"	53 (**52f**)
7[c] (**51g**)	Me	Me		85 (**52g**)
8[c] (**51h**)	Et	Me	"	no reaction
9 (**51i**)	Et	H	"	92 (**52i**)
10 (**51j**)	Et	Me		auxiliary recovered
11 (**51k**)	Me	H		degradation

[c] The racemates were used.

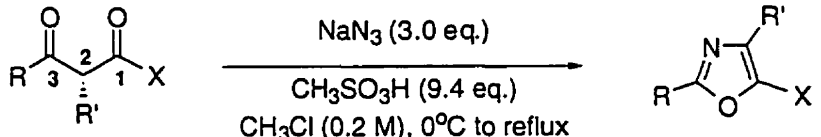
When acyclic amides were examined, decomposition or no reaction was observed (Table 6, entries 1 and 2, and Table 7, entries 1-3). In contrast, the desired isoxazole was obtained in 60% yield when the N,N-diisopropylamide derivative was reacted with

NH_2OH•HCl (Table 6, entry 3), but when the same substrate was reacted with NaN_3, the isoxazole was also isolated (Table 7, entry 4). This result may arise because the nitrogen of the amide is sufficiently nucleophilic that the displacement of N_2 occurs before the migration can take place (Scheme 14). Thus, an electronic effect of the oxazolidinone seemed necessary to obtain the desired heterocycles. The simplest unsubstituted oxazolidone was then prepared and furnished the expected compounds in decent to excellent yields depending on the nature of R (Table 6, entries 4-6 and Table 7, entry 5). However, substrates with larger substituents at C3 reacted with NaN_3 to furnish complex mixtures containing amino acids, oxazoles and additional products (Table 7, entries 6 and 7). A number of different conditions (solvent, temperature, azide source, Lewis acid) were tried to favor the formation of one product over the others but without success. Although this problem of obtaining complex mixtures was not observed with NH_2OH•HCl, it seemed that steric hindrance on the auxiliary was important. The 4,4-dimethyloxazolidinone derivative was synthesized and tested (Table 6, entry 7 and Table 7, entry 8). The desired isoxazole was obtained in 85% yield with NH_2OH•HCl and to our surprise the isoxazole was also formed in 80% yield with NaN_3. In this case, the presence of three methyl groups seemed to inhibit the formation of the oxazole. If the methyl group between the two carbonyls C1 and C3 is removed, the reactions with NH_2OH•HCl and NaN_3 proceeded quickly to give the isoxazole and oxazole in 92% and 25% yield respectively.

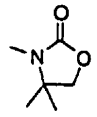
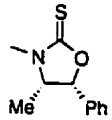
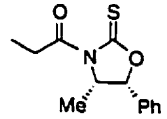
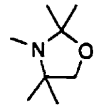
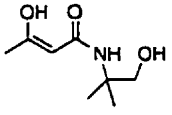
We next studied the effect of the nature of the auxiliary carbonyl on the reactivity of the starting materials. The oxazolidinethione derivative gave the retro Claisen product

in 45% yield when reacted with NaN_3 (Table 7, entry 10) and the auxiliary was recovered when the substrate was reacted with $NH_2OH{\bullet}HCl$ (Table 6, entry 10). The 2,2,4,4-tetramethyloxazolidine derivative which lacks the carbonyl group was not stable to the reaction conditions. In one case degradation was observed (Table 6, entry 11) and in the other the hydroxyketoamide corresponding to the starting material was recovered in 60% yield (Table 7, entry 11).

Table 7: Synthesis of Oxazoles (Achiral Auxiliaries)



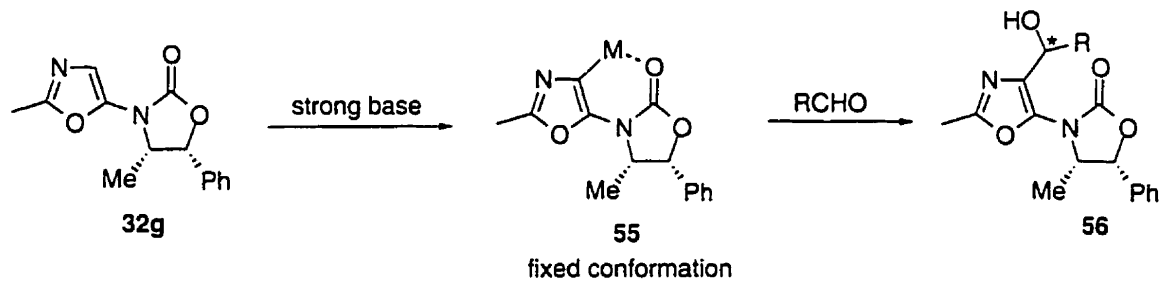
53 **54**

entry	R	R'	X	Yield **55** (%)
1[c] (**53a**)	Ph	Me	$N(Me)_2$	no reaction
2[c] (**53b**)	Me	Me	$N(Me)_2$	degradation
3[c] (**53c**)	Me	Me	$N(Et)_2$	degradation
4[c] (**53d**)	Me	Me	$N(i\text{-}Pr)_2$	70 (isoxazole **52c**)
5[c] (**53e**)	Me	Me		47 (**54e**)
6[c] (**53f**)	Et	Me	"	complex mixture
7[c] (**53g**)	$PhCH_2CH_2$	Me	"	25 (**54g**)
8[c] (**53h**)	Me	Me		80 (isoxazole **52g**)
9 (**53i**)	Et	H	"	25 (**54i**)
10 (**53j**)	Et	Me		
11 (**53k**)	Me	H		

[c] The racemates were used.

1.8 Attempts to Use Oxazoles as Chiral Templates

We then tried to extend the methodology and use the oxazoles formed as a chiral template to syntesize more complex molecules. An attractive strategy for the formation of a carbon-carbon bond at the 4 position of the oxazole, outlined in Scheme 15, would be the selective generation of a 4-lithio-2-methyl-5-*N*-oxazole **55** and its reaction with an electrophile. We hoped that the presence of the chiral auxiliary would induce a facial diastereoselectivity in the reaction product.

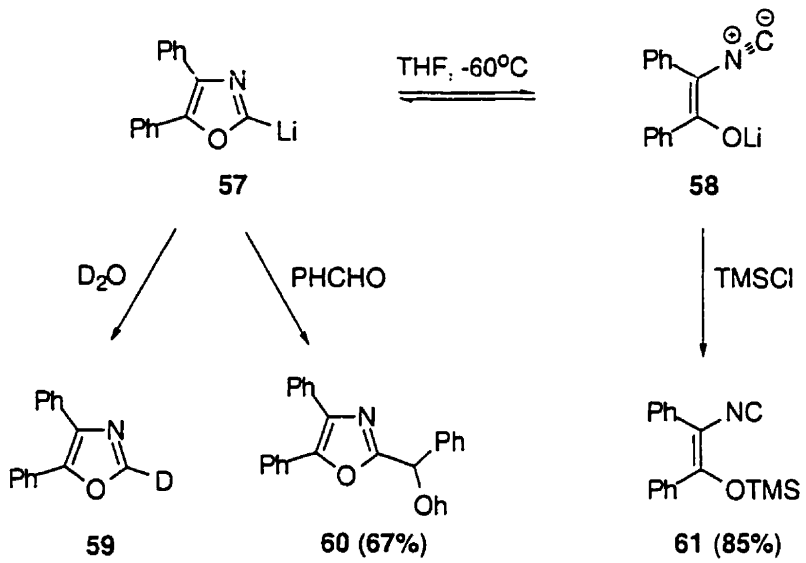


Scheme 15

1.8.1 Literature Precedents

To the best of our knowledge, the selective generation of an anionic lithium species at the 4 position is unprecedented. However, it has been reported that 4-phenyl-,[37] 4-methyl-5-phenyl-,[37] 5-methyl-4-phenyl-,[37] and 4,5-diphenyloxazole[38] could be metallated by *n*-butyllithium at the 2 position. The resulting 2-lithiated derivatives were trapped only with deuterium oxide. In 1975, Schröder *et al.*[39] showed that 4,5-diphenyloxazol-2-yllithium **57** exists in equilibrium with the ring-opened lithium enolate **58** and that the choice of trapping agent determined the product **59-61** (Scheme

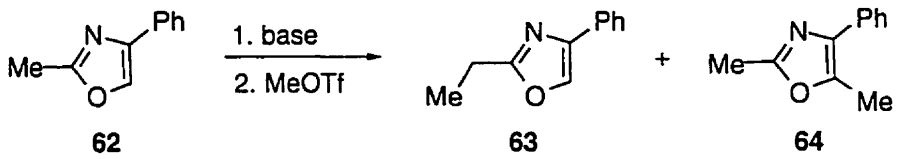
16). *n*-Butyllithium, lithium diisopropylamide (LDA), and lithium 2,2,5,5-tetramethylpiperidine (LiTMP) have been used to metallate oxazoles at the 2 position, without affecting the result or the ratio of the reaction.[40]



Scheme 16

Evans and co-workers recently reported a method which allows the selective formation of 2-(lithiomethyl)oxazole over the 5-lithiooxazole (Table 8).[41] Diethylamine (from lithium diethylamide) has been found to be a kinetically competent proton source that will mediate the equilibration of the kinetically formed 5-lithioxazole to its more stable 2-(lithiomethyl)oxazole counterpart. However, the ratio was inverted if *n*-BuLi or LDA were used.

Table 8: Base Survey for the Selective Formation of 2-(Lithiomethyl)oxazole



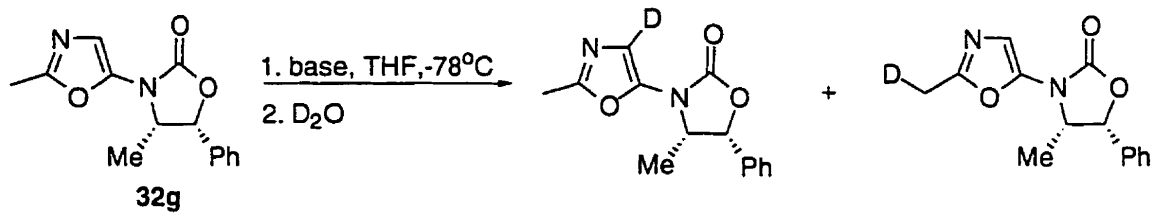
62 63 64

entry	base	Ratio 63 : 64
1	*n*-BuLi	9 : 91
2	LiN*i*Pr$_2$	9 : 91
3	**LiNEt$_2$**	**99 : 1**

1.8.2 Preliminary Results

Table 8 indicates that, in order to get a selective lithiation at the 4 position of the oxazole in our system, we had to avoid the use of LiNEt$_2$, otherwise it might react on the methyl at the 2 position. *n*-BuLi was also not a good base of choice because of its nucleophilicity (possible attack on the carbonyl of the oxazolidinone). Other bases were first surveyed and D_2O as used as the electrophile. The results are summarized in Table 9.

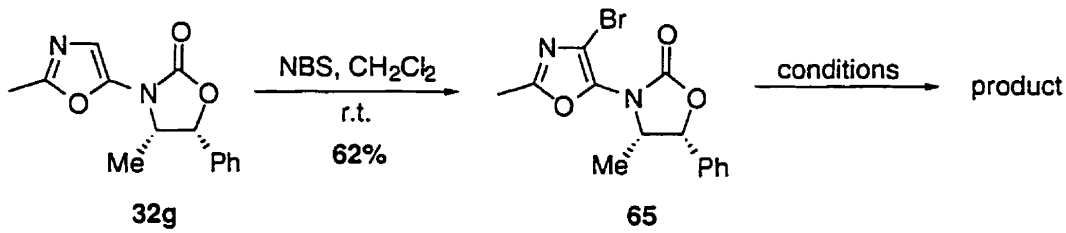
Table 9: Deprotonation Attempts



entry	base	results
1	*t*-BuOK then *n*-BuLi	decomposition
2	pre-formed *t*-BuOK/*n*-BuLi	S.M. recovered
3	*t*-BuLi	decomposition
4	*t*-BuOK	S.M. recovered
5	*n*-BuLi	addition on the oxazolidinone carbonyl

Substrate **32g** seemed rather unreactive towards bases, except with *n*-BuLi which resulted in the addition of Bu on the carbonyl of the oxazolidinone, as it might have been expected. We then considered converting **32g** into the corresponding bromide **65** using NBS,[42] and performing a metal-halogen exchange or a palladium catalyzed coupling. Several solvents and temperatures were tried to prepare the bromide (THF, $CHCl_3$, CH_2Cl_2, 0°C and r.t.). The best yields were obtained using 1.2 equivalents of NBS in CH_2Cl_2 at room temperature (Table 10).

Table 10: Reaction with Bromide 65



32g 65

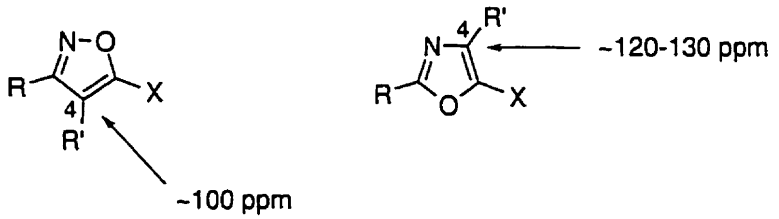
entry	conditions	results
1	1. *t*-BuLi. THF, -78°C 2. butyraldehyde	S.M. recovered
2	ethynyltributyltin, THF, $Pd(PPh_3)_4$, 50°C, 72 h	decomposition
3	styrene, $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 48 h	S.M. recovered

The 4 position on the oxazole seems quite hindered since no reaction occurred under the reaction conditions either with the unsubstituted 4 position or with the corresponding bromide. The reactivity of this substrate was not further investigated.

1.9 Conclusions

Several conclusions can be formulated at this stage of the study. First, the synthesis of two heterocycles, the oxazole and the isoxazole, can be achieved selectively, in most cases, in good yield from the same starting material under specific conditions. The best results to make isoxazoles and oxazoles are obtained with the chiral oxazolidinone derived from (1*R*,2*S*)-(−)-norephedrine. Second, oxazoles and isoxazoles are differentiable by ^{13}C NMR. A trend was indeed observed (with no exception):

isoxazoles show the peak corresponding to C4 at around 100 ppm whereas it is further down field for the isoxazoles (~120-130 ppm).



Another trend was observed: oxazoles are colorless oils whereas isoxazoles are white solids. Finally, it was shown that steric and electronic effects caused by the nature of the auxiliary have a significant influence on the reactivity of the substrate.

Samples of several synthesized chiral oxazoles and isoxazoles are now into the general screens throughout the Merck Company and are tested in many assays over an extended time. So far, there have been no hits from the compounds.

As far as the utilization of the oxazoles as chiral templates is concerned, not enough data have been collected to formulate reasonable conclusions. More experiments will have to be done to determine if deprotonation or another strategy can be successful.

1.10 Experimental

1.10.1 General Experimental

The following general experimental details apply to all following reactions.

All flasks were flame-dried under a stream of nitrogen or argon and cooled before use. Solvents and solutions were transferred with syringes and cannulas using standard inert atmosphere techniques.

^{1}H NMR spectra were recorded 400 MHz using a Varian XL400 spectrometer with $CDCl_3$ with 0.5 % TMS as reference standard (δ 0.0 ppm) or some other suitable solvent. Spectral features are tabulated in the following order: chemical shift (δ, ppm); number of protons; multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet, br-broad); coupling constants (*J*, Hz). ^{13}C NMR spectra were recorded at 100 MHz with $CDCl_3$ as reference standard (δ 77.0 ppm) or some other suitable solvent.

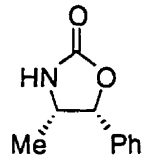
IR spectra were obtained using a Nicolet DX FT-JR spectrometer as neat film or in solution in $CHCl_3$, both between NaCl plates. High resolution mass spectra were obtained from a VG 70-250S (double focusing) mass spectrometer at 70 eV.

Analytical TLC was performed using EM Separations precoated silica gel 0.2 mm layer UV 254 fluorescent sheets. Column chromatography was performed as "Flash Chromatography" as reported by Still[43] using (200-400 mesh) Merck grade silica gel.

Diethyl ether, THF, benzene and toluene were distilled from sodium benzophenone ketyl immediately prior to use. CH_2Cl_2 was distilled from calcium hydride. DME was distilled from sodium benzophenone ketyl and stored. DMF and $CHCl_3$ were dried and stored over activated molecular sieves. Spectro grade MeOH was purchased from Fisher and used as such. All other reagents were obtained from Aldrich and used as received unless otherwise stated.

1.10.2 Spectral data

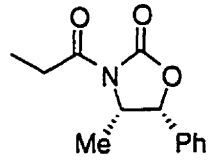
(4*S*,5*R*)-4-Methyl-5-phenyl-1,3-oxazolidin-2-one (27):



27

A mixture of (1*R*,2*S*)-(−)-norephedrine (7.62 g, 50.4 mmol), diethyl carbonate (13.5 mL, 111 mmol) and K_2CO_3 (696 mg, 5.04 mmol) was heated at ~80°C (until EtOH distill off from the reaction mixture) and the reaction mixture was stirred for 2.5 hours, allowing the distillation of EtOH. The heating was stopped and when the reaction mixture reached r.t. 20 mL of CH_2Cl_2 were added as well as 100 mL of EtOAc. The organic layer was washed with a saturated aqueous solution of NH_4Cl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude yellow solid was purified by recrystallization (hot EtOAc) and after filtration the mother liquors were purified by flash chromatography (Et_2O). The combined methods afforded 7.7 g of a white solid (88%). R_f = 0.57 (10% EtOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42-7.26 (5H, m), 6.25 (1H, br), 5.72 (1H, d, J = 8.1 Hz), 4.25-4.18 (1H, m), 0.82 (3H, d, J = 6.5 Hz); Mass calculated for $C_{10}H_{11}NO_2$: 177.204; Mass found: 177.200. The rest of the spectral data correspond to those reported in the literature.[44]

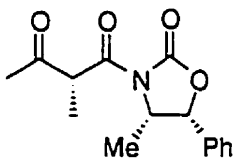
(4*S*,5*R*)-4-Methyl-5-phenyl-3-propionyl-1,3-oxazolidin-2-one (28):



28

To a cooled and colorless solution of **27** (7.57 g, 42.7 mmol) in dry THF (140 mL, 0.3 M) at -78°C was added dropwise *n*-BuLi (2.5 M/hexanes, 18.8 mL, 47.0 mmol). The clear solution turned dark orange at the end of the addition and the reaction mixture was stirred at -78°C for 45 minutes. Propionyl chloride (4.5 mL, 51.2 mmol) was then added and the solution became colorless. The reaction mixture was stirred at -78°C for 1 hour and then allowed to warm to r.t. before being quenched with saturated NH_4Cl. EtOAc was added (250 mL) and the two layers were separated. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. 10.0 g of pale yellow oil (100%) was isolated and used as such for the next step. R_f = 0.29 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS), δ 7.44-7.26 (5H, m), 5.67 (1H, d, J = 7.3 Hz), 4.77 (1H, apparent quintet, J = 6.8 Hz), 3.04-2.90 (2H, m), 1.19 (3H, t, J = 7.3 Hz), 0.90 (3H, d, J = 6.6 Hz); Mass calculated for $C_{13}H_{15}NO_3$: 233.269; Mass found: 233.263. The rest of the spectral data correspond to those reported in the literature.[45]

(4*S*,5*R*)-4-Methyl-3-[(2*R*)-2-methyl-3-oxobutanoyl]-5-phenyl-1,3-oxazolidin-2-one (29a):

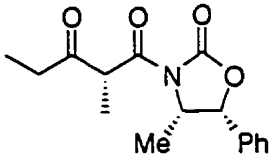


29a

Freshly distilled diisopropylamine (236 μL, 1.80 mmol) was dissolved in dry THF (1.5 mL, 1.2 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5 M/hexanes, 722 μL, 1.80 mmol). The pale yellow solution was stirred at 0°C for 20

minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28** (381 mg, 1.64 mmol) in dry THF (1.5 mL, 1.1 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 1 hour and then cannulated into a cooled solution of acetyl chloride (141 μL, 1.98 mmol) in dry THF (2.65 mL, 0.75 M) at -78°C. The reaction mixture was immediately quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (20% EtOAc in hexanes) and 336 mg (75%) of a white solid was isolated. R_f = 0.22 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS), δ 7.44-7.37 (3H, m), 7.30-7.26 (2H, m), 5.68 (1H, d, J = 7.3 Hz), 4.79 (1H, apparent quintet, J = 6.6 Hz), 4.55 (1H, q, J = 7.3 Hz), 2.34 (3H, s), 1.41 (3H, d, J = 7.1 Hz), 0.95 (3H, d, J = 6.6 Hz); Mass calculated for $C_{15}H_{17}NO_4$: 275.306; Mass found: 275.300. The rest of the spectral data correspond to those reported in the literature.[46]

(4*S*,5*R*)-4-Methyl-3-[(2*R*)-2-methyl-3-oxopentanoyl]-5-phenyl-1,3-oxazolidin-2-one (29b):

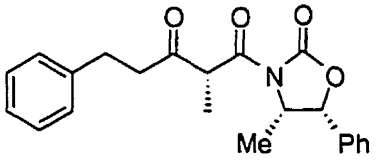


29b

Freshly distilled diisopropylamine (2.16 mL, 15.43 mmol) was dissolved in dry THF (40 mL, 0.4 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5

M/hexanes, 6.2 mL, 15.43 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28** (3.0 g, 12.86 mmol) in dry THF (10 mL, 1.3 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and then cannulated into a cooled solution of propionyl chloride (1.7 mL, 19.29 mmol) in dry THF (20 mL, 1.0 M) at -78°C. The reaction mixture was stirred at -78°C for 10 minutes and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (33% Et_2O in hexanes → 50% Et_2O in hexanes → 75% Et_2O in hexanes) and 3.03 g (81%) of a pale yellow solid was isolated (71% de). Subsequent recrystallization (hot Et_2O and hot EtOAc) afforded the pure major diastereomer as a white solid (2.56 g, 69%). $R_f = 0.16$ (33% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.26 (5H, m), 5.67 (1H, d, J = 7.3 Hz), 4.79 (1H, apparent quintet, J = 6.8 Hz), 4.53 (1H, q, J = 7.3 Hz), 2.79-2.60 (2H, m), 1.40 (3H, d, J = 7.2 Hz), 1.11 (3H, t, J = 7.2 Hz), 0.96 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 169.7, 153.1, 133.0, 128.6, 128.5, 125.5, 79.2, 54.7, 52.3, 33.7, 13.8, 12.6, 7.4; Mass calculated for $C_{16}H_{19}NO_4$: 289.333; Mass found: 289.326.

(4*S*,5*R*)-4-Methyl-3-[(2*R*)-2-methyl-3-oxo-5-phenylpentanoyl]-5-phenyl-1,3-oxazolidin-2-one (29c):

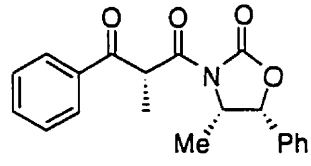


29c

Freshly distilled diisopropylamine (1.44 mL, 10.29 mmol) was dissolved in dry THF (10 mL, 0.1 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5 M/hexanes, 4.1 mL, 10.29 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28** (2.0 g, 8.57 mmol) in dry THF (9 mL, 0.95 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2.5 hours and then cannulated into a cooled solution of hydrocinnamoyl chloride (2.29 mL, 15.43 mmol) in dry THF (15 mL, 1.0 M) at -78°C. The reaction mixture was stirred at -78°C for 10 minutes and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (33% Et_2O in hexanes → 50% Et_2O in hexanes) and 1.88 g (60%) of a white solid was isolated (the 2 diastereomers could easily be separated and the minor diastereomer was not isolated). R_f = 0.20 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.18 (10H, m), 5.68 (1H, d, J = 7.3 Hz), 4.80 (1H, apparent quintet, J = 6.8 Hz), 4.52 (1H, q, J = 7.3 Hz), 2.96-2.90 (4H, m), 1.33 (3H, d, J = 7.3 Hz), 0.96 (3H, 2, J = 76.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 169.7, 153.3, 141.0, 133.0,

128.9, 128.7, 128.6, 128.52, 128.47, 128.4, 126.5, 126.1, 126.0, 125.7, 79.4, 55.0, 52.7, 42.5, 29.4, 14.0, 12.4; Mass calculated for $C_{22}H_{23}NO_4$: 365.431; Mass found: 365.422.

(4*S*,5*R*)-4-Methyl-3-[(2*R*)-2-methyl-3-oxo-3-phenylpropanoyl]-5-phenyl-1,3-oxazolidin-2-one (29d):

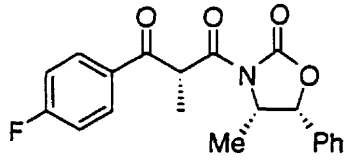


29d

Freshly distilled diisopropylamine (841 μL, 6.0 mmol) was dissolved in dry THF (10 mL, 0.6 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.3 M/hexanes, 2.6 mL, 6.0 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28** (1.0 g, 4.29 mmol) in dry THF (6 mL, 0.72 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2.5 hours prior to the addition of freshly distilled HMPA (4.2 mL, 24.2 mmol). A white precipitate appeared and the reaction mixture was stirred for 20 minutes at -78°C. By this time, the solution had turned orange. Benzoyl chloride (797 μL, 6.86 mmol) was added dropwise and the reaction mixture was stirred at -78°C for 50 minutes. It was subsequently warmed to 0°C over 40 minutes and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (33% Et_2O in hexanes) and 820 mg (57%) of a white solid was

isolated. The 2 diastereomers could easily be separated and the minor diastereomer was not isolated. R_f = 0.14 (33% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.99 (2H, d, *J* = 7.3 Hz), 7.59 (1H, t, *J* = 7.7 Hz), 7.50 (2H, t, *J* = 7.7 Hz), 7.42-7.36 (3H, m), 7.28 (2H, m) 5.70 (1H, d, *J* = 7.5 Hz), 5.40 (1H, q, *J* = 7.3 Hz), 4.85 (1H, apparent quintet, *J* = 6.6 Hz), 1.48 (3H, d, *J* = 7.3 Hz), 0.98 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 170.2, 153.2, 135.1, 133.2, 133.1, 128.7, 128.9, 128.62, 128.60, 125.6, 79.3, 54.8, 48.5, 14.0, 13.5; Mass calculated for $C_{20}H_{19}NO_4$: 337.377; Mass found: 337.369.

(4*S*,5*R*)-3-[(2*R*)-3-(4-Fluorophenyl)-2-methyl-3-oxopropanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one (29e):

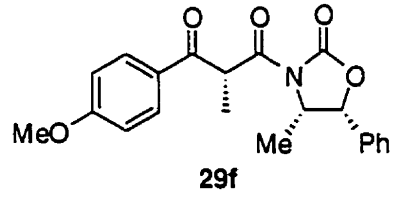


29e

Freshly distilled diisopropylamine (782 μL, 5.58 mmol) was dissolved in dry THF (10 mL, 0.6 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.3 M/hexanes, 2.4 mL, 5.58 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28** (1.0 g, 4.29 mmol) in dry THF (6 mL, 0.72 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours prior to the addition of a mixture of freshly distilled HMPA (1.2 mL, 6.86 mmol) and 4-fluorobenzoyl chloride (760 μL, 6.86 mmol) in dry THF (7 mL, 1 M). The reaction mixture was stirred for 20 minutes at -78°C and then warmed to r.t. The clear solution was quenched with a saturated aqueous

solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (33% Et_2O in hexanes → 50% Et_2O in hexanes) and 860 mg (57%) of a white solid was isolated. The 2 diastereomers could easily be separated and the minor diastereomer was not isolated. R_f = 0.14 (33% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.05-8.00 (2H, m), 7.42-7.33 (3H, m), 7.28-7.26 (2H, m), 7.19-7.14 (2H, m), 5.69 (1H, d, J = 7.3 Hz), 5.33 (1H, q, J = 7.3 Hz), 4.84 (1H, apparent quintet, J = 6.6 Hz), 1.46 (3H, d, J = 7.3 Hz), 0.97 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 169.9, 167.0, 164.5, 153.3, 133.0, 131.3, 131.2, 128.8, 128.6, 125.6, 115.9, 115.7, 79.3, 54.8, 48.4, 14.0, 13.5, Mass calculated for $C_{20}H_{18}FNO_4$: 355.368; Mass found: 355.360.

(4*S*,5*R*)-3-[(2*R*)-3-(4-Methoxyphenyl)-2-methyl-3-oxopropanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one (29f):

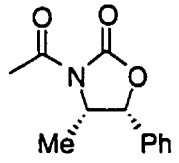


29f

Freshly distilled diisopropylamine (691 μL, 4.93 mmol) was dissolved in dry THF (10 mL, 0.5 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (1.75 M/hexanes, 2.81 mL, 4.93 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28** (1.0 g, 4.29 mmol) in dry THF (6 mL, 0.72 M) at (-78°C).

The yellow reaction mixture was stirred at -78°C for 2.5 hours prior to the addition of a mixture of freshly distilled HMPA (1.05 mL, 6.0 mmol) and 4-anisoyl chloride (1.02 g, 6.0 mmol) in dry THF (7 mL, 1.0 M). The reaction mixture was stirred for 1 hour at -78°C and then warmed to r.t. The clear solution was quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography with neutralized silica gel with 1% Et_3N (33% Et_2O in hexanes → 50% Et_2O in hexanes) and 758 mg (48%) of a white solid was isolated. R_f = 0.18 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.97 (2H, d, *J* = 8.9 Hz), 7.40-7.25 (5H, m), 6.96 (2H, d, *J* = 8.8 Hz), 5.66 (1H, d, *J* = 7.3 Hz), 5.34 (1H, q, *J* = 7.3 Hz), 4.83 (1H, m), 3.85 (3H, s), 1.46 (3H, d, *J* = 7.3 Hz), 0.96 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 170.3, 163.5, 153.1, 133.1, 130.9, 130.8,. 128.6, 128.5, 128.0, 125.6, 113.8, 79.1, 55.3, 54.7, 48.1, 13.9, 13.7; Mass calculated for $C_{21}H_{21}NO_5$: 367.404; Mass found: 367.395.

(4*S*,5*R*)-3-Acetyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one (28a):

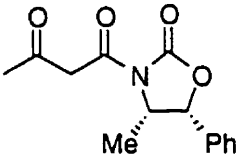


28a

To a cooled and colorless solution of **27** (1.0 g, 5.64 mmol) in dry THF (19 mL, 0.3 M) at -78°C was added dropwise *n*-BuLi (1.75 M/hexanes, 3.55 mL, 6.21 mmol). The reaction mixture was stirred at -78°C for 45 minutes prior to the addition of acetyl chloride (521

μL, 7.33 mmol). The pale yellow solution was then allowed to warm to r.t. The reaction was quenched with saturated NH_4Cl. EtOAc was added (50 mL) and the two layers were separated. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The desired product was purified by flash chromatography (50% Et_2O in hexanes) and 902 mg (73%) of a pale yellow oil was isolated and used as such for the next step. R_f = 0.73 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.26 (5H, m), 5.67 (1H, d, J = 7.3 Hz), 4.76 (1H, apparent quintet, J = 6.8 Hz), 2.57 (3H, s), 0.91 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 153.2, 133.2, 128.7, 128.6, 125.6, 78.9, 54.6, 23.8, 14.5; Mass calculated for $C_{12}H_{13}NO_3$: 219.242; Mass found: 219.237.

(4*S*,5*R*)-3-Acetoacetyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one (29g):

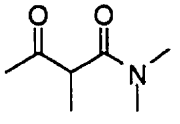


29g

Freshly distilled diisopropylamine (651 μL, 4.65 mmol) was dissolved in dry THF (10 mL, 0.47 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (1.75 M/hexanes, 2.66 mL, 4.65 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **28a** (815 mg, 3.72 mmol) in dry THF (6 mL, 0.6 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours. Acetyl chloride (423 μL, 5.95 mmol) was added dropwise to the reaction mixture and the solution was allowed to warm to r.t. It was subsequently quenched with a saturated aqueous solution of NH_4Cl.

The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (20% Et_2O in hexanes → 33% Et_2O in hexanes → 50% Et_2O in hexanes) and 220 mg (23%) of a white solid was isolated as well as 510 mg (62%) of recovered starting material. R_f = 0.20 (40% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.29 (5H, m) 5.71 (1H, d J = 7.5 Hz), 4.80 (1H, apparent quintet, J = 6.6 Hz, 4.06 (2H, s), 2.29 (3H, s), 0.93 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 166.7, 153.1, 133.0, 128.7, 128.6, 125.6, 79.1, 54.5, 51.3, 30.0, 14.3; Mass calculated for $C_{14}H_{15}NO_4$: 261.280; Mass found: 261.273.

***N,N*,2-Trimethyl-3-oxobutanamide (51a):**

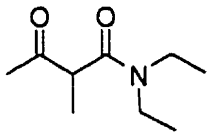


51a

Freshly distilled diisopropylamine (5.7 mL, 43.45 mmol) was dissolved in dry THF (40 mL, 1.1 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5 M/hexanes, 7.26 mL, 18.16 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of *N,N*-dimethylpropionamide (Aldrich, 4.0 g, 39.5 mmol) in dry THF (40 mL, 1.0 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 1 hour and then cannulated into a cooled solution of acetyl chloride (3.37 mL, 47.5 mmol) in dry THF (40 mL, 1.2 M) at -78°C. The reaction mixture was stirred at -78°C for 5

minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography using neutralized silica gel with 1% Et_3N (66% EtOAc in hexanes) and 3.52 g (62%) of a colorless oil was isolated. $R_f = 0.31$ (66% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.67 (1H, q, J = 7.0 Hz), 3.05 (3H, s), 2.99 (3H, s), 2.17 (3H, s), 1.37 (3H, d, J = 7.0 Hz); Mass calculated for $C_7H_{13}NO_2$: 143.187; Mass found: 143.184. The rest of the spectral data correspond to those reported in the literature.[47]

***N,N*-Diethyl-2-methyl-3-oxobutanamide (51b):**

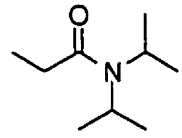


51b

Freshly distilled diisopropylamine (2.03 mL, 17.05 mmol) was dissolved in dry THF (16 mL, 1.05 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.15 M/hexanes, 7.9 mL, 17.05 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of *N,N*-diethylpropionamide (2.0 g, 15.5 mmol) in dry THF (16 mL, 1.0 M) at -78°C. The yellow reaction mixture was stirred at -40°C for 2 hours, cooled to -78°C and then cannulated into a cooled solution of acetyl chloride (2.16 mL, 12.9 mmol) in dry THF (16 mL, 0.8 M) at -78°C. The reaction mixture was stirred at

-78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography using neutralized silica gel with 1% Et_3N (75% Et_2O in EtOAc) and 760 mg (29%) of a colorless oil was isolated. R_f = 0.31 (75% Et_2O in EtOAc); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.62-3.56 (1H, m), 3.52-3.26 (4H, m), 2.19 (3H, s), 1.37 (3H, m), 1.24-1.11 (6H, m); Mass calculated for $C_9H_{17}NO_2$: 171.240; Mass found: 171.237. The rest of the spectral data correspond to those reported in the literature.[48]

***N,N*-Diisopropylpropanamide (190):**

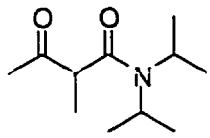


190

To a cooled solution of freshly distilled diisopropylamine (4.0 g, 39.5 mmol) in dry CH_2Cl_2 (90 mL, 0.2 M) at 0°C was added propionyl chloride (1.56 mL, 17.95 mmol) followed with DMAP (439 mg, 3.59 mmol). The reaction mixture was warmed to r.t and stirred for 3 hours. The organic extract was successively washed with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and evaporated to dryness. The desired product was purified by flash chromatography (100% Et_2O) and 2.82 g (100%) of a colorless oil was isolated. R_f = 0.19 (33% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.97 (1H, m), 3.49 (1H, br), 2.30 (2H, q, J = 7.3 Hz), 1.38 (6H, d, J = 6.6 Hz), 1.19 (6H,

d, J = 6.8 Hz), 1.12 (3H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 47.8, 45.1, 28.0, 20.6, 20.4, 9.3; Mass calculated for $C_9H_{19}NO$: 157.256; Mass found: 157.253.

_N,N_-Diisopropyl-2-methyl-3-oxobutanamide (51c):

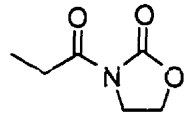


51c

Freshly distilled diisopropylamine (1.47 mL, 10.49 mmol) was dissolved in dry THF (20 mL, 0.5 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.34 M/hexanes, 4.48 mL, 10.49 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of *N,N*-diisopropylpropionamide **190** (1.5 g, 9.54 mmol) in dry THF (15 mL, 0.6 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and acetyl chloride (881 μL, 12.4 mmol) was added to it dropwise. The reaction mixture was stirred at -78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography using neutralized silica gel with 1% Et_3N (50% Et_2O in hexanes) and 1.39 g (77%) of a colorless oil was isolated. R_f = 0.23 (50% Et_2O in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.0 (1H, apparent heptuplet, J = 9.0 Hz) 3.57 (1H, q, J = 9.2 Hz), 3.49-3.40 (1H, br), 2.16 (3H, s), 1.40 (6H, dd, J_1 = 9.0 Hz, J_2 = 9.0 Hz), 1.34 (3H, d, J = 9.3 Hz), 1.19

(6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 138.9, 53.4, 46.0, 26.7, 20.9, 20.6, 20.5, 20.1, 13.6; Mass calculated for $C_{11}H_{21}NO_2$: 199.294; Mass found: 199.290.

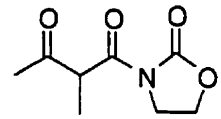
3-Propionyl-1,3-oxazolidin-2-one (31):



31

To a cooled and colorless solution of 2-oxazolidinone (Aldrich, 15 g, 172 mmol) in dry THF (500 mL, 0.35 M) at -78°C was added dropwise *n*-BuLi (2.5 M/hexanes, 75.7 mL, 189 mmol). The reaction mixture was stirred at 0°C for 2.5 hours prior to the addition of propionyl chloride (19.4 mL, 224 mmol). The pale yellow solution was stirred at 0°C for 30 minutes and then warmed to r.t. The reaction was quenched with saturated NH_4Cl. EtOAc was added (500 mL) and the two layers were separated. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The desired product was purified by recrystallization (hot EtOAc/hot Et_2O) and 16.94 g (69%) of a white solid was isolated. R_f = 0.6 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.41 (2H, t, J = 7.9 Hz), 4.03 (2H, t, J = 7.9 Hz), 2.94 (2H, q, J = 7.3 Hz), 1.18 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 153.5, 62.0, 42.4, 28.5, 8.1; Mass calculated for $C_6H_9NO_3$: 143.144; Mass found: 143.141.

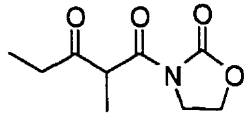
3-(2-Methyl-3-oxobutanoyl)-1,3-oxazolidin-2-one (51d):



51d

Freshly distilled diisopropylamine (1.09 mL, 7.76 mmol) was dissolved in dry THF (20 mL, 0.39 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5 M/hexanes, 3.1 mL, 7.76 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **31** (1.01 g, 7.06 mmol) in dry THF (5 mL, 1.4 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2.5 hours and then cannulated into a cooled solution of acetyl chloride (753 μL, 10.58 mmol) in dry THF (10 mL, 1.0 M) at -78°C. The reaction mixture was stirred at -78°C for 15 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (30% EtOAc in hexanes → 100% EtOAc) and 800 mg (62%) of a white solid was isolated. R_f = 0.58 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.57 (1H, q, *J* = 7.3 Hz), 4.48-4.39 (2H, m), 4.14-4.00 (2H, m), 2.31 (3H, s), 1.41 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 169.7, 153.7, 62.2, 52.7, 42.2, 28.0, 12.2; Mass calculated for $C_8H_{11}NO_4$: 185.182; Mass found: 185.177.

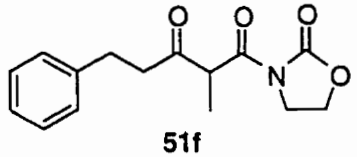
3-(2-Methyl-3-oxopentanoyl)-1,3-oxazolidin-2-one (51e):



51e

Freshly distilled diisopropylamine (2.55 mL, 18.16 mmol) was dissolved in dry THF (40 mL, 0.45 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5 M/hexanes, 7.26 mL, 18.16 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **31** (2.0 g, 13.97 mmol) in dry THF (10 mL, 1.4 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and then cannulated into a cooled solution of propionyl chloride (2.18 mL, 25.15 mmol) in dry THF (20 mL, 1.25 M) at -78°C. The reaction mixture was stirred at -78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (75% Et_2O in hexanes → 85% Et_2O in hexanes → 100% Et_2O) and 2.45 g (88%) of a white solid was isolated. R_f = 0.55 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.56 (1H, q, J = 7.3 Hz), 4.45-4.40 (2H, m), 4.14-4.00 (2H, m), 2.79-2.58 (2H, m), 1.40 (3H, d, J = 7.2 Hz), 1.08 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 170.4, 154.1, 62.6, 52.5, 42.7, 34.1, 13.0, 7.72; Mass calculated for $C_9H_{13}NO_4$: 199.209; Mass found: 199.204.

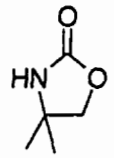
3-(2-Methyl-3-oxo-5-phenylpentanoyl)-1,3-oxazolidin-2-one (51f):



51f

Freshly distilled diisopropylamine (2.55 mL, 18.16 mmol) was dissolved in dry THF (40 mL, 0.45 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.5 M/hexanes, 7.26 mL, 18.16 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **31** (2.0 g, 13.97 mmol) in dry THF (10 mL, 1.4 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2.5 hours and then cannulated into a cooled solution of hydrocinnamoyl chloride (3.74 mL, 25.15 mmol) in dry THF (20 mL, 1.25 M) at -78°C. The reaction mixture was stirred at -78°C for 15 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (100% Et_2O) and 3.04 g (79%) of a white solid was isolated. R_f = 0.36 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.30-7.19 (5H, m), 4.55 (1H, q, J = 7.3 Hz), 4.46-4.39 (2H, m), 4.13-4.00 (2H, m), 3.06-2.83 (4H, m), 1.33 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 169.8, 153.8, 140.8, 128.3, 128.2, 126.0, 62.3, 52.4, 42.4, 42.3, 29.3, 12.4; Mass calculated for $C_{15}H_{17}NO_4$: 275.306; Mass found: 275.300.

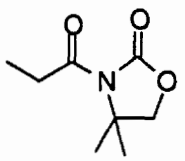
4,4-Dimethyl-1,3-oxazolidin-2-one (148):



148

A mixture of 2-amino-2-methylpropanol (Aldrich, 5.0 g, 56.1 mmol), diethyl carbonate (15.0 mL, 123.4 mmol) and K_2CO_3 (1.55 g, 11.22 mmol) was heated at ~80°C (until EtOH distill off from the reaction mixture) and the reaction mixture was stirred for 30 minutes, allowing the distillation of EtOH. The heating was stopped and the reaction mixture was allowed to cool to r.t. The reaction mixture was diluted in EtOAc and successively washed with a saturated aqueous solution of NH_4Cl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. 4.92 g (76%) of colorless oil was obtained and use as such for the next step. R_f = 0.37 (5% EtOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 5.57 (1H, br), 4.09 (2H, s), 1.37 (6H, s); Mass calculated for $C_5H_9NO_2$: 115.133; Mass found: 115.131. The rest of the spectral data correspond to those reported in the literature.[49]

4,4-Dimethyl-3-propionyl-1,3-oxazolidin-2-one (150):

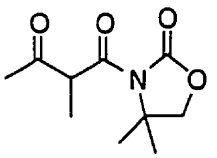


150

To a cooled and colorless solution of **148** (2.0 g, 17.4 mmol) in dry THF (50 mL, 0.35 M) at (78°C was added dropwise *n*-BuLi (1.75 M/hexanes, 10.9 mL, 19.1 mmol). The clear solution turned yellow at the end of the addition and the reaction mixture was stirred at

-78°C for 1 hour. Propionyl chloride (2.66 mL, 20.9 mmol) was then added dropwise at -78°C and the reaction mixture was allowed to warm to r.t. The reaction was then quenched with saturated NH_4Cl. EtOAc was added (100 mL) and the two layers were separated. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The desired product was purified by flash chromatography (25% Et_2O in hexanes → 33% Et_2O in hexanes) and 2.38 g (80%) of a colorless oil was isolated. R_f = 0.7 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.01 (2H, s), 2.90 (2H, q, J = 7.3 Hz), 1.58 (6H, s), 1.14 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 154.1, 75.1, 60.2, 30.4, 24.8, 8.2; Mass calculated for $C_8H_{13}NO_3$: 171.198; Mass found: 171.194.

4,4-Dimethyl-3-(2-methyl-3-oxobutanoyl)-1,3-oxazolidin-2-one (51g):

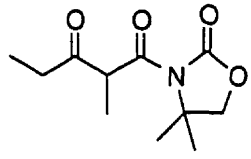


51g

Freshly distilled diisopropylamine (835 μL, 5.96 mmol) was dissolved in dry THF (10 mL, 0.6 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.27 M/hexanes, 2.63 mL, 5.96 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **150** (850 mg, 4.96 mmol) in dry THF (6 mL, 0.8 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and acetyl chloride (565 μL, 7.94 mmol) was added to it dropwise. The reaction mixture was stirred at -78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl.

The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (50% Et_2O in hexanes) and 340 mg (32%) of a white solid was isolated. R_f = 0.20 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.55 (1H, q, J = 7.3 Hz), 4.05-4.00 (2H, m), 2.29 (3H, s), 1.62 (3H, s), 1.60 (3H, s), 1.36 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 170.8, 154.4, 75.3, 60.5, 54.0, 28.3, 25.2, 24.6, 12.4; Mass calculated for $C_{10}H_{15}NO_4$: 213.236; Mass found: 213.230.

4,4-Dimethyl-3-(2-methyl-3-oxopentanoyl)-1,3-oxazolidin-2-one (51h):

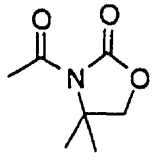


51h

Freshly distilled diisopropylamine (942 μL, 6.72 mmol) was dissolved in dry THF (10 mL, 0.67 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (1.75 M/hexanes, 3.8 mL, 6.72 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **150** (1.0 g, 5.84 mmol) in dry THF (6 mL, 1.0 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and propionyl chloride (970 μL, 7.59 mmol) was added to it dropwise. The reaction mixture was stirred at -78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed

by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (33% Et_2O in hexanes → 50% Et_2O in hexanes) and 1.09 g (82%) of a pale yellow oil was isolated. R_f = 0.11 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 5.39 (1H, q, J = 7.0 Hz), 4.03 (2H, s), 2.46 (2H, q, J = 7.5 Hz), 1.62 (3H, d, J = 7.0 Hz), 1.35 (6H, s), 1.22 (3H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 155.9, 134.9, 116.4, 75.4, 59.5, 27.3, 25.4, 11.7, 8.9; Mass calculated for $C_{11}H_{17}NO_4$: 227.262; Mass found: 227.257.

3-Acetyl-4,4-dimethyl-1,3-oxazolidin-2-one (167):

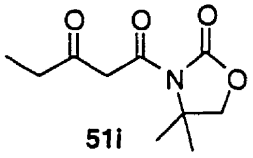


167

To a cooled and colorless solution of **148** (2.5 g, 21.7 mmol) in dry THF (50 mL, 0.43 M) at -78°C was added dropwise *n*-BuLi (2.03 M/hexanes, 11.8 mL, 23.9 mmol). The clear solution became a white suspension at the end of the addition and the reaction mixture was stirred at -78°C for 45 minutes. Acetyl chloride (2.0 mL, 28.2 mmol) was then added dropwise at -78°C and the reaction mixture turned successively orange, brown, and yellow before it was allowed to warm to r.t. The reaction was then quenched with saturated NH_4Cl. EtOAc was added (100 mL) and the two layers were separated. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The desired product was purified by flash chromatography (50% Et_2O in hexanes → 100% Et_2O) and 2.82 g (83%) of a yellow oil

was isolated. R_f = 0.56 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.01 (2H, s), 2.49 (3H, s), 1.58 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 154.1, 75.0, 60.0, 25.3, 24.6; Mass calculated for $C_7H_{11}NO_3$: 157.171; Mass found: 157.167.

4,4-Dimethyl-3-(3-oxopentanoyl)-1,3-oxazolidin-2-one (51i):

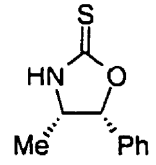


51i

Freshly distilled diisopropylamine (2.35 mL, 16.8 mmol) was dissolved in dry THF (20 mL, 0.84 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.03 M/hexanes, 8.3 mL, 16.8 mmol). The pale yellow solution was stirred at 0°C for 20 minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **167** (1.2 g, 7.64 mmol) in dry THF (12 mL, 0.64 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and propionyl chloride (1.1 mL, 8.4 mmol) was added to it dropwise. The reaction mixture was stirred at -78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (50% Et_2O in hexanes) and 720 mg (44%) of a pale yellow solid was isolated. R_f = 0.21 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (2H, s), 3.97 (2H, s), 2.56 (2H, q, J = 7.3 Hz), 1.62 (6H, s),

1.08 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 167.5, 154.2, 75.2, 60.2, 51.5, 35.9, 24.7, 7.3; Mass calculated for $C_{10}H_{15}NO_4$: 213.236; Mass found: 213.230.

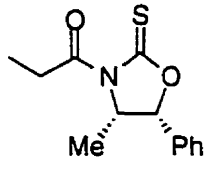
(4*S*,5*R*)-4-Methyl-5-phenyl-1,3-oxazolidine-2-thione (172):



172

To a mixture of (1*R*,2*S*)-(−)-norephedrine (1.0 g, 6.61 mmol), Na_2CO_3 (1.4 g, 13.22 mmol), and H_2O (14 mL, 0.47 M) was added CS_2 (600 μL, 9.92 mmol) at r.t. The solution was heated at 110°C for 1 hour. After cooling to r.t., the reaction mixture was extracted 3 times with CH_2Cl_2 and the organic extract was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was diluted in EtOAC. The combined methods afforded 1.45 g of a white solid (>100%). R_f = 0.66 (10% EtOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.38 (3H, m), 7.32-7.27 (2H, m), 7.15 (1H, br), 5.97 (1H, d, J = 8.1 Hz), 4.40 (1H, m), 0.87 (3H, d, J = 6.6 Hz); Mass calculated for $C_{10}H_{11}NOS$: 193.264; Mass found: 193.266. The rest of the spectral data correspond to those reported in the literature.[50]

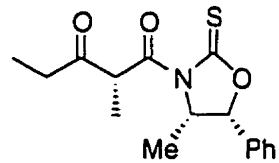
(4*S*,5*R*)-4-Methyl-5-phenyl-3-propionyl-1,3-oxazolidine-2-thione (174):



174

To a cooled suspension of NaH 95% (318 mg, 13 mmol) in dry THF (5 mL) at 0°C was added a cooled solution of **172** (1.28 g, 6.62 mmol) in dry THF (5 mL) at 0°C *via* cannula. 10 mL of dry THF (final concentration = 0.33 M) was added and the reaction mixture was stirred at 0°C for 10 minutes prior to the addition of propionyl chloride (1.1 mL, 8.61 mL). The reaction was warmed to r.t. and then quenched with H_2O. EtOAc was added, the two layers were separated, and the aqueous phase was extracted twice with EtOAc. The organic extract was dried over $MgSO_4$, filtered and evaporated to dryness. The desired compound was purified by flash chromatography (33% Et_2O in hexanes) and 1.55 g (94%) of a pale yellow oil was isolated. Rf = 0.58 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45-7.34 (5H, m), 5.76 (1H, d, J = 7.3 Hz), 5.01 (1H, apparent quintet, *J* = 6.7 Hz), 3.47-3.37 (1H, m), 3.30-3.20 (1H, m), 1.22 (3H, t, *J* = 7.3 Hz), 0.95 (3H, d, *J* = 6.6 Hz); Mass calculated for $C_{13}H_{15}NO_2S$: 249.335; Mass found: 249.330. The rest of the spectral data correspond to those reported in the literature.[51]

(2*R*)-2-Methyl-1-[(4*S*,5*R*)-4-methyl-5-phenyl-2-thioxo-1,3-oxazolidin-3-yl]-1-oxopentan-3-one) (51j):

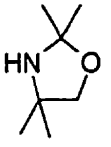


51j

Freshly distilled diisopropylamine (585 μL, 4.17 mmol) was dissolved in dry THF (10 mL, 0.4 M) and the solution was cooled to 0°C prior to the addition of *n*-BuLi (2.34 M/hexanes, 1.8 mL, 4.17 mmol). The pale yellow solution was stirred at 0°C for 20

minutes and then cooled to -78°C. The freshly prepared LDA solution was cannulated into a cooled solution of **174** (800 mg, 3.2 mmol) in dry THF (6 mL, 0.5 M) at -78°C. The yellow reaction mixture was stirred at -78°C for 2 hours and propionyl chloride (653 μL, 5.12 mmol) was added to it dropwise. The reaction mixture was stirred at -78°C for 5 minutes, warmed to r.t., and then quenched with a saturated aqueous solution of NH_4Cl. The desired product was isolated by dilution of the quenched reaction with H_2O followed by CH_2Cl_2 extraction. The organic extract was washed successively with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (33% Et_2O in hexanes) and 615 mg (62%) of a pale yellow oil was isolated. $R_f = 0.23$ (33% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.4-7.24 (5H, m), 5.81 (1H, d, J = 7.3 Hz), 5.50 (1H, q. J = 7.3 Hz), 4.50, (1H, m), 2.57 (2H, q, J = 7.2 Hz), 2.70 (3H, d, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 0.91 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 172.0, 136.2, 133.7, 128.8, 128.5, 126.1, 84.2, 60.1, 45.3, 26.9, 14.7, 11.2, 9.4; Mass calculated for $C_{16}H_{19}NO_3S$: 305.399; Mass found: 305.396.

2,2,4,4-Tetramethyl-1,3-oxazolidine (183):

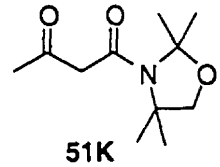


183

A mixture of 2-methyl-2-aminopropanol (25.0 g, 280 mmol), *p*-TsOH (5.33 g, 17 mmol), Na_2SO_4 (39.8 g, 280 mmol) in acetone (200 mL) was refluxed overnight. The solution was then filtered to remove Na_2SO_4 and the solvent was evaporated *in vacuo*. The

residue was diluted in Et_2O and the organic layer was successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was distilled under atmospheric pressure to afford 8.58 g (24%) of a colorless oil. R_f = 0.35 (10% EtOH in EtOAC); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.60 (2H, s), 1.75 (1H, br), 1.40 (6H, s), 1.26 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.1, 76.9, 59.3, 28.5, 28.0; Mass calculated for $C_7H_{15}NO$: 129.203; Mass found: 129.200.

4-Oxo-4-(2,2,4,4-tetramethyl-1,3-oxazolidin-3-yl)butan-2-one (51k):



51K

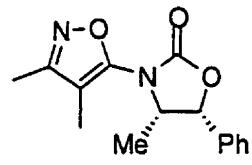
A solution of 2,2,4,4-tetramethyloxazolidinone **183** (1.0 g, 7.74 mmol) in dry THF (10 mL) was transferred *via* cannula into a suspension of NaH 95% (391 mg, 15.5 mmol) in dry THF (30 mL, final concentration = 0.2 M). The reaction mixture was stirred at r.t. for 1 hour prior to the dropwise addition of diketene (657 μL, 8.51 mmol). Freshly distilled Et_3N (1.08 mL 7.74 mmol) and DMAP (189 mg, 4.55 mmol) were subsequently added and the reaction mixture was stirred at r.t. for 10 minutes. TLC analysis revealed the completion of the reaction and the solution was then quenched with a saturated aqueous solution of NH_4Cl. The desired product was extracted several times with Et_2O and the organic extract was successively washed with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (50% Et_2O in hexanes) and 1.23 g (75%) of a colorless oil was isolated. R_f: 0.24 (50% Et_2O in hexanes); IR (NaCl, $CHCl_3$, cm^{-1}) 2979 (s), 2937 (s), 2866 (s), 1722 (s), 1634 (br), 1581 (s), 1472 (s), 1342 (s), 1198 (s), 1068 (s); ^1H NMR (400 MHz,

DMSO-d_6, 80°C) δ 3.75 (2H, s), 3.51 (1H, s), 3.10 (1H, s), 2.16 (1.5H, s), 1.92 (1.5H, s), 1.56 (3H, s), 1.52 (3H, s), 1.42 (3H, s), 1.38 (3H, s); Mass calculated for $C_{11}H_{19}NO_3$: 213.278; Mass found: 213.274.

Typical procedure for the synthesis of isoxazoles:

To a solution of compound **29a** (153 mg, 0.554 mmol) in MeOH (2.7 mL, 0.2 M) at 0°C was added NH_2OH•HCl (58 mg, 0.831 mmol) and NaOAc (2.3 mg, 0.028 mmol). The reaction mixture was heated at reflux for 20 hours. The solvent was removed *in vacuo* and the residue was diluted in EtOAc (15 mL). The organic layer was washed with brine (10 mL) and the aqueous layer was re-extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by chromatography on silica gel with CH_2Cl_2/hexanes/EtOAc 60/30/10 as eluent to afford 120 mg (80%) of **30a** as a white solid.

(4*S*,5*R*)-3-(3,4-Dimethyl-isoxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (30a):

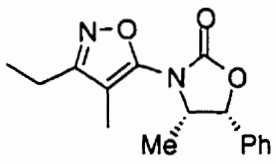


30a

R_f = 0.37 (6/3/1 CH_2Cl_2/hexanes/EtOAc); IR (NaCl, $CHCl_3$, cm^{-1}) 3027 (s), 3011 (s), 1772 (s), 1661 (s), 1218 (s); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42-7.30 (5H, m), 5.82 (1H, d, J = 7.5 Hz), 4.69-4.62 (1H, apparent quintet, J = 6.6 Hz), 2.21 (3H, s), 1.95 (3H, s), 0.84 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 155.0, 153.4, 133.9,

129.0, 128.7, 126.0, 106.2, 79.8, 57.2, 15.4, 10.7, 7.0; Mass calculated for $C_{15}H_{16}N_2O_3$: 272.299; Mass found: 272.116.

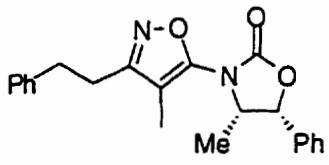
(4*S*,5*R*)-3-(3-Ethyl-4-methyl-isoxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (30b):



30b

R_f = 0.67 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46-7.37 (3H, m), 7.33 (2H, m), 5.84 (1H, d, *J* = 8.1 Hz), 4.68 (1H, apparent quintet, *J* = 6.8 Hz), 2.63 (2H, q, *J* = 7.5 Hz), 1.98 (3H, s), 1.30 (3H, t, *J* = 7.5 Hz), 0.84 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.9, 153.2, 133.8, 128.7, 128.5, 125.8, 105.6, 79.6, 57.0, 19.0, 15.2, 11.2, 6.6; Mass calculated for $C_{16}H_{18}N_2O_3$: 286.326; Mass found: 286.131.

(4*S*,5*R*)-4-Methyl-3-[-4-methyl-3-(2-phenylethyl)isoxazol-5-yl)-5-phenyl-1,3-oxazolidin-2-one (30c):

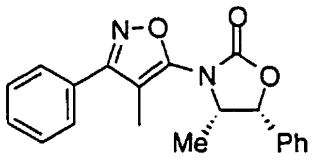


30c

R_f = 0.63 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45-7.36 (3H, m), 7.33-7.25 (4H, m), 7.22-7.19 (3H, m), 5.82 (1H, d, *J* = 8.0 Hz), 4.66 (1H, apparent quintet, *J* = 6.6 Hz), 3.04-2.99 (2H, m), 2.91-2.87 (2H, m), 1.87 (3H, s), 0.84 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 155.1, 153.2, 140.6, 133.9, 128.9, 128.6, 128.4, 128.3,

126.2, 125.9, 106.0, 79.7, 57.1, 33.4, 27.6, 15.3, 6.7; Mass calculated for $C_{22}H_{22}N_2O_3$: 362.422; Mass found: 362.164.

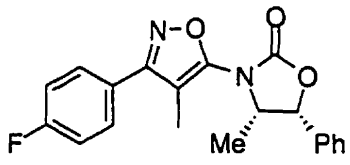
(4*S*,5*R*)-4-Methyl-3-(4-methyl-3-phenylisoxazol-5-yl)-5-phenyl-1,3-oxazolidin-2-one (30d):



30d

R_f = 0.42 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.68-7.65 (2H, m), 7.51-7.35 (8H, m), 5.89 (1H, d, *J* = 8.1 Hz), 4.75 (1H, apparent quintet, *J* = 6.6 Hz), 2.14 (3H, s), 0.92 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 156.3, 153.4, 133.9, 129.8, 129.1, 129.0, 128.80, 128.78, 128.7, 128.6, 128.0, 126.0, 106.1, 79.9, 57.4, 15.5, 8.3; Mass calculated for $C_{20}H_{18}N_2O_3$: 334.376; Mass found: 334.369.

(4*S*,5*R*)-3-[3-(4-Fluorophenyl)-(4-methylisoxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (30e):

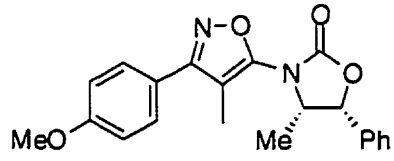


30e

R_f = 0.39 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.68-7.65 (2H, m), 7.47-7.41 (3H, m), 7.37-7.35 (2H, m), 7.21-7.16 (2H, m), 5.89 (1H, d, *J* = 8.1 Hz), 4.75 (1H, apparent quintet, *J* = 6.6 Hz), 2.13 (3H, s), 0.92 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.4, 162.4, 156.4, 153.3, 133.8, 130.0, 129.9, 129.0, 128.8,

126.0, 116.1, 115.9, 105.9, 80.0, 57.4, 15.5, 8.3; Mass calculated for $C_{20}H_{17}FN_2O_3$: 352.359; Mass found: 352.124.

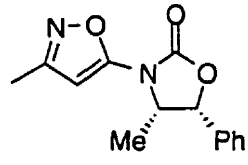
(4*S*,5*R*)-3-[3-(4-Methoxyphenyl)-(4-methylisoxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (30f):



30f

R_f = 0.22 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.62 (2H, d, *J* = 9.0 Hz), 7.48-7.35 (5H, m), 7.01 (2H, d, *J* = 9.0 Hz), 5.88 (1H, d, *J* = 7.9 Hz), 4.74 (1H, apparent quintet, *J* = 6.6 Hz), 3.87 (3H, s), 2.13 (3H, s), 0.92 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.8, 156.0, 153.4, 133.9, 129.3, 129.0, 128.8, 126.0, 121.6, 114.3, 105.9, 79.9, 57.4, 55.3, 15.5, 8.5; Mass calculated for $C_{21}H_{20}N_2O_4$: 364.403; Mass found: 364.395.

(4*S*,5*R*)-4-Methyl-3-(3-methylisoxazol-5-yl)-5-phenyl-1,3-oxazolidin-2-one (30g):

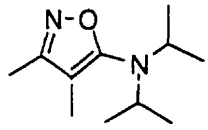


30g

R_f = 0.68 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47-7.34 (5H, m), 6.21 (1H, s), 5.84 (1H, d, *J* = 7.7 Hz), 4.83 (1H, apparent quintet, *J* = 6.6 Hz), 2.29 (3H, s), 0.99 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 159.6, 152.0, 133.1,

128.9, 128.7, 125.7, 89.0, 79.6, 56.0, 15.1, 11.7; Mass calculated for $C_{14}H_{14}N_2O_3$: 258.273; Mass found: 258.101.

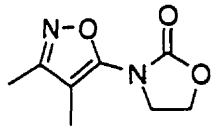
***N,N*-Diisopropyl-3,4-dimethylisoxazol-5-amine (52c):**



52c

R_f = 0.75 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.53 (2H, apparent heptuplet, J = 6.6 Hz), 2.16 (3H, s), 1.82 (3H, s), 1.12 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 160.9, 101.6, 49.6, 21.9, 11.0, 7.7; Mass calculated for $C_{11}H_{20}N_2O$: 196.293; Mass found: 196.289.

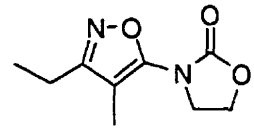
3-(3,4-Dimethylisoxazol-5-yl)-1,3-oxazolidin-2-one (52d):



52d

R_f = 0.45 (100% EtOAc); IR (NaCl, $CHCl_3$, cm^{-1}) 30010 (s), 2993 (s), 1775 (s), 1662 (s), 1434 (s), 1214 (s); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.57 (2H, dd, J_1 = 9.4 Hz, J_2 = 8.1 Hz), 4.12 (2H, dd, J_1 = 8.2 Hz, J_2 = 9.4 Hz), 2.22 (3H, s), 1.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 155.8, 153.9, 103.3, 63.4, 45.2, 10.8, 7.2; Mass calculated for $C_8H_{10}N_2O_3$: 182.181: Mass found: 182.177.

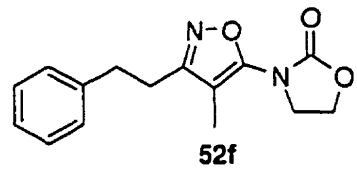
3-(3-Ethyl-4-methylisoxazol-5-yl)-1,3-oxazolidin-2-one (52e):



52e

R_f = 0.53 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.57 (2H, dd, J_1 = 7.7 Hz, J_2 = 8.3 Hz), 4.11 (2H, dd, J_1 = 7.7 Hz, J_2 = 8.5 Hz), 2.62 (2H, q, J = 7.7 Hz), 1.98 (3H, s), 1.28 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.6, 153.6, 102.5, 63.0, 45.0, 19.0, 11.4, 6.9; Mass calculated for $C_9H_{12}N_2O_3$: 196.208; Mass found: 196.203.

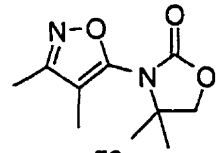
3-[4-Methyl-3-(2-phenylethyl)isoxazol-5-yl]-1,3-oxazolidin-2-one (52f):



52f

R_f = 0.74 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.33-7.22 (5H, m), 4.57 (2H, dd, J_1 = 7.4 Hz, J_2 = 8.8 Hz), 4.12 (2H, dd, J_1 = 8.1 Hz, J_2 = 8.8 Hz), 3.03-2.99 (2H, m), 2.90-2.86 (2H, m), 1.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 155.8, 153.5, 140.7, 128.5, 128.3, 126.3, 102.8, 63.1, 45.0, 33.4, 27.6, 6.9; Mass calculated for $C_{15}H_{16}N_2O_3$: 272.299; Mass found: 272.115.

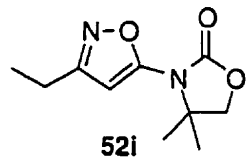
3-(3,4-Dimethylisozaxol-5-yl)-4,4-dimethyl-1,3-oxazolidin-2-one (52g):



52g

R_f = 0.40 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 4.23 (2H, s), 2.25 (3H, s), 1.90 (3H, s), 1.98 (3H, s), 1.46 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 154.9, 141.2, 108.5, 76.0, 61.0, 25.7, 10.7, 6.8; Mass calculated for $C_{10}H_{14}N_2O_3$: 210.235; Mass found: 210.230.

3-(3-Ethylisozaxol-5-yl)-4,4-dimethyl-1,3-oxazolidin-2-one (52i):



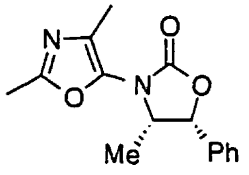
52i

R_f = 0.59 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 6.21 (1H, s), 4.18 (2H, s), 2.67 (2H, d, *J* = 7.7 Hz), 1.64 (6H, s), 1.28 (3H, t, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 160.1, 152.8, 89.7, 75.6, 61.0, 25.5, 19.8, 12.1; Mass calculated for $C_{10}H_{14}N_2O_3$: 210.230; Mass found: 210.102.

Typical procedure for the synthesis of oxazoles:

To a cooled solution of compound **29a** (106 mg, 0.385 mmol) in $CHCl_3$ (2.0 mL) at 0°C was added NaN_3 (75 mg, 1.16 mmol) followed by CH_3SO_3H (235 μL, 3.62 mmol). The cooling bath was removed and the reaction mixture was heated at reflux for 12 hours. The mixture was then poured into water (10 mL) and extracted with EtOAc. The organic layer was neutralized with sat. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel with CH_2Cl_2/hexanes/EtOAc 60/30/10 as eluent to afford 63 mg (60%) of **32a** as a colorless oil.

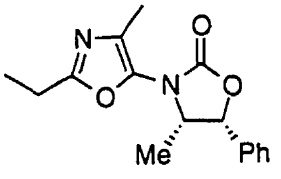
(4*S*,5*R*)-3-(2,4-Dimethyl-1,3-oxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (32a):



32a

R_f = 0.32 (50% Et_2O in CH_2Cl_2); IR (NaCl, $CHCl_3$, cm^{-1}) 2984 (s), 2929 (s), 1768 (s), 1673 (s), 1574 (s), 1382 (s); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46-7.32 (5H, m), 5.80 (1H, d, *J* = 8.0 Hz), 4.43 (1H, apparent quintet, *J* = 6.6 Hz), 2.40 (3H, s), 2.10 (3H, s) 0.81 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 155.2, 134.3, 131.8, 128.9, 128.7, 126.0, 79.5, 57.9, 15.3, 14.3, 11.1; Mass calculated for $C_{15}H_{16}N_2O_3$: 272.305; Mass found: 272.116.

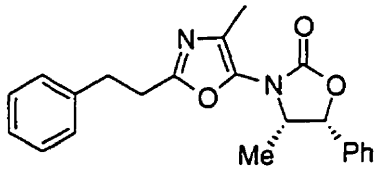
(4*S*,5*R*)-3-(2-Ethyl-4-methyl-1,3-oxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (32b):



32b

R_f = 0.31 (50% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46-7.31 (5H, m), 5.81 (1H, d, *J* = 8.1 Hz), 4.42 (1H, apparent quintet, *J* = 6.6 Hz), 2.11 (3H, s), 1.32 (3H, t, *J* = 7.5 Hz) 0.81 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 155.2, 136.1, 134.2, 131.4, 128.8, 128.7, 128.5, 125.9, 79.5, 57.8, 21.9, 15.2, 11.0, 10.7; Mass calculated for $C_{16}H_{18}N_2O_3$: 286.332; Mass found: 286.326.

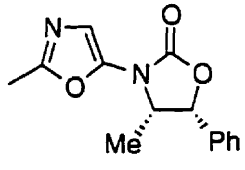
(4*S*,5*R*)-4-Methyl-3-[4-methyl-2-(2-phenylethyl)-1,3-oxazol-5-yl)-5-phenyl-1,3-oxazolidin-2-one (32c):



32c

R_f = 0.60 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45-7.40 (3H, m), 7.39-7.26 (4H, m), 7.22-7.18 (3H, m), 5.79 (1H, d, *J* = 8.1 Hz), 4.38 (1H, apparent quintet, *J* = 6.6 Hz), 3.08-2.98 (4H, m), 2.11 (3H, s), 0.76 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 155.1, 140.1, 136.2, 134.2, 131.6, 128.9, 128.7, 128.5, 128.2, 126.4, 126.0, 79.5, 57.8, 32.9, 30.3, 15.2, 11.1; Mass calculated for $C_{22}H_{22}N_2O_3$: 362.430; Mass found: 362.422.

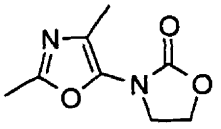
(4*S*,5*R*)-4-Methyl-3-(2-methyl-1,3-oxazol-5-yl)-5-phenyl-1,3-oxazolidin-2-one (32g):



32g

R_f = 0.20 (100% Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46-7.37 (3H, m), 7.34-7.28 (2H, m), 6.90 (1H, s), 5.82 (1H, d, *J* = 7.7 Hz), 4.52 (1H, apparent quintet, *J* = 6.6 Hz), 2.44 (3H, s), 0.87 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 133.8, 128.9, 128.7, 125.9, 118.0, 79.5, 57.5, 15.2, 14.1; Mass calculated for $C_{14}H_{14}N_2O_3$:258.273; Mass found: 258.100.

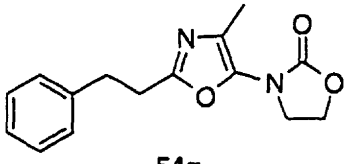
3-(2,4-Dimethyl-1,3-oxazol-5-yl)-1,3-oxazolidin-2-one (54e):



54e

R_f = 0.25 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.54 (2H, dd, J_1 = 7.9 Hz, J_2 = 8.0 Hz), 3.93 (2H, dd, J_1 = 8.1 Hz, J_2 = 7.9 Hz), 2.39 (3H, s), 2.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 155.5, 137.2, 129.5, 62.7, 46.4, 14.1, 10.9; Mass calculated for $C_8H_{10}N_2O_3$: 182.181; Mass found: 182.177.

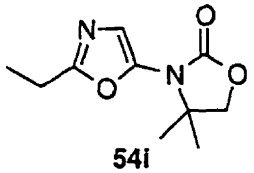
3-[4-Methyl-2-(2-phenylethyl)-1,3-oxazol-5-yl]-1,3-oxazolidin-2-one (54g):



54g

R_f = 0.58 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.32-7.19 (5H, m), 4.53 (2H, m), 3.93 (2H, m), 3.09-2.96 (4H, m), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 155.5, 140.2, 137.2, 129.5, 128.5, 128.3, 126.4, 62.7, 46.4, 32.9, 30.3, 11.1; Mass calculated for $C_{15}H_{16}N_2O_3$: 272.305; Mass found: 272.299.

3-(2-Ethyl-1,3-oxazol-5-yl)-4,4-dimethyl-1,3-oxazolidin-2-one (54i):

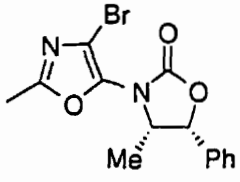


54i

R_f = 0.15 (100% Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.89 (1H, s), 4.22 (2H, s), 2.78 (2H, q, J = 7.5 Hz), 1.39 (6H, s), 1.34 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 164.2, 140.1, 122.3, 75.6, 60.1, 25.6, 21.9, 10.6; Mass calculated for $C_{10}H_{14}N_2O_3$: 210.230; Mass found: 210.101.

(4*S*,5*R*)-3-(4-Bromo-2-methyl-1,3-oxazol-5-yl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (65):



65

R_f = 0.70 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46-7.40 (3H, m), 7.35-7.33 (2H, m), 5.82 (1H, d, J = 8.1 Hz), 4.51 (1H, apparent quintet, J = 6.6 Hz), 2.46 (3H, s), 1.55 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 154.7, 142.0, 133.9, 129.1, 128.8, 126.1, 112.8, 79.9, 57.7, 15.4, 14.7; Mass calculated for $C_{14}H_{13}BrN_2O_3$: 337.175; Mass found: 337.169.

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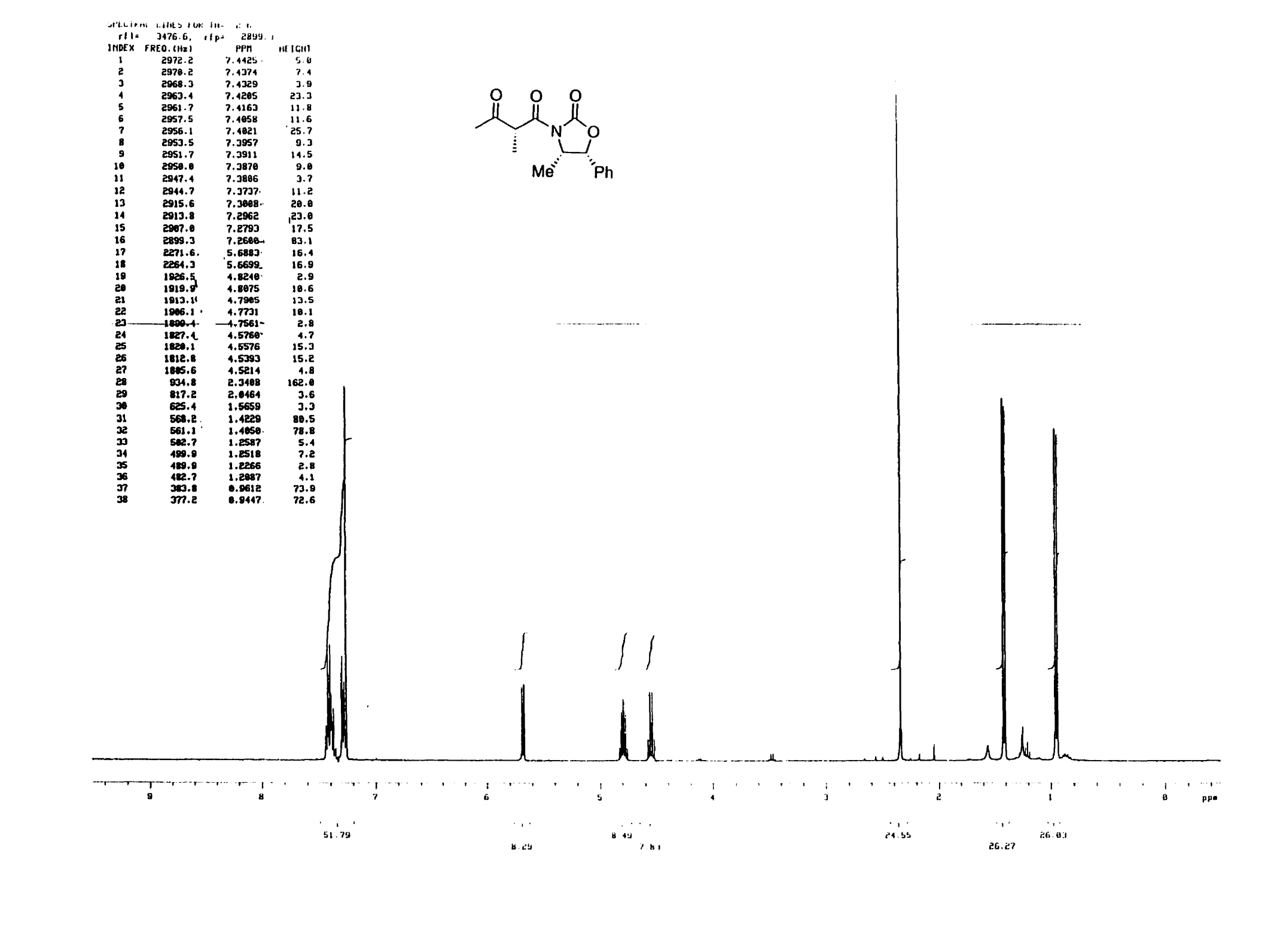

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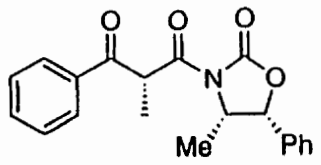
3	2968.3	7.4329	3.9
4	2963.4	7.4205	23.3
5	2961.7	7.4163	11.8
6	2957.5	7.4058	11.6
7	2956.1	7.4021	25.7
8	2953.5	7.3957	9.3
9	2951.7	7.3911	14.5
10	2950.0	7.3870	9.0
11	2947.4	7.3806	3.7
12	2944.7	7.3737	11.2
13	2915.6	7.3008	20.0
14	2913.8	7.2962	23.0
15	2907.0	7.2793	17.5
16	2899.3	7.2600	83.1
17	2271.6	5.6883	16.4
18	2264.3	5.6699	16.9
19	1926.5	4.8240	2.9
20	1919.9	4.8075	10.6
21	1913.1	4.7905	13.5
22	1906.1	4.7731	10.1
23	1899.4	4.7561	2.8
24	1827.4	4.5760	4.7
25	1820.1	4.5576	15.3
26	1812.8	4.5393	15.2
27	1805.6	4.5214	4.8
28	934.8	2.3408	162.0
29	817.2	2.0464	3.6
30	625.4	1.5659	3.3
31	568.2	1.4229	80.5
32	561.1	1.4050	78.8
33	502.7	1.2587	5.4
34	499.9	1.2518	7.2
35	489.9	1.2266	2.8
36	482.7	1.2087	4.1
37	383.8	0.9612	73.9
38	377.2	0.9447	72.6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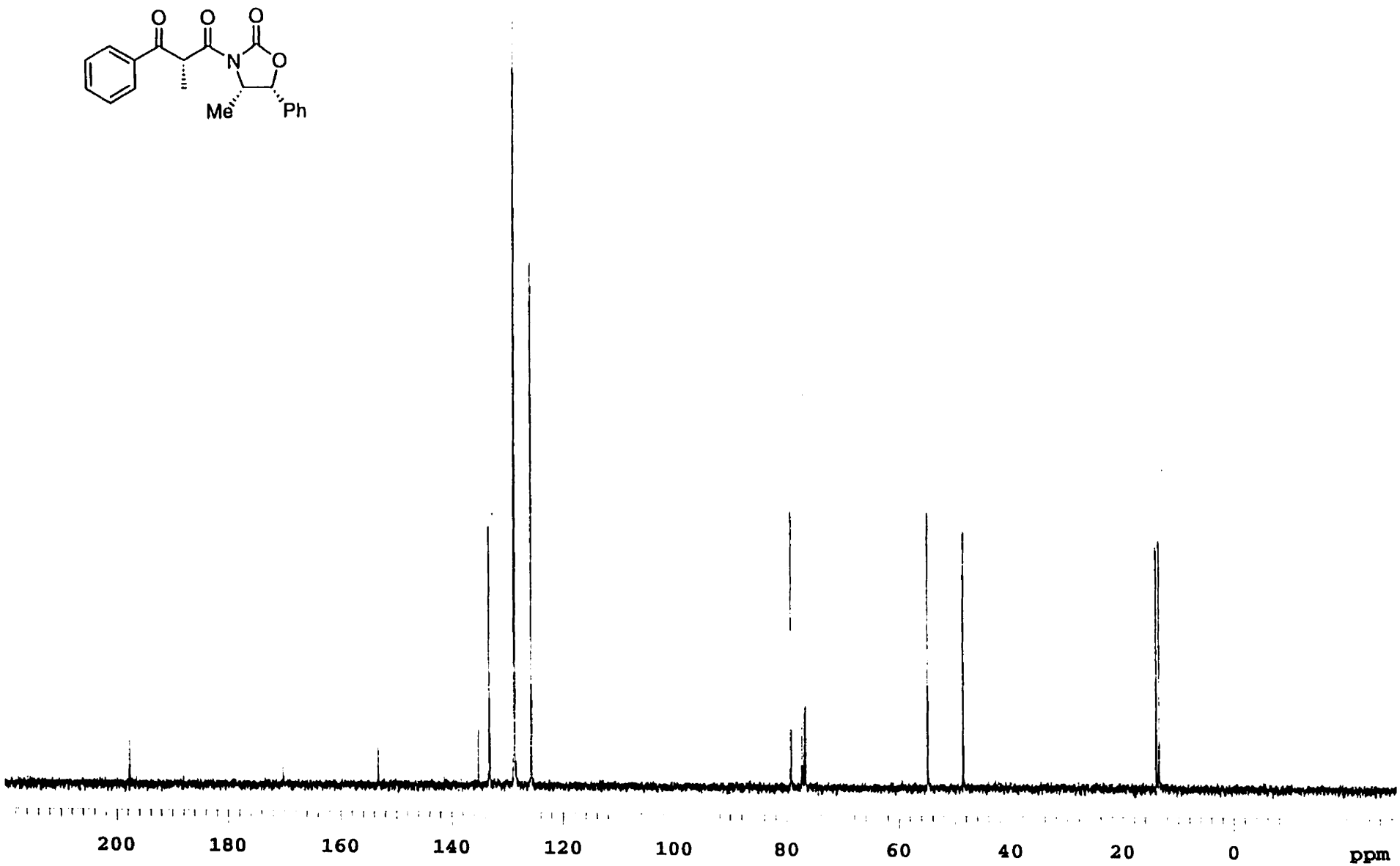
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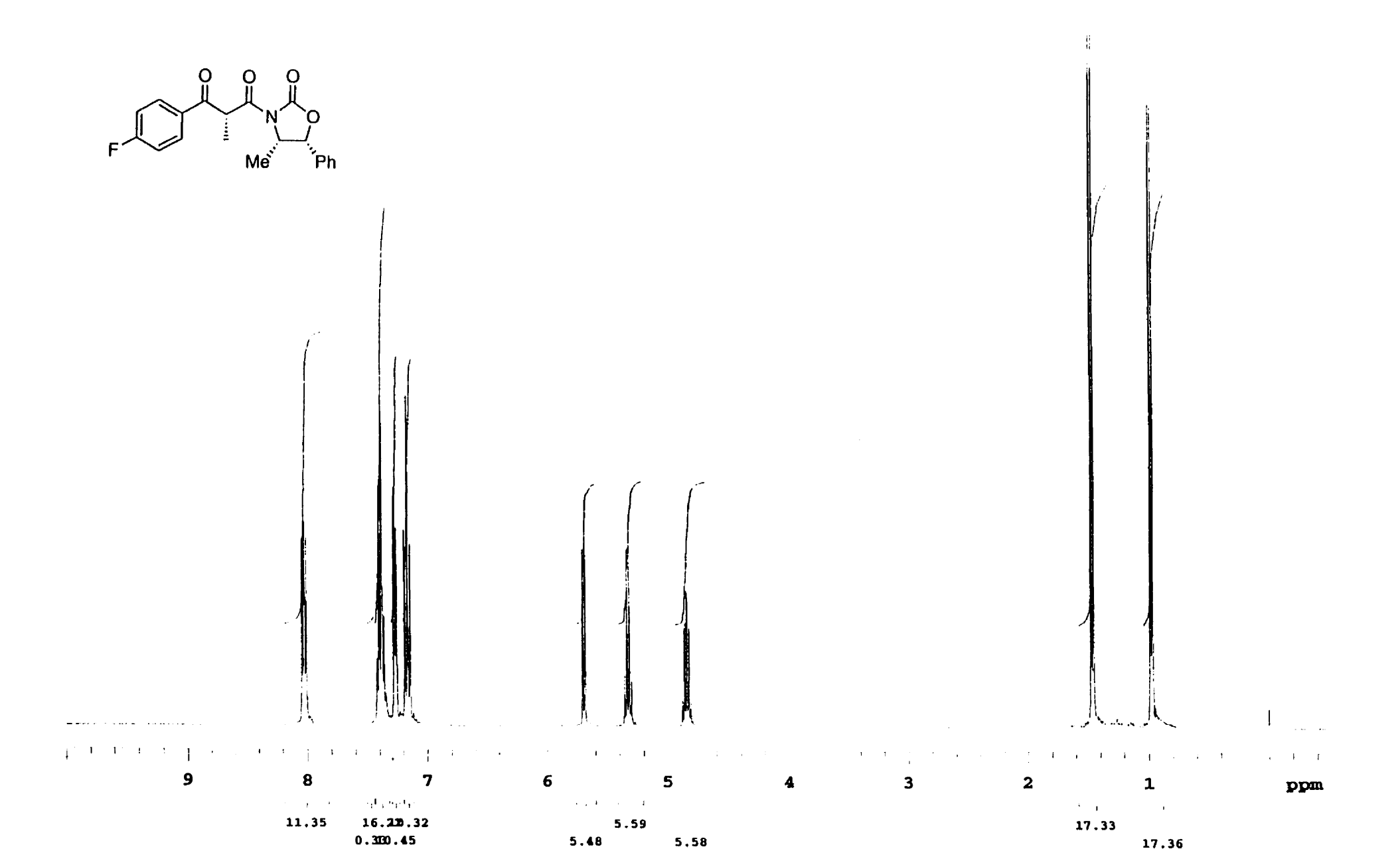
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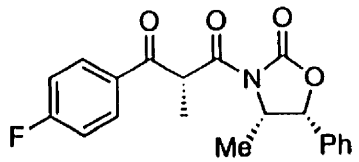
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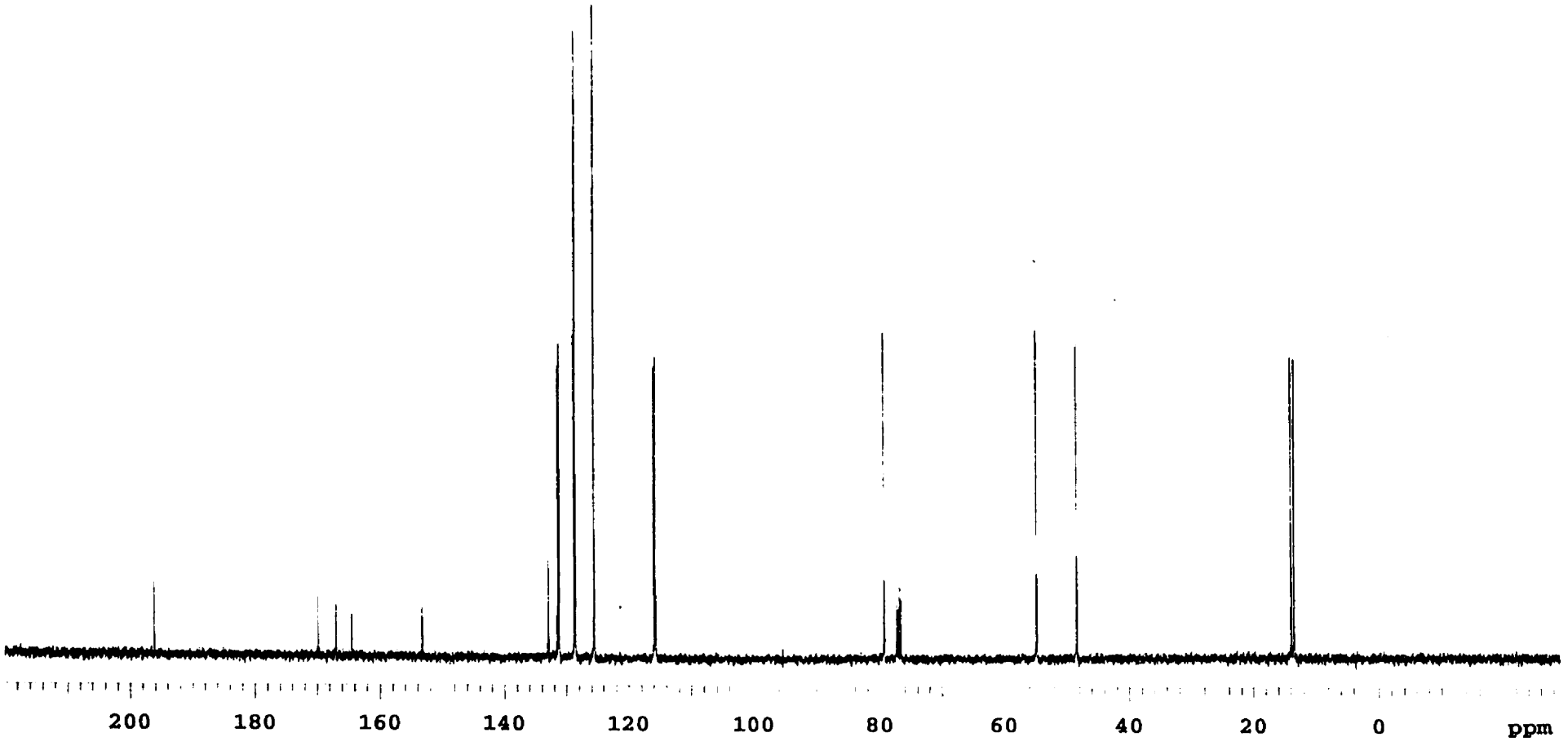
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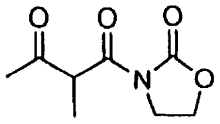

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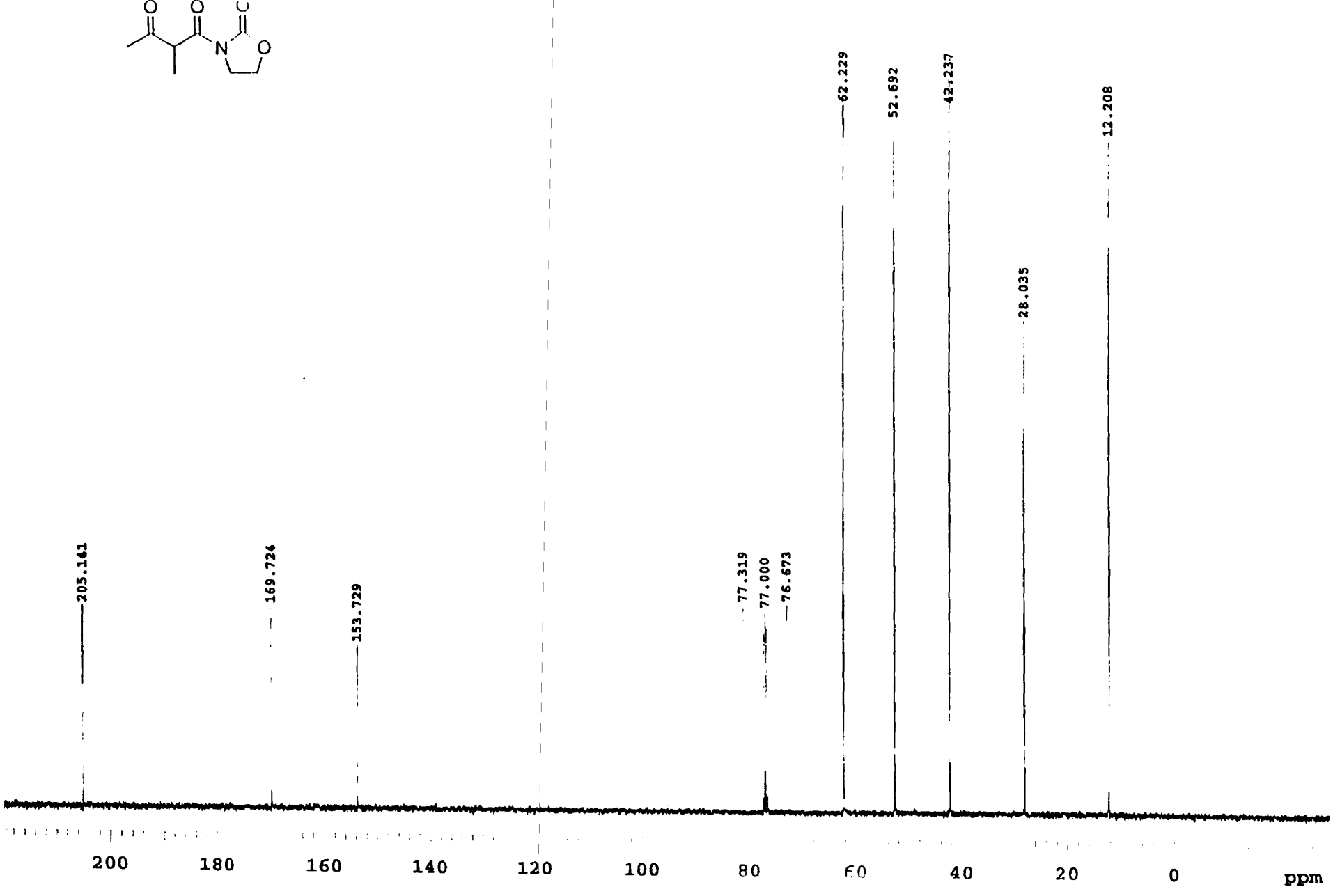
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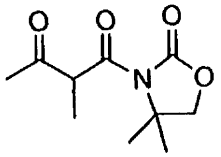

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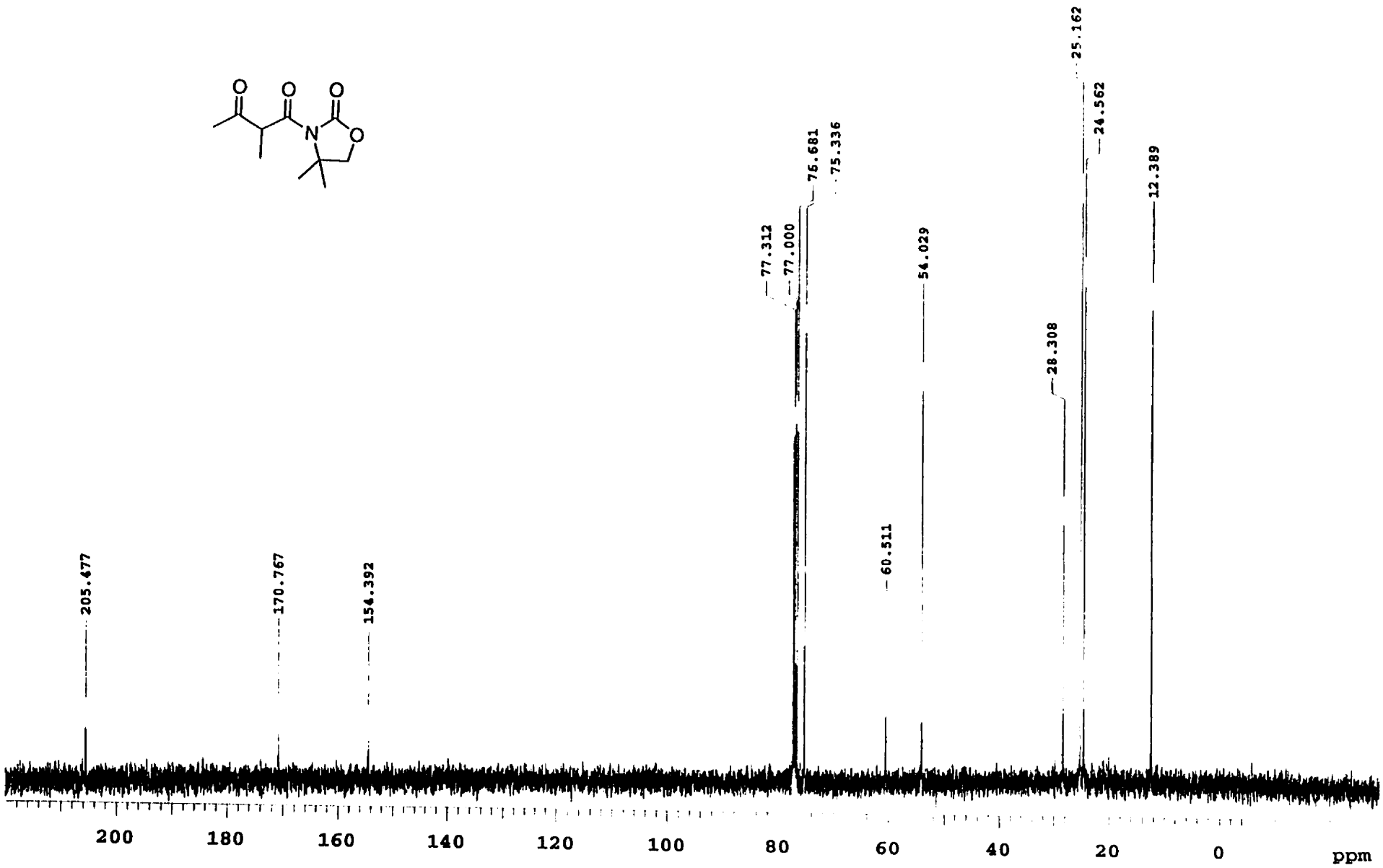
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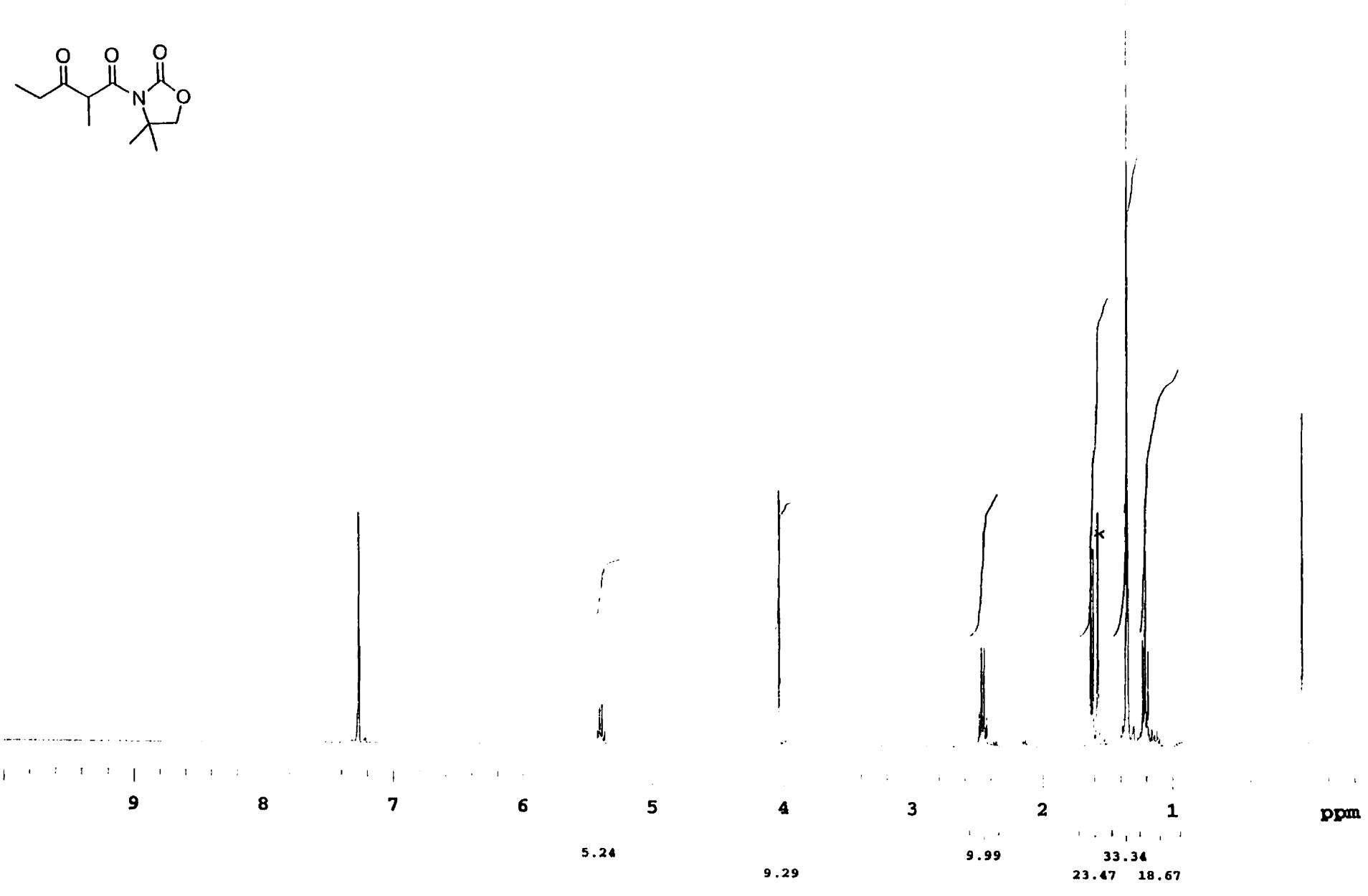
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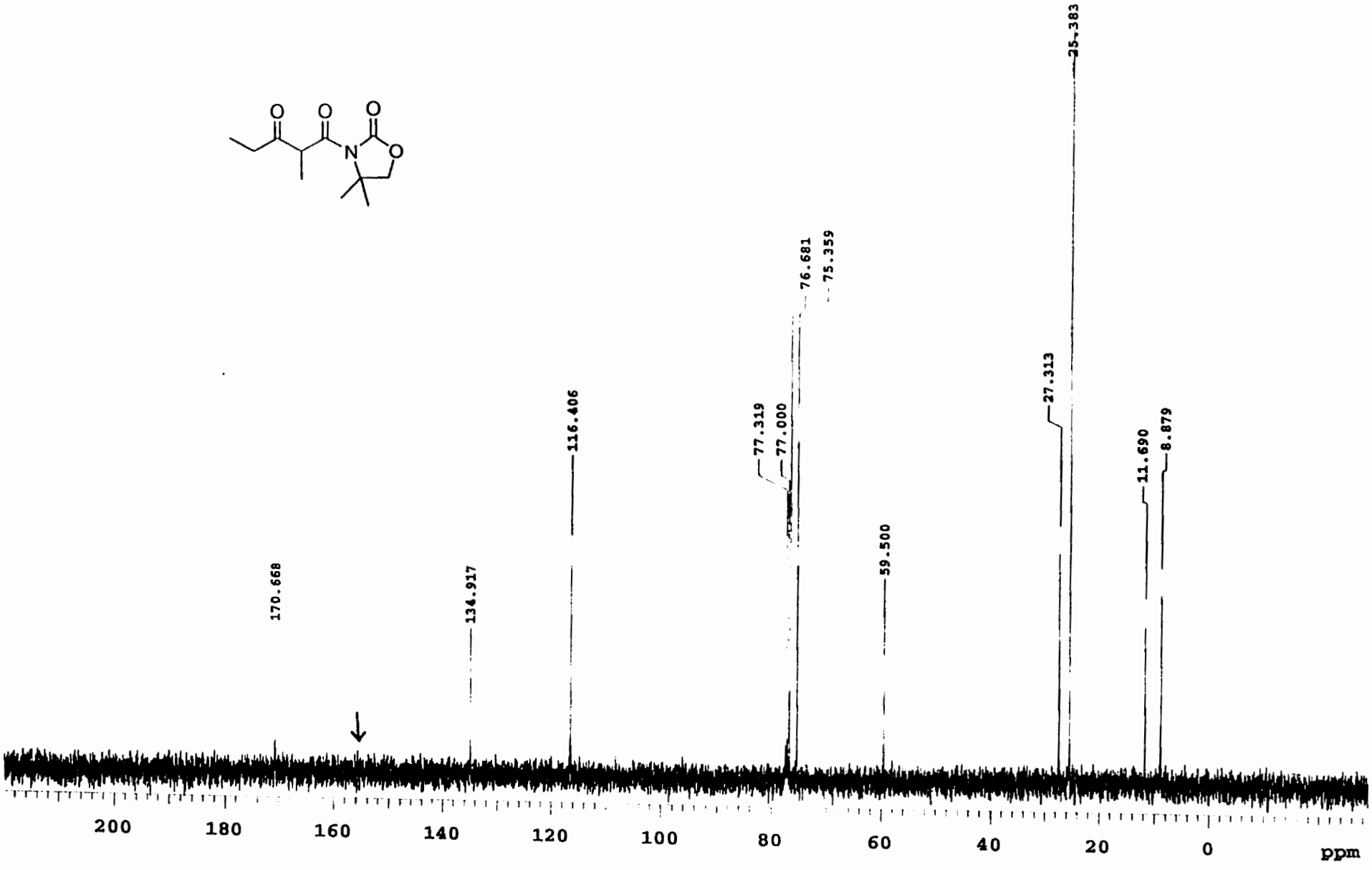
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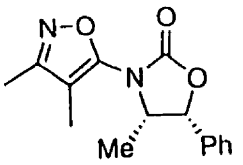
120
100
80
60
40
20
0
ppm

SPECTRAL LINES FOR THE [illegible]

rf1= 3475.3, rf2= 2891.3

INDEX	FREQ.(Hz)	PPM	HEIGHT
1	3003.9	7.5220	1.5
2	2971.5	7.4408	4.6
3	2969.5	7.4358	7.2
4	2967.8	7.4317	3.7
5	2962.9	7.4193	22.9
6	2961.1	7.4147	12.6
7	2955.4	7.4005	25.5
8	2952.5	7.3931	8.4
9	2950.6	7.3886	14.2
10	2949.2	7.3849	9.3
11	2946.4	7.3780	3.9
12	2943.9	7.3716	12.1
13	2940.8	7.3620	2.3
14	2937.8	7.3565	2.3
15	2936.3	7.3528	3.2
16	2923.7	7.3212	21.5
17	2922.1	7.3170	25.1
18	2915.7	7.3010	17.9
19	2891.7	7.2409	24.6
20	2891.3	7.2400	25.1
21	2329.7	5.8338	17.6
22	2321.7	5.8136	18.2
23	1874.2	4.6930	2.8
24	1867.6	4.6765	9.4
25	1861.0	4.6600	10.3
26	1859.7	4.6568	9.9
27	1853.1	4.6403	9.2
28	1846.5	4.6238	2.8
29	1688.8	4.2089	1.7
30	1674.8	4.1937	3.2
31	1668.6	4.1782	1.6
32	883.4	2.2121	155.5
33	808.3	2.0241	5.2
34	777.6	1.9471	153.1
35	626.5	1.5688	31.2
36	521.6	1.3061	1.5
37	516.5	1.2933	3.2
38	511.5	1.2809	2.0
39	500.5	1.2534	2.0
40	493.4	1.2355	3.4
41	490.7	1.2286	1.6
42	486.3	1.2176	1.6
43	364.9	0.9136	3.2

Index	[illegible]	PPM	HEIGHT
44	357.4	0.8948	6.5
45	354.4	0.8875	1.7
46	349.9	0.8761	4.1
47	347.5	0.8701	4.2
48	338.5	0.8476	67.6
49	331.9	0.8311	66.9



SPECTRAL LINES FOR IN= 6.2
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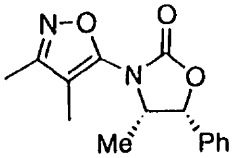
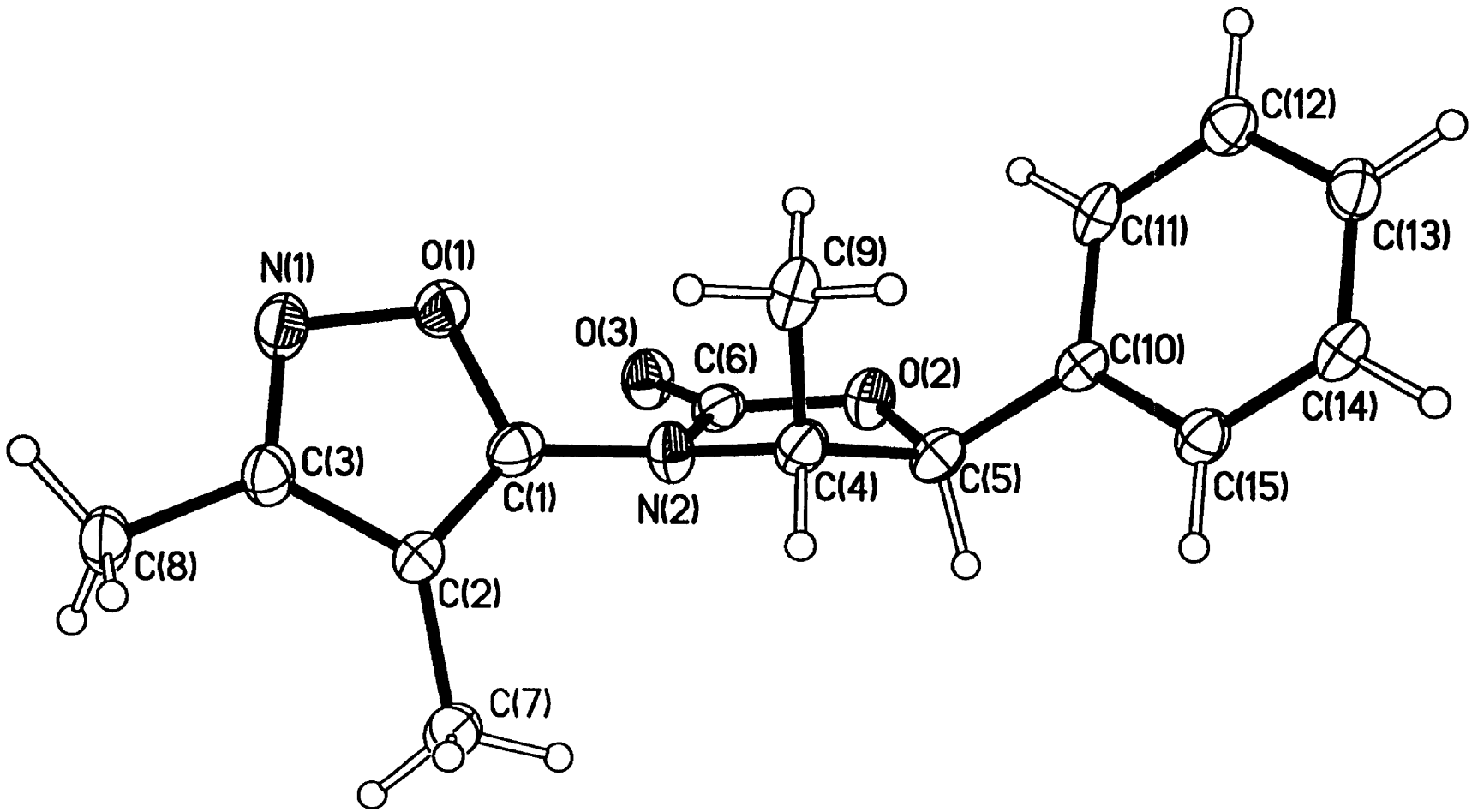
2	15564.8	154.986	10.5
3	15392.8	153.272	10.6
4	13450.0	133.927	16.2
5	12951.3	128.961	42.7
6	12929.3	128.743	92.5
7	12651.8	125.979	85.0
8	10662.8	106.174	16.5
9	8013.4	79.793	43.6
10	7764.4	77.314	273.8
11	7732.9	77.000	281.0
12	7700.7	76.679	279.9
13	5744.7	57.203	45.1
14	1550.9	15.443	37.6
15	1075.6	10.710	39.9
16	700.7	6.977	38.4

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C(13)
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C(15)
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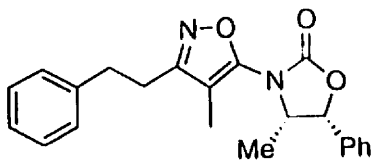
C(2)
C(7)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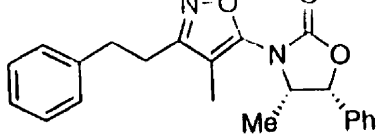
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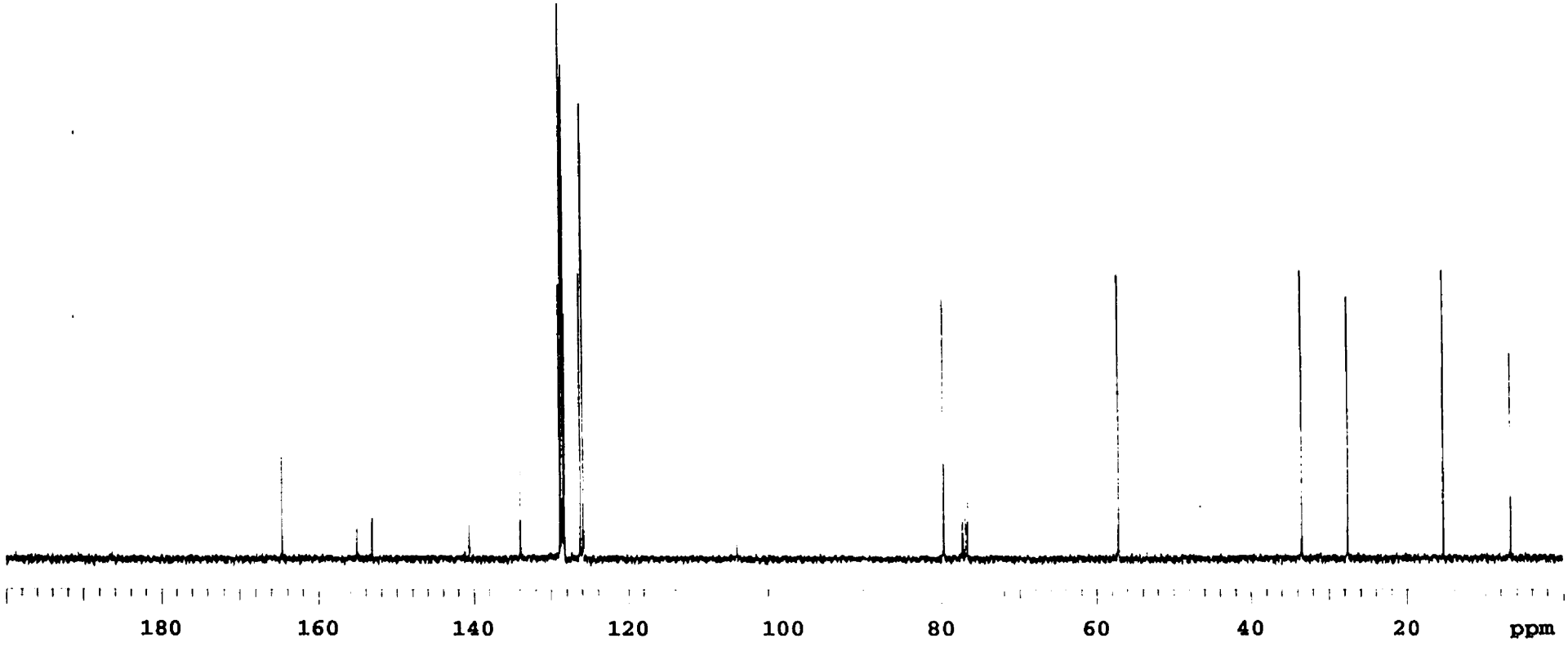
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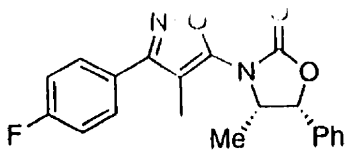
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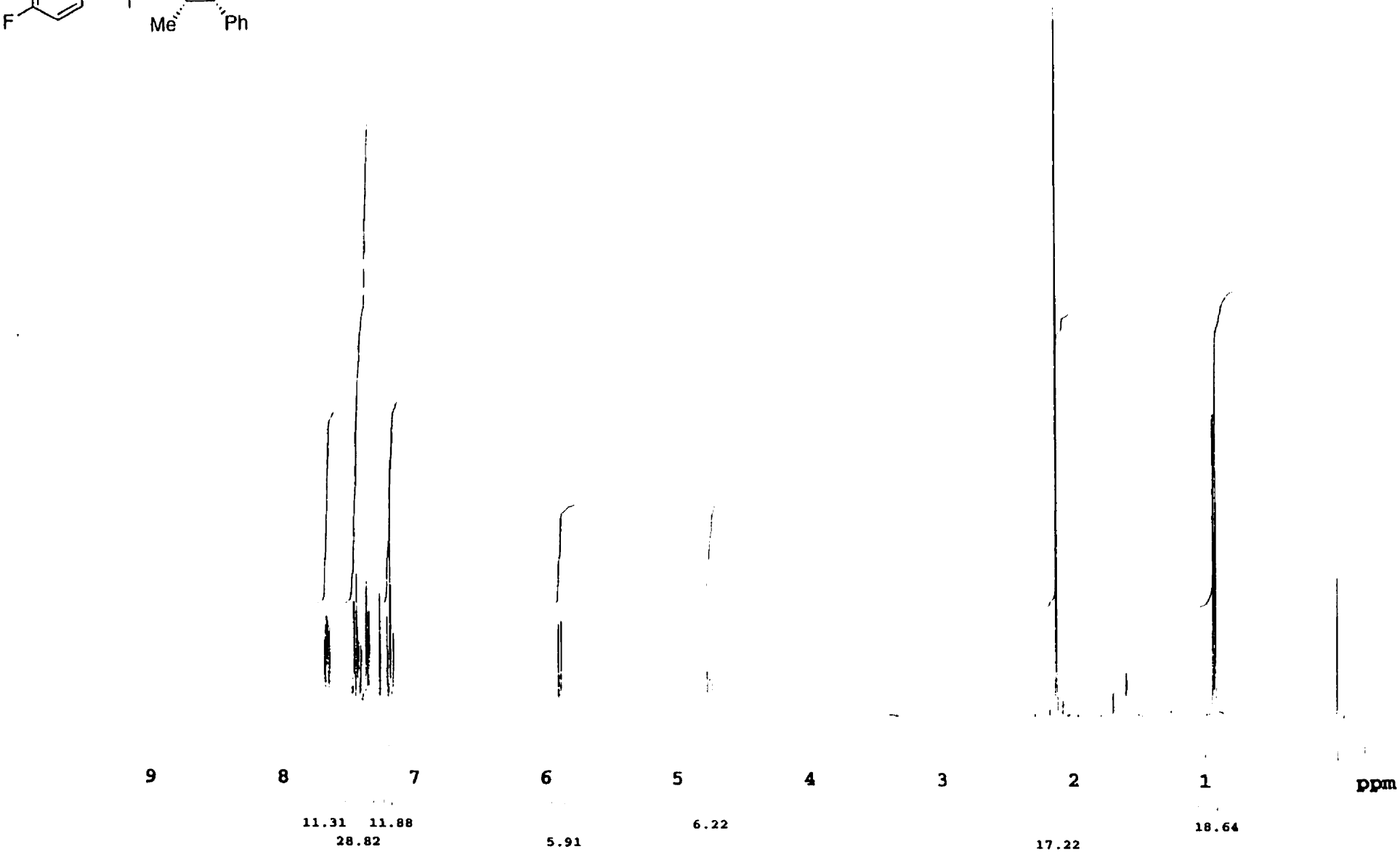
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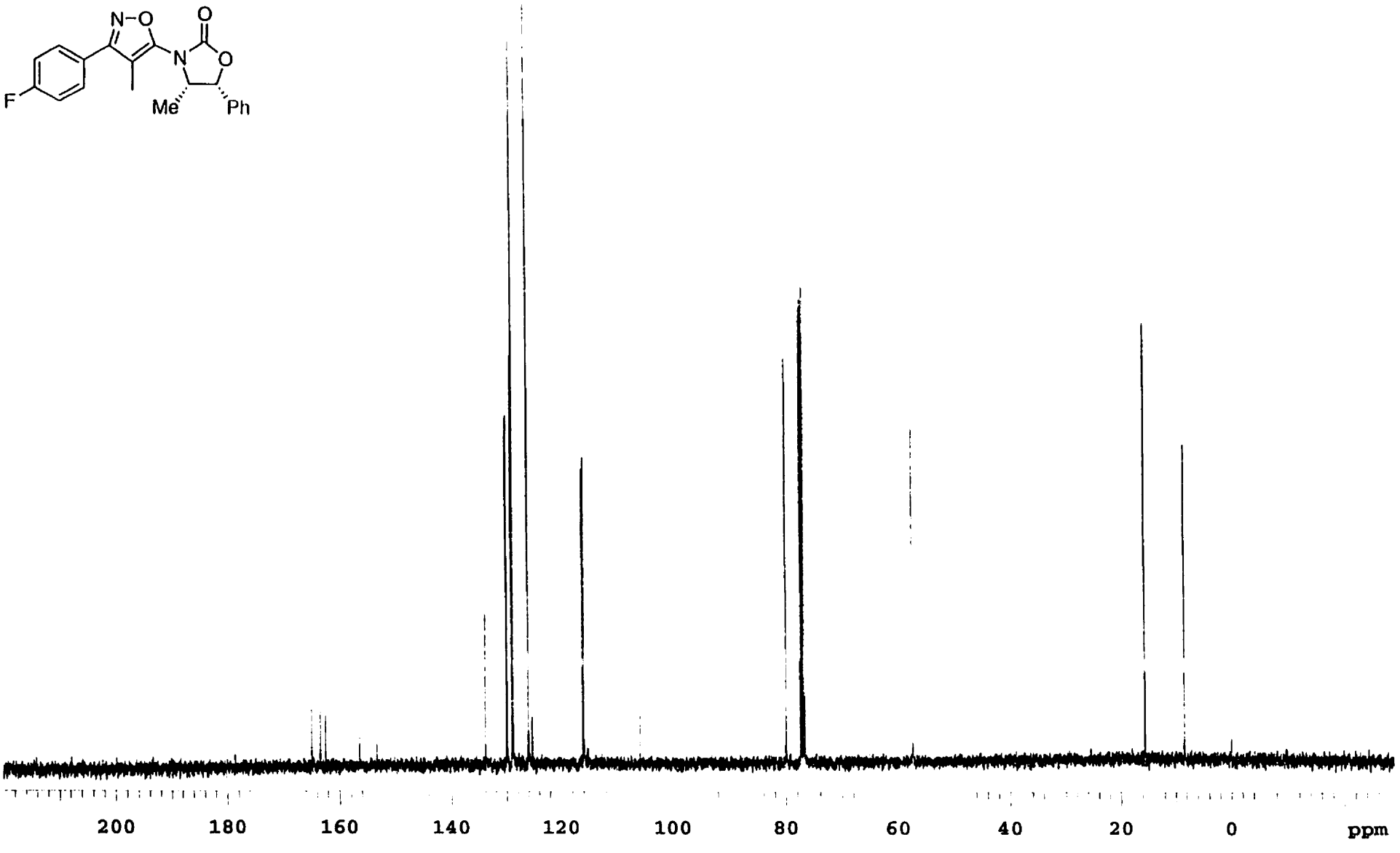
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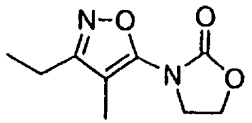
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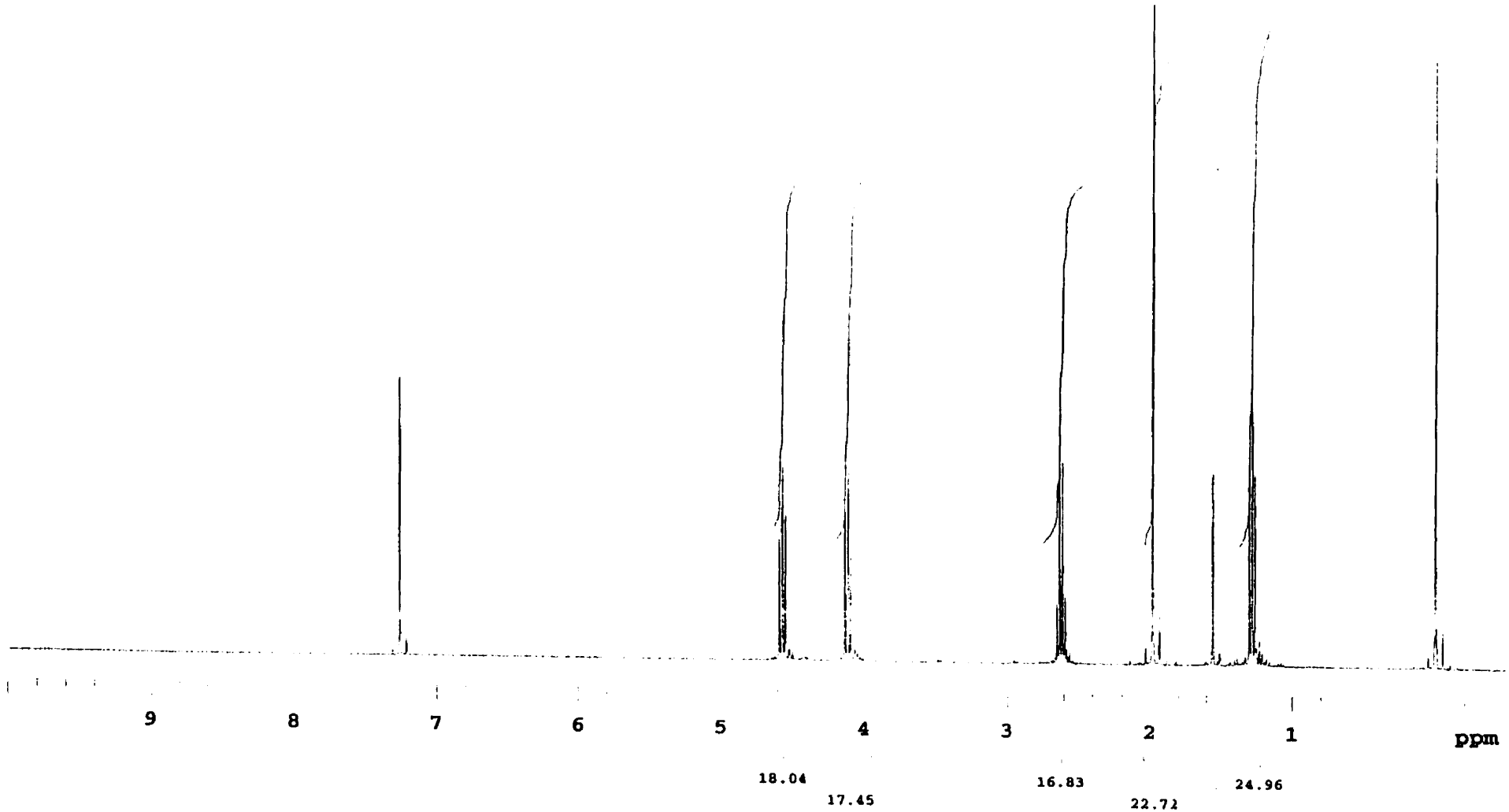
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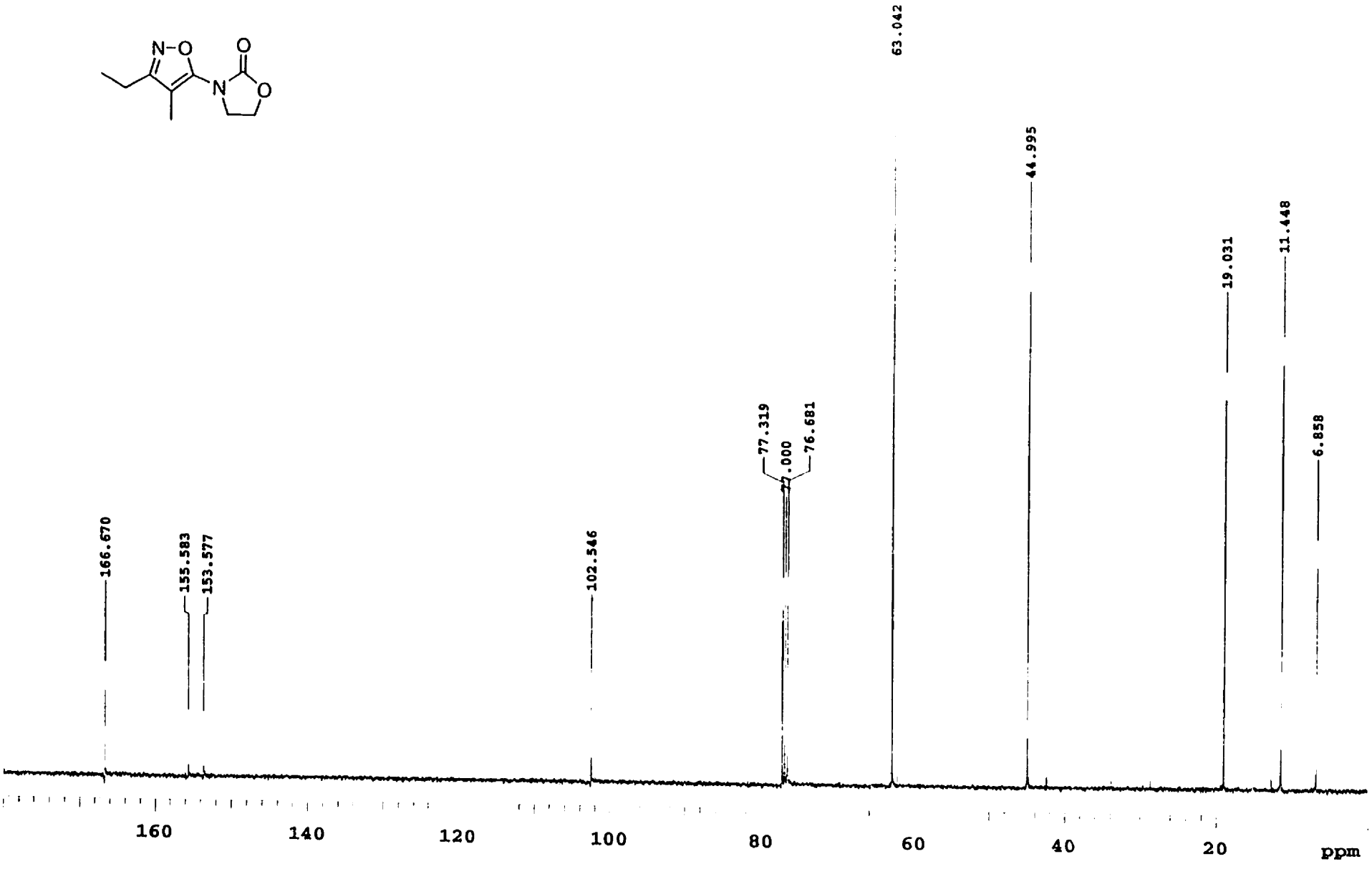
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40
20
ppm

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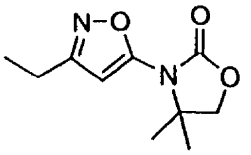

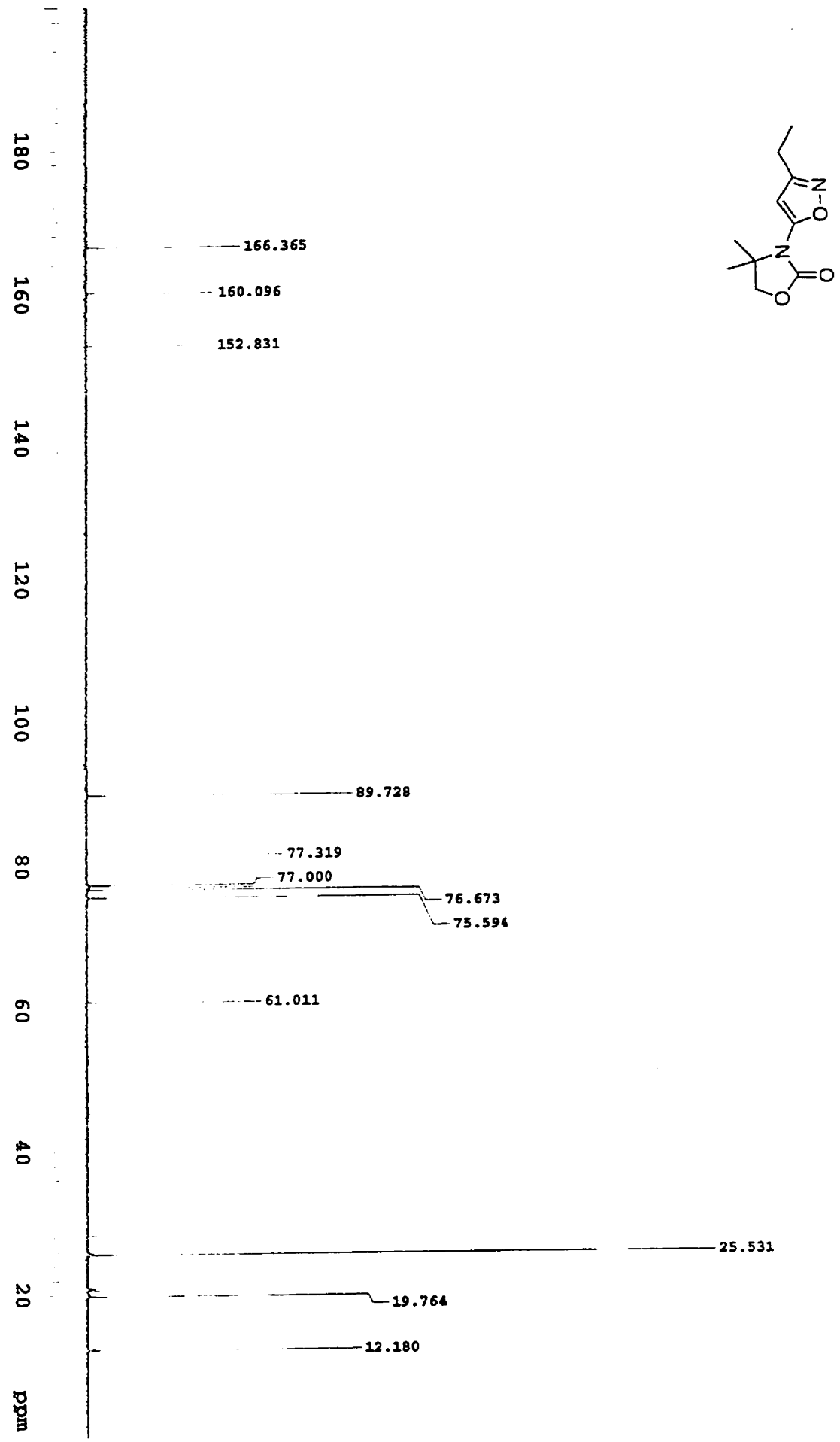
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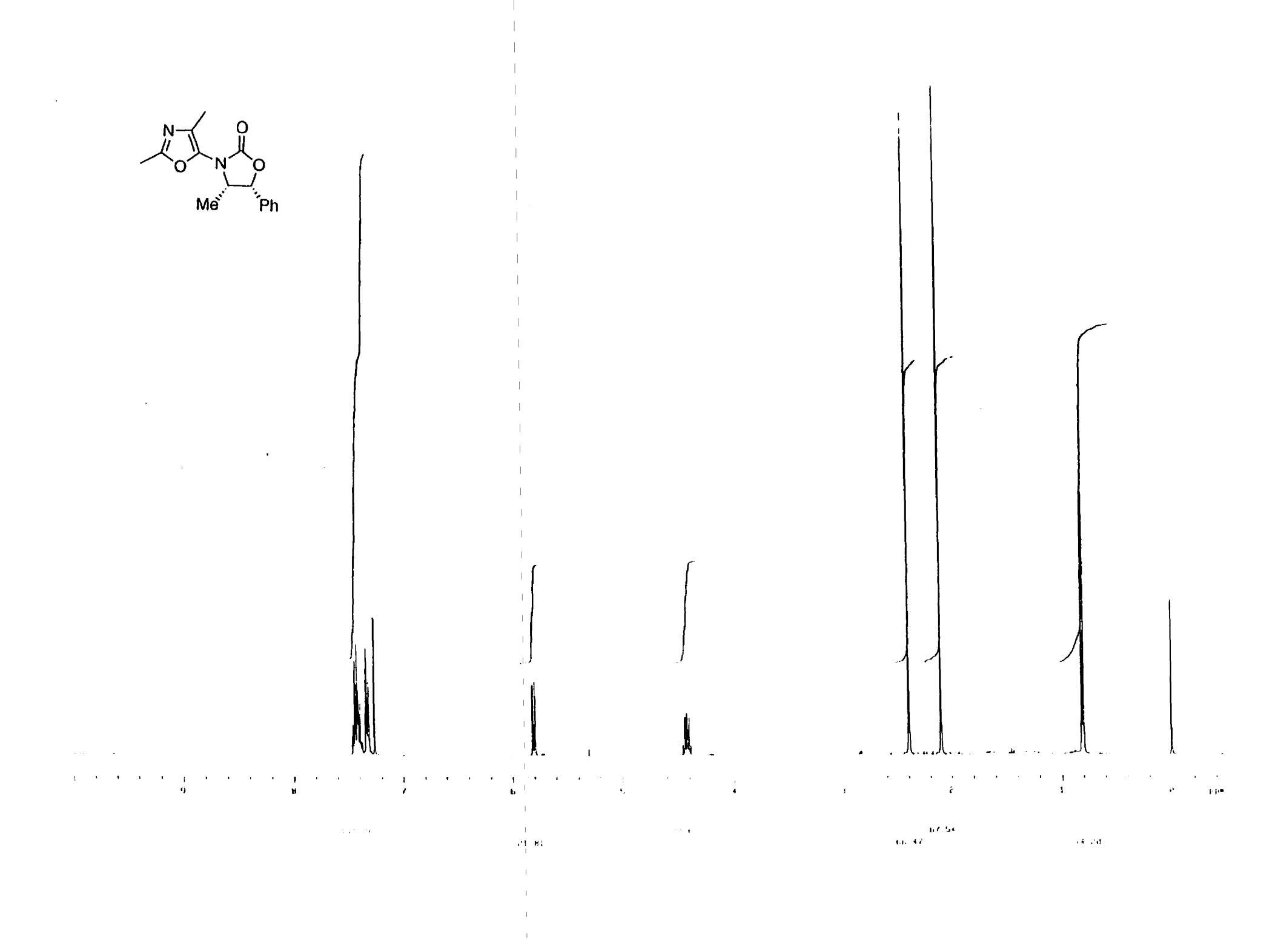
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O
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Ph

1 13C OBSERVE

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hs	nn		
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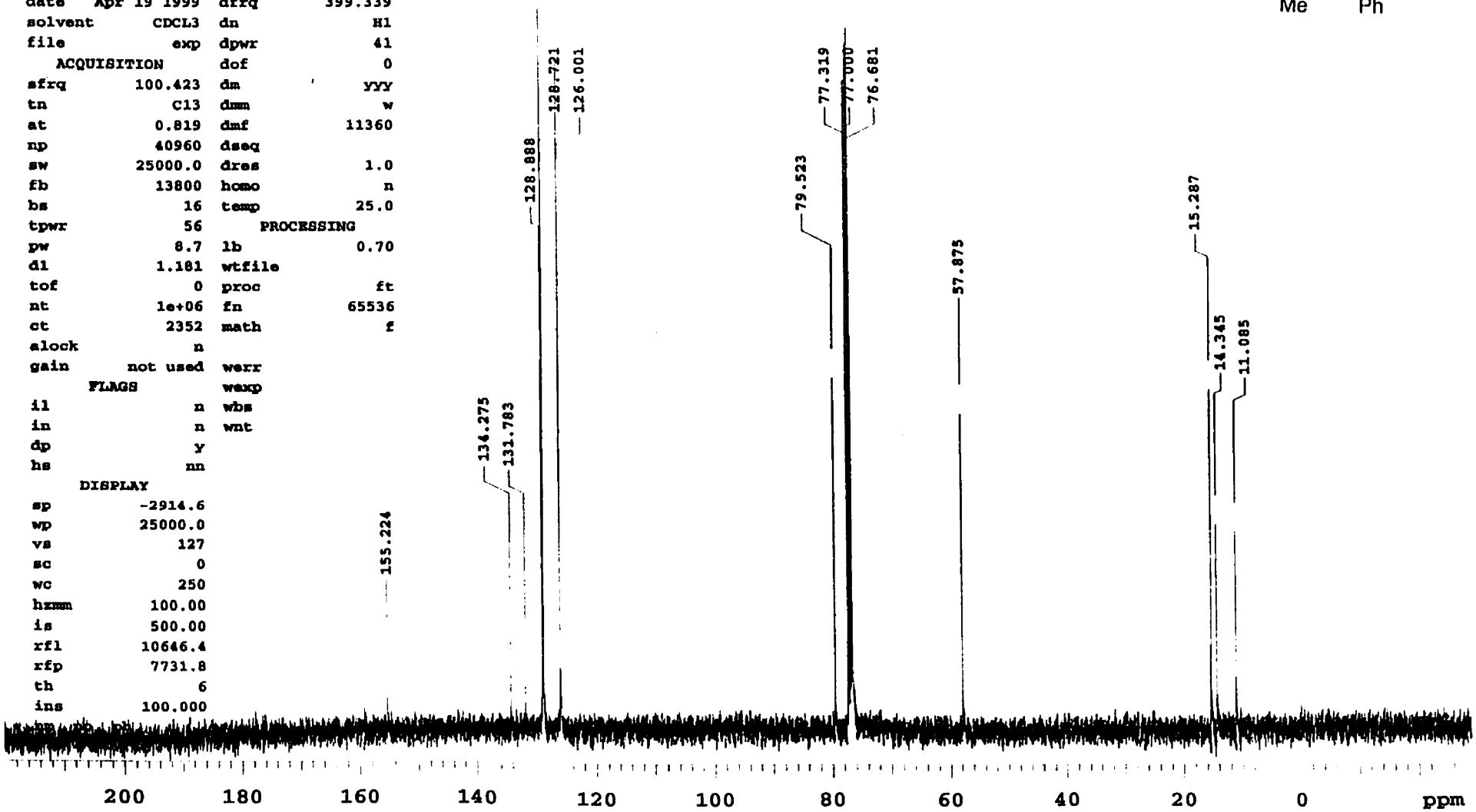

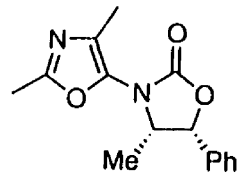

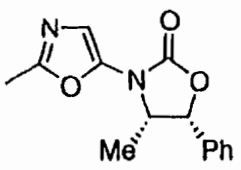
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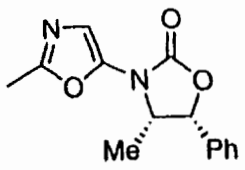
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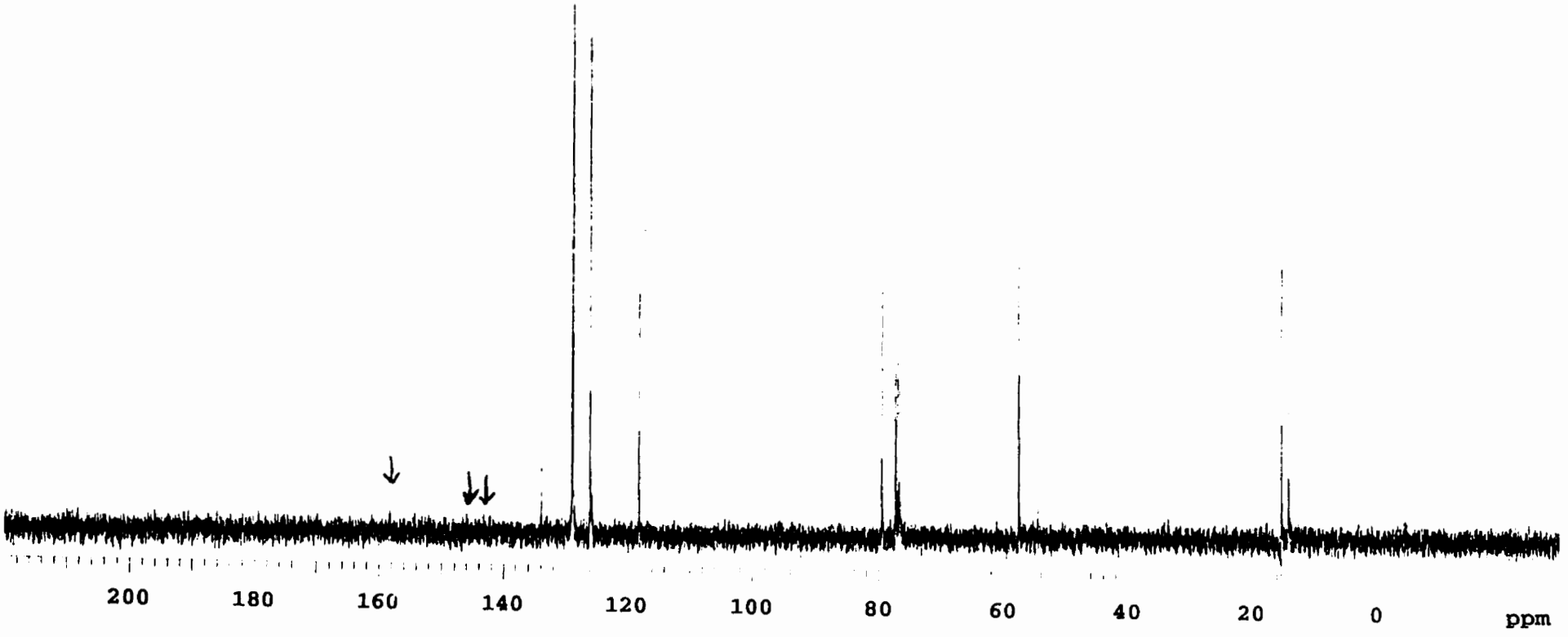
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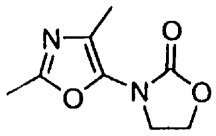
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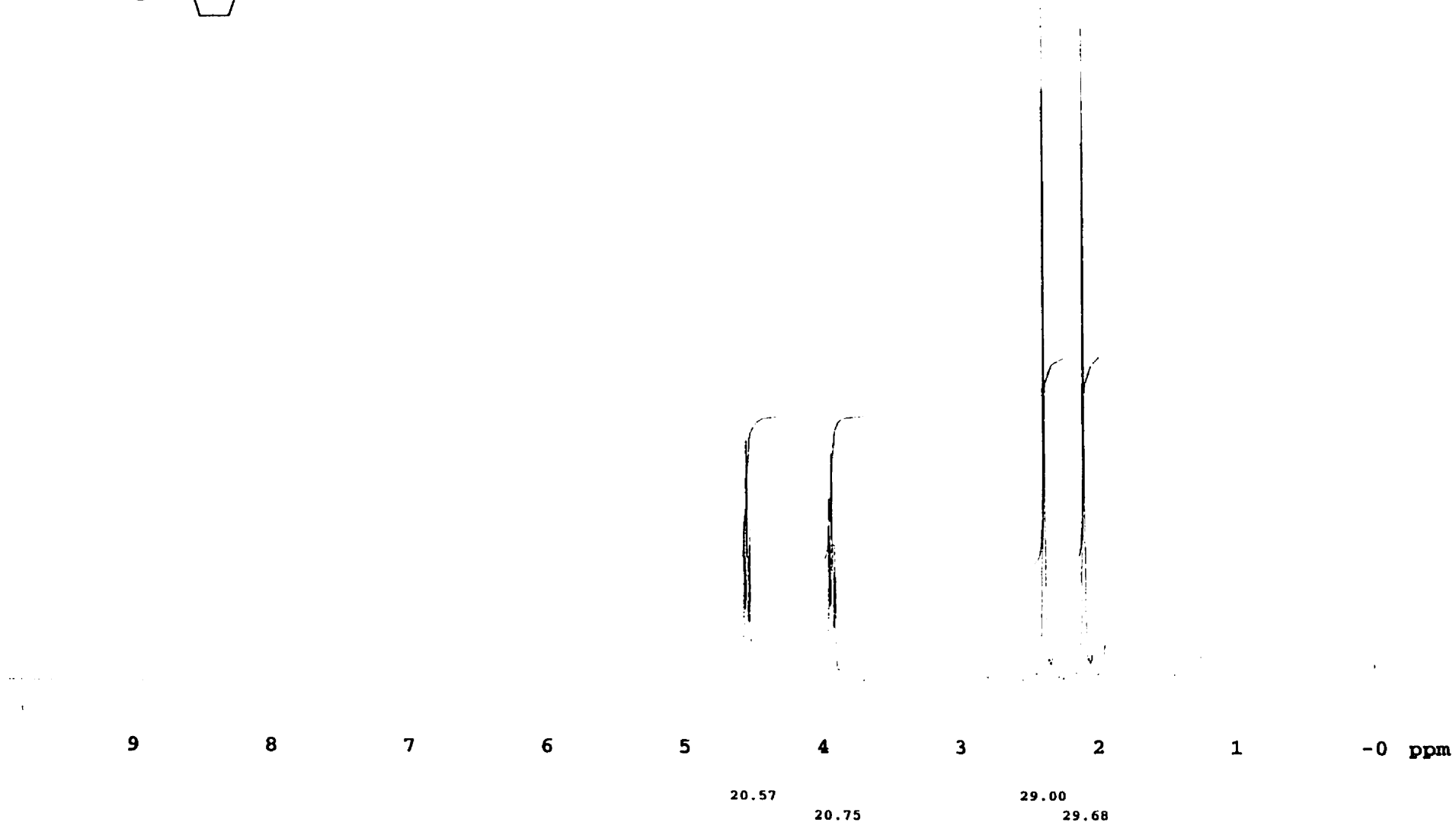
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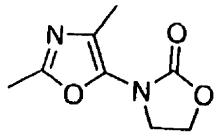
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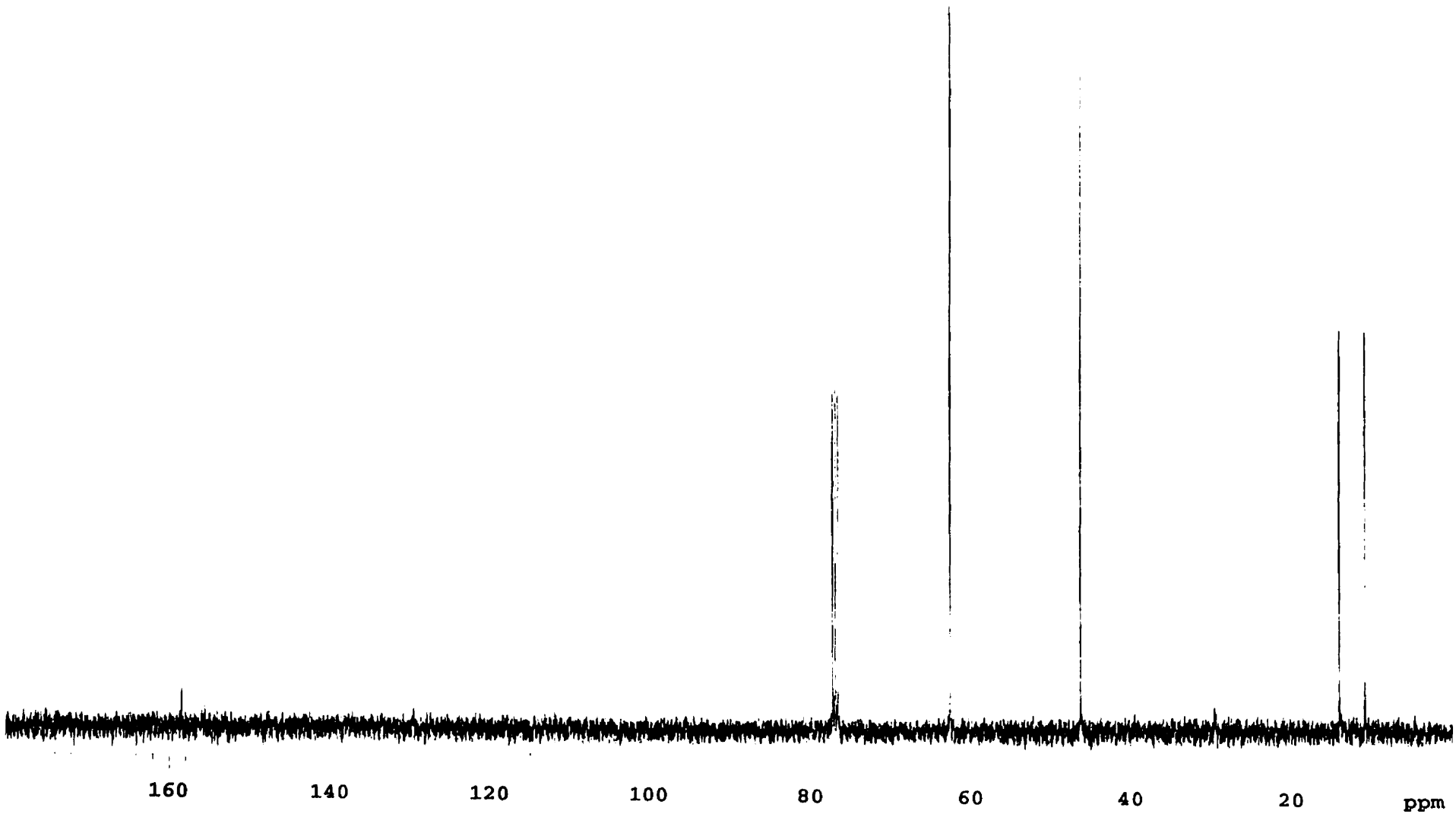
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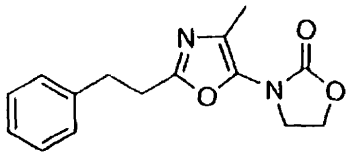
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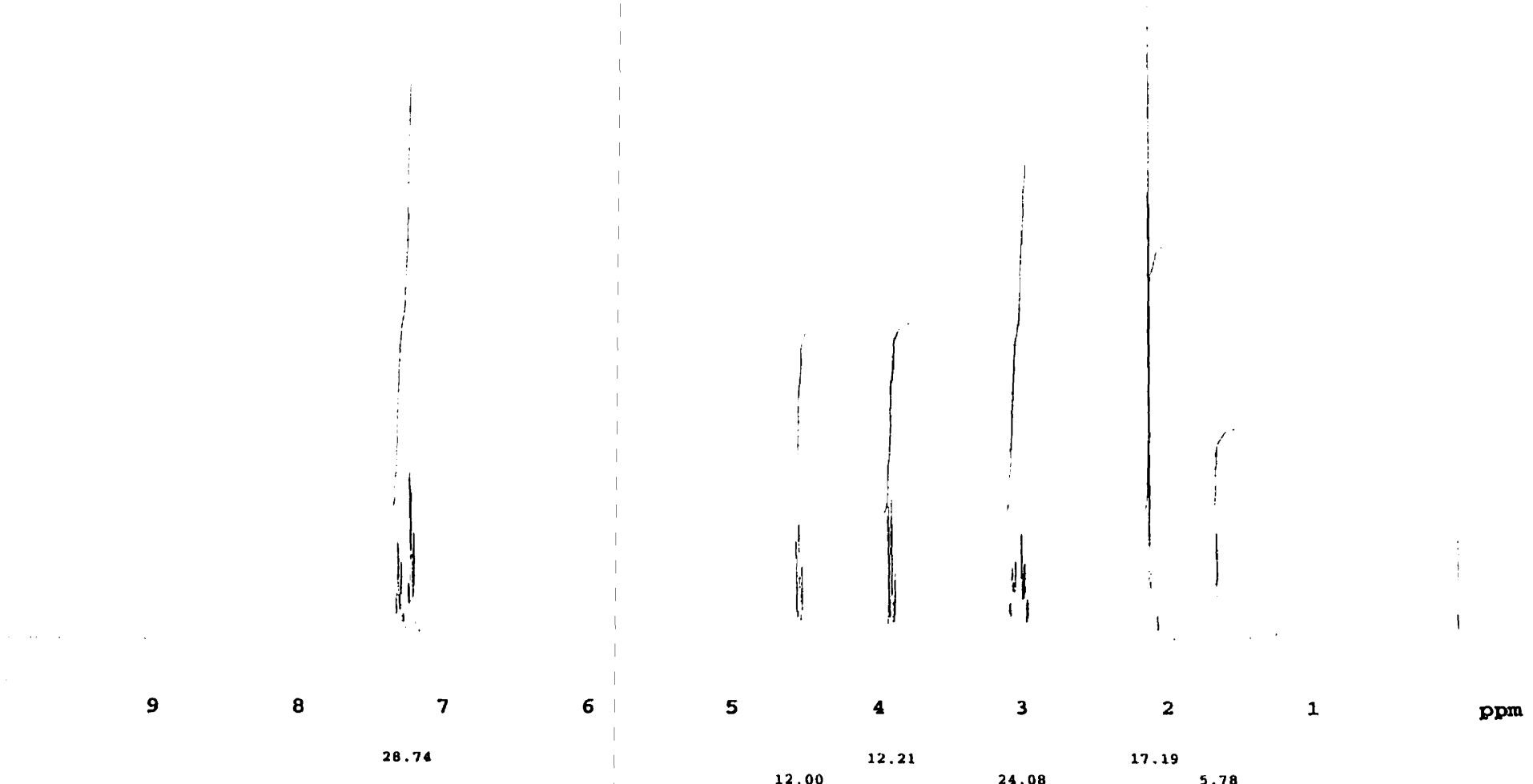
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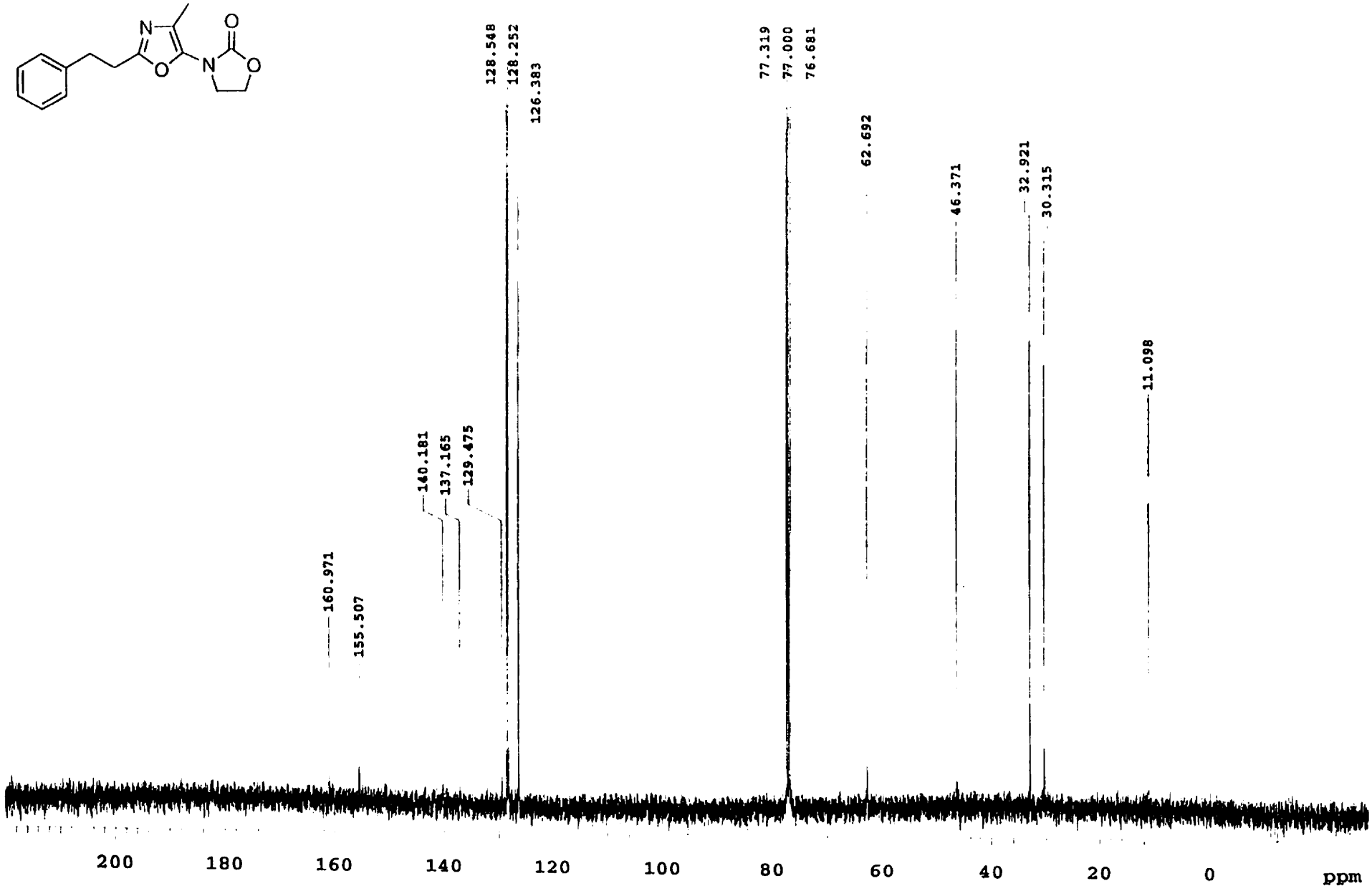
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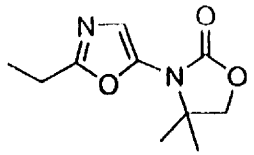
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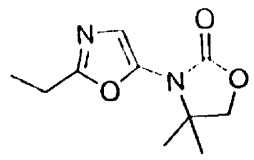
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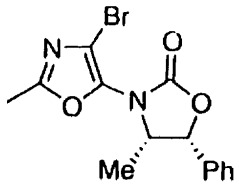
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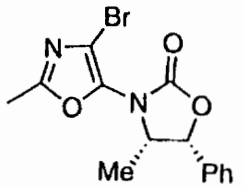
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O
Me
Ph

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20
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ppm

2. Aqueous Rhodium-Catalyzed Heck-Type Coupling Reactions Between Boronic Acids and Olefins

2.1 General Introduction

Transition metal catalyzed reactions are often perceived to require scrupulously anhydrous reaction conditions. However over the past few years, many reports have shown that some metal catalyzed reactions can be carried out equally or more effectively by using water as solvent.[1] The application of water in organic transition-metal catalysis has undergone a considerable amount of progress in the last two decades. It is usual to justify research on the use of water in catalytic processes by environmental reasons. Certainly, the trend to reduce the need for organic solvents is quite common for modern chemical technology. This means a decrease in the amount of uncontrolled release of toxic organic wastes into environment and a dramatic reduction of the hazards for both industrial personnel and consumers.

2.1.1 Interesting Characteristics of Water

The application of water in catalysis pursues several practical goals. Water may be a reagent, being the cheapest source of either oxygen for the formation of oxygen-containing products[2] (alcohols, acids, ketones, aldehydes, etc.) or hydrogen, as in some reduction processes.[3]

Water is a unique solvent, having a rare combination of properties which are not reproduced in full scope by any other liquid known, though any one of its properties

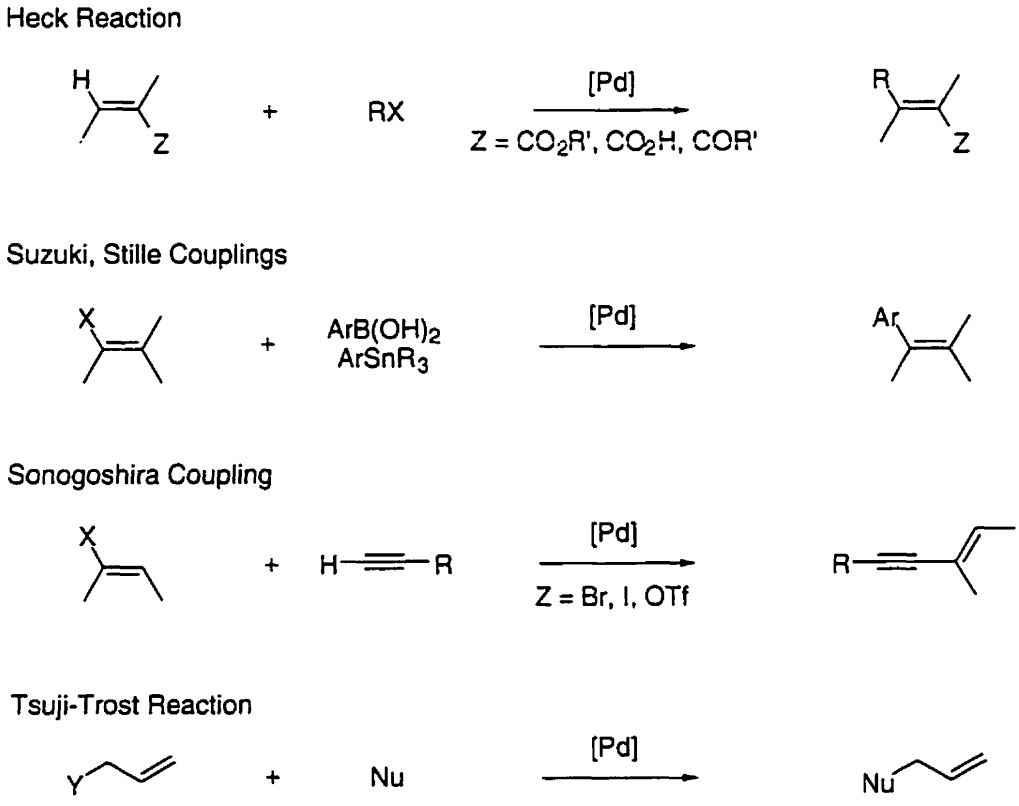
taken separately (polarity, polarizability, specific solvation due to hydrogen bonding, or basicity, etc.) is easily outperformed.

Water is a solvent that can be used to perform reactions combining the advantages of homogeneous and heterogeneous catalysis by distributing the reagents, products and catalysts between different phases or interphase. Usually reactions in neat water are feasible if the major reagents are soluble in water. Nevertheless, reactions in which at least one of the reacting compounds is insoluble in water can be either homogenized by the addition of a suitable water-miscible co-solvent, or carried out in heterogeneous systems, using phase-transfer, phase-separation, or solubilization techniques. Phase transfer requires the use of phase-transfer agents to furnish contact between the reagents, normally occupying different phases. In general, phase transfer is applied to ionic reagents, and thus transferred from the aqueous phase to the organic phase. However, there are cases in which a highly hydrophilic phase-transfer agent transfers hydrophobic compounds to the aqueous phase, forming a host-guest complex. The operation of water-soluble catalysts in heterogeneous systems often implies that phase transfer can occur within the catalytic cycle, when hydrophilic and hydrophobic species combined to form an amphibic intermediate.

2.1.2 Aqueous Palladium-Catalyzed Cross-Coupling Reactions

Among the large panel of transition metals frequently used in catalysis, palladium has a predominant role. One of the major contributions of palladium(0) catalysts in

organic synthesis is the formation of carbon-carbon bonds through many coupling reactions (Scheme 17).

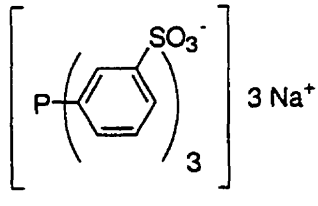


Scheme 17

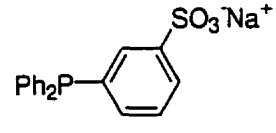
The use of water as a reaction medium for organic synthesis is very attractive for both economical and safety reasons. However until recently, palladium-promoted reactions in aqueous media, with water-soluble catalysts were still unexplored.[4] The excellent compatibility of water-soluble palladium catalysts offers new opportunities (mild conditions, new selectivity). The development of water-soluble catalysts offers several advantages as well for industrial production: easy separation of the product from the catalyst, high reactivity, recycling of catalyst.

2.1.2.1 Water-Soluble Ligands

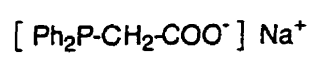
Since classical catalysts (e.g. $PdCl_2(PPH_3)_2$ and Wilkinson complex $RhCl(PPh_3)_3$) are strongly hydrophobic, the idea to study similar complexes with hydrophilic phosphines for catalytic processes in water-based media is quite natural. Phosphines can be converted into water-soluble derivatives by introduction of polar groups, including carboxylate, sulfonate, and ammonium (Scheme 18). The metal, complexed to the water-soluble ligands, goes into aqueous phase and catalytic reaction proceeds therefore in water. The hunt for new hydrophilic phosphines during about two decades led to dozens of examples of such ligands.[5] The popularity and performance of the sulfonated triphenylphosphine ligands, the so-called TPPMS (sodium salt of *m*-monosulfonated triphenylphosphine) and TPPTS (trisodium salt of *m*-trisulfonated triphenylphosphine), have earned them a privileged place among the hydrophilic ligands and made them the best-studied group of phosphines.

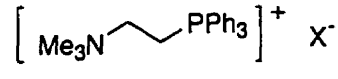


TPPTS



TPPMS

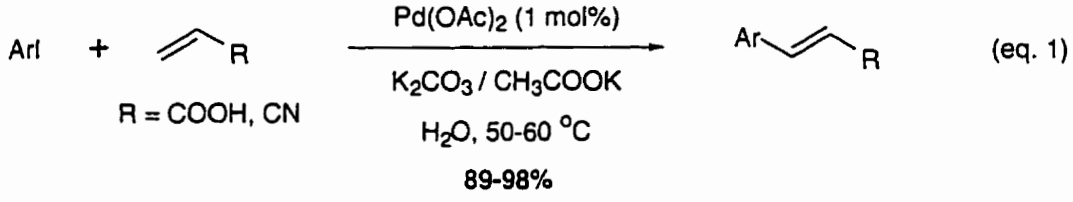




Scheme 18

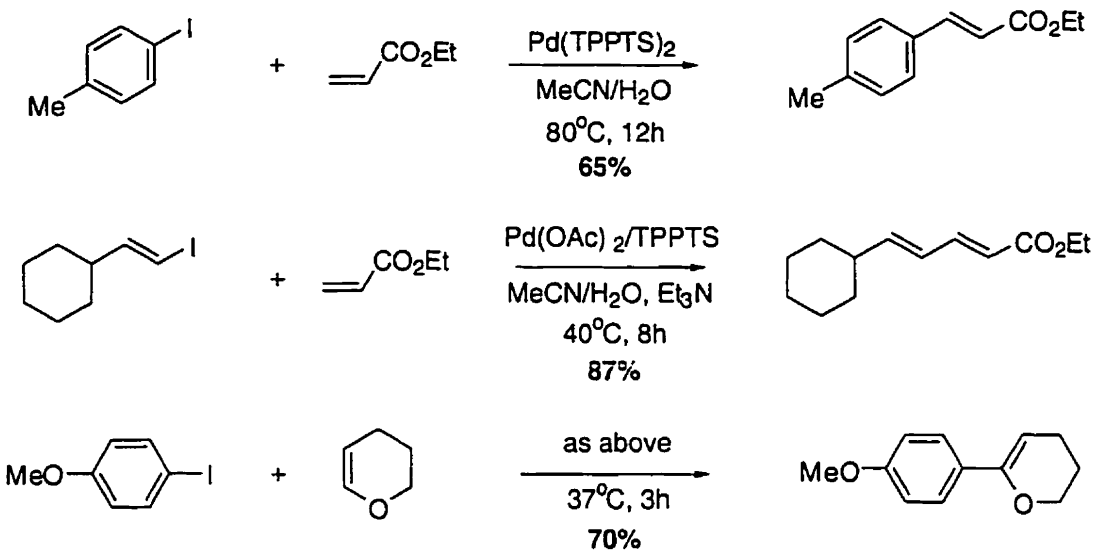
2.1.2.2 Literature Precedents

A pioneer chemist in the field of organic synthesis in aqueous media, Beletskaya, has shown that the coupling of acrylic acid and acrylonitrile with arylhalides was successful in neat water or in DMF-H_2O or HMPA-H_2O at 70-100°C with good yields (eq. 1)[6]. The Heck coupling reaction may be performed under milder conditions upon addition of potassium acetate.



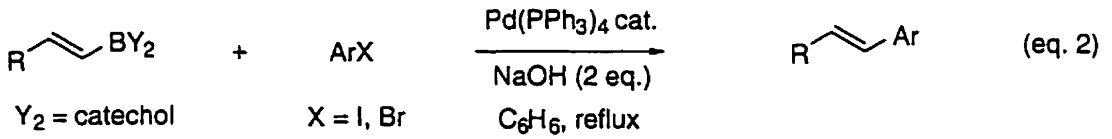
(eq. 1)

Heck reactions were also conducted in homogeneous aqueous medium (acetonitrile-water) in the presence of preformed $Pd(TPPMS)_3$ catalyst[7] or with $Pd(TPPTS)_3$ catalyst[8] produced in situ from 2.5 mol-% Pd(OAc) with 5 mol-% of *m*-sulfonated triphenylphospine (TPPTS) (Scheme 19).



Scheme 19

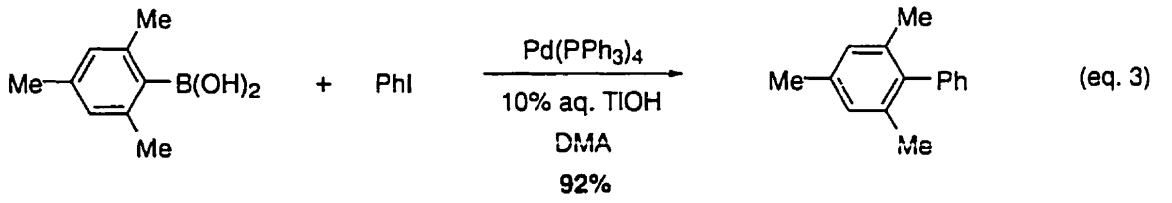
The palladium-catalyzed cross-coupling reaction of organometallic reagents with aryl halides was an important synthetic method for regio- and stereoselective bond formation between unsaturated carbon atoms. This coupling of alkenyl and aryl boranes or boronic acids (the Suzuki reaction) was catalyzed in organic solvents by $Pd(PPh_3)_4$ in the presence of an inorganic base.



(eq. 2)

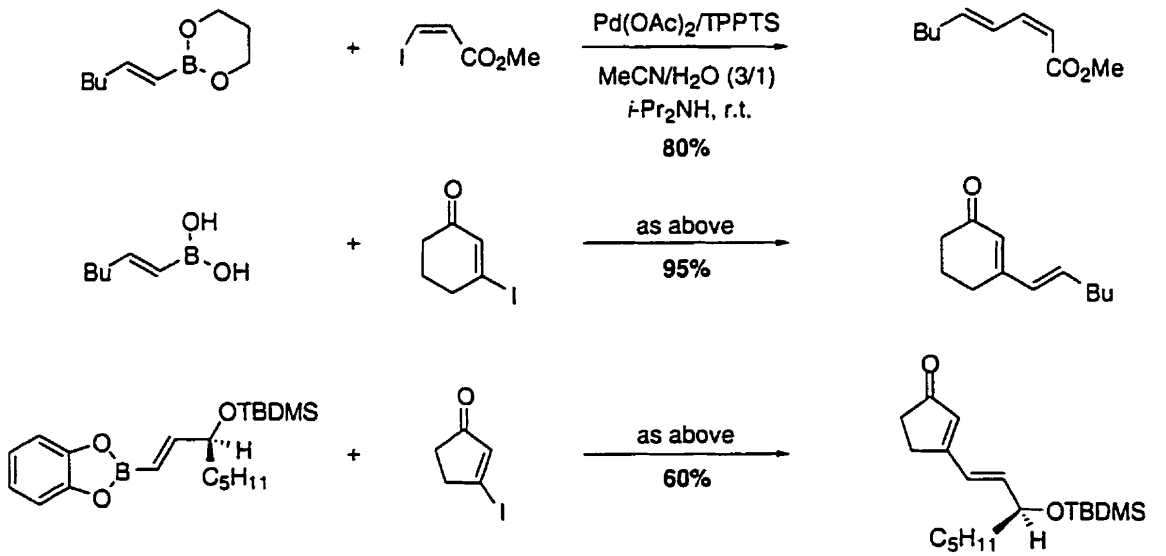
As organoboron compounds are often stable to protolytic decomposition by water, it seems attractive to perform the Suzuki reaction in water. An extensive study of this reaction under anhydrous and aqueous conditions was carried out, little difference could be noticed between these conditions.[9] On the other hand, in the case of the hindered

boronic acids such as mesityl boronic acid, the reaction proceeded with aqueous thallium hydroxide, under very mild conditions giving biphenyl derivatives in 92% yield (eq. 3).



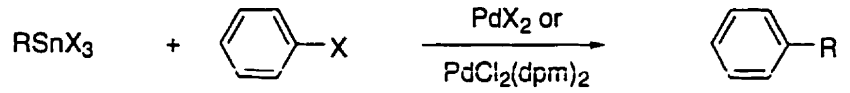
(eq. 3)

The cross-coupling reaction of phenylboronic acid with *p*-iodoanisole has shown that in acetonitrile-water (3/1) with a catalytic amount of hydrosoluble catalyst (Pd/TPPTS 2.5 mol-%), inorganic bases such as K_2CO_3, $Ba(OH)_2$ or Cs_2CO_3 were inefficient, while triethylamine and diisopropylamine led to the biphenyl product in good yield (Scheme 20).[10] A better yield was observed with diisopropylamine compared to triethylamine.



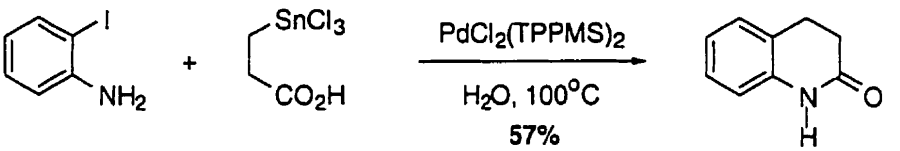
Scheme 20

Cross-coupling reactions with organostannanes is also possible in aqueous media. $RSnX_3$ can be used in aqueous medium and reacted with aryl iodides or bromides in the presence of palladium catalysts (eq. 4).[11]



(eq. 4)

This reaction was carried out using β-trichlorostannylpropionic acid and *o*-iodoaniline for the preparation of heterocycles (eq. 5).

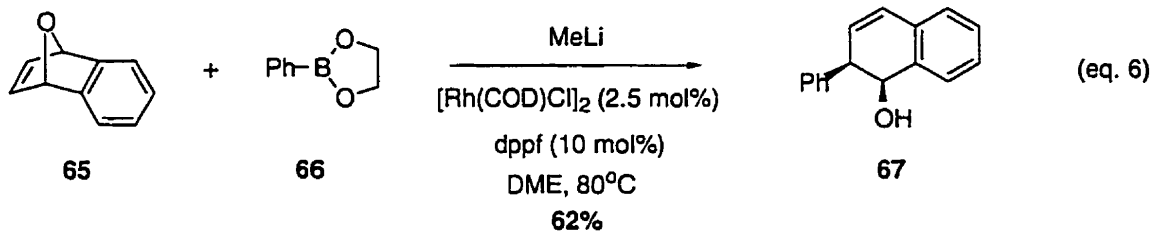


(eq. 5)

2.2 *Previous Work*

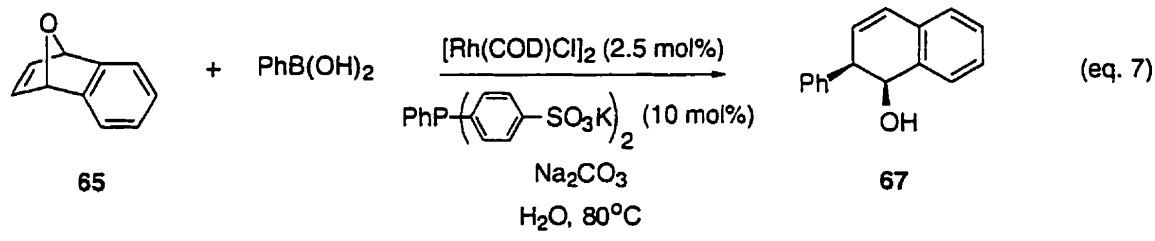
2.2.1 In the group

This project began with the work of Keith Fagnou, a graduate student in the group. He discovered that the rhodium-catalyzed addition reaction of activated aromatic organoboranes to oxabenzonorbonadiene **65** proceeded smoothly in dimethoxyethane (DME), furnishing dihydronaphthalene **67** in 62% yield (eq. 6).



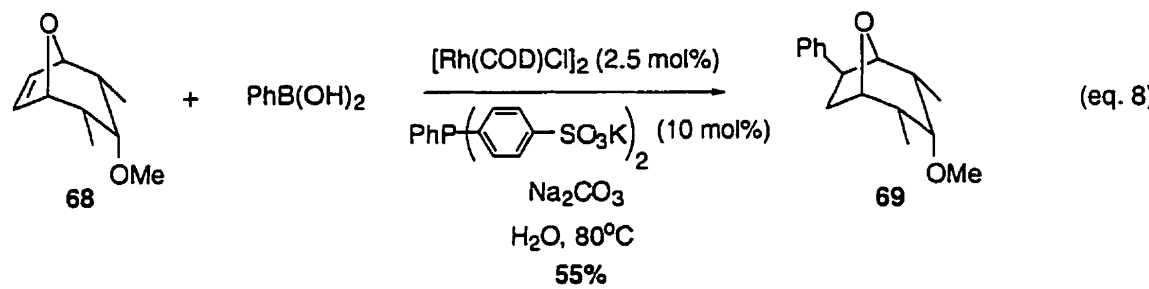
65 66 67 (eq. 6)

Later an aqueous version of this reaction was developed using phenylboronic acid and the water-soluble ligand TPPDS (eq. 7). The reaction was performed in neat water in the presence of sodium carbonate. The yield was comparable to that obtained in an organic solvent.



65 67 (eq. 7)

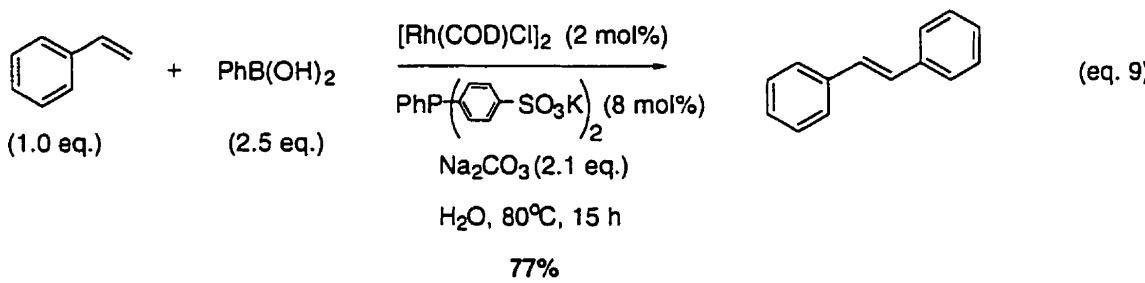
The reaction was then tried with a less activated oxabicycle [3.2.1] **68** under the aqueous reaction conditions (eq. 8).



68 69 (eq. 8)

The product of the reaction, obtained in 55% yield, was definitely intriguing because the mechanism for the rhodium-catalyzed reaction was different than the one for

equations 6 and 7. Indeed, the addition of the phenyl group actually occurred but without the ring-opening step, which took place in the other cases (eq. 6 and 7). The reaction still needed only a catalytic amount of rhodium and seemed to have a mechanism more similar to a Heck reaction but with no β-hydride elimination step (no *synperiplanar* hydride). The reaction was then tried with styrene, an even less activated olefin, under the same reaction conditions and stilbene was isolated in 77% yield (eq. 9).

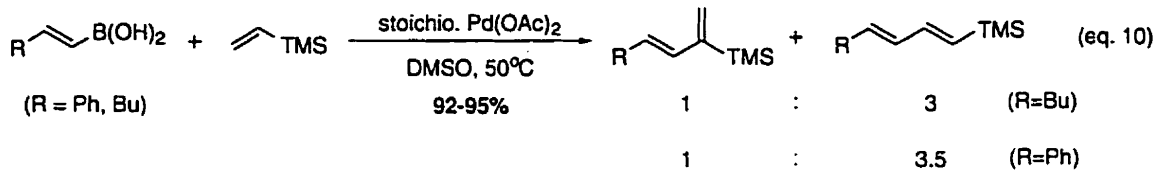


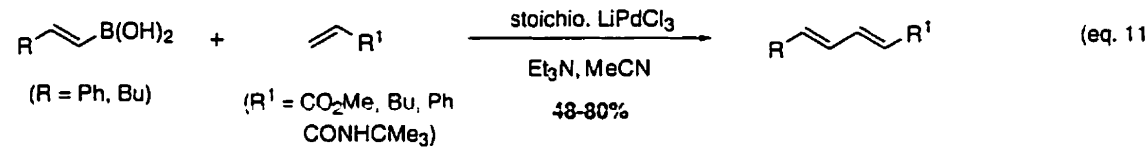
(eq. 9)

This result was exciting and opened the door to a new type of coupling with a new class of substrates. Also, the coupling reaction was occurring between and an alkene and a boronic acid, which are both considered as nucleophilic partners in the classical palladium-catalyzed Heck and Susuki cross-coupling reactions.

2.2.2 In the Literature

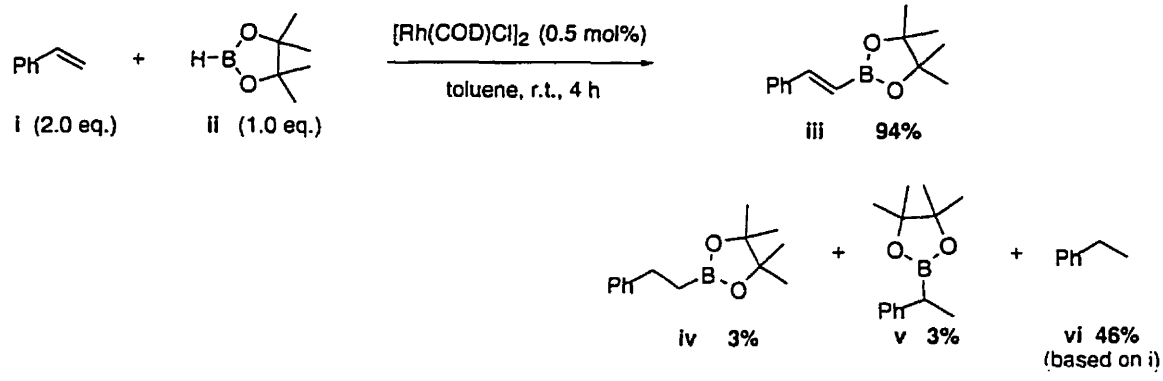
We could only find two examples in the literature reporting the coupling reaction between boronic acid and alkenes. Hallberg and co-workers reported in 1988 the coupling reaction between (*E*)-1-(2-phenyl)vinylboronic acid and (*E*)-1-hexenylboronic acid with vinyl tetramethylsilane in the presence of a **stoichiometric amount** of palladium in DMSO (eq. 10).[12] The regioselectivity of the addition is also an issue.





A Korean group reported the second example. They carried out the coupling reaction between the same boronic acids and several alkenes, also in the presence of a **stoichiometric amount** of lithium palladium trichloride in acetonitrile (eq. 11).[13] The yields range from 48% to 80%. The could perform the coupling reactions in the presence of a catalytic amount of palladium ($LiPdCl_3$ or $Pd(OAc)_2$) but a stoichiometric amount of $CuCl_2$ or $Hg(OAc)_2$ was necessary to oxidize and thus recycle the palladium.

An example of cross-coupling reaction between vinylarenes and boronic esters was also found. Masuda and co-workers reported a rhodium-catalyzed dehydrogenative coupling reaction of vinylarenes **i** with pinacolborane **ii** which led to the formation of vinylboronates (Scheme 21).[14]



Scheme 21

Dehydrogenative borylation by pinacolborane **iii** in the presence of phosphine-free rhodium catalyst proceeded predominantly over hyroboration (**iv** and **v**). However it has been reported that other borane reagents usual for catalytic hydroboration, such as catecholborane or *N*-methyl oxazaborolidine, were not suitable for selective dehydrogenative borylation.[15] Concurrently, ethylbenzene **vi** was generated in 46% yield based on **i**, indicating that styrene **i** acted as a hydrogen acceptor.

2.3 *Objectives*

To the best of our knowledge, no example of rhodium-catalyzed Heck-type coupling reaction between boronic acids and olefins carried out in water has been reported to date. Therefore we began this project with the goals of developing a broadly applicable coupling methodology and also we wanted to investigate the mechanism of the reaction, which was clearly different from the classical palladium-catalyzed coupling reactions (Heck, Suzuki, Stille, etc.). We also wanted to investigate the role of the water in the reaction: was it simply a polar solvent or was water playing a major role in one or several steps of the reaction.

2.4 Optimization Work: Phase 1

2.4.1 Ligand, Base, Temperature, Time

First we looked at the effect of the ligand, the base, the temperature, as well as the time of the reaction in order to optimize of the reaction conditions. The reaction was carried out using commercially available TPPTS as the water-soluble ligand. However one-third of the starting material remained after 15 hours at 80°C. The main differences between the two ligands are (1) the position of the sulfonate substituent on the aryl ring (*meta vs para*), (2) the number of substituted aryl rings (3 *vs* 2), and (3) the nature of the counterion. The electronic and steric effects caused by the substitution pattern noticeably affects the reaction. Another factor that could explain the lower conversion with TPPTS is the diminished quality of the purchased TPPTS ligand, which was contaminated with 10-15% of the oxide.

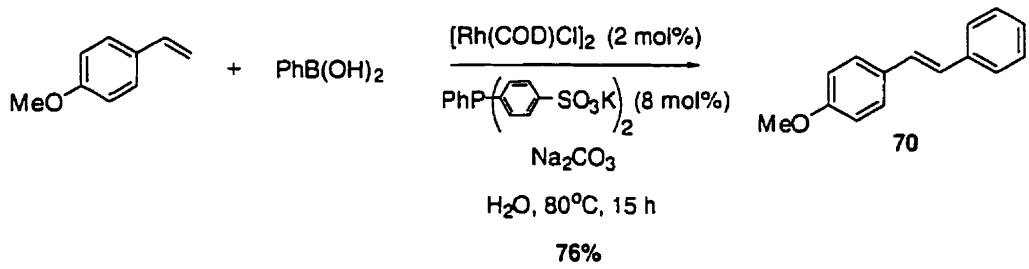
Several bases were surveyed in the course of the optimization work: K_2CO_3, Cs_2CO_3, Et_3N, and NaOAc. No significant improvement or change in the yield was observed, so Na_2CO_3 remained the base of choice.

The reaction was tried at temperatures lower than 80°C (set temperature of the heating bath). However no reaction occurred at 30°C or 50°C and the starting material was fully recovered.

When the reaction was stopped after 2 hours, a 6/1 ratio (product/starting material) was observed and even after 8 hours, the reaction remained incomplete (15/1

product/starting material). Consequently, the reactions were stirred overnight for more convenience.

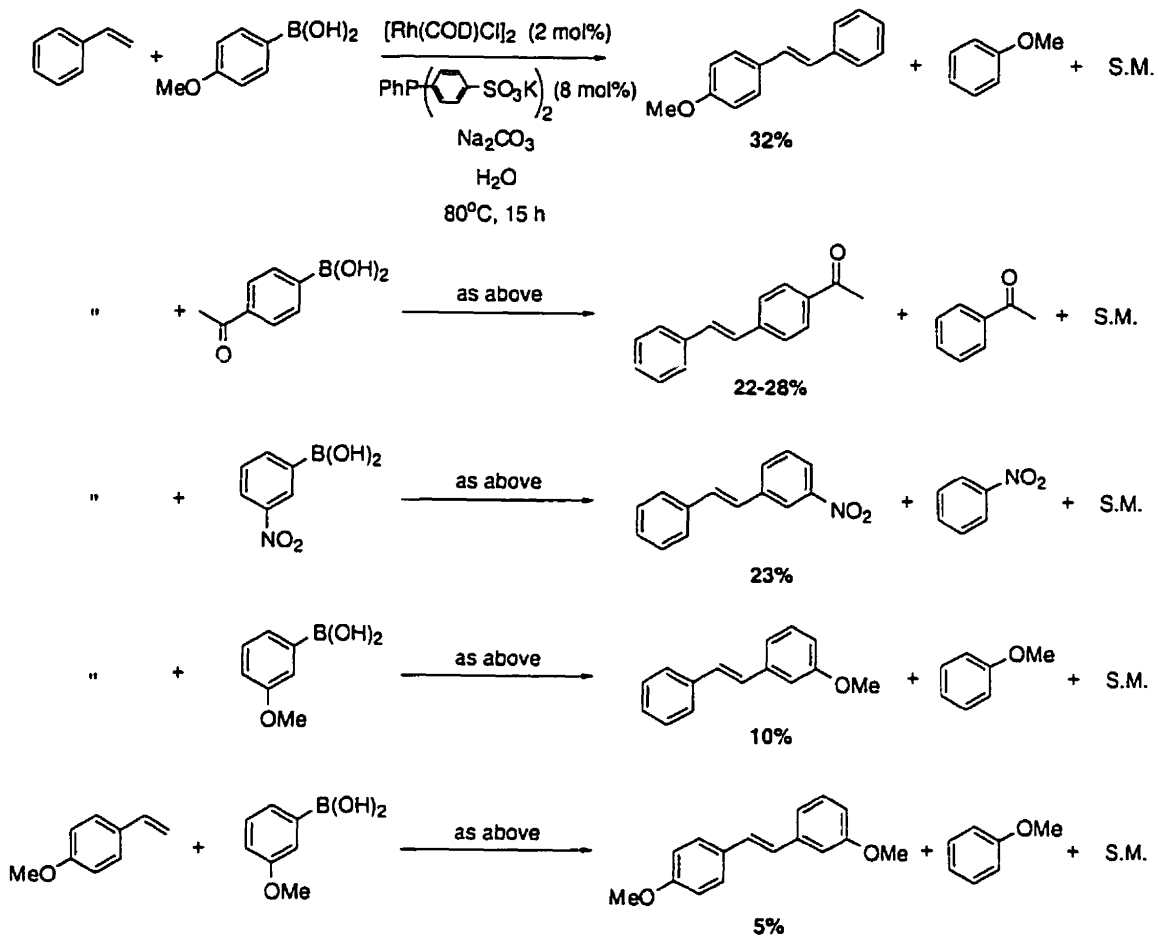
With the optimized conditions in hand, we wanted to explore the scope and the versatility of the reaction by trying the reaction with different alkenes and boronic acids. The rhodium-catalyzed coupling reaction was successful between *p*-methoxystyrene, an electron-rich olefin, and phenylboronic acid (eq. 12), furnishing **70** in 76% yield.



(eq. 12)

2.4.2 Competitive Reaction: Hydrolytic Deboronation

However, when the coupling reaction was carried out with substituted boronic acids, the yields were dramatically lower. Starting material was recovered as well as large quantities of the product arising from the deboronation of the boronic acids (Scheme 22).

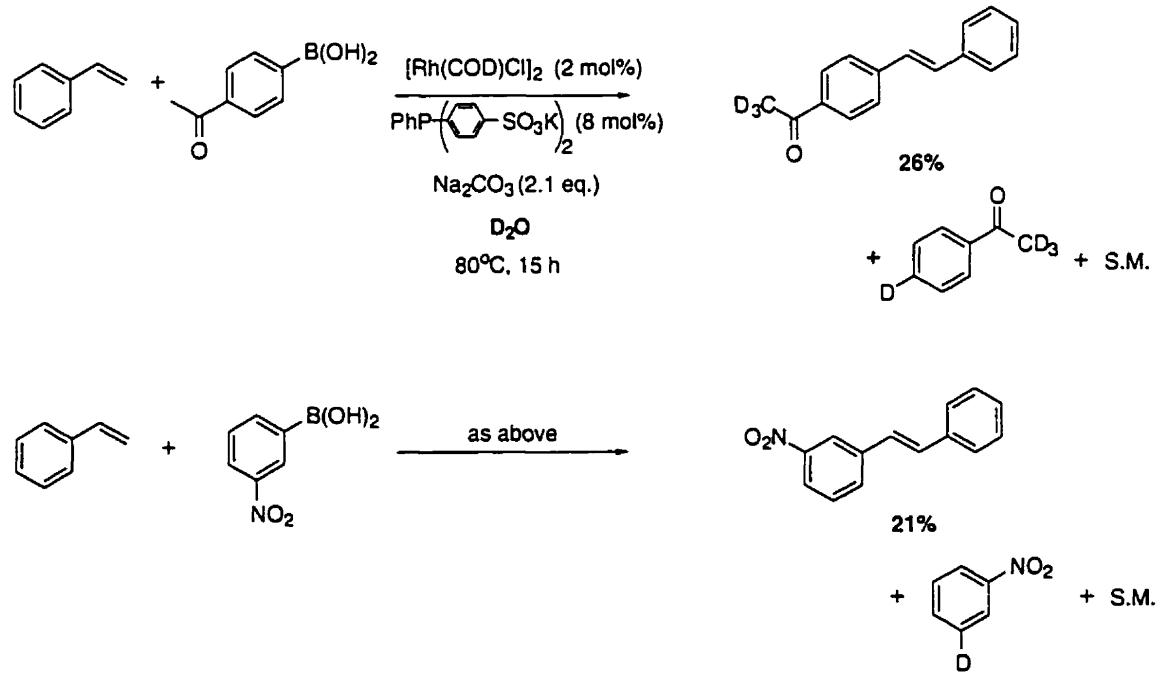


Scheme 22

Several papers reported a competitive side-reaction, the so-called "hydrolytic deboronation".[16] The authors reported that the problem was "solved" by using a large excess of boronic acid (5 eq.) or by using the boronic ester and carrying out the reaction in an organic solvent. The rate for the cleavage of $XC_6H_4B(OH)_2$ in water has been reported to be as follows (relative to phenylboronic acid): 2,6-dimethoxy (125), 2-F (77), 2-Cl (59), 2-MeO (11), 4-MeO (4.2), 2-Me (2.5), 3-F (2.3), 3-Me (2), 4-F (1.7).[17] Steric hindrance (e.g. 2,6-dimethyl) significantly decreases the competitive hydrolytic deboronation.

2.4.3 D_2O Experiment

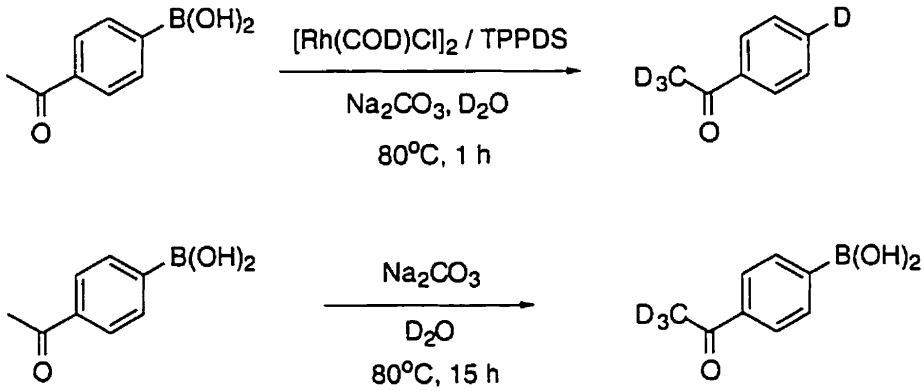
In order to identify at which step of the mechanism the hydrolytic deboronation occurred, two reactions were performed in D_2O (Scheme 23). The product corresponding to the deboronated boronic acid showed ONLY a deuterium. There was no trace of H-Ar by ^1H NMR 400 MHz. This result suggests that the solvent actually plays a role in the deboronation step. This result also demonstrates that the boronic acid does not play the role of hydrogen acceptor, otherwise H-Ar would be observed.



Scheme 23

In order to determine if the hydrolytic deboronation was actually rhodium-catalyzed, a control experiment was carried out. In one flask, 4-acetylboronic acid was mixed with a catalytic amount of $[Rh(COD)Cl]_2$ and TPPDS in D_2O in the presence of Na_2CO_3 at 80°C. In another flask, the same boronic acid was mixed in D_2O in the

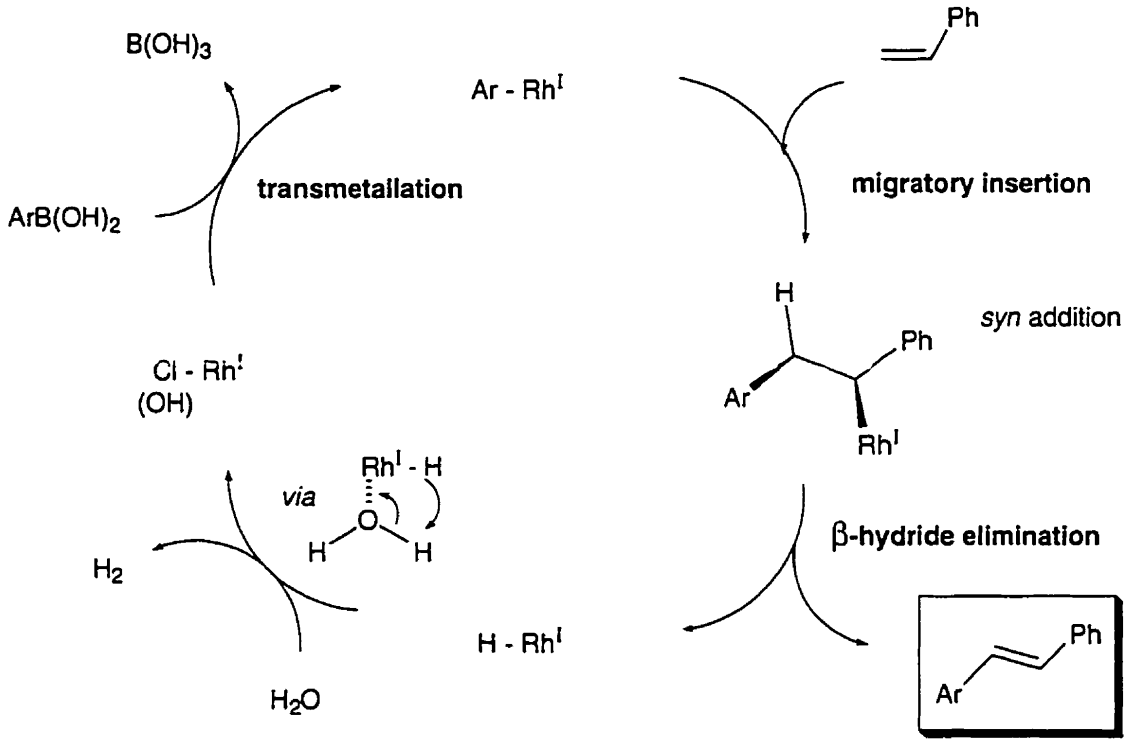
presence of Na_2CO_3 but with no rhodium catalyst (Scheme 24). In the flask containing rhodium, the ketone arising from the deboronation step was completely formed after one hour, whereas in the flask without rhodium, the boronic acid remained unchanged even after fifteen hours, except the more acidic α-positions which were deuterated.



Scheme 24

2.5 *Proposed Mechanism*

All these results provided some insights about the mechanism of the coupling reaction (Scheme 25).



Scheme 25

As described in the catalytic cycle, the rhodium(I)-chloride species first transmetalates with a molecule of arylboronic acid, forming an arylrhodium(I) intermediate. The subsequent step is the migratory insertion of arylrhodium(I) species on styrene. The insertion occurs in a *syn* manner and the oxidation state of rhodium is still Rh(I). Subsequent β-hydride elimination furnishes stilbene as well as rhodium(I) hydride. We speculate that the oxygen of water coordinates with rhodium, making the protons on water more acidic. It is then believed that a molecule of hydrogen is released, as well as the rhodium(I) hydroxide species, which then transmetalates with another molecule of arylboronic acid and the catalytic cycle can continue. We never observed hydrogen release when the coupling reactions were running. The coupling reactions proceed slowly (~15 hours) and they were typically done on a small scale (0.45 mmol),

making the possibility of visually observing hydrogen bubbling difficult. However, the transmetalation of hydroxyrhodium species with arylboronic acid has already been documented.[18]

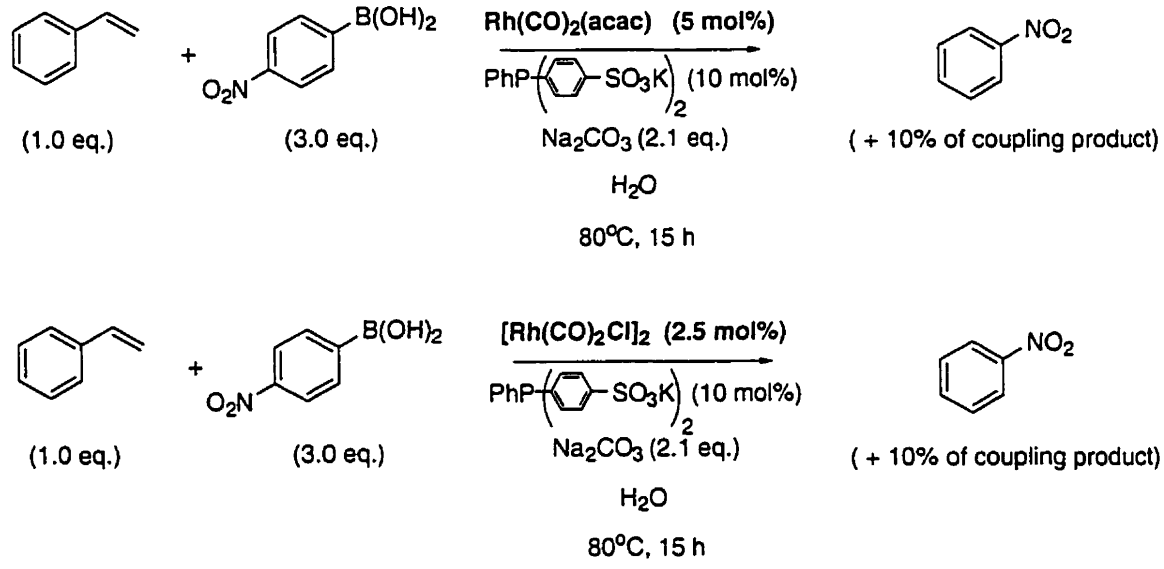
This mechanism suggests that a second equivalent of boronic acid is NOT necessary to recycle the rhodium(I) hydride species in arylrhodium(I) *via* a transmetalation. This hypothesis is also supported by the fact that only Ar-D is observed as side product (no Ar-H detected). The proposed mechanism also suggests that the arylrhodium(I) species is quenched by the solvent (water), and that this protonation is a competitive reaction with the migratory insertion with styrene.

2.6 Optimization Work: Phase 2

The way one could envisage to limit the amount of arylrhodium(I) being quenched by water is by maximizing the presence of the starting material, styrene, in water, especially since the reaction mixture was heterogeneous. Indeed, styrene micelles floating on the top of water could be observed. We considered increasing the presence of styrene in water by several different means. First, an excess of styrene in the reaction mixture could be added, instead of an excess of boronic acid. That way, the presence of the substrate around the rhodium catalyst should be increased. Second, one could make rhodium more nucleophilic and therefore more reactive by changing the ligands on the catalyst. Third, adding a water-miscible co-solvent to the aqueous reaction mixture could help the desired coupling reaction to proceed faster. Finally, the addition of a phase-transfer agent could homogenize the reaction mixture and thus increase the yield.

2.6.1 Catalyst Study

Performing the coupling reaction with an excess of styrene and one equivalent of boronic acid did not increase the amount of coupling compound produced. The styrene and rhodium catalyst did not seem to react better together. A short catalyst survey was done (Scheme 26). $Rh(CO)_2(acac)$ and $[Rh(CO)Cl]_2$ were tried but no improvement on the yield was noticed.

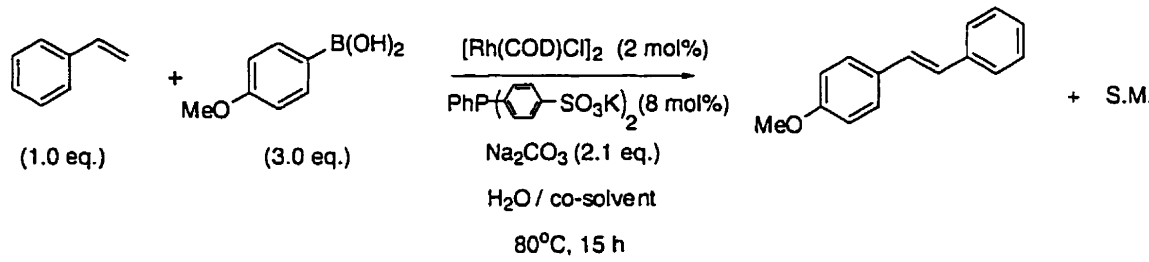


Scheme 26

2.6.2 Co-Solvent Study

The coupling reaction was then carried out using several co-solvents. The results are summarized in Table 11. Not only the yields were a little bit lower when a co-solvent was used (either water-miscible or not), but there was no reaction when the reaction was done in MeOH only (entry 6).

Table 11: Co-Solvent Study



entry	conditions	conversion (%)
1	H_2O : toluene 6.5 : 1	<10
2	H_2O : toluene 1 : 1	~15
3	H_2O : DME 1 : 1	<10
4	H_2O : THF 1 : 1	~15
5	H_2O : EtOH 1 : 1	~15
6	H_2O : MeOH 0 : 1	no reaction
7	H_2O : dioxane 10 : 1	no reaction

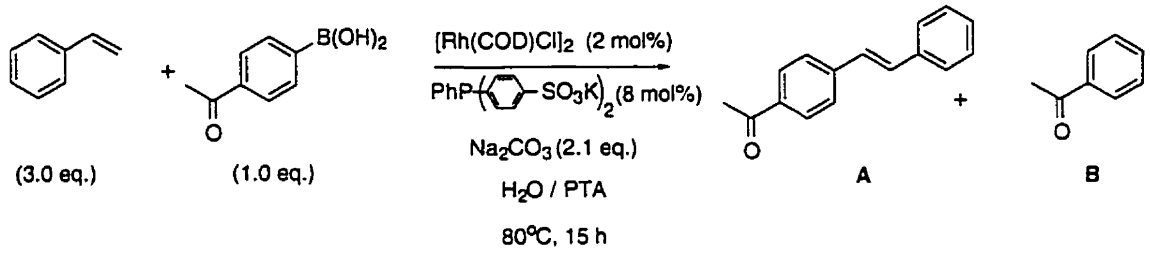
A completely "organic version" of the reaction was tried. Phenylborate **66** was reacted with styrene, in the presence of a catalytic amount of $[Rh(COD)Cl]_2$ and triphenylphosphine in toluene in the presence of anhydrous sodium carbonate at 100°C. No reaction took place.

2.6.3 Phase-Transfer Study

In an effort to improve the yield of the reaction, we examined different phase-transfer agents (Table 12). Quaternary ammonium salts like tetrabutylammonium chloride, Aliquat 336® ($CH_3N[(CH_2)7CH_3]_3Cl$), and tetrabutylammonium chloride were not beneficial for the coupling reaction (entries 1-3). However, when two equivalents of

sodium dodecylsulfate (SDS) were used, not only did the yield of the reaction improved to 43%, but the amount of the deboronated boronic acid could be restricted to 5% (entry 5).

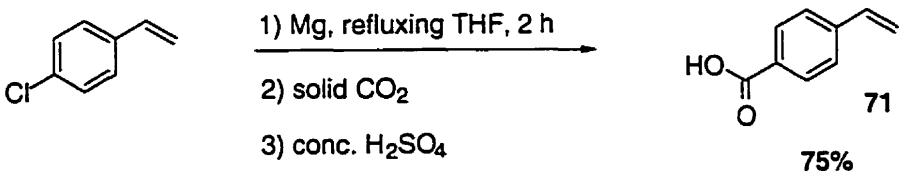
Table 12: Phase-Transfer Agent Study



entry	phase-transfer agent (eq.)	yield A (B)
1	*n*-Bu_4NI (3.0)	31 (37)
2	Aliquat® 336 (3.0)	0
3	*n*-Bu_4NCl (3.0)	15
4	SDS (3.0)	24 (55)
5	SDS (2.0)	43 (5)

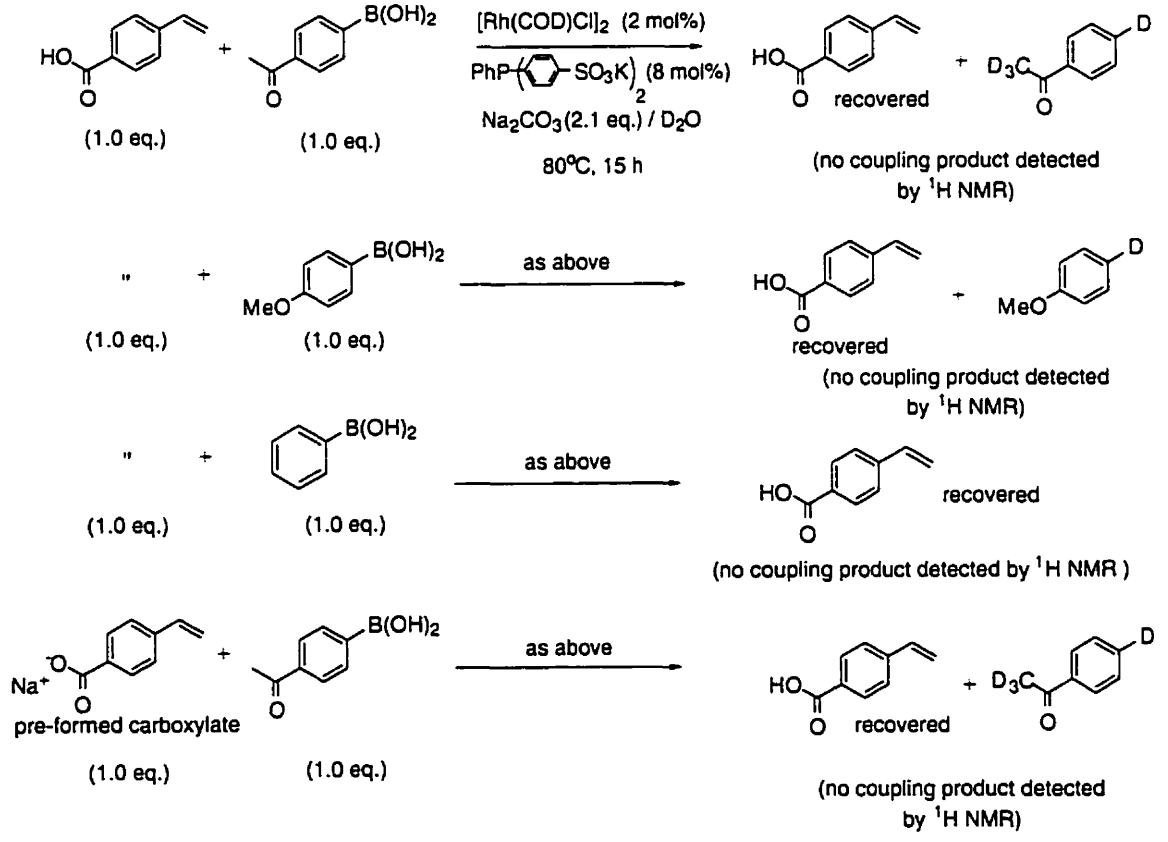
2.6.4 Water-Soluble Substrate

Finally, we carried out the coupling reaction using *p*-carboxystyrene **71**, a water-soluble substrate, which was synthesized from commercially available *p*-chlorostyrene using standard conditions (Scheme 27).



Scheme 27

The use of this substrate was designed to determine if the problem with the coupling reaction came from the low solubility of styrene in water. Of course, the versatility of the coupling reaction would be considerably diminished in only water-soluble substrates worked, but we would get a better understanding of the reaction itself. Acid **71** was submitted to the reaction conditions, using several arylboronic acids. Unfortunately, all the reactions failed, even when the pre-formed carboxylate of **71** was added in the reaction mixture (Scheme 28).

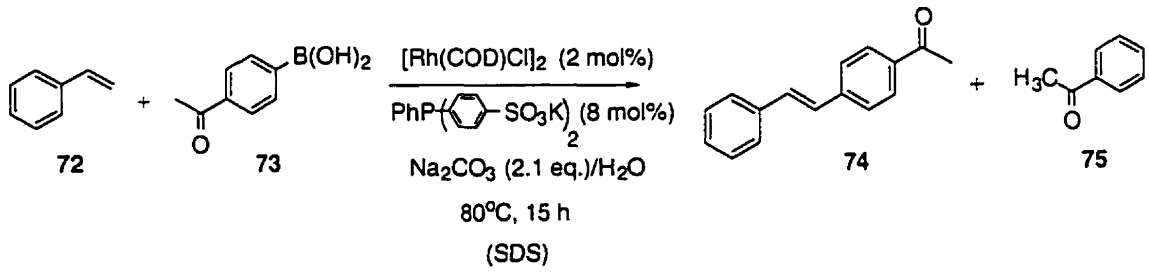


Scheme 28

2.6.5 Summary of Preliminary Screening Experiments

From the data collected, the following key points emerge. First, the coupling reaction worked well only when phenylboronic acid was used. As soon as the arylboronic acid was substituted, the reaction failed. Second, the use of an organic co-solvent proved to be harmful for the reaction. Third, several substrate/boronic acid ratios had been examined, with and without SDS, without significant success (Table 12).

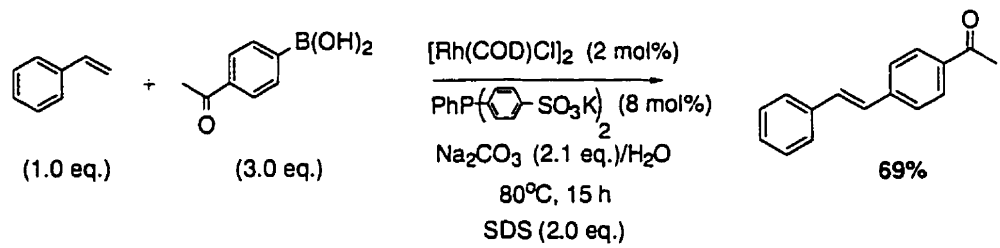
Table 13: Summary



entry	eq. of **72**	eq. of **73**	eq. of SDS	yield **74** (%)
1	**1**	**1**	**2**	**53**
2	1	1	0	6
3	**3**	**1**	**2**	**43**
4	3	1	0	7
5	1	3	0	22-28

The results in Table 13 indicate that the presence of SDS in the reaction mixture has a significant beneficial impact on the yield of the reaction (entries 1, 3). By carrying out the reaction using an excess of 4-acetylboronic acid with one equivalent of styrene *in the presence* of two equivalents of SDS, the desired coupling product was obtained in 69% yield (eq. 13). The most encouraging observation was that the reaction was 100%

complete: no styrene was detected in the crude ^{1}H NMR. Sodium dodecyl sulfate is known to be a good phase-transfer agent in the case of aqueous rhodium-catalyzed enantioselective hydrogenation of enamides and itaconic acid[19] as well as being the surfactant of choice for organic reactions in water using colloidal dispersions as reaction media.[20]



(eq. 13)

This result described in equation 13 suggests that the water-soluble rhodium catalyst complex, which undergoes transmetalation with the boronic acid in water, first enters the styrene micelles where the coupling reaction takes place. Rhodium hydride is released and this species subsequently goes in the water phase to form rhodium hydroxide, which then re-enters within the styrene micelles to continue the catalytic cycle. The role of the phase-transfer agent is to shuttle the compounds between the two non-miscible phases.

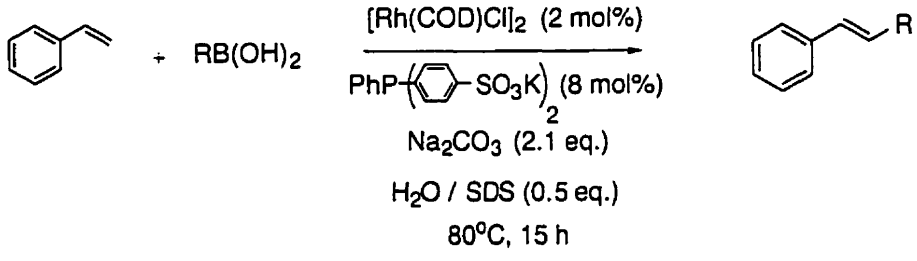
The reaction was subsequently attempted with *n*-Bu_4NI as the phase-transfer agent. Even though the reaction went to completion, the isolated yield was only 15%. Indeed, most of the product remained stuck at the interphase. The amount of SDS could eventually be reduced to 0.5 equivalents without altering the conversion. In fact, the

yield was slightly better (73%) and the work-up was greatly facilitated (no emulsion anymore).

2.7 *Aqueous Heck-Type Coupling Reaction with Styrene*

With the optimized conditions in hand, the aqueous rhodium-catalyzed Heck-type coupling reaction was carried out between styrene and different boronic acids. The results are summarized in Table 12.

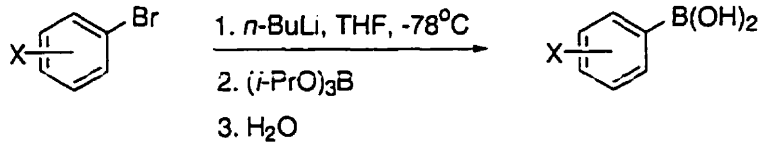
Table 12: Examples of Heck-Type Coupling Reactions Using the Optimized Conditions



entry	R	yield (%)
1	Ph	76
2	4-$MeOC_6H_4$*	85
3	3-$MeOC_6H_4$	95
4	3-$NO_2C_6H_4$	65
5	4-AcC_6H_4	73
6	3-IC_6H_4	72
7	2-MeC_6H_4*	86
8	1-naphthyl*	52
9	2-naphthyl*	67
10	2-thiophenyl	40

* Acid boronics prepared according to literature procedures

Boronic acids that were not commercially available were readily prepared from the corresponding bromides according to usual procedures (Scheme 29). In general, the isolated yields range from 75% to 85%.

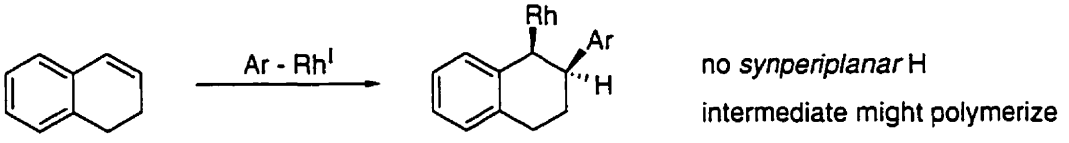


Scheme 29

The yields of the Heck-type coupling reaction range from 40% to 95%. The coupling reaction is successful with electron-donating groups on the boronic acid (entries 2 and 3), electron-withdrawing groups (entries 3-6), and sterically hindered boronic acids (entries 7 and 8). In the cases of 1-naphthyl- and 2-naphthylboronic acids, the yields are slightly lower (entries 8 and 9). Indeed, both the reaction product and naphthalene, which arises from the hydrolytic deboronation, are very non-polar and the separation of the two compounds is more difficult. Also, with the two naphthylboronic acids, a small quantity (5%) of the product corresponding to the reduction of the alkene was observed. The formation of such compounds might be attributed to the release of H_2 gas in the course of the coupling reaction and rhodium-catalyzed hydrogenation. In the case of 2-thiophenylboronic acid, the yield is rather poor and it could be due to the low quality of the boronic acid.

2.8 Aqueous Heck-Type Coupling Reaction: Various Substrates

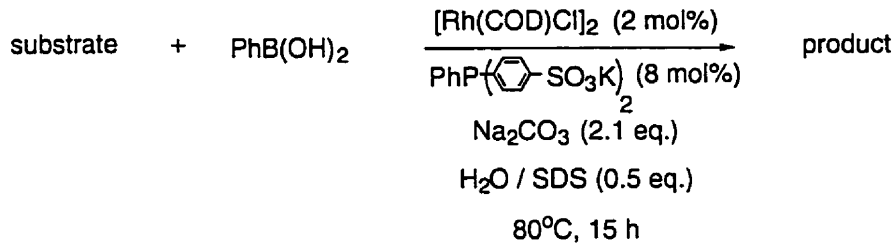
The coupling reaction was then carried out with several substrates in the presence of phenylboronic acid (Table 14). The expected coupling compound was obtained in good yield with an electron-rich olefin (entry 1) as well as an electron-poor alkene (entry 2). When dihydronaphthalene (entry 3) was submitted to the reaction conditions, only polymerization residues were isolated. This result supports the proposed mechanism since if the addition on styrene is actually done in a *syn* manner, the β-hydride elimination becomes impossible because there is no *synperiplanar* hydrogen (Scheme 30) and the rhodium intermediate may add to another molecule of alkene and polymerize.

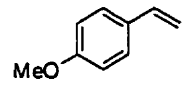
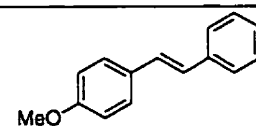
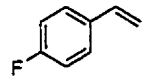
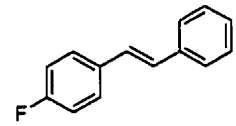
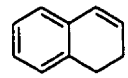
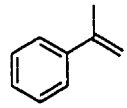
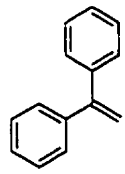
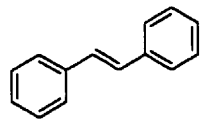
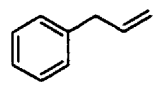
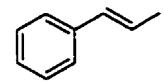
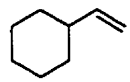
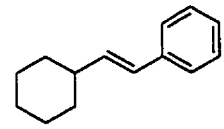


Scheme 30

α-Methylstyrene and *trans*-stilbene did not react under the reaction conditions (entries 4 and 5). When allylbenzene was submitted to the reaction conditions, the only product observed was the one corresponding to the isomerization of the double bond (entry 6). Finally, the reaction was carried out with a non-aromatic alkene, vinylcyclohexane (entry 7). The desired coupling product was isolated but only in low yield (~15-20% depending on the run). However, the starting material was all consumed so degradation or polymerization probably accounts for the rest of the mass balance.

Table 14: Examples with Other Olefins



entry	substrate	product	yield (%)
1			76
2			81
3		polymerization	—
4		no reaction (starting material recovered)	0
5		no reaction (starting material recovered)	0
6		no reaction (starting material recovered)	0
7			60
8			15-20

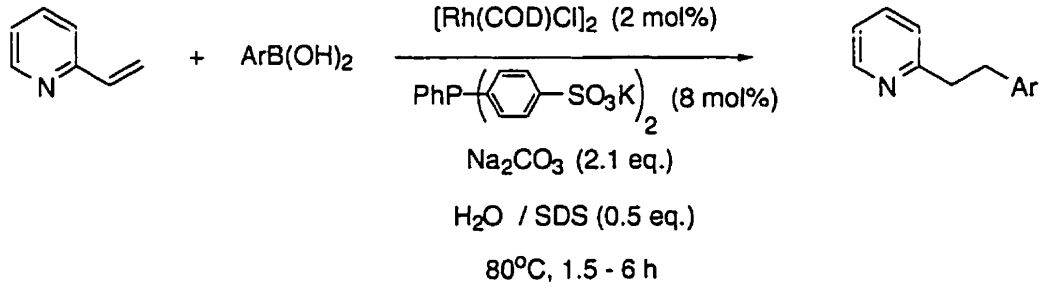
2.9 *Reactivity of 2-Vinylpyridine*

2.9.1 Various Boronic Acids

In the course of examining various substrates, the Heck-type coupling reaction was carried out with 2-vinylpyridine and phenylboronic acid in the presence of the water-soluble rhodium complex. The "reduced" coupled compound was obtained in good yield (Table 15, entry 1). At first, H_2 was believed to be responsible for the reduction of the alkene. However, since this product had not been observed before, at least not significantly, the hypothesis of the reduction by H_2 gas was unlikely. It is worth noting that the coupling reaction with 2-vinylpyridine is more rapid that the one with styrene and works well with sterically hindered boronic acids (Table 15, entries 2-4). Although the yield of the reaction with 2-bromophenylboronic acid is lower (entry 4), the coupling product thus formed is interesting and useful because further metal-catalyzed cross-coupling reactions can be envisaged. The reaction was also successful with electron-rich 4-methoxyphenylboronic acid (entry 5), but was less clean with 3-methoxyphenylboronic acid (entry 6). The reaction is significantly less successful with electron-withdrawing boronic acids (entries 7 and 8). For example, no reaction occurred with 3-nitrophenylboronic acid. When the reaction was carried out with (*E*)-1-(2-phenyl)vinyboronic acid, the yield was only 30% because of the competitive reaction occurring between styrene (arising from the hydrolytic deboronation of the boronic acid) and the boronic acid. The reaction was then tried with a larger excess of boronic acid to get the desired reaction to completion. However, the yield did not improve and the amount of the side product $Ph(CH)_4Ph$ increased. With *n*-hexen-1-ylboronic acid, we hoped that the side reaction would be less favored (alkyl olefins are less reactive than aryl

olefins). However, the yield was still moderate and a mixture of isomers coming from the isomerization of the double bond was obtained.

Table 15: Unexpected Reactivity of 2-Vinylpyridine



entry	Ar	yield (%)
1	Ph	84
2	2-MeC_6H_4*	87
3	1-naphthyl*	88
4	2-BrC_6H_4	60
5	4-$MeOC_6H_4$*	77
6	3-$MeOC_6H_4$	35
7	3-$NO_2C_6H_4$	0
8	4-AcC_6H_4	23
9	PhCH=CH*	31
10	*n*-BuCH=CH*	41 (mixture of isomers)

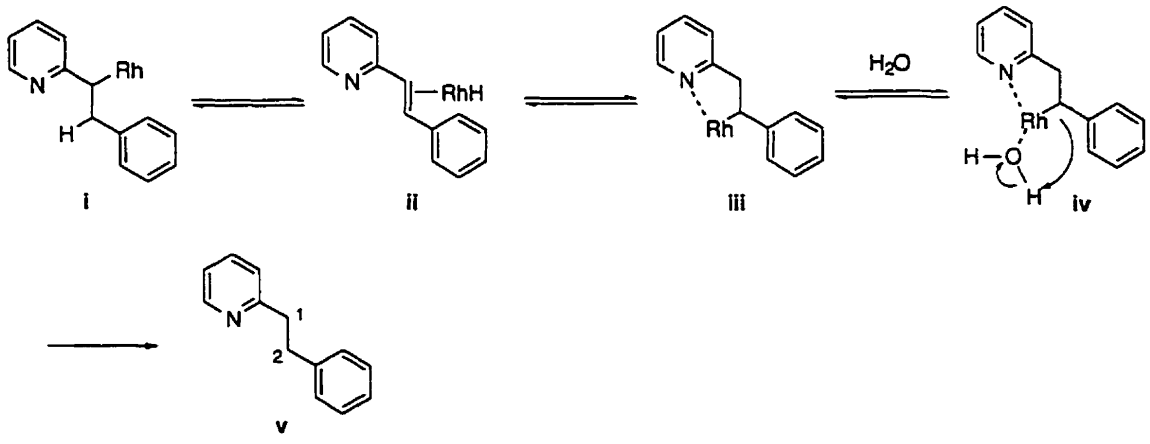
*Acid boronic prepared according to literature procedures

2.9.2 Mechanistic Investigation

We did verify that the reactions were rhodium-catalyzed and not acid- or base-catalyzed. Both the reactions with styrene and 2-vinylpyridine were carried out without

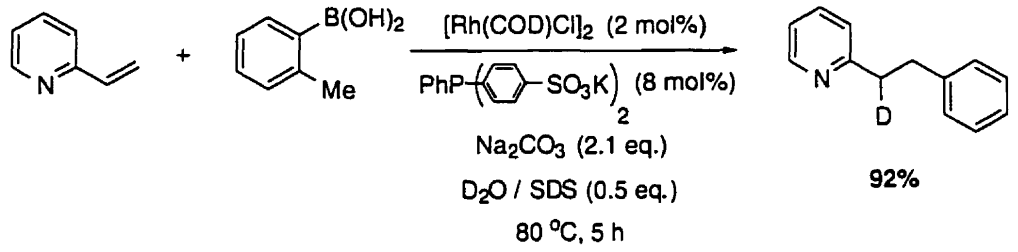
rhodium and no reaction took place after 24 hours. The reactions do occur with non water-soluble ligands such as triphenylphoshine (PPh_3) or in absence of any phosphine ligand. However, the reactions are much slower and thus remain incomplete because the boronic acid in the reaction mixture is consumed before the end of the reaction. Slow addition of boronic acid with a syringe pump was envisaged but the low solubility of the boronic acids in water made it difficult to execute. Therefore, the use of a water-soluble ligand is essential for the success of the coupling reaction.

Several mechanisms can be proposed to explain the special reactivity of 2-vinylpyridine. First it was envisaged that an equilibrium existed between intermediates **i**, **ii**, and **iii**, ultimately favoring the more stable species **iii** and giving rise to a five-membered ring where the nitrogen and rhodium are coordinated (Scheme 31). The fact that rhodium coordinates to heteroatoms to form five-membered rings is well documented, especially in the case of C-H activation.[21] Since the reaction is done is water, the solvent could then coordinate to the rhodium, making the hydrogens of water more acidic, and thus cleaving the carbon-rhodium bond.



Scheme 31

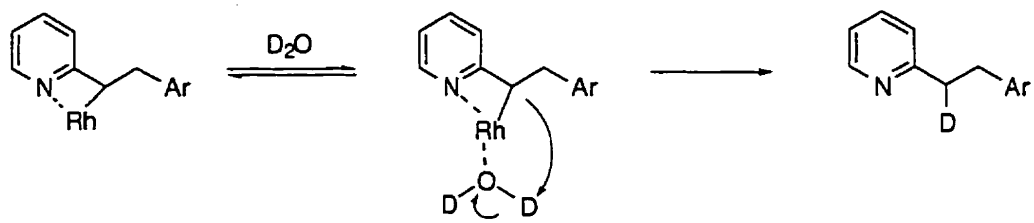
A D_2O experiment was carried out to verify the hypothesis. If the hypothesis was correct, the deuterium would appear on the methylene labeled 2 (Scheme 31, v). However, after the reaction, the deuterium was exclusively on the methylene next to the pyridine ring, as shown in equation 14.



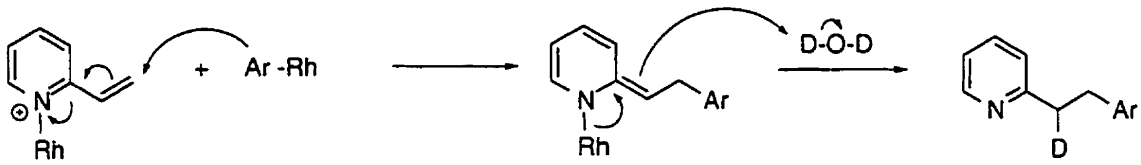
(eq. 14)

The structure was proved by ^1H and ^{13}C NMR as well as COSY, HSQC and HMBC. This result suggests that a four-membered ring, instead of a five-membered ring, could be formed with the rhodium coordinating with the nitrogen (Scheme 32). However, to the best of our knowledge, no case of coordination between nitrogen and rhodium giving rise to a four-membered ring have ever been reported, unlike the five-membered rings. Another possibility is that the mechanism is different from a Heck-type reaction and would be similar to the 1,4-addition of the rhodium(I)-aryl species on the "enaminate" (Scheme 32).

4-membered ring

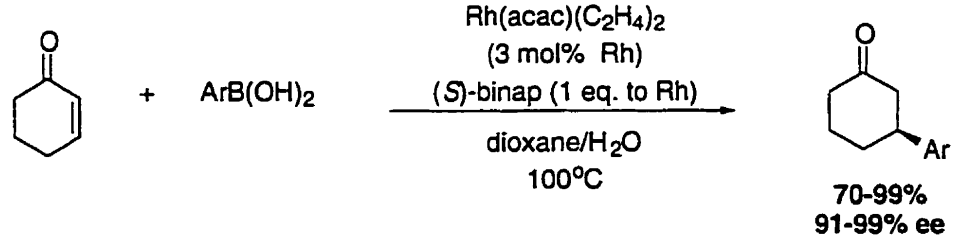


1,4-addition



Scheme 32

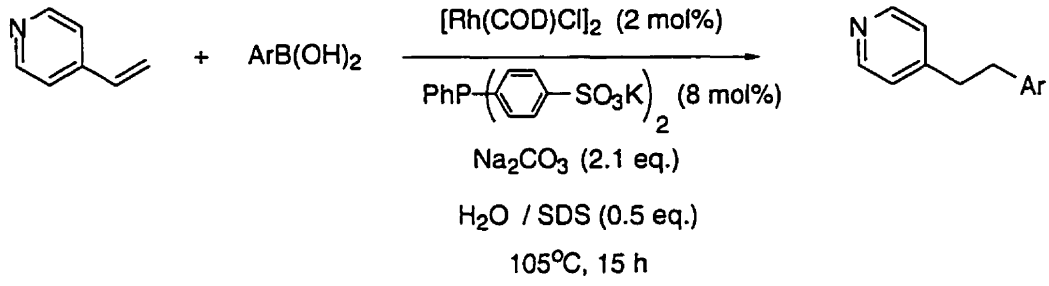
Indeed, Miyaura and co-workers recently reported the rhodium-catalyzed 1,4-conjugate addition reactions of aryl-and 1-alkenyl-boronic acids to enones, enals, and α,β-unsaturated esters in an aqueous mixture of solvents. This reaction mechanism is believed to proceed through a sequence of boron-rhodium transmetalation, yielding an organorhodium(I) species followed by its addition to the unsaturated system.[22] Hayashi and co-workers subsequently demonstrated asymmetric variants by using a rhodium(I)-chiral phosphine complex (eq. 15).[23]



(eq. 15)

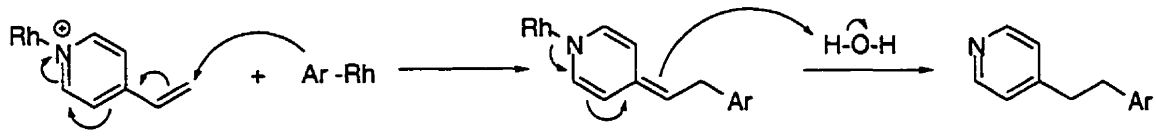
In order to determine which of the two hypotheses is correct, the reaction was carried out with 4-vinylpyridine. If the reaction gave the 1,2-diarylethyl derivative ("reduced" alkene), the hypothesis of the 1,4-addition would seem more reasonable than the four-membered ring, the latter being impossible with the 4-vinylpyridine. Initial attempts with 4-vinylpyridine and 2-metyhlphenylboronic acid under the usual reaction conditions were unsuccessful and the starting material was recovered. However, when the temperature of the reaction was increased to 105°C (set temperature of the heat bath), 4-5 equivalents of boronic acid were added to the reaction mixture and it was stirred for 15 hours, the 1,2-diarylethyl derivative was isolated in 95% yield (before purification). However, a significant quantity of coupling product was lost during the purification step with silica gel and the yield after purification dropped to 66%. Other arylboronic acids were then tried under the optimized reaction conditions. The results are summarized in Table 16. The coupling reaction works well with a variety of boronic acids (entries 1-4) but fails with electron-withdrawing 3-nitrophenylboronic acid.

Table 16: Coupling Reactions with 4-Vinylpyridine



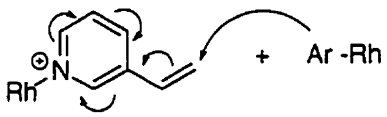
entry	Ar	yield (%)
1	Ph	80
2	2-MeC_6H_4	66 (95% crude)
3	2-naphthyl	79
4	4-$MeOC_6H_4$	86
5	3-$NO_2C_6H_4$	0

We found that 4-vinylpyridine is less reactive than 2-vinylpyridine. Indeed, the reactions with 4-vinylpyridine are longer (15-20 hours instead of 6 hours) and hence a greater amount of boronic acid has to be used due to the hydrolytic deboronation (competitive reaction). Unfortunately the boronic acid is consumed before the coupling reaction is actually complete. But since the product obtained with 4-vinylpyridine is the 1,2-diarylethyl derivative (reduced compound), it suggests that the mechanism is similar to a nucleophilic attack of the rhodium(I)-aryl species because the formation of the four-membered ring can not occur with 4-vinylpyridine. Rhodium may be coordinated to the nitrogen, thus activating the π system and making it more electrophilic (Scheme 33).

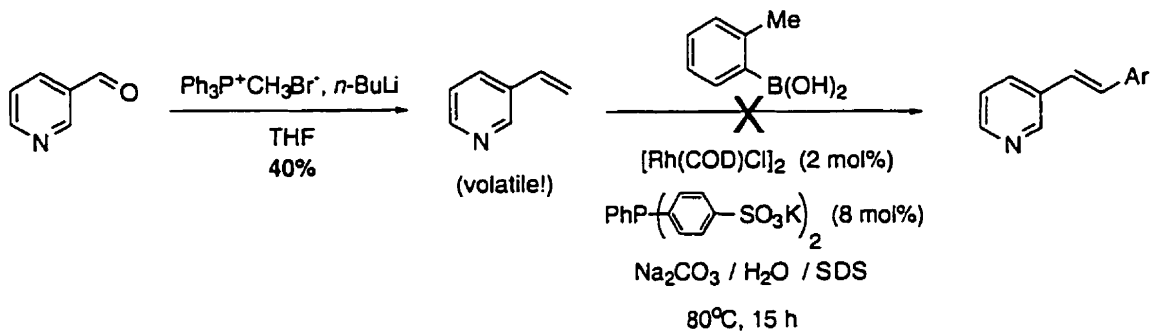


Scheme 33

In the case of the 2-vinylpyridine, it is possible that the proximity of the nitrogen with the olefin helps to increase the rate of the reaction by actually allowing the four-membered ring as well. When the reaction was carried out with 3-vinylpyridine, only degradation was observed. The conjugation of the π system of the 3-vinylpyridine does not allow the same mechanism than for the 2- and 4-vinylpyridine.



However, the normal Heck-type coupling product could have been expected, but was never observed. 3-Vinylpyridine, which proved to be very volatile, was prepared from commercially available 3-pyridinecarboxaldehyde *via* a Wittig reaction (Scheme 34).[24] The coupling reaction also failed between 2-ethynylpyridine and various arylboronic acids.



Scheme 34

2.9.3 Attempts with Lewis Acids

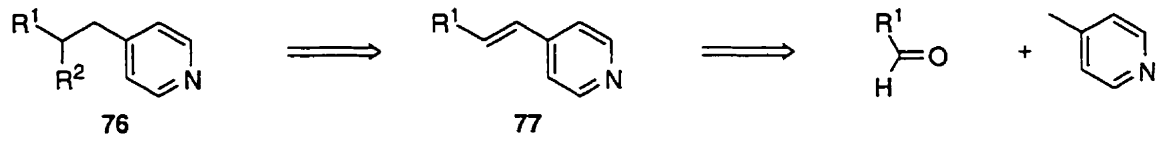
Since the mechanism seemed to involve the coordination of the nitrogen atom by rhodium, the coupling reaction with 2-vinylpyridine was carried out in the presence of Lewis acid catalysts stable in water.[25] Indeed, Kobayashi and co-workers have reported water-stable Lewis acids like lanthanides, scandium, and yttrium triflates, which can be used in several carbon-carbon bond forming reactions in aqueous media.[26] However, the coupling reaction failed in the presence of $Sc(OTf)_3$, $LiClO_4$, *p*-toluenesulfonic acid (*p*-TsOH), *p*-pyridium sulfonate (ppts), *d*-10-camphor sulfonic acid monohydrate ($CSA \bullet H_2O$), $Cu(OTf)_2$, or $Sm(OTf)_2$. Unreacted starting material and boronic acid were recovered. Thus, it appears that the rhodium catalyst is essential in the reaction mixture and that it has a more important role than simply acting as a Lewis acid.

2.10 Synthesis of Triaryl-Ethyl Derivatives

2.10.1 Literature Precedents

The synthesis of triaryl-ethyl derivatives containing one or more heteroatomic components has received considerable attention in Merck Research Laboratories due to the fact that these components have shown considerable phosphodiesterase IV (PDE IV) inhibitory activity.[27] The latter has been shown to have significant clinical benefit in the effective treatment of asthma. In the course of their studies towards the synthesis of these triaryl-ethyl compounds of general formula **76**, they became interested in the nucleophilic "conjugate" addition of carbanions to vinylpyridine. Construction of the triaryl-ethyl

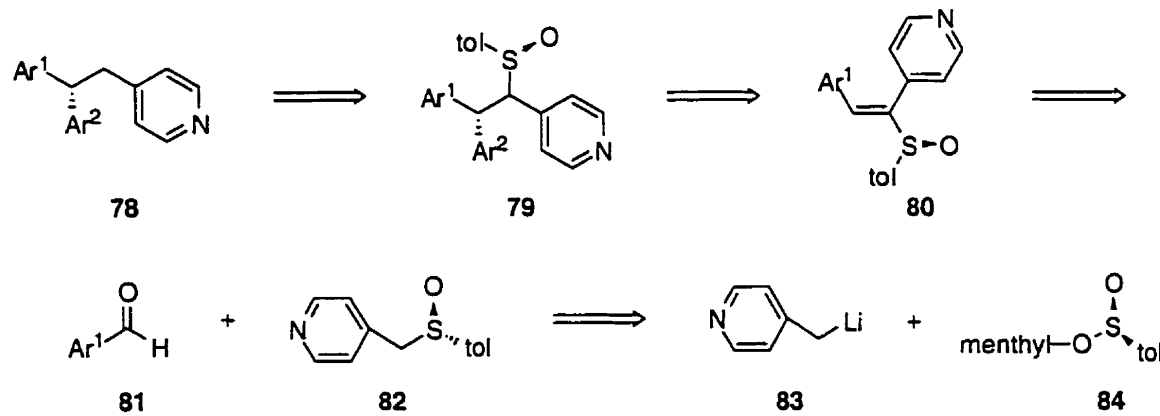
derivatives could be accomplished by the Ni-catalyzed addition of Grignard and zincate reagents to the β-substituted 4-vinylpyridine **77** (Scheme 35).[28] Without the presence of nickel, the yields for the nucleophilic addition are <10%. With a catalytic amount of nickel, they range from 70% to 95%.



R^1, R^2 = alkyl, vinyl, aryl

Scheme 35

The same authors also reported the use of chiral sulfoxide intermediates in order to synthesize non-racemic triaryl-ethylderivatives (Scheme 36).[29] Again, the best results were achieved by the use of organozincate reagents (Ph_3ZnLi and $Ph_3ZnMgBr$) via Ni catalysts.[30] The yields are greater than 90% and the ee's range from 82% to 92%.

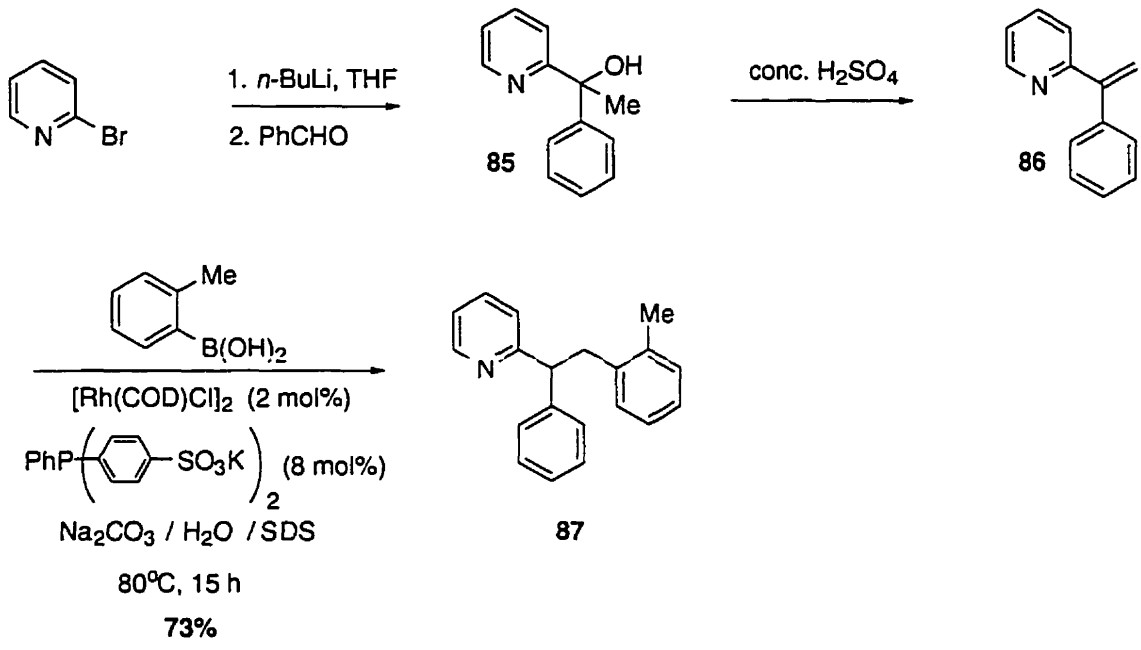


Scheme 36

2.10.2 Preliminary Results

We planed to use our rhodium-catalyzed cross-coupling methodology to synthesize the same kind of triaryl-ethyl derivatives, using readily available 2-bromopyridine as the starting material (Scheme 37).[31] The number of steps would be substantially shortened and the method more convenient (readily available starting materials and reagents, mild reaction conditions).

When 1-phenyl-1-(2-pyridyl)ethylene **86** was reacted with 2-methylphenylboronic acid in the presence of a catalytic amount of a water-soluble rhodium catalyst, the desired coupling product **87** was isolated in 73% yield. The presence of the pyridine ring tremendously enhances the reactivity of the starting material because the analogous 1,1-diphenylethylene did not react under the same reaction conditions (Table 14, entry 5). Current investigations in the group are aimed towards the development this methodology for the synthesis of triaryl-ethyl derivatives from of 1,1-diaryl-ethyl precursors.



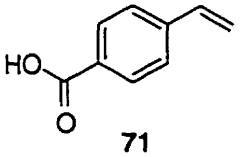
Scheme 37

2.11 Conclusions

We have developed the first methodology allowing the aqueous rhodium-catalyzed Heck-type cross-coupling reaction between olefins and boronic acids. The water-soluble ligand *p*-disulfonated triphenylphosphine TPPDS was used to form a water-soluble rhodium complex. A mechanism was proposed for this transformation, involving the conversion of rhodium(I)-hydride into rhodium(I)-hydroxide by water. Studies were first conducted on the cross-coupling reaction between styrene and various boronic acids. The optimized conditions were subsequently applied to extend the methodology to various olefins, although with modest success. The role of the water-soluble rhodium catalyst was demonstrated as being crucial for the success of the reaction. The new reactivity showed by 2- and 4-vinylpyridine was used to develop a novel methodology giving access to 1,2-diaryl- and 1,1,2-triaryl-ethyl derivatives.

2.12 Experimental

4-Carboxystyrene (71):



71

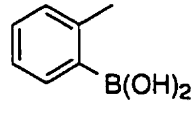
Mg turnings (1.45 g, 51 mmol) were dried in the oven overnight in a round-bottom flask. After cooling to r.t. under an argon atmosphere, dry THF (50 mL, 0.58 M) was added followed by 4-chlorostyrene (Aldrich, 4.02 g, 29 mmol) which was added dropwise over 20 minutes. The reaction mixture was heated with a heat gun until it refluxed and the temperature was maintained at 90°C for 2.5 hours. The colorless solution turned yellow and finally dark green. The reaction mixture was cooled to 40°C and poured into solid CO_2. The resulting dough was stirred with a rod and acidified with H_2SO_4 (5 M, 20 mL). The reaction mixture was extracted with Et_2O (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The recrystallization of the crude solid with Et_2O and pentane afforded 3.02 g (75%) of a white solid. R_f = 0.18 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 12.4-11.0 (1H, br), 8.07 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.4 Hz), 6.78 (1H, dd, J_{cis} = 11.2 Hz, J_{trans} = 17.6 Hz), 5.90 (1H, d, J_{trans} = 17.6 Hz), 5.42 (1H, d, J_{cis} = 11.2 Hz); ^{13}C NMR δ 172.0, 142.8, 135.9, 130.5, 128.4, 126.2, 117.0; Mass calculated for $C_9H_8O_2$: 148.162; Mass found: 148.063. The rest of the spectral data correspond to those reported in the literature.[32]

Typical procedure for the synthesis of arylboronic acids:

To a cooled mixture of 2-bromotoluene (Aldrich, 7.1 g, 41.6 mmol) in dry THF (140 mL, 0.3 M) at -78°C was added *n*-BuLi (1.91 M/hexanes, 28.3 mL, 54.1 mmol). At this point,

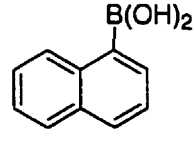
a precipitate usually crashed out of solution. The reaction mixture was stirred at -78°C for 30 minutes prior to the addition of triisopropyl borate (16.3 mL, 70.7 mmol). After the clear solution reached r.t., H_2O was added and the reaction mixture was stirred at r.t for 15 minutes. Concentrated HCl (5-7 mL) was added until the pH<4. The reaction mixture was extracted with Et_2O (3 x 200 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 (stirred for 30 minutes), filtered and concentrated. The crude solid was triturated overnight in Et_2O, and after filtration 3.15 g (56%) of a white solid was isolated.

2-Methylphenylboronic acid:



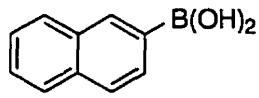
R_f = 0.12 (50% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.22 (1H, d, J = 7.6 Hz), 7.45 (1H, t, J = 7.6 Hz), 7.33-7.25 (2H, m), 2.82 (3H, s); Mass calculated for $C_7H_9BO_2$: 135.956. The rest of the spectral data correspond to those reported in the literature.[33]

1-Naphthylboronic acid:



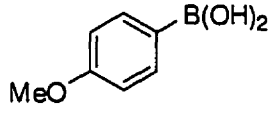
R_f = 0.15 (80% Et_2O in hexanes); ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (2H, s), 7.91-7.86 (2H, m), 7.72 (1H, m), 7.51-7.42 (3H, m); Mass calculated for $C_{10}H_9BO_2$: 171.988. The rest of the spectral data correspond to those reported in the literature.[34]

2-Naphthylboronic acid:



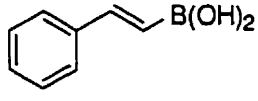
R_f = 0.13 (50% Et_2O in hexanes); ^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (1H, s), 8.18 (2H, s), 7.92-7.83 (3H, m), 7.55-7.48 (2H, m); Mass calculated for $C_{10}H_9BO_2$: 171.988. The rest of the spectral data correspond to those reported in the literature.[35]

4-Methoxyphenylboronic acid:



R_f = 0.20 (Et_2O); ^1H NMR (400 MHz, DMSO-d_6) δ 7.79 (2H, d, J = 11.6 Hz), 6.92 (2H, d, J = 11.6 Hz), 3.77 (3H, s); Mass calculated for $C_7H_9BO_2$: 135.959. The rest of the spectral data correspond to those reported in the literature.[36]

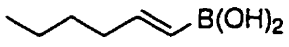
1-[(*E*)-(2-Phenylethenyl)]boronic acid:



Neat phenylacetylene (5.0 g, 49.0 mmol) was cooled to 0°C prior to the addition of catecholborane (1.0 M/THF, 49 mL). The yellow solution was stirred at 70°C for 3 hours and at 80°C for 1 hour. After cooling to r.t. H_2O (20 mL) was added and the reaction mixture was heated at 90°C for 3 hours. After cooling to r.t. the reaction mixture was acidified with concentrated HCl and extracted with Et_2O (150 mL). The aqueous phase was re-extracted with Et_2O (2 x 100 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 (stirred for 1 hour), filtered and evaporated. H_2O was

added and a pale yellow solid crashed out of solution. The solid was rinsed with hexanes and the yellow color disappeared. The white solid was dried under high vacuum and 3.61 g (50%) was isolated. R_f = 0.20 (Et_2O); ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (2H, d, J = 7.2 Hz), 7.37 (2H, t, J = 7.2 Hz), 7.27 (1H, dd, J_1 = 7.2 Hz, J_2 = 18.8 Hz), 6.73-6.58 (1H, ddd, J_1 = 4.0 Hz, J_2 = 6.0 Hz, J_3 = 50.0 Hz), 6.12 (1H, d, J_{trans} = 18.4 Hz); Mass calculated for $C_8H_9BO_2$: 147.967. The rest of the spectral data correspond to those reported in the literature.[37]

1-[(1*E*)-Hexen-1-yl]boronic acid:

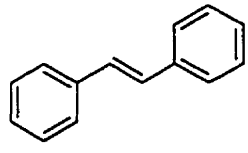


To 1-hexyne (6.0 g, 73 mmol) in dry CH_2Cl_2 (80 mL, 0.92 M) under N_2 at 5°C was added $HBBr_2$•SMe_2(1.0 M/CH_2Cl_2, 76.7 mL, 76.7 mmol) *via* syringe. After stirring the pale yellow reaction mixture at r.t. for 22 hours, CH_2Cl_2 was removed *in vacuo*, and the remainder of the material dissolved in Et_2O (100 mL). The resulting solution was cooled to -60°C and aqueous NaOH (2.0 M, 77 mL, 154 mmol) was added dropwise while maintaining a vigorous stirring. The mixture was warmed to r.t. and stirred for 3 hours. The two layers were separated, the aqueous phase was extracted with Et_2O (3 x 120 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude solid was triturated in hexanes for 2 hours and after filtration 4.94 g (53%) of a fluffy white solid was isolated. R_f = 0.10 (15% Et_2O in hexanes); ^1H NMR (400 MHz, DMSO-d_6) δ 7.00-6.93 (1H, m), 5.53 (1H, d, J_{trans} = 18.0 Hz), 4.19 (2H, s), 2.25-2.15 (2H, m), 1.48-1.29 (4H, m), 0.91 (3H, t, J = 7.2 Hz); Mass calculated for $C_6H_{13}BO_2$: 127.977. The rest of the spectral data correspond to those reported in the literature.[38]

Typical procedure for the synthesis of arylethenylbenzene:

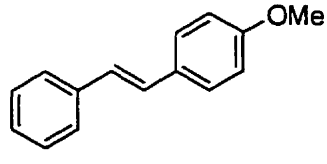
To a mixture of $[Rh(COD)Cl]_2$ (4.3 mg, 2 mol%), TPPDS (17.5 mg, 8 mol%) in H_2O (2.2 mL, 0.2 M) at r.t. was successively added phenylboronic acid (133 mg, 1.09 mmol), Na_2CO_3 (97 mg, 0.916 mmol), SDS (63 mg, 0.228 mmol), and styrene (50 μL, 0.436 mmol). The reaction mixture was heated at 80°C for 15 hours. After cooling to r.t. the colored solution was poured into Et_2O (25 mL) and the reaction flask was carefully rinsed with Et_2O. The heterogeneous mixture was vigorously stirred at r.t. for 2 hours. The two phases were separated, the aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by flash chromatography (1% Et_2O in hexanes) and 60 mg (76%) of a white solid was isolated.

[(*E*)-2-Phenylethenyl]benzene:



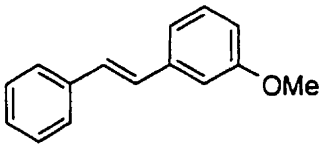
R_f = 0.30 (100% hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.53 (4H, d, J = 9.6 Hz), 7.37 (4H, t, J = 9.2 Hz), 7.29-7.24 (2H, m), 7.12 (2H, s); Mass calculated for $C_{14}H_{12}$: 180.249; Mass found: 180.245. The rest of the spectral data correspond to those reported in the literature.[39]

1-Methoxy-4-[(*E*)-2-phenylethenyl]benzene:



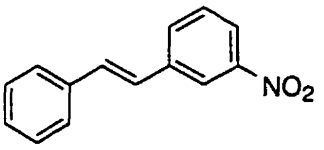
R_f = 0.33 (5% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.49 (2H, d, J = 7.6 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.34 (2H, t, J = 7.6 Hz), 7.23 (1H, t, J = 7.2 Hz), 7.09-6.95 (2H, dd, J_1 = 16.4 Hz, J_2 = 38.4 Hz), 6.90 (2H, d, J = 8.8 Hz), 3.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 137.6, 130.1, 128.6, 128.2, 127.7, 127.2, 126.6, 126.2, 114.1, 55.3; Mass calculated for $C_{15}H_{14}O$: 210.271; Mass found: 210.105.

1-Methoxy-3-[(*E*)-2-phenylethenyl]benzene:



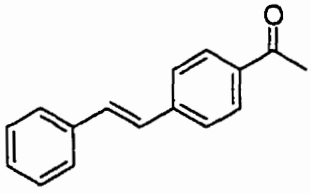
R_f = 0.40 (10% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.51 (2H, d, J = 8.0 Hz), 7.36 (2H, t, J = 7.2 Hz), 7.28 (2H, m), 7.13-7.05 (4H, m), 6.84-6.81 (1H, dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 138.8, 137.2, 129.6, 129.0, 128.7, 128.6, 127.7, 126.5, 119.2, 113.3, 111.7, 55.3; Mass calculated for $C_{15}H_{14}O$: 210.271; Mass found: 210.098.

1-Nitro-3-[(*E*)-2-phenylethenyl]benzene:



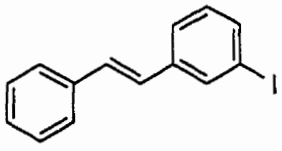
R_f = 0.17 (5% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.51 (2H, m), 8.32-8.29 (2H, m), 7.99-7.96 (2H, m), 7.71 (3H, m), 7.42-7.36 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 148.9, 144.8, 140.3, 133.0, 130.3, 128.1, 124.4, 123.3, 122.1, 115.8, 110.5; Mass calculated for $C_{14}H_{11}NO_2$: 225.248; Mass found: 225.171.

1-{4-[(*E*)-2-Phenylethenyl]phenyl}ethanone:



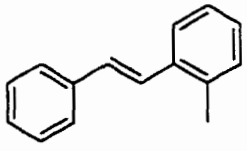
R_f = 0.25 (15% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.95 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.0 Hz), 7.54 (2H, d, J = 7.2 Hz), 7.38 (2H, t, J = 7.2 Hz), 7.32-7.28 (1H, m), 7.25-7.11 (2H, dd, J_1 = 16.8 Hz, J_2 = 40.8 Hz), 2.61 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 142.0, 136.7, 135.9, 131.4, 128.9, 128.8, 128.3, 127.4, 126.8, 126.5, 26.6; Mass calculated for $C_{16}H_{14}O$: 222.282; Mass found: 222.263.

1-Iodo-3-[(*E*)-2-phenylethenyl]benzene:



R_f = 0.56 (1% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.98 (1H, br), 7.93-7.85 (2H, m), 7.79 (1H, br), 7.70-7.30 (5H, m), 7.19-7.05 (2H, m); Mass calculated for $C_{14}H_{11}I$: 306.145; Mass found: 306.082.

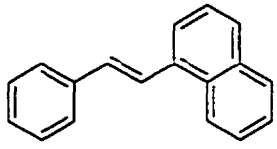
1-Methyl-2-[(*E*)-2-phenylethenyl]benzene:



R_f = 0.26 (pentane); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.60 (1H, d, J = 6.3 Hz), 7.53 (2H, d, J = 7.1 Hz), 7.40-7.14 (7H, m), 7.00 (1H, d, J = 16.2 Hz), 2.44 (3H, s); Mass

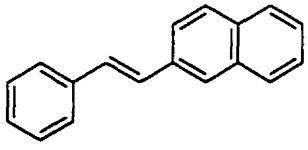
calculated for $C_{15}H_{14}$: 194.276; Mass found: 194.272. The rest of the spectral data correspond to those reported in the literature.[40]

1-[(*E*)-2-Phenylethenyl]naphthalene:



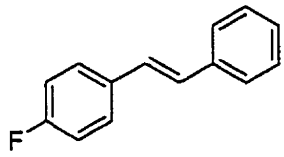
R_f = 0.16 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.22 (1H, d, J = 8.4 Hz), 7.91-7.86 (2H, m), 7.80 (1H, d, J = 8.0 Hz), 7.75 (1H, d, J = 7.2 Hz), 7.61 (2H, d, J = 7.6 Hz), 7.57-7.46 (2H, m), 7.40 (2H, t, J = 8.0 Hz), 7.32-7.28 (1H, m), 7.23-7.08 (2H, dd, J_1 = 21.6 Hz, J_2 = 37.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 135.0, 133.7, 131.8, 131.4, 128.7, 128.6, 128.4, 128.0, 127.8, 126.7, 126.1, 125.8, 125.7, 123.8, 123.6; Mass calculated for $C_{18}H_{14}$: 230.304; Mass found: 230.259.

2-[(*E*)-2-Phenylethenyl]naphthalene:



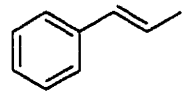
R_f = 0.30 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.97-7.74 (7H, m), 7.61-7.37 (7H, m); Mass calculated for $C_{18}H_{14}$: 230.304; Mass found: 230.258. The rest of the spectral data correspond to those reported in the literature.[41]

1-Fluoro-4-[(*E*)-2-phenylethenyl]benzene:



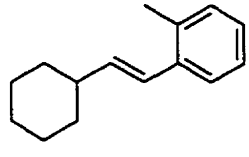
R_f = 0.17 (100% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.60 (1H, m), 7.60-7.44 (3H, m), 7.36 (2H, t, J = 11.6 Hz), 7.27 (1H, t, J = 8.0 Hz), 7.13-7.02 (4H, m); Mass calculated for $C_{14}H_{11}F$: 198.239; Mass found: 198.236. The rest of the spectral data correspond to those reported in the literature.[42]

(1*E*)-Prop-1-enylbenzene:



R_f = 0.49 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.34-7.27 (4H, m), 7.19 (1H, apparent triplet, J = 7.2 Hz), 6.41 (1H, d, J = 15.6 Hz), 6.24 (1H, dq, J_q = 6.4 Hz, J_d = 16.0 Hz), 1.89 (3H, dd, J_1 = 1.6 Hz, J_2 = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.0, 128.5, 126.7, 125.8, 125.7, 118.0, 18.5; Mass calculated for C_9H_{10}: 118.176. The rest of the spectral data correspond to those reported in the literature.[43]

1-Methyl-2-[(*E*)-2-cyclohexylethenyl]benzene:



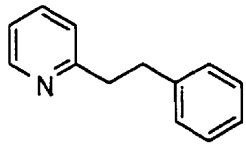
R_f = 0.78 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.41 (1H, d, J = 6.8 Hz), 7.16-7.10 (3H, m), 6.53 (1H, d, J = 15.6 Hz), 6.04 (1H, dd, J_1 = 6.8 Hz, J_2 = 15.6 Hz), 2.33 (3H, s), 2.18-2.10 (1H, m), 1.85-1.64 (4H, m), 1.34-1.15 (6H, m); Mass calculated for

$C_{15}H_{20}$: 200.323; Mass found: 200.298. The rest of the spectral data correspond to those reported in the literature.[44]

Typical procedure for the synthesis of 2-(2-arylethyl)pyridine:

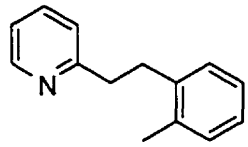
To a mixture of $[Rh(COD)Cl]_2$ (4.6 mg, 2 mol%), TPPDS (18.6 mg, 8 mol%) in H_2O (2.3 mL, 0.2 M) at r.t. was successively added phenylboronic acid (141 mg, 1.16 mmol), Na_2CO_3 (103 mg, 0.974 mmol), SDS (67 mg, 0.232 mmol), and 2-vinylpyridine (50 µL, 0.464 mmol). The reaction mixture was heated at 80°C for 6 hours. After cooling to r.t. the colored solution was poured into Et_2O (25 mL) and the reaction flask was carefully rinsed with Et_2O. The heterogeneous mixture was vigorously stirred at r.t. for 2 hours. The two phases were separated, the aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by flash chromatography (60% Et_2O in hexanes → 80% Et_2O in hexanes) and 71 mg (84%) of a colorless oil was isolated.

2-(2-Phenylethyl)pyridine:



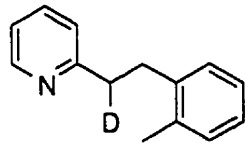
R_f = 0.33 (100% Et_2O); IR (neat, NaCl, cm^{-1}) 3061.7, 3026.4, 2925.3, 2856.0, 1590.9, 1569.0, 1495.0, 1474.4, 1454.0, 1435.2; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.57 (1H, m), 7.56 (1H, dt, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.29-7.07 (7H, m), 3.13-3.03 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 149.3, 141.6, 136.3, 128.5, 128.3, 125.9, 123.0, 121.1, 40.2, 36.0; Mass calculated for $C_{13}H_{13}N$: 183.249; Mass found: 184.108.

2-[2-(2-Methylphenyl)ethyl]pyridine:



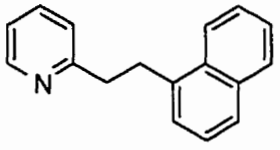
R_f = 0.16 (50% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3411.5, 3063.4, 3012.4, 2928.7, 2868.2, 1591.0, 1568.5, 1492.1, 1474.1, 1459.4, 1434.7, 1050.9; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.57 (1H, m), 7.57 (1H, apparent triplet, J_1 = 8 Hz), 7.17-7.07 (6H, m), 3.04 (4H, s), 2.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3. 149.3, 139.6, 136.2, 135.9, 130.1, 128.8, 126.0, 125.9, 122.8, 121.1, 38.9, 33.3, 19.2; Mass calculated for $C_{14}H_{15}N$: 197.276; Mass found: 197.119.

2-[1-Deuterium-2-(2-methylphenyl)ethyl]pyridine:



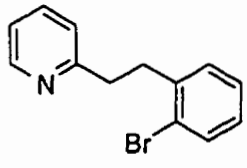
R_f = 0.24 (50% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3419.5, 3009.1, 2956.5, 2926.2, 2871.6, 2855.7, 1591.2, 1569.7, 1473.7, 1434.4, 969.8, 749.7; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.56 (1H, m), 7.57 (1H, dt, J_1 = 2 Hz, J_2 = 7.6 Hz), 7.14-7.05 (6H, m), 3.02 (3H, s), 2.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3. 149.3, 139.6, 136.2, 135.9, 130.1, 128.8, 126.0, 125.9, 122.8, 121.1, 38.5 (t, J = 19 Hz), 33.3, 19.2; Mass calculated for $C_{14}H_{14}DN$: 198.276; Mass found: 198.125.

2-[2-(1-Naphthyl)ethyl]pyridine:



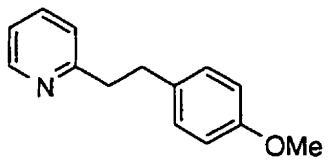
R_f = 0.27 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3060.5, 3026.4, 2947.2, 2875.0, 1589.5, 1562.8, 1493.2, 1474.8, 1451.9, 1429.8; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.61 (1H, m), 8.14 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 8.0 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.57-7.46 (3H, m), 7.37 (1H, t, J = 8.0 Hz), 7.31 (1H, m), 7.13 (1H, m), 7.07 (1H, d, J = 7.6 Hz), 3.52 (2H, m), 3.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 149.3, 137.6, 136.2, 133.8, 131.7, 128.7, 126.7, 126.0, 125.8, 125.5, 125.4, 123.7, 122.9, 121.1, 39.4, 33.1; Mass calculated for $C_{17}H_{15}N$: 233.313; Mass found: 233.308.

2-[2-(2-Bromophenyl)ethyl]pyridine:



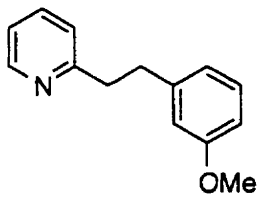
R_f = 0.32 (50% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3063.4, 3009.5, 2931.1, 2863.1, 1590.6, 1568.0, 1473.0, 1453.9, 1435.9, 1024.9; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.56 (1H, m), 7.58-7.53 (2H, m), 7.20-7.03 (5H, m), 3.19-3.07 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 158.5, 149.3, 136.3, 133.5, 130.2, 128.7, 126.3, 126.0, 122.5, 121.5, 39.5, 35.2; Mass calculated for $C_{13}H_{12}BrN$: 262.149; Mass found: 262.145.

2-[2-(4-Methoxyphenyl)ethyl]pyridine:



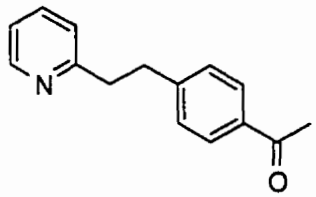
R_f = 0.27 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3061.4, 3012.8, 2939.5, 1594.3, 1572.0, 1471.2, 1454.2, 1435.2, 1280.6, 1078.9; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.55 (1H, m), 7.55 (1H, dt, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.10 (2H, d, J = 8.8 Hz), 7.06 (2H, m), 6.81 (2H, d, J = 8.8 Hz), 3.77 (3H, s), 3.08-2.97 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 157.8, 149.2, 136.2, 133.6, 129.3, 123.0, 121.1, 113.7, 55.2, 40.1, 35.1; Mass calculated for $C_{14}H_{15}NO$: 213.275; Mass found: 213.115.

2-[2-(3-Methoxyphenyl)ethyl]pyridine:



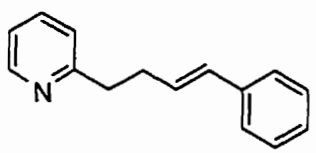
R_f = 0.22 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3063.4, 3011.8, 2945.8, 1590.1, 1574.5, 1478.8, 1450.6, 1433.1, 1274.9, 1072.3; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.56 (1H, m), 7.56 (1H, dt, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.19 (1H, dt, J_1 = 0.8 Hz, J_2 = 7.2 Hz), 7.13-7.08 (2H, m), 6.80 (1H, m), 6.73 (2H, m), 3.77 (3H, s), 3.11-3.01 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.6, 149.3, 143.2, 136.3, 129.3, 123.0, 121.2, 120.8, 114.1, 111.4, 55.1, 40.1, 36.1; Mass calculated for $C_{14}H_{15}NO$: 213.280; Mass found: 213.275.

1-[4-(2-Pyridin-2-ylethyl)phenyl]ethanone:



R_f = 0.12 (50% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3444.2, 3047.4, 3012.6, 2954.6, 2855.5, 1672.9, 1605.5, 1588.0, 1568.2, 1438.0, 1412.1, 1361.5, 1270.0. 822.2; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.57 (1H, m), 7.87 (2H, d, J_1 = 11.2 Hz), 7.57 (1H, dt, J_1 = 0.8 Hz, J_2 = 7.6 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.15-7.11 (1H, m), 7.06 (1H, m), 3.12 (4H, s), 2.58 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 160.5, 149.4, 147.3, 136.4, 135.1, 128.7, 128.5, 123.0, 121.3, 39.6, 35.8, 26.5; Mass calculated for $C_{15}H_{15}NO$: 225.286; Mass found: 225.115.

2-[(3*E*)-4-Phenylbut-3-enyl)]pyridine:

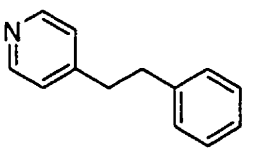


R_f = 0.18 (33% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3428.9, 3016.1, 2922.9, 1493.0, 1445.0, 1073.9, 981.9, 912.0, 825.6; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.55 (1H, m), 7.60 (1H, dt, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.33-7.26 (4H, m), 7.21-7.16 (2H, m), 7.13-7.10 (1H, m), 6.42 (1H, m), 6.30-6.23 (1H, m), 2.97 (2H, apparent triplet), 2.66 (2H, dd, J_1 = 8.0 Hz, J_2 = 15.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 149.6, 138.9, 136.3, 135.7, 131.2, 128.6, 128.7, 126.0, 125.8, 122.5, 121.6, 40.9, 36.2; Mass calculated for $C_{15}H_{15}N$: 209.291; Mass found: 209.286.

Typical procedure for the synthesis of 4-(2-arylethyl)pyridine:

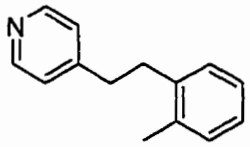
To a mixture of $[Rh(COD)Cl]_2$ (4.6 mg, 2 mol%), TPPDS (18.6 mg, 8 mol%) in H_2O (2.3 mL, 0.2 M) at r.t. was successively added phenylboronic acid (283 mg, 2.32 mmol), Na_2CO_3 (103 mg, 0.974 mmol), SDS (67 mg, 0.232 mmol), and 4-vinylpyridine (50 μL, 0.464 mmol). The reaction mixture was heated at 105°C for 15 hours. After cooling to r.t. the colored solution was poured into Et_2O (25 mL) and the reaction flask was carefully rinsed with Et_2O. The heterogeneous mixture was vigorously stirred at r.t. for 2 hours. The two phases were separated, the aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by flash chromatography (80% Et_2O in hexanes) yielding 68 mg (80%) of a white solid.

4-(2-Phenylethyl)pyridine:



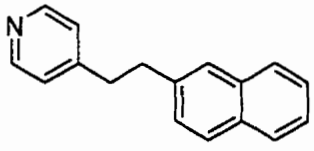
R_f = 0.27 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3061.7, 3026.4, 2925.3, 2856.0, 1590.9, 1569.0, 1495.0, 1474.4, 1454.0, 1435.2; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.48 (2H, d, J = 4.8 Hz), 7.30-7.06 (7H, m), 2.92 (4H, br); ^{13}C NMR δ 150.4, 149.7, 140.6, 128.4, 128.3, 126.2, 123.9, 37.0, 36.5; Mass calculated for $C_{13}H_{13}N$: 183.249; Mass found: 183.104.

4-[2-(2-Methylphenyl)ethyl]pyridine:



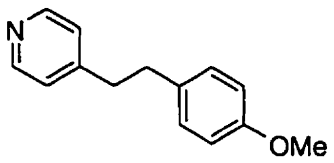
R_f = 0.45 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3068.8, 3022.8, 2947.3, 2246.8, 2216.6, 1602.0, 1560.2, 1492.8, 1461.7, 1416.7, 1250.2, 1220.3, 909.5, 732.7; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.49 (2H, d, J = 6.0 Hz), 7.15-7.00 (6H, m), 2.93-2.83 (4H, m), 2.29 (3H, s); ^{13}C NMR δ 150.8, 149.5, 138.8, 135.7, 130.9, 130.3, 128.7, 126.4, 126.0, 123.9, 114.8, 35.8, 33.9, 19.2; Mass calculated for $C_{14}H_{15}N$: 197.276; Mass found: 197.120.

4-[2-(2-Naphthyl)ethyl]pyridine:



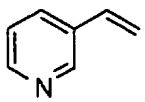
R_f = 0.23 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3060.8, 3013.5, 2945.9, 1599.2, 1558.8, 1491.4, 1461.1, 1417.4, 905.4, 733.7; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.48 (2H, m), 7.84-7.74 (3H, m), 7.57 (1H, s), 7.49-7.40 (2H, m), 7.29 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.09 (2H, m), 3.10-2.98 (4H, m); ^{13}C NMR δ 150.4, 149.7, 138.1, 133.5, 132.1, 128.0, 127.6, 127.4, 127.0, 126.5, 126.0, 125.4, 123.9, 36.9, 36.7; Mass calculated for $C_{17}H_{15}N$: 233.308; Mass found: 233.121.

4-[2-(4-Methoxyphenyl)ethyl]pyridine:



R_f = 0.37 (80% Et_2O in hexanes); IR (neat, NaCl, cm^{-1}) 3063.4, 3009.5, 2931.1, 2863.1, 1590.6, 1568.0, 1473.0, 1453.9, 1435.9, 1024.9; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.48 (2H, d, *J* = 6.0 Hz), 7.07-7.04 (4H, m), 6.82 (2H, d, *J* = 8.8 Hz), 3.79 (3H, s), 2.88 (4H, s); ^{13}C NMR δ 157.9, 150.5, 149.5, 132.6, 129.2, 123.9, 113.7, 55.1, 37.2, 35.6; Mass calculated for $C_{14}H_{15}NO$: 213.275; Mass found: 213.116.

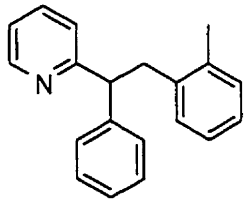
3-Vinylpyridine:



To a cooled suspension of $Ph_3P^+CH_3Br^-$ (4.60 g, 12.9 mmol) in dry THF (40 mL) at -78°C under an argon atmosphere was added dropwise *n*-BuLi (2.0 M/hexanes, 5.84 mL, 11.68 mmol). The yellow mixture was stirred for 30 minutes at -78°C and 45 minutes at 0°C. The resulting yellow solution was cooled to -78°C and 3-pyridine carboxaldehyde (Aldrich, 1.0 g, 9.34 mmol) in dry THF (10 mL, final concentration = 0.19 M) was added dropwise over a 10-minute period. The reaction mixture was stirred under argon, allowing the temperature to reach 25°C at which point it was stirred for another 15 minutes. TLC analysis showed the completion of the reaction and the reaction mixture was quenched with saturated NH_4Cl, the 2 layers were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The organic extract was washed with brine, dried over MgSO4, filtered and concentrated. The crude product was purified by flash

chromatography (80% Et_2O in hexanes) and 390 mg (40%) of a volatile colorless oil was isolated. R_f = 0.50 (80% Et_2O in hexanes); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.62 (1H, s), 8.49 (1H, d, J = 4.8 Hz), 7.73 (1H, d, J = 7.6 Hz), 7.27-7.24 (1H, m), 6.71 (1H, dd, J_{cis} = 10.8 Hz, J_{trans} = 17.6 Hz), 5.83 (1H, d, J_{trans} = 17.6 Hz), 5.39 (1H, d, J_{cis} = 11.2 Hz); Mass calculated for C_7H_7N: 105.139; Mass found: 105.137. The rest of the spectral data correspond to those reported in the literature.[45]

2-[2-(2-Methylphenyl)-1-phenylethyl]pyridine (87):



87

To a mixture of $[Rh(COD)Cl]_2$ (2.7 mg, 2 mol%), TPPDS (11.1 mg, 8 mol%) in H_2O (1.4 mL, 0.2 M) at r.t. was successively added 2-methylphenylboronic acid (94 mg, 0.69 mmol), Na_2CO_3 (61 mg, 0.580 mmol), SDS (40 mg, 0.138 mmol), and 1-phenyl-1-(2-pyridyl)ethylene **86** (50 mg, 0.276 mmol). The reaction mixture was heated at 80°C for 24 hours. After cooling to r.t. the colored solution was poured into Et_2O (25 mL) and the reaction flask was carefully rinsed with Et_2O. The heterogeneous mixture was vigorously stirred at r.t. for 2 hours. The two phases were separated, the aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by flash chromatography (20% Et_2O in hexanes → 33% Et_2O in hexanes) and 55 mg (73%) of a colorless oil was isolated. R_f = 0.42 (33% Et_2O in hexanes); IR (neat, NaCl, cm^{-1})

3061.7, 3024.2, 2924.8, 1589.2, 1568.8, 1493.5, 1471.8, 1432.7, 909.6; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.58 (1H, d, J = 4.4 Hz), 7.51 (1H, dt, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.30-7.00 (9H, m), 6.93 (1H, t, J = 7.6 Hz), 6.85 (1H, d, J 7.2 Hz), 4.34 (1H, t, J = 7.2 Hz), 3.63 (1H, dd, J_1 = 8.0 Hz, J_2 = 14.0 Hz), 3.34 (1H, dd, J_1 = 7.2 Hz, J_2 = 14.0 Hz); ^{13}C NMR δ 163.1, 149.2, 143.5, 138.4, 136.3, 130.0, 129.6, 128.3, 128.1, 126.4, 125.9, 125.5, 123.3, 121.4, 54.1, 38.5, 19.5; Mass calculated for $C_{20}H_{19}N$: 273.372; Mass found: 273.150.

2.13 References

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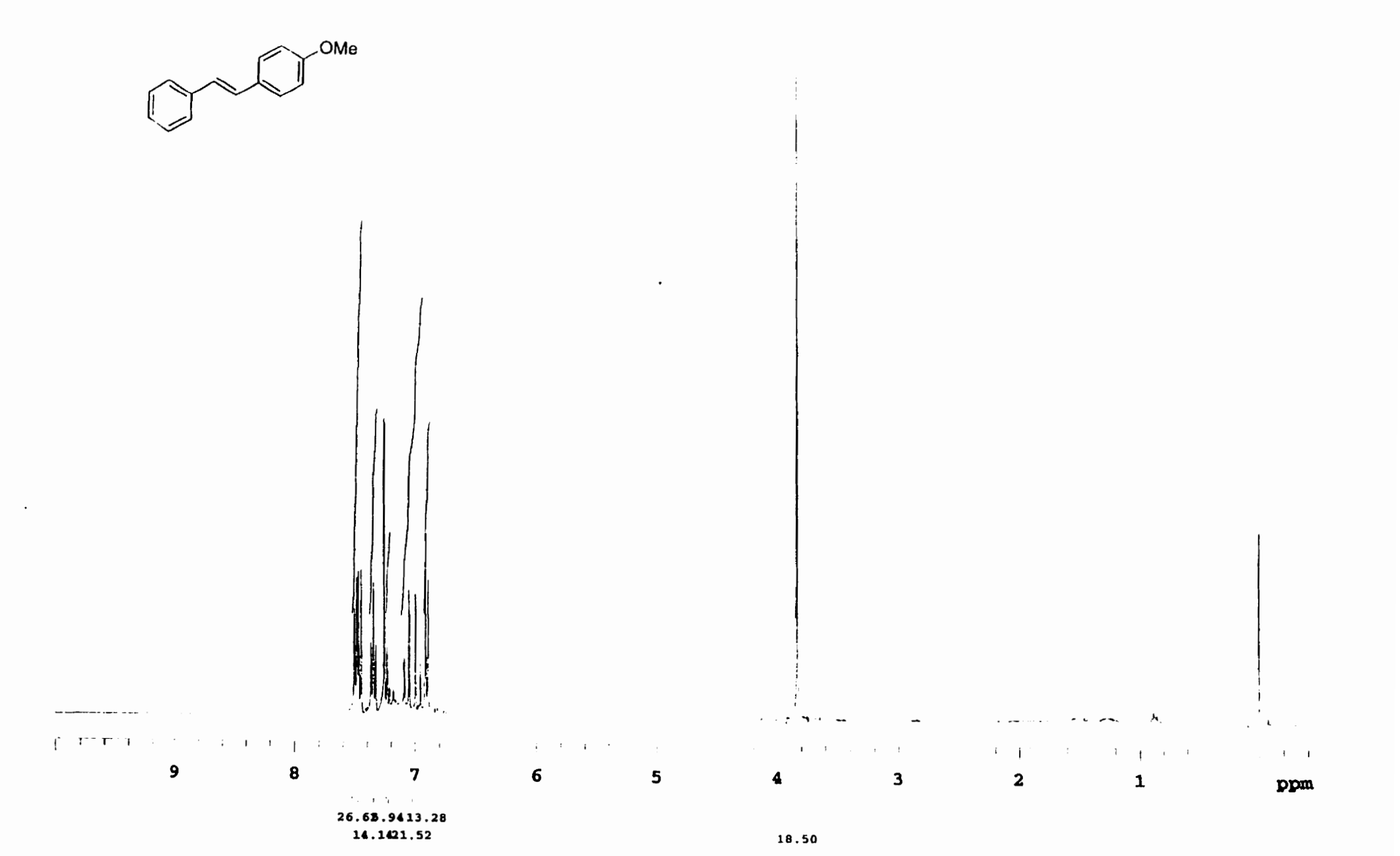
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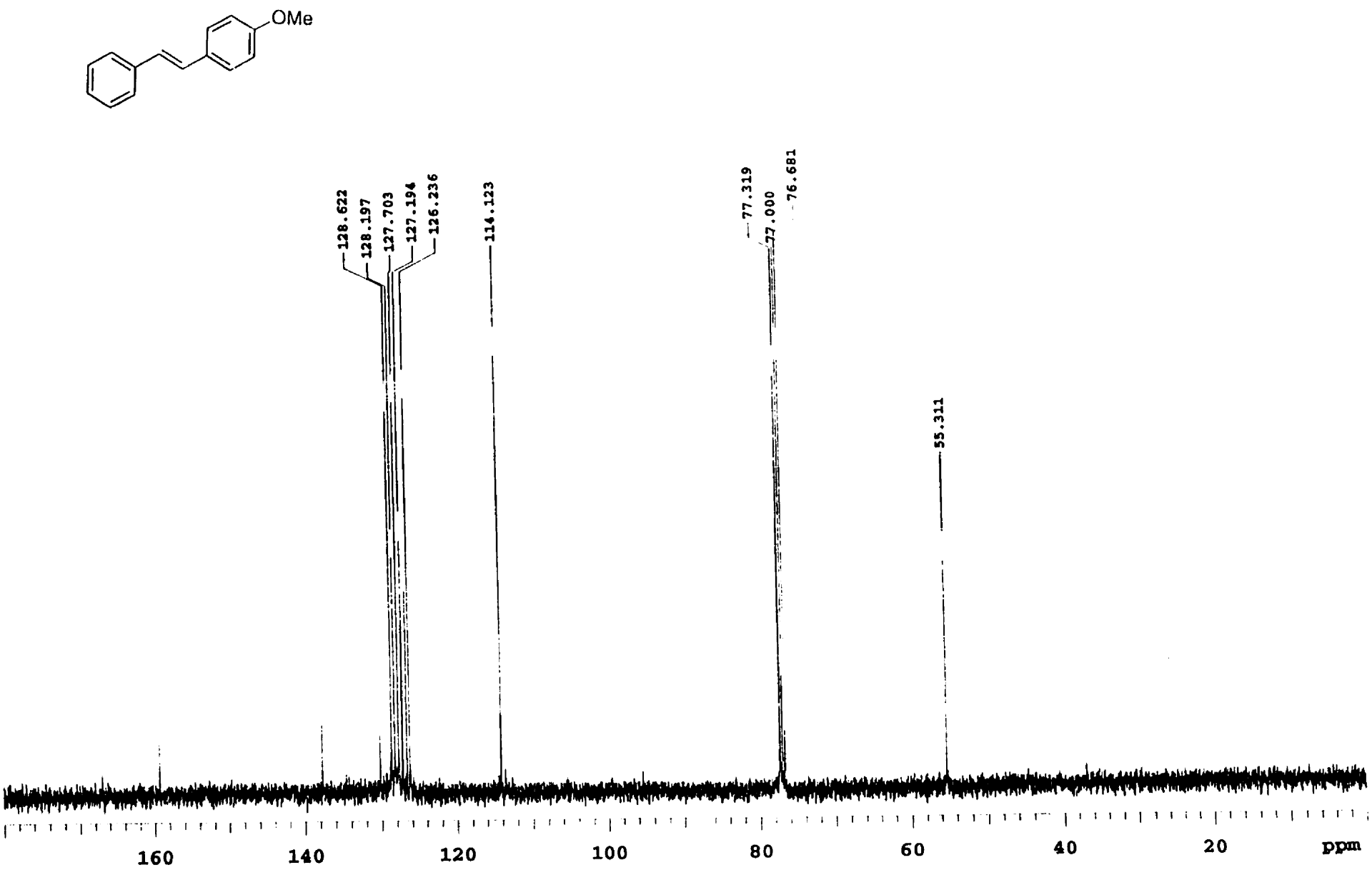
18.50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20
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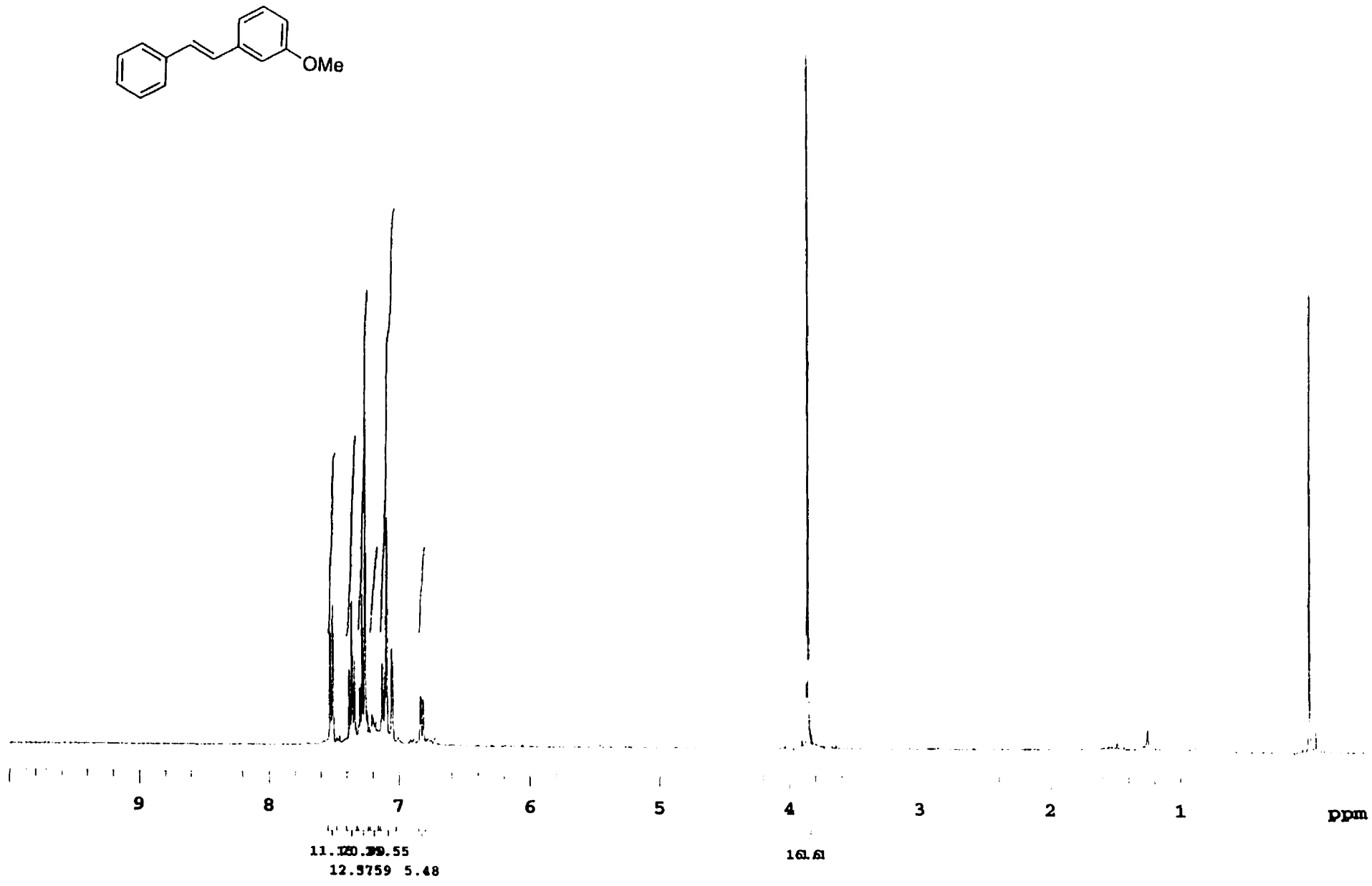
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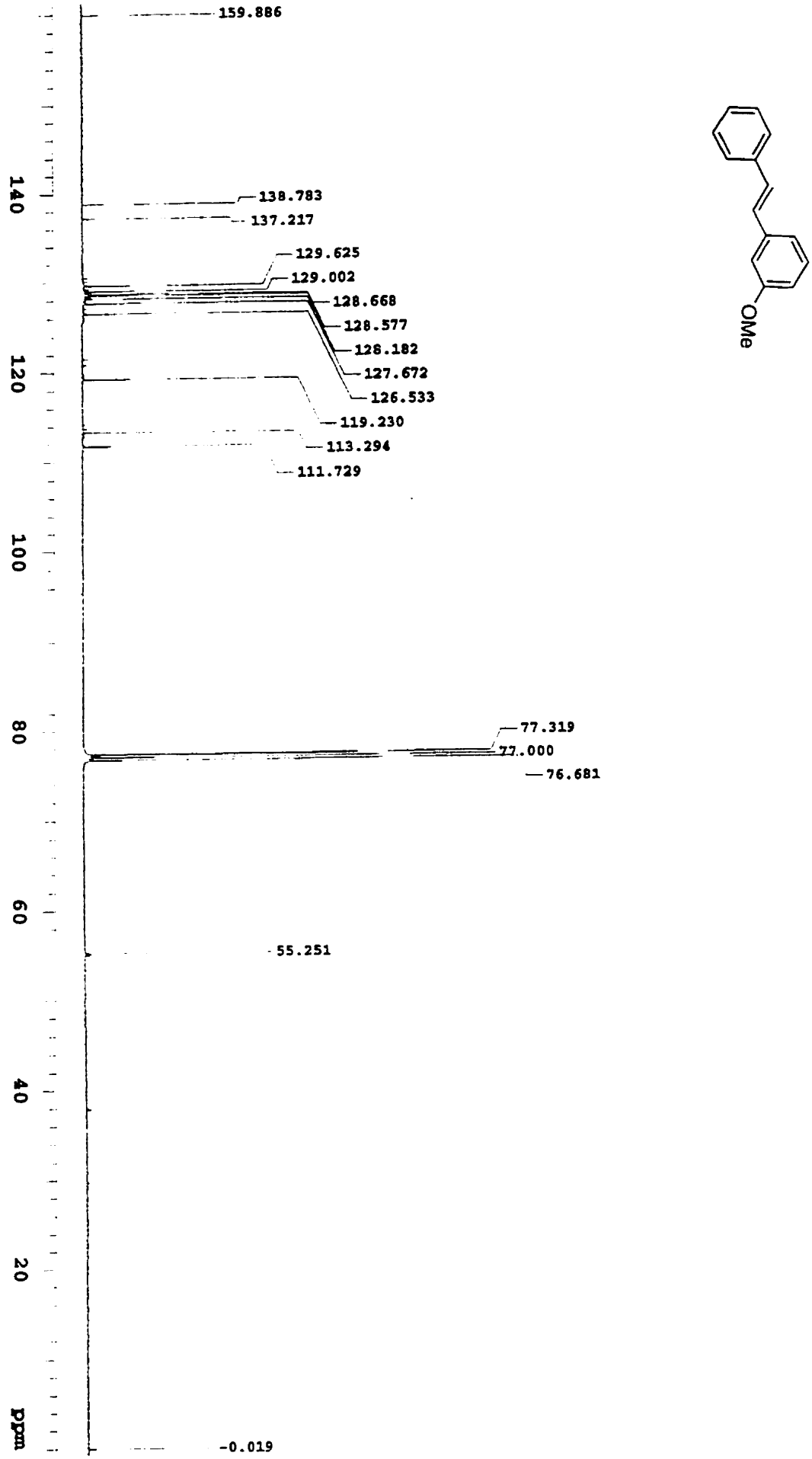
12.5759 5.48
161.61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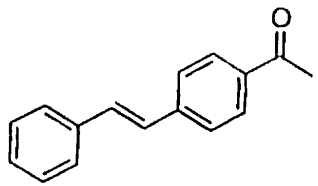
40
20
ppm
OMe



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6
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2.09
4.30
3.75
2.98

INDEX	FREQUENCY	PPM	HEIGHT
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2	14256.302	141.997	19.5
3	13722.228	136.678	17.2
4	13647.457	135.933	14.8
5	13197.309	131.449	64.7
6	12937.139	128.858	139.5
7	12929.509	128.782	129.5
8	12880.680	128.296	69.6
9	12792.939	127.422	58.8
10	12730.376	126.799	122.9
11	12698.332	126.479	121.9
12	7762.726	77.319	87.5
13	7750.518	77.198	10.4
14	7730.681	77.000	92.9
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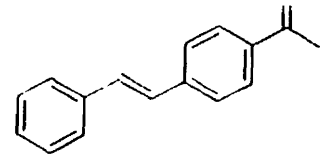

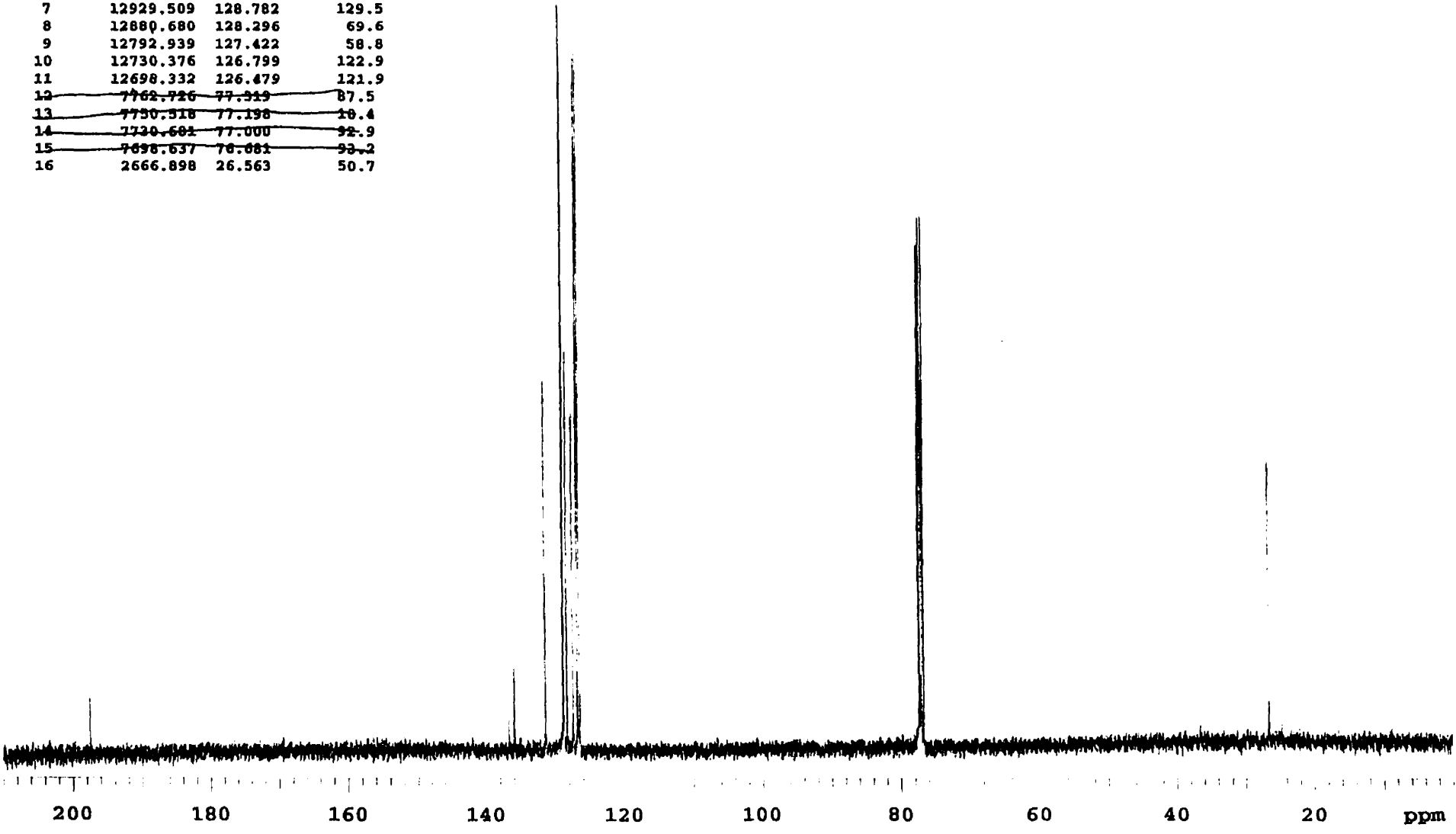

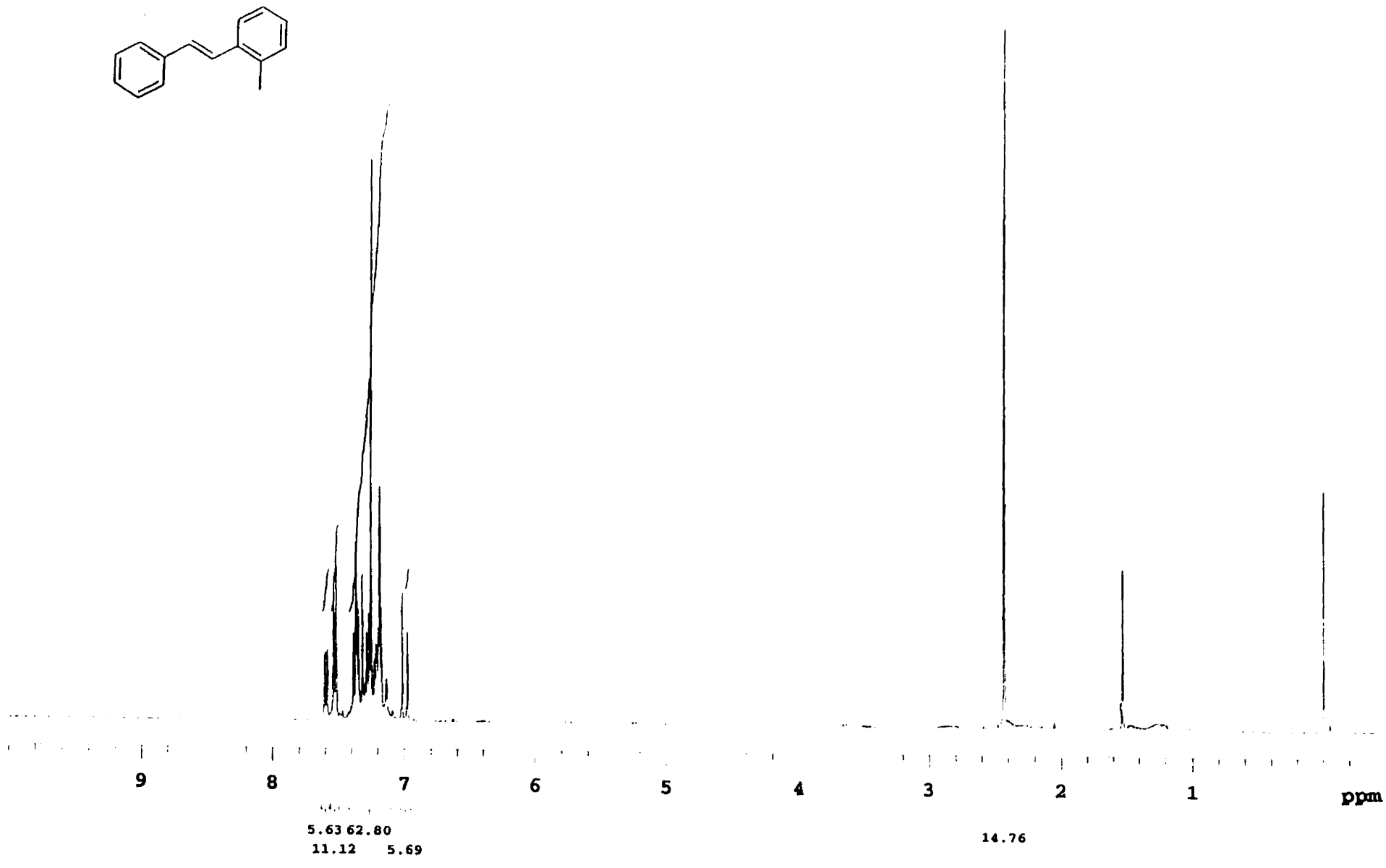
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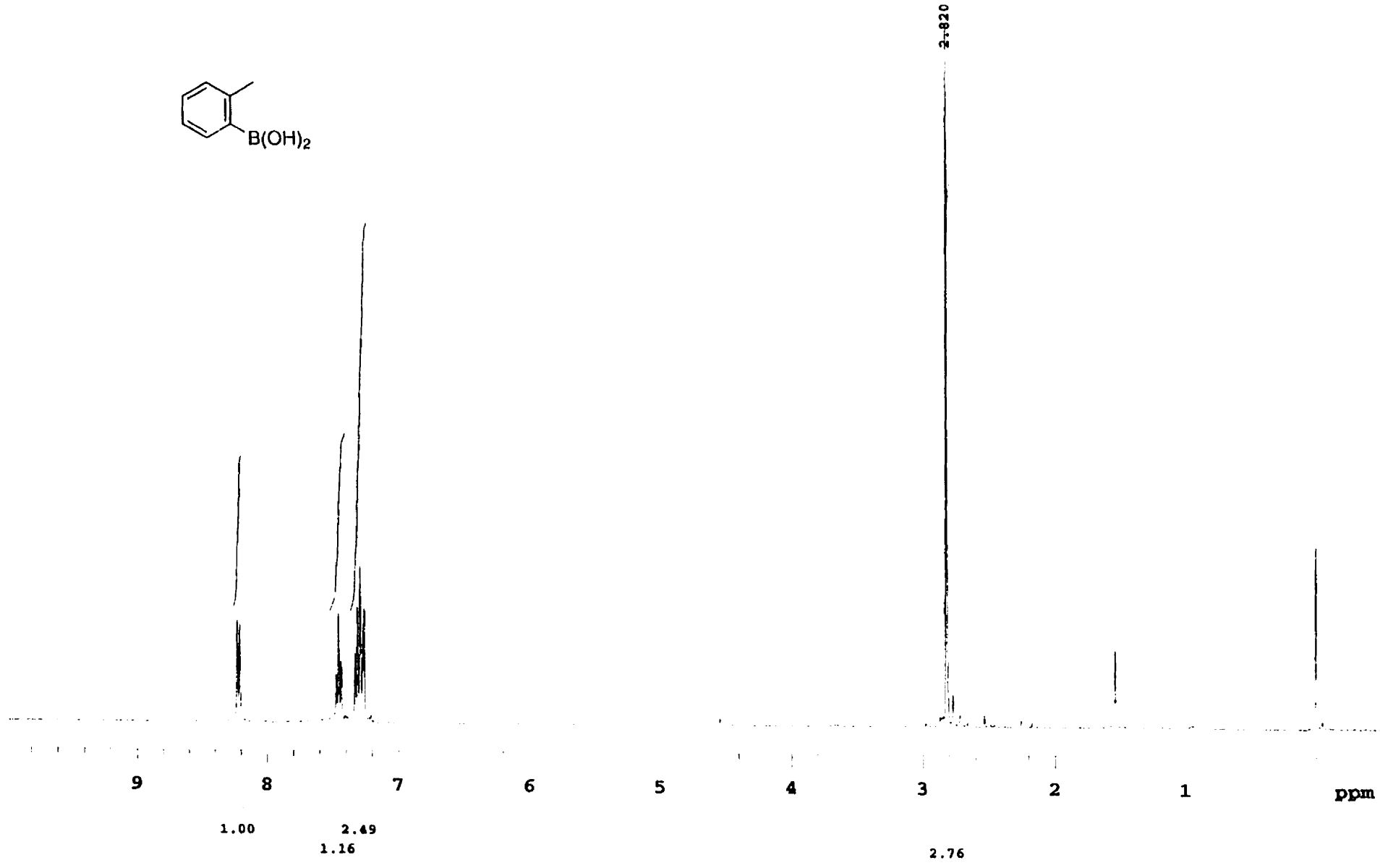
14.76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5
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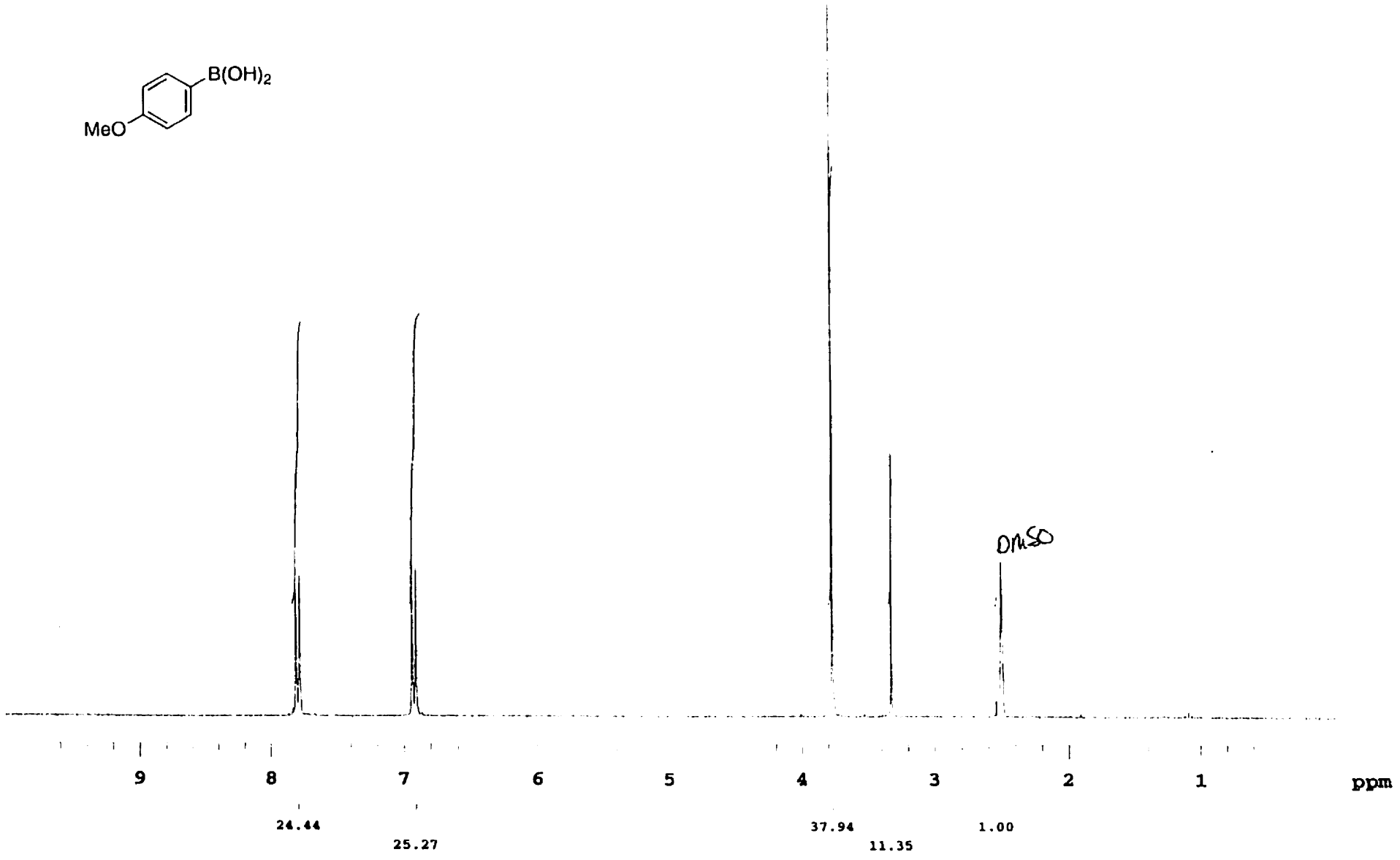
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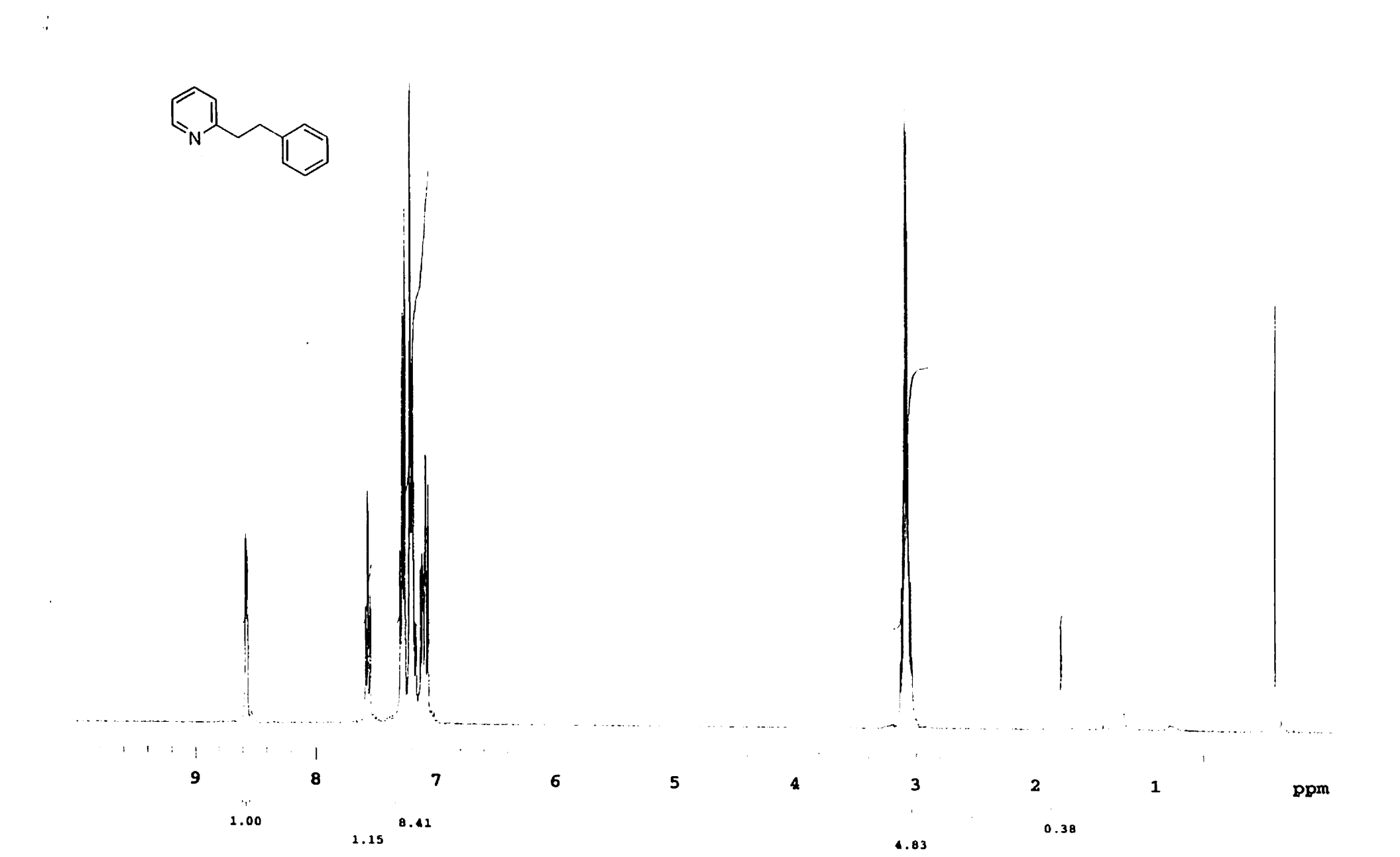
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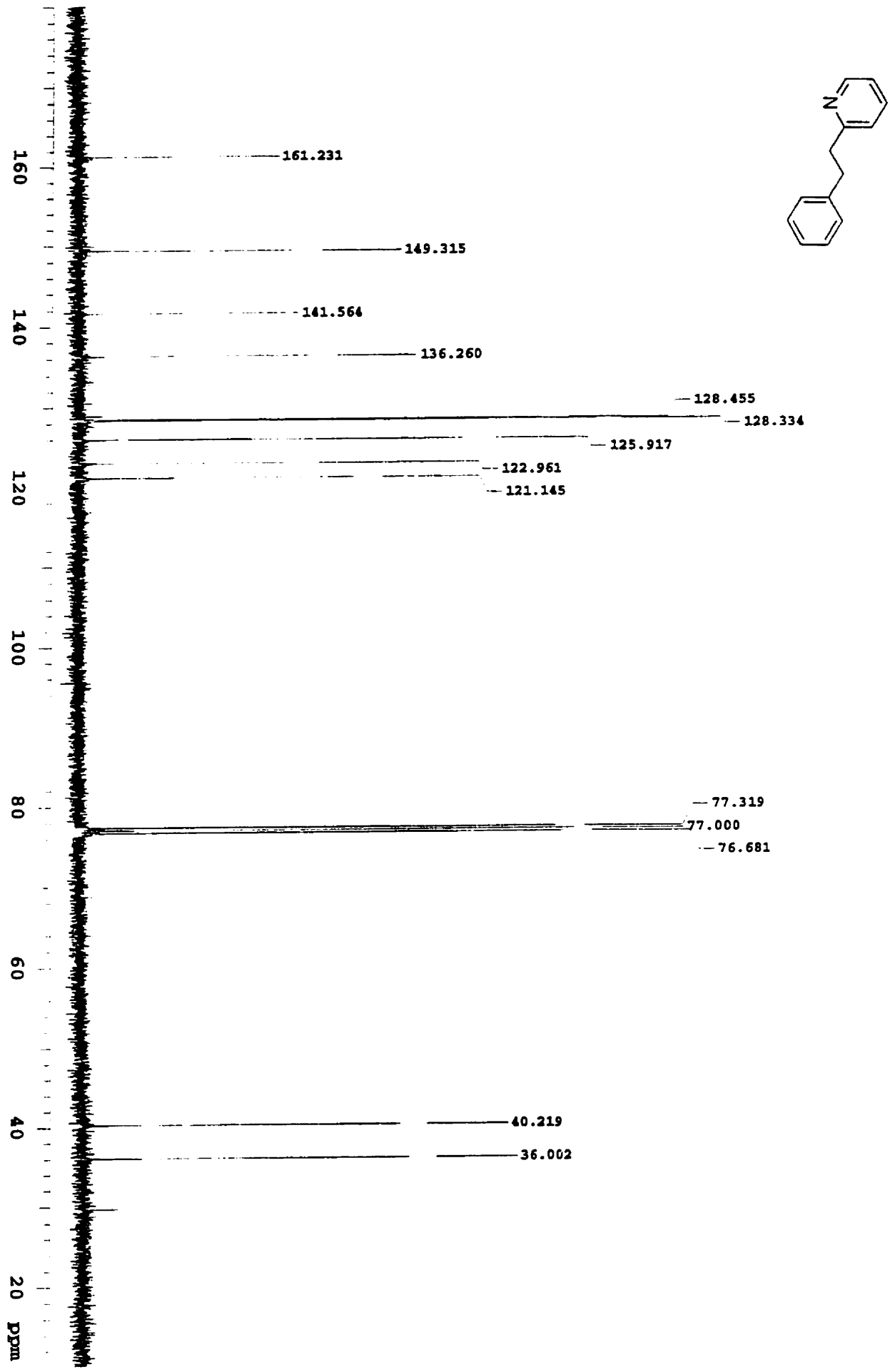
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ppm
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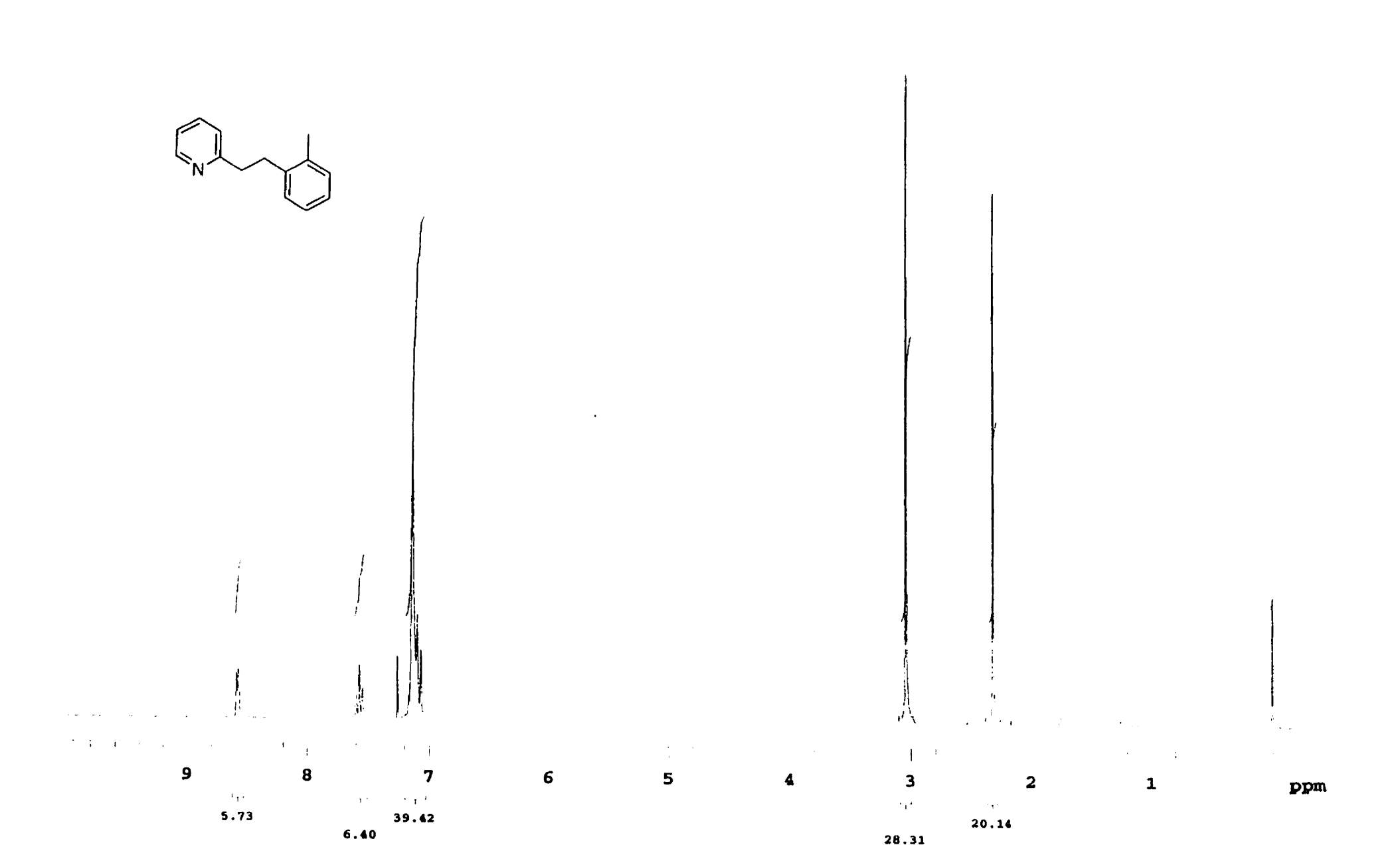
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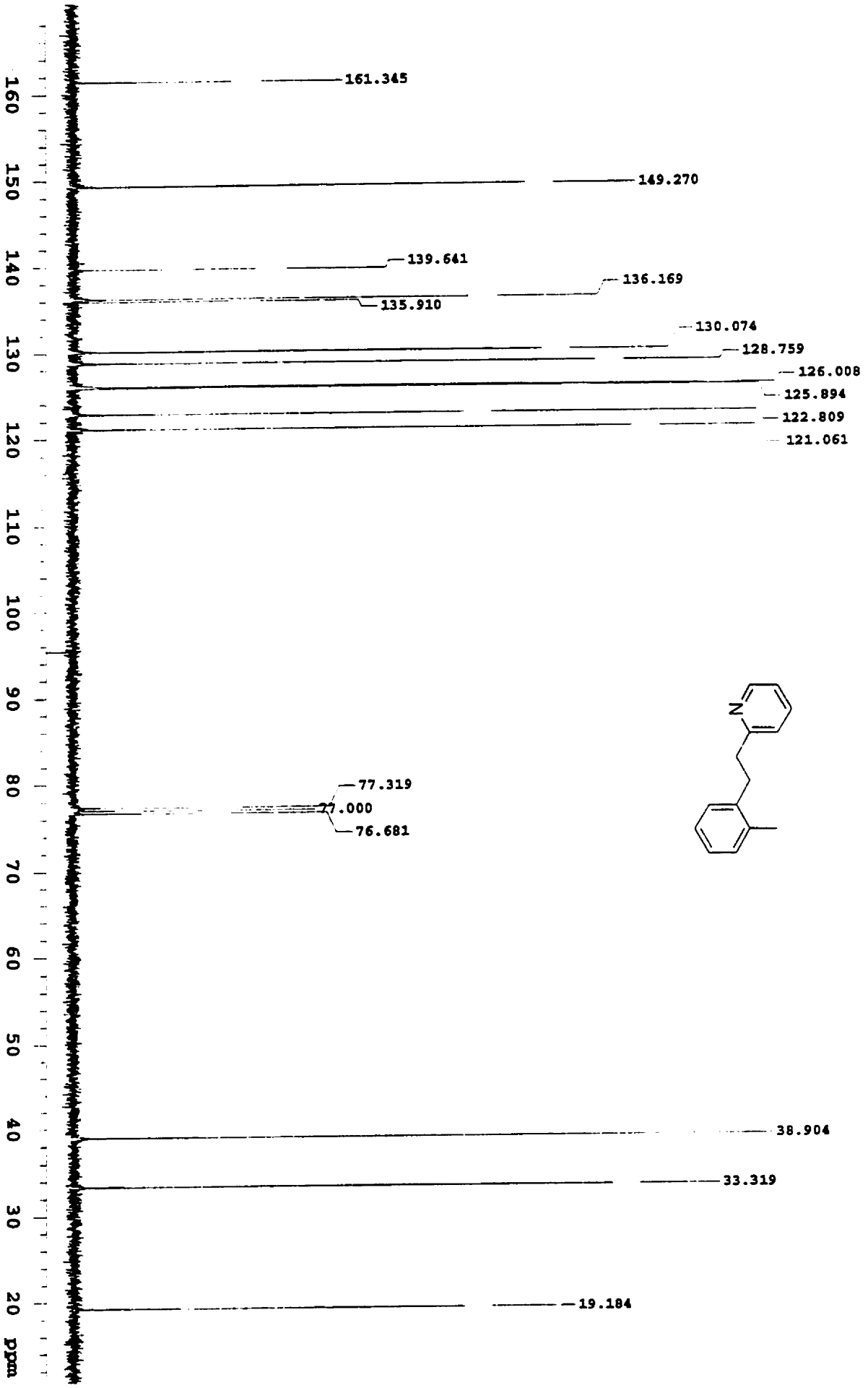
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76.681
38.904
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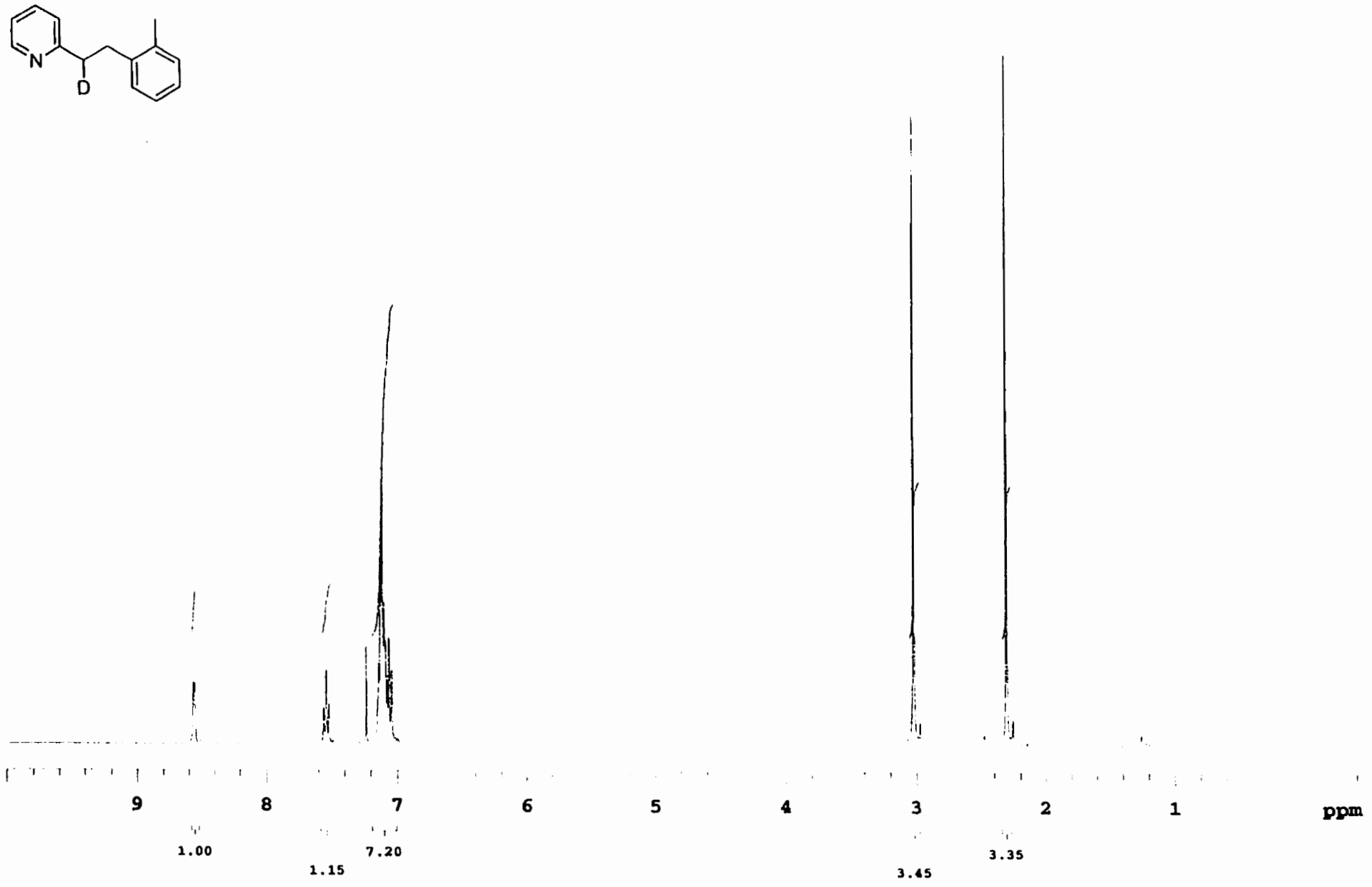
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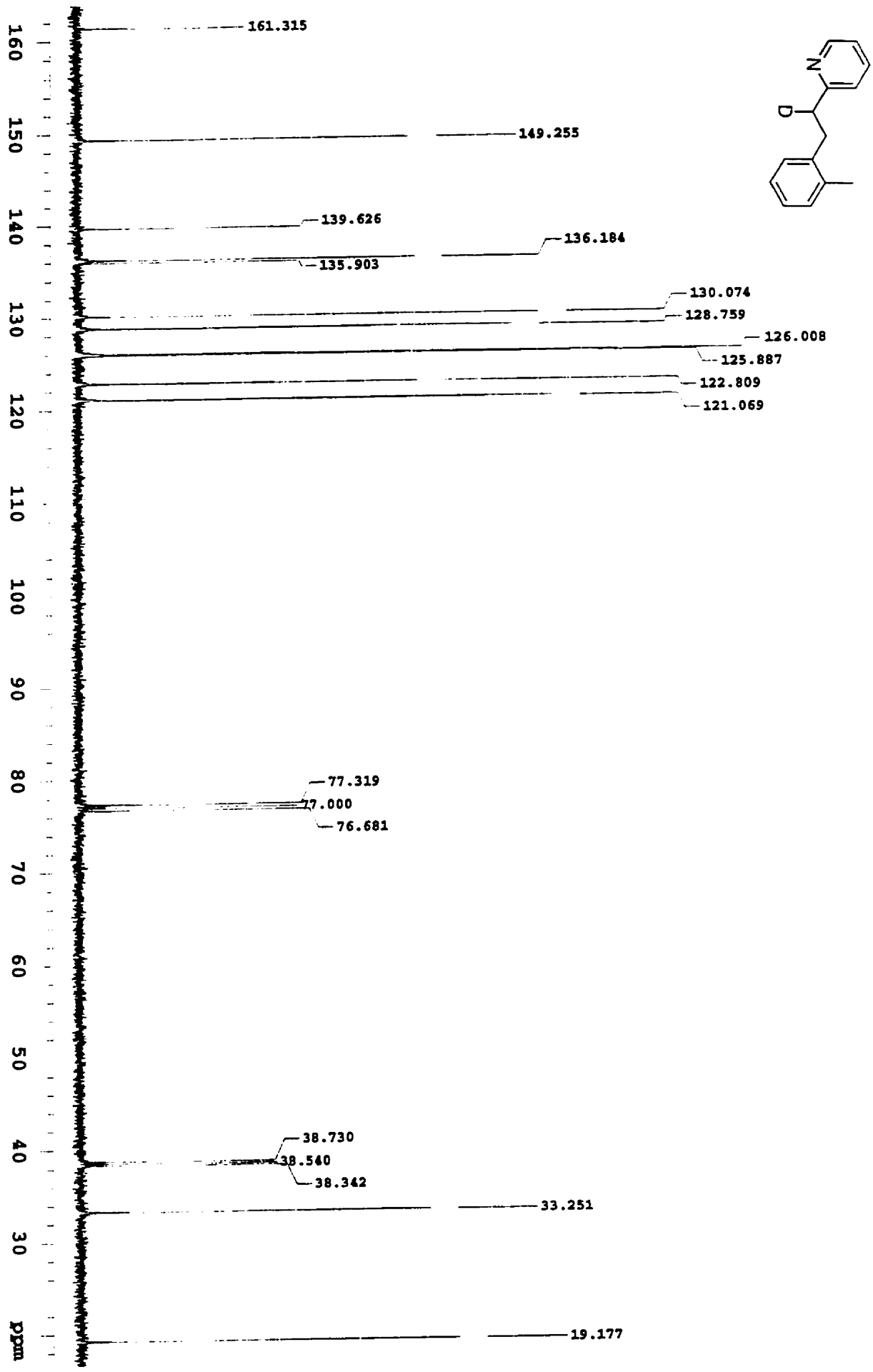
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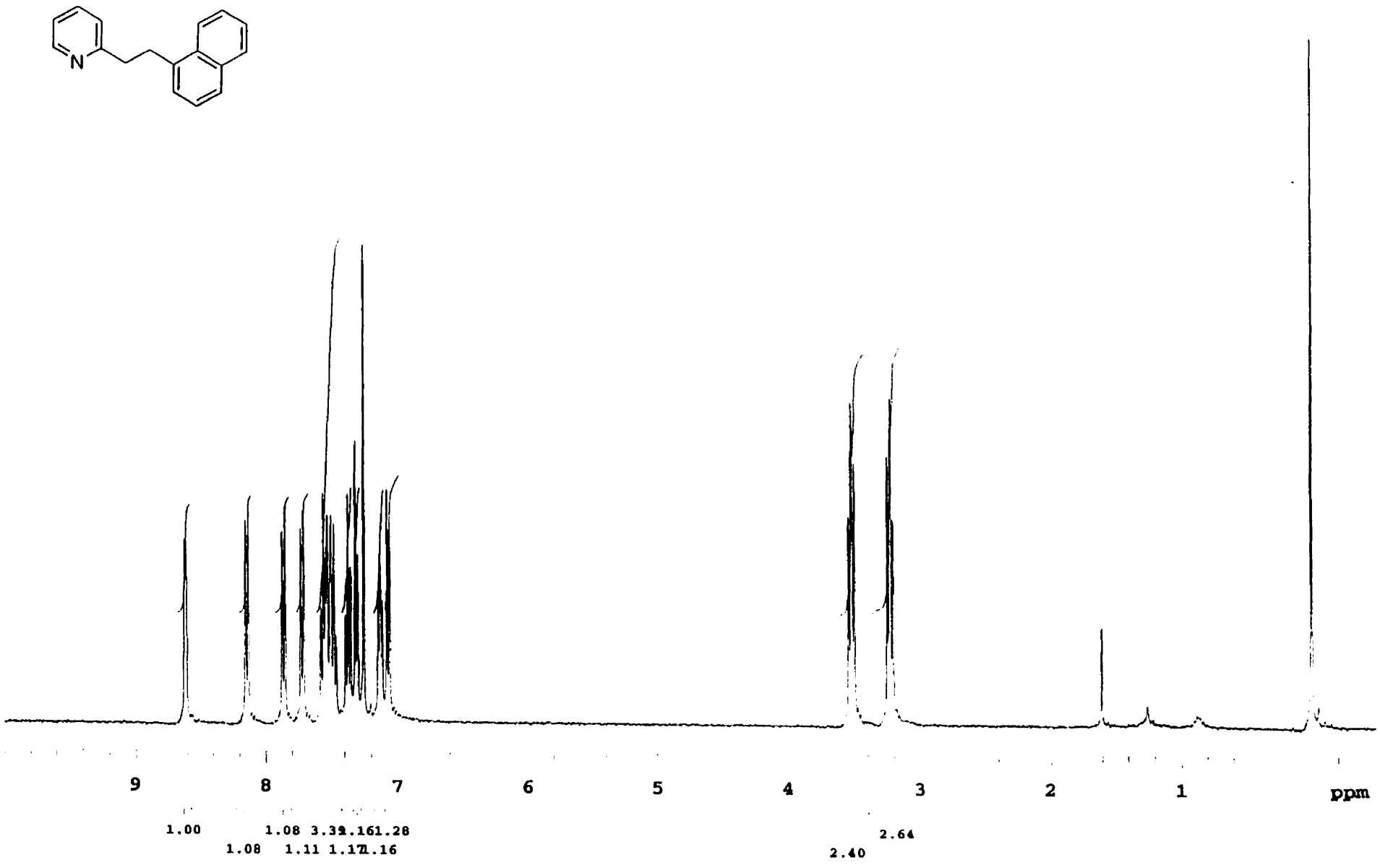
40
30
ppm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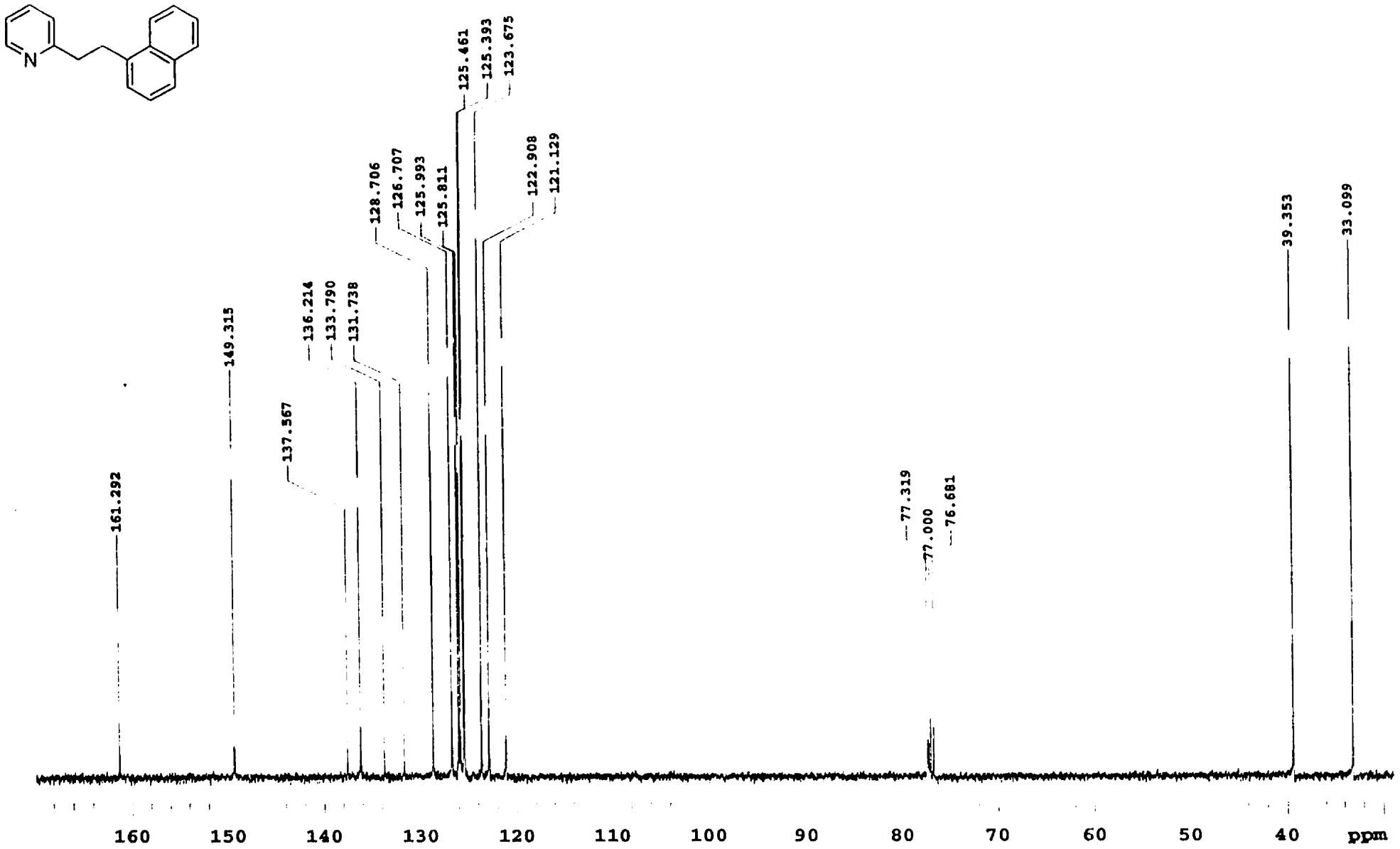
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121.129
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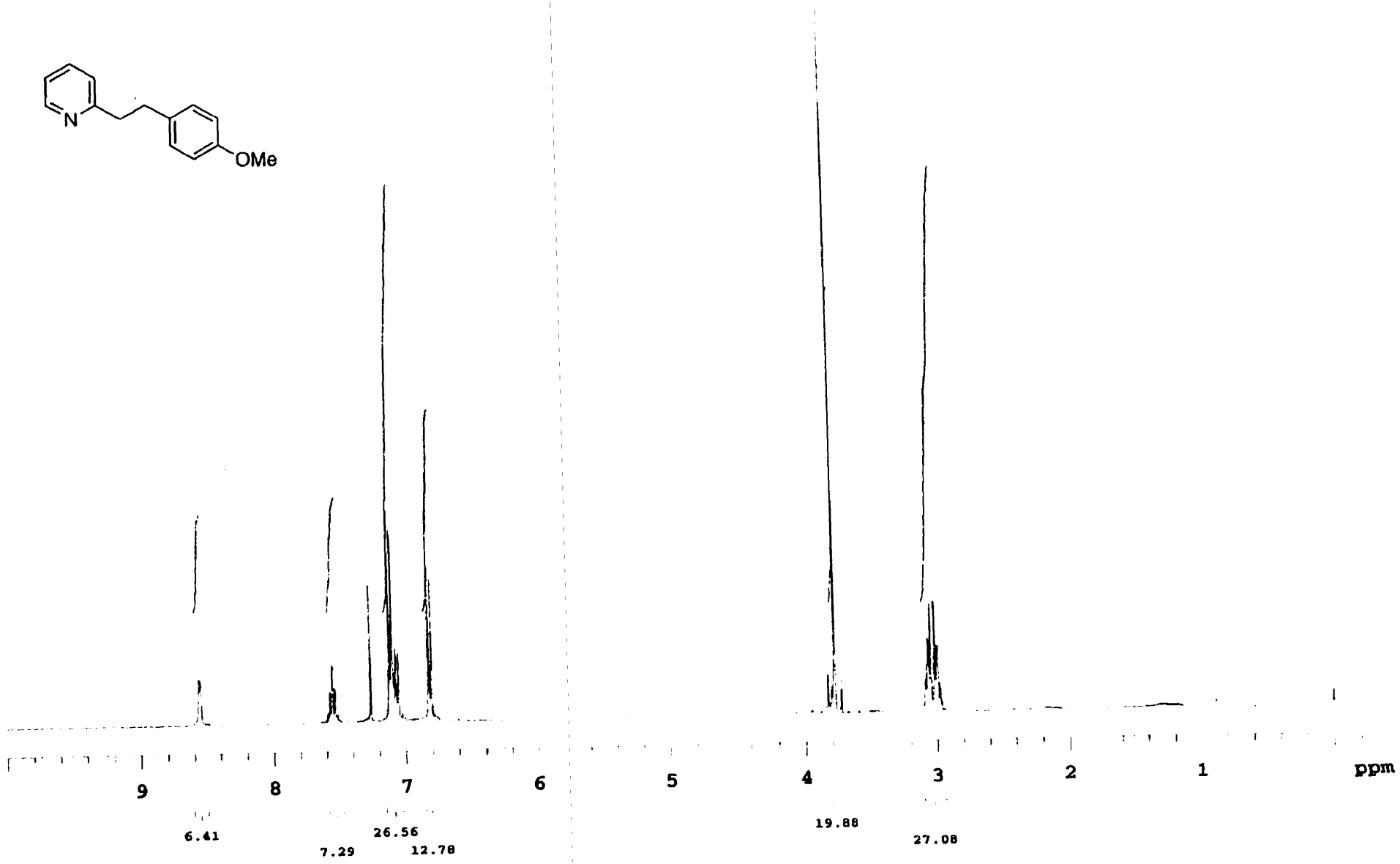
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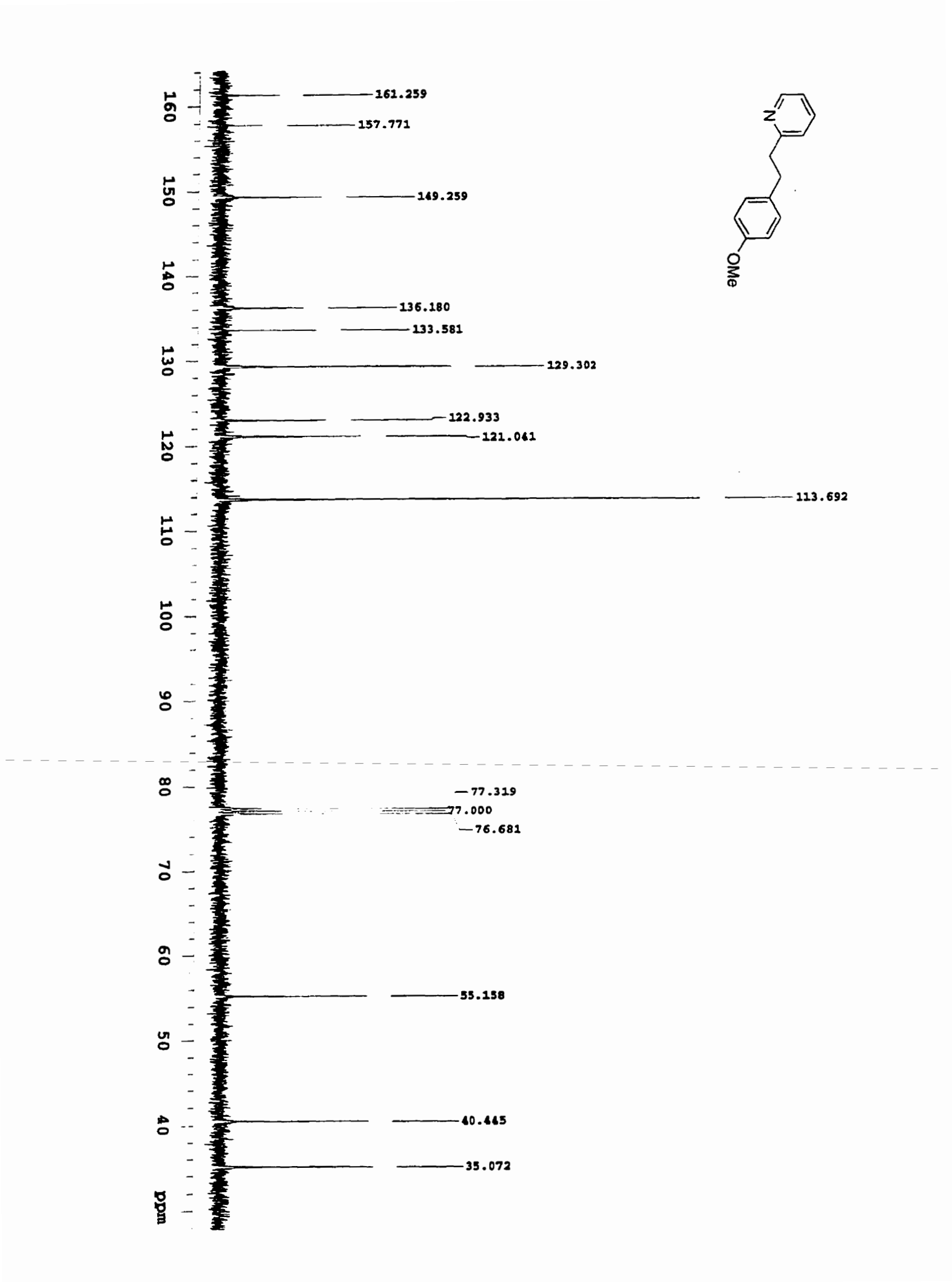
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55.158
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OMe
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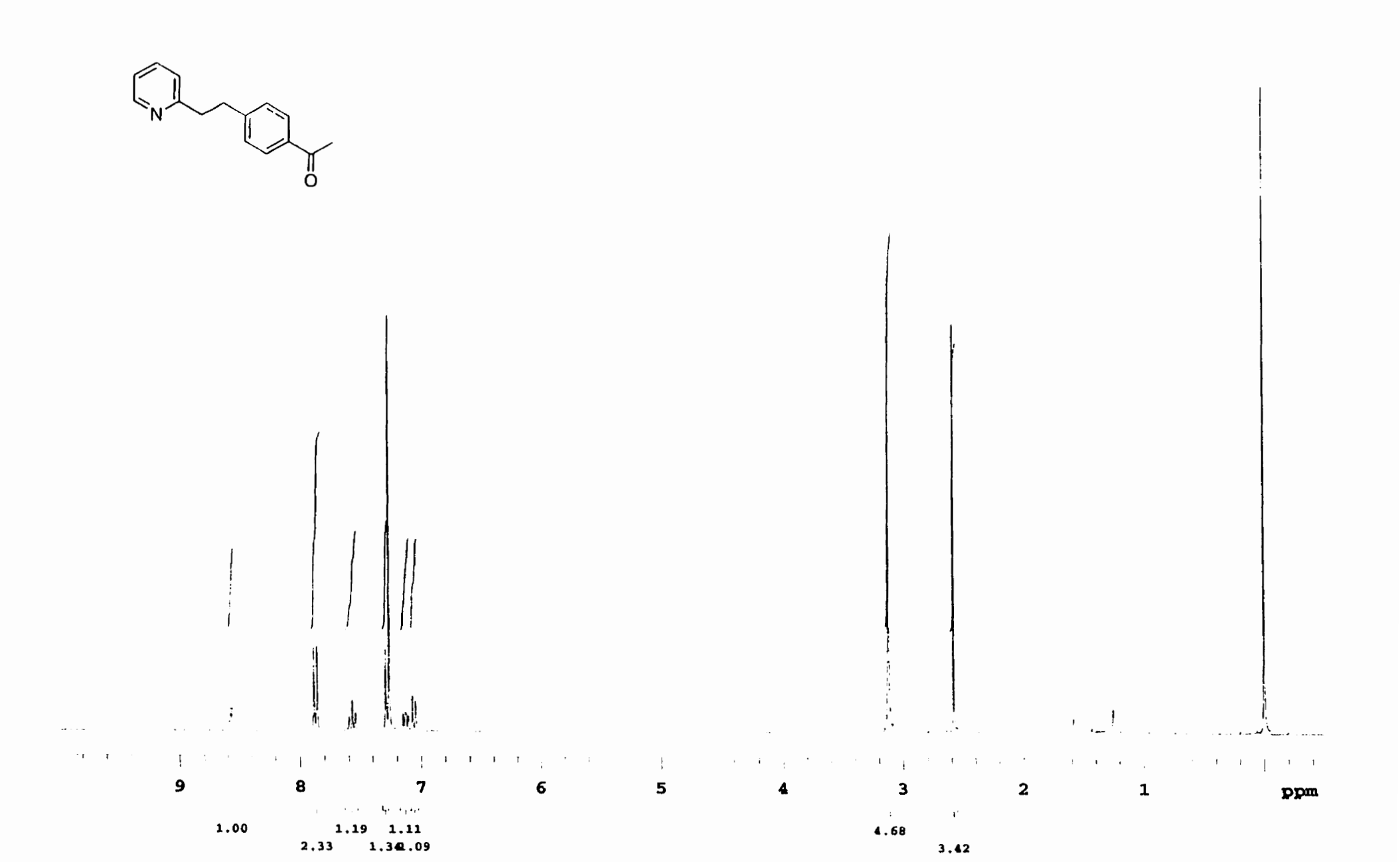
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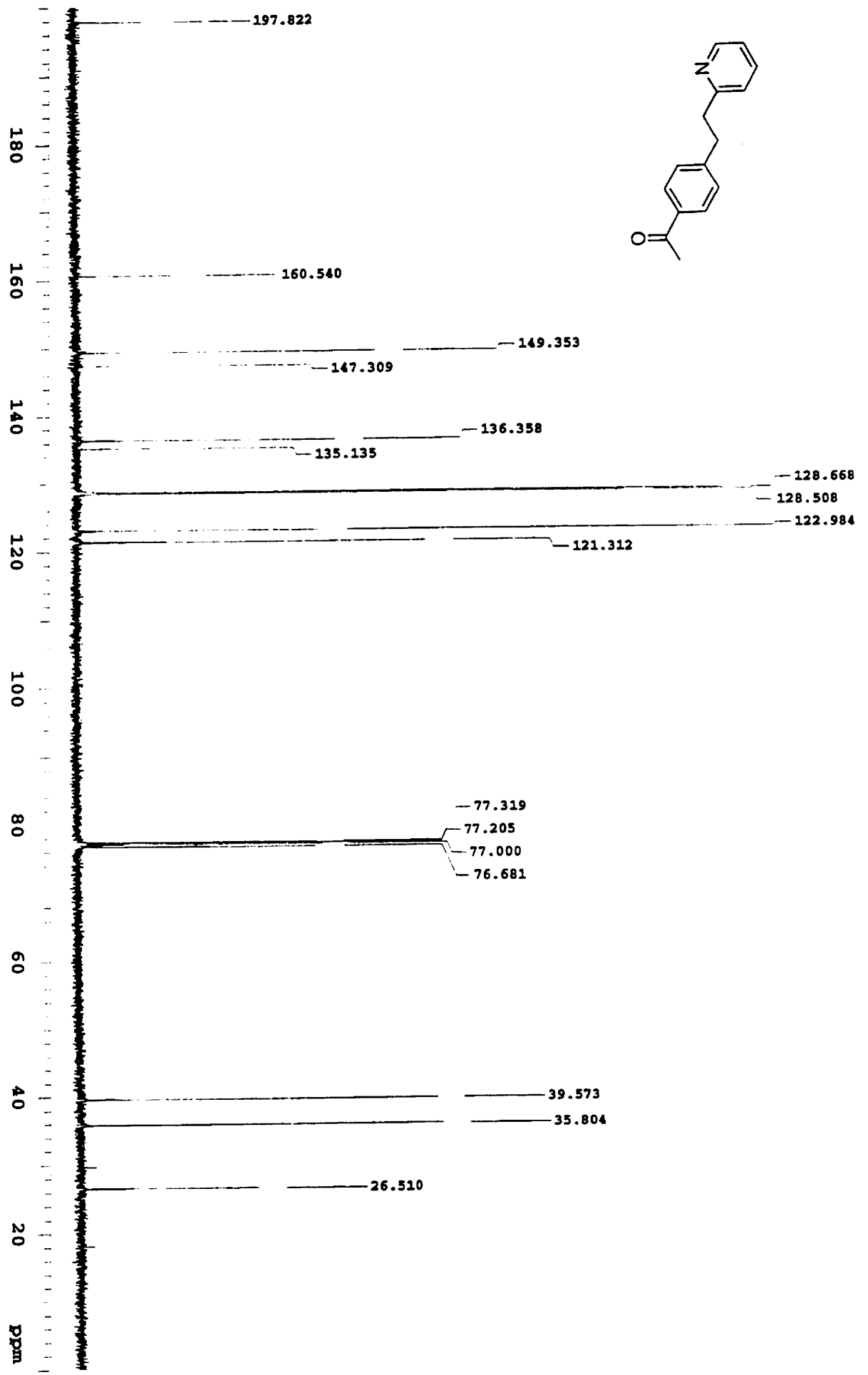
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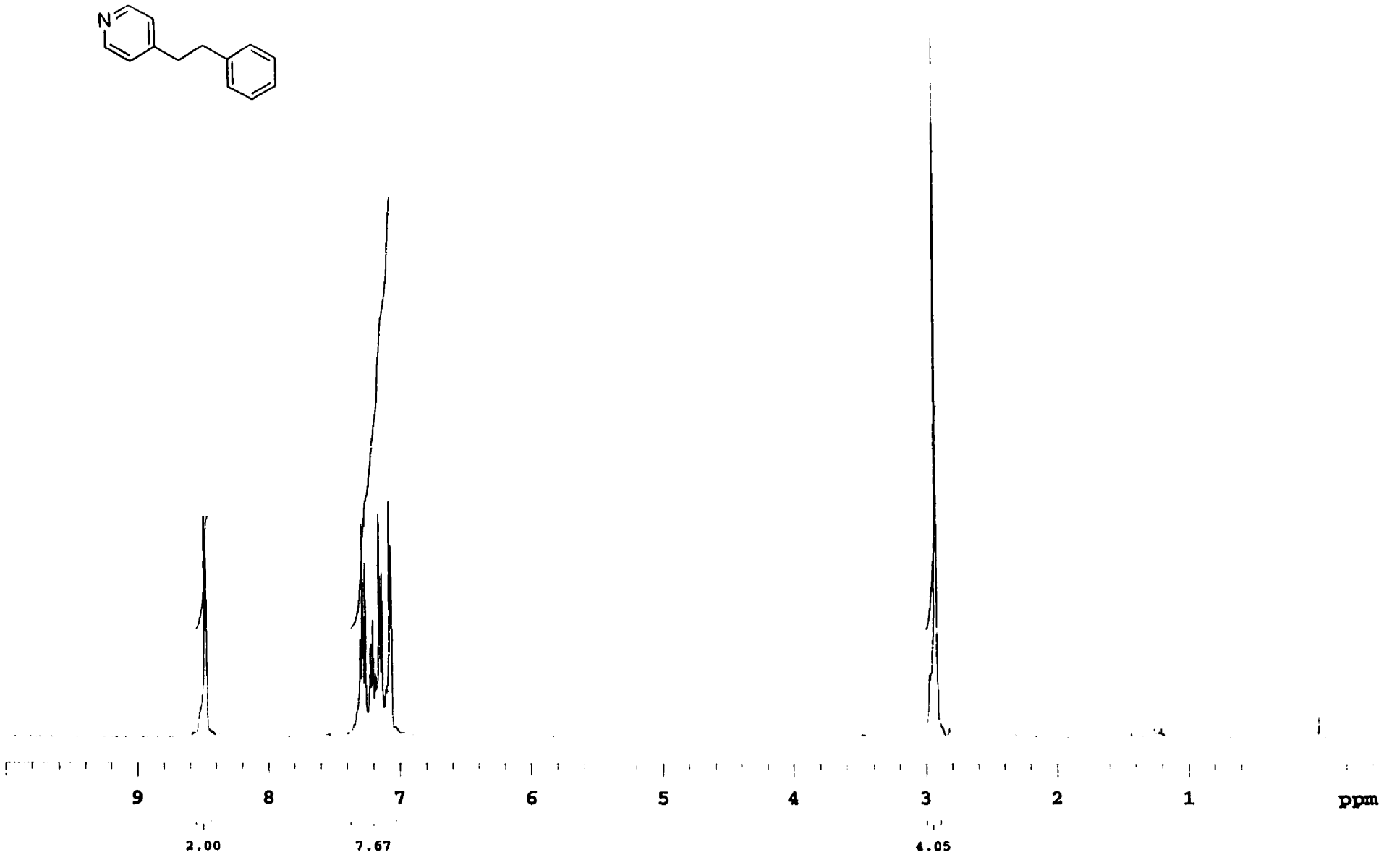
O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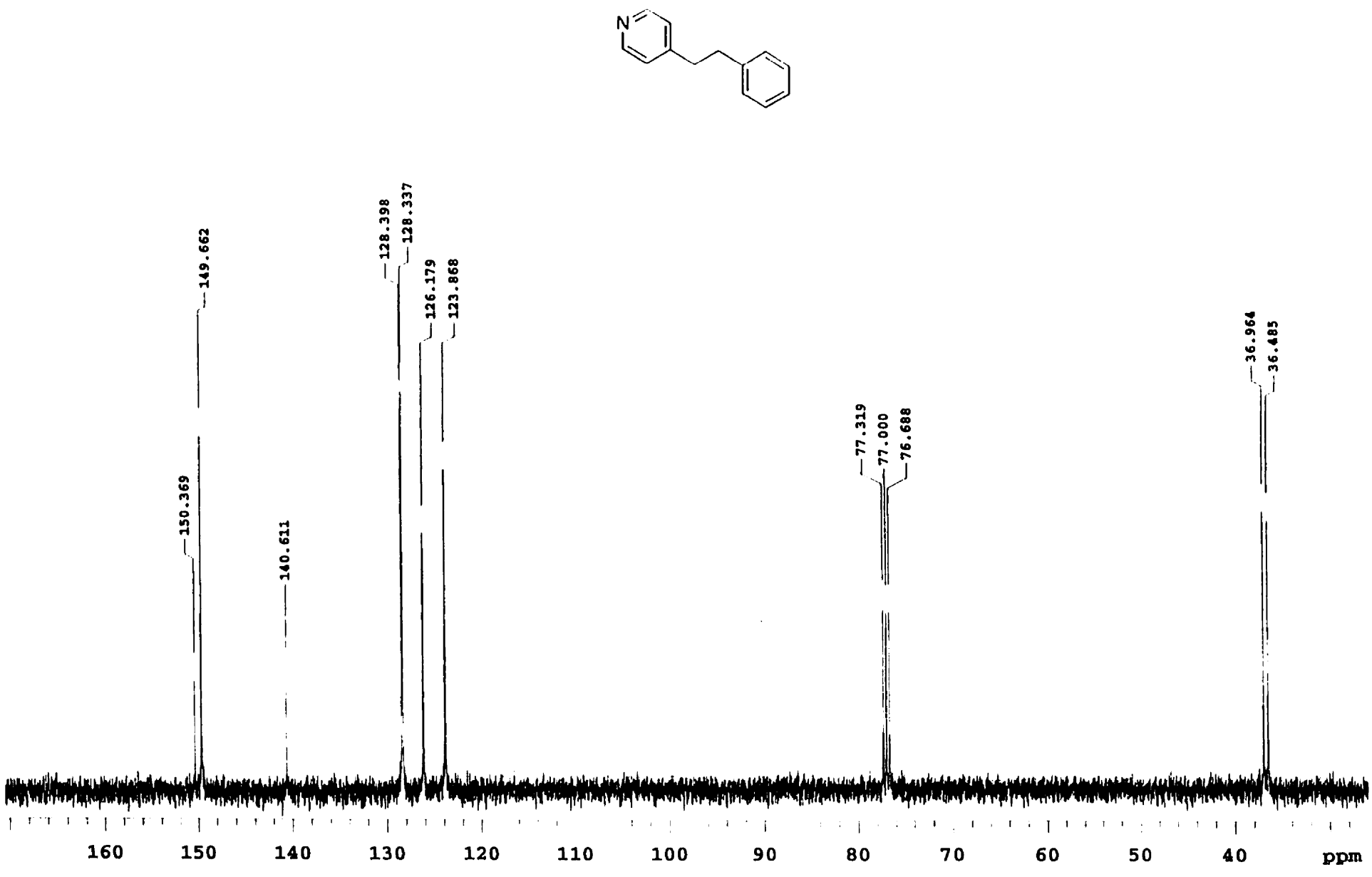
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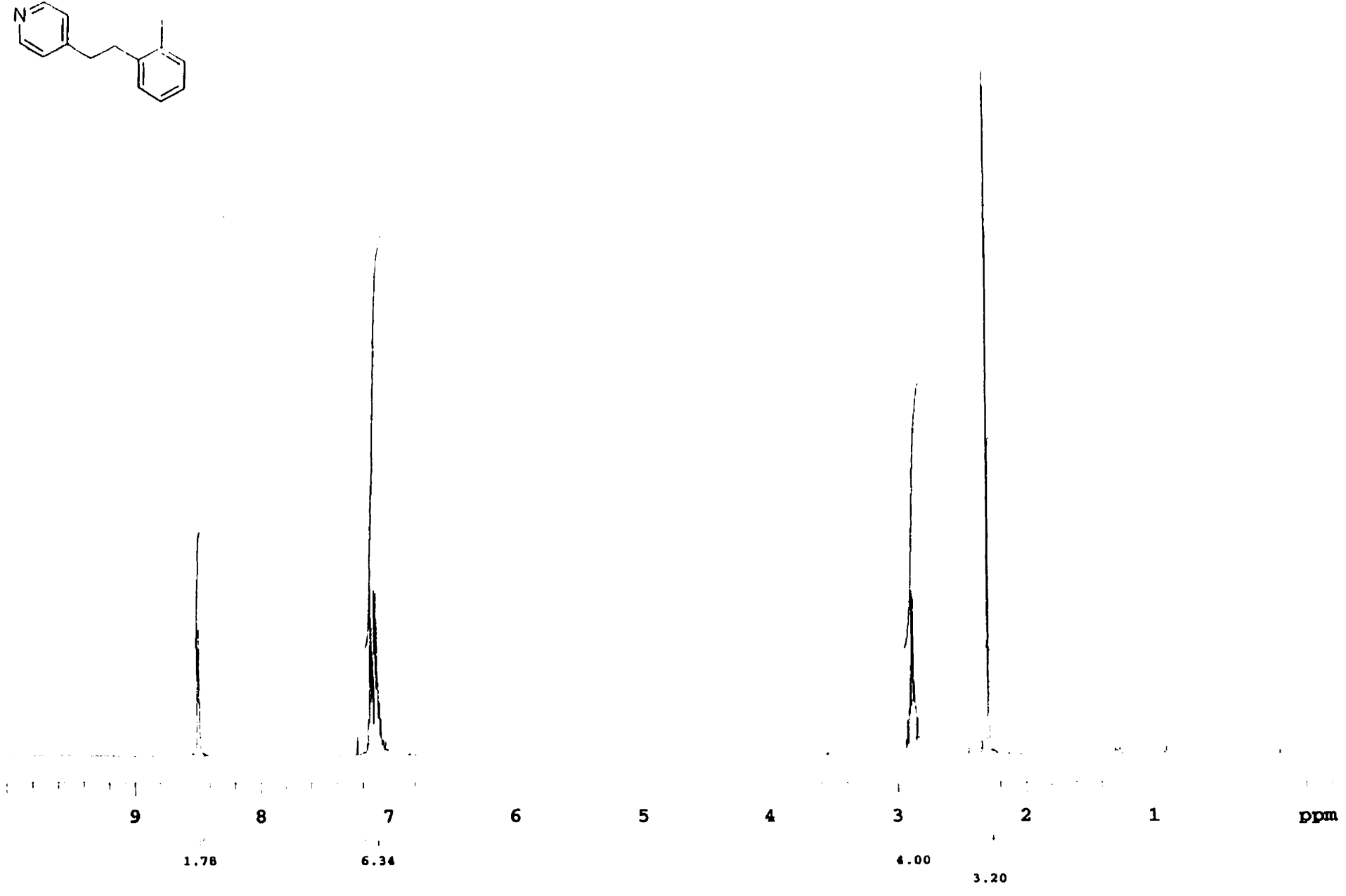
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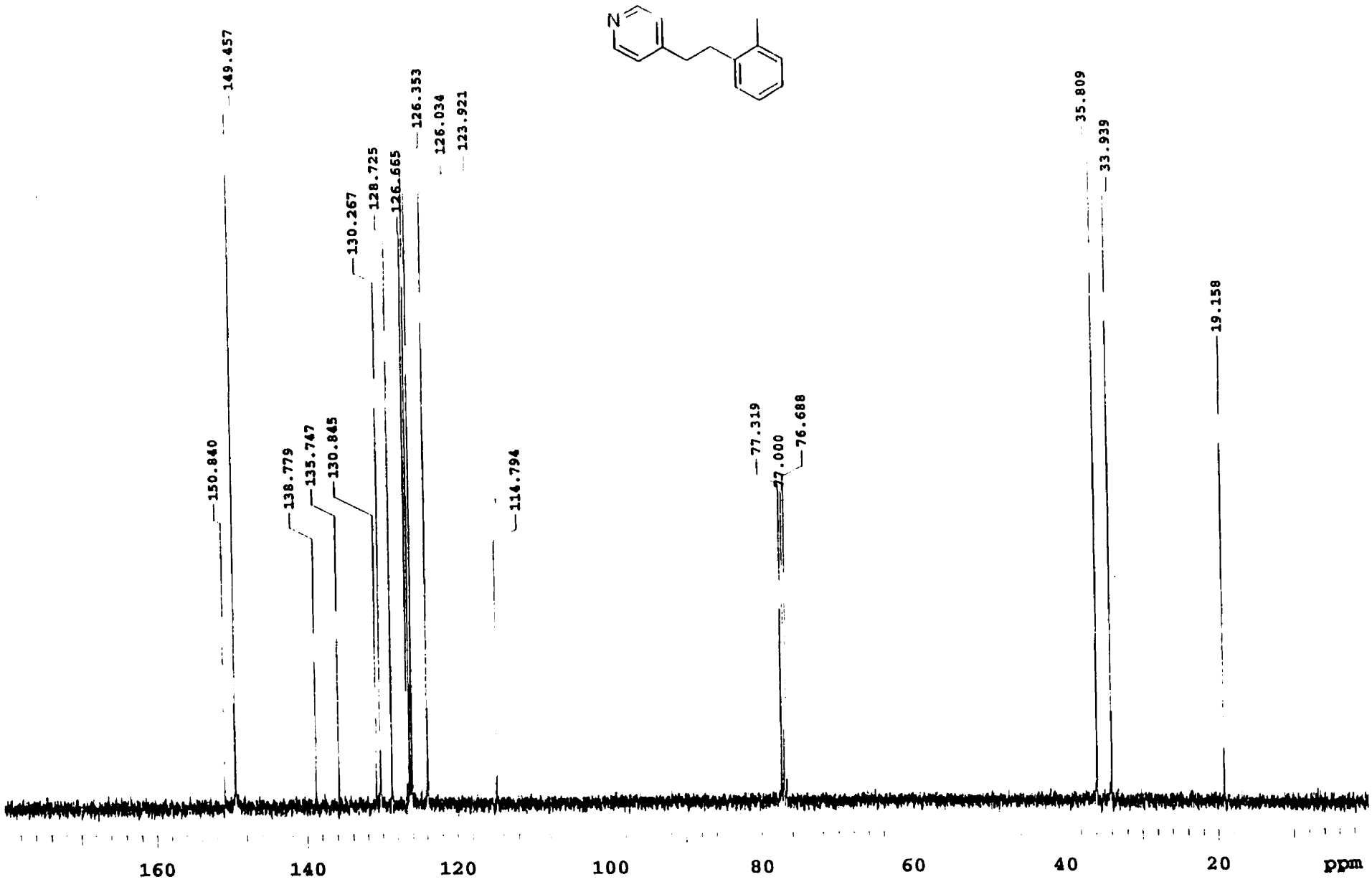
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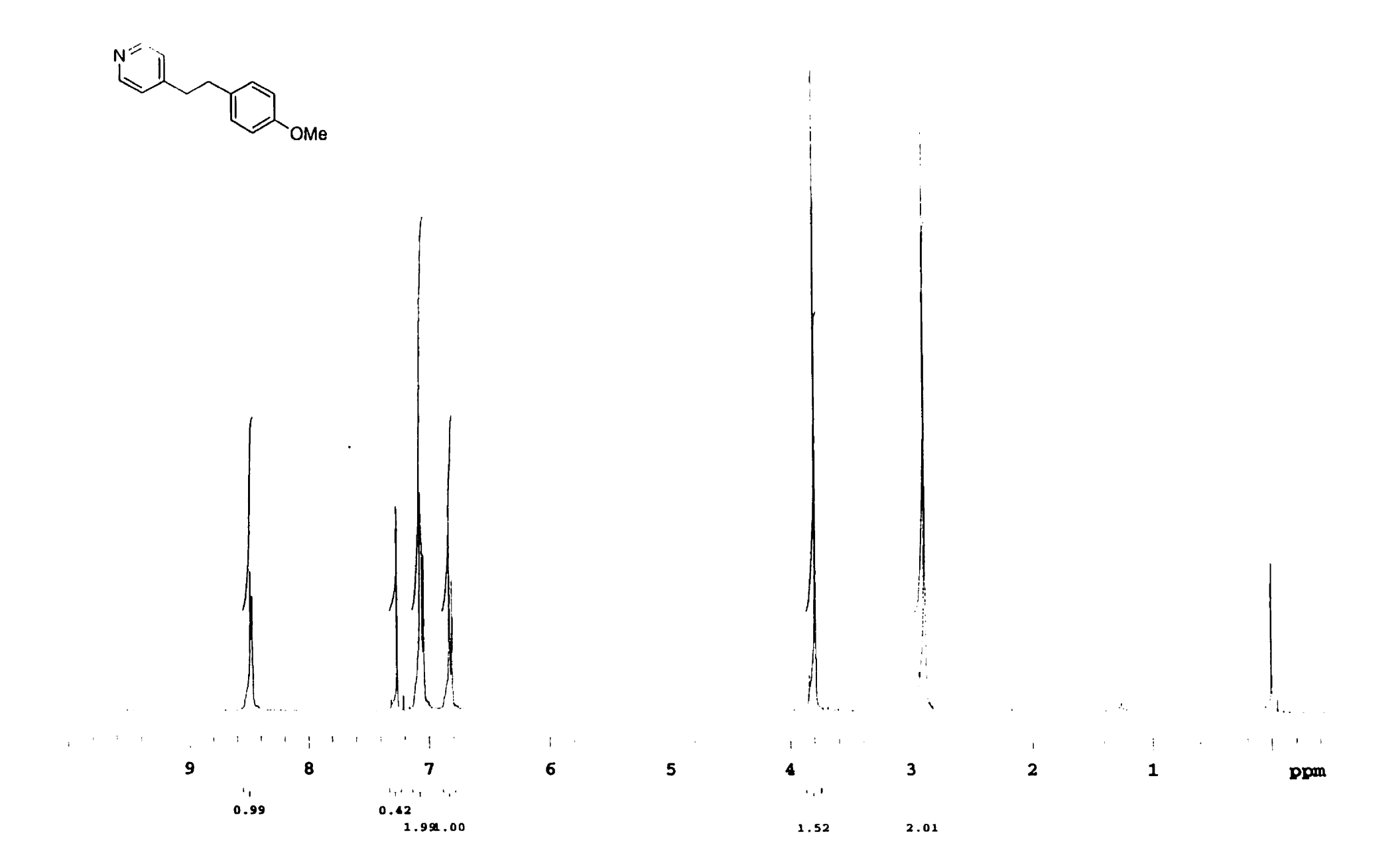
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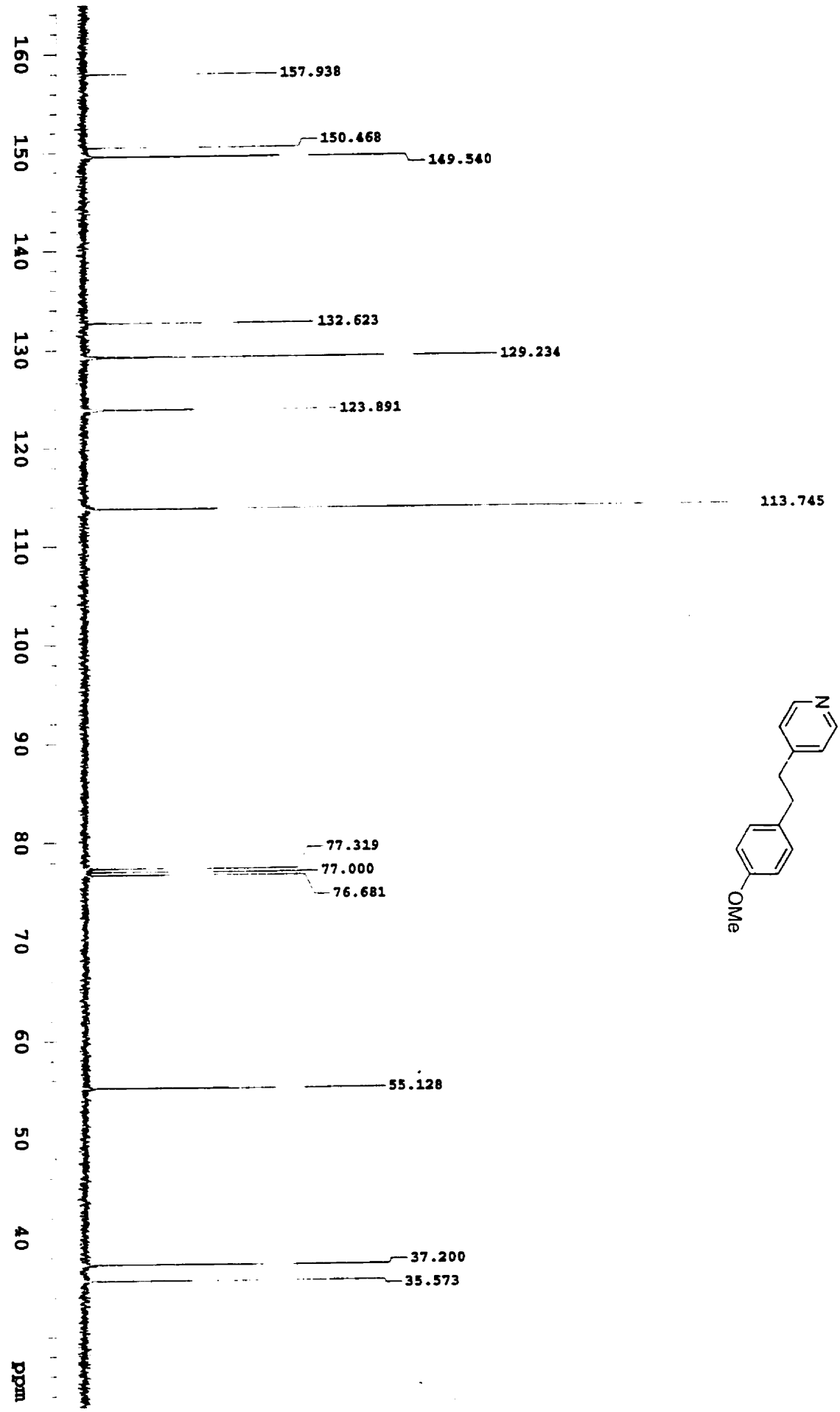
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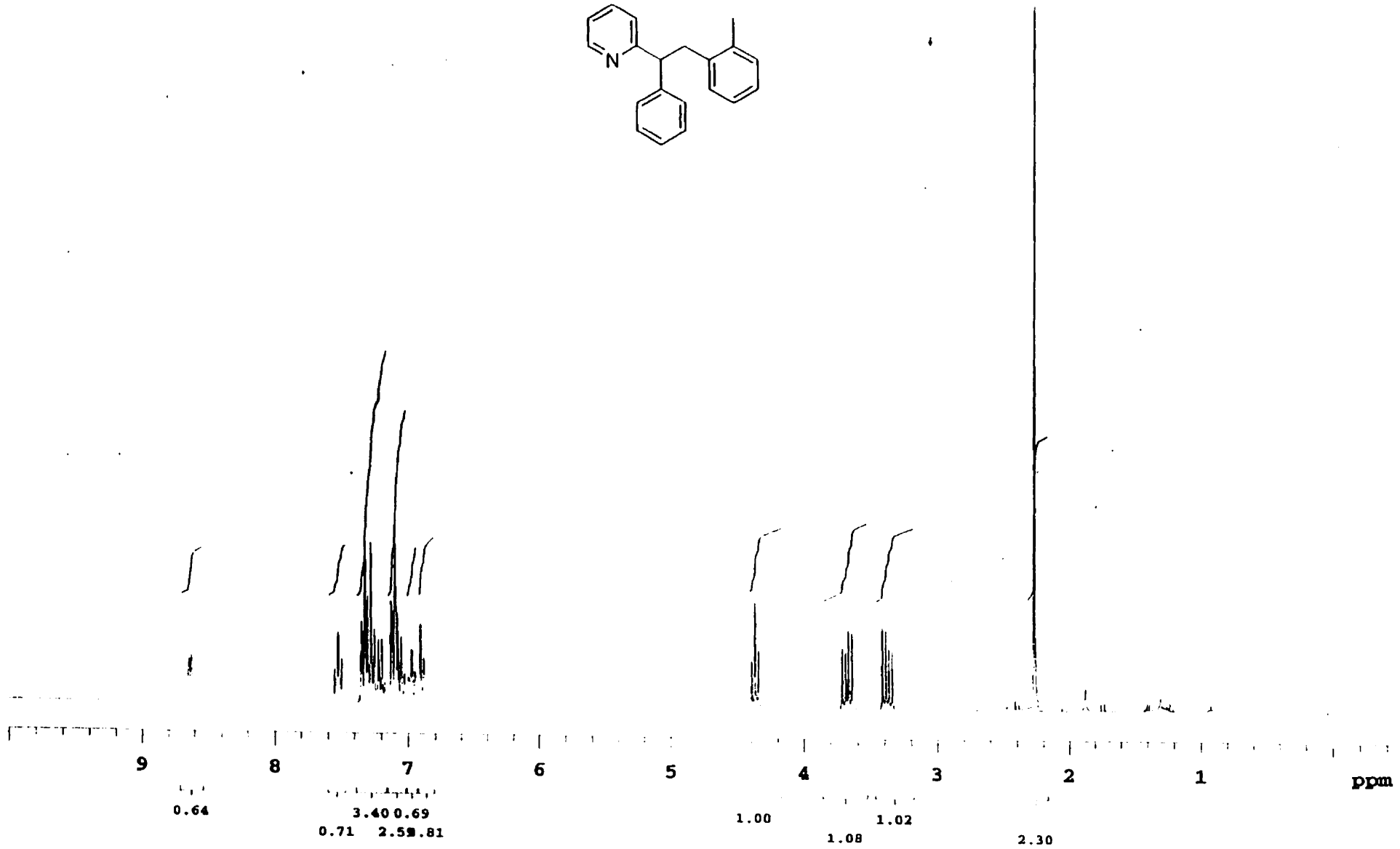
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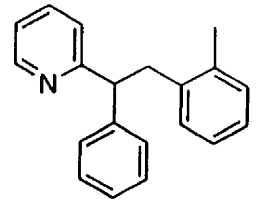
2.30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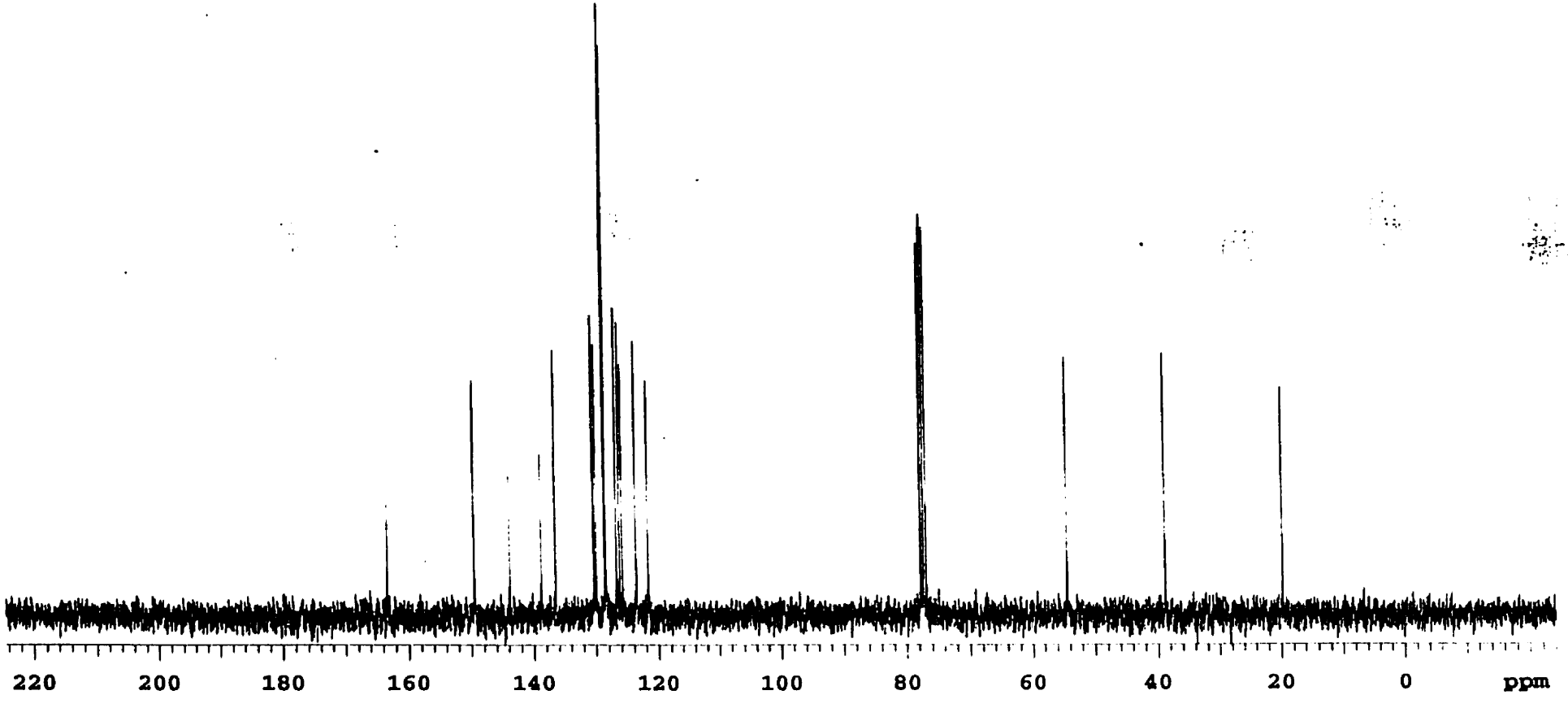
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