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APPENDIX

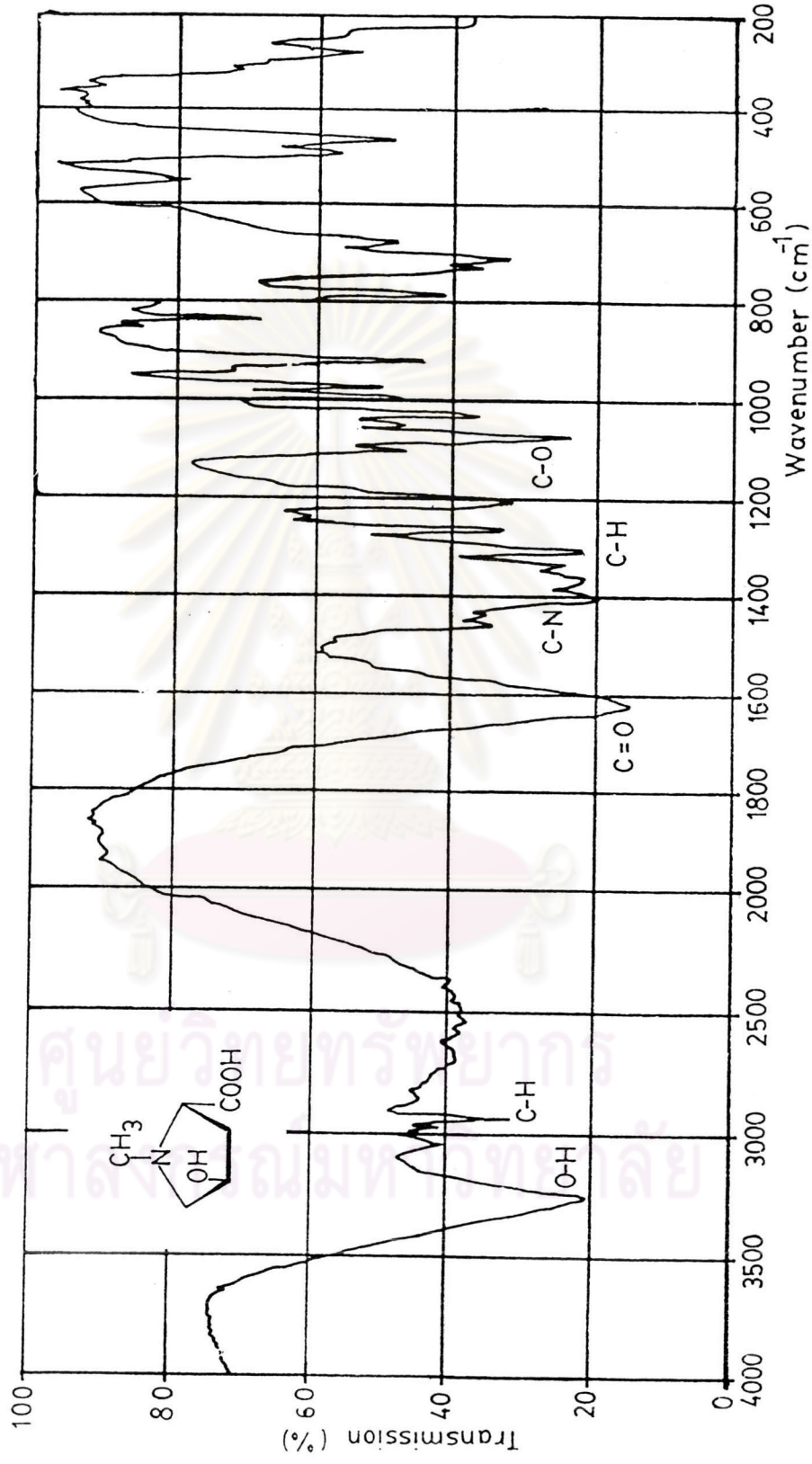


Figure 1 The IR spectrum of odoram

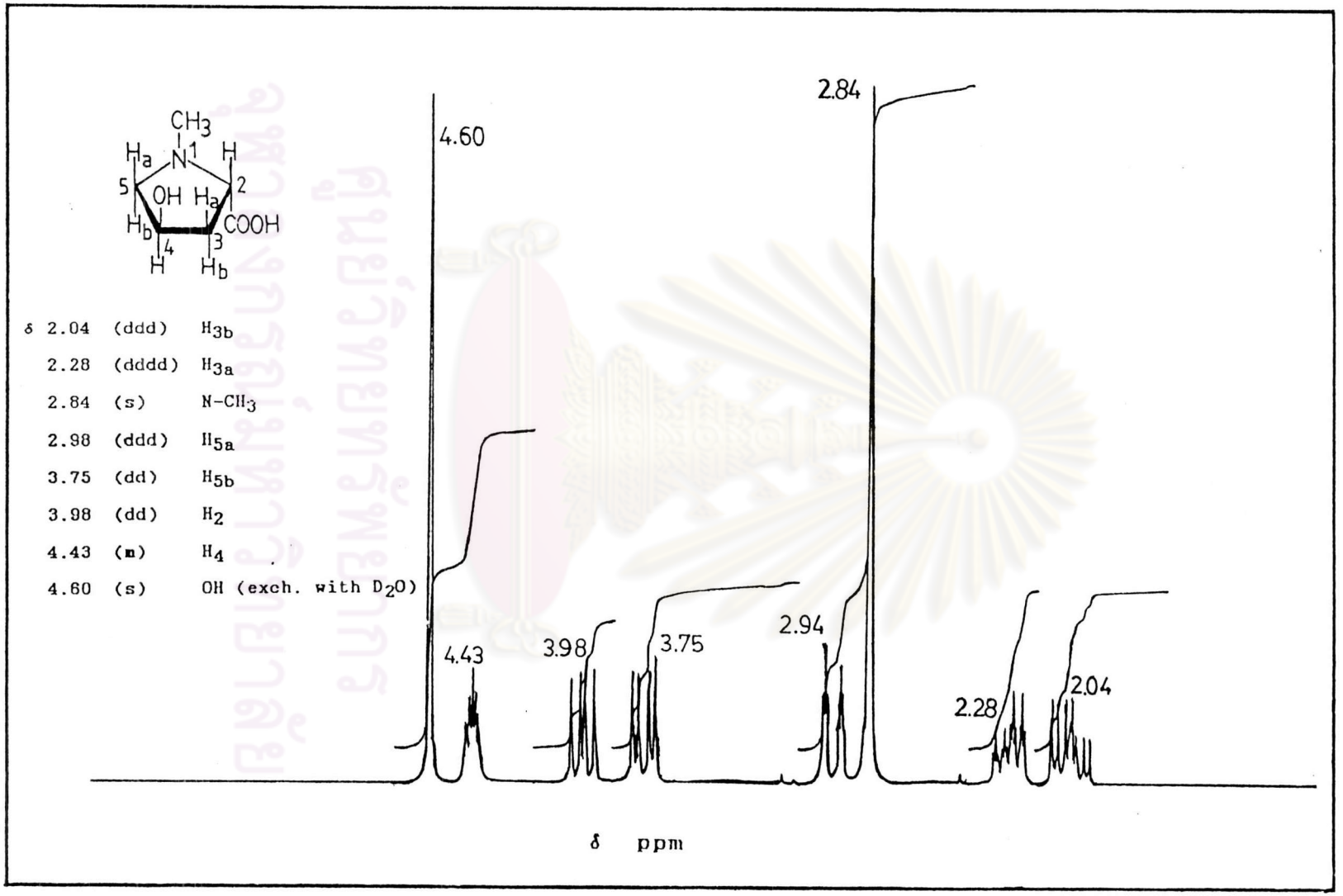


Figure 2 The PMR spectrum of odoram

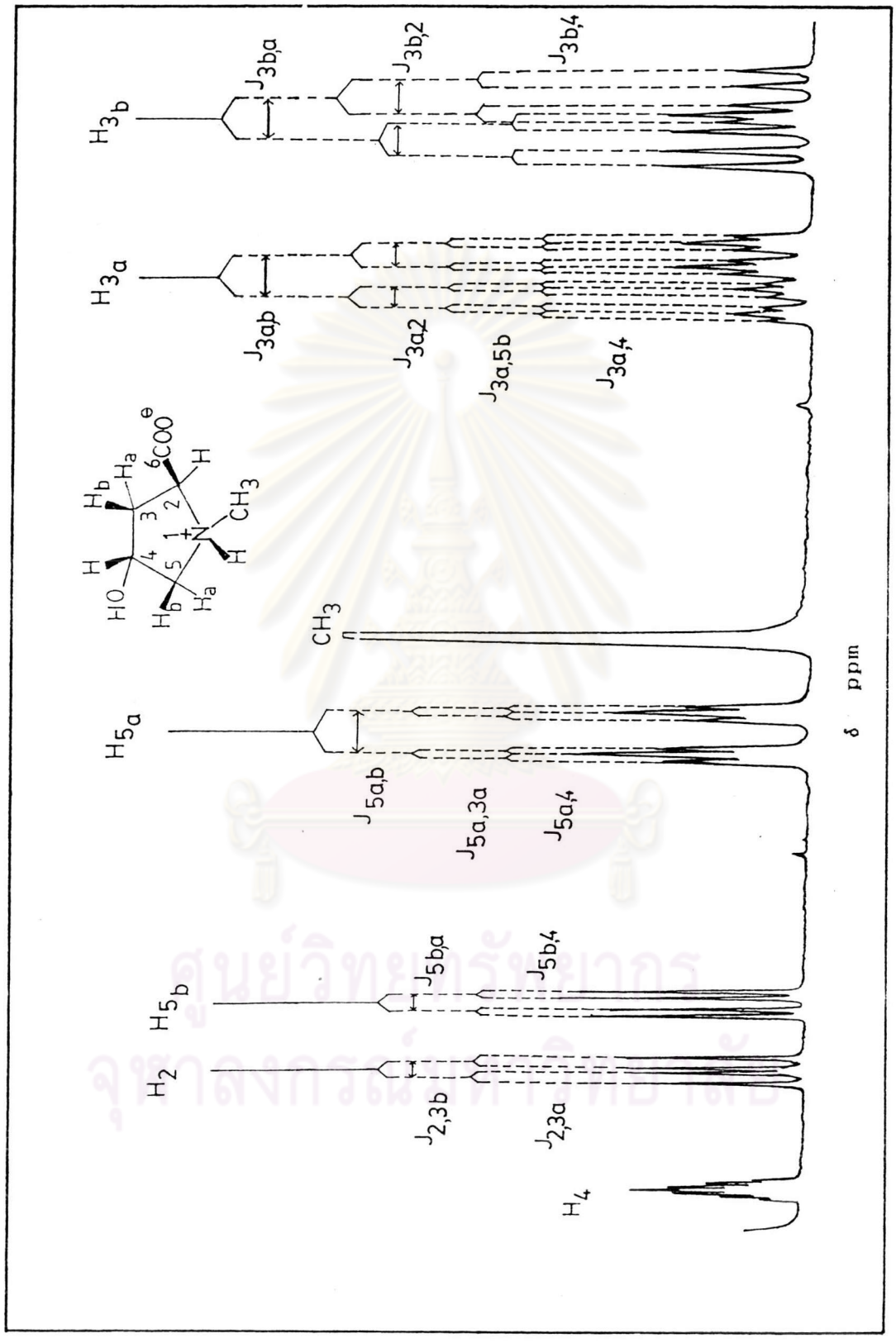


Figure 3 The PMR spectrum of odoram showed protons coupling and coupling constants

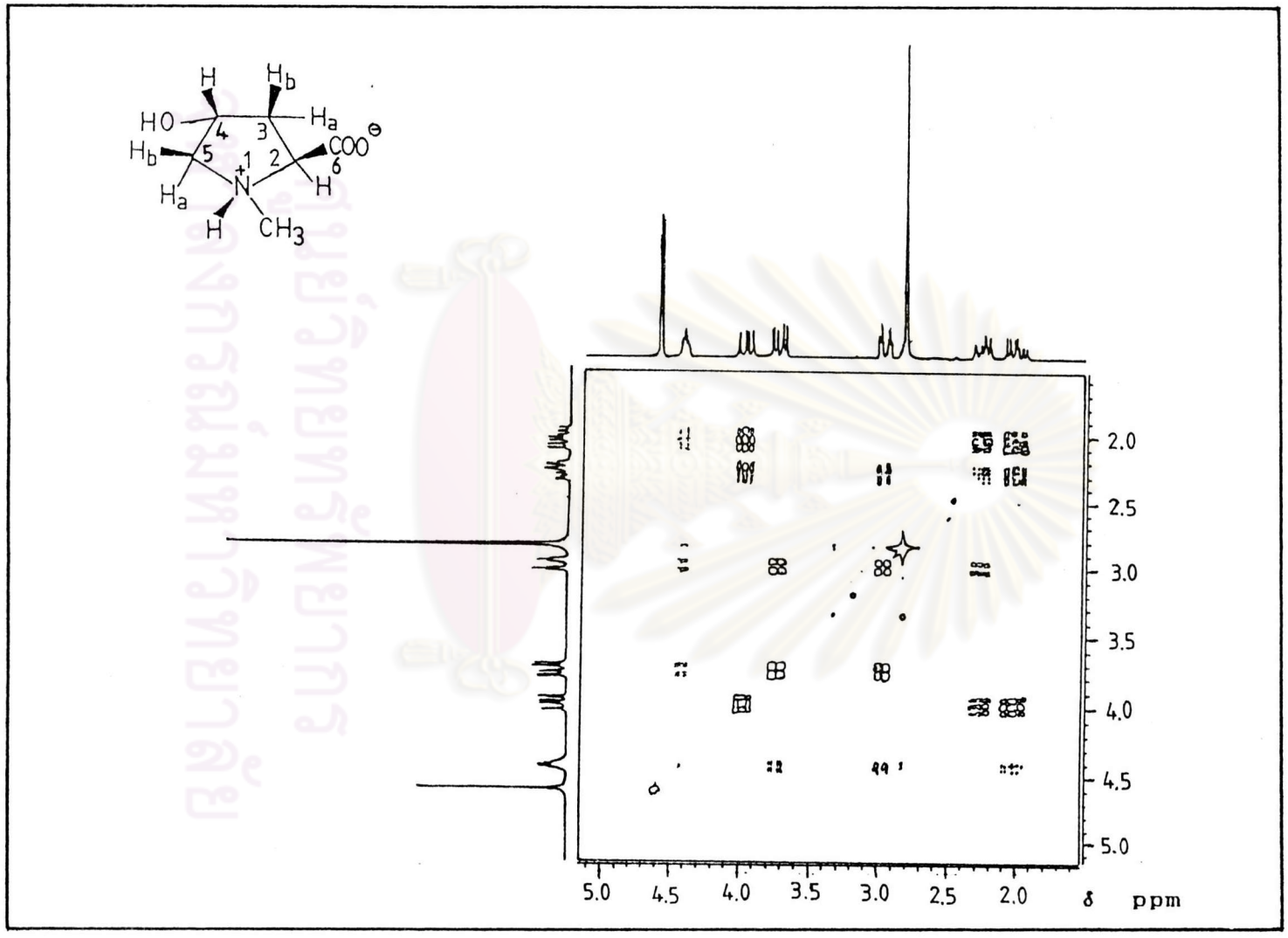


Figure 4 The ^{1}H COSY correlated spectrum of odoram

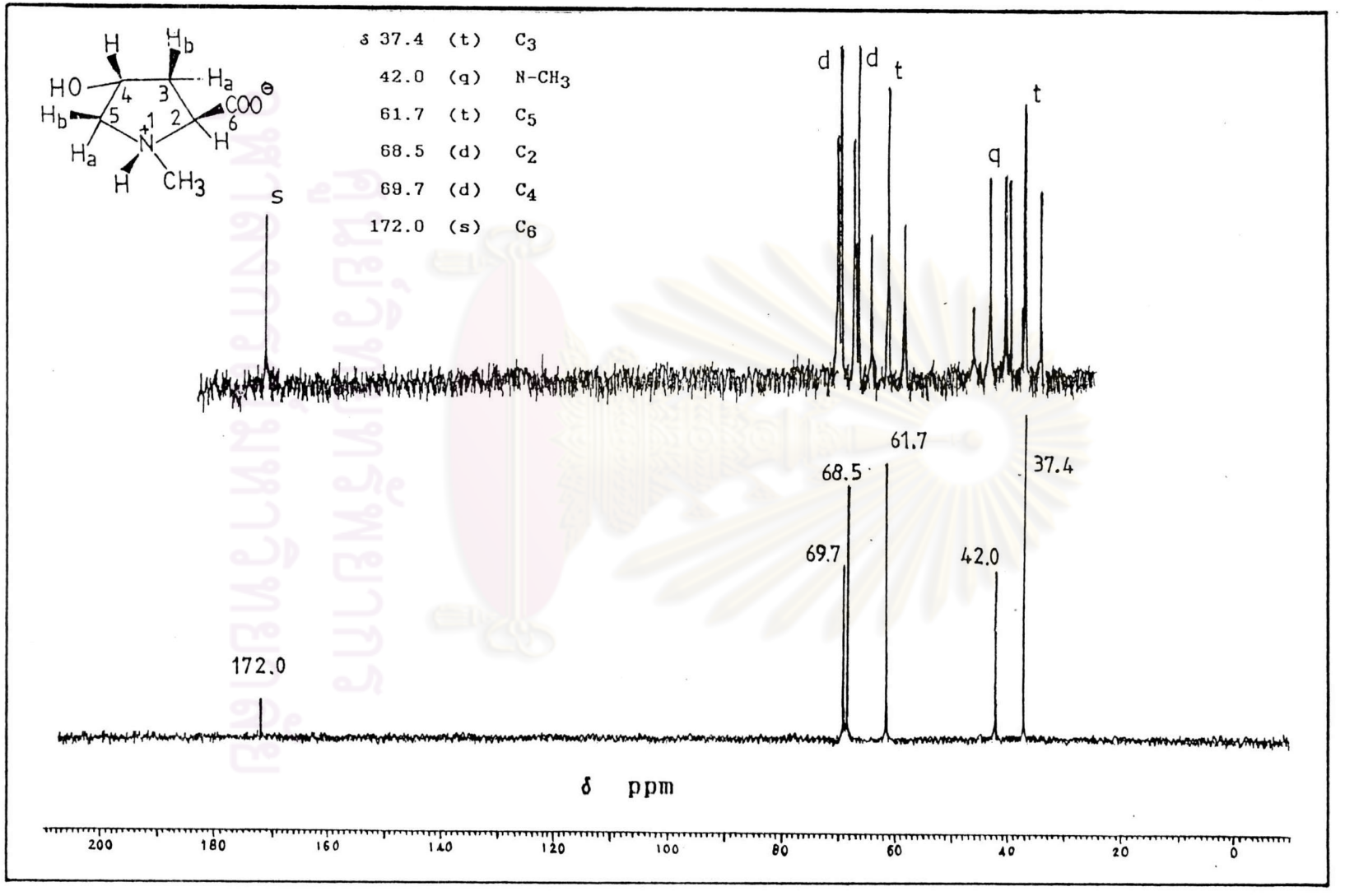


Figure 5 The CMR spectrum of odoram

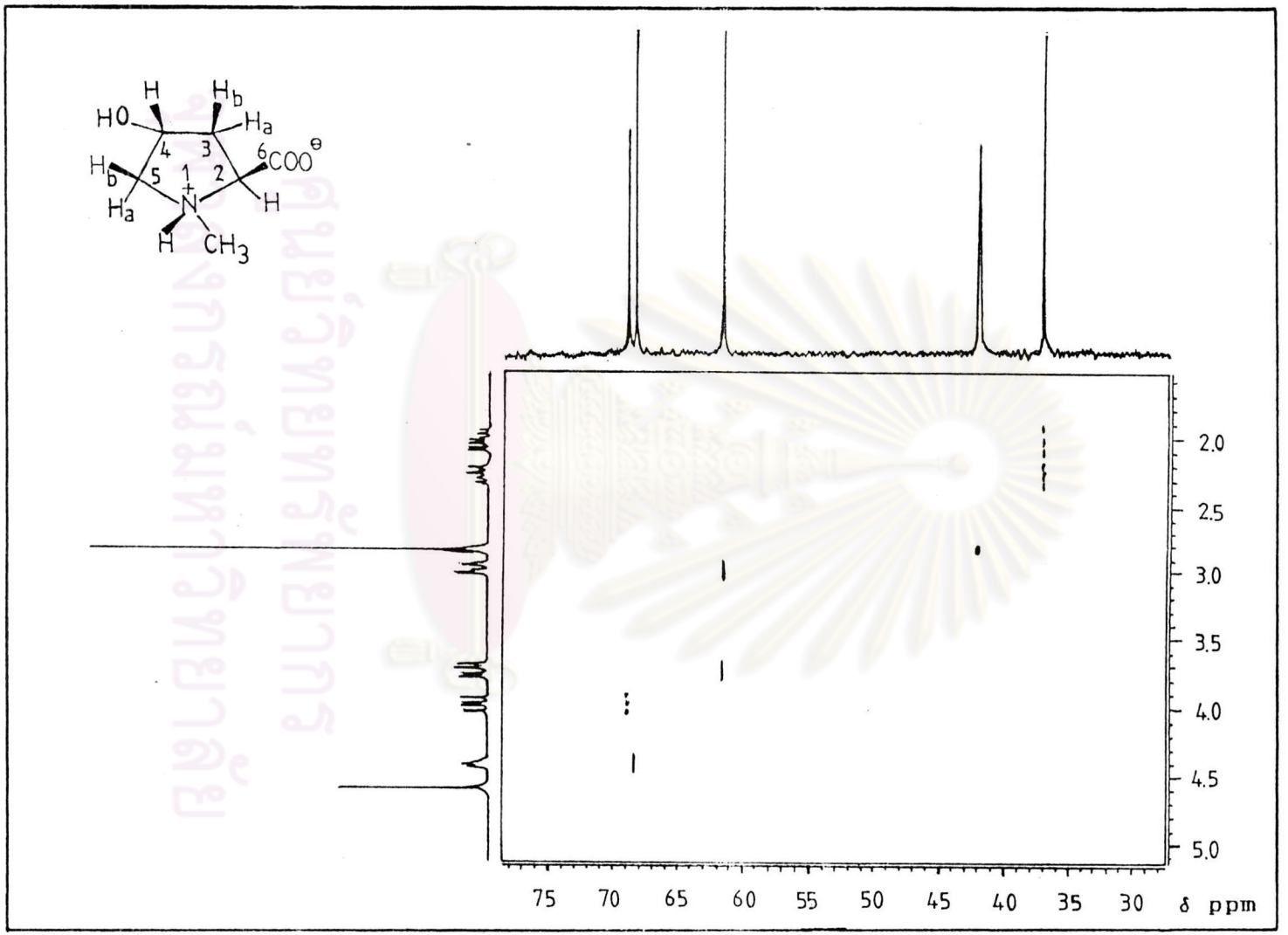


Figure 6 The $^{13}C/^{1}H$ two dimensional correlated spectrum of odoram

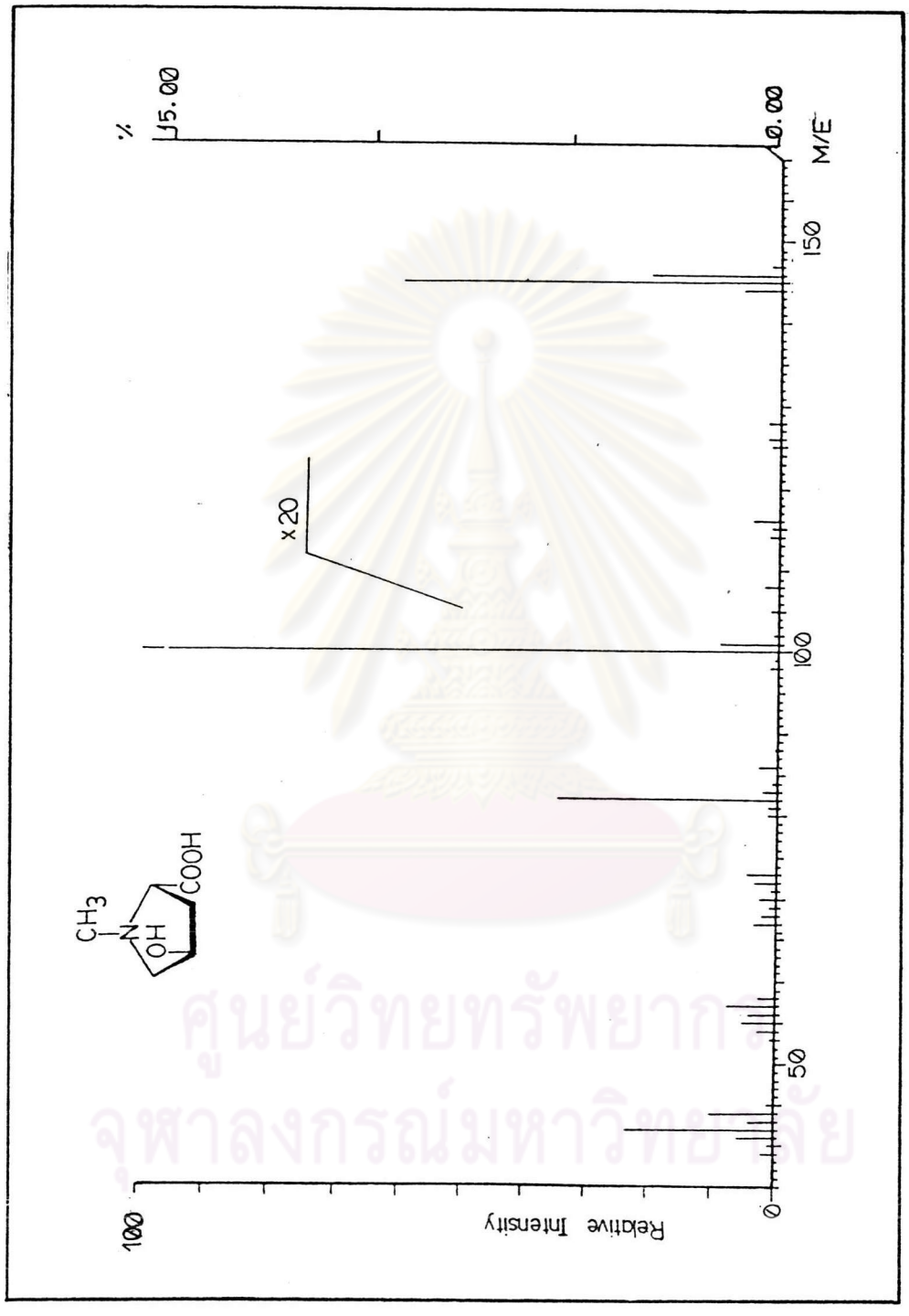


Figure 7 The mass spectrum of odoram

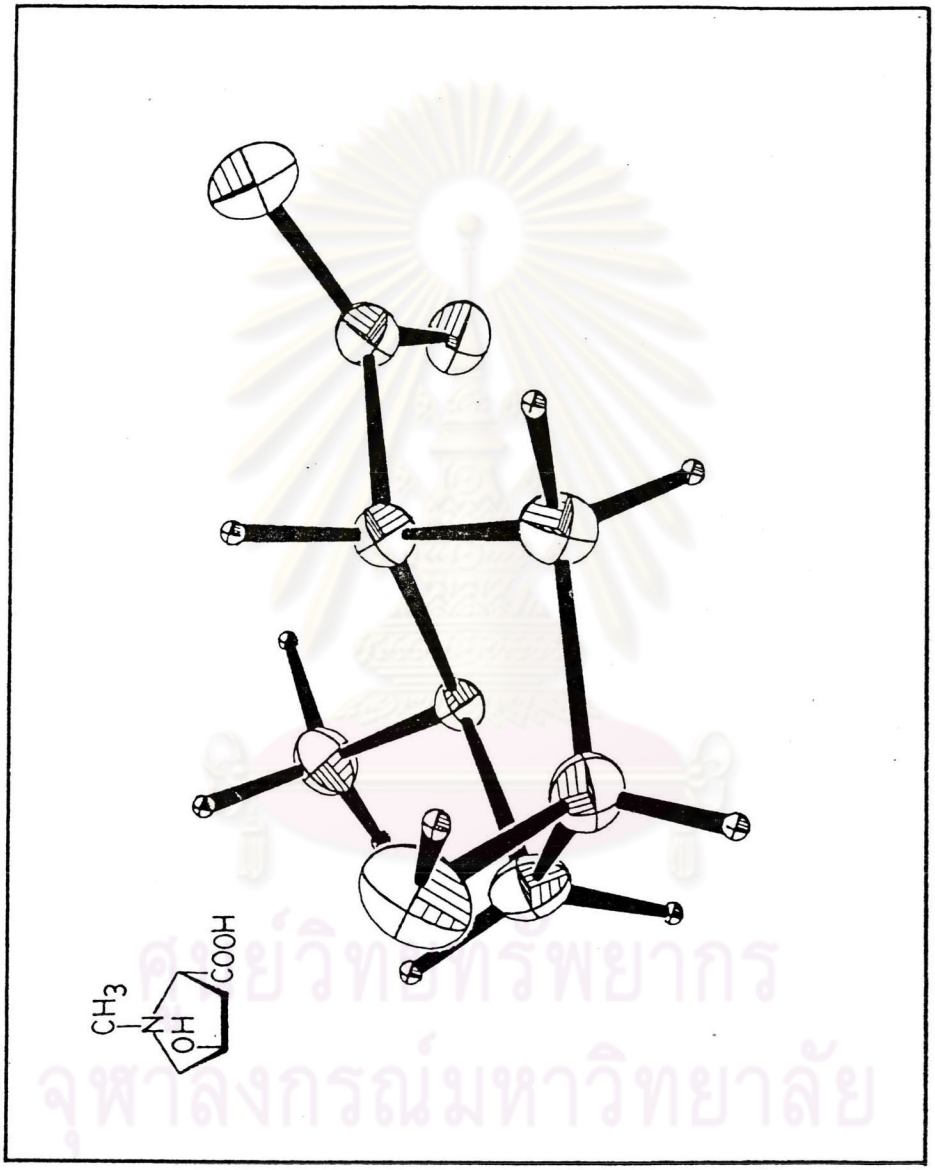


Figure 8 The X-ray crystallographic structure of odoram

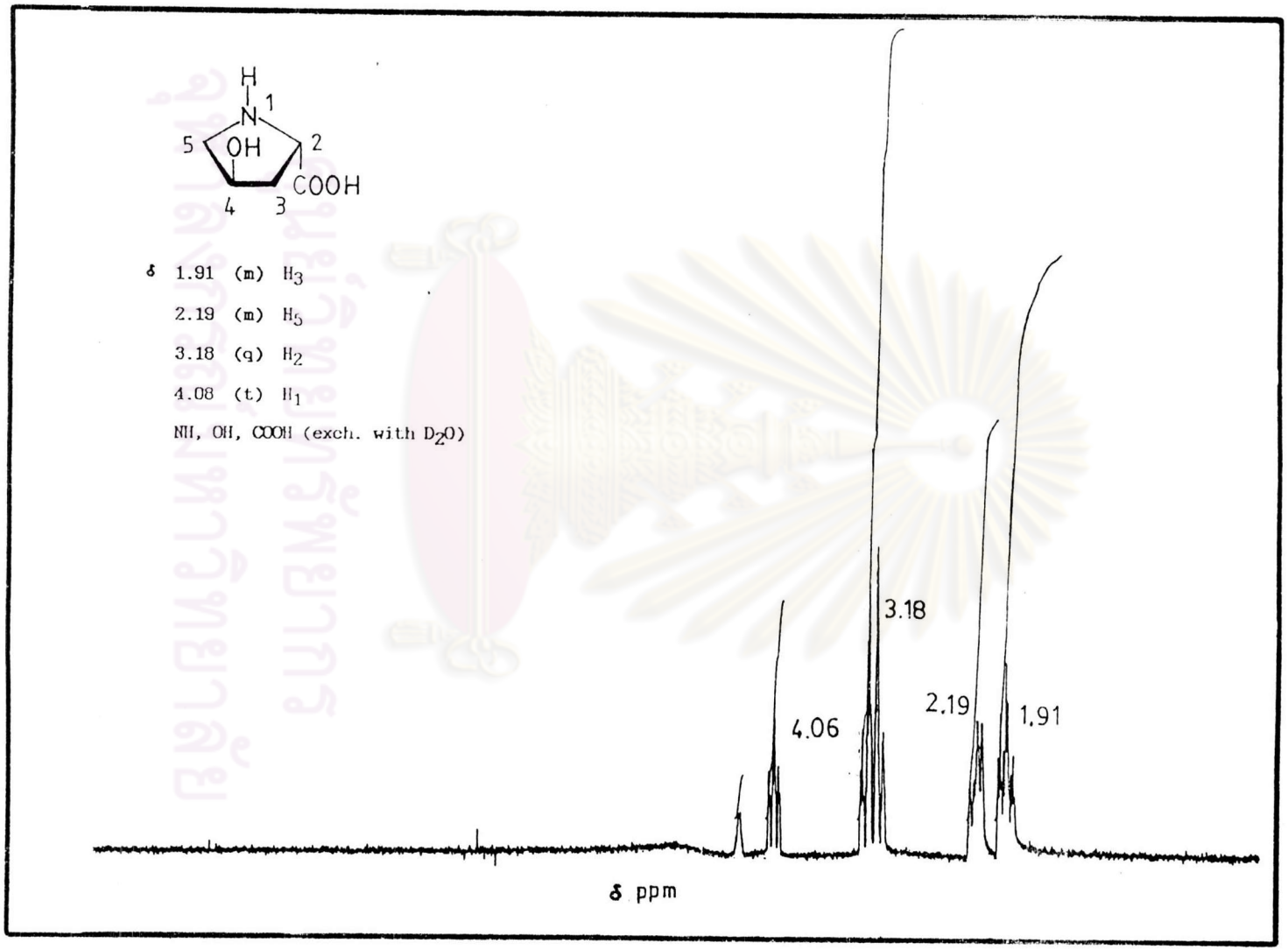


Figure 8 The PMR spectrum of *trans*-4-hydroxy-L-proline

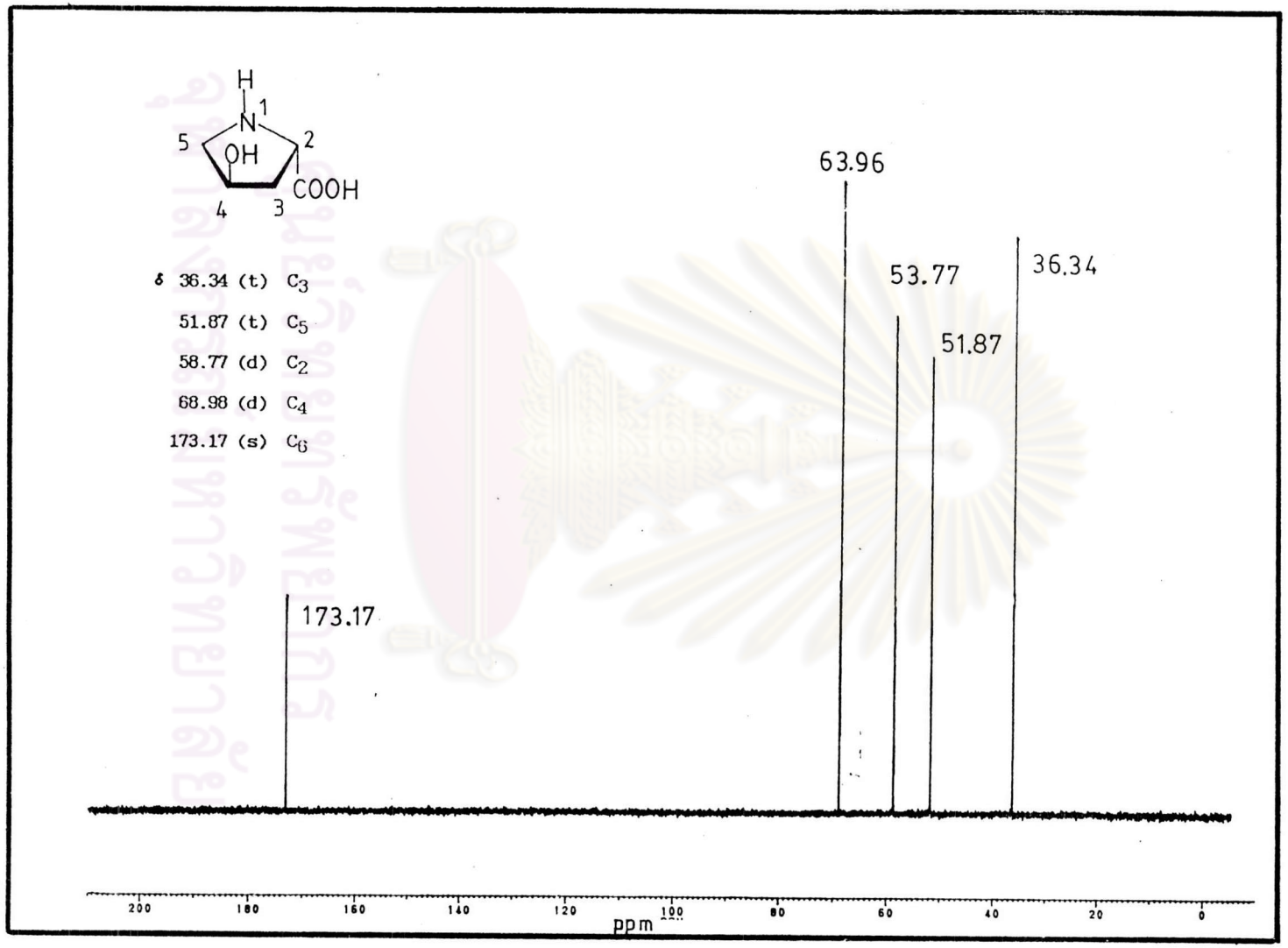


Figure 10 The CMR spectrum of *trans*-4-hydroxy-L-proline

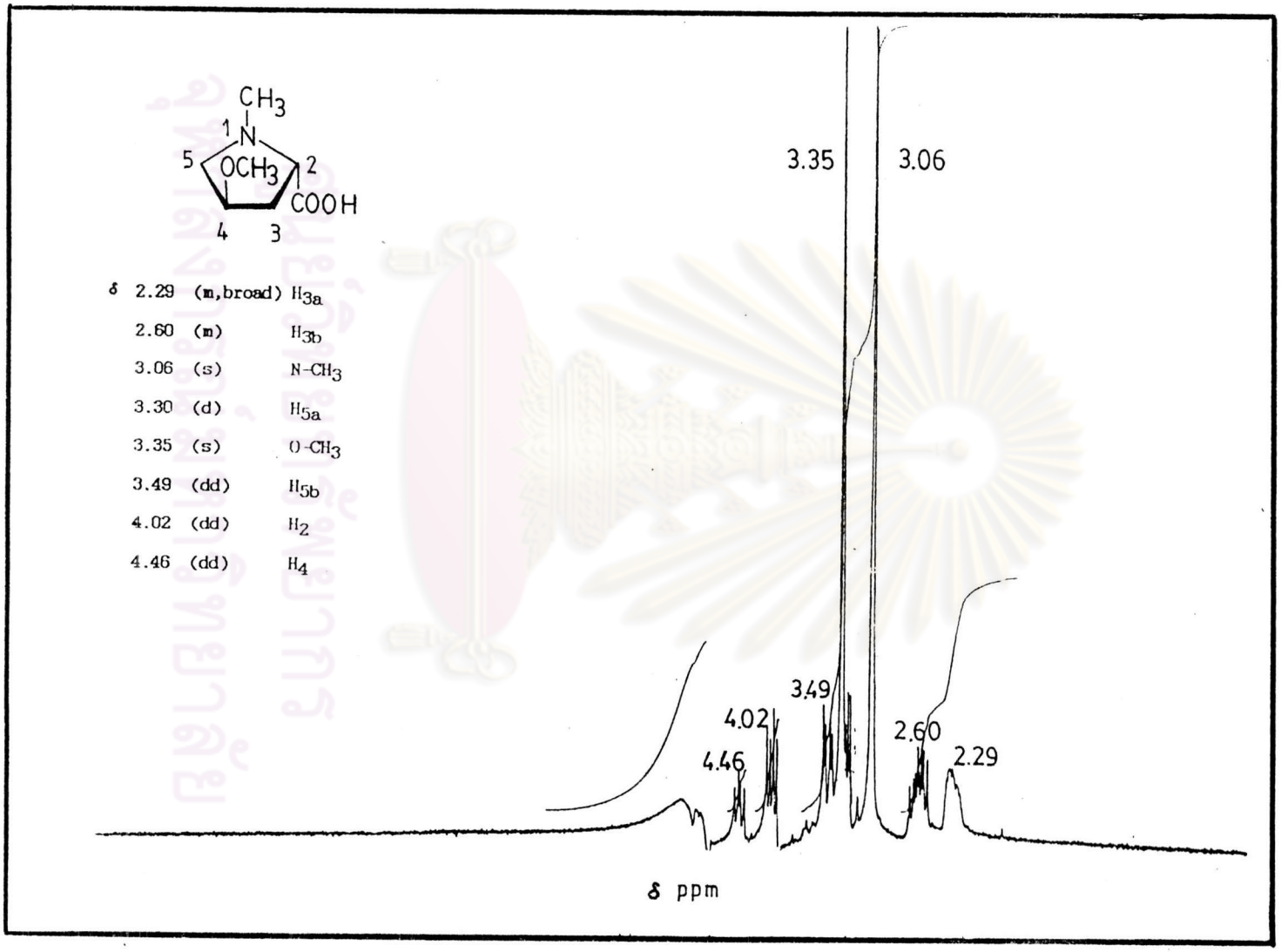


Figure 11 The PMR spectrum of *trans*-4-methoxy-*N*-methyl-L-proline

was synthesized from *trans*-4-hydroxy-L-proline

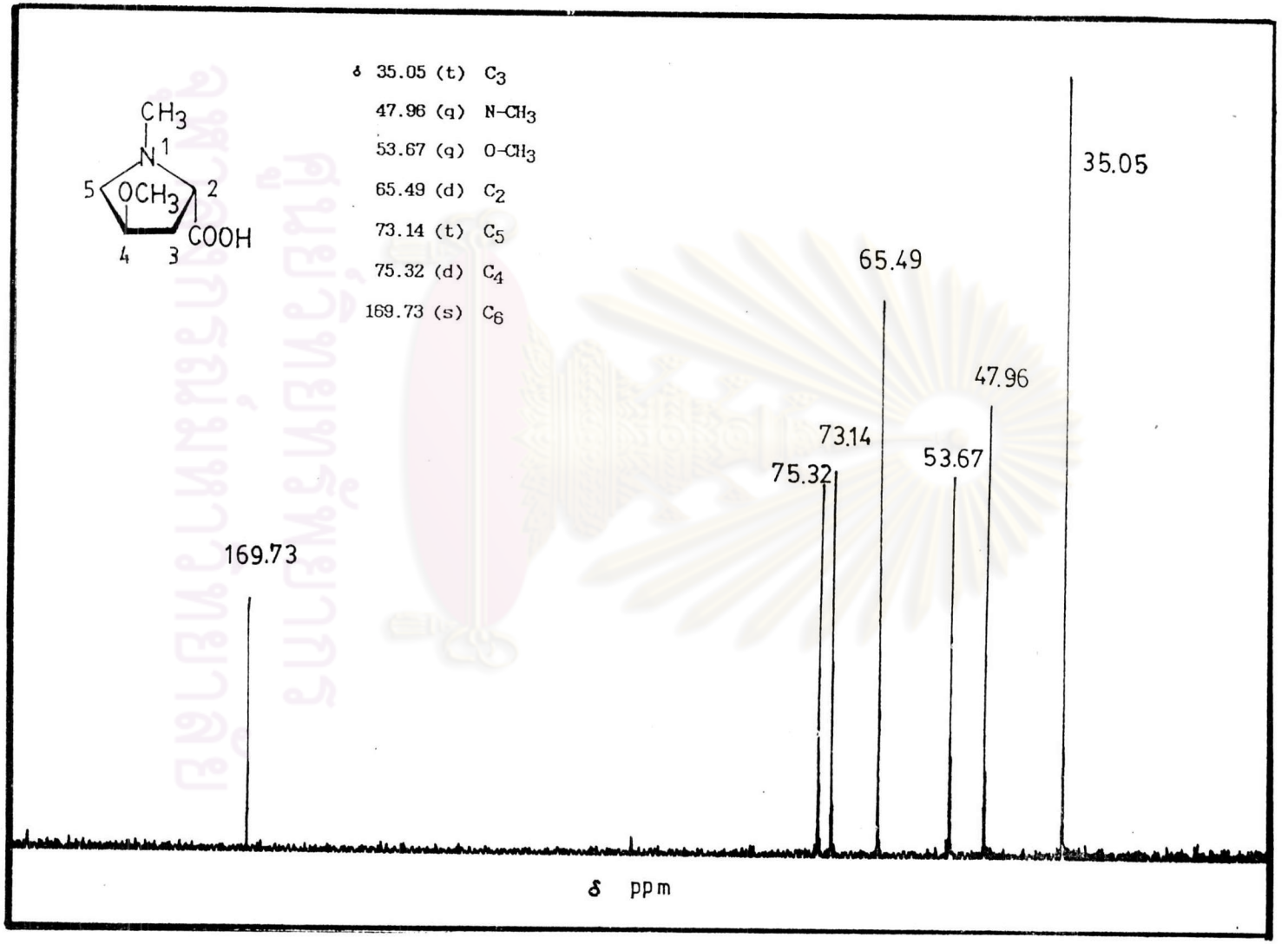


Figure 12 The CMR spectrum of *trans*-4-methoxy-*N*-methyl-L-proline

was synthesized from *trans*-4-hydroxy-L-proline

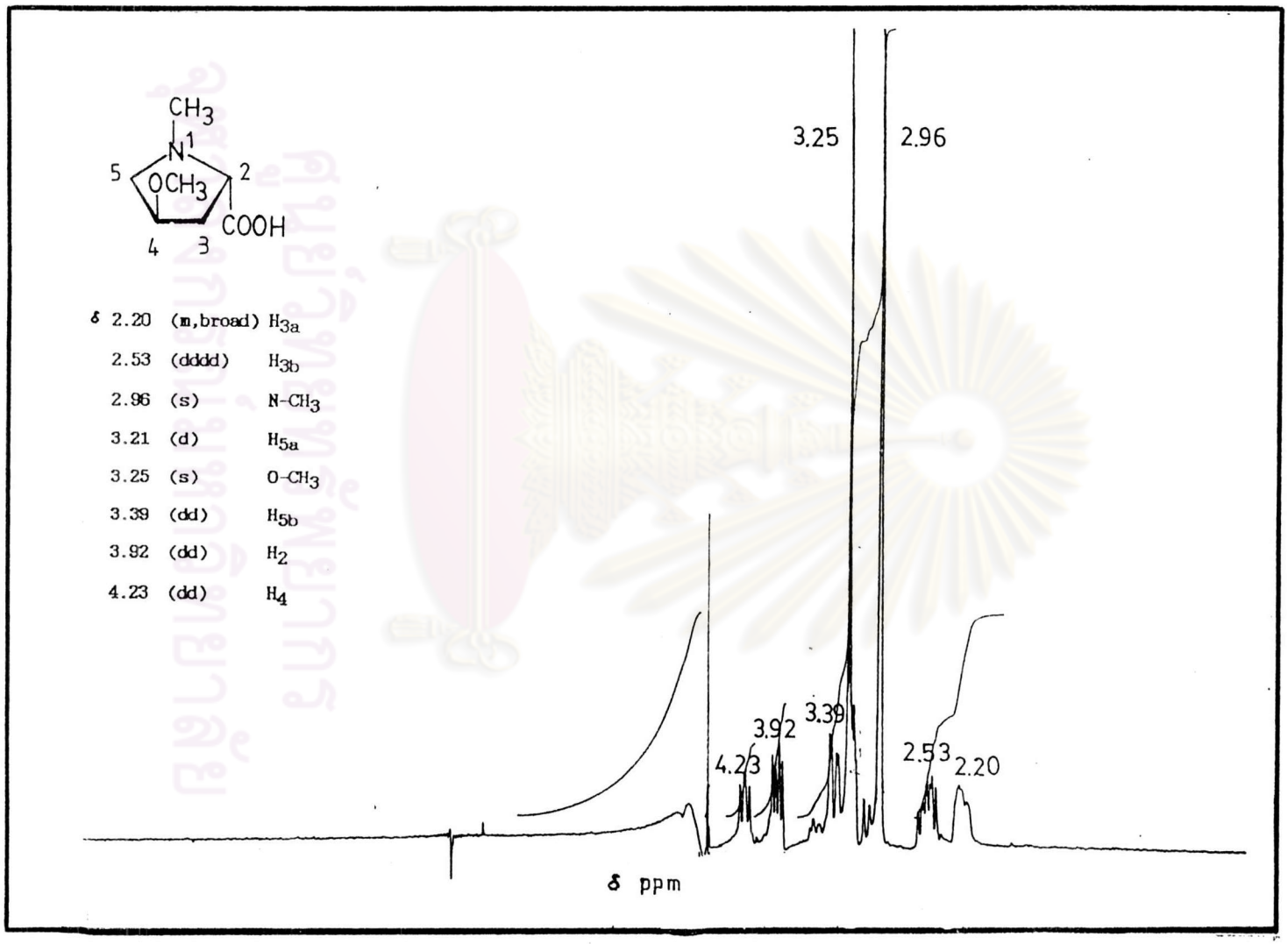


Figure 13 The PMR spectrum of *trans*-4-methoxy-*N*-methyl-L-proline

was synthesized from odoram

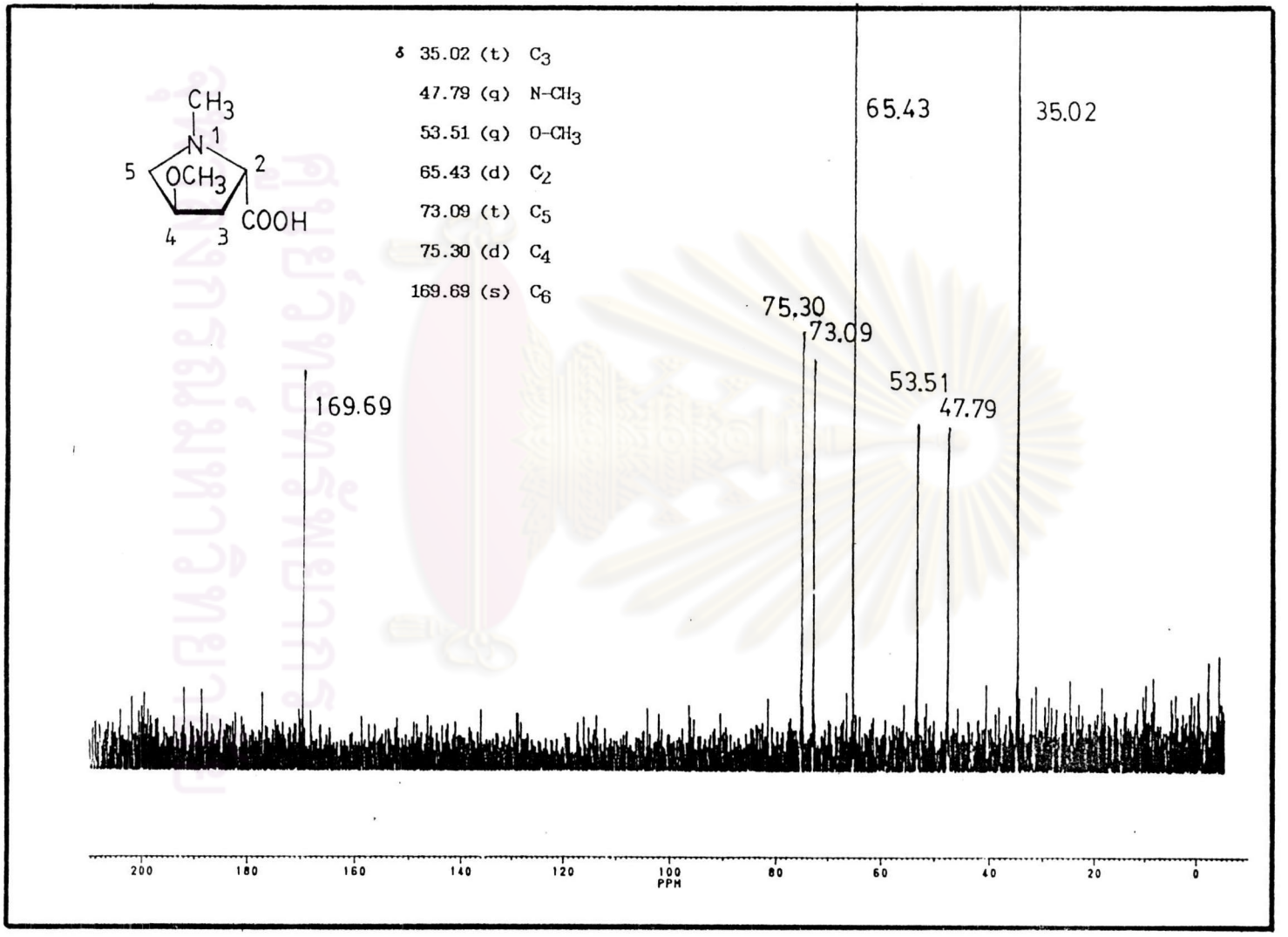


Figure 14 The CMR spectrum of *trans*-4-methoxy-*N*-methyl-L-proline

was synthesized from odoram

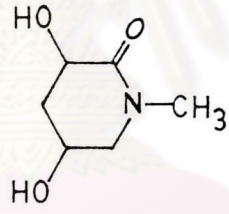
PART B

SYNTHESIS OF 1-METHYL-2-PIPERIDONE DERIVATIVES

CHAPTER I

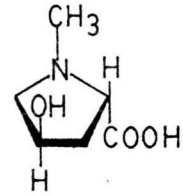
INTRODUCTION

Aglaia odorata Lour. is a small tree being found primarily in South-East Asia. Extracts of the plant have been used as medicine. Previous study established one of the chemical constituents of the flowers of A. odorata Lour. as a nitrogenous compound called "odoram" from the methanol extract.[1] The possible structure was identified by spectral evidences as six membered ring lactam compound, "3,5-dihydroxy-1-methyl-2-piperidone" (1) as shown below.



3,5-dihydroxy-1-methyl-2-piperidone (1)

However, X-ray crystallography indicated that this compound was, in fact, "1-methyl-4-hydroxy-L-proline" as shown by the structure below.



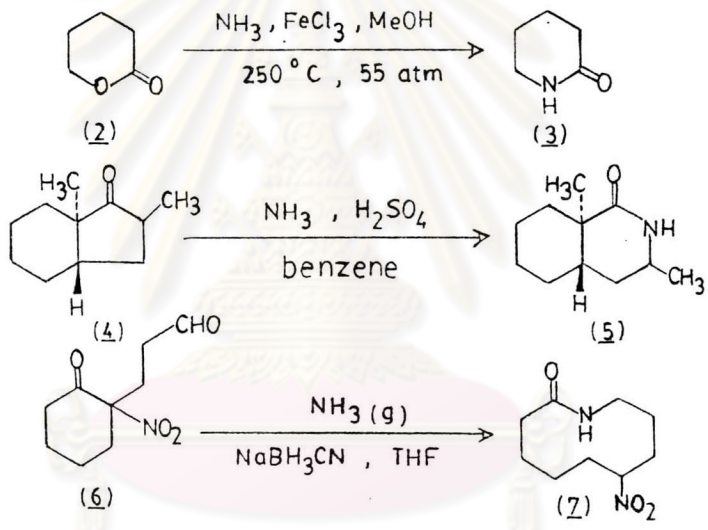
Nevertheless, the synthesis of 3,5-dihydroxy-1-methyl-2-piperidone and/or its derivative is still very interesting.

1.1 Preparation of Lactams

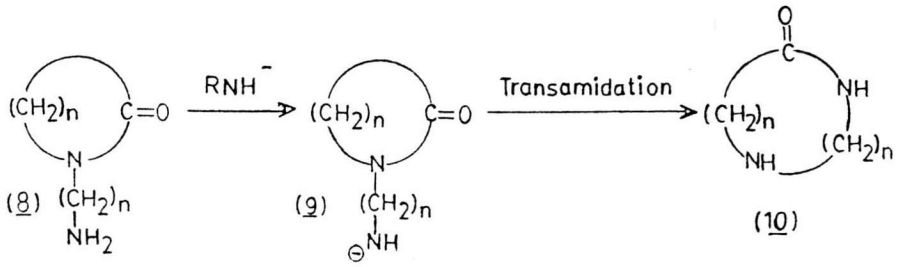
Lactam is a cyclic amide compound. There are many methods to synthesize lactams.[2]

1.1.1 Reaction of Cyclic Ketones, Lactones with Ammonia or Amine

Cyclic ketones and lactones, when treated with ammonia or primary amine , gave cyclic lactams. [2-5]

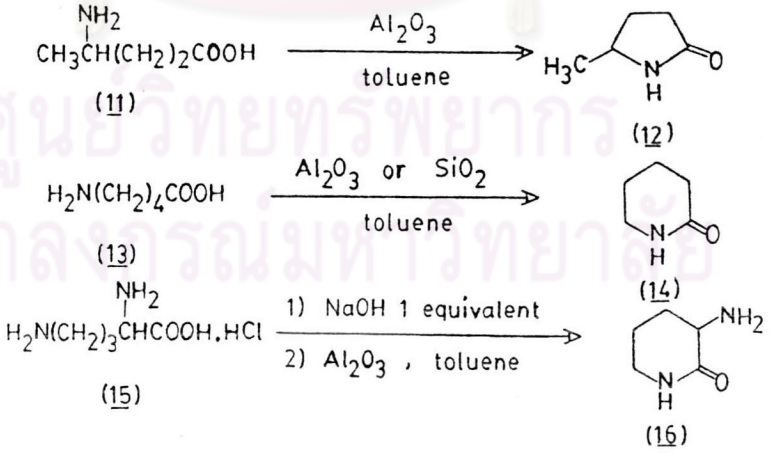


Lactams can be converted to ring-expanded lactams if a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^- which acts as a nucleophile , expanding the ring by means of a transamidation. [2]



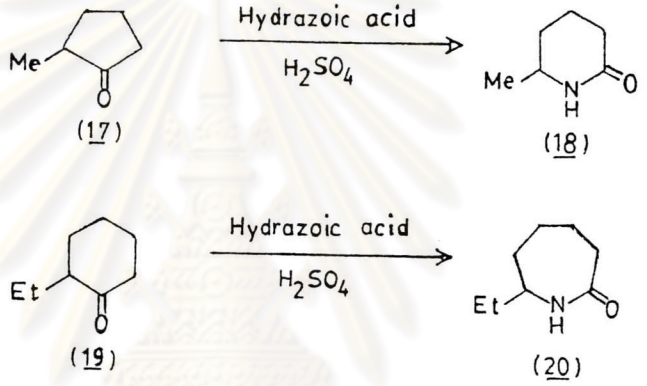
1.1.2 Cyclization of Amino Acids

Middle-size lactams were easily prepared based on the enhancing effect of γ-butyrolactone on cyclodehydration of γ-,δ-, and ε-amino acid by stirring and refluxing a mixture of ω-amino acid (1 part in weight) and alumina or silica gel (3-4 parts in weight) in boiling toluene (25-35 parts in volume). This method can be used with amino acid hydrochlorides provided that an equivalent amount concentrated aqueous sodium hydroxide is first added to free the amino acid. [6]



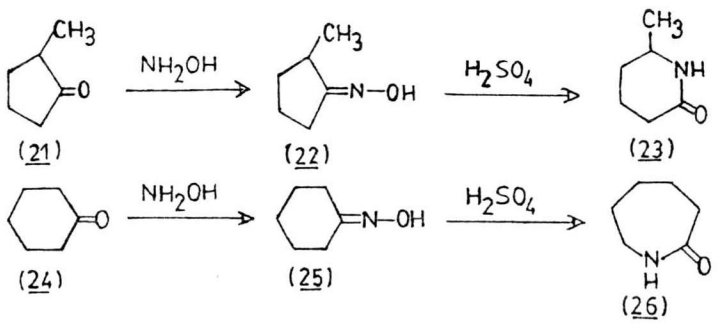
1.1.3 **The Schmidt Rearrangement**

The reaction between a monocyclic ketone (17) and (19) with hydrazoic acid in sulfuric acid gave 60-80 % isolated yields of lactams (18) and (20) derived by methine migration. The mechanism for insertion of NH^- between the carbonyl group and one R group, converted a ketone into an amide was called Schmidt rearrangement. [2,7]



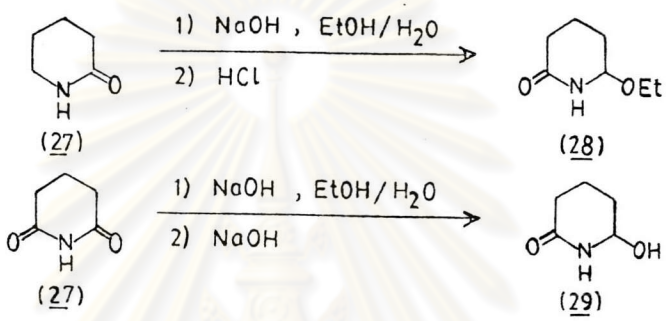
1.1.4 **Beckmann Rearrangement**

Oximes of ketone underwent a rearrangement in acidic conditions to give substituted amides. Oximes of cyclic ketone rearranged to give ring enlargement of cyclic amides, lactams. [2,7]



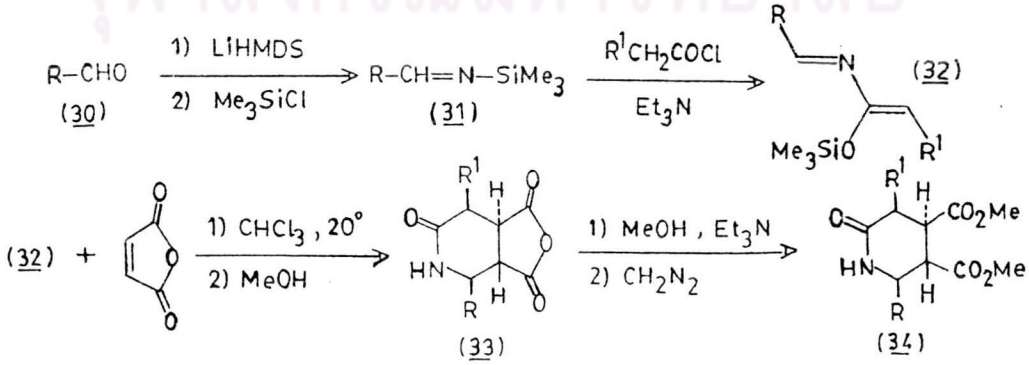
1.1.5 Reduction of Imides

The cyclic imides (27) were selectively reduced in ethanol by sodium borohydride followed by acidic work-up procedure gave the ethoxy compounds (28), when the reduction process was carried out in basic medium, hydroxy compounds (29) were obtained. [8]



1.1.6 Reaction of Imines

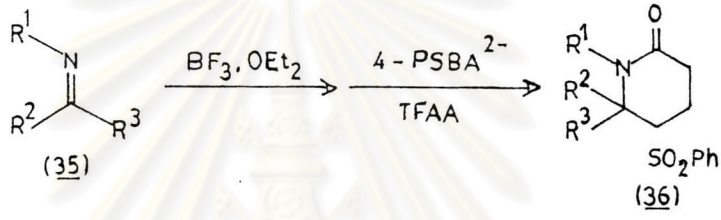
Aldehyde (30) were readily converted into the corresponding N-trimethylsilylimines (31) which were acylated in the presence of trimethylamine to yield the new 2-aza-1, 3-diene (32). When dienes (32) reacted with maleic anhydride at room temperature, substituted piperidone (33) and (34) were obtained with high diastereoselectivity. [9]



(34a) R = Ph , R^1 = H , 87 %

(34b) R = t-Bu , R^1 = H , 90 %

The dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA) reacted with imines (35) activated by boron trifluoride etharate to afford substituted 2-piperidone (36), after cyclization assisted by trifluoroacetic anhydride (TFAA) in good yield. [10]

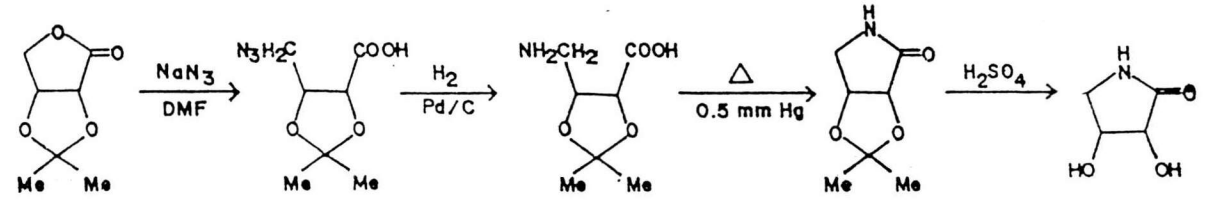


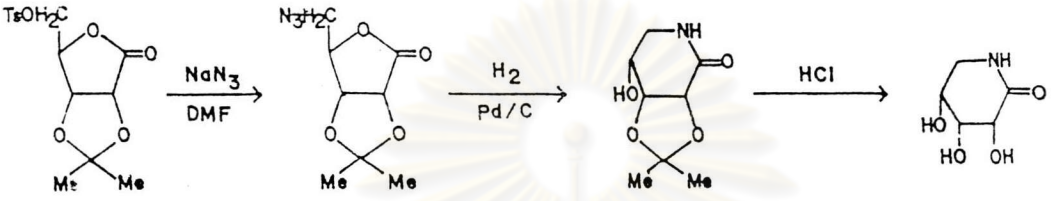
(36a) R^1 = CH_3 , R^2 = Ph , R^3 = H , 90 %

(36b) R^1 = CH_3 , R^2 = PhCH=CH , R^3 = H , 82 %

1.1.7 **Reductive Cyclization of Azido Lactones**

The synthesis of sugar lactams having five-, six-, and seven-membered rings, e.g. (41), (45), (49), were accomplished by the reductive cyclization of appropriate azido lactones or carboxylic acids. The ring expansion of amino lactones to lactams via an internal displacement of the lactone ring oxygen is a general reaction in the sugar series provided that the potential amino group is favorably situated in the molecule. [19]

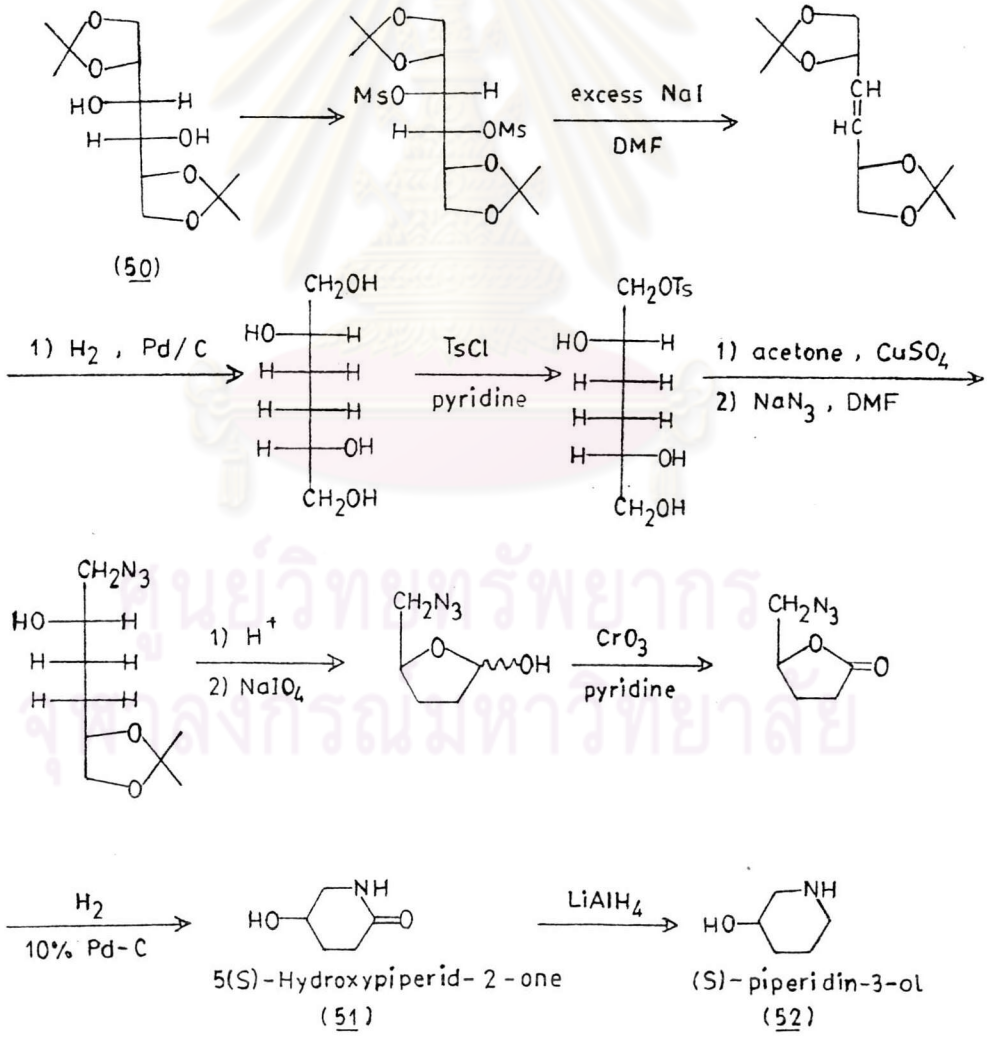




1.2 The Synthetic Pathway of 1-Methyl-2-Piperidone Derivatives

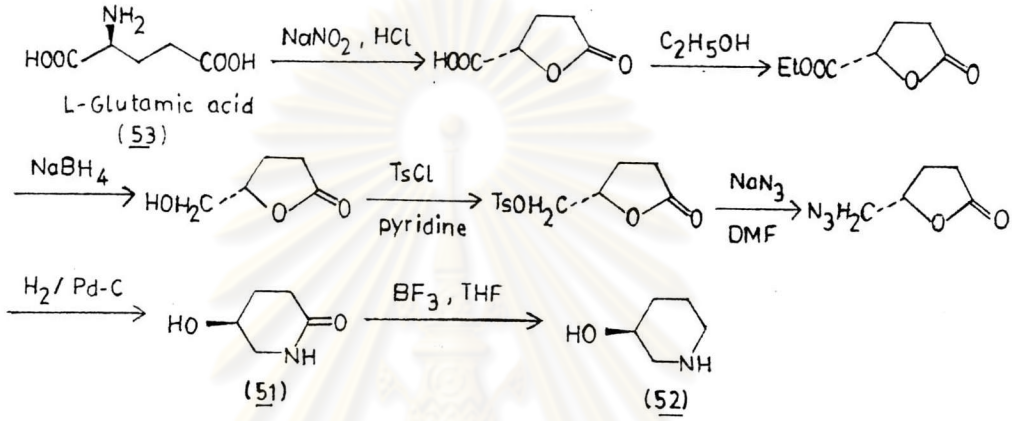
In 1969, C.C. Deane and T.D. Inch [3] studied the stereospecific synthesis of S-(-)-piperidin-3-ol (52) via a compound of which the structure was similar to (1) using 1,2:5,6-di-O-isopropylidene-D-mannitol (50) as a carbohydrate precursor as shown in scheme I. [11,12]

Scheme I The Stereospecific Synthesis of S-(-)-Piperidin-3-ol.



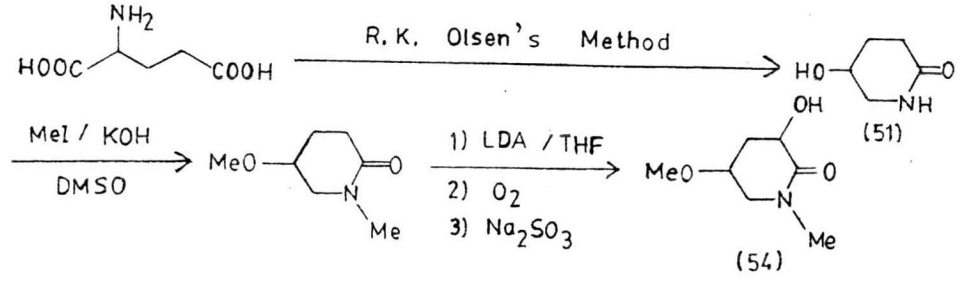
In 1985,R.K. Olsen et al. synthesized (S)-(-)-3-piperidinol (52) from L-glutamic acid (53) as the amino acid precursor via many compounds and (S)-5-hydroxy-2-piperidone (51) toward (S)-(-)-3-piperidinol (52) as shown in scheme II. [13-15]

Scheme II The Synthesis of (S)-(-)-3-Piperidinol.



In 1989, W. Rungruangkanokkul [16] successfully synthesized 3,5-dihydroxy-1-methyl-2-piperidone derivative via the synthetic approach of R.K. Olsen's method to (S)-5-hydroxy-2-piperidone (51) and then N-methylation and α-hydroxylation. The product of this synthetic pathway was named 3-hydroxy-5-methoxy-1-methyl-2-piperidone (54) as shown in scheme III.

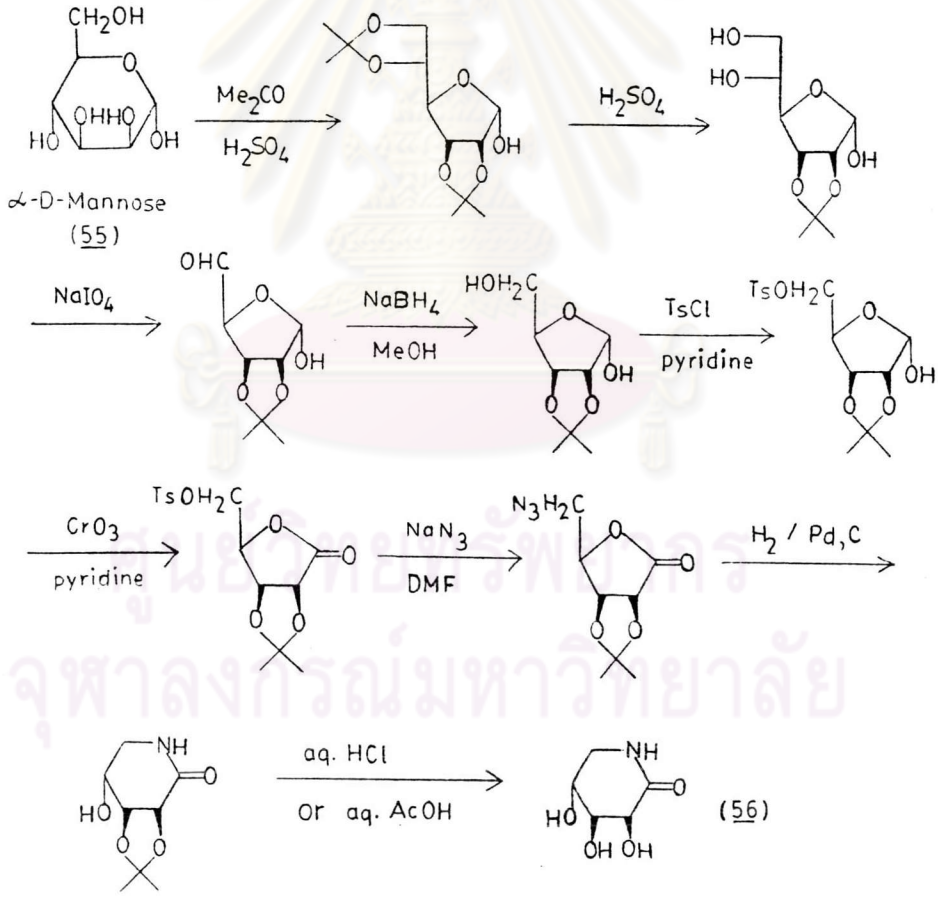
Scheme III The Synthetic Pathway of 3-Hydroxy-5-methoxy-1-methyl-2-piperidone.



From the above synthetic pathway, 3,5-dihydroxy-1-methyl-2-piperidone (1) could not be prepared from the amino acid precursor.

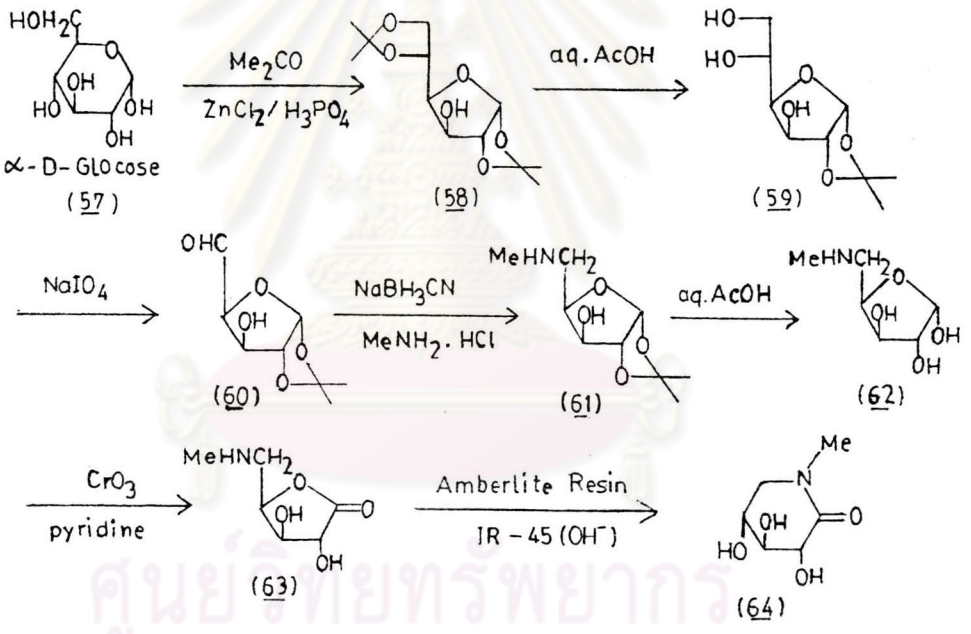
Furthermore, in 1963 O.Th. Schmidt [17], S. Hanessian and T.H. Haskell [18-20] synthesized a sugar derivative containing nitrogen as the ring atom, "5-amino-5-deoxy-D-ribonolactam" (56), using " α-D-Mannose" (55) as the starting material as shown in scheme IV.

Scheme IV The Synthesis of 5-Amino-5-deoxy-D-ribolactam.



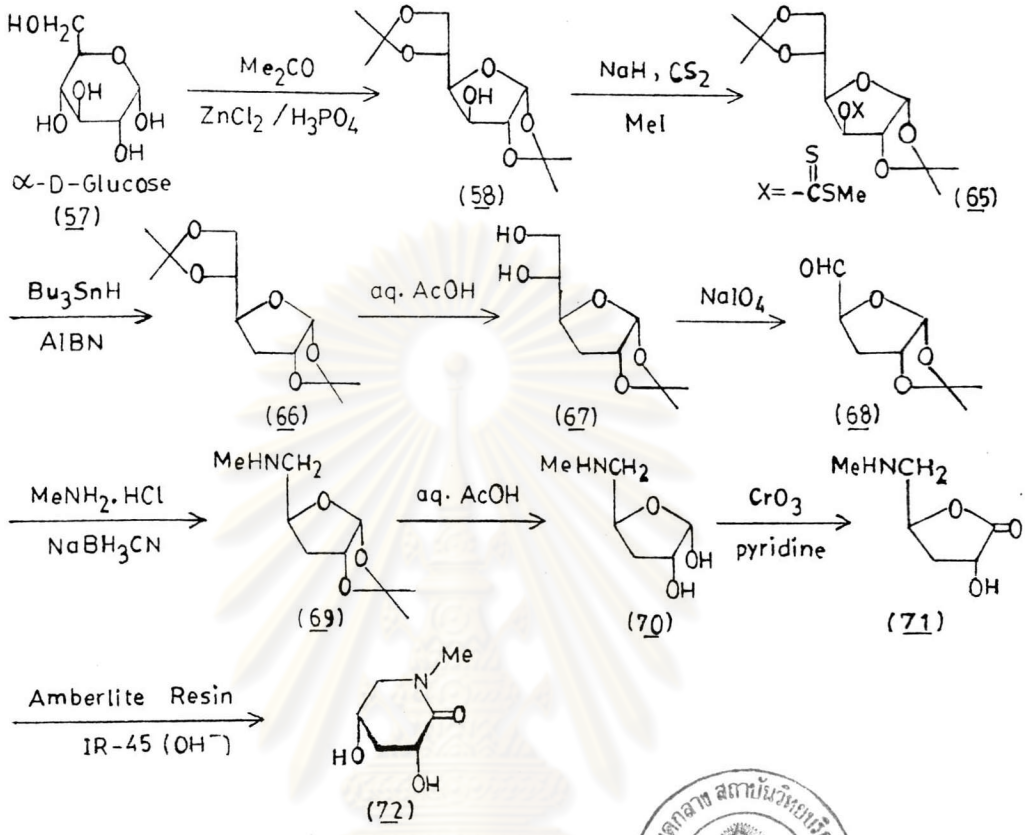
From the pathway in scheme IV, it obtained 5-amino-5-deoxy-D-ribonolactam which was one of the 1-methyl-2-piperidone derivatives. So the synthetic route to 1-methyl-2-piperidone derivatives could be proposed by using carbohydrate precursor. The retrosynthesis of 3,4,5-trihydroxy-1-methyl-2-piperidone (64) from α-D-glucose (57) as the starting material was shown in scheme V. [17-24]

Scheme V The Synthesis of 3,4,5-Trihydroxy-1-methyl-2-piperidone.



The synthesis of "3,4,5-trihydroxy-1-methyl-2-piperidone" (64) was used as model to synthesize "3,5-dihydroxy-1-methyl-2-piperidone" (72) as shown in scheme VI. [17-27]

Scheme VI The Synthesis of 3,5-Dihydroxy-1-methyl-2-piperidone.



CHAPTER II

EXPERIMENTS AND RESULTS

2.1 Instrumental Analyses and Equipments

2.1.1 Infrared Spectroscopy (IR)

The IR spectra were recorded on a Perkin-Elmer Model IR 781 and Model IR 1430 Infrared Spectrophotometer. Solid samples were generally examined as a pressed potassium bromide disc, while liquid samples were neatly examined on sodium chloride cell or nujol mull.

2.1.2 Mass Spectrometry (MS)

The MS spectra were obtained by Jeol Mass Spectrometer Model JMS-DX-300/JMA 2000 at 70 eV.

2.1.3 Proton and Carbon-13 Nuclear Magnetic Resonance Spectroscopy (PMR and CMR)

The ^{1}H (PMR) and ^{13}C (CMR) spectra were recorded on Bruker Model ACF 200 Spectrometer operating at 200.13 MHz for proton and 50.32 MHz for carbon-13 nuclei. Tetramethylsilane (TMS) was used as internal standard. The chemical shifts (δ) were given in ppm down field from the TMS. In this research, the deuterated solvents such as $CDCl_3$, D_2O, DMSO-d_6, CD_3OD were used as internal standards.

2.1.4 **Elemental Analyses**

The elemental analyses were made by using a Perkin-Elmer CHNO Analyzer Model 240C.

2.1.5 **Melting Point (m.p.)**

The melting point of compounds were determined on a Fisher-John melting point apparatus and were uncorrected.

2.1.6 **Rotary Evaporator**

This instrument was used for the rapid removal of a large quantity of volatile solvent from a solution of an organic compound (i.e. from a solvent extraction process or from drying compounds). Evaporation was conducted under reduced pressure (a water pump was the most convenient).

2.2 **Physical Separation Techniques**

2.2.1 **Column Chromatography (CC)**

Merck's silica gel 60G Art.7743 (70-230 mesh ASTM) was used as adsorbents for column chromatography. The ratio of mixture to be separated to the adsorbents was approximately 1:10-20 by weight.

Packing the column [28,29]

The column was a cylindrical glass tubing with a stopcock attached at the bottom of one end which was clamped upright in a vertical position.

A quantity of solvent was partially filled into the column and a loose plug of glass wool or cotton was tamped down into the bottom of the column with a long glass rod until all entrapped air was force out as bubbles.

A slurry was a mixture of the solvent and the solid adsorbent which should be stirred until it was homogeneous and relatively free of entrapped air bubbles. When the slurry was ready, the column was half filled with solvent, and the stopcock was adjusted to allow solvent to drain slowly into a large beaker. Alternately, the slurry was mixed again by stirring and poured in the portions on top of the draining column (a glass funnel might be used here).

The column was tapped constantly and gently on the side during the pouring operation, with a pencil fitted with a rubber stopper. Tapping was continued until all the material had settled, showing a well-defined level at the top of the column. Solvent from the collecting beaker might be re-added to the slurry in the column if it became too thick and the collected solvent should be passed through the column several times to ensure that settling was complete and the column was firmly packed.

Applying the sample to the column

Before applying the sample to the column, the solvent level was lowered to the top of the settled base by draining. The liquid (diluted or neat) or dissolved solid was added to form a small layer on the top of the settled adsorbent

with care inorder not to disturb the surface. This small layer of liquid was drained into the column until the top surface began to dry. A little of solvent was then added carefully and it was drained into the column until the column just dry again. Another layer of fresh solvent was added, if necessary, this process was repeated until it was clear that the sample was strongly absorbed on the top of the column. Finally, the column was fully filled with the solvent used as the developing eluent. Polarity of solvent was changed by mixing the more polarity solvent in order to increase the efficiency of sample separation.

2.2.2 **Thin-layer Chromatography (TLC)** [28,29]

Merck's silica gel 60G Art.7731 was used as adsorbents for thin-layer chromatography.

Preparation the Thin-layer plates

The glass plates, ((20 square cm.) or (5x20 cm.)) for used as the thin-layer plate should be washed with acetone, dried and placed on a sheet of tissue paper. The slurry should be made up in the ratio of about 1 gm of silica gel 60G to each 2 mL of water.

The 0.25 mm. thin-layer chromatoplates were prepared in the following manner:

A mixture of silica gel 60G (25.0 gm) and water (50.0 mL) was stirred until it became a slurry, then, it was applied to glass plates (20 square cm. or 5x20 cm.) using

a Desaga spreader. After being dried at room temperature for an hour, the plates were heated at 125 °C for 30 minutes, then cooled and stored in a descicator, ready to be used.

Before testing, two lines were drawn on each plate, one was 2.0 cm. from one edge ; this line was referred to the base line. The upper line was 14.0 cm. above and parallel to the first line. The solution containing the compounds to be investigated was applied as small spots on the base line of the plate at 1.0 cm. interval. And after the solvent evaporated, the plate was placed in a glass tank filled to a depth 1.0 cm. with the eluting solvent. The eluting solvent moved up the plate immediately. As the solvent front reached the upper line, the plate was removed, dried and detected with a suitable detector such as UV, I_2 and 5% sulfuric acid in ethanol to reveal the compounds.

2.3 Syntheses

The synthetic pathway of "3,4,5-trihydroxy-1-methyl-2-piperidone" and "3,5-dihydroxy-1-methyl-2-piperidone" were shown in scheme V and VI.

2.3.1 Preparation of 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose or Diacetone-α-D-glucose (58) [17,18]

A suspension of dry α-D-glucose (57) (15 g., 0.083 mol), anhydrous zinc chloride (12 g.,0.083 mol) and phosphoric acid (85 % V/V) (0.75 g.) in dry acetone (100 mL) were stirred at ambient temperature for 30 hours. Unchanged glucose was removed by filtration and washed with a little acetone. Inorganic salts were precipitated by the addition of a cool solution of sodium hydroxide (8.5 g.) in water (10 mL). The resulting suspension was filtered and washed with acetone. The almost colourless filtrate and washing were concentrated under reduced pressure,the residue was diluted with water (80 mL) and extracted with chloroform or dichloromethane (3x80 mL). The combined organic phase was dried over magnesium sulphate, filtered and concentrated on a rotary evaporator which gave a white crystalline residue of crude 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (58). Recrystallisation from light petroleum (b.p. 80-100 ^{o}C) gave product (58) (8.75 g., 40.3 % yield), m.p.109-110 ^{o}C (lit.17, m.p. 110-111 ^{o}C). Elemental analysis

found : C 55.48 %, H 7.56 % and $C_{12}H_{20}O_6$ required : C 55.38 %, H 7.69 %.

IR ν_{max}^{KBr} (cm^{-1}) : 3420, 2980, 2940, 2860, 1450, 1380, 1220, 1070, 840. (Fig.2)

PMR ($CDCl_3$) δ (ppm) : 1.30(s,3H);1.35(s,3H);1.43(s,3H);1.48(s,3H); 2.57(d, J=3.70 Hz, 1H exchanged with D_2O); 3.93-4.00(dd, J_1=8.56 Hz, J_2=5.68 Hz, 1H); 4.03-4.08(dd, J_1=7.55 Hz, J_2=2.75 Hz, 1H); 4.12-4.19(dd, J_1=7.59 Hz, J_2=6.14 Hz, 1H); 4.31 (m, 2H); 4.52 (d, J=3.64 Hz, 1H); 5.93 (d, J=3.59 Hz, 1H). (Fig.3)

CMR ($CDCl_3$) δ (ppm) : 25.08(q), 26.07(q), 26.68(q), 26.72(q), 67.50(t), 73.00(d), 74.74(d), 81.07(d), 85.07(d), 105.13(d), 109.44(s), 111.69(s). (Fig.5)

MS m/e (% rel. int.) : 261(M^++1, 0.16), 245(71.28), 187(26,70), 127(30.15), 101(100.00), 85(19.78), 59 (56.57), 43(72.05). (Fig.6)

2.3.2 **Preparation of 1,2-O-Isopropylidene-α-D-glucofuranose (59)** [17,21-24]

The compound (58) (5 g.,0.019 mol) was treated with 2 M acetic acid (60 mL) in methanol (25 mL ; 45 °C) with continuous stirring. The reaction was followed by thin-layer chromatography (10 % methanol in chloroform as mobile phase) until the starting material had been consumed (there was only

one new spot at R_f=0.33, no spot at the origin R_f=0.0 was observed). The reaction mixture was evaporated under reduced pressure at 50 °C to a syrup which diluted with water (50 mL) and extracted with chloroform (30 mL). The chloroform extract was dried over magnesium sulphate, filtered and evaporated to dryness under reduced pressure at 40 °C to give a white solid as the starting material (58).

The aqueous phase was neutralized with resin (Amberite 45, OH^- form) by continuous stirring until the pH was not acid to litmus paper, then filtered, washed the resin with water (2x30 mL), combined the total aqueous layer and evaporated under reduced pressure to give a white solid. The solid was recrystallised from methanol-ether to give colourless needles of 1,2-O-isopropylidene-α-D-glucofuranose (59) (3.45 g.,81.6 % yield), m.p. 159-160 °C (lit.17, m.p. 160-161 °C). Elemental analysis found : C 47.85 %, H 7.18 % and $C_9H_{16}O_6$ required : C 49.09 %, H 7.27 %.

IR ν_{max}^{KBr} (cm^{-1}) : 3430, 3320, 2950, 2930, 1380, 1220, 1090, 850, 650. (Fig.7)

PMR (D_2O) δ (ppm) : 1.18(s, 3H); 1.34(s, 3H);
3.44-3.50(dd, J_1=12.07 Hz, J_2=5.90 Hz, 1H);
3.59-3.66(dd, J_1=12.08 Hz, J_2=2.76 Hz, 1H);
3.69-3.78(m, 1H);
3.88-3.94(dd, J_1=8.89 Hz, J_2=2.60 Hz, 1H);
4.14(d, J=2.65 Hz, 1H);

PMR ($CDCl_3$) δ (ppm) : 4.51(d, J=3.71 Hz, 1H);
5.84(d, J=3.72 Hz, 1H).
(Fig.8) (OH in this compound exchanged with D_2O)

CMR (D_2O) δ (ppm) : 24.00(q), 24.42(q), 62.37(t), 67.26(d), 72.47(d), 78.62(d), 83.29(d), 103.58(d), 111.55(s). (Fig.11)

MS m/e (% rel. int.) : 221(M^++1, 0.16), 205(39.77), 159(32.62), 127(17.82), 101(13.65), 85(35.96), 73 (53.21), 59(100.00), 43(46.60). (Fig.13)

2.3.3 **Preparation of 1,2-O-Isopropylidene-α-D-erythropentodialdofuranose (60)** [18,28]

Add a solution of sodium metaperiodate ($NaIO_4$) (2.34 g., 0.011 mol) in water (5 mL) dropwise to a cool well-stirred solution of 1,2-O-isopropylidene-α-D-glucofuranose (59) (2.41 g., 0.011 mol) in methanol (20 mL). Stirring was allowed for one hour, then filtered out the precipitate and removed the solvent by evaporation under reduced pressure at a temperature below 50 °C. The solid residue was extracted with chlorofom (3x20 mL), filtered and dried the combined extract over magnesium sulphate, filtered and evaporated the solvent to give a pale yellow moderately viscous liquid (60) which was gradually hardened on standing. The product was isolated as dimer product (1.76 g., 85.46 % yield), R_f=0.66 (10 % methanol in chloroform). Elemental analysis found: C 48.72 %, H 6.88 %, and $C_8H_{12}O_5$

required : C 51.06 %, H 6.38 %.

IR ν_{max}^{nujol} (cm^{-1}) : 3450(broad), 2990, 2940, 1735, 1380, 1270-950. (Fig.14)

PMR (D_2O) δ (ppm) : 1.16(s); 1.33(s);
3.82-3.87(dd, J_1=7.61 Hz, J_2=2.78 Hz, 1H);
4.09(d, J=2.72 Hz, 1H);
4.49(d, J=3.61 Hz, 1H);
4.60-4.62(d, J=3.99 Hz, D_2O+OH);
4.94(d, J=7.69 Hz, 1H);
5.83(d, J=3.62 Hz, 1H). (Fig.15)

CMR (D_2O) δ (ppm) : 24.20(q), 24.68(q), 72.52(d), 81.67(d), 83.56(d), 87.03(d), 103.61(d), 111.71(s). (Fig.16)

MS m/e (% rel. int.) : 203(M^++CH_3,34.01), 173(M^+-CH_3, 20.02), 159 (44.51), 113(90.01), 85(60.75), 71(40.54), 59(100.00), 43(95.39). (Fig.18)

2.3.4 **Preparation of 1,2-O-Isopropylidene-α-D-xylo-furanose (60a)** [18,22]

A cool solution of sodiumborohydride ($NaBH_4$) (1.46 g., 0.038 mol) in methanol (20 mL) was added dropwise into a cool well-stirred solution of 1,2-O-isopropylidene-α-D-erythropentodialdofuranose (60) (4.50 g.,0.024 mol) in methanol (20 mL). Stirring was continued for an hour. The solvent was then removed on a rotary evaporator under reduced pressure at a

temperature below 45 °C. The solid residue was extracted with chloroform (3x20 mL), filtered and dried the combined extract over magnesium sulphate, filtered and evaporated the solvent under reduced pressure to give a white solid crystalline (60a). This solid product was moistened when it contacted the air. The melting point of this compound could not be determined. The isolated product weighted (4.53 g., 99 % yield). Elemental analysis found : C 26.47 %, H 4.19 % and $C_8H_{14}O_5$ required : C 50.52 %, H 7.37 %.

IR ν_{max}^{KBr} (cm^{-1}) : 3050-3700 (broad), 2950, 1650, 1380, 1150, 1080. (Fig.19)

PMR (D_2O) δ (ppm) : 1.17(s, 3H); 1.31(s, 3H); 3.82(broad, 1H); 3.88(d, J=1.81 Hz, 2H); 4.09(s, 1H); 4.40(d, J=3.33 Hz, 1H); 4.60(s); 5.84(d, J=2.88 Hz, 1H). (Fig.20)

CMR (D_2O) δ (ppm) : 24.17(q), 24.66(q), 58.94(t), 73.71(d), 75.30(d), 84.42(d), 103.82(d), 111.22(s). (Fig.21)

MS m/e (% rel. int.) : 201(30.50), 159(20.81), 129(17.50), 99(23.36), 85(25.53), 59(53.75), 44(70.61), 43(100.00) (Fig.22)

2.3.5 **Preparation of 1,2-O-Isopropylidene-5-O-toluene-*p*-sulphonyl-D-xylofuranose (60b)** [13,15,32-33]

Powdered *p*-toluenesulphonyl chloride (*p*-TsCl) (0.69 g.,3.60 mmol) was added in one portion to an ice-cooled and stirred solution of (60a) (0.57 g.,3 mmol) and N,N-dimethyl-aminopyridine (0.04 g.,30 mmol) in dry pyridine (20 mL). The mixture was stirred for 2 hours at temperature 0-10 °C. The solvent was removed under reduced pressure to dryness to give residue which was solubilized in ethyl acetate. The ethyl acetate solution was washed with water and saturated sodium chloride solution, dried over magnesium sulphate, filterd and evaporated under reduce pressure. The residue product was a pale brown liquid (0.50 g., 48.45 % yield).

PMR ($CDCl_3$) δ (ppm) : 1.31(s, 3H) ; 1.47(s, 3H) ;
2.47(s, 3H) ; 3.44(s) ;
4.06(d, J=3.74 Hz, 1H) ; 4.10-4.27(m, 1H);
4.30(d, J=3.59 Hz, 1H) ;
4.49(d, J=3.59 Hz, 1H) ;
5.84(d, J=3.69 Hz, 1H) ;
5.95(d, J=3.63 Hz, 1H) ;
7.25(s, $CDCl_3$) ; 7.58(dd, J_1=88.96 Hz,
J_2=8.49 Hz, 4H). (Fig.22a)

2.3.6 **Preparation of N-Methylbutylamine** [31]

The well-stirred solution of methylamine hydrochloride ($MeNH_2.HCl$) (3.75 g., 0.055 mol) in abs. methanol (20 mL) was added to the solution of butyraldehyde (1.59 g.,0.022 mol) in abs. methanol (20 mL). The mixture was adjusted to pH<7 (litmus paper) and stirred for 30 minutes. Then, sodiumcyano-borohydride ($NaBH_3CN$) (1.15 g.,0.018 mol) was added into the mixture and the mixture was continuous stirred for 20 hours. The solution was evaporated to dryness under reduced pressure and extracted with ether (3x20 mL). The conbined extracts were dried over magnesium sulphate, filtered and evaporated to give a pale yellow viscous liquid of N-methylbutylamine (0.85 g., 44.97 % yield).

Butyraldehyde showed the PMR signals below.

PMR ($CDCl_3$) δ (ppm) : 0.87(t, 3H) ; 1.58(m, 2H) ;
2.33(t, 2H) ; 9.65(s, 1H). (Fig.22b)

N-methylbutyraldehyde showed the PMR signals below.

PMR ($CDCl_3$) δ (ppm) : 0.96(t, 3H) ; 1.45(m, 2H) ;
1.81(m, 2H) ; 2.72(s, 3H) ;
2.97(t, 2H) ; 5.75(s,broad, 1H). (Fig.22c)

2.3.7 **Preparation of 5-N-Methyl-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (61)** [31]

The well-stirred solution of dimer product (60) (0.52 g., 0.003 mol) and methylamine hydrochloride (0.54 g.,0.008 mol) in abs. methanol (30 mL) was pH<7 (litmus paper). The acidic mixture was stirred for 30 minutes, then gradually added sodiumcyanoborohydride (0.16 g.,0.003 mol) to pH 7-8 (pH paper) and continuous stirring for 20 hours. The mixture was evaporated to dryness under reduced pressure and extracted with ether (3x20 mL), then filtered. The combined extracts were dried over magnesium sulphate, filtered and evaporated to give a pale yellow viscous liquid (0.25 g., 44.52 % yield).

PMR ($CDCl_3$) δ (ppm) : (Fig.22d)

2.3.8 **Preparation of 3-O-(1,2:5,6-Di-O-Isopropylidene-α-D-glucofuranose)-S-Methyl Dithiocarbonate (65)** [18,21,25]

The mixture of diacetoneglucose (58) (10.5 g.,0.04 mol), sodium hydride (2.0 g.,0.083 mol) and imidazole (0.2 g.) was stirred for 2 hours in dry THF (100 mL), in a 250 mL two necked round-bottom flask fitted with a reflux condenser. Carbon disulphide (7.2 mL, 0.120 mol) was added, and continued stirring for one hour. Then methyl iodide (2.6 mL, 0.04 mol) was added into the stirred orange mixture and stirring was continued for 30 minutes. The reaction was completed in 10 minutes and the yellow precipitate of sodium iodide was formed. Dichloromethane

or chloroform (80 mL) and water (150 mL) were added to the mixture, respectively, then the lower organic layer was separated and washed it with water until the water layer was colourless. The organic layer was dried over magnesium sulphate, filtered and removed the solvent on a rotary evaporator to give a yellow viscous liquid (13.83 g.,97.84 % yield). Elemental analysis found :C 48.40 %, H 6.46 % and $C_{14}H_{22}O_6S_2$ required: C 48.00 %, H 6.28 % (lit.21 found: C 48.3 %, H 6.4 %, S 18.7 %).

IR ν_{max}^{neat} (cm^{-1}) : 2990, 2940, 1450, 1380, 1210, 1070, 850. (Fig.23)

PMR ($CDCl_3$) δ (ppm) : 1.29(s, 3H); 1.30(s, 3H); 1.34(s, 3H); 1.39(s,3H); 2.57(s, 3H); 4.03-4.08(m, 2H); 4.26-4.30(m, 2H); 4.65(d, J=3.82 Hz, 1H); 5.87-5.90(dd, J_1=3.82 Hz, J_2=2.32 Hz, 2H). (Fig.24)

CMR ($CDCl_3$) δ (ppm) : 19.18(q), 25.16(q), 26.16(q), 26.58(q), 26.70(q), 66.87(t), 72.31(d), 79.72(d), 82.73(d), 84.15(d), 104.96(d), 109.23(s), 112.29(s), 214.64(s). (Fig.25)

MS m/e (% rel. int.) : 335(M^+-15,15.32), 317(22.07), 303(27.77), 245(9.42), 187(3.27), 159(6.01), 127 (10.07), 113(8.36), 101(100.00), 75(26.58), 59(18.82), 43(51.11). (Fig.26)

2.3.9 **Preparation of 3-Deoxy-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose or 1,2:5,6-Di-O-isopropylidene-α-D-ribo-hexofuranose (66)** [27,28]

A solution of tributyltin hydride (27.04 g.,0.092 mol) in dry toluene (60 mL) was placed in a three-necked flask equipped with a reflux condenser, a nitrogen gas inlet tube and a dropping funnel. The flask was flushed with nitrogen atmosphere. The solution was refluxed at 60 °C while a solution of S-methyl dithiocarbonate (65) (22.27 g.,0.064 mol) in dry toluene (80 mL) containing α, α´-azobisisobutyronitrile (AIBN) (3.02 g., 0.018 mol) was gradually added. Refluxing was continued overnight (~45 hours), and the solvent was removed on a rotary evaporator. The viscous liquid product was purified by the column chromatography on silica gel with hexane containing an increasing proportion of ether (5 % increments). After elution of tin compound, the deoxy-compound (66) was obtained as pale yellow oil (5.28 g.,34.02 % yield). Elemental analysis found : C 58.17 %, H 8.30 %, and $C_{12}H_{20}O_5$ required : C 59.82 %, H 8.19 %.

IR ν_{max}^{neat} (cm^{-1}) : 2980, 2940, 1450, 1370, 1210, 1060, 840. (Fig.27)

PMR ($CDCl_3$) δ (ppm) : 1.24(s,3H);1.29(s,3H);1.36(s,3H);1.45(s,3H);
1.61-1.78(ddd, J_1=13.48 Hz, J_2=10.07 Hz, J_3=4.79 Hz, 1H);
2.06-2.18(dd, J_1=13.47 Hz, J_2=4.19 Hz, 1H);
3.68-3.78(m, 2H);

PMR ($CDCl_3$) **δ** (ppm) : 3.98-4.14(m, 2H);

4.66-4.71(t, 1H);

5.73(d, J=3.67 Hz, 1H).

(Fig.28)

CMR ($CDCl_3$) **δ** (ppm) : 23.57(q), 24.53(q), 24.87(q), 25.16(q),

33.74(t), 65.51(t), 75.26(d), 78.79(d),

78.95(d), 103.98(d), 109.56(s), 111.0(s).

(Fig.30)

MS m/e (% rel. int.) : 245(M^++1,1.68), 229(65.14), 171(9.68), 143

(45.30), 111(46.60), 101(35.73), 85(60.65),

59(41.88), 43(100.00). (Fig.31)

2.3.10 **Preparation of 3-Deoxy-1,2-O-isopropylidene-α-D-glucofuranose (67)** [21-24]

The 3-deoxy sugar (66) (2.8 g., 0.011 mol) was treated with 2 M acetic acid (30 mL) in methanol (25 mL; 45 °C) by continuous stirring. The reaction was continued until no free sugar of 3-deoxy-α-D-glucose appeared (followed by TLC; 10 % methanol in chloroform) and there was only one new spot at R_f=0.50. The solvent was evaporated under reduced pressure at 50 °C to a syrup which dissolved in water (15 mL) and extracted with chloroform (20 mL). The chloroform extract dried over magnesium sulphate, filtered and evaporated to dryness on a rotary evaporator at 40 °C giving starting material (66). The aqueous phase was neutralized with resin (Amberite 45, OH^- form) by continuous stirring until the pH was not acidic to

litmus paper, then filtered, washed the resin with water (2x30 mL), combined the total aqueous layer and evaporated under reduced pressure to give a syrup. Keep the syrup in the desiccator for sevaral days. The syrup was recrystallised from methanol-ether to give a white solid (1.56 g., 66.63 % yield) m.p. 79-80 ^{o}C (lit.22, m.p. 83-84 ^{o}C ; lit. 24, m.p. 80-81 ^{o}C.). Elemental analysis found : C 50.85 %, H 7.91 % and $C_9H_{16}O_5$ required : C 52.91 %, H 7.84 %. (in lit.22, C 52.91 %, H 7.69 %).

IR ν_{max}^{KBr} (cm^{-1}) : 3500-3200, 2990-2880, 1430, 1380, 1210, 1080-1010, 845. (Fig.32)

PMR ($CDCl_3$) δ (ppm) : 1.27(s,3H); 1.48(s,3H); 1.71-1.88(ddd, J=13.25 Hz, J_2=10.15 Hz, J_3=4.63 Hz, 1H); 1.96-2.08(dd, J_1=13.28 Hz, J_2=4.18 Hz,1H); 3.05(s,broad,OH); 3.47-3.57(dd, J_1= 11.47 Hz, J_2=6.67 Hz, 1H); 3.63-3.70(dd, J_1= 11.45 Hz, J_2=3.46 Hz, 1H); 3.81-3.89(m, 1H); 4.11-4.21(m, 1H); 4.69-4.73(t, 1H); 5.76(d, J=3.65 Hz, 1H). (Fig.33)

CMR ($CDCl_3$) δ (ppm) : 26.02(q), 26.64(q), 33.63(t), 63.46(t), 72.11(d), 78.47(d), 80.48(d), 105.09(d), 111.27(s) (Fig.35)

MS m/e (% rel. int.) : 205(M^++1,4.86), 190(6.15), 189(63.63), 143(91.70), 85(88.98), 59(100.00), 43(90.57)

(Fig.36)

2.3.11 **Preparation of 1,2-O-Isopropylidene-3-deoxy-α-D-erythropentodialdofuranose (68)** [22,28]

To a stirred solution of 3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (67) (0.64 g., 0.003 mol) in methanol (20 mL) was added dropwise $NaIO_4$ (0.70 g.,0.003 mol) in water (10 mL). Stirring was continued for an hour, then the solvent was removed by a rotary evaporator at temperature below 50 °C. The residue was extracted with chloroform (3x15 mL) and dried the combined extracts over magnesium sulphate. After filtration and evaporation the solvent, a pale yellow, moderately viscous liquid (68) was obtained which was gradually hardened on standing. The product (68) was isolated as dimer product (0.37 g.,68.75 % yield), R_f=0.69 (10 % methanol in chloroform). Elemental analysis found :C 52.68 %, H 7.16 % and $C_8H_{12}O_4$ required:C 55.81 %, H 6.98 %. (lit.22 found C 54.27 %, H 7.59 %).

IR ν_{max}^{neat} (cm^{-1}) : 3450 (broad), 3000, 2950, 1735, 1450, 1380, 1280-950, 860. (Fig.37)

PMR ($CDCl_3$) δ (ppm) : 1.15(s, 3H); 1.32(s, 3H); 1.63-1.78(ddd, J_1=12.58 Hz, J_2=7.95 Hz, J_3=3.55 Hz, 1H);

PMR ($CDCl_3$) δ (ppm) : 1.93-2.03(dd, J_1=14.20 Hz, J_2=4.81 Hz,1H);
4.00-4.08(dd, J_1=10.60 Hz, J_2=4.95 Hz,1H);
4.60(s, D_2O); 4.79(t, 1H);
4.82(d, J=2.38 Hz, 1H);
5.74(d, J=3.14 Hz, 1H). (Fig.38)

CMR ($CDCl_3$) δ (ppm) : 24.14(q), 24.74(q), 32.05(t), 79.48(d),
81.69(d), 89.19(d) , 104.41(s), 111.21(s).
(Fig.39)

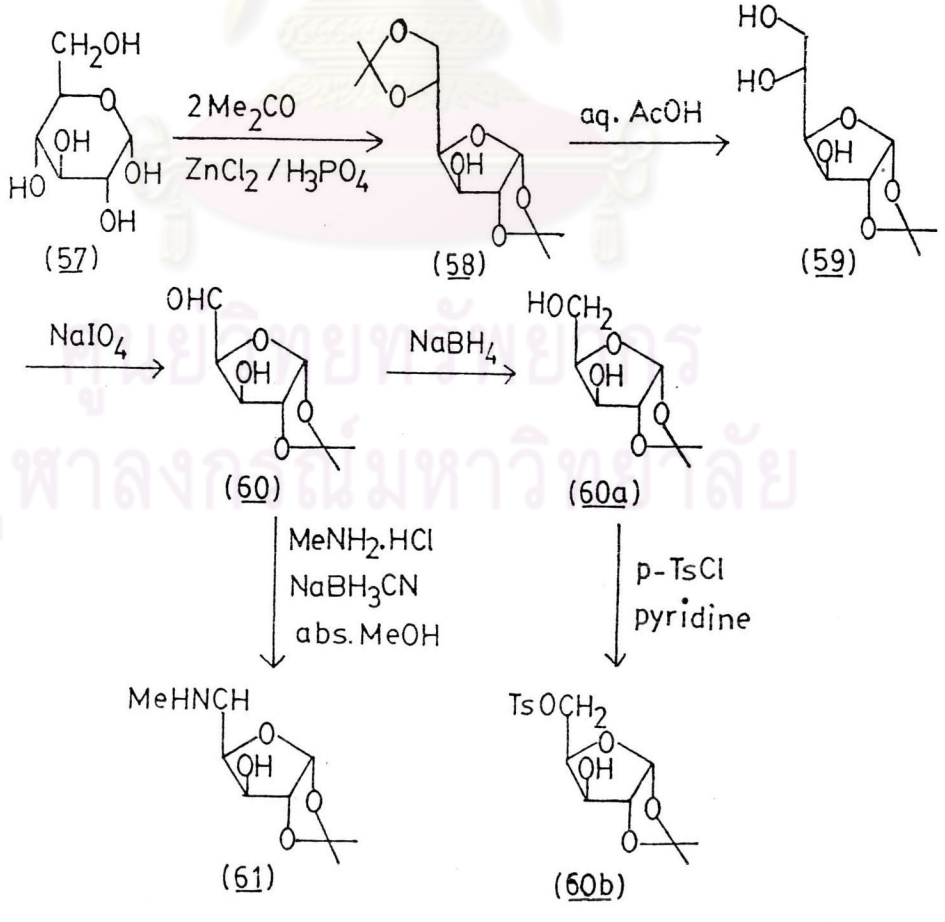
MS m/e (%rel. int.) : 189(M^++H_2O-H, 0.78), 173(M^++H, 1.24), 157
(M^+-CH_3, 49.32), 143(60.86), 85(53.08),
59(77.56), 43(100.00). (Fig.40)

CHAPTER III

RESULTS AND DISCUSSIONS

The synthesis of 1-methyl-2-piperidone and/or its derivative could be proceeded in various routes. In this research, 1,2-O-isopropylidene-α-D-xylofuranose (60a) was synthesized from α-D-glucose (57) as the carbohydrate precursor which was shown in the route 1 and 3,4,5-trihydroxy-1-methyl-2-piperidone (64) was not achieved as shown in scheme V.

3.1 Route 1



3.1.1 1,2:5,6-Di-O-isopropylidene- α-D-glucofuranose (58)

Reaction of α-D-glucose (57) with acetone in presence of zinc chloride and phosphoric acid as catalysts gave the five-membered cyclic acetal and furanose ring product (58). The formation of acetal was carried out to protect the *cis*-orientation of the hydroxyl groups at C_1, C_2, C_5 and C_6 in α-D-glucose by conversion into ether linkages.

The IR spectrum of (58) (Fig.2) gave important absorption peaks at 3420 cm^{-1} of the O-H streching of the hydroxyl group at C_3 and 1220 , 1070 cm^{-1} of the C-O streching in cyclic acetal and furanose ring product.

The PMR data (Fig.3) showed the signals of di-isopropylidene group at δ 1.30-1.48 ppm (4s,12H, $2(CH_3)_2C<$). The doublet at δ 2.57 ppm with the coupling constant of 3.70 Hz which disappeared when shaken with deuterium oxide , indicated hydroxyl proton. The doublet at δ 4.52 ppm with the coupling constant 3.64 Hz ($J_{2,1}$) was assigned to H_2 and δ 5.93 ppm ($J_{1,2}$=3.59 Hz) was assigned to H_1. The doublet of doublet at δ 3.97 ppm with coupling constants of 8.56 Hz ($J_{6b,6a}$) and 5.68 Hz ($J_{6b,5}$) was assigned to H_{6b}. The doublet of doublet at δ 4.06 ppm with coupling constants of 7.55 Hz ($J_{6a,6b}$) and 2.75 Hz ($J_{6a,5}$) was assigned to H_{6a}. The doublet of doublet at δ 4.16 ppm with coupling constants of 7.59 Hz ($J_{5,6b}$) and 6.14 Hz ($J_{5,6a}$) was assigned to H_5. The multiplet at δ 4.31 ppm was assigned to H_3 and H_4.

While the CMR spectrum (Fig.5) exhibited twelve signals which corresponded to twelve carbon atoms in this compound, four quartets at δ 25.08-26.72 ppm. were methyl carbons. A triplet at δ 67.50 ppm. was assigned to methylene carbon at C_6. There were five doublet signals which belonged to methine carbons as labeled at C_1, C_2, C_4, C_3, C_5, respectively. Two singlets at δ 109.44 and 111.69 ppm. were interpreted as quarternary carbons in di-isopropylidene groups.

The mass spectrum (Fig.6) displayed the molecular ion at m/e (% relative intensity) : 261 (0.16, M^++1), and other fragmentation ion peak at m/e 245 (71.28, M^+-CH_3), 187(26.70), 127 (30.15), 101 (100.00), 85 (19.78), 59 (56.57), 43 (72.05). The possible mass fragmentation pattern of this compound was shown in scheme 1.

3.1.2 1,2-O-Isopropylidene-α-D-glucofuranose (59)

The hydrolysis of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (58) with aq. acetic acid in methanol at 45 °C gave 1,2-O-isopropylidene-α-D-glucofuranose (59) after the mixture was neutralized with resin (Amberite 45 OH^- form) and removed the solvent under reduced pressure on a rotary evaporator.

The IR spectrum of triol compound (59) (Fig.7) showed the strong absorption of the hydroxyl group at 3430 and 3320 cm^{-1}.

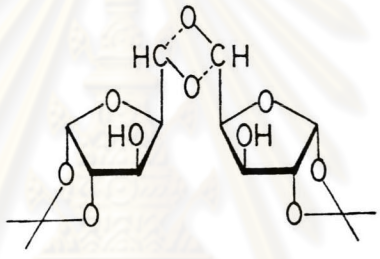
The **PMR** spectrum (Fig.8) displayed the signal of isopropylidene group at δ 1.18 and 1.34 ppm.. The doublet of doublet at δ 3.47 ppm. with coupling constants of 12.07 Hz ($J_{6b,6a}$) and 5.90 Hz ($J_{6b,5}$) was interpreted as H_{6b}. The doublet of doublet at δ 3.63 ppm. with coupling constants of 12.08 Hz ($J_{6a,6b}$) and 2.76 Hz ($J_{6a,5}$) was assigned to H_{6a}. The multiplet at δ 3.74 ppm. was translated to H_5. The doublet of doublet at δ 3.91 ppm. with coupling constants of 8.89 Hz ($J_{4,5}$) and 2.60 Hz ($J_{4,3}$) was assigned to H_4. Three doublets at δ 4.14 ppm. with the coupling constant of 2.65 Hz ($J_{3,4}$), δ 4.51 ppm. with the coupling constant of 3.71 Hz ($J_{2,1}$) and δ 5.84 ppm. with the coupling constant of 3.72 Hz ($J_{1,2}$) were assigned to H_3, H_2 and H_1, respectively. The hydroxyl groups were disappeared in the deuterium oxide as the solvent.

The **CMR** data (Fig.11) showed nine carbon signals in this product. Two quartets of methyl carbons and a singlet of a quarternary carbon at C_6 disappeared because they were hydrolyzed in aq. acetic.

The mass spectrum (Fig.13) showed the molecular ion peak at m/e (% rel. int.): 221 (0.16, M^++1), 205 (39.77, M^+-CH_3), 159 (32.62), 127 (17.82), 101 (13.65), 85 (35.96), 73 (53.21), 59 (100) and 43 (46.60). The possible mass fragmentation pattern of this compound was shown in scheme 2.

3.1.3 1,2-O-Isopropylidene- α-D-erythropentodialdofuranose (60)

The oxidaton of 1,2-O-isopropylidene- α-D-glucofuranose (59) with sodium metaperiodate ($NaIO_4$) in aq.methanol afforded 1,2-O-isopropylidene-α-D-erythropentodialdofuranose (60). After the mixture was extracted with chloroform and evaporated to give viscous liquid which gradually hardened on standing. This liquid product was isolated as dimer or hemiacetal compound that was shown in the possible structure below.



The IR absorption band of (60) (Fig.14) exhibited the important peaks of the hydroxyl group at 3440 cm^{-1} and the C=O streching of an aldehyde group at 1735 cm^{-1}.

The PMR data (Fig.16) showed the signal of isopropyl proton group at δ 1.16 and 1.33 ppm. The doublet of doublet at δ 3.85 ppm with coupling constants of 7.61 Hz ($J_{4,5}$) and 2.78 Hz ($J_{4,3}$) was assigned to H_4. Four doublets with coupling constants at δ 4.09 ppm ($J_{3,4}$=2.72 Hz), δ 4.49 ppm ($J_{2,1}$=3.61 Hz), δ 4.94 ppm ($J_{5,4}$=7.69 Hz) and δ 5.83 ppm ($J_{1,2}$=3.62 Hz) were translated to H_3, H_2, H_5 and H_1, respectively. The hydroxyl group was shown at δ 4.62 ppm next to the deuterium oxide at δ 4.60 ppm.

Moreover, the PMR spectrum in Fig.16(a) showed the aldehyde proton at δ 9.67 ppm and the CMR spectrum in Fig.17(b) showed the carbonyl carbon at δ 201 ppm when this product was dissolved in $CDCl_3$. This product did not show the aldehyde proton in Fig.16(b) when it was dissolved in DMSO-d_6. When it was heated at 80 ^{o}C in DMSO-d_6, the dimer compound was broken to obtain aldehyde product which showed the aldehyde proton at δ 9.58 ppm as shown in Fig.16(c).

The **CMR** spectrum (Fig.17) showed eight carbon atoms in this compound as labeled.

The mass spectrum (Fig.18) showed the molecular ion peak at m/e (% rel. int.) : 203(34.01, $M^{+}+CH_3$), 173(20.02, $M^{+}-CH_3$),159(44.51), 113(90.01), 85(60.75), 71(40.54), 59(100.00), 43(95.39).

3.1.4 1,2-O-Isopropylidene-α-D-xylofuranose (60a)

The dimer compound (60) was reduced with sodium borohydride in methanol to give alcoholic product (60a). The alcoholic solid was moistened easily when it was left in the air.

The IR spectrum of (60a) (Fig.19) showed the hydroxyl group at 3050-3700 cm^{-1} and no C=O streching of aldehyde group at 1735 cm^{-1}.

The **PMR** spectrum (Fig.20) illustrated the signals of protons which corresponded to the dimer compound (60) (Fig.15). The disappearance of the doublet signal at δ 4.94 ppm of the dimer proton in (Fig.20) indicated that the aldehyde

group had been converted to methylene group at δ 3.88 ppm and the hydroxyl group which was exchanged with the deuterium of deuterium oxide.

The structure of the compound (60a) was confirmed by the CMR spectrum (Fig.21) which revealed eight signals corresponded to eight carbons of this compound. Furthermore, the DEPT-135 CMR spectrum of compound (60a) in Fig.21(a) exhibited the methylene carbon at δ 58.17 ppm (phase down).

The mass spectrum of compound (60a) showed the fragmentation ion peak m/e (% rel. int.) : 201(30.50), 159(20.81), 99(23.36), 85(25.53), 59(53.75), 44(70.61), 43(100.00). This compound (60a) did not display the molecular ion peak.

3.1.5 1,2-O-Isopropylidene-5-O-toluene-*p*-sulphonyl-α-D-xylofuranose (60b)

1,2-O-Isopropylidene-5-O-toluene-*p*-sulphonyl-α-D-xylofuranose (60b) was prepared by tosylation of the hydroxyl compound (60a) with *p*-toluenesulphonyl chloride by using pyridine as solvent and N,N-dimethylaminopyridine as catalyst. The brown liquid product was not purified.

The PMR data (Fig.22a) showed the mixed signals of the starting substance (60a) and *p*-toluenesulphonyl chloride.

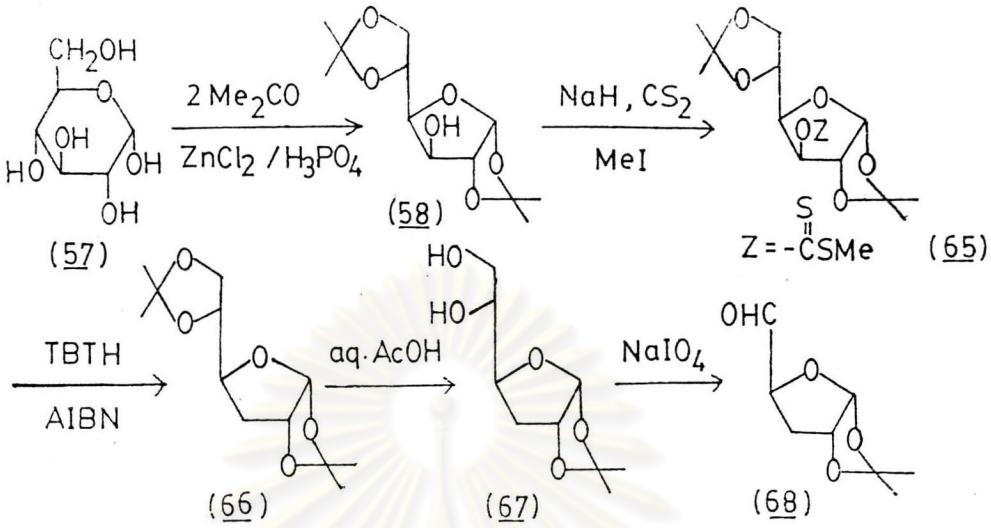
3.1.6 N-Methylbutylamine and 5-N-Methyl-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (61)

Reductive amination reaction of butyraldehyde with methylamine hydrochloride and sodium cyanoborohydride at pH 6-8 led to N-methylbuthylamine via reductive amination of the carbonyl group. This reduction reaction of butyraldehyde was used as form a model to optimize the reaction condition of dimer compound (60) methylamine hydrochloride and sodium cyanoborohydride in absolute methanol. A yellow liquid, compound (61) was obtained.

The PMR spectrum of compound (61) was shown in Fig.22d. The PMR spectrum of compound (61) indicated that it was not the title compound.

The synthesis of "1,2-O-isopropylidene-α-D-xylofuranose" (60a) was used as model to synthesize "1,2-O-isopropylidene-3-deoxy-α-D-erythropentodialdofuranose" (68) as shown in route 2. While the synthesis of 3,5-dihydroxy-1-methyl-2-piperidone" (72) from α-D-glucose (57) was not accomplished as shown in Scheme VI.

3.2 Route 2



3.2.1 3-O-(1,2:5,6-Di-O-isopropyl-α-D-glucofuranose)-S-methyl dithiocarbonate (65)

Alkaline metal of O-alkyl dithiocarbonate (e.g. $RO-CS-S^-Na^+$ or the xanthate) was prepared by the strong basic reaction of carbon disulphide with an alcohol (58) and sodium hydride. Imidazole was used as catalyst for the first step of the reaction in tetrahydrofuran. Alkylation of this xanthate salt with methyl iodide led to an O,S-dialkyl dithiocarbonate (e.g. RO-CS-SMe, the xanthate ester). [25]

$$R\text{-}OH \xrightarrow{NaH} RO^-Na^+ \xrightarrow{CS_2} ROCSS^-Na^+ \xrightarrow{MeI} ROCSSMe + NaI$$

The xanthate ester (65) was isolated by extraction with chloroform, dried over magnesium sulphate, filtered and then evaporated to give a viscous yellow liquid.

Some important absorption bands in the IR spectrum (Fig.23) of the xanthate ester (60) were 1130-1300 cm^{-1} of C=S streching and 1000-1130 cm^{-1} of C-O and C-S streching of the five-membered acetal ring and furanose ring.

The PMR spectrum (Fig.24) showed the signals of di-isopropylidene group at δ 1.29-1.39 ppm (4S,12H, $2(CH_3)_2<$). The singlet proton at δ 2.57 ppm was the methyl group which adjoined to sulfur atom (S-Me). The doublet at δ 4.65 ppm with the coupling constant of 3.82 Hz ($J_{2,1}$) was interpreted to H_2. The doublet of doublet at δ 5.88 ppm with coupling constants of 3.82 Hz ($J_{1,2}$) and 2.32 Hz ($J_{3,2}$) belonged to to H_1 and H_3. The multiplet at δ 4.05 ppm was assigned to H_5 and H_{6b} and the multiplet at δ 4.28 ppm was interpreted to H_4 and H_{6a}. The doublet of doublet at δ 5.88 ppm with coupling constants of 3.82 Hz ($J_{1,2}$) and 2.32 Hz ($J_{3,2}$) was assigned to H_1 and H_3.

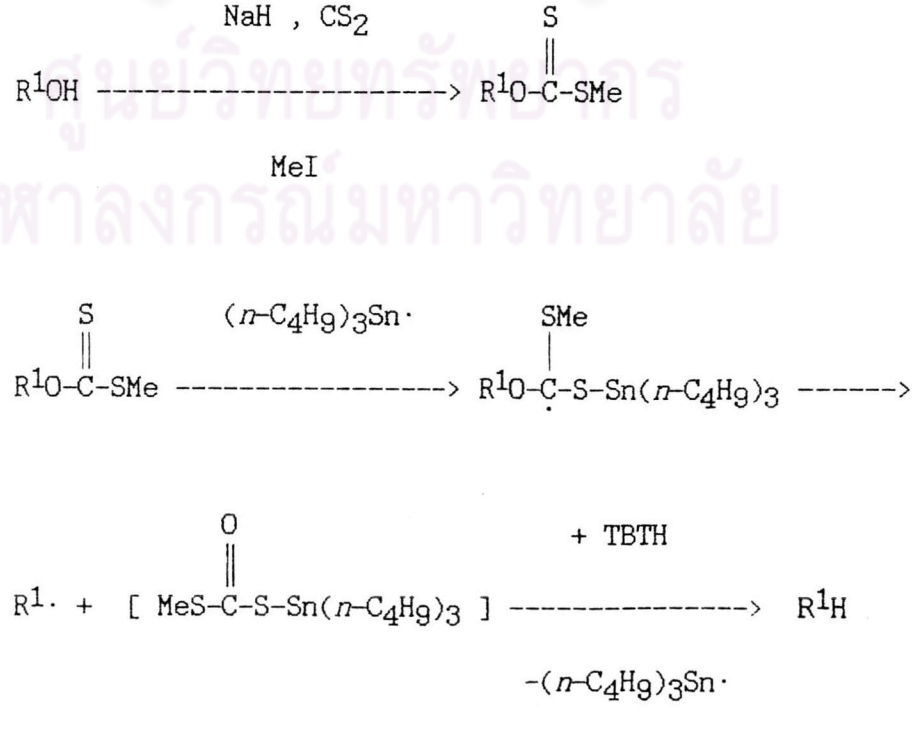
The CMR spectrum (Fig.25) indicated fourteen carbon signals which corresponded to fourteen carbon atoms in this spectrum. Four quartets at δ 25.26-26.70 ppm were assigned to methyl carbons. The other quartet at δ 19.18 ppm was the S-Me group. Five doublet signals were shown to be methine carbons as labeled to C_1, C_2, C_4, C_3, C_5, respectively. Two singlet carbons at δ 109.23 and 112.29 ppm exhibited the quarternary carbons in di-isopropylidene groups. A singlet at δ 214.64 ppm was assigned to carbonyl carbon in the xanthate ester.

The mass spectrum (Fig.26) exhibited the molecular ion peak at m/e (% rel. int.) : 335 (15.32, M^+-CH_3), 317 (22.07),

303 (27.77), 245 (9.42), 127 (10.07), 101 (100.00), 75 (26.58), 59(18.82), 43(51.11). The possible mass fragmentation pattern of this compound was shown in scheme 3.

3.2.2 **1,2:5,6-Di-O-isopropylidene-3-deoxy- α-D-gluco-furanose (66)**

The deoxygenation of secondary hydroxyl group was converted into O-alkyl S-methyldithiocarbonate (xanthate ester) and reduced directly with tri-*n*-butyltin hydride (TBTH) to give good yields of the corresponding hydrocarbon after chromatography. The mechanism of this reaction was radical character. Azobisisobutyronitrile (AIBN) was used as an initiator to initiate the chain reaction step at 60 °C. The radical R^1 was trapped by the hydride radical as illustrated in equation below. [27]



The **IR** spectrum of this compound **(66)** (Fig.27) showed the strong absorption peak of methylene group vibration at 1450 cm^{-1}.

The **PMR** data (Fig.28) indicated the signal of di-isopropylidene groups at δ 1.24-1.45 ppm (4S,12H,**2(CH_3)C<**). The doublet of doublet of doublet at δ 1.69 ppm with coupling constants of 13.48 Hz ($J_{3a,3b}$), 10.07 Hz ($J_{3a,4}$) and 4.79 Hz ($J_{3a,2}$) was assigned to H_{3a}. The doublet of doublet at δ 2.12 ppm with coupling constants of 13.47 Hz ($J_{3b,3a}$) and 4.19 Hz ($J_{3b,4}$) was interpreted to H_{3b}. Two multiplets at δ 3.73 ppm and δ 4.06 ppm were translated to H_4, H_5, H_{6a}, and H_{6b}. The triplet at δ 4.68 ppm was assigned to H_2. And the doublet of doublet at δ 5.73 ppm with coupling constant of 3.67 Hz ($J_{1,2}$) belonged to H_1.

The **CMR** data (Fig.30) showed twelve signals which was labeled to twelve carbons. The singlet at δ 214.64 ppm was disappeared and there was a singlet at δ 33.74 ppm which belonged to methylene carbon at C_3.

The mass spectrum (Fig. 31) exhibited the molecular ion peak at m/e (% rel. int.) : 245 (1.68,M^++1) and other fragmentation ion peak at m/e 229 (M^+-CH_3, 65.14), 171 (9.68), 143 (43.30) , 111 (46.60) , 101 (35.73) , 85(60.65), 59 (41.88) , 43 (100.00).

3.2.3 3-Deoxy-1,2-O-isopropylidene- α-D-glucofuranose (67)

The compound (66) was hydrolyzed with aq. acetic acid in methanol at 45 °C obtained 3-Deoxy-1,2-O-isopropylidene- α-D-glucofuranose (67).

Some important absorption bands in the IR spectrum (Fig.32) of this diol compound were 3500-3200 cm^{-1} of OH streching and 1210, 1080-1010 cm^{-1} of C-O stretching in cyclic acetal, furanose ring and hydroxyl group, respectively.

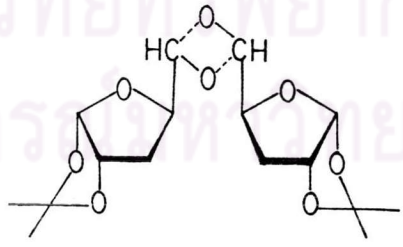
The PMR spectrum (Fig.33) revealed two singlets of isopropylidene group at δ 1.27 and 1.48 ppm. The doublet of doublet of doublet at δ 1.79 ppm with coupling constants of 13.25 Hz ($J_{3a,3b}$), 10.15 Hz ($J_{3a,4}$) and 4.63 Hz ($J_{3a,2}$) was assigned to H_{3a}. While the doublet of doublet at δ 2.02 ppm with coupling constants of 13.28 Hz ($J_{3b,3a}$) and 4.18 Hz ($J_{3b,4}$) belonged to H_{3b}. The broad singlet at δ 3.05 ppm showed the hydroxyl groups in this compound. Two doublet of doublet signals at δ 3.52 ppm with coupling constants of 11.47 Hz ($J_{6b,6a}$) and 6.67 Hz ($J_{6b,5}$) and δ 3.67 ppm with coupling constants of 11.45 Hz ($J_{6a,6b}$) and 3.46 Hz ($J_{6a,5}$) were interpreted as H_{6b} and H_{6a}, respectively. The triplet at δ 4.71 ppm belonged to H_2. Two multiplets at δ 3.85 ppm and δ 4.16 ppm were assigned to H_5 and H_4. The doublet at δ 5.76 ppm with the coupling constants of 3.65 Hz (J_1,J_2) was assigned to H_1.

The **CMR** spectrum of this compound (67) (Fig.35) exhibited nine signals. There were two quartets at δ 26.02 and 26.64 ppm which belonged to methyl carbon and the only singlet of a quarternary carbon was appeared at δ 111.27 ppm.

The mass spectrum (Fig.36) showed the molecular ion at m/e (% rel. int.) : 205 (4.86 , M^++1) and other fragmentation ion peak at m/e 190 (6.15) , 189 (63.63) , 143 (91.70) , 85 (88.98) 59 (100.00) , 43 (90.57).

3.2.4 1,2-O-Isopropylidene-3-deoxy-α-D-erythropentodialdofuranose (68)

The periodate oxidation of 1,2-O-isopropylidene-3-deoxy-α-D-glucofuranose (67) with sodium metaperiodate in aq. methanol gave 1,2-O-Isopropylidene-3-deoxy-α-D-erythropentodialdofuranose (68). The pale viscous yellow liquid product was isolated as dimer compound which gradually hardened on standing. The possible structure was shown below.



The **IR** absorption band (Fig.37) showed the important peak at 3450 (broad) cm^{-1} of OH streching because of there was a molecule of H_2O in this compound. The absortion peaks at 1735, 1380 and 1000 cm^{-1} were indicated to C=O streching of aldehyde, isopropylidene group and C-O streching

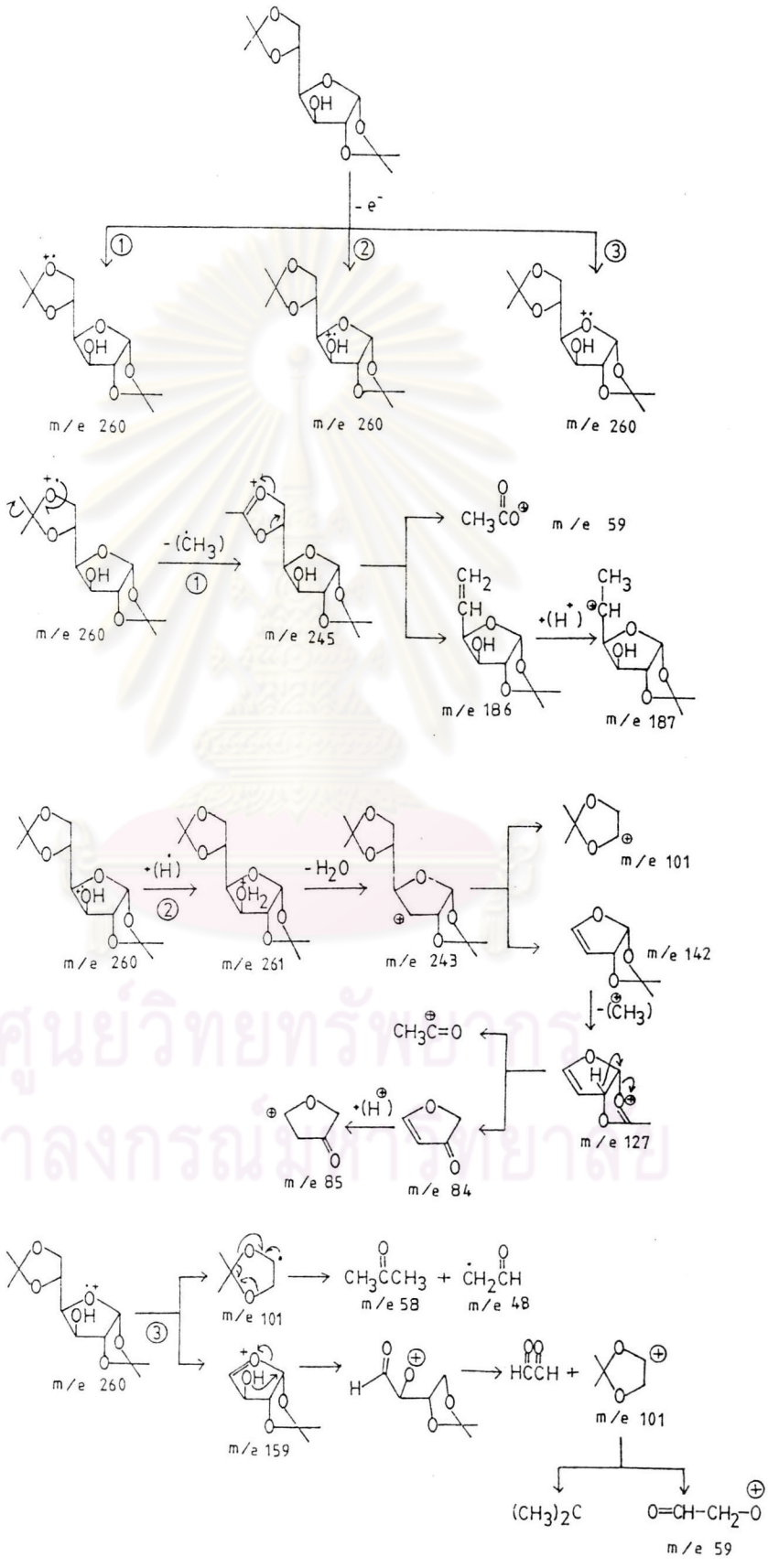
in acetal ring, respectively.

The **PMR** spectrum (Fig.38) showed the signals which corresponded to compound (67). The doublet at δ 4.82 ppm was assigned to aldehyde proton **(H_5)** which formed dimer product and the hydroxyl group and two doublet of doublet signals of H_{6a}, H_{6b} were diappeared. Moreover, the PMR spectrum of this compound in Fig.38(b) showed the aldehyde proton at δ 9.67 ppm and the CMR spectrum in Fig.39(a) showed the carbonyl carbon at δ 200 ppm when it was dissolved in $CDCl_3$.

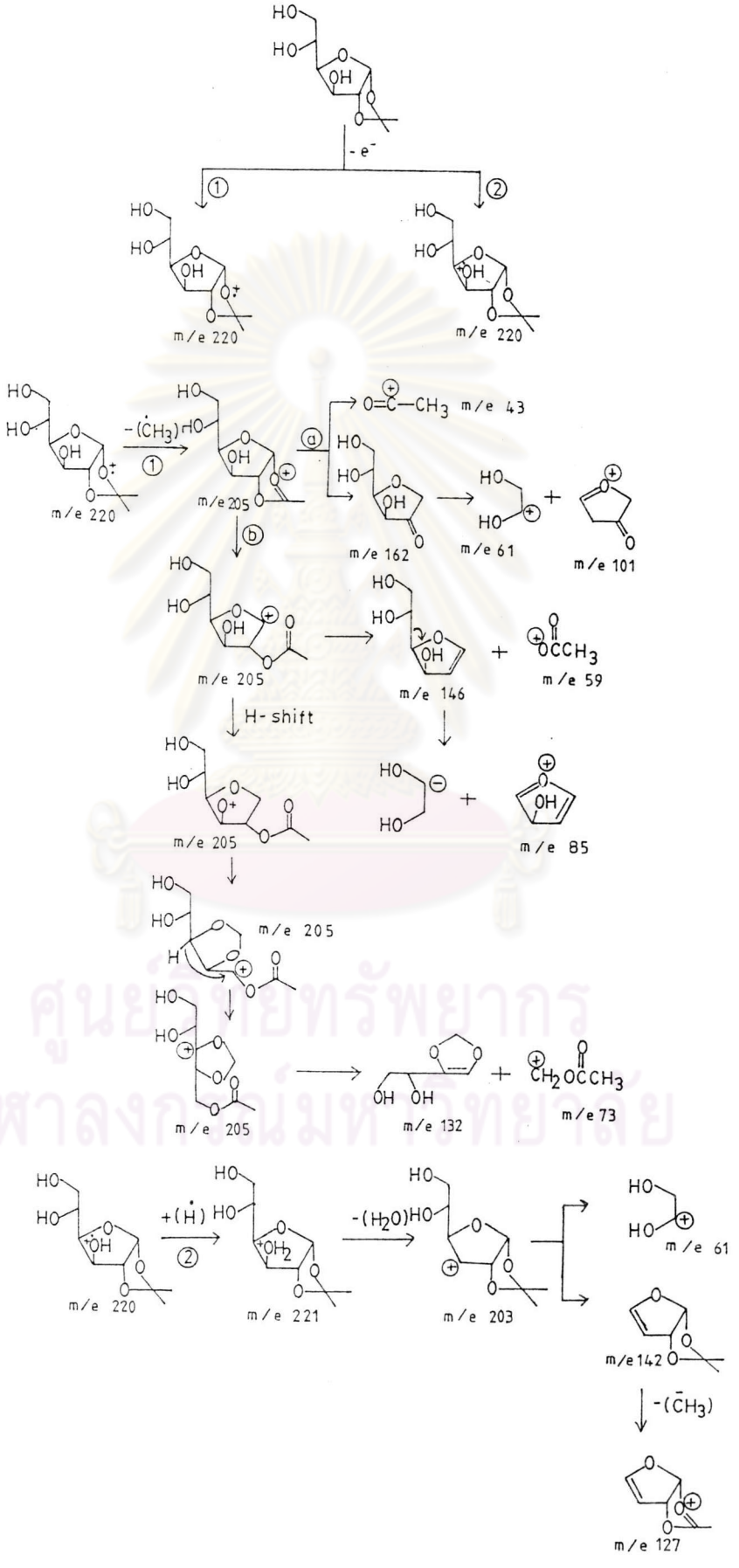
The **CMR** data (Fig.39) exhibited eight signals corresponding to the number of carbons of this product.

The mass spectrum (Fig.40) showed the molecular ion peak at m/e (% rel. int.) : 189(0.78, M^++H_2O-H), 173(1.24, M^++H) and other fragmentation ion peak at m/e 157(49.32, M^+-CH_3), 143(60.86), 85(53.08), 59(77.56) and 43(100.00).

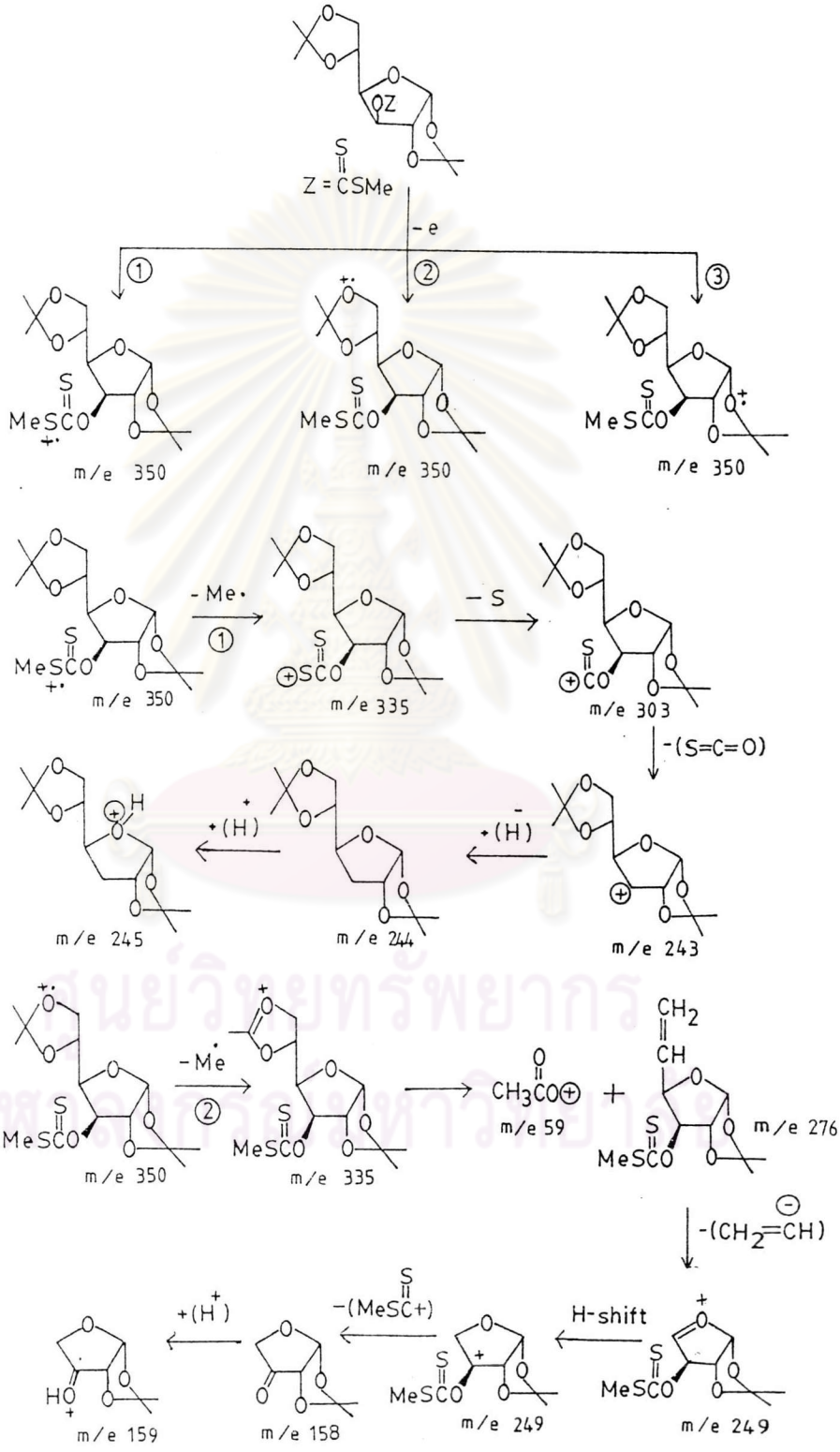
Scheme 1 The possible mass fragmentation of " 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose " (58)



Scheme 2 The possible mass fragmentation of " 1,2-O-isopropylidene-α-D-glucofuranose " (59)

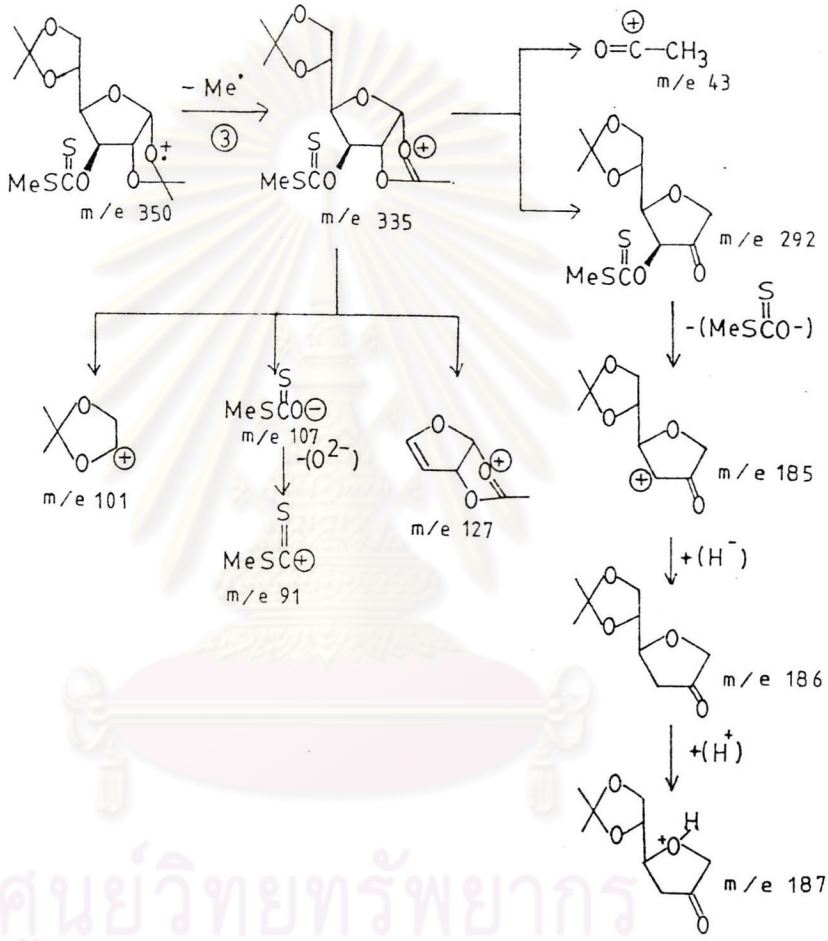


Scheme 3 The possible mass fragmentation of " 3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose) S-methyldithiocarbonate " (65)



Scheme 3 The possible mass fragmentation of " 3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose) S-methyldithiocarbonate " (65)

(continued)



CHAPTER IV

CONCLUSION

1,2-O-Isopropylidene-α-D-xylofuranose (60a) was prepared from the carbohydrate precursor, α-D-glucose (57). The synthesis was first carried out to protect the cis-orientation of the hydroxyl group by the formation of acetals and furanose ring compound (58). An acetal ring at 5,6-position of carbon was hydrolyzed to give 1,2-O-isopropylidene-α-D-glucofuranose (59) which converted to 1,2-O-isopropylidene-α-D-erythropentodialdo-furanose (60) by periodate oxidation method. The product (60) was obtained as a dimer compound whose structure was confirmed by the spectroscopic data. Noteworthy, the ^{1}H-NMR and ^{13}C-NMR did not show the signal of aldehyde proton and carbonyl carbon. The reduction of dimer compound (60) gave 1,2-ispropylidene-α-D-xylofuranose (60a).The reductive amination of butyradehyde with methylamine hydrochloride and sodium cyano-hydridoborate afforded *N*-methylbutylamine served as a model reaction. This reaction was used to optimize the reductive amination condition for the dimer product (60) but the expected amine compound (61) was not obtained under this reaction condition. The tosylation of hydroxyl compound (60a) was obtained as a brown liquid product (60b) which was not purified for the next step. Therefore, the synthesis of 3,4,5-trihydroxy-1-methyl-2-piperidone (64) which was a 1-methyl-2-piperidone

derivative, could not be prepared by this pathway.

In another synthetic pathway, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (58) was converted to O-alkyl-S-methyldithiocarbonate (xanthate ester) (65) and directly reduced with tri-n-butyltin hydride (TBTH) to give the deoxygenated compound, 1,2:5,6-di-O-isopropylidene-3-deoxy-α-D-glucofuranose (66). After hydrolysis under the same condition as in route 1, the diol product (67) was obtained in good yields. Periodate oxidation of compound (67) gave the dimer compound of the deoxygenated product, 1,2-O-isopropylidene-3-deoxy-α-D-erythropentadialdofuranose (68). This product was isolated as dimer compound (60) and (68) which gradually solidified on standing. The synthesis of 3,5-dihydroxy-1-methyl-2-piperidene was not achieved in this pathway because the yield of compound (68) was too little and could not be purified for the next step.

In this research work, some known compounds were prepared and their spectral data were identified as shown in figure 1-40 which were not previously reported.

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APPENDIX

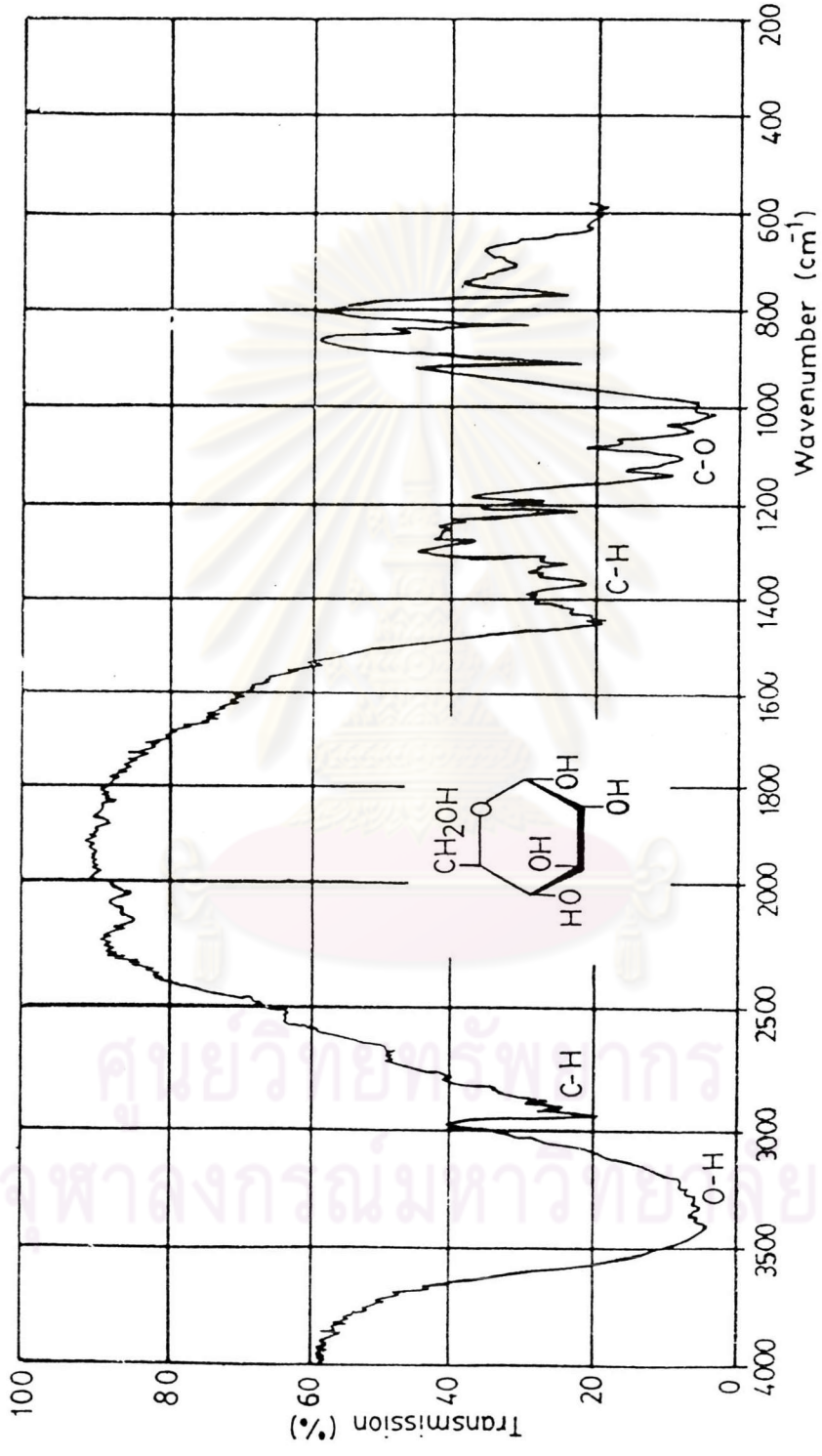

Figure 1 The IR spectrum of α-D-glucose (57)

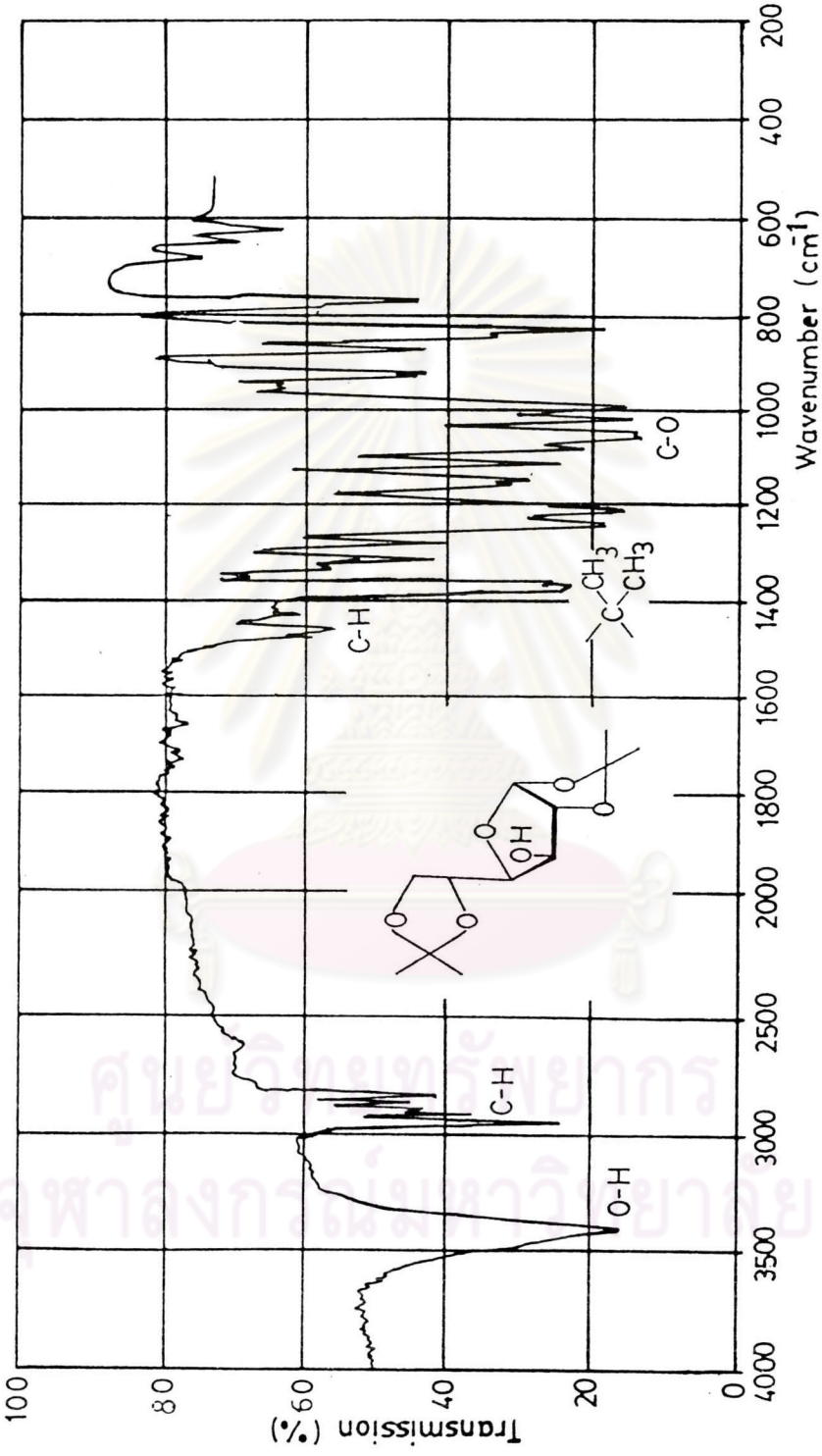

Figure 2 The IR spectrum of 1,2:5,6-di-O-isopropylidene- α -D- glucofuranose (58)

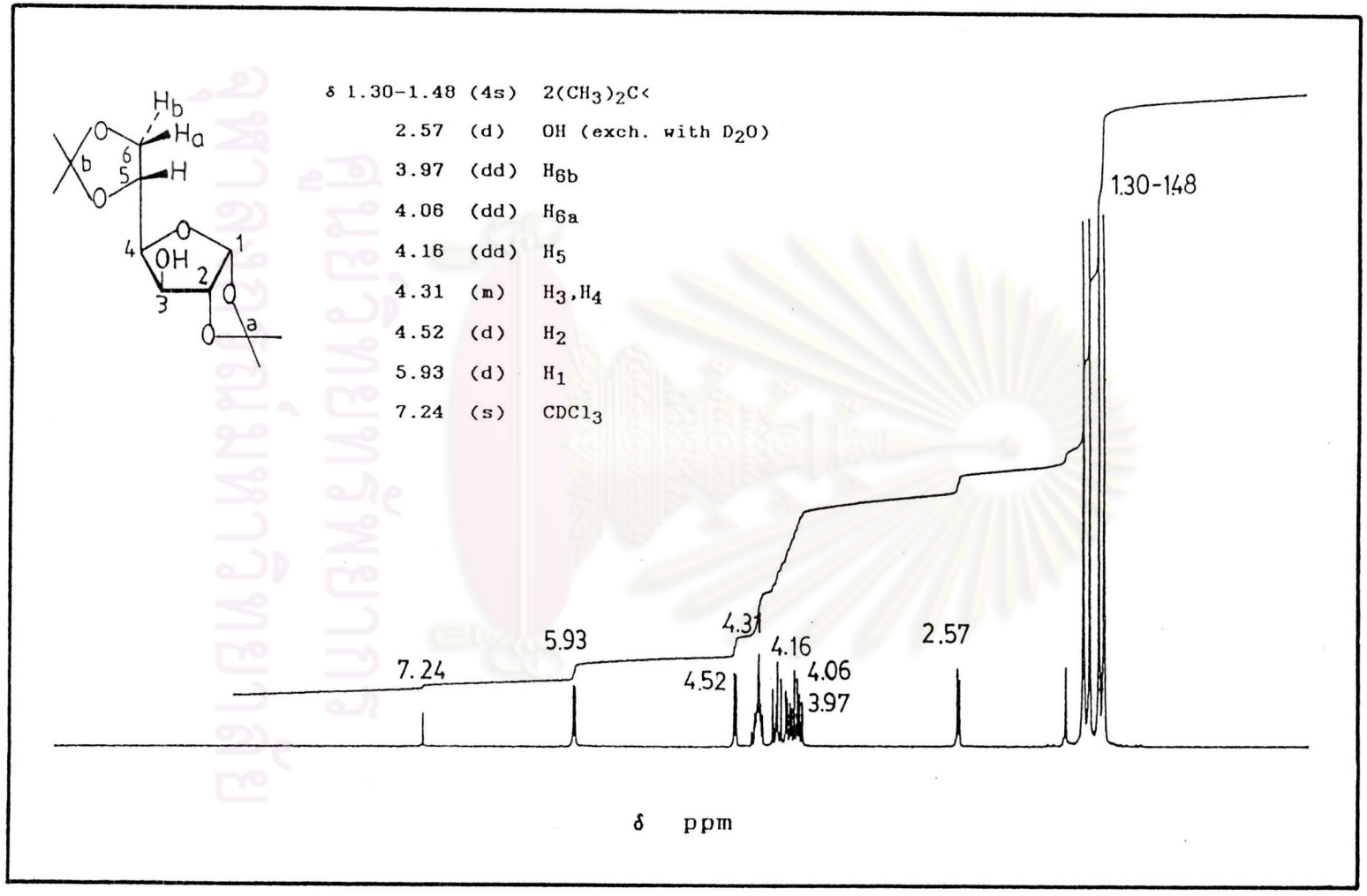

Figure 3 The PMR spectrum of 1,2:5,6-di-O-isopropylidene- α-D- glucofuranose (58)

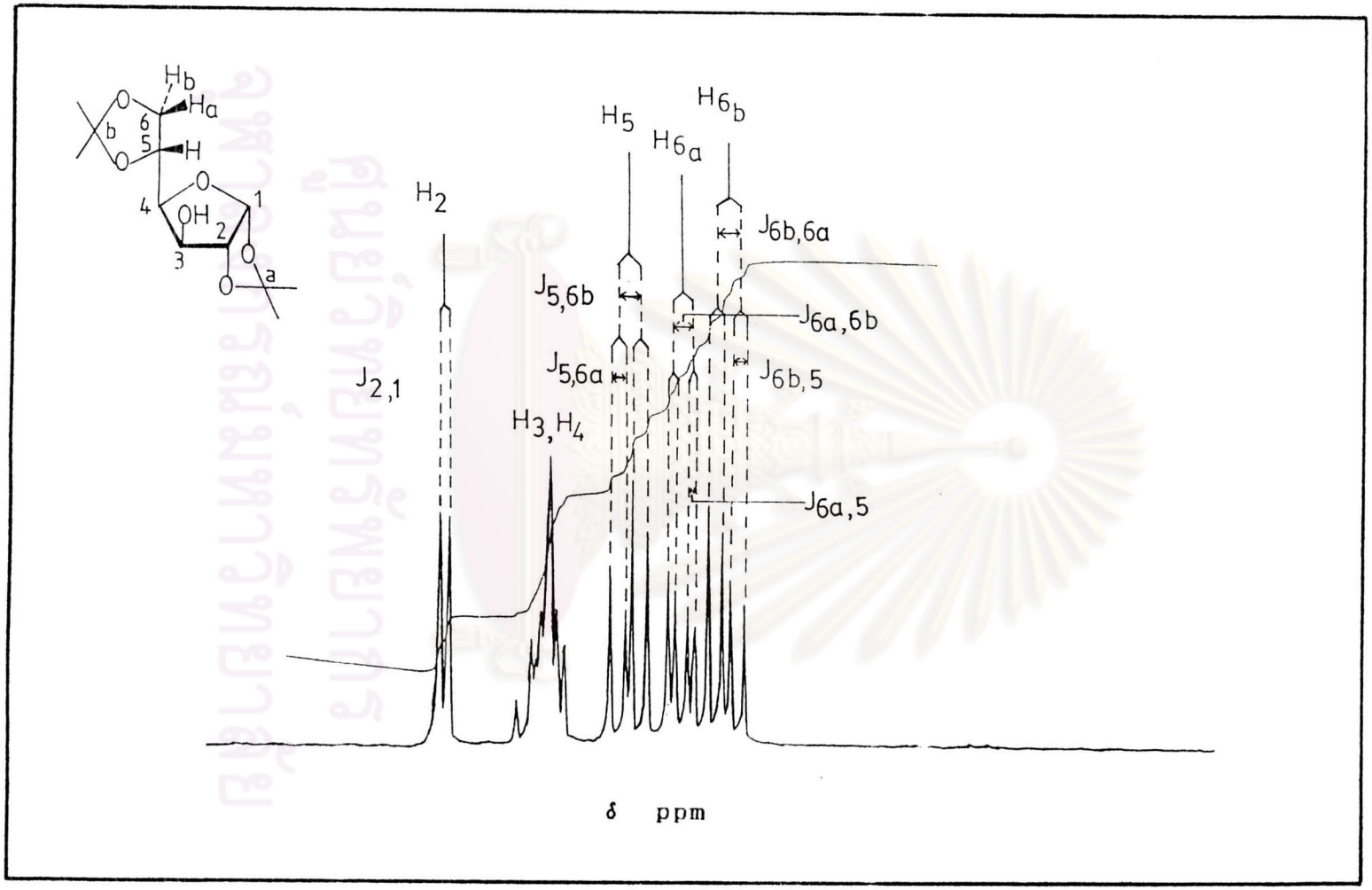

Figure 4 The PMR spectrum of compound (58) showed protons coupling and coupling constants

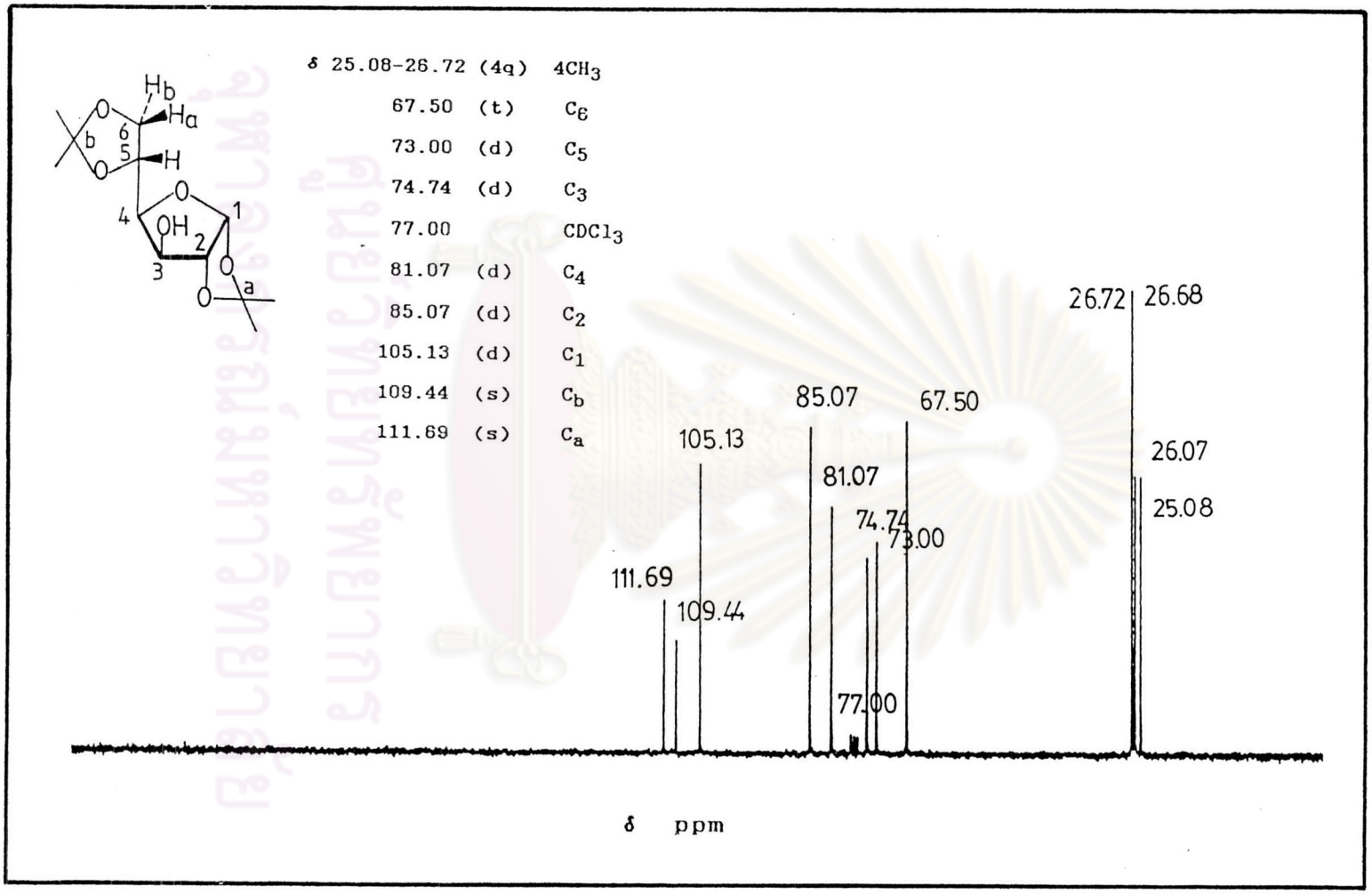

Figure 5 The CMR spectrum of 1,2:5,6-di-O-isopropylidene-α-D- glucofuranose (58)

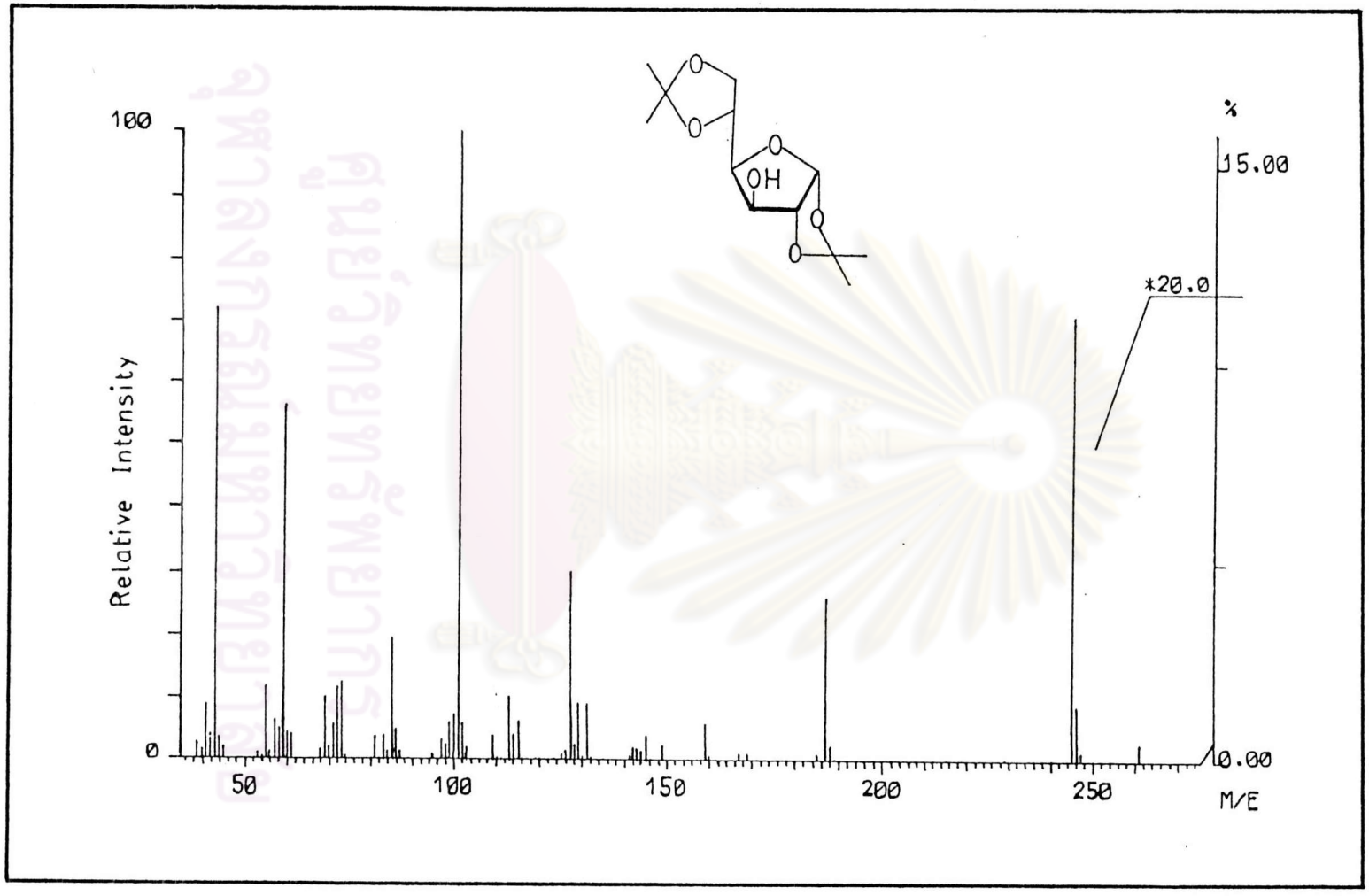

Figure 6 The mass spectrum of 1,2:5,6-di-O-isopropylidene-α-D- glucofuranose (58)

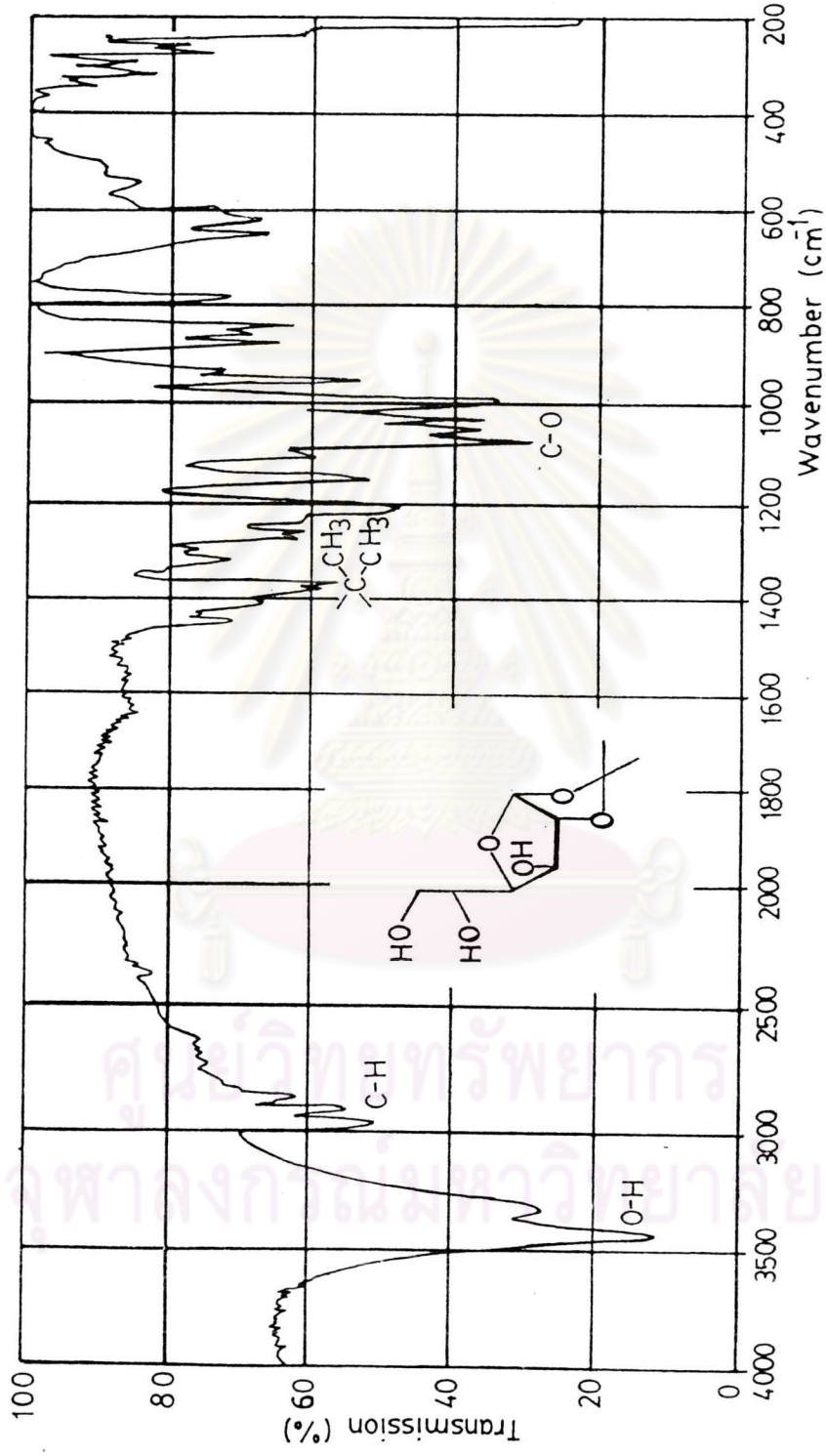

Figure 7 The IR spectrum of 1,2-O-isopropylidene- α-D-glucofuranose (59)

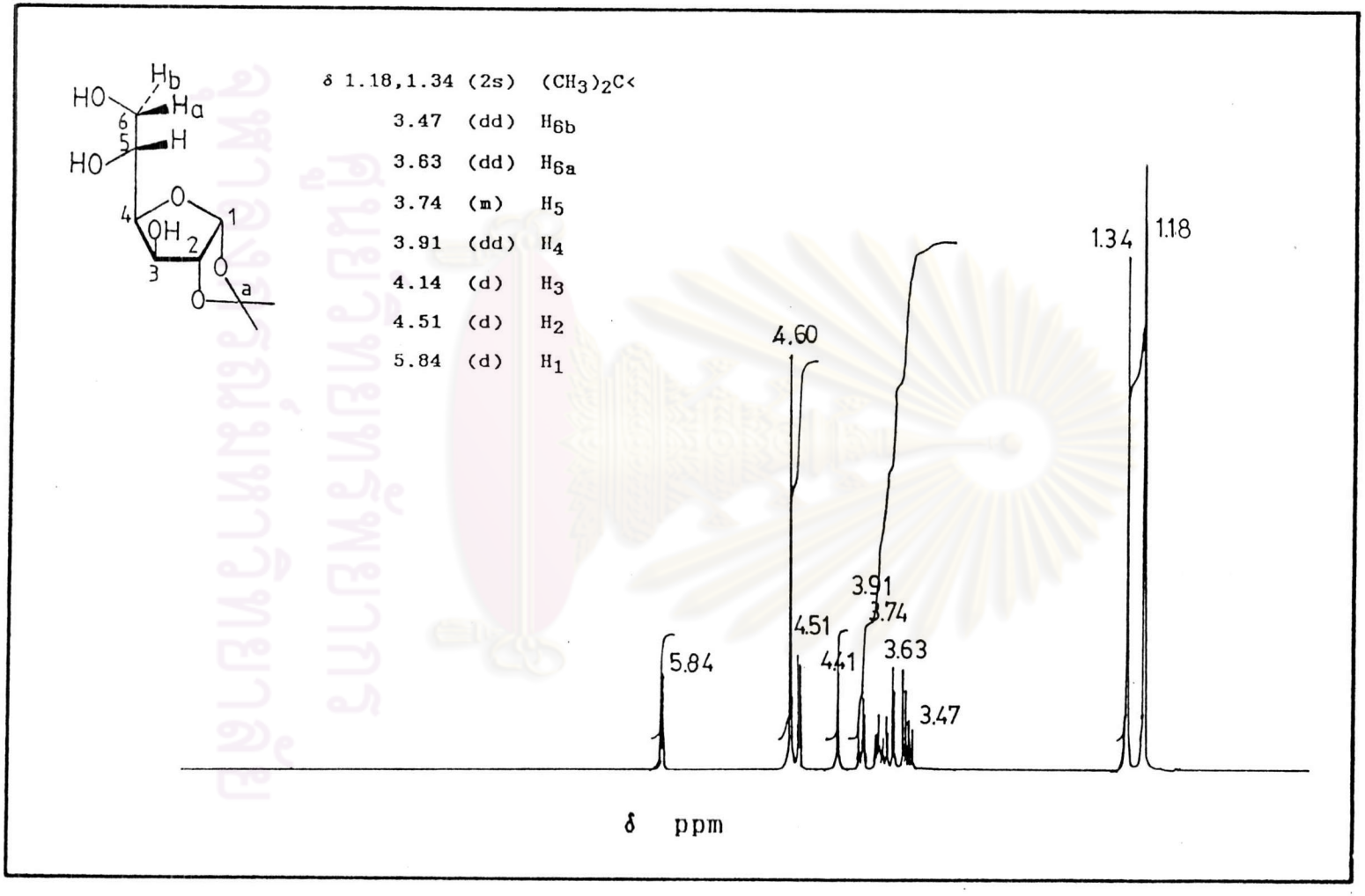

Figure 8 The PMR spectrum of 1,2-O-isopropylidene-α-D-glucofuranose (59)

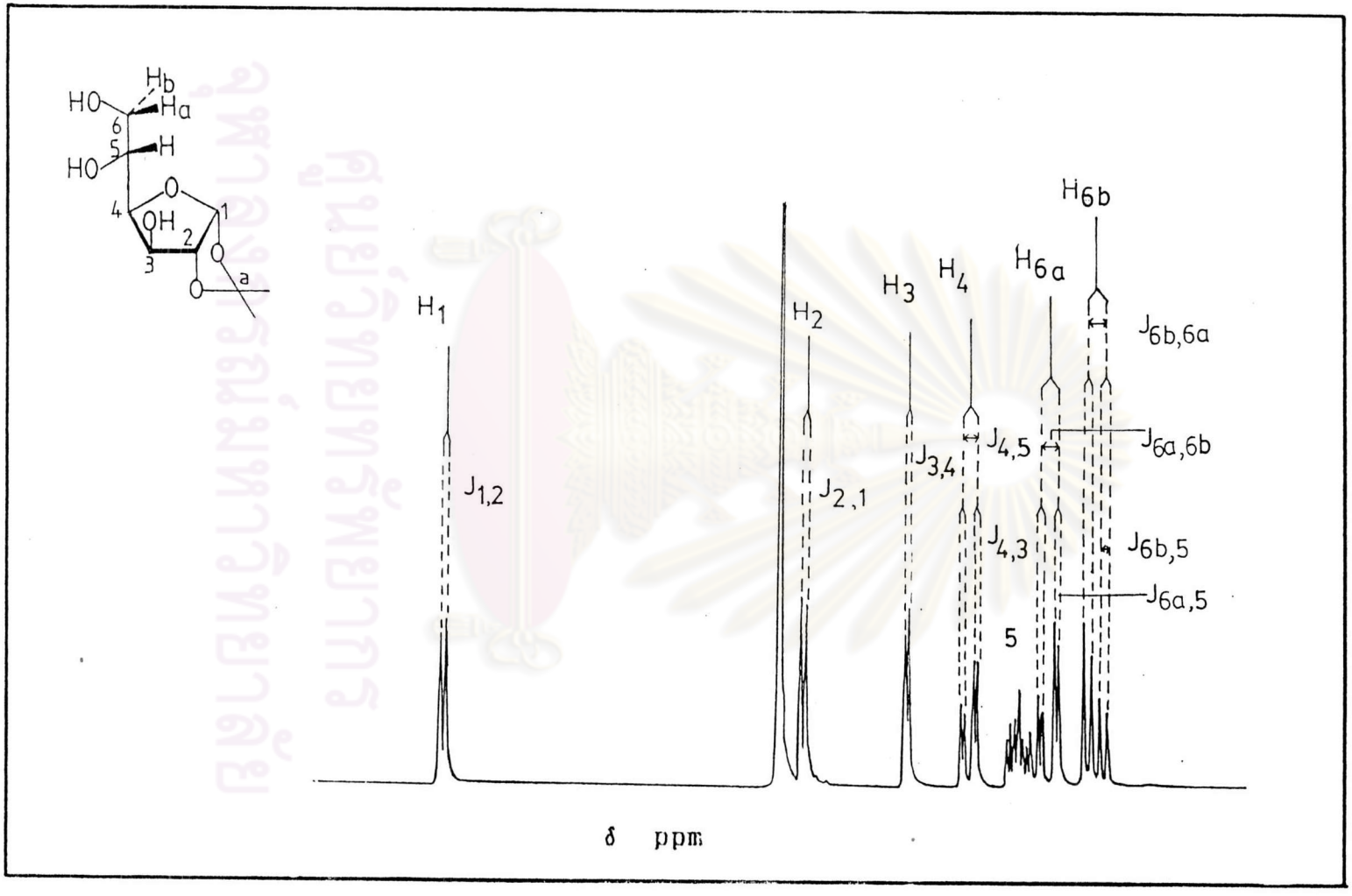

Figure 9 The PMR spectrum of compound (59) showed protons coupling and coupling constants

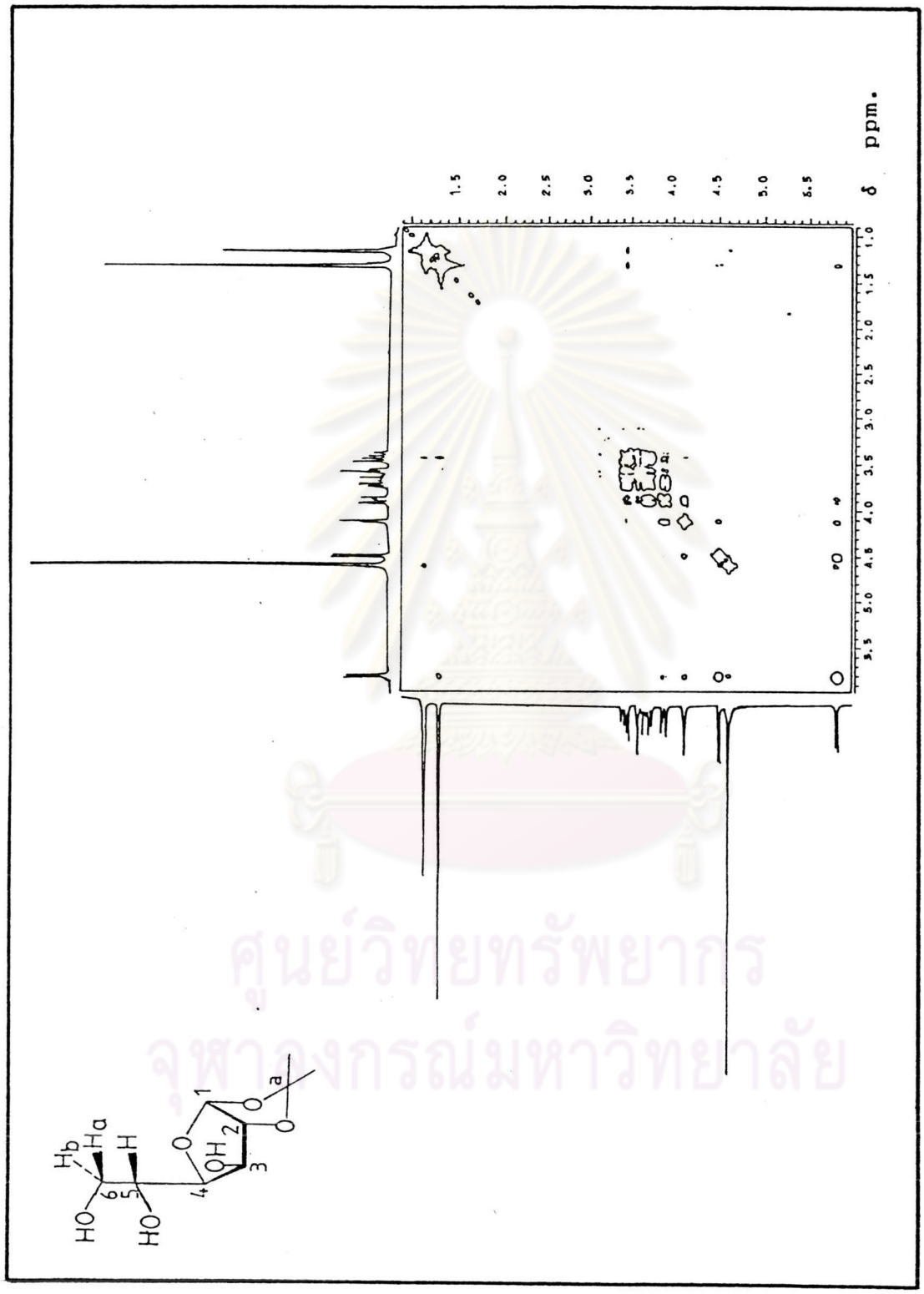

Figure 10 The ^{1}H COSY correlated spectrum of 1,2-O-isopropylidene-α-D-glucofuranose (59)

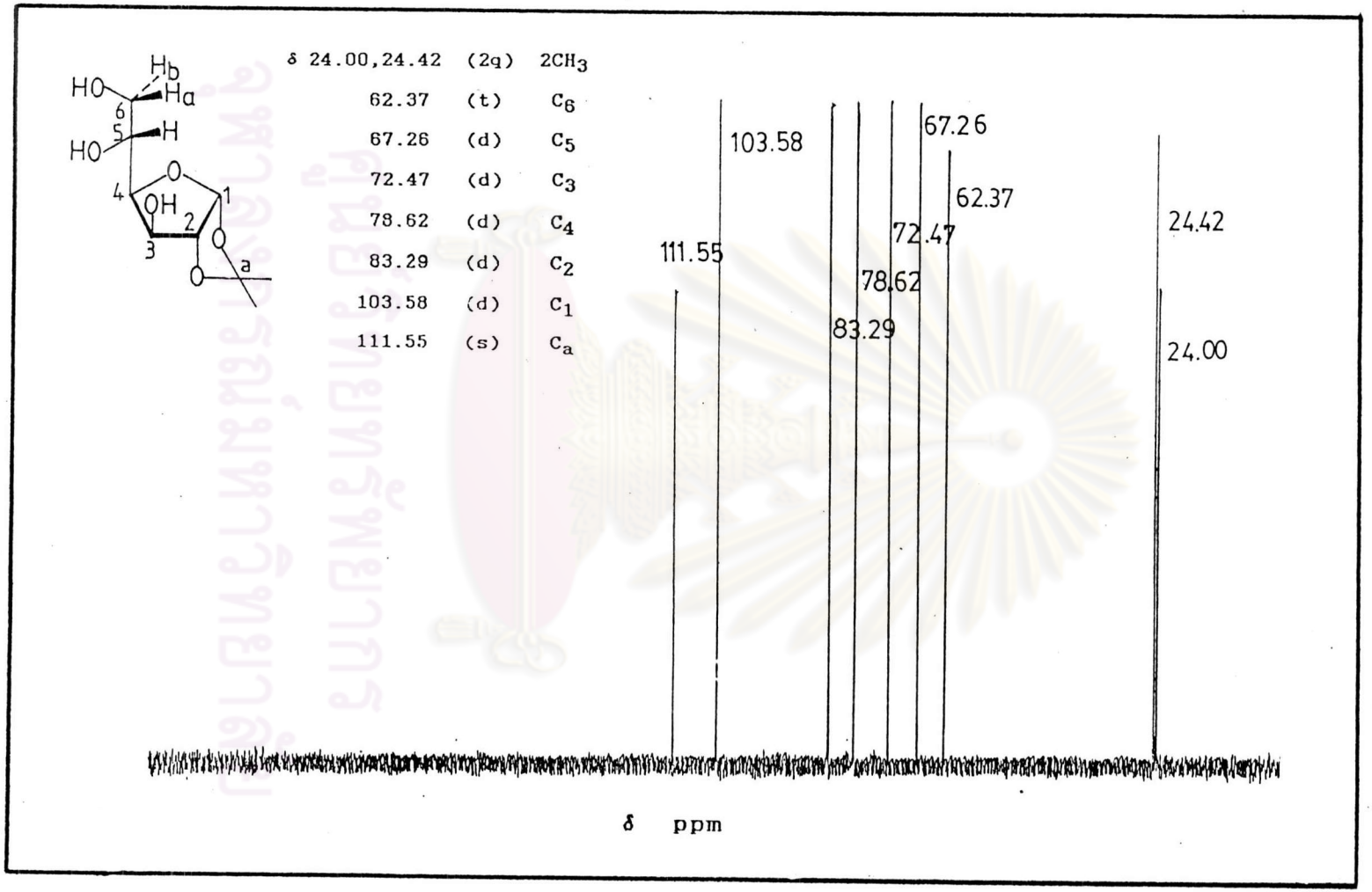

Figure 11 The CMR spectrum of 1,2-O-isopropylidene-α-D-glucofuranose (59)

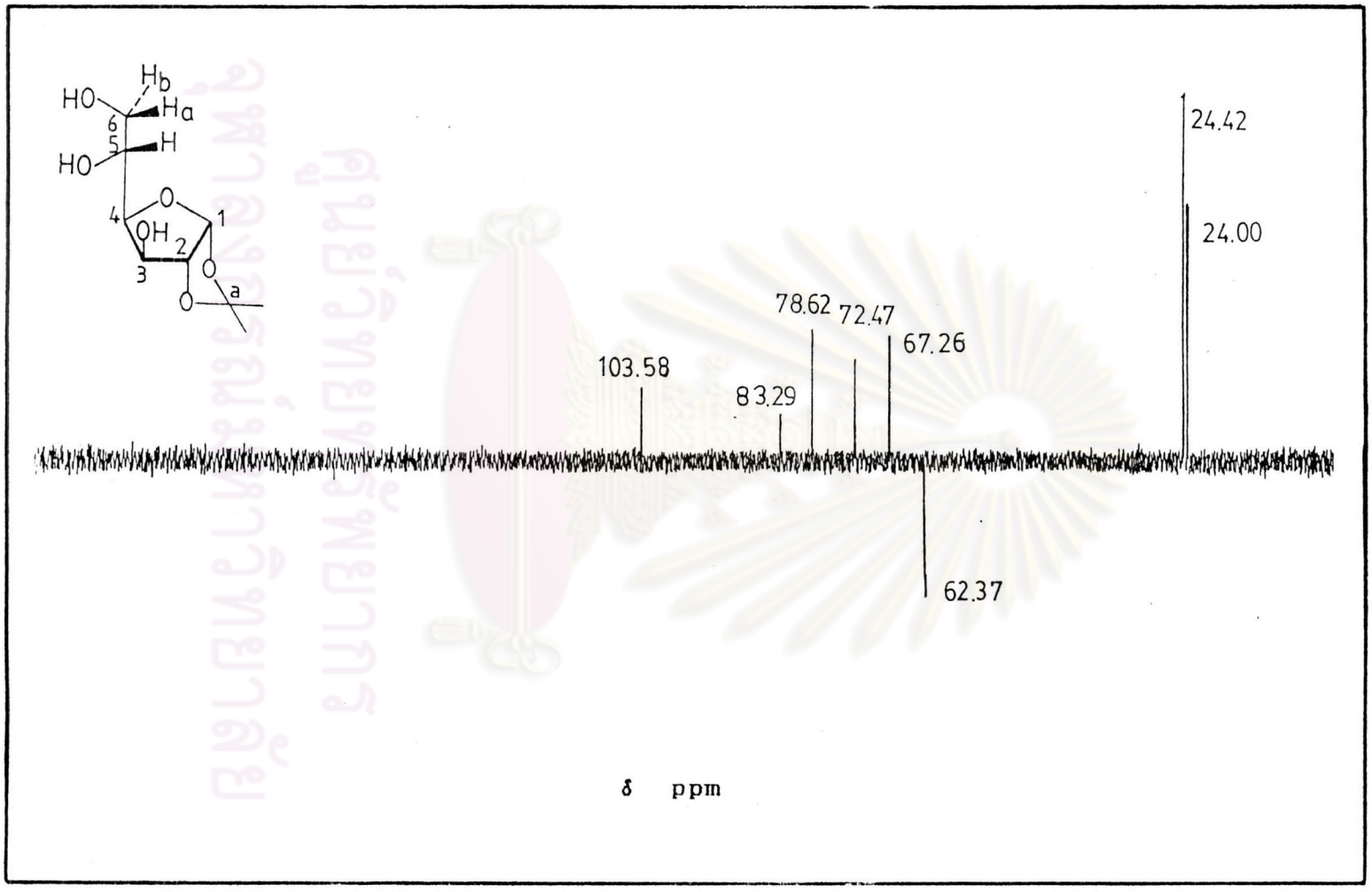

Figure 12 The DEPT-135 CMR spectrum of compound (59)

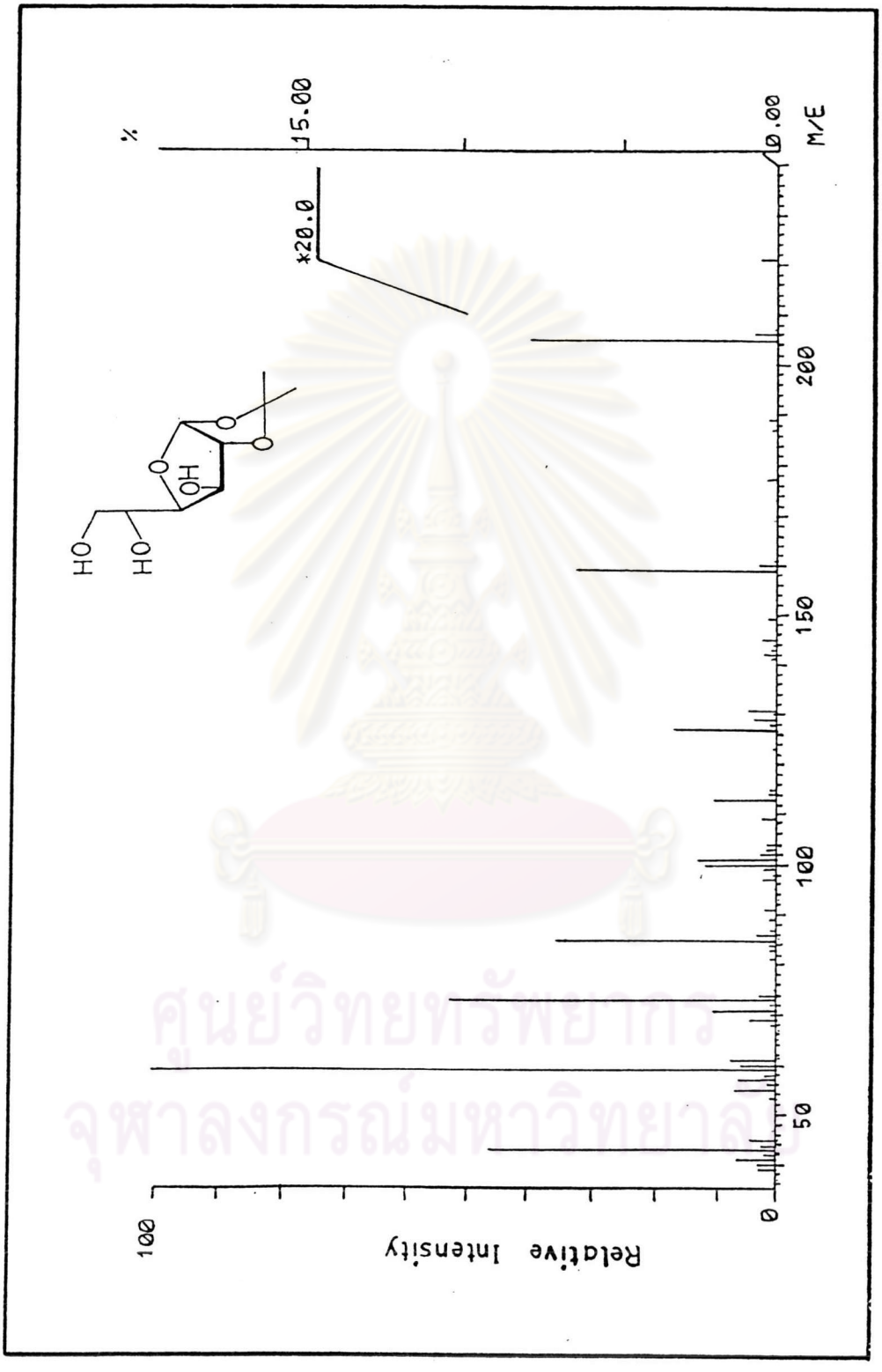

Figure 13 The mass spectrum of 1,2-O-isopropylidene-α-D-glucofuranose (59)

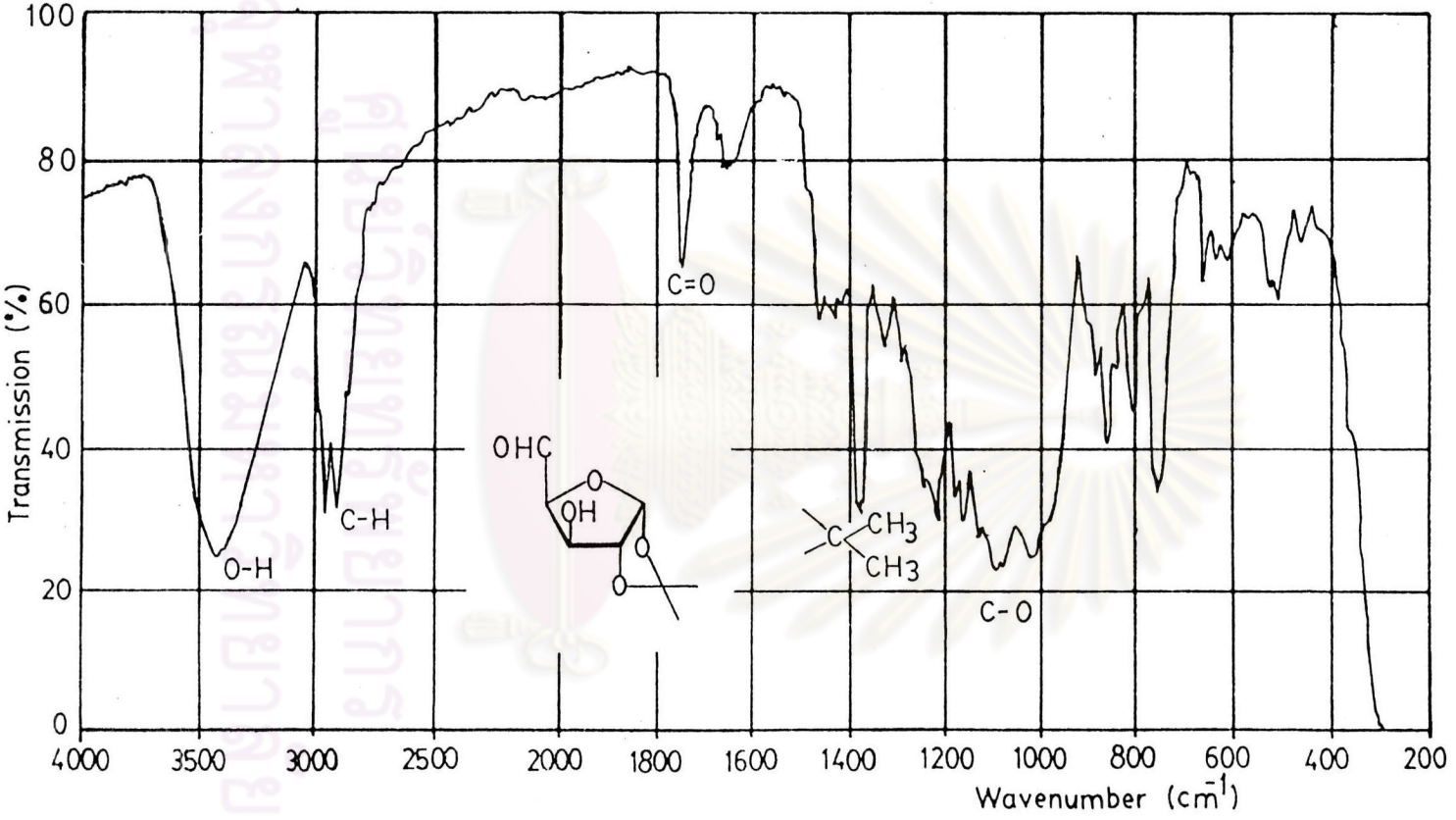

Figure 14 The IR spectrum of 1,2-O-isopropylidene- α-D-erythro pentodialdofuranose (60)

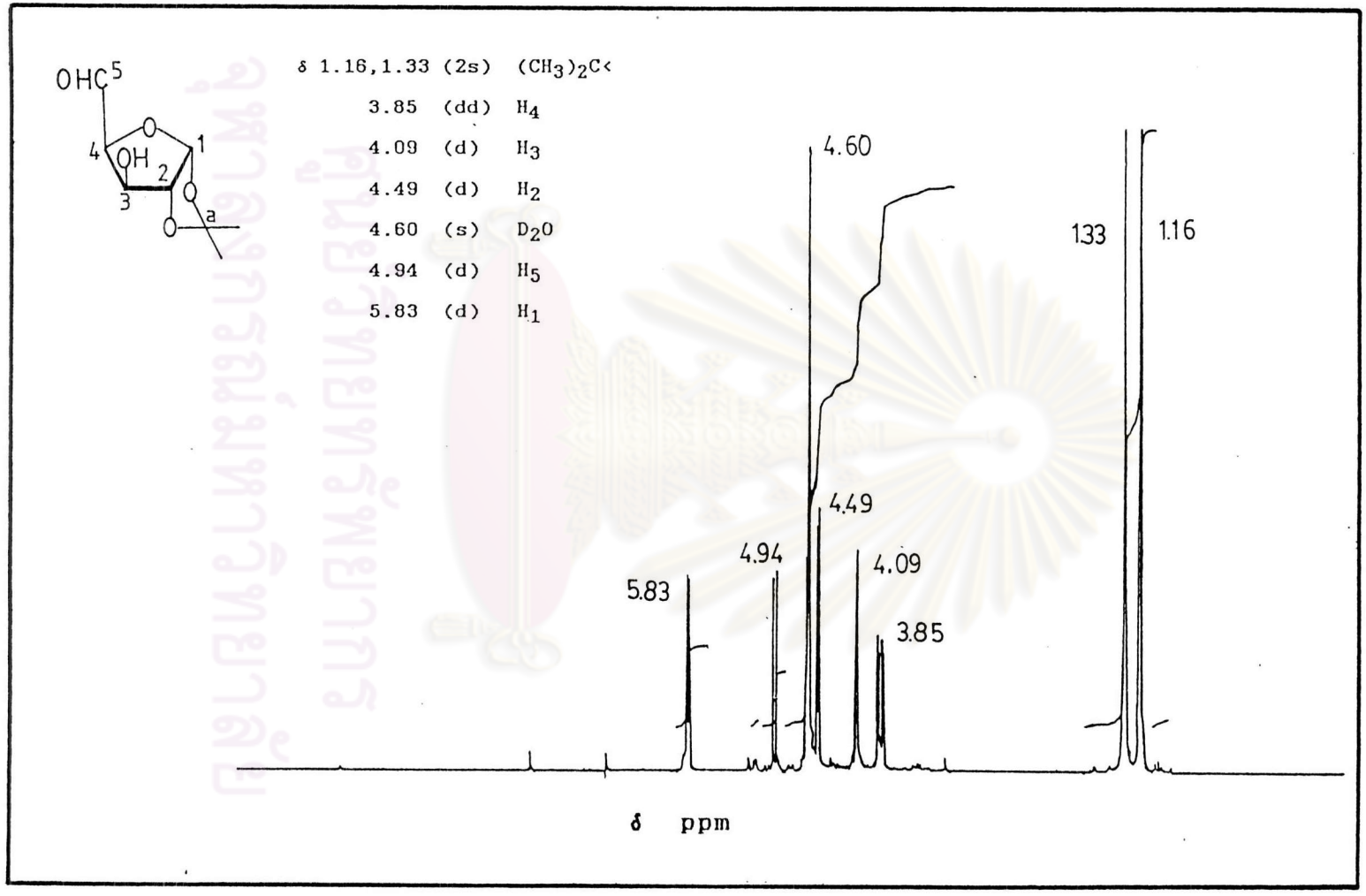

Figure 15 The PMR spectrum of 1,2-O-isopropylidene- α-D-erythro pentodialdofuranose (60)

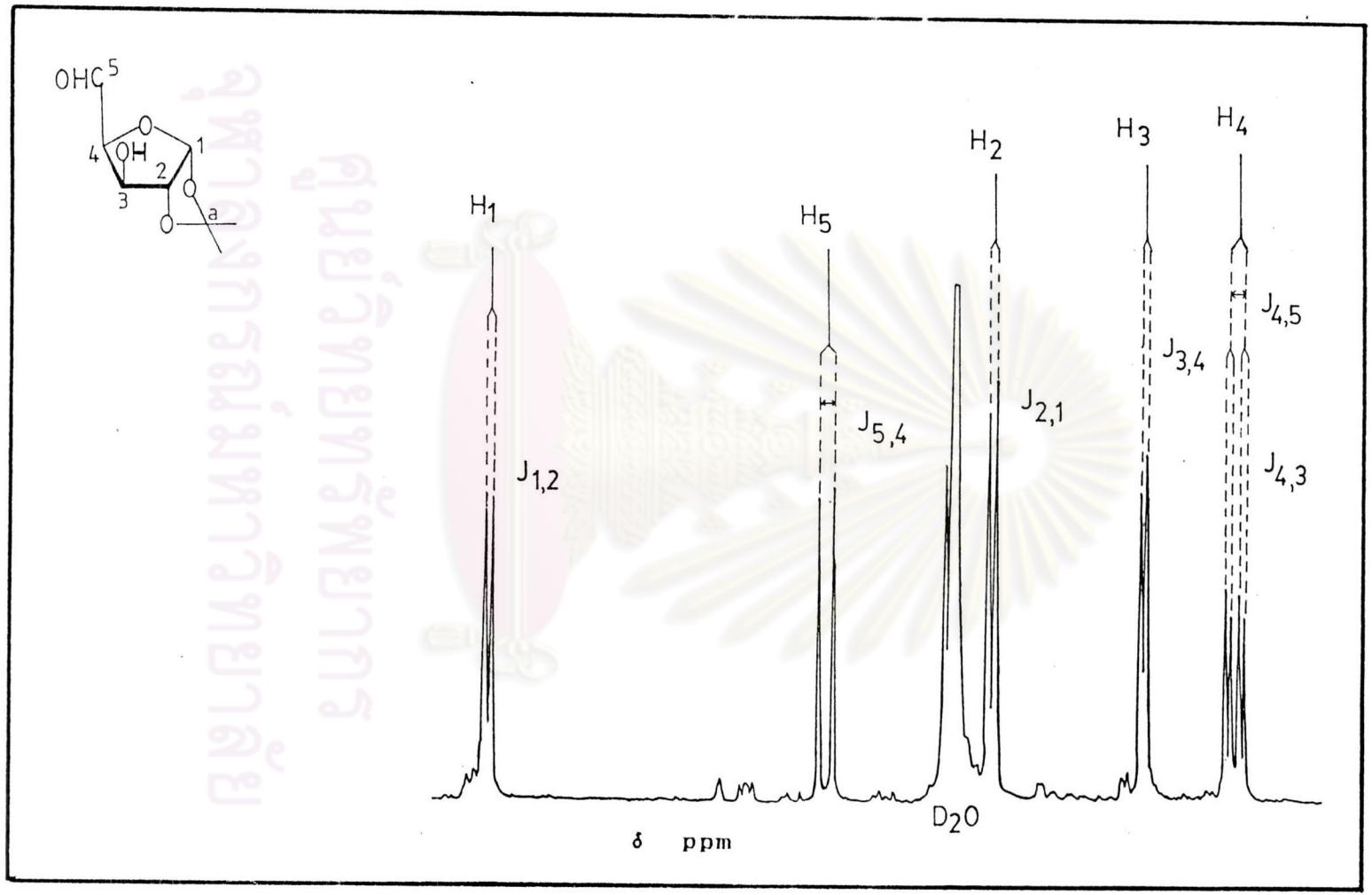

Figure 16 The PMR spectrum of compound (60) showed protons coupling and coupling constants

Figure 16(a) The PMR spectrum of compound (60) in $CDCl_3$ showed the aldehyde proton

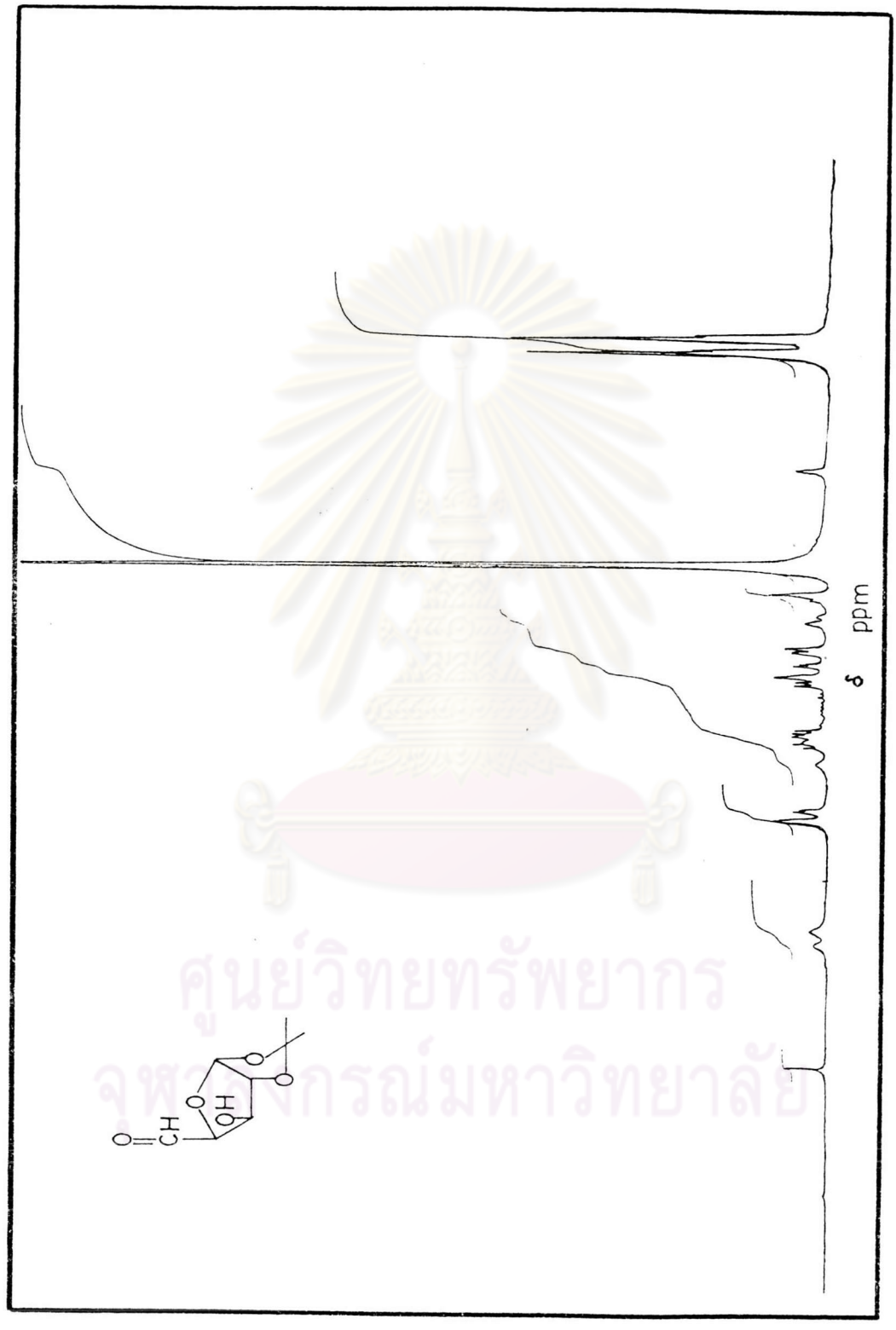

Figure 16(b) The PMR spectrum of compound (60) in DMSO-d_6

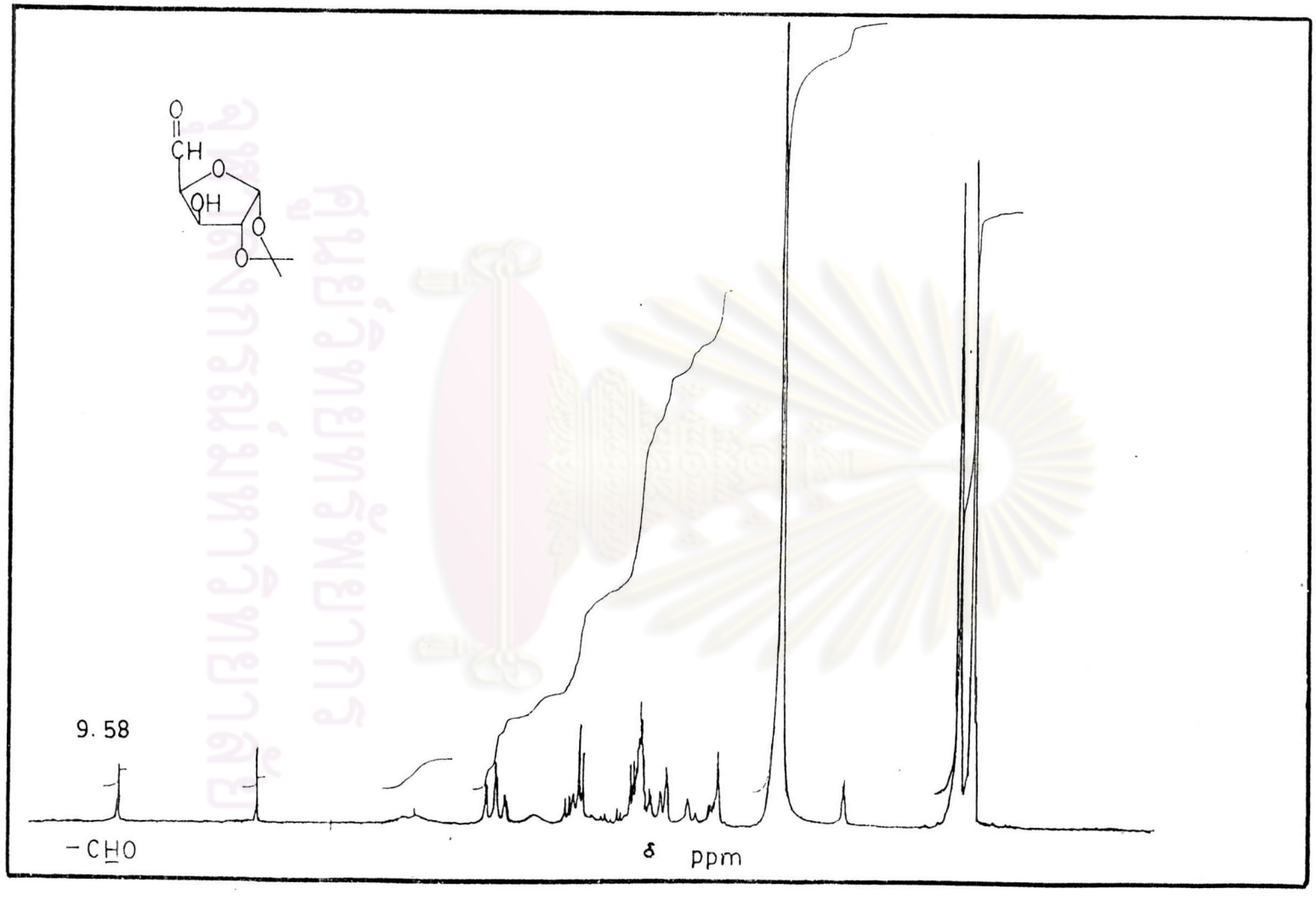

Figure 16(c) The PMR spectrum of compound (60) in DMSO-d_6 showed the aldehyde proton

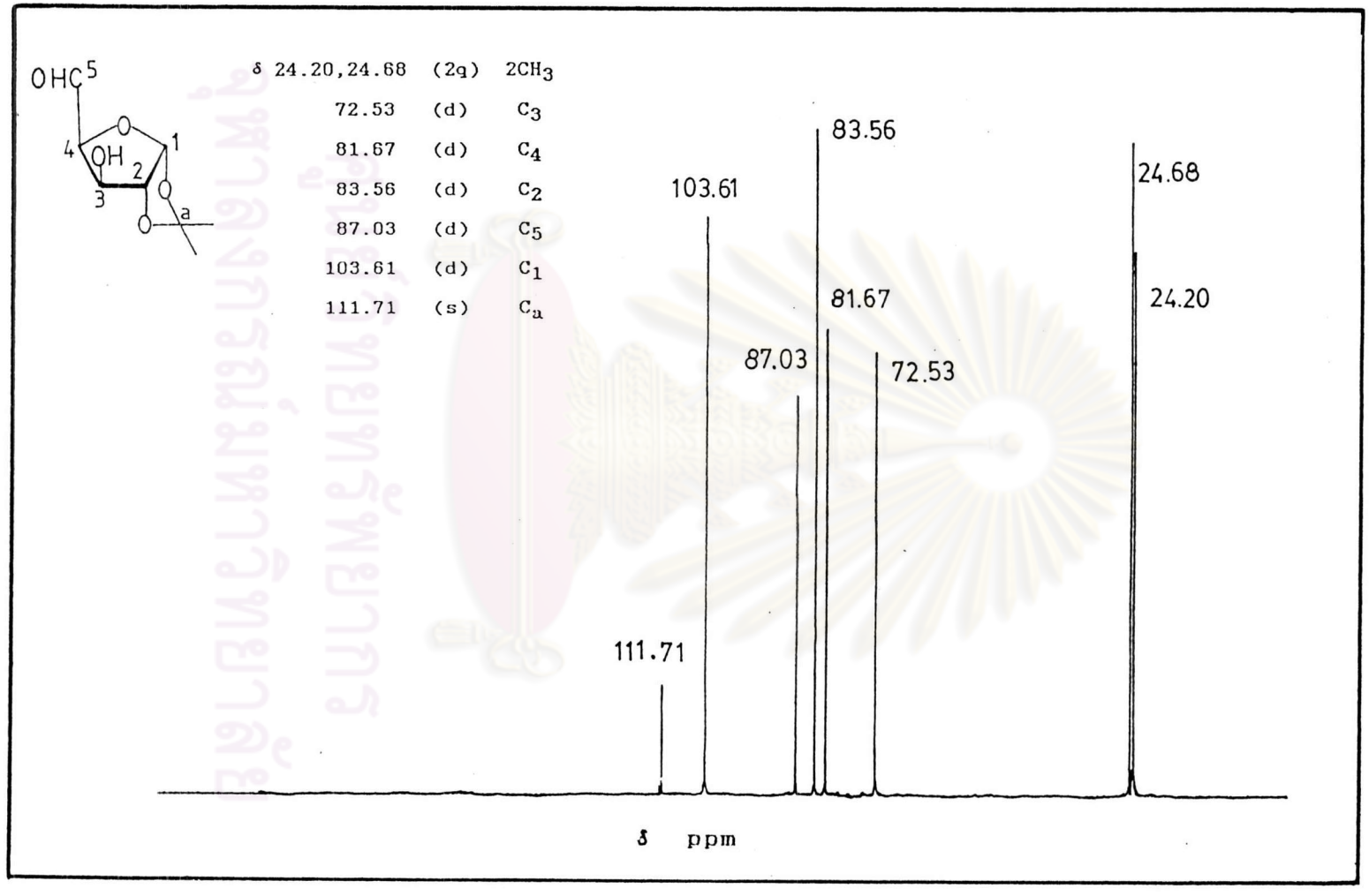

Figure 17 The CMR spectrum of 1,2-O-isopropylidene- α-D-erythro pentodialdofuranose (60)

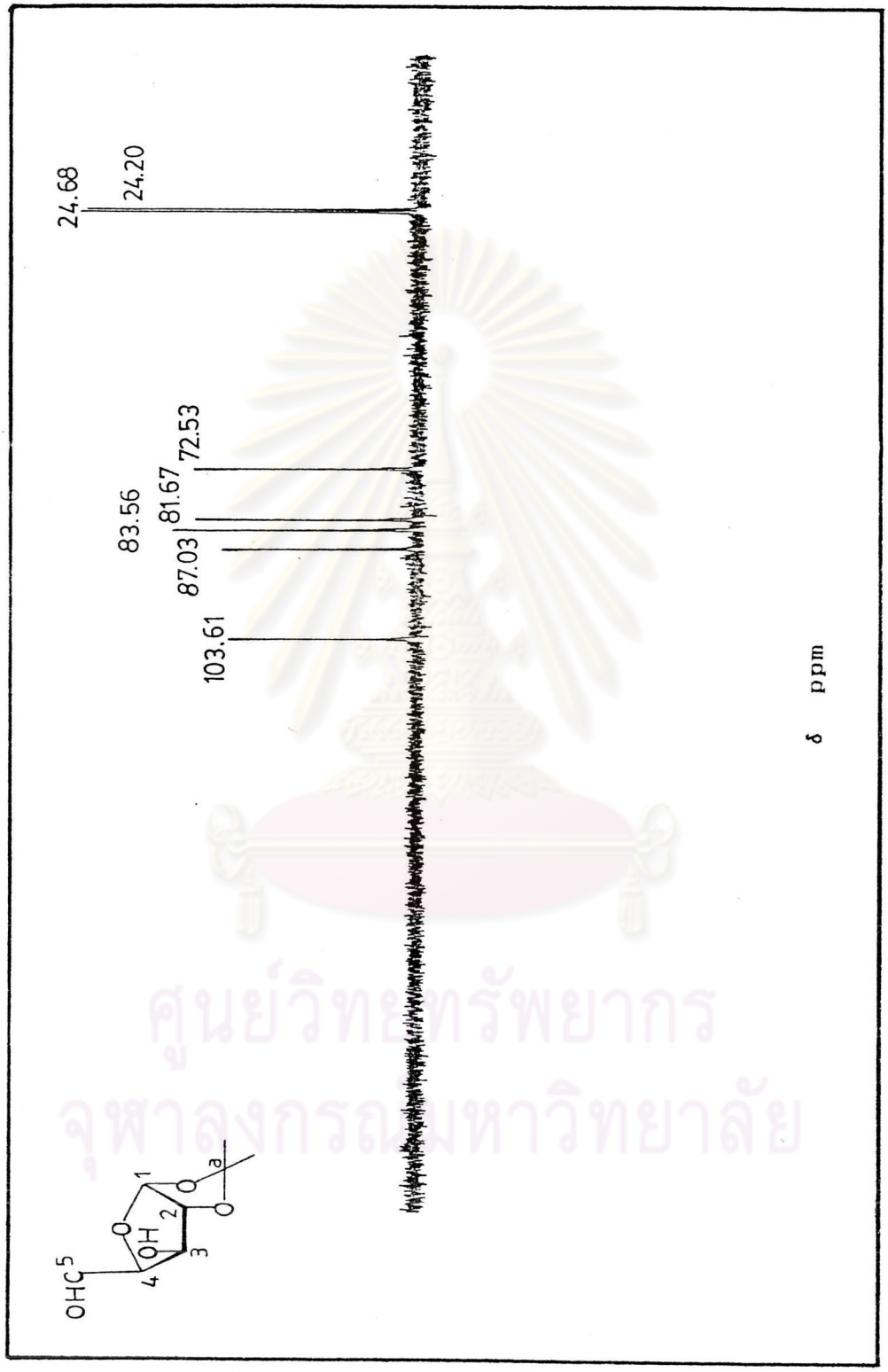

Figure 17(a) The DEPT-135 CMR spectrum of compound (60)

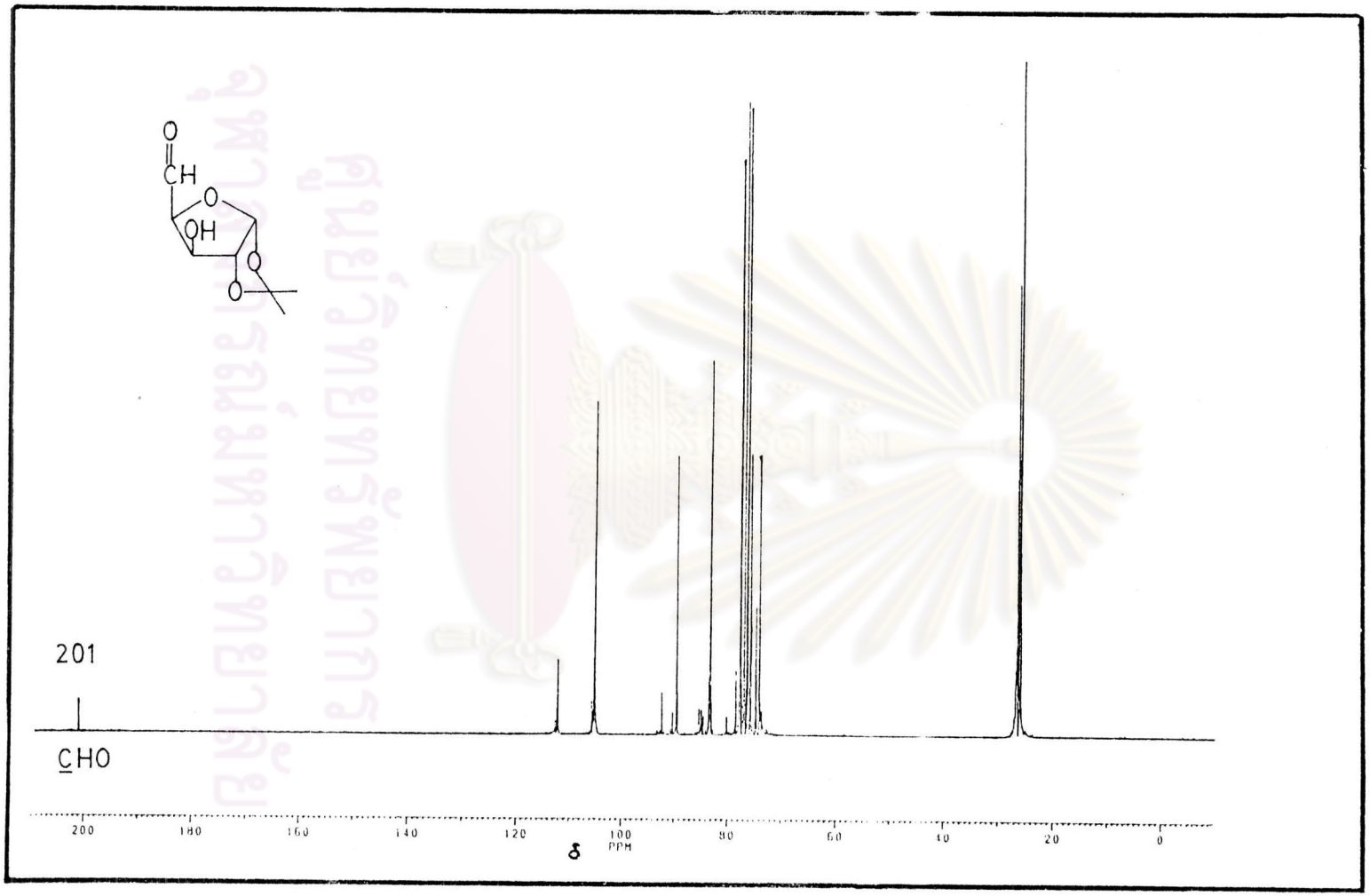

Figure 17(b) The CMR spectrum of compound (60) in $CDCl_3$ showed the aldehyde carbon

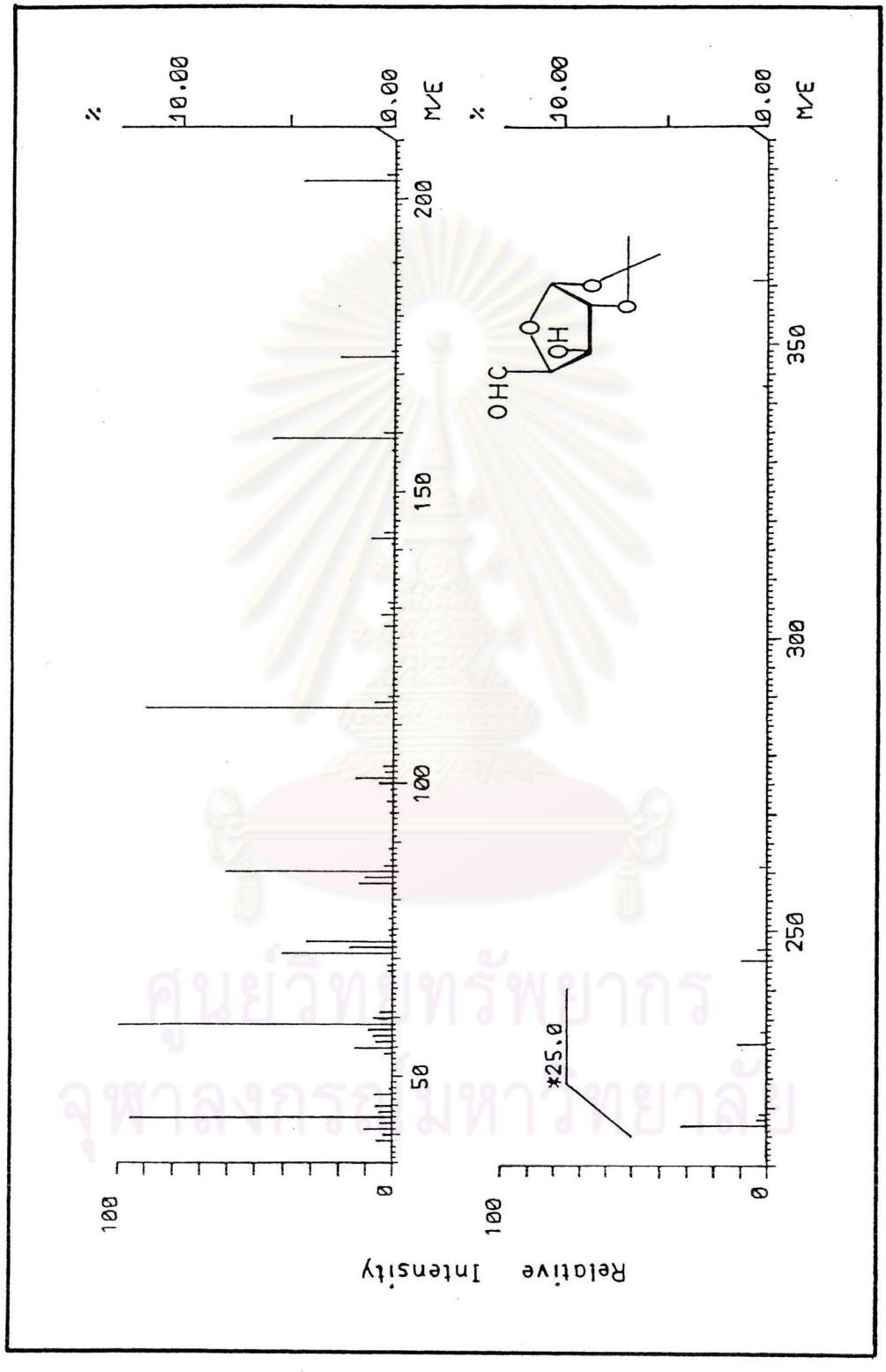

Figure 18 The mass spectrum of 1,2-O-isopropylidene- α -D-erythropentodialdofuranose (60)

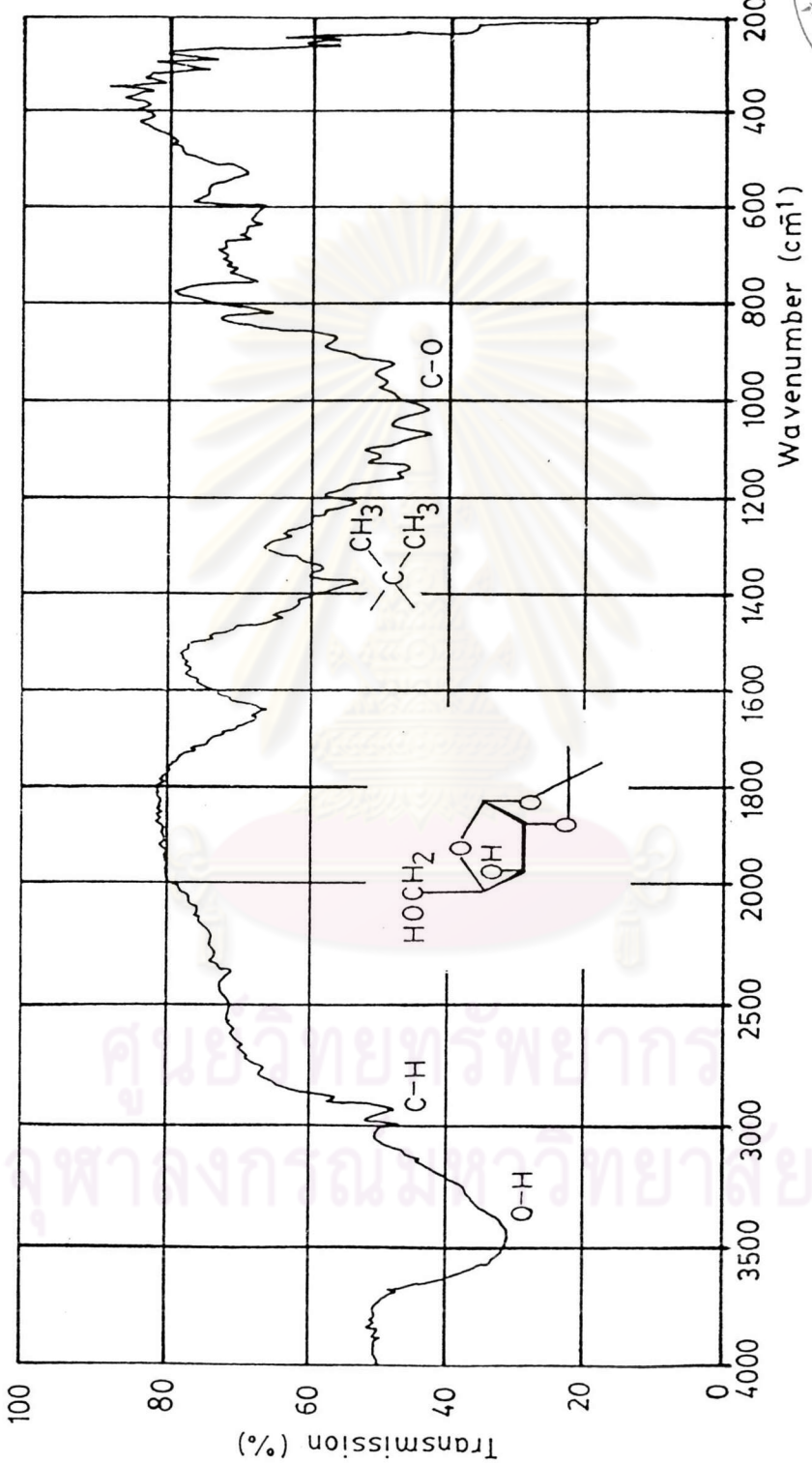

Figure 19 The IR spectrum of 1,2-O-isopropylidene-α-D-xylofuranose (60a)

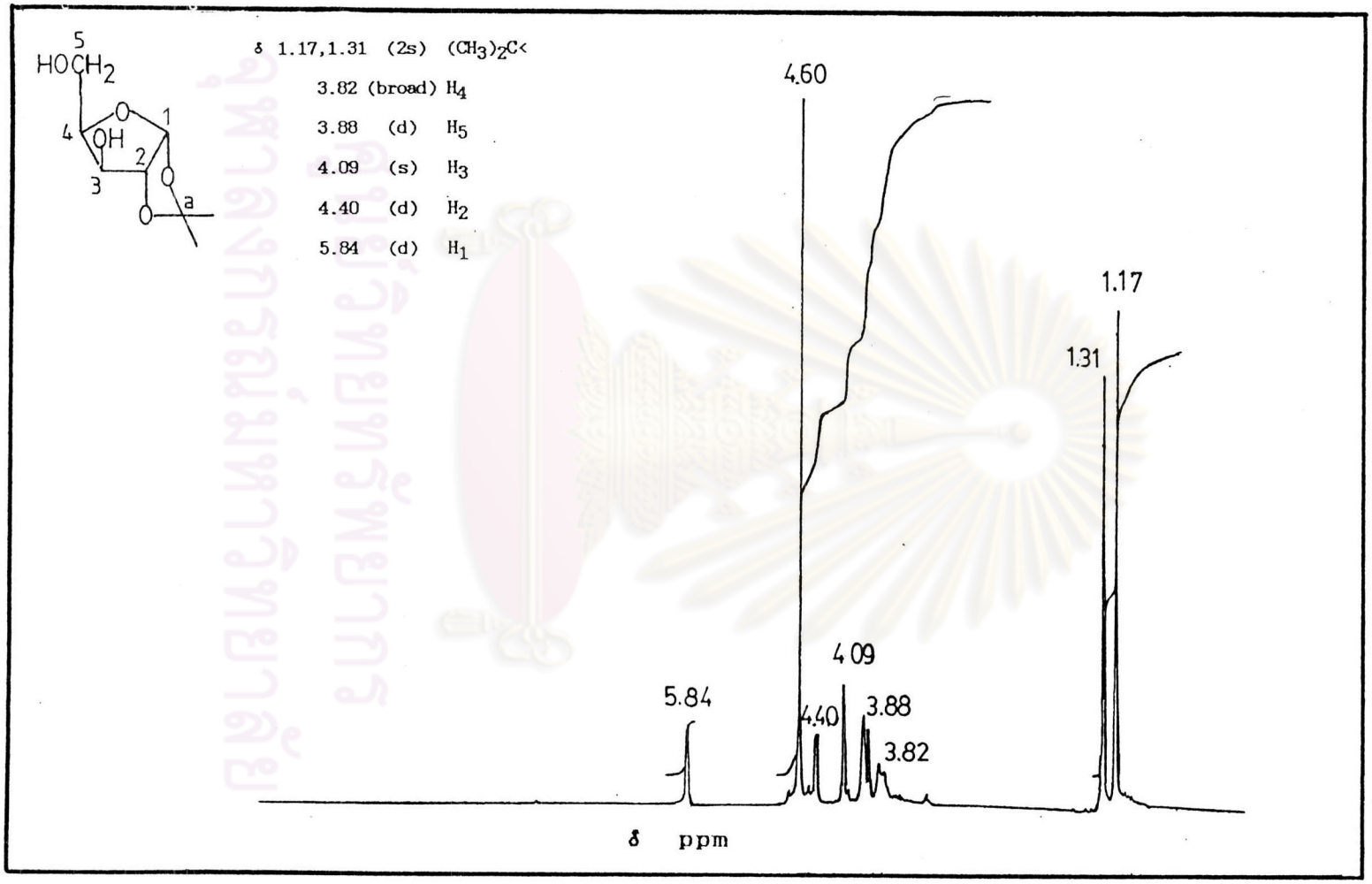

Figure 20 The PMR spectrum of 1,2-O-isopropylidene-α-D-xylofuranose (60a)

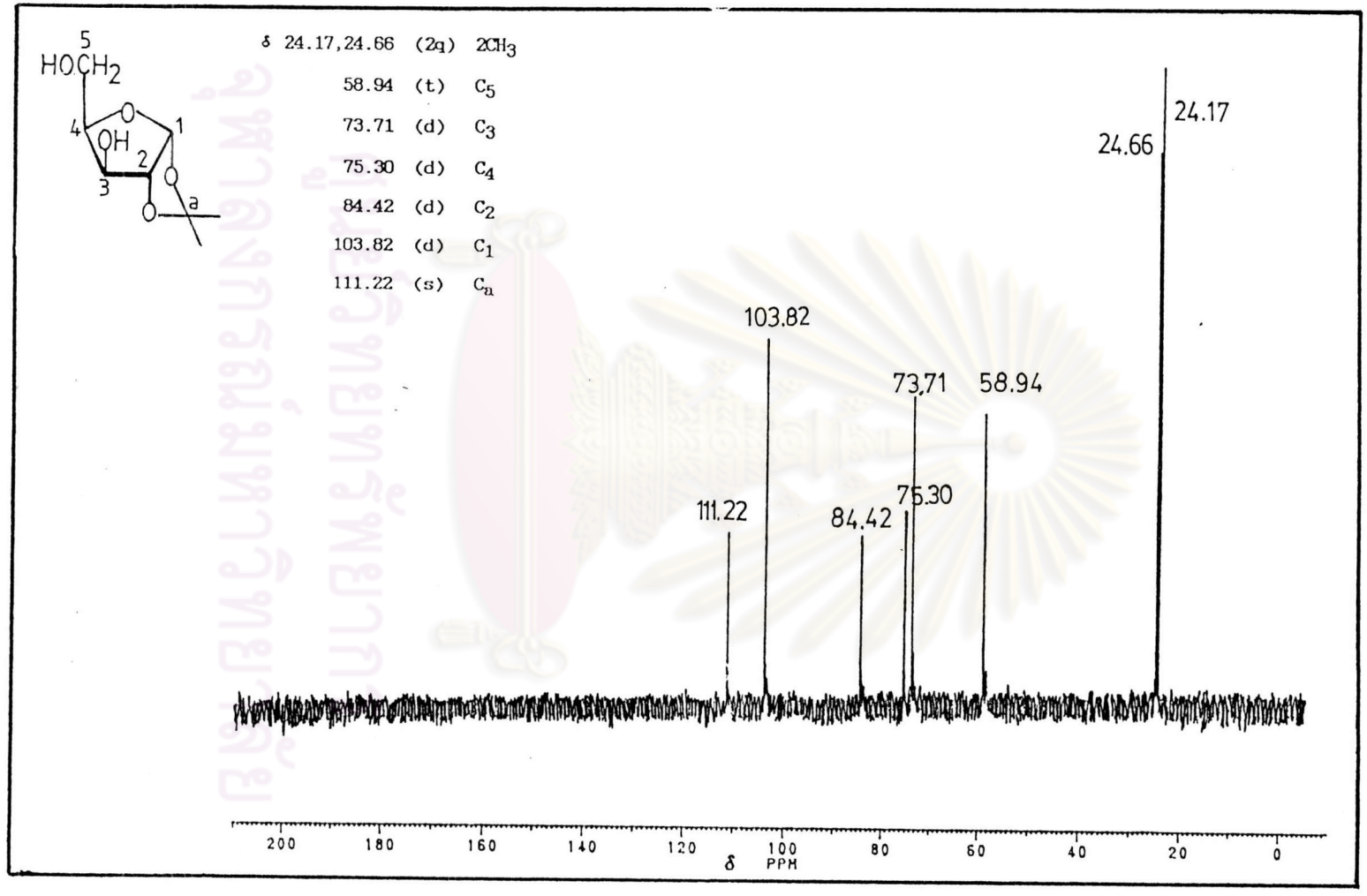

Figure 21 The CMR spectrum of 1,2-O-isopropylidene-α-D-xylofuranose (60a)

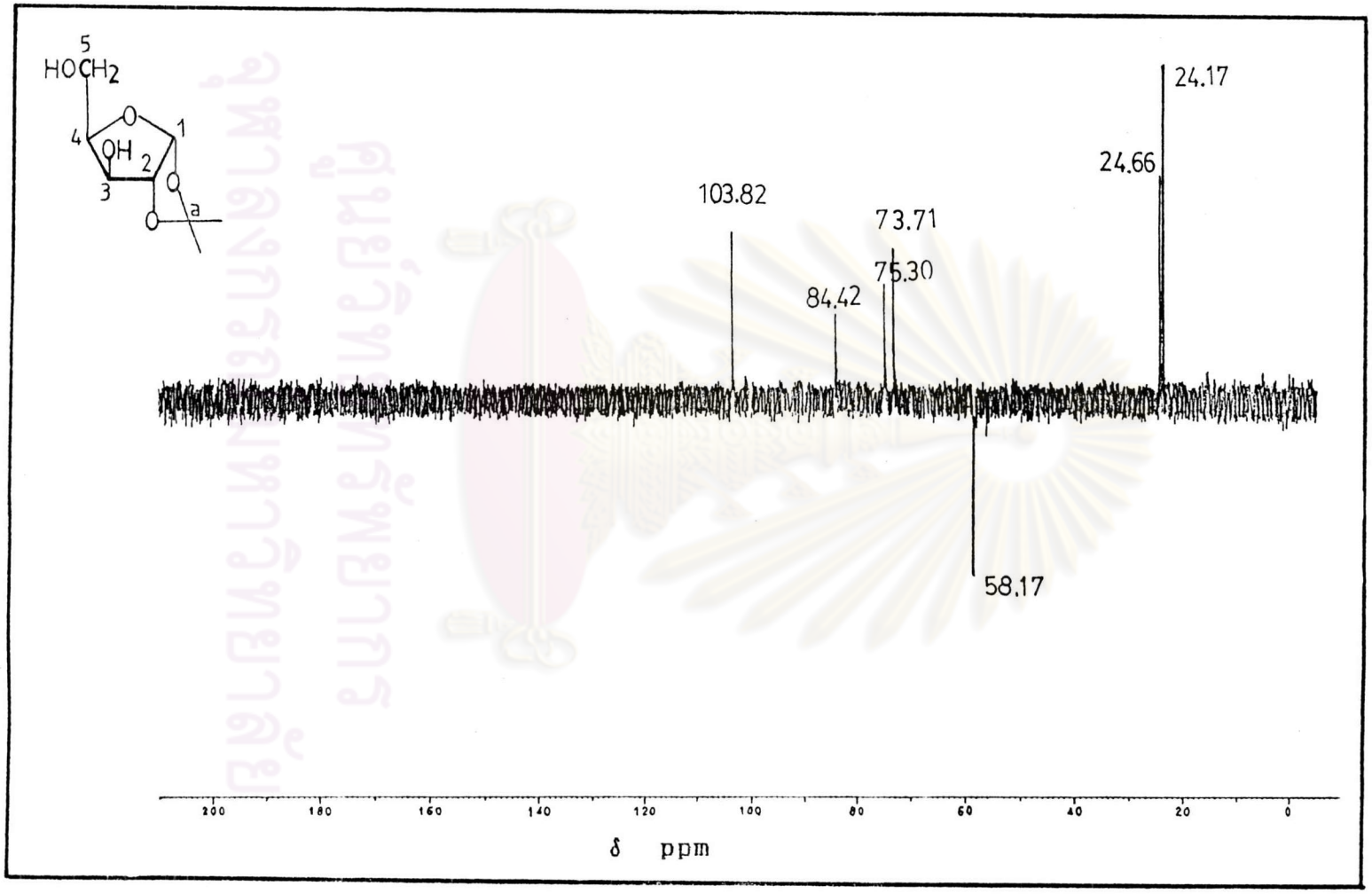

Figure 21(a) The DEPT-135 CMR spectrum of compound (60a)

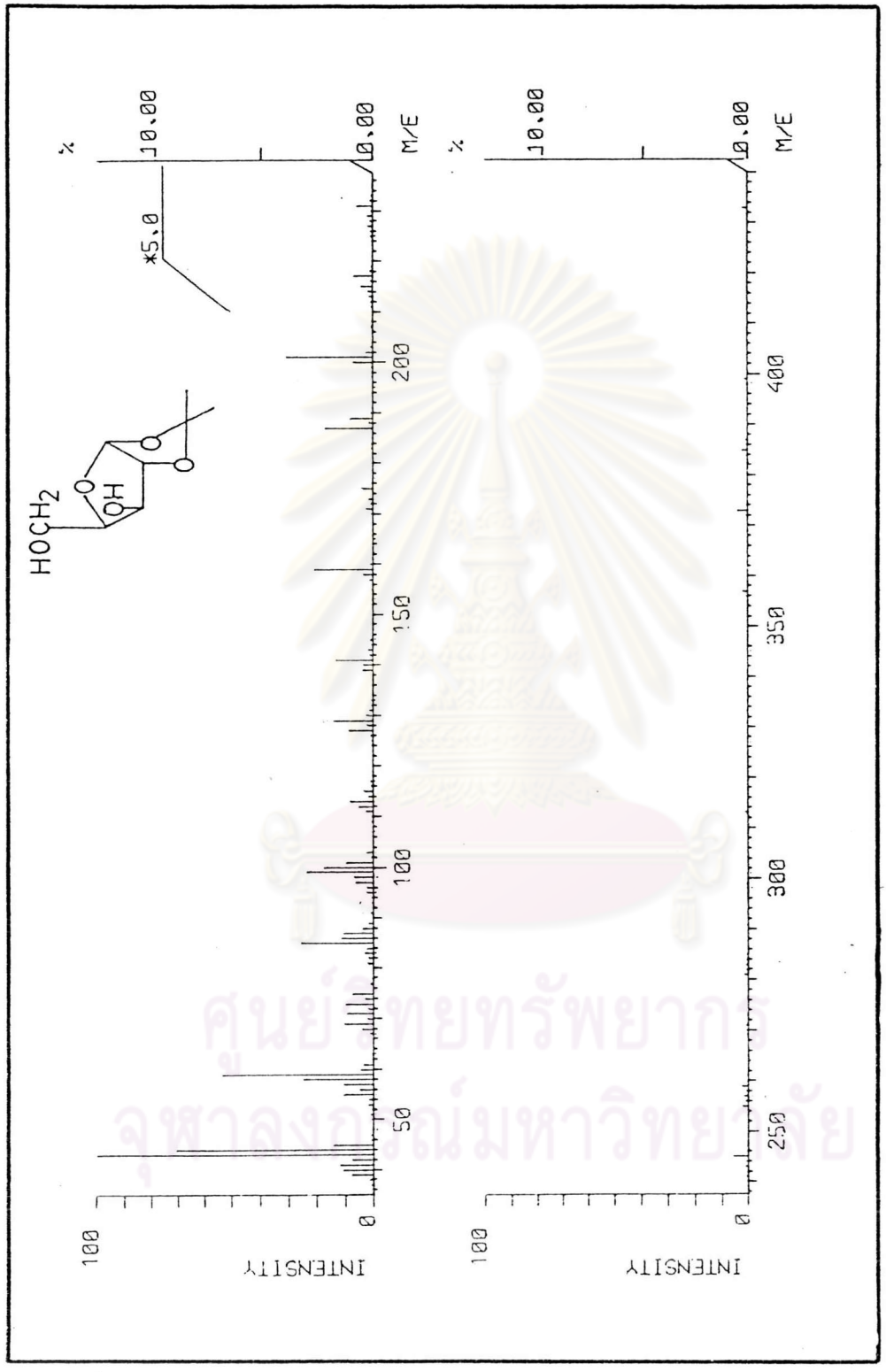

Figure 22 The mass spectrum of 1,2-O-isopropylidene- α-D-xylofuranose (60a)

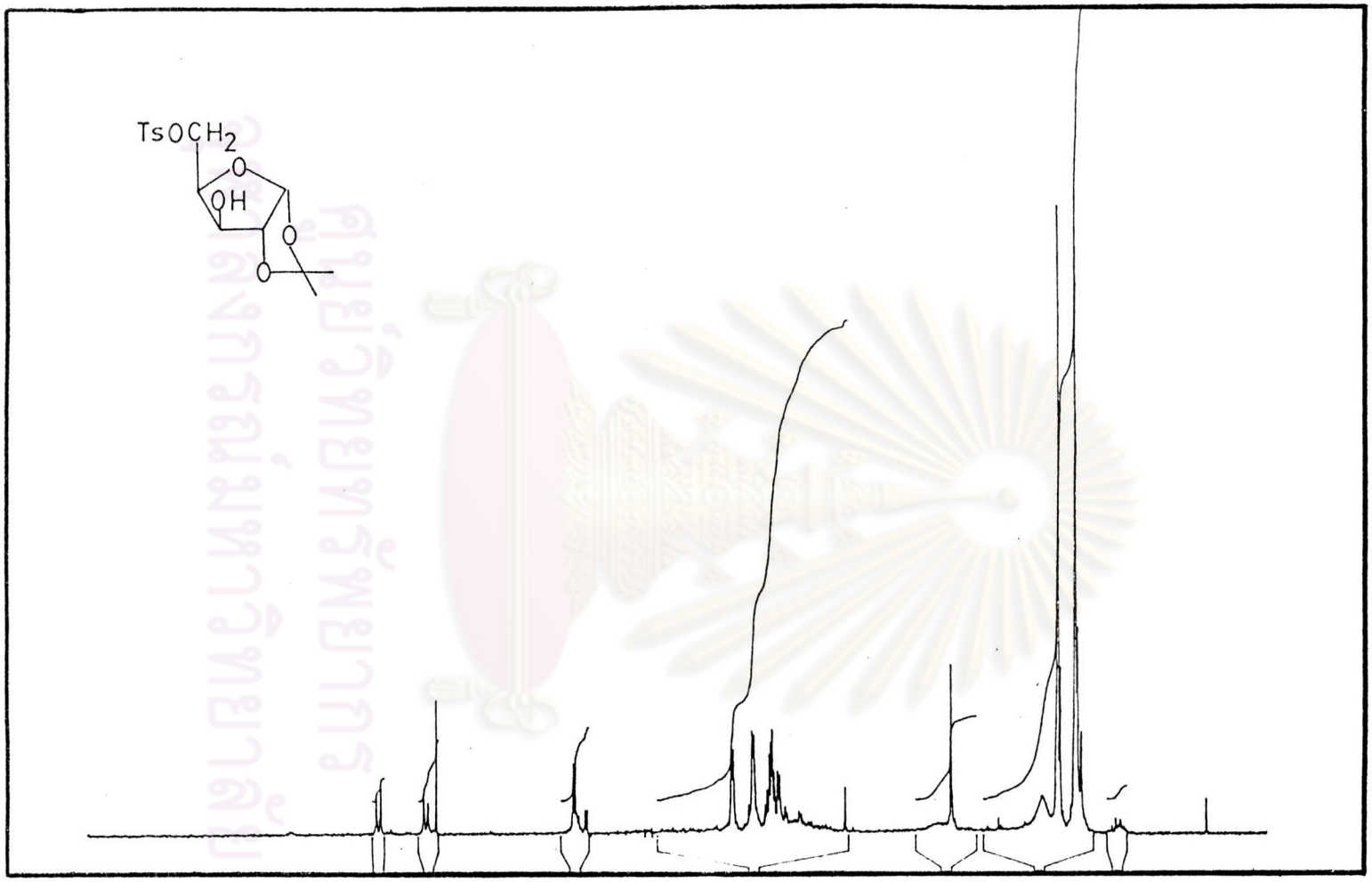

Figure 22a The PMR spectrum of 1,2-O-isopropylidene-5-O-toluene-*p*-sulfonyl-α-D-xylofuranose (60b)

Figure 22b The PMR spectrum of butyraldehyde

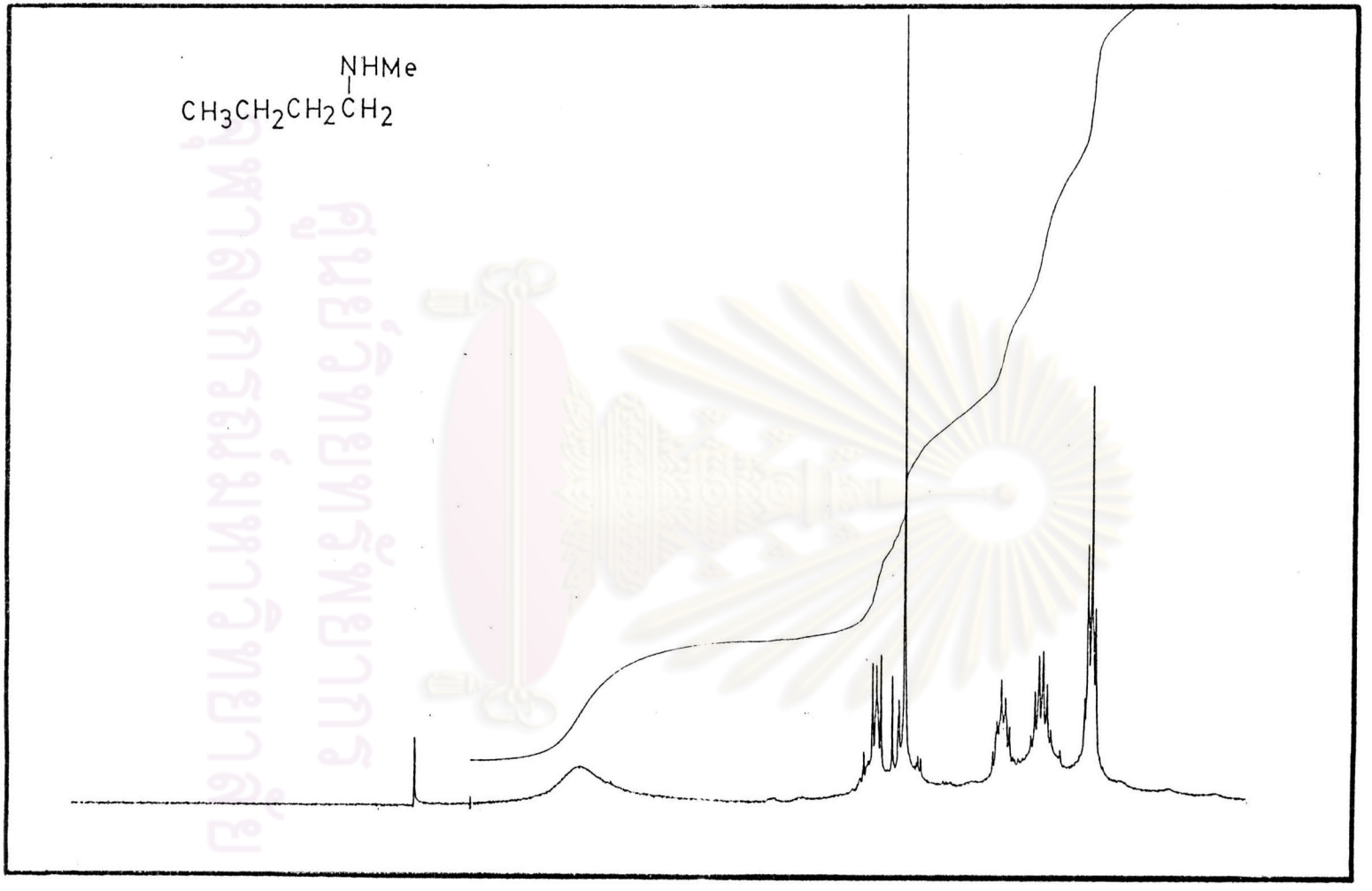

Figure 22c The PMR spectrum of N-methylbutyraldehyde

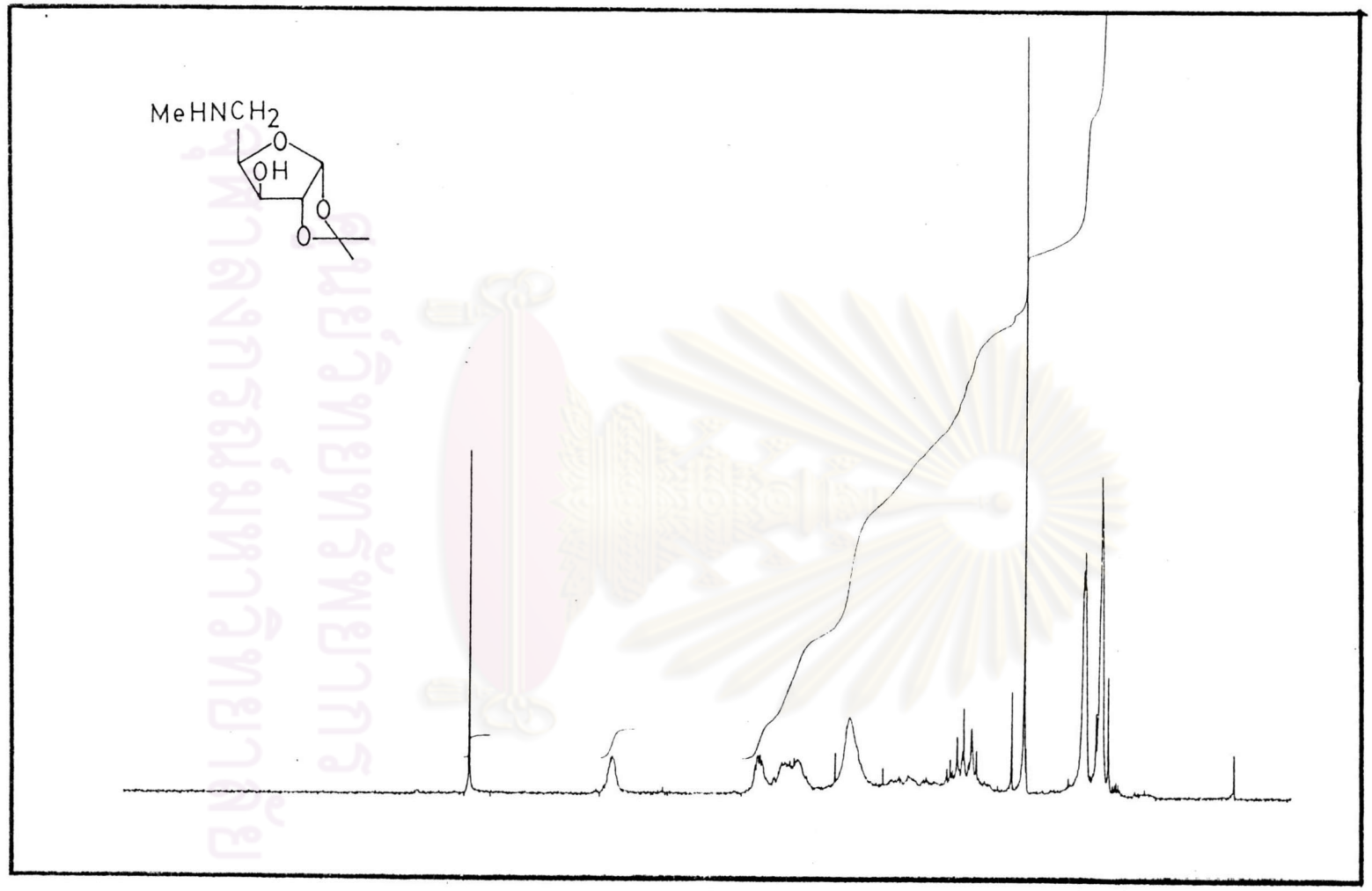

Figure 22d The PMR spectrum of 5-N-methyl-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (61)

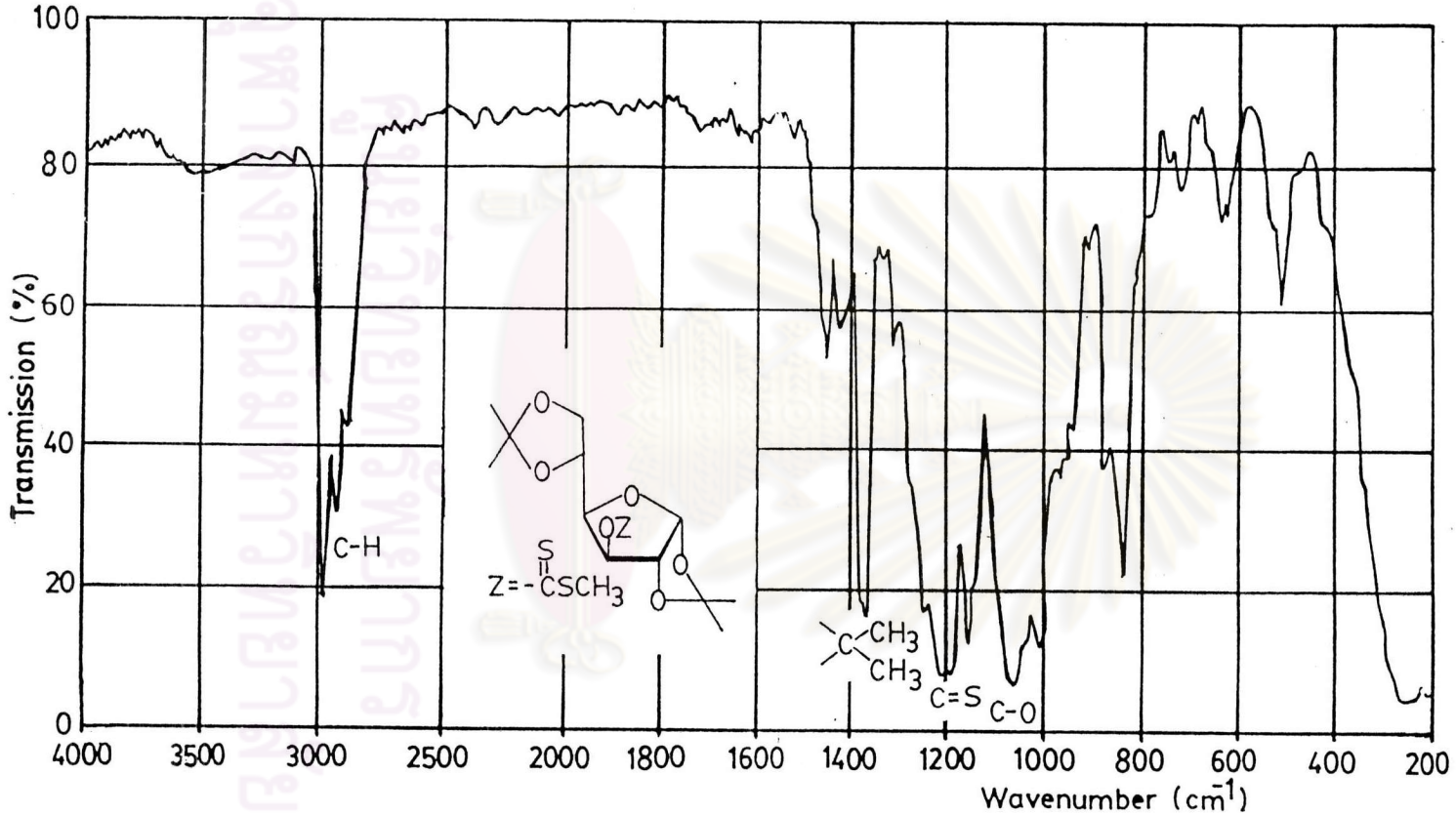

Figure 23 The IR spectrum of 3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)S-methyl dithiocarbonate (65)

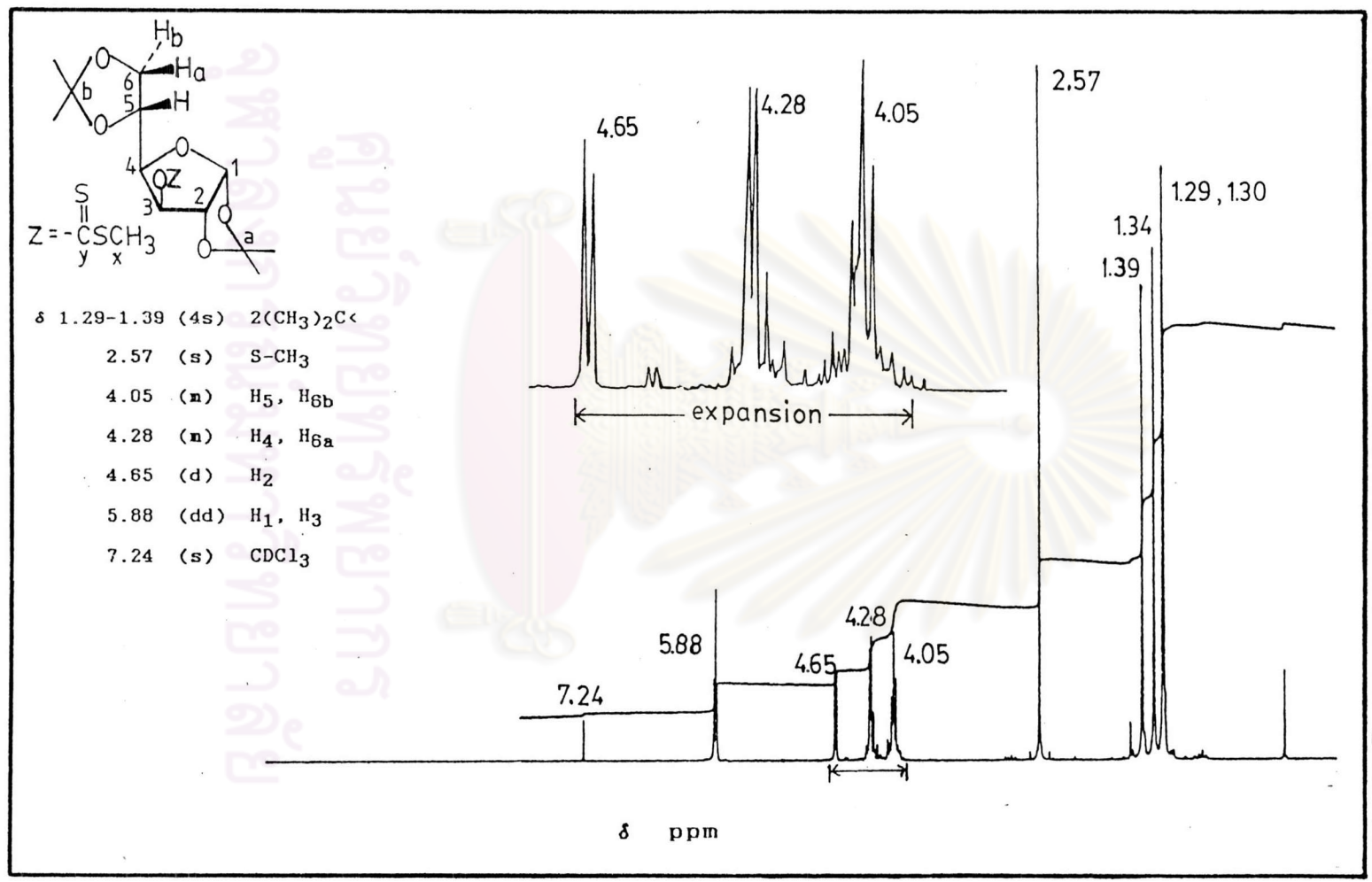

Figure 24 The PMR spectrum of 3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)S-methyl dithiocarbonate (65)

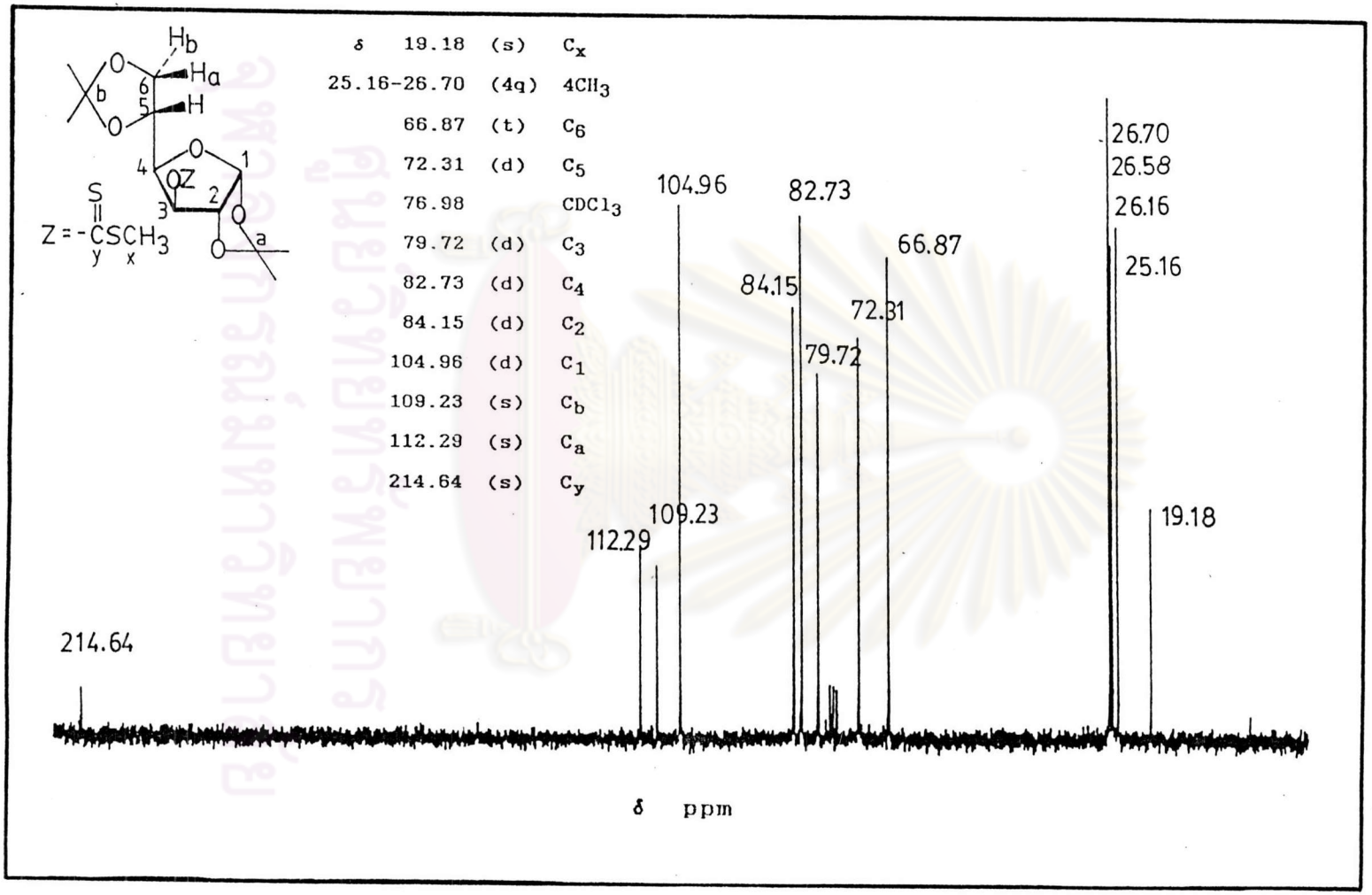

Figure 25 The CMR spectrum of 3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)S-methyl dithiocarbonate (65)

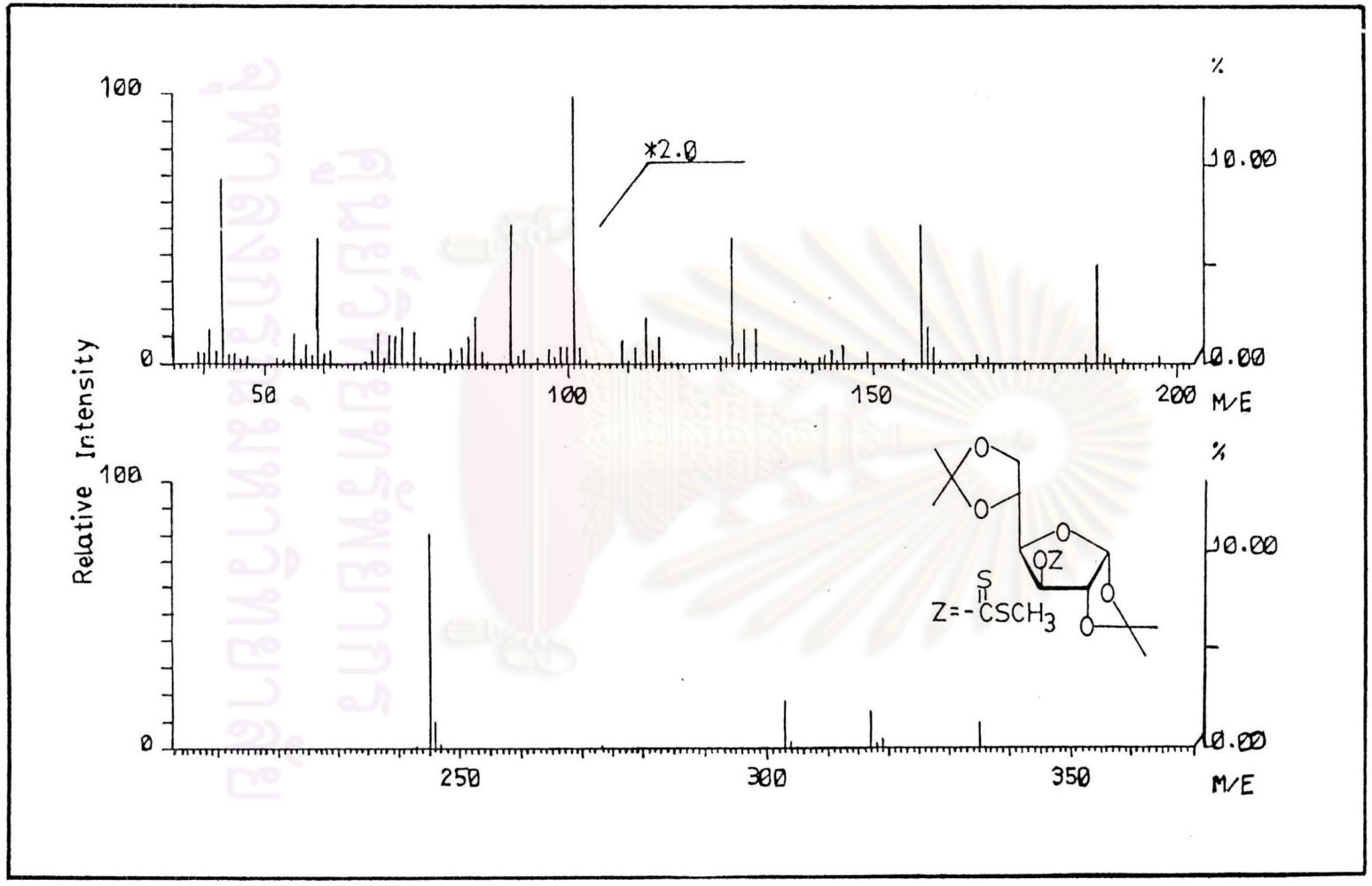

Figure 26 The mass spectrum of 3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose)S-methyl dithiocarbonate (65)

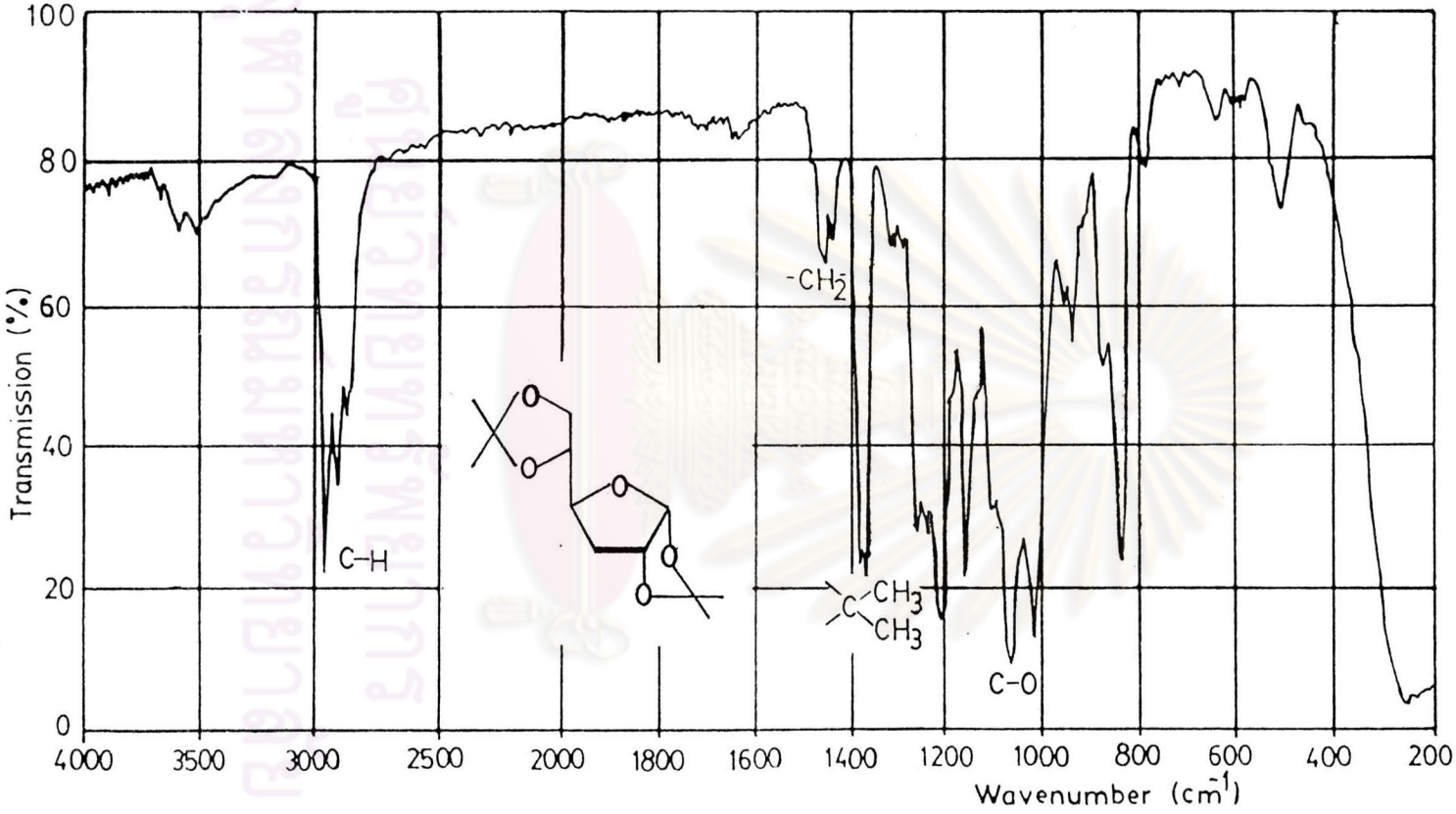

Figure 27 The IR spectrum of 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (66)

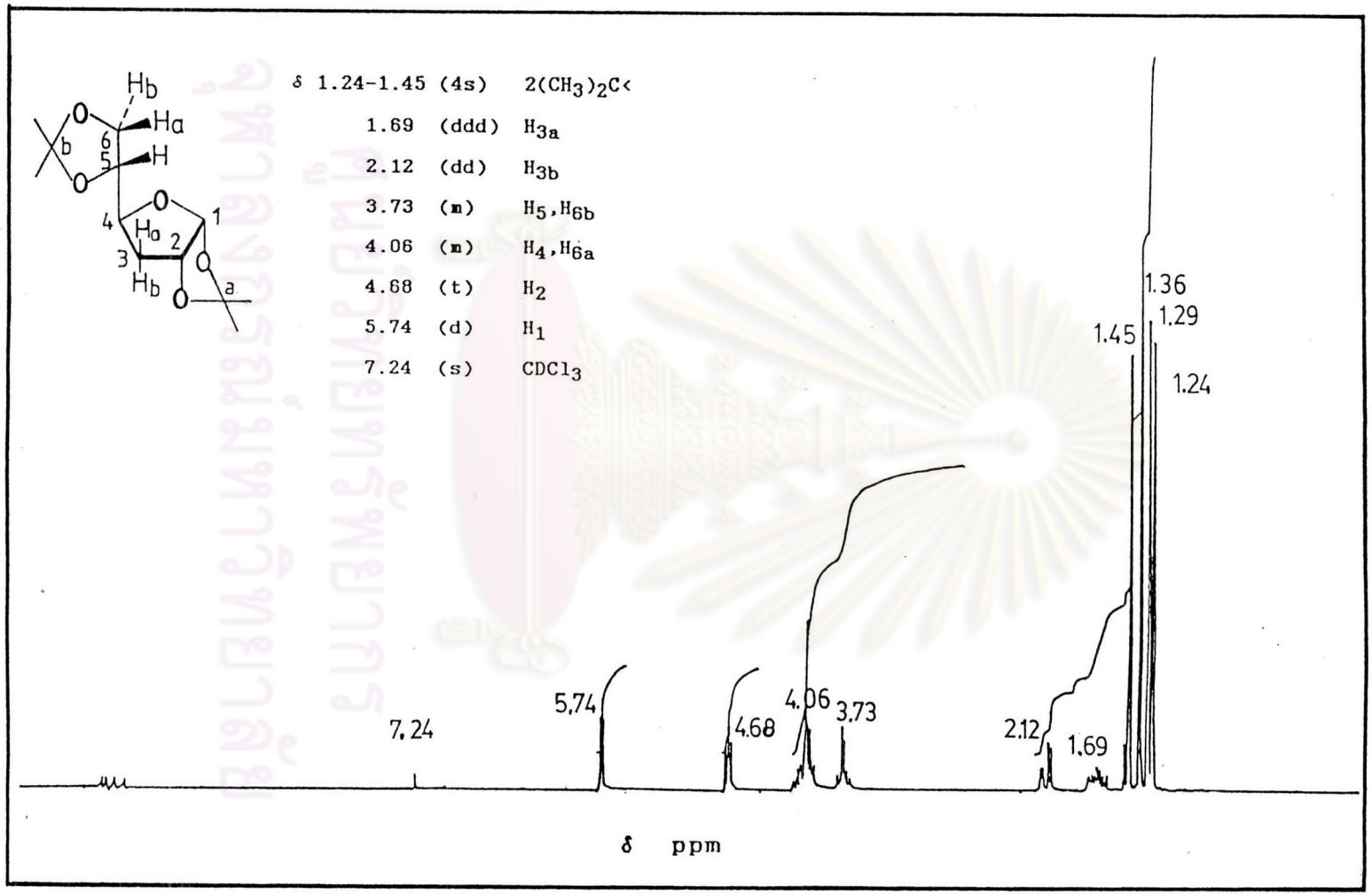

Figure 28 The PMR spectrum of 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (66)

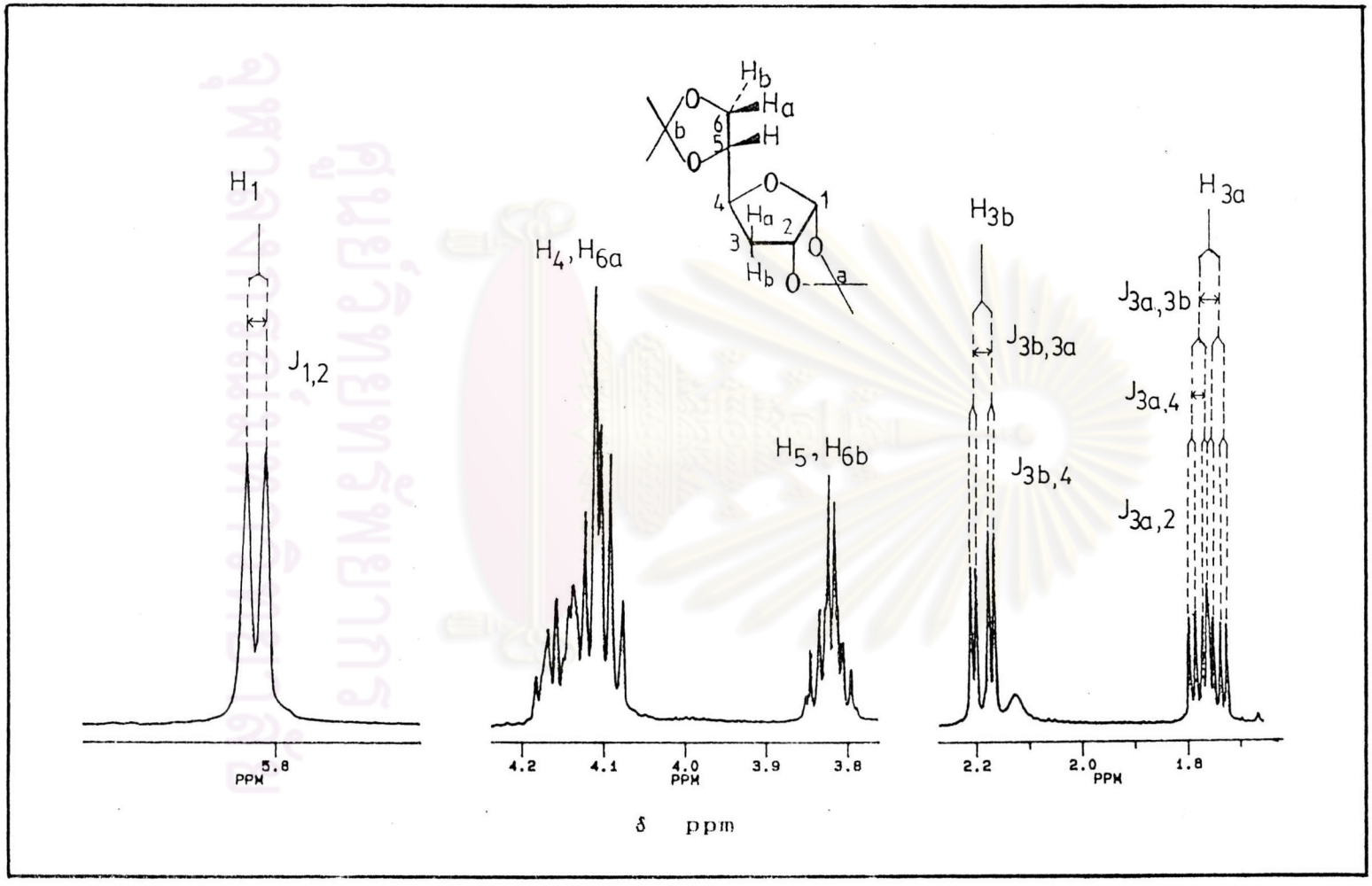

Figure 29 The PMR spectrum of compound (66) showed protons coupling and coupling constants

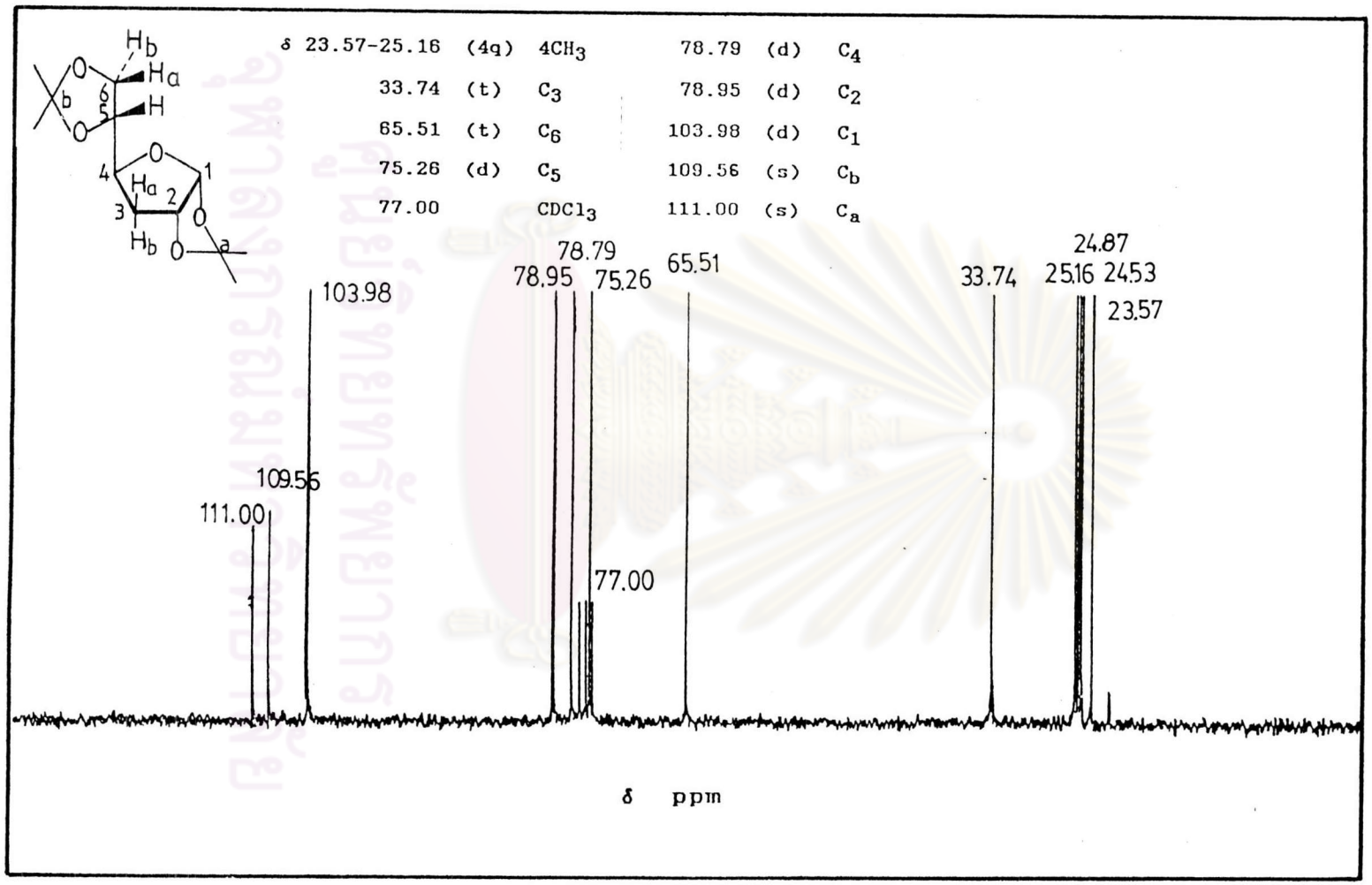

Figure 30 The CMR spectrum of 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (66)

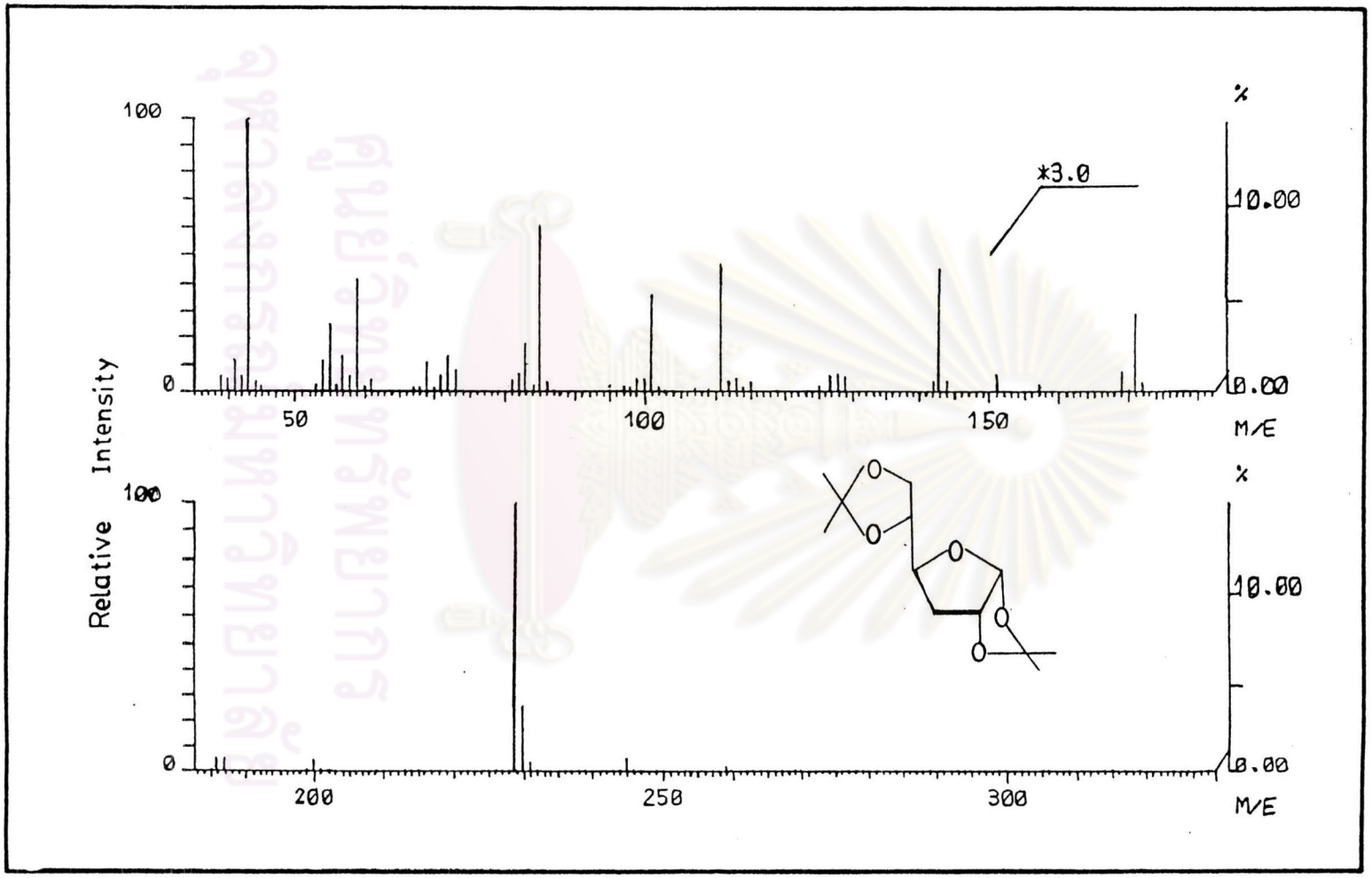

Figure 31 The mass spectrum of 3-deoxy-1,2:5,6-di-O-isopropylidene- α-D-glucofuranose (66)

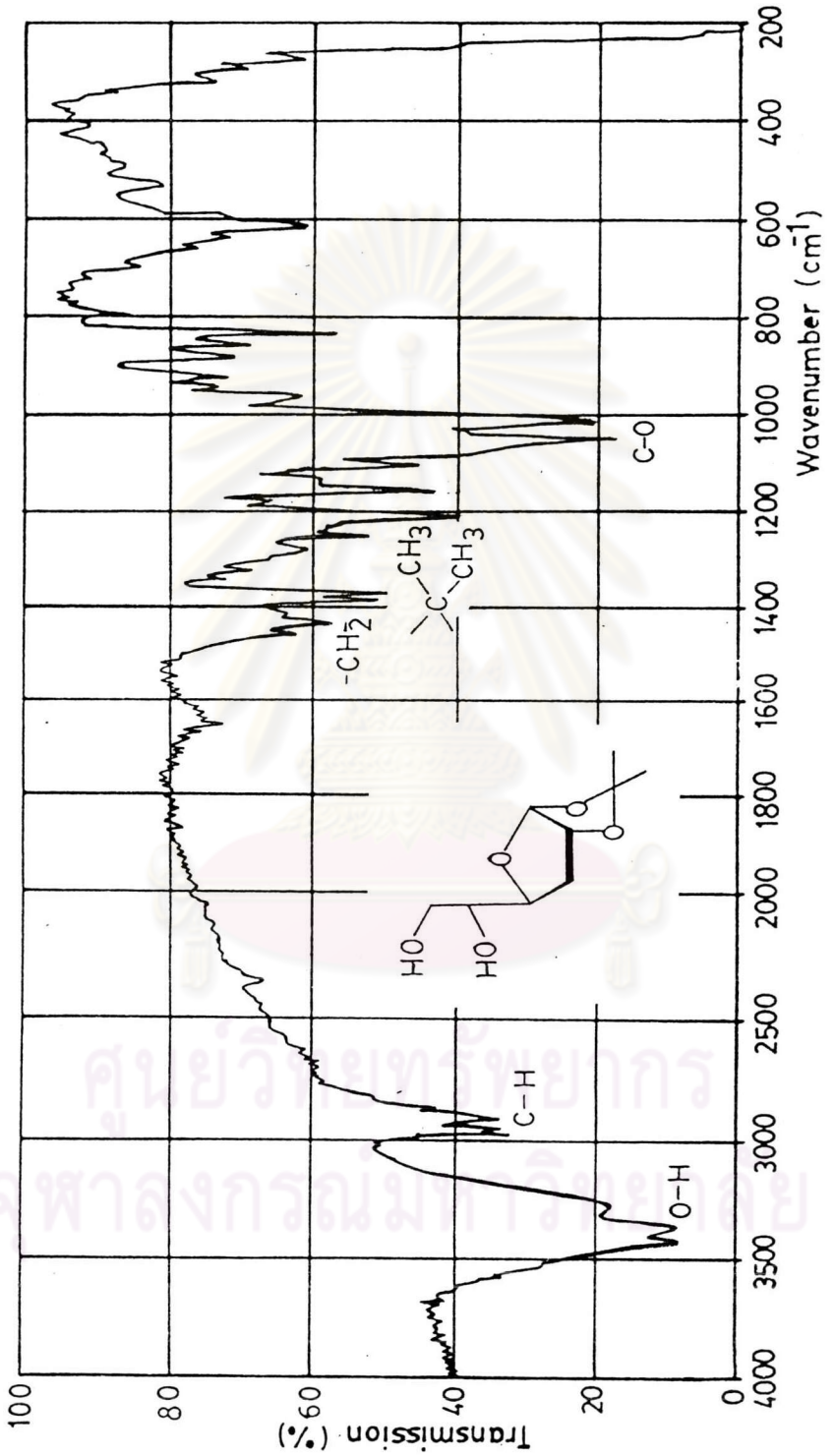

Figure 32 The IR spectrum of 3-deoxy-1,2-di-O-isopropylidene- α - D-glucofuranose (67)

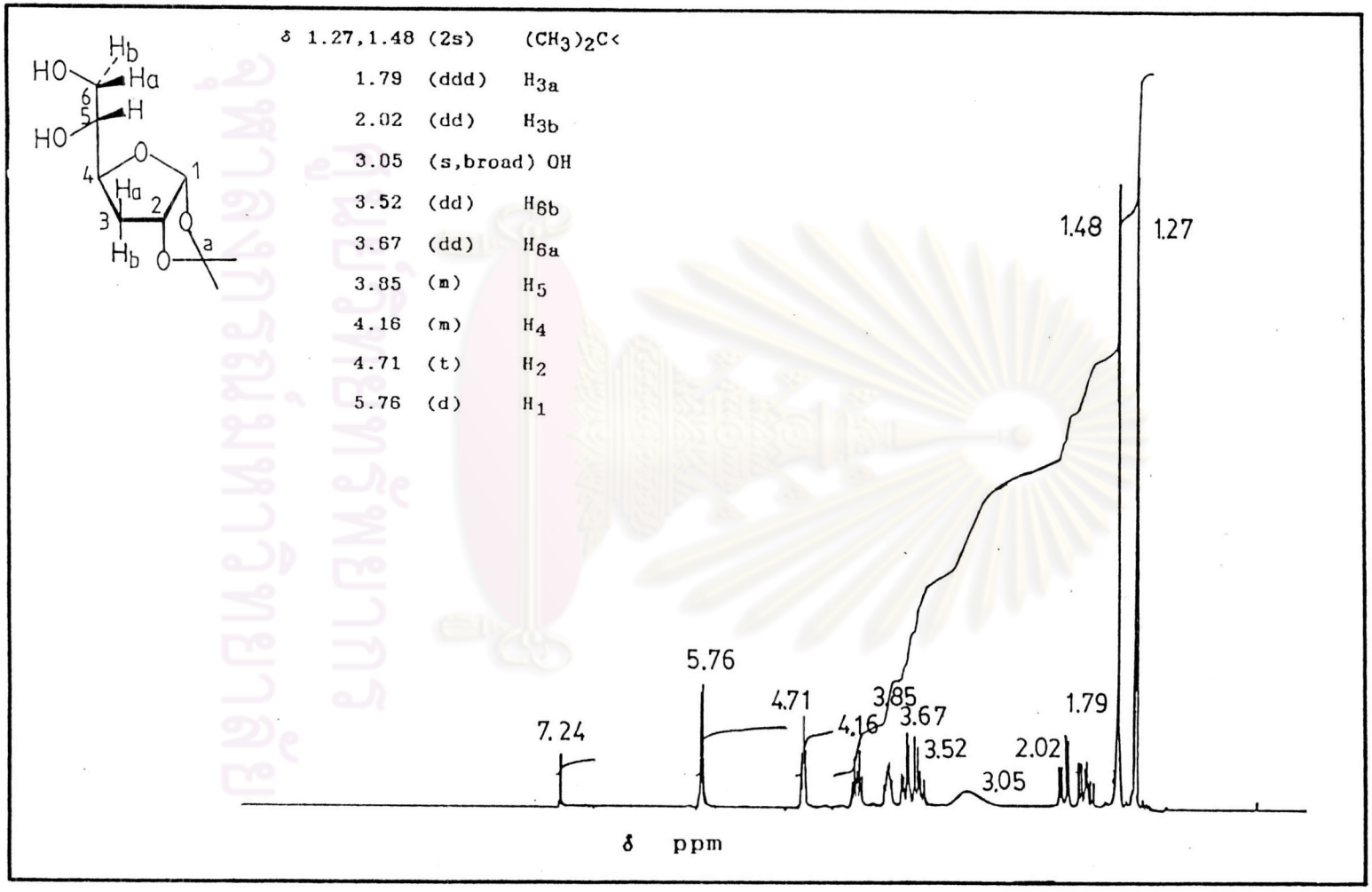

Figure 33 The PMR spectrum of 3-deoxy-1,2-di-O-isopropylidene-α-D-glucofuranose (67)

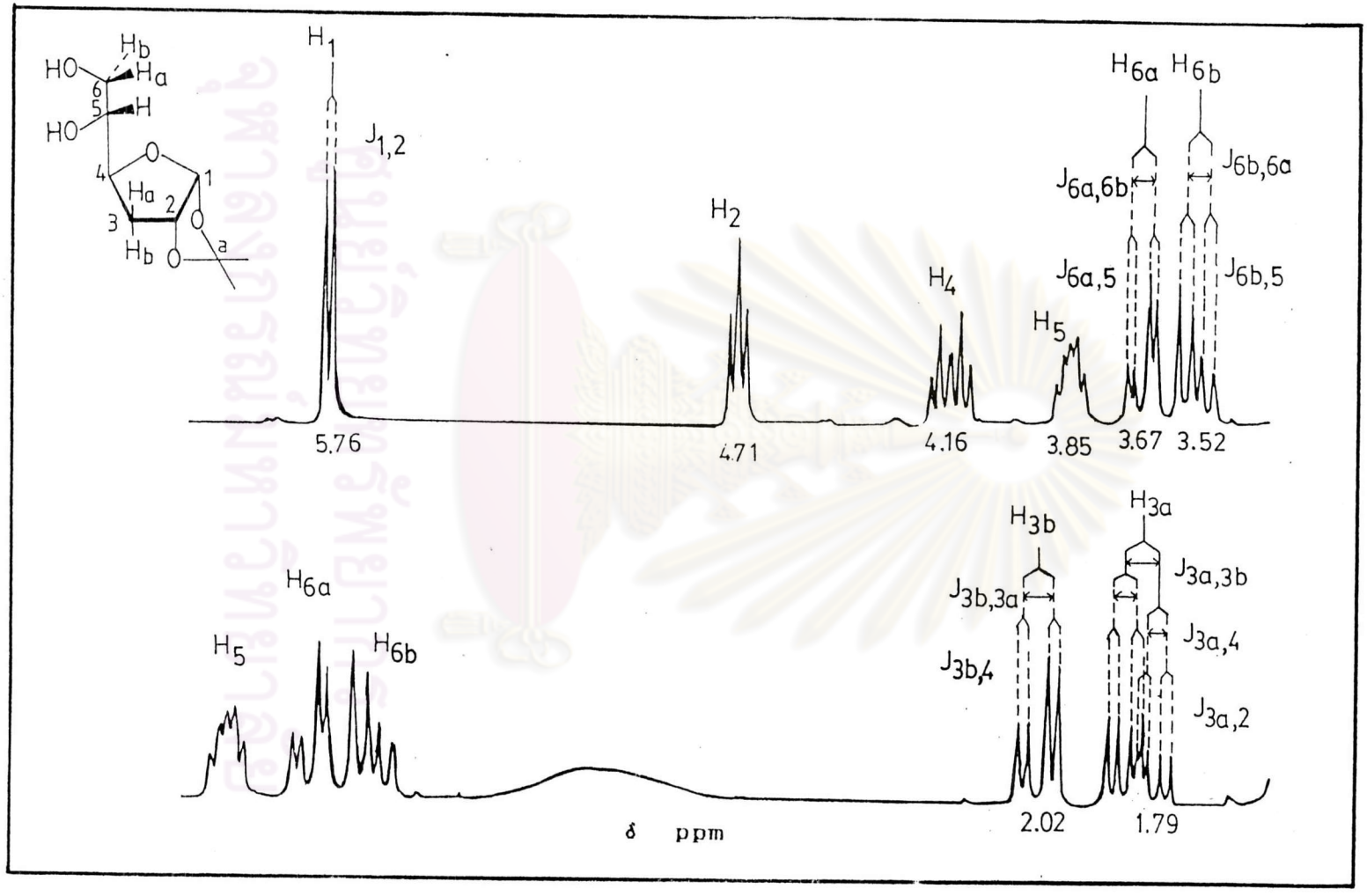

Figure 34 The PMR spectrum of compound (67) showed protons coupling and coupling constants

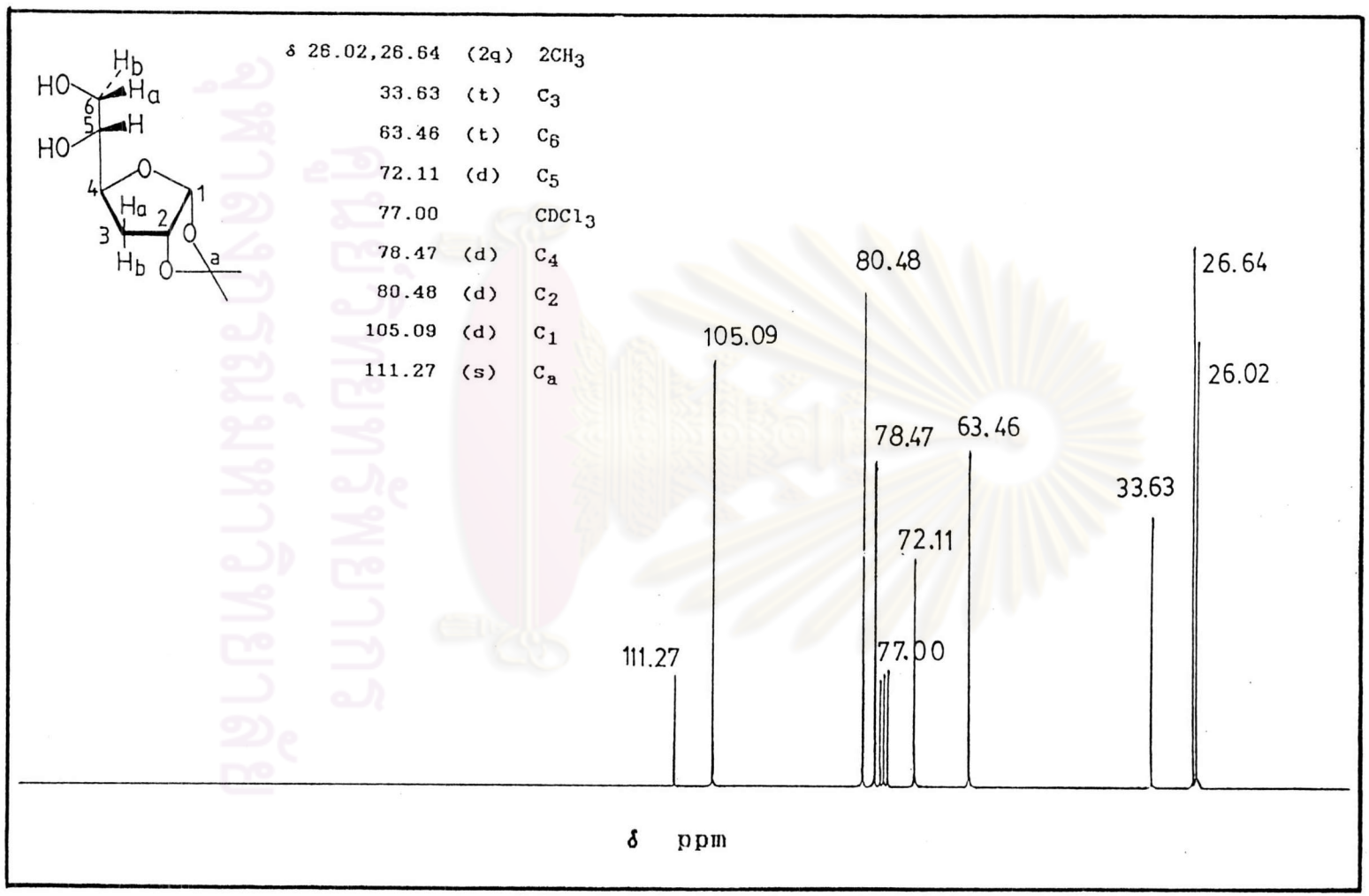

Figure 35 The CMR spectrum of 3-deoxy-1,2-di-O-isopropylidene-α-D-glucofuranose (67)

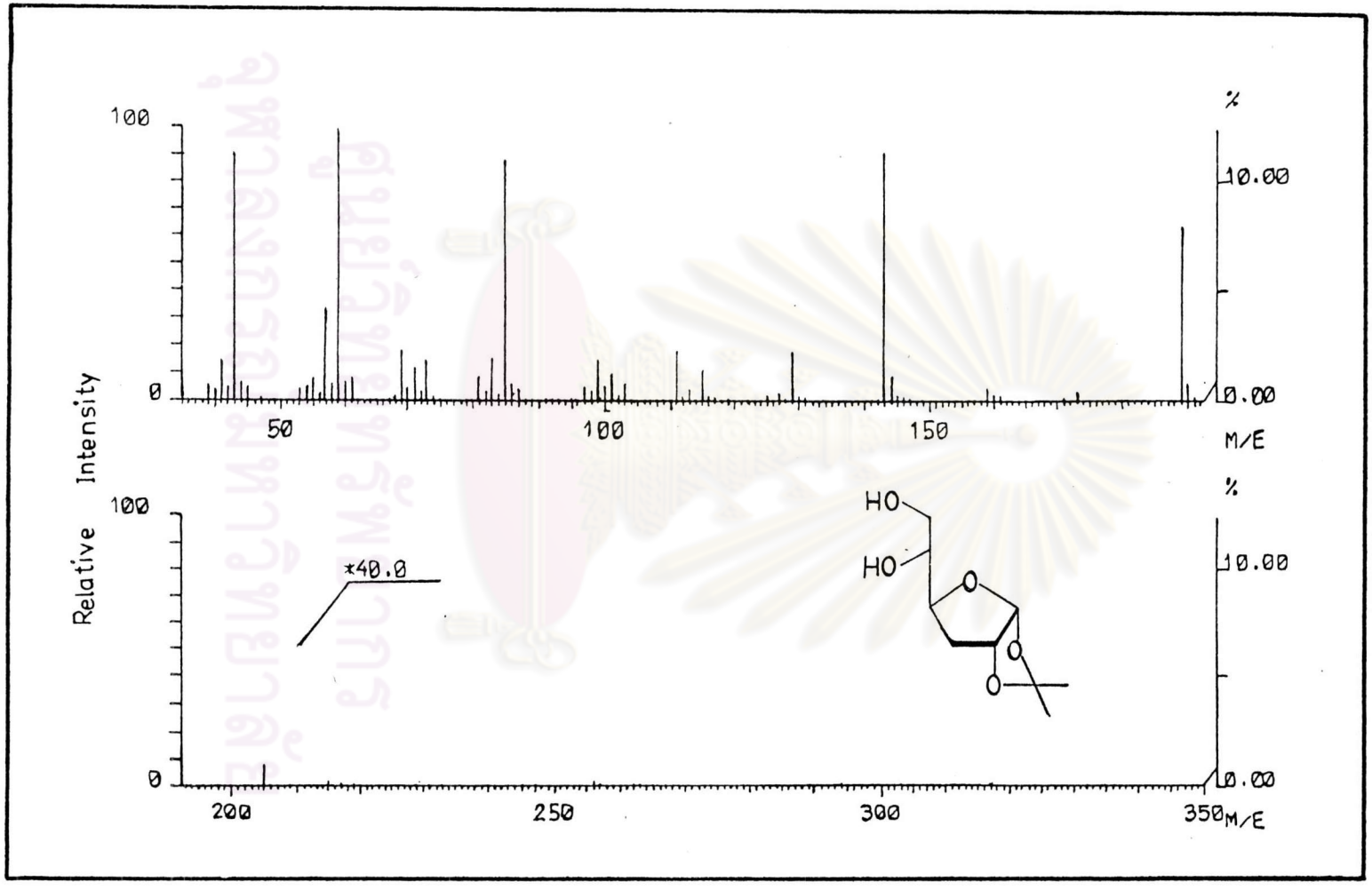

Figure 36 The mass spectrum of 3-deoxy-1,2-di-O-isopropylidene-α-D-glucofuranose (67)

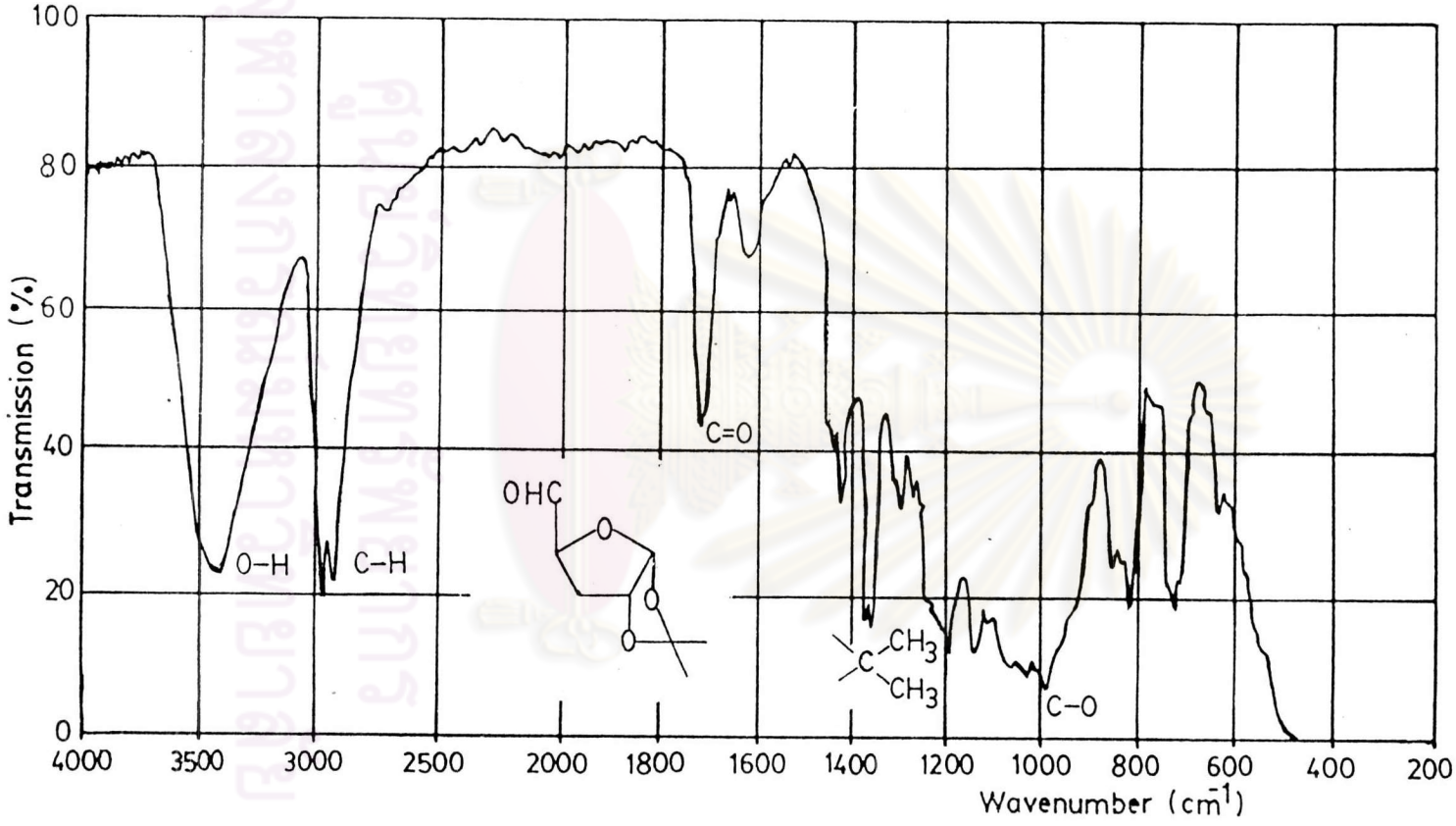

Figure 37 The IR spectrum of 1,2-O-isopropylidene-3-deoxy-α-D-erythropentodialdofuranose (68)

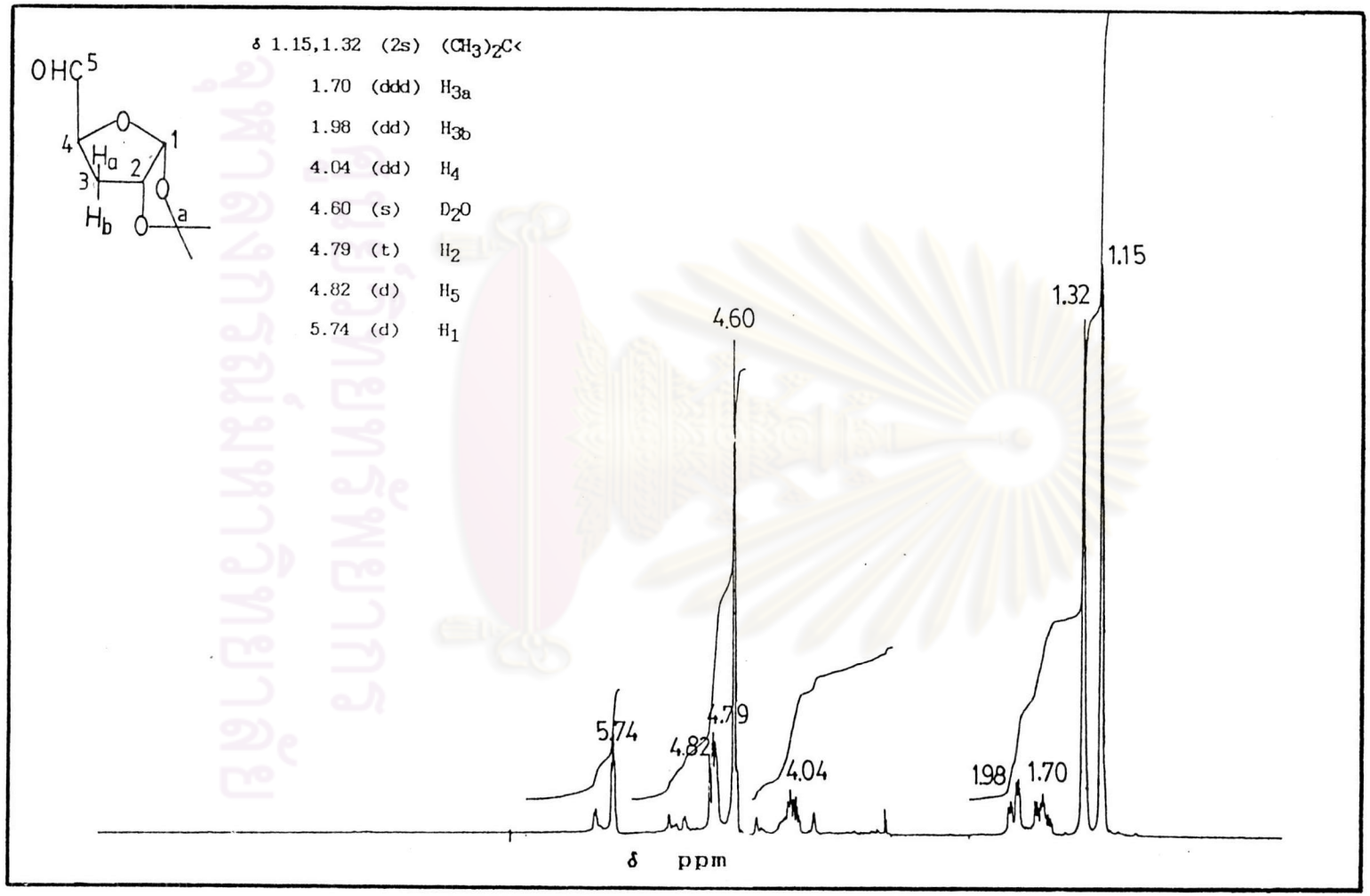

Figure 38 The PMR spectrum of 1,2-O-isopropylidene-3-deoxy-α-D-erythropentodialdofuranose (68)

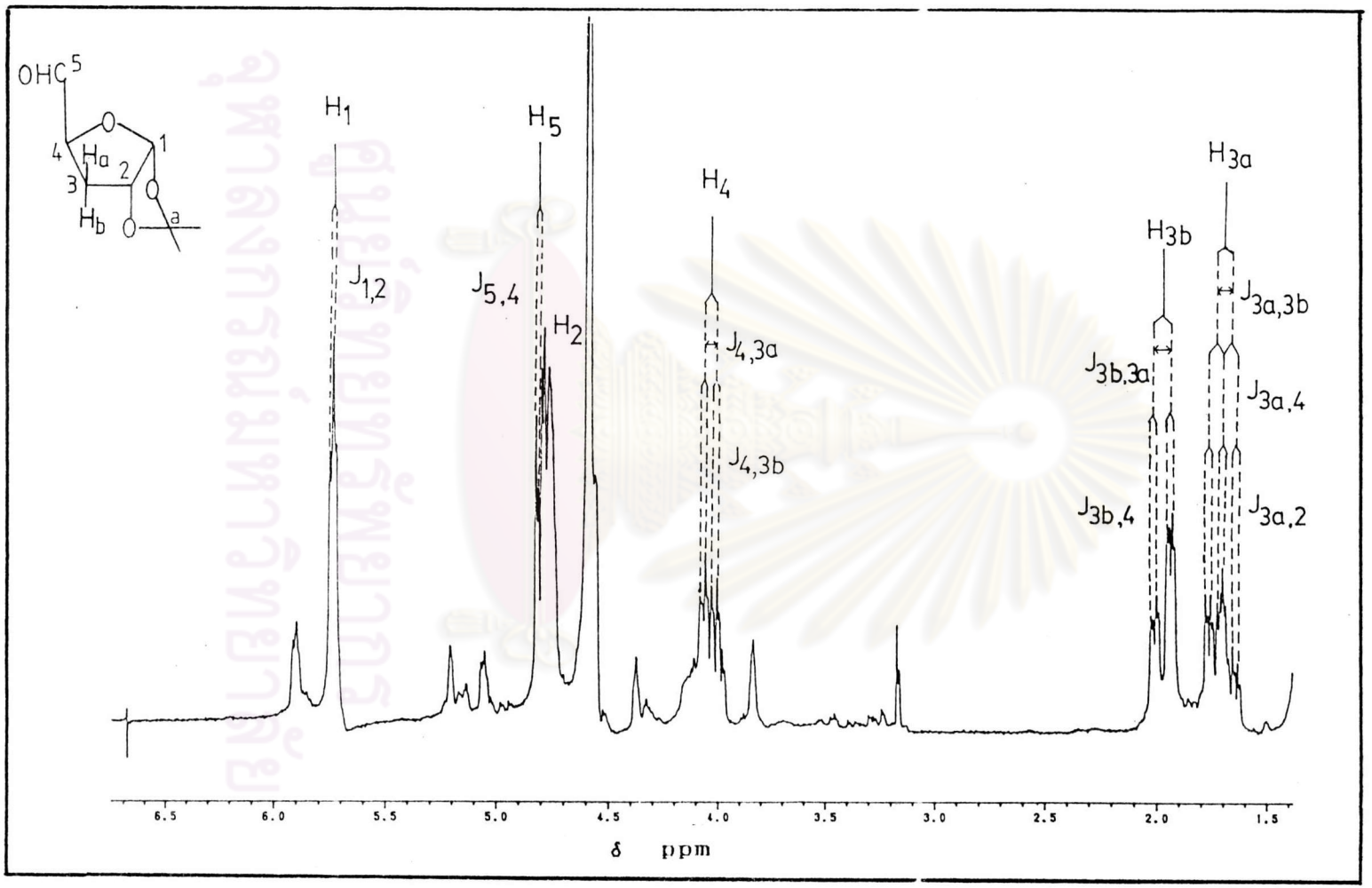

Figure 38(a) The PMR spectrum of compound (68) showed protons coupling and coupling constants

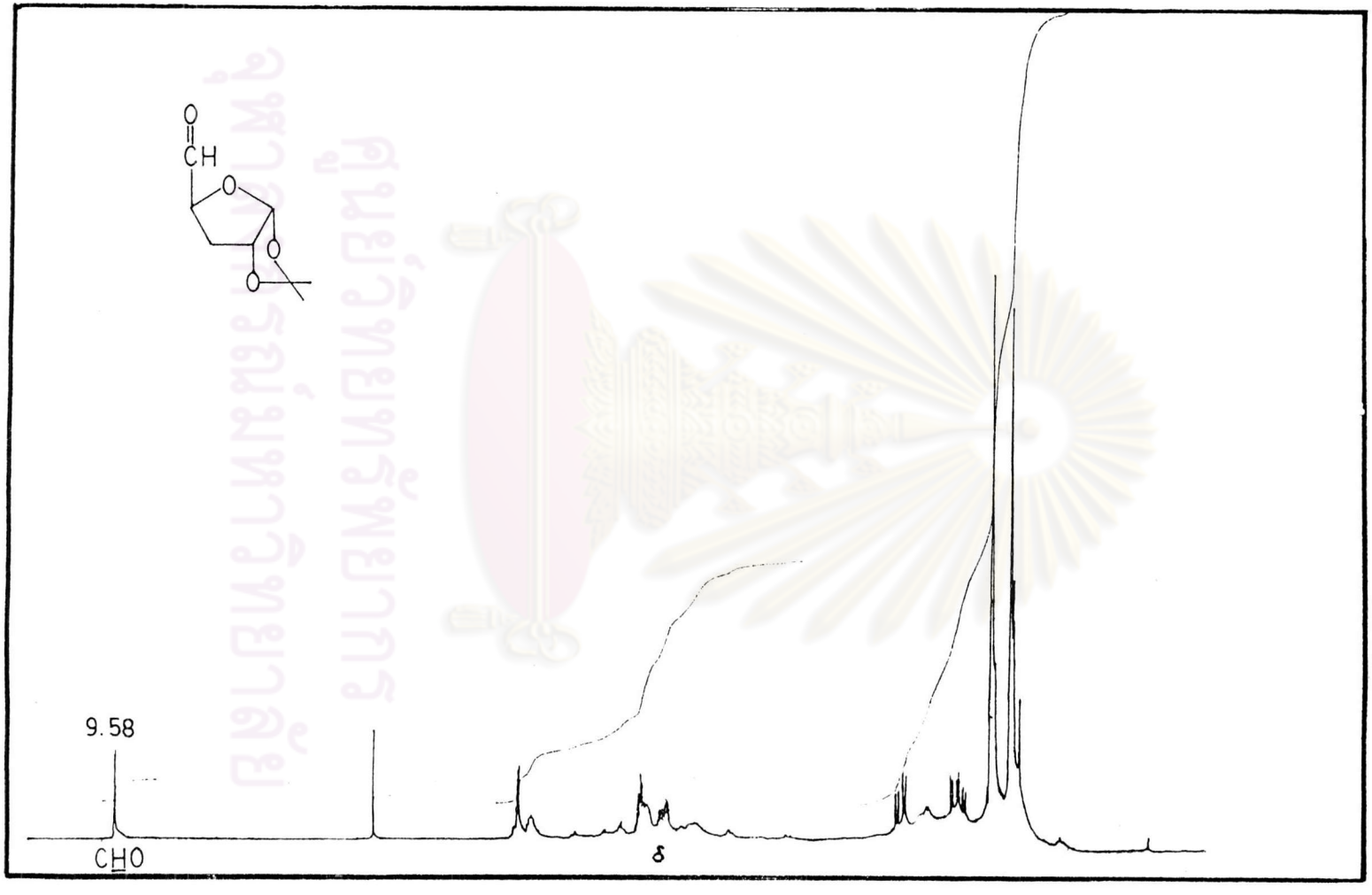

Figure 38(b) The PMR spectrum of compound (68) in $CDCl_3$ showed the aldehyde proton

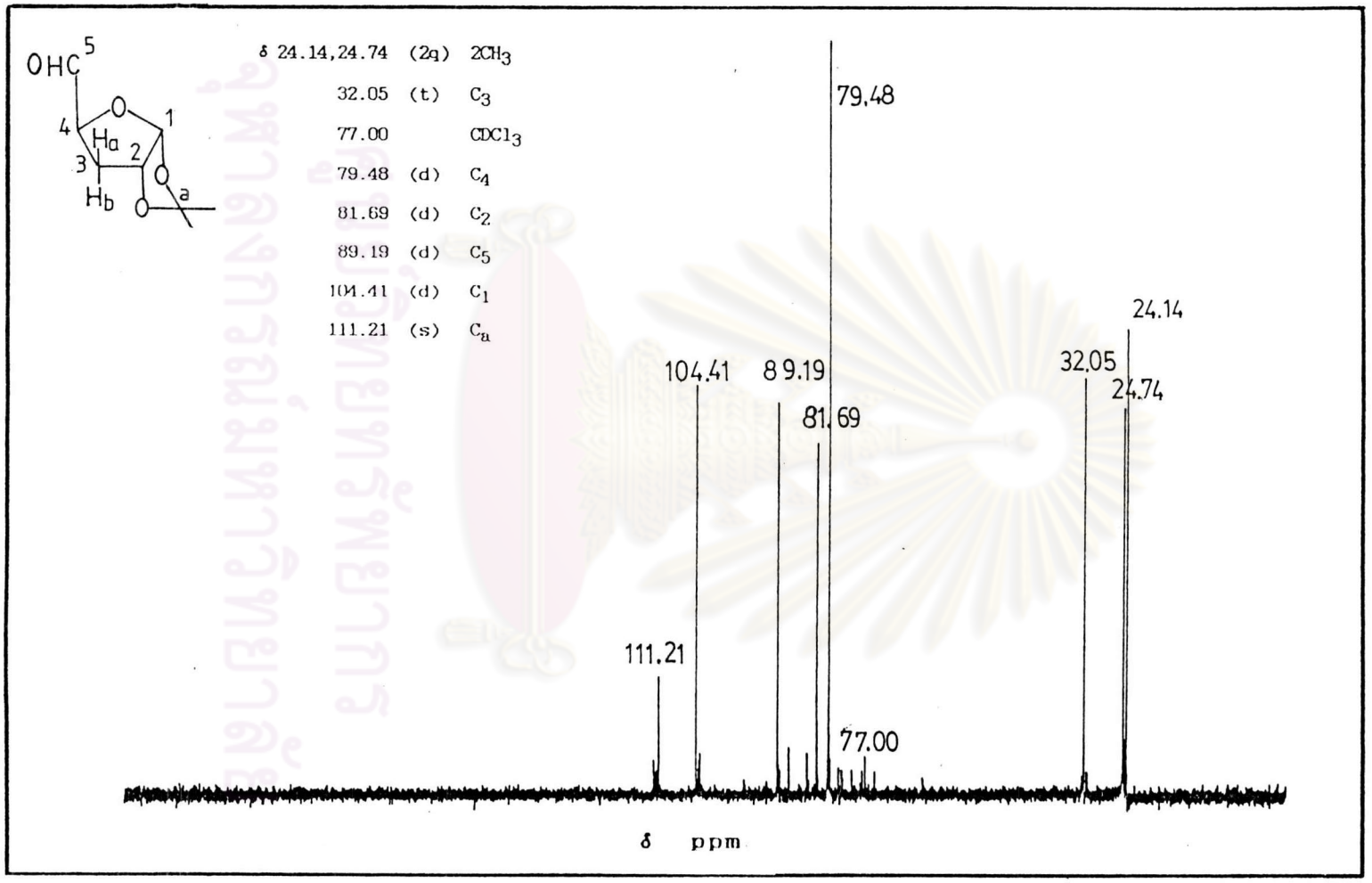

Figure 39 The CMR spectrum of 1,2-O-isopropylidene-3-deoxy-α-D-erythropentodialdofuranose (68)

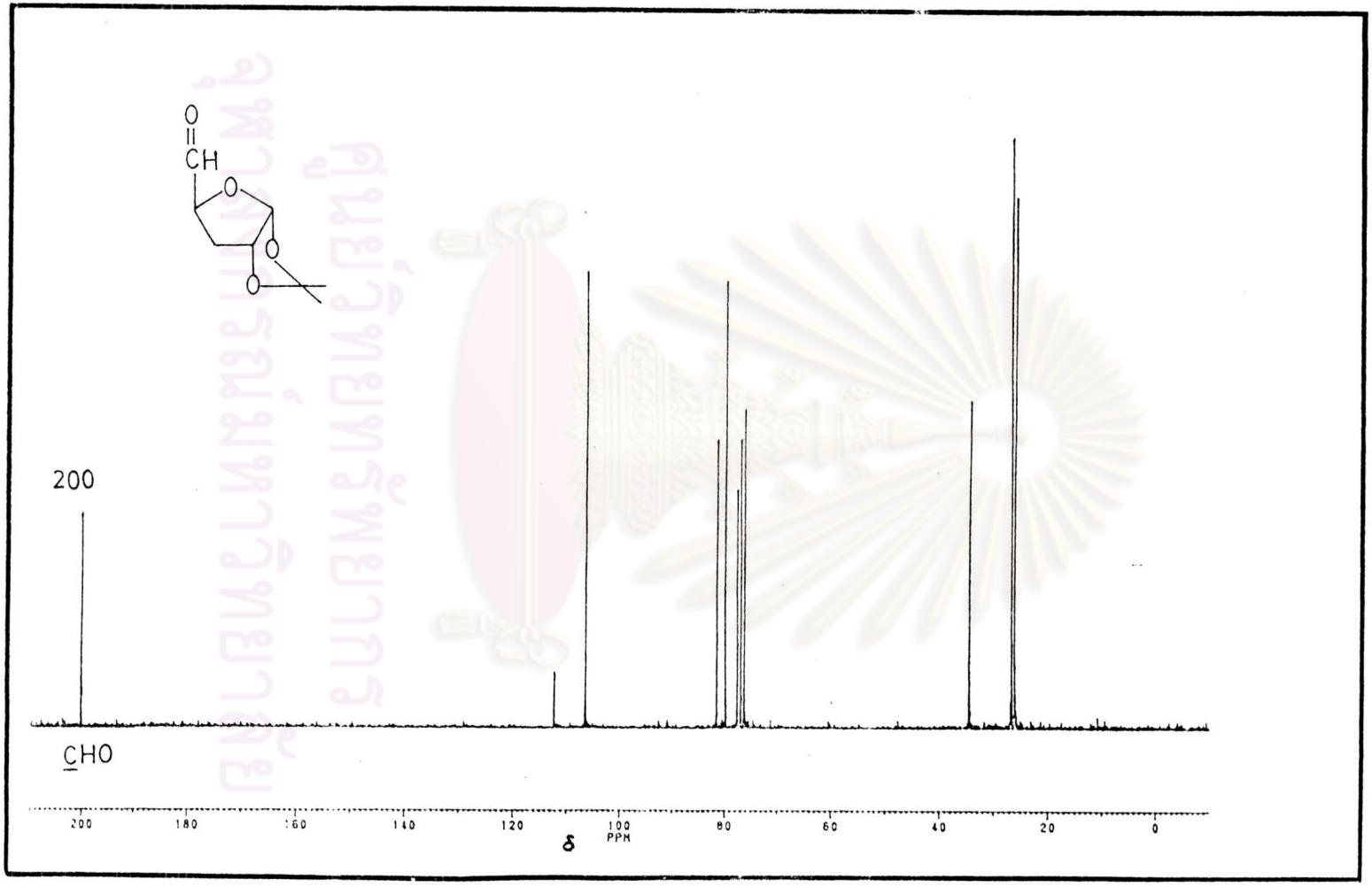

Figure 39(a) The CMR spectrum of compound (68) in $CDCl_3$ showed the aldehyde carbon

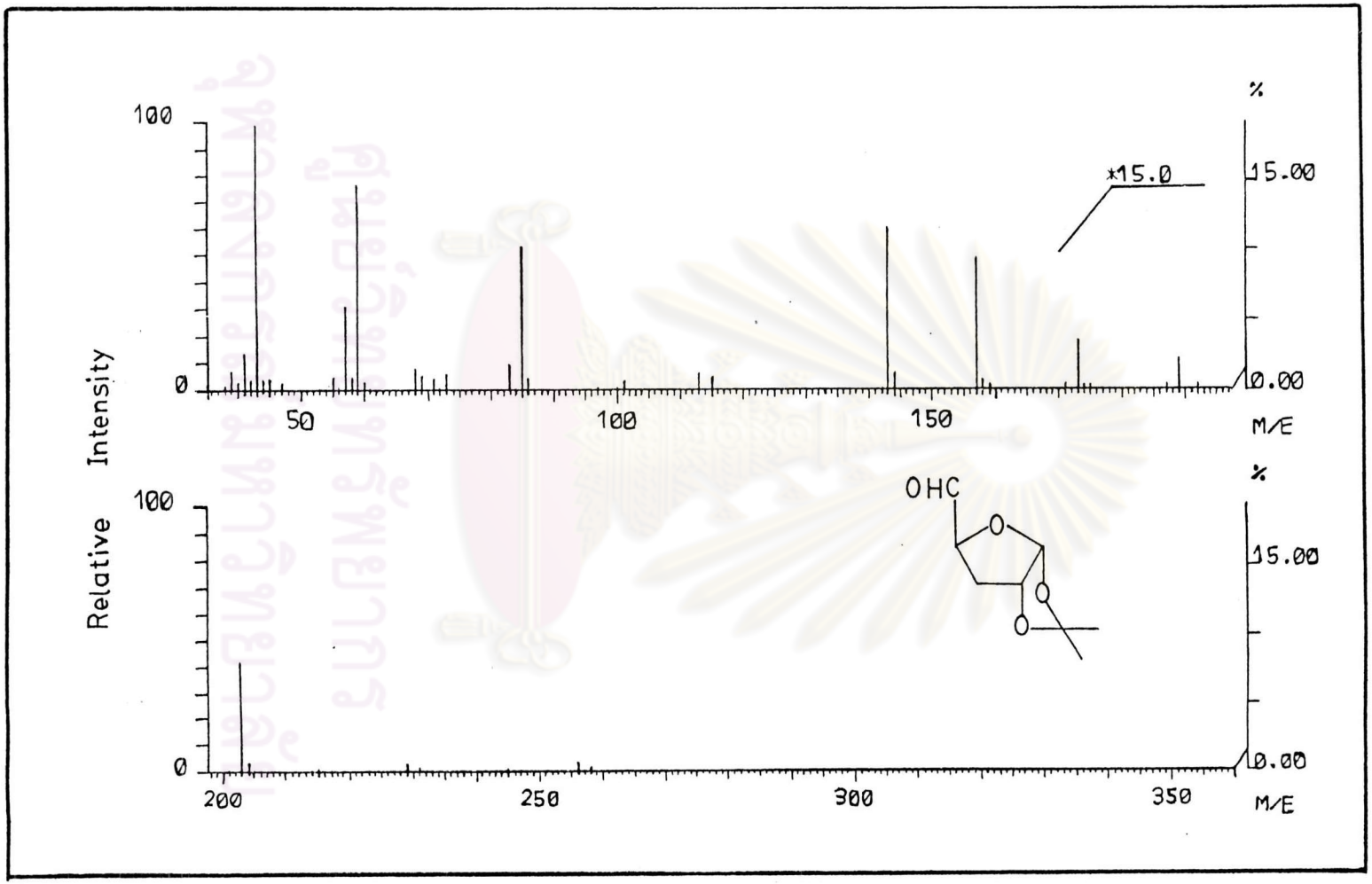

Figure 40 The mass spectrum of 1,2-O-isopropylidene-3-deoxy- α-D- erythropentodialdofuranose (68)

VITA

Miss Weeraya Lertwanitch was born on June 28,1967 in Bangkok,Thailand. She graduated with a Bachelor Degree of Science major in Chemistry from Kasetsart University in 1989. In the same year, she was a student in graduate school at Chulalongkorn University studying in Organic Chemistry and has been studying since then. She graduated with Master Degree of Science (Organic Chemistry) in 1992.