CHAPTER II

A NOVEL METHOD FOR THE SYNTHESIS OF PROSTAGLANDIN ANALOGUES

II.1 ABSTRACT

We present herein novel approach for the synthesis of PG analogues by using easily available starting materials such as citric acid and methyl oleate or methyl ricinoleate. This tandem sequence involves photochemical [2+2] cycloaddition and oxidative decarboxylation, which eliminates the use of expensive and complex reagents. All the key intermediates are isolated using chromatographic technique and characterized by using various spectral and elemental analysis.

II.2 INTRODUCTION

Prostaglandins (PGs) form a class of natural products with diverse and potent biological activities.[1] Natural PGs are unsaturated hydroxy fatty acids associated with most mammalian tissues and are implicated in an ever-increasing number of physiological systems.[1,2] Naturally occurring PGs may be regarded as derivatives of prostanoic acid, an organic acid with a substituted cyclopentane unit.[3]

In the total synthesis, prostaglandins show a formidable challenge to the synthetic organic chemists mainly because of the presence of the numerous asymmetric centers and their relative positions with respect to each other. Many of the approaches to PGs are multi-step sequences involving use of expensive/complex reagents and tedious work up procedures. In addition, some of the routes also lack adaptability on large-scale operations.

In spite of the challenges posed by the structural and stereochemical complexities posed by the prostaglandins, a number of synthetic routes have been successfully developed, as discussed in the first chapter.[4-7] A number of novel procedures and reagents have been developed for their synthesis.[8-10]

The terminology "prostanoid" was introduced by Cory, E. J., in 1971 in order to designate not only the compounds belonging to the natural PG families but also all other substances with a PG-like structures.[11] These are sometimes called modified PG, PG analogues or PG congeners.

The synthesis of PG analogues has made constant attention of an increasing number of synthetic organic chemists. Many of these studies on modified PG have involves either an alteration of the chains or the substitution pattern found in the five-

membered carbocyclic ring system of the natural prostanoids. In addition, a number of studies have concerned the modification of the functional groups either by the introducing new ones or by changing the stereochemistry and of the skeleton of natural PG. This has becomes an interesting and up going field for synthetic organic chemist because it is anticipated that some modified PG will display more target specific or higher biological activities than their natural counter PG/congeners. There is no doubt to achieve above mention target; it requires broad chemical knowledge and synthesis techniques during synthesis work of PG congeners.

The preparation of modified PG can be achieved in essentially three different ways.

The first approach consists of using a known total synthesis scheme and introducing appropriate modifications during the course of the work. The second alternative consists of developing a new total synthesis of the PG framework that allows the preparation of PG analogues and eventually natural PG as well. A third possibility consists of using a natural PG obtained from the natural resources, introducing new groups, functions or chains on the PG skeleton. This approach has the advantage of affording directly optically active compounds with the correct stereochemistry at most asymmetric centers.

Some of the ways by which cyclopentane nucleus of prostanoids can be generated are outlined in the **figure II.1**. Out of the pathways in **figure II.1**, we have chosen pathway "**C**" for the construction of the cyclopentane ring through C-9 and C-10 bond formation via aldol condensation.

Towards accomplishing the objective as stated earlier, we designed a strategy involving formation of a key intermediate cyclobutene derivative (**4**) from the oxidative-decarboxylation of the diacid (**3**), along with other sequences as outlined in retrosynthetic fashion.

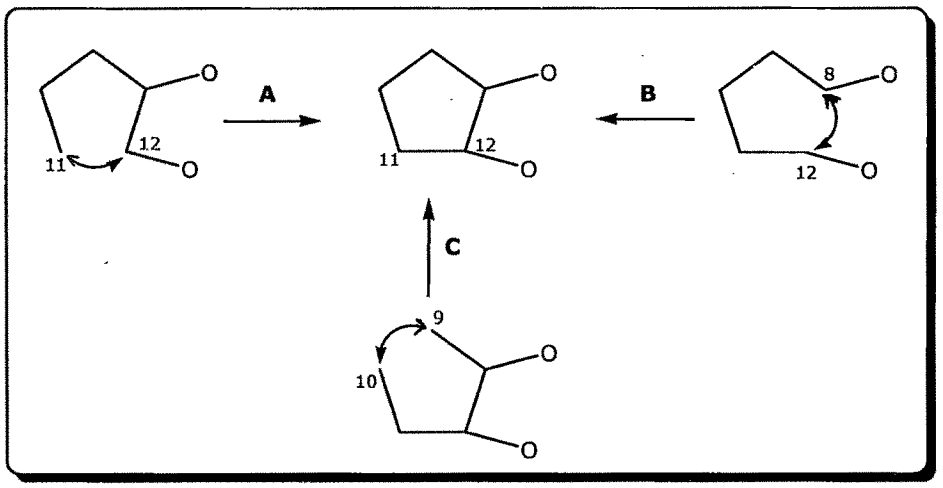
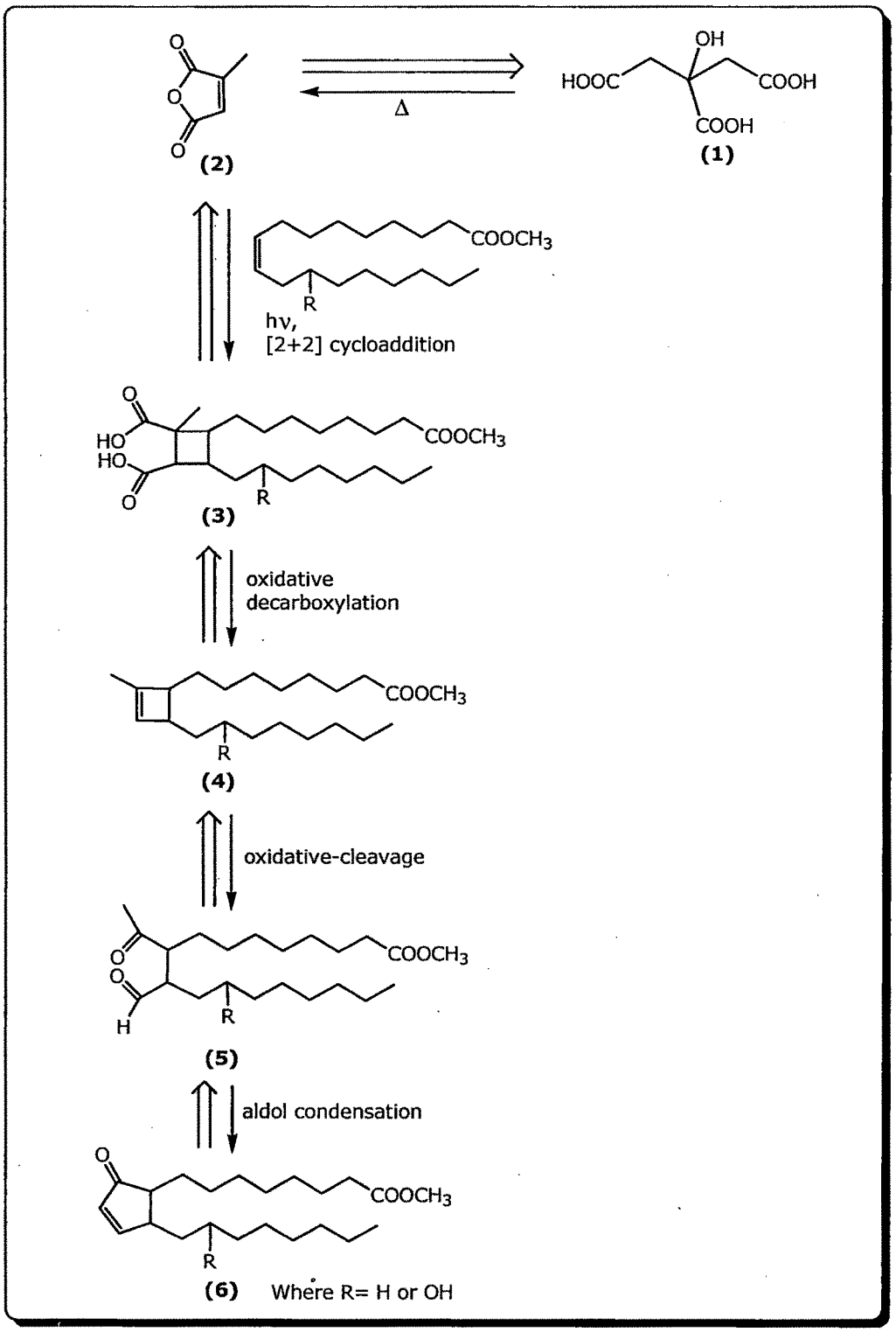


Figure II.1

It was envisioned that the PG analogue (**7, Scheme 1**) could be derived through the intramolecular condensation reaction of keto-aldehyde (**5**) under the mild alkaline medium reaction at 9 and 10 position. The keto-aldehyde (**5**) could be obtained through the oxidative cleavage of the cyclobutene derivative (**4**). The methyl cyclobutene derivative (**4**) was thought to be obtained through the oxidative decarboxylation of the diacid-monoester (**3**). The diacid-monoester (**3**) could be obtainable via hydrolysis of the photoadduct of $\pi^{2s} + \pi^{2s}$ photocycloaddition reaction between the citraconic anhydride (**2**) and the long chain fatty acid or ester. The anhydride (**2**) was obtained through the distillation of the citric acid (**1**).

Some of the salient features of the present strategy are as follows.

The proposed strategy would involve less number of chemical sequences compared to other methods as discussed previously, using easily available cheap starting materials like citric acid and methyl oleate/methyl ricinoleate. Incorporation of different types of anhydride and long chain fatty acids or esters would provide structural flexibility into the strategy. Depending upon the nature of the desired PG molecule, the starting anhydride could be appropriately selected.


(2)
Δ
HOOC
OH
COOH
COOH
(1)
COOCH3
R
hν,
[2+2] cycloaddition
HO
HO
(3)
oxidative
decarboxylation
(4)
oxidative-cleavage
H
(5)
aldol condensation
(6)
Where R= H or OH

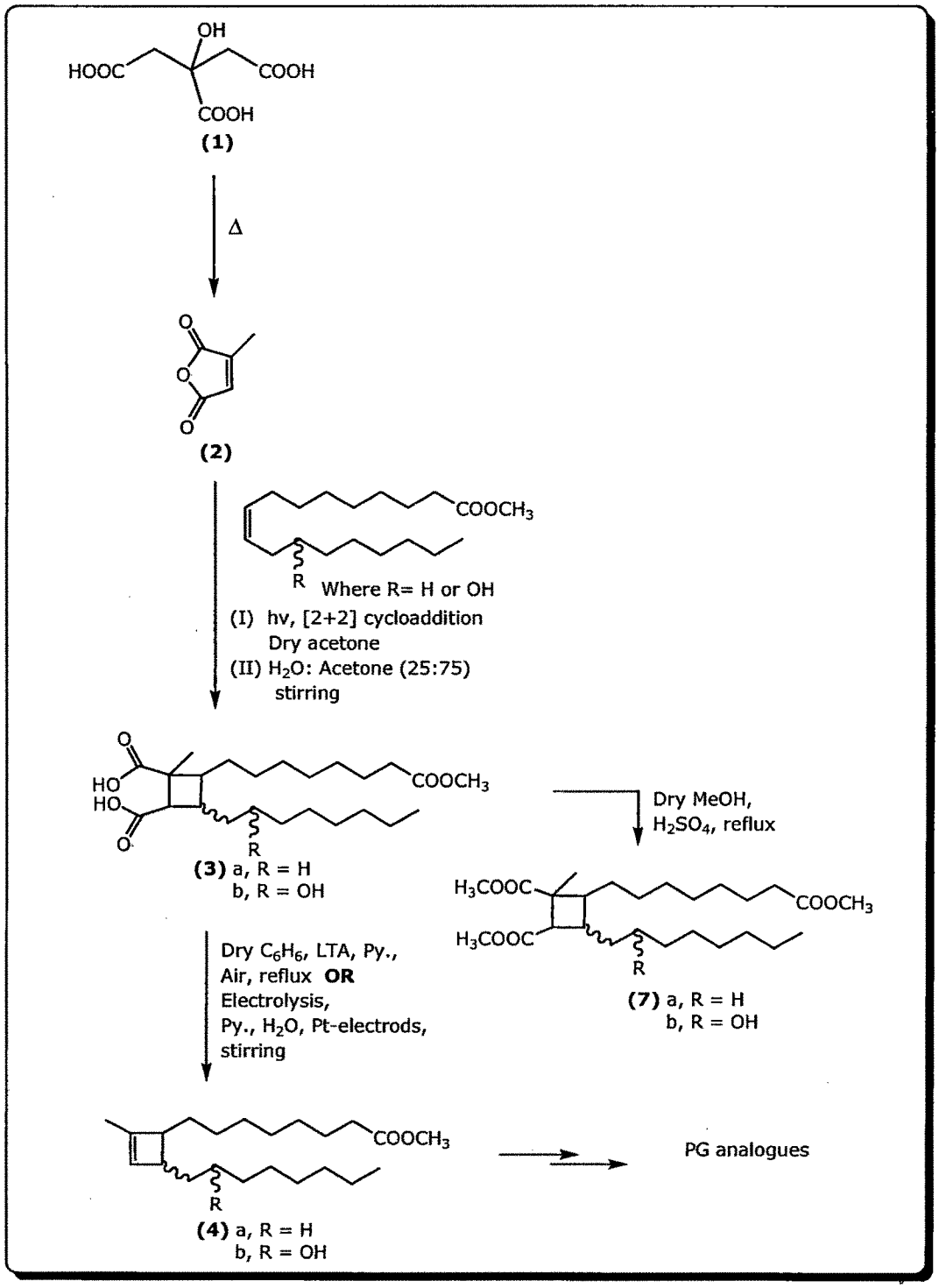
Scheme 1

II.3 RESULTS AND DISCUSSION

Towards accomplishing the objective as stated earlier, we designed a strategy (**Scheme 1**) involving formation of a key intermediate cyclobutene derivative (**4**), as the strategy outlined in **Scheme 1**, was first explored using methyl oleate as the C_{18} component. For conversion of (**2**) into the required key intermediate cyclobutene derivative (**4**) using the well-explored $\pi^{2s} + \pi^{2s}$ photocycloaddition reaction.[11] Of the two carbon units exploited for such reactions, our choice fell on the citraconic anhydride (**2**), because of its ready accessibility.

Citracinic anyhydride was prepared quantitatively by the Shriner's method from the easily available cheap citric acid (**1**) by thermal distillation.[13,14] The structure of the citraconic anhydride (**2**) was fully discernible from its FTIR, ^{1}H NMR, ^{13}C NMR and elemental analysis. It showed a very strong band at 1210 cm^{-1} for the C-O-C stretching for the anhydride along with 1760 and 1650 cm^{-1} for the characteristic carbonyl and alkene absorptions in its IR spectrum. Its ^{1}H NMR spectrum exhibited two sharp singlets at 2.22 and 6.74 indicating the presence of methyl group protons and olefinic protons. Its ^{13}C NMR showed separate signals at δ_c 22, 128, 138 and 166 for the one primary carbon, two olefinic carbons and one carbonyl carbon respectively. Elemental analysis of (**2**) was in good agreement with the required one. Found C; 53.48 %, H; 3.62 % requires C; 53.57 %, H; 3.57 % for $C_5H_4O_3$.

Using this citraconic anhydride, the photochemical cycloaddition reaction was performed with methyl oleate in dry acetone, in an immersion well-type photoreactor for 10 h. Removal of solvent gave the crude photoadduct, which was hydrolyzed in aqueous acetone (25:75) at room temperature for 15 h. Solvent was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer extracted further with sodium bicarbonate solution to remove any other side products. The bicarbonate layer was acidified (pH ~ 3) with concentrated acid, saturated with sodium chloride salt and extracted with ethyl acetate. The combined organic extract was washed with water, brine and dried using sodium sulphate. Removal of solvent under reduced pressure gave the diacid-monoester (**3a**) as a reddish-yellow thick gum having 84 % yields.


OH
HOOC
COOH
COOH
(1)
Δ
(2)
COOCH3
R
Where R= H or OH
(I) hv, [2+2] cycloaddition
Dry acetone
(II) H2O: Acetone (25:75)
stirring
HO
HO
COOCH3
R
(3) a, R = H
b, R = OH
Dry MeOH,
H2SO4, reflux
H3COOC
H3COOC
COOCH3
R
(7) a, R = H
b, R = OH
Dry C6H6, LTA, Py.,
Air, reflux OR
Electrolysis,
Py., H2O, Pt-electrods,
stirring
COOCH3
R
(4) a, R = H
b, R = OH
PG analogues

Scheme 2

It showed a very strong broad band for the –OH stretching between 3000-2500 cm^{-1} confirms the presence of the carboxylic acid groups in its IR spectrum. Its ^1H NMR spectrum exhibited sharp singlets at δ_H 3.87 and 10.62, indicating the presence of ester and carboxylic groups among other signals. Elemental analysis of **(3a)** was in good agreement with the required one. Found C; 79.01 %, H; 10.94 % requires C; 78.68 %, H; 11.47 % for $C_{24}H_{42}O_6$. The Structure of diacid-monoester was further confirmed by converting it into the triester **(7a)** by refluxing with conc. sulphuric acid in dry methanol. The resultant pale yellow liquid was chromatograph using mixture of light petroleum ether and ethyl acetate. Its IR spectrum showed sharp strong band at 2952, 2855 and 1739 cm^{-1} confirms the conversion of dicarboxylic acid groups into the ester. This was also confirms from its ^1H NMR spectrum, which exhibited sharp signals at 3.64 for the nine protons of the $-COOCH_3$. Its ^{13}C NMR showed two separate signals at 172 and 180 for the three carbons of the carbonyl groups along with the other signals. Elemental analysis of **(7a)** was in good agreement with the required one. Found C; 68.84 %, H; 10.11 % requires C; 68.72 %, H; 10.13 % for $C_{26}H_{46}O_6$.

Encouraged by these results, we attempted next step of our strategy, which involved the decarboxylation of the adjacent carboxyl groups of the diacid-monoeater **(3a)** by an oxidation process. When we looked into the literature, we found various methods and reagents like Lead tetraacetate (LTA)[15-19], transition metal catalysis[20,21], decomposition of peroxy esters[22], CuO-quinoline[23], anodic oxidation[24,25], etc. For which the diacid-monoester **(3a)** was taken in dry benzene and dry pyridine was added to it. The reaction mixture was refluxed in a stream of dry air[26] and lead tetraacetate was added at once. Refluxing was continued for another 3.5 hours and it was then brought to room temperature. It was diluted with ethyl acetate and HCl (1:1) was added to it after which it was filtered on a celite pad. The organic phase was separated and aqueous phase was further extracted with ethyl acetate. The combined organic extract was washed with HCl, water, $CuSO_4$ solution and finally with brine. Drying and removal of solvent followed by chromatography, over silica gel using light petroleum ether and ethyl acetate gave the colourless liquid as cyclobutene derivative **(4a)**, 28 % yield. The structure of the cyclobutene derivative **(4a)** was fully discernible from its FTIR, ^1H NMR, ^{13}C NMR, mass spectra and elemental analysis.

Its IR spectrum showed characteristic stretching at 1654 and 1636 cm^{-1} along with other signals, confirm the conversion of diacid-monoester into the cyclobutene derivative. Its ^1H NMR exhibited signals for the olefinic proton at δ_H 5.90-4.59. The bridging protons appeared at δ_H 2.35, along with the characteristic signals of the ester group at δ_H 3.67. Its ^{13}C NMR showed characteristic signals for olefinic carbons at δ_c 147 and 131 along with the other signals. Its Mass spectrum showed m/z: (M^+) at 335, 337 (M+1), along with 321, 293, 279, 265, 249, 209, 195, 179, 139, 123, 109, 95, 83, 69 and 55. Elemental analysis of **(4a)** was in good agreement with the required one Found C; 78.60 %, H; 11.641 % requires C; 78.57 %, H; 11.90 % for $C_{22}H_{40}O_2$.

Here the cyclobutene derivative is the key intermediate for the preparation of the PG analogue as depicted the **Scheme 1.**

Encouraged by above results, we attempted this method on other long chain monoester having –OH group as pendent. For this a solution of the methyl ricinoleate and citraconic anhydride **(2)** in dry acetone was placed in an immersion well-type photoreactor and was irradiated for 10 h, with a 250 W high pressure mercury vapour lamp. Removal of solvent gave the crude photoadduct, which was hydrolyzed in aqueous acetone at room temperature for 15 h. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer extracted further with sodium bicarbonate solution. The bicarbonate layer was acidified (pH ~ 3) with concentrated HCl., saturated with NaCl and extracted with ethyl acetate (4 × 35 ml). The combined organic extract was washed with water, brine and dried. Removal of solvent under reduced pressure gave the diacid-monoester **(3b)** as a light-brown colour thick gum 84 % yield.

It showed a very strong broad band for the –OH stretching between 3000-2500 cm^{-1} and at 3442, confirms the presence of the carboxylic acid groups and free -OH group in its IR spectrum. Elemental analysis of **(3b)** was in good agreement with the required one Found C; 65.11 %, H; 10.14 % requires C; 65.07 %, H; 9.48 % for $C_{24}H_{42}O_7$. The Structure of diacid-monoester was further confirmed by converting it into the triester **(7b)** by refluxing with conc. sulphuric acid in dry methanol. The resultant triester showed strong stretching for the –OH group at 3466 cm^{-1}, along with the sharp signals at 2928, 2856 and 1731 cm^{-1} for the ester groups. Its ^1H NMR exhibited sharp signal at δ_H 3.62 for

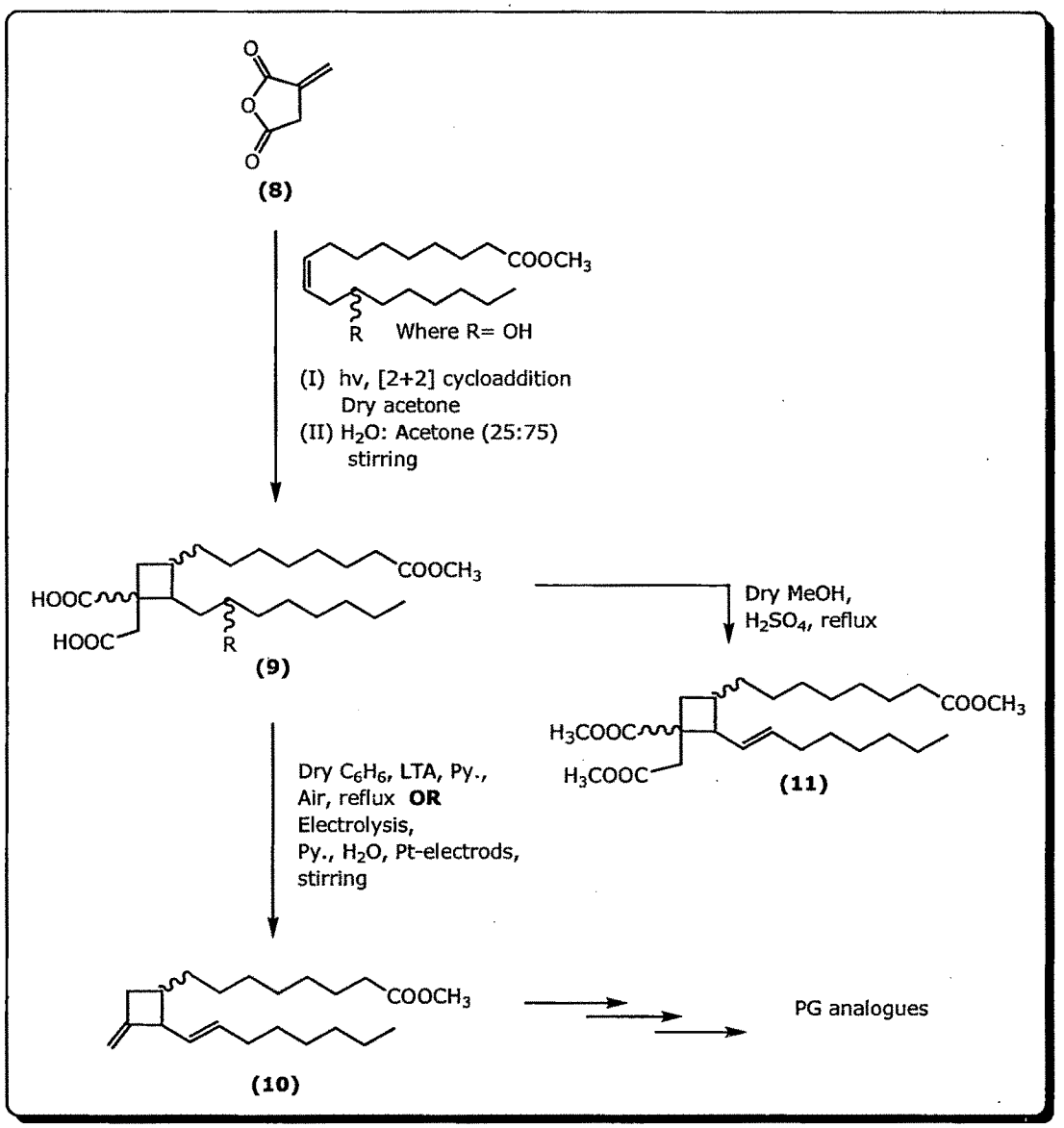
the three ester groups and the –OH appeared at δ_H 1.49 along with other signals. Its ^{13}C NMR showed signals at δ_c 54 for the three carbons of -COO<u>C</u>H$_3$ groups. The carbon bearing –OH group appeared at δ_c 74.5, whereas the three carbonyl carbons at δ_c 170 and 177. Elemental analysis of **(7b)** was in good agreement with the required one Found C; 65.97 %, H; 10.13 % requires C; 66.29 %, H; 9.77 % for $C_{26}H_{46}O_7$.

For the conversion of the diacid-monoester above obtain under went to the decarboxylation reaction and furnished the key intetmediate **(4b)** for the preparation of the PG analogue. The diacid-monoester **(3b)** was taken in dry benzene and dry pyridine was added to it. The reaction mixture was refluxed in a stream of dry air and lead tetraacetate was added at once. Refluxing was continued for another 3.5 hours and it was then brought to room temperature. It was diluted with ethyl acetate and HCl was added to it after which it was filtered on a celite pad. The organic phase was separated and aqueous phase was further extracted with ethyl acetate. The combined organic extract was washed with HCl, water, $CuSO_4$ solution and finally with brine. Drying and removal of solvent followed by chromatography, over silica gel using light petroleum ether and ethyl acetate gave the cyclobutene derivative **(4b)** having 23.28 % yield.

The structure of the cyclobutene derivative **(4b)** was fully discernible from its FTIR, ^1H NMR, ^{13}C NMR and elemental analysis. Its IR spectrum showed characteristics stretching signals at 3348 and 1650 for the free –OH group and alkene. Its ^1H NMR exhibited signals for the olefinic proton at δ_H 6.25-4.75. The bridging protons appeared at δ_H 2.35, along with the characteristic signals of the ester group at δ_H 3.65. Its ^{13}C NMR showed characteristic signals for olefinic carbons at δ_c 145 and 134 along with the other signals. Elemental analysis of **(4b)** was in good agreement with the required one Found C; 75.63 %, H; 10.84 % requires C; 75.00 %, H; 11.36 % for $C_{22}H_{40}O_3$.

Encouraged by above results, we attempted this method for other anhydride to check its versatility for the preparation of novel PG-analogue. For this $\pi^{2s} + \pi^{2s}$ photocycloaddition reaction between methyl ricinoleate and itaconic anhydride **(8, Scheme 3)** in an immersion well-type photoreactor was carried out and the crude photoadduct was hydrolyzed in aqueous acetone at room temperature. Acetone was removed under reduced pressure and after usual work up, the diacid-monoester **(9)** obtained in 86 % yield. It showed a very strong broad band for the –OH stretching

between 3000-2500 cm^{-1} and at 3461, confirms the presence of the carboxylic acid groups and free -OH group in its IR spectrum. Elemental analysis of (**9**) was in good agreement with the required one Found C; 64.91 %, H; 10.02 % requires C; 65.07 %, H; 9.48 % for $C_{24}H_{42}O_7$.



Scheme 3

The Structure of diacid-monoester (**9, Scheme 3**) was further confirmed by converting it into the triester (**11**) by refluxing with conc. sulphuric acid in dry methanol. After 6 h the usual work-up of the reaction mixture gave triester (**11**) as a pale yellow

liquid which was chromatograph using light petroleum ether and ethyl acetate gave light yellow liquid in 63 % yield. The resultant triester showed strong stretching at 2928, 2856 and 1731 cm^{-1} for the ester groups and there was absence of the stretching frequency for the free -OH group in its IR spectrum. Assumed that during the esterification reaction, the diacid-monoester (**9**) could under went dehydration reaction in the presence of strong sulphuric acid and gave (**11**) as the product. The structure of this product (**11**) was confirmed through various spectral analysis and elemental analysis. Its IR spectrum exhibited stretching frequency at 1655 cm^{-1} for alkene, confirmed the dehydrated product (**11**). Its ^{1}H NMR showed sharp signals at 5.5 for the olefinic protons and 3.65 for the protons of ester groups. Its ^{13}C NMR showed signals at δ_c 51, 53 and 54 for the three carbons of -COO$\underline{C}H_3$ groups. The olefinic carbons appeared at δ_c 125 and 133, whereas the three carbonyl carbons at δ_c 174.5 and 177.5. Elemental analysis of (**11**) was in good agreement with the required one Found C; 68.77 %, H; 10.11 % requires C; 68.93 %, H; 9.72 % for $C_{26}H_{44}O_6$.

Above prepared diacid (**9**) was converted into the cyclobutene derivative, which is the key intermediate for the synthesis of the novel PG analogues as shown in the **Scheme 5**. For this purpose the diacid-monoester (**9**) was taken in dry benzene and dry pyridine was added to it. The reaction mixture was refluxed in a stream of dry air and lead tetraacetate was added at once. Refluxing was continued for another 3.5 h and after completion of reaction usual work up followed by column chromatography gave the cyclobutene derivative (**10**) in 22 % yield. The structure of the cyclobutene derivative (**10**) was fully discernible from its FTIR, ^{1}H NMR, ^{13}C NMR and elemental analysis.
Its IR spectrum exhibited stretching frequency at 1660 and 1652 cm^{-1}, confirmed the dehydrated product alkene (**10**). Its ^{1}H NMR showed sharp signals at 5.55 and 5.56 for the olefinic protons and 3.64 for the protons of ester groups. Its ^{13}C NMR showed signals at δ_c 124, 138, 155.6 confirmed the presence of four olefinic carbons. Whereas, the signal at δ_c 174.5 indicated the presence of carbonyl carbon. Elemental analysis of (**11**) was in good agreement with the required one Found C; 78.84 %, H; 10.94 % requires C; 78.92 %, H; 11.36 % for $C_{22}H_{38}O_2$.

II.4 EXPERIMENTAL

Ultraviolet spectra were recorded on a Perkin-Elmer Lambda-19 Spectrometer. Infrared spectra were recorded on a Perkin-Elmer PC-16 FTIR Spectrophotometer. PMR (200 MHz or 300 MHz) spectra and ^{13}CMR (50 MHz) were recorded either on a Bruker-200-FT-NMR or on a Bruker-AC-300-FT-NMR using $CDCl_3$ as solvent containing tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu QP-5050-A mass spectrometer. Microanalyses were performed on a Perkin-Elmer 2400 series II Laser instrument.

Column chromatography was performed using Acme's silica gel (60–120 mesh size) and the elution was done using light petroleum and ethyl acetate mixtures. The percent yields are reported based on the isolated material after column chromatography. Thin layer chromatography was performed using Acme's silica gel for TLC and spots were visualized in iodine vapor.

Preparation of citraconic anhydride (2) from citric acid (1)

Citric acid monohydrate **(1)** (200 gm) was placed in Kjeldhl flask and heated with a free flame until melted. Then temperature was increased very rapidly and the distillation was completed as quickly as possible (12 to 15 minutes), at this stage superheating should be avoided. The distillate collected at 180-200 °C was consisted water and itaconic anhydride. The distillate was immediately poured into a sepaeatory funnel and the lower layer of itaconic anhydride was separated. The yield of the itaconic anhydride was 56 gm (49 %) and of sufficient pure for use in the preparation of citraconic anhydride.

Itaconic anhydride (56 gm) was distilled rapidly at atmospheric pressure in Claisen flask with fractionating column (15 cm length). The receivers for the distillate must be changed without interrupting the distillation. The distillate obtained below 200 °C was consisted water and other decomposition products. The fraction distilled at 210-215 °C was consisted citraconic anhydride **(2)** and was further purified by redistillation under reduced pressure gave 35.2 gm (63 %) of pure product having mp 7 °C.

White crystalline solid at low temp. (~ 3-5 °C) (63 %), mp 7 °C, ν_{max}: 3020, 1760, 1650 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 6.74 (s, 1H, olefinic), 2.22 (s, 3H at C<u>H</u>$_3$). δ_c (75.5 MHz, $CDCl_3$): 22 (-CH_3), 128 and 139 (two olefinic carbon), 166.20 (carbonyl carbon). Elemental analysis: Found C; 53.48 %, H; 3.62 % requires C; 53.57 %, H; 3.57 % for $C_5H_4O_3$.

Preparation of 4-(7-Methoxycarbonyl heptyl)-1-methyl-3-octyl-cyclobutane-1,2-dicarboxylic acid (3a)

A solution of the methyl oleate (4.35 gm, 0.0146 mole) and citraconic anhydride (**2**) (2.29 gm, 0.0222 mole) in dry acetone (~ 350 ml) was placed in an immersion well-type photoreactor and was irradiated for 9 h, with a 250 W high pressure mercury vapour lamp. Removal of solvent gave the crude photoadduct, which was hydrolyzed in aqueous acetone (25:75) at room temperature for 15 h. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (4 × 35 ml). The ethyl acetate layer extracted further with sodium bicarbonate ($NaHCO_3$) solution (15 %, 4 × 35 ml). The bicarbonate layer was acidified (pH ~ 3) with concentrated HCl., saturated with NaCl and extracted with ethyl acetate (4 × 35 ml). The combined organic extract was washed with water (3 × 25 ml), brine (35 ml) and dried using sodium sulphate (Na_2SO4). Removal of solvent under reduced pressure gave the diacid-monoester (**3a**) as a reddish-yellow thick gum (5.44 gm, 87 % yield).

Reddish-yellow thick liquid (87 %), ν_{max}: 2928, 2856, 2663, 1774, 1710, 1459, 1416, 1296, 1225, 940, 723 and 612 cm^{-1}. UV (λ_{max}): 270 nm. δ_H (300 MHz, $CDCl_3$): 10.39 (s, 2H, -COO<u>H</u> × 2), 4.12 (q, 1H at C_{10}), 3.67 (s, 3H, -COOC<u>H</u>$_3$), 3.0 (broad peak, 1H at C_{12}), 2.30 (m, 3H at C_3 and C_{13}), 2.05 (s, merged, 3H, -CH_3 at C_{22}), 1.85 (m, 2H, -C<u>H</u>$_2$), 1.54 (m, 8H, -CH_2 × 4), 1.26 (t, 16H, -CH_2 × 8), 0.88 (t, 3H, -CH_3 at C_{21}). Elemental analysis: Found C; 79.01 %, H; 10.94 % requires C; 78.68 %, H; 11.47 % for $C_{24}H_{42}O_6$.

4-(7-Methoxycarbonyl heptyl)-1-methyl-3-octyl-cyclobutane-1,2-dicarboxylic acid dimethyl ester (7a)

The diacid-monoester (**3a**) (5 gm, 0.0136 mole) was dissolved in dry methanol (40 ml) and concentrated sulfuric acid (0.8 ml) was added under reflux condition. After 6

hours the usual work-up of the reaction mixture gave trimester (**7a**) as a pale yellow liquid which was chromatograph using light petroleum ether and ethyl acetate gave light yellow liquid. (3.62 gm, 68 % yield)

Light yellow liquid (68 %), ν_{max}: 3452, 2952, 2927, 2855, 1978, 1739, 1459, 1377, 1355, 1434, 1291, 1171, 1197, 1151, 1036, 994, 922, 822, 772 and 556 cm^{-1}, UV (λ_{max}): 260 nm. δ_H (300 MHz, $CDCl_3$): 3.64 (s, 9H, -COOC<u>H</u>$_3$ × 3), 2.97 (d, 1H at C_{12}), 2.60 (m, 2H at C_{10} and C_{13}), 1.85 (m, 2H, -C<u>H</u>$_2$ at C_4), 1.36 (s, merged, 3H, -CH_3 at C_{22}), 1.09 (m, 22H, -CH_2 × 11), 0.97 (m, merged with t, 4H, -CH_2 × 2), 0.88 (t, 3H, - CH_3 at C_{21}). δ_c (75.5 MHz, $CDCl_3$): 14 and 20 (-CH_3 at C_{21} and C_{22}), 42, 45, 47, 49 (four carbons at C_1, C_{10}, C_{11} and C_{12}), 23, 24, 25, 27, 28, 29, 30, 32, 34, 35, 37 (methylene carbons), 172 and 180 (carbonyl carbons). Elemental analysis: Found C; 68.84 %, H; 10.11 % requires C; 68.72 %, H; 10.13 % for $C_{26}H_{46}O_6$.

Preparation of 8-(2-Methyl-4-octyl-cyclobut-2-enyl)-octanoic acid methyl ester (4a)

The diacid-monoester (**3a**) (5 gm, 0.0136 mole) was taken in dry benzene (100 ml) and dry pyridine (5.5 ml, 0.0682 mole) was added to it. The reaction mixture was refluxed in a stream of dry air and lead tetraacetate (9.5 g, 0.0214 mole) was added at once. Refluxing was continued for another 3.5 hours and it was then brought to room temperature. It was diluted with ethyl acetate (60 ml) and HCl (1:1) (45 ml) was added to it after which it was filtered on a celite pad. The organic phase was separated and aqueous phase was further extracted with ethyl acetate (3 × 35 ml). The combined organic extract was washed with HCl (10 %, 2× 30 ml), water (30 ml), $CuSO_4$ solution (10 %, 2 × 30 ml) and finally with brine (35 ml). Drying and removal of solvent followed by chromatography, over silica gel using light petroleum ether and ethyl acetate gave the colourless liquid as cyclobutene derivative (**4a**) (1.10 gm, 28 % yield).

Colourless liquid (28 %), ν_{max}: 3462, 2924, 2854, 1740, 1654, 1636, 1540, 1521, 1506, 1456, 1436, 1371, 1238, 1196, 1171, 1108, n1021, 969, 885, 723, and 608 cm^{-1}, UV (λ_{max}): 210 nm. δ_H (300 MHz, $CDCl_3$): 5.90-4.59 (broad peak, 1H, olefinic H at C_{12}), 3.67 (s, 3H, -COOC<u>H</u>$_3$), 2.35 (m, 2H at C_{10} and C_{13}), 2.25 (m, 4H, -C<u>H</u>$_2$ × 2), 1.68 (s, merged, 3H, -CH_3 at C_{22}), 1.58 (m, merged, 2H, -CH_2),1.32 (m, 22H, -CH_2 × 11), 0.90 (t,

3H, - CH_3 at C_{21}). δ_c (75.5 MHz, $CDCl_3$): 14 and 22 (two carbons at C_{21} and C_{22}), 44 and 52 (two carbons at C_1 and C_{10}), 23, 24.5, 25, 27, 28, 30, 32, 33, 35, 36, 37 (methylene carbons), 147 and 131 (two olefinic carbons) 171.5 (carbonyl carbon). m/z: (M^+) at 335, 337 (M+1), along with 321, 293, 279, 265, 249, 209, 195, 179, 139, 123, 109, 95, 83, 69 and 55. Elemental analysis: Found C; 78.60 %, H; 11.641 % requires C; 78.57 %, H; 11.90 % for $C_{22}H_{40}O_2$.

Preparation of 3-(2-Hydroxy-octyl)-4-(7-methoxycarbonyl-heptyl)-1-methyl-cyclobutane-1,2-dicarboxylic acid (3b)

A solution of the methyl ricinoleate (4.56 gm, 0.0146 mole) and citraconic anhydride **(2)** (2.3 gm, 0.0222 mole) in dry acetone (~ 350 ml) was placed in an immersion well-type photoreactor and was irradiated for 10 h, with a 250 W high pressure mercury vapour lamp. Removal of solvent gave the crude photoadduct, which was hydrolyzed in aqueous acetone (25:75) at room temperature for 15 h. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (4 × 35 ml). The ethyl acetate layer extracted further with sodium bicarbonate ($NaHCO_3$) solution (15 %, 4 × 35 ml). The bicarbonate layer was acidified (pH ~ 3) with concentrated HCl., saturated with NaCl and extracted with ethyl acetate (4 × 35 ml). The combined organic extract was washed with water (3 × 25 ml), brine (35 ml) and dried using sodium sulphate (Na_2SO4). Removal of solvent under reduced pressure gave the diacid-monoester **(3b)** as a light-brown colour thick gum (5.42 gm, 84 % yield).
Light-brown thick liquid (84 %), ν_{max}: 3442, 2932, 2858, 2666, 1770, 1712, 1456, 1417, 1276, 1226, 933 and 728 cm^{-1}. UV (λ_{max}): 222 nm. Elemental analysis: Found C; 65.11 %, H; 10.14 % requires C; 65.07 %, H; 9.48 % for $C_{24}H_{42}O_7$.

3-(2-Hydroxy-octyl)-4-(7-methoxycarbonyl-heptyl)-1-methyl-cyclobutane-1,2-dicarboxylic acid dimethyl ester (7b)

The diacid-monoester **(3b)** (6 gm, 0.0136 mole) was dissolved in dry methanol (40 ml) and concentrated sulfuric acid (0.8 ml) was added under reflux condition. After 6 hours the usual work-up of the reaction mixture gave trimester **(7b)** as a pale yellow

liquid which was chromatograph using light petroleum ether and ethyl acetate gave light yellow liquid. (4 gm, 63 % yield)

Light yellow liquid (63 %), ν_{max}: 3466, 2928, 2856, 1731, 1437, 1361, 1171, 1021 and 726 cm^{-1}, UV (λ_{max}): 254 nm. δ_H (300 MHz, $CDCl_3$): 3.62 (s, 9H, -COOC<u>H</u>$_3$ × 3), 3.39 (d, 1H at C_{12}), 3.01 (m, 1H at C_{15}), 2.36 (m, merged, 2H at C_{10} and C_{13}), 2.11 (m, 6H, -C<u>H</u>$_2$ × 3), 1.78 (s, merged, 3H, -CH_3 at C_{22}), 1.49 (s, merged with m, 3H, -O<u>H</u> and -C<u>H</u>$_2$), 1.22 (m, 16H, -C<u>H</u>$_2$ × 8), 0.97 (t, 3H, - CH_3 at C_{21}). δ_c (75.5 MHz, $CDCl_3$): 14 and 18.5 (-CH_3 at C_{21} and C_{22}), 20, 21, 23, 26, 28, 29, 30, 33, 35, 36, 37 (methylene carbons), 48, 49, 52 (three carbons at C_{10}, C_{11} and C_{12}), 54 (three carbons at C_1, C_{25} and C_{26}), 74.5 (one carbon at C_{15}), 170 and 177 (three carbonyl carbons). Elemental analysis: Found C; 65.97 %, H; 10.13 % requires C; 66.29 %, H; 9.77 % for $C_{26}H_{46}O_7$.

Preparation of 8-[4-(2-Hydroxy-octyl)-2-methyl-cyclobut-2-enyl]-octanoic acid methyl ester (4b)

The diacid-monoester **(3b)** (6 gm, 0.0136 mole) was taken in dry benzene (100 ml) and dry pyridine (5.5 ml, 0.0682 mole) was added to it. The reaction mixture was refluxed in a stream of dry air and lead tetraacetate (9.5 g, 0.0214 mole) was added at once. Refluxing was continued for another 3.5 hours and it was then brought to room temperature. It was diluted with ethyl acetate (60 ml) and HCl (1:1) (45 ml) was added to it after which it was filtered on a celite pad. The organic phase was separated and aqueous phase was further extracted with ethyl acetate (3 × 35 ml). The combined organic extract was washed with HCl (10 %, 2× 30 ml), water (30 ml), $CuSO_4$ solution (10 %, 2 × 30 ml) and finally with brine (35 ml). Drying and removal of solvent followed by chromatography, over silica gel using light petroleum ether and ethyl acetate gave the cyclobutene derivative **(4b)** (1.11 gm, 23.28 % yield).

colourless liquid (23.28 %), ν_{max}: 3448, 2928, 2855, 1737, 1650, 1459, 1437, 1372, 1171, 1033 and 740 cm^{-1}, UV (λ_{max}): 210 nm. δ_H (300 MHz, $CDCl_3$): 6.25-4.75 (broad peak, 1H at C_{12}), 4.31 (s, 1H at C_{15}), 3.65 (s, 3H, -COOC<u>H</u>$_3$), 2.35 (m, 4H at C_3, C_{10} and C_{13}), 2.11 (m, merged, 3H, -OH, and -C<u>H</u>$_2$), 1.68 (s, merged, 3H, -CH_3 at C_{22}), 1.58 (s, merged with m, 4H, -C<u>H</u>$_2$ × 2), 1.39 (m, 18H, -C<u>H</u>$_2$ × 9), 0.93 (t, 3H, - CH_3 at C_{21}). δ_c (75.5

MHz, $CDCl_3$): 14 and 21 (-CH_3 at C_{21} and C_{22}), 22, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 35, 37, 38 (methylene carbons), 44 (carbon at C_{10}), 52 (carbon at C_1), 72.5 (one carbon at C_{15}), 134 and 145 (two carbons at C_{11} and C_{12}), 171 (carbonyl carbon). Elemental analysis: Found C; 75.63 %, H; 10.84 % requires C; 75.00 %, H; 11.36 % for $C_{22}H_{40}O_3$.

Preparation of 1-Carboxymethyl-2-(2-hydroxy-octyl)-3-(7-methoxycarbonyl-heptyl)-cyclobutanecarboxylic acid (9)

A solution of the methyl ricinoleate (4.56 gm, 0.0146 mole) and itaconic anhydride (**8**) (2.3 gm, 0.0222 mole) in dry acetone (~ 350 ml) was placed in an immersion well-type photoreactor and was irradiated for 10 h, with a 250 W high pressure mercury vapour lamp. Removal of solvent gave the crude photoadduct, which was hydrolyzed in aqueous acetone (25:75) at room temperature for 15 h. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (4 × 35 ml). The ethyl acetate layer extracted further with sodium bicarbonate ($NaHCO_3$) solution (15 %, 4 × 35 ml). The bicarbonate layer was acidified (pH ~ 3) with concentrated HCl., saturated with NaCl and extracted with ethyl acetate (4 × 35 ml). The combined organic extract was washed with water (3 × 25 ml), brine (35 ml) and dried using sodium sulphate (Na_2SO4). Removal of solvent under reduced pressure gave the diacid-monoester (**9**) as a reddish-yellow thick gum (5.5 gm, 86 % yield).

Light-brown thick liquid (86 %), ν_{max}: 3461, 2929, 2865, 1730, 1460, 1375, 1176, 971, 725 and 613 cm^{-1}. UV (λ_{max}): 210 nm. Elemental analysis: Found C; 64.91 %, H; 10.02 % requires C; 65.07 %, H; 9.48 % for $C_{24}H_{42}O_7$

3-(7-Methoxycarbonyl-heptyl)-1-methoxycarbonylmethyl-2-oct-1-enyl-cyclobutanecarboxylic acid methyl ester (11)

The diacid-monoester (**9**) (6 gm, 0.0136 mole) was dissolved in dry methanol (40 ml) and concentrated sulfuric acid (0.8 ml) was added under reflux condition. After 6 hours the usual work-up of the reaction mixture gave triester (**11**) as a pale yellow liquid which was chromatograph using light petroleum ether and ethyl acetate gave light yellow liquid. (3.86 gm, 63 % yield)

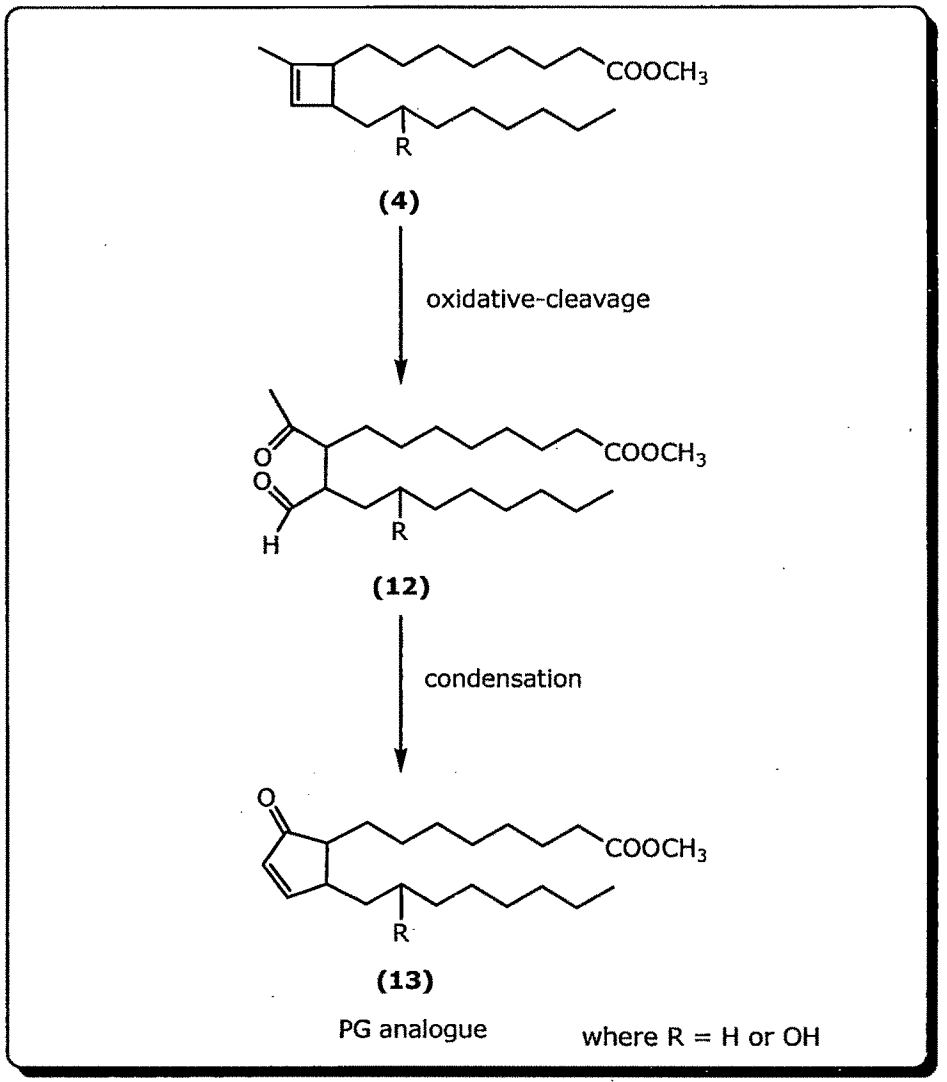
Light yellow liquid (63 %), ν_{max}: 2927, 2856, 2362, 1739, 1655, 1438, 1362, 1248, 1138, 1113, 1080, 1040, 861 and 725 cm^{-1}, UV (λ_{max}): 214 nm. δ_H (300 MHz, $CDCl_3$): 5.5 and 5.53 (m, 2H at C_{14} and C_{15}), 3.65 (s, 9H, -COOC<u>H</u>$_3$ × 3), 3.33 (d, 1H at C_{13}), 2.43 (t, 2H at C_{24}), 2.23 (t, 2H at C_{11}), 2.11 (m, 1H at C_{10}), 1.45 and 1.55 (m, 6H, -CH_2 × 3), 1.28 (m, 18H, -C<u>H</u>$_2$ × 9), 0.87 (t, 3H, - CH_3 at C_{21}). δ_c (75.5 MHz, $CDCl_3$): 14 (-CH_3 at C_{21}), 20, 21, 23, 26, 27, 28, 29, 30, 33, 35, 36, 37 (methylene carbons), 40.1 (carbon at C_{24}), 46.5 (carbon at C_{12}), 48 (carbon at C_{13}), 51, 53, 54 (three carbons at C_1, C_{25} and C_{26}), 125 and 133.5 (two carbons at C_{14} and C_{15}), 174.5 and 177.5 (three carbonyl carbons). Elemental analysis: Found C; 68.77 %, H; 10.11 % requires C; 68.93 %, H; 9.72 % for $C_{26}H_{44}O_6$.

Preparation of 8-(3-Methylene-2-oct-1-enyl-cyclobutyl)-octanoic acid methyl ester (10)

The diacid-monoester **(9)** (6 gm, 0.0136 mole) was taken in dry benzene (100 ml) and dry pyridine (5.5 ml, 0.0682 mole) was added to it. The reaction mixture was refluxed in a stream of dry air and lead tetraacetate (9.5 g, 0.0214 mole) was added at once. Refluxing was continued for another 3.5 hours and it was then brought to room temperature. It was diluted with ethyl acetate (60 ml) and HCl (1:1) (45 ml) was added to it after which it was filtered on a celite pas. The organic phase was separated and aqueous phase was further extracted with ethyl acetate (3 × 35 ml). The combined organic extract was washed with HCl (10 %, 2× 30 ml), water (30 ml), $CuSO_4$ solution (10 %, 2 × 30 ml) and finally with brine (35 ml). Drying and removal of solvent followed by chromatography, over silica gel using light petroleum ether and ethyl acetate gave the cyclobutene derivative **(10)** (~1 gm, 22 % yield).

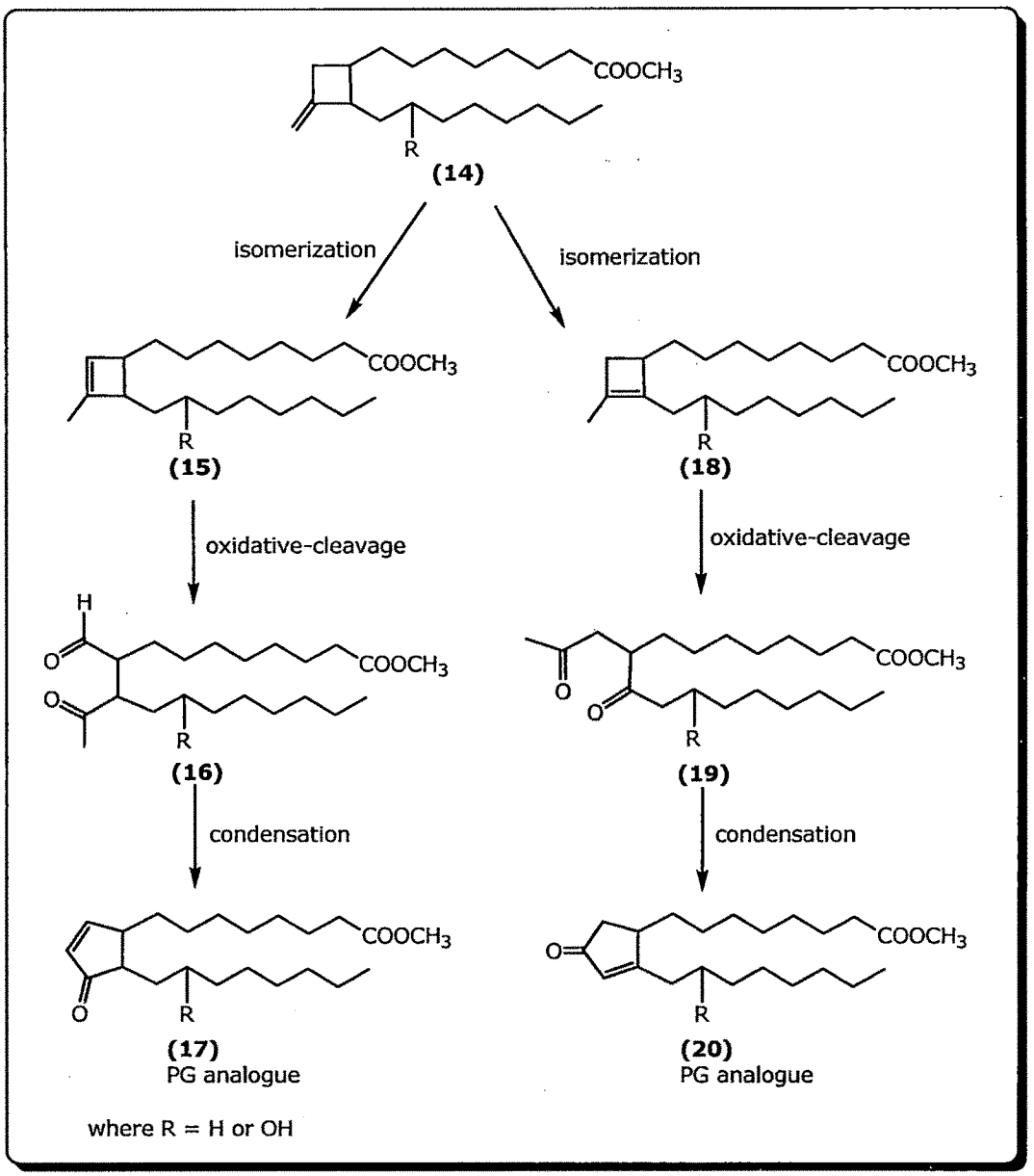
Colourless liquid (22 %), ν_{max}: 2929, 2857, 2368, 1746, 1660, 1652 1439, 1369, 1235, 1110, 1090, 10230, 969 and 800 cm^{-1}, UV (λ_{max}): 210 nm. δ_H (300 MHz, $CDCl_3$): 5.5 and 5.65 (m, 2H at C_{14} and C_{15}), 4.5 (d, 2H at C_{22}), 3.64 (s, 3H, -COOC<u>H</u>$_3$), 2.38 (t, 1H at C_{13}), 2.05 (m, 5H at C_{10}, C_{11} and C_3), 1.62 (m, 6H, -CH_2 × 3), 1.81 (m, 16H, -C<u>H</u>$_2$ × 8), 0.87 (t, 3H, - CH_3 at C_{21}). δ_c (75.5 MHz, $CDCl_3$): 15 (-CH_3 at C_{21}), 21, 22.5, 23, 25, 26.5, 28, 30.5, 32, 34, 35, 37 (methylene carbons), 39 (carbon at C_{10}), 39.5 (carbon at C_{11}), 51.5 (carbon at C_1 and C_{13}), 124 (carbons at C_{22}), 138 (two carbons at C_{14} and C_{15}),

155.6 (carbons at C_{12}), 174.5 (carbonyl carbons). Elemental analysis: Found C; 78.84 %, H; 10.94 % requires C; 78.92 %, H; 11.36 % for $C_{22}H_{38}O_2$.



Scheme 4

Future scope of the present work has been shown in the **Scheme 4** and **Scheme 5**. From the both Schemes it is clear that PG analogues can be synthesized by oxidative cleavage followed by the aldol condensation from the cyclobuteno PGs (**4a, 4b, 10**). Novel PGs will be design and synthesized by using present reaction sequences with appropriate selected anhydride and ling chain olefine.


COOCH3
R
(14)
isomerization
isomerization
COOCH3
R
(15)
COOCH3
R
(18)
oxidative-cleavage
oxidative-cleavage
H
O
O
COOCH3
R
(16)
O
O
COOCH3
R
(19)
condensation
condensation
O
COOCH3
R
(17)
PG analogue
O
COOCH3
R
(20)
PG analogue
where R = H or OH

Scheme 5

II.5 CONCLUSION

A new general protocol for the synthesis of PG analogues from the readily available precursors has been developed. Photochemical $\pi^{2s} + \pi^{2s}$ cycloaddition reaction between an anhydride and a long chain fatty acid or ester was explored and its application towards the efficient synthesis of the cyclobuteno PGs **(4a,4b,10)** has been demonstrated. It is obvious that depending upon the structure of the final Prostaglandin, the cycloaddition of a suitablely substituted anhydride and olefin may be used.

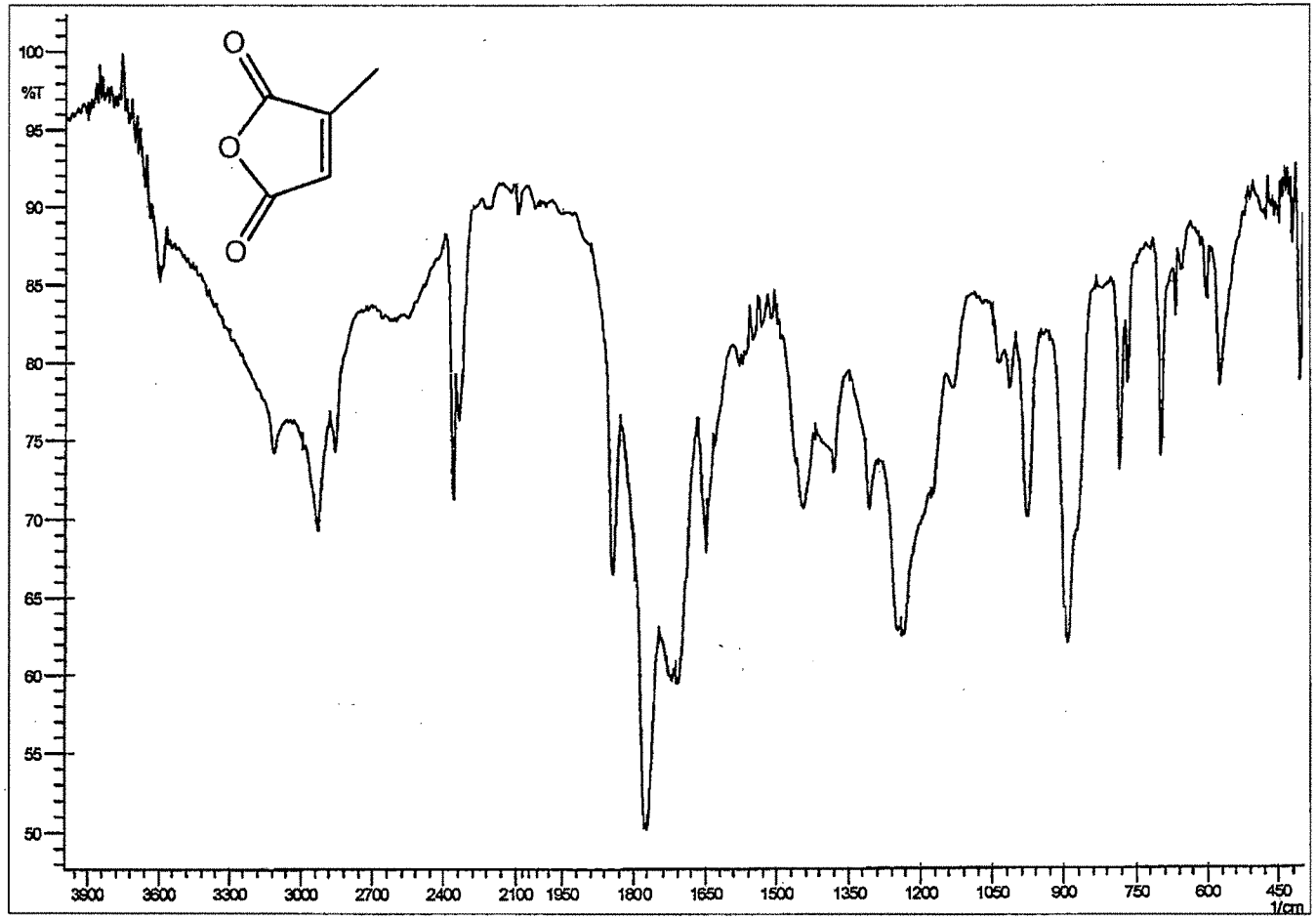


Figure II.2: FTIR Spectrum of the compound 2

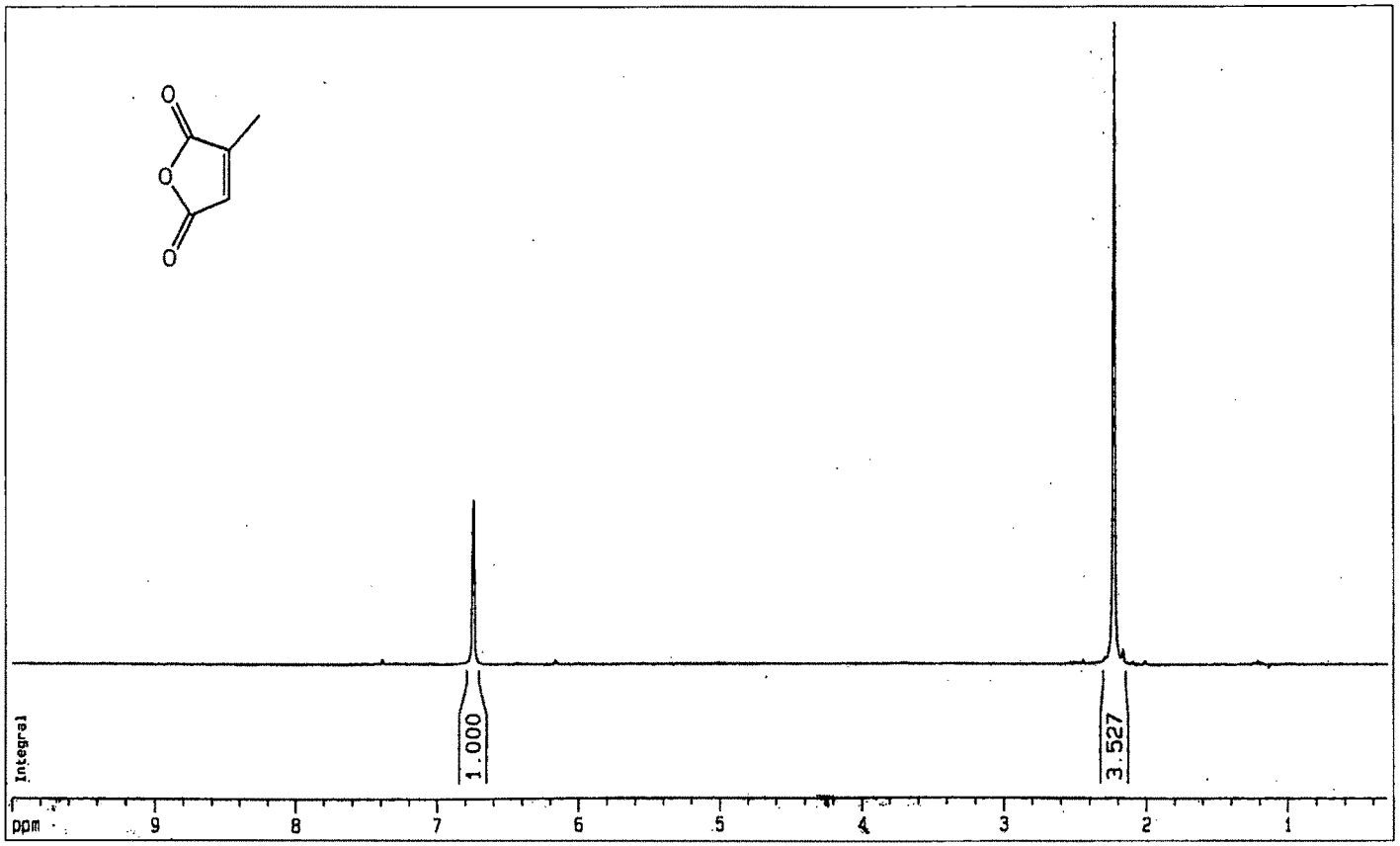


Figure II.3: PMR Spectrum of the compound 2

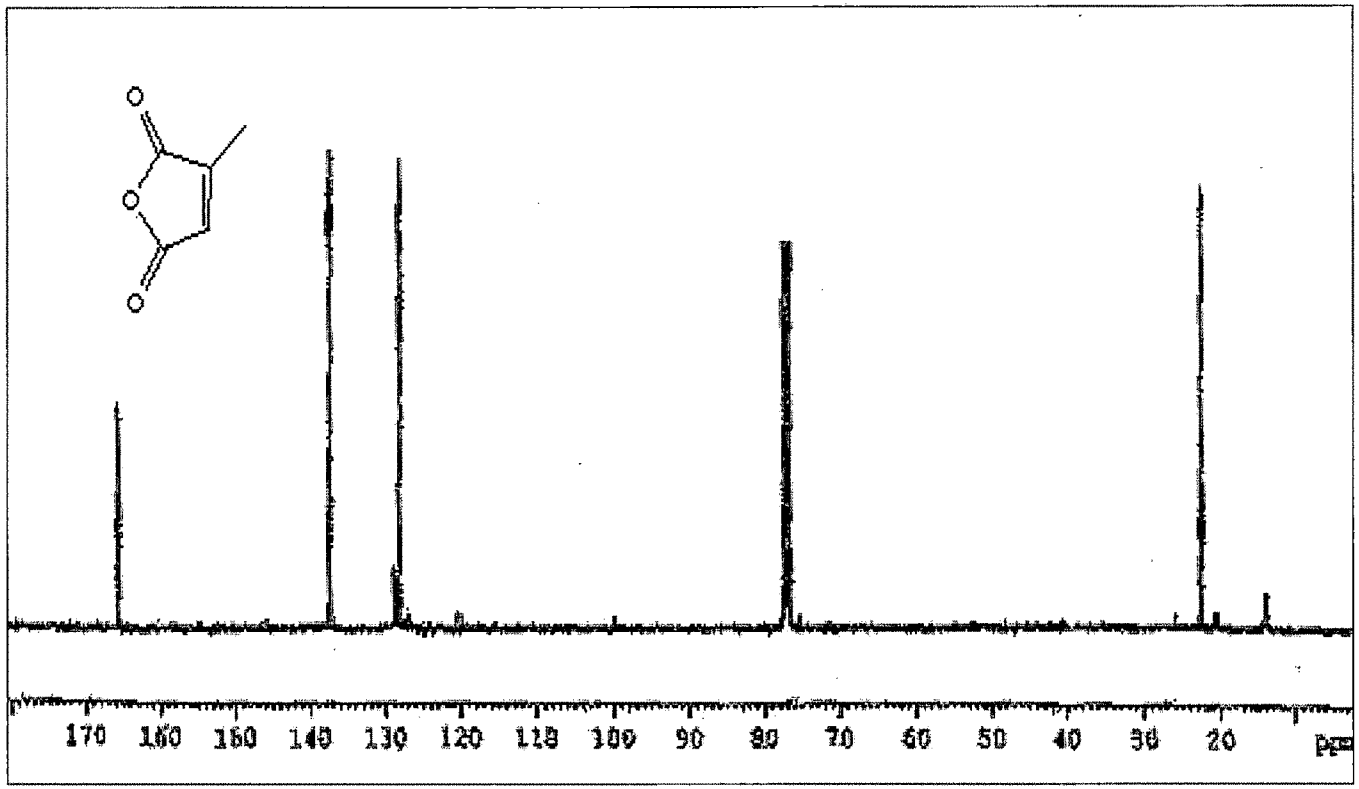


Figure II.4: ^{13}C NMR of the compound 2

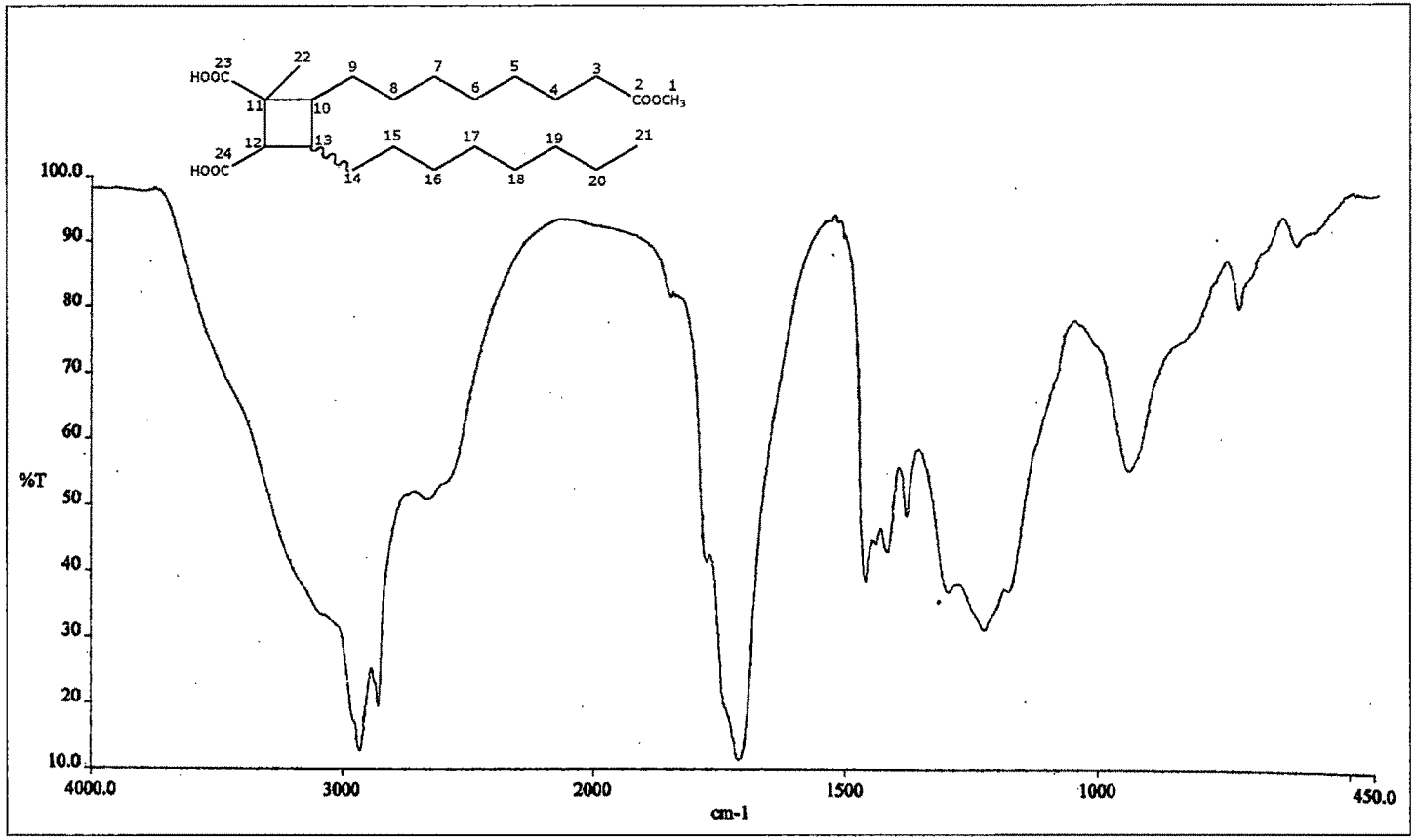


Figure II.5: FTIR Spectrum of the compound (3a)

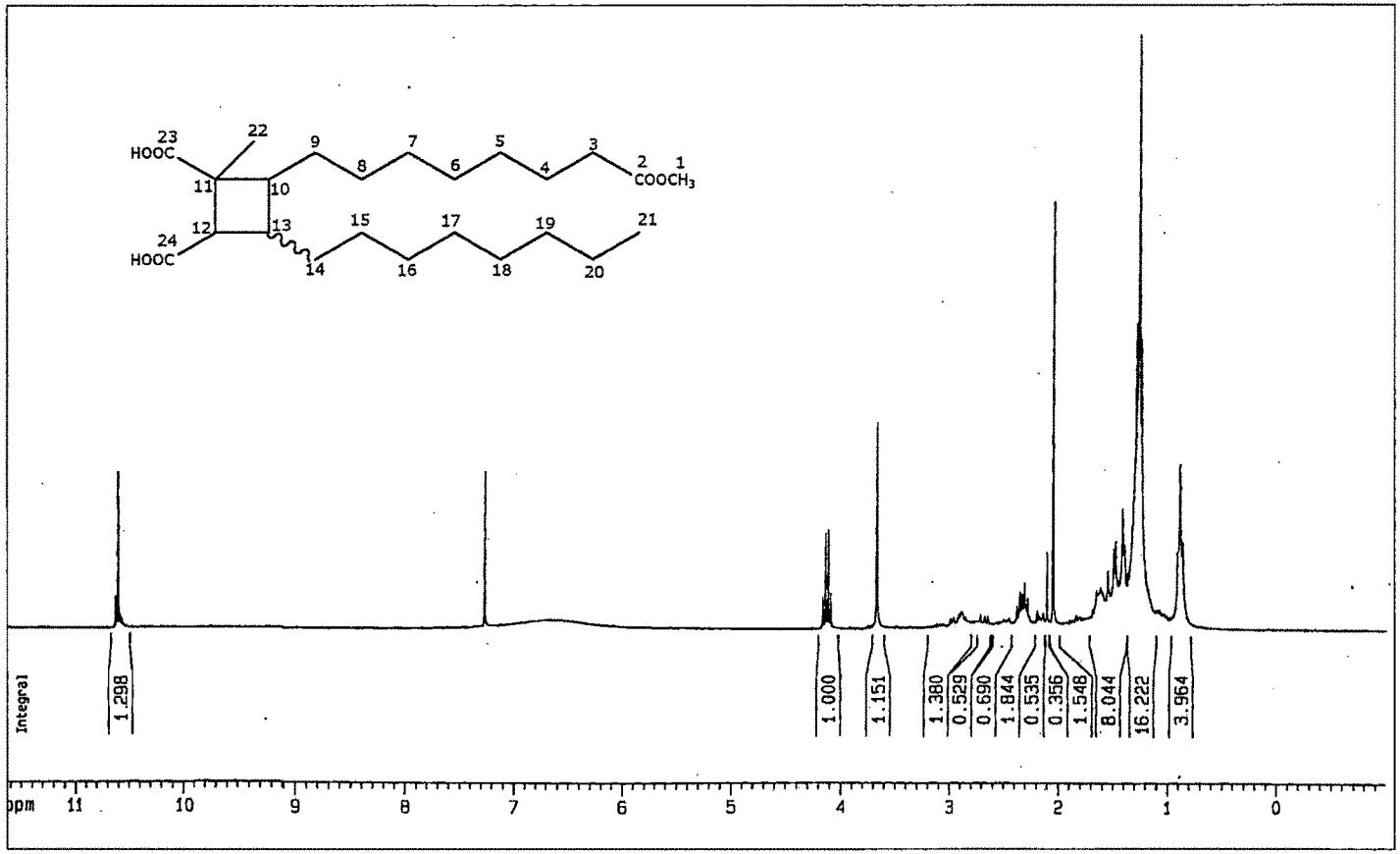


Figure II.6: PMR Spectrum of the compound (3a)

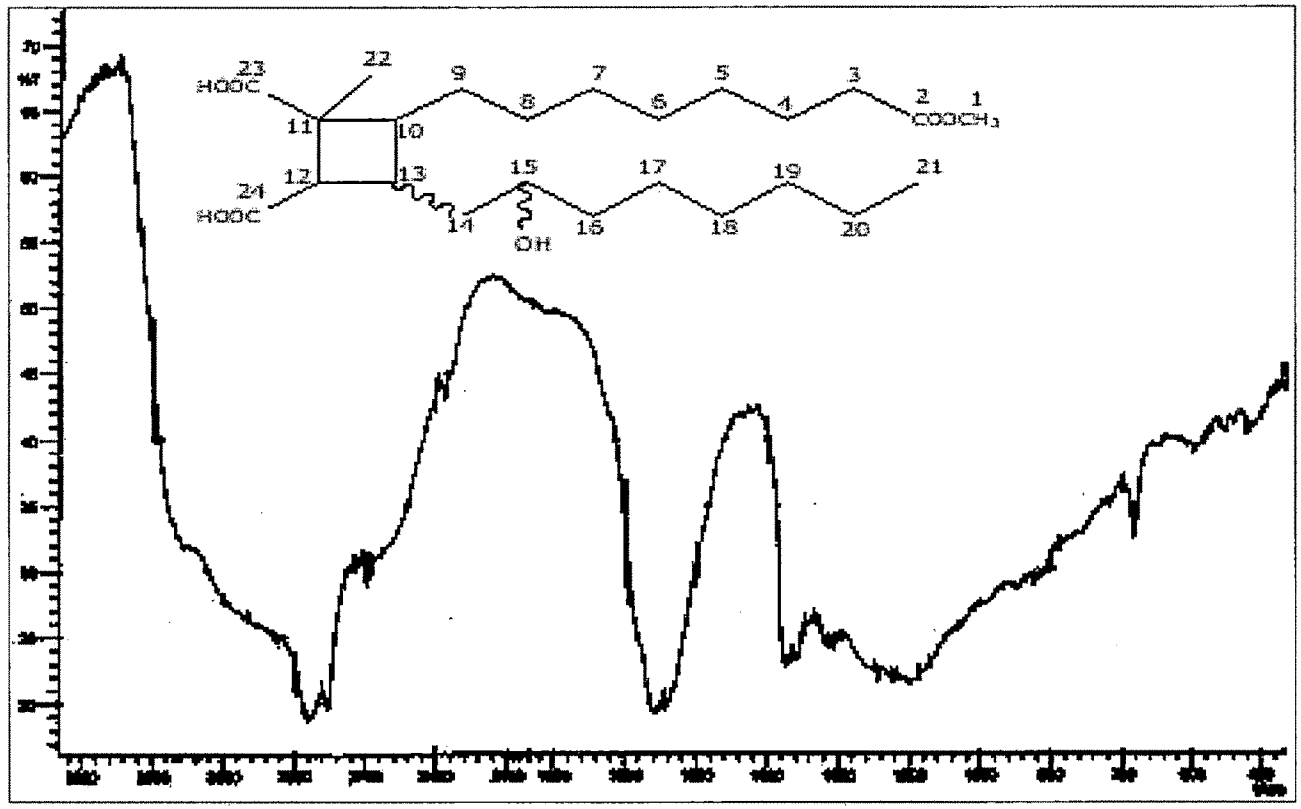


Figure II.7: FTIR Spectrum of the compound (3b)

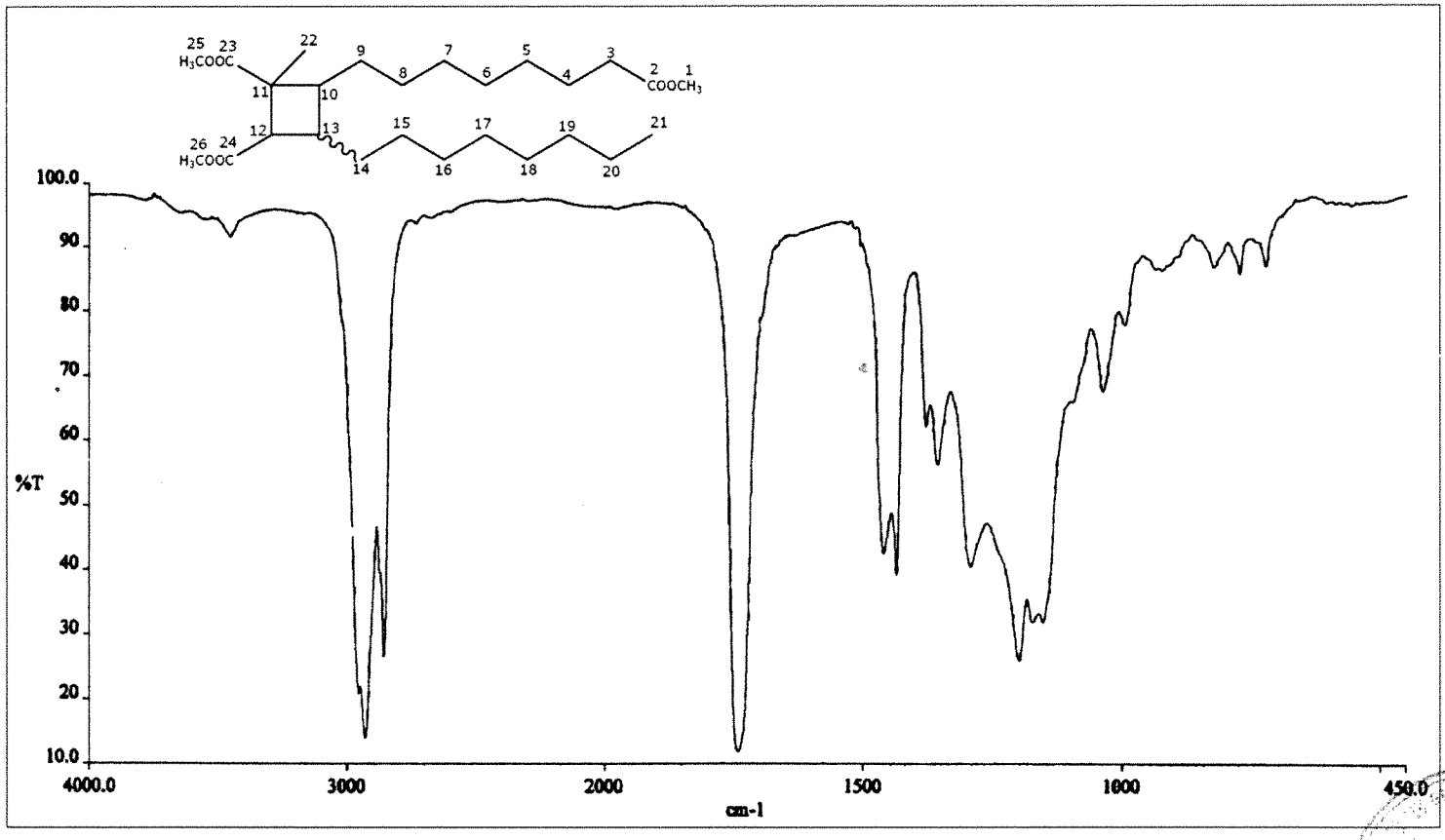


Figure II.8: FTIR Spectrum of the compound (7a)

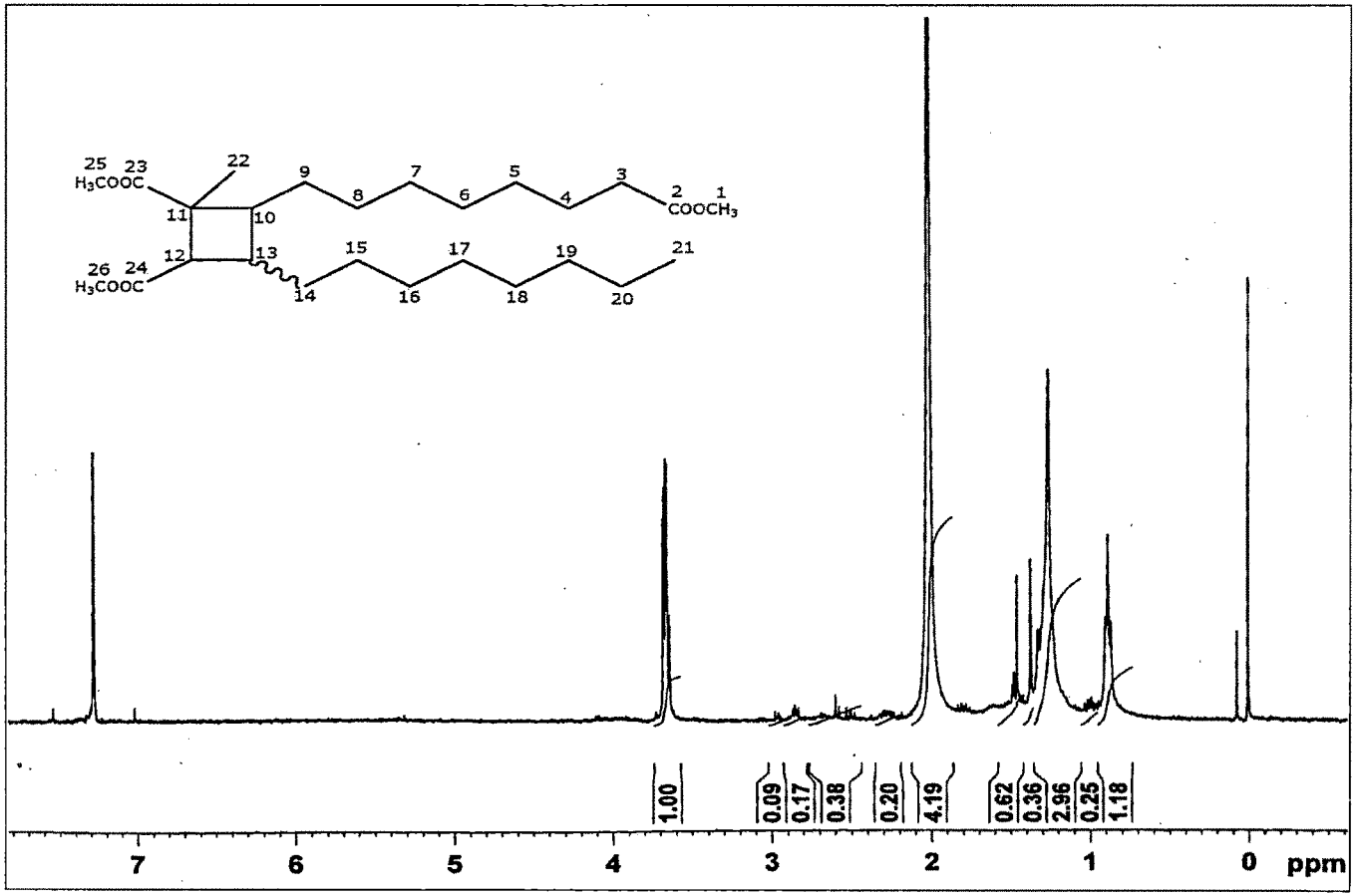


Figure II.9: PMR Spectrum of the compound (7a)

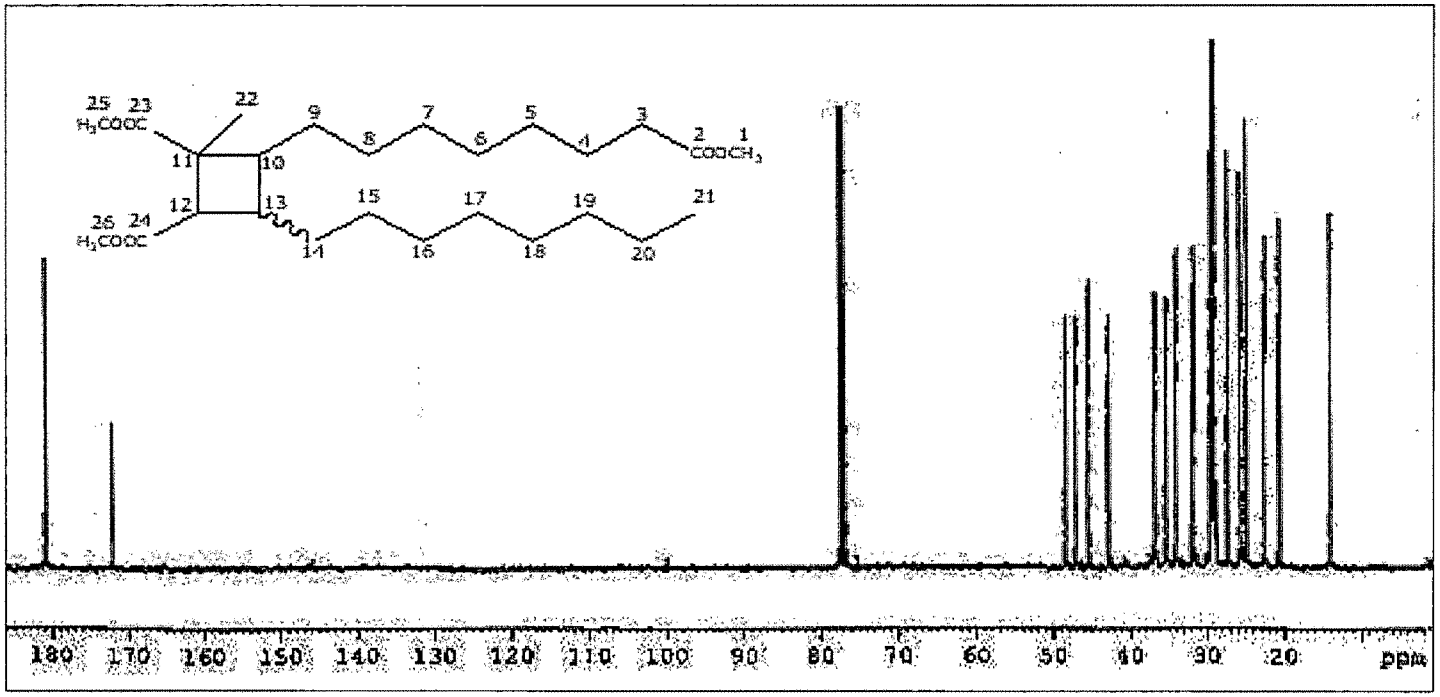


Figure II.10: ^{13}C NMR of the compound (7a)

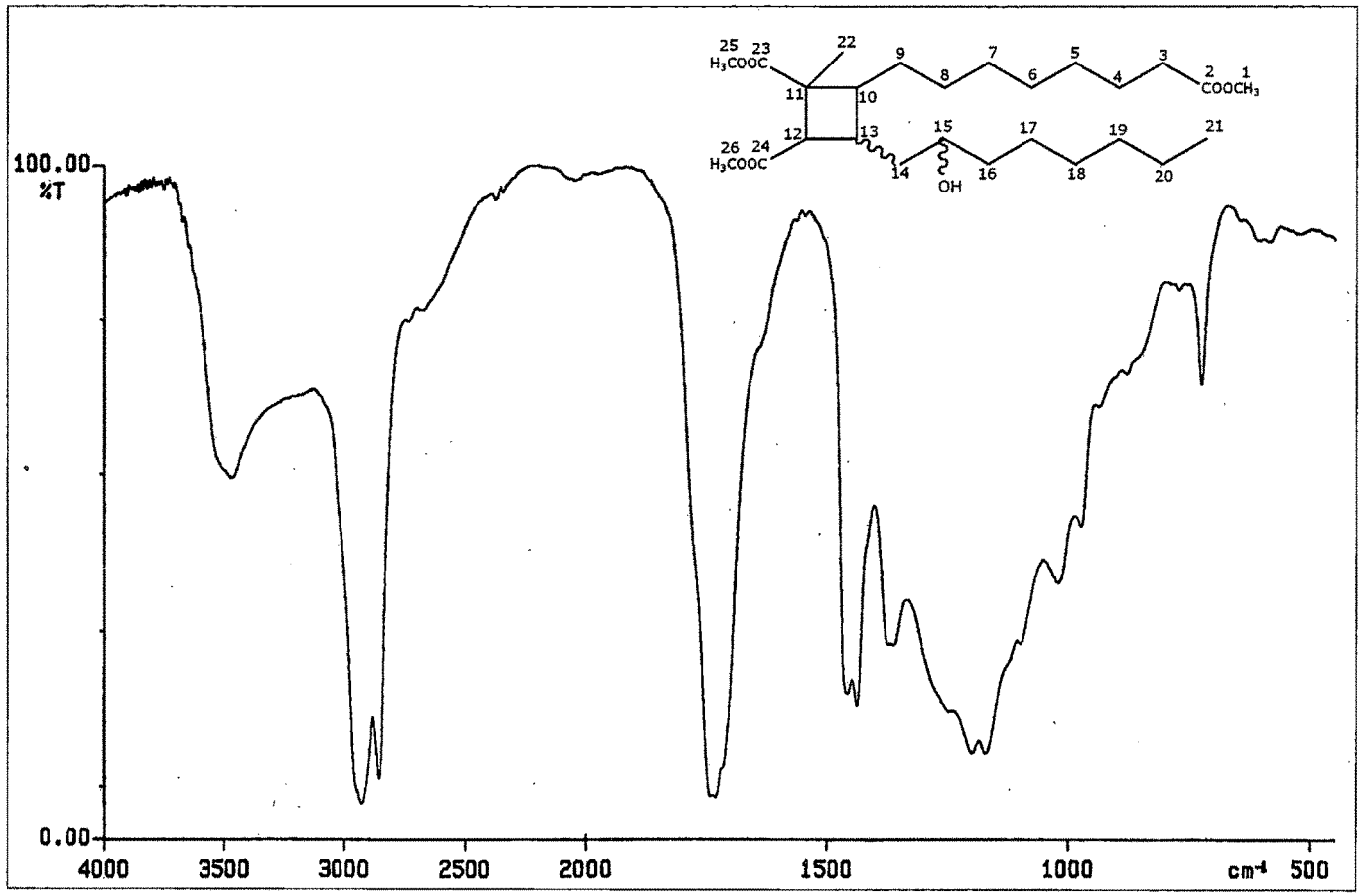


Figure II.11: FTIR Spectrum of the compound (7b)

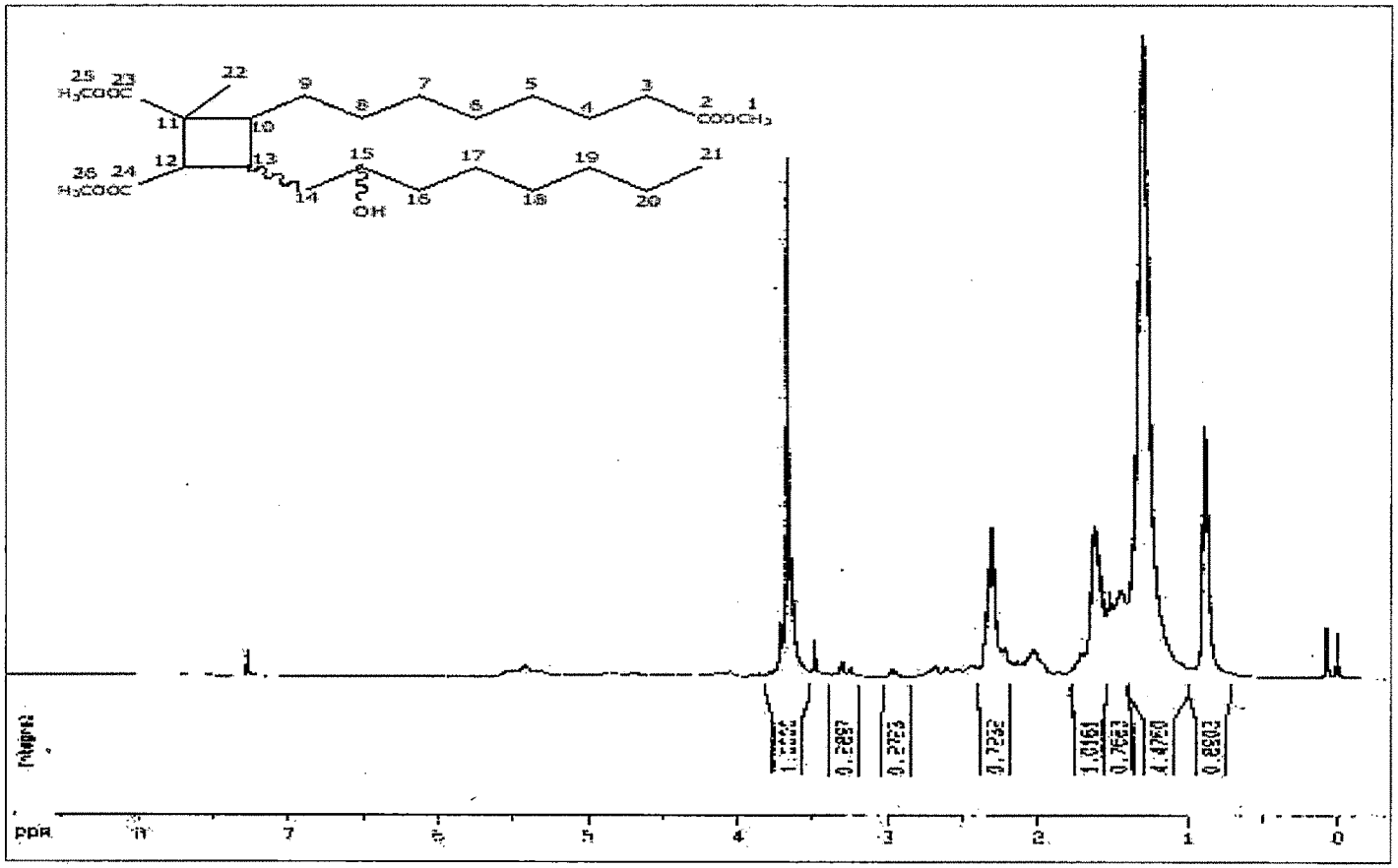


Figure II.12: PMR Spectrum of the compound (7b)

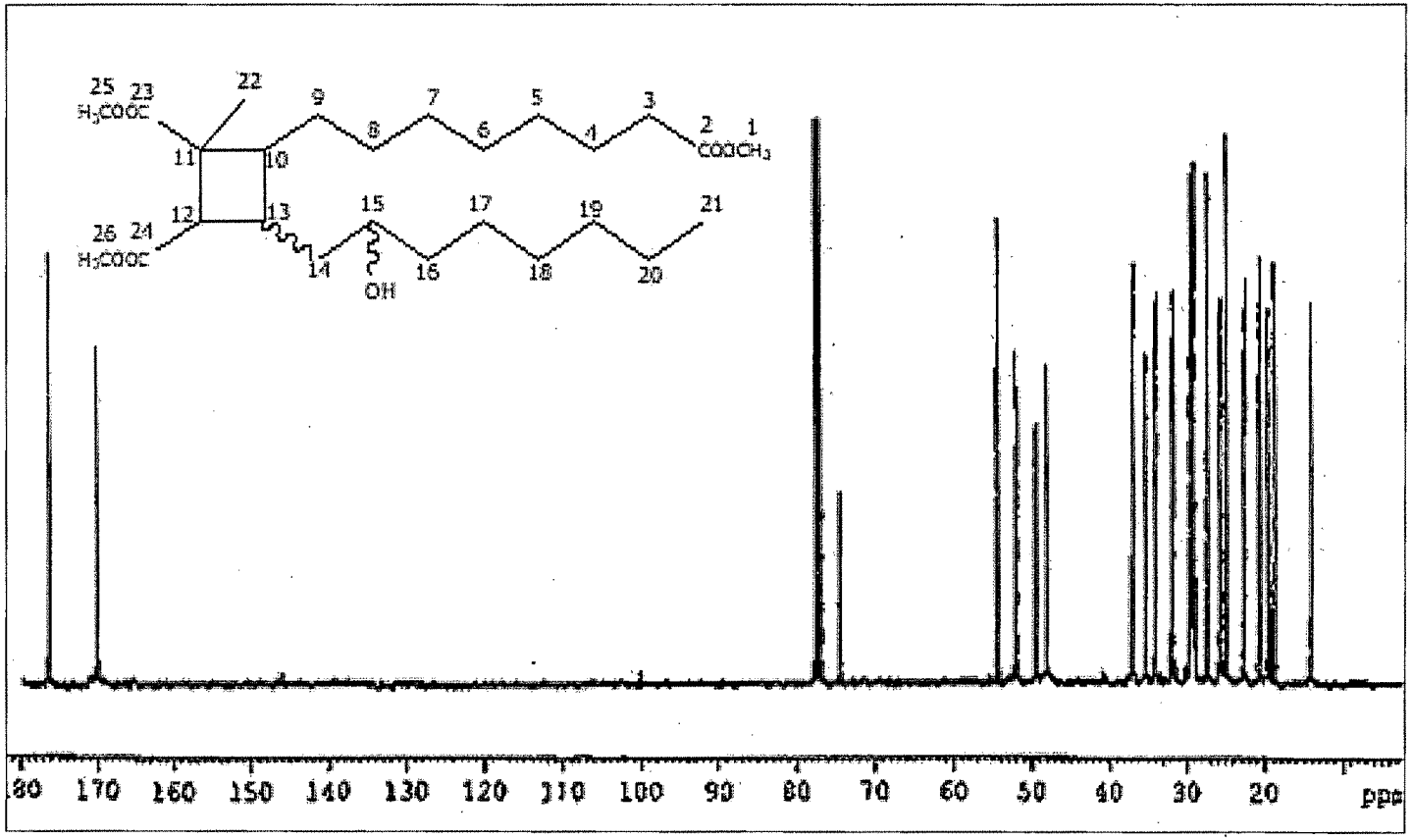


Figure II.13: ^{13}C NMR of the compound (7b)

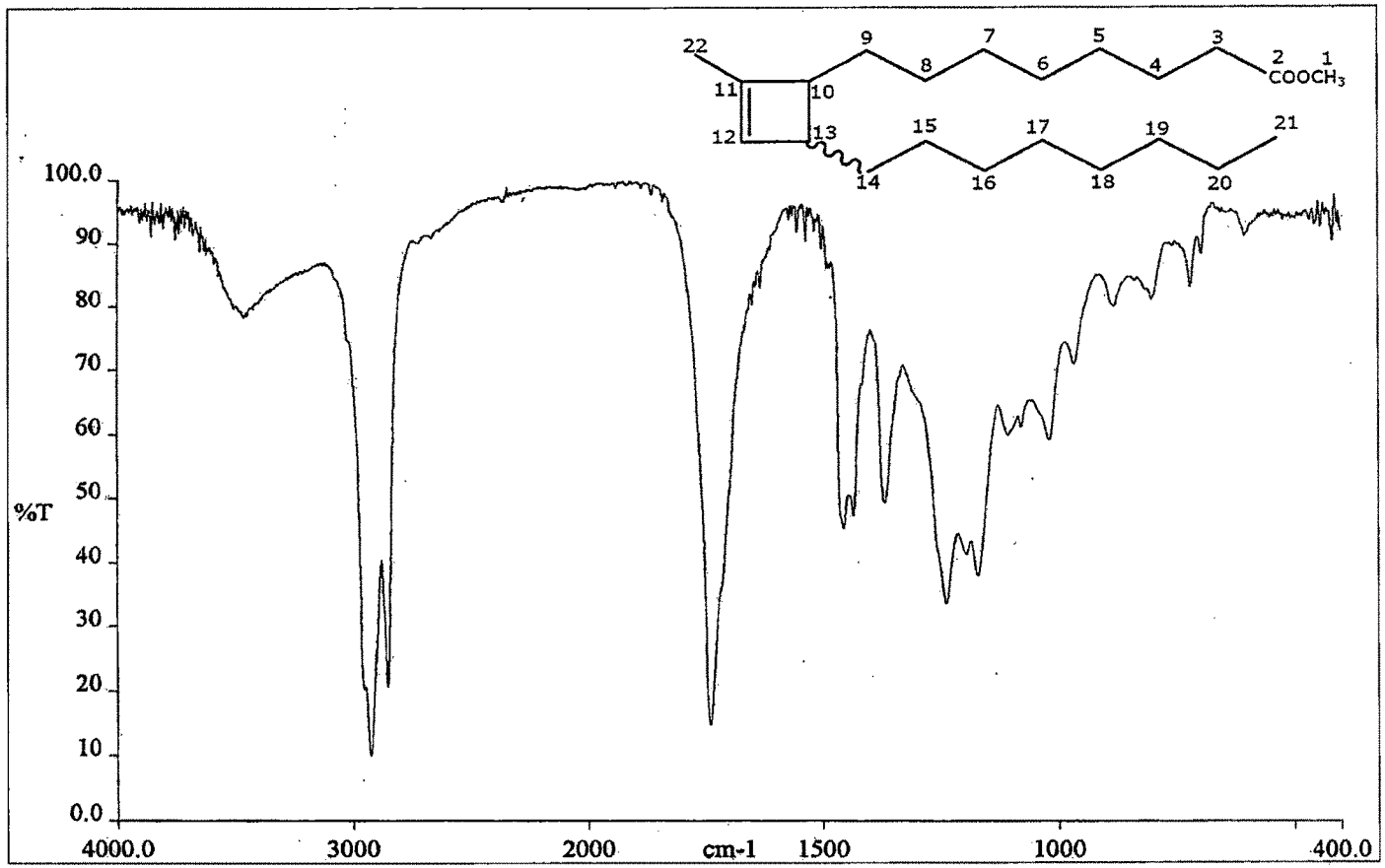


Figure II.14: FTIR Spectrum of the compound (4a)

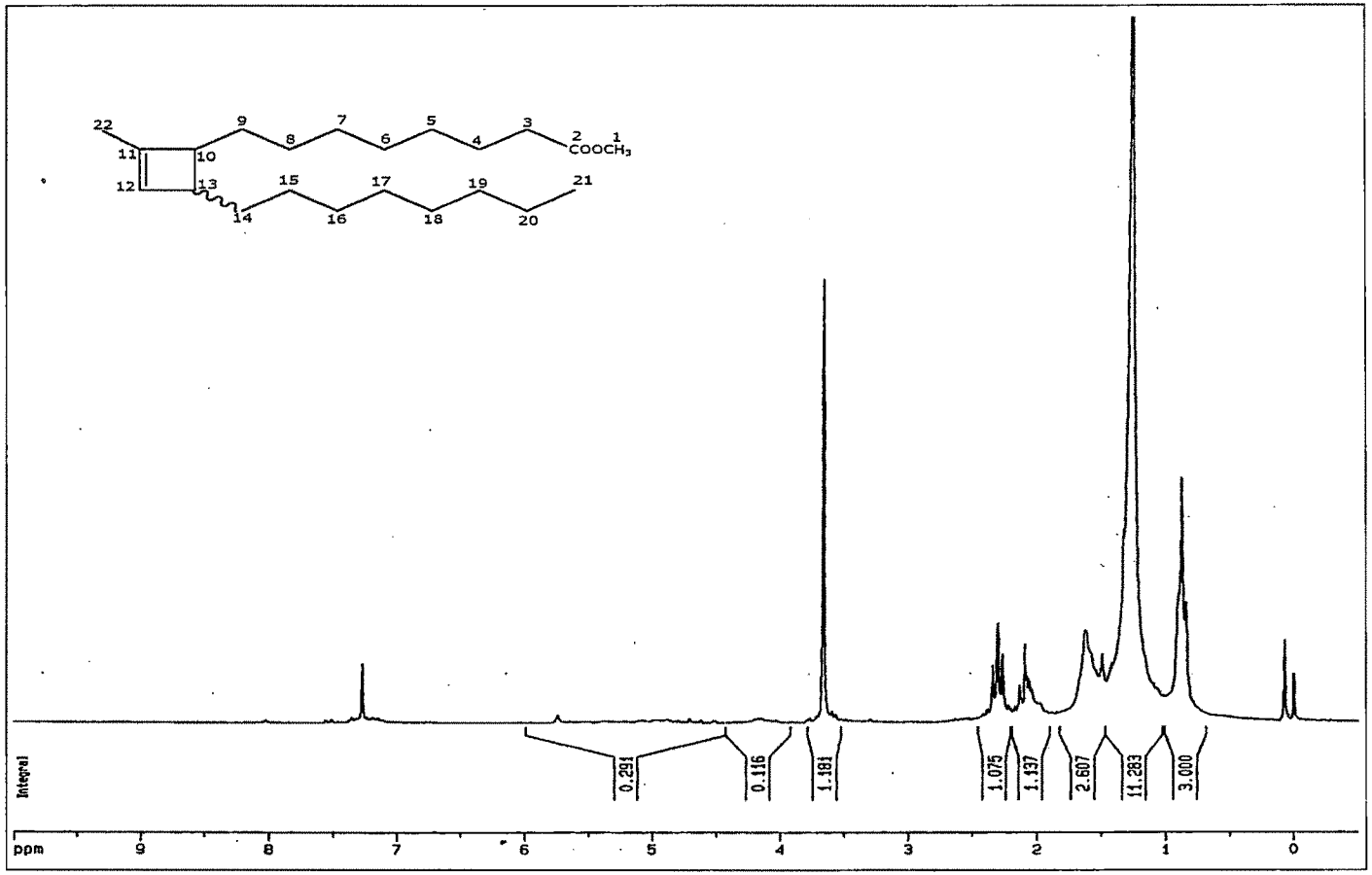


Figure II.15: PMR Spectrum of the compound (4a)

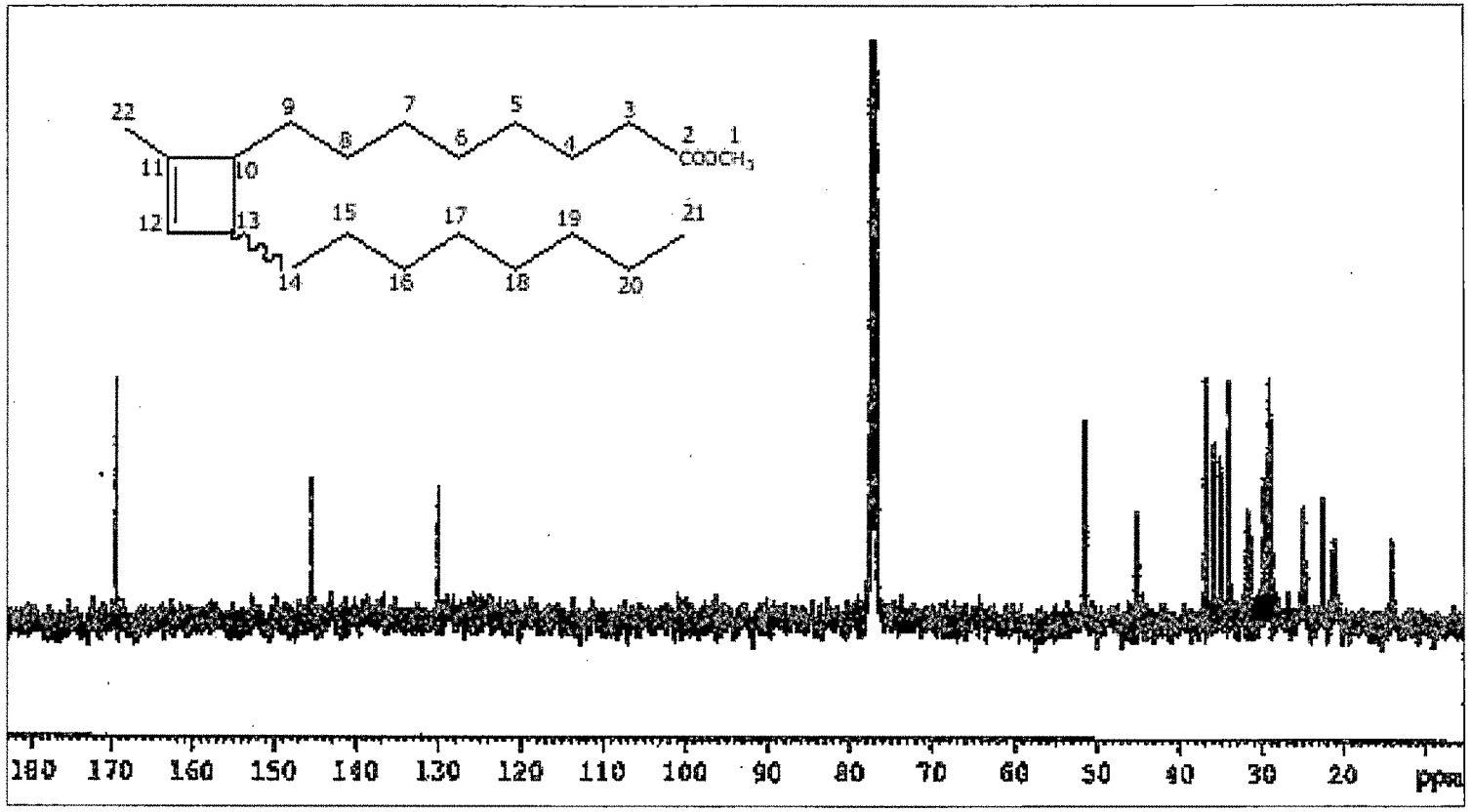


Figure II.16: ^{13}C NMR of the compound (4a)

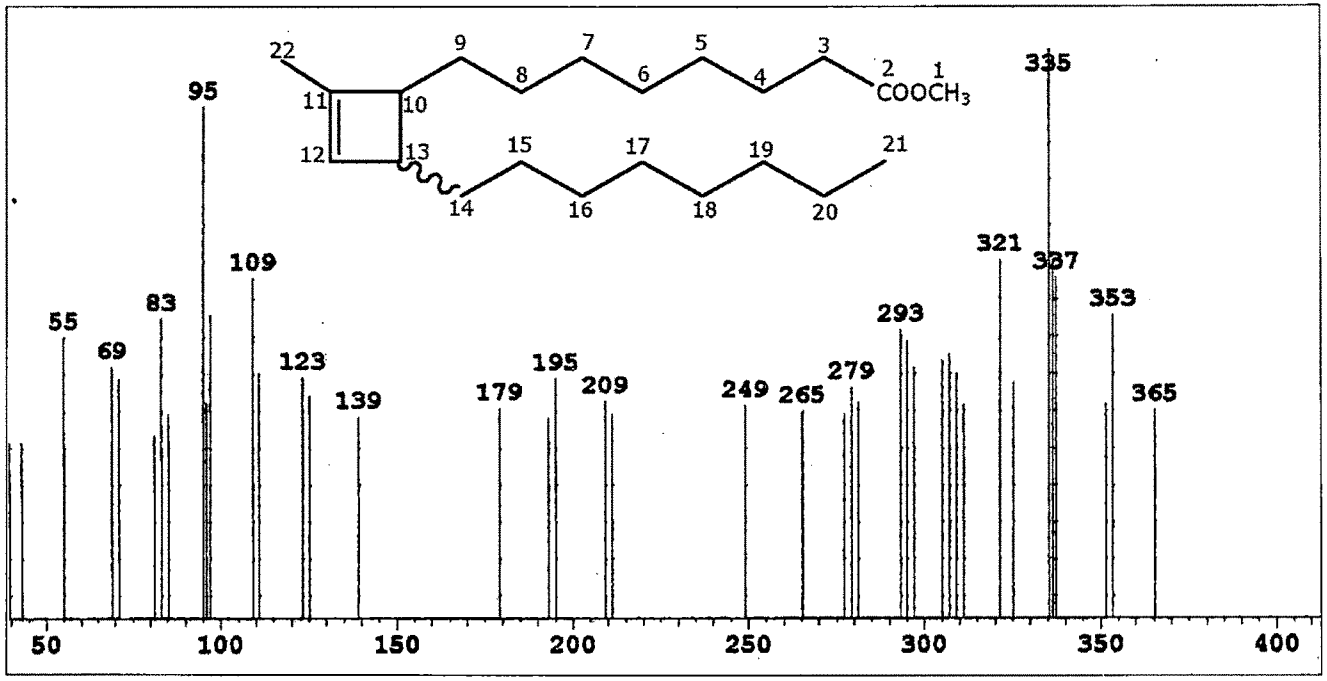


Figure II.17: Mass spectrum of the compound (4a)

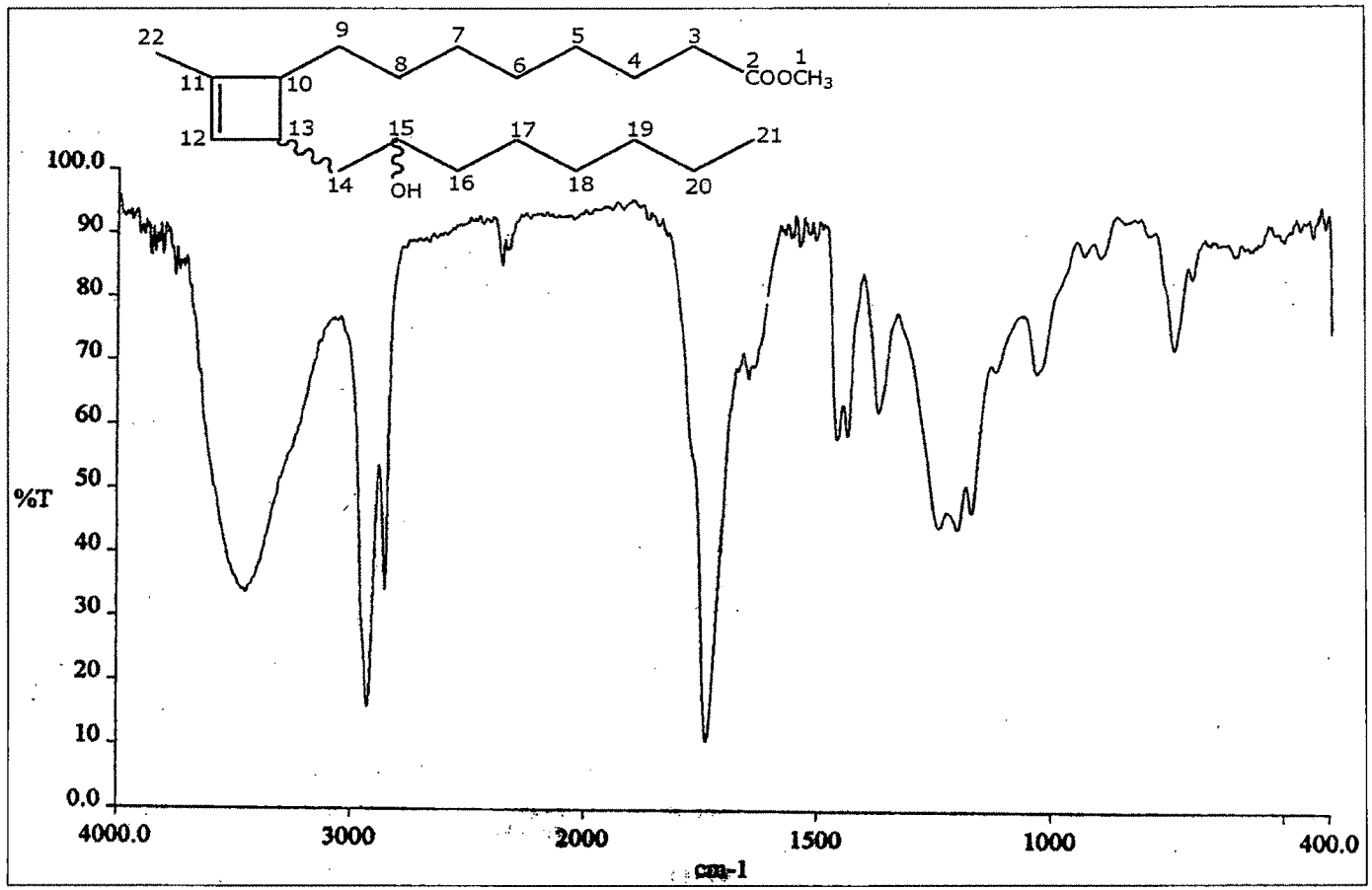


Figure II.18: FTIR Spectrum of the compound (4b)

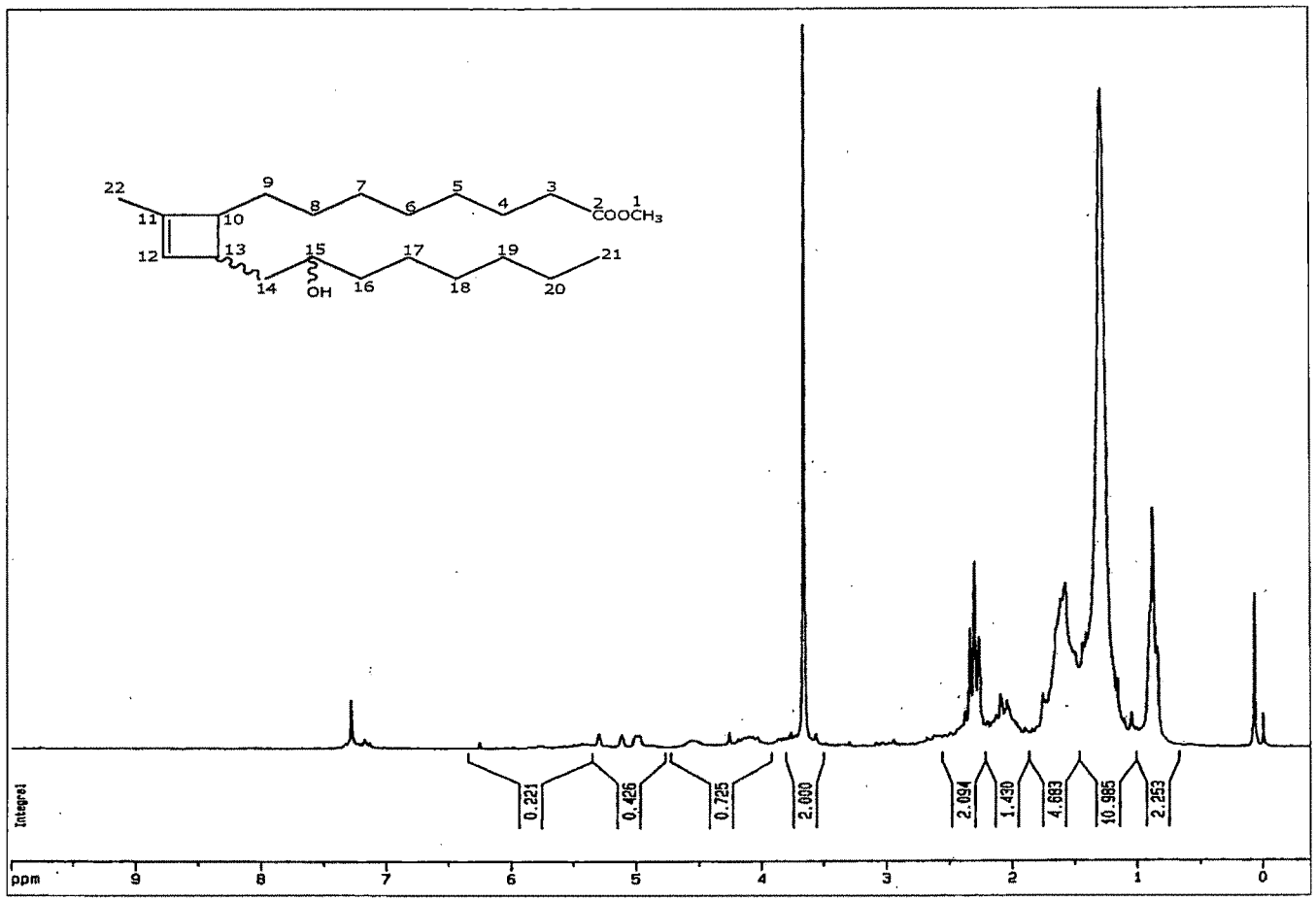


Figure II.19: PMR Spectrum of the compound (4b)

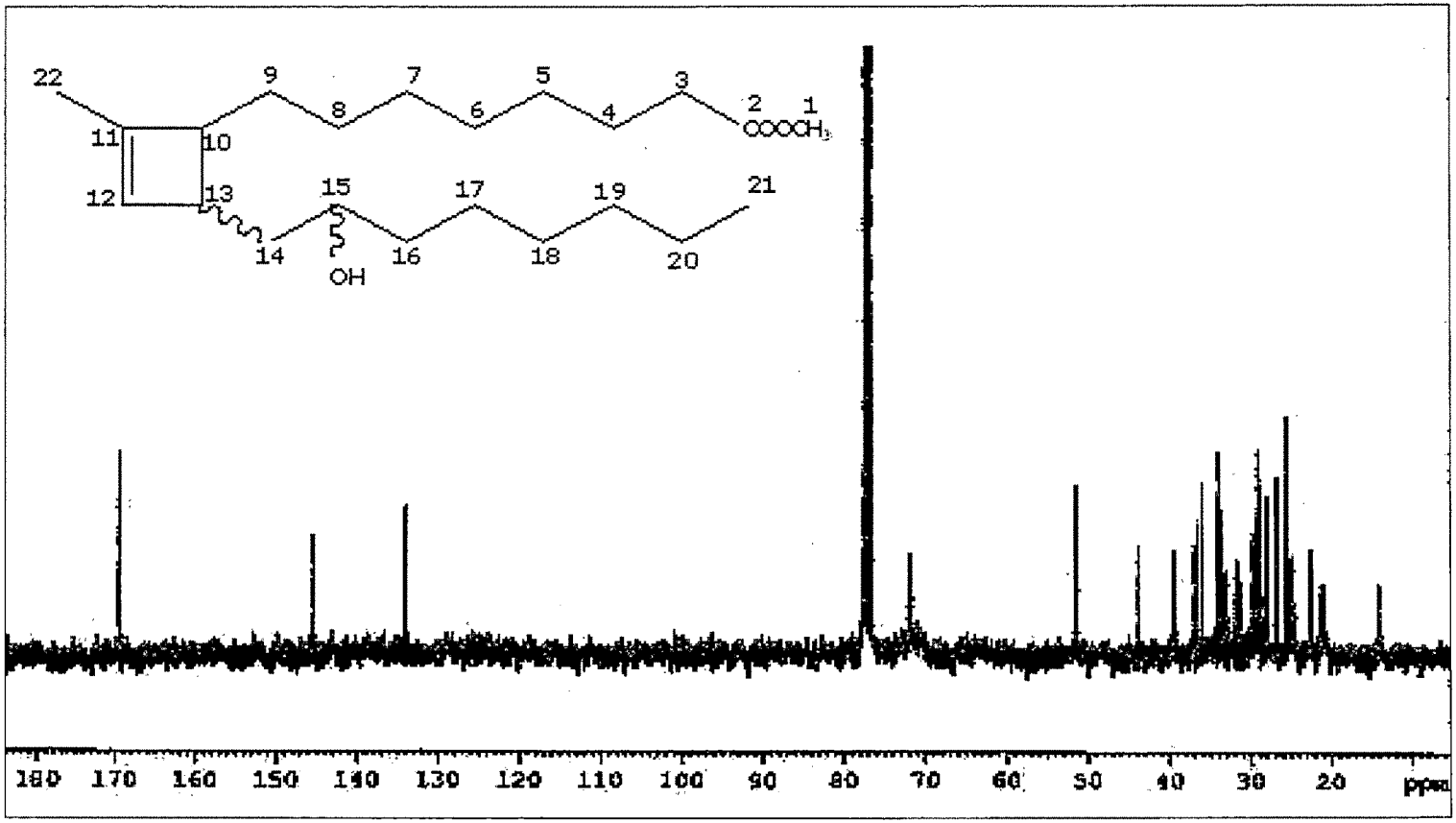


Figure II.20: ^{13}C NMR of the compound (4b)

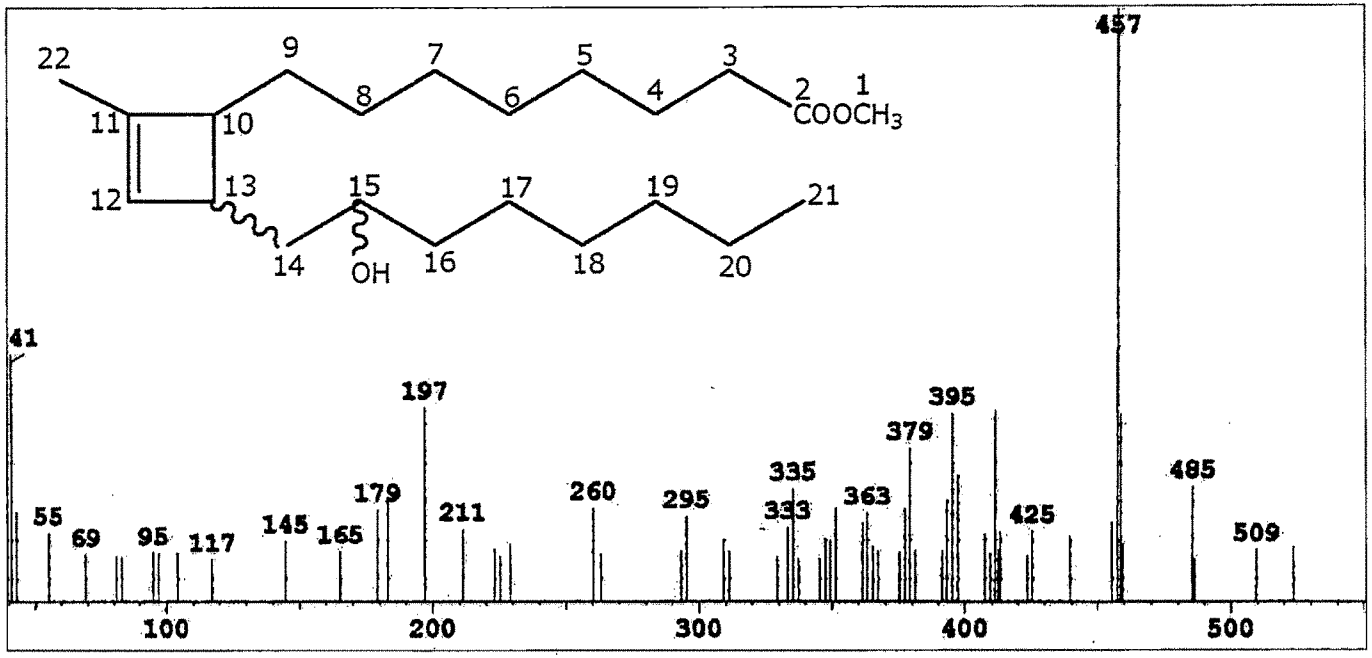


Figure II.21: Mass spectrum of the compound (4b)

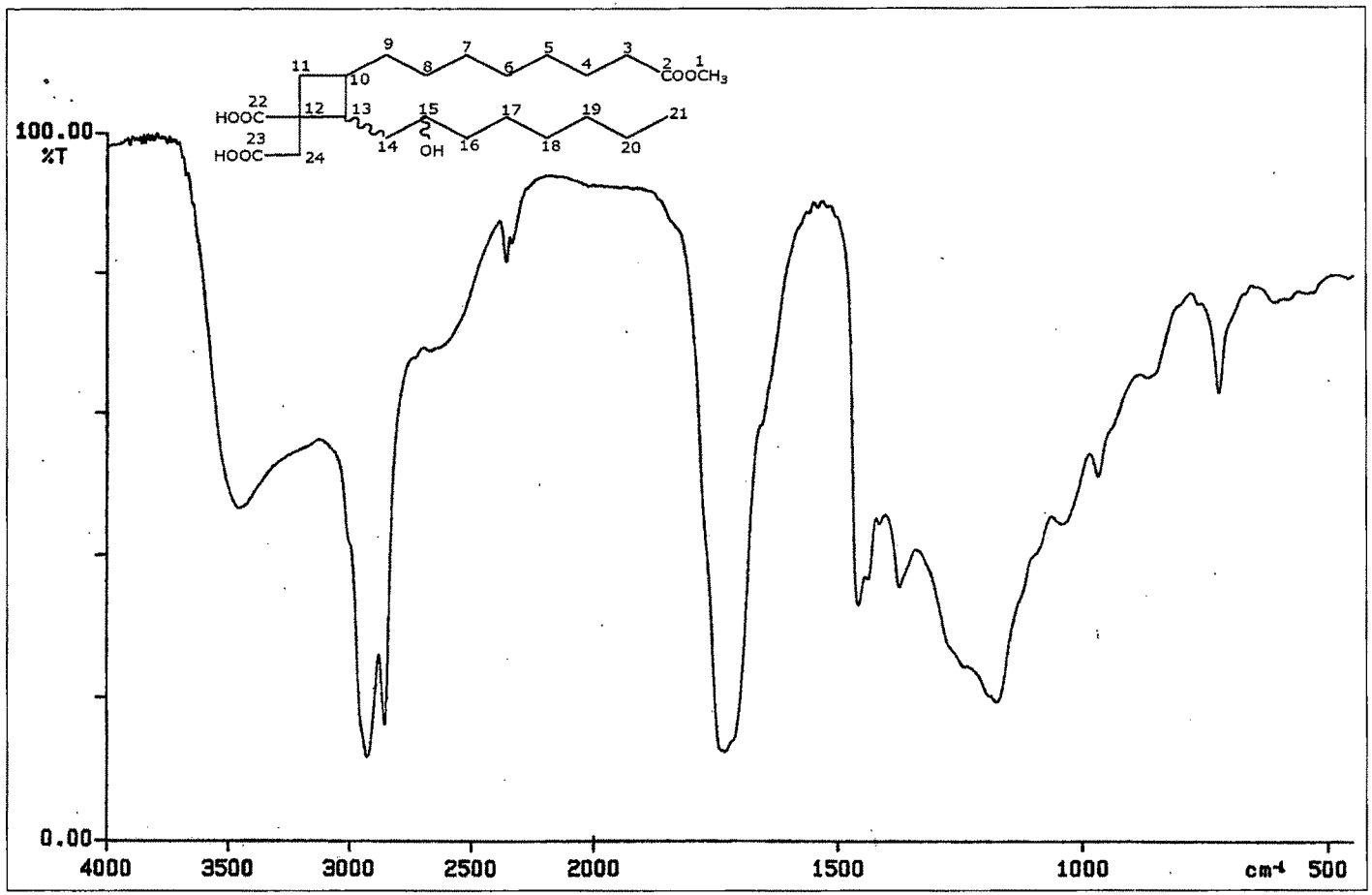


Figure II.22: FTIR Spectrum of the compound 9

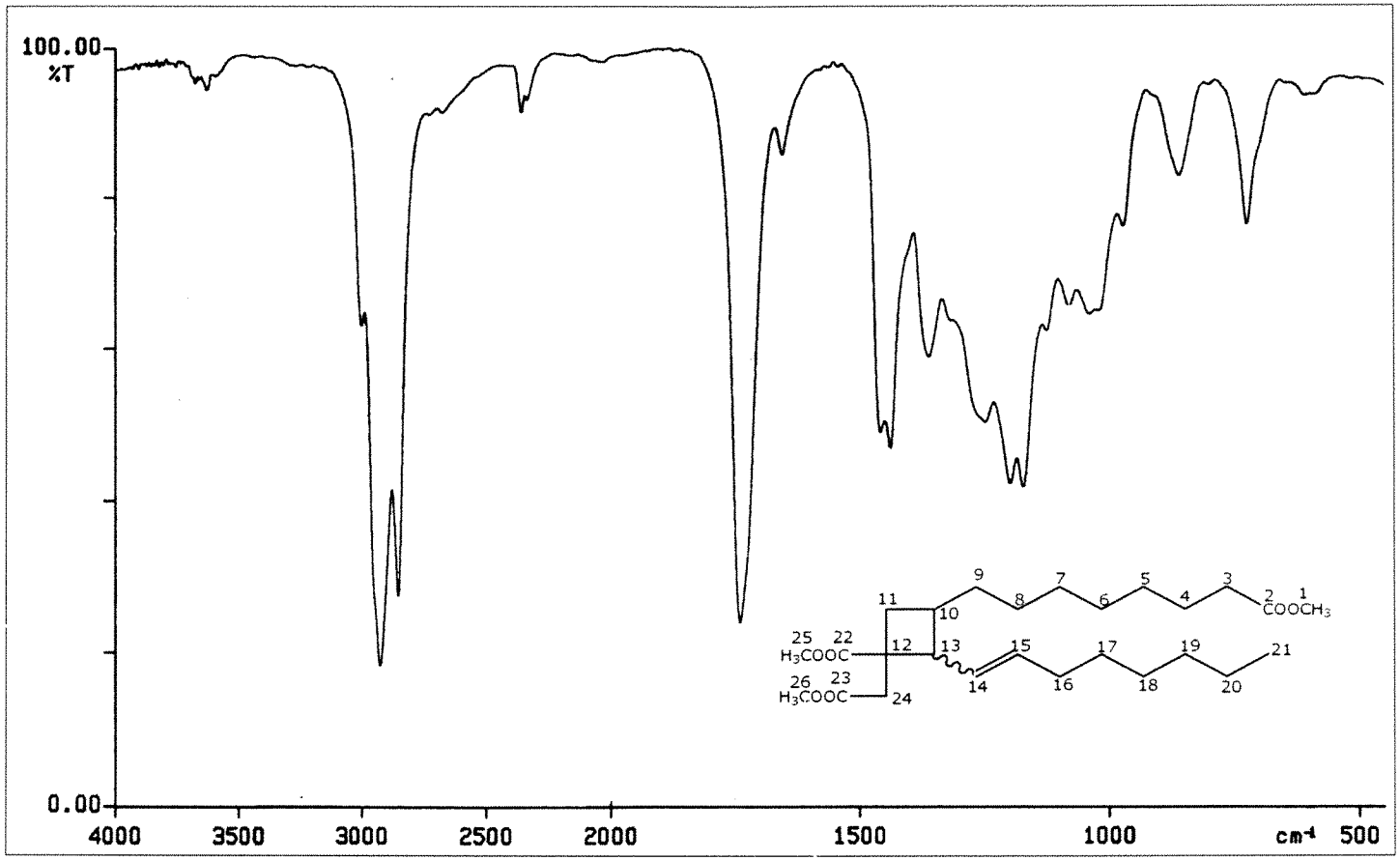


Figure II.23: FTIR Spectrum of the compound 11

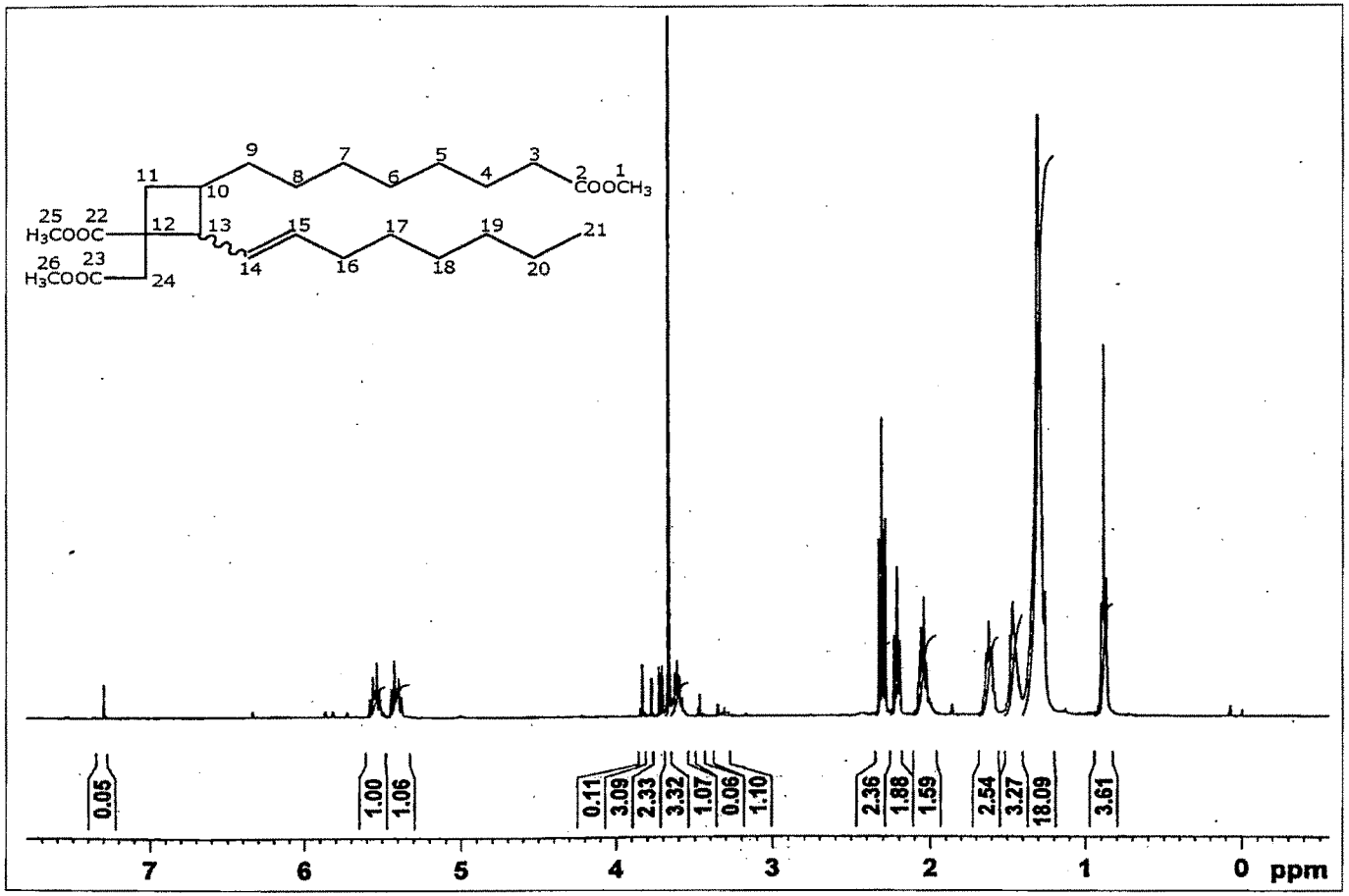


Figure II.24: PMR Spectrum of the compound 11

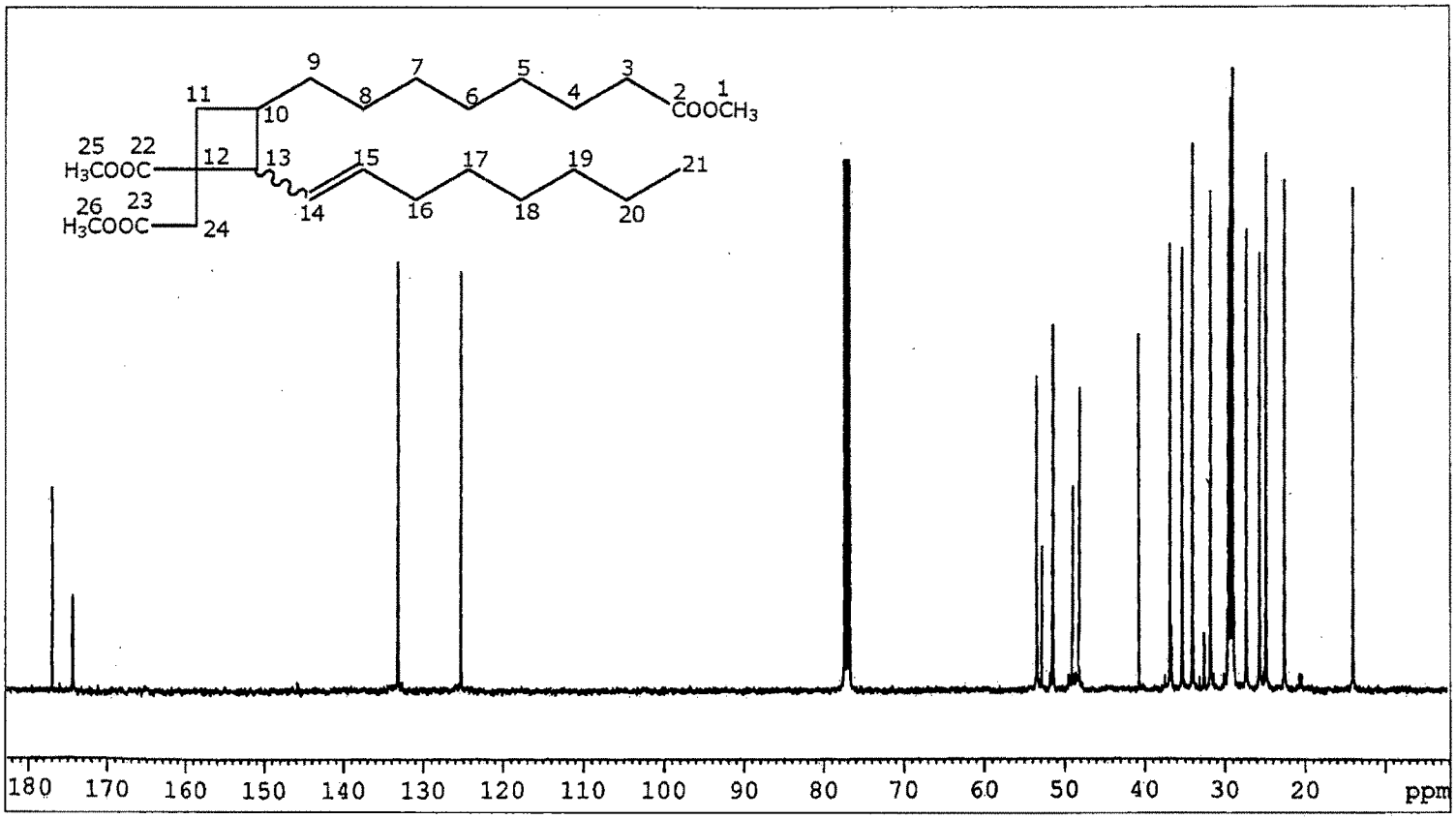


Figure II.25: ^{13}C NMR of the compound 11

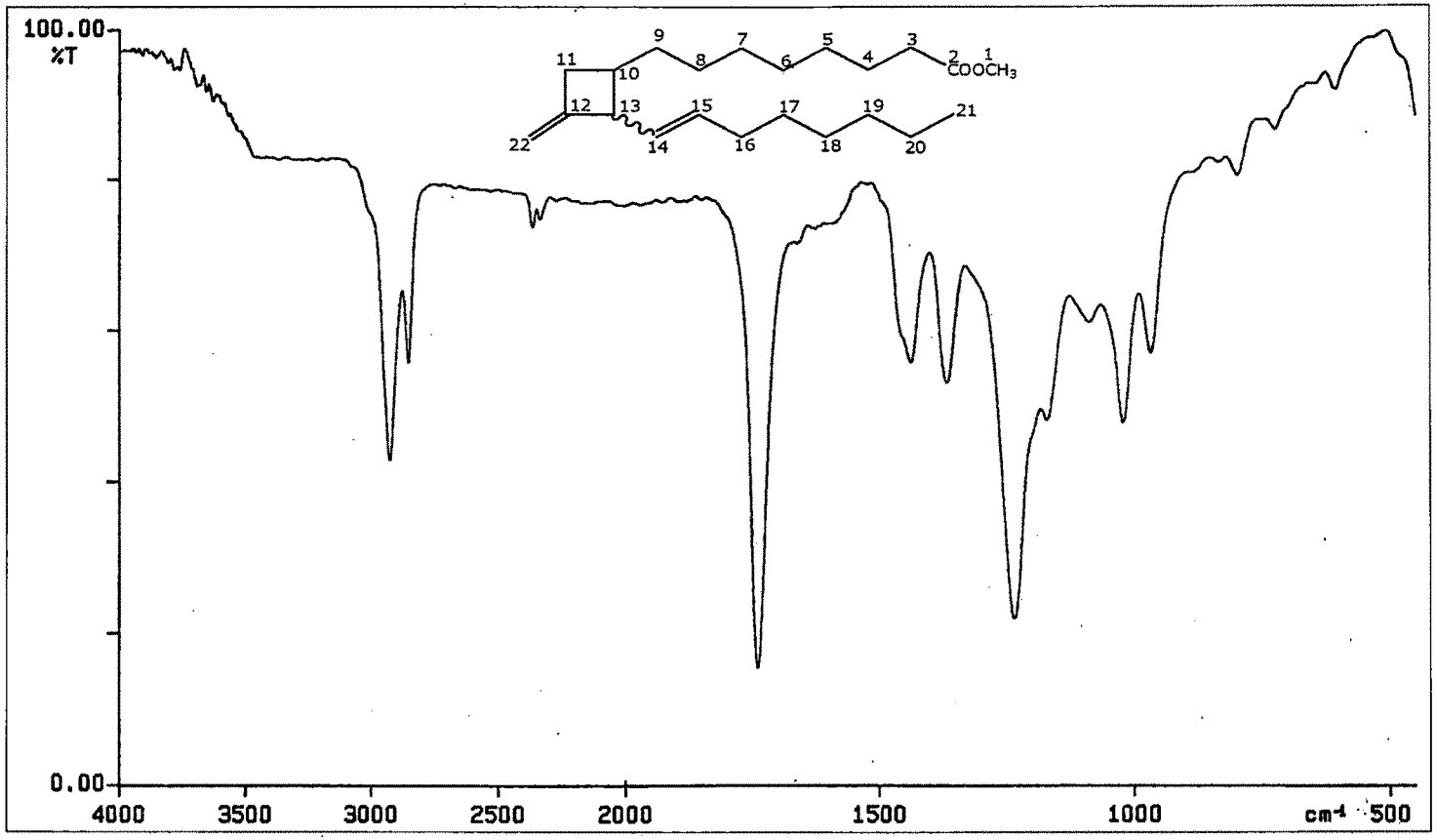


Figure II.26: FTIR Spectrum of the compound 10

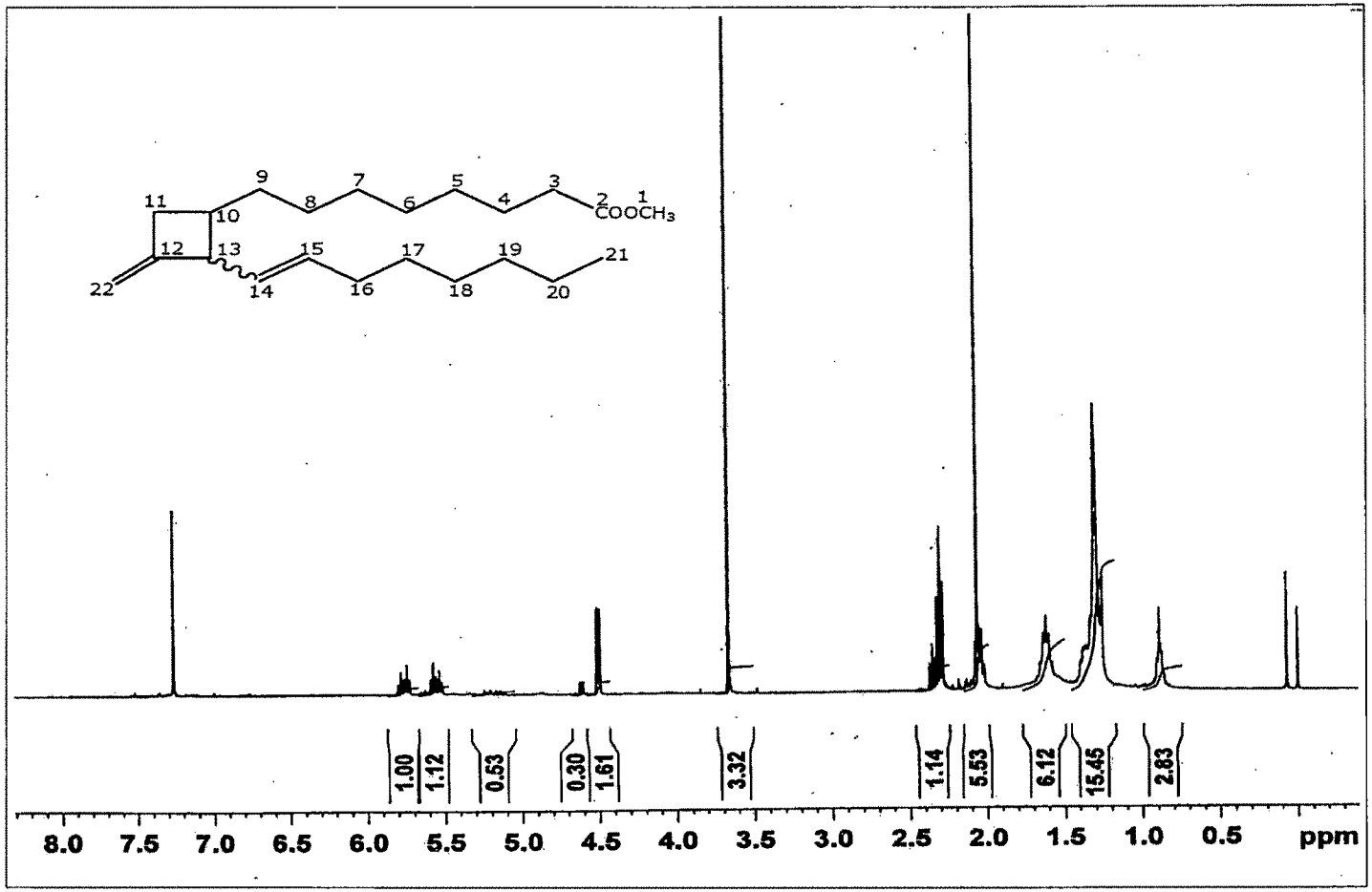


Figure II.27: PMR Spectrum of the compound 10

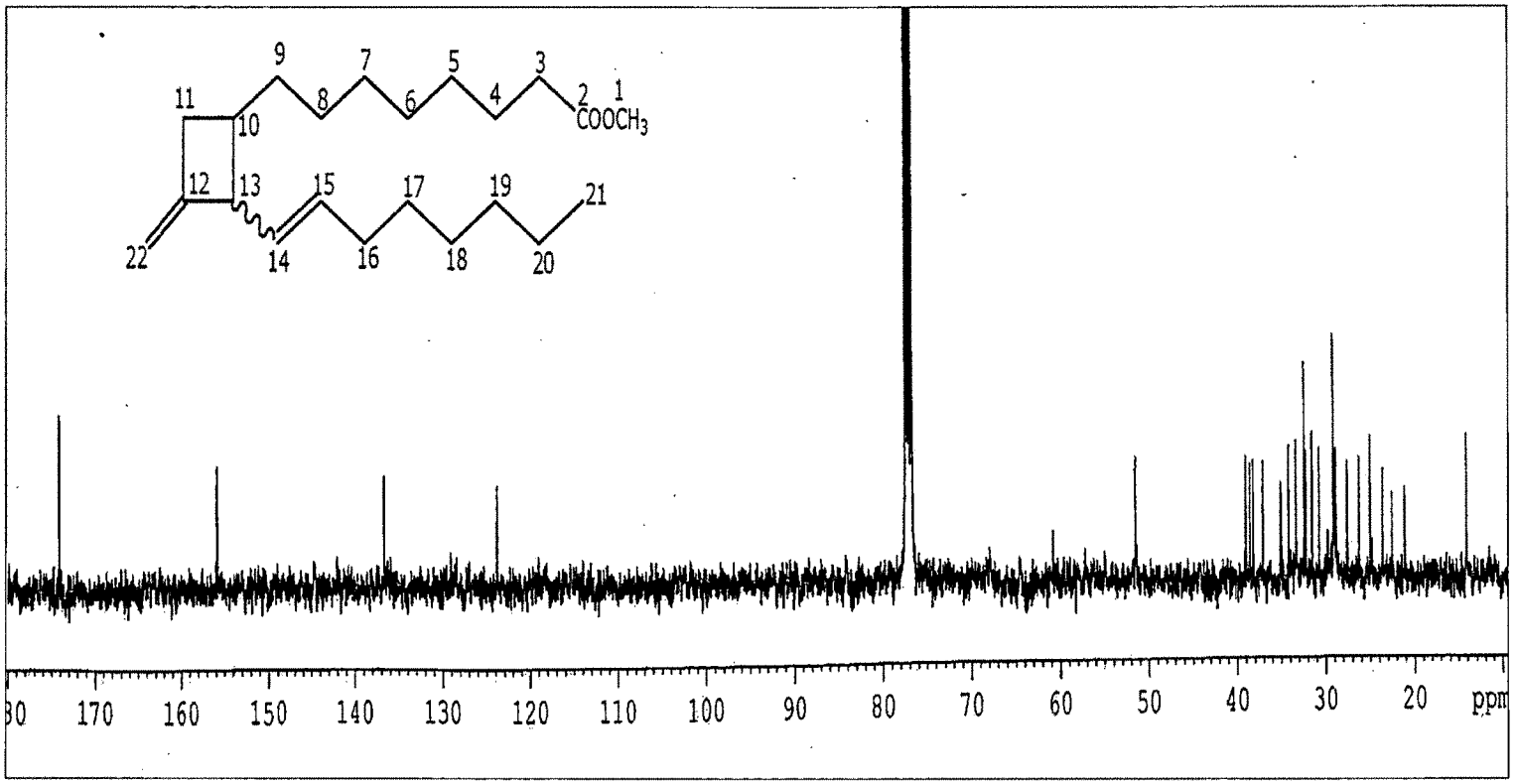


Figure II.28: ^{13}C NMR of the compound 10

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