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Studies Directed Toward The Diastereocontrolled Synthesis Of Heritol

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STUDIES DIRECTED TOWARD THE DIASTEREOCONTROLLED SYNTHESIS

OF HERITOL
(TITLE)

BY

PRASHANTH K. PADAKANTI

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STUDIES DIRECTED TOWARD THE DIASTEREOCONTROLLED SYNTHESIS OF HERITOL

PRASHANTH K. PADAKANTI

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Table of Contents

Abstract

3,3-Dichloro-4-indanyloxetan-2-one was synthesized and its double ring expansion in the presence of the Lewis acid magnesium bromide was investigated, which resulted only in a *trans*-fused butyrolactone in 25% yield. Of the natural products containing butyrolactones fused to 6-membered rings, *trans* is more common. This method of double ring expansion can be applied to the synthesis of the natural product heritol, whose core structure contains the butenolide moiety. A model study of the double ring expansion was performed with 3-chloro-4-indanyl-3-methyloxetane-2-one **B6**, but this study was not completed.

In order to apply the double ring expansion methodology to synthesize heritol, the preparation of 5-methoxy-3,6-dimethyl-1-indanone starting with *p*-methylacetophenone, was attempted. Since two key references discussing the synthesis of ester **C6** were found much later and some of the results were not reproducible, it's completion was not achieved.

The synthesis of 3,3-disubstituted-4-indanyl-β-lactones via [2+2] cycloaddition of 1-indanecarboxaldehyde with disubstituted ketenes and subsequent ring expansion, along with the attempted synthesis of 5-methoxy-3,6-dimethyl-1-indanone, the starting material for heritol synthesis, are discussed in detail.

Acknowledgement

I gratefully acknowledge Professor T. Howard Black for giving me an opportunity to work on this project. My experimental skills were greatly improved by his valuable guidance throughout my graduate work.

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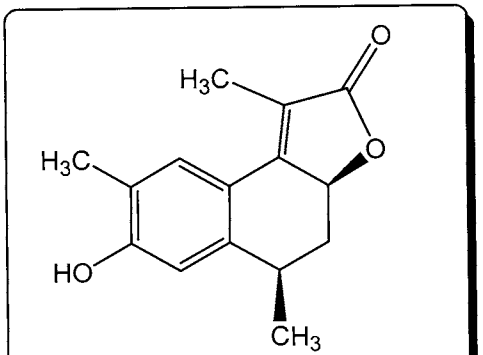
List of Figures

List of Schemes

Introduction



(±) Heritol

Heritol, a naturally occurring compound belonging to the cadinane group of sesquiterpenes, has been found to be toxic towards fish.[1] Miles and co-workers were the first to extract heritol in 1985 from the roots of *Heritiera littoralis,* a mangrove species used by fishermen in the Philippines as a fish toxin. The toxicity of this compound was tested on *Tilapia nilotica* fingerlings, which are a young and resistant species of fish able to survive in adverse conditions.[2] Heritol showed total mortality of ichthyotoxicity in 90 min[3] at a concentration of 20 ppm based on the quick screening test (QST). In this test, fish under investigation were first acclimatized to clean water in a glass tank and slowly the plant extract was added to the water, and mortality was observed. The time gap between the introduction of plant extract and the death of the first fish was considered initial mortality and the time gap between the introduction of the plant extract and the death of all the fish was considered total mortality.[2]

To isolate heritol, twenty one kilograms of the dried chopped roots of *H. littoralis* were continuously extracted with hexane for 16 hrs.[1] The resultant

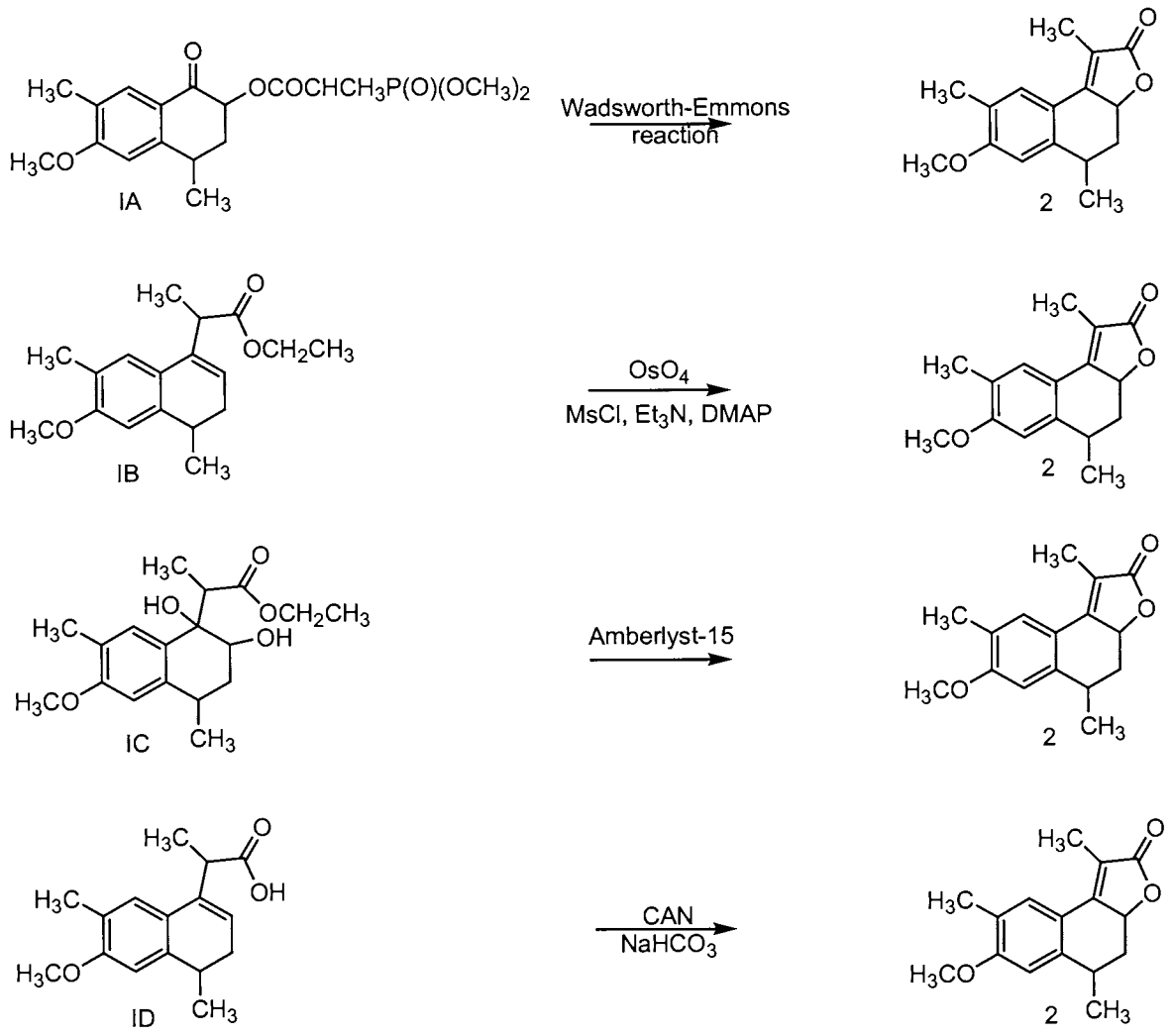
plant material was continuously extracted with 95% ethanol for 16 hrs and evaporation of the solvent gave 254 grams of crude extract which was partitioned between equal amounts of chloroform and water. Evaporation of the chloroform layer gave 38.4 grams of crude material. The methylene chloride soluble part of the crude material was subjected to separation on column chromatography using gradient hexane-benzene-chloroform-methanol solvent systems. The twenty percent benzene-chloroform fractions were collected and solvent evaporated. The residue was dissolved in minimum amounts of hot methanol. Heritol crystallized as white needles after 24 hrs.[1] The structure and relative stereochemistry of heritol were assigned based on mass spectrometry, NMR and UV spectroscopic data, and further verified by single crystal x-ray analysis.[1] Once it was isolated and purified, and it's structure elucidated, heritol became a popular target for synthetic researchers around the world.[4,5,6] The allure of heritol as a synthetic target is due to it's oxygenation pattern and the presence of an aromatic ring which is unusual for the cadinane skeleton.[1] The potential of heritol as a fish toxin suggests that compounds such as heritol could be a natural pesticide.[1]

Some research groups have synthesized heritol,[4,5] or performed studies toward synthesizing heritol,[6,7] but every synthesis has been stereorandom, meaning that there was no attempt at stereocontrol, despite the existence of only two chiral centers. The key in their syntheses of the lactone ring involved either intramolecular Wittig,[4] osmylation followed by making the secondary alcohol to a leaving group followed by intramoecular cyclization,[5a]

Amberlyst-15 mediated[5b] and ceric ammonium nitrate mediated[5c] cyclizations (**Figure I**). In order to obtain the product in a stereocontrolled manner, we planned to apply the "double ring expansion technique", a unique methodology developed in the Black laboratory in synthesizing *trans*-fused butyrolactones.[8]

Figure I

Previous methodologies for Heritol synthesis

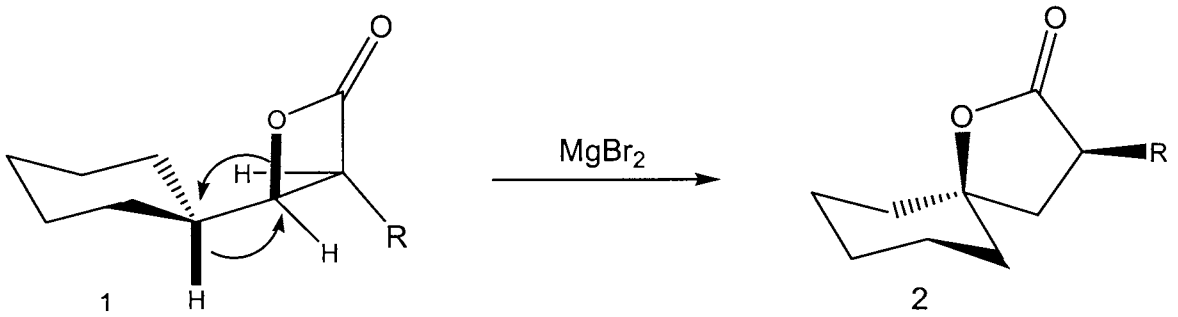


Much research has been done on β-lactone ring expansions.[9,10] β-Lactones are considered to be very useful synthetic intermediates because of their high strain energy (22 kcal/mol)[9] and resultant ease of opening by nucleophiles or Lewis acids; they also constitute an important class of organic compounds due to their presence in some antibiotics and many natural products.[10]

The β-lactone ring expansions, catalyzed by ethereal magnesium bromide were reported to be stereospecific, concerted examples of dyotropic rearrangements.[9] Later on, β-lactone ring expansions were also carried out in the presence of another Lewis acid, titanium tetrachloride.[10] In order for the β-lactone ring to expand to a γ-lactone, the migrating groups need to be in an antiperiplanar orientation. The example below (**Figure II**) shows that the carbon – oxygen bond and the migrating carbon – hydrogen bonds are anti to one another, resulting in spirolactone **II2**.[11]

Figure II

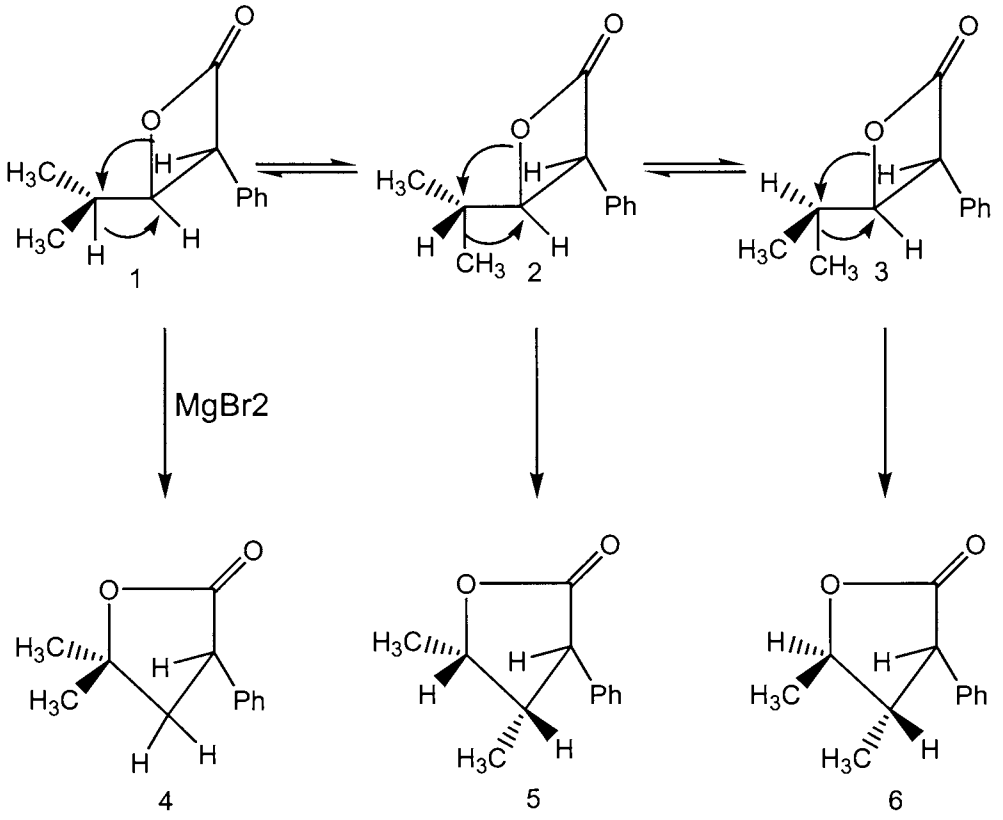
Ring expansion of cyclohexyl-b-lactone



In β-lactones where there are both hydrogen and methyl groups able to achieve the anti periplanarity to the C – O bond of the lactone, hydrogen migration is preferred to methyl migration (**Figure III**).[9] The β-lactone **III1** will be in equilibrium with its conformers **III2** and **III3** obtained by C – C rotation, but experimental results showed that butyrolactone **III4** is obtained in higher proportion (78%) compared to **III5** and **III6** whose yields were 7% and 15% respectively.[9] The evidence obtained can be explained in terms of a less stable secondary carbocation going to more stable tertiary carbocation. However, involvement of carbocationic intermediates in this process has not yet unambiguously been resolved.[10]

Figure III

Importance of anti-periplanar orientation of migrating bonds

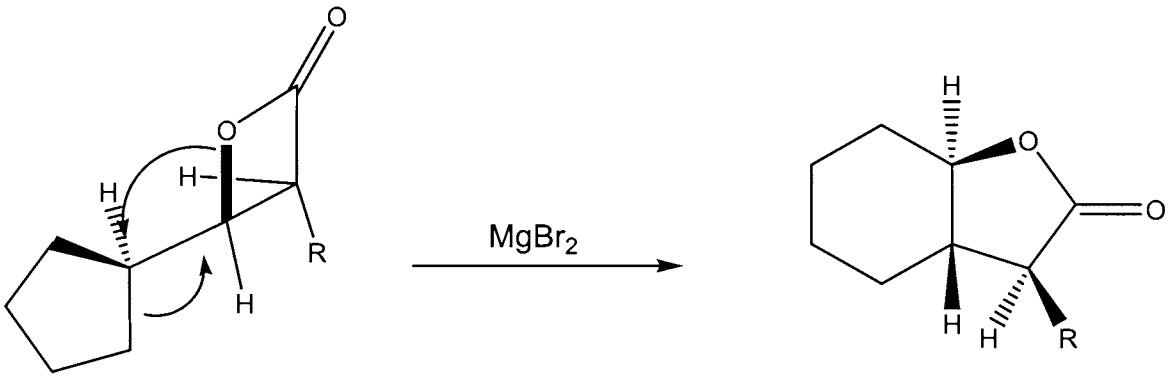


Double ring expansion of cyclopentyl β-lactone

In extending the above studies to cyclopentyl β-lactones, carbon migration was observed rather than hydrogen migration. This resulted in the expansion of two rings simultaneously, leading to the fused butyrolactone **IV2** (**Figure IV**).[11]

Figure IV

Double ring expansion of cyclopentyl -lactone



1 2

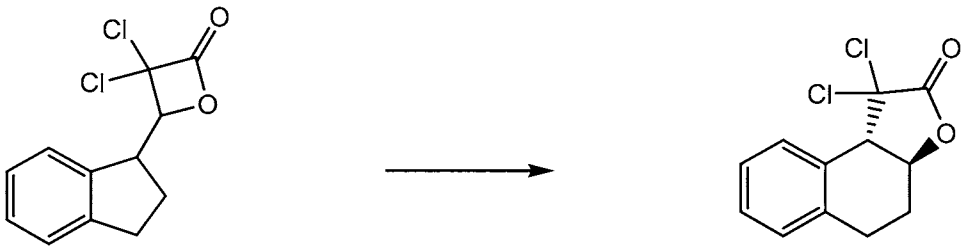
The carbon migration was observed in the above rearrangement due to the inherent strain in the cyclopentane ring in β-lactone **IV1** compared to the cyclohexane ring in γ-lactone **IV2**. Literature, employing molecular mechanics revealed that the inherent strain in cyclopentane is 6.14 kcal/mol higher than the strain in cyclohexane.[12] This inherent strain is thought to be the driving force for the carbon migration rather than the hydrogen (**Figure IV**).

In order to see whether the double ring expansion results in the cyclohexyl butyrolactone when a bicyclic group is attached to a β-lactone, a

model study of β-lactone ring expansion was performed earlier (Black, T. H personal communication) with 1-indanyl-β-lactone **V1 (Figure V)**.

Figure V

Double ring expansion of Indanyl-β-lactone



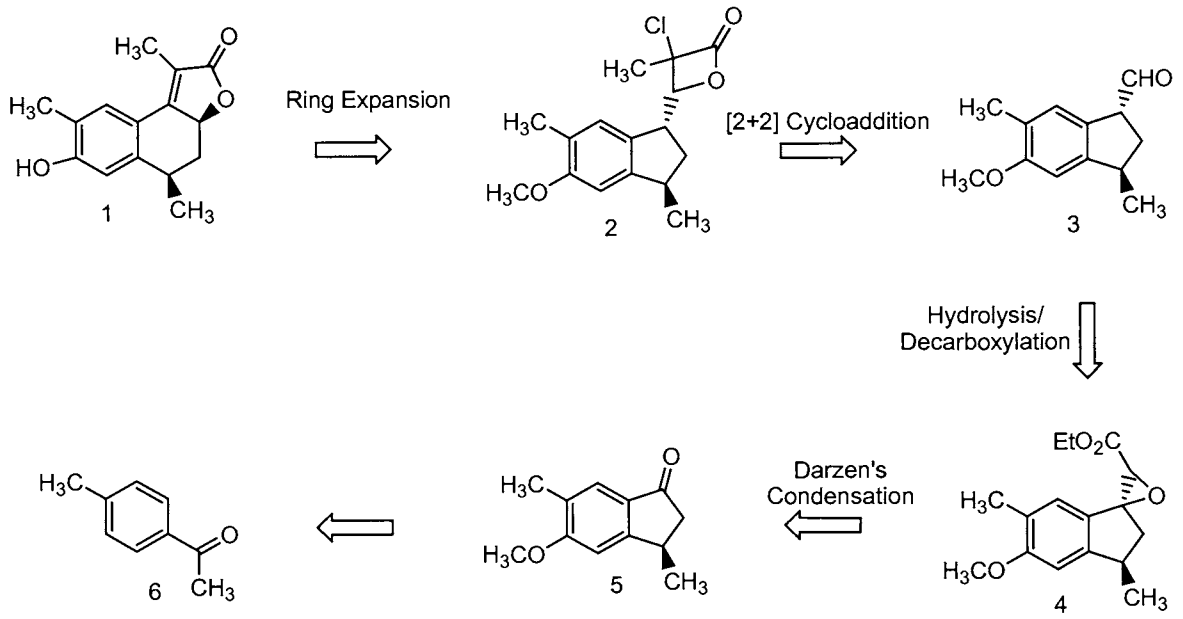
1 2

Retrosynthesis of heritol from Indanone starting material

The retrosynthetic analysis of heritol (Scheme A) envisioned the double ring expansion of the β-lactone **A2** to generate the desired *cis* stereochemistry of the fused ring in the target molecule **A1**. A [2+2] cycloaddition of chloromethyl ketene and aldehyde **A3** would give the β-lactone **A2**. Aldehyde **A3** can be synthesized by the Darzen's condensation of starting material ketone **A5** followed by hydrolysis/decarboxylation. The starting material **A5** can be synthesized by nitrating *p*-methylacetophenone **A6** and following simple functional group interconversions, Wittig reaction, reduction of the resultant olefin followed by cyclization.

Scheme A

Retrosynthetic analysis of Heritol



A key feature of the structure of heritol is a butenolide moiety fused to a six membered ring. Our plan was that the double ring expansion of 1-indanyl-β-lactone **A2** would result in the analogous γ-lactone **B8** that would easily be oxidized to the butenolide **A1**.

There are various methods to construct the butenolide ring,[4,5] the most common being the formation of a γ-lactone by intramolecular esterification followed by E-2 elimination. Formation of the butenolide rings by a single electron oxidant β,γ-unsaturated carboxylic acids has also been reported.[5c]

Our plan in constructing the butenolide ring involves synthesizing a β-lactone via the [2+2] cycloaddition of an aldehyde and ketene, followed by β-lactone ring expansion, and then creating the α,β-unsaturation in the lactone ring.

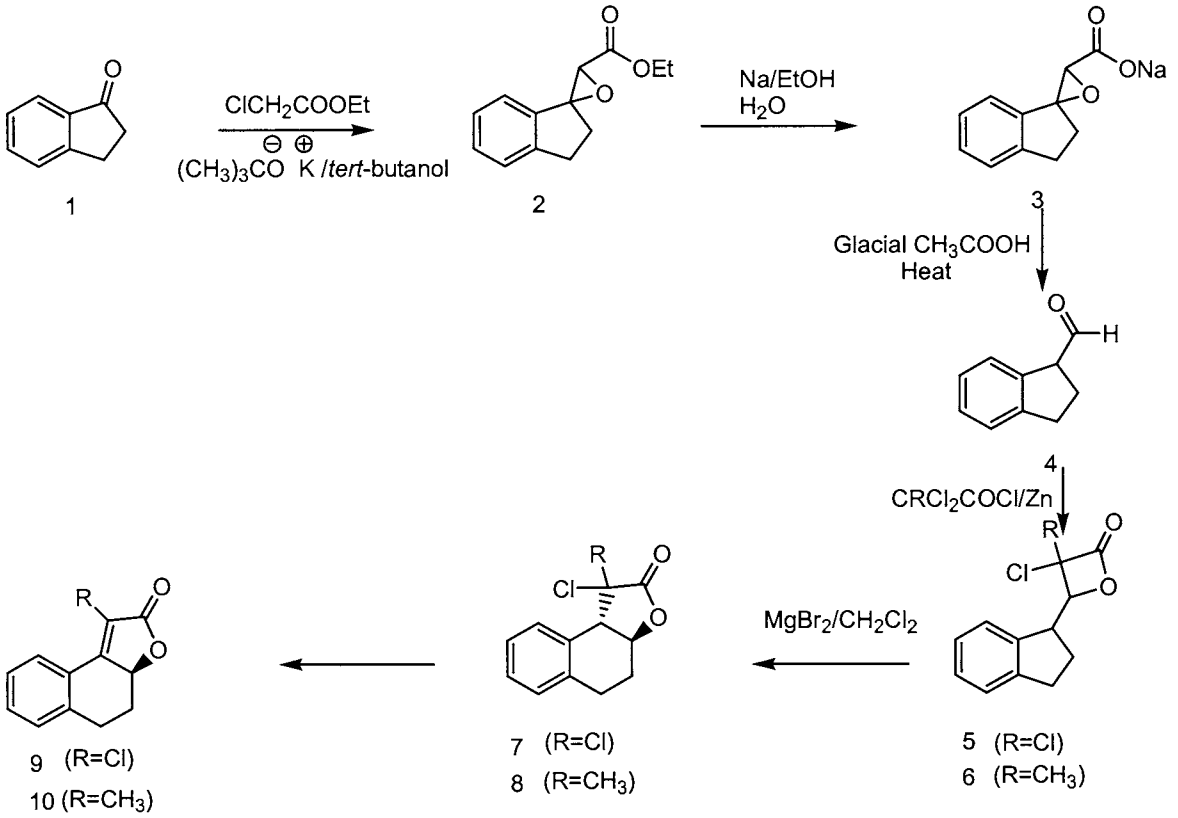
In order to create the double bond, a leaving group needs to be present in the lactone ring, which can be achieved by reacting an aldehyde with a ketene containing a leaving group.

Proposed Model study with 1-indanyl-β-lactone

A model study needs to be performed on a simple system with the closest molecular structure to the final target heritol. Based on the above known chemistry, the model study (Scheme B) was planned to start with 1-indanone **B1** and transform it into 1-indanyl-β-lactones **B5** and **B6** in order to synthesize cyclohexyl *trans*-fused butyrolactones **B7** and **B8**.

Scheme B

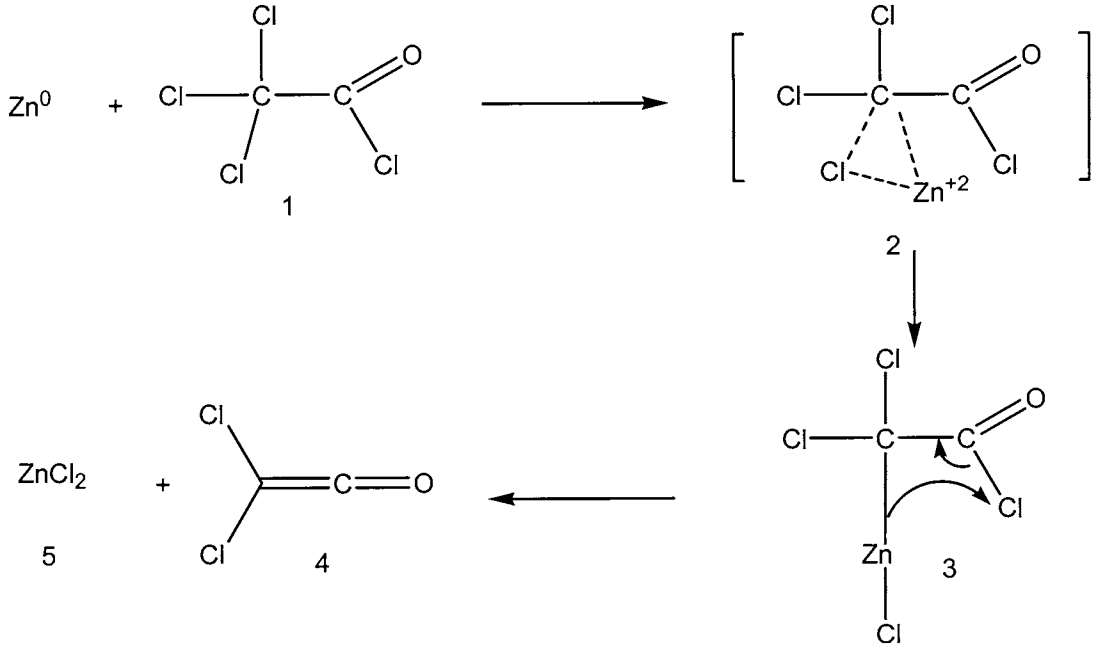
Proposed model study of Indanyl-β-lactone ring expansion



The model study starts with the transformation of 1-indanone **B1** to 1-indanecarboxaldehyde **B4** following the procedure of Kavadias *et al.*[13] Conversion of 1-indanecarboxaldehyde **B4** to the corresponding β-lactone **B5** was planned via Brady's procedure, which involves the dehalogenation of trichloroacetyl chloride in the presence of activated zinc (formed by treatment with copper sulfate solution)[14] to form a dichloroketene **VI4** which undergoes a [2+2] cycloaddition with 1-indanecarboxaldehyde **B4** (**Figure VI**)[15].

Figure VI

Mechanism of ketene formation



The crux of the dyotropic rearrangements of β-lactones **B5** and **B6** is the orientation of the migrating bonds, which, as seen earlier (**Figure II**), must be anti to each other, resulting in the butyrolactones **B7** and **B8**. Upon dehydrohalogenation in the presence of a hindered base like 1,8-

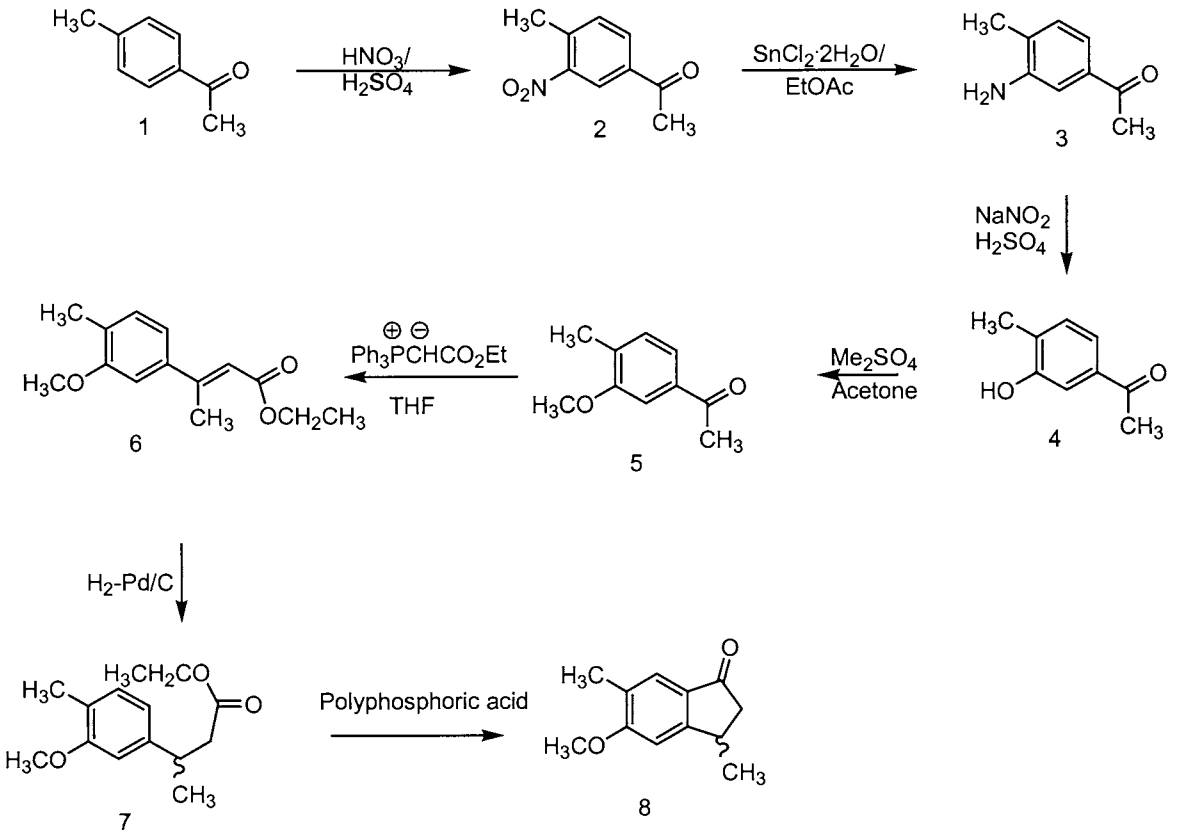
diazabicyclo[5.4.0]undec-7-ene (DBU), E2 elimination should result in the butenolides **B9** and **B10**.

Synthesis of starting material of heritol

In order to synthesize the starting material for the synthesis of heritol whose skeletal structure is similar to the 1-indanone **B1**, Scheme C was proposed. Much later, two articles were found describing syntheses of esters **C6**[16] and **C7**;[17] one of which used the same starting material **C1**.[17]

Scheme C

Our strategy to synthesize starting material of Heritol



The starting material **C8** can be synthesized from cheaply available *p*-methylacetophenone **C1**. Nitration of **C1** will result in the formation of 4-methyl-3-nitroacetophenone **C2**,[18] and reduction with tin (II) chloride dihydrate affords 3-amino-4-methylacetophenone **C3**.[19] Diazotization/hydrolysis of **C3** produces 3-hydroxy-4-methylacetophenone **C4**,[20] which is methylated with dimethylsulfate to give 3-methoxy derivative **C5**.[21] Treatment with (carbethoxymethylene)triphenyl phosphorane should afford *E*-isomer of unsaturated ester **C6**.[22] Catalytic reduction would provide a mixture of enantiomers **C7**,[23] which upon cyclization in the presence of polyphosphoric acid, should provide the starting material **C8**.[24]

The starting material **C8** will be used to synthesize heritol, following the method shown in Scheme D. Scheme D starts with the diastereocontrolled conversion of ketone **D1** to epoxy ester **D2** via a Darzens glycidic ester condensation reaction. Since the angle of attack of the nucleophile on the carbonyl should be 107° to the carbonyl C – O bond,[25] the attack of enolate of ethylchloroacetate on the carbonyl of **D1** will follow path b (**Figure VII**). The enolate cannot attack the carbonyl via path a because the methyl group in the ring B will sterically block the favored angle of attack, leading to the single diastereomer of the epoxy ester **D2**.[13]

Hydrolysis of the ester **D2** and its conversion to aldehyde **D4** would follow the Kavadias procedure.[13] The aldehyde **D4**, upon treatment with 2,2-dichloropropionyl chloride in the presence of zinc, would form β-lactone **D5**.[15]

Scheme D

Our approach to synthesize Heritol

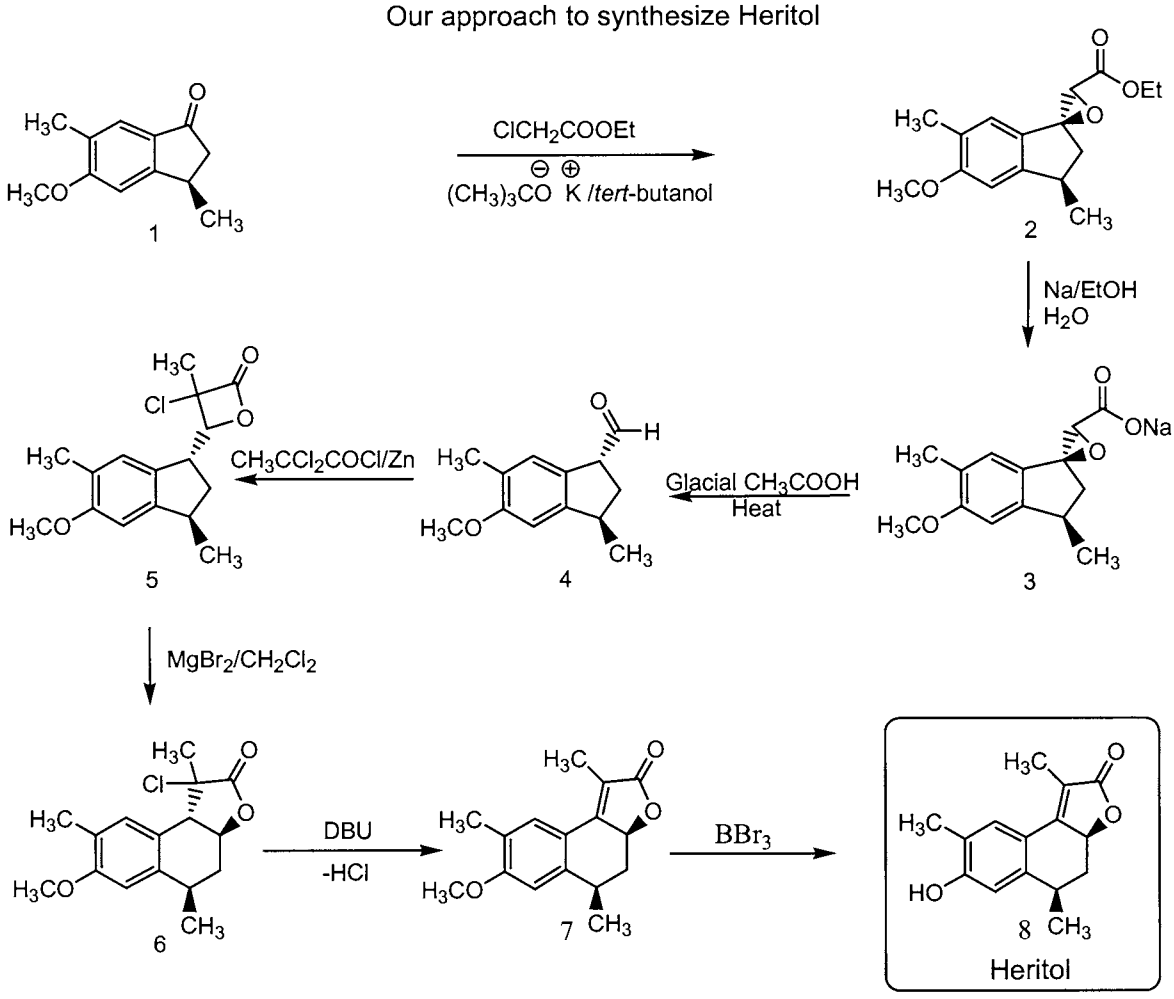
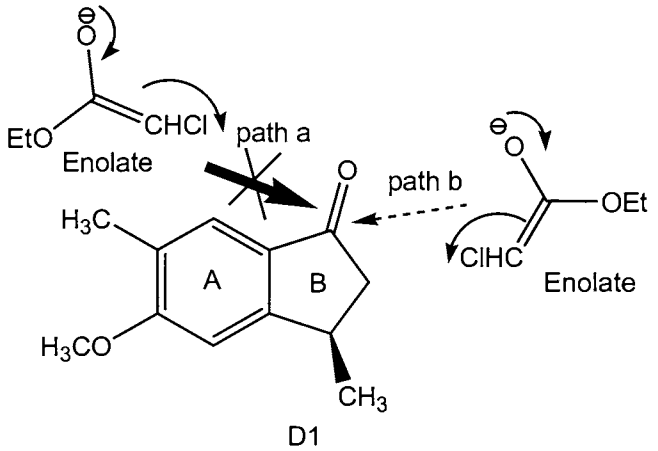


Figure VII

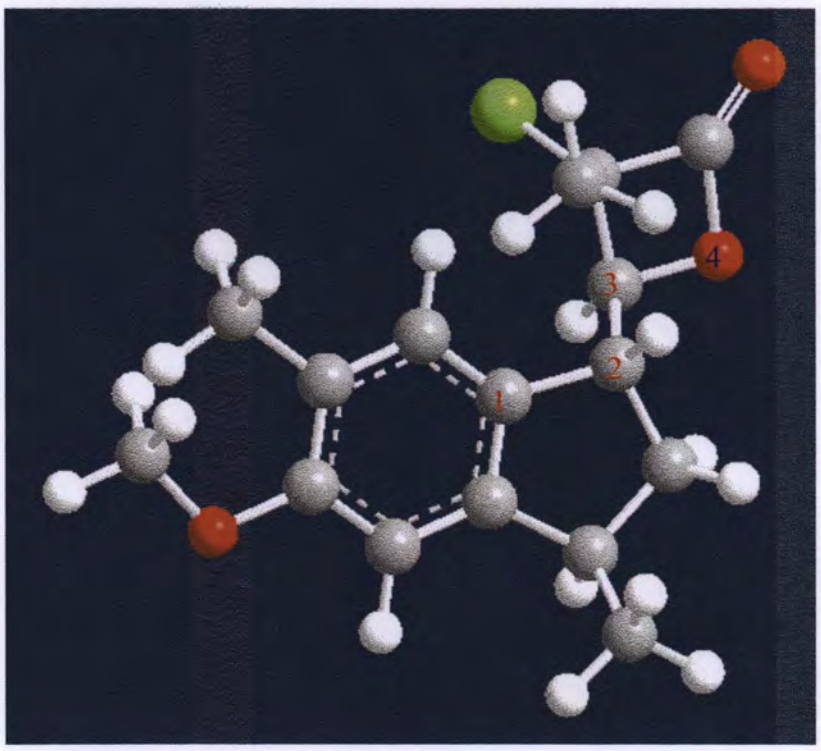
Diastereocontrolled step



Treatment of **D5** with anhydrous magnesium bromide would result in *trans*-fused butyrolactone **D6**.[8] In order for the β-lactone **D5** to transform to γ-lactone **D6**, the migrating bonds C – C (labeled as 1 and 2) of cyclopentyl group and C – O (labeled as 3 and 4) of lactone need to be anti to each other (**Figure VIII**). The energy-minimized structure of β-lactone **D5** (**Figure VIII**)[26] shows that these migrating bonds (1,2 and 3,4) are oriented in nearly the required fashion, and the cyclopentyl and β-lactone ring strains will favor the transformation from **D5** to **D6**. **D6** upon treatment with DBU, a hindered base, will undergo an E2 elimination and result in butenolide **D7**. An exocyclic double bond could also

Figure VIII

Anti-periplanar orientation of migrating bonds in substituted indanyl-β-lactone



D5

result from the E2 elimination, but this should isomerize[27] to butenolide **D7** in the presence of DBU due to the extended conjugation in **D7**. Upon treatment of **D7** with boron tribromide,[5a] demethylation will occur, leading to the target molecule heritol, **D8**. Thus, this synthesis will be the first diastereocontrolled total synthesis of heritol.

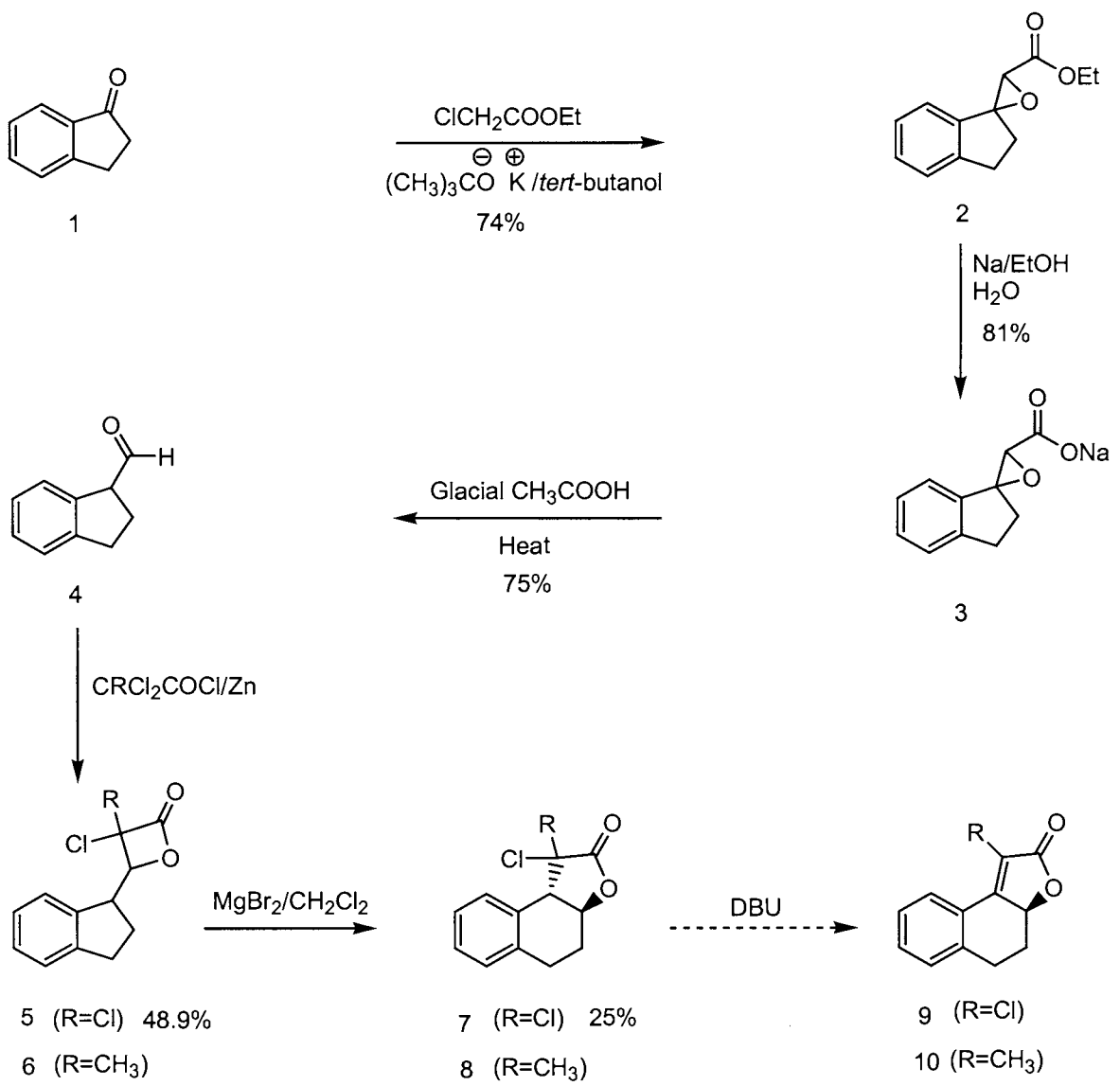
Results and Discussion

Model study of double ring expansion of 1-indanyl-β-lactone

The aim of this part of the project was to synthesize both 3,3-dichloro-4-indanyloxetane-2-one **B'5** and 3-chloro-4-indanyl-3-methyloxetane-2-one **B'6** from 1-indanone **B'1** and investigate their ring expansions leading to the *trans*-fused butyrolactones **B'7** and **B'8**.

Scheme B'

Results-Model study of double ring expansion of Indanyl- -lactone



1

2

3

4

5 (R=Cl) 48.9%

6 (R=CH_3)

7 (R=Cl) 25%

8 (R=CH_3)

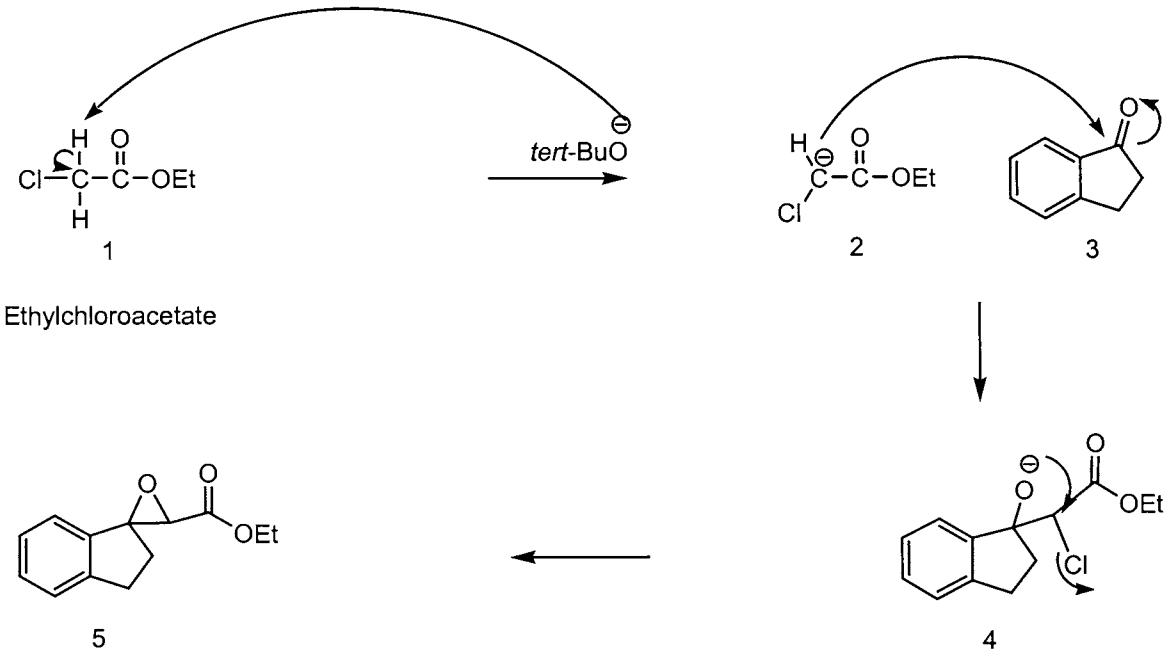
9 (R=Cl)

10 (R=CH_3)

The synthesis of the epoxy ester **B'2** followed the Darzens glycidic ester condensation[13] of 1-indanone **B'1** with ethyl chloroacetate. Mechanism of the Darzen's condensation is shown below (Scheme E).

Scheme E

Mechanism of Darzen's condensation



After completion of the reaction, carbon dioxide gas was passed through the reaction mixture with the help of a gas bubbler to generate carbonic acid, which neutralizes the basic reaction mixture; this turned the green reaction mixture to cream. The crude product, as brown oil, was obtained in 74% yield. The IR absorption for the carbonyl of the crude epoxy ester **B'2** showed an

intense band at 1748 cm^{-1}, corresponding to the literature value of 1745 cm^{-1}.[13] Purification of this compound (epoxy ester **B'2**) was not attempted.

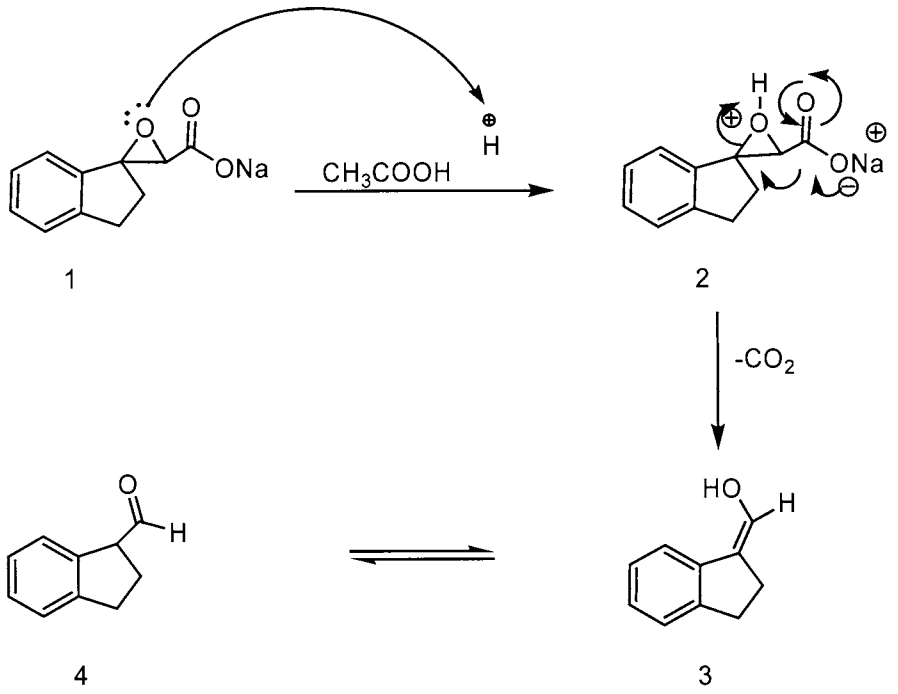
The hydrolysis of the glycidic ester **B'2** was followed according to the procedure followed by Kavadias.[13] Sodium ethoxide was prepared by the addition of the sodium metal to absolute ethanol; vigorous evolution of hydrogen gas was observed. Deionized water was added slowly to the sodium ethoxide to generate hydroxide ions, at which point the epoxy ester was added slowly resulting in the formation of pink solids. The resultant reaction mixture was stirred in an ice-bath for 15 min, and then at room temperature for 4 hrs. The sodium salt of the epoxy acid **B'3** was obtained as dirty pink powder in 81% yield. The IR absorption of the carbonyl of sodium salt of epoxyacid **B'3** showed a band at 1615 cm^{-1}, whereas the literature value is 1610 cm^{-1}.[13] The decrease in the IR absorption band is due to the resonance stabilization of carboxylate anion.

Thermal decarboxylation[13] of sodium salt **B'3** resulted in the formation of 1-indanecarboxaldehyde **B'4**, accompanied by the vigorous evolution of carbon dioxide gas (Scheme F). The crude 1-indanecarboxaldehyde **B'4** showed three spots on TLC (benzene) at R_f 0.44 (major), 0.08 (minor) and 0.00 (minor). The literature[13] values were 0.53 (major), 0.23 and 0.00 (minor).

Attempted distillation of the aldehyde from the crude product never afforded the pure aldehyde. Maybe the small amount of impurity also had the same boiling point as aldehyde **B'4**.

Scheme F

Mechanism of decarboxylation of Sodium Indane-1-spiro-2'-oxiran-3'-carboxylate



1 2 4 3

Even after bulb-to-bulb distillation, the material obtained showed three spots on TLC. The mixture was separated by column chromatography, using benzene as the eluent, to yield 26% of the aldehyde, which showed a major spot at R_f 0.34 and a minor spot at R_f 0.05. TLC value for the pure 1-indanecarboxaldehyde was not reported in the literature. In accordance with the literature,[13] the crude aldehyde **B'4** was used for the next step without further purification. The IR spectrum of the above compound **B'4** showed an intense band at 1722 cm^{-1}; The literature value is 1725 cm^{-1}.[13] The NMR spectrum showed a doublet at 9.6 ppm which is a significant value for the aldehyde proton; the enol form was not observed (if present, should observe a peak at ~12 ppm).[28]

The literature NMR value for the aldehyde proton was a doublet at 9.6 ppm.[13] A triplet of doublets for an α proton to the aldehyde carbonyl was observed at 4.0 ppm.

The dichloro-β-lactone **B'5** was synthesized using the [2+2] cycloaddition of dichloroketene[15] and 1-indanecarboxaldehyde **B'4**. When the trichloroacetylchloride was added to the mixture of 1-indanecarboxaldehyde **B'4** and activated zinc in ether, dichloroketene was formed *in situ*, which reacted with 1-indanecarboxaldehyde resulting in the formation of dichloro-β-lactone **B'5**. TLC (50% EtOAc/hexanes) showed presence of starting material after 16 hrs of stirring. So, additional trichloroacetylchloride and activated zinc was added, and a very faint spot for starting material was observed after stirring for an additional 7 hrs, at which point the reaction was stopped. The IR absorption for the carbonyl of the crude dichloro-β-lactone **B'5** showed an intense band at 1858 cm^{-1} (α,α-dichloro-β-lactones show carbonyl absorption at 1860 cm^{-1}).[29a] The crude dichloro-β-lactone **B'5** obtained in 48.9% yield was used for the next step without any purification.

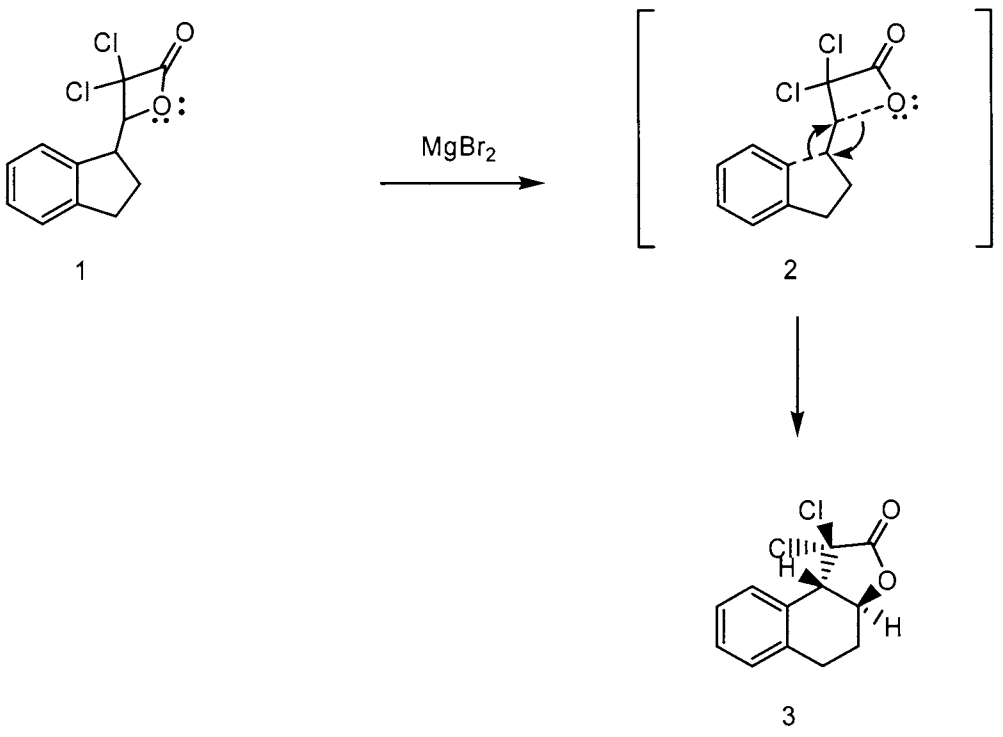
The transformation of dichloro-β-lactone **B'5** to *trans*-fused dichloro-γ-lactone **B'7** was catalyzed by magnesium bromide (Scheme G),[8] which was freshly prepared by a slow addition of 1,2-dibromoethane to the magnesium turnings in ether. After completion of the vigorous reaction, the solvent was removed via aspirator vacuum (using an in-line drying tube to exclude moisture) yielding magnesium bromide. Generally, the β-lactone ring expansions were

carried out in ether solvent. Due to the presence of chloro substituents in compound **B'5**, the solvent of choice is methylene chloride.

The product obtained was a gum, which was hot filtered in 95% ethanol; evaporation of the solvent yielded a brown solid, which showed three spots on TLC (methylene chloride). The dichloro-γ-lactone **B'7** was separated on silica gel column with methylene chloride as the eluent to give 0.1 g (25% yield) of yellowish brown solid. The overall yield for this section was 2%.

Scheme G

Mechanism of double ring expansion of Indanyl-β-lactone



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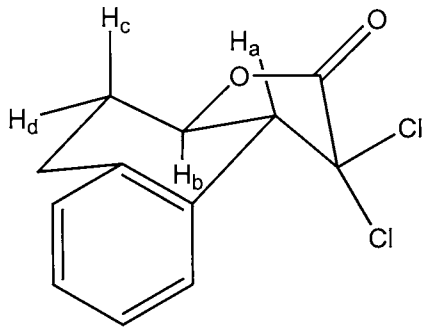
The IR spectrum of the dichloro-γ-lactone **B'7** showed the carbonyl absorption at 1805 cm^{-1} (the literature value for a dichloro-γ-lactone showed IR

absorption at 1800 cm^{-1}).[29b] The H^1 NMR spectrum showed a doublet at 3.8 ppm for the proton present on the β-carbon of the carbonyl (H_a) of fused γ-lactone (**G3**), with a coupling constant of 10.2 Hz (**Figure IX**) which indicates the product is *trans*-fused γ-lactone.[29c] (A *cis*-fused γ-lactone should show a doublet with an approximate coupling constant of 3 Hz).[29c] A doublet of doublet of doublet at 4.5 ppm was observed for H_b with a coupling constant values of 12.2, 10.2, 3.9 Hz due to the presence of three non-equivalent protons (H_a, H_c and H_d) present on the two adjacent carbon atoms.

Figure IX

Structure of trans-3,3-Dichloro-4,5,10,11-tetrahydronaphthofuran-2-one



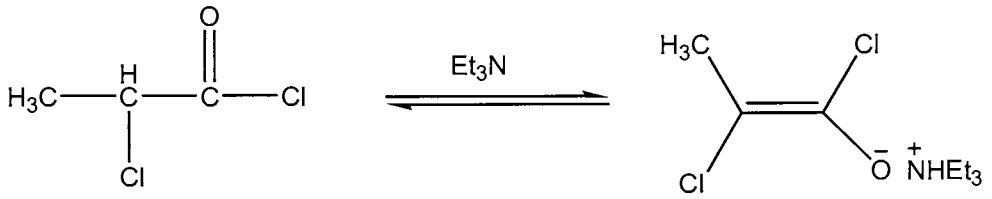
G3

The synthesis of 3-chloro-4-indanyl-3-methyloxetane-2-one **B'6** was attempted via the treatment of 1-indanecarboxaldehyde with chloromethyl ketene, formed *in situ* from α-chloropropionylchloride **H1** in the presence of triethylamine base.[30] The reaction was not successful, since the literature

suggests that when α-chloropropionyl chloride **H1** is treated with triethylamine, the enolate salt **H2**[31] rather than the expected ketene is obtained (Scheme H).

Scheme H

Reaction of 2-chloropropionyl chloride with triethylamine



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Therefore, the method previously used (**Figure VI**) to generate dichloroketene was employed, and chloromethyl ketene was generated *in situ* by the dehalogenation of 2,2-dichloropropionyl chloride[15] in the presence of activated zinc.[14]

2,2-Dichloropropionyl chloride was prepared by treating one equivalent of 2,2-dichloropropionic acid with more than two equivalents of thionyl chloride in methylene chloride and a catalytic quantity of N,N-dimethylformamide (DMF).[32] The DMF helps in generating highly reactive chloride ions, thereby enhancing the reaction rate. After refluxing for 10 hrs, the IR spectrum of the reaction mixture showed an intense band at 1779 cm^{-1} for the carbonyl of 2,2-dichloropropionyl chloride, indicating the conversion of 2,2-dichloropropionic acid to 2,2-dichloropropionyl chloride.[33] After the reaction was complete, unreacted thionyl chloride was collected by distillation at 84°C. (Literature boiling point of

2,2-dichloropropionyl chloride is 117-119°C).[34] The IR spectrum of the thionyl chloride distillate showed presence of 2,2-dichloropropionyl chloride.

When the 2,2-dichloropropionyl chloride/thionyl chloride mixture was added to 1-indanecarboxaldehyde **B'4** and activated zinc in the ether, 3-chloro-4-indanyl-3-methyloxetane-2-one **B'6** was produced in quantitative yield. The TLC (50% EtOAc/hexanes) showed complete disappearance of the starting material spot after 36 hrs, at which point the reaction was stopped. The green oil after the work up showed IR absorptions at 1837 cm^{-1} (the literature IR absorption value for the carbonyl of α-chloro-α-methyl-β-lactones is 1835 cm^{-1}).[35]

The transformation of 3-chloro-4-indanyl-3-methyloxetane-2-one **B'6** to the *trans*-fused γ-lactone **B'8** was again catalyzed by freshly prepared magnesium bromide; this time the reaction required five days of stirring for completion. The reaction progress was checked on TLC. Identification and purification of the compound obtained **B'8** was not attempted due to the time constraints.

Summary for the model studies

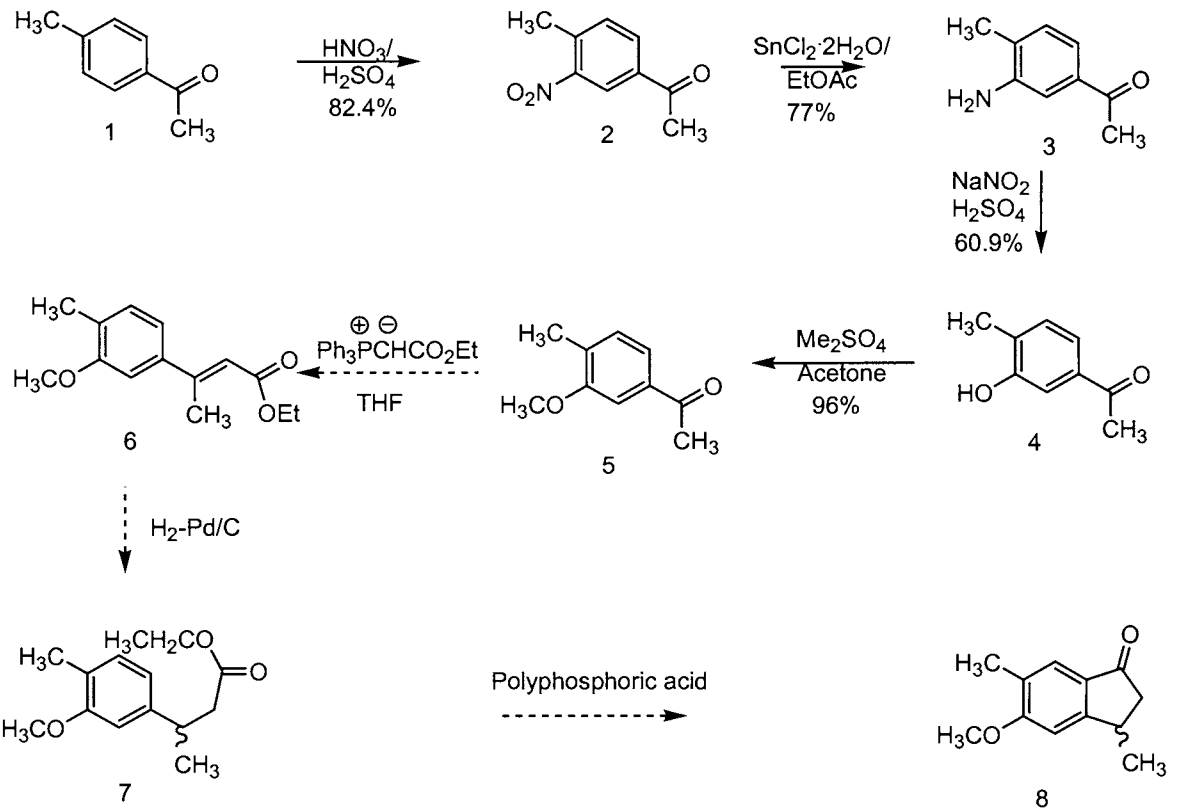
3,3-Dichloro-4-indanyloxetan-2-one **B'5** was synthesized starting from 1-indanone **B'1**. The model study of the double ring expansion of 3,3-dichloro-4-indanyloxetan-2-one **B'5** to the *trans*-3,3-dichloro-4,5,10,11-tetrahydro naphthofu-ran-2-one **B'7** was accomplished with 25% yield. The transformation of 3-chloro-4-indanyl-3-methyloxetane-2-one **B'6** to the corresponding γ-lactone was attempted but its study was not complete.

Synthesis of Heritol

The synthesis of heritol began with *p*-methylacetophenone **C'1** and followed the transformations depicted in Scheme C. Later, reference articles for the transformation from *p*-methylacetophenone **C'1** to esters **C'6**[16] and **C'7**[17] were found using different reaction conditions. *p*-Methylacetophenone **C'1**, which is commercially available and cheap, was used as the starting material for the synthesis of 5-methoxy-3,6-dimethyl-1-indanone **C'8**.

Scheme C'

Results-Starting material synthesis of Heritol



Nitration on *p*-methylacetophenone **C'1** was accomplished according to the procedure of Morgan and Pettet.[18] A solution of concentrated nitric acid and concentrated sulfuric acid (2:3 ratio) was added to the starting material, *p*-methylacetophenone **C'1**, and stirred at 0°C for an hour. The mixed acid needed to be added very slowly in order to control the temperature, which was critical in obtaining a high yield and to avoid decomposition. The best result obtained for this reaction was when the reaction temperature was maintained between -2°C and 6°C using a sodium chloride/crushed ice bath. The addition of 20 mL of mixed acid to the starting material took 8 hrs.

Literature revealed no information about the spectral analysis for this compound.[16,17,18,36,37] The IR absorption for the carbonyl of this compound showed a sharp band at 1693 cm^{-1}. The H^1 NMR spectrum showed a 6H singlet at 2.65 ppm for the protons on the methyl group of the aromatic ring and the methyl group adjacent to the carbonyl carbon. A doublet peak was observed 8.50 ppm and 7.50 ppm and a doublet of doublet was observed at 8.25. TLC showed a neat, single spot at R_f 0.42 in 25% EtOAc/hexanes as the eluent. The melting point reported in the literature was 62°C,[18] but the melting point observed for this compound was 54°C – 56°C. The compound obtained was pale yellow solid in 82.4% yield.

The reduction of the aromatic nitro compound **C'2** was first attempted according to Morgan and Pettet's method,[18] using iron in refluxing 1% hydrochloric acid. After the reaction mixture was refluxed for several hours, TLC (30% EtOAc/hexanes) showed many spots, indicating that the reaction was not

complete but had many byproducts. The IR absorption of the compound **C'2** after workup showed the presence of aromatic amine bands at 3433 and 3348 cm^{-1}. The compound was recrystallized in equal mixture of hexanes, EtOAc and EtOH. The compound obtained showed two spots on TLC (30% EtOAc/hexanes), with a major spot at R_f 0.33 and a faint spot at R_f 0.13, with and yield of 20%.

As the reaction was either not very clean (contained byproduct) or not reproducible, other methods were attempted. Reduction with hydrazine monohydrate[38] gave a product showing a long streak indicating either decomposition or contained many byproducts. Reduction with zinc in the presence of either ammonium formate or formic acid, following Gowda's procedure,[39] yielded many compounds.

Next, hydrogenation with 10% palladium on activated carbon following Hatanaka's procedure[40] was employed. The palladium was activated by treating a catalytic amount of 10% palladium on carbon with ethanol followed by shaking in a hydrogen atmosphere for 45 min before use in the reaction. The reaction was carried out at 3 atmospheres pressure and room temperature. The amine product obtained showed a single spot on TLC, the IR spectrum was in agreement with the compound and the yield obtained was 77%. Unfortunately, the result was not reproducible and the reason was not identified. This reaction was attempted at various temperatures and at various pressures but still the compound was not reduced completely, as TLC showed many spots.

At last, success was realized using tin(II)chloride dihydrate in ethyl acetate.[19] The compound was refluxed for 2 hrs with 1.22 g of tin(II)chloride

dihydrate and approximately 5 mL of ethyl acetate per 1 mmol of the nitro compound **C'2**, at which point TLC (50% EtOAc/hexanes) indicated the absence of starting material with a single, polar spot.

The reaction mixture was cooled, diluted with water, basified with concentrated ammonium hydroxide, and the amine product was extracted with ether and petroleum ether. The extraction was very tedious, as was filtering the compound, but the reaction was successful and reproducible. The IR spectrum showed aromatic amine bands at 3429 and 3348 cm^{-1} and the carbonyl absorption at 1667 cm^{-1}. A sharp band at 1692 cm^{-1} observed for the carbonyl of the nitro compound **C'2** disappeared. TLC (50% EtOAc/hexanes) showed a neat and single spot at R_f 0.29. The ^1H NMR spectrum of the amine compound **C'3** showed singlets at 2.2 and 2.5 ppm, which integrated to 3H, for the methyl protons of the aromatic ring and the methyl protons adjacent to the carbonyl carbon respectively. A singlet broad peak at 3.75 ppm, which integrated to 2H, represented the amine protons. The broad peak was due to hydrogen bonding. The region between 7.0 and 7.3 ppm showed a doublet for one proton and a multiplet for two protons of the aromatic ring. Literature revealed no information about the spectral analysis of this compound.[17,18,36,37] The melting point observed was 71°C-75°C (Literature melting point was 81°C).[18] The yield obtained was 77%.

Diazotization of the aromatic amine **C'3** to the hydroxy compound **C'4** followed Morgan and Pettet's[18] and Ungnade's[20] procedures. The amine **C'3** was added to dilute sulfuric acid, the mixture was heated to aid the dissolution,

and the resultant reaction mixture was cooled to 0°C. The reaction mixture became a thick liquid. At this point, sodium nitrite in water was added to the reaction mixture slowly, maintaining the temperature below 0°C. Stirring continued for an additional 30 min after adding the sodium nitrite mixture; urea in ice-cold water was added to the reaction mixture in small portions. The reaction mixture was filtered and the resultant solution containing diazonium salt was kept cold until it was added to boiling sulfuric acid. The reaction temperature dropped when the addition was fast, and the addition was stopped until the reaction mixture resumed boiling temperature. A black substance was formed when the cold diazonium solution was not added directly to the solution, so the cold diazonium solution was not allowed to touch the hot reaction flask. The reaction mixture was cooled to room temperature after the addition. Black solids were formed along with colorless needles while the reaction mixture was cooling to room temperature. The yield obtained was in 60.9%.

The IR spectrum of hydroxyl compound **C'4** showed a band at 3412 cm^{-1} for hydroxyl proton. The broad peak for aromatic amine protons at 3.75 ppm disappeared and a broad peak for hydroxy proton was observed at 5.8 ppm in the ^1H NMR spectrum. The protons ortho and para to the hydroxyl group moved downfield by approximately 2 ppm compared to the same protons in the amino compound **C'3**. The literature revealed no information about the IR and 1H NMR spectrum.[41] The TLC (50% EtOAc/hexanes) showed a neat and single spot at R_f 0.5. This melting point observed was 118°C-121°C.

The transformation of hydroxy **C'4** to methoxy **C'5** was carried out with dimethyl sulfate in acetone in the presence of anhydrous potassium carbonate following Konieczny's procedure.[21] Anhydrous potassium carbonate was used to neutralize the sulfuric acid generated in the reaction. The yield obtained was 96%.

The IR spectrum of the 3-methoxy-4-methylacetophenone **C'5** showed a sharp band at 1683 cm^{-1} for the carbonyl and 1271 cm^{-1} for the ether C – O bond. The ^1H NMR spectrum showed a singlet for three protons on the methyl group of the aromatic ring, the methyl group adjacent to carbonyl carbon and the methyl group of methoxy, at 2.18, 2.50 and 3.80 ppm respectively, A doublet signal for aromatic protons was observed at 7.14 and The protons ortho and para to the methoxy group moved up field by 1 ppm compared to the same protons in the hydroxy compound **C'4**. Both the IR spectrum and the ^1H NMR spectrum showed disappearance of the hydroxyl group and were in agreement with the literature values.[16] The overall yield for this section was 37.0%.

The transformation of the 3-methoxy-4-methylacetophenone **C'5** to ethyl3-(3-methoxy-4-methylphenyl)but-2-enoate **C'6** was first attempted with Wittig reagent (carbethoxymethylene triphenylphosphorane), and catalytic amounts of benzoic acid in benzene following Giannella's procedure.[42] The ^1H NMR spectrum after the work up of the reaction mixture did not show a peak for the vinylic proton, which should be observed at 6.13 ppm.[16] The transformation from **C'5** to ethyl3-(3-methoxy-4-methylphenyl)but-2-enoate **C'6** was attempted next with triethyl phosphonoacetate and sodium hydride (60% dispersion in

mineral oil) in dry tetrahydrofuran following Fuganti procedure,[16] which also did not show a peak for the vinylic proton. The sodium hydride was treated with hexanes before using in the reaction in order to wash away the mineral oil. These attempts to transform 3-methoxy-4-methylacetophenone **C'5** to ethyl3-(3-methoxy-4-methylphenyl)but-2-enoate **C'6** were not successful. The Reformatsky reaction between 3-methoxy-4-methylacetophenone **C'5** and ethyl bromoacetate followed by dehydration,[17,43] could accomplish this transformation. But due to time constraints further research was not continued.

Conclusions

3,3-Dichloro-4-indanyl-β-lactone **B'5** was synthesized using a [2+2] cycloaddition of dichloroketene and 1-indanecarboxaldehyde **B'4** and the stereospecific double ring expansion of the indanyl-β-lactone was successfully investigated, which resulted solely in the *trans*-fused butyrolactone **B'7** which was determined based on the coupling constant value (J=10.2 Hz) for the angular proton. The yield for the key ring expansion step from 3,3-Dichloro-4-indanyl-β-lactone **B'5** to the corresponding *trans*-fused butyrolactone **B'7** was 25%. The overall yield from 1-indanone **B'1** to *trans*-fused butyrolactone **B'7** was 2%.

Investigation of double ring expansion of 3-chloro-4-indanyl-3-methyl-β-lactone **B'6** was not completed but it was realized that dehalogenation of 2,2-dichloropropionyl chloride is the better method to generate chloromethyl ketene. When α-chloropropionyl chloride was reacted with triethyl amine at room temperature, an enolate salt was formed rather than the expected chloromethyl ketene.

Synthesis of the starting material 5-methoxy-3,6-dimethyl-1-indanone **C'8** was not complete. Many problems were encountered while attempting to reduce 4-methyl-3-nitroacetophenone **C'2** to 3-amino-4-methylacetophenone **C'3**, but at last was successful to reduce this compound with tin(II)chloride. Attempts to transform 3-methoxy-4-methylacetophenone **C'5** to ethyl3-(3-methoxy-4-methylphenyl)but-2-enoate **C'6** were not successful with the Wittig and the Horner-Emmons reagents. The Reformatsky reaction between

3-methoxy-4-methylacetophenone **C'5** and ethylbromoacetate followed by dehydration,[17,43] could accomplish this transformation. The synthesis of the starting material 5-methoxy-3,6-dimethyl-1-indanone **C'8** started with *p*-methyl acetophenone **C'1** with an overall yield of 37% to 3-methoxy-4-methyl acetophenone **C'5**.

Experimental

General Comments: IR spectra were obtained on a Nicolet DXB-20 FT-IR spectrophotometer using sodium chloride plates; absorption values are reported in wave numbers (cm^{-1}). Proton (^1H) NMR spectra were obtained on a GE QE-300 (300 MHz) Fourier Transform NMR spectrophotometer or a Varian T-60 (60 MHz) NMR spectrometer. Deuterated chloroform was used as a solvent for all NMR samples. Chemical shift values were reported in parts per million with respect to tetramethylsilane (TMS) as an internal reference standard. Peak multiplicities are referred as singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; broad, b. Column chromatography was carried out on silica gel 60Å (70-230 mesh) with benzene or methylene chloride as the eluent. All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Ethyl Indane-1-spiro-2'-oxiran-3'-carboxylate: **(B2)**[13]

A flame dried and nitrogen purged 1000 mL three necked flask was fitted with a dropping funnel, nitrogen inlet and magnetic stir bar. Approximately 20.0 g (151 mmol) of 1-indanone and 27.0 g (23.5 mL, 220 mmol) of ethyl chloroacetate were added and the mixture stirred and cooled in an ice-bath. A solution of 24.6 g (220 mmol) of potassium *tert*-butoxide in 250 mL of *tert*-butanol was added dropwise over 2 hrs. The light yellow solution turned to orange red, gradually became thick and the color turned to green. The reaction mixture was stirred for an additional 1.5 hrs.

At this point, carbon dioxide gas was passed through the reaction mixture with the help of a gas bubbler to neutralize the reaction mixture. Once the carbon dioxide started passing through, the green solution turned cream. The reaction mixture was concentrated by rotatory evaporation to give a reddish brown residue. To this, 250 mL of ether was added and the mixture was filtered through a bed of Celite. The Celite bed was washed with ether and the combined extracts were evaporated on a rotatory evaporator to obtain 24.4 g (74%) of brown oil.

IR (Neat): 3427, 2980, 1748, 1610, 1463, 1282, 1198, 1035, 763 cm^{-1}.

Sodium Indane-1-spiro-2'-oxiran-3'-carboxylate: **(B3)**[13]

To a solution of 0.42 g (18.2 mmol) of sodium metal in 7.5 mL of absolute ethanol was added 0.33 mL (18.3 mmol) of water and the solution was cooled in an ice-bath. A solution of 4.0 g (18 mmol) of ethyl indane-1-spiro-2'-oxiran-3'-carboxylate **B2** in 2.0 mL of absolute ethanol was slowly added to the above solution. The solution turned into a dark purple suspension and the mixture was stirred in an ice-cold bath for 15 min and at room temperature for 4 hrs. The solids were isolated through vacuum filtration and washed with 20 mL of ice-cold ethanol, and then twice with 50 mL of ether, to give 3.18 g (81%) of pink powder.

IR (Nujol): 3389, 1615 cm^{-1}.

1-Indanecarboxaldehyde: **(B4)**[13]

Sodium salt of the epoxy acid **B3** (2.1 g, 9.9 mmol) was placed in a 25 mL flask containing a magnetic stir bar, and 4.0 mL (69.8 mmol) of glacial

acetic acid was added while stirring. Stirring at room temperature was continued for 5 min.; vigorous evolution of carbon dioxide gas was observed. The reaction mixture was heated until the evolution of gases ceased (approx. 30 min), cooled to room temperature, diluted with 35 mL water, and extracted thrice with 20 mL portions of ether. The combined ether extracts were washed twice with 50 mL water and with 50 mL 10% sodium bicarbonate. The ether layer was dried over anhydrous magnesium sulfate and filtered through vacuum filtration. The solvent was removed under reduced pressure to provide 1.1 g (75%) of brown oil.

TLC (benzene): R_f 0.44, 0.08, 0.00

IR (Neat): 3418, 3069, 1722, 1478, 1458, 1218, 1111, 752, 668 cm^{-1}.

^1H NMR: δ 2.15-2.50 (m, 2 H), 2.70-3.20 (t, 2 H), 4.0 (td, 1 H, *J*=3.0, 1.0 Hz), 7.26 (s, 4 H) 9.6 (d, 1 H, *J*=3.1 Hz).

3,3-Dichloro-4-indanyloxetan-2-one: **(B5)**

A magnetic stir bar and 0.5 g (3.42 mmol) of 1-indane carboxaldehyde **B4** were placed in an oven dried three-neck flask equipped with a nitrogen inlet. Approximately 3.0 mL of ether was added to the flask, followed by 0.33 g (5.04 mmol) of activated zinc; the mixture was then stirred vigorously.

At this point, 0.38 mL (3.4 mmol) of trichloroacetylchloride in 2 mL of ether was added to the reaction mixture dropwise and the reaction mixture was stirred for 16 hrs. TLC (benzene) showed the presence of starting material, so 0.1 mL (0.89 mmol) of trichloroacetylchloride and 0.1 g (1.5 mmol) of activated zinc was added and stirring continued for additional 7 hrs. At this point, TLC (benzene) showed a very faint spot for starting material; therefore, the reaction

mixture was filtered to remove the zinc and washed with 10 mL of ether. Celite was added to the filtrate, the solvent evaporated on rotatory evaporator, and hexanes were added to the residue and filtered to remove the Celite. Hexanes were removed under reduced pressure to give 0.43 g of light green oil.

Yield: 48.9%.

TLC (50% EtOAc/hexanes): R_f 0.68, 0.44 (streak)

IR (Neat): 3550, 3069, 1858, 1779, 1224, 1123, 998, 756 cm^{-1}.

trans-3,3-Dichloro-4,5,10,11-tetrahydronaphthofuran-2-one: **(B7)**

Into an oven dried 100 mL three-neck flask equipped with a nitrogen inlet, reflux condenser and magnetic stir bar, was placed 0.24 g (9.9 mmol) of magnesium turnings and 15 mL ether. 0.84 mL (9.9 mmol) of 1,2-dibromoethane was added dropwise to the above mixture. The reaction was exothermic and vigorous evolution of gas was observed. The evolution of gas ceased after 2 hrs. At this point, ether was evaporated under nitrogen and a white residue of magnesium bromide was obtained. Eight mL of methylene chloride was added to the residue, followed by 0.4 g (1.5 mmol) of the dichloro-β-lactone **B5** in 5 mL methylene chloride, added dropwise to the above mixture and stirring continued for 36 hrs. The reaction was quenched by adding 20 mL of deionized water. The methylene chloride layer was separated and the solvent evaporated on rotatory evaporator to give an orange red solid. This solid was dissolved in ether and washed with 20 mL 10% sodium hydroxide followed by with 20 mL of brine. The ether layer was dried over anhydrous magnesium sulfate; vacuum filtered and evaporated under reduced pressure to give 0.47 g of a gum-like compound.

The gum like compound was hot filtered from 95% ethanol and the solvent removed to give a brown solid. The brown solid was purified on silica gel column with methylene chloride eluting solvent. The yield obtained was 25% (0.1 g)

IR (Neat): 3426, 2925, 1805, 1022, 956, 756 cm^{-1}.

^1H NMR: δ 2.00-2.17 (m, 1 H), 2.50-2.70 (m, 1 H) 3.00-3.22 (m, 2 H), 3.8 (d, 1 H, *J*=10.2 Hz), 4.5 (ddd, 1 H, *J*=12.2, 10.2, 3.9 Hz), 7.10-7.38 (m, 3 H), 7.60-7.70 (m, 1 H)

3-chloro-4-indanyl-3-methyloxetane-2-one: **(B6)**

Into an oven dried 100 mL three-neck flask equipped with a refluxing condenser, nitrogen inlet and magnetic stir bar, was placed 25 mL methylene chloride. Five drops of DMF followed by 3 mL (4.1 g, 28.6 mmol) of 2,2-dichloropropionic acid was added slowly to the 100 mL flask containing methylene chloride, with stirring. To the above mixture, 5 mL (7.3 g, 61.5 mmol) of thionyl chloride was added slowly and stirring continued. The reaction mixture was heated to boiling and refluxed for 10 hrs. At this point, the IR spectrum of the reaction mixture showed complete conversion of 2,2-dichloropropionic acid to 2,2- dichloropropionyl chloride. Thionyl chloride was boiled off from the reaction mixture but 2,2-dichloropropionyl chloride was also boiled along with thionyl chloride.

IR (Neat) (for 2,2-dichloropropionyl chloride): 3390, 1779, 1442, 1382, 1080, 958, 703, 618 cm^{-1}.

Another oven dried 25 mL three-neck flask was equipped with refluxing condenser, nitrogen inlet and magnetic stir bar. 0.47 g (3.2 mmol) of 1-indanecarboxaldehyde **B4** in 10 mL of ether was placed in the above flask, 0.5 g (7.6 mmol) of zinc was added and the mixture stirred vigorously. At this point, 1 mL (6.1 mmol) of 2,2-dichloropropionyl chloride in 3 mL ether was added slowly to the flask containing 1-indanecarboxaldehyde **B4** and the reaction mixture was stirred at room temperature for 10 hrs. TLC (benzene) showed the presence of starting material, so 0.25 mL (1.5 mmol) of 2,2-dichloropropionyl chloride was added to the reaction mixture and stirring continued for an additional 26 hrs, at which point the reaction mixture was filtered and residue washed with ether. Celite was added to the ether and the mixture was concentrated under reduced pressure and hexanes were added to the residue and the Celite was filtered by vacuum filtration. Hexanes were removed under reduced pressure to afford 1.4 g of impure dirty green oil. Reaction progress was checked on TLC (benzene).

TLC (benzene): R_f 0.69, 0.27, 0.16.

IR (Neat): 3071, 1837, 1731, 1446, 1382, 1272, 1079 cm^{-1}.

4-Methyl-3-nitroacetophenone: **(C2)**[18]

In a 250 mL three-neck flask equipped with a thermometer, dropping funnel and magnetic stir bar was placed 30 mL (480 mmol) of concentrated sulfuric acid. Approximately 13 mL (97.2 mmol) of *p*-methylacetophenone was added to the concentrated sulfuric acid while stirring. The resultant mixture was cooled to 0°C in an ice-bath, whereupon a cooled solution of 8 mL (144 mmol) concentrated nitric acid and 12 mL (225 mmol) concentrated sulfuric acid was

poured in the dropping funnel fitted to the 250 mL three-neck flask and added to the starting material very slowly, maintaining the temperature between -2° and 6°C. After completion of addition of the mixed acid, the reaction mixture was stirred for additional 15 min and poured onto 250 mL of crushed ice. Light yellow solids were formed. The solids formed were filtered through gravity filtration and washed with 600 mL of water followed by 30 mL ice-cold 95% ethanol. The solids obtained were recrystallized from 95% ethanol to give 14.4 g (82.4%) of pale yellow solid.

MP: 54-56°C.

TLC (25% EtOAc/hexanes): R_f 0.42

IR: (Nujol): 3356, 1693, 1614, 1524, 1254, 721 cm^{-1}.

NMR: δ 2.65 (s, 6 H), 7.50 (d, 1 H, *J*=3.1 Hz), 8.25 (dd, 1 H, *J*=3.1, 0.7 Hz), 8.5 (d, 1 H, *J*=0.7 Hz).

3-Amino-4-methylacetophenone: **(C3)**

A 150 mL quantity of ethyl acetate was placed in a 250 mL one neck flask equipped with a refluxing condenser and a magnetic stir bar. Approximately 7.0 g (39.0 mmol) of 4-methyl-3-nitroacetophenone **C2** was added to the flask containing ethyl acetate and the mixture stirred at room temperature. 47.6 g, (210.9 mmol, 1.22 g per mmol of starting material **C2**) of tin (II) chloride dihydrate was added to the reaction flask and the resultant mixture heated to aid dissolution and heating was continued. The reaction mixture was refluxed for 2 hrs and the reaction progress was checked on TLC (50% EtOAc/hexanes), which showed the disappearance of starting material. Heating was stopped and the

reaction mixture was allowed to cool to room temperature and diluted with 50 mL deionized water. The resultant reaction mixture was basified with concentrated ammonium hydroxide. The brown reaction mixture turned to a yellow viscous mixture. The free amine **C3** contained in the yellow viscous mixture was extracted with 700 mL of ether and solvent was removed under reduced pressure yielding 4.5 g (77%) of solid.

MP: 71-75°C.

TLC: (50% EtOAc/hexanes) R_f 0.29.

IR (Nujol): 3429, 3348, 1667, 1633, 1569, 722 cm^{-1}.

NMR: δ 2.21 (s, 3 H), 2.54 (s, 3 H), 3.75 (s, broad 2 H), 7.16 (d, 1 H, *J*=7.3 Hz), 7.25-2.35 (m, 2 H).

3-Hydroxy-4-methylacetophenone: **(C4)**[18]

In a 250 mL three-neck round bottom flask, equipped with a thermometer and a magnetic stir bar, was placed 7.5 g (50.3 mmol) of 3-amino-4-methylacetophenone **C3** and 60 mL of 3 M sulfuric acid. The mixture was heated to aid dissolution and then cooled to 0°C. At this point, 2.6 g (37.68 mmol) of sodium nitrite in 20 mL of water was added slowly to the starting material, maintaining the temperature between -0.5° and -2°C in sodium chloride/crushed ice bath. The reaction mixture was stirred for additional 30 min, at which point 0.86 g (14.3 mmol) of urea in 70 mL of ice-cold water was added in small portions.

Meanwhile, in another 500 mL three-neck flask equipped with reflux condenser, thermometer, and magnetic stir bar, was placed 200 mL of 3 M sulfuric acid, which was heated to boiling.

The brown reaction mixture was filtered with suction into an ice-cold flask at 0°C and the filtrate was kept cold until it was added to the boiling sulfuric acid. The filtrate, containing the diazonium salt, was added to the boiling sulfuric acid without affecting the boiling.

The reaction mixture was boiled for an additional 60 min and heating stopped. Stirring continued until the reaction mixture attained room temperature. Colorless needles along with the brown solids were formed while the reaction mixture was stirred after the heating was stopped. The solids formed were filtered through vacuum filtration and washed with 600 mL of water. The resultant solids were kept open to air overnight for the compound to dry. The yield obtained was 4.6 g (60.9%).

MP: 118-121°C

TLC (50% EtOAc/hexanes) R_f 0.50

IR (Nujol): 3412, 1662, 1605, 1581, 1421, 1349, 1291, 1070, 899, 689 cm^{-1}.

NMR: δ 2.24 (s, 3 H), 2.50 (s, 3 H), 5.8 (b, 1 H), 7.19 (d, 1 H, *J*=8.2 Hz), 7.44 (d, 1 H, *J*=8.2 Hz), 7.44 (s, 1 H).

3-Methoxy-4-methylacetophenone: **(C5)**

Into an oven dried 50 mL three-necked flask, equipped with reflux condenser, nitrogen inlet, and magnetic stir bar, was placed 25 mL of acetone, 0.75 g (5.0 mmol) of 3-hydroxy-4-methylacetophenone **C4**, and 0.82 g (5.8

mmol) of anhydrous potassium carbonate. The resultant mixture was stirred under nitrogen for 5 min. 0.52 mL (0.7 g; 5.5 mmol) of dimethyl sulfate was added to the reaction mixture, which was refluxed for 10 hrs. The reaction progress was checked on TLC (50% EtOAc/hexanes). TLC showed disappearance of the starting material spot.

The solvent was evaporated under reduced pressure and 30 mL of deionized water was added to the residue; the crude product was extracted by adding 50 mL of chloroform. The chloroform layer was washed thrice with 30 mL of water followed by 30 mL of 1 N hydrochloric acid, 30 mL of saturated sodium bicarbonate solution, twice with 30 mL of water and with 30 mL of brine, respectively. The chloroform layer was dried over anhydrous magnesium sulfate and filtered through vacuum filtration. The solvent was evaporated under reduced pressure to give 0.8 g (96%) of brown oil.

TLC (50% EtOAc/hexanes): R_f 0.65

IR (Neat): 3002, 2961, 1683, 1605, 1578, 1457, 1356, 1271, 1200, 1140 cm^{-1}

NMR: δ 2.18 (s, 3 H), 2.50 (s, 3 H), 3.80 (s, 3 H), 7.15 (d, 1 H, *J*=7.0 Hz), 7.35-7.41 (m, 2 H).

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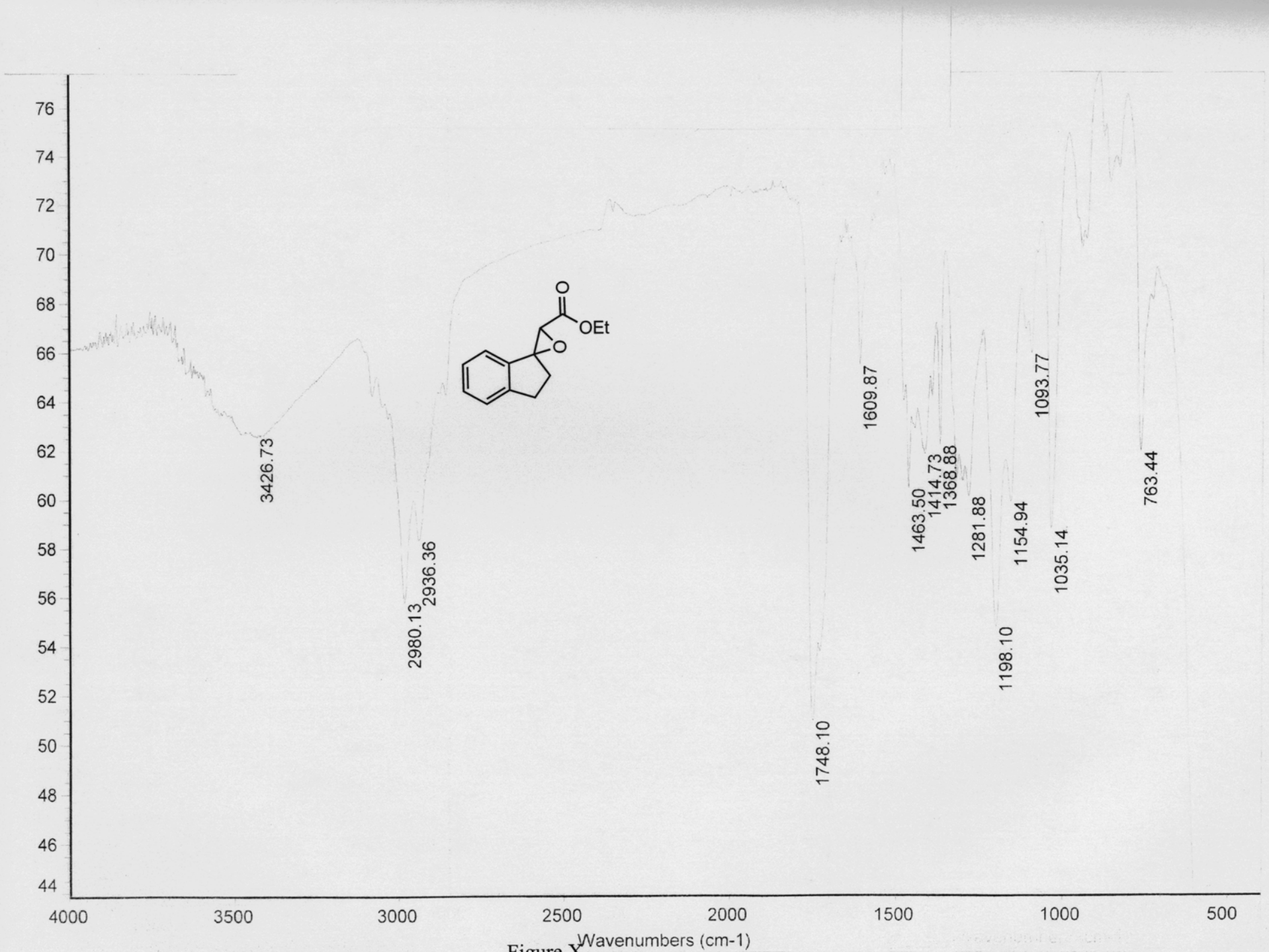

Figure X

IR spectrum (Neat) of Ethyl Indane-1-spiro-2'-oxiran-3'-carboxylate (B2)

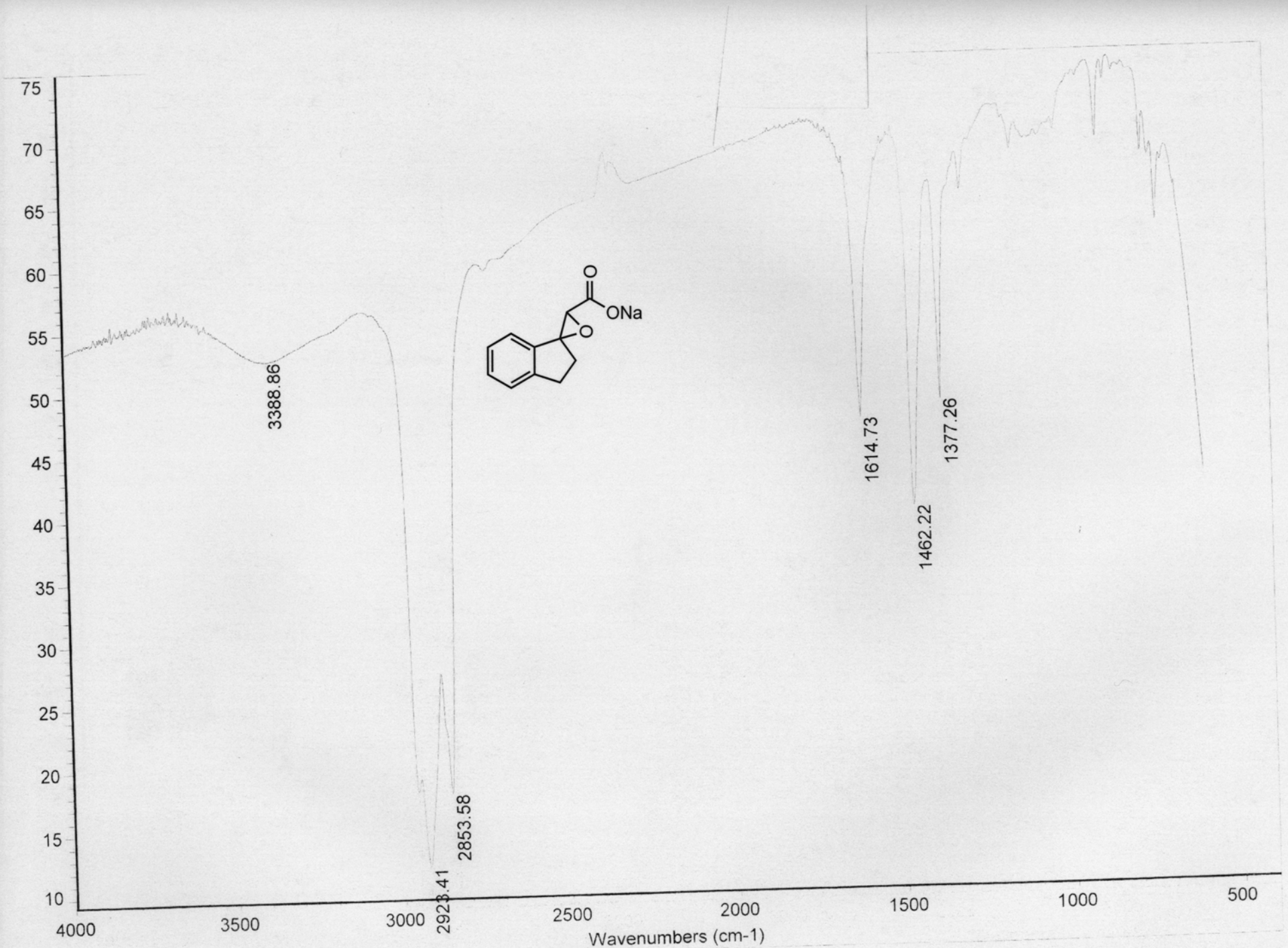

Figure XI

IR spectrum (Nujol) of Sodium Indane-1-spiro-2'-oxiran-3'-carboxylate (B3)

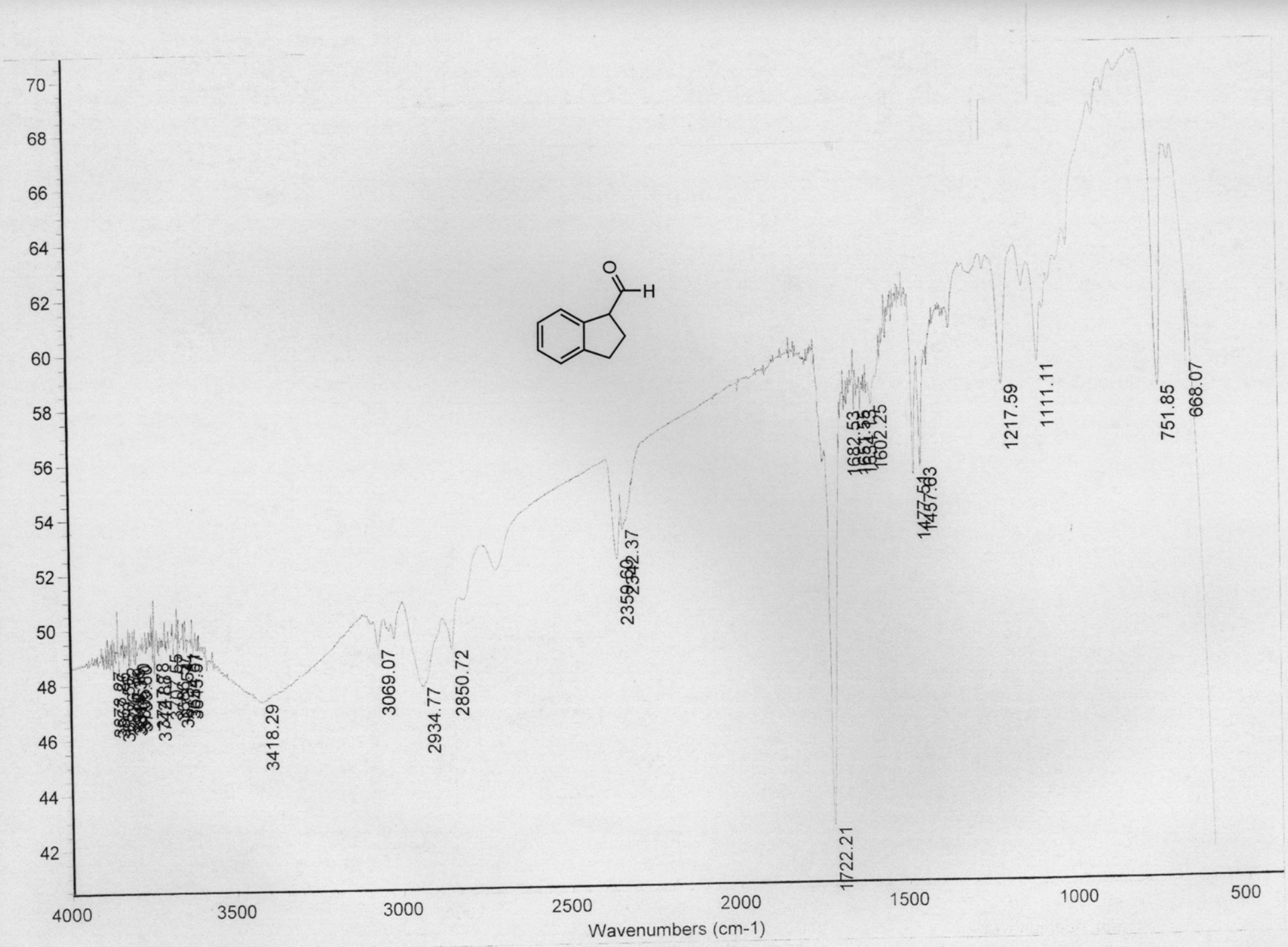

Figure XII
IR spectrum (Neat) of 1-Indanecarboxaldehyde (B4)

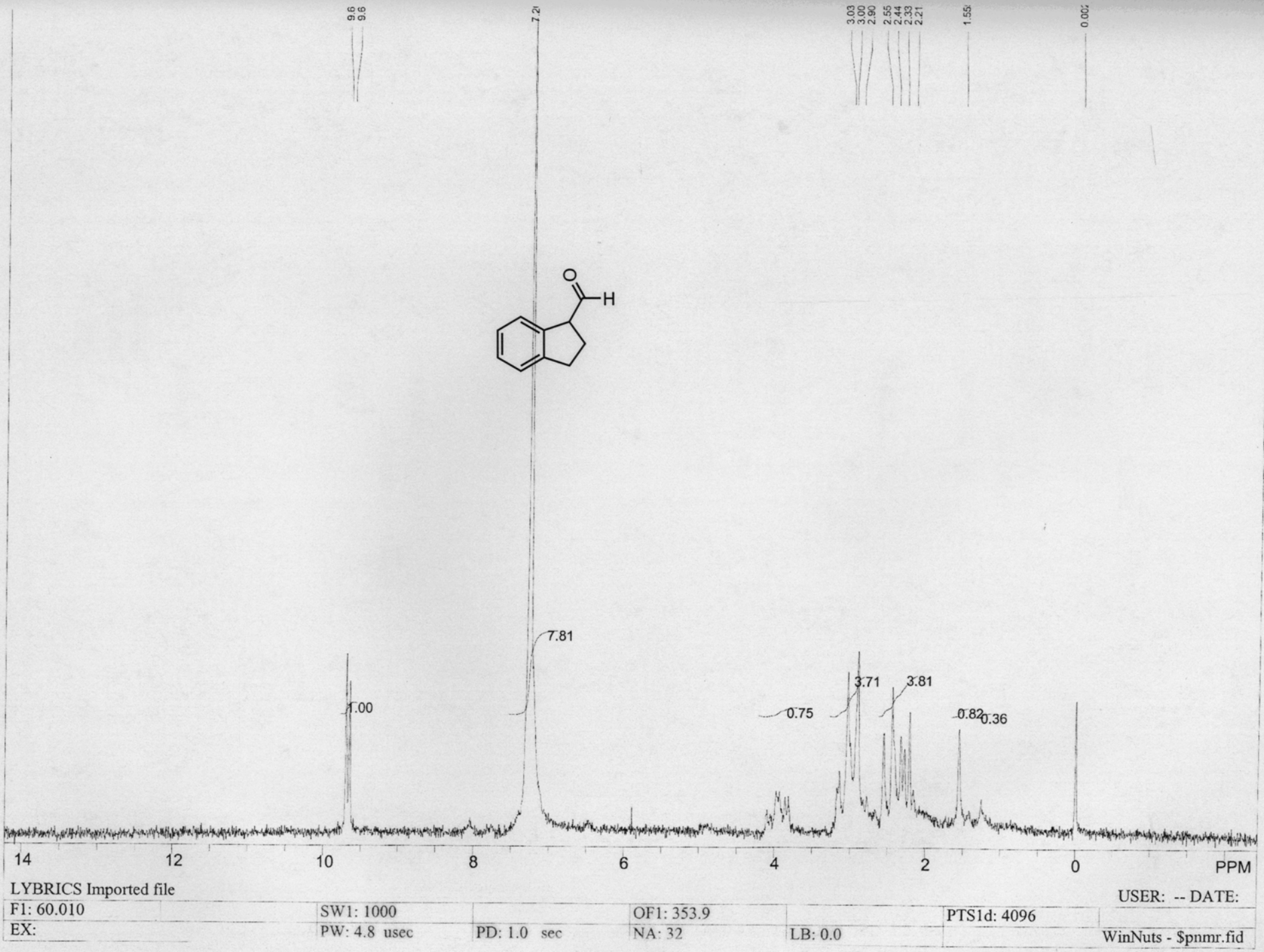

Figure XIII

^{1}H NMR spectrum (60 MHz) of 1-Indanecarboxaldehyde (B4)

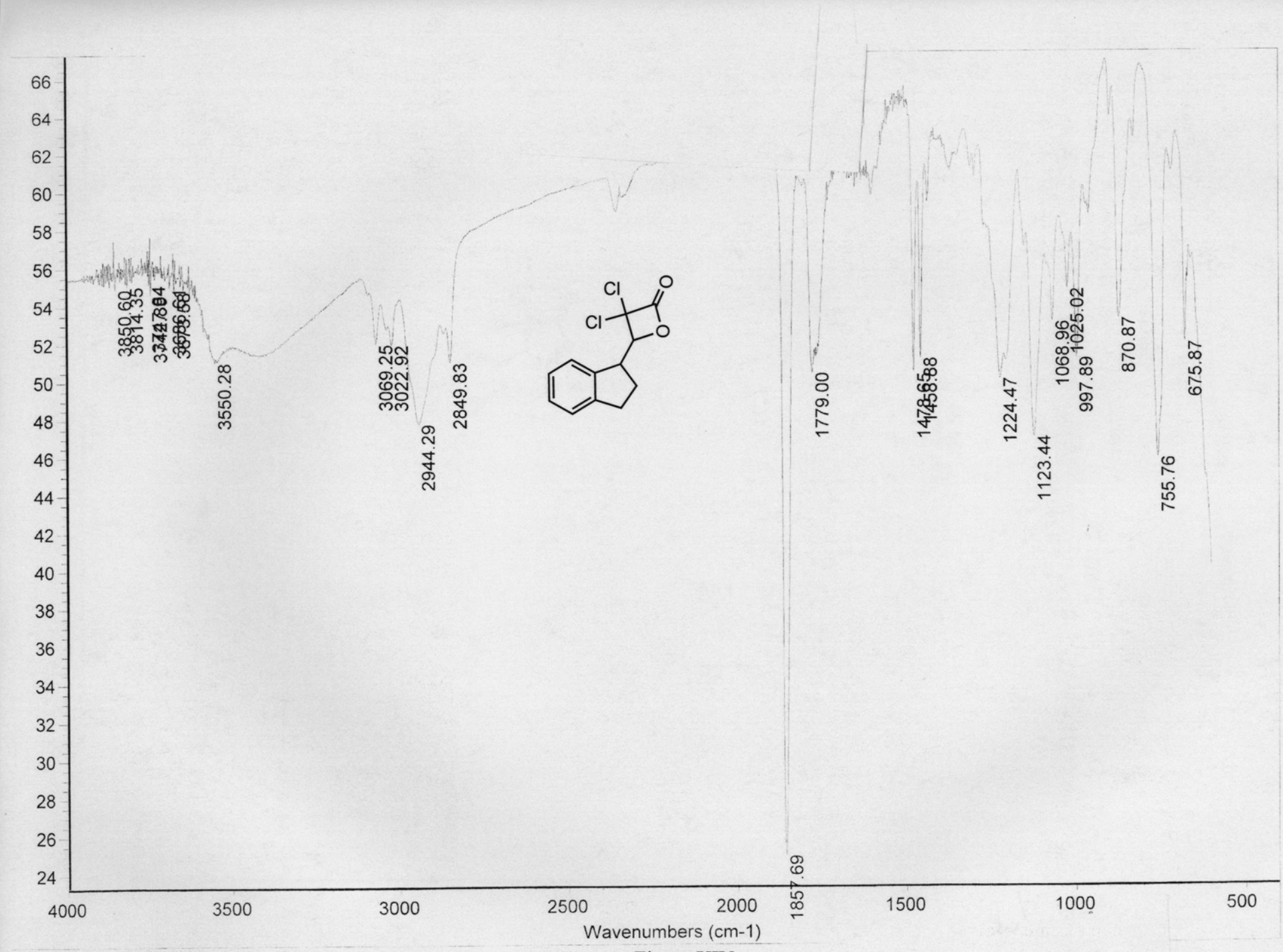

Figure XIV
IR spectrum (Neat) of 3,3-Dichloro-4-indanyloxetan-2-one (B5)

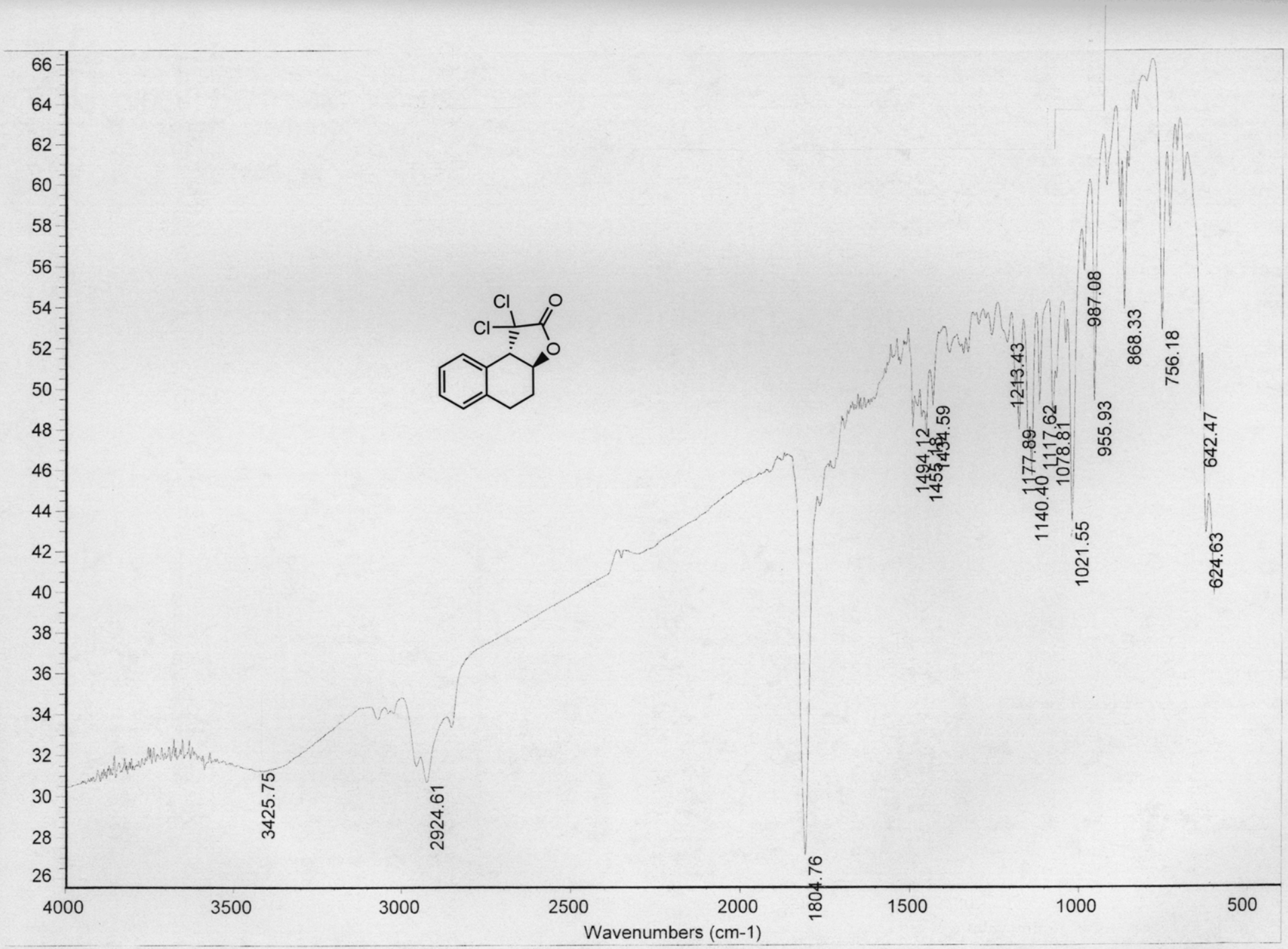

Figure XV
IR spectrum (Neat) of *trans*-3,3-Dichloro-4,5,10,11-tetrahydronaphthofuran-2-one (B7)

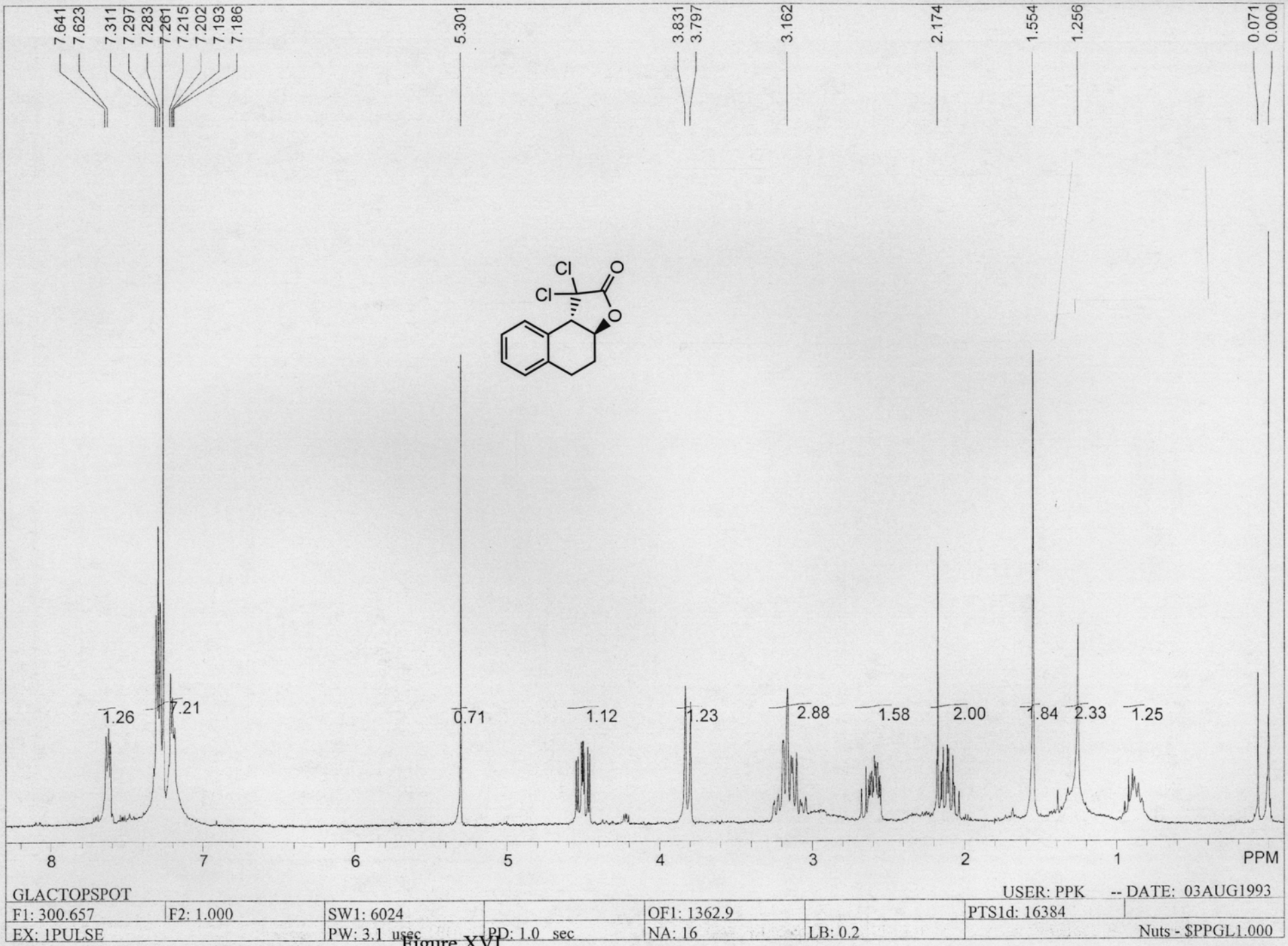

Figure XVI

^{1}H NMR spectrum (300 MHz) of *trans*-3,3-Dichloro-4,5,10,11-tetrahydronaphthofuran-2-one (B7)

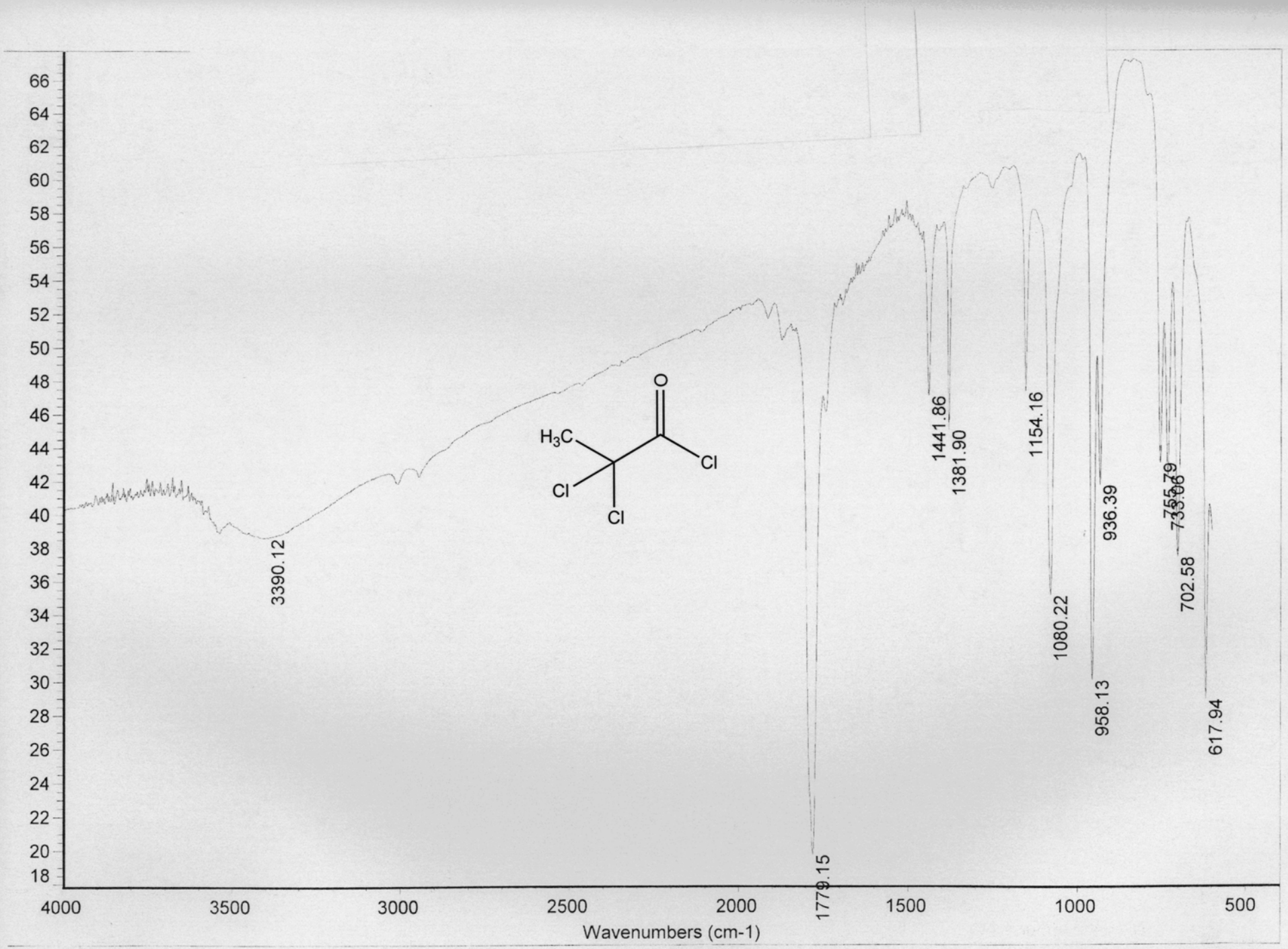

Figure XVII
IR spectrum (Neat) of 2,2-Dichloropropanoyl chloride

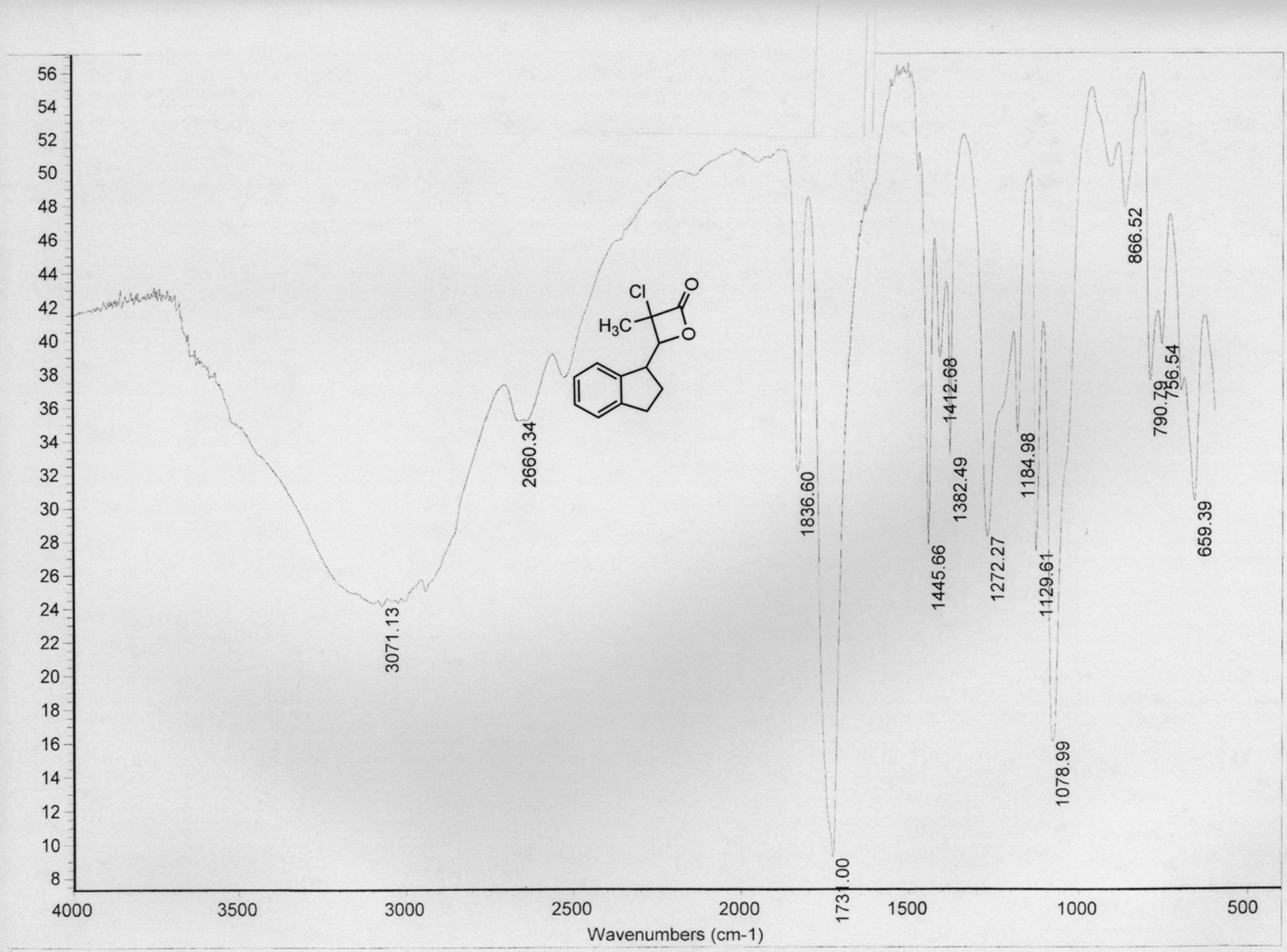

Figure XVIII
IR spectrum (Neat) of 3-chloro-4-indanyl-3-methyloxetane-2-one (B6)

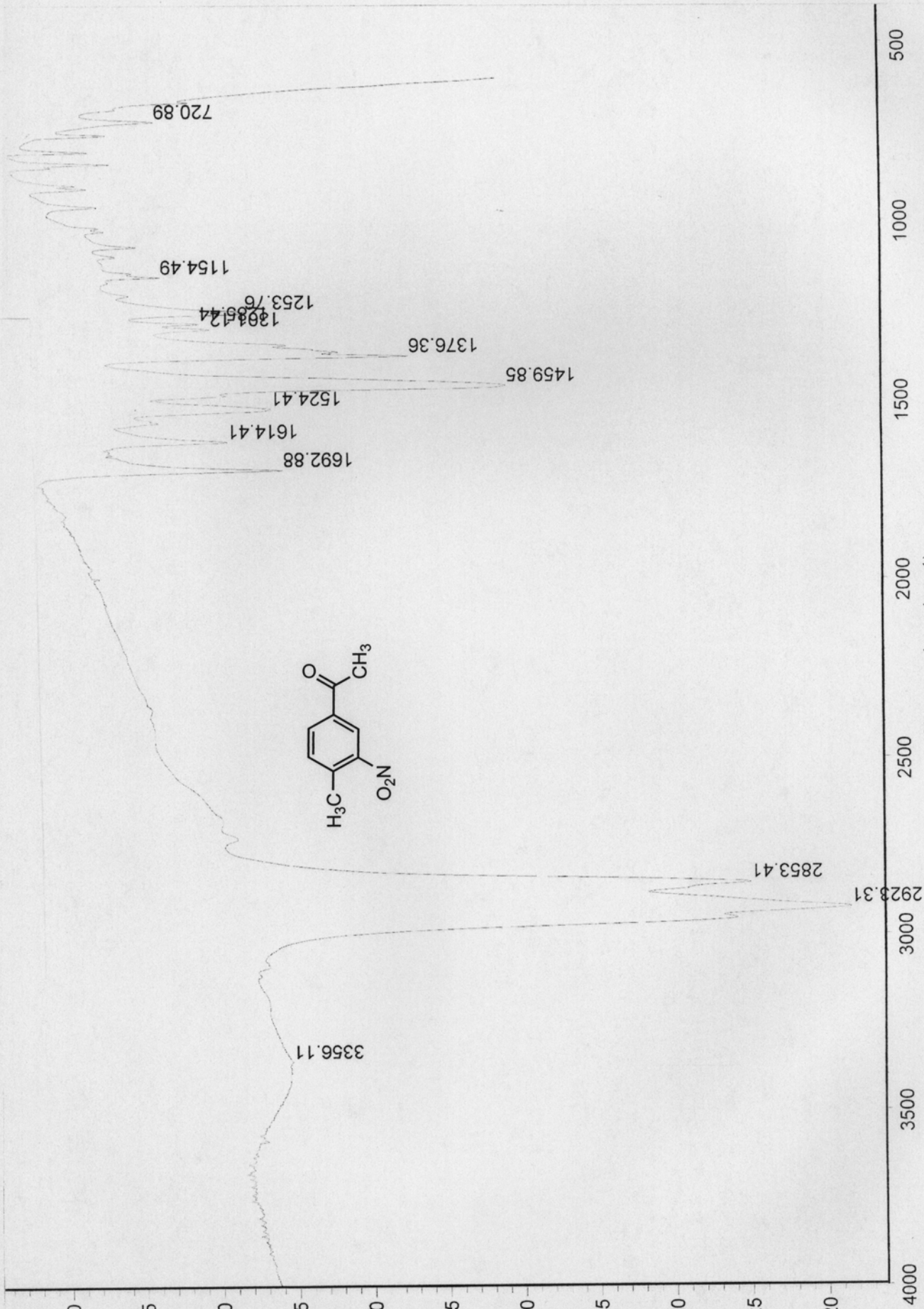

Figure XIX
IR spectrum (Nujol) of 4-Methyl-3-nitroacetophenone (C2)

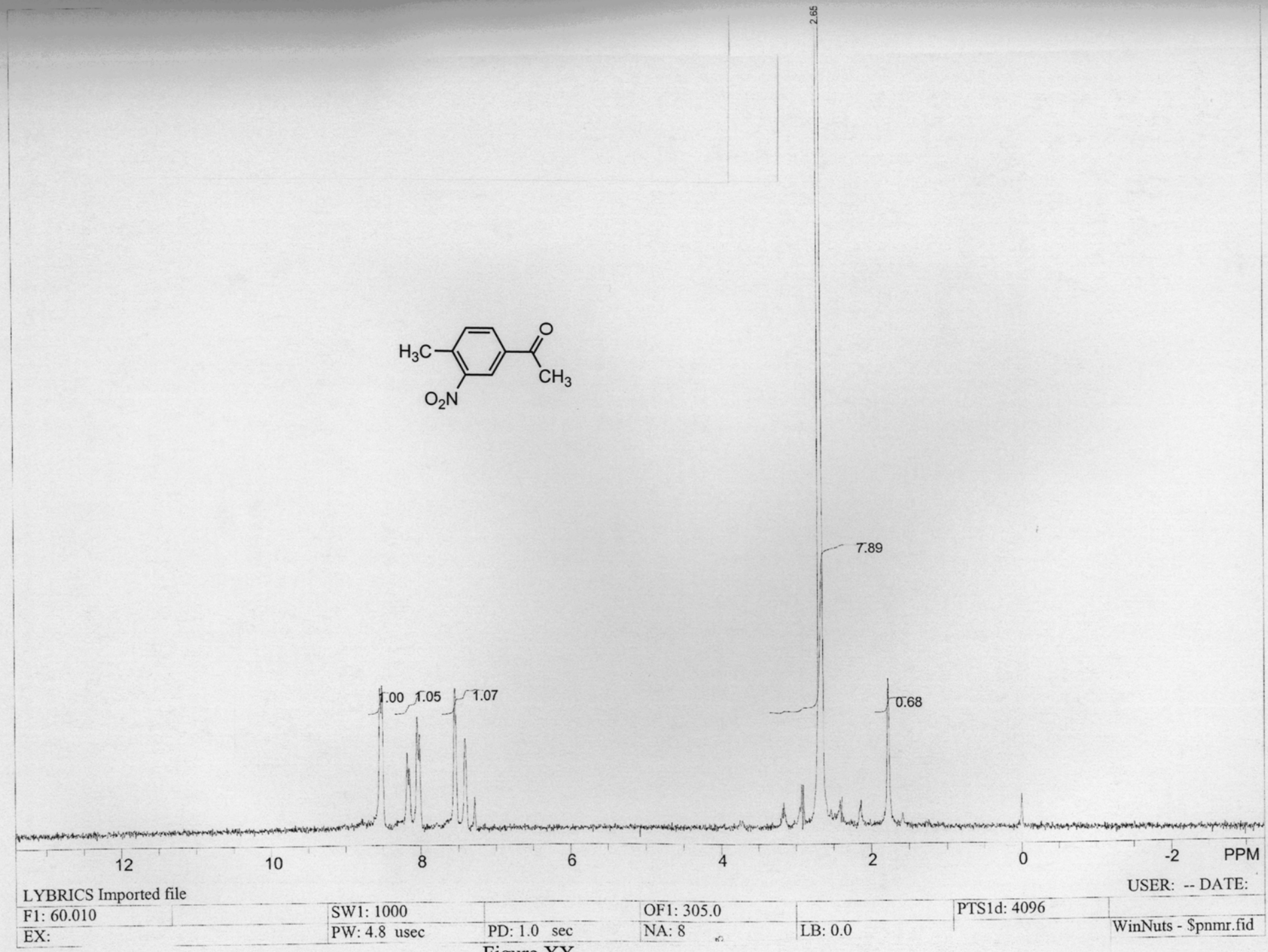

Figure XX

^{1}H NMR spectrum (60 MHz) of 4-Methyl-3-nitroacetophenone (C2)

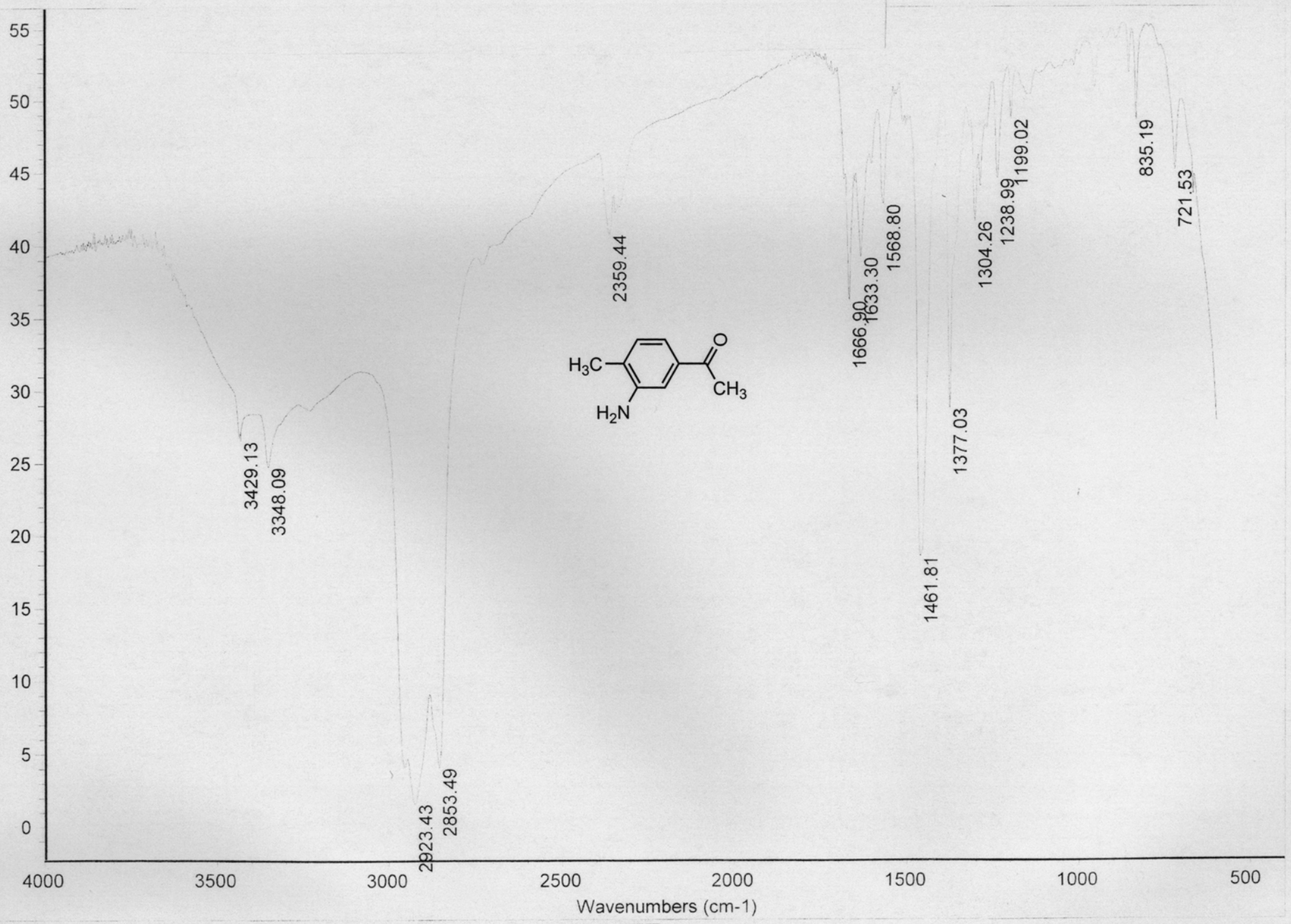

Figure XXI
IR spectrum (Nujol) of 3-Amino-4-methylacetophenone (C3)

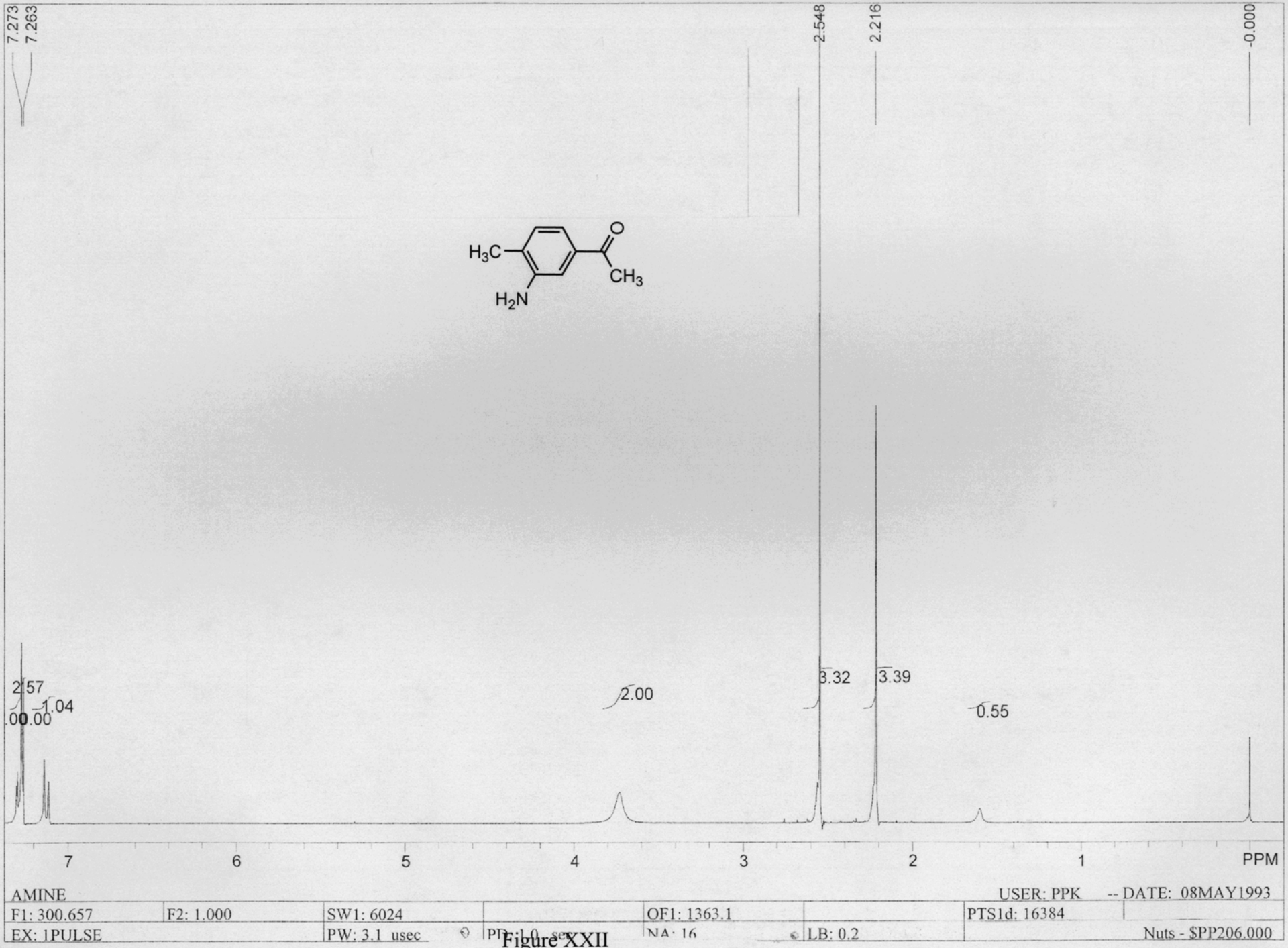

Figure XXII

^{1}H NMR spectrum (300 MHz) of 3-Amino-4-methylacetophenone (C3)

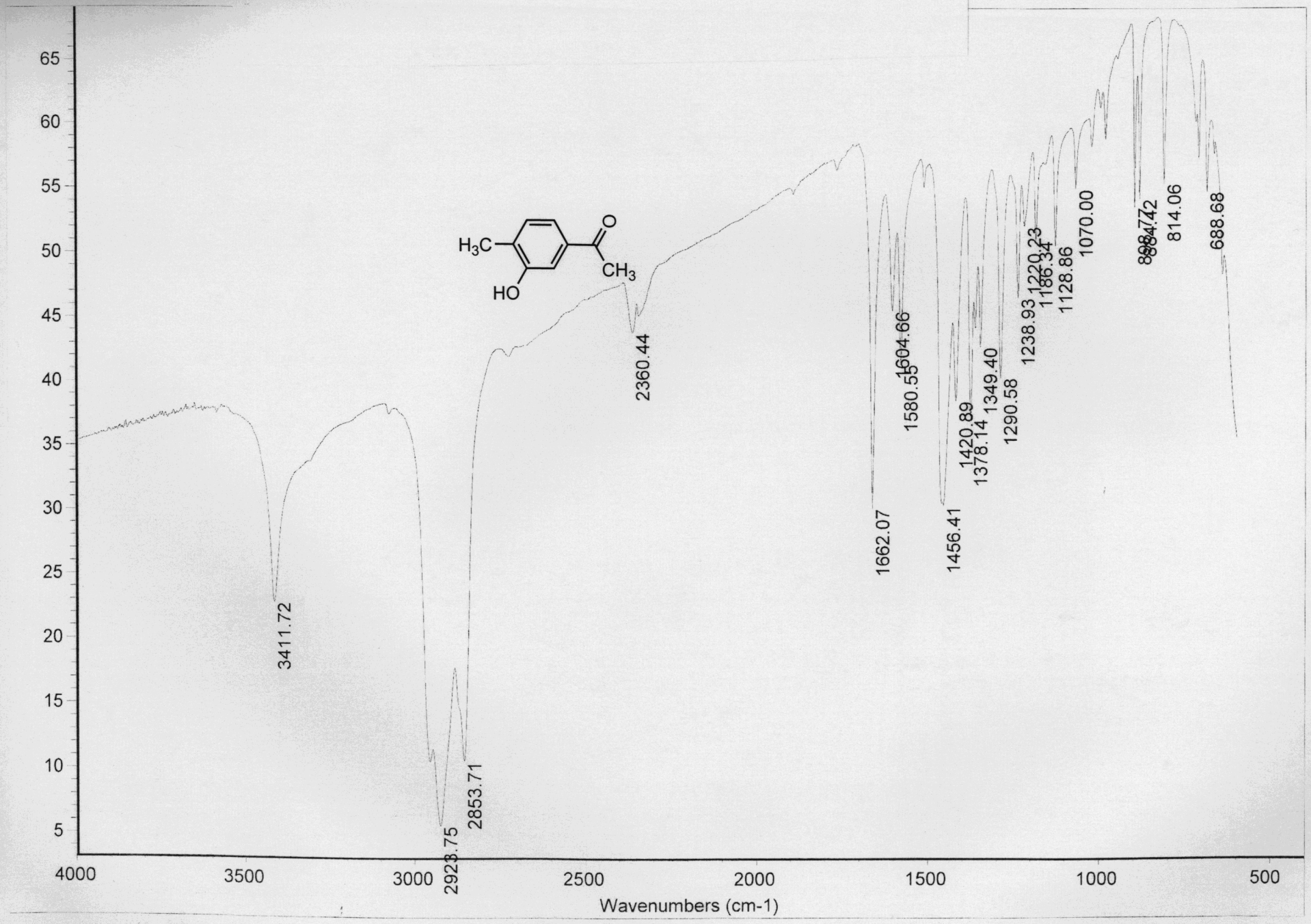

Figure XXIII
IR spectrum (Nujol) of 3-Hydroxy-4-methylacetophenone (C4)

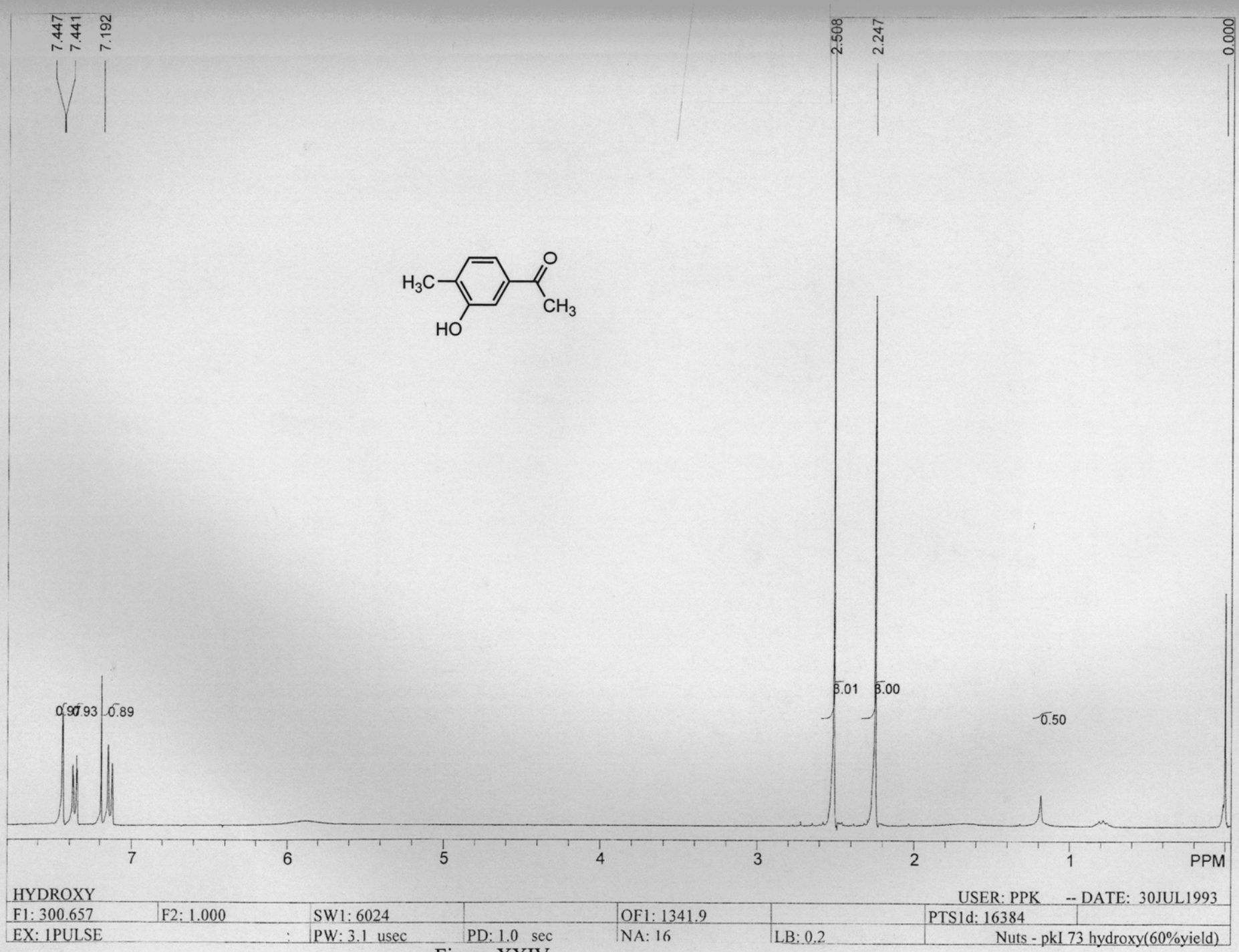

Figure XXIV

^{1}H NMR spectrum (300 MHz) of 3-Hydroxy-4-methylacetophenone (C4)

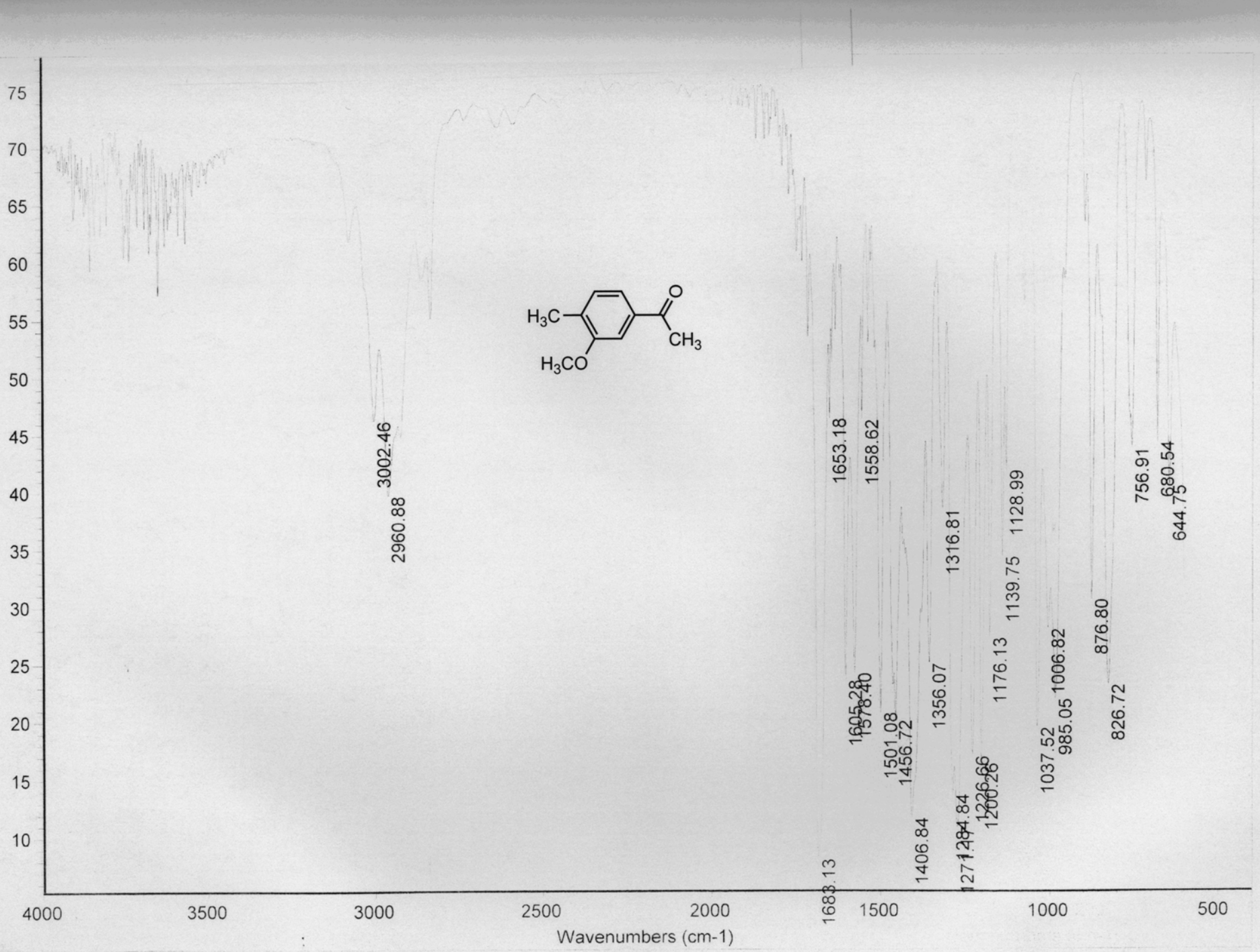

Figure XXV
IR spectrum (Neat) of 3-methoxy-4-methylacetophenone (C5)

Figure XXVI

^{1}H NMR spectrum (300 MHz) of 3-methoxy-4-methylacetophenone (C5)