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THE CONVERSION OF THE IRIDOID AUCUBIN TO A CHIRAL
PROSTANOID SYNTHON

City University of New York

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THE CONVERSION OF THE IRIICID AUCUBIN
TO A CHIRAL PROSTANOID SYNTHON

by

DAVID E. PIERCE

A dissertation submitted to the Graduate Faculty
in Chemistry in partial fulfillment of the
requirements for the degree of Doctor of
Philosophy, The City University of New York.

1981

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

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date

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The City University of New York

ABSTRACT

THE CONVERSION OF THE IRIDOID AUCUBIN TO A CHIRAL PROSTANOIC SYNTHON

by

David R. Pierce

Advisor: Professor William F. Berkowitz

The iridoid aucubin has been converted in good yield to a potential intermediate in the synthesis of prostaglandins and prostanoids, particularly those having an 11-deoxy-11-hydroxymethyl substituent. This has been achieved by converting aucubin to its hexaacetate, and hydrogenating the latter with rhodium on carbon in ethyl acetate to give the β -isomer of tetrahydroaucubin hexaacetate. Hydrolysis of this compound to the hemiacetal (the preferred structure for the hydroxyaldehyde) was achieved by a two step procedure through the hemithioacetal.

ACKNOWLEDGEMENT

I would like to express my thanks and appreciation to Dr. William F. Berkowitz for his constant encouragement and incisive critiques, without which this work would never have been completed, and for his allowing me the opportunity to pursue this thesis.

I would also like to thank the members of my committee, Doctors Engel, Haubenstock, and Wilen, who were very liberal with their time and ideas.

Finally, I thank my wife Janet who steadfastly insisted that I could do it.

CONTENTS

ABSTRACT	iii
ACKNOWLEDGEMENT	iv

<u>Chapter</u>	<u>page</u>
I. INTRODUCTION	1
The Prostaglandins	1
History	1
Structure and Nomenclature	3
Biological Activity	7
Synthetic Approaches	9
The Early Routes	9
Syntheses from Chiral Starting Materials	16
Corey's Bicycloheptane Synthesis	19
Other Approaches to Corey's Aldehyde	26
The Iridoids	30
History and Structure	30
Relationship of the Iridoids to Corey's Aldehyde	32
Aucubin	33
The Work of Ohno	36
The Work of Berkowitz	39
Statement of the Problem	42
References	48
II. RESULTS AND DISCUSSION	49
III. EXPERIMENTAL	64
Isolation of Aucubin	66
Synthesis of Aucubin Hexaacetate (AHA)	68
Synthesis of XV (THAHA)	70
Synthesis of XX AND XXI (Aglucone Diacetate)	72
Synthesis of XXIV AND XXV (Methyl Aglucone)	73
Preparation of XXVI (Tricyclic Acetal)	74
Synthesis of XXII AND XXIII (MAD)	74
Synthesis of Methyl Aglucone Dichalcate	75
Synthesis of XX AND XXI FROM XXII AND XXIII (MAD)	76
Synthesis of XXVIII (HTAAD)	77
Synthesis of XX AND XXI from XXVIII (HTAAD)	78
Modified Wittig Reaction	79
Synthesis of XVII	80

BIBLIOGRAPHY	82
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LIST OF FIGURES

<u>Figure</u>	<u>page</u>
1. Retrosynthetic Analysis of PGE and PGF	20
2. Compounds Used as Precursors to Corey's Aldehyde . .	27
3. Structures of Representative Iridoids.	31
4. Reactions Used in the Structure Determination of Aucubin.	34
5. Reaction Conditions Used in Attempts to Hydrolyze THAHA	52
6. Reaction Conditions Used in Attempts to Methanolyze THAHA	57
7. Reaction Conditions Used in Attempts to Hydrolyze MAD	60

INDEX OF SCHEMES

<u>Scheme</u>	<u>page</u>
1. The Biosynthesis of the Prostaglandins	10
2. The First Synthesis of a Prostaglandin-like Compound	11
3. The Just Synthesis of the Prostaglandins	12
4. The Fried Synthesis	16
5. Corey's Bicycloheptane Synthesis of Prostaglandins .	21
6. Ohno's Synthesis of Prostaglandins from Aucubin . . .	37
7. The Oxidative Route from Aucubin to Prostanoids . . .	40
8. The Proposal for Conversion of Aucubin to Prostanoids	46

Chapter I

INTRODUCTION

THE PROSTAGLANDINS

History

The biological activity of the prostaglandins was first noted in 1930 by Kurzrock and Lieb at Columbia University [1]. There had been indications of potent biological activity in extracts of the accessory genital glands several years before, but these people were the first to speculate that a single compound (erroneously conjectured to be acetylcholine) might be responsible for their observations of the effects of fresh human semen on the uterine tissue of hysterectomized women [2].

At that time, the physical methods for differentiating naturally occurring biologically active substances, as well as the means for identifying them, were not well developed, so it is perhaps not surprising that Kurzrock and Lieb went no further. However, only a few years later, von Euler [3] in Sweden, and Goldblatt [4, 5] in England, independently discovered that extracts of sheep vesicular glands and human seminal plasma had two effects. These extracts lowered the blood pressure of a variety of experimental animals, and they had a stimulatory action on a variety of isolated

smooth muscle. Von Euler then was able to show that this activity was not due to any of several other compounds, including adrenaline, histamine, or acetylcholine.

By the end of the 1930's, much was known about this material, primarily due to von Euler [6]. It was shown to be nitrogen free, lipid soluble, and acidic. Indeed, its barium salt was very stable, even in impure form, and proved to be important in relating the forthcoming structural work of Bergstrom to the early biological activity work. By this time it had also received a name, albeit a mistaken one. Because he believed that it was produced in the prostate gland, von Euler named it "prostaglandin". While the seminal plasma from humans is the richest vertebrate source (up to 30 micrograms per milliliter), prostaglandins have been found in virtually all mammalian tissues (although at concentrations less than 1% of that of semen). Indeed, the total prostaglandin production in the adult human is only on the order of 1 to 2 milligrams per day.

It is understandable that nearly twenty-five years would pass before any further work was done in this field when one considers the difficulties in isolating prostaglandin, the small amounts available, the intense research effort then being devoted to the steroids and antibiotics, and the deficiency in suitable methods for the separation and analysis of small molecules. But the work done by Bergstrom and his coworkers (mainly Sjovall and Samuelsson) at the end of this

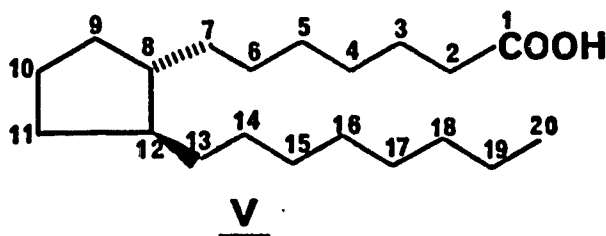
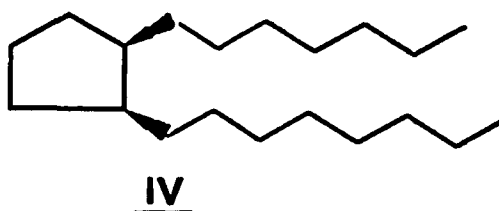
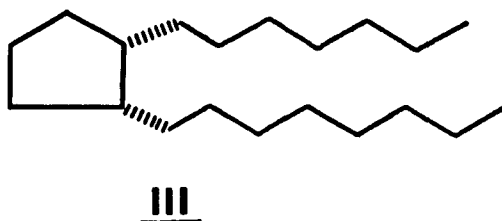
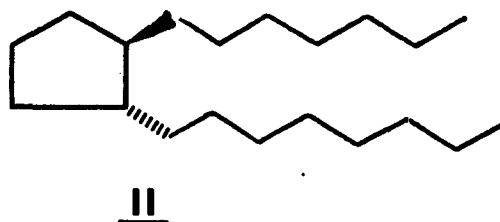
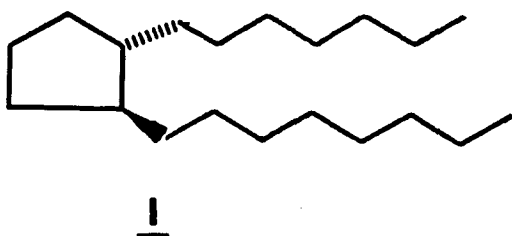
period was brilliant enough to make up for the loss of time. In a few short years, primarily from 1955 to 1965, they were able to show that "prostaglandin" was not a simple compound, but a family of related substances, and, relying heavily upon ultramicroanalytical techniques, and the newly developed instrumental techniques of infra-red, ultra-violet, proton magnetic resonance, and mass spectroscopy, along with gas chromatography, they proposed stereochemical structures including absolute configurations for some fifteen members of this family [7-17].

In the early 1960's, final confirmation of the structures was obtained from X-ray crystallographic studies on two of these [18, 19]. Later crystallographic studies done in the 1970's show how drastically the conformations and orientation of the side chains can be changed by structure modifications in the ring [20-24]. Although there is an on-going debate as to the significance of structure as determined in a crystal, and effects as determined in solution, it is easy to speculate that these conformational changes are important in the structure-activity relationships that these molecules exhibit.

Structure and Nomenclature

Even when the structure has been established, the systematic name describing it is usually so complex (partly for stereochemical reasons) that chemists continue to use the trivial name.

The prostaglandins are no exception to this statement by Fletcher et al. [25]. Indeed, chemists go even further in this field, since the prostaglandin "names" are acronyms. The major nomenclature system names these compounds with reference to the stereoisomeric hydrocarbons prostane I,

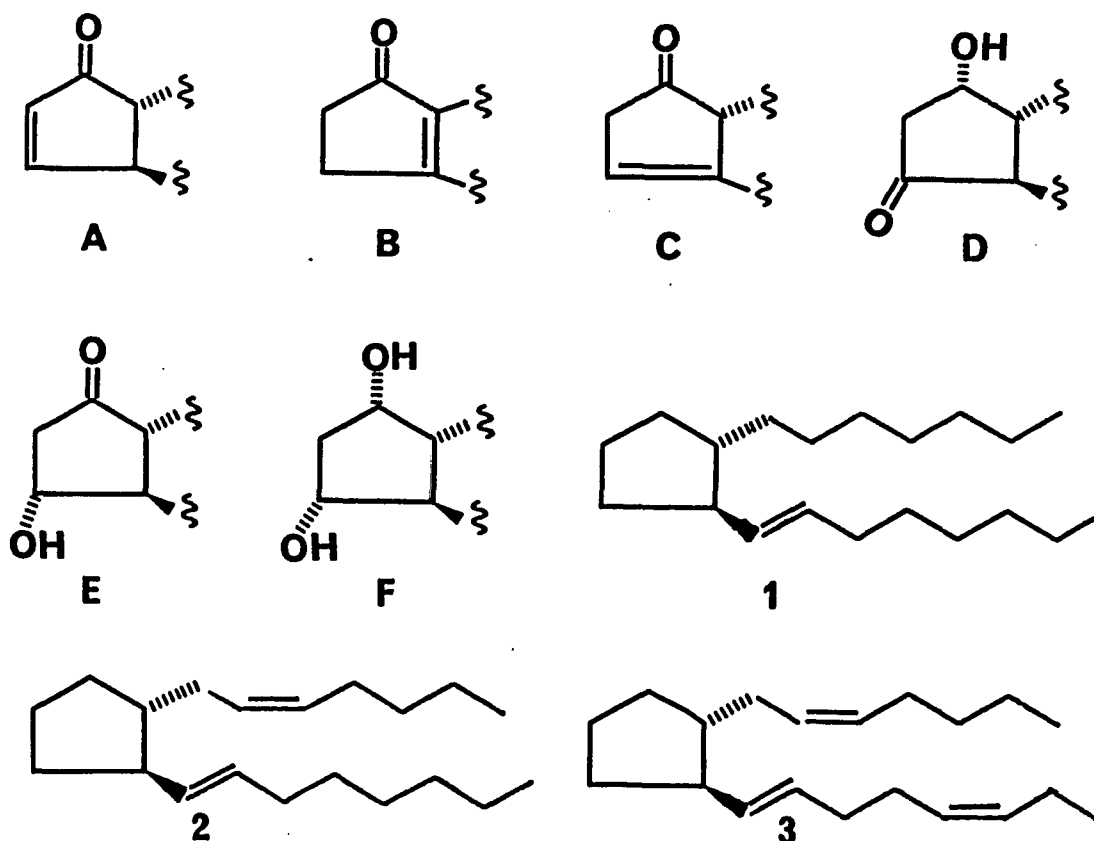


ent-prostane II, isoprostane III, ent-isoprostane IV, and the corresponding prostanoic acids (e. g. V). Only I and V (which determines the numbering of the prostaglandins) are utilized in the formal (i. e. Chemical Abstracts) nomenclature. Thus, one of the prostaglandins is formally named (5Z,13E,9S,11R,15S)-trihydroxy-prosta-5,13-diene-1-oic acid.

This conveys all of the available structural and stereochemical information, but is complex enough that the trivial name $\text{PGF}_{2\alpha}$ is much more commonly used.

The trivial nomenclature assumes (as always) that the reader or listener is familiar with the structure. It divides the prostaglandins into families based on the nature of the substituents around the cyclopentane ring. These families are designated by letters, and the word prostaglandin is reduced to the letters "PG" to conform. The letters were originally assigned by Bergstrom and Sjovall to differentiate the compounds based on their solubility and the method of their formation. Thus, when a mixture of the two major prostaglandins was partitioned between ether and a phosphate buffer (fosfate in Swedish) it was natural to call the ether soluble one PGE, and the other PGF. PCA was produced from PGE by treatment with acid, while base treatment produced PGE. The others, i. e., C, D, G, H and I, were assigned as fillers. Since the possibility existed that only the PGE's and F's were natural, and that the A's and B's were artifacts, the PGE and PGF families were classified as primary, and all the others as secondary. Today, much of the ongoing research actually involves the so-called secondary prostaglandins, which may have as much activity as the primary prostaglandins, and which may indeed be utilized in nature. The substituents corresponding to these letters (with the exception of G, H, and I, which do not really fol-

low this system), are shown in the following part structures.



These families are further subdivided into series depending on the number of double bonds present in the molecule exclusive of those possibly present in the cyclopentane ring. A subscripted "1" signifies that there is a trans 13,14 double bond present. A subscript "2" indicates the addition of a cis 5,6 double bond, while "3" means that another cis double bond is located at the 17,18 position. Unfortunately, there is no subscript which signifies a lack of double bonds, instead, the term "dihydro" is used with the subscript "1".

A subscripted Greek letter "alpha" or "beta" is used to indicate the stereochemistry of substituents around the cyclopentane ring. If no other indication is given, it refers to the 9 carbon. As in carbohydrate chemistry, "alpha" means the substituent is located below the plane of the ring, while "beta" is above.

There are extensions and modifications of this system currently being used, but a discussion of them is not germane to the work presented here. For a full discussion of all the conventions, the papers by Nelson and Andersen should be consulted [26, 27].

Biological Activity

Bergstrom and Sjovall received their first intimation that "prostaglandin" was not a single compound when they finally isolated a crystalline material (PGF) that failed to lower blood pressure but still stimulated smooth muscle strips. The hope that the activities of the prostaglandins might be due to several compounds, with each of them exhibiting only one activity, was short-lived however. In fact, PGE, the next compound isolated, exhibited both types of activity. It turned out that all of the prostaglandins exhibit a range of actions, some of them antagonistic.

The prostaglandins are usually regarded as local modulators of cell function, or as tissue hormones. As such, they are active even in nanogram/milliliter concentrations. They

have been implicated in the regulation of the endocrine, reproductive, nervous, digestive, hemostatic, respiratory, cardiovascular, and renal systems. The biological activity of the prostaglandins includes increasing or decreasing inflammation, stimulating or inhibiting smooth muscle contraction, inhibiting the production of stomach acid, opening bronchial tubes, constricting the pupils, inhibiting or enhancing the aggregation of blood platelets, blocking the breakdown of fats, and operating as a tissue or auto-defender. Manifestations of this last activity include fever, vomiting, inflammatory phenomena, and the regulation of blood flow in the organ being attacked.

Clinical studies have confirmed the effectiveness of both the natural prostaglandins and artificial analogs in bronchodilation, inhibition of gastric acid secretion, vasodilation, diuresis, and the stimulation of the uterine muscles at any time during pregnancy, leading either to birth or abortion. It has also been shown that many antiinflammatory, antipyretic, and analgesic drugs (including aspirin) inhibit the biosynthesis of prostaglandins. This effect may be responsible for the activity of these types of therapeutic agents.

Research has been conducted into the development of prostaglandin agonists and antagonists to treat such disparate conditions as ulcers, asthma, diabetes complications, arthritis, cholera, glaucoma, hypertension, shock, congestive heart failure, and thrombosis.

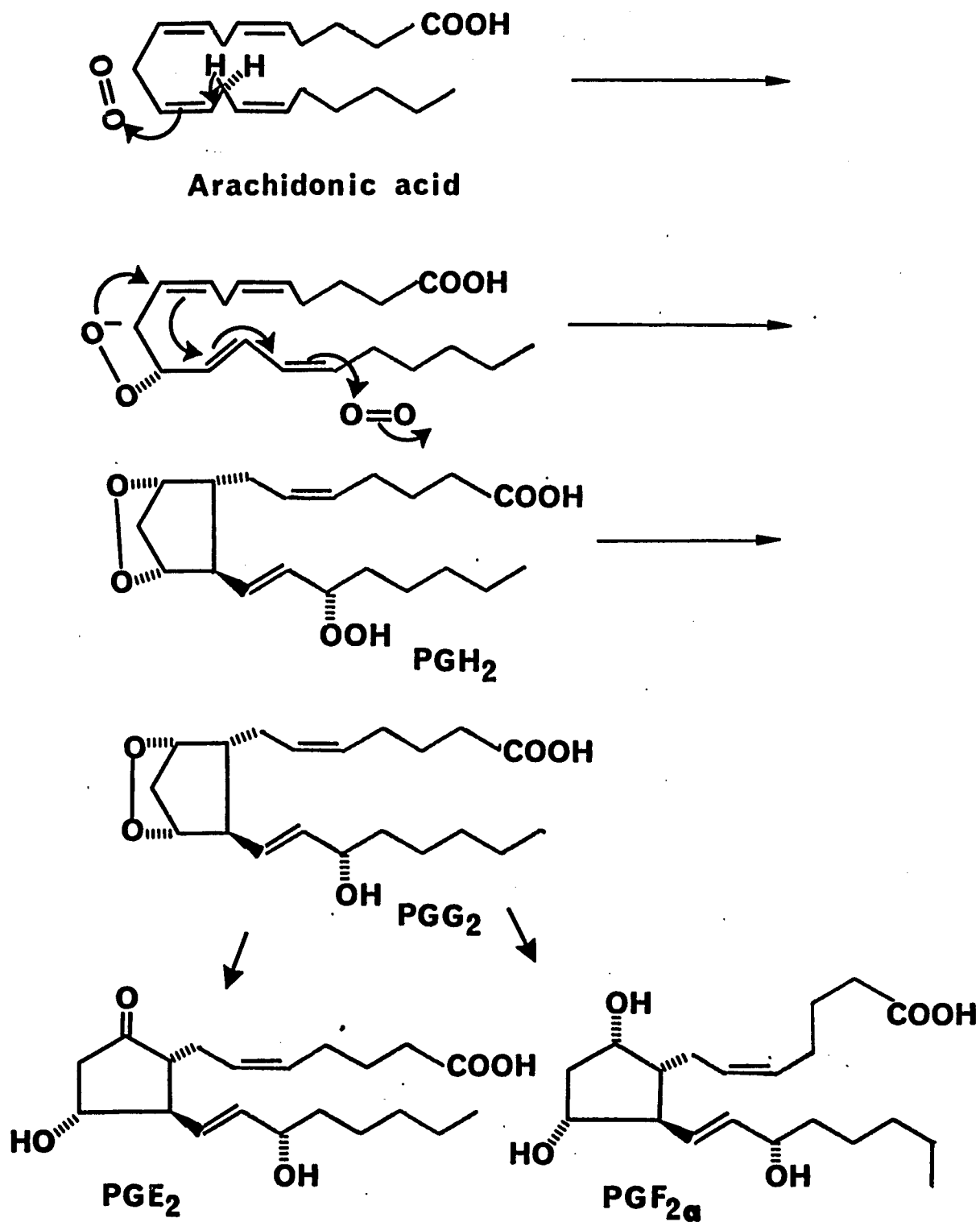
With so much research activity, it was apparent that the small amount of natural material available was insufficient. A large scale effort was mounted to synthesize the natural as well as new prostaglandins, both in an attempt to define and limit the range of biological activities, and also to discover the receptor sites available to these molecules.

Synthetic Approaches

The Early Routes

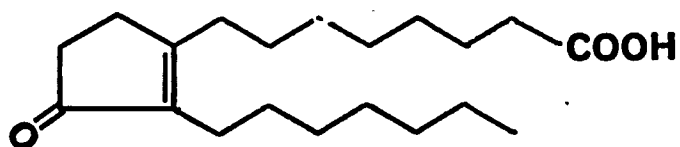
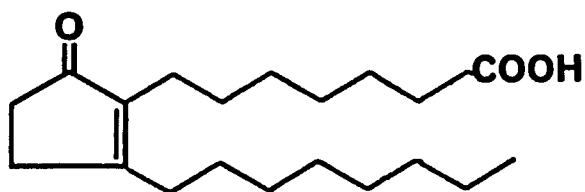
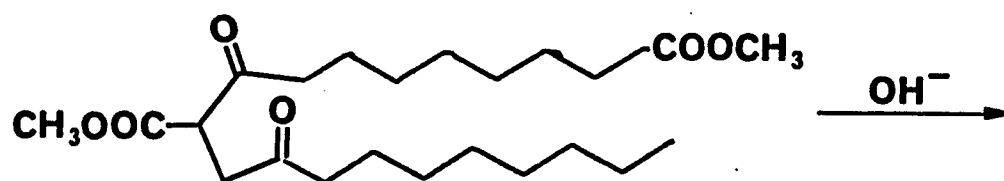
Nature is responsible for the first synthesis of the prostaglandins. This is believed to occur as outlined in Scheme 1, which was first proposed by Bengt Samuelsson [28]. The first laboratory synthesis was not of a prostaglandin, but of a prostanoid used to determine the structure of a degradation product of PGE (Scheme 2) [29]. The first laboratory synthesis of a naturally occurring prostaglandin was accomplished by Jost and Simonovitch at McGill University [30]. However, their synthesis as first reported was very poor in yield and, in fact, could not be repeated by other workers [31]. Later a modified route (Scheme 3) was published, that has been used to synthesize all of the primary and secondary prostaglandins, and many analogs [32-35]. However, this route has never attained the success of some of the other synthetic procedures.

SCHEME 1
The Biosynthesis of the Prostaglandins



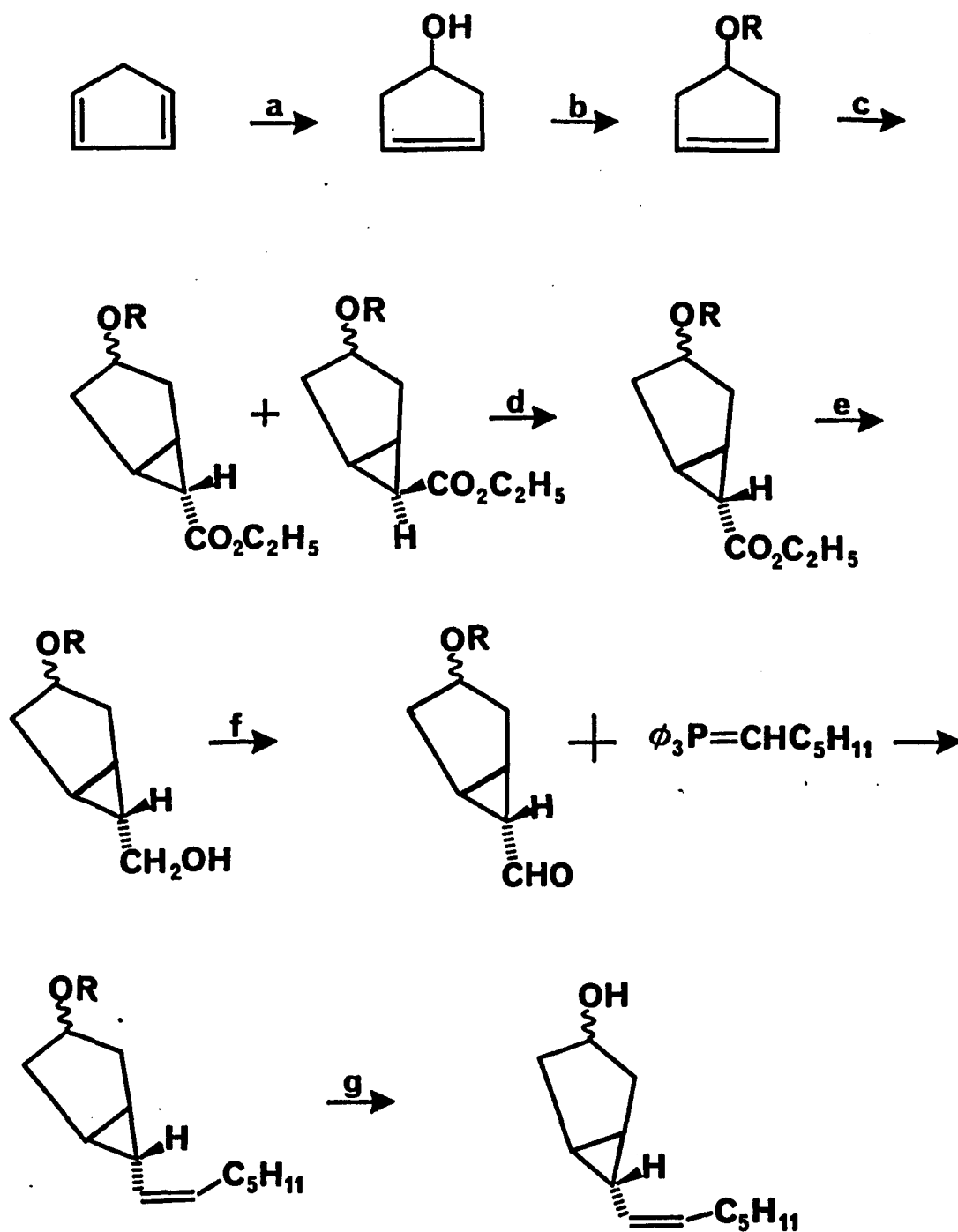
SCHEME 2

The First Synthesis of a Prostaglandin-like Compound



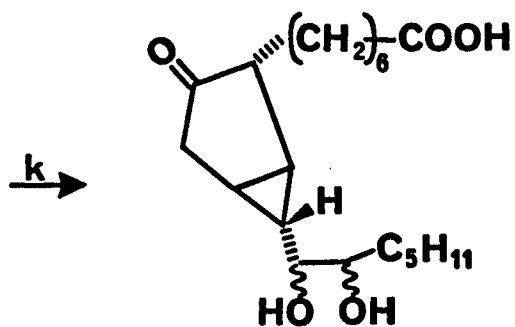
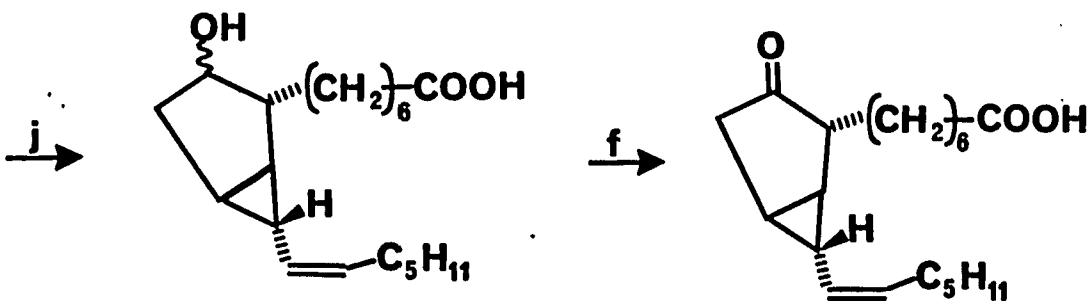
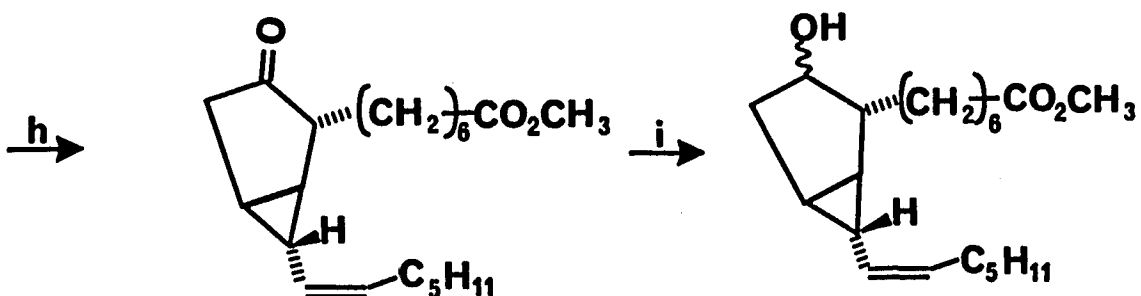
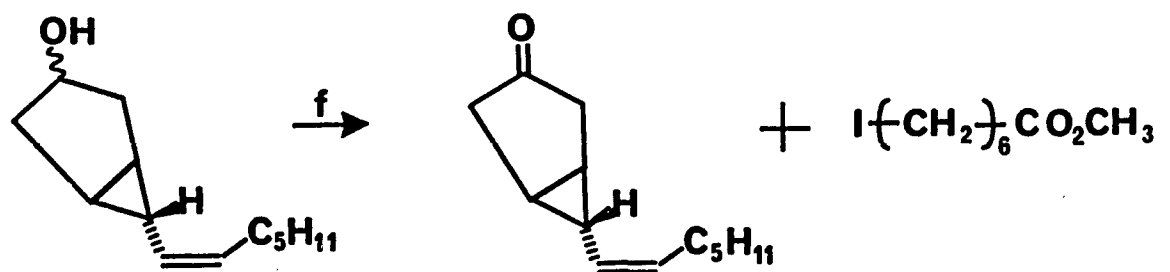
SCHEME 3

The Just Synthesis of the Prostaglandins



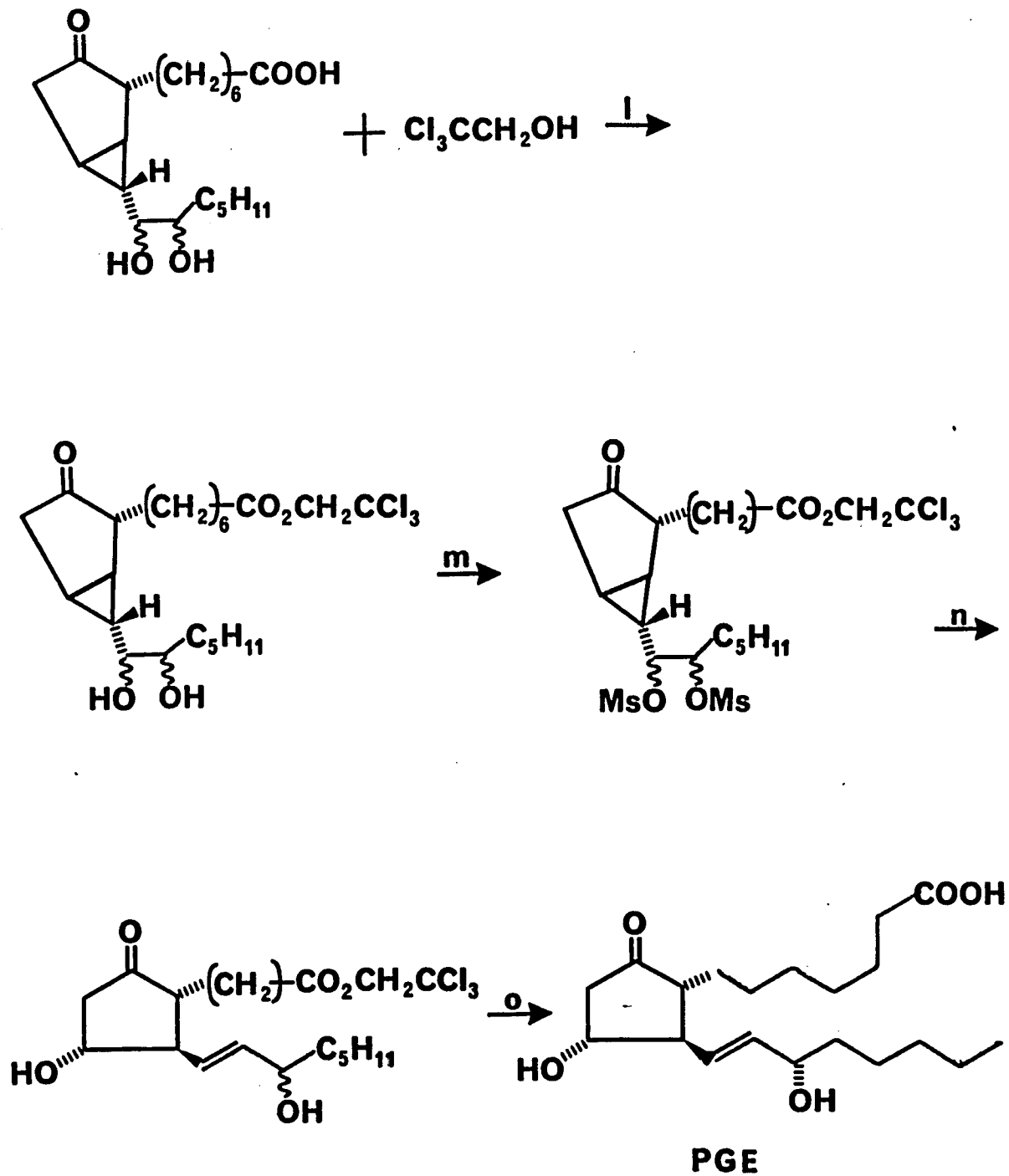
a, B_2H_6 , H_2O_2 ; b, DHP/ $POCl_3$; c, N_2CHCO_2Et , Cu; d, NaOMe, MeOH; e, LAH; f, Jones oxidation; g, $(COCH)_2$, MeOH.

SCHEME 3 (Continued)



h, $t\text{-BuOK}$; i, NaBH_4 ; j, NaOH ; k, HCOOH , H_2O_2 , NaHCO_3 .

SCHEME 3 (Continued)



1, DCC/Py; m, MsCl/Py ; n, $\text{H}_2\text{O/acetone (1:4)}$; o, Zn, HOAc .

The synthesis outlined in Scheme 3 is an example of the bicyclo-[3.1.0] approach, and is illustrative of one of the three main classes of prostaglandin synthetic endeavors. The three are:

1. syntheses in which the cyclopentane ring is formed from acyclic precursors,
2. syntheses in which the cyclopentane ring is already present, and to which the side chains are added, and
3. syntheses in which a bicyclic ring system is formed (usually to introduce more control over the stereochemistry around the cyclopentane ring) and then destroyed.

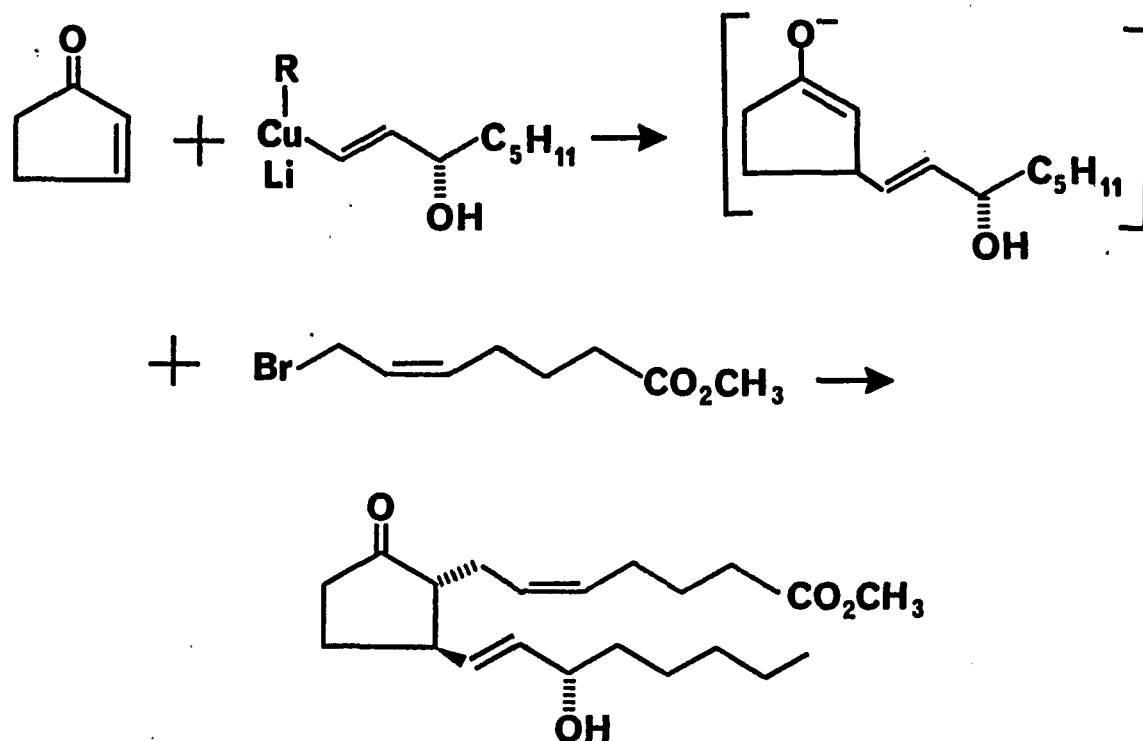
The synthesis of prostaglandins from natural products might seem to constitute a fourth class, but usually the synthesis can be classified under one of the above three types, depending of course on what the starting material is.

The biosynthetic process may be considered to be an example of the first class, which is also represented by the aldol condensation route of Samuelson and Stallberg leading to a prostanoid which was mentioned earlier (Scheme 2).

The second class is illustrated by the cuprate coupling reactions used by many people including Patterson and Fried (Scheme 4), which is a lovely example of the use of a one pot reaction to accomplish two steps, even though it does not work particularly well for the synthesis of prostaglandins [36]. Nowadays, the coupling reactions are normally

done in two steps, and lithiates, alanes, or alanates are also used, although the cuprates tend to dominate [37, 38].

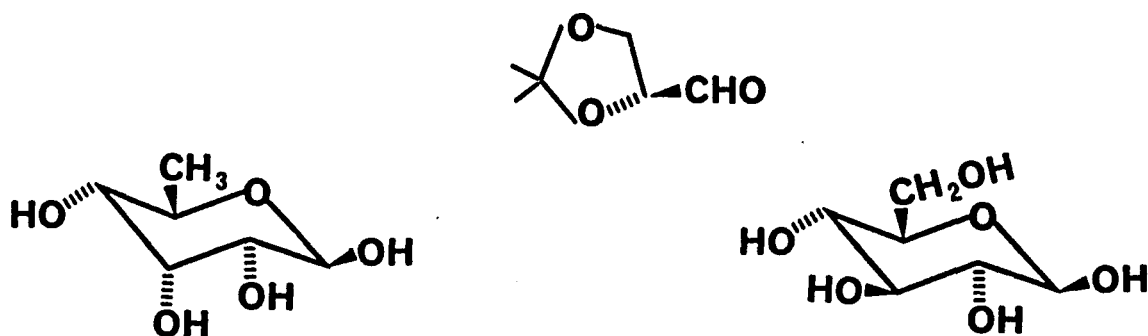
SCHEME 4
The Fried Synthesis



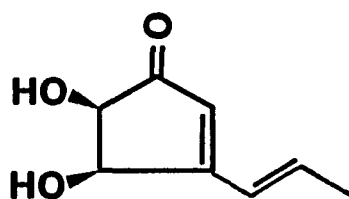
Syntheses from Chiral Starting Materials

Many groups have had the idea of starting prostaglandin syntheses with chiral starting materials, since this obviates the need for a resolution step at some point in the synthesis. Such a step gives a fifty percent yield at best and usually less. Among the best of these are:

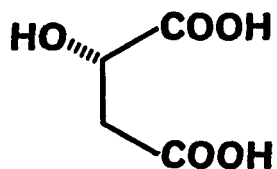
1. the Stork syntheses from rhamncse, glyceraldehyde, or glucose [39, 40, 41],



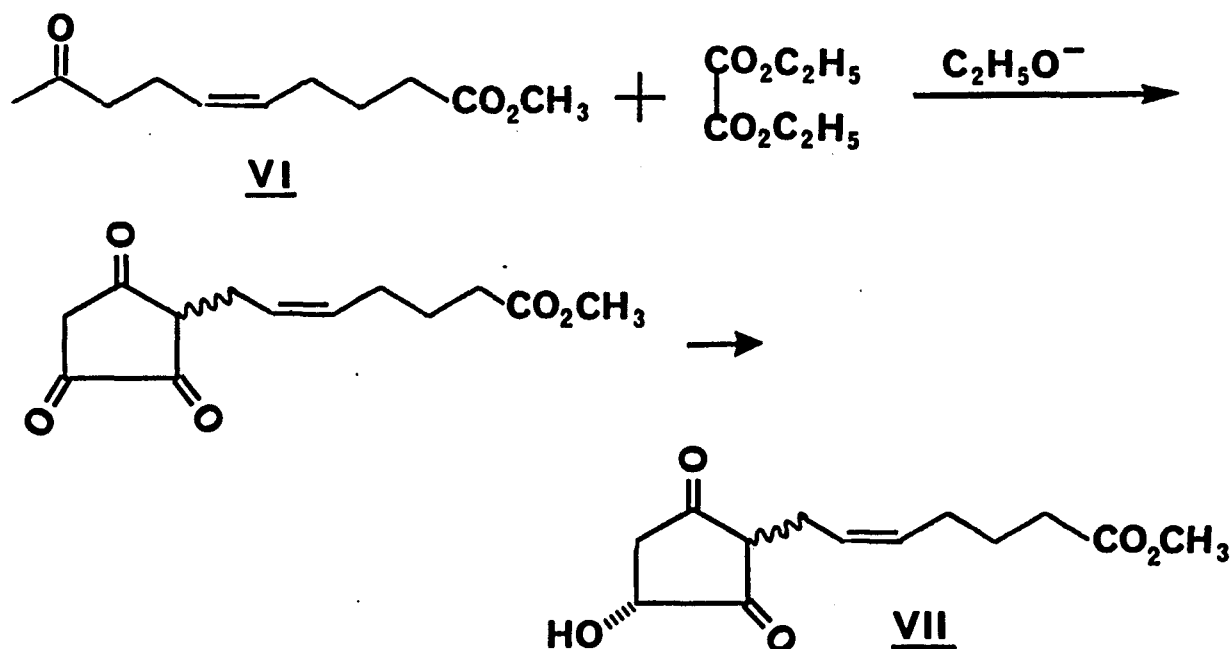
2. the syntheses by Mitscher from terrein [42, 43],



3. the Johnson synthesis from malic acid [44], and



4. microbiological syntheses as exemplified by that of Sih [45].



This last synthesis is included here even though the starting material VI is not chiral. Compound VII is isolated as an optically active material after microbial reduction, and may be considered as the chiral starting material.

Also included here are the syntheses from PGA_2 . In 1969 Weinheimer and Spraggins discovered that a sea coral, Plexaura homomalla, was a source of 15(R)- PGA_2 [46]. Later it was shown that the natural isomer was also present [47]. Both of these are also present as their 15-acetates. Naturally, attempts were made to synthesize the other prostaglandins from these compounds. Also, Crabbé, in particular, utilized PGA's to photochemically synthesize many analogs

[48]. The variety of analogs that can be synthesized from PGA_2 from this source, or indeed any source, is limited, because there is little opportunity for side chain modification without major degradation steps in the synthesis.

Corey's Bicycloheptane Synthesis

The primary routes used today to synthesize prostaglandins are the cuprate synthesis and routes utilizing Corey's bicyclic lactone aldehyde (X) (Figure 1) or its synthetic equivalents. Corey's aim was to produce as many of the prostaglandins as possible from a common resolved intermediate. To this end, he decided that if he could synthesize both $\text{PGF}_{2\alpha}$ and PGE_2 , he could be fairly certain that the other prostaglandins would be synthesizable also. A retrosynthetic analysis of these two compounds led to the two dialdehydes VIII and IX (Figure 1), by a retro Wittig cleavage of the double bonds. Formation of X would serve three functions: differentiation of the two aldehydes, differentiation of the two secondary alcohols (leading eventually to PGE versus PGF), and protection of one of those alcohols. These advantages led to the decision to attempt the synthesis of X . The utility of this scheme was demonstrated by the successful completion of the synthesis of $\text{PGF}_{2\alpha}$ (Scheme 5) [49, 50].

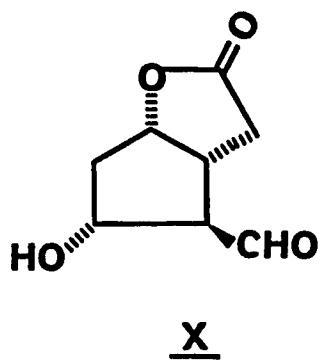
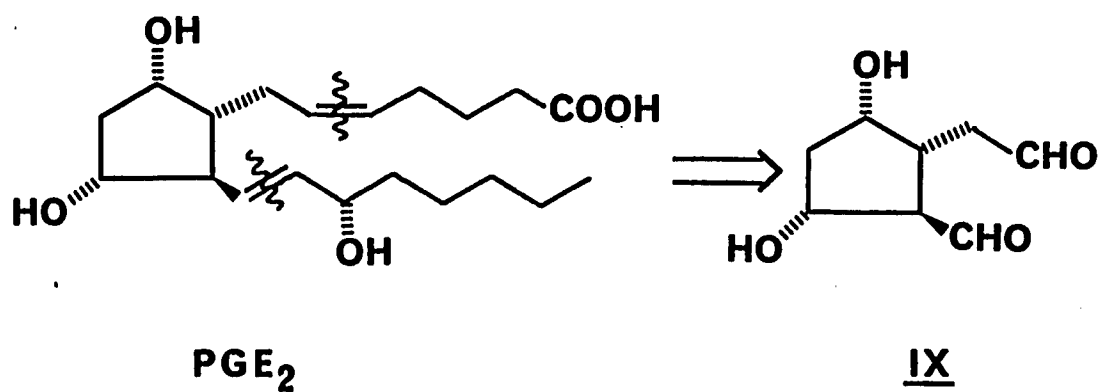
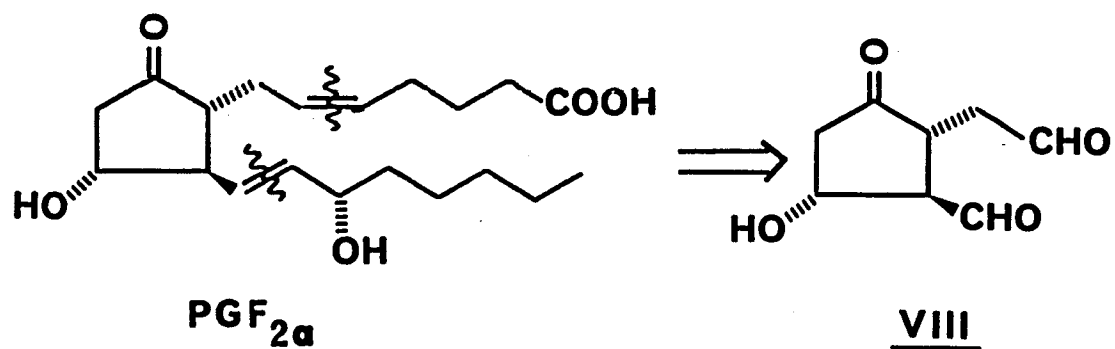
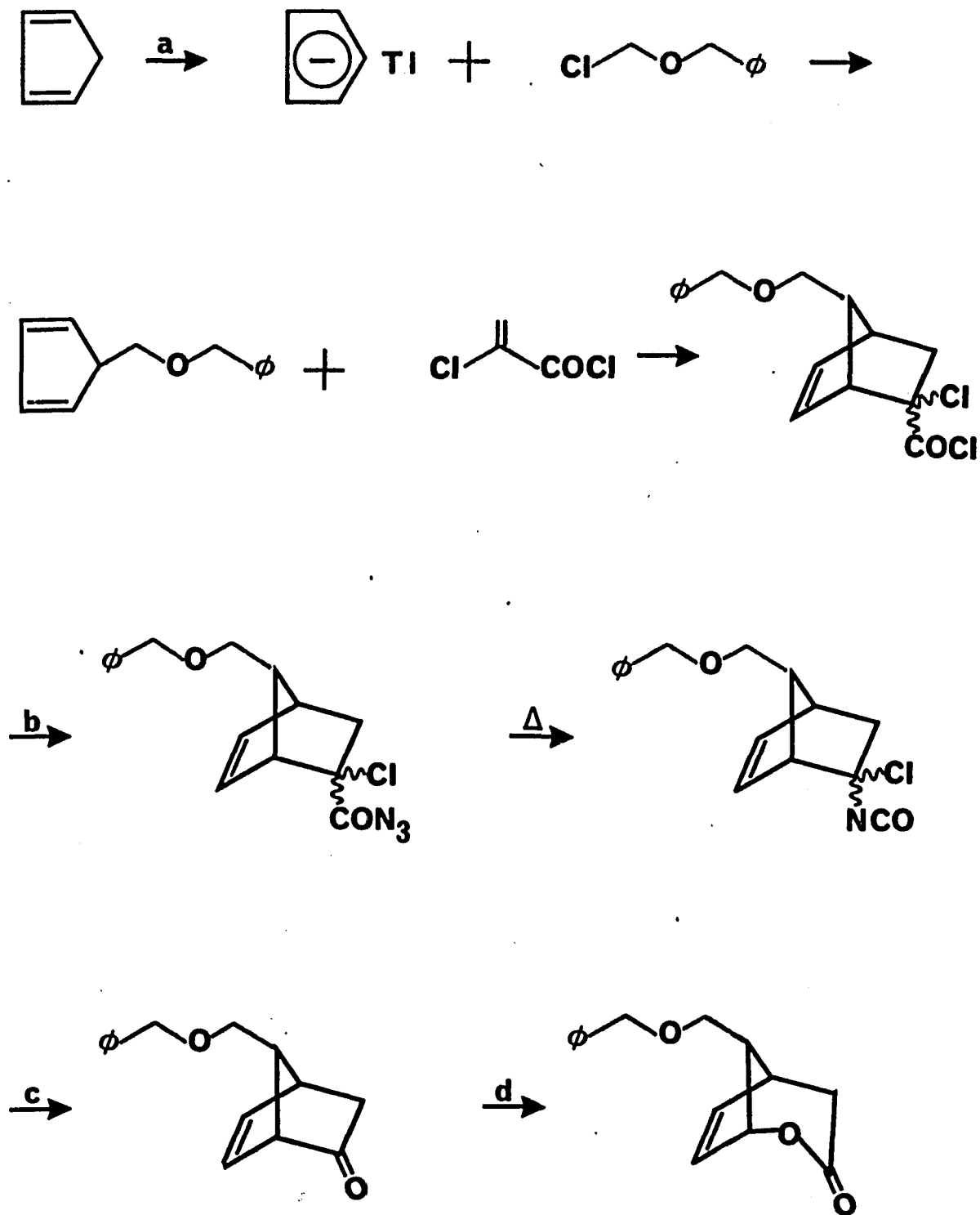


Figure 1: Retrosynthetic Analysis of PGE_2 and $\text{PGF}_{2\alpha}$

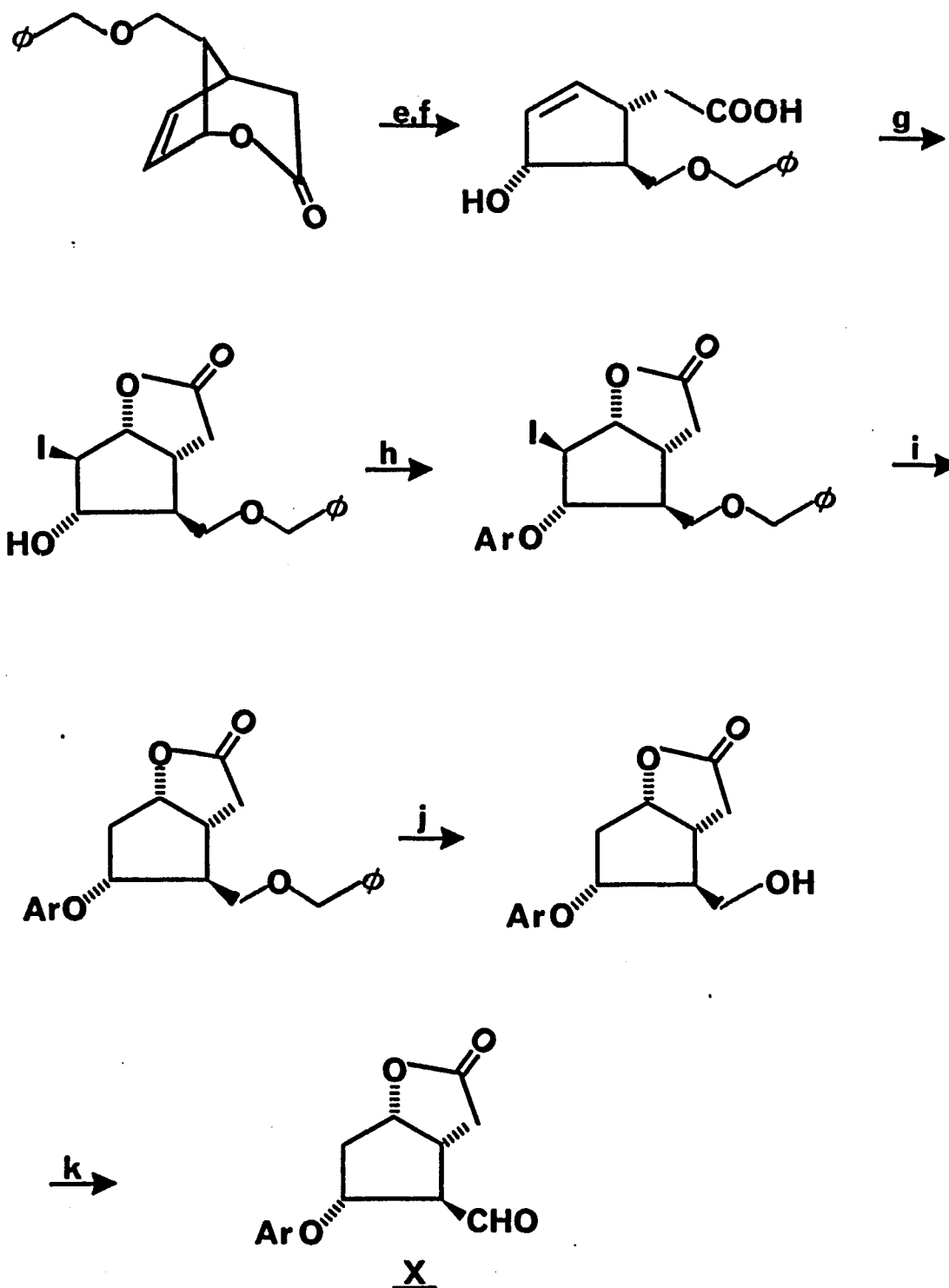
SCHEME 5

Corey's Bicycloheptane Synthesis of Prostaglandins



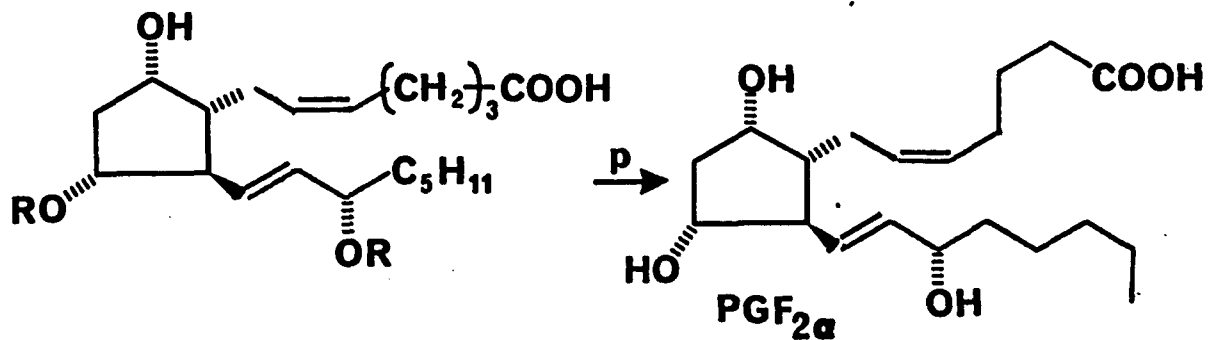
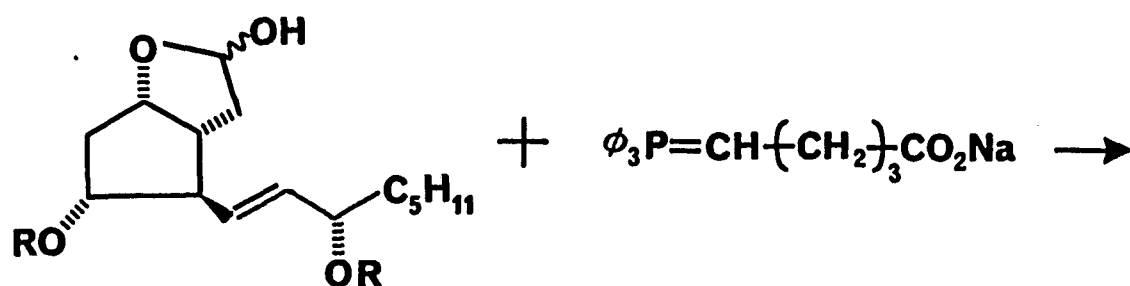
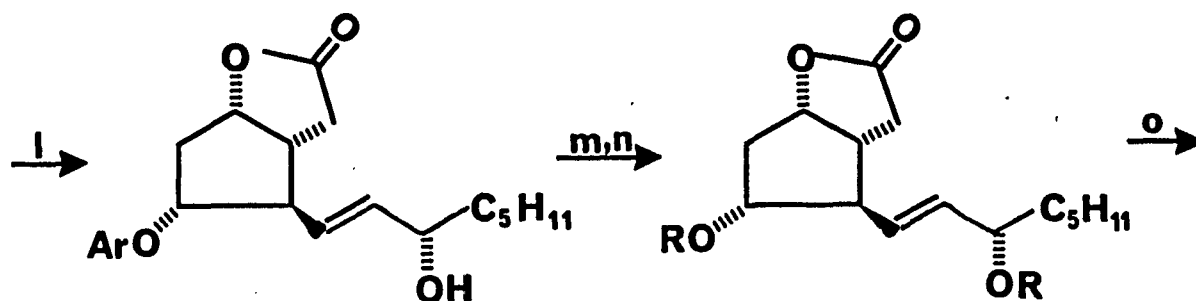
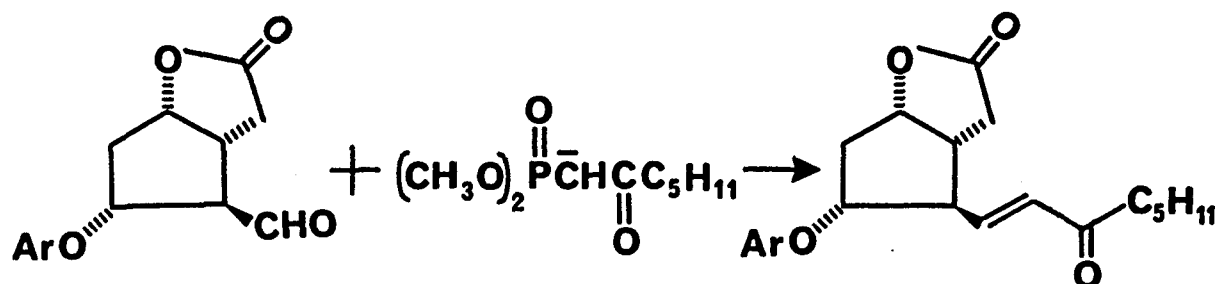
a, Tl_2SO_4 , KOH ; b, NaN_3 ; c, $\text{H}_2\text{O}/\text{HOAc}$; d, $m\text{-CPBA}$, NaHCO_3 .

SCHEME 5 (Continued)



e, NaOH; f, CO₂; g, KI₃; h, ArCOCl/Py; i, n-Bu₃SnCl or, NaBH₄; j, H₂, 5% Pd/C; k, Collins oxidation.

SCHEME 5 (Continued)

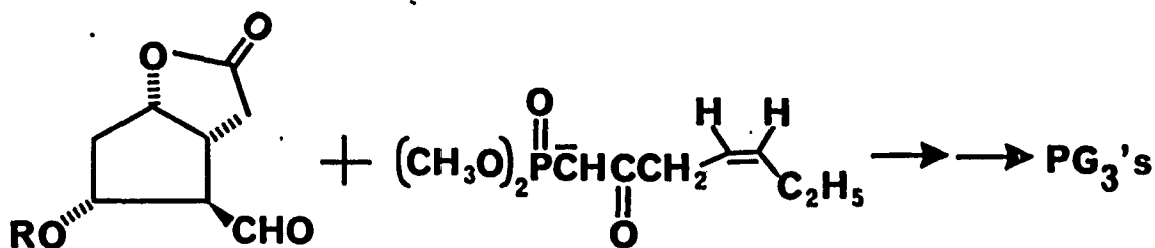
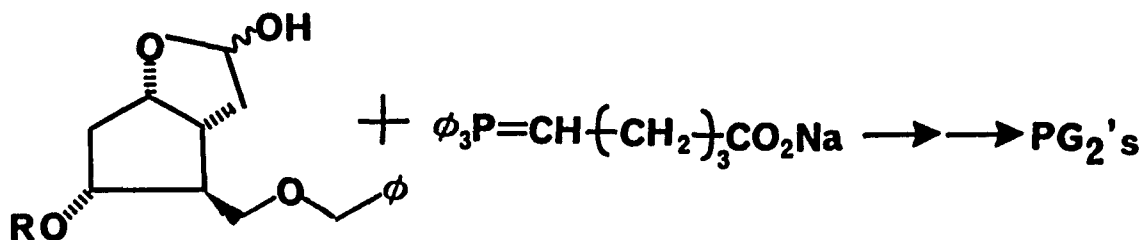
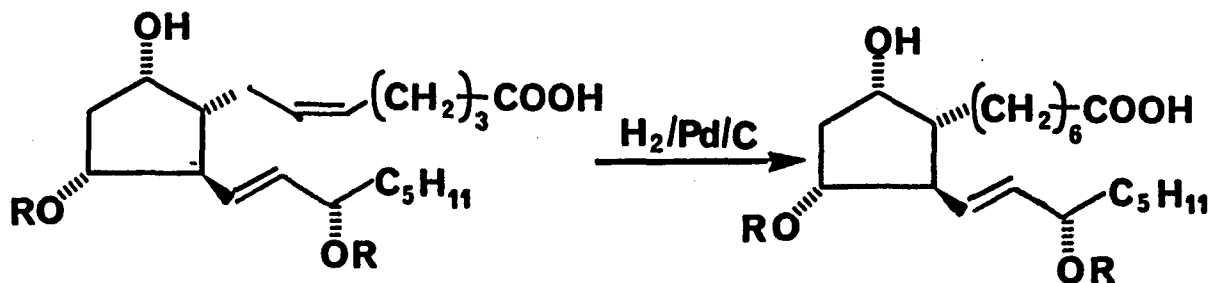


1, LiBR_3H ; m, K_2CO_3 , MeOH; n, DHP/TSOH; o, Dibal; p, $\text{H}_2\text{O}/\text{HOAc}$ (2:1).

Though various improvements have been made to this route by Corey and others, the original Corey synthesis is still considered a beautiful example of elegant synthetic organic work. In the original synthesis, sodium instead of thallium was used as the metal salt in the first step. Thallium gives better yields, since there are fewer side reactions in the work-up, but it does have its own problems, namely toxicity. Also, Corey originally used the chloromethyl methyl ether to create the methyl protected alcohol in the second step, but found complications in the hydrolysis of the methyl ether later in the scheme. Ketene equivalents other than 2-chloroacrylyl chloride have also been used in the Diels-Alder reaction in step three. Furthermore, Corey developed many different oxidation procedures for the conversion of a primary alcohol to an aldehyde. He developed other C-11 protecting groups to aid in the later asymmetric reduction of the conjugated ketone to the correct 15S allylic alcohol. Separation of the optical isomers was achieved in about 65% yield (33% of the total material) at the free acid stage.

All of the members of the PGE and PGF families, as well as members of the A, B, C, D, and I families have been synthesized by this route, or minor modifications of it. There was a complication which arose in the synthesis of members of the "1" series, in that it was necessary to selectively hydrogenate one double bond (the 5,6 cis) in the presence of

another (the 13,14 trans). This situation occurs because of the order in which the side chains were added, and was solved by Corey by putting bulky protecting groups on the C-11 and C-15 hydroxyls and depending on steric hindrance to



protect the 13,14 double bond [51]. Another scheme (and one more personally pleasing) to overcome this problem is to reverse the order of attachment of the side chains, but this route often exhibits lower yields. Synthesis of members of the "3" series is more straightforward. Today this route, or one of its many variations leading to the same key intermediate, lactone aldehyde **X** (Scheme 5 and Figure 1), account

for well over three-fourths of the prostaglandin analog syntheses reported in the literature.

Other Approaches to Corey's Aldehyde

Today, it is unexceptional to see a synthesis leading to Corey's aldehyde lactone (or its synthetic equivalent) accepted as a synthesis of all of the prostaglandins themselves. As can be seen from Figure 2, a great variety of compounds has been utilized as starting materials for the synthesis of Corey's aldehyde [52].

Some of the syntheses starting from these compounds used elements of other synthetic routes in arriving at their goal, and some attached the upper or α -chain before exposing the aldehyde for the connection of the lower or ω -chain. This would appear to be the preferred route, as it is much easier to synthesize members of the "1" series by this route, although as was just mentioned, this order often exhibits a reduced yield with respect to the inverted order, particularly in the syntheses of the natural prostaglandins.

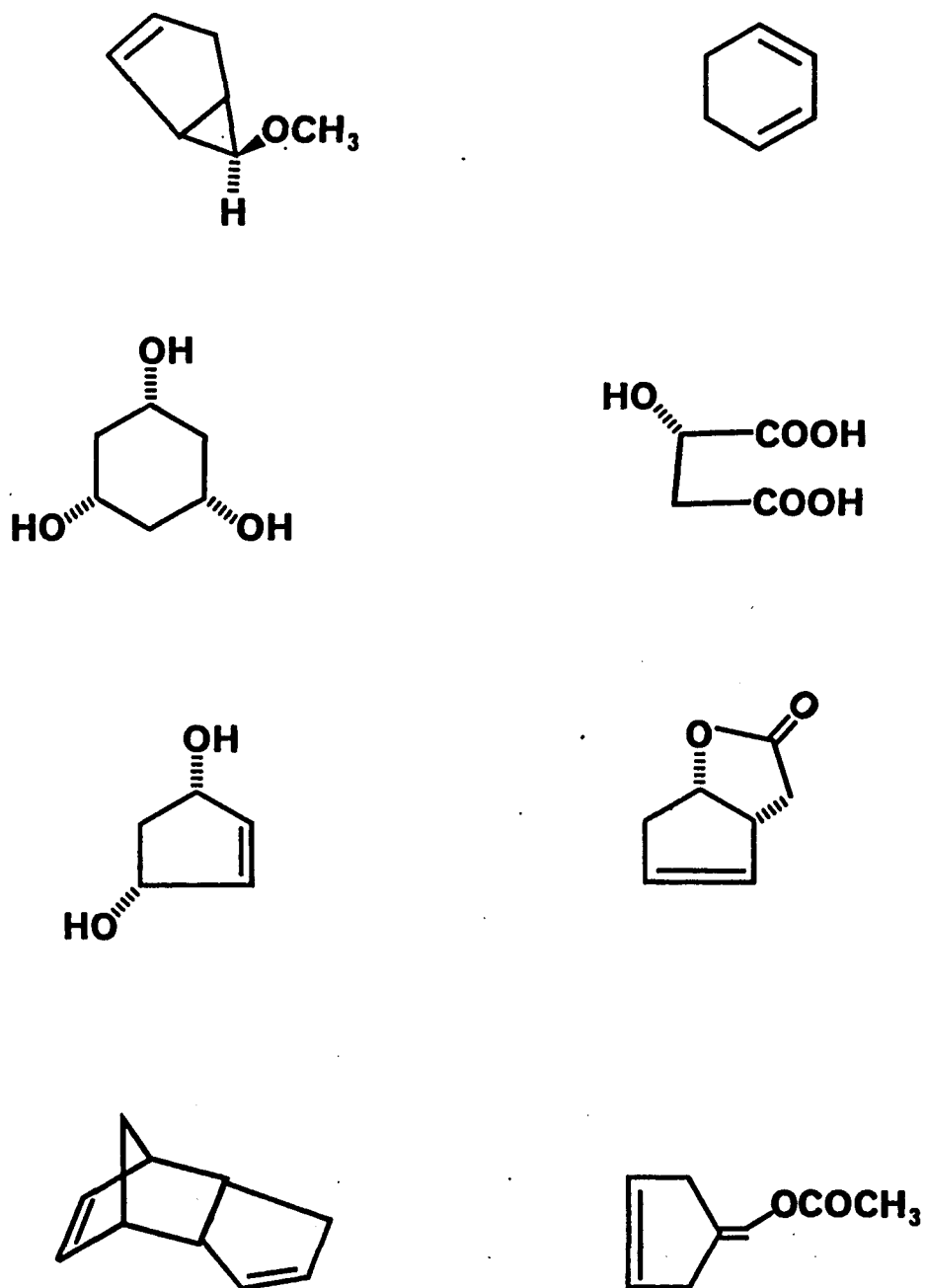


Figure 2: Compounds Used as Precursors to Corey's Aldehyde

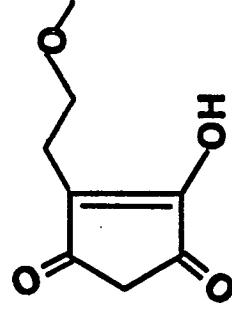
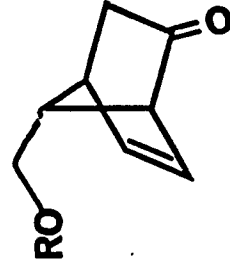
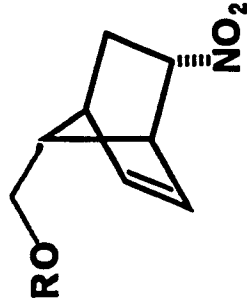
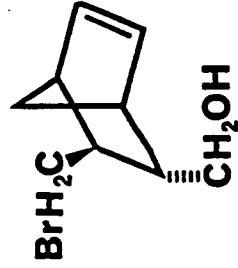
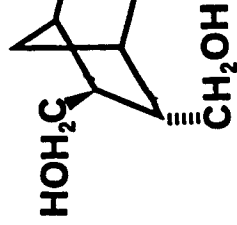
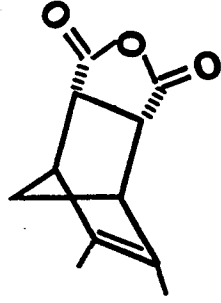
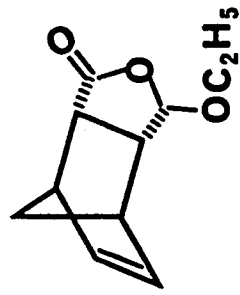
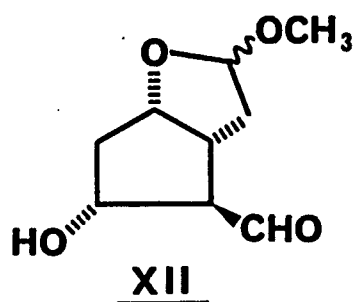
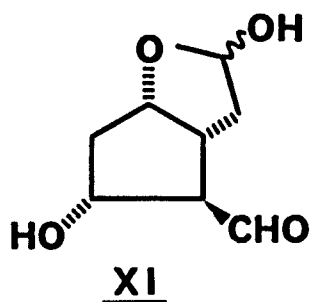


Figure 2 (Continued)

It should be emphasized that all but one route clearly differentiate at some point between the oxidation levels of carbons 6 and 13. The one exception, the Turner synthesis developed at Ccleran-Ricketts, uses the dialdehyde X itself (Figure 1) [53]. However, even here, the upper aldehyde exists preferentially in a hemiacetal form XI, and yields on the phosphonate reaction were much increased by protecting XI as the methyl acetal XII.



It can be seen that all of these routes lead to cyclopentane rings that are devoid of further ornamentation. In most cases, this is because the attempt was to synthesize the natural prostaglandins, or at most to make modifications only in the side chains. It can also be shown that substitution on the ring can sometimes be difficult to do, or even detrimental to the synthetic route. There exists therefore, a need for a readily available chiral material having two distinguishable aldehydic groups and other substituents correctly arranged around a cyclopentane ring.

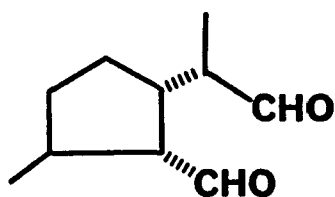
The iridoids would seem to be, not a compound, but a class of compounds, each of which meets these requirements, and which therefore, would allow the synthesis of analogs having a variety of substituents around the cyclopentane ring, while still allowing facile substitution in the side chains.

THE IRIDOIDS

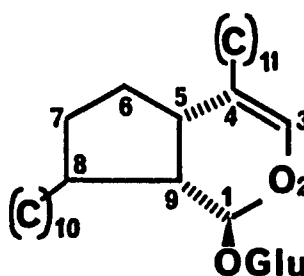
History and Structure

The iridoids were first recognized as a class of compounds in 1952 by Trim and Hill [54]. The structures of the individual members were deduced by many groups at different times. They are now recognized as being related to the compound iridodial. All the members of this class have a cy-

Glu = Glucose



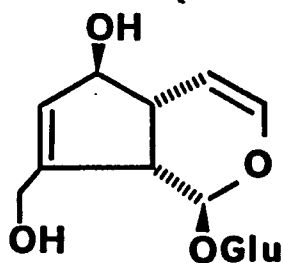
Iridodial



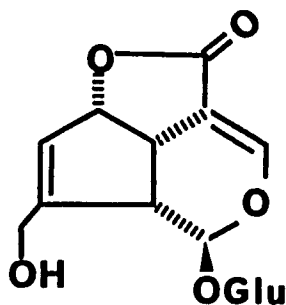
iridoid structure

clopentanopyran ring system numbered as shown, with the double bond between C-3 and C-4 giving rise to the characteristic enol ether system, and most are β -glucosides. Approximately one half of the iridoids have a carboxyl func-

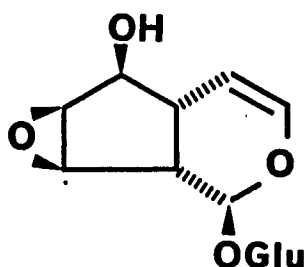
tion of some scit at C-11, and most have a carbon appendage at C-8. Otherwise, there is a variety of substitution (usually oxygenic in nature) around the cyclopentane ring. Over 40 members of this class of compounds are known. Since the last one discovered was reported in 1980, it is expected that others will be isolated.



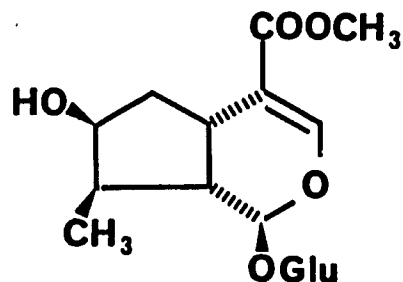
Aucubin



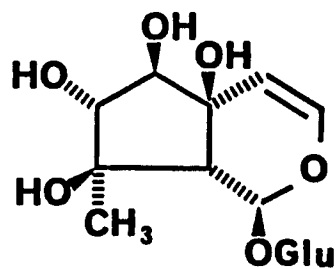
Asperulcside



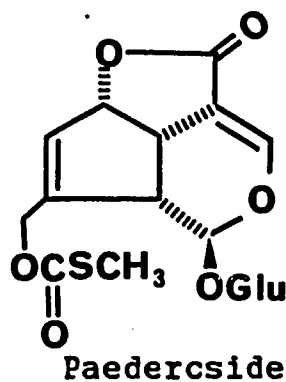
Unedoside



Loganin



Procumbide

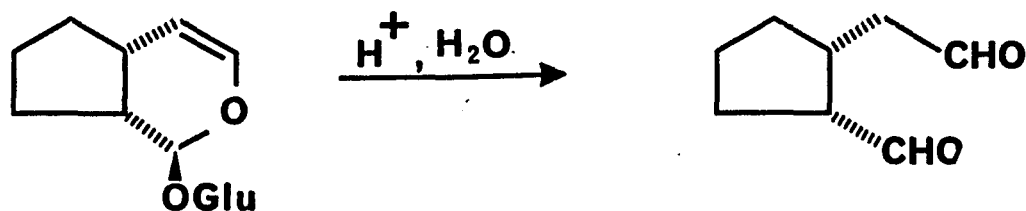


Paedericside

Figure 3: Structures of Representative Iridoids.

Relationship of the Iridoids to Corey's Aldehyde

As can be seen, hydrolysis of the enol ether and of the gly-



cosidic linkage of an iridoid would be expected to give a dialdehyde. However, it is not easy to produce this dialdehyde from the iridoids. Indeed, their overwhelming characteristic is their instability towards acids, leading to blue-black polymeric tars. This also forms the basis of a color test for the presence of iridoids in plant extracts, as well as giving rise to colored spots on thin layer chromatographic plates when they are developed with an acid spray. Enzymatic hydrolysis has occasionally led to the free aglucones, but these are exceptionally unstable except in a few instances. Fortunately, removal of the enol ether double bond confers stability on the free aglucone.

Aucubin

Aucubin (Figure 3) is a fairly representative member of the iridoid family. With respect to the natural prostaglandins it has the wrong configuration at C-6 and C-9, but this is not worrisome since C-6 can be easily inverted and C-9 can be readily epimerized when a free aldehyde is present at C-1.

Aucubin (also known as aucuboside and rhinanthin) was first isolated in 1856 by Ludwig [55, 56], and rediscovered in 1902 by Bcurquelot and Hérissé who named it aucubin [57-59]. It has since been found in many plants, and often constitutes as much as one percent or more by weight of the fresh green plant material, although this is dependent upon the time of the year in which the plants are harvested.

Three major groups were involved in the structure determination of aucubin: Fujise in Japan, Birch in England, and Schmid in Switzerland. Unfortunately, a key reaction, the bromination, (Figure 4) was at first misinterpreted, and several incorrect structures for aucubin were proposed before the correct structure was determined by Fujise [60]. All three groups quickly agreed on this structure, and on its stereochemistry.

Both aucubin and the prostaglandins have the same absolute configuration [61]. That is, the configuration around C-5 of aucubin is the same as that around C-8 of the prostaglandins. Therefore, aucubin seems an ideal candidate for

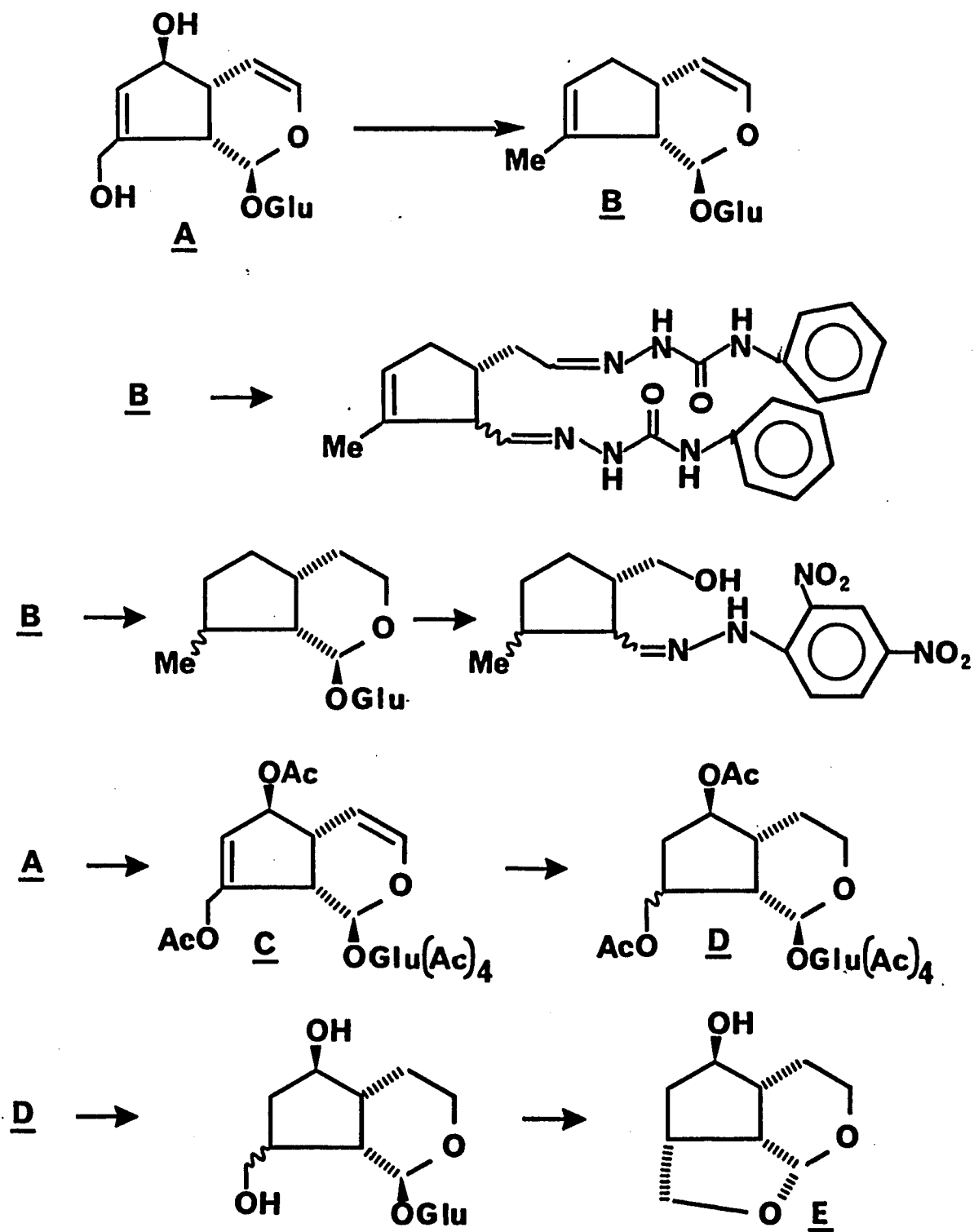
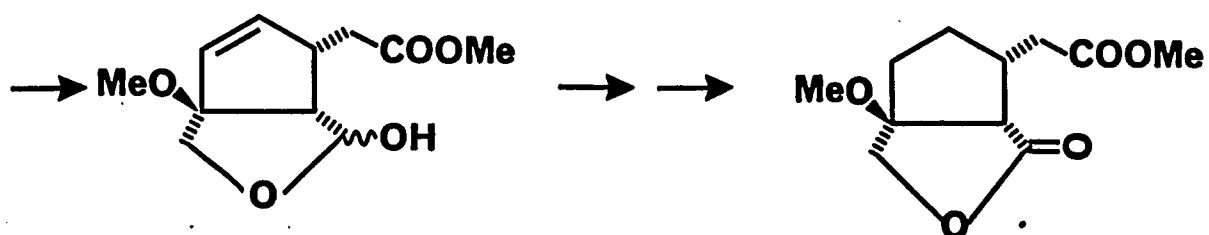
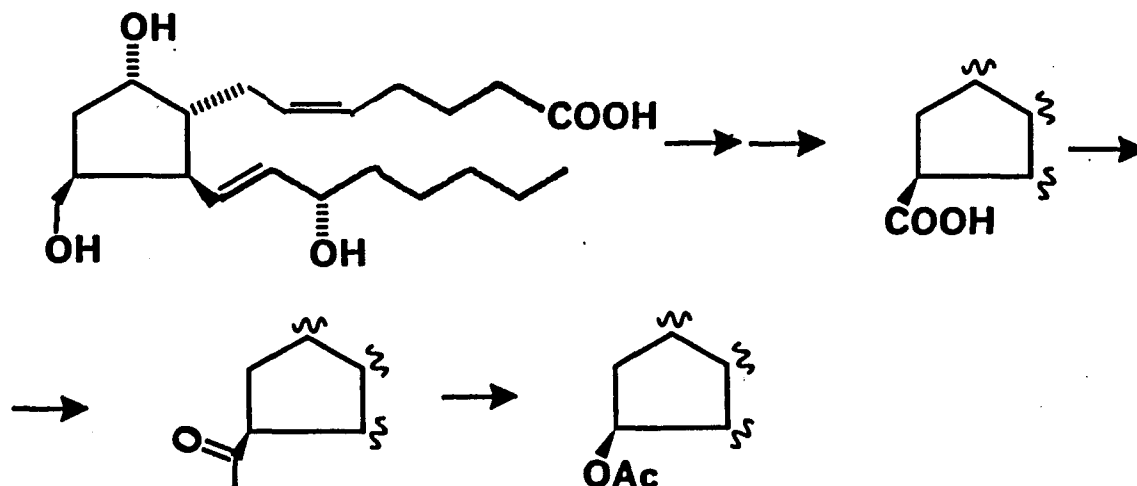


Figure 4: Reactions Used in the Structure Determination of Aucubin.



conversion to prostancids having an 11-hydroxymethyl substituent, which have been synthesized by other means [62, 63], or to the prostaglandins themselves by a simple chemical conversion.

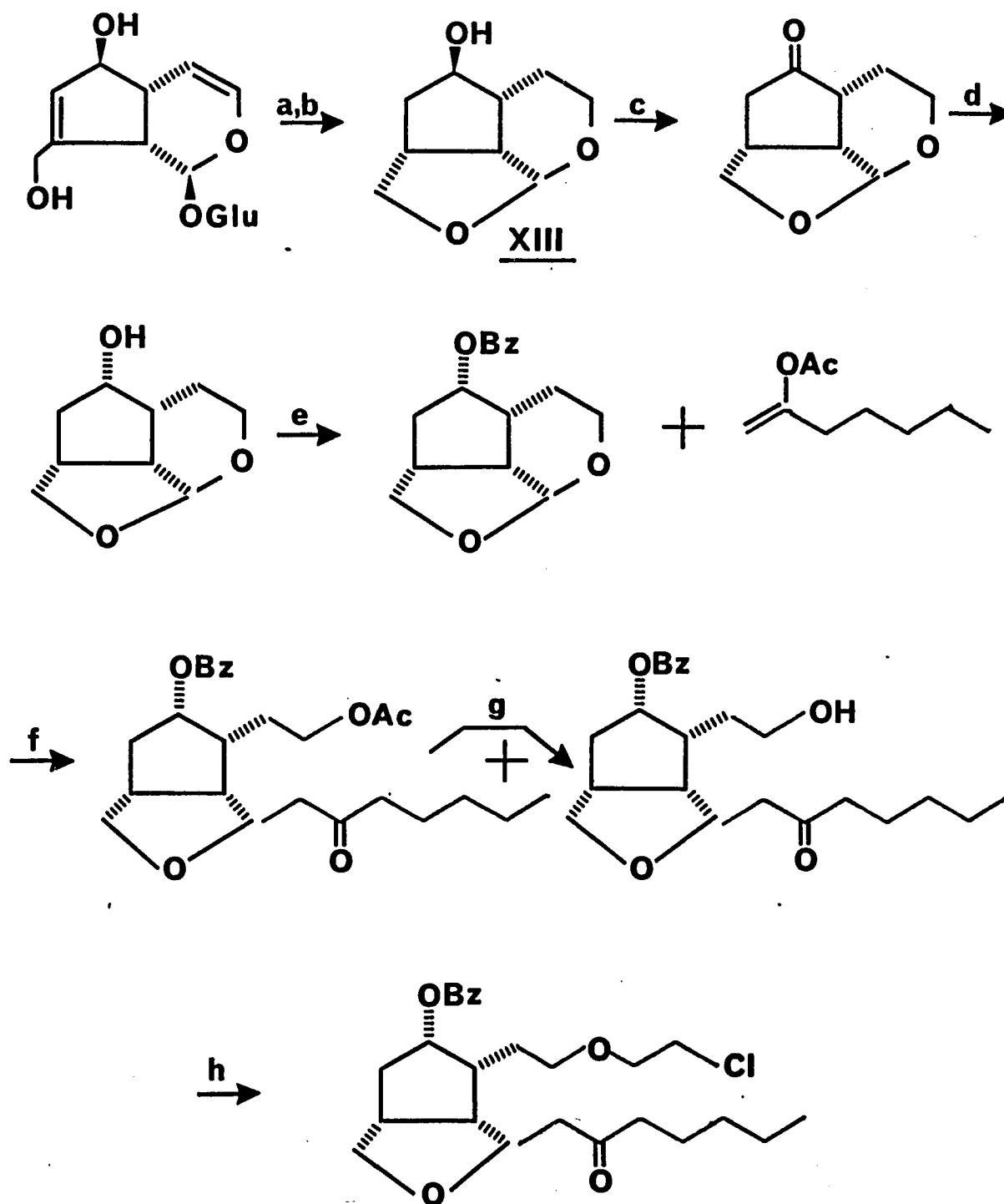


The Work of Ohno

While this dissertation was in progress, several papers were published by Ohno, in which this idea was realized [64-67]. His route (Scheme 6) differs slightly from our proposed synthesis (Scheme 8) and considerably from our actual synthesis. One of the major drawbacks to this synthesis is found at the very beginning. In none of Ohno's papers does he give a yield for the hydrogenation reaction leading to the α -hydroxymethyl epimer. Indeed, I have not seen a definite yield for this epimer in any paper on aucubin. However, this yield has been reported to be much less than that of the other (β) isomer, which has not previously been isolated in greater than a 50% yield [68, 69].

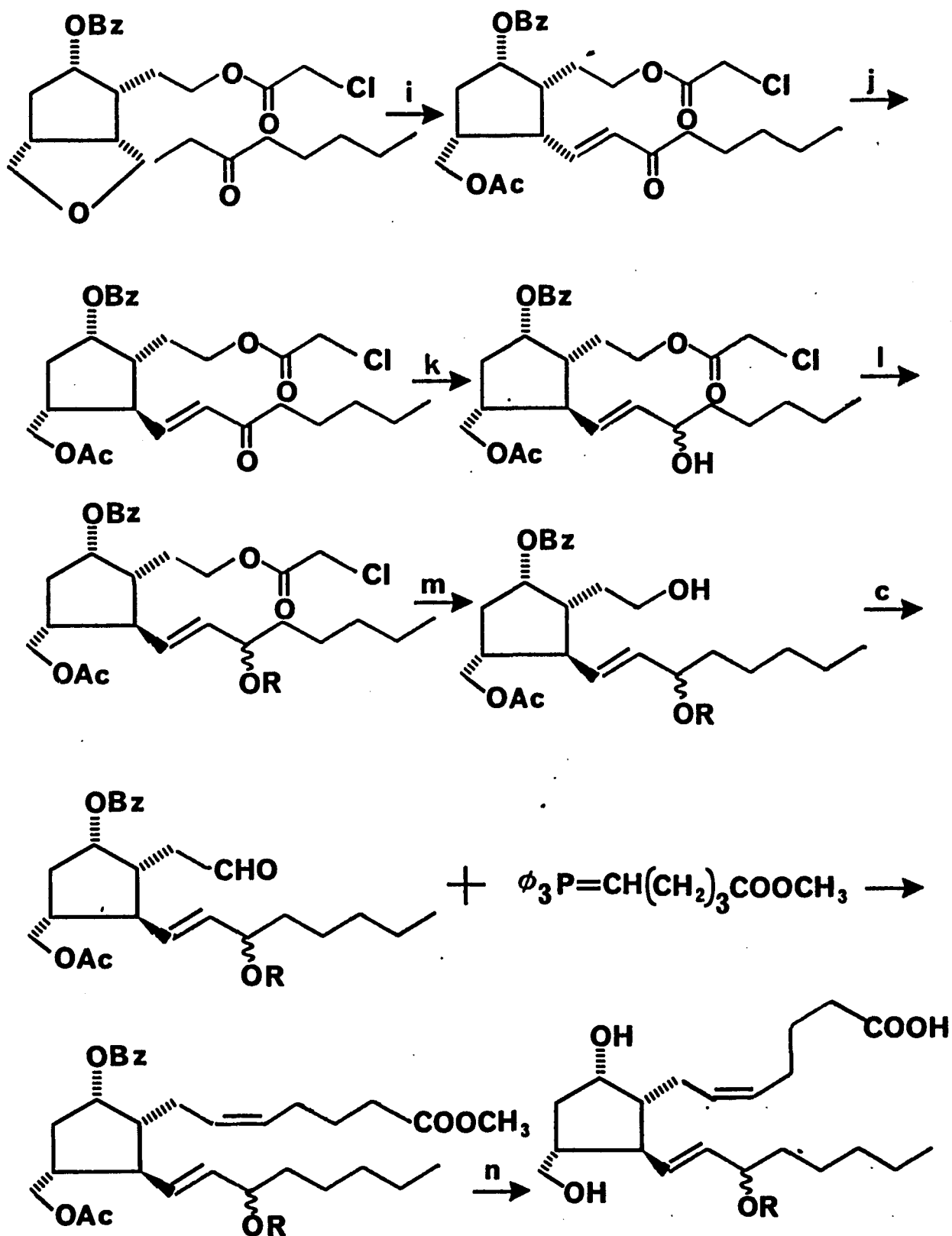
SCHEME 6

Ohno's Synthesis of Prostaglandins from Aucubin



a, H₂; b, H₃PO₄; c, Collins oxidation; d, LAH; e, Benzoyl chloride/Py; f, TiCl₄; g, TFA/MEOH; h, Chloroacetyl chloride/Py.

SCHEME 6 (Continued)



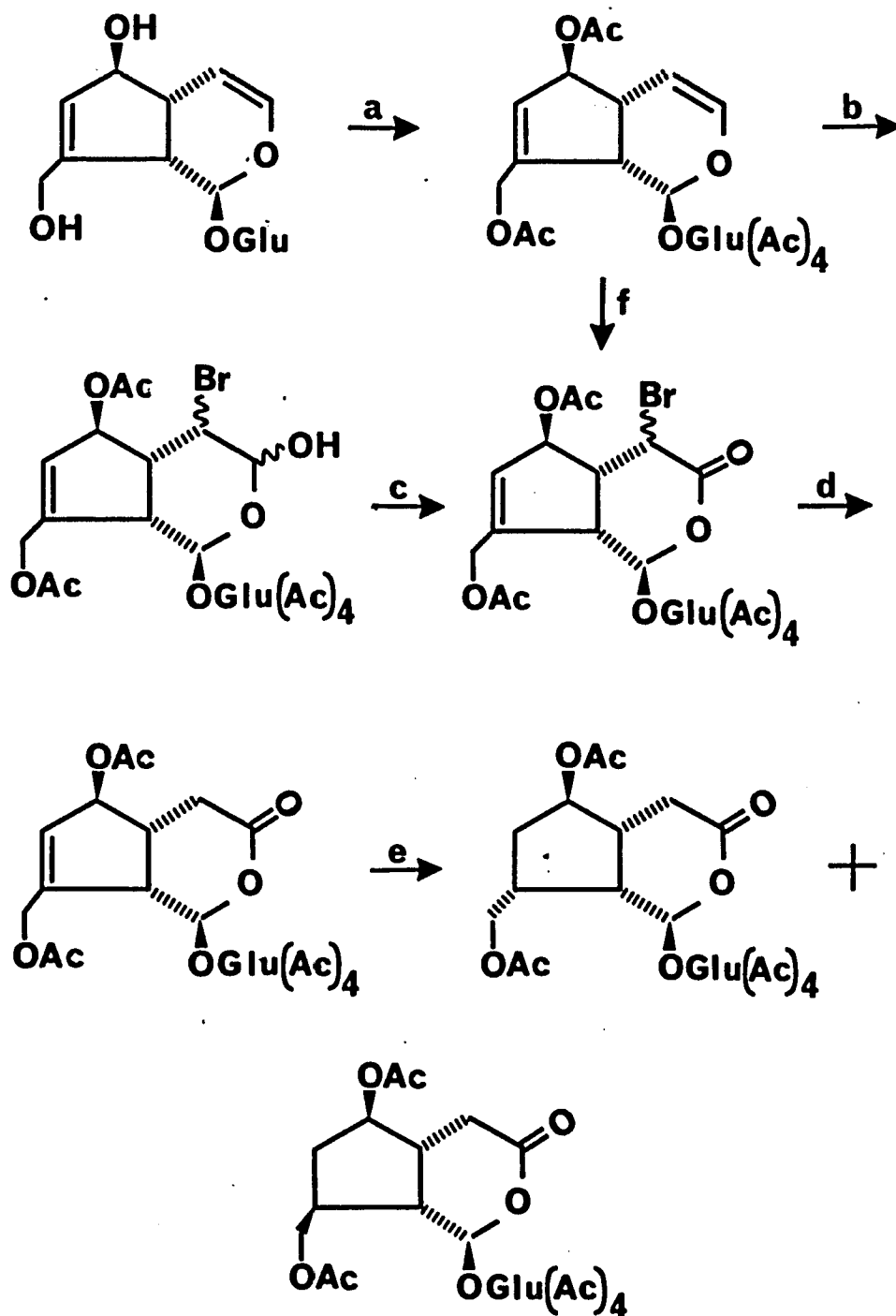
i, TSOH/Acetic anhydride; j, TSOH/Acetic acid; k, ZnBH_4 ; l, DHP/TSOH; m, Thiourea/ NaHCO_3 /EtOH; n, K_2CO_3 /MeOH.

The Work of Berkowitz

A conceptually much different route had earlier been attempted in this laboratory [70]. This synthesis (Scheme 7) was based on the bromination reaction which misled Karrer and Schmid. As mentioned earlier (page 32), it is necessary to remove the enol ether double bond before any attempt is made to hydrolyze the glycosidic linkage. This was accomplished by formation of the bromohydrin. After oxidation of the hemiacetal hydroxyl and removal of the bromine, the remaining double bond was hydrogenated. Unfortunately this led to a mixture of compounds. Under most conditions these mixtures contained large amounts of deacetylated material, since hydrocyclysis of the allylic esters (or of the unprotected alcohols) occurs very readily. Of course, there are also two stereoisomers formed, since the hydrogen can attack from either side of the five membered ring placing the acetoxymethyl group either up or down (Scheme 7). Eventually it was found that use of rhodium on carbon (5% Rh/C) as catalyst gave the least amount of hydrogenolysis, and that ethyl acetate was the preferred solvent, in that it gave an excess of one isomer. Unfortunately, this was the isomer with the wrong configuration at C-11 relative to the natural prostaglandins.

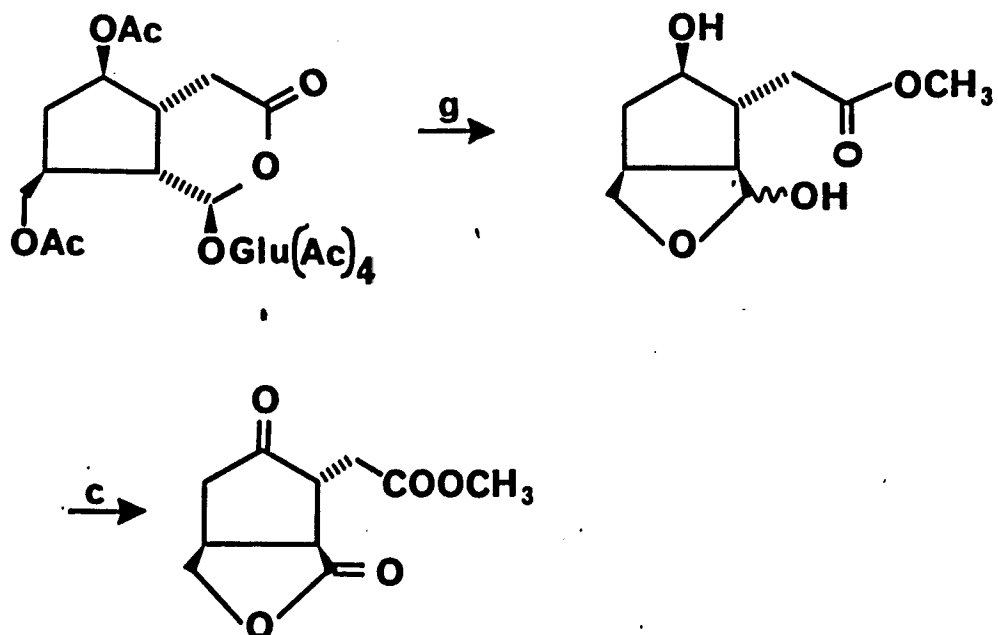
SCHHEME 7

The Oxidative Route from Aucubin to Prestanoids



a, Acetic anhydride/Py; b, NBS/H₂O/DMSO; c, Jones oxidation;
d, Zn/Acetic acid; e, H₂/Rh/C/EtOAc; f, NBS/dry DMSO.

SCHEME 7 (Continued)



g, MeOH/K₂CO₃.

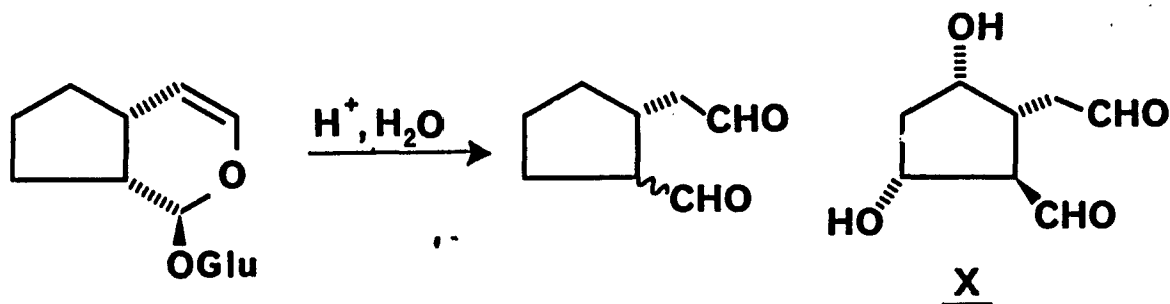
STATEMENT OF THE PROBLEM

The prostaglandins represent a two-fold challenge. They are structurally difficult to synthesize, and they are biologically very active (page 8). As a result, chemists have synthesized not only the natural forms, but also a variety of analogs. The analogs have been synthesized with two main purposes in mind: first to create a more stable molecule, and second to create a separation of the effects of the natural prostaglandins.

In these aims, chemists have been greatly aided by the synthesis of the Corey lactone aldehyde X. From this common intermediate it is very easy to create a virtually unlimited array of analogs having varied side chains. Of course, only the side chains are easily varied. An inherent waste of material is also evident if achiral starting materials are used. This second problem can be overcome by the use of chiral compounds as starting materials (typically natural products), but the first problem has received scant attention.

The iridoids have certain very noticeable advantages as precursors to the prostaglandins. First, they have many different groups already present on the cyclopentane ring. These may be useful in themselves as possible analog substituents, or they may be modified to other perhaps more desirable entities. Then, as noted before (page 32), hydrolysis of the iridoids leads directly to a dialdehyde similar

to X, which can be elaborated to give any desired side chain.



Of course, unless duplicate side chains are desired, it will be necessary to protect one of these aldehydes. This is probably most readily done before hydrolysis due to the instability of the free aglucones of the iridoids (page 32). As just noted in the preceding section, one way to accomplish this differentiation (with concurrent stabilization of the aglucone) is through oxidation of the enol ether double bond. There is, however, another way to remove the enol ether double bond -- hydrogenation. This too differentiates between the two latent aldehydic groups, and also confers stability upon the free aglucone. Indeed, most of the structure determination work for aucubin was done on tetrahydroaucubin and its derivatives (Figure 4). Unfortunately, the conditions for hydrogenating aucubin as reported by Karrer and Schmid [68] or Fujise [69], did not lead to a very high yield of tetrahydroaucubin having the correct stereo-

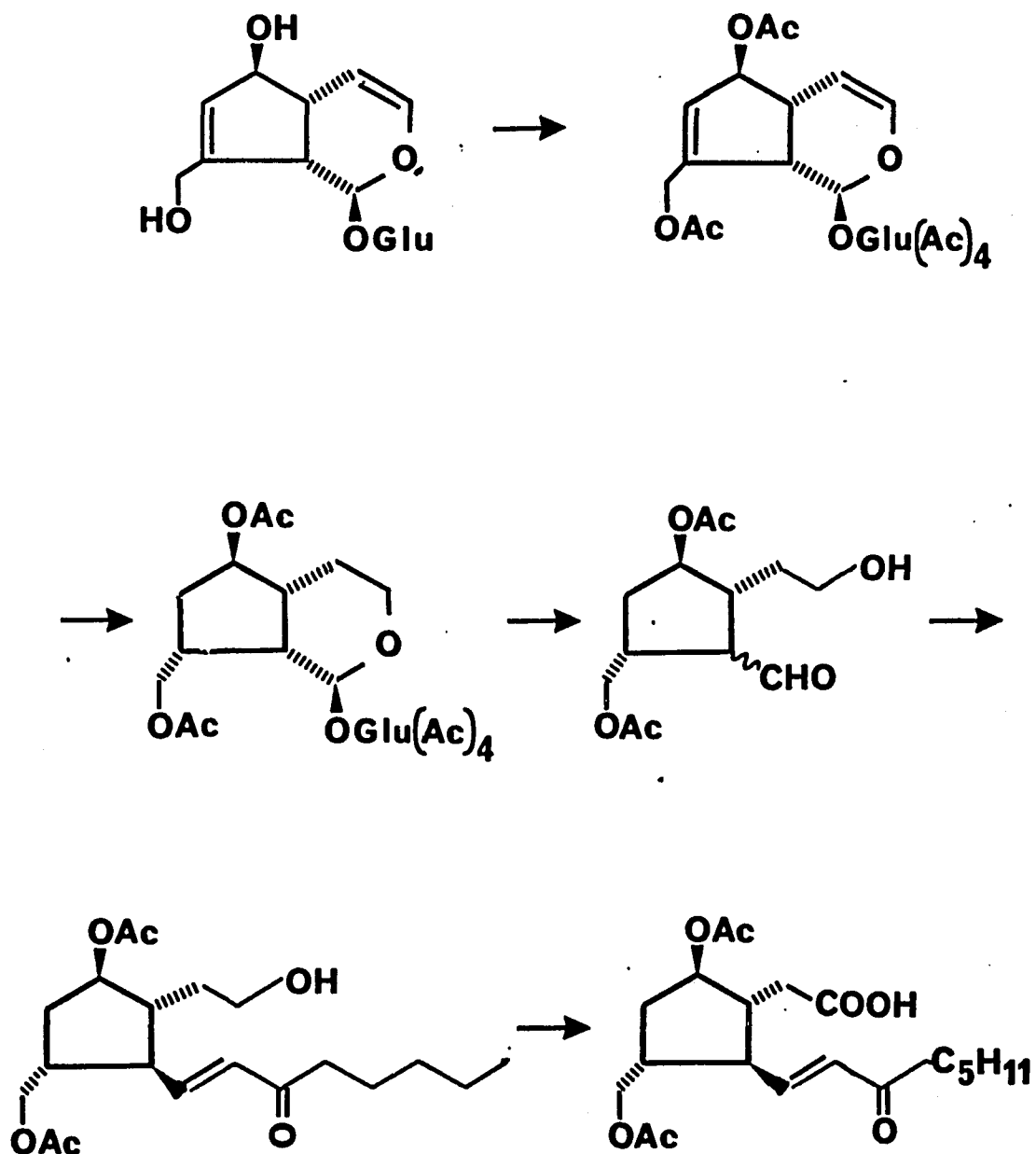
chemistry at C-8 (the only chiral center thereby created). That is, of the four chiral centers on the cyclopentane ring of the prostaglandins, three were already present on the aucubin nucleus. Of course, as was mentioned earlier, two of these (at C-6 and at C-9) would need to be inverted. However, we hoped to create the fourth chiral center (at what was to be C-11 of the prostaglandins) correctly, without the need to introduce other steps to change it to that of the natural prostaglandins.

Of course, under the conditions used by these authors, there really wasn't a very good yield of either stereoisomer, with the major portion of the material recovered after hydrogenation being composed (presumably) of hydrogenolysis products. Even in the best cases, only about 50% of the products retained all of the oxygen functionalities, with the isomer having the correct prostaglandin epimer at C-8 being isolated in less than 50% of this material. A recent report also indicates that (in the iridoid field at least) different stereoisomers can be created by the use of different hydrogenation catalysts although here only hydrogenolysis products were obtained [71]. However, these hydrogenations were done using platinum or palladium, and it is now recognized that rhodium is the preferred catalyst for avoiding hydrogenolysis [72]. Finally, knowing from previous work in our laboratory on a similar compound that 5% Rh/C gave little hydrogenolysis and variable ratios of two possi-

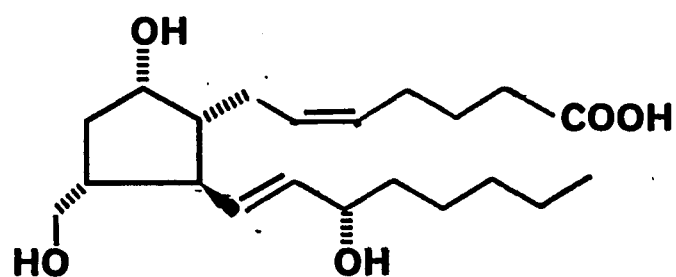
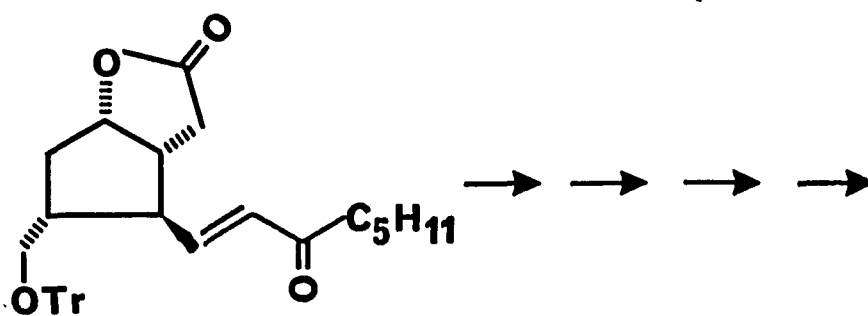
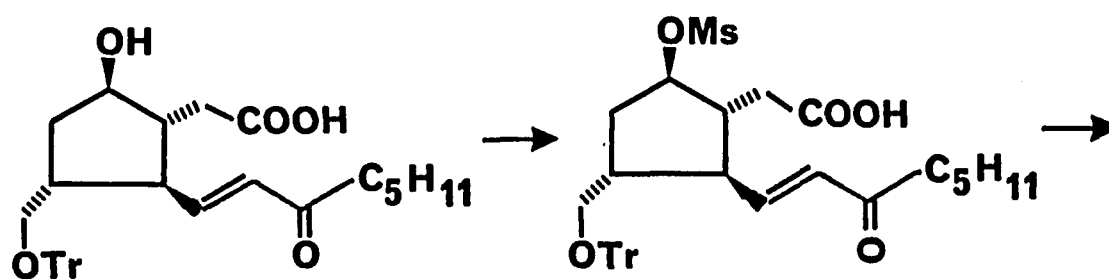
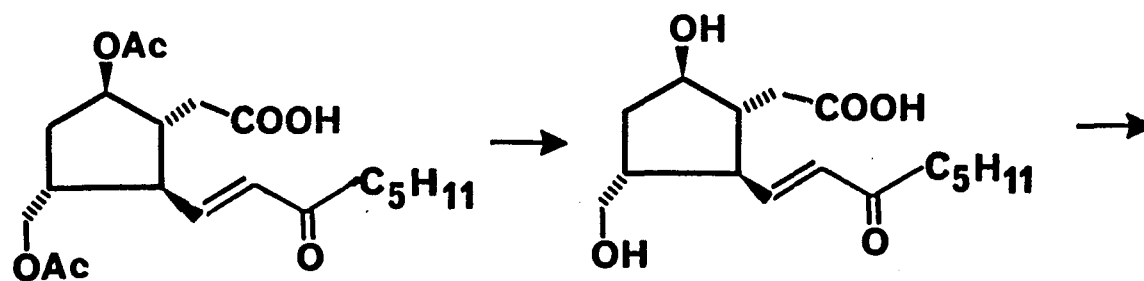
ble stereoisomers depending on the conditions chosen for the hydrogenation [70], we felt justified in proposing the following scheme (Scheme 8) for the conversion of aucubin to the prostanoid 11-deoxy-11-hydroxymethyl PGF_{2α}. Aucubin was chosen primarily because sources of it are readily available in this country, and it is usually very abundant in those sources (often 1-2% of the plant weight). Aucubin thus afforded us a reasonable opportunity to test the hypothesis that prostaglandins could be synthesized from the iridoids.

SCHEME 8

The Proposal for Conversion of Aucubin to Prostanoids



SCHEME 8 (Continued)



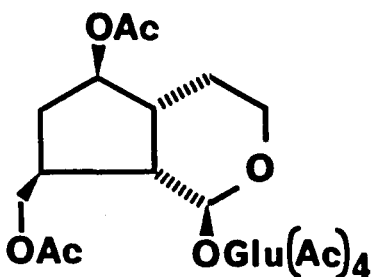
REFERENCES

The iridoids have been adequately described by Bobbitt and Segebarth in a chapter of a book edited by Taylor and Eattersby [73]. The prostaglandins have been the subject of many books as a result of their greater biological activity, and hence interest [74-86]. Two books specifically treat the synthesis of prostaglandins, one by Bindra and Bindra [87], and the other by Mitra [52]. Symposia have been devoted to their study [88-92], reviews have appeared practically every year since the late 1950's [93-131], and the total number of papers on prostaglandins must now be well over several thousand.

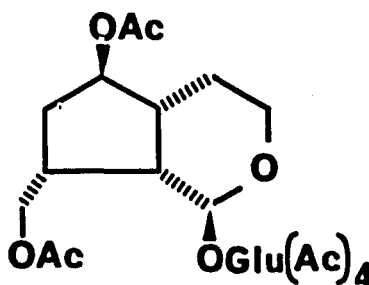
Chapter II

RESULTS AND DISCUSSION

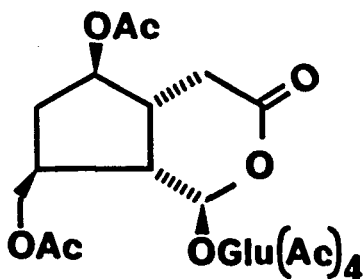
Aucubin has been found in many plants, sometimes to the extent of one or two percent of the dry weight of the plant material [54]. Aucubin was isolated by us from *Aucuba japonica* by a modification of the method of Duff [132], and purified as the hexaacetate. Hydrogenation of aucubin hexaacetate in the presence of rhodium on carbon (5% Rh/C) in ethyl acetate (previously shown to be an advantageous system on a related compound by Dr. Isaac Sasson in this laboratory) [70] gave one of the two possible tetrahydroaucubin



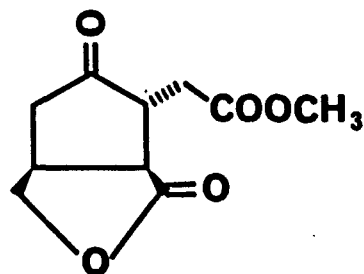
XV



XVI

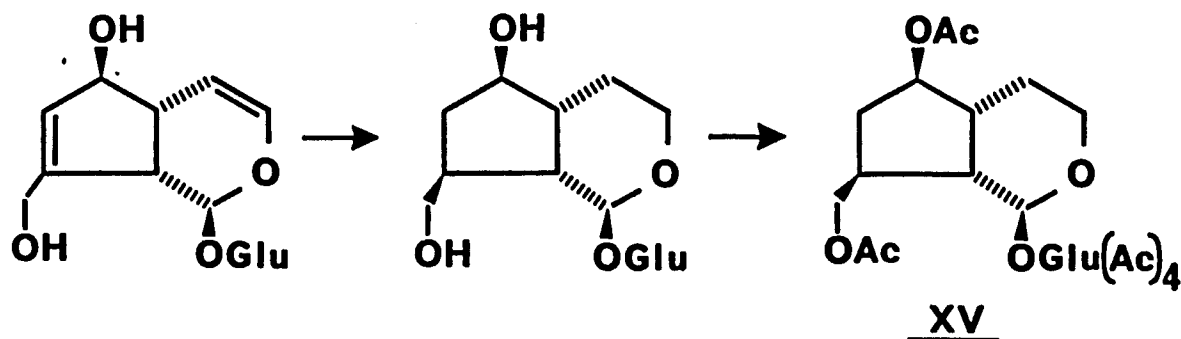


XVII



XVIII

hexaacetate isomers in nearly ninety percent isolated yield. This compound was assumed to be the β -hydroxymethyl isomer XV based on its melting point. Its structure was later confirmed by ruthenium tetroxide oxidation [133, 134] to the corresponding tetrahydroaucubin hexaacetate lactone XVII which had been previously prepared in this laboratory by a different route (Scheme 7) [70]. Lactone XVII has been chemically modified to compound XVIII (without affecting the stereochemistry at C-8) on which an X-ray crystallographic analysis has been performed [70].

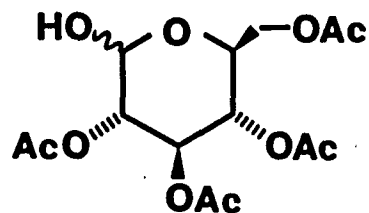
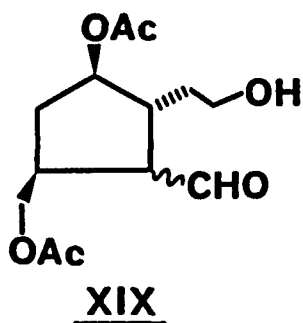


Alternatively, aucubin could be hydrogenated by 5% Rh/C in methanol (aucubin being insoluble in ethyl acetate) to give presumably tetrahydroaucubin. The hydrogenation products were acetylated to yield a mixture of compounds which was primarily tetrahydroaucubin hexaacetate XV, by TLC and HPLC.

The original aim of this dissertation (as outlined in Scheme 8) was to synthesize an analog of the prostaglandins

having the natural prostaglandin configurations at all four chiral centers on the cyclopentane ring. Since the hydrogenation gave such a good yield of the β -isomer, this aim was modified to synthesize instead a prostaglandin analog having the 11-*epi* configuration. This did not change our proposed scheme, only the final product.

At this point we needed to hydrolyze the tetrahydroaucubin hexaacetate to the free aglucone diacetate XIX, and



separate it from the glucose tetraacetate byproduct. Many procedures were tried and are summarized in Figure 5. Most of these gave many products, and when conditions were found that did give a reasonable yield of the aglucone diacetate (for example, entry 46 or 55 in Figure 5), it was found to be inseparable from the glucose tetraacetate.

Reagents: ACA= Acetic anhydride. ACCL= Acetyl chloride. ACE= Acetone. ACN= Acetonitrile. AFA= Acetic formic anhydride. CHL= Chloroform. CTC= Chromium trioxide. DCM= Dichloromethane (methylene chloride). DME= Dimethoxyethane. DOW= Dowex-50W-X8. DSIL= Silica gel dried overnight at 120°C. ETAC= Ethyl acetate. ETOH= Ethanol. FOR= Formic acid. HCL= Hydrochloric acid. HCL(g)= Hydrogen chloride gas. HOAC= Glacial acetic acid. JR= Jones' reagent (2.67M). KI= Potassium iodide. NAAC= Sodium acetate. CX= Oxalic acid. CZ= Ozone. PBS= Potassium bisulfate. SIL= Silica gel. SUL= Sulfuric acid. TEA= Triethylamine. THF= Tetrahydrofuran. TMSCL= Trimethylsilyl chloride. TMSI= Trimethylsilyl iodide. TSOH= Para-toluenesulfonic acid. W= Water.

Results: A= β -glucose diacetate. C= Glucose tetraacetate. T= Tetrahydroaucubin hexaacetate. HPLC= High Performance Liquid Chromatography. TLC= Thin Layer Chromatography. A = major component was A. 4 or n= 4 or n unidentified products.

Reagent	T°C	Time	Results by TLC (HPLC)
1. THF/1N HCL (2:1)	50	1 hr.	no react.
2. THF/1N HCL (2:1)	room	overnight	no react.
3. THF/1N HCL (5:2)	room	3 hr.	no react.
4. THF/1N HCL (5:2)	35	20 hr.	no react.
5. THF/1N HCL (5:1)	50-60	6 hr.	n
6. THF/HOAC/W (5:2:1)	room	overnight	no react.
7. THF/HOAC/W (5:2:1)	35	overnight	no react.
8. THF/HOAC/W (5:4:2)	reflux	overnight	G,n
9. THF/HOAC/W (5:4:2)	50	4 days	G,A,T
10. THF/HOAC/W (15:6:2)	reflux	overnight	n
11. THF/HOAC/1N HCL (5:4:2)	35	overnight	n
12. THF/HOAC/1N HCL (5:4:2)	room	overnight	n

Figure 5: Reaction Conditions Used in Attempts to Hydrolyze THAHA

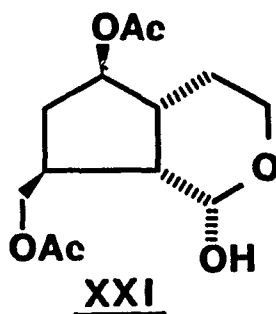
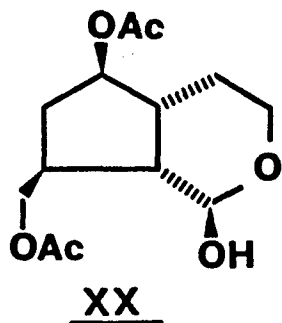
13.	THF/HOAC/1N HCL (5:4:2)	room	3 hr.	n
14.	THF/TSCH (1 eq.)	room	cvernight	<u>T</u> ,2
15.	THF/TSCH (1 eq.)	79	15 min.	G, <u>T</u> ,2
16.	THF/TSCH (1 eq.)	60	cvernight	n
17.	HOAC/W (5:1)	room	cvernight	no react.
18.	HOAC/W (1:1)	100	cvernight	n
19.	HOAC/W (4:1)	100	1 hr.	no react.
20.	HOAC/W (4:1)	100	cvernight	n
21.	HOAC/W (4:1)	100	2.5	<u>G</u> , <u>A</u> ,T,3
22.	ETOH/W/DOW (10:1:0.04)	room	cvernight	no react.
23.	JP/ACE	room	cvernight	no react.
24.	TMSI/CHL [135]	room	30 min.	T, <u>2</u>
25.	TMSCL/CHL	room	cvernight	T, <u>2</u>
26.	TMSCL/KI/ACE	room	cvernight	<u>T</u> ,2
27.	TMSCL/KI/ACN	room	cvernight	n
28.	TMSCL/ACN	room	cvernight	T, <u>2</u>
29.	TMSCL/CHL/TEA	room	cvernight	no react.
30.	TMSCL/CHL	0-room	cvernight	T, <u>2</u>
31.	ACA/HOAC/SUL (2:0.5:1 drop)	room	cvernight	2
32.	ACCL	room	19 hr.	n
33.	ACA/FCR (2:0.9)	50-75	2 hr.	no react.
34.	ACA/FOR (2:0.9)	room	14 hr.	n (2,n)
35.	AFA [136]	room	2 days	no react.

Figure 5 (Continued)

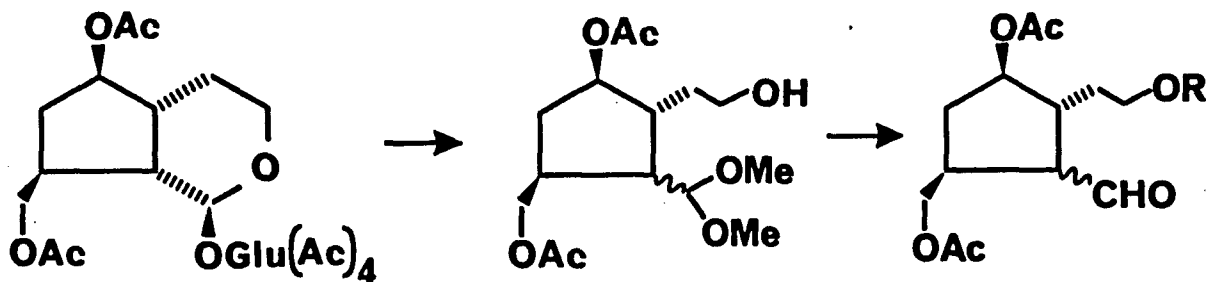
36.	AFA/FCR (1:0.1)	room	6 hr.	no react.
37.	AFA/SUL (2:1 drop)	room		decomp.
38.	HOAC/CTC	room	1 hr.	5
39.	OZ/DCM [137]	room	1 hr.	no react.
40.	OZ/ETAC	room	4 hr.	no react.
41.	OZ/ACA	room	cvernight	no react.
42.	OZ/ACA/NAAC	room	16 hr.	1
43.	SIL/10% OX/DME [138]	room	2 days	no react.
44.	SIL/10% SUL/DME	room	cvernight	no react.
45.	SIL/15% SUL/DME	room	cvernight	G,A,T,n
46.	DSIL/15% SUL/DME	room	cvernight	<u>G</u> , <u>A</u> ,n
47.	DSIL/15% SUL/DME	room	7 hr.	no react.
48.	DSIL/15% SUL/CHL	room	cvernight	<u>G</u> ,T, <u>1</u>
49.	DSIL/15% SUL/THF	room	2 days	no react.
50.	ACN/0.006N HCL (tr.)	reflux	cvernight	T,A,G,n
51.	ACN/0.006N HCL (tr.)	reflux	2 hr.	T,A,G,n
52.	ACN/0.006N HCL (tr.)	room	2 hr.	T,A,G,n
53.	ACN/PBS (1:0.01)	room	cvernight	no react.
54.	ACN/PBS (1:0.01)	reflux	2 hr.	<u>A</u> , <u>G</u> ,T
55.	ACN/HCL (g)	room	10 sec.	G,A (<u>G</u> ,A,1)
56.	DCM/HCL (g)	room	10 sec.	<u>G</u> , <u>A</u> ,3
57.	DCM/TSOH	room	10 min.	G,A,1
58.	DME/TSOH	room	10 min.	G,A,T,2

Figure 5 (Continued)

High pressure liquid chromatography (HPLC) of the hydrolysis mixture gave an impure product which was thought to be a mixture of the hemiacetals XX and XXI, as well as glucose tetraacetate.

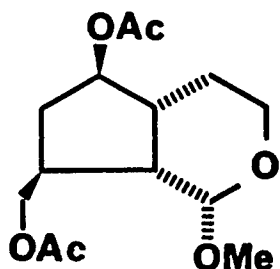


The two step procedure of methanolysis followed by hydrolysis was also examined.

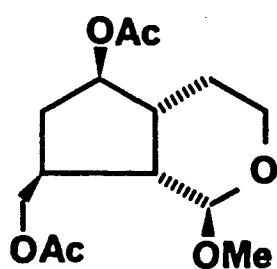


Here also, most procedures (Figure 6) gave many products. In this case, the methanolysis mixture from a successful reaction could be cleanly separated by HPLC to give two products characterized as the two mono-methyl acetal anomers

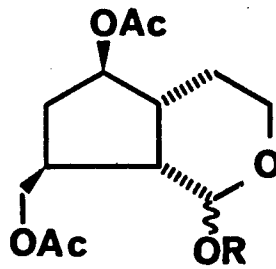
XXII and XXIII. Other alcohols (including ethylene glycol)



XXII



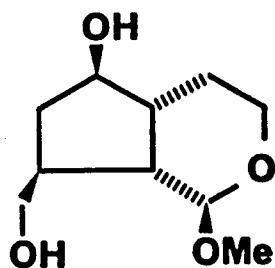
XXIII



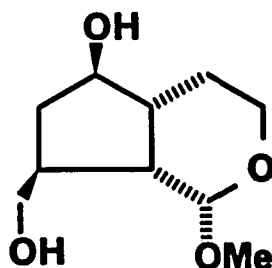
R = Et; *i*-Pr; EtOH; Ph

gave corresponding compounds.

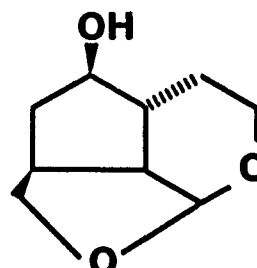
Either XXII or XXIII, or the mixture, could be hydrolyzed by a variety of methods (Figure 7) to give a mixture of XX and XXI. The same mixture of hemiacetal ancmers could also be produced by a three step procedure involving methanolysis with concomitant loss of all of the acetates to give XXIV, XXV, and XXVI, and the two methyl glucosides which were eas-



XXIV



XXV



XXVI

ily removed. After separation of XXVI, the remaining mixture of XXIV and XXV could be acetylated to give XXII and XXIII. XXVI was characterized as a tricyclic compound on

Reagents: ACN= Acetonitrile. BTF-ETH= Bcrn trifluoride etherate. DCM= Dichloromethane (methylene chloride). DOW= Dowex-50W-X8. DSIL= Silica gel dried overnight at 120°C. HCL= Hydrochloric acid. HCL(g)= Hydrogen chloride gas. HOAC= Glacial acetic acid. IPRC= Isopropanol. MECH= Methanol. MSHCL(g)= Methanol previously saturated with gaseous hydrogen chloride. OX= Oxalic acid. PES= Potassium bisulfate. SIL= Silica gel. SUL-M= Sulfuric acid in methanol. TMOF= Trimethyl orthoformate. WU= Added in workup.

Results: A= Aglucone diacetate. G= Glucose tetraacetate. MA= Methyl aglucone. MAD= Methyl aglucone diacetate. MGT= Methyl glucose tetraacetate. T= Tetrahydroaucubin hexaacetate. TC= Tricyclic compound. HPLC= High Performance Liquid Chromatography. TLC= Thin Layer Chromatography. A = major component was A. 4 or n= 4 or n unidentified products.

	Reagent	T°C	Time	Results by TIC (HPLC)
1.	MECH/0.12N HCL (tr.)	room	42 hr.	no react.
2.	MECH/0.12N HCL (3:4)	room	2 hr.	n
3.	MECH/BTF-ETH (tr.)	room	3 hr.	n
4.	MECH/HOAC (10:1)	reflux	overnight	no react.
5.	MECH/HOAC (1:1)	reflux	overnight	3 (MAD, MGT, A, G, T)
6.	MECH/DOW	room	overnight	n
7.	MECH/DOW	reflux	1 hr.	T, n
8.	MECH/PBS [139]	reflux	.5 hr.	T, 2
9.	MECH/PBS	reflux	4 hr.	T, 3 (MAD, MGT, n)
10.	MECH/PBS	room	overnight	n
11.	MECH/DCM/PES	room	overnight	no react.
12.	MECH/DCM/PES	reflux	3 hr.	T, n

Figure 6: Reaction Conditions Used in Attempts to Methanolyze THAHA

13.	MEOH/TMOF/PBS	room	cvernight	no react.
14.	DSIL/10% SUL-M/MEOH	room	cvernight	n
15.	DSIL/10% SUL-M/DCM	room	cvernight	MG,T,1 (12)
16.	DSIL/10% SUL-M/DCM	room	1 hr.	MG,G (MAD,MGT, A,G,T,3)
17.	DSIL/10% CX-M/DCM	room	cvernight	nc react.
18.	DSIL/10% CX-M/MEOH	room	cvernight	no react.
19.	DSIL/TMOF/ 10% SUL-M/DCM	0	5 hr.	<u>T</u> ,2
20.	DSIL/TMOF/ 10% SUL-M/DCM	0-room	cvernight	n
21.	MSHCL (g)	0	1 hr.	no react.
22.	MSHCL (g)	room	2 hr.	TC,MA,1
23.	MSHCL (g)	0	cvernight	<u>T</u> ,TC,MA,1
24.	MEOH/MSHCL (g) (2:1)	0	cvernight	T,TC,MA,1
25.	DCM/MSHCL (g) (1:1)	room	2 hr.	T, <u>n</u>
26.	MEOH/DCM/MSHCL (g) (1:1:1)	room	2 hr.	T, <u>n</u>
27.	MEOH/MSHCL (g) (2:1)	room	2 hr.	T, <u>n</u>
28.	DCM/MEOH/MSHCL (g) (1:1:0.01)	room	2 hr.	no react.
29.	DCM/MEOH/MSHCL (g) (1:1:0.01)	room	cvernight	T, <u>n</u>
30.	DCM/MSHCL (g) (1 eq.)	room	cvernight	n
31.	MEOH/HCL (g)	room	10 sec.	TC,MA,1
32.	MEOH/HCL (g)	room	2 min.	TC,MA,1
33.	MEOH/HCL (g)	0	2 min.	TC,MA,1
34.	MEOH/HCL (g)	reflux	.5 hr.	MA,1

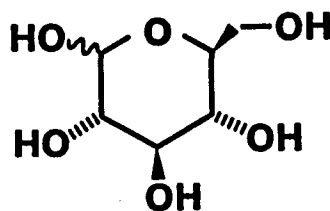
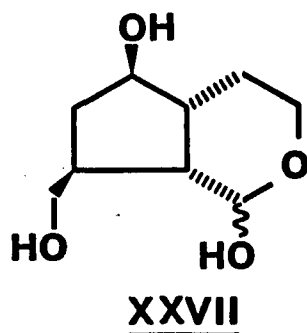
Figure 6 (Continued)

35.	MEOH/MSHCl (g) (1:0.001)	reflux	overnight	<u>T</u> ,n
36.	MECH/MSHCl (g) (1:0.002)	reflux	2 hr.	<u>T</u> ,n
37.	MECH/MSHCl (g) (1:0.004)	reflux	.5 hr.	<u>T</u> ,n
38.	IPro/HCl (g)	room	10 sec.	n
39.	ACN/HCl (g) /MEOH (WU)	room	10 sec.	<u>MAD</u> , <u>G</u> , <u>T</u> (MAD, MGT,A,G,T)

Figure 6 (Continued)

the basis of its elemental analysis, NMR, IR, and its conversion to a mono-acetate. We believe that XXVI is a C-8 and C-9 epimer of the key intermediate (XIII) in the Ohno synthesis (Scheme 6), based on its method of formation [66, 68].

The direct hydrolysis of tetrahydroaucubin hexaacetate to give the aglucone of tetrahydroaucubin (XXVII) and glucose was unsuccessful [140].



Reagents: ACCL= Acetyl chloride. ACN= Acetonitrile. BTB= Boron tribromide. CHL= Chloroform. DCM= Dichloromethane (methylene chloride). DCW= Dowex-50W-X8. DSIL= Silica gel dried overnight at 120°C. HCL= Hydrochloric acid. HCL(g)= Hydrogen chloride gas. HOAC= Glacial acetic acid. PBS= Potassium bisulfate. SUL= Sulfuric acid. THF= Tetrahydrofuran. TMSCL= Trimethylsilyl chloride. TMSI= Trimethylsilyl iodide. TSOH= Para-toluenesulfonic acid. TTC= Titanium tetrachloride. W= Water.

Results: A= Aglucone diacetate. MAD= Methyl aglucone diacetate. HPLC= High Performance Liquid Chromatography. TLC= Thin Layer Chromatography. A = major component was A. 4 or n = 4 or n unidentified products.

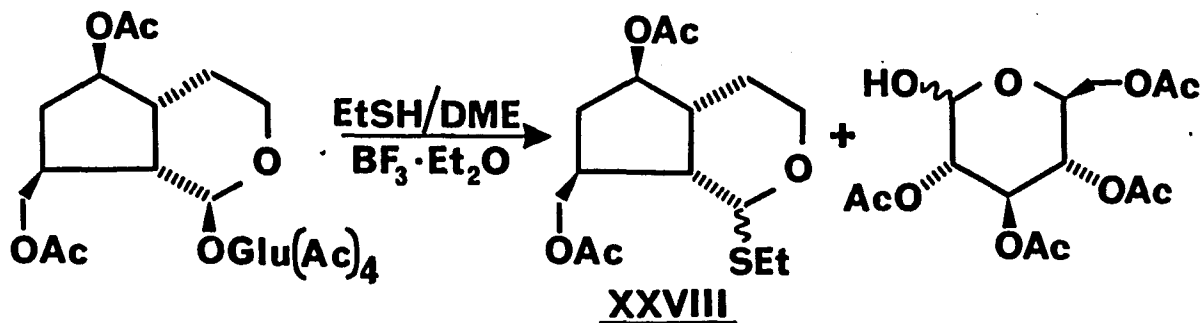
	Reagent	T°C	Time	Results by TIC (HPLC)
1.	HOAC/W (1:1)	100	5 hr.	A, <u>MAD</u>
2.	HOAC/1N HCL (1:1)	100	1 hr.	n
3.	HOAC/W (4:1)	room	overnight	(<u>MAD</u> , 1)
4.	HOAC/W (4:1)	100	1 hr.	(<u>MAD</u> , 2)
5.	HOAC/W (4:1)	100	2 hr.	(MAD, <u>A</u>)
6.	THF/W/HOAC (9:3:1)	room	overnight	A, <u>MAD</u>
7.	THF/1N HCL (9:2)	room	overnight	n
8.	THF/TSOH	room	overnight	n
9.	THF/PBS	reflux	3 hr.	no react.
10.	THF/PES/W (TR)	reflux	overnight	n
11.	THF/W/PBS (3:1)	reflux	4 hr.	n
12.	THF/W/PBS (3:1)	room	overnight	MAD, n
13.	TMSI/CHL	room	.5 hr.	n
14.	TMSCL/CHL	room	overnight	n
15.	TMSCL/ACN/KI	room	.5 hr.	n, MAD, <u>A</u>
16.	DCM/BTB	-78-room	3 hr.	n (MAD, 4)

Figure 7: Reaction Conditions Used in Attempts to Hydrolyze MAD

17.	DSIL/15% SUL/DCM	room	1 hr.	nc react.
18.	DSIL/15% SUL/DCM	room	overnight	MAD,A
19.	DSIL/15% SUL/DCM	room	6 days	MAD,A
20.	TTC/DCM	room	.5 hr.	A,MAD,1
21.	TTC/DCM/ACCL [140]	room	1 hr.	(MAD,n)
22.	TTC/ACCL	-78	15 min.	(MAD,A,1)
23.	ACN/0.06N HCL (1:5 drops)	room	overnight	A,MAD,2
24.	ACN/0.06N HCL (1:5 drops)	reflux	2 hr.	A,MAD,2
25.	ACN/0.06N HCL (1:5 drops)	room	2 hr.	MAD,A
26.	ACN/HCL(g)	room	10 sec.	A

Figure 7 (Continued)

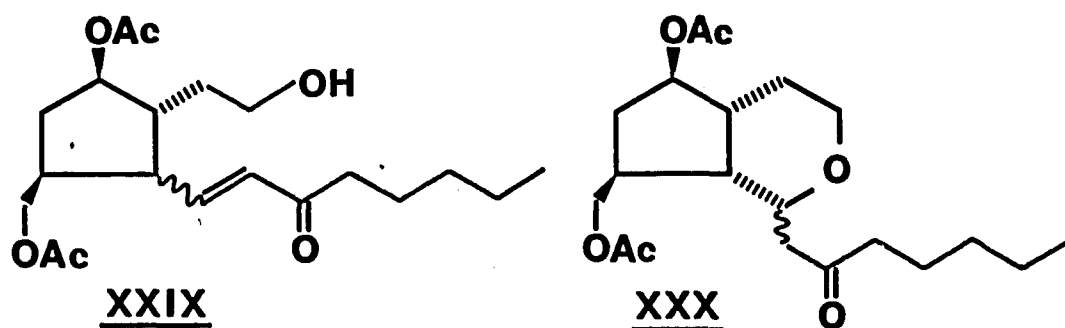
Finally, it was found that tetrahydraucubin hexaacetate could be cleaved asymmetrically by ethanethiol in dimethoxyethane in the presence of boron trifluoride etherate cata-



lyst to give the hemithioacetal aglucone diacetate XXVIII

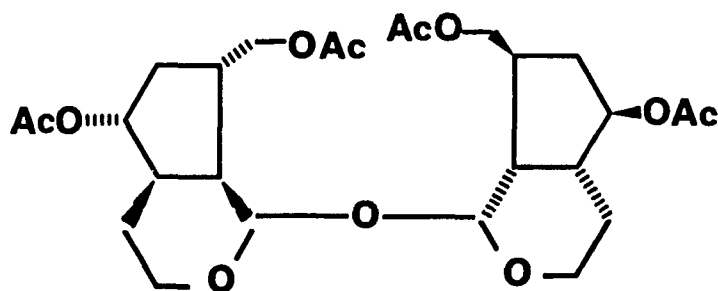
and glucose tetraacetate rather than the hemithioacetal of glucose tetraacetate [64]. These were readily separated, and the hemithioacetal XXVIII was easily cleaved in good yield by a mixture of copper chloride and copper oxide to one of the two anomers XX or XXI [141]. The other anomer, if present, could not be detected.

The phosphonate anion modification of the Wittig reaction [142, 143] (Wadsworth-Emmons or Horner-Emmons) carried out under various conditions, failed to give any of the desired



product XXIX, however. Instead, the only product isolated and characterized was the Michael adduct XXX in very low yield. A similar cyclic β -ether ketone has been converted to an enone by Ohno (Scheme 6) by treatment with acid in acetic anhydride. Other material from these reactions was examined, but failed to exhibit a reasonable NMR spectra for the enone.

One possible explanation for this anomalous behavior is that we do not have the hemiacetal. Instead, we may have the "dimer" of this compound. One piece of evidence in fa-



vor of this structure is the elemental analysis. The calculated values for $C_{26}H_{38}O_{11}$ are C; 59.30, H; 7.27. The experimental results from three different analyses are: C; 58.91, H; 7.27; C; 58.80, H; 7.62; and C; 59.28, H; 7.33. Note that while these are not totally acceptable, one of them is, and the average of the three is very good also. Arrayed against this structure, are all the other pieces of evidence (see Experimental for details). The IR indicates an alcohol, while the PMR shows that there is one exchangeable proton. The mass spectrum (from chemical ionization) shows only the peaks expected from loss of water from the hemiacetal. However, a rationalization of these spectra is possible. Thus, the "dimer" would be expected to give the same mass spectrum if the parent ion were too unstable to be seen. Similarly, one mole of water of hydration per mole of "dimer" might give IR and PMR spectra that would look like the hemiacetal. Alternatively, the overnight drying of the hemiacetal over phosphorus pentoxide and under vacuum might have dehydrated the hemiacetal to the "dimer".

Chapter III

EXPERIMENTAL

Melting points were determined in open capillaries using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin Elmer IR 237B or 598 or on a Beckmann IR 20 using 0.1 mm NaCl solution cells and were consistent with the structures assigned. Proton NMR spectra were recorded at 60 MHz on a Varian EM 360 instrument with tetramethylsilane (TMS) as an internal standard. Data are reported in parts per million downfield from TMS with the multiplicity (d = doublet; t = triplet; q = quartet; dd = doublet of doublet; dt = doublet of triplet; s = singlet; br = broad; m = multiplet).

Silica gel thin layer chromatography was performed using Machery-Nagel silica gel N-HR on plastic sheets. Unless otherwise noted, these were developed with ether and visualized by spraying with 10% sulfuric acid in methanol and heating to 250°C. Analytical high pressure liquid chromatographic analyses were done using a Waters Associates (Milford, Mass.) system consisting of two 4 mm by 30 cm microporasil silica columns in series, a 6000 SDS pump, U6K injector and model 401 differential refractometer. Analyses were performed at a flow rate of 2 mL/min using 1:1 ethyl acetate/

hexane or ethyl acetate where appropriate. Preparative HPLC separations were performed on a Waters Prep 500 instrument with two silica columns in series at a flow rate of 0.2 L/min using 1:1 ethyl acetate/hexane or ethyl acetate where necessary. The starting material, aucubin, was purified using Celite in a 10 cm diameter column obtained from Glencoe (Houston, Texas). The solvent was delivered to the column from a stainless steel reservoir under 7×10^6 Pascals of air pressure. Concentration of large quantities of liquid was most efficiently done using a "Cyclone" circulatory evaporator (Scientific Glass Apparatus Co., Bloomfield, N.J., cat. no. JD 9350) at water pump pressure.

Methylene chloride and dimethyl sulfoxide were distilled (DMSO in vacuo) from calcium hydride and kept over freshly activated 4A molecular sieves for at least 48 hours prior to use. Sodium hydride was employed as a 57% oil dispersion. Silica gel for hydrolyses was dried for at least twelve hours at 120° prior to use. All other chemicals and solvents were used as purchased, unless otherwise noted.

Aucuba japonica plant parts were purchased from Ingleside Plantation Nurseries, Oak Grove, Westmoreland County, Virginia, and extracted as described below.

Hydrogenation catalysts were obtained from Engelhard Industries, Newark, New Jersey. Rhodium on carbon catalyst (5%) purchased prior to 1975 seemed superior.

Microanalyses were performed by Spang Microanalytical (Eagle Harbor, Mich.) or Galbraith (Knoxville, Tenn.) Laboratories.

ISOLATION OF AUCUBIN

(1E,4aR,5R,7aR)-1,4a,5,7a-Tetrahydro-5-hydroxy-7-(hydroxymethyl) cyclopenta[c]pyran-1-yl β-D-glucopyranoside

Aucuba japonica leaf and stem trimmings (22 Kg) were coarsely chopped and placed in a large pot. Calcium carbonate (100 g) was added to the trimmings, which were then immersed in water (app. 30 L) and boiled for several hours. After cooling, the solution was decanted, and the extraction repeated with a fresh volume of water. The aqueous solutions were filtered through a large plug of glass wool, combined, and initially concentrated under reduced pressure in a cyclone evaporator, then taken to dryness on a Buchi rotavapor. The dry material was redissolved in 7.5 liters of water. When one hundred milliliters of this solution was taken to dryness, the resulting material weighed 25 grams. Therefore the total weight of extracted material was approximately 1800 grams.

Celite (650 g) was added to 2.3 liters (out of 7.5 L) of the above solution, and the mixture taken to dryness in three separate portions on the rotavapor. The Celite impregnated with the extract was slurried in n-butanol saturated with water and applied to the top of a Celite column

prepared as follows: Celite (2 Kg) was mixed and equilibrated with water (2 L) overnight. This wet Celite (1.75 Kg) was slurried in n-butanol saturated with water and poured into a ten centimeter column in three portions. After each addition, air pressure (7×10^6 Pascals) was applied while solvent was flowing to compact the Celite.

The column was then eluted with n-butanol saturated with water under air pressure (7×10^6 Pascals), at a flow rate of approximately 30 mL/min. A first fraction of 3.5 liters, a second fraction of 2.5 liters, and a third fraction of 0.5 liters were collected and tested for the presence of iridoids by the use of a standard iridoid test solution [54]. The first two fractions were devoid of iridoids, but the third gave a positive blue color when an aliquot was heated gently with the test solution. A fourth fraction of 3.5 liters was collected, then the eluant was checked for iridoids after every 0.5 liters. A total of 38 liters was collected, and found to contain aucubin by thin layer chromatography. These were concentrated nearly to dryness under reduced pressure on the cyclone evaporator, then taken to dryness on the rotavapor. The residue was dissolved in one liter of hot methanol with a small amount of calcium carbonate, treated with charcoal, and after suction filtration through Celite, again taken to dryness. The amorphous solid residue could not be crystallized.

The column was then washed with water and all the remaining aucubin came off in the first two liters. This was added to the remaining 5.2 L of aqueous extract which was then concentrated and chromatographed in a similar manner (in two batches). The total combined aucubin containing residues, 440 g, were dissolved in one liter of methanol. Thin layer chromatography (2:1 95% ethanol/acetone) showed a large non-aucubin streak, Rf 0.08 to 0.42, as well as aucubin, Rf 0.55.

SYNTHESIS OF AUCUBIN HEXAACETATE (AHA)

(1R,4aR,5R,7aR)-1,4a,5,7a-Tetrahydro-5-hydroxy-7-(hydroxymethyl) cyclopenta[c]pyran-1-yl β-D-glucopyranoside hexaacetate

The above methanolic solution (55 mL) of crude aucubin was taken to dryness in a 500 mL round bottom flask on the rotavapor, and then placed under high vacuum for several minutes. The impure aucubin foams under these conditions, and care must be taken in the application of the vacuum to avoid losing material. The weight of the material was nearly six grams, but it was almost certainly not completely dry. Pyridine (120 mL, 1.49 mol) was added, and the flask placed in an ice bath. Acetic anhydride (50 mL, 0.53 mol) was added with swirling. As the solid mass dissolved only with difficulty while cold, the flask was removed from the ice bath and the solution allowed to warm. As solution oc-

curred, the mixture grew very warm and started to boil, and was then placed back in the ice bath, and kept overnight. The resulting brown solution was poured into 500 mL of water, put into the refrigerator, and left overnight.

The off-white precipitate which formed was filtered, washed with water, dissolved in chloroform and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed on the rotavapor, and the resulting oil was recrystallized from methanol. Yield 9.5 grams, mp 127.5-129.5°C (lit. mp 128°C [68]), PMR 6.13 (dd,1,J=6,2 Hz.), 5.8 (t,1,J=2 Hz), 5.3-4.65 (m,9), 4.19 (d,2,J=4 Hz), 3.87-3.6 (m,1), 3.3-2.97 (m,1), 2.95-2.85 (m,1) 2.1 and 2.02 (s and s,18).

The above procedure was used with minor variations on the remainder of the crude aucubin obtained by chromatography. The aqueous mother liquors of the acetylation mixture were extracted with chloroform, which was dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotavapor. The solid residue was re-acetylated with a 1:1 (v/v) solution of acetic anhydride and pyridine. Occasionally it was necessary to heat the original acetylating mixture to ensure complete solution, and thereby as complete a reaction as possible. In contrast, the secondary acetylation was always heated on a steam bath for at least one hour. The product from the second acetylation was treated as before. Fractional crystallization of the acetylated material from

methanol gave pure aucubin hexaacetate (364 g, mp 127-128°C), (combined first crops). Evaporation of the combined mother liquors gave a semisolid residue which was crudely chromatographed by passage through a short silica gel column with hexane containing increasing amounts of ethyl acetate. The aucubin hexaacetate containing fractions were then combined, stripped, and chromatographed on the Prep 500 with a recycle for best separation. Total yield 380 grams (1% of aucubin based on fresh plant weight).

SYNTHESIS OF XV (THAHA)

(1R,4aR,5R,7S,7aR)-Octahydro-5-hydroxy-7-(hydroxymethyl) cyclopenta[c]pyran-1-yl β-D-glucopyranoside hexaacetate

(1) To 2.5395 g (4.24 mmol) of AHA in ethyl acetate (1 L) was added 0.1185 g of Englehardt 5% Rh/C catalyst. Hydrogen gas was introduced at atmospheric pressure. The uptake of hydrogen was smooth, continuous, and fairly rapid for nearly three hours. After 3.5 hours the reaction was stopped, and the catalyst removed by suction filtration. The solvent was removed on the rotavapor, and the solid residue recrystallized from hot ethyl acetate. The precipitate was filtered and washed with ether. After drying under vacuum overnight, the product weighed 1.6235 g (63.5%), mp 155-157°C (Lit. mp 157°C [68]), homogeneous by TLC and HPLC, PMR 5.28-4.68 (m,6), 4.27-3.88 (m,4), 3.82-3.4 (m,3), 2.6-1.85 (m,20, including 2 s at 2.1 and 2.08), 1.75-1.2 (m,3). Anal. Calcd.

for $C_{27}H_{38}O_{15}$: C, 53.82; H, 6.36. Found: C, 53.78; H, 6.32.

Upon refrigeration overnight, the combined mother liquor and ether wash deposited 0.3555 g (13.9%), mp 155-157°C of further product of equal purity (TLC). The mother liquor from this crystallization was stripped on the rotavapor, and the residue recrystallized from 3:1 ether/ethyl acetate to give another 0.1545 g (6%) of the same product. Total yield 83%. There was still more THAHA present in the mother liquor from the last recrystallization, but it could not be induced to crystallize. It could be obtained by chromatography, however, but this was done only on the combined residues of several reactions.

(2) To 11.8932 g (19.97 mmol) of AHA in 500 mL of ethyl acetate was added 18.689 g of Englehardt 5% Rh/Alumina catalyst. The solution was cooled to -78°C and hydrogen admitted at atmospheric pressure. The dry ice bath was replaced with an ordinary ice bath, and the uptake of hydrogen observed. After two hours the uptake suddenly ceased, and after 2.25 hours, the reaction was stopped. The catalyst was removed by filtration, and the solvent removed on the rotavapor. The solid product was fractionally crystallized from 3:1 ether/methylene chloride or ether solution, affording 8.0633 g (68%) of material identical (mp, pmr, hplc) to that obtained above. The mother liquors still contained further product which was isolated as before by chromatography of the combined residues of several reactions.

(3) Aucubin (0.1 g, 0.3 mmol) was dissolved in 10 mL of methanol and hydrogenated for seven hours with 0.02 g of 5% Rh/C at atmospheric pressure and room temperature. After filtration the solvent was removed on the rotavapcr, and the residue treated with 1 mL each of pyridine (12 mmol) and acetic anhydride (11 mmol) at room temperature overnight. Normal aqueous work-up gave a material identical to that above by TLC and HPLC. No further characterization was attempted.

SYNTHESIS OF XX AND XXI (AGLUZONE DIACETATE)

(4aR,5R,7S,7aR)-Octahydro-1,5-dihydroxy-7-(hydroxymethyl)
cyclopenta[c]pyran 5,7-diacetate

THAHA (2.1292 g, 3.53 mmol) was dissolved in fifty mL of acetonitrile, and hydrogen chloride gas passed over the surface of the solution for approximately ten seconds. The opalescent solution turned a green color upon the addition of solid sodium bicarbonate and eventually became a pale yellow when neutralization was complete. After drying over anhydrous magnesium sulfate and treatment with charcoal, the solution was nearly colorless. The product after removal of the solvent on the rotavapor was separated on the Prep 500 to give nearly 0.6 g of slightly impure aglucone diacetate as an oil. Yield 66%, PMR 5.10 (t,1), 4.88 (m,1), 4.25-3.31 (m,5, including d 4.05, J=6 Hz, and one exchangeable proton (deuterium oxide)), 2.7-1.9 (m,9, including 2 s at 2.1 and

2.08), 1.7-1.3 (m,3). IR (4% CHCl₃) 3690, 3625 (OH), 3030, 2985, 1745 (Ac).

SYNTHESIS OF XXIV AND XXV (METHYL AGLUCONE)

(4aR,5R,7S,7aR)-Octahydro-5-hydroxy-7-(hydroxymethyl)-1-methoxy-cyclopenta[c]pyran

Hydrogen chloride gas was passed through a suspension of 1.9967 g (3.31 mmol) of THAHA in 20 mL of methanol until all of the THAHA dissolved. This took approximately two minutes. The hot solution was then gently refluxed on a steam bath for 0.5 hour. After cooling, the solution was carefully poured over solid sodium bicarbonate. More solid sodium bicarbonate was added until gas evolution ceased, then anhydrous magnesium sulfate was added to dry the solution. After suction filtration, the solvent was removed on the rotavapor. The oily residue was extracted once with methylene chloride, and a second time with boiling chloroform. The combined organics were again dried over anhydrous magnesium sulfate, filtered, and the solvents removed on the rotavapor. Yield 0.5682 g (85%) of oily acetal, pure by TLC, PMR 4.58 (m,1), 4.3-2.8 (m,10, including s 3.39, and 2 exchangeable H's (deuterium oxide)), 2.6-1.85 (m,4), 1.78-0.8 (m,3). An acceptable analysis was not obtained.

PREPARATION OF XXVI (TRICYCLIC ACETAL)

(2aS,4R,4aR,7bR)-Octahydro-4-hydroxy-2H-1,7-dioxacyclopent-[bc]indene

From incompletely reacted attempts to make the methyl aglucones XXIV and XXV, a faster moving impurity (on TLC and HPLC) could be isolated by HPLC. The combined material from several reactions was recrystallized from hexane to give an analytically pure sample of the tricyclic monohydroxy acetal XXVI. mp 83.5-85°C. PMR 4.99 (d,1), 4.35-3.3 (m,5), 2.9-2.2 (m,3), 2.2-1.35 (m,5, with one exchangeable H (deuterium oxide). IR (5% CHCl₃) 3610, 3450 (OH), 2950, 2890. Anal. Calcd. for C₉H₁₄O₃: C, 63.51; H, 8.29. Found: C, 63.29; H, 8.41.

SYNTHESIS OF XXII AND XXIII (MAD)

(4aR,5R,7S,7aR)-Octahydro-5-hydroxy-7-(hydroxymethyl)-1-methoxy-cyclopenta[c]pyran diacetate

To 1.6131 g (5.92 mmol) of the methyl aglucones XXIV and XXV in 10 mL (0.12 mol) of pyridine and 10 mL (0.11 mol) of acetic anhydride, was added 0.25 g (2 mmol) of 4-dimethylaminopyridine. After standing overnight, the solution was poured into ethyl acetate, and washed in order with water, three portions of 5% hydrochloric acid, water, 5% sodium bicarbonate solution, water, and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvents removed

on the rotavapor. The residue was separated on the Prep 500 to give 1.1864 g (52%) of an oil, PMR 5-4.28 (m,2, including br s, 4.53 and d, 4.4,J=3 Hz) 4.23-3.3 (m,6, including d, 4,J=6 Hz, and two s 3.36 and 3.35), 2.82-1.82 (m,10, including 2 s, 2.06 and 2), 1.8-1 (m,3). Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.52; H, 7.82.

Major component after separation on the analytical HPLC 4.81 (br d,1,J=4 Hz), 4.61 (br s,1), 4.08 (br d,2,J=7 Hz), 3.9-3.2 (m,5, including s, 3.4), 2.7-1.9 (m,10, including 2 s, 2.08 and 2.01), 1.83-1 (m,3). Minor component 4.92 (m,1), 4.47 (d,1,J=3 Hz), 4.39-3.15 (m,7, including s, 3.4), 2.75-1.8 (m,10, including 2 s, 2.07 and 2.03), 1.78-1 (m,3).

SYNTHESIS OF METHYL AGLUCONE DICHALCATE

(4aR,5R,7S,7aR)-Octahydro-5-hydroxy-7-(hydroxymethyl)-1-methoxy-cyclopenta[c]pyran diethoxycarbonate

Pyridine (5 mL, 0.06 mol) and 0.5682 g (2.09 mmol) of methyl aglucones XXIV and XXV were mixed and magnetically stirred while being cooled in an ice bath. Ethyl chloroformate (1 mL, 12.5 mmol) was slowly dripped in, followed by approximately 0.12 mg (1 mmol) of 4-dimethylaminopyridine. After removing the ice bath, the two phase system was stirred for two hours, then poured into ethyl acetate, and washed twice with water, four times with 5% hydrochloric acid, water, 5% sodium bicarbonate solution, water, and saturated sodium chloride solution. The organic layer was

dried over anhydrous magnesium sulfate, filtered, and the solvents removed on the rotavapor. The residual oil weighed 0.5230 g (72%) and showed only minor impurities on TLC. This was combined with the product of two other reactions (from a total of 1.2 g (4.4 mmol) of methyl aglucones) and separated on the Prep 500 to give a total of 0.5714 g (28%) of analytically pure product. PMR 4.82-2.9 (m,13, including a double q, 4.4-3.9,J=7 Hz, and 2 s, 3.4 and 3.38), 2.7-1 (m,13, including a t,J=7 Hz). Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.24; H, 7.64.

SYNTHESIS OF XX AND XXI FROM XXII AND XXIII (MAD)

To a solution of 0.4713 g (1.2 mmol) of MAD in 2 mL of acetonitrile was added 5 drops of 0.06 N hydrochloric acid. This solution was kept overnight, then neutralized with solid sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotavapor to give 0.3441 g (77%) of slightly impure product, essentially identical to the previously prepared material, by HPLC and pmr. An acceptable analysis for this material was not obtained, but see Results and Discussion.

SYNTHESIS OF XXVIII (HTAAD)

(4aR,5R,7S,7aR)-Octahydro-1-ethylthio-5-hydroxy-7-(hydroxymethyl) cyclopenta[c]pyran diacetate

To 5.3381 g (8.86 mmol) of THAHA in 100 mL of dry dimethoxyethane was added 3 mL each of ethanethiol (40.5 mmol) and distilled boron trifluoride etherate (24.4 mmol). After the mixture was swirled for approximately two minutes, all of the THAHA dissolved, and the solution was stoppered and kept at room temperature for 1.5 hours. The solution was then poured into 100 mL of 10% sodium bicarbonate solution, and extracted three times with methylene chloride. The combined organics were twice washed with a saturated sodium chloride solution, then dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotavapor. The oily residue was applied to the top of a 2.5 by 20 cm, 100 g, column of silica gel packed in methylene chloride, and eluted with three 500 mL portions of methylene chloride. Almost all of the product came off the column in the second fraction, while the glucose portion did not come off even after further elution with 1.5 liters of chloroform. After removing the solvent in vacuo, the weight of the slightly impure material was 2.8498 g (102%). PMR 4.2-4.12 (br d, 1, J=2 Hz), 4.92-4.7 (m, 1), 4.37-3.82 (m, 3, including d, 4.07, J=6 Hz), 3.7-2.9 (m, 2, including dt, 3.5, J=4, 11 Hz), 2.8-0.88 (m, 17, including q, 2.5, J=7 Hz, 2 s, 2.1 and 2.05, and t, 1.3, J=7 Hz). A portion was purified by HPLC,

and sent for analysis. Anal. Calcd. for $C_{15}H_{24}O_5S$:
C, 56.94; H, 7.65; S, 10.13. Found: C, 57.02; H, 7.74; S, 10.21.

SYNTHESIS OF XX AND XXI FROM XXVIII (HTAAD)

To 0.5824 g (1.84 mmol) of hemithioacetal aglucone diacetate in 20 mL of acetone was added 0.33 g (1.9 mmol) of cupric chloride dihydrate and 0.29 g (3.6 mmol) of cupric oxide [141]. The solution was stirred for fifteen minutes, while a black precipitate developed. The solvent was then removed on a rotavapor without filtering. The solid residue was washed with methylene chloride, filtered, and passed through 5.5 g of silica gel. A green substance was left at the origin. The column was next eluted with 50 mL of ether which was combined with the methylene chloride. The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotavapor, to give 0.4591 g (92%) of an oil, identical by HPLC and PMR to one of the two anomers previously prepared. PMR 5.25-5 (π ,1), 4.95-4.65 (m,1), 4.4-0.85 (m,22, including d, 4.09, $J=6$ Hz, br dt, 3.72-3.3, $J=12$ and 4 Hz, 2 s, 2.11 and 2.05, and t, 1.3, $J=7.5$ Hz). IR (4% $CHCl_3$) 3690, 3625 (CH), 3030, 2985, 1745 (Ac). MS m/e 255 ($m+1-H_2O$), 195 (-HOAC), 135 (-HOAC). An acceptable analysis was again not obtained, but see Results and Discussion.

MODIFIED WITTIG REACTION

(4aR,5R,7S,7aR)-Octahydro-5-hydroxy-7-(hydroxyethyl)-1-(2-oxoheptyl)cyclopenta[c]pyran diacetate

To 0.018 g of 50% sodium hydride dispersion (.375 mmol) in 1 mL of dry dimethoxyethane was added 0.076 mL of dimethyl (2-oxoheptyl)phosphonate (0.365 mmol). Hydrogen evolution occurred and a white slurry gradually formed. Then 0.1058 g (0.389 mmol) of the hemiacetal of the tetrahydroaucubin hexaacetate aglucone was added in 1 mL of dimethoxyethane. A further mL of dimethoxyethane was added to facilitate stirring, after which the mixture was stirred overnight at room temperature. The resulting solution was poured into ethyl acetate, extracted with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent removed in vacuo. The resulting oil was separated by flash chromatography using ether as the eluant to remove unreacted phosphonate and gave 0.0445 g (31%) of an oil having two spots on TLC. This oil was separated on HPLC to give an analytically pure product weighing 0.0145 g (10%). PMR 5.15 (m,1), 4.38-3.22 (m,6, including d, 4,J=6), 2.9-.8 (m,25, including t, 2.48,J=6 Hz, s, 2.08, and t, 0.9,J=5 Hz). Anal. Calcd. for $C_{20}H_{32}O_6$: C, 65.21; H, 8.75. Found: C, 65.16; H, 8.58.

Several variations of this reaction were tried. The amount of sodium hydride was varied from one to six equivalents. The phosphonate was also varied from one to six

equivalents, with the ratio of base to phosphonate varying from one to two. The solvent was either dimethoxyethane or dimethylsulfoxide. The time of reaction varied from two hours to two days, and the temperature was usually at room temperature, but one reaction in DME was run at reflux. Several reactions were also run utilizing butyl lithium as the base. These reactions were run in either DMSO, or hexane [144]. Varying the reaction time or the reaction temperature was not effective in these trials either. None of these variations gave an increased yield of this product, nor was any product isolated which appeared to be the desired adduct having the free hydroxyl and the conjugated ketone system.

SYNTHESIS OF XVII

(1R,4aR,5R,7S,7aR)-1-(β-D-Glucopyranosyloxy) hexahydro-5-hydroxy-7-(hydroxymethyl) cyclopenta[c]pyran-3(1H)-one hexacetate

To .9987 g (1.66 mmol) of THAHA in 10 mL of carbon tetrachloride was added 0.5 g (3.03 mmol) of ruthenium tetroxide in 10 mL of carbon tetrachloride. After refluxing for two days (protected by a calcium chloride drying tube), the solution was filtered to remove the black precipitate of ruthenium dioxide, dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotavapor. The resulting oil was crystallized from ether and then recrystallized from

3:1 ether/chloroform to give 0.0545 (5%) of product identical by mp, mixed mp, HPLC, IR, and PMR to a compound previously prepared in this laboratory by a different route [70]. mp 133-4°C (Lit. mp 133-4°C [70]). Only one peak could be seen after four recycles of a co-injection on HPLC. PMR 5.52 (s,1), 5.23-4.5 (m,6), 4.3-3.95 (m,4), 2.83-1.75 (m,24), 1.70-1.2 (m,1). IR (2% CHCl₃) 3000, 1745 (Ac), 1350, 1050, 1015, 990, 940. Anal. Calcd. for C₂₇H₃₆O₁₆: C, 52.60; H, 5.89. Found: C, 52.87; H, 6.02.

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