SYNTHETIC STUDIES TOWARD ASYMMETRIC C-18 ANALOG OF ANTITUMOR AGENT, 20(*S*)- CAMPTOTHECIN

by

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Major Professor

ABSTRACT

Synthetic routes leading to the construction of the C-18 analog of 20(*S*)-camptothecin were investigated by 2 different methods. First, the 1, 4 addition reaction / ring closure reaction of the anion of (*R*)-3[[(4-methylphenyl)sulfinyl]-methyl]-1*H*-pyrrolo[3, 4-b]quinoline (**15**) with methyl 3-ethyl-1,3-cyclohexadiene-1-carboxylate (**28**) was investigated. The synthesis of methyl 3-ethyl-1,3-cyclohexadiene-1-carboxylate gave unexpected isomers in the Diels-Alder reaction.

Second, the Friedlander condensation reaction of *o*-aminobenzaldehyde with 1-oxo-1,2,3,5,5a,6,7,8,9,9a-decahydro-10-[(4-methylphenyl)sulfenyl]-9-tri(isopropyl)silyloxy-5-oxopyrrolo[1, 2-b]isoquinoline (**38**) was planned. Some model reactions have been done for this second method. During the model study, the condensation reaction of *o*-aminobenzaldehyde with 1-oxo-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfenyl]-5-indolizinone (**34**) was investigated. In this process, methyl 1-cyclohexen-3-(triisopropylsilyoxy)-1-carboxylate (**47**) was synthesized by the SeO_2 oxidation of methyl 1-cyclohexene-1- carboxylate (**45**) followed by protection of the alcohol using triisopropylsilyl chloride.

ACKNOWLEDGMENT

I would like to take this opportunity to express my deepest and sincere appreciation and acknowledgment to my major advisor **Prof. Duy H. Hua** for the time and helpful advice he has given to me from the beginning to the finish of this work. Also I would like to express appreciation to the other members of my master's committee, Prof. Keith R. Buszek and Prof. R. M. Hammaker. I would like to thank to my group members for their help in producing this document. My appreciation goes to all of the staff members and graduate students who have lent their time to help me achieve my goals.

Last, but certainly not least, a very special thanks goes to my husband, Amal, his love, support, and encouragement have been with me throughout my graduate program and always.

DEDICATION

To my parents, husband, and the late Professor Karl R. Stromberg.

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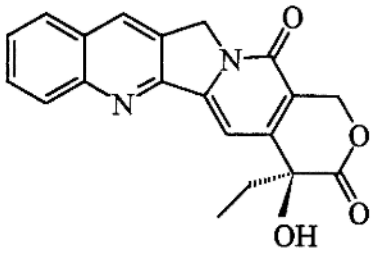
STRUCTURE CORRELATION DIAGRAM

1.



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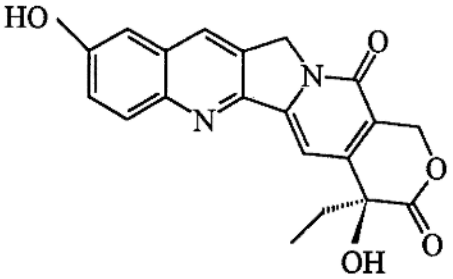

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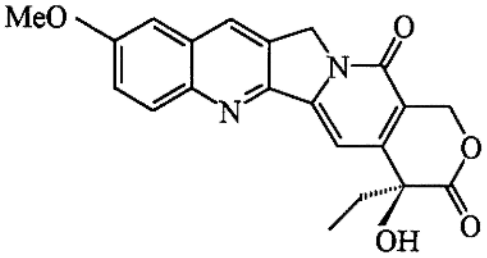

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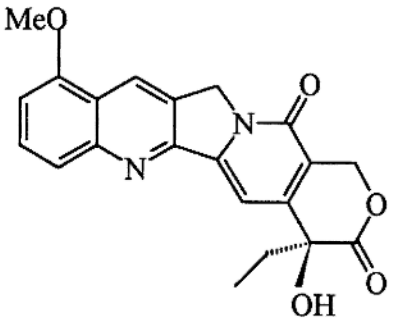

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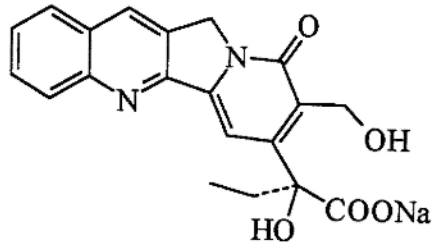

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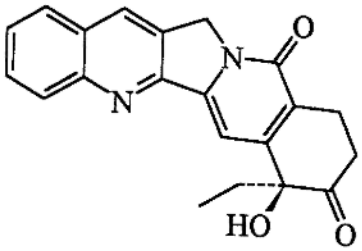

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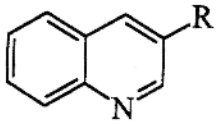

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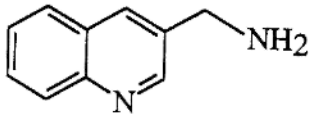

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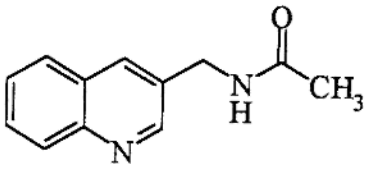

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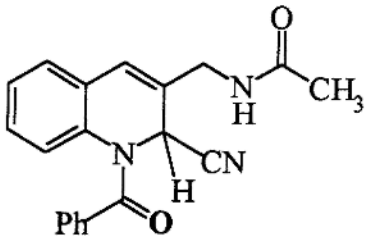

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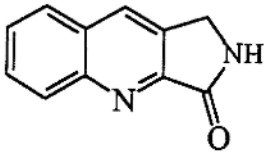

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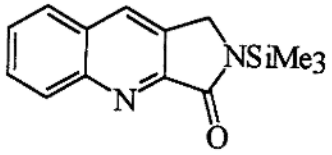

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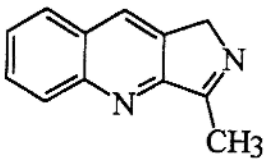

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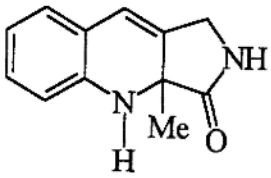

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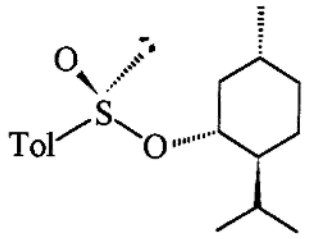

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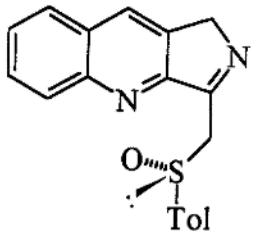

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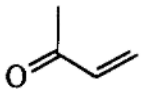

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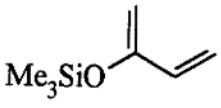

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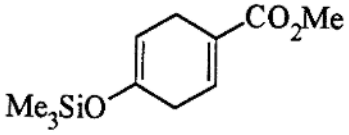

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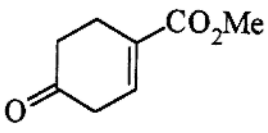

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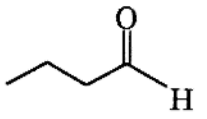

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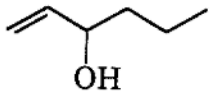

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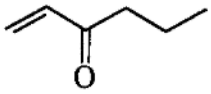

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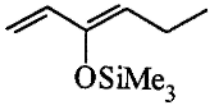

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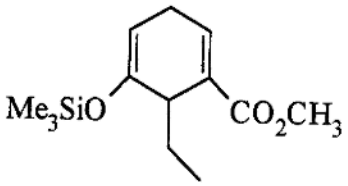

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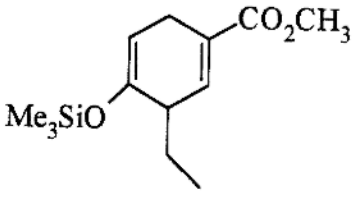

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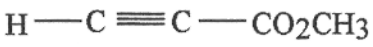

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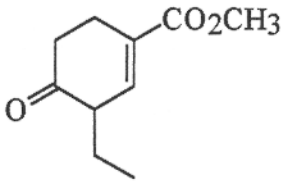

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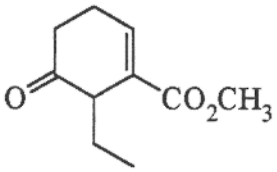

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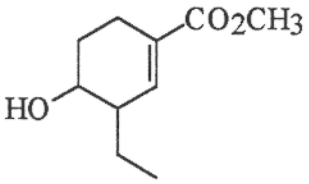

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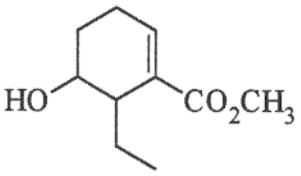
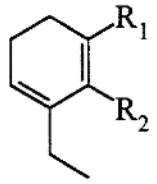


28a. $R_1 = CO_2CH_3$, $R_2 = H$

28b. $R_1 = H$, $R_2 = CO_2CH_3$



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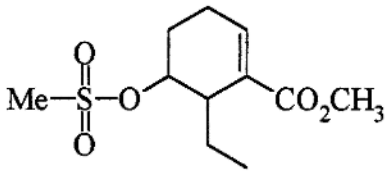

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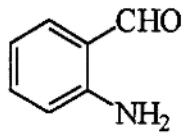

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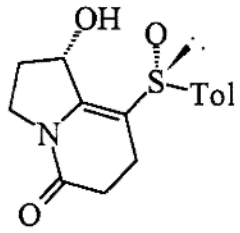

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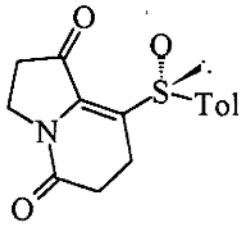

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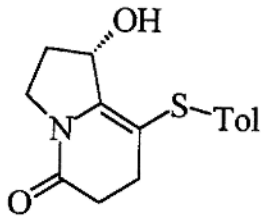

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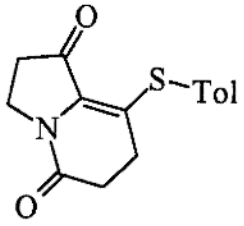

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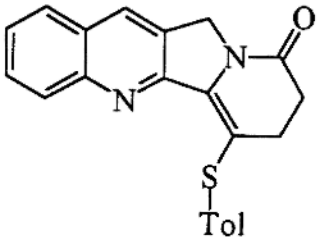

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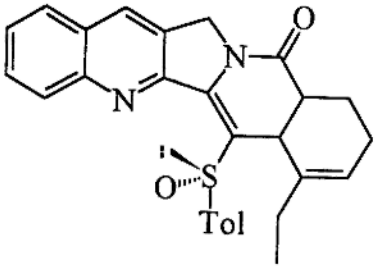

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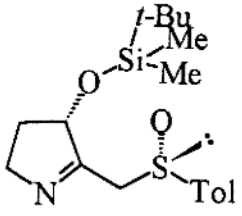

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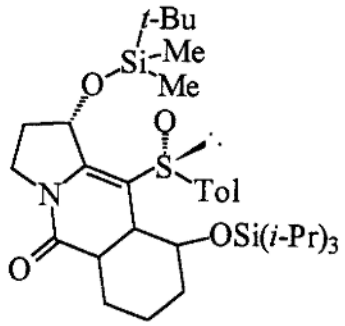

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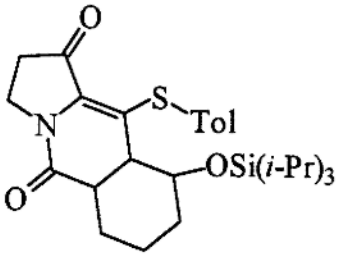

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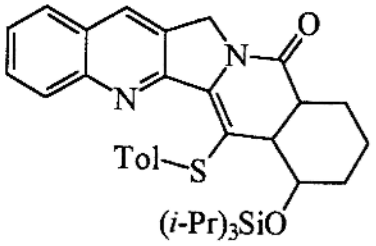

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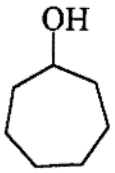

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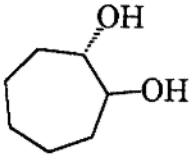

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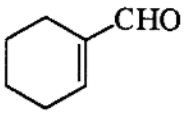

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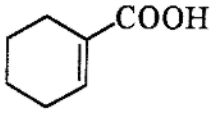

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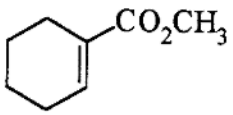

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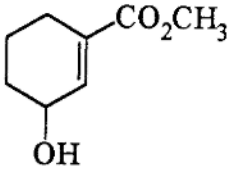
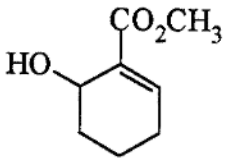


46b.



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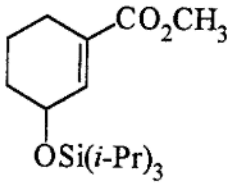

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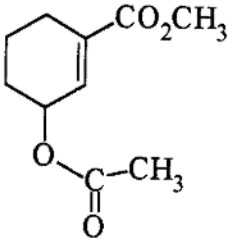
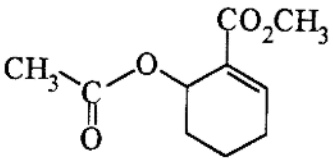


48b.



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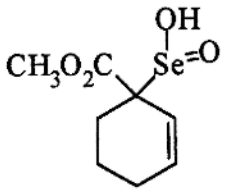

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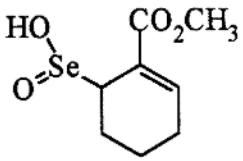

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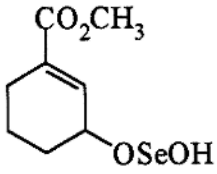

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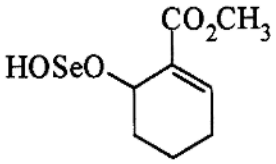
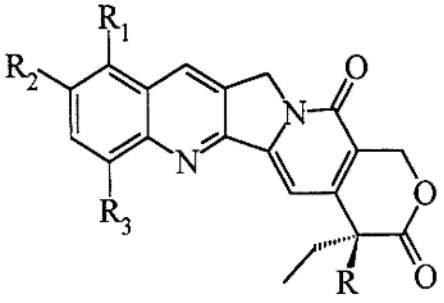
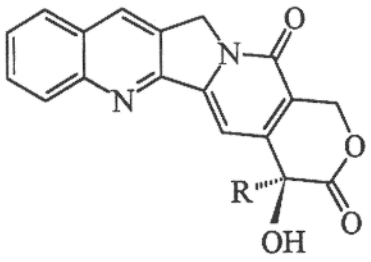


51. R = OAc, $R_1 = R_2 = R_3 = H$
52. R = Cl, $R_1 = R_2 = R_3 = H$
53. $R = R_1 = R_2 = R_3 = H$



54. R = $CH_2CH{=}CH_2$



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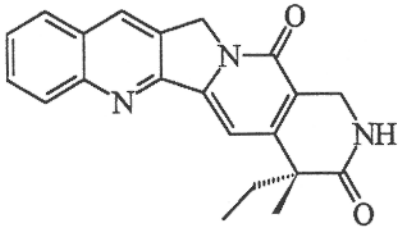

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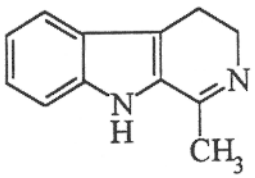

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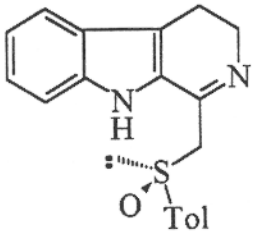
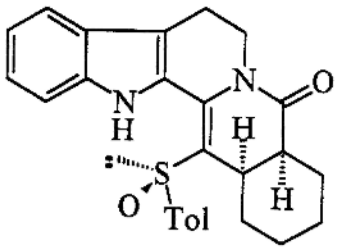


58.



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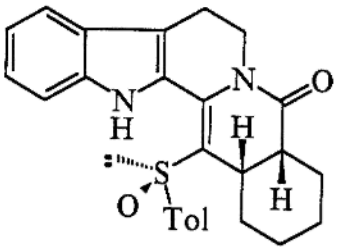


List of Tables

CHAPTER 1

BACKGROUND

20(S)-Camptothecin (**1**) is a novel plant antitumor agent, which was isolated by Wall and coworkers[1] in 1966 from *Camptotheca acuminata* Decaisne (Nyssaceae). *C. acuminata* is a small tree native to China, found in several southern provinces of China, notably Szechwan, and requires frost-free and relatively mild climates for successful growth..

Camptothecin is a high-melting compound which is insoluble in water. Indeed, it is insoluble in virtually all organic compounds except dimethylsulfoxide in which it exhibits moderate solubility.[1] Some of the more important physical properties of camptothecin are listed below.

Properties of Camptothecin[1-3]

Light yellow needles, m.p. 264-267° (dec.)

Intense blue fluorescence under UV

$[\alpha]_D^{25}$, $+31.3^0$

M^+ at m/e, 348.1117

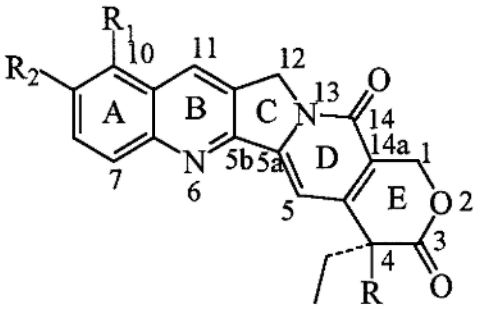
Calcd. for $C_{20}H_{16}N_2O_4$: 348.1111

Some of the unique structural features involve the presence in the E-ring of a α-hydroxylactone system and in ring D a conjugate pyridinone moiety. Camptothecin has

only one asymmetric carbon, C20, with 20(*S*) configuration (Fig.1) being the natural form.

Compound **1** (Fig. 1) has an unusually broad spectrum of activity toward leukemia and solid tumor systems ; this compound has also been the subject of intensive investigation in regard to its mode of action on mammalian cells and their viruses.[4] In particular, camptothecin is a potent inhibitor of nucleic acid synthesis[4] by the inhibition of topoisomerase I. Both camptothecin (**1**) and 10-hydroxycamptothecin (**2**) have high activity against L-1210 and P-388 mouse leukemia. Both compounds are active in certain solid tumor systems. Thus **1** and **2** have good activity against B-16 melanoma. The former has also been tested against Walker 256 carcinosarcoma showing very high activity. Both **1** and **2** are inactive against the Lewis lung tumor.[2]

Naturally occurring analogues of camptothecin (Fig. 1) have been reported. 10-Hydroxycamptothecin (**2**) (Fig. 1) and 10-Methoxycamptothecin (**3**) were isolated from *C. acuminata* by Wani and Wall in 1969.[5] 9-Methoxycamptothecin (**4**) was isolated from *Mappia foetida* by Govindachari and Viswanathan in 1972.[6] All of these ring A hydroxylated substances are found only as trace constituents along with the major product camptothecin. The hydroxylated compounds may well be produced as a result of further plant metabolism.



1. R = OH, $R_1 = R_2 = H$ (20(*S*)-Camptothecin)*

2. $R = R_2 = OH$, $R_1 = H$ (10-Hydroxycamptothecin)

3. R= OH, R_2= OMe, R_1 = H (10-Methoxycamptothecin)

4. R = OH, R_1 = OMe, R_2 = H (9-Methoxycamptothecin)

* The numbering system in the ring here is based on *Chem. Absts.*

Figure 1. Camptothecin and its natural analogues

Camptothecin itself contains the α-hydroxy lactone moiety in the E-ring, which is absolutely required for antitumor activity (Sugasawa *et al.*[7] stated that their data confirmed the earlier studies of Wall[1] in 1969 which stressed the importance of the α-hydroxy lactone ring for antitumor activity). In the presence of base it can be quantitatively converted to the sodium salt **5** by ring opening of the lactone (Fig. 2) which is clinically inactive.[5] Table 1 shows a list of compounds that had been tested for antitumor activity. The sodium salt of **1** is soluble in water and recyclizes to **1** in dilute acid. The pH of blood is 7.2, and at this pH the sodium salt of camptothecin cannot regenerate the α-hydroxy lactone ring required for antitumor activity.[2] Also under physiological conditions, **1** is converted into **5** (Fig. 2) in a significant amount. This fact

was demonstrated in the analysis of the organs after treatment of **1**.

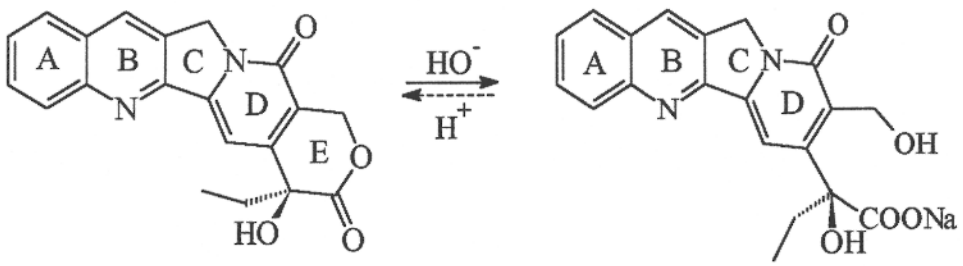
Table 1.

Antileukemic Activity and Cytotoxicity* of Camptothecine and Analogues[2, 29]

Compound #	Tumor system	Dose range (mg/kg)	Optimal dose (mg/kg)	Lowest toxic dose (mg/kg)	9KB ED_{50} (μg/mL)
1	L-1210	3.2 - 0.2	1.60	3.2	2×10^{2}
	P-388	8 - 0.5	4.00	8.0	
2	L-1210	4 - 0.25	2.00	4.0	2×10^{2}
	P-388	8 - 0.5	4.00	8.0	
3	L-1210	20 - 1.25	10.00	20.0	2×10^{2}
	P-388	4 - 0.5	0.50	1.0	
4	L-1210	2.25 - 1.0	2.25	-	
	P-388	4 - 0.5	1.00	4.0	NT[a]
5	L-1210	160 - 5	80.00	160.0	
	P-388	80 - 2.5	40.00	80.0	2×10^{-1}
51	L-1210	2 - 0.13			
52	L-1210	6 - 1.0			NT
53	L-1210	15 - 3.0	15.00	-	NT
54	P-388	50 - 2.0	25.00	50.0	NT
55	L-1210		80.00		NT

* tested on animals

[a] NT = not tested



1 5

Figure 2.

The water soluble sodium salt **5** has received more extensive animal leukemia L-1210 and solid tumor P-388 tests than camptothecin. But in general, **5** is somewhat less active and always less potent than the parent compound.[2,5,7,29]

The structural elucidation of **1** was accomplished in 1968[8] and with the initial report of its potent antileukemic L-1210[9] an antitumor P-388 activity, many attempts were made to synthesize camptothecin, culminating in a number of successful total syntheses.[9-12] The X - ray structure of **1** had also been reported.[13]

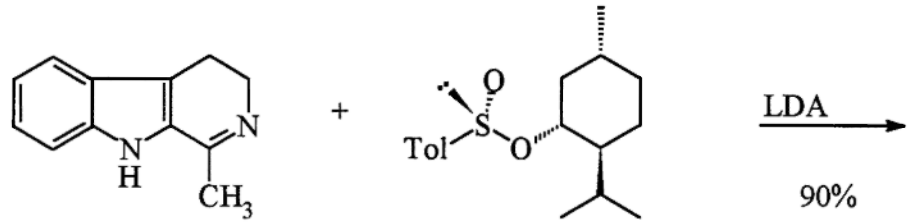
Our target was to prepare an α-hydroxy ketone derivatives of **1** such as **6** to prevent the ring opening under physiological conditions.

In the study of the enantioselective synthesis of cyclic alkaloids having a nitrogen-atom ring junction, the addition reactions of chiral α-sulfinyl ketimines with various ene esters were investigated in Dr. Hua's laboratory. Hua *et al.* have reported[27] the

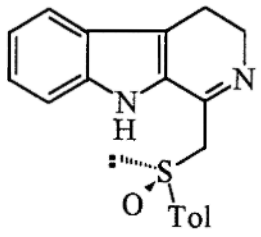
asymmetric induction exhibited in the conjugate addition reaction of the carbanion derived from α-sulfinyl ketimines (such as **57**) possessing an asymmetric sulfur with various acyclic and cyclic ene esters, and the subsequent cyclization to lactams. The 1,4-addition reaction of the anion of (-)-**57** (generated from the reaction of (-)-**57** with LDA in THF) with ene ester **45** was reported by Hua *et al* [27]

Treatment of **56** with 2 equiv of LDA in THF at 0 °C followed by the addition of *d*-(+)-(*R*)-menthyl *p*-toluenesulfinate (**14R**) at -50 °C gave a 90% yield of (-)-**57** (Scheme 1.1). The *S* configuration at the sulfur atom shows that the nucleophilic substitution at sulfur of **14R** with the anion of **56** proceeds with complete inversion of configuration.

Scheme 1.1



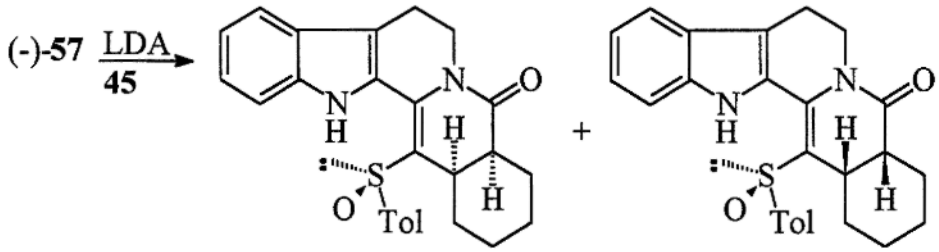
56 **14R**



(-)-57

The addition reaction of the anion (-)-**57** with methyl 1-cyclohexenecarboxylate (**45**) at 25 ^{0}C for 1 hour, and then 60 ^{0}C for 14 hours gave a 42% yield of **58**, 5% yield of **59**, and 35% recovery of (-)-**57** (separated by column chromatography) (Scheme 1.2). [27] The absolute configuration at C-15 and 20 of **58** and **59**, respectively, have been determined by a different reaction. [27]

Scheme 1.2



58 **59**

Based on these known chemistry, we extended our efforts to synthesize **35b** (discussed in Chapter 2) on treatment of ene ester **28** with the anion of **15** generated from the sulfoxide and LDA in THF.

CHAPTER 2

STUDIES IN THE ASYMMETRIC SYNTHESIS OF AN C-18 ANALOG (6) OF 20(S)-CAMPTOTHECIN (1)

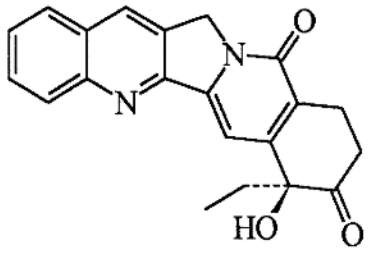
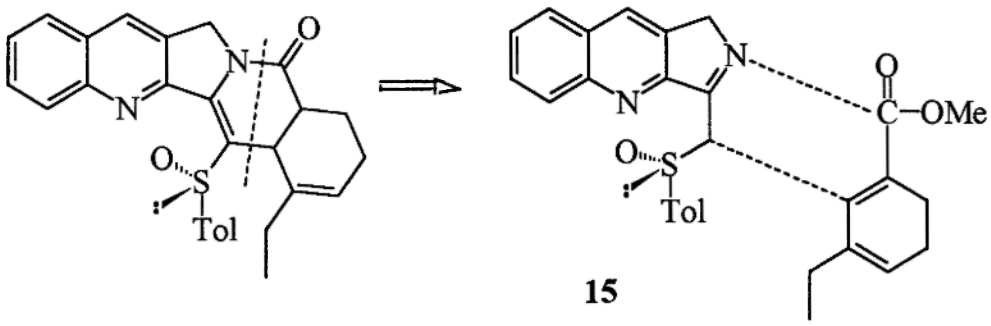


Figure 2.1. A chiral C-18 analog (**6**)

Because of its interesting features in the structure of **6** (Fig. 2.1), an approach for the construction of the tricyclic ring system **15** (Scheme 2.1) utilizing the Reissert reaction [14] was planned. In addition to that, the synthetic procedure for the E-ring utilizing Diels-Alder reaction was planned (discussed in Chapter 3). A simple disconnection approach for the construction of the pentacyclic ring system **35b** is outlined below (Scheme 2.1).

The in *situ* 1,4-addition / ring closure reactions of anions of α-sulfinyl ketimine derivatives such as **15** with cyclic ene esters such as **28** offer a simple, convenient route for the construction of chiral cyclic alkaloids such as **35b** having a nitrogen-atom ring juncture. Asymmetric induction in the conjugate-

Scheme 2.1

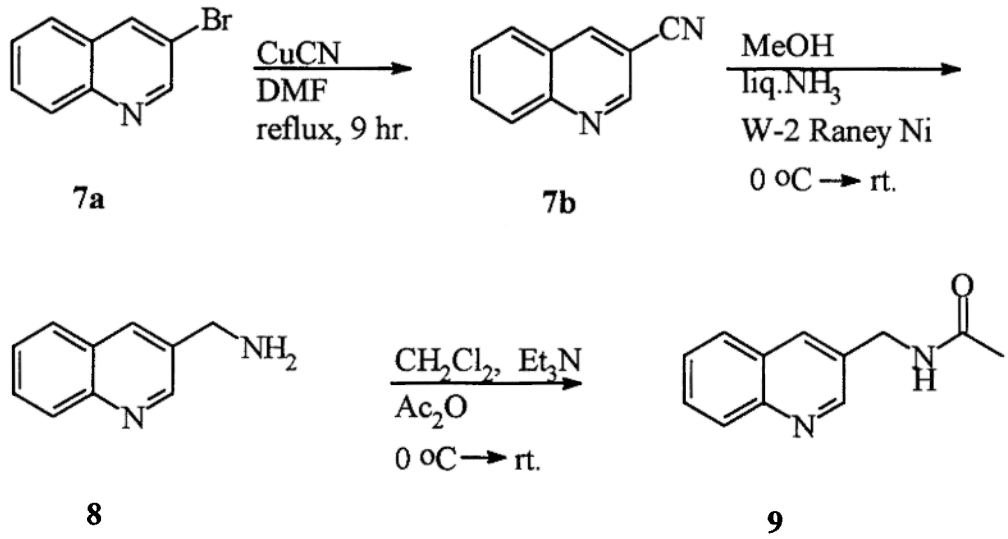


35b **28**

addition reaction of the carbanion derived from **15** possessing chiral sulfur with the cyclic ene ester **28**, subsequent ring-closure reaction was utilized.

One phase of the research program toward a quinoline alkaloid required the preparation of 2,3-dihydro-1*H*-3-oxo-pyrrolo[3,4-b]quinoline (**11**). This compound was obtained from **9** via the compound **10**[14] followed by acid-hydrolysis, as shown in Scheme 2.3.

Scheme 2.2

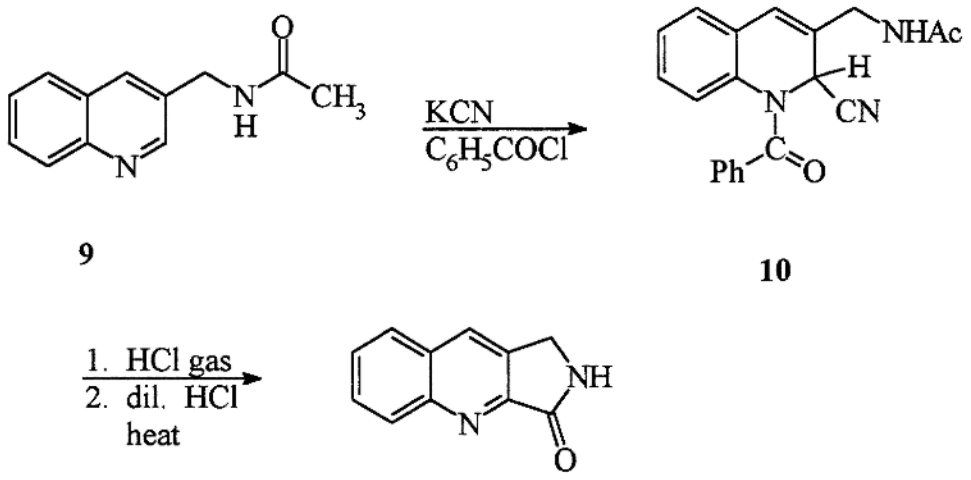


7a **7b**

8 **9**

The synthesis of 2,3-dihydro-1*H*-3-oxo-pyrrolo[3, 4-b]quinoline (**11**) was reported by Sugasawa, Toyoda, Sasakura, and Hidaka in 1971.[14] The compound **9** was obtained from commercially available 3-bromoquinoline (**7a**) as shown in Scheme 2.2 : Treatment of 3-bromoquinoline (**7a**) with CuCN in DMF under reflux condition for 9 hours gave the corresponding 3-cyanoquinoline (**7b**)[15 16] in 93% yield. Compound **7b** was then reduced[17] to the corresponding

Scheme 2.3



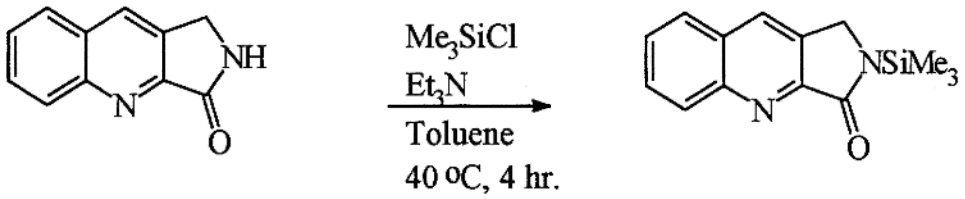
9 **10**

11

amine **8** in 88% yield using W-2 Raney Ni.[18] On treatment with acetic anhydride in the presence of Et_3N, amine **8** gave the desired product **9** in 81% yield. Reissert compound **10** was prepared by the treatment of **9** with KCN and benzoyl chloride (Scheme 2.3). The crude product of **10** was obtained in 77% yield. The crude product of **10** was hydrolyzed with mineral acid, HCl, to give the desired 3-membered ring system **11** in 79% yield.

Lactam **11** was carefully protected by using chlorotrimethylsilane as shown in Scheme 2.4. The protected lactam **12** (readily hydrolyzed with trace

Scheme 2.4

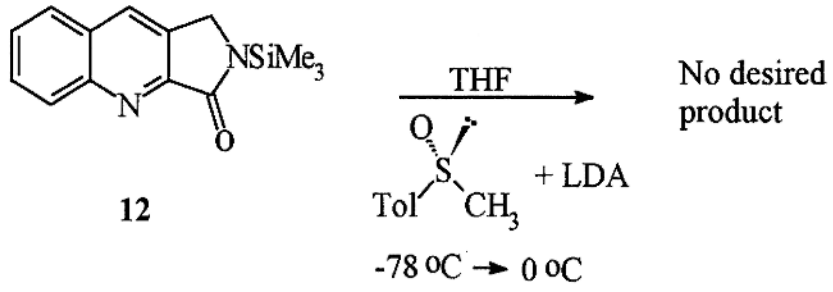


11 **12**

amount of water) was obtained in 90% yield. The product was contaminated with triethyl ammonium hydrochloride salt and bis(trimethylsilyl) ether. The starting material **11** was detected in 10% yield, when the product **12** hydrolyzed in the NMR tube with a trace amount of water.

Then we extended our efforts to synthesize the tricyclic ring system **13**. On treatment of compound **12** with the anion of (*R*)-methyl *p*-tolyl sulfoxide (Scheme 2.5), generated from the sulfoxide and lithium diisopropylamide (LDA) in THF,

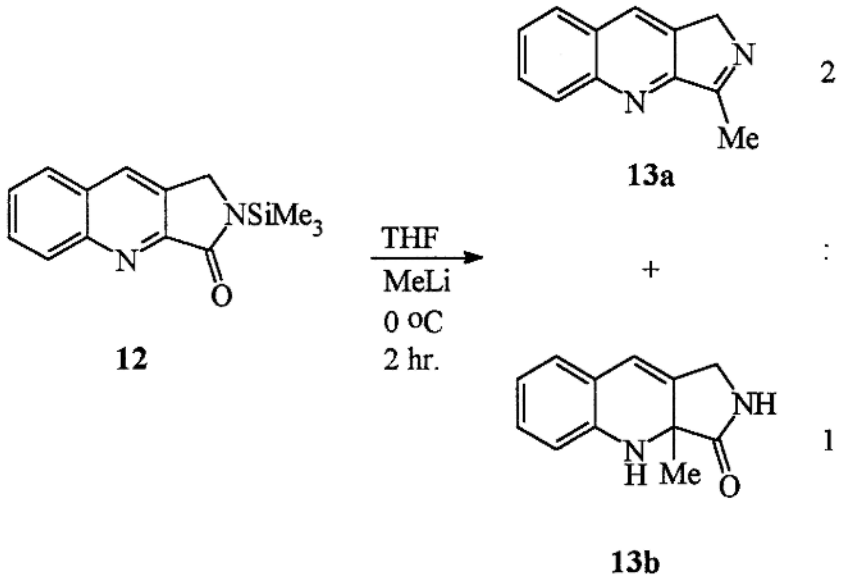
Scheme 2.5



12

no desired product was obtained. Instead, we isolated compound **11**. Because of this discouraging result, the protected lactam was first converted to the stable imine **13a** (Scheme 2.6) using methyllithium. The ^{1}H NMR of the crude

Scheme 2.6

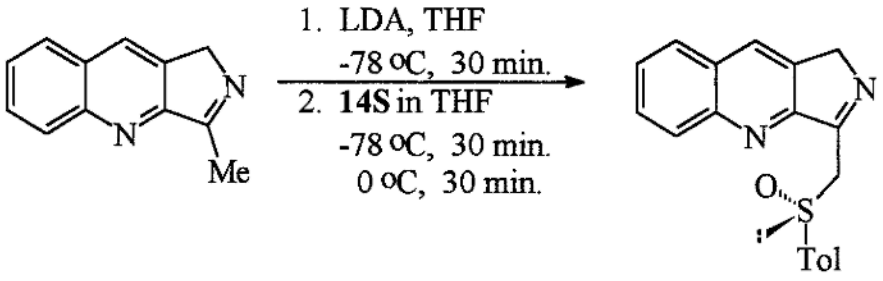


product indicated that the desired imine **13a** and undesired product **13b** were present in a ratio 2 : 1 (determined by ^{1}H NMR). An attempted separation using column chromatography was unsuccessful. The product was lost during column chromatography. Unfortunately we were not able to repeat the reaction.

The imine **13a** (crude product) was then treated with LDA followed *l*-(-)-(*S*)-menthyl *p*-toluenesulfinate (**14S**)[19] to give the desired tricyclic product **15** (Scheme 2.7). An attempt to purify the crude product **15** by column chromatography was

unsuccessful. Instead, we isolated a mixture of compounds (compound **15**, starting material **13a** and (*S*)-*p*-toluenesulfinate-1-menthol). An attempt recrystallization of **15** with hexane-ether was unsucessful. Because of unsuccessful attempts at purification of **15**, **13a**, and the very unstable nature of intermediate **12** (readily hydrolyzed with trace amount of water), we changed our plan for the synthesis of our target molecule **6**. We did not study the above reactions further. Several model reactions were investigated for our new plan, and they are discussed in Chapter 4.

Scheme 2.7



13a **15**

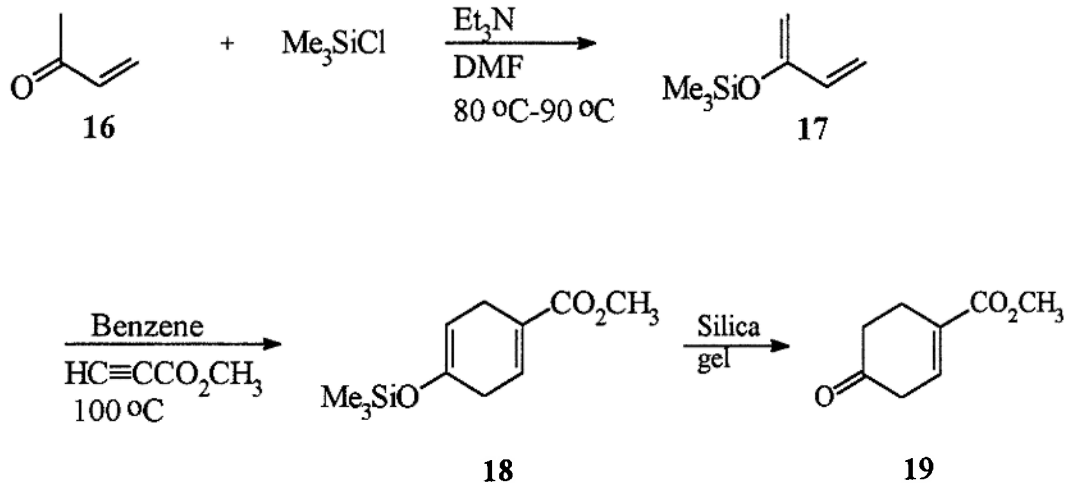
CHAPTER 3

STUDIES IN THE SYNTHESIS OF THE E-RING 28 VIA DIELS-ALDER REACTION

An asymmetric C-18 analog **6** of (*S*)-Camptothecin (**1**) has an interesting carbon skeleton structure. The most interesting and challenging part of this molecule is the synthesis of E-ring **28**.

We now report the synthesis of E-ring **28** that uses a [4+2] (Diels-Alder) cycloadition reaction . The viability of the key [4+2] cyclization reaction was first demonstrated in a simple model reaction.[20] Readily available methyl vinyl ketone (**16**) was silylated to give 2-trimethylsilyloxy-1,3-butadiene (**17**) (Scheme 3.1) in 16% yield.

Scheme 3.1

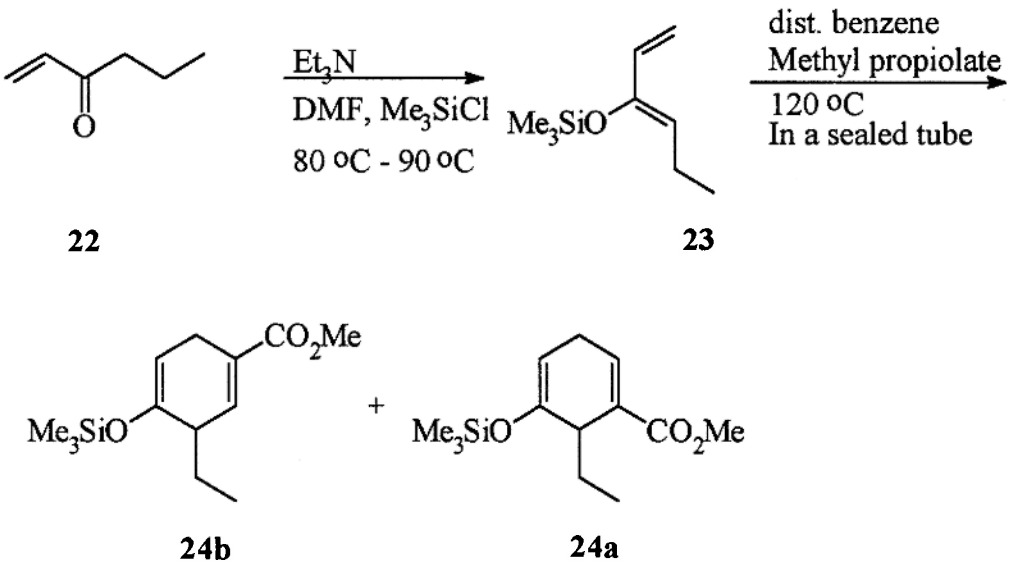


16 **17** **18** **19**

In turn, **17** reacted with methyl propylate (**25**) under thermal conditions similar to those that we developed for reactions of diethylfumarate.[20] To a benzene solution of **17** (1 equiv.) was added methyl propiolate (**25**) and heated (100 ^{0}C) for 12 hours. After column chromatographic separation we isolated compound **18** in 50% yield we also isolated ketone **19** in 45% yield from the same reaction after column chromatography. The desired silyl ether compound **18** was hydrolyzed to the corresponding ketone in silica gel column.

We extended our effort to synthesize **24b** by using 1-hexene-3-one (**22**) instead of methyl vinyl ketone to react with methyl propiolate under similar reaction conditions as that of Scheme 3.2. .

Scheme 3.2

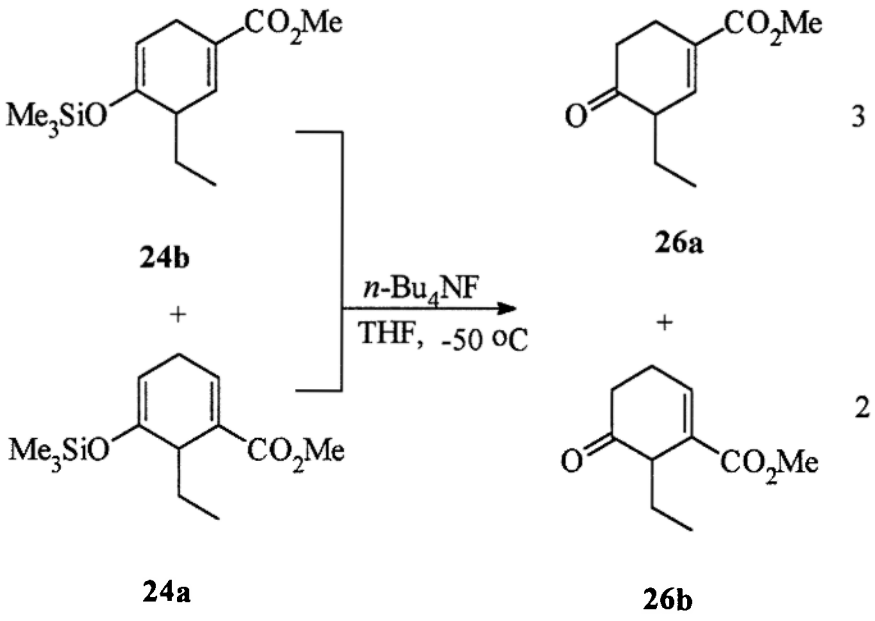


22 **23**

24b **24a**

During the column chromatography, the products **24b**, and **24a** were hydrolyzed to the corresponding ketones **26a**, **26b**, (as we saw in the model reaction) and the mixture of **24a** and **24b** was isolated in 23% yield. According to the original plan the next step was the conversion of **24b** to the corresponding ketone **26a**. We carried out this reaction without doing an aqueous work up. The crude product of the mixture of **24a**, and **24b** was stored on a silica gel column for 2 days. But the silyl ether compounds **24a** and **24b** did not convert to ketones completely, as we expected. Because of these results the desilylation reaction step (as shown in Scheme 3.3) was carried out with the crude product of the mixture of **24a** and **24b** (2 : 3 ratio, determined by ^{1}H NMR) with tetrabutylammonium fluoride at -50 °C for 30 minutes and gave

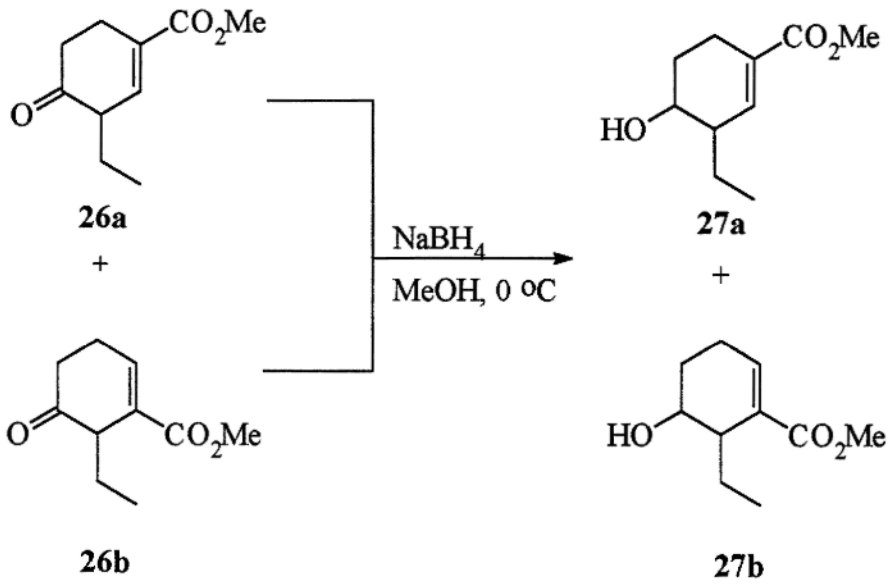
Scheme 3.3



26a and **26b** in a ratio of 3 : 2 (determined by ^{1}H NMR). The overall yield of the mixture of **26a** and **26b** was 33% from compound **23**. The ^{1}H NMR indicates 2 different vinylic protons at 6.8 ppm (dt, J = 4.6, 1.3 Hz ; **26a**) and 7.2 ppm (t, J = 4.2 Hz ; **26b**) corresponding to **26a** and **26b** respectively.

Then this inseparable mixtute of ketones **26a** and **26b** (3 : 2 ratio) was reduced to the corresponding alcohols **27a** and **27b** using sodium borohydride (Scheme 3.4).

Scheme 3.4

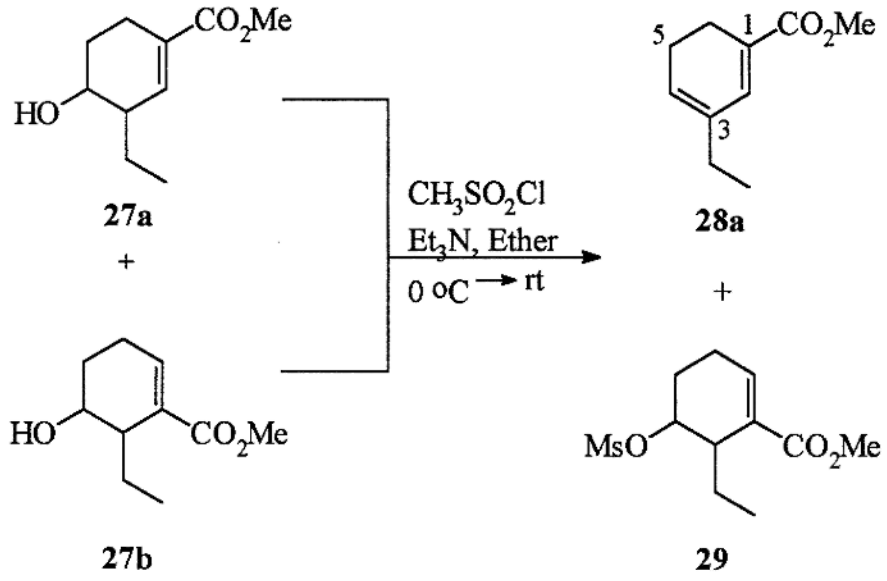


The mixture of alcohols **27a** and **27b** were obtained in 3 : 2 ratio (determined by ^{1}H NMR). Unfortunately, neither the alcohols **27a** and **27b**, nor their *cis* and *trans* stereoisomers are seperable under the conditions we used.

In an effort to construct the target molecule E-ring (**28**) using Diels-Alder reaction, unusual problems were encountered and unexpected isomers formed. Finally,

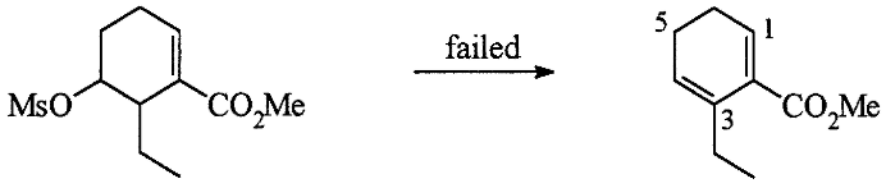
a different procedure was developed to construct the E-ring moiety. These results are discussed in Chapter 4. However the inseparable alcohols **27a** and **27b** (3 : 2 ratio) were treated with methanesulfonyl chloride (MsCl) to give the desired product **28a** (E-ring) in 30% yield (Scheme 3.5) and mesylated product **29** in 51% yield.

Scheme 3.5



An attempt was made to dehydromesiylate the mesylated product to produce the corresponding diene by using 1,5-diazabicyclo[4, 3, 0]non-5-ene (DBN) (Scheme 3.6), but the reaction was not successful (recovered starting material **29**, 52% yield) . The reaction was not studied further.

Scheme 3.6.



29 **28b**

Structure **29** was further studied by Dr. Hua using a ^{1}H NMR and 2D COSY experiment.

Vinylic proton (C1H) of compound **28b** is more shielded than vinylic proton (C2H) of compound **28b**. We would expect a triplet (J = ~3.8 - 4.2 Hz) with downfield shift (around 6.8 ppm) for C1H of **28b**. Vinylic proton (C2H) of compound **28a** indicates a doublet (page 81) at 6.9 ppm with a small coupling constant (J = 1.3 Hz).

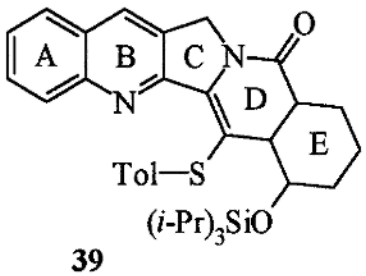
CHAPTER 4

MODEL STUDY FOR THE SYNTHESIS OF 6 VIA FRIEDLANDER REACTION

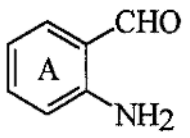
Because of the unexpected purification problems of compounds **15**, **13a**, and **12** (as mentioned in Chapter 2), an approach for the construction of the pentacyclic ring system utilizing a Friedlander condensation reaction was planned. A model study of this approach was investigated.

A simple disconnection approach for the construction of the pentacyclic ring system **39** (a model), using a Friedlander synthesis reaction is outlined below (Scheme 4.1).

Scheme 4.1

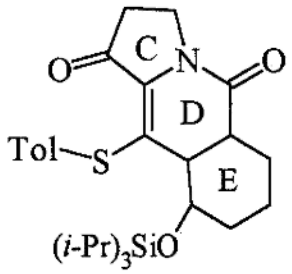


39



30

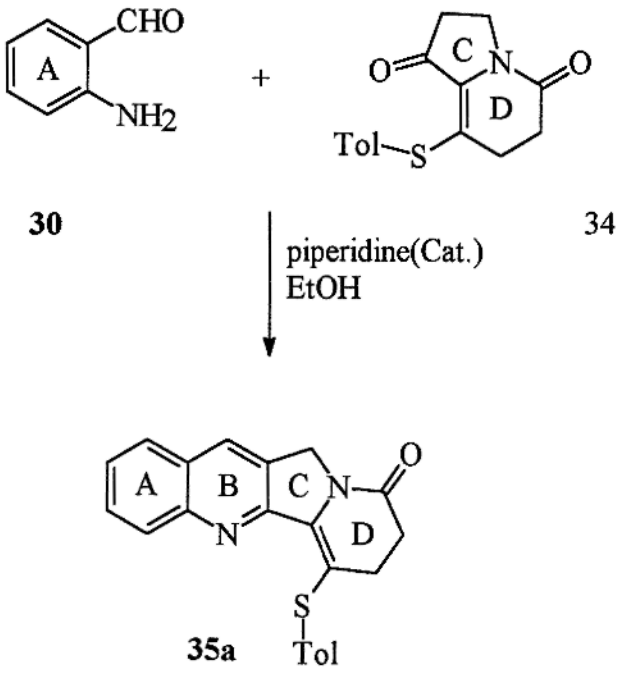
+



38

A model study of this approach was investigated. In the model study, two important model reactions were attempted. First, the Friedlander condensation reaction used piperidine as a condensation reagent for the construction of the A, B, C, D ring system **35a** (Scheme 4.2). For this model reaction, 8 mg (0.034 mmol) of indolizidinone **34** and 2-aminobenzaldehyde (**30**) were used. The desired product **35a** was obtained in a small amount using a preparative thin layer chromatographic (PTLC) purification method. The bicyclic ring **34** was obtained from the known bicyclic ring system **31**[21] (to be discussed later in this chapter). Unfortunately we were not able to repeat this reaction because of lack of the ketimine compound **31**.

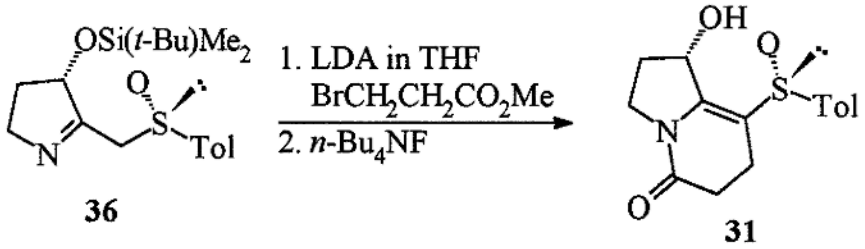
Scheme 4.2



Construction of C, D ring system 34 from known bicyclic ring system 31[28]

The compound **31** was synthesized by a previous student in Dr. Hua's laboratory, on treatment of (3*S* S*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3H-pyrrole (**36**) with LDA and methyl 3-bromopropionate followed by deprotection of the alcohol with *n*-Bu_4NF to give **31** (Scheme 4.3). The oxidation of the alcohol group in the known bicyclic ring system **31**, using the oxidizing agent pyridium chlorochromate (PCC) in methylene chloride, was attempted. In this case, the oxidation at the C-1 position of the bicyclic ring system was not successful (Scheme 4.3). In this attempt only starting material **31** was recovered.

Scheme 4.3



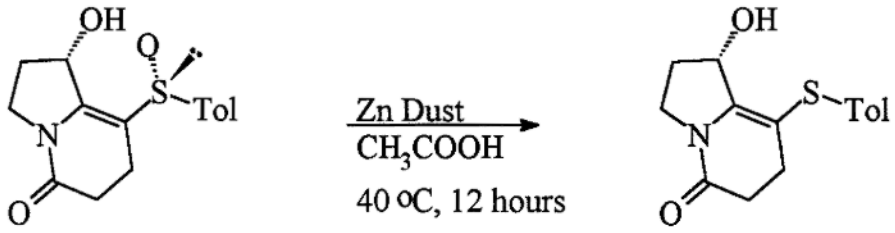
36 **31**

CH_2Cl_2
PCC
3 Å molecular sieves
rt.

recovered some starting material

This unsuccessful attempt is explained by considering the complexation of the sulfinyl group with chromium metal that hinders the approach of the chromate group for the oxidation reaction or the chelating effect of the O-atom of the sulfinyl group with chromium metal. Because of this unsuccessful attempt, the subsequent reduction reaction of the sulfinyl group using activated Zn dust in acetic acid was carried out (Scheme 4.4). The compound **33** was obtained in 83% yield.

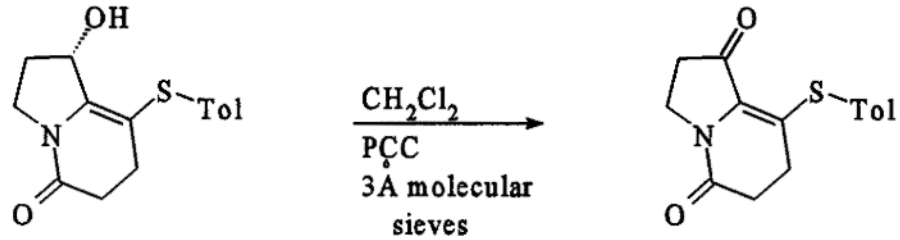
Scheme 4.4



31 **33**

Then treatment of hydroxy compound **33** with pyridium chlorochromate (PCC) in methylene chloride provided the corresponding ketone **34** in 46% yield (Scheme 4.5), and recovered starting material **33** in 5% yield.

Scheme 4.5

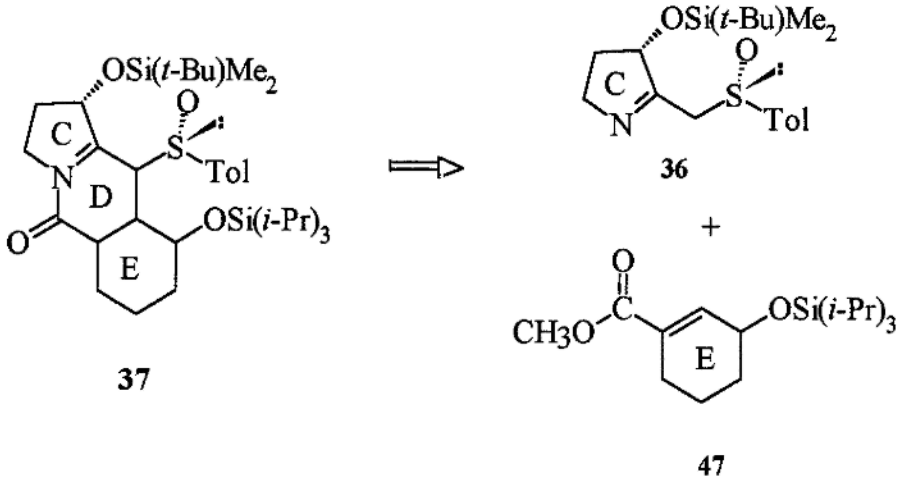


33 **34**

After its successful synthesis, diketone **34** was then condensed with *o*-aminobenzaldehyde (**30**) to give a low yield of tetracyclic ring system **35a** (as shown in Scheme 4.2), following purification by the preparative thin layer chromatographic (PTLC) method. Some starting material **34** was recovered. Unfortunately we were not able to study this condensation reaction further, because of lack of bicyclic ketone **31**.

A simple disconnection approach for the second model reaction is described in Scheme 4.6. In this second model reaction, the 1,4 addition reaction of known chiral α-sulfinyl ketimine **36**[28a,28b] with ene ester **47** was attempted. In this model reaction an interesting and challenging part was the synthesis of the E-ring (**47**).

Scheme 4.6

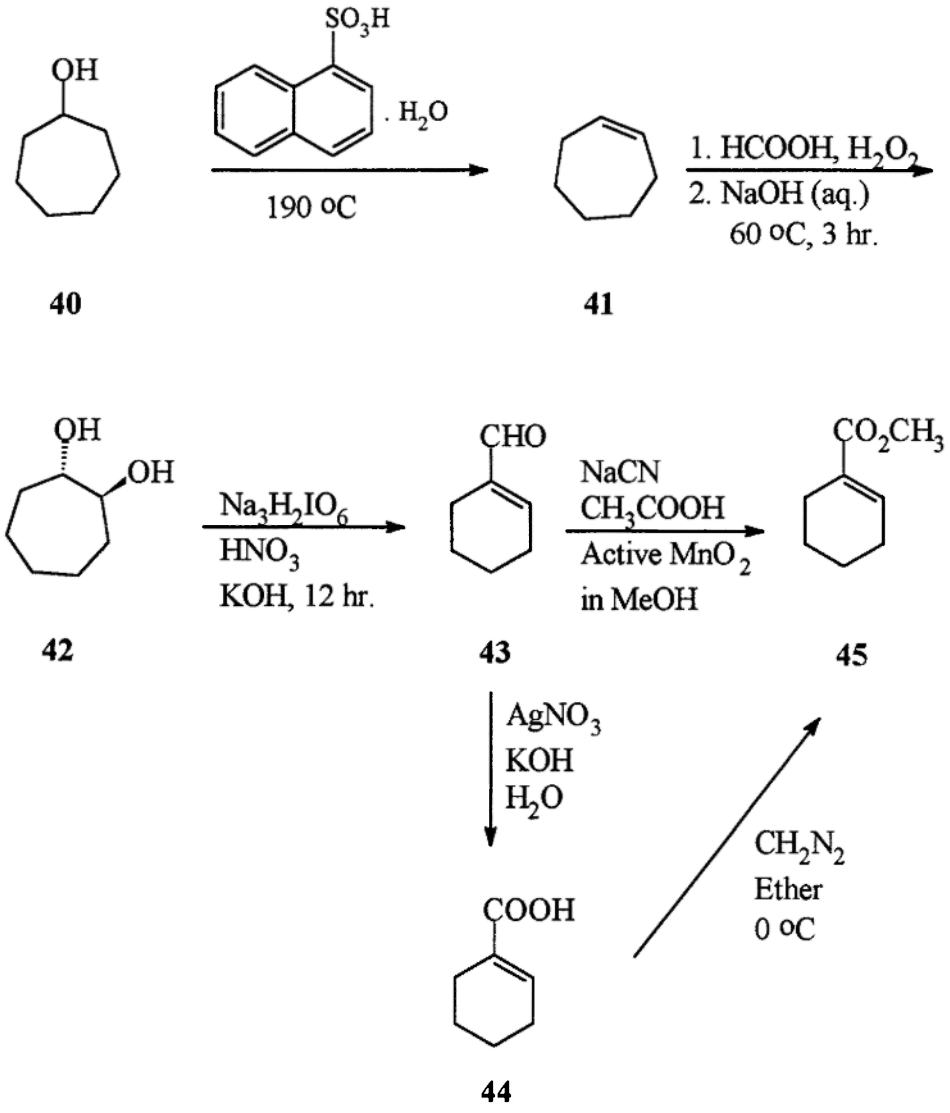


Construction of the E-ring 47 for the second model reaction

Cycloheptanol was treated with 1-napthalenesufonic acid[22] at 190 °C to give the corresponding alkene **41** in 91% yield (Scheme 4.7). Oxidation of alkene **41** with

hydrogen peroxide gave *trans*-diol **42** in 72% yield.[23] The diol then treated with sodium periodate to give aldehyde **43** in 90% yield. The esterification of **43** using

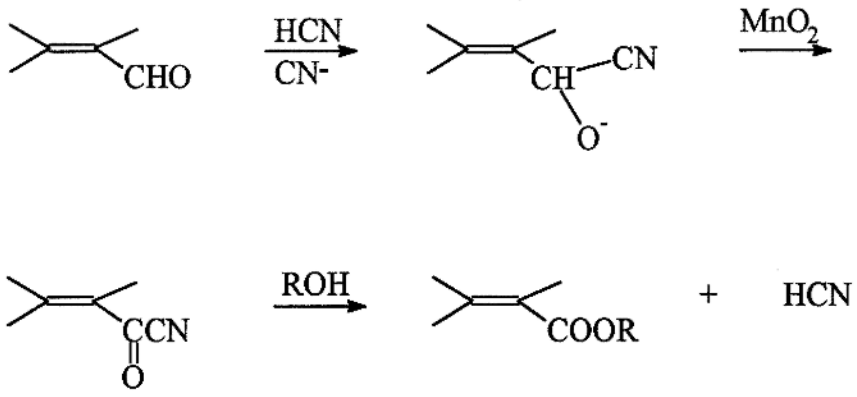
Scheme 4.7



activated manganese dioxide[24] (in MeOH) in the presence of HCN and sodium cyanide gave the desired ester **45**. Manganese dioxide[24] is an effective and selective

oxidizing agent that cleanly converts allylic aldehydes to conjugated ester[25] without significant further oxidation to carboxylic acids (Scheme 4.8). It was anticipated, however, that in the presence of HCN and cyanide ions a conjugated aldehyde would be converted to the cyanohydrin, which could be susceptible to

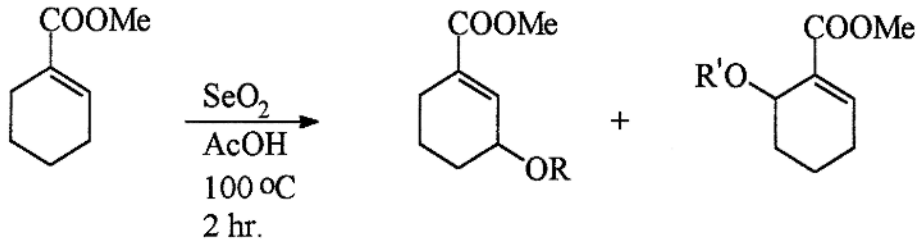
Scheme 4.8



further oxidation by manganese dioxide to an acyl cyanide leading finally in an alcoholic medium to an ester.

After its successful synthesis from cycloheptanol (**40**) (Scheme 4.7) methyl 1-cyclohexene-1-carboxylate (**45**), was then oxidized (Scheme 4.9) using selenium

Scheme 4.9



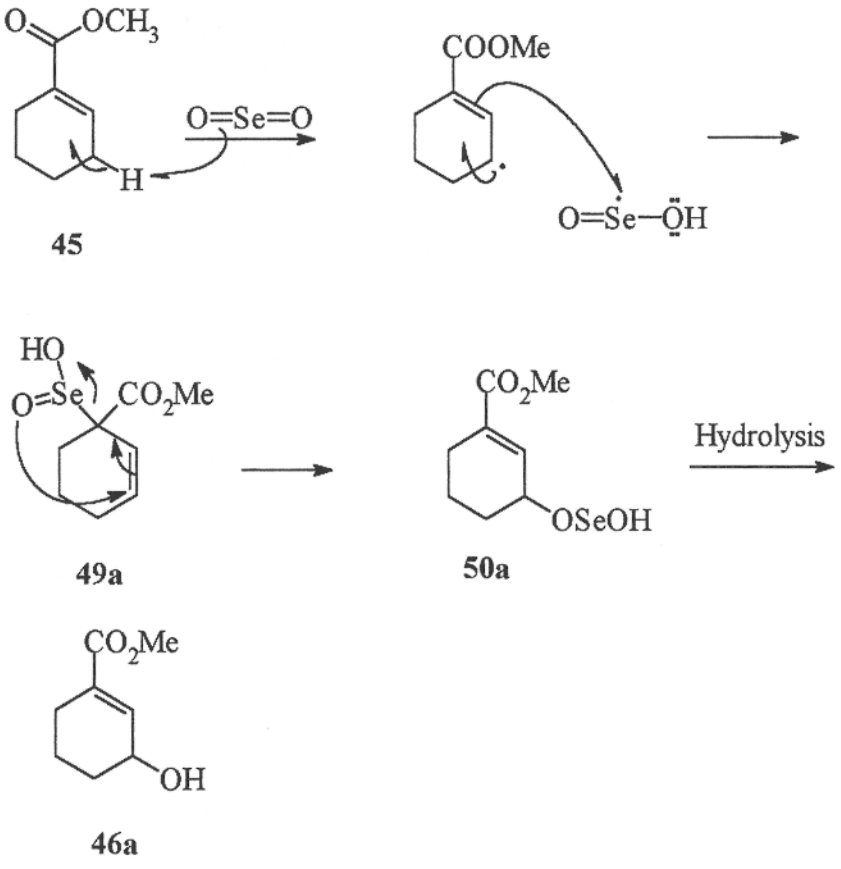
45

46a R = H (40%) **46b** R' = H (20%)
48a R = Ac (5%) **48b** R' = Ac (16%

dioxide in acetic acid as an oxidizing agent, under refluxed condition to furnish the desired alcohol **46a** in 40% yield and its corresponding acetate **48a** in 5% yield. The isomeric C-2 alcohol **46b** and its corresponding acetate **48b** were isolated in 20% yield and 16% yield, respectively.

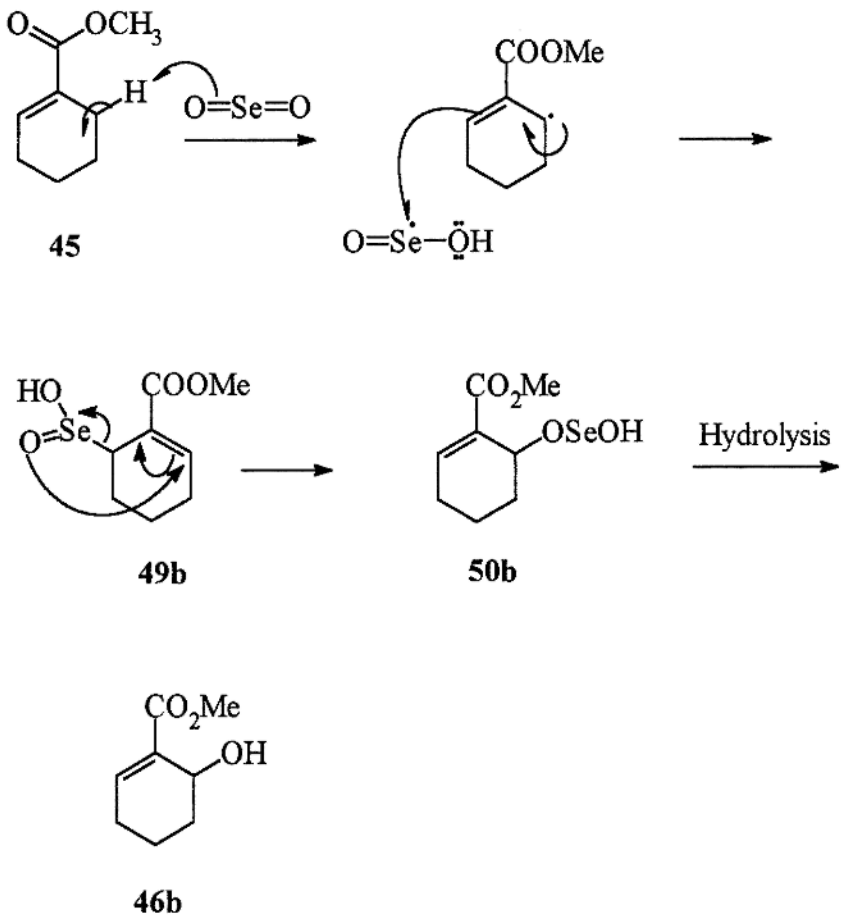
The oxidation of **45** with selenium dioxide probably involves the abstraction of the C-3-H (or C-6-H) of **45** by selenium dioxide followed by the formation of allylic selenic acid **49a** (or **49b**) (Scheme 4.10, and Scheme 4.11).

Scheme 4.10



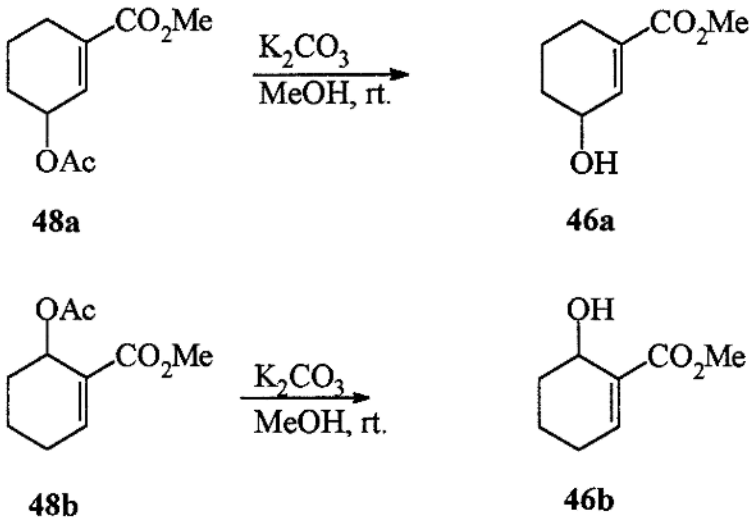
Subsequently **49a** (**49b**) undergoes a [2,3]-sigmatropic rearrangement[26] to provide selenate **50a** (**50b**), which was then hydrolyzed to form the corresponding alcohol **46a** (**46b**).

Scheme 4.11



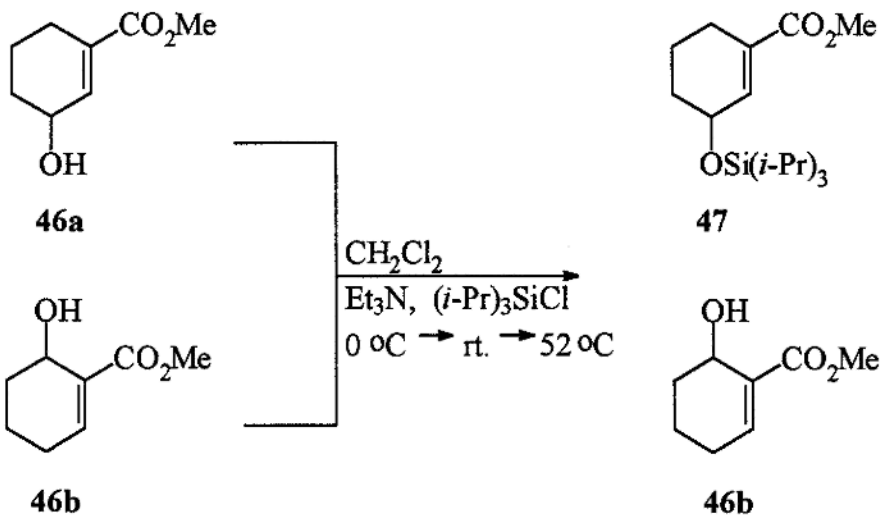
Deacetylation of acetate **48a** and **48b** separately, with potassium carbonate in MeOH gave **46a** (crude product, 86% yield) and **46b** (crude product, 68% yield) (Scheme 4.12).

Scheme 4.12



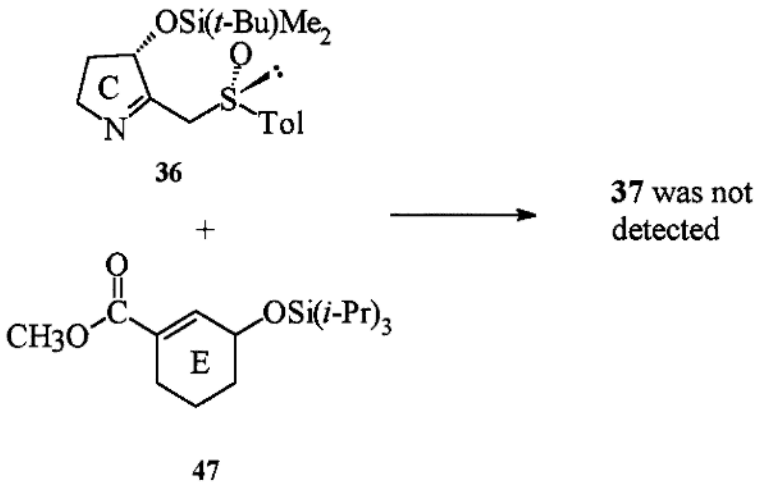
Finally, the mixture of alcohols **46a** and **46b** (2 : 1 ratio) was treated with 3 equiv. of triisopropylsilyl chloride in methylene chloride (Scheme 4.13) in the presence of Et_3N and 4-dimethylaminopyridine at 52 ^0C to furnish the desired protected alcohol **47** in 42% yield. The starting materials **46a** and **46b** were recovered in 2 : 1 ratio (determined by ^1H NMR), after column chromatography (Scheme 4.13). The alcohol **46b** did not give the corresponding protected alcohol, perhaps due to the H-bonds between the H atom of hydroxyl group and the O atom of carbonyl group.

Scheme 4.13



An attempted coupling reaction of **47** with the anion of α-sulfinyl ketimine **36**[28a, 28b] was not successful (Scheme 4.14). The reaction was not studied further.

Scheme 4.14



EXPERIMENTAL SECTION

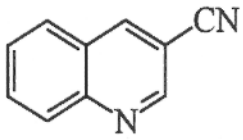
General : Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were obtained on a Varian-400 NMR spectrometer using 400 MHz for H, 100 MHz for ^{13}C using $CDCl_3$ as the solvent. H spectra are reported in ppm (δ units) down field of internal tetramethylsilane (TMS). ^{13}C spectra are reported in ppm (δ units) using $CDCl_3$ (77 ppm) as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer 1330 spectrometer. Optical rotations of optically active compounds were determined with a Perkin-Elmer 241 Polarimeter. Mass spectra were obtained from a Hewlett Parkared GC/HPLC 5989A mass spectrometer using either EI, CI or FAB (*m*-nitrobenzyl alcohol was used as the matrix).

Dried THF and ether were obtained by distillation over Na-benzophenone prior to the reaction. Methylene chloride, triethylamine, and DMF were distilled over CaH_2. Chloroform was distilled over phosphorus pentoxide. Methanol was distilled over Mg. Flash chromatography was performed by using Davisil silica gel (Grade 643, 230-425 mesh). Merck precoated TLC plates, silica gel 60F-254, were used in TLC analysis.

1. Preparation of W-2 Raney Ni[18]

To a solution of 64 g (1.6 mol) of NaOH in 250 mL of distilled water (contained in a 125-mL Erlenmeyer flask equipped with a large magnetic stirring bar) was added 50 g of 50/50 nickel-aluminum powder in small portions at 0 ^{0}C. When all the alloy had been added (about 30 min.), the Erlenmeyer was removed from the ice bath, and the contents were allowed to warm to room temperature without stirring. After the evolution of hydrogen became slow, the reaction mixture was allowed to heat on a steam bath overnight. After heating (often the evolution of hydrogen again became slow) the nickel was allowed to settle and most of the liquid was decanted. Distilled water was then added to bring the solution to the original volume. Then the nickel was suspended by stirring, again allowed to settle and the solution was decanted. The nickel was then transferred to a 50-mL Erlenmeyer flask with the aid of distilled water, and the water was again decanted. A solution of 8.4 g (0.21 mol) of NaOH in 84 mL of distilled water was added to the nickel. The catalyst was suspended and allowed to settle and the alkali was decanted. The nickel was washed by suspension in distilled water (about 35 mL) until the washing were neutral. Then the nickel was washed 10 more times with distilled water (50 mL each) to remove the alkali completely. The washing process was repeated three times with 8.4 mL of 95% ethanol and three times with absolute ethanol (20 mL each). W-2 Raney nickel was then stored in a tightly closed bottle under absolute ethanol in a refrigerator.

2. Synthesis of 3-quinolinecarbonitrile (7b)[15,16]



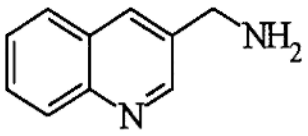
To a solution of 1.3 g (6.26 mmol, 0.85 mL) of 3-bromoquinoline (**7a**) in 20 mL of DMF was added 1.15 eq (7.2 mmol, 645 mg) of copper cyanide. The reaction mixture was stirred for 9 hours under refluxed condition. To the above hot mixture was added a mixture of ethylene diamine and water (1 : 3) (20 mL). The dark blue aqueous layer was extracted 4 times with CH_2Cl_2 (70 mL each). The organic layer was washed with 50 mL of 10% aqueous NaCN, washed with 50 mL of distilled water, dried ($MgSO_4$), and concentrated. The solvent (DMF) was distilled off (12 mm Hg, bp. 42 °C) , and the residue was column chromatographed on silica gel (33 x 5 cm column) using a gradient mixture of hexane and ether solvent system as eluant to give 93% yield (based on recovered starting material) of the desired product **7b** and 6.8% of starting material **7a**.

^{1}H NMR : 9.1 (d, J = 1.8 Hz, 1 H, C2H), 8.6 (d, J = 1.8 Hz, 1 H, C4H), 8.2 (dd, J = 8, 1 Hz, 1 H, C8H), 7.9 (m, 2 H, C7H and C5H, overlap), 7.7 (td, J = 8, 1 Hz, 1 H, C6H).

^{13}C NMR : 149.4 (d, C2), 148.5 (s, C8a), 141.2 (d, C4), 132.5 (d, C8), 129.6 (d, C5), 128.2 (d, C7), 128 (d, C6), 125.9 (s, C3), 116.9 (s, C4), 106.3 (s, CN).

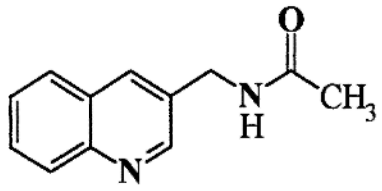
3. Reduction of 3-quinolinecarbonitrile (7b) with W-2 Raney Ni

Synthesis of 3-(aminomethyl)quinoline (8)[17]



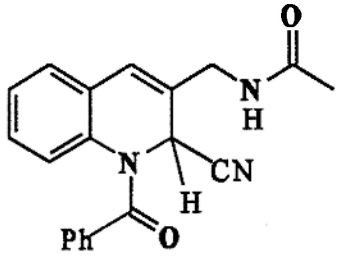
To a three-necked round-bottomed flask under a H_2 atmosphere, 357 mg (2.32 mmol) of nitrile **7** was added followed by 5 mL of distilled MeOH via syringe. The mixture was stirred at room temperature until the solid was dissolved. Then it was cooled to 0 °C, and NH_3 gas was introduced over 5 minutes. Then the reaction became cloudy and the substrate precipitated. Then the mixture was warmed up to room temperature and 2 mL of distilled MeOH was added to redissolved the substrate. One big spatula of freshly prepared W-2 Raney Ni was added. The reaction mixture was stirred at room temperature for 2.5 hours. The reaction mixture was filtered through Celite, the filter cake was washed carefully three times with MeOH : NH_4OH (aqueous ; concentrated) = 19 : 1 mixture (20 mL each). The filtrate was concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant to give 0.3 g (88% yield) of the desired product **8**. H NMR : 8.9 (d, J = 2 Hz, 1 H, C4H), 8.1 (broad d, J = 2 Hz, 2 H, C8H and C2H overlap), 7.8 (d, J = 8 Hz, 1 H, C5H), 7.7 (t, J = 8 Hz, 1 H, C7H), 7.5 (t, J = 8 Hz, 1 H, C6H), 4.1 (s, 2 H, CH_2), 3.5 (broad s, 2 H, NH_2) ^{13}C NMR : 150.7 (d, C2), 147.2 (s, C8a), 134.6 (s, C3), 133.6 (d, C4), 129.4 (d, C8), 127.9 (d, C5), 127. 8 (s, C4a), 127.5 (d, C7), 126.7 (d, C6), 43.6 (t,

4. 3-(*N*-Acetylaminomethyl)quinoline (9)



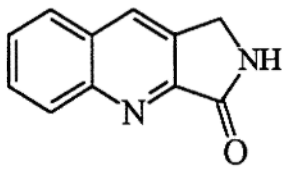
To a solution of 1.7 g (10.8 mmol) of **8** in 57 mLof CH_2Cl_2 was added 2 eq of Et_3N (21.6 mmol) and 1.1 eq of acetic anhydride (11.9 mmol) at 0 ^{0}C. The reaction mixture was stirred further at 0 ^{0}C for 5 minutes. Then it was slowly warmed up to room temperature. After stirring 3 hours at room temperature, the mixture was diluted with 30 mL of 1 *N* NaOH solution, and washed with 150 mL of brine solution. The water layer was extracted 3 times with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (5 x 20 cm column), using a gradient mixture of hexane and ethyl acetate as eluant to give 1.75 g (81% yield) of **9** as yellow solid. Mp 80 ^{0} - 82 ^{0}C. ^{1}H NMR : 8.8 (d, J = 2 Hz, 1 H , C2H), 8.1 (d, J = 8.5 Hz, 1 H, C8H), 8.1 (d, J = 2 Hz, 1 H, C4H), 7.8 (d, J = 8 Hz, 1 H, C5H), 7.7 (ddd, J = 8.5, 8.0, 1.2 Hz, 1 H, C7H), 7.6 (td, J = 8.0, 1.2 Hz, 1 H, C6H), 6 (broad s, 1 H, NH), 4.6 (s, 2 H, CH_2N), 2.1 (s, 3 H, MeCO).

5. 3-[(*N*-Acetylamino)methyl]-2-cyano-1-(benzoyl) 1,2-dihydroquinoline (10)[14]



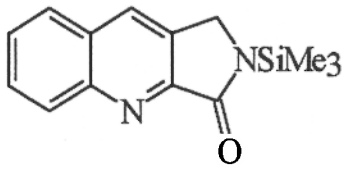
To a cold (0 °C) stirred suspension of 0.3846 g (1.9 mmol) of amide **9** and 0.75 g (6 eq, 11.4 mmol) of KCN in 3.5 mL of water, 0.9 g (6.4 mmol) of benzoyl chloride was added portionwise over 15 minutes and the reaction mixture was stirred for a further 2 hours at room temperature. The crystals which separated were filtered off, washed with water (10 mL), and dissolved in 18 mL of CH_2Cl_2. The CH_2Cl_2 layer was washed with water (75 mL). The water layer was extracted 3 times with CH_2Cl_2 (125 mL each). The combined organic layer was dried ($MgSO_4$), and concentrated to give 0.5 g (50% yield) of crude product. ^{1}H NMR : 7.5 (t, J = 7.2 Hz, 1 H, *p*-H, Ph), 7.4 (d, J = 7.2 Hz, 2 H, *o*-H, Ph), 7.3 (t, J = 7.2 Hz, 2 H, *m*-H, Ph), 7.27 (dd, J = 8.0, 2.0 Hz, 1 H, C8H), 7.16 (td, J = 7.5, 1.0 Hz, 1 H, C7H), 6.99 (td, J = 8.0, 2.0 Hz, 1 H, C6H), 6.77 (s, 1 H, C4H), 6.64 (d, J = 8.0 Hz, C5H), 6.1 (s, 1 H, C2H), 5.84 (broad s, 1 H, NH), 4.3 (dd, J = 15.0, 5.5 Hz, 1 H, CH_2N), 4.2 (dd, J = 15.0, 5.5 Hz, 1 H, CH_2N), 2.1 (s, 3 H, NCOMe).

6. 2,3-Dihydro-1H-3-oxo-pyrrolo[3, 4-b]quinoline (11)[14]



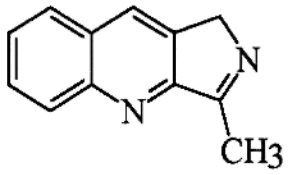
To a cold (0 °C) solution of 2.59 g (7.8 mmol) of **10** in 60 mL of $CHCl_3$ and 25 mL of absolute f-dioxane, HCl-gas was introduced while the solution was stirred, till the beginning of turbidity appeared (about 15 minutes). After being stirred at 0 °C overnight (HCl gas inlet was disconnected) the precipitated solid was separated. The resulting solid (5.31 g) was dissolved in 68.7 mL of water and the refluxed with 0.35 mL of 2 *N* HCl for 20 hours. Then the mixture was cooled to room temperature and was suspended in 10% aqueous sodium carbonate (pH = 8 - 9). The solution was extracted 5 times with $CHCl_3$: MeOH = 5 : 1. The organic layer was dried ($MgSO_4$), and concentrated. The pure desired product **11** (by ^{1}H NMR) was obtained in 69% yield (0.99 g). The mother - liquor from the filtration of the refluxed reaction mixture was treated with 10% sodium carbonate (pH = 8 - 9), worked up in the same way as above, and column chromatographed on silica gel using a gradient mixture of ethyl acetate and methanol as eluant to give 0.15 g of desired product **11**. The total yield was 79% (total product 1.14 g). ^{1}H NMR : 8.4 (d, J = 8.7 Hz, 1 H, C8H), 8.3 (s, C9H), 7.9 (d, J = 8.7 Hz, 1 H, C5H), 7.8 (t, J = 8.7 Hz, 1 H, C7H), 7.68 (t, J = 8.7 Hz, 1 H, C6H), 6.9 (broad s, 1 H, NH), 4.67 (s, 2 H, CH_2).

7. 2,3-Dihydro-1H-3-oxo-2-(trimethylsilyl)-pyrrolo[3, 4-b]quinoline (12)



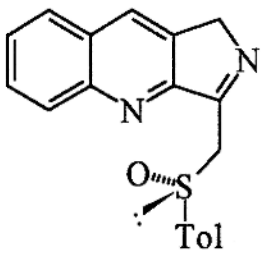
To a solution of 0.1 g of **11** (0.543 mmol) in 1.2 mL of distilled toluene was added 0.15 mL of distilled Et_3N (1.5 mmol). The mixture was stirred at 40 °C for 15 minutes. Then 0.14 mL (1.3 mmol) of distilled chlorotrimethylsilane (Me_3SiCl) (Chlorotrimethylsilane was distilled over CaH_2 under argon and then kept with 20% Et_3N in a bottle). The precipitated Et_3N^+HCl was not used only the upper clear liquid was added, and stirred further for 4 hours. Then the solvent was evaporated to give 37% (by NMR) of desired product **12** and 63% of starting amide **11**. ^1H NMR : 8.4 (d, J = 8.7 Hz, 1 H, C8H), 8.2 (s, 1 H, C9H), 7.9 (d, J = 8.2 Hz, 1 H, C5H), 7.8 (ddd, J = 10.6, 9.1, 2.0 Hz, 1 H, C7H), 7.6 (ddd, J =8.20, 6.87, 1.22 Hz, 1 H, C6H), 4.6 (d, J = 0.99 Hz, 2 H, CH_2N), 0.5 (s, 9 H, $SiMe_3$). The impurities were triethylamine hydrochloride and bis(trimethylsilyl)ether. This reaction was also conducted by Corrie Carnes and Dr. Hua, and ^1H NMR indicated 90% of product **12** and 10% of starting material **11**. Compound **11** must have formed in the NMR tube from the hydrolysis of **12** with the trace amount of water in the NMR tube and solvent. Hence this crude product (presumably 100% **12**) was used in next step without further purification.

8. 3-Methyl-1H-pyrrolo [3, 4-b]quinoline (13a)



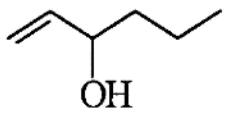
To a solution of 0.1 g (0.391 mmol) of **12** (crude product from the previous reaction) in 5 mL of distilled THF was added 1.2 mL (1.583 mmol) of a 1.4 M ether solution of MeLi at -78 °C under argon. The yellow color solution turned to dark green immediately. Then the mixture was stirred at -78 °C for 30 minutes. Then it was warmed up to 0 °C. After being stirred at 0 °C for 2 hours, the reaction was then worked up by diluting with CH_2Cl_2 (50 mL) and washing with 30 mL of water. The water layer was extracted 3 times with CH_2Cl_2 (75 mL each), and the combined organic layer was dried ($MgSO_4$) and concentrated to give 59 mg (60%) of crude product. ^{1}H NMR of the crude product indicates the desired product **13a** and undesired product **13b** in 2 : 1 ratio (determined by ^{1}H NMR). ^{1}H NMR : **13a** : 8.0 (d, J = 8.6 Hz, 1 H, C8H), 7.95 (s, 1 H, C9H), 7.7 (d, J = 7.5 Hz, 1 H, C5H), 7.66 (t, J = 7.5 Hz, 1 H, C7H), 7.5 (t, J = 7.64 Hz, 1 H, C6H), 4.6 (d, J = 5.8, 2 H, CH_2N), 2.7 (s, 3 H, Me). **13b** : 7.8 (d, J = 8.2 Hz, 1 H, C8H), 7.3 (t, J = 7.14 Hz, 1 H, C7H), 6.7 (t, J = 7.2 Hz, 1 H, C6H), 6.6 (d, J = 7.1 Hz, 1 H, C5H), 6.3 (s, 1 H, C9H), 4.6 (d, J = 4.9, 2 H, CH_2N), 1.2 (s, 3 H, CH_3). Column chromatographic separation of the crude product gave a very small amount of **13a** indicating that the product hydrolyzes on the silica gel column.

9. (*R*)-3-[[(4-Methylphenyl)sulfinyl]-methyl]-1H-pyrrolo[3, 4-b]quinoline (15)



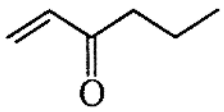
To a cold solution of 30 mg (0.165 mmol) of crude product of ketimine **13a** (obtained from the previous reaction) in THF (1 mL) at -78 °C under argon was added 0.2 mmol (28 μL) of lithium diisopropylamide (LDA) solution (-30 °C) via cannula. The resulting yellow solution was stirred at -78 °C for 30 minutes, then a cold solution of *l*-(-)-(S)-menthyl *p*-toluenesulfinate **14S** (1.2 eq, 0.198 mmol, 58 mg) in THF (1 mL) was added via cannula. The solution was stirred at 78 °C for 30 minutes and then at 0 °C for 30 minutes. Then the mixture was diluted with CH_2Cl_2 and washed with brine solution. The organic layer was dried (Na_2SO_4) and concentrated. The ^1H NMR indicates mainly *l*-menthyl *p*-touenesulfinate **14** and a trace amount of the desired product. The column chromatography was not successful.

10. 1-Hexene-3-ol (21)



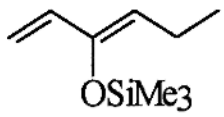
To a cold (-30 ^{0}C) solution of 18.75 mL (15 g, 0.21 mol) of butyraldehyde (**20**) in 300 mL of distilled ether was added 1 eq (210 mL) of vinylmagnesium bromide (1 M solution in tetrahydrofurane) under argon. The mixture was stirred further for 15 minutes. It was warmed up to 0 ^{0}C and stirred for 2 hours. To the reaction mixture, water was then added and the resulting solution was extracted with ether. The ether layer was dried ($MgSO_4$), and distilled under normal pressure to give 1-hexene-3-ol (**21**) (bp 134 ^{0} - 135 ^{0}C). ^{1}H NMR : 5.8 (ddd, J = 17.0, 10.4, 6.2 Hz, 1 H, C2H), 5.2 (dt, J= 17.0, 1.4 Hz, 1 H, C1H), 5.1 (dt, J = 10.4, 1.4 Hz, 1 H, C1H), 4.1 (td, J= 12.0, 6.2 Hz, 1 H, C3H), 1.5 (m, 2 H, CH_2), 1.4 (m, 2 H, CH_2), 0.9 (t, J = 7.2 Hz, 3 H, Me).

11. 1-Hexene-3-one (22)



Alcohol **21** (1.84 g, 0.0184 mol) was dissolved in 31 mL of CH_2Cl_2 under argon and 3 Å molecular sieves (about 1 g) was added. Then 1.5 eq of pyridinium chlorochromate (PCC) (5.95 g, 0.0276 mol) was added into the mixture. The mixture was stirred at room temperature for 1 hour, filtered through Celite, washed with 70 mL of aqueous copper sulfate solution and then 50 mL of brine. The organic layer was dried ($MgSO_4$), and filtered. The desired product **22** was obtained in 59% yield (1.1 g) after distilling off the solvents under normal pressure. H NMR : 6.4 (dd, J = 17.6, 10.5 Hz, 1 H, C2H), 6.2 (dd, J = 17.6, 1.2 Hz, 1 H, C1H), 5.8 (dd, J = 10.5, 1.2 Hz, 1 H, C1H), 2.6 (t, J = 7.3 Hz, 2 H, C4H), 1.7 (sextet, J = 7.3 H, 2 H, CH_2), 0.98 (t, J = 7.3 Hz, 3 H, Me).

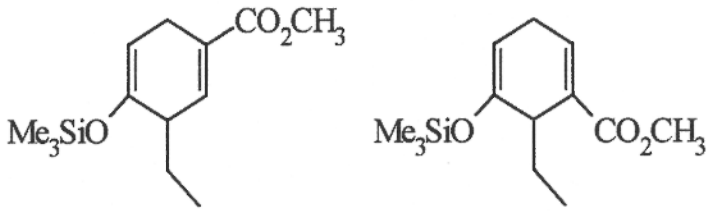
12. 3-(Trimethylsilyloxyl)-1,3-hexadiene (23)



An oven-dried 500 mL three-necked, round-bottomed flask was fitted with two oven dried additional funnels and a magnetic stirrer and placed in a 80 - 90 °C oil bath. Under argon, 8.1 g (0.083 mol) of propyl vinyl ketone (**22**) in 9.4 mL of distilled *N,N*-dimethylformamaide (DMF) and 24.14 g (28.2 mL, 0.222 mol) of distilled chlorotrimethylsilane (distilled over CaH_2 under argon) in 14.12 mL of distilled DMF were added separately from the two additional funnel over 30 minutes into a magnetically stirred solution of distilled Et_3N (25.88 g, 0.256 mol) in 128 mL of distilled DMF. The reaction gradually became darkened from light yellow to dark brown, and a precipitate of triethylamine hydrochloride was formed. The reaction was allowed to stirr at 90 °C overnight. The reaction was cooled to room temperature, filtered through Celite and transferred to a 1-L separatory funnel containing 96 mL of pentane. To this solution was added 380 mL of cold 5% sodium bicarbonate solution to facilitate the separation of phases and remove the DMF. The pentane layer was separated quickly and the aqueous layer was extracted twice with 100 mL portion of pentane. The pentane extracts were combined, washed with 64 mL of cold distilled water, dried over anhydrous Na_2SO_4, and filtered. The pentane and other volatile materials were removed by distillation under normal pressure with a vigreux column to remove low boiling materials, and then

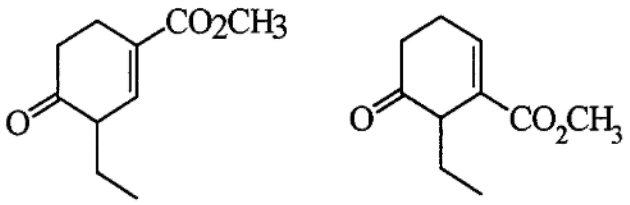
transferred to a 100-mL round-bottomed flask for fractional distillation under reduced pressure. A water aspirator vacuum was applied, and 4.2 g (33%) of diene **23** was distilled as a colorless oil at boiling point 90 - 95 °C/60 mm Hg. ^{1}H NMR : 6.2 (dd, J = 16.1, 10.7 Hz, 1 H, =CH), 5.3 (d, J = 17.1 Hz,, 1 H, =CH_2), 4.96 (d, J = 10.6 Hz, 1 H, =CH_2), 4.8 (t, J = 7.3 Hz, 1 H, C4H), 2.1 (pentet, J = 7.3 Hz, 2 H, CH_2), 0.98 (t, J = 7.3 Hz, 3 H, CH_3), 0.21 (s, 9 H, Me_3Si). Some impurities, Et N and hexamethyldisiloxane, were also contained in the product..

13. Methyl 3-ethyl-4-trimethylsilyloxy-1,4-cyclohexadiene-1-carboxylate (24b) and Methyl 3-ethyl-4-trimethylsilyloxy-1,4-cyclohexadiene-2-carboxylate (24a)



To a solution of 1.72 g (10.11 mmol) of **23** in 3 mL of distilled benzene under argon was added 1.1 eq (11.12 mmol, 0.93 g) of methyl propiolate (**25**) in a sealed tube. The mixture was heated at 120 °C for 12 hours. Then the mixture was cooled to room temperature, diluted with 20 mL of ether, transferred to a round bottom flask (used 30 mL of ether to rinse the tube), and concentrated to give 1.8 g (80% yield) of the crude product. The H NMR of crude product indicates the mixture of **24a** and **24b** in a ratio 2 : 3. Chemical shifts are derived from the crude H NMR. H NMR : **24b** : 6.8 (dt, J = 4.0, 1.7 Hz, 1 H, C2H), 4.9 (t, J = 3.4 Hz, 1 H , C5H), 3.74 (s, 3 H, OMe), 2.96 (m, 1 H, CH), 1.7 (m, 2 H, CH_2), 0.8 (t, J = 7.5 Hz, 3 H, Me), 0.2 (s, 9 H, Me_3Si). **24a** : 7.0 (t, J = 4.0 Hz, 1 H, C1H), 4.82 (t, J = 3.2 Hz, 1 H, C5H), 3.73 (s, 3 H, OMe), 2.98 (m, 1 H, C3H), 2.8 (m, 2 H, C6H), 2.1 (m, 2 H, CH_2), 0.7 (t, J = 7.5 Hz, 3 H, Me), 0.19 (s, 9 H, Me_3Si).

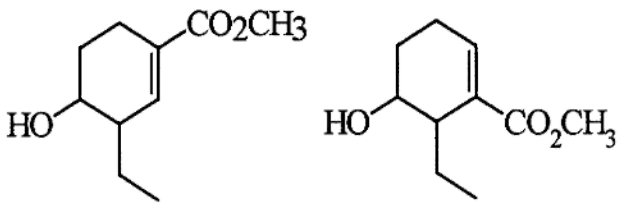
14. Methyl 3-ethyl-4-oxo-1-cyclohexene-1-carboxylate (26a) and methyl 3-ethyl-4-oxo-1-cyclohexene-2-carboxylate (26b)



To a solution of crude product of **24a** and **24b** (2 : 3 ratio ; obtained from the previous reaction) (1.8 g, 8 mmol) in 8 mL of THF under argon was added 1 eq (0.8 mL, 8 mmol, 1 M solution in THF) of *n*-Bu_4NF (*n*-tetrabutylammonium fluoride) at -50 °C via syringe. The reaction became yellow. After the reaction was stirred at -50 °C for 30 minuets under argon, 30 mL of NaCl solution was added, and the resulting solvent was extracted with ether. The ether layer was dried ($MgSO_4$), concentrated, and column chromatograph on silica gel using a gradient mixture of hexane, ether as eluant to give 0.6 g (33%, over all yield) of **26a** and **26b** in a ratio of 3 : 2 (determined by ^{1}H NMR). Chemical shifts are derived from a mixture of **26a** and **26b**. ^{1}H NMR of **26a** : 6.8 (dt, J = 4.6, 1.3, 1 H, C2H), 3.8 (s, 3 H, OMe), 3.4 (m, 1 H, C3H), 2.6 (m, 2 H, C5H), 2.34 (m, 2 H, C6H), 2.2 (m, 1 H, CH_2), 2.0 (dqd, J = 14.0, 7.5, 4.5 Hz, 1 H, CH_2), 1.03 (t, J = 7.5 Hz, 3 H, Me). ^{13}C NMR of **26a** : 210.8 (s, C4), 166.0 (s, OC=O), 138.5 (d, C2), 132.6 (s, C1), 51.7 (q, OMe), 49.6 (d, C3), 35.3 (t, CH_2), 25.6 (t, CH_2), 24.7 (t, CH_2), 10.9 (q, CH_3). H NMR of **26b** : 7.2 (t, J = 4.2 Hz, 1 H, C1H), 3.8 (s, 3 H, OMe), 3.2 (dd, J = 5.6, 4.5 Hz, 1 H, C3H), 2.6 (m, 2 H, C5H), 2.4 (m, 2 H, C6H), 2.24

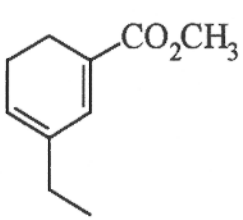
(m, 1 H, CH_2). 0.9 (t, J = 7.5 Hz, 3 H, Me). ^{13}C NMR of **26b** : 197.9 (s, C4), 172.5 (s, OC=O), 141.8 (s, C2), 139.6 (d, C1), 52.2 (q, OMe), 41.7 (d, C3), 36.6 (t, CH_2), 25.9 (t, CH_2), 22.3 (t, CH_2), 12.4 (q, Me).

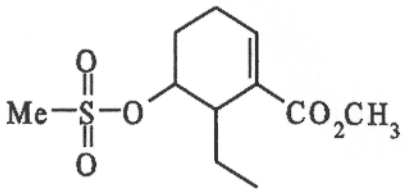
15. Methyl 3-ethyl-4-hydroxy-1-cyclohexene-1-carboxylate (27a) and methyl 3-ethyl-4-hydroxy-2-cyclohexene-2-carboxylate (27b)



To a solution of 169 mg (0.929 mmol) of **26a** and **26b** (3 : 2 ratio, determined by H NMR) in 8 mL of distilled MeOH was added 1.2 eq of sodium borohydride (42.3 mg, 1.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Methanol was removed by rotatory evaporation. The residue was then diluted with CH_2Cl_2 , added distilled water, and 2 drops of concentrated HCl. The aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$), concentrated, and column chromatography on silica gel using a gradient mixture of hexane, ether as eluant. But the column chromatograph was not completely successful, and obtained 0.1294 g (76% yield) of the partially pure mixture of **27a** and **27b** in a ratio of 3 : 2 (by H NMR). Chemical shifts are derived from the partially pure mixture of **27a** and **27b.** H NMR of **27a** : 5.6 (d, J = 7.3 Hz, 1 H, C2H), 3.96 (m, 1 H, C4H), 3.71 (s, 3 H, OMe), 2.75 (dt, J = 5.7, 5.5 Hz, 1 H, C3H), 0.99 (t, J = 7.5 Hz, 3 H, Me), 2.3 - 2.2 (a series of m, 2 H). ^{1}H NMR of **27b** : 6.83 (t, J = 3.8 Hz, 1 H, C1H), 4.13 (broad s, 1 H, C4H), 3.13 (broad m,1 H, C3H), 1.06 (t, J = 7.5 Hz, 3 H, Me), 1.8 - 1.6 (a series of m, 2 H). Due to the poor resolution, splitting did not show well.

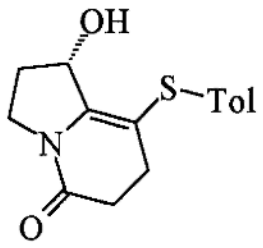
16. Methyl 3-ethyl-1, 3-cyclohexadiene-1-carboxylate (28a) and methyl 3-ethyl-4-mesyloxy-1-cyclohexen-1-carboxylate (29)





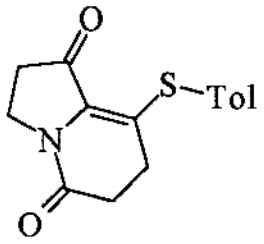
To a solution of 110 mg (0.598 mmol) of partially pure alcohols **27a** and **27b** (3 : 2 ratio) in 5 mL of distilled ether under argon was added 3 eq of distilled Et_3N (1.79 mmol, 0.25 mL) at 0 °C. To the resulting mixture was then added 70 μL of methanesulfonyl chloride (1.5 eq, 0.897 mmol). The reaction was stirred at 0 °C, then warmed up to room temperature for 3 hours under argon. Then the reaction was heated to reflux for 5 hours. Then the reaction mixture was diluted with 50 mL of ether, washed with 20 mL of brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant to give 30 mg (30% yield) of desired product **28a** and 51% yield of **29**. H NMR : **28a** : 6.9 (d, J = 1.3 Hz, 1 H, C2H), 5.8 (td, J = 4.4, 1.3 Hz, 1 H, C4H), 3.8 (s, 3 H, OMe), 2.4 (t, J = 9.7 Hz, 2 H, C6H), 2.2 (td, J = 9.7, 4.4 Hz, 2 H, C5H), 2.1 (q, J = 7.5 Hz, 2 H, CH_2), 1.04 (t, J = 7.5 Hz, 3H, Me). **29** : 6.86 (t, J = 3.7 Hz, 1 H, C1H), 4.9 (ddd, J = 16, 9, 4 Hz, 1 H, C4H), 3.7 (s, 3 H, OMe), 3.05 (s, 3 H, MeS), 3.0 (q, J = 4 Hz, 1 H, C3H), 2.4 (m, 2 H, C6H), 2.1 - 2.0 (a series of m, 2 H, CH_2), 1.7 (pentet, J = 7.4 Hz, 1 H, CH_2), 1.48 (pentet, J = 7.4 Hz, 1 H, CH_2), 1.0 (t, J = 7.4 Hz, 3 H, Me).

17. 1-Hydroxy-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfenyl]-5-indolizinone (33)



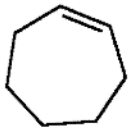
To a solution of 28 mg (96.2 mmol) of **31**[28] in 18.2 mL of acetic acid was added one spoonful of activated Zn dust under argon. The reaction mixture was stirred at room temperature for few minutes., and then heated at 45 °C overnight. Then the reaction mixture was diluted with 30 mL of ether, filtered through Celite, washed with 2 *N* NaOH solution (150 mL). Then the organic layer was washed with 15 mL of brine solution, dried ($MgSO_4$), and concentrated. The compound **33** was obtained in 83% yield (22 mg). $[\alpha]_D^{22} = +42.9^{\circ}$ (c, 1.105, CH_2Cl_2). ^{1}H NMR : 7.2 (d, J = 8 Hz, 2 H, Ar), 7.1 (d, J = 8 Hz, 2 H, Ar), 5.13 (dd, J = 6.4, 3.6 Hz, 1 H, CH-O), 3.82 (t, J = 6.1 Hz, 2 H, C3H), 2.57 (m, 2 H, C6H), 2.49 (m, 2 H, C7H), 2.3 (s, 3 H, *p*-Me), 2.18 (m, 2 H, CH_2). ^{13}C NMR : 176.3 (s, C5), 147.4 (s, C=), 139.8 (s, Ar), 131.2 (s, Ar), 130 (d, Ar), 128.6 (d, Ar), 102.8 (s, C=), 71.5 (d, C1), 43.99 (t, C3H), 31.6 (t, CH_2), 30.5 (t, CH_2), 27.4 (t, CH_2), 20.97 (q, *p*-Me).

18. 1-Oxo-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfenyl]-5-indolizinone (34)



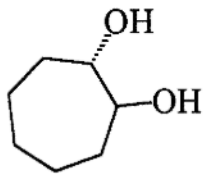
To a solution of 21.8 mg (79.3 mmol) of **33** in 2.2 mL of distilled CH_2Cl_2 under argon at 0 [C, was added 1.5 eq (25.64 mg, 118.95 mmol) of pyridinium chlorochromate (PCC) and 3Â molecular sieves. The mixture was stirred at room temperature for 30 minutes. The mixture was diluted with 10 mL ether, and passed through a small Florisil column to remove the chromium salt using ether (150 mL) as eluant. Then the eluate was concentrated, and column chromatographed on silica gel (0.5 x 9 inch column) using a gradient mixture of hexane and ether as eluant, to give 10 mg (46% yield) of **34**, 1.2 mg (5% recovery) of **33**.. H NMR : 7.29 (d, J = 7.9 Hz, 2 H, Ar), 7.13 (d, J = 7.9 Hz, 2 H, Ar), 3.7 (t, J = 5.2 Hz, 2 H, C3H), 2.6 (t, J = 3 Hz, 2 H, C6H), 2.58 (t, J = 3 Hz, 2 H, C7H), 2.38 (s, 3 H, *p*-Me), 2.3 (t, J = 5.2 Hz, 2 H, C2H). ^{13}C NMR : 200.7 (s, C1), 169.3 (s, C5), 163 (s, C=), 141 (s, C=), 137.7 (s, Ar), 137.0 (d, Ar), 130.4 (d, Ar), 125.4 (s, Ar), 44.8 (t, C2H), 35.2 (t, CH_2), 29.23 (t, CH_2), 27.8 (t, CH_2), 21.4 (q, *p*-Me).

19. Cycloheptene (41)[22]



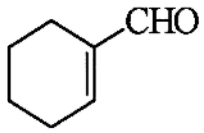
To a solution of 25 g (0.2193 mol) of cycloheptanol was added 0.4 g (1.62 mmol) 0f 1-napthalenesulfonic acid. The reaction mixture was heated in a flask fitted with a distilating apparatus at 190 °C. Pure cycloheptene was obtained in 91% yield (19.06 g) at boiling point 112 - 116 °C. ^{1}H NMR : 5.8 (ddd, J = 8.2, 3.4, 1.0 Hz, 2 H, =CH), 2.1 (td, J = 5.6, 3.4 Hz, 4 H, CH_2), 1.7 (pentet, J = 5.6 Hz, 4 H, CH_2), 1.5 (pentet, J = 5.6, Hz, 2 H, CH_2).

20. *trans*-Cycloheptene-1,2 diol (42)[23]



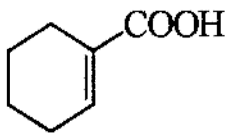
Cycloheptene (21 g, 0.219 mol) was added to 88% formic acid (5.2 eq., 1.1375 mol, 59.4 mL) (in 60 mL water) in a 500-mL three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel. The temperature of the mixture was raised to 35 °C. Then 3.7 eq (55.04 mL, 0.8094 mol) of a 50% solution of hydrogen peroxide was added during 1.5 hours with stirring (at the interface between the 2 phases) and cooling with the internal temperature being maintained at 55 °C - 60° C ; the mixture finally becoming homogeneous. Formic acid was removed by rotatory evaporation. Then to a solution of 17.5 g (2 eq, 0.4375 mol) of NaOH in 95.5 mL water was added the above residue. Then the reaction mixture was heated at 60 °C for 3 hours. It was then neutralized with 6 *N* HC solution. The mixture was saturated with NaCl, and extracted 3 times with CH_2Cl_2. The organic layer was dried ($MgSO_4$), and concentrated to give 20.542 g (72% yield) of desired product **42**. ^{1}H NMR : 3.4 (dt, J = 11.5, 8.2 Hz, 2 H, CH-O), 1.9 (td, J = 5.5, 3.5 Hz, 4 H, CH_2), 1.6 (pentet, J = 5.6 Hz, 4 H, CH_2), 1.5 (pentet, J = 5.6 Hz, 2 H, CH_2).

21. 1-Cyclohexenal (43)



To a stirred suspension of 56.1 g (0.1908 mol) of sodium periodate in 654 mL of water was added 23.4 mL of 70% HNO_3 solution. After the mixture became clear, 20 g (0.1538 mol) of *trans*-diol **42** in 15 mL of water was added. To the resulting mixture was added 2 *N* NaOH solution until the pH became 4. The reaction mixture was stirred at room temperature overnight. Then the resulting mixture was diluted with 116 mL of ether. To it was added 1.5 eq (12.92 g, 0.2308 mol) of KOH in 57 mL water. The mixture was stirred at room temperature for 2 hours. It was extracted 5 times with ether (150 mL each), dried ($MgSO_4$), and concentrated. The crude product was distilled (20 mm Hg, bp. 80 °C) to give 15.228 g (90% yield) of pure aldehyde **43**. ^{1}H NMR : 9.4 (s, 1 H, CHO), 6.81 (tt, J = 3.9, 1.8 Hz, 1 H, C2H), 2.34 (td, J = 6.9, 1.8 Hz, 2H, C3H), 2.18 (td, J = 6.9, 1.0 Hz, 2H, CH_2), 1.66 (m, 4H, $2CH_2$ overlap). ^{13}C NMR : 194 (d, CHO), 151 (d, C2), 141 (s, C1), 26.3 (t, CH_2), 21.9 (t, CH_2), 21.1 (t, CH_2), 20.9 (t, CH_2).

22. 1-Cyclohexene-carboxylic acid (44)

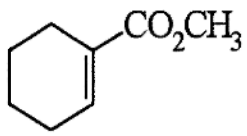


To a solution of 5.2 g (47.3 mmol) of aldehyde **43** in 104 mL of distilled MeOH (distilled over Mg) were added 2.2 eq (0.1041 mol, 18 g) of $AgNO_3$ in 300 mL of water and 5.5 eq (0.26 mol, 14.6 g) of KOH in 145 mL of water. Then the reaction mixture was stirred at room temperature for 3 hours., filtered to remove the silver salt, neutralized (pH = 7) with 25 g of concentrated HCl, extracted with CH_2Cl_2 , dried ($MgSO_4$), and concentrated to give 5.0083 g (84%) of crude product. ^{1}H NMR : 7.13 (tt, J = 3.9, 1.6 Hz, 1 H, C2H), 2.24 (m, 4 H, C3H, CH_2 overlap), 1.64 (m, 4 H, $2CH_2$ overlap).

23. Preparation of active Manganese Dioxide[24]

A solution of manganese sulphate (monohydrate, 59.43 g) in 107 mL of water and a solution of NaOH (40%, 82.7 mL) were added simultaneously during 30 minutes to a stirred solution of 67.83 g of potassium permanganate in 425 mL of water. Manganese dioxide was precipitated soon after the start as a fine brown solid. Stirring was continued for one hour and transfered to plastic bottels. The solid was then collected with a centrifuge (rpm = 3000, 30 minutes) and washed 4 times with water. The solid was dried in an oven at 100 ° - 120 °C and ground to a fine powder (61.2 g).

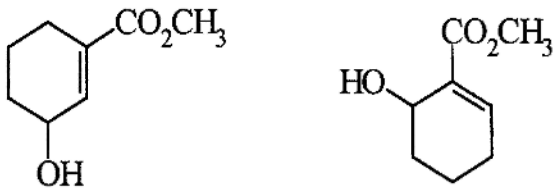
24. Methyl 1-cyclohexene-1-carboxylate (45)



Method A : To a solution of 5 g (39.7 mmol ; from a previous crude product) of carboxylic acid **44** in 8 mL of ether was added 1.25 eq (50 mmol) of diazomethane in 5 mL ether at 0 °C. The mixture was stirred at 0 °C for 1 hour. Ether was removed by rotatory evaporation. The residue was distilled (bp. 60 °C / 8 mm Hg) to give 3.42 g (62% yield) of pure ene ester **45**. ^{1}H NMR : 6.98 (tt, J = 4.0, 4.0 Hz, 1 H, C2H), 3.72 (s, 3 H, OMe), 2.25 (td, J = 6.3, 1.7 Hz, 2 H, CH_2), 2.18 (td, J = 6.3, 1.7 Hz, 2 H, CH_2), 1.62 (m, 4 H, $2CH_2$ overlap).

Method B[25] : To a mixture of 3 g (27.3 mmol) of **43** and 5.08 g (104 mmol) of NaCN in 2.4 mL of acetic acid was added 36 g (409 mmol) of active manganese dioxide in 156 mL MeOH. The mixture was stirred at room temperature overnight. The mixture was filtered through Celite. Ether and MeOH were removed by rotatory evaporation. The residue was diluted with 10 mL of brine and extracted 3 times with CH_2Cl_2 (50 mL each). The combined organic layer was dried ($MgSO_4$), concentrated, and distilled (5 mm Hg) to give pure product **45**.

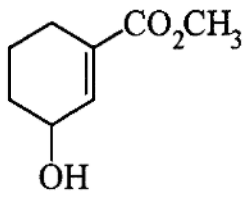
25. Methyl 3-hydroxy-1-cyclohexene-1-carboxylate (46a) and Methyl 6-hydroxy-1-cyclohexene--1-carboxylate (46b)



To a solution of 2.73 g (19.5 mmol) of ene ester **45** in 130 mL of acetic acid was added 4 eq (78 mmol, 8.66 g) of selenium dioxide. The mixture was stirred at 100 °C for 2 hours. The mixture was filtered through Celite, and the filter cake was washed three times with CH_2Cl_2 (20 mL each). Acetic acid was removed by rotatory evaporation. The residue was diluted with 150 mL of CH_2Cl_2 and washed with sodium bicarbonate solution until the washing was neutral (used 25 mL each time). The aqueous layer was extracted three times (75 mL each) with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant to give 1.21g (40% yield) of **46a**, 0.6 g (20% yield) of **46b**, 0.19 g (5% yield) of **48a**, and 0.61 g (16% yield) of **48b**.. ^{1}H NMR of **46a** : 6.87 (dt, J = 2.5, 0.8 Hz, 1 H, C2H), 4.35 (m, 1 H, C3H), 3.77 (s, 3 H, OMe), 2.66 (m, 2 H, C6H), 1.79 (m, 3 H, C4H and CH_2 overlap), 1.58 (m, 1 H, CH_2). ^{13}C NMR of **46a** : 167.7 (s, CO), 140.3 (d, C2), 131.7 (s,C1), 65.6 (d, C3), 51.6 (q, OMe), 30.8 (t, CH_2), 24.0 (q, Me), 19.0 (t, CH_2). ^{1}H NMR of **46b** : 7.11 (t, J = 4.0 Hz, 1 H, C2H), 4.55 (t, J = 4.0 Hz, 1 H, C6H), 3.78 (s, 3 H, OMe), 2.29 (dtd, J

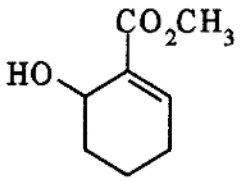
= 19.7, 5.0, 4.4 Hz, 1 H, C3H), 2.13 (dtd, J = 19.7, 8.0, 3.7 Hz, 2 H, C3H), 1.79 (m, 3 H, C4H and CH_2 overlap), 1.6 (m, 1 H, CH_2). ^{13}C NMR of **46b** 167.7 (s, CO), 143.2 (d, C2), 132.0 (s, C1), 63.1 (d, C6), 51.6 (q, OMe), 29.8 (t, CH_2), 26.0 (t, CH_2). 17.1 (t, CH_2). ^1H NMR of **48a** 6.8 (dt, J = 3.5, 1.8 Hz, 1 H, C2H), 5.4 (m, 1 H, C3H), 3.7 (s, 3 H, OMe), 2.3 (m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 2.1 (s, 3 H, OCMe), 1.7 (m, 2 H, CH_2) ^{13}C NMR of **48a** 170.3 (s, CO), 167 (s, CO), 135.6 (d, C2), 135.5 (s, C1), 67.8 (d, C3), 51.7 (q, OMe), 27.5 (t, CH_2), 24.0 (t, CH_2), 21.0 (q, Me), 18.9 (t, CH_2) ^1H NMR of **48b** 7.2 (dd, J = 4.9, 2.8 Hz, 1 H, C2H), 5.7 (t, J = 4.8 Hz, 1 H, C6H), 3.8 (s, 3 H, OMe), 2.4 (m, 2 H, CH_2), 2.3 (m, 2 H, CH_2), 2.0 (s, 3 H, Me), 0.6 (m, 2 H, CH_2). ^{13}C NMR of **48b** 169.8 (s, CO), 166.0 (s, CO), 145.4 (d, C2), 128.5 (s, C1), 64.4 (d, C6), 51.4 (q, OMe), 28.0 (t, CH_2), 25.6 (t, CH_2), 20.9 (q, Me), 16.3 (t, CH_2).

26. Methyl 3-hydroxy-1-cyclohexene-1-carboxylate (46a)



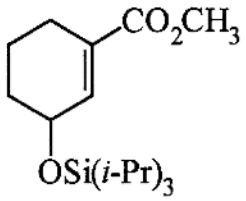
To a solution of 0.18 g (0.91 mmol) of **48a** in 2 mL of distilled MeOH was added 2 eq (0.251 g, 1.82 mmol) of potassium carbonate at room temperature. The mixture was stirred at room temperature for 4 hours. It was then diluted with brine solution, extracted with ether, dried ($MgSO_4$), and concentrated, to give 0.122 g (86%) of crude product **46a**. H NMR is as in experiment 25. For the spectra of **46a** see experimant 25.

27. Methyl 6-hydroxy-1-cyclohexene--1-carboxylate (46b)



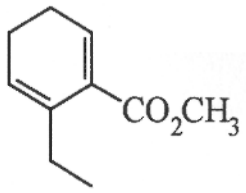
To a solution of 27 mg (0.1364 mmol) of **48b** in 1 mL of distilled MeOH was added 2 eq (0.2728 mmol, 38 mg) of potassium carbonate at room temperature. The mixture was stirred at room temperature for 4 hours. It was then diluted with brine solution, extracted with ether, dried ($MgSO_4$), and concentrated, to give 13 mg (68%) of crude product **46b**. For the spectra of **46b** see experimant 25.

28. Methyl 1-cyclohexen-3-(tri-isopropylsilyloxy)-1-carboxylate (47)



To a solution of 0.42 g (2.688 mmol) of a mixture of **46a** and **46b** (2 : 1 ratio, determined by H NMR) in 6 mL CH_2Cl_2 under argon were added 1.5 eq (14.79 mmol, 2.06 mL) of Et_3N, 3 eq (8.073 mmol, 1.76 mL) of distilled tri-isopropylsilyl chloride, and 0.1 eq (0.269 mmol, 0.033 g) of 4-(dimethylamino)pyridine at 0 °C under argon. The mixture was stirred at 52 °C for 24 hours. The mixture was diluted with 70 mL of ether, 15 mL of 1 *N* HC solution, washed with sodium bicarbonate solution, and brine solution, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel (2 x 12 inch) using a gradient mixture of hexane and ether as eluant to give 0.393 g of desired product **47**, 0.137 g (33% yield) of a mixture of **46a** and **46b** in a ratio 1 : 2 ratio (determined by ^{1}H NMR). The desired product **47** (0.393 g) was distilled using the bul- to-bulb method to give 0.3535 g (42% yield) of pure **47**. ^{1}H NMR : 6.8 (dt, J = 2.4, 2.0 Hz, 1 H, C2H), 4.4 (m, 1 H, C3H), 3.7 (s, 3 H, OMe), 2.2 (m, 2 H, C6H), 1.83 (m, 2 H, CH_2), 1.54 (m, 2 H, CH_2), 1.04 (s, 21 H, (i-Pr)$_3$).

29. Methyl 3-ethyl-1, 3-cyclohexadiene-2-carboxylate (28a)



To a solution of 62 mg (0.24 mmol) of **29** in 2.2 mL of toluene under argon was added 1.2 eq (0.28 mmol) of DNB (1,5-diazabicyclo[4,3,0]non-5-ene) at room temperature. The mixture was stirred at 60 °C for overnight. The mixture was diluted with 15 mL of ether and 20 mL of distilled water. It was then added 10 mL of ammonium chloride solution. The aqueous layer was extracted three times (40 mL each) with ether. The combined organic layer was extracted dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant. No desired product was obtained, recovered 21 mg (51% yield) of starting material **29**. For the spectra of **29** see experimant 16.

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21. The compound **31** was synthesized by a previous student in Dr. Hua's laboratory : Treatment of (3*S* S*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3H-pyrrole (**36**) with LDA and methyl 3-bromopropionate followed by deprotection of alcohol with *n*-Bu_4NF gave **31**.

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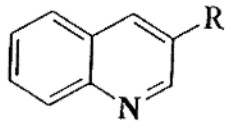
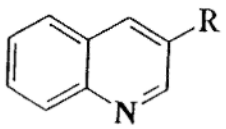
^{1}H NMR of compound **7b** :



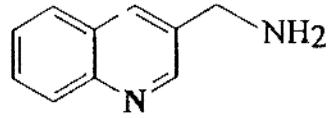
R = CN

^{13}C NMR of compound **7b** :

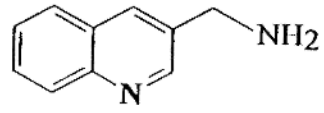


R = CN

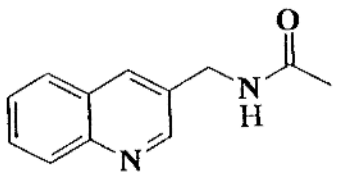
^{1}H NMR of compound **8** :



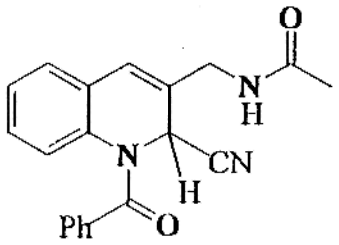
^{13}C NMR of compound **8** :



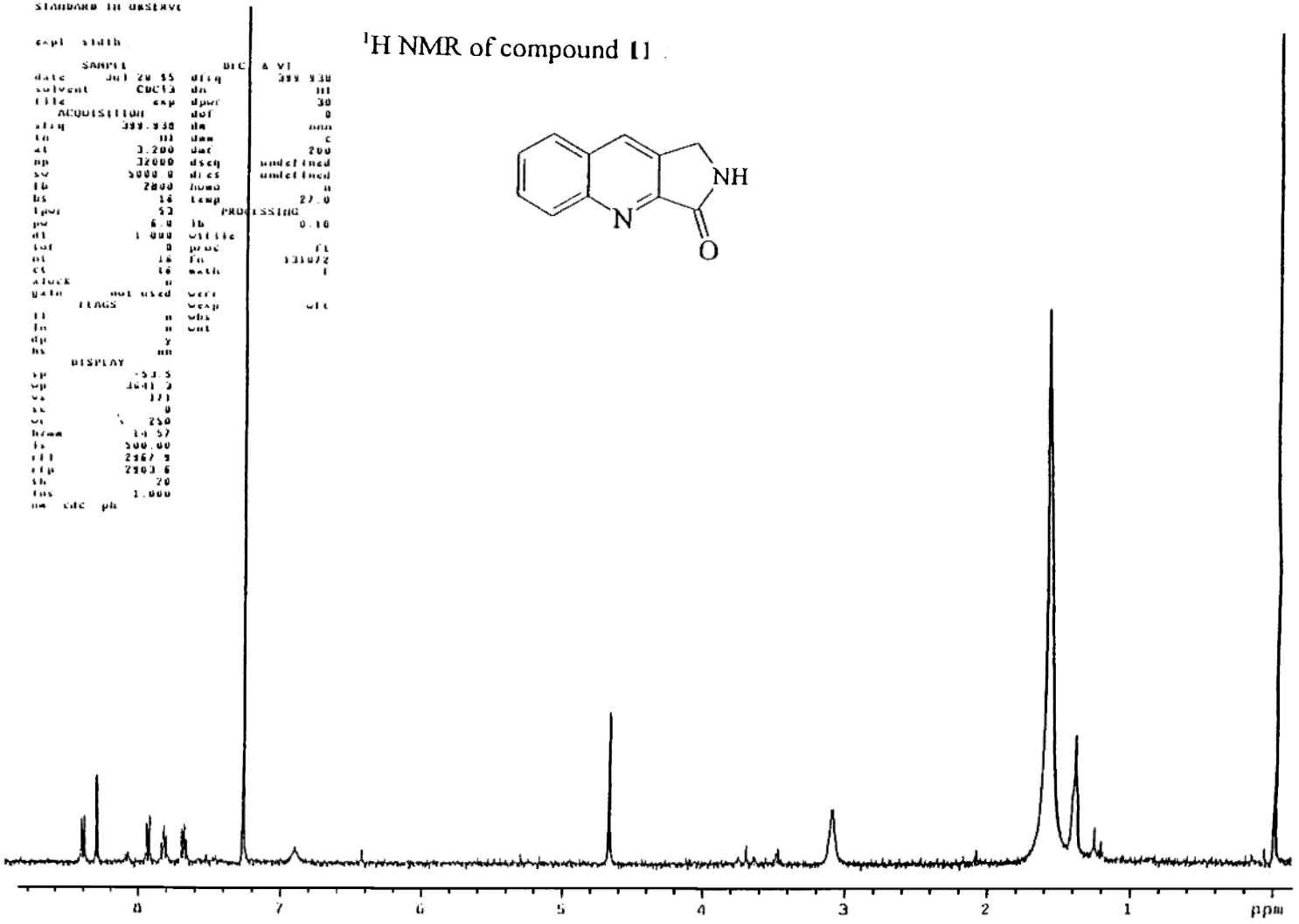
^{1}H NMR of compound **9** :



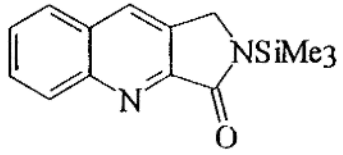
^{1}H NMR of compound **10** :



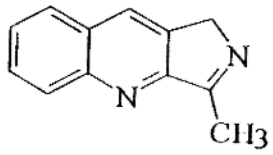
^{1}H NMR of compound **1**



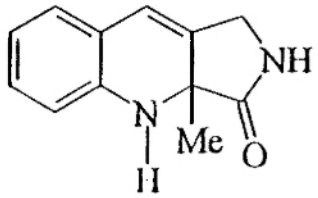
^{1}H NMR of compound **12** :



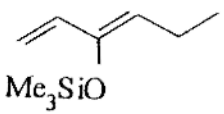
^{1}H NMR of compound **13a**



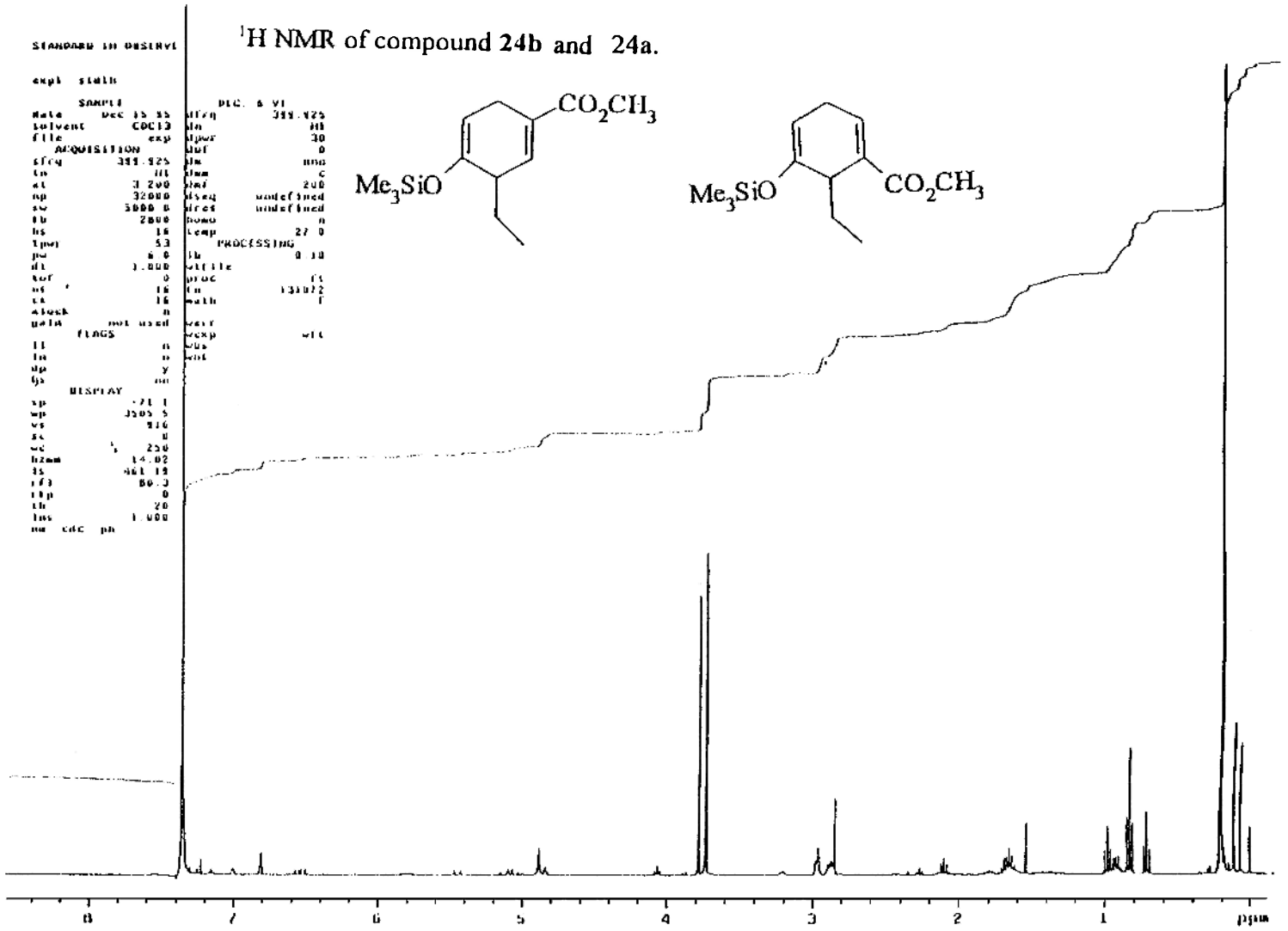
^{1}H NMR of compound **13b** :



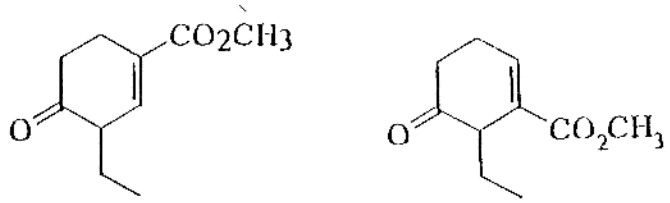
^{1}H NMR of compound **23** :



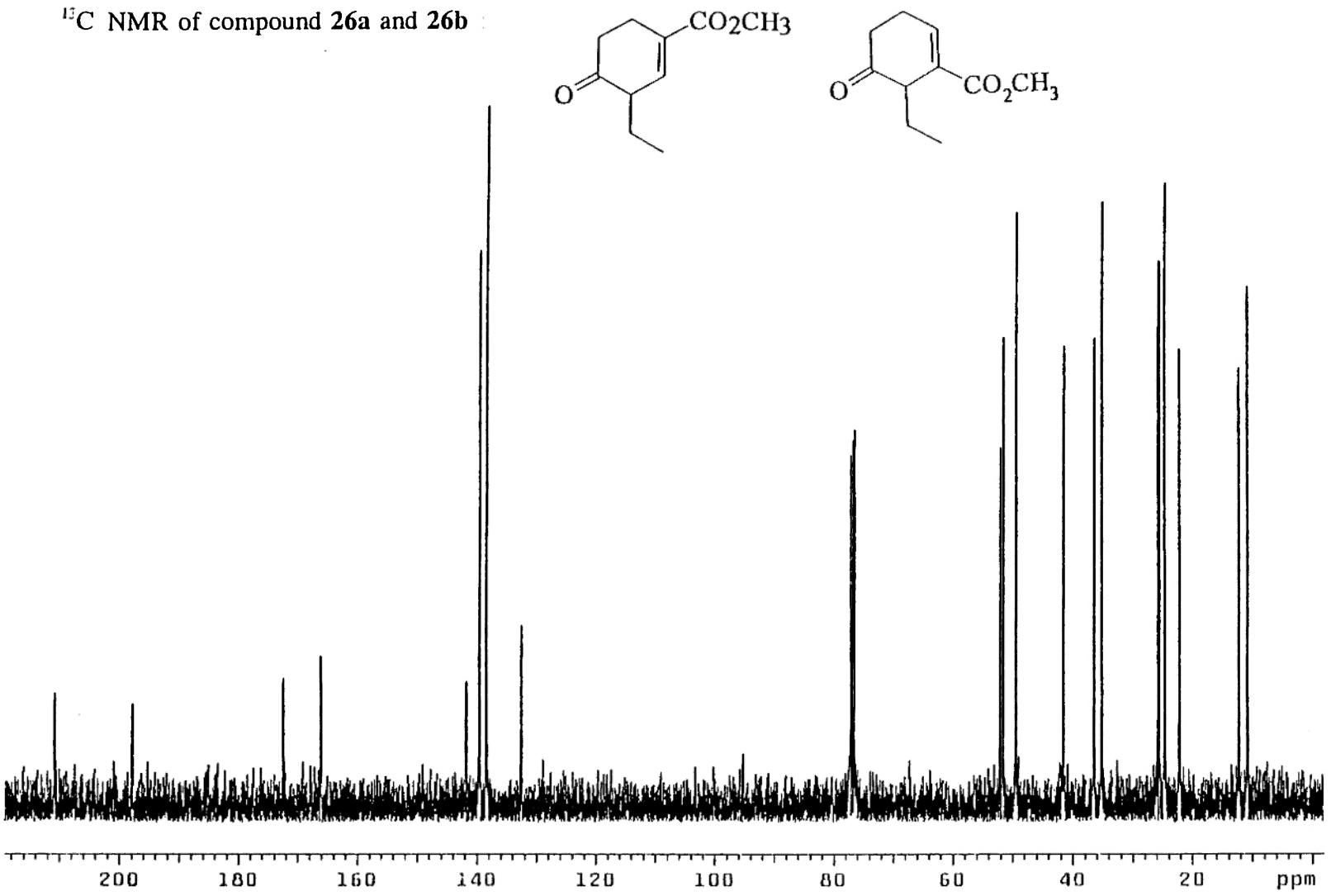
^{1}H NMR of compound **24b** and **24a**.



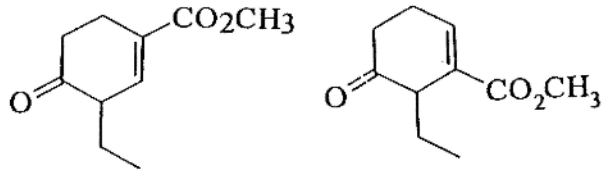
^{1}H NMR of compound **26a** and **26b**

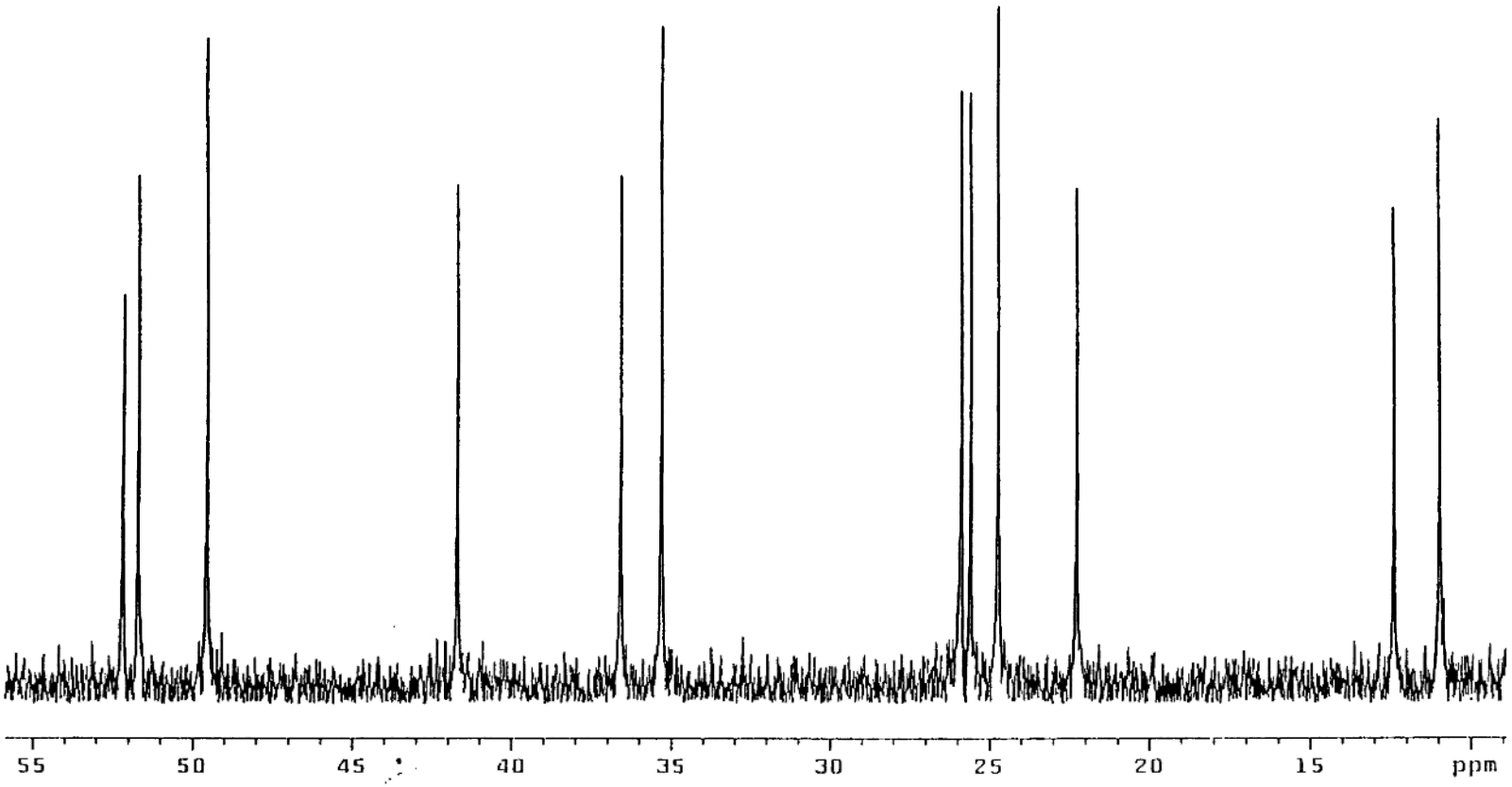


^{13}C NMR of compound **26a** and **26b**

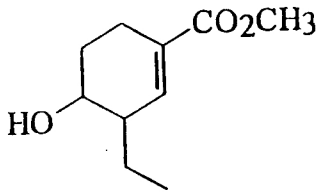


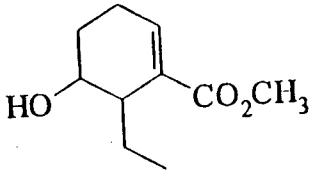
^{13}C NMR of compound **26a** and **26b** : Expansion



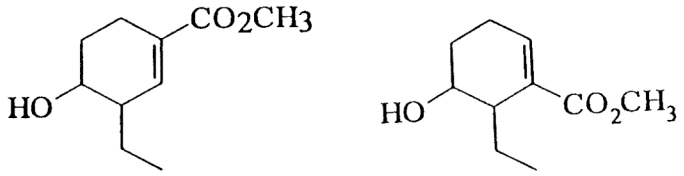


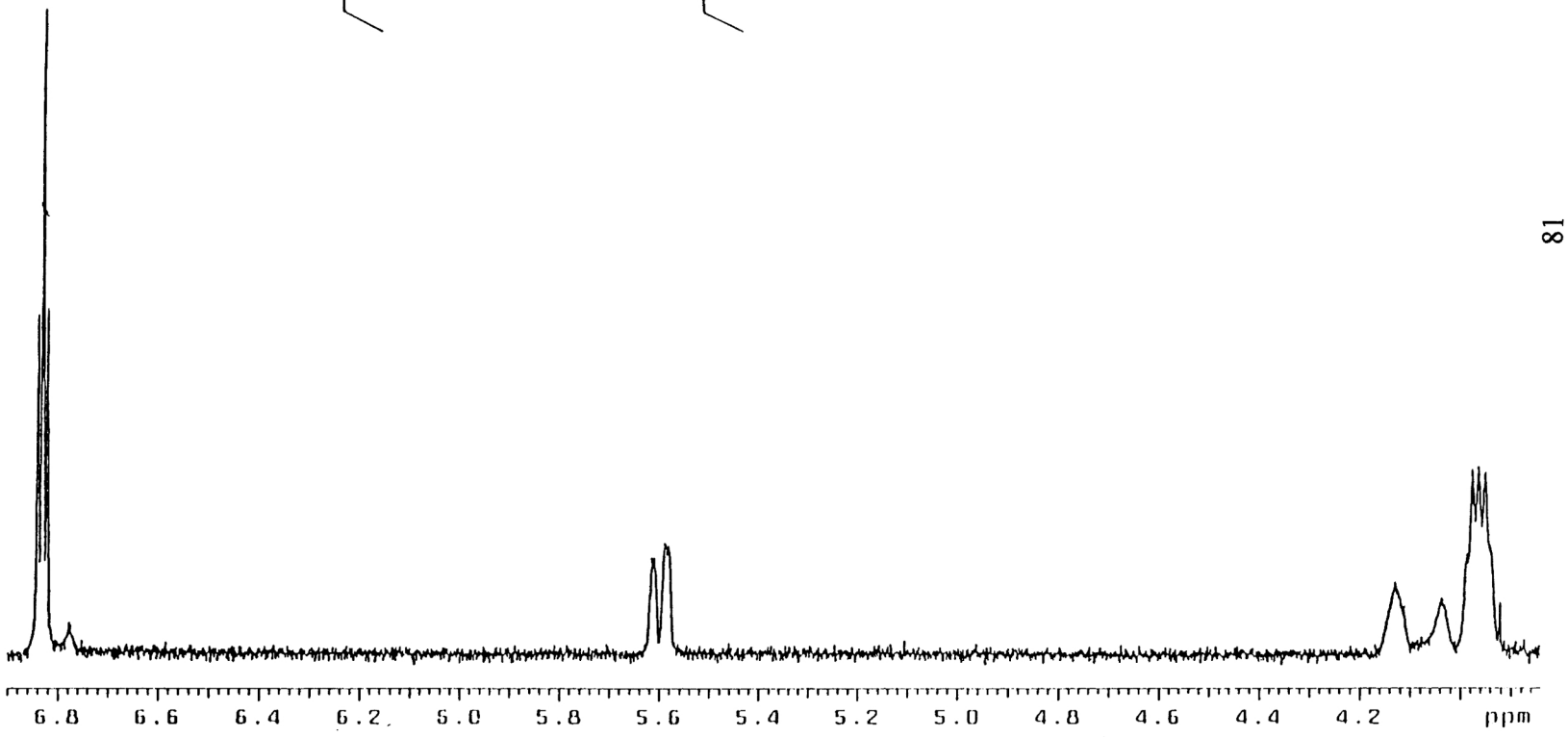
^{1}H NMR of compound **27a** and **27b** :



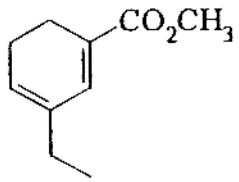


^{1}H NMR of compound **27a** and **27b** : Expansion

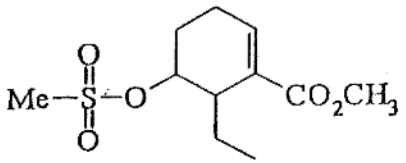




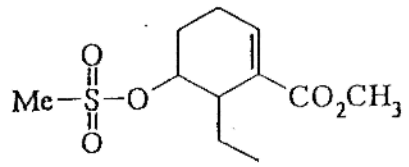
^{1}H NMR of compound **28**

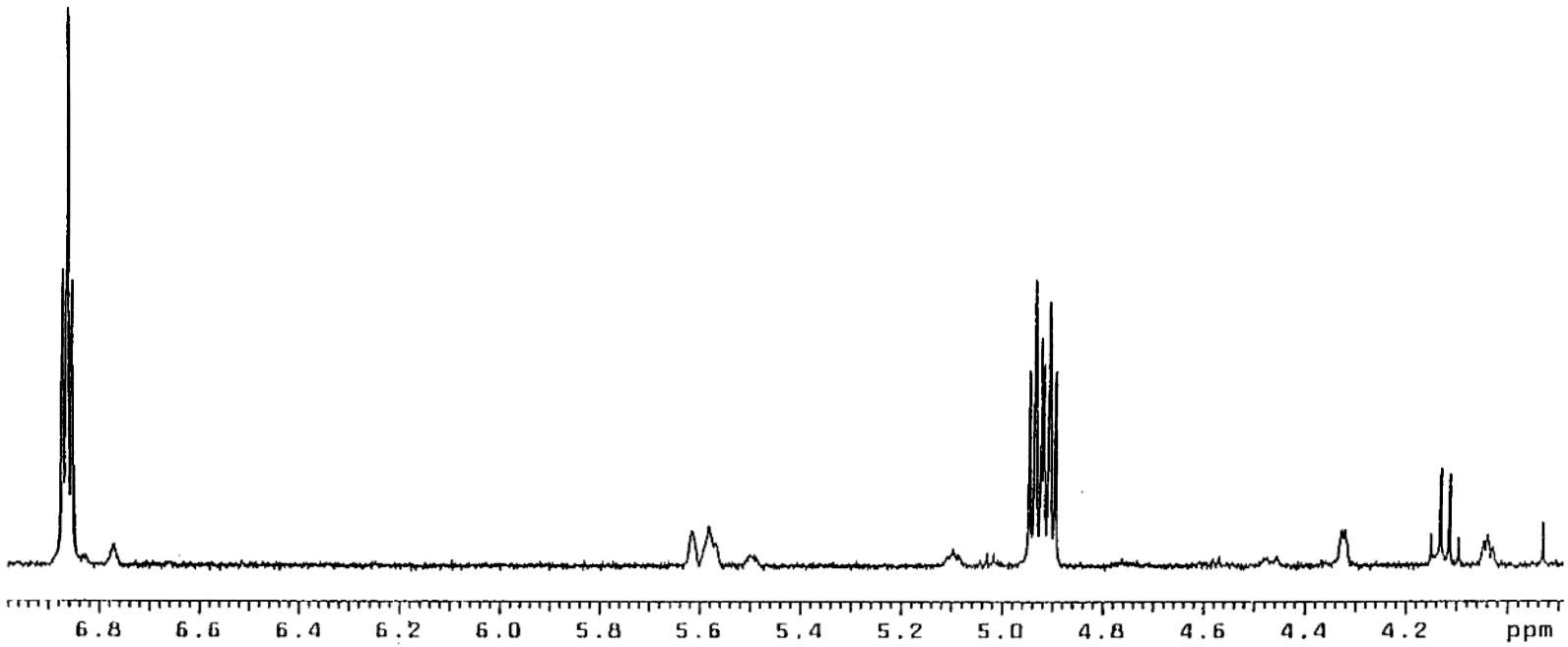


^{1}H NMR of compound **29** :



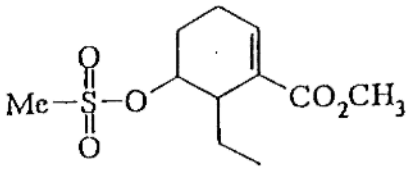
^{1}H NMR of compound 29. Expansion

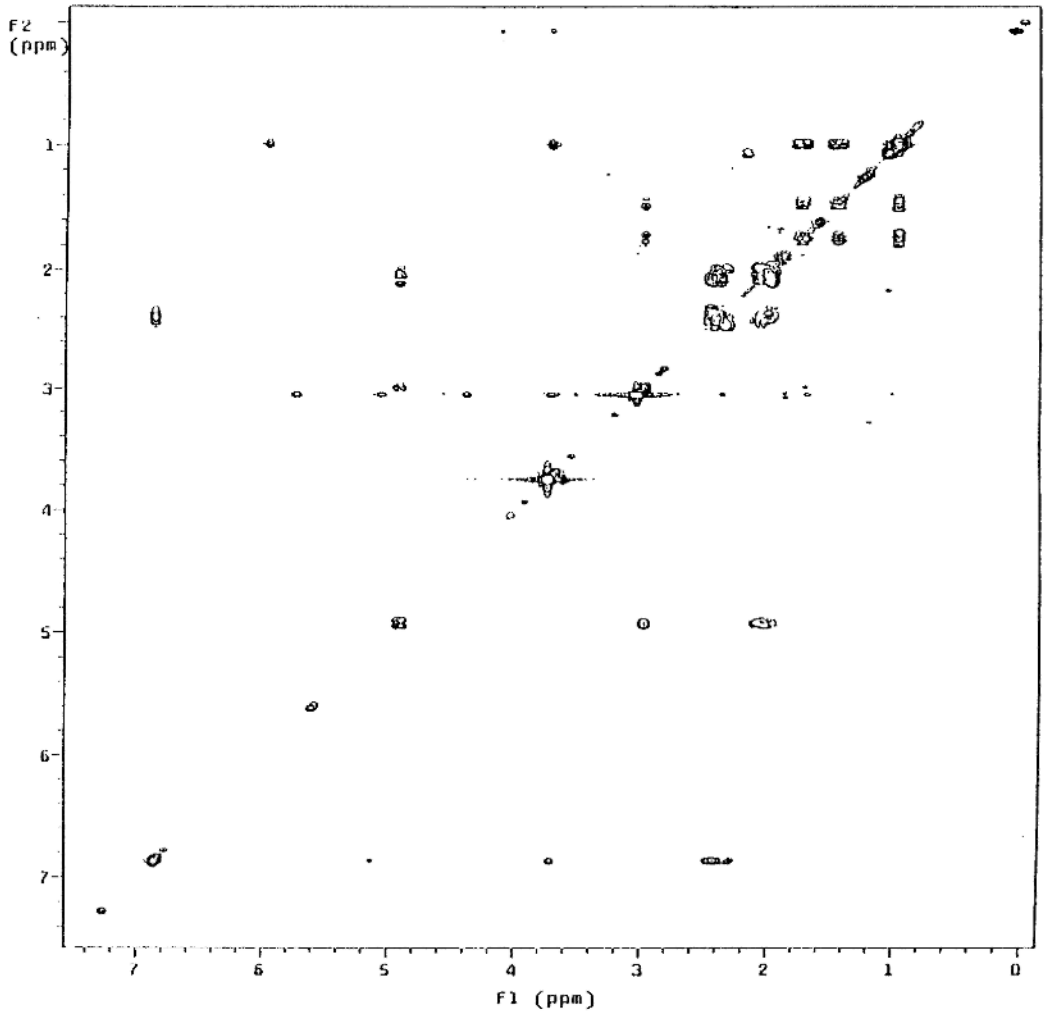




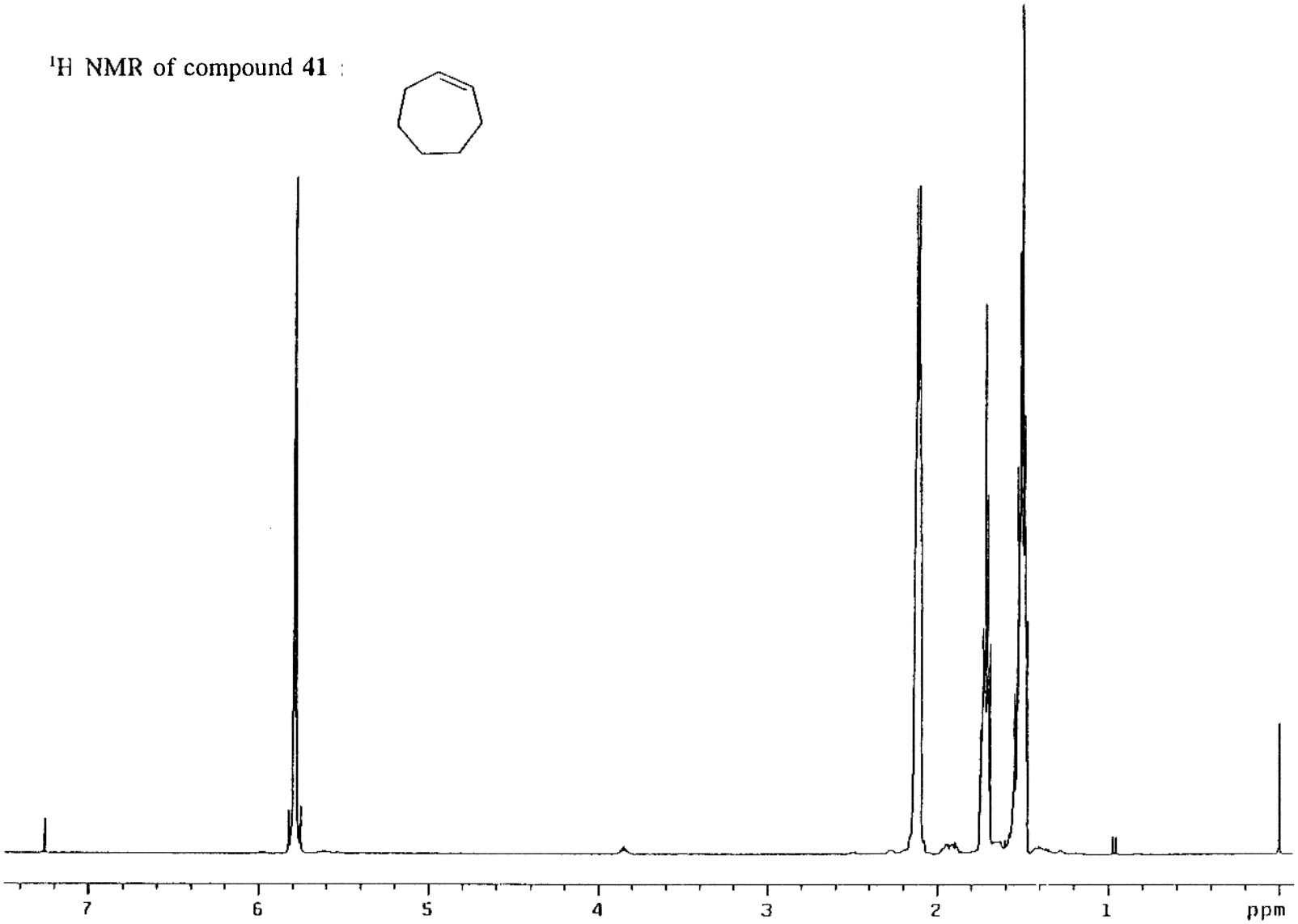
2D COSY Experiment

for compound **29** :

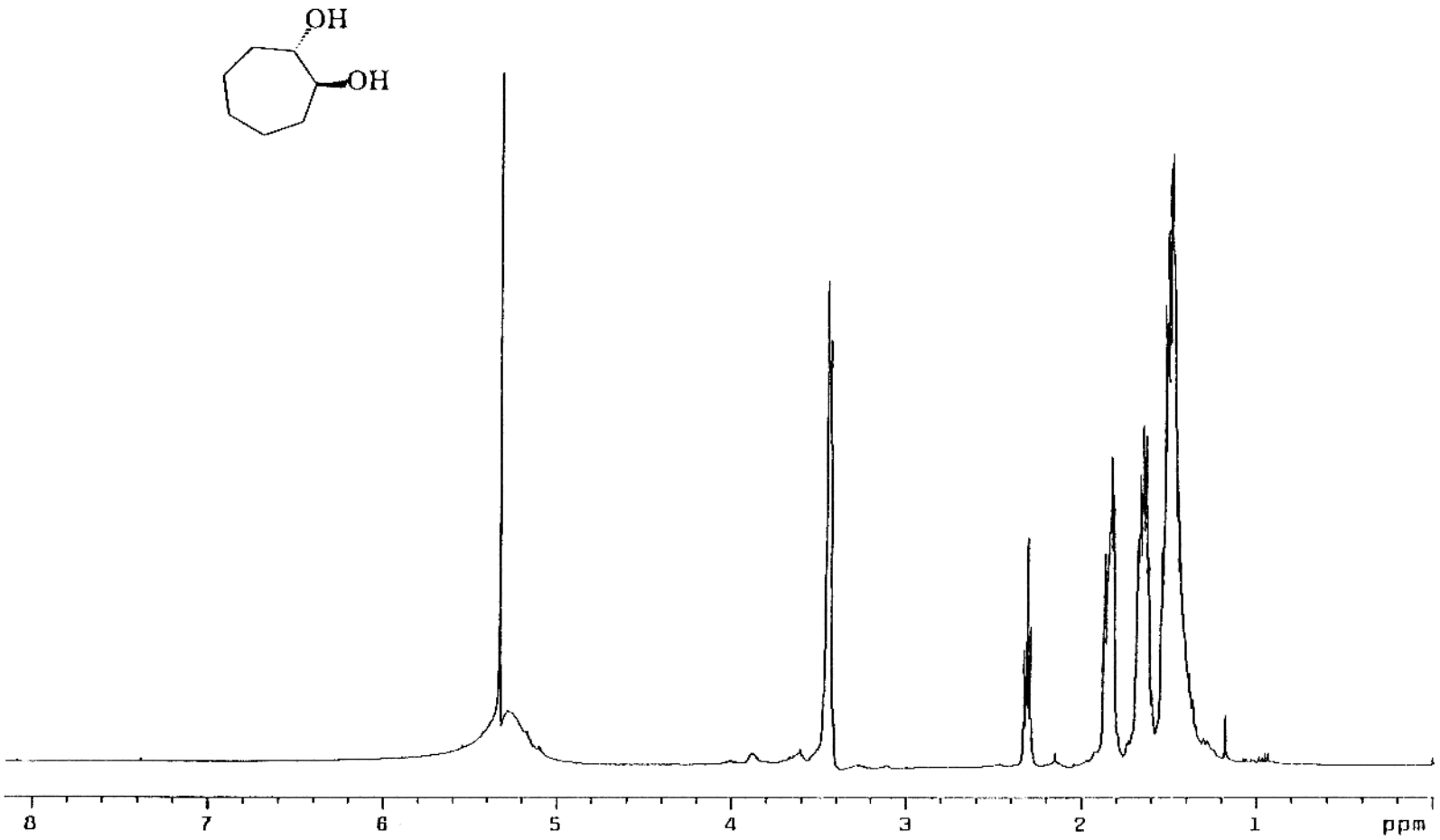




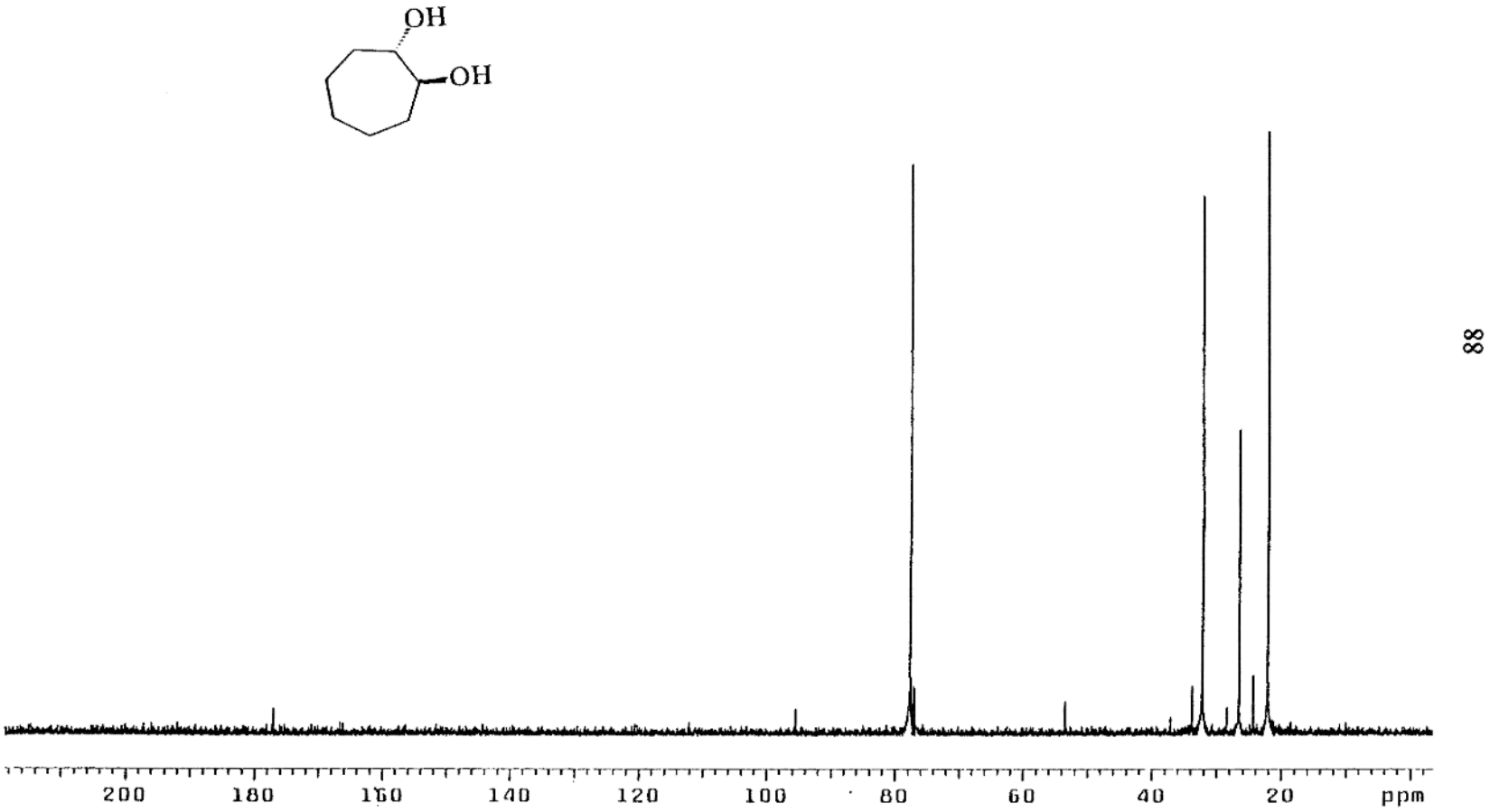
^{1}H NMR of compound **41** :



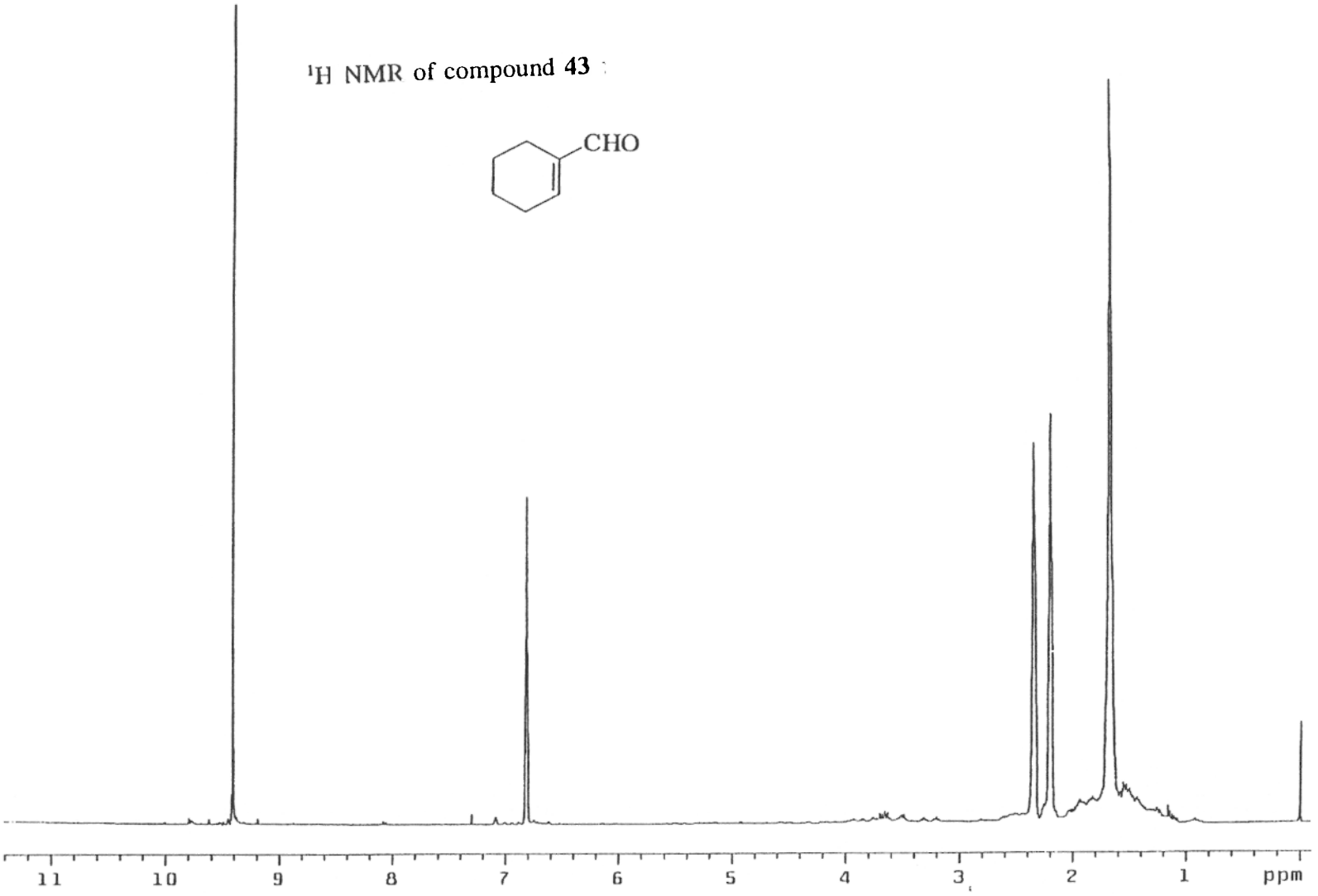
^{1}H NMR of compound **42** :



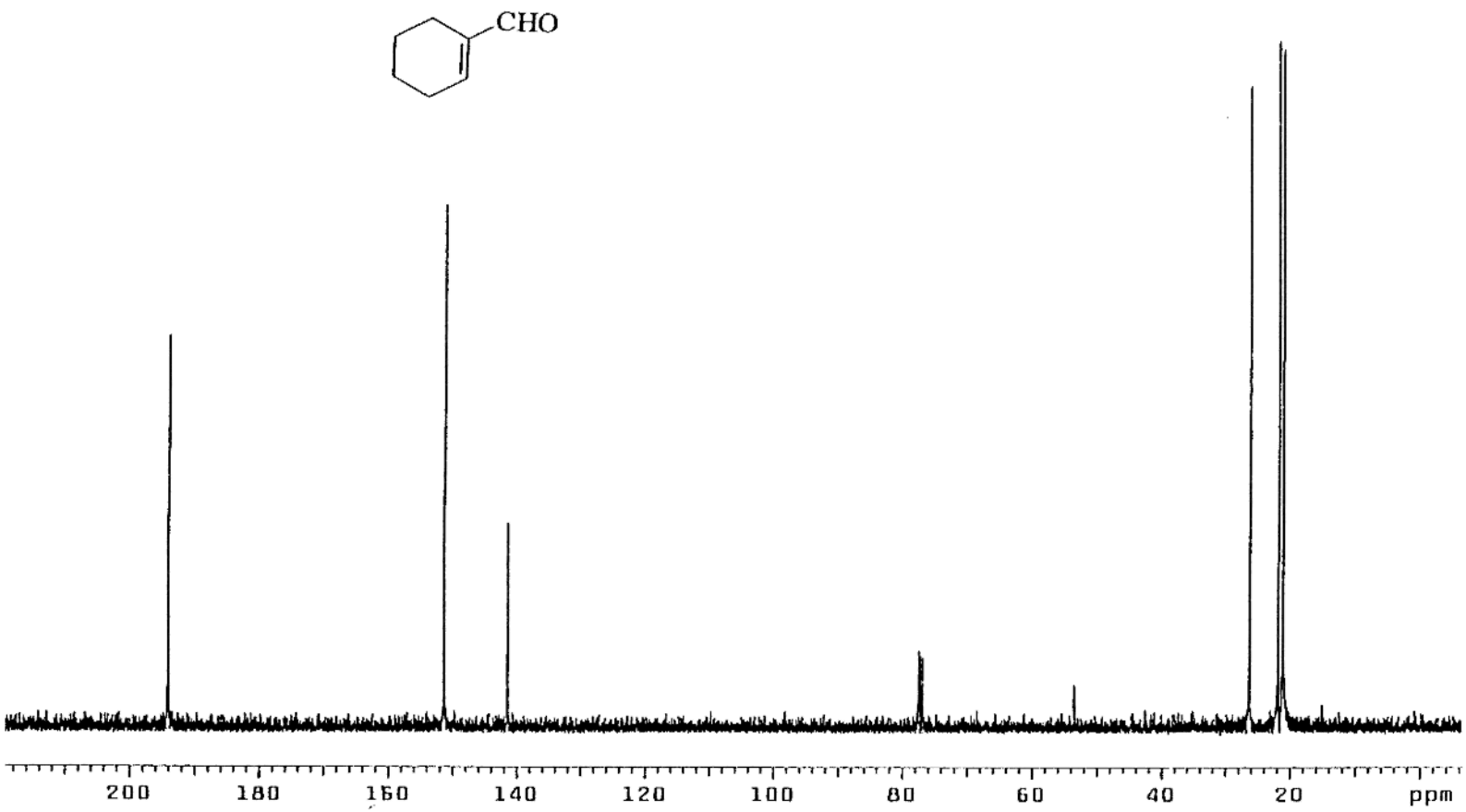
^{13}C NMR of compound **42**



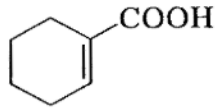
^{1}H NMR of compound **43**

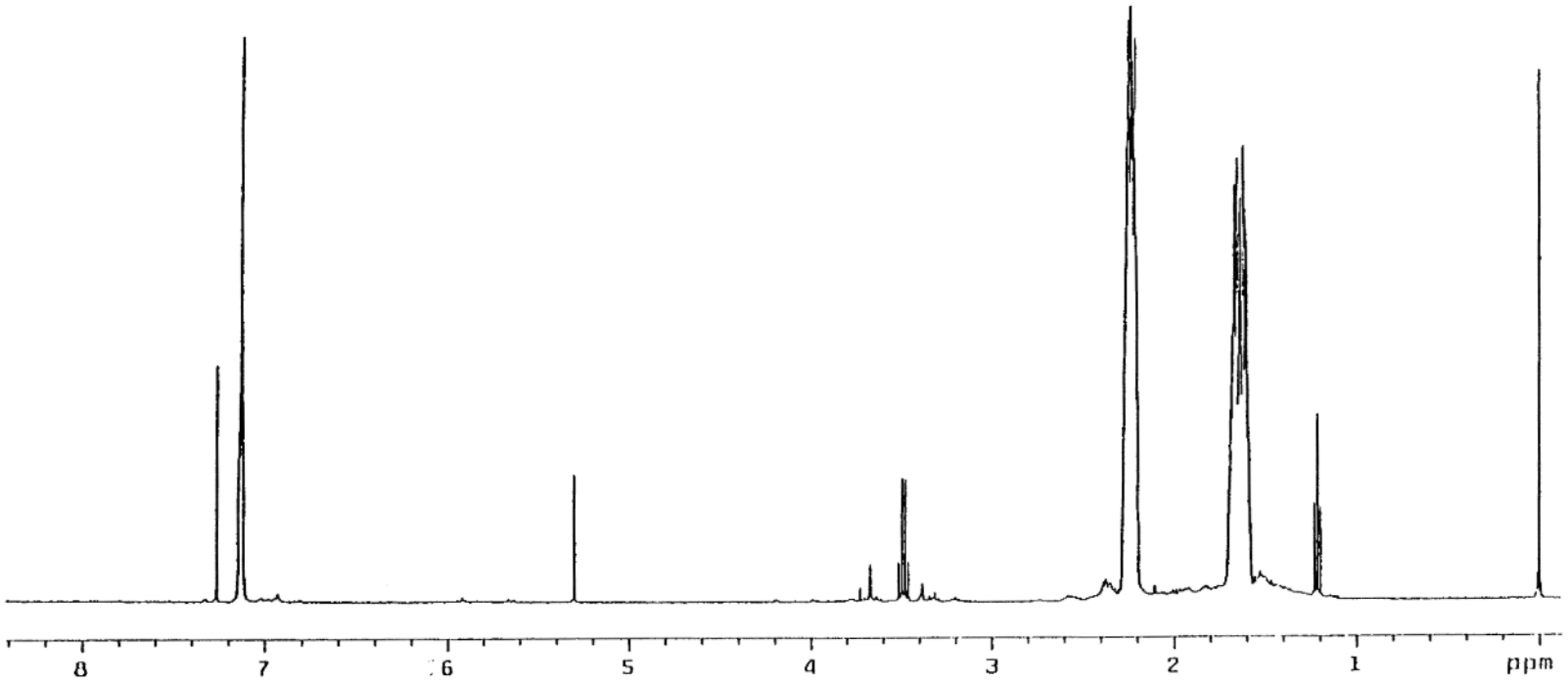


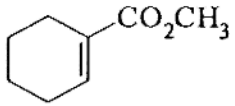
^{13}C NMR of compound **43**



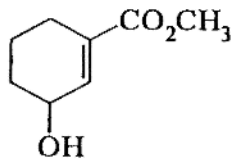
^{1}H NMR of compound **44** :



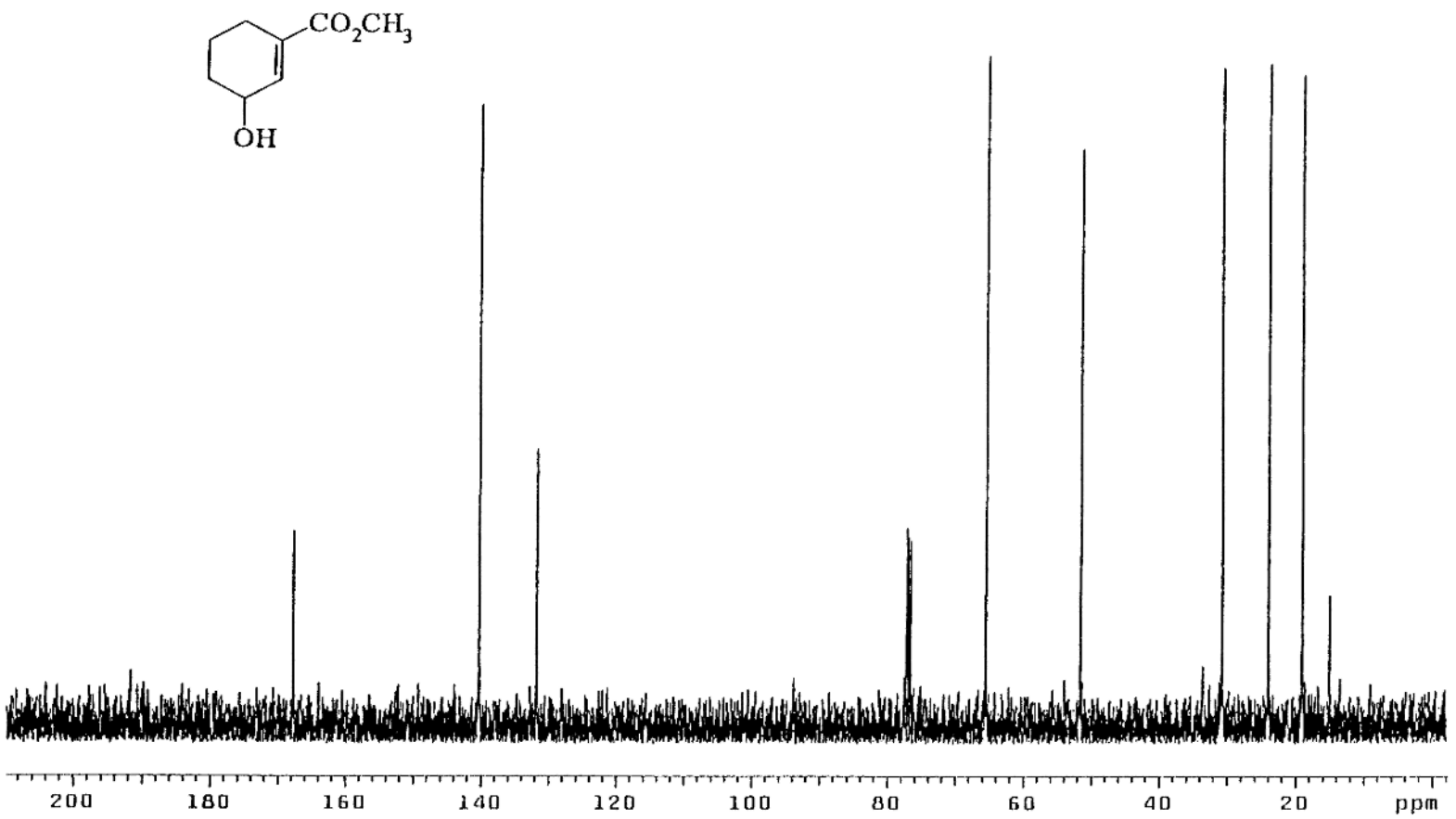


^{1}H NMR of compound **45** : 

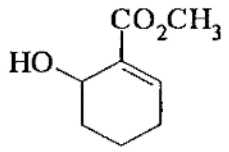
^{1}H NMR of compound **46a**



^{13}C NMR of compound **46a** :



^{1}H NMR of compound **46b** :



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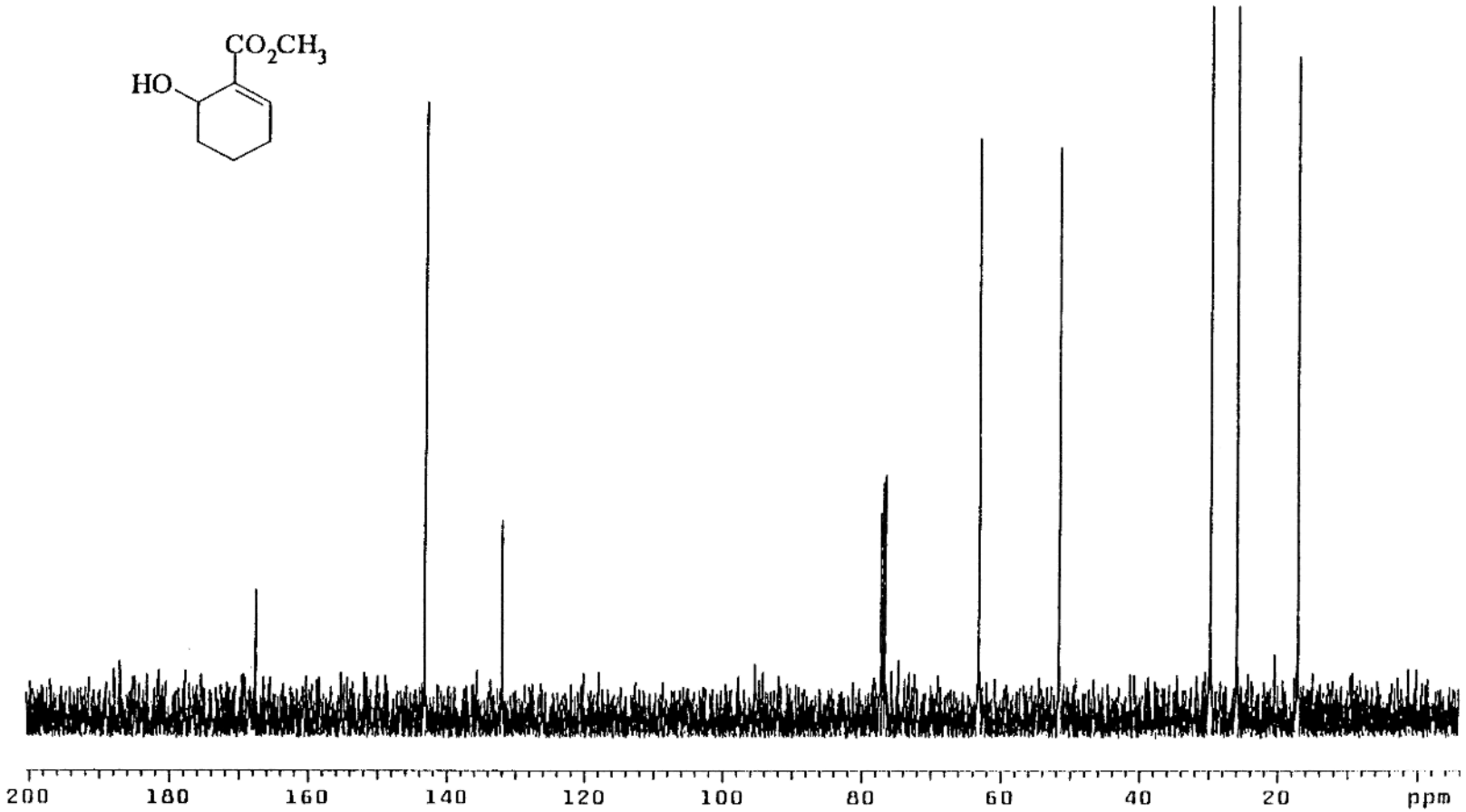
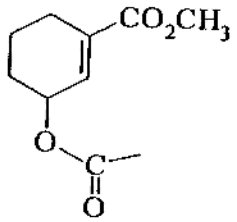
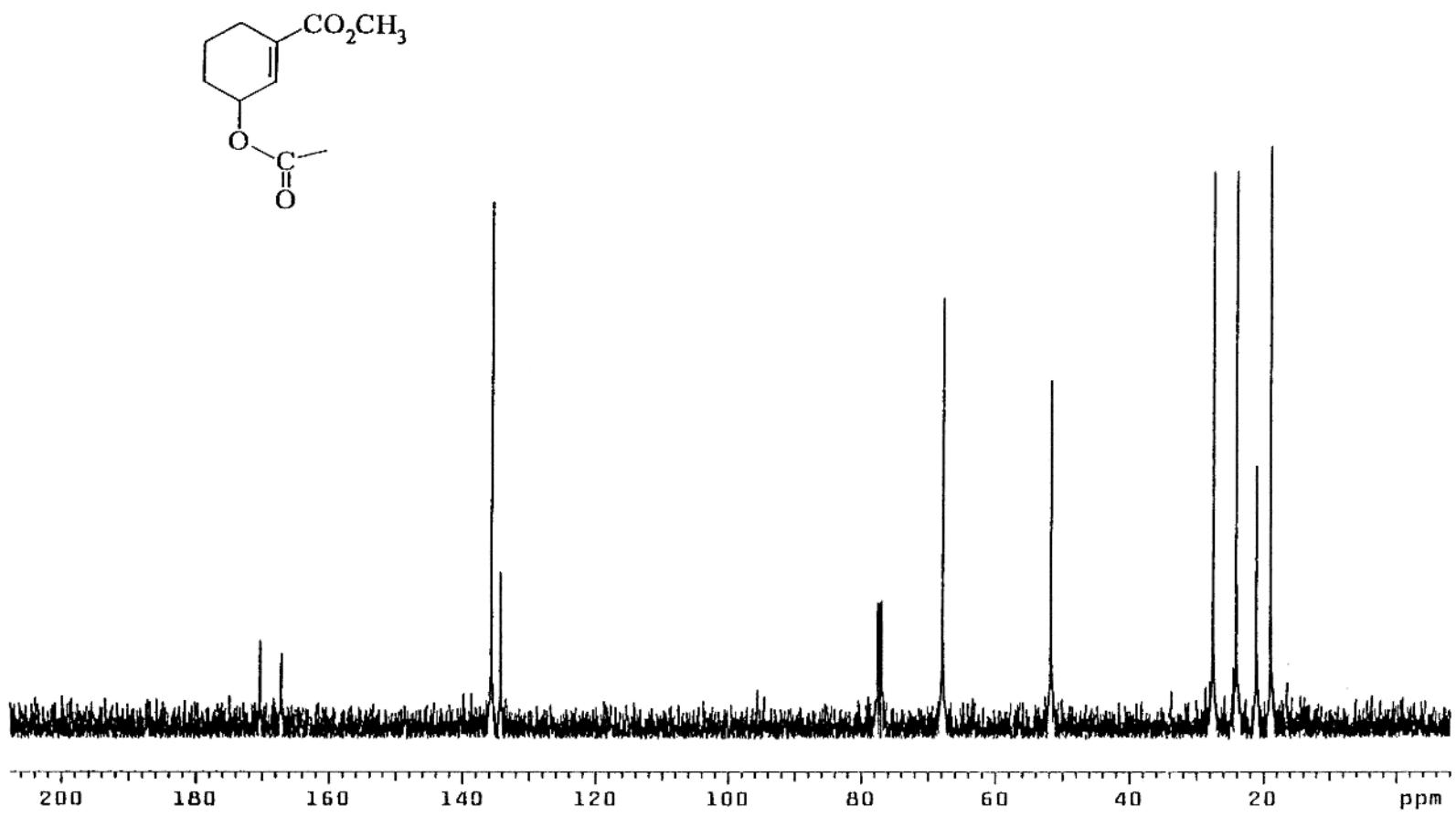


^{1}H NMR of compound **48a**



^{13}C NMR of compound **48a** :



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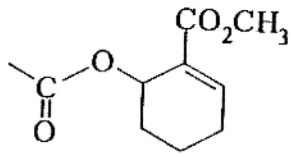

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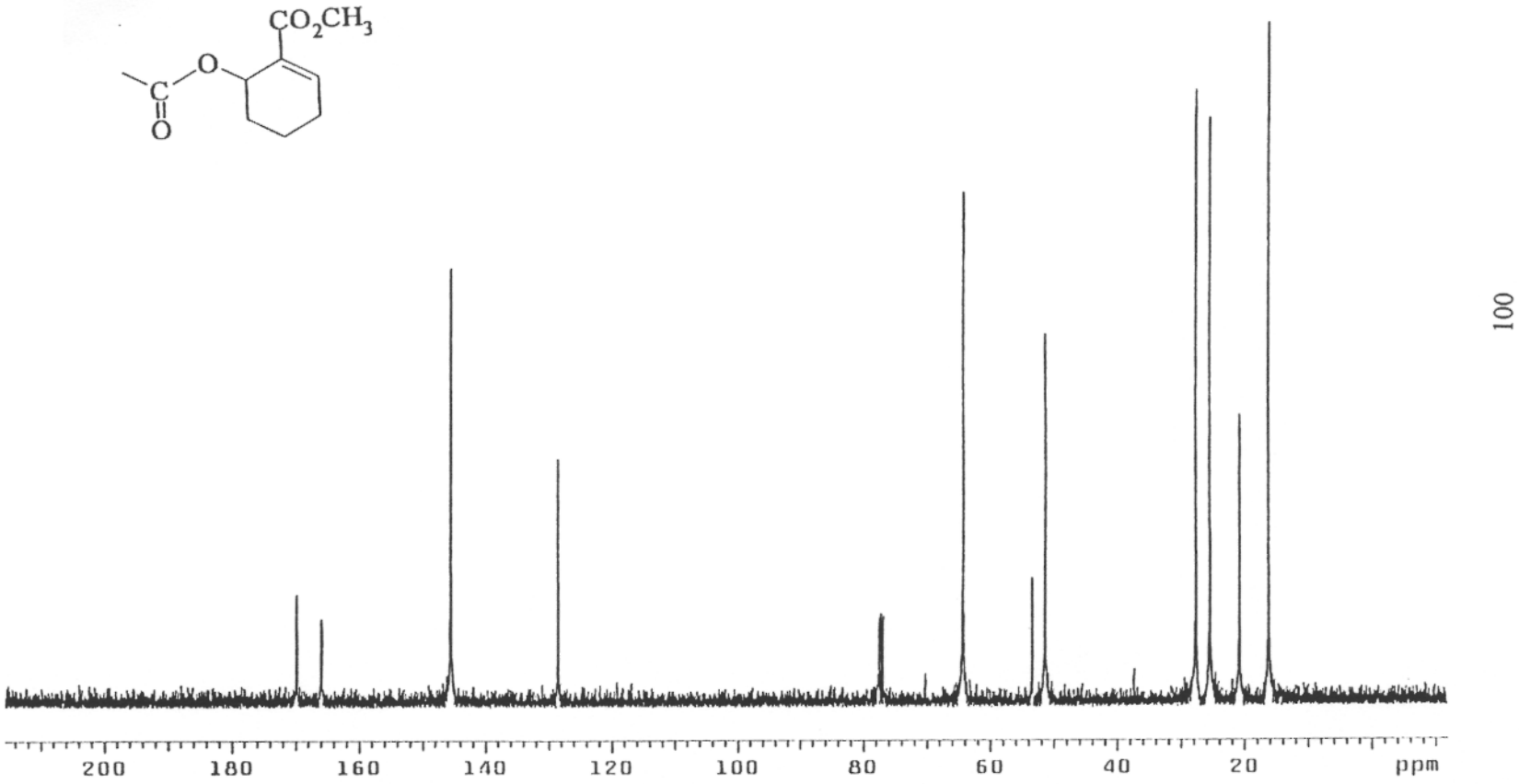

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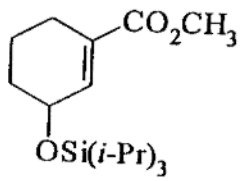
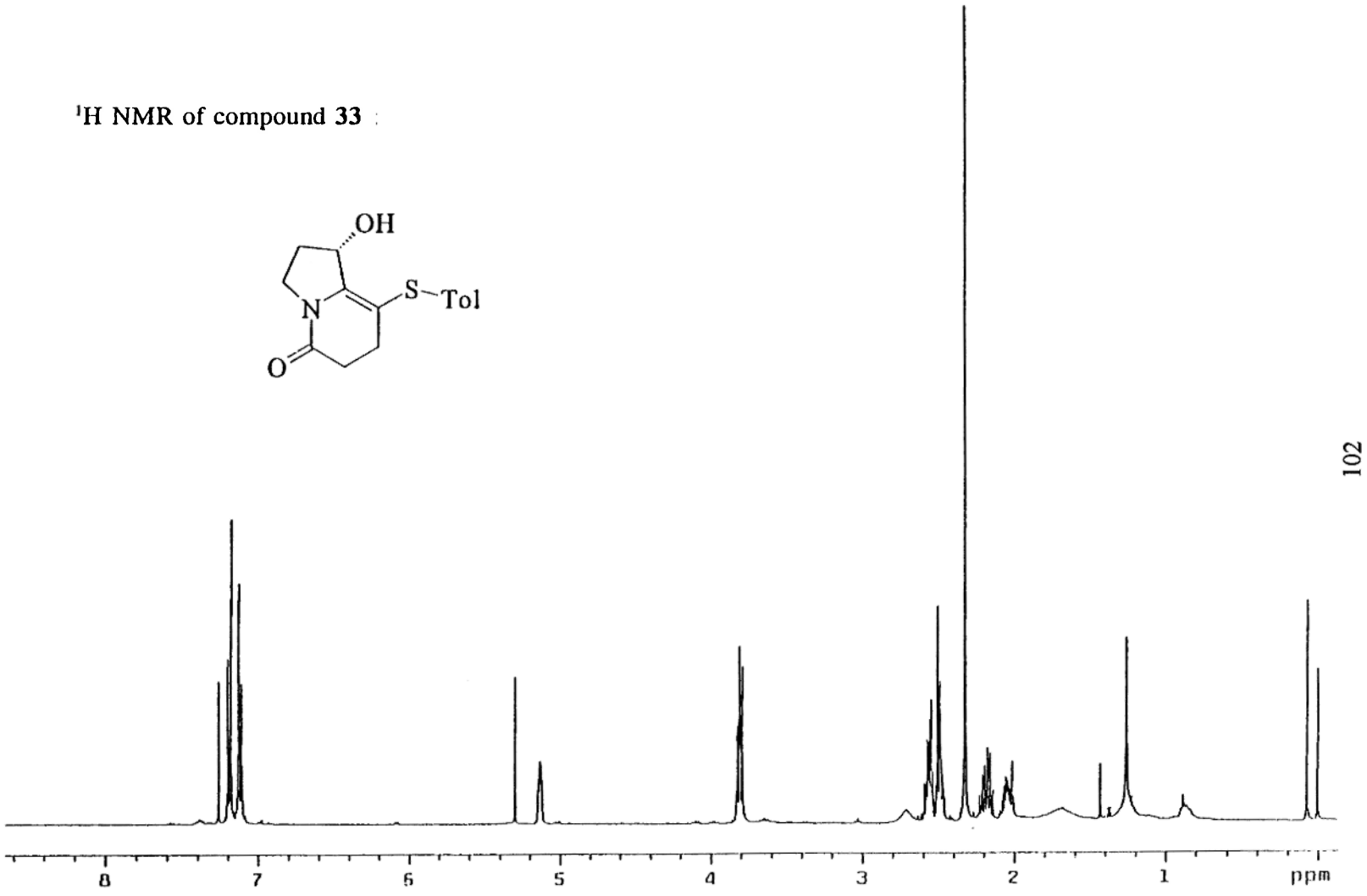
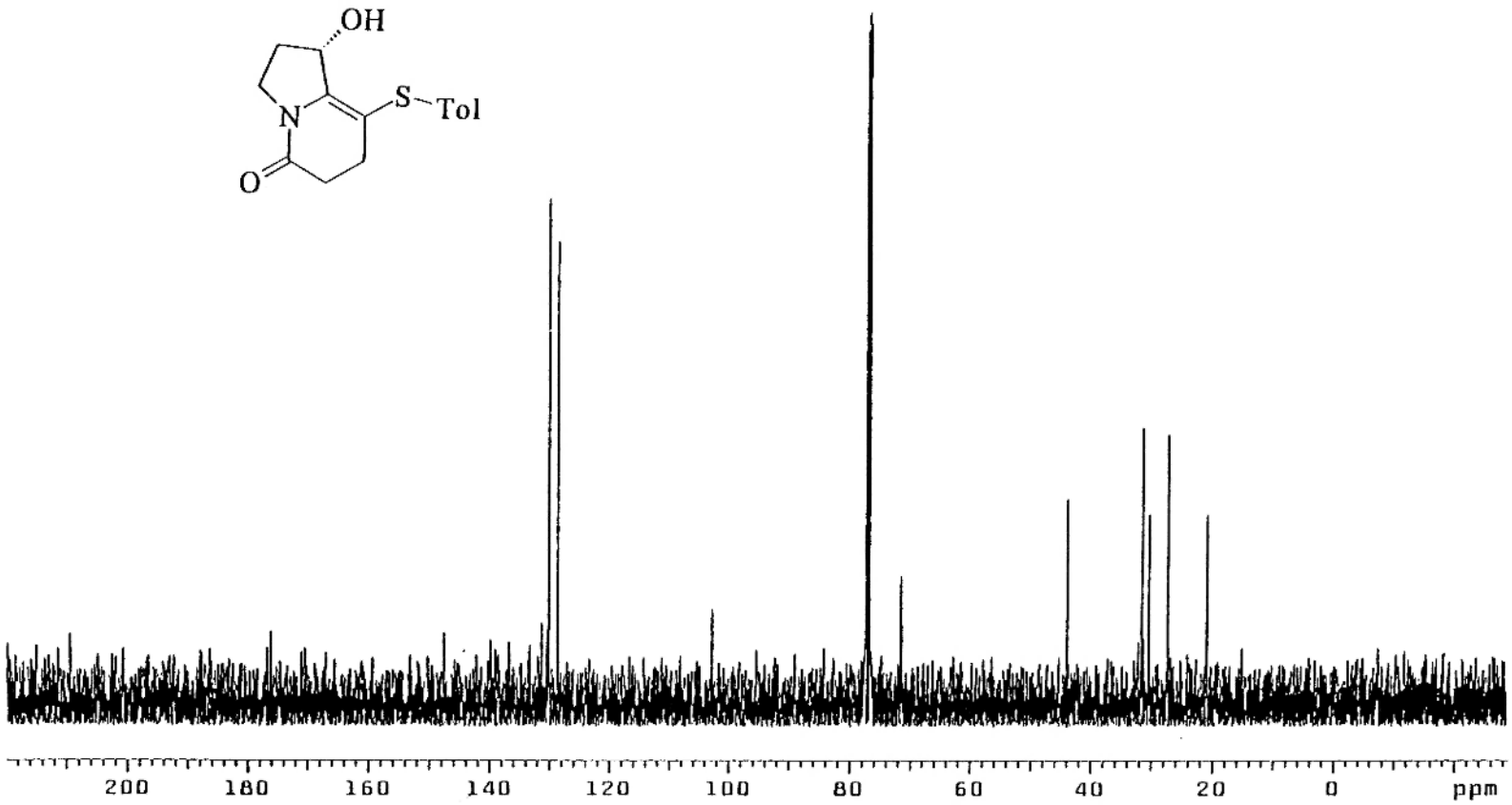


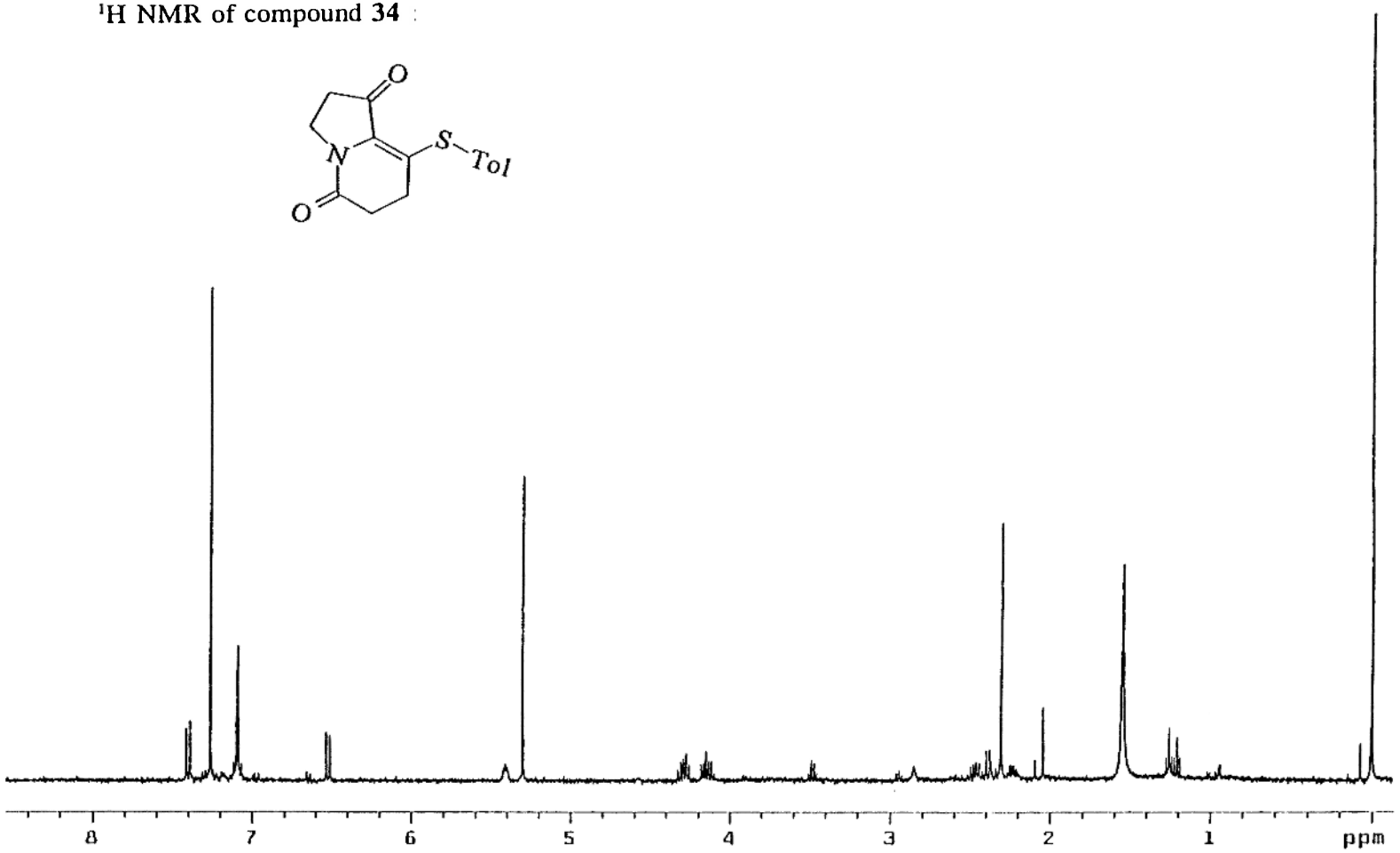
^{1}H NMR of compound **33** :



^{13}C NMR of compound **33** :



^{1}H NMR of compound **34** :



^{13}C NMR of compound **34** :