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THE CONVERSION OF ASPERULOSIDE TO AN OPTICALLY ACTIVE PROSTAGLANDIN INTERMEDIATE

City University of New York PH.D. 1981

THE CONVERSION OF ASPERULOSIDE TO AN OPTICALLY ACTIVE PROSTAGLANDIN INTERMEDIATE

by

SATISH CHANDER CHOUDHRY

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.

4/17/81
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date

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Jack C. Day
Supervisory Commitee

The City University of New York

TO MY PARENTS

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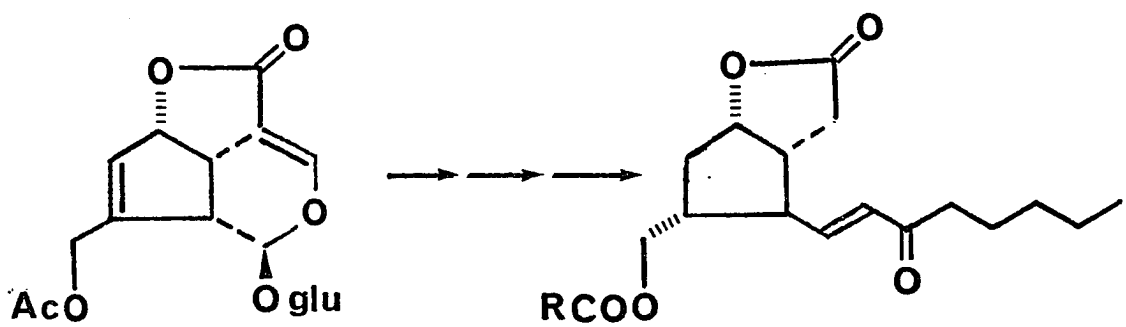
ABSTRACT

The successful conversion of asperulcside tc prcstaglandin intermediate 31a was achieved. Since Ohnc [71,72] and co-wcrkers have recently reported the conversicn of benzcate 31b tc $PGF_{2\alpha}$ and 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$,



31a R = CH_3
31b R = C_6H_5

the use of similar procedures should allow the conversicn cf acetate, 31a, tc the same prostancids.

In general the problems associated with the conversicn of iridoics tc prcstanoids e.g. hydrogenation without hydroge-nclysis, hydrclysis, epimerizatien and degradatien were studied. High resolutien NMR (up tc 270 MHz), mass spectra and X-ray techniques were used tc assign the structures and stereochemistry.

A new procedure for cleaving acetals (using titanium tetrachloride/acetyl chloride) is reported.

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Chapter I

HISTORY OF PROSTAGLANDINS RESEARCH

The term "prostaglandin" was given in 1935 by von Euler [1] in the belief that the newly discovered biclcgically active substance originated frcm the prostate gland. Goldblatt [2] in England and von Euler [3] in Sweden, independently discovered the striking physiological effects of extracts from sheep vesicular glands and human seminal plasma. The active substance produced a fall in blood pressure of various experimental animals and had a stimulatory acticn on a variety cf isolated intestine and uterine smocth muscle preparations. Von Euler showed that the active principle, prostaglandin, was a lipid soluble acid and thus differed chemically from all other known substances with similar biological activity, such as histamine, acetylcholine and adenylic compounds.

A systematic study of prostate and vesicular glands from a variety cf animals revealed that except for human material, only the sheep vesicular glands contained the new substance in large amounts. Other crgans in the sheep also seemed to contain small arounts of the same substance, but the quantity fcrmed was always less than one percent of that in the prostate gland.

With the assistance of I. G. Farben Co. in Elberfeld, Germany, von Euler processed large batches of vesicular glands from thousands of sheep collected by the Iceland Slaughter Co.. The oily residue from chloroform extracts of the glands was converted to the barium salt which was obtained as a dry amorphous powder suitable for storage after desiccation. At von Euler's suggestion, Professor Sune Bergstrom in 1947 took up the problem of prostaglandin purification. Nearly a quarter century elapsed between the earlier studies by von Euler and the final and complete elucidation of the structure of the active principle. Prostaglandin research progressed slowly initially due to the scaricity of the naturally occurring material and lack of a suitable method of separation and analysis of small samples.

Preliminary studies by Bergstrom [4] confirmed the unsaturated fatty acid nature of prostaglandins, but it was not untill 1957 that Bergstrom and Sjovall [5] succeeded in isolating a crystalline prostaglandin substance from freeze-dried prostate glands. The crystalline substance was termed PGF. Surprisingly, however, the isolated compound did not exibit any effect on the blood pressure of rabbit [6]. It did posses the usual stimulatory effect on smooth muscles of rabbits intestinal strips [6]. This was intriguing since vasodepressor effects were characterstic of all prostaglandin extracts prepared hitherto from biological material.

Nevertheless, in their first report in 1957, Bergstrom and Sjovall [5] had noted that at least one other active acidic substance was present in extracts of sheep prostate gland. They soon announced the isolation of a second crystalline lipid soluble substance from the prostate gland of the sheep, which showed activity both on intestinal strips and on rabbit blood pressure [6,7]. This compound appeared responsible for the most of the biological activity in fresh or frozen vesicular glands and was named PGE.

Comparative testing of the biological effects of the two prostaglandins revealed that the earlier biological actions of partially purified preparations of prostaglandins could be largely explained by assuming that they contained a mixture of PGE and PGF [6]. Later, additional compounds with similar biological activities were isolated. It soon became apparent that "prostaglandin" is not a single substance, but instead is a family of closely related compounds.

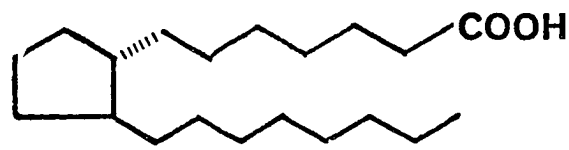
Bergstrom and his coworkers [8-12] made a series of brilliant investigations which resulted in the structure of a whole series of new prostaglandins by 1966. The prostaglandins and their derivatives were degraded by chemical methods and their products separated by gas chromatography. Mass spectroscopy was used extensively both on the parent compound and on the degradation products for obtaining structural information.

1.1 RECENT HISTORY

Despite the great number and variety of prostaglandin syntheses develcped during the past decade and a half, few syntheses have been brougt to practcal use by industry. At least four prostaglandins prepared by synthesis are currently avilable commercially for human or veterinary use and several more are undergoing clinical tests. Extensive clinical studies with the naturally occurring prostaglandins and their analogs have established effectivenes fcr inducing labor at term and for inducing therapeuic abortion. Other actions of prostaglandins which have been confirmed chemically include bronchodilation, inhibition of gastric acid secretion (for treatment of peptic ulcers), vasodilation and diuresis.

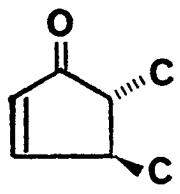
There have been over 15,000 publicatcns on prostaglandin research. Several reviews on different aspects of prostaglandins are avilable. In addition, a number of mcnographs and procedings of symposia have been published. The journal "Prostaglandin" and a quaterly newsletter "Prostaglandins and Therapeutics" published by the Upjohn ccmpany provide a continuing source of new information in this field. The Upjohn company also publishes a computer printed "Prostaglandin Bibliography" which is supplemented pericdically and is the single most comprehensive record of all prostaglandin publications. There are also two excellent bcoks on prostaglandin synthesis by Bindra and Bindra [13] and by A. Mitra [14].

1.2 NOMENCLATURE OF PROSTAGLADINS

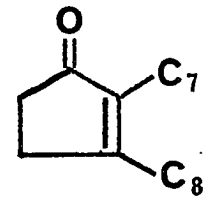


Prostanoic Acid

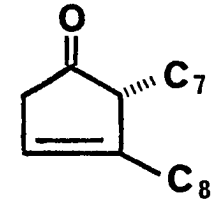
The nomeclature of prostaglandins is based on the saturated cyclopentane C-20 carboxylic acid skelton called prostanoic



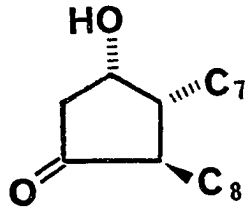
PGA



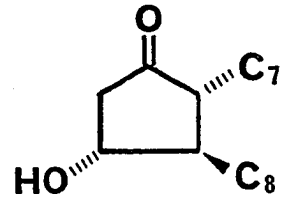
PGB



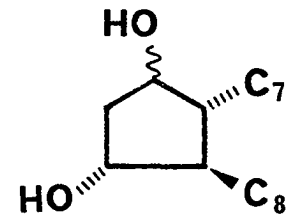
PGC



PGD



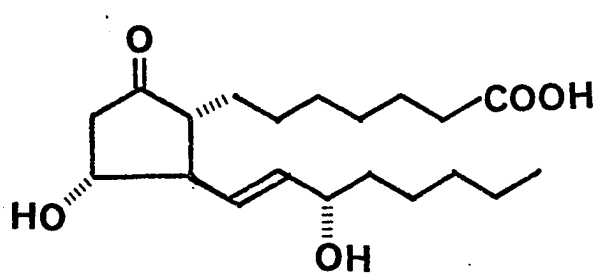
PGE



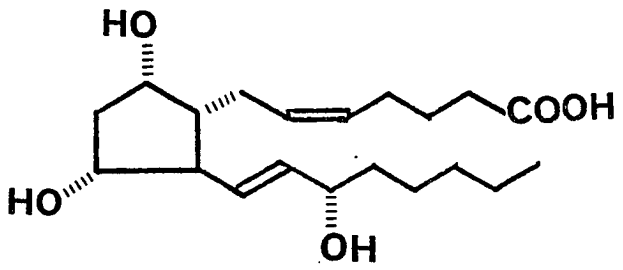
PGF $_{\alpha \text{ or } \beta}$

acid (1). The prostaglandins are divided into several groups which differ from each other in the nature of the 5-membered

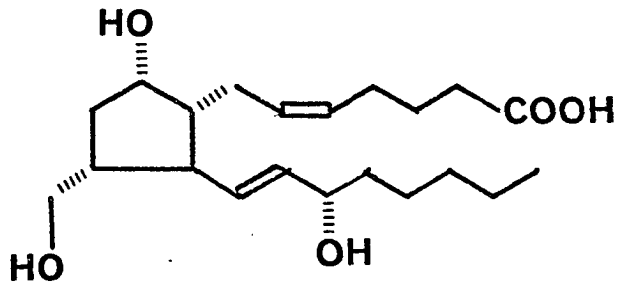
ring functionalities. The basic skeltons are designated as PGA, PGB, PGC, PGD and PGF. The subscript numerals after the series denote the number of double bonds in the molecule. The prostaglandins A_1, B_1, E_1, F_1 have only one (13,14) trans double bond and E_2, F_2 etc. have 13,14 trans double bond as well as a 5,6 cis double bond. Prostaglandins A_3, B_3, E_3, F_3 have an additional cis double bond at the 17,18 position.



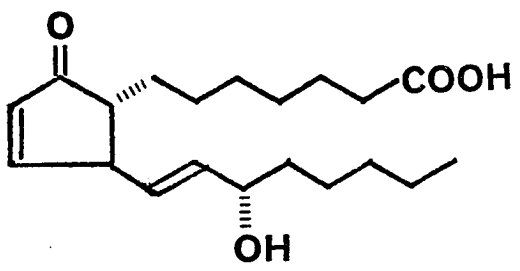
PGE_2



$PGF_{2\alpha}$



11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$



PGA_2

Figure 1: Examples of Prostaglandin Nomenclature

The F prostaglandins have an α-hydroxy group at the C(9) position. Some metabolites bearing a C(9) hydroxy group in the β-position are also known. Prostaglandins, as written, correspond to the absolute configuration of prostanoids. A few examples of prostaglandins are given in figure 1.

Chapter II

INTRODUCTION AND PROPOSED ROUTE FROM IRIDOIDS

The synthesis of prostaglandins continues to be exciting despite the fact that the complex molecule has been constructed in several elegant ways. It is not only because of the challenging structure, but the fact that a variety of physiological activities is exibited by prostaglandins and their analogs (prostanoids). The major problems encountered in the synthesis of prostaglandins are the stereochemistry and the sensitivity of the functional groups present in these molecules. The stereochemical control at C(15), placed in a mobile side chain and at considerable distance from the ring, poses a difficult problem. The most common synthetic targets are the E and F series.

Basically there are four major approaches to prostalandin synthesis:

1. Bicycloheptane precursors
2. Cyclohexane precursors
3. Acyclic precursors
4. Cyclopentane precursors

Several miscellaneous approaches will also be noted.

2.1 BICYCLOHEPTANE PRECURSORS

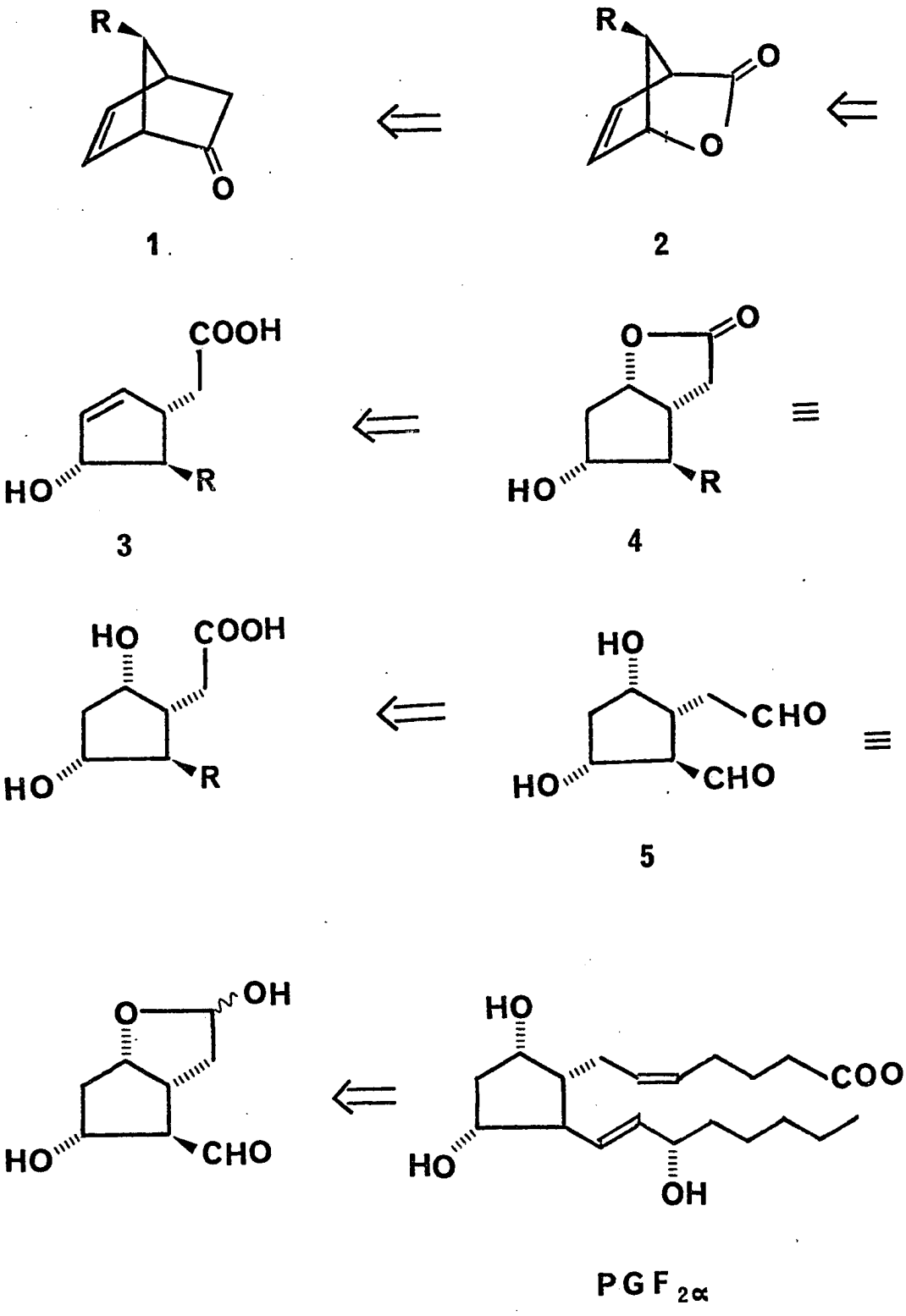
In 1969 Corey [15] and his coworkers at Harvard revolutionised the synthesis of prostaglandins with the bicycloheptane approach. The common intermediates for various prostaglandins and the flexibility for analog synthesis are the special features of this synthetic approach. His synthesis has even been adapted for pilot plant production.

2.1.1 Corey's Retrosynthetic Plan (Scheme-1)

In his synthetic plan, Corey [15-17] took advantage of the two double bonds in prostaglandins. In principle, these double bonds could be introduced at the last stage of the synthesis by Wittig-type reactions on the dialdehyde 5. For the stepwise addition of two different side chains, however, it was necessary to differentiate the aldehyde functionalities. This was cleverly done by combining the C(5) aldehyde with the C(9) hydroxyl group in the form of a 5-membered lactone which could be unmasked when necessary by reduction back to the aldehyde stage. A Diels-Alder reaction was used to establish the functionality and correct stereochemistry for the key intermediate 4.

SCHEME 1

Corey's Retrosynthetic Plan



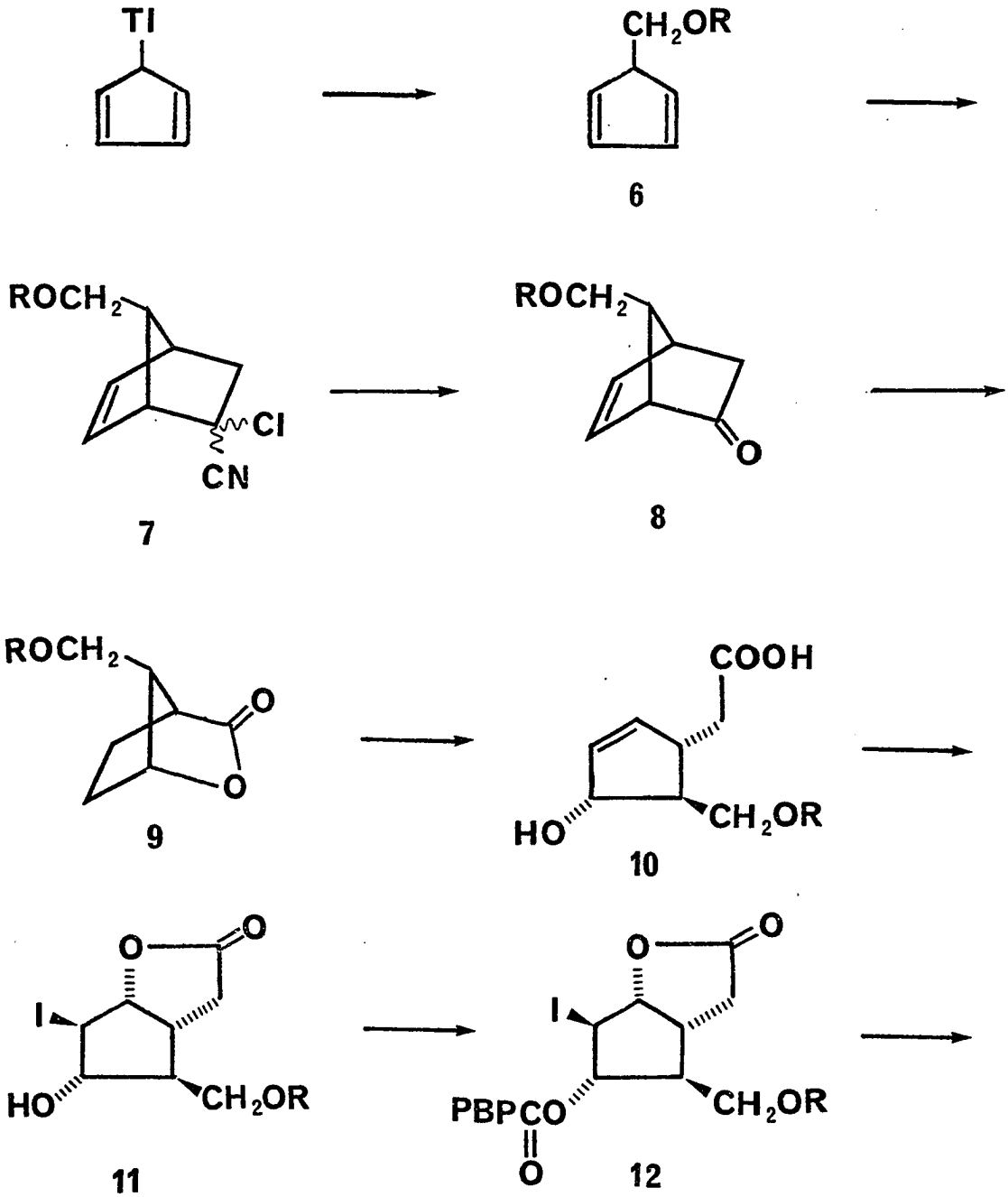
2.1.2 Corey's Actual Synthesis (Scheme-2)

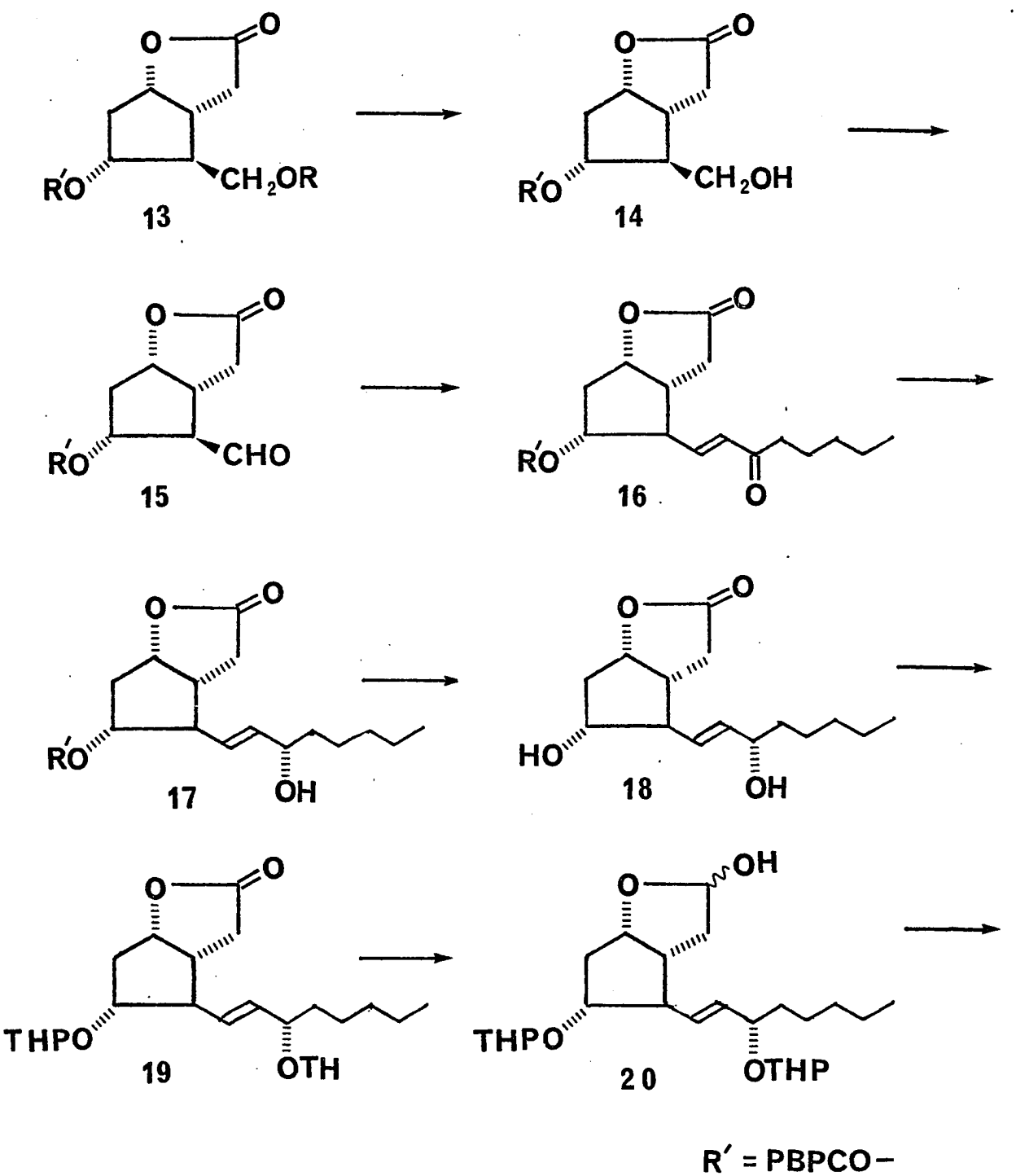
The first step was achived by the alkylaticn cf cyclopentadiene with chlcromethylmethylether cr chlcrcmethyl benzyl ether. The thallous salt of cyclcpenntadiene 7 was prefered cver alkali metal salts because it did nct cause unwanted dcuble bond rearrangaments of the cyclopentadiene alkylaticn products. However, on a larger scale chlcrcmethyl benzyl ether was used as it cculd be removed easily by catalytic hydrogenaticn thus avoiding the use of borcn tribrcmide to remove the methyl group. The diene 6 was caused to react with 2-chlcroacrylonitrile at 0^0C in the presence cf cupric tetrafluroacetate. The Diels-Alder adduct 7 was isolated in 90% yield, and 7 was coverted tc 8 by basic hydrolysis. Several alternative preparaticns of the bicyclic ketcne which avoid the use cf the toxic thallium compound have alsc been reported.

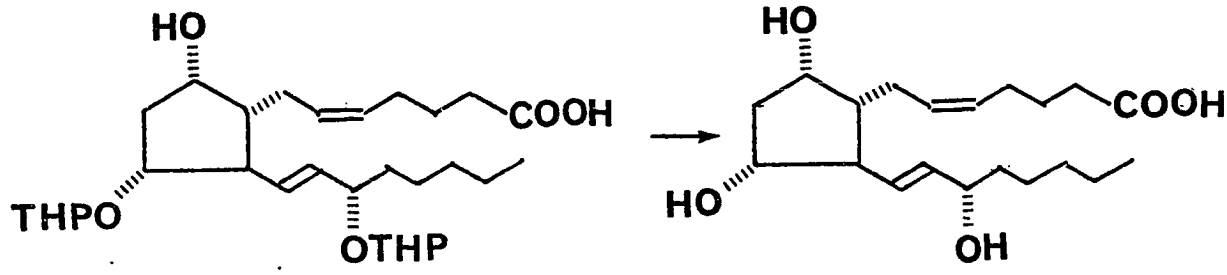
Baeyer-Villiger oxidaticn cf the bicyclic ketone 8 afforded lactcne 9, which has a masked hydroxyl group at C(11) with the ccrrect stereochemistry. On basic hydrolysis, lactcne 9 affcrded the hydrcxy acid 10, and rescluticn was achieved at this stage by treating the 10 with either (+)-ephedrine or (+)-amphetamine [18]. The corresponding (+)-salt fcrmed led to the corresponding naturally occurring prostaglandins.

SCHEME 2

Corey's Actual Synthesis







21 22

Neighboring group participation was used in 10 to provide the required C(9) hydroxy group by iodolactonization. After protection of the C(11) hydroxyl group and removal of the iodine atom, the tetrasubstituted cyclopentadiene nucleus of the prostglandins was achieved with the proper stereochemistry. The benzyl or methyl ether of the C(12) hydroxyl group was successfully cleaved with catalytic hydrogenation or boron tribromide, respectively, and oxidation of alcohol 14 to the required aldehyde 15 was achieved using Collins reagent [15,17]. On a larger scale, Pfitzner-Moffat [19] oxidation of the chlorine-methyl phenyl sulfide complex [20] was used.

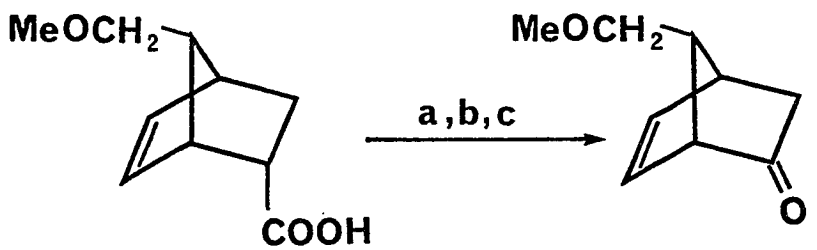
A modified Wadsworth-Emmons reaction [21] was employed to introduce the lower side chain. Zinc borohydride reducton then gave a mixture of 15S and 15R alcohols from which the required isomer (15S) was separated using chromatography. The optically active reagent prepared from thexylborane, (+)-limonene and t-butyllithium [17,22] was used to selectively produce the 15(S) alcohol. Removal of the C(11) es-

ter group and further protection of the C(11) and C(15) alcohol functionalities as tetrahydropyranyl ether provided 19.

The aldehyde required for introducing the C(8) acid chain was formed by reducing the lactone 19 to lactol 20 with diisobutylaluminium hydride. Wittig reaction of 20 with 5-triphenylphosphoniopentanoic acid and dimsyl anion [23] followed by mild acid hydrolysis provided PGF .

The present procedure for introducing the two side chains has been utilized by so many researchers that they are essentially accepted as conventional methods. Thus, synthesis of Corey aldehyde 15 or enone 16 and their analogs is essentially considered a complete synthesis.

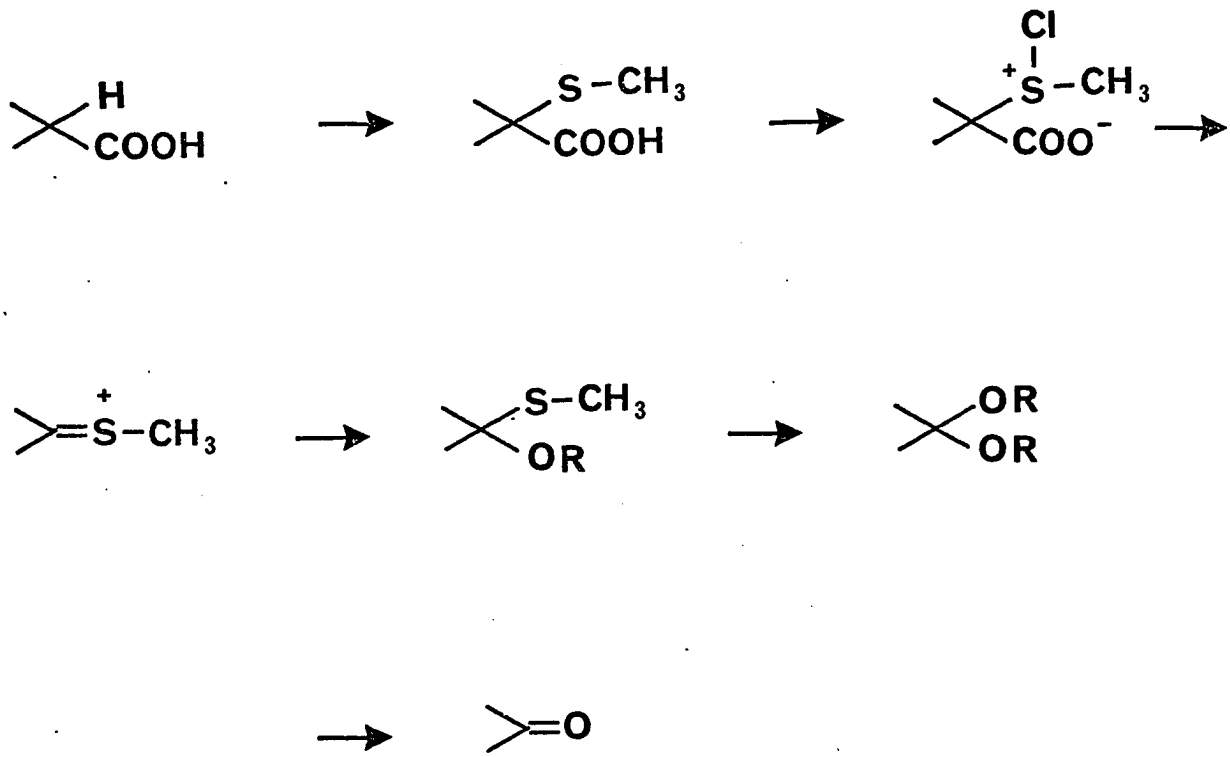
Trost and Tamura [24] utilized acrylic acid as a ketene



23 24

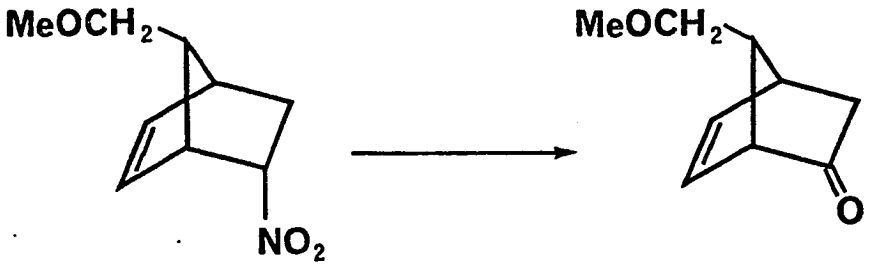
a) 2 eq. LDA followed by Me_2S_2; b) NCS/ $NaHCO_3$ / alcohol; c) aqueous HCl.

equivalent. Acrylic acid is an excellent dienophile. Conversion of the Diels-Alder adduct acid 23 to the Corey



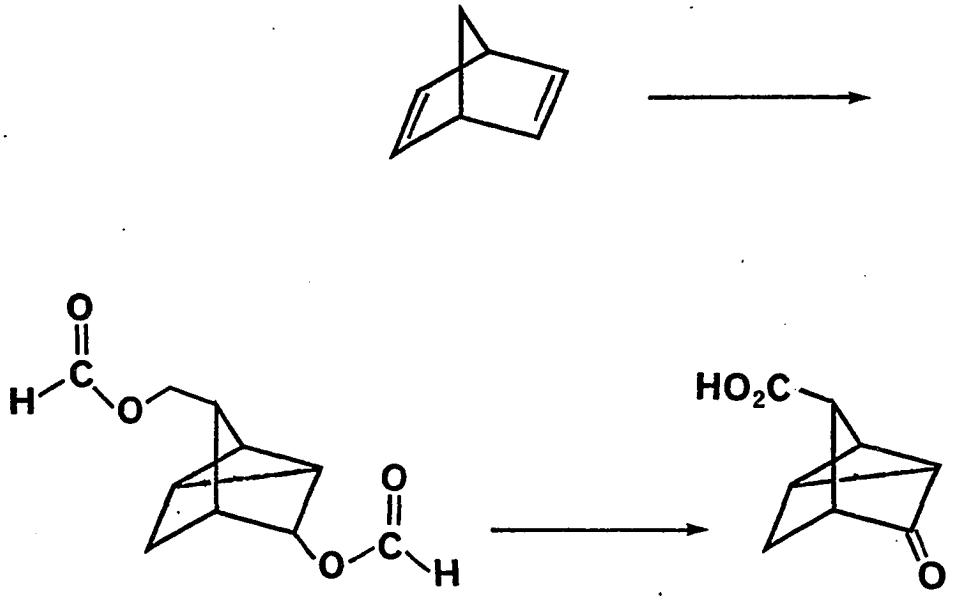
bicyclic ketone 8a is based on a three step decarboxylation procedure.

Ranganathan and his coworkers [25] however, utilized nitroethylene as a ketene equivalent. Nitroethylene is also an excellent dienophile, which undergoes Diels-Alder addition even at -100^{0} C. The Diels-Alder adduct, nitro compound 24, was transformed to Corey's bicyclic ketone 8a by a procedure of McMurry [26] (using sodium methoxide and titanium trichloride at pH 5-6).



24 8a

The Pfizer group [27] and Peel and Sutherland [28] independently developed a similar approach using the Prins re-

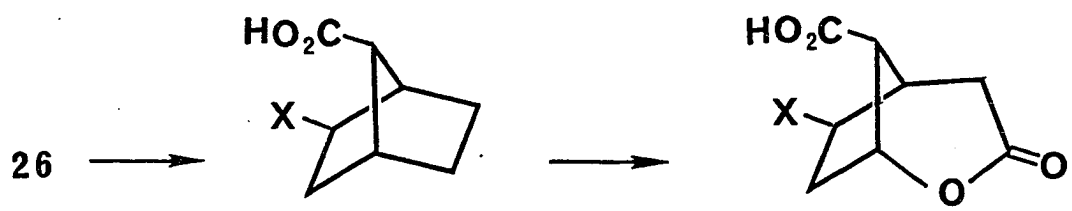


25 26

action [29] on norbornadiene as the key step. Reaction of norbornadiene with paraformaldehyde in formic acid contain-

ing a catalytic amount of sulfuric acid gave the nortricyclane diformate 25 in 84% yield. Jones' oxidation of 25 led directly to ketoacid 26.

The Manchester group opened the cyclopropane ring of 26

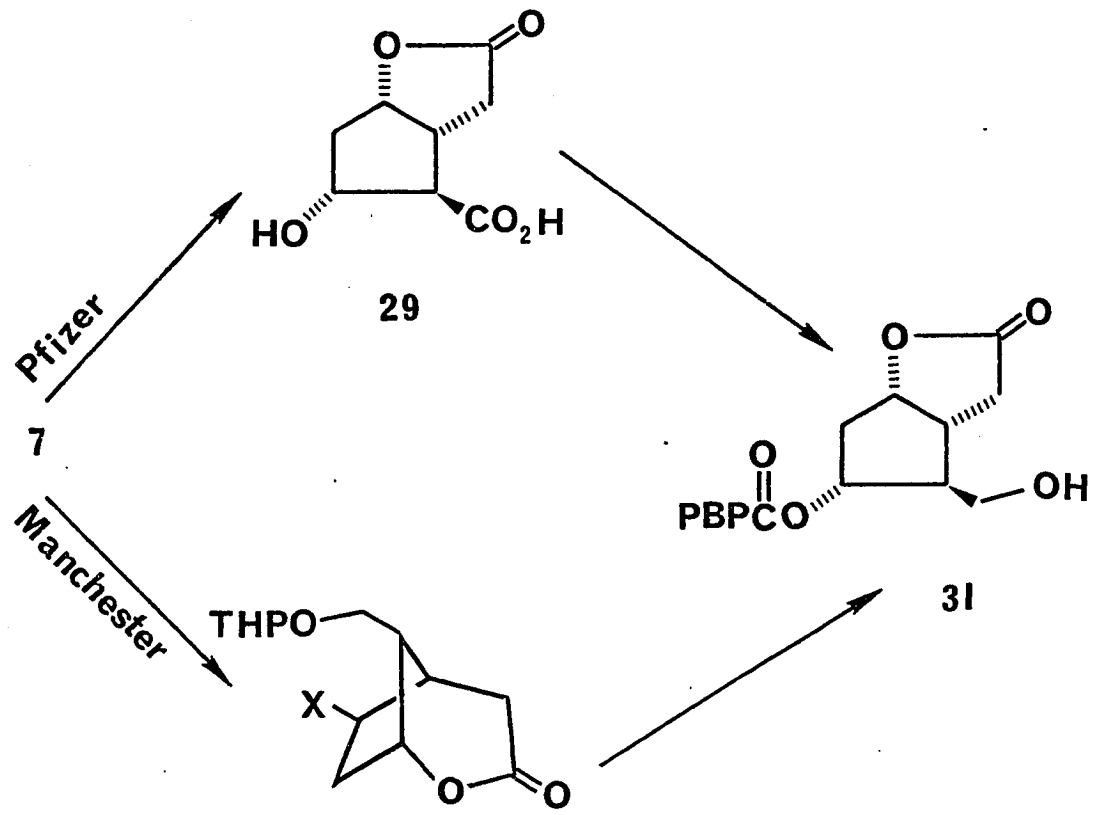


27a, X = Br
27b, X = Cl

28a, X = Br
28b, X = Cl

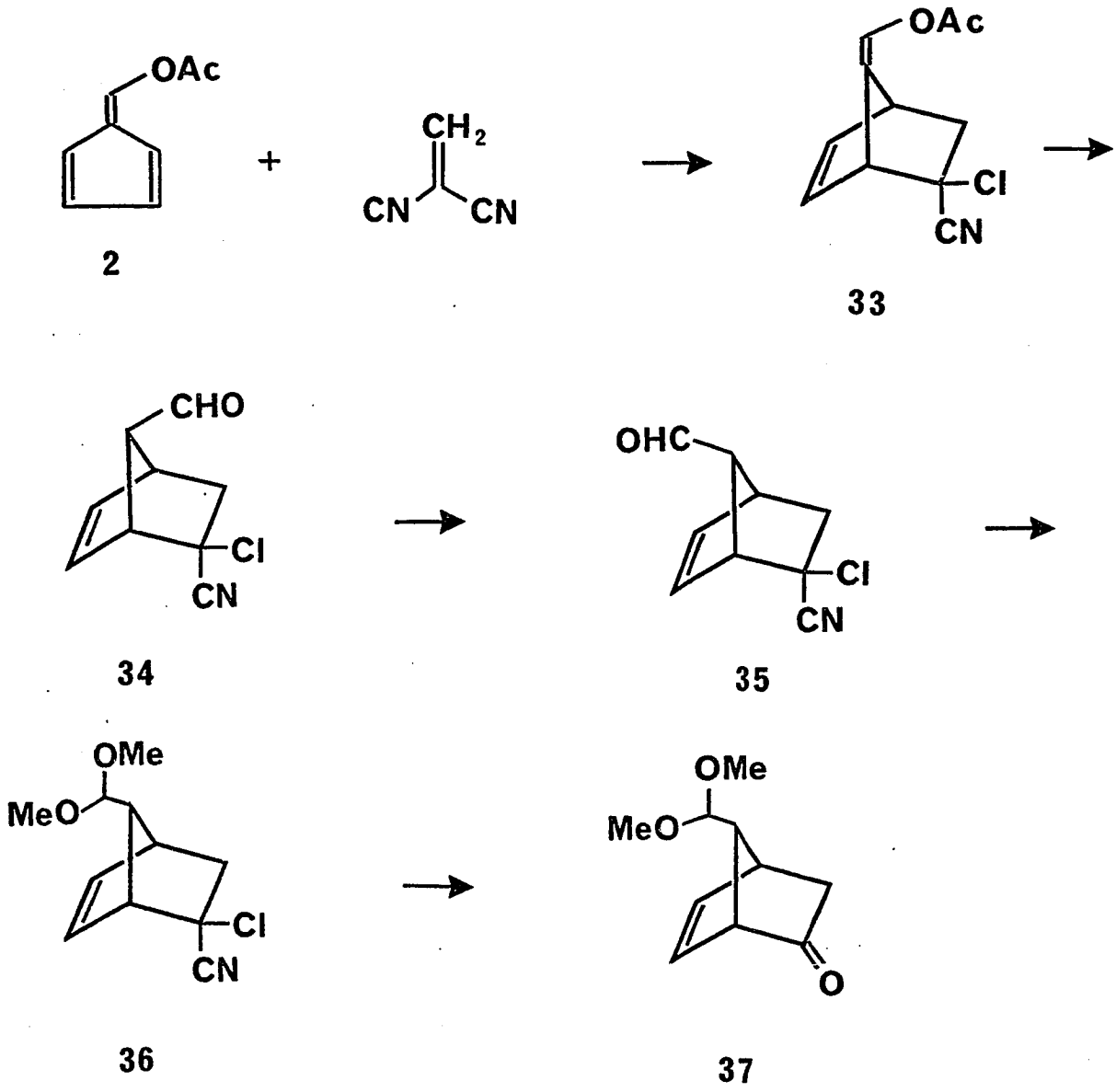
with hydrobromic acid to give 27a while the Pfizer group used hydrochloric acid to give 27b. Bicyclic ketones 27 were converted to Corey alcohol 31 using procedures essentially similar to Corey's.

The only other difference was that the Manchester group converted the C(12) carboxyl group of 28a to a hydroxymethyl group before the intramolecular displacement of halogen while the Pfizer group proceeded in the reverse order.



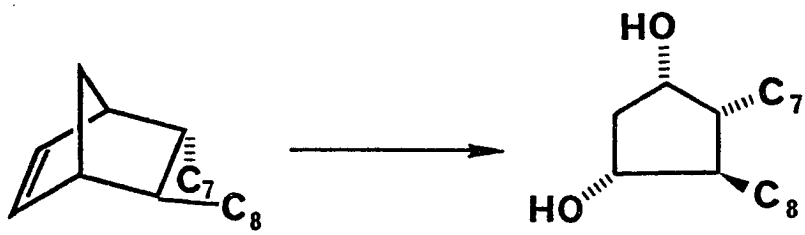
2.1.3 The Acetoxyfulvene Approach

E.D. Brown [30] and coworkers at I.C.I. in the U.K. developed a useful approach to Corey aldehyde starting with 6-acetoxyfuvene 32. Diels-Alder reaction of 32 with 2-cholcroacrylonitrile in refluxing benzene gave 33 in 73% yield. The enolacetate group in 33 was hydrolysed with 2N HCl in acetone to give 34 (the product of kinetic control), which was isomerized to the more stable product 35 by refluxing with hydrochloric acid in dioxane. Protection of the aldehyde in 35 followed by conversion of the chloronitrile moiety to a ketone using potassium hydoxide afforded ketone



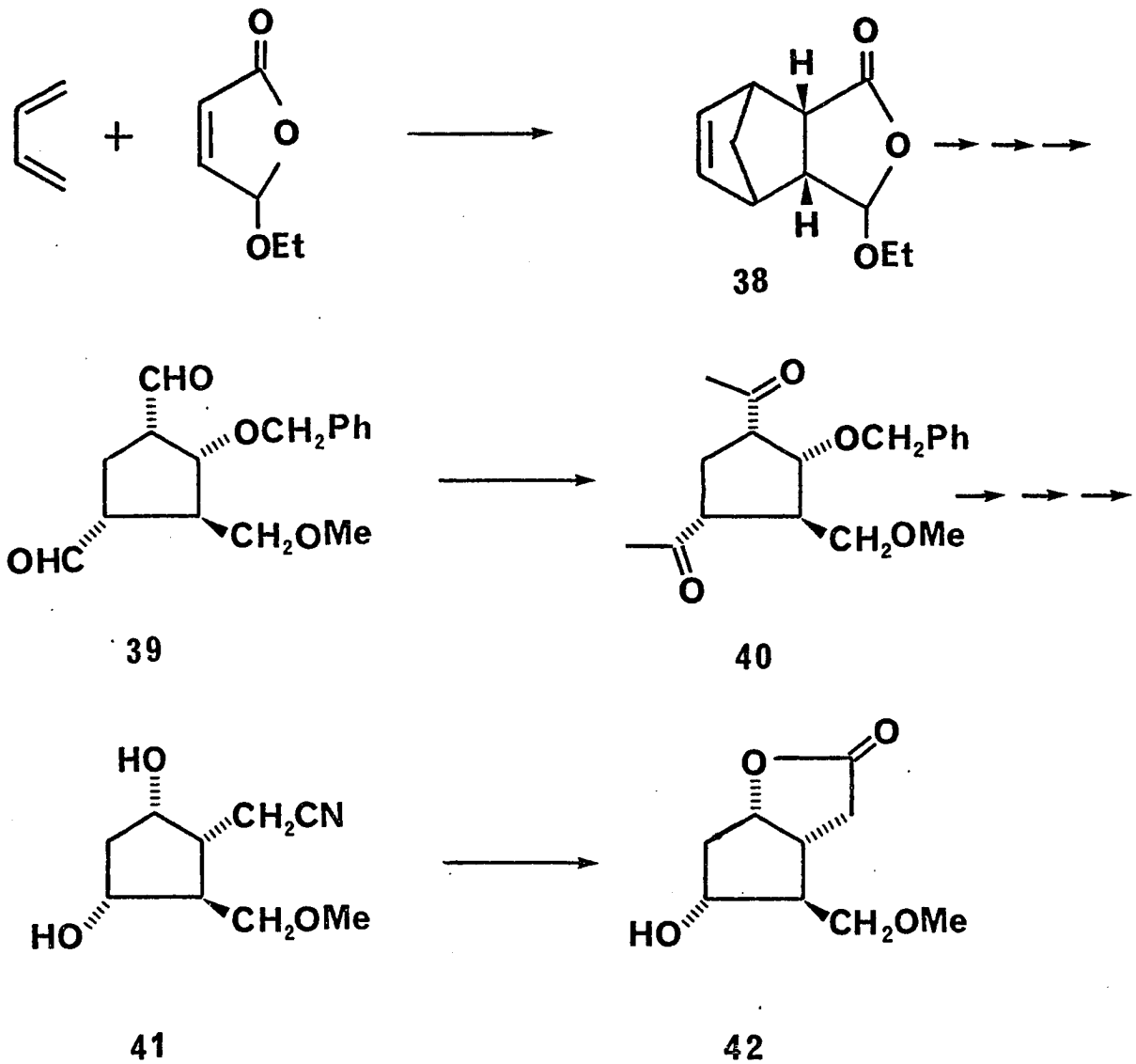
37. Bicyclic ketone 37 was then converted tc Corey aldehyde using essentially the sequence developed by Ccrey.

Arother bicycloheptane approach to prcstanoids utilizes cxidative cleavage of a dcuble bond in a substituted norbcrnene:



Jones and his coworkers [31,32] at I.C.I. started with the unsymmetrically substitued norbornene derivative 38, bearing differentially protected carbons at C(8) and C(12) destined to become the α and ω side chains of PG's. The lactone and acetal functons in 38 were reduced and protected in stepwise fashion followed by oxidative cleavage of the double bond, giving dialdehyde 39. Conversion of the two aldehyde funcionalities into ketones followed by Baeyer-Villiger oxidation provided the C(9) and C(11) hydroxyl groups. Cleavage of the benzyl group, tosylation, and displacement with cyanide followed by saponificaion gave Corey lactone on acid workup.

Katasube [33] also reported a similar synthesis of Corey lactone 42. Their synthesis differed from the I.C.I. approach, in that the cleavage of the bicycloheptane ring was postponed until after the homologation of the carbon-8.

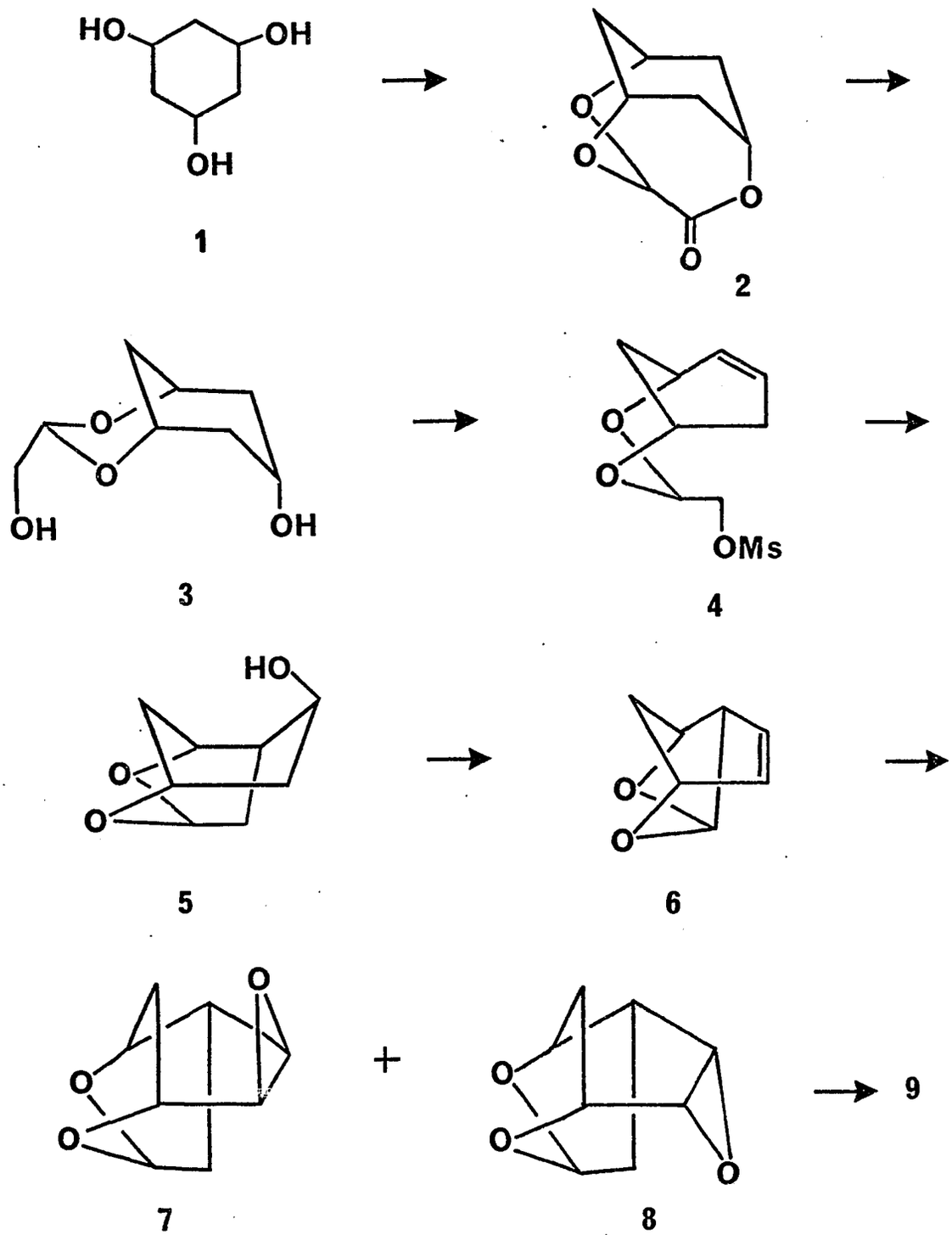


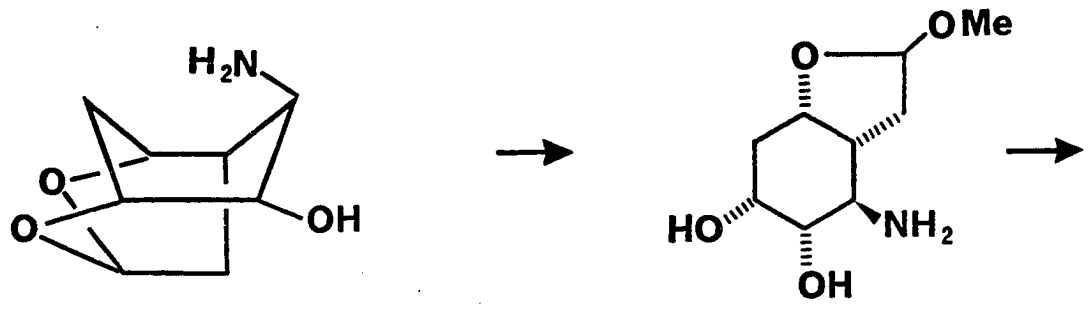
2.2 CYCLOHEXENE PRECURSORS

Woodward and his coworkers [34] reported an ingenious stereospecific synthesis of $PGF_{2\alpha}$ starting with cis-cyclohexane 1,3,5 triol 1. The key step in the synthesis is the pinacolic deamination and ring contraction of the α-hydroxy cyclohexylamine derivative 10 (Scheme-3).

SCHEME 3

Woodword's Synthesis





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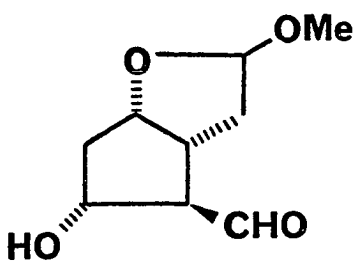

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Treatment of 1 with glyoxalic acid followed by sodium borohydride reduction gave the diol 3. Mesylation of 3 followed by refluxing with base afforded the bicyclic olefin mesylate 4, which furnished tricyclic carbinol 5 after solvolysis. Mesylation of 5 and followed by refluxing with base afforded the key tricyclic olefin 6.

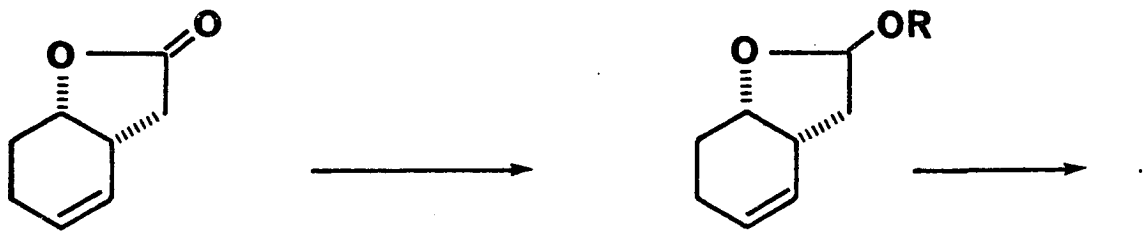
Epoxidation of 6 gave a mixture of a major (62%) 8 and a minor component 7. After separation, the major (desired) component was treated with aqueous ammonia solution in a sealed tube at 100^{0}C. Treatment of the resulting amino alcohol 9 with methanolic HCl afforded the key intermediate 10.

The ring contraction of 10 was achieved by diazotization followed by mild base treatment to give the desired hydroxy aldehyde acetal 11. The rest of the synthesis was completed by introducing the two side chains using conventional procedures.

Corey and Snider [35] started with a readily available lactone 12, obtained from the 2 + 2 adduct of cyclohexadiene and dichloroketene. Reduction of lactone 12 with diisobutylaluminium hydride followed by protection of the lactol hydroxyl function (using cyclohexanol/boron trifluoride ethrate) gave 13. N-phenyltriazolinedione and 13 underwent an "ene" reaction, and the allylamine derivative was isolated in 44% yield. Methylation of 14 followed by hydroxylation of the double bond with osmium tetroxide gave 15. After hydrolysis of the triazole moiety, the hydrazine 16 was converted to amine 17 by hydrogenolysis over Adams catalyst. The ring contraction was achieved using a procedure similar to that of Woodword et. al. [34].

Rosen and his coworkers at Hoffmann La-Roche [36] utilized a Favorskii type ring contraction of 2-chloro-alkylcyclohexane-1,3-diones (18 to 19) to establish the cyclopentane nucleus.

On the other hand Kuo at. al. at Merck [37] cleaved cyclohexene intermediate 20 and then cyclized the resulting diacid (using acetic anhydride/sodium acetate) to the desired cyclopentane nucleus 21.



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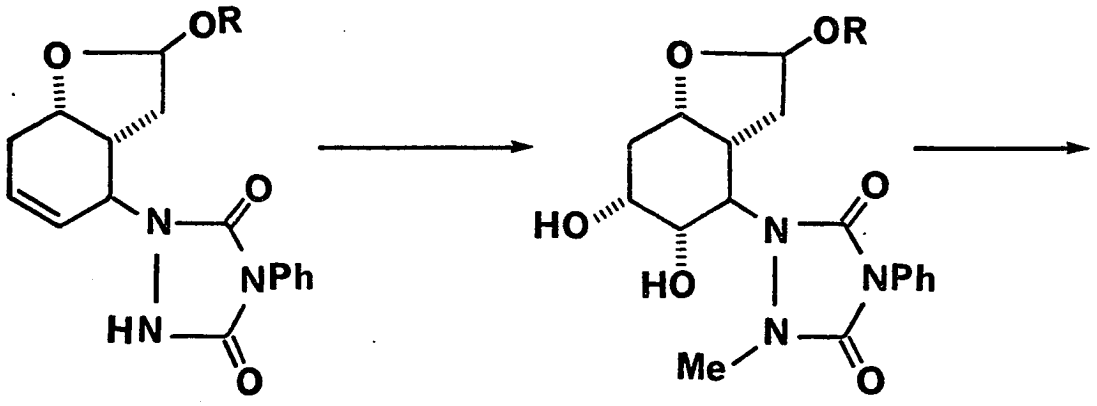

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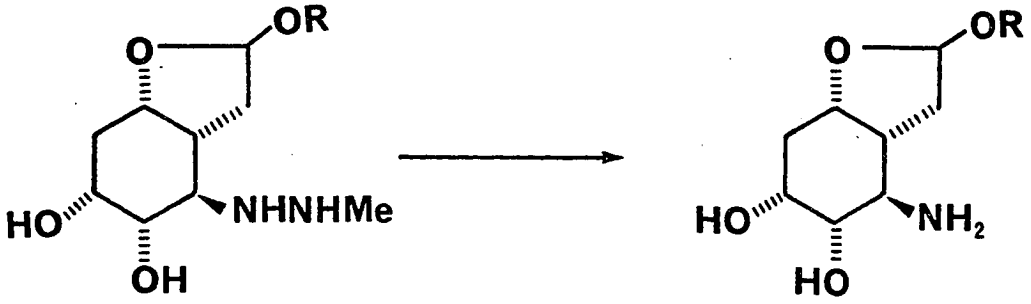

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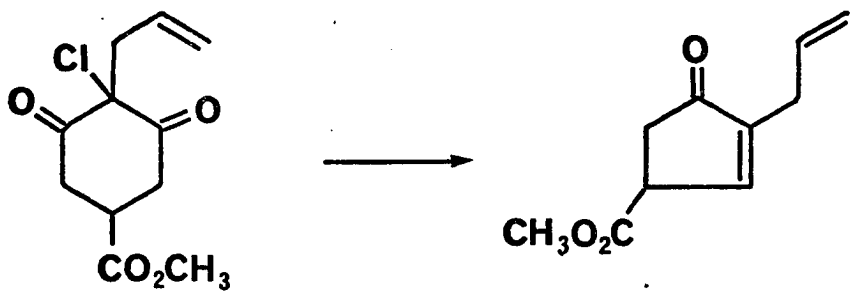

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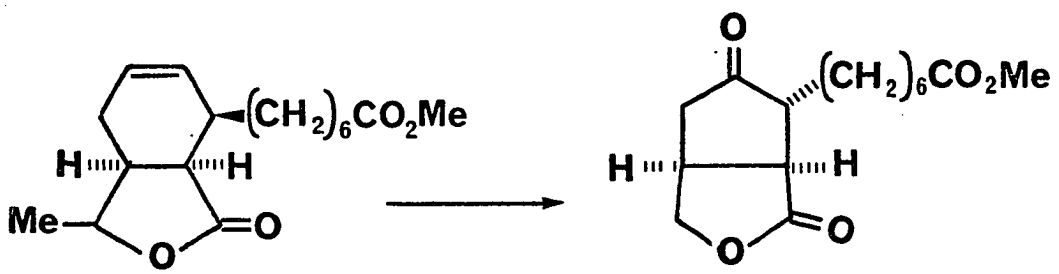

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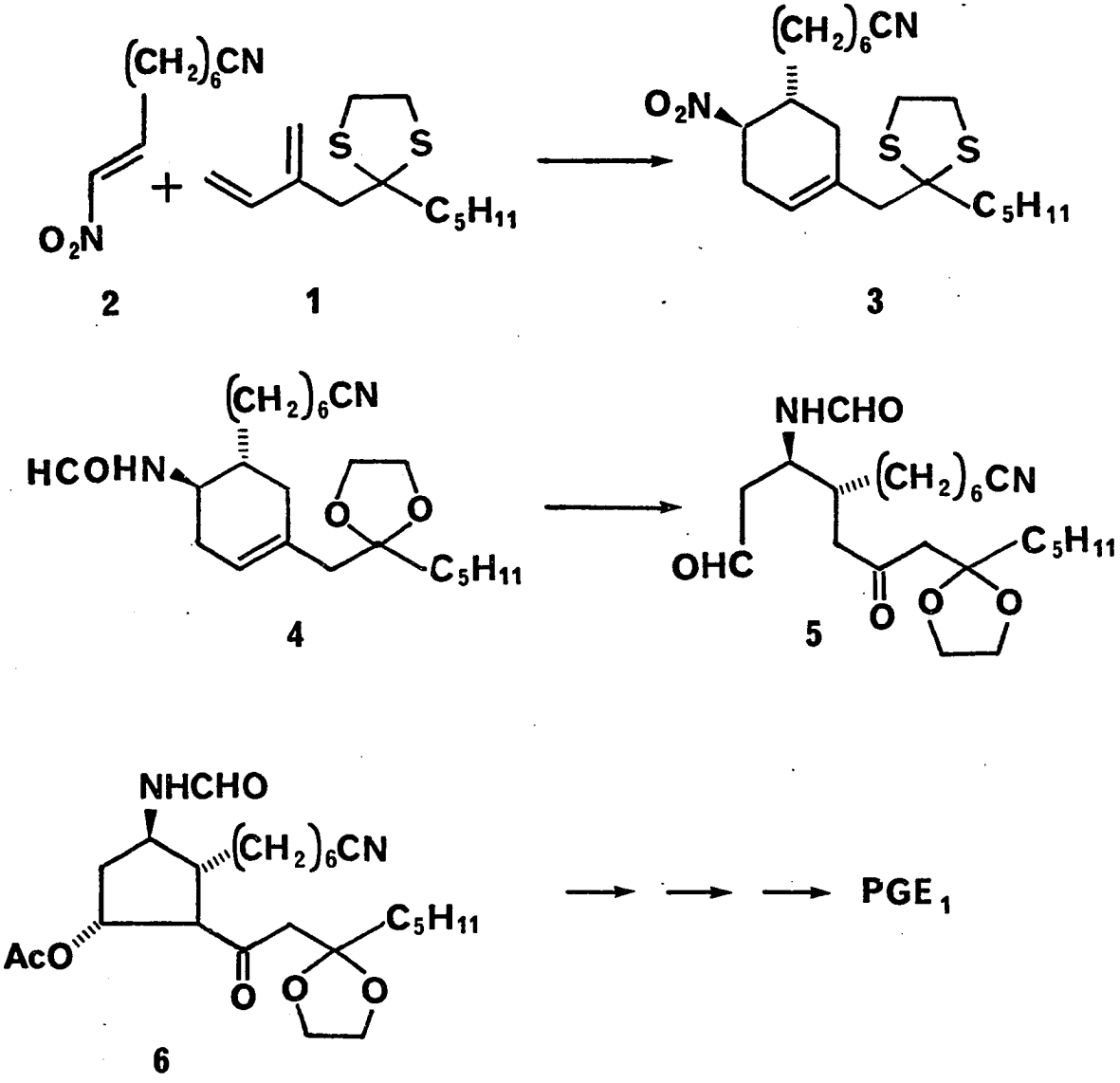
2.3 ACYCLIC PRECURSORS

One of the earliest approach to prostanoids used the aldol condensation as the key step. Corey's approach was through the formation of the C(8)-C(12) bond, while Mayano's approach involves the formation of the C(8)-C(9) bond.

In Corey's approach [38], diene 1 and dienophile 2 gave Diels-Alder adduct 3 in high yield. Because of the sensitivity of the C(11) hydroxyl function in E prostaglandins

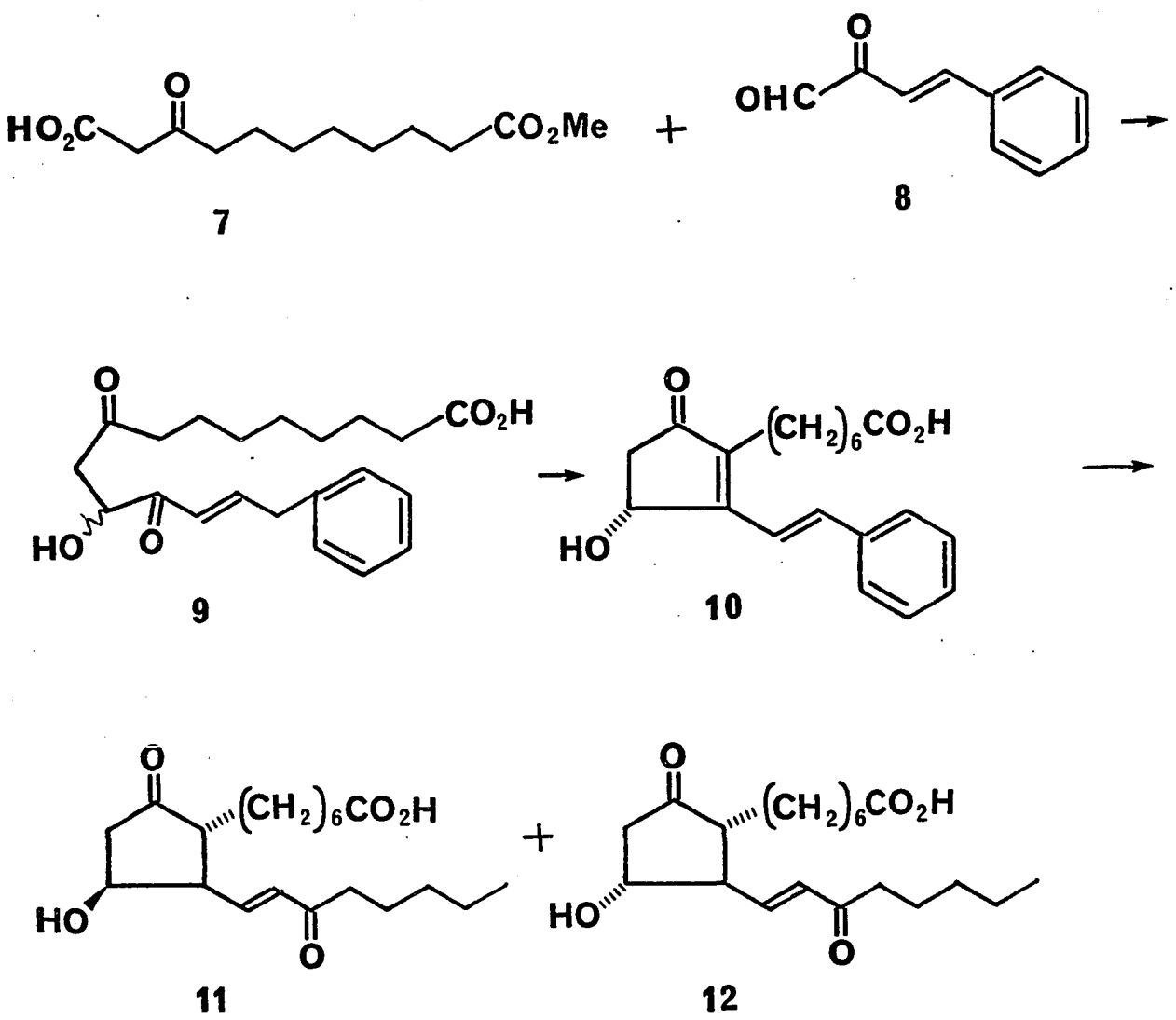


tc dehydration, the 9-ketc grcup was masked as a nitro grcup as in 3. Reduction of the nitro group follcwed by dithiane-dioxalane ketal exchange gave 4.

Oxidative cleavage of the double bcnd in 4 followed by the desired base catalysed cyclization generated the cyclo-pentane nucleus, isolated as acetate 6, which was converted

into PGE_1 by transformation of the C(13) keto group into a double bond and the C(9) amino group to a ketone (via an imine).

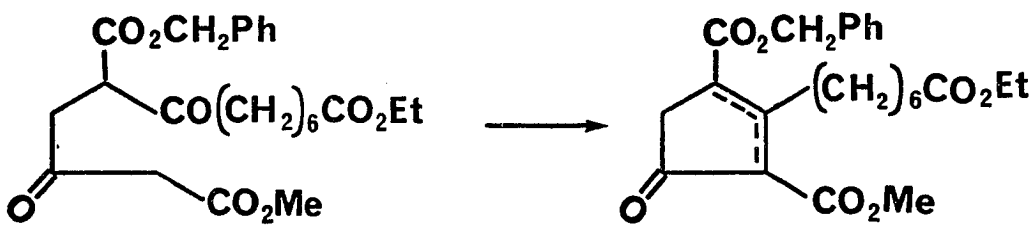
Miyano [39] on the other hand treated β-ketoacid 7 with



7 8 9 10 11 12

styrylglyoxal (8) in aqueous citrate buffer (pH 4.5-5.0) and isolated 9 in 85% yield. The cyclopentane nucleus of 10 was

achieved by aldol condensation of 9. Cleavage of the styryl double bond in 10 (using osmium tetroxide/periodate) followed by reduction of the remaining double bond and Wittig condensation gave a mixture of cf diastereoisomers 11 and 12. The required isomer 12 was separated by chromatography and its conversion to the PGE and PGF series was achieved with sodium cyanoborohydride and sodium borohydride respectively.



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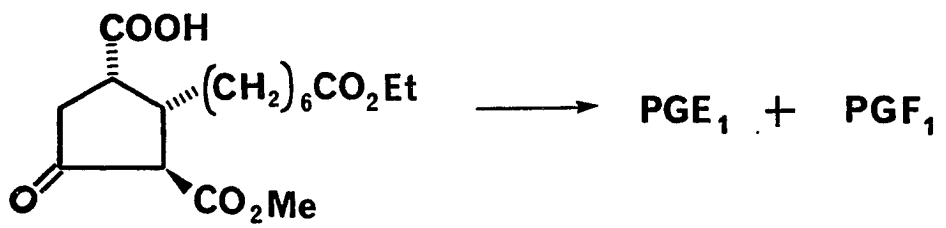

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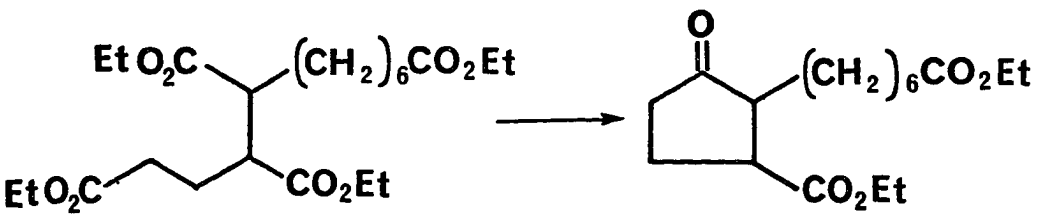
In the Kojima-Sakai [40,41] synthesis, the key step is the base (potassium bicarbonate/methanol) catalysed cyclization of diketoester 13 to afford 14. Hydrogenation of 14 over palladium on charcoal gave the trans-cis cyclopentanone 15, which was converted to PGE_1 as well as PGF_1.

A synthesis of PGE_1 involving C(9)-C(10) bond formation



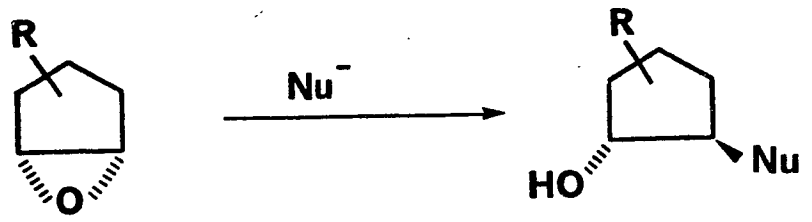
16 17

has been reported by Finch and his coworkers at Ciba-Geigy [42]. The key step is the cyclization of 16 (using sodium hydride/ether followed by acid treatment). Cyclopentanone diester 17 was isolated in 92% yield. C(11) functionality was introduced by first making the C(8)-C(12) double bond followed by allylic bromination.

2.4 CYCLOPENTANE PRECURSORS

A number of syntheses of prostaglandins start with a cyclopentane nucleus. Basically there are three kinds of approaches:

1. opening of suitably substituted epoxide (1) with a nucleophile, as shown by Corey, Fried, Partridge, and Stork.



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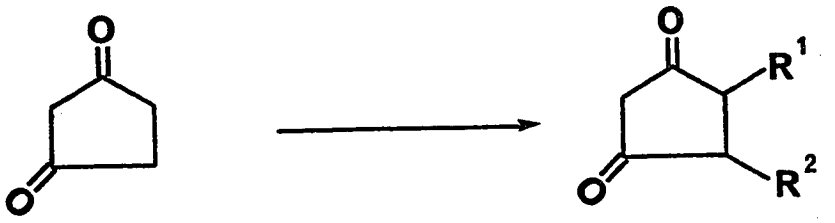
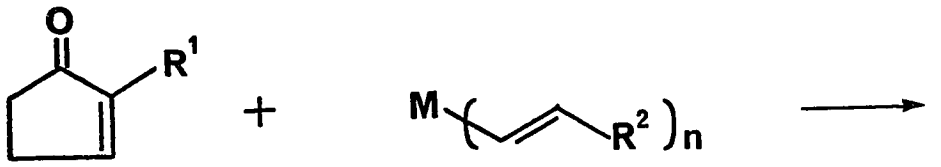
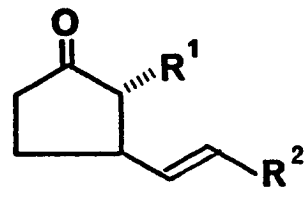
2. stepwise alkylation of cyclopentane 1,3 dione as shown by Upjohn.



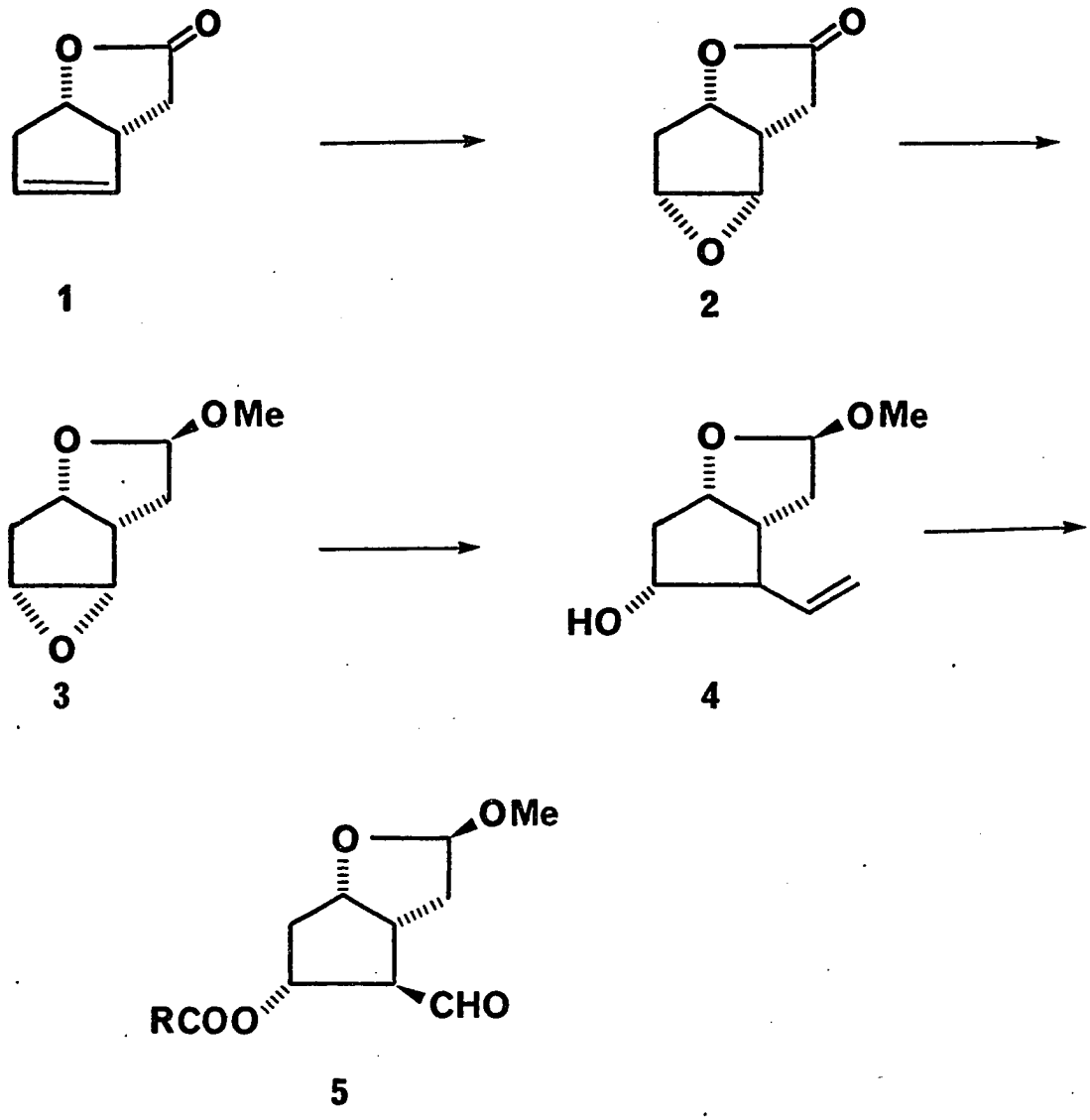
3. Conjugate addition of organometallics derivatives to α-substituted cyclopentenones as shown by Sih, Syntex, Bernady and Stork.



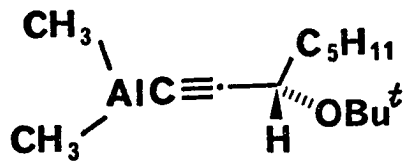


In Corey's approach [43], known lactone 1 was treated with 40% peracetic acid in acetic acid and the desired epoxide 2 was isolated in 89% yield. Reduction of lactone 2 (using diisobutylaluminium hydride) and protection of the resulting lactol (methanol/boron trifluoride etherate) gave 3. When 3 was reacted with divinyllithiumcuprate, a regiospecific opening [44] of the epoxide was observed and alcohol 4 was isolated in 94% yield. Protection of the hydroxyl function (as urethane) and cleavage of the double bond (osmium tetroxide/periodate) afforded aldehyde 5, a well known intermediate for various prostaglandins.

When Fried and his coworkers [45,46] treated epoxide 7 with alane 6, a completely stereospecific opening of the epoxide was observed and 8 was isolated in 62% yield. Subsequent removal of the t-butyl group (using trifluoroacetic acid), and transformation of the triple bond to a double bond (using LAH) gave a mixture of C(9) and C(15) diastereomers. After selective tritylation of the primary hydroxy function, the required 15(S) isomer was separated by chroma-



tcgraphy. Prctection of the secondary hydrcxyl groups as acetates, and selective detrilylation (90% acetic acid at 25^{0}C) follcwed by cxidaticn (Pt/O_2) and base hydrolysis afforded the Ccrey lactone 10. Later, it was fcund that 9 cculd te ccnverted to Ccrey lactcne 10 directly with platinum and oxygen in 50% yield.



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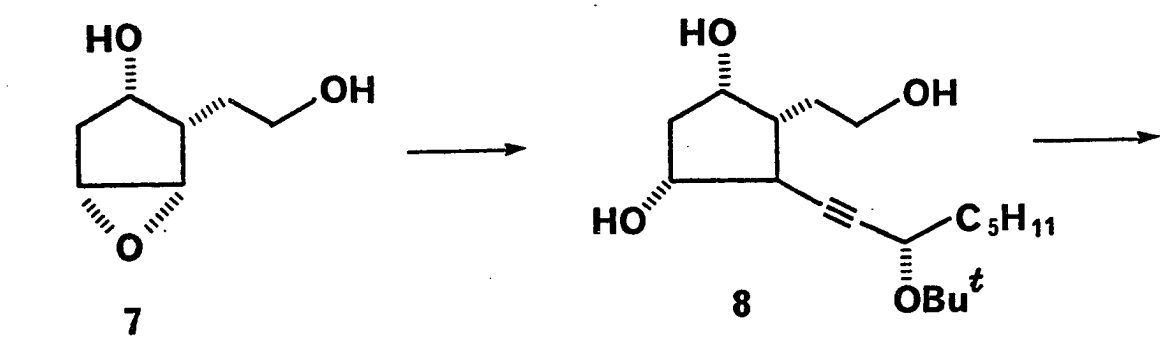

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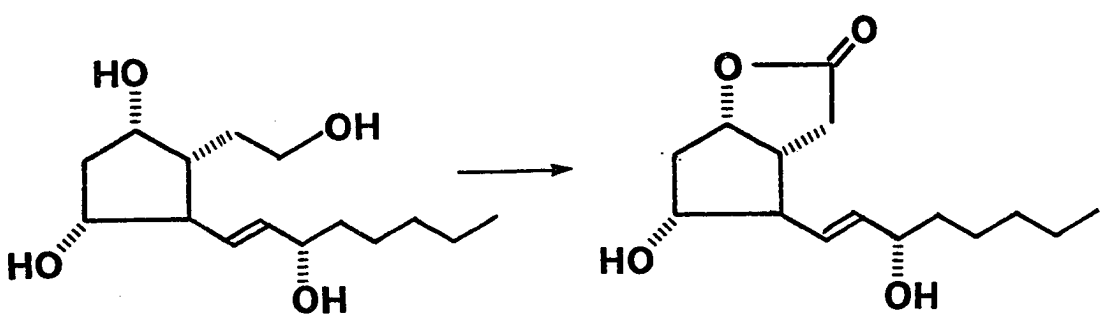

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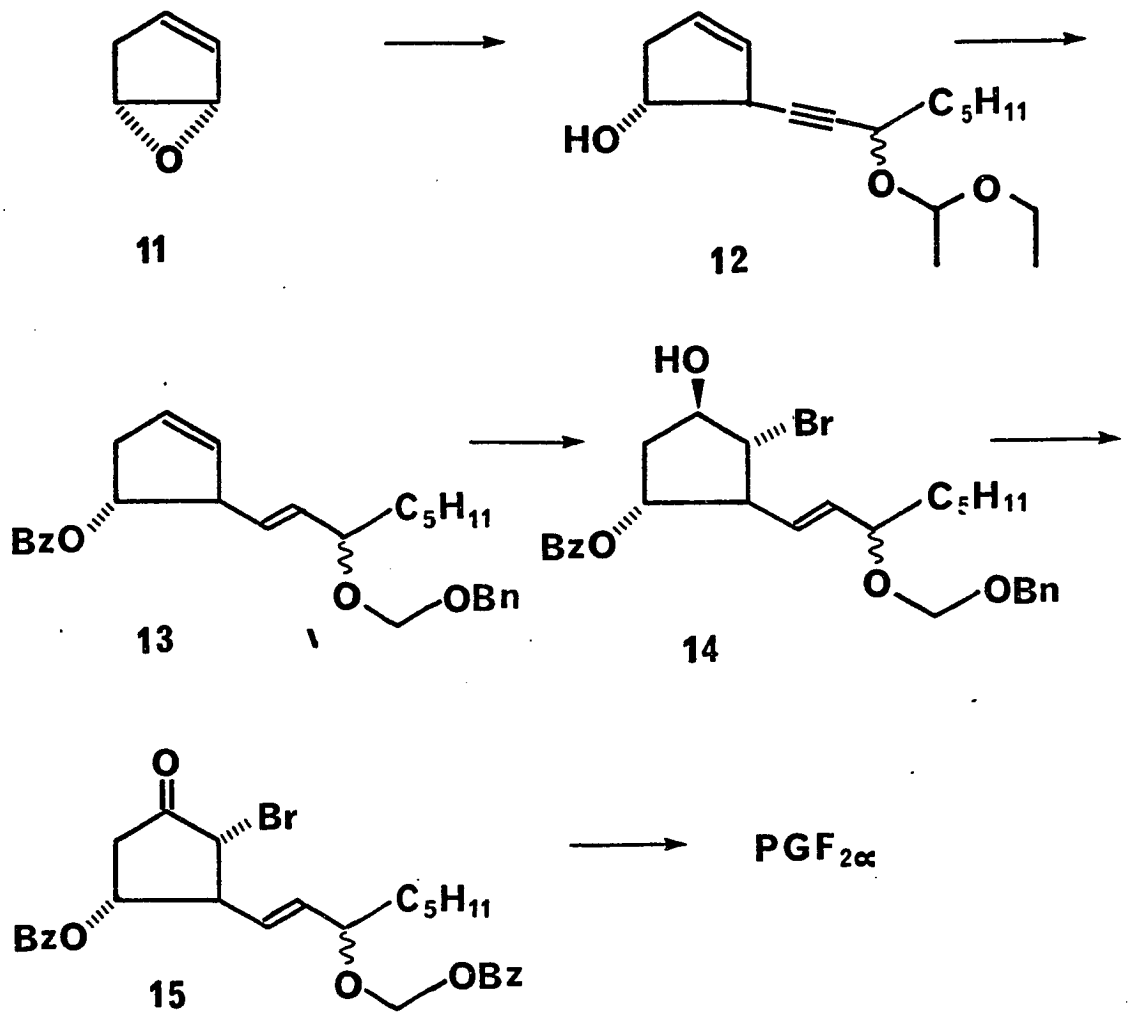
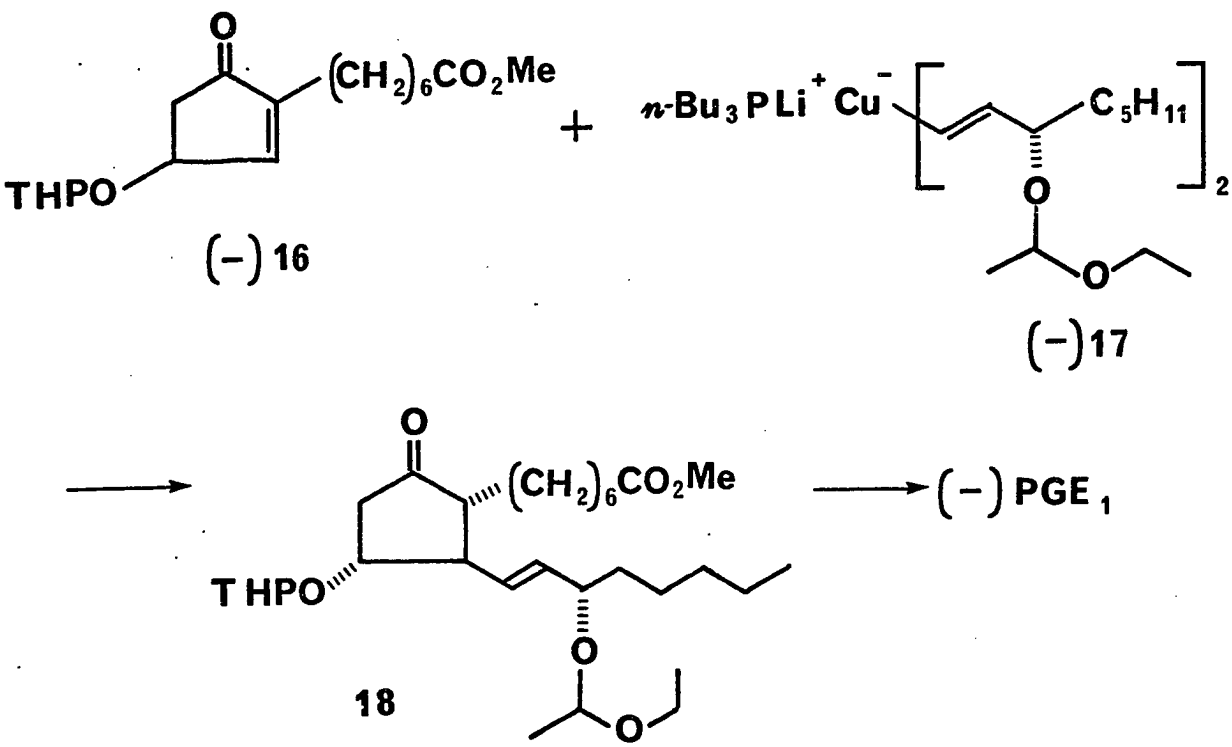
Stork [47] treated cyclopentadiene cxide 11 with the lithium salt of the ethoxyethylether cf 1-cctyn-3-ol and cbtained cyclopentenol 12, isolated in 45% yield. The free hydroxy group was protected as the benzyl ether, followed by



selective removal of the ethoxyethyl group, and treatment with benzyl chloromethyl ether to give 13, which was converted to 14 by regiospecific addition of hypobromous acid (NBS in DMSO-H_2O). Oxidation of bromohydrin 14 with Jones' reagent followed by addition of the top chain completed the synthesis.

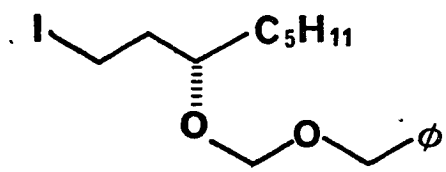
Sih and his coworkers [48] in 1972 reported the first synthesis of prostanoids, 15-deoxy PGE_1, utilizing the con-



jugate addition of suitably substituted cyclpentenones. Later he extended the use of conjugate addition to synthesize PGE [49,50].

When substituted optically active cyclopentenone 16 was treated with organocuprate 17, obtainable from 3(S)-hydroxy-1-iodo-1-trans octene, a stereospecific addition was obseved and (-)-PGE_1 methyl ester was isolated in 65-70% yield [51,52]. A similar conjugate addition was used for the preparation of (-)-PGE_2 [52,53].

Stork and Isobe [54] reported another application of conjugate addition. When 4-cumyloxy-2-cyclopentenone 19 was



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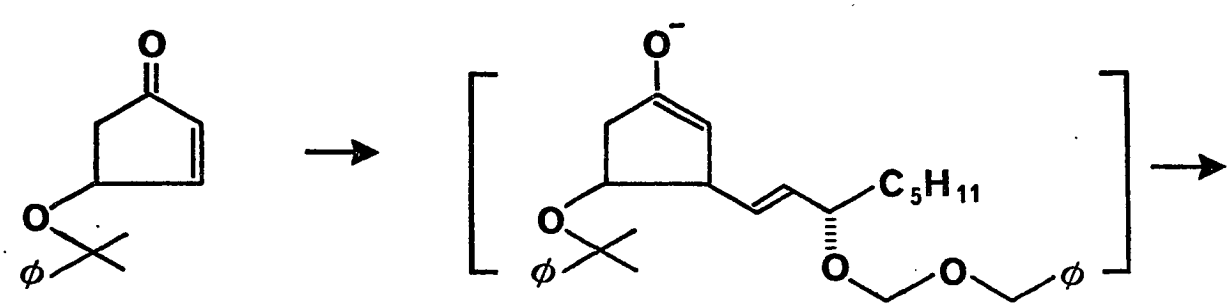
reacted with the cuprate-tri-n-butylphosphine complex from 3(S)-trans-1-iodo-octene-3-ol benzyloxy methyl ether (20), followed by formaldehyde, a ca. 1.3:1 ratio of (resp.) 23 and 22 were obtained. Hydroxymethylcyclopentanone 23 was converted to methylenecyclopentanone 24 by mesylation followed by base treatment. Addition of 24 to the divinylcuprate obtained from the vinyl iodide 25 gave 26. Removal of the ethoxyethyl group, oxidation and reduction of the C(9) keto group using tri-isobutyllithium borohydride completed the synthesis [55].



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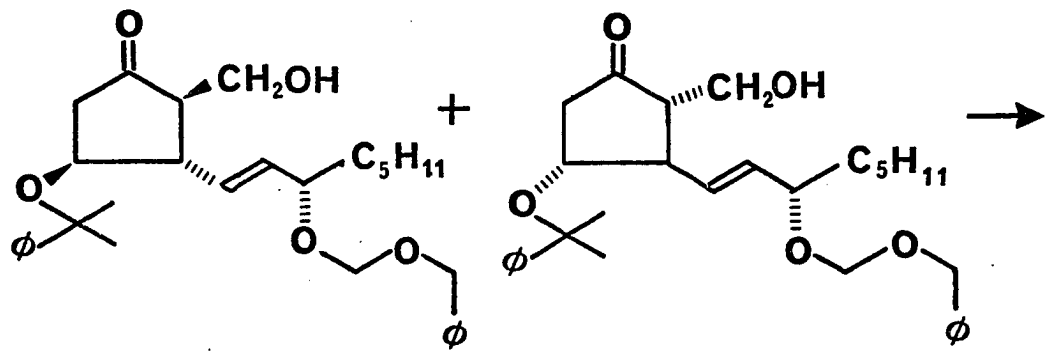

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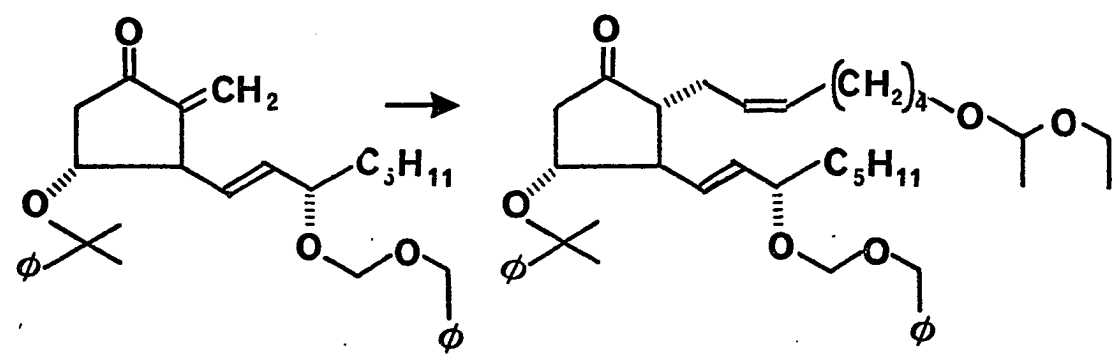

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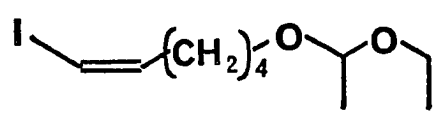

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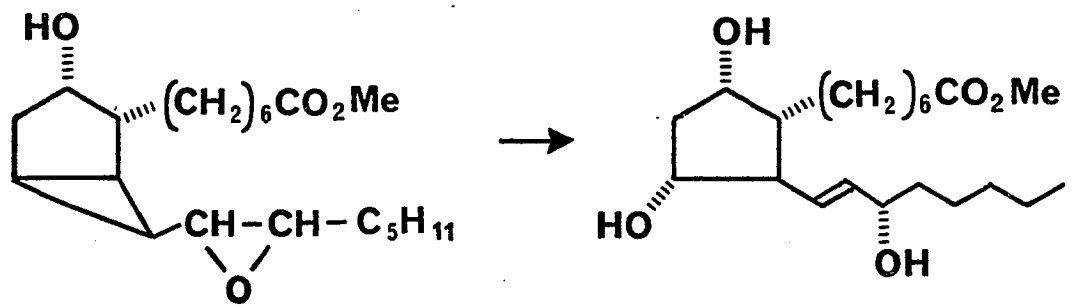
2.5 MISCELLANEOUS APPROACHES

There are less common approaches to Prostancids starting with bicyclohexane, bicyclooctane and bicyclononane derivatives.

Originally developed by Just and Simonovitch [56] and later modified in collaboration with the Upjohn group [57], epoxide 1 was treated with either formic acid at room temperature or trifluoroacetic acid at 40°C, giving a mixture from which dl-$PGF_{1\alpha}$ methyl ester could be isolated in 2-3% yield.



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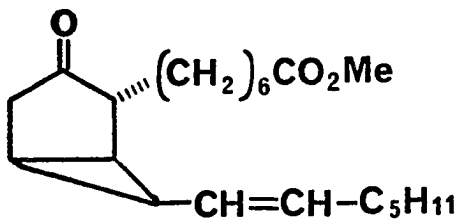
dl-$PGF_{1\alpha}$ methyl ester + 15-epimer

Later the Upjohn group [58] modified the procedure by treating 2 with osmium tetroxide, giving a mixture of four diastereoisomeric glycols. Conversion to the corresponding bis-methanesulfonates 3 and then treating them with acetone-



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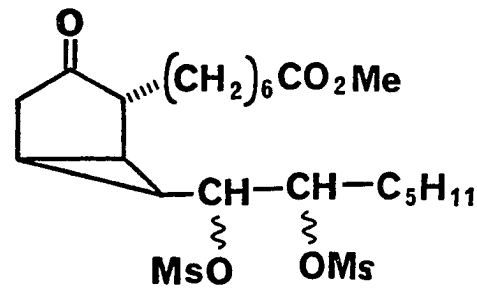

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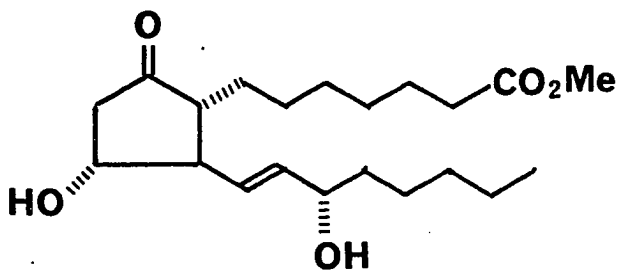
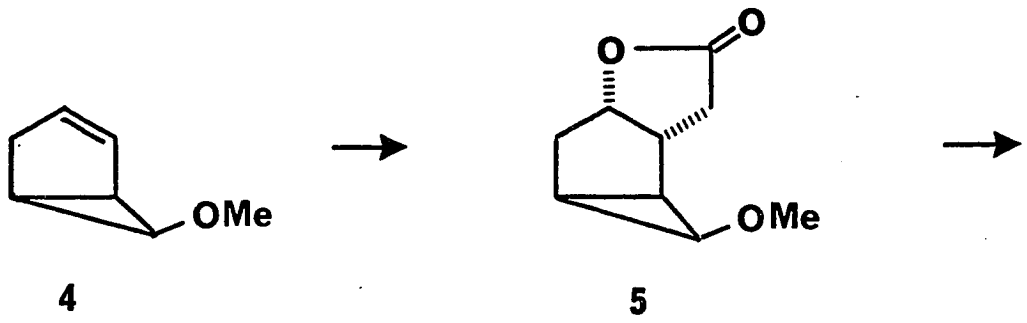


dl-PGE_1 methyl ester + 15-epimer

water gave approximately 5% of dl-PGE_1 methyl ester. Just and Fernadi [59] applied this procedure to the preparation of dl-PGE_2 methyl ester.

The Upjohn group found that when an endo-bicyclohexane isomer derivative was treated under similar conditions, the yield of PGE_2 methyl ester was improved to 15%.

Corey [60] on the other hand started with 6-methoxy-bicyclo[3,1,0]hex-1-ene 4. Treating 4 with dichloroketene followed by dechlorination and Baeyer-Villiger oxidation gave 5, which after cleavage of the methyl ether group using boron tribromide provided the key intermediate 6.



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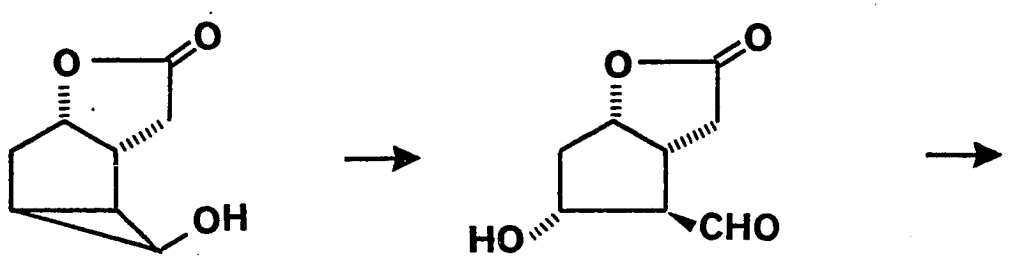

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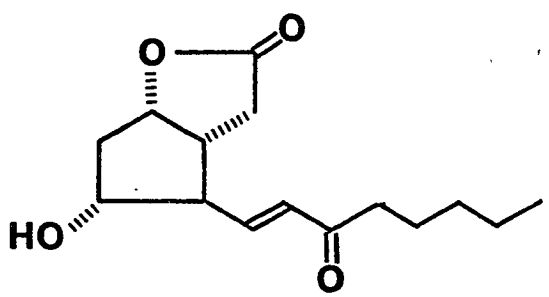

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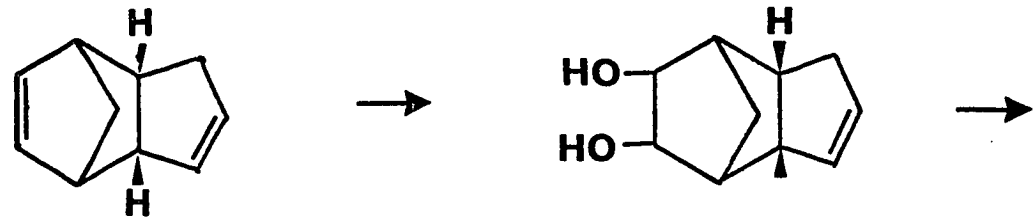
Oxidation of 6 with chromic acid gave Corey aldehyde 7 which was immediately converted by Emmons-Horner reaction to enone 8 which was isolated in 12% yield (based on 6).

Turner's synthesis [61], the only example with a bicyclo[3,3,0]octane precursor, starts with the inexpensive, commercially available dicyclopentdiene (dimer) 9. This was

converted to glycol 10 in 28% yield by cold potassium permanganate. Cleavage of the glycol (10 to 11) and conversion of the dialdehyde to a diketone gave 12. Osmium tetroxide oxidation of the remaining double bond, acetylation and Bayer-Villiger oxidation provided tetraacetate 14. Saponification of 14 and the periodate cleavage of the resulting tetraol 15 afforded Corey lactol 16, and the rest of the synthesis was completed using conventional methods.



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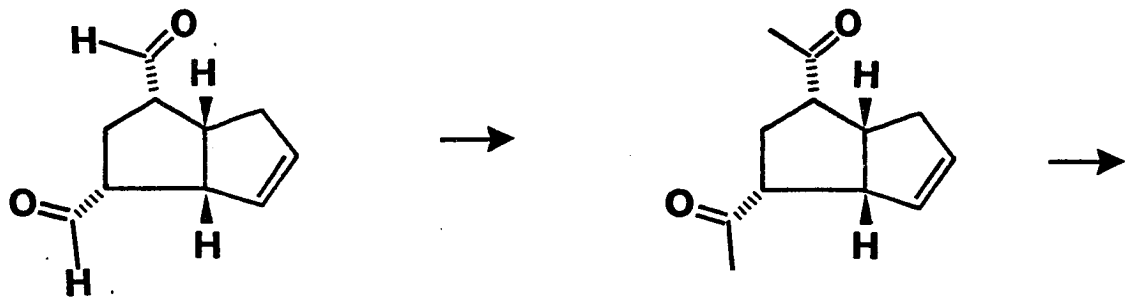

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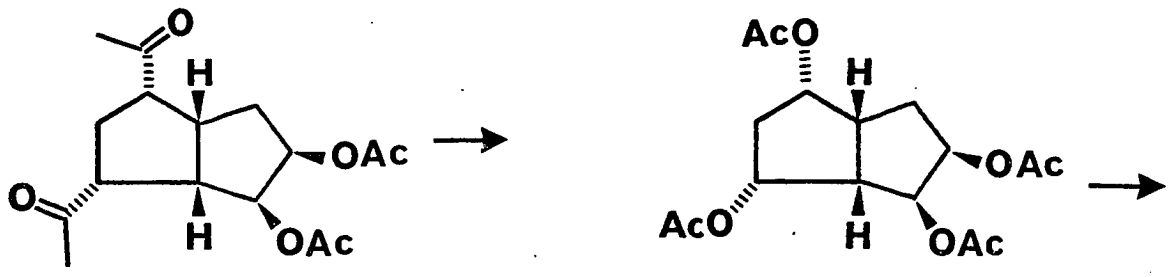

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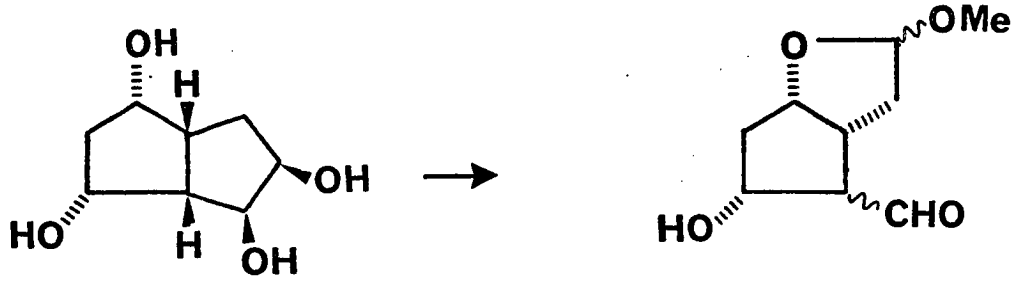

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2.6 CHIRAL PROSTAGLANDIN SYNTHESIS

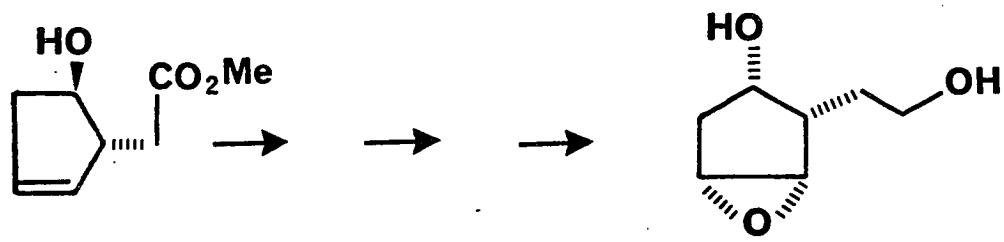
Basically there are two kinds of approaches in obtaining optically active prostaglandins without going through the time consuming, inefficient procedures of chemical resoluton i.e. either the chirality should be introduced at some point in the synthesis by the use of chiral reagents, or one should start from readily available optically active starting materials.

2.6.1 Introducing the Chirality

2.6.1.1 The Hoffmann La-Roche Approach

Partridge, Chadha and Uskokovic at Hoffmann La-Roche [62] developed an asymetric synthesis of epoxy diol 3, which had been previously converted to prostaglandins by Fried and his coworkers. When cyclopentadiene substituted ester 1 was treated with (+)-di-3-pinanylborane followed by alkaline hydrogen peroxide, optically active hydroxy ester 2 was isolated in 45% yield. The product was of 96% optical purity. Subsequently 2 was converted to optically active prostaglandin intermediate 3 by simple chemical transformations.

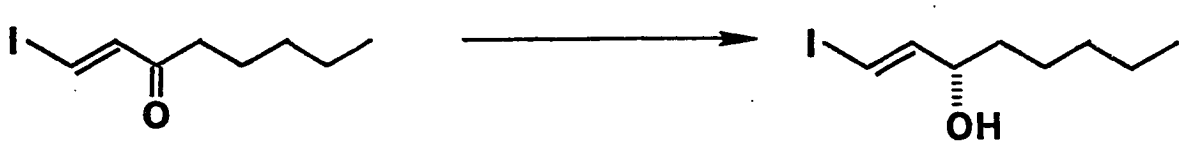
1



2 3

2.6.1.2 Micrcbial Transformation

Microbial transformations have also been used as an alternate way to obtain optically active prostaglandis. Sih et. al. [52] obtained (+)-3(S)-icdcalcohol 2 in 10% yield by microbial reduction of 1 using washed cells cf Penicillium decumbens.



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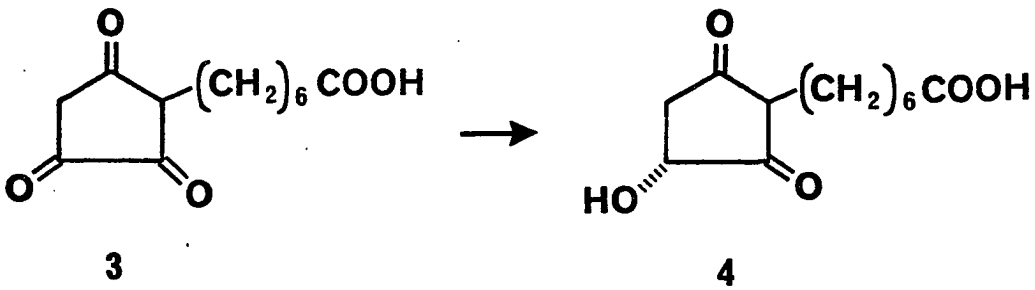
Sih et. al. [52] also found that the most suitable microbe for the reduction of 3 to 4 and 5 to 6 was Dipodascus



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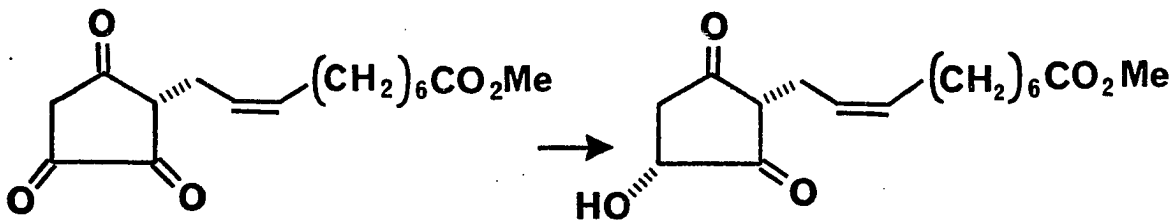


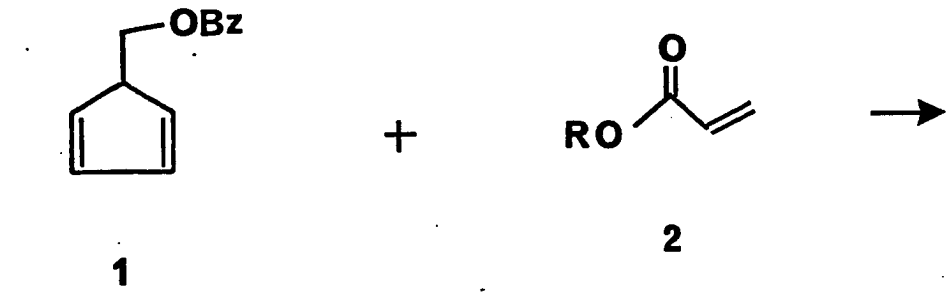
5 6

uninucleatus which effected completely stereospecific reduction (100% optical purity).

2.6.1.3 Chiral Synthesis of Bicyclic Ketone

Lewis acid catalysed Diels-Alder reaction has been used in the preparation of optically active Corey bicyclic ketone 4. Diels-Alder reaction of (-)-menthyl acrylate 2 with cyclopentadiene 1 gave adducts with up to 50% assymmetric induction. However Corey and Ensley [63] have found that the chi-

ral alcohol 6 prepared from S-(-)-pulegone is superior to that from (-)-menthol as a chirality transfer agent.



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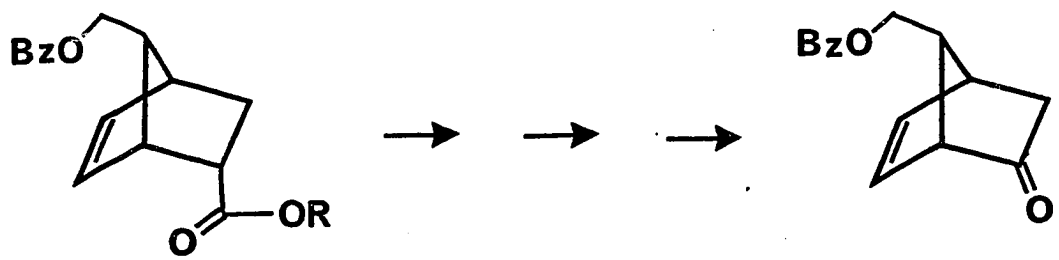
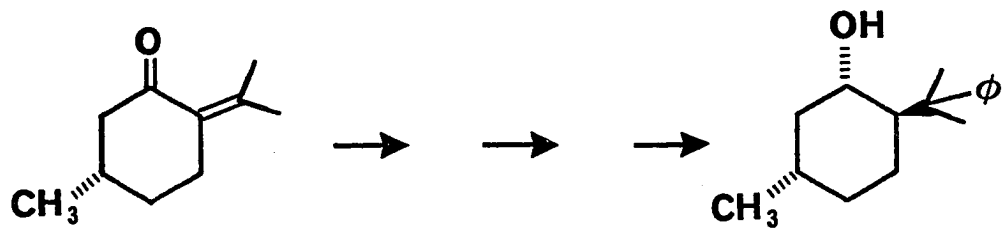


3 4



5 6

2.7 OPTICALLY ACTIVE PRECURSORS

In last few years, a few chiral syntheses of prostaglandins have been reported starting from optically active, naturally occurring materials.

2.7.1 Johnson's Synthesis

Johnson and his coworkers [64] reported the preparation of Corey-alcohol starting from naturally occurring sugar S-(-)-malic acid.

2.7.1.1 Retrosynthetic Analysis (Scheme-4)

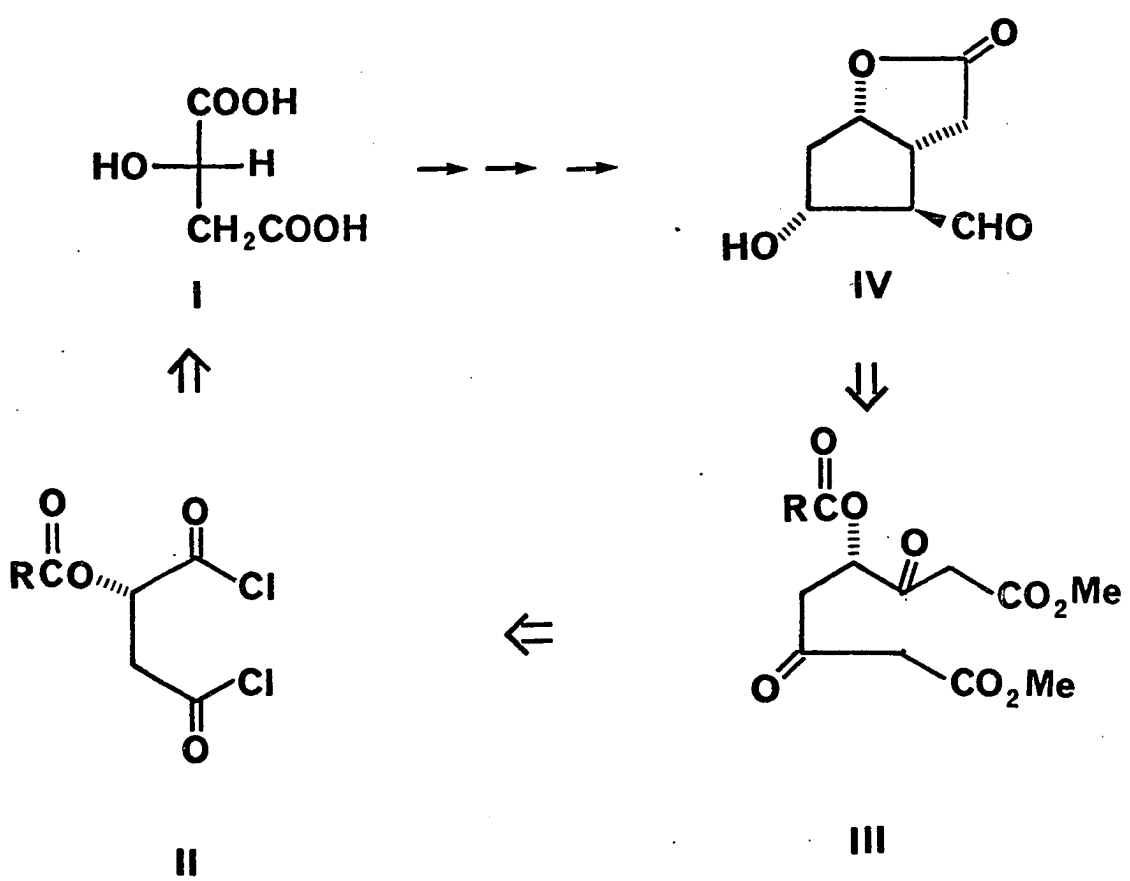
By breaking the C(8)-C(12) bond, the Corey aldehyde IV could be derived from III by the use of aldol condensation. Alkylation of protected S-(-)-malic acid dichloride II could give III and subsequent transformation to Corey aldehyde.

2.7.1.2 Actual Synthesis (Scheme-5)

Treatment of S-(-)-malic acid 1 with acetyl chloride afforded S-(-)-2-acetoxy succinic anhydride 2, which was converted to the corresponding succinyl chloride 3 in 80% overall yield by refluxing with dichloromethyl ether in the presence of zinc chloride as a catalyst. Alkylation of acid chloride 3 was achieved by treating it with 5 eq. of the dianion of methyl hydrogen malonate (derived from methyl hydrogen malonate and isopropyl magnesium bromide) at 0^0C in tetrahydrofuran. The product, (-)-4(S)-acetoxy 3,6-dioxosuberate 4,

SCHEME 4

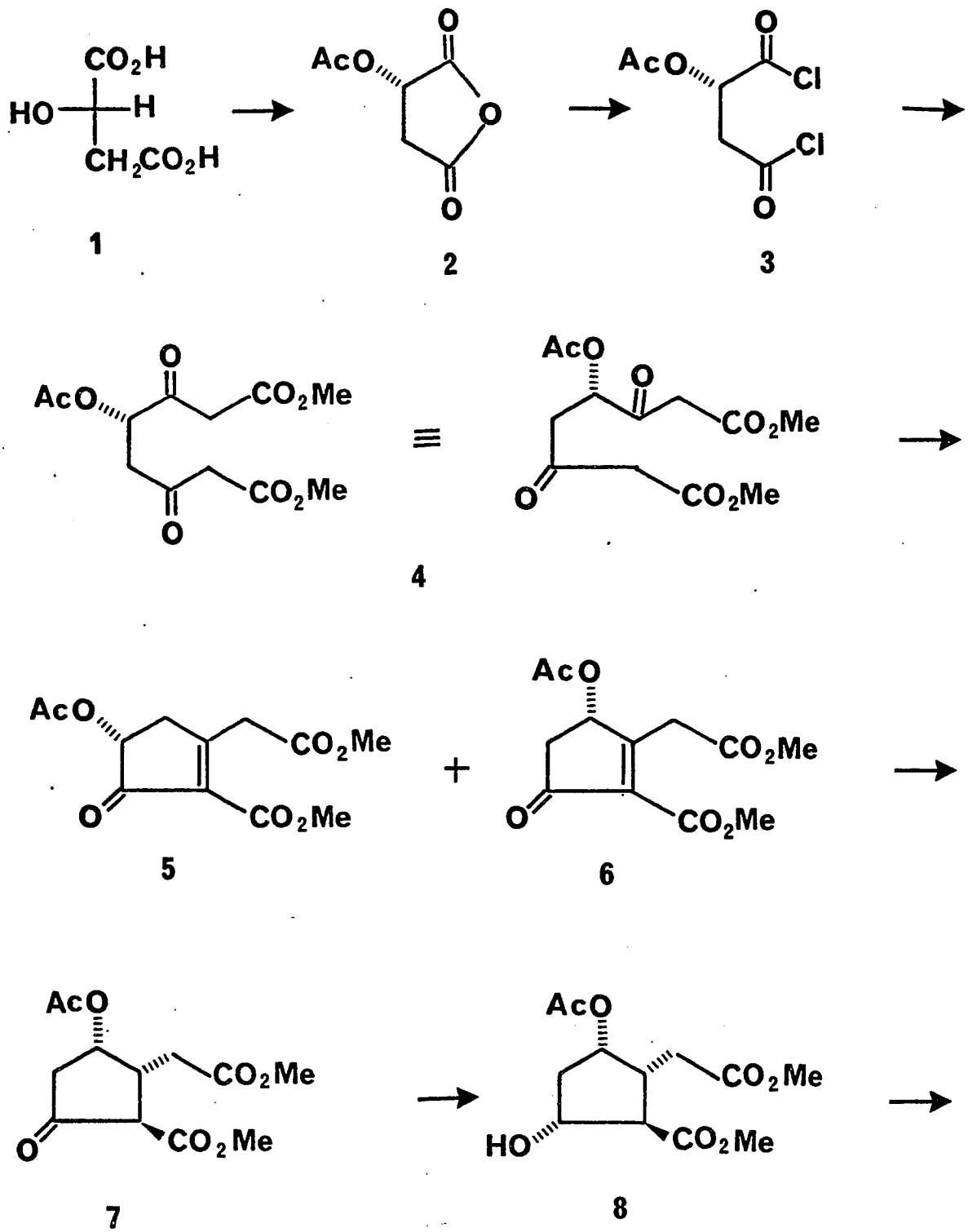
Johnson's Retrosynthetic Plan

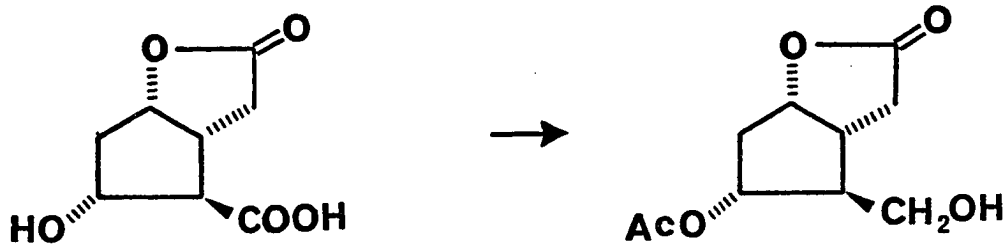


isolated as an unstable oil in 70% yield, was then subjected tc Dieckmenn cyclizaticn with a buffer (triethanclamine/ triethanolamine hydrochlcride) at pH 8.5. The cyclizaticn was complete in 30 minutes and gave a mixture of cyclopene-ncnes 5 and 6. As 6 was the majcr product, the difference may lie in the transitiсn states (i) and (ii) leading tc 5 and 6 respectively. In the case cf (i) the desired crienta-tion may nct be achieved as easily because cf the interac-tion of the acetoxy group with the enclate cxygen atcm.

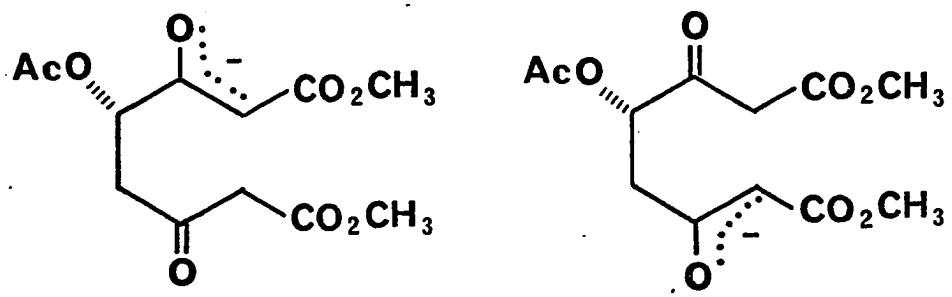
SCHEME 5

Johnson's Synthesis





9 10



(i) (ii)

The major product, 6, was purified by direct crystalliaization (50% overall yield from 3). Catalytic hydrogenation (5% $Pd/BaSO_4$) afforded the cyclcpentenone 7 in 95% yield. Either cis addition of the hydrcgen to the double bcnd fcllowed by spontaneous equilibration cf the resulting β-keto ester cr 1,4-addition tc the α,β-unsaturated ketone fcllowed by ketonizatiocn would explain the thermcdynamically stable trans-stereochemistry found in 7. Scdium borchydride reduction cf 7 followed by hydrolysis (potassium hydrcxide/methanol) and acidificatiocn afforded lactone 9 in 69% overall yield from 7. The subsequent reductiocn of the car-

hcxyl group of 9 was accomplished after prctection of the hydroxyl grcup as an acetate (100%), followed by its conversion tc the acid chloride using dichlorcmethyl ether in the presence of zinc chloride and reduction with sodium bcrchydide. The overall yield of prostaglandin precursor 10 exceeds 30%.

2.7.2 Stork's Approach

Stork's group at Coloumbia develcped an abundant chiral scurce for prostaglandins, namely carbohydrates. Because of the relatively simple structure of the cyclcpentane nucleus, he started with PGA and later extended a similar methodclcgy to the PGE and PGF series.

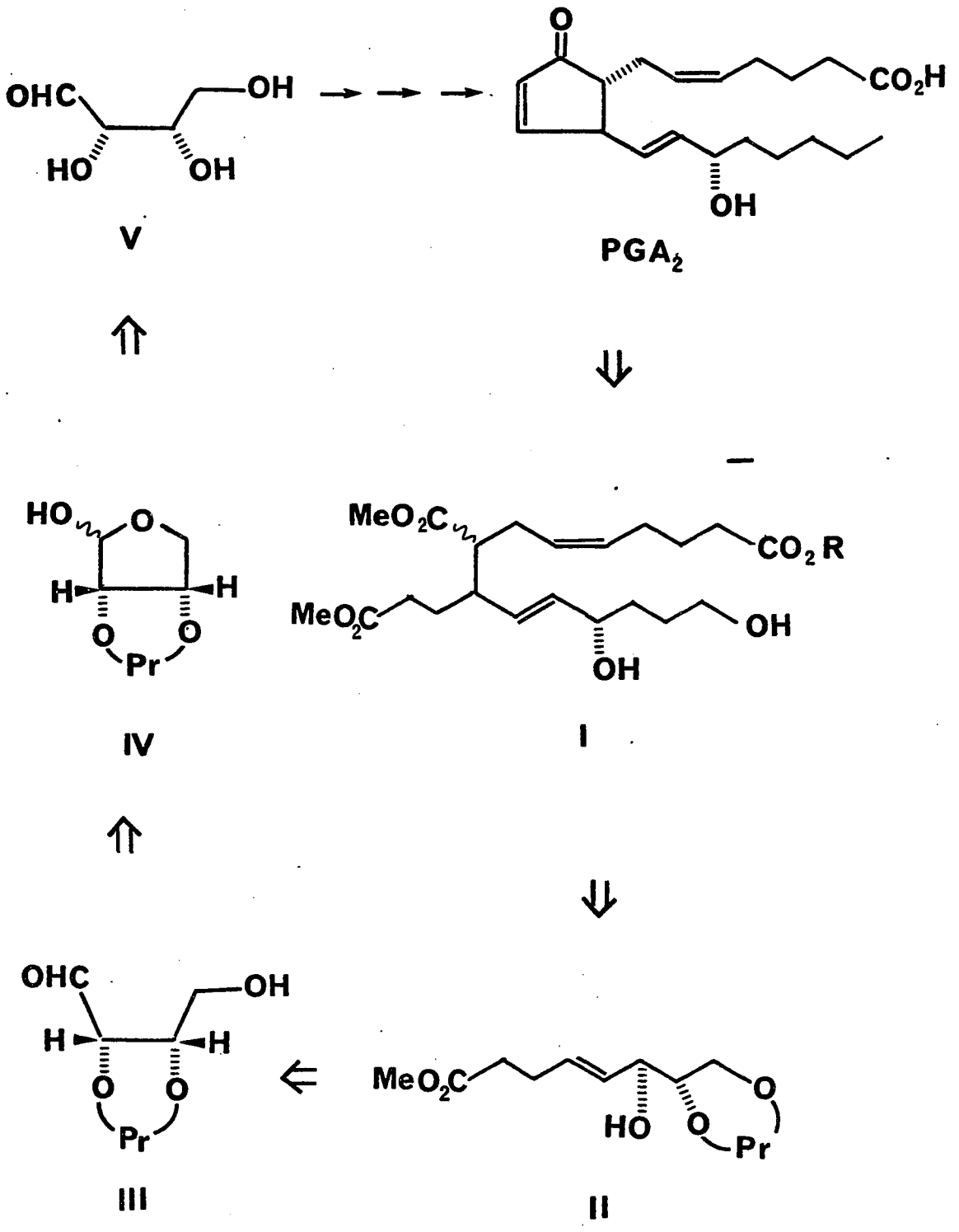
2.7.2.1 Stork-Raucher's Approach

2.7.2.2 Retrcsynthetic Analysis (Scheme-6)

From a stereochemical point of view, the segment C(12) to C(15) seems tc be the mcst impcrtant in the structure cf PGA_2. The stereochemistry at C(8) was of nc ccncern since this is an epimerizable carbon and can be brought to the thermodynamically favorable configuration at any time in the synthesis. PGA could be derived from I by the use cf Dieckmann cyclizatien. Completion cf the side chain cculd be dcne through a differentiation between a primary and seccndary alcoholic groups. I can be derived from II thrcugh the use

SCHEME 6

Stork-Raucher' Retrosynthetic Plan



of an orthoester-Claisen rearrangemennt. Wittig reaction of III (in equilibrium with hemiacetal IV) should lead to II. There is a known precursor for IV, the abundent natural source L-erythrose V.

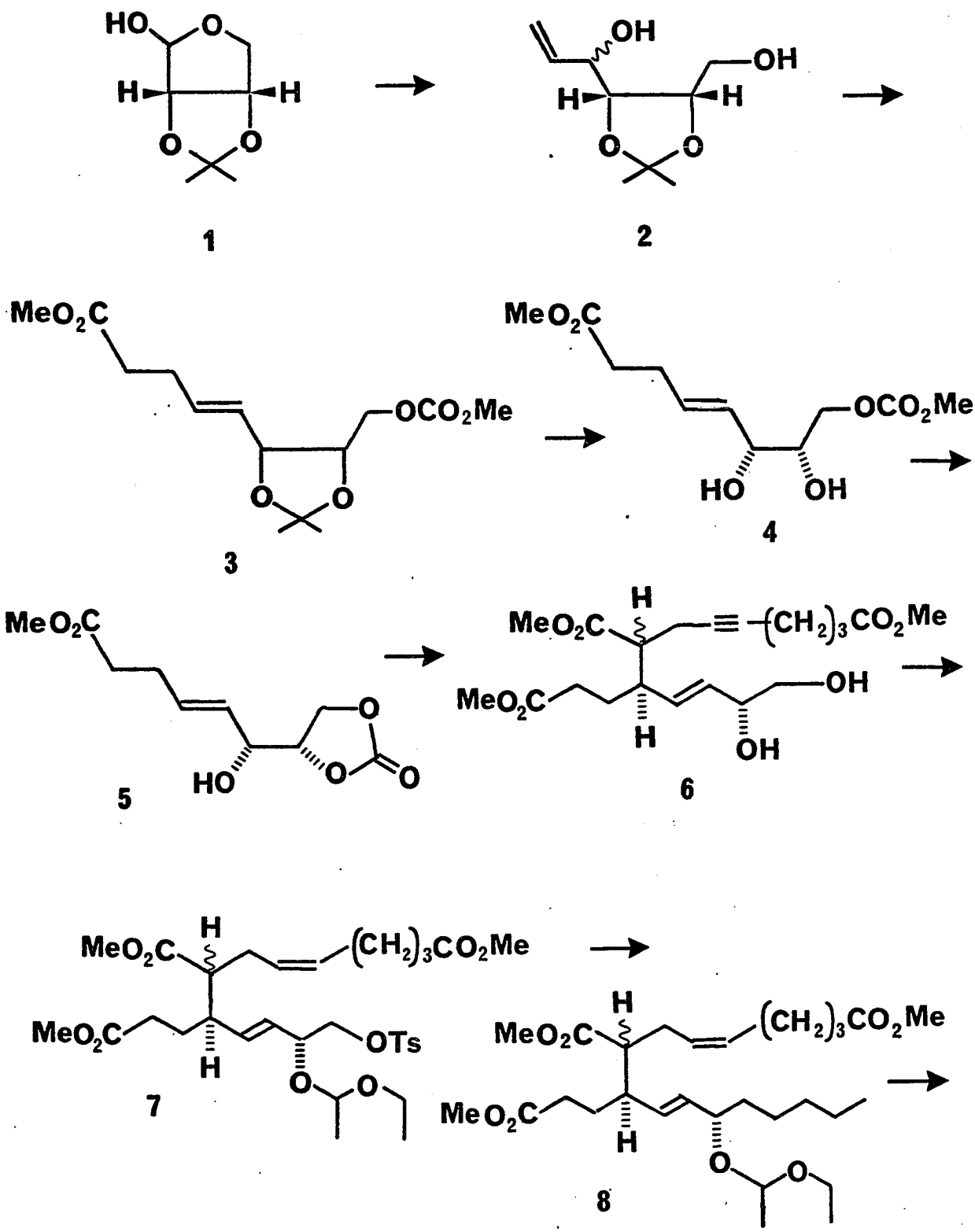
2.7.2.3 Actual Synthesis (Scheme-7)

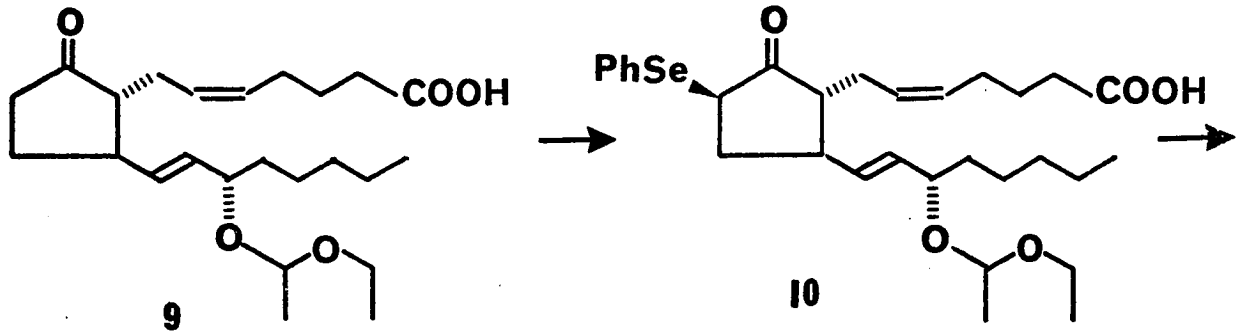
Reaction of 2,3-isopropylidene-L-eythrose with vinyl magnesium bromide gave the allylic alcohol 2. Protection of the primary alcohol in 2 as the methyl carbonate ester followed by orthoester-Claisen rearrangement with trimethylorthoacetate and mild hydrolysis gave 4. The choice of a chloroformate ester for the protection of the primary alcohol group was essential to the success of the next Claisen rearrangement which required that the allylic alcohol functon, which was masked as its acetonide in 3, be made selectively available. In fact, mild acid hydrolysis of 3 followed by treatment with triethylamine (1 eq. in methylene chloride) gave the allylic alcohol-cyclic carbonate 5. Orthoester Claisen rearrangement of 5 to 6 was now carried out with the orthoester 11 and the resulting product was hydrolysed with potassium carbonate in dry methanol. The diol 6 was isolated in 59% overall yield from the acetonide 3.

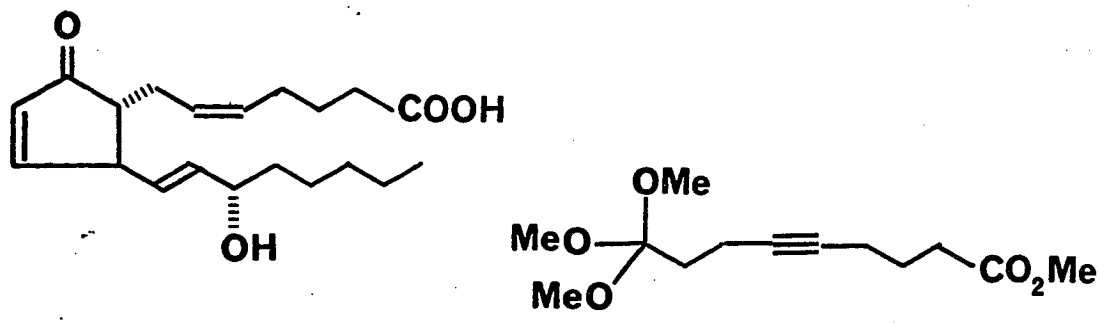
The crucial transfer of chirality in the transformation of 5 to 6 took place as predicted presumably because the carbonate ring preferred in the equatorial orientation in the chair transition state, as shown in 12. Since there is

SCHEME 7

Stork-Raucher's Synthesis

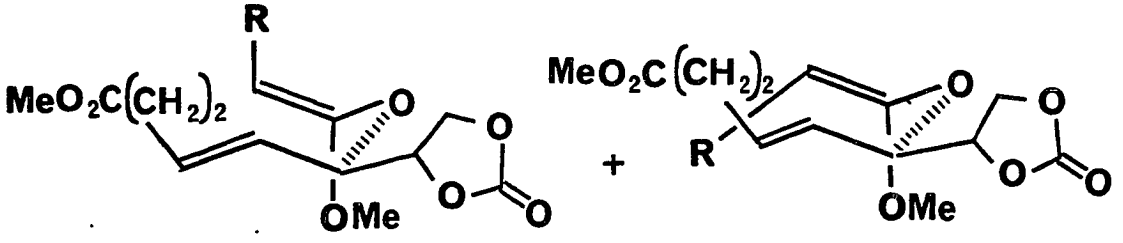






PGA_2 II

nc specially preferred crientation for the chain R in 12, it was expected that the Claisen prcduct 6 wculd be a mixture cf diastereoiscmers at carbcn-8, as shown. Since C(8) is an epimerizable carbon, it cculd be brcught tc the thermodynamically more stable stereochemistry at the end. Partial hydrogenation of the triple bond over 5% $Pd/BaSC_4$, selective protection cf the primary alcohcl (as tosylate) followed by protection of the secondary alcchcl (ethyl vinyl ether) gave the tosylate 7 in 79% overall yield from 6. Reaction cf 7 with di-n-butylcuprate completed the lcwer side chain. Dieckmann cyclization of 8 followed by acidification gave the 11-deoxy PGE_2 derivative 9, in which the acid chain has also



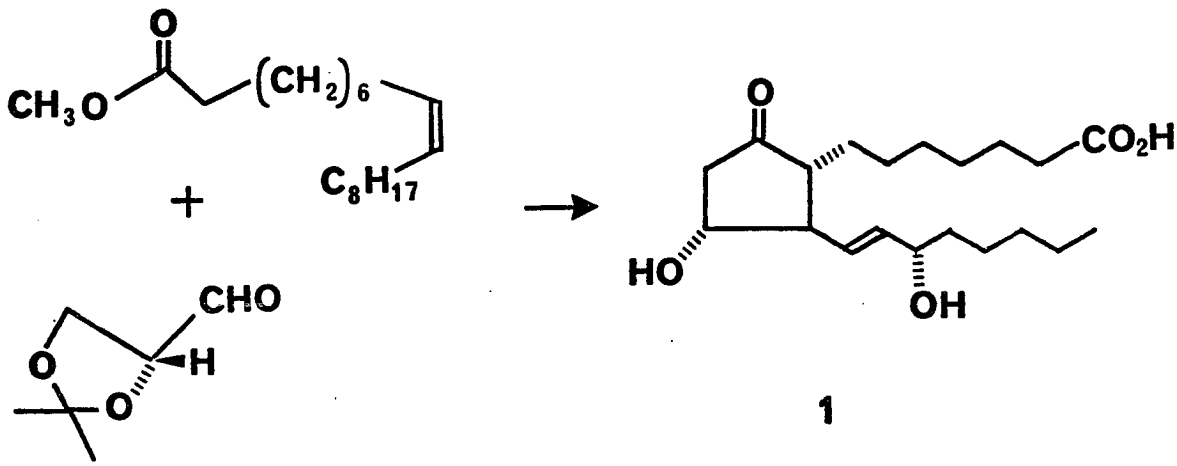
12

been equilibrated to the correct epimer. The required double bond in the cyclopentane nucleus for PGA series was introduced by selective α-selenation followed by oxidation. After removal of the ethoxyethyl protecting group, (+)-PGA_2 was obtained in 7.7% overall yield from 1.

2.7.2.4 Stork-Takahashi's Approach (Scheme-8)

Stork extended his methodology to the synthesis of PGE_1. The absolute configuration at C(11) was produced from D-glyceraldehyde

Methyl oleate was the choice for constructing the C(1)-C(9) segment because of the fact that its double bond ends up at the proper place to be a latent carboxyl of the eventual heptanoic acid chain. Once the intermediate 2 was formed, the configuration of the rest of the PGE_1 molecule was completed by an efficient means of kinetic resolution.



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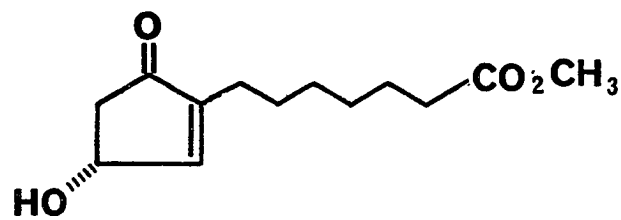

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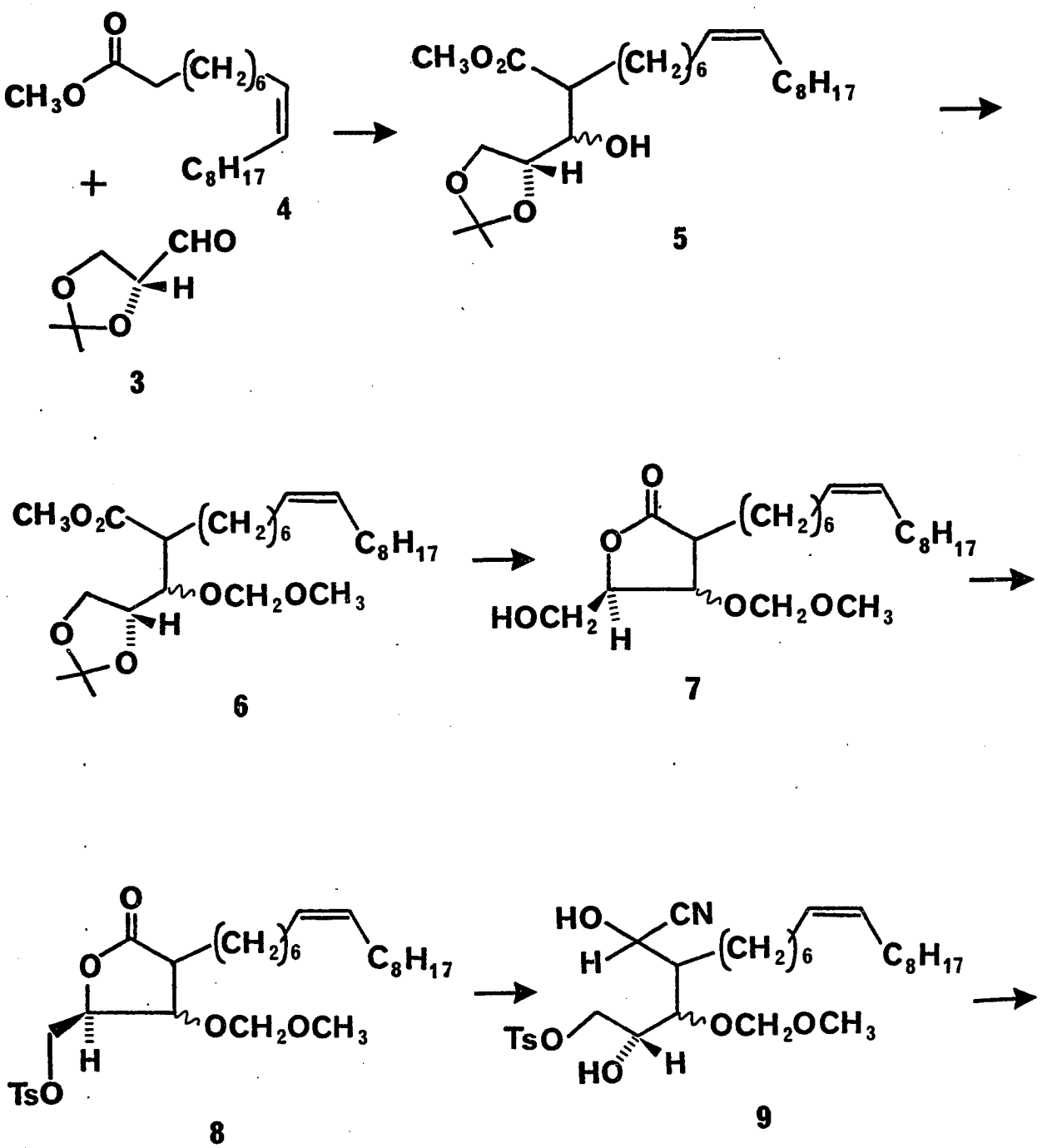
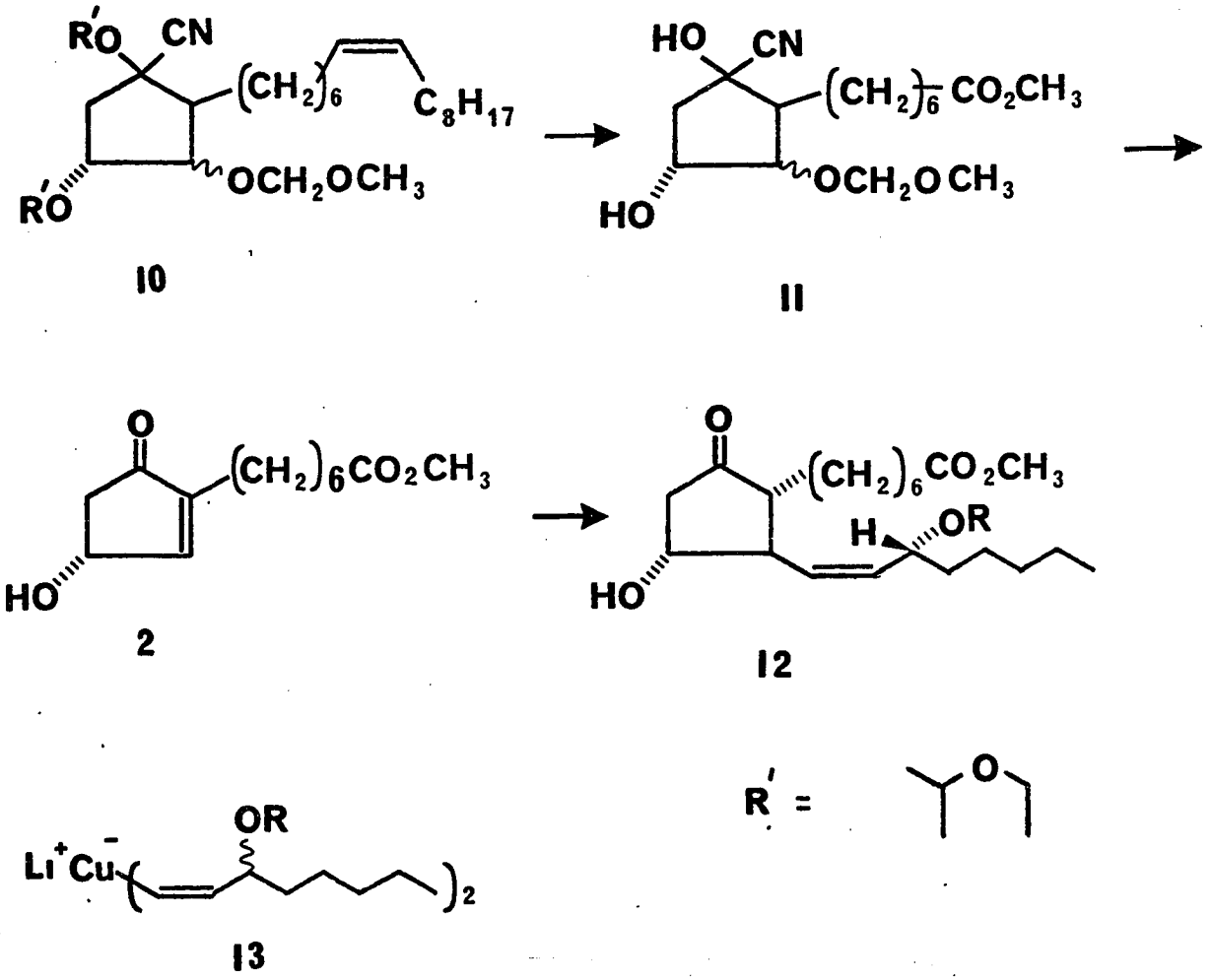
2.7.2.5 Actual Synthesis

Addition of 3 in tetrahydrofuran to the anion of 4 (lithium-diisopropylamide in THF, 10% hexamethylphosphoramide, -78^{0}C) gave 5 after 2 hours. Protection of the secondary hydroxyl group (excess chloromethyl methyl ether, diisopropylamine)

SCHEME 8

Stork-Takahashi's Approach





gave 6 in 86% yield. Removal of the isopropylidene group and simultaneus lactonizatiocn (10% sulfuric acid-THF, rt, 48 hr) gave 7.

Conversion to the tosylate 8 was followed by its transformation to the hydroxy aldehyde cyanohydrin 9 via the lactol (using diisobutylaluminium hydride). After protection of the hydroxyl grcups (ethyl vinyl ether), the cyclopentane ring of 10 was formed by refluxing in benzene for 6 hours with 3 equivalents of scdium hexamethyldisilazane.

Cleavage of the double bond with sodium periodate-potassium permanganate, removal of the ethoxyethyl protecting group with aqueous acid and esterification with diazomethane gave 11 in 46% yield. Treatment of 11 in ether-THF with 2% sodium hydroxide provided cyclopentenone 2 in 80% yield.

When 2 was treated with 3 equivalents of cuprate derived from racemic vinyl iodide 13 under kinetically controlled conditions, only the desired isomer 12 was obtained. Transformation of the C(13)-cis-C(15R) sequence of 12 to the C(13)-trans-C(15S) arrangement of PGE_1 has been previously done and thus completes the remarkable synthesis of optically active PGE_1.

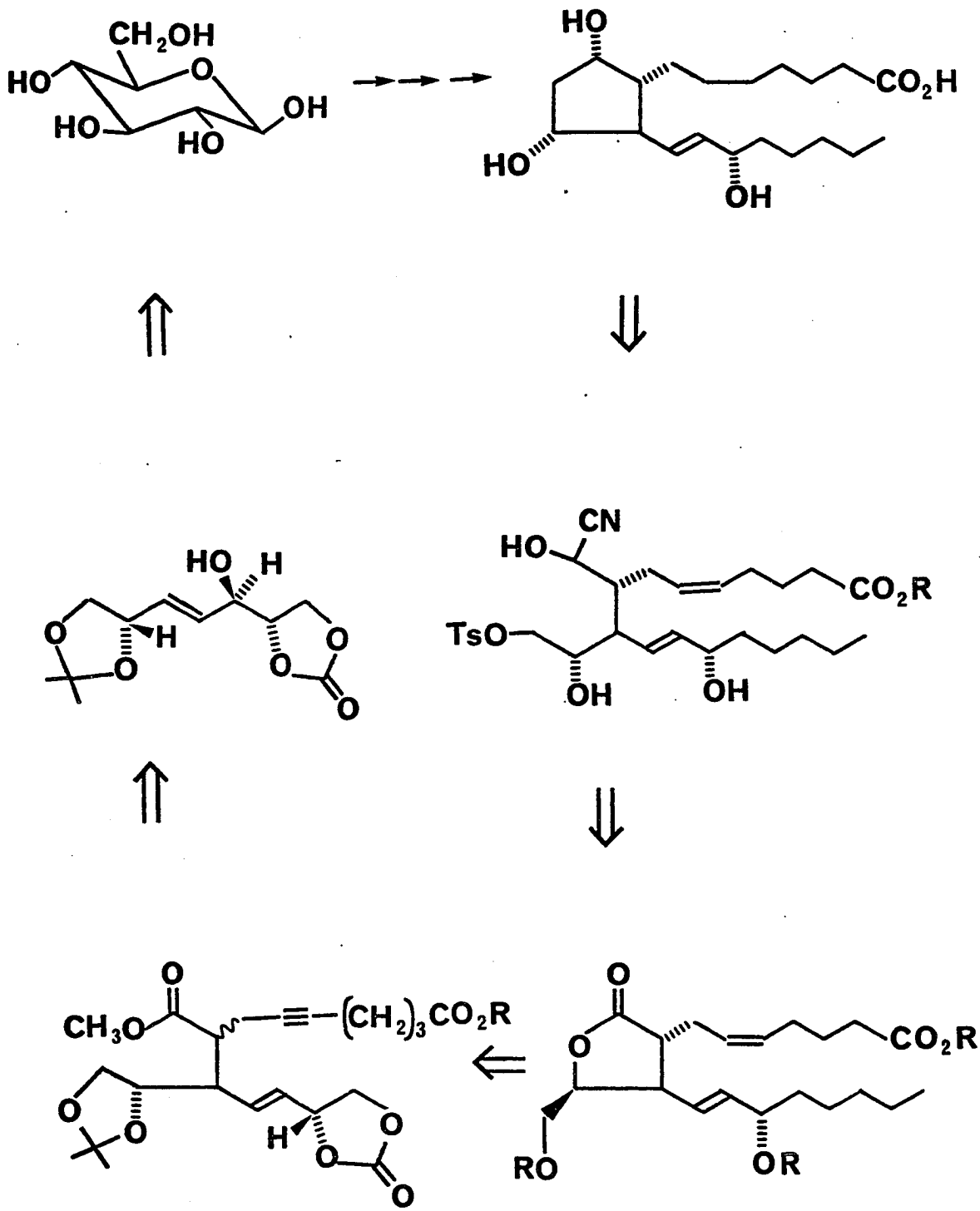
2.7.2.6 From D-Glucose (Scheme-9)

Soon after synthesizing PGA_2 from a four carbon sugar, L-erythrose, Stork also utilized another carbohydrate, this time a six carbon sugar, D-glucose in such a way that the chirality at C(11) as well as at C(15) were introduced together [67].

By addition of of one carbon, using HCN, and simple chemical reactions, glucose was converted to the key intermediate 1. The cirality at the eventual C(12) center was effected using the orthoester-Claisen method (to produce 3). The construction of the allylic side chain C(16) to C(20) was completed by using essentially the same sequence of re-

SCHEME 9

From D-Glucose 'Retrosynthetic Plan'



actions as used in the synthesis of PGA . The crude product 4 was simultanecusly deprctected and lactonized to 5 (aqueous H_2SO_4/THF/rt).

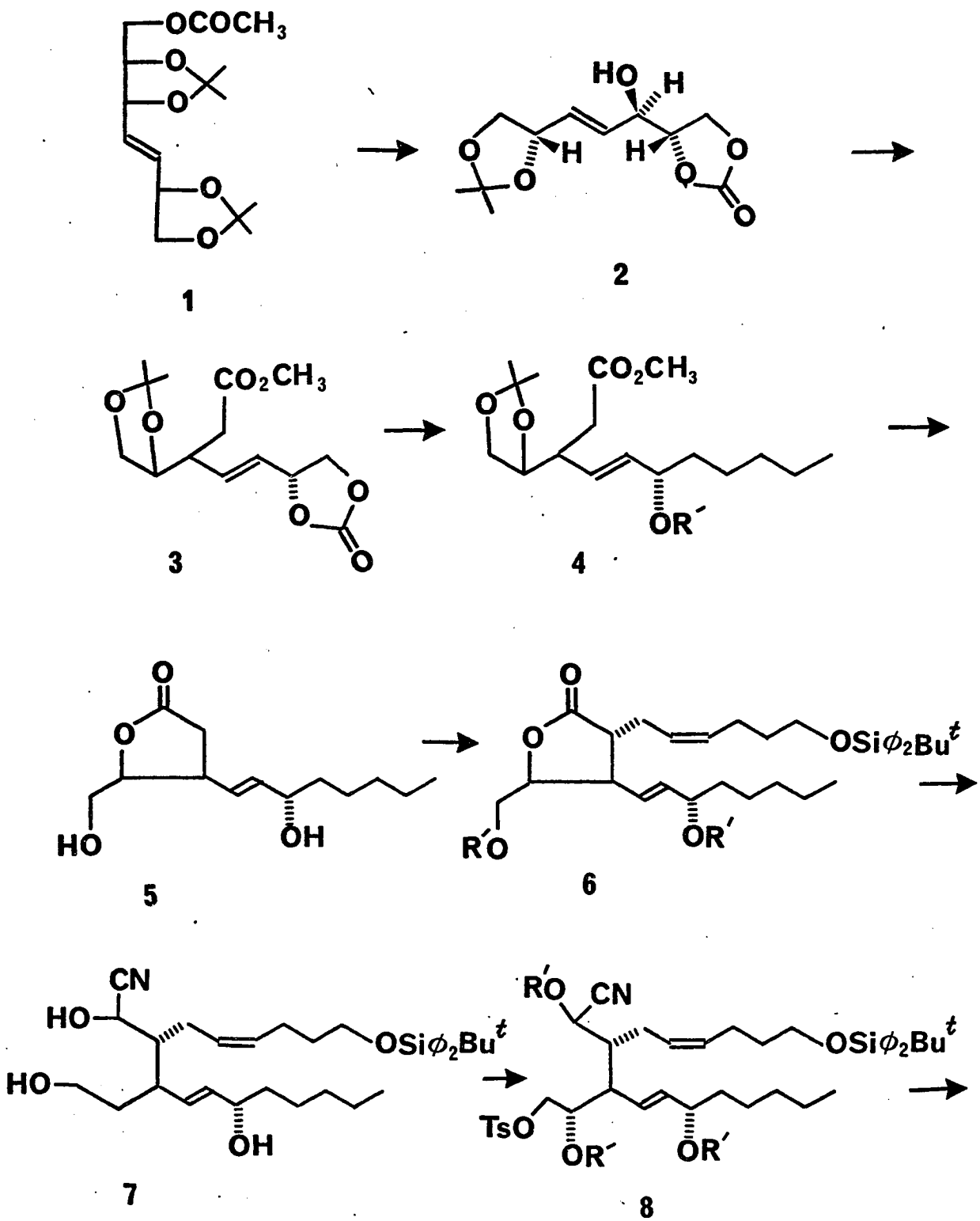
After protecting both of the free hydroxyl groups in 5 as as ethoxyethyl ethers, it was alkylated with the t-butyldiphenylsilyl ether cf 7-bromo-cis-5-heptene-1-ol to give 6. Reduction of the lactone to the hemiacetal (using diisobutylaluminium hydride) was followed by the addition of HCN and the removal of the ethoxyethyl groups. Selective tcsylation of only the primary alcchol and protection of the remaining alcohols gave 8.

Cyclizaticn was achieved by treating 8 with 6 equivalents of potassium hexamethyldisilazane. The silyl protecting group was remcved with fluoride ion and the resulting alcohcl was oxidized first to aldehyde (using Collins reagent) and then to an acid (silver nitrate/aqueous-alcoholic potassium hydrcxide), affording 10 in 83% isolated yield (from 9).

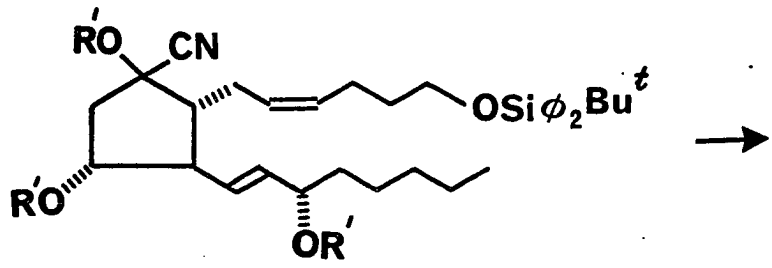
The synthesis was completed by remcval cf the protecting group in 10 (50% AcCH/THF) followed by reduction of the ketone group thus uncovered with lithium selectride.

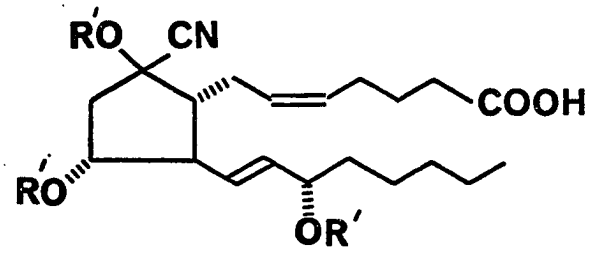
SCHEME 10

From D-glucose 'Actual Synthesis'



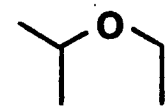
1 2 3 4 5 6 7 8





→ $PGF_{2\alpha}$

10

R' = 

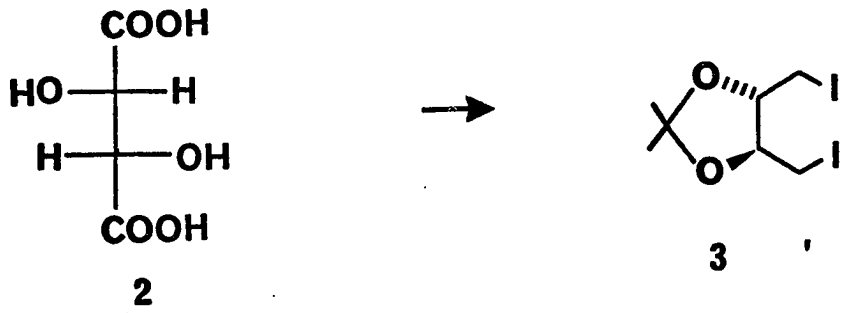
2.7.3 From Tartaric Acid (Scheme-11)

Ogura and his coworkers [68] reported the conversion of D- and L-tartaric acid acid to 4(R)- and 4(S)-hydroxy-2-cyclopentenones respectively. Since Stork and Isobe have converted (+)-4-cumyloxy-2-cyclopentenones to prostaglandins, the use of R-4-hydroxy-2-cyclopentenone can provide optically active prostaglanndins of the natural series.

The pathway for making 4(R)-hydroxy-2-cyclopentenone is summarized in scheme-11. Protection of the glycol moiety in D-tartaric acid with dimethoxypropane, reduction of both the carbonyl groups to alcohols, formation of tosylates and

SCHEME 11

From Tartaric Acid



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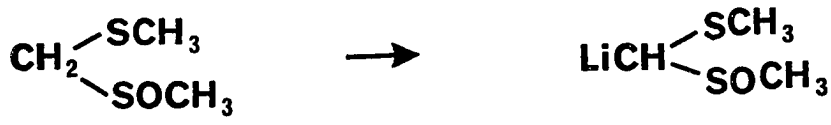

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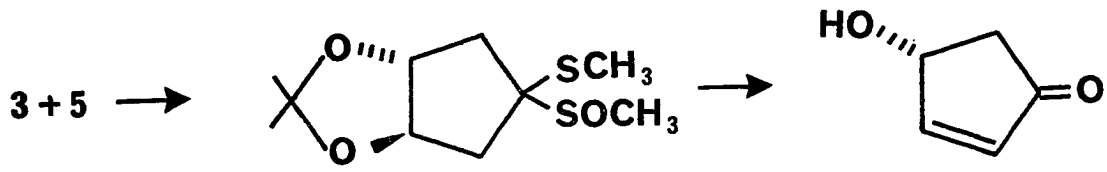


I

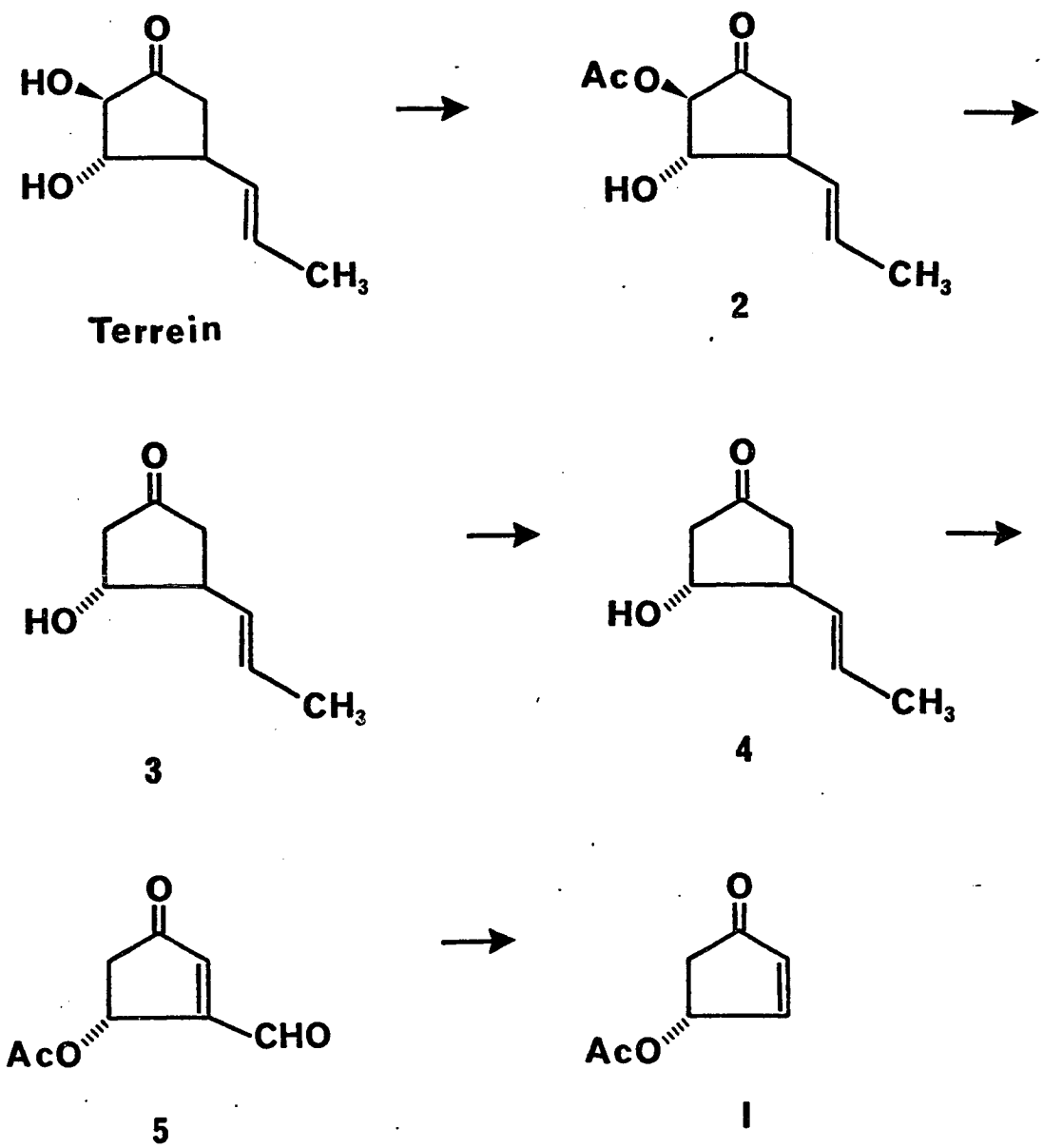
their displacement with iodide, provided optically active 1,4-diiodo-2,3-isopropylidenedioxybutane 3 in 42% yield. This was reacted with the lithio derivative (5) of methyl thiomethylsulfoxide (4) followed by acid hydrolysis to give 4(R)-hydroxy-2-cyclopentenone in 52.5% yield.

2.7.4 From Terrein (Scheme-12)

Mitscher and his coworkers [69] reported the preparation of 4(R)-acetoxy-2-cyclopentenone, similarly useful as a

SCHEME 12

From Terrein



prostaglandin synthon, from terrein. Terrein is a metabolite of Aspergillius fitcherii and has the correct absolute configuration needed for prostaglandins.

Terrein was selectively converted to 5-acetyl derivative 2 by treating it with acetic anhydride (1 equivalent) and sodium acetate (1.5 equivalent) for 4β hours at 65 C. Reduction of 2 with chromous chloride in acetone afforded 3 in 99% yield. 3 was acetylated and the resultant dieneone 4 was cleaved using osmium tetroxide/sodium periodate oxidation in aqueous acetone. Decarbonylation of 5 was achieved using Wilkinson's reagent and cyclopentenone 1 was isolated in 56% yield.

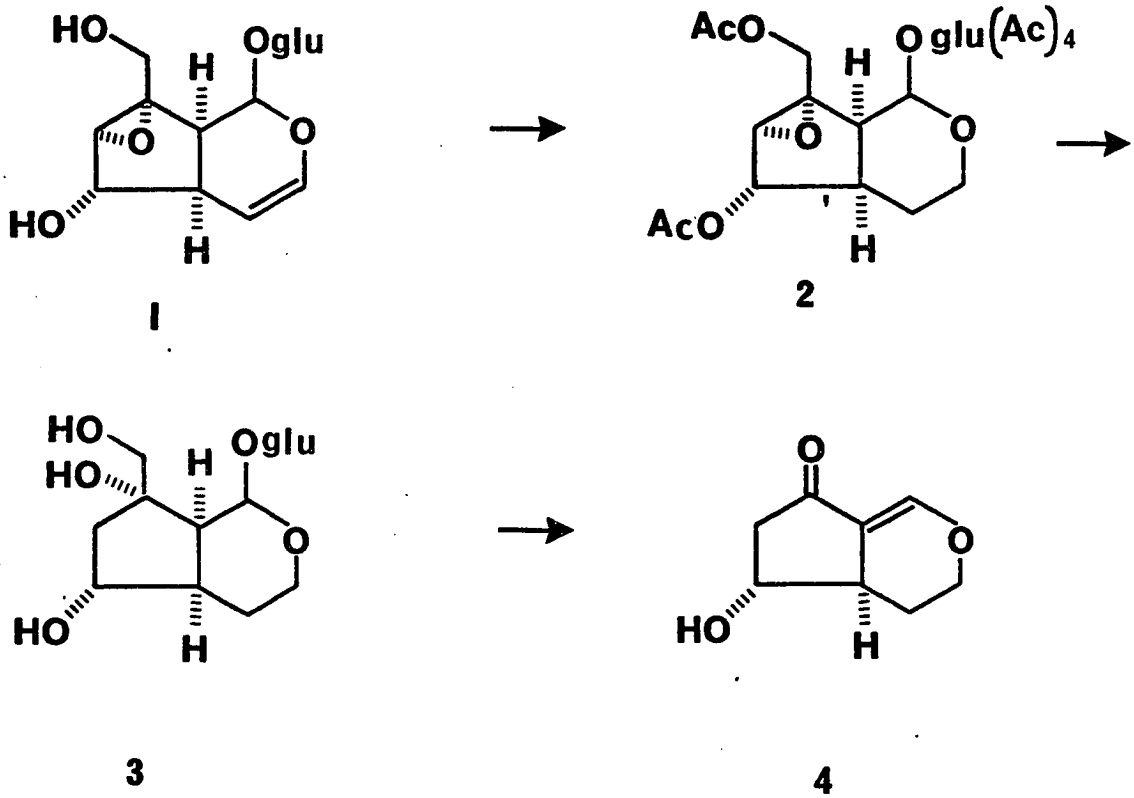
2.7.5 Weinges's Approach (Scheme-13)

Weinges et. al. [70] have recently converted catalpol (1) to optically active tetrasubstituted cyclopentenone 4 and have shown their desire to convert 4 into naturally occurring forms of prostaglandins.

The cyclopentenone nucleus of 4 is the same as that of the PGE series and besides, it also has two side appendages in the oxidation states of alcohol and aldehyde, which could be used in the stepwise introduction of two side chains. Hexaacetyl dihydrocatalpol 2 was isolated in almost quantitative yield by acetylation and subsequent hydrogenation from catalpol, which after LAH reduction in tetrahydrofuran

SCHEME 13

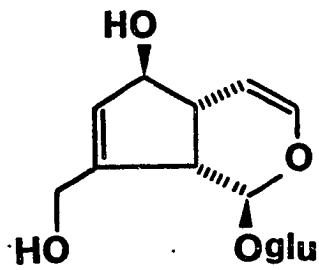
Weinges's Approach



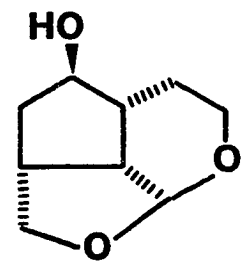
gave 3 via a regioselective epoxide cleavage. On treating 3 with sodium periodate 4 was obtained in 78% yield. The configuration at C(6) of 4 should be the same as that of catalpol and corresponds to the C(11) configuration of prostaglandins.

2.7.6 Ohno's Approach (Scheme-14)

Ohno and coworkers [71,72] have successfully converted aucubin 1 to $PGF_{2\alpha}$ as well as 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$.



1



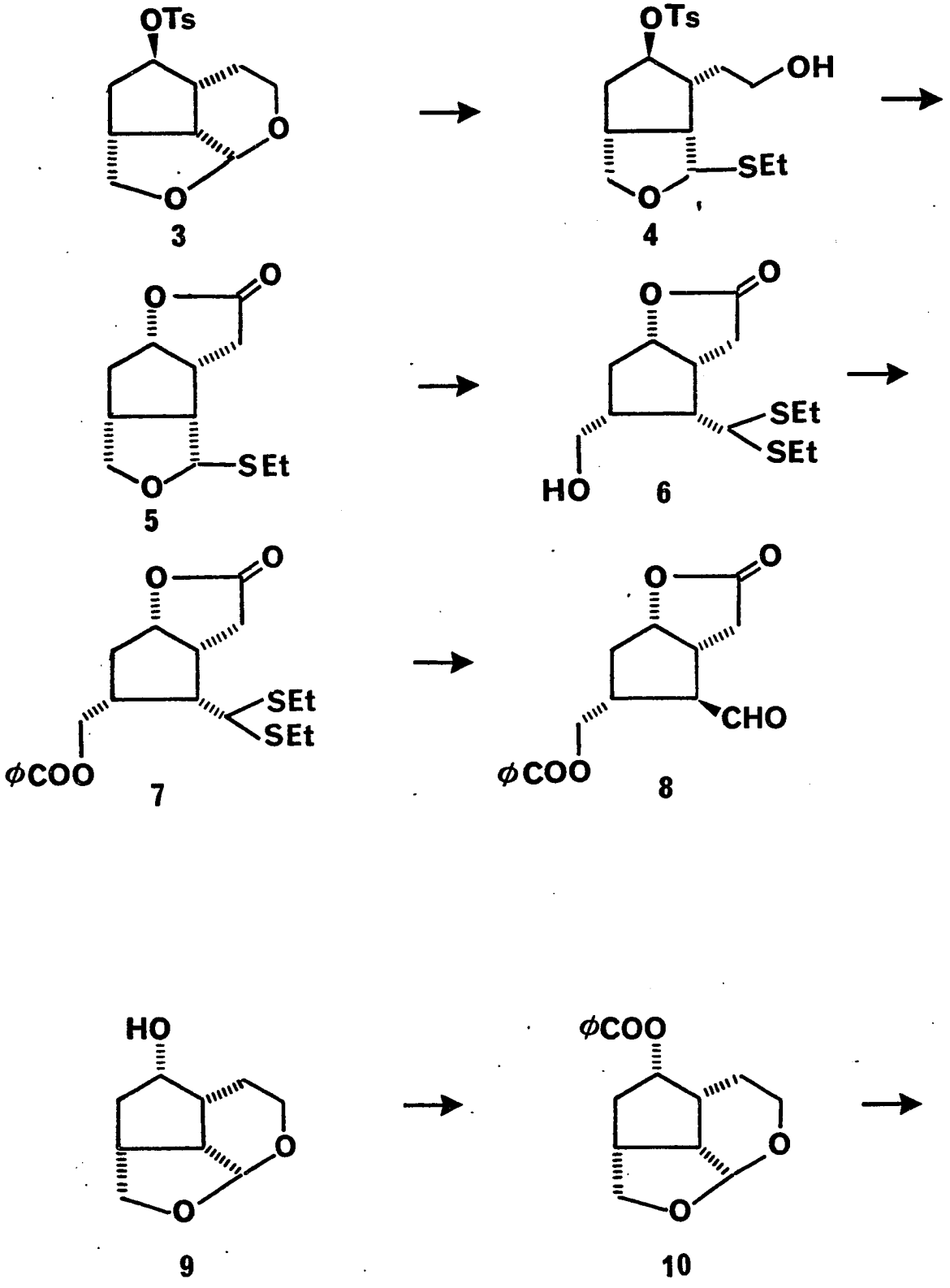
2

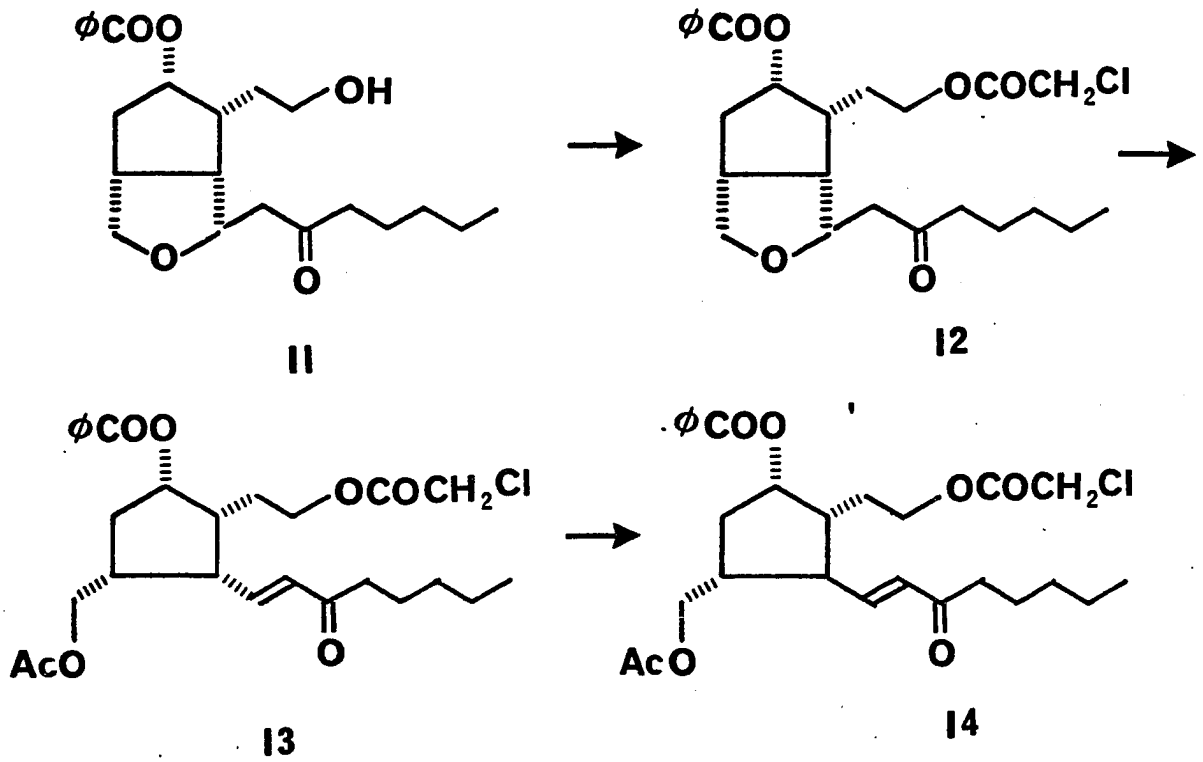
They started with the known tetrahydroanhydrocacubigenin 2, obtained from aucubin by catalytic hydrogenation followed by acid treatment.

The known tosylate 3 obtained from 2 was treated with excess ethanedithiol in dimethoxyethane and boron trifluoride etherate (2.4 eq.) to give the monothioacetal 4 in quantitative yield [71]. Cornforth oxidation of 4 gave the lactone 5. On treating 5 with boron trifluoride etherate (2.0 equivalent) in ethanethiol, the dithio acetal 6 was produced quantitatively. After benzoylation (75% yield), the dithio acetal group of 7 was deprotected using N-chlorosuccinimide-silver nitrate in acetonitrile/water. The resulting epimeric mixture of aldehydes was converted to the more stable isomer 8 by treating with potassium acetate/methanol in 68% overall yield. This is homolog of Corey aldehyde was converted to 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$ using conventional procedures. For naturally occurring prostaglandins, the 11-hydroxymethyl group of 8 was converted to 11-hydroxy

SCHEME 14

Ohno's Approach





group using a known procedure of decarboxylative rearrangement [36].

In an alternate procedure [72], the free hydroxl group of tetrahydroanhydroaucubigenin (2) was inverted by first oxidation and then reduction by lithium aluminium hydride. The resulting alcohol (9) was converted to its benzoate 10. Treatment of 10 with 1.1 equivalent of 2-acetoxy-1-heptene and 1.1 equivalent of titanium tetrachloride gave 11 as the major product.

Reaction of the hydroxyketone 11 with chloroacetylchloride afforded the chlorcacetate 12, and treatment of 12 with

p-toluenesulfonic acid in acetic anhydride at 70°C for 2.5 hours gave the enone 13. Isomerization of 13 to the more stable enone 14 was achieved using a catalytic amount of p-toluenesulfonic acid in acetic acid at 105°C for 4 hours. Reduction of the enone, removal of chlorocacetyl group and introduction of the C(8) acid chain by established procedures completed the conversion of aucubin to 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$.

2.8 ENANTIOCONVERGENT APPROACH

There is a third approach in obtaining optically active prostanoids. Unlike the more common approaches which rely on classical chemical resolution and loss of the undesired enantiomer, in this approach there is no intrinsic loss of material.

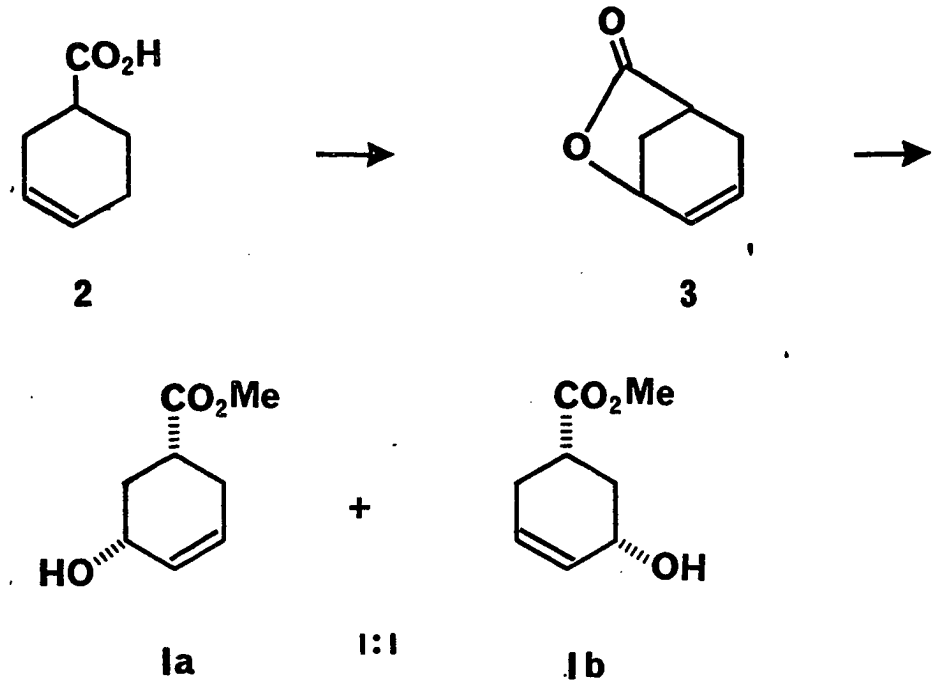
2.8.1 Trost's Approach (Scheme-15)

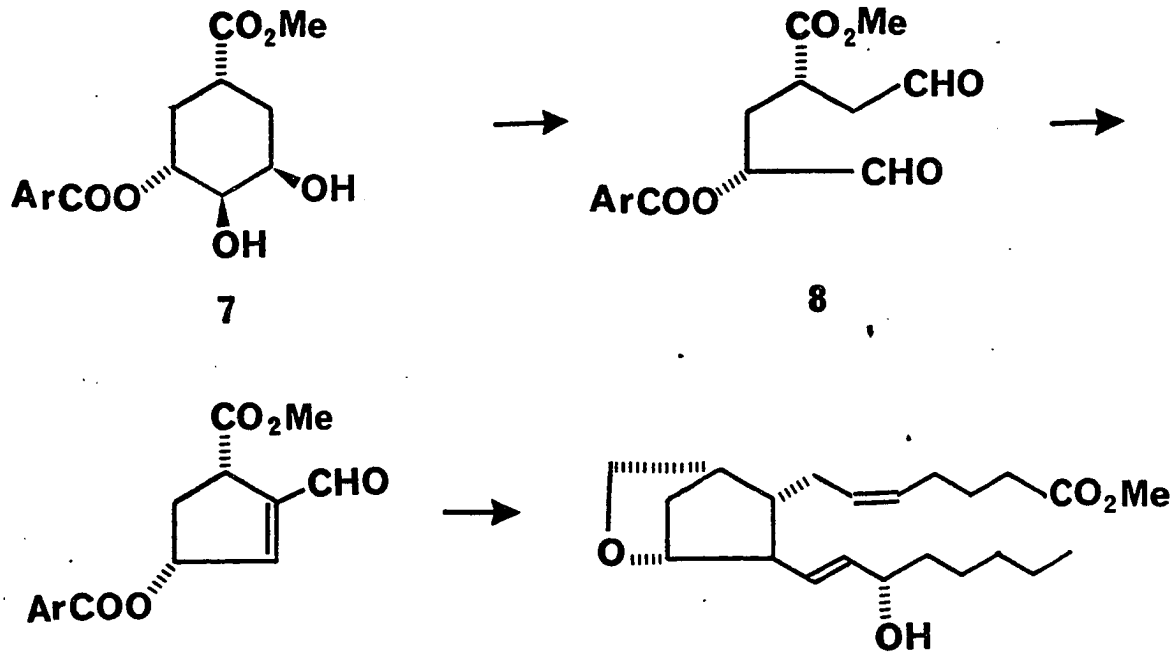
Trost's key intermediate is such that a 1,3-hydroxyl shift interconverts the enantiomers [74]. The separation of the required enantiomer and equilibration of the remaining mixture could convert the whole mixture to any single enatiomer.

The Diels-Alder adduct 2 of butadiene and acrylic acid gave 1, as shown in scheme 15. The urethanes (4 and 5) of 1 with an optically active amine were brought to equilibrium by mercury(II) trifluoroacetate catalysed allylic rearrange-

SCHEME 15

Trost's Approach





ment. The required diastereoisomer 5 was separated and the remainder (4) was subjected to the equilibrium conditions again. Thus the racemate was converted eventually to the single enantiomeric isomer 1a.

The p-phenylbenzoate ester 6 of 1a was hydroxylated with osmium tetroxide and cleavage of the glycol followed by condensation of the dialdehyde 8 provided chiral prostaglandin intermediate 9. Several prostanoids can be prepared from this intermediate, however Trost carried intermediate 9 to a known prostanoid 10.

2.8.2 Terashima's Approach (Scheme-16)

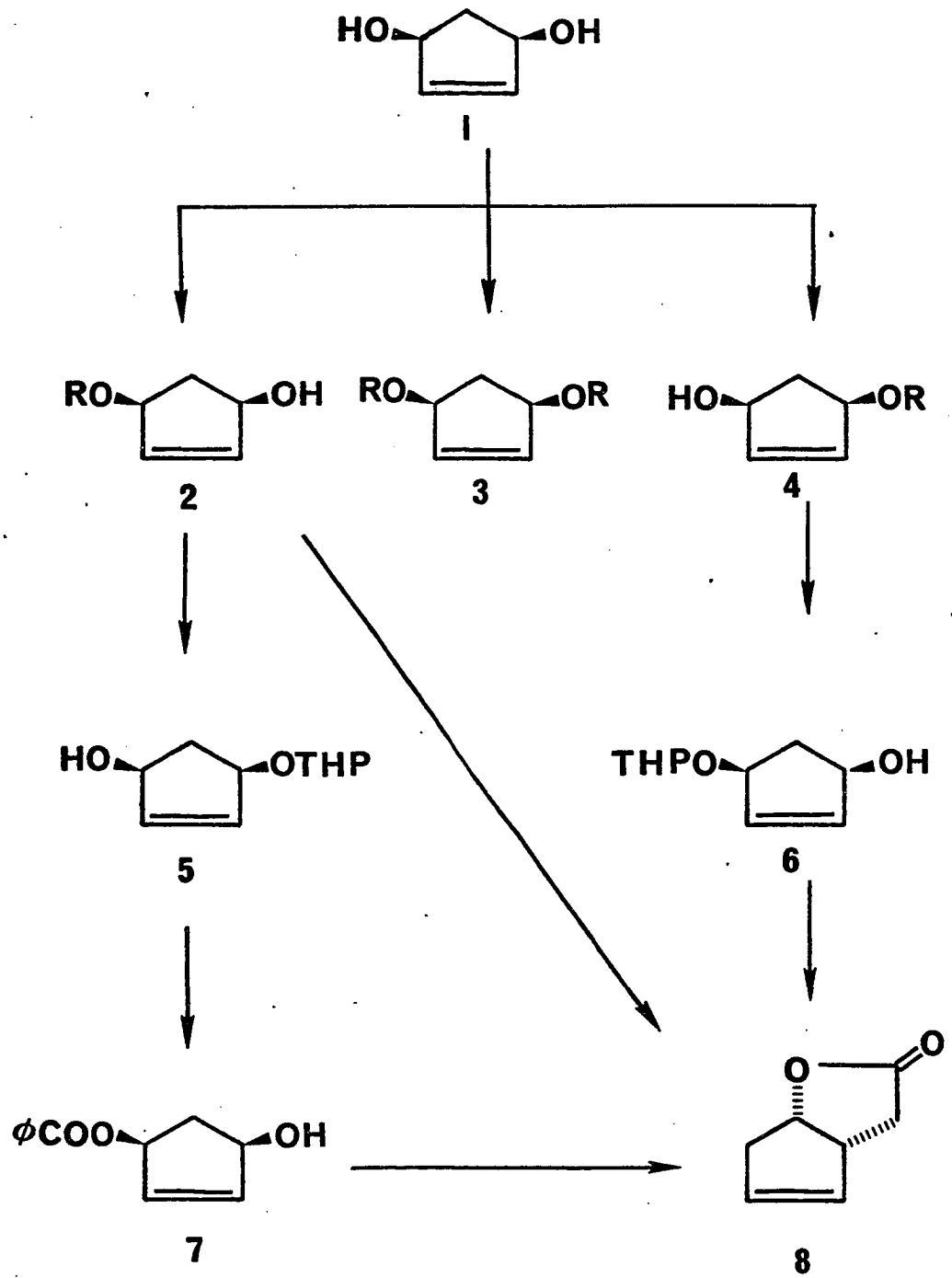
Terashima, Yamada and Nara [74] started with a symmetric compound, cis-2-cyclopentene-1,4-diol 1. When they treated 1 with (S)-N-methylsulfonylphenylalanyl chloride (1.0 eq.) in pyridine (rt, 15 hours), they obtained a mixture of monoesters (2 and 4) in 51% yield and the diester 3 in 24% yield. 2 and 4 were converted to a single optically active prostaglandin intermediate 8, whereas the diester 3 was converted back to the starting material.

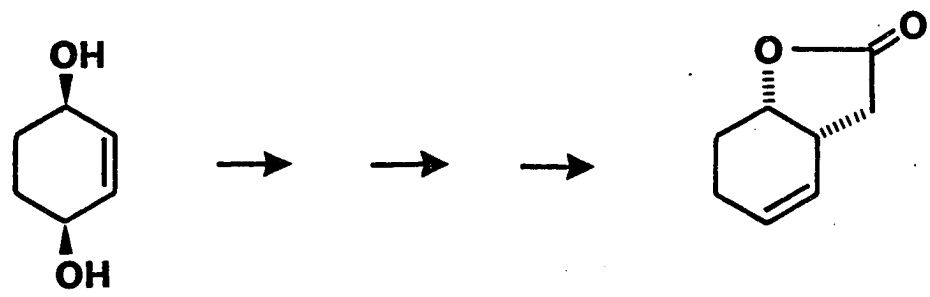
Protection of the alcoholic function of 4 as the tetrahydropyranyl ether followed by hydrolysis of the chiral acyl group gave 6. When 6 was submitted to orthoester-Claisen rearrangement with triethylorthoacetate, it gave optically active 8 after alkaline hydrolysis and lactonization. The same optically active isomer 8 was also obtained by orthoester Claisen rearrangement on straight 2 or its benzoate. Thus 2 and 4 were converted to a single optically active prostaglandin intermediate 8.

By similar methodology, the same group of researhers have also converted cis-cycyclohexene-1,4-diol to the optically active cyclohexene lactone [75]. This cyclohexene lactone is an important prostaglandin intermediate as shown by Corey and his coworkers. This work showed that the total amount of meso compound could be converted to a single enantiomer.

SCHEME 16

Terashima's Apprcach

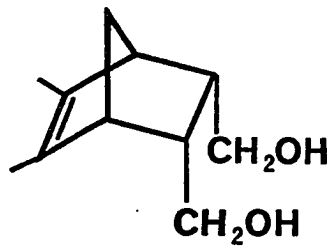




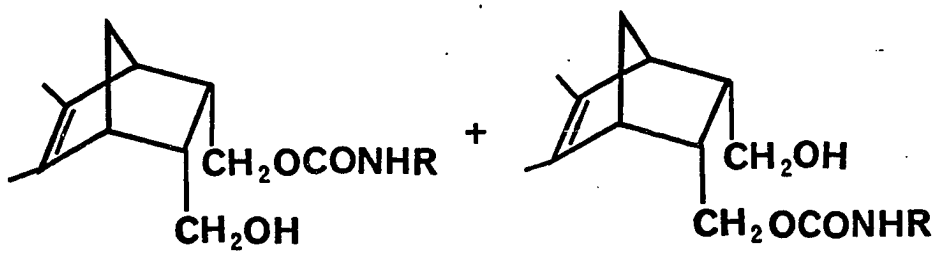
9 10

2.8.3 Hoffmann La-Roche Approach

The Hoffmann La-Roche group [77], on the other hand, started with a symmetrically substituted norbornene derivative, 1.



1



2 3

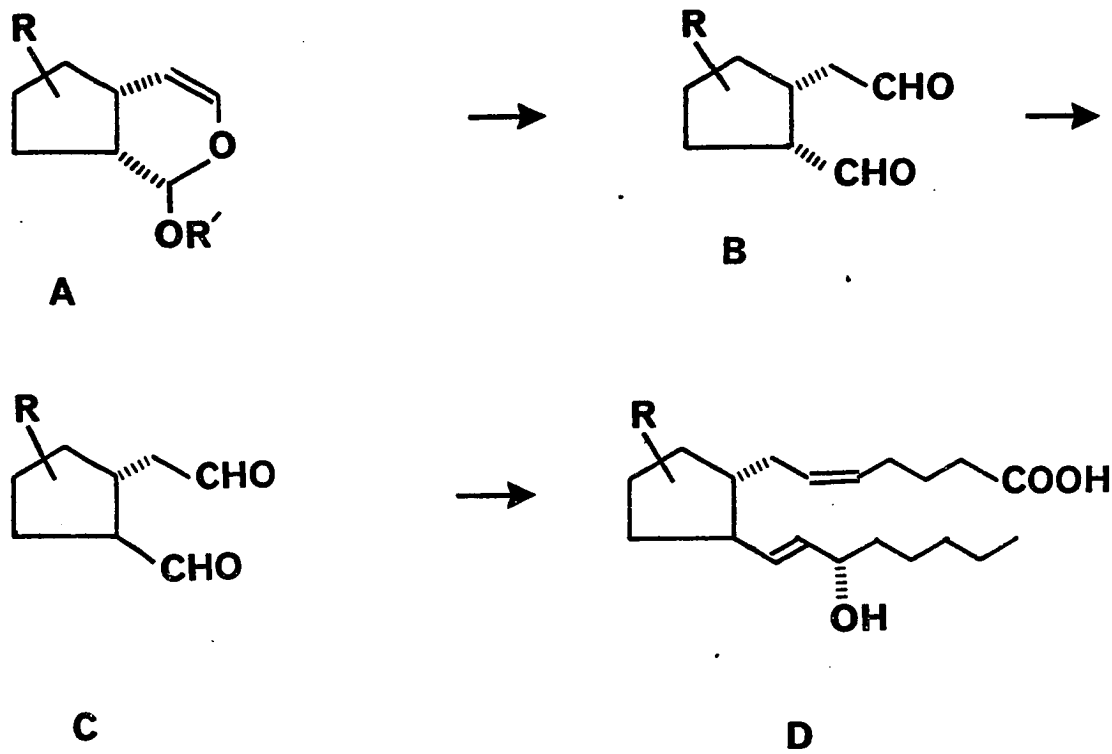
Meso intermediate 1 was treated with a chiral reagent and the desired isomer 2 was separated by fraction crystallization. Since the undesired enantiomer is readily recycled, the chiral efficiency of this synthesis is very high.

2.9 PROPOSED ROUTE FROM IRIDOIDS

Most of the syntheses mentioned above require either a chemical resolution or an assymmetric induction, in both of which the efficiency is generally low, is inapplicable to large scale reaction, or the undesired isomer has to be discarded or recycled. Although a few syntheses of optically active prostaglandins have been reported which start with naturally occurring chiral substances, theses are generally fairly long, e.g. 17-21 steps from carbohydrates [64-67]. The syntheses starting from terrein [69] or tartaric acid [68] require 5 steps to bring them as far as 4-substituted cyclopentanone stage.

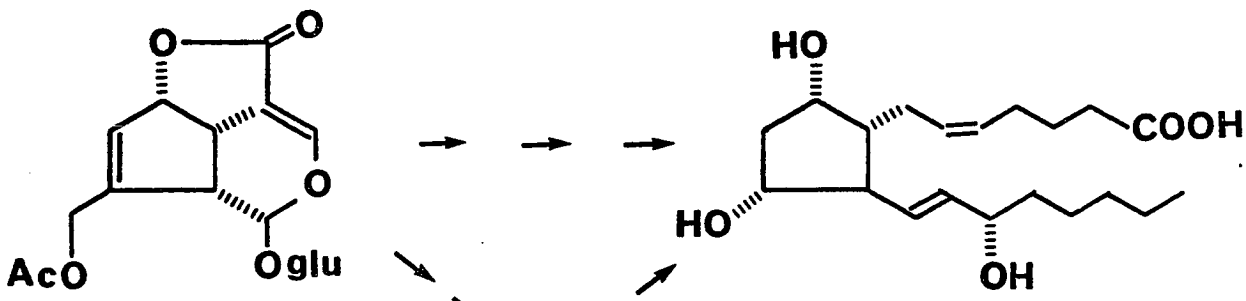
We believe, there is a shorter route to optically active prostaglandins starting from another natural source, iridoids. The iridoids are optically active, cyclopentanoid terpene glycosides [77] and are structurally very similar to prostaglandins. Many iridoids (e.g. asperuloside, aucubin) as well as the prostaglandins are tetrasustituted at the cyclopentane nucleus. The hydrolysis of the encl ether-acetal moiety in A could provide the dialdehyde B, which could be epimerized to the dialdehyde C, an important potential pros-

tagladin itermediate. The two side chains cf prcstaglandins could then be introduced by the use of successive Wittig or



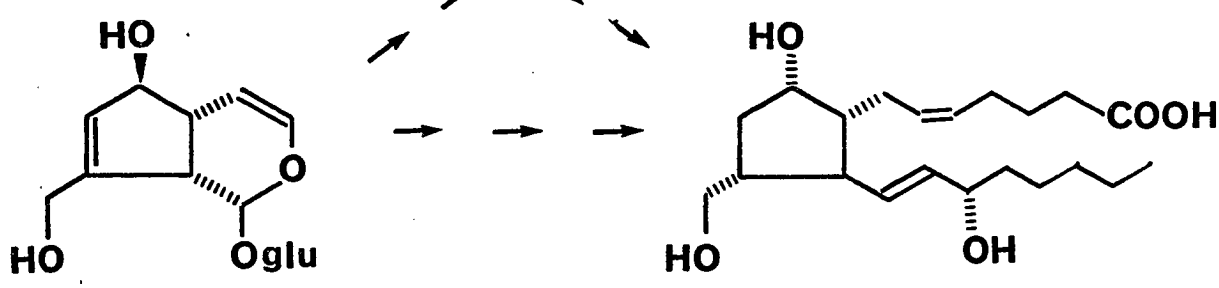
Wadswcrth-Emmons reactiон. The variations at the cyclopentane nucleus cf iridoids could also provide new, yet unknown, prostancids for investigation of their biological activity. A few structural variations at the cyclopentane nucleus of iridcids and their possible conversion tc prostancids are given below.

Initially, it was decided to investigate the mcdification cf aucubin and asperuloside, in order tc study the problems asscciated with the enol-acetal system, the extra carboxyl carbon for asperuloside, hydrcgenaticn (without hy-



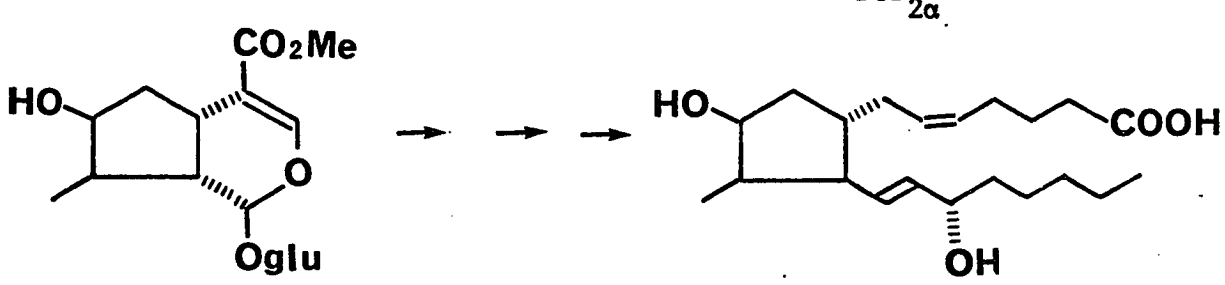
Asperuloside

$PGF_{2\alpha}$

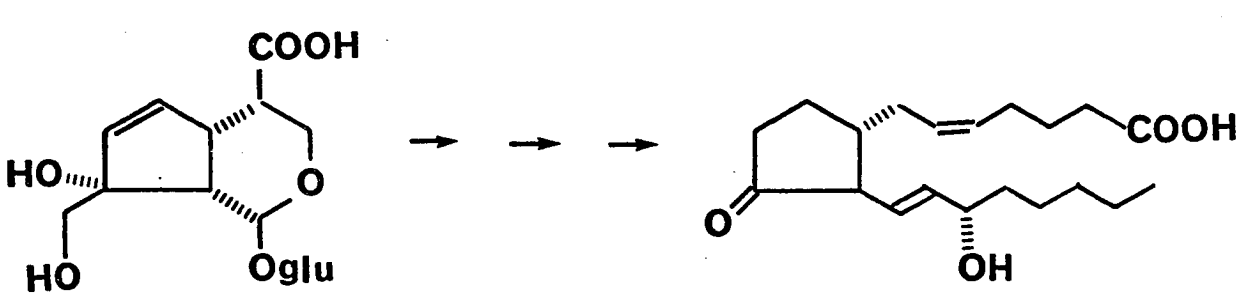


Aucubin

11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$



Loganin



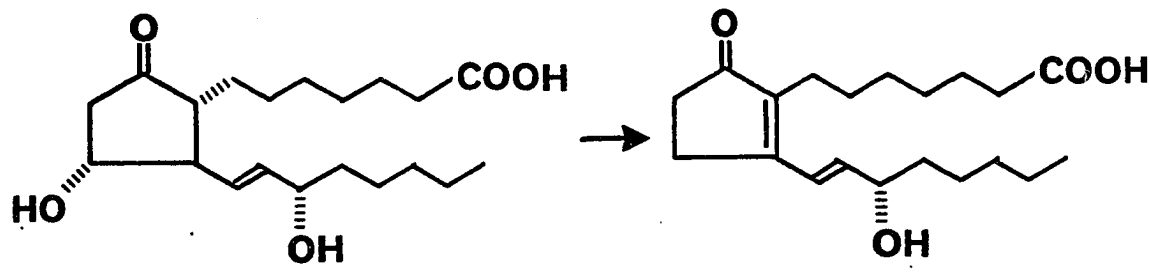
Monotropein

drogenclysis) with proper stereochemitry, problems common to the conversion of many iridoids to prostancids. The primary objective has been to prepare a known compound of known physiological activity. Since this project was started, Ohno and his coworkers reported (sec. 2.8.7) successful conversions of aucubin to prostancids. Weinges (sec. 2.5.6) also reported the conversion of catalpol to a possible prostaglandin intermediate.

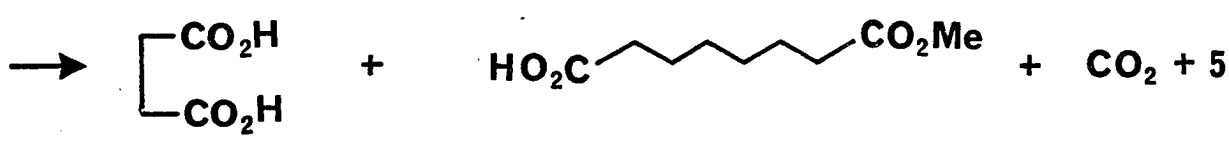
2.10 THE ABSOLUTE CONFIGURATION OF IRIDOIDS AND PROSTAGLANDINS

Bergstrom and his coworkers in a series of brilliant investigations revealed the structure of the whole family of prostaglandins purely by chemical degradation and characterization of the isolated products. Final proof of the structure along with the stereochemical array of the molecule was obtained by Abrahmson [79,80] from a three dimensional single crystal X-ray analysis of the tris p-bromobenzoate of the methylester of PGF . Recently the structures of PGE_1, PGE_2, $PGF_{1\alpha}$, PGA_1 and PGB_1 have also been determined by X-ray diffraction. However, although the relative stereochemistry of all groups was firmly established by this procedure, the absolute configuration remained to be determined.

Since all these prostaglandins have been either interconverted or derived from each other, they undoubtedly have the same absolute configuration. The correct absolute con-



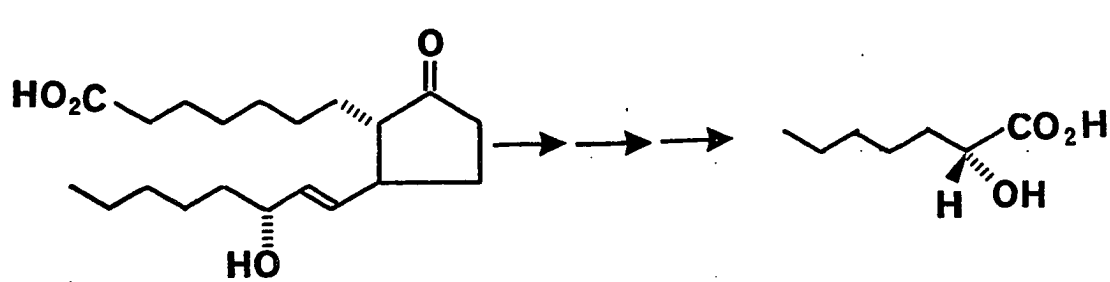
1 2



4 3

5

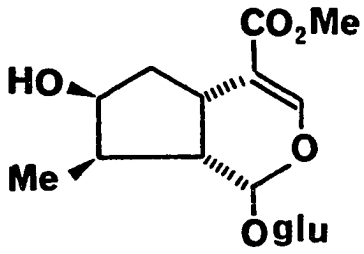
S-2-hydroxy Heptanoic Acid



6 7

figuration of prostaglandins was assigned [81] on the basis of chemical degradation studies. Dehydration of PGE_1 (1) by 0.5N sodium hydroxide at room temperature resulted in the formation of a new compound, PGB_1 (2) which was converted to its methyl ester with diazomethane. PGB_1 methyl ester was then subjeted to oxidative ozonolysis and the products, monomethyl suberate 3, succinic acid 4 and α-acetoxyheptanoic acid 5 were isolated. Saponification of the isolated α-acetoxyheptanoic acid and measurement of the optical rotation of the resulting acid as well as its sodium salt revealed that it was 2(S)-hydroxyheptanoic acid. The formation of 2(S)-hydroxyheptanoic acid therefore requires 1 to be the absolute structure of PGE . If the absolute structure were 7 instead, one would have expected the formation of 2(R)-hydroxyheptanoic acid (7).

The structure and absolute configuration of loganin 1 was found by X-ray crystallographic analysis of the bromomethoxide pentaacetate 2, using heavy atom techniques [81]. Asperuloside 3 has been previously correlated with loganin [82] by its transformation to loganin pentaacetate: Selective catalytic hydrogenolysis of asperuloside tetraacetate followed by esterification with diazomethane gave dialkene 4. Oxidation of 4 with m-chloro perbenzoic acid followed by treatment with boron trifuoride gave ketone 6, which was reduced with sodium borohydride. The resulting hydroxy group was inverted by tosylation followed by treatment with tetra-



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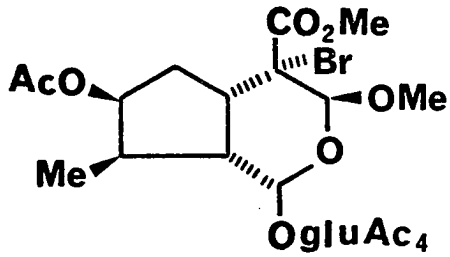

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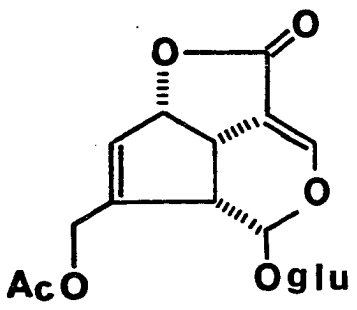

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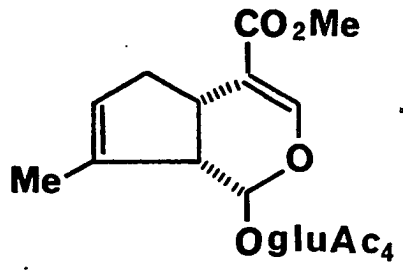

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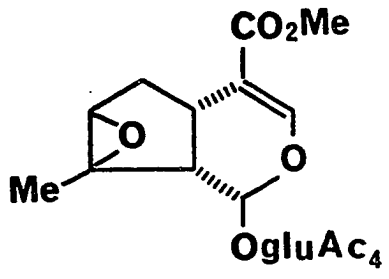

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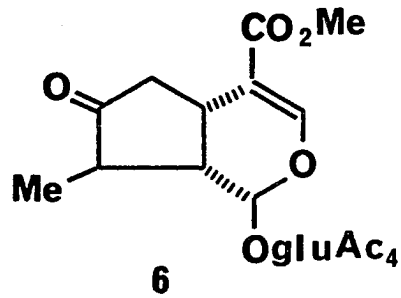

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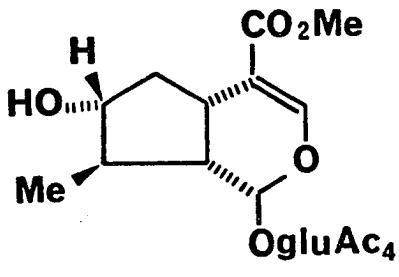

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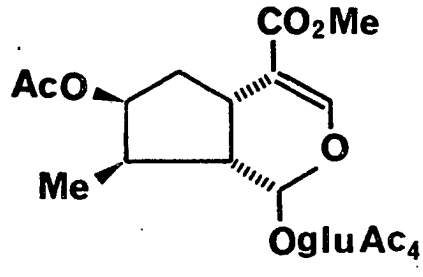


8

ethyl ammonium acetate. the resulting loganin pentaacetate was identical to the one obtained from naturally occurring loganin. Therefore asperuloside has the same absolute configuration [83] as loganin and its conversion to prostanoids will provide the correct absolute stereochemistry.

Chapter III

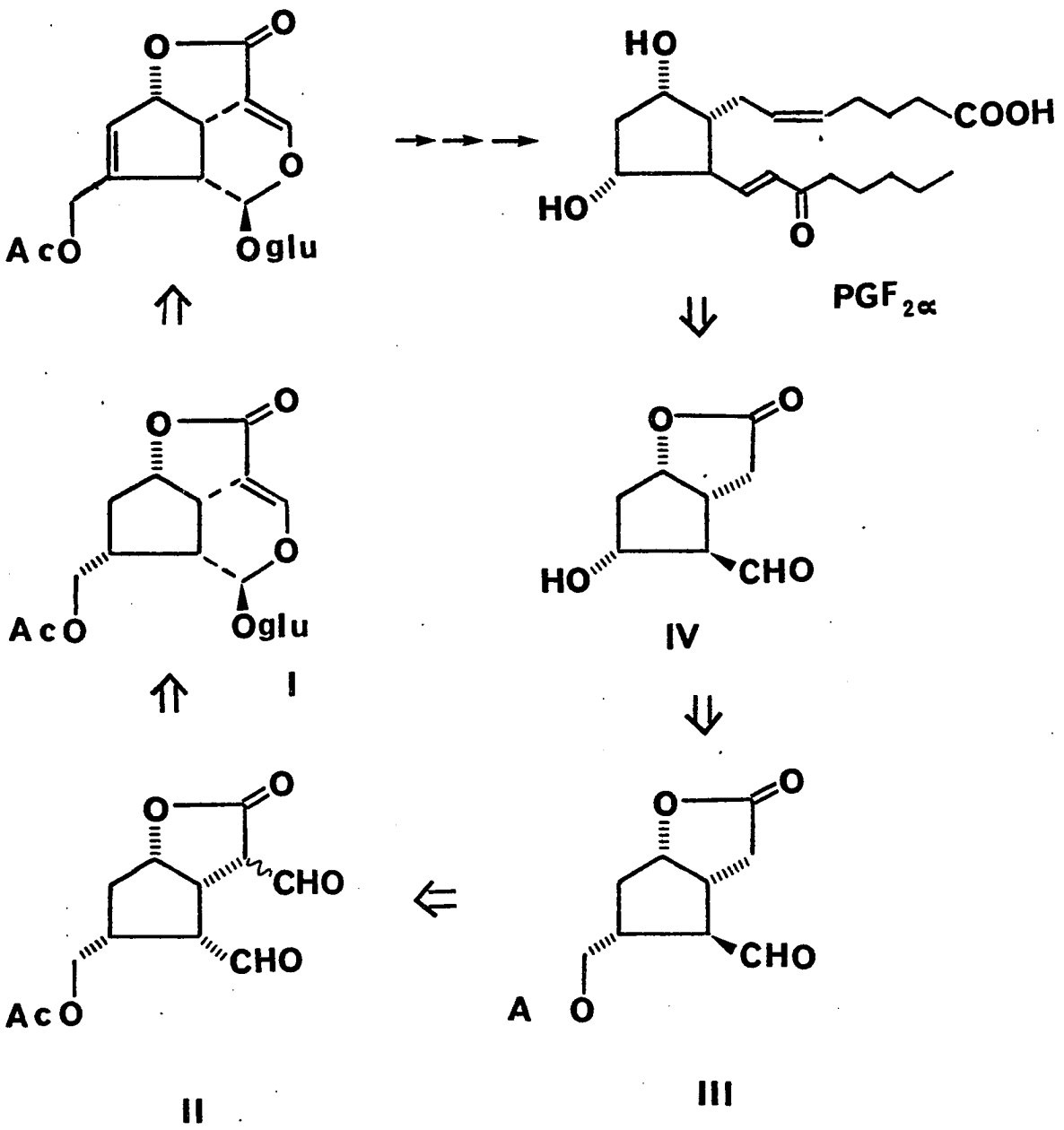
RETROSYNTHETIC PLAN

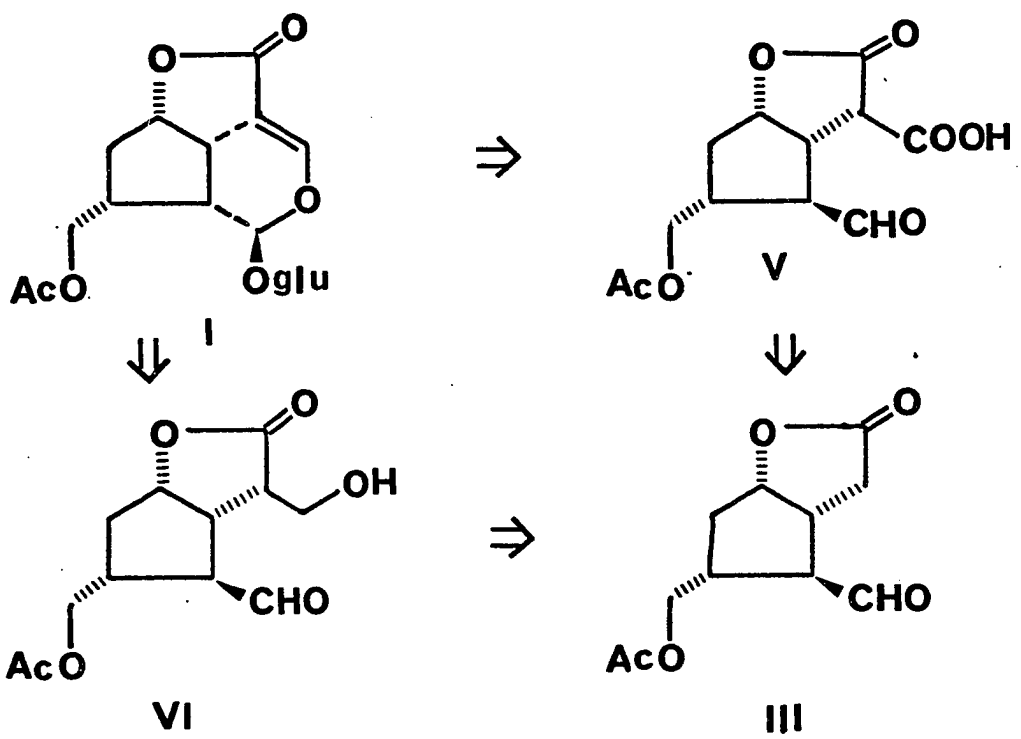
For most of the syntheses of naturally occurring prostaglandins, the Corey aldehyde (IV) has been the key intermediate. Both asperulcside and the Corey aldehyde are tetrasubstituted at carbons 8,9,11 and 12 of the cyclopentane nucleus. However asperuloside possesses an extra double bond [C(7)-C(8)] and also two extra carbons C(3) and C(10). Reduction of the double bond frcm the more accessible (convex) side cf the molecule and hydrolysis of the enol acetal system (for removal of glucose) would release dialdehyde intermediate II. Removal of the C(3) aldehyde group and epimerizaticn of the C(13) aldehyde group will provide the 11-homclog cf the Corey aldehyde III, further degradation of which by a one carbon unit will give Corey aldehyde IV.

The two aldehyde groups in II have to be differentiated so that C(3) aldehyde group will not interfere during introduction of the ω- side chain upon Wittig or Wadsworth-Emmons reaction of the C(1) aldehyde. This may be accomplished by the oxidation cf the encl-ether system to give aldehyde-acid V or reduction to give aldehyde-alcohol VI which may be oxidized to V after protecting the aldehyde grcup. The acid V

SCHEME 17

Conversion cf Asperuloside to Prostaglandins 'Retrosynthetic Plan'





is a malonic acid derivative which could be converted to the homolog of Corey aldehyde III, the key intermediate, by the loss of carbon dioxide.

The problems associated with the conversion of asperuloside to the key intermediate (III) are the following:

1. Hydrogenation of the C(7)-C(8) double bond from the β-face.

2. Removal of the glucose.

3. Removal of the enol ether carbon, C(3).

4. Epimerization of the C(12) carbon.

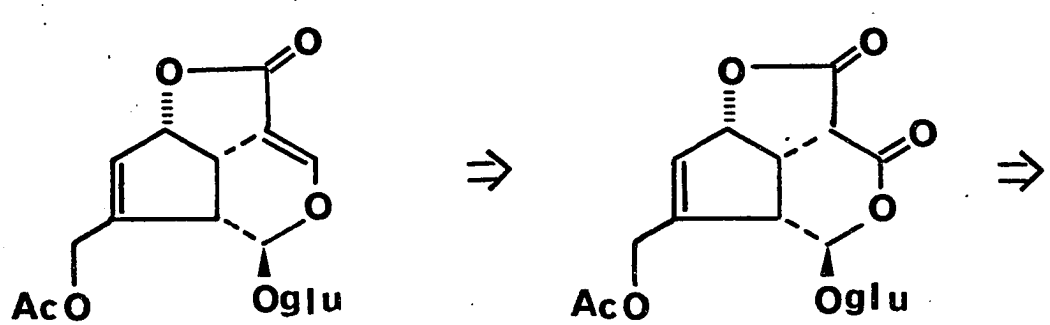
5. Eventual loss of C(10) if $PGF_{2\alpha}$ is the desired goal.

The above transformations could be achieved by the following routes :

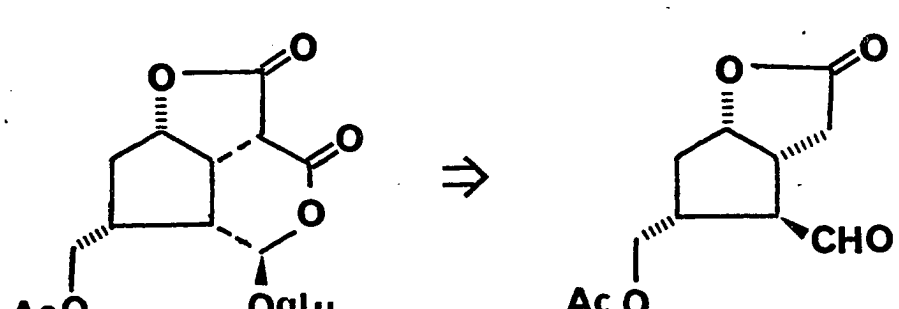
3.1 OXIDATION ROUTE (SCHEME-18)

SCHEME 18

Oxidation Route



VII



C VIII

III

Oxidation of the enol ether carbon of asperulcside can provide the dilactone VII. Reduction of the double bond (VII

tc VIII), hydrclysis, and decarboxylation and epimerization can then give the thermodynamically more stable Corey aldehyde homolcg III, a key intermediate.

3.2 REDUCTION ROUTE (SCHEME-19)

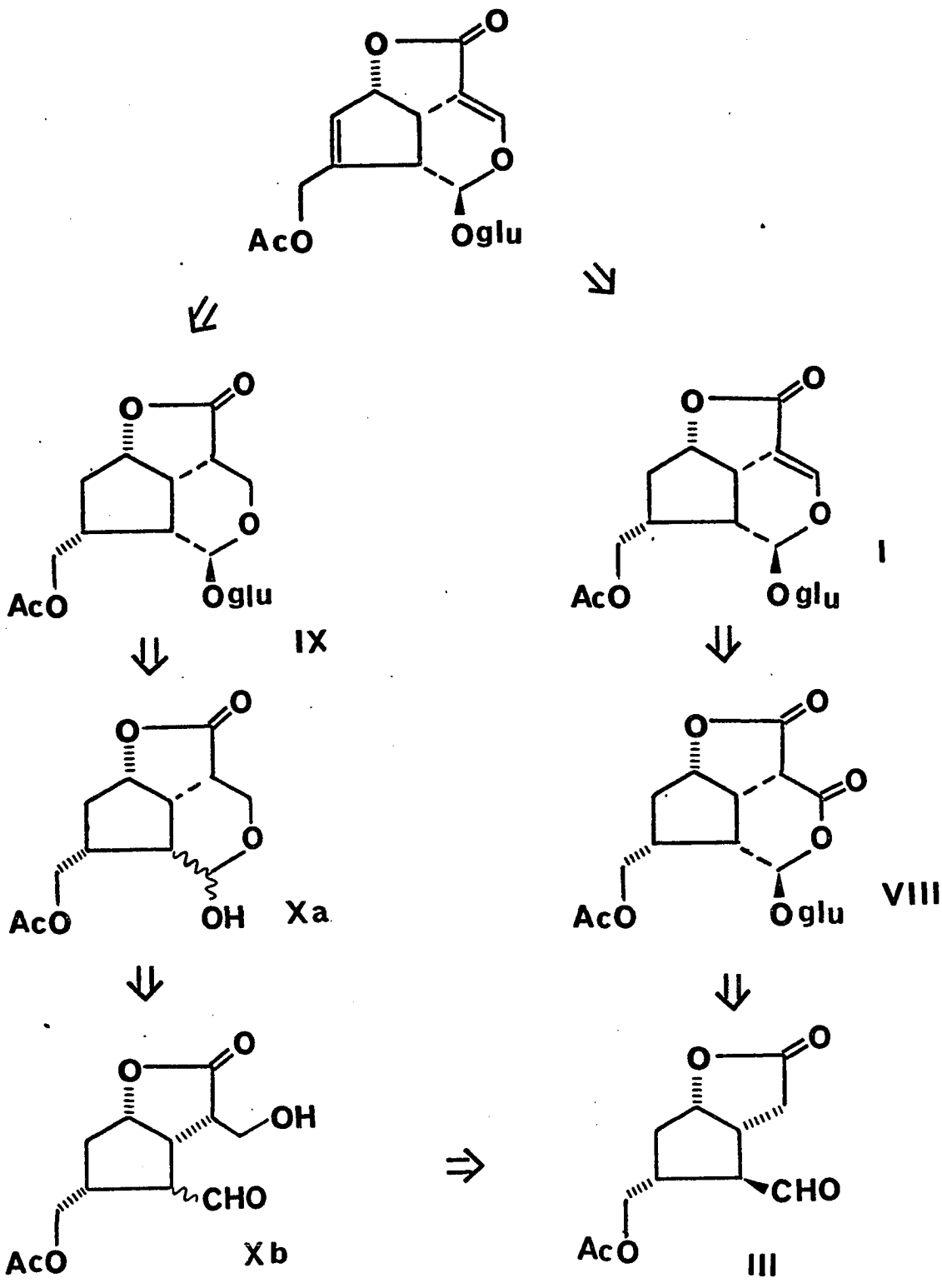
Ccnversion of asperuloside to its tetrahydrc derivative IX, followed by acid hydrolysis (for removal of glucose) can provide the hemiacetal Xa. Hemiacetal Xa is in equilibrium with the hydrcxy aldehyde Xb, which has a hydroxymethyl group on the 5-membered lactone. Oxidatien cf the hydroxymethyl group tc the aldehyde or the acid follcwed by the retro Claisen or decarboxylation should provide the key intermediate III.

If it were possible to isolate the dihydroprcduct I from hydrogenation of the C(7)-C(8) double bond, the remaining enol ether bond could be oxidized to the lactone stage, as in the oxidation route above, giving an alternative synthesis of VIII.

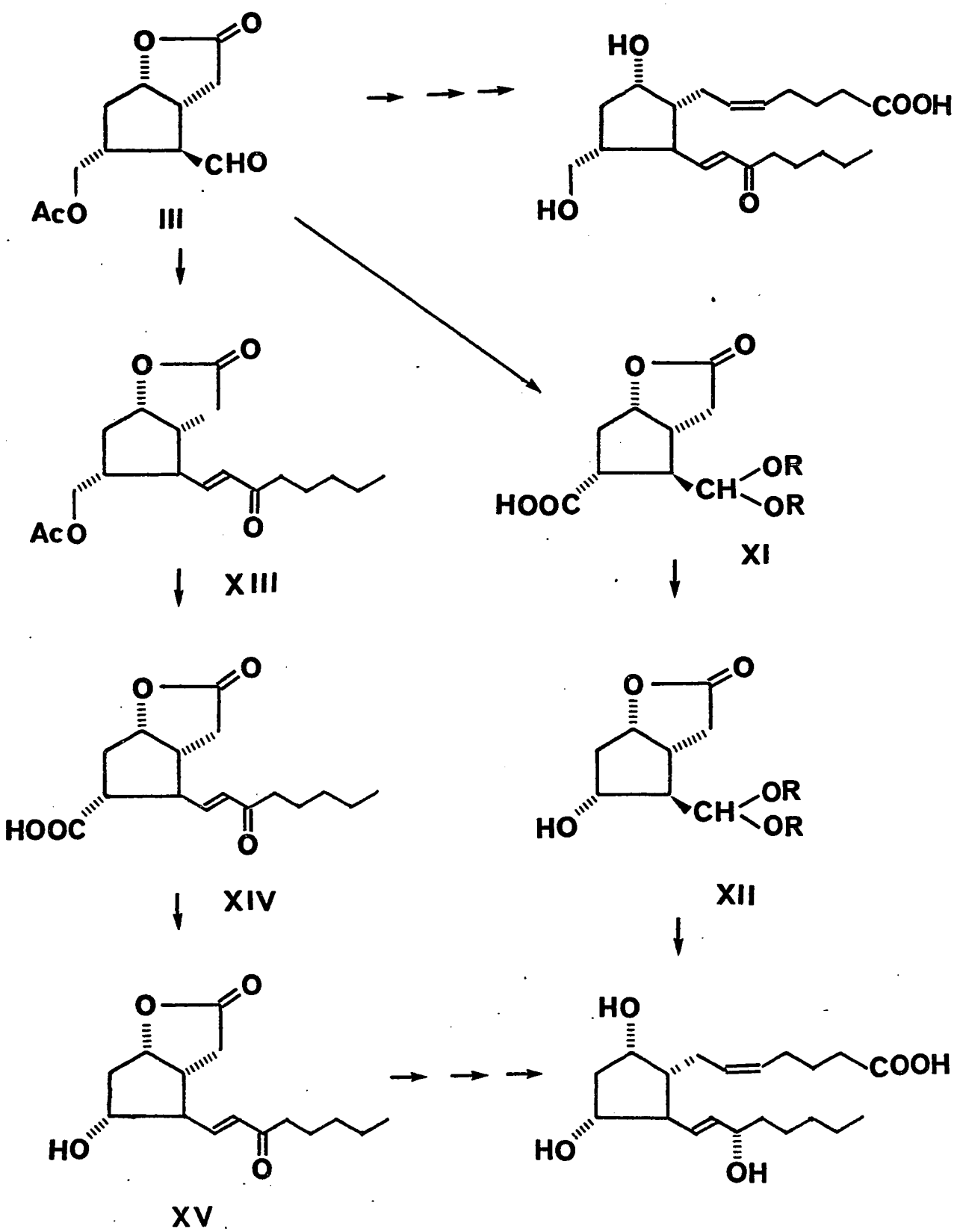
The basic difference between the oxidation and reduction routes is that in the former, the oxidation of unwanted carbon C(3), fcr eventual removal is taken care of first, while in the reduction route, the hydrogenation of the C(7)-C(8) [C(10)-C(11) of prostaglandins] double bond is planed first, and cxidatien of C(3) at a later stage.

SCHEME 19

Reduction Route



Cnce obtained, III could be converted to 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$ in a manner [13,14] essentially similar to that cf the conversion of the Corey aldehyde to $PGF_{2\alpha}$ itself. On the other hand, by protecting the aldehyde of III, and cxidizing the hydroxymethyl group to carboxylic acid (XI), the protected Corey aldehyde XII, a well known intermediate for $PGF_{2\alpha}$, could be cbtained using a known [36] degradation procedure. Alteratively one could first convert III to XIII by Emmons-Horner reaction followed by oxidation and degradation to XV, also a known intermediate fcr $PGF_{2\alpha}$ synthesis.



Chapter IV

EXTRACTION OF ASPERULOSIDE

Historically, asperuloside has been known under several names, such as chlorogenin [84], rubichloric acid [85] and alstonin. It was not until 1925 however, when Herissey [86] isolated it for the first time in crystalline form from Asperulo odorata, that the name asperuloside was coined. The correct structure was finally assigned only in 1963 by Briggs and his coworkers [87].

The isolation of iridoids is known to be complicated by their instability to acid. Asperuloside presents a special problem of being unstable to bases as well as acids.

Briggs [87] isolated asperuloside from five coprosma species: c. tenuifolia (2.9%), c. arborea (0.6%), c. robusta (1.2%), c. repens (1.7%) and c. lucida, and detected its presence by color reaction in 68 other species. The dried bark of asperuloside rich plants was extracted with ethyl acetate or acetone using a Soxhlet apparatus for 50-100 hours. After filtration and concentration, the acetone extract deposited colorless needle-like crystals of asperuloside (mp 154^{0}C). The ethyl acetate extraction, on the other hand was allowed to stand for two days after which the su-

pernatant liquid was decanted. The residual viscous liquid was triturated with alcohol, washed with hct acetone and crystallized frcm methanol to yield asperulcside.

Fcr our purpcse, the best source of asperulcside in the United States was Coprcsma repens, which we obtained frcm Hines Wholesale Nurseies, Santa Ana, Caif. and Strying Arbcretum, San Franciscc, Calif.. Initially when we tried Brigg's extraction procedure, not even a trace of asperulcside was detected even after 200 hours of extraction.

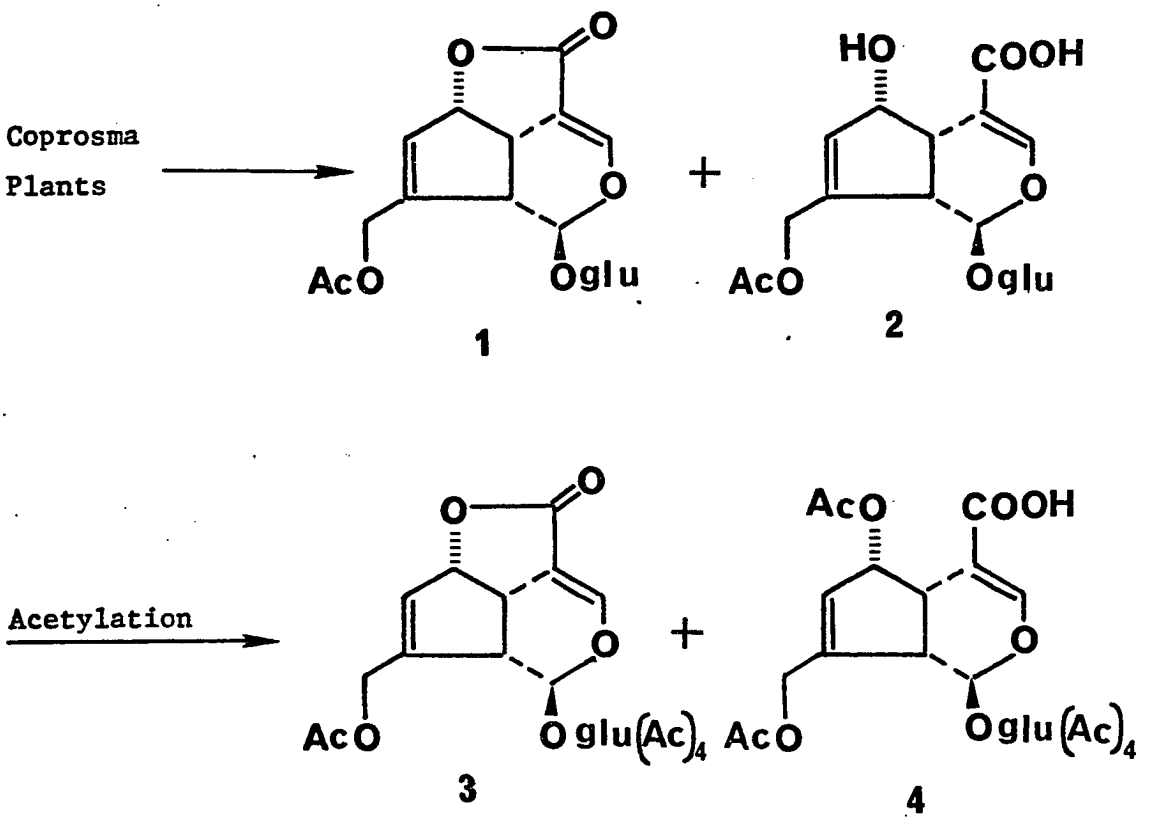
With the failure in extracting asperulcside by a knowm procedure, we decided to apply a variation cf Duff's procedure [88] which we had employed in the isclation cf a different iridoid, aucubin. For aucubin, we bciled the plant cuttings with hot water containing some calcium carbonate. The water extract was ccncentrated, adsorbed on celite and loaded on the top of a celite column pre-equilibrated with butancl-saturated water. The cclumn was then eluted with water-saturated butanol; the fractions containing aucubin were collected and concentrated.

When we applied similar prccedures for asperuloside, we did not have any success initially. However, when we omitted the additon cf calcium carbonate, a mixture cf asperuloside (Rf=0.88) and a slower moving ccmpound (Rf=0.73) appeared on TLC (when developed in 2/1 95% ethyl alcchcl-acetone and sprayed with sulfuric acid, both gave a blue cclored spot).

As with aucubin, the water extract was concentrated to a dark brown gum and adsorbed on celite. The adsorbed material was loaded on the top of a celite column previously equilibrated with butanol-saturated water, and the column was eluted with water-saturated butanol. All fractions giving blue spots on TLC, namely asperuloside and the slightly slower moving compound were collected and concentrated to give a brown gum. When acetylated (acetic anhydide/pyridine) the brown gum gave two products. One of the products appeared (TLC) to be the same as asperulcside tetraacetate prepared from an authentic sample of asperulcside given to us by Dr. J. Bobbitt (University of Connecticut, Storrs). The column chromatography of this mixture on silica gel (3/2 ethyl acetate-hexane) afforded pure asperulcside tetraacetate in 45% yield. The identity of the material was confirmed by the elemental composition and by comparision of its IR and NMR spectra with those of a sample prepared from authentic (Bobbitt) asperuloside.

It has been reported [87] that when asperuloside is boiled with water it suffers lactone ring opening. When an authentic sample of asperulcside was boiled with water, it was found that this was indeed true and a compound slower moving than asperuloside was formed (TLC). This slower moving product has the same Rf value (compared side by side) as the one we had obtained from the extraction of c. repens.

The formation of two products during extraction and after acetylation can be interpereted as the formation of asperuloside (1) and open lactone 2 during extraction, which on acetylation gave 3 (asperuloside tetraacetate) and hexaacetate 4. The yield of asperuloside tetraacetate by this method was improved when acetic anhydride was added a few hours before the addition of pyridine (presumably some of



the slower moving compound 2 underwent lactone formation). Asperuloside tetraacetate was thus obtained in 0.15% yield based on the weight of the fresh plant material committed to extraction. Since the plant material we had initially obtained was fairly old, we assume that all the asperuloside

was in the open, free carboxylic acid form (2) and acetone was not able to extract it.

Because the water extraction procedure is tedious and rather long, other possible methods of extraction were explored. A variation of Brigg's hot acetone method [87] worked out successfully.

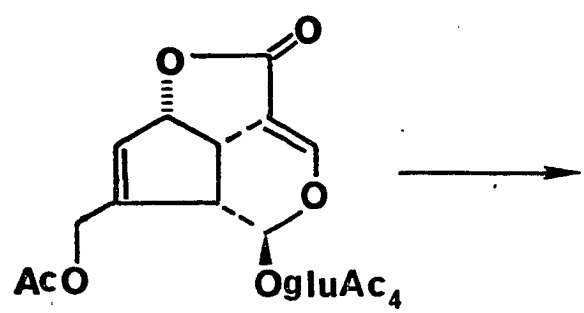
We boiled young coprosma plants with acetone twice, decanted and concentrated the extract. The concentrate was loaded on the top of a short silica column and eluted with acetone followed by absolute alcohol. The fractions giving blue spots on TLC (developed in 2/1 ethyl alcohol-acetone and sprayed with sulfuric acid) were concentrated. On the small scale (100 grams), we were able to isolate asperuloside in 0.48% yield and the slower moving (open-lactone) compound in 0.25% yield.

However, on a larger scale (20 kilograms), we acetylated the whole concentrate after desiccation, and asperuloside tetraacetate was isolated by a combination of chromatography and crystallization in 0.2% yield based on the weight of the fresh plant material.

Chapter V

HYDROGENATION

Our objective was to hydrogenate the C(7)-C(8) double bond of asperuloside tetraacetate 3 to either the dihydro-product 5 or the tetrahydro-product 6, and with the all-cis stereochemistry as shown:



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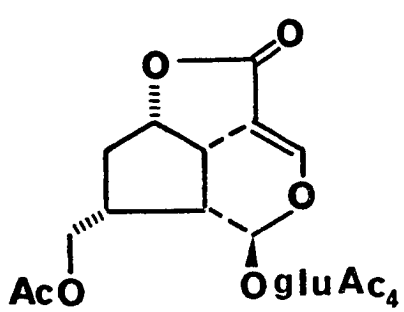
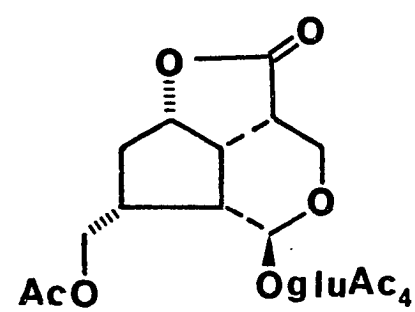


OR



5 6

Note that the outcome of hydrogenation for the C(3)-C(4) double bond does not really matter since after removing the unwanted carbon C(3), C(4) will become achiral. It was hoped

and expected that hydrogenation would occur from the top side only, to mimic the the stereochemistry (α) at C(11) found in natural prostaglandins (because of the complex shape of the molecule).

As we had discovered [89] that 5% Rhodium on Carbon in ethyl acetate was an effective catalyst/solvent combination for the hydrogenation of another iridoid (aucubin) with little hydrogenolysis, we applied this sequence (successfully) to asperuloside as well. However, the temperature was found to be the biggest factor in controlling the number of products.

It was found that when the hydrogenation was done at 0^0C, there was one major produt and few minor products. The major product could be isolated either by double crystallization or HPLC (Prep 500). However when the temperature was raised from -30^0C to 0^0C over a period of 3 hours, the same (major) product was produced in quantitative yield.

After carefully monitoring the reaction on TLC, it was found that an intermediate (slower moving than starting material) was formed at ca. -15^0C and as the temperature was raised to -5^0C, the intermediate product was converted to the final product. It was presumed that one double bond hydrogenates at -15^0C and the other at -5^0C. However no attempt was made to isolate the intermediate since it was always found to be contaminated with the starting material and presumably the tetrahydro-product.

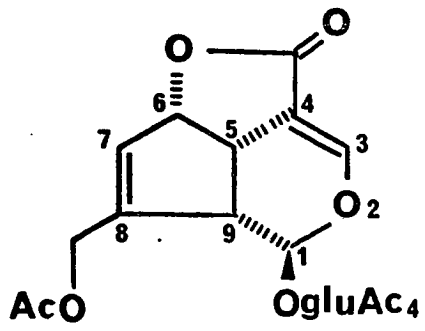
The elemental composition of the dihydro and tetrahydro products are within experimental error of each other, and therefore must be differentiated by other means. The parent peaks were absent from the mass specra of both asperuloside tetraacetate and the hydrogenated product, but several major

$Asp(Ac)_4$	$Asp(Ac)_4H_4$
---	255
235	239
193	197
175	179

fragments with a mass difference of four were present, we concluded, therefore, that we had probably prepared a tetrahydroproduct. That the product was indeed tetrahydroasperuloside tetraacetate was later confirmed by finding the molecular ion peak (m/e 196) of aglucone (tetracyclic acetal) 14.

5.1 HIGH RESOLUTION NMR OF THE TETRAHYDRO PRODUCT

From the NMR spectrum (270 MHz) of the hydrogenation product, it was easy to see that the C(3)-C(4) bond had been hydrogenated, since the peak at δ7.23 corresponding to the C(3) proton of asperuloside tetraacetate [77,87] was absent.



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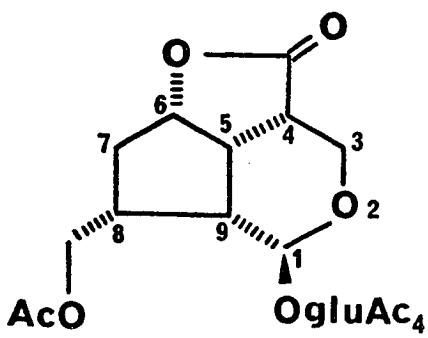


6

NMR data of Asperuloside Tetraacetate (3):

H_3 = δ7.03, H_7 = δ5.76

H_5 = δ3.48, H_9 = δ3.23

H_6 = δ5.51

NMR data of Tetrahydroasperuloside Tetraacetate (6):

H_1 = δ5.40, H_3 = δ3.89

H_5 = δ3.74, H_6 = δ5.03

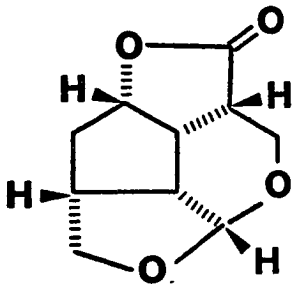
H_8 = δ2.57, H_9 = δ2.35

J(9,5) = 10.5 Hz, J(9,8) = 8 Hz, J(9,1) = 0 Hz.

The C(9) proton (δ3.23) was found to be a doublet of a doublet (J=10.5, 8 cps). However when the C(1) proton was irradiated (at δ5.4), the C(9) proton still remained a doublet of doublets except that it became slightly sharper. Therefore C(9)-C(1) protons do not couple significantly and their coupling constant [J(9,1)] is almost zero.

When the C(8) proton was irradiated (at δ2.6), the C(9) proton became a doublet (J=10.5 cps). And when the C(5) proton was irradiated (at δ3.7), the C(9) proton was still a doublet with J=8 cps. Therefore J(9,5) is 10.5 cps and J(9,8) is 8 cps.

For a cyclopentane ring, the dihedral angle for cis protons is about 0^0 and J would be expected to be about 8 cps, while for trans protons the dihedral angle is 90^0 and J would be expected to be 0 cps. Since the observed coupling constant J(9,8) of the tetrahydroproduct (6) is 8 cps, the cis relationship of hydrogens at C(8) and C(9) is warrantable. Note that this is the stereochemistry at C(11) of prostaglandins. The assignment of cis-stereochemistry was later confirmed by the X-ray analysis of the tetracyclic acetal 14



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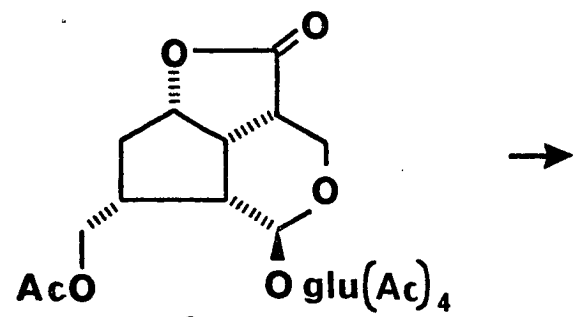
Chapter VI

HYDROLYSIS

After achieving success in hydrogenating the C(7)-C(8) double bond of asperuloside tetraacetate, our next objective was to get the aglucone 15 by removing the glucose moiety from tetrahydroasperuloside tetraacetate (6). It was necessary to remove the glucose without removing the primary acetate since oxidation of another yet unformed primary alcohol is required later.



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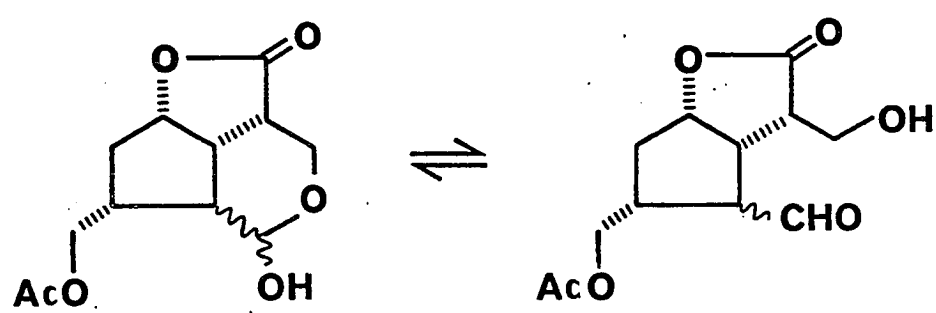
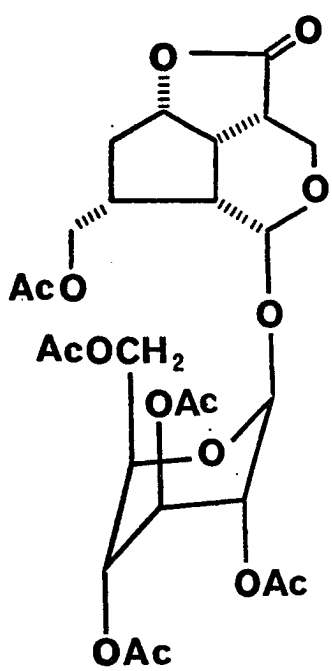


15 15a

Hemiacetal 15 has a masked aldehyde (15a) group which could be used for the introduction of the lower side chain common to prostaglandins by the use of Wittig or its Wadsworth-Emmons modification.



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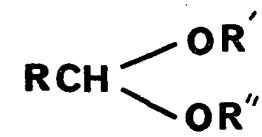

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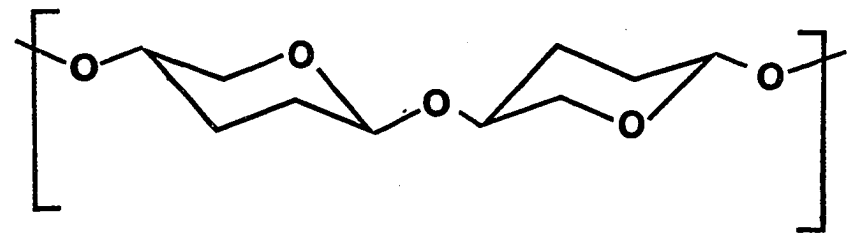
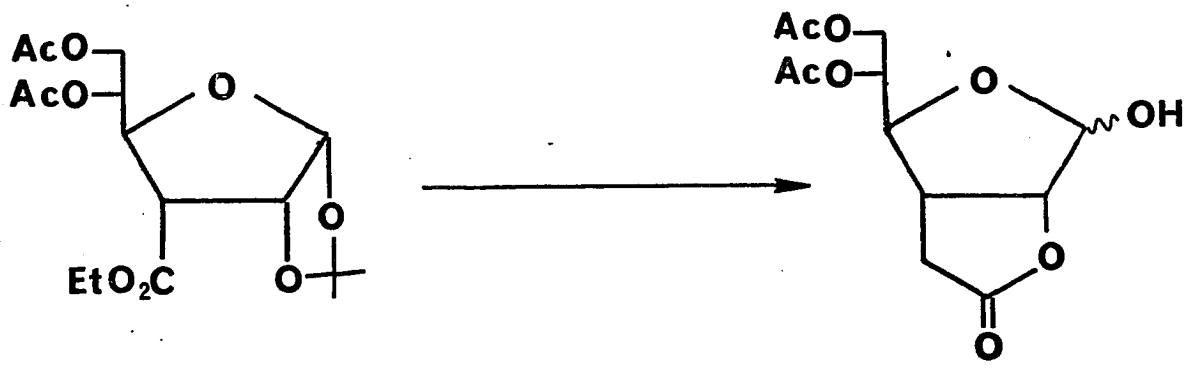


17

The acetal structure of tetrahydroasperuloside tetraacetate 6 is similar to that of the (non-reducing) polysaccharide 17 and as extensive work has been done in hydrolysing the later, we decided to apply methods for hydrolysing simple acetals (16) as as well as of cf polysaccharides (17).

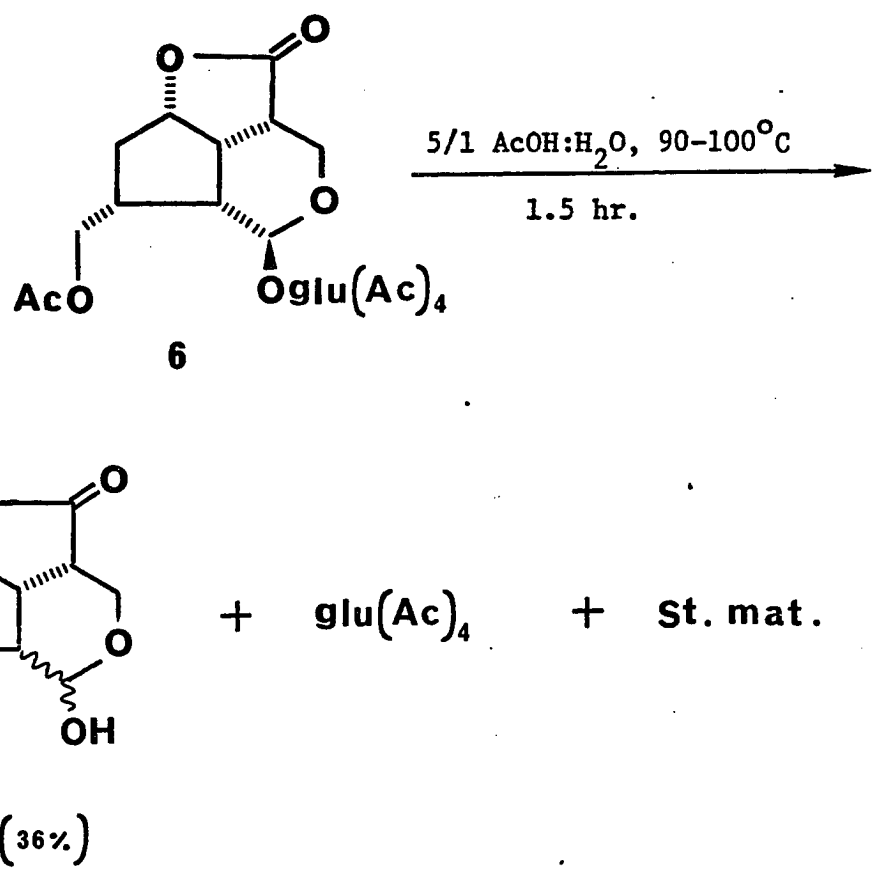
6.1 ACETAL METHODS

Most of the acetal hydrolyses we tried were either too mild, giving no significant amount of cleavage or were too strong, providing many products (TLC). The following example from the literature [90], however, provided the method of choice.



18 19

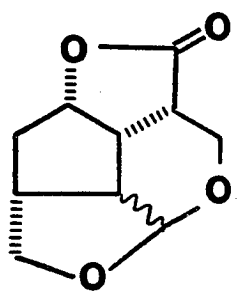
We considered this to be a good example, since the functionalities common to our aglucone 15 (acetate group, 5-membered lactone and the hemiacetal) survived under the reaction conditions. Under similar conditions (90^0, 3 hr), the reaction of 6 was only partially complete, but we decided to isolate and characterize the components because 15 is the key intermediate. Aglucone 15 was separated from glucose tetraacetate and unreacted starting material by flash chromatography [91] and was isolated in 36% yield. The analytical data (elemental composition, IR, NMR) were consistent with the structure shown. Since this was an important



potential intermediate in our synthetic plan, we decided to study this reaction thoroughly and find the conditions under which the reaction was clean and complete.

When the reaction was continued for longer times, the product was found to be a mixture of two aglucones, A and B (TLC), which were separated by column chromatography using absolute alcohol as the eluting solvent. It was found that the best (isolated) yield of aglucone 15 was only about 50% when refluxing was maintained for 24 hours; longer periods of time gave lower yields. The yield of aglucone-B (yet unknown structure) increased with reaction time but apparently at the expense of aglucone-A (15). By monitoring the reac-

tion on TLC, it was found that refluxing for at least four days was necessary for complete disappearence of aglucone-A with formation of only aglucone-B. In practice the reaction was allowed to reflux for 8 to 12 days, after which it was easier to separate the by-products (presumably glucose or its decomposition products) by simple liquid-liquid (water/chloroform) extraction. By this procedure aglucone-B was isolated in 86-92% yield. The formation of aglucone-B from aglucone-A (15), the observed elemental composition and the absence of the acetate group in the NMR suggested that aglucone-B might have one of the following three stuctures:



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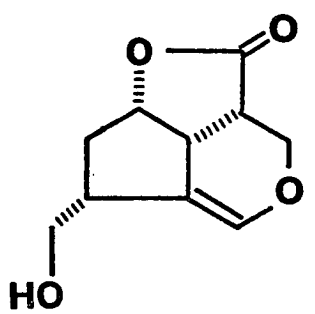

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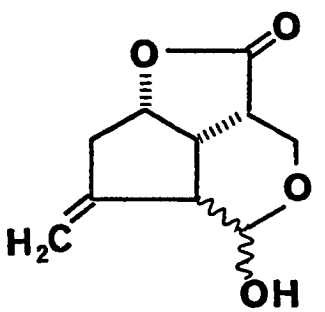
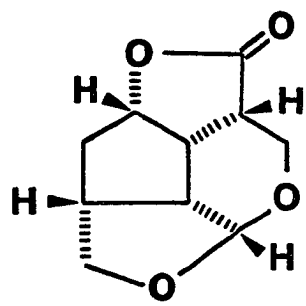


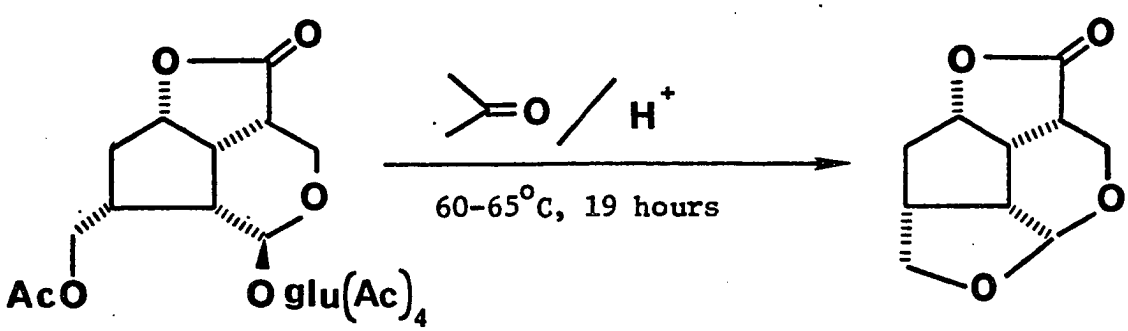
21

The absence of a peak due to a free hydroxyl group in the IR as well as the inertness of aglucone-B toward acetylation (treatment with acetic anhydride/pyridine gave only recovered starting material) ruled out the possibility of structures 20 or 21, and therefore structure 14 was tentatively accepted. That the real structure was indeed 14 was later confirmed by X-ray analysis, and is all cis as shown:



14

The same tetracyclic acetal 14 was also obtained in moderate yields (43%) by refluxing tetrhydroasperuloside tetraacetate in acetone with a catalytic amount of sulfuric acid. Note here the similarity of 14 to the tricyclic acetal obtained from aucubin by Chno [72] (10, pg 72) (and previously by Schmid [92]). Thus this is not an unexpected result.

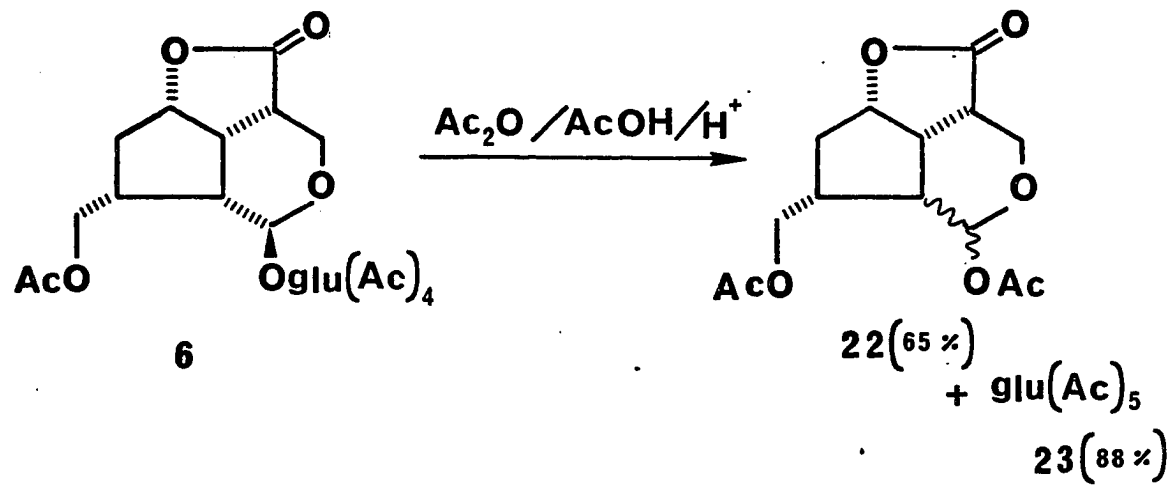


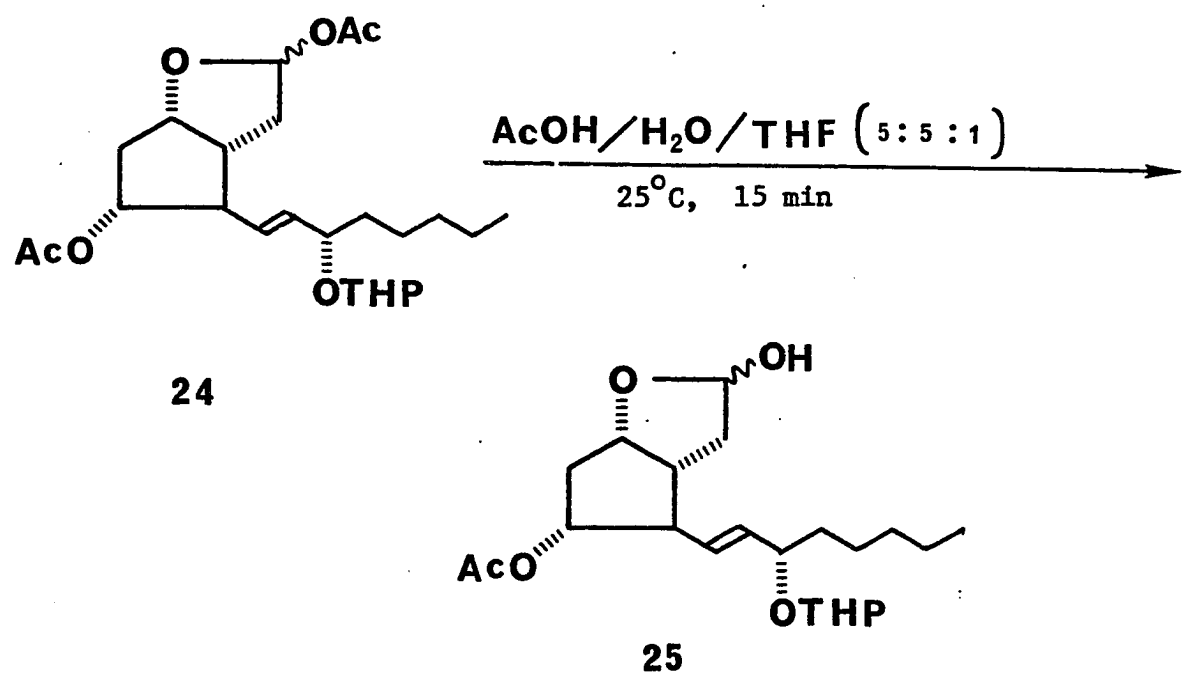
6 14

6.2 POLYSACCHARIDE METHOD

From literature survey [93] it was found that polysaccharides could be cleaved by treating them with a mixture of acetic anhydride and sulfuric acid. When this was tried on 6, heating on a steam bath, there was very little cleavage even after 5.5 hours. However when few drops of acetic acid were added, the starting material disappeared at room temperature in 5 hr.. The products were found to be aglucone 22 and glucose pentaacetate 23 and were separated by column chromatography. The NMR of 23 was identical to that of authentic β-anomer, except for the signal due to one (acetal) proton; it appears that we have prepared the α-anomer.

Literature [94] shows that a hemiacetal acetate can be cleaved in the presence of acetate (24 to 25) (with $AcOH/H_2O$ /THF, 5/5/1; 25°, 15 min). Under similar conditions, however aglucone diacetate 22 gave no reaction even up to 1





hr.. Cn the other hand, the hydrolysis of tetrahydroasperuloside tetraacetate 6 gave variable yields cf the aglucone diacetate 22 (0-65%). Careful investigaticn showed that part of aglucone 22 was hydrolysed during the aquecus work-up to give the aglucone 15 (which stayed in the water layer).

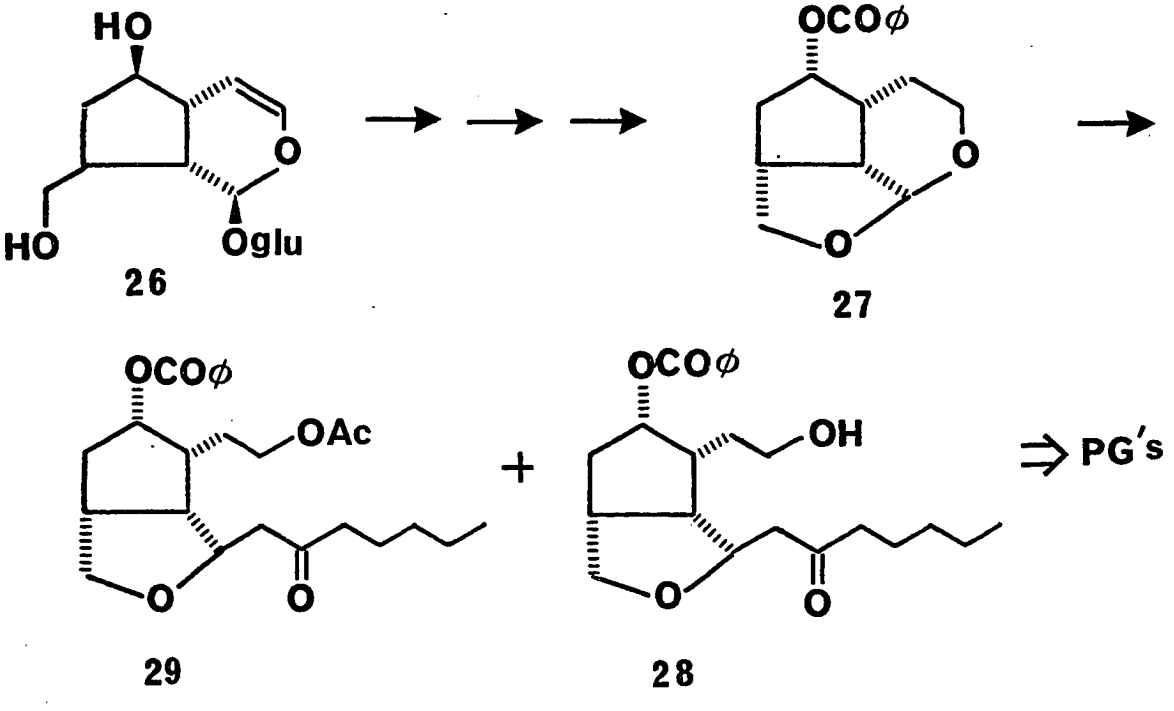
6.3 SUMMARY

We were unable to find a simple one step prccedure for making pctential aglucone 15 from tetrahydoasperuloside tetraacetate, althcugh it seems possible that the two step procedure, namely, treating tetrahydroasperulcside tetraacetate with acetic anhydride/acetic acid/sulfuric acid followed by aqueous acid wcrkup could lead to aglucone 15 in good yield. Cn the other hand, a very high yield (86-92%), one step procedure for making tetracyclic acetal 14 without chromatographic separation was found.

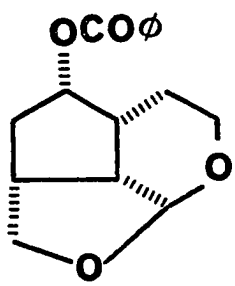
Chapter VII

A NEW PROCEDURE FOR CLEAVING ACETALS

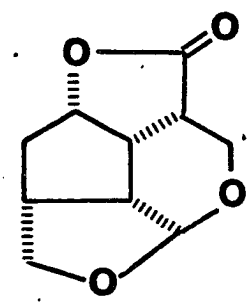
Chno and cowcrkers [72] repcrted an elegant synthesis of cptically active prostaglandin from a different iridoid, aucubin. A key step was the use of the Mukaiyama reaction [95] on the known tricyclic intermediate 27 obtained from aucubin (26). When 27 was treated with titanium tetrachloride (1.1equivalent) and 2-acetoxy-1-heptene (1.1 equivalent), 28 was obtained as a major product and 29 as a minor prcduct. The major ccmpcnent was separated using chromatography, and was then carried on to prostaglandins.



Considering the similarities of the tricyclic acetal 27 with tetracyclic aglucone (acetal) 14, and knowing a high yield procedure of obtaining 14 from asperulcside tetraace-



27

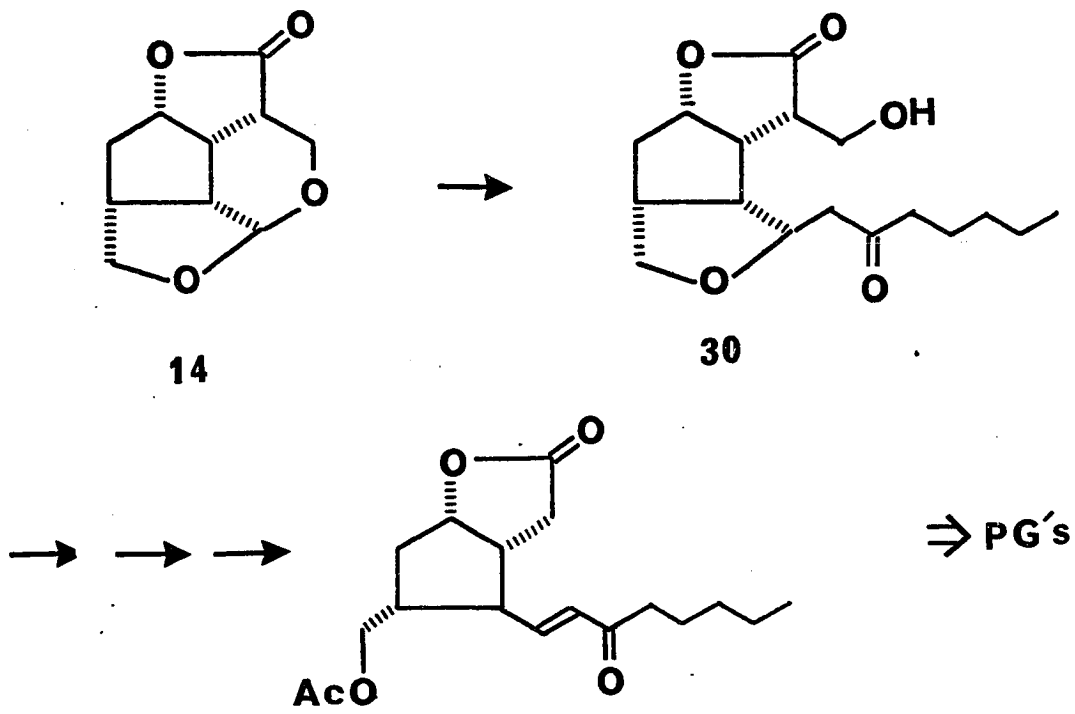


14

tate without any chromatographic separation, we were tempted to try a similar procedure with the hope of getting intermediate 30 (Scheme 20). which in turn could be converted to 31a and then to prostaglandins.

The whole scheme amounted to finding a good source for enol acetate 33. During the literature survey to find a good preparative method for 33, it was found that House and Kramer [96] had made 2-acetoxy-1-heptene from 2-heptanone (32) by first making the kinetically controlled enolate anion, using lithium diisopropylamide, followed by quenching the reaction mixture with acetic anhydride. A mixture of enolate acetates was isolated in 36% yield but it was not easy to separate the required (kinetic) enolate acetate 33

SCHEME 20

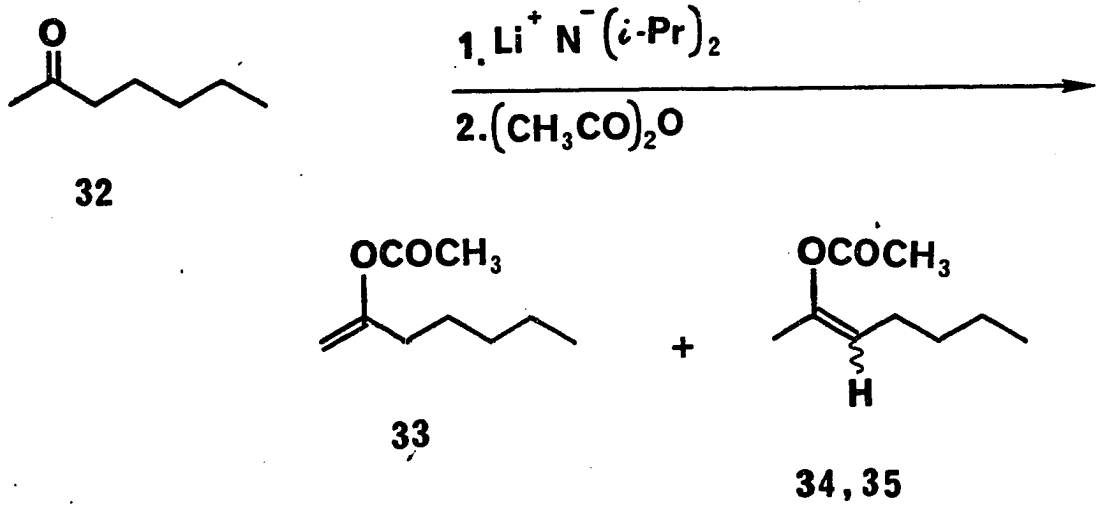


14 30 31a

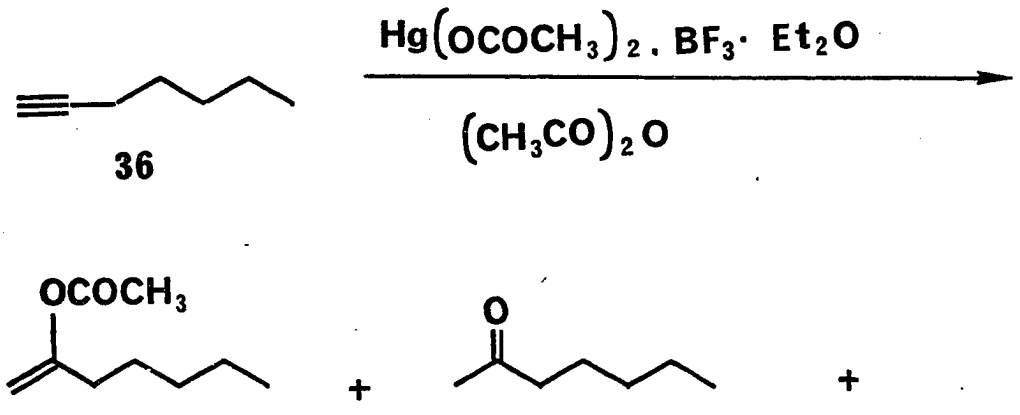
from the thermodynamically controlled isomers 34 and 35. Therefore we could not use this procedure for preparative purpose and a different approach was sought.

Hudrlik and Hudrlik [97] have made 2-acetoxy-1-hexene as well as 2-acetoxy-1-octene (kinetically controlled enol acetates of 2-hexanone and 2-octanone) from 1-hexyne and 1-octyne, respectively. This is the procedure (also used by Chno [72]) which we decided to try. The required major product 37 was easily separable from the minor products on

GC. Useful amcunts were obtained by this prccedure in 23% (isolated) yield starting from 1-heptyne.

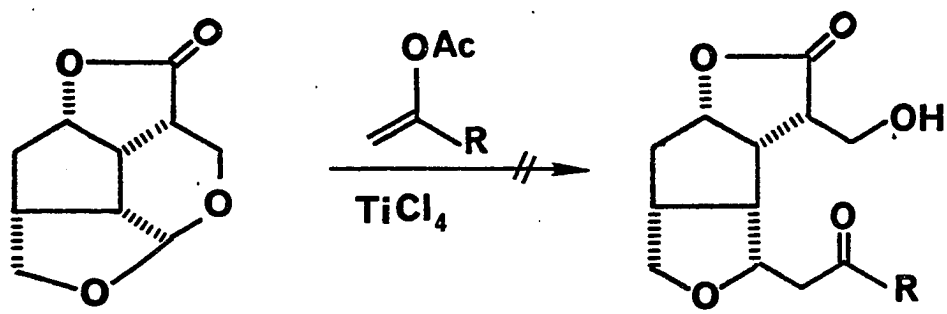


32 33 34,35



36 33 32 38

Hcwever, the Mukaiyama reaction of 14 with either 2-acetcxy-1-heptene (37) cr iscprcpenyl acetate under conditions similar to those of Ohno or Mukaiyama, gave no reac-



14

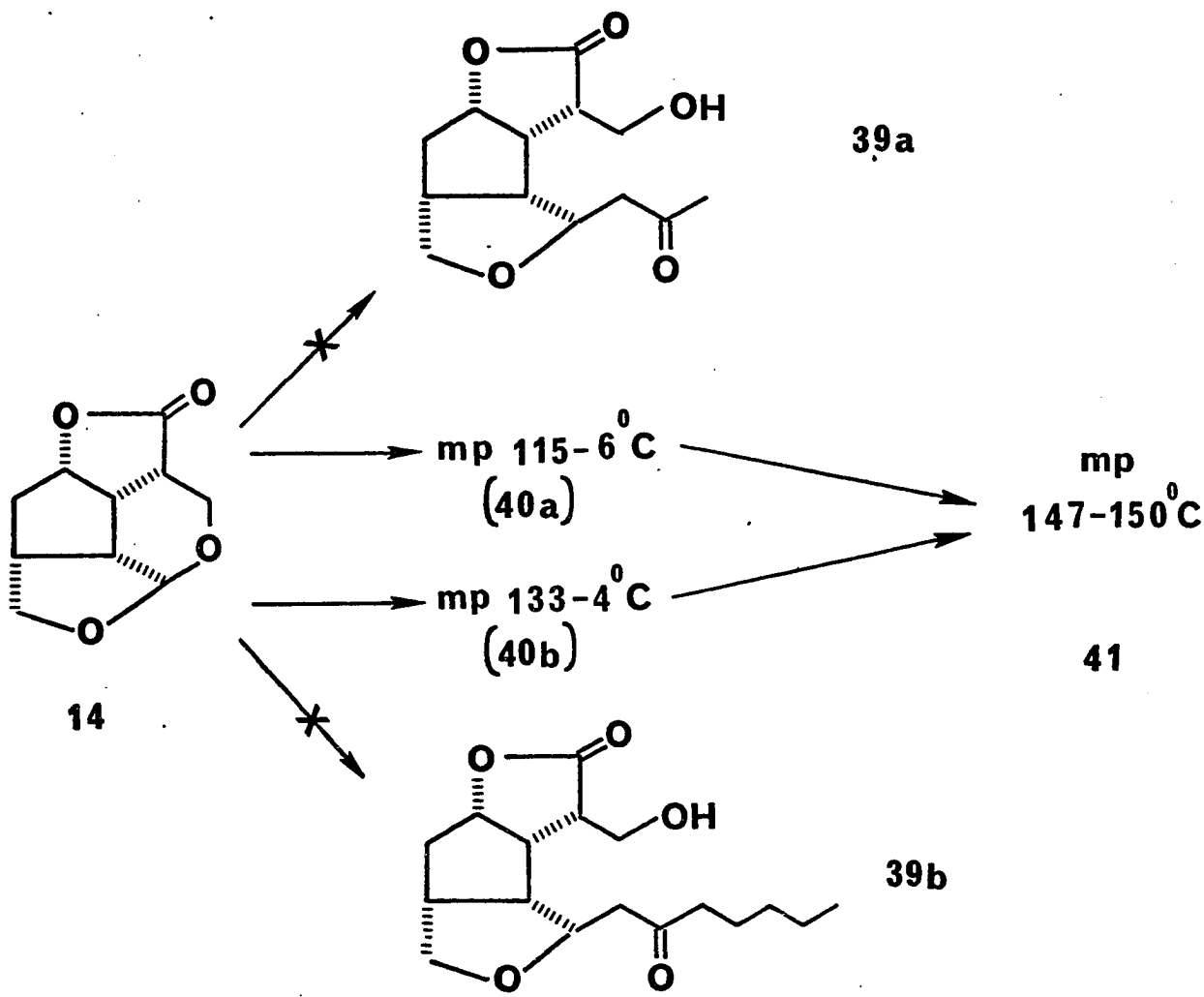
39a, R = $-CH_3$

39b, R = $-C_5H_{11}$

tion, and only starting material was recovered. When the reaction was investigated more carefully, it was discovered that only 43-57% (isolated) of the starting material was recovered by using the usual workup procedure. Similar to Chno's results [72], a majcr (slower moving) and a minor (fast moving) products were found by TLC examination of the reactien mixture. These products disappeared during usual basic workup.

We finally resolved this workup problem by first adding a few drops cf water to the reaction mixture followed immediately by adding excess solid sodium bicarbcnate cr carbo-

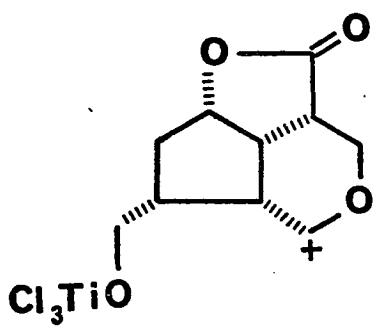
nate. The titanium dioxide formed in this manner was chunky and separated easily. The organic layer was simply decanted or filtered off and the organic products were then isolated in 88% yield, simply by concentration. The major product was separated by crystallization using hot ethyl acetate.



Elemental analysis of the major product from reaction of tetracyclic acetal 14 with either isopropenyl acetate or 2-acetoxy-1-heptene did not correspond to the expected structures 39a and 39b. In fact, the elemental composition of the two were identical! Repeated crystallization of 40a(mp 115-6°C)

or 40b (mp 133-34^{0}C) gave a single new product (41) with mp 147-150^{0}C.; the process is catalysed by adding few drops of methanol.

The mystery was finally resolved when it was found that 41 was identical in mp, mix mp, IR, NMR and elemental composition to 15, which was isolated previously by refluxing tetrahydroasperuloside tetraacetate in 5/1 acetic acid-water. 40a, 40b and 41 are probably epimers at C(1) and/or C(9). No attempt was made to completely characterize the minor product, which is probably 42. The formation of products in the above fashion is explained in Scheme 21. The difference might be due to the presence of the extra ring (5-membered lactone). We also do not know yet why the 5-membered oxonium ion 48 in Ohno's system reacts with the enol acetates while the 6-membered ion 43 in our case does not.



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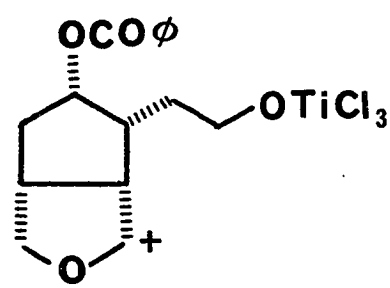

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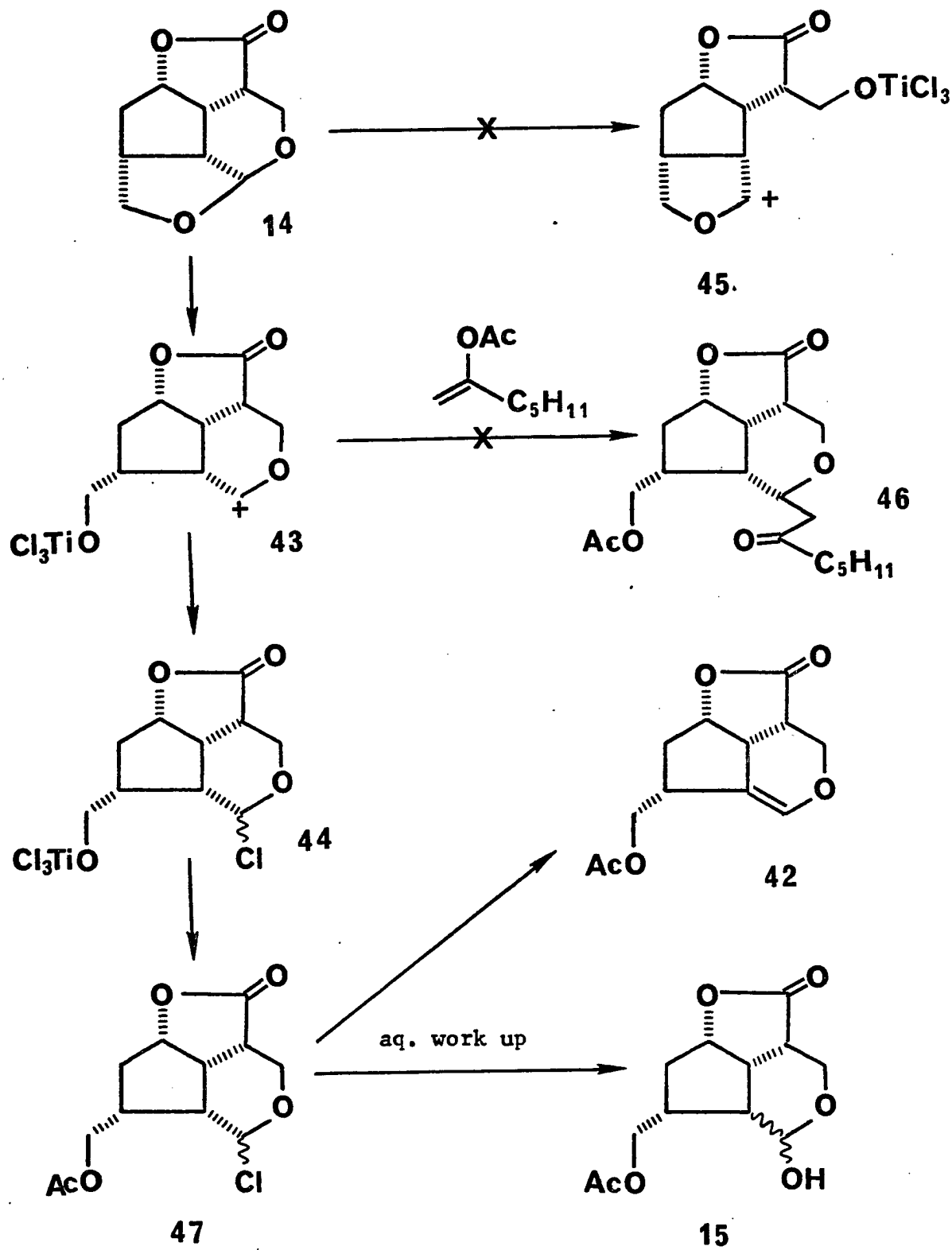
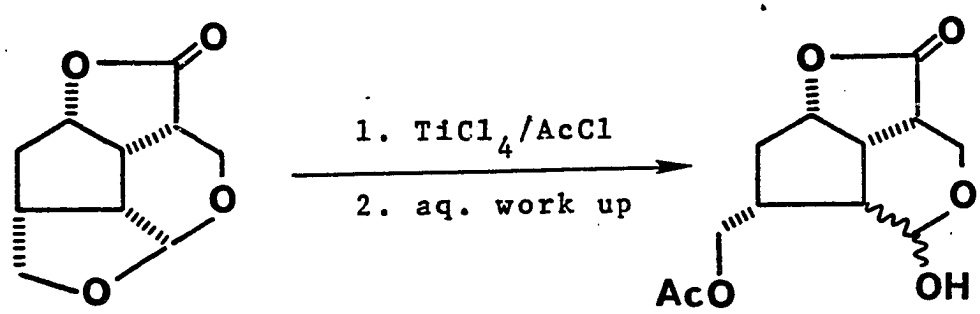
SCHEME 21



$$R\text{-}OTiCl_3 \xrightarrow{AcCl} R\text{-}O\text{-}Ac + TiCl_4$$

49 50

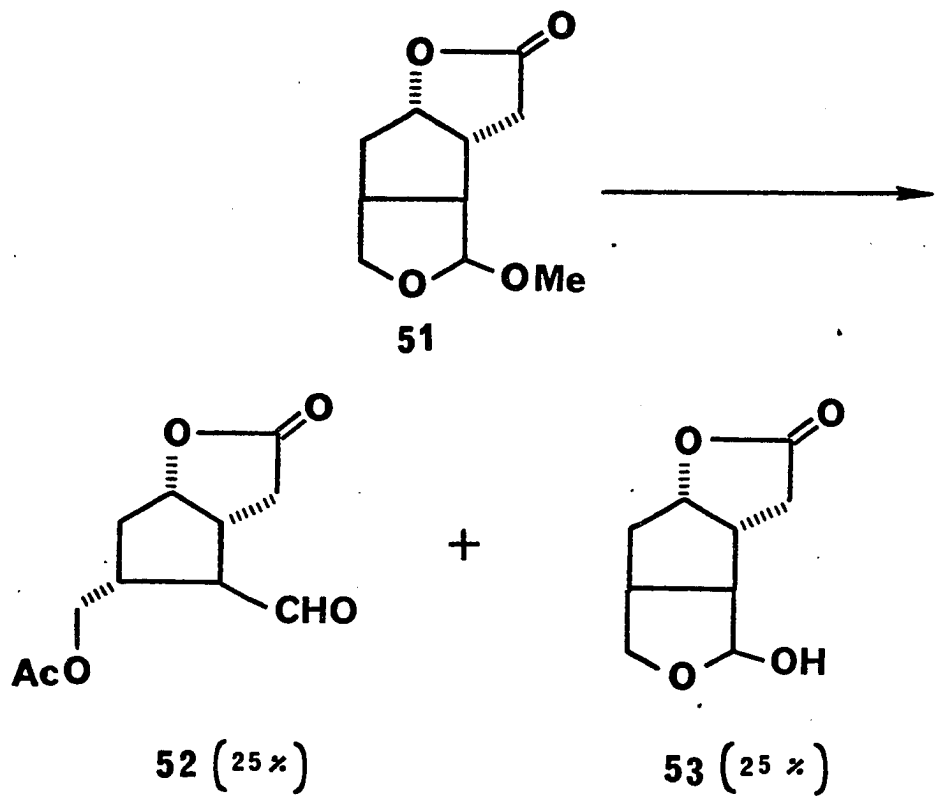
From these studies, it was found that the enol acetate is apparently doing nothing more than replacing the $-OTiCl_3$ group by the -OAc group. It occured to us that, in principal, the same thing could also be done by using acetyl chloride.



14 15

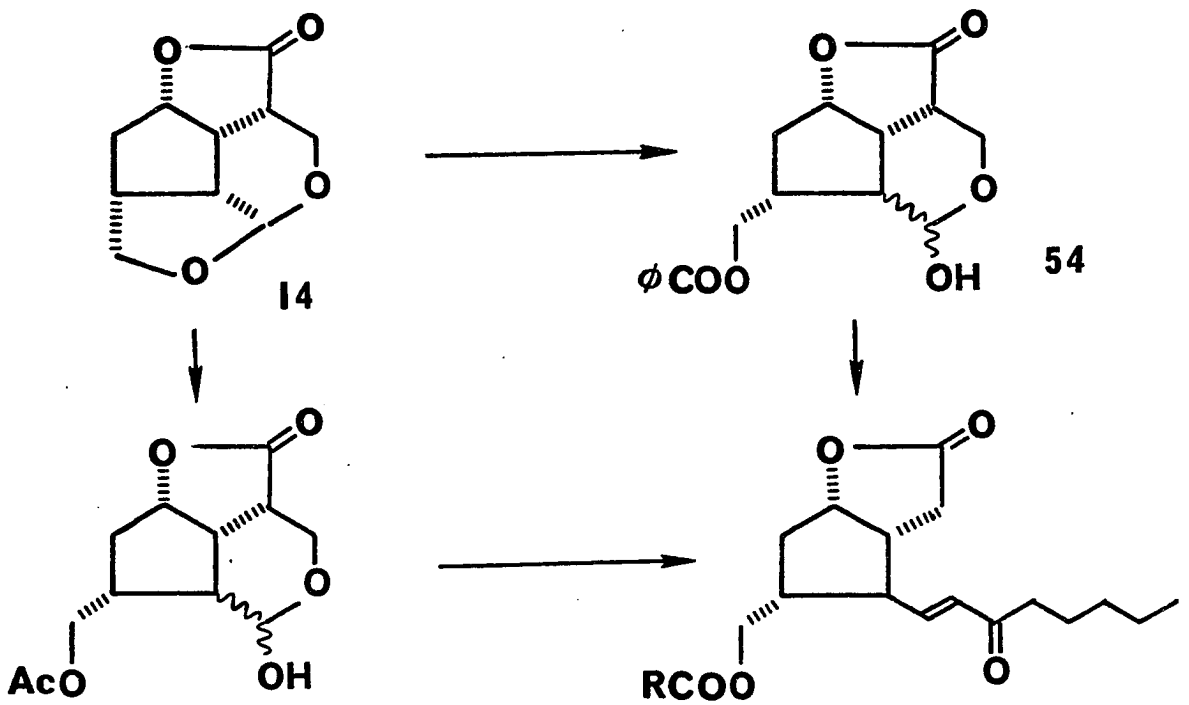
When tried, the success was beyond our expectations and the potential aglucone 15 was isolated in 95% yield using this procedure. Failure of the Mukaiyama reaction on our system and our determination to find conditions under which this will work led us to the discovery of this new method of cleaving acetals. Although it is a two step procedure for obtaining the aglucone 15 from tetrahydroasperuloside tetraacetate, it does give a high overall yield and needs no chromatogrphic separation.

Application of this reaction to 51 [98], obtained from aucubin gave an equal amounts of aceylated aldehyde 52 and



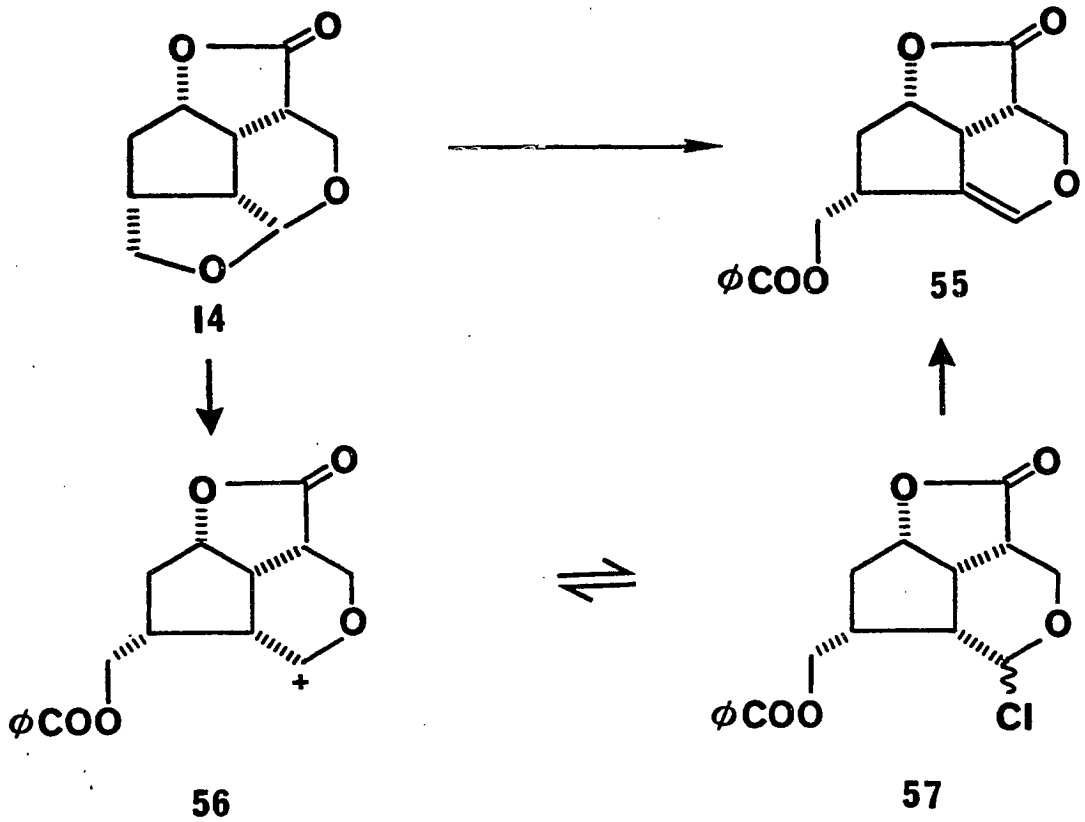
hemiacetal 53 (no search was made for methyl acetate). Lower yields were primarily due to the small scale of the experiment.

Since Ohno and his coworkers [71] have carried the benzoate 31b to both $PGF_{2\alpha}$ and 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$, we attempted to alter our procedure to produce benzoate 31b instead of acetate 31a. It seemed reasonable that titanium tetrachloride/benzoyl chloride reaction with 14 would produce the benzoate hemiacetal 54, which could then



be transformed to 31b. However, when attempted, we found that there was practically no reaction even after 3 hrs. at room temperature (vs. 15 min. with $TiCl_4$/AcCl at 0^0C). When we continued this reaction for a longer period of time (2 days/rt), a new product, 55, was isolated in 74% yield.

The process does not seem unreasonable, since the longer reaction time (2 days) and higher temperature (rt vs 0^0C) required to produce the intermediate 56 (oxonium ion) should also have ionized chloride 57. Eventual loss of a proton to give the product (enol ether) 55, would occur irreversibly, similar to the formation of the minor component 42 formed during the titanium tetrachloride/acetyl chloride or enol acetate reaction on our tetracyclic acetal 14.

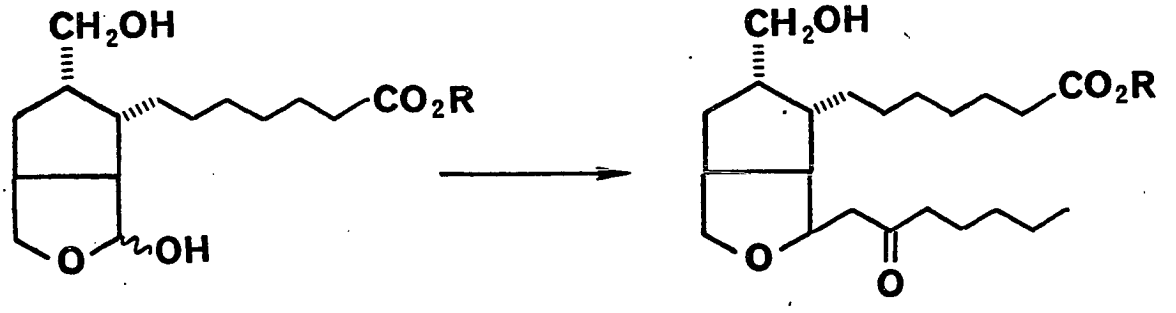


Therefore the hope of getting the benzoate 31b had to be given up and we diverted our attention back to obtaining the acetate 31a, as had originally been planned.

Chapter VIII

INTRODUCTION OF THE LOWER SIDE CHAIN

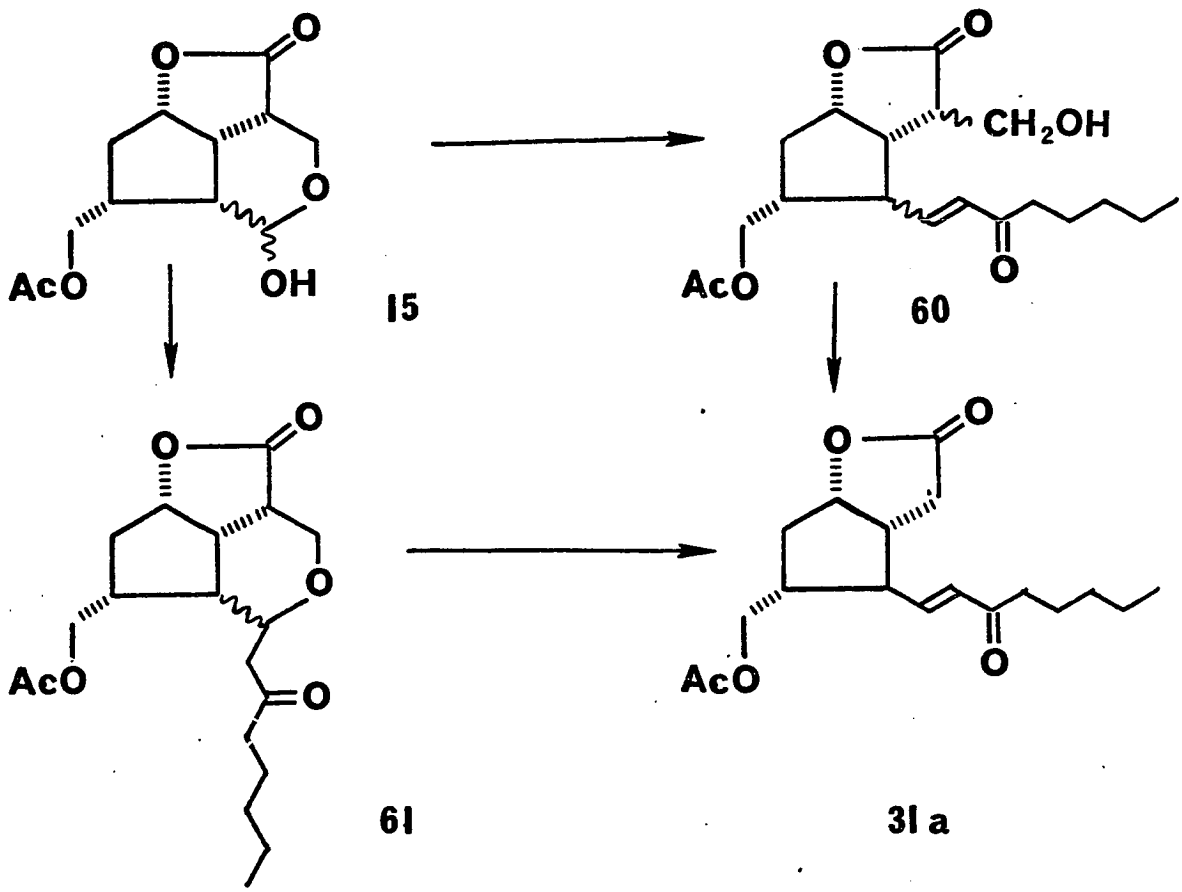
During the literature survey, it was found that Harrison and his coworkers [99] have introduced the lower side chain by the use of the Wadsworth-Emmons modification of the Wittig reaction on a hemiacetal (5-membered) 58. However the resulting hydroxymethyl added to the enone portion in a Michel



58 59

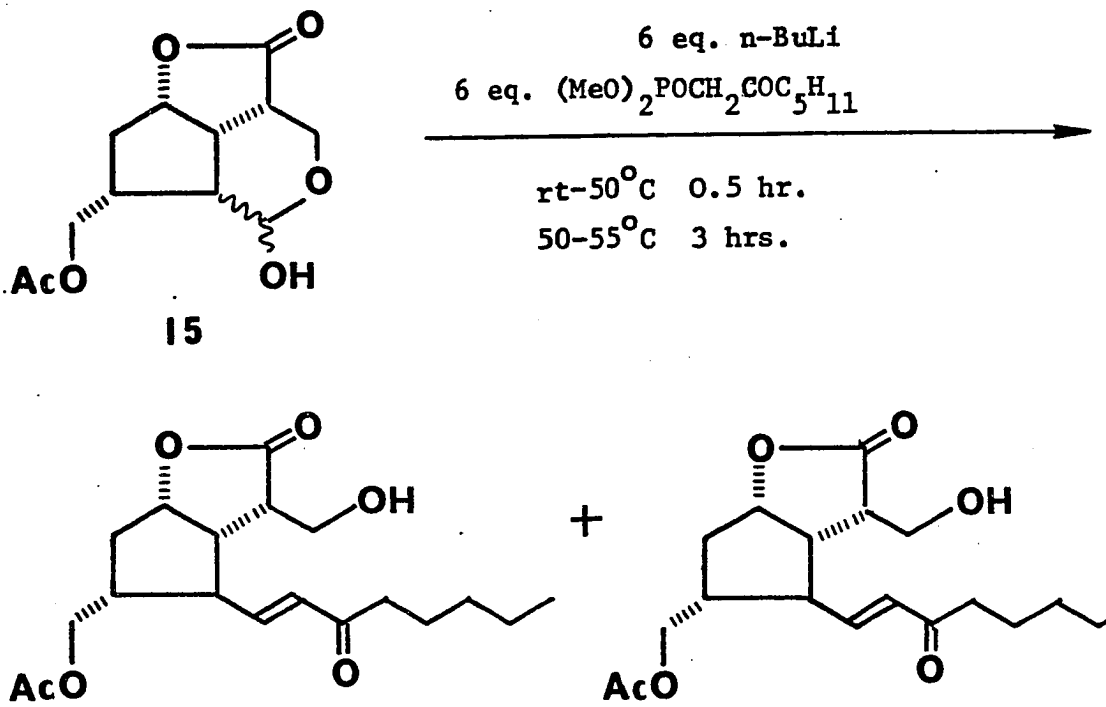
reaction and only the adduct 59 was isolated. Similar use of the Wadsworth-Emmons or Wittig reaction on our hemiacetal (6-membered) 15 could provide the enone 60 or the Michael adduct 61, each of which in principle could be converted to prostaglandin intermediate 31a.

Dimethylsulfoxide was initially found to be the most suitable solvent. Although sodium hydride did not give reproducible results on the small scale we used due to the in-



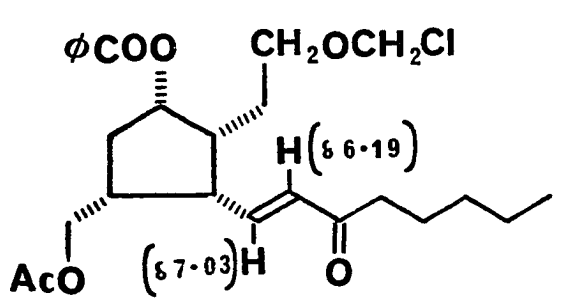
homogeniety of the sodium hydride sample, butyllithium worked well. After studying the reaction with various equivalents of base, phosphonate and at different temperatures, the set of conditions (shown below) was found to be the best. The product was ultimately isolated in 73% yield.

The Wittig product 60 was found to be a mixture, separable on HPLC, of two diastereoisomers 60a,b in a ratio of approximately 8 to 1. The evidence suggests them to be epimers at C(7) rather than at C(12). From the literature [72] it was found that when the four groups on the cyclopentane

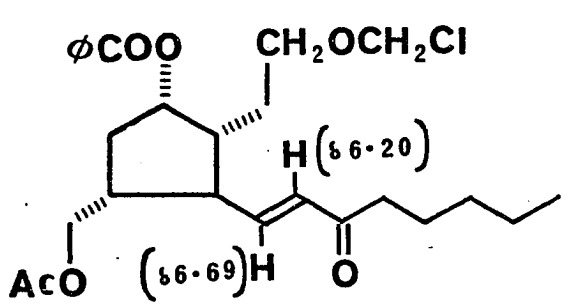


15

60 a,b (73%)



62 a



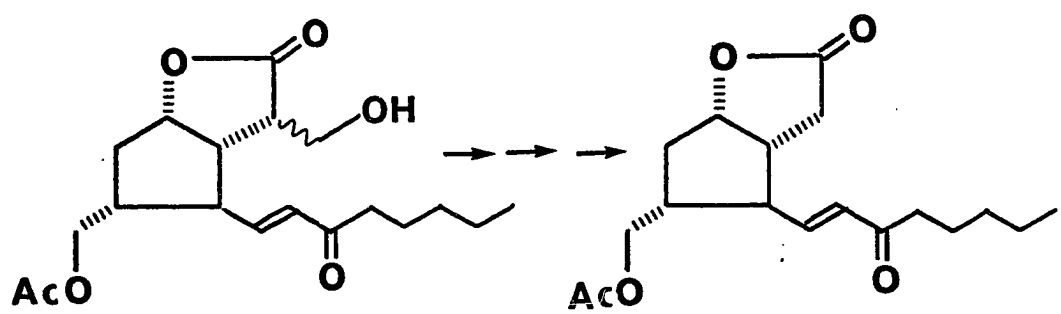
62 b

nucleus were in a cis-cis-cis configuration as shown in 62a, the chemical shifts of the enone protons appear at δ7.03 and δ6.19. On the other hand, in the cis-trans-trans configuration as shown in 62b, the enone protons appear at δ6.69 and δ6.20. Since both products 62a and 62b showed enone protons at δ6.65 and δ6.20, it seems very likely that the lower side chain is attached β to the cyclopentane ring (and was epimerized either during the Wittig reaction or the previous step). The coupling constant (J = 16) of the vinyl protons confirmed the presence of a trans double bond. Thus 62a and 62b must be epimers about the only other epimerizable carbon, C(7).

Chapter IX

CXIDATION AND DECARBOXYLATICN

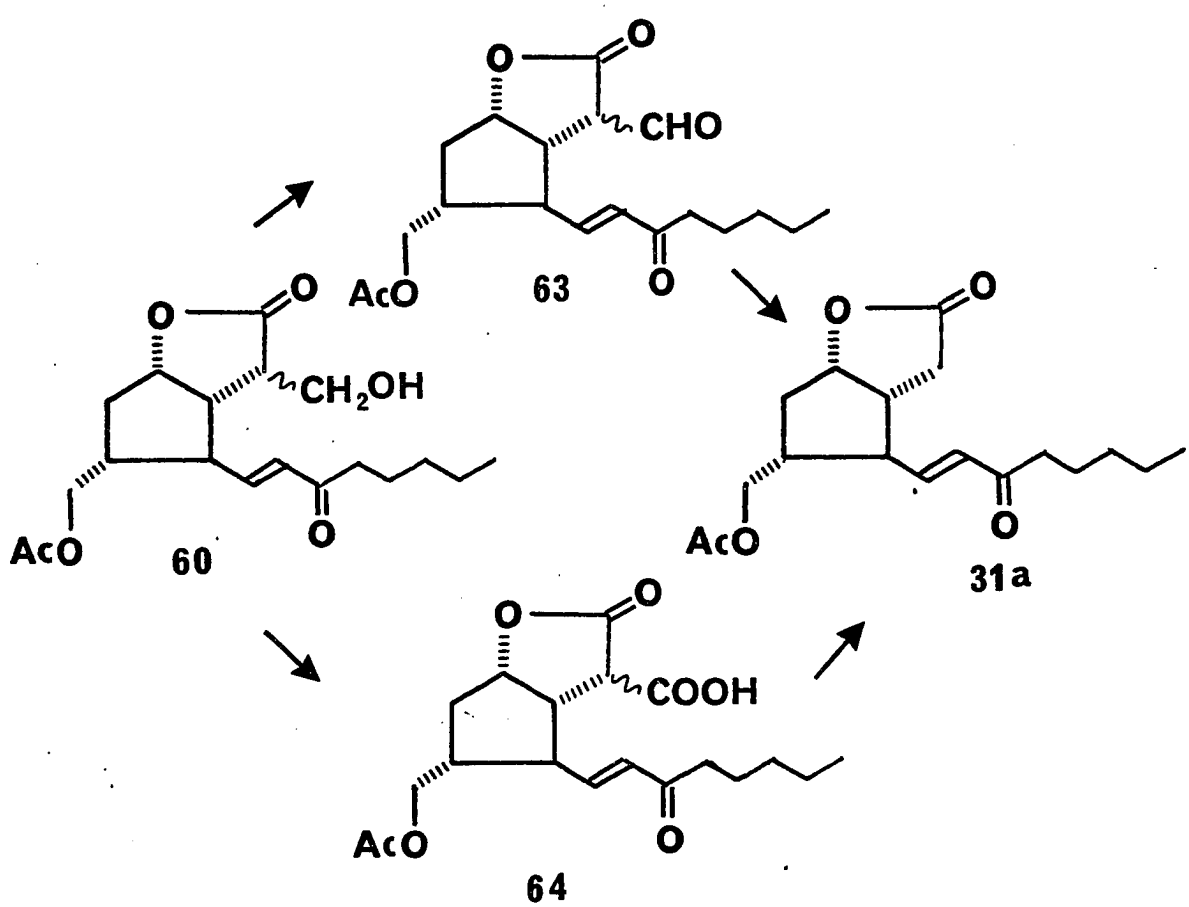
The last stage cf our synthesis required the remcval of the hydroxymethyl group from 60 withcut destrcying the lactcne, enone cr the acetate moieties.



60 31a

Direct remcval of the hydroxymethyl grcup (retrcaldcl) under neutral, acidic cr basic conditions was not successfull and rather gave a mixture cf products. We thcught however, that cxidation of the hydroxymethyl grcup cf 60 tc the aldehyde 63 followed by retrc Claisen reactien or cxidatien tc carboxylic acid 64 followed by decarbcxylatien could posssibly lead to the target molecule 31a.

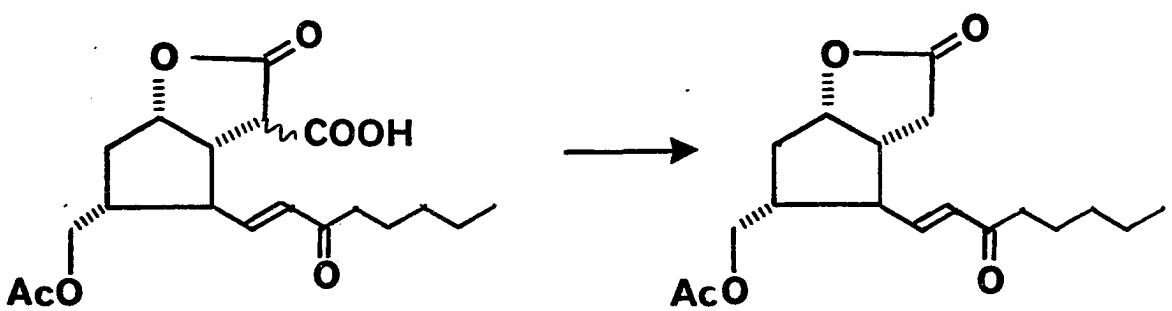
All attempts to oxidize the hydroxymethyl group of 60 (Collins, Ccrey's procedure [100] using pyridinium dichrc-



mate) were unsucessfull. When an insufficient amount of Collins reagent was used, a new product, presumably 63 appeared (HPLC), only to disappear with sufficient or excess reagent. No attempt was made to isolate or characterize this new product because of its formation in very poor yield. Attempts to oxidize the hydroxymethyl group to a carboxyl group with pyridinium dichromate in dimethylformamidee (Corey's procedure [100]) were also unsuccessfull. Compounds a having hydroxy group β to the keto or ester groups are known to break at the adjacent carbon carbon bond. However we can only speculate and do not know for sure what is happening.

Initial attempts to oxidize 60 using Jones' reagent under mild conditions for a short period gave back the starting material. Higher temperature (refluxing acetone) and short exposure worked well however and exposure of 60 to Jones' reagent for only 60 seconds in refluxing acetone gave the carboxylic acid as a mixture of two components (a major and a minor, both soluble in sodium bicarbonate) in greater than 90% yield.

The crude carboxlic acid was finally decarboxylated by refluxing in glacial acetic acid for 3.5 hours. The overall



64 31a

yield of oxidation and decarboxylation (two steps) was found to be 74%.

Chapter X

CONCLUSION

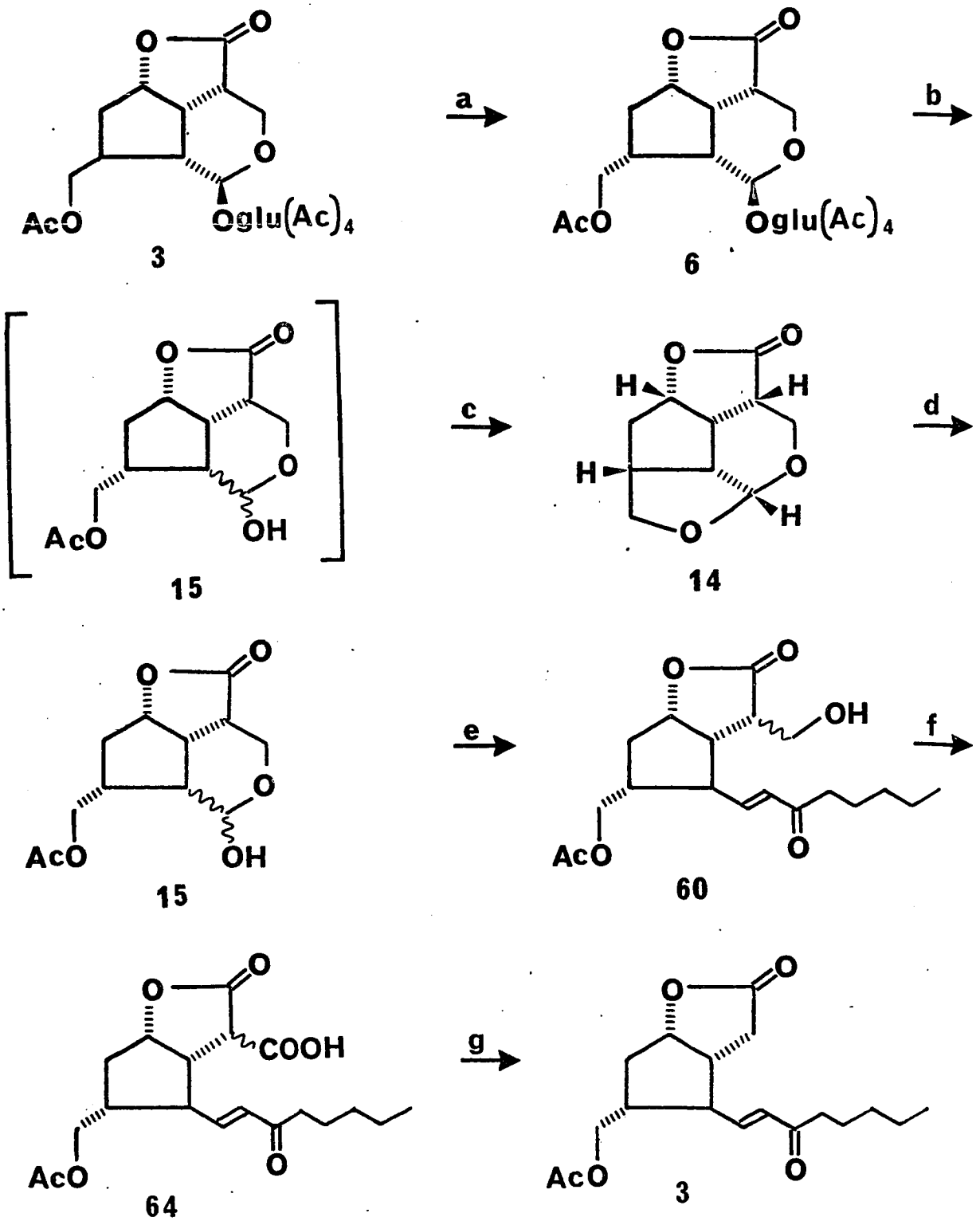
Our sucessfull conversion of asperuloside [101] is described in Scheme-22. Asperuloside tetraacetate 3 was hydrogenated over 5% Rhodium on carbon in ethyl acetate at 1 atm. by starting at -30°C and raising the temperature slowly to 0°C during 3 hours. Tetrahydrasperuloside tetraacetate 6 was isolated in virtually quantitative yield. Hydrolysis of 6 in refluxing acetic acid/water (5/1) for 8 days at 100-110°C afforded all cis tetracyclic acetal 14 in 86-92% yield.

When 14 was treated with $TiCl_4$ (1.25 eq.) and AcCl (2.5 eq.) in methylene chloride for for 45 min. at 0°C, hemiacetal 15 was isolated in 95% yield. Wadsworth-Emmons reaction [21] of 15 proceeded smoothly with 2-oxoheptylphosphonate (6 eq.) and n-butyllithium (6 eq.) in DMSO for approximately 3 hours at 50°C, giving a mixture of 60a/b (8/1 ratio) in 73% yield. Exposure of 60 to Jones's reagent in refluxing acetone gave unstable carboxylic acid 64, which was decarboxylated without further purification by refluxing in glacial acetic acid, to give 31a in 74% overall yield.

Since Chne and coworkers [71,72] have converted the benzoate 31b to $PGF_{2\alpha}$ as well as 11-deoxy-11α-hydroxymethyl

SCHEME 22

Conversicn of Asperulcside to Prostaglandin Intermediate



a) H_2, 5% Rh/C, EtOAc, -30°C to 0°C, 3 hr.; b) 5/1 AcOH/H_2C,

reflux, 8 days; c) 1.25 eq. $TiCl_4$, 2.5 eq. AcCl, 45 min., 0^0C; d) 6 eq. n-BuLi, 6 eq. $(MeO)_2POCH_2COC_5H_{11}$, rt-50^0C, 0.5 hr.; 50-55^0C, 3 hrs.; Jones' reagent, refluxing acetone, 60 seconds. f) glacial acetic acid, reflux, 3.5 hr..

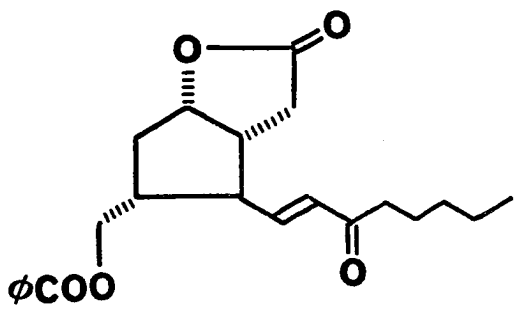
$PGF_{2\alpha}$, we assume that our acetate 31a would give the same prostanoids using similar procedures.

10.1 CONVERSION OF BENZOATE 31b TO $PGF_{2\alpha}$:

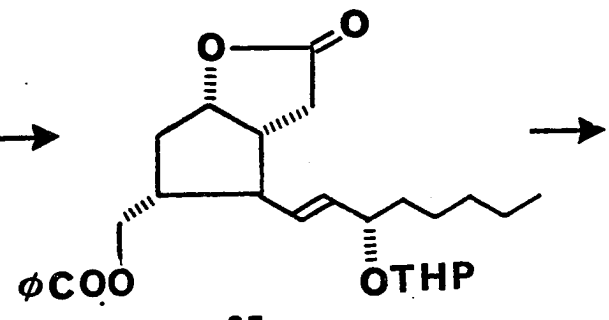
Ohno and coworkers [71] treated the enone 31b with zinc borohydride, and obtained a mixture of 15(S) and 15(R) alcohols. They isolated the required 15(S) isomer by column chromatography on silica gel using ethyl acetate as eluent. Protection of the desired alcohol (dihydropyran/p-toluene sulfonic acid) followed by methanolysis with an equimolar amount of potassium carbonate in methanol gave the alcohol 66, which was converted to the carboxylic acid by reacting with Cornforth's reagent [102]. Condensation of carboxylic acid 67a with m-chloroperbenzoic acid followed by decarboxylative rearrangement by the known procedure [36] gave 68.

Methanolysis of 67b with potassium carbonate in methanol produced the alcohol 69. Hydrolysis of 69 using acetic acid/water (2:1) at 40^0C aforded the known diol 70, which has been previously converted to naturally occurring forms of prostaglandins by Corey and coworkers [15].

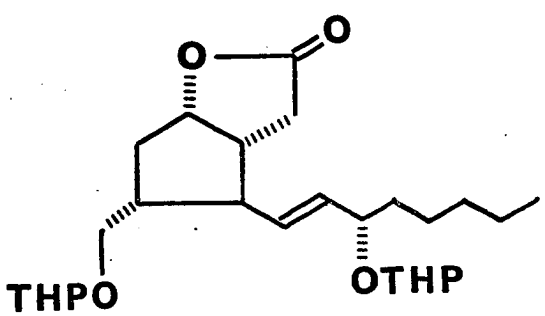
SCHEME 23



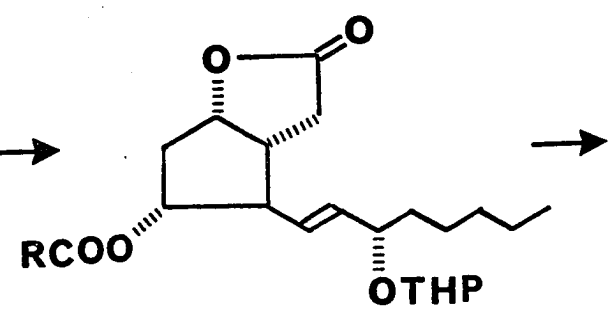
31b



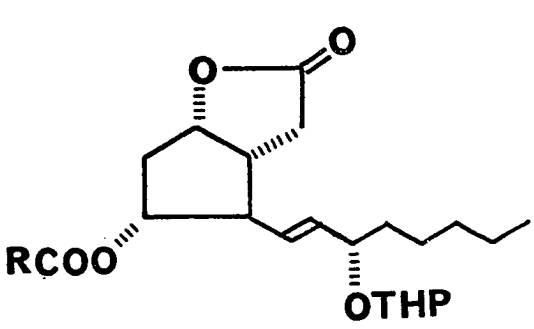
65



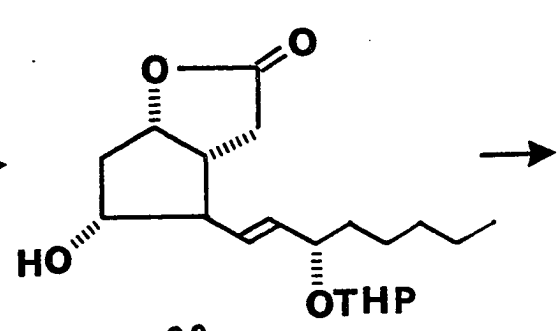
66



67a R=H
67b R = m Cl-$C_6H_4CO_2$



R = m Cl-C_6H_4- 68



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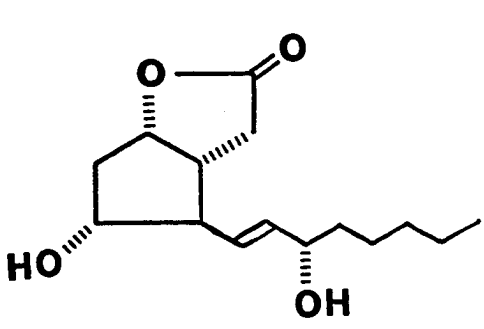
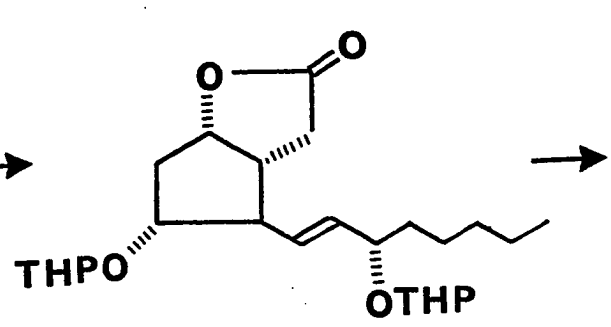


70



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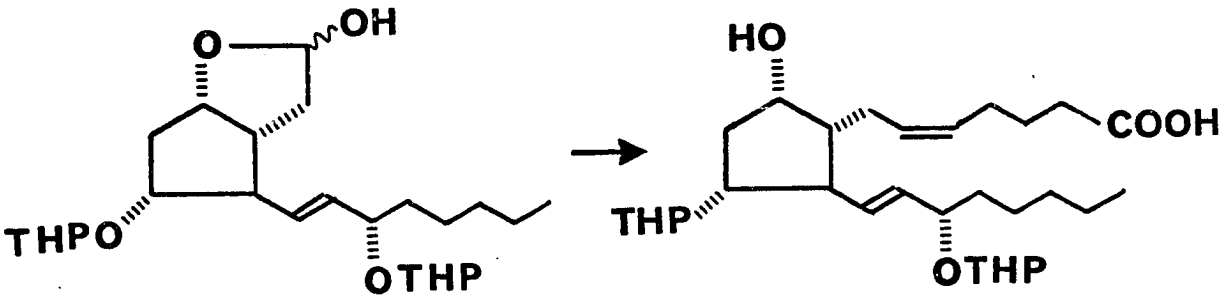
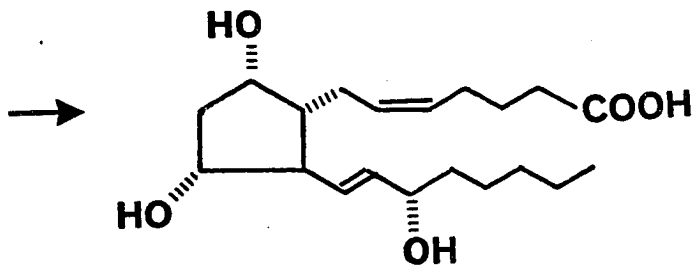


72

73



$PGF_{2\alpha}$

Corey converted 70 to 71 using dihydropyran and p-toluenesulfonic acid. However, from a synthetic point of view, the monoprotected alcohol 69 does not need deprotection to 70 before reprotection of both the alcohol functionalities and can be converted directly to 71. Reduction of lactone 71 to lactol 72 using diisobutylaluminium hydride followed by Wittig reaction with 5-triphenylphosphonopentanoic acid provided 73. Deprotection of 73 (2/1 acetic acid-water) gave the naturally occurring $PGF_{2\alpha}$.

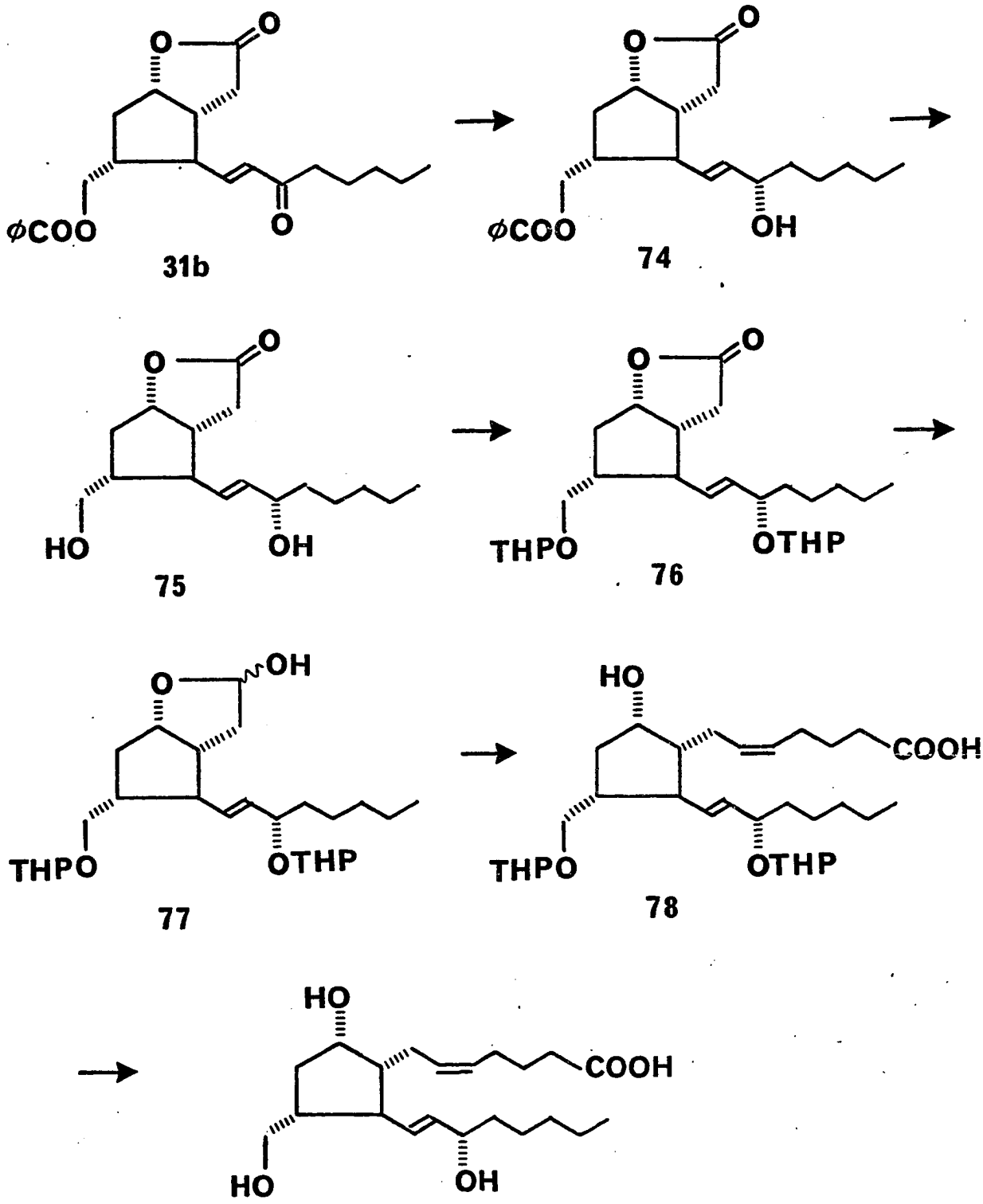
We assume that our acetate 31a would give a common intermediate 66 under conditions similar to the Chno's benzoate 31b and asperuoside could be a good synthon for obtaining optically active $PGF_{2\alpha}$.

10.2 CONVERSION OF THE BENZOATE 31b TO 11-DECXY-11-HYDROXYMETHYL $PGF_{2\alpha}$

The benzoate 31b was converted to 11-deoxy-11α-hydrcxymethyl $PGF_{2\alpha}$ using essentially conventional procedures [71]. Zinc borohydride reduction cf 31b and separation cf the required 15S alcohol using columnm chromatography provided 74. Methanolysis of 74 with potassium carbonate in methanol gave 75. Protection of the dialcohcl 75 (using dihydrcpyran/p-toluenesulfonic acid), reduction of the resulting lactone 76 provided lactcl 77. Wittig reaction cf 77 with 5-triphenylphosphoniopentanoic acid follwed by unmasking of tetrahydropyranyl ether afforded 11-deoxy-11α-hydrcxymethyl $PGF_{2\alpha}$.

We alsc assume that our acetate 31a would provide 11-deoxy-11α-hydroxymetyl $PGF_{2\alpha}$ under similar conditicns through the common intermediate 75.

SCHEME 24



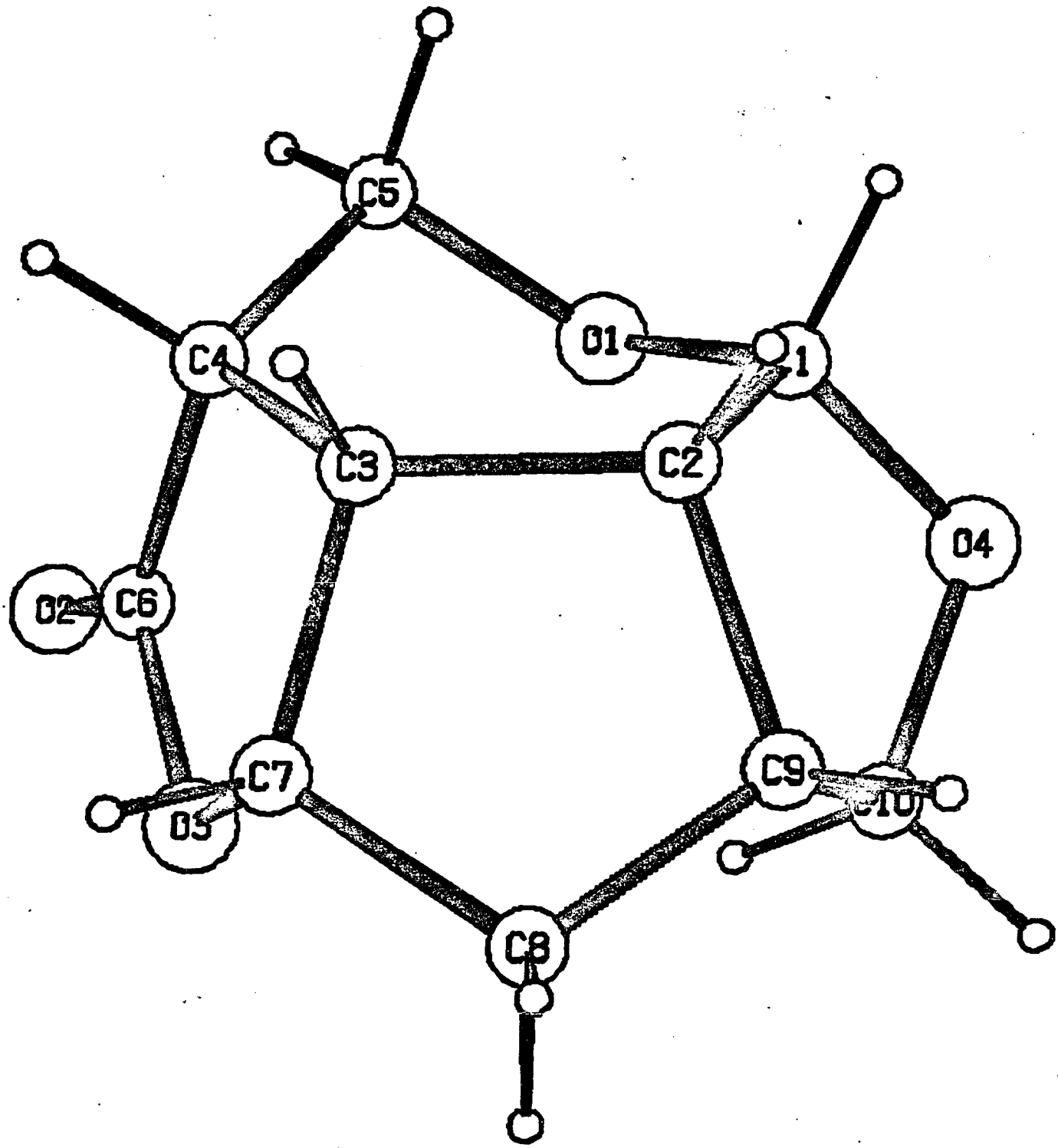
10.3 STEREOCHEMISTRY

On the basis of NMR studies (Sec. 5.1), we had previously concluded that hydrogenation of asperuloside tetraacetate (3) proceeded with delivery of hydrogen from the top side (convex face) to give the desired (α) stereochemistry at C(11). The X-ray structure of the tetracyclic intermediate 14 (figure-2), (graciously performed by Dr. John Blount of Hoffmann La-Roche) proved that the the tetracyclic acetal is indeed all cis. Subsequent transformation would not have affected the stereochemistry at C(11), and we indeed were correct in our assignment.

The coupling constants (J=16) of the vinyl protons in 31a reconfirmed the presence of a trans double bond. The chemical shifts of the enone protons (δ6.6 and δ6.2) also prove that the arrangements on the cyclopentane ring is a cis-trans-cis [72].

In the conversion of asperuloside to prostaglandin intermediate 31a, no reaction has been used that would affect the C(5) stereochemistry, and therefore 31a has the same stereochemistry as asperuloside. As noted earliear, the absolute stereochemistry of asperulcside C(5) and prostaglandin C(8) are the same. Consequently the conversion of 31a to prostanoids will result in a material of the correct, natural, absolute configuration.

Figure 2: X-ray Structure of Tetracyclic Acetal, 14.



Chapter XI

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer model 237B or 598 using 0.1 mm NaCl soluton cells. The proton NMR spectra were determined at 60 MHz with a Varian mcdel EM-360. High field NMR were obtained at the Southern New England High Field NMR Facility at Yale university (270 Hz) or at Columbia university (250 MHz). The chemical shifts are expressed in values (part per million) relative to Me_4Si internal standard and the J values (splitting constants) are expressed in Hertz. Mass spectra were determined at 70 ev using a Varian MAT CH-5 for medium resolution, an AEI MS-9 for high resolution, and the services of Dr. Frank Field of Rockefeller Uiversity for chemical ionization mass spectrometry. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter.

All gas chromatographic analysis were carried out on a Varian Aerograph series model 920 gas chromatcgraph equipped with a thermal conductivity detector and helium as the carrier gas (flow rate 120 mL/min at ambient temperature) using a (10 ftX3/8 in) column packed with 20% Apiezon-L on chromosorb-W. Silica gel precoated glass plates (E. Merck,

1563-9H) were used for thin layer chromatography (TLC). Silica gel (E. Merck-60, 9385) was used for "flash" [91] or column chromatography. TLC plates were develcped by spraying with 10% methanolic sulfuric acid and heating on a hot plate. High Pressure Liquid Chromatography (HPLC) analyses were performed on Waters Associates micro-porasil columns (two 4 mmX30 cm silica 10 columns in series) using Waters Associates 600-SDS pump, U-6K injector equipped with a model 401 index of refraction detector. HPLC preparations were conducted on a Waters Asscciates Prep-500 LC with two silica columns in series. The starting material, asperuloside, was purified using a 10 cm diameter column obtained from Glencoe (Houston, Texas). The solvent was delivered to the column from a stainless steel reservoir under 6 psi 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 vac) from calcium hydride and kept over freshly activated molecular sieves of type 4A for at least 48 hours prior to use. Sodium hydride was employed as a 57% oil dispersion which was washed with dry hexane immediately before use. For all anhydrous reactions performed under an atmosphere of dry N_2 or Ar, the equipment was dried in the oven at 120^0C for 1 hour prior to use. Rhodium on Carbon

(5%) was obtained from Engelhard Industries (Newark, N.J.). Batches prior to 1975 appeared superior, for unknown reasons. A given batch of catalyst was used at least three times in succession with little loss of activity.

All micro analysis were performed by either Spang Microanalytical laboratory, Eagle Harbor, Michigen or Galbraith laboratories, Knoxville, Tennessee.

EXTRACTION OF ASPERULOSIDE USING DUFF's PROCEDURE:

Coprosma plants (17.7 Kg) were chopped and boiled with 32 L of water for one hour. The liquid was decanted and the residue was extracted with the same amount of water. The combined extracts were concentrated to 2 L and adsorbed on 500 g of acid washed Celite-535.

A column was packed with 1700 g of Celite (previously mixed with 1700 mL of butanol-saturated water and equilibrated overnight) in a 10 cm diameter column. The Celite adsorbed plant extract was put on the top of the packed column and eluted with water-saturated butanol (flow rate 90 mL/min, pressure 6 psi). The fractions showing blue spots on TLC (Rf=0.88, 0.73; 2/1 95% ethanol-acetone) were collected and concentrated to give 140 g of brown gum.

For acetylation, 78.5 g of this gum was mixed with 195 mL (2.1 moles) of acetic anhydride, stirred mechanically for 35 hours, then diluted with 30 mL (0.4 mole) of pyridine and stirred for an additional 24 hours. The reaction was quenched by pouring into ice/water and the aqueous mixture was extracted with chloroform (3X300 mL). The chloroform extracts were combined and washed with 5% aqueous HCl followed by saturated aqueous sodium carbonate and, finally water. The combined organic extracts were then dried over anhydrous magnesium sulfate, filtered and concentrated to give 64.9 g of yellow gum.

This gum (50 g) was purified by silica gel column chromatography (17" longX1.7" diameter) using 3/2 ethyl acetate-hexane as the eluting solvent. This afforded 22.6 g of crude asperuloside tetraacetate as an oil, which gave 10.3 g of pure asperuloside tetraacetate, mp 148-150^{0}C, upon crystallization from absolute ethanol. The analytical sample was recrystallized from absolute alcohol: mp 150-151^{0}C (lit [87] mp 154^{0}C). The yield was about 0.13-0.15% based on the weight of fresh plant material committed for extraction. NMR and IR data were identical with the literature data [77,87] and with that of asperuloside tetraacetate prepared from an authentic sample of asperuloside given to us as a gift by Dr. J. Bobbitt.

Analysis calculated for asperuloside tetraacetate $C_{26}H_{30}O_{25}$: C 53.60, H, 5.22. Found: C, 53.60; H, 5.20.

EXTRACTION OF ASPERULOSIDE USING HOT ACETONE METHOD:

One hundred grams of fresh coprosma plant cuttings were refluxed with 2 L of acetone for two hours. The acetone extract was filtered and the residue washed with 200 mL of acetone which was combined with the acetone extract. The combined acetone extracts on concentration gave 4.9 g of green gum. The green gum was adsorbed on 20 g of silica and loaded on the top of silica column (10" longX1.5" diameter). The column was then eluted, first with acetone, and then with absolute ethanol. The fractions giving blue spots on TLC (2/1 95% ethanol/acetone, compared side by side with an authentic sample of asperuloside) on concenntration gave 480 mg (0.48%) of asperuloside and 250 mg (0.25%) of slow-asperuloside (open-lactone).

However on larger scale (20 Kg), fresh plants were boiled twice with 50 gallons of acetone (most kindly done by the direction of Dr. W. Schreiber of International Flavors and Fragrances, N.J. and Dr. V. Paragamian of McNeil Laboratories, PA., to whom we are greatly indebted). The acetone extract was concentrated and dried in vacuo to give approximately 400 g of brown gum. This gum (78 g) was mixed with

500 mL of ether and left for a week after which the ether extract was decanted, replaced with fresh ether and kept for a week. This process removed most of the chlorophyll. The residue was dried in vacuo to give 65 g of brown gum which was acetylated (acetic anhydride/pyridine) without futher purification. The crude acetylated product (58 g) was partially purified by placing on a (6" longX2" diameter) silica column and eluting it with 1.5 L of ethyl acetate which on concentration gave a yellow gum (50 g).

Final purification of the acetylated product was achieved by a combination of high pressure liquid chromatography (1/1 ethyl acetate/hexane) and crystallization (absolute alcohol), affording 6.3 g (approx. 0.2%), mp 148-150^{0}C of pure asperuloside tetraacetate.

PREPARATION OF TETRAHYDROASPERULOSIDE TETRAACETATE:

Asperuloside tetraacetate (14.13 g, 24.3 mmol), 13.9 g of 5% Rh/C (see above) and 2 L of ethyl acetate (either distilled or HPLC grade) were placed in a three neck, 5 litre round bottom flask connected to a hydrogen reservoir and fitted with a closed system magnetic stirrer. The flask was cooled to -30^{0}C and filled with hydrogen. Stirring was commenced and the temperature was allowed to rise to 0^{0}C during a period of 3 hours. The solution was then filtered and concen-

trated to give 15.4 g, 108% (one spot on TLC, Rf=0.35, 4/1 ether-ethyl acetate; one peak at 6.6 min on HPLC: 2/1 ethyl acetate/hexane) of tetrahydroasperuloside tetraacetate as a white foamy solid. Recrystallization gave 11.3 g(80%), mp 148-9^{0}C of pure tetrahydro product. The crude material, however, could be used directly for hydrolysis. It was found that used catalyst works as well as new, and was used over and over again. NMR(270 MHz, $CDCl_3$): 2.35 (C-9, 1H, dd, J(1,8)=0 Hz, J(5,9)=10.5 Hz,(1H,m); J(8,9)=8 Hz); 2.57 (C-8, 1H, m); 3.74 (C-5, 1H, ddd); 5.03 (C-6, 1H, m); 5.40 (C-1, 1H, s); 3.89 (C-3, 2H, m).

Analysis calculated for $C_{26}H_{34}O_{15}$: C,53.24; H,5.50. Found: C,53.48; H,5.83.

PARTIAL HYDROLYSIS OF TETRAHYDROASPERULOSIDE TETRAACETATE USING 5/1 ACETIC ACID WATER:

Tetrahydrasperuloside tetraacetate 6 (4.5 g, 7.7 mmol), 200 mL of acetic acid and 40 mL of water were mixed in a 500 mL round bottom flask fitted with a magnetic stirrer and a refluxing condenser. The temperature was raised from room temperature to 90^{0}C over a period of 1 hour and then maintained at 90-100^{0}C for additional 1.5 hours.

The mixture was concentrated in the rotavap and the residue was dried in vacuo to give 4.4 g of white foamy sol-

id. TLC examination showed it to contain glucose pentaacetate 23 (Rf=0.59), tetrahydroasperuloside tetraacetate 6 (Rf=0.51), tetracyclic acetal 14 (Rf=0.37) and hemiacetal 15 (Rf=0.26) when developed in 2/3 methylene chloride-ethyl acetate. The hemiacetal 15 was isolated from this mixture by column chromatography on a (10" longX1.5" diameter) silica gel (230-400 mesh) column using 2/3 methylene chloride-ethylacetate as the eluting solvent. Concentration of the last fraction gave 703 mg (36.1%) of hemiacetal 15 (mp 140-145^{0}C). Double crystallization of this material from ethyl acetate gave 195 mg (mp 151-2^{0}C) of analytical sample.

NMR (DMSO): 2.0(3H,s,acetate). IR: 1770 cm (5-membered lactone), 1738 cm (acetate),33-3600 cm^{-1} (-OH).

Analysis calculated for $C_{12}H_{16}O_6$: C, 56.35; H,6.29. Found: C, 55.98; H, 4.46.

PREPARATION OF TETRACYCLIC ACETAL 14 BY HYDROLYSIS OF TETRAHYDROASPERULOSIDE TTETRAACETATE USING 5/1 ACETIC ACID-WATER:

A solution of 14.72 g (25.1 mmol) of tetrahydroasperuloside tetraacetate 14 was refluxed in 360 mL of 5/1 acetic acid-water (100-115^{0}C) for 12 days. The resulting mixture was concentrated on the rotavap and the residue was dried in vacuo to give a brown gum. To this was added 400 mL of water and 200 mL of chloroform and the mixture was

crganic layer was separated and the aqueous extract was extracted again with chlcroform (2X200 mL). All the organic extracts were ccmbined and washed with water, dried cver anhydrous magnesium sulfate, decolcrized with carbcn and ccncentrated to give 4.76 g of white solid (mp 103-6^{0}C). The solid was crystallized from chlcrcform/ether to give 4.23 g (86%) of tetracyclic acetal 14, mp 111-3^{0}C (anal. mp 113-4^{0}C).

In general, refluxing was ccntinued fcr 8-12 days and the acetal 14 was isolated in 86-92% yield.

IR: 1773 cm^{-1} (5-membered lactone). Mass Spectra: Mclecular icn peak at m/e 196 (M^+,20), m/e 128 (100%). Optical rotaticn: $[\alpha]_D^{25}$ -61.5^0 (c 0.036, chloroform).

X-ray Analysis: The all cis-structure was ccnfirmed by X-ray analysis (Figure-2) most kindly performed by Dr. John Blount of Hcffmann-LaRcche (Nutley, N.J.). The crystals were trigonal, space group $P3_2$. The data he provided is reproduced in appendix-B.

PREPARATION CF TETRACYCLIC ACETAL 14 BY HYDRCLYSIS OF TETRAHYDROASPERULCSIDE TETRAACETATE WITH ACETONE AND H^+:

Tetrahydroasperuloside tetraacetate (128 mg, .22 mmcl) was refluxed with 20 mL of acetone and 0.12 mL (2.3 mmol) of sulfuric acid fcr 19 hours. The reaction was quenched by

pouring it intc 25 mL of water. The water solution was extracted with chloroform (2X25 mL) and the ccmbined organic extracts were washed with water and 5% aqueous scdium bicarbonate. The organic extract was then dried cver magnesium sulfate, concentrated and dried in vacuo tc give 217 mg of brown cil.

The tetracyclic acetal was isolated frcm this brown cil by column chrcmatography on a silica gel cclumn, eluting first with ether and then with 4/1 ether-ethyl acetate, affording pure tetracyclic acetal 14 (19.4mg, 43%), mp 112-3^{0}C. The IR, NMR and mp were identical with the previous sample obtained by refluxing tetrahydrcasperuloside tetraacetate in 5/1 acetic acid-water.

Analysis calculated for $C_{10}H_{12}O_4$: C,61.22; H,6.16. Found: C,61.05; H,6.15.

PREPARATION CF DIACETOXY AGLUCONE 22 BY HYDRCLYSIS CF TETRAHYDROASPERULOSIDE TETRAACETATE USING ACETIC ANHYDRIDE/ACETIC ACID/H^+:

Acetic anhydride (20 mL, 21.6 g, 0.22 mole), 0.5 mL (0.27 mmol) water and 0.5 mL (9.4 mmol) ccnc. sulfuric acid were mixed and stirred for 30 minutes. Tc this mixture was added 485 mg (0.83 mmcl) of tetrahydrasperuloside tetraacetate and stirring was ccntinued for an additional 1 day. The reaction was quenched by pouring this mixture into 50 mL of ice cold

water. The aqueous mixture was extracted with chloroform (2X50 mL). The organic extract was washed with saturated aqueous sodium bicarbonate followed by 25 mL of water, and then dried over anhydrous magnesium sulfate and concentrated to give 335 mg of white gum. Three components of this gum were separated using column chromatography (4/1 ether-ethyl acetate) to give 193 mg (60%) of glucose pentaacetate and 90 mg (consisting of a major mp 112-114^{0}C and a minor component) of diacetoxy aglucone 22 (analytical sample mp 114-115^{0}C was recrystallized from ether/chloroform). It was found that the isolated yield of diacetoxy aglucone 22 varied (0-65%), and TLC examination showed that part of 22 hydrolysed during workup to give hemiacetal 15.

Analysis calculated for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found (major component): C, 56.13; H, 5.92.

PREPARATION OF 2-ACETOXY-1-HEPTENE USING HUDRLIK's PROCEDURE:

A mixture of 110 mL (1.21 mole) of acetic anhydride, 197 mg (0.62 mmol) of mercuric acetate and 0.3 mL (2.4 mmol) of boron trifluoride etherate was stirred for 5 minutes. To this mixture 7.33 g (76.3 mmol) of 1-heptyne was added and stirring was continued for an additional 3 hours.

The reaction was quenched by pouring into a 20% potassium hydroxide solution (1000 mL) overlayed with 700 mL of ether (precooled to 0^0C). The layers were separated and the ether layer was washed with brine solution, dried over anhydrous magnesium sulfate and the ether was evaporated. The residue was distilled bulb to bulb (1 atm) to give 5.9 g of colorless oil. Pure 2-acetoxy-1-heptene was isolated by gas chromatography (200^0C). The fraction with retention time Rt= 21.0 min was collected. Multiple injections afforded to 4.35 g of the product (36.5% yield).

NMR ($CDCl_3$): 0.9(3H,t), 2.1(3H,s), 4.5-4.6(2H); Lit. [96] NMR (ØH): 1.75(3H), 4.59,4.78(2H,m).

PREPARATION OF HEMIACETAL 15 BY TREATING TETRACYCLIC ACETAL 14 WITH TITANIUM TETRACHLORIDE AND ISOPROPENYYL ACETATE:

A solution of 1% (3.1 mL, 1.1 eq.) titanium tetrachloride in dry methylene chloride and 7 mL (2.5 eq.) of a 1% solution of isopropenyl acetate in dry methylene chloride were mixed at -15^0C in a 25 mL round bottom flask under argon atmosphere. To this mixture was added 50 mg (0.255 mmol) of tetracyclic acetal 14 in 2 mL of dry methylene chloride, dropwise over a period of 10 minutes. The resulting mixture was stirred for 2 hours, during which the temperature rose to -5^0C. A further 10 mL (3.6 eq.) of 1% titanium tetrachloride solution was added and the mixture was stirred for one more hour at -5^0C.

The reaction was quenched by adding 450 mg of solid sodium bicarbonate and 4 drops of water and was stirred for 0.5 hour during which chunky titanium dioxide precipitated. Filtration and concentration gave 56 mg (86%) of organic substances containing major (Rf=0.20) and minor (Rf=0.64) components (TLC, 3/2 methylene chloride-ethyl acetate). The major component was separated by crystallization from methylene chloride-ethyl acetate, affording 32 mg (49%) of white crystals, mp 115-6^{0}C. When recrystallized from ethyl acetate-methanol, this material afforded a new compound mp 147-9^{0}C but with the same Rf value.

Analysis calculated for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found (for sample mp 115-6^{0}C): C, 56.34; H, 6.27.

PREPARATION OF HEMIACETAL 15 BY TREATING TETRACYCLIC ACETAL 14 WITH TITANIUM TETRACHLORIDE AND 2-ACETOXY-1-HEPTENE:

Tetracyclic acetal 14, 100 mg (0.51 mmol) was dissolved in 1 mL of methylene chloride in a 25 mL round bottom flask with a magnetic stirrer under an argon atmosphere at -10^{0}C. To this solution, 148 mg (1.9 eq.) of 2-acetoxy-1-heptene in 2 mL of methylene chloride was added. To this was then added 8 mL (1.5 eq.) of a 1% solution of titanium tetrachloride in methylene chloride dropwise over a period of 10 minutes, and the resulting mixture was stirred for 2 hours. During this period the temperature rose to +15^{0}C.

The reaction was quenched by adding 365 mg of solid sodium bicarbonate and 4 drops of water and stirring for 0.5 hour, during which chunky titanium dioxide precipitated. The solution was dried over anhydrous potassium carbonate and filtered. The residue was washed with ethyl acetate, the wash was combined with the filtrate and evaporated to give 115 mg of white solid (mp 136-7^{0}C). The white solid was crystallized from ethyl acetate/methanol, and afforded 64 mg of white crystals (mp 147.5-149^{0}C).

Analysis calculated for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.23; C, 6.26.

PREPARATION OF HEMIACETAL 15 BY TREATING TETRACYCLIC ACETAL 14 WITH TITANIUM TETRACHLORIDE/ACETYL CHLORIDE:

A solution of 1.000 g (5.1 mmol) of tetracyclic acetal 14 in 80 mL of dry methylene chloride was placed in a 250 mL three neck round bottom flask fitted with a magnetic stirrer, refluxing condenser and a dropping funnel under an argon atmosphere and surrounded by ice/water mixture. To this flask was then added 4.6 mL (12.95 mmol, 2.5 eq.) of a 20% solution of acetyl chloride in dry methylene chloride, followed by 7.0 mL (6.5 mmol, 1.25 eq.) of a 10% solution of titanium tetrachloride in dry methylene chloride diluted with 20 mL of dry methylene chloride, added dropwise over a period of 10 minutes. During the addition of titanium tetrachloride

solution, the reaction mixture turned pale yellow. The reaction mixture was stirred for an additional 45 minutes.

The reaction was quenched by adding 5 g of potassium carbonate, 100 mL of methylene chloride and 2 mL of water and stirring for 2 hours. During this time chunky titanium dioxide precipitated and carbon dioxide gas was evolved. The resulting mixture was decanted, dried over anhydrous potassium carbonate and filtered. The residue was boiled with 100 mL of ethyl acetate, filtered and combined with the the previous filtrate. The combined filtrates were concentrated, and the resulting residue was dried in vacuo to give 1.24 g (95%) of white solid, mp 122-8^{0}C, which on crystallization from ethyl acetate gave 1.08 g of hemiacetal 15, mp 144-7^{0}C (anal. mp 149-151^{0}C).

NMR and IR spectra were identical with those obtained from the product of partial hydrolysis of tetrahydroasperuloside tetraacetate with acetic acid/water.

PREPARATION OF BENZOATE 55 BY TREATING TETRACYCLIC ACETAL 14 WITH TITANIUM TETRACHLORIDE/BENZOYL CHLORIDE:

A solution of 50 mg of tetracyclic acetal 14 (.255 mmol) and 0.22 mL (0.379 mmol, 1.5 eq.) of a 20% solution of benzoyl chloride in dry methylene chloride and 0.35 mL (0.318 mmol, 1.25 eq.) of titanium tetrachloride were mixed at 0^{0}C. The

temperature of the mixture was allowed to rise to room temperature and stirring was continued for a total of 42 hours.

The reaction was quenched by adding 15 mL of methylene chloride, a few drops of water and 500 mg of potassium carbonate and stirring for three hours. The mixture was the dried over anhydrous potassium carbonate, filtered and concentrated to give 82.2 mg of brown gum. This brown gum was loaded on the top of a silica column (7" longX1.5" diameter) and eluted with 3/2 ethyl acetate-hexane. The eluent was concentrated to give 58.6 mg (white gum) of 55 (74%) which on crystallization from chloroform/ether gave 14.9 mg (mp 129.5-131^{0}C) of white solid.

There was no detectable (TLC) formation of products when the reaction was tried at 0^0C for 1 hour. However it seems from TLC and NMR examination that the reaction had progressed 30%, when the reaction mixture was stirred for overnight period and temperature was allowed to rise to rt from 0^0C.

NMR ($CDCl_3$): 7.3-8.2 (5H,m), 6.5 (1H). IR: 1776 cm^{-1} (5-membered lactone).

Analysis calculated for $C_{17}H_{16}O_5$: C, 67.99; H, 5.73. Found: C, 67.53; H, 5.50.

PREPARATION OF ENONE 60 USING WITTIG REACTION

n-Butyllithium 10.4 mL (16.7 mmol, 1.6M in hexane) was added dropwise to 20 mL of dry dimethylsulfoxide under a nitrogen atmosphere and stirred for 20 minutes. To this dimsyl anion solution, 3.6 mL (17.4 mmol) of dimethyl 2-oxo-heptyl phosphonate was added dropwise during 5 minutes and the mixture was stirred for an additional 15 minutes. Hemiacetal 15, 724.4 mg (2.83 mmol) in 3 mL of dry dimethylsulfoxide was then injected at room temperature. The flask containing the 15 was rinsed with two 3 mL portions of dimethylsulfoxide which were also added to the reaction mixture. The temperature of the reaction mixture was then raised to 50^{0}C over a period of 0.5 hour and maintained at 50-55 C^{0}for an additional 3 hours.

The reaction mixture was then cooled to room temperature and quenched by adding 3.4 mL of glacial acetic acid, poured into 100 mL of water and extracted with 3X75 mL of methylene chloride. The combined organic extracts were washed with 50 mL of water which was back extracted with 50 mL of methylene chloride. The back wash was combined with the original organic extract, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was dried in vacuo for 4 hours at 100-110^{0}C, giving 1.409 g of brown gum.

This brcwn gum was chromatographed on a silica column (9" longX1.5" diameter), eluting with 600 mL of 2/1 ethyl acetate-hexane. The eluent was concentrated to 774 mg (73.7%) of a mixture of enones 60a,b (major: 6.6 min; minor: 8.3 min, in approx. 8/1 ratio, on HPLC: 2/1 ethyl acetate-hexane, 2 mL/min) as a yellow gum.

NMR (major component, $CDCl_3$): 6.65 (1H, dd, J=6,16); 6.2 (1H, d, J=16); 4.9 (1H, m); 3.8-4.2 (4H); 2.1 (3H, s); 0.9 (3H, t). IR = 3150-3600 (b), 1760 (s), 1740 (s) cm . The NMR and IR cf minor compcnent were virtually indistinguishable to that of the major component.

Analysis calculated for $C_{19}H_{26}O_6$: C, 64.75; H, 8.01. Found (major): C, 64.64; H, 8.09. (minor): C, 64.04; H, 8.23. The analysis of the minor component was not repeated due to insufficient material.

PREPARATION CF CARBOXYLIC ACID 64:

Jones' [104] reagent (4 mL) was added drop by drop to 16 mL of acetone maintained at reflux by an oil bath at 59-60^{0}C. To this refluxing mixture, a sclution of 173.6 mg (0.49 mmol) of alcohcl 60 in 5 mL cf acetone was injected over a period of 10 seconds and refluxing was continued fcr an additional 50 seconds.

The reaction was then quenched by adding excess isopropanol (10 mL), poured into 200 mL of water and extracted with ether (4X100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated and the residue dried in vacuo to give 168 mg (0.46 mmol, >90%) of crude carboxylic acid 64 which was used for decarboxylation without further purification.

The carboxylic acid was found to be a mixture of two components (Rf=0.57, major; Rf=0.88, minor; absolute ethanol). Both components were soluble in 5% sodium bicarbonate and reappeared in the organic extract when acidified with 5% hydrochloric acid. NMR shows a broad singlet at δ 6.9, which disappeares after addition of D_2O. Although δ 6.9 might appear uncharacteristic of the carboxyl proton, there are several examples in the literature of intramolecular hydrogen bonded carboxyl group with similar chemical shift [105].

DECARBOXYLATION OF CARBOXYLIC ACID 64:

Crude carboxylic acid 64 (168 mg, 0.46 mmol) was refluxed with 100 mL of glacial acetic acid for 3.5 hours. The mixture was concentrated and dried in vacuo to give a brown gum. This brown gum was dissolved in 10 mL of methylene chloride and poured over the top of a 1 in thick layer of silica gel in a sintered glass funnel and eluted with 100 mL

of methylene chloride followed by 100 mL of ethyl acetate. The combined filtrates were concentrated and dried in vacuo to give 115.3 mg (0.36 mmol, 78%) of white gum , one spot on TLC (Rf=0.52, 1/1 ethyl acetate-hexane) and one peak on HPLC (7.3 min 1/1 ethyl acetate-hexane). The product 31a was isolated in 72-74% overall yield for oxidation and decarboxylation.

H^1NMR: (250 MHz, $CDCl_3$): 6.183(1H,d,J=15.6), 6.613(1H,dd,J=15.6,8.6), 2.024(3H,s), 4.05,4.16(2H,dd), 4.974(1H,m), 2.518(2H,t,J=7.4), 0.886(3H,t,J=6.8), 1.286(2H,m). IR: 1767, 1733, 1689, 1629 cm^{-1}. Optical rotation $[\alpha]_D^{25}$ -28^0 (c 0.073, chloroform).

Analysis calculated for $C_{18}H_{24}O_5$: C, 67.06; H, 8.13. Found : C, 67.14; H, 8.14.

Appendix A

THE X-RAY DATA FOR THE TETRACYCLIC ACETAL 14

Table I. Final Atomic Parameters for
with Standard Deviations in Parentheses

Atom	X	Y	Z	B
O(1)	0.7434(3)	0.7823(3)	0.4193	*
O(2)	0.4252(3)	0.5568(3)	0.3992(6)	*
O(3)	0.5041(3)	0.5056(3)	0.6987(7)	*
O(4)	0.9094(3)	0.7442(5)	0.5172(8)	*
C(1)	0.8432(4)	0.8105(4)	0.5803(9)	*
C(2)	0.7909(4)	0.7635(4)	0.8185(7)	*
C(3)	0.6429(4)	0.7194(4)	0.8629(7)	*
C(4)	0.5654(4)	0.7318(4)	0.6661(7)	*
C(5)	0.6536(5)	0.8265(4)	0.4898(8)	*
C(6)	0.4891(4)	0.5924(5)	0.5706(8)	*
C(7)	0.5720(4)	0.5682(5)	0.9077(7)	*
C(8)	0.6768(5)	0.5336(4)	0.9648(8)	*
C(9)	0.8066(4)	0.6393(4)	0.8561(8)	*
C(10)	0.8397(6)	0.6139(6)	0.6182(10)	*
H(1)	0.908	0.910	0.582	6.0
H(2)	0.849	0.835	0.928	5.0
H(3)	0.635	0.768	0.997	5.0
H(4)	0.501	0.760	0.721	6.0
H(5)A	0.598	0.826	0.360	7.0
H(5)B	0.706	0.920	0.553	7.0
H(7)	0.506	0.543	1.033	7.0
H(8)A	0.651	0.442	0.905	8.0
H(8)B	0.688	0.534	1.131	8.0
H(9)	0.885	0.663	0.958	7.0
H(10)A	0.898	0.572	0.623	10.0
H(10)B	0.755	0.554	0.534	10.0

* Anisotropic thermal parameters are given in Table II

Table II. Final Anisotropic Thermal Parameters for
with Standard Deviations in Parentheses

Atom	$B11 \times 10^4$	$B22 \times 10^4$	$B33 \times 10^4$	$B12 \times 10^4$	$B13 \times 10^4$	$B23 \times 10^4$
O(1)	156(3)	164(4)	293(8)	70(3)	19(4)	11(4)
O(2)	151(4)	259(5)	432(10)	71(4)	-73(6)	-50(6)
O(3)	140(3)	143(3)	505(11)	23(3)	-46(5)	15(5)
O(4)	139(4)	292(7)	679(15)	111(5)	91(6)	15(8)
C(1)	114(5)	147(6)	477(16)	33(4)	33(7)	19(7)
C(2)	124(4)	105(4)	329(11)	43(3)	-58(6)	-54(6)
C(3)	157(5)	151(5)	233(9)	97(4)	-10(6)	-33(6)
C(4)	167(5)	183(6)	303(11)	128(5)	4(7)	-33(7)
C(5)	222(7)	144(5)	361(14)	116(5)	-46(8)	-19(7)
C(6)	102(4)	194(6)	348(13)	64(4)	-4(7)	-21(8)
C(7)	141(5)	185(6)	344(14)	68(5)	23(7)	48(7)
C(8)	222(7)	148(5)	436(15)	93(5)	-51(9)	24(8)
C(9)	138(5)	165(5)	457(15)	94(5)	-83(7)	-61(8)
C(10)	207(7)	245(9)	685(24)	171(7)	-21(10)	-74(11)

The anisotropic temperature factor has the form

$$\exp(-(\underline{h}^2 B11 + \underline{k}^2 B22 + \underline{\ell}^2 B33 + 2\underline{hk}B12 + 2\underline{h\ell}B13 + 2\underline{k\ell}B23))$$

Table III. Bond Lengths (A) in
with Standard Deviations in Parentheses

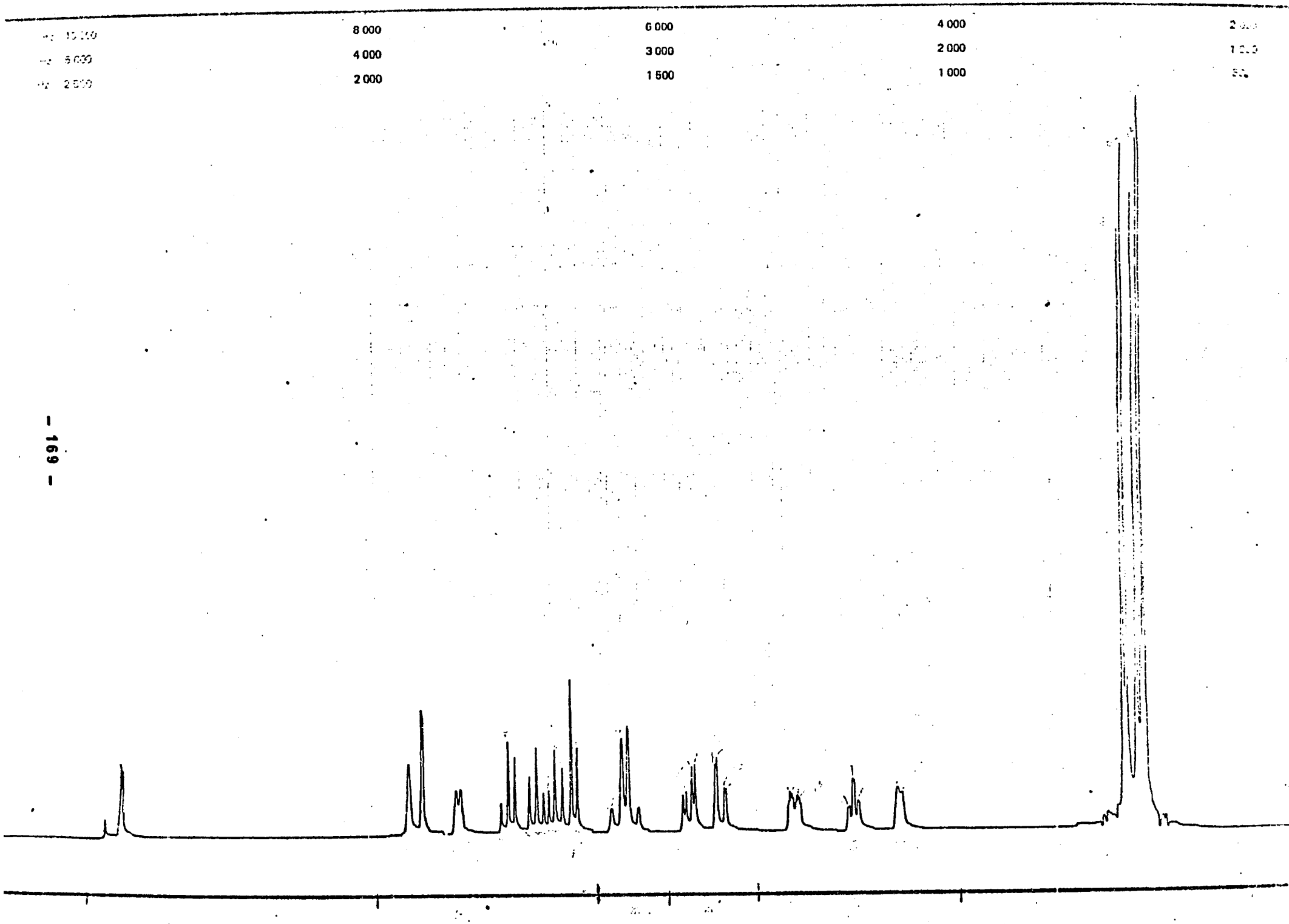
O(1)- C(1)	1.402(5)	C(2)- C(9)	1.538(7)
O(1)- C(5)	1.419(7)	C(3)- C(4)	1.521(7)
O(2)- C(6)	1.203(6)	C(3)- C(7)	1.526(6)
O(3)- C(6)	1.332(7)	C(4)- C(5)	1.486(6)
O(3)- C(7)	1.453(6)	C(4)- C(6)	1.498(6)
O(4)- C(1)	1.369(8)	C(7)- C(8)	1.482(8)
O(4)-C(10)	1.428(7)	C(8)- C(9)	1.517(5)
C(1)- C(2)	1.530(6)	C(9)-C(10)	1.532(8)
C(2)- C(3)	1.532(6)		

Table IV. Bond Angles (°) in
with Standard Deviations in Parentheses

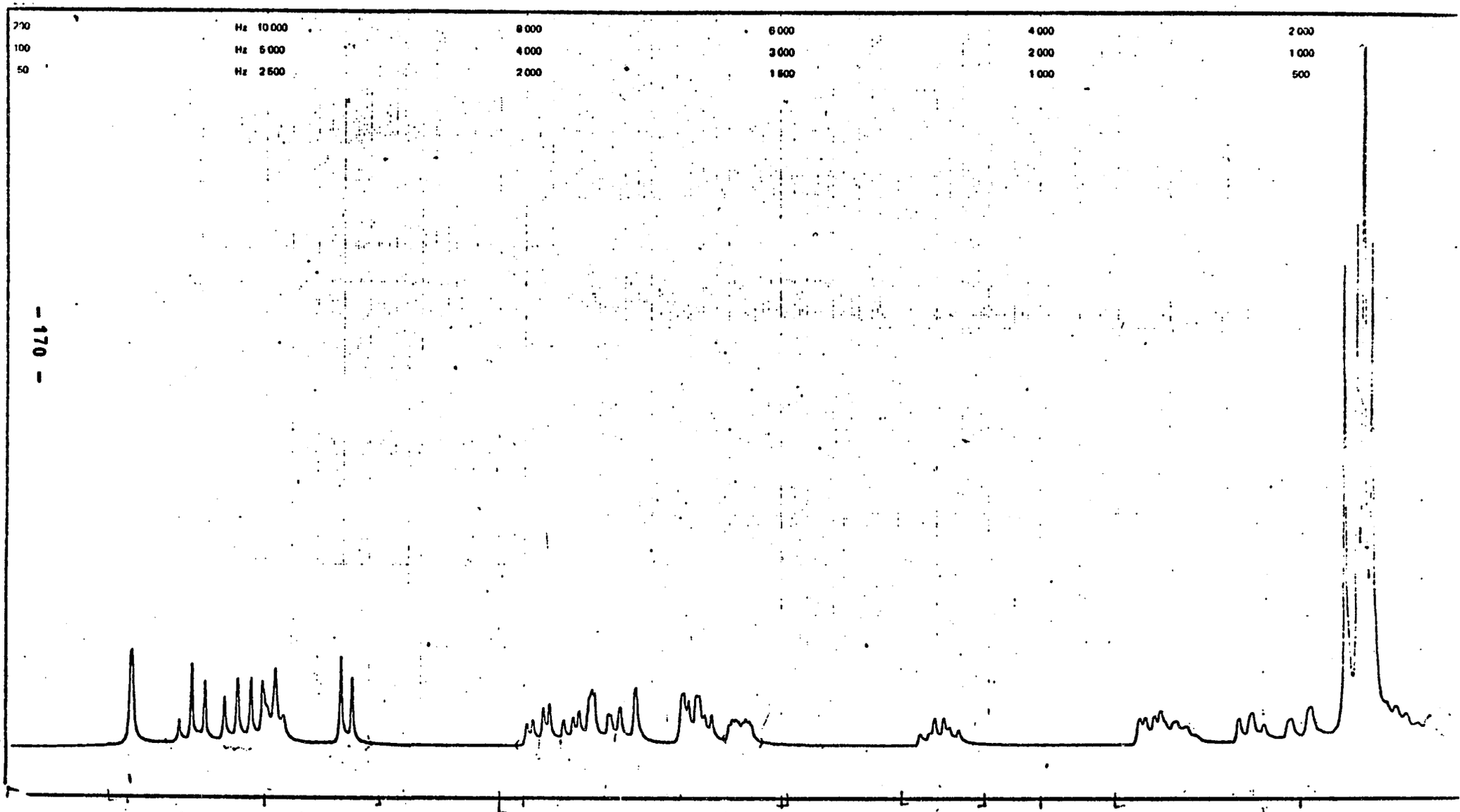
C(1)- O(1)- C(5)	111.7(3)
C(6)- O(3)- C(7)	111.0(4)
C(1)- O(4)-C(10)	106.8(4)
O(1)- C(1)- O(4)	107.5(4)
O(1)- C(1)- C(2)	115.0(3)
O(4)- C(1)- C(2)	106.7(4)
C(1)- C(2)- C(3)	116.8(4)
C(1)- C(2)- C(9)	104.8(4)
C(3)- C(2)- C(9)	107.0(3)
C(2)- C(3)- C(4)	116.1(3)
C(2)- C(3)- C(7)	106.2(4)
C(4)- C(3)- C(7)	103.7(3)
C(3)- C(4)- C(5)	113.4(4)
C(3)- C(4)- C(6)	104.4(4)
C(5)- C(4)- C(6)	109.4(4)
O(1)- C(5)- C(4)	107.4(4)
O(2)- C(6)- O(3)	121.1(5)
O(2)- C(6)- C(4)	128.0(5)
O(3)- C(6)- C(4)	110.8(4)
O(3)- C(7)- C(3)	105.1(4)
O(3)- C(7)- C(8)	111.7(4)
C(3)- C(7)- C(8)	107.6(3)
C(7)- C(8)- C(9)	106.9(4)
C(2)- C(9)- C(8)	106.3(4)
C(2)- C(9)-C(10)	101.3(4)
C(8)- C(9)-C(10)	118.7(4)
O(4)-C(10)- C(9)	104.7(5)

Appendix B

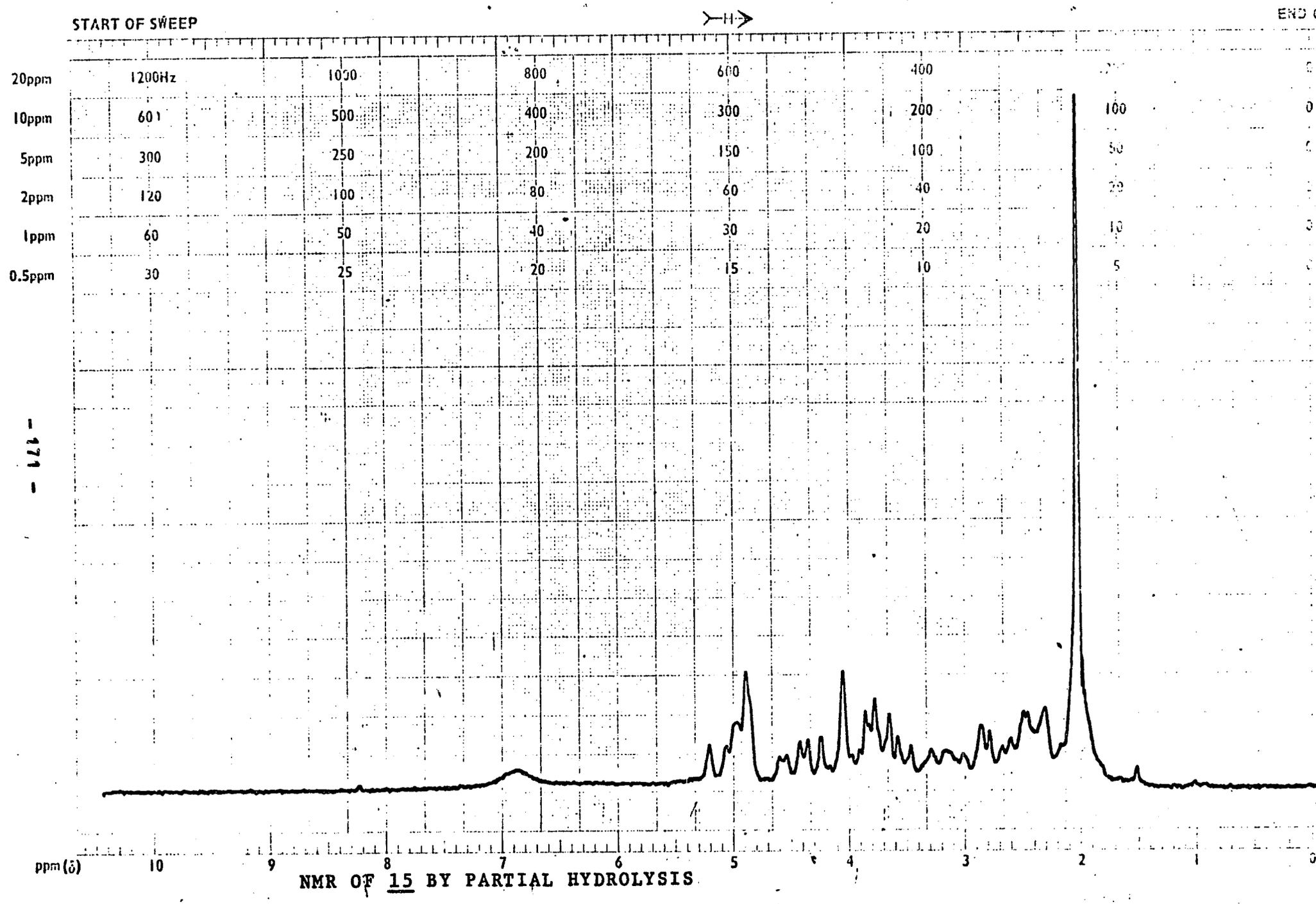
SPECTRA



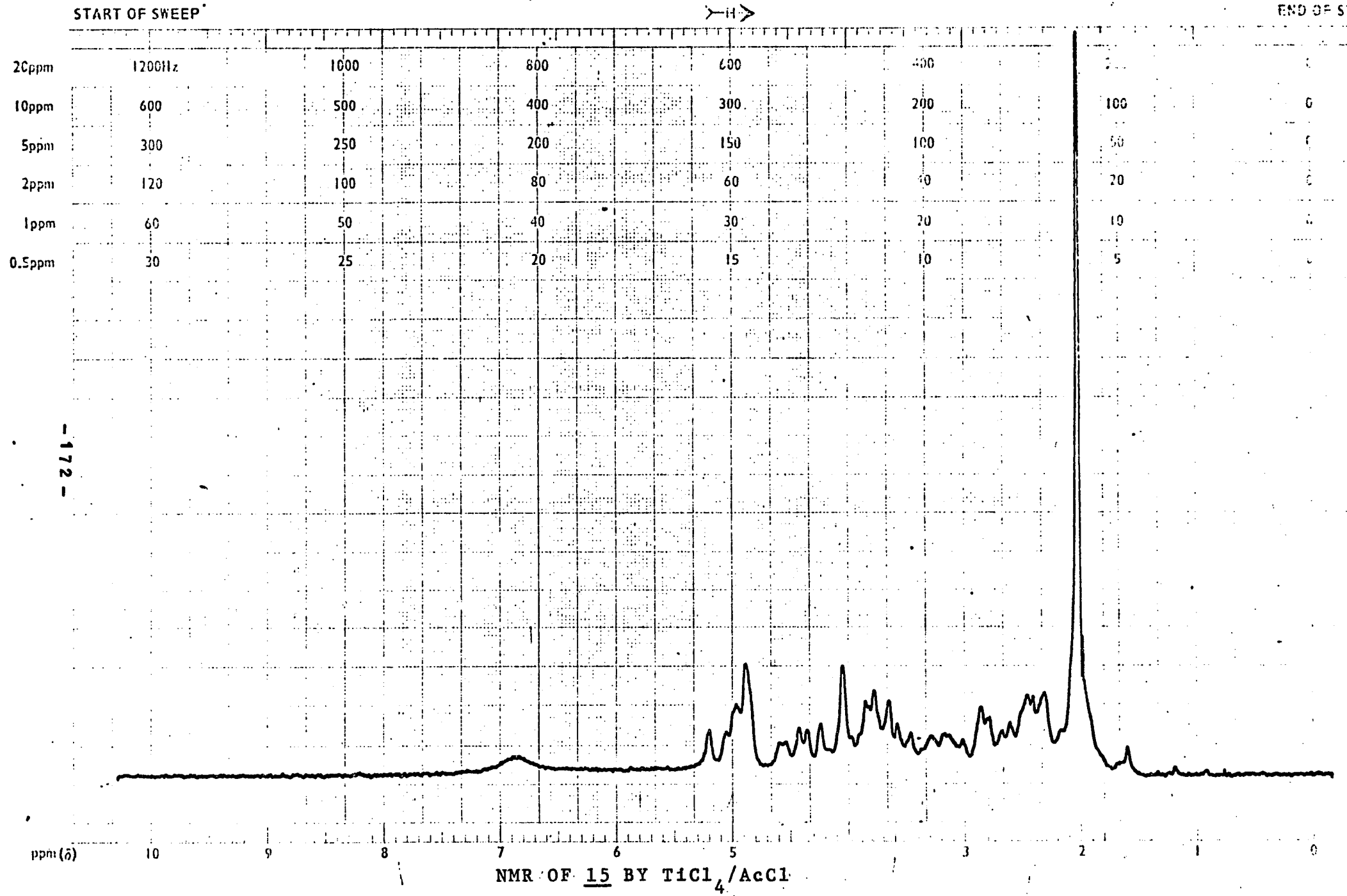
NMR OF ASPERULOSIDE TETRAACETATE



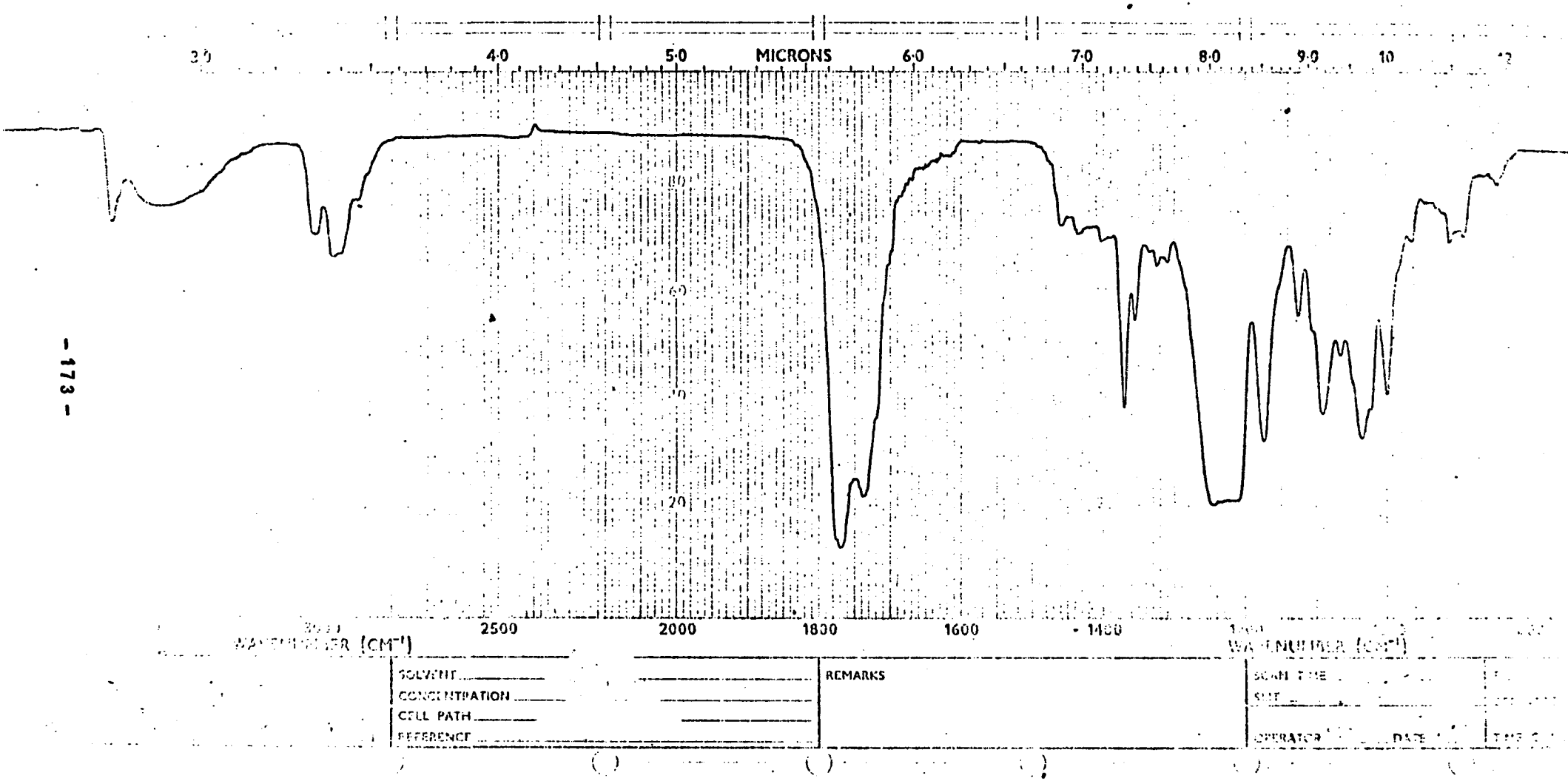
NMR OF TETRAHYDROASPERULOSIDE TETRAACETATE



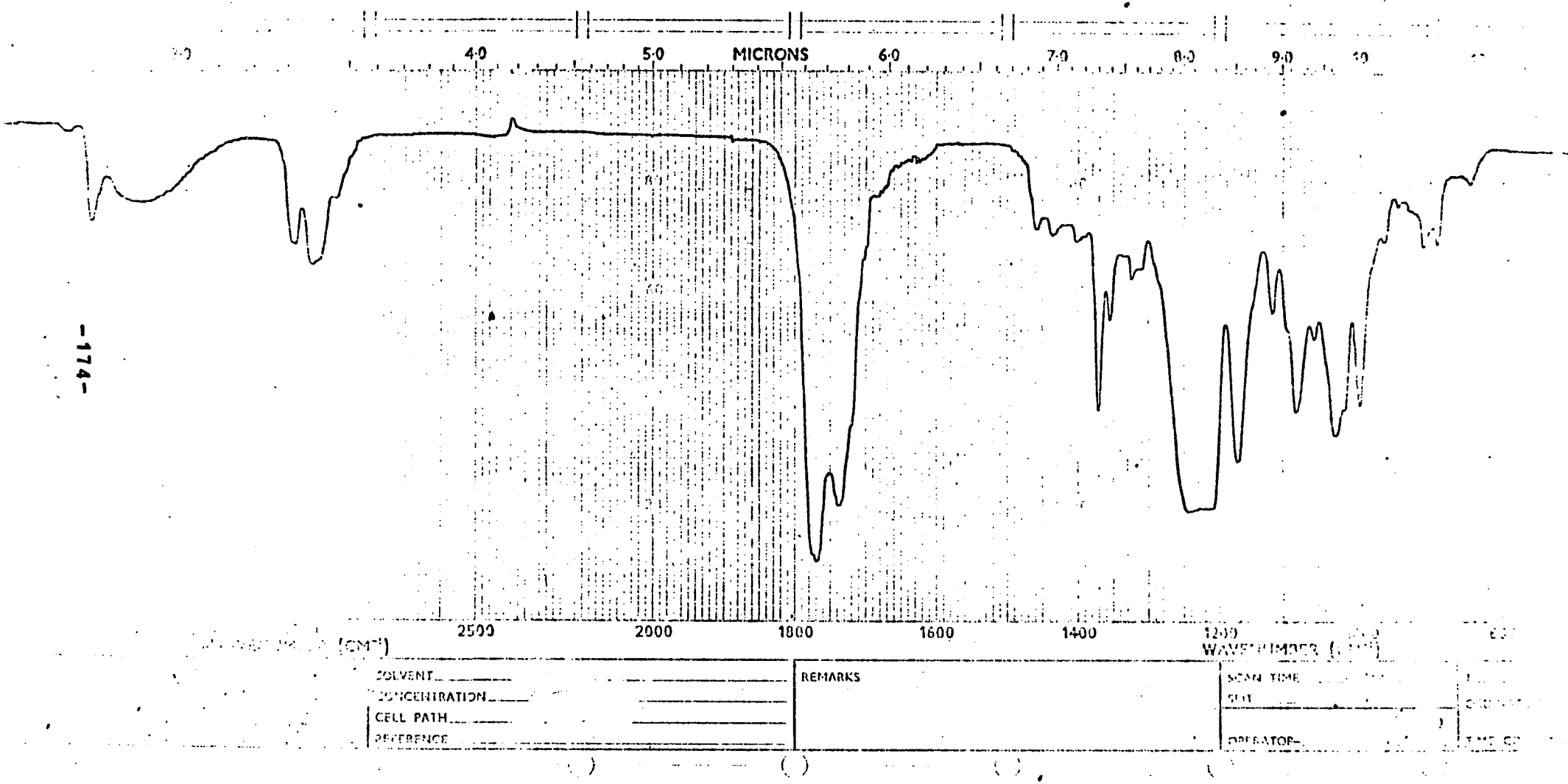
NMR OF 15 BY PARTIAL HYDROLYSIS



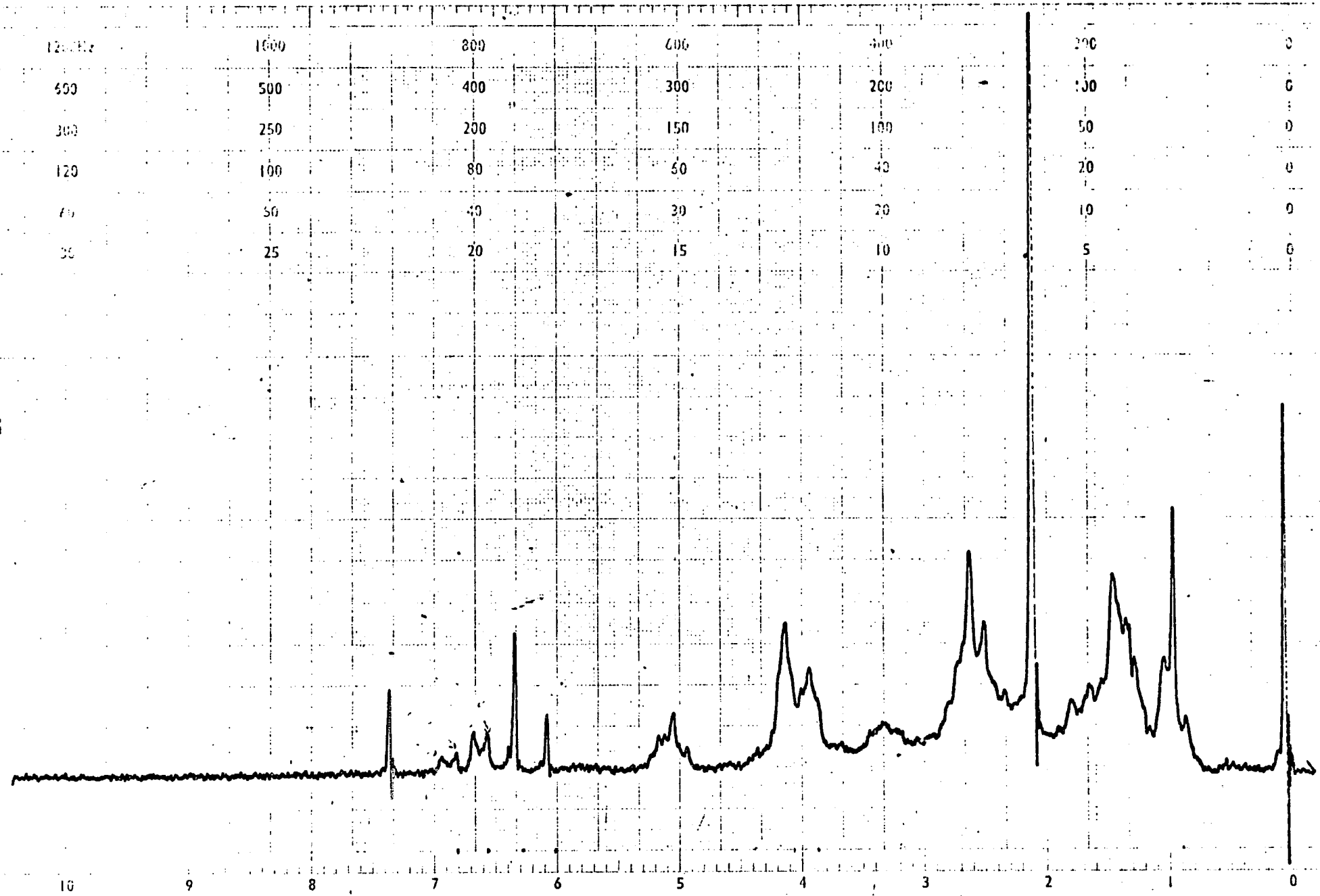
NMR OF 15 BY $TiCl_4$/AcCl



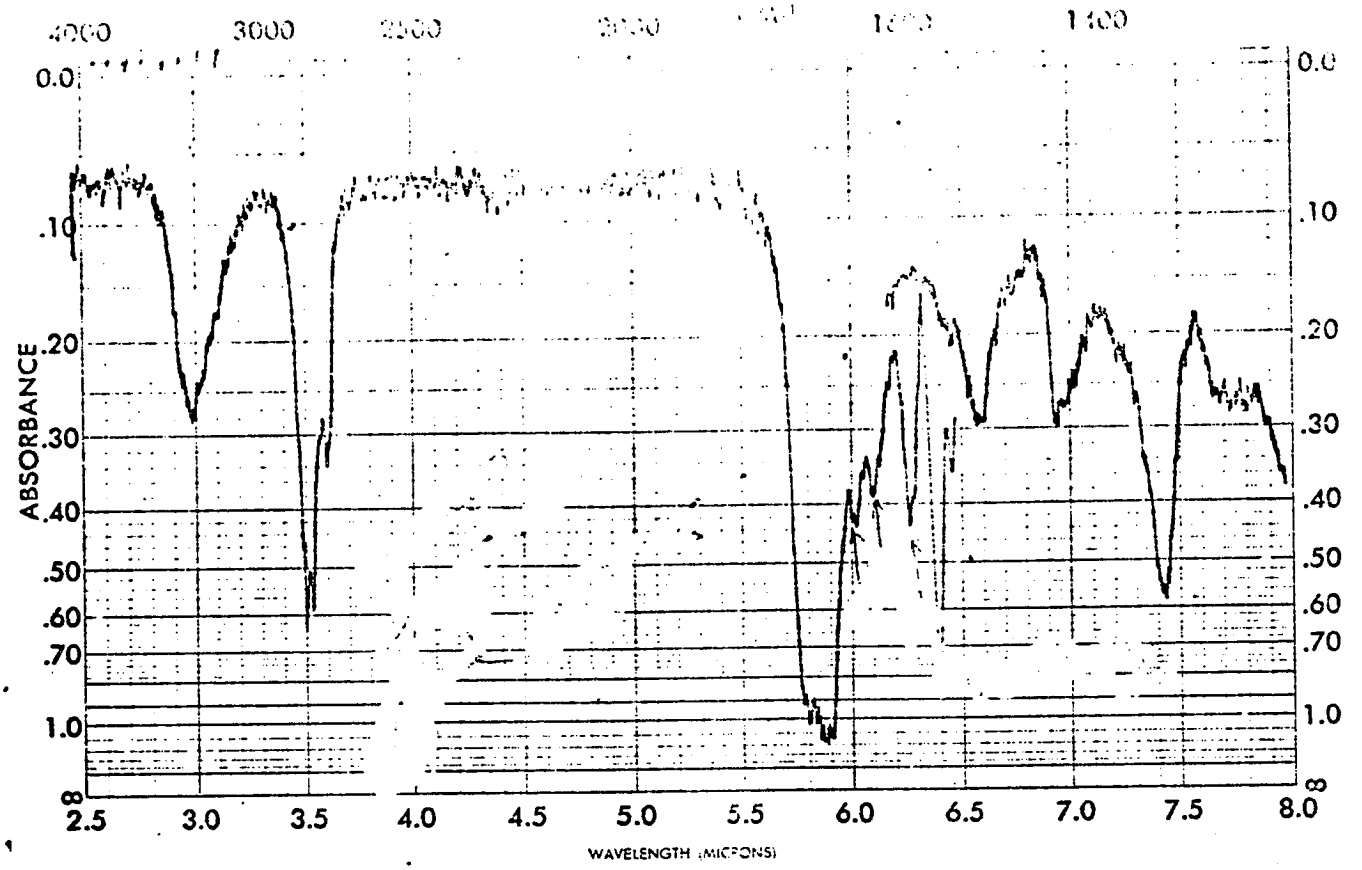
IR OF HEMIACETAL 15 BY PARTIAL HYDROLYSIS

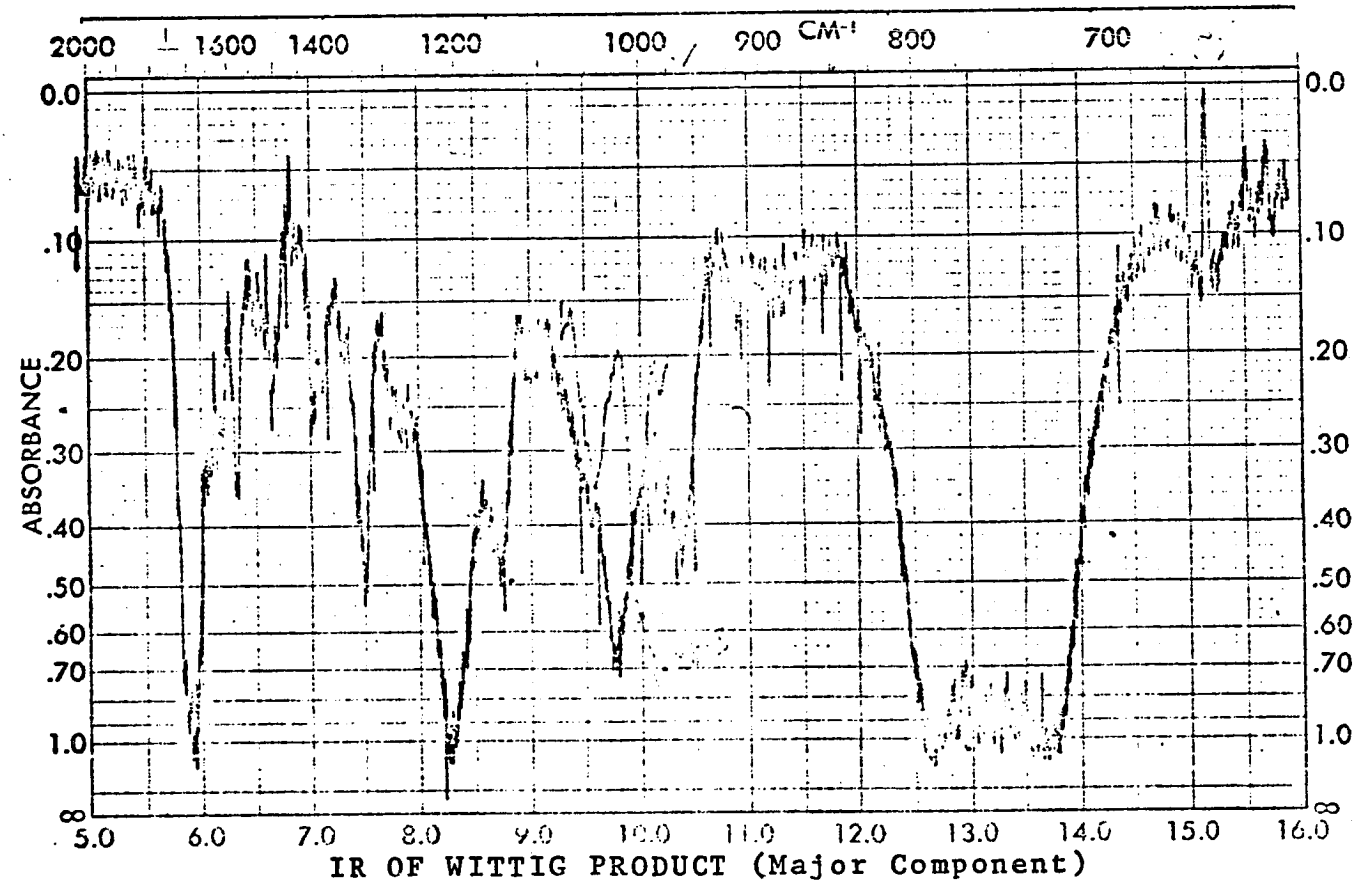


IR OF HEMIACETAL 15 BY $TiCl_4$/AcCl

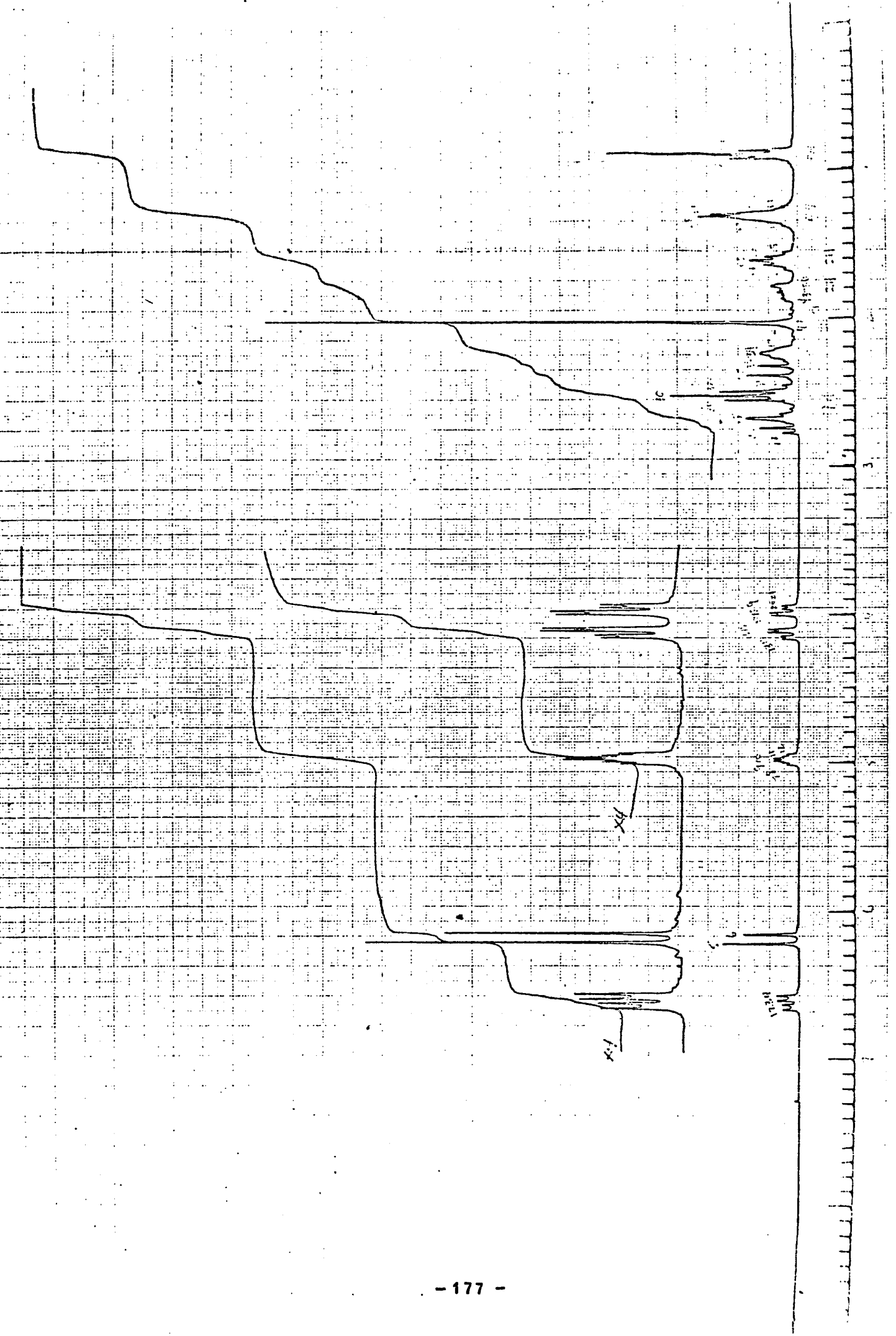


NMR OF WITTIG PRODUCT (Major Component)

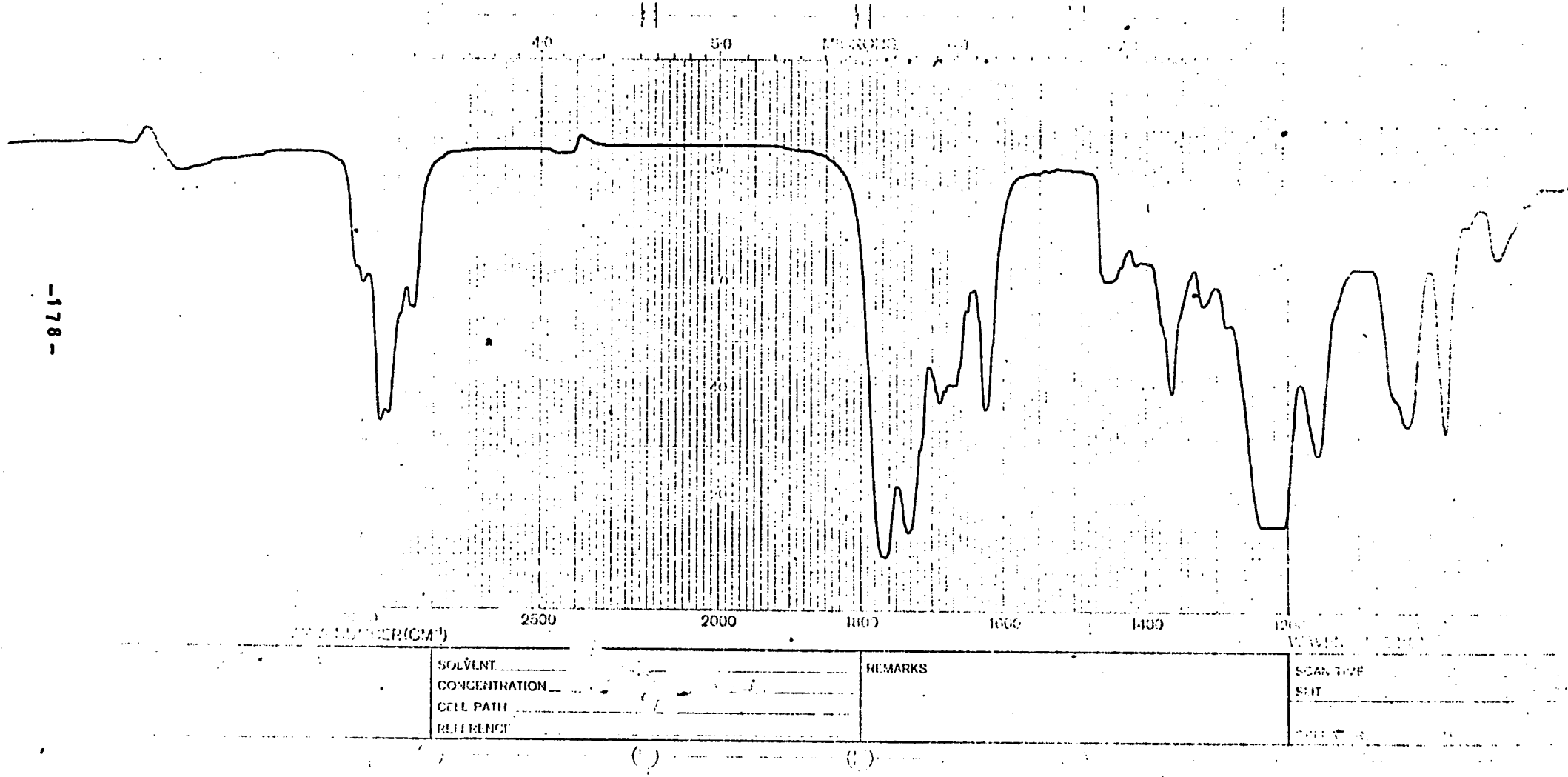




IR OF WITTIG PRODUCT (Major Component)



NMR OF ENONE 31a



IR OF ENONE 31a

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