Synthesis of Arachidonic Acid Metabolite Derivatives

A Thesis

by

Danilo G. Crosilla

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Danilo G. Crosilla

Department of Chemistry

McGill University

Montreal, Quebec, Canada

Abstract

The synthesis of Methyl 15-Hydroxy-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12(R)-oxy-eicosa-13-ynoate, an arachidonic acid metabolite derivative, is described. As well, three methods for the attachment of the C_{13}-C_{20} prostaglandin side-chain were studied and the results are described. These methods involved three synthons: compounds 53, 71 and 102. The reduction of the C-15 keto group on a model compound was performed and was found to have the same behavior as in the prostaglandins.

A partial structure proof of L.S. Wolfe's and C. Pace-Asciak's compound, 9,12-oxy-8,11,15-trihydroxy-13-enoic acid is given.

Synthèse de derivatifs d'un métabolite de l'acide arachidonique.

Danilo G. Crosilla
Département de Chimie
Université McGill
Montréal, Québec, Canada

Résumé

La synthèse du méthyle 15-hydroxy-8(R)-méthoxy-11(R)-p-nitrobenzoyloxy-9(S),12(R)-oxy-eicosa-13-ynoate, un derivatif d'un métabolite de l'acide arachidonique, est décrite. Sont décrits aussi les résultats d'une étude de trois méthodes d'attachement du groupement C_{13}-C_{20} de les réactif suivants: composés 53, 71 et 102. La réduction, sur un composé modèle, du groupe cétone en C-15, a été étudiée, et cette cétone agi de la même manière que le groupe cétone C-15 des prostaglandines.

On présente une preuve partielle de la structure du composé de L.S. Wolfe et de C. Pace-Asciak, l'acide 9,12-oxy-8,11,15-trihydroxy-13-enoique.

DEDICATION

To my wife Pauline

Acknowledgements

I would like to express my sincere gratitude to my research director, Dr. George Just, for his guidance and continuous encouragement throughout my stay in his laboratory.

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Table of Contents

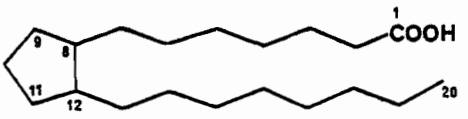
Chapter I	Introduction	1
Chapter II	Model Studies Towards the Synthesis of 9,12-Oxy-8,11,15-trihydroxyeicosa-5,13-dienoic Acid.	25
Chapter III	Studies on the Synthesis of Furanose and Pyranose Sugars from Nitro-Olefins.	58
Chapter IV	Studies Towards the Synthesis of Furanose and Pyranose Sugars via an Unsaturated Ketene Dithioacetal S-Oxide.	79
Chapter V	Synthesis of Arachidonic Acid Metabolite Derivative 150	91
Contributions to Knowledge		128
General Experimental		129
Experimental Chapter II		131
Experimental Chapter III		149
Experimental Chapter IV		159
Experimental Chapter V		164
Bibliography		178

CHAPTER I

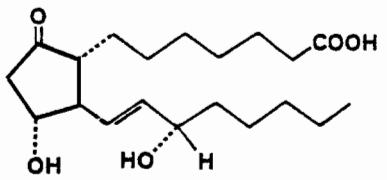
The Prostaglandins:

The prostagladin story began nearly fifty years ago when the New York gynaecologists, Kurzrok and Lieb reported that strips of human uterus could react by strong contraction or relaxation in response to fresh human semen[1]. Shortly afterwards Goldblatt[2] in Britain studied the stimulating activity of human seminal fluid extracts on smooth muscle. Almost simultaneously von Euler[3] in Sweden prepared extracts of monkey, sheep and goat seminal fluids and observed their activity on smooth muscles and their effect on blood pressure. Because of the source of his extracts, mammalian accessory genital glands, von Euler coined the term "prostaglandin" for the active ingredient present.

The next major development in the field took place about twenty years later when Bergstom and Sjovall[4,5], isolated and elucidated the structure of prostaglandin E_1 (1) and $F_{2\alpha}$ (2), thereby showing that prostaglandin was not a single substance but a family of chemically related compounds derived from the hypothetical prostanoic acid.

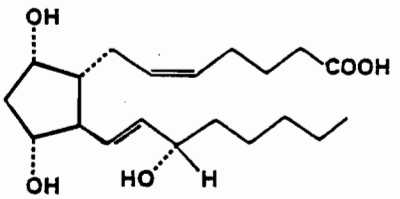


PROSTANOIC ACID



PGE_1

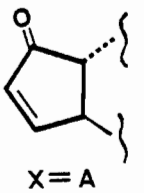
(1)



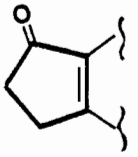
$PGF_{2\alpha}$

(2)

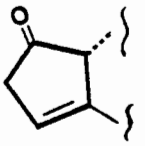
This was followed by the discovery of other prostaglandins (PGX_n) shown below:



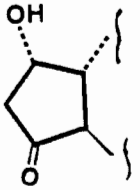
X = A



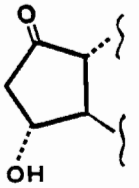
X = B



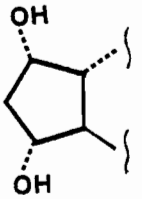
X = C



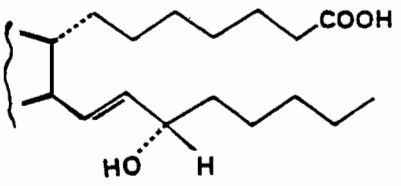
X = D



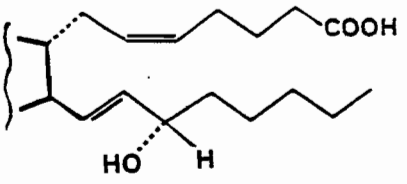
X = E



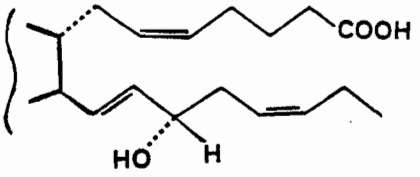
X = F



n = 1



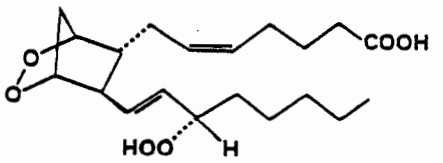
n = 2



n = 3

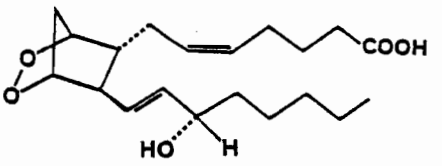
Although first discovered in male accessory sexual glands and their secretions, it has been shown that prostaglandins are very widespread throughout mammalian tissues and body fluids[6].

During subsequent studies on the formation of prostaglandins from unsaturated fatty acids, Samuelsson discovered that the oxygen atoms of the keto group and the hydroxyl group in the five membered ring of PGE_1 (1) originated from the same molecule of oxygen[7]. On the basis of this finding it was proposed that an endoperoxide structure is the intermediate in the biosynthesis of prostaglandins. In 1973 endoperoxides PGG_2 (3) and PGH_2 (4) were isolated and characterized[8].



PGG_2

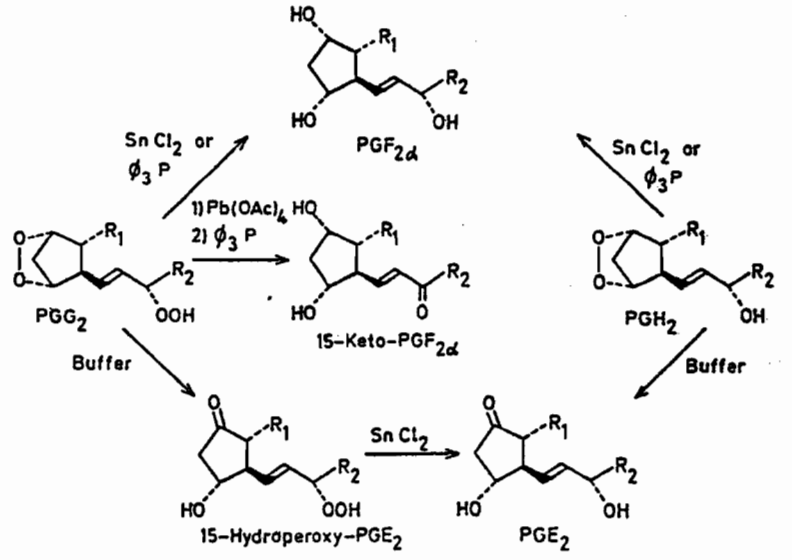
(3)



PGH_2

(4)

The structures of PGG_2 and PGH_2 were established by three sets of experiments. Treatment of PGG_2 (3) with a mild reducing agent such as tin chloride and triphenylphosphine (Ph_3P) gave $PGF_{2\alpha}$. This showed the presence of a peroxide bridge between C-9 and C-11, but did not discriminate between a hydroxyl and a hydroperoxyl group at C-15. In the second experiment PGG_2 was reacted with lead tetraacetate in benzene followed by addition of Ph_3P. The major product was found to be 15-keto-$PGF_{2\alpha}$. Lead tetraacetate effects dehydration of hydroperoxides into ketones; therefore the formation of this product strongly indicated the presence of a hydroperoxyl group at C-15. In the third experiment PGG_2 was converted to 15-hydroperoxy-PGE_2 by treatment with a buffer, which gave independent evidence for a peroxide group at C-15.



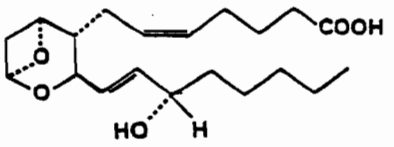
Reactions carried out on PGG_2 and PGH_2. R_1 = $CH_2CH{=}CH{-}(CH_2)_3{-}COOH$; R_2 = $(CH_2)_4{-}CH_3$; ϕ = phenyl.

Similar experiments were carried out on PGH_2 and the data pointed to the fact that this intermediate had a peroxide bridge between C-9 and C-11, but had a hydroxyl instead of a hydroperoxyl group at C-15.

PGG_2 was 50 to 200, and PGH_2 100 to 400 times more active than $PGF_{2\alpha}$ in aggregation of human platelets. The half-lives of these two intermediates in aqueous medium at 37^{o} was of the order of 5 minutes.

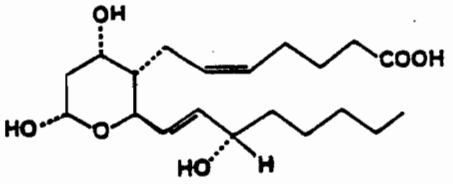
Continued research by Samuelsson and co-workers led to the discovery of a new group of biologically active compounds: the thromboxanes[9,10]. The name comes from the fact that they were isolated from thrombocytes (platelets) and contain an oxane structure. The unstable intermediate thromboxane A_2 (TXA_2) (5), with a biological half-life of approximately 30 seconds, was trapped by the addition of methanol, ethanol or sodium azide to suspensions of washed human platelets incubated with arachidonic acid.

(5)



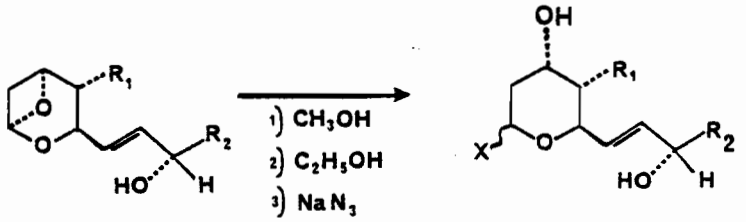
Thromboxane A_2

(6)



Thromboxane B_2

Thromboxanes have been implicated as cellular mediators in platelet aggregation and muscle contraction[11].



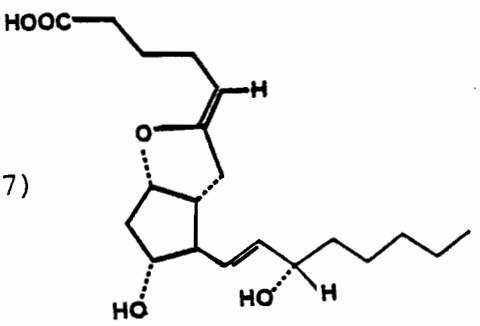
R_1=-$CH_2CH{=}CH(CH_2)_3COOH$

R_2=-C_5H_{11}

1) X = -OCH_3
2) X = -OC_2H_5
3) X = -N_3

In their search for thromboxane synthetase Drs. S. Moncada and J.R. Vane, from Wellcome Laboratories, discovered an enzyme that converts prostaglandin endoperoxides into an unstable substance called prostacyclin (PGI_2)[12] (7). This new prostaglandin was found to be a potent inhibitor of platelet aggregation and caused relaxation in some vascular smooth muscles[13,14]. It appears that while both prostacyclin (PGI_2) (7) and thromboxane A_2 (TXA_2) (5) are produced by enzymatic transformation of the prostaglandin endoperoxides, they play opposite roles in the body.

(7)

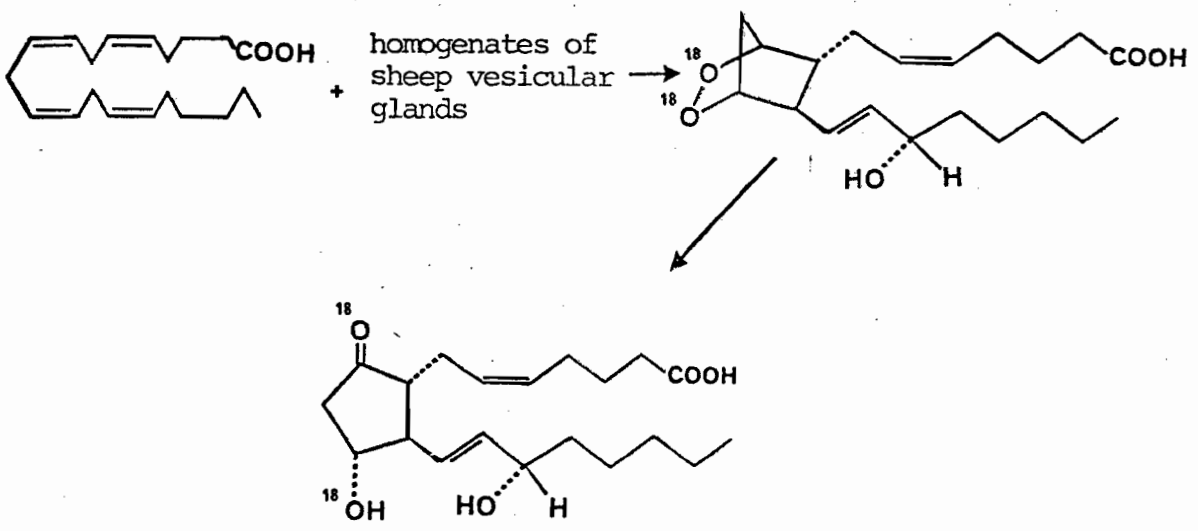


Prostacyclin

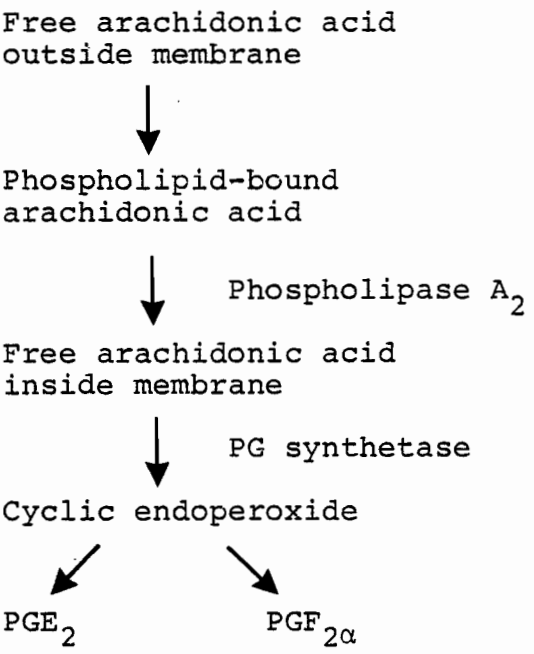
Biosynthesis:

The structural similarity of prostaglandins to the essential fatty acids, especially arachidonic acid, led investigators[15,16] to believe that the dietary fatty acids might be their precursors. The first prostaglandin to be studied was PGE_2 and shortly thereafter it was shown that $PGF_{2\alpha}$[17] also originated from arachidonic acid.

The most conclusive results concerning the biosynthesis of prostaglandins were obtained from the use of labelled molecular oxygen ($^{18}O_2$) or a mixture of labelled and non-labelled oxygen ($^{18}O_2$ and $^{16}O_2$) during incubation of the substrate with cyclooxygenase. When arachidonic acid was incubated with homogenates of sheep vesicular glands and labelled oxygen, it was shown that three oxygen atoms were incorporated in PGE_1. It was further shown that the two oxygen atoms on the ring of PGE_1 originated from the same oxygen molecule[18]. From this study evolved the concept of an endoperoxide intermediate, which was isolated a few years later[8].

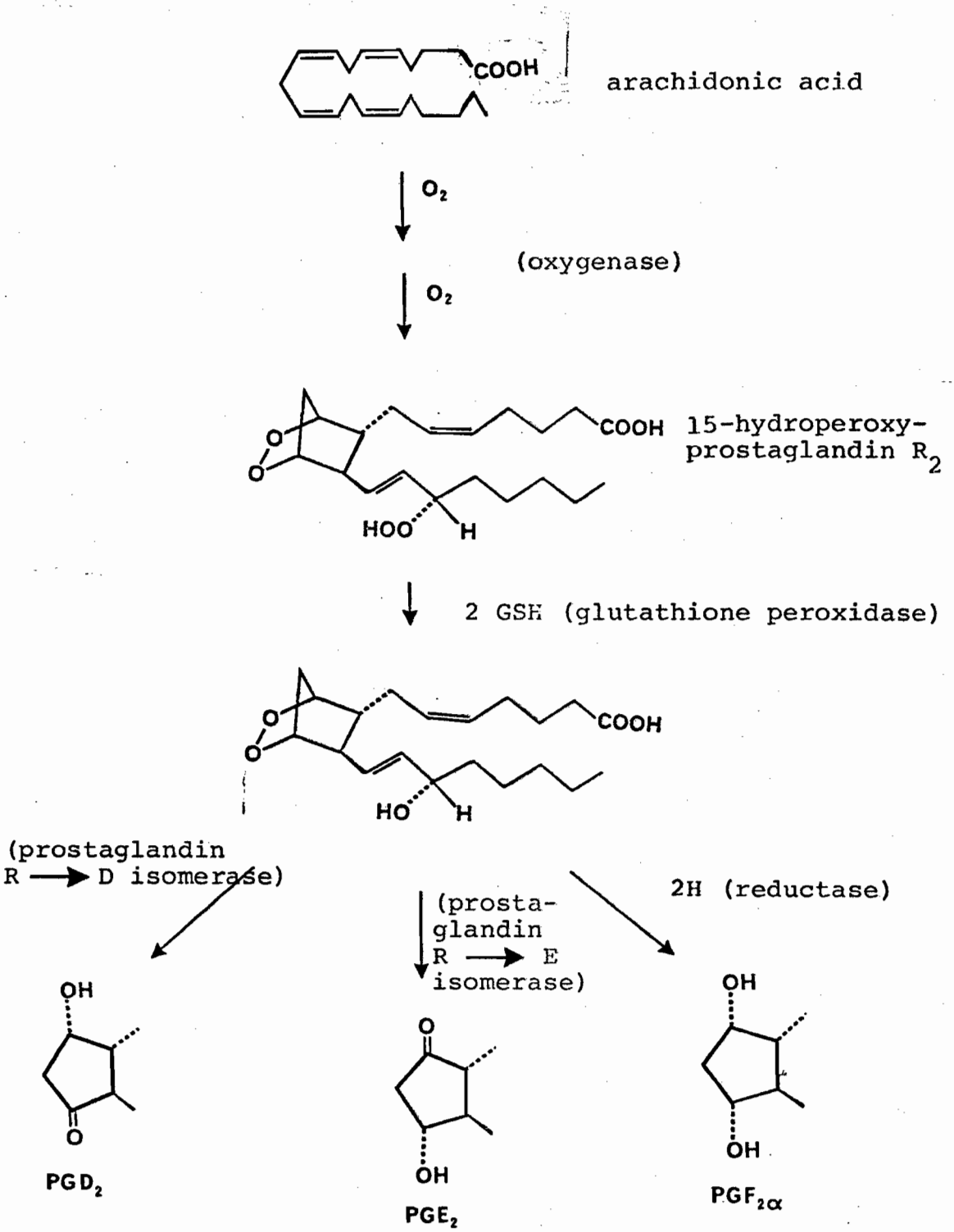


Once the fact that the prostaglandins originated from the fatty acids was well established, investigators began their search for the enzyme complexes responsible for these conversions. Two groups of workers, Van Dorp et al.[6], in Holland, and Bergstrom et al.[16], in Sweden, independently produced the following scheme:

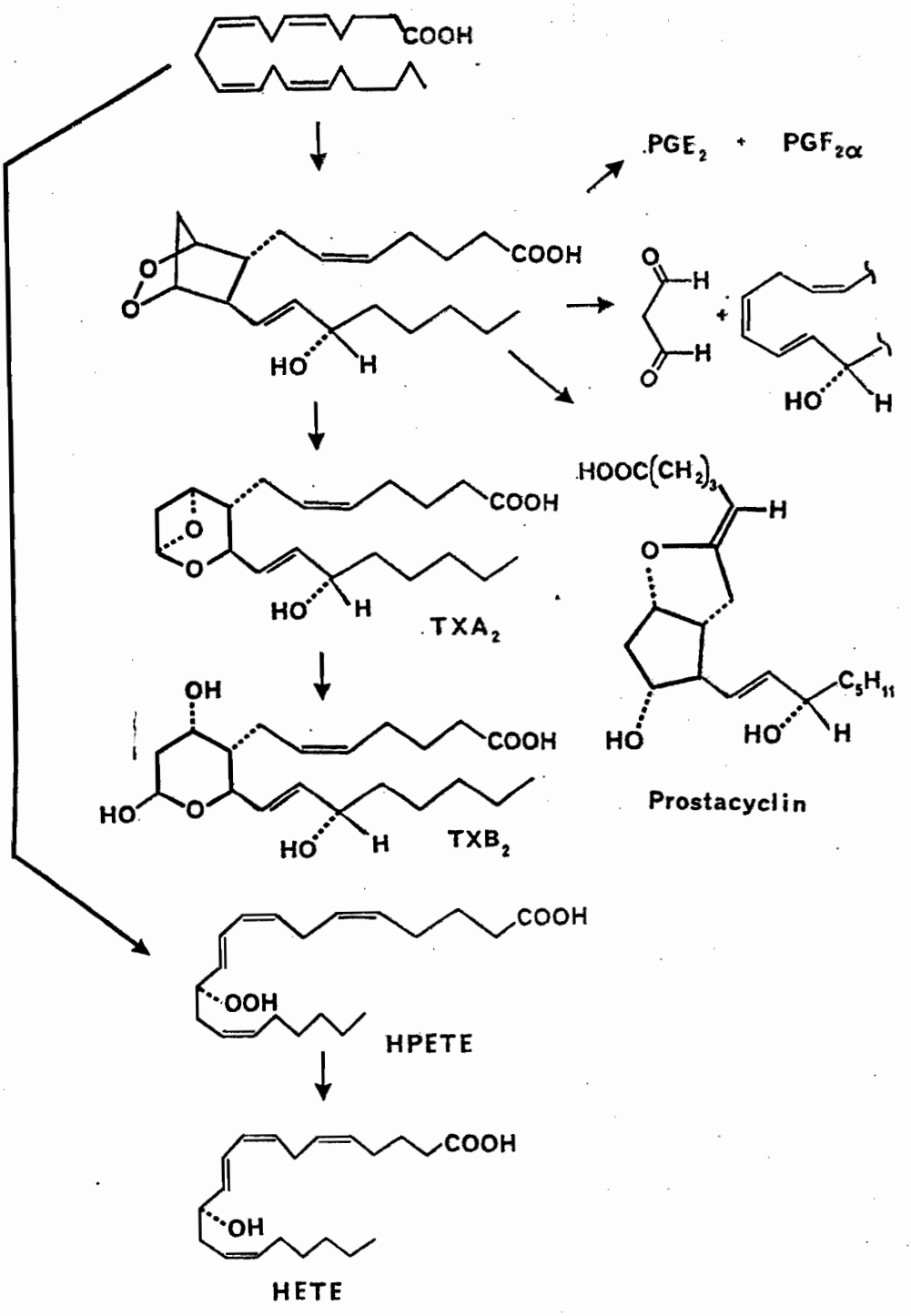


In nature, fatty acids are mainly incorporated into phospholipids in the cell membranes and released by an enzyme called phospholipase A_2. These free fatty acids are then converted to the cyclic endoperoxide by a different enzyme system called PG synthetase. It should be pointed out that this prostaglandin synthetase system is composed of many different enzymes; each is responsible for a specific transformation. The figure[19] below indicates the chemical

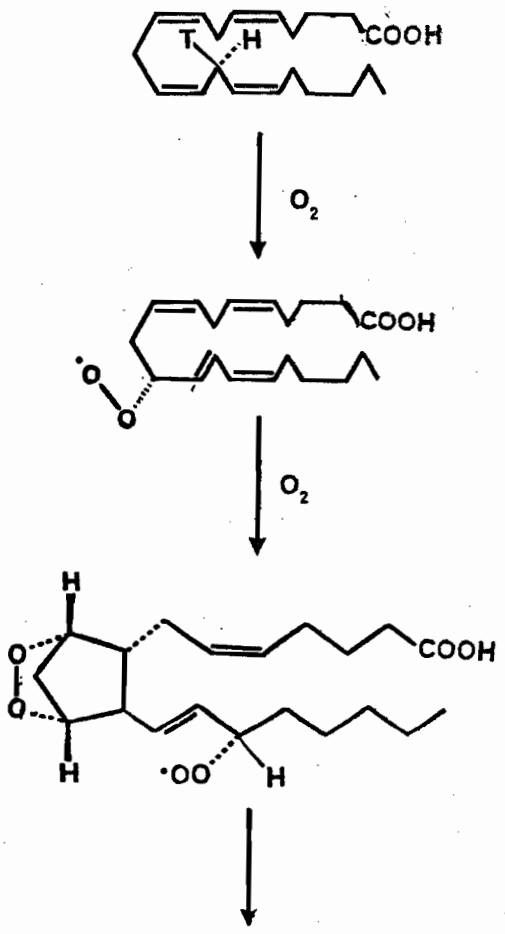
transformation and the enzyme responsible for that transformation.



From the endoperoxide intermediate, all the classical prostaglandins, thromboxanes, HPETE, HETE, and prostacyclin originate. At this point the metabolic pathways of arachidonic acid seem to be complete, and are illustrated in the figure below.



Because the endoperoxide was an intermediate for all the prostaglandins, its conversion to its biological products was studied further. Samuelsson[20] found that the initial step consisted of a lipoxygenase-like reaction in which the hydrogen at C-13 was removed, the Δ^{11}-double bond was isomerized into the Δ^{12}-position, and oxygen was inserted at C-11 (see figure).



all other prostaglandins

This unstable intermediate spontaneously cyclizes with the addition of another molecule of oxygen to afford PGG_2.

Several other possible mechanisms for the conversion of arachidonic acid to the endoperoxide intermediate are also in agreement with the isotopic experiments, but seem to be less likely and therefore will not be discussed here.

Biological and Biochemical Properties:

Although the precise physiological role of prostaglandins has not been clearly defined, it has been shown that they are associated with most mammalian tissues and implicated in physiological systems[21].

As more sensitive and specific methods of analysis are being devised, the presence of prostaglandins is being demonstrated in an ever-increasing number of different tissues, such as lung[22], thymus[23], brain and spinal cord[24], kidney[25] and many more. This unusual spectrum of activities gives the prostaglandins a great therapeutic potential. Listed below are some of their clinical applications[26]:

SYSTEM	MODE OF ACTION	APPLICATION
Reproductive	Stimulation of uterine smooth muscle, luteolysis.	Induction of labour or termination of pregnancy, menstrual regulations and control of estrus cycle.
Respiratory	Relaxation of bronchial smooth muscle, broncho-dilation.	Treatment of asthma and broncho-constriction.
Gastrointestinal	Inhibition of gastric acid secretion.	Treatment of peptic ulcer.

SYSTEM	MODE OF ACTION	APPLICATION
Cardiovascular	Vasodilation, increased cardiac output.	Treatment of hypertension, shock, congestive heart failure.
Renal	Regulation of renal blood flow and sodium excretion.	Impaired renal failure.
Platelets	Inhibition of platelet aggregation.	Treatment and prevention of thrombosis.

Biosynthesized in the cell membrane from simple fatty acids, the prostaglandins act locally and rapidly, in small amounts. It is for this reason that they are sometimes termed "local hormones". Ordinary hormones are produced by specific glands and then sent via the circulatory system to the organ which requires them. In contrast, many prostaglandins seem to be biosynthesized at the specific site where they act.

A perfect example of this type of mode of action is the blood-clotting mechanism postulated by J.R. Vane and co-workers[27]. Vane suggested that platelets interacting with a normal cell wall release endoperoxides which serve as a substrate for prostacyclin synthetase in the vessel wall, generating PGI_2 (platelet aggregation inhibitor) which protects the vessel against platelet deposition. When the vessel wall is destroyed or damaged the platelets will start adhering to the exposed (subendothelial) layers which produce less PGI_2 and contain pro-aggregating materials such as collagen. The endoperoxides released by the adhering

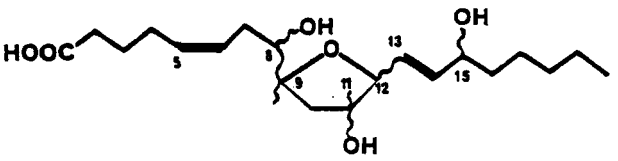
platelets will undergo bio-transformation to Thromboxane A_2 (TXA_2), which will cause further aggregation.

With isotope-labelled prostaglandins, it has been shown that prostaglandins have an extremely short lifetime. They are rapidly inactivated enzymatically into shorter oxidized and hydroxylated fragments[28,29].

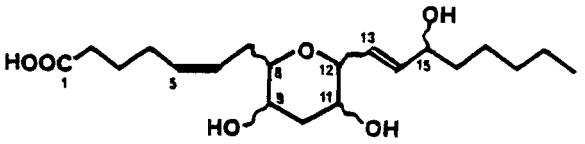
Not only do they react very quickly but their biological action may be observed at concentrations of 0.01 ng/ml *in vitro* and 10 ng/kg *in vivo*. In this respect they are among the most potent compounds known.

Hydroxylated By-Products of Arachidonic Acid:

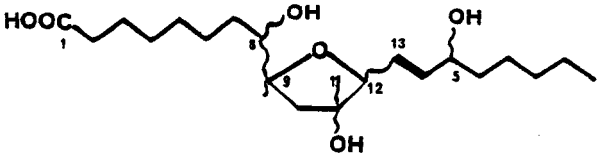
The conversion of polyunsaturated fatty acids to prostaglandins by sheep seminal vesicles has been well documented[16,30,31,32]. A few years ago, C. Pace-Asciak and L.S. Wolfe[33,34] reported three new hydroxylated arachidonic and eicosatrienoic acid by-products. They found that the prostaglandin E_2 fraction, after treatment with alkali to convert PGE_2 to PGB_2, still contained three major compounds tentatively identified as 8, 9, and 10.



(8)



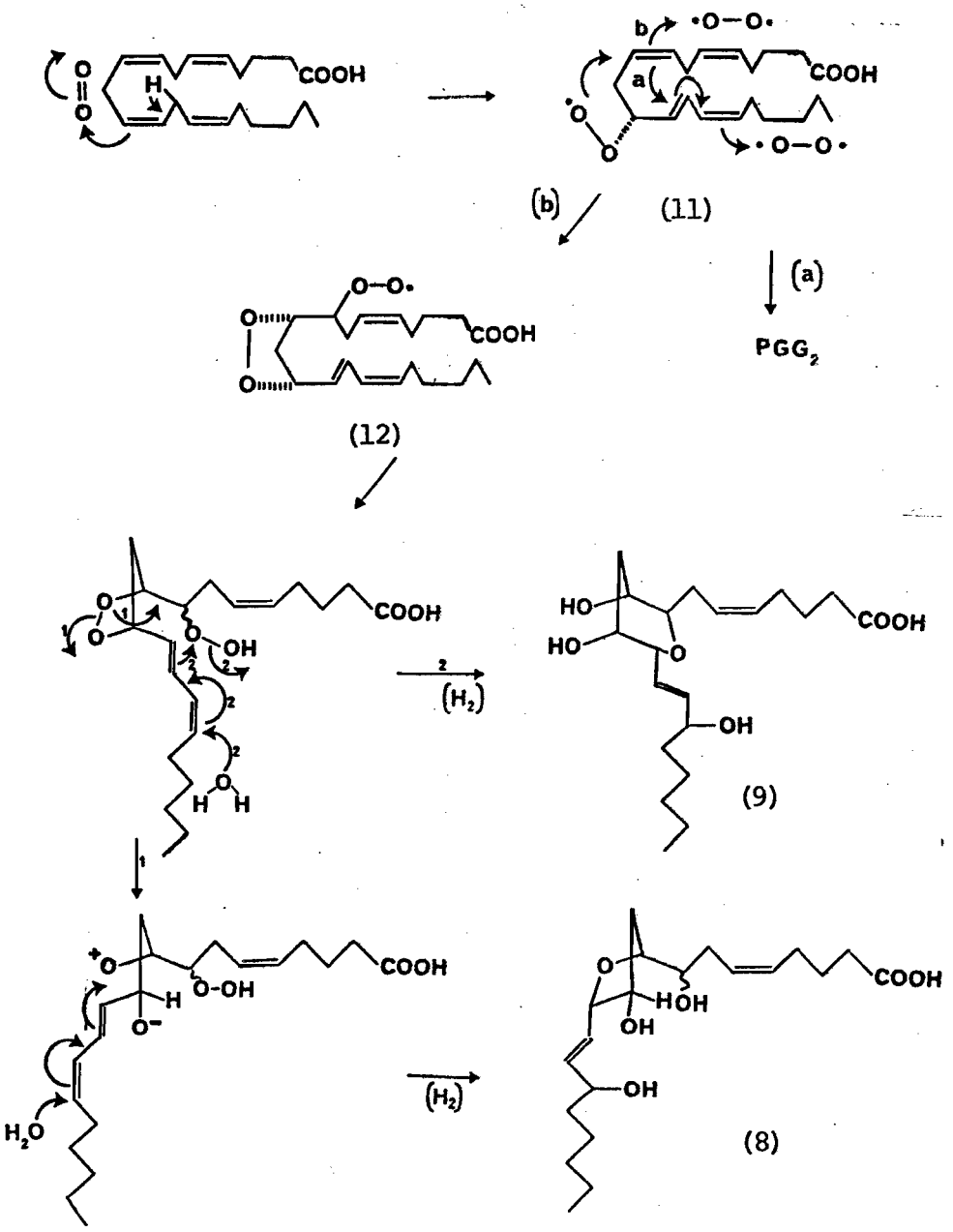
(9)



(10)

The individual amounts of purified compounds 8, 9 and 10 were 2% of the amount of PGE_2. Their structure was determined from mass spectrometric data, nuclear magnetic resonance data and degradation studies. The stereochemistry of the asymmetric centers (8,9,11,12 and 15 in compounds 8, 9 and 10) are not known. C. Pace-Asciak and L.S. Wolfe[33] proposed a mechanism for the bio-conversion of arachidonic acid into 8 and 9, which follows, in part, the scheme suggested for the biosynthesis of the prostaglandins[30], and which is presented here in a somewhat more elaborate form.[127]

Arachidonic acid undergoes the same oxidation as in the PG bio-synthesis to give the intermediate 11, which either cyclizes to give PGG_2 or traps oxygen to give the hydroperoxyl compound 12. This unstable intermediate can either cyclize to give the product 9, or rotate through 120°, after cleavage of the C-9 and C-11 peroxide bridge, and then cyclize with the $\Delta^{12,13}$ double bond to give compound 8. A similar mechanism is envisaged for the formation of 10 from 8,11,14-eicosatrienoic acid which is also present in significant amounts in sheep seminal vesicles[35].


COOH
b
•O—O•
a
(11)
(b)
(a)
PGG2
(12)
OH
(H2)
(9)
HO
HO
(8)
H2O

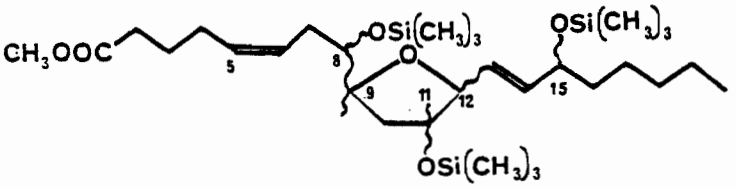
B. Axelrod[36,37] and co-workers recently reported that compound 8, 9,12-oxy-8,11,15-trihydroxyeicosa-5,13-dienoic acid, is formed when an isoenzyme of soybean lipoxygenase, L-2, acts on arachidonic acid. Contrary to the earlier view[33] that lipoxygenase catalyzed one dioxygenation of arachidonic acid, B. Axelrod showed that soybean lipoxygenase (L-2)[38] could promote this bis-hydroperoxidation of arachidonic acid, consuming two moles of oxygen per mole of arachidonic acid[39]. It was also shown that L-2 also catalyzes double dioxygenation of arachidonate compounds. Moreover a variety of products are obtained, of which 15% appears to be compound 8. In view of B. Axelrod's findings, Wolfe's proposed mechanism for the bio-conversion of arachidonic acid to 9,12-oxy-8,11,15-trihydroxyeicosa-5,13-dienoic acid seems very plausible.

Arachidonic acid by-products 8 and 9 may be essential metabolites which control prostaglandin production, or may have some other regulatory function. However, this is only speculation which will have to be proven in future studies.

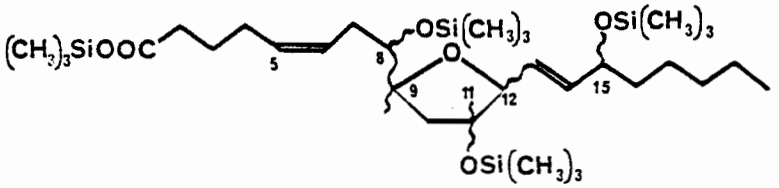
Mass Spectral Data:

The first compound to be studied by L.S. Wolfe and co-workers[34] was the furano compound 8, along with its

derivatives, the methyl ester 13 and the trimethylsilyl ester 14.



(13)



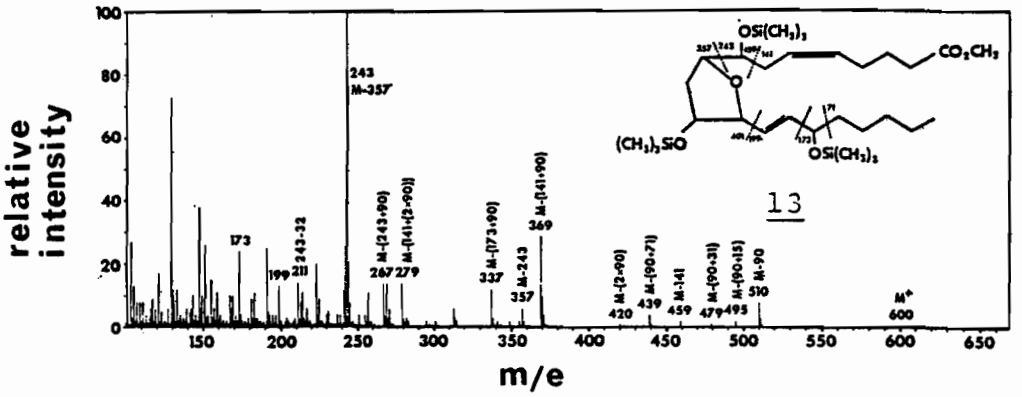
(14)

The nuclear magnetic resonance data for compound 8 displayed resonances at 5.55 and 5.75 ppm due to olefinic protons. The positions of the double bonds were determined by oxidative ozonolysis and were found to be at positions 5 and 13.

The infrared data showed significant absorptions at 3300, 2900 and 2800 cm^{-1} for hydroxyl and alkyl groups

respectively.

The mass spectral data gave the most significant information. The methyl ester derivative 13 was the first to be examined and was found to have a molecular ion of 600 m/e which is in accordance with the formula of this compound. Closer examination of the spectrum of compound 13 revealed the following molecular ions:



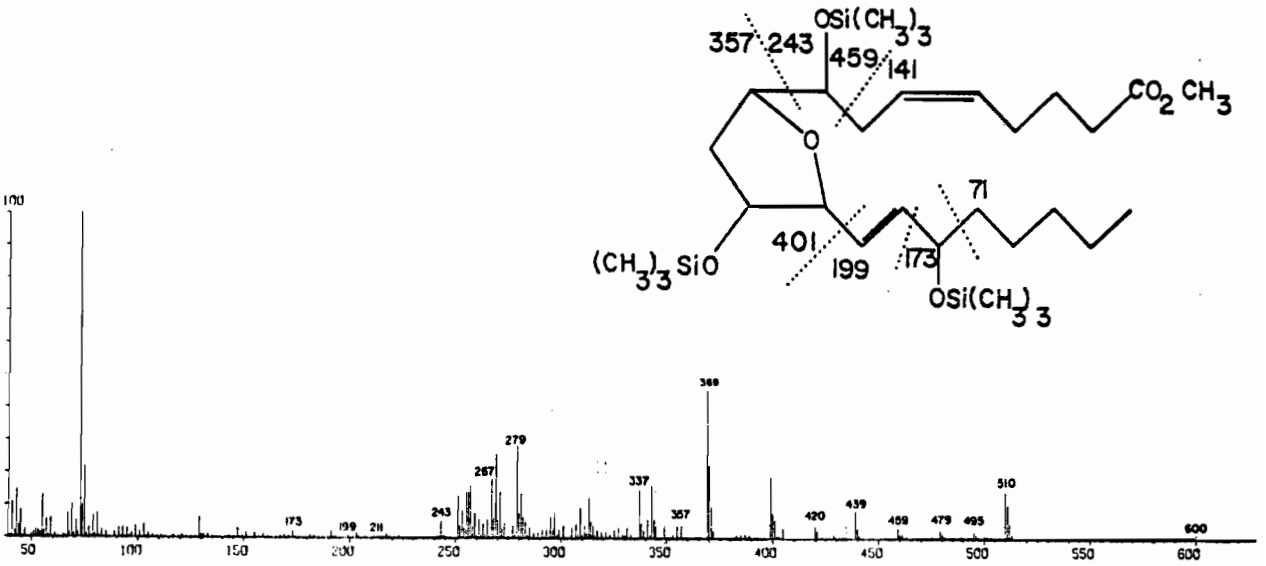
Ion	m/e
M^+	600
$(M-90)^+$ loss of Me_3SiOH	510
$(M^+-(90+15))^+$	495
$(M^+-(90+71))^+$ loss of Me_3SiOH and C_5H_{11}	439
$(M^+-(2x90))^+$	420
$(M^+-(173+90))^+$ loss of $Me_3SiOHCHC_5H_{11}$ and Me_3SiOH	337
$Me_3SiOCHCH_2CH=CH(CH_2)_3COOH_3$	243

To aid in its interpretation, the mass spectrum on the preceding page was compared to that of the trimethylsilyl ester 14 . The molecular ion was found to be 658 mass units which is consistent with the formula of derivative 14. Fragments containing the ester group in compound 14 are now displaced by 58 mass units from the corresponding fragments from the methyl ester 13 . Ions of structural significance arise from the loss of 71 and 173 mass units in both spectra, of 141 mass units for the methyl ester and of 199 mass units for the trimethylsilyl ester derivatives. These latter two fragments are ions arising from the cleavage of the side chain containing the ester group. Further examination places the hydroxyl groups at C-8 and at C-15. The position of the third hydroxyl group, C-11, was determined from degradation studies. Confirmation of the above spectral interpretation was secured via derivatives obtained from catalytic reduction with hydrogen and deuterium gases.

The structure of compound 10 was determined in the same manner as was compound 8. Direct comparison of their mass spectra also gave further evidence for the structure of compound 10.

As previously mentioned, B. Axelrod and co-workers[36] recently reported the formation of Pace-Asciak's compound 8 by soybean lipoxygenase - 2. The mass fragmentation pattern of Axelrod's compound was nearly identical to that of the cyclic ether 9,12 -oxy-8,11,15-trihydroxyeicosa-5,13-

dienoic acid (8) reported by Pace-Asciak. The molecular ion, 600 m/e, is consistent with the molecular formula.



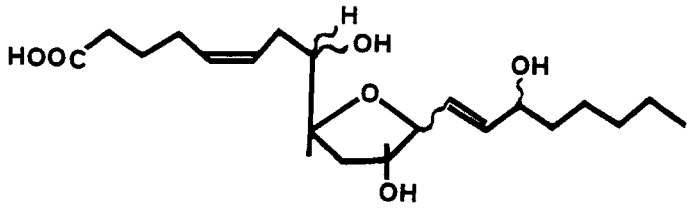
Mass spectrum of compound 13

With the data obtained by these two teams, and by their direct comparison, one can be fairly certain that the proposed structures are correct. However, further structural evidence would be desirable before attempting to prepare all the possible stereoisomers, since mass spectral data do give but little stereochemical information.

Aim of Project:

Because the biological functions of arachidonic acid metabolites 8, 9 and 10 are unknown, and indeed may have important functions such as regulation of prostaglandin production, their chemical synthesis became an important necessity. However the primary aim of this project was to confirm, by direct comparison, the structures proposed by L.S. Wolfe and B. Axelrod as well as to devise an efficient synthesis of all possible stereoisomers of furano PG 8, PG 10 and pyrano PG 9 in order to determine the stereochemistry of the chiral centers in the natural products.

Because of the size of this task, this work will be limited to those compounds with fixed stereochemistry at certain centers. If the biosynthesis follows somewhat that of prostaglandins, the chirality of the C-11 center is fairly certain and therefore this center will be fixed as designated in 15, 16 and 17. Also, the chirality of the C-9 carbon, although much less certain, is likely to be as indicated. Since these compounds originate from arachidonic acid and the Δ^5-double bond is not involved in the conversion, its stereochemistry should remain unchanged and therefore should still be cis in the products 8 and 9. All the other chiral centers are not known and therefore will have to be determined by direct comparison.



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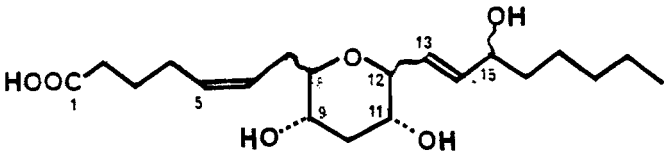

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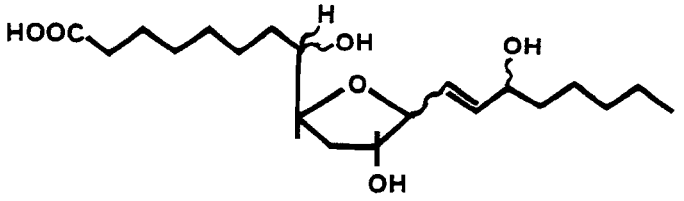


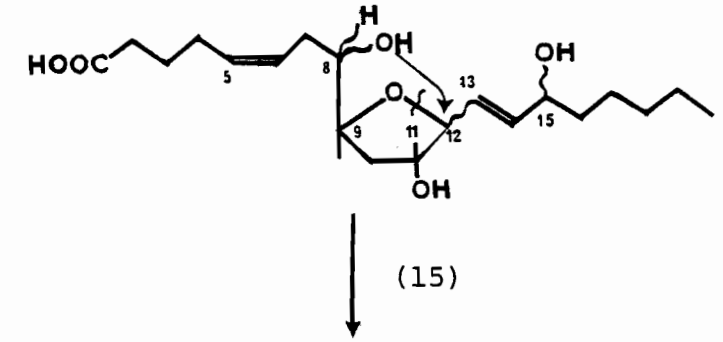
(17)

CHAPTER II

Model Studies Towards the Synthesis of 9,12 -oxy-8,11,15-trihydroxyeicosa-5,13-dienoic acid.

Introduction:

Examination of the compounds to be synthesized, namely 9,12 -oxy-8,11,15-trihydroxyeicosa-5,13-dienoic acid (15) and pyrano-PG 16 , reveals that they differ only in that the C-8 hydroxyl function and the C-9 ether function of 15 are reversed in 16.



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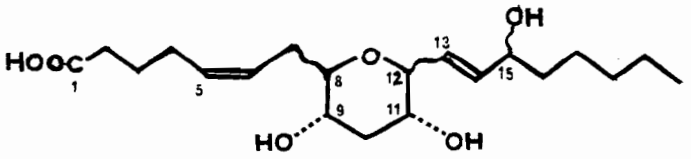
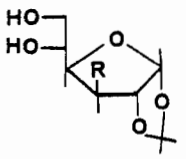


(16)

Because of this interconversion, one can envisage an intermediate which, through chemical transformation, would lead to both compounds.

Since there are many chiral centers in these two compounds, and chemical resolutions are very inefficient, it was decided that a cheap, naturally-occurring chiral substrate, possessing a maximum number of chiral centers which could be directly incorporated, would be the best choice for a starting material. For these reasons, the readily available 1,2-O-isopropylidene-α-D-glucofuranose (18) was chosen.



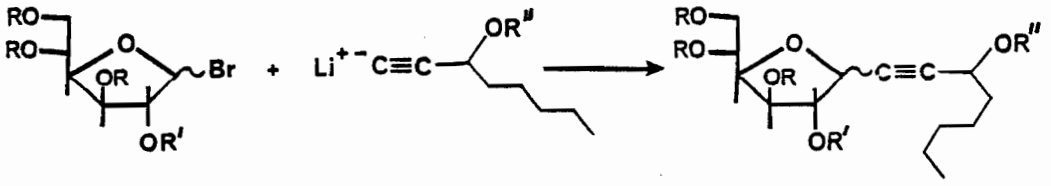
(18) R = -OH

(19) R = -H

Compound 18 has all the necessary functionalities which would allow the appropriate transformations. At C-1, a potential aldehyde exists, the hydroxy groups at C-2 and C-5 are as in compound 15 and a third hydroxyl group at C-6 allows for the attachment of the C_1-C_7 side-chain. The only disadvantage with this starting material is that it also contains a hydroxyl group at C-3. However, methods[40,41,42,43,44,45] exist which allow for the conversion of compound 18 to the 3-deoxyglucose derivative 19.

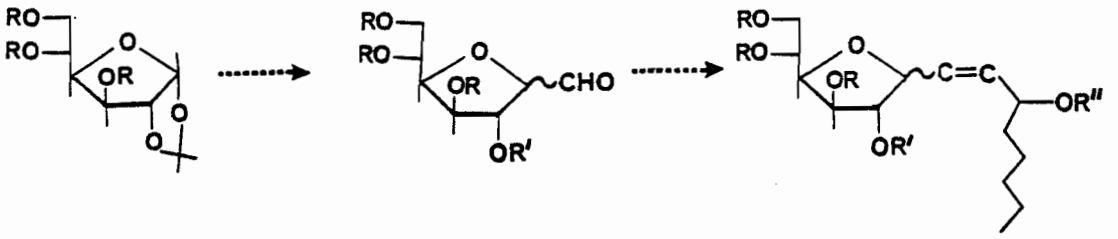
Because compound 15 was the major component isolated, it was chosen as the first one to be synthesized. Model compounds were used, since methods for the formation of 3-deoxyglucose derivatives described at the time when this work was initiated were quite cumbersome. It was decided to carry out studies on the attachment of the C_{13}-C_{20} side-chain to the anomeric center. Once the methodology is well established, the same techniques could be applied to the 3-deoxy furanose derivative.

Several methods[46,47] exist for the attachment of the side chain to the closed furano-compound. From these, two were chosen: the first, being a displacement of bromide at the anomeric center by an appropriate acetylenic anion and the second a one-carbon extension at C-1 with



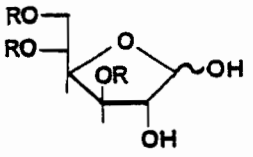
R,R' and R" are appropriate protecting groups

generation of an aldehyde group. Once the aldehyde is



R,R' and R" = protecting groups

generated, a Horner-Wittig reaction could be done with the appropriate phosphonate anion. In both the above possibilities, the 1,2-isopropylidene group has to be hydrolyzed and the resultant diol used. Therefore our first concern was the generation of the 1,2 diol 20 .

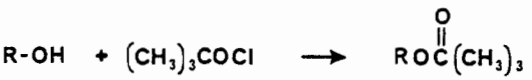


(20)

R = protecting group

3,5,6-Tri-O-methyl-D-glucofuranose (31)

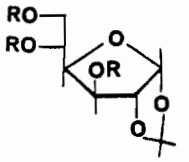
It became obvious that in order to make 1,2-O-isopropylidene-α-D-glucofuranose (18) a successful model compound, the three hydroxyl groups would have to be very well protected. The first protecting group to be considered was the pivalate ester group.



(21) pivalate

The pivalate group offers certain features which are advantageous for our model studies. It may be removed by alkaline hydrolysis or with aqueous methylamine or methylamine in aqueous alcoholic solution. Another feature is that it does not migrate too readily, because of its bulk. In view of these facts the triol 18 was reacted[48,49] with three equivalents of trimethylacetyl chloride (21) in dry pyridine at 0° to afford the protected triester 22.

This compound was identified by its spectral data. Its p.m.r. spectrum showed two singlets, one at 1.10 ppm integrating for nine protons and the other at 1.20 ppm for eighteen protons, corresponding to the three privalate esters. The two

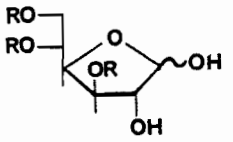


$R = -COC(CH_3)_3$

(22)

methyl groups of the isopropylidene group showed up as two singlets at 1.30 ppm and 1.50 ppm. The anomeric hydrogen showed up at 5.80 ppm as a doublet with a coupling constant of $J_{1,2}$=3 Hz which indicates, as expected, that it is cis to the hydrogen on C-2. As well, the infrared and mass spectra were in accordance with structure 22.

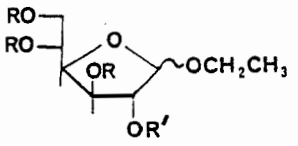
Now that the three hydroxyl groups were well protected, an acid hydrolysis of the 1,2-isopropylidene could be attempted. Because of the large hydrophobic character of compound 22, a mixed solvent system had to be used. Compound 22 was therefore dissolved in an ethanol-water mixture (3:2) which was 0.4 N in sulfuric acid, and the resulting solution heated at 100° for 90 minutes. The p.m.r. spectrum of the product showed two triplets at 1.25 and 1.30 ppm which, together, integrated for three protons, and the mass spectrum did not correspond to the diol 23.



$R = -COC(CH_3)_3$

(23)

In order to characterize the product obtained, it was acetylated by overnight treatment with acetic anhydride in pyridine, at room temperature. After work-up the p.m.r. spectrum showed two singlets at 2.05 and 2.10 ppm together integrating for three protons, corresponding to one acetate. Closer examination of both its p.m.r. and infrared spectra revealed that the acetylated product has structure 24.



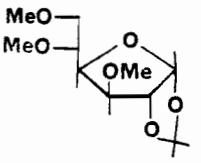
(24) $R = -COC(CH_3)_3$ $R' = -COCH_3$

(25) $R = -COC(CH_3)_3$ $R' = -H$

From this it was obvious that the "hydrolysis" product was the hydroxy-acetal 25.

Since ethanol and not water was the nucleophile in the solvolysis, this mixed solvent system could not be used. Also, because of the large number of protons from the three pivalate groups it was decided that a smaller protecting group would be more appropriate for easy spectral interpretation.

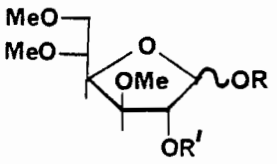
Examination of the hydroxyl-protecting groups available revealed that the best group would be the methyl ether. This group has a very simple p.m.r. spectrum, is stable to both acid and base and, because these are model compounds, its removal is not necessary. The triol 18 was therefore methylated[50] by treatment with 4 equivalents of the dimethylsulfoxide anion, generated by reacting dimethyl sulfoxide with sodium hydride at 55°, followed by quenching at room temperature with methyl iodide to produce the protected compound 26.



(26)

The p.m.r. spectrum was very clean, showing two singlets at 1.30 and 1.50 ppm for the isopropylidene group, three singlets at 3.40, 3.45 and 3.50 ppm for the three methyl ethers and a clean doublet at 5.90 ppm for the anomeric proton. Both the infrared and mass spectra were consistent with structure 26.

Before hydrolyzing the 1,2-isopropylidene group to generate the diol, it was decided to confirm our previous findings that an ethanol-water mixture would give the mixed acetal 27, and not the terminal hemi-acetal 31. Therefore



(27) R = $-CH_2CH_3$ R' = -H

(28) R = $-CH_2CH_3$ R' = $-COCH_3$

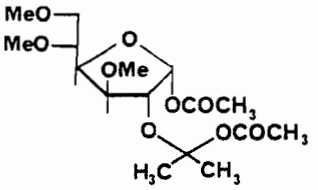
(29) R = -H R' = $-COCH_3$

the isopropylidene compound 26 was treated with an ethanol-water mixture that was 0.4 N in sulfuric acid, for 3.5 hours at 100°. As expected, the spectral data showed that the product obtained was the acetal 27 which was further identified through its acetate derivative 28.

Treatment of the isopropylidene compound 26 with

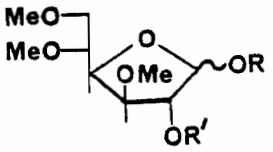
80% aqueous acetic acid at 90° for 10 hours resulted in the formation of the hemi-acetal 29. The p.m.r. spectrum showed the acetate group to be on the C-2 hydroxyl group since the anomeric hydrogen had a chemical shift of 5.10 ppm. Both the infrared and mass spectra obtained were consistent with structure 29.

Further investigation of this hydrolysis revealed that treatment of 26 with a mixture of acetic anhydride and acetic acid containing catalytic amounts of p-toluene-sulfonic acid afforded compound 30. The p.m.r. spectrum of 30 displayed singlets at 1.50 (two methyl groups), 2.20 (two acetates), 3.40 (methyl ether), 3.50 (methyl ether) and 3.60 ppm (methyl ether). A quartet at 5.10 ppm corresponding to the proton on C-2 and a doublet at 6.30 ppm for the anomeric proton were also observed. Both the infrared and mass spectra were consistent with structure 30.



(30)

Finally, the diol 31 was obtained by treatment of 26 with 0.5 N aqueous hydrochloric acid at 70^0 for 1 hour.



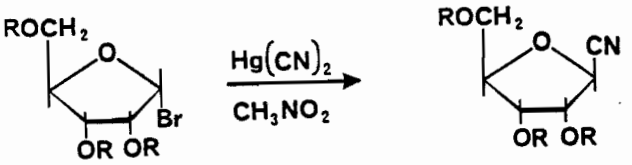
(31) R = R' = -H

(32) R = R' = $-COCH_3$

The product, a 1:1 mixture of α- and β-anomers, was further characterized as its di-acetate[51] derivative 32. All the spectral data obtained for both compounds 31 and 32 were consistent with the given structures.

2-O-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-β-D-gluco-furanosyl cyanide (40).

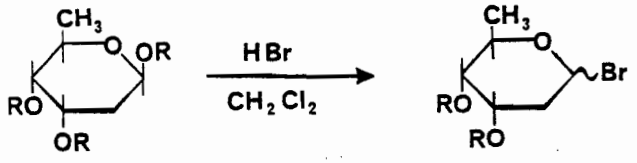
J. Farkas and M. Bobek[52] reported in 1968 a one-carbon extension at the anomeric center. They used 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (33) as their starting material, and reacted it with mercuric cyanide in nitromethane to afford the ribofuranosyl cyanide 34.



(33) (34)

R = $-COC_6H_5$

W.W. Zorbach and T.A. Payne Jr.[53] published reactivity studies of pyranosyl bromides, and showed that their reactivity towards S_N2 displacement is under steric control and is influenced primarily by the degree of shielding around C-1, provided by substitution at C-2[54]. Acetates 35a, benzoates 35b and p-nitrobenzoates 35c were prepared and the stability of their corresponding glycosyl bromides 36a, 36b, 36c, described.



(35) (36)

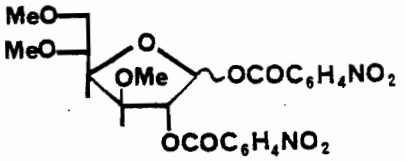
(a) R = $-COCH_3$

(b) R = $-COC_6H_5$

(c) R = $-COC_6H_4NO_2$

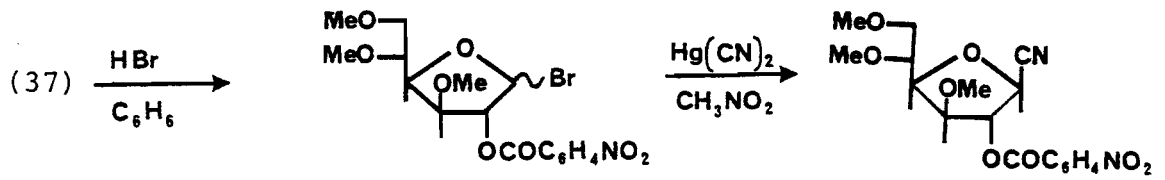
The most stable was found to be the p-nitrobenzoyl derivative 36c. Not only was the glycosyl bromide of this ester stable but the p-nitrobenzoic acid generated during the reaction was recovered quantitatively by filtration, making its purification very easy.

In view of this[52,53], the diol 31 was treated with p-nitrobenzoyl chloride in dry pyridine at 0° for 3 days to give 1,2-di-O-p-nitrobenzoyl-3,5,6-tri-O-methyl-D-gluco-furanose (37) as a crystalline solid. An approximately 1:1 mixture of α- and β-anomers was obtained. The p.m.r. spectrum showed a singlet and a doublet ($J_{1,2}$=4 Hz) at 6.70 and 6.90 ppm respectively for the anomeric proton. The infrared spectrum showed the characteristic peaks for a nitro-benzoate, namely at 1740, 1620 and 1540 cm^{-1} for a carbonyl group, an aromatic ring and a nitro group, respectively. The elemental analysis was consistent with a molecular formula of $C_{23}H_{24}N_2O_{12}$, which is in accordance with p-nitrobenzoate 37.



(37)

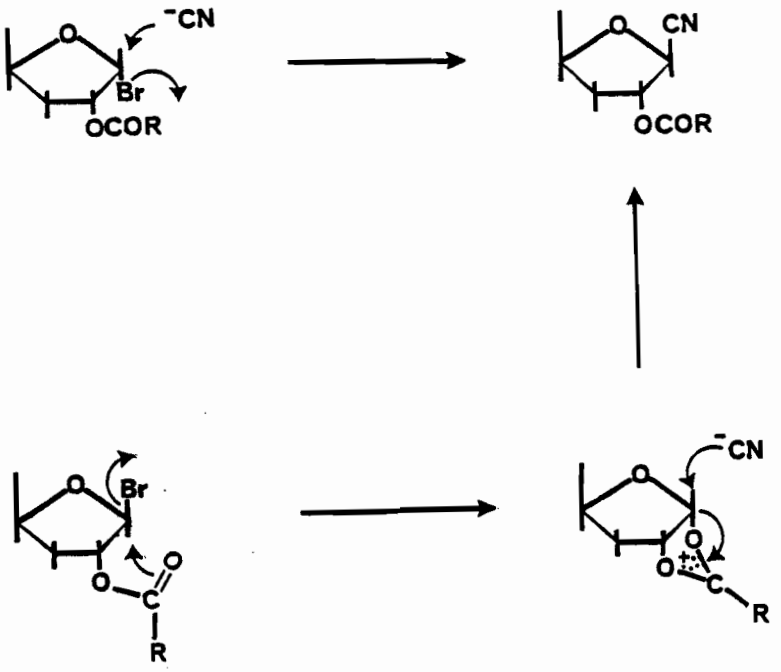
A benzene solution of the di-p-nitrobenzoate 37 was saturated with dry gaseous hydrogen bromide at 0^{o} in the course of 30 minutes. The resulting p-nitrobenzoic acid was filtered off, the oily glycosyl bromide dissolved in dry nitromethane and treated with pre-dried mercuric cyanide to give the crude glycosyl cyanide[52,55,56] 38. When purification of the crude glycosyl cyanide 38 was attempted on a silica gel column, it decomposed to give unknown products. Therefore, cyanide 38 was purified on an alumina column to give pure product as a crystalline solid.



(37 a) (38)

G.T. Rogers and T.L.V. Ulbricht[57] reported on the rules regarding the anomeric configuration produced by the reaction of glycosyl halides with heavy metal salts. In the case of sugar derivatives with a participating group, such as (-OCOR) at position 2, both 1,2-cis-and trans-glycosyl bromides give 1,2-trans -glycosyl cyanide as the product with mercuric cyanide, by single or double displacement reactions, respectively,

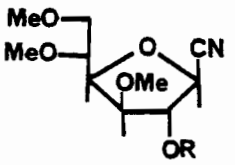
as shown below, although similar instances where both isomers were obtained are known.



$$R = -C_6H_4NO_2$$

Examination of the p.m.r. spectrum of the pure glycosyl cyanide 38, revealed that the β-anomer was the sole product. This was indicated by the broad singlet at 4.90 ppm in the p.m.r. spectrum for the anomeric proton, meaning that the dihedral angle between the C-1 and C-2 hydrogens is very close to 90^{o}[58,59]. Their disposition is therefore trans-, and the cyano group has therefore the β-configuration. The hydrogen on C-2 showed another broad singlet at 5.90 ppm also indicating that the cyano group is in the β-position.

The p-nitrobenzoate ester of compound 38 was hydrolyzed with 1 equivalent of sodium hydroxide in a (1:2) mixture of tetrahydrofuran and water to give the oily alcohol 39 in 62% yield. The free hydroxyl group was silylated with dimethyl-t-butylsilyl chloride in dry dimethylformamide[60], with imidazole as the catalyst, to afford the silyl ether 40.



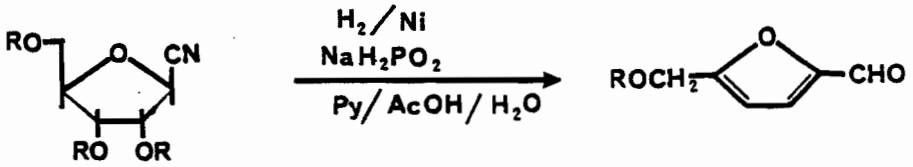
(39) R = -H

(40) R = -Si(t-Butyl)Me_2

2,5-Anhydro-3-O-(t-butyldimethyl)silyl-4,6,7-tri-O-methyl-D-glycero-D-gulo-heptose (46).

From the protected alcohol 40, one can envisage a reductive hydrolysis to give an aldehyde, and a Wittig-type addition of the appropriate side-chain to give the desired product. A survey of the literature[61] revealed that the cyano function could be hydrolyzed and reduced in one step with Raney nickel and monosodium hypophosphite in a mixture of pyridine, acetic acid and water, to afford the aldehyde.

However, in 1976 J.G. Moffatt et al[62] reported that when they attempted this hydrolytic reduction on their furanosyl cyanide 41, the aldehyde which they generated was unstable under the given conditions and elimination gave the furfuraldehyde derivative 42.



(41) (42)

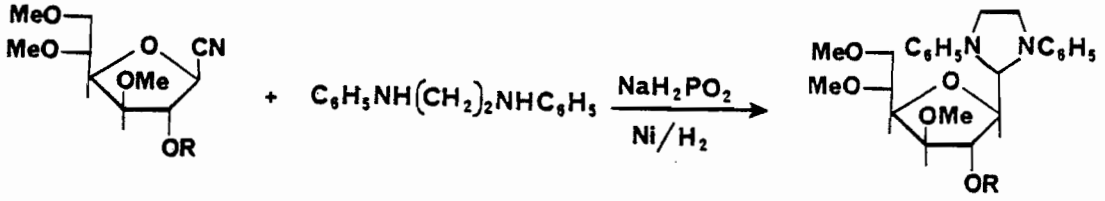
R = $-CH_2C_6H_5$

This very facile elimination reaction was avoided by conducting the reductive hydrolysis reaction in the presence of N,N'-diphenylethylenediamine (43). This reagent was developed by Wanzlick and Loehel[63] for the selective conversion of aldehydes into 1,3-diphenylimidazolidine derivatives and has previously been used to trap aldehydes formed by hydrogenation of nitriles[64].

$C_6H_5NH(CH_2)_2NHC_6H_5$

(43)

Treatment of the cyano compound 40 with sodium hypophosphite and Raney nickel[65] in the presence N,N'-diphenylethylenediamine (43) in aqueous pyridine - acetic acid for 1.5 hours afforded the crude protected aldehyde 45[62,66]. Because the R_f values of the product 45 and of N,N'-diphenylethylenediamine (43) are very similar, separation of the two was difficult.



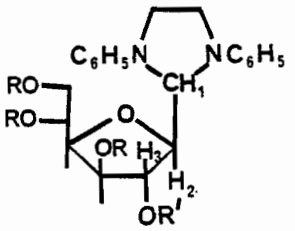
(39) R = -H

(40) R = -Si(t-butyl)Me_2

(44) R = -H

(45) R = Si(t-butyl)Me_2

In any case, the protected aldehyde 45 was obtained in pure form as a white cystalline solid after plate chromatography. The p.m.r. spectrum showed two singlets at 0.15 and 0.90 ppm for the silyl group, a singlet at 3.30 ppm for the two methylene groups in the imidazolidine ring, a broad doublet at 3.90 ppm with a coupling constant of $J_{2,1}$= 8 Hz for H-2, a broad singlet

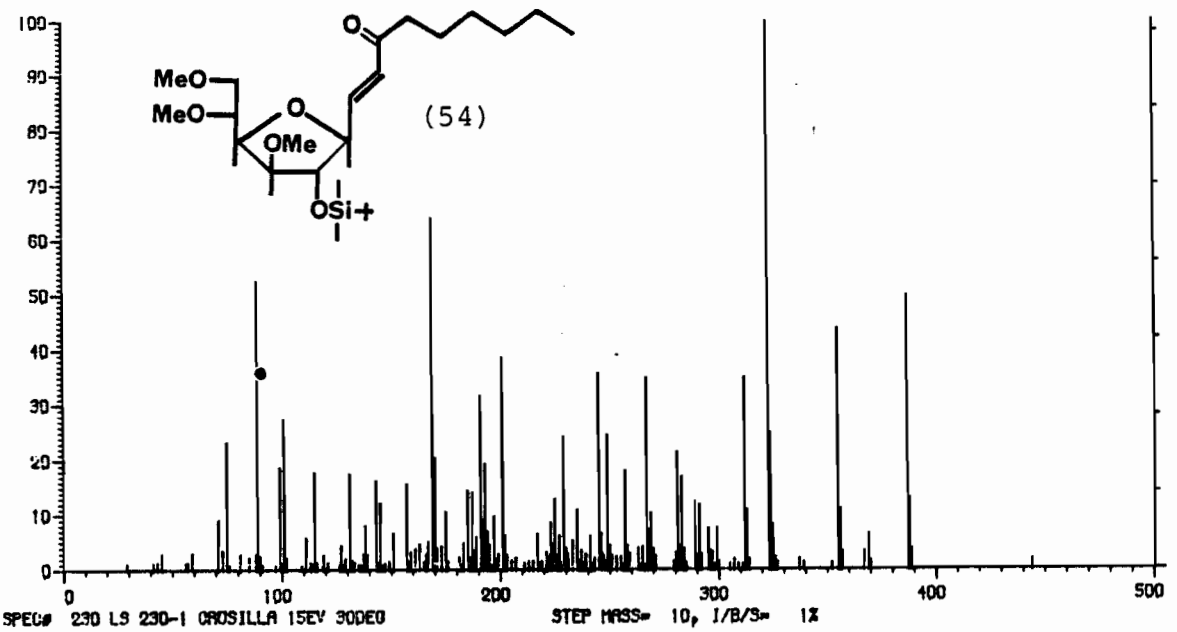


(45)

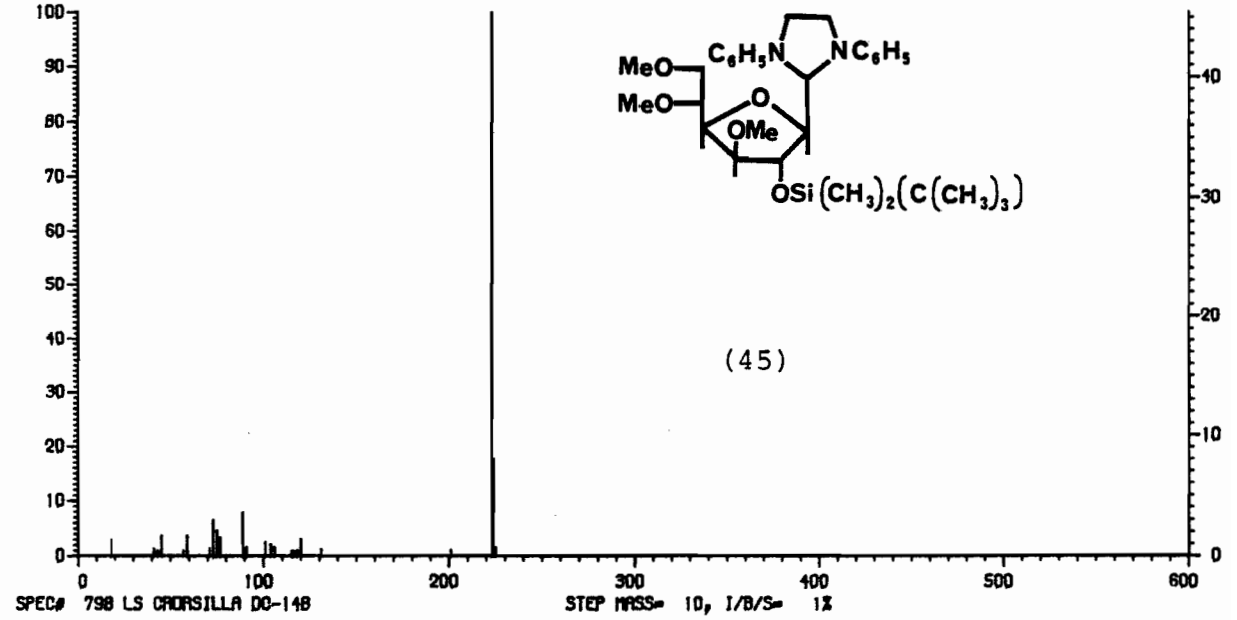
R = -Si(t-butyl)Me_2

at 4.30 ppm for H-3, and finally a doublet at 5.50 ppm with a coupling constant of $J_{1,2}$=8 Hz for H-1. Because the coupling constant between H-2 and H-3 is close to 0 Hz it can be assumed that the imidazoline ring is in the β-position. Both the infrared and the mass spectra, and elemental analysis were in accordance with structure 45.

Because of the difficulties encountered during purification of 45, it was decided to attempt the hydrolytic reduction on the alcohol 39, hoping that the R_f value of the product 44 would be sufficiently different from that of N,N'-diphenylethylenediamine (43). Therefore the cyanide 39 was treated with Raney nickel and monosodium hypophosphite in a mixture of pyridine, acetic acid and water containing the diamine 43. As expected the imidazolidine compound 44 was produced in 70% yield, and its R_f value was sufficiently different from that of 43 to allow for easy separation. The p.m.r., i.r.



Mass spectrum of compound 54.

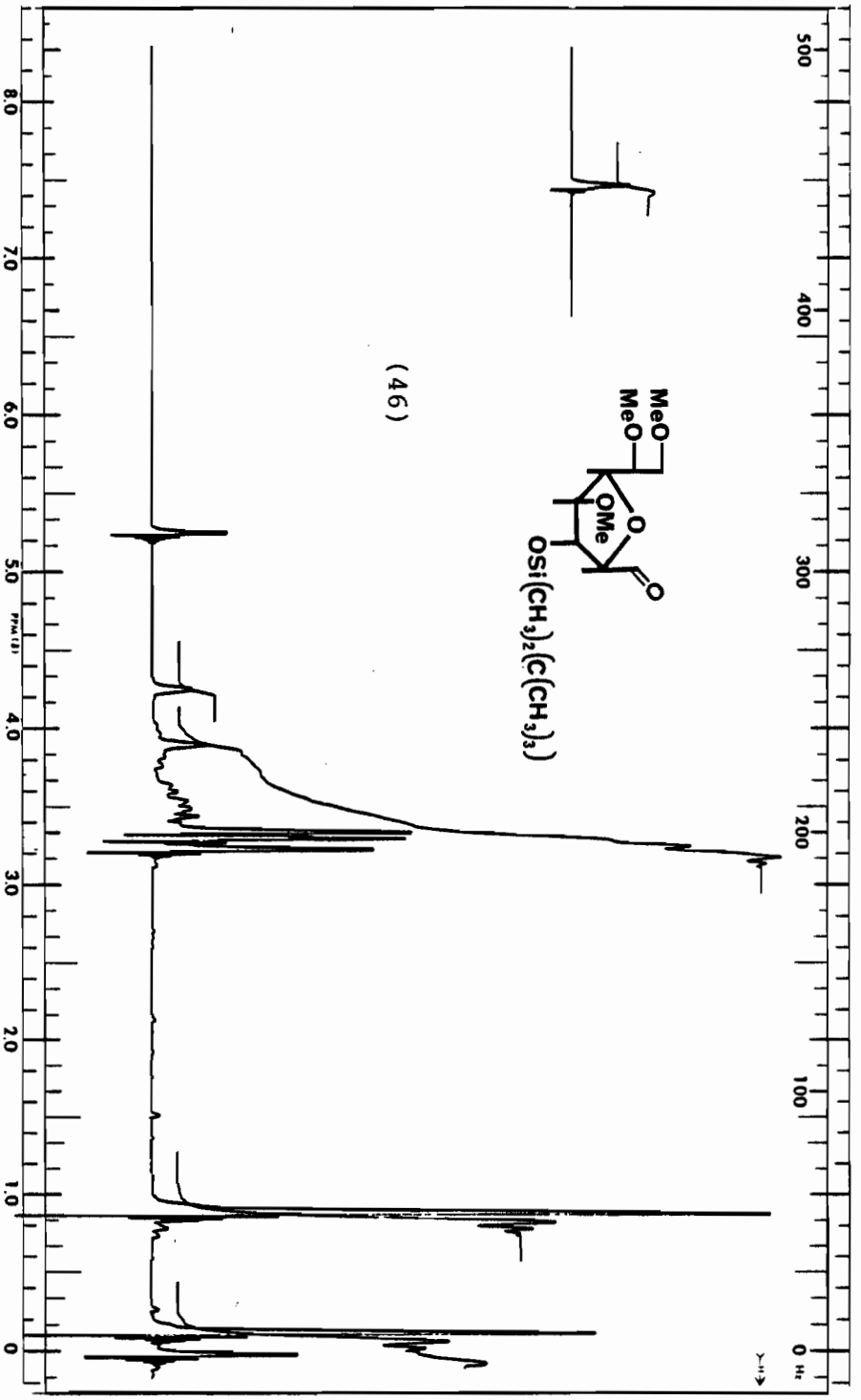


Mass spectrum of compound 45.

and mass spectra obtained were consistent with the proposed structure for compound 44.

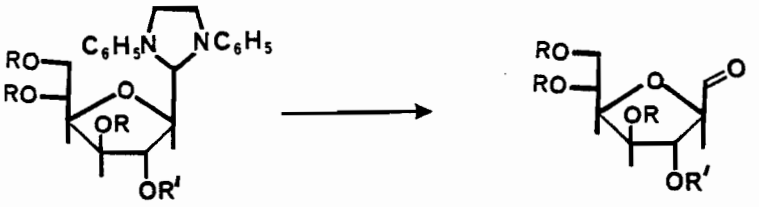
Because of foreseeable difficulties in future reactions the hydroxyl function of compound 44 was silylated to give compound 45. The silylation[60] was carried out with dimethyl-t-butylsilyl chloride and imidazole in dry N,N'-dimethylformamide. The silylated compound 45 obtained in this manner had spectra identical to those of the compound obtained in the previous reaction sequence.

Regeneration of the free aldehyde function from 1,3-diphenylimidazolidine derivatives has usually been achieved by treatment with a heterogeneous mixture of ether and 3 to 6 N hydrochloric acid[64,67]. The aldehydes can, however, be liberated under much milder conditions by treatment with 2.5 - 3.0 molar equivalents of p-toluenesulfonic acid monohydrate in a mixture of acetone and methylene chloride at 0-20° [68]. Such treatment of the imidazolidine compound 45 led to several products. The silyl ether probably did not survive the p-toluenesulfonic acid treatment thereby giving the aldehydo-alcohol which could dimerize or polymerize. A further literature search[62,69] revealed that the imidazoline ring could be removed with Dowex-50 (H^+) resin in aqueous tetrahydrofuran. This procedure is convenient since all traces of basic hydrolysis products are bound by the resin and can be removed by simple filtration. When the silyl imidazolidine compound 45 was treated with Dowex 50W-X8 (H^+) resin in a



P.m.r. spectrum of compound 46

(2:1) mixture of tetrahydrofuran and water, the aldehyde 46 was obtained very pure without chromatography. Its p.m.r. spectrum showed two singlets at 0.10 and 0.90 ppm for the silyl group, three singlets at 3.20, 3.30 and 3.35 ppm for the three methyl ethers, and a broad singlet at 4.25 ppm for the anomeric hydrogen. The aldehyde proton appeared as a broad singlet at 9.10 ppm. Because there is very little coupling between the anomeric hydrogen and the one on C-2, the stereochemistry of the anomeric center still had the β-configuration.



(45) (46)

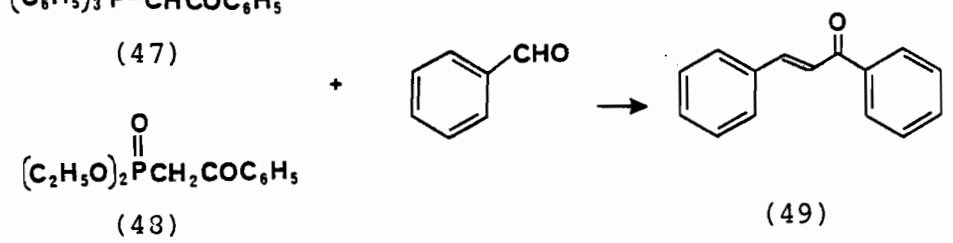
R = $-CH_3$

R' = $-Si(t\text{-butyl})Me_2$

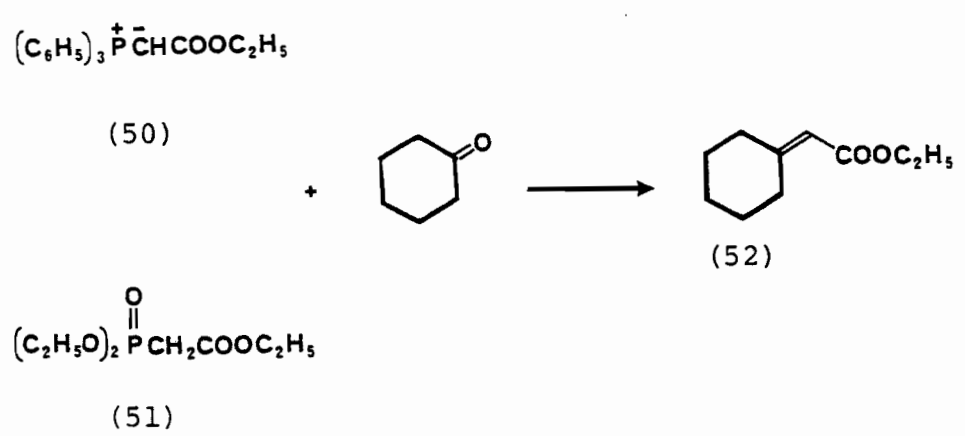
The infrared spectrum of compound 46 showed no hydroxyl absorption but had a carbonyl absorption at 1760 cm^{-1}, indicating that the silyl ether was intact and that an aldehyde was present.

E-1-(2-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl)-3-hydroxy-1-octene (55).

The commonly used Wittig reagents[70] for the synthesis of olefins from aldehydes and ketones are phosphonates and phosphoranes. The phosphonate anions have in many instances a number of advantages over the triarylphosphoranes. They are normally less expensive and they react with a wider variety of aldehydes and ketones, usually under much milder conditions. For example, the reaction of triphenylphenacylidenephosphorane (47) with benzaldehyde was done by refluxing both reagents in tetrahydrofuran for thirty hours[71]. The analogous reaction of the anion of diethyl phenacylphosphonate (48) was exothermic at room temperature and gave the same yield of olefin 49 [72].



Also, G. Wittig et al.[73,74] found that although triphenylcarbethoxymethylidenephosphorane (50) reacts with benzaldehyde, it fails to react with cyclohexanone. The anion of diethyl carbethoxymethylphosphonate (51) however, reacted exothermically with cyclohexanone to give a good yield of olefin 52 [71].



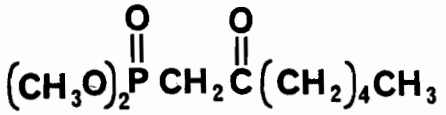
(50)

(51)

(52)

The anion is usually prepared by adding an excess of the phosphonate at room temperature to a slurry of sodium hydride in 1,2-dimethoxyethane, since excess sodium hydride causes unwanted side-reactions due to the acidity of the hydrogen α to the carbonyl group. Higher temperatures are usually undesirable for the stabilized phosphonates since the anion can easily self-condense[72].

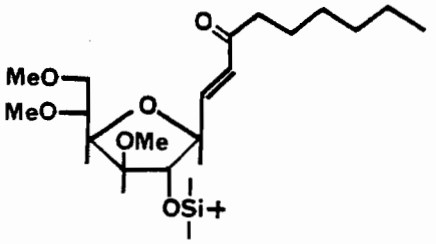
In order for the chain to have the appropriate length, dimethyl 2-oxoheptylphosphonate (53) will have to be reacted with the aldehyde 46. This reagent can be prepared from ethyl hexanoate and dimethyl α-lithiomethanephosphonate[75,76].



(53)

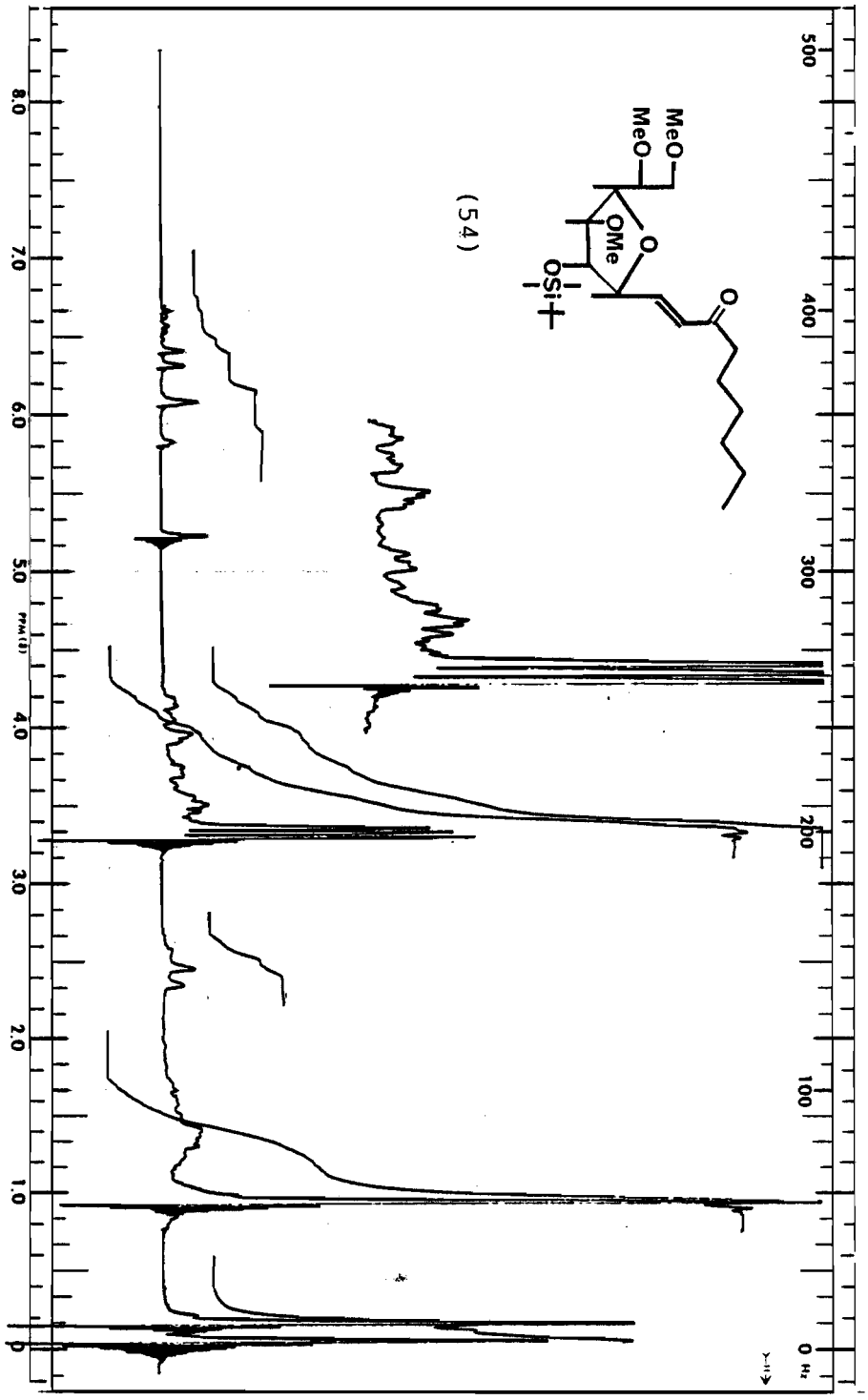
It is also comercially available.

The α,β-unsaturated ketone 54 was synthesized by first generating the phosphonate anion of compound 53 with sodium hydride and then by adding to this anion a solution of the aldehyde 46 in dimethoxyethane. The resulting solution was stirred at room temperature for 90 minutes, quenched with water, and the product extracted with ether.

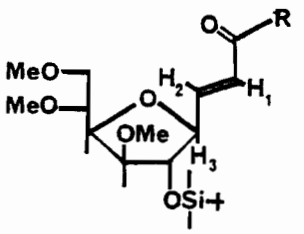


(54)

The p.m.r. spectrum of 54 showed two singlets at 0.10 and 0.90 ppm for the silyl ether, a multiplet between 1.00 and 1.90 ppm for side-chain protons and a broad triplet at 2.40 ppm for the two hydrogens α to the ketone. The three methyl ethers showed up as usual as three singlets at 3.20, 3.25 and 3.30 ppm and the olefinic protons showed up at 6.20 ppm as an AB portion of an ABX pattern with the following coupling constants: $J_{1,2}$= 14 Hz, $J_{1,3}$= 1 Hz and $J_{2,3}$= 6 Hz. Because trans-olefinic protons usually have coupling constants of 12-18 Hz[77], the trans-stereochemistry can safely be assigned to compound 54. The infrared spectrum



P.m.r. spectrum of compound 54



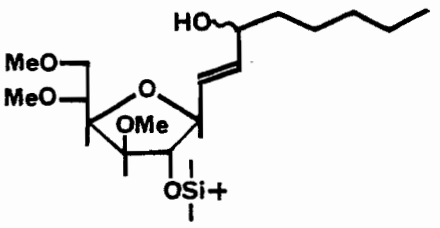
(54)

$R = -C_5H_{11}$

was consistent with the structure of 54 and the mass spectrum showed a molecular ion of 444 m/e which is in accordance with the formula of 54.

To complete our model studies the only transformation remaining was a reduction of the ketone to the alcohol. Several reducing reagents such as sodium borohydride and zinc borohydride have been used in analogous reductions in the prostaglandin series, depending on the sensitivity of the other functional groups. If both diastereomers are required, as in our case, then sodium borohydride is usually used[78]. Because the stereochemistry of the C-15 alcohol in compound 8 is not known both isomers will have to be generated in our synthesis and then compared with the natural product in order to determine which is the correct one.

Therefore the unsaturated ketone 54 was treated with sodium borohydride in absolute ethanol at 0° for 30 minutes, and, as expected, a 1:1 mixture of the two diastereomeric alcohols 55a and 55b was obtained.



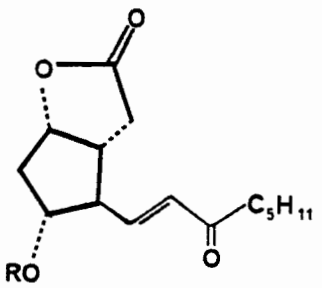
(55, a:b = 50:50)

The p.m.r., i.r. and mass spectra obtained on the mixture were consistent with the structures 55a and 55b. The infrared spectrum had no carbonyl absorption but did have a strong hydroxyl absorption at 3460 cm^{-1}. The mass spectrum showed a fragment of 428 m/e corresponding to the loss of water and the elemental analysis was within acceptable limits.

Because the diastereomeric alcohols had sufficiently different retention times on silica gel, a separation was attempted using a new chromatographic technique called "flash chromatography"[79]. This consists of a medium pressure column on a finer mesh of silica (32-63μ) than used in the standard chromatographic technique. Using this

technique, only the less polar alcohol was obtained pure, and was fully characterized.

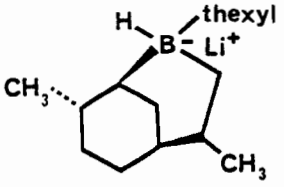
Because of the similarity between our natural product 8, 9,12-oxy-8,11,15-trihydroxyeicosa-5,13-dienoic acid, and the prostaglandins, reagents used for the reduction of the C-15 ketone of the prostaglandins were also examined. E.J. Corey et al.[80] developed trialkylborohydride reagents which would produce the naturally occurring 15(S) isomer in high yields. If the prostaglandin series parallel our series, then these should perhaps allow for the preparation of the more polar 15(S)isomer, which is the naturally occurring prostaglandin. The reductions were carried out on a prostaglandin model of the type 56. Since Corey obtained the correct isomer via



(56)

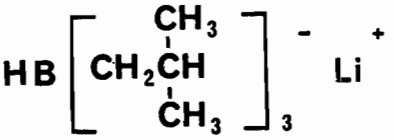
attack by a bulky reducing agent from the least hindered side, and since attack from the least hindered side of 54 would produce the same C-15 configuration, the use of a bulky reducing agent is perhaps justified. Below is a table listing the various reducing agents and the ratio

of 15(S) and 15(R) isomers obtained:

REAGENT	SUBSTRATE 56	RATIO (15(S):15(R)
	R = p-$C_6H_5C_6H_4CO$-	82:18
thexyl di-sec-butyl[81] borohydride	R = p-$C_6H_5C_6H_4NHCO$-	88:12
tri-sec-butyl borohydride	R = p-$C_6H_5C_6H_4NHCO$	89:11

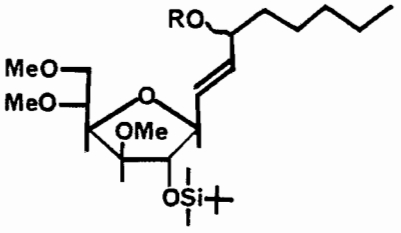
The ketone 54 was therefore reduced with L-Selectride (57)[83] at -70° over a one hour period. After work-up, the alcohols 55a and 55b were obtained as expected. However, whereas sodium borohydride produced a 50:50 mixture of (R) and (S) alcohols, the L-Selectride produced an approximate 85:15 mixture with the more polar isomer being the predominant one.

In order to improve the separation of the two isomeric alcohols 55, it was decided to acylate them,



(57)

hoping that the difference in retention times of the acylated products would be greater than that of the alcohols. Compound 55 was therefore treated with acetic anhydride and pyridine overnight to afford the acetylated product 58.



(58) R = $-COCH_3$

(59) R = $-COC_6H_4NO_2$

The infrared spectrum showed a carbonyl absorption at 1740 cm^{-1} and the mass spectrum had a molecular ion at 488 m/e. However, thin-layer chromatography allowed no separation of

the two diastereomers.

In a last attempt to obtain a better separation of the mixture of alcohols 55a and 55b they were converted to their p-nitrobenzoate esters 59. This was done by dissolving the alcohols 55 in pyridine and adding this solution to p-nitrobenzoyl chloride in pyridine at 0°. After leaving this mixture at 0° for 3 days the p-nitrobenzoates 59 were extracted with ether. The p.m.r., i.r. and mass spectra were all consistent with the structure of compound 59. Again, however, no separation on thin-layer chromatography was observed. There is, however, little doubt that HPLC (High Pressure Liquid Chromatography) should allow for a clean separation, which, however, was not deemed necessary at this stage.

Conclusion:

The desired compound 55 was obtained, and the methodology for attaching the C_{13}-C_{20} side-chain was developed. However this sequence allowed only for the synthesis of one isomer at the C-12 position and as previously discussed both isomers are desired. What is now required is a sequence which would allow for the synthesis of the other C-12 isomer in the furano series and both C-12 isomers in the pyrano series.

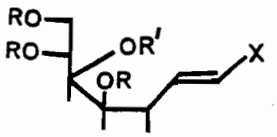
It also seems that the reduction behavior of the C-15 ketone in our series parallels that of the prostaglandins, although full proof can only be obtained by an oxidative degradation of the 15(S) and 15(R) isomers of the final product.

CHAPTER III

Studies on the Synthesis of Furanose and Pyranose Sugars from Nitro-Olefins.

Introduction:

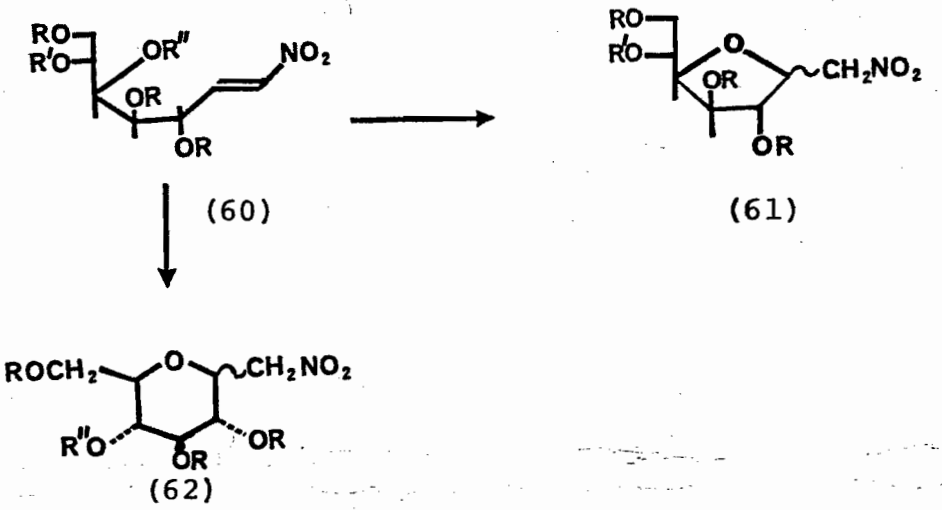
Although the model studies were successful in that a method to attach the C_{13}-C_{20} side-chain was developed, work was still required in order to obtain the other C-12 isomer. An ideal solution to the problem is would be to have a compound of the type shown below where the hydroxyl groups are protected differently. Selective removal of these protecting groups followed by cyclization[84,85,86] would lead to the desired compounds.



X = some stabilizing group

Therefore a compound of type 60 is required, where the hydroxyl groups on C-5 and C-6 are protected differently. If the protecting group on the C-5 hydroxyl group is removed

and the freed hydroxyl group allowed to cyclize, it would give the furano-sugar 61. On the other hand, if the hydroxyl group on C-6 is liberated, then cyclization would result in the pyrano-sugar 62. Most likely both the α- and the β-anomers in each series would be produced.



R = protecting group

R' = protecting group

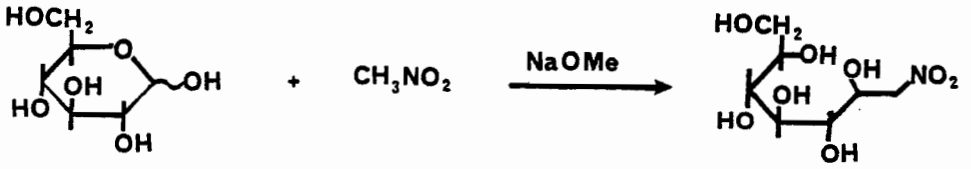
R'' = protecting group

The nitro furanose 61 and nitro pyranose 62 could then be converted to the corresponding aldehydes and the side-chain attached via a Wittig-Horner reaction. This chapter will therefore deal with this type of approach based on the above

scheme.

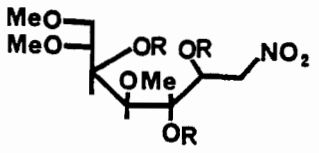
E-3,5-Di-0-acetyl-1,2-dideoxy-1-nitro-4,6,7-tri-0-methyl-D-gluco-hept-1-enitol (66).

D.T. Williams and M.B. Perry[87] recently reported that D-Glucose can be converted to the nitro sugar 63. D-Glucose was condensed with nitromethane in the presence of sodium methoxide, and the nitronate salt filtered, dissolved in water, and acidified by the use of an acidic resin to produce good yields of 63.



(63)

Subjecting the diol 31 (pg.35) to the same conditions[88,89] resulted in the nitro sugar 64.



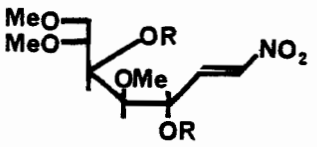
(64) R = -H

(65) R = $-COCH_3$

It is well known[86,87] that β-acetoxynitroalkanes easily undergo base-catalyzed elimination of acetic acid to give nitro olefins. M.M.A. Abdel-Rahman[90] reported an elimination of acetic acid to produce the nitro olefin by the use of anhydrous potassium carbonate in benzene.

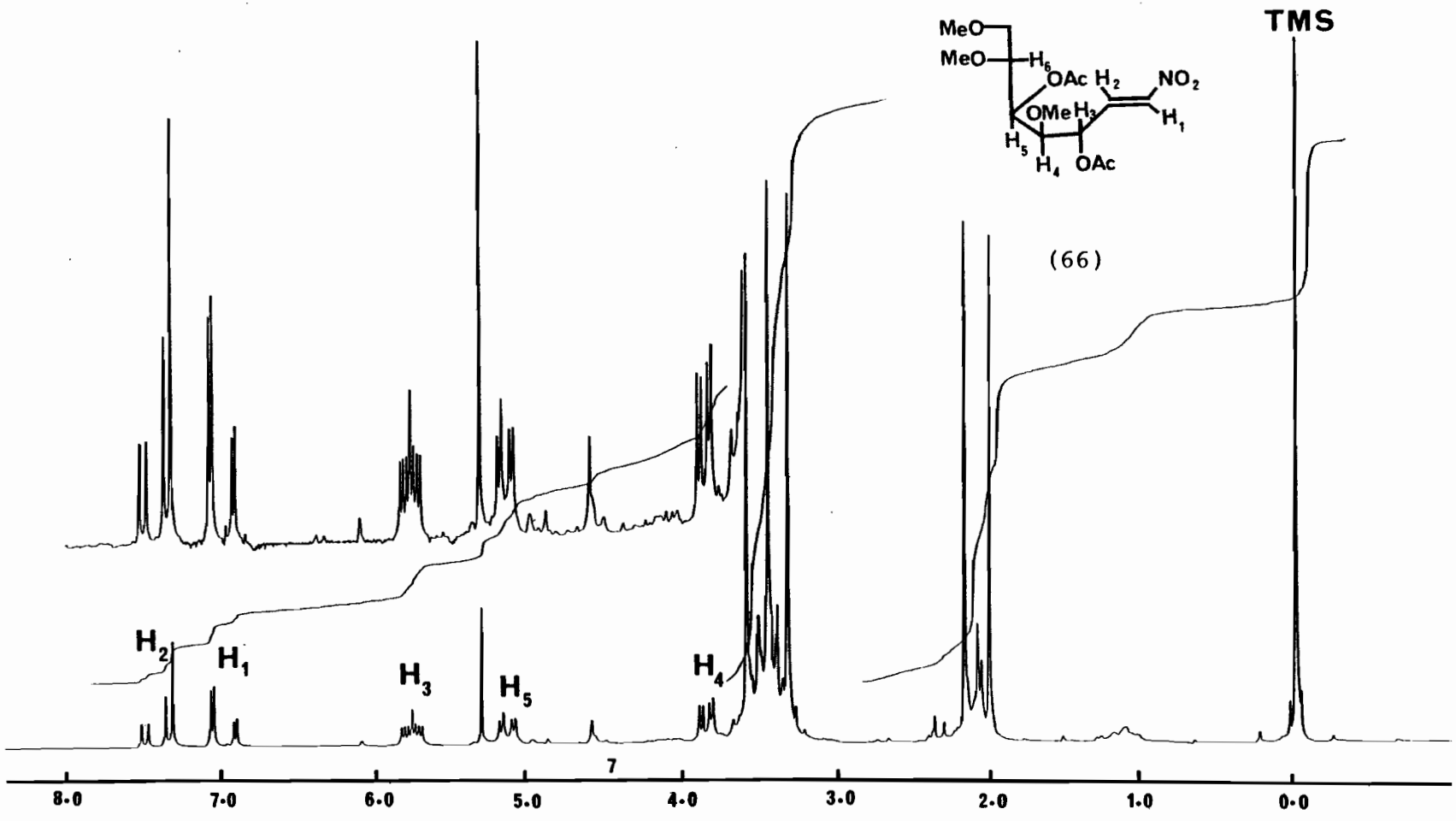
The nitro alcohol 64 was therefore acetylated using acetic anhydride and p-toluenesulfonic acid to afford a very unstable triacetate 65. This method of acetylation had to be used instead of the normal acetic anhydride/pyridine method because both the nitro alcohol and the nitro acetate are not stable to basic conditions. The nitro acetate 65 was so

unstable that it spontaneously eliminated acetic acid during the work-up, to give approximately 50% of nitro olefin 66. This mixture of nitro acetate and nitro olefin was therefore treated with powdered anhydrous potassium carbonate in dry benzene at room temperature for 6 hours to afford an 82% yield of nitro olefin 66.

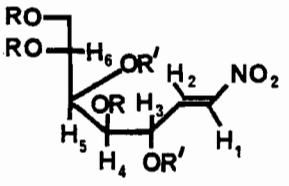


(66) R = $-COCH_3$

The nitro olefin 66 was identified by its p.m.r., i.r. and mass spectra. The 90 mHz p.m.r. spectrum showed two singlets at 2.00 and 2.20 ppm for the two acetate groups, three singlets at 3.40, 3.50 and 3.65 ppm for the three methyl ethers, a doublet of doublets at 3.90 ppm for the hydrogen on C-4 with coupling constants of $J_{4,5}$= 3 Hz and $J_{4,3}$= 6 Hz, another doublet of doublets at 5.20 ppm for the proton on C-5 with coupling constants of $J_{5,4}$= 3 Hz and $J_{5,6}$= 7 Hz and a multiplet at 5.80 ppm for the C-3 hydrogen with coupling constants of $J_{3,4}$= 6 Hz, $J_{3,2}$= 4 Hz and $J_{3,1}$= 2 Hz.



90 mH_z p.m.r. spectrum of compound 66.



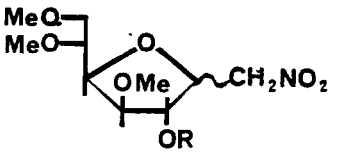
(66)

R = $-CH_3$

R' = $-COCH_3$

The double bond was assigned a trans stereochemistry because of the coupling constant between the two olefinic protons. They displayed the AB portion of an ABX system with the hydrogen having a resonance at approximately 7.00 ppm with coupling constants of $J_{1,2}$ = 14 Hz and $J_{1,3}$ = 2 Hz and the hydrogen on C-2 at approximately 7.50 ppm with coupling constants of $J_{2,1}$ = 14 Hz and $J_{2,3}$ = 4 Hz. The coupling constant between C-1 and C-2 is 14 Hz, which is within the range of coupling constants for trans-olefins. The infrared spectrum had a carbonyl absorption at 1760 cm^{-1}, an olefinic absorption at 1660 cm^{-1} and a strong nitro absorption at 1530 cm^{-1}. The mass spectrum of the compound was in accordance with the formula of nitro olefin 66.

At this point several cyclization reactions were attempted. The first attempt involved a methanolysis of the



(67a) R = -H

(67b) R = $-COCH_3$

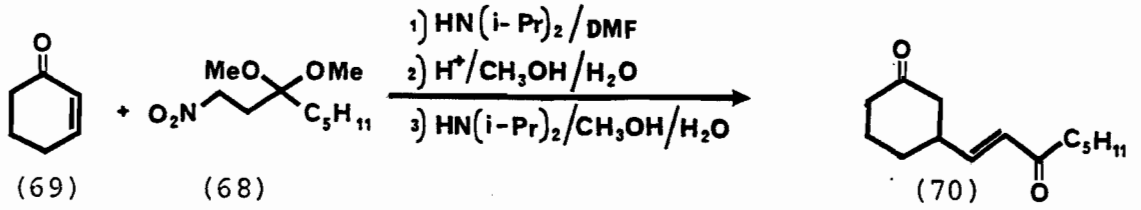
two acetates with sodium methoxide in methanol and a spontaneous cyclization by the alkoxide anion generated to give the furanose sugar 67a. The p.m.r. spectrum of the product obtained showed strong evidence of the formation of the closed sugar. In order to further characterize this product it was acetylated in the usual manner to give the acetate derivative 67b. The p.m.r. spectrum of this compound also gave strong, but not definite, proof of the existence of a closed sugar.

Since it seemed that furano sugars could be formed by an intra-molecular cyclization[91] of a hydroxyl group and a nitro ofelin it was decided to apply this method to the synthesis of our desired compound.

E- and Z-1,2-Dideoxy-1-C-(2,2-dimethoxypropyl)-3,5-O-isopropylidene-1-nitro-4,6,7-tri-O-methyl-D-gluco-hept-1-enitol (82).

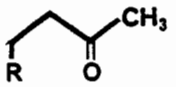
P. Bakuzis et al.[92] developed a new method of attaching the C-8 prostaglandin side-chain using nitro ketals. Because nitro compounds add readily to aldehydes and reactive enones under mild basic conditions[93]; and because β-nitro esters, lactones, ketones and phosphonates[94] eliminate nitrous acid, under similar conditions with the formation of the respective α,β-unsaturated compounds, P. Bakuzis combined these two modes of reaction and developed a method of generating an α,β-unsaturated compound. By this method, the nitro ketal 68 was reacted with cycohexenone (69) and diisopropylamine to give, after hydrolysis and elimination, the adduct 70. This reaction is outlined below.

The reagent 71 for the model side chain was first used in order to simplify the p.m.r. spectrum of the adduct.



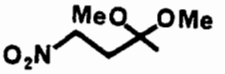
(69) (68) (70)

β-Chlorovinyl ketones can be made via a Friedel-Crafts reaction.[95] Thus, chloroketone 72 was synthesized by



(72) R = -Cl

(73) R = $-NO_2$



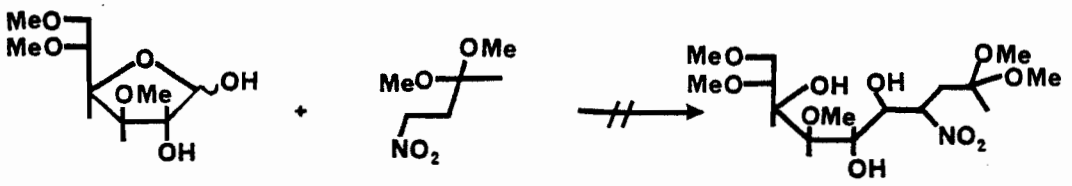
(71)

bubbling ethylene gas into a mixture of acetyl chloride and aluminum trichloride under a nitrogen atmosphere. The isolated product had a p.m.r. spectrum which showed a singlet at 2.10 ppm for the terminal methyl group and two triplets at 2.80 and 3.60 ppm for the methylene groups. The chloro ketone 72 was then treated[96] with sodium nitrite and potassium iodide in dimethylsulfoxide to afford the nitro ketone 73. This product was isolated by distillation and its p.m.r. spectrum showed a singlet at 2.30 ppm for the methyl group and two triplets at 3.20 and 4.60 ppm for the two methylene groups. The methylene protons α to the nitro group were shifted downfield from 3.60 to 4.60 ppm. The infrared spectrum of this compound had a very strong nitro absorption at 1550 cm^{-1}.

The ketalization of the ketone group was accomplished

by treating the nitro ketone 73 with trimethylorthoformate, methanol and catalytic amounts of p-toluenesulfonic acid[97]. The p.m.r. of the nitro ketal 71 showed a singlet at 1.20 ppm for the terminal methyl group , a singlet at 3.10 ppm for the two methyl groups forming the ketal and two triplets at 2.30 and 4.30 ppm for the two methylene groups. The infrared spectrum of this compound had no carbonyl absorption but did have a strong nitro absorption at 1550 cm^{-1}.

The ketal 71 was reacted with the diol 31, in the same manner as described for nitromethane.



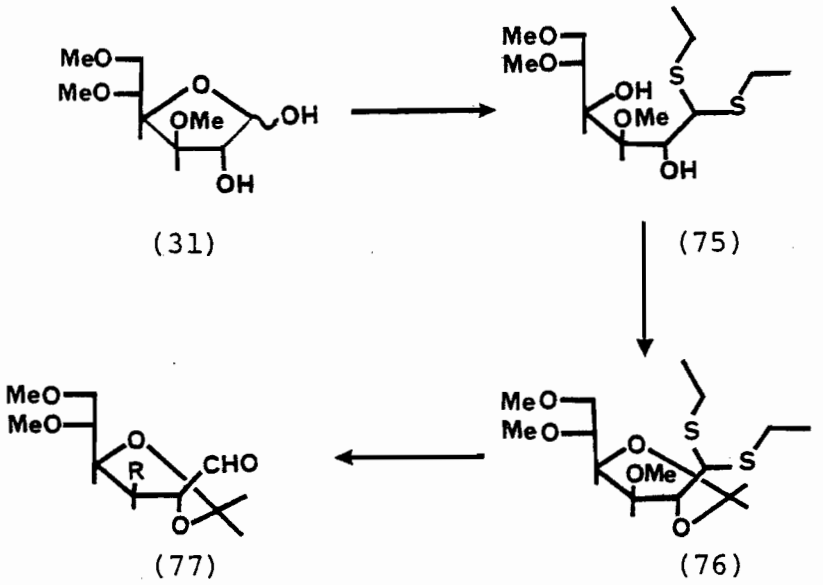
(31) (71) (74)

However, no evidence of the formation of adduct 74 was obtained. Several other sets of conditions were tried, to no avail.

Since the sugar did not react in its hemi-acetal form, the free aldehyde was next prepared. There are several methods

available for the ring-opening of sugars, the most efficient being the zinc chloride catalyzed reaction between a free sugar and ethanethiol[98,99]. The reaction was done by dissolving the diol 31 in ethanethiol and adding anhydrous zinc chloride at 0°. After work-up, an 79% yield of the dithioacetal 75 was obtained. Its p.m.r. spectrum showed a triplet at 1.30 ppm for the two methyl groups β to the sulfur atoms, two quartets at 2.75 ppm for the methylene groups α to the sulfur atoms and three singlets at 3.40, 3.50 and 3.70 ppm for the three methyl ethers. The infrared spectrum showed a strong hydroxyl absorption at 3450 cm^{-1} and the mass spectrum had a molecular ion at 328 m/e in accordance with the formula.

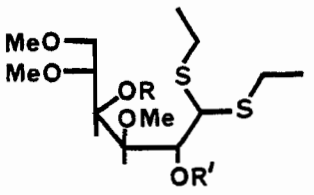
The next step in the sequence was the protection of the two hydroxyl functions. The first protecting group to be tried was the dimethyl-t-butylsilyl group. The advantage with this group is that upon its removal with fluoride ion the oxy anion could spontaneously cyclize. However, when the diol 75 was silylated with dimethyl-t-butylsilyl chloride in the presence



of imidazole in dimethylformamide at room temperature, two products were obtained. These two products were separated by flash column chromatography and identified by their p.m.r., i.r. and mass spectra. They were both found to contain one hydroxyl group and one silyl ether each. Closer examination revealed that the two products obtained were the mono-silylated alcohols 78 and 79. After several trials with harsher

reaction conditions had failed, this approach was dropped and a new protecting group investigated.

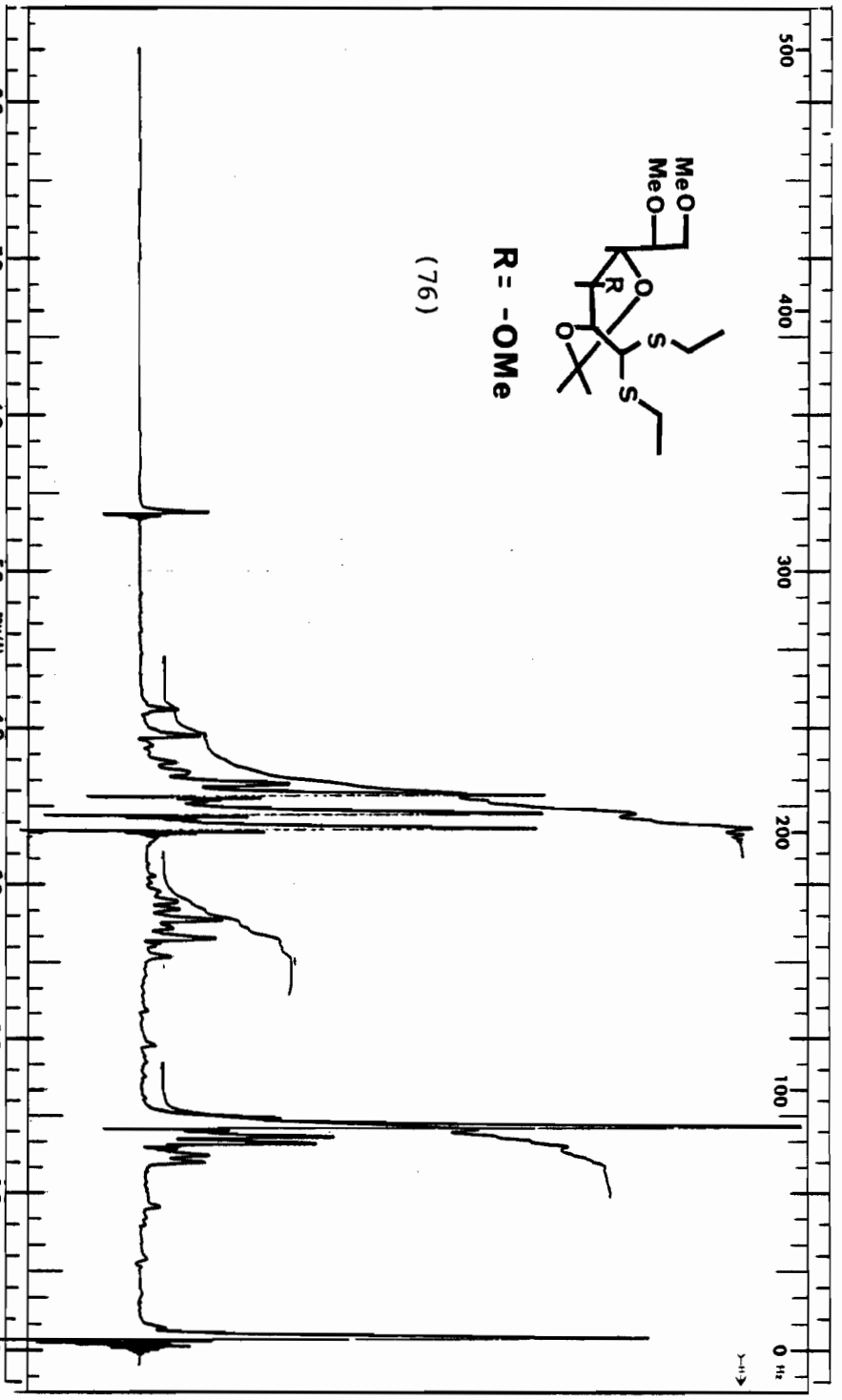
What was needed was a protecting group which would



(78) R = -H R' = -Si(t-butyl)Me_2

(79) R = -Si(t-butyl)Me_2 R' = -H

be stable to base and could be removed under mild acidic or neutral conditions. The isopropylidene group was chosen, not only because it fills the necessary requirements, but also because of its simple p.m.r. spectrum. Therefore the diol 75 was treated with anhydrous copper sulfate and catalytic amounts of sulfuric acid in acetone to give the protected dithioacetal 76 [100]. The p.m.r. spectrum of this compound showed two triplets at 1.20 and 1.30 ppm and a multiplet between 2.40 and 3.00 ppm corresponding to the two ethyl groups of the dithioacetal. The two isopropylidene methyl groups showed as a singlet at 1.40 ppm and the three methyl ethers showed as three singlets at 3.30, 3.40 and

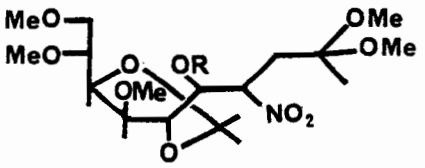


P.m.r. spectrum of compound 76.

and 3.50 ppm. The mass spectrum of this compound had a molecular ion at 368 m/e in accordance with the formula.

The dithioacetal 76 was easily hydrolyzed in good yield to the aldehyde 77 using mercuric chloride and mercuric oxide in a mixture of acetone and water[101,102]. The p.m.r. spectrum showed two singlets at 1.38 and 1.42 ppm for the isopropylidene group and a singlet at 9.60 ppm for the aldehyde proton. The infrared spectrum showed a strong carbonyl absorption at 1740 cm^{-1}. Now that the aldehyde had been obtained, the nitro ketal 71 could be reacted with it to give the required nitro adduct.

Thus, treatment of the aldehyde 77 with the nitro ketal 71 and diisopropylamine in dimethylformamide, at room temperature for 3 hours, afforded the adduct 80, presumably as a mixture of four diastereomers, in good yield. The

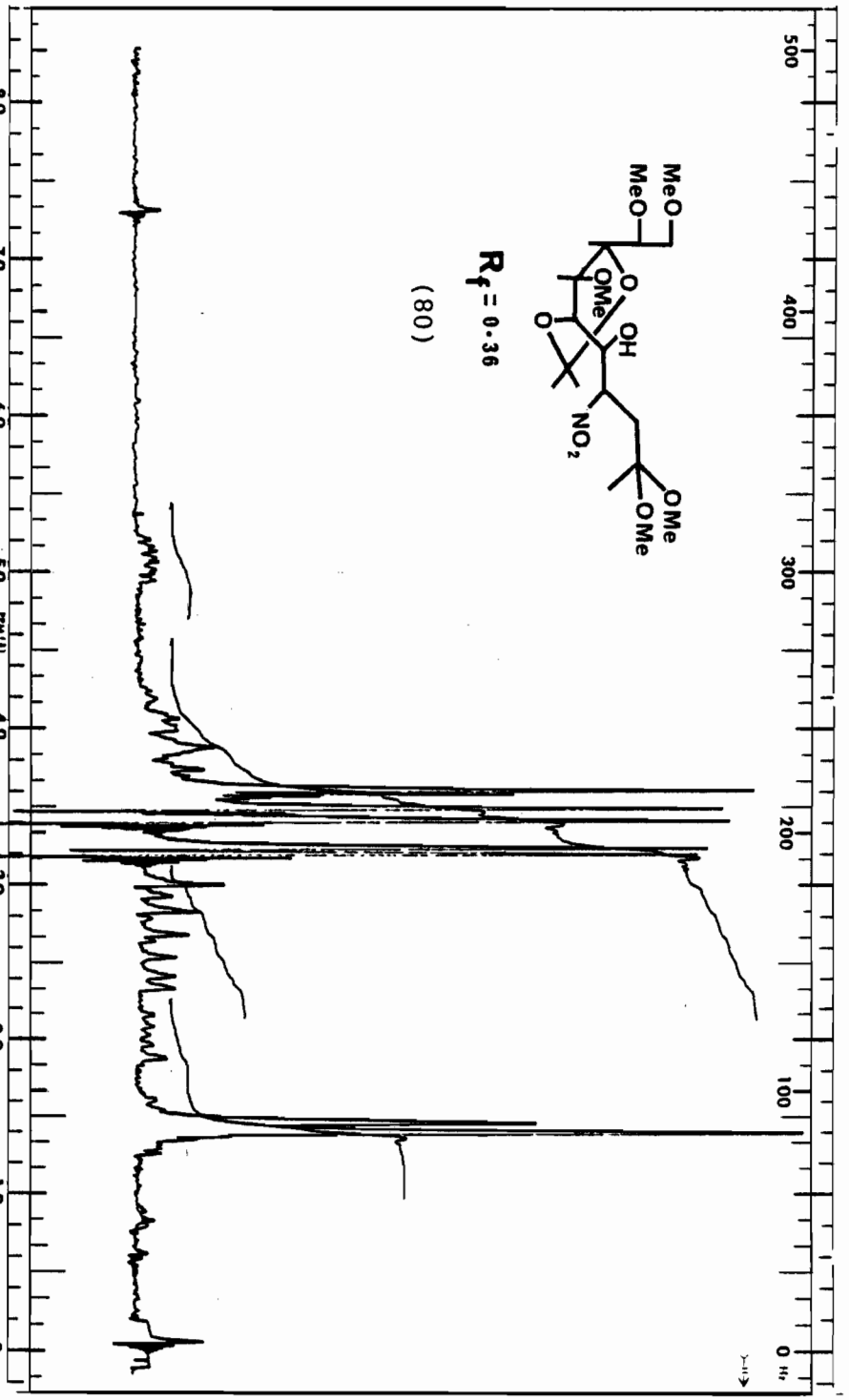


(80) R = -H

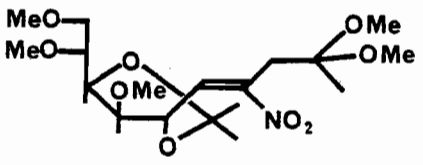
(81) R = $-COCH_3$

mixture appeared as two spots (R_f=0.36 and 0,42) on thin layer chromatography. Upon separation two fractions were obtained, each containing two compounds, as ascertained by p.m.r. The p.m.r. spectrum of the mixture having a R_f value of 0.36 showed two broad singlets at 1.30 and 1.40 ppm for the isopropylidene and terminal methyl groups, two singlets at 3.10 and 3.20 ppm for the ketal, three more singlets at 3.30, 3.40 and 3.50 ppm for the three methyl ethers, and finally a multiplet between 4.80 and 5.10 ppm for the proton α to the nitro group. The other mixture (R_f=0,42) had a similar p.m.r. spectrum. The infrared spectrum of both these mixtures had a hydroxyl absorption at 3440 cm^{-1} and a nitro absorption at 1550 cm^{-1}. The mass spectra were consistent with the structure of the adduct 80.

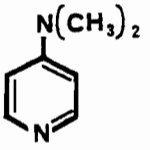
In order to carry out the elimination and obtain the desired nitro olefin 82, the nitro alcohol 80 had to be first, acetylated and then treated with base. The acetylation was first attempted using the same conditions as before, namely acetic anhydride and p-toluenesulfonic acid. However these conditions gave several products which could not be identified.



P.m.r. spectrum of compound 80.



(82)



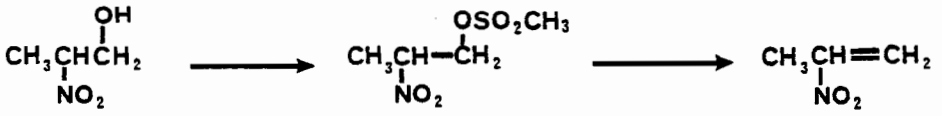
(83)

Next the nitro alcohol 80 was treated with acetic anhydride and N,N-dimethylaminopyridine[103] (83) in anhydrous ether to afford the nitro acetate 81 in good yield. The p.m.r. spectrum of the nitro acetate 81 displayed a singlet at 1.20 ppm for the terminal methyl group, a broad singlet at 1.40 ppm for the isopropylidene methyls, a sharp singlet at 2.10 ppm for the acetate, two singlets at 3.05 and 3.10 ppm for the dimethyl ketal and a multiplet between 5.10 and 5.30 ppm for the proton α to the nitro group. The infrared spectrum

had a carbonyl absorption at 1760 cm^{-1}, a nitro absorption at 1570 cm^{-1} and both the mass spectrum and the elemental analysis were consistent with the structure of compound 81.

The next step was the elimination reaction in order to generate the nitro olefin 82. The first method which was attempted was the standard method, using powdered potassium carbonate in dry benzene. However, this only gave starting material. Potassium carbonate with 0.2 equiv.of 18-crown-6 in dry benzene was then tried, and this gave several unidentifiable products.

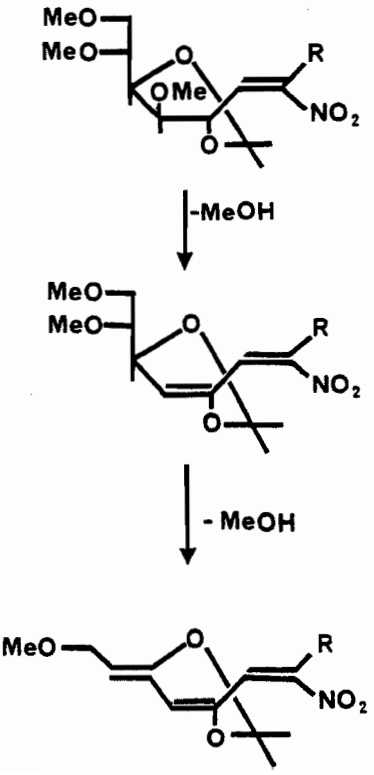
J. Melton and J.E. McMurray[104] reported that conversion of 2-nitro-3-pentanol (84) into the mesylate 85, and then the elimination by the use of triethylamine to afford the nitro olefin 86. When this was attempted on our nitro alcohol 80, no sign of nitro olefin was observed. Several other bases



(84) (85) (86)

such as D.B.U., tetra n-butyl ammonium fluoride, potassium fluoride and sodium methoxide were tried. The nitro olefin was however never obtained.

In view of this, the approach was dropped and a new approach investigated. It should be noted, that Mr. H.Oh, in our laboratory, repeated this sequence with the appropriate 9-carbon side-chain reagent with apparent success. This adduct does not have a methoxy group on C-3 which is one reason why the elimination reaction proceeded cleanly. When the nitro acetate 81 was treated with potassium carbonate and 18-crown-6 several products were obtained. It probably eliminated methanol to give the nitro olefin 82 which could further eliminate methanol, as shown below, to give several products. These eliminations cannot occur in the 3- deoxy series.



(82) R = $-CH_2C(OCH_3)_2CH_3$

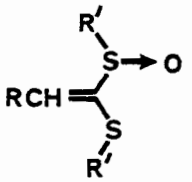
CHAPTER IV

Studies Towards the Synthesis of Furanose and Pyranose Sugars via an Unsaturated Ketene Dithioacetal S-Oxide.

Introduction:

A review of why the nitro approach was abandoned revealed that in the case of the adduct 81, the nitro olefin could not be obtained. In order to circumvent this problem, the nitro group had to be replaced by some other group which had the same basic properties and would lead to the desired compound.

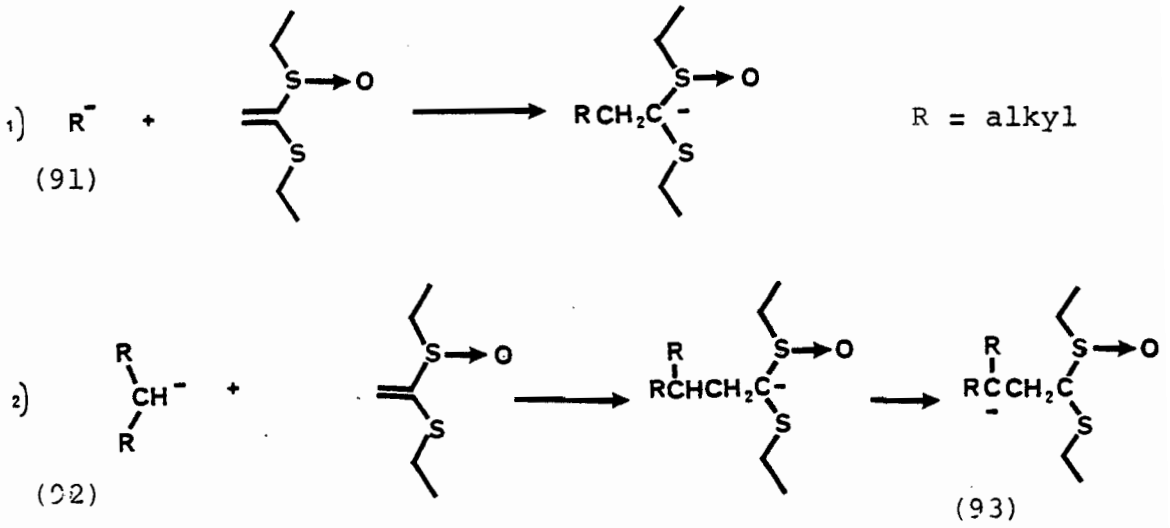
A literature search revealed that compounds of the type 87 have been coupled with anions from ketones, esters[105], β-ketoesters[105], β-diketones[105], malonates[106], α,β-unsaturated esters[105,106].



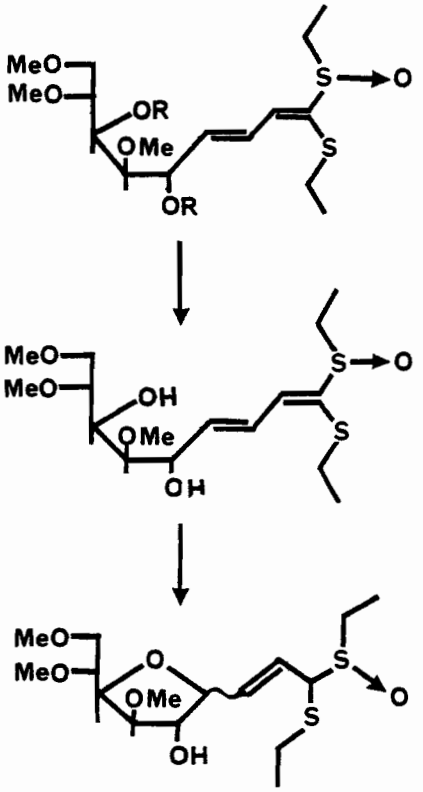
R = R' = alkyl

(87)

product. It should be noted that the addition of oxygen nucleophiles to this type of sulfoxide system is not well documented.



If this methodology is applied to our synthesis then the following sequence is foreseeable:

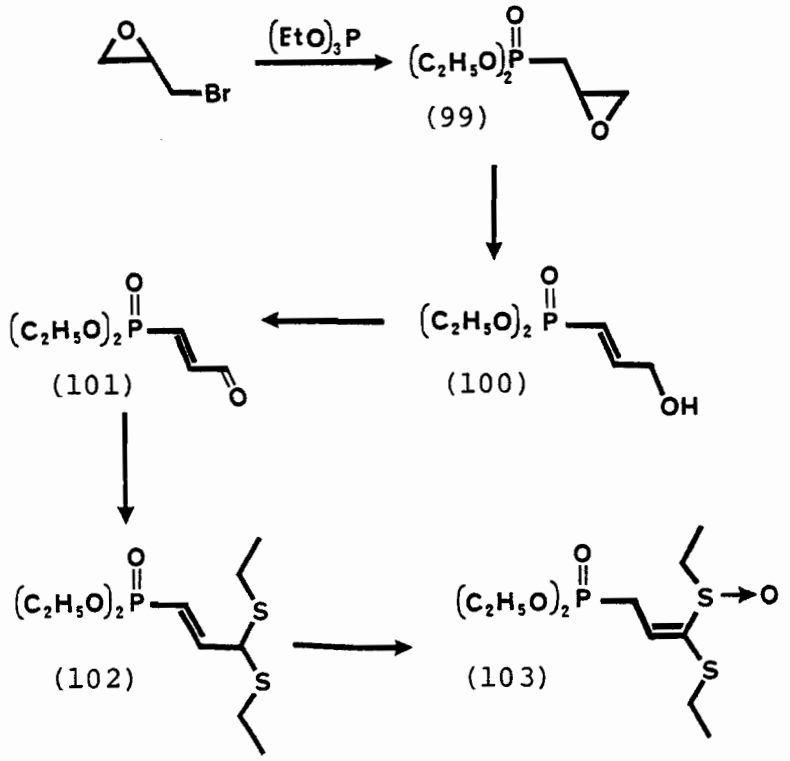


R = protecting group

If a precursor with structure 94 could be synthesized, where the two hydroxyl groups are protected, then removal of these protecting groups could lead to the cyclized sugar 96.

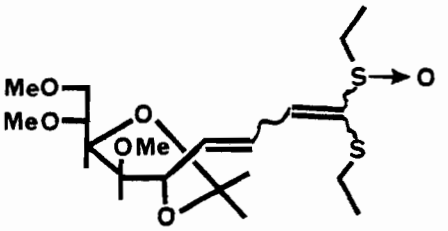
1,2-Dideoxy-1-C-(2,2-di(thioethyl)vinyl)-3,5-O-isopropylidene-4,6,7-tri-O-methyl-D-gluco-heptitol-1-ene S-Oxide (104).

Before these ideas could be implemented, compound 94 had to be synthesized. One possible method is to carry out a Wittig type reaction on aldehyde 77 with diethyl 3,3-di-(ethylthio)prop-2-enylphosphonate S-Oxide (103). The reagent was prepared for other purposes in our laboratory by Mr. P. Potvin using the following sequence:



Epibromohydrin was reacted with triethyl phosphite to afford the epoxy phosphonate 99 [108], which was rearranged to the allylic alcohol 100 with sodium methoxide[109]. This alcohol was oxidized using E.J. Corey's reagent[110], pyridinium chlorochromate, to the aldehydo phosphonate 101. The aldehyde underwent thioacetalization with ethanethiol and zinc chloride to afford diethyl 3,3-di(ethylthio)-prop-1-enylphosphonate (102), which was oxidized to the S-oxide 103 with m-chloroperbenzoic acid. It was noted from the p.m.r. spectrum that the double bond had shifted in conjugation with the sulfoxide moiety upon oxidation.

Now that the required reagent had been developed the Horner-Wittig reaction could be attempted. Reaction of the phosphonate S-oxide 103 with aldehyde 77 at -20°, using potassium t-butoxide as the base, resulted in low yields of the adduct 104 as a mixture of isomers. The p.m.r. spectrum of this compound displayed a broad triplet at 1.30 ppm

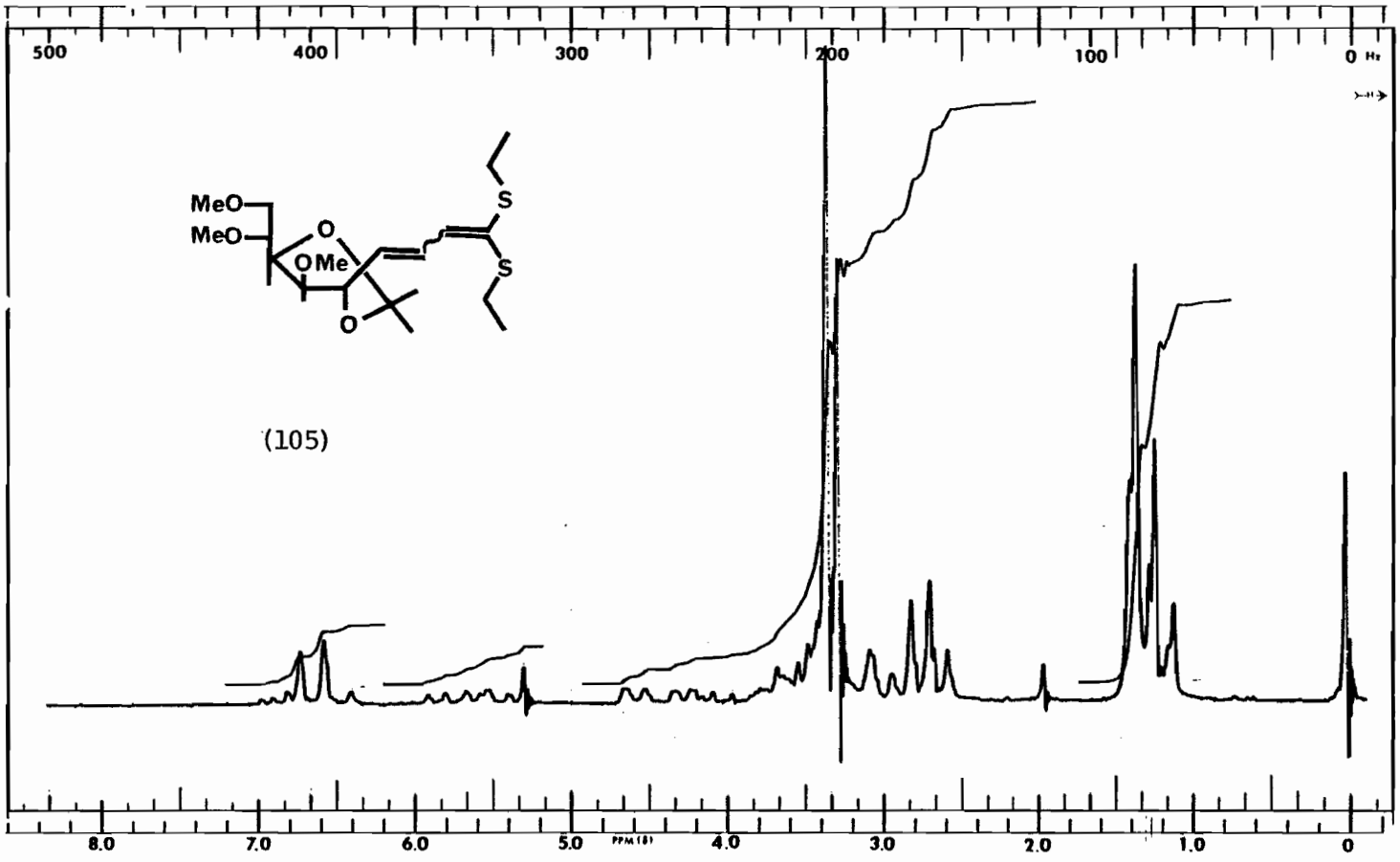


(104)

for the methyl groups in the thioethyl groups, a broad singlet at 1.40 ppm for the isopropylidene group, a broad quartet at 2.80 ppm for the methylene groups α to the sulfur atoms, two singlets at 3.30 and 3.40 ppm for the methyl ethers and a multiplet between 5.70 and 7.70 ppm for the olefinic protons. The infrared spectrum was consistent with the above structure, and the ultraviolet spectrum showed a $\lambda_{max}^{ethanol}$ at 267 nm for the diene sulfoxide system.

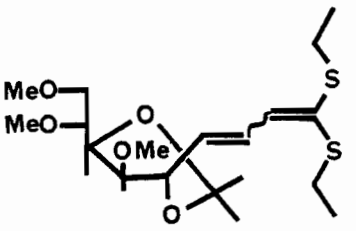
In order to improve the yield of the above reaction, the Horner-Wittig reaction was attempted using diethyl 3,3-di-(ethylthio)-prop-1-enylphosphonate (102) as the reagent, and followed by an oxidation to the sulfoxide. The aldehyde 77 was therefore reacted with phosphonate 102 and potassium t-butoxide at -20° to afford the adduct 105 in 74% yield. The p.m.r. spectrum of this compound displayed two triplets 1.25 and 1.30 ppm, instead of a broad triplet as in compound 104. The only other changes in the spectrum were the olefinic protons which now appeared between 6.30 and 7.00 ppm. The infrared spectrum had the expected absorptions and the mass spectrum displayed a molecular ion of m/e 406.

The ketene dithioacetal 105 was oxidized to the mono S-oxide 104 by treatment with m-chloroperbenzoic acid in methylene chloride at 0°. All the spectral data were identical to those already obtained for compound 104.



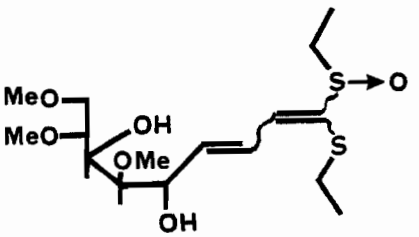
(105)

P.m.r. spectrum of compound 105.



(105)

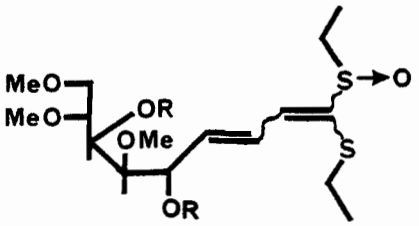
In order to attempt the cyclization, the isopropylidene group was hydrolyzed by stirring compound 104 in a mixture of aqueous hydrochloric acid and tetrahydofuran. After chromatographic purification the diol 106 was obtained as an oil.



(106)

Its p.m.r., infrared and mass spectra were all consistent with the proposed structure.

The diol 106 was then acetylated with acetic anhydride and N,N-dimethylaminopyridine in dry ether to afford the diacetate 107 in good yield. All the spectral data of this compound were also in accordance with the structure of compound 107.



R = $-COCH_3$

(107)

The cyclization of compound 107 was attempted using varying conditions. The first attempt involved methanolysis of the acetates with sodium methoxide in the hope that the oxy-anion generated would cyclize spontaneously to the desired compound 96, as in the nitromethane case already discussed. This reaction afforded several products which were isolated. The chemical ionization mass spectrum of one of the isolated products did show evidence of the presence of 96. Also, this compound had an U.V. absorption of 210 nm indicating that the diene sulfoxide chromophore was no longer present.

However, the identification of this compound was not possible because of its complex p.m.r. spectrum. Varied conditions were used in an attempt to reduce the number of products obtained, but to no avail.

Conclusion:

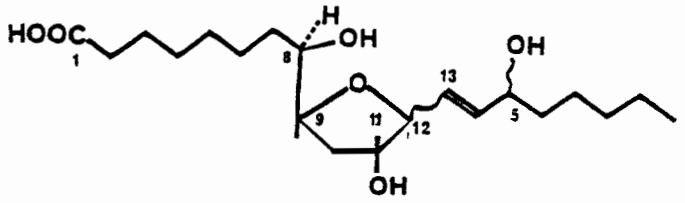
It is well possible that this cyclisation reaction failed for the same reasons as those described for the elimination of acetic acid from the nitro acetate 81, namely the presence of a methoxy group vinylogously β to the sulfoxide (or nitro) function. Repeating the sequence with an appropriately substituted 3-deoxyglucose derivative may well give the desired compound.

CHAPTER V

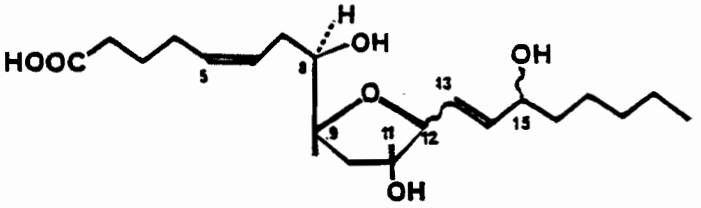
Synthesis of Arachidonic Metabolite Derivatives

Introduction:

In the previous two chapters, alternate methods for the synthesis of both α- and β-anomers of the furano- and pyrano-ring system were investigated. Because of the problems encountered, it was decided to apply the cyano scheme discussed in Chapter I to the synthesis of the natural product 17a. The saturated compound 17a was chosen over the unsaturated compound 15a because of forseeable problems in distinguishing between the olefin and the cyano group which would arise when the Raney nickel reaction would be attempted. Raney nickel has been known[111] to reduce olefins to saturated hydrocarbons.

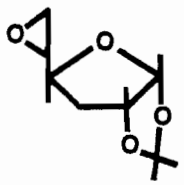


(17a)

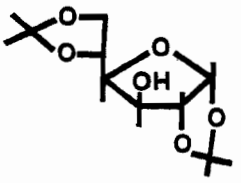


(15a)

A synthetic scheme has been devised by C. Luthe, in our laboratory, in which the side-chain containing the carboxylic acid group is attached to the sugar moiety via the 5,6-epoxide. The epoxide intermediate 108 was made available in large scale[112] starting from 1,2:5,6-di-O-isopropylidene-D-α-gluco furanose (109).



(108)

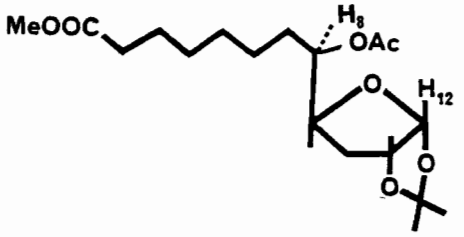


(109)

The synthetic path by which the epoxide was made will not be discussed here. Our discussion will begin with the epoxide and progress to the desired product.

It should be noted that in the previous chapters, the carbohydrate nomenclature has been used. However, in this chapter, the nomenclature will change to the prostaglandin terminology. The chirality of the carbons will be specified accordingly. The carboxylic carbon will therefore be C-1, the junction of the side chain with the furan ring at C-9, and the anomeric center will become C-12. It should also be noted that when referring to the p.m.r. spectra, the hydrogen

on any carbon will have the same number as that assigned to the carbon. An example is given below:

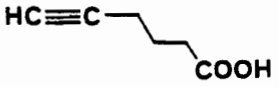


Methyl 8(R),11(R)-Diacetoxy-12-cyano-9(S),12-oxy-dodecanoate (125).

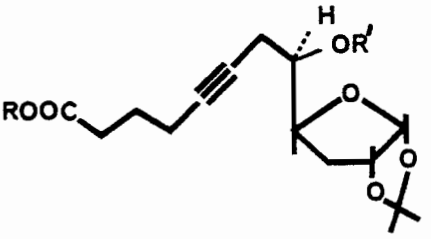
The epoxide 108 was reacted at 0^{o} under a nitrogen atmosphere with the acetylenic acid 110 and n-butyllithium to afford the adduct 111. This adduct was methylated *in situ* with diazomethane in ether to give the stable methyl ester 112. The procedure for this addition reaction was devised by C. Luthe in our laboratory. The acetylenic side chain 110 was made via a scheme devised by Mr. H. Oh[113].

The first step in the synthesis was the protection of the C-8 hydroxyl group, which was accomplished by a simple acetylation using acetic anhydride and N,N -dimethyl-amino-pyridine in anhydrous ether. The acetate 116 was characterized by its p.m.r., infrared and mass spectra. The acetate group

was chosen because it is quite stable to acid but can be easily removed under alkaline conditions.



(110)

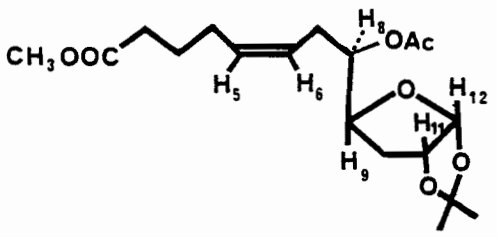


(111) R = R' = -H

(112) R = $-CH_3$ R' = -H

(116) R = $-CH_3$ R' = $-COCH_3$

The acetylenic compound 116 was hydrogenated with hydrogen gas at 40 p.s.i. and palladium on charcoal as the catalyst, to afford the olefin 117 instead of the desired saturated compound.

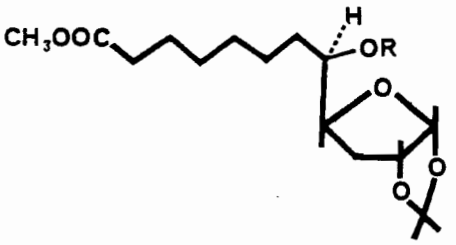


(117)

The p.m.r. spectrum of this compound displayed two singlets at 1.30 and 1.50 ppm for the isopropylidene group, a singlet at 2.10 ppm for the acetate group, another singlet at 3.60 ppm for the methyl ether, a quartet with a coupling constant of $J_{9,8}$=6 Hz at 4.10 ppm for the proton on C-9, a broad triplet at 4.70 ppm for the hydrogen on C-11, a broad quartet at 5.00 ppm with coupling constants of $J_{8,9}$=6 Hz and $J_{8,7}$=6 Hz for the proton on C-8, a multiplet between 5.30 and 5.45 ppm for the two olefinic hydrogens and finally a doublet at 5.80 ppm with a coupling constant of $J_{12,11}$=4 Hz for the proton on C-12. A cis-stereochemistry was assigned to the olefinic protons by direct comparison of our p.m.r. spectrum to the p.m.r. spectrum of the same compound synthesized by reducing the acetylenic compound 116 with hydrogen gas and a nickel catalyst. This nickel boride catalyst is known[114,115] to give the cis-isomer as the sole product. The infrared spectrum had the appropriate absorptions and the chemical

ionization mass spectrum showed a fragment of 357 m/e which corresponds to $(M^{+}+1)$.

In view of the fact that the hydrogenation stopped at the olefinic stage, compound 117 was further hydrogenated, this time with platinum oxide as the catalyst at 40 p.s.i. It is a well known fact[116] that platinum oxide is a much stronger catalyst, and, as expected, after 30 minutes, compound 117 was fully hydrogenated to the saturated compound 118.



(118) R = $-COCH_3$

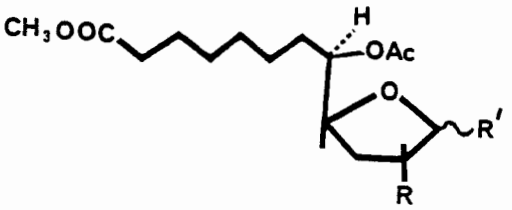
(128) R = $-CH_3$

The compound was identified by its p.m.r., infrared and mass spectra.

Now that it was known that platinum oxide and hydrogen would reduce the olefin to the saturated compound, this procedure was applied to the acetylenic compound 116. As expected, after 30 minutes, compound 116 was fully converted to the desired product 118. All the spectral data for the

compound obtained were identical to those of compound 118 previously synthesized.

The isopropylidene compound 118 was hydrolyzed with an acetic acid-water mixture at 60° to afford the crystalline hemi-acetal 119 as a mixture of C-12 isomers. The p.m.r., infrared, mass spectral, and microanalytical data were all consistent with the proposed structure.



(119) $R = R' = -OH$

(120) $R = R' = -OCOC_6H_4NO_2$

(121) $R = -OCOC_6H_4NO_2$ $R' = -CN$

(122) $R = -OH$ $R' = -CN$

(123) $R = R' = -OCOCH_3$

(124) $R = -OCOCH_3$ $R' = -Br$

(125) $R = -OCOCH_3$ $R' = -CN$

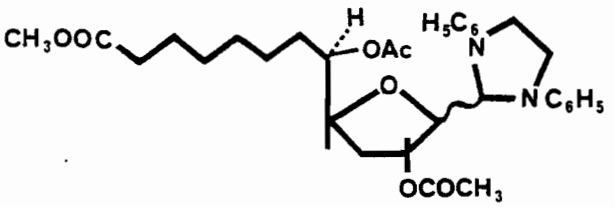
The diol 119 was then acylated with p-nitrobenzoyl chloride in pyridine at 0^{o} to afford the di-p-nitrobenzoate 120 as a mixture of isomers. The p.m.r. spectrum displayed a singlet at 6.50 ppm and a doublet at 6.70 ppm for the proton on C-12. The C-12 (S) isomer (β-anomer) displays the singlet since the dihedral angle between the hydrogens on C-11 and C-12 is close to 90^{o}, and the C-12 (R) isomer (α-anomer) displays the doublet because this dihedral angle is close to 0^{o}. The infrared spectrum showed carbonyl absorptions at 1730 cm^{-1}, aromatic absorptions at 1610 cm^{-1} and absorptions at 1530 cm^{-1} for the nitro group. The mass fragmentation pattern was in accordance with the proposed structure.

As was done before, the di-p-nitrobenzoate 120 was converted to the cyano p-nitrobenzoate 121 by doing a displacement of the C-12 p-nitrobenzoate with gaseous hydrogen bromide in anhydrous ether at 0^{o}. This bromo glycoside was then treated with mercuric cyanide in nitromethane to afford the desired compound 121, as a 1:1 mixture of C-12 isomers[57]. The p.m.r., infrared and mass spectra corresponded to the structure of cyano p-nitrobenzoate 121.

Because Raney nickel reduces nitro groups to amines[118], the p-nitrobenzoate ester had to be removed. Several base hydrolyses on compound 121 were attempted; however all failed probably because of the instability of glycosyl cyanides to base[117]. Also the C-8 acetate is prone to hydrolysis, thereby generating an alcohol which might

undergo other reactions. In order to eliminate the hydrolytic step, it was decided to replace the p-nitrobenzoyl group by an acetyl group.

The hemi-acetal 119 was therefore acetylated with acetic anhydride and N,N-dimethylaminopyridine in anhydrous ether to afford a (R,S) mixture of acetates 123 . The p.m.r. spectrum of compound 123 displayed a broad multiplet between 1.10 and 1.80 ppm for the side-chain protons, a broad singlet at 2.00 ppm for the acetate groups, a singlet at 3.60 ppm for the methyl ester, a multiplet between 4.00 and 4.40 ppm for the hydrogen on C-9, another multiplet between 4.60 and 5.20 ppm for the proton on C-8 and finally at singlet at 6.00 ppm and a doublet at 6.20 ppm for the hydrogen on C-12. The infrared and mass spectra were both consistent with the structure of compound 123. The triacetate 123 was then converted to the bromo compound 124 in the usual manner, and the bromo compound 124, after treatment with mercuric cyanide in nitromethane, gave the cyano acetate 125. The cyano acetate was then treated with Raney nickel, sodium hypophosphite and N,N-diphenylethylene diamine (43), in a mixture of pyridine, acetic acid and water. The expected product 126 was not obtained; only starting material was recovered.



(126)

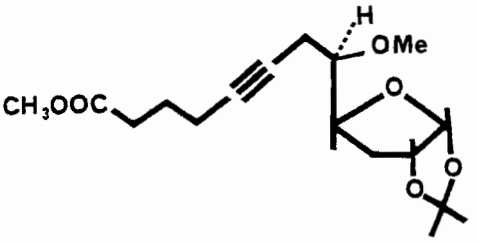
Methyl 12-Cyano-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12-oxy-dodecanoate (132).

Because of the incompatibility of the protecting groups in the cyano compound 121, it was decided to replace the acetate group on C-8 by a more stable methyl ether. This protecting group would offer two advantages:

1. It would allow for a wider range of possible reaction conditions because of its stability.
2. It would make our compound more similar to the model compound 39, thereby increasing the chances for a successful synthesis.

The epoxide 108 was therefore treated with the dilithio derivative of the acetylenic side-chain 110, in the same manner as before. However, this time, the reaction was quenched with methyl iodide and the mixture heated to 60° for two hours,

thereby affording the methyl ether 127. The procedure for this preparation was also devised by Ms. C. Luthe in our



(127)

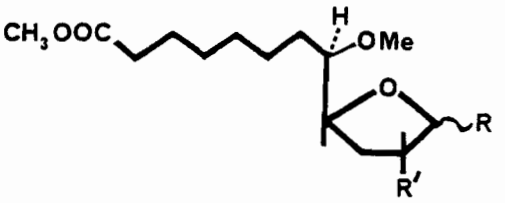
laboratory.

The acetylenic compound 127 was hydrogenated in ethyl acetate at 40 p.s.i. with platinum oxide as the catalyst to afford the saturated product 128. Its p.m.r. spectrum displayed singlets at 1.25 and 1.40 ppm for the isopropylidene group, at 3.35 ppm for the methyl ether, 3.60 ppm for the methyl ester and a doublet at 5.60 ppm for the hydrogen on C-12. Both the infrared and mass spectra were in accordance with the compound obtained. As well, the elemental analysis was within acceptable limits.

The isopropylidene group in compound 128 was hydrolyzed in an acetic acid-water mixture at 60^{o} to give the hemi-acetal 129 as a mixture of C-12 isomers. The p.m.r. spectrum of this compound in a mixture of deuterated chloroform and water

displayed the same spectrum as for compound 128, except for the two missing isopropylidene singlets. As well, the methyl ether peak, which was a singlet, became a doublet. The C-12 proton now showed two resonances, a singlet at 5.10 ppm (β-anomer) and a doublet at 5.30 ppm (α-anomer). The infrared spectrum had a strong hydroxyl absorption at 3400 cm^{-1}.

This diol was acylated with p-nitrobenzoyl chloride and pyridine to afford the di-p-nitrobenzoate 130 as a mixture of C-12 isomers. The p.m.r., infrared, mass spectral, and microanalytical data obtained were all consistent with the proposed structure of compound 130.



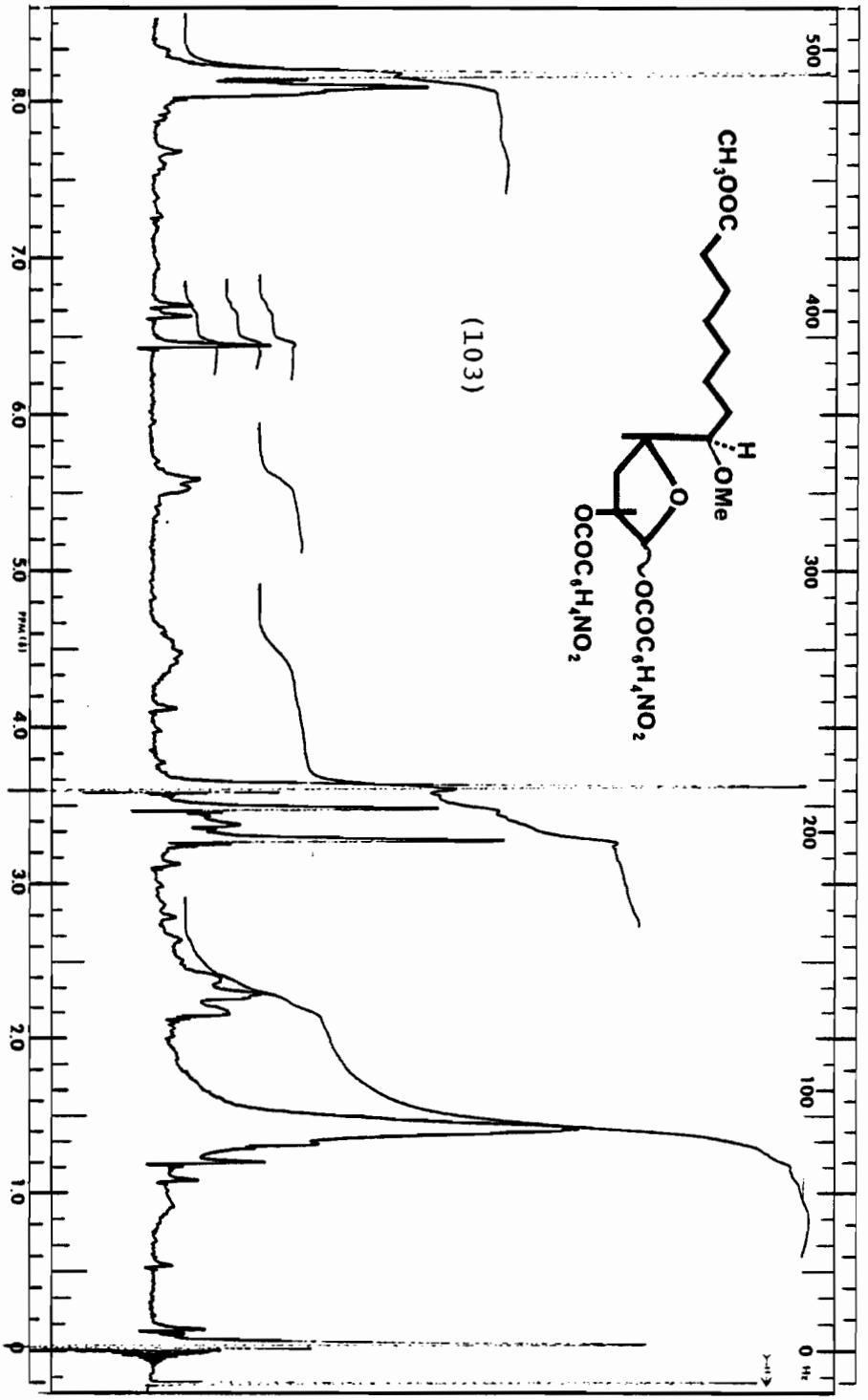
(129) R = R' = -OH

(130) R = R' = $-OCOC_6H_4NO_2$

(131) R = -Br R' = $-OCOC_6H_4NO_2$

(132) R = -CN R' = $-OCOC_6H_4NO_2$

(133) R = -CN R' = -OH

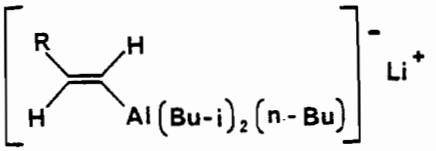


P.m.r. spectrum of compound 130.

Treatment of the di-p-nitrobenzoate with hydrogen bromide, followed by mercuric cyanide, in the same manner as was done for compound 120, afforded the cyano compound 132, as a mixture of (R) and (S) C-12 isomers. All the spectral data obtained for this compound were consistent with the proposed structure.

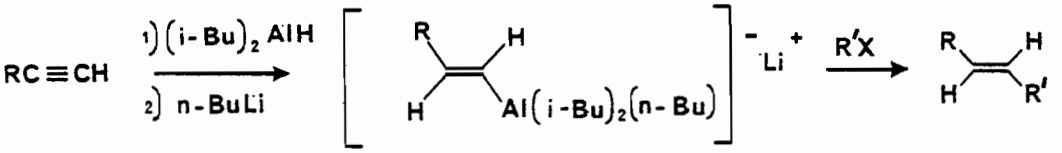
The next step in our synthesis was the hydrolysis of the p-nitrobenzoate ester in compound 132. Several conditions were attempted, the first being sodium hydroxide in tetrahydrofuran and water, which resulted in the formation of an unidentified product. Hydrolysis with sodium carbonate or sodium bicarbonate in a methanol-water mixture gave several compounds in approximately equal proportions. The final attempt was a transesterification between the p-nitrobenzoyl group in compound 132 and methanol in the presence of p-toluenesulfonic acid. This reaction also afforded a mixture of products, none of which was the desired alcohol 133.

In view of the above results, the planned synthetic scheme had to be redesigned. A survey of the literature[119] revealed that trans-olefins can be prepared by the reaction of trans-alkenyltrialkyaluminates of type 134 with alkyl halides. The alkenylaluminate can be prepared by the reaction



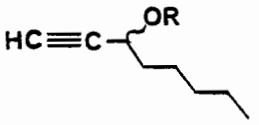
(134)

of alkynes with diisobutylaluminum hydride (DIBAL) followed by treatment with an equimolar amount of n-butyllithium. The stereochemistry of the olefins obtained has been established by a combination of ^{1}H and ^{13}C n.m.r. data[119]. Ei-ichi Negishi found that the reaction proceeds better with more reactive halides and sulfonates, such as methyl iodide, allyl bromide, propargyl bromide, benzyl iodide and α-chloromethyl methyl ether. An overall view of the reaction is represented below:



(134)

If this methodology were to be applied to our synthetic scheme, then the acetylenic compound to be used would be compound 135 or 136, and the reactive halide would be the bromo compound 131. Since the bromine in the bromo compound 131 is activated by the ring oxygen, an attempt at this reaction was justified. It should be noted that glycosyl bromides do undergo Grignard reactions[121] quite readily. Compound 135 had previously been synthesized[120] in our laboratory and therefore was the first to be tried.



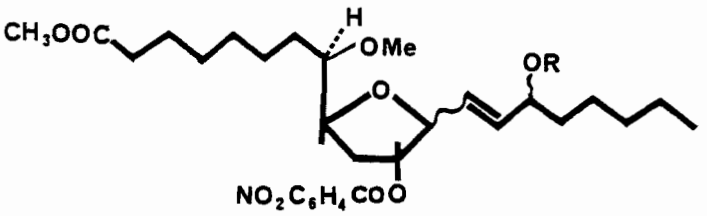
(135) R = $-CH(CH_3)OCH_2CH_3$

(136) R = $-Si(t\text{-butyl})Me_2$

(143) R = $-H$

This acetylenic compound was thus first treated with diisobutylaluminum hydride (DIBAL) at room temperature, and then with n-butyllithium in dry tetrahydrofuran. The resulting solution was cooled to -78^{o} and a solution of the bromo compound 131, in dry tetrahydrofuran, was added dropwise. After allowing the reaction to stir for 2 hours

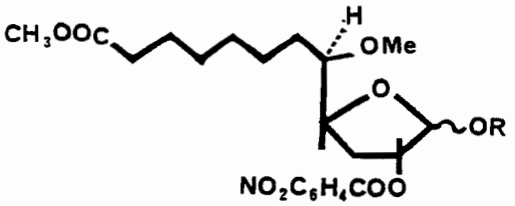
at room temperature, it was quenched with water. Instead of the desired adduct 137, the product of hydrolysis 138 was isolated. This compound was further characterized as its



R = $-CH(CH_3)OCH_2CH_3$

(137)

acetylated derivative 139. Because of the results obtained this approach was abandoned.



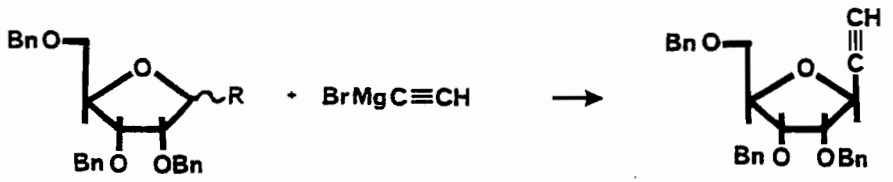
(138) R = -H

(139) R = $-COCH_3$

Methyl 15-(t-Butyldimethyl)silyloxy-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12(R)-oxy-eicosa-13-ynoate (145).

J.G. Buchanan et al.[120] reported the reaction between ribofuranosyl chloride 140 and ethynyl magnesium bromide 141 to afford the ribo compound 142. This preparation allows for the attachment of an acetylenic compound to a glycosyl chloride or bromide. This methodology could be applied to our specific problem. For convenience of preparation the lithium salt of the acetylenic chain was chosen.

Because of the complexity of the p.m.r. spectrum of compound 135, the vinyl ether protecting group was replaced by a t-butyldimethylsilyl group. Compound 136 was prepared by silylation of the alcohol 143 in the usual manner. The p.m.r. spectrum of this ether displayed two singlets at 0.20 and 0.22 ppm for the two methyl groups on the silicon atom, a broad singlet at 1.00 ppm for the t-butyl group and the terminal

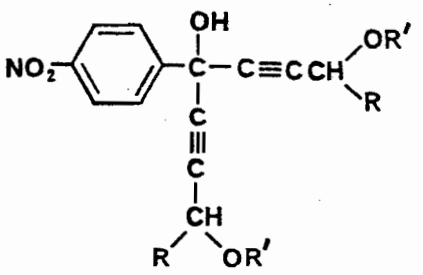


R = -Cl

(140) (141) (142)

methyl, a multiplet between 1.20 and 1.80 ppm for the methylene groups, a doublet at 2.30 ppm for the acetylenic proton and a multiplet between 4.20 and 4.50 ppm for the hydrogen next to the silyl ether.

The lithium salt of compound 136 was generated by reacting the acetylenic compound with n-butyllithium in dry tetrahydrofuran. This lithium salt solution was added dropwise to the bromo compound 131 in a mixture of dry hexamethylphosphoramide and dry tetrahydrofuran at -78°. After stirring the reaction mixture at -78° for 2 hours, it was quenched with pH 4.4 buffer and the products were extracted with ether. Thin layer chromatography indicated the production of four compounds. Each of these compounds was isolated by preparative plate chromatography. The first product was found to have a R_f value of 0.91 and was identified as being compound 144.

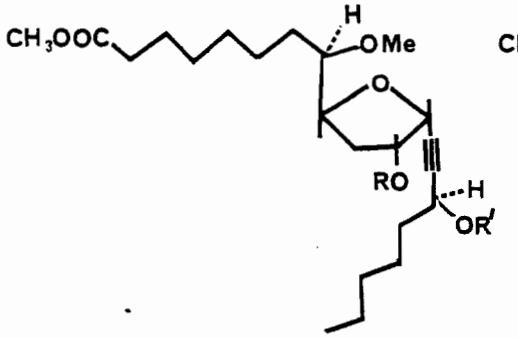


$R' = -Si(t\text{-butyl})Me_2$

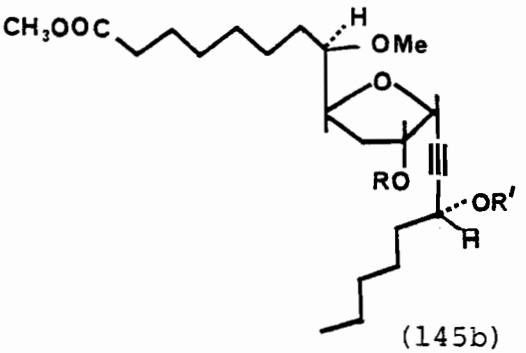
$R = -C_5H_{11}$

(144)

This product is the result of a double attack by the acetylenic anion on the p-nitrobenzoate ester. The compounds having R_f values of 0.76 and 0.60 were found to be the desired adducts 145a and 145b. The stereochemistry at C-12 was assigned by way of the coupling constant between the C-12 and C-11 protons. The p.m.r. spectrum of compound 145, which has a R_f value of 0.76 and was the major component, displayed singlets at 0.20 ppm for the methyl groups on the silicon atom, at 3.40 ppm for the methyl ether, at 3.60 ppm for the methyl ester, a multiplet between 4.80 and 5.10 ppm for the proton on C-11, a doublet at 6.00 ppm with a coupling constant of $J_{11,12}$=4 Hz* and a quartet at 8.00 ppm for the aromatic protons. Because of the large coupling constant between the C-11 and C-12 hydrogens a (R) stereochemistry was assigned to the C-12 carbon. The mass spectrum of the compound showed fragments of 604 m/e corresponding to the loss of a t-butyl



(145a)

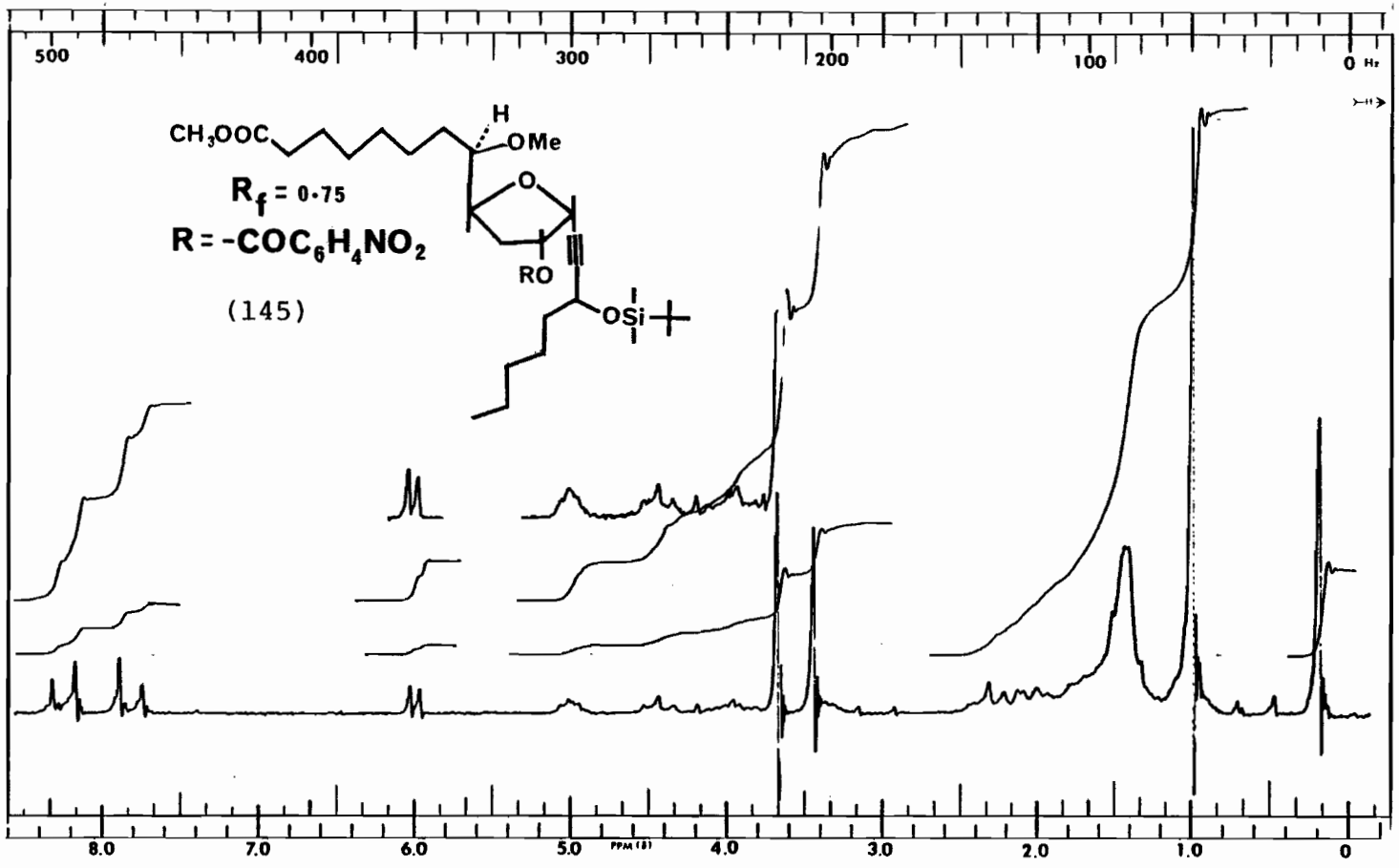


(145b)

R = $-COC_6H_4NO_2$

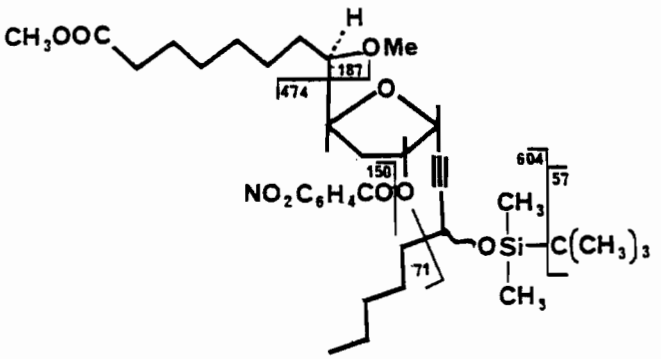
R' = $-Si(t\text{-butyl})Me_2$

* Examples exist in the literature where a coupling constant similar to that of $J_{11,12}$ has been assigned to protons on a furano ring which have a trans relationship.



P.m.r. spectrum of compound 145 having an R_f value of 0.75.

group, 590 m/e for a loss of 71 m/e, 474 m/e (loss of 187 m/e), 187, 150, 71 and 57 m/e. The infrared spectrum had a carbonyl absorption at 1740 cm^{-1}, an aromatic absorption at 1610 cm^{-1} and a nitro absorption at 1530 cm^{-1}. The spectral data for



the compound having a R_f value of 0.60 were only slightly different from those of the above compound (having a R_f value of 0.76). The p.m.r. spectrum of this isomer also had a coupling constant of 4 Hz for the hydrogens on C-11 and C-12. Because of the great similarity between their spectral data, the specific stereochemistry could not be assigned to the two C-15 isomers. It should be noted that the two diastereomers were not produced in equal amounts since the compound having an R_f value of 0.76 was preferentially formed. The overall yields of compounds 145a and 145b was calculated as being approximately 40%.

The fourth compound to be isolated and characterized had a R_f value of 0.18. From the p.m.r. and infrared spectra this compound was identified as the hemi-acetal 138. The presence of this hemi-acetal would indicate that there was not enough of the side-chain derivative 136 and therefore the unreacted compound 131 may have well reacted with water during the work-up to give the hemi-acetal 138.

In order to make this reaction more efficient, the p-nitrobenzoyl protecting group would have to be replaced by a less electrophilic group. Because of the urgent need for the desired compound 8, it was decided to postpone both the study towards a suitable C-11 protecting group and the optimization of the coupling reaction conditions, and to proceed with the material at hand.

The major obstacle which the acetylenic compound 145 presented was the reduction of the triple bond to a trans-olefin. Several reagents[121] exist which perform this transformation. Lithium aluminum hydride is commonly used for this purpose. However, it has the disadvantage that it reacts with many functional groups, such as esters. C.E. Castro[122] reported that acetylenes can, however, be reduced to trans-olefins by chromous sulfate. They found the acetylenic bond to be one of the most effective multiply-bonded structural units to effect the oxidation of Cr(II) to Cr(III), while it is in turn reduced to the olefin. This reaction has been known for quite some time, since acetylene

to ethylene conversions have been accomplished in acidic media with chromous chloride[123]. The homogeneous reduction of acetylenes by chromous sulfate proceeds readily at room temperature in water or aqueous dimethylformamide, under a nitrogen atmosphere. It should be noted that isomerization of cis- or trans-olefins does not occur under the reaction conditions necessary for this reduction. C.E. Castro also reported that the reduction of acetylenes by Cr(II) can be cleanly controlled to stop at the olefin[122] stage. However, olefins bearing electron-withdrawing substituents can be reduced, under the same reaction conditions, to the corresponding alkane. Qualitatively, the reactivity of acetylenes towards chromous sulfate can be grouped as follows:

1. very reactive - instantaneous
   ($HOCH_2C{\equiv}CCH_2OH$)
2. moderately reactive - 2-3 hours
   ($HC{\equiv}CCH_2OH$)
3. slow - 24 hours
   ($CH_3C{\equiv}CCH_2OH$)
4. inert ($C_6H_5C{\equiv}CC_6H_5$)

The preparation[124] of chromous sulfate 148 involved a reduction of hydrated chromic sulfate 147 with purified zinc powder, in water, under a nitrogen atmosphere. This reagent can be stored for weeks in an aqueous solution under an

$$Cr_2(SO_4)_3 + Zn \xrightarrow{H_2O} 2\ CrSO_4 + ZnSO_4$$

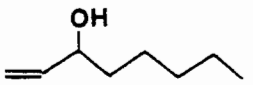
(147) (148)

inert atmosphere. The oxidation of Cr(II) to Cr(III) can easily be detected since the Cr(II) ion is blue, and the Cr(III) ion is dark green.

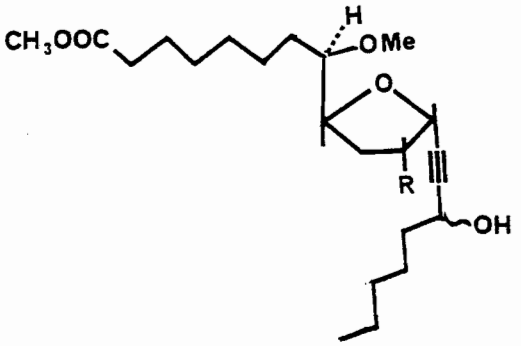
In order to test the reactivity of propargyl alcohols and obtain the precise reaction conditions necessary, it was decided to try the reagent on a model compound. The compound chosen was the acetylenic side-chain 143. After preparing the chromous sulfate reagent 148, it was reacted with the acetylenic compound 143 in a 1:1 mixture of dimethylformamide and water. The reaction was monitored by changes in the p.m.r. spectrum of the reaction mixture. The p.m.r. spectrum of the resulting olefin 149 was found to have a multiplet between 5.20 and 5.80 ppm for the two terminal olefinic protons and another multiplet between 5.80 and 6.50 ppm for the remaining olefinic proton.

In view of the fact that the acetylenic alcohol 143 was cleanly reduced to the olefin, it was decided to try the chromous sulfate reduction on compound 150. In order to obtain this compound, the silyl protecting group in compound

145 had to be hydrolyzed.[125,126] The silyl compound 145 was



(149)



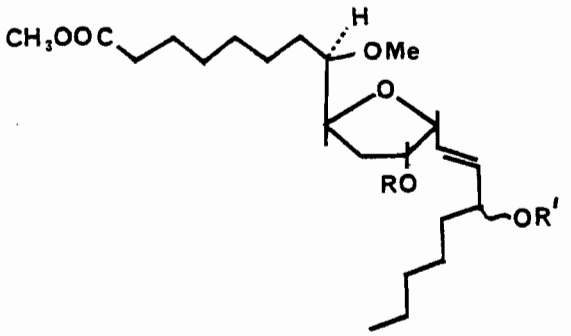
(150) R = $-OCOC_6H_4NO_2$

(151) R = $-OCOC_6H_4NH_2$

thus treated with 80% acetic acid at 80° for 3 hours to afford the alcohol 150 in 81% yield, as an oil which was purified by preparative plate chromatography[125,126]. The 90 mHz p.m.r. spectrum of a pure sample displayed a broad triplet at 0.95 ppm for the terminal methyl group, a singlet at 3.50 ppm for the methyl ether, another singlet at 3.75 ppm for the methyl ester, a multiplet between 5.05 and 5.25 ppm for the proton on C-11,

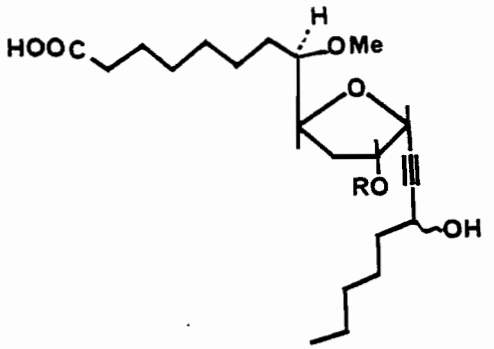
a doublet with a coupling constant of $J_{12,11}$=4 Hz for the C-12 proton and a quartet at 8.25 ppm for the aromatic protons. The infrared spectrum had a strong hydroxyl absorption at 3430 cm^{-1}, carbonyl absorptions at 1740 cm^{-1} and 1720 cm^{-1}, an aromatic absorption at 1610 cm^{-1} and finally a strong nitro absorption at 1530 cm^{-1}. These data are fully consistent with structure 150. However, the mass spectrum showed one major peak of 190 m/e only, in addition to a few minor peaks, and it defied any interpretation.

The acetylenic compound 150 was treated, as before, with a chromous sulfate solution in a mixture of water and dimethylformamide at room temperature. After the work-up, the spectral data of the product showed that the desired compound 152 was not obtained, but that the nitro group was reduced to an amine instead, thereby giving compound 151. The presence of an amino group was found by way of the p.m.r., infrared and mass spectra of the compound. The 90 mHz p.m.r. spectrum of the amino compound 151 was very similar to that



(152) R = $-COC_6H_4NO_2$ R' = H

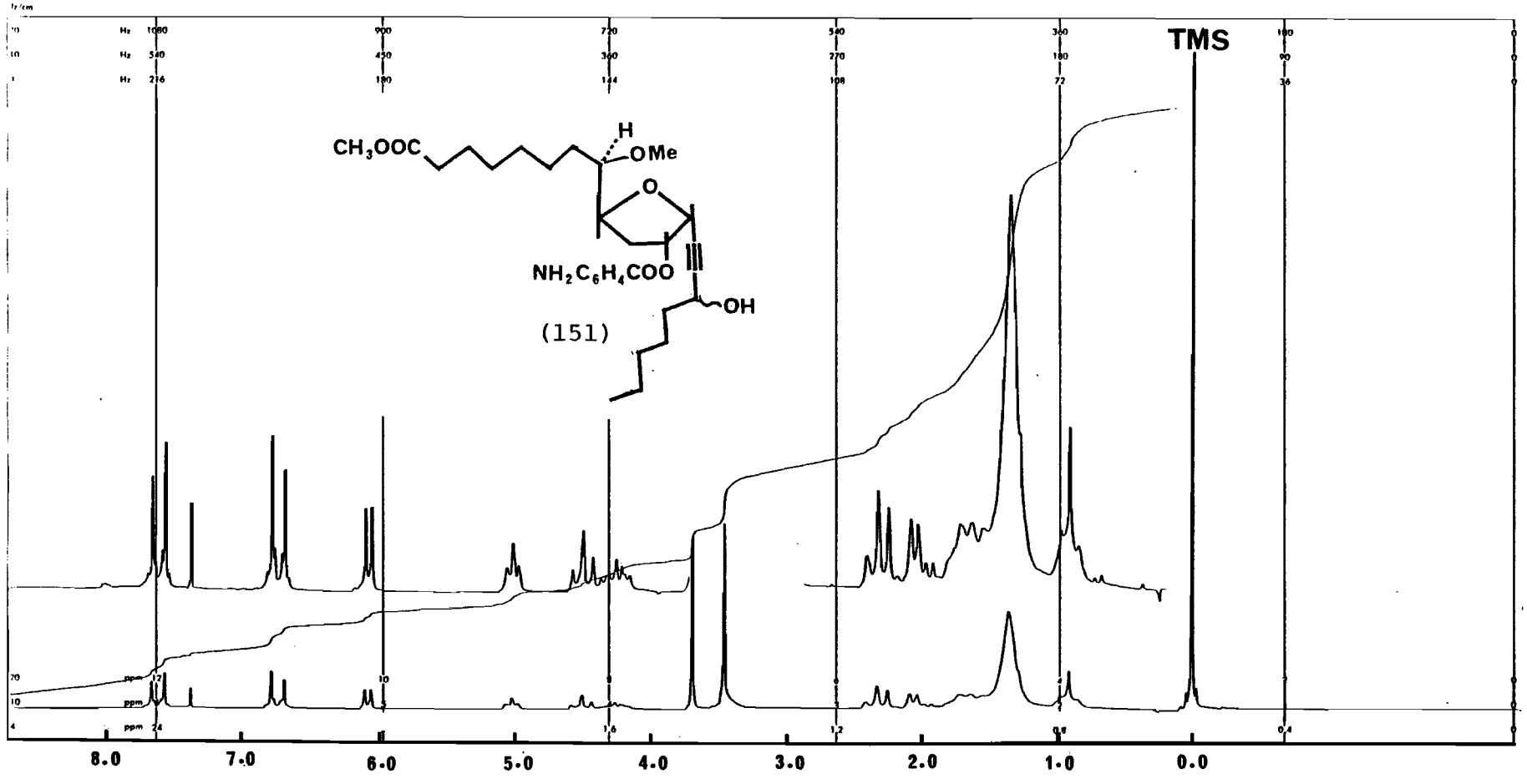
(153) R = $-COC_6H_4NO_2$ R' = $-Si(t\text{-butyl})Me_2$



R = $-COC_6H_4NO_2$

(154)

of the nitro compound 150. The only major difference was that the aromatic quartet had shifted from 8.25 ppm to 7.20 ppm. This shift is due to the increase of electron density in the aromatic ring, caused by the absence of the nitro group. The infrared spectrum had an amine absorption at 3480 cm^{-1}, a hydroxyl absorption at 3380 cm^{-1}, a carbonyl absorption at 1730 cm^{-1} and an aromatic absorption at 1610 cm^{-1}. The mass

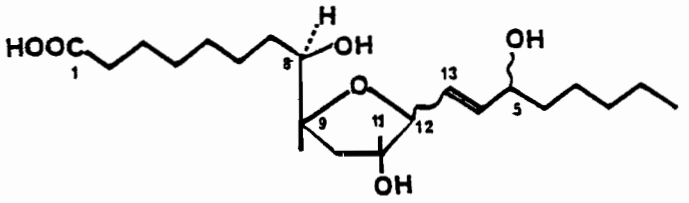


90 mHz P.m.r. spectrum of compound 151.

spectrum of compound 151 showed a molecular ion at 517 m/e and fragments at 486 m/e for the loss of (OMe)· and 120 m/e for the $(H_2N\text{-}C_6H_5CO)\cdot$ fragment.

Because the acetylenic bond had remained untouched during the reduction, the reaction was repeated using a large excess of reducing reagent and the reaction time was extended. These conditions, however, only resulted in the formation of a complex reaction mixture. When a hydrolysis of the p-nitrobenzoate ester in compound 150 was attempted using 1.1 equivalents of sodium hydroxide in aqueous methanol, only the methyl ester was hydrolyzed to produce the acid 154. Further treatment of this compound with another equivalent of sodium hydroxide, at room temperature, failed to cause further hydrolysis, and elevated temperatures (60^{o}) produced a complex reaction mixture.

Since the stereochemistry of the $\Delta^{13,14}$-double bond is not known for certain, it was decided to attempt a catalytic hydrogenation of the acetylenic bond using a nickel boride catalyst[114,115], in the hope that these conditions would not cause reduction of the nitro group.



(17)

When the alkyne 145 was treated with sodium borohydride and nickel diacetate in catalytic amounts, for the usual reaction time, no evidence of any reduction was observed. When, however, extended reaction times were used very complex reaction mixtures were obtained.

Because the reduction of the alkyne 145 to the alkene 153 presented major difficulties the synthesis was stopped at this point.

Conclusion :

This chapter dealt with the attachment of the C_{13}-C_{20} side-chain and, in this respect, we were successful. Several

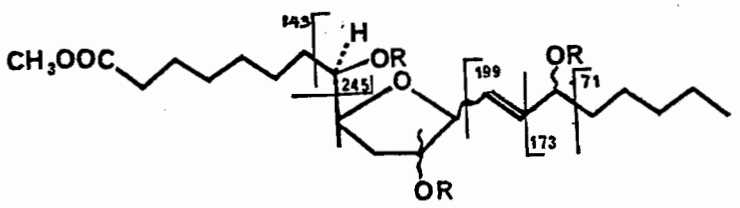
methods for the attachment of this side-chain were examined, and one, the displacement of the glycosyl bromide with an acetylenic anion, was found to produce the desired adduct. This reaction resulted in only one C-12 isomer, namely the (R) (α) isomer. Because of the difficulties encountered during the reduction of the acetylenic bond in 145 to the olefinic bond, the desired compound 17a could not be obtained. A closer study of this synthetic scheme revealed that, with certain improvements, the final product could perhaps be obtained. A study on the generation of glycosyl bromides by displacement of good leaving groups other than esters could be undertaken to avoid the reaction of the acetylenic anion with ester groups, as observed with compound 131, and thus increase the yield of the coupling reaction. An alternative, and perhaps more feasible improvement would be the successful differentiation of the C-11 and C-12 hydroxyl groups of compound 129. The hypothetical precursor to the glycosyl bromide would then have an ester group at C-12 (for displacement by bromide ion), and a group at C-11 which would be insensitive to the conditions of the bromide displacement, the acetylenic anion displacement and the reduction of the triple bond. Such a group might be the t-butyldiphenylsilyl group.

Implementation of the above improvements, according to

a modified synthetic scheme, entails the study of the differentiation of the C-11 and C-12 hydroxyl groups and/or the study of the generation of glycosyl bromides by displacement of non-ester groups, both of which are beyond the scope of this thesis.

Mass Spectral Comparisons:

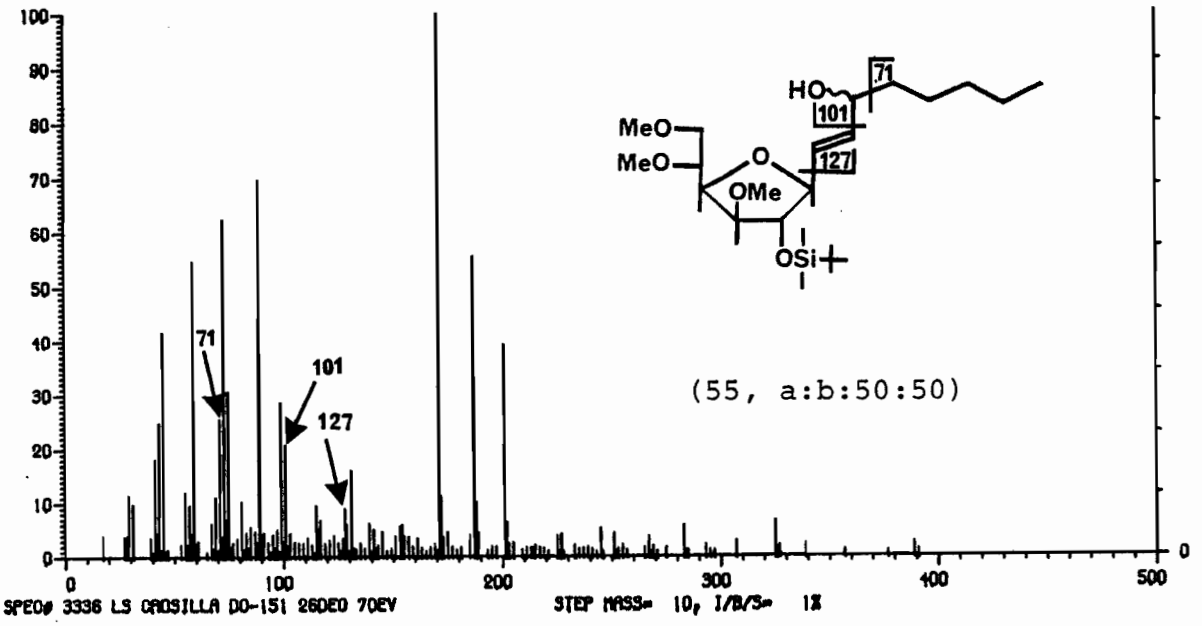
Even though the final product is, as yet, not available, enough mass spectral data have been obtained from the compounds already synthesized , to make constructive comparisons with L.S. Wolfe's spectra of the methylated and silylated natural product. Chapter I dealt with the attachment of the C_{13}-C_{20} side-chain. Comparison of the mass spectrum of compound 55 with the spectrum of L.S. Wolfe's compound 155 should give an indication of whether or not the C_{13}-C_{20} side-chain in structure 155 is correct. A mass spectrum and a mass spectral fragmentation pattern of the silylated and methylated natural product is shown below:



$R = Si(CH_3)_3$

(155)

Close examination of the mass spectrum of compound 55, which is displayed on the following page, reveals that it is not unlike that of compound 155. As expected, the fragment having a mass of 71 m/e, corresponding to C_5H_{11}, is very prominent in the fragmentation of compound 55. As well, L.S. Wolfe's compound 155 cleaved between C-14 and C-15 giving a fragment having a mass of 173 m/e. Compound 55 does not have a silyl ether at this position, but does cleave in the same manner giving a fragment with a mass of 101 m/e. A third fragment of L.S. Wolfe's compound had a mass of 199 m/e corresponding to the cleavage between C-12 and C-13. The exact cleavage is observed in compound 55 as shown below.

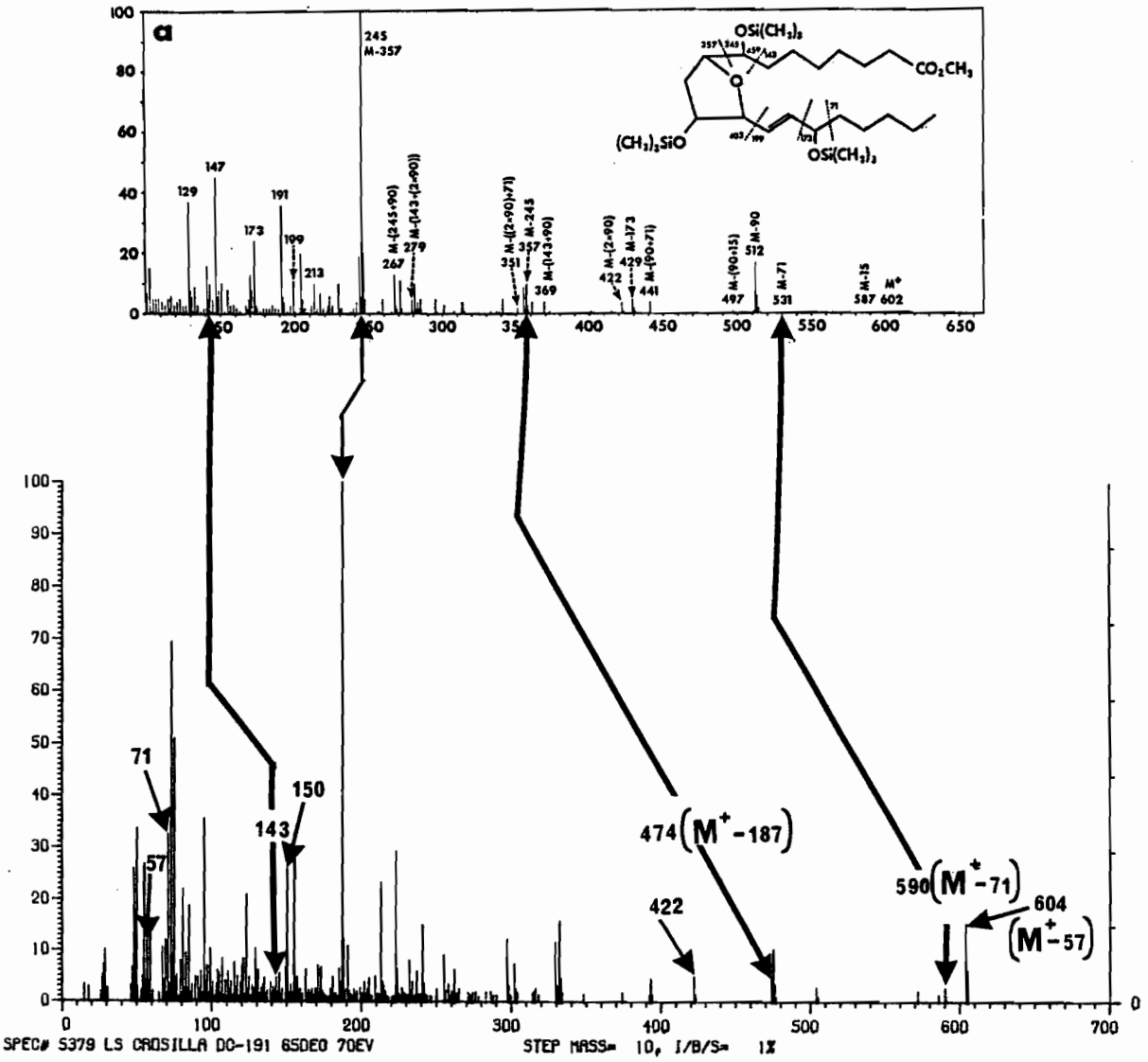


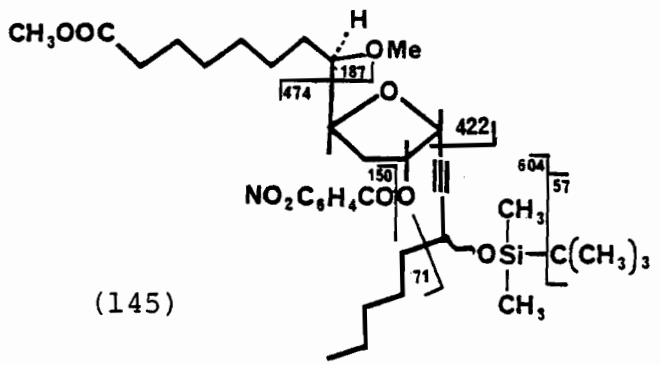
Mass spectrum of compound 55.

Other fragments also exist but will not be discussed because they have little bearing on the structural determination of the C_{13}-C_{20} side-chain. From these brief comparisons, some evidence can be found in support of the existence of the C_{13}-C_{20} side-chain as indicated by L.S. Wolfe and C. Pace-Asciak in structure 155.

Chapter V dealt with the synthesis of the natural product 17. The total synthesis was not accomplished but a very similar compound was obtained. Comparison of compounds 145a and 145b with the methylated and silylated natural product 155 reveals that the only basic difference is that there is a $\Delta^{13,14}$ acetylenic bond in compounds 145a and 145b instead of an olefinic bond. If the structure proposed by L.S. Wolfe is correct, then it should have a similar fragmentation pattern to compounds 145a and 145b. Since compounds 145a and 145b differ only in the chirality of the C-15 carbon, and since they have almost identical mass spectra, only one of them, that with R_f 0.76, will be discussed.

Examination of the mass spectrum of L.S. Wolfe's compound 155 reveals that the C_1-C_8 side-chain cleaves between C-7 and C-8 giving a fragment of mass 143 m/e having a small relative intensity. Examination of the mass spectrum of compound 145, shown on the following page, also displays the analogous fragment with a relative intensity of 4.8%. The base peak of compound 155 is the result of the fragmentation between C-8 and C-9, which corresponds exactly to the base





(145)

Comparison of mass spectra of compound 145 (R_f=0.75) and L.S. Wolfe's and C. Pace-Asciak's compound 155.

Contributions to Knowledge:

1. The C_{13}-C_{20} prostaglandin side-chain was attached to a model compound and the reduction of the 15-keto group was studied, and found to behave in a manner similar to that found in the prostaglandins.
2. The addition of a nitro-containing synthon to a model sugar was studied, and found to proceed only when the sugar was in its aldehydo-form.
3. A method for a three carbon extension at the anomeric center in sugars was examined using diethyl 3,3-di(ethylthio)-prop-1-enylphosphonate and its S-oxide. Also a brief study was carried out on the cyclization of the C-5 hydroxyl group in order to generate the glucofuranose.
4. A compound closely related to a natural product, methyl 15-hydroxy-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12(R)-oxy-eicosa-13-ynoate (150) was synthesized.
5. The mass spectral fragmentation of compound 55 and 145 was compared to the fragmentation of the silylated and methylated natural product 155, thereby providing strong additional evidence for the structure of L.S. Wolfe's and C. Pace-Asciak's arachidonic acid metabolite 17.

General Experimental

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra (m.s.) were obtained on an AEl-MS-902 mass spectrometer or on an LKB-900 mass spectrometer using a direct insertion probe. Infrared (i.r.) spectra were obtained on Unicam SP1000 and 297 spectrophotometers. Ultraviolet spectra were obtained on a Cary 17 and rotations on a Perkin-Elmer 141 Polarimeter. Proton magnetic resonance (p.m.r.) spectra were recorded on Varian T-60, T-60A and on Brucker FT 90 spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in the δ scale in parts per million. Doublets ('d'), triplets ('t') and quartets ('q') were recorded at the center of the peaks, and multiplets ('m') as their range of absorption; other abbreviations used: singlet ('s') and broad ('b'). Chemical shifts are described as they appeared even though they might represent a more complex pattern.

Analytical thin layer chromatography (t.l.c.) was performed on silica gel-coated plates (Machery Nagel Polygram G or Merck Silical Gel 60) and on a preparative scale on silica gel (Merck HF 254) coated glass plates (20 cm x 20 cm x 1 mm). Merck silica gel 60, Woelm alumina (neutral) and Camag alumina (supplied by Ventron) were used for normal chromatography. Silical Woelm 32-63 was used for flash chromatography.

Solvents were reagent grade unless otherwise specified. All evaporations were done under reduced pressure (water

aspirator) with a bath temperature of 25-40° unless otherwise specified.

Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Indiana.

EXPERIMENTAL

CHAPTER II

1,2-O-Isopropylidene-3,5,6-tri-O-pivaloyl-α-D-glucofuranose (22)

The triol 18 (2.20g, 10 mmol) was dissolved in dry pyridine (10 ml) and to this was added pivaloyl chloride (21) (4.83 g, 40 mmol), dropwise, at 0°. The resulting solution was allowed to warm up to room temperature, and then stirred overnight. The product was partitioned between water (50 ml) and ether (30 ml). The layers were separated and the organic layer was washed with water (3 x 20 ml), 5% hydrochloric acid (3 x 20 ml), 10% sodium bicarbonate solution (2 x 20 ml) and water (1 x 20 ml) again. Drying ($MgSO_4$) and evaporation afforded the crude product 22. Chromatography on silica gel using methylene chloride as the eluent afforded 3.54 g (75%) of the pure product 22, as an oil. $(\alpha)_D^{22} = -2.6^\circ$ (c=3.05, chloroform). P.m.r. ($CDCl_3$):δ 1.10 (s,9H, $COC(CH_3)_3$), 1.20 (s, 18H, 2 $COC(CH_3)_3$), 1.30 and 1.50 (s and s, 6H, $C(CH_3)_2$), 3.80 - 4.80 (m, 4H), 5.10-5.30(m, 2H), 5.80 (d, $J_{1,2}$=3 Hz, 1H, C_1H) ppm. I.r. (film): ν_{max} 1740 (carbonyl) cm^{-1}. M.s. (70 eV): m/e 457 (M^+-15), 85, 57.

1-O-Ethyl-3,5,6-tri-O-pivaloyl-D-glucofuranose (25).

The isopropylidene compound 22 (944 mg, 2 mmol) was heated at 100° for 1.5 hours in a mixture of ethanol (33 ml)

and 1.2 N aqueous sulfuric acid (17 ml). After cooling the ethanol was removed, and the mixture neutralized with 10% sodium bicarbonate solution and extracted with methylene chloride (3 x 20 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated to afford 800 mg (87%) of the oily product 25, as a mixture of anomers. $[\alpha]_D^{22} = -26.6^{\circ}$ (c=5.40, chloroform). P.m.r. ($CDCl_3$): δ 1.10 (s, 9H, $COC(CH_3)_3$), 1.20 (s, 18H, 2 $COC(CH_3)_3$), 1.25 and 1.30 (t, 3H, $OCH_2\underline{CH_3}$), 3.00-5.00 (m, 10 H) ppm. I.r. (film): ν_{max} 3350 (hydroxyl), 2960, 2860, 1750 (carbonyl) cm^{-1}. M.s. (70 eV): m/e 415 ($M^+ - CH_3OCH_2$), 57.

2-O-Acetyl-1-O-ethyl-3,5,6-tri-O-pivaloyl-D-glucofuranose (24).

The alcohols 25 (216 mg, 0.5 mmol) were dissolved in dry pyridine (10 ml). To this was added the acetic anhydride (500 mg, 5 mmol) at 0°. The resulting solution was allowed to warm up to room temperature overnight. Water (50 ml) and methylene chloride (50 ml) were added. After stirring for 2 hours the layers were separated and the organic layer was washed with water (3 x 20 ml), dried ($MgSO_4$) and evaporated to afford 180 mg (72%) of the acetate 24, as a mixture of anomers. P.m.r. ($CDCl_3$): δ 1.20 (s, 9H, $CO(CH_3)_3$), 130 (s, 18H, 2 $CO(CH_3)_3$), 1.10-1.40 (m, 3H), 2.05 and 2.10 (s and s, 3H, $COCH_3$), 3.30-5.30 (m, 9H) ppm. I.r. (film): ν_{max} 2950, 2900, 2840, 1740 (carbonyl) cm^{-1}.

1,2-O-Isopropylidene-3,5,6-tri-O-methyl-α-D-glucofuranose (26).

Into a dry 300 ml, three-necked flask, was added sodium hydride (1.73 g of a 55% oil dispersion, 40 mmol). The sodium hydride was washed three times by stirring with n-pentane (30 ml) and decanting the wash. After the third wash, the flask was fitted with a thermometer and a stoppered condenser, and the residual n-pentane was removed by successive evacuations with a vacuum pump. Then, dimethyl sulfoxide (18 ml), distilled over potassium hydroxide and stored over dried molecular sieves (3Å), was added. The resulting mixture was heated to 50° for 45 minutes.

The triol 18 (2.2 g, 10 mmol) was dissolved in dry dimethyl sulfoxide (50 ml) in a 300 ml three-necked flask. To this was added the base solution (40 mmol). A gel formed and, upon stirring for 30 minutes at 25°, a viscous solution formed. The solution was cooled to 20° and methyl iodide (2.5 ml, 40 mmol) was added slowly. Water (500 ml) was then added, and the product was extracted with ether (3 x 100 ml). The extracts were washed with water (5 x 20 ml), dried ($MgSO_4$) and evaporated to give 2.5 g (95%) of the product 26, as an oil. $[\alpha]_D^{22} = -31.6°$ (c=6.90, chloroform). P.m.r. ($CDCl_3$): δ 1.30 (s, 3H, CCH_3), 1.50 (s, 3H, CCH_3), 3.40 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.40-3.90 (m, 4H), 3.90-4.30 (m, 1H), 4.60 (d, $J_{2,1}$=4 Hz, 1H, C_2H), 5.90 (d, $J_{1,2}$=4 Hz, 1H, C_1H) ppm. I.r. (film):

ν_{max} 2970, 2920, 2880, 2800, 1370 cm^{-1}. M.s. (70 eV): m/e 263 (M^++1), 247 (M^+-15), 173 (M^+-CH(OCH_3)(CH_2OCH_3)), 89, 45.

1-0-Ethyl-3,5,6-tri-0-methyl-D-glucofuranose (27).

The isopropylidene compound 26 (524 mg, 2 mmol) was heated at 100° for 3.5 hours in a mixture of ethanol (33 ml) and 1.2 N aqueous sulfuric acid (17 ml). The mixture was then cooled and the ethanol removed under vacuum. Neutralization with 10% sodium carbonate solution, to basic pH, extraction with ethyl acetate (4 x 20 ml), drying ($MgSO_4$) and evaporation afforded 300 mg (60%) of the oily acetal 27, as a mixture of anomers. P.m.r. ($CDCl_3$):δ 1.25 and 1.30 (2t, 3H, $OCH_2C\underline{H}_3$), 3.40-4.40 (m, 9H), 3.40 (s, 3H, OCH_3), 3.45 (s, 6H, 2 OCH_3), 4.90 and 5.20 (s and d, 1H, C_1H) ppm. I.r. (film): ν_{max} 3420 (hydroxyl), 2960, 2910, 2810 cm^{-1}.

2-0-Acetyl-1-0-ethyl-3,5,6-tri-0-methyl-D-glucofuranose (28).

The alcohols 27 (190 mg, 0.76 mmol) were dissolved in dry pyridine (3 ml) and to this was added the acetic anhydride (510 mg, 5 mmol) at 0°. The resulting solution was stirred overnight at room temperature. Water (20 ml) and methylene chloride (20 ml) were then added, and stirred for an additional hour. The layers were then separated and the organic layer washed with water (5 x 20 ml), dried ($MgSO_4$), and concentrated to afford 210 mg (94%) of the oily acetate 28, as a mixture of

anomers. $[\alpha]_D^{22} = -2.2^\circ$ (c=7.54, chloroform). P.m.r. ($CDCl_3$): δ 1.20 and 1.25 (2t, 3H, $OCH_2\underline{CH_3}$), 2.05 and 2.10 (2s, 3H, $OCOCH_3$), 3.45 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.40-4.00 (m, 5H), 4.10-4.40 (m, 1H, C_2H), 5.10 and 5.20 (d and s, 1H, C_1H) ppm. I.r. (film): ν_{max} 2990, 2940, 2840, 1750 (carbonyl) cm^{-1}. M.s. (70 eV): m/e 261 (M^+-OCH_3), 247 ($M^+-CH_3OCH_2$), 203 ($M^+-CH(OCH_3)(CH_2OCH_3)$), 89, 59, 43.

2-O-Acetyl-3,5,6-tri-O-methyl-D-glucofuranose (29).

The isopropylidene compound 26 (1.46 g, 5.6 mmol) was heated in 80% aqueous acetic acid (20 ml) at 90° for 10 hours. Water was then added (50 ml) and the product extracted with ethyl acetate (3 x 50 ml). The ethyl acetate extracts were washed with 10% sodium bicarbonate solution (5 x 50 ml), dried ($MgSO_4$) and concentrated to afford the crude product. Purification by column chromatography (silica gel), using methylene chloride-ether (1:1) as the eluent, afforded 1.0 g (67%) of pure oily acetate 29 as a mixture of α- and β-anomers. $[\alpha]_D^{22} = -21.1^\circ$ (c=3.92, chloroform). P.m.r. ($CDCl_3$):δ 2.10 and 2.20 (2s, 3H, $OCOCH_3$), 3.45 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.10-4.50 (m, 6H), 4.10-4.40 (m, 1H), 5.10 and 5.50 (d and s, 1H)ppm. I.r. (film):ν_{max}3400 (hydroxyl), 2920, 2800, 1740 (carbonyl) cm^{-1}. M.s. (70 eV: m/e 247 (M^+-17), 219 ($M^+-CH_3OCH_2$), 205 ($M^+-OCOCH_3$), 43.

1-O-Acetyl-2-O-(1'-methyl-1'-acetoxy) ethyl-3,5,6-tri-O-methyl-α-D-glucofuranose (30)

The isopropylidene compound 26 (1.05 g, 4 mmol) was dissolved in acetic anhydride (15 ml), acetic acid (5 ml) and catalytic amounts of p-toluenesulfonic acid. Water (50 ml) and methylene chloride (50 ml) were then added and the mixture stirred for 1 hour at 25°. The layers were separated and the organic layer was washed with 10% sodium bicarbonate solution (3 x 20 ml), dried ($MgSO_4$) and concentrated to afford the crude product 30. Purification on a silica gel column, using ether as the eluent, afforded 900 mg (67%) of the pure product 30, m.p. 78-79°. $(\alpha)_D^{22}$= +33.6° (c=11.09, chloroform). P.m.r. ($CDCl_3$):δ 1.50 (s, 6H, $c(CH_3)_2$), 2.20 (s, 6H,2 $OCOCH_3$), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3),3.60 (s, 3H, OCH_3), 3.40-4.00 (m, 4H), 4.40 (q, 1H, C_3H), 5.10 (q, 1H, C_2H), 6.30 (d, 1H, $J_{1,2}$=3 Hz, C_1H) ppm. I.r. (KBr):ν_{max} 2960, 2860, 2820, 2800, 1760 (carbonyl) cm^{-1} M.s. (70 eV): m/e 349 (M^+-15), 59, 43.

3,5,6-Tri-O-methyl-D-glucofuranose (31).

The isopropylidene compound 26 (262 mg, 1 mmol) was heated at 70° for 1.5 hours in 10 ml of 0.5 N hydrochloric acid. The resulting solution was cooled, neutralized with sodium carbonate to pH 7.0 and the solvent removed. The water was totally removed by azeotroping with toluene.

The product was dissolved in hot ethyl acetate, filtered, and the solution was dried ($MgSO_4$). Removal of the ethyl acetate afforded 210 mg (95%) of the oily product 31, as a mixture of anomers. $[\alpha]_D^{22} = -34.5^\circ$ (c=4.53, chloroform). P.m.r. ($CDCl_3$): δ 3.40 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.40-4.40 (m, 8H), 5.10 and 5.40 (s and d, 1H, C_1H) ppm. I.r. (film): ν_{max} 3400 (hydroxyl), 2960, 2910, 2800 cm^{-1}. M.s. (70 eV):

Probe temperature: 37°: m/e 177 ($M^+ - CH_3OCH_2$), 89, 45.
65°: m/e 204 ($M^+ - 18$), 89.

1,2-Di-O-acetyl-3,5,6-tri-O-methyl-D-glucofuranose (32).

The hemi-acetal 31 (160 mg, 0.72 mmol) was dissolved in dry pyridine (3 ml). To this was added acetic anhydride (0.5 ml, 5.3 mmol), and the resulting solution was stirred overnight. Water (5 ml) was then added and the mixture was stirred for an additional 30 minutes. The product 32 was partitioned between water (20 ml) and ethyl acetate (20 ml). The aqueous extracts were re-extracted with ethyl acetate (3 x 5 ml), and the combined organic extracts were washed with 5% copper sulfate solution (5 x 10 ml), and water (1 x 10 ml), dried ($MgSO_4$) and concentrated to afford 128 mg (58 %) of the pure product 32, as a mixture of anomers. $[\alpha]_D^{22} = +11.6^\circ$ (c=8.34, chloroform). P.m.r. ($CDCl_3$): δ 1.95 and 2.00 (2s, 6H, 2 $OCOCH_3$), 3.20 (s, 3H, OCH_3), 3.30 (s, 6H, 2 OCH_3),

3.10-3.80 (m, 4H), 3.90-4.20 (m, 1H), 4.90 and 4.95 (s and q, 1H), 5.75 and 6.00 (s and d, 1H) ppm. I.r. (film): ν_{max} 2940, 2820, 1760 (carbonyl) cm^{-1}. M.s. (70 eV): m/e 261 ($M^{+}-CH_2OCH_3$), 89, 59, 45, 43.

1,2-Di-O-p-nitrobenzoyl-3,5,6-tri-O-methyl-D-glucofuranose (37).

The hemi-acetal 31 (444 mg, 2 mmol) was dissolved in dry pyridine (5 ml). This solution was added to p-nitrobenzoyl chloride (1.2 g, 6.5 mmol) in dry pyridine (25 ml) at 0° under a nitrogen atmosphere. The mixture was stirred for 1 hour at 0° and set aside in the refrigerator (-10°) for 2 days. After this time, the mixture was allowed to stand at room temperature for 1 hour. It was then added to a rapidly stirred ice-water mixture (250 ml) and the stirring was continued until all the ice had melted. The product 37, a mixture of α- and β-anomers (728 mg, 70%), was filtered, washed with ether and recrystallized from acetone-water. M.p.: 143-146°. $(\alpha)_D^{22} = -20.7°$ (c=4.51, chloroform). P.m.r. ($CDCl_3$): δ 3.55 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.40-4.10 (m, 3H), 4.10-4.30 (m, 1H), 4.40-4.70 (m, 1H), 5.70-5.90 (m, 1H, C_2H), 6.70 and 6.90 (s and d, 1H, $J_{1,2}$=4 Hz, C_1H), 8.10-8.50 (m, 8H, aromatic protons) ppm. I.r. (KBr): ν_{max} 2980, 2920, 2820, 1740 (carbonyl), 1620 (aromatic), 1540 (nitro) cm^{-1}. M.s. (70 eV): m/e 475 ($M-CH_2OCH_3$), 150, 89. Anal. Calcd. for $C_{23}H_{24}N_2O_{12}$: C, 53.07; H, 4.61; N, 5.30. Found: C, 53.12; H, 4.71; N, 5.15.

2-O-p-Nitrobenzoyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl Cyanide (38) and 2-O-p-nitrobenzoyl-3,5,6-tri-O-methyl-D-glucofuranosyl Bromide (37a).

A solution of the di-p-nitrobenzoate 37 (520 mg, 1 mmol) in dry benzene (4 ml) under a nitrogen atmosphere was saturated at 0° with gaseous hydrogen bromide in the course of 30 minutes. The p-nitrobenzoic acid was filtered off and washed with more benzene. The benzene was then removed under vacuum (40°) and the residue co-evaporated with more benzene (4 ml). The syrupy material was dissolved in nitromethane (3 ml, dried by distillation over phosphorous pentoxide), and treated with mercuric cyanide (500 mg), pre-dried at 140°/15 mm Hg for 3 hours. The whole reaction mixture was stirred at room temperature for 20 hours under a nitrogen atmosphere. The insoluble portion was filtered off and washed with benzene. The filtrates were combined and evaporated under diminished pressure. The oil was then dissolved in ethyl acetate (5 ml) and washed with 5% potassium iodide solution (2 x 2 ml), water (2 x 2 ml) and dried ($MgSO_4$). Concentration under reduced pressure afforded the crude product 38, as an oil. Purification on an alumina column with a methylene chloride-chloroform (2:1) mixture afforded 204 mg (54%) of the pure product 38, m.p.: 111-113°. $(\alpha)_D^{22} = -46.0°$ (c=0.28, chloroform). P.m.r. ($CDCl_3$): δ 3.50 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.40-4.00 (m, 3H), 4.00-4.50 (m, 2H), 4.90

(s, 1H, C_1H), 5.70 (s, 1H, C_2H), 8.20-8.40 (m, 4H, aromatic protons) ppm. I.r. (KBr):ν_{max} 3000, 2940, 2910, 2830, 1730 (carbonyl), 1610 (aromatic), 1530 (nitro) cm^{-1}. M.s. (70 eV): m/e 336 ($(M^+ +1)-45$), 335 ($M^+ - CH_2OCH_3$), 150, 89, 45. Anal. Calcd. for $C_{17}H_{20}O_8N_2$: C, 53.68; H, 5.26; N, 7.36. Found: C, 52.97; H, 5.15; N, 7.03.

3,5,6-Tri-O-methyl-β-D-glucofuranosyl Cyanide (39).

To the p-nitrobenzoate 38 (190 mg, 0.5 mmol) in tetrahydrofuran (3 ml) was added 0.097 N sodium hydroxide solution (5.7 ml, 0.55 mmol). The resulting solution was stirred overnight at room temperature. The tetrahydrofuran was evaporated and the product extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with water (1 x 10 ml), 10% sodium bicarbonate solution (1 x 10 ml) and with water (1 x 10 ml) again, dried ($MgSO_4$) and concentrated to afford the crude product 39. Purification on a silica gel column using chloroform-ether (5:1) as the eluent afforded 102 mg (62%) of the pure product 39, as an oil. $[\alpha]_D^{22} = -60.1^\circ$ (c=10.44, chloroform). P.m.r. ($CDCl_3$):δ 3.35 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.30-3.80 (m, 5H), 4.10-4.30 (m, 1H), 4.40-4.60 (m, 2H) ppm. I.r. (film):ν_{max} 3400 (hydroxyl), 2990, 2940, 2840 cm^{-1}. M.s. (70 eV): m/e 232, 89. Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.95; H, 7.36; N, 6.06. Found: C, 51.92; H, 7.39; N, 5.81

2-O-t-Butyldimethylsilyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl Cyanide (40).

The alcohol 39 (231 mg, 1 mmol) was dissolved in dry dimethylformamide (1 ml) under a nitrogen atmosphere. To this was added t-butyldimethylsilyl chloride (181 mg, 1.2 mmol) and imidazole (170 mg, 2.5 mmol). The resulting solution was stirred overnight at room temperature. Water (15 ml) was then added and the product extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to give the crude product 40. Purification on a silica gel column using a hexane-methanol (19:1) mixture as the eluent afforded 310 mg (90%) of the pure ether 40, as an oil. $(\alpha)_D^{22} = -45.3^o$ (c=3.76, chloroform). P.m.r. ($CDCl_3$):δ 0.20 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 3.30 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.30-4.00 (m, 5H), 4.30 (d, 1H), 4.55 (s, 1H) ppm. I.r. (film):ν_{max} 2940, 2900, 2860, 2830, 1120 cm^{-1}. M.s. (70 eV): m/e 300 ($M^+-CH_2OCH_3$), 288 ($M^+-C(CH_3)_3$), 256 ($M^+-CH(CH_2OCH_3)(OCH_3)$), 89, 45.

1,3-Diphenyl-2-(3,5,6-tri-O-methyl-β-D-glucofuranosyl) imidazolidene (44).

Cyanide 39 (231 mg, 1 mmol) was added to a vigorously stirred suspension of Raney nickel (1.8 g, 3.0 ml) in a solution of sodium hypophosphite (NaH_2PO_2) (943 mg) and

N,N-diphenylethylenediamine (43) (399 mg, 1.88 mmol) in a mixture of pyridine, acetic acid, and water (2:1:1, 14 ml). The mixture was stirred at room temperature for 1.25 hours and then filtered. The residue was washed thoroughly with chloroform (3 x 10 ml) and the combined filtrates were diluted with more chloroform and washed with water (3 x 20 ml), dried ($MgSO_4$) and concentrated to afford the crude product 44. Purification on a silica gel column using ether-hexane (5:1) as the eluent afforded 300 mg (70%) of the pure product 44, as an oil. $[\alpha]_d^{22} = -29.7^o$ (c=4.00, chloroform). P.m.r. (CCl_4): δ 3.10 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.00-4.00 (m, 11H), 4.10-4.20 (m, 1H), 5.50 (d, 1H), 6.40-7.30 (m, 10 H, aromatic protons) ppm. I.r. (film): ν_{max} 3600, 3440 (hydroxyl), 2900, 2840, 1600 (aromatic), 1500 cm^{-1}. M.s. (70 eV): m/e 101, 89, 45.

1,3-Diphenyl-2-(2-0-(t-butyldimethyl)silyl-3,5,6-tri-0-methyl-β-D-glucofuranosyl)imidazolidene (45) from Cyanide 40.

Cyanide 40 (345 mg, 1 mmol) was added to a vigorously stirred suspension of Raney nickel (1.4 g) in a solution of sodium hypophosphite (NaH_2PO_2) (943 mg) and N,N-diphenyl-ethylenediamine (43) (399 mg, 1.88 mmol) in a (2:1:1) mixture of pyridine, acetic acid and water (14 ml). The mixture was stirred at room temperature for 1.25 hours and then filtered. The residue was washed thoroughly with chloroform (3 x 10 ml) and the combined filtrates were then diluted

with more chloroform and then washed with water (3 x 20 ml). The chloroform solution was dried ($MgSO_4$) and concentrated to give the crude product 45. Preparative layer chromatography using ether-hexane (1:1) as the solvent afforded 271 mg (50%) of the pure product 45, m.p. 113-114°. $[\alpha]_D^{22} = -11.4°$ (c=5.33, chloroform). P.m.r. (CCl_4):δ 0.15 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_2$), 3.30 (s, 4H), 3.60 (s, 9H), 3.20-3.80 (m, 5H), 3.90 (bd, 1H), 4.30 (s, 1H), 5.50 (d, 1H), 6.50-7.40 (m, 10 H, aromatic protons) ppm. I.r. (KBr):ν_{max} 2960, 2940, 2890, 2880, 1600 (aromatic), 1500, 1470, 1380 cm^{-1}. M.s. (15 eV): m/e 542 (M^+), 223. Anal. Calcd. for $C_{30}H_{46}N_2O_5Si$: C, 66.42; H, 8.49; N, 5.16. Found: C, 66.22; H, 8.49; N, 5.18.

1,3-Diphenyl-2-(2-0-(t-butyldimethyl)silyl-3,5,6,-tri-0-methyl-β-D-glucofuranosyl)imidazolidene (45) from Alcohol 44.

To alcohol 44 (250 mg, 0.58 mmol) dissolved in dry dimethylformamide (1 ml) was added t-butyldimethylsilyl chloride (106 mg, 0.70 mmol) and imidazole (99 mg, 1.45 mmol). The resulting solution was stirred overnight at room temperature. Water (15 ml) was then added and the product extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to afford the product 45. Crystallization from methanol afforded 250 mg (80%) of pure silyl ether 45,

m.p.: 113-114°. Its spectral data were identical to that of compound 45 synthesized from compound 40.

2,5-Anhydro-3-O-(t-butyldimethyl)silyl-4,6,7-tri-O-methyl-D-glycero-D-gulo-heptose (46)

The protected aldehyde 45 (542 mg, 1 mmol) was stirred at 50° in a (2:1) mixture of tetrahydrofuran and water (30 ml) containing 50W-X8(H^+) resin (3.2 g) for 1 hour. The resin was then filtered, and the tetrahydrofuran removed under vacuum. The product was extracted with ether (3 x 10 ml), dried ($MgSO_4$) and concentrated to afford 300 mg (86%) of pure aldehyde 46, as an oil. $[\alpha]_D^{22} = +12.2°$ (c=8.80, chloroform). P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 3.20 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.20-3.70 (m, 4H), 3.70-4.00 (m, 2H), 4.25 (S, 1H), 9.10 (s, 1H, CHO) ppm. I.r. (film): ν_{max} 2960, 2930, 2890, 2860, 2810, 1760 (carbonyl), 1460 cm^{-1}.

E-1-(2-(t-Butyldimethyl) silyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl)-3-keto-1-octene (54).

Sodium hydride (58% oil dispersion, 32 mg, 0.078 mmol) was placed in dry 1,2-dimethoxyethane (4 ml, distilled from calcium hydride). The slurry was then cooled to 20° and dimethyl 2-oxoheptylphosphonate (53) (190 mg, 0.178 ml, 0.86 mmol) was added dropwise, with stirring, under a nitrogen atmosphere. After the addition, the solution was stirred at

room temperature for 1 hour. To this solution, the aldehyde 46 (300 mg, 0.86 mmol) in 1,2-dimethoxyethane (2 ml) was added dropwise, and the mixture was stirred at room temperature for 1.5 hours. After cooling, water (10 ml) was added, the product was extracted with ether (3 x 10 ml), the solution was dried ($MgSO_4$) and removal of the solvent afforded the crude product 54. Purification on a silica gel column, using an ether-hexane (1:1) mixture as the eluent, afforded 300 mg (78%) of pure product 54, as an oil. $(\alpha)_D^{22} = -52.1^o$ (c= 5.07, chloroform). P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 1.00-1.90 (m, 9H), 2.40 (bt, 2H), 3.20 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.30-4.20 (m, 7H), 5.95 (B portion of an ABX system, 1H, $J_{1,2}$=14 Hz, $J_{1,3}$=1 Hz, $OC_3HC_2H{=}C_1\underline{H}CO$), 6.50 (A portion of an ABX system, 1H, $J_{2,1}$=14 Hz, $J_{2,3}$=6 Hz, $C_3HC_2\underline{H}{=}C_1HCO$) ppm. I.r. (film): ν_{max} 2960, 2930, 2860, 2830, 1700, 1680 (carbonyl), 1630 (olefin) cm^{-1}. M.s. (15 eV): m/e 444 (M^+), 387 (M^+-57), 355 (M^+-89), 89.

E-1-(2-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl)-3-hydroxy-1-octene (55, a:b=50:50)

The ketone 54 (150 mg, 0.34 mmol) was dissolved in absolute ethanol (3 ml) and the solution cooled to 0^o. To this was added sodium borohydride (13 mg, 0.34 mmol), and the mixture stirred for 1 hour at 0^o. Buffer (pH 4.4, 3 ml) was added and the solution allowed to warm up to room

temperature for 30 minutes. The ethanol was then removed and the product extracted with ether (3 x 5 ml). The solution was dried ($MgSO_4$) and concentrated to afford 130 mg (85%) of pure oily product 55, (a:b=50:50)as a 1:1 mixture of diasteromers. P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 12H, $C(CH_3)_3$, CH_2CH_3), 1.00-1.60 (m, 8H), 2.40 (bs, 1H), 3.20 (s, 3H, OCH_3),3.30 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.30-3.70 (m, 6H), 3.75-4.00 (m, 2H), 5.40 (m, 2H, CH=CH) ppm. I.r. (film):ν_{max} 3460 (hydroxyl), 2960, 2930, 2860, 2820, 1460 cm^{-1}. M.s. (70 eV): m/e 428 (M^+-18), 389 (M^+-$C(CH_3)_3$), 89, 57, 45. Anal, Calcd. for $C_{23}H_{46}O_6Si$: C, 61.88; H, 10.31. Found: C,62.03; H, 10.32

E-1-(2-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl)-3-hydroxy-1-octene(55,a:b=85:15)

A tetrahydrofuran solution of L-Selectride (57) (0.45 ml of a 1 M solution) was added over a 1 minute period to a stirred solution of the ketone 54 (200 mg, 0.45 mmol) in tetrahydrofuran (1 ml) at -78°, under a nitrogen atmosphere. After 1 hour the acetone-dry ice bath was replaced with an ice-water bath and 3 ml of a 7:5 mixture of 10% sodium hydroxide and 30% hydrogen peroxide was added, and the resulting solution was stirred overnight at room temperature. The aqueous layer was separated and extracted with hexane (3 x 10 ml). The combined organic layers were washed with water (2 x 2 ml), 10% sodium bisulfite solution (2 x 2 ml)

and with saturated salt solution (1 x 2 ml). The organic solution was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 100 mg (50%) of pure oily alcohol 55, as an approximately 85:15 mixture of diastereomers, as established by thin layer chromatrography. P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (bs, 12H), 1.40 (m, 8H), 2.00 (bs, 1H), 3.30 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.40-4.20 (m, 8H), 5.55 (m, 2H, CH=CH) ppm. I.r. (film): ν_{max} 3450 (hydroxyl), 2960, 2930, 2860, 1460 cm^{-1}.

E-1-(2-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl)-3-acetoxy-1-octene (58).

The diastereomeric alcohols 55 (a:b=50:50)(44 mg, 0.1 mmol) were stirred overnight in acetic anhydride (0.25 ml) and pyridine (0.5 ml) at room temperature. The resulting solution was co-distilled with toluene (10 ml) until the acetic anhydride, acetic acid and pyridine were no longer present, affording 40 mg (82%) of pure acetate 58, as an oil. $[\alpha]_D^{22} = -31.3^{\circ}$ (c=0.97, chloroform). P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 12H), 1.10-1.70 (m, 8H), 1.95 and 1.97 (s and s, 3H, $OCOCH_3$), 3.30-4.00 (m, 17H), 5.40-5.60 (m, 2H, CH=CH) ppm. I.r. (film): ν_{max} 2960, 2930, 2860, 2830, 1740 (carbonyl) cm^{-1}. M.s. (70 eV): m/e 488 (M^+), 431 (M^+-57), 399 (M^+-89), 365 (M^+-123), 89, 59, 45, 43.

E-1-(2-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-β-D-glucofuranosyl)-3-p-nitrobenzoyloxy-1-octene (59).

The diastereomeric alcohols 55 (a:b=50:50) were dissolved in dry pyridine (1 ml). This was added to a solution of p-nitrobenzoyl chloride (31 mg, 0.16 mmol) in pyridine (1 ml), at 0°, and the mixture was set aside in the refrigerator (-10°) for 48 hours. It was then allowed to warm up to room temperature for 1 hour, poured on an ice-water (20 ml) mixture and extracted with ether (3 x 10 ml). The combined extracts were washed with water (5 x 5 ml) and dried ($MgSO_4$). Concentration under reduced pressure afforded 40 mg (42%) of the oily product 59, as a mixture of diastereomers. $[\alpha]_D^{22} = -7.7^{\circ}$ (c=0.95, chloroform). P.m.r. (CCl_4):δ 0.10 and 0.15 (s and s, 6H, $Si(CH_3)_2$), 0.85 and 0.90 (s and s, 9H, $C(CH_3)_3$), 0.80-2.00 (m, 11H), 3.30 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.20-4.20 (m, 8H), 5.60-5.80 (m, 2H, CH=CH), 8.20 (s, 4H, aromatic protons) ppm. I.r. (film): ν_{max} 2960, 2930, 2860, 2820, 1730 (carbonyl), 1600 (olefin), 1530 (nitro), 1460 cm^{-1}. M.s. (70 eV): m/e 595 (M^+), 538 ($M^+-C(CH_3)_3$), 506 ($M^+-CH(OCH_3)OCH_2(CH_3)$, 150, 89, 45.

EXPERIMENTAL

CHAPTER III

1-Deoxy-1-nitro-4,6,7-tri-O-methyl-D-glycero-(D-ido and D-gulo)-heptitols (64).

The diol 30 (444 mg, 2 mmol) was dissolved in a mixture of methanol (2 ml) and nitromethane (1 ml) under a nitrogen atmosphere. To this was added a solution of sodium metal (70 mg) in dry methanol (1 ml). The resulting mixture was stirred overnight. The solvent was then removed under reduced pressure and the solid mass dissolved in water (5 ml). The aqueous solution was passed through a column of IR-120 (H^+ form) Amberlite resin (5 ml of suspension in water). The eluate was concentrated under reduced pressured and dried by azeotropic distillation with benzene (2 x 20 ml) to afford 510 mg (90%) of crude adduct 64, homogeneous by thin layer chromatography, as an oil. P.m.r. ($CDCl_3$): δ 3.10 (s, 3H, OCH_3), 3.20 (s, 6H, 2 OCH_3), 3.00-3.70 (m, 7H), 3.75-3.90 (m, 1H), 4.00-4.40 (m, 4H) ppm. I.r. (film): ν_{max} 3350 (hydroxyl), 2980, 2920, 2810, 1560 (nitro) cm^{-1}.

3,5-Di-O-acetyl-1,2-dideoxy-1-nitro-4,6,7-tri-O-methyl-D-gluco-hept-1-enitol (66) and 1-Deoxy-1-nitro-2,3,5-tri-O-acetyl-4,6,7-tri-O-methyl-D-glucero-(D-ido and D-gulo)-heptitols (65).

A solution of the diol 64 (283 mg, 1 mmol) in acetic

anhydride (6 ml), containing catalytic amounts of p-toluene-sulfonic acid (50 mg), was stirred overnight at room temperature. The reaction mixture was then slowly poured on an aqueous solution of sodium bicarbonate and stirred for 30 minutes. The product was extracted with chloroform (3 x 10 ml). The extracts were washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to afford the crude product (mixture of triacetate 65 and nitro-olefin 66). This mixture was then dissolved in dry benzene (6 ml) and powdered anhydrous potassium carbonate (142 mg) was added. The suspension was stirred for 6 hours at room temperature, and filtered through a celite pad. The filtrate was concentrated to afford the crude product 66, as an oil. Purification through a silica gel column, using ether as the eluent afforded 315 mg (90%) of pure nitro-olefin 66, as an oil. $[\alpha]_D^{22} = -4.4^o$ (c=3.20, chloroform). P.m.r. (90 mHz, $CDCl_3$): δ 2.00 (s, 3H, $OCOCH_3$), 2.20 (s, 3H, $OCOCH_3$), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.30-3.80 (m, 3H), 3.90 (dd, 1H, $J_{4,5}$=3 Hz, $J_{4,3}$=6 Hz, C_4H), 5.20 (dd, 1H, $J_{5,4}$=3 Hz, $J_{5,6}$=7 Hz, C_5H), 5.80 (m, 1H, $J_{3,4}$=6 Hz, $J_{3,2}$=4 Hz, $J_{3,1}$=2 Hz, C_3H), 7.02 (B portion of an ABX system, 1H, $J_{1,2}$=14 Hz, $J_{1,3}$=2 Hz, C_1H), 7.42 (A portion of an ABX system, 1H, $J_{2,1}$=14 Hz, $J_{2,3}$=4 Hz, C_2H) ppm. I.r. (film): ν_{max} 2970, 2920, 2820, 1760 (carbonyl), 1660 (olefin), 1530 (nitro) cm^{-1}. M.s. (70 eV): m/e 305 (M^+), 290 (M^+-$OCOCH_3$), 89, 45, 43. U.v.: $\lambda_{max}^{ethanol}$ 220 (ε 5560), 290 (ε 1500) nm ($CH=CH-NO_2$).

2,2-Dimethoxy-4-nitrobutane (71).

The ketone 73 (480 mg, 4.1 mmol) was stirred overnight at room temperature with trimethylorthoformate (477 mg, 4.5 mmol, 0.492 ml) and methanol (0.2 ml), containing catalytic amounts of p-toluenesulfonic acid. Water (30 ml) and saturated sodium bicarbonate solution (1 ml) were then added and the resulting solution extracted with ether (3 x 10 ml). The extracts were dried ($MgSO_4$) and evaporated to afford the crude product 71. Distillation (b.p. 60-65°, 1 mm) of the crude product afforded 600 mg (90%) of pure nitro ketal 71. P.m.r. (CCl_4):δ 1.20 (s, 3H, CH_3), 2.30 (bt, 2H, $CH_2C(OCH_3)_2$), 3.10 (s, 6H, 2 OCH_3), 4.30 (t, 2H, CH_2NO_2) ppm. I.r. (film): ν_{max} 2990. 2940, 2830, 1550 (nitro), 1440, 1380, 1350 cm^{-1}.

4-Chlorobutan-2-one (72).

To dry methylene chloride (60 ml) was added aluminum trichloride (16.0 g, 0.12 mol), at 0°, under a nitrogen atmosphere. Acetyl chloride (7.85 g, 7.13 ml, 0.1 mol) was added to this, dropwise, under a nitrogen atmosphere. Ethylene was then bubbled in at a rapid flow rate. Bubbling was continued for 30 minutes after the rapid uptake ceased. The ice bath was then removed and the mixture stirred for 1 hour at room temperature, poured on an ice-water mixture, and stirred for an additional hour. Extraction with methylene chloride (3 x 20 ml), drying of the extracts with $MgSO_4$,

and removal of the solvent under reduced pressure afforded the crude product 72. The product was purified by distillation, to give 7.62 g (72%) of pure chloro compound 72, b.p. 105-110°. P.m.r. (CCl_4):δ 2.10 (s, 3H, CH_3), 2.80 (t, 2H, CH_2CO), 3.60 (t, 2H, CH_2Cl) ppm. I.r. (film): ν_{max} 2970, 1720 (carbonyl) cm^{-1}.

4-Nitrobutan-2-one (73)

The chloro compound 72 (1.98 g, 0.0186 mol), potassium iodide (150 mg) and sodium nitrite (1.28 g, 0.0186 mol) were stirred overnight in dry dimethylsulfoxide (15 ml) at room temperature. Water (150 ml) was then added and the product extracted with ether (3 x 10 ml). The combined extracts were washed with water (3 x 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude product 73. The product was purified by distillation, to give 1.1 g (50%) of nitro ketone 73. b.p. 90-93°, 2 mm. P.m.r. ($CDCl_3$):δ 2.30 (s, 3H, CH_3), 3.20 (t, 2H, CH_2CO), 4.60 (t, 2H, CH_2NO_2) ppm. I.r. (film): ν_{max} 3000, 2960, 2920 1720 (carbonyl), 1550 (nitro) cm^{-1}.

3,5,6-Tri-O-methyl-D-glucose 1,1-Diethylmercaptal (75) Using Hydrochloric Acid as the Catalyst.

The alcohol 31 (1.11 g, 5 mmol) were dissolved in concentrated hydrochloric acid (1 ml). To this was added

ethanethiol (633 mg, 10.2 mmol, 0.88 ml). The resulting solution was stirred for 30 minutes and then extracted with ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated with the necessary traps to afford the crude product 75. This was purified by passing it through a flash silica gel column, using ethyl acetate-petroleum ether (2:1) as the eluent. Concentration of the appropriate fractions afforded 980 mg (60%) of pure product 75, as an oil. $(\alpha)_D^{22} = +2.70^\circ$ (c=5.08, chloroform). P.m.r. ($CDCl_3$): δ 1.30 (t, 6H, $CH_2\underline{CH}_3$), 2.50-3.00 (m, 4H, $\underline{CH}_2CH_3$), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.20-4.20 (m, 9H) ppm. I.r. (film): ν_{max} 3450 (hydroxyl), 2970, 2730, 2830, 1450, 1370 cm^{-1}. M.s. (15 eV): m/e 328 (M^+), 296 (M^+-32), 193 (M^+-$(CH_3CH_2S)_2CH$), 135, 119, 89, 45, 31.

3,5,6-Tri-O-methyl-D-glucose 1,1-Diethylmercaptal (75) Using Zinc Chloride as the Catalyst.

The alcohol 31 (22 mg, 1 mmol) were added to ethanethiol (620 mg, 10 mmol, 0.74 ml). The mixture was cooled in an ice bath and anhydrous zinc chloride (250 mg) was added. The flask was stoppered and allowed to stand overnight in the freezer (-4°). The ethanethiol was blown away with nitrogen and warming and the residue dissolved in ethyl acetate (5 ml). Sodium bicarbonate solution (5 ml) was added and the mixture filtered through a celite pad. The precipitate was washed with more ethyl acetate (5 ml) and the combined filtrate and

washings were separated from the aqueous layer. The aqueous layer was re-extracted with ethyl acetate (3 x 5 ml). The combined extracts were dried ($MgSO_4$) and concentrated to afford 260 mg (79%) of pure product 75, as an oil. The spectral data of this product were identical to that of product 75 obtained from 31 using hydrochloric acid as the catalyst.

2,4-O-Isopropylidene-3,5,6-tri-O-methyl-D-glucose 1,1-Diethylmercaptal (76).

To a solution of the dithioacetal 75 (328 mg, 1 mmol) in acetone (15 ml) was added anhydrous copper sulfate (750 mg) and 3 drops of concentrated sulfuric acid at room temperature. The resulting mixture was stirred overnight. The solution was then neutralized by bubbling in ammonia at room temperature until alkaline (pH 9). The blue precipitate was filtered (celite) and concentrated to afford the crude product 76. This was purified by flash chromatography (silica gel), using petroleum ether-ethyl acetate (4:1) as the eluent. Concentration of the appropriate fractions afforded 290 mg (78%) of pure isopropylidene compound 76, as an oil. $[\alpha]_D^{22} = +4.2^\circ$ (c=5.45, chloroform). P.m.r. (CCl_4): δ 1.20 (t, 3H, $CH_2\underline{CH}_3$), 1.30 (t, 3H, $CH_2\underline{CH}_3$), 1.40 (s, 6H, $C(CH_3)_2$), 2.40-3.00 (m, 4H, $C\underline{H}_2CH_3$), 3.30 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.20-4.10 (m, 7H) ppm. I.r. (film): ν_{max} 2970 (hydrocarbon), 2930, 2830, 1450, 1380

1260 cm^{-1}. M.s. (15 eV): m/e 368 (M^+), 233 ($M^+ - (CH_3CH_2S)_2CH$), 191, 135, 89.

2,4-O-Isopropylidene-3,5,6-tri-O-methyl-D-glucose (77).

The dithioacetal 76 (310 mg, 0.84 mmol) was stirred for 2.5 hours with mercuric chloride (420 mg, 1.5 mmol) and mercuric oxide (420 mg, 1.94 mmol) in a mixture of water (0.2 ml) and acetone (3 ml), at room temperature. The mixture was then filtered through a celite pad and the precipitate washed with acetone. The combined filtrate and washings were rid of acetone by evaporation and the resulting oil was treated with chloroform (10 ml). A white precipitate formed which was filtered off and washed with more chloroform (10 ml). The combined filtrates were washed with water (1 x 10 ml), 5% potassium iodide solution (2 x 5 ml) and again with water (1 x 10 ml). Drying ($MgSO_4$) of the chloroform layer and evaporation afforded 196 mg (89%) of pure aldehyde 77, as an oil. $(\alpha)_D^{22} = 29.3^\circ$ (c=0.72, chloroform). P.m.r. (CCl_4): δ 1.38 (s, 3H, $C(CH_3)$), 1.42 (s, 3H, $C(CH_3)$), 3.30 (s, 6H, 2 OCH_3), 3.40 (s, 3H, OCH_3), 3.30-3.80 (m, 5H), 4.10 (bd, 1H), 9.60 (bs, 1H, CHO) ppm. I.r. (film): ν_{max} 3000, 2940, 2900, 2840, 1740 (carbonyl), 1460, 1380, 1370 cm^{-1}. M.s. (70 eV): m/e 247 (M^+-15), 173 ($M^+ - CH(OCH_3)(CH_2OCH_3)$), 101, 89, 45, 31.

4-O-(t-Butyldimethyl)silyl-3,5,6-tri-O-methyl-D-glucose 1,1-Diethylmercaptal (79) and 2-O-(t-butyldimethyl)silyl-3,5,6-tri-O-methyl-D-glucose 1,1-Diethylmercaptal (78).

The diol 75 (250 mg, 0.76 mmol), t-butyldimethylsilyl chloride (298 mg, 1.98 mmol) and imidazole (258 mg, 3.8 mmol) were stirred overnight at room temperature in dry dimethylformamide (2 ml). Water (20 ml) was then added and the product extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to afford the products. Flash chromatography through a silica gel column, using ethyl acetate-petroleum ether (1:2) as the eluent, afforded the mono-silylated compounds 78 and 79 as oils, having R_f values of 0.40 and 0.65 on thin layer chromatography with ethyl acetate and petroleum ether (2:3) as the solvent.

Compound with R_f 0.40: P.m.r. (CCl_4):δ 0.10 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.90 (S, 9H, $C(CH_3)_3$), 1.40 (t, 6H, 2 $SCH_2\underline{C}H_3$), 2.60 (m, 4H, 2 $S\underline{C}H_2CH_3$), 3.30 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.20-3.60 (m, 5H), 3.65 (bs, 1H), 3.80 (d, 1H), 42.0 (dd, 1H) ppm. I.r. (film): ν_{max} 3500 (hydroxyl), 3020, 2920, 1480, 1280 cm^{-1}.

Compound with R_f 0.65: P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 1.30 (t, 6H, $SCH_2\underline{C}H_3$), 2.65 (q, 2H, $S\underline{C}H_2CH_3$), 2.75 (q, 2H, $S\underline{C}H_2CH_3$), 3.30 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.30-3.80 (m, 6H), 3.85-4.10 (m, 2H) ppm. I.r. (film): ν_{max} 3500 (hydroxyl),

3040, 3000, 2920, 1480, 1280 cm^{-1}.

Nitro Alcohol 80.

The aldehyde 77 (170 mg, 0.65 mmol) was stirred at room temperature for 4 hours with 2,2-dimethoxy-4-nitrobutane (71) (114 mg, 0.70 mmol) and diisopropylamine (73 mg, 0.72 mmol) in dry dimethylformamide (1 ml). Methanol (3 ml) was then added and the solution stirred for an additional 3 hours. The methanol was then removed under vacuum, and water (10 ml) was added. The product was extracted with ether (3 x 5 ml). The combined extracts were dried ($MgSO_4$) and concentrated to afford the crude product 80. Purification through a silica gel flash column, using ethyl acetate-petroleum ether (2:1) as the eluent, afforded 232 mg (84%) of oily mixture of diastereomeric nitroalcohols 80. $(\alpha)_D^{22} = +6.9^\circ$ (c=0.29, chloroform). P.m.r. ($CDCl_3$) (R_f 0.36, ether): δ 1.30 (s, 6H), 1.40 (s, 3H), 2.20-3.00 (m, 3H), 3.10 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.20-4.20 (m, 7H), 5.00 (m, 1H, $CHNO_2$) ppm. P.m.r. ($CDCl_3$) (R_f 0.42, ether): δ 1.40 (bd, 9H), 2.00-3.00 (m, 3H), 3.10 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.10-4.40 (m, 7H), 4.80-5.10 (m, 1H, $CHNO_2$) ppm. I.r. (film): ν_{max} 3440 (hydroxyl), 2920, 2940, 2830, 1550 (nitro), 1380 cm^{-1}. M.s. (70 eV): m/e 379 (M^+-NO_2), 89, 45.

Nitro Acetate 81

The mixture of alcohols 80 (106 mg, 0.25 mmol) was stirred at room temperature for 45 minutes in dry ether (1 ml) containing acetic anhydride (33 mg, 0.32 mmol) and catalytic amounts (0.013 mmol) of 4-dimethylaminopyridine. The ether was removed under diminished pressure, and the acetic anhydride co-distilled with toluene (5 ml). The product was then dissolved in ether (10 ml) and washed with 1% hydrochloric acid (1 x 5 ml), water (1 x 5 ml) and the solution dried ($MgSO_4$). Removal of the ether afforded 108 mg (92%) of pure acetate 81, as an oily mixture of diastereomers. $[\alpha]_D^{22}=+11.1^{o}$ (c=2.62, chloroform). P.m.r. ($CDCl_3$):δ 1.20 (s, 3H), 1.40 (bs, 6H), 2.10 (s, 3H, CH_3COO), 2.30-2.80 (m, 2H), 3.05 (s, 3H, OCH_3), 3.10 (s, 3H, OCH_3), 3.30 (s, 6H, 2 OCH_3), 3.40 (s, 3H, OCH_3), 3.10-4.00 (m, 7H), 5.10-5.30 (m, 1H) ppm. I.r. (film): ν_{max} 3080, 3040, 2980, 2920, 1760 (carbonyl), 1570 (nitro) cm^{-1}. M.s. (70 eV): m/e 452 (M^{+}-15), 89, 45, 43. Anal. Calcd. for $C_{20}H_{37}NO_{11}$: C, 51.39; H, 7.92; N, 3.00. Found: C, 51.53; H, 7.92; N, 3.10.

EXPERIMENTAL

CHAPTER IV

1,2-Dideoxy-1-C-(2,2-di(thioethyl)vinyl)-3,5,-O-isopropylidene-4,6,7-tri-O-methyl-D-gluco-heptitol-1-ene S-Oxide (104) from Diethyl 3,3-di(ethylthio)prop-2-enylphosphonate S-Oxide (103).

To potassium t-butoxide (112 mg, 1 mmol) in tetrahydrofuran (1 ml) at -20°, under a nitrogen atmosphere, was added dropwise, the phosphonate 103 (345 mg, 1.1 mmol) in dry tetrahydrofuran (1 ml). The resulting solution was stirred at -20° for 15 minutes. The aldehyde 77 (262 mg, 1 mmol) in dry tetrahydrofuran (1 ml) was added dropwise at -20° to the phosphonate anion solution. The resulting mixture was stirred at -20° for 30 minutes, then quenched with water (10 ml). The tetrahydrofuran was removed under vacuum, and the product extracted with ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated to afford the crude product 104. Purification by silica preparative plates, using chloroform with 4% methanol as the solvent, afforded 120 mg (28%) of pure adduct 104, as an oil. P.m.r. (CCl_4): δ 1.30 (bt, 6H), 1.40 (bs, 6H, $C(CH_3)_2$), 2.80 (bq, 4H), 3.30 (s, 3H), 3.40 (s, 6H), 3.10-4.10 (m, 5H), 4.40-4.90 (m, 1H), 5.70-7.70 (m, 3H, olefinic protons) ppm. I.r. (film): ν_{max} 3060, 3000, 2960, 2920, 1480, 1400, 1300 cm^{-1}. U.V.: $\lambda_{max}^{ethanol}$ 267 nm.

1,2-Dideoxy-1-C-(2,2-di(thioethyl)vinyl)-3,5-O-isopropylidene-4,6,7-tri-O-methyl-D-gluco-heptitol-1-ene from Diethyl 3,3-Di-(ethylthio)-prop-1-enylphosphonate (102).

The phosphonate 102 (328 mg, 1.1 mmol) in dry tetrahydrofuran (1 ml) was added dropwise to a solution of potassium t-butoxide (112 mg, 1 mmol) in dry tetrahydrofuran (1 ml) under a nitrogen atmosphere, at -20°. The resulting solution was stirred at -20° for 30 minutes. To this was then added, dropwise, the aldehyde 77 (262 mg, 1 mmol) in dry tetrahydrofuran (2 ml). This solution was stirred for an additional 30 minutes while it warmed up to room temperature. The mixture was then quenched with water and the tetrahydrofuran removed under vacuum. Water (10 ml) was then added and the product extracted with ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$), and concentrated to afford 300 mg (74%) of pure adduct 105, as an oil. P.m.r. (CCl_4):δ 1.25 (t, 3H), 1.30 (t, 3H), 1.40 (s, 6H, $C(CH_3)_2$), 2.80 (bq, 4H, $S\underline{CH}_2CH_3$), 3.30 (s, 3H, OCH_3), 3.40 (s, 6H, 2 OCH_3), 3.00-3.90 (m, 5H), 3.90-4.80 (m, 1H), 5.30-6.00 (m, 1H), 6.30-7.00 (m, 2H) ppm. I.r. (film):ν_{max} 3060, 3000, 2980, 1370, 1400, 1300 cm^{-1}. M.s. (70 eV): m/e 406 (M^+), 391 (M^+-15), 89, 45, 29.

1,2-Dideoxy-1-C-(2,2-di(thioethyl)vinyl)-3,5-0-isopropylidene-4,6,7-tri-0-methyl-D-gluco-heptitol-1-ene S-Oxide (104) from 1,2-Dideoxy-1-C-(2,2-di(thioethyl)vinyl)-3,5,-0-isopropylidene-4,6,7-tri-0-methyl-D-gluco-heptitol-1-ene (105).

To the dithioacetal 105 (170 mg, 0.42 mmol) in dry methylene chloride (2 ml) was added, dropwise, a solution of m-chloroperbenzoic acid (85 mg, 0.49 mmol) in dry methylene chloride (2 ml), under a nitrogen atmosphere, at 0°. After allowing the reaction mixture to warm up to room temperature for 1 hour, it was washed with saturated sodium bicarbonate solution (3 x 10 ml), water (1 x 10 ml), dried ($MgSO_4$) and evaporated to afford the crude sulfoxide 104. The product was purified by flash chromatography, using methylene chloride with 4% methanol as the eluent. Concentration of the appropriate fractions afforded 150 mg (85%) of pure product 104, as an oil. The spectral data for this compound were identical to those of compound 104 synthesized from 103.

1,2-Dideoxy-1-C-(2,2-di(thioethyl)vinyl)-4,6,7-tri-0-methyl-D-gluco-heptitol-1-ene S-Oxide (106).

The isopropylidene compound 104 (170 mg, 0.40 mmol) was dissolved in a mixture of tetrahydrofuran (3 ml) and water (2 ml). To this was added concentrated hydrochloric acid (0.2 ml) and the resulting solution stirred overnight at room temperature. The tetrahydrofuran was removed under

reduced pressure and the aqueous solution neutralized to pH 7.0 with sodium bicarbonate. The water was then removed under diminished pressure and the residue treated with ether. The sodium chloride was filtered and washed with ether (3 x 5 ml). The combined washings were dried ($MgSO_4$), and concentrated to afford the crude diol 106. Purification on preparative plates (silica gel) using chloroform with 10% methanol as the solvent, afforded 120 mg (78%) of the pure diol 106, as an oil. P.m.r. ($CDCl_3$):δ 1.20 (t, 3H), 1.30 (t, 3H), 2.60-3.20 (m, 4H), 3.40 (s, 3H), 3.45 (s, 3H), 3.50 (s, 3H), 3.20-3.80 (m, 6H), 4.00-4.70 (m, 2H), 5.80-7.80 (m, 3H) ppm. I.r. (film): ν_{max} 3460 (hydroxyl), 3060, 3000, 2960 cm^{-1}. M.s. (50 eV): m/e 382 (M^+), 365 (M^+-17), 89, 45, 29.

3,5-Di-O-acetyl-1,2-dideoxy-1-C-(2,2-di(thioethyl)vinyl)-4,6,7-tri-O-methyl-D-gluco-heptitol-1-ene S-Oxide (107).

The diol 106 (120 mg, 0.314 mmol) was stirred at room temperature for 1 hour in anhydrous ether (1 ml) containing acetic anhydride (82 mg, 0.804 mmol, 0.076 ml) and catalytic amounts of 4-dimethylaminopyridine (5 mg, 0.04 mmol). The ether was then removed under reduced pressure and the acetic anhydride co-distilled with toluene. The product was then dissolved in ether and the solution washed with 1% hydrochloric acid (1 x 5 ml), water (1 x 5 ml) and dried ($MgSO_4$).

Removal of the ether under diminished pressure afforded the crude diacetate 107. Purification by flash chromatography (silica gel), using ethyl acetate-acetone (98:2) as the eluent, afforded 110 mg (75%) of pure diacetate 107, as an oil. $[\alpha]_D^{22} = +6.7$ (c=5.10, chloroform). P.m.r. ($CDCl_3$): δ 1.20-1.50 (m, 6H), 2.05, 2.10 and 2.15 (3s, 6H, $OCOCH_3$), 2.60-3.20 (m, 4H), 3.30 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.20-3.80 (m, 5H), 5.00-5.30 (m, 1H), 5.30-7.80 (m, 3H) ppm. I.r. (film): ν_{max} 3060, 3020, 1750 (carbonyl), 1480, 1400, 1270 cm^{-1}. M.s. (70 eV): m/e 466 (M^+), 437 (M^+-29), 421 (M^+-45), 407 (M^+-59), 89, 59, 45, 43. UV.: $\lambda_{max}^{ethanol}$ 267 nm.

EXPERIMENTAL

CHAPTER V

Methyl 8(R)-Acetoxy-11(R),12(R)-isopropylidenedioxy-9(S), 12(R)-oxy-dodecanoate (118) from 117.

The olefin 117 (240 mg, 0.67 mmol) was hydrogenated overnight at 40 p.s.i. with platinum oxide (25 mg) catalyst in ethyl acetate (15 ml). The catalyst was then filtered and washed with more ethyl acetate (5 ml). Removal of the ethyl acetate from the combined organic layers under diminished pressure afforded 230 mg (95%) of pure product 118, as an oil. P.m.r. ($CDCl_3$):δ 1.35 (s, 3H, $C(CH_3)$), 1.50 (s, 3H, $C(CH_3)$), 2.10 (s, 3H, $OCOCH_3$), 1.10-2.50 (m, 14H), 3.60 (s, 3H, OCH_3), 4.20 (q, 1H), 4.70 (bt, 1H), 5.00 (bq, 1H), 5.70 (d, 1H) ppm. I.r. (film):ν_{max} 2990, 2940, 2860, 1750 (carbonyl) 1440 cm^{-1}.

Methyl 8(R)-Acetoxy-11(R),12(R)-isopropylidinedioxy-9(S), 12(R)-oxy-dodecanoate (118) from 116.

The alkyne 116 (1.18 g , 3.33 mmol) was hydrogenated, in the same manner as the olefin 117, to afford 1.13 g (95%) of product 118, as an oil. The spectral data of this product were identical to those of product obtained from 117.

Methyl 8(R)-Acetoxy-11(R),12(R)-isopropylidenedioxy-9(S),12(R)-oxy-dodec-5-enoate (117).

The alkyne 116 (250 mg, 0.7 mmol) was hydrogenated overnight at 40 p.s.i. in ethyl acetate (15 ml) containing 10% Pd on charcoal (25 mg). The catalyst was then filtered and washed with more ethyl acetate (10 ml). Concentration of the combined organic fractions under diminished pressure afforded 240 mg (95%) of pure olefin 117, as an oil. P.m.r. ($CDCl_3$): δ 1.30 (s, 3H, $C(CH_3)$), 1.50 (s, 3H, $C(CH_3)$), 2.10 (s, 3H, $OCOCH_3$), 1.10-2.50 (m, 10 H), 3.60 (s, 3H, OCH_3) 4.10 (q, 1H, $J_{9,8}$=6 Hz, C_9H), 4.70 (bt, 1H, $C_{11}H$), 5.00 (bq, 1H, $J_{8,9}$=6 Hz, $J_{8,7}$=6 Hz, C_8H), 5.30-5.45 (m, 2H, CH=CH), 5.80 (d, 1H, $J_{12,11}$=4 Hz, $C_{12}H$) ppm. I.r. (film): ν_{max} 3000, 2960, 2940, 1745 (carbonyl), 1440, 1380 cm^{-1}. M.s. (70 eV, CI isobutane): m/e 357 (M^++1).

Methyl 8(R)-Acetoxy-11(R),12-dihydroxy-9(S),12-oxy-dodecanoate (119).

The isopropylidene compound 118 (150 mg, 0.42 mmol) was stirred in a mixture of acetic acid (2.9 ml) and water (5.5 ml) for 16 hours at 60°. Sodium chloride and saturated sodium chloride solution was then added and the product extracted with ethyl acetate (3 x 10 ml). The organic layers were washed with a mixture of saturated sodium bicarbonate and saturated sodium chloride solution until neutral. Drying ($MgSO_4$) and

concentration afforded 110 mg (82%) of diol 119, m.p. 61-63°. P.m.r. ($CDCl_3$):δ 1.25 (bs, 10 H), 2.00 (s, 3H, $OCOCH_3$), 1.90-2.50 (m, 4H), 3.60 (s, 3H, $COOCH_3$), 3.60-4.60 (m, 4H), 4.70-5.40 (m, 2H) ppm. I.r. (KBr):ν_{max} 3420 (hydroxyl), 2960, 2940, 2860, 1730 (carbonyl), 1440, 1370 cm^{-1}. M.s. (70 eV): m/e 300 (M^+-18), 43. Anal. Calcd. for $C_{15}H_{26}O_7$: C, 56.60; H, 8.18. Found: C, 56.63; H, 8.32.

Methyl 8(R)-Acetoxy-11(R),12-di-p-nitrobenzoyloxy-9(S),12-oxy-dodecanoate (120).

To dry pyridine (5 ml), under a nitrogen atmosphere, was added p-nitrobenzoyl chloride (186 mg, 1 mmol) and the mixture kept at 0°. The diol 119 (100 mg, 0.32 mmol) in dry pyridine (1 ml) was added dropwise, and the resulting mixture was kept at 0° for 1.5 hours and then allowed to warm up to room temperature for 0.5 hours. Water (60 ml) was then added and the product extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with 1% hydrochloric acid (until acidic), water (1 x 10 ml) and dried ($MgSO_4$). Concentration under diminished pressure afforded the crude product 120. Purification by flash chromatography (silica gel), using petroleum ether (30°-60°)-ethyl acetate (5:2) as the eluent, afforded 130 mg (67%) of pure di-p-nitrobenzoate 120, as an oil. P.m.r. ($CDCl_3$):δ 1.10-1.80 (m, 10 H), 1.97 and 2.00 (s and s, 3H, $OCOCH_3$), 2.00-2.55 (m, 4H), 3.68 (s, 3H, $COOCH_3$), 4.40-4.70 (m, 1H), 4.90-5.10 (m, 1H, C<u>H</u>$COOCH_3$), 5.60-5.70

(m, 1H), 6.50 and 6.70 (s and d, 1H, $OCHOCOC_6H_5NO_2$), 8.00-8.25 (m, 8H) ppm. I.r. (film): ν_{max} 3120, 3080, 3060, 2940, 2860, 1730 (carbonyl), 1610 (aromatic), 1530 (nitro), 1520 (nitro), 1430 cm^{-1}. M.s. (70 eV): m/e 585 (M^+-31), 450 (M^+-$OCOC_6H_4NO_2$), 401 (M^+-215), 215, 150, 43.

Methyl 8(R)-Acetoxy-12-cyano-11(R)-p-nitrobenzoyloxy-9(S), 12-oxy-dodecanoate (121).

A solution of the di-p-nitrobenzoate 120 (110 mg, 0.18 mmol) in benzene (1 ml) was saturated, under ice-cooling, with gaseous hydrogen bromide in the course of 30 minutes, under a nitrogen atmosphere. The mixture was then allowed to stand at room temperature for an additional 30 minutes. The p-nitrobenzoic acid was filtered off and washed with benzene (1 ml). The combined benzene solutions were then evaporated under diminished pressure (40°), and the residue co-evaporated with more benzene (2 ml). The sirupy material was then dissolved in nitromethane (1 ml, dried by distillation over P_2O_5). The solution was treated with powdered mercuric cyanide (100 mg) which was pre-dried at 140° for 3 hours under vacuum (15 mm mercury). The whole reaction mixture was stirred for 20 hours at room temperature under a nitrogen atmosphere. The insoluble portion was filtered off and washed with benzene (2 ml). The filtrates were combined and evaporated under diminished pressure. The residue was dissolved in ethyl acetate (2 ml), and the solution was washed

with 5% potassium iodide solution (2 x 2 ml), water (1 x 1 ml), dried ($MgSO_4$) and concentrated to afford the crude product 121. Purification through an alumina (Al_2O_3) column, using petroleum ether-ethyl acetate (3:2) as the eluent, afforded 45 mg (53%) of pure oily cyanide 121, as a 1:1 mixture of the C_{12} epimers. P.m.r. ($CDCl_3$):δ 1.20-1.90 (bm, 10 H), 2.10 and 2.20 (s and s, 3H, $OCOCH_3$), 2.00-2.60 (m, 4H), 3.70 (s, 3H, OCH_3), 4.20-4.60 (m, 1H), 4.80-5.80 (m, 3H), 8.00-8.30 (bs, 4H) ppm. I.r. (film):ν_{max} 3120, 3080, 3060, 2940, 2860, 1730 (carbonyl), 1610 (aromatic), 1530 (nitro), 1440 cm^{-1}. M.s. (70 eV): m/e 450 (M^+-CN), 445 (M^+-31), 261, 215, 150, 43.

Methyl 8(R),11(R),12-Triacetoxy-9(S),12-oxy-dodecanoate (123).

The diol 119 (318 mg, 1 mmol) was dissolved in dry ether (10 ml). To this was added acetic anhydride (408 mg, 4 mmol, 0.38 ml) and catalytic amounts of N,N-dimethyl-4-aminopyridine. The resulting solution was stirred for 1 hour at room temperature. The ether was then removed under vacuum and the mixture co-distilled with toluene (10 ml). The resulting oil was then redissolved in ether (30 ml) and the solution was washed with 1% hydrochloric acid (1 x 20 ml), 10% sodium bicarbonate solution (2 x 20 ml), water (2 x 20 ml) and dried ($MgSO_4$). Concentration under reduced pressure afforded 340 mg (85%) of pure product 123, as an oil. P.m.r. (CCl_4):δ 1.10-1.80 (m, 10 H), 2.00 (bs, 9H, 3 $OCOCH_3$),

1.90-2.40 (m, 4H), 3.60 (s, 3H, OCH_3), 4.00-4.40 (m, 1H), 4.60-5.20 (m, 2H), 6.00 and 6.20 (s and d, 1H) ppm. I.r. (film): ν_{max} 2940, 2860, 1745 (carbonyl), 1440 cm^{-1}. M.s. (70 eV): m/e 371 (M^+-31), 343 (M^+-$OCOCH_3$), 215, 187, 59, 43.

Methyl 12-Cyano-8(R),11(R)-Diacetoxy-9(S),12-oxy-dodecanoate (125) and Methyl 12-Bromo-8(R),11(R)-Diacetoxy-9(S),12-oxy-dodecanoate (124).

The triacetate 123 (180 mg, 0.45 mmol) was reacted in the same manner as compound 120 to afford the crude product 125. Purification through an alumina (Al_2O_3) column, using chloroform with 4% methanol as the eluent, afforded 100 mg (60%) of pure cyanide 125, as an oily mixture of isomers. P.m.r. ($CDCl_3$): δ 1.10-1.80 (m, 10 H), 1.90-2.40 (m, 4H), 2.00, 2.02, 2.05 and 2.10 (all s, 6H, 2 $OCOCH_3$), 3.60 (s, 3H, OCH_3), 4.00-4.50 (m, 1H), 4.50-5.40 (m, 3H) ppm. I.r. (film): ν_{max} 2950, 2940, 2860, 1740 (carbonyl), 1460, 1430 cm^{-1}. M.s. (70 eV): m/e 343 (M^+-26), 338 (M^+-31), 215, 154, 43.

Methyl 11(R),12(R)-Isopropylidenedioxy-8(R)-methoxy-9(S),12(R)-oxy-dodecanoate (128).

The alkyne 127 (940 mg, 2.88 mmol) was hydrogenated, in the same manner as in the olefin 117, to afford the crude product 128. Purification by flash chromatography (silica gel), using petroleum ether-ethyl acetate (3:1) as the eluent,

afforded 577 mg (61%) of the pure product 128, as an oil. $[\alpha]_D^{22} = -9.4^{\circ}$ (c=6.05, chloroform). P.m.r. (CCl_4): δ 1.25 (s, 3H, $C(CH_3)$), 1.40 (s, 3H, $C(CH_3)$), 1.20-2.00 (m, 12H), 2.00-2.40 (m, 2H), 3.10-3.30 (m, 1H), 3.35 (s, 3H, OCH_3), 3.60 (s, 3H, $COOCH_3$), 3.80-4.20 (m, 1H), 4.50-4.70 (m, 1H), 5.60 (d, 1H) ppm. I.r. (film): ν_{max} 2980, 2940, 2860, 1740 (carbonyl), 1460, 1430, 1380 cm^{-1}. M.s. (70 eV): m/e 315 (M^+-15), 187, 155, 143, 85. Anal. Calcd. for $C_{17}H_{30}O_6$: C, 61.82; H, 9.17. Found: C, 62.02; H, 9.09.

Methyl 11(R),12-Dihydroxy-8(R)-methoxy-9(S),12-oxy-dodecanoate (129).

The isopropylidene compound 128 (330 mg, 1 mmol) was reacted in the same manner as 118 to afford 190 mg (66%) of pure diol 129, as an oil. P.m.r. ($CDCl_3$-D_2O): δ 1.20-2.50 (m, 14H), 3.40 and 3.45 (s and s, 3H, OCH_3), 3.60 (s, 3H, $COOCH_3$), 3.10-3.50 (m, 1H), 4.00-4.50 (m, 2H), 5.10 and 5.30 (s and d, 1H) ppm. I.r. (film): ν_{max} 3400 (hydroxyl), 2940, 2860, 1740 (carbonyl) cm^{-1}. M.s. (70 eV): m/e 241, 187, 125.

Methyl 11(R),12-Di-p-nitrobenzoyloxy-8(R)-methoxy-o(S),12-oxy-dodecanoate (130).

The diol 129 (150 mg, 0.52 mmol) was reacted in the same manner as compound 119, to afford 275 mg (90%) of di-p-nitrobenzoate 130, as an oil. Flash chromatography using petroleum

ether-ethyl acetate (3:1) as the eluent afforded an analytically pure sample as a 1:1 mixture of epimers. P.m.r. (CCl_4): δ 1.10-1.70 (m, 10 H), 1.90-2.60 (m, 4H), 3.20 (s, 3H, OCH_3), 3.40 and 3.60 (s and s, 3H, $COOCH_3$), 3.10-3.40 (m, 1H), 4.20-4.60 (m, 1H), 5.50 (bd, 1H), 6.35 and 6.60 (s and d, 1H), 7.90-8.20 (m, 8H, aromatic protons) ppm. I.r. (film): ν_{max} 3110, 3080, 3050, 2840, 2860, 1730 (carbonyl), 1610 (aromatic), 1530 (nitro), 1435 cm^{-1}. M.s. (70 eV): m/e 557 (M^+-31), 422 (M^+-166), 187, 166, 150. Anal. Calcd. for $C_{28}H_{32}N_2O_{12}$: C, 57.14; H, 5.44; N, 4.76. Found: C, 57.40; H, 5.47; N, 4.57.

Methyl 12-Cyano-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12-oxy-dodecanoate (132) and Methyl 12-Bromo-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12-oxy-dodecanoate (131).

The di-p-nitrobenzoate 130 (140 mg, 0.24 mmol) was reacted in the same manner as compound 120, to afford the crude product 132. Purification by simple chromatography (Al_2O_3), using petroleum ether-ethyl acetate (1:1) as the eluent, afforded 65 mg (61 %) of the pure product 132, as an oil. P.m.r. ($CDCl_3$): δ 1.20-1.80 (m, 10 H), 2.10-2.40 (m, 4H), 3.30-3.60 (m, 1H), 3.50 (s, 3H, OCH_3), 3.60 (s, 3H, $COOCH_3$), 4.00-4.60 (m, 1H), 4.70 (bs, 1H), 5.50-5.80 (m, 1H), 8.20 (bs, 4H) ppm. I.r. (film): ν_{max} 3110, 3080, 3060, 2940, 2860, 1730 (carbonyl), 1610 (aromatic), 1530 (nitro), 1435, 1410, 1350 cm^{-1}.

3-(t-Butyldimethyl)silyloxy-oct-1-yne (136).

To the alcohol 143 (1.26 g, 10 mmol) in dry dimethylformamide (3 ml) under a nitrogen atmosphere was added t-butyldimethylsilyl chloride (1.81 g, 12 mmol) and imidazole (1.70 g, 25 mmol). The resulting mixture was stirred overnight at room temperature. Water (30 ml) was then added and the product extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with water (5 x 20 ml), dried ($MgSO_4$) and concentrated under diminished pressure to afford 2.20 g (92%) of the silylated compound 136. P.m.r. (CCl_4): δ 0.20 and 0.22 (s and s, 6H, $Si(CH_3)_2$), 1.00 (bs, 12H), 1.20-1.80 (m, 8H), 2.30 (d, 1H, C≡CH), 4.20-4.50 (m, 1H) ppm. I.r. (film): ν_{max} 3320, 2960, 2940, 2860, 1470 cm^{-1}.

Methyl 12-Hydroxy-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12-oxy-dodecanoate (138) and Its 12-acetate 139.

To the acetylenic compound 135 (100 mg, 0.5 mmol) in dry hexane (3 ml), under a nitrogen atmosphere, was added, dropwise, diisobutylaluminum hydride (0.31 ml, 0.55 mmol, of a 25 g/100 ml toluene solution) at room temperature. The resulting solution was heated to 55° for 4 hours, cooled to room temperature and treated with 1.7 M n-butyllithium solution in hexane (0.55 mmol, 0.32 ml). Tetrahydrofuran (3 ml) was then added and the solution cooled to -78°. The bromo compound 131 (251 mg, 0.5 mmol) was added dropwise

to this solution, under a nitrogen atmosphere, and the mixture allowed to stand at room temperature for 2 hours. The solvent was then removed under diminished pressure, water (10 ml) added and the product extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with water (3 x 5 ml), dried ($MgSO_4$) and concentrated to afford several products. Purification by preparative plate chromatography, using petroleum ether-ethyl acetate (2:1) as the solvent, afforded 120 mg (55%) of pure alcohol 138, as an oily mixture of diastereomers. P.m.r. (CCl_4):δ 1.00-1.80 (m, 10 H), 1.80-2.40 (m, 4H), 3.40 (s, 3H, OCH_3), 3.50 (s, 3H, $COOCH_3$), 3.00-3.60 (m, 1H), 3.60-4.00 (m, 1H), 4.00-4.40 (M, 1H), 5.10-5.30 (m, 2H), 8.10 (m, 4H) ppm. I.r. (film):ν_{max} 3420 (hydroxyl), 3110, 3080, 3060, 2940, 2860, 1730 (carbonyl), 1610 (aromatic), 1530 (nitro), 1440 cm^{-1}. Acetylation, using acetic anhydride in ether and N,N-dimethyl-4-aminopyridine as the catalyst, afforded the acetate 139. P.m.r. (CCl_4):δ 1.00-1.90 (m, 10 H), 2.10 and 2.20 (s and s, 3H, $OCOCH_3$), 190-2.50 (m, 4H), 3.40 and 3.45 (s and s, 3H, OCH_3), 3.00-3.50 (m, 1H), 3.60 (s, 3H, $COOCH_3$), 4.00-4.40 (m, 1H), 5.30 (bd, 1H), 6.10 and 6.30 (s and d, 1H), 8.10 (s, 4H, aromatic protons) ppm. I.r. (film):ν_{max} 2940, 2860, 1740 (carbonyl), 1610 (aromatic), 1530 (nitro), 1440, 1350 cm^{-1}.

Methyl 15-(t-Butyldimethyl)silyloxy-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12(R)-oxy-eicosa-13-ynoate (145).

The lithium salt of the side-chain derivative 136 was prepared by treating 136 (375 mg, 1.5 mmol), in dry tetrahydrofuran (2 ml), with a 1.6 M solution of n-butyllithium in hexane (1 ml). This was stirred for 30 minutes, and added, dropwise, to a solution of the bromo compound 131 (251 mg, 0.5 mmol) in dry tetrahydrofuran (3 ml) and hexamethylphosphoramide (0.2 ml), at -78°, under a nitrogen atmosphere. This mixture was stirred for 2 hours at -78° and quenched with buffer solution (pH 4.4). The tetrahydrofuran was removed under diminished pressure, water (5 ml) was added, and the product extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (5 x 5 ml), dried ($MgSO_4$) and evaporated to afford the crude product 145. Purification by preparative chromatography, using ethyl acetate-petroleum ether (1:3) as the solvent, afforded 80 mg (24%) of one diastereomer (R_f=0.76) and 60 mg (18%) of the other diastereomer (R_f=0.60).

Compound with R_f=0.76:

P.m.r. (CCl_4): δ 0.20 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 12H), 1.20-2.40 (m, 22H), 3.20-3.50 (m, 1H), 3.40 (s, 3H, OCH_3), 3.60 (s, 3H, $COOCH_3$), 3.80-4.10 (m, 1H), 4.20-4.60 (m, 1H), 4.80-5.10 (m, 1H), 6.00 (d, 1H, $J_{12,11}$=4 Hz, $OCHC{\equiv}C$), 7.70-8.30 (q, 4H, aromatic protons) ppm. I.r. (film): ν_{max} 2960, 2930, 2860, 1740 (carbonyl), 1610 (aromatic), 1530 (nitro),

1460, 1435 cm^{-1}. M.s. (70 eV): m/e 604 (M^+-57), 590 (M^+-71), 474 (M^+-187), 187, 150, 71, 57.

Compound with R_f=0.60:

$[\alpha]_D^{22}$= 6.4° (c=1.05, chloroform). P.m.r. (CCl_4):δ 0.10 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 12H), 1.10-2.50 (m, 22H), 3.20-3.50 (m, 1H), 3.40 (s, 3H, OCH_3), 3.60 (s, 3H, $COOCH_3$), 4.20-4.90 (m, 3H), 5.80 (d, 1H, $J_{12,11}$=4 Hz, $OCHC{\equiv}C$), 7.50-8.30 (q, 4H, aromatic protons) ppm. M.s. (70 eV): m/e 646 (M^+-15), 604 (M^+-71), 474 (M^+-187), 187, 150, 71, 57, 45. Anal. Calcd. for $C_{35}H_{55}NO_9Si$: C, 63.54; H, 8.32; N, 2.12. Found: C, 63.80; H, 8.40; N, 1.92.

3-Hydroxy-oct-1-ene (149).

Into a 50 ml three-neck flask equipped with a magnetic stirring bar, a nitrogen inlet, and a serum cap was introduced 8 ml of 0.71 N $CrSO_4$ reagent solution. The alkyne 143 (126 mg, 1 mmol) in N,N-dimethylformamide solution (8 ml) was then added. The colour changed from blue to green, instantaneously. The resulting green solution was stirred overnight at room temperature under a nitrogen atmosphere. The solution was saturated with ammonium sulfate and extracted with ether (4 x 5 ml). The ethereal extracts were combined, washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated under diminished pressure to afford 120 mg (94 %) of pure olefin 149. P.m.r. (CCl_4):δ 1.10-1.40 (m, 3H), 1.40-2.00 (m, 8H), 3.50 (s, 1H), 4.10-4.50 (m, 1H), 5.20-

5.80 (m, 2H), 5.80-6.50 (m, 1H) ppm.

Methyl 15-Hydroxy-8(R)-methoxy-11(R)-p-nitrobenzoyloxy-9(S),12(R)-oxy-eicosa-13-ynoate (150).

The silyl compound 145 (30 mg, 0.045 mmol (R_f=0.76)) was heated to 80° for 3 hours in 80% aqueous acetic acid (1 ml). Water (10 ml) was then added and the product extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (5 x 10 ml), water (1 x 5 ml), dried ($MgSO_4$) and concentrated under diminished pressure to afford the crude product. Purification by preparative plate chromatography, using petroleum ether-ethyl acetate (2:1) as the solvent, afforded 20 mg (81%) of pure oily alcohol 150, as a mixture of C-15 diastereomers. P.m.r. (90 mHz, $CDCl_3$):δ 0.95 (bt, 3H), 1.25-2.50 (m, 22H), 3.30-3.55 (m, 2H), 3.50 (s, 3H, OCH_3), 3.75 (s, 3H, $COOCH_3$), 3.95-4.20 (m, 1H), 4.40-4.60 (m, 1H), 5.05-5.25 (m, 1H), 6.25 (d, 1H, $J_{12,11}$=4 Hz), 7.95-8.60 (q, 4H) ppm. I.r. (film): ν_{max} 3430 (hydroxyl), 2940, 2860, 1740 (carbonyl), 1720 (carbonyl), 1650, 1610 (aromatic), 1530 (nitro), 1350 cm^{-1}. M.S. (70 eV): m/e 517, 425, 414, 190, 150.

Methyl 11(R)-p-Aminobenzoyloxy-15-hydroxy-8(R)-methoxy-9(S),12(R)-oxy-eicosa-13-ynoate (151).

The alkyne 150 (40 mg, 0.07 mmol) in N,N-dimethyl-

formamide (0.4 ml) was added to a stirred mixture of 0.71 N $CrSO_4$ solution (0.4 ml) and water (0.1 ml) under a nitrogen atmosphere. The resulting solution turned from blue to green instantaneously and it was then stirred at room temperature for an additional 1.5 hours. The solution was saturated with ammonium sulfate and extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with water (3 x 5 ml), dried ($MgSO_4$), and concentrated under diminished pressure to afford the crude product 151. Purification by preparative plate chromatography, using ethyl acetate-petroleum ether (2:1) as the solvent, afforded 30 mg (79 %) of pure amine 151, as an oil. P.m.r. (90 mHz, $CDCl_3$):δ 0.90 (bt, 3H), 1.20-1.90 (m, 18H), 2.00-2.50 (m, 4H), 3.45 (s, 3H, OCH_3), 3.390-3.60 (m, 3H), 3.70 (s, 3H, $COOCH_3$), 4.10-4.60 (m, 3H), 4.95-5.10 (m, 1H), 6.10 (d, 1H, $J_{12,11}$=4Hz), 7.20 (q, 4H, aromatic protons) ppm. I.r. (film): ν_{max} 3480 (amine), 3380 (hydroxyl), 2940, 2860, 1730 (carbonyl), 1630, 1610 (aromatic), 1430 cm^{-1}. M.s. (70 eV): m/e 517 (M^+), 486 (M^+-31), 330 (M^+-187), 187, 120 ($NH_2C_6H_4CO$), 92, 71, 45.

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