SYNTHESIS OF FERROCENYL SUBSTITUTED AZIRIDINES

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IN
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Approval of the Graduate School of Natural and Applied Sciences

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ABSTRACT

SYNTHESIS OF FERROCENYL SUBSTITUTED AZIRIDINES

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A new method for the efficient synthesis of ferrocenylenones was developed. Acryloyl, methacryloyl, crotonyl, cinnamoyl, and β-methylcrotonyl chlorides reacted with ferrocene in the presence of a Lewis acid ($EtAlCl_2$ or $EtAlCl_2$-Me_3Al) to give the corrosponding ferrocenylenones (acryloyl, methacryloyl, crotonyl, cinnamoyl, and β-methylcrotonylferrocenes) in good isolated yields.

Using the Gabriel-Cromwell reaction, acryloyl and crotonoylferrocenes were converted to the novel ferrocenyl substituted aziridines with benzylamine, isopropylamine and furfurylamine. The aziridines were isolated in good to excellent yields.

Keywords: Aziridines; Ferrocenylenones; Friedel-Crafts acylation; Lewis acids; Gabriel-Cromwell reaction.

ÖZ

FERROSENİL SÜBSTİTE AZİRİDİNLERİN SENTEZİ

Zeytinci, Serhat
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Doç. Dr. Özdemir Doğan

Haziran 2006, 77 sayfa

Ferrosenilenonların yüksek verimli sentezi için yeni bir yöntem geliştirilmiştir. Akriloyil, metakriloyil, krotonoyil, sinnamoyil, ve β-metilkrotonil klorürler ferrosenle Lewis asitli ($EtAlCl_2$ ya da $EtAlCl_2$-Me_3Al) ortamda tepkime vererek, beklenen ferrosenilenonları (akriloyil, metakriloyil, krotonoyil, sinnamoyil, ve β-metilkrotonillferrosen) iyi verimlerle oluşturmuşlardır.

Akriloyil ve krotonilferrosen, benzilamin, *iso*-propilamin ve furfurilamin ile Gabriel-Cromwell tepkimesi vererek yeni ferrosenil sübstite aziridinlere dönüştürülmüşlerdir. Aziridinler iyi ile çok iyi arasında değişen verimlerle izole edilmişlerdir.

Anahtar kelimeler: Aziridinler; Ferrosenilenonlar; Friedel-Crafts açillemesi; Lewis asitler; Gabriel-Cromwell tepkimesi.

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I would like to thank to especially Alper İşleyen and all organic group members for their relative-like friendship.

To you

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LIST OF ABBREVIATIONS

br	broad (spectral)
^{o}C	degrees Celcius
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
g	gram(s)
Hz	hertz
IR	infrared
i-Pr	isopropyl
J	coupling constant
m	multiplet (spectral)
mL	milliliter(s)
min	minutes
mmol	millimole(s)
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
Pr	propyl
q	quartet
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
TLC	thin layer chromatography
$TMSN_3$	trimethylsilylazide

CHAPTER 1

INTRODUCTION

1.1.Aziridines

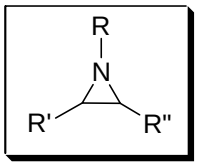

Figure 1. Aziridine

Aziridines are a group of organic compounds sharing the aziridine functional group(Figure 1), which is a three-membered heterocycle with one amine group and two methylene groups and first discovered by Gabriel in 1888. They are important as the starting materials in the synthesis of different organic compounds [1], as biologically active compounds [2], and as chiral ligands [3]. In addition, due to the ability of aziridines to undergo highly regio- and stereoselective ring opening reactions [4], aziridines are synthetically important compounds. This ability has not gone unnoticed in nature, where a number of compounds possessing an aziridine ring have been shown to exhibit potent biological activity, which is intimately associated with the reactivity of the strained heterocycle.

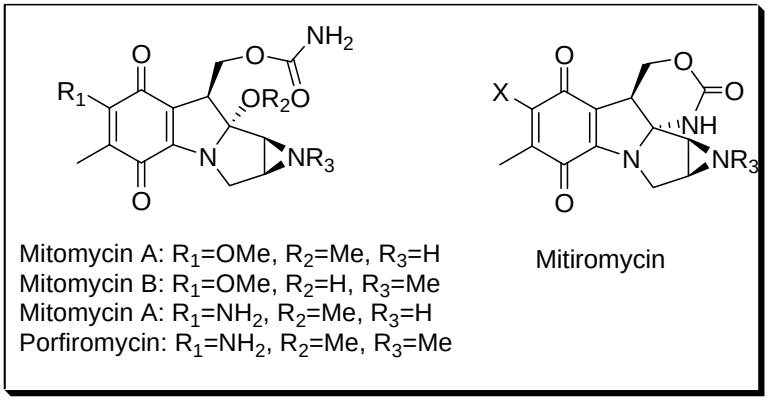

Figure 2. Naturally occurring biologically active aziridines

For example; *mitomycin* **A, B** and **C,** together with *porfiromycin* and *mitiromycin* [5] (Figure 2), represent an important class of naturally occurring mitosanes, isolated from soil extracts of *Streptomyces verticillatus* [6].

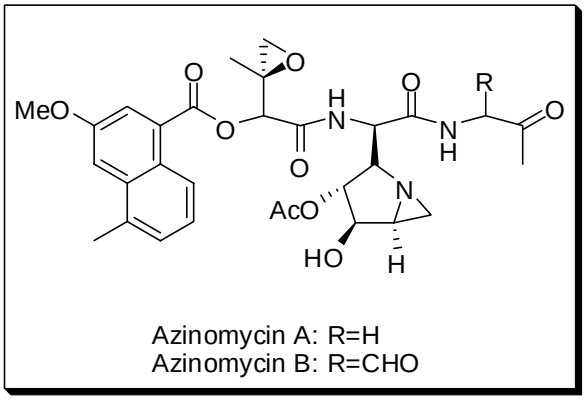

Figure 3. Biologically active *azinomycins*.

Azinomycins [7] (Figure 3), which were isolated from *Streptomyces griseofuscus* by Nagaoka and his friends in 1986, are also biologically active aziridines. These are

the naturally occurring aziridines which show activity against a wide range of tumours.

Biologically active aziridines (Figure 4) have also been synthesized. For example, 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid [40] and 2-(3-carboxypropyl)aziridine-2-carboxylic acid [41] are irreversible inhibitors of the bacterial enzyme diaminopimelic acid epimerase and glutamate racemase, respectively.

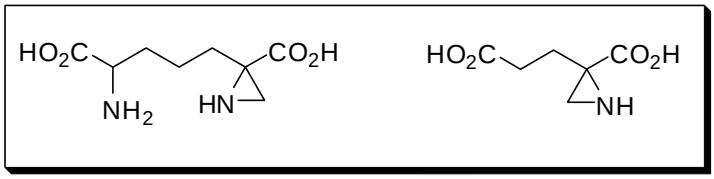

Figure 4. Biologically active synthetic aziridines.

In the literature, different methods [8] have been employed for the synthesis of these compounds. Among these methods, the most common ones are the synthesis of aziridines;

- From amino alcohols
- From epoxides
- Via cyclic sulfate formation
- From nitrene addition to alkene
- From imines
- From sulfilimines
- Via Gabriel-Cromwell reaction

1.2. Aziridination methods

1.2.1. From amino alcohols

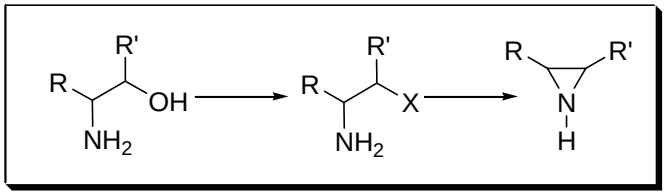

Figure 5. Aziridine synthesis from amino alcohols

Aziridines can be synthesized from 1,2-amino alcohols. Hydroxyl functional group is converted to a leaving group. Intramolecular nucleophilic displacement reaction by either the amide anion or the amine lone pair then yields the aziridine ring (Figure 5). Asymmetric synthesis of monochiral aziridines is possible by using enantiopure amino alcohols. Early examples of this synthetic transformation to prepare achiral aziridines were reported by Wenker [9] and Gabriel [10].

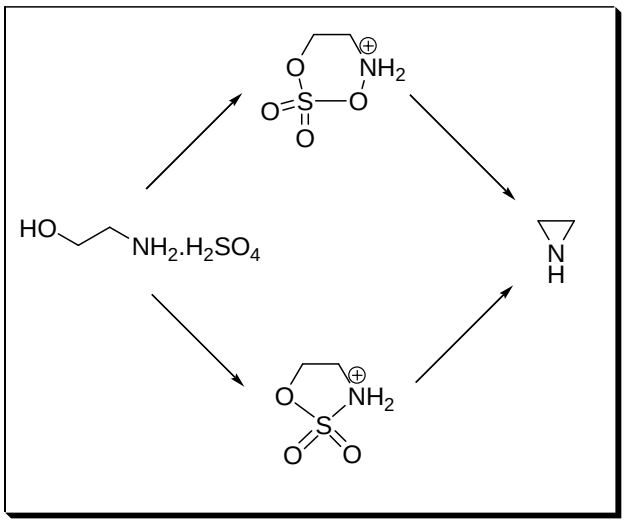

Figure 6. Wenker's aziridine synthesis

For example, Wenker converted ethanolamine to ethylene imine via, it was claimed, 'β-aminoethyl sulphuric acid'. Given the modern insight of the reactivity of cyclic sulfates and sulfamidates, however, the intermediate of the reaction might reasonably be considered to be the cyclic sulfamidate of ethanolamine.

This method is efficient for simple amino alcohols but it is unsatisfactory for tertiary alcohol for which elimination causes an alkene in preference to cyclization. This reaction is usually stereospecific and relies upon the ability of the amine and leaving group to adopt trans coplanar relationship. If enantiomerically pure amino alcohols are utilized, this method yields enantiopure aziridines [11].

Gabriel [10] showed that aziridines can be synthesized from 2-haloamines. Their intramolecular nucleophilic ring-forming reaction is similar to the Wenker method and is also stereospecific.

1.2.2. From epoxides

The regiospecific ring opening of epoxides by azide ion has frequently exploited to enable the synthesis of aziridines [12]. Reduction of the azide moiety of the first-formed azido alcohol, for example with triphenylphosphine in the Staudinger reaction [13], yields first an imino phospharane and then an oxazaphospholine intermediate which is normally not be isolated prior to thermally-induced cyclization to yield an aziridine.

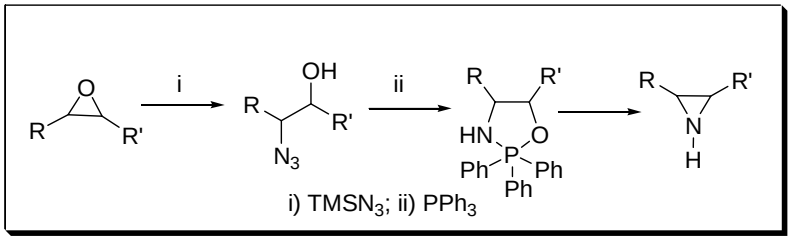

Figure 7. Aziridine synthesis via Staudinger reaction

When enantiomerically pure epoxides are used in this reaction sequence, access to non-racemic aziridines is feasible [14].

The ready availability of enantiomerically pure epoxides from allylic alcohols via the Sharpless asymmetric epoxidation [15] allows the routine preparation of possible stereoisomers of a given hyroxymethylaziridine.

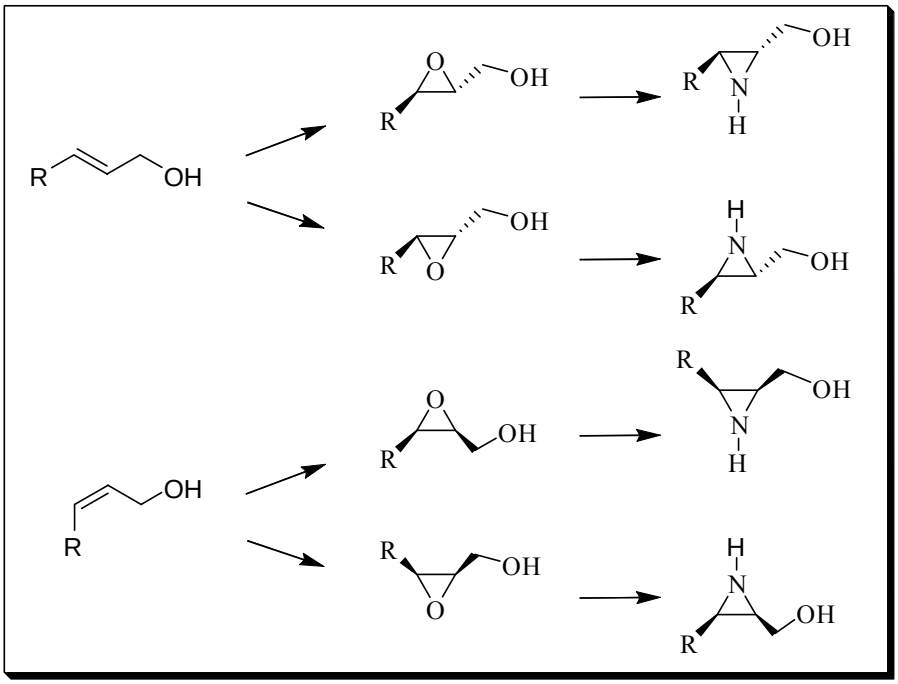

Figure 8. Synthesis of all possible stereoisomers of a hydroxymethyl aziridine.

1.2.3. Via cyclic sulfate formation

In a reaction sequence exactly analogous to the azide opening/Staudinger sequence shown above (Figure 7), cyclic sulfates obtained from asymmetric dihydroxylation products are easily transformed into aziridines (Figure 9) [16]. Two pathways are possible for the conversion of the cyclic sulfate intermediate to aziridines: both

involve two consecutive nucleophilic displacement reactions with the final displacement reaction being intramolecular.

Thus, facile entry to a range of enantiopure N-protected and N-unprotected aziridines is possible in excellent overall yields using amine and azide nucleophiles respectively.

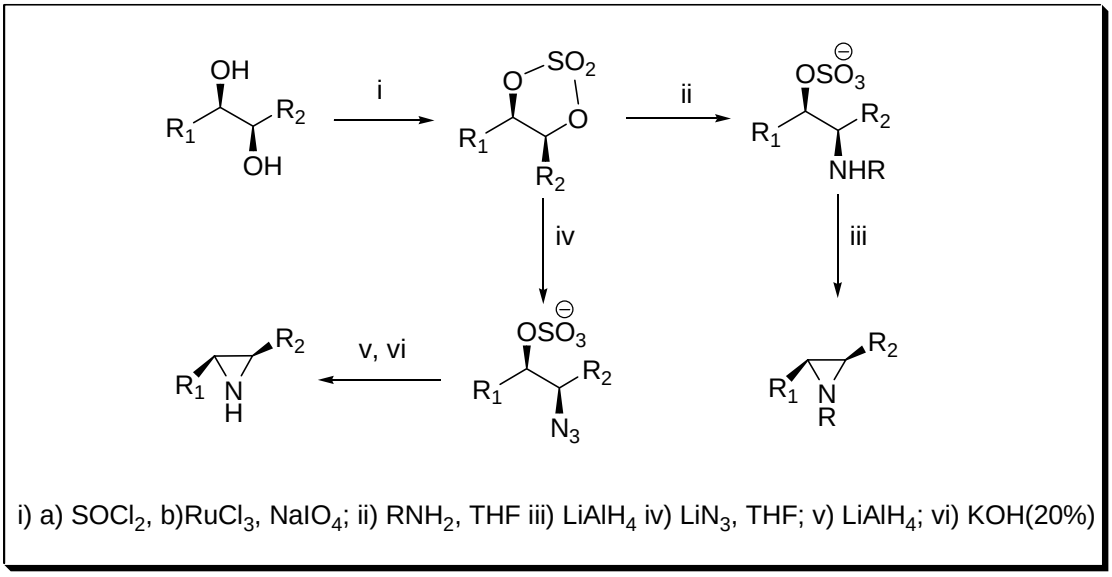

Figure 9. Aziridine synthesis via cyclic sulfate formation

1.2.4. From nitrene addition to alkene

Aziridination utilizing direct nitrene addition to alkenes, the reaction conceptually closest the peracid epoxidation of alkenes, has been improved over recent years by the development of new, mild conditions for nitrene generation [17]. The addition of free nitrenes to an alkene is, however, generally not well stereochemically-controlled, mixtures of *cis*- and *trans*- aziridines being formed [18]. This is due to the rapid interconversion of the singlet and triplet nitrene states (Figure 10).

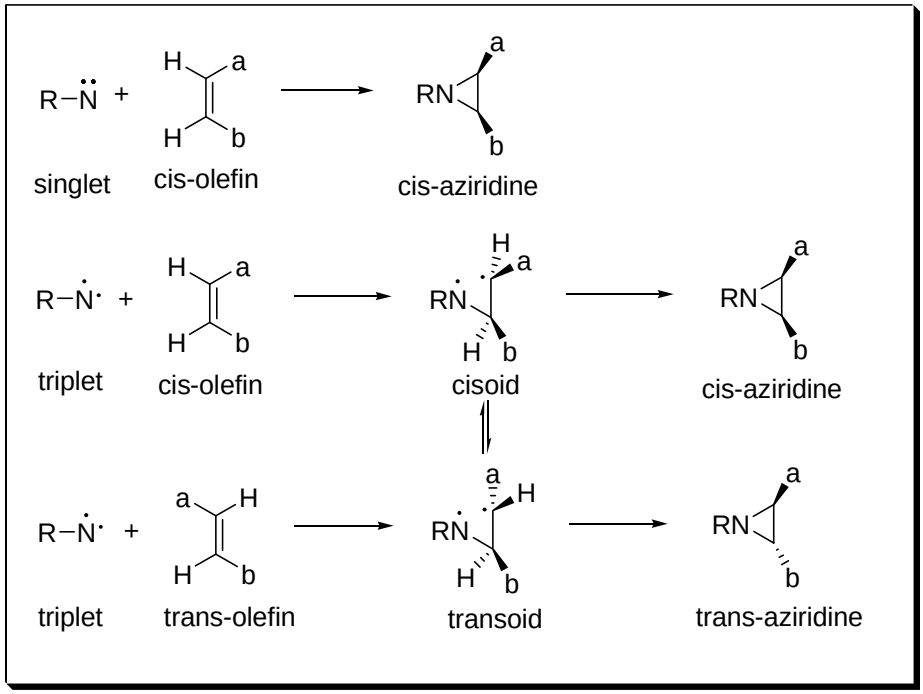

Figure 10. Synthesis of aziridines via nitrene addition to alkenes.

1.2.5. From imines

It has recently proved possible to elaborate traditional methods which have been used for the synthesis of racemic aziridines from imines to allow for asymmetric synthesis of aziridines from imines (Figure 11). Enantiocontrol is generally obtained by using chiral imines, chiral nucleophiles or chiral catalyst. For example, Copper catalyzed diazoacetate decomposition in the presence of an imine represents a complementary alternative to nitrene addition to alkenes for the synthesis of aziridines [19].

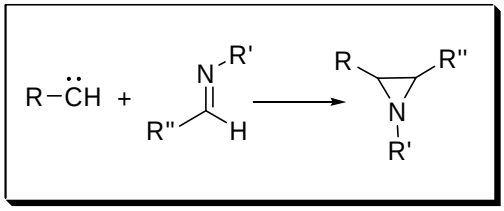

Figure 11. Carbene addition to imine

In addition, the nucleophilic addition of a range of anions bearing α-leaving groups to N-Ar or N-Alkyl imines have also been reported as plausible synthetic routes to N-Ar or N-Alkyl aziridines [20] (Figure 12).

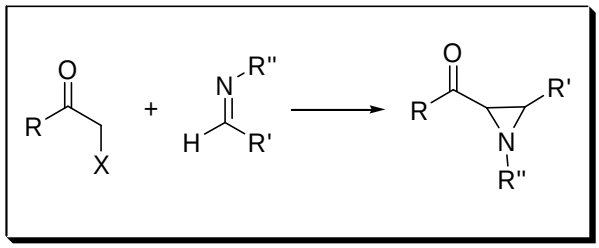

Figure 12. Aza-Darzens reaction

1.2.6. From sulfilimines

Electrophilic alkenes react with sulfilimines in good yields, with the elimination of diphenyl sulfide [21] (Figure 13).

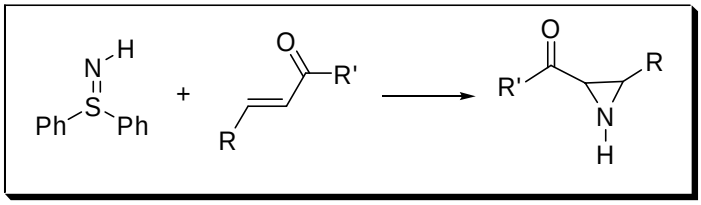

Figure 13. Reaction of sulfilimine with electrophilic alkene

1.2.7. Via Gabriel-Cromwell reaction

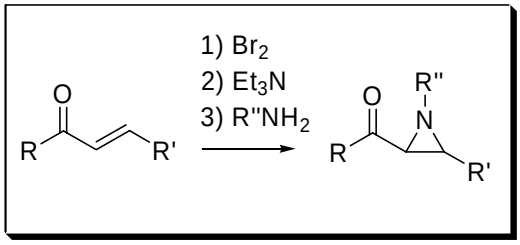

Figure 14. Gabriel-Cromwell reaction

1,2-Dibromo carbonyl compounds, prepared via addition of bromine to α,β-unsaturated carbonyl compounds, can be elaborated to yield racemic aziridines on treatment with amines [22] (Figure 14). Following this procedure Garner described the asymmetric synthesis of C-3 unsubstituted aziridine-2-carboxylates using as chiral auxiliary the Oppolzer's camphor-derived sultam [23]. Unfortunately the reaction resulted in a 1:1 diastereomeric mixture when applied to the preparation of 3-methyl aziridines. Also aziridines were synthesized from α-iodoenones by using this method [24]. In addition, this method can be applied even in solid phase as demonstrated by Silvia N. Filigheddu at al [25].

1.2.7.1. Mechanism of Gabriel-Cromwell Reaction

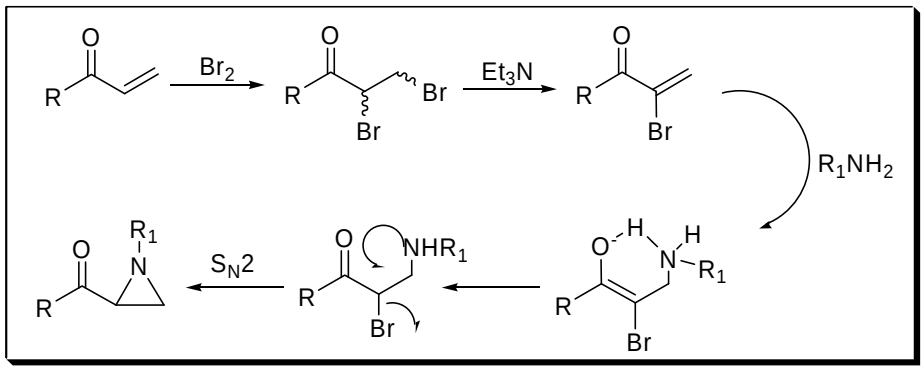

Figure 15. Mechanism of Gabriel-Cromwell reaction

Starting with an α-β,unsaturated carbonyl compound, the overall reaction sequence includes five distinct mechanistic steps: First, bromination of unsaturated group, second, β-elimination with triethylamine, then 1-4 addition of primary amine to α-bromo α-β unsaturated carbonyl compound and proton transfer, finally S_N2 ring closure which gives aziridine-2-carboxylate.

1.3.Ferrocene

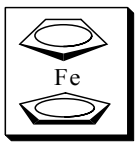

Figure 16. Ferrocene

Ferrocene ($Fe(C_5H_5)_2$) (Figure 16) is a metallocene, a type of organometallic compound consisting of two cyclopentadienyl rings bound on opposite sides of a central iron atom and forming an organometallic sandwich compound. It was first made unintentionally from the reaction of cyclopentadiene and iron powder in 1951, originally designed to couple the diene. A light orange powder was obtained instead, which had a melting point of about 173 º C and a staggered configuration in the solid state and an eclipsed form in the gas phase. The structure of the compound was confirmed by NMR and X-Ray studies. In ferrocene, the pi electrons of both the cyclopentadiene rings are shared with the central iron ion, giving it an inert gas electron configuration. This is what makes ferrocene stable. Ferrocene is also air stable and also stable at temperature greater than 500 º C. Ferrocene undergoes many reactions characteristic of aromatic compounds, notably Friedel-Crafts reactions.

Ferrocenyl substituted organic molecules hold great potential due to their biological activity [27], as well as increasing application in material science [28] and asymmetric catalysis [29]. Chiral ferrocene ligands have been widely used in asymmetric catalysis. The advantages of using ferrocene as a scaffold for chiral ligands are planar chirality, rigid bulkiness, and ease of derivatization.

1.4.Ferrocenylenones

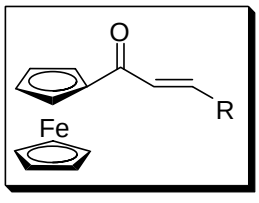

Figure 17. Ferrocenylenone

Ferrocenylenones (Figure 17) are important starting materials for the synthesis of substituted ferrocenes [30] and polymers [31]. They found many applications in the literature. They are used as dienophiles in Diels–Alder reactions [32], and as dipolarophiles in 1,3-dipolar cycloaddition reactions [33]. Synthesis of hetero- and carbocyclic-ferrocene derivatives are also based on the use of ferrocenylenones [34]. Syntheses of ferrocenylenones are carried out in different ways. One common method is the Friedel–Crafts acylation reaction. Although this method worked efficiently in the synthesis of crotonoyl-, cinnamoyl-, and β-methylcrotonoylferrocene using $AlCl_3$ as the Lewis acid, the same method failed in the synthesis of acryloyl- and methacryloylferrocene. In the last two cases, Friedel–Craft acylation reaction with $AlCl_3$ resulted in the formation of corresponding ferrocenophan-1-ones [35]. For this reason, alternative methods were used especially in the synthesis of acryloylferrocene. These methods are:

- Reaction of ferrocenoylsilanes with vinylmagnesium bromide in the presence of $CeCl_3$ [39].
- Elimination of ethyl methyl sulfide from 1-ferrocenyl-3-(ethylsulfanyl)propan-1-one [38].
- HCl elimination from 3-chloropropionylferrocene [37].
- Mannich reaction of acetylferrocene with formaldehyde and secondary amines [36].

1.5.Synthesis of ferrocenylenones

1.5.1. Reaction of ferrocenoylsilanes with vinylmagnesium bromide

Ferrocenoylsilanes can react with excess amount of vinylmagnesium bromide in the presence of $CeCl_3$ to form vinyl ferrocenyl ketone in 49 % yield. (Figure 18)

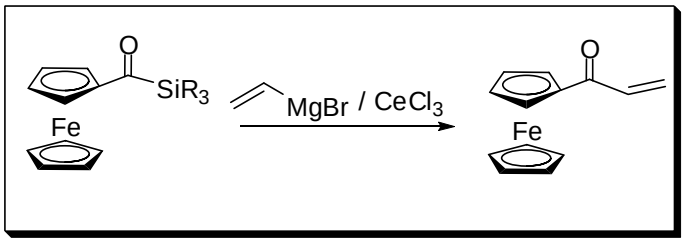

Figure 18. Synthesis of acryloyl ferrocene from ferrocenoylsilanes

1.5.2. Elimination of ethyl methyl sulfide from 1-ferrocenyl-3-(ethylsulfanyl)propan-1-one

Methylation of 1-ferrocenyl-3-(ethylsulfanyl)propan-1-one with methyl triflate and elimination with aqueous $KHCO_3$ gives vinyl ferrocenyl ketones in good yields. (Figure 19)

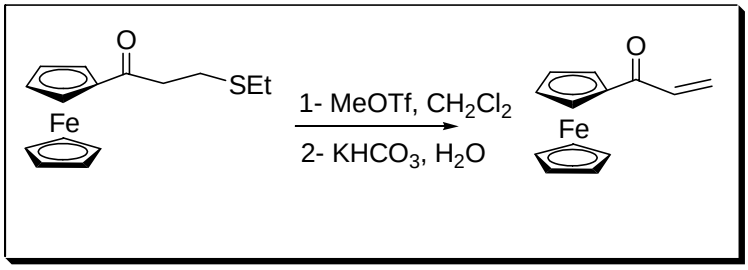

Figure 19. Acryloyl ferrocene from 1-ferrocenyl-3-(ethylsulfanyl)propan-1-one

1.5.3. HCl elimination from 3-chloropropionylferrocene

Acrloyl ferrocene can be obtained in high yield with the elimination of HCl from 3-chloropropionylferrocene (Figure 20)

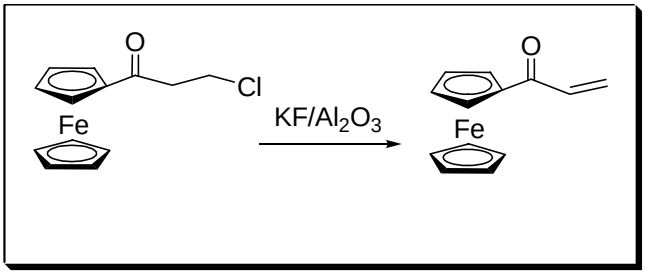

Figure 20. HCl elimination from 3-chloropropionylferrocene

1.5.4. Mannich reaction of acetylferrocene with formaldehyde and secondary amines

Acetylferrocene was condensed with formaldehyde and dimethylamine hydrochloride to form Mannich type salts, which were converted to the free amines and to acryloylferrocene. (Figure 21)

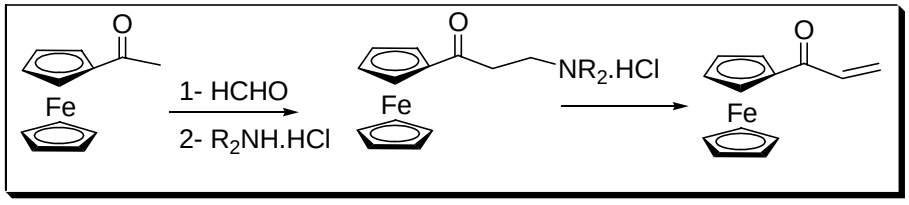

Figure 21. Reaction of acetyferrocene with formaldehyde and secondary amines

All these methods require two steps and the yields range between 46-80%.

1.6.Aim of the work

The major purpose of this research is to synthesize new ferrocenyl substituted aziridines by employing the Gabriel-Cromwell reaction. The synthesis of aziridines and ferrocenyl substituted organic molecules are important. These compounds hold great potential due to their biological activity and increasing application in asymmetric catalysis and material science.

To realize above purpose, we had to synthesize starting ferrocenylenones used for the aziridines in gram quantities. There is no method which gives acryloylferrocene at a single step. Therefore we also aimed to develop an efficient method for the synthesis of this compound.

CHAPTER 2

RESULTS and DISCUSSION

2.1. Synthesis of starting materials (ferrocenylenones)

For the synthesis of aziridines it was necessary to prepare starting ferocenylenones in gram quantities. Although crotonyl, cinnamoyl, methylcrotonoyl ferrocenes can be synthesized easily in a single step by Friedel-Crafts method using $AlCl_3$, the same method fails for the synthesis of acryloyl and metacryloylferrocene. For this reason, we looked for a better procedure to synthesize these compounds. We tried different Lewis acids and used $EtAlCl_2$, Me_3Al and the mixture of $EtAlCl_2$-Me_3Al.

2.1.1. Synthesis of acryloylferrocene 5 in the presence of $AlCl_3$

Literature studies [42] showed that Friedel-Crafts acylation of ferrocene (**1)** with acryloyl chloride in the presence of $AlCl_3$ gave an unexpected product (ferrocenophan-1-ones) **4**. Watts and Turbitt [42-a] explained this result by the formation of a metal–alkenyl intermediate **2** which was converted to an aluminium enolate **3** by methylene group migration from the iron atom to the cyclopentadienyl ring followed by proton loss (Figure 22).

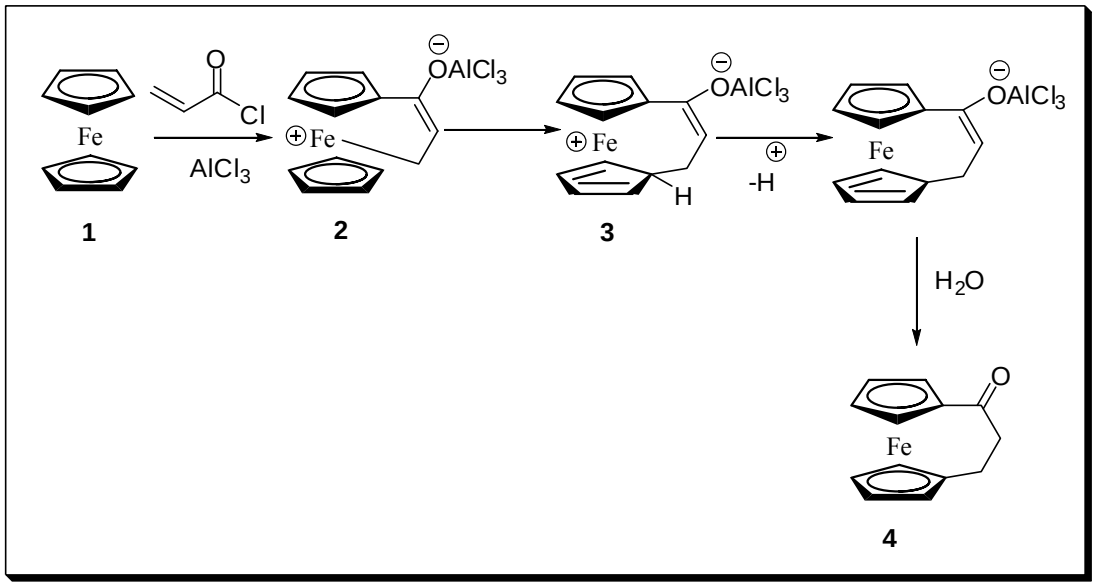

Figure 22. Reaction mechanism for ferrocenophan-1-one formation

They also believe that HCl formed during the Friedel-Crafts reaction is effective in ferrocenophane **4** formation. In order to find out whether ferrocenophane formation is taking place after acryloyl ferrocene formation, they treated pure acryloylferrocene **5** with $AlCl_3$ or $AlCl_3$–HCl and observed no ferrocenophane **4** formation. Second reaction gave simple HCl addition product **6** (Figure 23).

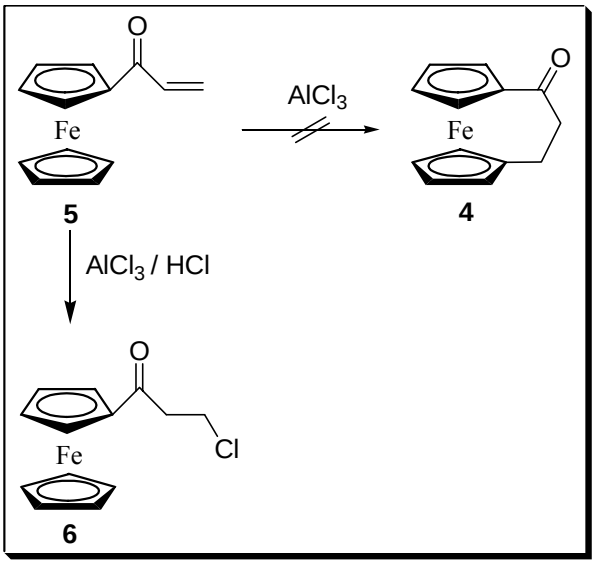

Figure 23. Treatment of acryloylferrocene with $AlCl_3$ and $AlCl_3$–HCl.

Based on this literature information if HCl is effective in the mechanism of ferrocenophane **4** formation, alkyl Lewis acid should be a simple solution. To test this idea, we decided to use $EtAlCl_2$ as the Lewis acid. When ferrocene was reacted with acryloyl chloride in the presence of $EtAlCl_2$ three compounds, acryloylferrocene **5**, ferocenophane **4**, and (3-chloropropanoyl)ferrocene (**6**) were obtained in 55, 15 and 8% yields, respectively (Figure 24).

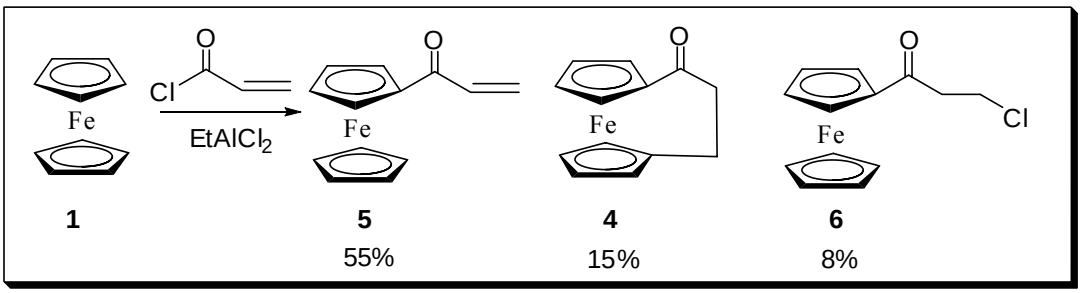

Figure 24. Synthesis of acryloylferrocene **5** by using $EtAlCl_2$

Clearly alkyl Lewis acid reduced the amount of ferrocenophane **4** and increased the amount of desired product. But the yield of the desired product was not satisfactory. Therefore, we decided to use highly alkylated Lewis acid Me_3Al. Repeating the same reaction with this Lewis acid, acryloylferrocene **5** was obtained in 30% yield without any side products (Figure 25).

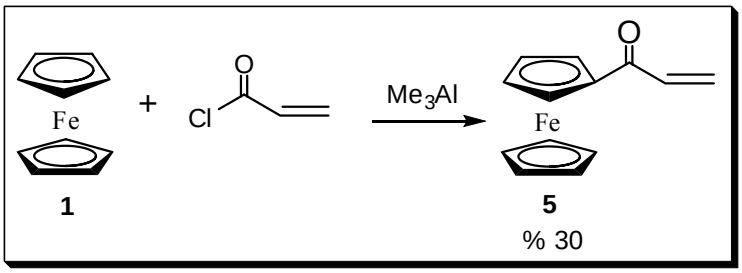

Figure 25. Synthesis of acryloylferrocene **5** by using Me_3Al

From this experiment it was concluded that this Lewis acid was not strong enough to activate acryloyl chloride to give Friedel-Crafts reaction with ferrocene. As a result it was decided to use a mixture of $EtAlCl_2$ and Me_3Al as the Lewis acid. When the reaction was carried out in the presence of these Lewis acids, acryloylferrocene **5** was formed in 83% yield with ferrocenophan-1-one **4** obtained in less than 5% (Figure 26).

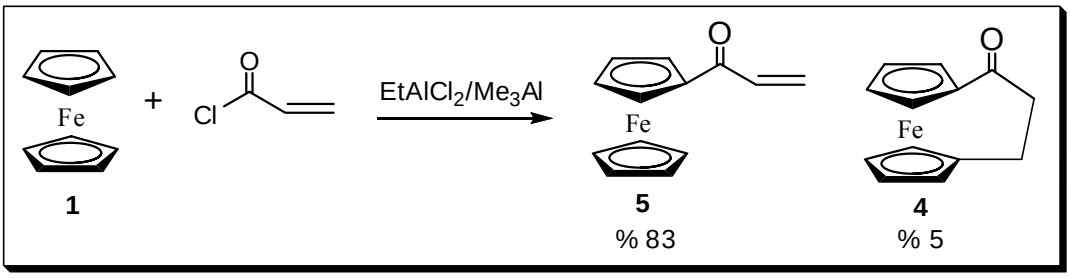

Figure 26. Synthesis of acryloylferrocene **5** by using $EtAlCl_2$-Me_3Al

Although the effect of HCl in the formation of ferrocenophane **4** is not known, preventing the HCl formation in the reaction medium reduced the amount of undesired product to less than 5%. Normally, Friedel-Crafts reactions produce HCl. When only $EtAlCl_2$ is used as the Lewis acid, it reacts with HCl to form $AlCl_3$ and EtH [51] (Figure 27). Strong Lewis acidity of $AlCl_3$ increases the ferrocenophane **4** formation. To get rid of this problem we used Me_3Al to trap HCl formed in the reaction medium [52].

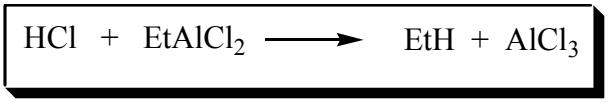

Figure 27. Formation of $AlCl_3$ from the reaction between HCl and $EtAlCl_2$

2.1.2. Synthesis of methacryloylferrocene 7

After obtaining satisfactory results, we wanted to apply the same procedure to the synthesis of the other ferrocenylenones. When methacryloyl chloride was reacted with ferrocene **1** in the presence of $EtAlCl_2$-Me_3Al, methacryloylferrocene **7** was isolated in 71% yield. For this compound, literature has only one patent reference for its polymers but no information about the synthesis [43]. This work is also the first example of a one step synthesis of methacryloylferrocene.

Table 1. Friedel-Crafts reactions of acyl chlorides with ferrocene

Entry	Acyl Chloride	Lewis Acid	Product	Yield(%)[a]
1	H_2C=CHCOCl	$EtAlCl_2$	**5, 4, 6** (6.9/1.9/1.0)	78[b]
2	H_2C=CHCOCl	Me_3Al	**5**	30[c]
3	H_2C=CHCOCl	$EtAlCl_2/Me_3Al$	**5**	83[c]
4	H_2C=CMeCOCl	$EtAlCl_2/Me_3Al$	**7**	71
5	MeHC=CHCOCl	$EtAlCl_2$	**8**	87
6	PhHC=CHCOCl	$EtAlCl_2$	**9**	89
7	Me_2C=CHCOCl	$EtAlCl_2$	**10**	80
8	$ClCH_2COCl$	$EtAlCl_2/Me_3Al$	**11**	56

[a] Yields are isolated yields. Unreacted ferrocene, 5-10% for the entries 1, 3, 4, 5, 6, and 7 and around 35% for the entries 2 and 8, was recovered.

[b] Extending the time to 6 h did not change the yield and the product ratio significantly, numbers in parenthesis show the approximate ratio of the compounds, respectively.

[c] Minor amounts of **3** and **5** were also seen on the ^{1}H-NMR spectrum of the crude reaction mixture.

Ferrocenophane formation did not take place with β-substituted acryloyl chloride derivatives because the β-substituent destabilizes metal–carbon bond of intermediate **2** (Figure 22) both electronically and sterically. Therefore we were able to synthesize β-substituted acryloyl ferrocene derivatives using only $EtAlCl_2$ as the Lewis acid (Figure 28) .

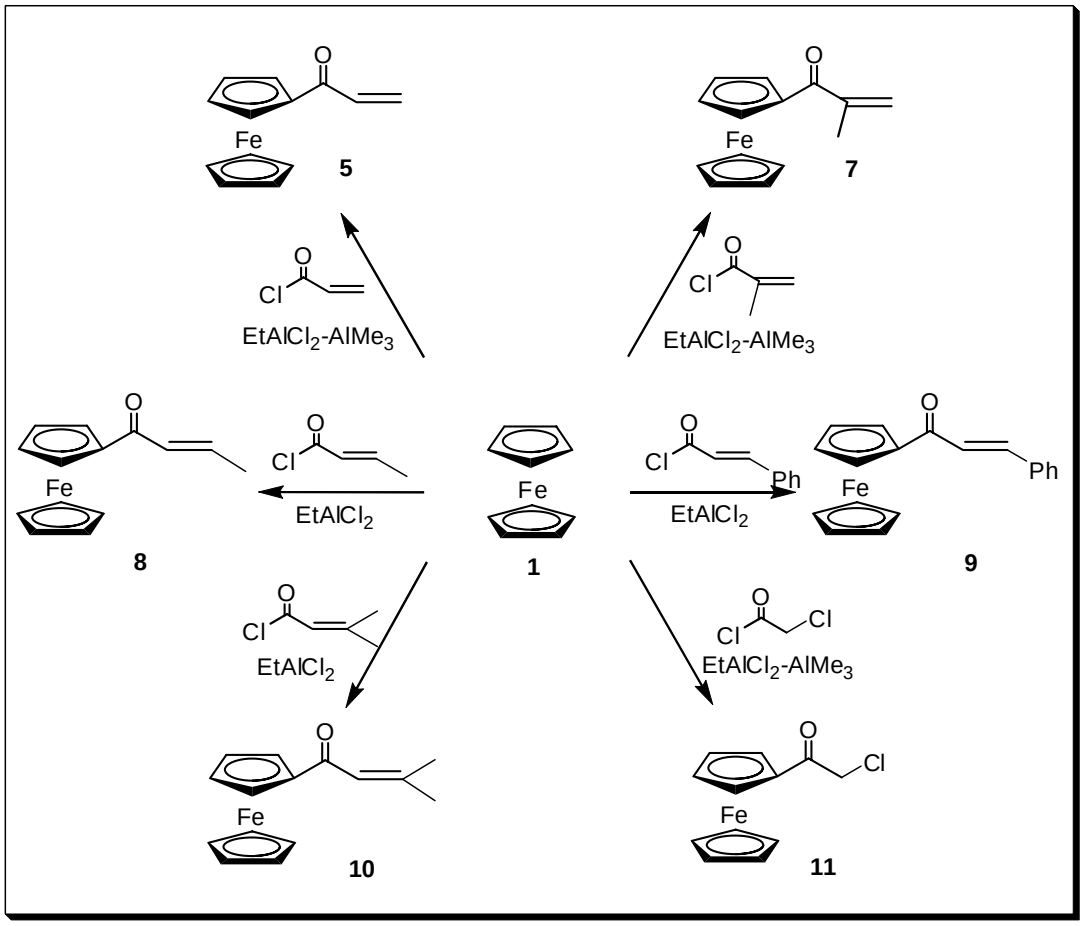

Figure 28. Synthesis of ferroceneylenones

2.1.3. Synthesis of crotonyl ferrocene 8

We have also applied this method to the synthesis of crotonoylferrocene. Reaction of crotonoyl chloride with ferrocene in the presence of $EtAlCl_2$ gave expected crotonoylferrocene **8** in 87% isolated yield.

2.1.4. Synthesis of cinnamoylferrocene 9

The commonly used method for the synthesis of this compound is the aldol condensation of acetylferrocene and benzaldehyde [44]. Using our method (cinnamoyl chloride + ferrocene + $EtAlCl_2$), the title compound **9** was synthesized in 93% yield.

2.1.5. Synthesis of β-methylcrotonoylferrocene 10

In this series, β-methylcrotonoyl chloride was used as the last substrate which resulted in the formation of β-methylcrotonoylferrocene **10** in 80% isolated yield.

2.1.6. Synthesis of α-chloroacetylferrocenes 11

α-Haloacetylferrocenes are important starting materials especially in the synthesis of ferrocenyl-substituted heterocyclic compounds [45]. In the literature, α-chloroacetylferrocene **11** was synthesized by Friedel–Crafts acylation of chloroacetyl chloride and ferrocene with $AlCl_3$ in about 43% yield, together with acetylferrocene [46]. Lower yield was attributed to an electron transfer from ferrocene to acylium ion to give the oxidised ferrocenium cation in high yield [47]. Our method gave the same compound in a better isolated yield (56%).

2.2. Synthesis of Aziridines

Since aziridines are very useful compounds, we decided to synthesize new ferrocenyl substituted aziridines by using Gabriel-Cromwell reaction.

2.2.1. Gabriel-Cromwell reaction by using acryloylferrocene 5 as a starting material

In the first series, readily available acryloylferrocene **5** was first brominated to give the corresponding dibromo compound **12** in 98% isolated yield (Figure 29).

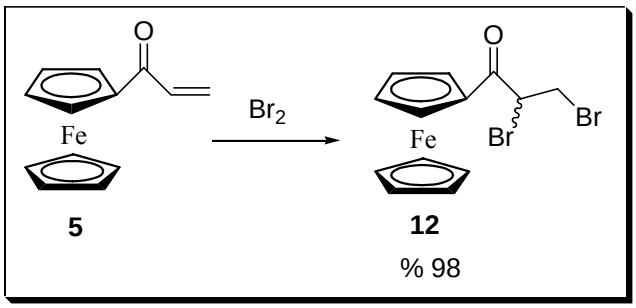

Figure 29. Bromination of acryloyl ferrocene

Initially we had difficulties in direct bromination of acryloylferrocene **5** since it is not an easy reaction. We tried different reaction temperatures, concentrations, and slow addition of bromine but none of them was successful. Bromine reacts with the cyclopentadienyl units of ferrocene moiety and also with iron to give salts.

To solve this problem, W. Liu at al. [48] trapped the ferrocenyl unit in β-cyclodextrin and carried out the bromination just by adding bromine to the reaction medium (Figure 30). Although the reaction gave the dibromo compound in 84% yield, it is not practical, requires two extra steps (cyclodextrin protection and removal). In addition protection and deprotection steps are not easy and high yielding steps.

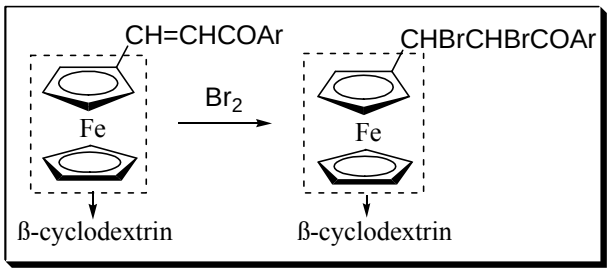

Figure 30. Bromination via protection of ferrocene moiety with β-cyclodextrin

After finding a simple procedure (fast addition of bromine to a vigorously stirred acryloylferrocene solution at -78 ^{o}C), for bromination and synthesizing the dibromo compound in high yield, the next step was the synthesis of α-bromoacryloyferrocene **13** which was easily achieved by treatment of dibromo compound with Et_3N. Compound **13** can be purified by flash chromatography or reacted with benzylamine in the same reaction flask to give aziridine **14** in 93% isolated yield (Figure 31).

Under the same reaction conditions, isopropylamine gave aziridine **16** in 90% isolated yield. A similar reaction of furfurylamine resulted in the formation of aziridine **15** in 91% yield after simple flash chromatography (Figure 31).

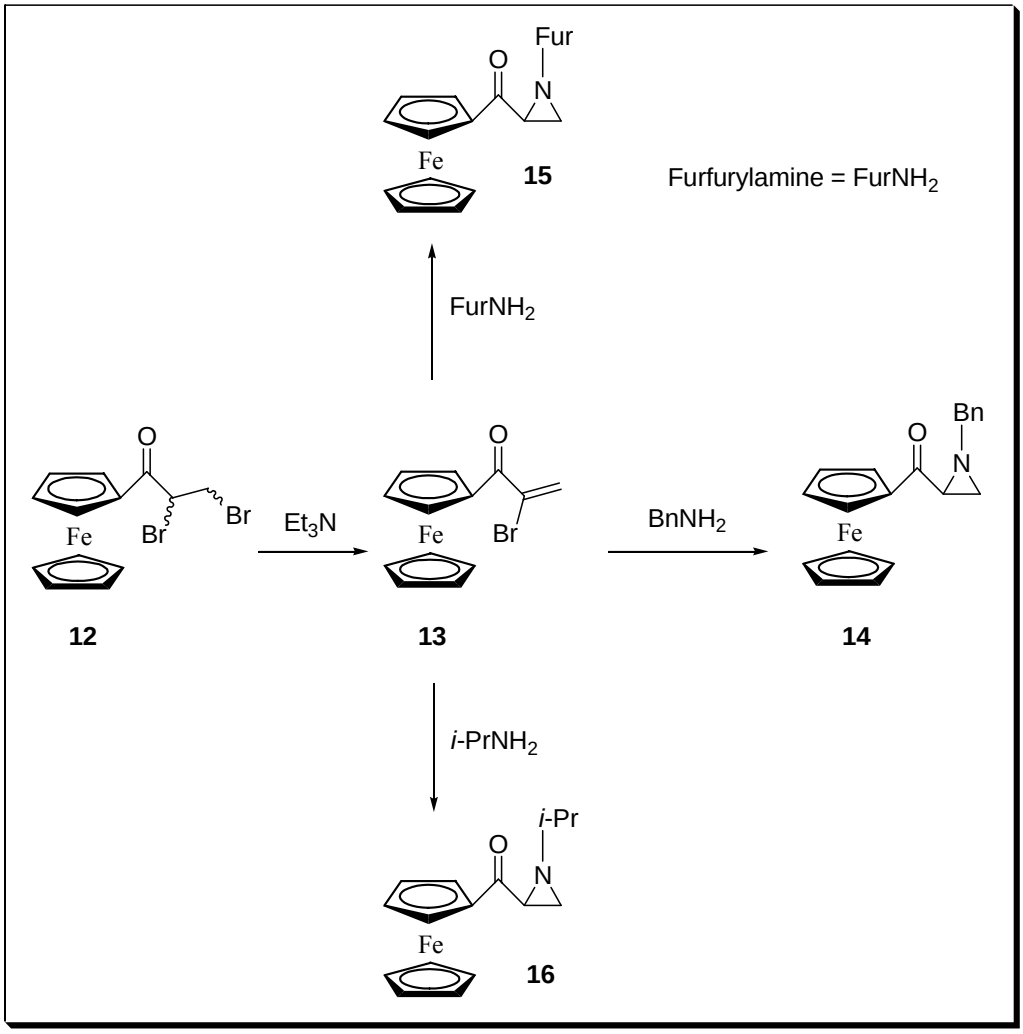

Figure 31. Synthesis of aziridines **14**, **15**, and **16**.

2.2.2. Gabriel-Cromwell reaction by using crotonylferrocene as a starting material

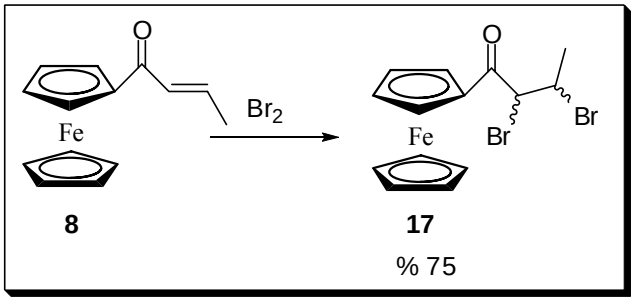

Figure 32. Bromination of crotonylferrocene

In the second series, crotonoylferrocene **8** was used as the starting material for the aziridination reaction. Bromination reaction of **8** gave the dibromo compound **17** in 75% isolated yield (Figure 32). The procedure used for the bromination of acryloylferrocene was not successful in this case. We tried bromination at low temperatures (-78 ^{o}C, -50 ^{o}C, and 0 ^{o}C), at low concentrations (0.05M, 0.30M, and 0.10M), and in different solvents (dichloromethane, chloroform, and pentane). The best results were obtained with slow addition of 1.50 mol equivalent of bromine in CCl_4 to 0.10 M solution of starting material in pentane. During bromination, a dark colored residue containing both starting material **8** and dibromo compound **17** was formed. To isolate these compounds, the residue was dissolved in dichloromethane and extracted with HCl (see the experimental). We were unable to characterize the remaining part of this residue, but we speculate that it was a halogenated form of ferrocenyl unit [48].

To synthesize the aziridines, dibromo compound **17** was treated with the same amines used in the first series. When triethylamine (for β-elimination) was reacted with dibromocompound **17**, *cis* and *trans* isomers of compound **18** were formed These compounds can be isolated and characterized. The reaction of **18** with

benzylamine gave the corresponding aziridine **19** as a 1:1 mixture of *cis* and *trans* isomers in 90% yield (Figure 33).

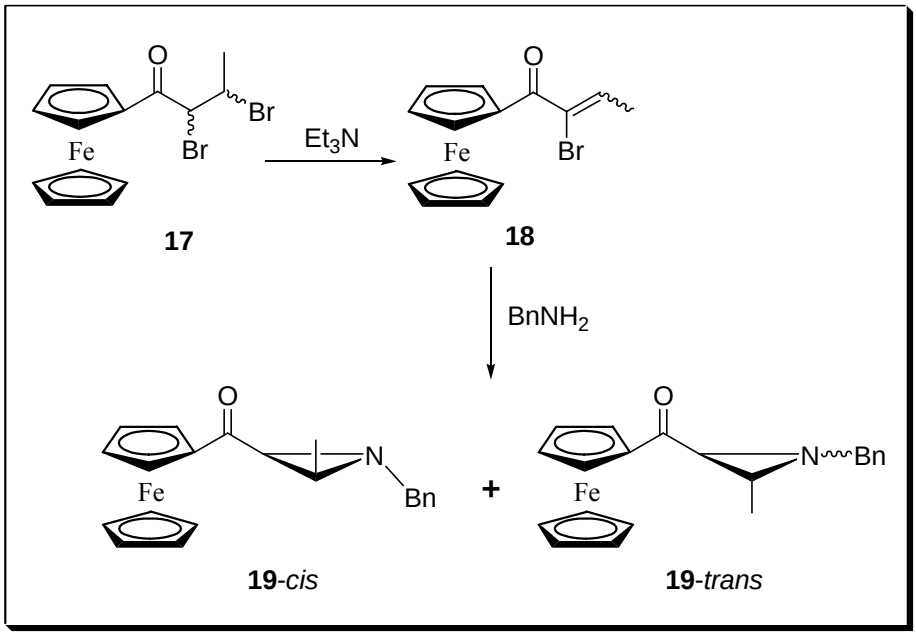

Figure 33. Aziridination with benzyl amine

When furfurylamine was used in the aziridination reaction, aziridine **20** was formed as a 1:1 mixture of *cis* and *trans* isomer in 89 % yield (Figure 34).

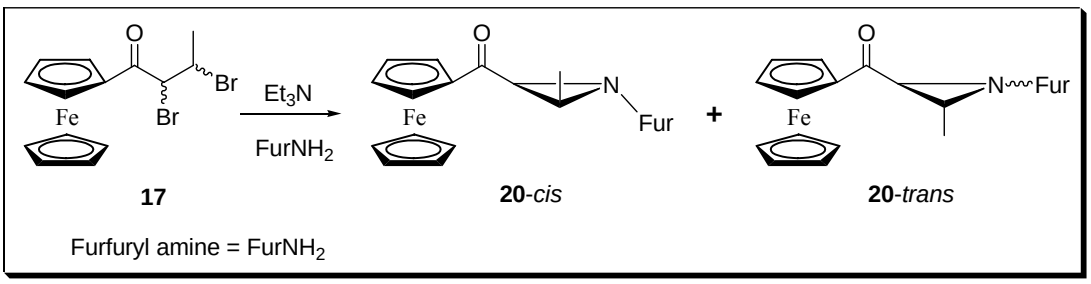

Figure 34. Aziridination with furfuryl amine

By using the same procedure with *i*-propylamine, aziridines **21** was synthesized as a 1:1 mixture of *cis* and *trans* isomers in 91 % yield (Figure 35).

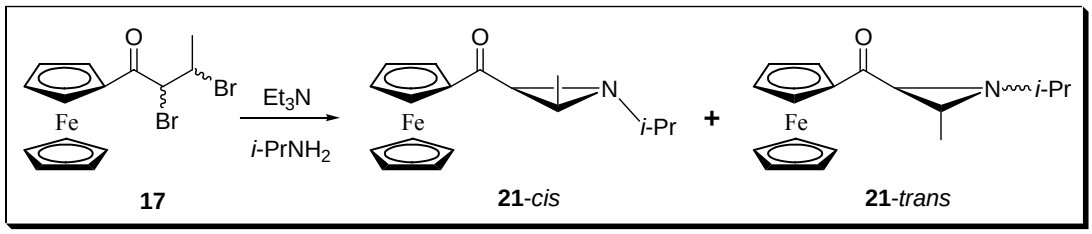

Figure 35. Aziridination with *i*-propyl amine

On the ^{1}H-NMR spectrum of aziridine **19-***cis* all the protons are seen clearly (Figure 36). Phenyl protons give signals between 7.0 and 8.0 ppm as multiplet. For the ferrocenyl unit unsubstituted ring gives a sharp signal for its five protons at 4.0 ppm and three signals for its substituted ring between 4-5 ppm. There is an AB-system for the benzylic protons at 3.3 and 4.0 ppm. The signals of the aziridine ring appear at 2.7, 2.1 and 1.2 ppm. The signal corresponding to the methyl protons is seen at 1.2 ppm.

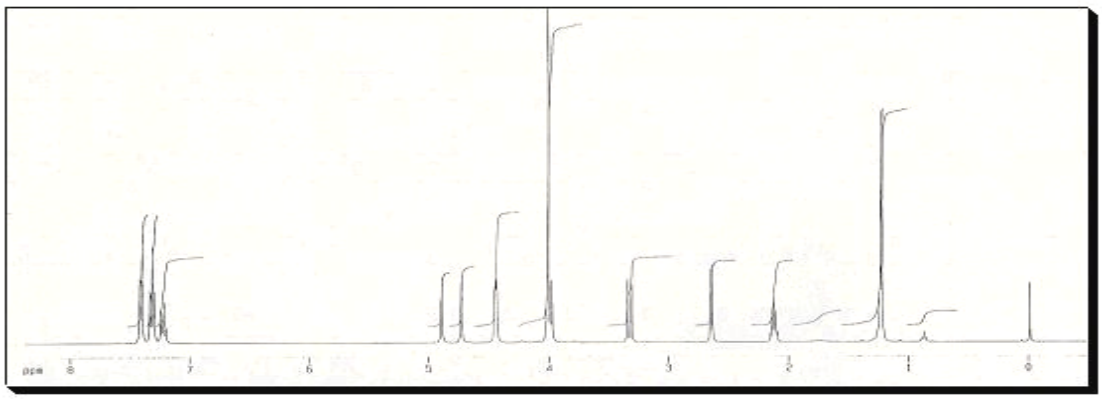

Figure 36. NMR spectrum of cis isomer of **19**-*cis*

Although clear ^{1}H-NMR (Figure 36) and ^{13}C-NMR (Figure A 16) spectra were obtained for the *cis*-aziridines, the same spectra of *trans*-aziridine **19**-*trans* were obtained as a mixture of N-invertomers [49] (Figure 37).

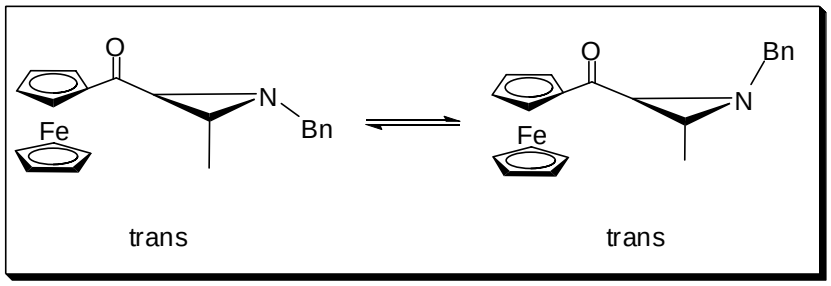

Figure 37. Invertomers of trans isomer **19**-*trans*

The signals of the *trans* aziridines are doubled on the ^{1}H-NMR (Figure 38) and ^{13}C-NMR spectra (Figure A18).

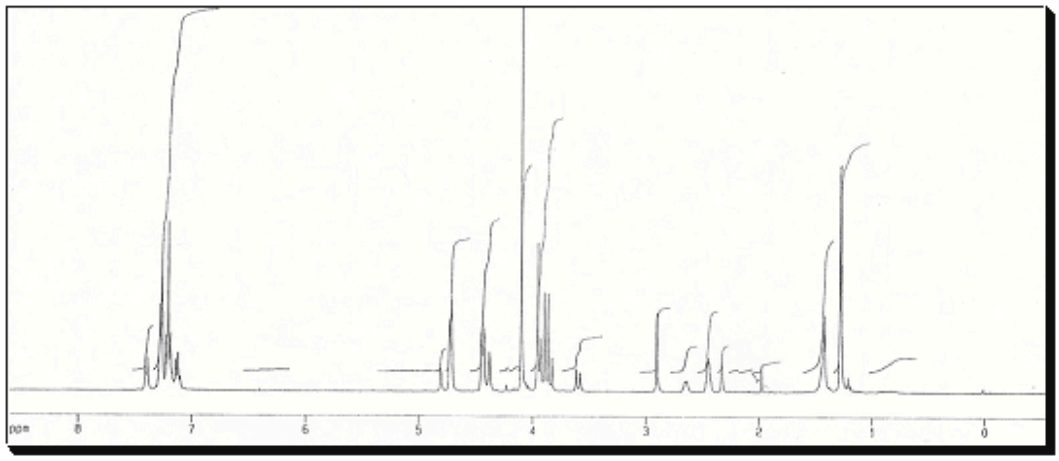

Figure 38. NMR spectrum of trans invertomers

In the case of aziridine **19-***trans*, x-ray crystal structure was obtained (Figure 39) [50]. On this structure, the ferrocenoyl and methyl groups are *trans* to each other and the benzyl group on the nitrogen lies on the same side as the ferrocenoyl group.

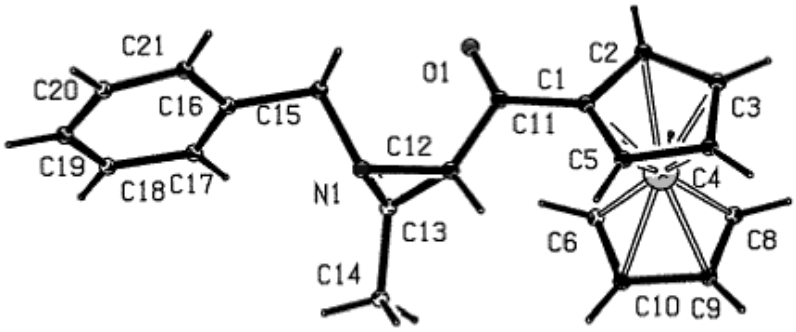

Figure 39. Crystal Structure of aziridine **19**-*trans*

CHAPTER 3

CONCLUSION

We have synthesized synthetically important novel aziridines having a ferrocenyl group successfully by Gabriel-Cromwell reaction. Starting from acryloyl and crotonoylferrocene novel aziridines were synthesized in excellent yields. Aziridines with *trans*-2,3-disubstituents were obtained as nitrogen invertomers which were easily observed in the ^{1}H and ^{13}C NMR spectra of these compounds. In addition, all new aziridines have been fully characterized.

Also, we developed a very efficient method for the synthesis of ferrocenylenones and α-chloroacetylferrocene using alkylaluminum Lewis acids ($EtAlCl_2$–Me_3Al). By using this method acryloylferrocene was synthesized in a single step on gram quantities. Although the isolated yield is lower in the case of α-chloroacetylferrocene, the reaction is very clean and a considerable amount of unreacted ferrocene (around 35%) is recovered.

A new procedure for the direct bromination of acryloyl and crotonoylferrocenes was also developed in this study.

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained in CCl_4-$CDCl_3$ (2:3) solvent system, recorded in a Brucker Spectrospin Avance DPX-400 Ultra shield instrument and reported in ppm on the δ scale relative to residual $CHCl_3$ (δ 7.24 and 77.0). IR spectra were obtained in CH_2Cl_2 unless otherwise indicated, recorded on a Perkin Elmer 1600 series FT-IR spectrometer and reported in reciprocal centimeters (cm^{-1}). All acyl chlorides and amines were distilled and kept under argon/nitrogen atmosphere for couple of months. Reagent grade solvents were used in the experiments. Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh). The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. Melting points are uncorrected. New compounds were named by using ChemDraw Ultra 8.0 program.

4.1. Synthesis of ferrocenylenones (General procedure 1)

To a stirred solution of ferrocene (199 mg, 1.07mmol) and α,β-unsaturated acyl chloride/chloroacetylchloride (1.28 mmol, freshly distilled) in CH_2Cl_2 (3.6mL, dried over CaH_2) at 0 ^{o}C was added Me_3Al (0.27mL, 0.53 mmol, 2 M in hexanes) and $EtAlCl_2$ (1.07mL, 1.07 mmol, 1 M in hexanes) drop by drop over 10min consecutively. This procedure was applied to the synthesis of compounds **5**, **7**, and **11.** For the synthesis of compounds **8**, **9**, and **10** only $EtAlCl_2$ (1.28mL, 1.28 mmol, 1 M in hexanes) was used as the Lewis acid. The resulting mixture was stirred for another 20 min (in the case of chloroacetyl chloride stirring continued for 80 min) at this temperature. At the end of this time, deep blue colored reaction mixture was hydrolyzed with water (10 mL), and more CH_2Cl_2 (10mL) was added to the

reaction flask. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel.

4.1.1. Synthesis of acryloylferrocene 5

Using the general procedure 1, ferrocene (3.00g, 16.13mmol), acryloyl chloride (1.75g, 19.30 mmol), Me_3Al (4.04mL, 8.07 mmol, 2 M in hexanes) and $EtAlCl_2$ (16.13mL, 16.13 mmol, 1 M in hexanes) gave the compound **5** (3.21 mg, 13.34 mmol) in 83.0% isolated yield.

R_f = 0.44, 5:1 hexanes/EtOAc; ^{1}H-NMR δ 6.79 (dd, *J* = 17.0 and 10.3 Hz, 1H, CH-α), 6.44 (dd, *J* = 17.0 and 1.6 Hz, 1H, olefinic proton trans to CH-α), 5.70 (dd, *J* = 10.3 and 1.6 Hz, 1H, olefinic proton *cis* to CH-α), 4.77 (t, *J* = 1.85 Hz, 2H, Fc), 4.54 (t, *J* = 1.85 Hz, 2H, Fc), 4.17 (s, 5H, Fc); ^{13}C-NMR δ 192.9, 133.3, 126.6, 80.1, 73.0 (2 x C), 70.4 (5 x C), 70.1 (2 x C); IR (KBr) 1653.7, 1598.7,1458.9, 1400.1, 1264.1, 1077.1, 998.9, 820 cm^{-1}.

4.1.2. Synthesis of methacryloylferrocene 7

Using the general procedure 1, ferrocene (3.00g, 16.13mmol), methacryloyl chloride (2.02g, 19.30 mmol), Me_3Al (4.04mL, 8.07 mmol, 2 M in hexanes) and $EtAlCl_2$ (16.13mL, 16.13 mmol, 1 M in hexanes) gave the compound **7**. (2.91g, 11.45mmol) in 71.0% isolated yield.

R_f = 0.37, 5:1 hexanes/EtOAc; ^{1}H-NMR δ 5.72 (s, 1H, olefinic proton), 5.52 (s, 1H, olefinic proton), 4.75 (s, 2H, Fc), 4.42 (s, 2H, Fc), 4.10 (s, 5H, Fc), 1.98 (s, 3H, CH_3); ^{13}C-NMR δ 200.6, 145.7, 121.3, 78.5, 72.7 (2 x C), 71.6 (2 x C), 70.5 (5 x C), 20.0; IR (KBr) 1640.1, 1445.5, 1377.9 1224.6, 1066.5, 824.4, 482.1 cm^{-1}; Anal. Calc. for $C_{14}H_{14}FeO$: C, 66.17; H, 5.55. Found: C, 65.95; H, 5.40.

4.1.3. Synthesis of crotonylferrocene 8

Using general procedure 1, ferrocene (3.00g, 16.13mmol), crotonyl chloride (2.02g, 19.30 mmol) and $EtAlCl_2$ (19.36mL, 19.36 mmol, 1 M in hexanes) gave the compound **8**. (3.57g, 14.03mmol) in 87.0% isolated yield.

R_f = 0.59, 5:1 hexanes/EtOAc; ^{1}H-NMR δ 7.03 (dq, *J* = 15.2 and 6.94 Hz, 1H, CH-α), 6.52 (dd, *J* = 15.2 and 1.6 Hz, 1H, olefinic proton), 4.79 (t, *J* = 1.86 Hz, 2H, Fc), 4.50 (t, *J* = 1.86 Hz, 2H, Fc), 4.17 (s, 5H, Fc), 1.97 (dd, *J* = 6.94 Hz and 1.6 Hz, 3H, CH_3); ^{13}C-NMR δ 192.4, 140.4, 128.1, 80.1, 72.3 (2 x C), 69.9(5 x C), 69.6 (2 x C), 18.3; IR (KBr) 2359.5, 1661.4,1609.3, 1458.9, 1294.9, 980.6, 823.5, 668.2 cm^{-1}.

4.1.4. Synthesis of cinnamoylferrocene 9

Using general procedure 1, ferrocene (3.00g, 16.13mmol), cinnamoyl chloride (3.22g, 19.30 mmol) and $EtAlCl_2$ (19.36mL, 19.36 mmol, 1 M in hexanes) gave the compund **9** (4.54g, 14.36 mmol) in 89.0% isolated yield.

R_f = 0.52, 5:1 hexanes/EtOAc; ^{1}H-NMR δ 7.78 (d, *J* = 15.6Hz, 1H, CH-α), 7.64 (m, 2H, Ph), 7.41 (m, 3H, Ph), 7.11 (d, *J* = 15.6 Hz, 1H, CH-β), 4.90 (t, *J* = 1.84 Hz, 2H, Fc), 4.57 (t, *J* = 1.84 Hz, 2H, Fc), 4.20(s, 5H, Fc); ^{13}C-NMR δ 192.4, 140.9, 135.2, 130.0, 128.9 (2 x C), 128.2 (2 x C), 122.9, 80.7, 72.6 (2 x C), 70.0 (5 x C), 69.7 (2 x C); IR (KBr) 2362.5, 1647.9, 1597.7, 1447.9, 1376.9, 992.2, 757.9, 687.5 cm^{-1}.

4.1.5. Synthesis of β-methylcrotonylferrocene 10

Using general procedure 1, ferrocene (3.00g, 16.13mmol), 3-methylcrotonyl chloride (2.29g, 19.30 mmol) and $EtAlCl_2$ (19.36mL, 19.36 mmol, 1 M in hexanes) gave the compound **10** (3.46g, 12.90 mmol) in 80.0% isolated yield.
R_f = 0.40, 5:1 hexanes/EtOAc; ^{1}H-NMR δ 6.34 (s, 1H,olefinic proton), 4.75 (t, *J* = 1.86 Hz, 2H, Fc), 4.44 (t, *J* = 1.86 Hz, 2H, Fc), 4.16 (s, 5H, Fc), 2.21 (s, 3H, CH_3), 1.97 (s, 3H, CH_3); ^{13}C-NMR δ 194.6, 153.5, 122.3, 82.0, 72.2 (2 x C), 70.1 (5 x C), 69.8 (2 x C), 28.3, 21.3; IR (KBr) 3085.6, 1647.9,1602.6, 1456.0, 1375.0, 1263.2, 1109.8, 1053.9, 1000.9, 826.4, 790.7, 506.2 cm^{-1}.

4.1.6. Synthesis of α-chloroacetylferrocene 11

Using the general procedure 1, ferrocene (3.00g, 16.13mmol), α-chloroacetyl chloride (2.18g, 19.30 mmol), Me_3Al (4.04mL, 8.07 mmol, 2 M in hexanes) and $EtAlCl_2$ (16.13mL, 16.13 mmol, 1 M in hexanes) gave the compound **11** (2.37g, 9.03 mmol) in 56.0% isolated yield.

R_f = 0.5, 5:1 hexanes/EtOAc; ^{1}H-NMR δ 4.82 (t, *J* = 1.84 Hz, 2H, Fc), 4.57 (t, *J* = 1.84 Hz, 2H, Fc), 4.37 (s, 2H, CH_2), 4.23 (s, 5H, Fc); ^{13}C-NMR δ 194.8, 76.0, 72.9 (2 x C), 70.1 (5 x C), 69.7 (2 x C), 45.8; IR (KBr) 2925.5, 1677.8, 1452.1, 1405.9, 1239.1, 1069.3, 822.5, 720.3, 491.8 $cm^{-1.}$

4.2.Synthesis of aziridines

4.2.1. Procedure 2. Representative experimental procedure for bromination

Bromine (4.57 mmol, 0.6M in CH_2Cl_2) was added to a vigorously stirred solution of acryloylferrocene (1.00g, 4.17 mmol) in CH_2Cl_2 at -78 ^oC in less than 5 min. At the end of this addition period, the reaction was judged to complete by TLC. Crude

reaction mixture was filtered from a short column using silica gel and $CHCl_3$ as the eluent. Evaporation of the solvent gave a pure dibromo compound **12** (1.63g, 4.08 mmol) in 98.0% yield.

Since the same procedure failed to give the dibromocompound **17** in high yield, we employed a different procedure: Bromine (1.18 mmol, 1M in CCl_4) was added slowly over 30 min to a stirred solution of crotonoylferrocene **8** (200 mg, 0.787 mmol) in pentane (2.5 mL) at room temperature. At the end of this addition period, the reaction was judged to complete by TLC and quenched with water. More hexane (10 mL) was added to the reaction flask and two layers were separated. Aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The black residue remaining in the reaction flask was dissolved in CH_2Cl_2 (10 mL) and extracted with 1N HCl (10 mL). All the organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by chromatography on silica gel gave pure dibromo compound (244 mg, 0.590 mmol) in 75.0% isolated yield.

4.2.2. Procedure 3. Representative experimental procedure for aziridine formation

Triethylamine (0.75 mmol, 105 μL) and benzylamine (1.00 mmol, 105 μL) were added to a stirred solution of 2,3-dibromopropanoylferrocene (**12**) (200mg, 0.5mmol) in $CHCl_3$ (2 mL) at rt. The mixture was stirred for 6-10 h at which point TLC analysis showed no starting material. Thus, the reaction mixture was applied to a flash column for purification, no workup was necessary. From the column, aziridine **14** (160 mg, 0.464 mmol) was isolated in 93.0% yield.

4.2.3. Synthesis of 2-Bromo-1-ferrocenylprop-2-en-1-one (**13**)

Treatment of dibromo compound **12** (200mg, 0.5mmol) in CH_2Cl_2 (2 mL) with triethylamine (0.75 mmol, 105 μL) gave compound **13** (155mg, 0.485mmol) in 97.0% isolated yield.

R_f = 0.3, 9:1 hexanes/EtOAc; mp: 67-69 °C; ^{1}H-NMR δ 6.48 (br s, 1H, H-β), 6.19 (br s, 1H, H-β), 4.88 (s, 2H, Fc), 4.58 (s, 2H, Fc), 4.23 (s, 5H, Fc); ^{13}C-NMR δ 191.3, 128.2, 123.1, 74.7, 72.1, 70.1, 69.6; IR 1647.7, 1444.3, 1276.7, 1049.4, 828.0 cm^{-1}. Anal. Calcd. for $C_{13}H_{11}BrFeO$: C, 48.95; H, 3.48. Found: C, 48.84; H, 3.39.

4.2.4. Synthesis of (1-Benzylaziridin-2-yl)(ferrocenyl)methanone (**14**)

Using general procedure 3, dibromo compound **12** (200mg, 0,50mmol), triethylamine (0.75 mmol, 105 μL) and benzylamine (1.00 mmol, 109 μL) gave compound **14** (161mg, 0.466mmol) in 93.0% isolated yield.

R_f = 0.1, 2:1 hexanes/EtOAc; mp: 106-108 °C; ^{1}H-NMR δ 7.43-7.26 (5H, Ph), 4.83 (s, 1H, Fc), 4.77 (s, 1H, Fc), 4.46 (s, 2H, Fc), 4.03 (s, 5H, Fc), 3.92 (d, *J* = 13.3 Hz, 1H, ½ CH_2Ph), 3.30 (d, *J* = 13.2 Hz, 1H, ½ CH_2Ph), 2.56 (dd, *J* = 6.1 & 3.0 Hz, 1H, H-α), 2.39 (m, 1H, H-β), 1.82 (d, *J* = 6.3 Hz, 1H, H-β); ^{13}C-NMR δ 199.7, 138.5, 128.9, 128.7, 127.8, 78.7, 72.8, 72.6, 70.1, 70.0, 69.9, 65.3, 42.3, 36.9; IR 3042.7, 1665.8, 1456.4, 1396.6, 1259.0, 1145.3, 1103.4, 1073.5, 1025.6, 828.2 cm^{-1}. Anal. Calcd. for $C_{20}H_{19}FeNO$: C, 69.58; H, 5.55; N, 4.06. Found: C, 69.46; H, 5.48; N, 4.01.

4.2.5. Synthesis of (1-Isopropylaziridin-2-yl)(ferrocenyl)methanone (**16**)

Using general procedure 3, dibromo compound **12** (200mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and *i*-propyl amine (1.00 mmol, 85 μL) gave compound **16** (134mg, 0.450mmol) in 90.0% isolated yield.

R_f = 0.1, 2:1 hexanes/EtOAc; mp: 59-61 °C; ^{1}H-NMR δ 4.94 (s, 1H, Fc), 4.87 (s, 1H, Fc), 4.51 (s, 2H, Fc), 4.21 (s, 5H, Fc), 2.46 (dd, *J* = 6.2 & 2.7 Hz, 1H, H-α),

2.27 (br s, 1H, H-β), 1.66 (d, *J* = 6.4 Hz, 1H, H-β), 1.60 (m, 1H, $CHMe_2$), 1.24 (d, *J* = 6.2 Hz, 3H, CH_3), 1.20 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C-NMR δ 200.0, 78.8, 72.8, 72.7, 70.2, 70.1, 69.8, 62.0, 41.8, 36.1, 22.7, 22.3; IR 2970.9, 1665.8, 1456.4, 1384.6, 1342.7, 1259.0, 1175.2, 1067.5, 1001.7, 828.2 cm^{-1}. Anal. Calcd. for $C_{16}H_{19}FeNO$: C, 64.67; H, 6.44; N, 4.71. Found: C, 64.58; H, 6.40; N, 4.68.

4.2.6. Synthesis of (1-((Furan-2-yl)methyl)aziridin-2-yl)(ferrocenyl)methanone (**15**)

Using general procedure 3, dibromo compound **12** (200mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and furfuryl amine (1.00 mmol, 88 μL) gave compound **15** (152mg, 0.464mmol) in 91.0% isolated yield.

R_f = 0.1, 2:1 hexanes/EtOAc; mp: 97-99 °C; ^{1}H-NMR δ 7.38 (s, 1H, furyl), 6.33 (s, 1H, furyl), 6.31 (s, 1H, furyl), 4.89 (s, 1H, Fc), 4.82 (s, 1H, Fc), 4.49 (s, 2H, Fc), 4.14 (s, 5H, Fc), 3.85 (d, *J* = 13.8 Hz, 1H, ½ CH_2furyl), 3.41 (d, *J* = 13.9 Hz, 1H, ½ CH_2furyl), 2.67 (m, 1H, H-α), 2.34 (br s, 1H, H-β), 1.83 (d, *J* = 6.2 Hz, 1H, H-β); ^{13}C-NMR δ 199.5, 152.0, 142.6, 110.8, 108.8, 78.7, 72.9, 72.7, 70.2, 70.0, 69.9, 56.4, 41.6, 35.6; IR 2253.0,1665.8, 1456.4, 1061.5, 1001.7, 906.0, 792.3 cm^{-1}. Anal. Calcd. for $C_{18}H_{17}FeNO_2$: C, 64.50; H, 5.11; N, 4.18. Found: C, 64.44; H, 5.04; N, 4.12.

4.2.7. Synthesis of 2,3-Dibromo-1-ferrocenylbutan-1-one (**17**)

Using general procedure 2, compound **8** (200 mg, 0.787 mmol) and bromine (1.18 mmol, 1M in CCl_4) gave dibromo compound **17** (244 mg, 0.590 mmol) in 75.0% isolated yield

R_f = 0.33, 5:1 hexanes/EtOAc; mp: 88-90 °C; ^{1}H-NMR δ 4.88 (m, 1H, Fc), 4.85 (d, *J* = 10.5 Hz, 1H, H-α), 4.76 (m, 1H, Fc), 4.65 (dq, *J* = 10.5, 6.7 Hz, 1H, H-β), 4.60 (m, 1H, Fc), 4.55 (m, 1H, Fc), 4.31 (s, 5H, Fc), 2.01 (d, *J* = 6.7 Hz, 3H, CH_3);

^{13}C-NMR δ 195.1, 76.4, 72.6, 72.5, 70.3 (5C), 69.8, 69.7, 51.7, 44.8, 24.8; IR (KBr) 1660.9, 1452.2, 1373.9, 1282.6, 1243.4, 1017.4, 808.7 cm^{-1}. Anal. Calcd. for $C_{14}H_{14}Br_2FeO$: C, 40.62; H, 3.41. Found: C, 40.51; H, 3.33.

4.2.8. Synthesis of 2-Bromo-1-ferrocenylbut-2-en-1-one (**18**-*E/Z)*

Treatment of dibromo compound **17** (207mg, 0.5mmol) in CH_2Cl_2 (2 mL) with triethylamine (0.75 mmol, 105 μL) gave compound **18-***E/Z* (79mg, 0.24mmol) in 48.0% isolated yield.

R_f = 0.31, 9:1 hexanes/EtOAc; mp: 84-86 °C; ^{1}H-NMR δ 6.30 (q, *J* = 7.4 Hz, 1H, H-β), 4.87 (t, *J* = 1.9 Hz, 2H, Fc), 4.58 (t, *J* = 1.9 Hz, 2H, Fc), 4.28 (s, 5H, Fc), 1.72 (d, *J* = 7.4 Hz, 3H, CH_3); ^{13}C-NMR δ 195.9, 132.3, 117.1, 77.3, 73.4, 71.1, 71.0, 17.3; IR 1647.7, 1450.2, 1264.8, 1067.3, 828.0 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}BrFeO$: C, 50.50; H, 3.93. Found: C, 50.42; H, 3.87.

4.2.9. Synthesis of 2-Bromo-1-ferrocenylbut-2-en-1-one (**18**-*E/Z)*

Treatment of dibromo compound **17** (207mg, 0.5mmol) in CH_2Cl_2 (2 mL) with triethylamine (0.75 mmol, 105 μL) gave compound **18-***E/Z* (79mg, 0.24mmol) in 48.0% isolated yield.

R_f = 0.27, 9:1 hexanes/EtOAc; mp: 50-52 °C; ^{1}H-NMR δ 6.89 (q, *J* = 6.7 Hz, 1 H, H-β), 4.84 (t, *J* = 1.9 Hz, 2 H, Fc), 4.54 (t, *J* = 1.9 Hz, 2 H, Fc), 4.21 (s, 5 H, Fc), 2.00 (d, *J* = 6.7 Hz, 3 H, CH_3); ^{13}C-NMR δ 192.7, 135.7, 126.7, 77.3, 73.0, 71.6, 70.8, 18.0; IR 1641.7, 1438.3, 1264.8, 828.0 cm^{-1}. Anal. Calcd. for $C_{14}H_{13}BrFeO$: C, 50.50; H, 3.93. Found: C, 50.44; H, 3.85.

4.2.10. Synthesis of (1-Benzyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**19**-*cis*)

Using general procedure 3, dibromo compound **17** (207mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and benzylamine (1.00 mmol, 109 μL) gave compound **19-*cis*** (81mg, 0.225mmol) in 45.0% isolated yield.

R_f = 0.18, 2:1 hexanes/EtOAc; mp: 100-102 °C; ^{1}H-NMR δ 7.42 (d, *J* = 7.4 Hz, 2H, Ph), 7.33 (t, *J* = 7.5 Hz, 2H, Ph), 7.24 (m, 1 H, Ph), 4.91 (s, 1H, Fc), 4.74 (s, 1H, Fc), 4.46 (m, 2H, Fc), 4.02 (s, 5H, Fc), 4.00 (d, *J* = 13.1 Hz, 1H, ½ CH_2Ph), 3.34 (d, *J* = 13.6 Hz, 1H, ½ CH_2Ph), 2.65 (d, *J* = 6.8 Hz, 1H, H-α), 2.13 (m, 1H, H-β), 1.24 (d, *J* = 5.6 Hz, 3H, CH_3); ^{13}C-NMR δ 198.8, 138.6, 128.8, 128.4, 127.7, 79.8, 72.5, 70.1, 70.0, 69.6, 64.8, 47.6, 44.7, 13.4; IR 1665.8, 1456.4, 1265.0, 1073.5, 828.2 cm^{-1}. Anal. Calcd. for $C_{21}H_{21}FeNO$: C, 70.21; H, 5.89; N, 3.90. Found: C, 70.19; H, 5.85; N, 3.88.

4.2.11. Synthesis of (1-Benzyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**19**-*trans*)

Using general procedure 3, dibromo compound **17** (207mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and benzylamine (1.00 mmol, 109 μL) gave compound **19-*trans*** (81mg, 0.225mmol) in 45.0% isolated yield.

R_f = 0.24, 2:1 hexanes/EtOAc; mp: 111-113 °C; ^{1}H-NMR δ 7.39-7.09 (m, 5H, Ph), 4.80 (br s, Fc), 4.72 (m, Fc), 4.43 (m, Fc), 4.37 (br s, Fc), 4.09 (s, Fc), 3.94 (s, Fc), 3.87 (q, *J* = 13.5 Hz), 3.59 (d, *J* = 13.9 Hz, CH_2Ph), 2.89 (d, *J* = 2.7 Hz), 2.64 (m), 2.44 (m), 2.32 (m), 1.42 (d, *J* = 5.9 Hz, CH_3), 1.27 (d, *J* = 5.4 Hz, CH_3); ^{13}C-NMR δ 198.9, 198.3, 138.6, 137.9, 127.4, 127.2, 127.1, 126.9, 126.1, 125.7, 79.8, 77.3, 71.5, 71.4, 71.2, 71.0, 69.3, 68.6, 68.5, 67.6, 54.4, 53.5, 48.7, 44.3, 42.1, 41.2, 17.6, 10.2; IR (CH_2Cl_2) 2253.0, 1647.9, 1456.4, 906.0, 780.0 cm^{-1}. Anal. Calcd. For $C_{21}H_{21}FeNO$: C, 70.21; H, 5.89; N, 3.90. Found: C, 70.16; H, 5.83; N, 3.87.

4.2.12. Synthesis of (1-Isopropyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**21**-*cis*)

Using general procedure 3, dibromo compound **17** (207mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and *i*-propyl amine (1.00 mmol, 85 μL) gave compound **21**-*cis* (72mg, 0.228mmol) in 45.5% isolated yield.

R_f = 0.67, 5:1 Ether/CH_2Cl_2; mp: 75-77 °C; ^{1}H-NMR δ 4.88 (s, 1H, Fc), 4.75 (s, 1H, Fc), 4.42 (br s, 2H, Fc), 4.15 (s, 5H, Fc), 2.49 (d, *J* = 6.8, 1H, H-α), 1.90 (m, 1 H, H-β), 1.59 (m, $CHMe_2$), 1.15 (m, 9H, CH_3); ^{13}C-NMR δ 198.9, 79.9, 72.5, 72.4, 70.0, 69.7, 62.0, 47.4, 43.8, 22.2, 22.1, 13.7; IR 1731.6, 1372.6, 1247.0, 1043.6, 906.0, 786.3 cm^{-1}. Anal. Calcd. for $C_{17}H_{21}FeNO$: C, 65.61; H, 6.80; N, 4.50. Found: C, 65.56; H, 6.77; N, 4.44.

4.2.13. Synthesis of (1-Isopropyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**21**-*trans*)

Using general procedure 3, dibromo compound **17** (207mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and *i*-propyl amine (1.00 mmol, 85 μL) gave compound **21**-*trans*. (72mg, 0.228mmol) in 45.5% isolated yield.

R_f = 0.60, 5:1 Ether/CH_2Cl_2; mp: 77-79 °C; ^{1}H-NMR δ 4.86 (s, Fc), 4.75 (br s, Fc), 4.45 (m, Fc), 4.14 (s, Fc), 2.86 (br s), 2.72 (m), 2.55 (m), 2.34 (br s), 2.20 (br s), 1.42 (br s), 1.27 (br s), 1.15 (m), 1.06 (br s), 0.80 (br s); ^{13}C-NMR δ 200.6, 199.3, 81.2, 79.0, 73.0, 72.8, 72.5, 72.4, 71.2, 70.1, 70.0, 69.7, 69.3, 68.5, 51.9, 50.3, 48.8, 46.1, 42.8, 42.1, 23.3, 23.0, 22.9, 19.4, 11.4; IR 2982.9, 1731.6, 1444.4, 1372.6, 1270.9, 1247.0, 1043.6, 906.0, 786.3, 762.4 cm^{-1}. Anal. Calcd. for $C_{17}H_{21}FeNO$: C, 65.61; H, 6.80; N, 4.50. Found: C, 65.52; H, 6.72; N, 4.42.

4.2.14. Synthesis of (1-((Furan-2-yl)methyl)-3-methylaziridin-2-yl)(ferrocenyl)methanone (**20**-*cis*)

Using general procedure 3, dibromo compound **17** (207mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and furfuryl amine amine (1.00 mmol, 88 μL) gave compound **20**-*cis* (79mg, 0.223mmol) in 44.5% isolate yield.

R_f = 0.11, 2:1 hexanes/EtOAc; mp: 69-71 °C; ^{1}H-NMR δ 7.36 (br s, 1H, furyl), 6.32 (br s, 2H, furyl), 4.92 (s, 1H, Fc), 4.78 (s, 1H, Fc), 4.48 (s, 2H, Fc), 4.16 (s, 5H, Fc), 3.90 (d, *J* = 14.0 Hz, 1H, ½ CH_2furyl), 3.43 (d, *J* = 14.0 Hz, 1H, ½ CH_2furyl), 2.77 (d, *J* = 6.6 Hz, 1H, H-α), 2.15 (m, 1H, H-β), 1.21 (d, *J* = 5.0 Hz, 3H, CH_3); ^{13}C-NMR δ 198.6, 152.1, 142.4, 110.8, 108.4, 79.6, 72.6, 70.1, 70.0, 69.6, 56.3, 47.0, 43.4, 13.3; IR 2253.0, 1665.8, 1456.4, 906.0, 798.3 cm^{-1}. Anal. Calcd. for $C_{19}H_{19}FeNO_2$: C, 65.35; H, 5.48; N, 4.01. Found: C, 65.30; H, 5.45; N, 3.98.

4.2.15. Synthesis of (1-((Furan-2-yl)methyl)-3-methylaziridin-2yl)(ferrocenyl)methanone (**20**-*trans)*

Using general procedure 3, dibromo compound **17** (207mg, 0.50mmol), triethylamine (0.75 mmol, 105 μL) and furfuryl amine amine (1.00 mmol, 88 μL) gave compound **20**-*trans* (79mg, 0.223mmol) in 44.5% isolated yield.

R_f = 0.15, 2:1 hexanes/EtOAc; mp: 70-72 °C; ^{1}H-NMR δ 7.36, 7.31, 6.32, 6.22, 6.08 (s, furyl) 4.90, 4.80, 4.78, 4.53, 4.51, 4.47, 4.20, 4.13 (s, Fc), 3.94 (q, *J* = 14.1 Hz, CH_2furyl), 3.65 (d, *J* = 14.2 Hz, CH_2furyl), 2.96 (d, *J* = 2.8 Hz), 2.66 (m), 2.51 (m), 2.31 (s), 2.26 (s), 1.50 (d, *J* = 5.91 Hz, CH_3), 1.34 (d, *J* = 5.4 Hz, CH_3); ^{13}C-NMR δ 199.1, 153.1, 141.8, 125.9, 110.4, 110.0, 107.5, 107.1, 80.7, 72.6, 72.5, 72.3, 72.1, 70.4, 69.6, 69.4, 68.5, 49.5, 48.1, 47.2, 44.9, 43.0, 41.5, 21.3, 18.4, 11.2; IR 1647.9, 1456.4, 1265.0, 1079.5, 1007.7, 828.2 cm^{-1}. Anal. Calcd. for $C_{19}H_{19}FeNO_2$: C, 65.35; H, 5.48; N, 4.01. Found: C, 65.27; H, 5.42; N, 3.96.

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APPENDIX A

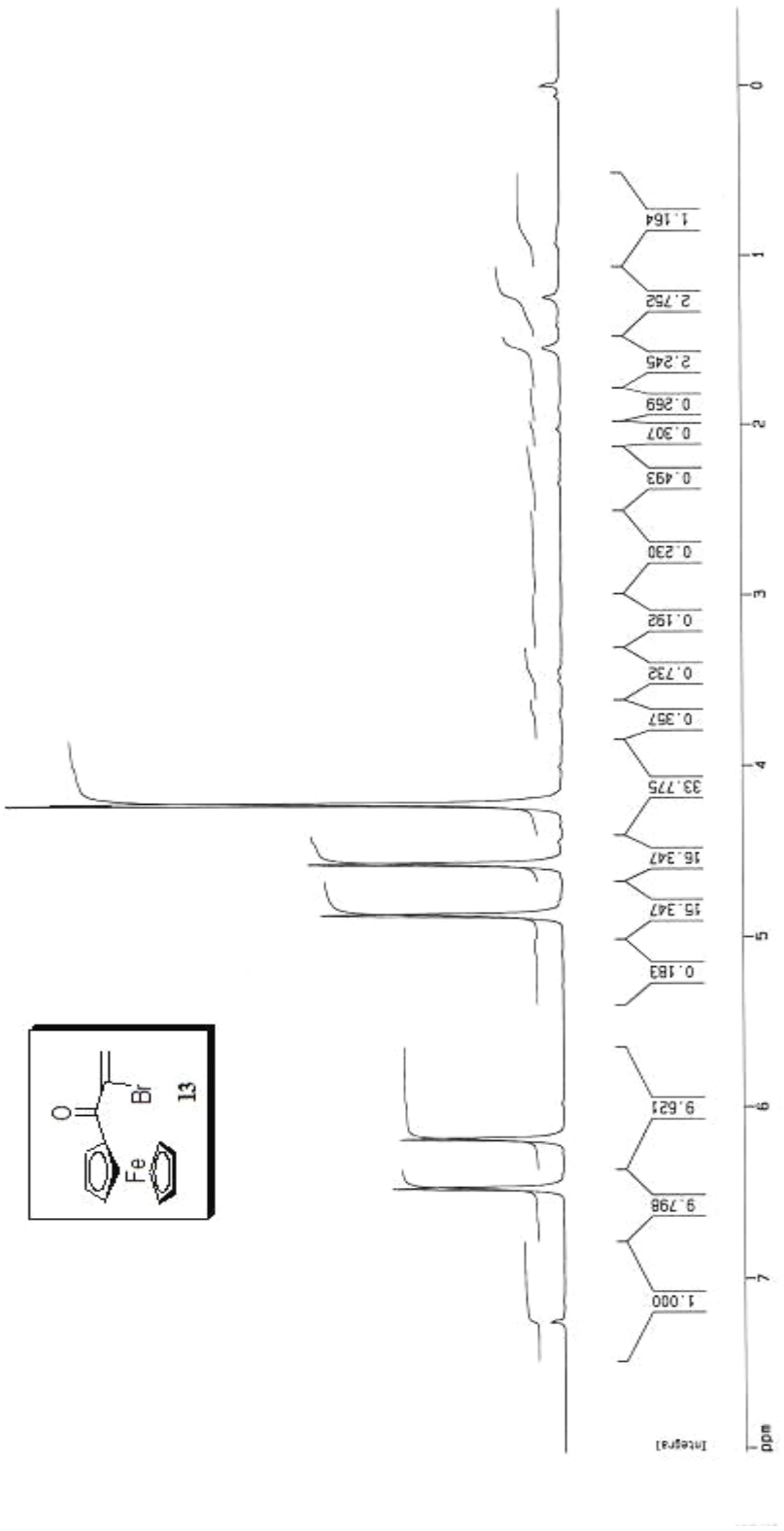

Figure A1. ^{1}H-NMR Spectrum (400 MHz) of 2-Bromo-1-ferrocenylprop-2-en-1-one (**13**)

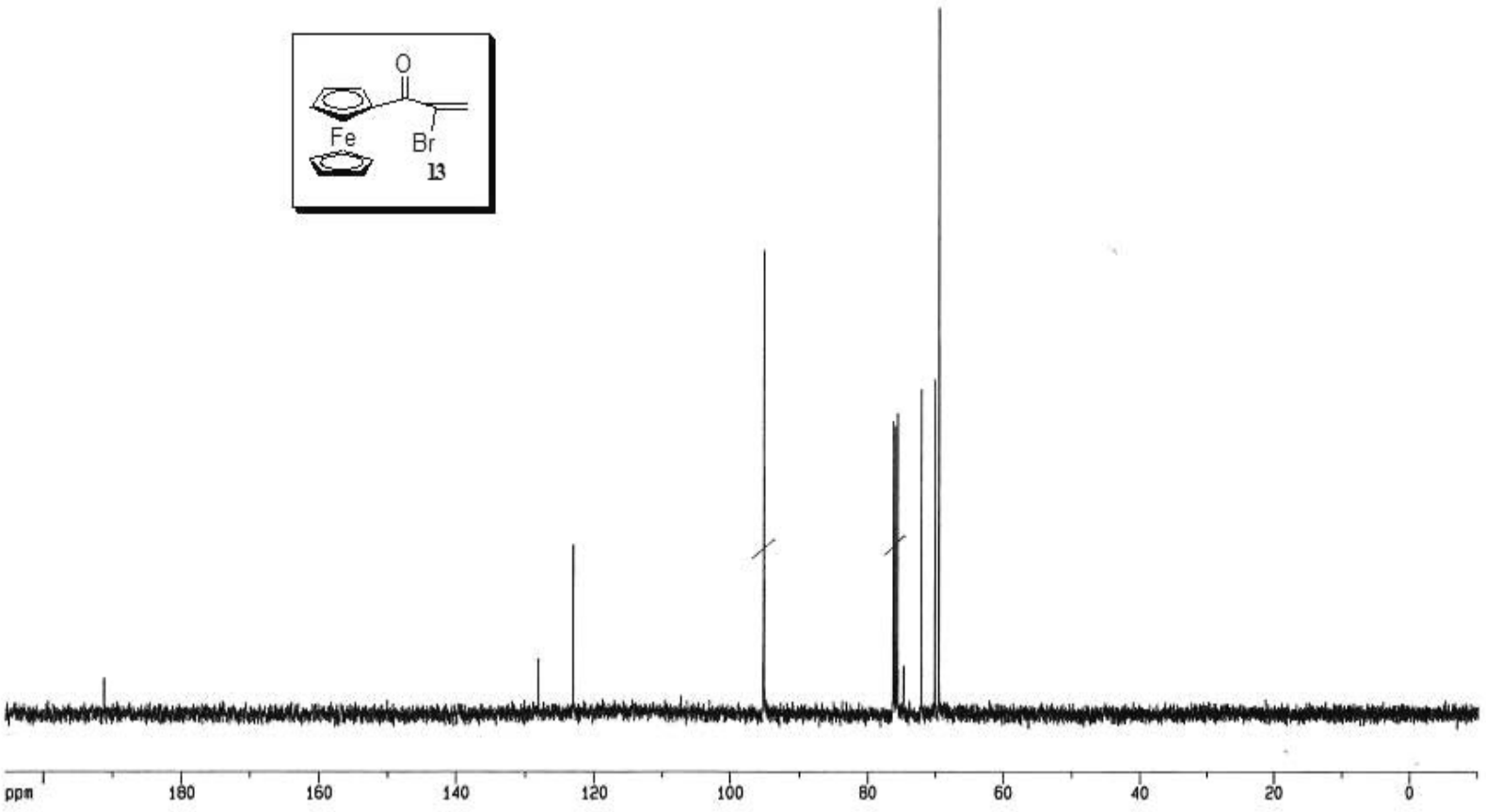

Figure A 2. ^{13}C-NMR Spectrum (40 MHz) of 2-Bromo-1-ferrocenylprop-2-en-1-one (**13**)

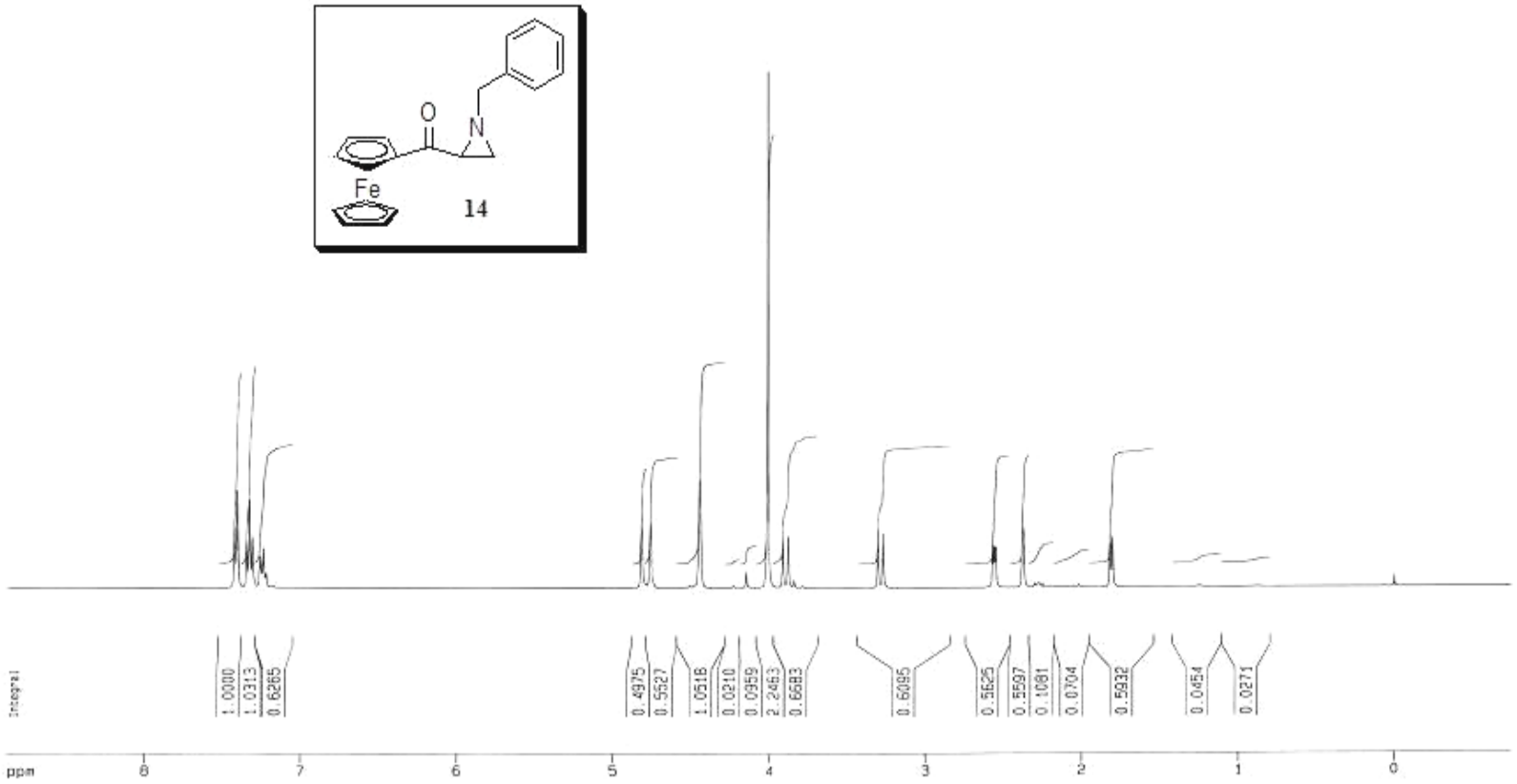

Figure A 3. ^{1}H-NMR Spectrum (400 MHz) of (1-Benzylaziridin-2-yl)(ferrocenyl)methanone (**14**)

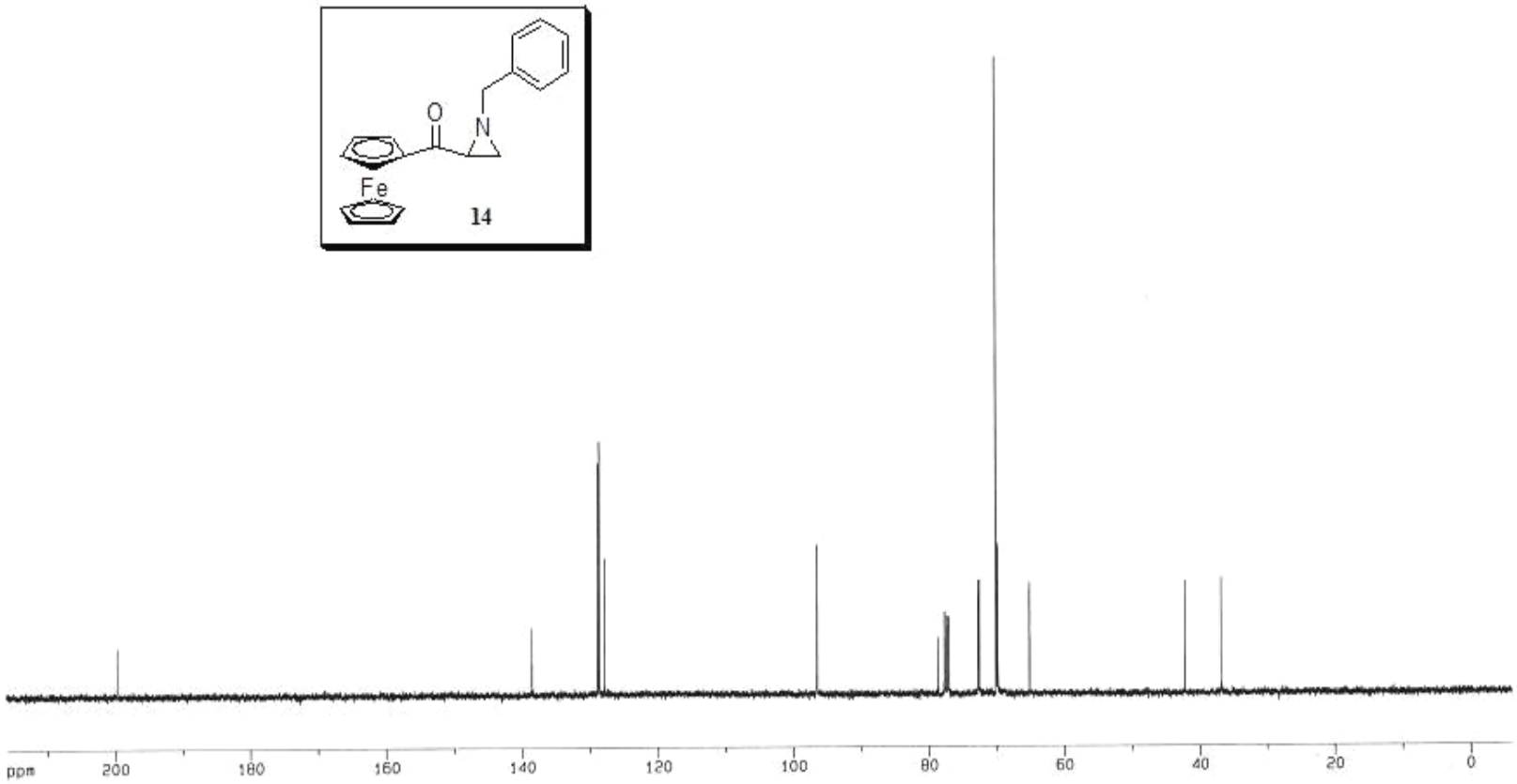

Figure A 4. ^{13}C-NMR Spectrum (400 MHz) of (1-Benzylaziridin-2-yl)(ferrocenyl)methanone (**14**)

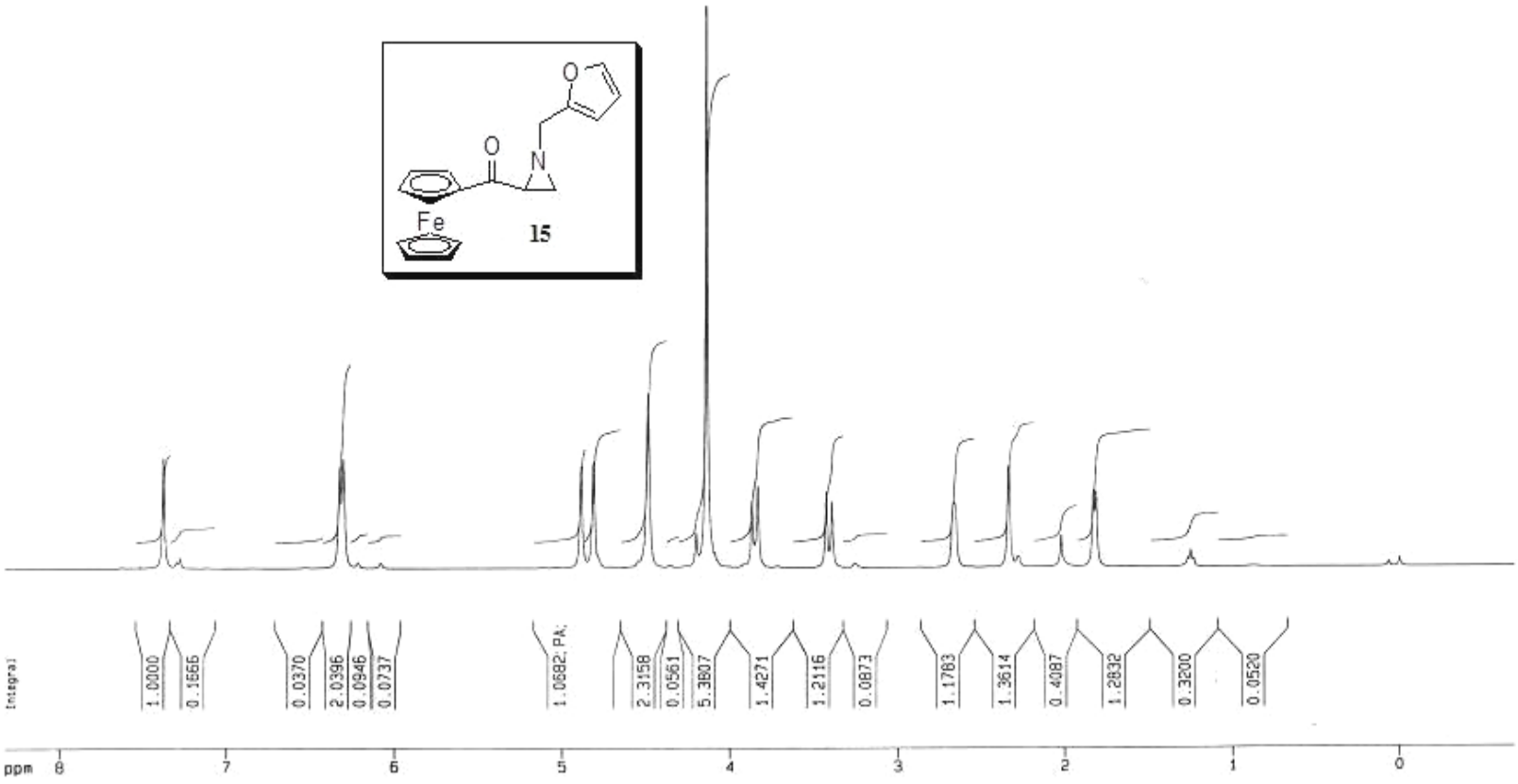

Figure A 5. ^{1}H-NMR Spectrum (400 MHz) of (1-((Furan-2-yl)methyl)aziridin-2-yl)(ferrocenyl)methanone (**15**)

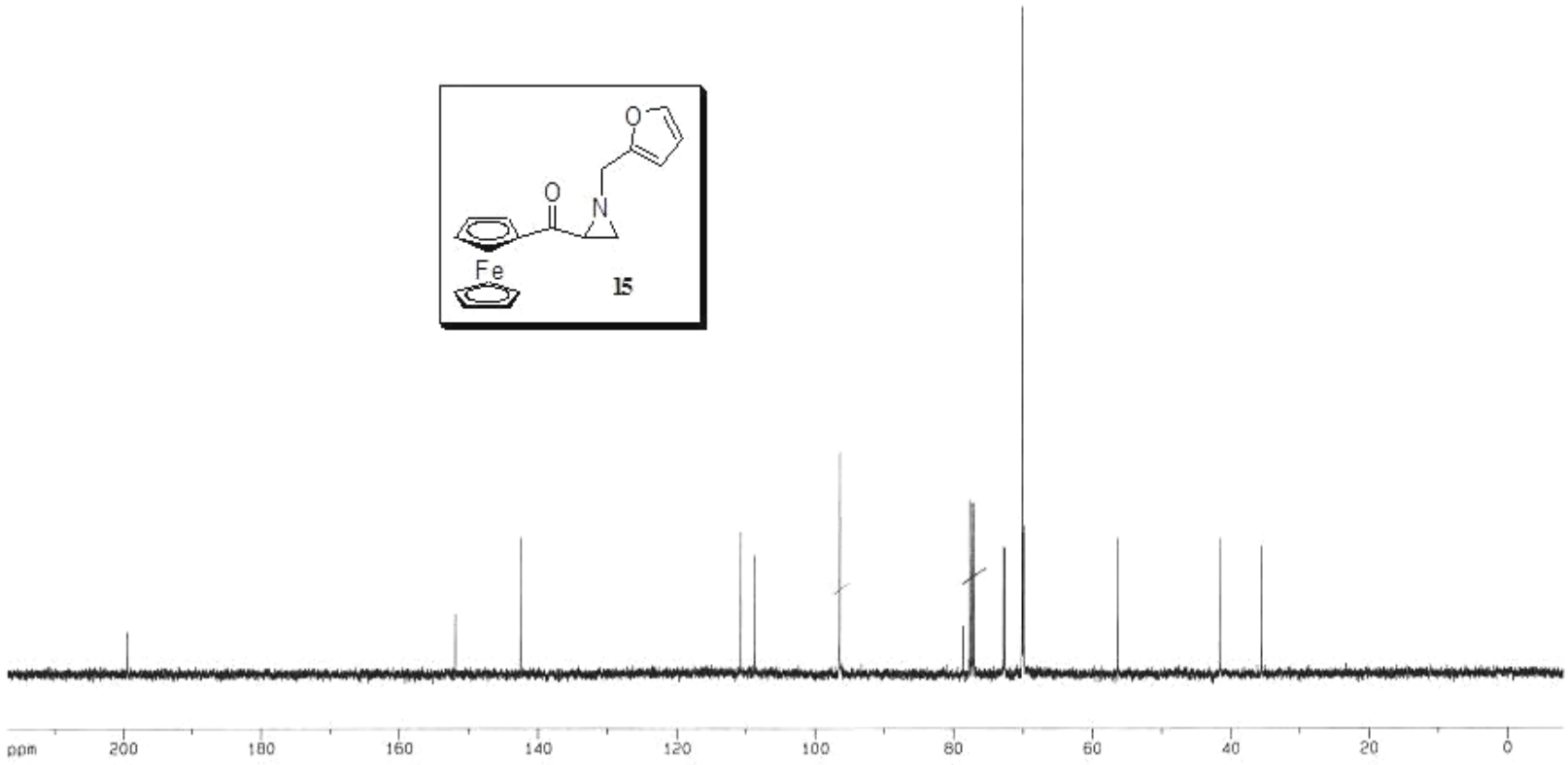

Figure A 6. ^{13}C-NMR Spectrum (400 MHz) of (1-((Furan-2-yl)methyl)aziridin-2-yl)(ferrocenyl)methanone (**15**)

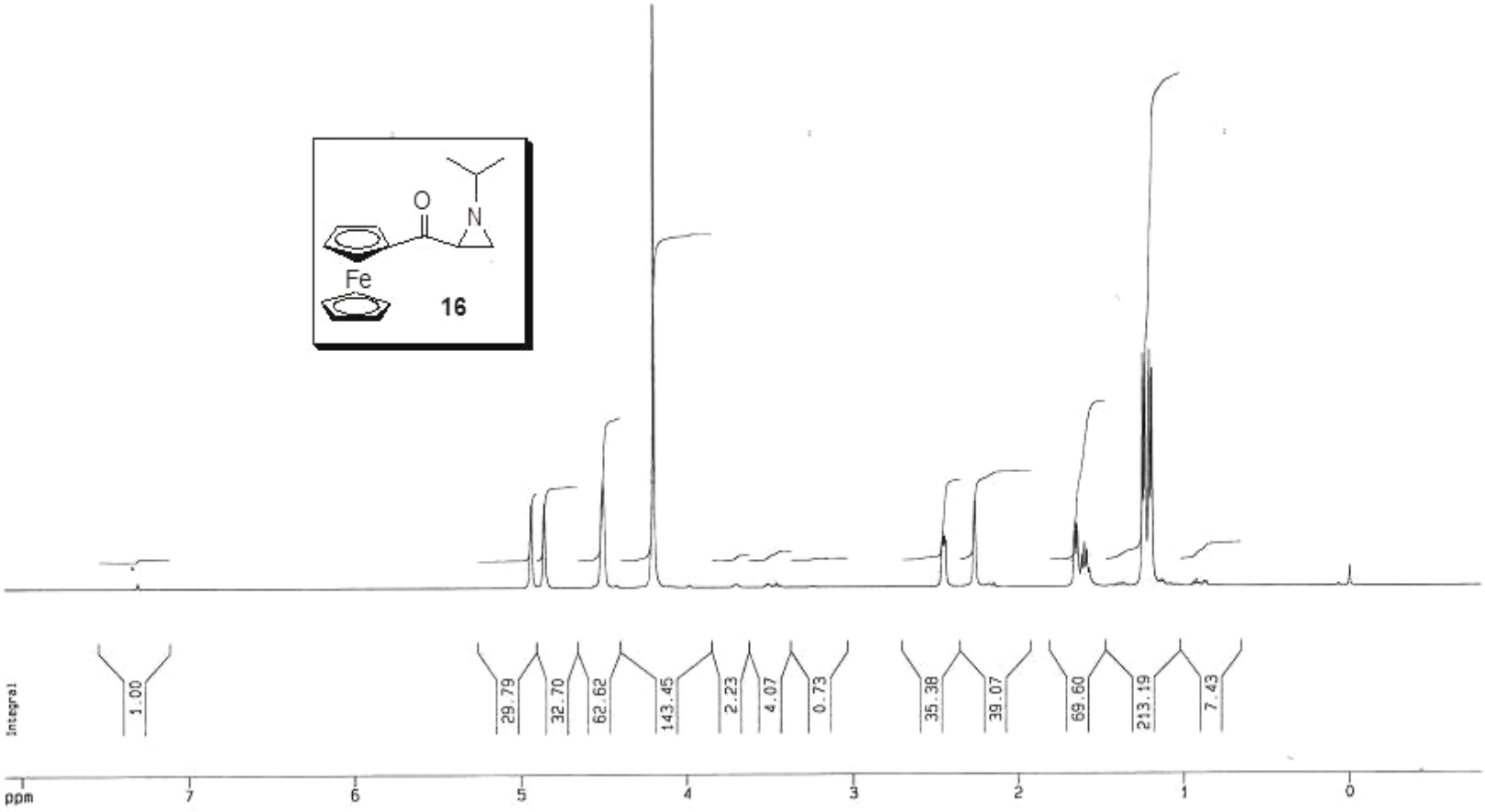

Figure A 7. ^{1}H-NMR Spectrum (400 MHz) of (1-Isopropylaziridin-2-yl)(ferrocenyl)methanone (**16**)

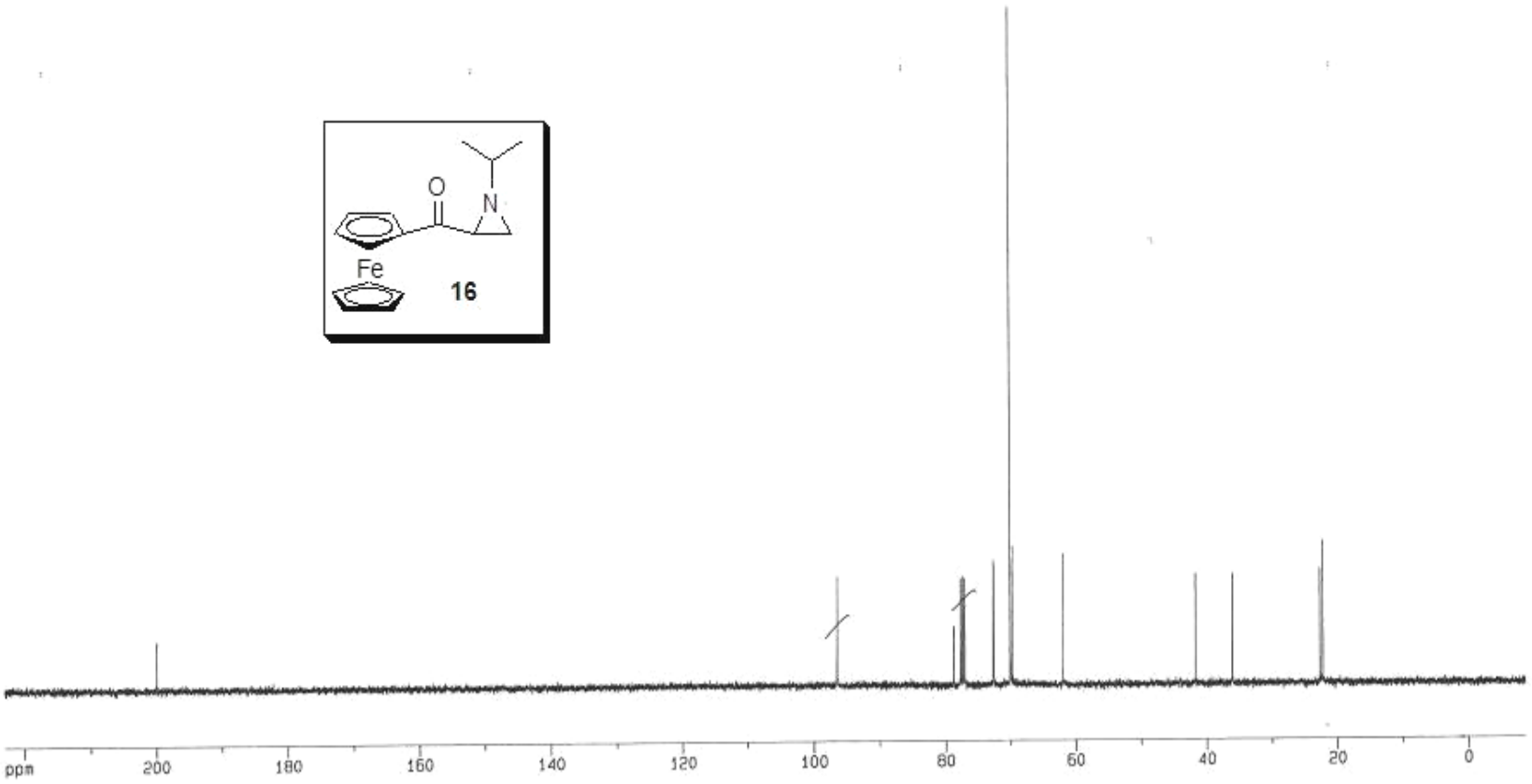

Figure A 8. ^{13}C-NMR Spectrum (400 MHz) of (1-Isopropylaziridin-2-yl)(ferrocenyl)methanone (**16**)

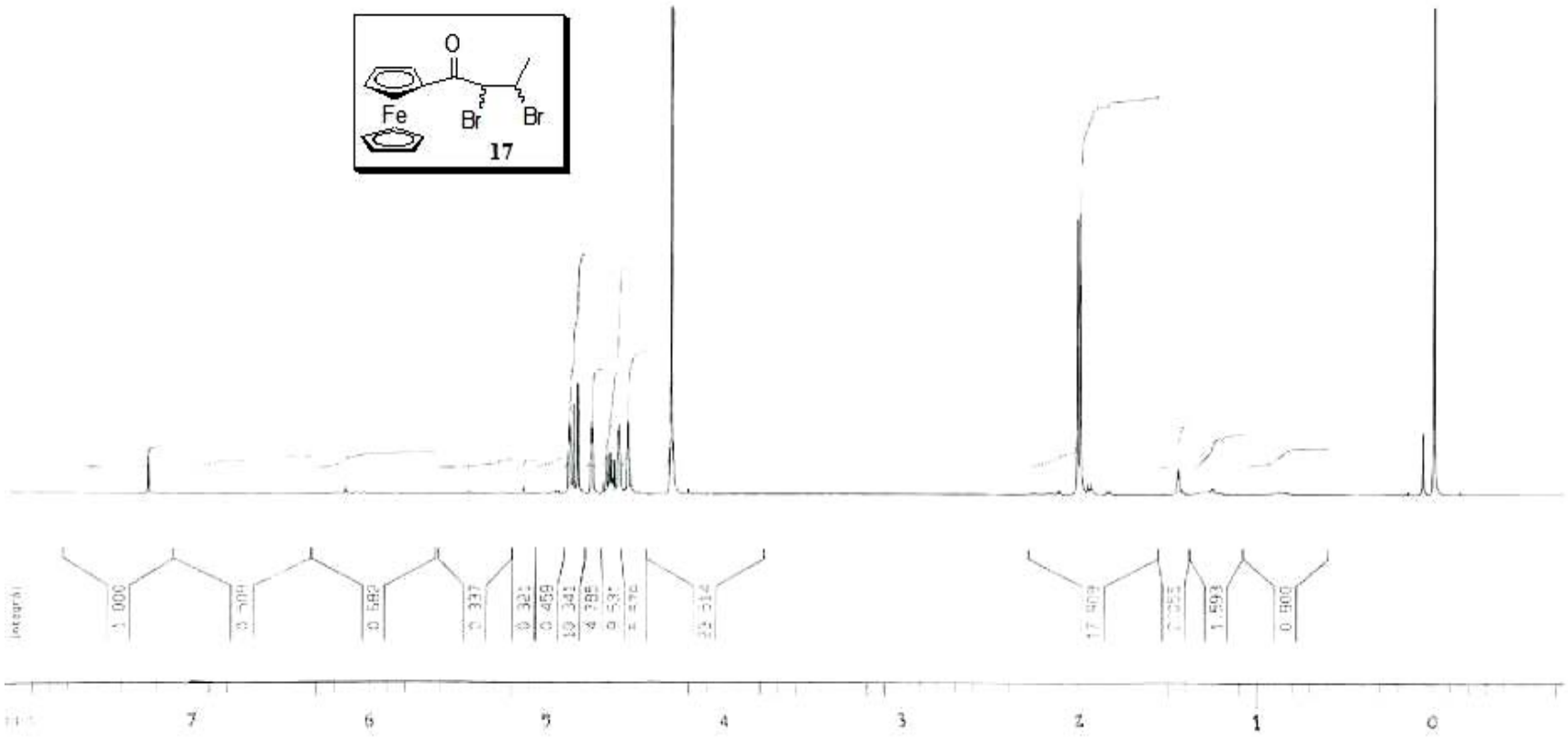

Figure A 9. ^{1}H-NMR Spectrum (400 MHz) of 2,3-Dibromo-1-ferrocenylbutan-1-one (**17**)

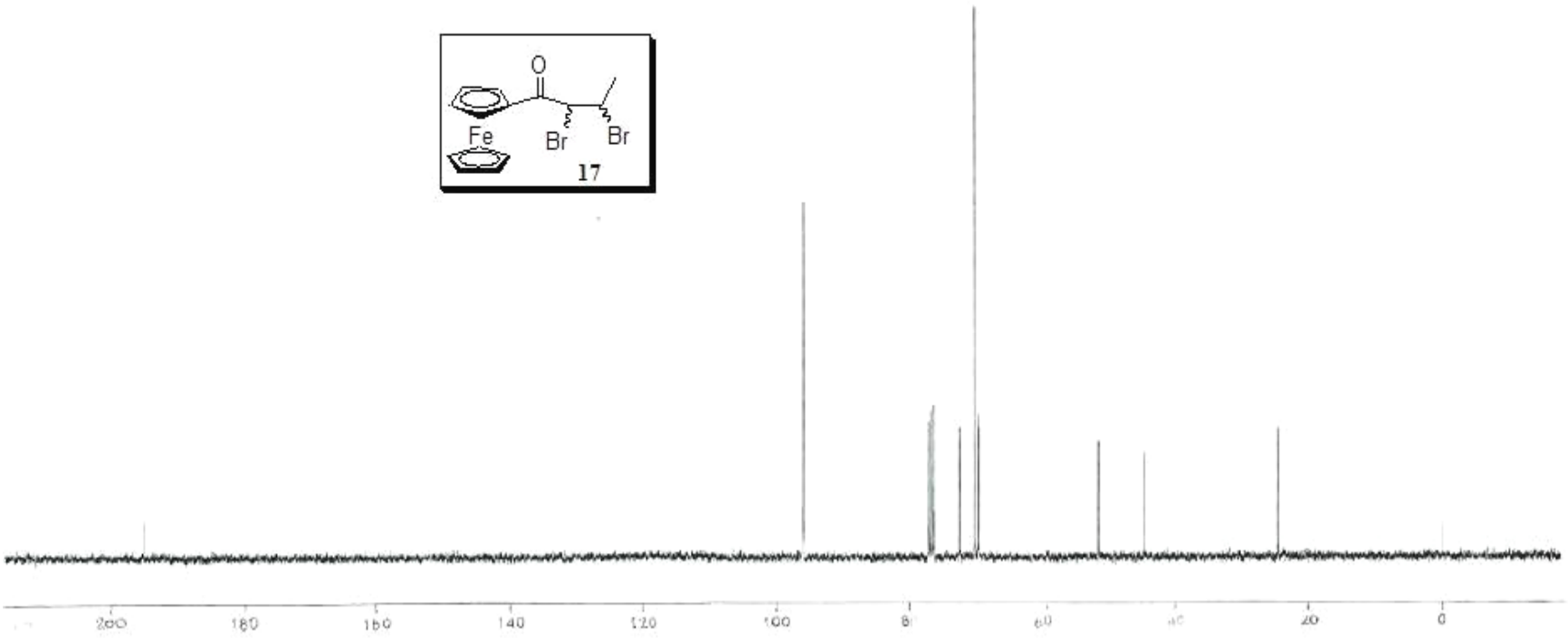

Figure A 10. ^{13}C-NMR Spectrum (400 MHz) of 2,3-Dibromo-1-ferrocenylbutan-1-one (**17**)

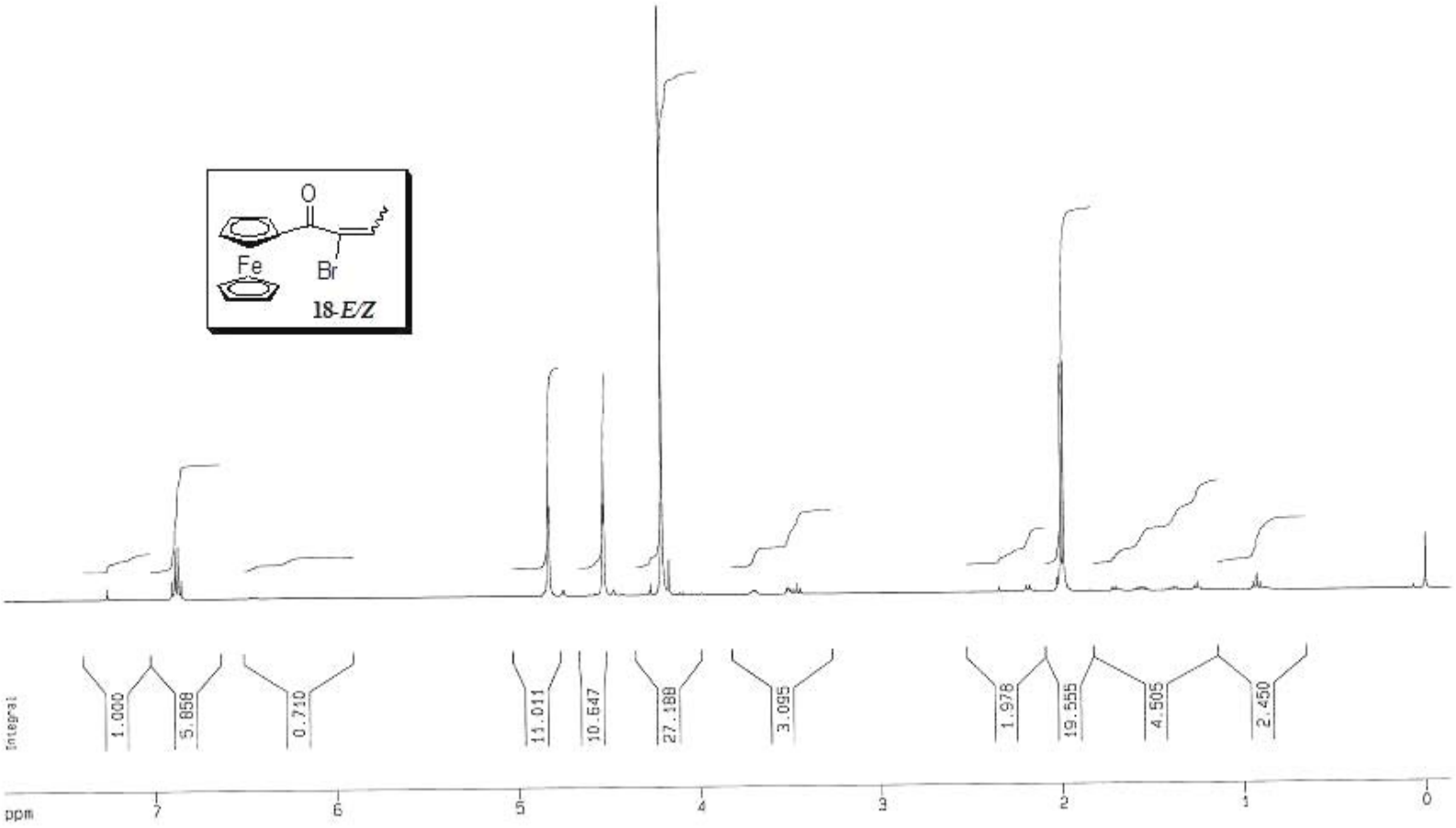

Figure A 11. ^{1}H-NMR Spectrum (400 MHz) of 2-Bromo-1-ferrocenylbut-2-en-1-one (**18**-*E*/*Z*)

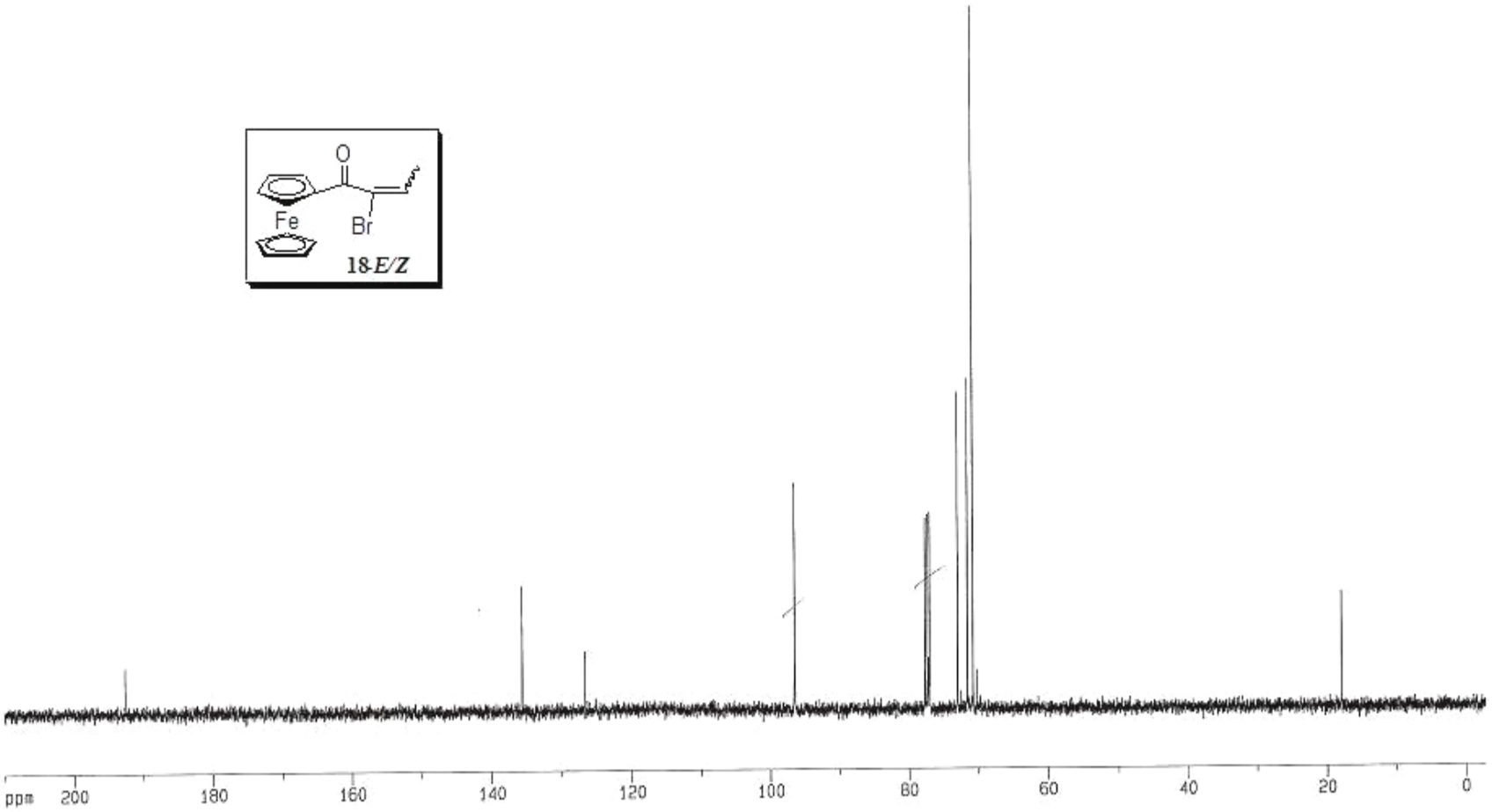

Figure A 12. ^{13}C-NMR Spectrum (400 MHz) of 2-Bromo-1-ferrocenylbut-2-en-1-one (**18**-*E/Z*)

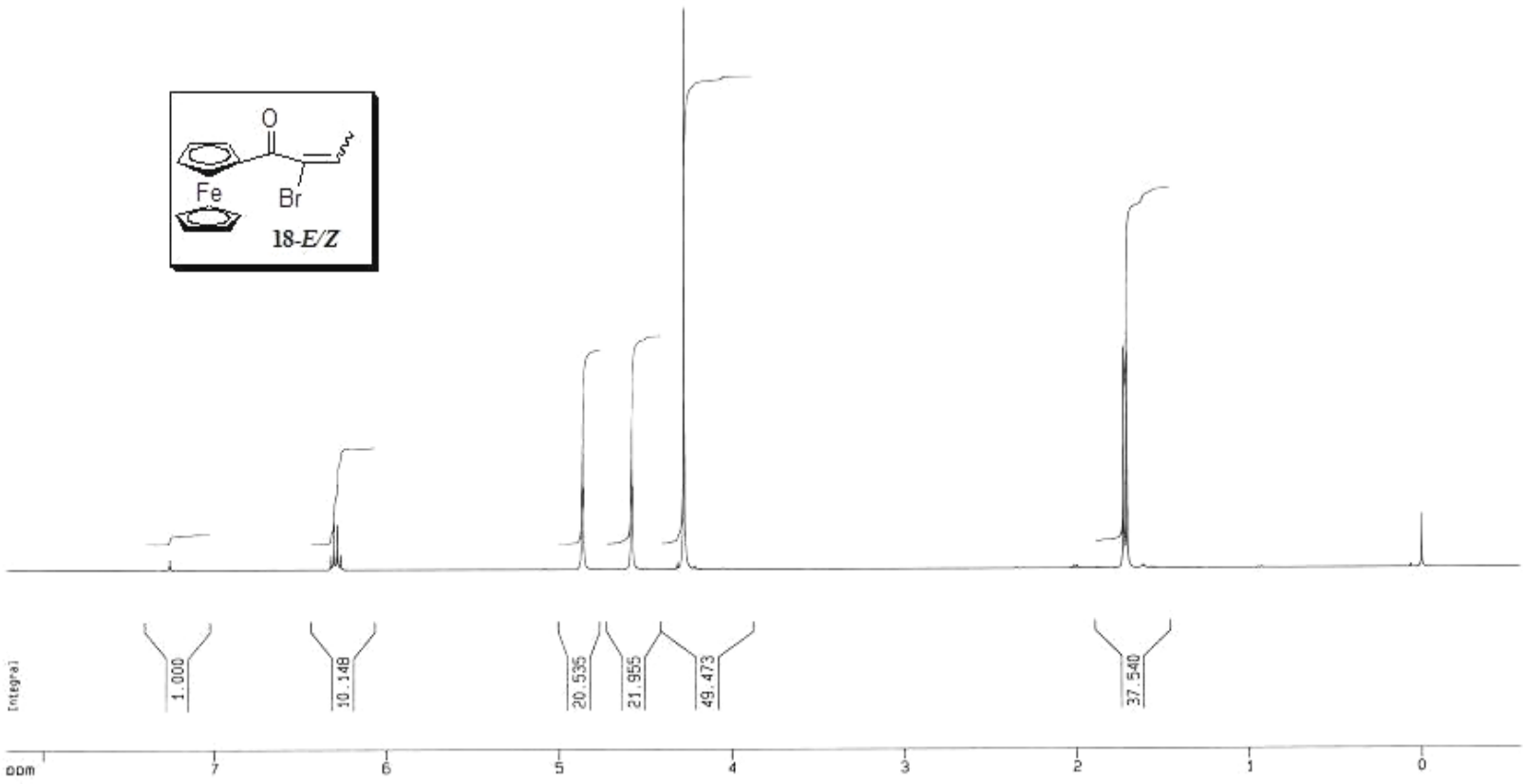

Figure A 13. ^{1}H-NMR Spectrum (400 MHz) of 2-Bromo-1-ferrocenylbut-2-en-1-one (**18**-*E*/*Z*)

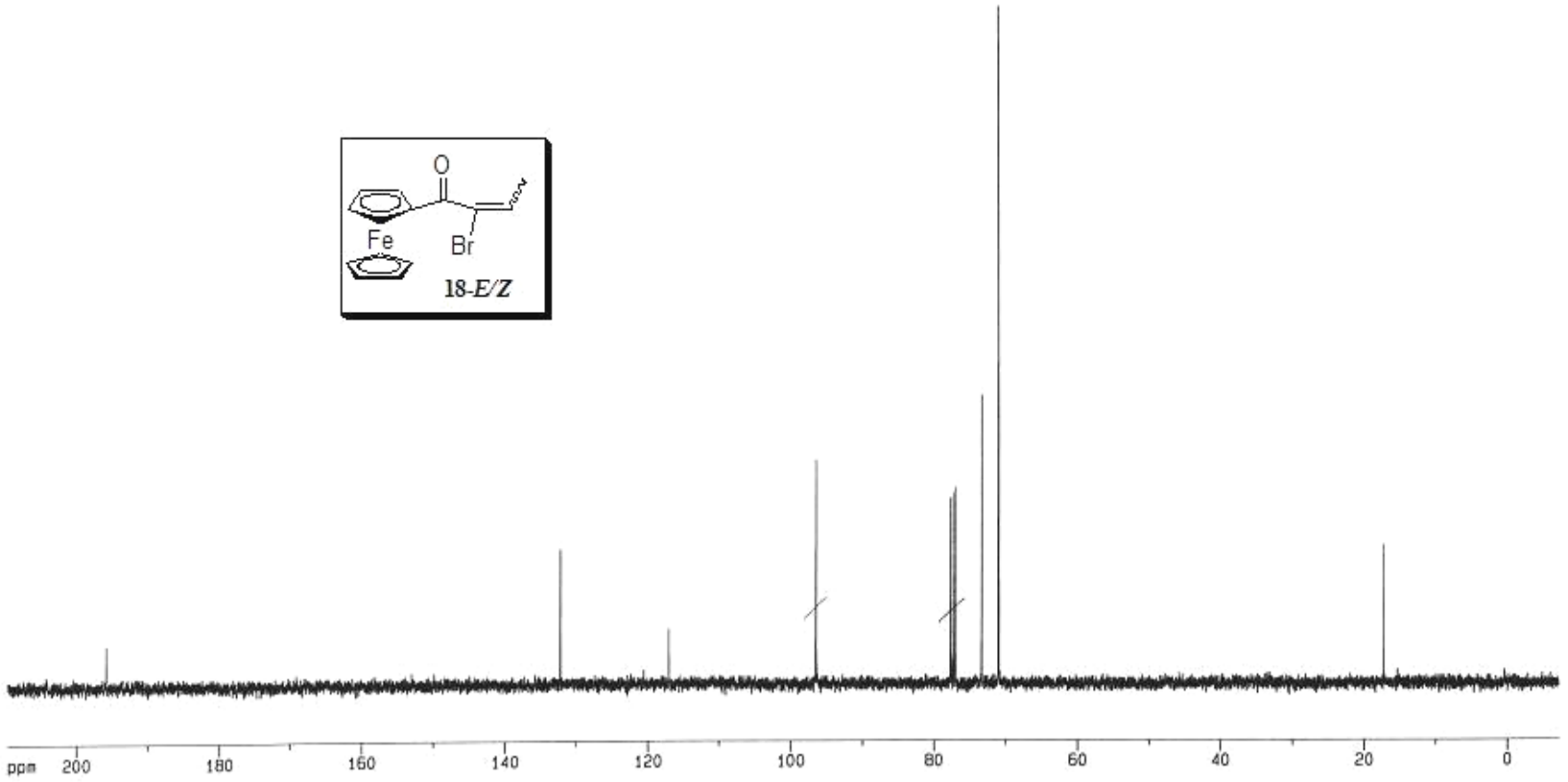

Figure A 14. ^{13}C-NMR Spectrum (400 MHz) of 2-Bromo-1-ferrocenylbut-2-en-1-one (**18**-*E*/*Z*)

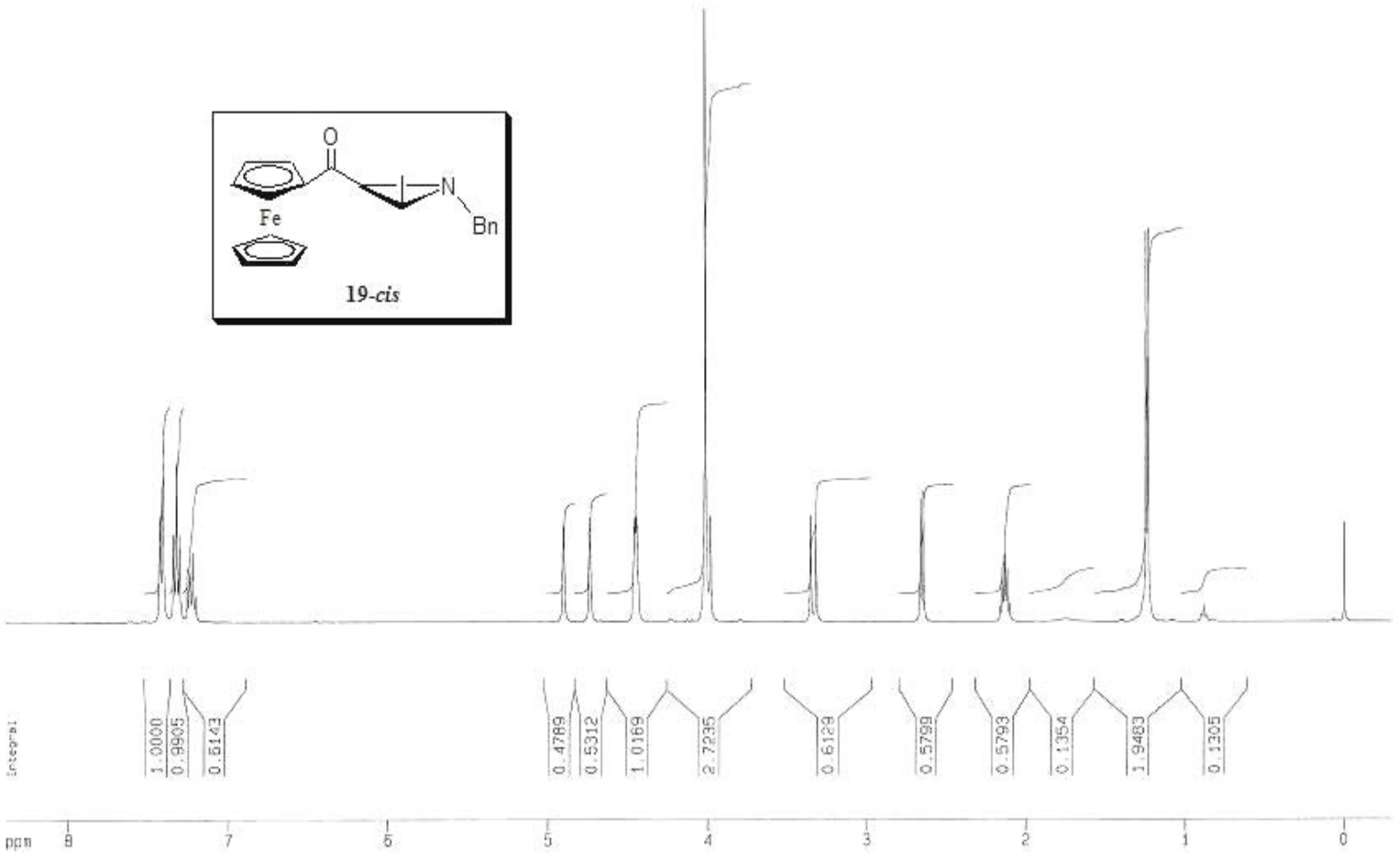

Figure A 15. ^{1}H-NMR Spectrum (400 MHz) of (1-Benzyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**19**-*cis*)

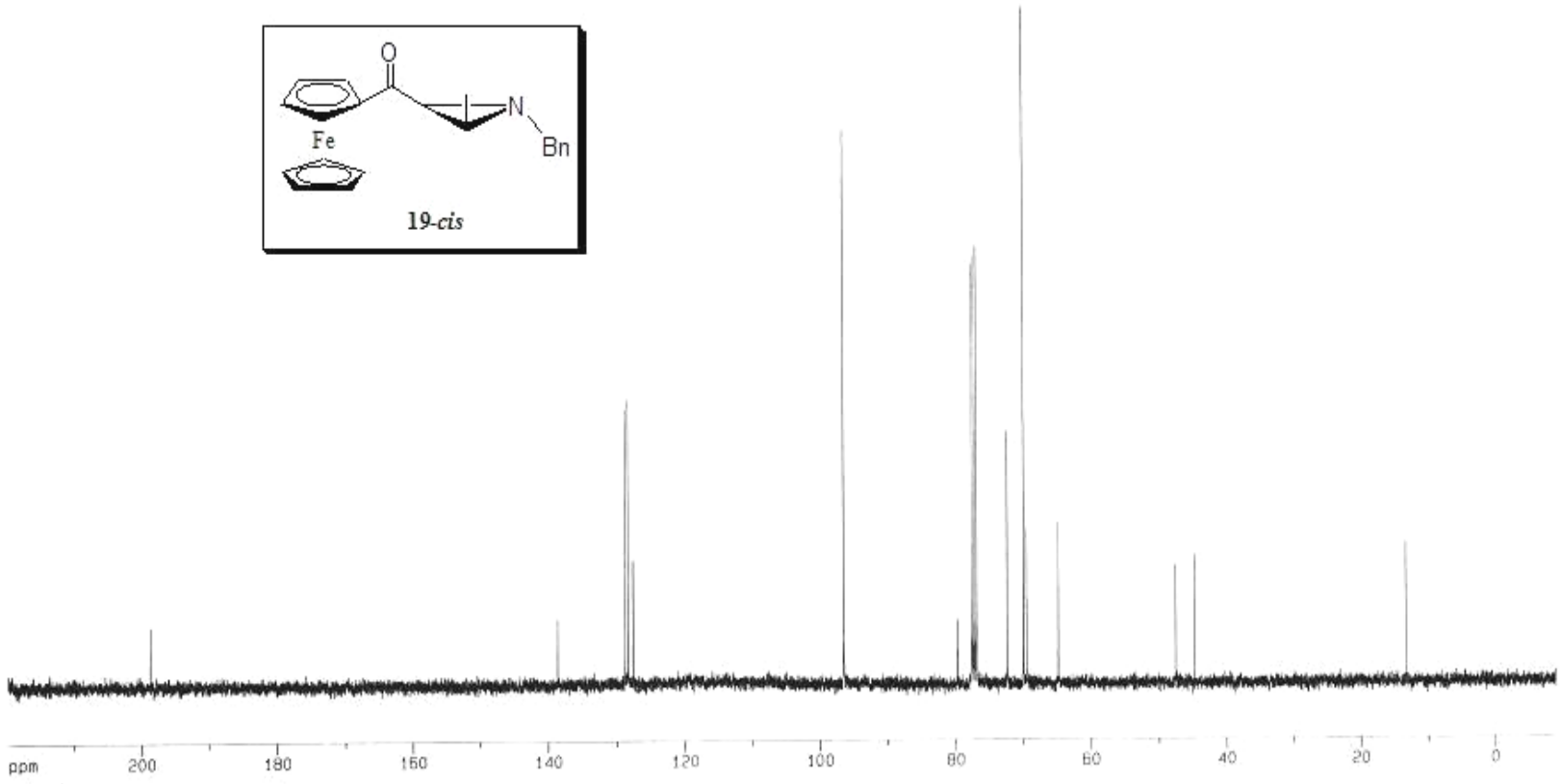

Figure A 16. ^{13}C-NMR Spectrum (400 MHz) of (1-Benzyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**19**-*cis*)

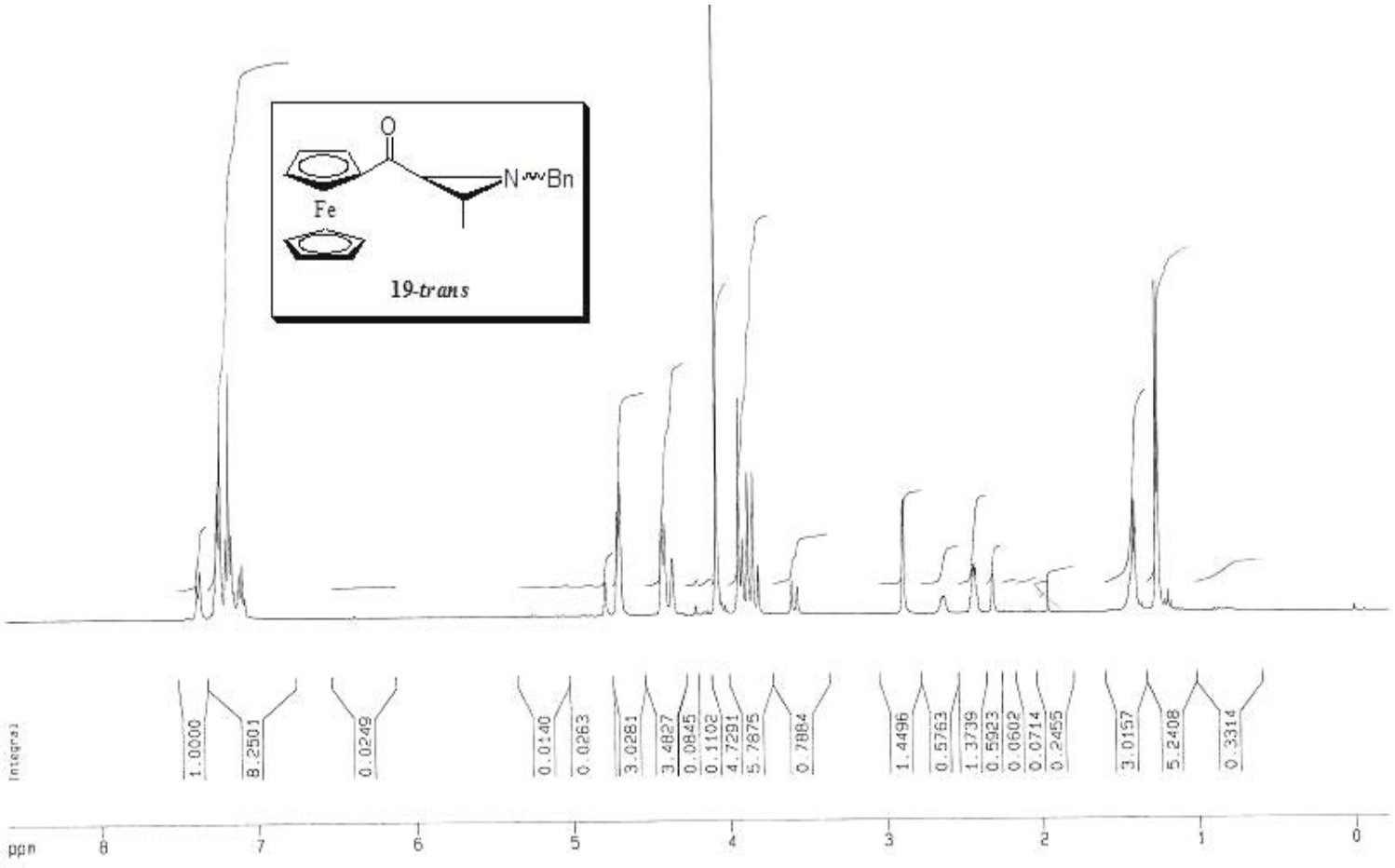

Figure A 17. ^{1}H-NMR Spectrum (400 MHz) of (1-Benzyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**19**-*trans*)

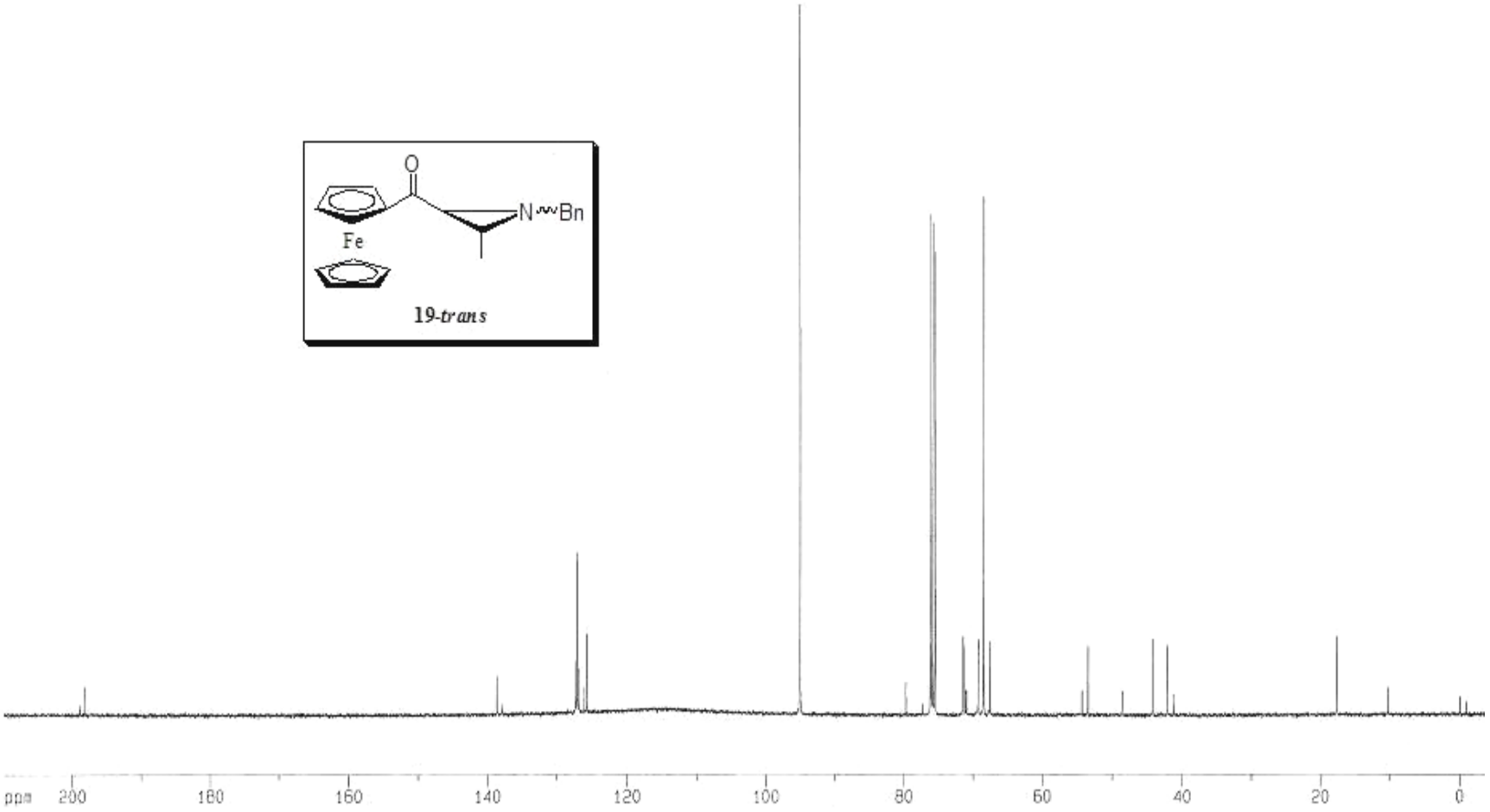

Figure A 18. ^{13}C-NMR Spectrum (400 MHz) of (1-Benzyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**19**-*trans*)

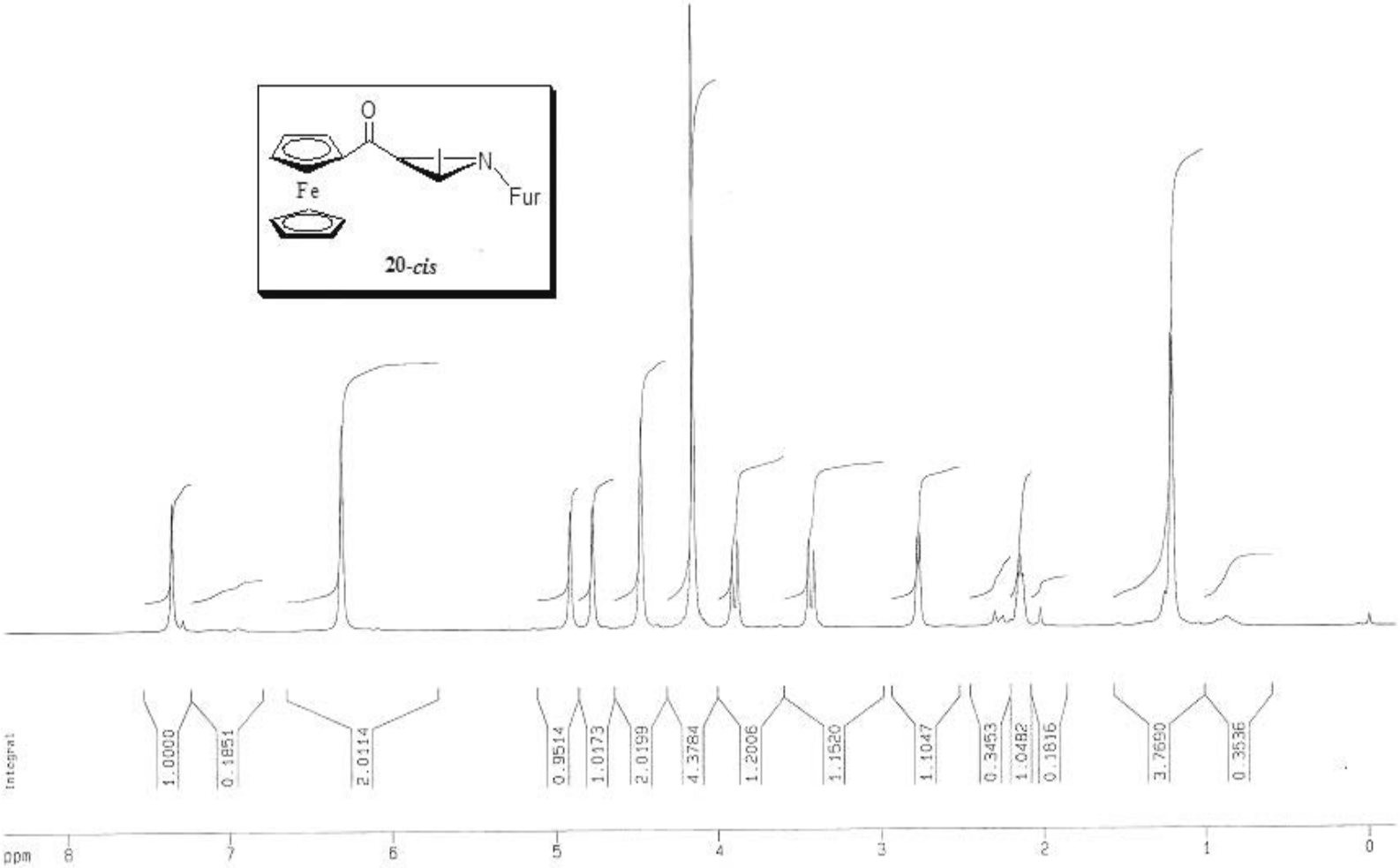

Figure A 19. ^{1}H-NMR Spectrum (400 MHz) of (1-((Furan-2-yl)methyl)-3-methylaziridin-2yl)(ferrocenyl)methanone **(20-*cis*)**

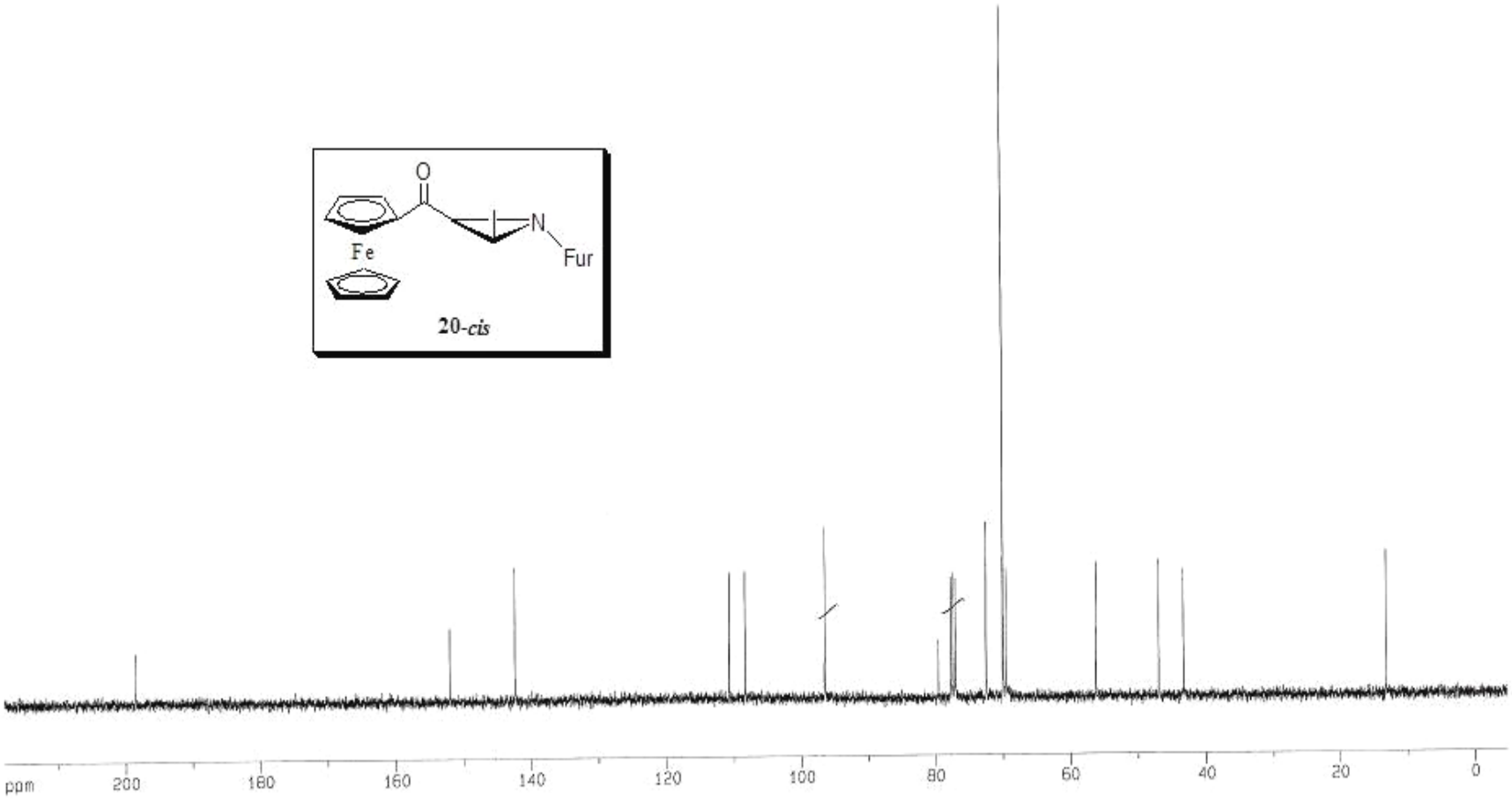

Figure A 20. ^{13}C-NMR Spectrum (400 MHz) of (1-((Furan-2-yl)methyl)-3-methylaziridin-2yl)(ferrocenyl)methanone (**20**-*cis)*

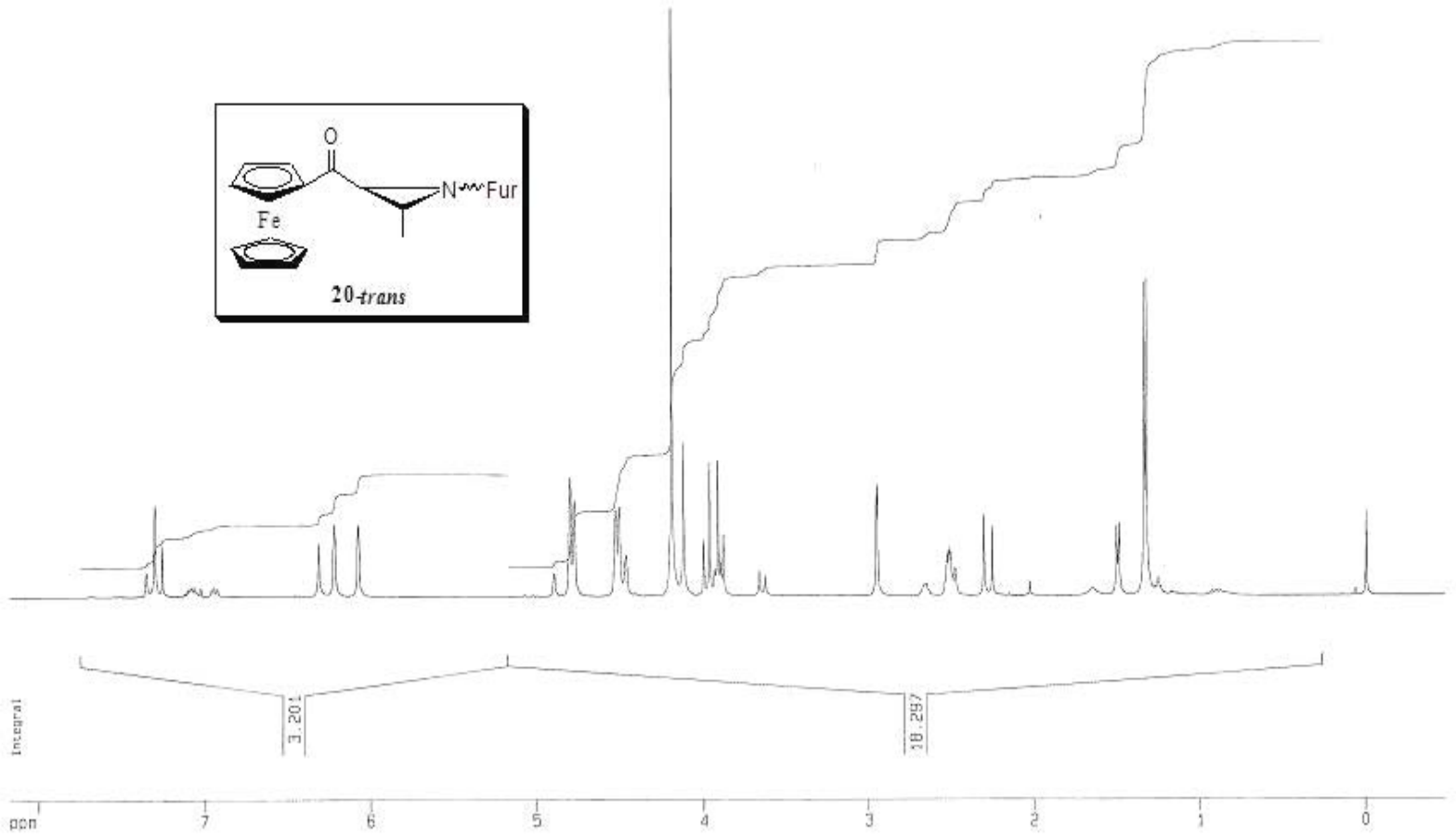

Figure A 21. ^{1}H-NMR Spectrum (400 MHz) of (1-((Furan-2-yl)methyl)-3-methylaziridin-2yl)(ferrocenyl)methanone (**20**-*trans)*

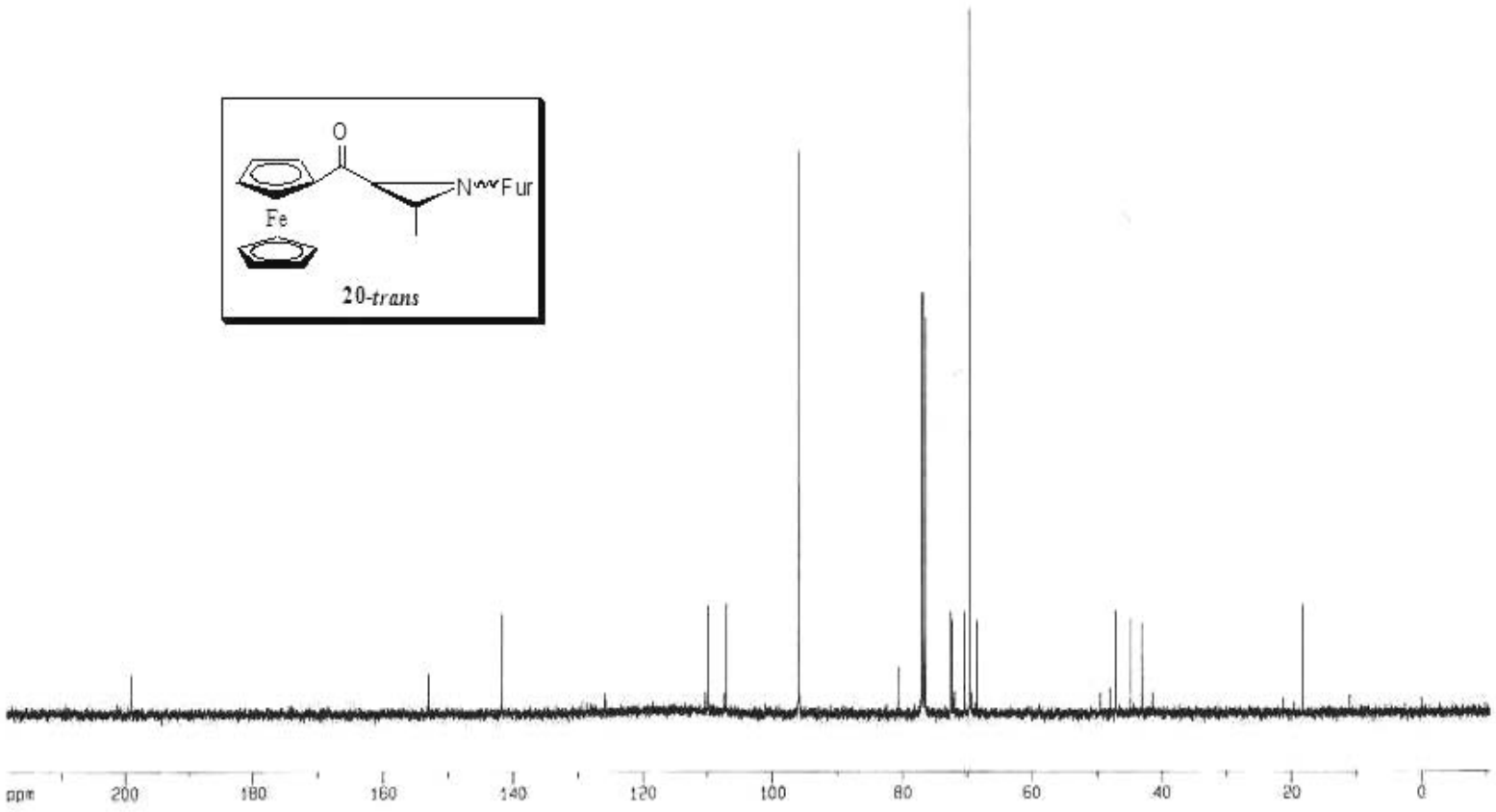

Figure A 22 ^{13}C-NMR Spectrum (400 MHz) of (1-((Furan-2-yl)methyl)-3-methylaziridin-2yl)(ferrocenyl)methanone(**20**-*trans)*

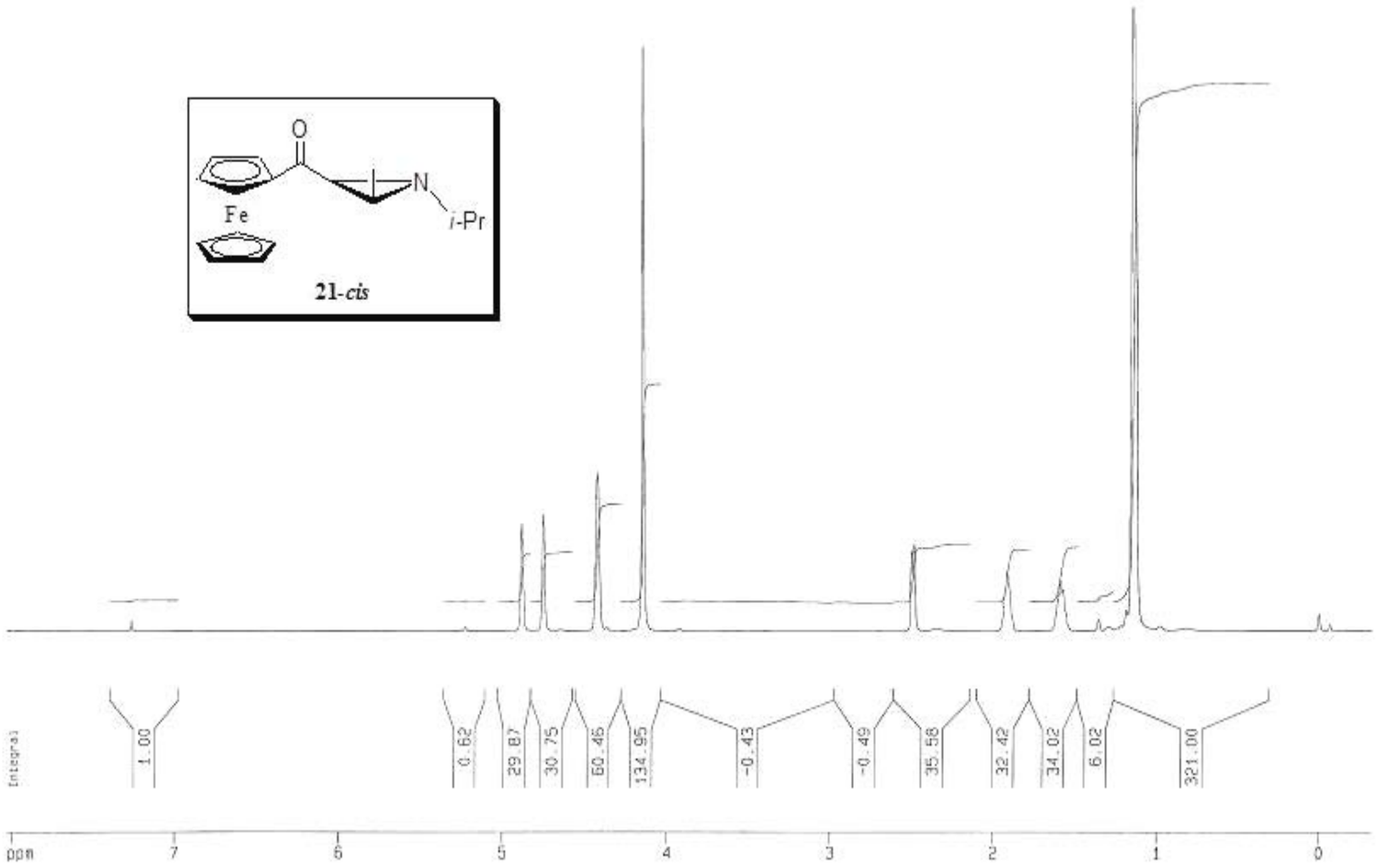

Figure A 23. ^{1}H-NMR Spectrum (400 MHz) of (1-Isopropyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**21**-*cis*)

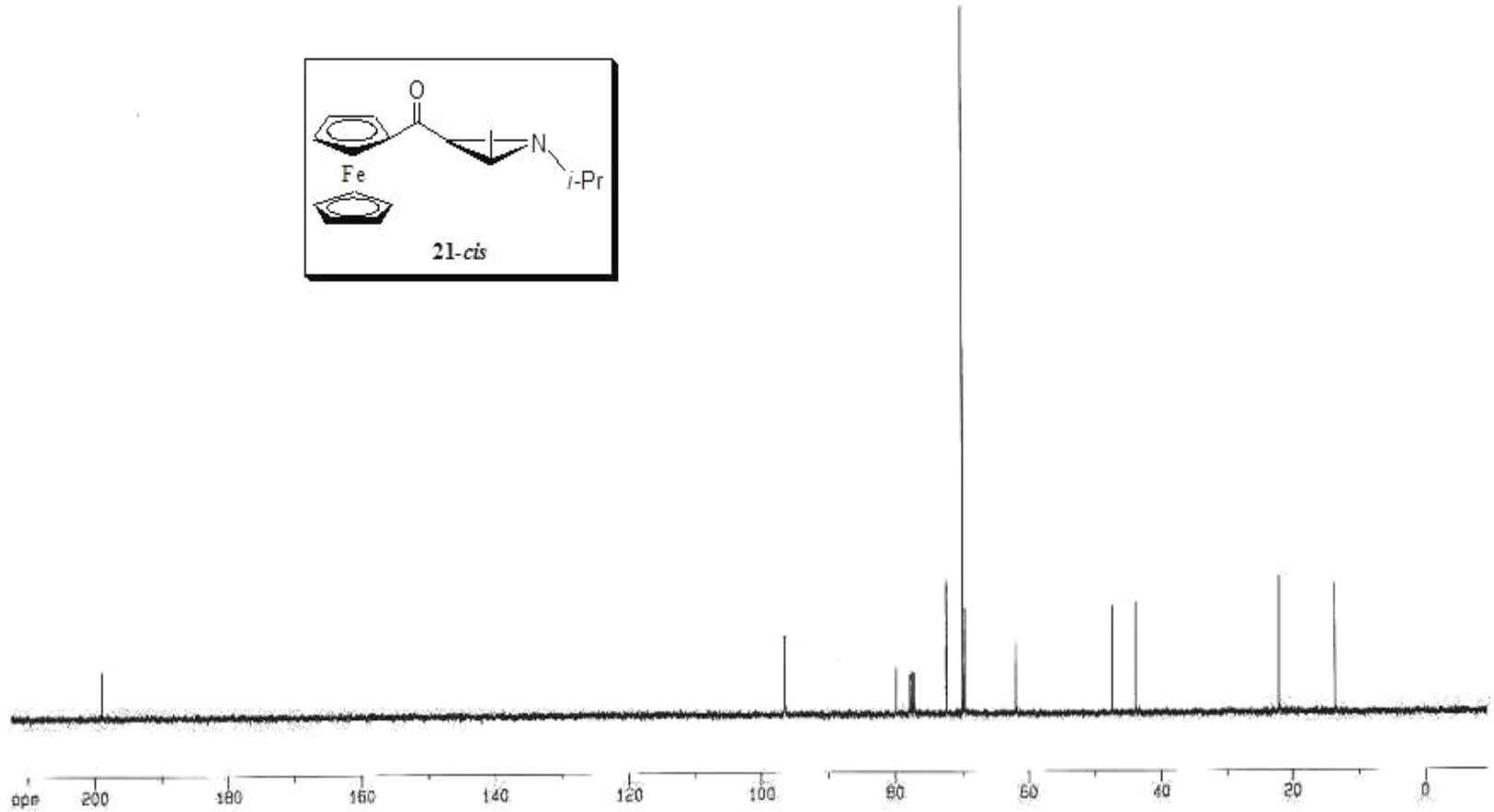

Figure A 24. ^{13}C-NMR Spectrum (400 MHz) of (1-Isopropyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**21**-*cis*)

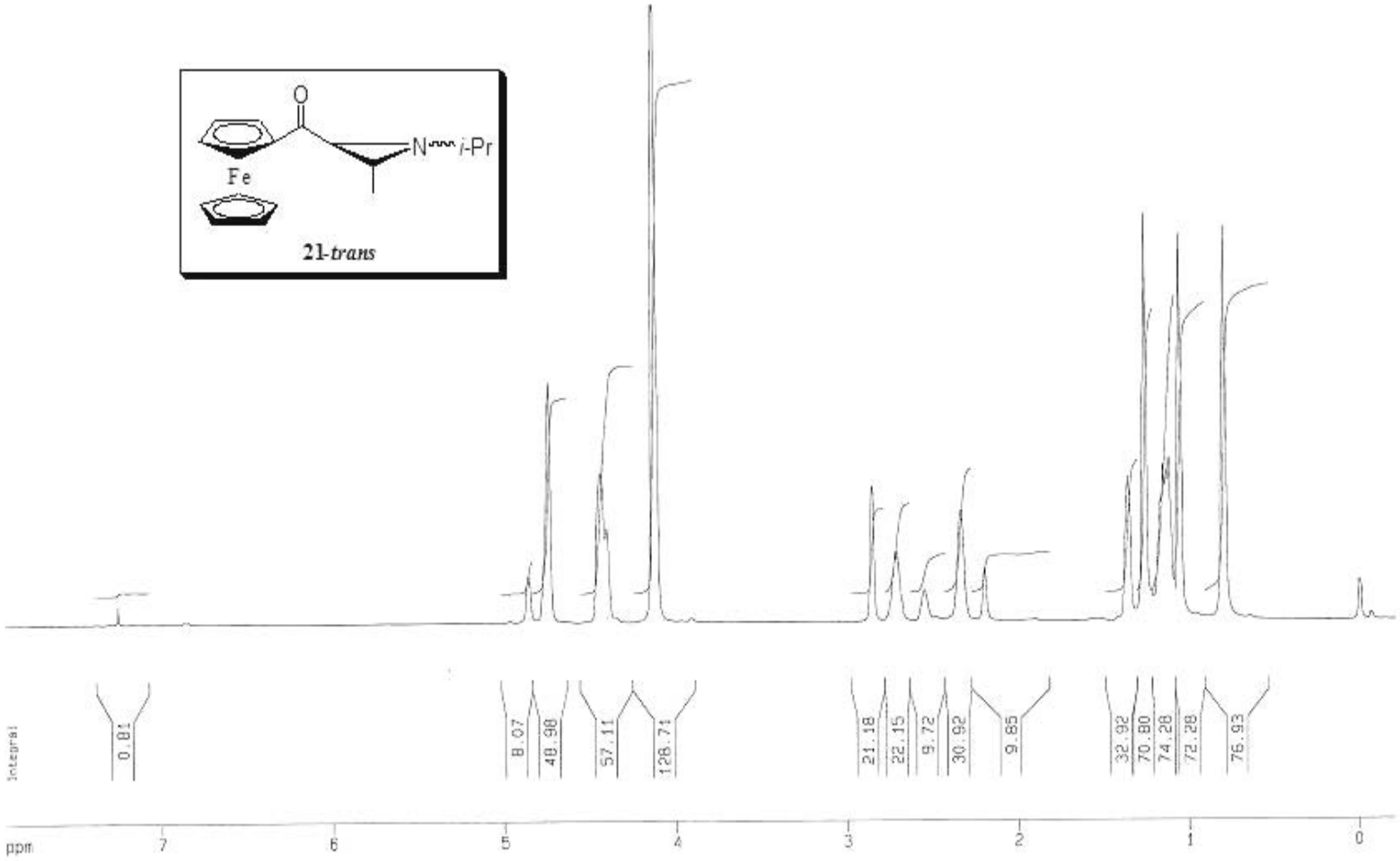

Figure A 25. ^{1}H-NMR Spectrum (400 MHz) of (1-Isopropyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**21**-*trans*)

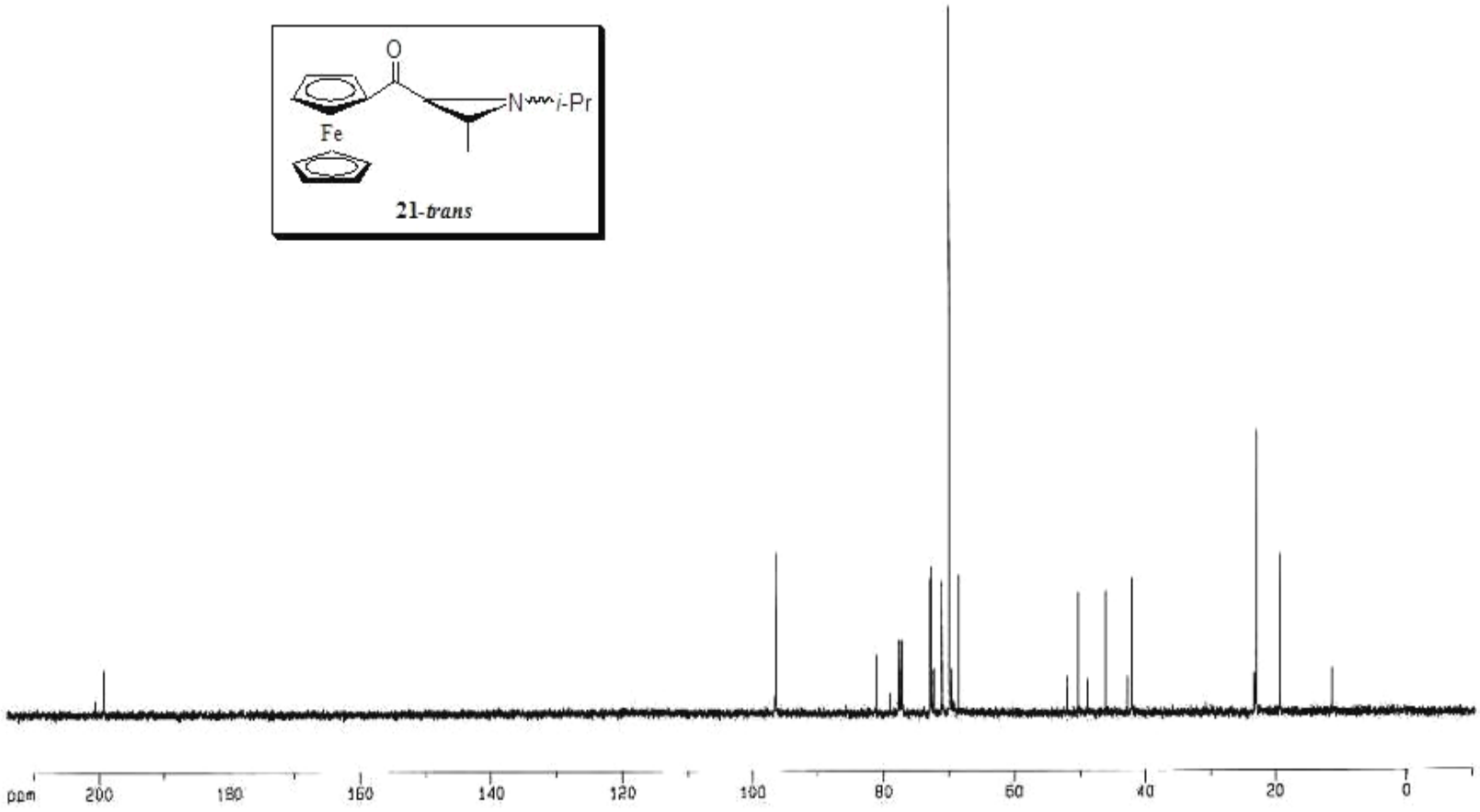

Figure A 26. ^{13}C-NMR Spectrum (400 MHz) of (1-Isopropyl-3-methylaziridin-2-yl)(ferrocenyl)methanone (**21**-*trans*)