C. SIMONOVITCH

THE TOTAL SYNTHESIS OF PROSTAGLANDIN

Ph.D. Department of Chemistry

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Two routes are described which lead to the same intermediate, 6(1-heptenyl)-3-oxo-bicyclo[3.1.0]-hexane-2-heptanoic acid which has been transformed directly to prostaglandin E_1 and A_1 by the addition of hydrogen peroxide and formic acid, or indirectly to prostaglandin $F_1\alpha$ by appropriate modification of the procedure.

THE TOTAL SYNTHESIS OF PROSTAGLANDIN

A THESIS

BY

CHAIM SIMONOVITCH

Submitted to the Faculty of Graduate Studies and Research of McGill University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Ph.D.

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ACKNOWLEDGMENT

I wish to express my deep gratitude to my Research Director Dr. G. Just, for continuous encouragement and stimulating discussions which made the work under his supervision most pleasant and fruitful.

Grateful acknowledgment is made to:

Dr. J. E. Pike, The Upjohn Company, for the helpful suggestions concerning isolation, purification and treatment of the prostaglandins and for sending samples of natural prostaglandin E_1, $F_1\alpha$ and $F_1\beta$.

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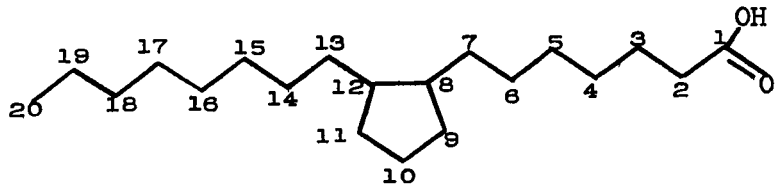
Abbreviations

t or tert	tertiary
THF	tetrahydrofuran
THP	tetrahydropyran
DMSO	dimethylsulfoxide
DMF	dimethylformamide
t BuOK	potassium tertiary butoxide
t Amyl ONa	sodium tertiary amyloxide
$(Ph)_3CNa$	triphenylmethyl sodium
DBN	1,5-diaza-bycyclo[4.3.0]nonene (5)

CHAPTER I

Isolation and structure

The prostaglandins are C_{20} unsaturated oxygenated fatty acids which incorporate a cyclopentane ring. They all have the same skeleton, prostanoic acid, but they differ from one another by the degree of



unsaturation and the number of ketonic or hydroxylic functions on the cyclopentane ring.

The first observation of a phenomenon related to the prostaglandins was made by Kurzrok and Lieb (1), who found that the human uterus reacted by contraction and relaxation upon instillation of human semen. Goldblatt and von Euler (2-5) independently demonstrated the presence of smooth muscle stimulating and blood pressure reducing agents in the human seminal plasma.

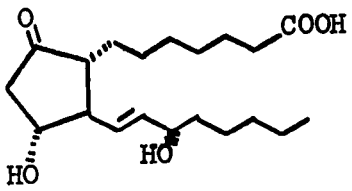
The same factors were found by von Euler and Hammarstrom (6) to be present in the sheep semen and in the glandula vescalis of male sheep. Von Euler prepared concentrates from the sheep glands and demonstrated that the physiological activity was due to lipid soluble acids which he called prostaglandin.

About twenty years later Bergström et.al (7, 8) were able to isolate prostaglandin E_1 and $F_1\alpha$ in pure crystalline form and to determine their structure (9). Four other prostaglandins were subsequently isolated and their structure elucidated (10-21).

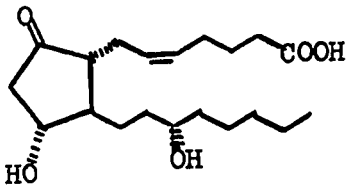
The prostaglandins (PG's) are classified into two main groups, the primary PG's and the secondary PG's. The primary are subdivided into the E and the F series. Both the E and the F type PG's have no double bond inside the cyclopentane ring, and all the E compounds have a keto group in the 9 position on the cyclopentane ring and respectively one, two and three double bonds. The Fα series have an identical structure but have an α hydroxyl group on the 9 position. The secondary prostaglandins are cyclopentenone derivatives and are subdivided into two groups according to the position of the double bond in the cyclopentene ring.

The A series (PG-217) has one double bond at the 10 position, inside the ring and respectively one or two double bonds on the side chains. The "B" series (PGE-278), has a double bond between the 8 and 12 carbons and respectively one and two double bonds in the side chains. The "A" and "B" series are characterized by their U.V. absorption at 217 and 278 mμ respectively (14, 16).

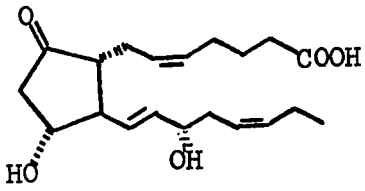
Primary PG's



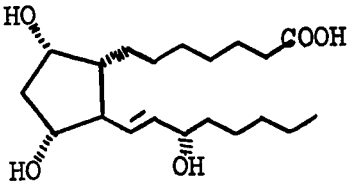
PGE_1



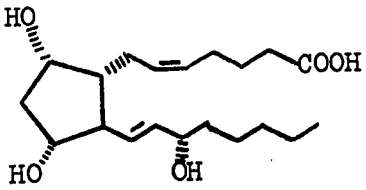
PGE_2



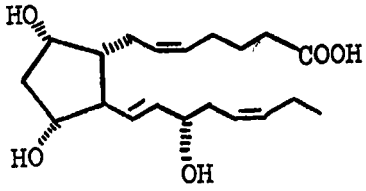
PGE_3



$PGF_1\alpha$

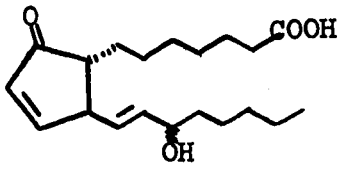


$PGF_2\alpha$

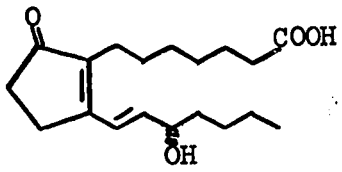


$PGF_3\alpha$

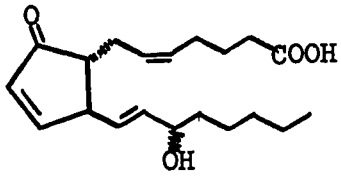
Secondary PG's



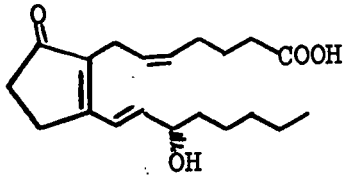
PGA_1



PGB_1



PGA_2



PGB_2

FIGURE 1

The secondary A series could be obtained from the primary E series by treatment with acid or weak base (0.5 N sodium hydroxide) which caused the elimination of the β hydroxy ketone at the 11 position.

Prolonged treatment with base causes the rearrangement of the double bond to 8, 12 position to form the B series.

The secondary prostaglandins were found to occur in the human seminal plasma (22 - 24) in considerable amounts and are formed in the body presumably by the above mentioned dehydration and rearrangement.

Another type of secondary prostaglandin which does not originate by dehydration of their primary analogs (25), are the PG's which have an additional hydroxyl at the 19 position. The structures of the various PG's are summarized in Figure 1.

The structures of the prostaglandins were elucidated by chemical and physical methods using, mainly mass spectrometry. The following degradation reactions were used to characterize PGE_1 chemically:

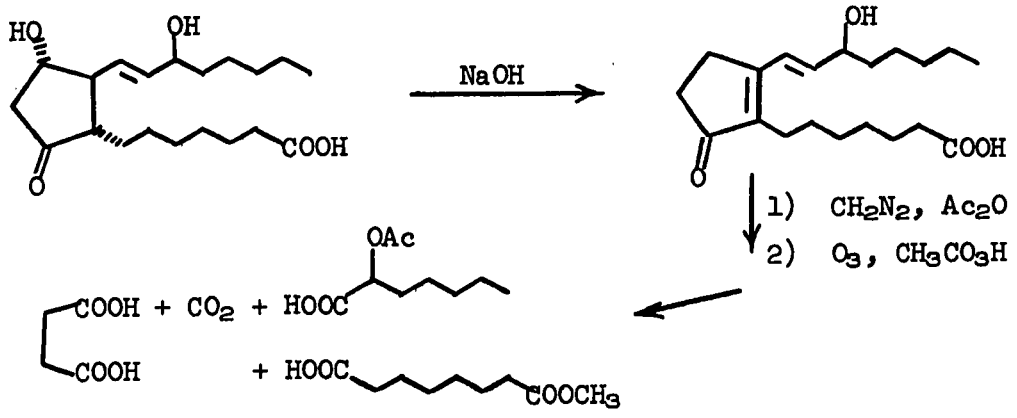


CHART 1

Oxydative ozonolysis of the acetylated methyl ester of PGB_1 (PGE_1-278) gave as degradation products succinic acid, monomethyl suberate and acetoxyheptanoic acid, which account for 19 of the 20 carbon atoms, the last carbon being degraded to carbon dioxide (see chart 1). The isolation of the α acetoxyheptanoic acid, provided a way to assign the absolute stereochemistry of the hydroxyl at C_{15}.*

A similar type of chemical degradation was carried out on the hydrogenated PGB_1:

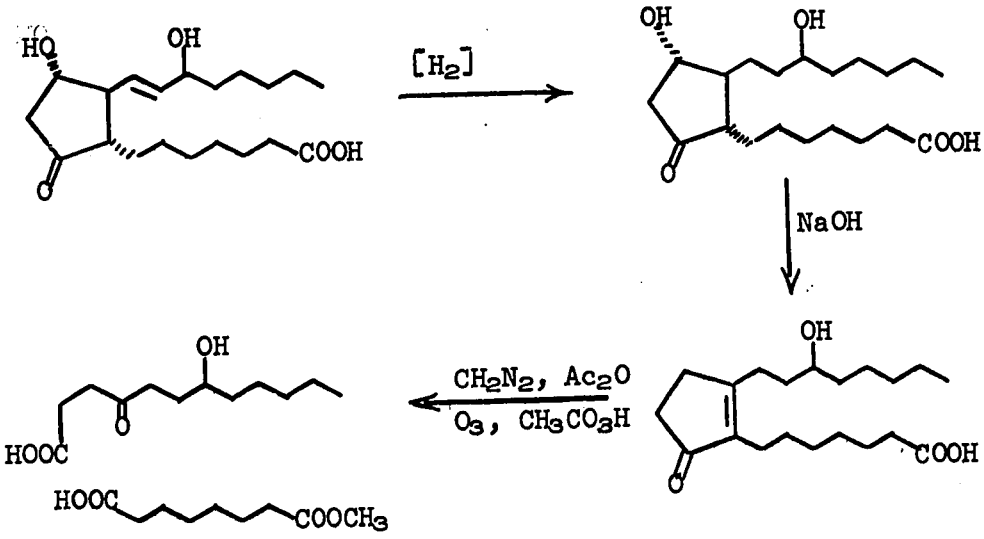


CHART 2

7-Acetoxy-4-oxododecanoic acid was obtained from this degradation.

* It has been found by Nugteren et al (20a)that the configuration of the α hydroxy heptanoic acid obtained from the above mentioned degradation is L, and not the mistaken D assignment made by Abrahamson et al (20).

A third type of chemical degradation is summarized in chart 3, and differs from the other two in that the degradation was carried out of a PGA rather than a PGB.

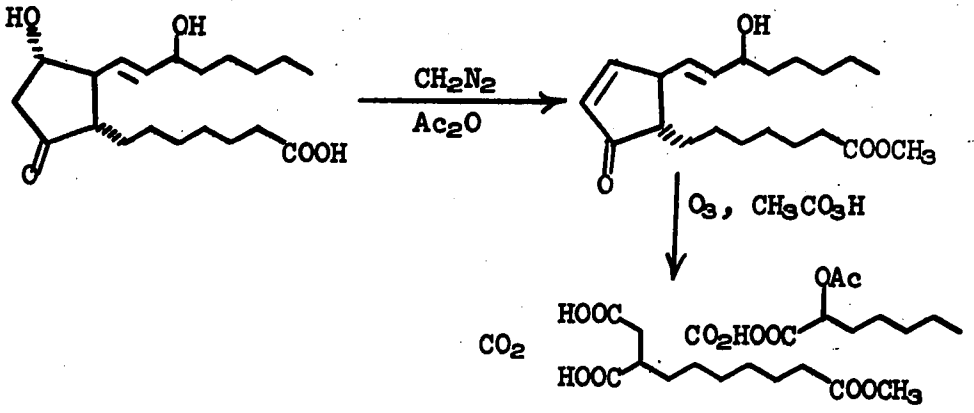


CHART 3

The assignment of the hydroxyl function in the 11 position follows from its lability to acids and bases and from the failure of reactions typical to α-hydroxyketones to occur.

The structure of PGE_1 was further confirmed by three-dimensional single crystal X-ray analysis (26) of tri—p-bromobenzoate of $PGF_1\beta$ and by preparing a synthetic specimen of 9-oxo-prost-8-enoic acid (27).

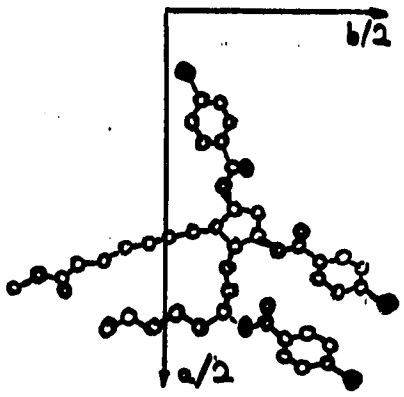


Fig. 2-Scale drawing of the tri-p-bromobenzoate of the methyl ester of compound $PGF_1\beta$ in the correct absolute configuration; deduced from the electron density map.

The structures of PGE_2 and PGE_3 were established by the use of mass spectrometry, N.M.R. spectroscopy (28) and chemical degradation.

The geometry of the double bonds in the 13 position of all the prostaglandins is trans, (exhibiting an absorption of 965 cm^{-1} in the infrared). Additional double bonds of the natural PG's at 5 and 17 positions are cis (29).

Occurence

Though the prostaglandins were first isolated from the human seminal plasma, it is evident today that they are distributed widely in several organs of the humans and other animals as established by methods by Bygdeman and Samuelsson (23-24). The sources from which PG's were isolated are summarized in Table 1:

Tissue	E_1	E_2	E_3	F_1	F_2	F_3	Ref.
semen (human)	+	+	+	+	+		30, 31
semen (sheep)	+						12
sheep vesicalis gland	+	+	+	+			8, 14, 32
human menstrual fluid		+			+		33
lung (human)					+		32
lung (monkey)					+		32
lung (ox)					+	+	32
lung (pig)					+		13
lung (sheep)		+		+	+	+	32, 13
lung (guinea pig)					+		32
brain (ox)					+		34
thymus (calf)	+						32, 35
iris (sheep)					+		36

Table 1

The Sources of the PG'S

Physiological activity

All the known prostaglandins are extremely potent in causing various biological responses. For that reason, these compounds might be useful for pharmacological purposes (37a). A few of those biological responses are systemic arterial blood pressure lowering in the case of PGE_1 and $PGF_1\beta$, pressor activity for $PGF_1\alpha$, smooth muscle stimulation, antilipolytic activity as shown by antagonism of epinephrine-induced mobilization of free fatty acids or inhibition of the spontaneous release of glycerol from isolated rat fat pods, blocking of the action of vasopressin on the bladder thus altering fluid transport, lowering of serum cholesterol, activity on the central nervous system, and inhibition of platelet aggregation (37b). The relative activities of the PGE's and the PGF's are summarized in Table 2.

Biological preparation	Response	E_1/F_1	E_2/F_2	Ref.
Cat isolated trachea	inhibition	500	30*	44, 45, 46
Guinea pig isolated ileum	contraction	45, 43		45
Chicken jejunum	contraction	40		45
Cow isolated iris	contraction	>30		45
Rabbit B.P.	depressor	>20, 13		45, 46
Chick	sedation		>15*	47, 48
Rat isolated jejunum	contraction	12		45
Cat	stupor		>6*	47, 48
Cat skeletal muscle blood vessels	dilatation	4.5		46
Hamster isolated colon	contraction	4.2		46
G.P. isolated uterus	contraction	3		45
Fat mobilization	inhibition	>2		49
Chicken rectal caecum	contraction	1.8		45
Rat isolated uterus	contraction	0.5, 1		45, 46
Rabbit isolated jejunum	contraction	0.6, 0.45		45, 46
Rabbit isolated uterus	contraction	<0.5		45
Rabbit oviduct in vivo	inhibition PGF's contract			45

Table 2 (37): Relative biological activities of PGE and PGF's on various tissues.

* Figure was calculated from results obtained from two sources.

Horton (37) compared the prostaglandins to the catecholamines and showed the similarity in their effects. He also suggested that like the catecholamines, the PG's may have different physiological activities at different sites. The prostaglandins are active even at very low concentration levels and their biological half life is very short. Because of the many biological responses, the known prostaglandins are useful to prevent, control or alleviate a wide variety of diseases and undesirable physiological conditions in birds and mammals, including humans and useful domestic animals, and in laboratory animals, for example mice, rats and rabbits. For example PGE_1, $PGF_1\alpha$ or $PGF_1\beta$ can be used to control blood pressure in hypertensive or hypotensive situations. They can be used to stimulate smooth muscle, for example, in fertility control. They can be used to study and treat animal disease conditions associated with abnormally high plasma free fatty acid levels, for example diabetic ketosis (38). They can be used as fat metabolic regulatory agents, for example in the study and control of obesity, and as serum cholesterol lowering agents to study and prevent the onset of arterosclerosis.

Prostaglandin synthesis

In spite their great physiological importance, the prostaglandins are available only in limited quantities through biosynthetic methods. It was therefore of great importance to devise synthetic routes to make the PG's available on a large scale and permit preparation of chemical analogs with extended biological half life. The first syn-

thetic specimen of prostanoic acid was prepared by Samuelsson and Ställberg (19). The aim of the synthesis was to establish the carbon skeleton of the prostaglandins. Two different routes were used and are summarized in chart 4.

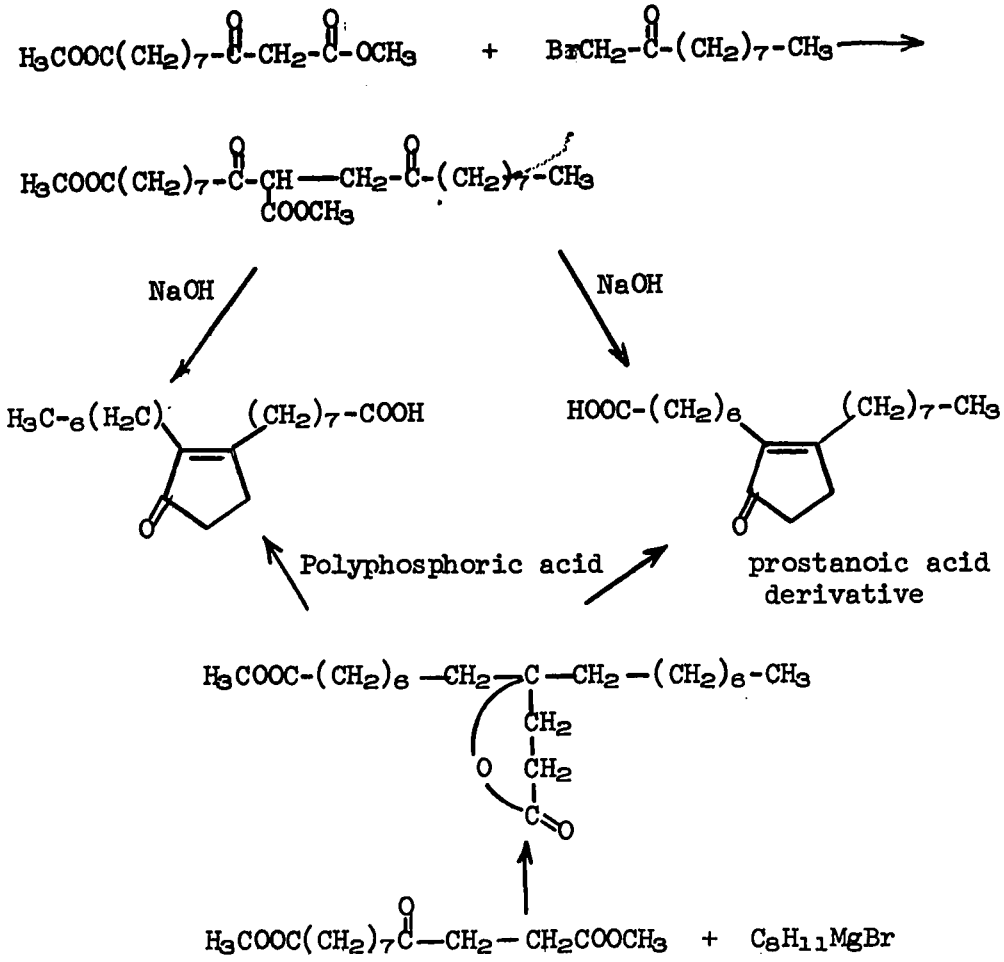
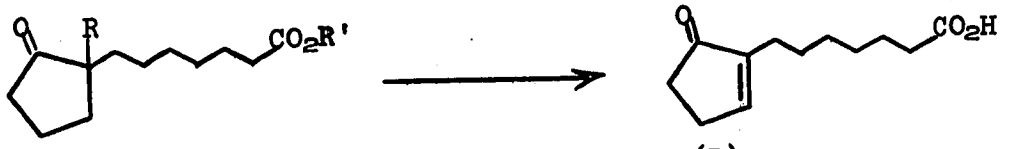


CHART 4

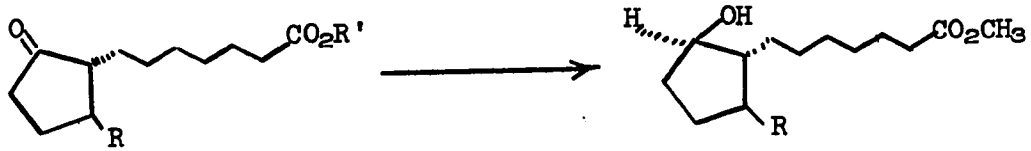
No physiological activities were reported on these simple prostanoic derivatives.

Bagli et al (39, 40) synthesized the first physiologically active non-natural 11-deoxyprostaglandin $F_1\beta$ as a racemic mixture. The main features of their synthesis are summarized in chart 5.



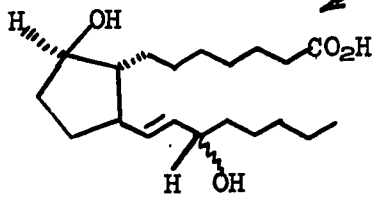
(1) R = CO_2Et, R' = Et
(2) R = R' = H

(3)



(4) R = CN, R' = H; (5) R = CO_2H, R' = H
(6) R = CO_2H, R' = CH_3; (7) R = COCl;
(8) R' = CH_3; (9) R = CO-CH=CHCl, R' = CH_3
(10) R = $CO{\cdot}CH_2{\cdot}CH(OCH_3)$, R' = CH_3

(11) R = $CHOH-CH_2-CH(OCH_3)_2$
(12) R = CH=CH-CHO



(13)

CHART 5

The first total synthesis of a natural occurring prostaglandin metabolite, the racemic ethyl ester of dihydro-PGE_1, was achieved by Beal et al (41). The synthesis involved 11 steps and the starting material was the readily available 3-ethoxy-2-cyclopentenone.

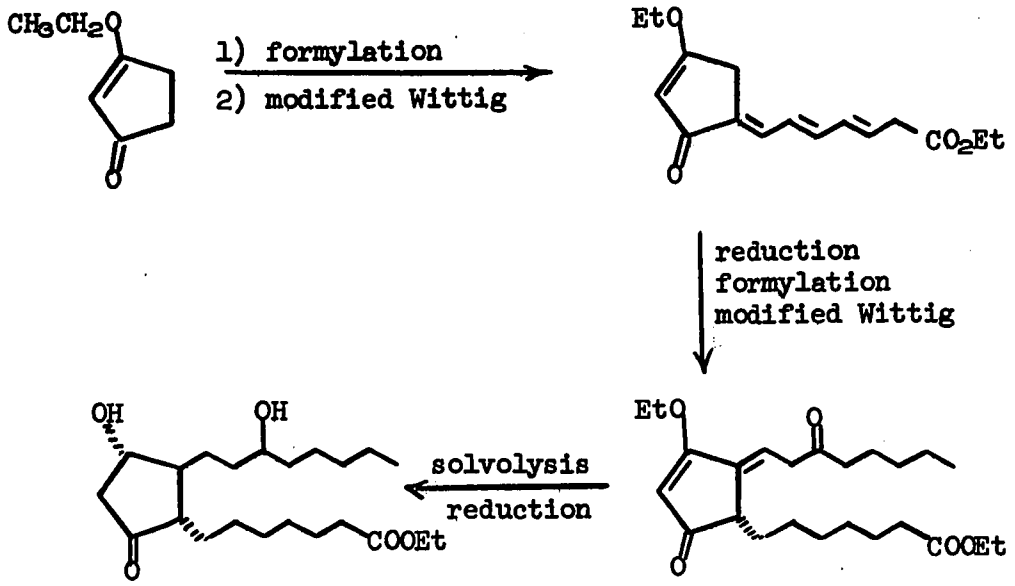
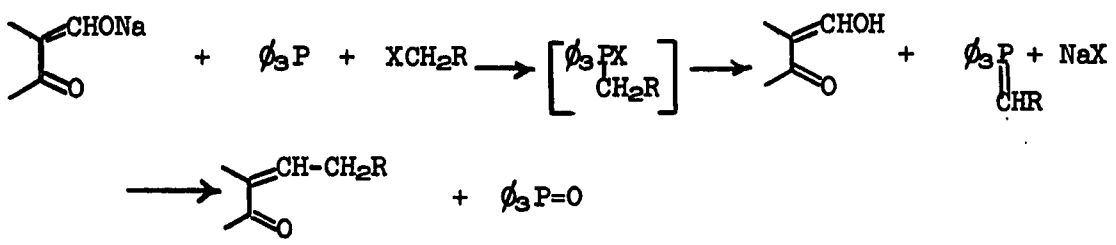


CHART 6

The key step to this synthesis was a modified Wittig reaction, in which the alkyl phosphonium bromide could react directly with the sodium salt of a formyl derivative, to produce the olefinic compound directly.



With the aim to synthesize a natural occurring PGE_1 and PGF_1 the present synthesis was devised.

The solvolysis of cyclopropyl carbinyl ions to give rearranged allyl carbinyl cyclobutyl and cyclopropyl type derivatives is well known and was studied extensively (42) Of special interest was a study made by Wiberg and Ashe (43) on the solvolysis of the tosylate of exo and endo bicyclo (3.1.0) hexane-6-methanol in acetic acid. Their results are summarized in chart 7.

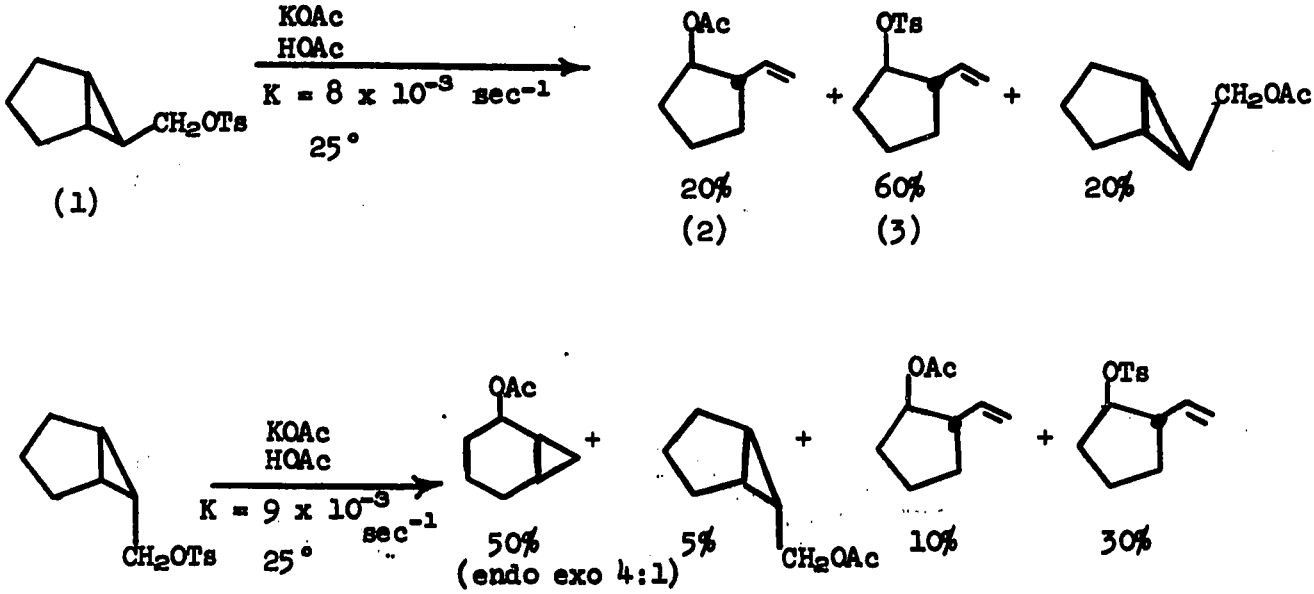
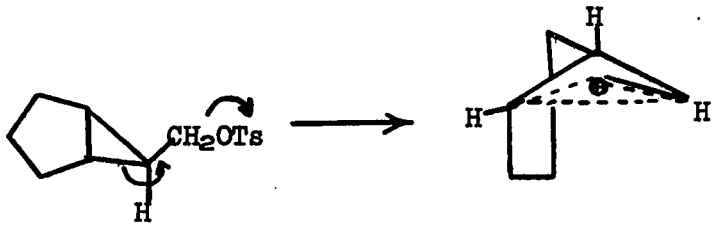
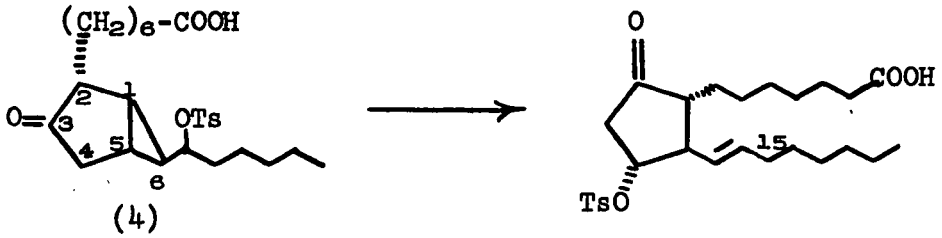


CHART 7

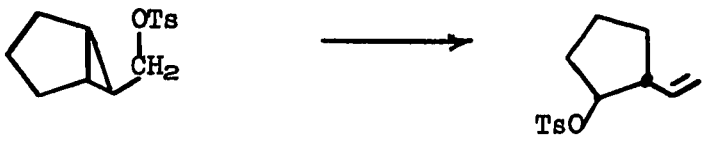
The rearrangement was suggested to proceed via bicyclobutonium ion in the following manner:



By comparing the structure of the vinyl cyclopentanols 2 and 3 to that of the prostaglandin, it can be immediately observed that 2 and 3 have the same carbon skeleton as the C_8-C_{14} portion of the latter and that the oxygen function in the vinyl cyclopentanol corresponds to the 11-hydroxy group in the PG. Addition of the appropriate functionalities at 2 and 3 positions and on the carbinol in the bicyclo (3.1.0) hexane 1 to form 4 which could then perhaps be solvolyzed in the same manner to give a prostanoic acid derivative, which lacks the oxygen function in the 15-position.

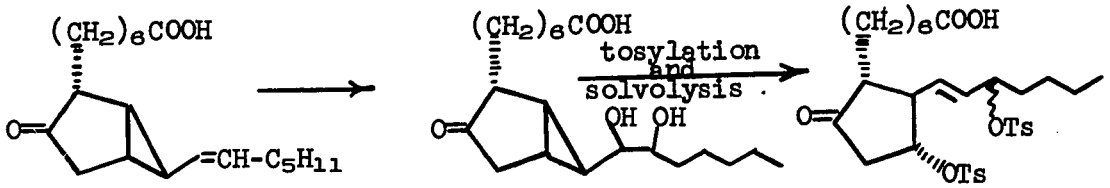


(4)



The oxygen in the 15-position could be introduced via modification of the structure of 4. The modification can be done in two different ways.

In both cases an initial introduction of a double bond, to form a vinyl cyclopropyl derivative(5) is required. The double bond in 5 is transformed to the glycol 6, which could be solvolyzed in the above mentioned conditions. With the knowledge that the homoallylic tosylate solvolysis is much faster than that of its neighbor (a secondary tosylate), it could be expected that most of 6 would solvolyze in the desired manner.

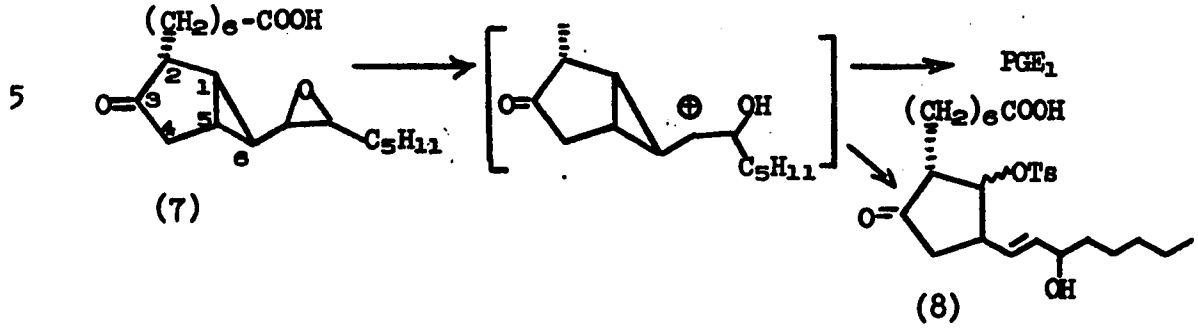


(5) (6)

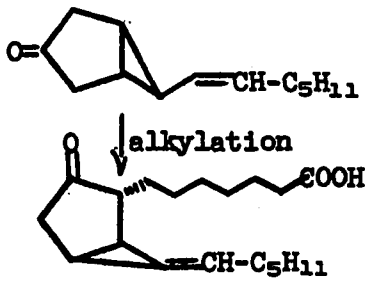
However, complications were expected to arise, since in the PGE_1, an allylic tosylate in the 15-position is formed which could solvolyze easily and might cause side reactions like diene formation or allylic rearrangement. By preparing an epoxide from the double bond in 5 the allylic tosylate problem could perhaps be solved.

It is known that reaction of olefines with hydrogen peroxide in formic acid will lead to the formation of an epoxide which under the reaction conditions will open to give a glycol monoformate, a carbonium ion being the intermediate.

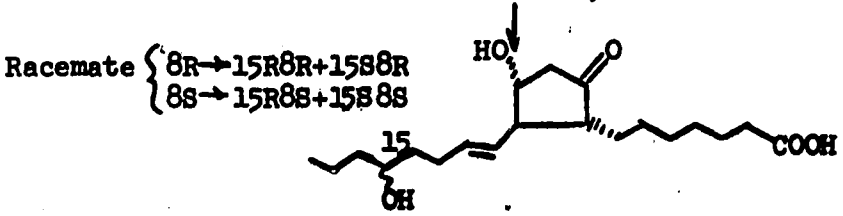
It was expected that treatment of epoxide compound 7 under these conditions could give rise to a homoallylic carbonium ion which would rearrange to give prostaglandin E formates or 8. However it was anticipated the PGE_1 would be the major product since solvation



is less hindered at the 5 position than in the 1 position in 7 (or 6). In the prostaglandins, there are 4 asymmetric centers at 8, 11, 12 and 15 positions. The synthesis outlined (see chart 8 on page 20) ensures that the OH group at the 11 position and the side chains at 8 and 12 have the proper trans relation. It can also be seen that the side chain at 8 if introduced by alkylation of ketone IX (see chart 8) should upon equilibration give the more stable trans compound as shown in 5 (50). No way to control the stereochemistry of the 15 hydroxy group could be devised. The following scheme demonstrates the possible diastereoisomers thus obtained (50A):



dl mixture, absolute configuration 8R, 8S.



15R 8R }	racemic	15R 8S }	racemic
15S 8S }	mixture	15S 8R }	mixture

Based on these considerations the following synthetic scheme was attempted. Details of the synthesis are described in Chapter II. In Chapter III another synthesis is outlined which circumvents the major difficulty encountered in the first synthesis.

CHAPTER II

The Total Synthesis of Prostaglandin - Route I

Cyclopent-3-enol(I) was readily obtained by hydroboration in diglyme of cyclopentadiene and subsequent treatment with alkaline hydrogen peroxide of the alkyl borane (51).

The alcohol group of the cyclopentenol (I) was protected as the tetrahydropyranyl ether because of its inertness to many chemical reactions, its ease of formation and quantitative cleavage in the presence of weak acids. In this second step of the synthesis some difficulties were encountered. When normal reaction conditions were applied (room temperature, chloroform as solvent and hydrochloric acid as a catalyst)(38)extensive dehydration of the alcohol occurred and the desired product was contaminated with dicyclopentadiene. Similar results were obtained when using phosphorous oxychloride or p-toluenesulfonic acid as catalysts. It was found, however, that a quantitative yield of the tetrahydropyranyl ether was obtained when alcohol I was mixed with dihydropyran and phosphorous oxychloride at 5° and allowed to react at that temperature for four hours.

The addition of ethyl diazoacetates to II was studied using different reaction conditions.(52). No solvent was used, as it was found that higher yields were obtained at a given temperature by using a mixture of pure compounds. The yield of the products was temperature dependent. The reactions were carried out between 60°-150°, and it was found that the highest yields were obtained at 100°.

FIRST ROUTE

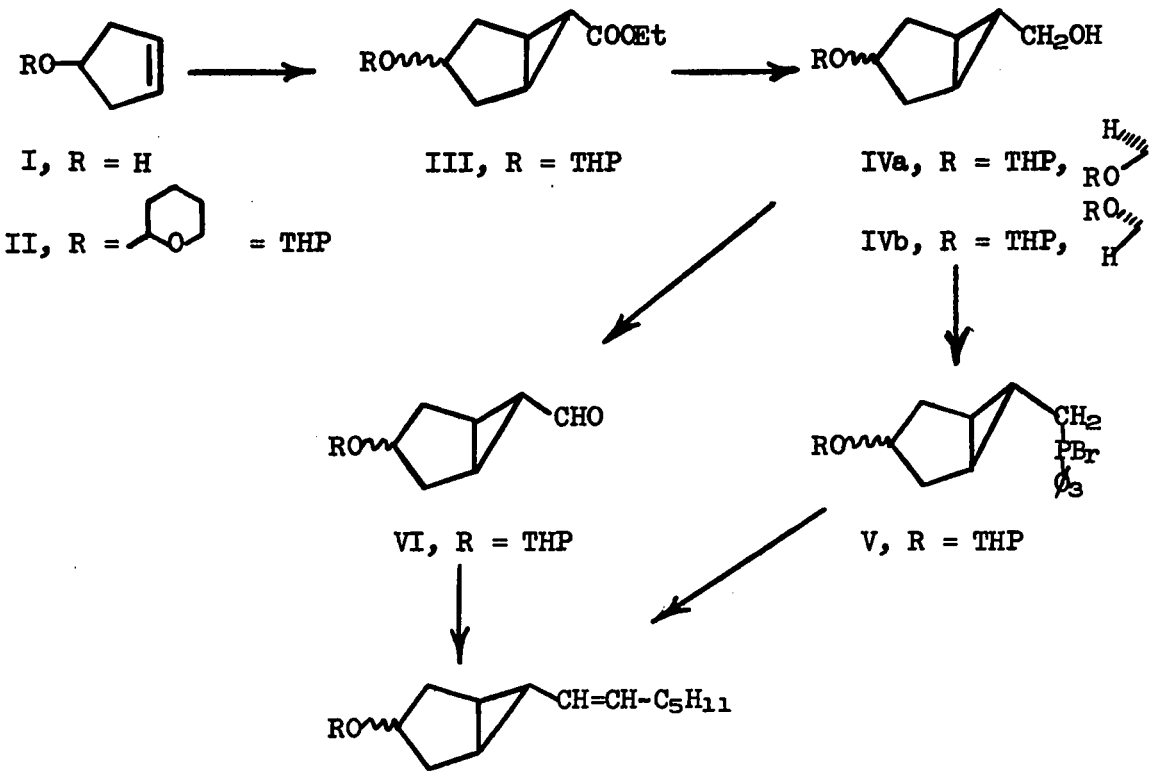


Chart 8

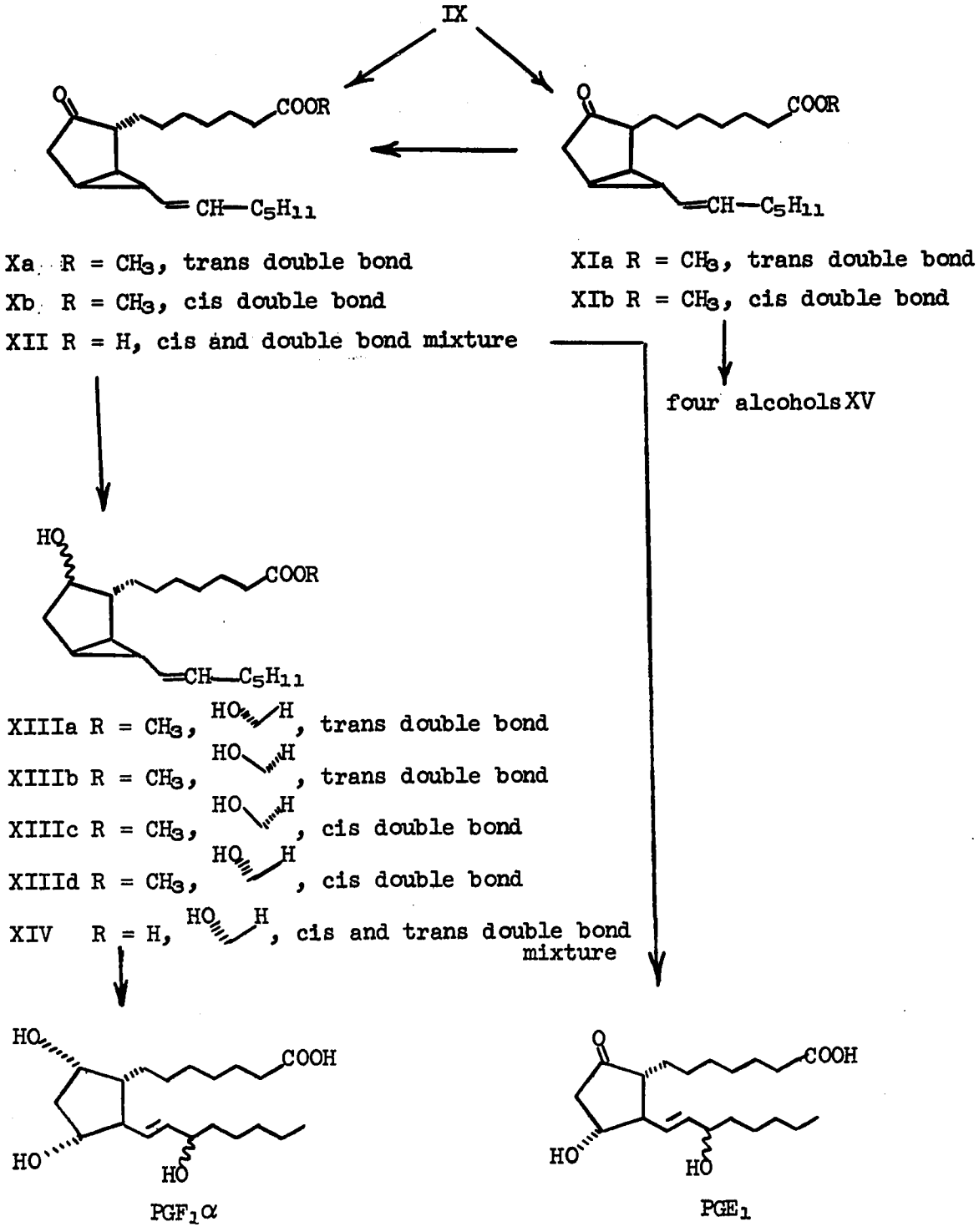


Chart 8 (cont'd.)

The catalyst used also affected the yields. Using copper sulfate pentahydrate caused extensive cleavage of the pyranyl ether and the yield of III was very low. However by using copper powder as catalyst, the reaction gave the expected products in 60% yield. The product distribution was not affected by the reaction conditions. Wiberg and Ashe (43) have shown that the addition of ethyl diazoacetate to cyclopentene gave similar bicyclic adducts in which the exo to endo ratio was 4:1. G.L.C. examination of the reaction products indicated the formation of four compounds.

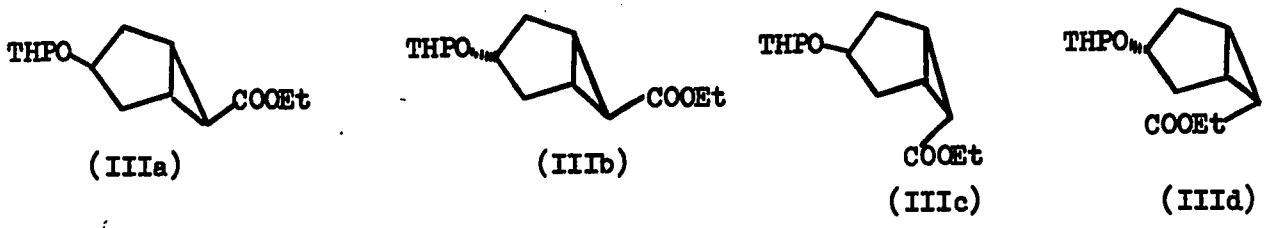


FIGURE 3

The two major products IIIa and IIIb were present in a ratio of 2:1, IIIc and IIId were obtained with the same ratio, the ratio of exo to endo products (IIIa: IIIc, IIIb: IIId) was 4:1.

Treatment of the mixture of III with methanolic sodium methoxide under reflux resulted in the epimerization of the two minor products IIIc and IIId to the corresponding exo epimers IIIa and IIIb. The epimerization reaction and the relative ratio of the products formed the basis of the stereochemical assignment, in analogy to the results obtained by Wiberg and Ashe.

Reduction of the mixture of III (IIIa, IIIb, exo, α and β pyranyloxy relative to cyclopropyl) with lithium aluminum hydride,

gave a mixture of two epimers. The two alcohols had different chromatographic mobilities and could be separated easily using t.l.c. or g.l.c. The two compounds had essentially identical i.r. and n.m.r. spectra.

In the oxidation of alcohol IV to the corresponding aldehyde VI the problem was to keep the protective group from cleaving in the usually acidic conditions of the oxidation and to stop the oxidation at the aldehyde stage. In order to overcome the first difficulty oxidation with lead tetraacetate in pyridine (53) and the Sarrett oxidation (chromic acid in pyridine) was tried. However, the yields were very low. Even though the alcohols were in contact with the oxidizing agent for a long period of time, large amounts of starting material were recovered.

It was found that the Jones oxidation (54) gave moderate yields of aldehyde VI at 20°, the remainder being the corresponding carboxylic acid and products arising from cleavage of the protecting group and subsequent oxidation. By reducing the temperature higher yields of the aldehyde were obtained. The highest yield (80%) was obtained at -15°, and the reaction was complete at that temperature after 7 minutes. The two aldehydes obtained could not be separated by chromatography. Both exhibited a strong carbonyl band at 1700 cm^{-1} (C=O α to cyclopropyl). In the n.m.r. spectrum the aldehyde protons of the two isomers appeared at δ= 9.2 ppm (major) and δ= 9.0 ppm (minor). The isomers ratio was 2:1. If the equilibration from endo to exo was not carried out on II, it could be done at this stage by using sodium tert. amyloxide in tert. amyl alcohol. The equilibration could be followed by disappearance

of the signal for the aldehydic protons of the endo isomers (δ= 9.4 ppm) in the n.m.r. spectrum.

The Wittig reaction (55) on VI to give VII was also carried out under different reaction conditions in order to maximize yields. The results obtained with different solvents and bases are summarized in Table 3.

Phosphonium salt	Base	Solvent	Temp.	Time	Yield	Ref.
Hexyltriphenyl phosphonium bromide	$(DMSO)^-Na^+$	DMSO	55-60°	6 hr.	15%	56
"	NaH	Benzene	boiling	7	15%	
"	NaH	THF	boiling	7	30%	
"	D.B.N.	DMSO	80°	4	0	
"	BuLi	Benzene	boiling	7	20%	
"	"	THF	boiling	6	50-80%	
formation of phosphorane in ether						

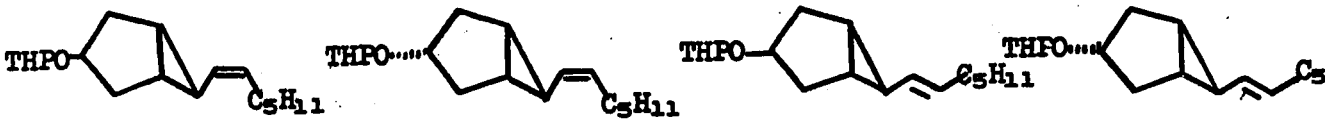
TABLE 3

Wittig reaction of aldehyde VI with hexyltriphenyl phosphonium bromide.

The formation of the phosphorane was dependent on the base used. It was found that it was formed rapidly and completely by using butyl lithium in the tetrahydrofuran.

The reaction of the aldehyde and the phosphorane was very fast and indication of it was the disappearance of the deep orange color of the phosphorane and formation of a heavy white precipitate. The breakage of the betaine was solvent dependent and the highest yields were obtained by using boiling tetrahydrofuran. Since Wittig reactions are not stereo-selective, four isomers of VII were expected, due to geometric isomerism

around the double bond and syn and anti relation to the cyclopropyl group of the tetrahydropyranyloxy function.



(VIIa) (VIIb) (VIIc) (VIIα)

FIGURE 4

The isomers of VII had very similar chromatographic mobilities and could not be separated. On gas chromatography four products were detected in the ratio 2:2:1:1. Since the ratio of the α to β isomers was 2:1, it followed that cis and trans isomers were formed in the ratio of 1:1.

A different path to obtain VII could be followed by transformation of the alcohol IV to the phosphonium salt V (57) and submitting it to Wittig reaction with n - hexanal. This alternative had the disadvantage of giving a low (30%) yield of V.

Having now a compound which had a cyclopropyl vinyl system, which was expected to be sensitive to acids, it was thought that the acidic cleavage of the protecting pyranyl group to give VIII might result in ring opening as well. The cleavage could be effected using oxalic acid in methanol, without any of the cyclopropyl ring opening.*

* Later it was found that the alcohols were also stable to methanolic hydrochloric acid.

The four alcohols thus obtained could be separated by t.l.c. or by g.l.c. and were characterized by their relative ratio and i.r, and n.m.r. spectra. These data are summarized below.

Relative stereo chem. of OH	Ring carbinolic proton in δ ppm	Geometry of double bond	Isomer ratio
α	3.94	trans	2
β	4.32	trans	1
α	3.96	cis	2
β	4.38	cis	1

TABLE 4

The mixture of the alcohols was oxidized with dilute Jones reagent (54)at -5° to give ketone IX in 80% yield. Two ketones were detected on t.l.c. (silica gel G impregnated with 3% silver nitrate) and g.l.c. They were separated and characterized by their i.r. and n.m.r. spectra. One ketone exhibited a strong bond at ν = 960 cm^{-1} which could be assigned to the trans double bond. The other isomer did not exhibit any absorption at this region and was therefore the cis isomer. In the n.m.r. the vinylic protons in both cases exhibited a complex pattern. From a simple analysis (spectra 3,4 - pp. 74,75) it appeared that J_{H-H} (vinyl) was 11 cps for the cis compound and 15 cps the trans compound.

The alkylation of IX presented major difficulties. In part the difficulty was due to concurrent reactions like rearrangement of the formed enol to form a cyclopentenone derivative, aldol condensation of IX and dialkylation.

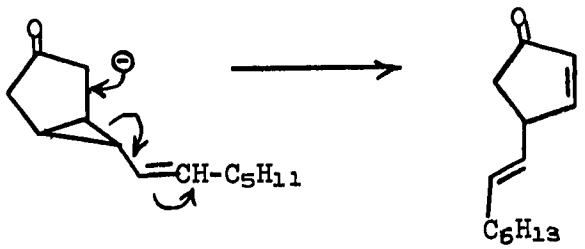


FIGURE 5

With the aim to achieve a reasonably satisfactory yield, numerous different reaction conditions were used. Various bases, solvents, leaving groups on the alkylating agent and different solvent volumes for a given amount of reactants were employed. It was also found that the order of adding the reactants and the presence of oxygen affected the yield of products and side products greatly, resulting in subsequently difficulties in purification. Some of the reaction conditions used are summarized in Table 5.

Base	Solvent	Ratio base/	Ratio ester/ketone	Reaction temp.	Yield of X
t. BuOK	t. BuOH	2, 3	6	room temp. b.p. of solv.	0. 5%
t. BuOK	D.M.S.O.	2, 3	6	80°	10%
t. BuOK	benzene	2, 4	6	b.p. of solv.	5%
t. BuOK	T.H.F.	2	6	b.p. of solv.	25%
t. BuOK	D.M.E.	2, 4	6	"	35%
t. amylONa	t. amylOH	2	6	"	0%
t. amylONa	toluene	3	6	"	10%
t. amylONa	D.M.F.	2	6	"	10%
$NaNH_2$	T.H.F.	2, 3	6	"	25%
$NaNH_2$	toluene	2	6	"	0
NaH	benzene	3	6	"	5%
PhCNa	ether	1	6	"	0
Na(D.M.S.O.)	D.M.S.O.	2	6	80°	5%

TABLE 5

Reaction conditions used for alkylation of ketone IX with methyl-7-iodoheptanoate.

As can be seen from table 5 the highest yields were obtained by using potassium t-butoxide in boiling dimethoxyethane, or boling tetrahydrofuran. Dialkylation occurred to the extent of about 10% and caused difficulties in the purification.

In order to obtain higher yields, the leaving group of the alkylating agent was changed. Four different 7-substituted derivatives were used; methyl 7-bromo, 7-iodo, 7-mesyloxy and 7-tosyloxyheptanoate. No drastic changes in the yield were observed when methyl 7-iodo, mesyloxy or tosyloxyheptanoate were used. The bromo compound proved to be relatively unreactive. The stereochemistry of the alkylation was dependent on the amount of base used in the reaction mixture. By using at least two fold excess of base, only the trans-alkylated compound (Xa or Xb) were formed. However, when only one mole of base was used, cis alkylation was observed (XIa or XIb) and the ratio of XI to X was 65:35 (as detected on g.l.c.)(57A). It can be concluded then that XI was the kinetically controlled product, which was then converted to the thermodynamically more stable X.

Alkylation reactions were carrired on IXa and IXb separately. No difference in the yield or in product distribution was observed. In the isolation of X some more difficulties were encountered. They were partly due to the instability of X, and the similar chromatographic mobilities of IX, X and methyl 7-iodoheptanoate. It was especially hard to get rid of the iodo ester which was present in the large excess. This difficulty was overcome by stripping off the iodo ester in high vacuo (57A) and subsequent chromatography on deactivated alumina. An alternative way was the selective reduction of the keto group in X with sodium borohydride, to give XIIIa,XIIIb,XIIIc and XIIId in which XIIIb, XIIIc

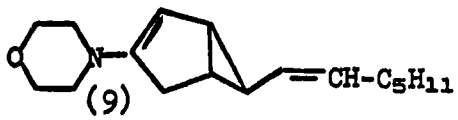
were obtained in a slightly higher ratio. The same reduction was carried for XIa and XIb and four alcohols were obtained. The alcohols had different chromatographic mobilities and could be separated on t.l.c. The relative stereochemistry of the alcohol function in the 8 alcohols was assigned, based on the chemical shifts of the ring carbinolic protons (57B) (see Table 6) and on their relative ratio.

Stereo Chemistry of C_7 side chain relative to cyclopropyl	Ring carbinolic proton in	Relative stereochemistry at OH	Geometry of double bond	Relative ratio
β	3, 4	α	cis	0.90
β	4, 2	β	cis	1.00
β	3.22	α	trans	0.90
β	4.05	β	trans	1.00
α	3.87	α	cis	0.75
α	3.92	β	cis	1.25
α	3.82	α	trans	0.75
α	3.88	β	trans	1.25

TABLE 6

The esters (Xa, Xb) and (XIa, XIb) could be obtained in 80% yield state by reoxidation with Jones reagent of these alcohols.

An alternative route for the alkylation consisted of transforming IXa and IXb to its morpholinoenamine 9 (58), which was then treated with methyl 7-iodo, mesyloxy or tosyloxy heptanoate in dioxane, dimethoxyethene,

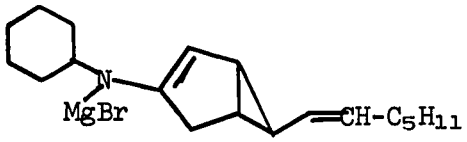


(9)

xylene and dimethyl sulfoxide. The highest yield, 10 - 20%, was obtained

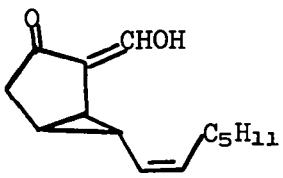
by using dimethyl sulfoxide as a solvent. The keto ester XI obtained through this method was highly contaminated by nitrogen containing compounds which had similar chromatographic mobilities. The nature of these compounds was not investigated.

Another method tried was the alkylation of the magnesium salt of N substituted imine 10 (49),but no improvement in the yield (10 - 20%) was observed.



(10)

The approach toward alkylation of IX having an α-activating group such as a hydroxy methylene group (60),the magnesium carbonate group (13, formed by reaction of IX with 4 moles of methyl magnesium carbonate in dimethyl formamide) (61)failed to increased the yield of X, because of the low yields of formation of the above mentioned compounds.



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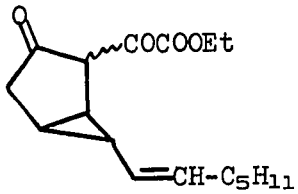

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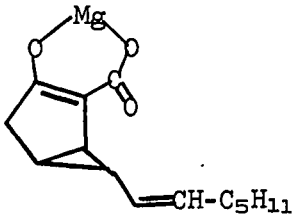

(13)

The free acid XII could not be obtained directly by saponification of the ester X, because of partial destruction in the basic medium. However, the saponification of the ester alcohol XIII could be carried out smoothly to give the acid XIV. Reoxidation of XIV with Jones reagent gave the acid XII in 70% yield.

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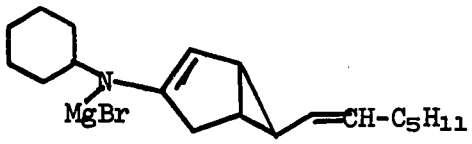

(10)

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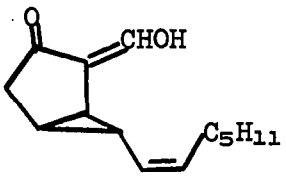

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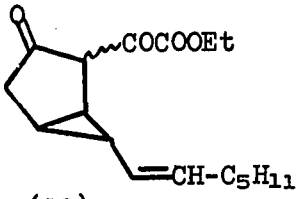

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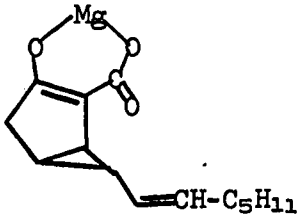

(13)

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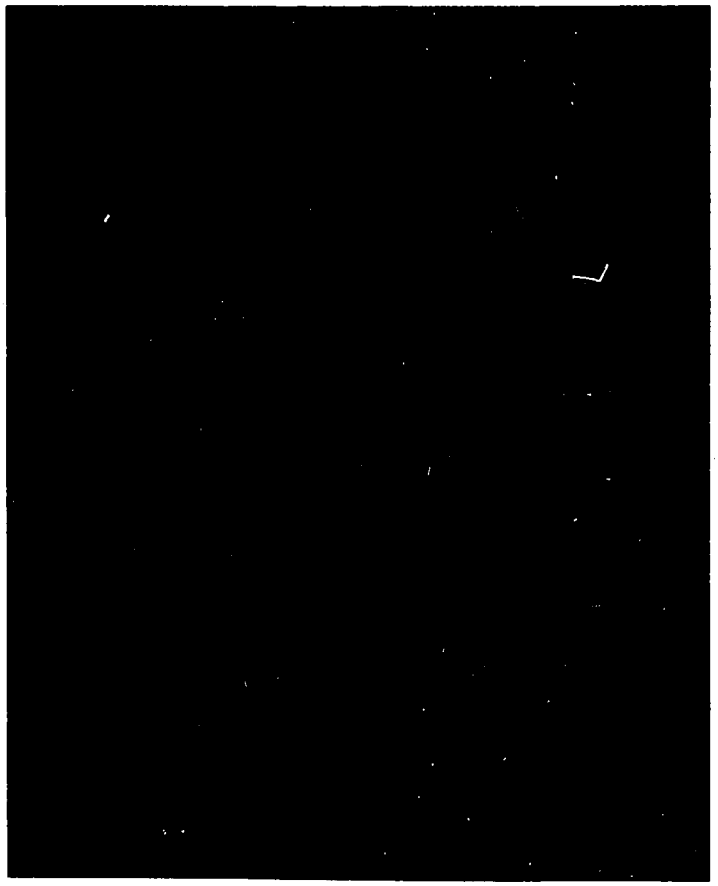
Acid XIV (mixture of cis and trans) was dissolved in ice cold formic acid (97 - 100%, 1% solution) buffered with two equivalents of sodium formate and was treated with one equivalent of 30% hydrogen peroxide for 30 minutes at room temperature. The mixture of formates thus obtained was hydrolyzed with 10% aqueous sodium carbonate and the mixture of alcohols was separated on t.l.c. Spots corresponding to $PGF_1\alpha$, traces of $PGF_1\beta$ and the non-rearranged glycol, together with two other spots were detected. $PGF_1\alpha$ was isolated by using preparative t.l.c. The compound was not crystalline and was characterized mainly by its mass spectrum which was identical to that of the natural $PGF_1\alpha$ except for the intensities of some peaks below M/e = 100.

Bioassay on the synthetic product showed high physiological activity, ranging from 40 - 90% of that of the natural compound in different tests.

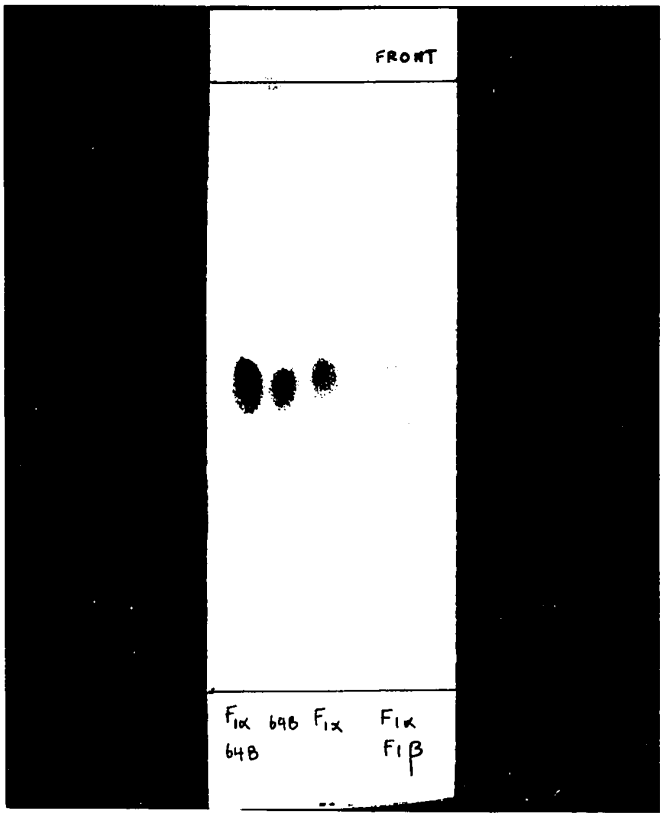
Treatment of X and XII with formic acid in the above mentioned conditions, showed on t.l.c. the formation of PGE_1 and its methyl ester respectively. However, the main products were PGA_1 and its methyl ester respectively. Since the amounts of X and XII available were very small, it was impossible at this stage to isolate and characterize the prostaglandin E and A formed. A further indication of the formation of PGE_1 was the appearance of the 278 mμ peak in the u.v., when the crude mixture was treated with 0.5 N NaOH.

Biological assay on this material which had been obtained from XIIcontaining 30 - 50% unalkylated ketone IX was 20 - 30%.



Synthetic $PGF_1\alpha$ in comparison to authentic samples.

From left to right: A mixture of synthetic and natural $PGF_1\alpha$, synthetic $PGF_1\alpha$ (trace of $PGF_1\beta$), natural $PGF_1\alpha$, mixture of natural $PGF_1\alpha$ and $PGF_1\beta$.


FRONT
$F_{1\alpha}$ 64B $F_{1\alpha}$
$F_{1\alpha}$
$F_1\beta$

CHAPTER III

The Total Synthesis of Prostaglandin - Route II

In order to overcome the inadequacy of the alkylation procedure and the difficulties in the saponification of XI to XII which resulted in low yield of XII, the following alternate synthesis was devised. Its main features are summarized in chart 9.

Cyclopentadiene monoepoxide XVI (62)was treated in absolute tetrahydrofuran with 7-pyranyloxy-1-heptyl magnesium bromide to give a mixture of compounds in which XVII was the major product. An extensive concurrent polymerization of XVI accompanied the reaction and in order to minimize it, numerous reaction conditions were used. The highest yield was obtained by slow addition of an excess of XVI to the tetrahydrofuran solution of the Grignard reagent, below 20°. The alcohol was characterized through its i.r., n.m.r. and mass spectra.

When XVII was treated with manganese dioxide for a long period of time no ketone formation was observed. The alcohol was therefore not allylic.

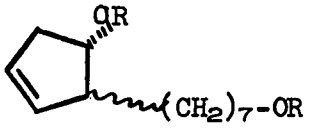
The cis configuration of the functionalities was assigned in accordance to similar openings of this epoxide (62) but was not proven.

Alcohol XVII was converted to its di-tetrahydropyranyl ether XVIIa using the same reaction conditions as described for preparation of II, with the only difference that two moles of dihydropyran were used.

Reaction of XVIIa with ethyl diazoacetate at 100° in the presence of copper powder (52)gave the bicyclo(3.1.0)hexane derivative XVIII in

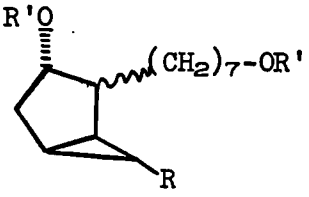
SECOND ROUTE

XVI



XVII R' = H R = THP

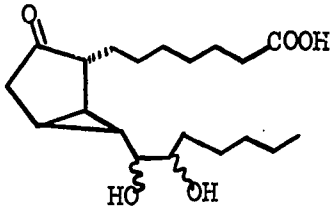
XVIIa R = R' = THP



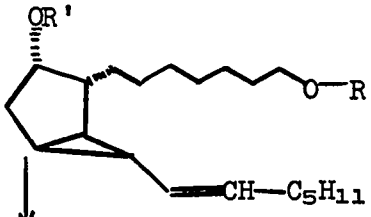
XVIII R = COOEt R' = THP

XIX R = CH_2OH R' = THP

XX R = CHO R' = THP

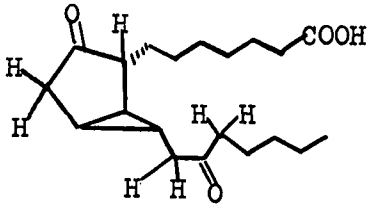


6 (p. 16)



XXI R' = R = THP (cis and trans double bond)

XXII R' = R = H



XXIII

XIV → $PGF_1\alpha$

XII → PGE_1 + PGA_1

Chart 9

about 50% yield, as a 4:1 mixture of exo and endo isomers as ascertained by gas chromatography. The exo and the endo isomers were separated by thin layer chromatography and were characterized through their i.r. spectra.

When the mixture of the exo and endo isomers was heated under reflux with methanolic sodium methoxide, exo XVIII containing less than 5% of the endo compound was obtained. It appears that the addition of the carbene was stereospecific, the cyclopropane ring being added most likely in a trans manner with respect to the alkyl and pyranyloxy groups.

Reduction of XVIII(exo) with etheral lithium aluminum hydride gave alcohol XIX in quantitative yield. The alcohol could be easily purified on t.l.c. from the remainder of the endo compound, and was characterized by its i.r. and n.m.r. spectra.

Jones oxidation of XIX at -15° gave aldehyde XX in 60% yield. The relatively low yield was due to cleavage of the primary tetrahydropyranyl ether during the oxidation reaction. The aldehyde exhibited a strong C=O band at 1700 cm^{-1} and in the n.m.r. a doublet at 9.2 ppm.

If equilibration was not carried on XVIII it could be established at this stage using sodium tertiary amyloxide in tertiary amyl alcohol. The equilibration could be followed by the disappearance of the signal for the endo aldehyde at 9.4 ppm. The aldehyde failed to give a crystalline derivative with dinitrophenyl hydrazine and similar reagents.

Wittig reaction (55) of XX with hexyltriphenylphosphorane in tetrahydrofuran gave XXI as a 1:1 mixture of geometric cis and trans isomers. Having similar chromatographic mobilities, the two isomers could not be separated at this stage.

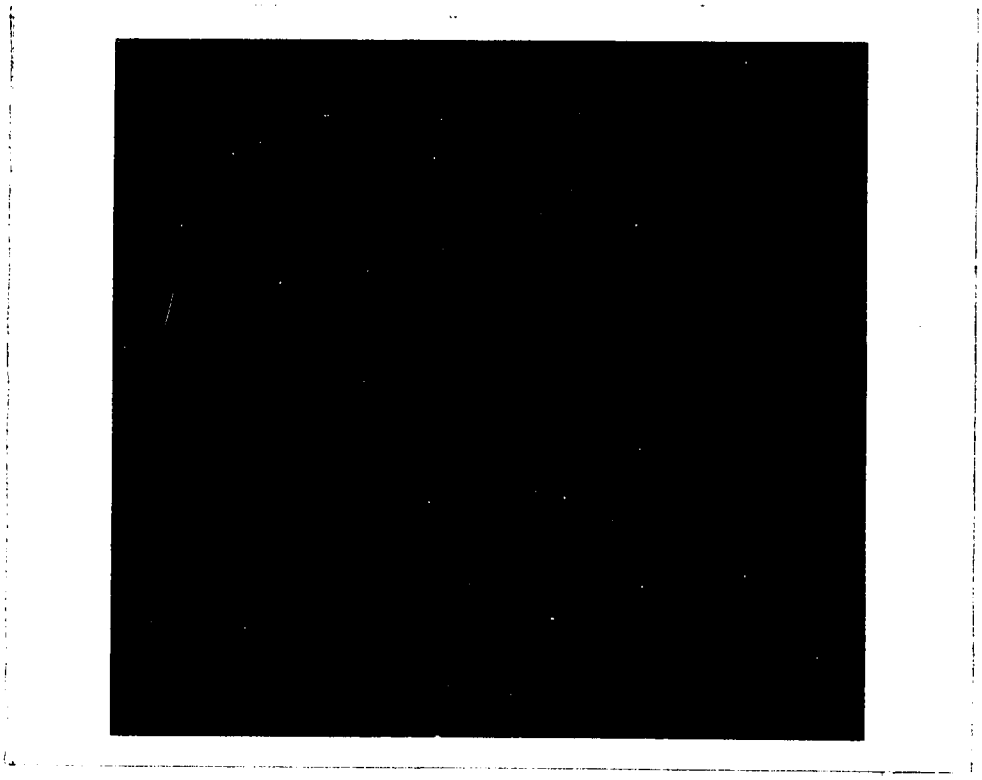
Hydrolysis of XXI with a 0.5% solution of oxalic acid in methanol gave diol XXII as a mixture of cis and trans isomers. The two isomers were easily separated on t.l.c. and characterized by their i.r. spectra. The cis isomer showed a strong band at 730 cm^{-1} and the trans isomer at 960 cm^{-1}. XXIIa and XXIIb were oxidized with dilute Jones reagent at 0-5° and XIIa and XIIb were obtained. The i.r. spectrum and R_f values of these acids were identical to those obtained by the first route. The acids could be converted to their methyl esters by treatment with diazomethane. The two esters had R_f values identical to those obtained by the first route.

In order to minimize the formation of PGA_1 (Chapter II, p. 31), the solvolysis was carried out in numerous ways. It was found that the amount of sodium formate used as a buffer had a large effect on the product distribution. The optimal conditions were obtained when a 0.5 N solution of sodium formate in formic acid was used as a reaction medium. (The t.l.c. of the crude mixture after the solvolysis using optimal conditions in illustrated in picture 2).

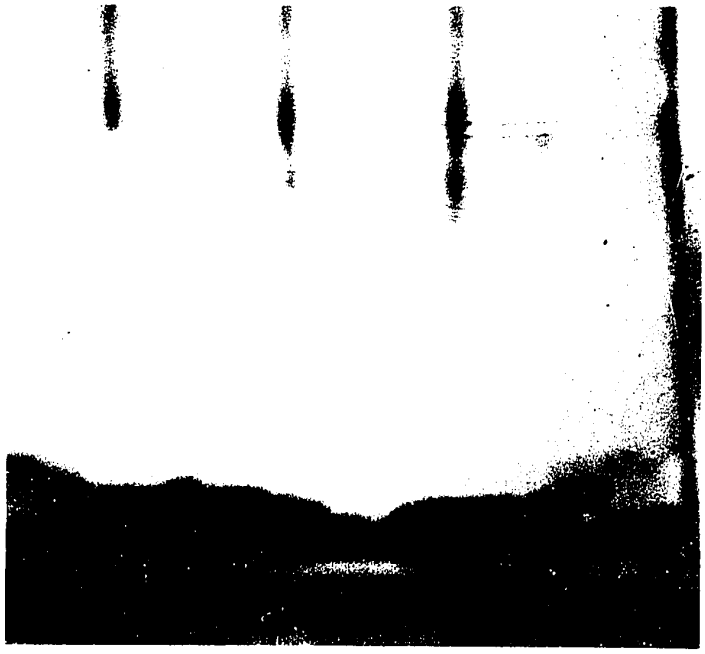
Higher concentration of sodium formate led mainly to the formation of the unopened glycol and the amount of PGE_1 was small. On the other hand, concentrations lower than 0.5 N of the buffer or pure formic acid led to the formation of PGA_1 as the principal product.*

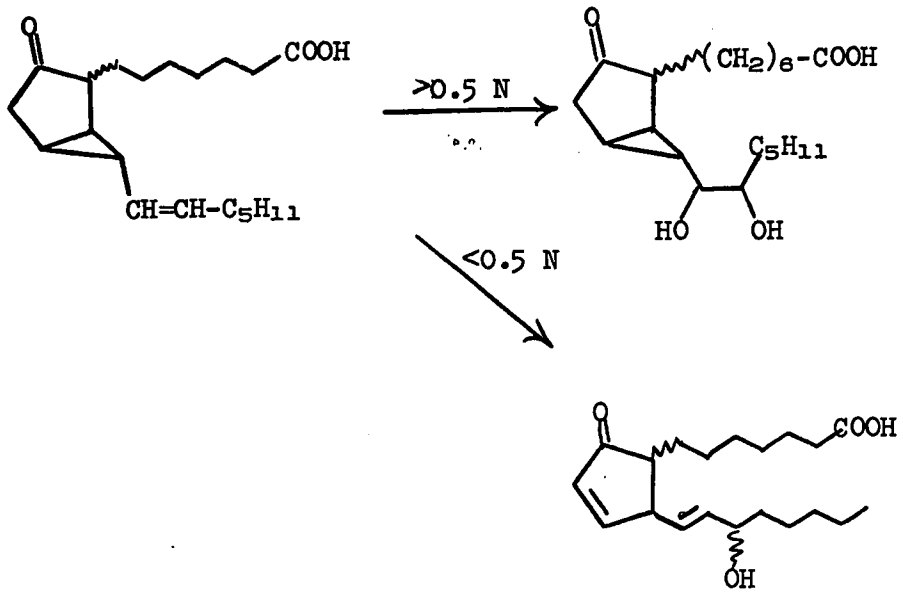
---

* The formation of the prostaglandins could be followed by t.l.c. and estimation of the amounts were made by measuring the 217 mμ absorption of the crude (for PGA_1) and the 278 mμ after treating the crude with NaOH 0.5N(for PGE_1 and PGA_1).



Thin layer chromatography of the crude mixture from the solvolysis of acid XII, the reference spot on the right is PGE_1. (The run on the left side faded before the photography was made.)





In addition to the above mentioned buffering of the reaction, the reaction medium was kept as anhydrous as possible in order to avoid elimination of the 11-hydroxyl group by using 100% formic acid, and an equivalent amount of 90% hydrogen peroxide.

Solvolysis of XI in the above mentioned optimum conditions at room temperature for three hours, gave after evaporation a mixture of products which was hydrolyzed by treatment with methanolic sodium carbonate. Acidification in the cold to pH2 and ether extraction gave a mixture of products, which was resolved on t.l.c., using a modified A-II system (63). Products having the following R_f values were obtained. 1). 0.47; 2) 0.54 - 0.58; 3) 0.67 - 0.88 (a streak).*

The spot at R_f = 0.54 had the same R_f value as natural PGE_1.

A better resolution of the compound at R_f = 0.54 to 0.58 was achieved by a thin layer chromatography, on silica gel G impregnated

* For the compounds present at this region see Experimental - Chapter III.

with 3% boric acid. On preparative scale, however, they could not be separated, since the two compounds appeared as one band only.

Treatment of the compounds with R_f 0.54 - 0.58 with manganese dioxide in tetrahydrofuran, gave one spot on t.l.c. which had the same R_f value as natural PGE_1 oxidized in the same manner. The two compounds are therefore most likely the two diastereoisomeric racemic mixtures (see p. 17). The mass spectrum of a mixture of the two compounds was identical to that of the natural PGE_1 except for deviations of some intensities. The n.m.r. spectrum of the mixture was identical to that of PGE_1 except for the shape of the allylic protons. When keto acid XII was reduced with sodium borohydride in sodium hydroxide aqueous solution (64) mixture of alcohol XIV was obtained. Their R_f values were the same as for those obtained from XIII in the first route. Oxydative formolysis of XIV gave $PGF_1\alpha$ and $PGF_1\beta$ respectively which were accompanied

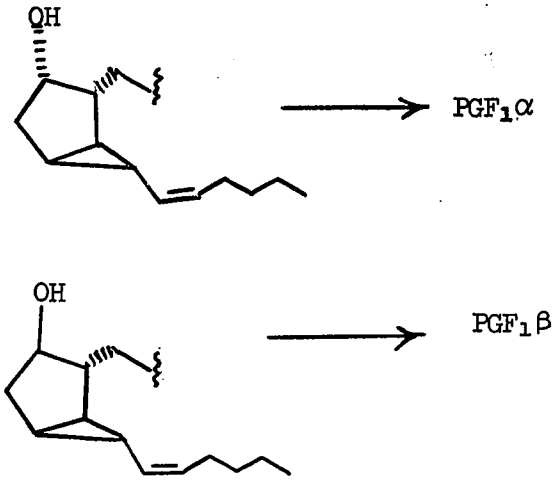


FIGURE 10

by unopened glycol and two minor compounds, which have not been identified.

CHAPTER IV

Spectroscopic Data

Many of the compounds described in the previous chapters had similar spectral features. These features served as a guide line throughout the synthesis to indicate the presence or absence of certain groups. These features and other spectral data will be summarized in this chapter.

The existence of the pyranyloxy protecting group could be very easily seen both in the i.r. and n.m.r. spectra. In the i.r. spectra, four bands at ν = 1000, 1023 - 1040, 1080 and 1120 - 1140 cm^{-1} (see spectra No. 16, 17, 20, 22) were assigned as characteristic to the tetrahydropyranyl group (65). The 1080 cm^{-1} band has been ascribed to the C - O stretch, the doublet usually seen at ν = 1120 - 1140 cm^{-1} to the C-O-C-O-C stretch (65). Cleavage of the pyranyl group caused the disappearance of the above mentioned bands except for the one at 1080 cm^{-1}. In the n.m.r. spectra the C-O-$\overset{H}{C}$-O-C proton had a very strong absorption at δ= 4.45 ppm. A complex structure which was centered at δ= 3.4 ppm (see spectra 1,2) was assigned to the protons α to the oxygen in the ether system $-H_2C-O\overset{|}{C}-O-CH_2-$.

The presence of the cyclopropyl could be deduced by the use of i.r. spectra. N.m.r. spectra was not an efficient tool, since conjugation of the cyclopropyl proton with the double bond or carbonylic function, shifted it to lower field where it was hidden under the CH_2 envelope. The C-H stretching bands of the cyclopropyl function could be seen at 3100, 3070 and 3030 cm^{-1} region. It appeared that a better

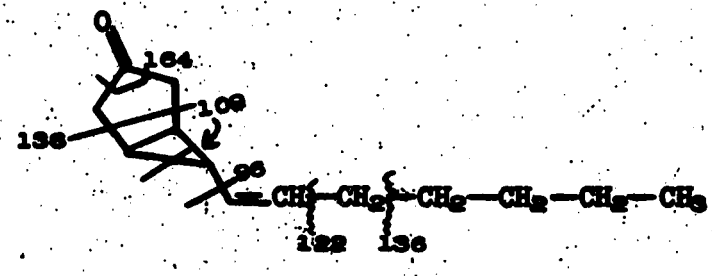
resolution of those bands were achieved with the bicylohexane rings bearing a carbonyl group. (compare spectra No. 16 and 20). In the compounds that had an alcohol function instead of a carbonyl, the peaks at 3100 and 3070 cm^{-1} could not be seen clearly. Bands at 1020 and 860 cm^{-1} also indicated the presence of the cyclopropyl function (66). Another indication of the cyclopropyl presence was the shift of the C = O stretch in the aldehyde to 1700 cm^{-1} and in the ester to 1725 cm^{-1} (67), a shift which is typical of carbonyls α to cyclopropane rings (see spectra 17). In the n.m.r. spectra the cyclopropyl proton at the 6 position could be seen as a multiplet at δ = 0.76 only in compound IV.

The double bond formed by Wittig reaction, could be identified by its characteristic absorptions in i.r. and n.m.r. spectra.

The geometry of the double bonds could be obtained from the i.r. spectra of the compounds. The trans olefins had a prominent absorption at 960 cm^{-1} and the cis at 700 - 730 cm^{-1}. The latter overlapped with the $(CH_2)_4$ band at 725 cm^{-1}, so the absence of the 960 cm^{-1} band was taken to an indication of the cis geometry.

The relative stereochemistry of the other functionalities with respect to the cyclopropane ring (which was considered always in a β position), were obtained from their relative ratio together with the chemical shift of the carbinolic proton in the 3 position of the bicyclo(3.1.0) hexane, in agreement with similar assignments made by Winstein et al (68).

Mass spectrometry was used as an additional proof for the structure proposed for the various intermediates. It was especially useful in the final structure proofs of the synthetic prostaglandins. The fragmentation of the principal intermediates is indicated below:



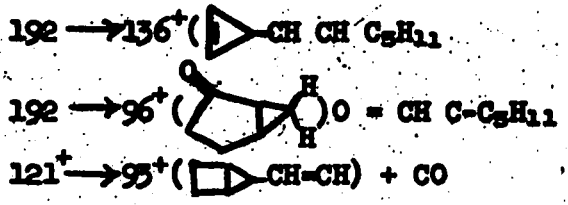
$M^+ = 192^+$

$192 = 164^+ + CO$

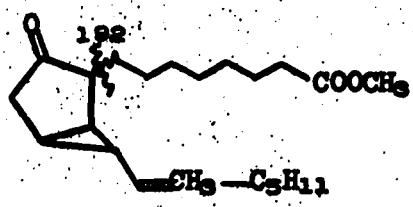
$192 \longrightarrow 149^+ + C_3H_7$

$192 \longrightarrow 109^+ + HC \equiv C - CH - C_5H_{11}$

$192 - 121^+ + 71$



The alkylated ketone X exhibited similar cleavage in addition to molecular ion peak at 334 and cleavage of the side ester chain α to the carbonyl:

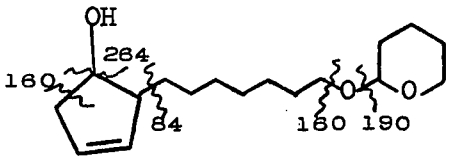


$M^+ = 334^+$

M-side chain = 192^+

The mass spectra of the synthetic prostaglandins and that of natural PGE is shown in the spectra no. 16.

In the second route, the key intermediate was the alkyl cyclopentenol, obtained from the opening of the epoxide. The final structure proof was achieved again with the aid of mass spectra. The fragments are summarized below:



$M^+ = 282^+$

$M - 18 = 264^+$

$M - 84 = 198^+$

$198 - 18 = 160^+$

M - side chain = $84^{\oplus}$

EXPERIMENTAL

Chapter II

Cyclopenten-4-ol (I)

The compound was prepared in 45% yield according to the procedure described by Winstein and co-workers (51, 68). The yield was improved by using preparative gas-liquid chromatography.

Tetrahydropyranyl Ether of Cyclopenten-4-ol (II)

A mixture of I (3.29 g.) and dihydropyran (3.39 g.) was cooled to 0° and two drops of phosphorous oxychloride were added. The mixture was stirred for one hour at 0° and three hours at room temperature. It was then washed with 10% aqueous potassium hydroxide and water and dried over magnesium sulfate. Chromatography on aluminum oxide (activity II-III) gave II, b.p. 120°/1 mm, 46°/0.05 mm, in quantitative yield; $n_D^{21.5}$ 1.4709. ν = 3030, 1625, 1140, 1070 cm^{-1}.
δ = 5.42 (2H, HC=CH), 2.24 (4H CH_2-C=C) 3.52 (2H CH_2-O) 4.45 (COC-O-C).
H

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.32; H, 9.59.
Found: C, 71.59; H, 9.27.

Ethyl-[(tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]-6-carboxylate (III)

Diazoethyl acetate (69a-c) 0.07 M was added at 100° over a period of 7-9 hours to a vigorously stirred mixture of II (0.01 M), and copper powder (1 g.) (52). After the end of the addition the mixture

was cooled down, hexane was added and the copper powder filtered. Chromatography on aluminum oxide (activity II-III) using hexane-benzene mixtures as eluents gave in 55% yield III, as mixture of four isomers.

Isomerization of III (Exo:Endo 4:1)

Ethyl-[(tetrahydropyran-2-yl)oxy]-bicyclo(3.1.0)-6-carboxylate (exo endo α,β isomers) (2.8 g.) in methanol (50 ml.) containing sodium methoxide (150 mg.) was heated under reflux for 4 hours. Evaporation and extraction with ether gave two products (exo, α, β) which were detected g.l.c. (Apieson L. column temperature 210°, retention times 10, 12 minutes). B.p. of the exo mixture 133°/1.1 mm. ν = 3100, 3070, 3030, 1725, 1272, 1140, 1020 cm^{-1}. δ = 3.92 (2H, quartet), 1.09 (3H triplet), 4.45 (O$\underset{H}{C}$-O), [illegible] (2H CH_2-O).

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72.

Found: C, 66.60; H, 8.59 (for the mixture).

3-[(Tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]-hexane-6-methanol (IV)

Ester III 2.5 g. in 20 ml. ether was added to lithium aluminum hydride (0.5 g.) in 20 ml. ether in such a rate that slow reflux occurred. The excess of the hydride was destroyed with ethyl acetate and water. The reaction mixture was diluted with water and extracted with ether. The combined ether extracts were dried on sodium sulfate and evaporated leaving viscous oil which consists of two alcohols which could be separated easily by using thin layer chromatography using silica gel G. (R_f = 0.76 major, R_f = 0.82 minor, ether as eluent). The ratio of these alcohols was 2:1.

The two alcohols had similar I.R. spectra that differed in the intensities of some bands (spectra 19, 20). , B.p. 130-135°/0.05 mm. ν = 3400, 3030, 1040, 1020 cm^{-1}. δ in both isomers = 0.76 (1H cyclopropyl multiplet), 4.45 (1H) 3.32 (3H).

Anal. Calcd. for both isomers: $C_{12}H_{20}O_3$: C, 67.89; H, 9.50.

Found: (IVa) C, 68.02; H, 9.59.

Found: (IVb) C, 67.58; H, 9.61.

3-[(Tetrahydropyran-2-yl)oxy]bicyclo [3.1.0]-hexane-6-carboxaldehyde (VI)

A mixture of alcohols IV (252 mg.) was dissolved in 10 ml. of acetone and cooled to -10°. Jones reagent (54) 0.5 ml., diluted with 0.5 ml. of acetone, was added dropwise with vigorous stirring over a period of 3 minutes and the mixture was stirred at that temperature for an additional 7 minutes.

A few drops of i-propanol were added to destroy the excess of the reagent. The mixture was diluted with 50 ml. of water and extracted several times with ether. The ether was washed with water and 10% sodium carbonate aqueous solutions, then it was dried over magnesium sulfate and evaporated leaving 10 g. (80% yield) of aldehyde VI as a mixture of α and β pyranyloxy. The aldehydes could not be separated on t.l.c. or on g.l.c. (1 peak retention time 14 minutes, 5% DC 710, on acid washed Cromosorb W, 160°C. ν = 3097, 3070, 3030, 2730, 1700, 1140, 1020 cm^{-1}. δ = 9.2 (-C$\overset{O}{\underset{H}{}}$) for the

major isomer and δ= 9.0 for the minor, 4.5 (1H) 3.5 (3H) ppm.

By oxidizing separately, alcohols IVa and IVb, the two aldehydes were obtained in pure state and were characterized as their dinitrophenylhydrazones (m.p. 202° for the major isomer; exo-α-pyranyloxy) and m.p. 195° for the minor-exo β pyranyloxy).
Anal. Calcd. for $C_{18}H_{22}N_4O_8$: C, 55.38; H, 5.68; N, 14.35.
Found: C, 55.48; H, 5.61; N, 14.23 (exo, α) and C, 55.42; H, 5.61; N, 14.25 (exo, β).

Upon treatment of a non-equilibrated mixture of exo and endo aldehyde with one mole of sodium t. amyloxide in boiling t.amyl alcohol for 5 minutes, the endo compounds were transformed completely to the exo, as was judged by the disappearance of the doublet at 9.5 ppm.

3-[(Tetrahydropyran-yl)oxy]bicyclo[3.1.0]-hexane-6-methyl-triphenyl-phosphonium Bromide (V)

The compound was prepared according to a procedure described by H. J. Bestmann (57).

The alcohol IV (IVa, IVb mixture)(0.432 g.)and 5.56 g. of triphenylphosphine hydrobromide (prepared by passing dry HBr gas through a benzene solution of triphenylphosphine), were dissolved in 50 ml. of dry tetrahydrofuran and the solution was stirred at room temperature for 40 hours (the product begins to crystallize out after 7 hours). After that period the solution was filtered with suction, the precipitate washed twice with cold tetrahydrofuran and was let to dry in vacuum over potassium hydroxide pellets. The yield was 30% m.p. 149-150° (not corrected). ν = 3100,

1075, 1050, 1015, 1450, 1020 cm^{-1}.

Anal. Calcd. for $C_{30}H_{34}O_2PBr$: C, 67.03; H, 6.33; Br, 14.85.
Found: C, 67.35; H, 6.40; Br, 14.25.

6(1-Heptenyl)-3-[(Tetrahydropyran-2-yl)oxy]-bicyclo[3.1.0]-hexane (VII)

To hexyltriphenyl phosphonium bromide (70)(21.4 g.), m.p. 198°, prepared from 1 mole of triphenyl phosphine and 1.5 mole of hexyl bromide in refluxing benzene for 40 hours) in 300 ml. of anhydrous ether was added 19.5 ml. of 22.22% solution of butyl lithium in hexane, in a dry nitrogen atmosphere. A bright orange coloration indicated the formation of the phosphorane. After stirring for 10 minutes 7 g. of aldehyde VI was added, causing immediate precipitation of the betaine. Most of the ether was evaporated and 250 ml. of dry tetrahydrofuran (previously distilled over lithium aluminum hydride) was added. The mixture was refluxed for 5 hours, the solvent evaporated and the residue extracted several times with ether. The combined ether extracts were washed twice with water, dried over magnesium sulfate and evaporated in vacuum. The residue was chromatographed on aluminum oxide (activity II-III). Elution with hexane-benzene (3:1) gave 9.5 g. of VIIwhich appeared on one spot on t.l.c. with various solvent systems. On g.l.c. four poorly resolved products could be detected (Apison L. column, 220°, retention time 15 minutes). Since it was difficult to characterize at this stage the characterization of the individual isomers were carried on alcohol VIII. The mixture had the following spectral features: ν= 3100, 3075, 3030, 1650, 1140, 1020, 960, 735 cm^{-1}; λ_{max} 198 mμ (ethanol), δ = 5.2 (H-C=C-H complex) 4.45 (1H) 3.52 (3H) 0.9 (3H terminal methyl) ppm.

Alternate Route to VII Using Phosphonium Salt V and Hexanal (57)

To 90 mg. of sodium hydride previously washed with hexane and dried with nitrogen stream, was added 15 ml. of anhydrous dimethylsulfoxide. The dispersion was kept under nitrogen at 70-75° for 15 minutes. To the solution was added 2.5 g. of the phosphorane V in one portion causing a red coloration of the solution. To the resulting ylid 200 mg. of hexanal in 5 ml. of dimethylsulfoxide, was added during 5 minutes. The mixture was then stirred for 5 hours at 70-75°. Ice and water were then added, and the solution was extracted 3 times with ether. The ether extracts were back-washed twice with water and it was dried over sodium sulfate and evaporated. The residue was chromatographed on aluminum oxide (act. II-III). Elution with hexane-benzene 3:1 gave VII in 25% yield. The ratio of isomers was the same as in the previous route.

6-(1-Heptenyl)bicyclo[3.1.0]hexan-3-ol (VIII)

To 350 ml. of 0.5% oxalic acid in methanol solution was added 8.5 g. of VII and the mixture was refluxed for three hours. After that period the methanol was evaporated, ether was added and the ether solution washed twice with 10% sodium carbonate aqueous solution. The ether extract was then dried over sodium sulfate and evaporated, leaving a viscous oil. The oil showed on t.l.c. four spots (benzene ether 8:2) at R_f 0.36 (trans double bond β OH), 0.40 (cis double bond β OH), 0.54 (trans double bond α OH) and 0.62 (cis double bond α OH). The bands were separated and their relative ratio was determined as 1:1:2:2 (in the same

order of the above mentioned R_f's). The four isomers had very similar I.R. spectra. The most prominent absorptions were at ν = 3375, 3050, 1625, 1070, 1020, and 725 cm^{-1}. The trans isomers showed additional band at 960 cm^{-1}. In the n.m.r. spectra, the cis and trans isomers had different patterns at δ = 5.2 ppm for the vinylic protons and the position of the carbinolic proton was different in the α and β hydroxy isomers (see Chapter II, p. 26); Yield 95%.

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41.

Found: C, 80.82; H, 11.26 (VIIa); C, 79.81; H, 11.40 (VIIIb); C, 80.11; H, 11.39 (VIIIc); C, 80.60; H, 11.50 (VIIId).

6-(1-Heptenyl)bicyclo [3.1.0]-hexan-3-one (IX)

Alcohol VII (mixture of 4 isomers, 900 mg.) was dissolved in 30 ml. acetone and cooled to -5° and 1.2 ml. of Jones reagent (54) in 6 ml. acetone was added during 1 minutes. The solution was stirred at the same temperature for an additional 5 minutes. After that period a few drops of isopropanol were added to destroy the excess of the reagent. The mixture was diluted with 100 ml. of cold water, and extracted with ether. The ether extract was wash twice with 10% sodium carbonate solution, dried over sodium sulfate and evaporated. T.l.c. showed the existance of 2 compounds at R_f = 0.85 (IXa) and R_f = 0.80 (IXb) (silica gel G impregnated with 3% silver nitrate, elution with benzene:ether 6:4). G.l.c. (Apieson L 230°): 10 min. for IXa and 11 min. IXb. The i.r. spectra of the two compounds was essentially identical (spectra 26, 27). The trans compound exhibited absorption at ν = 960 cm^{-1}. The mass spectrum of a mixture of the two isomers is described in Chapter IV, p. 41.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48.
Found: C, 81.15; H, 10.40 (cis); C, 81.10; H, 10.10 (trans).
Mol. weight 192 (mass spectrum).

Methyl 6-(1-heptenyl)-3-oxo-bicyclo [3.1.0]-hexane-2-heptanoate (Xa, Xb) Direct Alkylation

To a suspension of 0.4 mM. of potassium hydroxide in 10 ml. of anhydrous dimethoxyethane, under nitrogen atmosphere, was added 0.2 mM. of bicyclo ketone IX,(cis trans mixture) and the reaction was stirred for 15 minutes. Methyl 7-iodo-heptanoate (1.2 mM.)in 20 ml. dimethoxy-ethane was then added slowly. After the end of the addition, the mixture was refluxed for 37 hours (the reaction was followed by t.l.c. and interrupted, when decomposition of keto ester X was noticable). The reaction mixture was cooled in ice bath and the basic solution was acidified in the cold with dilute (10%) hydrochloric acid. Extraction with ether followed. The ether extracts were dried over sodium sulfate and evaporated, leaving a crude which consisted of starting materials, product X and dialkylated product. The excess of the iodo ester and ketone IX was removed by vacuum distillation (40-70 microns) (57A). The remainder was chromatographed on alumina act. II-III. Elution with benzene gave the rest of the unreacted starting material (ketone IX and some methyl iosoheptanoate). Elution with benzene ether 8:2 solution gave the keto ester in 35% yield slightly contaminated with ketone IX. Elution with benzene ether 7:3 gave the dialkylated product (57A) in 10% yield. The ester could be further purified by reduction with sodium borohydride, chromatography on silica gel and reoxidation with Jones reagent, in the same manner as described for the oxidation of alcohol VIII. (The

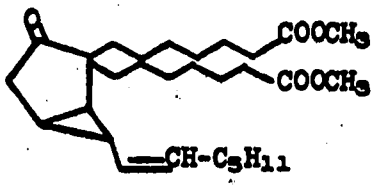
exact details of the sodium borohydride reduction are described in a subsequent paragraph). Xa and Xb had the same R_f value and were poorly resolved on g.l.c. In order to obtain the esters in pure state oxidation of XIIIa XIIIb for the trans and XIIIc XIIId for the cis, is required (see procedure, p. 56). The two esters had similar i.r. and n.m.r. spectra. The two compounds had bands in the i.r. spectra at ν= 3100, 3030, 1750 (C=O and ester) 1890, 1020, 735 cm^{-1}. The trans keto ester exhibited an extra band at 960 cm^{-1}. The n.m.r. spectra is essentially similar, the only difference was in the shape and coupling for the complex vinyl protons absorption at δ= 5.2 ppm.

The fragmentation upon electron impact is described in Chapter IV.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.45; H, 10.46.
Found: C, 75.10; H, 10.00 (cis); C, 74.82; H, 10.10 (trans).
M.W. 334 (mass spectra).

On alkylation under same conditions but using 1 mole of base instead of 2, XIa XIb and Xa Xb were obtained in the ratio of about 65:35 (as judged by g.l.c.) (Four ft. 3% silicon rubber column, 245°)(57A). Reflux of the resulting products with 2 mole equivalents of potassium t. butoxide in tetrahydrofuran for two hours resulted in a complete conversion of XIa and XIb to Xa and Xb respectively.

The structure of the dialkylated product was deduced from its mass (57A) and n.m.r. spectra. It had a molecular ion of 476 (molecular weight) and the n.m.r. spectrum had the ratio of olefinic protons (4, 5 - 5.7 ppm.) to methyl ester protons (3.73 ppm.) of 2:6 consistent with the structure.



Indirect Alkylation

a) Preparation of Morpholinoenamine of IX

Ketone IX (100 mg.) was refluxed in 50 ml. of benzene with 2 ml. of morpholine and few crystals of p-toluenesulfonic acid for 18 hours, in a flask fitted with a Dean-Stark water collector. After that period the reaction mixture was cooled and washed once with a saturated solution of sodium bicarbonate. The benzene layer was dried over sodium sulfate and evaporated leaving a viscous brown oil. No further purifications were carried out on the enamine, and it was used as it is for further reactions. The completion of the reaction was determined by the i.r. of the product (spectrum 30).

b) Alkylation of the Enamine

To a solution of 200 mg. of enamine in 70 ml. of anhydrous dimethylsulfoxide, was added under nitrogen atmosphere 1 g. of methyl-7-iodoheptanoate by means of a syringe. The mixture was then heated to 60-70° and stirred for 4 hours. After that period the reaction mixture was cooled, 280 ml. of cold water were added and the suspension stirred at room temperature for 3 hours, and extracted with ether. The ether extract was back-washed with water, dried over sodium sulfate and evaporated. The crude was chromatographed in the manner described before to give keto ester X in 20% yield.

c) Preparation of Hydroxymethylene Derivative of IX

To a solution of 300 mg. of ketone IX (cis and trans) in 15 ml. of dry benzene, was added 2 ml. of ethyl formate and the mixture was cooled to 10°. Sodium hydride (52% in oil) 87 mg. was then added in small portions

with stirring. After the end of the addition, the suspension was allowed to warm up to room temperature and was stirred for 14 hours. Cold water was added and the aqueous solution extracted twice with ether. The water layer was acidified in the cold and extracted with ether. The ether extract was washed with water to neutrality dried and evaporated, yielding the hydroxymethylene derivative in 10% yield.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09.

Found: C, 75.96; H, 9.32. No alkylation was carried on this derivative.

d) Alkylation of the Magnesium Carbonate Derivative of IX

Ketone IX (cis and trans 100 mg.) in 2 ml. of dimethylformamide was heated for one hour at 110-120, with four molar equivalents of methyl magnesium carbonate (61). The reaction mixture was cooled to 25° and 600 mg. of methyl 7-iodoheptanoate in 5 ml. dimethylformamide was added. The resulting mixture was stirred at 70-75° for 14 hours. The mixture was then poured into 5 g. crushed ice containing 2 ml. of concentrated hydrochloric acid, and the mixture stirred for 5 minutes. The acidified mixture was extracted several times with ether. The combined ether extracts were washed with cold water and twice with a 10% aqueous solution of sodium carbonate. The basic extract was acidified in the cold, and the liberated acid extracted with ether. The ether extract was dried over sodium sulfate and evaporated.

The crude product was dissolved in 10 ml. dimethylformamide containing 50 mg. of copper sulfate pentahydrate. The mixture was refluxed for 2 hours, then poured into 100 ml. of water. The aqueous suspension was extracted with ether. The ether extract dried and evaporated. The

residue was chromatographed on silicic acid as described above yielding keto ester X in 3% yield.

Acid hydrolysis of the magnesium carbonate complex of IX (p. 31) in the same manner yielded 6-(1-heptenyl)-2-carboxy-3-oxo-bicyclo [3.1.0]-hexane in 30%.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.18; H, 8.47.

Found: C, 71.50; H, 8.20.

Methyl 7-Bromoheptanoate

The compound was prepared from 7-bromoheptanoic acid (71,72) according to a procedure described by Ames et al. (72). Boiling point 110°/5 mm.

Methyl 7-iodoheptanoate

To a solution of 1.12 g. of sodium iodide in 10 ml. of acetone was added a solution of 1.1 g. of methyl 7-bromoheptanoate in 5 ml. acetone. A slight coloration developed immediately and precipitation of sodium bromide started shortly thereafter. After standing at room temperature for 3 hours the reaction mixture was filtered and the acetone evaporated. The residue was dissolved in ether and a little water, the ether separated and washed once with 5% sodium thiosulfate solution and three times with water. After drying over anhydrous sodium sulfate, the ether was stripped under reduced pressure at room temperature leaving 1.2 g. of product (72A). The compound was identical to methyl 7-iodoheptanoate prepared via a known route (73).

Methyl 7-mesyloxyheptanoate

To a solution of 2 g. methyl 7-hydroxyheptanoate (74) in 35 ml. of pyridine, cooled to 0° was added in four portions, 5.5 ml. of mesyl chloride, and the mixture was kept at 0-5° for 2 hours. After that period the pyridine was removed by pouring the reaction mixture into crushed ice containing hydrochloric acid. The organic residue was extracted with ether. The ether extract was washed to neutrality with saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated leaving 2 g. of crude product. Filtration of a benzene solution of the crude on a short (15 g.) column of aluminum oxide activity II-III gave 1.8 g. of methyl 7-mesyloxyheptanoate.

Anal. Calcd. for $C_9H_{18}O_4S$: C, 48.61; H, 8.11; S, 14.41.
Found: C, 48.30; H, 8.00; S, 14.15.

Methyl 7-tosyloxyheptanoate

Methyl 7-tosyloxyheptanoate was prepared from methyl 7-hydroxyheptanoate (74)according to the procedure described above, with the exception that the reaction was carried at room temperature for 2 hours.

Anal. Calcd. for $C_{15}H_{22}O_4S$: C, 60.05; H, 7.43; S, 10.72.
Found: C, 60.30; H, 7.02; S, 11.35.

Methyl 6-(1-heptenyl)-3-ol bicyclo[3.1.0]-2-heptanoate (XIII)

A solution of 50 mg. of keto ester X (cis and trans mixture) slightly contaminated with ketone IX in 2.6 ml. of dimethylformamide was cooled to 15° C. and was treated rapidly with stirring with a solution of

110 mg. of sodium borohydride in 0.65 ml. of water (75). Additional stirring at 18-20° for four hours was carried on. The reaction mixture was cooled to 5°. The excess of the hydride was destroyed with 10% aqueous acetic acid. The solution was poured into 25 ml. of cold water and the suspension formed extracted with ether. The ether extract was back-washed with water, dried and evaporated. T.l.c. showed four spots at R_f = 0.58 (βOH, cis double bond),0.49 (βOH trans double bond), 0.35 (αOH, cis double bond) and 0.32 (αOH trans double bond) (solvent system benzene:ether 1:1). The compounds were identified according to the chemical shift of the carbinolic proton (see Chapter II, p.29 and Chapter IV, p. 39). The ratio was about 1.5:1.5:1:1.

The four alcohols have bands at ν= 3450, 3080, 3030, 1750, 1625, 1180, 1020 and 735 cm^{-1}. XIIIa and XIIIb have an additional band at 960 cm^{-1}. The n.m.r. of those compounds is shown in spectra no. 5, 6, 9, 10

A similar reduction of XI (cis and trans mixture) gave a mixture of four alcohols (XV) which had similar R_f value as the α side chain series with benzene-ether system. Different R_f values were achieved by using ethyl acetate cyclohexane 1:3 mixtures. For the trans double bonds series: R_f 0.18 (βOH α side chain), 0.15 (αOH α side chain), 0.21 (βOH, β side chain), 0.14 (αOH β side chain). For the cis double bond series: 0.21 (βOH α side chain), 0.18 (αOH α side chain), 0.25 (βOH β side chain), 0.15 (βOH β side chain) (57B). The n.m.r. spectra of the alcohols is shown in pp. 76-83.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 75.00; H, 10.71.

Found for trans double bond series: C, 75.10, H, 10.31; C, 74.91, H, 10.30; C, 74.95, H, 10.30; C, 74.78, H, 10.80. For the cis double bond series: C, 74.99, H, 10.40; C, 74.89, H, 10.40; C, 74.82, H. 10.20;

C, 74.95, H, 10.53.

6(1-Heptenyl-3-ol-bicyclo[3.1.0]hexane-2-heptanoic Acid (XIV)

A mixture of XIIIa and XIIId (30 mg.) was hydrolyzed in 10 ml. 10% methanolic sodium carbonate solution, for 10 hours at room temperature The reaction mixture was diluted with 100 ml. cold water and extracted with ether. The aqueous layer was acidified in the cold with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water, dried and evaporated leaving 27 mg. of crude acid XIV. The mixture had absorption bands in the i.r. at ν = 3400 (OH) 3100, 3030, 1750, 1700, 1020, 735 cm^{-1} The two acids could be separated, on t.l.c. (silica gel G impregnated with 3% silver nitrate, ethyl acetate: acetic acid 99:1 as eluent). The faster moving acid was identified according to its i.r. as the trans acid.

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.53; H, 10.55.

Found: C, 74.10, H, 10.45 (trans acid); C, 74.35, H, 10.55 (cis acid).

6(1-Heptenyl)-3-one bicyclo[3.1.0]-hexane 2-heptanoic Acid (XII)

Alcohol acid XIV (cis trans mixture) (32 mg.) was dissolved in 3 ml. of acetone and cooled to -5°. Jones reagent (54) 0.1 ml. in 0.5 ml. of acetone was added rapidly, and the mixture stirred at -5° for 7 minutes. A few drops of isopropanol were added to destroy the excess of the reagent and mixture was diluted with 15 ml. of cold water and extracted with ether. The ether extract was washed twice with cold water and twice with 10 ml. portions of 10% sodium carbonate aqueous solution. The basic extract was washed

with ether and acidified with cold diluted (1:10) hydrochloric acid and extracted several times with ether. The combined ether extracts were washed with water to neutrality, dried over magnesium sulfate and evaporated leaving 28 mg. of crude keto acid.

For characterization purposes an ethereal solution of the acids was treated with excess of an ether solution of diazomethane at 5° for 20 minutes. The ether was evaporated, and the residue chromatographed in the same manner as described for keto ester X. The methylation products were identical by their i.r. and n.m.r. spectra and R_f values to methyl esters Xa and Xb obtained by alkylation of ketone IX.

Oxidative Formolysis of XIV to $PGF_1\alpha$

Acid XIV (27 mg.) was dissolved in 3 ml. of ice cold formic acid 97-100% containing 2 equivalents of sodium formate. 1.1 equivalent of hydrogen peroxide was added rapidly with vigorous stirring (76). The reaction was allowed to warm up to room temperature (26°) and was stirred at that temperature for 0.5 hour. The solvent was evaporated in vacuo (bath temperature 26°) and the resulting powder was shaken with 3 ml. of 10% aqueous solution of sodium carbonate for 1.5 hours. The solution was acidified with cold dilute (1:10) hydrochloric acid to pH 2 and extracted several times with ether. The ether extract was washed to neutrality dried over sodium sulfate and evaporated. The residue was separated by t.l.c. (silica gel G, impregnated with 3% silver nitrate elution with AII system (-ethyl acetate-methanol acetic acid-isooctane-water 110:30:35:10:100,)

detection was accomplished by spraying with 10% solution of phosphomolybdic acid in ethanol (31)and heating at 120° for 25 minutes. For quantitative purposes the plates were sprayed with water and the compounds detected by their opaque lines).

Bands corresponding to starting material, prostaglandin $F_1\alpha$, traces of $PGF_1\beta$ and three other products were detected. The band corresponding to $PGF_1\alpha$ was eluted out with methanol. Evaporation of the methanol yielded $PGF_1\alpha$ highly contaminated with silica gel. Treatment with acetone liberated the prostaglandin from the silica gel.

The yield of d,l $PGF_1\alpha$ was approximately 30%. The i.r. and the mass spectrum of the synthetic specimen was identical to that of $PGF_1\alpha$, except for differences in intensities below m/e 100 in the mass spectrum.

Bioassay indicated physiological activities 40-90% of natural $PGF_1\alpha$ in various different tests.

Oxidative Formolysis of X and XII into PGE_1 and PGE_1-methyl ester

By treatment of 2 mg. of XII(cis and trans mixture) in formic acid/ sodium formate and hydrogen peroxide in the same manner as described above for $PGF_1\alpha$, there was an indication on t.l.c. of the formation of PGE_1. (AII solvent system with natural PGE_1 as reference). Treatment of the crude with 1 ml. 0.5 N NaOH for 60 minutes, gave material having the same R_f as PGB_1 and the crude had a strong absorption at λ = 278 mμ.

The solvolysis of X was carried on in the same manner and PGE_1 methyl ester was observed on t.l.c. but it appeared that the yield of this compound was very low.

Chapter III

Cyclopentadiene-mono-epoxide (XVI)

The compound was prepared in 30% yield according to a procedure by Korach et al.(62) δ = 6 ppm (2H H-C=C-H complex), 3.73 ppm. (2H  complex), 2.35 (2H complex) ppm.

7-Tetrahydropyranyloxyheptyl Magnesium Bromide

7-Bromoheptanol (77) b.p. 116°/2 mm. was treated with a small excess of dihydropyran and a few drops of phosphorous oxychloride for a few hours at room temperature. A small amount of aqueous potassium hydroxide was added. The solution shaken for a moment, and then extracted with ether and the ether solution washed to neutrality. The ether was dried over sodium sulfate and evaporated in vacuo. The crude product upon distillation gave the tetrahydropyranyl ether, b.p. 113°/2 mm.

Anal. Calcd. for $C_{12}H_{23}O_2Br$: C, 52.40; H, 8.30.
Found: C, 52.16; H, 8.47.

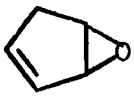
The yield of the distillate was relatively low, mainly because of the cleavage of the pyranyloxy function during the distillation. For preparative use a hexane solution of the crude was passed over a short column of aluminum oxide (Act II-III) and the compound used as such after evaporation (yield 90%).

To 90 mg. of magnesium powder (preactivated by washing with dilute HCl, water, acetone and dried by a stream of nitrogen), and few crystals

of iodine in 2 ml. of anhydrous tetrahydrofuran, was added 1.13 g. of the bromo-7-pyranyloxyheptane in 15 ml. of tetrahydrofuran.

After initiation of the reaction, the mixture was heated under reflux until most of the magnesium had disappeared. Vigorous stirring was essential for fast and complete reaction.

2-(7-α-Pyrnayloxyheptyl)cyclopent-3-en-αol (XVII)

 + $BrMg(CH_2)_7$-OTHP ⟶ A + XVII + B

To the Grignard reagent prepared above, in a nitrogen atmosphere, was added very slowly 0.6 ml. of cyclopentadiene monoepoxide (XVI) in 10 ml. of anhydrous tetrahydrofuran.

The temperature was kept between 17-20°, since extensive polymerization occurred above these temperatures and it appeared that by keeping the temperature between 0 - 5° the reaction rate was slow.

Upon completion of the addition (2 hours) the reaction mixture was stirred for another 1.5 hours. The solution was then poured onto crushed ice and ammonium chloride and extracted several times with ether. The ether extract dried over sodium sulfate and evaporated, leaving 1 g. of crude material. The crude product was triturated with dry hexane whereupon the polyether (62) precipitated (0.2 g.). The ethereal filtrate showed three peaks on g.l.c. (5% DC 710 on acid washed chromosorb W, 205° 7, 9, 11 min.) at a ratio of 1:8:2 (compound A, XVII and B).

The crude (0.8 g.) was chromatographed on 75 g. of aluminum oxide

activity II-III. Elution with hexane gave some starting material and pyranyloxyheptane. Elution with hexane:benzene (8:2) gave compound A, whose nature was not investigated. Elution with benzene gave XVII in 40% yield. The i.r. of XVII shows bands at: ν= 3400 (broad OH), 3050 (CH=CH), 1630 (C=C), 1470, 1070, 1040, 735 cm^{-1}. The n.m.r. of the compound is shown in spectrum no. 13. The mass spectrum is consistent with the structure proposed (p. 41). Elution with benzene: ether 1:1 gave compound B which had essentially the same i.r. spectrum as XVII (spectrum 28, 29). Its n.m.r. spectrum differed from that of XVII only by the shape of the allylic protons resonance absorption. A tentative structure of 2-(7-α-pyranyloxyheptyl)cyclopent-3-en-β-ol was assumed, but no reactions to prove it were carried on. Elution with ether gave several ketolic compounds (total yield 3%). The nature of those compound was not investigated.

Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71.

Found: C, 71.97; H, 11.19. M.W. 282 (M.S.).

Found for compound B: C, 71.89; H, 10.84.

Oxidation of XVII with Manganese Dioxide

Alcohol XVII (100 mg.) was dissolved in 10 ml. of anhydrous THF containing 5 equivalents of activated manganese dioxide (78)and the mixture refluxed for 24 hours. The reaction mixture was cooled down, the oxide filtered and the tetrahydrofuran evaporated. T.l.c. and i.r. spectra of the residue did not show the formation of a cyclopentenone derivative.

Di-tetrahydropyranyl Ether of 2-(7-hydroxyheptyl)cyclopent-3-enol (XVIIa)

Alcohol XVII was treated with two equivalents of dihydropyran and few drops of phosphorous oxychloride at 10-15° for three hours. (The reaction mixture turned black after a few minutes.) Dilute KOH was added, and the mixture was shaken for a short while, and extracted with ether. The combined ether extracts were washed with cold water to neutrality, dried over sodium sulfate and evaporated in vacuo. A hexane solution of the crude was filtered through a short column of aluminum oxide activity II-III gave XVIIa in 75% yield, as a viscous oil. ν = 3050, 1625, 1035 and 725 cm^{-1}. δ = 5.6 ppm. (2H, H-C=C-H), 4.5 (2H O-CHO), 3.2 (complex structure 6H, CH_2-O), 2.27 (3H, CH_2-C=C).

Anal. Calcd. for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45.
Found: C, 71.83; H, 10.20.

Ethyl 2(7-Tetrahydropyranyloxyheptyl)-3-tetrahydropyranyloxy-bicyclo [3.1.0]-hexane-6-carboxylate (XVIII)

Ethyl diazoacetate (6 ml.) was slowly added to XVIIa (4 g.) and copper powder (0.25 g.) previously heated to 100° with vigorous stirring. The mixture was then cooled, diluted with hexane, the copper filtered off and the filtrate chromatographed on 100 g. of aluminum oxide (activity II-III). Elution with hexane gave unreacted starting material. Elution with benzene gave in 70% yield a mixture of two isomers, exo and endo XVIII in the ratio 4:1. The two isomers could be separated by t.l.c. (benzene:ether 7:3). The major isomer (exo XVIII) had R_f = 0.75. The minor (endo XVIII) R_f = 0.69. The i.r. spectra of endo and exo XVIII

were very similar. ν = 3095, 3075, 3030 (cyclopropyl), 1725 (COOEt), 1170, 1030, 1020 cm^{-1}. δ = 3.91 (2H, quartet), 1.09 3H (triplet), 4.45 (2H O-CH-O), 3.52 (6H CH_2-O).

Anal. Calcd. for $C_{26}H_{44}O_5$: C, 68.99; H, 9.80.

Found: C, 68.70; H, 9.68 [exo] molecular weight 452 (mass spectra).
C, 68.82; H, 9.68 [endo].

Isomerization of Exo and Endo(XVIII)

The mixture of exo and endo (XVIII) obtained above was refluxed in 45 ml. of 1% methanolic sodium methoxide for 4 hours. The methanol was evaporated, ether was added and the ether extract washed twice with water, dried over sodium sulfate and evaporated. The product obtained consisted mainly of exo (XVIII) (t.l.c.).

2-(7-Tetrahydropyranyloxyheptyl)-3-tetrahydropyranyloxy-bicyclo[3.1.0]-hexane-6-methanol (XIX)

Exo XVIII (2.6 g.) in 10 mg. of anhydrous ether was added to 265 mg. of lithium aluminum hydride in 10 ml. of ether. The addition was in such a rate that a slight reflux was maintained. Additional stirring at room temperature for 1 hour followed. The excess of the hydride was destroyed with ethyl acetate and water. The ether layer was separated, washed with water, dried over sodium sulfate and evaporated, yielding alcohol XIX in quantitative yield as viscous oil. T.l.c. (benzene:ether 55:45) showed a major spot at R_f = 0.48 (exo XIX) and a very weak spot at R_f = 0.56, which corresponded to endo XIX (reduction of a mixture of endo and exo XVIII gave products having the same R_f's). The

n.m.r. and i.r. spectra of both products were very similar and consistent with the structure assigned (spectra, p.90) δ = 4.45 (2H), 352 (7H), 0.8 (1H multiplet of cyclopropyl proton) ppm.

Anal. Calcd. for $C_{24}H_{42}O_5$: C, 70.20; H, 10.31.

Found: C, 69.99; H, 10.77 (endo).

C, 70.00; H, 10.42 (exo).

2-(7-Tetrahydropyranyloxyheptyl)-3-tetrahydropyranyloxy-bicyclo[3.1.0]-hexane-6-carboxaldehyde (XX)

To alcohol XIX dissolved in 12 ml. of acetone was added rapidly at -10°, 2.7 ml. of Jones reagent (54) diluted with 5 ml. of acetone. The mixture was stirred for another 7 minutes at -12°. Isopropyl alcohol and water were added and the reaction product was extracted with ether. The ether extracts were washed neutral with 10% sodium carbonate solution and water. After drying over sodium sulfate, the ether was evaporated, leaving 1.2 g. of aldehyde XX. No crystalline derivatives of XX could be obtained. ν = 3100, 3030 (cyclopropyl), 2710, 1700, 1030, 725 cm^{-1}. δ = 9.2 (doublet) ppm. (major exo XX), 9.4 (doublet) ppm (trace endo XX).

Upon treatment of the mixture of epimers XX with one equivalent of sodium t.amyloxide in boiling t.amyl alcohol for 5 minutes, the doublet at 9.4 ppm. disappeared almost completely.

6-(1-Heptenyl)-2(7-tetrahydropyranyloxyheptyl)-3-tetrahydropyranyloxy-[3.1.0]-hexane (XXI)

To hexyltriphenyl phosphonium bromide (2.5 g.) suspended in 25 ml. of anhydrous ether, was added under a nitrogen atmosphere 0.15 ml. of butyl

lithium (22.22% solution in hexane). An immediate orange coloration indicated the formation of the ylid. A solution of 622 mg. of XX in 10 ml. of anhydrous ether was introduced by means of a syringe. Immediate precipitation occurred. Most of the solvent was evaporated by blowing a stream of dry nitrogen over the solution. Anhydrous tetrahydrofuran (40 ml.) was then added and the mixture was heated to reflux for 6 hours. After cooling the solvent was removed in vacuo, and the residue extracted several times with ether. The ether solution was washed twice with water and dried over sodium sulfate. Evaporation of the ether yielded 1.2 g. of semi-solidified oil. Chromatography on 30 g. of aluminum oxide (activity II-III) and elution with hexane-benzene (3:1) gave 350 mg. of XXI (45% yield) as an oil (pungent odor). The cis and the trans isomers formed could not be separated by t.l.c. or g.l.c. The i.r. spectrum of XXI showed bands at 3090, 3070, 3030 cm^{-1}, (cyclopropyl), 1650 (double bond), 1030 (C-O), 1020 (cyclopropyl) cm^{-1}. N.m.r. spectra of mixture showed absorptions at 5.2 ppm. (complex for vinylic protons).

Anal. Calcd. for $C_{30}H_{52}O_4$: C, 75.54; H, 11.00.

Found: C, 75.00; H, 11.00. (For mixture).

6-(1-Heptenyl)-2-(7-hydroxyheptyl)bicyclo[3.1.0]-hexan-3-ol (XXII)

To 40 ml. of 0.5% solution of oxalic acid in methanol was added 840 mg. of XXI. The mixture was heated to reflux for three hours. After that period the methanol was removed in vacuum and ether was added. The ether extract washed to neutrality with 10% sodium carbonate solution, dried and evaporated. T.l.c. (benzene-ether 55:45) separated two major

products, with R_f's 0.56 and 0.32. (When hydrolysis was done for a shorter period an additional product at R_f = 0.62 was observed.) This product according to its i.r. and n.m.r. spectra still contained the 3-pyranyl group. This could be further hydrolyzed to end products. The products at Rf = 0.32 and R_f = 0.56, had nearly identical n.m.r. spectra which were consistent with the structure of XXII. Both major compounds had bands in the i.r. spectra at 3350 (OH), 3050 and 3010 (cyclopropyl and double bond), 1650 (CH=CH), 1060 (C-O), 1020 and 725 cm^{-1}. The compound with R_f = 0.56 had no band at 960 cm^{-1} and a strong band at 730 cm^{-1} and was therefore assigned the structure of the cis XXII.

The compound at R_f = 0.32 had a band at 960 cm^{-1} and a weak band at 730 cm^{-1} and was assigned the structure of the trans XXII.

The common features in the n.m.r. spectra for both isomers were δ = 4.15 (H$\times$OH), 3.75 (triplet CH_2-O), 1.00 (triplet-terminal methyl) ppm. Different patterns were observed for the cis and the trans vinylic protons at a complex centered at 5.2 ppm.

A product in a very small amount was detected also at R_f = 0.44. It showed a strong band at 960 cm^{-1} and was most likely endo trans XXII.

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76.

Found: (R_f 0.56) C, 77.42; H, 11.40.

Found: (R_f 0.32) C, 77.42; H, 11.52.

6-(1-Heptenyl)-2-(7-carboxyheptyl)bicyclo[3.1.0]-hexan-3-one (XII)

A mixture of cis and trans XXII (140 mg.) in 14 ml. of acetone was cooled to 0° and 1.4 ml. of Jones reagent (54) in 14 ml. acetone was added rapidly. The mixture was stirred at 0-3° for 15 minutes and was allowed to warm up to 5° over a period of 5 minutes. A few drops of isopropyl alcohol was then added to destroy excess chromic acid and followed by 90 ml. of water. The mixture was extracted with ether and the ether extract was washed twice with ice water and three times with 20 ml. of 10% aqueous sodium carbonate solution.

The carbonate extract was cooled in an ice bath and carefully acidified with concentrated hydrochloric acid. The acidified suspension was extracted with ether. The ether extract was washed twice with ice water and dried over magnesium sulfate. Evaporation of the ether gave 120 mg. of keto acid XII (cis and trans). I.r. spectra and R_f values of these two compounds were the same as of those obtained from the first route. (For analytical data see Experimental, chapter II.) Pure cis XXII was oxidized in a similar manner, giving cis XII, having the same i.r. spectrum as the mixture except for the absence of the band at 960 cm^{-1} (spectra, p. 96). Pure trans XXII was oxidized also to XII trans. Methylation with diazomethane gave esters Xa and Xb correspondingly (identical i.r., n.m.r. spectra and some R_f value in different solvent systems).

6-(1-Heptenyl)-2-(7-carboxyheptyl)bicyclo[3.1.0]-hexan-3-ol (XIV)

To a solution of 10 mg. of sodium borohydride in 2 ml. of 0.2 N aqueous sodium hydroxide, was added dropwise with stirring a solution of 162 mg. of the keto acid XXII (cis and trans) in 2 ml. of water containing 40 mg. of NaOH. The solution was stirred at room tempeature. After that period, the mixture was cooled to 5° cautiously acidified with hydrochloric acid and extracted with saturated aqueous solution of sodium bicarbonate. The basic extract was acidified in the cold with hydrochloric acid and then extracted with ether. The ether solution was dried over magnesium sulfate and evaporated leaving a mixture of 4 hydroxy acids.

Treatment of the 4 products with diazomethane (79) gave four ester alcohols which were identified according to their R_f's values and n.m.r. spectra, to be XIIIa-d.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 75.00; H, 10.71. (Methyl ester). Found: C, 74.65, H, 11.00; C, 74.80, H, 10.80; C, 74.95, H, 10.50, C, 75.15, H, 10.80.

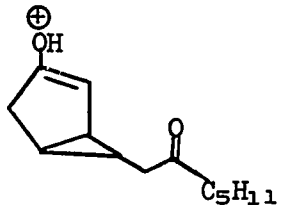
Oxidative Solvolysis of Acid XII to PGE_1

To a well stirred 0.5 N solution of sodium formate in absolute formic acid (4 ml.) under nitrogen atmosphere, was added 25 mg. of keto acid XII (cis and trans mixture). The solution was cooled (bath temperature 5°) until turbidity appeared and 1.1 equivalent of hydrogen peroxide 90% was added. The mixture was allowed to warm up to room temperature and stirred for 3 hours. The formic acid was removed in

high vacuum (freeze dry evaporation). To the waxy residue was added 3 ml. of 10% aqueous methanolic solution of sodium carbonate (water: methanol 4:1) and the resulted clear solution stirred at room temperature for 12 hours, under nitrogen atmosphere. Water was then added (15 ml.) and the solution cooled in an ice bath and acidified with 1 N hydrochloric acid to pH2 and extracted with ether. The ether extract washed to neutrality with cold water and dried over magnesium sulfate and evaporated, leaving 20 mg. of crude material.

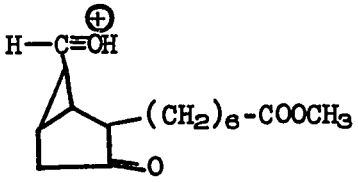
The crude was chromatographed on silicic acid column (7 g.). Elution with benzene:ethyl acetate 8:2 gave a mixture of two compounds, one of them had the same R_f value as PGA_1. U.V. examination of the fraction showed an absorption of λ_{max} 217 mμ, treatment with 0.5 NaOH for 1 hour converted only the material corresponding to PGA_1 to PGB_1 with the same R_f as the natural one and having a U.V. absorption maximum at 278 mμ, the other material was not changed by the treatment of alkali. Estimation of the yield of the PGA_1 from its U.V. absorption was about 5%. (On other runs no PGA_1 was found and this fraction consisted mainly on the other product which according to its i.r. and n.m.r. spectrum was found to be compound XXIII, (Chart 9)

N.m.r. complex centered at δ = 2.65 ppm. (CH_2-C(=O)); 1.38 ppm (CH_2 envelope); 0.9 ppm (CH_3 terminal); 0,5 ppm cyclopropyl; m.s.(methylester), 350 $m^{\oplus}$, 332 (m-28), 319 (m-31), 208 =



Elution with benzene:ethyl acetate 6:4 mixture of two compounds which according to the i.r. and n.m.r. spectra found to be non-rearranged products (chart 9, p. 33). I.R. ν= 3460 (OH), 1745, 1730 (C=O), 1200, 1215, 1190, 1175, 1005, 735 cm.$^{-1}$ N.m.r. complex centered at δ4.1 ppm (CH-O), 0.76 () ppm, 0.9 ppm (terminal methyl).

Mass spectra - (methyl ester) 368 (M^+), 350 (M-18), 337 (M-31), 319 (350-31), 267 .



Fraction eluted with ethyl acetate benzene 6:4 gave two products with R_f value of 0.54 and 0.47 (silica gel G impregnated with 3% silver nitrate detection with 10% phosphomolybdic acid in ethanol A-II system). The spot at R_f 0.54 corresponded to natural PGE_1. T.l.c. on silica gel impregnated with 3% boric acid gave three materials at R_f, 0.75, 0.77 and 0.67 (elution with A-II system diluted with 1.5 volumes of ether). The compound at R_f 0.75 was corresponding to PGE_1. Quantitative t.l.c. on silica gel 3% boric acid (detection of bands by opaque zones created by spraying with water, extraction of the material from the plate, by several washings with methanol) was not able to separate PGE_1 from the compound with R_f = 0.77. (Yield of combined products 12%.)

The n.m.r. spectra of the mixture of the two compounds was identical to that of PGE_1, except for the shape of the allylic protons. (N.m.r. spectra was taken on a small sample by using c.a.t. technique.)

Mass spectrum of the mixtures methyl esters of PGE_1 and the compound with

R_f = 0.77 was identical to that of PGE_1 methylester (spectrum 16) except for the intensities of some bands.

Treatment of 2 mg. of methylesters of the synthetic PGE_1 and compound R_f = 0.77 with 20 mg. manganese dioxide in 5 ml. of THF overnight, at room temperature, gave 1 spot (same t.l.c. conditions as above) which had the same R_f as of the oxidation product of natural PGE_1 in the same conditions.

The above mentioned mixture of synthetic PGE_1 (2 mg.) was dissolved in 1 ml. of 0.5 N sodium hydroxide, and the mixture was stirred at room temperature for 1 hour. The solution was cooled and acidified with 6 N HCl in the cold, and extracted with 5 ml. ether. The ether extract was dried over magnesium sulfate and evaporated. T.l.c. of the crude revealed the existance of only one spot while had the same R_f as PGB_1. The crude showed a very pronounced u.v. absorption at 278 mμ (ϵ = 24,000).

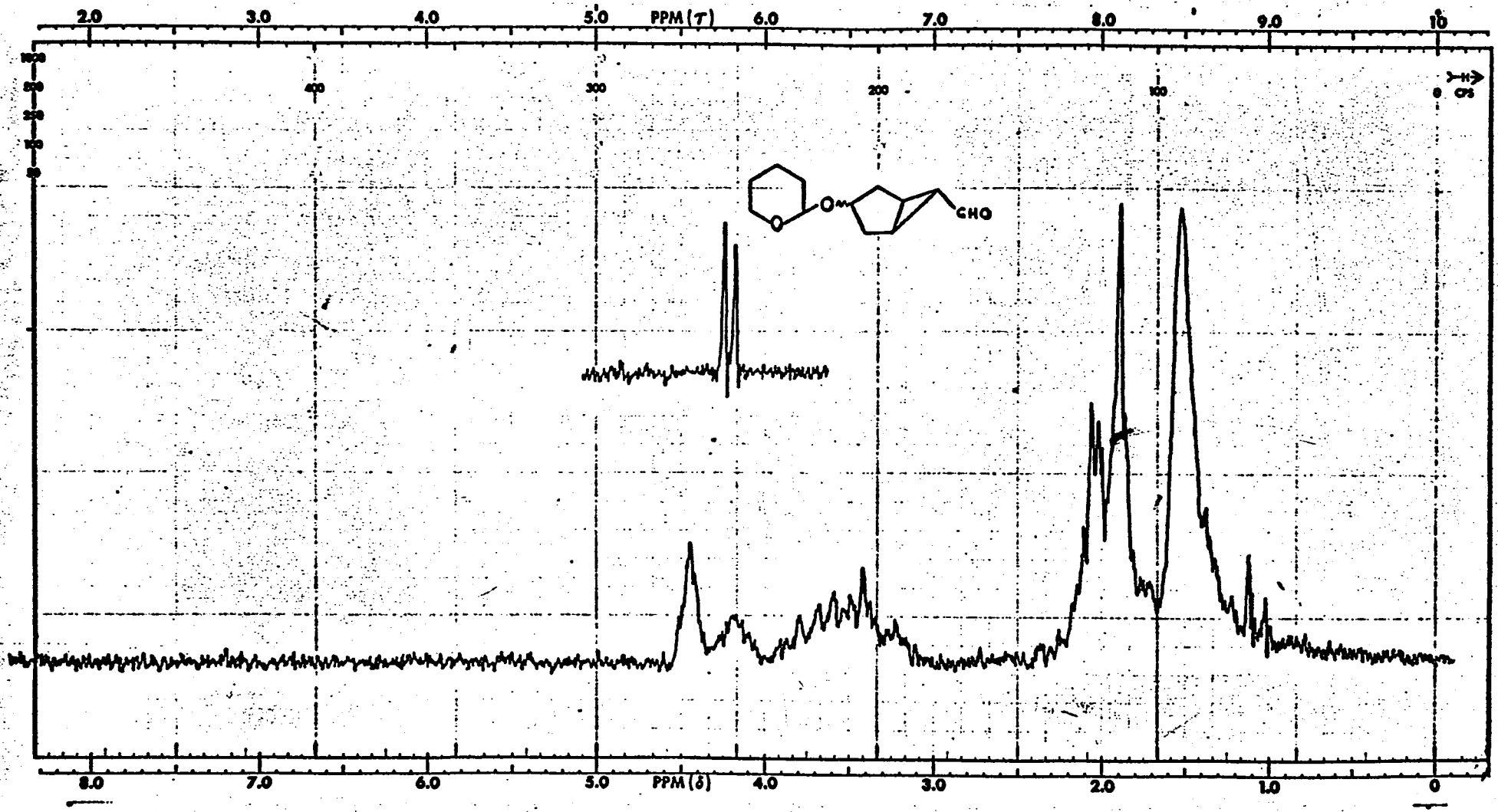
Oxidative Formolysis of XIV

Oxidative formolysis on acid XIV was carried in the same manner as described before (Experimental, p. 57) t.l.c. indicated the formation of $PGF_1\alpha$, but no separations were carried in this reaction.

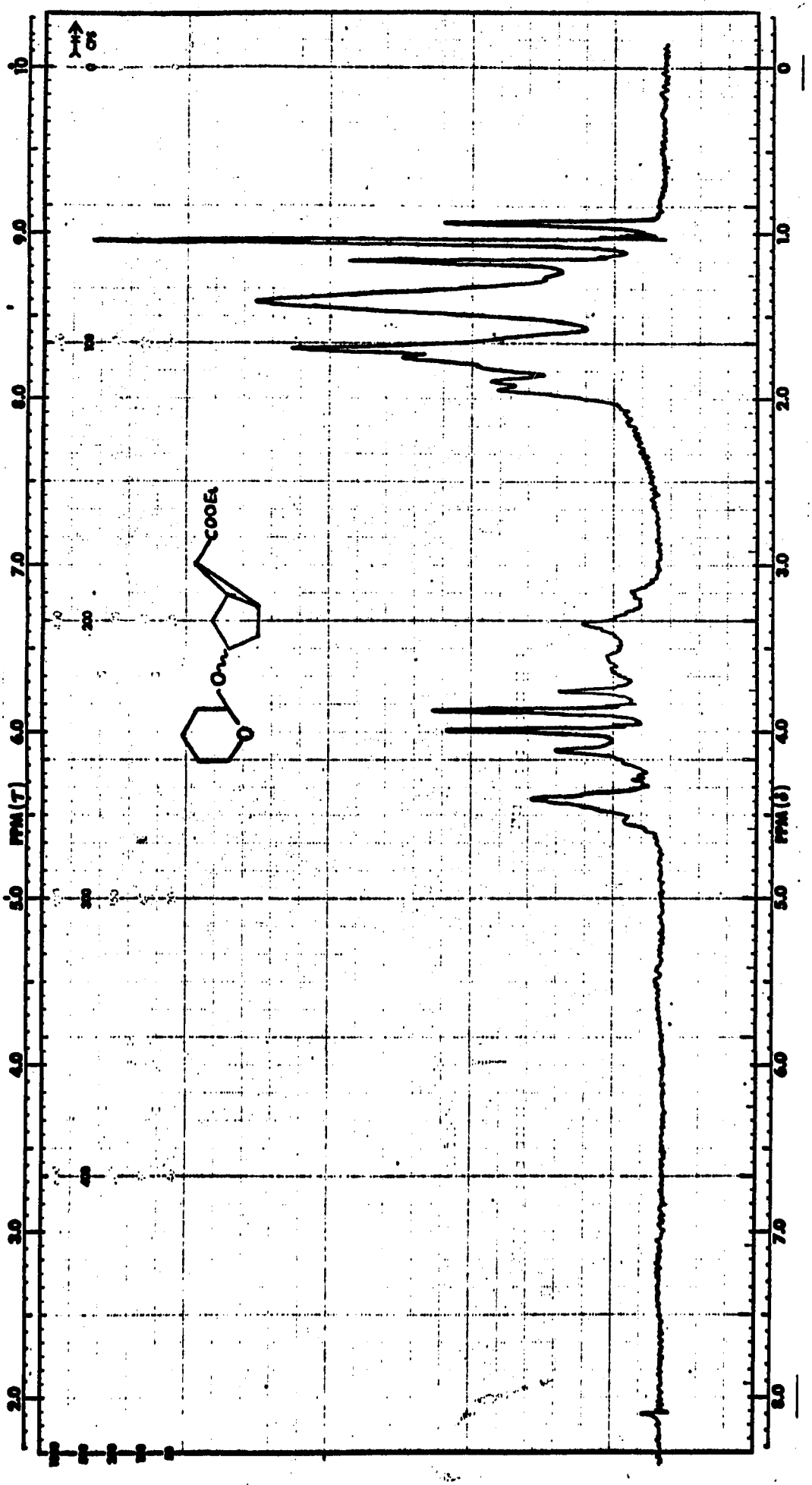
N.m.r. spectra were taken in deuterochloroform unless specified otherwise with tetramethylsilane = 0. ppm. Infrared were taken as films between KBr or NaCl plates. Silica gel G used for t.l.c. was first boiled in methanol, filtered and reactivated at 110°.

Mass spectra were taken by Morgan and Schaeffer Corporation, Montreal.

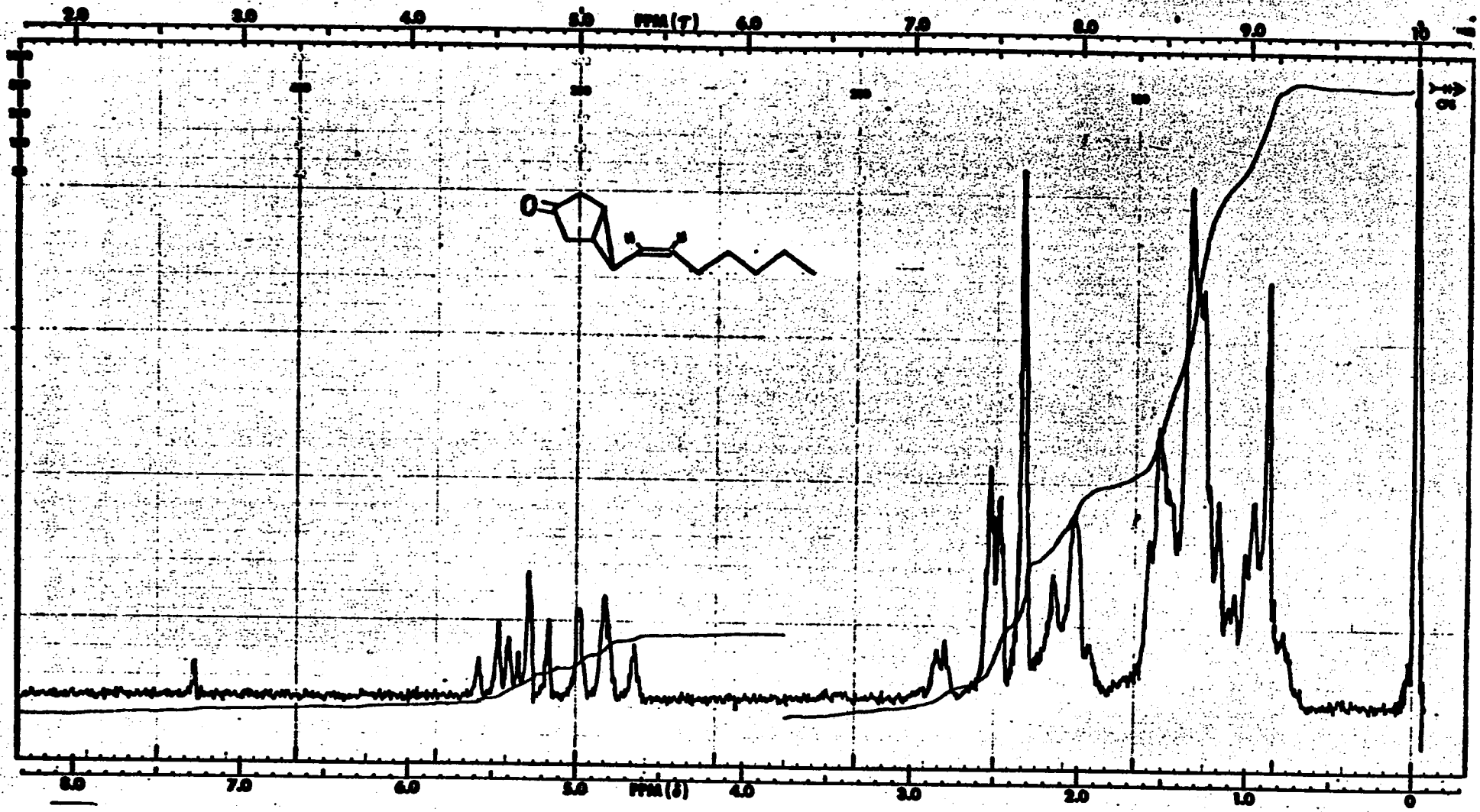
Elemental analysis was made by Beller, Mikroanalytisches Laboratorium, Göttingen, Germany.



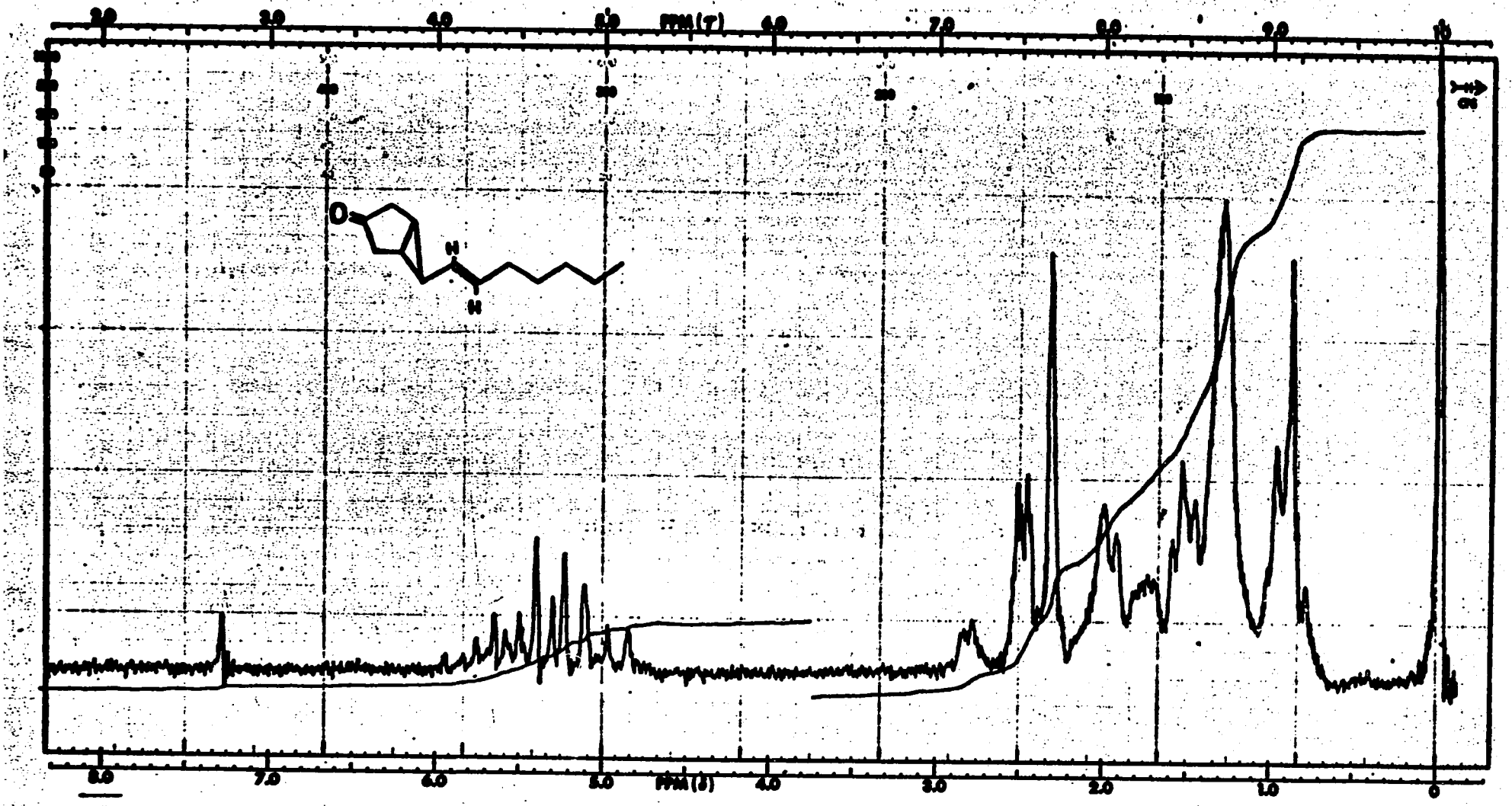
Spectrum No. 1 - 3-[(Tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]hexan-6-exo-carboxaldehyde. VI



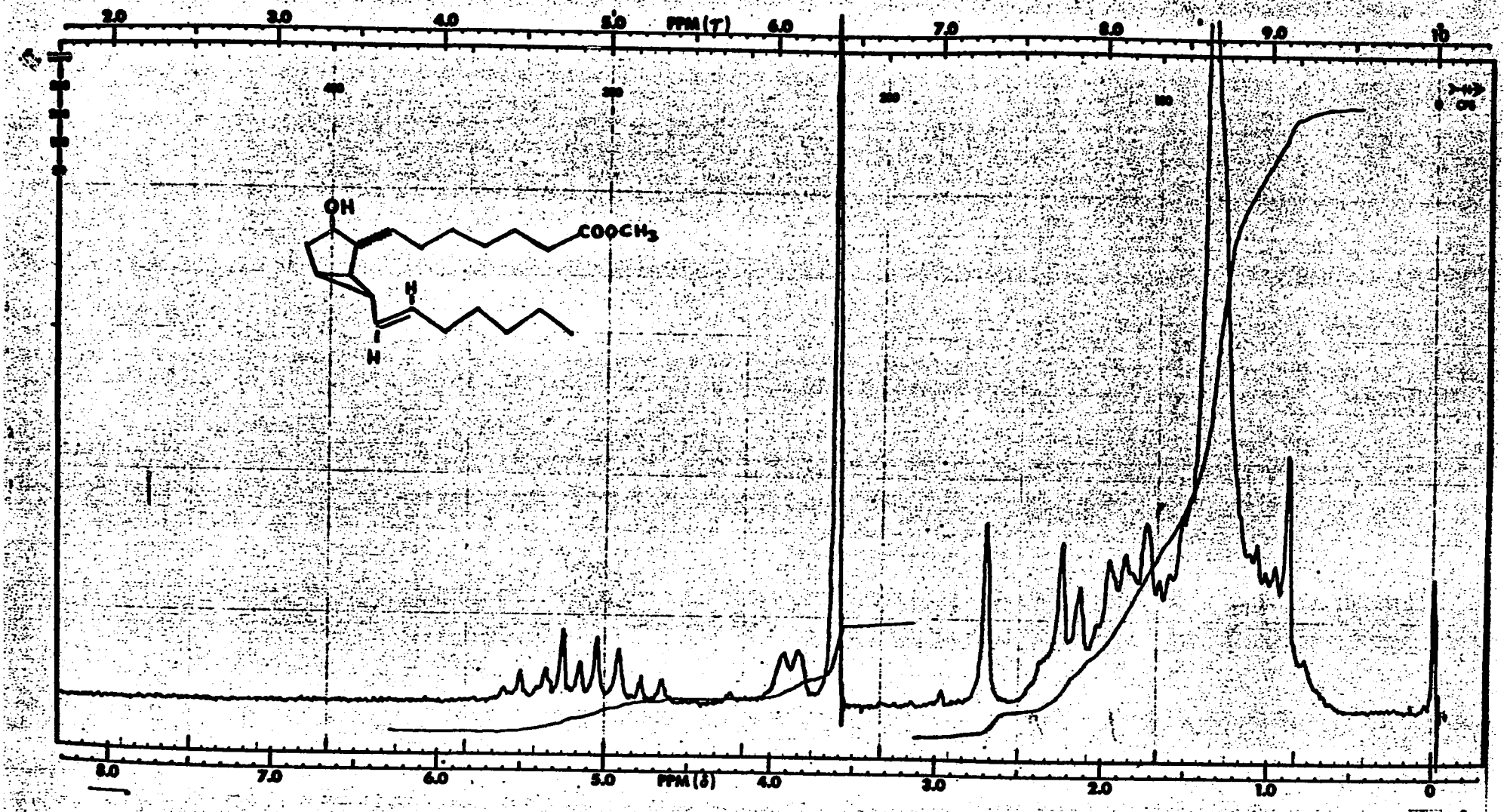
Spectrum No. 2 - Ethyl-3-[(tetrahydropyran-2-yl)oxy] bicyclo[3.1.0]hexan-6-exo-carboxylate. III



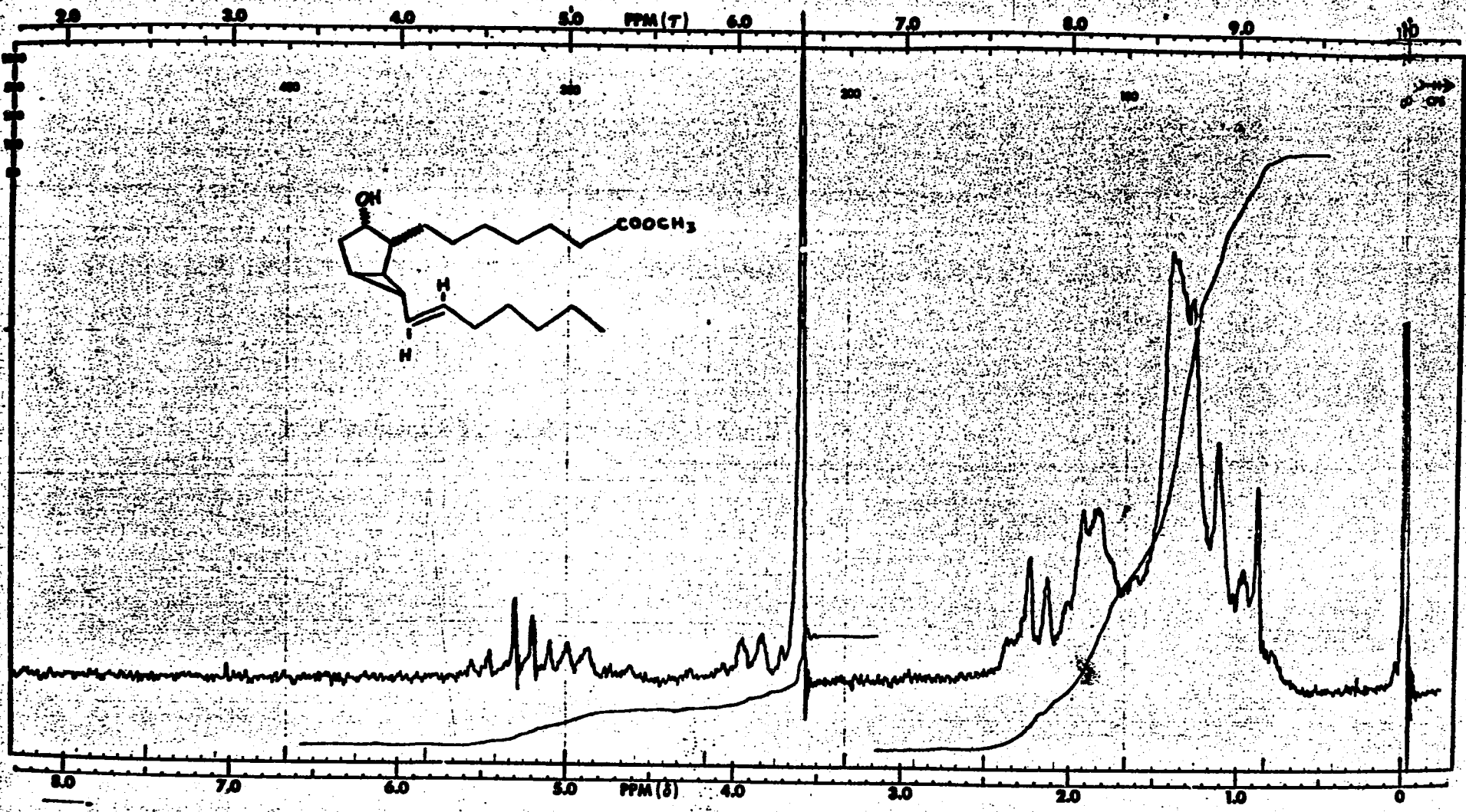
Spectrum No. 3 - 6(Cis-1-heptenyl)bicyclo[3.1.0]hexan-3-one. IXb (80)



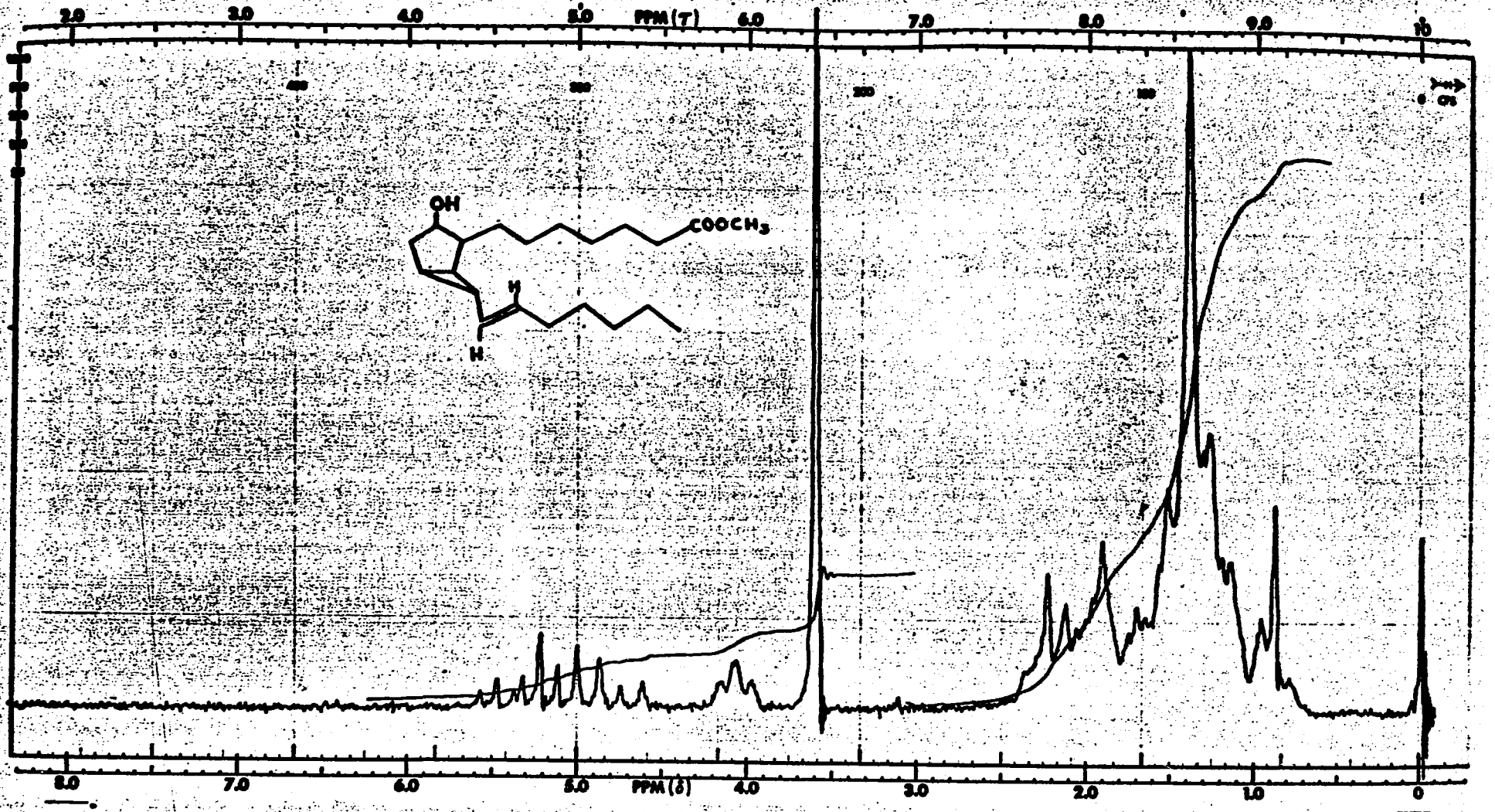
Spectrum No. 4 - 6(trans-1-heptenyl)bicyclo[3.1.0]-hexan-3-one. IXa (80)



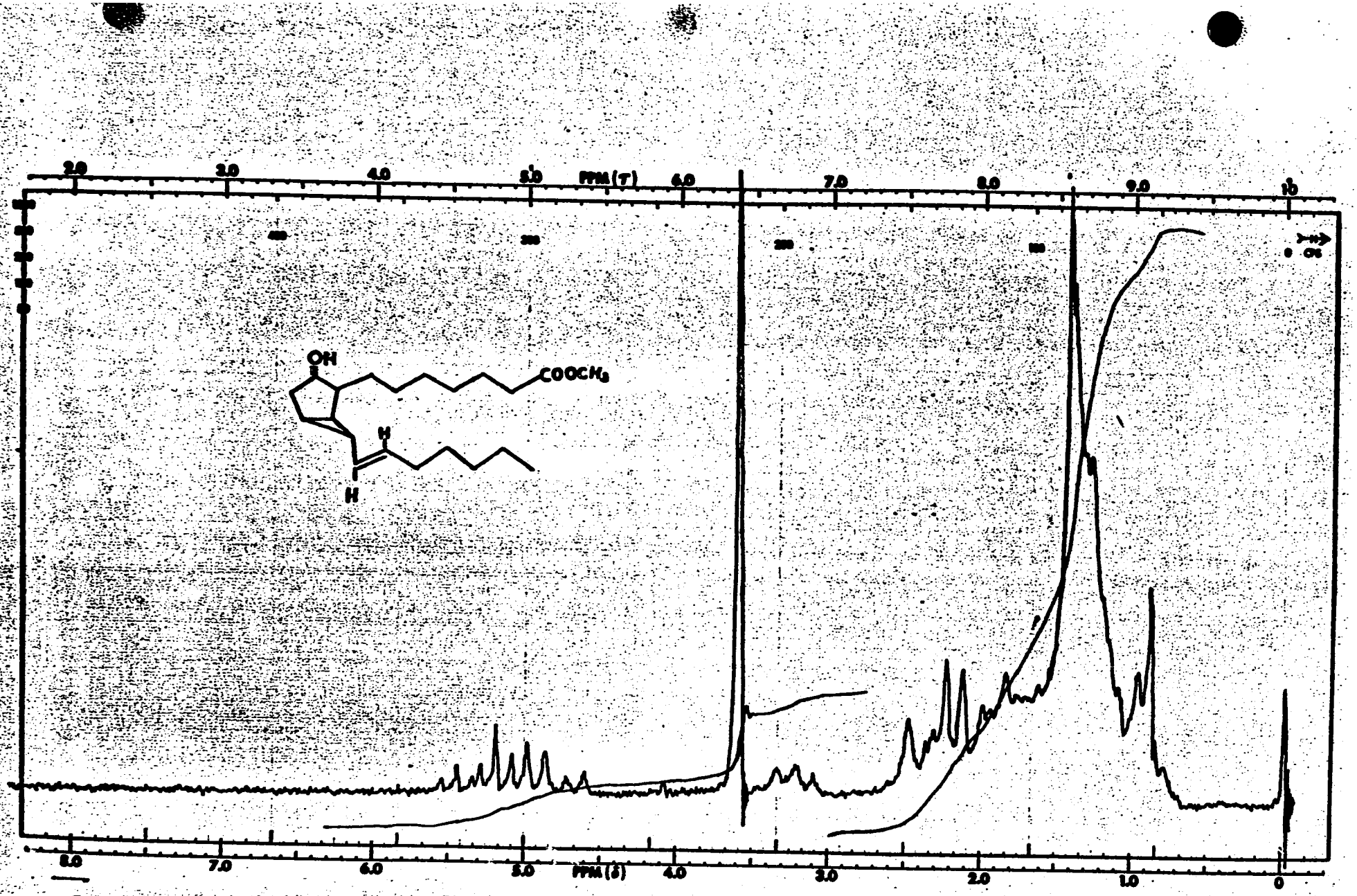
Spectrum No. 5 - Methyl-6(trans 1-heptenyl)-3β-ol-bicyclo[3.1.0]hexane-2α-heptanoate, XIIIb (80)



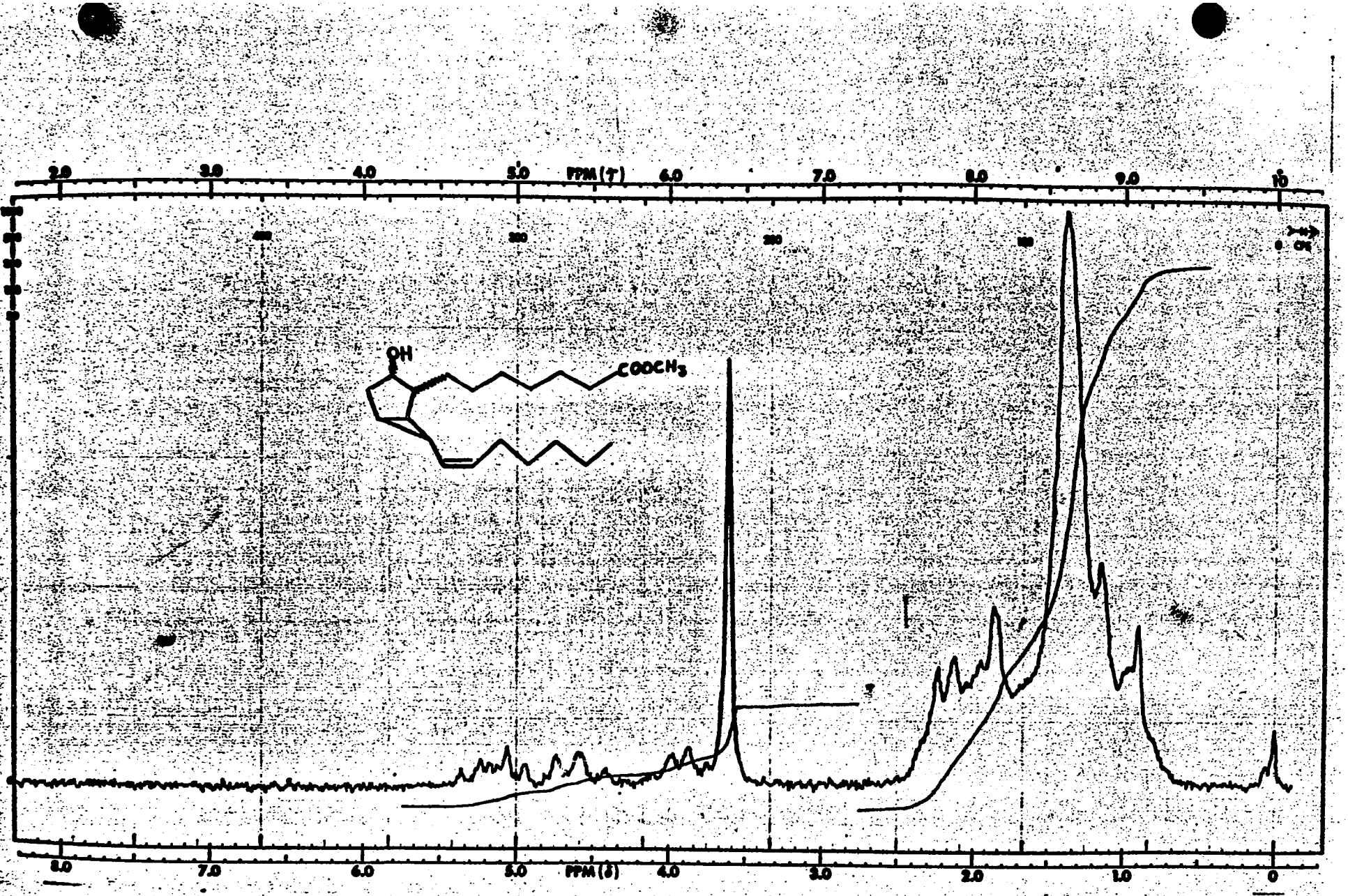
Spectrum No. 6 - Methyl 6(trans 1-heptenyl)-3α-ol-bicyclo[3.1.0]hexane-2α-heptanoate. XIIIa (80)



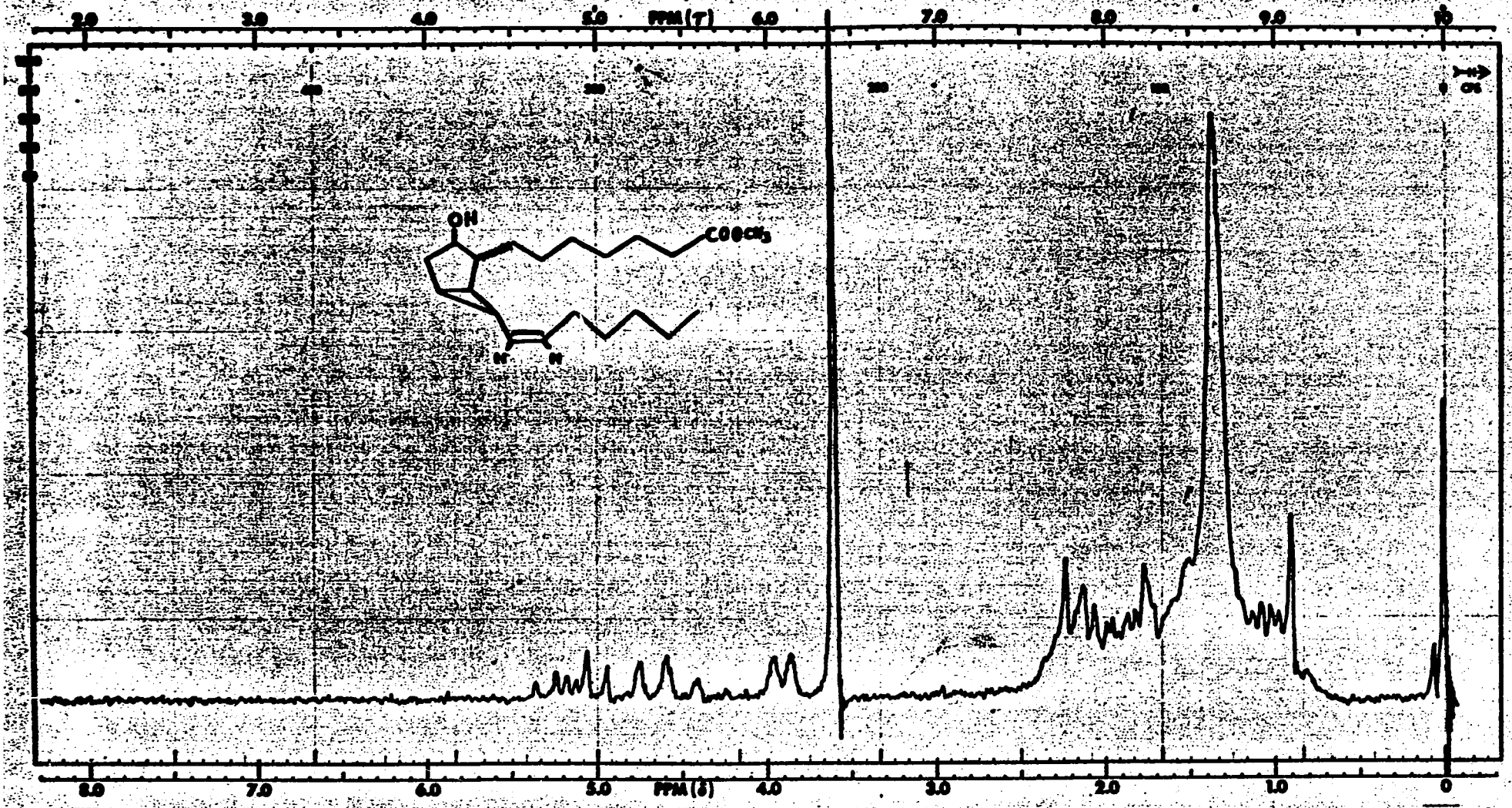
Spectrum No. 7 - methyl 6(trans-1-heptenyl)-4β-ol bicyclo[3.1.0]hexane-2β-heptanoate. XVb (80)



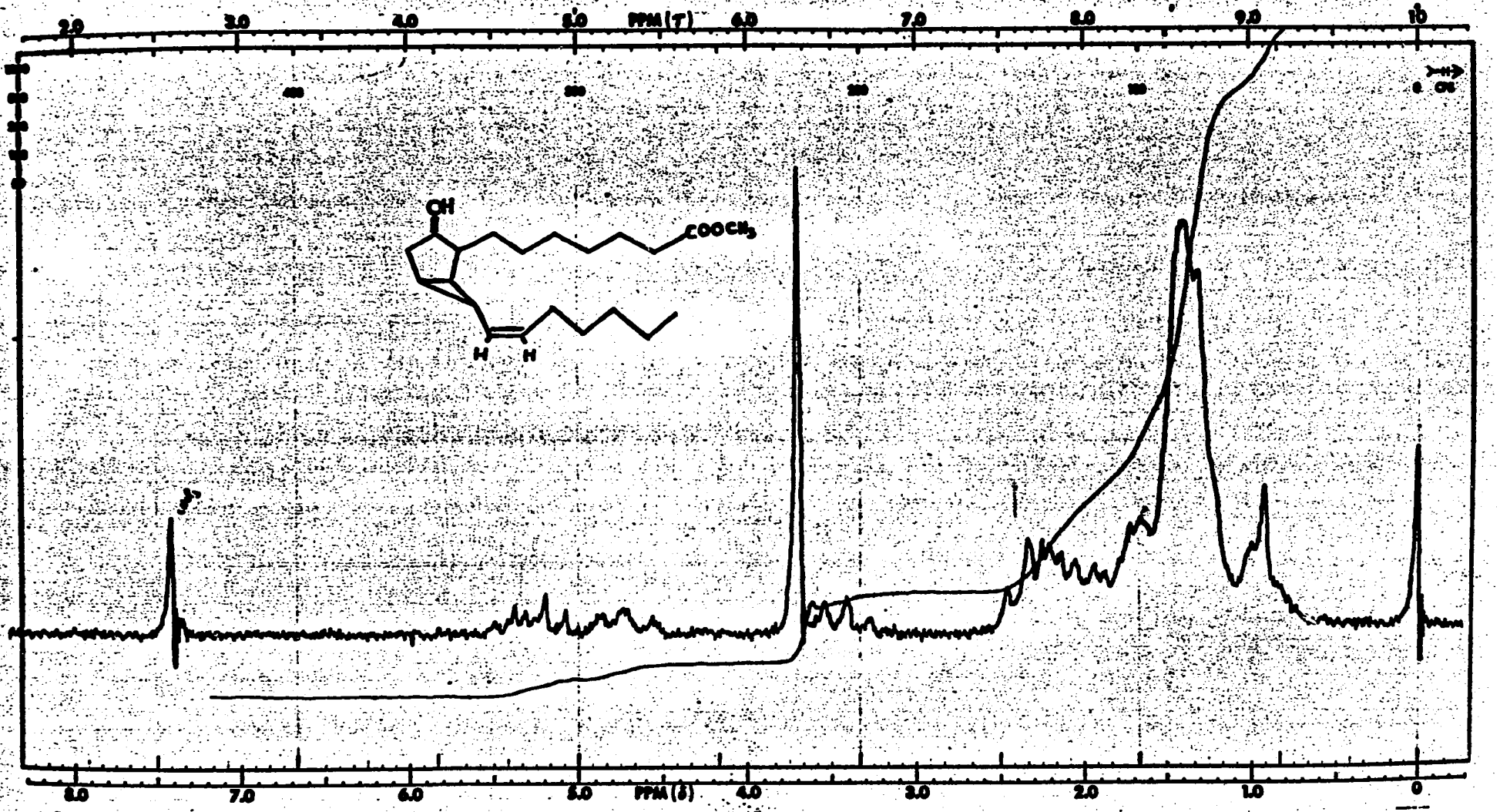
Spectrum No. 8 - methyl 6(trans-1-heptenyl)-3α-ol-bicyclo[3.1.0]hexane-2β-heptanoate. XVa (80)



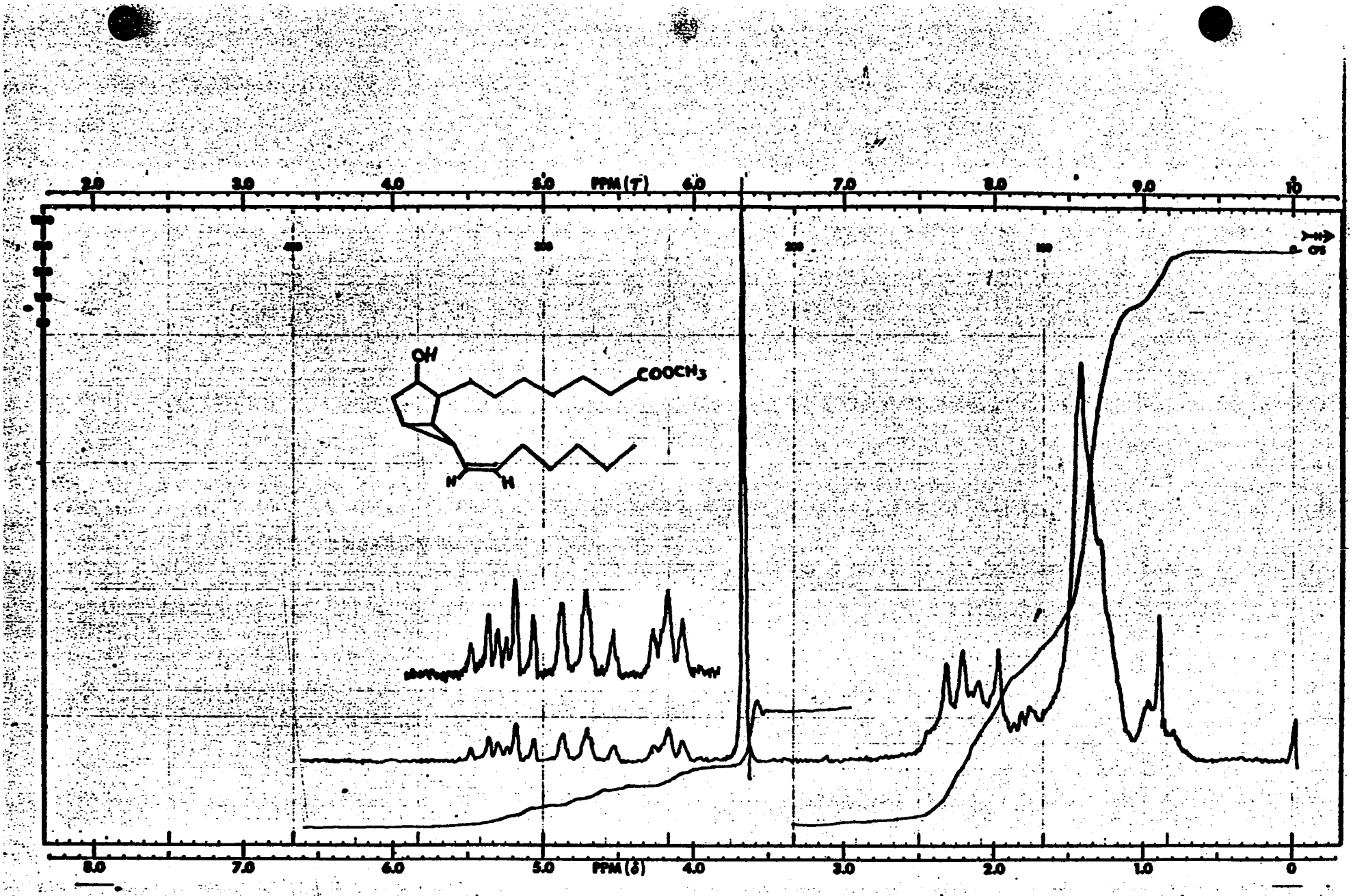
Spectrum No. 9 - Methyl 6(cis-1-heptenyl)-3α-ol bicyclo 3.1.0]bicyclohexane-2α-heptanoate. XIIIa (80)



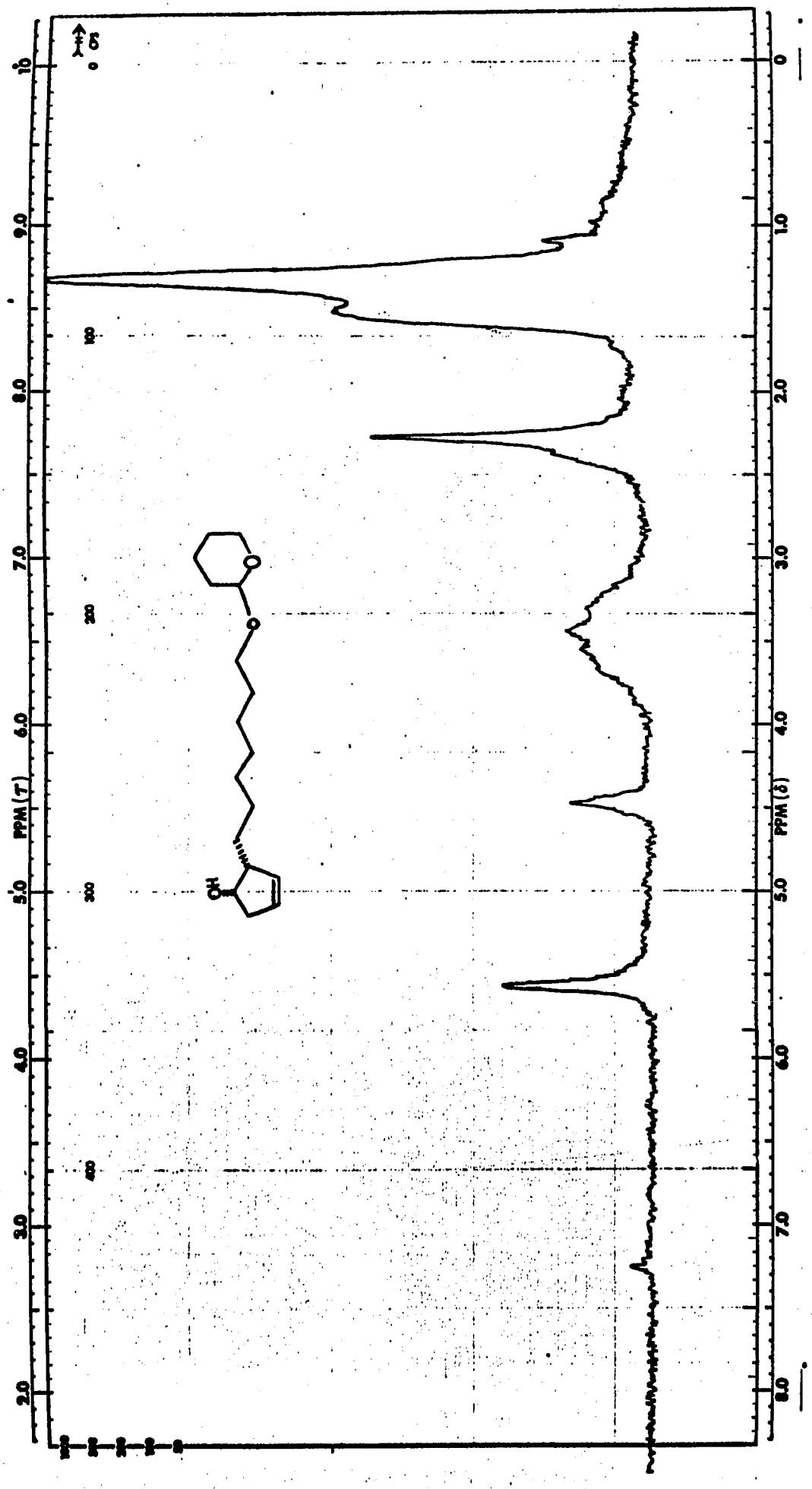
Spectrum No. 10 - Methyl 6(cis-1-heptenyl)-3β-ol bicyclo[3.1.0]hexane-2α-heptanoate. XIIIc (80)



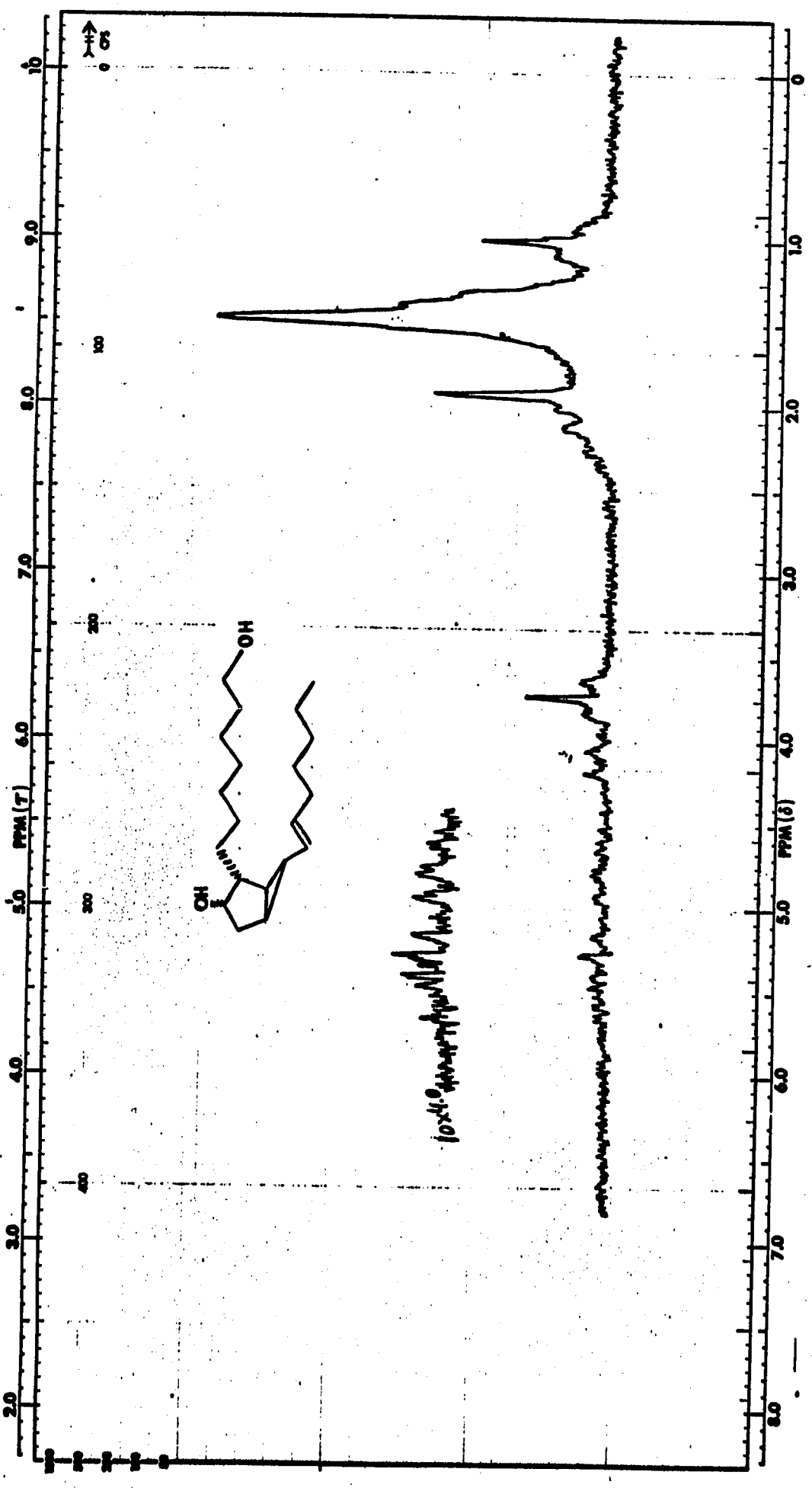
Spectrum No. 11 - Methyl 6(cis-1-heptenyl)-3α-ol bicyclo[3.1.0]hexane-2β-heptanoate. XVd (80)



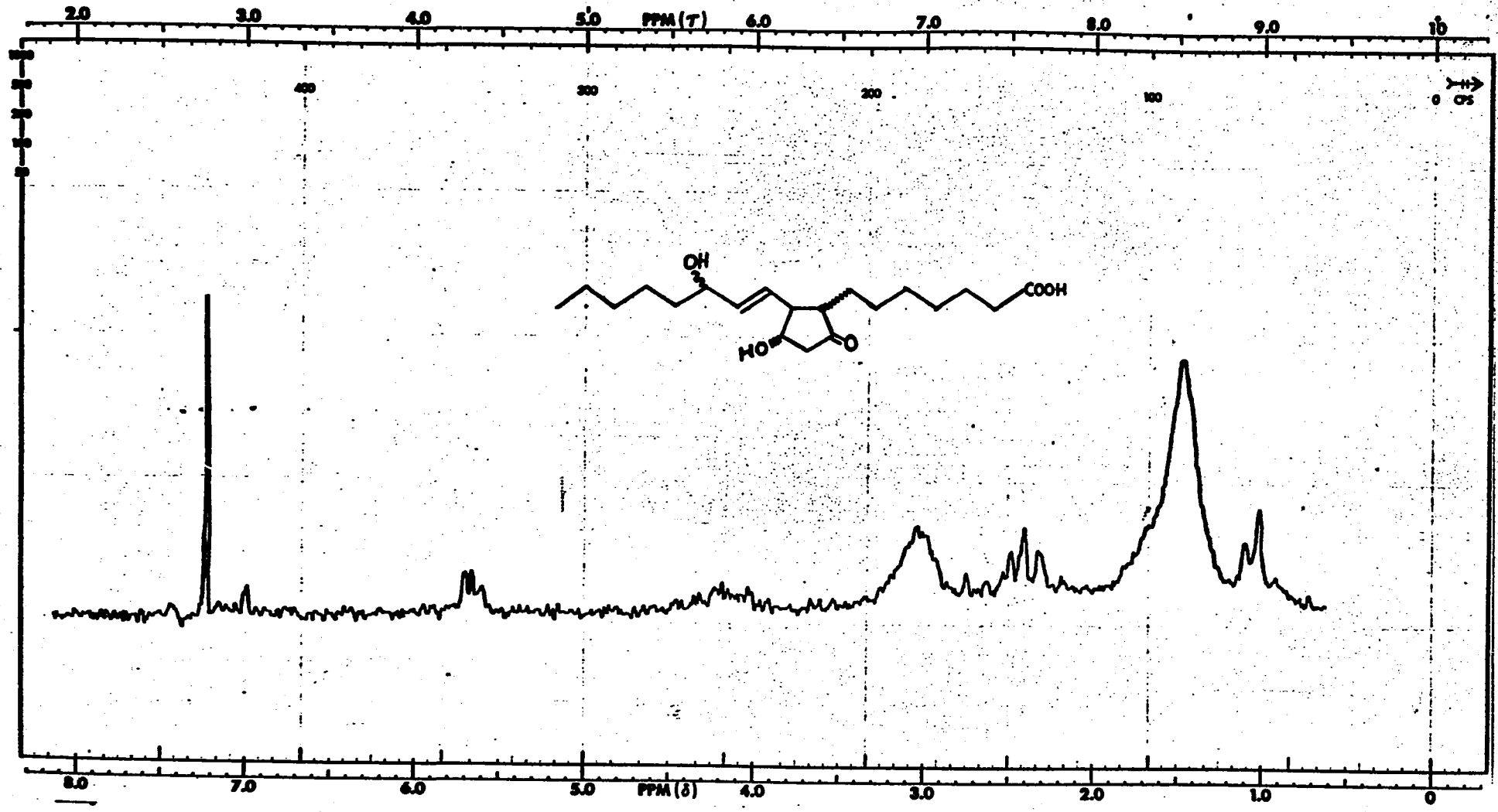
Spectrum No. 12 - Methyl 5(cis-1-heptenyl)-3β-ol bicyclo [3.1.0]hexane-2β-heptanoate. XVc (80)



Spectrum No. 13 - 2-(7-Pyranyloxyheptyl)cyclopent-3-enol. XVII



Spectrum No. 14 - 6(Trans 1-heptenyl)3α-ol bicyclo[3.1.0]hexane-2α(7-hydroxy)heptane. XXII



Spectrum No. 15 - Synthetic PGE_1

COMPRESSED SCAN

GAIN 10 PGE-ester

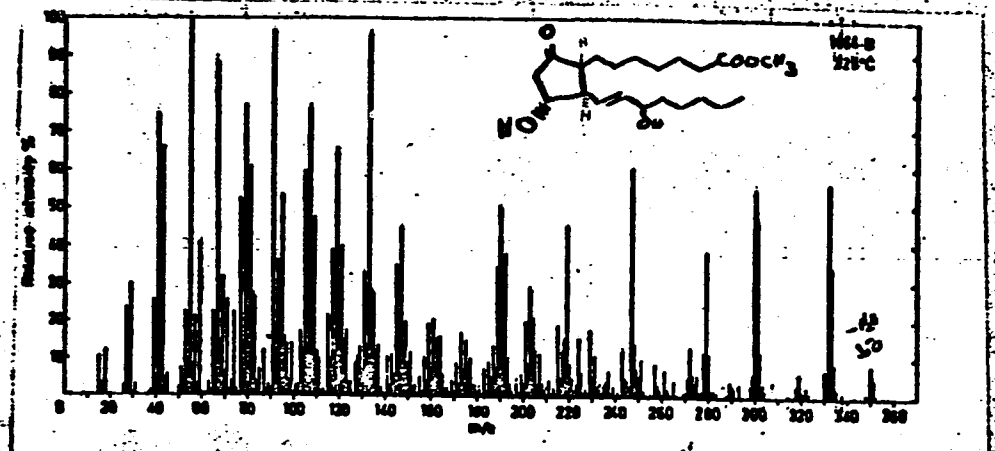
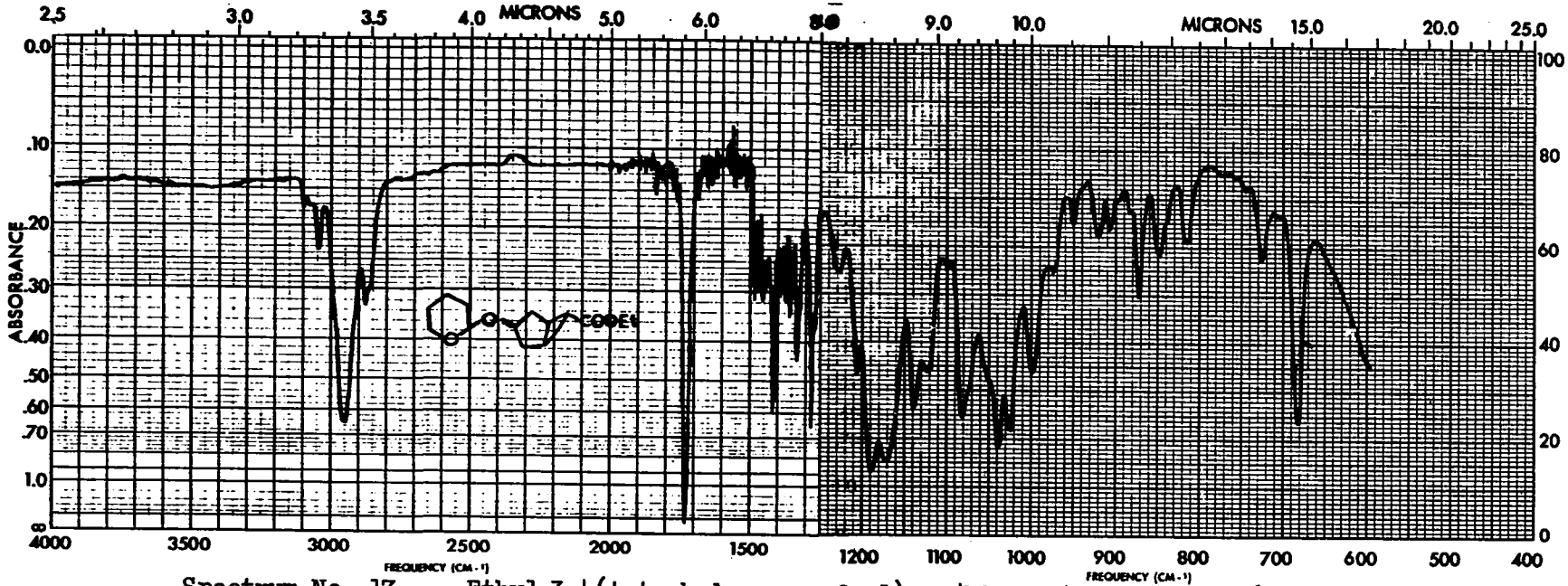


Fig. 2. Mass spectrum of the methyl ester of PGE_1.

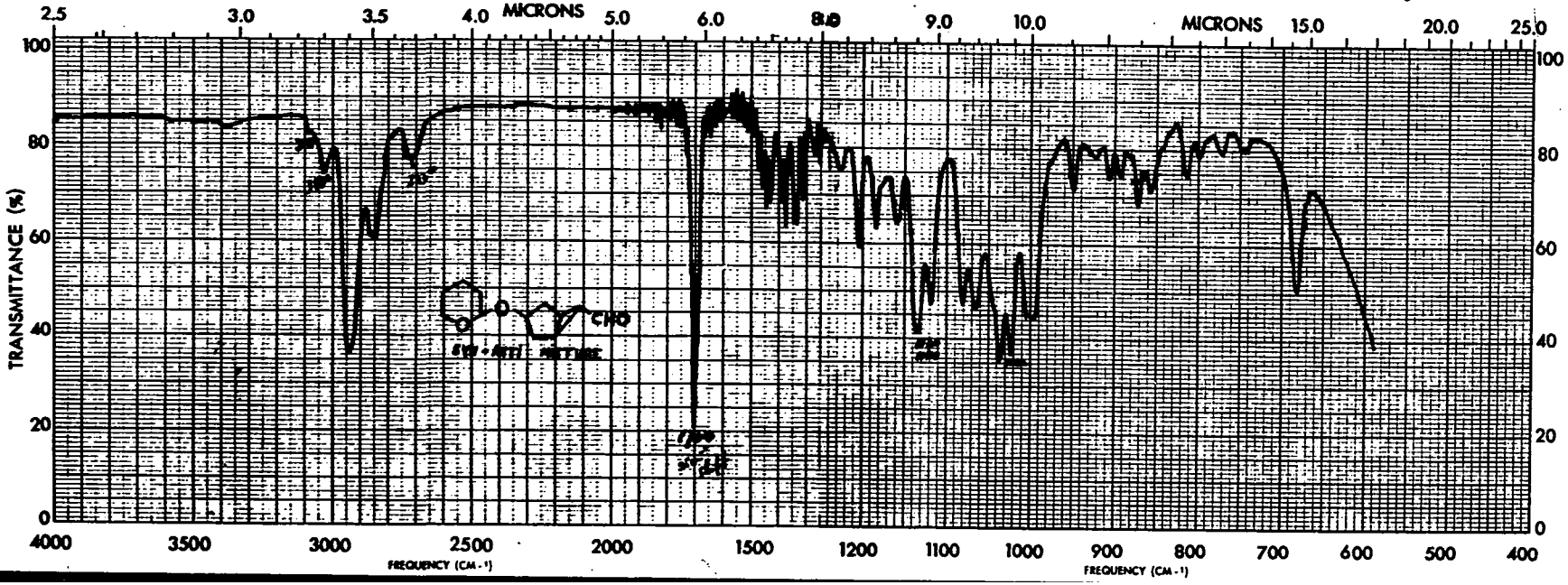
(1) $M^+ = 368$
(2) M-18 = 350
(3) M-(2 x 18) = 332
(2)-21 = 329
(3)-31 = 301
(2)-71 = 279
(3)-71 = 261
(3)-143 + 1 = 190
329-72 = 247

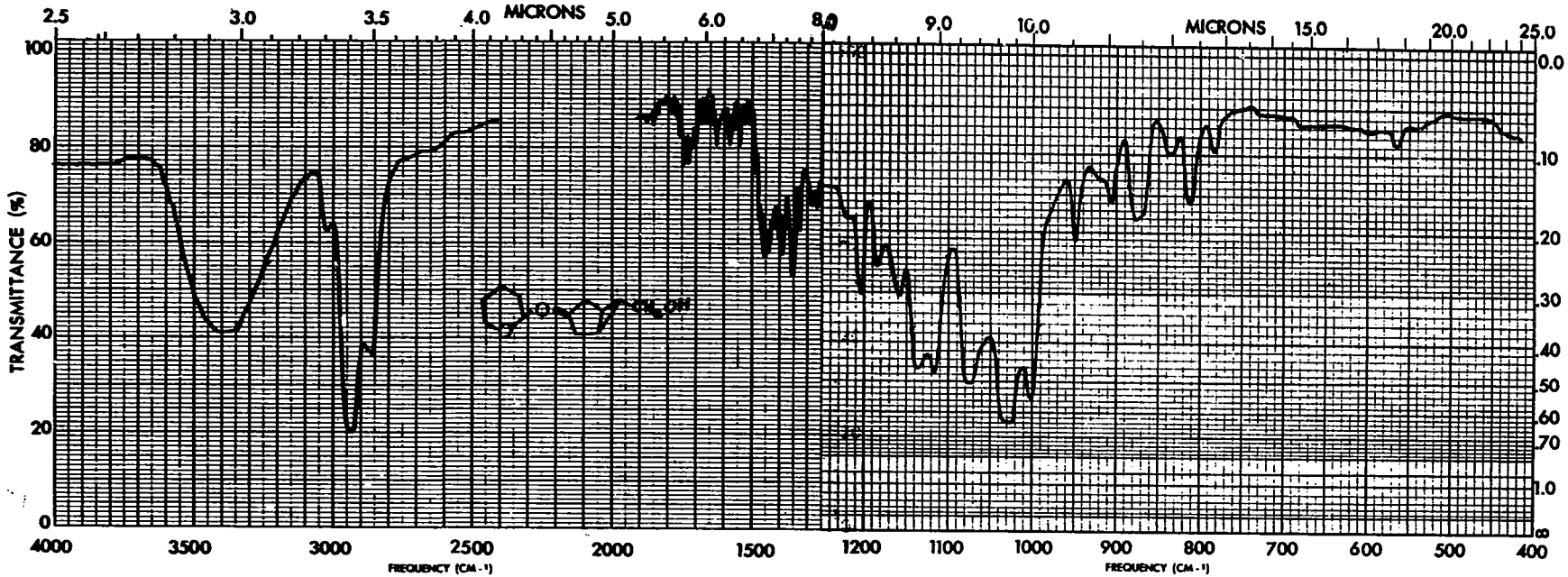
Spectrum No. 16 - Synthetic PGE_1 ester in comparison to natural PGE_1



Spectrum No. 17 - Ethyl 3-[(tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]hexan-6-exo carboxylate. III

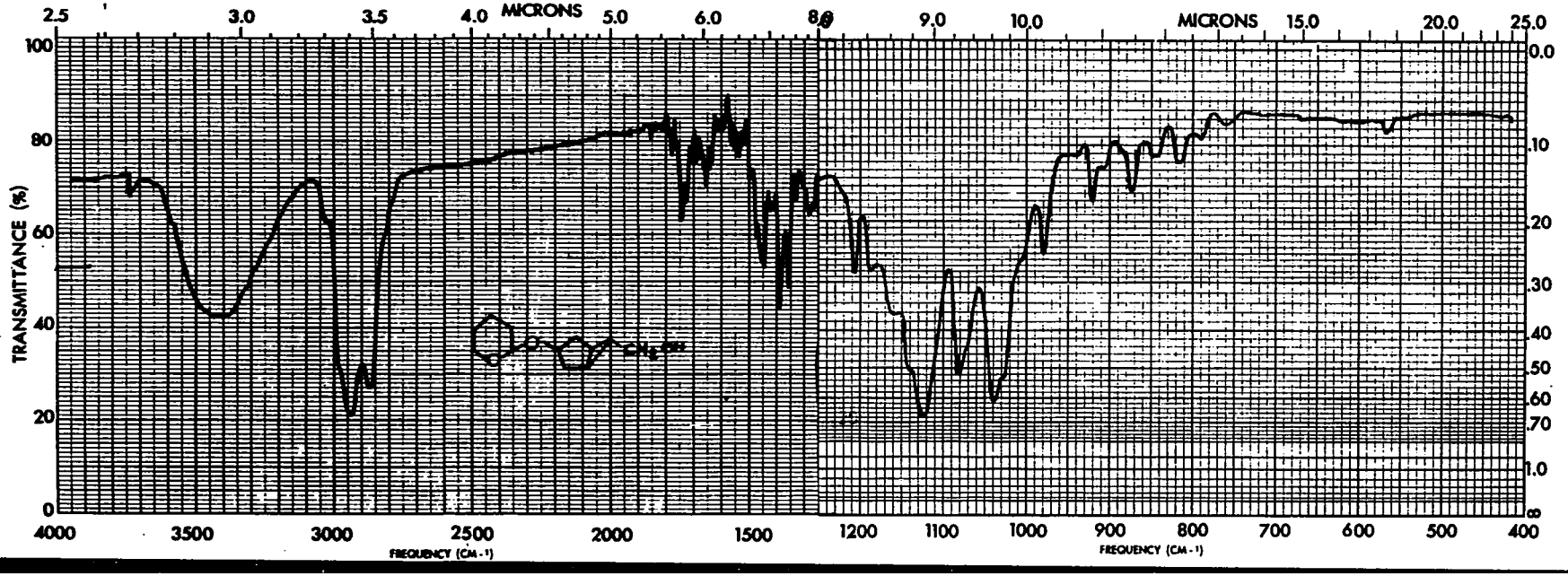
Spectrum No. 18 - 3-[(Tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]hexan-6-exo-carboxaldehyde. VI

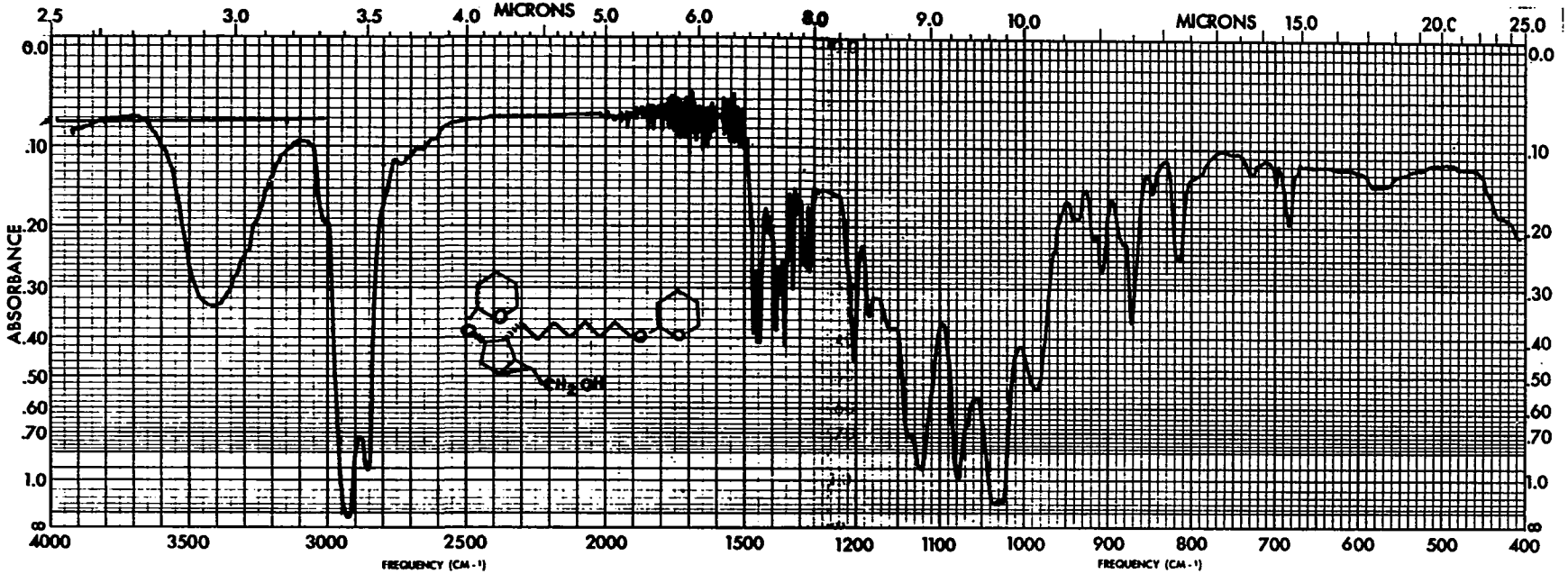




Spectrum No. 19 - 3α[(Tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]hexan-6-exo methanol. IVb

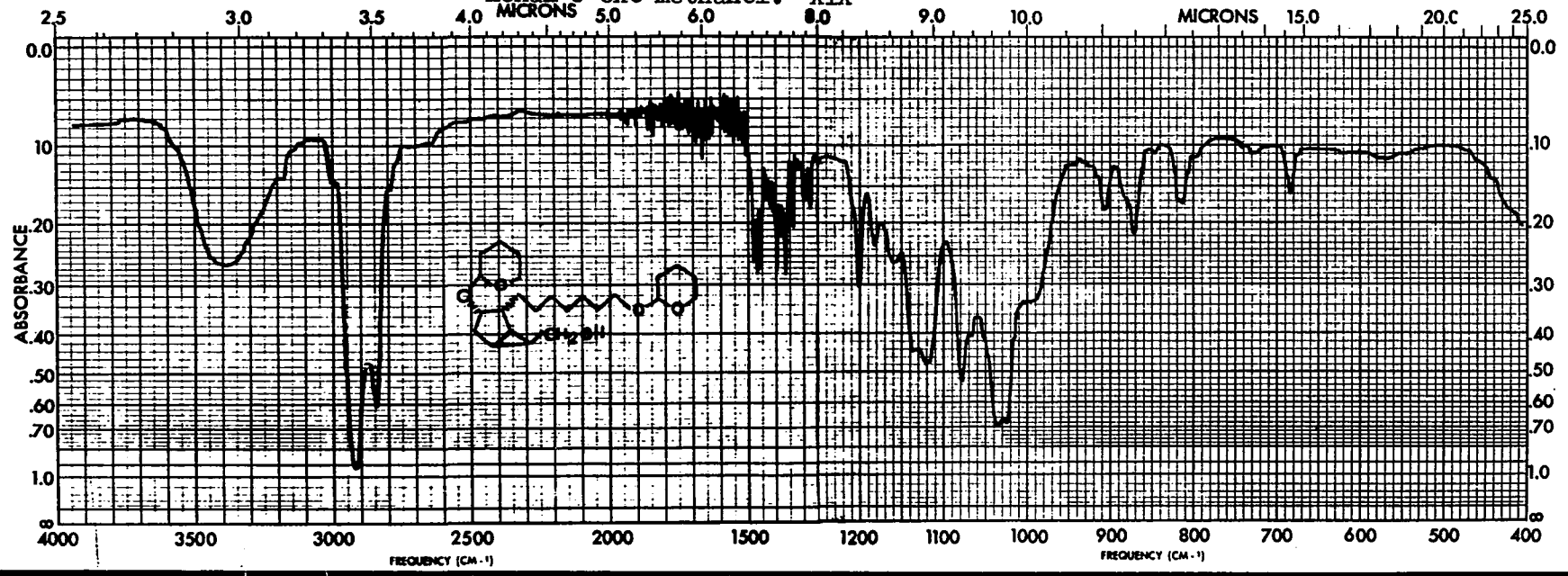
Spectrum No. 20 - 3β[(Tetrahydropyran-2-yl)oxy]bicyclo[3.1.0]hexan-6-exo methanol. IVa

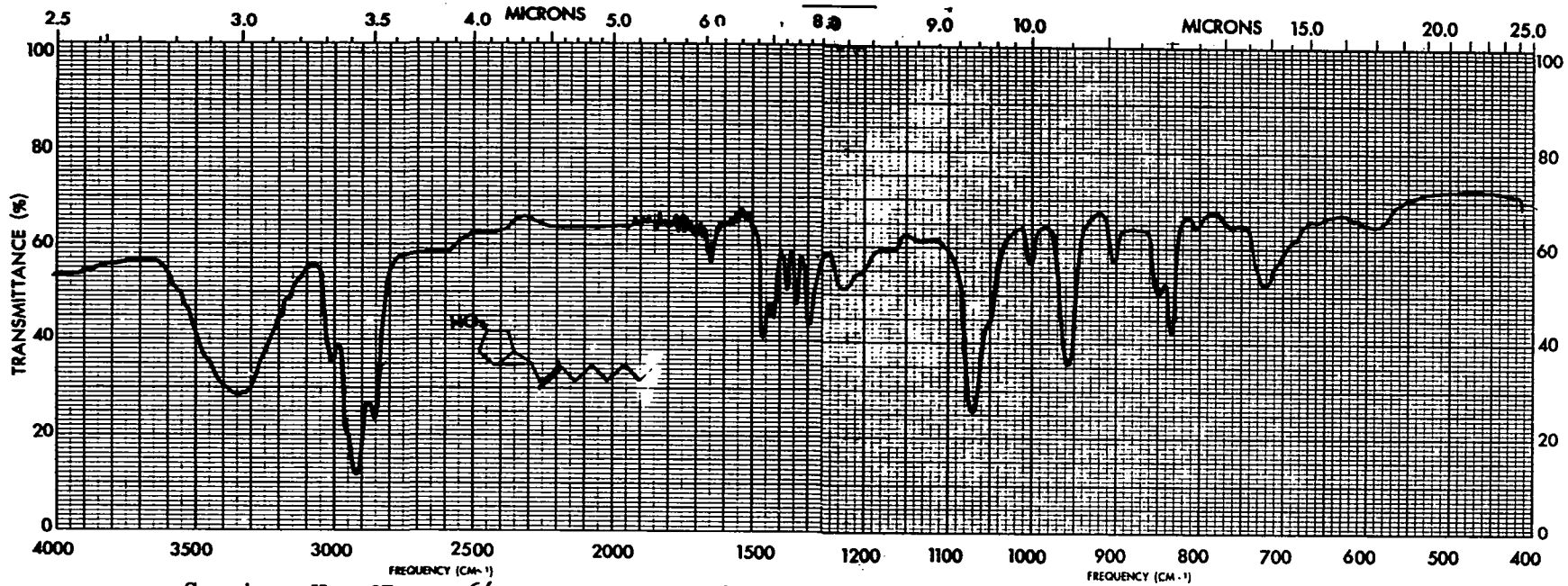




Spectrum No. 21 - 2(7-Tetrahydropyranyloxyheptyl)-3α-tetrahydropyranyloxy bicyclo[3.1.0] hexan-6-endo methanol. XIX

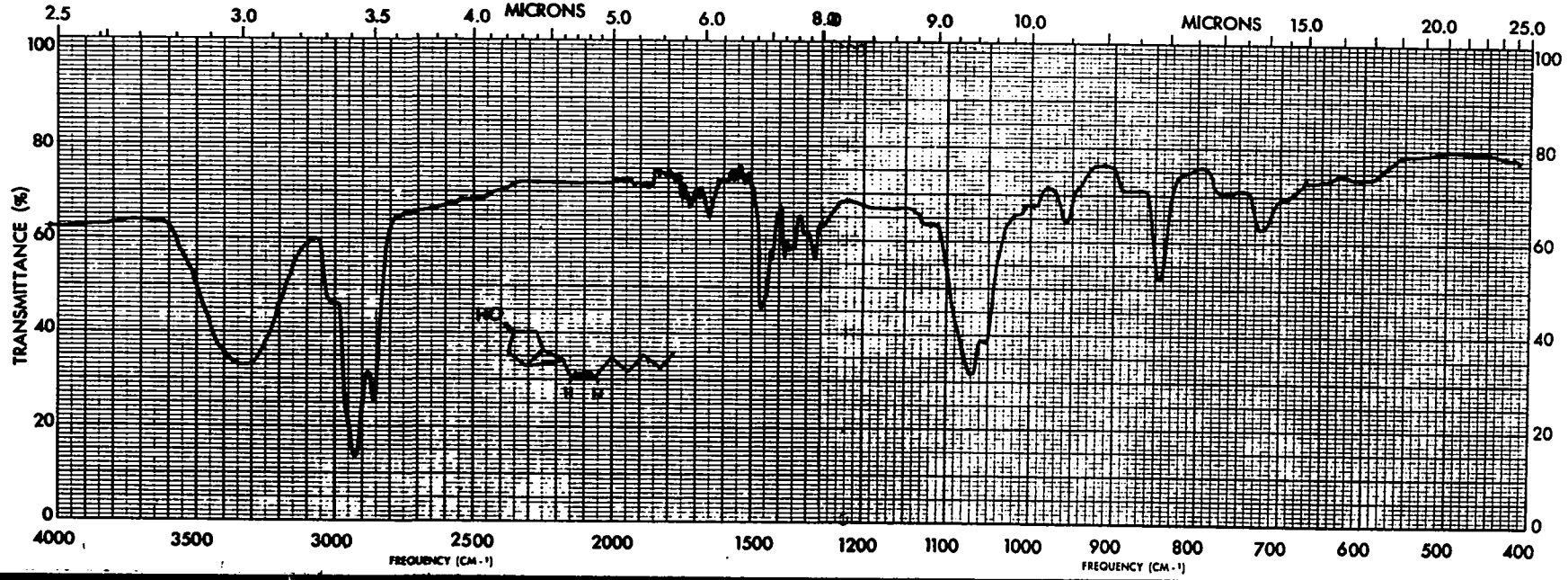
Spectrum No. 22 - 2(7-Tetrahydropyranyloxyheptyl)-3α-tetrahydropyranyloxy bicyclo[3.1.0] hexan-6-exo methanol. XIX

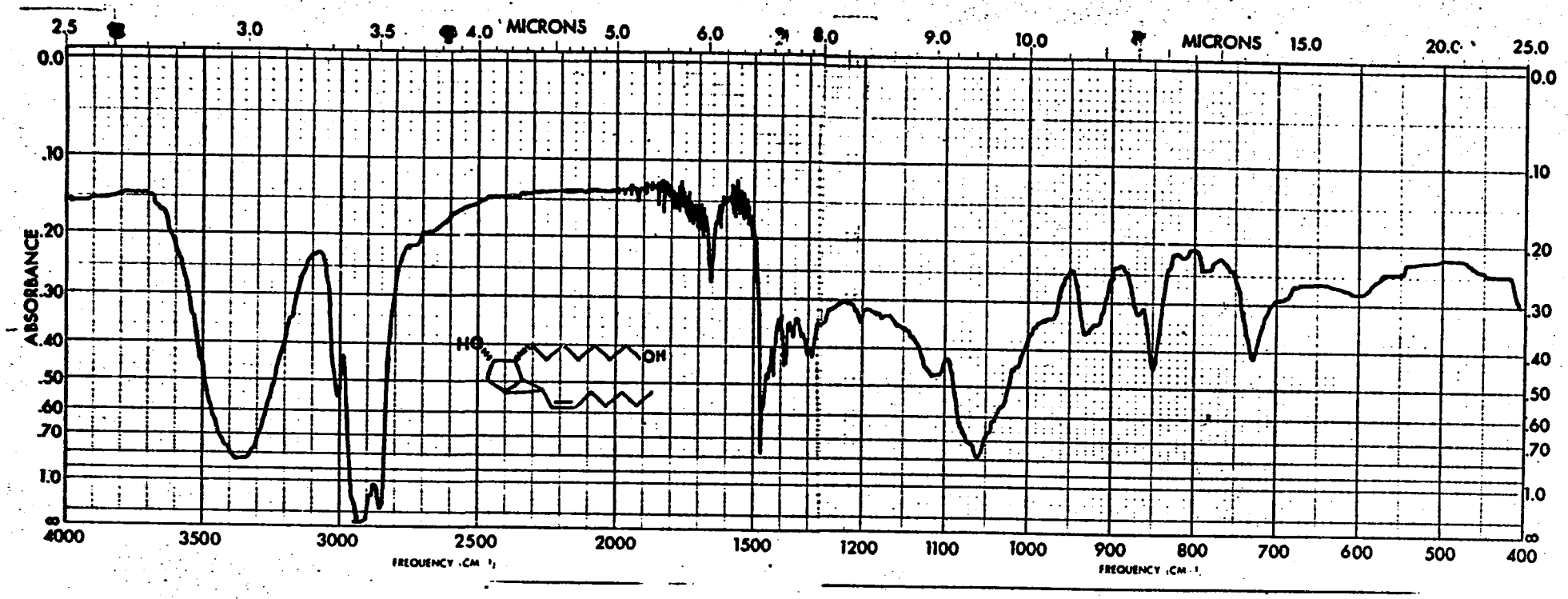




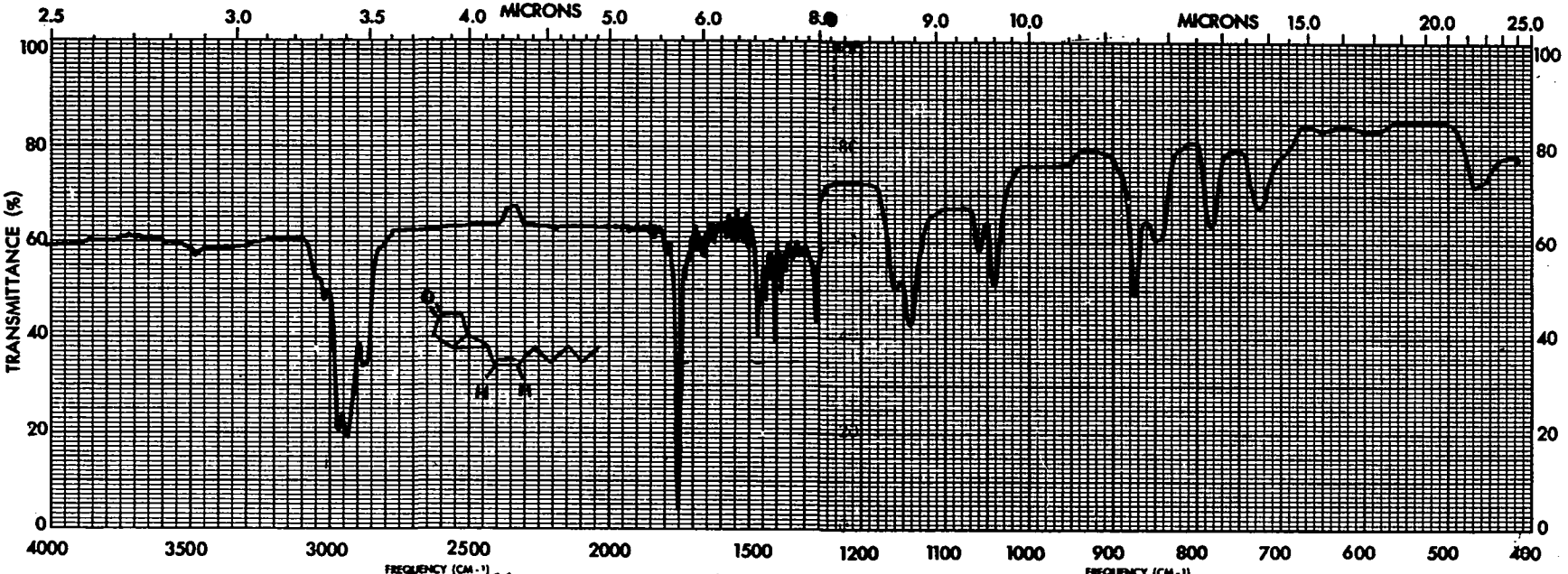
Spectrum No. 23 - 6(Trans-1-heptenyl)-bicyclo[3.1.0]-hexan-3α-ol. VIIIa

Spectrum No. 24 - 6(Cis-1-heptenyl)-bicyclo[3.1.0]-hexan-3α-ol. VIIIc



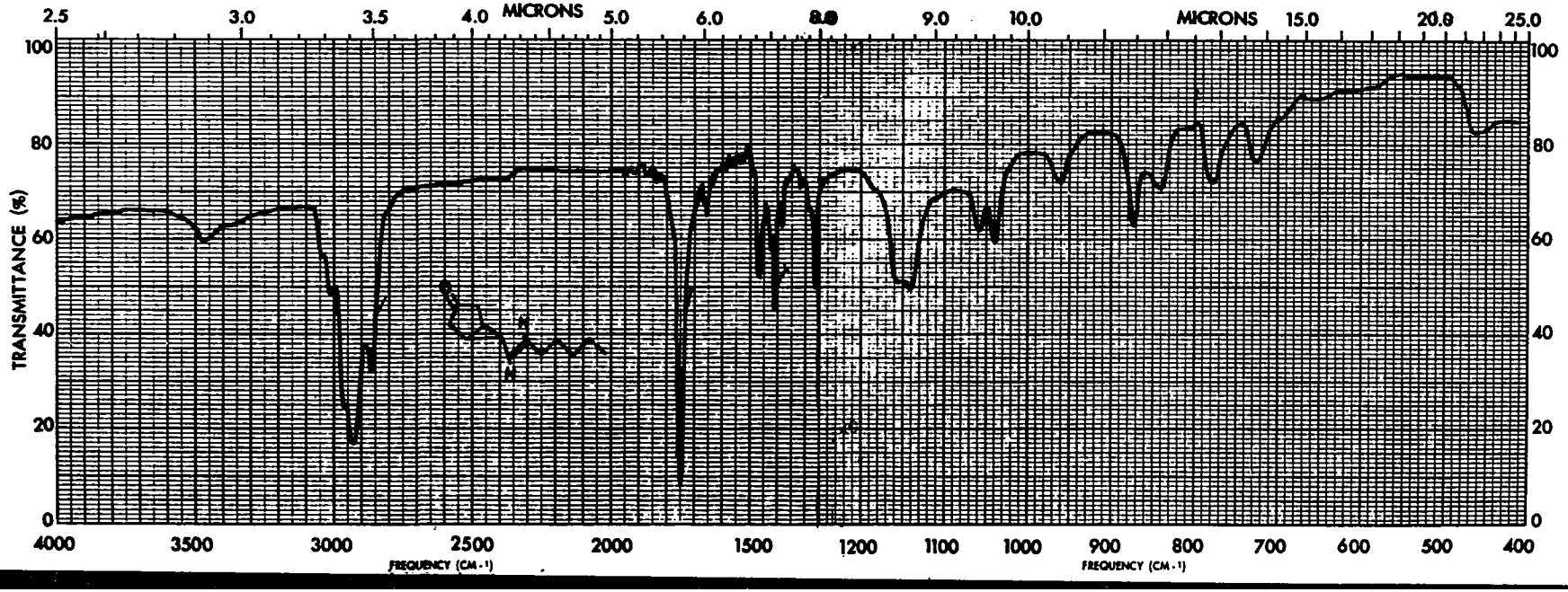


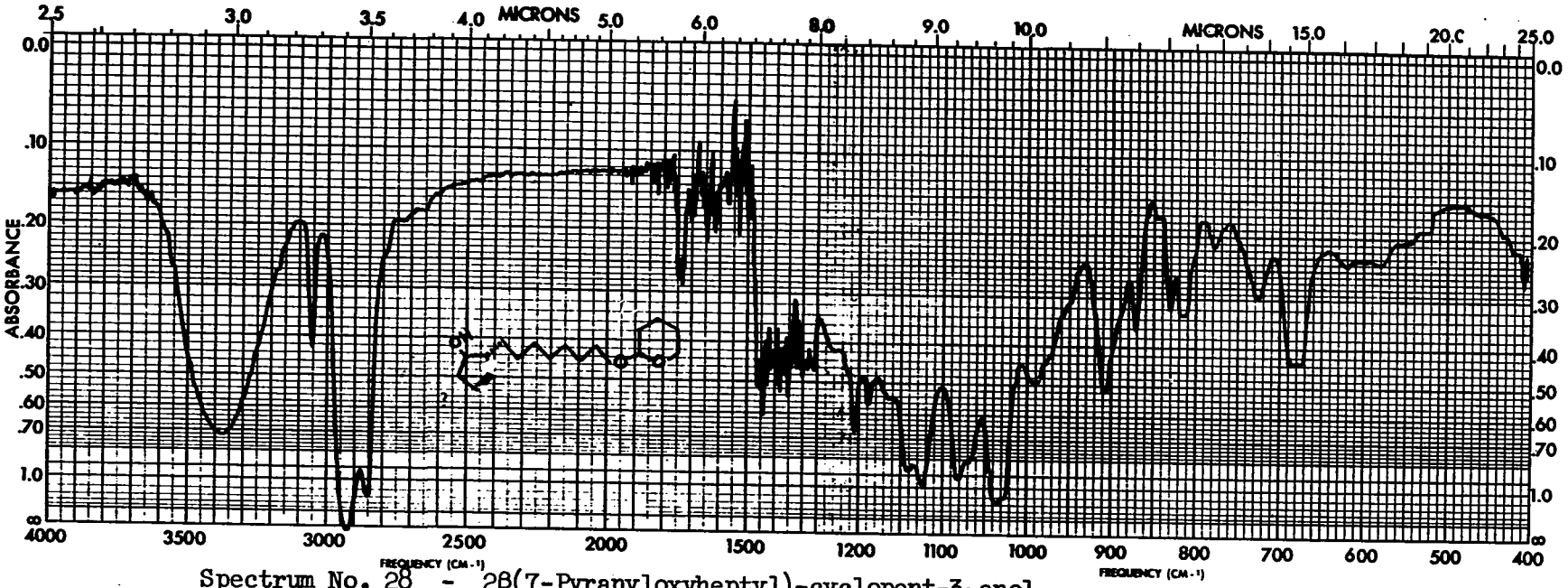
Spectrum No. 25 - 6(Cis-1-heptenyl)-3α-ol-bicyclo[3.1.0]hexane-2α(7-hydroxy)heptane. XXII



Spectrum No. 26 - 6(Cis-1-heptenyl)-bicyclo[3.1.0]hexan-3-one. IXb

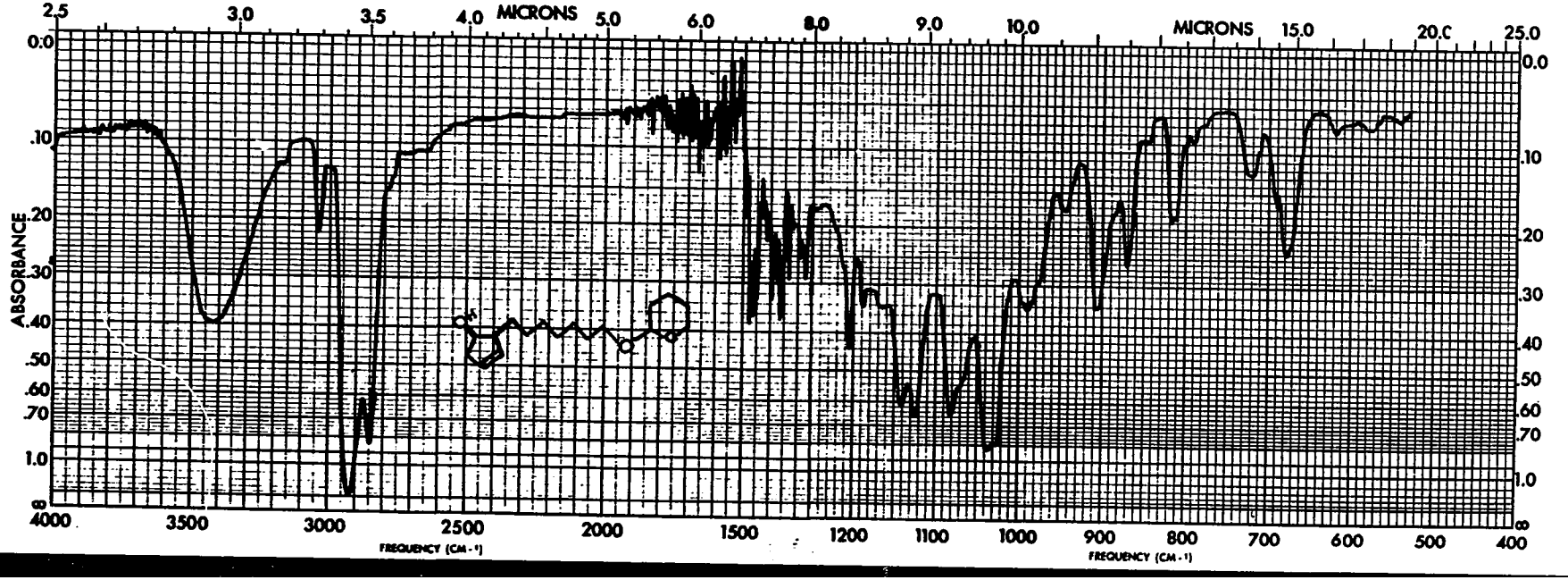
Spectrum No. 27 - 6(Trans-1-heptenyl)-bicyclo[3.1.0]hexan-3-one. IXa

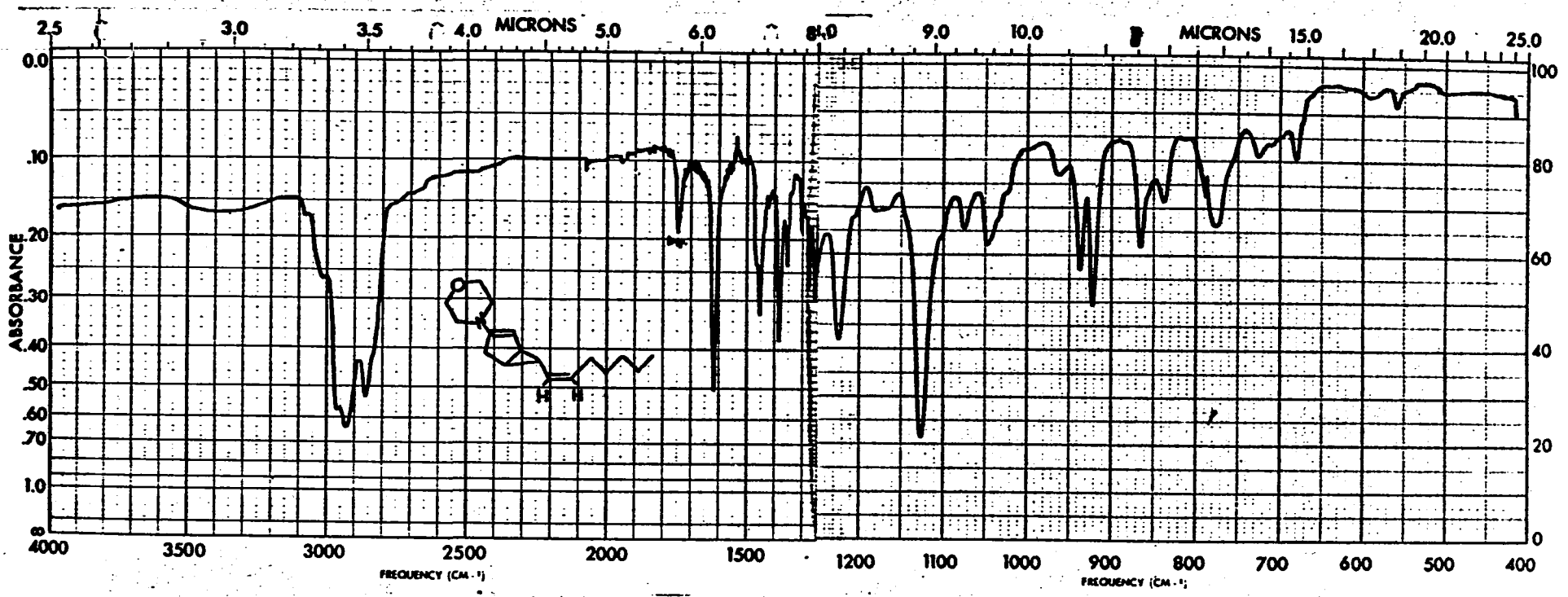




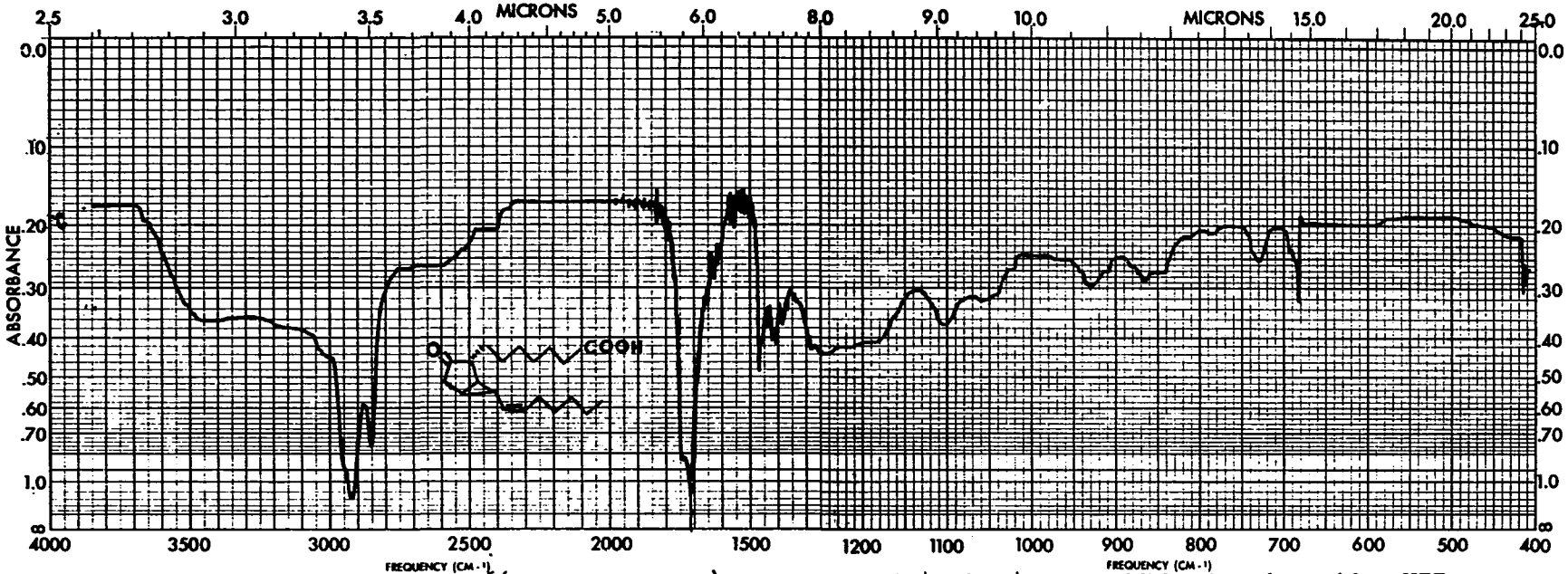
Spectrum No. 28 - 2β(7-Pyranyloxyheptyl)-cyclopent-3-enol

Spectrum No. 29 - 2α(7-Pyranyloxyheptyl)-cyclopent-3-enol. XVII



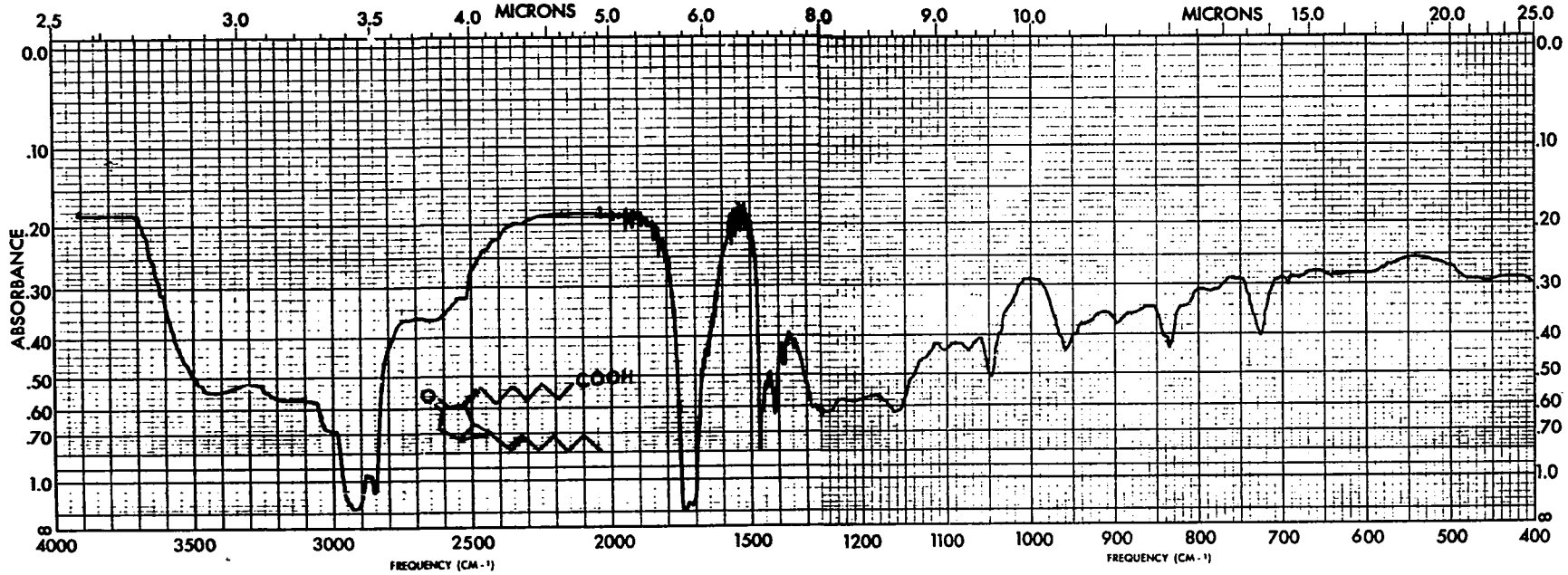


Spectrum No. 30 - Morpholinoenamine of ketone. IX



Spectrum No. 31 - 6(Cis-1-heptenyl)-3-oxo-bicyclo[3.1.0]hexane-2α-heptanoic acid. XII

Spectrum No. 32 - 6(Trans-1-heptenyl)-3-oxo-bicyclo[3.1.0]hexane-2α-heptanoic acid. XII



CONTRIBUTION TO KNOWLEDGE

The total synthesis of prostaglandin $F_1\alpha$ and prostaglandin E_1 has been accomplished using a novel opening of a bicyclo[3.1.0]-hexane system.

Oxidative formolysis (using hydrogen peroxide and formic acid) of 6(cis and trans 1-heptenyl)-2-one bicyclo[3.1.0]-hexane-2-heptanoic acid gave a mixture from which material corresponding to PGE_1 in a mixture with PGE_1 epimeric at the 15 position. The mixture was identified by its relative R_f value to natural PGE_1, its n.m.r. and mass spectra.

Oxidative formolysis (using hydrogen peroxide and formic acid) of 6(cis and trans 1-heptenyl)-3α-ol bicyclo[3.1.0]hexane-2-heptanoic acid gave a mixture from which material corresponding to $PGE_1\alpha$ was isolated. The compound was identified according to its relative R_f value to natural $PGF_1\alpha$, its i.r. and mass spectra, and similar physiological activities.

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