universität wien

DIPLOMARBEIT

Titel der Diplomarbeit

Total Synthesis of (-)-Paeonisuffrone mono- and diacetate

Verfasserin

Elisabeth Felbermair

angestrebter akademischer Grad:

Magistra der Naturwissenschaften (Mag. rer. nat.)

Wien, 2011

Studienkennzahl lt. Studienbuchblatt	A 419
Studienrichtung lt. Studienbuchblatt	Diplomstudium Chemie
Betreuer	Ao. Univ.-Prof. Dr. Wolfgang Reischl

CONTENTS

1. Introduction 7

2. Antecedents 9
2.1 Synthesis of (-)-Paeonisuffrone and (+)-Paeonisuffrone 9
2.2 (-)-Paeoniflorigenin and (-)-Paeoniflorin 11

3. Objectives 13

4. Methods 15

5. Results and Discussion 18
5.1 Preparation of the starting material: (R)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)-2,3-epoxy-1-propanol pivalate (mixture of epoxides) . 18
5.2 Study of the radical cyclization reaction promoted by Ti(III) . . 20
5.3 Protection of the diol by formation of the bencylidene acetal . . 22
5.4 Allylic oxidation of the cyclohexyl skeleton 23
5.5 Obtention of the tetracyclic system via intramolecular Michael addition 24
5.6 Deprotection of the benzyliden acetal 25
5.7 Formation of (-)-Paeonisuffrone mono- and diacetate 26

6. Conclusion 28
6.1 Summerization 28
6.2 Future Prospects 32

7. Experimental Section 36
7.1 General techniques 36
7.1.1 Optical rotation 36
7.1.2 NMR spectra 36
7.1.3 Mass spectrometry 36

7.1.4 IR spectroscopy 36
7.2 Reagents and solvents 37
7.3 Chromatographic techniques 37
7.3.1 Flash column chromatography 37
7.3.2 Thin layer chromatography 37
7.4 (*R*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-enone 38
7.5 (*R*)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)allyl acetate 39
7.6 (*R*)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-enone . . . 40
7.7 (*R*)-5-((*S*)-2-(hydroxymethyl)oxiran-2-yl)-2-methylcyclohex-2-enone 41
7.8 ((*R*)-2-((*R*)-4-methyl-5-oxocyclohex-3-en-1-yl)oxiran-2-yl)methyl pivalate 42
7.9 (1-hydroxy-6-(hydroxymethyl)-2-methylbicyclo[3.1.1]hept-2-en-6-yl)methyl pivalate 43
7.10 ((2*R*,4a*R*,8a*S*)-8-methyl-2-phenyl-4,4a,5,6-tetrahydro-5,8a-methanobenzo-[d][1,3]dioxin-4a-yl)methyl pivalate 45
7.11 ((2*R*,4a*R*,8a*S*)-8-methyl-6-oxo-2-phenyl-4,4a,5,6-tetrahydro-5,8a-methanobenzo[d][1,3]dioxin-4a-yl)methyl pivalate 46
7.12 (2*R*,4a*S*,5*R*,8*S*,8a*R*)-8-methyl-2-phenyldihydro-4H-8,4a-(epoxymethano)-5,8a-methanobenzo[d][1,3]dioxin-6(5H)-one 48
7.13 (-)-Paeonysuffrone 49
7.14 (-)-Paeonysuffrone mono- and diacetate 50

8. Table of Carbons 52

9. Spectroscopic Data 55
9.1 Spectra of compound **2** 55
9.2 Spectra of compound **3** 59
9.3 Spectra of compound **4** 63
9.4 Spectra of compound **5** 67
9.5 Spectra of compound **6** 71
9.6 Spectra of compound **7a** 75
9.7 Spectra of compound **7b** 83
9.8 Spectra of compound **8** 91
9.9 Spectra of compound **9a** 100
9.10 Spectra of compound **9b** 109
9.11 Spectra of compound **10** 116
9.12 Spectra of compound **11** 124

9.13 Spectra of compound **12** 132
9.14 Spectra of compound **13** 138

Bibliography 144

10. Appendix 146
Abbreviations 146
Abstract 147
Lebenslauf 148

ACKNOWLEDGMENTS

First of all, I want to thank both my thesis advisors, Mr. Francisco Bermejo of the Universidad de Salamanca, and Mr. Wolfgang Reischl of the Universität Wien, for making this project possible by their cooperation.
To Mr. Francisco Bermejo I owe special thanks for all the support offered during these past months of laboratory work, and the help in resolving all problems.

Furthermore, I am very grateful for all the assistance provided by my laboratory collegues, above all Mr. David Clemente and Mrs. Raquel Galán Fernández to whom I am especially indebted for their aid at the NMR spectrometer, and for making the hours and weeks spent in the laboratory so agreeable.

Also, I am very thankful to my family who not only supported me financially but also were always there for me during when difficulties arose, even though they were far away at times. I am glad to be able to share my happiness about the completed master thesis with them!

1. INTRODUCTION

Paeoniae are herbaceous perenniel plants belonging to the flowering plant family *Paeoniceae*. They are native to Asia, southern Europe and western North America, where their roots are commonly used as medicine, especially in China, Japan, Korea and Bulgaria. This is due to their biological activities as antioxidant, antitumor, antipathogenic, anticoagulant, anti-inflammatory, analgesic, sedative, and against female diseases.
Over 260 compounds have been isolated from the plants of *Paeoniceae* which account for their biological activity. Besides flavonoids, tannins, stilbenes, steroids, triterpenoids etc. also an abundance of monoterpenes with a very compact α-pinene structure have been obtained (Fig. 1.1).

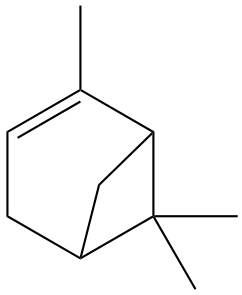
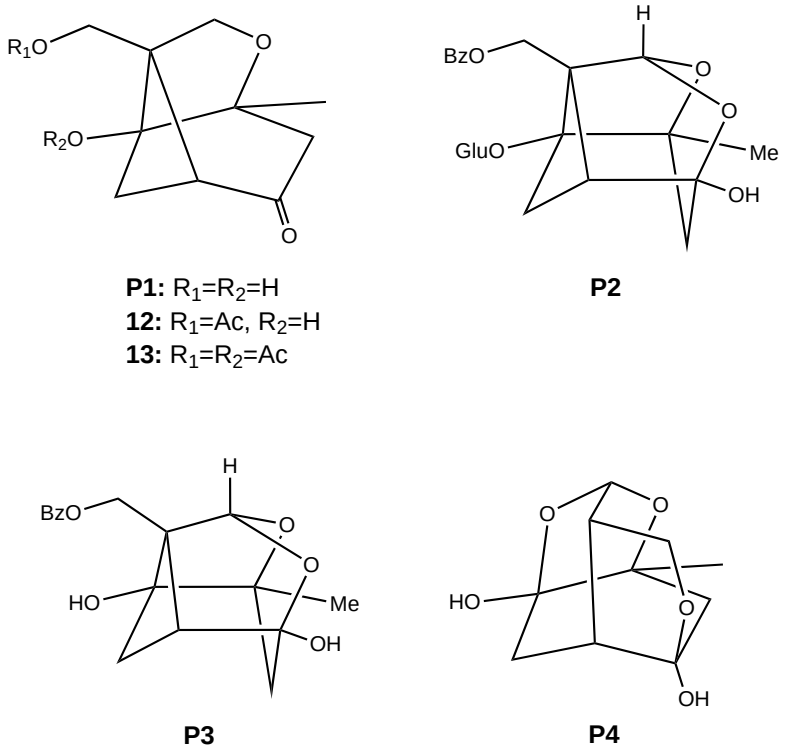


Fig. 1.1: α-Pinene structure

Paeoniflorin (**P2**) and its aglycone Paeoniflorigenin (**P3**) were isolated from *Paeonia albiflora* PALLAS by Shibata and collaborators already in the 1960ies. [1] Only recently, Paeonisuffrone (**P1**) and its mono- (**12**) and diacetate (**13**), and Paeonisuffral (**P4**) were isolated from *Paeonia suffruticosa* ANDREWS and their absolute stereostructures determined by Yoshikawa et al. (Fig. 1.2). [2, 3] These compounds account for the biological activity of japanese *Shakuyaku*, which is applied in oriental medicine as analgesic, anti inflammatory drug, antispasmodic, astringent and sedative. [4, 5]

Also, the diminishing effect on cognitive dysfunctions of cholinergic origin of *Shakuyaku-San*, a herbal medicine prepared from the roots of *Paeonia*, has been discovered. Therefore, it is applied in the treatment of Alzheimer's disease. The high interest in its synthesis lies not only in its bioactivity, but also in the difficulty that arises from the somewhat complicated access to its structure of a highly oxidated, compact pinene skeleton.



P1: R_1=R_2=H
12: R_1=Ac, R_2=H
13: R_1=R_2=Ac

P2

P3

P4

Fig. 1.2: Monoterpenes isolated from *Paoeniae*

2. ANTECEDENTS

2.1 Synthesis of (-)-Paeonisuffrone and (+)-Paeonisuffrone

(-)-Paeonisuffrone has been obtained in its optically active form starting from the tricyclic ketone **I** (Fig.2.1) by Hatakeyama and collaborators. [6]
Racemic resolution was performed by means of transformation into the optically active acetate **III** via the O-methyl mandelate ester **II**. Oxidative degradation of the isopropyl group, applying the conditions described by Criegee [7, 8], resulted in the hydroxyacetate **IV** and allowed subsequent transformation of **V**, obtained by deprotection and anew protection as bencylidene acetal, into (-)-Paeonisuffrone (**P1**).

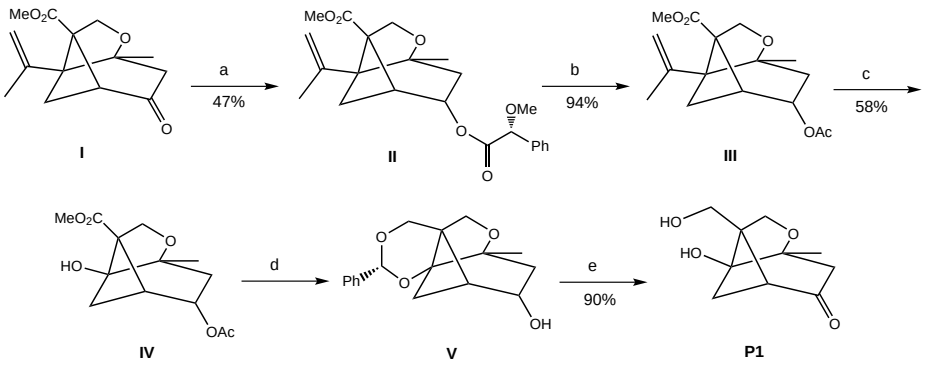


Fig. 2.1: **a**: (i) $NaBH_4$, MeOH, -20°C. (ii) (*R*)-O-methyl mandelic acid, DCC-DMAP (cat.); **b**: (i) LAH, THF; (ii) Ac_2O, pyr, DMAP (cat); **c**: O_3, MeOH, -78°C, p-$NO_2C_6H_4COCl$, Et_3N-DMAP (cat), CH_2Cl_2; **d**: (i) NaOMe, MeOH; (ii) PhCHO, pTsOH·H_2O (cat.), benzene, reflux; **e**: (i) $(COCl)_2$, DMSO, CH_2Cl_2, -60°C, Et_3N; (ii) H_2, $Pd(OH)_2$, MeOH-AcOEt-H_2O

(+)-Paeonisuffrone was synthesized in the university group of Prof. Francisco Alberto Bermejo González starting from *S*-(+)-Carvone, using similar methods as in this work (Fig.2.2). [9]

Once obtained the epoxy pivalate **6'**, a Ti(III) promoted radical cyclization gives the bicyclic compound **7a'**. After protection of the diol as benzylidene acetal, an allylic oxidation reaction is carried out to give **9'**, which can easily be transformed into the tetracyclic compound **10'** by applying a slightly basic milieu. Finally, deprotection of the diol via hydrogenation leads to the target molecule (+)-Paeonisuffrone (**11'**).

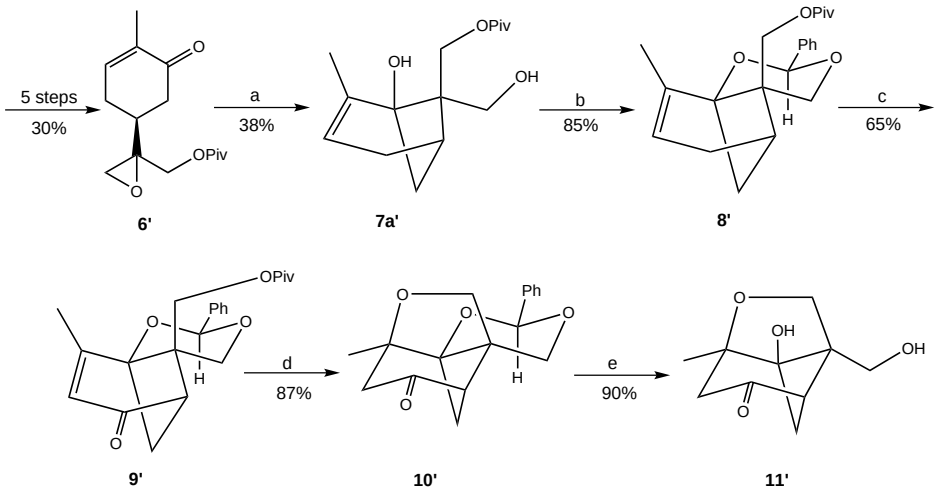


Fig. 2.2: **a**: Cp_2TiCl_2, Zn, THF, 24h, rt; **b**: BDMA, PPTS, CH_2Cl_2, 24h, rt; **c**: CrO_3, DMP, CH_2Cl_2, 4h, -20°C; **d**: NaOH 10M, CH_3OH, 24h, rt; **e**: H_2, Pd/C, etyhl acetate, rt

2.2 (-)-Paeoniflorigenin and (-)-Paeoniflorin

Regarding the synthesis of (-)-Paeoniflorigenin and (-)-Paeoniflorin, there exist notable precedent synthetic studies performed by Hatakeyama, Takano and Corey. [10, 11, 12]

The strategies of Hatakeyama and Takano (Fig.2.3) with regard to the obtention of the tricyclic derivative **I** are based on the [2+2] intramolecular photocyclization of the insaturated diene ester **VII** which is obtained in ten steps starting from the 3-ethylen dioxy butanal **VI** with an overall yield of 47%. Transformation of racemic **I**, obtained with a yield of 64% in one step starting from **VII**, into the enantiomeric pure cyclohexanone **VIII** was performed in three steps via the O-methyl mandalate ester **II** with 35% yield. Subsequently, the hydroxycarbonate aglycone **IX** was synthesized with a yield of 21%, carrying out a sequency of six steps and, finally, the natural product **P2** was obtained in two steps with 67% yield. This gives an overall yield for the synthesis of (-)-Paeoniflorin of about 1.5%.

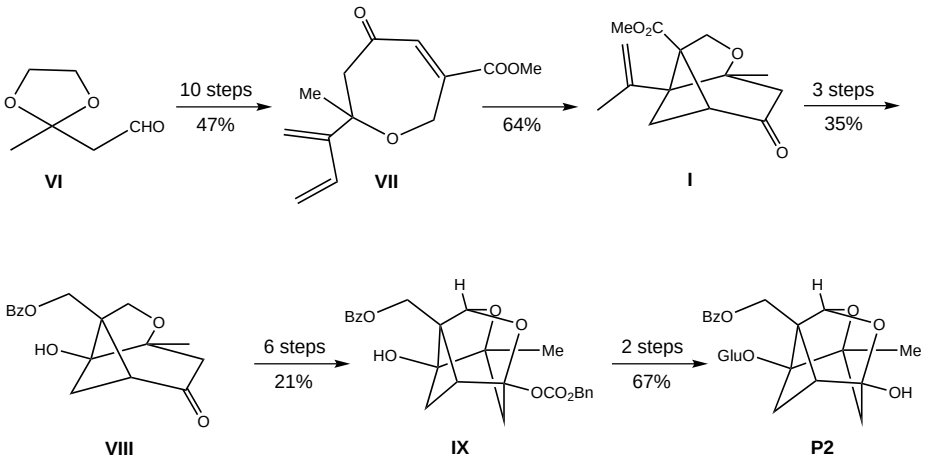


Fig. 2.3: strategy followed by Hatakeyama et all

The strategy of Corey (Fig.2.4) is based on two key cyclization processes (cationic and radical, respectively). The first cyclization step consists in the rearrangement of the epoxy lactol **XI**, which can be obtained in four steps from the triisopropylsilyl ether of dihydro *m*-Cresol (**X**) with an overall yield of 17%, pro-

moted by the triisopropylsilyl triflate, and gives compound **XII** with 35% yield. The second key step is the radical cyclization of the chloroacetone **XIII** induced by Samarium(II) iodide. This gives access to the tricyclic sceleton of (-)-Paeoniflorin (**XIV**) and occurs with 93% yield. Consequently, **XV** is obtained with a yield of 47% through transformations of the functional groups in seven steps. Finally, the application of a three-step reaction sequence leads to the target molcule **P2**, obtained with an overall yield of 17%. The overall yield for the synthesis of (-)-Paeoniflorin is therefore of about 0.5%.

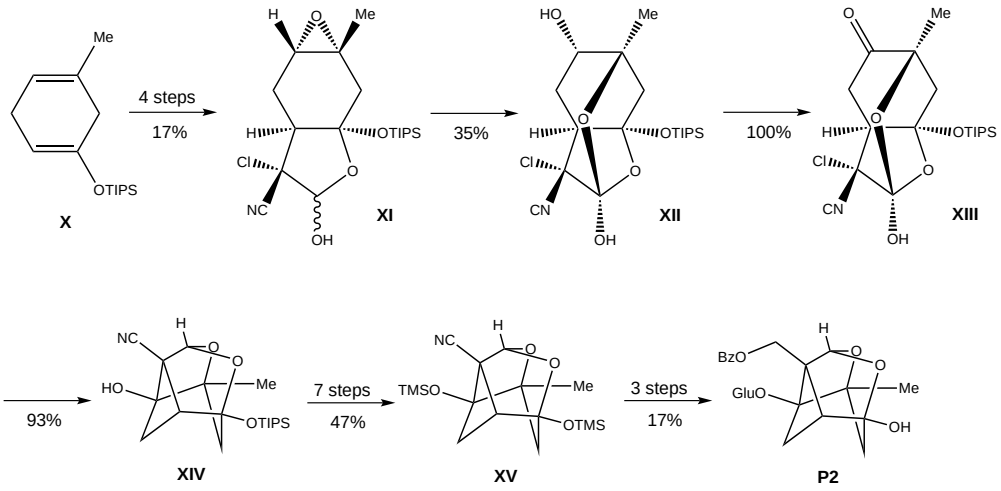


Fig. 2.4: strategy followed by Corey et al.

3. OBJECTIVES

The main objective of the presented work is the sythesis of the (-)-Paeonisuffrone mono- and diacetate, respectively, starting from (*S*)-(-)-Carvone following the retrosynthetic scheme as shown below (Fig. 3.1).

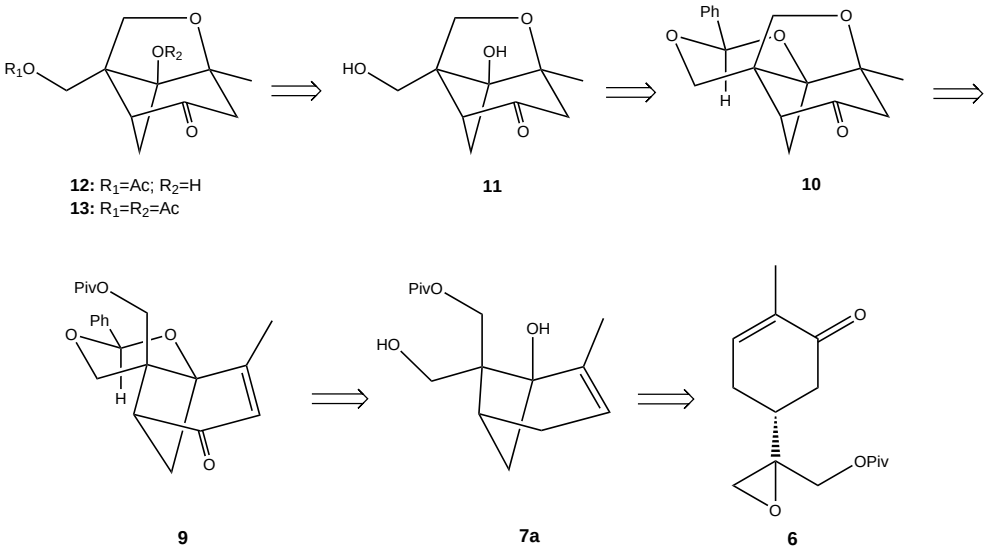


Fig. 3.1: retrosynthetic analysis

During the synthesis, the following problems need attention:

1. Radical cyclization of the epoxy enone **6** promoted by Ti(III) and the stereoselectivity of the reaction.
2. Protection of the diol **7a** in acidic milieu, avoiding Grob fragmentation. [13]
3. Allylic oxidation of the cyclohexane skeleton of the diol pivalate **8**.

4. Intramolecular Michael cyclization: The hydrolisis of compound **9** should promote the intramolecular cyclization of the hydroxy function of the hydroxy derivative **9a** on the double bond of the bicyclic cyclohexanone.

5. Deprotection of the benzylidene actetal **10** in reductive milieu resulting in the diol **11**.

6. Regioselective protection of the primary alcohol only, or of both alcohol functions to obtain the target molecules **12** and **13**, respectively.

4. METHODS

Starting from the natural product R-(-)-Carvone, we planned to synthesize the epoxy pivalate **6**, which after cyclization formed the basis for the α-pinene structure of the target molecules, in five steps.

First, a radical allylic halogenation of the double bond was expected to give the chloride **2**. Nucleophilic substitution followed by the saponification of the resulting acetate in basic milieu should result in the formation of (-)-10-Hydroxycarvone **4**. Subsequently, the primary double bond would be epoxidized by treatment with tert-butyl hydroperoxide and, finally, by protecting the remaining free hydroxyl group with pivaloyl chloride we anticipated to get structure **6**. [14, 15, 16]

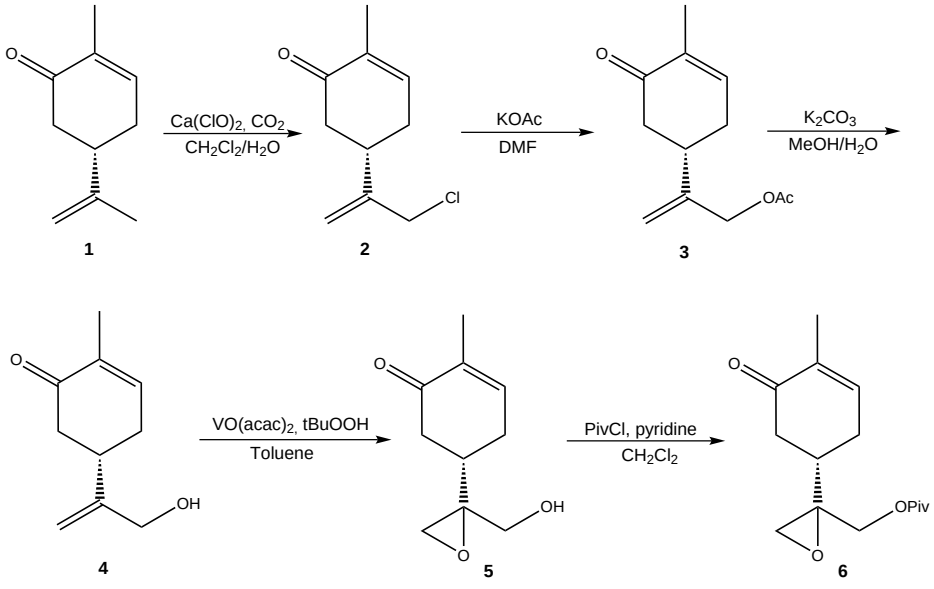


Fig. 4.1: Synthetic scheme leading to epoxy pivalate **6**

The key step of the synthesis of these natural monoterpenes is the radical cyclization of the epoxy pivalate **6**, promoted by Ti(III) (Fig.4.2). Experience gained by the university group of Prof. Francisco Alberto Bermejo González during the last four years allowed us to admit the low diastereoselection of the process (**7a:7b** $\approx$ 2:1) with 67% yield. [17].
Isolation of the diol **7a** and its protection with the benzylidene acetal was expected to allow the formation of the bicyclic pivalate **8**. Correspondingly, we anticipated the formation of **8b** parting from the diol **7b**.

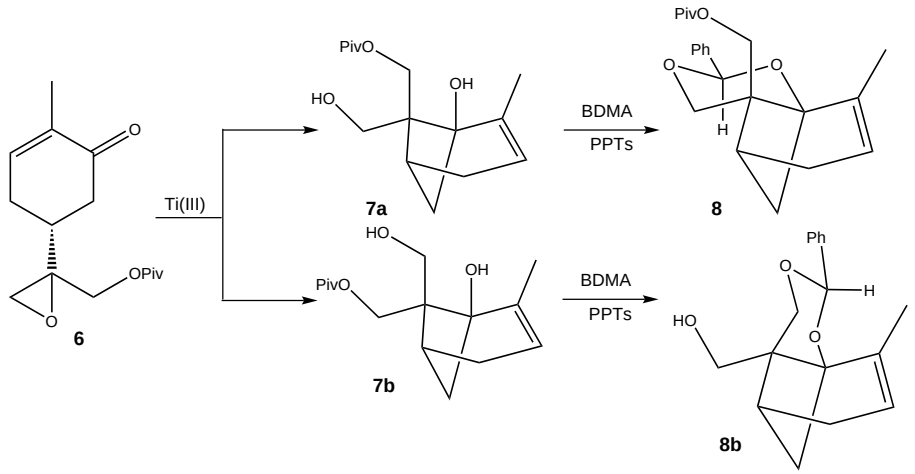


Fig. 4.2: Synthetic scheme of Ti(III) promoted cyclization

Allylic oxidation of **8** followed by an intramolecular Michael cyclization of the primary alcohol **9b** on the enone functionality should allow us to isolate the tricyclic derivative **10**.
Subsequently, deprotection by hydrogenolysis with Pd/C catalysis should give (-)-Paeonisuffrone as product (**11**) (Fig.4.3).

Furthermore, treatment of **11** with acetic anhydride (1.1 eq) and pyridine in dichloromethane at 0°C was expected to allow the isolation of **12** and **13** with 26% and 15% yields, respectively (Fig.4.4).

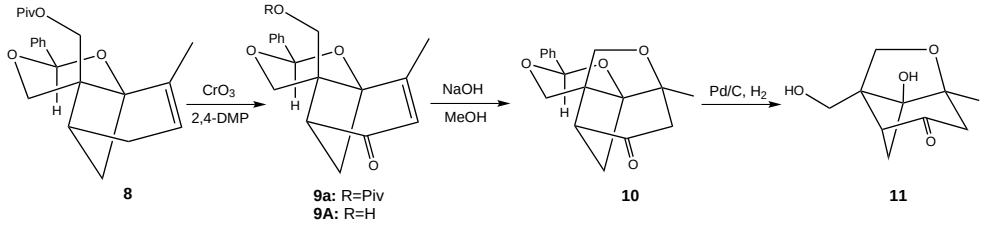


Fig. 4.3: Synthetic scheme leading to (-)-Paeonysuffrone

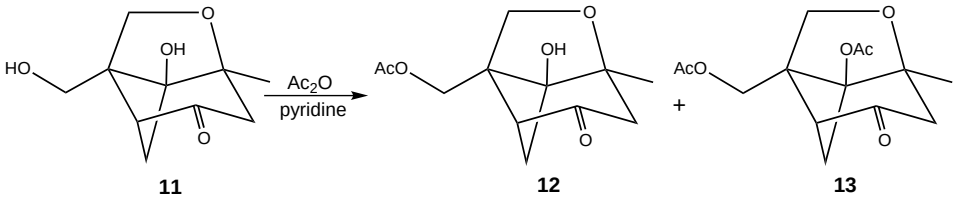


Fig. 4.4: Acetylation of diol **11**

5. RESULTS AND DISCUSSION

5.1 Preparation of the starting material: (R)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)-2,3-epoxy-1-propanol pivalate (mixture of epoxides)

The synthesis of the starting material for the obtention of functionalized α-pinenes, the epoxy pivalate **6** was accomplished starting from (R)-(-)-Carvone (Fig. 5.1). [14, 15, 16]

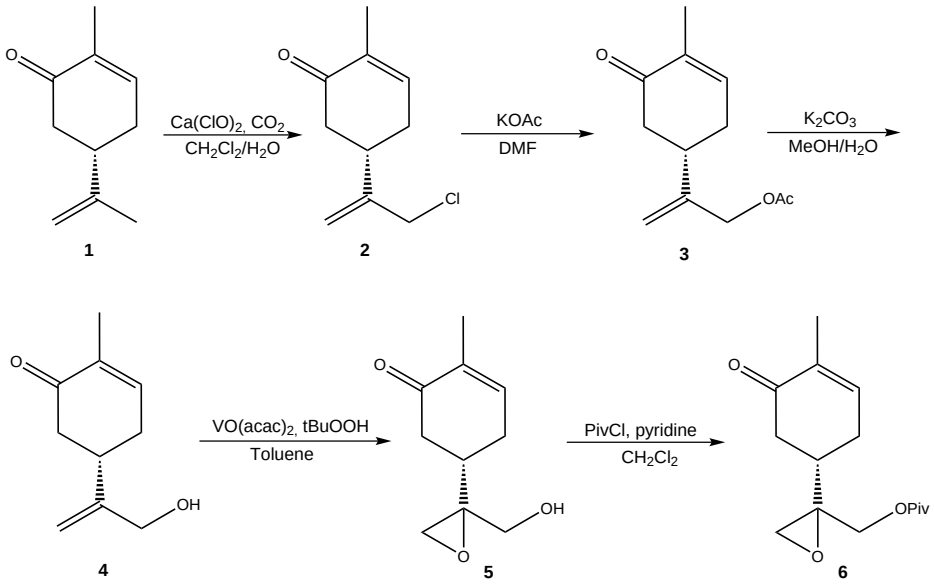


Fig. 5.1: Scheme 1

First, the radical allylic halogenation of (R)-(-)-Carvone was performed by treatment of **1** with an aqueous suspension of calcium hypochlorite for 2h. The pure allylic chloride **2** was obtained after purification by flash column cromatography with 90% yield.

The spectroscopic properties (Figs. 9.1-9.4) were identical to those described for (R)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-enone. [16]

Furthermore, the allylic acetate was obtained by displacement of the chloride with potassium acetate in DMF at 55°C for 24h. By fractionation of the crude product by flash column cromatography we were able to isolate pure **3** with 83% yield.
The spectroscopic properties obtained for this compound were found identical to those described previously for (R)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)allyl acetate (Figs. 9.5-9.8). [16]

Subsequently, the acetate was saponified by treatment of the acetate **3** under basic conditions at room temperature for 2h. Fractionation of the crude product by flash column chromatography led to the isolation of **4** with 83% yield.
The spectroscopic properties of the obtained alcohol (Figs. 9.9-9.12) were found identical to those described for (R)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-enone. [16]

Thereafter, epoxidation of the allylic double bond was achieved by treatment of the alcohol **4** with tBuOOH in Toluene for 2h at 80°C. Standard workup procedures and purification of the crude product by flash column chromatography led to the isolation of **5** with 88% yield.
The spectroscopic properties obtained for **5** were found identical to those described for (R)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)-2,3-epoxypropan-1-ol (Figs. 9.13-9.16)

Finally, the alcohol functionality was protected by reaction of the epoxy alcohol **5** with pivaloyl chloride and pyridine. The epoxy pivalate **6** was obtained with 98% yield by fractionation by flash chromatography.
The spectroscopic properties (Figs. 9.17-9.20) obtained for **6** were found identical to those described in literature for (R)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)-2,3-epoxy-1-hidroxy pivalate.

The overall yield of these five steps is therefore 53%. Since these reactions were all already very well studied and not known to give problems while working with larger quantities, we were able to synthesize some reserve for further experimantation.

5.2 Study of the radical cyclization reaction promoted by Ti(III)

The radical cyclization of the epoxy pivalates **6** was accomplished by treatment of the starting material with Cp_2TiCl, obtained by reduction of the titanocene chloride Cp_2TiCl_2 with metallic Zn in THF. [18, 19, 20, 21, 22, 23, 24, 25, 26, 27]

The product turned out to be a diastereoisomeric mixture of the diols **7a** and **7b**, and the elimination product **7c** in very small quantities (Fig. 5.2).

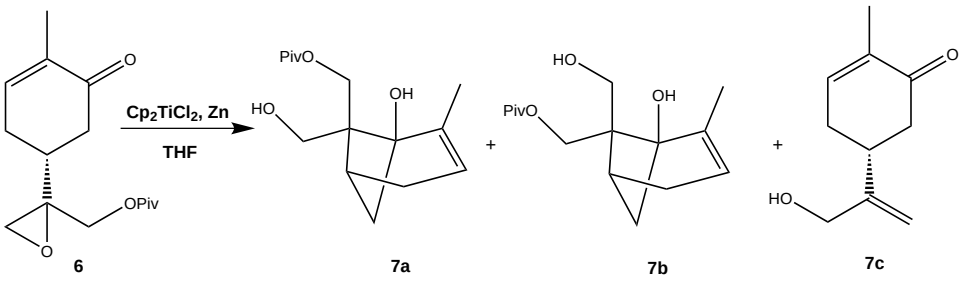


Fig. 5.2: Scheme 2

The diastereoselectivity was found to be rather low with a

$$\textbf{7a} : \textbf{7b} = 2 : 1 \text{ ratio.}$$

This was not only problematic because of the loss of substance since the diastereomer **7b** did not give the wanted product in the next step, but also because separation of the two diastereomers by flash column cromatography was somewhat problematic and time-consuming.
Another problem of this reaction is the fact that while working with increasing

amounts the yield drops. Therefore we confined ourselves to work with amounts of starting material **6** not exceeding 250 mg per attempt.

It is known in literature that the formation of Cp_2TiCl is accompanied by the formation of $ZnCl_2$. The latter is considered to be a Lewis acid and can therefore promote the aperture of the epoxide and its transformation into the correspondent alcohol, known as Grob fragmentation reaction. [13]
The formation of **7c** can be rationalized in terms of the elimination process of the pivalate functionality and simultaneous formation of a double bond in the titanoxy anion **6b**. The anion is formed by the transference of a second electron from the Ti(III) reagent to the titanoxy radical **6a** (Fig. 5.3).

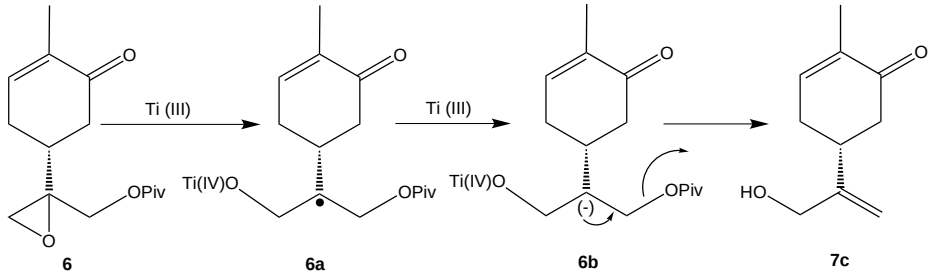


Fig. 5.3: Scheme 3

The structural assignment of both isomers **7a** and **7b** was achieved by careful analysis of the spectroscopic data (Figs. 9.21- 9.36), mainly the HMBC and the ROESY spectra.

The $^{1}H/^{13}C$-correlations along two and three bonds (HMBC, Figs. 9.26, 9.34) enabled us to identify the signals of the CH_2 group next to the pivalate function in the structures **7a** and **7b**. The signals in the ROESY spectra (Figs. 9.24, 9.24) allowed the identification of the Nuclear Overhauser Effect between the exo proton of the bridge of the cyclobutane and the hydroxymethyl group next to it in both diastereomers (Fig. 5.4).

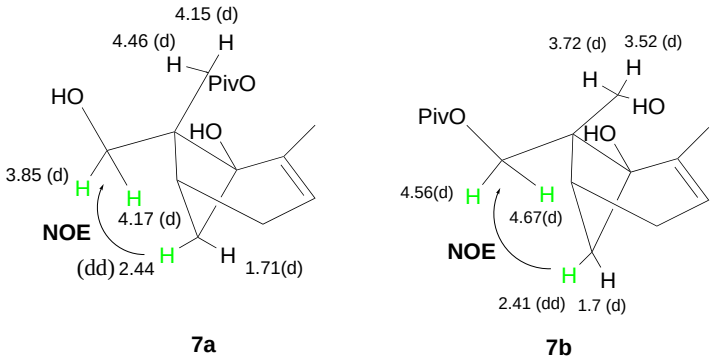


Fig. 5.4: NOE in structures **7a** and **7b**

5.3 Protection of the diol by formation of the bencylidene acetal

Once obtained the diol **7a**, we proceeded to the protection of the two free hydroxyl groups by treatment with benzaldehyde dimethyl acetal (BDMA) under acidic conditions (Fig. 5.5).

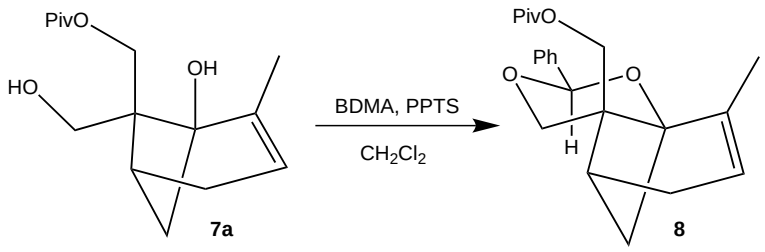


Fig. 5.5: Scheme 4

By fractionation of the crude reaction product by flash chromatography we were able to isolate **8** with 67% yield. [28]

The proposed structure for the acetal **8** was affirmed by the study of the spectroscopic properties, above all the HMBC (Fig. 9.42) and ROESY (Fig. 9.40) spectra.
The correlations along three bonds enabled the identification of the signals of the CH_2 group next to the pivalate functionality. In the ROESY spectrum could be observed the NOE between the *exo* proton of the bridge of the cyclobu-

tane (δ = 3.24ppm), the hydroxymethyl group of the acetal (δ = 4.25ppm and δ = 4.43ppm) and the bencylic proton (δ = 5.93ppm) of the molecule (Fig. 5.6).

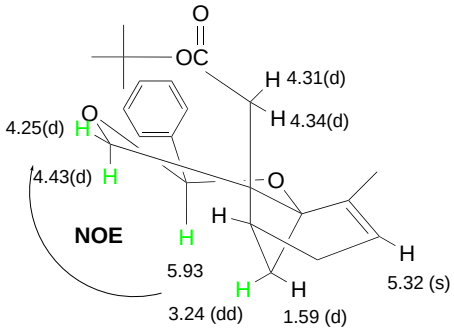


Fig. 5.6: NOE in stucture **8**

5.4 Allylic oxidation of the cyclohexyl skeleton

The allylic oxidation of the acetal **8** was achieved using Cr(VI) oxide and DMP. The reaction was carried out by stirring at -20°C for 5h (Fig. 5.7). [29]

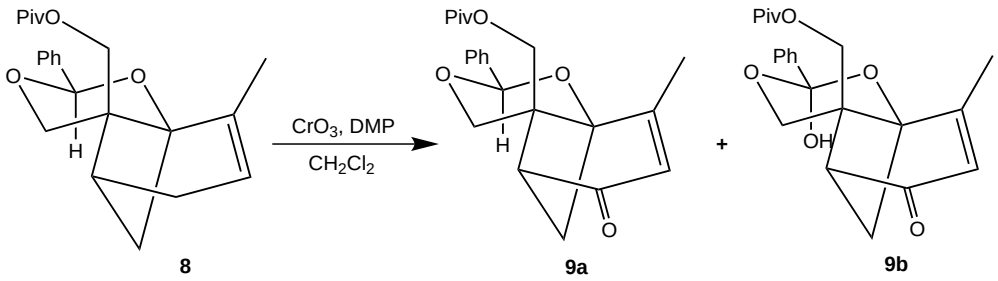


Fig. 5.7: Scheme 5

The crude product was fractionated by flash chromatography and the tricyclic enones **9a** and **9b** were obtained with 65% and 25% yields, respectively.

Study of the spectroscopic data confirmed the proposed structure for **9b** and the assumption that a second oxidation took place at the bencylic position due to excess of CrO_3.

The spectroscopic properties of **9a** (Figs. 9.46-9.54) and **9b** (Figs. 9.55-9.61) allowed the confirmation of the proposed structures by similar studies of the spectra to those already described for the compounds **7a**, **7b** and **8**.
The signals of the CH_2 group next to the pivalate function were identified using HMBC (Figs. 9.51, 9.60). Careful study of the ROESY spectra (Figs. 9.49, 9.58) led to establishing the correlation between the *exo* proton of the cyclobutane bridge and the hydroxymethyl group bonded to the bencyldene acetal (Fig. 5.8).

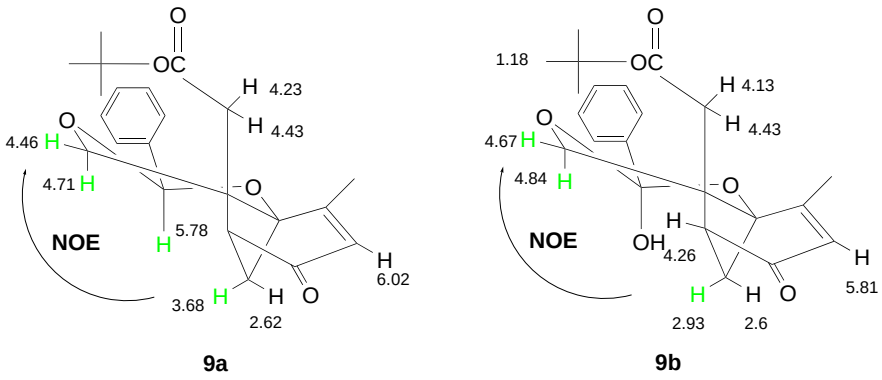


Fig. 5.8: NOE in structures **9a** and **9b**

5.5 Obtention of the tetracyclic system via intramolecular Michael addition

The formation of the oxymethylenic bridge via cyclization of the hydroxyl funtion reacting with the enone funcitonality was achieved by treatment of **9a** in basic conditions (Fig. 5.9).

After purification by flash column chromatography, the tetracyclic compound **10** was isolated with 42% yield.
Structural assignment of **10** was achieved by means of its complete spectroscopic analysis (Figs. 9.62-9.69), basically consulting its HMBC (Fig. 9.67) and ROESY (Fig. 9.65) spectra (Fig. 5.10).
Successful transformation could be asserted through the disappearance of the ^{1}H-NMR signal of the pivalate group (δ = 1.17ppm) present in structure **9a** (Fig. 9.46).

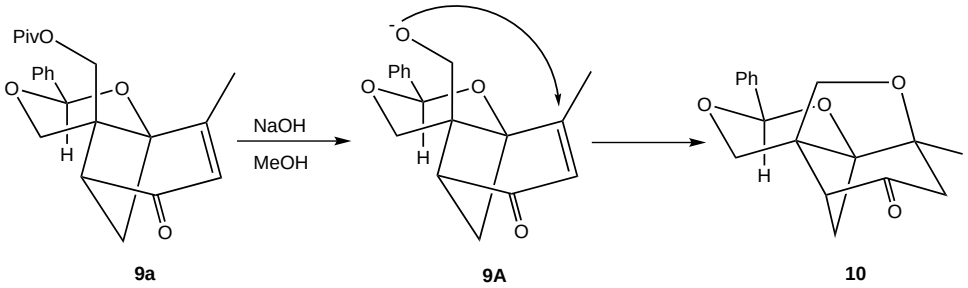


Fig. 5.9: Scheme 6

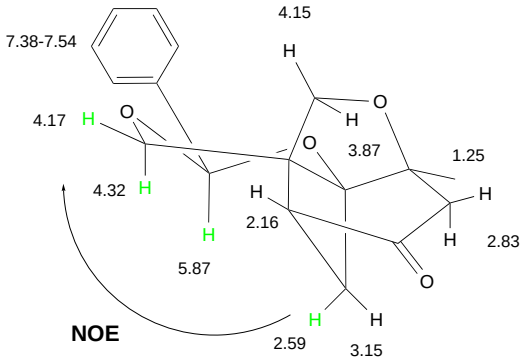


Fig. 5.10: NOE in structure **10**

5.6 Deprotection of the benzyliden acetal

Deprotection of the benzyliden acetal **10** was achieved by Palladium catalized hydrogenolysis (Fig. 5.11).

Compound **10** was stirred with the catalyst under hydrogen atmosphere at room temperature to give the free diol **11** with 90% yield.
The isolated compound (Fig. 5.12) resulted to be (-)-Paeonisuffrone by comparison of its spectroscopical properties (Figs. 9.70-9.77) with those described by Yoshikawa et all. [2, 3]

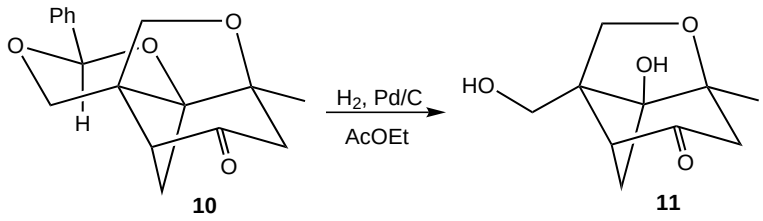


Fig. 5.11: Scheme 7

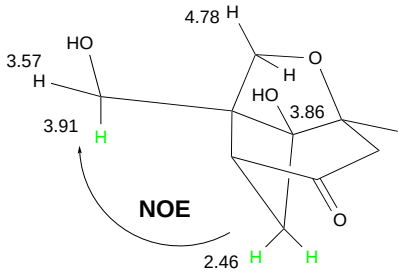


Fig. 5.12: NOE in structure **11**

5.7 Formation of (-)-Paeonisuffrone mono- and diacetate

To obtain the target molecule **12**, specific protection of the primary alcohol function only was carried out (Fig. 5.13).

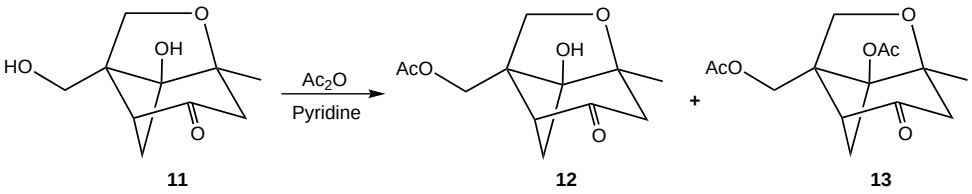


Fig. 5.13: Scheme 8

(-)-Paeonisuffrone was stirred with acetic anhydride and pyridine under argon atmosphere for 20 hours. Due to excess of acetic anydride, part of the tertiary alcohol function reacted also, and the diacetate **13** formed.
Fractionation of the crude product by flash column chromatography led to the isolation of the mono- and diacetates **12** and **13** with 26% and 15% yield.

Full study of the spectroscopic data of **12** (Figs. 9.78-9.83) and **13** (Figs. 9.84-9.89) was performed and the structures proposed confirmed by the signals of the acetate functions:
For compound **12** we find the characteristic ^{1}H-NMR signal at $\delta = 2.11$ppm (s), the ^{13}C signal of the carboxyl group at $\delta = 171.5$ppm and an additional peak at $\delta \approx 20$ppm which corresponds to the methyl group of the acetate.
For compound **13** the corresponding signals are found at $\delta = 2.08$ppm (s) and $\delta = 2.12$ppm (s) in the ^{1}H-NMR spectrum. In the ^{13}C-NMR signals at $\delta = 169.5$ppm and $\delta = 170.5$ppm and two additional peaks at $\delta \approx 20$ppm can be seen, which correspond, as above, to the carboxyl groups and the methyl groups of the acetates, respectively.

The synthesis of the target molecules, the (-)-Paeonisuffrone acetates **12** and **13**, in 11 steps was successful with a somewhat low overall yield of less than 1%, which is mostly due to the loss of substance in step 6 when two diastereomers form and step 8, in which oxidation on two sites may occur producing the byproduct **9b**.

6. CONCLUSION

6.1 Summerization

1. Preparation of the epoxy pivalate **6** in 5 steps starting form the natural product R-(-)-Carvone was successfully carried out with an overall yield of 53% following the sythetic route shown in Fig. 6.1.

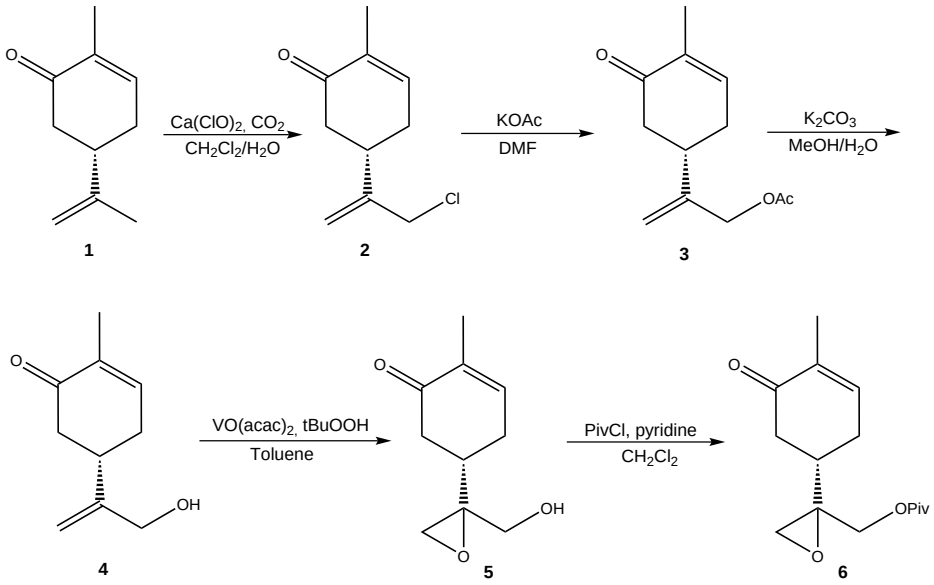


Fig. 6.1: Synthetic route to epoxy pivalate **6**

2. Intramolecular radical cyclization of the epoxy pivalate **6**, promoted by Ti(III), led to the formation of the diastereomeric diols **7a** (49% yield) and **7b** (27% yield) (Fig.6.2). Separation via flash column chromatography on silica gel rendered possible the isolation and complete charactarization of both isomers. The proposed structures were confirmed by study of the spectroscopic data of the compounds, especially of the HMBC

(Figs. 9.26, 9.34) and ROESY spectra (Figs. 9.24, 9.32).

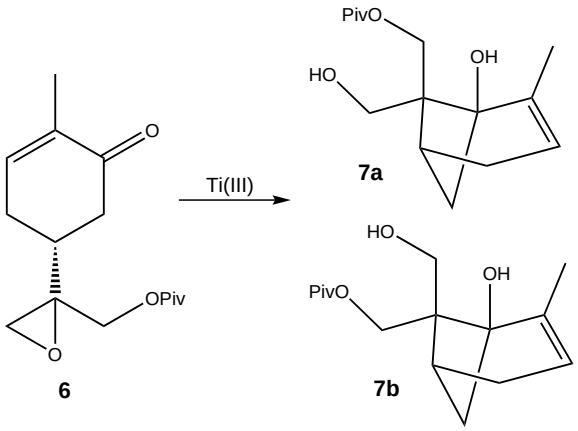


Fig. 6.2: Cyclization reaction giving **7a** and **7b**

3. Protection of the diol **7a** using benzaldehyde dimethyl acetal (BDMA) and pyridinium p-toluenesulfonate (PPTs) in CH_2Cl_2 was successful (Fig.6.3). Isolation of the benzylidene acetal **8** by flash column chromatography allowed its structural assignment based on its spectroscopic data (Figs. 9.37-9.44).

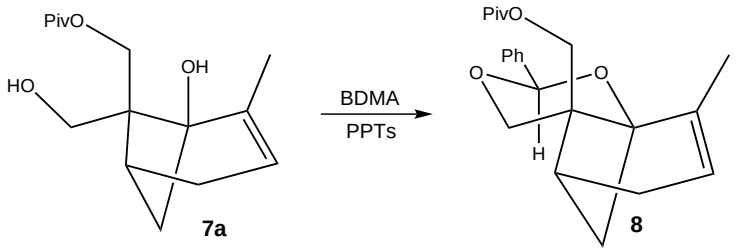


Fig. 6.3: Protection of diol

Unfortunately, the same conditions applied to the diol **7b** lead to **7c**, the product of Grob fragmentation [13] of the starting material (Fig.6.4).

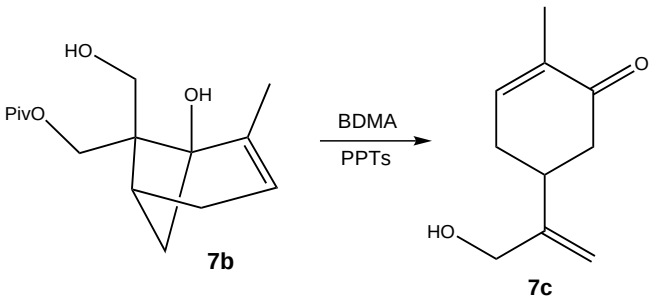


Fig. 6.4: Grob fragmentation

4. Allylic oxidation of the cyclohexenyl derivative **8** by treatment with the oxidant complex CrO_3·DMP yielded the enone **9a** with 16% yield. The tertiary alcohol **9b** was isolated as a byproduct (Fig.6.5).

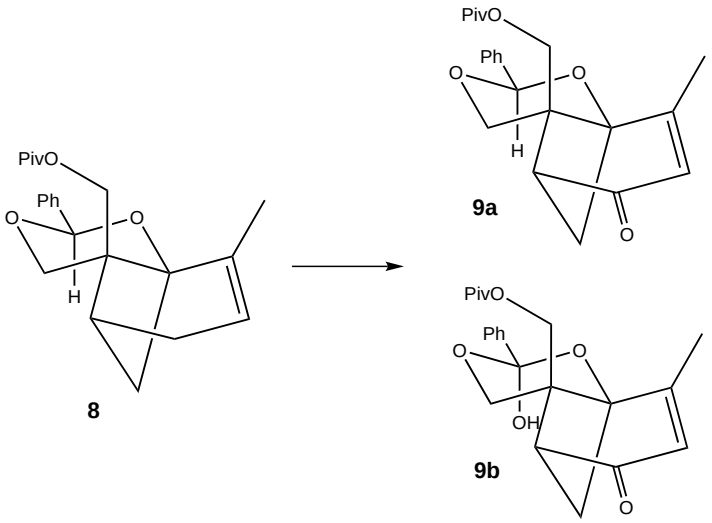


Fig. 6.5: Allylic oxidation

5. Intramolecular cyclization of the pivalate on the enone functionality of **9a** was performed under basic conditions by treatment with NaOH (5M) in methanol, and subsequent acidification of the crude reaction product (Fig.6.6). After purification by flash column chromatography on silica gel, the pure product resulted to be the tricyclic compound **10** based on its spectroscopic properties, which was obtained with 42% yield.

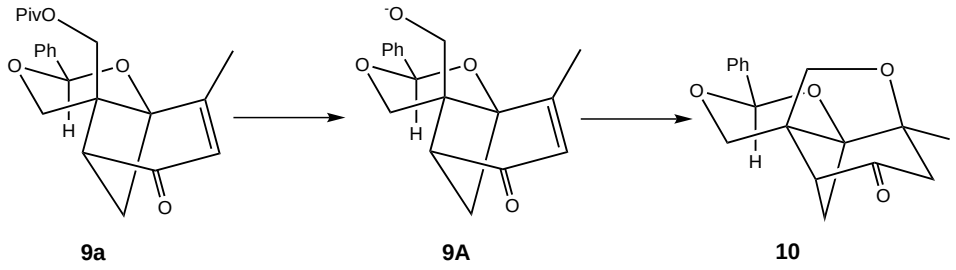


Fig. 6.6: Intramolecular Michael cyclization

6. Deprotection of the benzylidene acetal **10** was successfully carried out by Palladium catalyzed hydrogenolysis at room temperature (Fig.6.7). The transformation to (-)-Paeonysuffrone was quantitative.

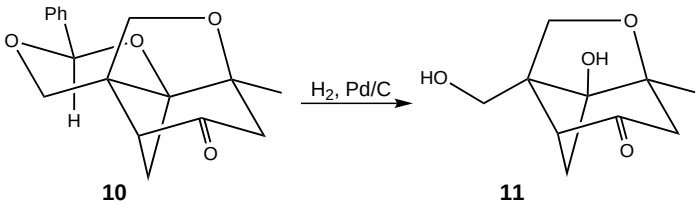


Fig. 6.7: Deprotection via Palladium catalyzed hydrogenolysis

7. Treatment of a dichloromethane solution of **11** with acetic anhydride in pyridine afforded a mixture of the (-)-Paeonysuffrone monoacetate **12** and the diacetate **13** with 26% and 15% yields, respectively.

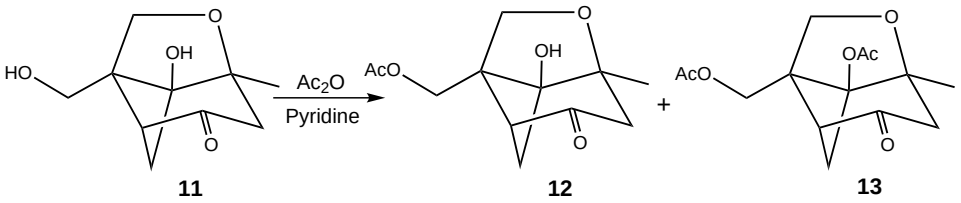


Fig. 6.8: Acetylation of diol **11**

6.2 Future Prospects

The roots of chinese peonies still provide an abundance of investigation topics. Not all of its components are known yet and a lot of the ones isolated have not been obtained via synthesis.

The group of Prof. Francisco Alberto Bermejo González goes on working on this subject and has developed strategies to synthesize a variety of components of Paeoniceae (Paeoniflorin **XVIIa**(**P2**) and its aglycone **XVIIb**; Albiflorin **XVIIIa** and its aglycone **XVIIIb**; Paeoniflorigenone **XIXa**, 7R-Paeonimetabolin-I **XIXb** and 7S-Paeonimetabolin-I **XIXc**; the three bicyclic lactones Paeonilactone A **XXa**, Paeonilactone B **XXb** and Paeonilactone C **XXc**; Paeonisuffral **XXIa** and its methyl ether **XXIb**; Paeonisuffrone **XXII**) starting from the cyclic enone **XVI** (Fig. 6.9).

They are now actively working on a new strategy to synthesize the byciclic enone **XVI**, different from the rout presented in this work, but still starting from the natrual product R-(-)-Carvone, and on the synthesis of Albiflorin (**XVIIIa**) and its aglycone **XVIIIb**.

Compound **XXIII** has already been obtained by way of an 11 step synthesis with an overall yield of 5% and should be easily transformed into **XVI** (Fig. 6.10).

As shown in this work, compound **XVI** (equivalent to structure **7a**) can be transformed into the bencylidene acetal **10** in 3 steps. The resulting protected (-)-Paeonisuffrone may then give way to the synthesis of Albiflorin (**XVIIIa**) and Paeoniflorin (**XVIIa**), and their aglycones **XVIIIb** and **XVIIb**, respectively (Fig. 6.11).

Finally, the synthesis of the Albiflorin aglycone **XVIIIa** would give access to the Paeonilactones A (**XXa**), B (**XXb**), and C (**XXc**) by way of its rearrangement in acidic milieu (Fig 6.12).

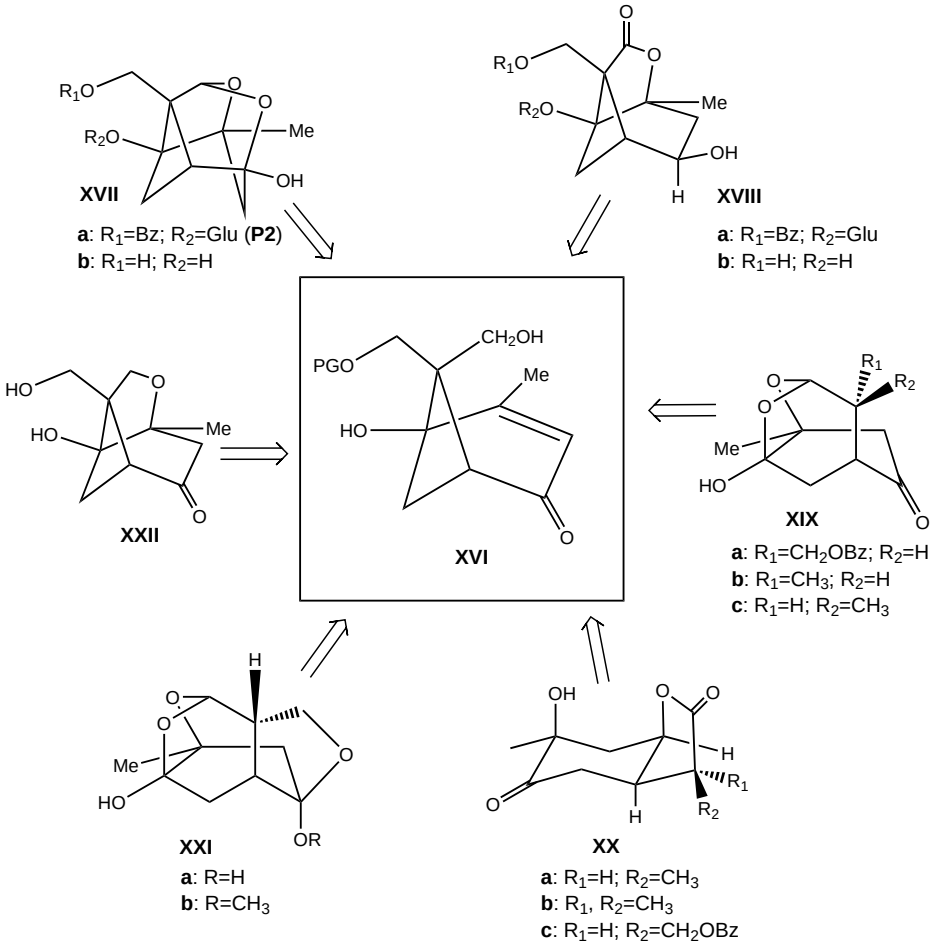


Fig. 6.9: Overview of accessible molecules starting from structure **XVI**

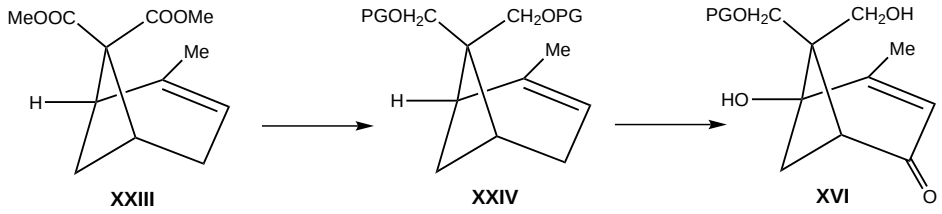


Fig. 6.10: Alternative synthetic route to **XVI**

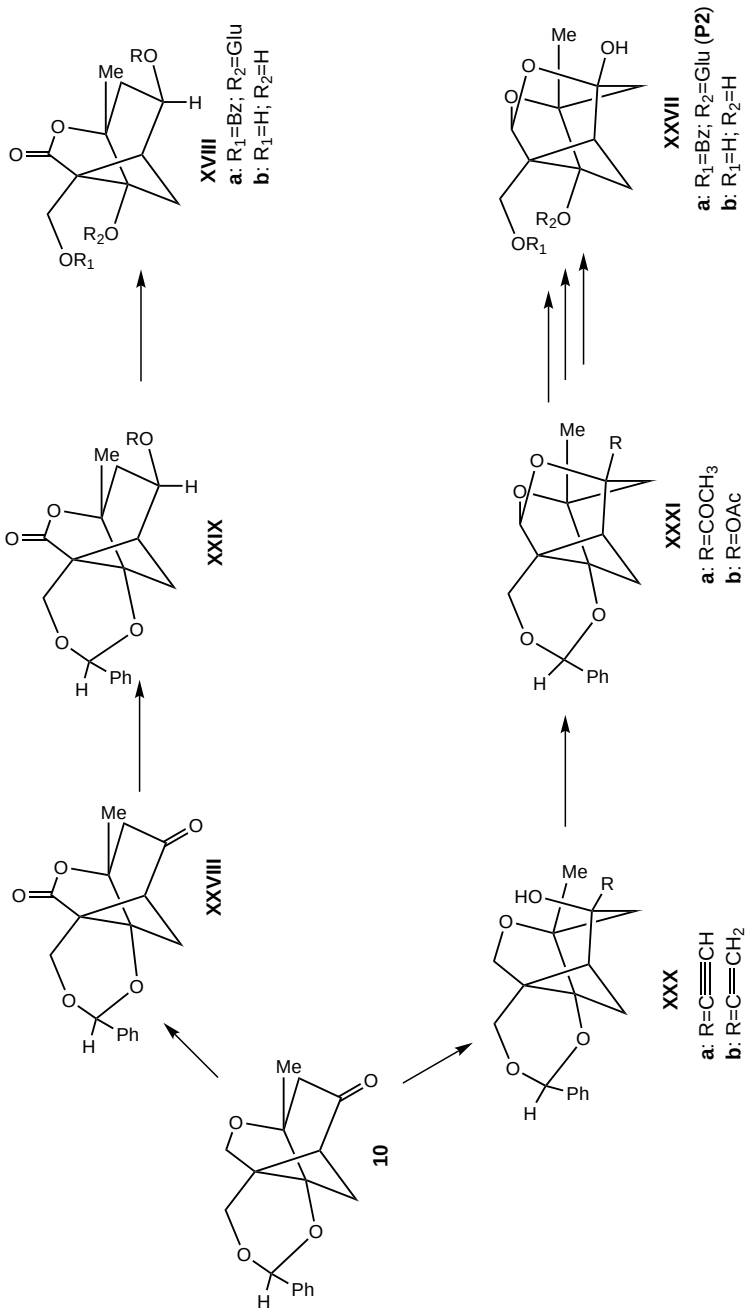


Fig. 6.11: Synthetic route to Albiflorin (**XVIIIa**) and Paeoniflorin (**XVIIa**), and their aglycones **XVIIIb** and **XVIIb**, respectively

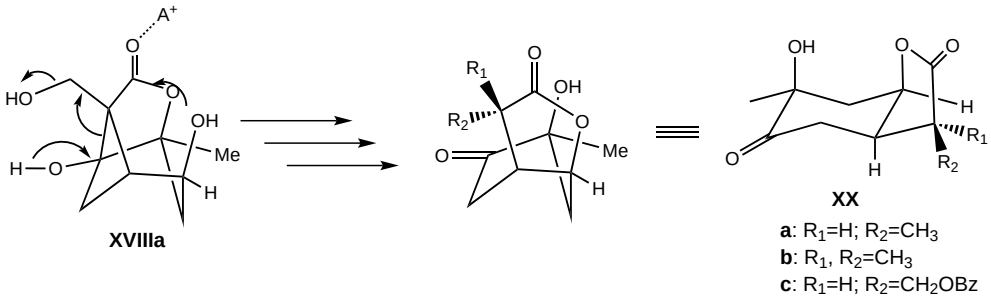


Fig. 6.12: Synthetic route to the Paeonilactones A (**XXa**), B (**XXb**), and C (**XXc**)

7. EXPERIMENTAL SECTION

7.1 General techniques

7.1.1 Optical rotation

The optical rotation values were measured using a Perkin Elmer 241 digital polarimeter with a cell of 1 dm length.

7.1.2 NMR spectra

Most of the spectra were obtained using a Varian Mercury spectrometer (200 MHz), although a few were measured on a Bruker Mod. WP-200-SY spectrometer (200 MHz) and a Bruker Avance spectrometer (400 MHz), respectively.
Chemical shifts δ are expressed in ppm with reference to the magnetic field of the spectrometer, and coupling constants in Hz.

7.1.3 Mass spectrometry

A quadrupole mass spectrometer Shimadzu QP5000 applying EI ionization technique was used for obtaining gas phase mass spectrometry data. A DB-5 column of 30 m length, 0.25 mm diameter, and 0.25 μm thickness of the stationary phase was used.
HRMS spectra were obtained using a hybrid spectrometer of cuadrupole-TOF Applied Biosystems QSTAR XL operating with ESI ionization technique. The samples were introduced into the spectrometer via infusion of a solution in methanol and were ionized at 5 KV. The indicated precision, measuring masses inferior to 400 Da, was 5 ppm.

7.1.4 IR spectroscopy

All IR spectra wer obtained using a Nicolet IR100 spectrometer with a resolution of 4 cm^{-1}.

7.2 Reagents and solvents

The solvents THF, toluene and hexane were depurated by distillation of the commercial product over metallic sodium in argon atmosphere for immediate use.
Dichloromethane and ethyl acetate were distilled over calcium hydride in argon atmosphere for immediate use.
Other liquid reagents and solvents were distilled immediately before use.

7.3 Chromatographic techniques

7.3.1 Flash column chromatography

Silica gel Merck 60 (0.040-0.063 mm) was used for all flash column chromatographies, and pressure was applied using pumps. Eluents consisted of mixtures of hexane and ethyl acetate in different ratios, as indicated in every case. The composition of the obtained fractions was checked by TLC.

7.3.2 Thin layer chromatography

Plates of the type F 1500/ LS254 were used for TLC. The Visualization was achieved using an UV lamp with wavelengths of 254 and 300 nm, or by colouring with a solution of anisaldehyde in H_2SO_4/ethanol (25:75) and subsequent heating to about 120°C.

7.4 (R)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-enone

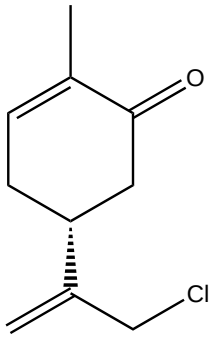


Fig. 7.1: **2**

To a solution of $Ca(ClO)_2$ (17.13 g, 119.82 mmol, 1.2 eq) in water (26 mL) was added a solution of *R*-(-)-Carvone (15.00 g, 99.85 mmol, 1.0 eq) in CH_2Cl_2 (262.5 mL). While stirring, dry ice was added little by little during two hours of reaction.

The formed salts were filtered. The aqueous layer of the resulting filtrate was separated and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4 anhydrous, and the solvent evaporated under reduced pressure.

The residue was chromatographed over silica gel, eluting with hexane/ethyl acetate (8:2) to give the chloro substituted product **2** (yellow oil, 16.47 g, 89.68 mmol, 90%).

$[\alpha_D^{20}]$ = -43.3° (c = 1.14 mg/mL, $CHCl_3$)

^{1}H-NMR: ($CDCl_3$) (Fig. 9.1) δ[ppm] = 1.79 (s, 3H), 2.1-2.7 (m, 5H), 4.09 (s, 2H), 5.06 (s, 1H), 5.26 (s, 1H), 6.77 (s, 1H)

^{13}C-NMR: ($CDCl_3$) (Fig. 9.2) δ[ppm] = 15.34 (q), 31.25 (t), 37.85 (d), 42.90 (t), 46.67 (t), 114.88 (t), 135.42 (s), 143.65 (d), 146.54 (s), 198.37 (s)

IR: (Fig. 9.3) ν[cm^{-1}] = 3453, 2957, 2924, 1726, 1672, 1463, 1433, 1370, 1254, 1109, 1057, 905

MS-EI: (Fig. 9.4) m/z (%): 184 (4) (M^+), 149 (15), 107 (13), 93 (29), 82 (100), 69 (6)

7.5 (R)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)allyl acetate

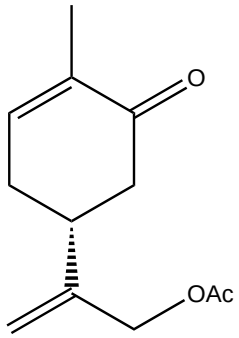


Fig. 7.2: **3**

To a solution of **2** (4.00 g, 21.33 mmol, 1.0 eq) in DMF (50 mL) was added potassium acetate (4.46 g, 45.49 mmol, 2.1 eq). The reaction mixture was stirred at 55°C under argon atmosphere for six hours.
After cooling to room temperature, water (50 mL) was added and the aqueous layer extracted with diethyl ether (7 x 30 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (2 x 50 mL), dried over Na_2SO_4 anhydrous, and the solvent evaporated under reduced pressure.
The residue was purificated via flash column chromatography over silica gel, eluting with hexane/ethyl acetate (7:3) to give the acetate **3** (clear oil, 3.72 g, 17.87 mmol, 83%).

$[\alpha_D^{20}]$ = 59.58° (c = 1.685 mg/mL, $CHCl_3$)
^{1}H-NMR: ($CDCl_3$) (Fig. 9.5) δ[ppm] = 1.75 (s, 3H), 2.05 (s, 3H), 2.28-2.57 (m, 5H), 4.55 (s, 2H), 5.01 (s, 1H), 5.14 (s, 1H), 6.71 (s, 1H)
^{13}C-NMR: ($CDCl_3$) (Fig. 9.6) δ[ppm] = 15.35 (q), 20.60 (q), 31.18 (t), 38.37 (d), 42.50 (t), 65.41 (t), 113.32 (t), 135.36 (s), 143.78 (d), 145.19 (s), 170.21 (s), 198.62 (s)
IR (film): (Fig. 9.7) ν[cm^{-1}] = 2953, 2924, 2890, 1742, 1674, 1433, 1371, 1231, 1111, 1045, 1030, 905
MS-EI: (Fig. 9.8) m/z (%): 208 (5) (M^+), 182 (18), 148 (100), 106 (56), 82 (97)

7.6 (R)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-enone

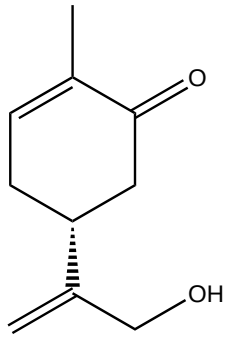


Fig. 7.3: **4**

To a solution of **3** (3.70 g, 17.70 mmol, 1.0 eq) in methanol/water (1:1) (50 mL) was added a saturated solution of potassium carbonate in water (11 mL). The mixture was stirred rigorously during two hours of reaction.
Afterwards, the methanol was evaporated under reduced pressure and the remaining aqueous solution saturated with NaCl and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na_2SO_4 anhydrous, and the solvent was evaporated under reduced pressure.
The residue was cleaned chromatographically over silica gel, eluting with hexane/ethyl acetate (1:1) to give the alcohol **4** (clear oil, 2.45 g, 14.76 mmol, 83%).

$[\alpha_D^{20}]$ = -90.82° (c = 1.22 mg/mL, $CHCl_3$)
^{1}H-NMR: ($CDCl_3$) (Fig. 9.9) δ[ppm] = 1.78 (s, 3H), 2.2-3.0 (m, 5H), 4.15 (s, 2H), 4.95 (s, 1H), 5.15 (s, 1H), 6.73 (s, 1H)
^{13}C-NMR: ($CDCl_3$) (Fig. 9.10) δ[ppm] = 15.28 (q), 31.45 (t), 38.06 (d), 43.05 (t), 64.32 (t), 110.01 (t), 135.21 (s), 144.64 (d), 150.18 (s), 199.54 (s)
IR: (Fig. 9.11) ν[cm^{-1}] = 3424, 2924, 2888, 1667, 1433, 1370, 1248, 1111, 1044, 905
MS-EI: (Fig. 9.12) m/z (%): 166 (26) (M^+), 148 (30), 133 (8), 106 (69), 82 (100), 65 (11)

7.7 (R)-5-((S)-2-(hydroxymethyl)oxiran-2-yl)-2-methylcyclohex-2-enone

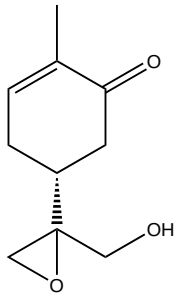


Fig. 7.4: **5**

To a solution of **4** (2.35 g, 14.14 mmol, 1.0 eq) and Vanadyl acetylacetonate (37 mg, 0.14 mmol, 0.01 eq) in toluene (25 mL) was added tert-butyl hydroperoxide (1.9 mL, 16.97 mmol, 1.2 eq) at 80°C under argon atmosphere and the reaction was stirred for two hours.
After cooling to room temperature, a solution of $Na_2S_2O_3$ 10% (4.5 mL) was added and the mixture stirred for 15 minutes. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na_2SO_4 anhydrous, and the solvent was evaporated under reduced pressure.
The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (1:3) to give the epoxy alcohol **5** (slightly yellow oil, 1.60 g, 12.44 mmol, 88%).

$[\alpha_D^{20}]$ = -49.22° (c = 1.46 mg/mL, $CHCl_3$)
^{1}H-NMR: ($CDCl_3$) (Fig. 9.13) δ[ppm] = 1.73 (s, 3H), 2.0-3.0 (m, 7H), 3.5-4.0 (m, 3H), 6.70 (s, 1H)
^{13}C-NMR: ($CDCl_3$) (Fig. 9.14) δ[ppm] = 15.408 (q), 28.014 (t)*, 36.780 (d)*, 39.269 (t)*, 48.519 (t)*, 60.567 (s), 62.243 (t)*, 135.493 (s), 143.775 (d)*, 198.354 (s)*
IR: (Fig. 9.15) ν[cm^{-1}] = 3472, 2926, 2891, 1738, 1713, 1672, 1433, 1370, 1165, 1109, 1049
MS-EI: (Fig. 9.16) m/z (%): 182 (2) (M^+), 164 (3.5), 151 (10), 108 (100), 82 (64), 67 (17)

7.8 ((R)-2-((R)-4-methyl-5-oxocyclohex-3-en-1-yl)oxiran-2-yl)-methyl pivalate

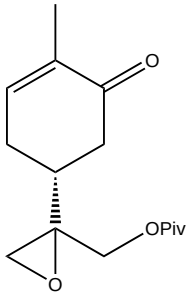


Fig. 7.5: **6**

To a solution of **5** (1.55 g, 8.51 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) were added pyridine (0.82 mL, 10.21 mmol, 1.2 eq) and pivaloyl chloride (1.18 mL, 9.57 mmol, 1.125 eq) at 0°C. The reaction mixture was stirred at room temperature under argon atmosphere for 24 hours.
Afterwards, the solution was diluted with CH_2Cl_2 and washed with HCl 0.5M (2 x 15 mL), a saturated solution of $NaHCO_3$ (2 x 15 mL), and brine (2 x 15 mL). The organic layer was dried over Na_2SO_4 anhydrous and evaporated under reduced pressure.
The residue was cleaned chromatographically over silica gel, eluting with hexane/ethyl acetate (1:1) to give the epoxy pivalate **6** (clear oil, 2.22 g, 8.35 mmol, 98%).

$[\alpha_D^{20}] = 17.63$ (c = 1.685 mg/mL, $CHCl_3$)
^{1}H-NMR: ($CDCl_3$) (Fig. 9.17) δ[ppm] = 1.22 (s, 9H), 1.78 (s, 3H), 2.0-2.5 (m, 7H), 3.5-3.7 (m, 2H), 6.65 (s, 1H)
^{13}C-RMN: ($CDCl_3$) (Fig. 9.18) δ[ppm] = 15.43 (q), 26.14 (t), 27.00 x 3 (q), 37.71 (t), 38.74 (d), 46.36 (t), 58.25 (s), 64.32 (t), 73.76 (s), 135.18 (s), 144.23 (d), 178.32 (s), 198.86 (s)
IR: (Fig. 9.19) ν[cm^{-1}] = 3460, 2974, 1733, 1674, 1482, 1281, 1154, 1037, 906, 757
HRMS-EI: (Fig. 9.20) M^+Na calculated for $C_{15}H_{22}O_4Na$: 289.1410, experimental: 289.1419

7.9 (1-hydroxy-6-(hydroxymethyl)-2-methylbicyclo[3.1.1]hept-2-en-6-yl)methyl pivalate

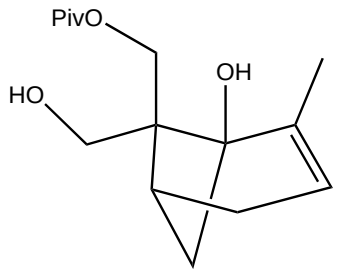


Fig. 7.6: **7a**

Dry THF (15 mL) was desoxydated by passing through argon during one hour.

Solution A: Titanocene Cp_2TiCl_2 (854 mg, 3.43 mmol, 3.65 eq) and zinc (448 mg, 6.85 mmol, 7.3 eq) were dissolved in desoxydated, dry THF (6 mL) and the solution was stirred for one hour under argon (change of color of the solution from red to green).

Solution B: The epoxy pivalate **6** (250 mg, 0.94 mmol, 1.00 eq) was dissolved in dry, desoxydated THF (9 mL) under argon.

Solution B was added to solution A via cannula, and the reaction mixture stirred for 20 hours under argon atmosphere (change of color of the solution from green to red).
Afterwards, a saturated solution of KH_2PO_4 (30 mL) was added and the mixture stirred for five hours. The formed salts were filtered and washed with ethyl acetate. The aqueous layer of the resulting filtrate was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na_2SO_4 anhydrous, and the solvent evaporated under reduced pressure.
The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (8:2) to give the diastereoisomers **7a** (yellow oil, 124.1 mg, 0.46 mmol, 49%) and **7b** (yellow oil, 67.1 mg, 0.25 mmol, 27%). This corresponds to a global yield of 75%.

7a:

$[\alpha_D^{20}]$ = -14.4 (c = 0.25 mg/mL, $CHCl_3$)
^{1}H-NMR: ($CDCl_3$) (Fig. 9.21) δ[ppm] = 1.21 (s, 9H), 1.60 (s, 1H), 1.71 (d, J=8.7 Hz, 1H), 1.78 (s, 3H), 2.2-2.3 (m, 2H), 2.44 (t, 1H), 2.69 (s, 1H), 3.37 (s, 1H), 3.88 (d, J=11.7 Hz, 1H), 4.15 (d, J=11.5 Hz, 1H), 4.17 (d, J=11.7 Hz, 1H), 4.46 (d, J=11.5 Hz, 1H), 5.30 (s, 1H)
^{13}C-NMR: ($CDCl_3$) (Fig. 9.22) δ[ppm] = 16.78 (q), 27.20 x 3 (q), 29.89 (d), 30.48 (t), 38.91 (s), 39.87 (t), 48.85 (s), 62.87 (t), 64.23 (t), 77.77 (s), 117.60 (d), 145.70 (s), 179.39 (s)
IR: (Fig. 9.27) ν[cm^{-1}] = 3418, 2964, 2363, 1726, 1711, 1296, 1172
HMQC: (Fig. 9.25), HMBC (Fig. 9.26), COSY (Fig. 9.23), ROESY (Fig. 9.24)
HRMS-EI: (Fig. 9.28) M^+Na calculated for $C_{15}H_{24}O_4$Na: 291.1567, experimental: 291.1553

7b:

$[\alpha_D^{20}]$ = +26.18° (c = 0.615 mg/mL, $CHCl_3$)
^{1}H-NMR: ($CDCl_3$) (Fig. 9.29) δ[ppm] = 1.1-1.3 (m, 9H), 1.7 (d, 1H), 1.80 (s, 3H), 1.9-2.5 (m, 5H), 2.41 (dd, 1H), 3.52 (d, J=11.28 Hz, 1H), 3.72 (d, J=11.28 Hz, 1H), 4.56 (d, J=11.88 Hz, 1H), 4.67 (d, J=11.88 Hz, 1H), 5.31 (s, 1H)
^{13}C-NMR: ($CDCl_3$) (Fig. 9.30) δ[ppm] = 16.87 (q), 27.21 x 3 (q), 29.91 (d), 30.57 (t), 39.02 (t), 39.90 (s), 50.52 (s), 60.23 (t), 64.41 (t), 77.80 (s), 117.59 (d), 145.27 (s), 179.51 (s)
IR: (Fig. 9.35) ν[cm^{-1}] = 3432, 2959, 1716, 1462, 1288, 1165, 1026
HMQC: (Fig. 9.33), HMBC (Fig. 9.34), COSY (Fig. 9.31), ROESY (Fig. 9.32)
HRMS-EI: (Fig. 9.36) M^+Na calculated for $C_{15}H_{24}O_4$Na: 268.1747, experimental: 268.1740

7.10 ((2R,4aR,8aS)-8-methyl-2-phenyl-4,4a,5,6-tetrahydro-5,8a-methanobenzo[d][1,3]dioxin-4a-yl)methyl pivalate

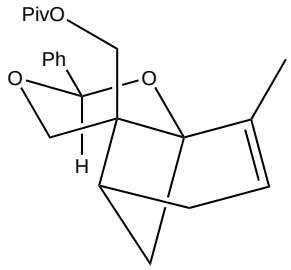


Fig. 7.7: **8**

To a solution of **7a** (100.0 mg, 0.37 mmol, 1.0 eq) in dichloromethane (10 mL) were added PPTs (tip of a spatula) and BDMA (0.062 mL, 0.41 mmol, 1.1 eq), and the reaction mixture was stirred for 20 hours under argon atmosphere at room temperature.
Afterwards, a saturated solution of $NaHCO_3$ (10 mL) was added and stirred for 10 minutes, and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na_2SO_4 anhydrous and the solvent evaporated under reduced pressure.
The residue was cleaned chromatographically on silica gel, eluting with hexane/ethyl acetate (95:5) to give the protected compound **8** (clear oil, 88.4 mg, 0.25 mmol, 67%).

$[\alpha_D^{20}] = +74.71°$ (c = 0.60 mg/mL, $CHCl_3$)
^{1}H-NMR: (Fig. 9.37) δ[ppm] = 1.18 (s, J=0.24 Hz, 9H), 1.59 (d, J=4.56 Hz, 1H), 1.81 (s, 3H), 2.13-2.34 (m, 3H), 3.24 (dd, J=3.44 Hz J=4.5 Hz, 1H), 4.25 (d, J=0.88, 1H), 4.31 (d, J=0.96 Hz), 4.34(d, J=0.9 Hz, 1H), 4.43 (d, J=6.0 Hz, 2H), 5.33 (s, 1H), 5.93 (s, 1H), 7.26-7.51 (m, 5H)
^{13}C-NMR: (Fig. 9.38) δ[ppm] = 16.38 (q), 27.16 x 3 (q), 30.12 (t), 30.53 (t), 32.42 (d), 38.88 (s), 41.07 (s), 62.81 (t), 70.19 (s), 77.80 (s), 96.11 (d), 117.49 (d), 126.25 x 2 (d), 128.15 (d), 128.81 x 2 (d), 138.49 (s), 144.13 (s), 178.57 (s)
IR: (Fig. 9.43) ν[cm^{-1}] = 2968, 1728.24, 1478.98, 1452.89, 1392.97, 1227.73, 1072.09, 749.84

7.11 ((2R,4aR,8aS)-8-methyl-6-oxo-2-phenyl-4,4a,5,6-tetrahydro-5,8a-methanobenzo[d][1,3]dioxin-4a-yl)methyl pivalate

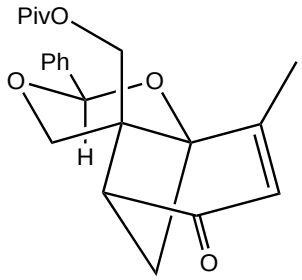


Fig. 7.8: **9a**

A solution of DMP (431 mg, 4.49 mmol, 20 eq) and CrO_3 (449.0 mg, 4.49 mmol, 20 eq) in CH_2Cl_2 (8 mL) was stirred at -20°C under argon atmosphere for 10 minutes. Afterwards, **8** (80.0 mg, 0.22 mmol, 1 eq) in CH_2Cl_2 (4 mL) was added via cannula, and the reaction mixture stirred at -20°C under argon atmosphere overnight.

Subsequently, a solution of NaOH 5M (2 mL) was added and the mixture stirred during one hour at 0°C. The organic layer was washed with a solution of HCl 0.1M (2 x 10 mL), with water until neutralized, and with brine (2 x 20 mL), dried over Na_2SO_4 anhydrous, and the solvent evaporated under reduced pressure.

The residue was cleaned chromatographically on silica gel, eluting with hexane/ethyl acetate (8:2) to give the oxidized products **9a** (13.0 mg, 0.035 mmol, 16%) and **9b** (in small amounts as byproduct).

9a:

$[\alpha_D^{20}] = +84.4°$ (c = 0.97 mg/mL, $CHCl_3$)
^{1}H-NMR: (Fig. 9.46) δ[ppm] = 1.17 (s, 9H), 2.21 (s, 3H) 2.28-2.51 (m, 1H), 2.82 (dd, J_1=0.94 Hz , J_2=3.26 Hz, 1H), 3.68 (dd, J_1=3.34 Hz, J_2=4.86 Hz, 1H), 4.23 (d, 1H), 4.43 (d, 1H), 4.46 (s, 2H), 5.79 (s, 1H), 6.02 (s, 1H), 7.38-7.49 (m, 5H)
^{13}C-NMR: (Fig. 9.47) δ[ppm] = 17.53 (q), 27.07 x 3 (q), 38.86 (s), 42.45 (t), 46.39 (d), 54.61 (s), 62.99 (t), 69.84 (t), 76,72 (d), 96.73 (d), 121.07 (d), 126.17 x 2 (d), 128.30 (d), 129.25 x 2 (d), 137.53 (s), 169.13 (s), 178.22 (s), 198.57 (s)
IR: (Fig. 9.52) ν[cm^{-1}] = 2960.45, 2923.16, 2852.77, 1728.24, 1688, 1457.08, 1227.23
HMQC (Fig. 9.50), HMBC (Fig. 9.51), COSY (Fig. 9.48), ROESY (Fig. 9.49).
HRMS-EI: (Fig. 9.54) M^+Na calculated for $C_{22}H_{26}O_5$Na: 393.1656, experimental: 389.1998.
UV: (Fig. 9.53) λ_{max} = 205 nm (ϵ = 12024); λ_{max} = 254 nm (ϵ = 4780)

9b:

$[\alpha_D^{20}] = +31.22°$ (c = 0.6 mg/mL, $CHCl_3$)
^{1}H-NMR: (Fig. 9.55) δ[ppm] = 1.18 (s, 9H), 2.14 (d, J=0.74 Hz, 3H), 2.60 (d, J=4.34 Hz, 1H), 2.93 (c, J=3.34 Hz, 2H), 4.13 (d, J=5.94 Hz, 1H), 4.43 (d, J=5.94 Hz, 1H), 4.67 (d, J=6.1 Hz, 1H), 4.84 (d, J=6.1 Hz, 1H), 5.81 (t, J=0.92 Hz, 1H), 7.44-8.04 (m, 5H)
^{13}C-NMR: (Fig. 9.56) δ[ppm] = 18.31 (q), 27.09 x 3 (q), 38.90 (s), 45.06 (s), 46.55 (d), 48.15 (t), 62.78 (t), 62.94 (t), 77.62 (s), 121.01 (d), 127.80 x 2 (d), 128.53 (d), 129.33 (s), 129.69 x 2 (d), 133.47 (d), 166.80 (s), 171.09 (s), 199.53 (s)
HMQC (Fig. 9.59), HMBC (Fig. 9.60), COSY (Fig. 9.57), ROESY (Fig. 9.58).
HRMS-EI: (Fig. 9.61) M^+Na calculated for $C_{22}H_{26}O_6$Na: 409.16216, experimental 409.1329

7.12 (2R,4aS,5R,8S,8aR)-8-methyl-2-phenyldihydro-4H-8,4a-(epoxymethano)-5,8a-methanobenzo[d][1,3]dioxin-6(5H)-one

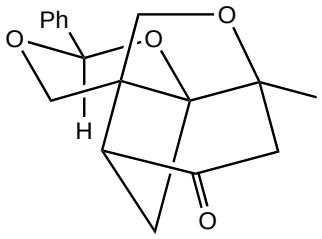


Fig. 7.9: **10**

To a solution of **9a** (40 mg, 0.11 mmol, 1.0 eq) in methanol (1 mL) was added NaOH 5M (0.11 mL, 0.55 mmol, 5.0 eq) and the reaction stirred for 24 hours. This time elapsed, the solvent methanol was evaporated under reduced pressure, the residue dissolved in water and extracted with CH_2Cl_2 (5 x 8 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na_2SO_4 anhydrous, and the solvent evaporated under reduced pressure.
The crude product was fractionized via flash column chromatography on silica gel, eluting with hexane/ethyl acetate (8:2) to thus give the tetracyclic compound **10** (white crystals, 13.3 mg, 0.05 mmol, 42%).

$[\alpha_D^{20}]$ = -0.88° (c = 1.13 mg/mL, $CHCl_3$)
^{1}H-NMR: (Fig. 9.62) δ[ppm] = 1.25 (s, 3H), 2.16 (d, J=5.72 Hz, 1H), 2.59 (d, J=8.98 Hz, 1H), 2.83 (dd, J_1=3.5 Hz, J_2=4.58 Hz, 1H), 3.15 (dd , J_1=3.44Hz, J_2=5.72 Hz, 1H), 3.87 (d, J=5 Hz, 1H), 4.15 (s, 1H), 4.17 (d, J=1.44 Hz, 2H), 4.32 (d, J=6.06 Hz, 1H), 5.88 (s, 1H), 7.38-7.54 (m, 5H)
^{13}C-NMR: (Fig. 9.63) δ[ppm] = 18.06 (q), 25.21 (q), 49.05 (d), 49.15 (t), 51.84 (s), 68.18 (t), 70.70 (t), 79.81 (s), 86.67 (s), 96.81 (s), 126.41 x 2 (d), 128.34 (d), 129.31 x 2 (d), 137.40 (s), 208.34 (s)
IR:(Fig. 9.68) ν[cm^{-1}] = 2960.08, 2923.80, 2854.66, 1728.67, 1143.80, 1014.07
HMQC (Fig. 9.66), HMBC (Fig. 9.67), COSY (Fig. 9.57), ROESY (Fig. 9.65)
HRMS-EI: (Fig. 9.69) M^+Na calculated for $C_{17}H_{18}O_4$Na: 309.1108, experimental 309.1205

7.13 (-)-Paeonysuffrone

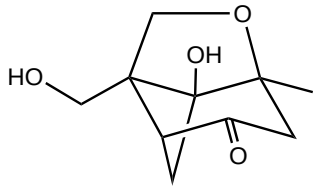
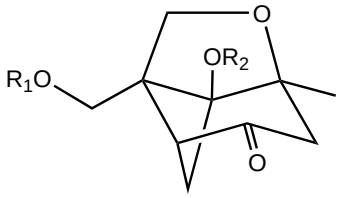


Fig. 7.10: **11**

A suspension of Pd/C (20 mg) in ethyl acetate (1 mL) was stirred for 15 minutes under hydrogen atmosphere. This time elapsed, a solution of **10** (45 mg, 0.16 mmol, 1.0 eq) in ethyl acetate (2 mL) was added via cannula and the reaction mixture stirred for four hours under hydrogen atmosphere.
Subsequently, the residue was filtered over a column of celite, eluting with ethyl acetate, and the solvent evaporated under reduced pressure to give the deprotected diol **11** (white crystals, 28.6 mg, 0.14 mmol, 90%).

$[\alpha_D^{20}]$ = -17.34° (c = 0.80 mg/mL, $CHCl_3$)
^{1}H-NMR: (Fig. 9.70) δ[ppm] = 1.31 (s, 3H), 2.20 (d, J=5.32 Hz, 2H), 2.29 (d, J=0.38 Hz, 1H), 2.33 (d, J=0.36 Hz, 2H), 2.46 (dd, J_1=3.54 Hz, J_2=4.82 Hz, 1H), 2.86 (d, J=3.5 Hz, 1H) 2.91 (d, J=8.8 Hz, 1H), 3.57 (d, J=5.06 Hz, 1H), 3.86 (ddd, J_1=5.8 Hz, J_2=10.42 Hz, J_3=15.46 Hz, 1H) 4.88 (s, 1H)
^{13}C-NMR: (Fig. 9.71) δ[ppm] = 19.23 (q), 33.10 (t), 49.97 (t), 50.13 (t), 62.71 (t), 63.03 (s), 71.75 (t), 82.16 (s), 87.59 (s), 212.93 (s)
IR: (Fig. 9.76) ν[cm^{-1}] = 3372, 1727, 1458, 1240, 1166, 1052
HMQC (Fig. 9.74), HMBC (Fig. 9.75), COSY (Fig. 9.72), ROESY (Fig. 9.73)
HRMS-EI: (Fig. 9.77) M^+Na calculated for $C_{10}H_{14}O_4$Na: 221.0787, experimental 213.1127

7.14 (-)-Paeonysuffrone mono- and diacetate



12: R_1=Ac; R_2=H
13: R_1=R_2=Ac

Fig. 7.11: (-)-Paeonysuffrone acetates

To a solution of **11** (27.6 mg, 0.14 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) were added pyridine (17 μL, 0.17 mmol, 1.5 eq) and acet anyhdride (16 μL, 0.17 mmol, 1.2 eq). The reaction mixture was stirred under argon atmosphere for 20 hours. $NaHCO_3$ sat. (2 mL) and chunks of ice were added. The mixture was stirred for 30 minutes, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (1 x 10 mL), HCl 1M (2 x 10 mL), and brine (2 x 10 mL), dried over Na_2SO_4 anhydrous and and the solvent evaporated under reduced pressure.
By means of flash column chromatography on silica gel, eluting with hexane/ethyl acetate (1:2) the monoacetate **12** (white crystals, 8.7 mg, 0.04 mmol, 26%) and the diacetate **13** (white crystals, 6.0 mg, 0.02 mmol, 15%) were isolated.

12:

^{1}H-NMR: (Fig. 9.78) δ[ppm] = 1.40 (s, 3H), 2.11 (s, 3H), 2.20 (d, 1H), 2.46 (m, 1H), 2.52 (dd, 1H), 2.83 (m, 2H), 3.68 (d, 1H), 3.89 (d, 1H), 4.36 (d, 1H), 4.41 (d, 1H)
. ^{13}C-NMR: (Fig. 9.79) δ[ppm] = 18.92 (q), 20.87 (q), 31.24 (t), 48.36 (t), 48.47 (d), 59.82 (s), 62.71 (t), 69.53 (t), 81.25 (s), 85.70 (s), 171.59 (s), 208.98 (s)
HMQC (Fig. 9.82), HMBC (Fig. 9.83), COSY (Fig. 9.80), ROESY (Fig. 9.81)

13:

^{1}H-NMR: (Fig. 9.84) δ[ppm] = 1.36 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 2.51 (d, 1H), 2.75 (m, 2H), 2.92 (d, 1H), 2.99 (m, 1H), 3.71 (d, 1H), 3.92 (d, 1H), 4.35 (d, 1H), 4.41 (d, 1H)
^{13}C-NMR: (Fig. 9.85) δ[ppm] = 19.73 (q), 20.74 (q), 20.96 (q), 31.78 (t), 48.75 (t), 50.87 (d), 58.90 (s), 63.00 (t), 70.37 (t), 85.50 (s), 85.93 (s), 69.57 (s), 70.85 (s), 208.17 (s)
HMQC (Fig. 9.88), HMBC (Fig. 9.89), COSY (Fig. 9.86), ROESY (Fig. 9.87)

8. TABLE OF CARBONS

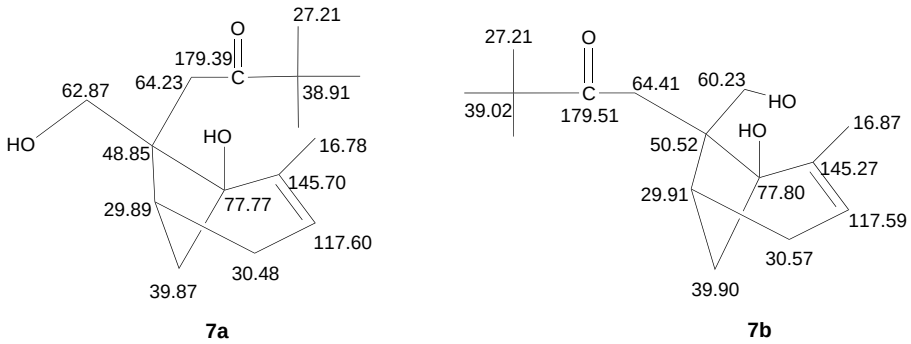


Fig. 8.1: table of carbons of compounds **7a** and **7b**

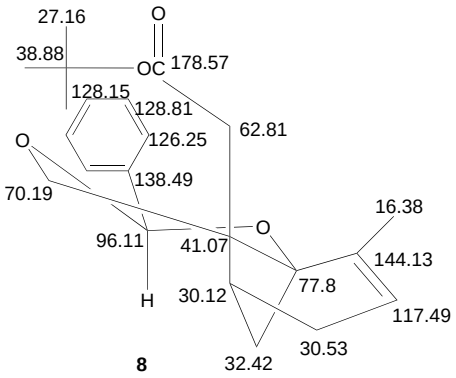


Fig. 8.2: table of carbons of compound **8**

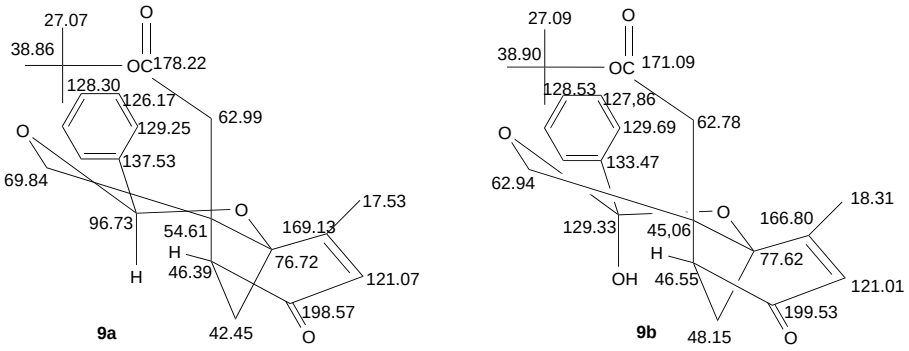


Fig. 8.3: table of carbons of compounds **9a** and **9b**

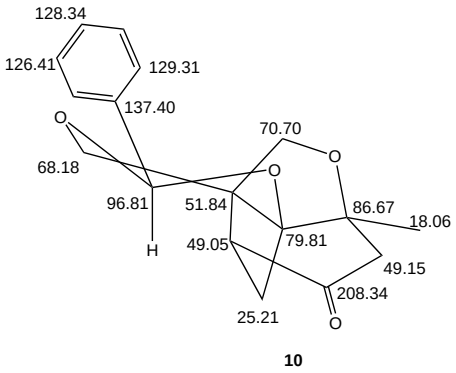


Fig. 8.4: table of carbons of compound **10**

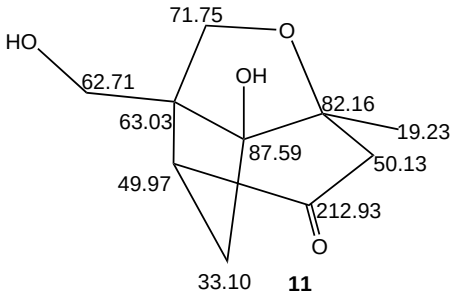


Fig. 8.5: table of carbons of (-)-Paeonisuffrone (**11**)

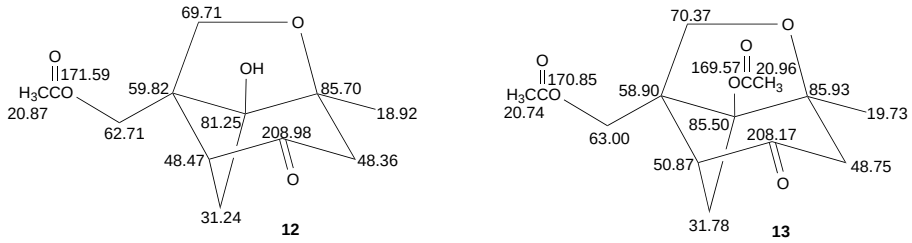


Fig. 8.6: table of carbons of (-)-Paeonisuffrone mono- (**12**) and diacetate (**13**)

9. SPECTROSCOPIC DATA

9.1 Spectra of compound ***2***

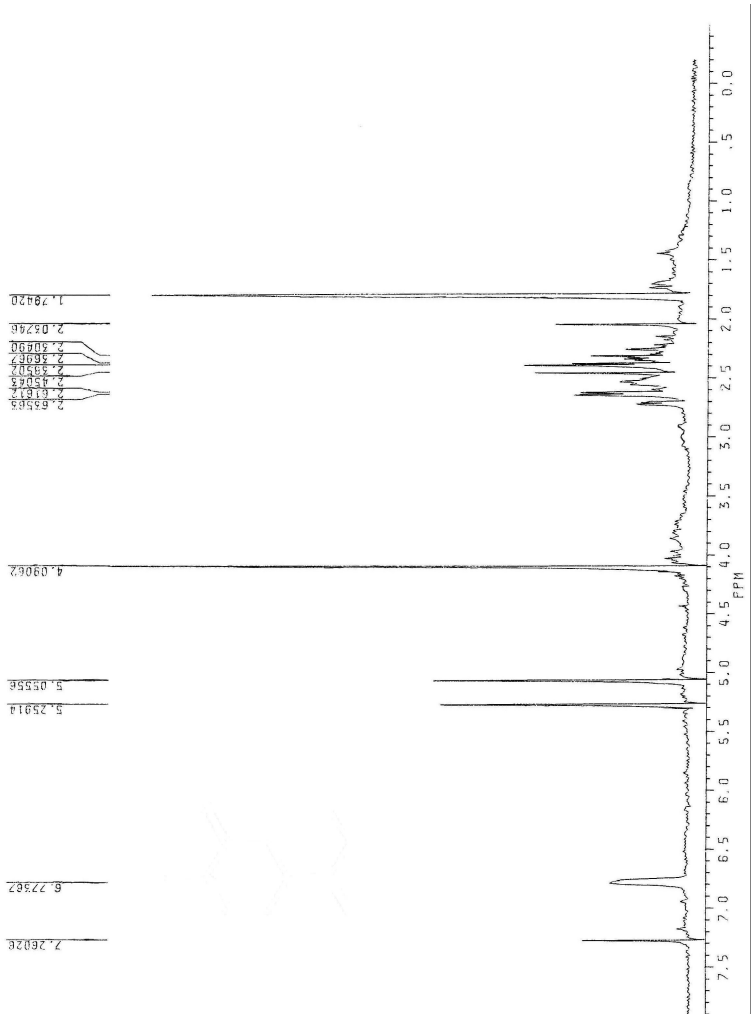


Fig. 9.1: ^{1}H-NMR spectrum of **2**

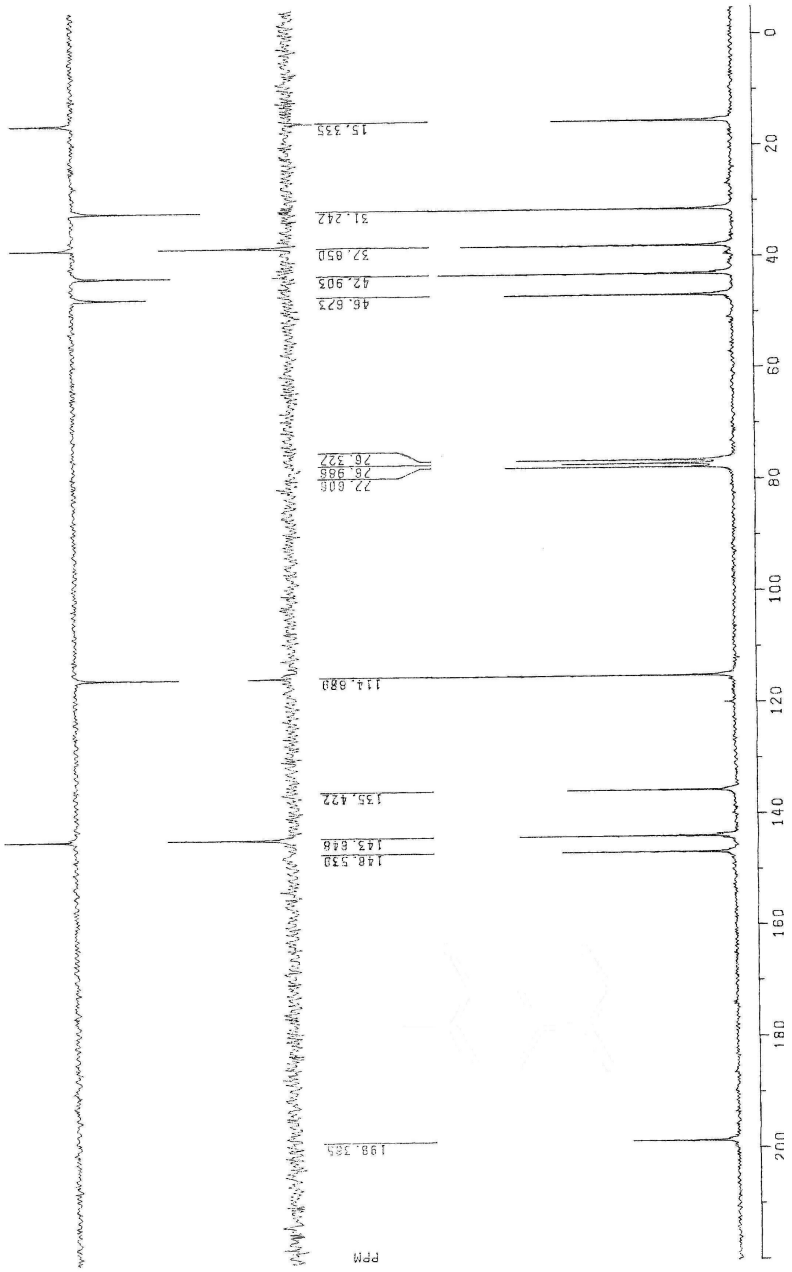


Fig. 9.2: ^{13}C-NMR spectrum of **2**

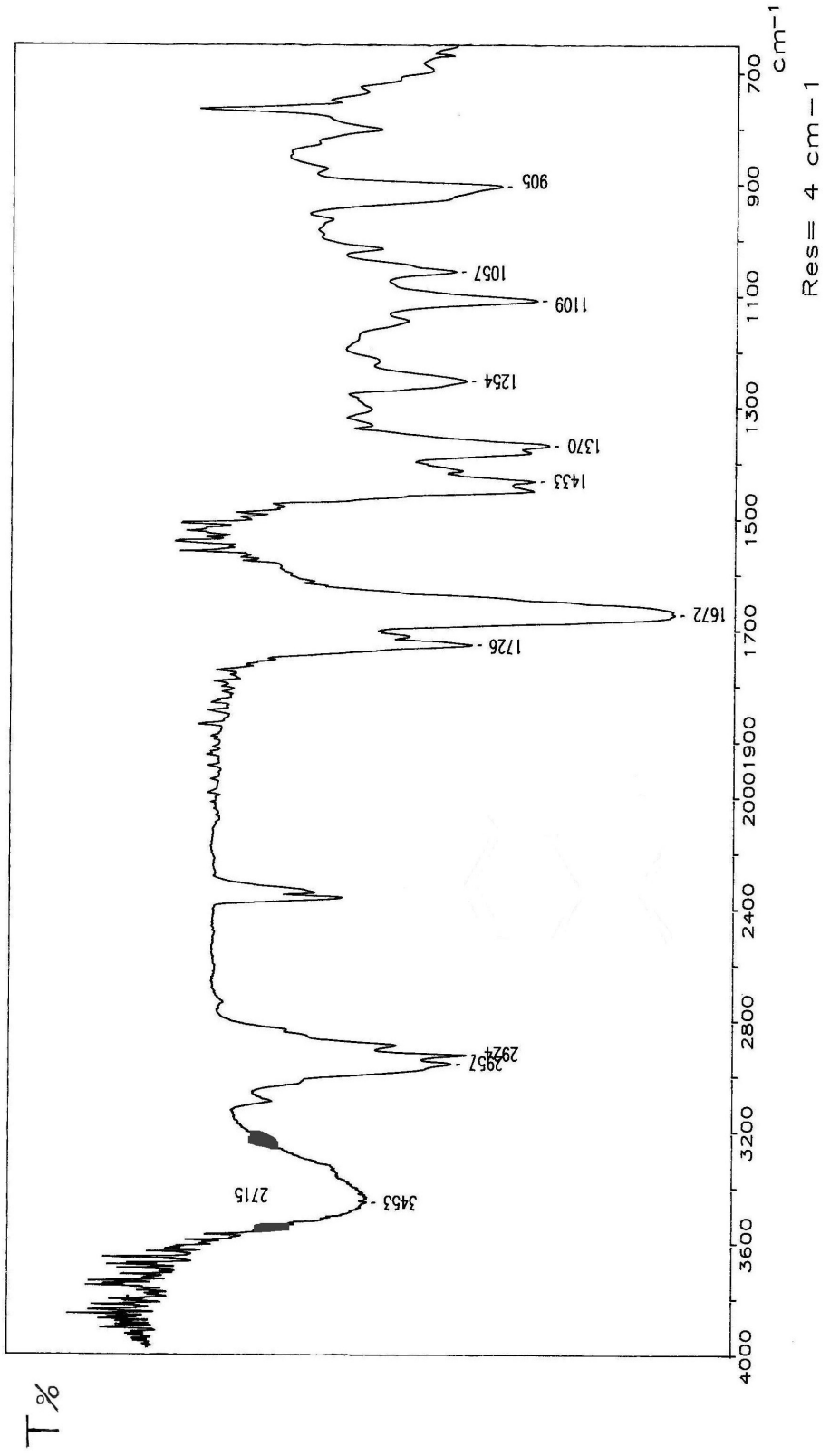


Fig. 9.3: IR spectrum of **2**

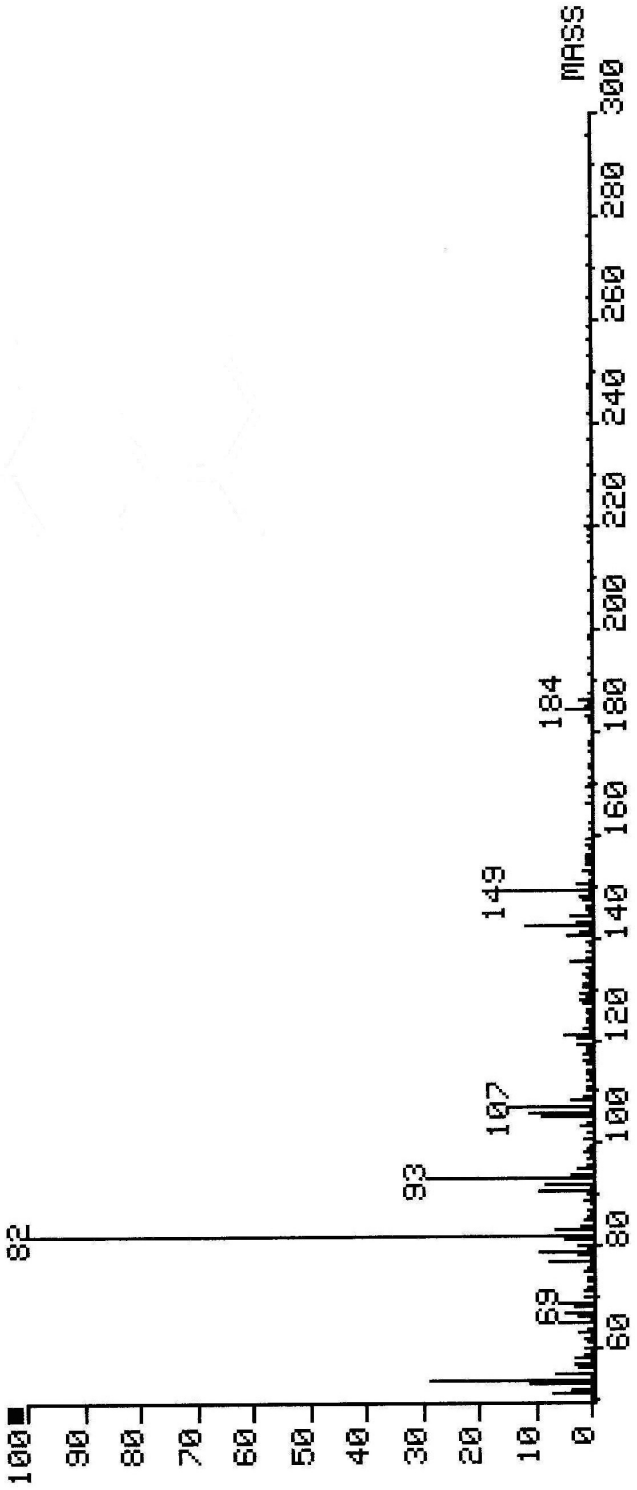


Fig. 9.4: mass spectrum of **2**

9.2 Spectra of compound **3**

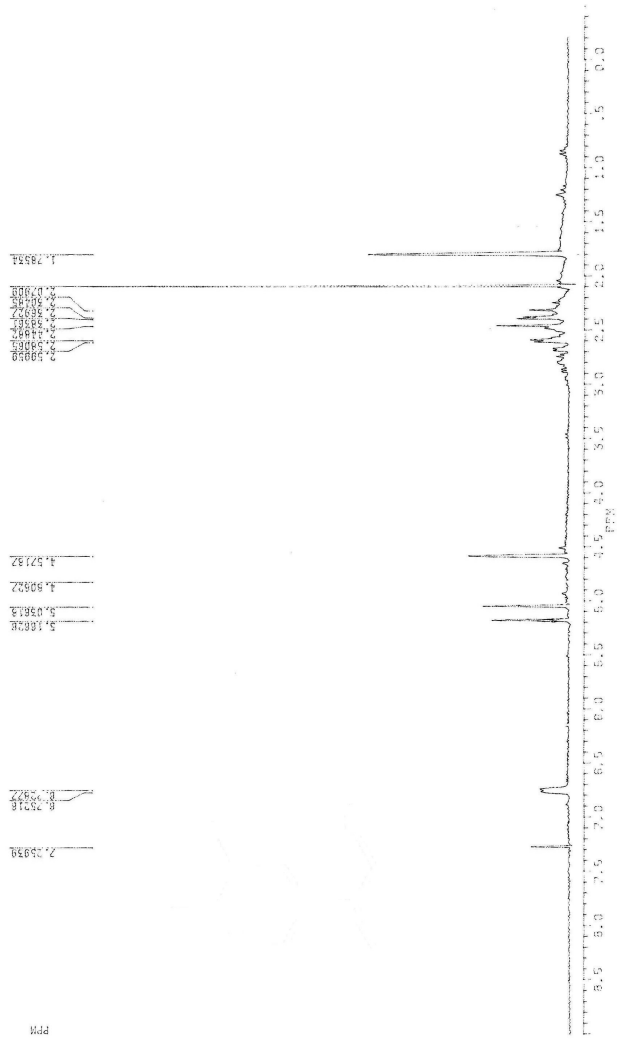


Fig. 9.5: ^{1}H-NMR spectrum of **3**

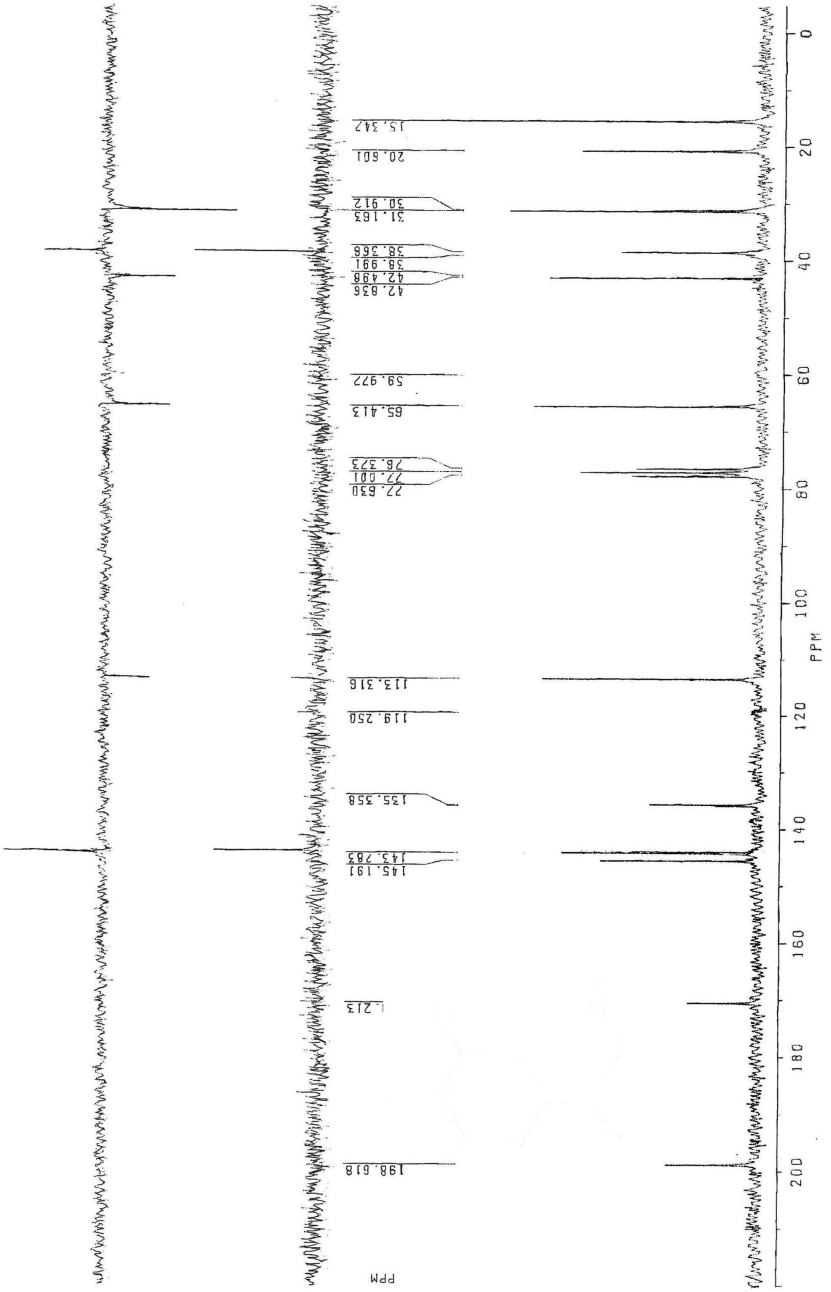


Fig. 9.6: ^{13}C-NMR spectrum of **3**

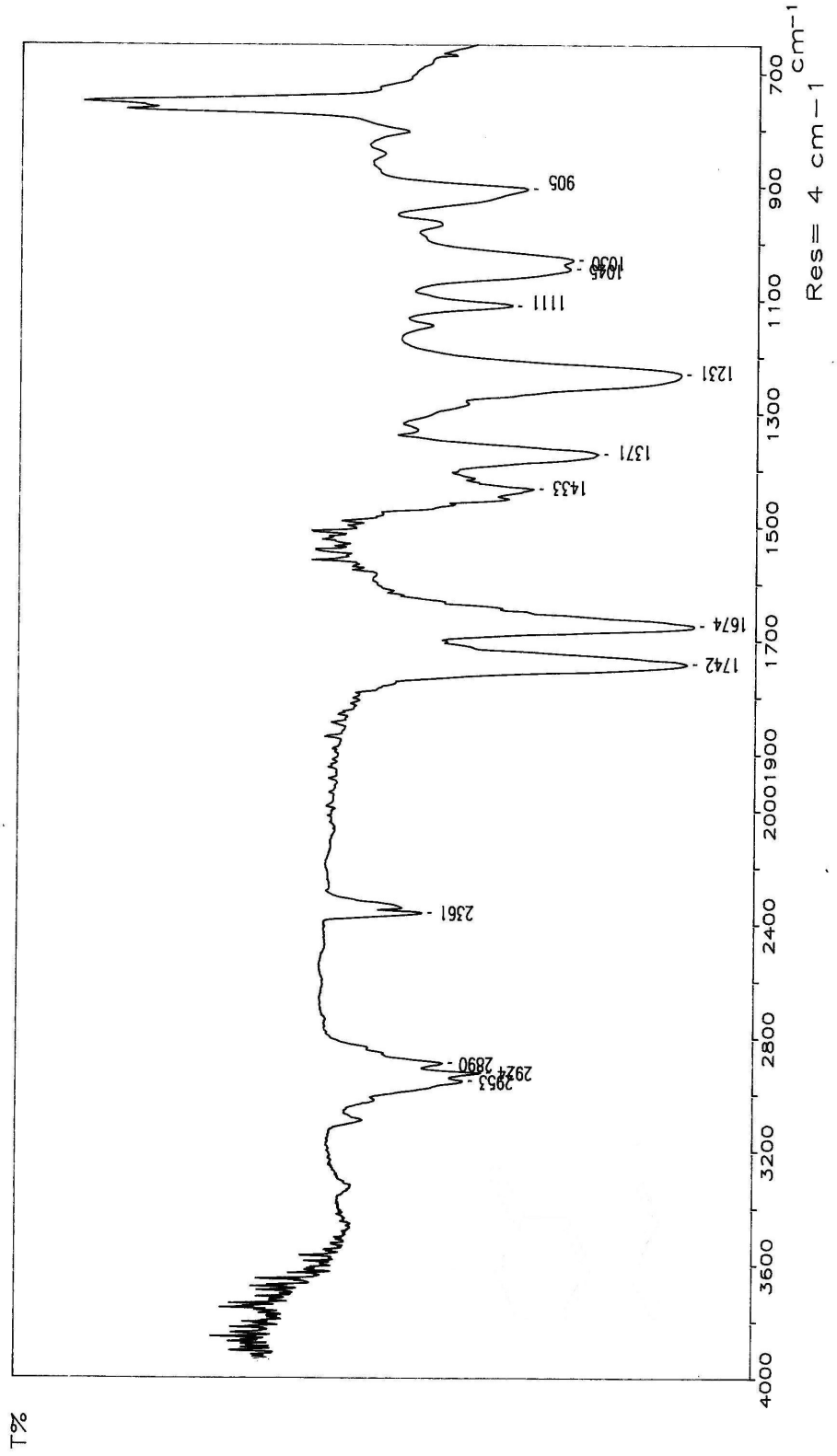


Fig. 9.7: IR spectrum of **3**

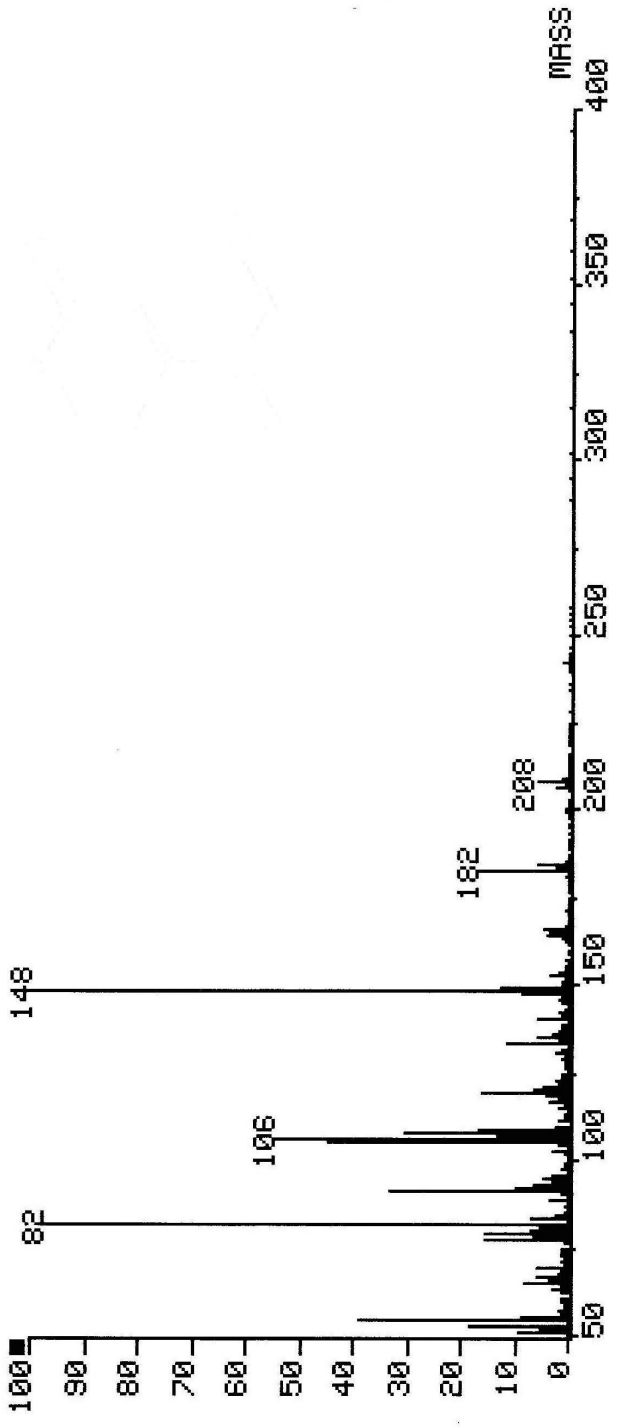


Fig. 9.8: mass spectrum of **3**

9.3 Spectra of compound **4**

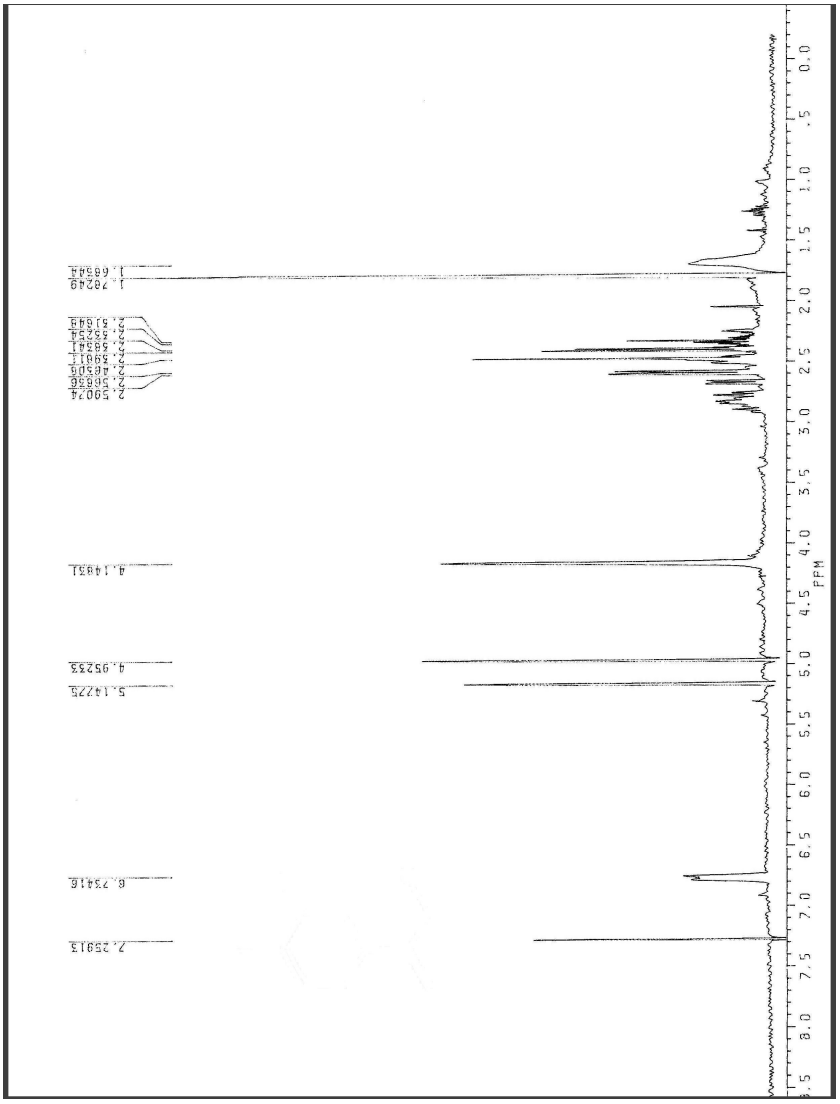


Fig. 9.9: ^{1}H-NMR spectrum of **4**

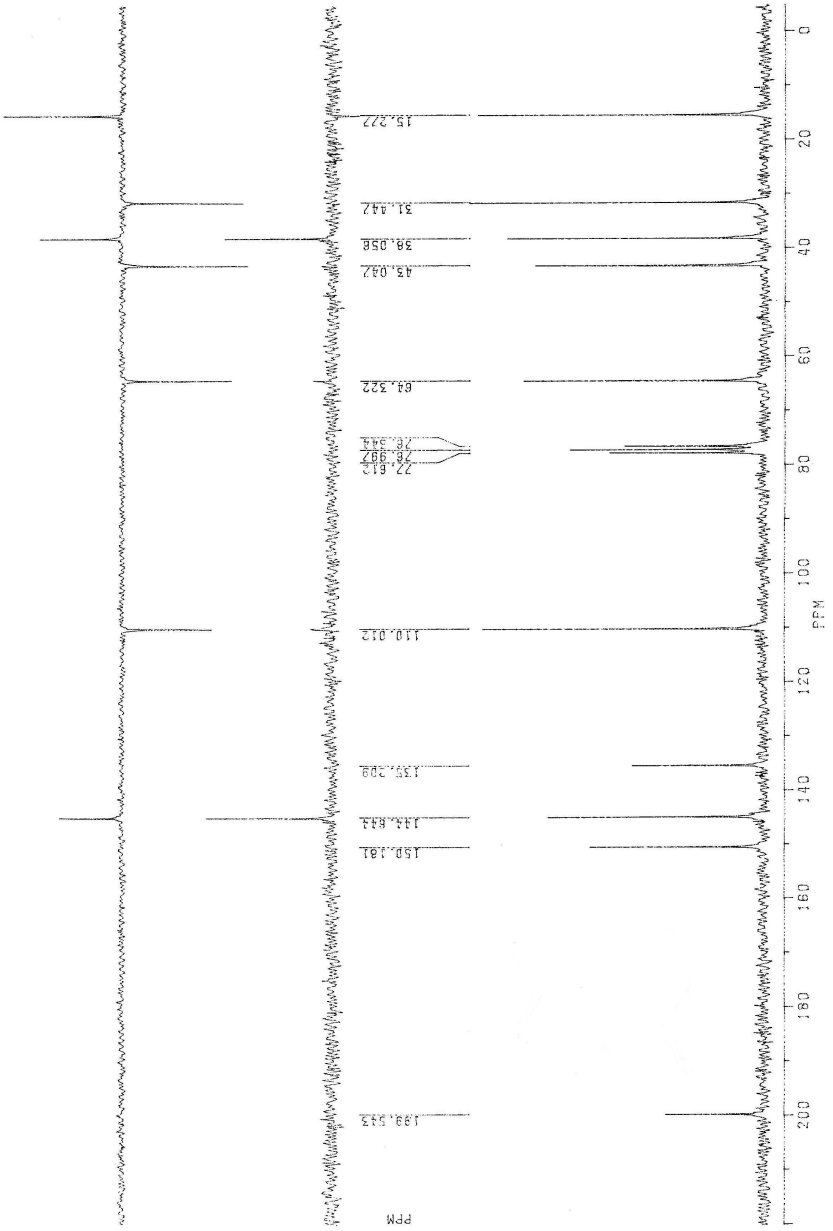


Fig. 9.10: ^{13}C-NMR spectrum of **4**

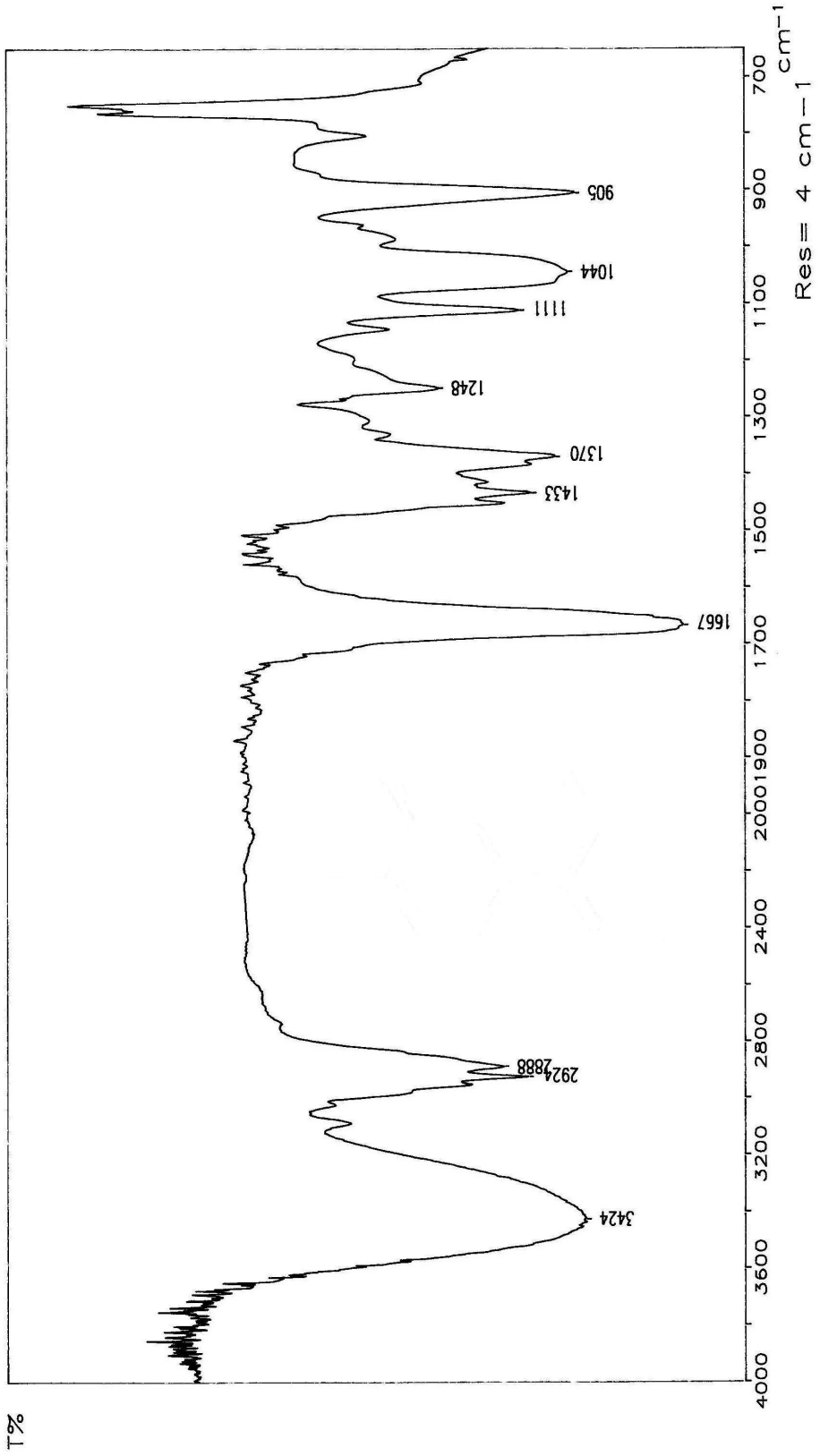


Fig. 9.11: IR spectrum of **4**

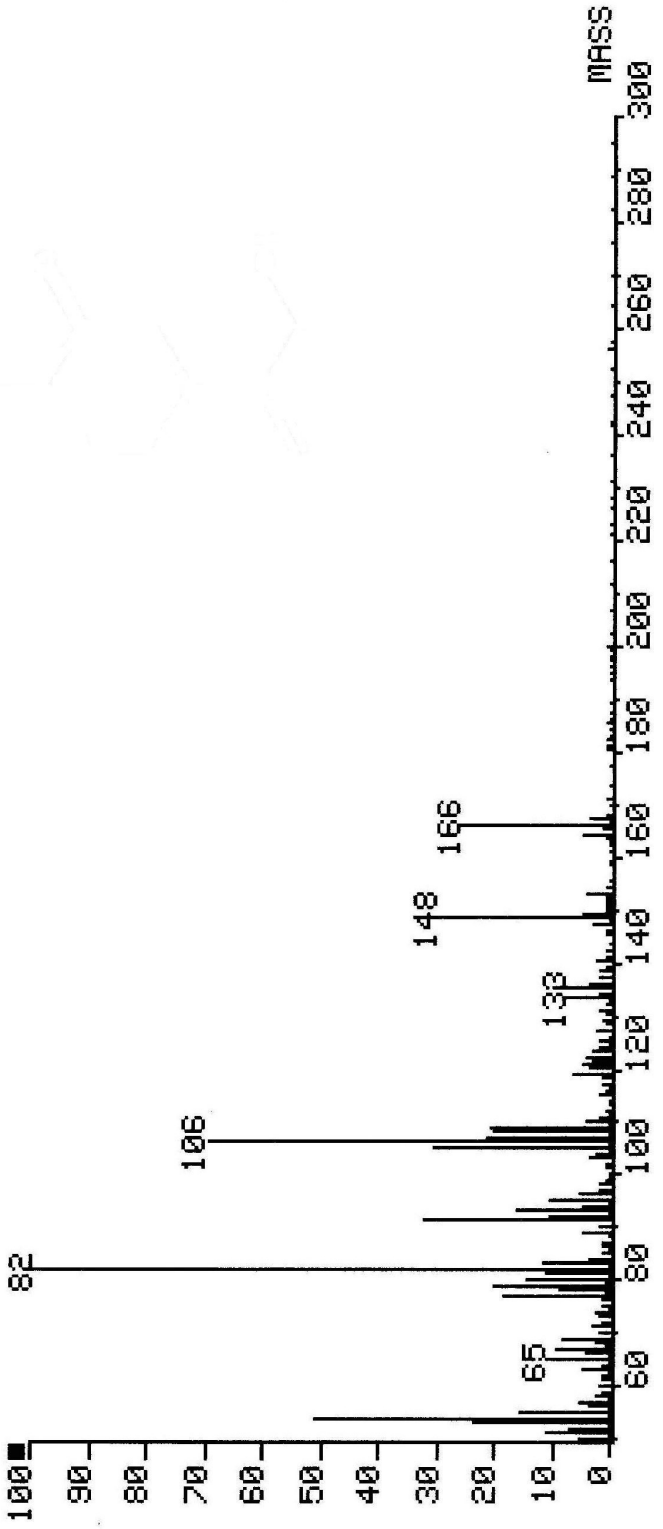


Fig. 9.12: mass spectrum of **4**

9.4 Spectra of compound **5**

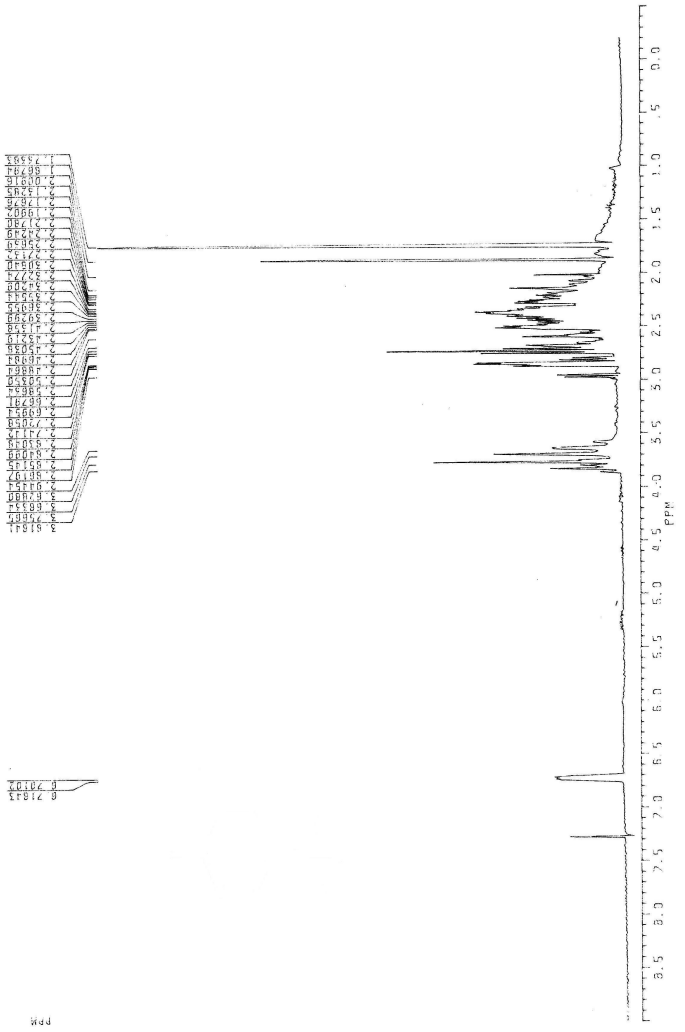


Fig. 9.13: ^{1}H-NMR spectrum of **5**

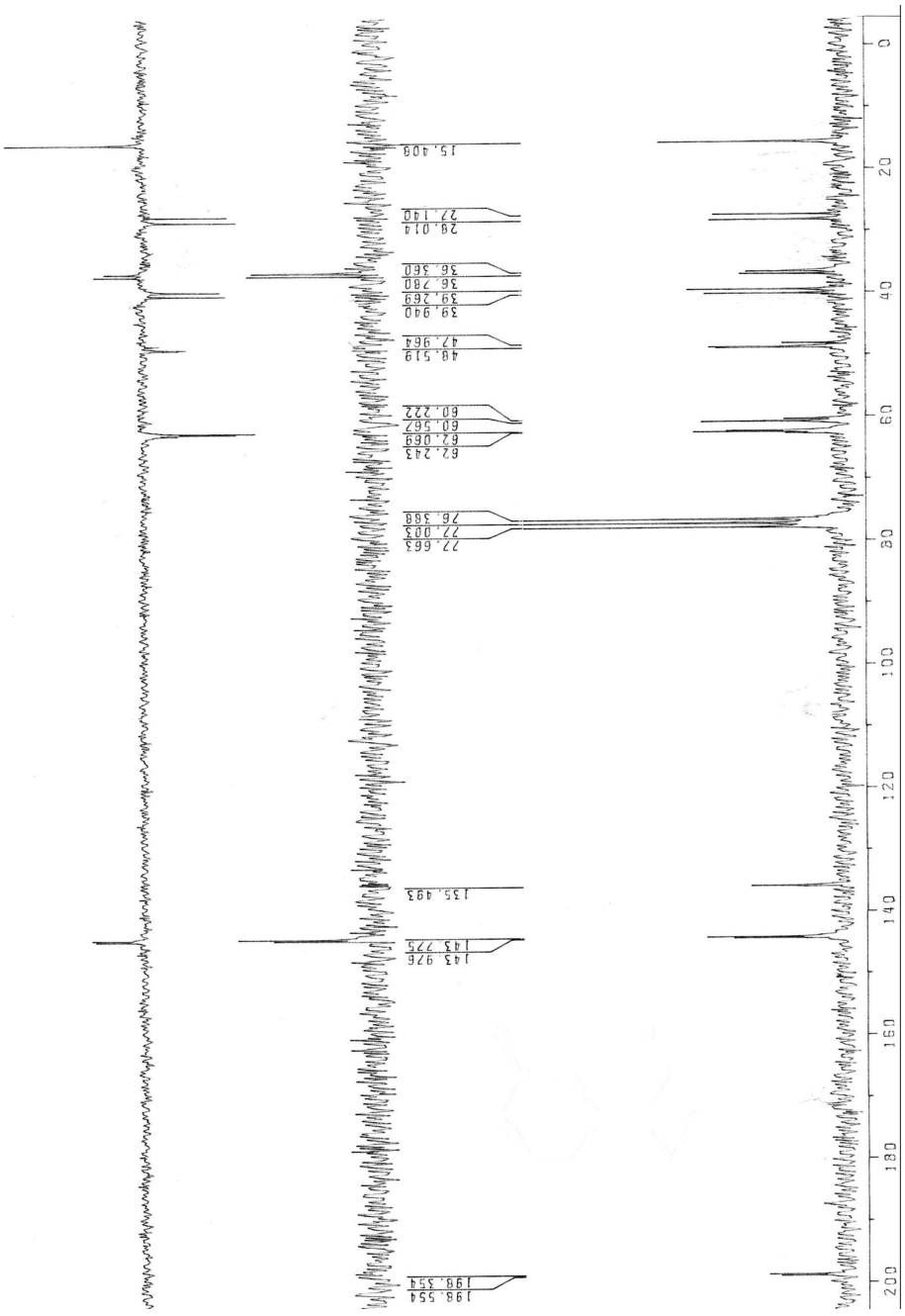


Fig. 9.14: ^{13}C-NMR spectrum of **5**

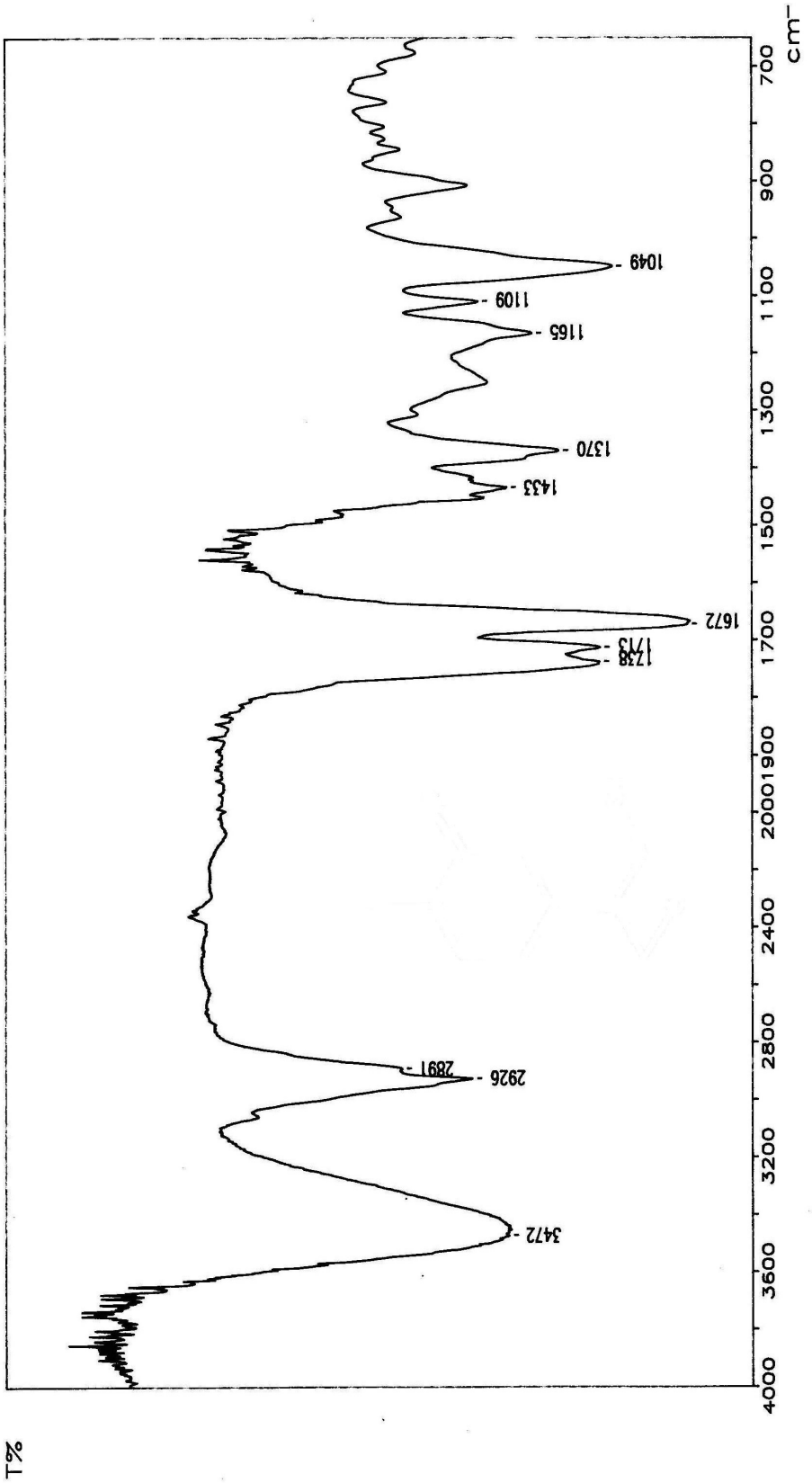


Fig. 9.15: IR spectrum of **5**

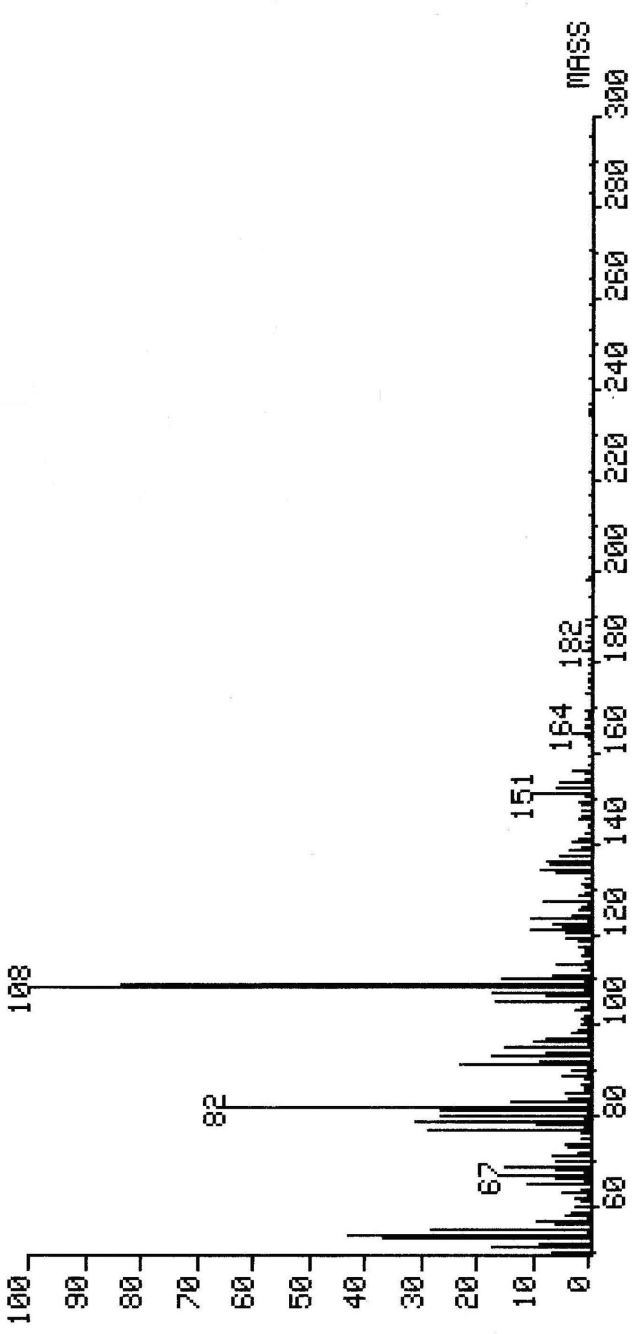


Fig. 9.16: mass spectrum of **5**

9.5 Spectra of compound **6**

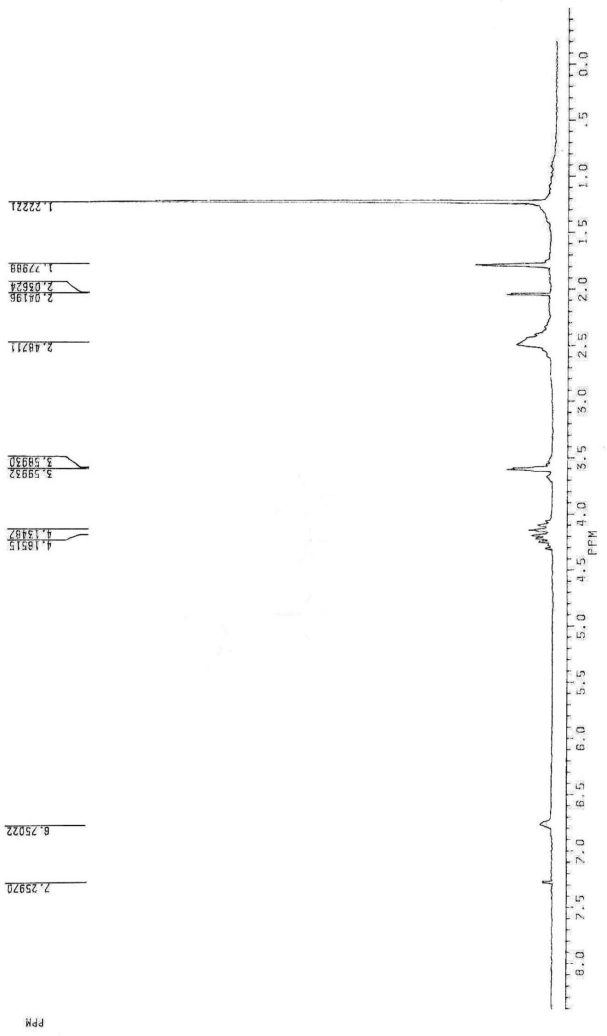


Fig. 9.17: ^{1}H-NMR spectrum of **6**

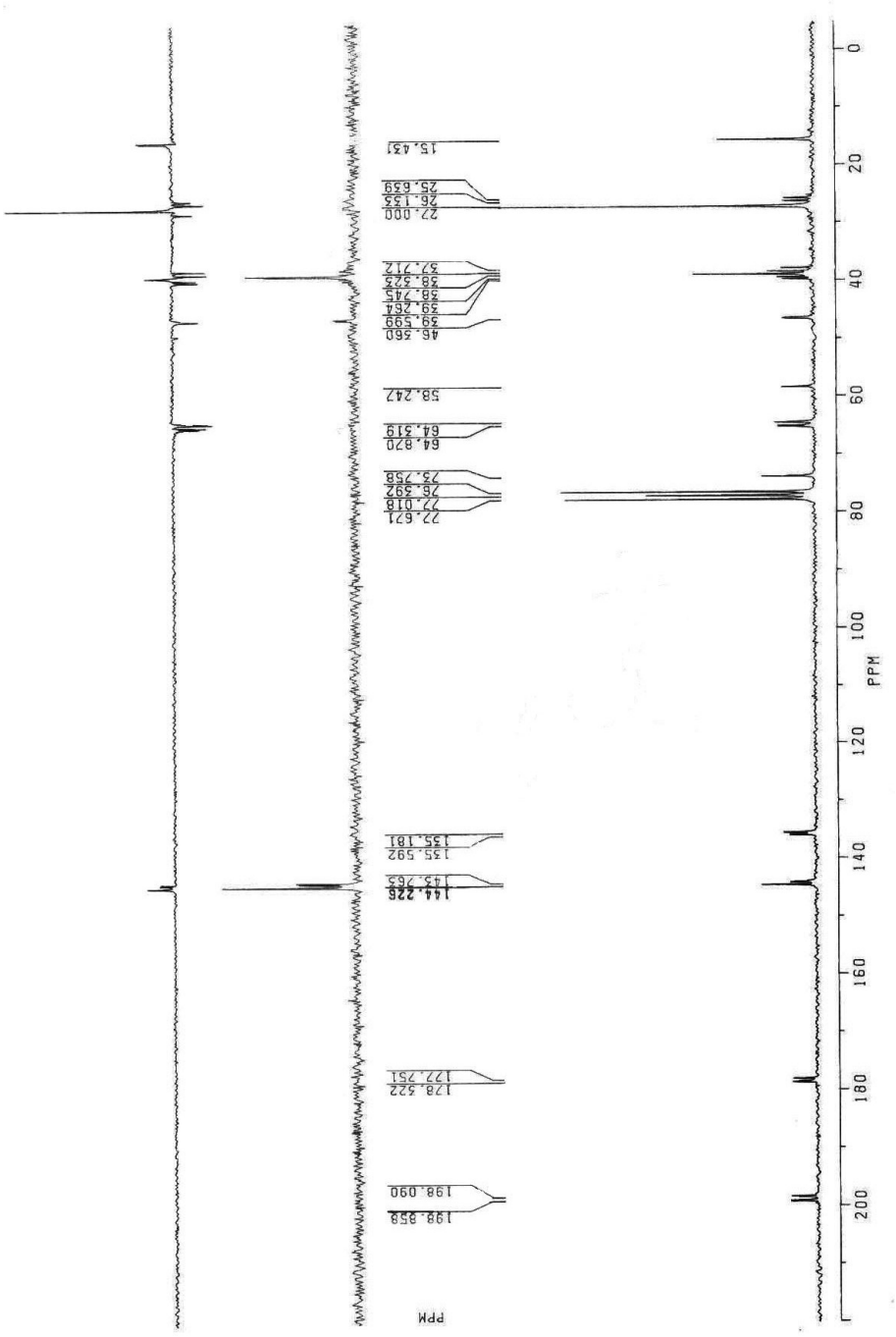


Fig. 9.18: ^{13}C-NMR spectrum of **6**

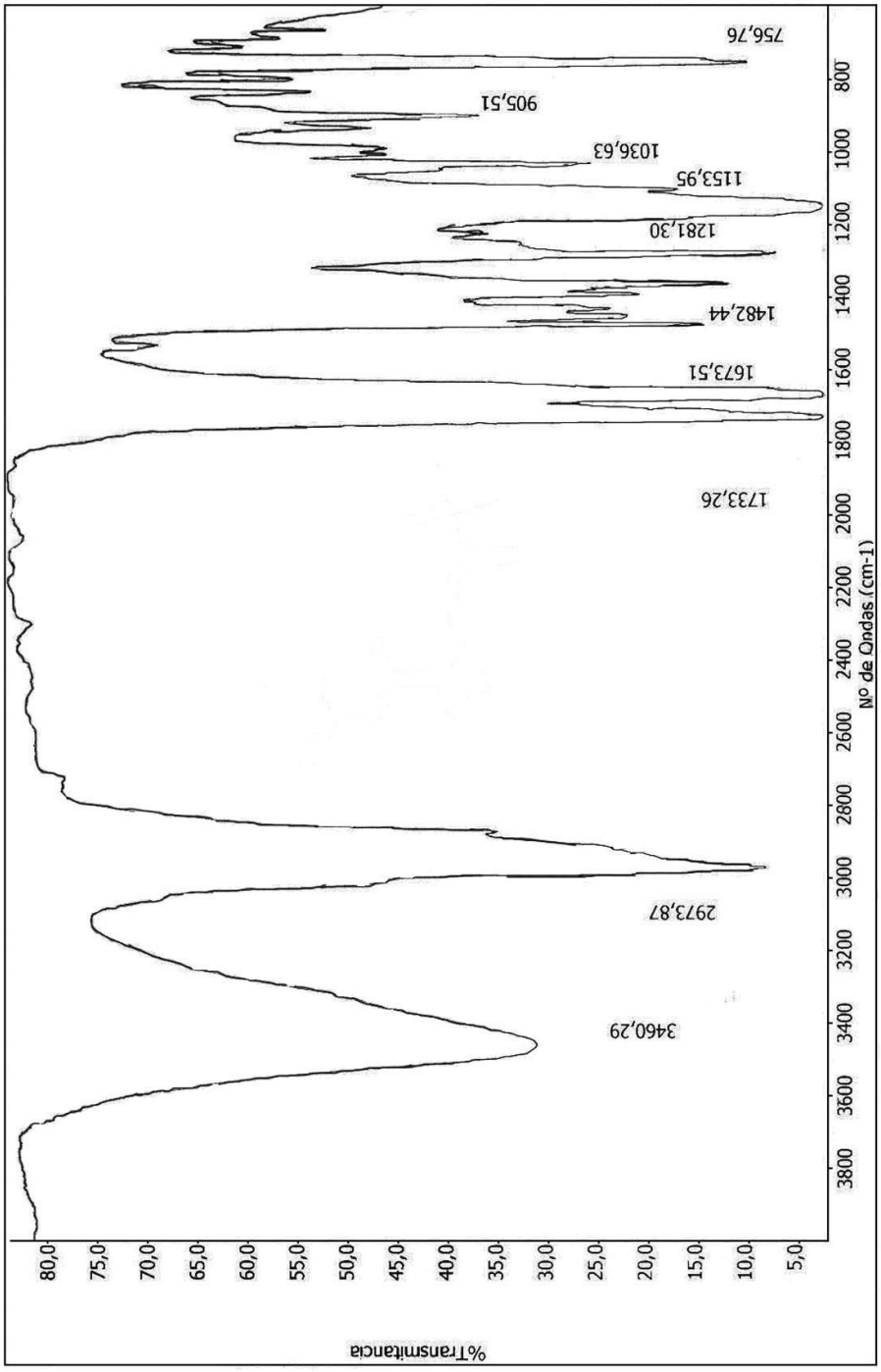
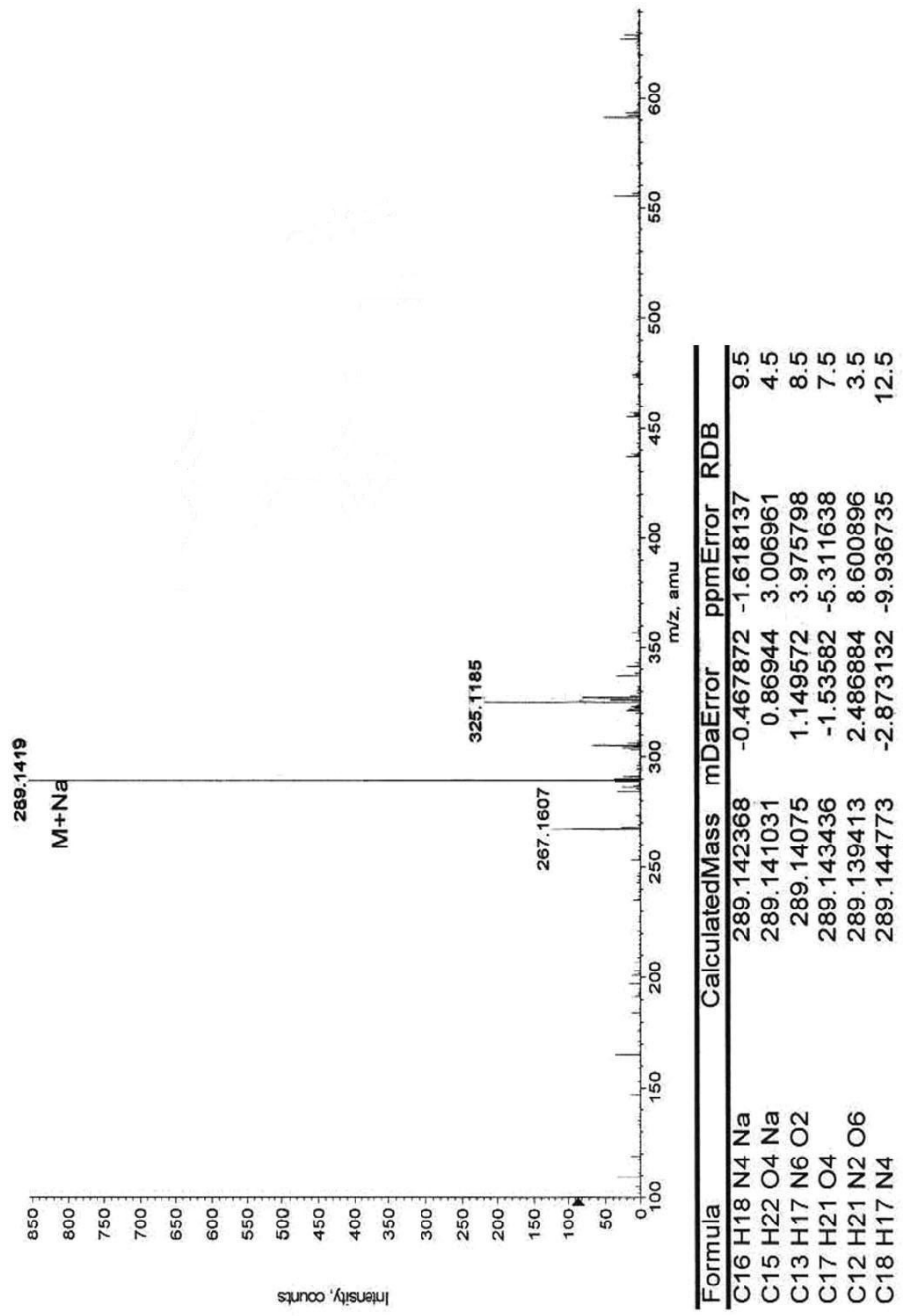


Fig. 9.19: IR spectrum of **6**



Formula	CalculatedMass	mDaError	ppmError	RDB
C16 H18 N4 Na	289.142368	-0.467872	-1.618137	9.5
C15 H22 O4 Na	289.141031	0.86944	3.006961	4.5
C13 H17 N6 O2	289.14075	1.149572	3.975798	8.5
C17 H21 O4	289.143436	-1.53582	-5.311638	7.5
C12 H21 N2 O6	289.139413	2.486884	8.600896	3.5
C18 H17 N4	289.144773	-2.873132	-9.936735	12.5

Fig. 9.20: mass spectrum of **6**

9.6 Spectra of compound **7a**

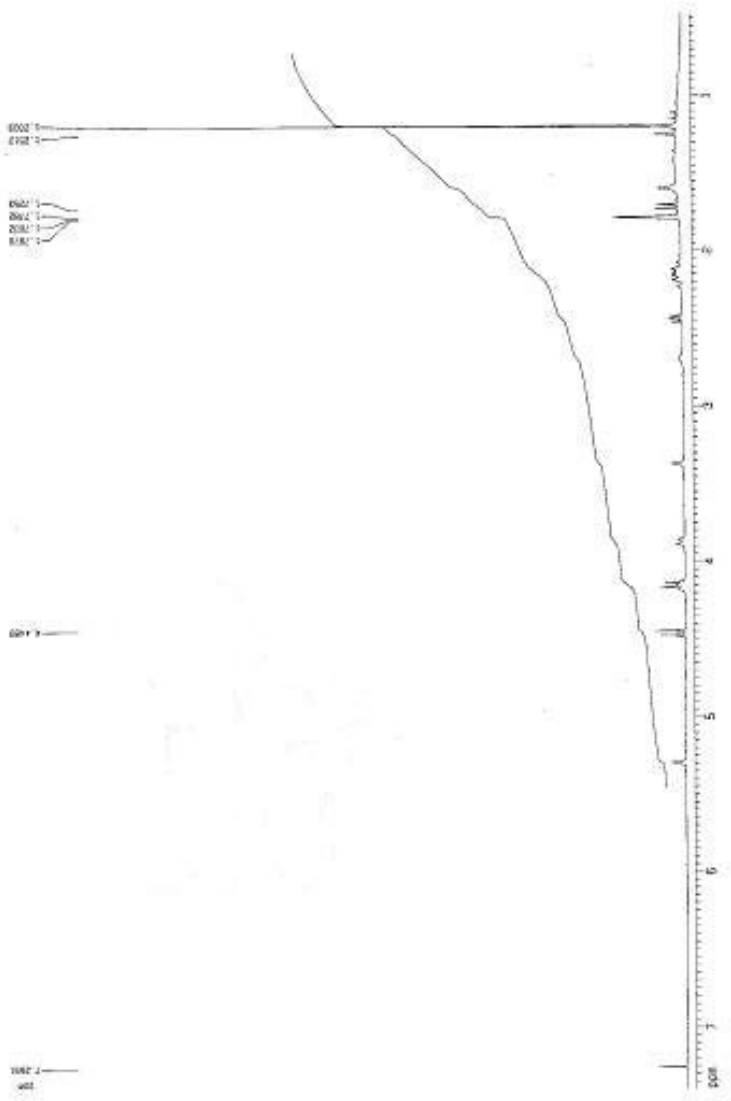


Fig. 9.21: ^{1}H-NMR spectrum of **7a**

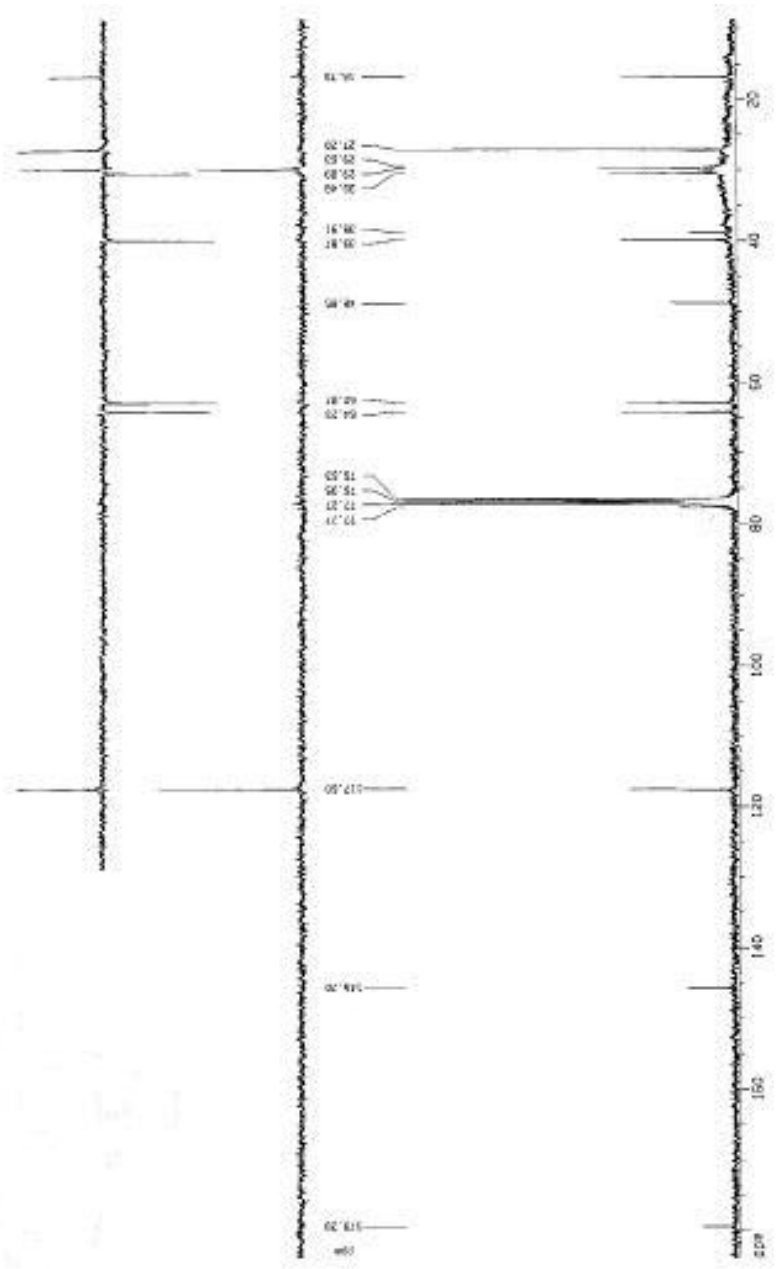


Fig. 9.22: ^{13}C-NMR spectrum of **7a**

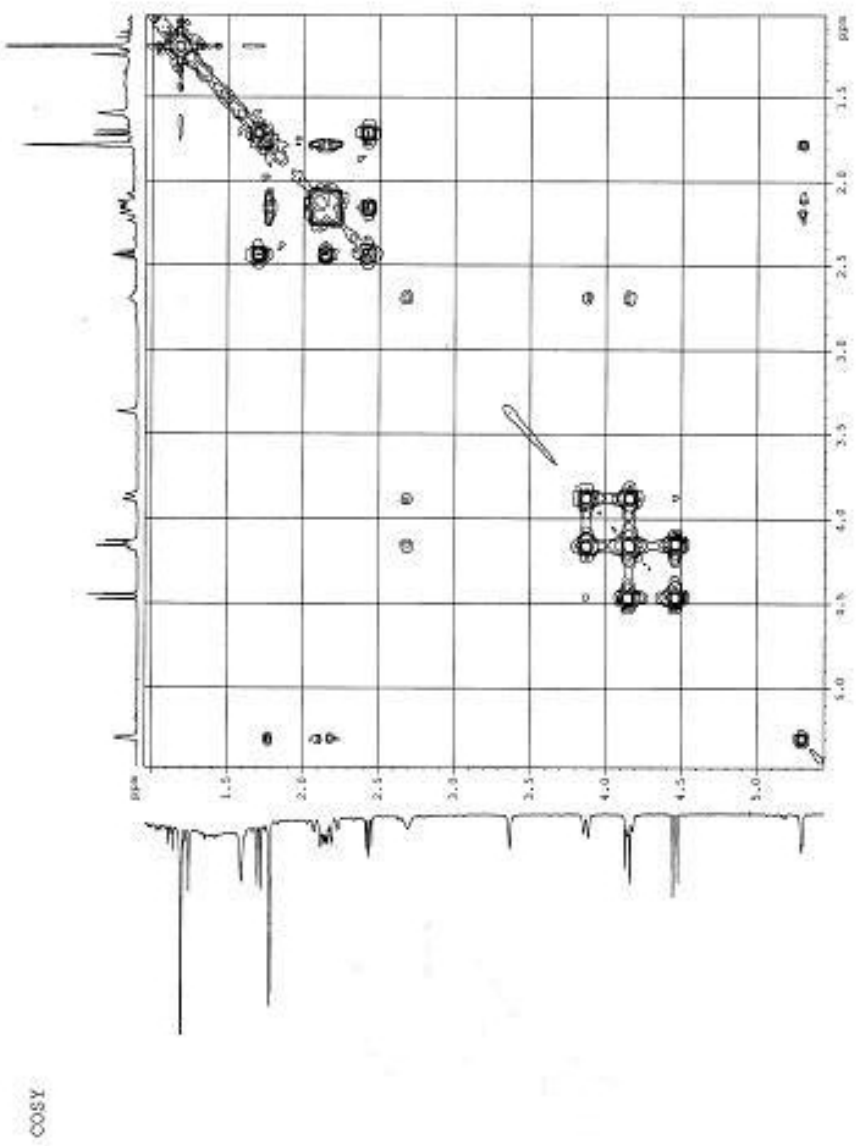


Fig. 9.23: COSY-NMR spectrum of **7a**

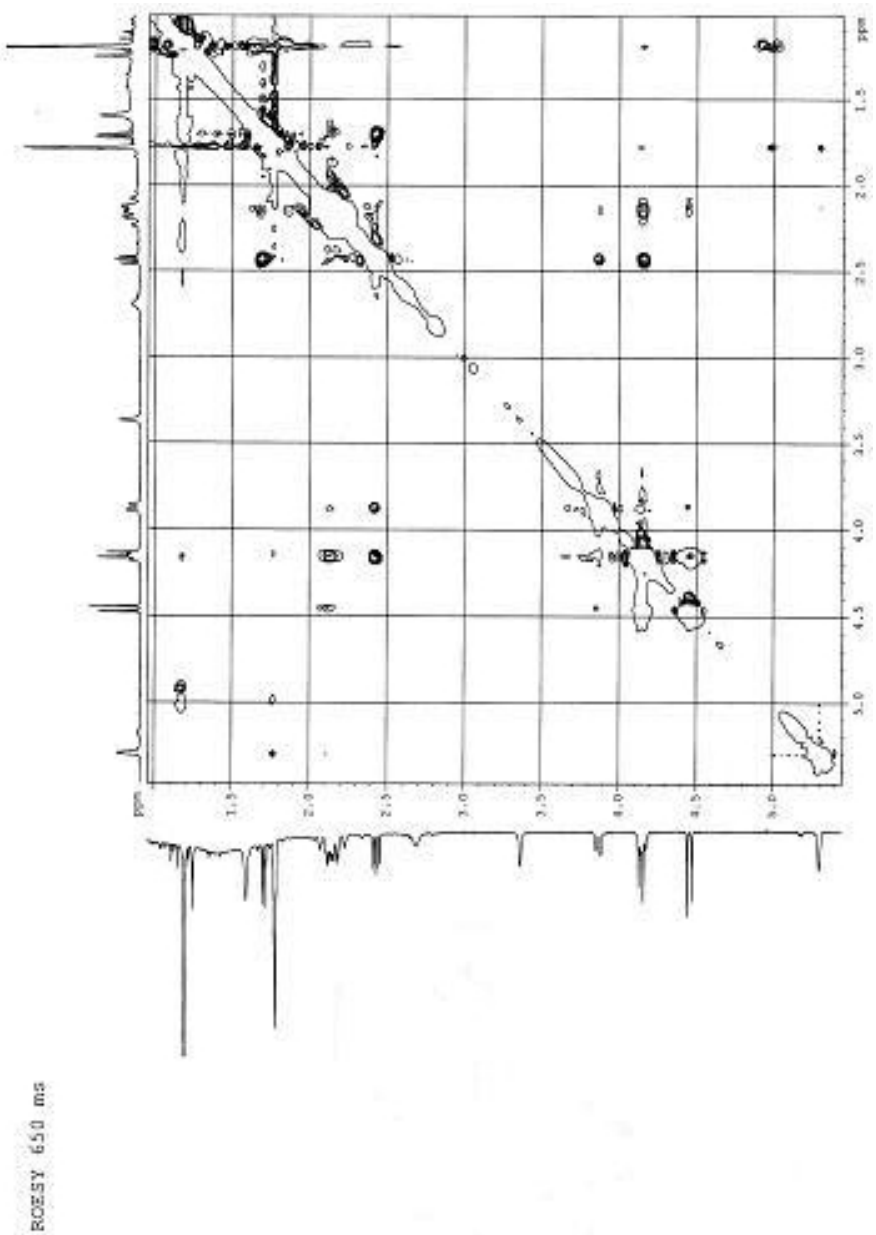


Fig. 9.24: ROESY-NMR spectrum of **7a**

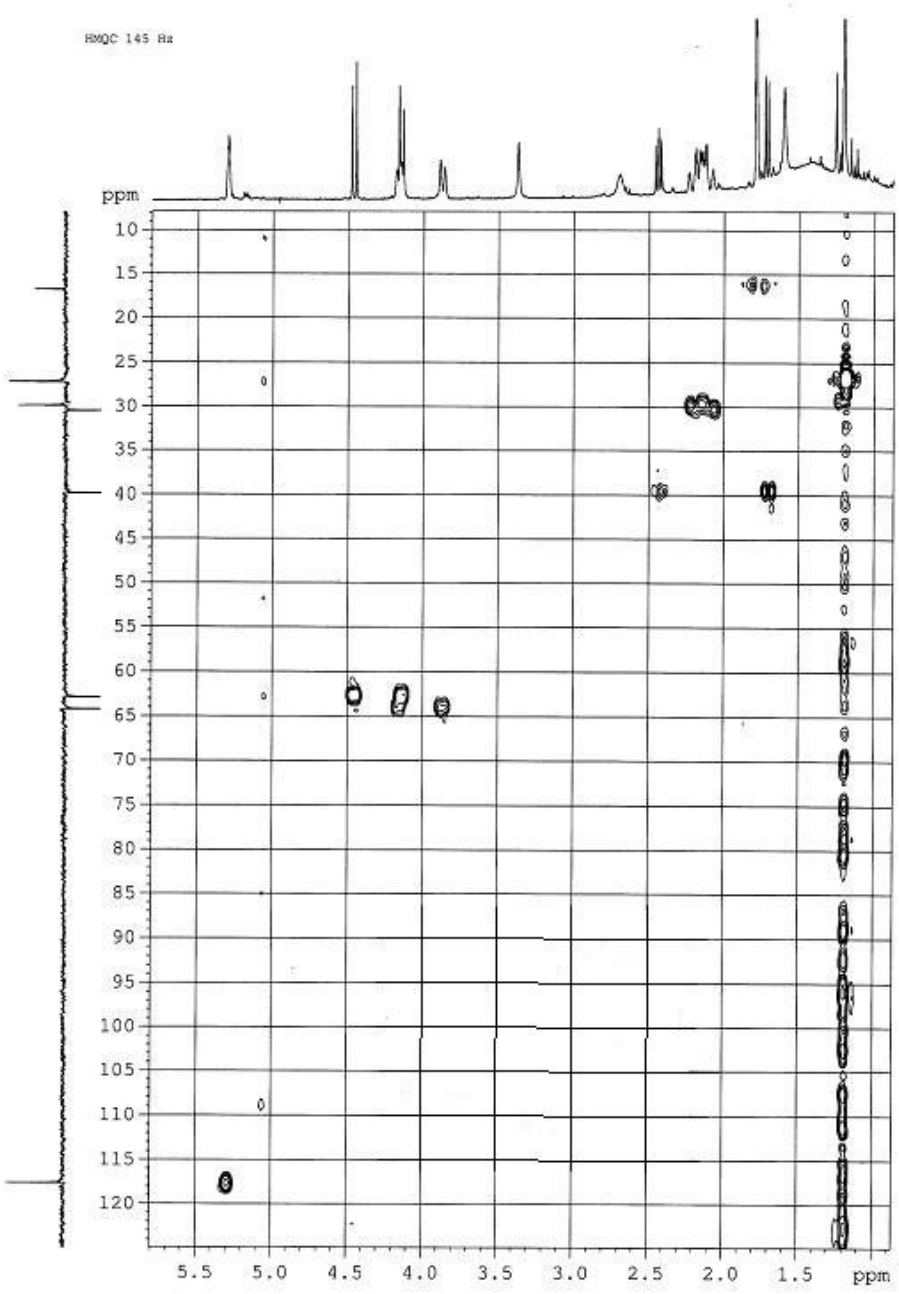


Fig. 9.25: HMQC-NMR spectrum of **7a**

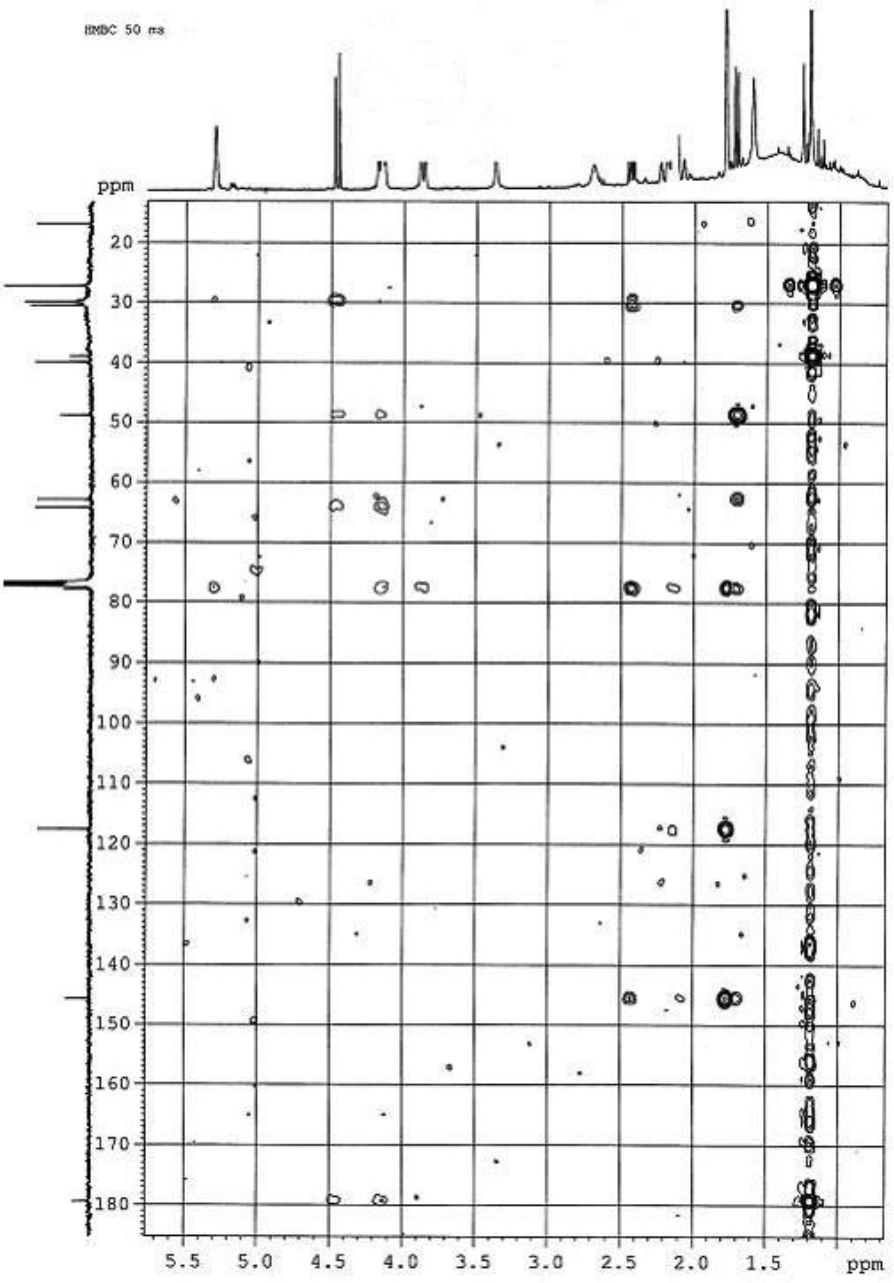


Fig. 9.26: HMBC-NMR spectrum of **7a**

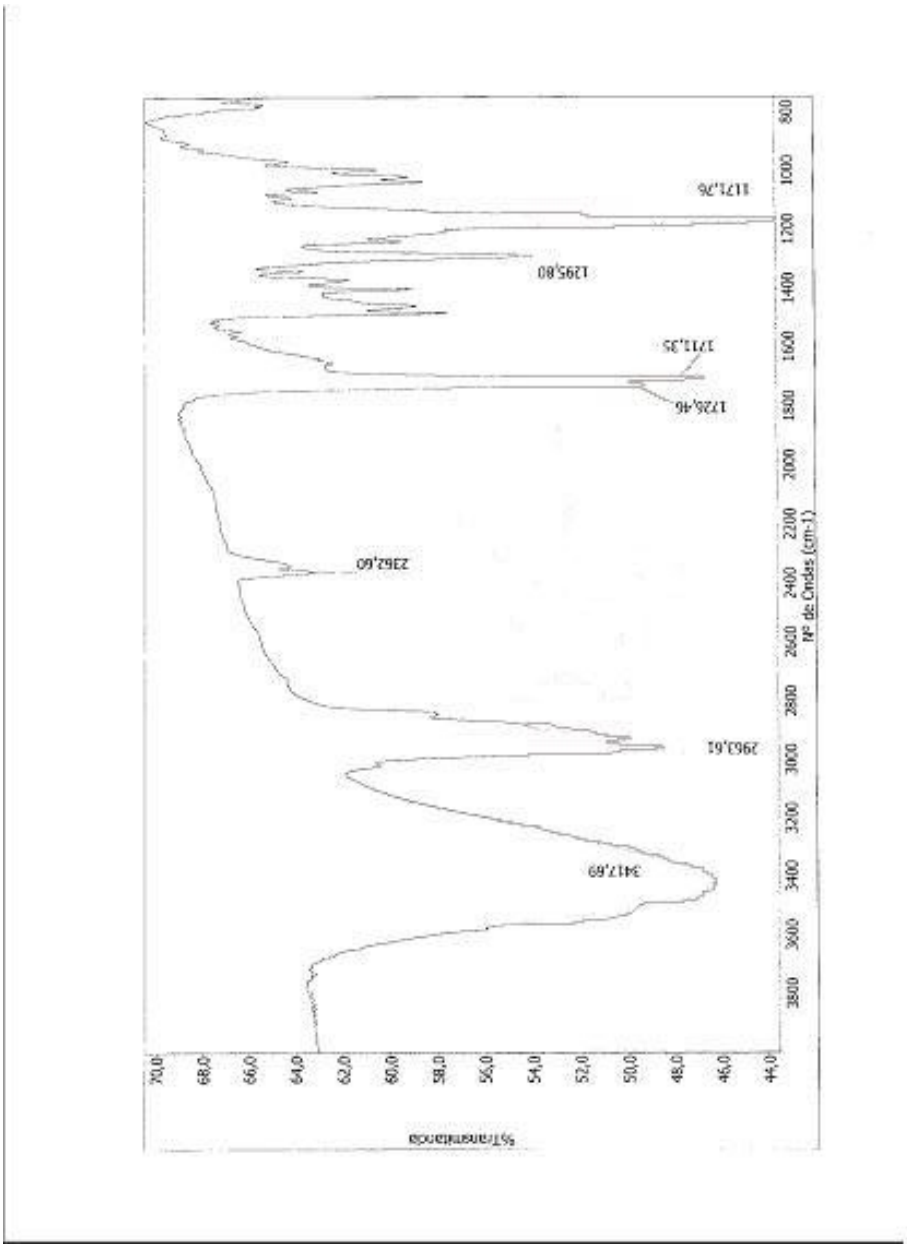
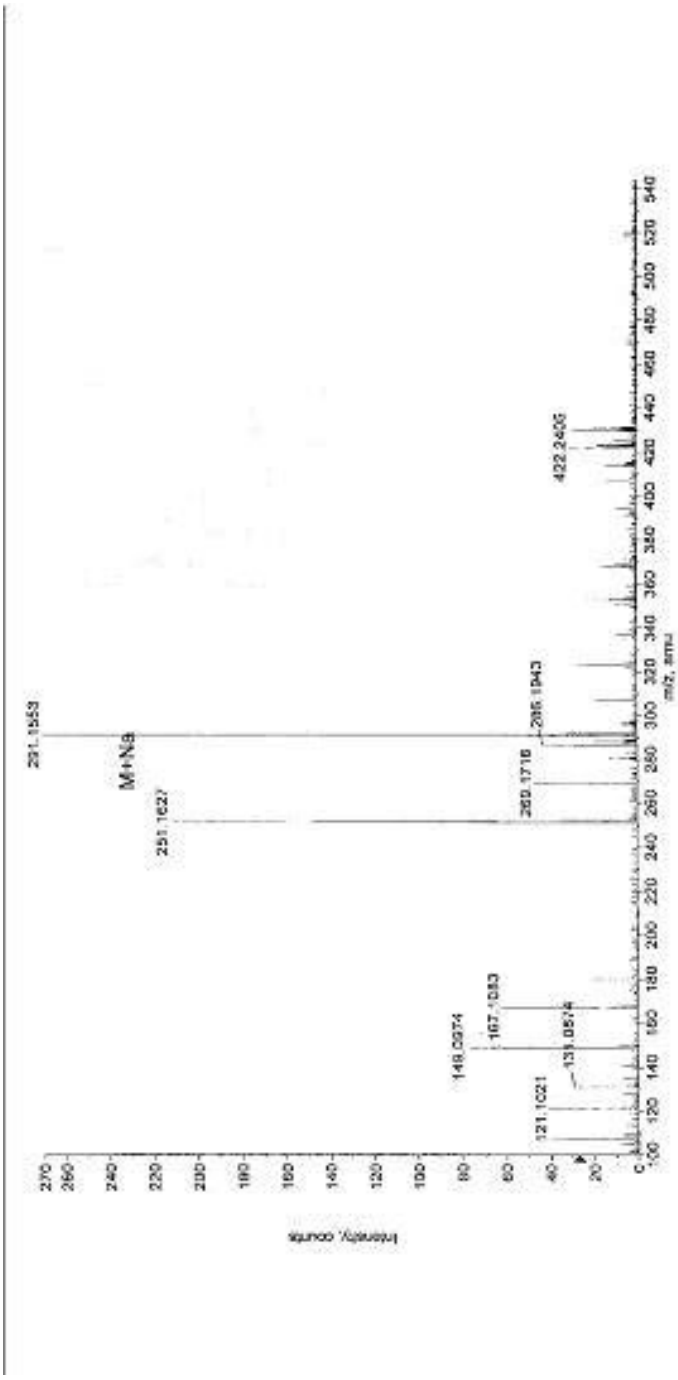


Fig. 9.27: IR spectrum of **7a**



Formula	CalculatedMass	mDaError	ppmError	RDB
C12 H23 N2 O6	291.155053	0.236804	0.813324	2.5
C13 H19 N6 O2	291.156401	-1.100508	-3.77979	7.5
C11 H20 N6 O2 Na	291.153995	1.304752	4.481284	4.5
C15 H24 O4 Na	291.156681	-1.38064	-4.741928	3.5
C10 H24 N2 O6 Na	291.152658	2.642064	9.074398	-0.5
C16 H20 N4 Na	291.158018	-2.717952	-9.335042	8.5

Fig. 9.28: mass spectrum of **7a**

9.7 Spectra of compound **7b**

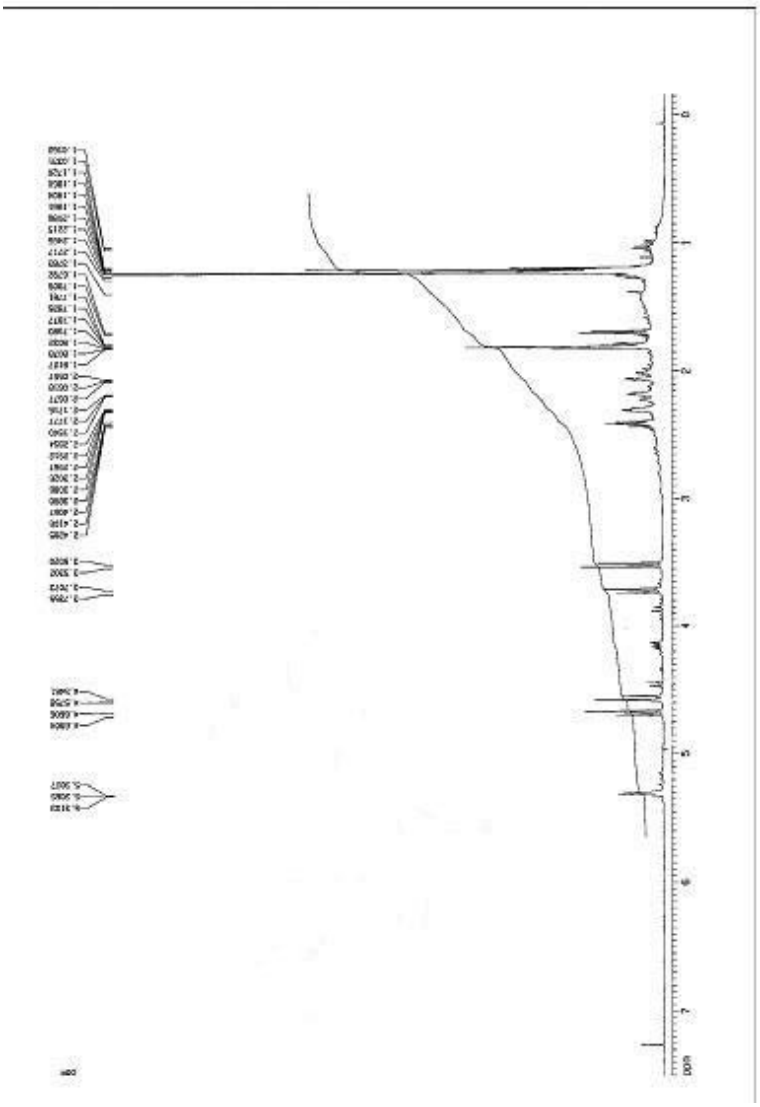


Fig. 9.29: ^{1}H-NMR spectrum of **7b**

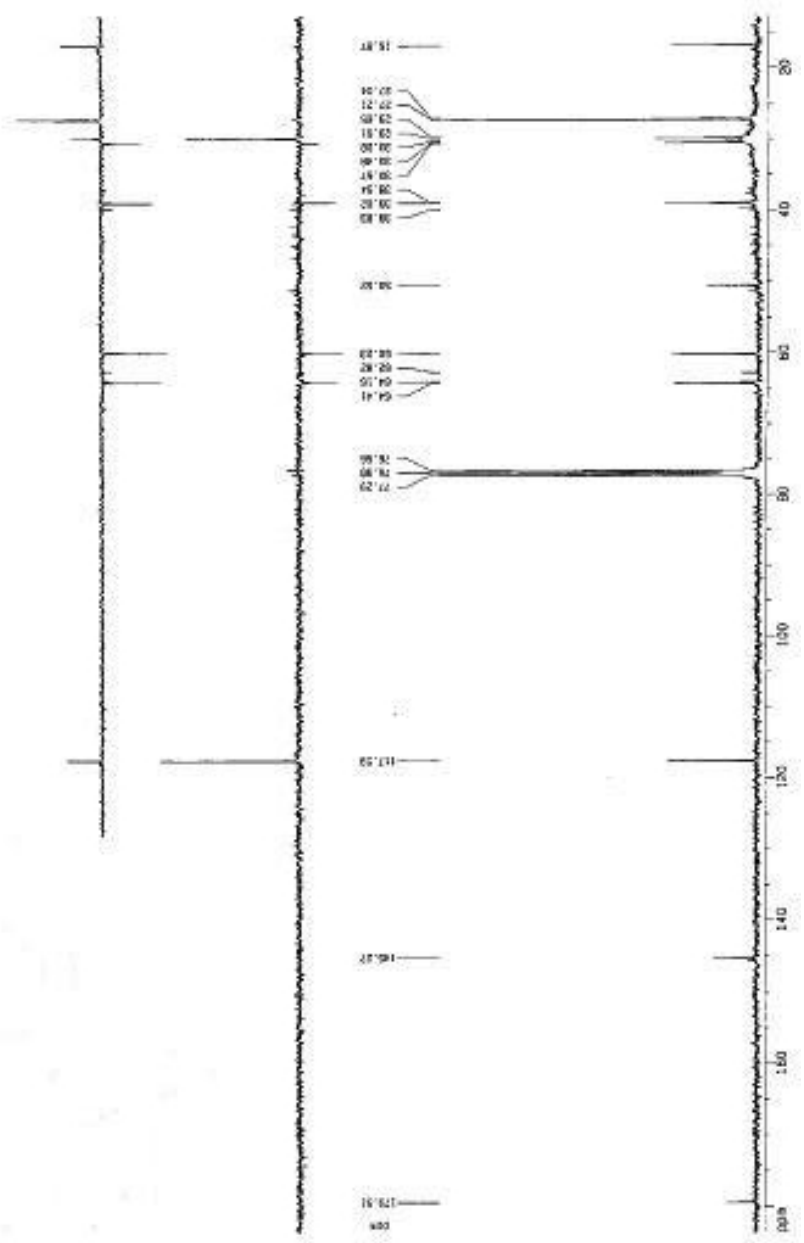


Fig. 9.30: ^{13}C-NMR spectrum of **7b**

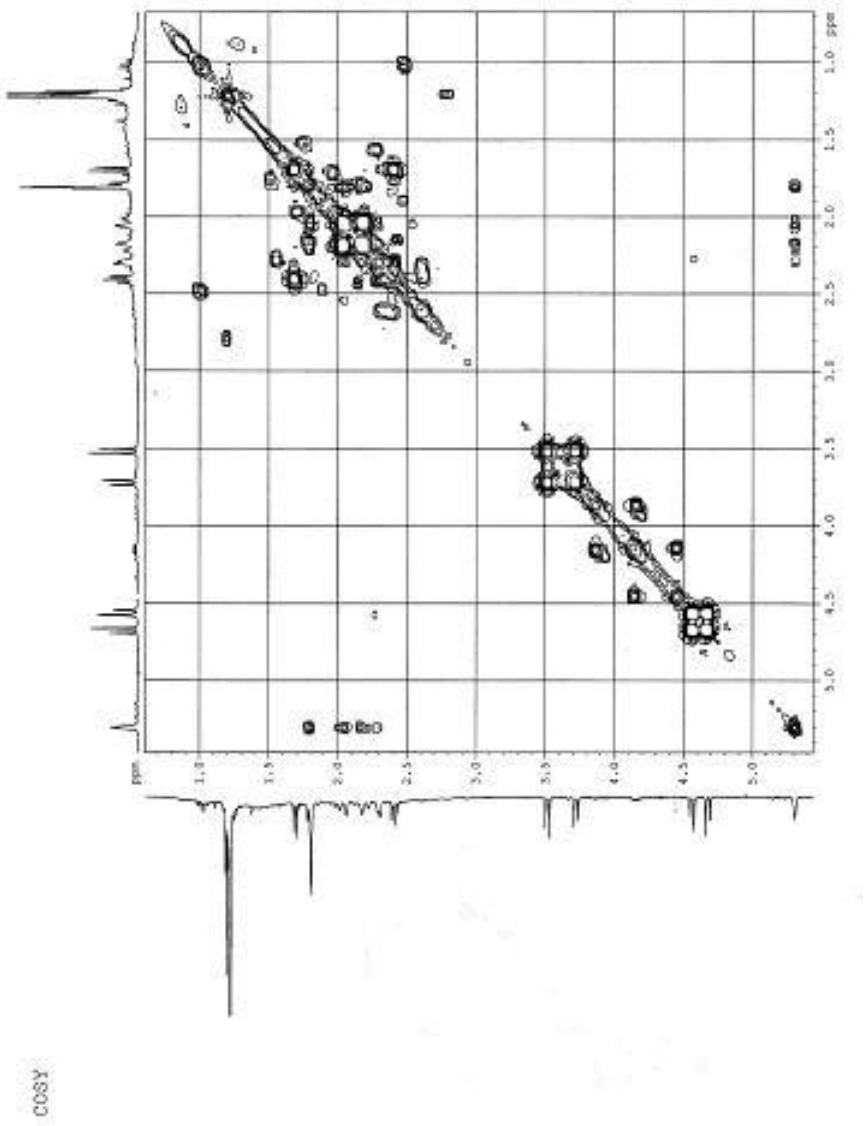


Fig. 9.31: COSY-NMR spectrum of **7b**

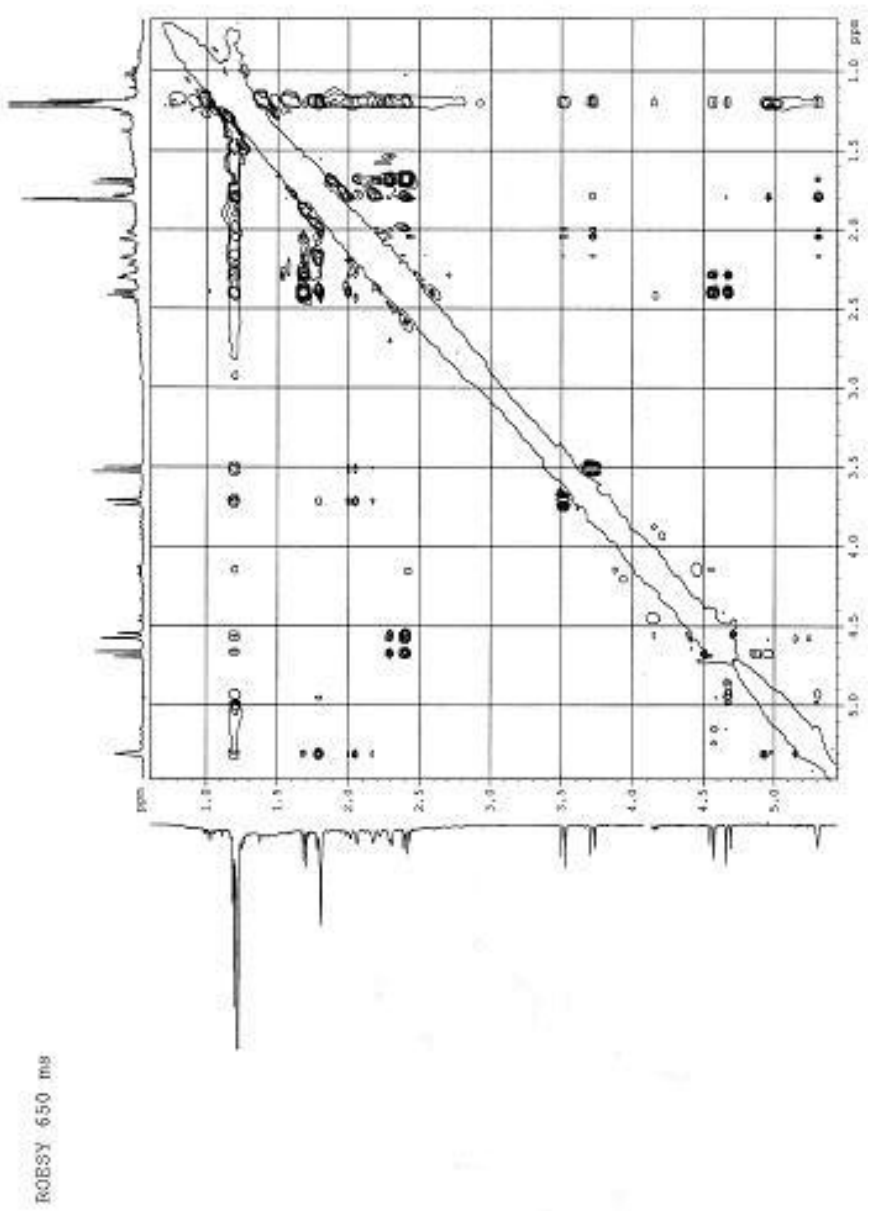


Fig. 9.32: ROESY-NMR spectrum of **7b**

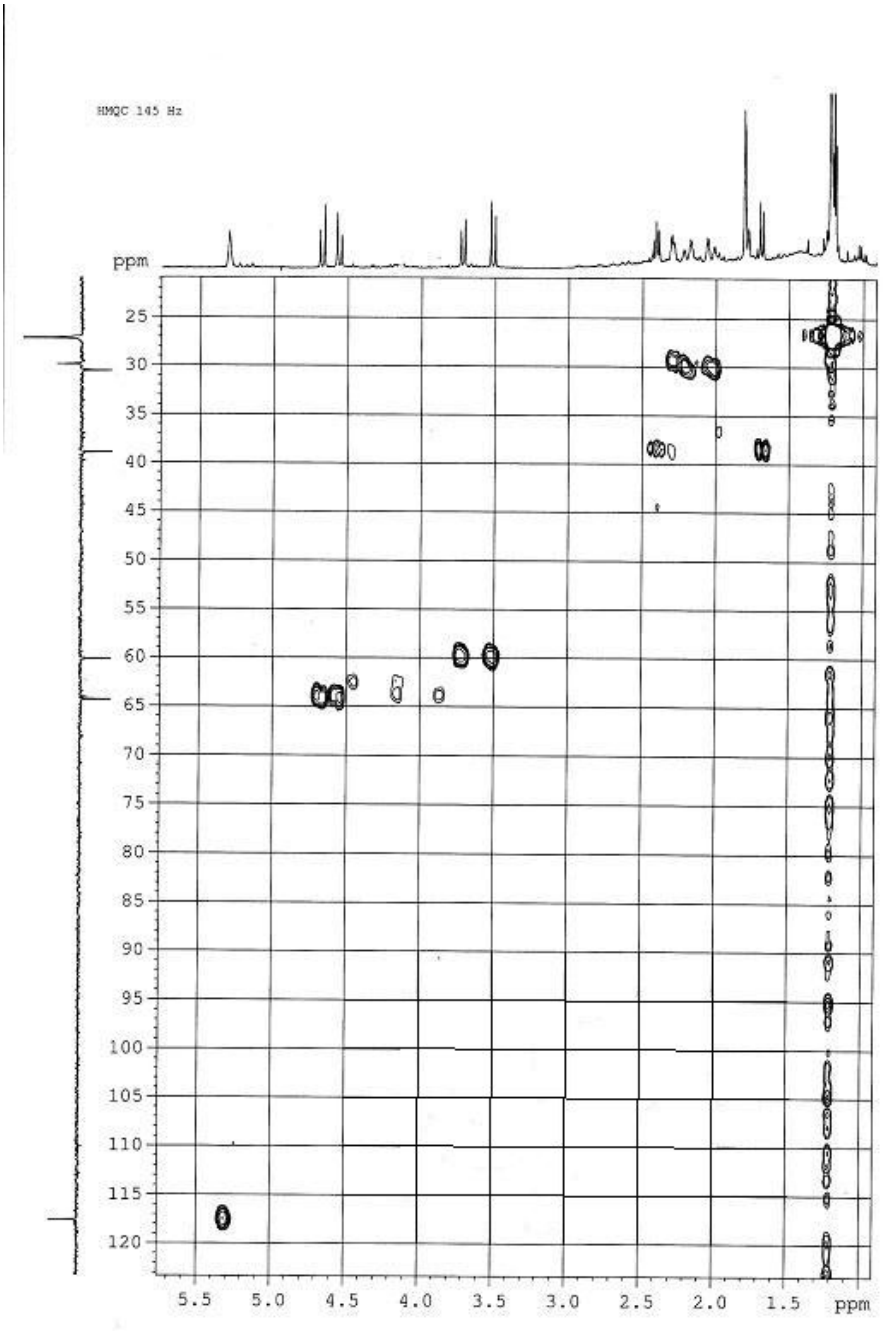


Fig. 9.33: HMQC-NMR spectrum of **7b**

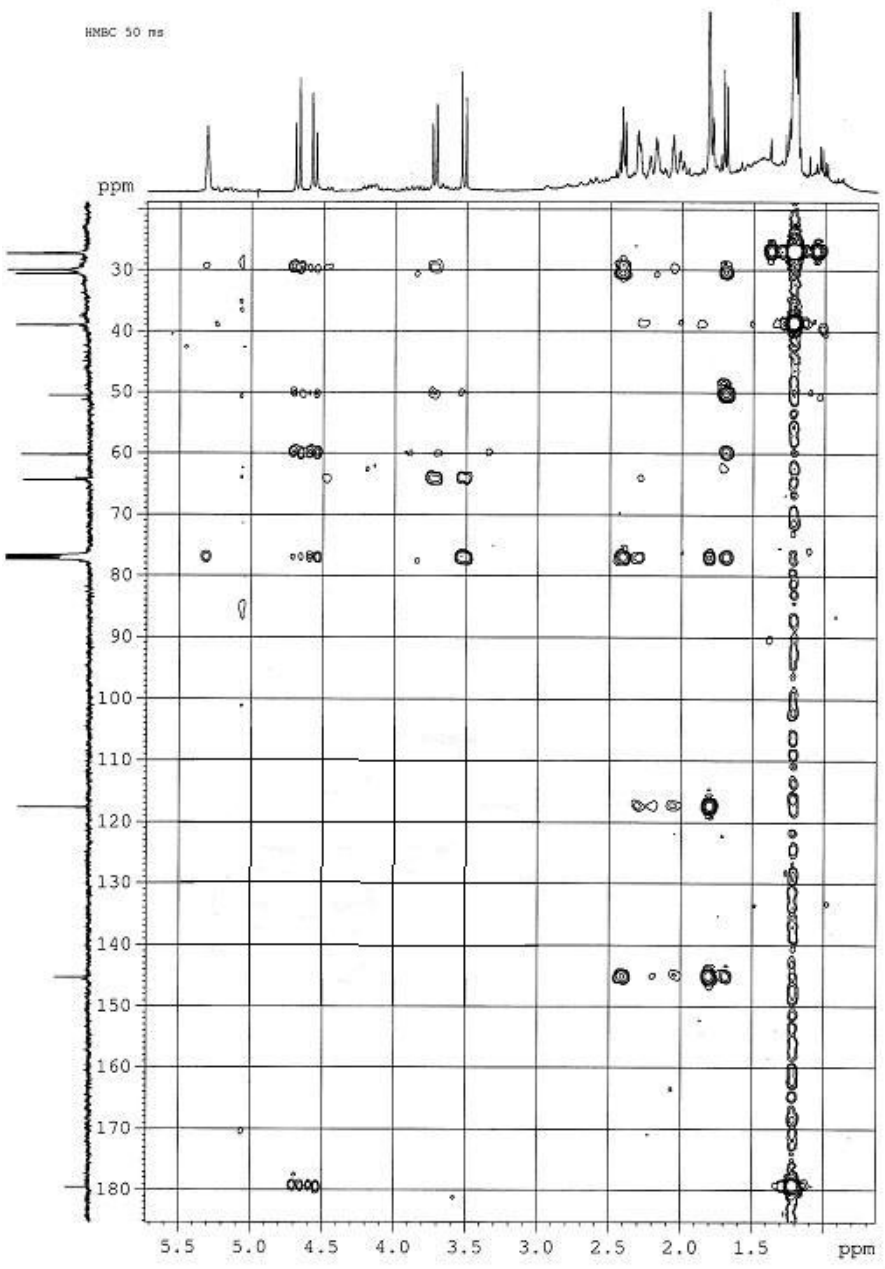


Fig. 9.34: HMBC-NMR spectrum of **7b**

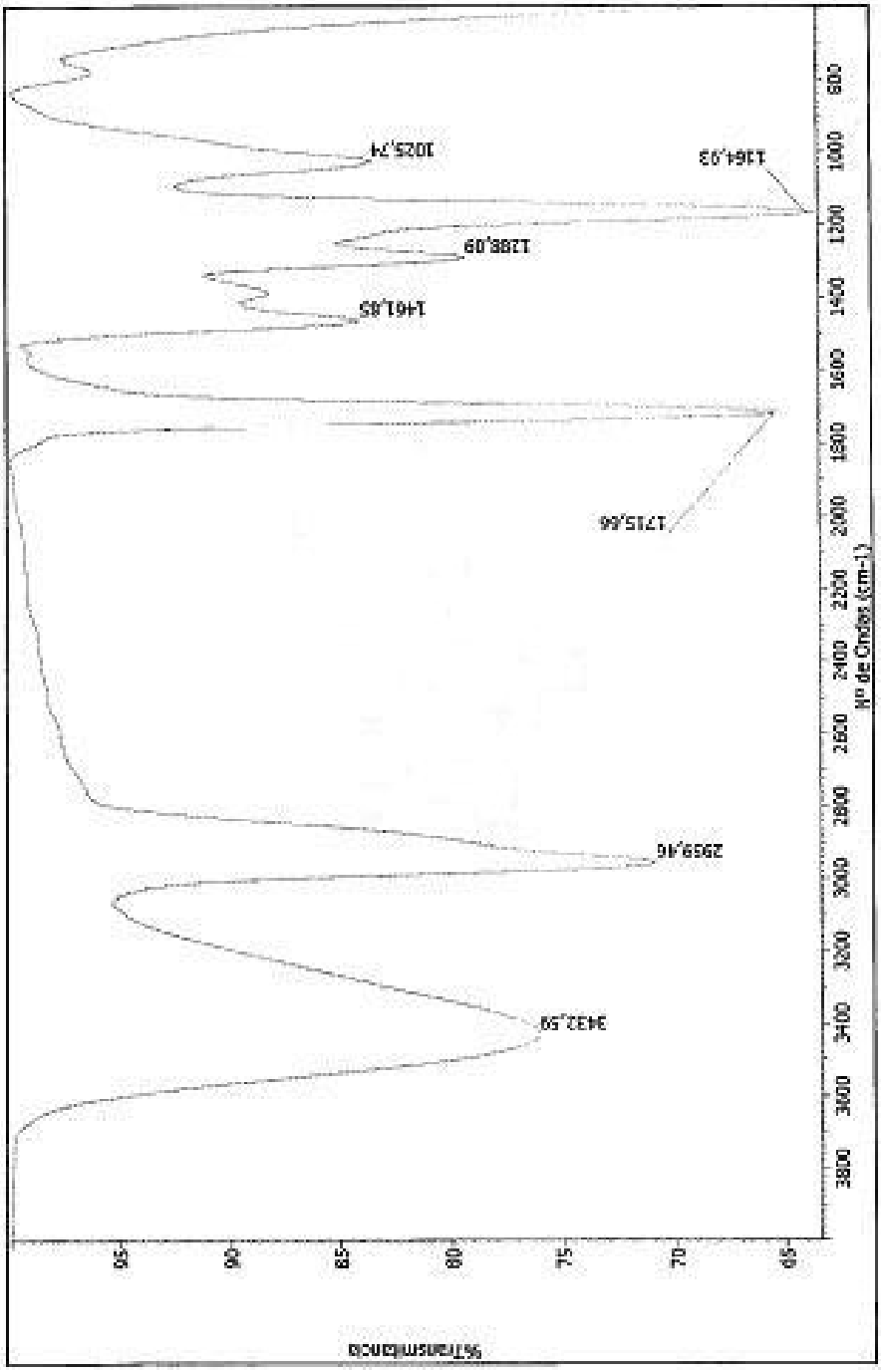
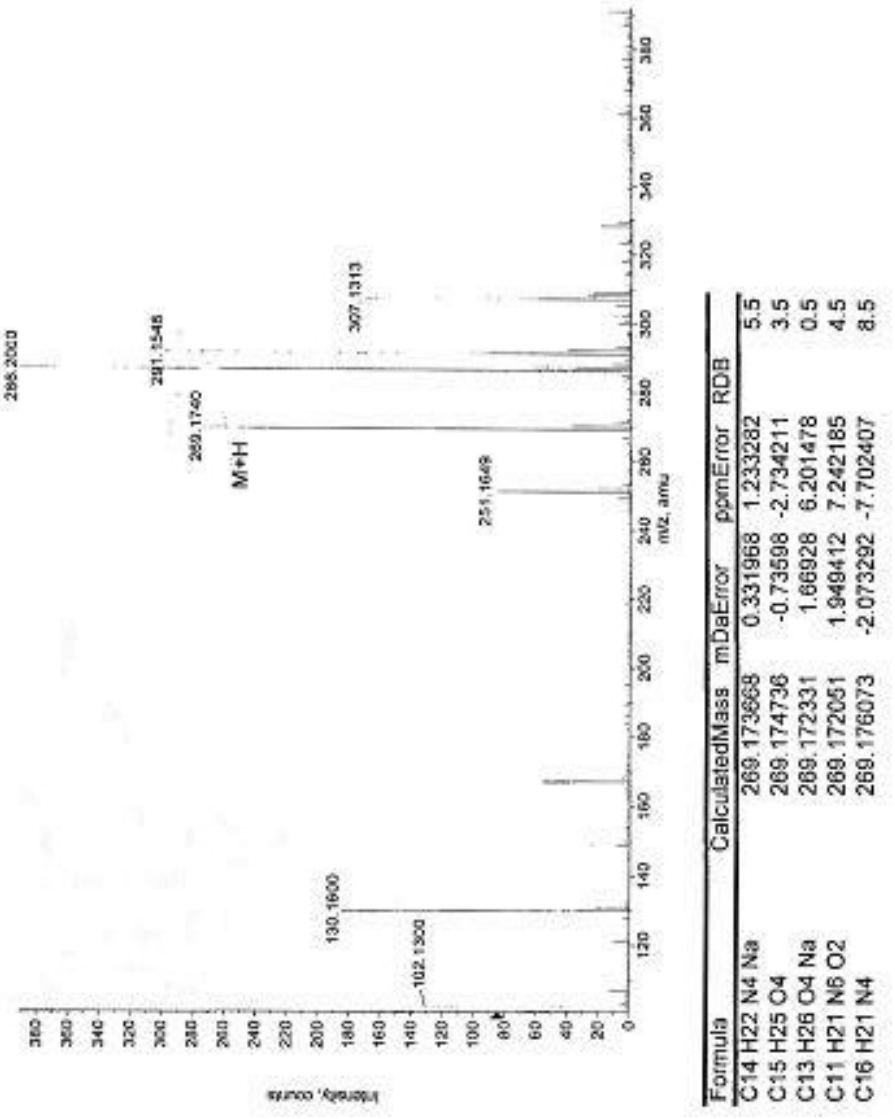


Fig. 9.35: IR spectrum of **7b**



Formula	CalculatedMass	mDaError	ppmError	RDB
C14 H22 N4 Na	269.173668	0.331968	1.233282	5.5
C15 H25 O4	269.174736	-0.73598	-2.734211	3.5
C13 H26 O4 Na	269.172331	1.66928	6.201478	0.5
C11 H21 N6 O2	269.172051	1.949412	7.242185	4.5
C16 H21 N4	269.176073	-2.073292	-7.702407	8.5

Fig. 9.36: mass spectrum of **7b**

9.8 Spectra of compound **8**

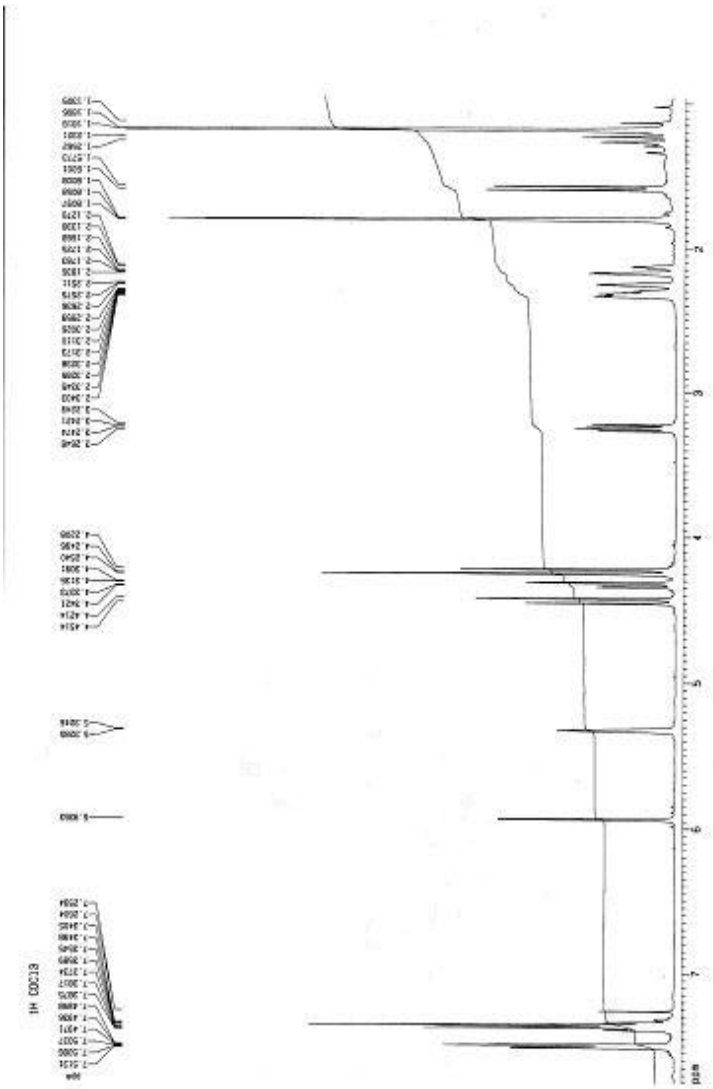


Fig. 9.37: ^{1}H-NMR spectrum of **8**

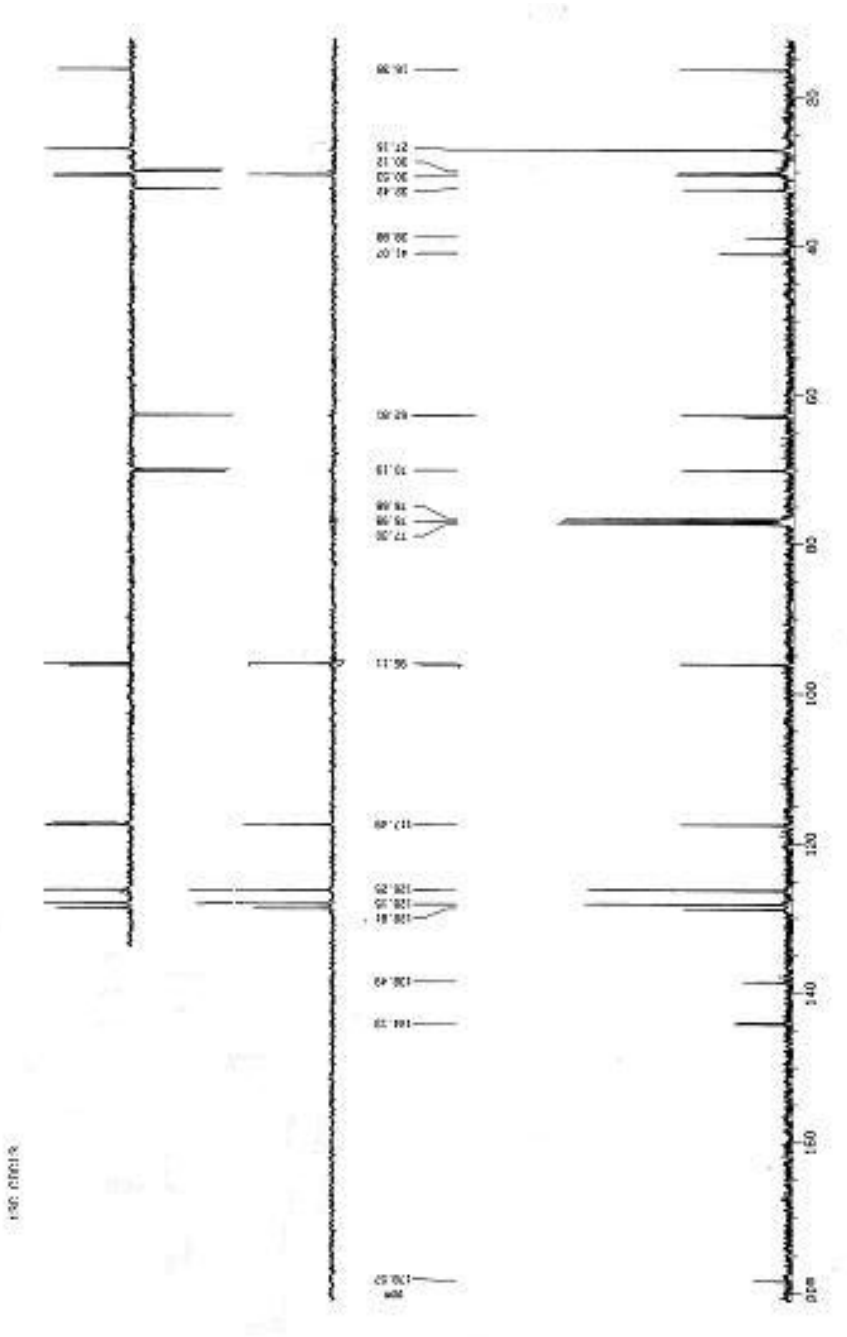


Fig. 9.38: ^{13}C-NMR spectrum of **8**

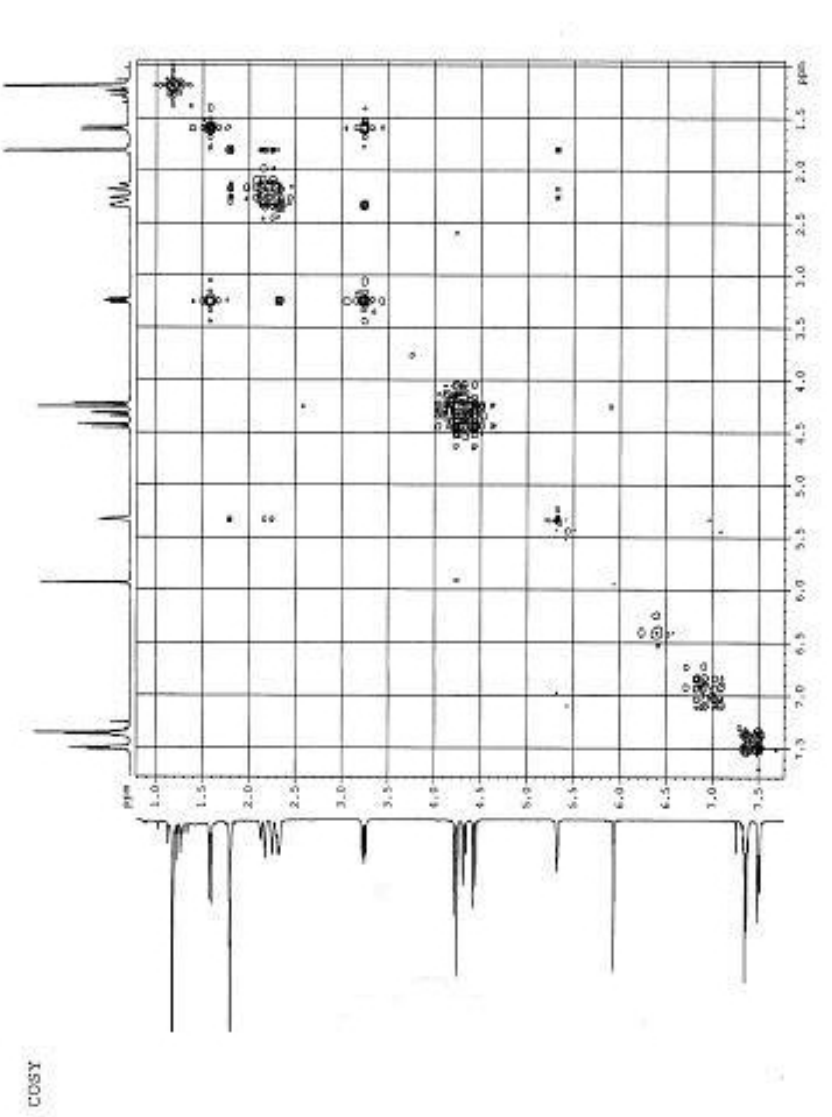


Fig. 9.39: COSY-NMR spectrum of **8**

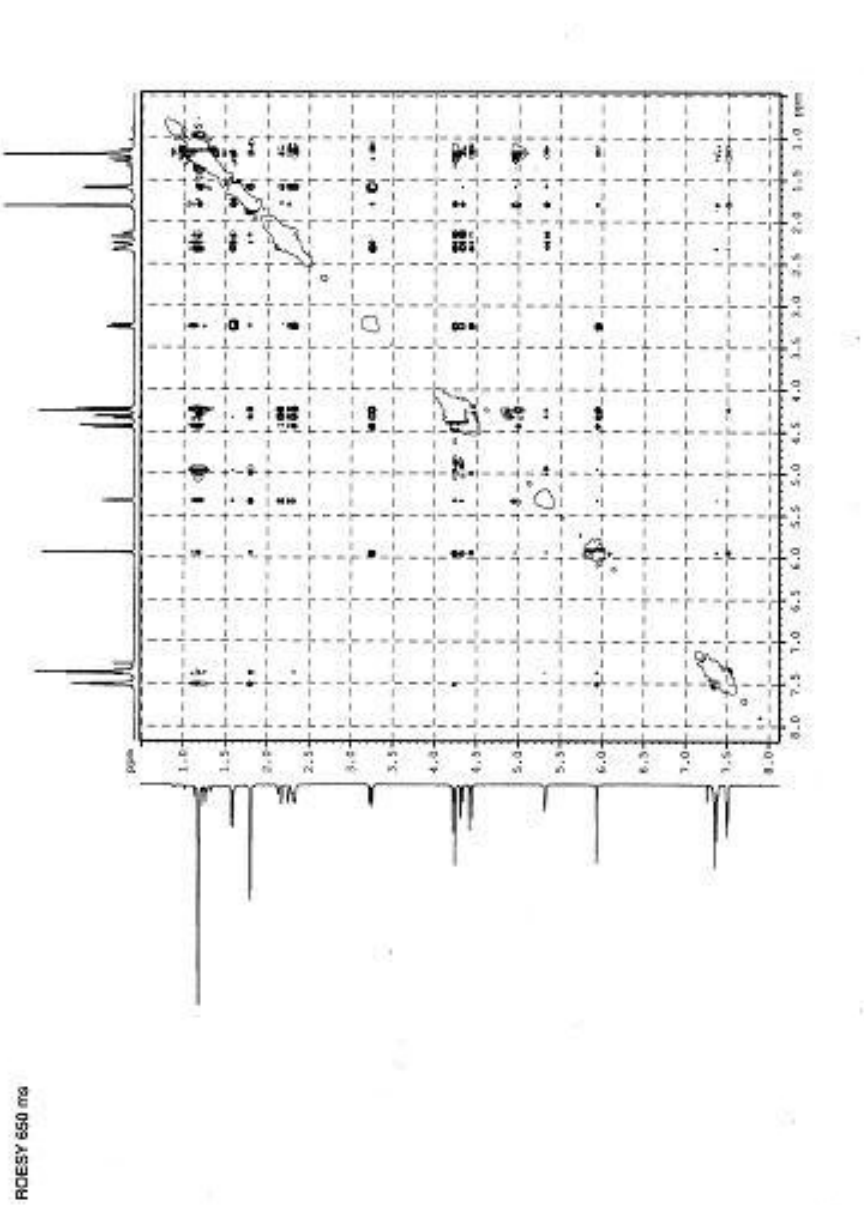


Fig. 9.40: ROESY-NMR spectrum of **8**

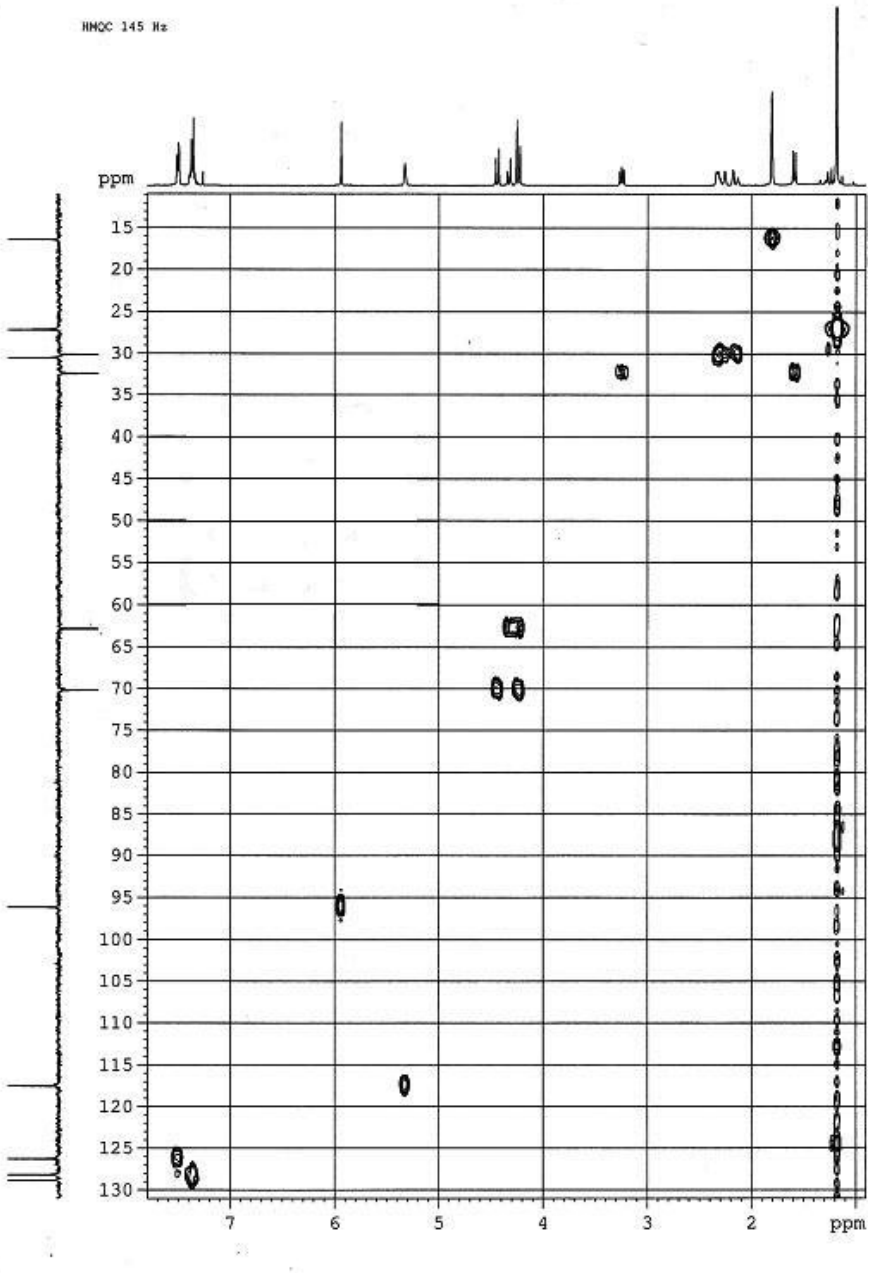


Fig. 9.41: HMQC-NMR spectrum of **8**

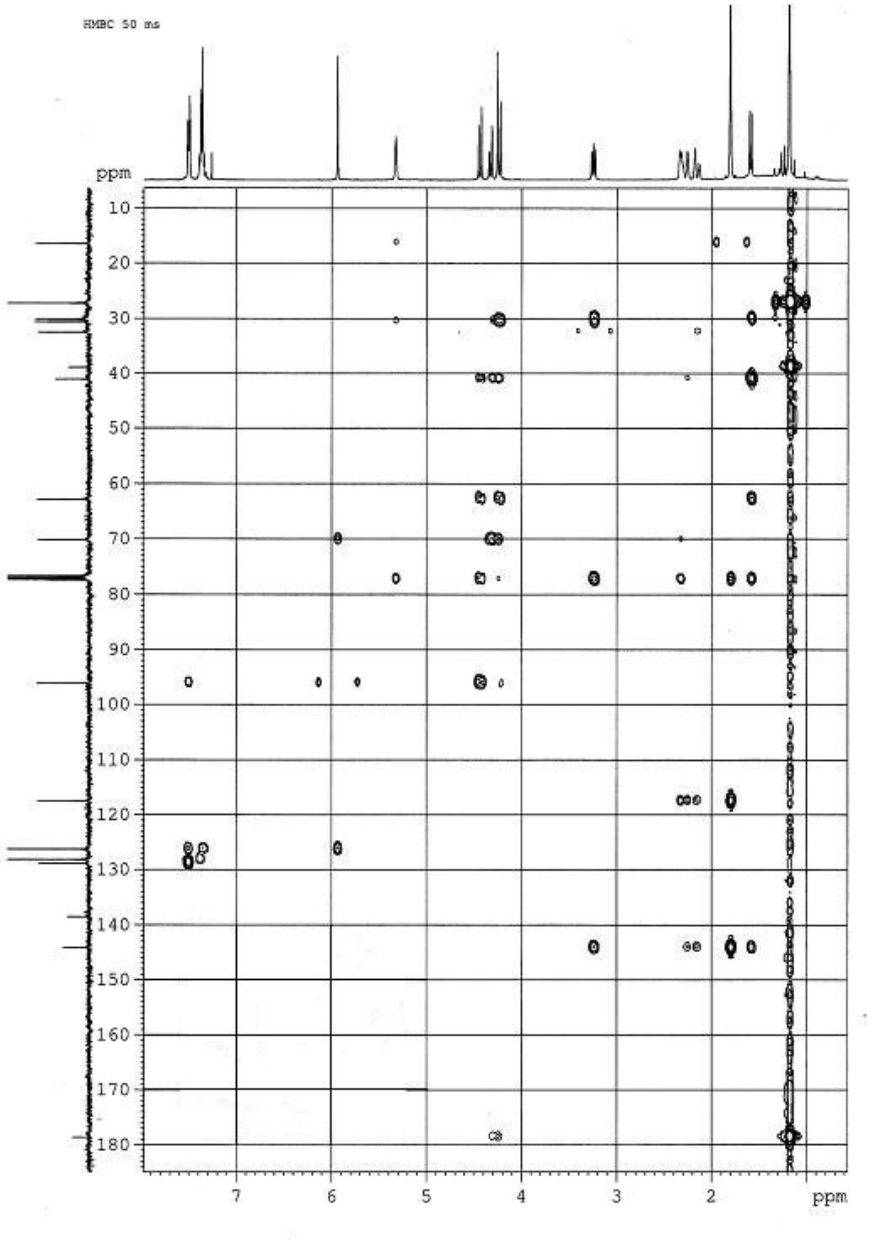


Fig. 9.42: HMBC-NMR spectrum of **8**

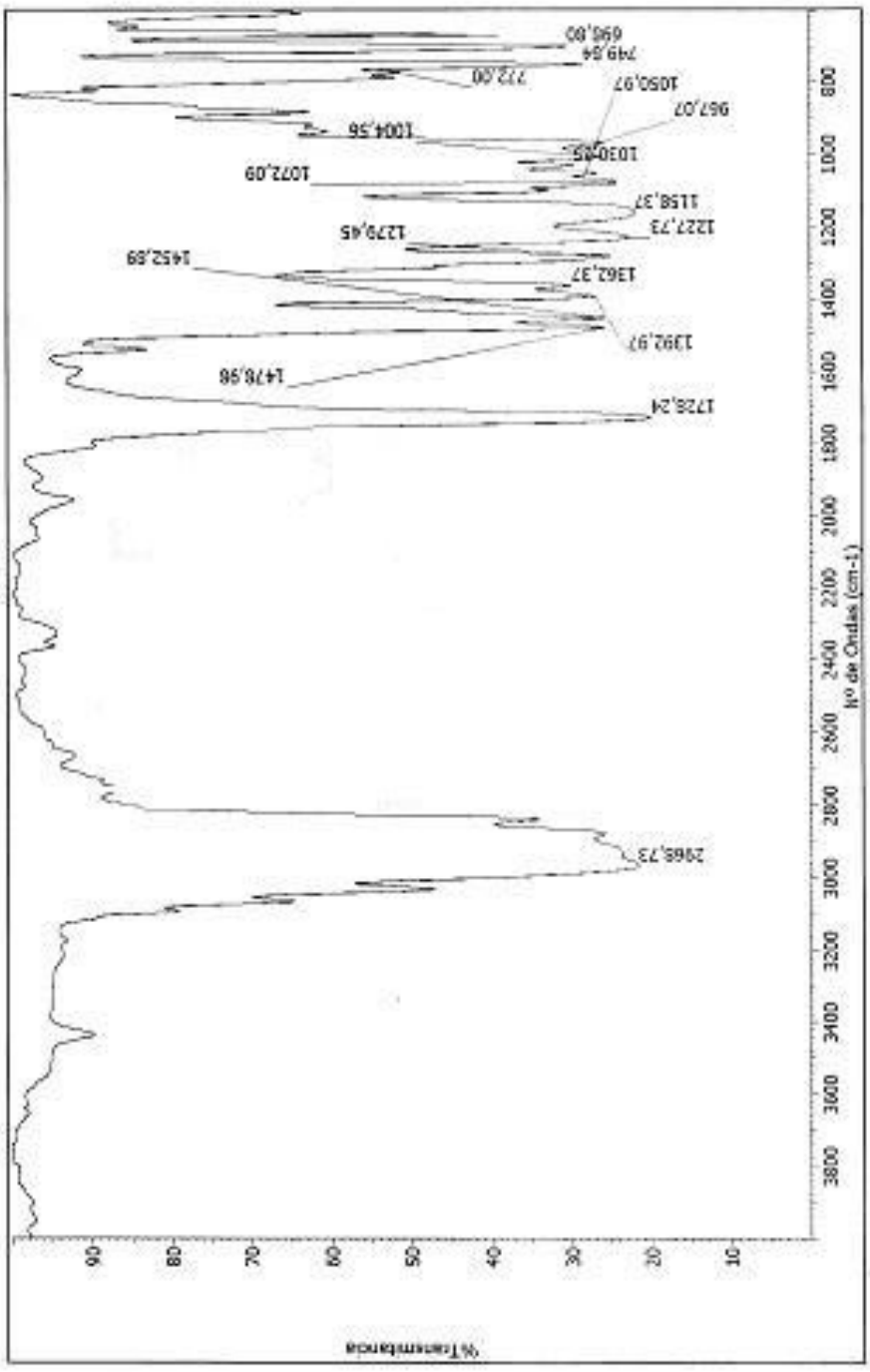
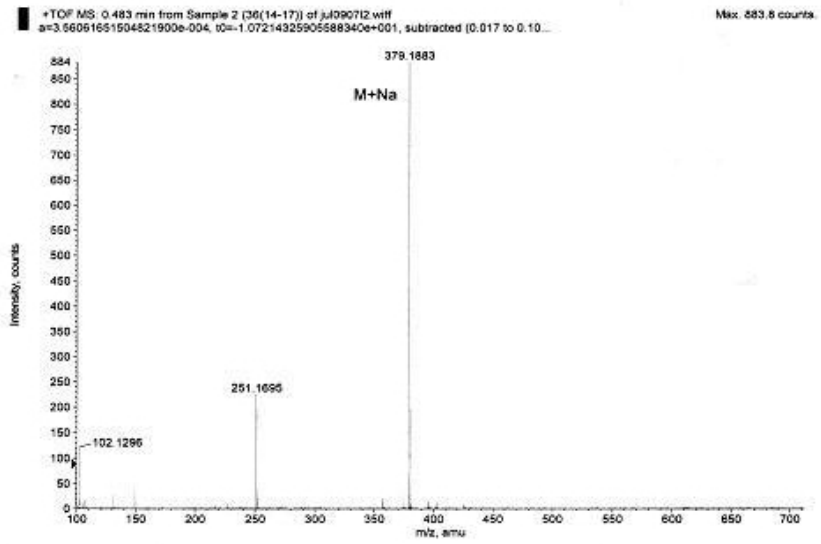


Fig. 9.43: IR spectrum of **8**



Formula	CalculatedMass	mDaError	ppmError	RDB
C7 H24 N12 O5 Na	379.188483	-0.183376	-0.483601	1.5
C22 H28 O4 Na	379.187981	0.3192	0.841797	8.5
C20 H23 N6 O2	379.187701	0.599332	1.580563	12.5
C23 H24 N4 Na	379.189318	-1.018112	-2.684973	13.5
C8 H27 N8 O9	379.189551	-1.251324	-3.300002	-0.5
C4 H23 N14 O7	379.186866	1.434068	3.781936	0.5
C19 H27 N2 O6	379.186363	1.936644	5.107334	7.5
C24 H27 O4	379.190386	-2.08606	-5.501375	11.5
C9 H23 N12 O5	379.190889	-2.588636	-6.826772	4.5
C11 H28 N6 O7 Na	379.191169	-2.868768	-7.565539	0.5
C18 H24 N6 O2 Na	379.185295	3.004592	7.923735	9.5
C16 H19 N12	379.185015	3.284724	8.662502	13.5
C25 H23 N4	379.191723	-3.423372	-9.028145	16.5

Fig. 9.44: mass spectrum of **8** using the TOF technique

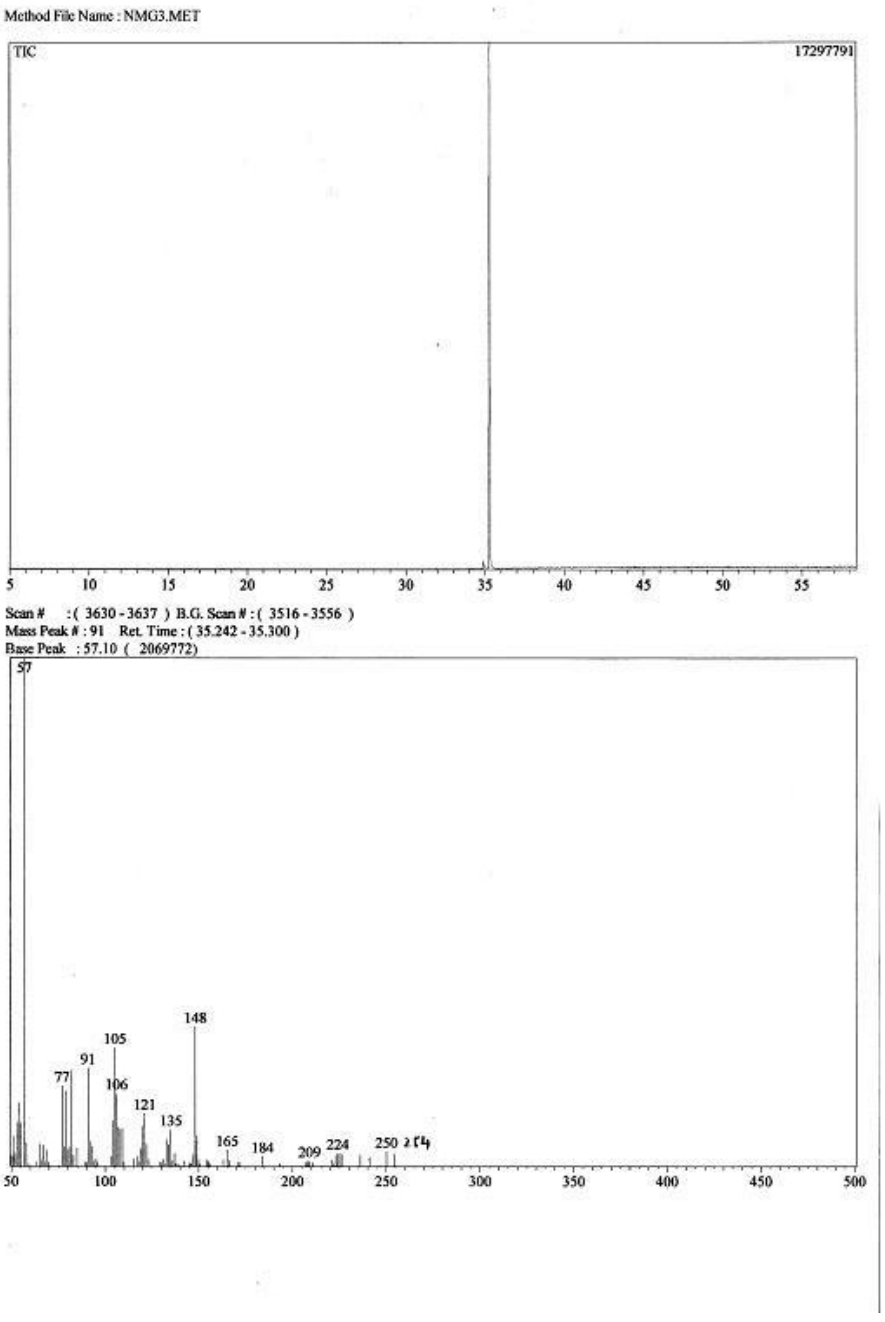


Fig. 9.45: mass spectrum of **8**

9.9 Spectra of compound **9a**

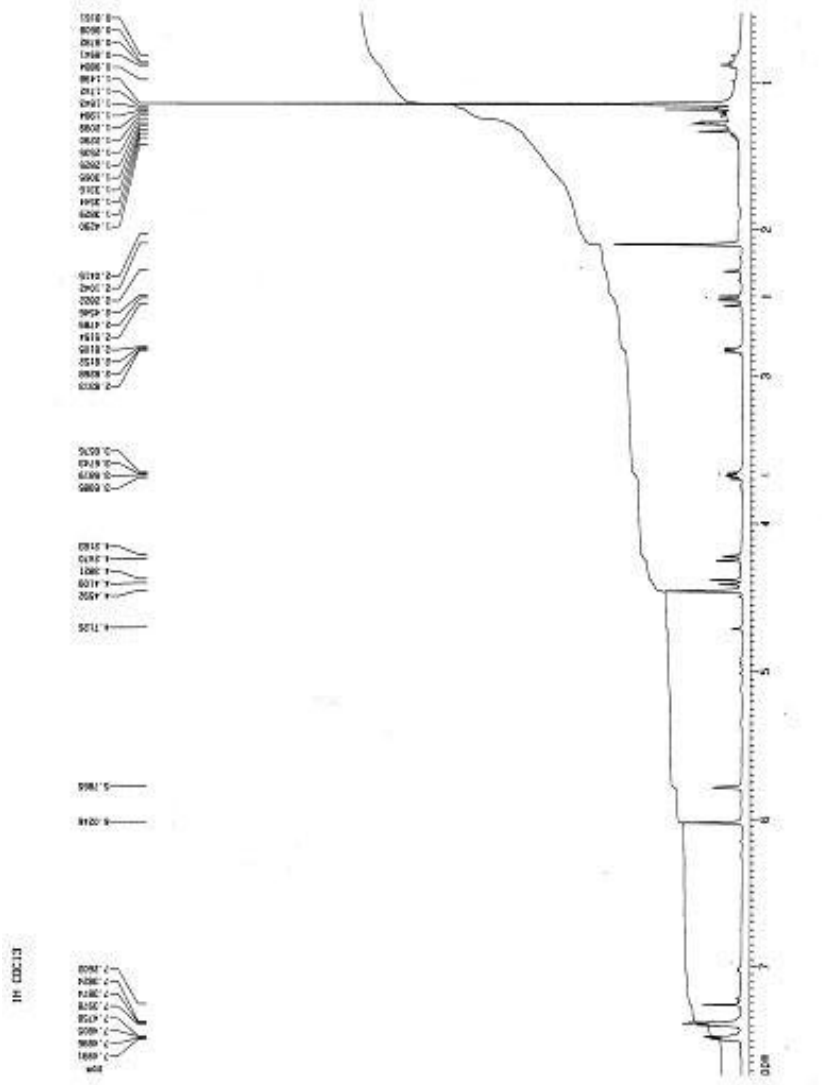


Fig. 9.46: ^{1}H-NMR spectrum of **9a**

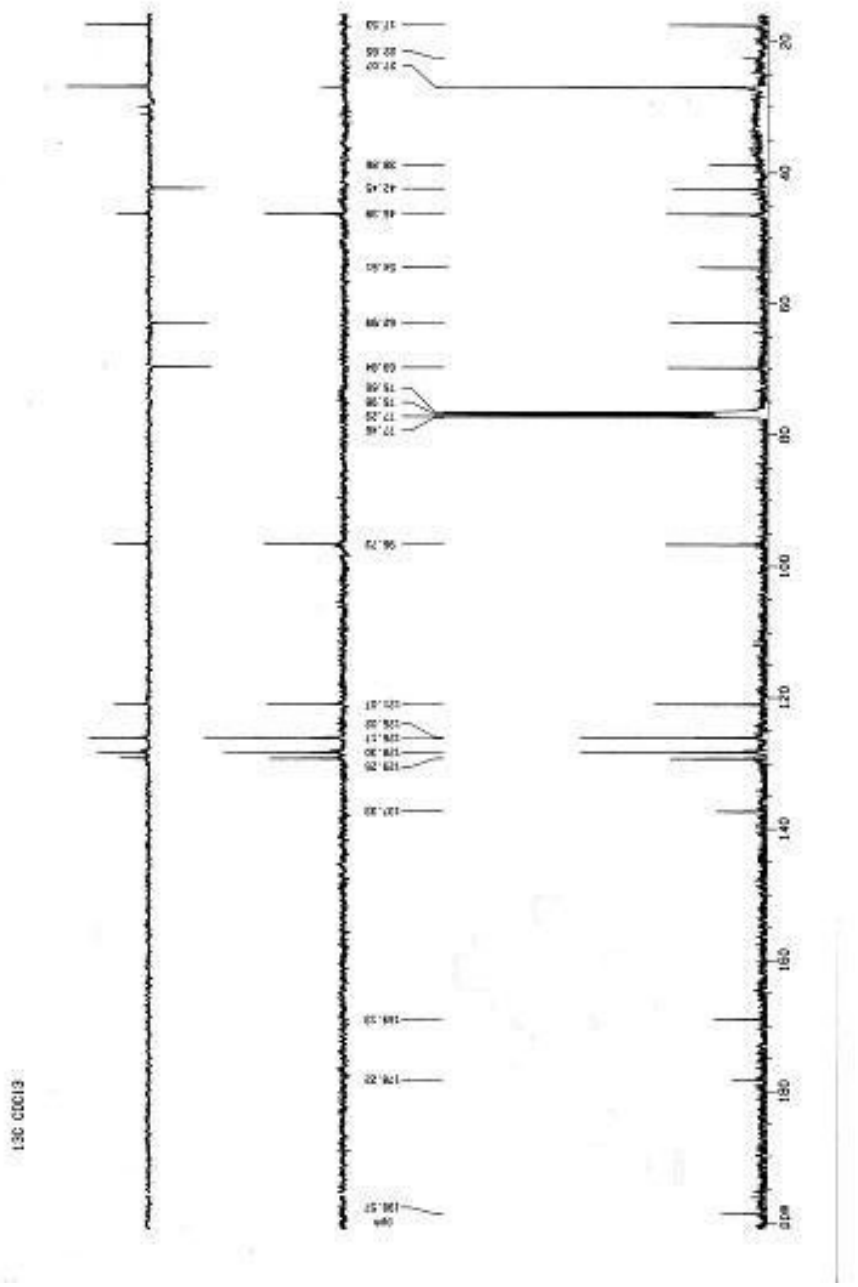


Fig. 9.47: ^{13}C-NMR spectrum of **9a**

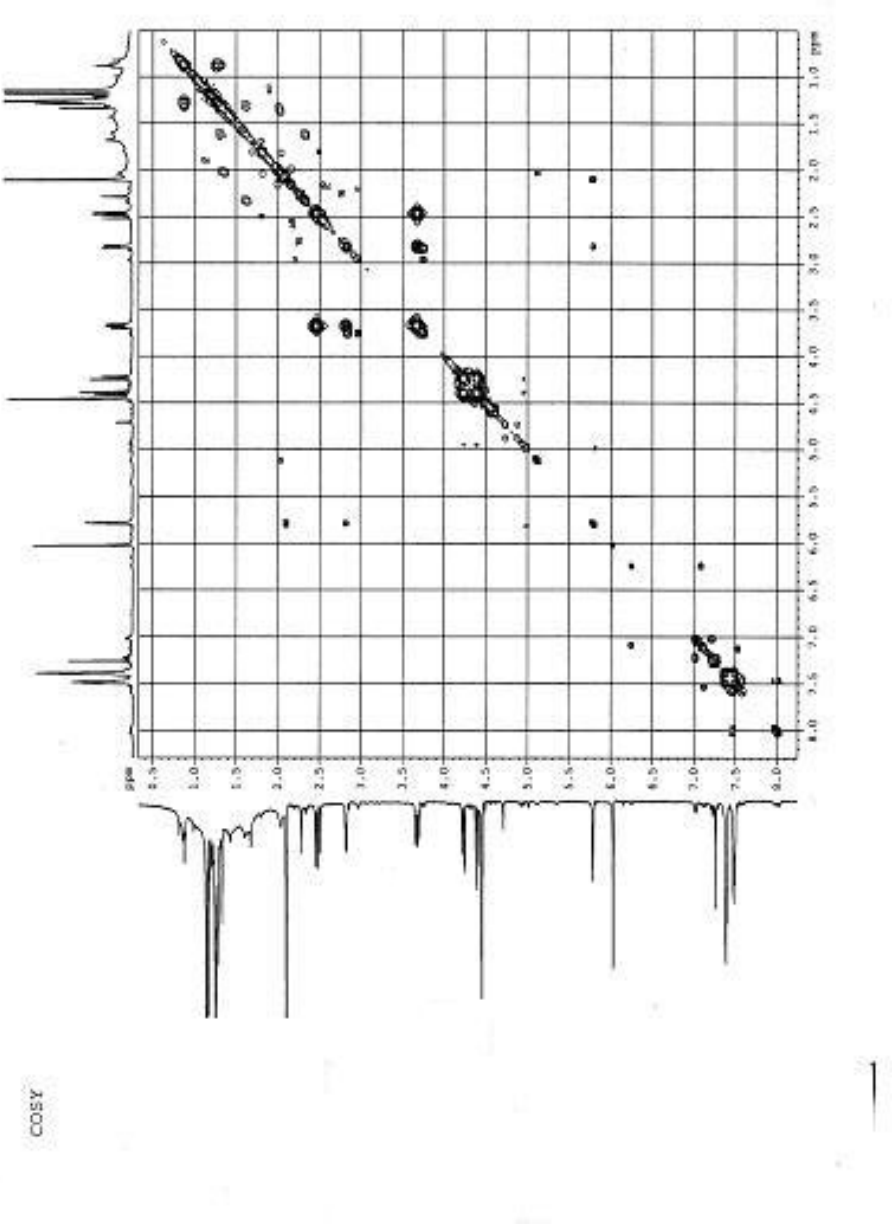


Fig. 9.48: COSY-NMR spectrum of **9a**

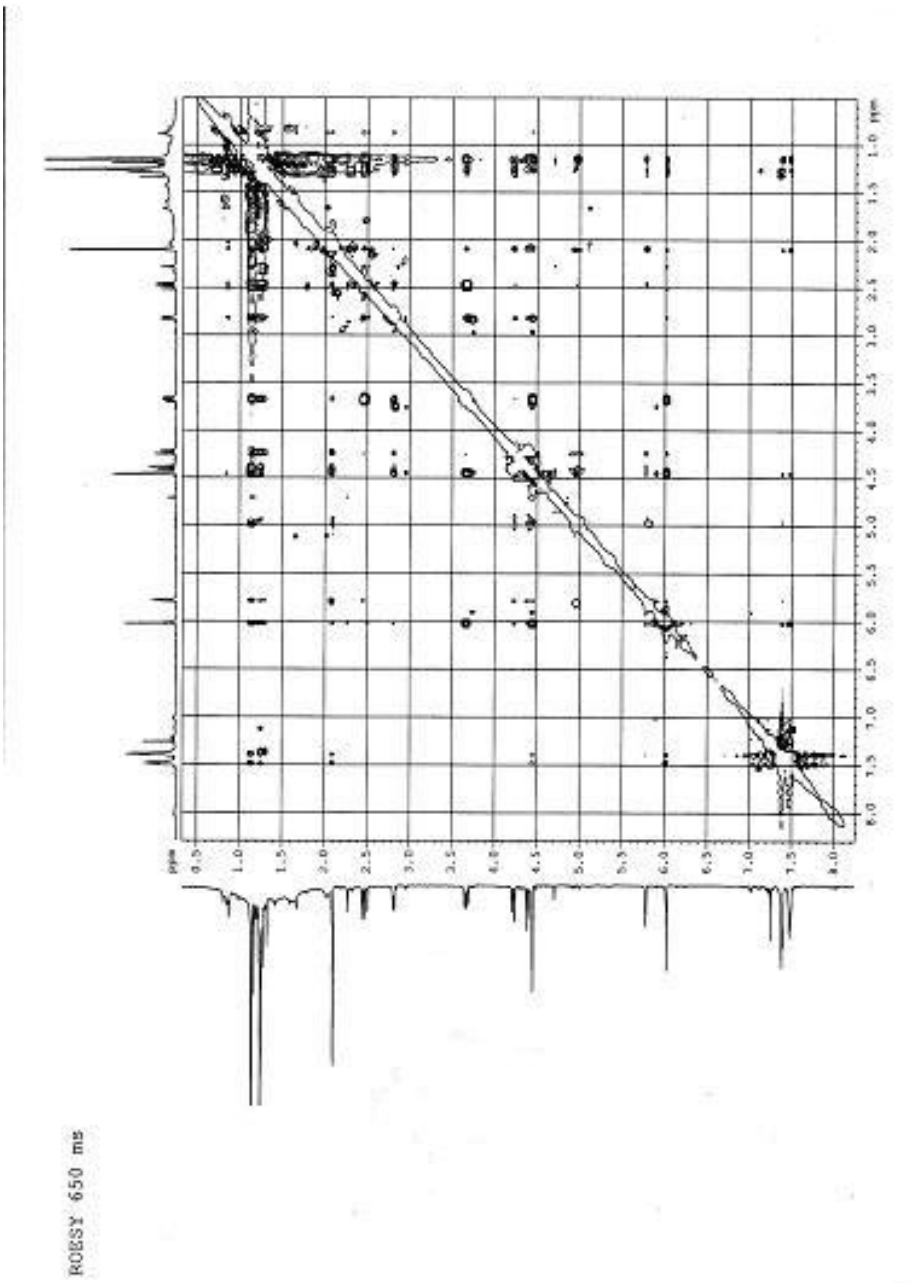


Fig. 9.49: ROESY-NMR spectrum of **9a**

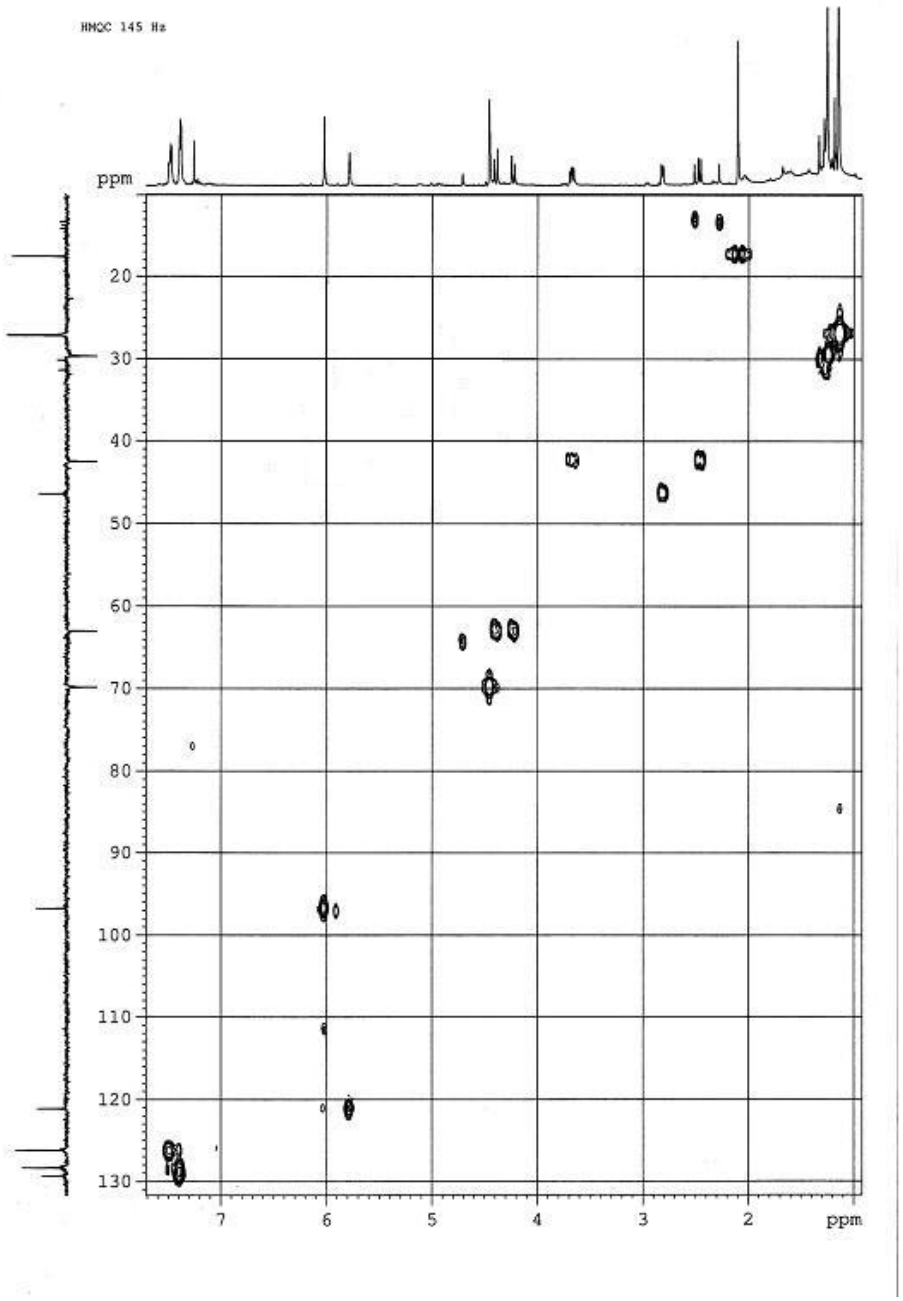


Fig. 9.50: HMQC-NMR spectrum of **9a**

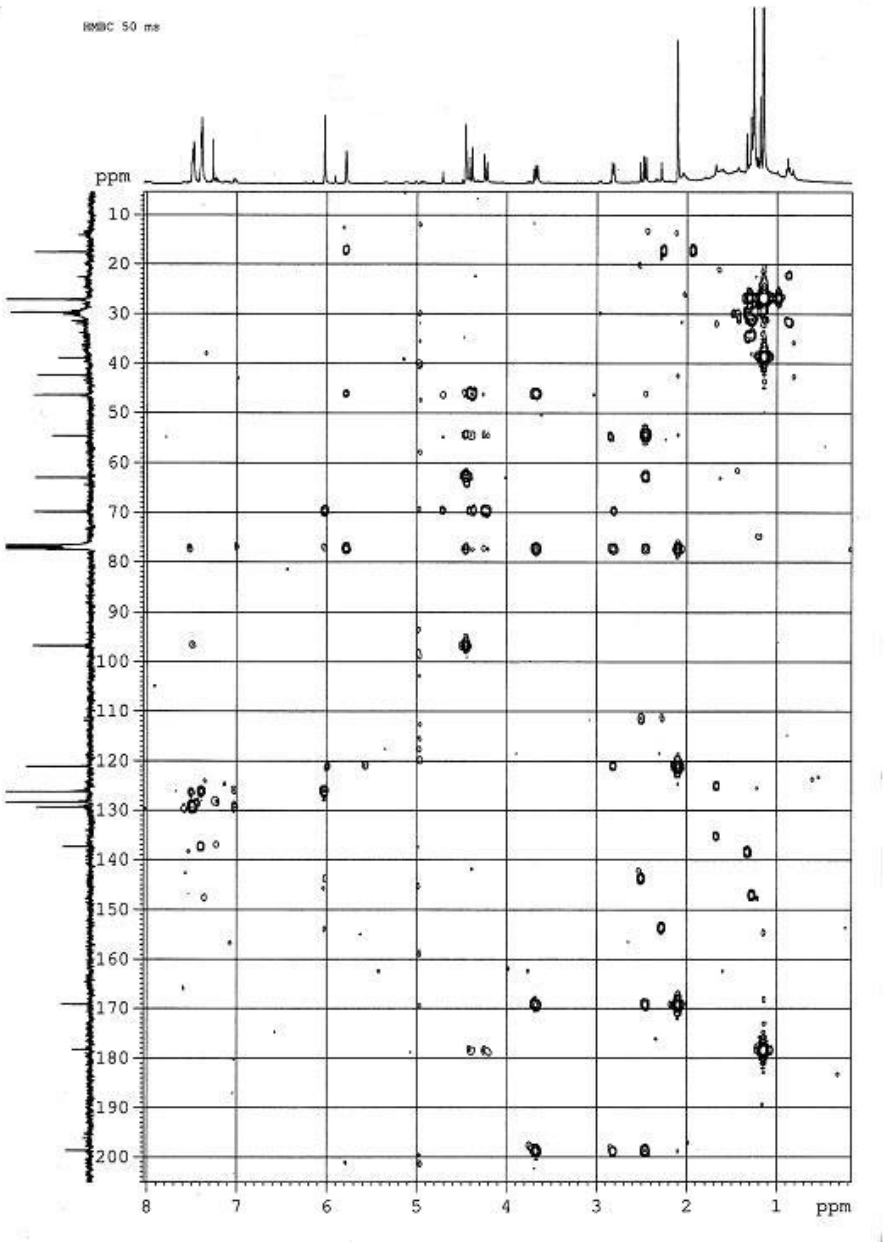


Fig. 9.51: HMBC-NMR spectrum of **9a**

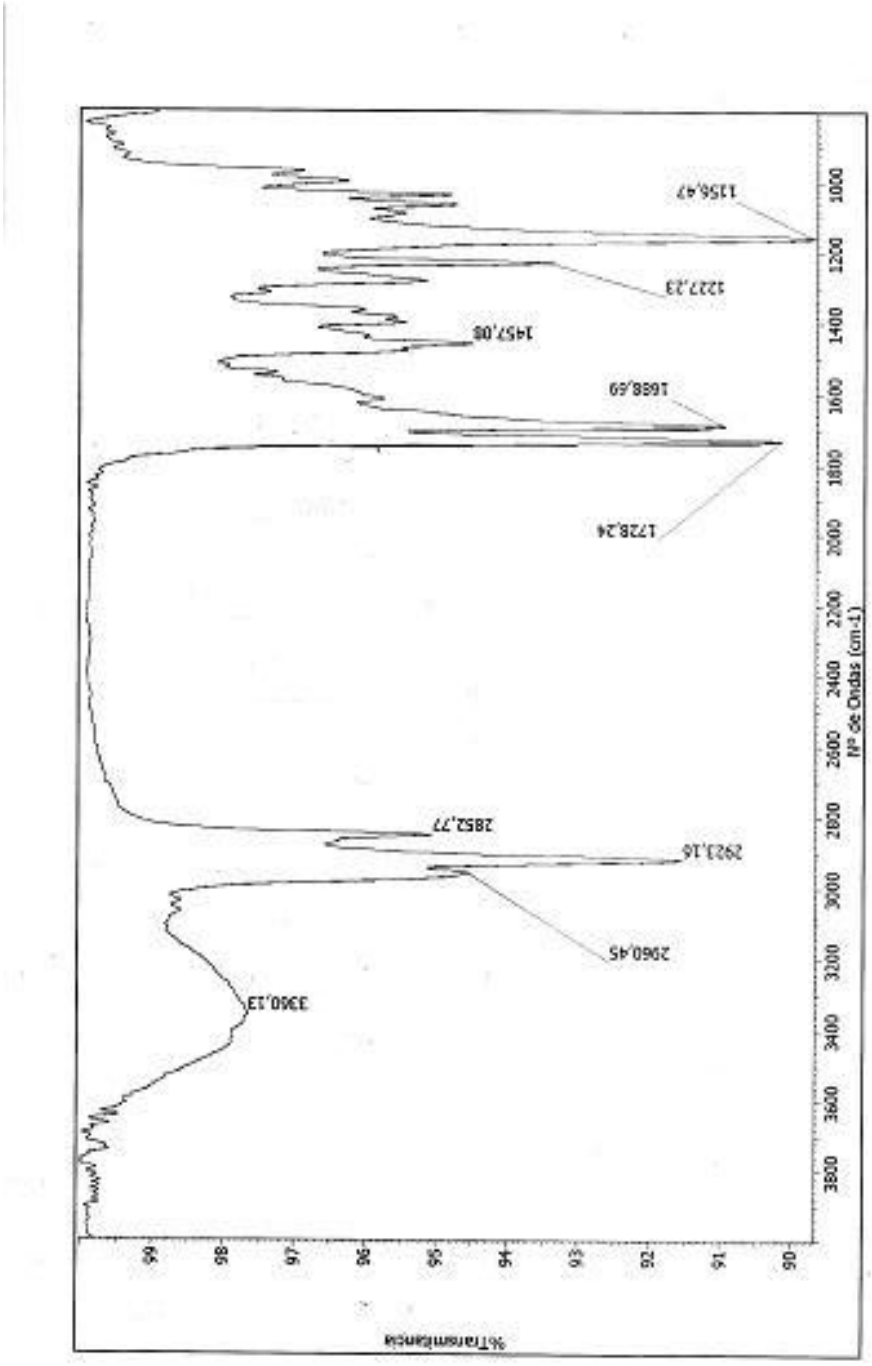


Fig. 9.52: IR spectrum of **9a**

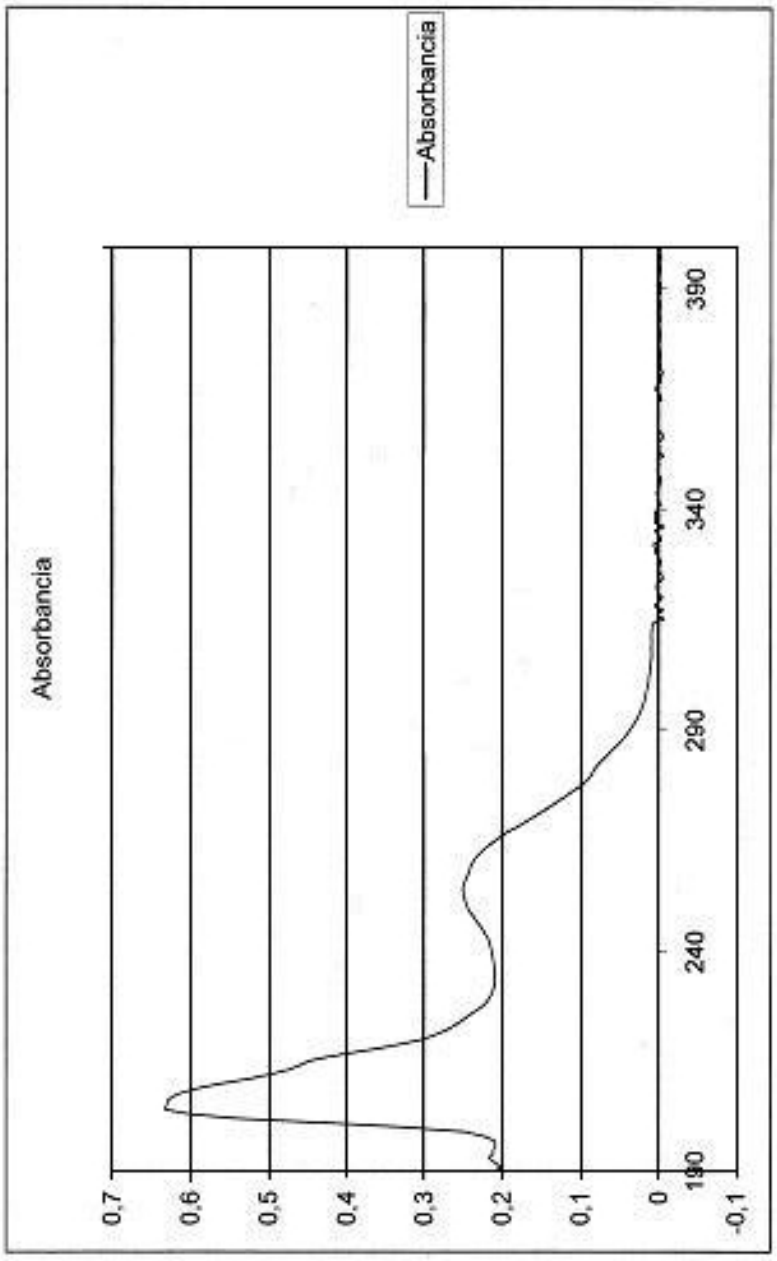
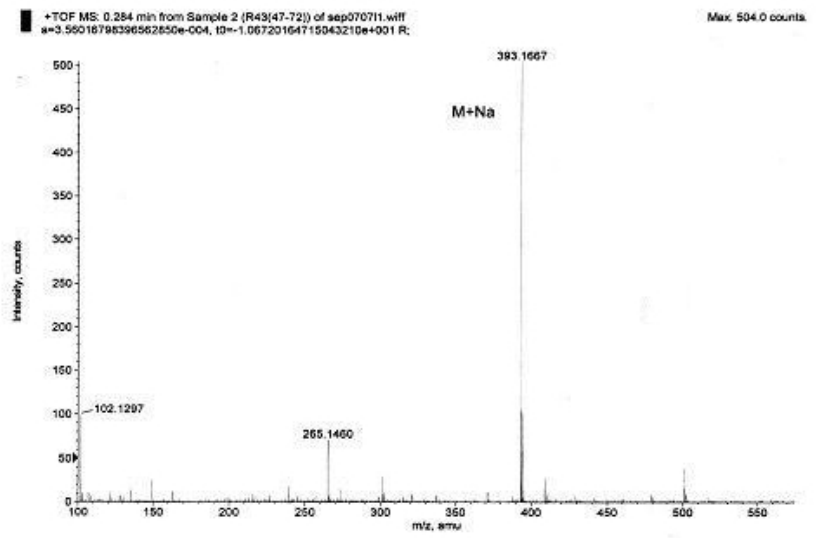


Fig. 9.53: UV spectrum of **9a**



Formula	CalculatedMass	mDaError	ppmError	RDB
C20 H21 N6 O3	393.166965	-0.265228	-0.674593	13.5
C22 H26 O5 Na	393.167245	-0.54536	-1.387094	9.5
C19 H25 N2 O7	393.165628	1.072084	2.726789	8.5
C23 H22 N4 O Na	393.168583	-1.882672	-4.788476	14.5
C8 H25 N8 O10	393.168816	-2.115884	-5.381638	0.5
C18 H22 N6 O3 Na	393.16456	2.140032	5.443058	10.5
C31 H21	393.163777	2.92274	7.433834	21.5
C24 H25 O5	393.169651	-2.95062	-7.504745	12.5
C17 H26 N2 O7 Na	393.163223	3.477344	8.84444	5.5
C11 H26 N6 O8 Na	393.170433	-3.733328	-9.495521	1.5
C15 H21 N8 O5	393.162943	3.757476	9.55694	9.5

Fig. 9.54: mass spectrum of **9a**

9.10 Spectra of compound **9b**

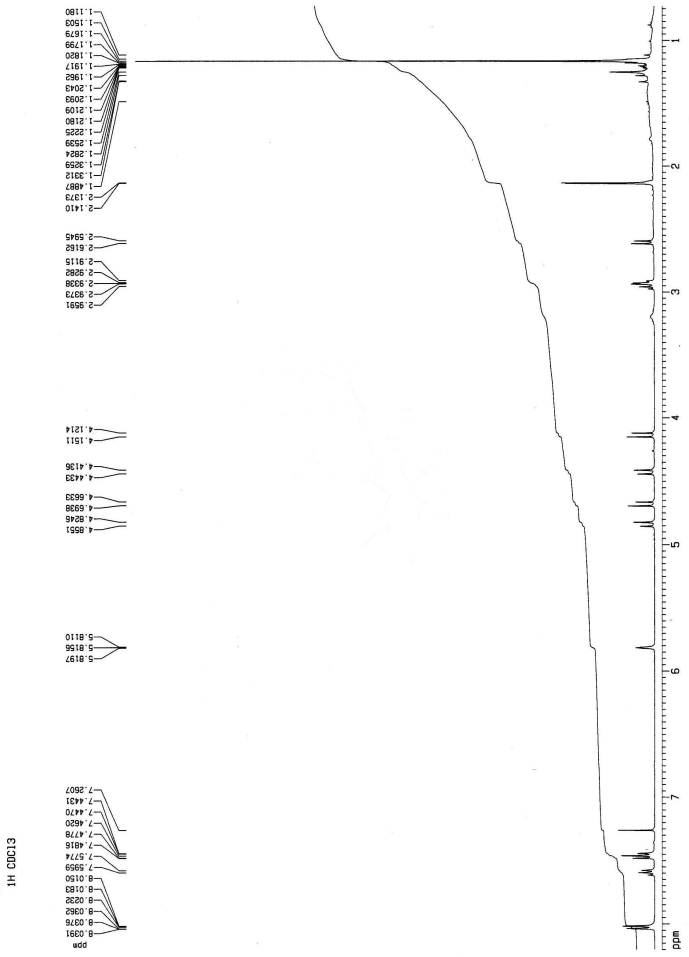


Fig. 9.55: ^{1}H-NMR spectrum of **9b**

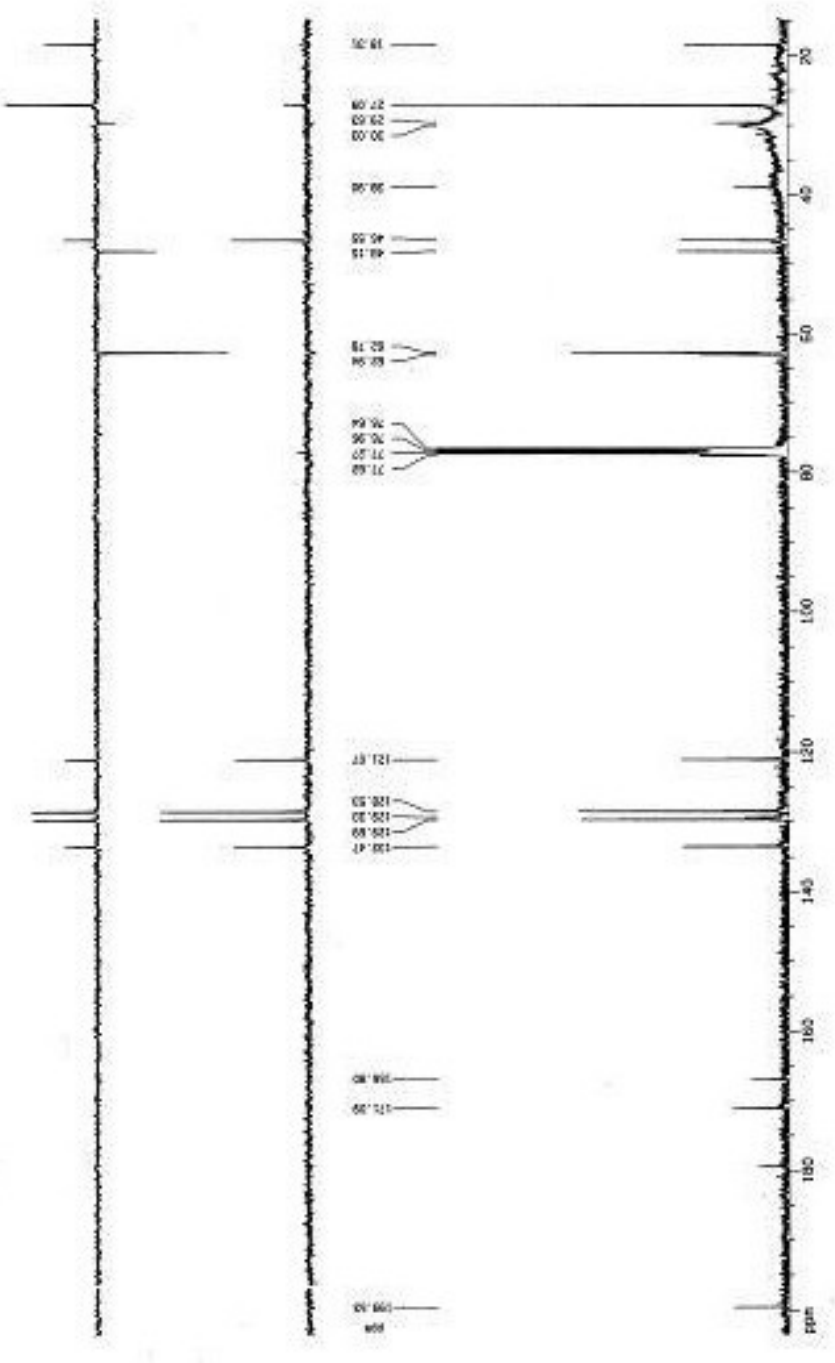


Fig. 9.56: ^{13}C-NMR spectrum of **9b**

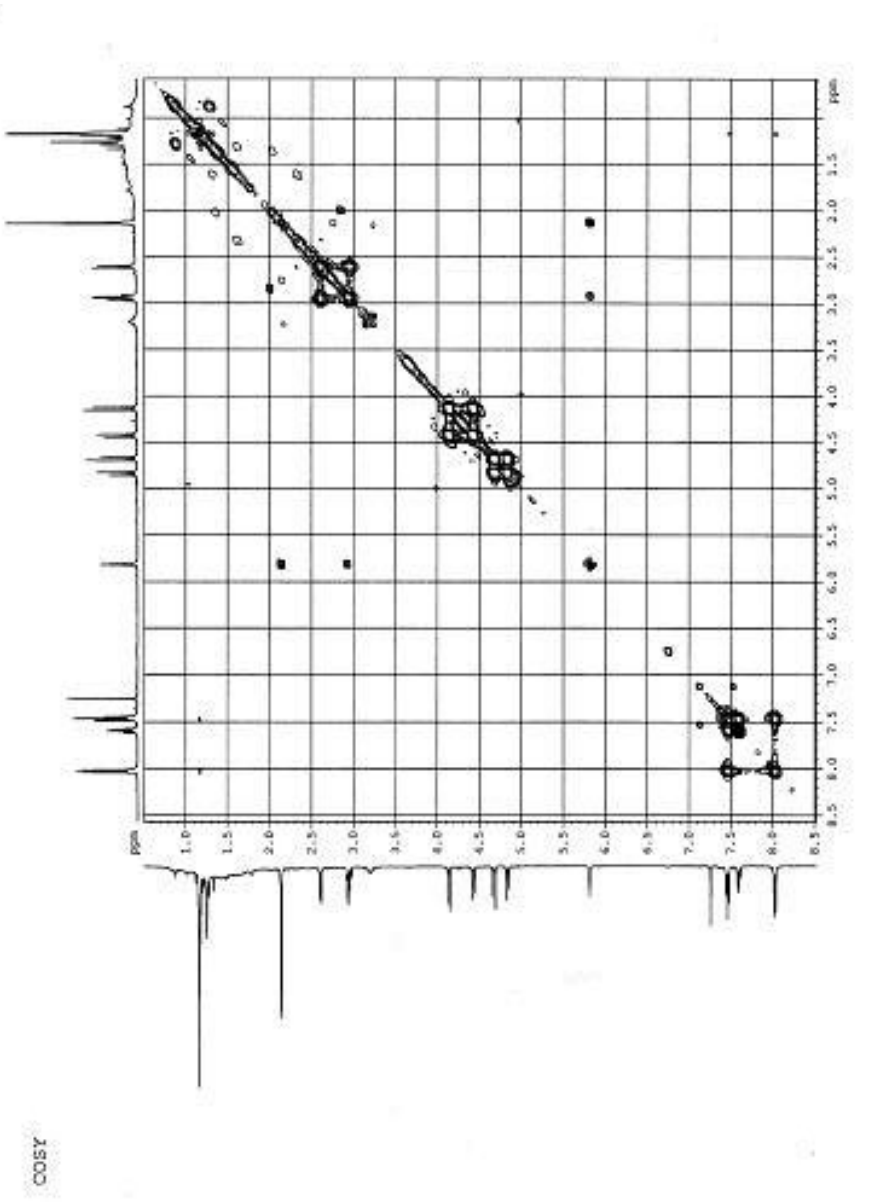


Fig. 9.57: COSY-NMR spectrum of **9b**

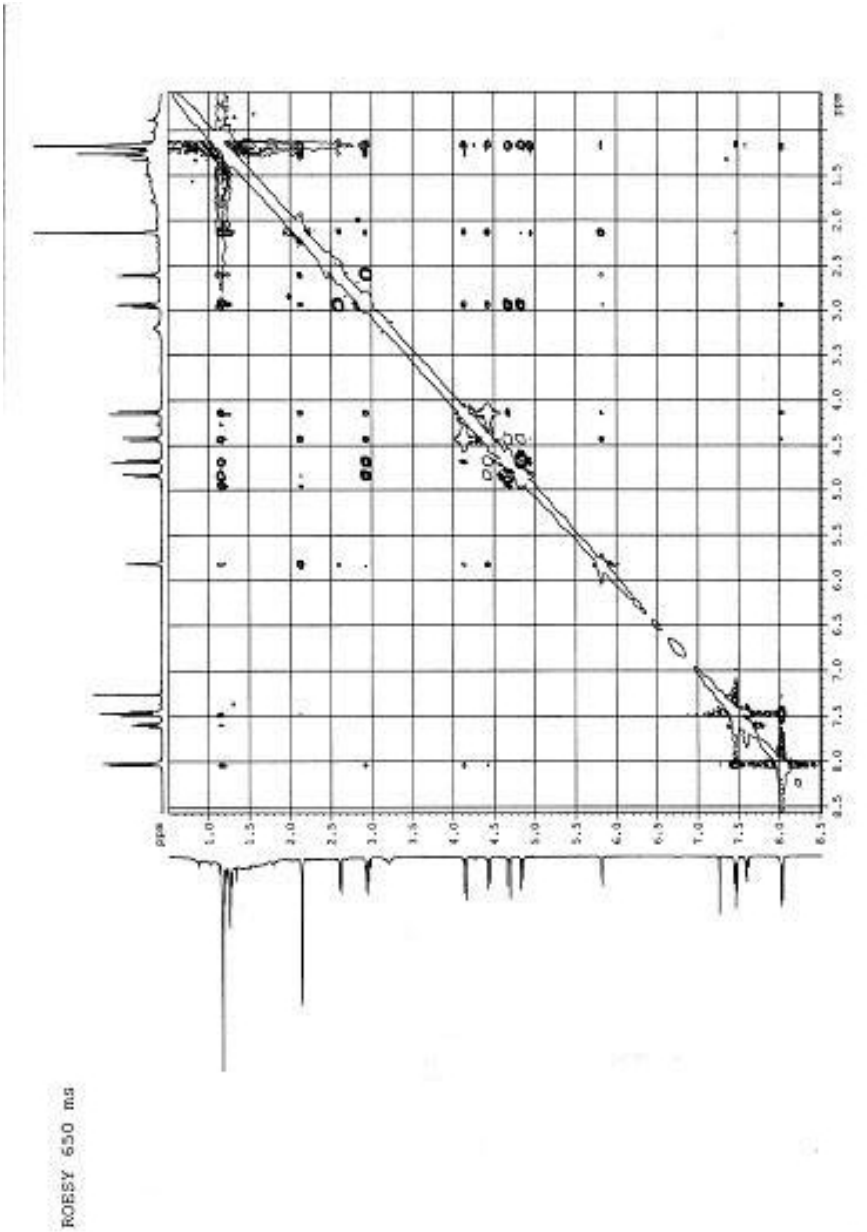


Fig. 9.58: ROESY-NMR spectrum of **9b**

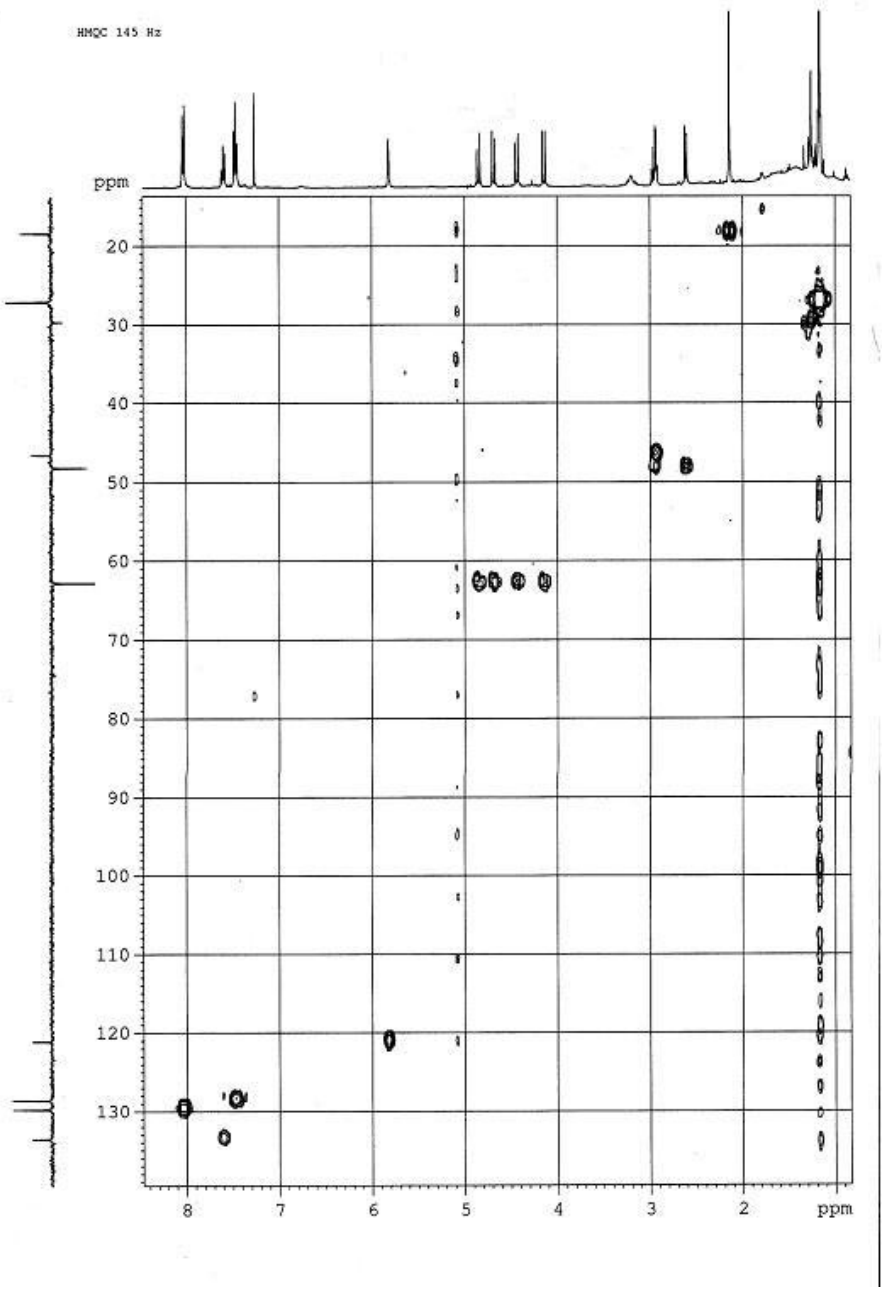


Fig. 9.59: HMQC-NMR spectrum of **9b**

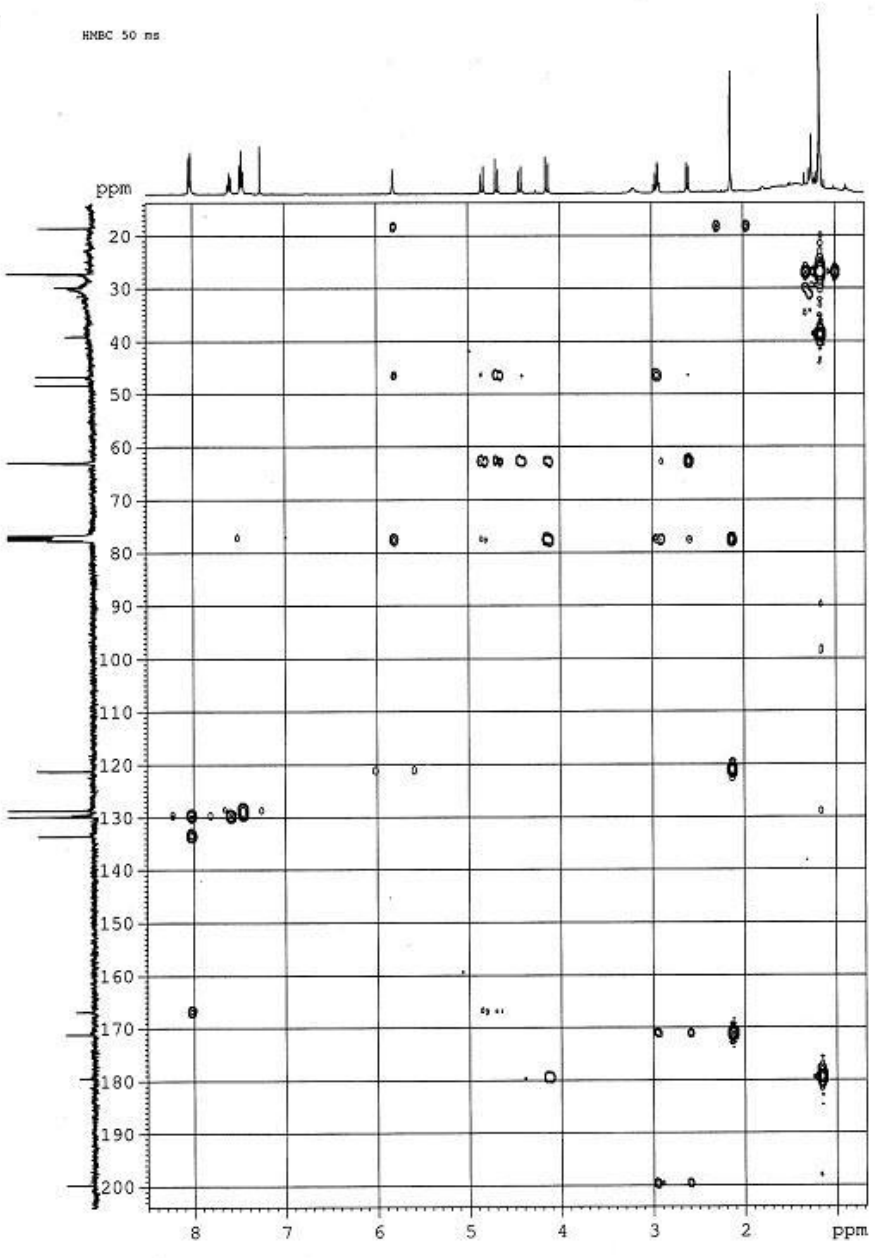
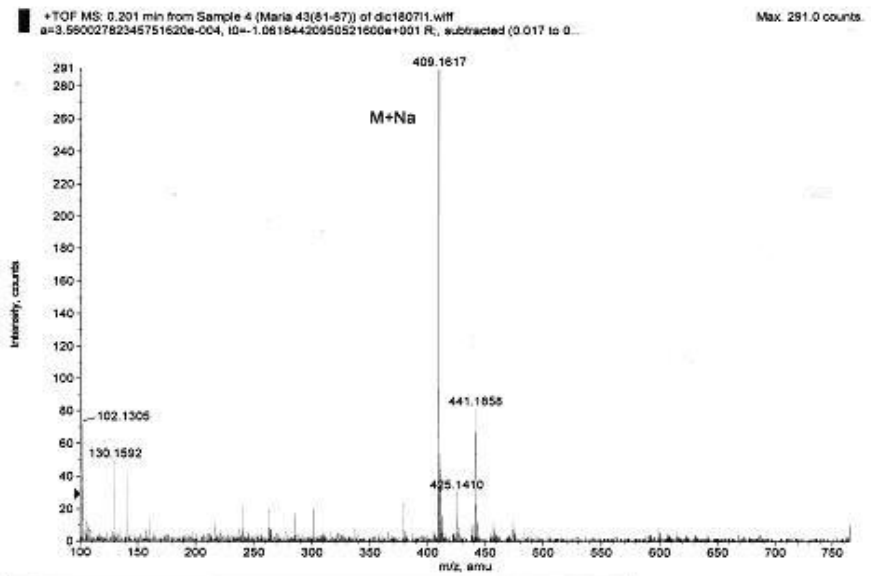


Fig. 9.60: HMBC-NMR spectrum of **9b**



Formula	CalculatedMass	mDaError	ppmError	RDB
C20 H21 N6 O4	409.16188	-0.179868	-0.439601	13.5
C22 H26 O6 Na	409.16216	-0.46	-1.124248	9.5
C19 H18 N10 Na	409.160812	0.88808	2.170484	15.5
C19 H25 N2 O8	409.160543	1.157444	2.828814	8.5
C21 H17 N10	409.163217	-1.51718	-3.708016	18.5
C23 H22 N4 O2 Na	409.163497	-1.797312	-4.392663	14.5
C8 H25 N8 O11	409.163731	-2.030524	-4.962638	0.5
C18 H22 N6 O4 Na	409.159475	2.225392	5.438899	10.5
C24 H25 O6	409.164565	-2.86526	-7.002748	12.5
C31 H21 O	409.158692	3.0081	7.351851	21.5
C17 H26 N2 O8 Na	409.158137	3.562704	8.707314	5.5
C11 H26 N6 O9 Na	409.165348	-3.647968	-8.9157	1.5
C15 H21 N8 O6	409.157857	3.842836	9.391961	9.5

Fig. 9.61: mass spectrum of **9b**

9.11 Spectra of compound **10**

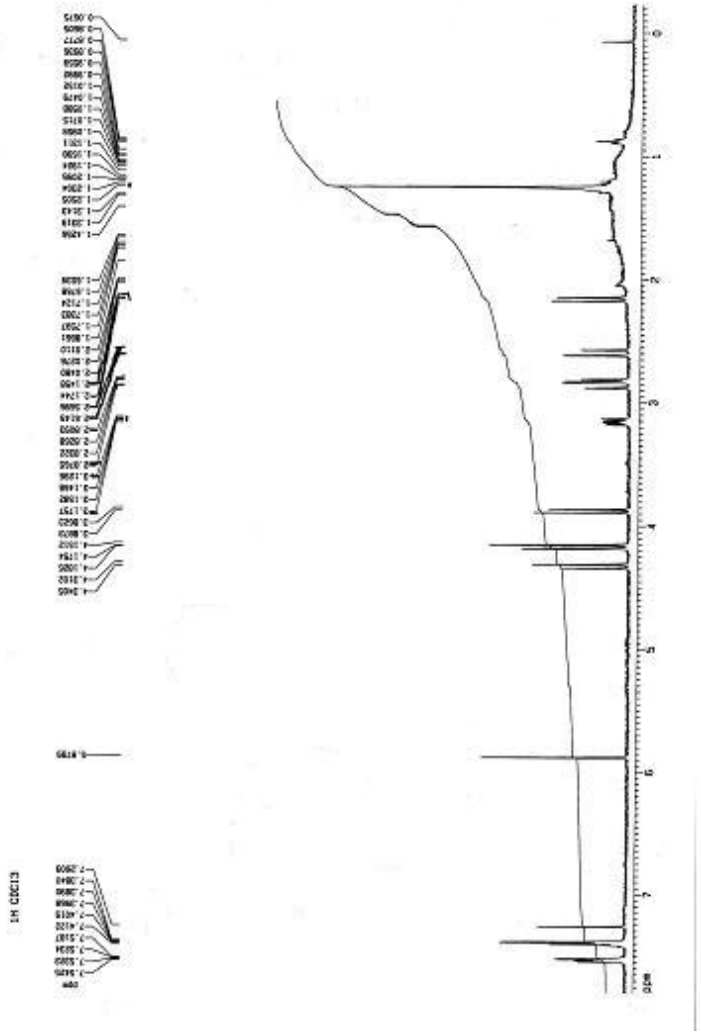


Fig. 9.62: ^{1}H-NMR spectrum of **10**

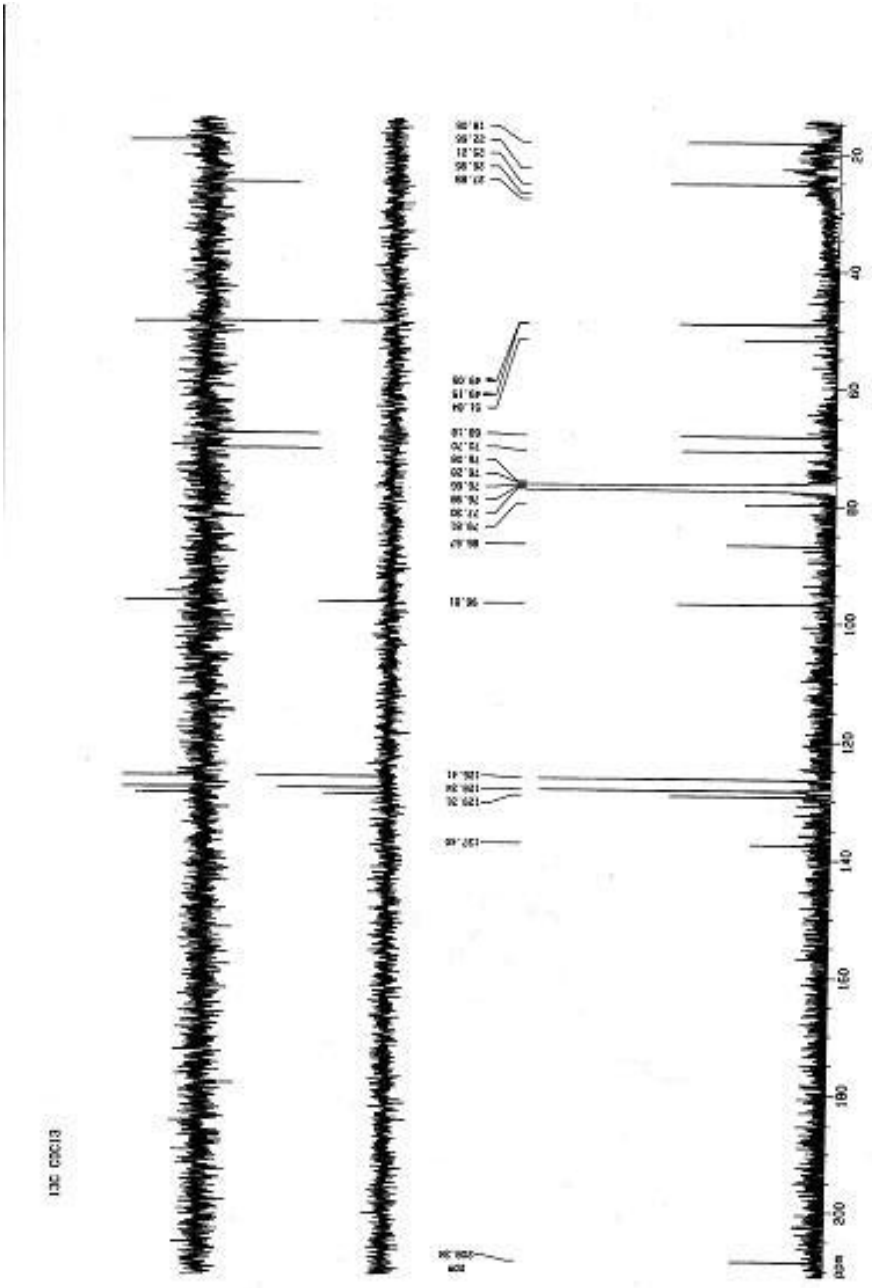


Fig. 9.63: ^{13}C-NMR spectrum of **10**

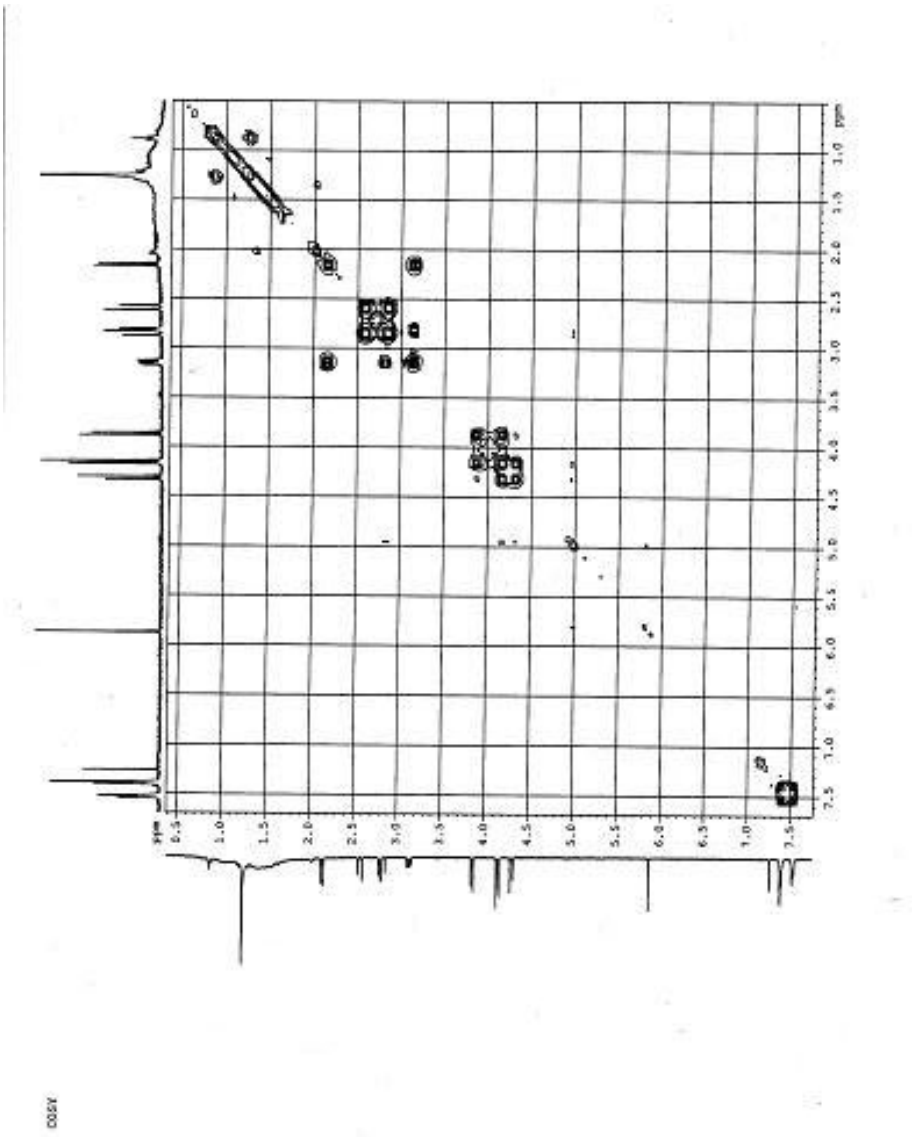


Fig. 9.64: COSY-NMR spectrum of **10**

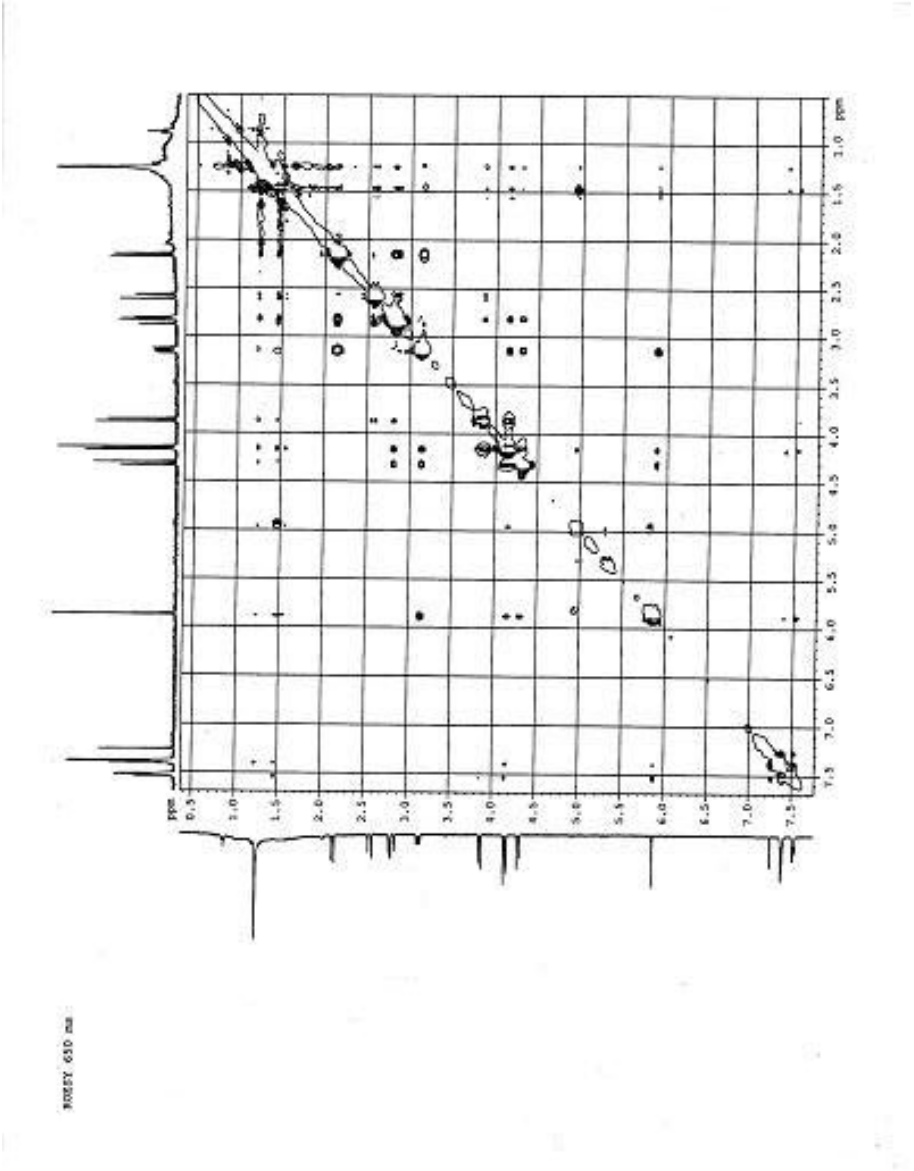


Fig. 9.65: ROESY-NMR spectrum of **10**

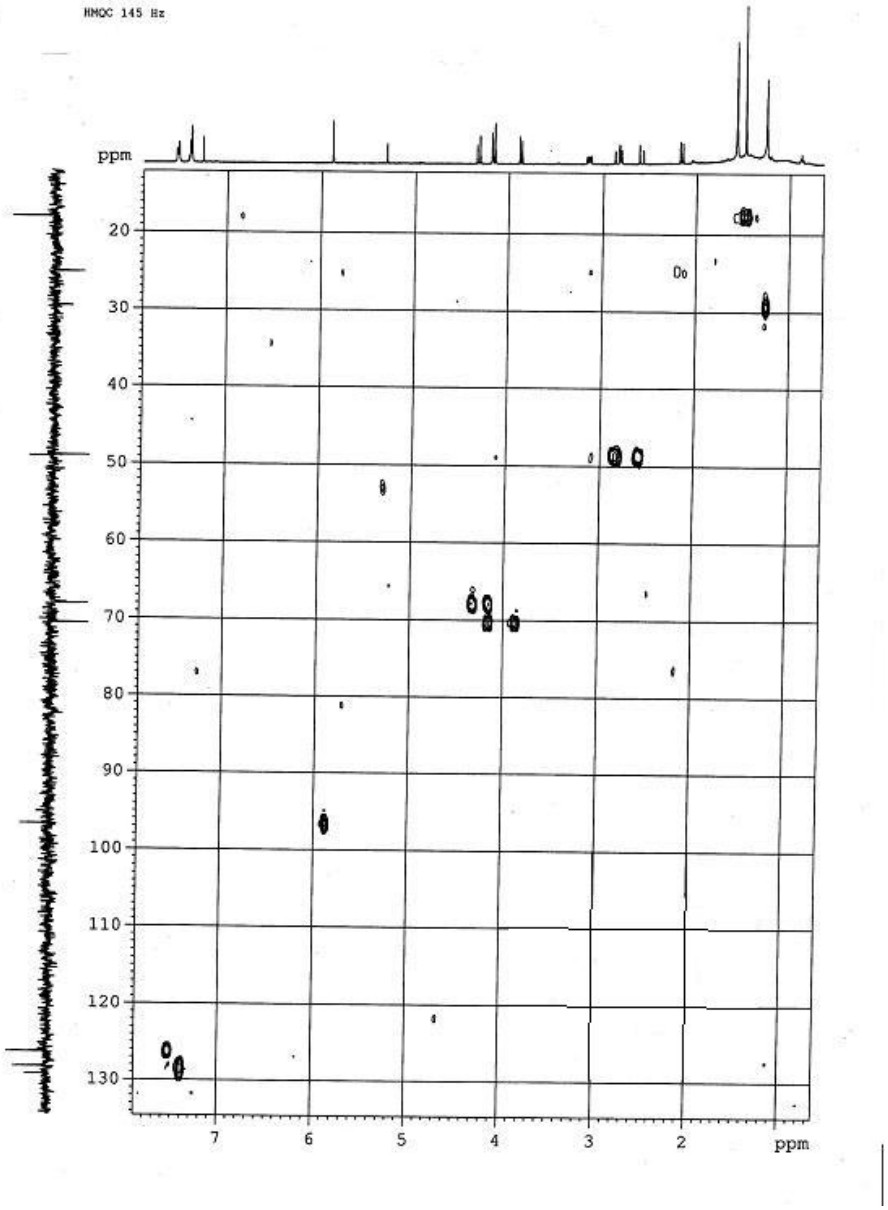


Fig. 9.66: HMQC-NMR spectrum of **10**

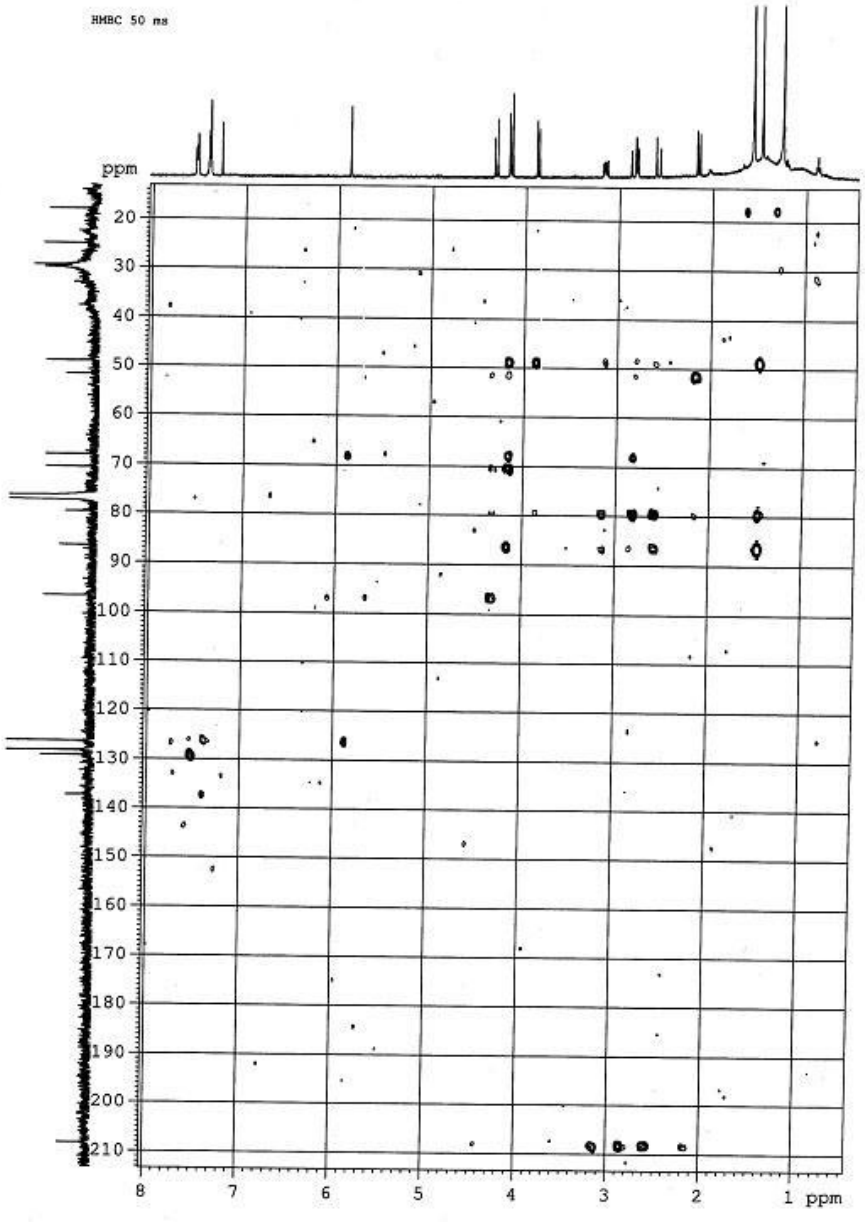


Fig. 9.67: HMBC-NMR spectrum of **10**

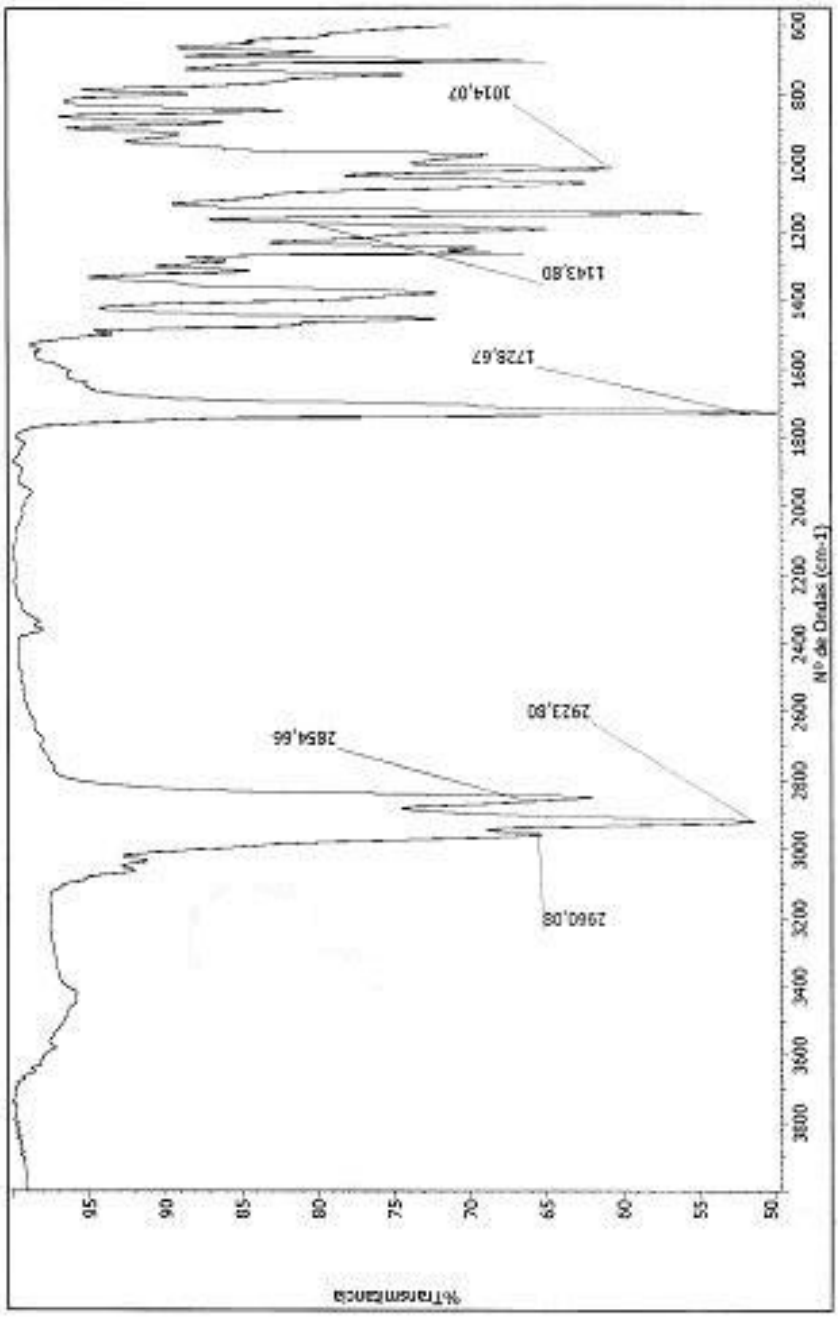
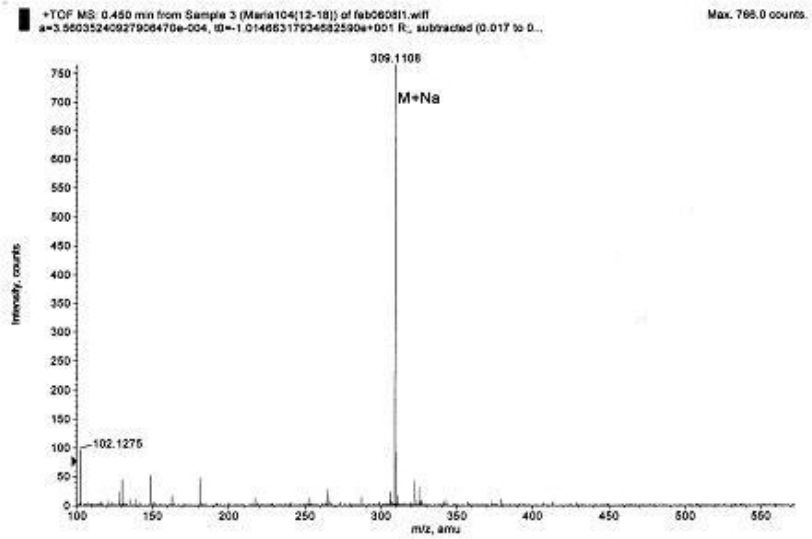


Fig. 9.68: IR spectrum of **10**



Formula	CalculatedMass	mDaError	ppmError	RDB
C18 H14 N4 Na	309.111068	-0.267712	-0.86607	13.5
C3 H17 N8 O9	309.111301	-0.500924	-1.620529	-0.5
C17 H18 O4 Na	309.10973	1.0696	3.460242	8.5
C19 H17 O4	309.112136	-1.33566	-4.320967	11.5
C15 H13 N6 O2	309.10945	1.349732	4.366491	12.5
C6 H18 N6 O7 Na	309.112918	-2.118368	-6.85309	0.5
C20 H13 N4	309.113473	-2.672972	-8.647279	16.5
C14 H17 N2 O6	309.108113	2.687044	8.692803	7.5

Fig. 9.69: mass spectrum of **10**

9.12 Spectra of compound **11**

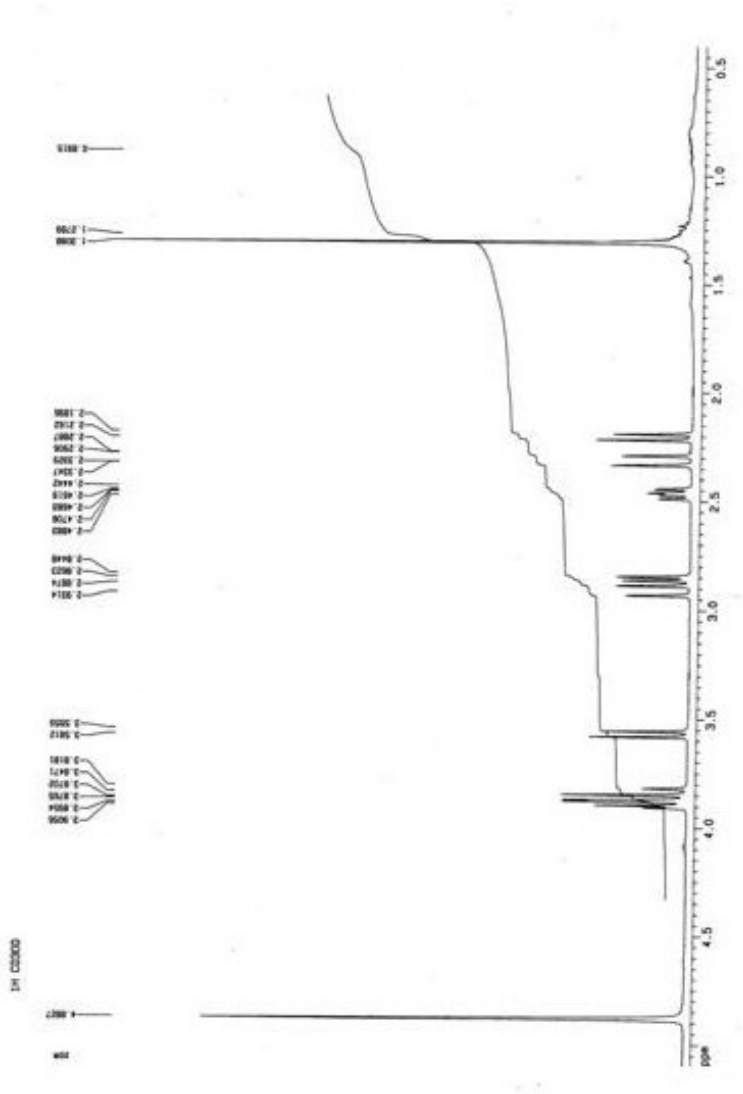


Fig. 9.70: ^{1}H-NMR spectrum of **11**

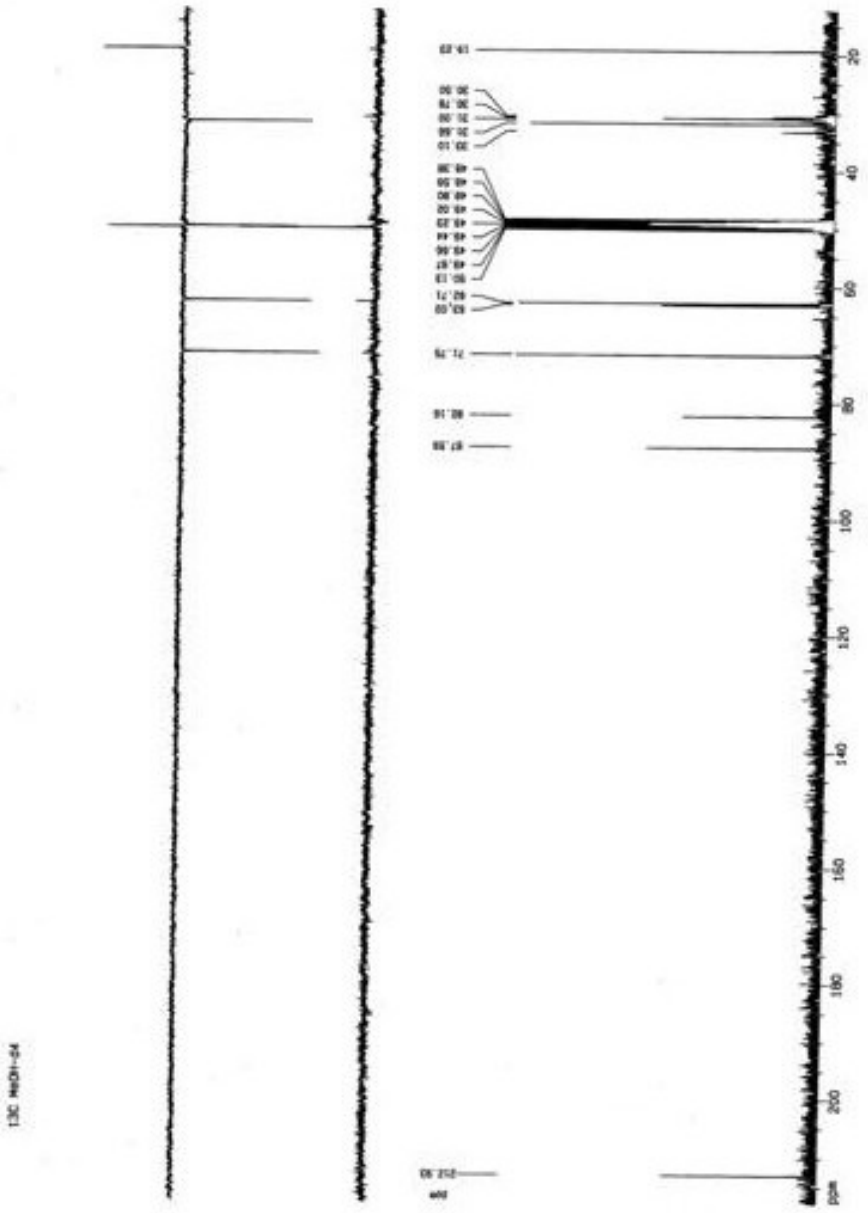


Fig. 9.71: ^{13}C-NMR spectrum of **11**

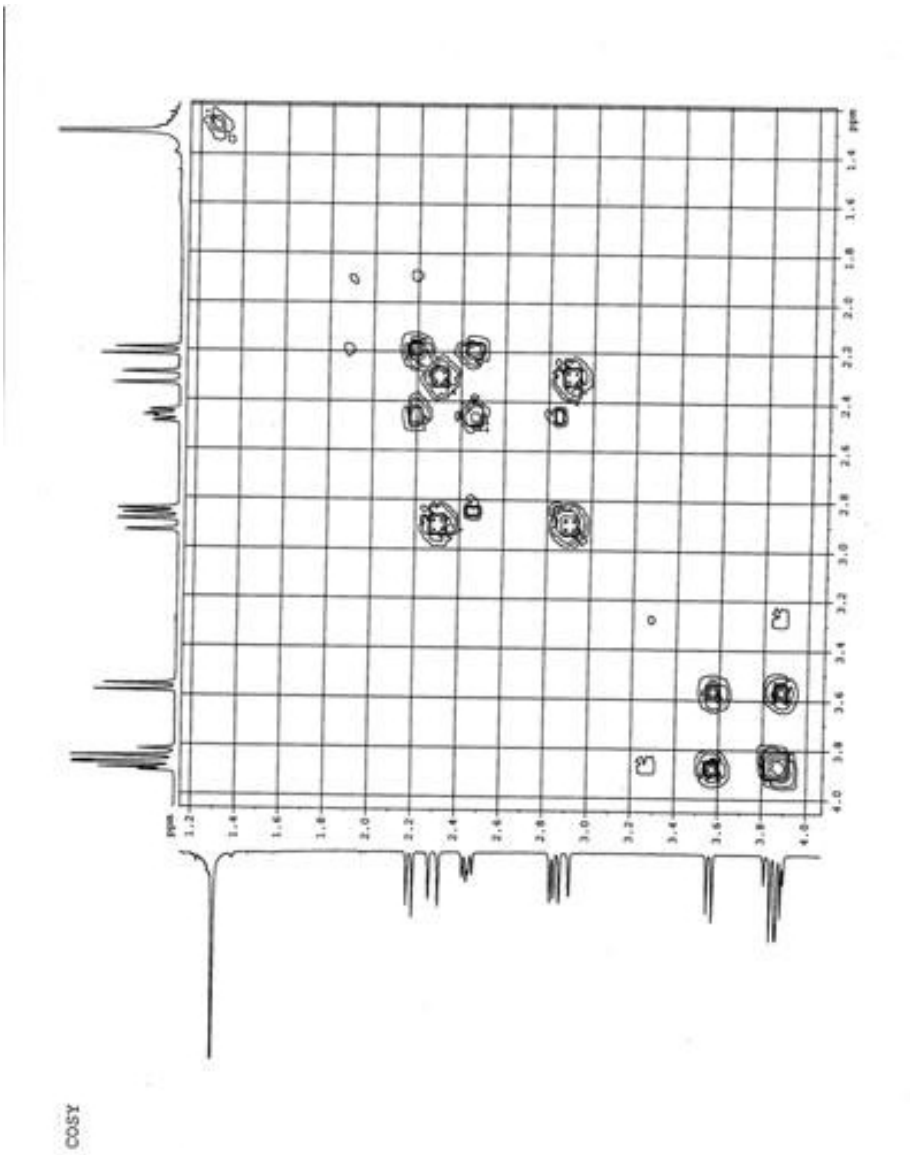


Fig. 9.72: COSY-NMR spectrum of **11**

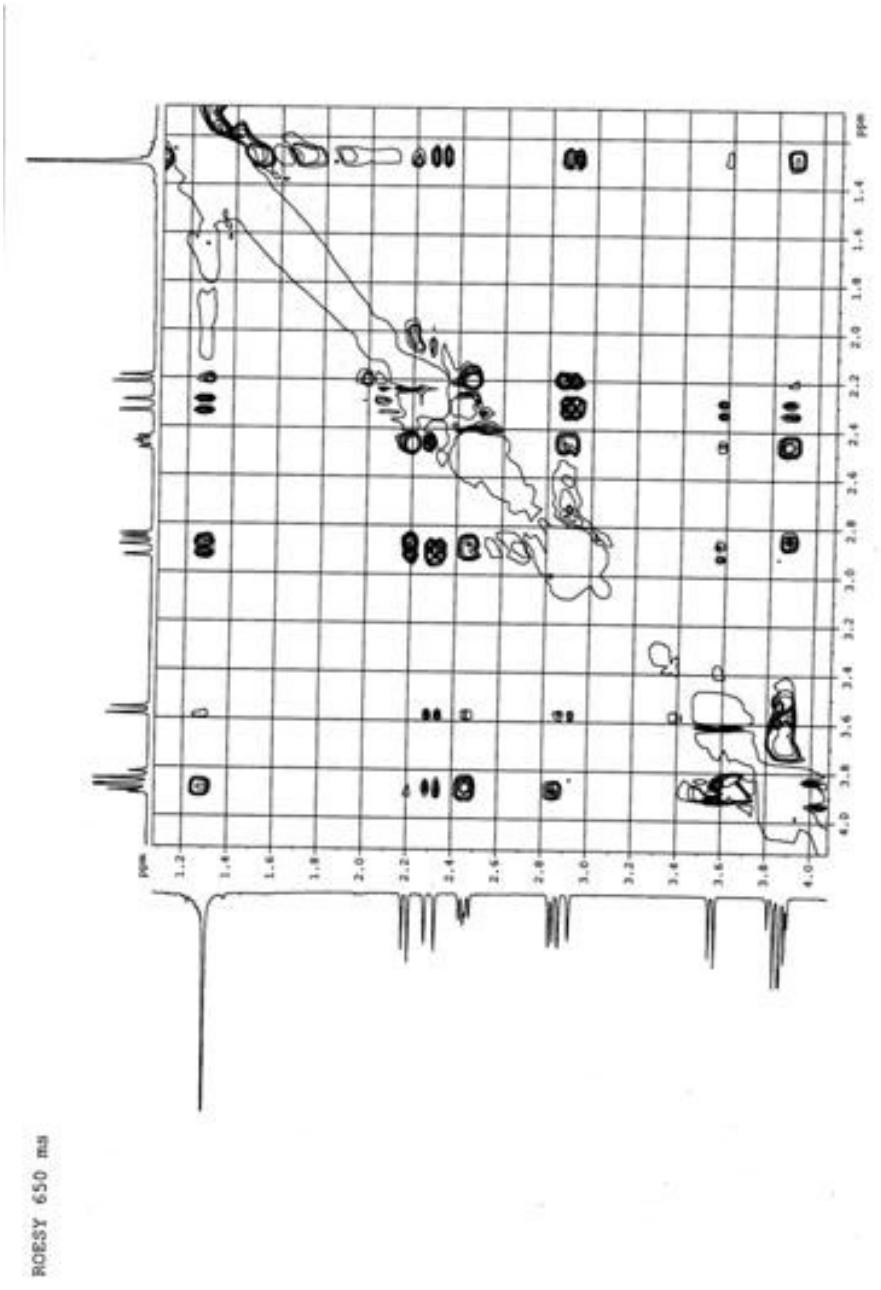


Fig. 9.73: ROESY-NMR spectrum of **11**

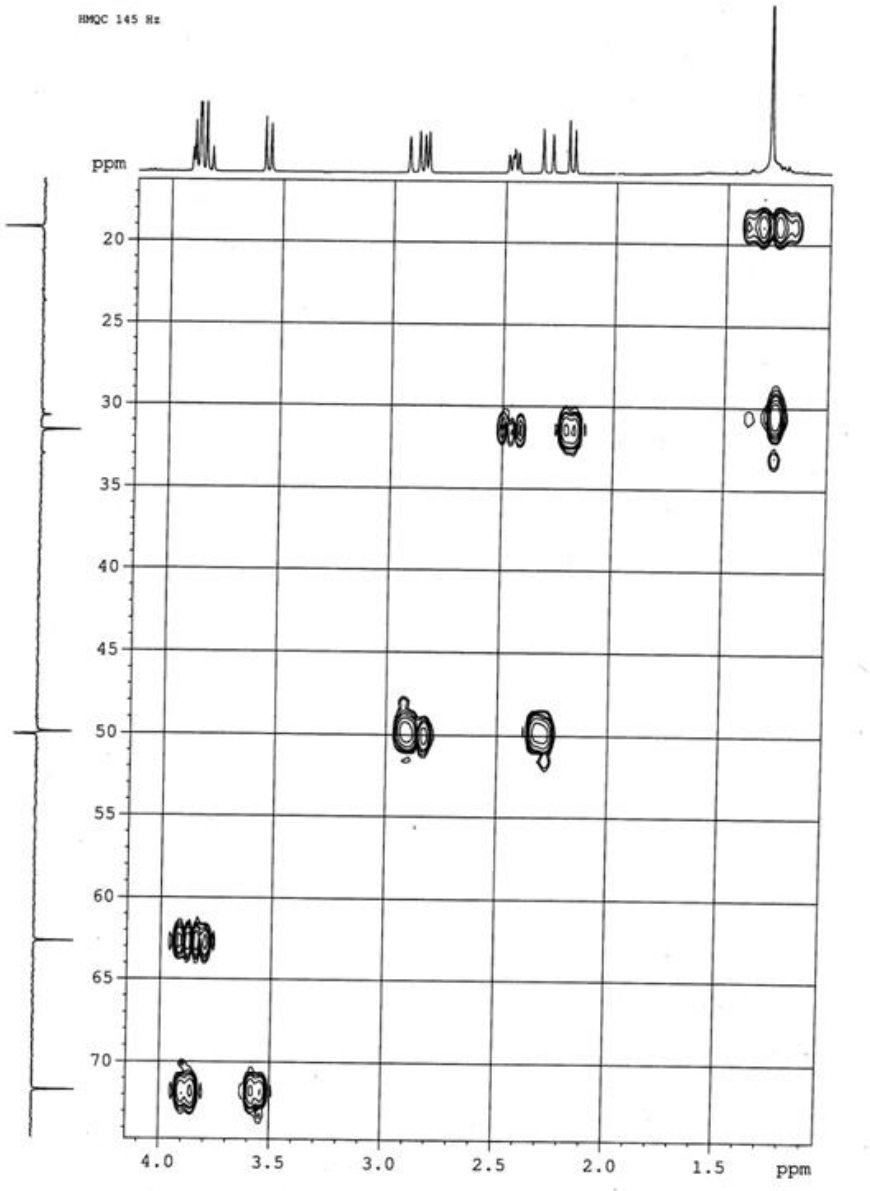


Fig. 9.74: HMQC-NMR spectrum of **11**

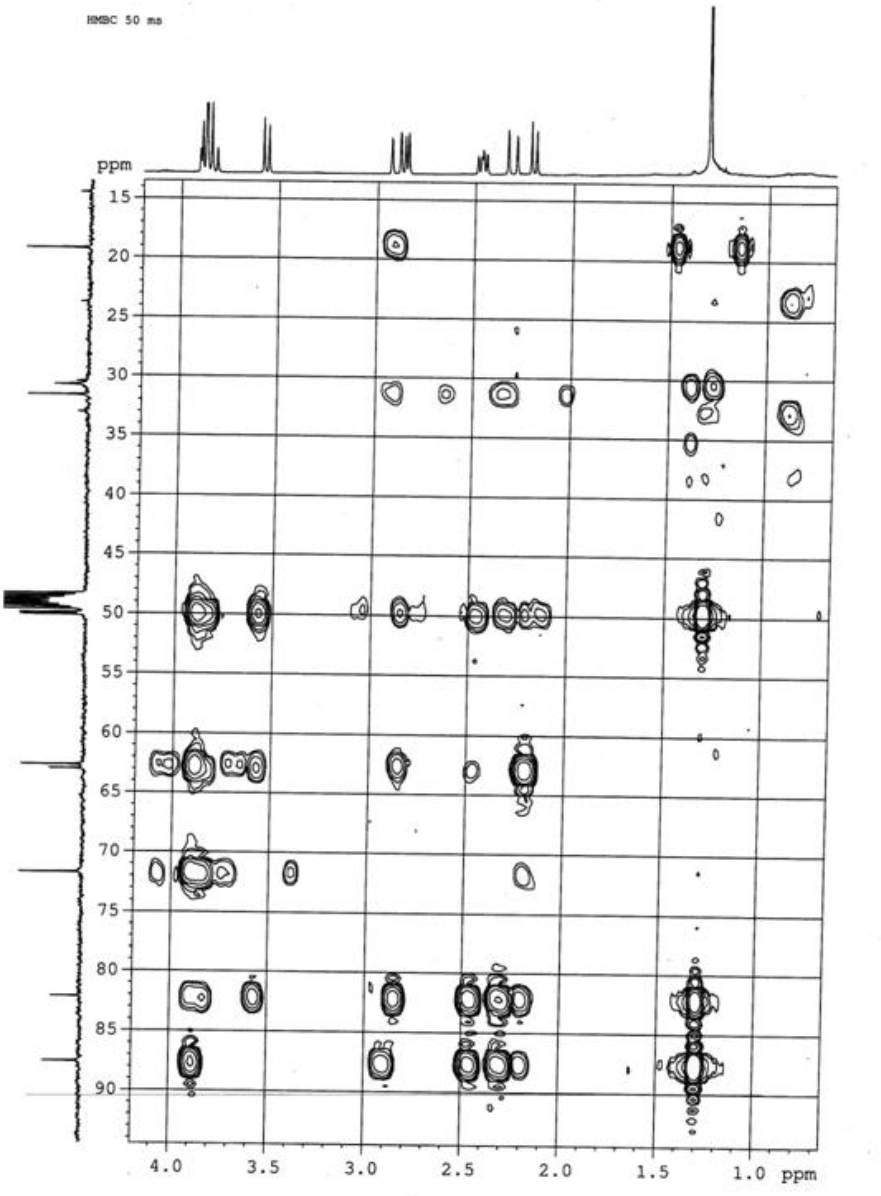


Fig. 9.75: HMBC-NMR spectrum of **11**

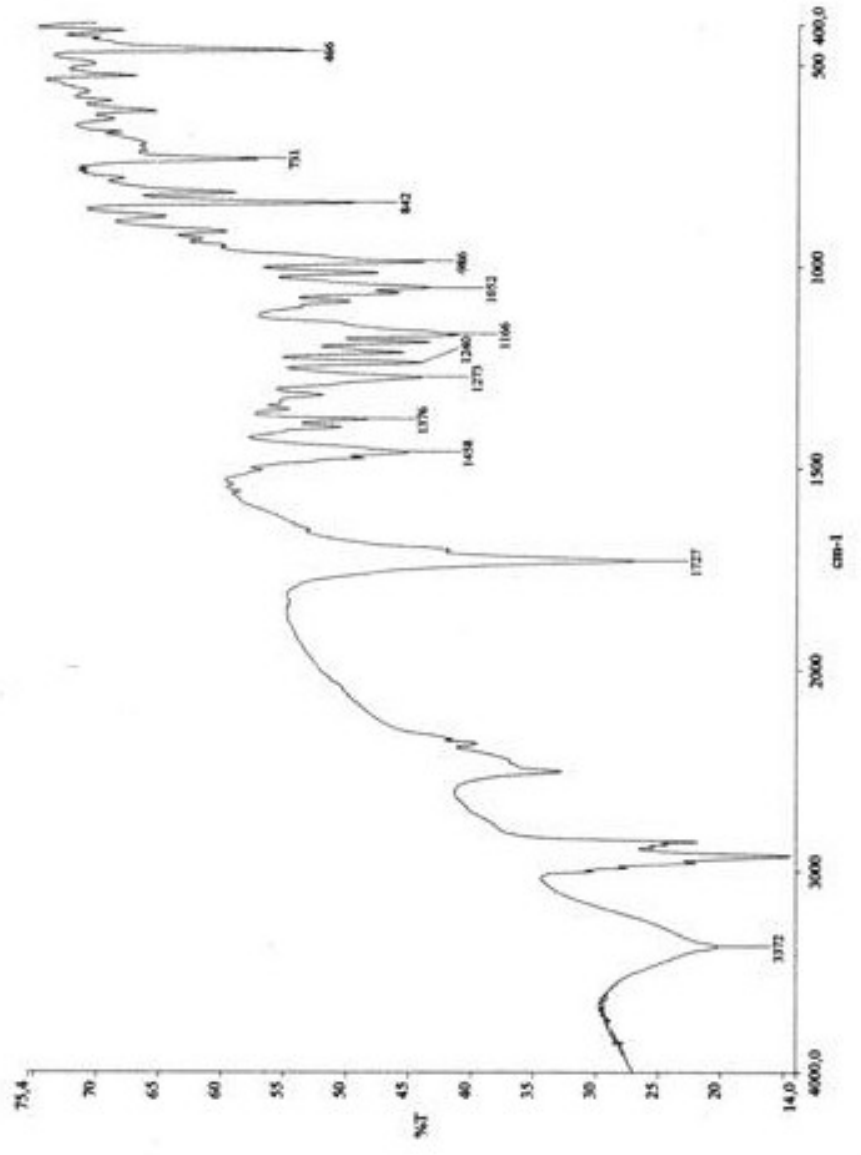
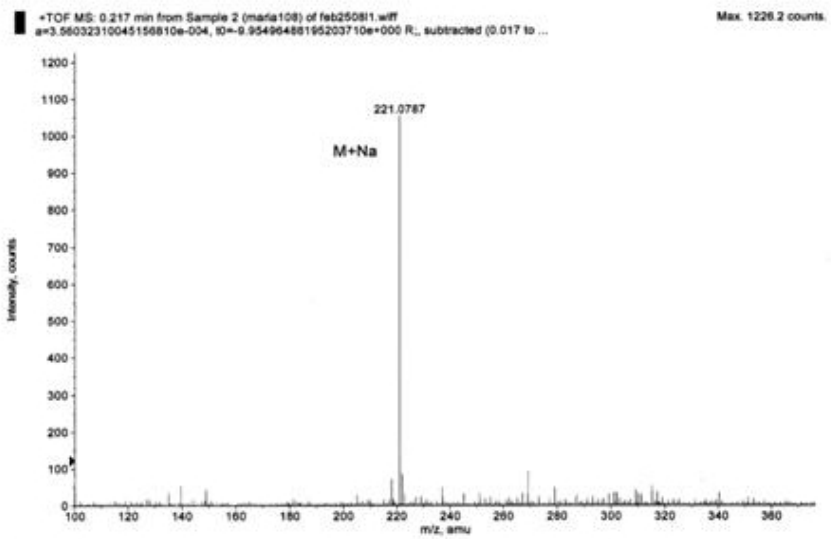


Fig. 9.76: IR spectrum of **11**



Formula	CalculatedMass	mDaError	ppmError	RDB
C10 H14 O4 Na	221.07843	0.26976	1.220196	3.5
C8 H9 N6 O2	221.07815	0.549892	2.487307	7.5
C11 H10 N4 Na	221.079768	-1.067552	-4.82882	8.5
C7 H13 N2 O6	221.076813	1.887204	8.536324	2.5
C12 H13 O4	221.080836	-2.1355	-9.659432	6.5

Fig. 9.77: mass spectrum of **11**

9.13 Spectra of compound **12**

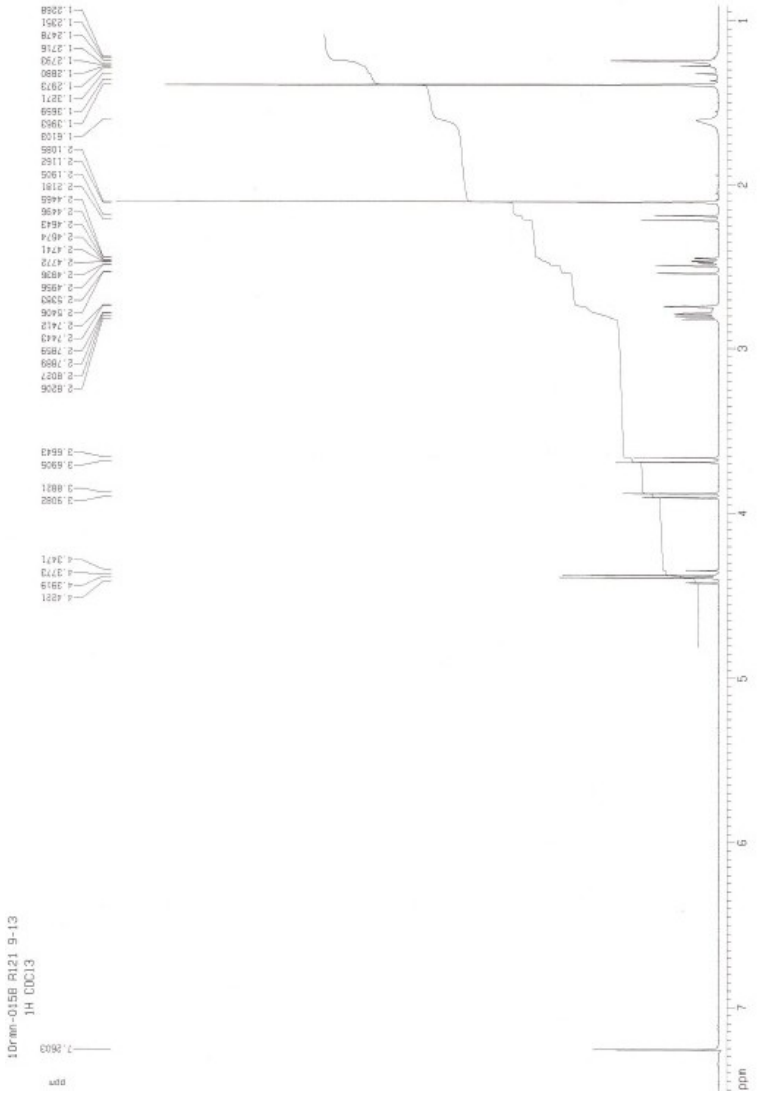


Fig. 9.78: ^{1}H-NMR spectrum of **12**

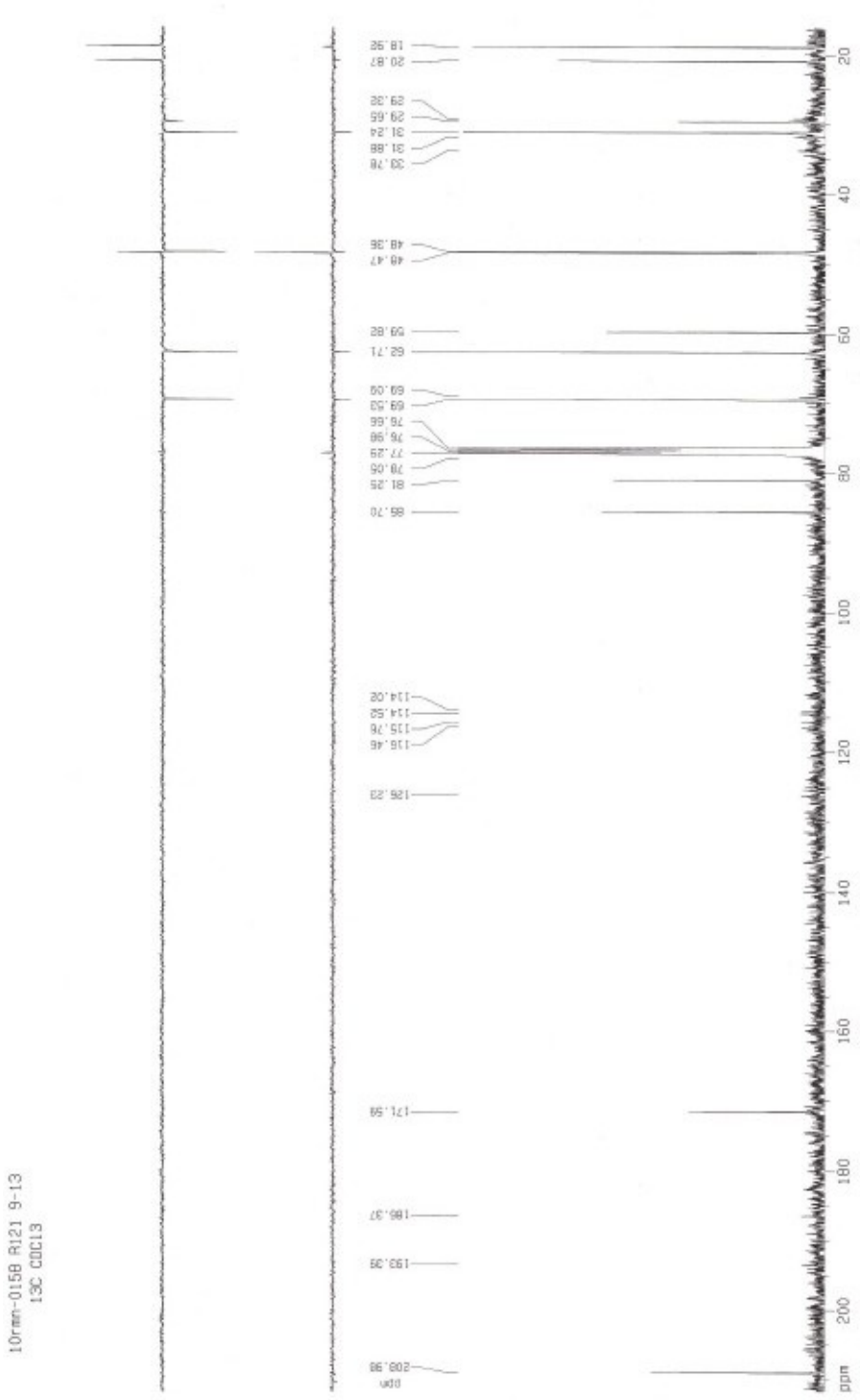


Fig. 9.79: ^{13}C-NMR spectrum of **12**

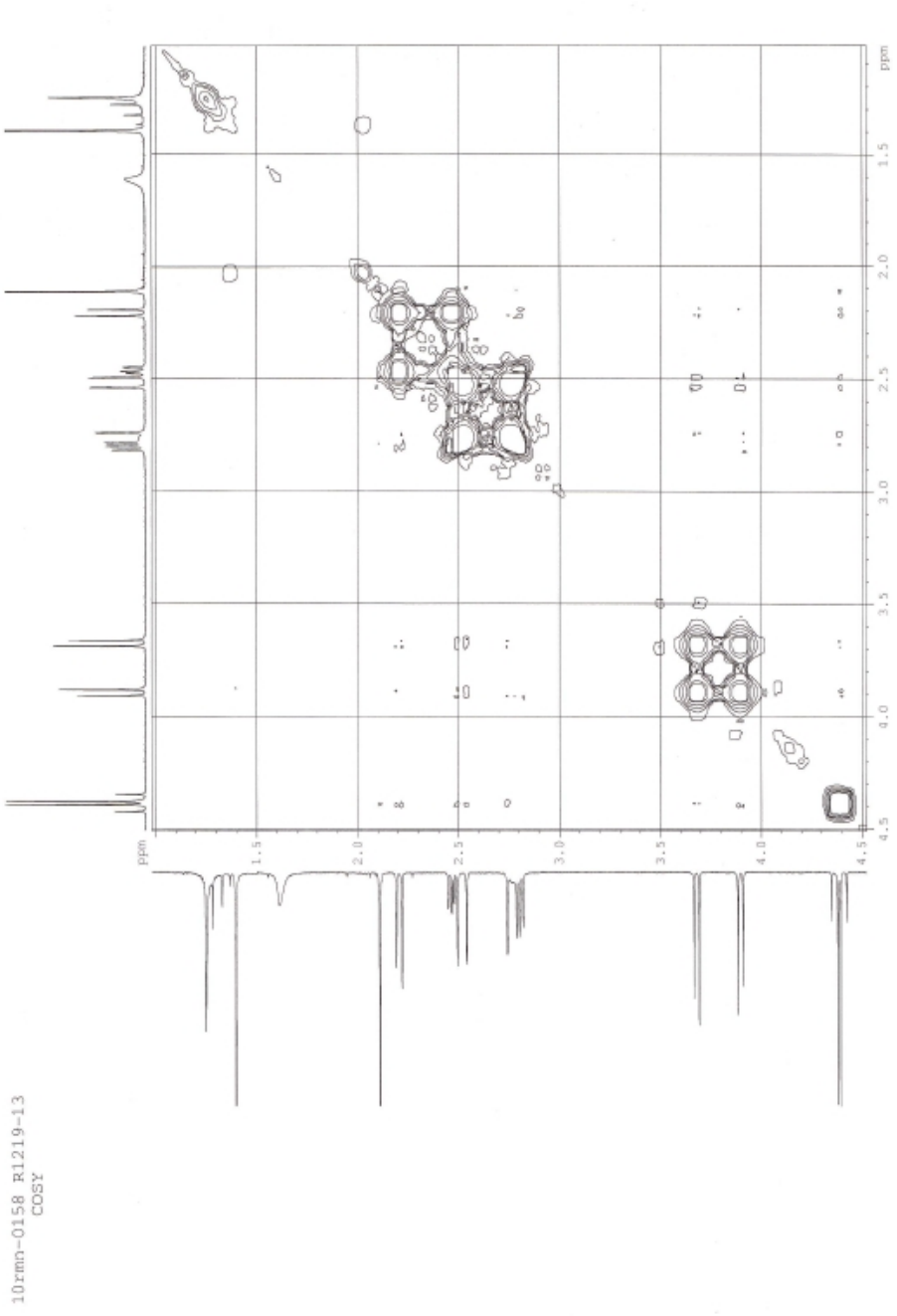


Fig. 9.80: COSY-NMR spectrum of **12**

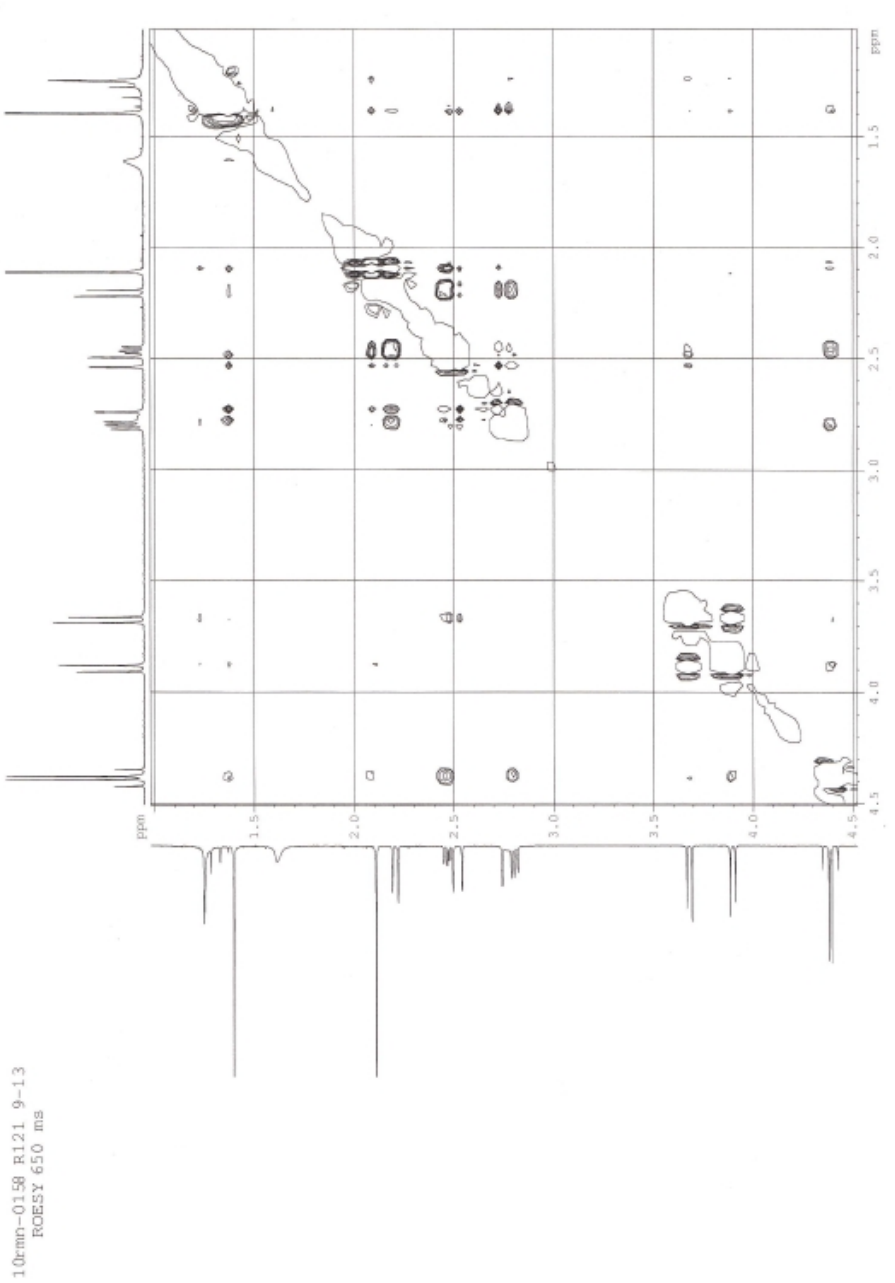


Fig. 9.81: ROESY-NMR spectrum of **12**

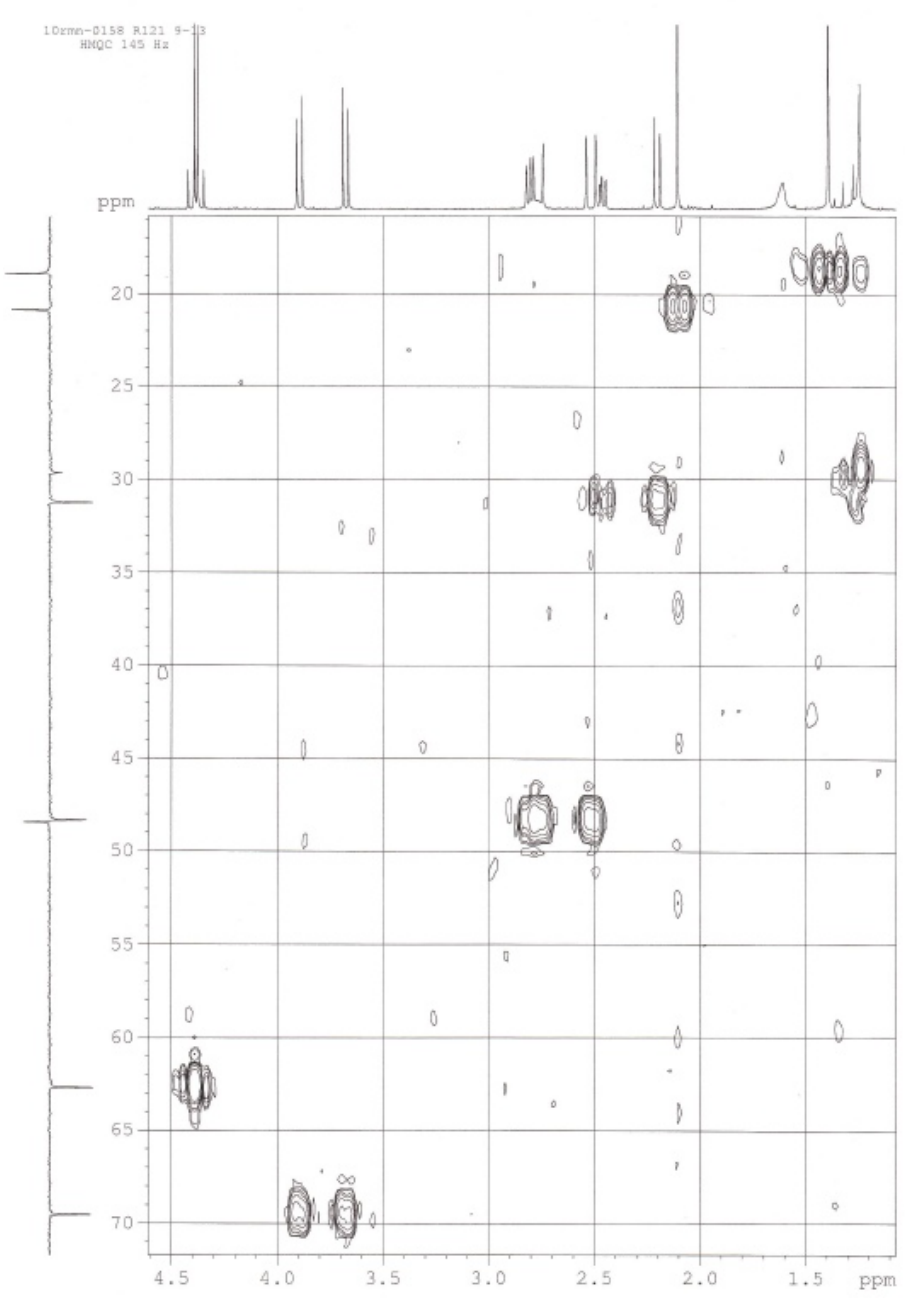


Fig. 9.82: HMQC-NMR spectrum of **12**

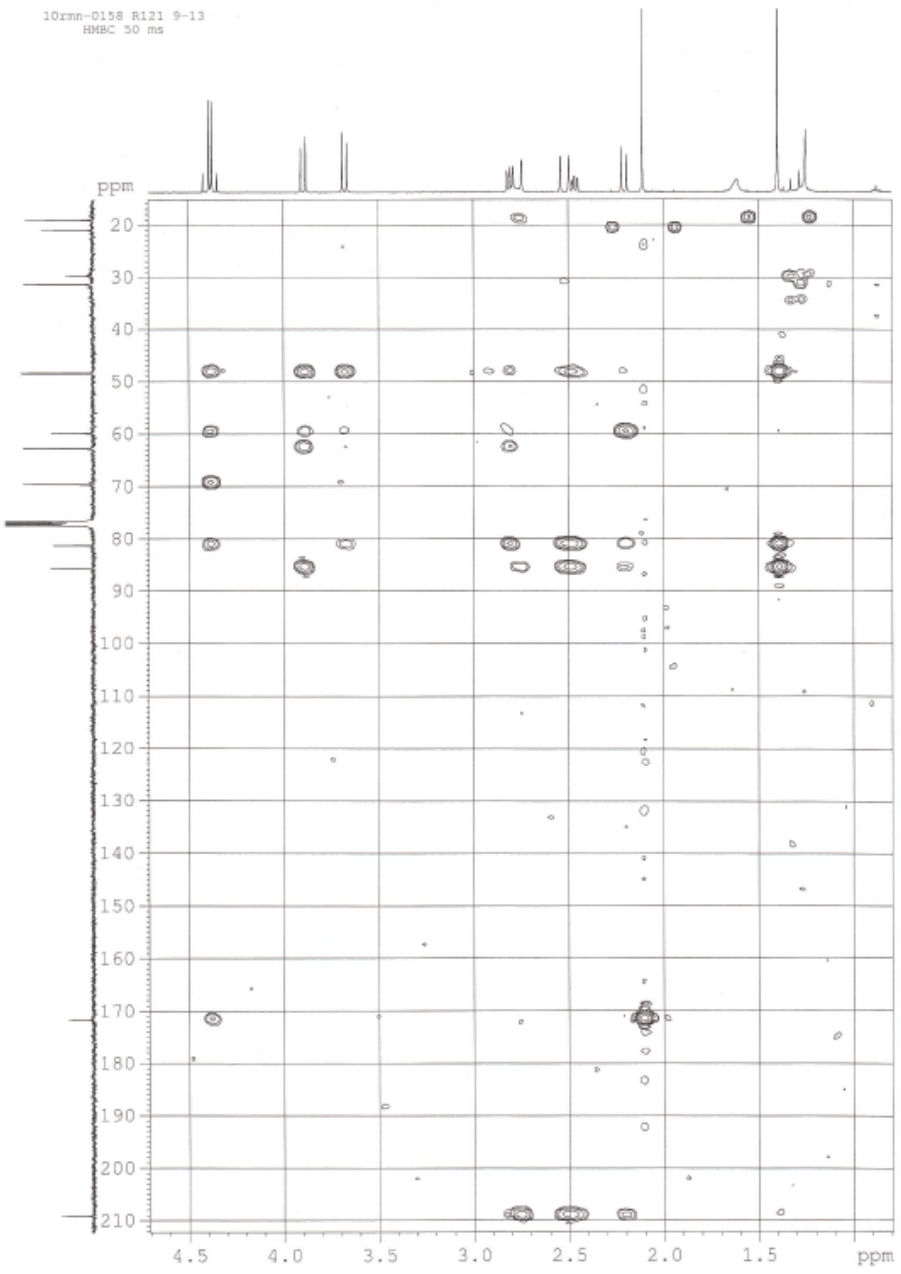


Fig. 9.83: HMBC-NMR spectrum of **12**

9.14 Spectra of compound **13**

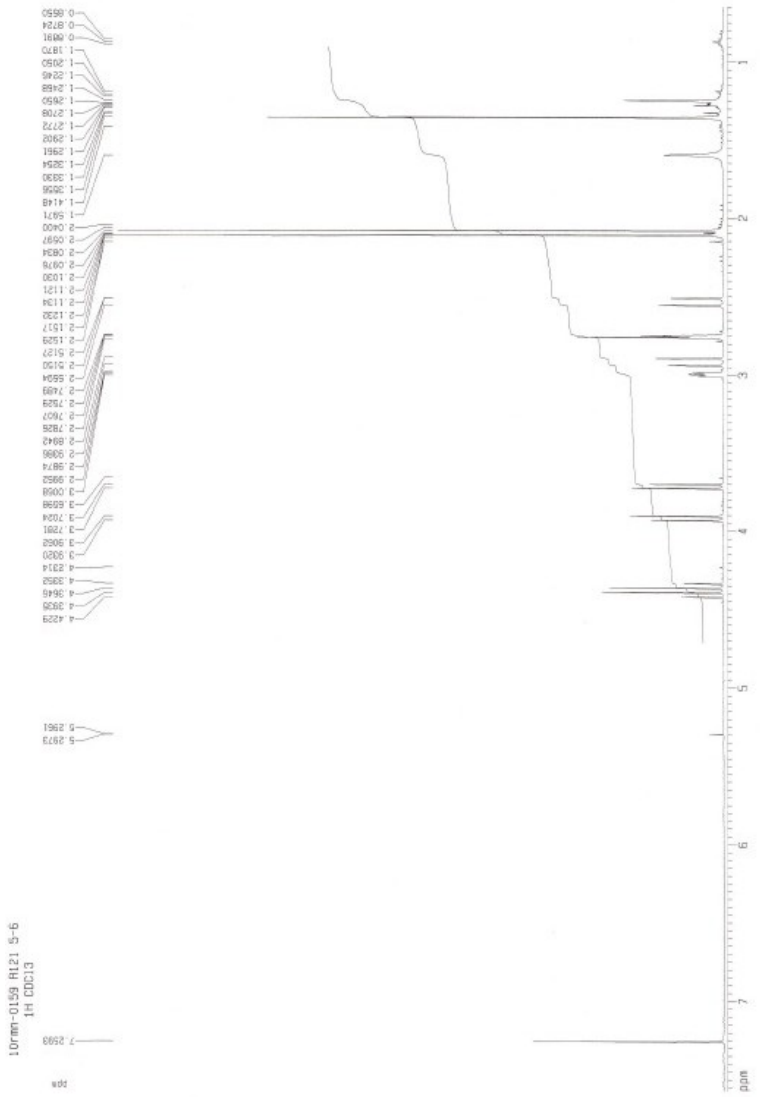


Fig. 9.84: ^{1}H-NMR spectrum of **13**

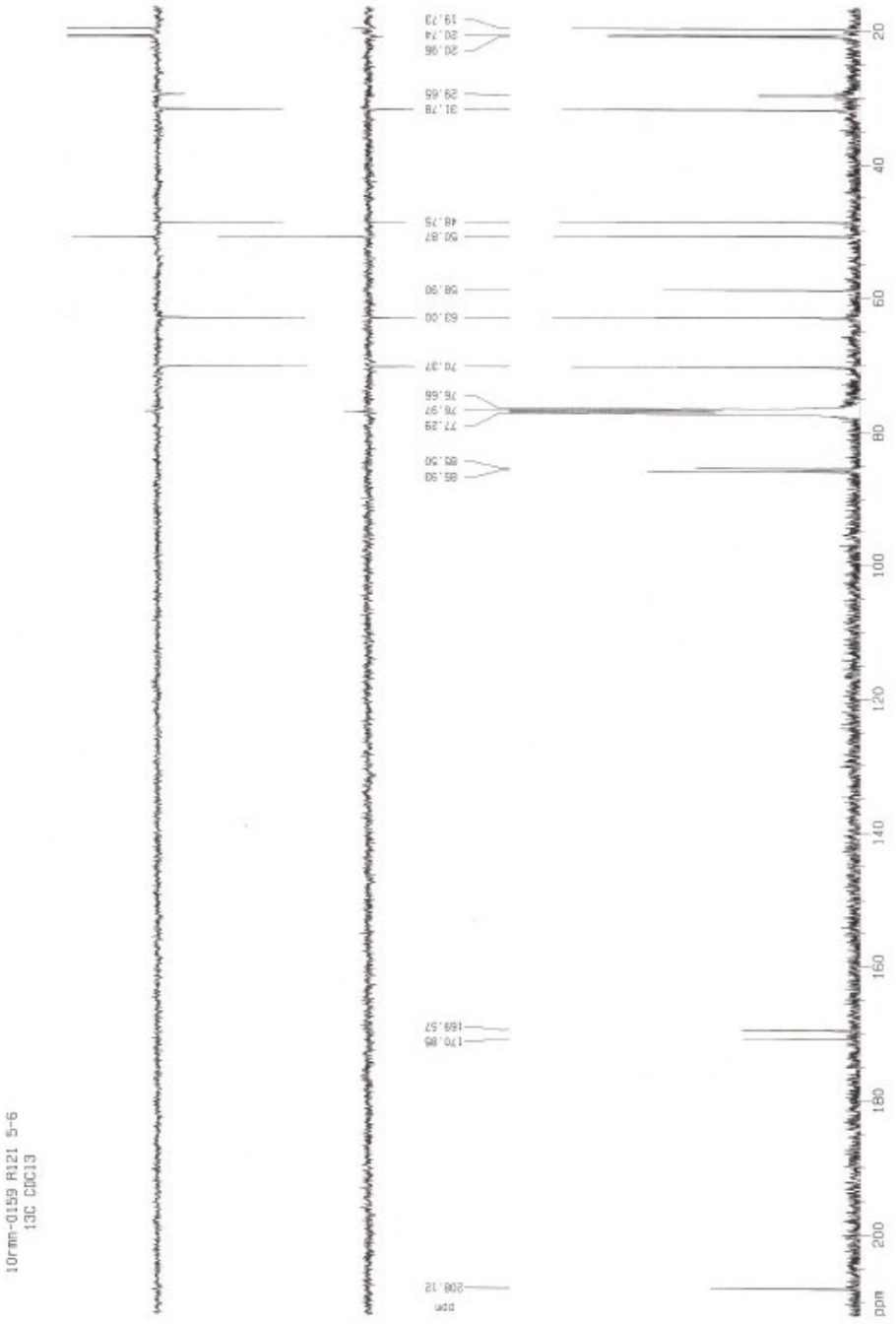


Fig. 9.85: ^{13}C-NMR spectrum of **13**

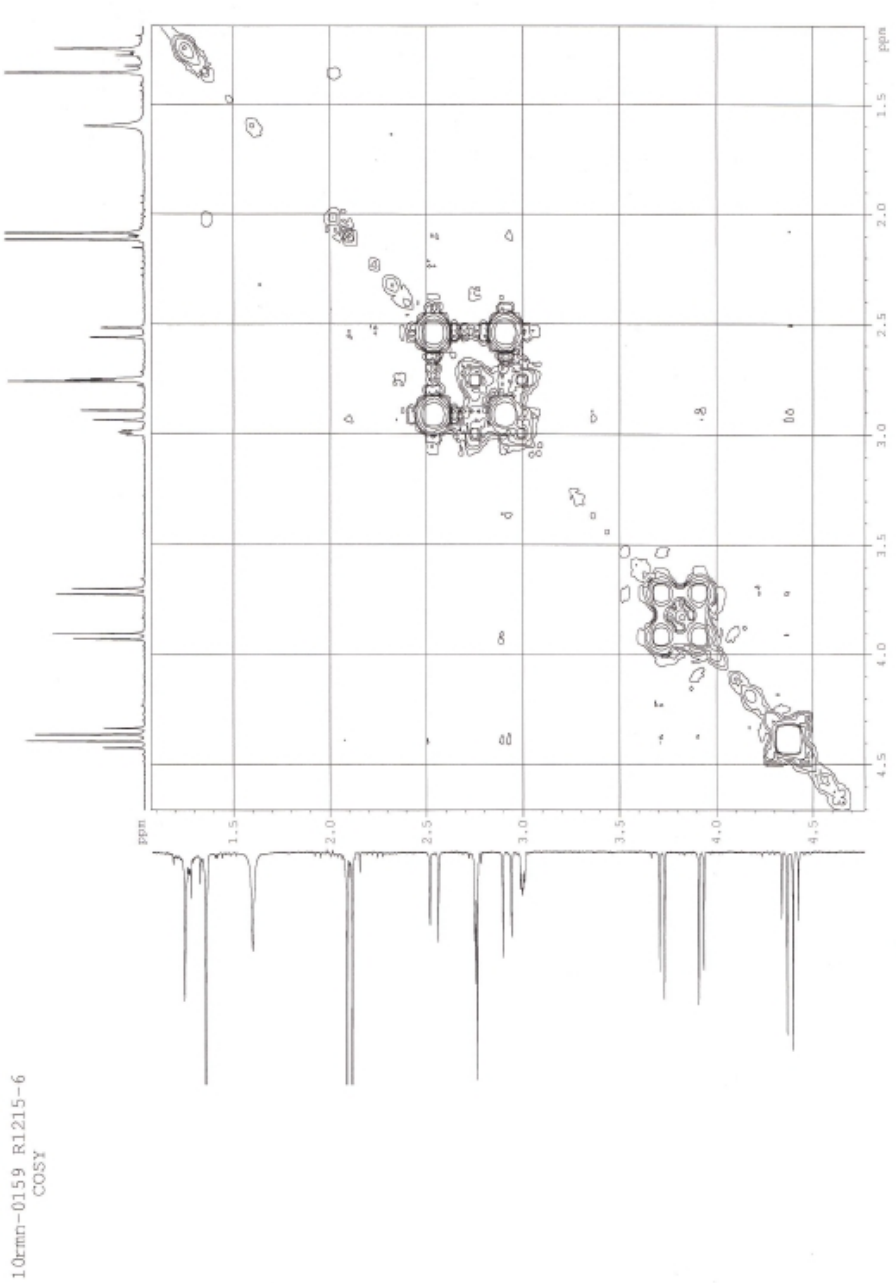


Fig. 9.86: COSY-NMR spectrum of **13**

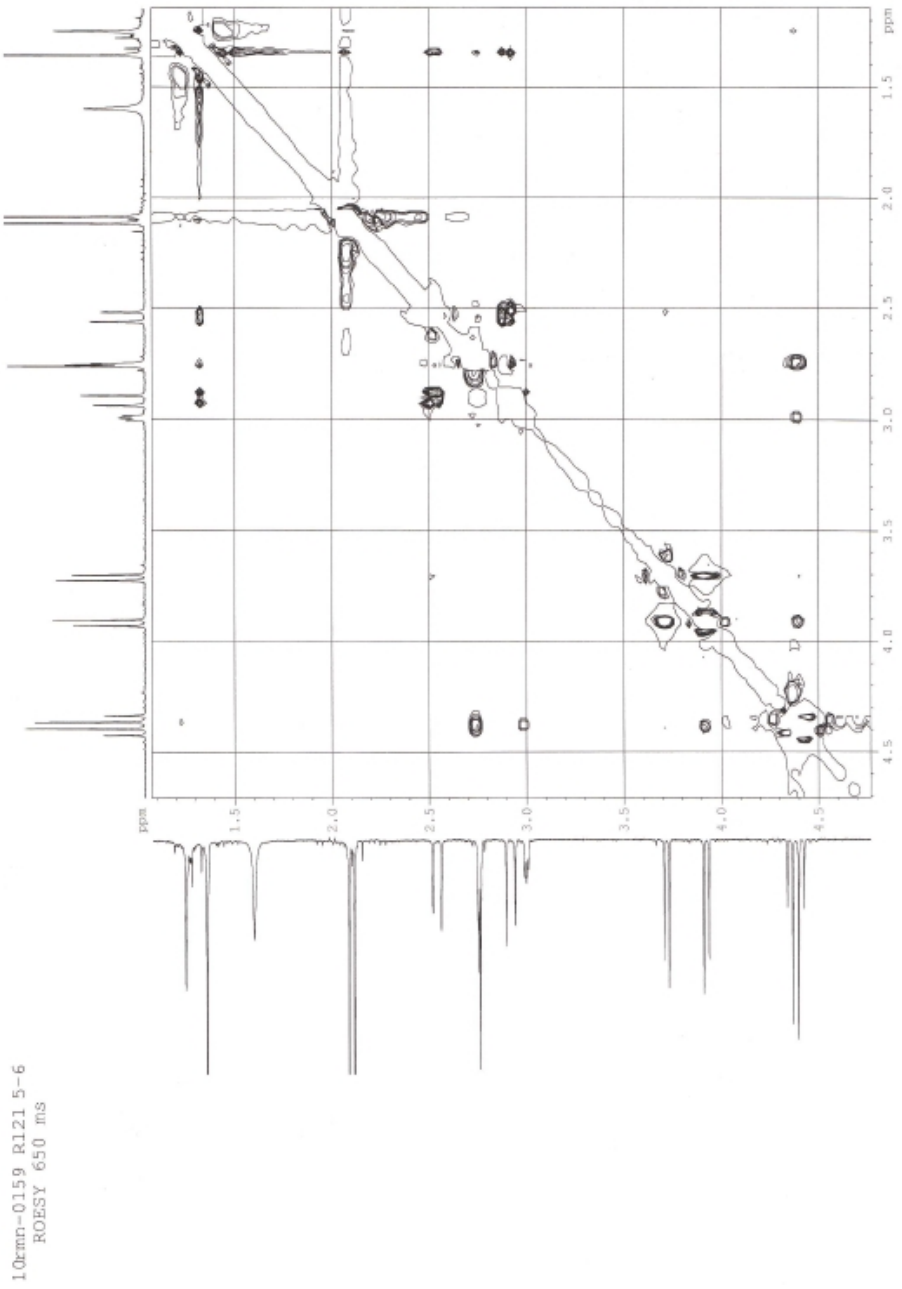


Fig. 9.87: ROESY-NMR spectrum of **13**

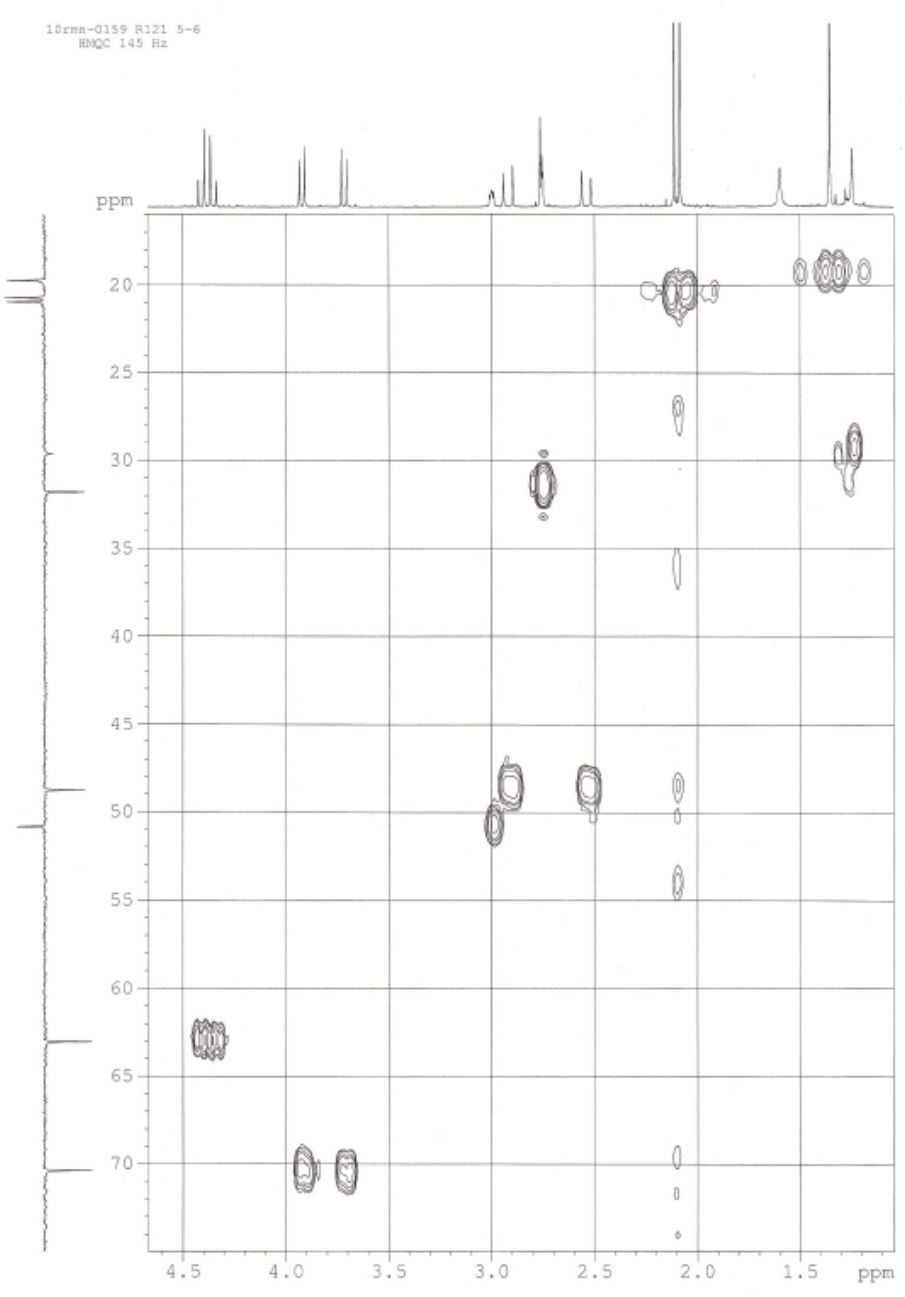


Fig. 9.88: HMQC-NMR spectrum of **13**

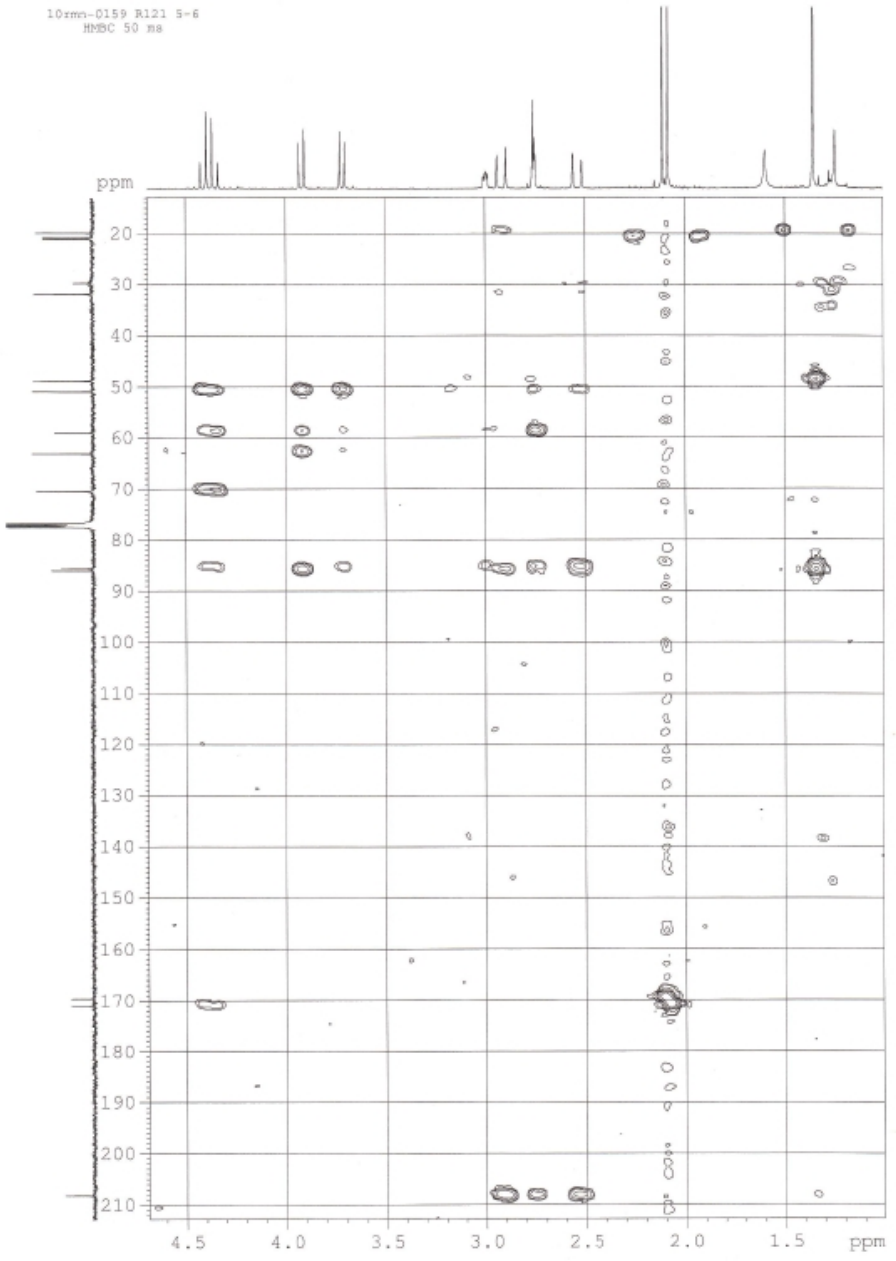


Fig. 9.89: HMBC-NMR spectrum of **13**

BIBLIOGRAPHY

[1] S. Shibata and M. Nakahara *Chem. Pharm. Bull.*, vol. 11, 1963.

[2] M. Yoshikawa, H. E., A. Kawagrichi, J. Yamahara, N. Murakami, and I. Kitagawa *Chem. Pharm. Bull.*, vol. 41 (3), 1993.

[3] M. Yoshikawa, T. Ohta, A. Kawaguchi, and H. Matsuda *Chem. Pharm. Bull.*, vol. 48 (9), 2000.

[4] H. Wagner, H. Hikino, and N. R. Farnsworth, *Economic and medicinal Plant Research*. London, England: Academic Press, Inc, 1985.

[5] M. Fujiwara *J. Neuropsychopharmacology*, vol. 12, 1990.

[6] S. Hatakeyama, M. Kawamura, Y. Mukugi, and H. Irie *Tetrahedron Letters*, vol. 36, 1995.

[7] R. Criegee *Chem. Ber.*, vol. 77, 1944.

[8] R. Criegee and R. Kaspar *Liebigs Ann. Chem.*, 1948.

[9] M. Martín-Rodríguez, R. Galán-Fernández, A. Marcos-Escribano, and F. A. Bermejo *J. Org. Chem. Note*, vol. 74, 2009.

[10] S. Hatakeyama, M. Kawamura, E. Shimanuki, K. Saijo, and S. Takano *Synlett*, 1992.

[11] S. Hatakeyama, M. Kawamura, and S. Takano *J. Am. Chem. Soc.*, vol. 116, 1994.

[12] E. J. Corey and Y.-J. Wu *J. Am. Chem. Soc.*, vol. 115, 1993.

[13] C. A. Grob and W. Baumann *Helv. Chim. Acta*, vol. 38, 1955.

[14] S. G. Hedge, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, and J. Wolinsky *Tetrahedron Letters*, vol. 21, 1980.

[15] S. G. Hedge and J. Wolinsky *J. Org. Chem.*, vol. 47, 1982.

[16] K. Weinges and G. Schwartz *Liebigs Ann. Chem.*, 1993.

[17] R. Lago, 2006.

[18] A. Gansäuer, M. Pierobon, and H. Bluhm *Synthesis*, 2001.

[19] K. Nakai, M. Kamoshita, T. Doi, H. Yamada, and T. Takahashi *Tetrahedron Letters*, vol. 42, 2001.

[20] Y. Haruo, T. Hasegawa, H. Tanaka, and T. Takahashi *Synlett*, 2001.

[21] A. F. Barrero, J. M. Cuerva, M. M. Herrador, and V. M. V. *J. Org. Chem.*, vol. 66, 2001.

[22] A. F. Barrero, J. M. Cuerva, M. M. Herrador, and V. M. V. *Tetrahedron Letters*, vol. 43, 2002.

[23] A. F. Barrero, J. E. Oltra, C. J. M., and A. Rosales *J. Org. Chem.*, vol. 67, 2002.

[24] J. Justicia, J. E. Oltra, and J. M. Cuerva *J. Org. Chem.*, vol. 69, 2004.

[25] A. Rosales, R. E. Estévez, J. M. Cuerva, and J. E. Oltra *Angew. Chem. Int. Ed.*, vol. 44, 2005.

[26] A. Rosales, R. E. Estévez, J. M. Cuerva, and J. E. Oltra *Angew. Chem. Int. Ed.*, vol. 44, 2005.

[27] J. Justicia, A. Rosales, E. Buñuel, J. L. Oller-López, M. Valdivia, A. Haidour, J. E. Oltra, A. F. Barrero, D. J. Cardenas, and J. M. Cuerva *Chem. Eur. J.*, vol. 10, 2004.

[28] R. M. Kanada, D. Itoh, M. Nagai, J. Niijima, N. Asai, Y. Mizui, S. Abe, and Y. Kotake *Angew. Chem. Int. Ed.*, vol. 46, 2007.

[29] W. G. Salmond, . B. M. A., and J. L. Havens *J. Org. Chem.*, vol. 43(10), 1978.

10. APPENDIX

Abbreviations

AcOEt: ethyl acetate
AcOK: potassium acetate
BDMA: benzaldehyde dimethyl acetal
^{13}C-NMR: Carbon Nuclear Magnetic Resonance Spectroscopy
Da: Dalton
DMAP: 4-Dimethylaminopyridine
DMF: dimethyl formamide
DMP: dimethyl pyrazole
EI: electron (impact) ionization
ESI: Electron Spray Ionization
Fig.: figure
^{1}H-NMR: Proton Nuclear Magnetic Resonance Spectroscopy
Hex: hexane
HMBC: Heteronuclear Multiple Bond Correlation experiment
HMQC: Heteronuclear Multiple Quantum Coherence
HRMS: High Resolution Mass Spectrometry
Hz: Hertz
NOE: Nuclear Overhauser effect
PivCl: pivaloyl chloride
ppm: parts per million
PPTS: pyridinium p-toluenesulfonate
Pyr.: pyridine
ROESY: rotating frame NOE
tBuOOH: $tert$-Butyl hydroperoxide
THF: Tetrahydrofurane
TLC: thin layer chromatography
TOF: time of flight mass analyzer

Abstract

In der vorliegenden Arbeit wird die Totalsynthese von (-)-Paeonisuffron Mono- und Diacetat ausgehend von R-(-)-Carvon beschrieben. Dies sind zwei Bestandteile der Wurzeln der chinesischen Pfingstrosen (*Päonien*), welche in der traditionellen Medizin von Japan, China, Korea und Bulgarien Anwendung finden. Die Synthese verläuft über elf Stufen, wobei die Titan-katalysierte Zyklisierung den Schlüsselschritt darstellt. Diese wird ausgelöst durch die Öffnung des zuvor synthetisierten Epoxids durch Elektronentransfer. Dabei entsteht die hochoxidierte α-Pinen-Grundstruktur, welche in den Zielmolekülen und anderen komplexen, biologisch aktiven Terpenoiden vorhanden ist. Somit eröffnet diese Reaktion neue, effektive Wege zu deren Synthese.

In the presented work, the total synthesis of (-)-Paeonisuffrone mono- and diacetate starting from R-(-)-Carvone is described. These are two components of the roots of chinese peonies which are used in the traditional medicins of Japan, China, Korea and Bulgaria.
The synthesis consists of eleven steps, the Titanium catalyzed cyclization being the key step. This is initiated by the opening of the before synthesized epoxide by electron transfer. In this reaction, the highly oxidized α-pinene structure is formed, which is present in the target molecules and other complex, biologically active terpenoids. Thus, this reaction provides a new and effective approach to their synthesis.

Lebenslauf

Kontakt

Weintraubengasse 24/2/24
1020 Wien
AUSTRIA
Tel.: +43/(0)650/9830032
E-Mail: a0505296@unet.univie.ac.at

Persönliche Information

geboren in Braunau/Inn, 29. Dezember 1986

Österreichische Staatsbürgerin

Ausbildung

Volksschule Laab, Braunau/Inn, 1993–1997

Bundesgymnasium und Bundesrealgymnasium Braunau/Inn, 1997–2005

Diplomstudium Chemie, Universität Wien, Wintersemester 2005–derzeit

Erasmus-Aufenthalt an der Universidad de Salamanca, Facultad de Ciencias Químicas, 09/2009–07/2010

Diplomarbeit bei Prof. Dr. Francisco Bermejo González (Universidad de Salamanca, Departamento de Química Orgánica)

Erwerbstätigkeit

ALU-Stiftung GmbH Ranshofen, 4 Monate während der Sommer- und Semesterferien 2003, 2006 und 2007

Dr. Hans Rant & Dr. Kurt Freyler Rechtsanwälte OEG, 2 Monate während der Sommerferien 2004 und 2005

wiss. Mitarbeiterin von Prof. Dr. Walter Weissensteiner, Institut für organische Chemie, Universität Wien, Februar und August 2008

Tutorin im organisch-chemischen Praktikum, Institut für organische Chemie, Universität Wien, Studienjahr 2008/09

AMAG Ranshofen, Abteilung Technologie-Oberfläche, 6 Wochen während der Sommerferien 2009

Wien, 2011