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Synthesis of Prostaglandin E_2 Methyl Ester & Related Compounds.

THE SYNTHESIS OF PROSTAGLANDIN E_2 METHYL ESTER

AND

RELATED COMPOUNDS

by

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A thesis submitted to the Faculty of Graduate Studies
and Research, McGill University, in partial fulfillment
of the requirements for the degree of Doctor of Philosophy.

Department of Chemistry
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March 1969

To my parents and Carma

ABSTRACT

The synthesis of methyl 11α,15-dihydroxy-9-oxo-prost-5, 13-dienoates (PGE_2 methyl esters), having the natural and unnatural configuration at C-15, are described. Methyl 15-hydroxy-9-oxo-prost-5,10,13-trienoate (PGA_2 methyl ester), was also obtained and is described. This synthesis is based on the PGE_1 and $F_{1\alpha}$ synthesis of Just and Simonovitch[17,18]. Two new acetylenic prostaglandins-- methyl 11α,15-dihydroxy-9-oxo-prost-5-yn-13-enoate and its 15-epimer -- obtained as intermediates in the PGE_2 methyl ester synthesis, are described.

ACKNOWLEDGEMENTS

I wish to express my deep gratitude to Dr. G. Just for helpful discussions and suggestions on the many problems encountered throughout the course of the synthesis. Much of the success of this work is due to his professional guidance. His personal interest and generous assistance throughout my years, but particularly in the last few months spent at McGill, is greatly appreciated.

I wish to thank Dr. T-H. Chan for his interest and helpful discussions on aspects of the synthesis. Also, I wish to thank my fellow students for providing a stimulating atmosphere in the laboratory. I am particularly grateful to Mr. H. Wong for preparation of the Lindlar catalyst used in the last step of the synthesis.

I wish to thank Canadian Industries Limited for their fellowship in 1966-67 and the Department of Chemistry, McGill University for financial assistance in the other years.

I wish to thank the Upjohn Co., Kalamazoo, Michigan for a sample of natural PGE_2, comparison samples of the intermediates, 2α and β alkylated bicyclic ketone X, used in the PGE_1 synthesis; and generous supply of exo-6-(1'-heptenyl)bicyclo[3.1.0]hexan-3-one (XXIV) used in this synthesis.

I wish to thank Messrs. C. Valentin and V. Yu for taking innumerable 60 MC n.m.r. spectra and Mr. N. Ness for taking the 100 MC n.m.r. spectra.

I wish to thank Mr. H. Zbinden for taking the mass spectra.

I wish to thank Dr. L. Wolfe of the Montreal Neurological Institute and Dr. J.R. Weeks of the Upjohn Company for carrying out the bioassays.

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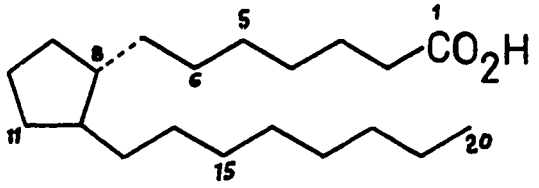
INTRODUCTION

In 1933 and 1934, Golblatt and von Euler[1], recognized that human seminal plasma contained some principle with striking pharmacodynamical actions that could be differentiated from the then known compounds. This active principle was not identified until the late fifties and early sixties when Bergstrom and co-workers[2] were able to isolate no less than thirteen different related compounds. These compounds were derivatives of a C_{20} fatty acid, called prostanoic acid (I) (which is not found in nature) and became known as the prostaglandins[3] (PG's).



I

There are six basic or primary compounds (Figure 1)* from which all the

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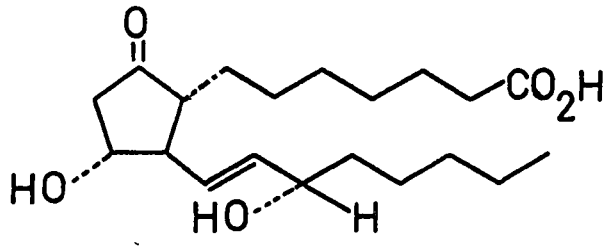
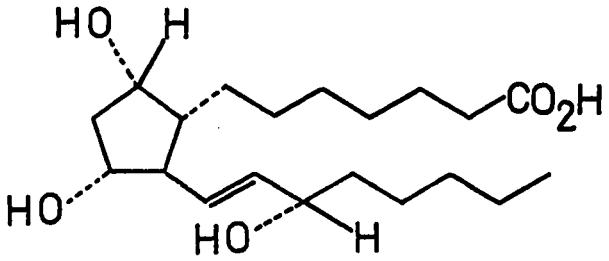
* The configuration of the natural PG around the ring is such that the C-8 and C-11 substituents are on the same side (α) and the C-12 substituent is on the opposite side (β). The 8-iso epimer has the C-8 substituent β. At C-15, the natural PG configuration is written as indicated in Figure I. In this thesis, the unnatural configuration at C-8 and C-15 will be referred to as "8-iso-" and "15-epi-PG" respectively. Otherwise the natural configuration will be implied.

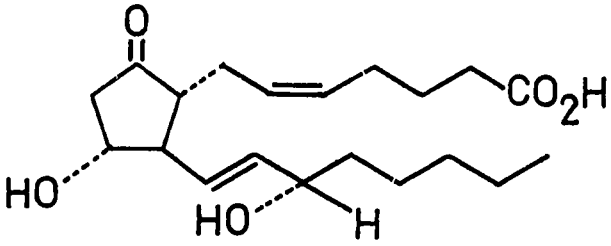
Figure I



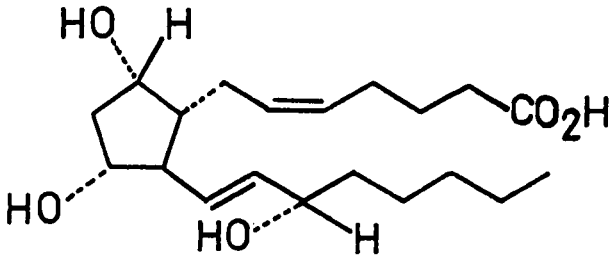
PGE_1



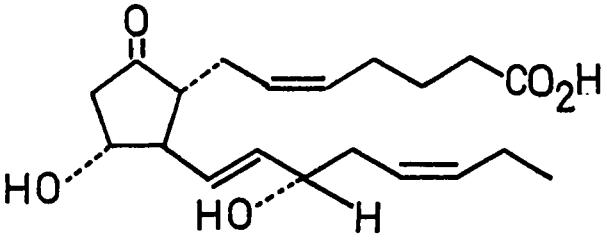
PGF_{1a}



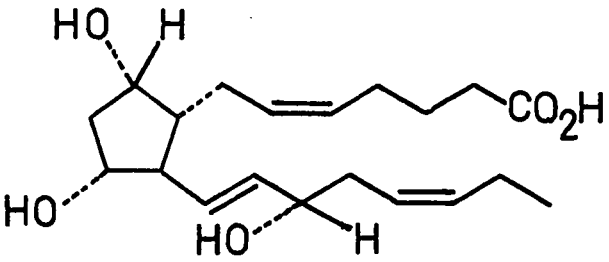
PGE_2



PGF_{2a}



PGE_3

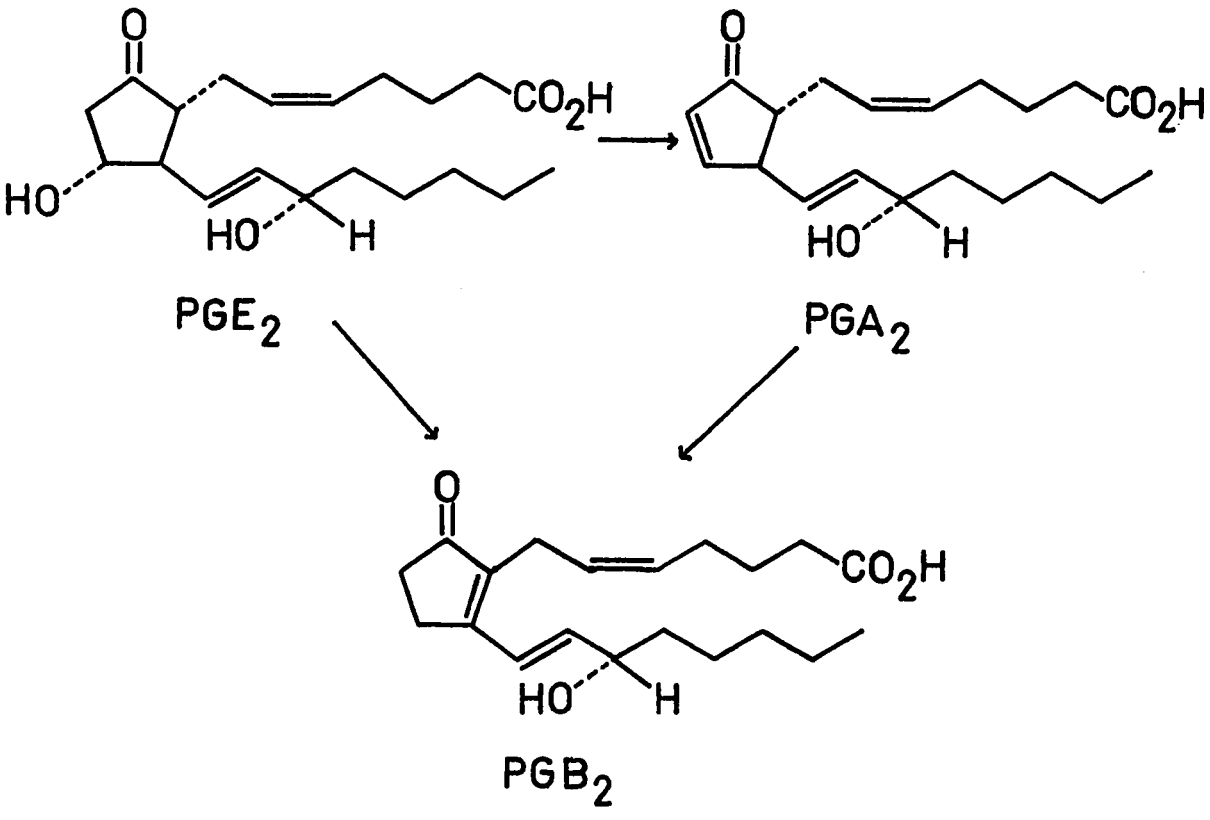


PGF_{3a}

others are derived: prostaglandin E's (PGE) have oxo and hydroxy substituents whereas the prostaglandin F's (PGF) have two hydroxy substitutents in the ring. The three E's (and three F's) differ only in their degree of unsaturations. The compounds in the E series have four asymmetric centers at C-8, C-11, C-12, C-15. In the F series, there is an additional asymmetric center at C-10.

In the E series the 11-hydroxy group is very sensitive to both acid and base. For example, PGE_2 will eliminate water to form the α,β unsaturated ketone, PGA_2, with acid or mild base (Scheme I). With further base treatment, this bond shifts into conjugation to form PGB_2. These compounds have characteristic ultraviolet absorption (PGA_2: λ_{max} 217 mμ, ϵ 10,700 and PGB_2: λ_{max} 278 mμ, ϵ 28,000) which gives a good test for the presence of prostaglandins $E_{(1-3)}$.

Scheme I



The structure of PGE_1 was elucidated from studies of the fragments obtained by oxidative ozonolysis of three derivatives, PGB_1, PGA_1 and PGE_1-237. The degradation products of these compounds were separated by gas chromatography and identified by mass spectrometry. The structure of the other compounds was elucidated in a similar manner. An account of this work has been given by Samuleson.[7] Using X-ray crystalographic techniques on the tris-p-bromobenzoate of $PGF_{1\beta}$, the relative configuration of the prostaglandins was postulated and their structure was confirmed by Abrahamsson and co-workers.[8a,b] The absolute configuration was recently established by Nugteren and co-workers[83] by determination of the optical rotation of 2-hydroxyheptanoic acid derived from oxidative ozonolysis of PGE_1 methyl ester.

Prostaglandins have pronounced physiological and pharmacological activity which can be classified into four major areas:[4]

A. Smooth Muscle Stimulation.

Studies on the PG stimulated contractions of the human myometrium (muscular wall of the uterus) and the relatively large concentration of PG's in seminal fluid have linked them with the reproductive process, particularly sperm transport into the fallopian tubes. Other smooth-muscle organs which are stimulated by PG's are the gastro intestinal tract, respiratory tract, and reproductive tract.

B. Cardiovascular Responses.

Intravenous injection of PG's causes lowering of blood pressure and increased heart rate. However, marked quantitative and qualitative differences occur between species as well as between various parts of the cardiovascular system.

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C. Nervous System.

Extracts with prostaglandin-like behaviour have been prepared from the central nervous system of various animals. Stimulation of peripheral nerves increased the release of these substances. Such release in the criterion for a neurohumoral transmitter substance and these results implicated the PG's in such a role.

D. Metabolic Effects.

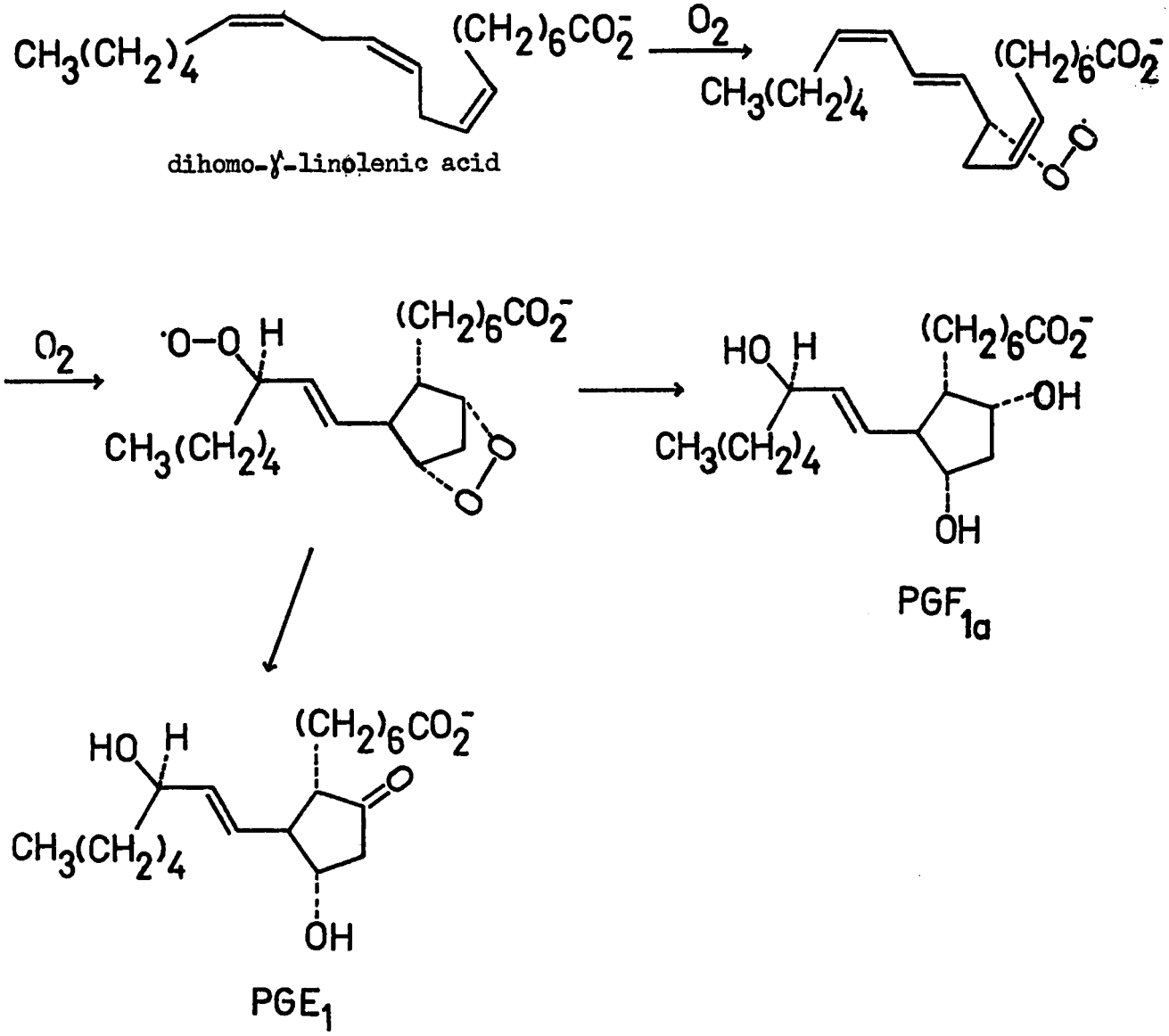
PG's inhibit lipolysis (fat breakdown) induced by catecholamine (in vivo) or adrenaline and noradrenaline (in vitro). Free fatty acid (FFA) mobilization was found to increase with the presence of PG's. It has been shown that PGE_1 inhibits the cyclic adenosine 5-phosphate (AMP) accumulation induced by epinephrine. Cyclic-AMP is thought to be an intermediate in activation of the hormone-sensitive lipase of adipose tissue which leads to mobilization of FFA.

Prostaglandins seem to have a wide distribution in the human as well as other animal bodies.[5] They have been detected in seminal plasma, menstrual fluid, lungs, iris, thymus, pancreas, brain, spinal cord and kidney, but in most organs the concentration is very small. The largest number of individual prostaglandins occur in human seminal plasma.

Tritium labelling experiments have shown that all prostaglandins are metabolized in the body relatively fast and by apparently similar mechanisms. The prostaglandins in the E series are metabolized by reduction of the Δ^{13} double bond and oxidation of the secondary alcohol group at C-15.[6] $PGF_{1\alpha}$, on the other hand, was metabolized to a considerable degree to 2,3-dinor-$PGF_{1\alpha}$,[6] i.e. by β-oxidation.

Using ^{14}C-labelled precursors, it has been demonstrated[9] that prostaglandins are produced enzymatically in vesicular grands and lung tissue by autoxidation of dihomo-γ-linolenic and arachidonic acids. The biosythesis involved two molecules of oxygen as indicated in the biosynthesis of PGE_1 and $PGF_{1\alpha}$ in Scheme II.

Scheme II



Recently, this autoxidation was found to take place non-enzymatically in very low yield.[10]

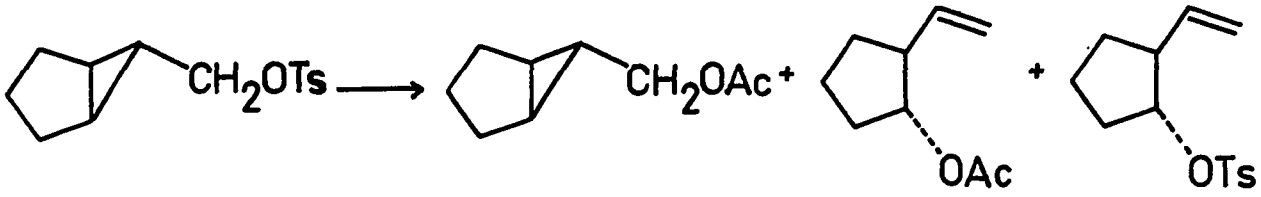
The biochemical importance and potential medical usefulness of prostaglandins has stimulated much interest in their total synthesis. The main features or problems involved in the synthesis of the primary prostaglandins are: a) the functionalities and stereochemistry of the substituents on the ring, b) the various points of unsaturation differing in stereochemistry about the double bond (this is not a problem in the synthesis PGE_1, or its derivatives), c) the allylic 15-hydroxy group, and d) the sensitive 11-hydroxy group in the E series.

Some less complicated derivatives and structurally related prostaglandins were the first to be synthesized. J.F. Bagli et al[13] synthesized 9β, 15ϵ-dihydroxyprost-13-enoic acid in thirteen steps starting the ethyl 2-cyclopentanone carboxylate. A short time later, an elegant synthesis of dihydro-PGE_1 ethyl ester, a natural prostaglandin, and the corresponding dihydro-$PGF_{1\beta}$ methyl ester was published.[14] E. Hardegger et al.[15] subsequently published synthesis of PGB_1 and PGE_1-237 starting from an intermediate described in the synthesis of the prostanoic acid derivative.[13] Finally, J. Fried et al.[16] have reported the synthesis of (±)-7-oxaporstaglandin $F_{1\alpha}$, a novel prostaglandin containing an ether linkage at the 7-position. Except for the final introduction of the 15-hydroxy group, this synthesis was stereospecific.

The first synthesis of the primary prostaglandins, PGE_1 and PGF_1 , was achieved by G. Just and Ch. Simonovitch[17,18](Scheme IV). The critical step in this synthesis was the solvolytic opening of a cyclopropyl ring which introduced the 11 ,15-hydroxy groups and the trans Δ^{13} double bond in one step. This approach was based on a solvolysis of bicyclo[3.1.0]hexane-6-methyl tosylate (II) in potassium acetate buffered acetic acid which gave a reaction mixture containing 75%

ring opened product[19](Scheme III).

Scheme III



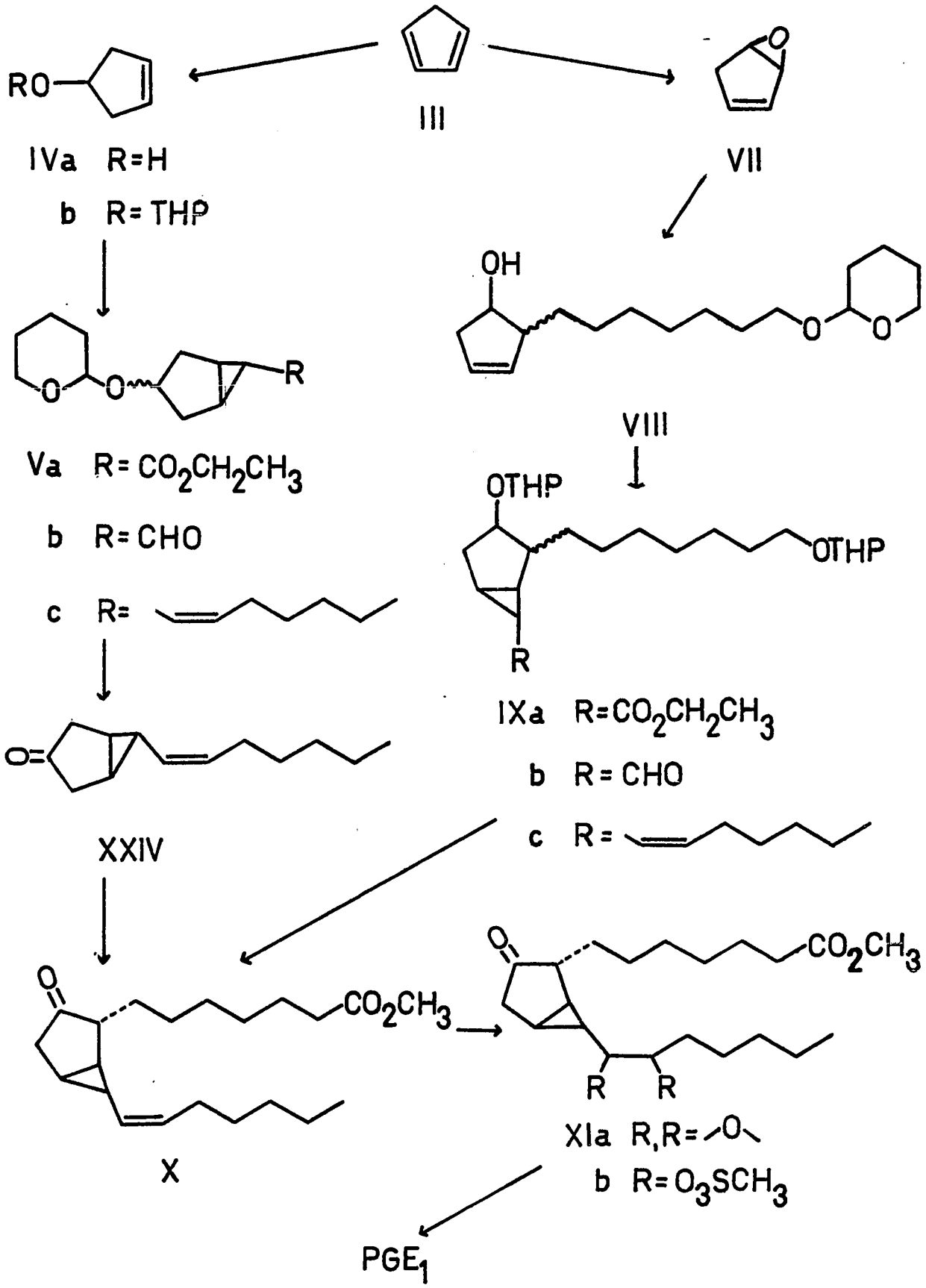
II 25% 25% 50%

The endo isomers, solvolyzed under the same conditions, gave a much more complicated mixture of products and a much smaller percentage (19.5%) of ring opening.

The aim in the PGE_1 synthesis was to make 6-exo-(1'-heptenyl)-2-(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (X), and to carry out a ring opening solvolysis similar to that reported by Wiberg and Ashe.[19]

The bicyclic ketone X was synthesized by two routes[17,18]. In the first sequence, cyclopentadiene was converted to cyclopent-3-en-1-ol (IVa)[23] which was then treated with dihydropyran and a few drops of phosphorus oxychloride[86] to form the tetrahydropyranyl (THP) ether (IVb). Addition of ethyl diazoacetate[26] to IVb gave a mixture of exo and endo bicyclic ethyl esters which could be epimerized to the exo isomer Va with methanolic sodium methoxide. Reduction of Xa with lithium aluminum hydride followed by oxidation with Jones reagent[28] gave the exo aldehyde Vb. This compound was then subjected to a Wittig reaction[24] with hexyltriphenyl phosphomium bromide from which the cis olefin Vc was obtained in good yield. Cleavage of the tetrahydropyranyl ether in mild acid followed by oxidation with Jones reagent gave the bicyclic ketone

Scheme IV


III
IVa R=H
b R=THP
VII
Va R=CO2CH2CH3
b R=CHO
c R=
VIII
IXa R=CO2CH2CH3
b R=CHO
c R=
XXIV
X
XIa R,R=O
b R=O3SCH3
PGE1

XXIV. Alkylation of XXIV with methyl ω-bromo(or iodo)heptanoate gave X in 25-35% yield[17,18,21]. In the alkylation there were two isomers formed: the α isomer (trans configuration) X was the major product of kinetic control. However, on equilibration, the β isomer (cis configuration) was predominant by a ratio of 35:65[21].

The second sequence leading to X avoided the alkylation steps. Cyclopentadiene (III) was epoxidized with peracetic acid[27] to give 1,2-epoxycyclopentene (VII). Grignard reagent displacement on the epoxide VII using 7-pyranyloxyheptyl magnesium bromide gave VIII of undefined stereochemistry in 30% yield. Pyranylation of VIII followed by addition of ethyl diazoacetate and epimerization, as in the first sequence, gave the bicyclic ester IXa, also of unknown stereochemistry. The final steps to X involved reduction of IXa with lithium aluminum hydride followed by oxidation to the aldehyde IXb. This was again reacted with hexyltriphenyl phosphonium bromide to give IXc. Cleavage of the tetrahydropyranyl ether with mild acid, oxidation with excess Jones reagent, and esterification with diazomethane gave the keto ester X.

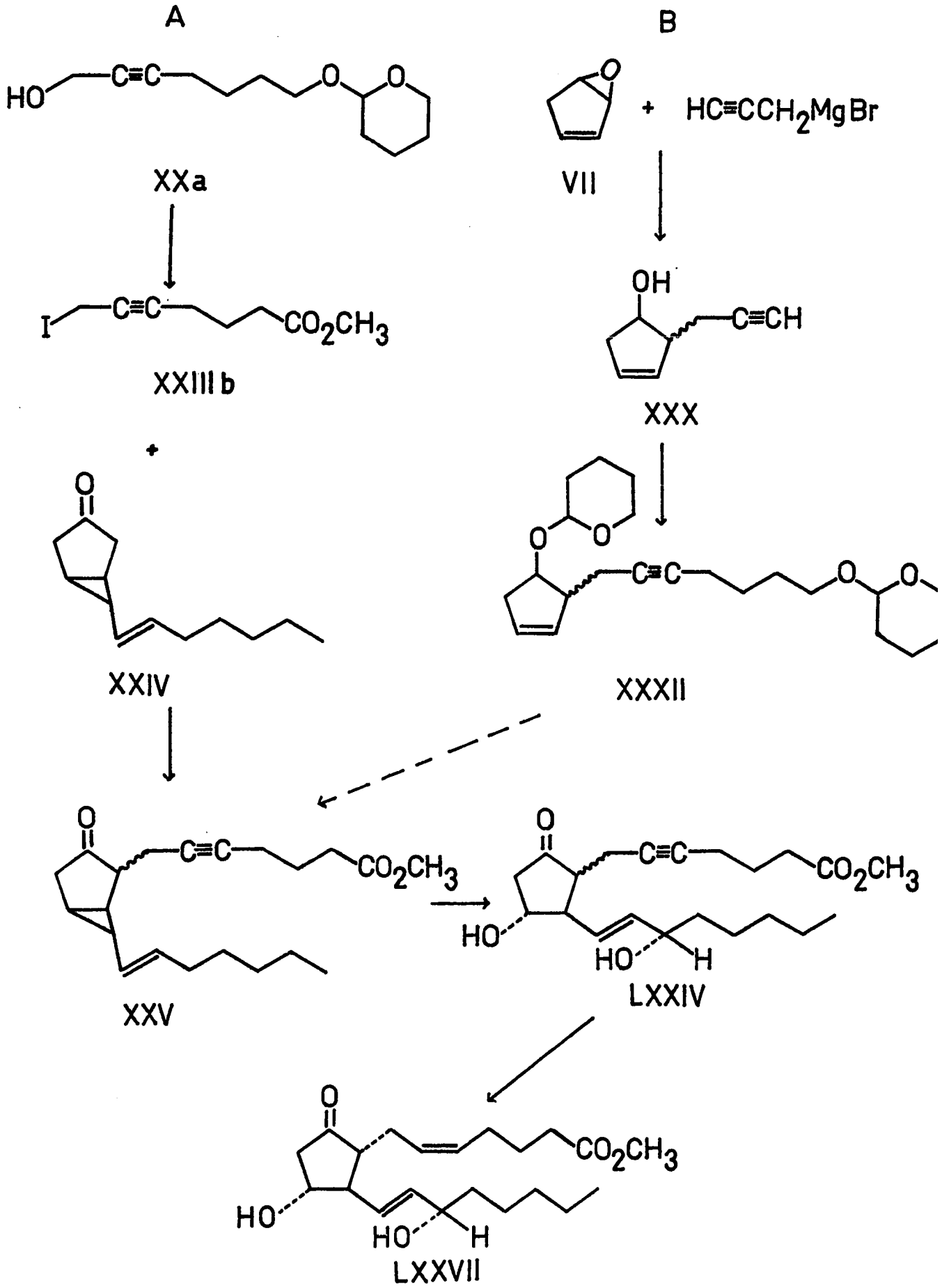
The solvolysis was achieved[17,18] in buffered formic acid and hydrogen peroxide but the yields of products obtained were low. The results were challenged by R.G. Holden et al.[20]. However, the reaction has been repeated and the conditions improved to that $PGF_{1\alpha}$ and $PGF_{1\beta}$ were isolated in 2-8% yield as crystalline products[21]. Best results were obtained when the solvolysis was carried out on the isolated epoxide XIa in trifluoroacetic or formic acids. When the corresponding

dimesylate XIb was solvolyzed in acetone-water 2:1 at 25°C, crystalline dl-PGE_1 methyl ester and the C-15 epimer were each isolated in 5-10% yields[22].

Using a totally different approach, E.J. Corey et al[29] have synthesized pure dl PGE_1,-$F_{1\alpha}$,-$F_{1\beta}$,-A_1 and -B_1. In a second synthesis[30], a route to the C-11 epimers of the natural E_1 and F_1 hormones as well as their corresponding C-15 epimers was provided. Both sequences were designed to give a key intermediate which was subsequently converted to PGE_1 and its epimers in eight steps.

The approach to PGE_2 methyl ester (Scheme VA and B) described in this thesis was based on the previously discussed PGE_1 synthesis of Just and Simonovitch[17,18]. Two routes leading to the intermediate XXV were explored. In Chapter I, the synthesis of the acetylenic side chain XXIIIb and the subsequent alkylation of the previously synthesized[17,18] bicyclic ketone XXIV (Scheme VA) will be discussed. Chapter II deals with attempts to synthesize XXV by another route (Scheme VB). In Chapter III various attempts to rearrange the cyclopropyl carbinyl system will be described and the transformation of XXV to PGE_2 methyl ester will be discussed.

Scheme V


A
B
HO
C≡C
O
O
XXa
VII
+ HC≡CCH2MgBr
OH
C≡CH
XXX
I
C≡C
CO2CH3
XXIII b
+
XXIV
XXXII
XXV
LXXIV
LXXVII

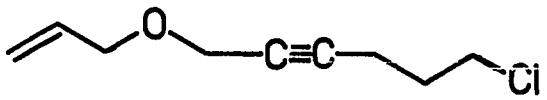
CHAPTER I

Synthesis of Methyl 7-iodo-5-heptynoate

The first problem in the synthesis of PGE_2 methyl ester was the construction of the unsaturated (C_1-C_7) side chain having a Δ^5-cis olefinic bond or an acetylenic bond at the 5 position which could later be reduced to the cis olefin, such as methyl 7-iodo-5-heptynoate (XXIIIb).

The synthesis of this propargylic iodide XXIIIb was based on the selective C-alkylation of propargylic alcohols with alkyl halides in liquid ammonia using lithium amide as the base[31]. D'Engenieres and co-workers[31] had found that when sodium amide was used as base, both O- and C-alkylation took place. If, however, lithium amide was used as base, the C-alkylated alcohol was the only compound isolated.

On repeating this reaction with propargyl alcohol (XIIa) and 1-bromo-3-chloropropane using lithium amide as the base, the chloride XIIIa was obtained as the major product (Scheme VI). A minor product (20%) which was not fully characterized was also separated[25]. From the n.m.r. (δ 4.03 ppm, 2H, t, J = 2.0 cps; δ 3.62 ppm, 2H, t, J = 6.0 cps; δ 6.5 - 5.5 ppm, 3H, multiplet) and infrared spectra (ν_{max} 3070, 2230, 1650, 1085 cm^{-1}), and the carbon - hydrogen elemental analysis, XXVI is



XXVI

the probable structure of the by-product.

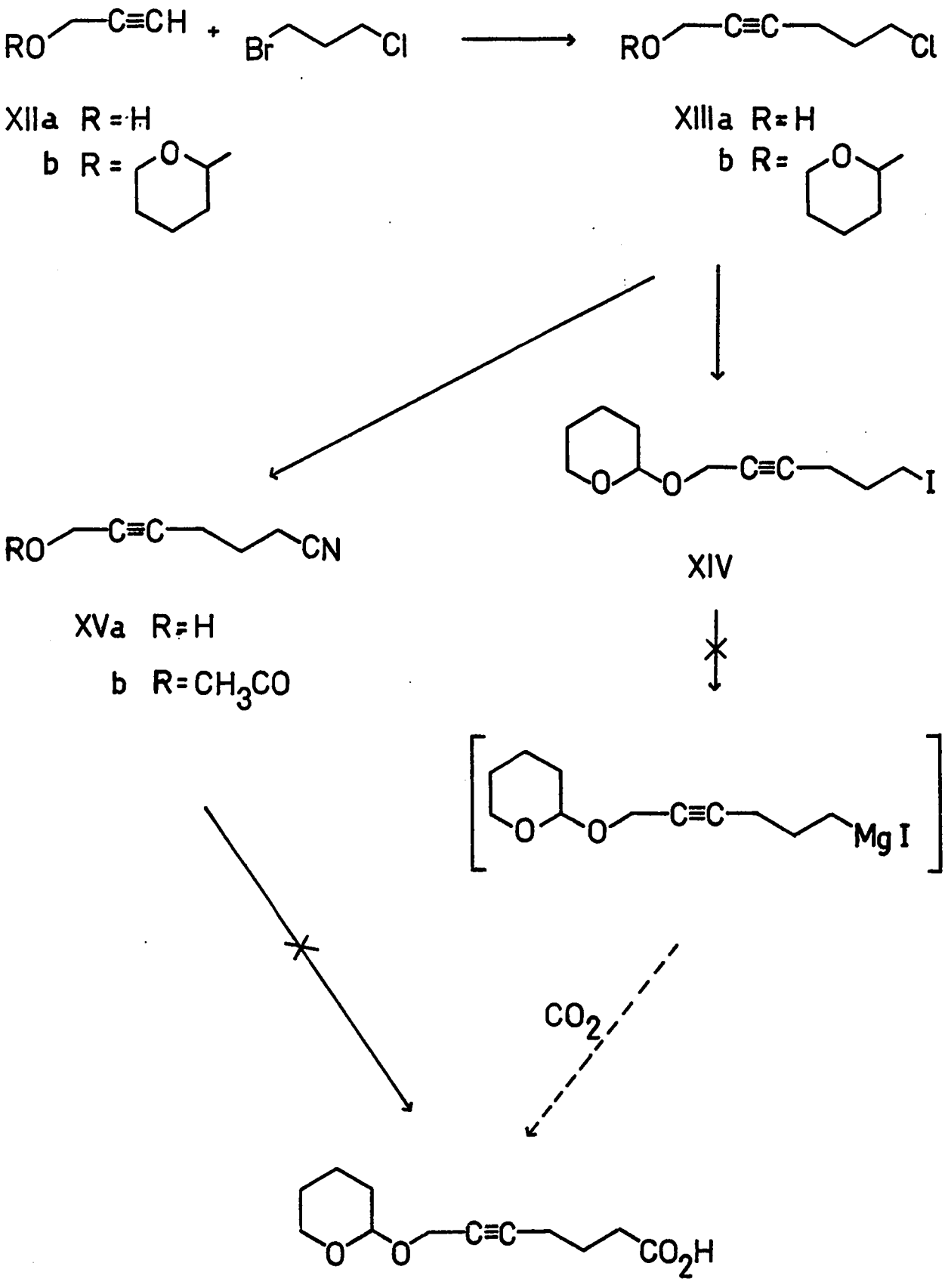
Alkylation of 3-tetrahydropyranyloxypropyne (XIIb) with 3-bromo-1-chloropropane gave only the monoalkylated chloride XIIIb in good yield.

The displacement of the chloride of XIIIb by iodide was achieved in good yield using sodium iodide in refluxing acetone. The conversion of the resulting iodide XIV to 7-hydroxy-5-heptynoic acid (XVI) via its Grignard reagent and carbonation of the latter, was not successful. The Grignard reagent could not be generated in either diethyl ether or tetrahydrofuran (THF). In all cases the magnesium powder used was first washed with dilute hydrochloric acid to remove surface oxides, then, after drying, activated with iodine.

An alternative method for preparing the acid XVI from the chloride XIIIa involved conversion of XIIIa to the nitrile, followed by hydrolysis. The chloride XIIIa was converted to the cyano acetylene XVa with sodium cyanide in dimethyl sulfoxide. Since XVa was difficult to separate from traces of dimethyl sulfoxide, it was converted to its acetate XVb by means of pyridine and acetic anhydride and purified by column chromatography on silica gel.

Acid hydrolysis of the nitrile acetate XVb gave a mixture of neutral compounds. The acetylenic bond probably had been hydrated[36] since the $\nu(C\equiv C)$ band in the infrared spectrum had disappeared. Multiplets at δ 6.2-4.9 ppm in the n.m.r. spectrum, characteristic of olefinic proton resonance, indicated that the compound had reacted in an undesired manner under these conditions. Basic hydrolysis of the nitrile gave predominately an acid fraction. However it was a mixture from which the desired acid XVI could not be isolated.

Scheme VI


RO
C≡CH
+
Br
Cl
RO
C≡C
Cl
XIIa R=H
b R=
O
XIIIa R=H
b R=
O
O
O
C≡C
I
XIV
RO
C≡C
CN
XVa R=H
b R=CH3CO
O
O
C≡C
Mg I
CO2
O
O
C≡C
CO2H

Since it was found difficult to add a one carbon unit to the chlorohexyne XIII, an attempt was made to produce the C_7 chain by reaction of propargyl alcohol with a C_4 unit, 4-tetrahydropyranyloxybutyl bromide (XIXb).

4-Tetrahydropyranyloxybutyl bromide (XIXb) was synthesized in four steps (Scheme VII) starting with γ-butyrolactone (VII). Treatment of the lactone with saturated aqueous hydrogen bromide at reflux for 15 hours gave 4-bromo butyric acid (XVIIIa)[34]. This was esterified with diazomethane[35], and the ester was reduced with excess lithium aluminum hydride in diethyl ether at -50°C to give 4-bromo-butanol (XIXa). Finally, treatment of the bromo alcohol XIXa with dihydropyran and a trace of phosphorus oxychloride[86], gave XIXb. Yields of better than 90% were realized for each step in this sequence.

Reaction of XIXb with propargyl alcohol by the previously described method of D'Engenieres[31] gave 7-tetrahydropyranyloxyhept-2-yn-1-ol (XXa) in 50-60% yield. Only moderate yields were realized because of the formation of the two by-products XXb (2.5%) and XXc (25%) which resulted from O-alkylation of propargyl alcohol and XXa, respectively.

The iodo-ester XVIII was obtained from XXa by the following sequence. The hydroxy groups of XXa were mesylated by first forming the lithium alcoholate with butyl lithium followed by slow addition of mesyl chloride in diethyl ether at 0° under nitrogen. 7-Tetrahydropyranyloxy-2-heptynyl mesylate XXIa was then treated with sodium iodide in dry acetone for 1.5 hours[37] to give the corresponding iodide XXIc. The bromide XXIb was similarly prepared by refluxing the mesylate with anhydrous lithium bromide in acetone for 24 hours[38]. Cleavage of the

tetrapyranyl ether with dilute methanolic hydrochloric acid gave 7-iodohept-5-yn-ol (XXId) which was oxidized with excess Jones reagent at 0° to the carboxylic acid XXIIIa. Finally, esterification of XXIIIa with diazomethane gave methyl 7-iodo-5-heptynoate (XXIIIb) in 20% overall yield starting from XXa.

Alkylation of Exo-6-(1'-heptenyl)-bicyclo[3.1.0]hexan-3-one (XXIV)

In the PGE_1 synthesis[18], one of the most difficult steps had been the alkylation of 6-(1'-heptenyl)-bicyclo[3.1.0]hexan-3-one (XXIV) with methyl 7-iodo-heptanoate. In this synthesis, the leaving groups of the alkylating agent was propargylic and therefore more reactive than its saturated counterpart. Better yields of the alkylated product were therefore anticipated. This expectation was not realized.

It was found that the reaction conditions were extremely critical: the solvent (THF) had to be completely anhydrous and the reaction had to be done in a dry nitrogen atmosphere; there had to be a large excess of alkylating agent present compared to the ketone, otherwise (paradoxically) dialkylation predominated; the addition of freshly prepared potassium t-butoxide* dissolved in anhydrous THF had to be done slowly so that the temperature was maintained at 0-5°. Best results in the alkylation reaction in the PGE_1 synthesis had been obtained when potassium t-butoxide dissolved in dimethoxyethane or THF was used as the base and it was added to a mixture of the ketone and alkylating agent[18,21]. Therefore no variations with respect to base were attempted.

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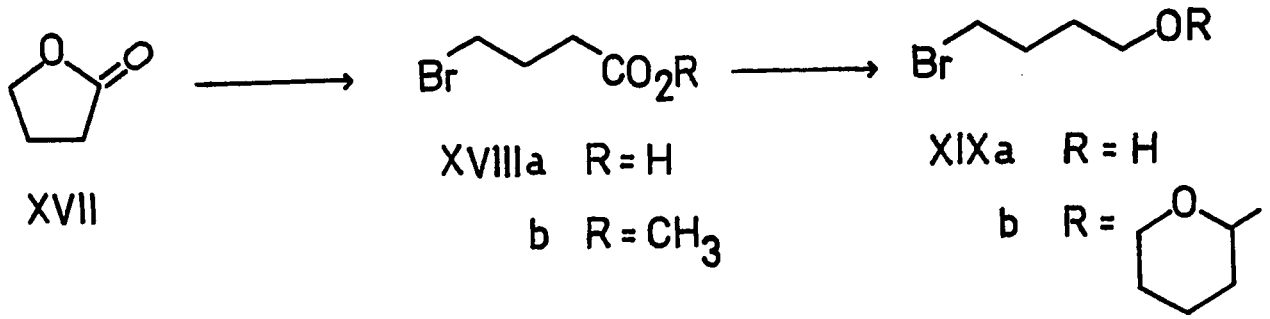
* Commercial potassium t-butoxide was found to be unsatisfactory.

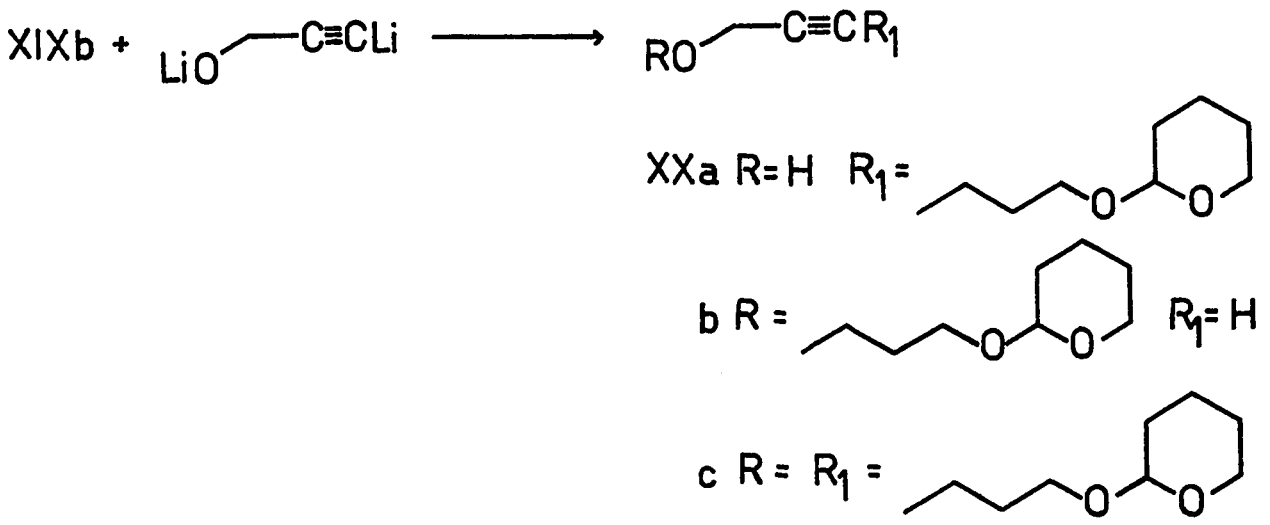
In the first alkylation attempts, the tetrahydropyranyl ether intermediates XXIa-c with three different leaving groups (X = mesylate, bromide, iodide) were used as the alkylating agents. Of these, only the iodide XXIc gave any alkylated product.

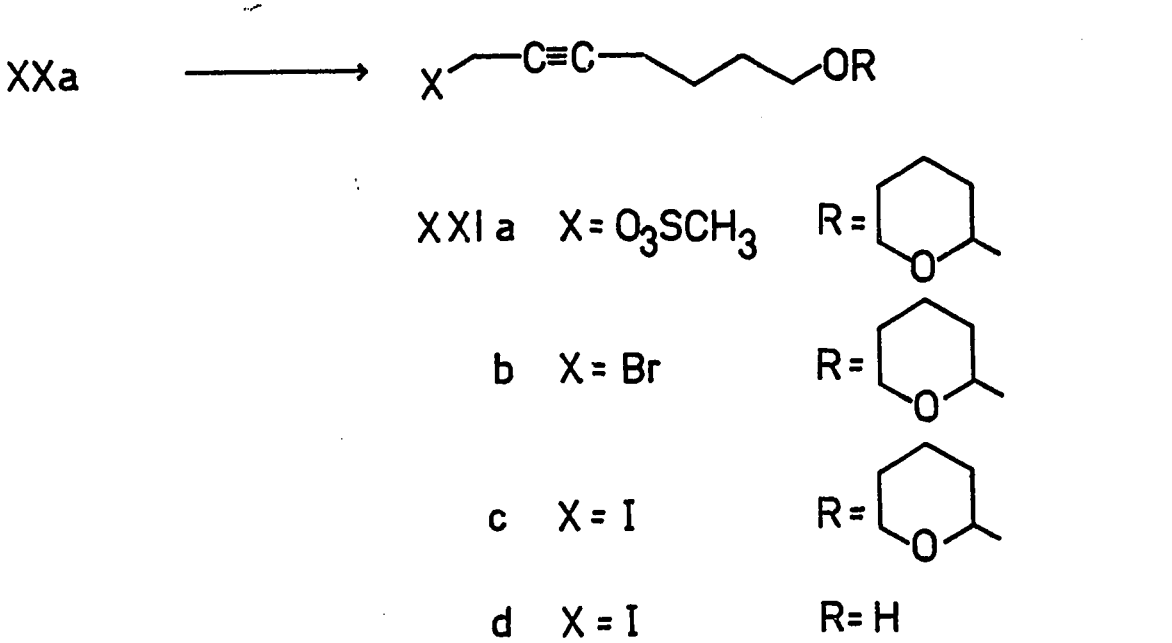
When the ratio of iodide to ketone was 1:1, 30% dialkylated material was isolated. In the n.m.r. spectrum of this compound the ratio of the olefin protons (δ 5.5-4.6 ppm), ketal protons (4.53 ppm), and ether protons (3.9-3.1 ppm) was found to be 2:2:8. This is the precise ratio of these protons in the dialkylated molecule, while for the monoalkylated compound the ratio is 2:1:4. For further proof, the compound was converted to the keto acid by reducing the ketone with lithium aluminum hydride, cleaving the tetrahydropyranyl ether with mild acid, and finally oxidizing the triol with excess Jones reagent. The n.m.r. spectrum of this keto acid showed a carboxylic acid proton resonance at δ 9.45 ppm and an olefinic proton resonance at δ 5.9-4.8 ppm in the ratio 1:1, confirming the assignment since for the monoalkylated product the ratio would be 1:2.

When this reaction was repeated using a two-fold excess of the iodide XXIc, and a longer addition time, the monoalkylated products XXVa were obtained in 19% yield. (The cis and trans isomers were not isolated, but by analogy with the alkylation results obtained in the PGE_1 synthesis[21], they were probably both present.) The n.m.r. spectrum clearly showed the characteristic olefinic proton multiplet (δ 5.6-4.6 ppm), the ketal protons (4.58 ppm) and the ether protons (4.0-3.2 ppm) in the correct ratio of 2:1:4. The mass spectrum gave no parent peak, although there was a large peak at m/e 302 corresponding to M^+-84, or loss of the

Scheme VII


XVII
XVIIIa R = H
b R = CH3
XIXa R = H
b R =


XIXb +
LiO
C≡CLi
RO
C≡C R1
XXa R=H R1 =
b R =
R1 = H
c R = R1 =

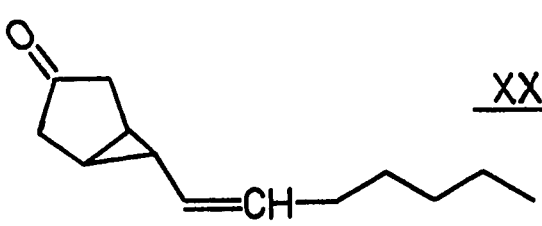

XXa
X
C≡C
OR
XXI a X = O3SCH3
R =
b X = Br
R =
c X = I
R =
d X = I
R = H

Scheme VII, (cont.)

XXId

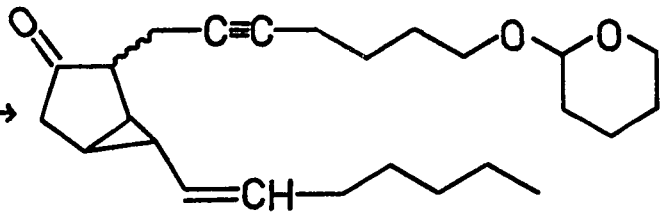
XXIIIa R=H

b R=CH_3



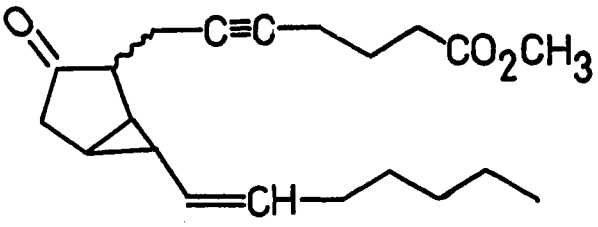
XXIV

XXIc →



XXVa

XXIIIb ↓



XXV

\+ di-, tri-, and tetra-alkylated ketones

tetrahydropyranyl ether group which is not unusual for such ethers[54]. When the ether was cleaved with mild acid, the mass spectrum of the resulting keto-alcohol gave the correct parent peak: M^+ 302. The cleavage of the tetrahydropyranyl ether was followed by TLC and verified by the disappearance of the characteristic THP bands (1138, 1120, 1075, 1060, 1033 1020 cm^{-1}) in the infrared spectrum.

Oxidation of the above keto alcohol with Jones reagent gave an acid, but in poor yield. The major product was a mixture of neutral compounds which probably resulted from hydration of the triple bond in the acidic oxidation conditions. Because of the poor yields in this oxidation step, the iodide XXIc was first converted to the iodo ester XXIIIb as described above. It was then condensed with the ketone XXIV. The oxidation of the iodo alcohol, XXId to the corresponding acid with Jones reagent also gave poor results, a large portion of the reaction product being neutral. TLC of the mixture indicated that this neutral fraction consisted of about five compounds which were not further investigated.

Alkylation of the ketone XXIV with a three fold excess of the iodo ester XXIIIb gave four alkylated products which were separated from the unreacted starting material by column chromatography on silica gel, and then from each other by preparative TLC on silica gel (benzene - ether, 9:1). The major product was the monoalkylated compound XXV (M^+ 330), obtained as a mixture of cis and trans (α and β) isomers in 23% yield (based on the total ketone XXIV used in the reaction). The other three products were the di- (M^+ 468), tri- (M^+ 606) and tetra- (M^+ 744) alkylated compounds obtained in 8, 11, and <5% yields respectively.

The structure of these compounds was confirmed by their infrared, n.m.r. and mass spectra. The detailed assignments are given in the Experimental Section.

The results of all the alkylation reactions are summarized in Table I.

Gas liquid chromatography (GLC) of the monoalkylated product (6', 3% SE30 on chromosorb W, 200°C) indicated that there were two compounds present (R_t = 2.90 min. and R_t = 4.75 min.) in the ratio 3:7. In the PGE_1 series, the analogous alkylation products had retention times of 3.05 min. and 4.67 min. on the same GLC column and had been obtained in the ratio 28:72[21]. The minor component (R_t = 3.05 min.) had been assigned the trans configuration, since it had been converted to $PGF_{1\alpha}$. Based on the close parallelism of the two sets of reactions, the minor and major components must be the trans(α) and cis(β) compounds of XXV.

GLC of the dialkylated product (6', 3% SE30 on chromosorb W, 248°C) showed two peaks (R_t = 5.25 min. and R_t = 3.50 min.) in the ratio 5:1. Too little was known to make a structural assignment for the two dialkylated products. However, it has been shown[11] that the second condensation reaction occurs predominantly at the more substituted carbon.

The tri- and tetra-alkylated products were not eluted off the column at temperatures up to 250°.

Table I

Conditions and results of direct alkylation experiments on exo-6-(1'-heptenyl)-bicyclo[3.1.0]hexan-3-one (XXIV)

Equivalents of t-BuOK	Alkylating agent	Equiv. of alkylating agent	Equiv. of ketone, XXIV	Solvent	Reaction time	Temperature of reaction	% alkylated products isolated
1.5	XXVIIIa	1	1	THF	30 min.	-10°C	none
1.5	XXVIIIa	3	1	THF	2 hrs.	0 - 5°C	
					12 hrs.	22°C	none
					21 hrs.	reflux	
1.5	XXVIIIa	1	1	THF	24 hrs.	22°C	none
1.5	XXVIIIa	1	1	DME	15 hrs.	22°C	none
					2 hrs.	reflux	
1.5	XXVIIIb	3	1	THF	30 min.*	0 - 5°C	none
1.5	XXVIIIc	1	1	THF	60 min.*	0 - 5°C	30% dialkylated
1.5	XXVIIIc	2	1	THF	4 hrs.*	0 - 5°C	19% monoalkylated
1.5	XVIII	3	1	THF	6 hrs.*	0 - 5°C	23% mono- 8% di- 11% tri- 5% tetra-

* addition time: worked-up immediately after addition

Figure II: I.r.(CCl_4) and n.m.r.(CCl_4) of 7-tetrahydropyranyloxyhept-2-yn-1-ol (XXa).

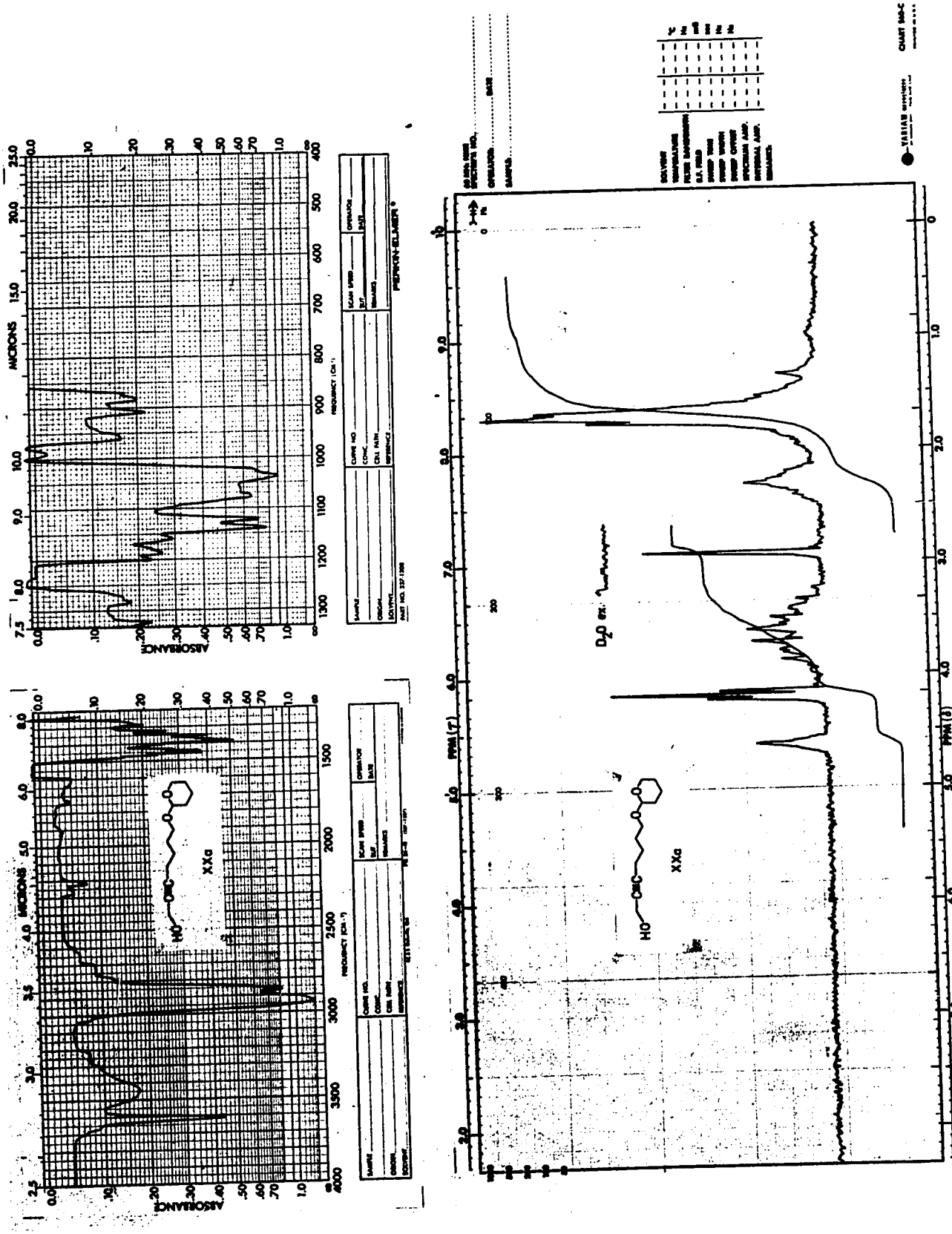
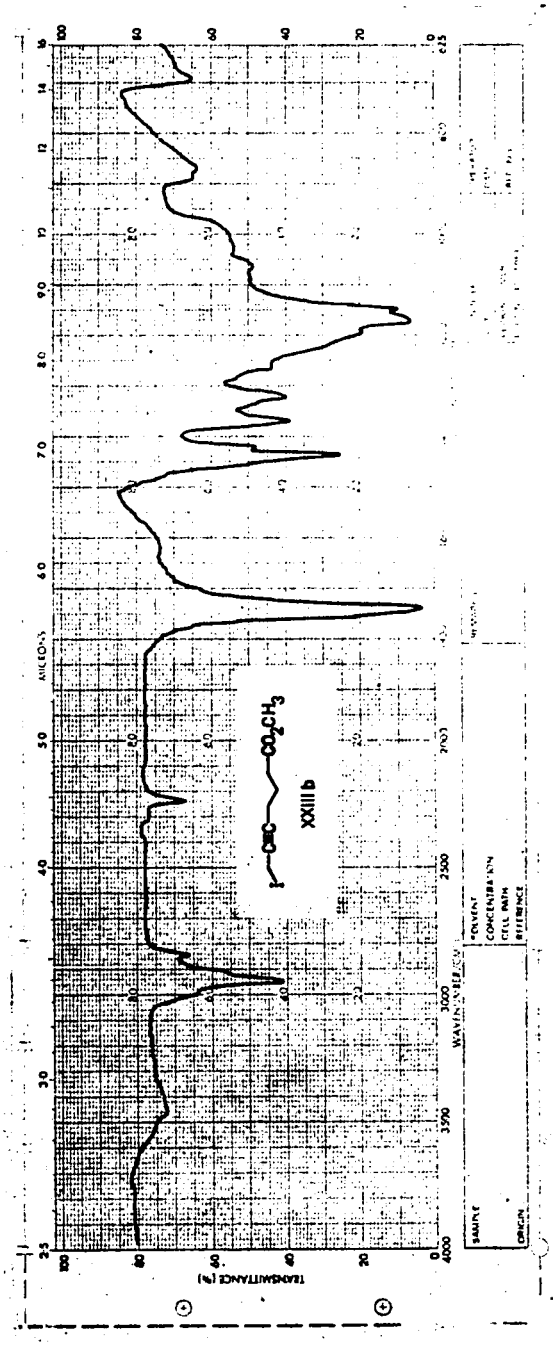

ABSORBANCE
MICRONS
FREQUENCY (CM⁻¹)
PERKIN-ELMER
XXa
HO
OBC
D₂O ex.
PPM (τ)
PPM (δ)
VARIAN
CHART 86-C

Figure III: I.r.(CCl_4) and n.m.r.(CCl_4) of methyl 7-iodo-5-heptynoate (XXIIIb).


XXIII b
TRANSMITTANCE (%)
WAVENUMBER (cm⁻¹)
MICRONS
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SAMPLE
ORIGIN

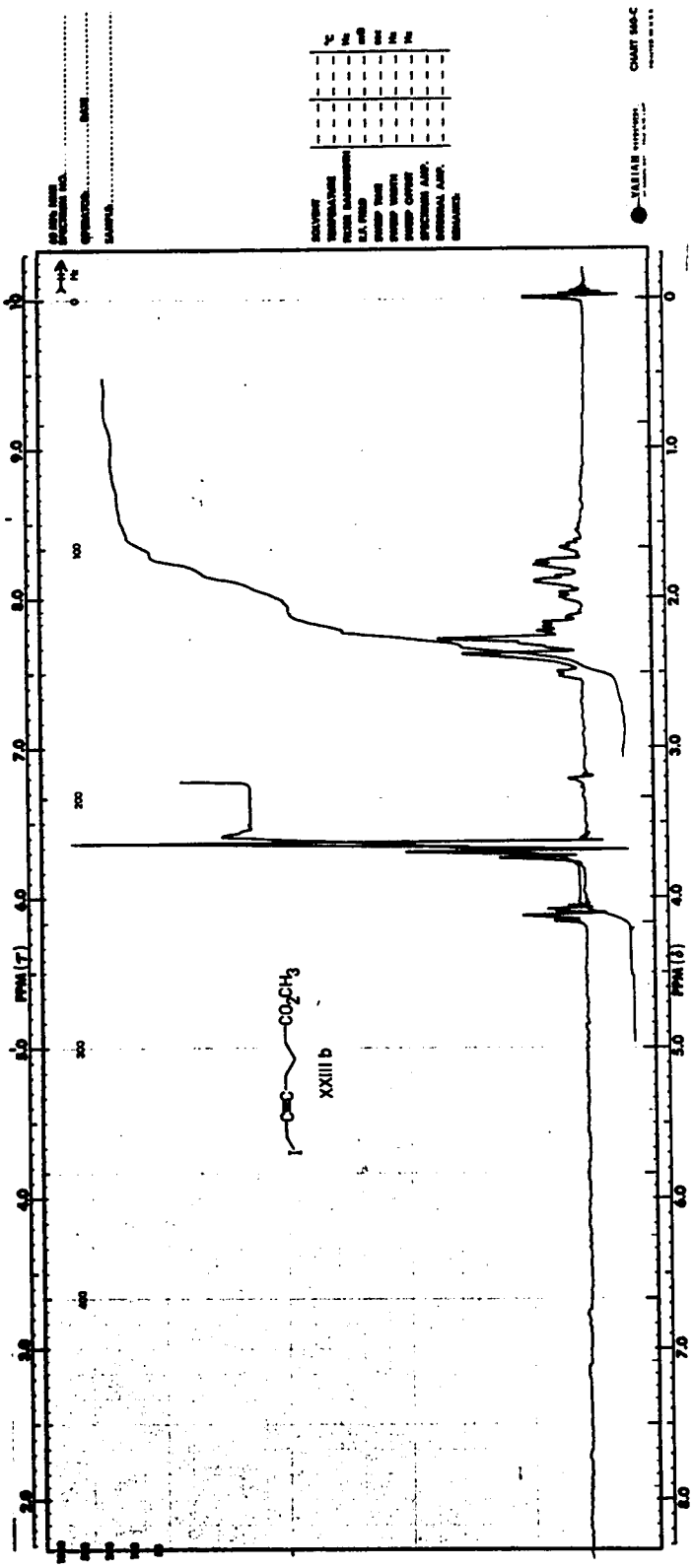
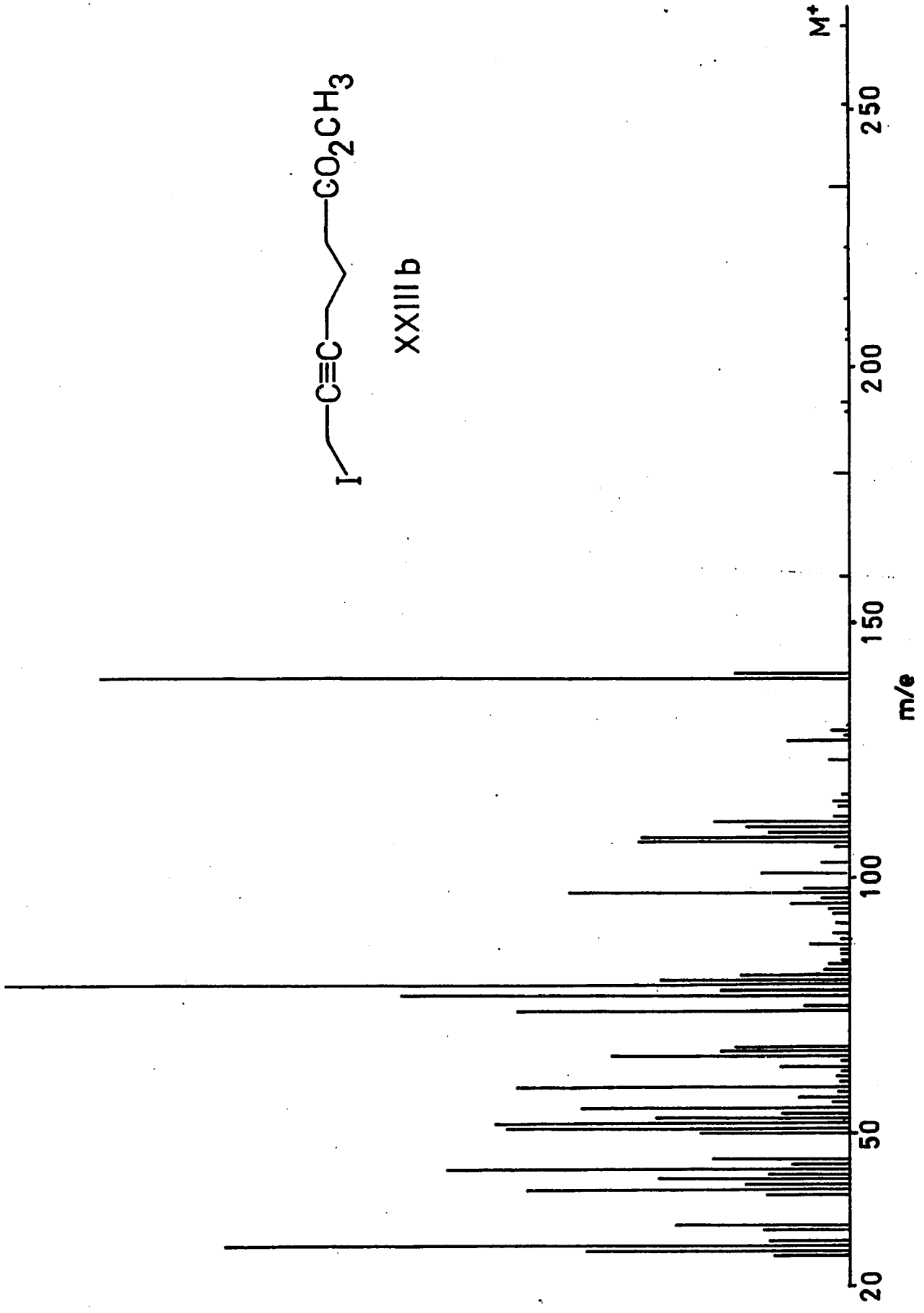

XXIII b
PPM (τ)
PPM (δ)
CHART 566-C

Figure IV: Mass spectrum of methyl 7-iodo-5-heptynoate (XXIIIb).



XXIII b

Figure V: I.r.(film) and n.m.r.($CDCl_3$) of exo-6-(1'-heptynyl)-2α and β-(6''-carbomethoxy-2-hexynyl)-bicyclo[3.1.0]-hexan-3-one (XXV).

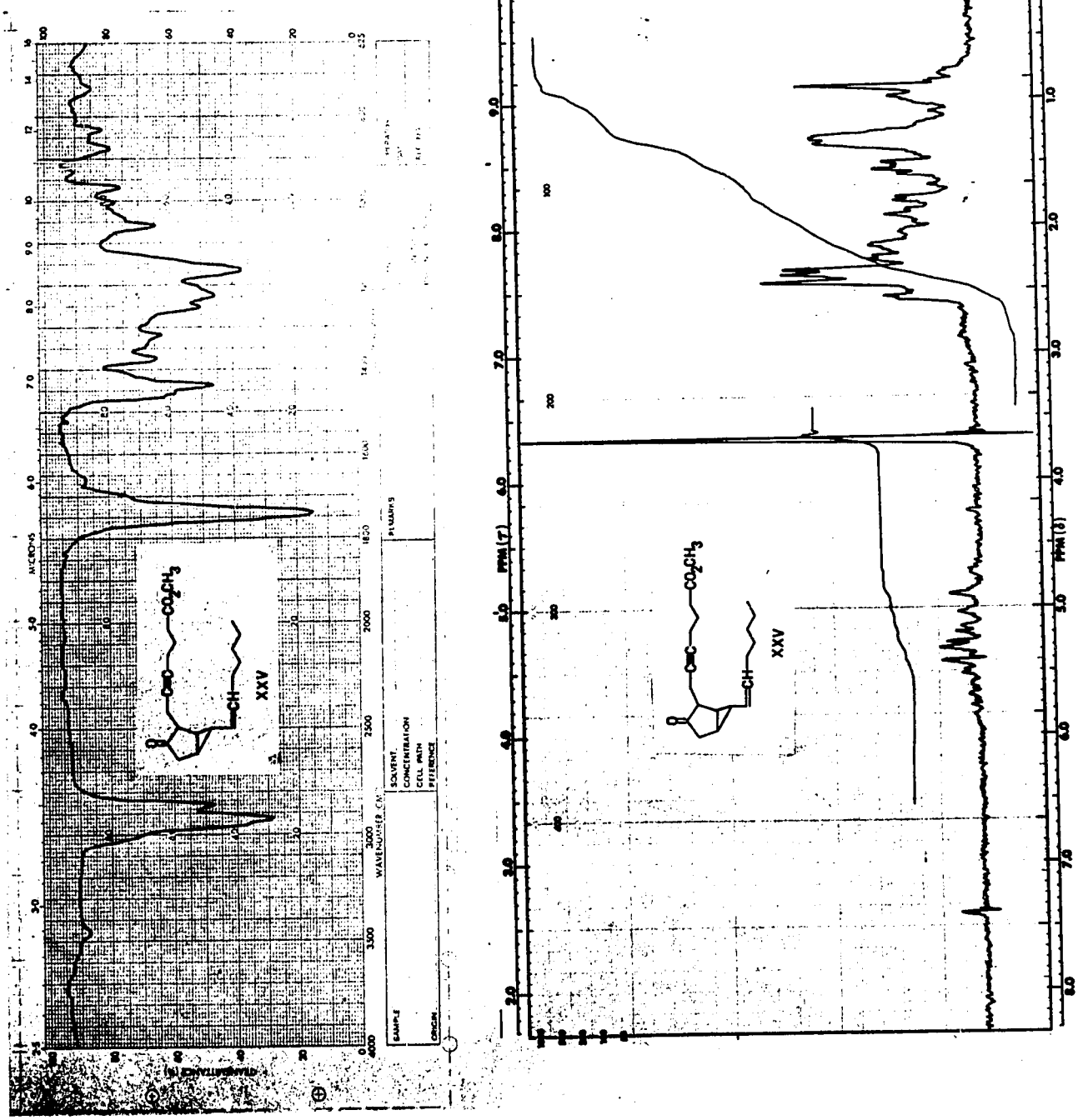
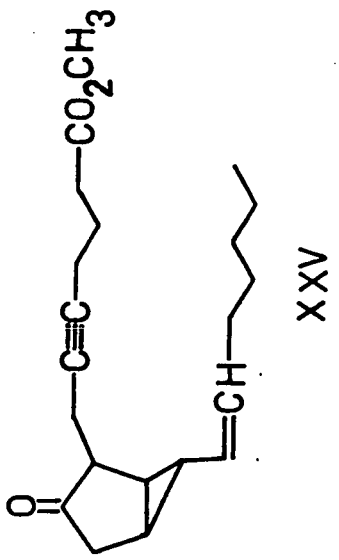

XXV
XXV

Figure VI: Mass spectrum of exo-6-(1'-heptynyl)-2α and β-(6''-carbomethoxy-2-hexynyl)-bicyclo[3.1.0]-hexan-3-one (XXV).



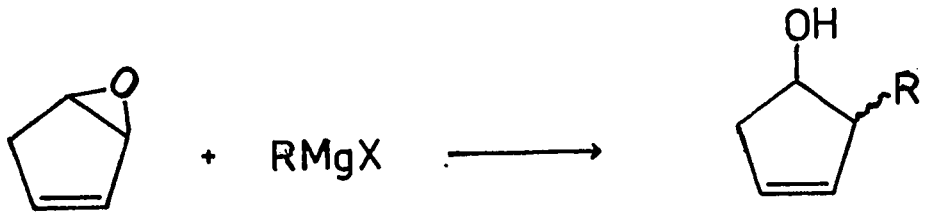
XXV

CHAPTER II

The Exploration of Other Routes to Exo-6-(1''-heptenyl)-trans-2-(6''-carbomethoxy-2-hexynyl)-bicyclo 3.1.0 hexan-3-one

Route A

In order to avoid the alkylation step described in Chapter I, a second route was explored. It was based on the alternative scheme described by Simonovitch[18] and outlined in the Introduction. This route involved introduction of the acid side chain by a Grignard reaction on 1,2-epoxycyclopentene (VII).

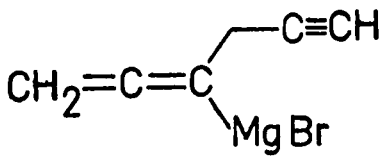


VII

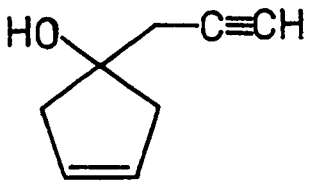
The Grignard reagent used in this case was propargyl magnesium bromide (XXIX) which was easily prepared[40] in diethyl ether when the reaction temperature was maintained below 20°. If the temperature was above 20°, or if tetrahydrofuran was used as solvent, undesired side reaction occurred which involved the formation of an allene[41].

The slow addition of 1,2-epoxycyclopentene (VII) to excess propargyl magnesium bromide at 0° gave, along with polymeric material, a mixture of alcohols from which two major products could be isolated by careful column chromatography on silica gel (Scheme VIIIA). The

desired alcohol 2-propargylcyclopent-3-en-1-ol (XXX)--formed by displacement at the most electrophilic (C-3) position--was obtained as the major product (32-40%). The other major component (10-12%) was 4-propargylcyclopent-2-en-1-ol (XXXI). This compound was formed by either 1,2 displacement at C-2, followed by allylic rearrangement on work up, or direct 1,4 displacement at C-4. The minor products were not completely characterized. They consisted first, of a mixture of allenes (3%) which polymerized on standing. These allenes (ν_{max} 1955 cm^{-1}) probably resulted from the reaction of the allene Grignard reagent[41] XXVII with the epoxide. Second, there was isolated a tertiary alcohol (10%).



XXVII

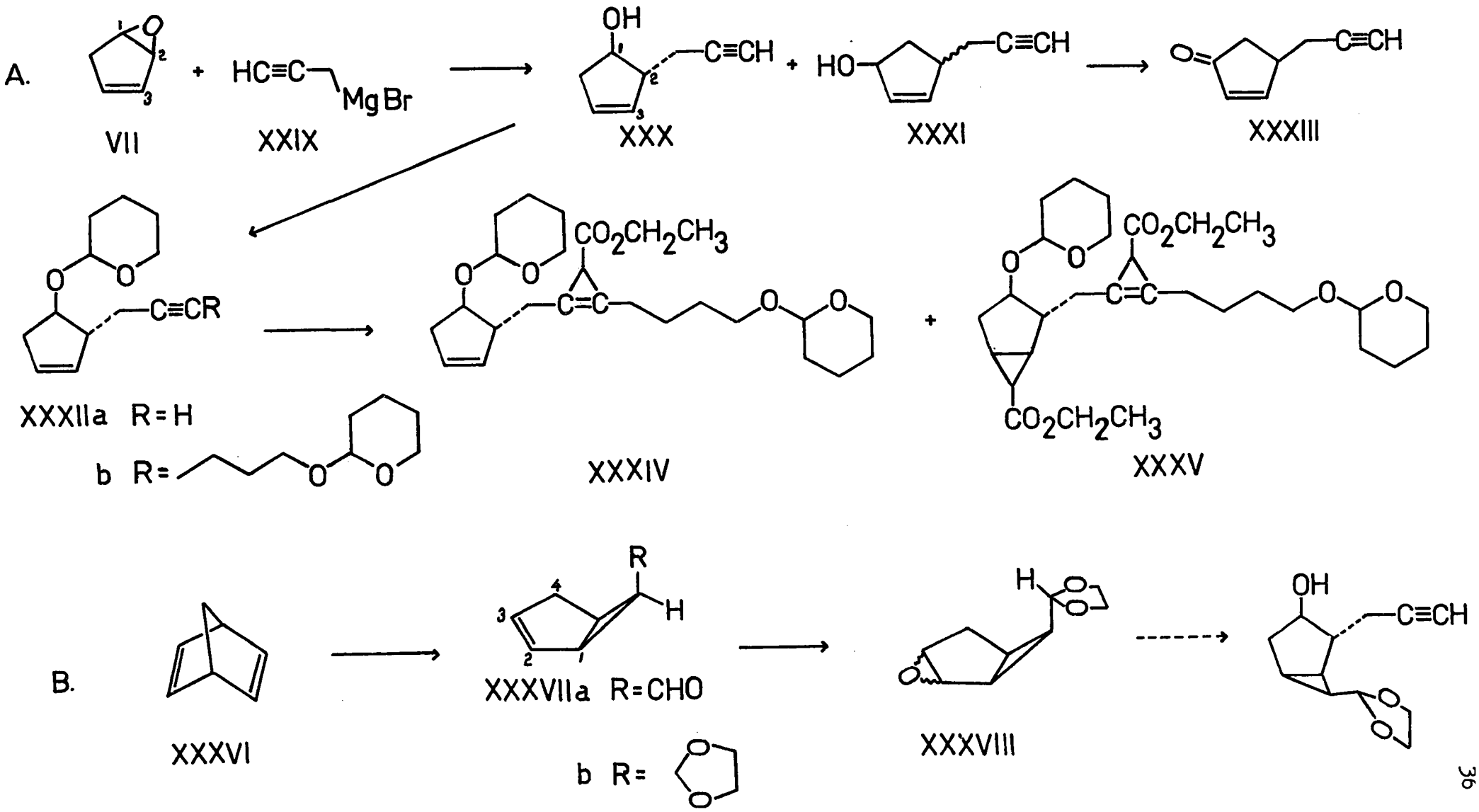


XXVIII

The n.m.r. and infrared spectra (detailed in the Experimental section) and elemental analysis suggested XXVIII as the structure of this by-product. The product probably resulted from the reaction of the Grignard reagent with the ketone impurity which was always found to contaminate the epoxide (ν_{max} 1755 cm^{-1}, 1680 cm^{-1}) to the extent of 10-15% (judged from the relative intensities of the bands.)*

*If XXVIII is the correct structure for this by-product, the ketone impurity contaminating the epoxide VII was probably 3-cyclopentenone.

Scheme VIII


A.
VII
XXIX
XXX
XXXI
XXXIII
XXXIIa R=H
b R=
XXXIV
XXXV
B.
XXXVI
XXXVIIa R=CHO
b R=
XXXVIII

Scheme VIII

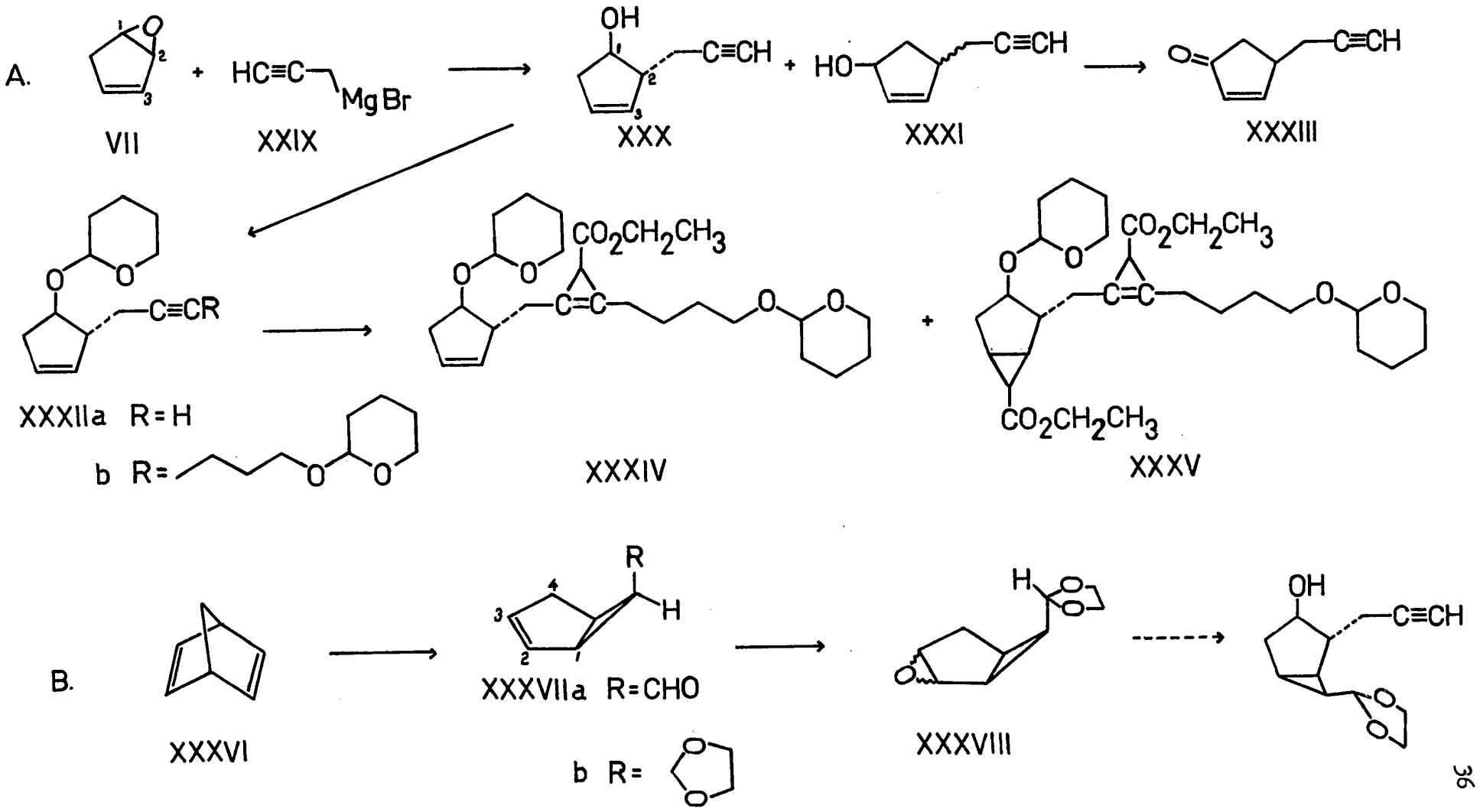
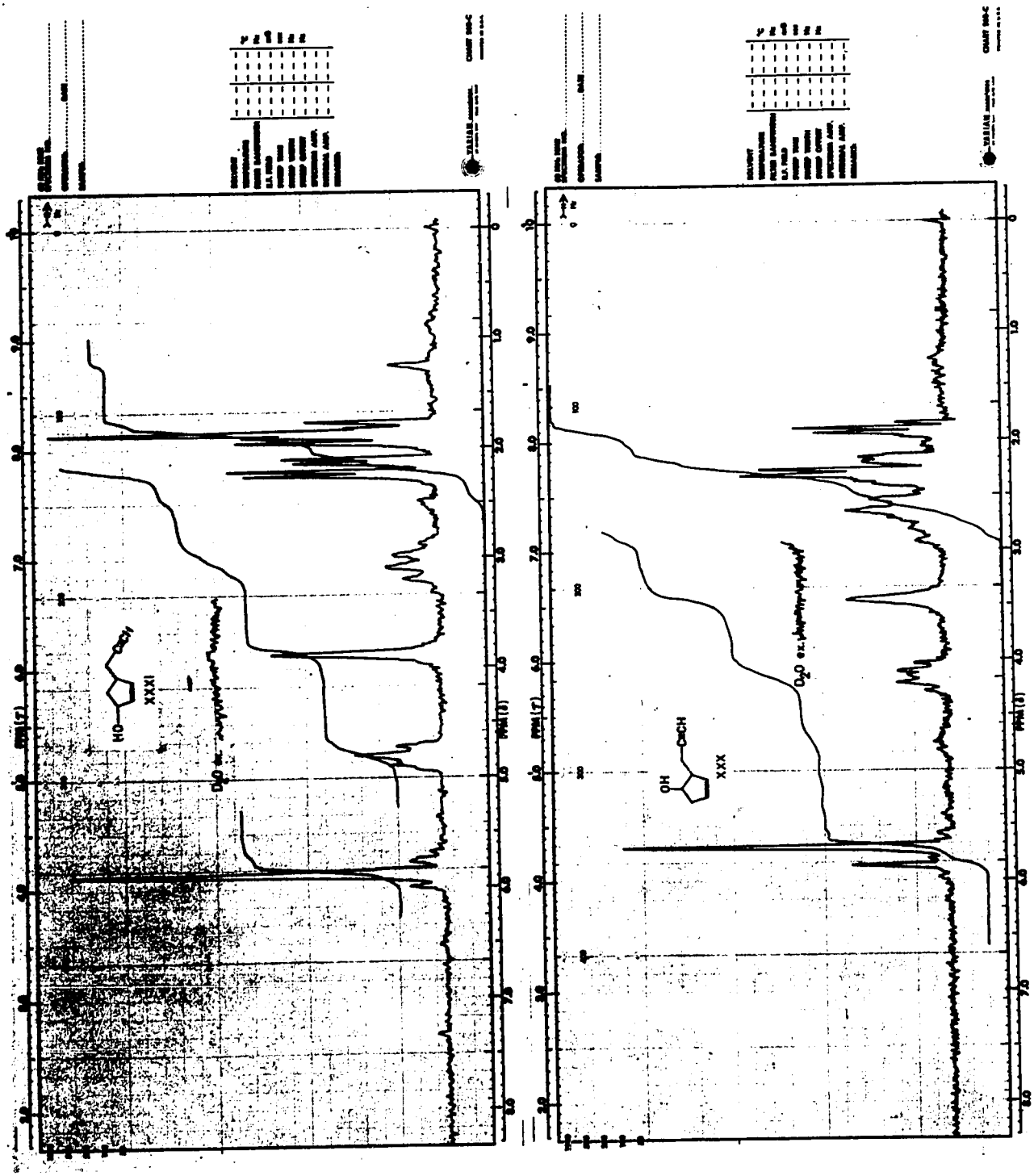

A.
VII
XXIX
XXX
XXXI
XXXIII
XXXIIa R=H
b R=
XXXIV
XXXV
B.
XXXVI
XXXVIIa R=CHO
b R=
XXXVIII

Figure VII: N.m.r.(CCl_4) spectra of 2-propargylcyclopent-2-en-1-ol (XXX) and 4-propargylcyclopent-3-en-1-ol (XXXI).


XXXI
D2O ex.
XXX
D2O ex.

The structure of the two major products XXX and XXXI was proven in the following manner. Both alcohols were treated with excess active manganese dioxide[87] in refluxing pentane for 24 hours. The alcohol XXXI gave an α,β unsaturated ketone (ν_{max} 3055, 1725, 1650 cm^{-1}; λ_{max}^{MeOH} 217 mμ, ϵ 10,900) whereas, XXX was not oxidized under these conditions. Since manganese dioxide is known to oxidize only allylic alcohols[42], XXXI was an allylic alcohol and XXX was not. This conclusion was substantiated by comparison of the chemical shift of the proton α to the hydroxy group for the two alcohols. For XXX, the chemical shift for this proton was 4.27 ppm while for XXXI, it was 4.91 ppm. The down-field shift of 0.63 ppm in the latter compound was due to the deshielding of the proton by the double bond next to it[43]. The n.m.r. spectrum of XXXI also showed a quintet centered at 3.09 ppm which integrated to one proton. This was interpreted to be the C-4 allylic hydrogen atom. On the basis of this interpretation, the substitution of XXXI was postulated to be 1,4 rather than the equally possible 1,2. If the substitution were 1,2, there would be two allylic protons at C-4 resonating in the same region (3.0 ppm) which would be expected to be split into a doublet.

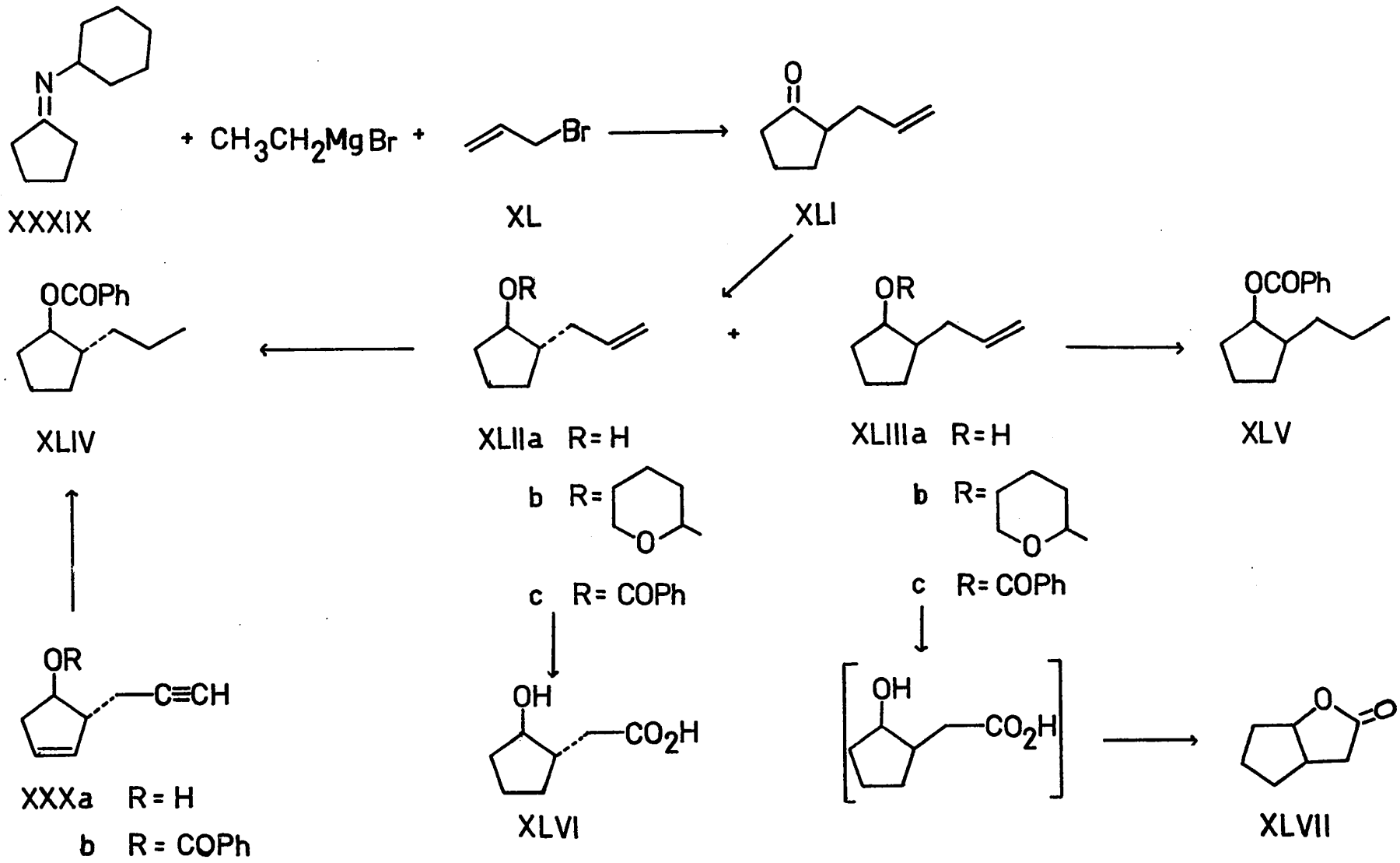
The stereochemistry of XXX, was not certain. Based on melting points of derivatives, Korach and co-workers[39] reported that 1,2-epoxycyclopentene, after hydrolysis and hydrogenation, gave mainly cis-1,2-cyclopentanediol. This was an unexpected result since epoxide displacement reactions usually result in the formation of trans products[47].

The stereochemical course of the Grignard displacement of 1,2-epoxycyclopentene was proven in the following manner. The alcohol XXX was benzoylated and completely hydrogenated. The resulting benzoate XLIV was then compared with cis and trans benzoates of 2-n-propylcyclopentan-1-ol (XLV and XLIV) which were synthesized by another route (Scheme IX).

The benzoates XLIV and XLV were synthesized in the following manner. Cyclopentanone was alkylated with allyl bromide (XL) via the magnesium salt of its cyclohexylimine XXXIX to give 2-allyl cyclopentanone XLI in moderate yield[44]. Reduction of XLI with lithium aluminum hydride in diethyl ether gave both cis and trans-2-allylcyclopentan-1-ol (XLIIIa and XLIIa) which were separated by careful column chromatography on silica gel. Each separated isomeric alcohol was then benzoylated with benzoyl chloride in pyridine[69] and catalytically hydrogenated to give cis- and trans-(2-n-propyl cyclopentyl) benzoate (XLV and XLIV) respectively.

In order to prove the stereochemistry of XLIV and XLV, the isomeric alcohols XLIIa and XLIIIa were first transformed into their respective tetrahydropyranyl ethers XLIIb and XLIIIb[85]. The olefinic linkage was then cleaved to the corresponding acid using sodium periodate with a trace of potassium permanganate in an aqueous potassium carbonate solution at room temperature[46]. The resulting potassium carboxylate was then acidified with 10% sulfuric acid and stirred at room temperature for four hours. Under these conditions the tetrahydropyranyl ether cleaved to give a hydroxy acid. In the case of XLIIIb, the product isolated after this sequence of reactions was the γ-lactone XLVII

Scheme IX


XXXIX
+ CH3CH2MgBr +
Br
XL
O
XLI
OCOPh
XLIV
OR
XLIIa R=H
b R=
O
c R=COPh
OR
XLIIIa R=H
b R=
O
c R=COPh
OCOPh
XLV
OR
C≡CH
XXXa R=H
b R=COPh
OH
CO2H
XLVI
OH
CO2H
O
O
XLVII

(ν_{max} 1776 cm^{-1}). The hydroxy acid must therefore have had the cis configuration. Under the same reaction conditions, the epimer XLIIb gave the hydroxy acid XLVI (ν_{max} 3610, 3370, 3300-2500, 1710 cm^{-1}) with no evidence of lactonization. The acid XLVI must therefore have the trans configuration. The assignment was further corroborated by the TLC behaviour of the corresponding olefinic alcohols XLIIIa and XLIIa, in which the cis-compound XLIIIa had a larger R_f value than its epimer XLIIa.

Having thus identified the cis- and trans-(2-n-propylcyclopentyl) benzoate, a direct comparison could be made with benzoate obtained from 2-propargylcyclopent-3-en-1-ol (XXX). Comparison of infrared and n.m.r. spectra, and R_f values on TLC system showed that the saturated benzoate obtained from XXX was identical with trans-(2-n-propylcyclopentyl) benzoate (XLIV) and different from the cis isomer (XLV). The comparisons of the n.m.r. spectra gave the best proof for this assignment. The chemical shift of the proton α to the benzoate group in the cis isomer XLV was 5.32 ppm while that of the trans isomer XLIV was 4.95.

The stereochemistry of the displacement of 1,2-epoxycyclopentene was, therefore, found to be consistent with the general stereochemical course of S_N2 reactions on epoxides[47].

Trans-2-propargylcyclopent-3-en-1-ol (XXX) was pyranylated in the usual way[86]. The terminal acetylene of the tetrahydropyranyl ether XXXIIa was then alkylated with 4-tetrahydropyranyloxybutyl bromide XIXb using lithium amide in liquid ammonia[31]. This gave 2-[7-tetrahydropyranyloxy-2-heptyne]-1-tetrahydropyranyloxycyclopent-3-ene (XXXIIb) in 80% yield.

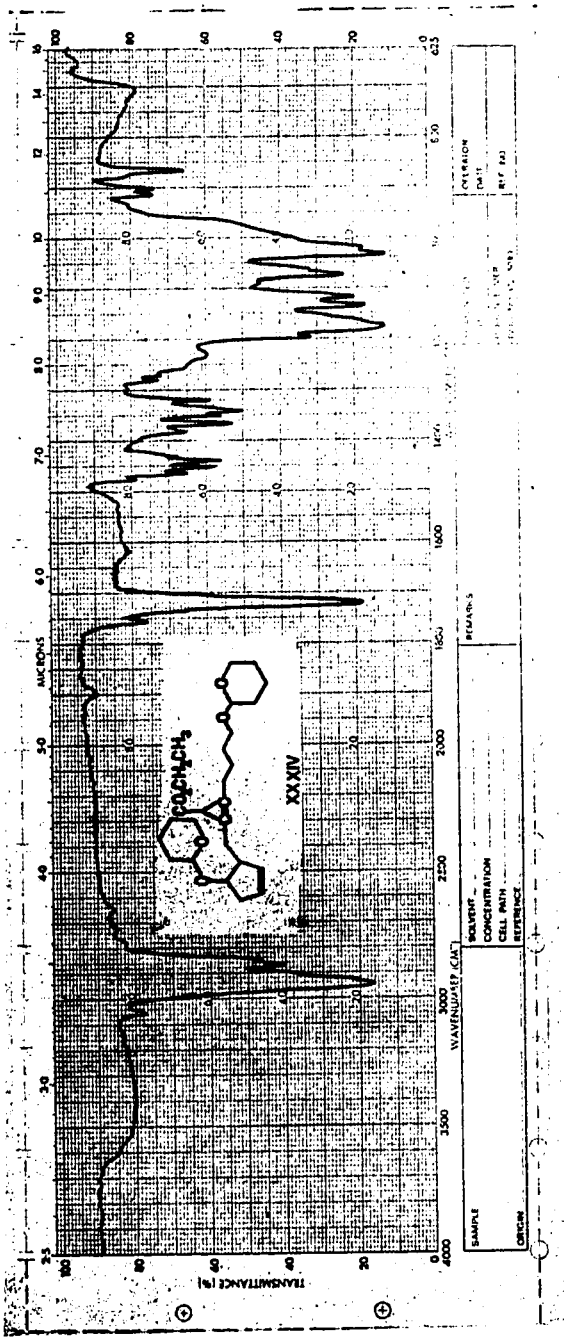
The next step was the addition of carboethoxy carbene to the

double in XXXIIb in order to introduce the [3.1.0]-bicyclic system. Although this carbene, generated from ethyl diazoacetate by heating with copper powder catalyst, will add to triple bonds[12,32,48], the addition has been found to be selective to the double bond on reaction with hex-1-en-4-yne[49]. Also, since triple bonds are generally less susceptible to electrophilic attack than double bonds[36], it was thought that the desired selectivity would be achieved on XXXIIb.

When the reaction was carried out at 100°, two products were isolated from the reaction mixture in approximately equal amounts. In the first compound, XXXIV, obtained in 24% yield, the carbene added only to the triple bond forming a cyclopropene (M^+468; ν_{max}1900 cm^{-1}; δ5.70 ppm) while in the second compound, XXXV, obtained in 26% yield, addition occurred both to the triple and double bonds (M^+554, ν_{max}1900 cm^{-1}). All spectroscopic data was consistent with the structures proposed for these two compounds. A detailed interpretation of these data is given in the Experimental section. The rest of the reaction mixture contained only unreacted XXXIIb, diethyl maleate, and diethyl fumarate. There was no evidence of any selective addition to the double bond. When the same reaction was carried out at 50° instead of 100° only addition to the triple bond occurred, i.e., only XXXV was isolated in 20-25% yield. The rest of the reaction mixture consisted of unreacted XXXIV, and diethyl maleate (no diethyl fumarate was observed). Again there was no evidence of addition to the double bond.

The reason for the preferential addition to the triple bond in the presence of the double bond by the carboethoxy carbene was not clear. One explanation could be that the positions of the large tetra-

Figure VIII: Ir(CCl_4) and n.m.r.(CCl_4) spectra of 2-[1'-methenyl-2'-carboethoxy-3'-(4''-tetrahydropyranyloxybutyl)-cyclopropene]-1-tetrahydropyranyloxycyclopent-3-ene (XXXIV).


XXXIV
$COCH_2CH_3$
MICRONS
WAVENUMBER (CM⁻¹)
TRANSMITTANCE (%)
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SAMPLE
ORIGIN

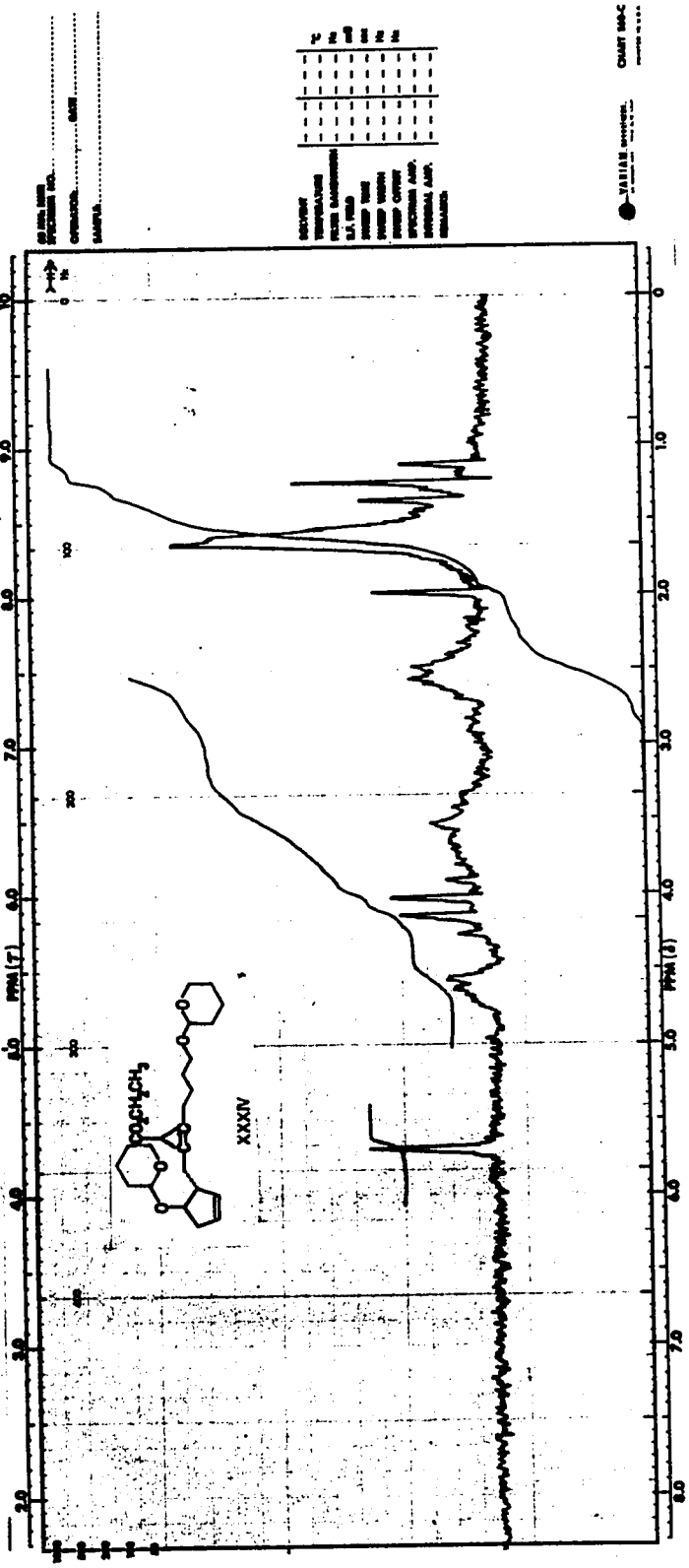
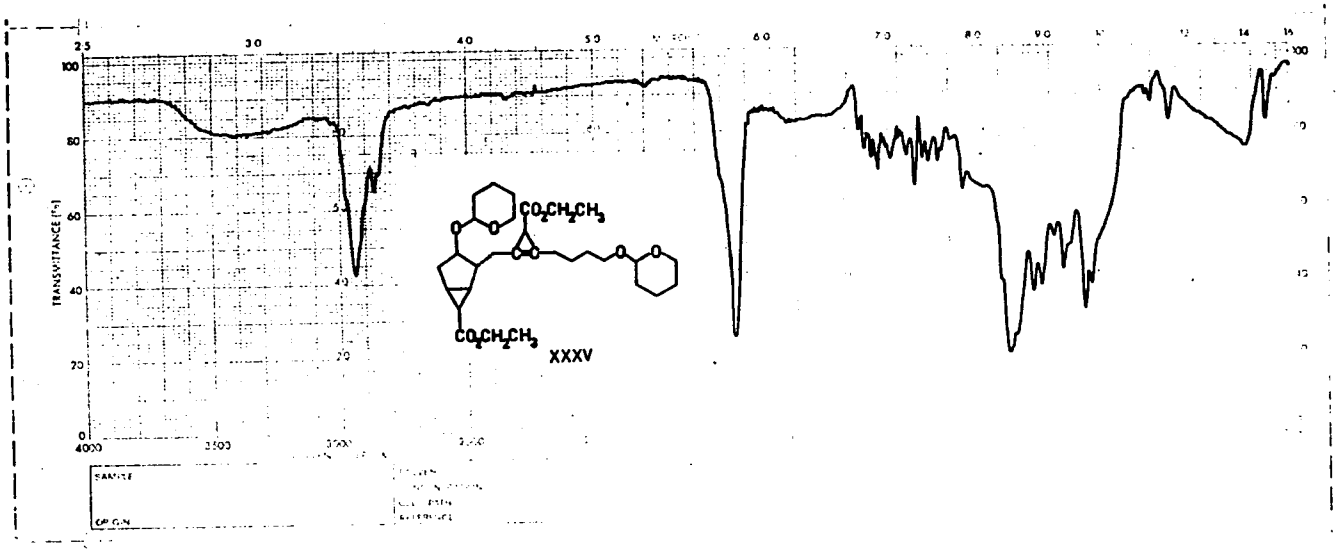

XXXV
$COCH_2CH_3$
PPM (τ)
PPM (δ)
SOLVENT
TEMPERATURE
SWEEP WIDTH
SWEEP OFFSET
SPECTRAL AMP.
RFGAINS
SAMPLE
OPERATOR
DATE
CHART SPEED

Figure IX: Ir(CCl_4) and n.m.r.(CCl_4) spectra of 2-[1'-methyenyl-2'-carboethoxy-3'-(4''-tetrahydropyranyloxybutyl)cyclopropene]-6-carboethoxy-2-tetrahydropyranylbicyclo[3.1.0]hexane (XXXV).


TRANSMITTANCE (%)
$CO_2CH_2CH_3$
$CO_2CH_2CH_3$
XXXV

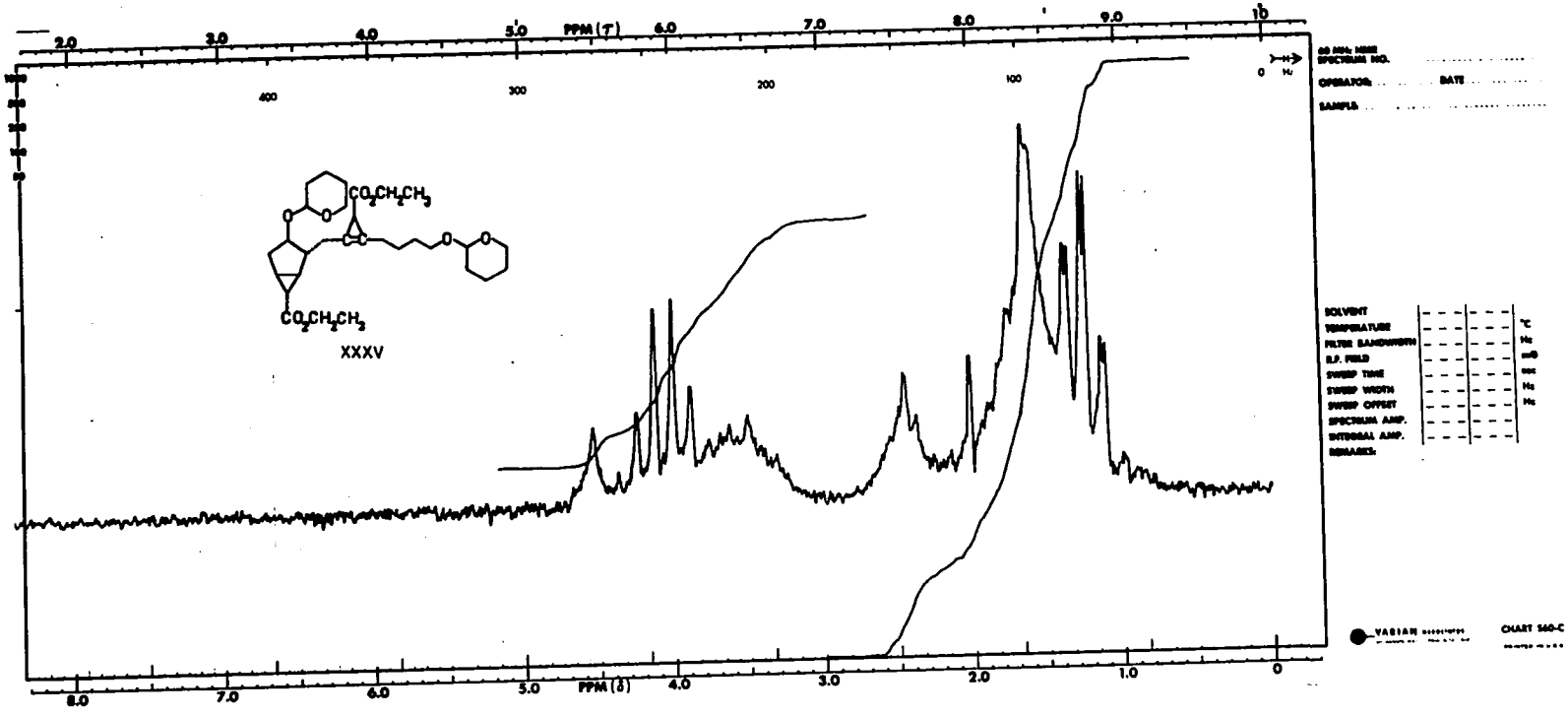
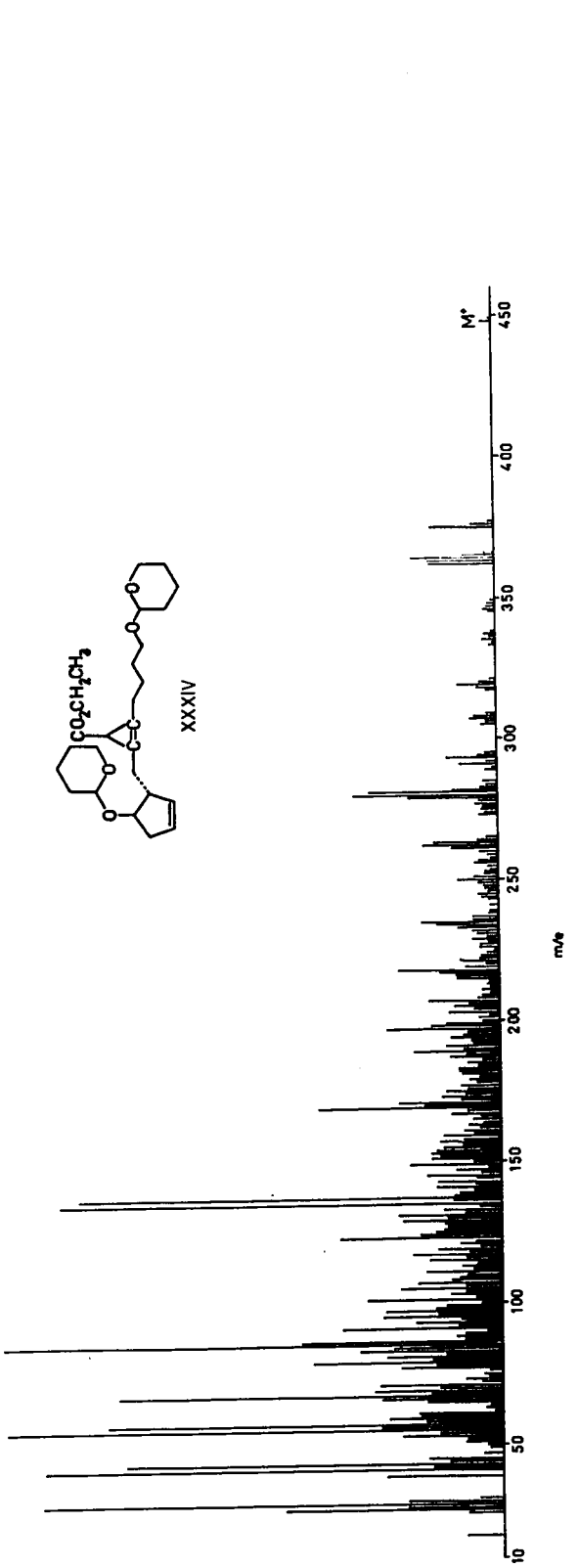
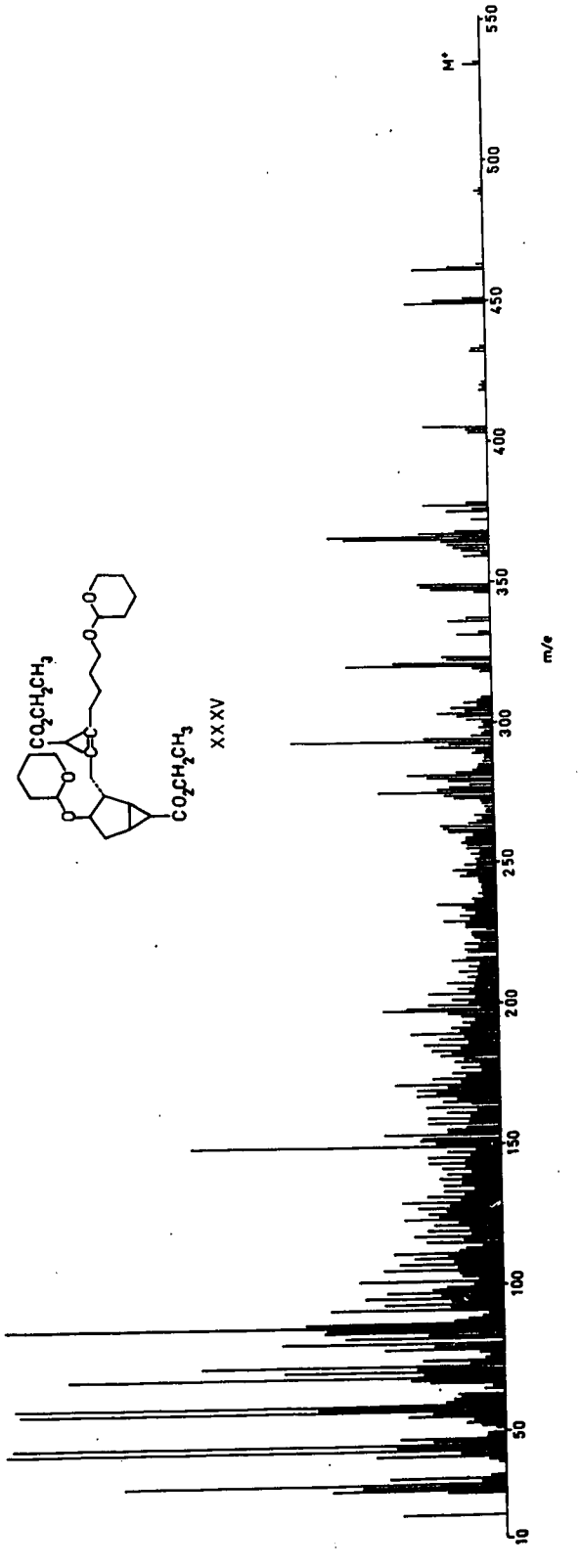

PPM (τ)
PPM (δ)
$CO_2CH_2CH_3$
$CO_2CH_2CH_3$
XXXV
SOLVENT
TEMPERATURE
FILTER BANDWIDTH
R.F. FIELD
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
INTEGRAL AMP.
REMARKS
VARIAN
CHART 160-C

Figure X: Mass Spectra of XXXIV and XXXV.


M+
450
400
350
300
250
200
150
100
50
10
m/e

XXXIV


M+
550
500
450
400
350
300
250
200
150
100
50
10
m/e

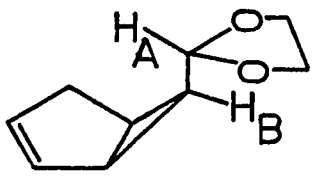
XXXV

hydropyranyl group on the ring and the long side chain trans to it sufficiently hindered both sides of the double bond so that the carbene added faster onto the triple bond. This conclusion was supported by the fact that the cyclopropene was formed at 50° to the exclusion of any cyclopropane formation.

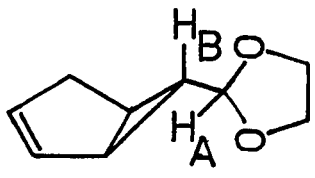
Route B

It was known that bicyclo[2.2.1]heptadiene (XXXVI) on reaction with peracetic acid, gave, instead of an epoxide, bicyclo[3.1.0]-hex-3-en-6-endo-carboxaldehyde (XXXVIIa) in good yield[26]. Therefore it was thought that the carbene reaction could be avoided by starting with XXXVI instead of cyclopentadiene (Scheme VIIIB).

The endo aldehyde XXXVIIa was ketalized with ethylene glycol in benzene containing a trace of p-toluenesulfonic acid. The infrared spectrum of the resulting ketal XXXVIIb was consistent with the structure proposed. However, the n.m.r. spectrum showed two doublets at δ 4.33 ppm, J = 8.0 cps and 4.52 ppm, J = 5.5 cps in the ratio 3:1. The absorption was due to the methine proton H_A coupled with the cyclopropyl proton H_B. The two doublets indicated that the resulting ketal consisted probably



endo



exo

of a mixture of endo and exo isomers. Not enough was known to make a definitive assignment. It cannot be completely ruled out that the two doublets are due to two conformers of the endo isomer arising from hindered rotation. This possibility is however unlikely.

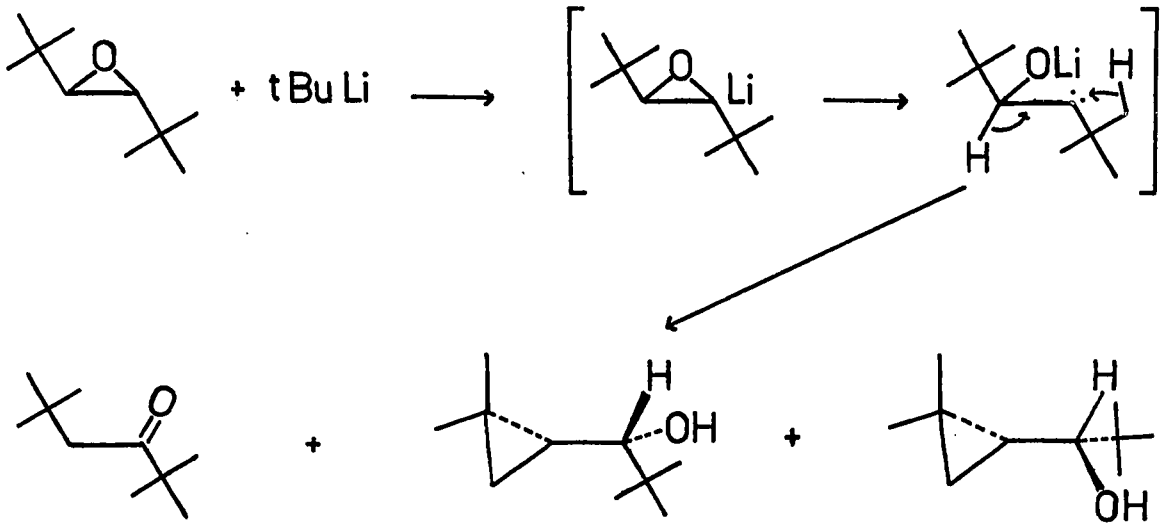
The ketal mixture XXXVIIb was reacted with peracetic acid at 0° to give recovered ketal XXXVIIb and the epoxide XXXVIII in 58% yield. (In this case the two methine doublets were reversed -- the one with the larger coupling constant being at lower field.) The epoxide XXXVIII probably consisted of a mixture of α and β epoxides, the double bond having been oxidized from both sides. In the exo ketal, in particular, both sides would be relatively unhindered.

The mixture of epoxides was then added to propargyl magnesium bromide in diethyl ether, to effect a Grignard displacement similar to the one obtained for 1,2-epoxycyclopentene. Since cyclopropyl rings have some π character, it was assumed that the most electrophilic position would be at C-2 and that the major compound, as in the previous case, would be the desired 3-hydroxy product. After chromatographing the product on silica gel, it was found, however, that the reaction mixture consisted of only 17% displacement products which in turn was found by TLC to be a mixture of six compounds. (Six isomers would be expected if one started with α and β exo and α endo epoxides.)

Most of the reaction mixture consisted of a ketonic fraction (25%) (ν_{max} 1750 cm^{-1}) and a mixture of saturated alcohols (23%) which did not contain a propargyl group. Epoxides reacting with strong, non-nucleophilic bases are known to undergo rearrangements[53]. This type of

transformation was demonstrated by Cope and co-workers[88] to proceed by the mechanism outlined in Scheme X.

Scheme X[53]



In the Grignard reaction on XXXVIII, rearrangements rather than displacement probably predominated because the β side of the epoxide, particularly the endo-epoxide, was sterically shielded by the ketal group.

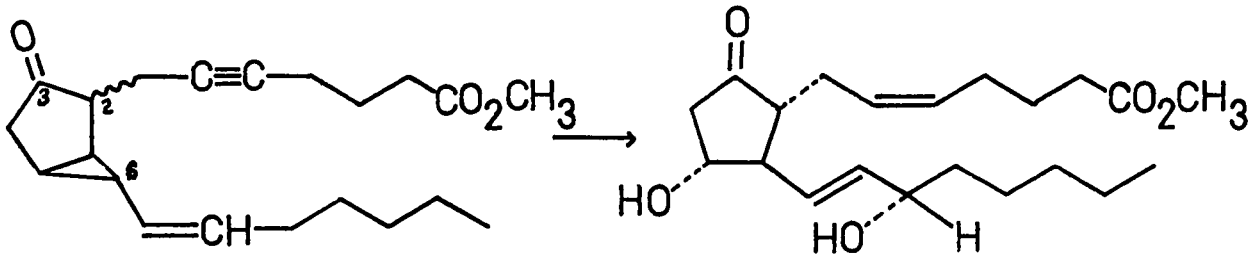
The rest of the reaction mixture (35%), was not recovered from the column, and probably consisted of polymeric material.

This route to XXV was also abandoned because of the unexpected poor yields and the large number of isomers in the displacement products. There was, therefore, no advantage in this approach over the sequence discussed in Chapter I.

CHAPTER III

Final Steps to the Synthesis of PGE_2 Methyl Ester

To complete the synthesis, the bicyclic ketone XXV had to be transformed to prostaglandin E_2 methyl ester (LXXVII).



XXV LXXVIIb

This involved basically four steps:

1. The transformation of the olefinic linkage to an appropriate leaving group which would give the ring opened homoallylic system upon solvolysis.

2. The separation of PG like material from its 15-epimer.* In the synthesis of PGE_1[21], 15-epi PGE_1 methyl ester could be separated from the solvolysis reaction mixture by chromatography.

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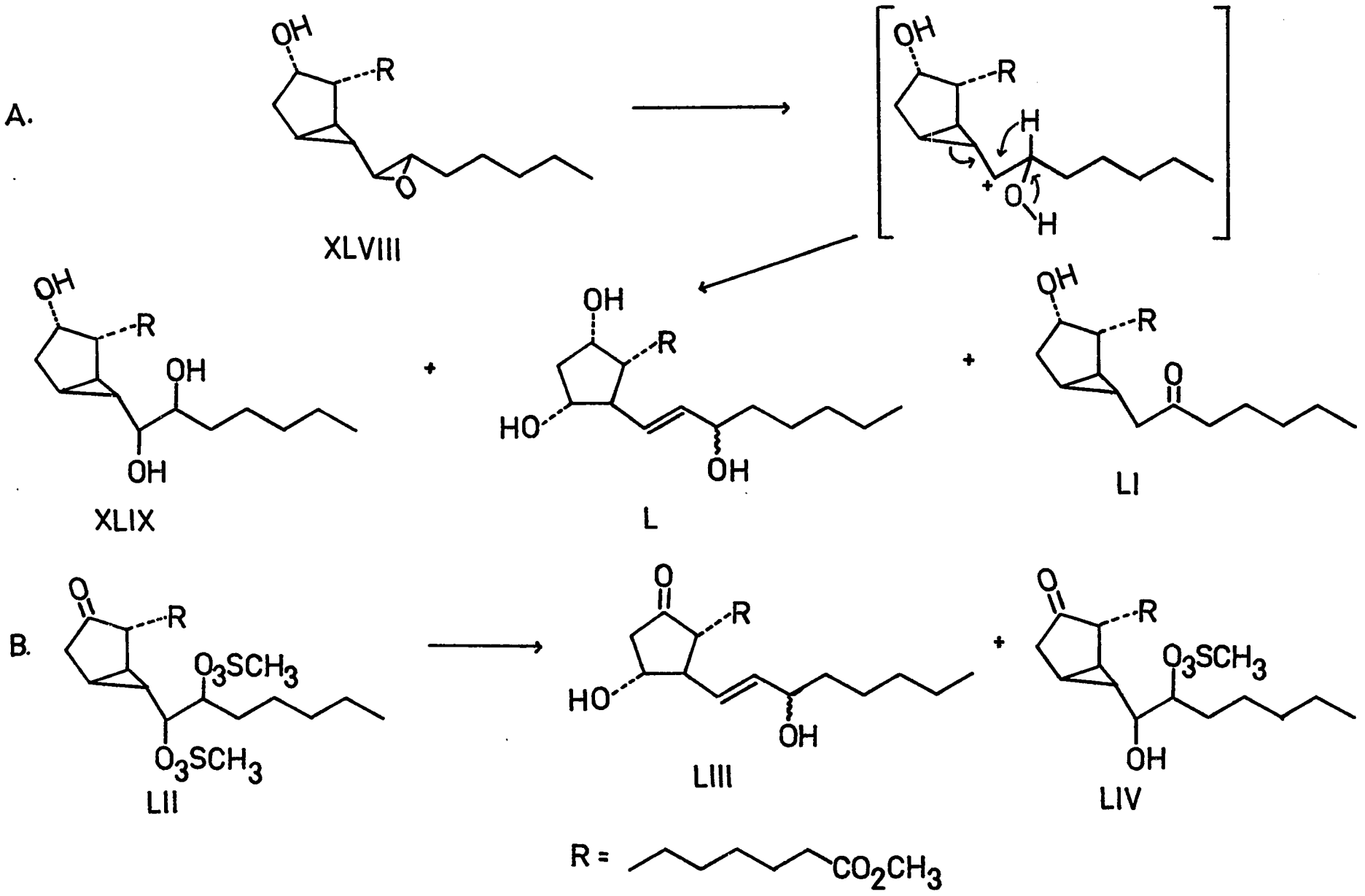
* c.f. the footnote on p. 1 of this thesis.

Scheme XI



3. The reduction of the triple bond to a cis-double bond. This step can in principle be done by catalytic hydrogenation using Lindlar catalyst[85].

4. The epimerization of 8-iso PGE_2 to PGE_2 methyl ester or separation of the two isomers. This step was necessary since the bicyclic ketone XXV was a mixture of C-2α and C-2β epimers (Chapter I). This problem was recently resolved[70] when 8-iso-PGE_1 was isomerized to PGE_1 by the reaction of potassium acetate in ethanol at room temperature. The equilibrium mixture consisted of PGE_1 and 8-iso-PGE_1 in the ratio of 9:1.

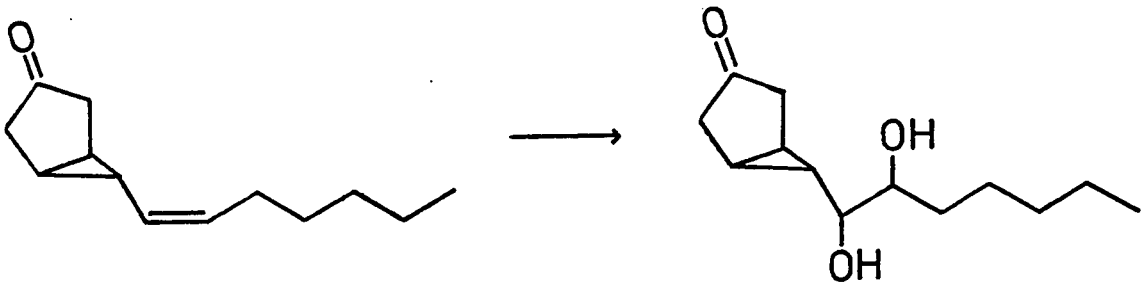
As has been mentioned in the Introduction, the initial solvolysis attempts in the PGE_1 synthesis[17,18,20] were difficult to reproduce. In this reaction, the olefin had been transformed to an epoxide with performic acid and solvolyzed, in situ, with formic acid. When the epoxide XLVIII in the F series had been isolated and solvolyzed with formic or trifluroacetic acids, PGF_1 methyl ester (L) and its C-15 epimer had been isolated in 2.5-10% yields[21], implying 5-20% ring opening. The major product in the reaction had been the corresponding unrearranged glycol XLIX. A pinacol rearrangement giving LI had also been found[18] to compete with the cyclopropyl carbinyl rearrangement (Scheme XIA). Recently it has been reported[22] that the solvolysis of the dimesylate LII in aqueous acetone at room temperature gave PGE_1 and 15-epi-PGE_1 methyl esters (LIII) each in 5-10% yield. The only other product isolated was the glycol monomesylate LIV which could be recycled (Scheme XIB).

In any case, the solvolysis of the epoxide or dimesylate under conditions of kinetic control gave only 15-20% of the desired rearrangement products. In many instances, it was known that the rearrangement of cyclopropyl carbinyl system gave, under kinetic control, the cyclopropyl carbinol as the major product[50,51,52,61,62,64], but that under thermodynamically controlled conditions, the homoallylic system was favored[57,58].

In principle, thermodynamic control would be achieved by treating the glycol XLIX with mineral acid. However, one competing reaction -- a pinacol rearrangement -- and, in the E-series, the known acid instability of the PG which is dehydrated to the PGA compounds, made this route unsuitable. It was thought that the problem could be solved by solvolyzing the ditrichloroacetate in trichloroacetic acid. Under these conditions, any regenerated ditrichloroacetate would be resolvolyzed, giving effectively thermodynamic control.

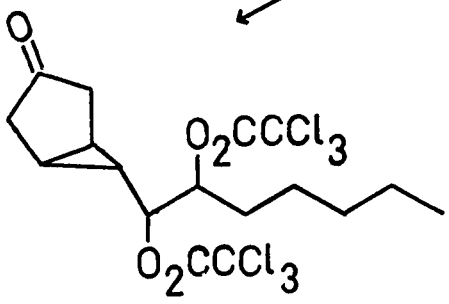
Because of the difficulty in synthesizing the alkylated bicyclic ketone XXV and since the side chain should not greatly affect the yields of rearranged products, the unalkylated ketone XXIV was used as a model in the subsequent solvolysis studies.

The ditrichloroacetate LVI was prepared by treating the diol LV with excess trichloroacetyl chloride in pyridine. The glycol LV was prepared by first reacting the olefin XXIV with performic acid in buffered formic acid and then hydrolyzing the resulting hydroxy formate with sodium carbonate in aqueous methanol[89].



XXIV

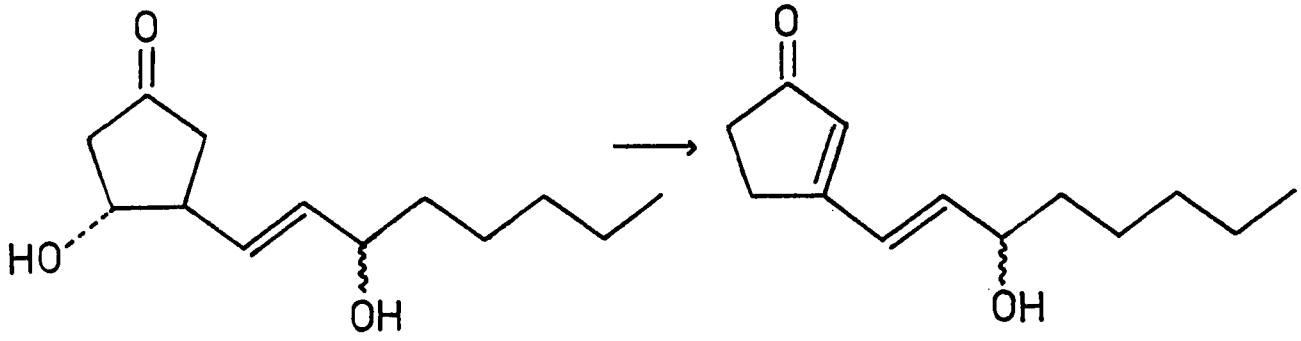
LV



LVI

The solvolysis of the ditrichloroacetate was carried out at various temperatures in : trichloroacetic acid, trichloroacetic acid and dioxane 1:1, and trichloroacetic acid containing some p-toluene-sulfonic acid. Pyrolysis of the ditrichloroacetate was also attempted. In order to determine if rearrangement had taken place, the reaction mixture was taken up in ether and washed with 5% sodium bicarbonate and water to remove all the acid solvent. Some of the resulting material was then treated with 0.5% sodium hydroxide in methanol at 50-60° for 10 minutes. If rearrangement had taken place, the resulting β-hydroxy ketone LVII would be converted to the conjugated ketone LXVI in the same way that PGE_{1-3} were converted to PGB_{1-3}. This compound would be

easily identified by its ultraviolet spectrum (λ_{max} 268 mμ, ε 26,000).



LVII LXVI

The results of the solvolyses are summarized in Table II. There was no detectable rearrangement of any of the solvolysis reaction carried out in trichloroacetic acid. TLC of the products on silica gel (benzene - ether, 7:3) showed only recovered ditrichloroacetate. Pyrolysis at 230° gave a small amount of rearrangement along with considerable charring. At 120-140°, no reaction took place.

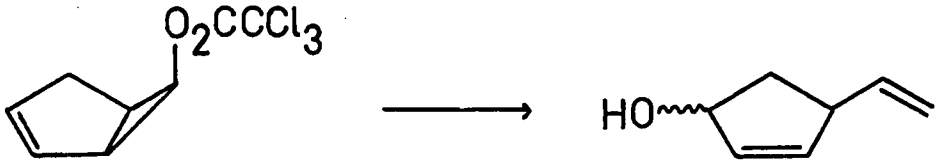
A solvolysis of the ditrichloroacetate was also attempted in refluxing acetone-water 1:1. These conditions were based on a solvolysis of the trichloroacetate of endo-bicyclo [3.1.0] hex-2-en-6-yl-methanol (LVIII) in refluxing aqueous acetone reported by Lumb and Whitham[56]. This solvolysis gave a mixture of epimeric 4-vinylcyclopentenols (LVIX) in 90% yield. When these conditions were applied to LVI

TABLE II

Conditions and results of the solvolysis of exo-6-(1',2'-ditrichloroacetoxyheptanyl)-bicyclo[3.1.0]hexan-3-one (LVI).

Solvent	Temperature	Time	% Rearrangement*
Cl_3CCO_2H	60-65°C	5 min.	NONE
		30 min.	
		19 hours	
	80°C	45 min.	NONE
		1.5 hours	
		13 hours	
		15 hours	
	140°C	15 hours	NONE
Cl_3CCO_2H/pTSA	60°C	12.5 hours	NONE
dioxane/Cl_3CCO_2H 1:1	reflux	12 hours	NONE
NONE	230°C	8 min.	4% + decomposition
	120-140°C	1 hour	NONE
acetone/H_2O	reflux	4 days	2%

*Percent rearrangement was determined from the extinction of the λ_{max} 268 mμ in the ultraviolet spectrum after the base treatment.



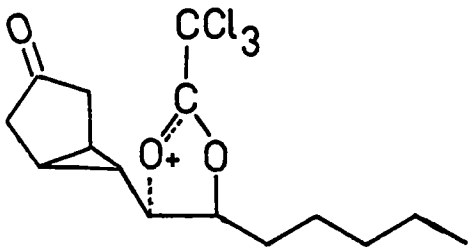
LVIII LVIX

(the solution having been boiled for four days), 65% of the recovered reaction mixture consisted of the starting ditrichloroacetate. The remainder consisted of glycol LV and about 2% homoallylic diol LVII.

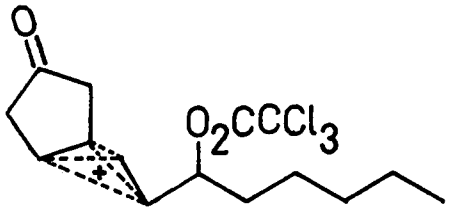
The reason for the failure of this reaction is not clear. Two possible explanations are the following:

1) The reaction might be very slow. No extensive data on the reactivity of trichloroacetates, or the solvolysing ability of trichloroacetic acid have been reported.

2) The neighbouring trichloroacetate group may stabilize the incipient carbonium ion to such an extent that participation by the cyclopropyl group is greatly reduced so that the transition state looks more like LXa than LXb.



LXa



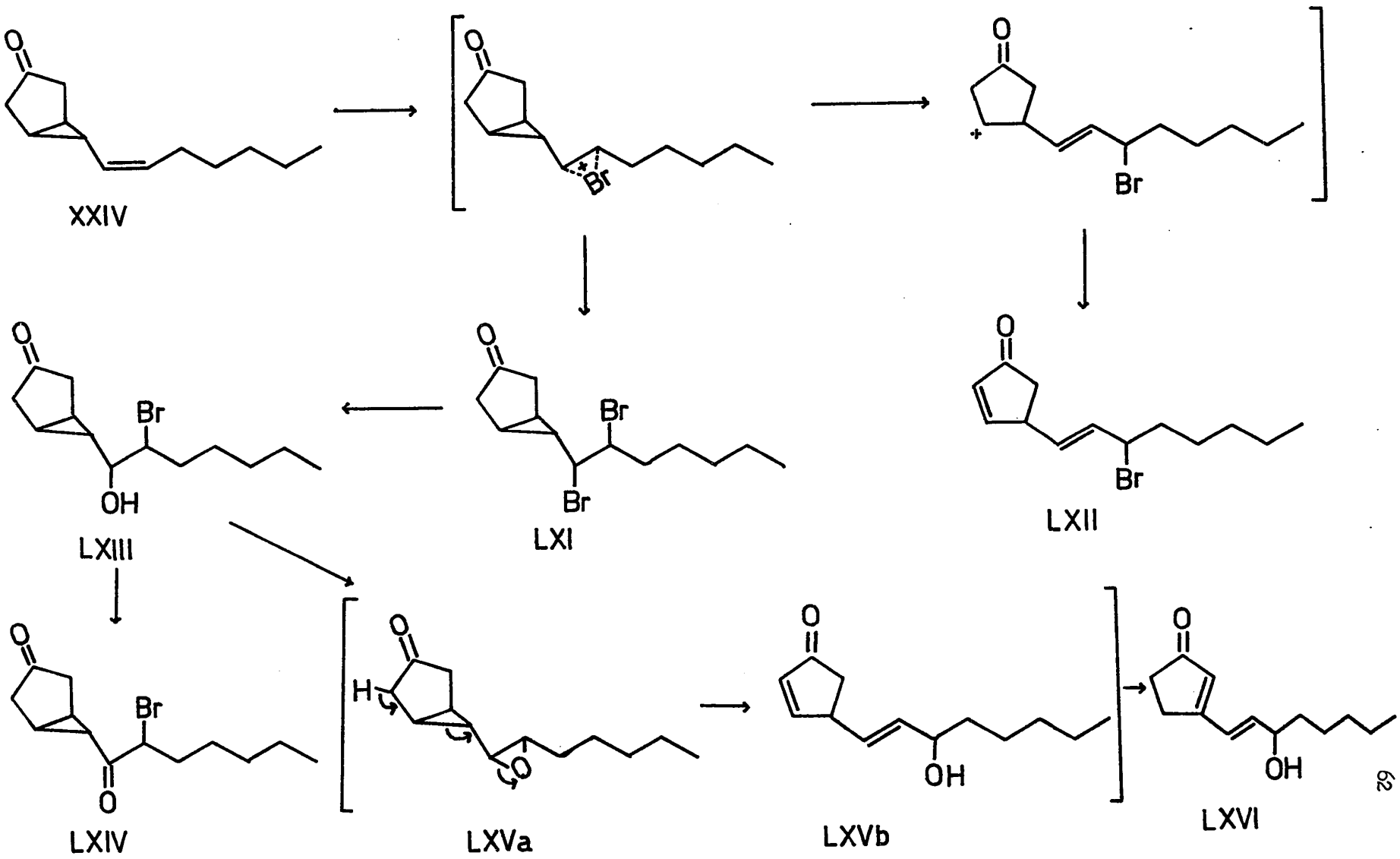
LXb

Next, it was decided to investigate the solvolysis of the dibromide LXI (Scheme XII). This compound should react in a manner similar to the dimesylate LII[22] but can be prepared from the olefinic ketone XXIV in one rather than the two steps required for the dimesylate.

The dibromide LXI was prepared by treating XXIV with pyridinium hydrobromide perbromide[71] in anhydrous chloroform at room temperature. Two products were obtained. The major (55% yield) desired dibromide was separated with much difficulty by column chromatography from a minor product. This minor product could not be completely separated from the dibromide. However, the infrared spectrum of the mixture showed bands at 1720 and 1630 cm^{-1} which suggested an α,β unsaturated, five-membered ring ketone. Such a compound would be formed if, during the bromination reaction, rearrangement occurred as well. Since the reaction was done under slightly acidic conditions in an aprotic solvent, elimination might occur to give the α,β unsaturated ketone LXII as shown in Scheme XII.

The dibromide LXI was solvolyzed in aqueous acetone at room temperature. The reaction was followed by TLC on silica gel (benzene-ether 7:3). After 62 hours two spots different from the dibromide (R_f 0.86) were observed. The first (R_f 0.39) was much more intense than the second spot (R_f 0.05). The compounds were separated by preparative TLC after solvolysing for 112 hours. The compounds recovered from the reaction mixture consisted of the dibromide LXI (63%), the unrearranged

Scheme XII



bromohydrin LXIII (15%), (M^+ 289, 291; m/e 210, $M^+-{}^{79}Br$, ^{81}Br) and a slow moving fraction (5%) which was found to be a mixture of four compounds. The low R_f value of this mixture suggested that it consisted of diols. Probably the mixture contained some rearranged product, but there was not enough material available to characterize it properly.

It was at first thought that rearrangement had occurred because when the crude product was treated with 0.5% sodium hydroxide in methanol at 50°, a compound was obtained that gave the correct ultraviolet absorption for LXVI (λ_{max}^{MeOH} 268 mμ, ε 8,500). It was subsequently found that LXVI had indeed formed, but via the epoxide LXVa, which in turn, was formed from the bromohydrin LXIII. It has been shown[20], that under these basic conditions the epoxide LXVa will rearrange to LXVb. With further base treatment, LXVb isomerizes to the completely conjugate ketone LXVI.

The structure of the bromohydrin LXIII was proven by synthesizing it directly from XXIV using N-bromosuccinimide[80]. Oxidation of LXIII with Jones reagent at 0° gave LXIV in good yield (ν_{max} 1748, 1700 cm^{-1} [81] 4.27 ppm, 1H, triplet, J = 6.5 cps.)

The dibromide solvolysis was much slower than that of the dimesylate but faster than that of the ditrichloroacetate. This order of reactivity of the leaving groups is the expected one[59].

Since the generation of a "normal" carbonium ion gave products of rearrangement in less than 20% yield, it was decided to try to generate a "hot" carbonium ion, LXIX, by nitrous acid deamination of the amine[82] LXVIII (Scheme XIII).

Addition of iodine isocyanate[60] to the olefin XXIV gave the iodo isocyanate LXVII in good yield. The mode of addition follows from subsequent reactions. The isocyanate was hydrolyzed to the amine LXVIII in aqueous acetone. This was not isolated but treated, in situ, with formic acid and sodium nitrite at -4°. After one hour at this temperature and 3.5 hours at 25°, the only compound isolated was the unrearranged iodohydrin LXX (M^+ 336; m/e 209, M^+-I). If any rearrangement did occur, it was to an extent of less than 10%, and certainly no higher than in the dimesylate solvolysis.

The structure of the iodohydrin LXX was proven by its n.m.r. spectrum which showed no olefinic proton resonance in the δ 6.0-5.5 ppm region. Its Jones oxidation product LXXI showed a low field triplet at 4.48 ppm, J = 4.0 cps (100 MC n.m.r.) as in the case of the bromoketone LXIV.

Considerable work has been done to study the cyclopropylcarbinyl solvolysis and to understand the nature of the carbonium ion which was involved.[55] Although rate enhancement of the solvolysis due to the participation of the cyclopropyl group adjacent to the leaving group has been widely demonstrated[19,61,50,51,52]*, the exact nature of the carbonium ion is controversial[55,57,62] and the extent of rearrangement in various cyclopropylcarbinyl systems under similar solvolytic conditions is quite unpredictable[19,56,67,63].

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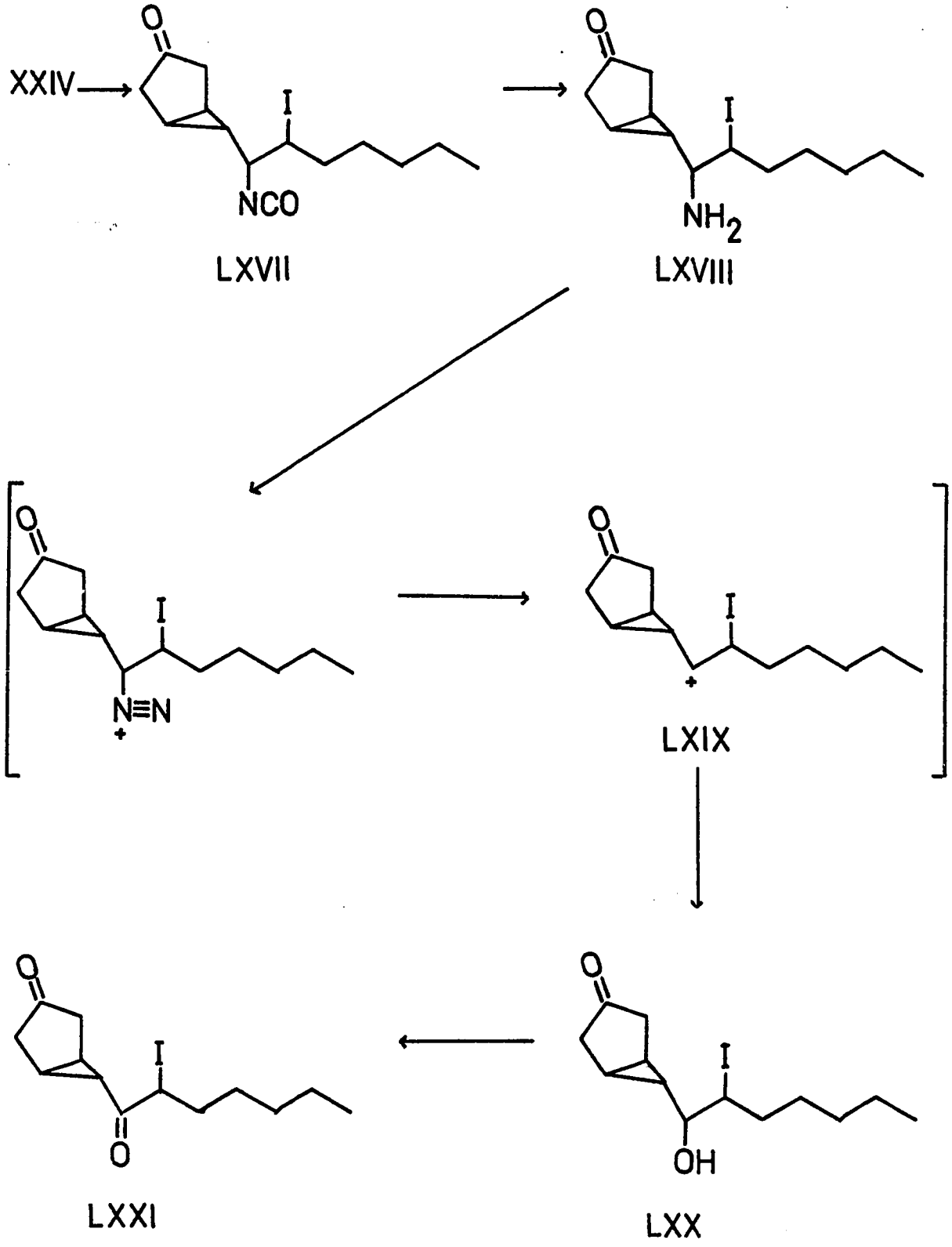
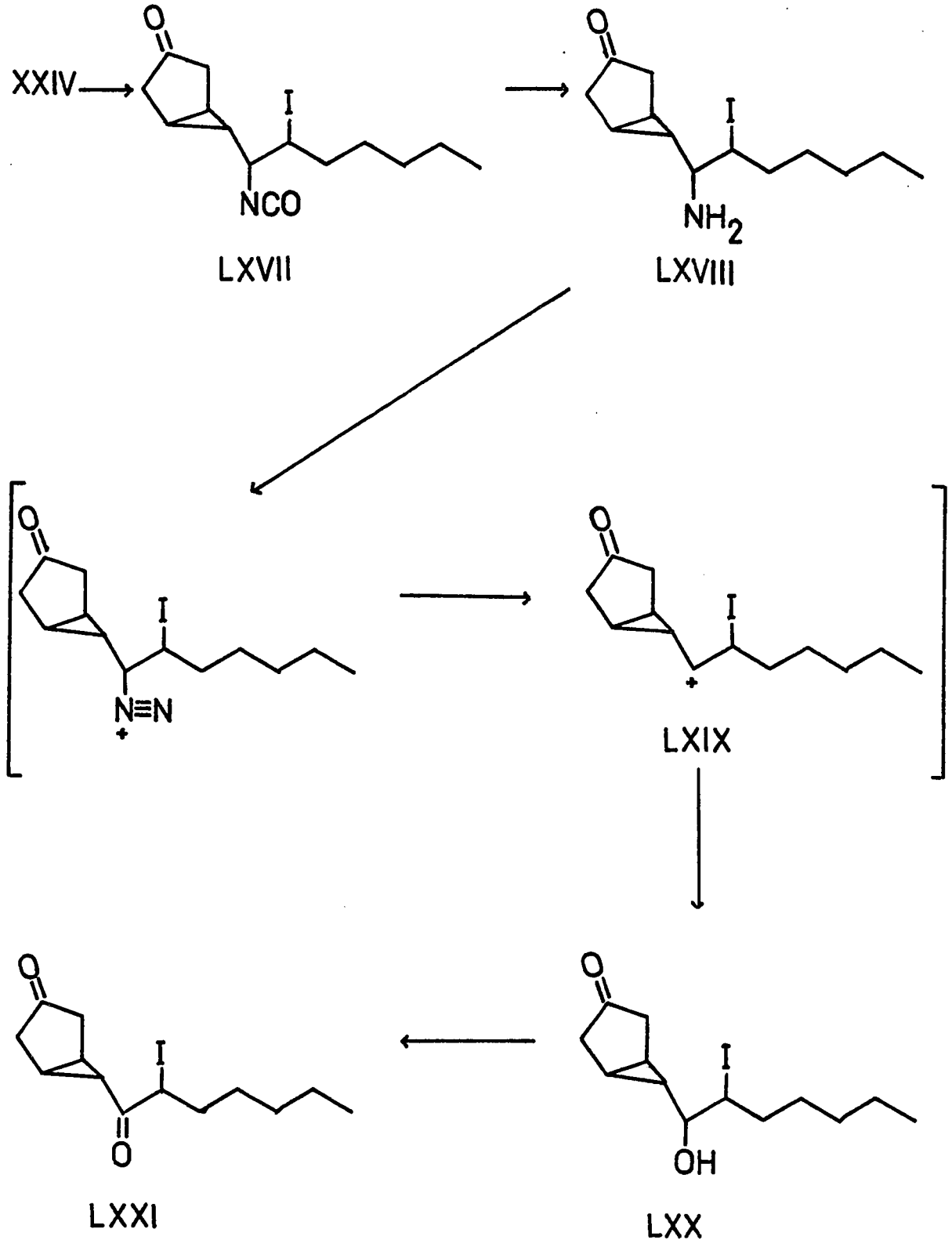
* The solvolysis results obtained in this work also support this conclusion. The leaving group adjacent to the cyclopropyl ring in the dibromide LXI and iodo amine LXVIII deamination was solvolyzed much faster than the other one. In the case of the iodohydrin LXX, the iodide could not be solvolyzed to the diol when refluxed in aqueous acetone for 24 hours.

Scheme XIII



Scheme XIII



The reason for the limited rearrangement in the bicyclic system discussed in this chapter may depend on a number of factors. The most probable explanation (which was previously discussed) is the participation of the neighbouring group with the formation of the carbonium ion of type LXa which minimizes the effect of the cyclopropyl group. Each of the neighbouring groups (bromine, trichloroacetate, mesylate, iodine) was able, in principle, to participate in such a way. However, the higher rate of solvolysis of the group next to cyclopropyl ring suggests some participation by it. Therefore other factors must also influence the extent of rearrangement. The stereochemical arrangement of the leaving groups to the migrating bond[19,65] and the amount of ring strain in the transition state caused by bond breaking and rearranging[63,64,65] have been found to greatly influence the type of products obtained in a solvolysis. In the solvolysis reactions discussed above, only the exo-bicyclic ketone XXIV was used, based on the results of Wiberg and Ashe[19]. However the compounds studied by this group are quite different from XXIV and more favorable results might be obtained if the configuration of XXIV were endo.

Since the solvolysis of the dimesylate in aqueous acetone gave best yields of rearranged compounds of the systems that were investigated, and since the by-product of the reaction, the hydroxy mesylate, could be recycled this seemed to be the best system to use for the final steps in the PGE_2 methyl ester synthesis (Scheme XIV).

6-Exo-(1'-heptenyl)-2$\alpha$and β-(6''-carbomethoxy-2-hexynyl) bicyclo[3.1.0]hexan-3-one (XXV) obtained from the alkylation reaction

described in Chapter I, was reacted in buffered formic acid with 30% hydrogen peroxide[89]. The resulting hydroxy formate was hydrolysed with sodium carbonate in aqueous methanol, to give the diol LXXIIa in 87% yield (M^+ 364, m/e 263 vicinal diol cleavage). Since both the cis and trans olefins were present in XXV, the diol consisted of a mixture of erythro and threo isomers[21].

The diol was then treated with an excess of methanesulfonyl chloride in anhydrous pyridine at -10°C. The reaction was worked up in the cold and gave the corresponding dimesylate LXXIIb in 78-85% yields. The n.m.r. spectrum of the crude dimesylate, which consisted of eight isomers (threo and erythro configurations for each cis and trans orientation of the ring substituents) showed four peaks due to the methyl protons of the mesylate groups (189.8, 189.1, 188.0, 187.2 cps). TLC on silica gel (benzene-ethyl acetate 1:1) of the crude dimesylate, however, showed only one spot.

The solvolysis of the dimesylate was carried out in acetone-water (2:1) at room temperature (22-25°) for 36 hours in a nitrogen atmosphere. The reaction was followed by TLC on silica gel (benzene-ethyl acetate 1:1) and was found to be more than 95% complete after this time. The products had less mobility than the dimesylate on silica gel in either benzene-ethyl acetate 1:1 or ethyl acetate, and were clearly separable from the starting material. Using ethyl acetate as the solvent system, the mixture was found to consist of five components. The two major products (R_f 0.62 and 0.48) were hydroxy mesylates LXIII, where eight isomers would be expected as in the case of the starting dimesylate. A minor product (R_f 0.37) was also hydroxy mesylate but it

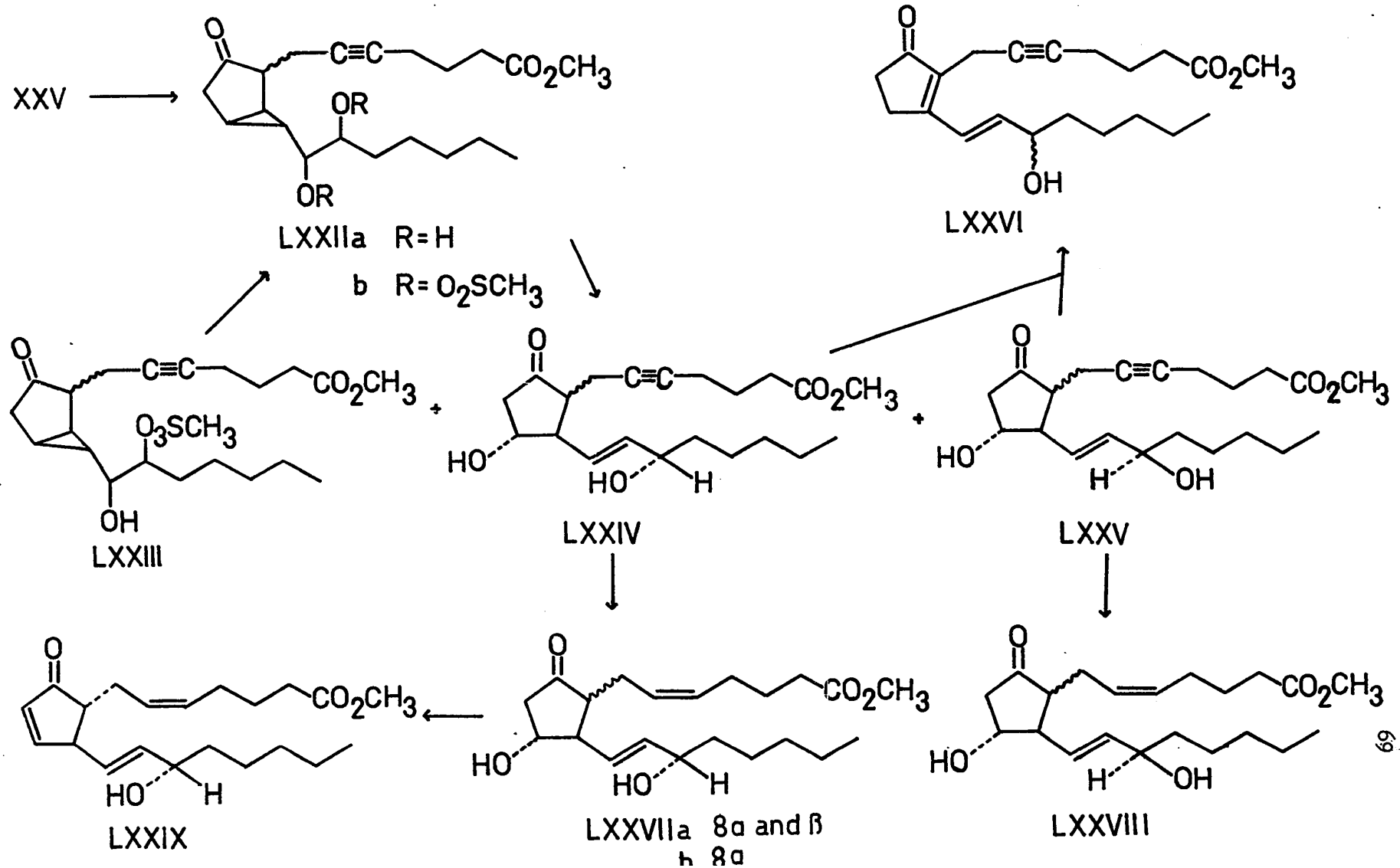
was never obtained pure for proper characterization. The two other bands (R_f 0.29 , 0.19) were identified as 15-epi-5-dihydro PGE_2 (LXXV) and 5-dehydro PGE_2 (LXXIV) methyl esters respectively. Each epimer consisted of a mixture of 8-α and β isomers. A small amount (1-2%) of dimesylate was also recovered.

The yield of the recovered hydroxy mesylates based on the starting dimesylate was 70-80%. The 100 MC n.m.r. spectrum of each of the major products was identical. Each compound exhibited two sharp peaks at 310.0 and 307.9 cps assigned to the methyl protons of the mesylate. When two major hydroxy mesylates, R_f 0.62 and 0.48, were remesylated and solvolyzed independently, the same mixture of products as described above, was obtained.

The two epimeric prostaglandins LXXIV and LXXV were obtained in 11-16% yield from the dimesylate. The slower moving epimer LXXIV was found to have the same R_f value on silica gel as PGE_2 methyl ester using ethyl acetate as the solvent system. On 10% silver nitrate impregnated silica gel, the PGE_2 methyl ester had lower mobility than LXXIV and LXXV, which virtually moved together in both the MIII and AIX solvent systems[90]. Also, it was found that LXXIV was more active than LXXV in a bioassay on a smooth muscle (Table IV). The PG with natural configuration at C-15 is known to be more active than its 15-epimer.[93] Therefore LXXIV was postulated to have the natural and LXXV the unnatural configuration at C-15.

Spectroscopic data were consistent with the prostaglandin structure for both LXXIV and LXXV. The mass spectrum of both compounds was identical except for small differences in intensities of some peaks.

Scheme XIV

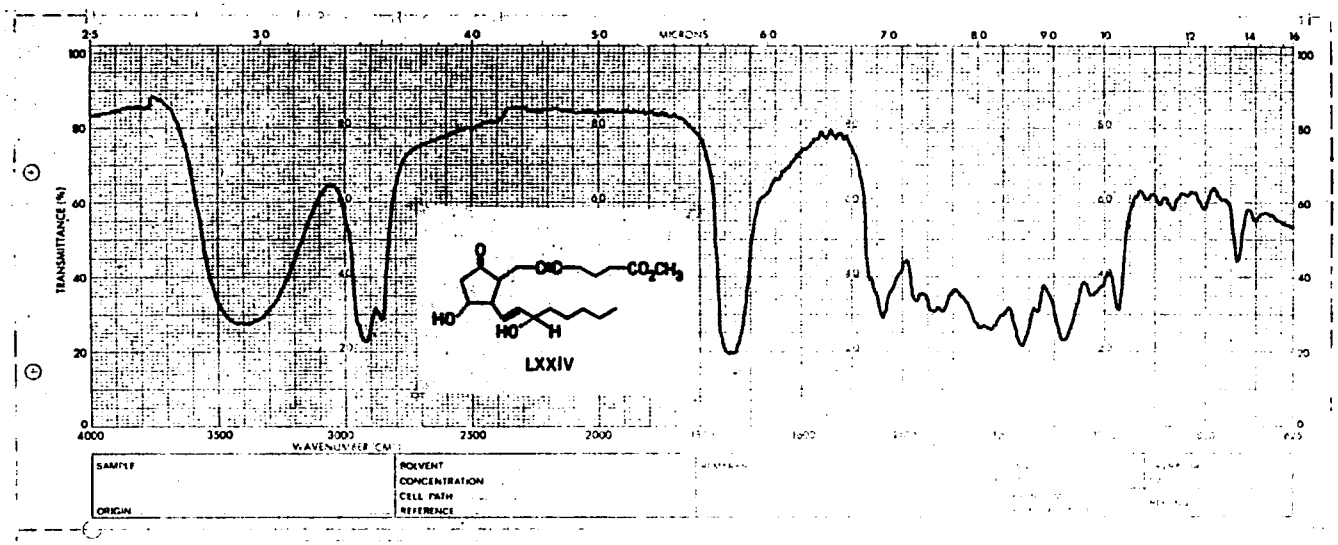

XXV
LXXIIa R=H
b R=O2SCH3
LXXVI
LXXIII
LXXIV
LXXV
LXXIX
LXXVIIa 8α and ß
b 8α
LXXVIII

The fragmentation pattern was consistent with the structure and some of the more important fragments are listed in Table III. The 100 MC n.m.r. spectrum of LXXIV and LXXV was consistent with the structure (δ 5.9-5.2 ppm, 2H, multiplet, $\underline{H}C=C\underline{H}$; 4.1 ppm, 2H, multiplet, $C\underline{H}-O$; 3.68, 3H, singlet, $OC\underline{H}_3$). The spectrum of the two epimers differed slightly in the chemical shift of the olefinic proton multiplet and the protons to the hydroxy group. In the 15-epi-5-dihydro PGE_2 methyl ester (LXXV) these protons absorbed at slightly lower field (2-3 cps) than in 5-dehydro-PGE_2 methyl ester (LXXIV). The infrared spectrum was identical for the two compounds and consistent for a compound having two hydroxy groups, a methyl ester and five-membered ring ketone (ν_{max} 3400, 1740, 1163, 1080 cm^{-1}). The infrared spectrum of PGE_2 methyl ester obtained from natural PGE_2 differed only slightly in the finger print region from that of the 5-dehydro-PGE_2.

A small amount of the mixture of LXXIV and LXXV was treated with 0.5% sodium hydroxide in methanol at 38-48° for 1.5 hours. The ultraviolet spectrum of the reaction mixture was taken in methanol at various times as the reaction progressed. After 5 minutes at 38° ϵ_{275} was 18,000. This rose to 28,300 after 1.5 hours. The compound formed was 5-dehydro-PGB_2 methyl ester (LXXVI) confirming that LXXIV and LXXV were PGE like material. When the solution was further heated or if the reaction was carried out in refluxing methanol (66°) even for short times (15 to 20 minutes), the chromophore was found to disappear. Presumably LXXVI decomposes under these more vigorous conditions.

In an attempt to get the pure 5-dehydro-PGE_2 methyl ester

Figure XI: Ir(film) and 100 MC n.m.r.($CDCl_3$) spectra of 8α and β - 5-dehydro-PGE_2 methyl ester (LXXIV).


TRANSMITTANCE (%)
MICRONS
WAVENUMBER CM
SAMPLE
ORIGIN
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
LXXIV

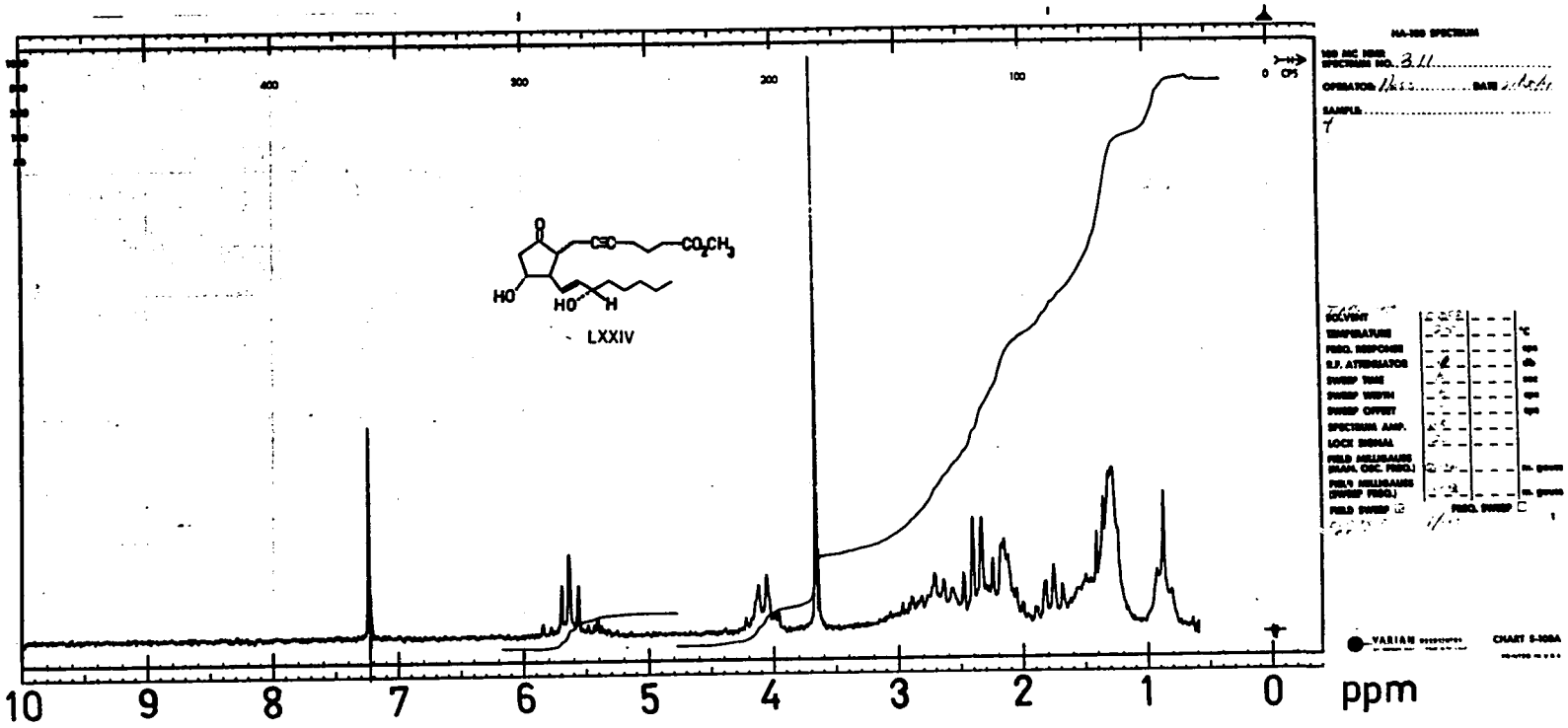
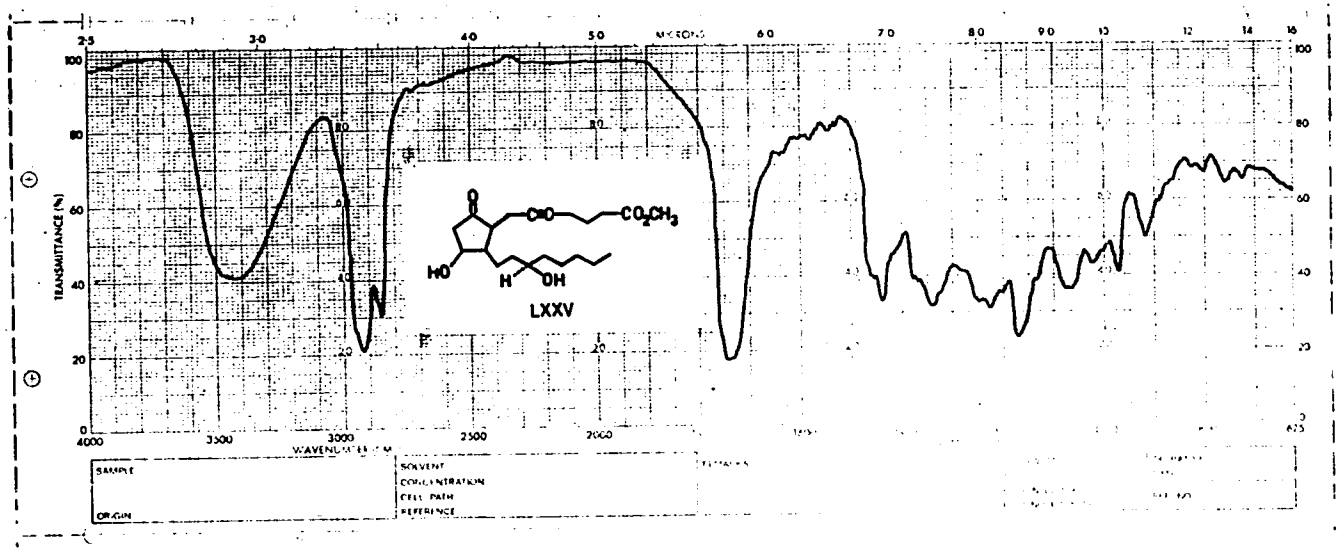

LXXIV
10
9
8
7
6
5
4
3
2
1
0
ppm

Figure XII: Ir(film) and 100 MC n.m.r.($CDCl_3$) spectra of 8α and β-15-epi-5-dehydro PGE_2 methyl ester (LXXV).


TRANSMITTANCE (%)
WAVENUMBERS (cm⁻¹)
MICRONS
SAMPLE
ORIGIN
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

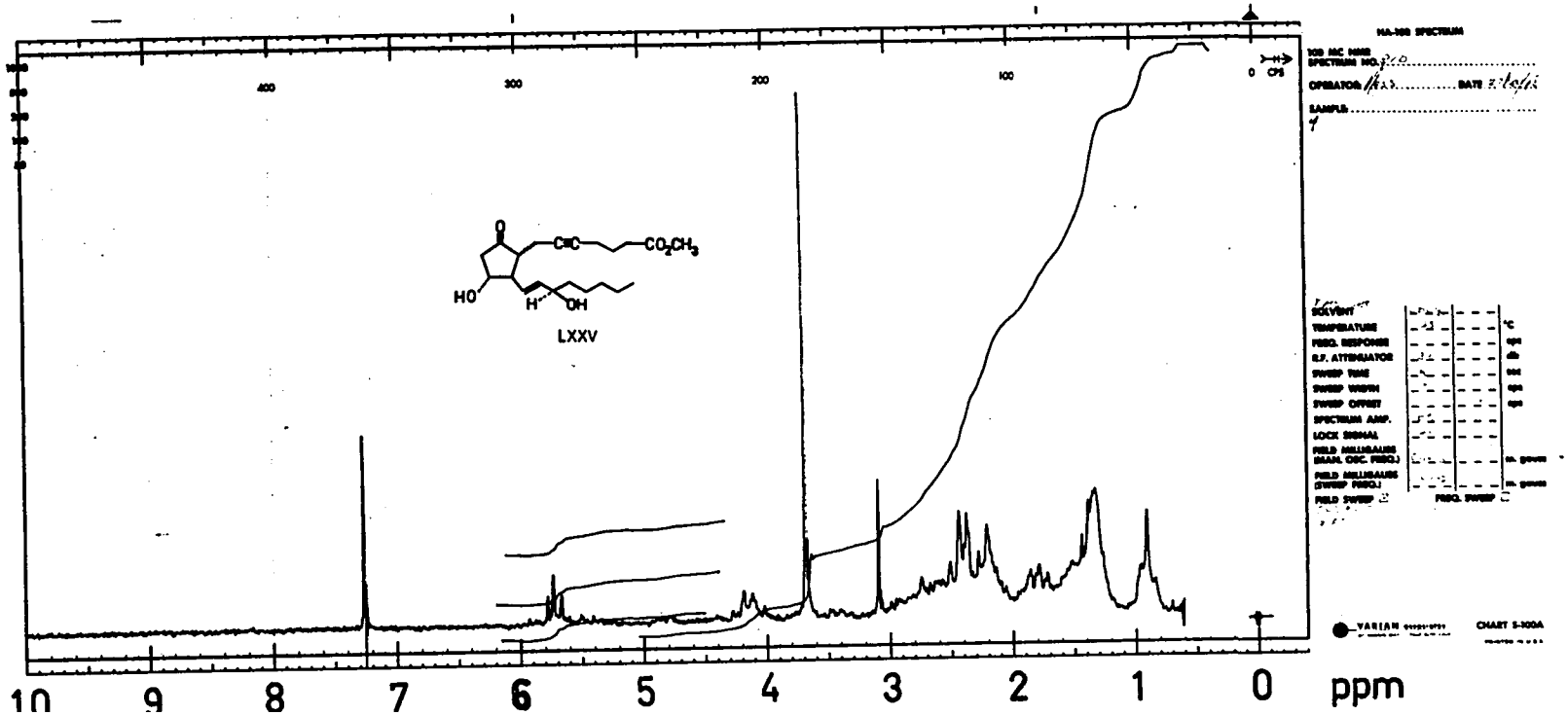
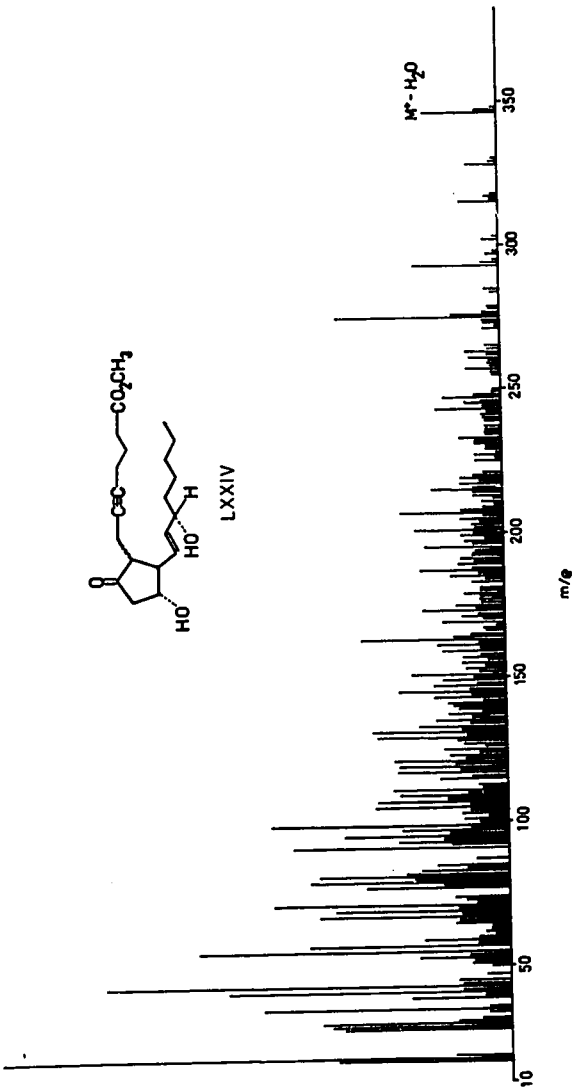

HA-100 SPECTRUM
SOLVENT
TEMPERATURE
FREQ. RESPONSE
R.F. ATTENUATOR
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
LOCK SIGNAL
FIELD MILLIGAUSS
FIELD SWEEP
FREQ. SWEEP
VARIAN
CHART S-100A
10 9 8 7 6 5 4 3 2 1 0 ppm

Figure XIII: Mass spectra of 8α and β-5-dehydro-PGE_2 methyl ester (LXXIV) and 8α and β-15-epi-5-dehydro-PGE_2 methyl ester (LXXV).


LXXIV
M⁺ - H₂O
m/e

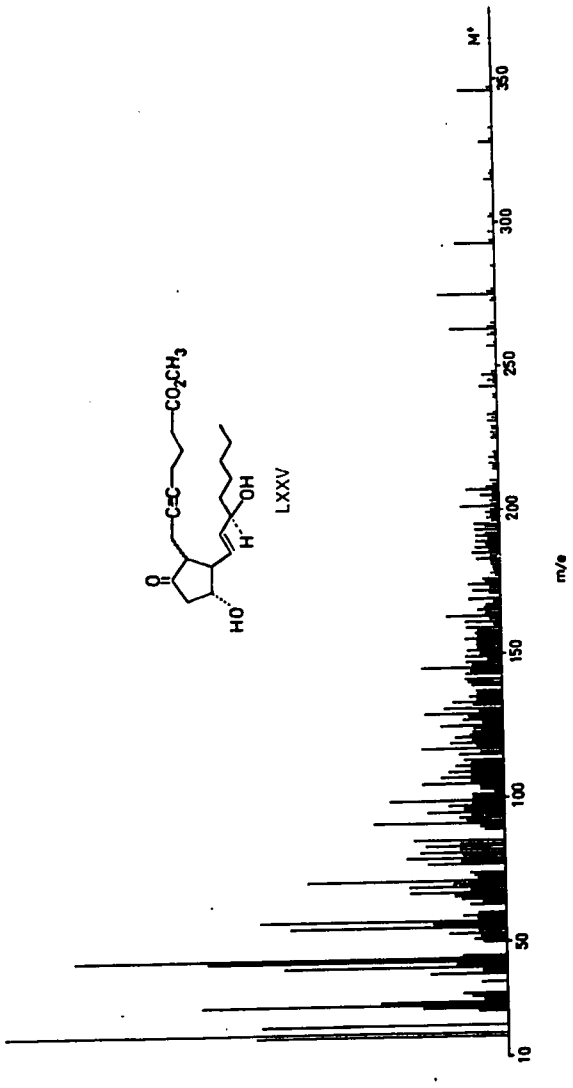

LXXV
M⁺
m/e

TABLE III

Interpretation of the major fragments of 5-dehydro-PGE_2 methyl esters LXXIV and LXXV, and PGE_2 methyl esters LXXVII and LXXVIII

Compound	m/e	Fragment
5-dehydro-PGE_2 methyl esters (LXXIV) and (LXXV)	346	M^+-H_2O
	328	M^+-2H_2O
	315	m/e $346-OCH_3$
	297	m/e $328-OCH_3$
	285	m/e $328-C_3H_7$
	293	$M^+-C_5H_{11}$
	275	m/e $346-C_5H_{11}$
	317	m/e $346-HC\equiv O$
	207	m/e $346-C_8H_{11}O_2$
PGE_2 methyl esters (LXXVII) and (LXXVIII)	348	M^+-H_2O
	330	M^+-2H_2O
	317	m/e $348 - OCH_3$
	316	m/e $348 - HOCH_3$
	299	m/e $330 - OCH_3$
	298	m/e $330 - HOCH_3$
	299	$M^+ - C_5H_{11}$
	277	m/e $348 - C_5H_{11}$
	208	m/e $348 - C_8H_{12}O_2$
	190	m/e $208 - H_2O$

(uncontaminated with the 8-isoepimer), the isomeric mixture LXXIV was treated with 5% sodium acetate in methanol for seven days at room temperature. This was too long a time since an appreciable amount of 5-dehydro-PGB_2 methyl ester (LXXVI) had formed and the 5-dehydro-PGE_2 could not be obtained pure from the reaction mixture. However, this impure product was submitted for bioassay along with the isomeric mixtures of LXXIV and LXXV.

The bioassay was done in vitro on a strip of isolated smooth muscle, rat stomach fundus, using natural PGE_1 as the reference. This did not give a quantitative measure of the 5-dehydro-PGE_2 methyl ester activity. However, a qualitative measure and relative activity was obtained. It was found that the activity of the synthetic, acetylenic prostaglandins was less than that of PGE_1. The pattern of relative activity, which has been observed for other prostaglandins[93], was also noted in this series. That is, the unnatural, 15-epi LXXV was found to be considerably less active than the natural C-15 isomer, LXXIV. Also, isomerization of LXXIV increased its activity suggesting that the natural isomer at C-8, which should predominate under the reaction conditions[70], was more active than the 8-iso epimer. The results are summarized in Table IV.

The final step in the synthesis of PGE_2 methyl ester was the reduction of the acetylenic bond to a cis double bond. This was achieved by catalytic hydrogenation using Lindlar catalyst poisoned with quinoline[85]. The reaction, however, was very sluggish with the prostaglandins (simple acetylenic compounds such as phenyl acetylene were easily reduced) and the reaction was incomplete even when it was

allowed to continue for 24 hours. (The reaction should be complete in 10 to 90 minutes[85].) It was found that when the catalyst was poisoned with only 1-3% quinoline* (by weight), the reaction was complete and 8α and β-PGE_2 methyl ester(LXXVIIa) was isolated in 63% yield. The 15-epi-5-dehydro-PGE_2 methyl ester was hydrogenated in the same way to LXXVIII.

The 15-epi PGE_2 methyl ester (LXXVIII) was characterized by its mass spectrum. The fragmentation was the same as for the PGE_2 methyl ester obtained by Bergstrom et al[91]. The interpretation of the major peaks is given in Table III. Exact mass measurement of m/e 348 was correct for $C_{21}H_{32}O_4$ (Calcd 348.230045; Found: 348.229694). The fragment m/e 190 was particularly characteristic of PGE_2 methyl ester since it was one of the most abundant fragments. Exact mass measurement was consistent with an empirical formula $C_{13}H_{20}O_2$ (Calcd. 190.135758; Found, 190.135990) or the loss of the ester side chain with hydrogen transfer and loss of water from $C_{21}H_{32}O_4$. The fragmentation could have occurred by one of two ways: 1) side chain cleavage followed by hydrogen capture or 2) a concerted hydrogen transfer involving an eight-membered ring. Since such a fragmentation was not found in the 5-dehydro-PGE_2 methyl ester and since m/e 190 was a very abundant fragment, the hydrogen capture mechanism was ruled out. The proposed fragmentation scheme is given below.

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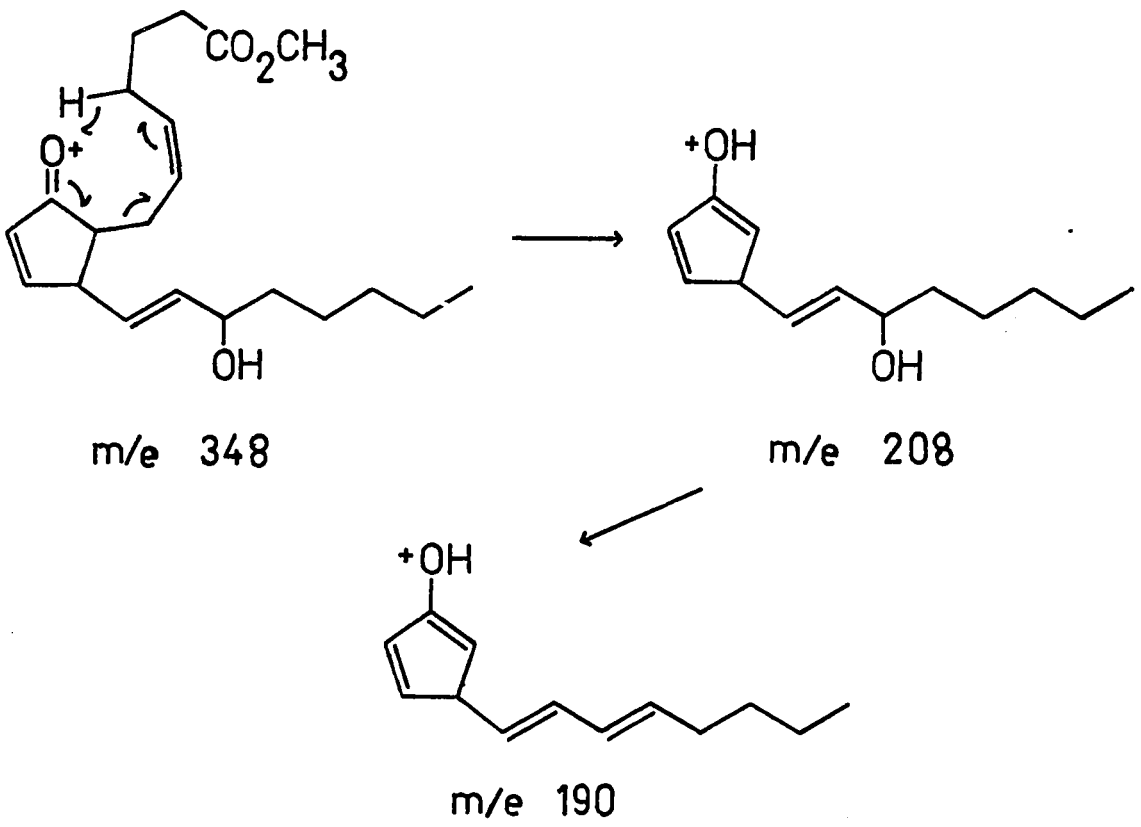
* The original procedure[85] uses 5% or more quinoline.



TLC comparison of mobilities of synthetic PGE_2 methyl ester and its C-15 epimer with the methyl ester of natural PGE_2 on silica gel (ethyl acetate) and 10% silver nitrate impregnated silica gel (MIII) confirmed the stereochemical assignment of LXXVIIa and LXXVIII at C-15 (Table V).

The mixture of 8α and β-PGE_2 methyl ester was treated with 3% ethanolic potassium acetate solution for 94 hours at 22°. The resulting reaction mixture consisted of mainly 8α-PGE_2 methyl ester LXXVIIb(80%), 8α-PGA_2 methyl ester (LXXIX) (18%) (λ_{max} 217 mμ, ϵ 9,000; M^+ 348) and PGB_2 methyl ester (2%) (λ_{max} 277 mμ). The stereochemical assignment at C-8 was made on the basis of the bioassay

Table IV

Results of the bioassay of: A. the synthetic 5-dehydro PGE_2 methyl ester for smooth muscle stimulating activity using the rat stomach fundus*, B. the synthetic PGE_2 methyl esters for smooth muscle stimulating activity using gerbil colon‡.

Compounds tested	Weight ($\times 10^{-9}$g) of material required for equivalent contraction	Potency
A. Natural PGE_1	20	1.0
8α and β-15-epi-5-dehydro PGE_2 methyl ester(LXXV)	720	0.028
8α and β-5-dehydro methyl ester (LXXIV)	192	0.10
Epimerized LXXIV	160	0.13
Mixture of LXXIV and LXXV	256	0.078
B. 8α and β-15-epi PGE_2 methyl ester(LXXVIII)		0.21
8α PGE_2 methyl ester (LXXVIIb)		3.38

*Bioassay carried out by Dr. L. Wolfe, Montreal Neurological Institute, Montreal, Canada.

‡Bioassay carried out by Dr. J.R. Weeks, The Upjohn Company, Kalamazoo, Michigan.

on the smooth muscle, gerbil colon[94] (Table IV) and by analogy to the results of the epimerization of 8-iso-PGE_1[70].

The isomerization product LXXVIIb was found to be of very high biological activity, and in the expected order of potency[93]. Although PGE_1 and PGE_2 activity has not been compared on gerbil colon, it was estimated[93] that PGE_2 would be several fold more potent. On the rabbit duodenum, the activity of PGE_2 was about three fold PGE_1 and they were about equal on guinea-pig ileum[95]. Further, in tests on other prostaglandins, it has not been found that esterification with methyl has any great effect on activity in isolated muscle baths.

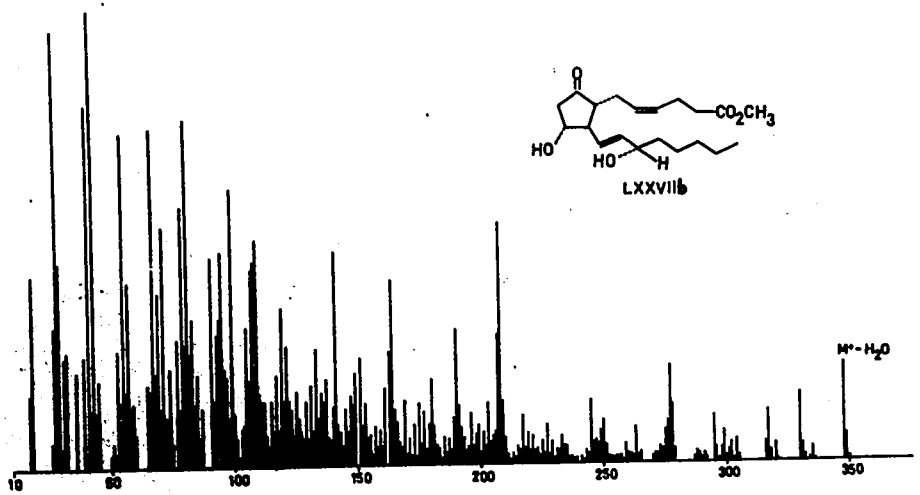
TABLE V

R_f values on silica gel

	10% $AgNO_3$/MIII	Ethyl acetate
PGE_2 methyl ester from natural PGE_2	0.31	0.27
PGE_2 methyl ester LXXVIIb	0.31	0.27
15-epi-PGE_2 methyl ester LXXVIII	0.32	0.35
5-dehydro-PGE_2 methyl ester LXXIV	0.39	0.27

The n.m.r. (100 MC) spectrum of LXXVIIb was consistent with the structure. The spectrum was the same as that for 5-dehydro PGE_2 methyl ester (LXXIV) except that a second multiplet appeared in the

Figure XIV: 100 MC n.m.r.($CDCl_3$) and mass spectra of synthetic PGE_2 methyl ester (LXXVIIb).


HO
HO
H
CO_2CH_3
LXXVIIb
$M^+ - H_2O$
10
50
100
150
200
250
300
350

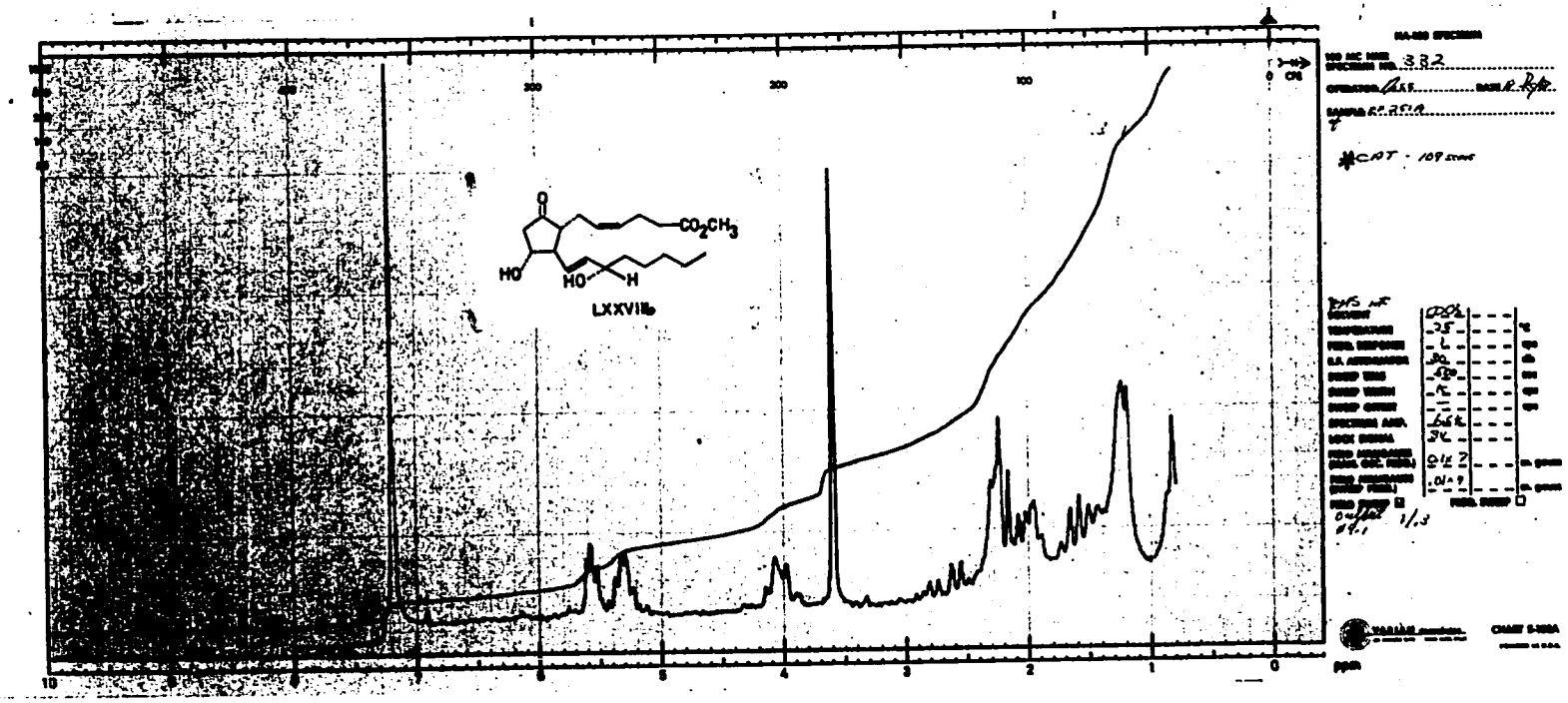
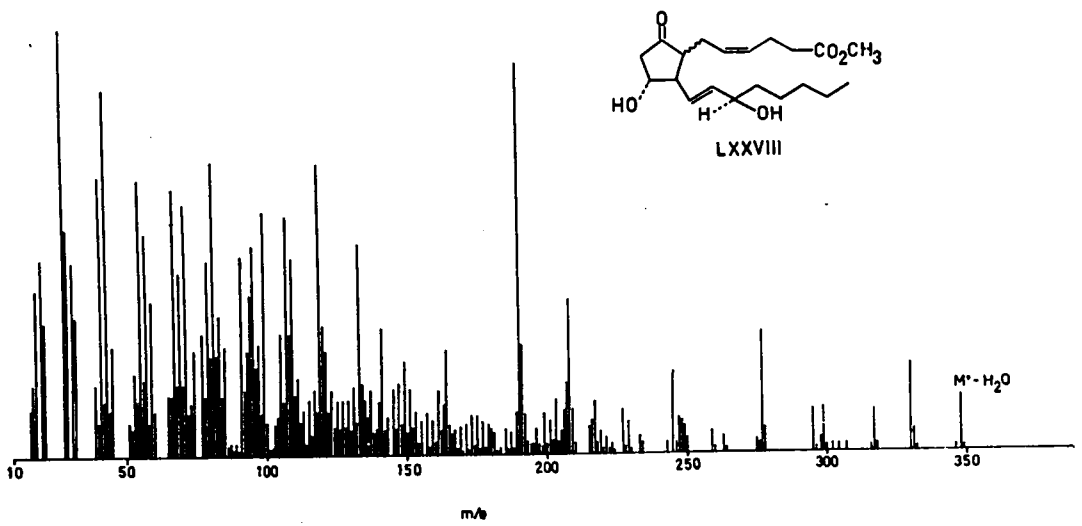
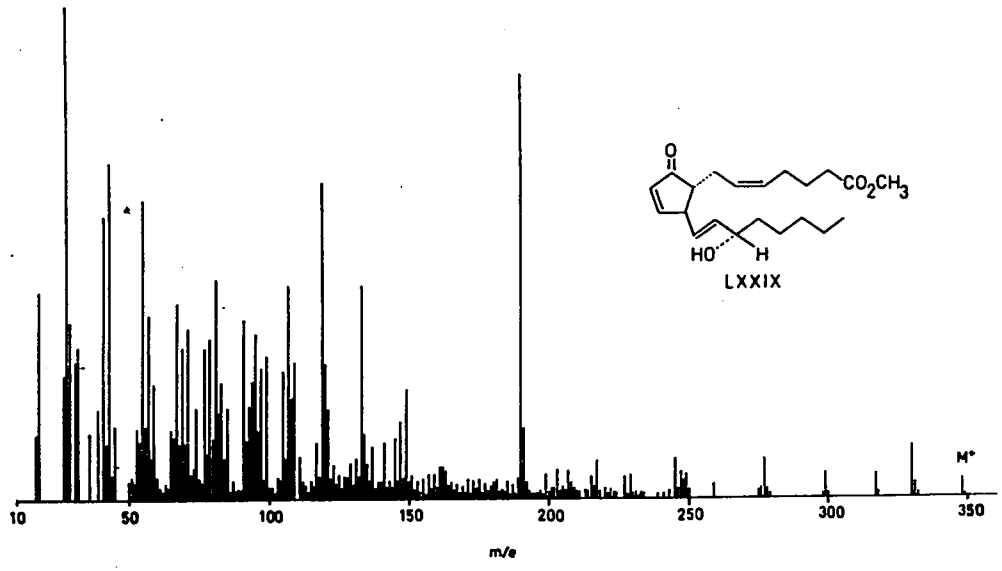

HO
HO
H
CO_2CH_3
LXXVIIb
10
9
8
7
6
5
4
3
2
1
0
ppm

Figure XV: Mass spectra of 8α and β-15-epi-PGE_2 methyl ester LXXVIII and 8α-PGA_2 methyl ester LXXIX.


O
CO_2CH_3
HO
H
OH
LXXVIII
$M^+ - H_2O$
10
50
100
150
200
250
300
350
m/e


O
CO_2CH_3
HO
H
LXXIX
M^+
10
50
100
150
200
250
300
350
m/e

olefinic proton region (δ 5.4 ppm) which integrated for two protons. The olefin, α-hydroxy and ester methoxy protons were found to be in the correct ratio (4:2:3) for PGE_2 methyl ester.

The infrared spectrum of LXXVIIIb was identical with that of the natural PGE_2 methyl ester.

The mass spectrum of LXXVIIb was identical with that of LXXVIII and the natural PGE_2 methyl ester except for the intensities of the fragments m/e 190 and 208. In the case of LXXVIIb the m/e 208 fragment was consistently more abundant than the m/e 190 fragment. Although when the spectrum was taken at 155° and the probe was kept in the source for 40 minutes, the relative abundance of the two masses changed and became nearly the same. In the spectrum of natural PGE_2 methyl ester taken on the same mass spectrometer at 160° gave a more abundant m/e 190 mass, the m/e 208 fragment being about 62% as abundant. On the other hand, in the mass spectrum reported by Bergstrom et al.[91], the m/e 208 fragment was only 13% as abundant as m/e 190. In the spectrum of PGA_2 methyl ester also taken at 160°, m/e 190 was again found to be very abundant, while the relative intensity of m/e 208 was only 2% of the m/e 190 fragment. The reason for this variation in relative intensities of the m/e 190 and 208 fragments was not understood. From the rest of the fragmentation pattern, other spectral data, mobility on TLC and results of the bioassay, it was clear that PGE_2 methyl ester had been obtained.

EXPERIMENTAL

CHAPTER I

1-Tetrahydropyranyloxy-2-propyne (XIIb). The ether XIIb was prepared according to the procedure of H.B. Henbest et al.[66].

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63

Found : C, 68.40; H, 8.77

6-Chloro-2-hexyn-1-ol (XIIIa). The chloro alcohol XIIIa was prepared according to the procedure of M. Duchon D'Engenieres et al.[31]

Anal. Calcd. for C_6H_9OCl: C, 54.11; H, 6.79; Cl, 26.79

Found: C, 54.39; H, 6.75; Cl, 26.09

The by-product XXVI isolated[25] from the reaction mixture was assigned this structure on the basis of the following spectral and analytical data: i.r.(CCl_4) 3070 cm^{-1}(=CH) 2230 cm^{-1}(C≡C), 1650 cm^{-1}(C=C), 1085 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 6.5-5.5 (m,3H, $H_2C{=}CH$), 4.03 (t, 2H, J = 2.0 cps, $OCH_2C{\equiv}$), 3.9 (m, 2H, $=CCH_2O$), 3.62 (t, 2H, J = 6.0 cps, CH_2Cl), 2.6-1.8 (m, 4H, $\equiv CCH_2CH_2$).*

Anal. Calcd. for $C_9H_{13}OCl$: C, 62.61; H, 7.54

Found : C, 63.21; H, 7.55

1-Tetrahydropyranyloxy-6-chloro-2-hexyne (XIIIb). This was prepared according to the procedure of M. Duchon D'Engenieres et al.[31]

Anal. Calcd. for $C_{11}H_{17}O_2Cl$: C, 60.93; H, 7.91; Cl, 16.39

Found: C, 61.08; H, 7.76; Cl, 16.31

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* In n.m.r. descriptions, s = singlet, d = doublet, t = triplet, qu = quartet, q = quintet, m = multiplet.

1-Tetrahydropyranyloxy-6-iodo-2-hexyne (XIV). 1-Tetrahydropyranyloxy-6-chloro-2-hexyne (XIIIb) (2.1g) was placed in 50 ml acetone containing 1.1 equivalents of sodium iodide. The solution was refluxed for 15 hours with stirring. A white precipitate (sodium chloride) formed as the reaction progressed. After cooling the mixture to room temperature, the reaction was worked up as usual with ether.* The yield of XIV was 96%: i.r. (film) 665 cm^{-1} (C-Cl); n.m.r.(CCl_4) δ 3.30 ppm (t, 2H, J = 6.0 cps, $\underline{CH_2}I$) instead of δ 3.57 ppm ($\underline{CH_2}Cl$). Otherwise there was no change from the spectrum of XIIIb in either i.r. or n.m.r.

6-Cyano-2-hexyn-1-ol (XVa). 6-Chloro-2-hexyn-1-ol (XIIIa) (6.75 g) was dissolved in 30 ml anhydrous DMSO (freshly distilled over calcium hydride under nitrogen). To this was added 1.1 equivalents of sodium cyanide which had been dried overnight at 90° in vacuo. The reaction solution was always kept under a stream of dry nitrogen to ensure anhydrous conditions. The mixture was then heated at 90° in an oil bath while the solution was magnetically stirred.[67] On heating, the granular sodium cyanide crystals were replaced by a galatious precipitate. After heating for 5 hours, the solution was cooled to room temperature, diluted with water and worked up as usual with chloroform. The resulting oil, which still contained DMSO,

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* Unless otherwise mentioned, the term "worked up as usual" means extraction with a specified solvent, washing the combined extracts with water and saturated aqueous sodium chloride, drying over anhydrous sodium sulfate or magnesium sulfate filtering and finally evaporating the solvent in vacuo.

was chromatographed through a column of silica gel (benzene-ether 9:1) and the hydroxy nitrile XVa was obtained in 90% yield: i.r. ($CHCl_3$) 3580, 3420 cm^{-1} (OH), 2250 cm^{-1} (C≡N, C≡C); n.m.r. ($CDCl_3$) δ 4.48 (t, 2H, J = 2.0 cps, $O\underline{CH_2}C\equiv$), 3.0-2.4 (m, 4H, $\equiv C\underline{CH_2}$, $\underline{CH_2}C\equiv N$), 2.3-1.8 (m, 2H, $\underline{CH_2}$), 2.72 (s, 1H, exchangeable, $\underline{OH}$).

1-Acetoxy-6-cyano-2-hexyne (XVb). The crude hydroxy nitrile XIIIa was dissolved in 100 ml dry pyridine and a slight molar excess of acetic anhydride was added. This was heated at 60° for 1.5 hours. The pyridine was then stripped off in vacuo and the residue was eluted through a silica gel column with benzene followed by benzene-ether 9:1. The yield of the acetate was 82% based on the starting hydroxy chloride, XIIIa: i.r. (CCl_4) 2244 cm^{-1} (C≡N, C≡C), 1745 cm^{-1} (C=O), 1268 cm^{-1} (C-O-C); n.m.r. (CCl_4) δ 4.58 (t, 2H, J = 2.0 cps, $O\underline{CH_2}C\equiv$), 2.02 (s, 3H, $\underline{CH_3}CO$).

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.45; H, 6.67; N, 8.48.
Found: C, 65.29; H, 6.73; N, 8.55.

Methyl 4-bromobutyrate (XVIIIb). The crude 4-bromo butyric acid (XVIIIa), prepared from the procedure of Avison et al.[34], was treated with ethereal diazomethane[35] at 0°. The ether was then removed in vacuo. The product distilled at 77°/15 mm: i.r. (CCl_4) 1778, 1740 cm^{-1} (C=O); n.m.r. (CCl_4) δ 3.59 (s, 3H, $O\underline{CH_3}$), 3.38 (t, 2H, J = 6.0 cps, $\underline{CH_2}Br$), 2.63-1.96 (m, 4H, $\underline{CH_2}\underline{CH_2}CO$).

Anal. Calcd. on $C_5H_9O_2Br$: C, 33.15; H, 4.97; Br, 44.19
Found: C, 33.42; H, 5.06; Br, 43.98

4-Bromobutanol (XIXa). A one liter, three-necked, round-bottom flask was fitted with a thermometer (low temperature), dropping funnel, mechanical stirrer and nitrogen gas inlet and outlet. Under a stream of nitrogen, the flask was charged with 250 ml of anhydrous ether and 3.05 g lithium aluminum hydride. The stirred slurry was cooled to -60° in a dry ice-methanol bath and 23.8 g (0.130 moles) of ester XVIIIb, dissolved in 200 ml anhydrous ether, was slowly added so that the temperature did not go above -50°. After addition, the reaction was kept below -60° for 1.5 hours, then slowly allowed to warm to -10°. The reaction was then quenched with 200 ml of 2N sulfuric acid and worked up as usual with ether. The resulting alcohol XIXa was obtained in 95% yield (b.p. 48-49°/3mm): i.r.(CCl_4) 3630, 3300 cm^{-1} (OH), 1060 cm^{-1} (C-O); n.m.r.(CCl_4) δ 3.68 (t, 3H, J = 6.5 cps, $\underline{CH_2}O$), 3.46 (t, 3H, J = 6.0 cps, $\underline{CH_2}Br$), 2.25-1.50 (m, 4H, $CH_2\underline{CH_2}$), 4.62 (s, 1H, exchangeable, O$\underline{H}$).

Anal. Calcd for C_4H_9OBr: C, 31.37; H, 5.88; Br, 52.22
Found: C, 31.49; H, 5.83; Br, 51.98

4-Tetrahydropyranyloxybutyl bromide (XIXb). One equivalent of the above alcohol was treated (neat) with a slight molar excess of 3,4-dihydropyran and three drops of phosphorus oxychloride. A vigorous exothermic reaction started almost immediately after the phosphorus oxychloride had been added (in one instance, the reaction started without addition of catalyst, probably because the mixture was contaminated with some mineral acid). The reaction temperature was controlled with an ice-water bath. After the exothermic reaction had subsided, the reaction mixture was stirred at room temperature

for three hours. The mixture was then taken up in ether and washed twice with 5% aqueous potassium hydroxide, followed by the usual work up procedure. The resulting tetrahydropyranyl ether could be distilled at 82-84°/2mm as long as the distillation apparatus was acid free, otherwise the tetrahydropyranyl ether would cleave. Purification was also achieved by column chromatography on silica gel using hexane, then hexane-benzene mixtures (2.5 to 20%) as the solvent system. The yield of XIXb was better than 95%: i.r.(CCl_4) 1143, 1130, 1038, 1028 cm^{-1} (C-O-C), 914, 872 cm^{-1} (C-C-C); n.m.r.(CCl_4) δ 4.53 (m, 1H, HC ketal), 4.05-3.18 (m, 6H, 2 (OCH_2), CH_2Br), 2.25-1.35 (m, 10H, CH_2).

Anal. Calcd. for $C_9H_{17}O_2Br$: C, 45.59; H, 7.17; Br, 33.75
Found: C, 45.33; H, 7.38; Br, 33.93

7-Tetrahydropyranyloxy-2-heptyn-1-ol (XXa). A 500 ml, three-necked, round-bottom flask was fitted with a Claisen adapter on the middle neck, and a stop-cock adapter (nitrogen inlet) and dropping funnel on the other two necks. A mechanical stirrer was passed through the middle neck and a dry-ice condenser was placed on the other arm of the Claisen adapter. The system was flushed with nitrogen gas and flame dried. The reaction flask was charged with 0.22 moles lithium amide, the flask and condenser were then cooled to -80° (isopropyl alcohol-carbon dioxide), and 200 ml ammonia was distilled through the condenser into the flask. It was not found necessary to redistill the ammonia from sodium metal. After the distillation, the system was again flushed with nitrogen and the dropping funnel was charged

with 0.10 moles propargyl alcohol in 30 ml of anhydrous ether. The alcohol was added dropwise with stirring. The coolant from the flask was then removed and the solution was stirred for 2 hours. After this time, the dropping funnel was charged with 0.09 moles of the bromide (XXVIb), in 20 ml of anhydrous ether under a positive nitrogen pressure. The bromide was added dropwise and then the reaction mixture was stirred for 6 hours at -33° (refluxing ammonia). After this time the reaction was quenched by the addition of 0.05 moles of ammonium chloride and the ammonia was allowed to evaporate overnight. The resulting solid mass was then taken up in water and ether. The ether was separated and the aqueous phase was further extracted (six times) with ether. The work up was then continued in the usual way. The crude reaction product was chromatographed on a silica gel column (30 g silica gel to 1 g mixture). The column was eluted with hexane containing increasing amounts of ethyl acetate (2.5%-20%).

The compounds that were isolated from the reaction mixture are given below in the order that they were eluted off the column.

1. 4-Tetrahydropyranyloxybutyl propargyl ether (XXb) was eluted with 2.5-5% ethyl acetate in hexane and obtained in 2.5-5% yield: i.r. (CCl_4) 3310 cm^{-1} (≡CH), 2120 cm^{-1} (C≡C, terminal), 1124, 1105, 1079, 1038, 1023 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 4.53 (m, 1H, HC ketal), 4.09 (d, 2H, J = 2.5 cps, $OCH_2C\equiv$), 3.9-3.1 (m, 6H, OCH_2), 2.57 (t, 1H, J = 2.5 cps, ≡CH), 1.8-1.4 (m, 10H, CH_2).

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

Found: C, 68.10; H, 9.66

2. 4-Tetrahydropyranyloxybutyl-7-tetrahydropyranyloxy-2-heptynyl ether (XXc) was eluted with 5-10% ethyl acetate in hexane and obtained in 20-25% yield: i.r.(CCl_4) 2230 cm^{-1} (C≡C), 1145, 1130, 1085, 1075, 1045, 1030 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 4.59 (m, 2H, HC ketals), 4.09 (t, 2H, J = 2.0 cps, $\equiv CCH_2O$), 4.0-3.2 (m, 10H, CH_2O), 2.2 (m, 2H, $CH_2C\equiv$) 1.9-1.3 (m, 20H, CH_2).

Anal. Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85

Found: C, 68.04; H, 9.74

3. 7-Tetrahydropyranyloxy-2-heptyn-1-ol (XXa) was eluted off the column with 20% ethyl acetate in hexane and obtained in 50-60% yield. Distillation of this compound was unsatisfactory because of tetrahydropyranyl ether cleavage: i.r.(CCl_4) 3610, 3450 cm^{-1} (OH), 2220 cm^{-1} (C≡C), 1140, 1123, 1039, 1025 (C-O-C); n.m.r.(CCl_4)δ4.60(m, 1H, HC ketal), 4.17(t, 1H, J = 2.0 cps, $OCH_2C\equiv$), 4.0-3.2(m, 4H, CH_2O), 2.5-2.1(m, 2H, $CH_2C\equiv$), 2.0-1.4(m, 10H, CH_2), 2.91(s, 1H, exchangeable, OH).

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

Found: C, 68.09; H, 9.63

7-Tetrahydropyranyloxy-2-heptynyl mesylate (XXIa). A solution of n-butyl lithium (Alfa Inorganics) in hexane (66 g of 22.6% by weight) was transferred under nitrogen in a ''glove bag'' into a one liter, three-necked flask. The flask was then fitted with a nitrogen inlet stopcock, mechanical stirrer, dropping funnel and nitrogen outlet. Under a stream of nitrogen, the solution was cooled to 0° (ice-water bath) and the dropping funnel was charged with 45 g (0.212 moles) of alcohol XXa in 100 ml of anhydrous ether. The ethereal solution

of alcohol was slowly added with stirring over a period of 1 hour, then stirred at 0°C for an additional hour to ensure complete salt formation. Mesyl chloride (24.3 g) in 70 ml anhydrous ether was placed into the dropping funnel and slowly added at 0°. A precipitate formed immediately. After addition (about 1 hr) the solution was allowed to stand an additional three hours. The reaction was then quenched with ice water and worked up as usual in ether. The yields of the crude mesylate were better than 95% and was used as such for conversion to the iodide XXIc. The mesylate was purified by column chromatography on silica gel and elution with 2.5-10% ethyl acetate-hexane. This purified material was used for the alkylation: i.r. (CCl_4) 2245 cm^{-1} (C≡C), 1390, 1188 cm^{-1} (SO_2), 1145-1025 cm^{-1} (C-O-C).

1-Iodo-7-tetrahydropyranyloxy-2-heptyne (XXIc). Sodium iodide (75g), which had been heated in the oven at 120° for two hours, was placed in a 2-liter, three-necked flask fitted with a nitrogen gas inlet, outlet and mechanical stirrer. The sodium iodide was dissolved in 500 ml anhydrous acetone and the resulting solution was cooled to 0° under nitrogen. The crude mesylate XXIa (113g) dissolved in 500 ml anhydrous acetone was added at once with stirring. The solution became cloudy, and finally turned into a thick, light brown slurry. This was stirred at 0°-20° for 1.5 hours, then diluted with ether and worked up the usual way. The crude iodide XXIc, obtained in 85-90% yields, was purified by column chromatography on silica gel using 2.5-10% ethyl acetate in hexane as the solvent system: i.r.(CCl_4) 2240 cm^{-1} (C≡C),

1155-1032 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 4.60 (m, 1H, HC ketal), 3.76 (t, 2H, J = 2.0 cps, CH_2I), 3.9-3.2 (m, 4H, CH_2O), 2.30 (m, 2H, $CH_2C\equiv$), 1.9-1.4 (m, 10H, CH_2).

1-Bromo-7-tetrahydropyranyloxy-2-heptyne (XXIb). The mesylate XXIa (1.55 g) was dissolved in anhydrous acetone under nitrogen. A slight molar excess of anhydrous lithium bromide was added and the solution was heated at 80°C for one hour. After cooling the solution was concentrated in vacuo, taken up in ether and worked up as usual. The bromide XXIb, obtained in 85% yield, was purified by column chromatography on alumina III-IV using hexane as the solvent system: i.r.(CCl_4) 2245 cm^{-1} (C≡C), 1142-1025 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 4.43 (m, 1H, HC ketal), 3.79 (t, 2H, J = 2.0 cps, $BrCH_2C\equiv$), 3.7-3.1 (m, 4H, CH_2O), 2.21 (m, 2H, $CH_2C\equiv$), 1.8-1.3 (m, 10H, CH_2).

Anal. Calcd. for $C_{12}H_{19}O_2Br$: C, 52.36; H, 6.91; Br, 29.09

Found : C, 52.13; H, 7.10; Br, 28.89

1-Iodo-2-heptyn-7-ol (XXId). The iodide XXIc (0.39 moles) was dissolved in 500 ml of methanol in a one liter, three-necked flask containing a magnetic stirrer. Under a stream of nitrogen, 1 ml of concentrated hydrochloric acid was added and the solution was stirred at room temperature for four hours. Most of the methanol was then removed in vacuo at room temperature, and the residue was diluted with ether, and washed with 5% sodium carbonate. The aqueous fraction was extracted with ether in the usual manner. The crude hydroxy iodide XXId was not purified but oxidized directly with Jones reagent: i.r.(CCl_4) 3635, 3460 cm^{-1} (OH), 2240 cm^{-1} (C≡C), 1063 cm^{-1} (C-O); n.m.r.(CCl_4)

δ 3.73 (t, J = 2.0 cps, $IC\underline{H}_2C\equiv$), 3.9-3.4 (m, $C\underline{H}_2O$), 2.23 (m, $C\underline{H}_2C\equiv$), 1.8-1.2 (m, $C\underline{H}_2$), 3.99 (s, exchangeable, $O\underline{H}$).

Methyl 7-iodo-5-heptynoate (XXIIIb). The crude hydroxy iodide XXId was dissolved in 1 l. acetone in a two liter three-necked flask fitted with a mechanical stirrer, dropping funnel and thermometer. The solution was cooled to 5° and stirred while molar excess Jones reagent was added at such a rate that the temperature did not go above 10°. (The addition took about 2.5 hours.) After the addition, isopropyl alcohol was added to destroy excess chromic acid, and the reaction mixture was diluted with water and ether. The aqueous phase was separated and extracted five times with ether. The combined, ether fraction was then extracted with 5% sodium bicarbonate. This basic fraction was reacidified with 6N hydrochloric acid and back extracted with ether. The ethereal solution was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude acid was then again dissolved in anhydrous ether, cooled to 0° and treated with an ethereal solution of diazomethane. Concentration of this solution gave a brown oil which was chromatographed on a silica gel column using 10% ethyl acetate in hexane as the solvent system. The pure iodo ester XXIIIb was obtained as a colorless liquid in 20% overall yield from XXa: i.r.(CCl_4) 2240 cm^{-1} ($C\equiv C$), 1740 cm^{-1} ($C=O$), 1163 cm^{-1} ($C-O-C$); n.m.r.(CCl_4) δ 3.70 (t, J = 2.0 cps, $IC\underline{H}_2C\equiv$), 3.64 (s, OCH_3), these peaks overlap but integrate together to 5H, 2.5-2.1 (m, 4H, $C\underline{H}_2CO$, $C\underline{H}_2C\equiv$), 1.83 (m, 2H, $C\underline{H}_2$); mass spectrum: M^+ 266; m/e 235, $M^+ - OCH_3$; m/e 207, $M^+ - CO_2CH_3$; m/e 179, $M^+ - CH_2CH_2CO_2CH_3$;

m/e 139, M^+ - I; m/e 193, M^+ - $CH_2CO_2CH_3$.

6-Exo-(1'-heptenyl)-2-α and β-(6''-carbomethoxy-2-hexynyl)-bicyclo[3.1.0]hexan-3-one (XXV). A two liter, three-necked flask was fitted with a stopcock adapter (nitrogen inlet), charged with the purified iodo ester, XXIIIb (0.0752 moles) and the bicyclic ketone XXIV* (0.026 moles) and connected to a distillation apparatus as the receiving flask. Tetrahydrofuran (THF) had been heated to reflux over lithium aluminum hydride for 12-16 hours in the apparatus. The still head (Ace Glass, Inc. No. 9214) of the distillation apparatus was such that the receiving portion could be independently flushed with nitrogen. Therefore after connecting the flask and flushing it with nitrogen, 400 ml anhydrous THF was distilled into it. The flask was then removed under a stream of nitrogen, fitted with a mechanical stirrer, a mercury trap and thermometer. The solution was then cooled to 3° in an ice-water bath. Finally a one liter dropping funnel containing potassium t-butoxide (0.0395 moles) dissolved in 900 ml of anhydrous THF was fitted onto the three-necked flask.

Since commercial grade potassium t-butoxide was unsatisfactory (it contained too much potassium hydroxide which was not soluble in THF) the base had to be freshly prepared each time. An excess of t-butanol was distilled over potassium in a nitrogen atmosphere into a one-liter three-necked flask containing potassium (0.0395 moles). After all the metal had dissolved, the excess t-butanol was removed in vacuo leaving a white solid. The flask was then connected, under nitrogen, to the above mentioned distillation apparatus and 900 ml THF was distilled

* This compound was generously supplied by the Upjohn Company.

into it. The clear solution was then transferred into a dropping funnel in a ''glove bag'' under nitrogen.

The base was now slowly added to the stirred solution of the ketone and iodide over a period of six hours with the temperature being maintained between 0-5°. After about 30 minutes of addition, the solution became cloudy and assumed a beige colour which did not change throughout the addition although the solution became thicker. This was probably due to potassium iodide precipitating out. After the base had been added, the reaction was quenched with 50 ml of 5% hydrochloric acid. The solution was then concentrated on an aspirator to about 300 ml, diluted with water and extracted with ethyl acetate (5 times, 100 ml). The combined dark organic fraction was then washed with 5% sodium thiosulfate to remove iodine and with brine and finally dried over sodium sulfate. The solution was then filtered and concentrated. A brown oil (19.1 g) was obtained.

Attempts to strip off unreacted ester and ketone failed at a vacuum of 5μ at 100°. A more efficient vacuum was required but was not available. The material was then chromatographed on a 1 kg silica gel column, eluted with hexane followed by 2.5-40% ethyl acetate in hexane. The components of the mixture eluted in the following order:

1. Unreacted XXV and XXIIIb (5% EtOAc) which were identified by TLC comparison with the pure compounds.

2. Monoalkylated ketone XXV (5-10% EtOAc) was obtained in 23% yield: i.r.(film) 1740 cm^{-1} (C=O) ketone and ester, 1165 cm^{-1} (C-O-C); n.m.r.($CDCl_3$) δ 5.6-4.6 (m, 2H, $\underline{H}C=C\underline{H}$), 3.62 (s, 3H, $OC\underline{H}_3$). Mass spectrum: M^+ 330; m/e 299, $M^+ - OCH_3$; m/e 271, $M^+ - CO_2CH_3$;

m/e 302, M^+ - CO; m/e 243, M^+ - $(CH_2)_2CO_2CH_3$; m/e 191, M^+ - $CH_2C{\equiv}C(CH_2)_3CO_2CH_3$; m/e 273, M^+ - C_4H_9.

3. Dialkylated ketone (10-20% ethyl acetate) was obtained in 8% yield; i.r.(film) 1740 cm^{-1} (C=O) ketone and ester, 1168 cm^{-1} (C-O-C); n.m.r.($CDCl_3$) δ 5.6-4.7 (m, 2H, HC=CH), 3.66 (s, 6H, OCH_3). Mass spectrum: M^+ 468; m/e 437, M^+ - OCH_3; m/e 409, M^+ - CO_2CH_3; m/e 440, M^+ - CO; m/e 329, M^+ - $CH_2C{\equiv}C(CH_2)_3CO_2CH_3$; m/e 425, M^+ - C_3H_7; m/e 411, M^+ - C_4H_9.

4. Trialkylated ketone (20-40% ethyl acetate) was isolated in 11% yield: i.r.(film) 1740 cm^{-1} (C=O) ester and ketone, 1168 cm^{-1} (C-O-C) n.m.r.($CDCl_3$) δ 5.6-4.6 (m, 2H, HC=CH), 3.68 (s, 9H, OCH_3). Mass spectrum: M^+ 606; m/e 575, M^+ - OCH_3; m/e 547, M^+ - CO_2CH_3; m/e 578, M^+ - CO; m/e 549, M^+ - C_4H_9; m/e 467, M^+ - $CH_2C{\equiv}C(CH_2)_3CO_2CH_3$.

5. Tetraalkylated ketone (20-40% EtOAc) was isolated in 5% yield: i.r.(film) 1740 cm^{-1} (C=O) ester and ketone, 1168 cm^{-1} (C-O-C); n.m.r.($CDCl_3$) δ 5.6-4.6 (m, 2H, HC=CH), 3.79 (s, 12H, OCH_3). Mass spectrum: M^+ 744; m/e 713, M^+ - OCH_3; m/e 685, M^+ - CO_2CH_3; m/e 716, M^+ - CO; m/e 699, M^+ - C_4H_9; m/e 605, M^+ - $CH_2C{\equiv}C(CH_2)_3CO_2CH_3$.

The four alkylated products were purified by preparative TLC on silica gel HF 254 using benzene-ether 9:1 as the solvent system. The yields were calculated on the total amount of XXIV used in the reaction.

GLC of the monoalkylated product (6', 3% SE 30 on chromosorb W, 200°) showed two peaks (R_t 2.9 min and 4.75 min) in the ratio 3:7. On the same column the retention time of Xα was 3.05 min and Xβ were

4.67 min.* Also on the same column (248°) the dialkylated ketone showed two peaks (R_t 3.50, 5.25) in the ratio 1:5. The tri- and tetra-alkylated products did not come off the column at this temperature.

Alkylation of XXIV with 1-iodo-7-tetrahydropyranyloxy-2-hexyne (XXIc).

a) The procedure was used as described above except that the molar ratio of ketone to iodide was 1:1. Column chromatography of the product on silica gel (hexane and ethyl acetate solvent system) gave only one alkylated product in 30% yield. Spectral and elemental analysis showed this to be dialkylated: i.r.(CCl_4) 1750 cm^{-1} (C=O), 1145-1025 cm^{-1} (C-O-C) tetrahydropyranyl group; n.m.r.(CCl_4) δ 5.6-4.6 (m, 2H, HC=CH), 4.52 (m, 2H, HC ketals); 4.1-3.1 (m, 8H, CH_2O).

Anal. Calcd for $C_{25}H_{38}O_3$ (monoalkylated): C, 77.67; H, 9.91

Calcd for $C_{37}H_{56}O_5$ (dialkylated): C, 76.51; H, 9.72

Found: C, 75.23; H, 11.31

b) The procedure was the same as described above except that the molar ratio of ketone to iodide was 1:2. Column chromatography on silica gel using hexane and hexane-ethyl acetate mixtures as eluents gave the monoalkylated ketone XXVa in 19% yield. No serious attempt was made to isolate polyalkylated materials.

I.r.(CCl_4) 1775 cm^{-1} (C=O); 1138-1025 cm^{-1} (C-O-C) tetrahydropyranyl ether; n.m.r.(CCl_4) δ 5.5-4.6 (m, 2H, HC=CH), 4.50 (m, 1H, HC ketal), 4.0-3.0 (m, 4H, CH_2O). Mass spectrum: m/e 302, M^+ - dihydropyran[54];

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* Xα and Xβ are the two isomers obtained in the alkylation step in the PGE_1 synthesis (c.f. Introduction). The samples were supplied by the Upjohn Co.

m/e 84, $C_5H_8O^+$ (dihydropyran); m/e 274, 302 - CO; m/e 245, 302 - C_4H_9; m/e 243, 302 - C_3H_7O; m/e 272, 302 - CH_2O; m/e 191, 302 - side chain.

Cleavage of THP group of XXVa. The alkylated ketone XXVa (200 mg) was refluxed in methanol containing a drop of concentrated hydrochloric acid for 30 minutes. The resulting hydroxy ketone was obtained in quantitative yield: i.r.(CCl_4) 3640, 3460 cm^{-1} (OH), 1745 cm^{-1} (C=O), 1055 cm^{-1} (C-O); Mass spectrum: M^+ 302, the rest of the fragmentation was the same as for XXVa.

CHAPTER II

1,2-Epoxycyclopentene (VII). This was prepared from cyclopentadiene by the method of Korach et al[39]. It was consistently found to be contaminated with a carbonyl compound (i.r. 1755 cm^{-1}, 1680 cm^{-1}). In the reaction described below the contamination was about 10-15%, estimated from the intensity of the carbonyl band.

Propargyl magnesium bromide (XXIX). This was prepared as described by Gaudemar et al.[40] A 500 ml three-necked flask was fitted with a thermometer, water condenser, dropping funnel, magnetic stirrer, nitrogen inlet and mercury trap on top of the condenser. The flask was flame dried and cooled under a stream of nitrogen. Magnesium powder .367 moles) was placed into the flask along with a few crystals of mercuric chloride and covered with anhydrous diethyl ether, and a small amount of this was added to the magnesium to start the reaction. Once the reaction was initiated, the mixture was cooled in an ice-water bath, and the rest of the bromide was added at such a rate that the temperature of the reaction was kept below 20°. When the addition was complete, the solution was stirred an additional hour below 20° to complete the reaction.

2-Propargylcyclopent-3-en-1-ol (XXX). The propargyl magnesium bromide was cooled to 0° in an ice-water bath and 1,2-epoxycyclopentene (0.126 moles) was slowly added in 25 ml of anhydrous ether with stirring.

The rate of addition was such that the temperature remained between 3-7°. After addition, the reaction was stirred an additional two hours at this temperature. The reaction was then quenched by the addition of a saturated aqueous ammonium chloride solution, and the reaction was worked up in the usual way with ether. The reaction mixture consisted of five compounds, as determined by TLC. The desired and major product could be isolated by careful column chromatography on silica gel eluting with benzene followed by benzene-ether mixtures. The components of the mixture were eluted from the column in the following order:

1. Allene mixture (3%) eluted from the column with 2.5% ether; i.r.(CCl_4) 3605, 3585, 3480 cm^{-1} (OH), 3320 cm^{-1} (≡CH), 3060 cm^{-1} (=CH), 2110 cm^{-1} (C≡C terminal), 1955 cm^{-1} (C=C=C), 1618 cm^{-1} (C=C), 1063 cm^{-1} (C-O), 852 cm^{-1} ($C=C=CH_2$).

2. 1-Propargylcyclopent-3-en-1-ol (XXVIII) was obtained in 10% yield and eluted from the column with 2.5-5% ether: i.r.(CCl_4) 3695, 3605, 3490 cm^{-1} (OH), 3320 cm^{-1} (≡CH), 3060 cm^{-1} (=CH), 2110 cm^{-1} (C≡C terminal), 1618 cm^{-1} (C=C), 1070 cm^{-1} (C-O); n.m.r.(CCl_4) δ 5.67 (s, 2H, HC=CH), 2.50 (m, 6H, $CH_2C=$, $CH_2C\equiv$), 1.98 (t, 1H, J = 2.5 cps, HC≡), 3.11 (s, 1H, exchangeable, OH).

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25

Found: C, 78.90; H, 8.35

3. 2-Propargylcyclopent-3-en-1-ol (XXX) was obtained in 32% yield and eluted from the column with 5% ether in benzene: i.r.(CCl_4) 3610, 3580, 3465 cm^{-1} (OH), 3060 cm^{-1} (=CH), 3320 cm^{-1} (≡CH), 2120 cm^{-1}

(C≡C terminal), 1612 cm^{-1} (C=C), 1070 cm^{-1} (C-O); n.m.r.(CCl_4) δ 5.81 ppm (s, 2H, HC=CH), 4.27 (m, 1H, HCO), 2.18-2.95 (m, 5H $H_2CC=$, $H_2CC=$, HCC=) 1.89 (t, 1H, J = 2.5 cps, ≡CH), 3.13 (s, 1H, exchangeable, OH).

Anal. Calcd. for $C_8H_{10}O$: C, 78.65, H, 8.25

Found: C, 78.86, H, 8.49

4. 4-Propargylcyclopent-2-en-1-ol (XXXI) was obtained in 10% yield and eluted from the column in 10% ether in benzene: i.r.(CCl_4) 3620, 3605, 3460 cm^{-1} (OH), 3320 cm^{-1} (≡CH, terminal), 3060 cm^{-1} (=CH), 2110 cm^{-1} (C≡C, terminal); 1615 cm^{-1} (C=C), 1062 cm^{-1} (C-O); n.m.r. (CCl_4) δ 5.89 (s, 2H, HC=CH), 4.91 (m, 1H, =CCH-O), 3.09 (q, 1H, J = 6.5 cps, =CCH-), 2.18 (d, 2H, J_{AB} = 2.5 cps, J_{BC} = 7.0 cps, $H_A C{\equiv}CCH_2{}_B - CH_C$), 1.99(m, 3H, HC≡$CH_2$), 3.87 (s, 1H, exchangeable OH).

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25

Found: C, 77.15; H, 7.85

Oxidation of XXX with manganese dioxide. The acetylenic alcohol XXX was refluxed in pentane for 24 hours with a large excess of active manganese dioxide[87]. There was no evidence of oxidation from spectral (i.r. or UV) analysis of the product indicating that the compound does not have an allylic alcohol.

Oxidation of XXXI with manganese dioxide to XXXIII. The acetylenic alcohol XXXI was refluxed in pentane for 24 hours with a large excess of active manganese dioxide[87]. Oxidation occurred and from the spectral data on the product and the starting alcohol, the resulting ketone was assigned structure XXXIII: i.r.(CCl_4) 3320 cm^{-1} (≡CH),

3050 cm^{-1} (=CH), 2110 cm^{-1} (C≡C, terminal), 1725 cm^{-1} (C=O), 1650 cm^{-1} (C=C); n.m.r.(CCl_4)δ7.67 (qu, 1H, =C<u>H</u>OO), 6.19 (qu, 1H, <u>H</u>C=), 3.13 (m, 1H, =CC<u>H</u>), 2.52-1.98 (m, 5H, ≡C<u>H</u>, ≡CC<u>H</u>$_2$, C<u>H</u>$_2$OO); uv max (CH_3OH) 217 mμ (ε 10,900).

<u>Anal.</u> Calcd. for C_8H_8O: C, 79.97; H, 6.71

Found: C, 79.75; H, 6.74

<u>2-Propargyl-1-tetrahydropyranyloxycyclopent-3-ene (XXXIIa).</u> The alcohol XXX was mixed (neat) with a slight excess of 3,4-dihydropyran and two drops of phosphorus oxychloride. The exothermic reaction started almost immediately and was controlled with an ice-water bath. After the initial reaction had subsided, the mixture was stirred at room temperature for 3-4 hours. The reaction mixture was taken up in ether and washed with 5% potassium hydroxide followed by water and brine. The organic phase was then treated in the usual way. The tetrahydropyranyl ether XXXIIa obtained in 90% yield, was purified by column chromatography on silica gel using hexane ether 7:3 as the solvent system: i.r.(CCl_4) 3300 cm^{-1} (≡CH), 3050 cm^{-1} (=CH), 2110 cm^{-1} (C≡C), 1610 cm^{-1} (C=C), 1135-1025 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 5.69 (s, 2H, <u>H</u>C=C<u>H</u>), 4.70 (m, 1H, <u>H</u>C ketal), 4.3-3.2 (m, 3H, C<u>H</u>$_2$O).

<u>Anal.</u> Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80

Found: C, 75.86; H, 8.63

<u>2-(7'-Tetrahydropyranyloxy-2'-hexynyl)-1-tetrahydropyranyloxycyclopent-3-ene (XXXIIb).</u> The apparatus was set up for a liquid ammonia reaction as was previously described for the preparation of XXa (Chapter I) using a 500 ml three-necked flask. Lithium amide (24.0 mmoles) was placed into the flask and about 170 ml liquid ammonia was

distilled into the flask from a condensed sodium-ammonia solution. The tetrahydropyranyl ether, XXXIIa 22.5 moles, in 20 ml of anhydrous ether was then slowly added with stirring. The solution gradually turned pink. After addition and stirring the solution for an hour, 4-tetrahydropyranyloxybutyl bromide XIXb (22.3 mmoles) in 10 ml anhydrous ether was slowly added. The solution gradually changed from pink to brown as the addition proceeded. The reaction was stirred for nine hours at -33° (refluxing ammonia) and then the ammonia was allowed to evaporate over night. The residue was taken up in ether and worked up in the usual manner. The product, purified by column chromatography on 30 g alumina III using hexane as the solvent system, was obtained in 87% yield: i.r.(CCl_4) 3058 cm^{-1} (=CH), 2215 cm^{-1} (C≡C), 1620 cm^{-1} (C=C), 1138-1025 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 5.69 (s, 2H, HC=CH), 4.6 (m, 2H, HC ketal), 4.3-3.2 (m, 7H, CH_2O).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45

Found: C, 71.83; H, 9.89*

Ethyl diazoacetate addition on XXXIIb

a) XXXIIb (1.02 g) was placed into a 50 ml three-necked flask fitted with a magnetic stirrer, dropping funnel, and gas outlet. Copper powder (100 mg) was added to the flask and the mixture was heated in an oil bath at 108°. The mixture was vigorously stirred and ethyl diazoacetate (1.5 ml) in 10 ml anhydrous ether was added slowly over a period

* This sample was contaminated by impurities in the hexane used as eluent in the chromatography. From the spectral data of the compound and the products of the subsequent reaction, there was no doubt about its structure.

of four hours. After the addition was complete, the mixture was heated another hour, with stirring, at 100°. The mixture was then cooled to room temperature, diluted with ether and filtered through celite to remove the copper powder. Concentration of the ethereal solution gave 2.34 g of crude product which was chromatographed on a column of alumina III - IV (35 g) using hexane and hexane-benzene (up to 50% benzene) as the solvent system. The components of the mixture were eluted from the column in the following order:

1. Mixture of starting material XXXIIb, diethyl fumarate, diethyl maleate: n.m.r.(CCl_4) δ 6.78 (diethyl fumarate), 6.16 (diethyl maleate), 5.65 (XXXIIb).

2. 2-[1'-Methenyl-2'-carboethoxy-3'-(4''-tetrahydropyranylbutyl)-cyclopropene]-1-tetrahydropyranyloxycyclopent-3-ene (XXXIV) was eluted from the column with 10% benzene in hexane in 24% yield: i.r.(CCl_4) 3055 cm^{-1} (=CH), 1720 cm^{-1} (C=O), 1900 cm^{-1} (C=C, cyclopropene), 1618 cm^{-1} (C=C), 1175 cm^{-1} (C-O-C, ester), 1133-1025 cm^{-1} (C-O-C, tetrahydropyranyl ether); n.m.r.(CCl_4) δ 5.70 (s, 2H, $\underline{H}C{=}C\underline{H}$), 4.62 (m, 2H, $C\underline{H}$ ketal), 4.2-3.2 (m, $C\underline{H}_2O$)--includes quartet, 4.08 (J = 7.25 cps, $OC\underline{H}_2$ ester), 3.0-2.2 (m, $C\underline{H}_2C{\equiv}$, $C\underline{H}_2C{=}$), 1.99 (s, cyclopropene $C\underline{H}$), 1.6 (m, $C\underline{H}_2$), 1.23 (t, J = 7.25 cps, $C\underline{H}_3$ ester). Mass spectrum: M^+ 448; m/e 385, $M^+ - CO_2CH_2CH_3$; m/e 363, $M^+ - C_5H_9O$ (tetrahydropyranyl); m/e 105, $CH_2OC_5H_9O$; m/e 85, C_5H_9O.

2-[1'-Methenyl-2'-carboethoxy-3'-(4''-tetrahydropyranylbutyl)cyclopropene]-6-carboethoxy-2-tetrahydropyranyloxy-bicyclo[3.1.0]hexane (XXXV) was eluted from the column with 20% benzene in hexane in 26% yield:

i.r.(CCl_4) 3035 cm^{-1} (CH, cyclopropyl) 1900 cm^{-1} (C=C, cyclopropene), 1725 cm^{-1} (C=O), 1180, 1165 cm^{-1} (C-O-C, ester), 1133-1025 cm^{-1} (C-O-C, tetrahydropyranyl ether); n.m.r.(CCl_4) δ 4.53 (m, 2H, HC ketal), 4.4-3.15 (m, 11H, OCH_2) -- this region includes a quartet 4.08 (J = 7.25 cps, OCH_2, ester); 2.8-2.2 (m, CH_2C=) -- this includes a singlet 2.02 (HC, cyclopropene); 2.0-1.1 (m, CH_2) -- this includes two triplets 1.27 and 1.08, J = 7.25 cps (CH_3 of the two ester groups); 1.1-0.8 (m, CH, cyclopropyl). Mass Spectrum: M^+ 534; m/e 489, $M^+ - OCH_2CH_3$; m/e 461, $M^+ - CO_2CH_2CH_3$; m/e 449, $M^+ - C_5H_9O$ (tetrahydropyranyl); m/e 105, $CH_2OC_5H_9O$; m/e 85, C_5H_9O.

b) The above reaction was repeated at 50°C using 0.49 g XXXIIb, 65 mg copper powder, and 0.80 ml ethyl diazoacetate in ether which was slowly added over a period of 1.5 hours. The only isolated product was XXXIV (by TLC and infrared spectrum comparisons.) The rest of the recovered mixture was the starting material XXXIIb, and a considerable amount of diethyl maleate (diethyl fumarate was not formed at this temperature).

Bicyclo[3.1.0]hex-2-ene-6-endo-carboxaldehyde (XXXVIIa). This compound was prepared from norborna-2,5-diene (XXXVI) according to the procedure of Meinwald et al.[51]

Bicyclo[3.1.0]hex-2-ene-6-carboxaldehyde ethylene ketal (XXXVIIb). A 500 ml three-necked flask was fitted with a stopcock adapter, a dropping funnel, magnetic stirrer, Dean-Stark separator and condenser. Aldehyde XXXVIIa (7.66 g) was dissolved in 100 ml dry benzene and placed in the dropping funnel. The flask was charged with 200 ml dry benzene and

50 mg of p-toluenesulfonic acid. The benzene was then refluxed for one hour under nitrogen to remove any water. After cooling the benzene an excess of ethylene glycol (26.1 g) was added, followed by XXXVIIa in benzene. The solution was then refluxed for 24 hours in which time an equivalent of water had separated out. After 12 hours, another 10 g of ethylene glycol was added to ensure that it was in excess. The benzene was then removed by distillation at atmospheric pressure and the product was distilled in vacuo (b.p. 56.5°C/3mm). The yield of distilled product was 47%; i.r.(CCl_4) 3055 cm^{-1} (=CH), 3035 cm^{-1} (CH, cyclopropyl), 1673 cm^{-1} (C=C), 1102 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 6.0-5.4 (m, 2H, $\underline{H}C=C\underline{H}$), 4.52 (d, 1/3H, J = 5.5 cps, exo $C\underline{H}$ ketal), 4.32 (d, 2/3H, J = 8.0 cps, endo $C\underline{H}$ ketal), 4.0-3.2 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 2.7-2.2 (m, 2H, $C\underline{H}_2C=$), 2.2-1.6 (m, 2H, $\underline{H}C_1C_5\underline{H}$), 1.3-0.8 (m, 1H, $C_6\underline{H}$).

2,3-Epoxybicyclo[3.1.0]hexan-6-carboxaldehyde ethylene ketal (XXXVIII). The bicyclic ketal XXXVIIb (32.1 mmoles) was dissolved in 30 ml methylene chloride. Anhydrous sodium carbonate (40 mmoles) was added and the suspension was cooled to 0-5° in an ice-water bath. Peracetic acid (41%, 18.0 mmoles), previously treated with 0.2 g sodium acetate to neutralize any sulfuric acid that was present, was added at such a rate that the temperature did not go above 10°. After addition, the solution was stirred at 5° until all the peracid had reacted (3 hours). The reaction was followed by iodometric titration. The reaction mixture was then filtered and the filter cake washed with methylene chloride. The methylene chloride was removed by atmospheric distillation. Distillation in vacuo gave first unreacted olefin XXXVIIb (58°/3mm)

followed by the epoxide XXXVIII (b.p. 96-98°/1mm) in 55% yield: i.r.(CCl_4) 3030 cm^{-1} (CH, cyclopropyl), 1105 cm^{-1} (C-O-C, ketal), 945 cm^{-1} (C-O-C, epoxide); n.m.r.(CCl_4) δ 4.69 (d, 2/3H, J = 7.5 cps, C<u>H</u> endo ketal), 4.56 (d, 1/3H, J = 5.0 cps, C<u>H</u> exo ketal), 4.1-3.8 (m, 4H, O<u>CH</u>$_2$ <u>CH</u>$_2$O), 3.48 (m, 1H, C_4<u>H</u>), 3.16 (m, 1H, C_3<u>H</u>), 2.2-1.7 (m, 3H, C_2<u>H</u>$_2$ and C_5<u>H</u>), 1.4-0.8 (m, 2H, C_1<u>H</u>C_6<u>H</u>).

<u>Addition of Propargyl magnesium bromide to XXXVIII</u>. The reaction was carried out in the same way as previously described in the synthesis of 2-propargylcyclopent-3-en-1-ol (XXX). The reaction mixture was chromatographed on a silica gel column using hexane-ethyl acetate as the solvent system. The components of the mixture were eluted in the following order:

1. A ketonic fraction was first eluted with 5% EtOAc in hexane in 25% yield: i.r.(CCl_4) 3035 cm^{-1} (CH, cyclopropyl), 1750 cm^{-1} (C=O), 1112-1000 cm^{-1} (C-O-C).

2. Alcoholic fraction containing no unsaturation, eluted with 5-20% EtOAc in hexane, was obtained in 25% yield: i.r.(CCl_4) 3600, 3470 cm^{-1} (OH), 3042 cm^{-1} (CH, cyclopropyl), 1125, 1110, 1030 cm^{-1} (C-O-C, ketal), 1090 cm^{-1} (C-O, alcohol).

3. Alcoholic fraction containing a terminal acetylene group eluted with 20-50% EtOAc in benzene, was obtained in 15% yield: i.r.(CCl_4) 3605, 3460 cm^{-1} (OH), 3320 cm^{-1} (≡CH), 3030 cm^{-1} (CH, cyclopropyl), 2110 cm^{-1} (C≡C, terminal), 1135, 1113, 1040 cm^{-1} (C-O-C, ketal), 1088 cm^{-1} (C-O, alcohol).

Cyclohexylimine of cyclopentanone[68] (XXXIX). Cyclopentanone (0.1 mole) was dissolved in 300 ml dry benzene containing 0.2 mole of cyclohexylamine and a trace (50 mg) of p-toluenesulfonic acid in a 500 ml round bottom flask fitted with a Dean-Stark separator. The solution was refluxed for 16 hours although most of the theoretical amount of water had separated after six hours. The benzene was removed by distillation at atmospheric pressure. The resulting imine, distilled at 63°/0.25 mm. (lit.[68] 143-4°/18 mm). was obtained in 90% yield: i.r.(CCl_4) 1685 cm^{-1} (C=N).

2-Alkylcyclopentanone (XLI). This was prepared according to the method described by Stork[44]. A 500 ml three-necked flask was fitted with a condenser, stopcock adapter (nitrogen inlet), dropping funnel and magnetic stirrer. The system was flame dried under a stream of nitrogen. The flask was then charged with magnesium turnings (0.0525 moles) and a crystal of iodine. Ethylbromide (0.0505 moles) in 50 ml anhydrous THF was slowly added until the reaction started. The reaction was controlled by cooling the flask in an ice-water bath as more ethylbromide was added. After the addition, the solution was refluxed for 3 to 4 hours to ensure completion of the reaction. The Grignard reagent was then cooled to room temperature. The imine XXXIX (0.0515 moles) in 25 ml THF was slowly added with stirring and the resulting solution was refluxed for 6 hours. The reaction mixture was again cooled to room temperature and allyl bromide (0.0515 moles) was slowly added in 50 ml THF. The solution was then refluxed for 20 hours. After this time, the mixture was cooled, the THF was removed in vacuo and the resulting crude imine was hydrolyzed by refluxing it for 3 hours in 10% aqueous hydrochloric

acid. The aqueous fraction was then extracted with ether in the usual manner. The crude product was chromatographed on a column of silica gel. Elution with hexane-ether 95:5 gave a 36% yield of 2-allylcyclopentanone: i.r.(CCl_4) 3080 cm^{-1} (=CH), 1750 cm^{-1} (C=O), 1650 cm^{-1} (C=C) 990, 920 cm^{-1} ($CH=CH_2$); n.m.r.(CCl_4) δ 5.87-4.61 (m, 3H, $\underline{H}C=C\underline{H}_2$), 2.46-1.17 (m, 9H, $\underline{CH}_2$, $=C\underline{CH}_2$).

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74

Found: C, 77.30; H, 9.80

Cis and trans-2-allylcyclopentanol (XLIIa and XLIIIa). Lithium aluminum hydride (4.80 mmoles) was added to 100 ml anhydrous ether in a 500 ml three-necked flask under nitrogen. The flask was also fitted with a dropping funnel, gas outlet connected to a mercury trap and magnetic stirrer. The slurry was cooled to 0° in an ice-water bath and XLI (9.65 mmoles) was added dropwise in 50 ml ether. After addition, the reaction mixture was stirred an additional hour at room temperature, then quenched at 0° with 25 ml 2N sulfuric acid. The solution was further diluted with water and worked up in the usual manner in ether. The crude product consisted of two alcohols. Column chromatography on 60 g of silica gel and elutinn with hexane-ether, gave XLIIa (45%) and XLIIIa (45%) as pure compounds, the latter coming off the column first: i.r.(CCl_4) 3600, 3490 cm^{-1} (OH), 3080 cm^{-1} (=CH), 1650 cm^{-1} (C=C), 990, 920 cm^{-1} ($CH=CH_2$).

Trans-2-allylcyclopentyl benzoate (XLIIc). The alcohol XLIIa was benzoylated according to the procedure of Shriner and Fuson[69]; i.r.(CCl_4)

3080 cm^{-1} (=CH), 1720 cm^{-1} (C=O), 1650 cm^{-1} (C=C), 1275 cm^{-1} (C-O-C), 990, 920 cm^{-1} ($CH=CH_2$).

Trans-2-n-propylcyclopentyl benzoate (XLIV). A 50 ml hydrogenation flask was connected to a low pressure hydrogenator and charged with 70 mg. 5% palladium on calcium carbonate catalyst, 5 ml absolute ethanol and a magnetic stirrer. The system was flushed and filled with hydrogen. The alcohol XLIIc (200 mg), dissolved in a small amount of ethanol, was added to the hydrogenation mixture in the flask. Most of the theoretical amount of hydrogen had been picked up after 20 minutes. After an additional 10 minutes reaction time, the catalyst was filtered through celite and washed with ethanol. The solvent was then evaporated in vacuo and the benzoate XLIV, purified by preparative TLC on silica gel (benzene-ether 7:3), was obtained in 80% yield: i.r.(CCl_4) 1720 cm^{-1} (C=O), 1275 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 7.99 (m, 2H, ortho C<u>H</u>), 7.40 (m, 3H, meta and para C<u>H</u>), 4.98 (m, 1H, C<u>H</u>-O), 2.25-0.65 (m, 14H, $C\underline{H}_2$ and $C\underline{H}_3$).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68

Found: C, 77.59; H, 8.74

Cis-2-allylcyclopentyl benzoate (XLIIIc). The alcohol XLIIIa was benzoylated according to the procedure of Shriner and Fuson[69]: i.r.(CCl_4) 3080 cm^{-1} (=CH), 1720 cm^{-1} (C=O), 1650 cm^{-1} (C=C), 1273 cm^{-1} (C-O-C) 990, 920 cm^{-1} ($HC=CH_2$).

Cis-2-n-propylcyclopentyl benzoate (XLV). The hydrogenation was carried out on XLIIIc in the same way as described for the hydrogenation of

XLIIc: i.r.(CCl_4) 1720 cm^{-1} (C=O), 1273 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 8.00 (m, 2H, ortho C<u>H</u>), 7.43 (m, 3H, meta and para C<u>H</u>), 5.32 (m, 1H, C<u>H</u>-O), 2.11-0.68 (m, 14H, $C\underline{H}_2$, $C\underline{H}_3$).

<u>Anal.</u> Calcd. for $C_{15}H_{10}O_2$: C, 77.55; H, 8.68

Found: C, 77.63; H, 8.65

<u>2-n-Propylcyclopentyl benzoate from (XXX).</u> The acetylenic alcohol XXX was first benzoylated according to the procedure in Shriner and Fuson[69], then hydrogenated in the same way as described for XLIIc and XLIIIc. In this case, the benzoate (2.5 mmoles) using 128 mg of 5% Pd-$CaCO_3$ catalyst required 12 hours for complete hydrogenation. Work up and purification was the same as described for the reaction of XLIIc and XLIIId: i.r.(CCl_4) 1720 cm^{-1} (C=O), 1275 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 7.99 (m, 2H, ortho C<u>H</u>), 7.40 (m, 3H, meta and para C<u>H</u>), 4.98 (m, 1H, C<u>H</u>-O), 2.25-0.65 (m, 14H, $C\underline{H}_2$ and $C\underline{H}_3$).

<u>Anal.</u> Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68

Found: C, 77.07; H, 8.82

<u>Stereochemical assignment of cis and trans-2-allylcyclopentanol</u>

A. The hydroxyl group of the alcohol XLIIa was protected as the tetrahydropyranyl ether in the usual way[25] to give XLIIb in good yield; i.r.(CCl_4) 1135, 1118, 1078, 1037, 1026 cm^{-1} (C-O-C, bands of the THP ether).

The double bond was then cleaved according to the procedure of Lemieux et al[52]. The tetrahydropyranyl ether XLIIb (1.11 mmoles) was dissolved in 20 ml acetone and mixed with potassium carbonate (3.0 mmoles), potassium permanganate (0.13 mmoles) and sodium periodate (8.0 mmoles)

in 400 ml water. The reaction was stirred for 40 hours at room temperature and then acidified with 10% sulfuric acid. The acidified solution was further stirred for 4 hours at room temperature. The reaction mixture was then extracted several times with ether. The combined ether extracts were washed with water, brine, dried over anhydrous sodium sulfate, and concentrated. The infrared spectrum of crude product (60 mg) clearly indicated that it was a hydroxy acid. No lactonization had taken place: i.r.(CCl_4) 3610, 3370 cm^{-1} (OH, alcohol), 3300-2500 cm^{-1} (OH, acid), 1710 cm^{-1} (C=O), 1282, 1232, 1078 cm^{-1} (C-O, acid and alcohol).

B. The alcohol XLIIIa was subjected to the same reactions under identical conditions as described above for XLIIa. The product after the cleavage reaction was the γ-lactone XLVII: i.r.(CCl_4) 1776 cm^{-1} (C=O, γ-lactone), 1160, 1175 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 5.00 (m, 1H, C<u>H</u>-O).

<u>Anal.</u> Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99

Found: C, 66.42; H, 8.04

CHAPTER III

Exo-6-(1',2'-dihydroxyheptyl)-bicyclo[3.1.0]hexan-3-one (LV). Exo-6-[1'-heptenyl]-bicyclo[3.1.0]hexan-3-one (XXIV) (5.0×10^{-3} moles) was dissolved in 25 ml ice cold 97-98% formic acid buffered with 25×10^{-3} moles sodium carbonate in a 100 ml three-necked flask fitted with a magnetic stirrer. The solution was cooled to 0° in an ice-water bath and 5×10^{-3} moles hydrogen peroxide was added as a 30% solution with stirring. The solution was brought to room temperature and stirred for 30 to 40 minutes under a stream of nitrogen. The formic acid was then stripped off on a vacuum pump and the residue was dissolved in 80 ml of methanol. To this was added with stirring 18 g sodium carbonate dissolved in 50 ml water and the suspension was stirred at room temperature for three hours. The mixture was then acidified with 3N hydrochloric acid, diluted with water, extracted with methylene chloride in the usual manner. The yield of the diol was 85%: i.r.(CCl_4) 3620, 3590 cm^{-1} (OH), 3030 cm^{-1} (CH, cyclopropyl), 1745 cm^{-1} (C=O), 1060 cm^{-1} (C-O).

Exo-6-(1',2'-ditrichloroacetoxyheptyl)-bicyclo[3.1.0]hexan-3-one (LVI). Anhydrous pyridine (20 ml) was placed into a 50 ml three-necked flask fitted with a magnetic stirrer, gas inlet and outlet, and a thermometer. The pyridine was cooled to 0° in an ice-water bath and trichloroacetyl chloride (20 mmoles) was added. To the cold solution was then added LV (4 mmoles) in 5 ml pyridine at such a rate that the temperature did not

go above 10°. The mixture was stirred at 0° for 2 hours. The reaction mixture was then poured onto crushed ice and extracted with methylene chloride in the usual way. The pyridine was stripped off in vacuo and the ditrichloroacetate LVI was obtained in 95% yield: i.r.(CCl_4) 1768 cm^{-1} (C=O, acetate), 1748 cm^{-1} (C=O, ketone), 3035 cm^{-1} (CH, cyclopropyl), 1223 cm^{-1} (C-O-C); n.m.r.(CCl_4) δ 5.31 (m, 1H, $C_7\underline{H}$-O), 4.77 (m, 1H, C_6H-O).

Anal. Calcd. for $C_{17}H_{20}O_5Cl_6$: C, 39.45; H, 3.87; Cl, 41.00

Found: C, 39.83; H, 3.80; Cl, 40.09

Example of a solvolysis of ditrichloroacetate LVI in trichloroacetic acid. A 25 ml three-necked flask was fitted with a magnetic stirrer, stopcock adapter (nitrogen inlet) and condenser. The system was flushed with nitrogen and 1.5 g anhydrous trichloroacetic acid was added. The acid was heated to 60-65° and of the ditrichloroacetate (6.0 mg), dissolved in a few drops of THF, was added. After 5 minutes the reaction mixture was cooled, diluted with ether and poured onto crushed ice. The ether was separated and the aqueous layer was extracted with ether. The combined ether fractions were washed with 5% sodium bicarbonate, water and dried over magnesium sulfate. The ether was then filtered and concentrated. The product was spotted on silica gel TLC plate along with the starting material and eluted with benzene-ether 7:3. The rest of the product was diluted with methanol and a portion heated in 0.5% sodium hydroxide in methanol at 50°C for 10 minutes and an ultraviolet spectrum was taken of the sample before and after the base treatment. The results of the solvolysis reactions that were carried out are tabulated in Table II.

Exo-6-(1',2'-dibromoheptyl)-bicyclo[3.1.0]hexan-3-one (LXI). The bicyclic ketone XXIV (3.1 mmoles) was dissolved in 40 ml anhydrous chloroform in a 100 ml three-necked flask. The solution was stirred magnetically and under a stream of nitrogen an equivalent of pyridinium hydrobromide perbromide[71] was added at room temperature over a period of 20 minutes. The pyridinium salt gradually disappeared leaving a yellow solution. The chloroform solution was then washed with water, dried over magnesium sulfate, filtered and concentrated. The crude product was chromatographed on silica gel column (30 g) eluting with hexane-ethyl acetate mixtures. Two compounds were separated.

1. The dibromide LXI, eluted first, was obtained in 55% yield: i.r.(CCl_4) 3040 cm^{-1} (CH, cyclopropyl), 1748 cm^{-1} (C=O) 1140 cm^{-1} (C-C-C, ketone); n.m.r.(CCl_4) δ 4.18 (m, 1H, $C_7\underline{H}$), 3.72 (m, 1H, $C_6\underline{H}$).

2. Mixture of the dibromide LXI and monobromide LXII: i.r.(CCl_4) 3040 cm^{-1} (=CH), 1725 (C=O, α, β-unsaturated ketone on five-membered ring[81]), 1650 cm^{-1} (C=C), 1140 cm^{-1} (C-C-C, ketone).

Solvolysis of the dibromide LXI. The dibromide LXI (200 mg) was placed in a 50 ml flask with 30 ml of acetone-water 2:1 mixture. The solution was stirred at room temperature for 112 hours. After this time the solution was diluted with water and extracted with chloroform in the usual manner. The crude products were then separated by preparative TLC using benzene-ether 7:3 as solvent system. The mixture consisted of the following components:

1. Starting dibromide LXI (R_f 0.86), recovered as the major component (63%), was identified by TLC (benzene-ether 7:3): i.r.(CCl_4)

3040 cm^{-1} (CH, cyclopropyl), 1748 cm^{-1} (C=O), 1140 cm^{-1} (C-C-C, ketone).

2. Bromohydrin LXIII (R_f 0.39), isolated in 15% yield: i.r.(CCl_4) 3620, 3565, 3480 cm^{-1}(OH), 3040 cm^{-1} (CH, cyclopropyl), 1748 cm^{-1} (C=O), 1140 cm^{-1} (C-C-C, ketone), 1060 cm^{-1} (C-O). Mass spectrum: M^+ 291, 289 for ^{81}Br and ^{79}Br respectively; m/e 271, 273, $M^+ - H_2O$; m/e 260, 262, M^+ -HCO; m/e 210, M^+ - Br; m/e 209, M^+ - HBr; m/e 191, 271 - ^{79}Br, 273 - ^{81}Br; m/e 181, 260 - ^{79}Br, 262 - ^{81}Br; m/e 81, ^{81}Br; m/e 79,^{79}Br. The sturcture was further proved by TLC comparison with the bromohydrin LXIII prepared from XXIV.

3. Mixtures of four components (R_f 0.02-0.05) obtained in 5% yield could not be characterized because of lack of material.

Exo-6-[1'-bromo-2'-hydroxyheptyl]-bicyclo[3.1.0]hexan-3-one (LXIII). This compound was prepared according to the procedure of Guss and Rosenthal[80]. The bicyclic ketone XXIV (5.21 mmoles) was mixed with 95% N-bromosuccinimide (5.25 mmoles) in 25 ml water at room temperature. The reaction was stirred until all the solid N-bromosuccinimide had disappeared (4 hours). The usual work-up in chloroform followed by column chromatography on silica gel (30 g, benzene-ether mixture elutions) gave the bromohydrin LXIII in 60% yield: i.r.(CCl_4) 3625, 3570 cm^{-1} (OH) 3035 cm^{-1} (CH, cyclopropyl), 1748 cm^{-1} (C=O), 1140 cm^{-1} (C-C-C, ketone) 1058 cm^{-1} (C-O); n.m.r.(CCl_4) δ 4.08 (m, 1H, C<u>H</u>-O), 3.4 (m, 1H, C<u>H</u>Br), 3.43 (s, 1H, exchangeable, O<u>H</u>).

<u>Anal</u>. Calcd. for $C_{13}H_{21}O_2Br$: C, 53.97; H, 7.26; Br, 27.28

Found: C, 53.90; H, 7.40; Br, 27.50

6-(α-bromoheptanoyl)-bicyclo[3.1.0]hexan-3-one (LXIV). The bromohydrin LXIII (200 mg) was dissolved in 20 ml acetone in a 50 ml flask. The solution was cooled in an ice-water bath and stirred magnetically. A slight molar excess of Jones reagent was added dropwise and the solution was stirred for 20 minutes at 0°. After this time, the mixture was diluted in water and extracted with ether in the usual way. The diketo bromide LXIV was obtained in 80% yield: i.r. (CCl_4) 3045 cm^{-1} (CH, cyclopropyl), 1748 cm^{-1} (C=O, ring ketone), 1700 cm^{-1} (C=O, ketone α to cyclopropyl ring[81]); n.m.r.(CCl_4) δ 4.27 (t, 1H, J = 6.5 cps, CHBr adjacent to CH_2).

Exo-6-(1'-iodo-2'-isocyanoheptyl)-bicyclo[3.1.0]hexan-3-one (XLVII). This compound was prepared according to the procedure of Hassner et al[60]. The silver isocyanate was freshly prepared before the reaction [60,84]. The bicyclic ketone XXIV (5.21 mmoles) was dissolved in 25 ml anhydrous ether in a 100 ml three-necked flask fitted with a nitrogen inlet, thermometer, gas outlet, and magnetic stirrer. The flask was cooled in an ice-salt bath to -10°, and silver isocyanate (15.6 mmoles) was added with stirring. The reaction mixture was then cooled to -13°, and iodine (5.3 mmoles) was added. The solution became dark purple. It was then stirred 2 hours in the cold and another 6 hours at room temperature. By this time the colour of the solution was canary yellow. The silver salts were then filtered through celite and the ether was removed in the cold in vacuo. The yield of the iodo isocyanate was 75%: i.r.(CCl_4) 3030 cm^{-1}(CH, cyclopropyl), 2245 cm^{-1} (NCO, v. strong), 1748 cm^{-1} (C=O).

Hydrolysis and nitrous acid deamination of iodoisocyanate (XLVII). The iodo isocyanate XLVII (75 mg) was placed in a 50 ml three-necked flask fitted with a magnetic stirrer, nitrogen inlet, outlet and thermometer. The flask was cooled to -10° in an ice-salt bath and 10 ml of aqueous acetone (30% water) was added to hydrolyze the isocyanate. The solution was then cooled to -8° and sodium nitrite (4.7 mmoles) was added in 1 ml water followed by formic acid (4.7 mmoles). The solution was stirred at 0° for one hour and then 3.5 hours at room temperature. The reaction mixture was then diluted with water and extracted with ether in the usual way. Purification by preparative TLC (benzene-ether 7:3) gave the iodohydrin LXX (R_f 0.58) in approximately 60% yield: i.r.(CCl_4) 3545, 3520, 3460 cm^{-1} (OH), 3035 cm^{-1} (CH, cyclopropyl), 1743 cm^{-1} (C=O), 1137 cm^{-1} (C-C-C, ketone), 1060 cm^{-1} (C-O); n.m.r.(CCl_4) 100 MC δ 4.19 (m, 1H, C<u>H</u>-O), 3.22 (m, 1H, C<u>H</u>I), 0.59 (m, C<u>H</u>, cyclopropyl). Mass spectrum: M^+ 336; m/e 318, $M^+ - H_2O$; m/e 308, $M^+ - CO$; m/e 209, $M^+ - I$; m/e 191, 318 - I; m/e 181, 308 - I.

Exo-6-(α-iodoheptanoyl)-bicyclo[3.1.0]hexan-3-one (LXXI). The iodohydrin LXX (60 mg), obtained from the hydrolysis and deamination of the iodo isocyanate LXVII, was oxidized with Jones reagent by the same procedure as described for the oxidation of the bromohydrin LXIII. The resulting diketoiodide LXXI was obtained in 80% yield: i.r.(CCl_4) 3030 cm^{-1} (CH, cyclopropyl), 1745 cm^{-1} (C=O, ring ketone), 1695 cm^{-1} (C=O, ketone α to cyclopropyl group[81]); n.m.r.(CCl_4) 100 MC δ 4.48 (t, 1H, J = 4.0 cps, C<u>H</u>I adjacent to CH_2).

Exo-6-(1',2'-dihydroxyheptyl)-2α and β-(6''-carbomethoxy-2-hexynyl)-bicyclo[3.1.0]hexan-3-one (LXXIIa). The olefinic bicyclic keto ester XXV was treated with performic acid in buffered formic acid in the same way as the unalkylated ketone XXIV. The diol LXXIIa was obtained in 87% yield: i.r.(film) 3440 cm^{-1} (OH); 3035 cm^{-1} (CH, cyclopropyl), 1740 cm^{-1} (C=O, ketone and ester), 1165 cm^{-1} (C-O-C, ester) 1065 cm^{-1} (C-O, alcohol); n.m.r.($CDCl_3$) δ 3.69 (s, 3H, OCH_3), 3.7-2.7 (m, 4H, CH-O and OH). Mass spectrum: M^+ 364; m/e 333, $M^+ - OCH_3$; m/e 305, $M^+ - CO_2CH_3$; m/e 225, $M^+ - CH_2C{\equiv}C(CH_2)_3CO_2CH_3$; m/e 263, $M^+ - C_5H_{11}OH$; m/e 293, $M^+ - C_5H_{11}$; m/e 289, $M^+ - C_4H_8$; m/e 346, $M^+ - H_2O$; m/e 315, 346 - OCH_3.

Exo-6-(1',2'-dimesyloxyheptyl)-2α and β-(6''-carbomethoxy-2-hexynyl)-bicyclo[3.1.0]hexan-3-one (LXXIIb). A 50 ml round bottom flask was fitted with a stopcock adapter, thermometer, gas outlet and a magnetic stirrer. Anhydrous pyridine (10 ml) was added to the flask and it was cooled to -15° in an ice-salt bath. A molar excess of methansulfonyl chloride (3.26 mmoles) was added to the stirred solution under nitrogen. After the temperature was again at -15°, the diol LXXIIa (1.20 mmoles) in 5 ml pyridine was added. The reaction was stirred in the cold for 3 hours and then kept at -10°C over night. The cold reaction mixture was then poured onto crushed ice, saturated with sodium chloride and extracted with ethyl acetate in the usual way. The ethyl acetate was evaporated in vacuo at room temperature and traces of pyridine were removed on a vacuum pump. The yield of the dimesylate was 78-85%:

i.r.(film) 3030 cm^{-1} (CH, cyclopropyl), 1740 cm^{-1} (C=O, ketone and ester), 1350, 1180 cm^{-1} (SO_2); n.m.r.($CDCl_3$) δ 4.83 (m, 1H, $C_7\underline{H}$), 4.30 (m, 1H, $C_6\underline{H}$), 3.65 (s, 3H, $OC\underline{H}_3$), four singlets: 189.8, 189.1, 188.0, 187.2 cps (6H, $SO_2C\underline{H}_3$).

Solvolysis of the dimesylate LXXIIb. A solution of the dimesylate LXXIIb (380 mg) in 20 ml acetone-water (2:1) was stirred in a nitrogen atmosphere at room temperature for 36 hours.* The mixture was then diluted with water and extracted with methylene chloride. The methylene chloride extract was dried over anhydrous sodium sulfate, filtered and concentrated. The reaction products were separated by preparative TLC on silica gel using ethyl acetate as the solvent system. The components of the mixture were detected on the TLC plates in the following manner: Silica gel HF 254 (E. Merck) was used which enabled the detection of the hydroxy mesylate bands on the plates by means of short wavelength ultraviolet light. The prostaglandin bands could be detected only by spraying with 10% phosphomolybdic acid in ethanol, a destructive process. In order to recover the prostaglandins, a small part of the mixture was sacrificed for detection purposes and applied only a 4 x 10 cm plate. The remainder was spread on 20 x 20 cm plates and separated by measuring the R_f obtained from the small plate. This made the separation difficult since the bands did not travel uniformly.

The silica gel was extracted a few times with methanol. The

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* In another run lasting 24 hours, similar results were obtained.

methanol was then evaporated and the residue was taken up in methylene chloride, dried over sodium sulfate and filtered through celite. The recovery by this procedure was better than 95%.

The components of the reaction mixture separated on the TLC plates were the following:

1. Exo-6-(1'-hydroxy-2'-mesyloxyheptyl)-2-(6''-carbomethoxy-2-hexynyl)-bicyclo[3.1.0]hexan-3-one (LXXIII), was obtained in 70-80% yield from the starting dimesylate LXXIIb. Three hydroxymesylates were obtained (R_f 0.62, 0.48, 0.37). The latter (R_f 0.37) was obtained only in small amounts and could not be obtained pure for proper characterization. The first two (R_f 0.62, 0.48) had identical infrared and n.m.r. spectra. Both gave the same prostaglandin mixture on recyclising, therefore no stereochemical assignment could be made: i.r.(film) 3475 cm^{-1} (OH), 3030 cm^{-1} (CH, cyclopropyl), 1740 cm^{-1} (C=O, ketone and ester), 1355, 1180 cm^{-1} (SO_2), 1070 cm^{-1} (C-O); n.m.r.($CDCl_3$) 100 MC δ 4.72 (m, 1H, C<u>H</u>, mesylate), 3.68 (s, 3H, OC<u>H</u>$_3$), 3.34 (m, 1H, C<u>H</u> alcohol), 3.09, 3.07 (s, 3H, $SO_2C\underline{H}_3$), 0.64 (m, C<u>H</u> cyclopropyl).

2. 8α and 8β-5-Dehydro-15-epi-PGE_2 methyl ester (LXXV) (R_f 0.29) was obtained in 5-8% yield from the starting dimesylate LXXIIb: i.r.(film) 3440 cm^{-1} (OH), 1740 cm^{-1} (C-O, ester and ketone), 1170 cm^{-1} (C-O-C, ester), 1070 cm^{-1}(C-O); n.m.r.($CDCl_3$) 100 MC δ 5.9-5.2 (m, 2H, <u>H</u>C=C<u>H</u>), 4.1 (m, 2H, C<u>H</u>-O), 3.66 (s, 3H, OC<u>H</u>$_3$). Mass spectrum: m/e 346, $M^+ - H_2O$ (c.f. Table III for detailed interpretation of the major fragments.)

3. 8α and 8β-5-Dehydro-PGE_2 methyl ester (LXXIV) (R_f 0.19) was

obtained in 5-8% yield from the starting dimesylate LXXIIb: i.r.(film) 3400 cm^{-1} (OH), 1740 cm^{-1} (C=O ketone, ester), 1163 cm^{-1} (C-O-C, ester), 1080 cm^{-1} (C-O); n.m.r.($CDCl_3$) 100 MC δ 5.9-5.2 (m, 2H, HC=CH), 4.1 (m, 2H, CH-O), 3.68 (s, 3H, OCH_3). Mass spectrum: m/e 346, $M^+ - H_2O$. The fragmentation was identical with that of the 15-epi LXXV (c.f. Table III for detailed interpretation of the fragments).

8α and β-PGE_2 methyl ester (LXXVII). 8α and β-5-dehydro PGE_2 methyl ester (LXXIV) (10.3 mg) was placed in a sample cup with a small amount of ethyl acetate. Lindlar catalyst[85] (75 mg) was placed into a micro-hydrogenation flask and connected to a low pressure hydrogenation apparatus[92]. Ethyl acetate (3 ml), containing 1 mg quinoline*, was added to the flask. The sample cup was put into place and the system was flushed with hydrogen for 15 minutes. The system was then closed and the burette was filled with hydrogen. After the system had equilibrated, the sample was introduced and the solution was stirred. Hydrogen was slowly picked up. After four hours the reaction was complete. The solution was filtered through celite and the solvent was evaporated in vacuo. The crude products were chromatographed on silica gel (TLC) using ethyl acetate solvent system. The PG band was detected and extracted as was previously described. The isomeric mixture of LXXVIIa was obtained in 63% yield: n.m.r.($CDCl_3$) 100 MC δ 5.62 (m, 2H, trans HC=CH), 5.38 (m, 2H, cis HC=CH), 4.1 (m, 2H, CH-O), 3.70 (s, 3H, OCH_3).

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* More than 3% quinoline, by weight, to the amount of catalyst makes the reaction very slow. Best results were obtained using 1-2% quinoline.

Mass spectrum: m/e 348, $M^+ - H_2O$; a detailed interpretation of the major fragments is given in Table IV.

15-Epi-8α and β-PGE_2 methyl ester (LXXVII The hydrogenation on 15-epi-5-dehydro PGE_2 methyl ester LXXV was carried out in the same way as described for LXXIV. Because of lack of material, an n.m.r. spectrum could not be taken.

Mass spectrum: m/e 348, $M^+ - H_2O$. Mass measurement found: 348.229694; calcd. for $C_{21}H_{32}O_4$: 348.230045; other possible empirical formulae for this mass are: $C_{16}H_{32}N_2O_6$, $C_{19}H_{30}N_3O_3$ and $C_{24}H_{30}NO$. These are ruled out because LXXVIII could not contain any nitrogen. Mass measurement of m/e 190: 190.135990; calcd. for $C_{13}H_{18}O$, 190.135758; another possible empirical formula for this mass is $C_{11}H_{16}N_3$ which is again ruled out because LXXVIII contains no nitrogen.

Epimerization of the isomeric mixture of LXXVII The 8α and β-PGE_2 methyl ester (LXXVII mixture (6.3 g) was dissolved in 3 ml of a 3% ethanolic potassium acetate solution and stirred at room temperature for 94 hours. The reaction mixture was then diluted with water and extracted with pure methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Preparative TLC separation on silica gel, ethyl acetate of the crude mixture gave two compounds:

1. 8α-PGA_2 methyl ester (LXXIX) consisted of 18% (0.7 mg) of the reaction mixture: UV (MeOH) 217 mμ, ε 9,000; mass spectrum: M^+ 348,

m/e 330, $M^+ - H_2O$; m/e 317, $M^+ - OCH_3$; m/e 299, 330 - OCH_3; m/e 298, 330 - CH_3OH; m/e 287, 330 - C_3H_7; m/e 190, 330 - $C_7H_{10}CO_2CH_3$ + H transfer); m/e 207, $M^+ - C_7H_{10}CO_2CH_3$; m/e 141, $[C_7H_{10}CO_2CH_3]^+$. The PGA_2 was contaminated with about 2% PGB_2 methyl ester: UV (MeOH) 277 mμ, ε 2,200.

2. Mainly 8α-PGE_2 methyl ester (LXXVIIb) consisted of 80% (2.9 mg) of the reaction mixture: 100 MC n.m.r.($CDCl_3$) using 109 scans which were analyzed with a computer of average transients (C.A.T.): δ 5.6 (m, 2H, trans HC=CH), 5.3 (m, 2H, cis HC=CH), 4.1 (m, 2H, CH-O) 3.6 (s, 3H, OCH_3). Accurate chemical shifts were not obtained because of drifting in the spectrometer. Mass spectrum: m/e 348, $M^+ - H_2O$; the spectrum was identical to the PGE_2 methyl ester spectrum taken before epimerization.

CLAIMS TO ORIGINAL RESEARCH

1. Total synthesis of PGE_2 methyl ester.
2. Synthesis of 15-epi-8α and β-PGE_2 methyl ester.
3. Synthesis of PGA_2 methyl ester.
4. Synthesis of the acetylenic prostaglandins:
   8α and β-5-dehydro PGE_2 methyl ester and
   15-epi-8α and β-5-dehydro PGE_2 methyl ester.

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