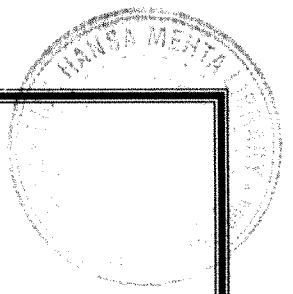


CHAPTER I

INTRODUCTION

I.1 HISTORY

The prostaglandins (PGs) form a class of natural products with diverse and potent biological activities. The natural PG are unsaturated hydroxylated fatty acids, all derivatives of the parent compound, Prostanoic acid **1** (**Figure I.1**). Their precise physiological role has not been clearly defined, but their potency and activity in many apparently unrelated biological systems have awakened the interest of scientists of various disciplines. Indeed, PGs are associated with most mammalian tissues and implicated in an ever-increasing number of physiological systems .[1]

From the historical point of view, in 1930 Kurzrok and Lieb showed that the human semen could induce strong contractions or relaxations when applied to a human uterus.[2] A few years later, Von Euler and Goldblatt demonstrated independently the presence of a vasodepressor agent and a stimulating factor of muscles in human seminal plasma and sheep vesicular glands.[3] Von Euler indicated that the biological activity was due to a lipid-soluble material with acidic properties and named as it prostaglandin.[4]
About 30 years after the discovery of the biological activity of PG, the structure elucidation of two of them was done. The reasons why this field remained inactive for so long are many and in part are due to the technical difficulties encountered earlier in the isolation of natural PGs. In addition, the dramatic development of antibiotics and hormone therapy made during the past 30 years somehow caused PG research to fall into oblivion. In 1957, Bergstrom and Sjovall isolated the crystalline PGE_1 **2** and $PGF_{1\alpha}$ **3** from sheep vesicular seminal extracts.[5] Short time later, Bergstrom, Sjovall, and Samuelsson were able to differentiate then isolate thirteen different substances. It was only after this isolation and structure work when PGs were shown to be biologically active entities that the field came to life. Previously their biological properties had been attributed to other known substances.[6-9]

I.2 NOMENCLATURE, STRUCTURE AND STEREOCHEMISTRY

Natural occurring PGs may be regarded as derivatives of prostanoic acid **1**.[10] The natural PGs are divided into three "series" namely, the first which presents only one double bond between position 13 and 14, the second with an additional olefinic bond between C-5 and C-6, and the last with

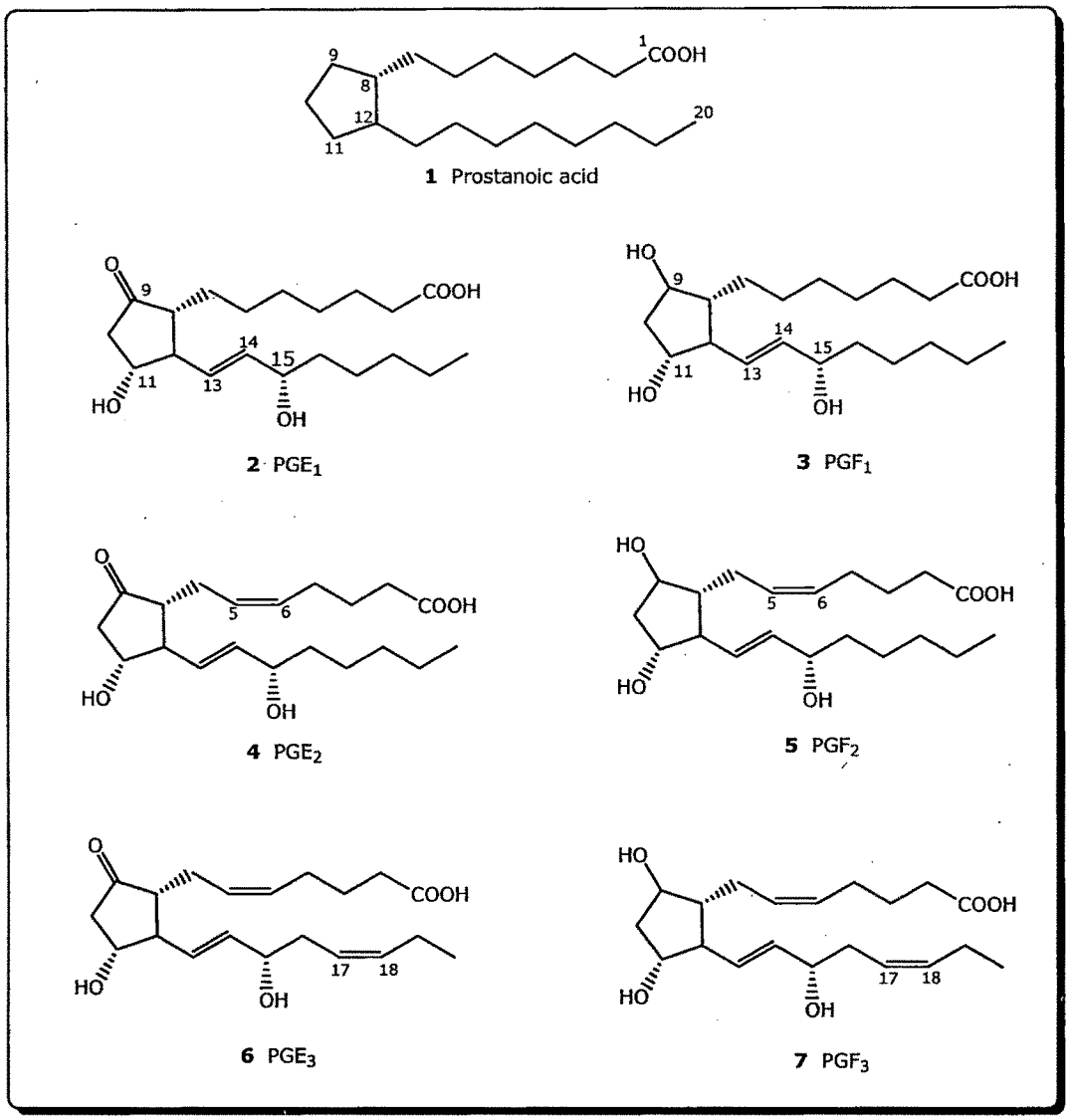


Figure I.1

a third double bond located between C-17 and C-18. Furthermore, natural PGs form two major groups, Primary and Secondary. In primary PGs including the members of E and F families, as shown in **Figure I.1**. Where as the members of the A, B, C, D, G and H families forming the Secondary PGs, some of which are shown in the **Figure I.2**. The six primary PGs present an oxygen at 9th position (ketone in E series, hydroxyl in F series)

and C-11 and C-15 (α-hydroxyl groups), as well as a trans double bond between C-13 and C-14.

Rules for the nomenclature have been proposed [10] using the prostane skeleton (**1**) as the basic unit. For example, PGA_2 (**8**) is called 5*Z*,13*E*,15(S)-hydroxy-9-oxoprosta-5,10,13-triene-1-oic acid, although the commonly accepted abbreviation PGA_2 will be used more often for convenience.

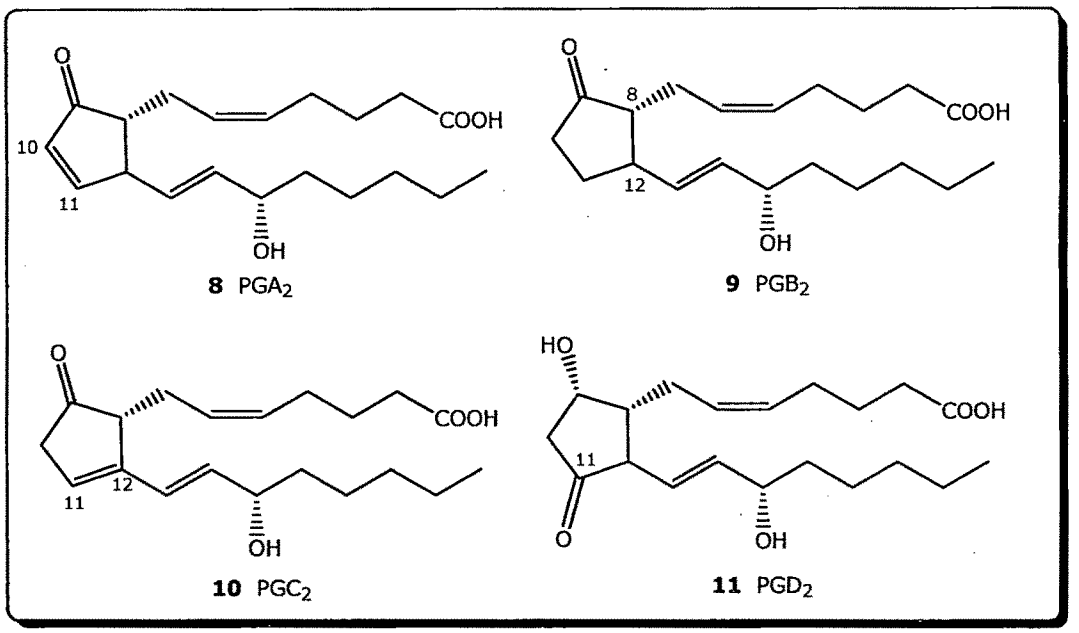


Figure I.2

The stereochemistry, in the configuration of the hydroxyls at C-9(S), C-11 (R) and C-15 (S),[11] as well as that of the chains located at C-8 & C-12 (8α and 12β in most natural PGs) and the chain double bonds (*cis* or *Z* at C-5 and *trans* or *E* at C-13), is important for biological activity.

Besides the primary PGs, PGA_2 **8**, PGB_2 **9** [12] and PGC_2 **10** [13] are of particular interest. These three natural prostanoids possess a carbonyl group at position 9 (PGs in E series), but they differ by the position of the double bond in the five-membered ring. Prostaglandins of the D family, [14-16] such as PGD_2 **11**, are 11-oxoprostanoids, whereas PGG_2 **12** and PGH_2/PGR_2/LASS (labile aggregation-stimulating substance) **13** are biosynthetic endoperoxide intermediates.[16] Recently, Samuelsson *et al* have indicated that PGG_2 **12** and PGH_2 **13** readily metabolize to give newly isolated compound

thromboxane A_2 **14** and then thrombxane B_2 **15**.[17] Interest in PGs of the D family has been increased by observing that PGD_2 **11** is one of the products formed during

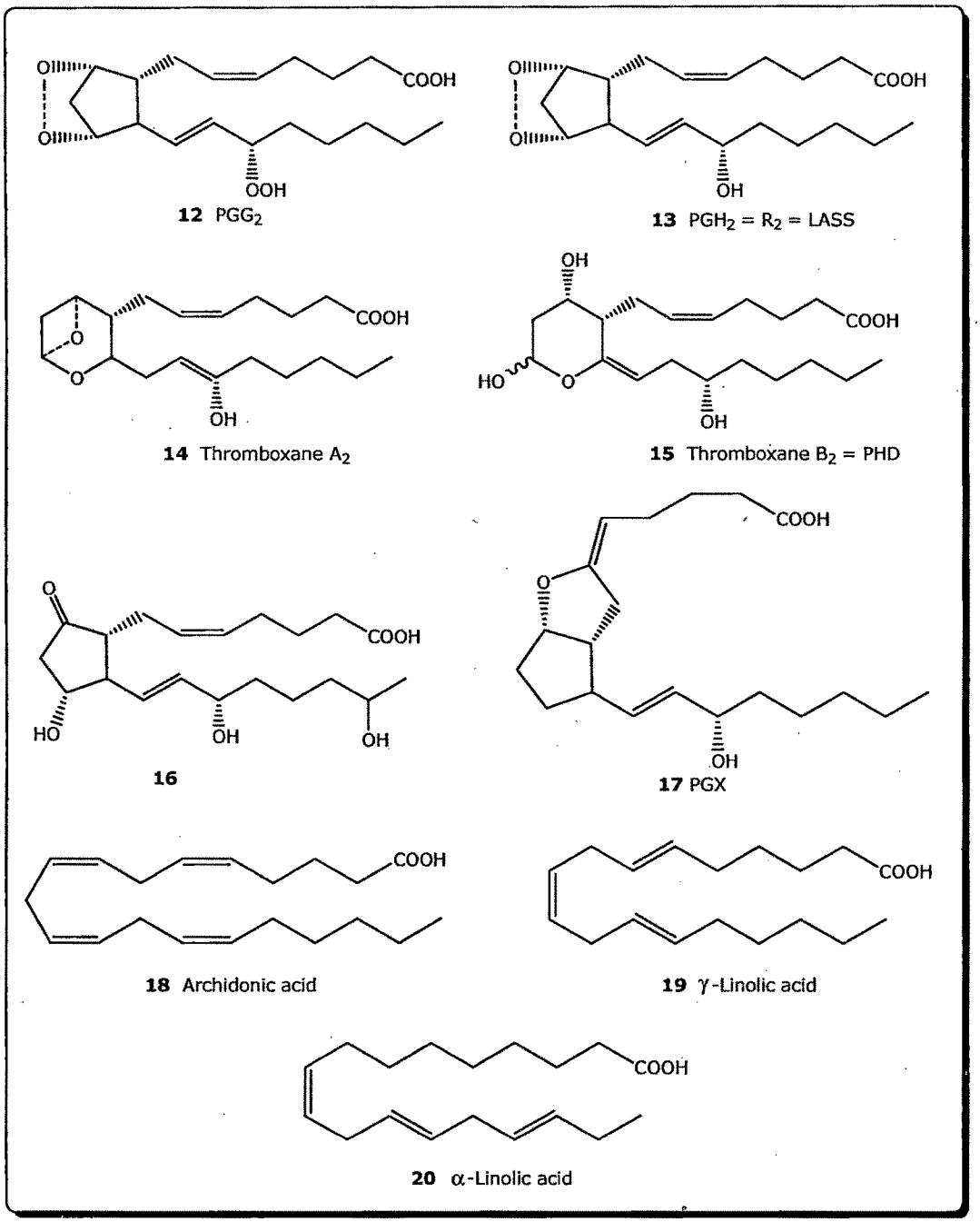


Figure I.3

nonenzymatic decomposition of the endoperoxide PGH_2 **13** derived from the arachidonic acid **18**.[15,16] PGD_2 **11** has also been obtained by incubation of arachidonic acid **18** with microsomes of sheep vesicular gland [15,16] and believed to be biologically active. **Figure I.3** represents biologically important natural PGs of the A and E families.[18] Vane *et al.* reported the isolation and structure determination of PGX (prostacyclin) **17**, which inhibits platelet aggregation.[18a]

I.3 NATURAL OCCURRENCE

The biosynthetic aspects of PGs have shown that γ-linolenic acid **19** and arachidonic acid **18 (Figure I.3)** occur not only in higher animals, but also in the lower flora and fauna.[19] Arachidonic acid **18** has been demonstrated to be present in considerable quantities in protozoa, algae, mosses and ferns; γ-linolenic acid **19** has been shown to be present in fungi, protozoa, the oil seeds of hops and hemp, boraginaceae and lilicceae. Euglena gracilis (an organism) has the ability to synthesize the polyenoic acids that are characteristic of higher plants and animals. Cells of Euglena gracilis, which grow while exposed to light, produce a number of saturated fatty acids, mainly α-linolenic acid **20.**[20] This acid is not formed in cells that grow in the dark. In the absence of light, in a poor culture medium, a large amount of arachidonic acid is formed. It is known that such unsaturated acids in the cell are incorporated in the phospholipids, which, in turn, are used as building units of membranes. They are formed by normal fatty acid synthesis and subsequently are dehydrogenated. They occur in the oils of the seeds of higher plants and, in addition to their role in membranes, they may also constitute a source of energy. They are the food for the seed.

When the function of these unsaturated fatty acids is mentioned, it is always associated with the word "membrane." It is assumed that the chain length and the degree of unsaturation of the fatty acid in the membrane contribute to its specific physical properties. It is not known whether unsaturated fatty acids have any other function in the plant. No specific process has been found in which they play a role.[20]

In the animal kingdom, the situation is different. linoleic acid and arachidonic acid are essential fatty acids in mammals, while in the lower animals there are clear indications that specific fatty acids are also essential. In the cabbage interlooper

(*Trichoplusia ni*), for instance, α-linolenate was shown to be an essential nutrient that could not be replaced by linoleate. It is possible that α-linolenate does not act per se, but only after conversion into a biologically active compound.[20] In the animal kingdom, the polyunsaturated fatty acids are structurally important because of the physical properties they give to membranes. They may also maintain various enzymes in the membranes in a particular state. They play a role in lipid transport and are part of certain enzymes with a lipoprotein character. These sounds very similar to what is known about plants and these functions are accomplished by many acids. However, in addition, in animals some specific acids, such as linoleic acid, γ-linolenic acid, and arachidonic acid, take part in a number of fascinating reactions leading to the formation of PGs.

PGs are known to be widely distributed in mammals, [19] and van Drop *et al.* [20] have reported the comparative aspects of PG biosynthesis in different animals. Prostaglandins have been found in the urinary bladder [20] and intestine [21] of the frog, as well as in the gastrointestinal tract of the shark *Triakis scyllia;* [22] PGs Synthesis has been found in mussels and lobsters.[20] In addition, PGs have been identified in the testes and semen of Teleosts.[23] Prostaglandins mainly A_2 and E_2 have also been isolated in rather large amounts from animals as simple as the marine soft coral *Plexaura homomalla* (Esper).[12]

In mammals, PGs found in low concentrations in numerous tissues and fluids, as well as in a large number of organs, such as in the iris of eye, the brain, the thymus, the bronchials, the lungs, the human seminal plasma, the seminal fluid, the ovary, and the uterus. After appropriate stimulation, PGs were identified in the intestine, the adrenal glands, the stomach, the kidneys, the nervous tissues, etc.[16] However, the total PG production in the adult human is only of the order of 1 to 2 mg per 24 hours.[16]

I.4 BIOLOGICAL PROPERTIES

The pharmacological properties of PGs constitute the topic of active research. Programs are underway to develop PGs to treat gastric ulcers, asthma, some kinds of heart diseases, and some complications of diabetes. Some possible applications of them include treatment of arthritis, cholera and glaucoma.[24-29]

These developments are due to the fact that PGs are perhaps the most versatile, ubiquitous and powerful substances found in humans.[24-29] Furthermore, many PGs are characterized both by their multiplicity of effects and their generally short lifetime. It has been suggested that the biological activity of the PG molecule is associated with a right-handed chirality, best visualized as right-handed wedge in which all the hydrophilic functional groups are oriented to one side and the hydrophobic groups to the other side of the molecule while both ends are hydrophilic.[30]

Biosynthesized in the cell membrane from simple fatty acids PGs act locally and rapidly, in small amounts, and with an unusual variety of activities. One of their functions seems to regulate the intracellular activity caused by the arrival of hormone-messengers from other parts of the body. It also appears that at least some PGs regulate the function of the cell, probably acting under the influence of a cellular membrane enzyme. For this reason, PGs are considered as regulators or modulators of intracellular metabolism.[24, 29]

PGE_1 **2 (Figure I.1)** has been found variously to increase or decrease inflammation, to stimulate smooth muscle contraction, to inhibit production of stomach acid, to open bronchial tubes, to block the breakdown of fats, and to constrict the pupil of the eye.[24-29] It has also been shown that PGs are involved in tissue defense and auto-defense mechanisms, some of which are manifested in obvious ways such as fever, vomiting and inflammatory phenomena.[31] Others manifest themselves by regulation of the blood flow in the aggressed organ.

There is a general consensus that the site of action of PGs is the membrane and numerous studies have demonstrated interaction of PGs with membrane components. It is reported that binding sites showing specificity and affinity similar to those of known hormonal receptors.[30-33]

PGE_1 and PGE_2 act at the hypothalamus level to control pituitary hormone release. Although participation of PGs in the regulation of ovarian function has been extensively studied, little is known about their role in relation to the hypothalamic axis. Prostaglandins can effect pituitary secretion of luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin. This effect is probably mediated by the hypothalamus, and it is possible that PGs are intermediaries in the release of all hypothalamic hypophyseal stimulating and inhibiting hormones.[34]

At this stage, the precise mechanisms of action of PG are only hypothetical, but their utilization in fertility control and contraception, as well as in induction of labor and abortion, present potential applications in medicine and pharmacology. Hence, they constitute potential means to contribute to the solution of population related problems. [35, 36] A potential use of PG and some analogues as abortifacients as a result of luteolysis in human pregnancy exists.[24-29, 37] Luteolysis or luteolytic effect is the ability of a compound to decrease progesterone secretion from an ovary containing a corpus luteum.

PGE_2 **5** **(Figure I.1)** act exclusively at the renal level, whereas the PGA_2 **8** seems to go into the systemic circulation and, not sensitive to lung metabolism, seems to stimulate surrenal aldosterone synthesis and vasopressin release.[38-40] PGA_2 **8** may ultimately find an important role in the clinical treatment of essential hypertension.[40, 41]

It has been shown that both PGE and PGF are almost completely metabolized by passage through the lungs, whereas PGA_2 **8** is not. These results suggest that PGA_2 **8** could function systemically as a circulating "hormone".[43] Most PG metabolize rapidly, after their introduction in the circulation. Since their lifetime is extremely short, they get rapidly degraded in shorter, oxidized and hydroxylated fragments.[44] The major difference between hormones and many PGs is that hormones are elaborated by specific glands and then are sent through the blood vessels in the organism where they are necessary. In contrast, most PGs seem to be synthesized at the specific site where they act, by the same tissues, and do not circulate. Cells do not store PGs, but have the capacity to synthesize and release them at the slightest provocation. For this reason sometimes they are called "local hormones."

The role of PGs in the function of blood platelets has also been studied, and evidence indicates that some PG may be able to play a role in controlling blood clots, by acting on the platelets, the cells that are essential to the clotting process. One has shown that PGX **17** **(Figure I.3)**, around thirty times more active than PGE_1 **2** **(Figure I.1)**, is probably one of the most potent inhibitors of platelet aggregation yet described.[18a] PGE_1 **2** produces a rapid rise in platelet CAMP.[24-29, 45]

PGD_2 **11** **(Figure I.2)** has also been found to be a potent inhibitor of platelet aggregation. Aggregation of human platelets by adenosine diphosphate (ADP), collagen, and PGG_2 **12** was inhibited more strongly by PGD_2 **11** than PGE_1 **2**. Although ADP-

induced aggregation of rabbit platelets was inhibited more strongly by PGE_1 than PGD_2, the latter PG gave a more long-lasting inhibitory effect on platelet aggregation following intravenous or oral administration. These results, coupled with the finding that PGD_2 **11** has less hypotensive effects on the cardiovascular system than PGE_1 **2**, suggest the possible use of PGD_2 **11**, as an antithrombic agent.[45a] It has been shown that pure PGH_2 **13** is more potent as a platelet aggregator than other putative thrombotic mediators. The aggregation response is Ca^{+2} dependent and apparently requires a plasma factor such as fibrinogen. Activity of PGH_2 **13** appeared to be attributable to a peroxide that could be changed nonenzymatically to authentic PGE_2 **4** and $PGF_{2\alpha}$ **5**.[42, 46]

Convincing evidence has been presented that PGs may be one of several mediators of the inflammatory response, it has also been mentioned that PGE_1 **2** & PGE_2 **4** play part in the genesis of pain, PGE_1 **2** in fever and inflammation. In that respect, Vane *et al.* reported that nonsteroidal anti-inflammatory agents, such as indomethacin, phenylbutazone, aspirin, and naproxen, own their activity to inhibition of PGs Synthesis.[47] It is conceivable that these anti-inflammatory agents inhibit the formation of the cyclic endoperoxide of type **13**, considered to be an active entity. Consequently, it is possible that a lipoperoxide intermediate in the PG biosynthetic pathway may have pain-producing properties.[48]

Calcium ions are necessary for the development of a contractile or relaxant response to PG and interference with calcium ion binding sites markedly affects these responses. The inhibitory effect of PGE_2 **4** on noradrenaline secretion is consistent with the possibility that PGE_2 **4** depresses neural secretion by facilitating efflux of intraaxonal calcium.[49] Moreover, calcium ions are required for platelet aggregation and oppose the inhibitory effect of PGE_1 **2**. The intervention of calcium ions has been demonstrated in a number of dynamic physiological phenomena, often indicative of the presence of membrane elements. Studies on the interference Ca^{+2} - PG at the membrane level allow one to say that some PG have an influence on the motions of calcium ions through membrane. A general hypothesis has been proposed, suggesting that PG could act at the membrane level on the distribution of calcium ions, which would transmit their effect.[50] This could be the mode of action of PG on uterine contractibility.[51]

Some PGs have been shown to affect normal functioning of the respiratory, gastric, digestive, renal, reproductive, nervous, endocrine, and cardiovascular systems. This unusual breadth of activities has stimulated intensive efforts to develop means for potentiating or blocking their effects. This is why scientists hope that in the future PG will be useful as drugs to decrease blood pressure, to prevent formation of blood clots, to treat thrombosis, to against nasal congestion, to cure asthma as well as other respiratory diseases, to control gastric secretion, to cure gastric ulcers, and so forth. In addition, PG may constitute a useful means to regulate fertility both in men and women.[8, 9, 24-29]

I.5 TOTAL SYNTHESIS

A major difficulty in the biological evaluation and practical application of prostaglandins (PGs) was due to the fact that the supply of primary PGs from natural sources, such as sheep vesicular glands, was not sufficient to permit broad testing.

This problem was overcome in several different ways. In 1965, scientist at Unilever in the Netherlands[52] and at the Karolinska Institute in Stockholm[53] simultaneously discovered how to prepare relatively large quantities of PG by incubation of fatty acids with sheep glands. In addition, as a consequence of the worldwide impetus in PG clinical research, several chemical laboratories decided to undertake the synthesis of these C-20 carboxylic acids, with the first report of complete total synthesis appearing in 1967.[54] Moreover, the isolatation of PGA_2 from the marine corals [55] provides continues supply of it to the scientists, for synthesis of primary PGs, as well as for the preparation of modified entities.

In spite of the fact that the total synthesis of PG constitutes a challenge for organic chemists, numerous conceptually different synthetic routes have been explored with considerable success. A primary difficulty that one faces in their synthesis is the introduction of a number of functional groups of different nature in the same molecule. Secondly, the stereochemistry of the PGs, *in extenso* the geometry of the double bonds, the configuration of the chains at C-8 and C-12 and the configuration of hydroxyls at position 9,11 and 15, is critical for the bioactivity. In addition, five asymmetric centers are present in many natural PGs and their incorporation into a total synthesis scheme constitutes a formidable objective, as most chemical reactions afford mixtures of isomers.

The PG molecules are not easy to handle technically, since most of them are unstable in acidic or alkaline medium and are sensitive to air and heat.

It was only shortly after the final proof of the structure and the determination of the stereochemistry of primary PG that the first total synthesis of PG was published by Just and Simonovitch from McGill University in Canada.[54] This was followed by a number of imaginative, unusual, and elegant approaches. The result of such effort has given access to practical as well as some industrial methods for producing large quantities of these entities for better biological, pharmacological and clinical evaluations.

I.5 (1) INTERCONVERSION REACTIONS

Prostaglandins of different families (A, B, C, D, E, F, etc.) and series (1, 2 or, 3 double bonds) can be interrelated by appropriate reactions. Although initially these interconversions were effected for structural elucidation purposes, they are now used to prepare specific PGs from more readily available entities. This has given opportunity to learn some specific properties of PG and the influence of steric effects on functional groups. Thus, these interconversions are important both for the discussion of the synthetic work as well as for the methodology that they imply.

I.5 (1a) Interconversions among Primary PGs

One of the first and simplest conversions is the transformation of PGs of the E family **(a)** into their F analogues **(b)** by the action of a reducing agent.[56]

The presence of the carboxyl group requires that the reducing agents display well-defined properties that do not affect this functional group. Initially, the transformation **(a) → (b) (Figure I.4)** was performed with simple hydrides such as sodium borohydride. This introduced the complication of a mixture of isomers at position 9 in a 1:1 ratio. Since the biological properties of PGF_{α} are usually higher and/or different from these of PGF_{β}, reducing complexes with large steric requirements were introduced in order to increase substantially the proportion of 9α-alcohol, formed by the approach of the reagent from the more accessible β-face.[57]

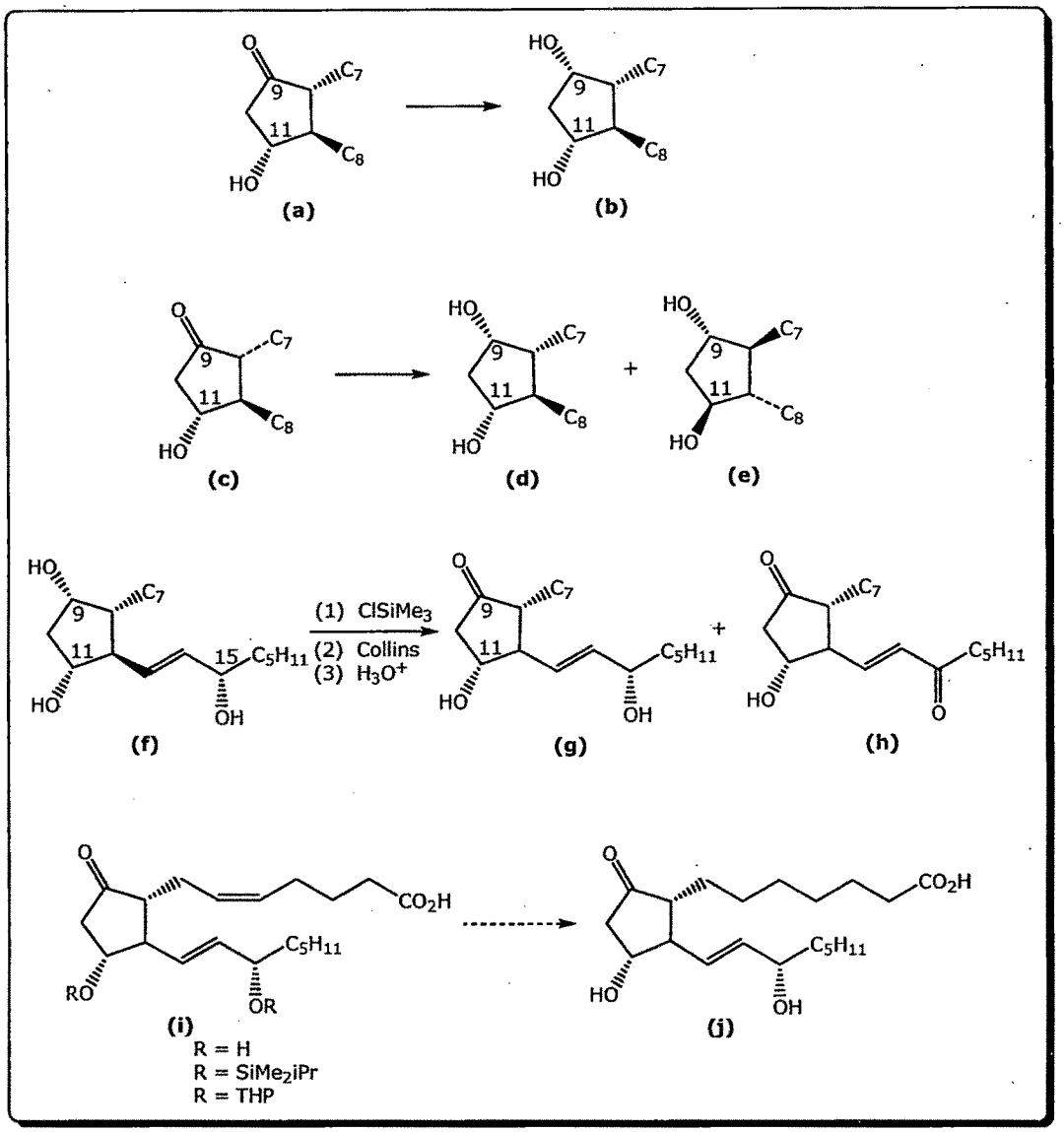


Figure I.4

The stereospecific conversion of PGE_1 (**c**) and PGE_2 to PHF_{1_α} (**d**) and PHF_{2_α} has also been achieved with yeast [58], but the yields were low and the reduction was slow. When the corresponding racemates (**c**) were used as substrates, a mixture of natural PGF_{1_α} and the enantiomer (**e**) of PGF_{1_β} resulted, thus showing the stereospecificity of yeast in this reduction, which gives the 9(S)-alcohols with each enantiomer of the racemate. This approach constitutes an alternative for the resolution of racemates of the E series.

The reverse transformation, *in extenso* the conversion of the F (**f**) to the E family (**g**), obviously presents difficulties due to the three hydroxyl groups that are present in the molecule. Fried and co-workers [59] have achieved the conversion of $PGF_{2\alpha}$ (**f**) into PGE_2 (**g**) through selective protection of the hydroxyl groups at C-11 and C-15 as trimethylsilyl ethers. The Collins oxidation procedure [60] at C-9, followed by acid hydrolysis of the protecting groups and chromatographic separation provided PGE_2 (**g**) in 45 % yield. In addition, 15-dehydro-PGE_2 (**h**) was also isolated from $PGF_{2\alpha}$ (**f**).

These results, supported by other similar observations [61], indicate that the steric requirements of the three hydroxyl groups in the PGF_α family are in the order C9>C15>C11.

Another transformation that falls into this group is the reduction of the 5, 6-double bond of PGE_2 (**i**) to PGE_1 (**j**), reported for the first time by Samuelsons [62] and then by other authors, for ditritiated 5, 6-PGE_1. Later, more detailed hydrogenation studies showed that it is possible to transform PGE_2 (**i**) directly to PGE_1 (**j**) and $PGF_{2\alpha}$ (**f**) to PGF_1 without protecting groups, using the soluble Wilkinson catalyst, tristriphenylphosphine chloro rhodium $[RhCl(PPh_3)_3]$.[63,64]

I.5 (1b) Interconversions between Primary and Secondary PG

The β-hydroxy-keto system of the PG belonging to the E family (**k**) permits a controlled dehydration, thus affording PG of the A family (**l**).[63] The reverse transformation (**l**) → (**k**) (**Figure I.5**) is also possible. This conversion has become particularly important now that PGA_2 derivatives have been isolated in reasonable amounts from marine corals.[55,65]

So far, all the methods reported for this conversion from PGA_2, or derivatives thereof, use the 10,11-epoxide (**m**), followed by hydrogenation of the carbon-oxygen bond at position 10.[66]

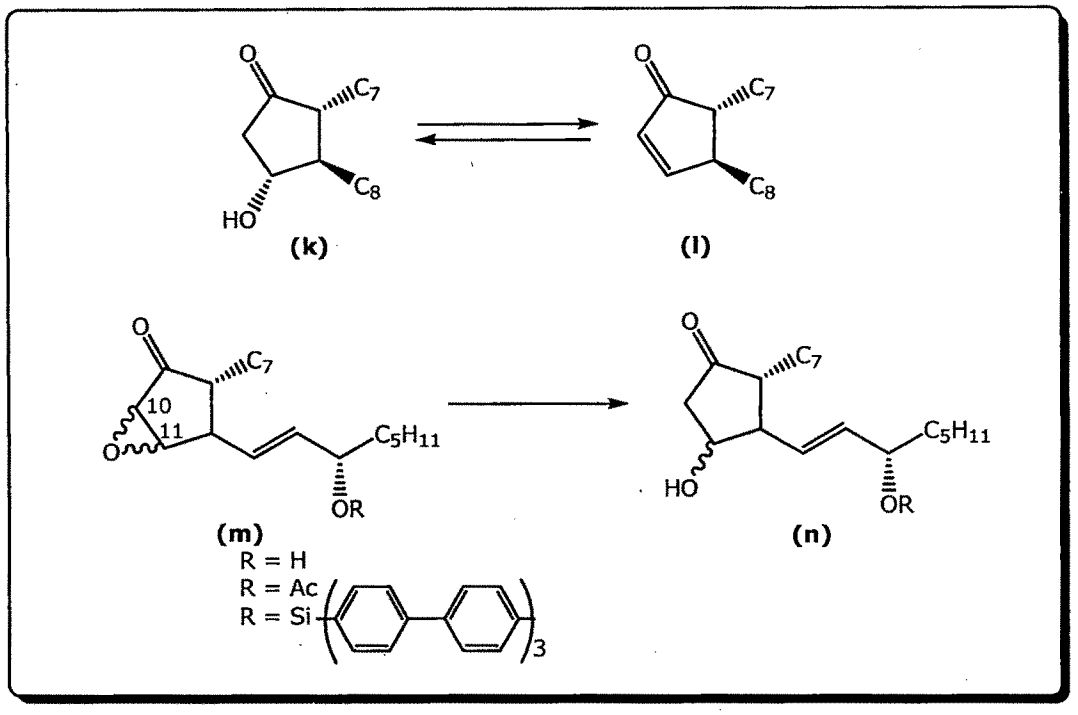


Figure I.5

I.5 (1c) Interconversions between Secondary PG

The transformation best known in this group is the conversion of PGA (**o**) into PGC (**p**) and then PGB (**q**) (**Figure I.6**) by base treatment.[67] This isomerization, also observed with compounds of similar structure [68], is extremely fast and indicates that PG of the B family are thermodynamically more stable than the starting entities.[67] The biological point of view the intermediates of the C family (**p**) exhibit more interesting properties than their counterparts from the A (**o**) or B (**q**) family.[67]

The chemical conversion of PGA_2 (**r**) to PGC_2 (**t**) through the trienolate intermediate (**s**), followed by selective protonation at C-10 [69] has been reported. Among all the bases that were used the weakest (potassium tert-butoxide and sodium tert-amylate) turned out to be the most effective.

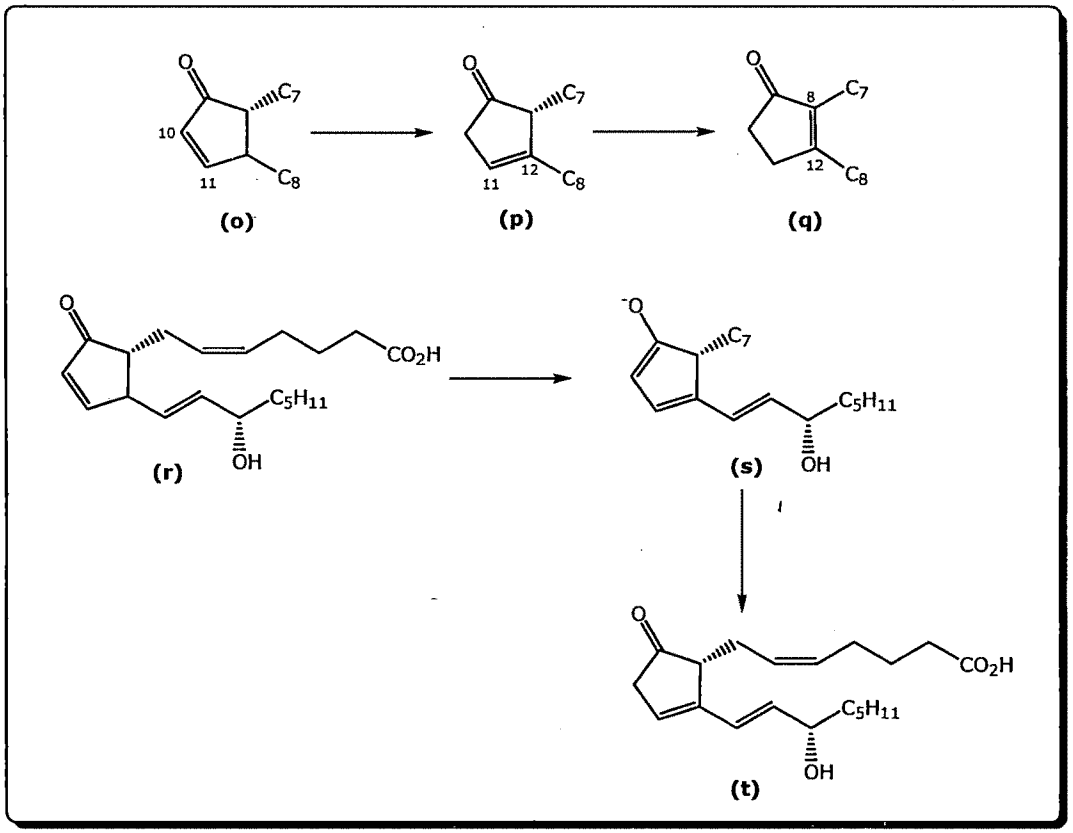


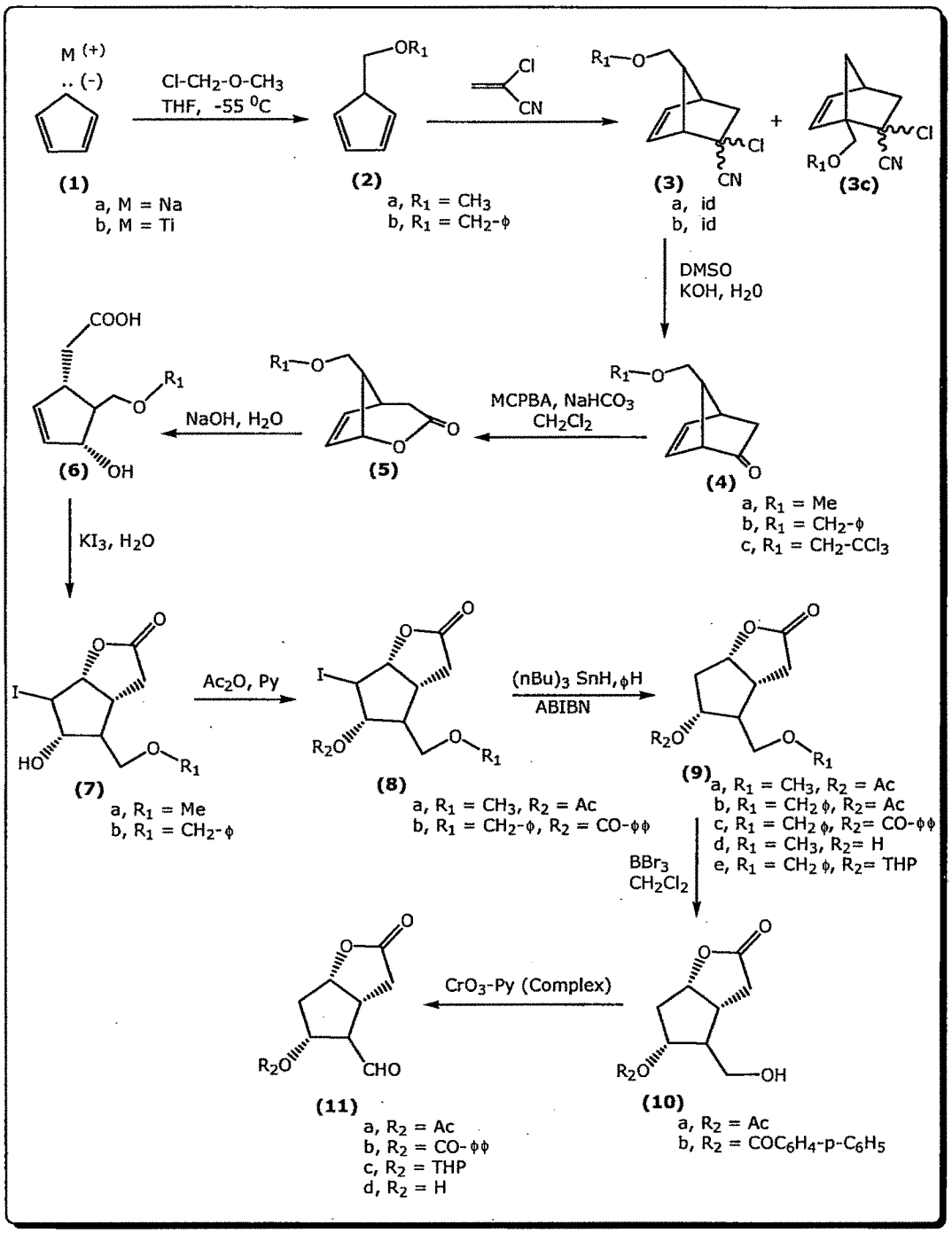
Figure I.6

I.5 (2) THE BICYCLIC LACTONE ROUTE

This is how the highly versatile substituted cyclopentane unit (**11**) was conceived. Although various alternatives in PG synthesis have been envisaged, it is of interest to discuss the preparation of the bicyclic lactone (**11**), as this approach is still the most used and optimized route to PG.

The original approach (**Scheme 1**) [70] used as starting material sodium salt of cyclopentadiene (**1a**), which was alkylated with chloromethyl methyl ether to give the intermediate (**2a**), then immediately submitted to Diels-Alder reaction with 2-chloroacrylonitrile. The bicyclic derivative (**3a**), sometimes contaminated with its isomer (**3c**), was hydrolyzed with base to provide the β,γ-unsaturated ketone (**4a**) in high yield. Baeyer-Villiger oxidation of ketone (**4a**) with m-chloroperbenzoic acid (MCPBA) in the presence of sodium bicarbonate, or with hydrogen peroxide and sodium hydroxide [72], gave the lactone almost quantitatively (**5**). Base hydrolysis of the lactone group furnished

the acid (**6**), which by iodolactonization produced the key intermediate (**7a**), having correct stereochemistry, as well as functionality, necessary to complete the synthesis.



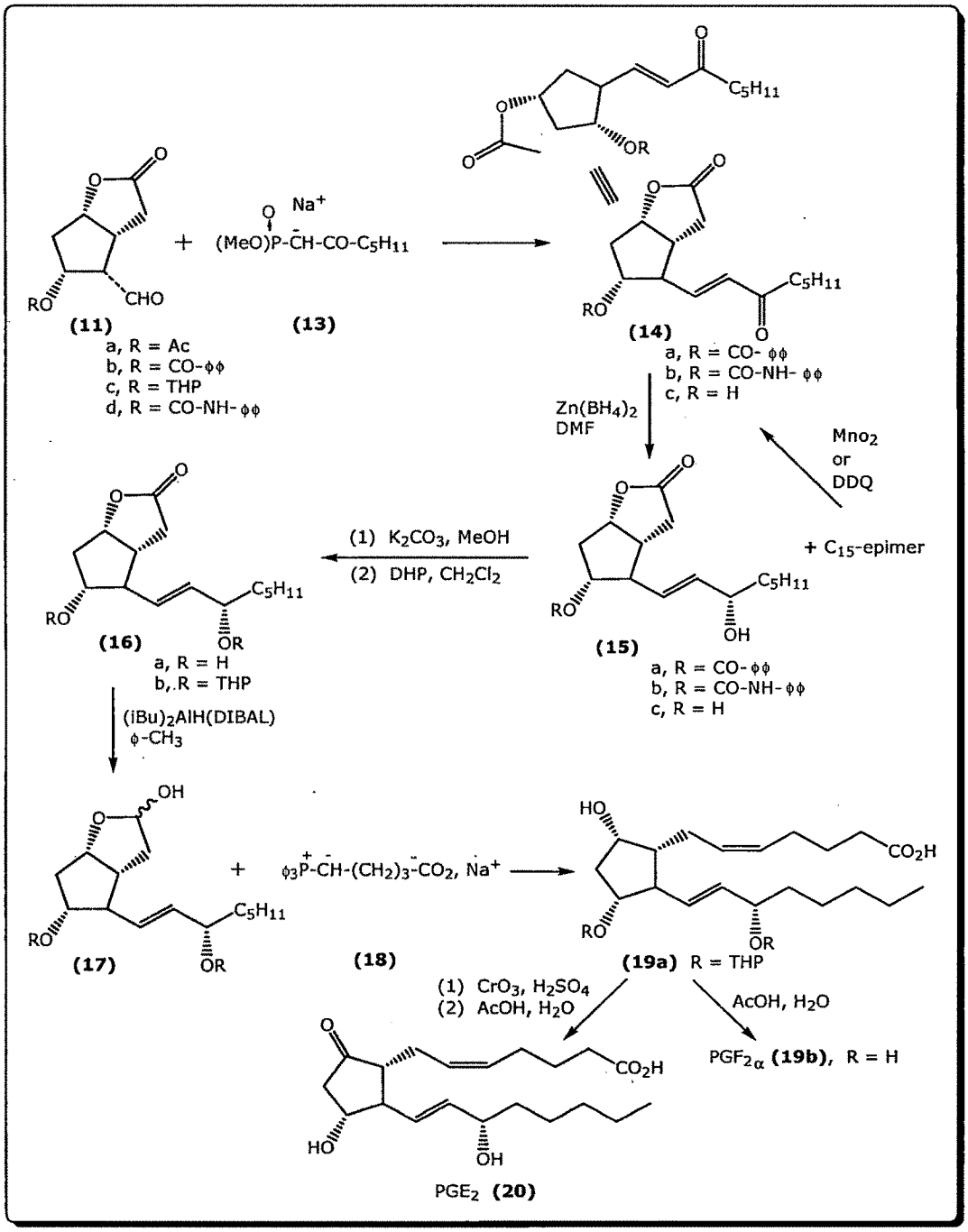
Scheme 1

Esterification of the secondary alcohol group produced the acetate **(8a)**, deiodination with tributyltin hydride gave the acetoxy-lactone **(9a)**, and cleavage of the methyl ether group with boron tribromide afforded the primary alcohol **(10a)**. Collins oxidation then gave the corresponding aldehyde **(11a)**, suitable for a Horner Fmmons reaction[71] of the aldehyde **(11b)** with the sodium salt of dimethyl 2-oxoheptylphosphonate **(13)**. This allowed the enon **(14a)** with the carbonyl at position 15 to give access to the corresponding secondary hydroxyl group. Reduction of the keto group with zinc borohydride, or aluminium isopropoxide [73], prevent the 1,4-reduction product sometimes observed in hydride reductions, and gave a mixture of 15(*R*)- and 15(*S*)-isomers, separated by chromatography. The 15(*R*)-epimer could be recycled by oxidation to the enone **(14)** with dichlorodicyanobenzoquinone (DDQ). Alkaline hydrolysis of the ester group at position 11 (acetate, p-phenylbenzoate, etc.) in the synthetic intermediate **(15)** gave the corresponding 11,15-diol **(16a)**. The hydroxyls at C-11 and C-15 were protected as the bistetrahydropyranyl ether **(16b)**, and the lactone group was then reduced with diisobutylaluminium hydride (DIBAL) in toluene solution [74], thus yielding the hemiacetal **(17)** **(Scheme 2)**.

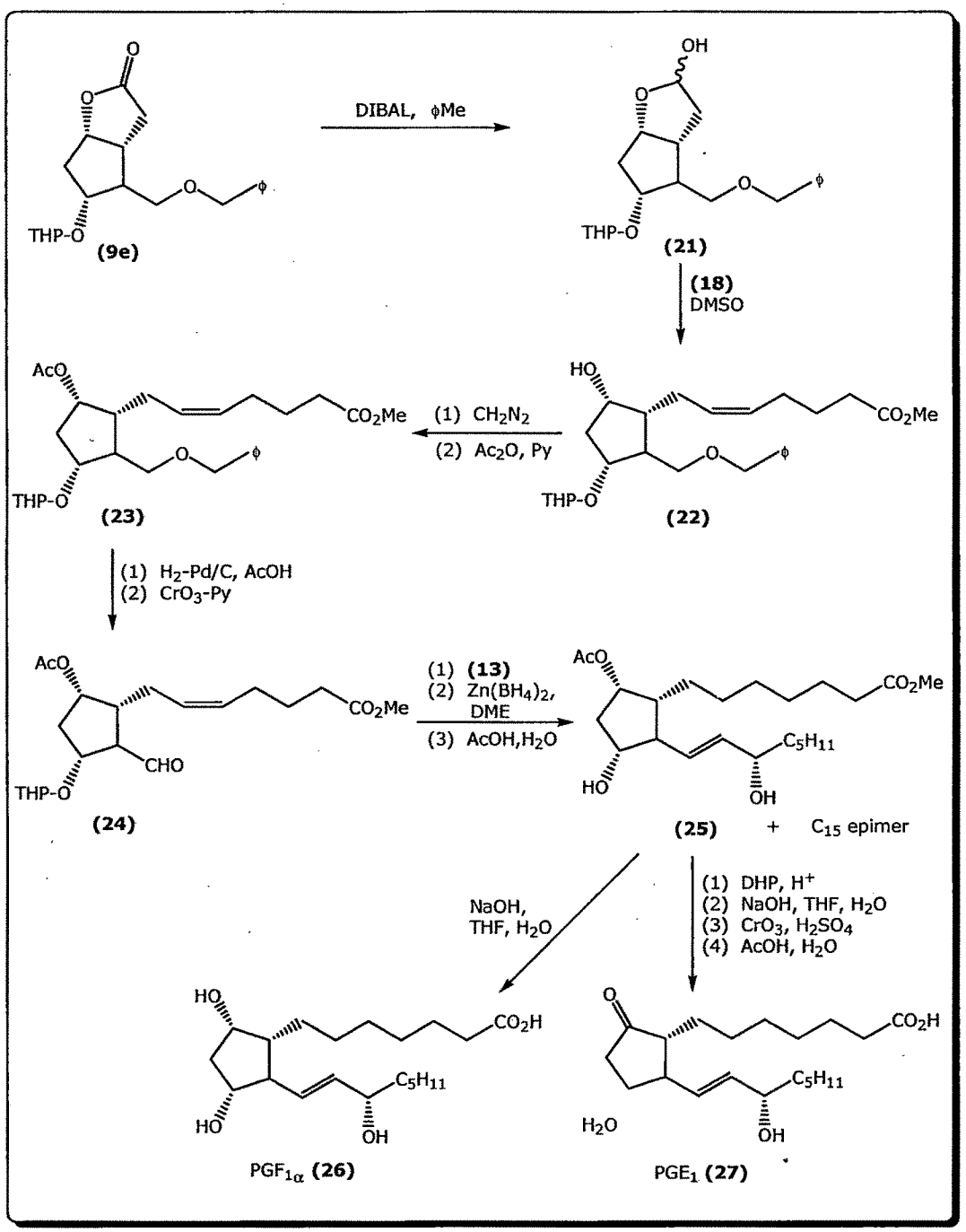
Witting reaction between the intermediate **(17)** and the ylid **(18)** generated from (4-carboxybutyl) triphenylphosphonium bromide and dimsyl sodium in dimethyl sulfoxide (DMSO) provided the bistetrahydropyranyl (THP) ether derivative of $PGF_{2\alpha}$ **(19a)**. Acid hydrolysis of the ether groups in **(19a)** afforded $PGF_{2\alpha}$ **(19b)**. Jones oxidation [75] of the 9-hydroxy group of the bis-THP ether **(19a)** followed by acid treatment yielded PGE_2 **(20)**. From the practical point of view, one of the drawbacks of this synthesis is that it is completely linear, with the consequence of a rapid decrease in yields.

Although PGE of the 2-series can be converted to the 1-series by catalytic hydrogenation, the versatility of the lactone intermediate **(9)** has allowed the preparation of optically active PG in the 1-series by inverting the order of elaboration of the chains **(see Scheme 3)**.[76] Reduction of the lactone **(9e)** with DIBAL gave the lactol **(21)**, which by the Wittig reaction afforded the olefin **(22)**. Catalytic hydrogenation of the intermediate **(22)** properly protected as the methyl ester (C-1)-acetate (C-9), simultaneously reduced the double bond and hydrogenolyzed the ether group to give the primary alcohol, precursor of the aldehyde **(24)**, converted by the conventional sequence to $PGF_{1\alpha}$ **(26)** and E_1 **(27)**.

Finally, PG of the 3-series, i.e., $PGF_{3\alpha}$ **(33)** and E_3 **(34)** have been prepared by a similar route by alkylating the optically active aldehydolactone **(11c)** **(Scheme 1)** with the Wittig reagent **(29)** prepared from (*S*)-(-)-malic acid **(28)** **(Scheme 4)**.[77]

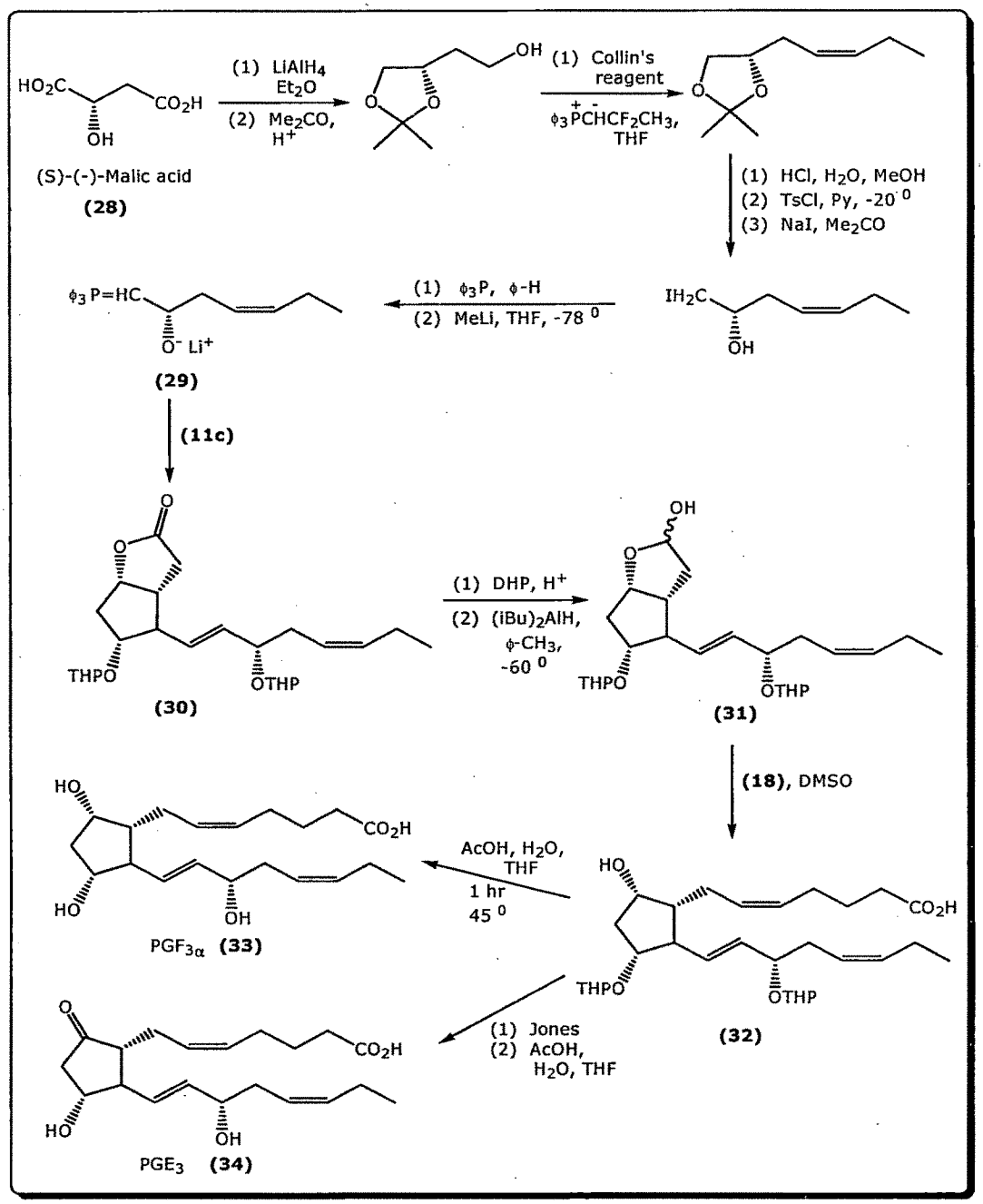


Scheme 2



Scheme 3

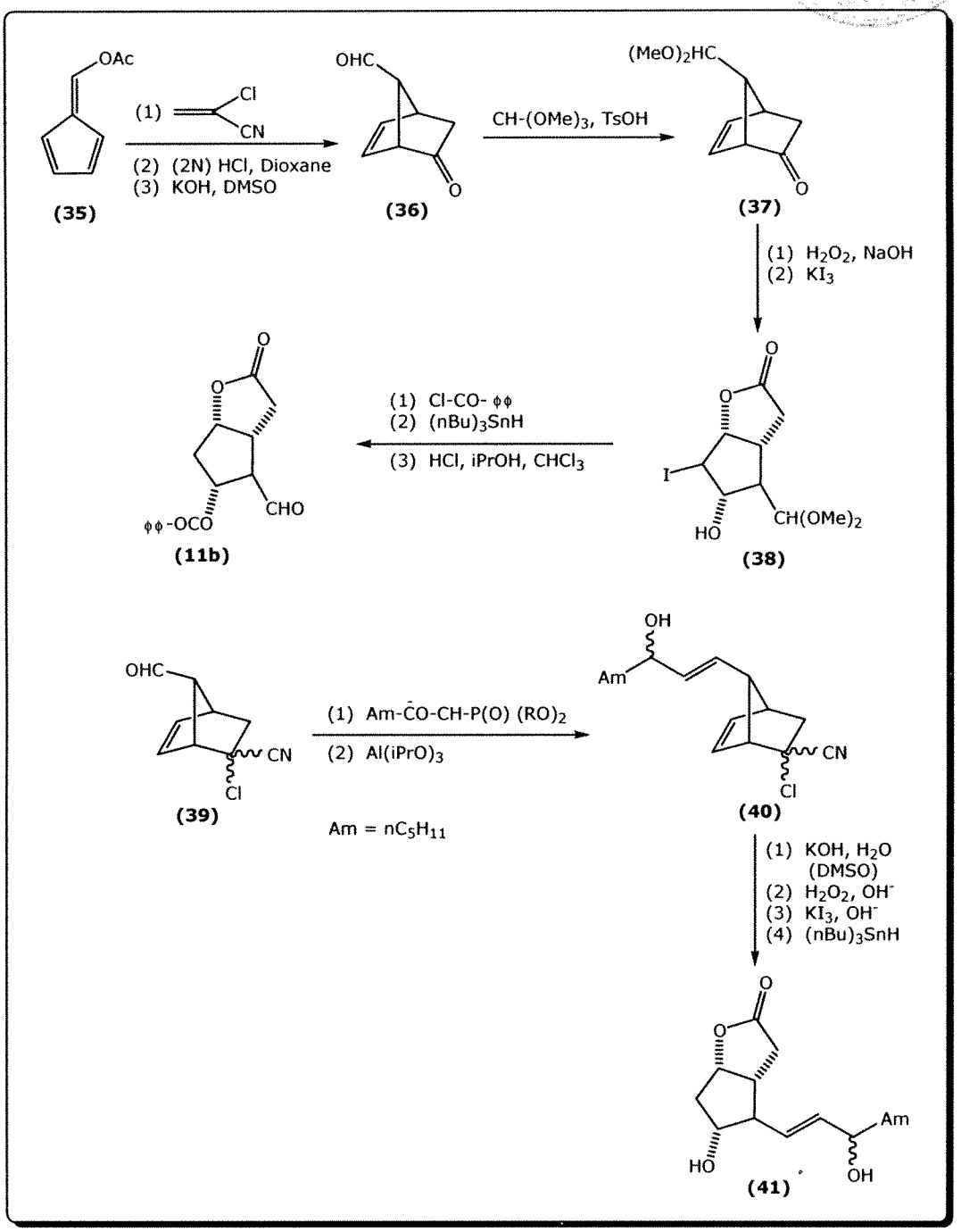
It is interesting to note that condensation of the phosphorane (**29**) with the aldehyde (**11c**) produced the *trans* double bond in contrast to the reaction of the phosphorane (**18**) with the hemiacetal (**17**), which gave the *cis*-olefin.



Scheme 4

A different introduction of the appropriate oxygen functionality in the cyclopentane ring consisted in the use of the acetoxyfulvene (**35**), which was converted to the bicyclic lactone (**11b**) as shown on **Scheme 5**.[79] This route has the advantages over the initial synthesis of not giving isomers before or during the Diels-Alder reaction and of

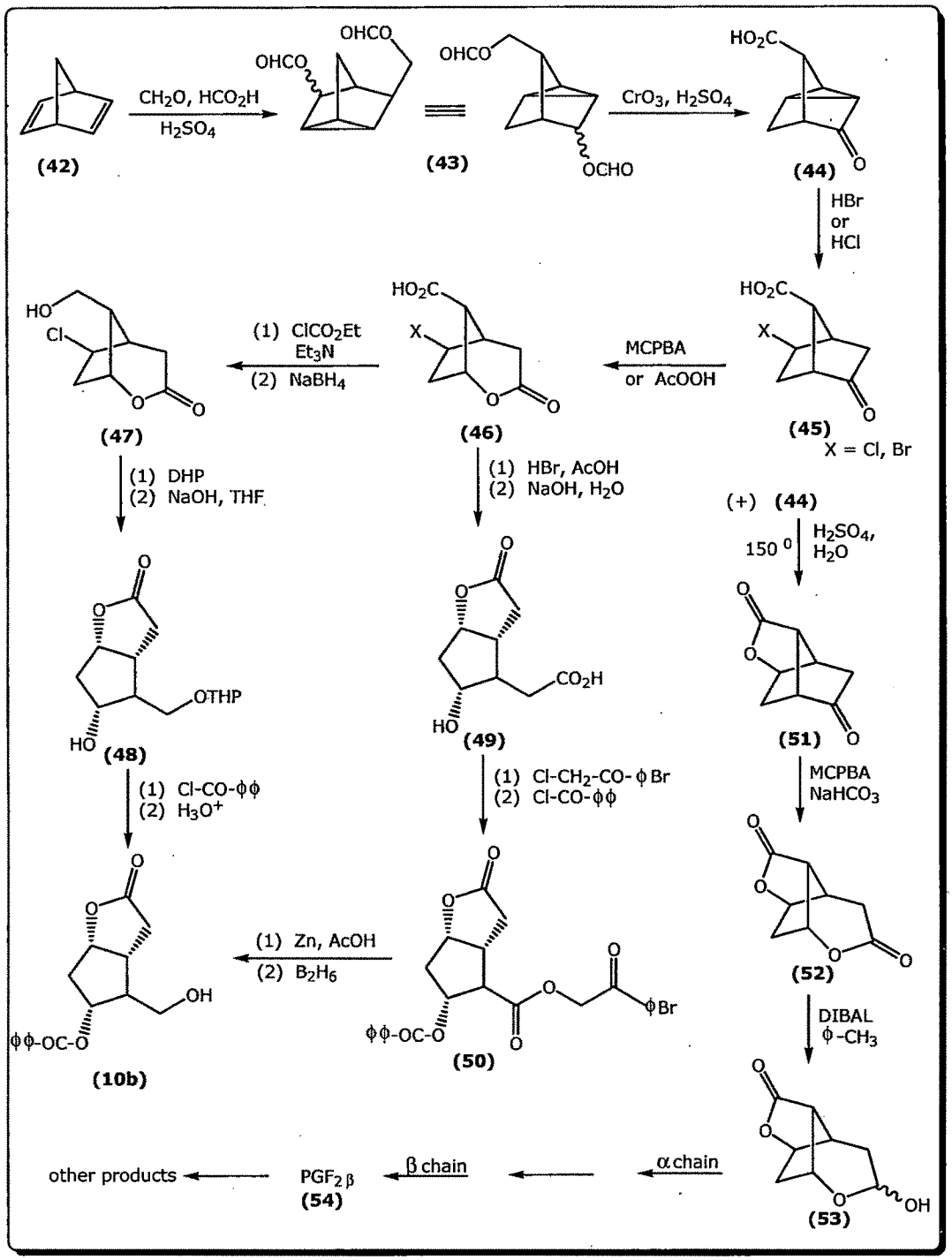
yielding directly the 12-aldehyde group. In order to avoid the use of protecting groups the aldehyde intermediate **(39)** was used to build the chain and then the intermediate **(44)** was transformed to the bicyclic lactone **(41)**.[79]



Scheme 5

As shown in **Scheme 6**, a Prins reaction between norbornadiene (**42**) and formaldehyde plus formic acid yielded the diformate (**43**), which was oxidized to the tricyclic keto acid (**44**). Treatment with either hydrogen chloride or hydrogen bromide gave the corresponding haloketones (**45**), converted to the bicyclic lactones (**46**) by Baeyer-Villiger reaction.[80] The intermediates (**46**) were then transformed to the bicyclic lactone (**45**) by two different routes as shown in **Scheme 6**.[80]

This synthetic pathway presents several attractive features that are worth mentioning. Optically active natural PG can be obtained by this sequences through resolution of the tricyclic acid (**44**) as its (-)-α-methylbenzylammonium salt.[80] Since the dextrorotatory acid (**44**) could be transformed into the hemiacetal lactone (**53**), as shown in **Scheme 6**, this constitutes an attractive potential route for the preparation of a number of PG through $PGF_{2\beta}$ (**54**).


(42)
CH2O, HCO2H
H2SO4
OHCO
OHCO
(43)
OHCO
OCHO
CrO3, H2SO4
HO2C
O
(44)
HBr
or
HCl
HO2C
X
(45)
X = Cl, Br
MCPBA
or AcOOH
HO2C
X
O
(46)
(1) ClCO2Et
Et3N
(2) NaBH4
HO
Cl
O
(47)
(1) DHP
(2) NaOH, THF
(1) HBr, AcOH
(2) NaOH, H2O
(+) (44)
150 0
H2SO4,
H2O
(51)
MCPBA
NaHCO3
(52)
DIBAL
ϕ-CH3
OTHP
HO
(48)
CO2H
HO
(49)
(1) Cl-CH2-CO-ϕBr
(2) Cl-CO-ϕϕ
(1) Cl-CO-ϕϕ
(2) H3O+
OH
ϕϕ-OC-O
(10b)
(1) Zn, AcOH
(2) B2H6
ϕϕ-OC-O
ϕBr
(50)
OH
(53)
α chain
β chain
PGF2β
(54)
other products

Scheme 6

I.5 (3) THE BICYCLO [3.1.0] HEXANE ROUTE

The ring strain in the bicyclo[3.1.0] hexane system makes it very reactive giving rearranged products under appropriate conditions.[49] Thus, with good leaving groups at C-6, bicyclic derivatives of type (**u, Figure I.7**) give cyclohexenols (**v**) under solvolytic conditions.

However, if a carbonium ion can be formed on a carbon atom adjacent to the cyclopropane (**x**), 1,2-alkenyl cyclopentenols (**w**) are formed.[81]

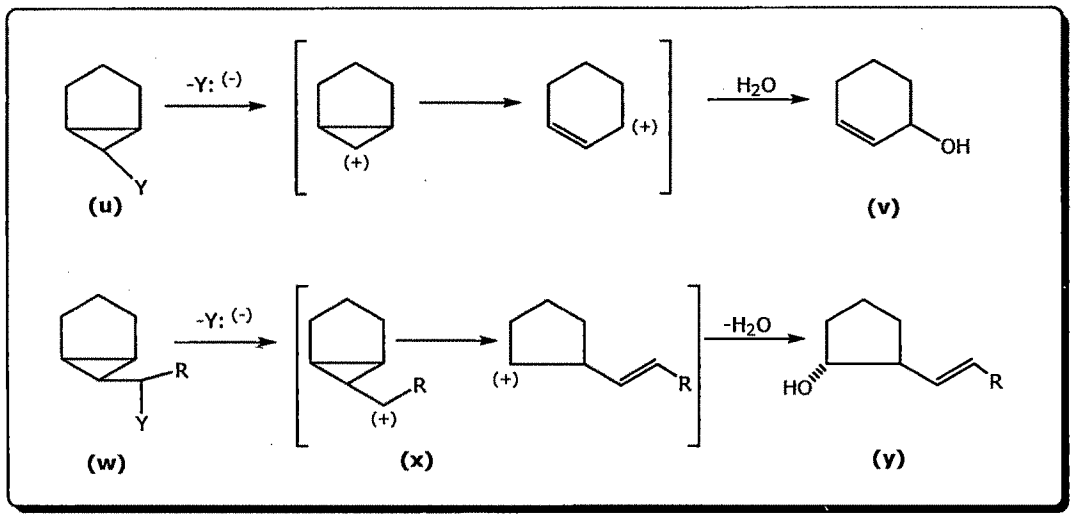
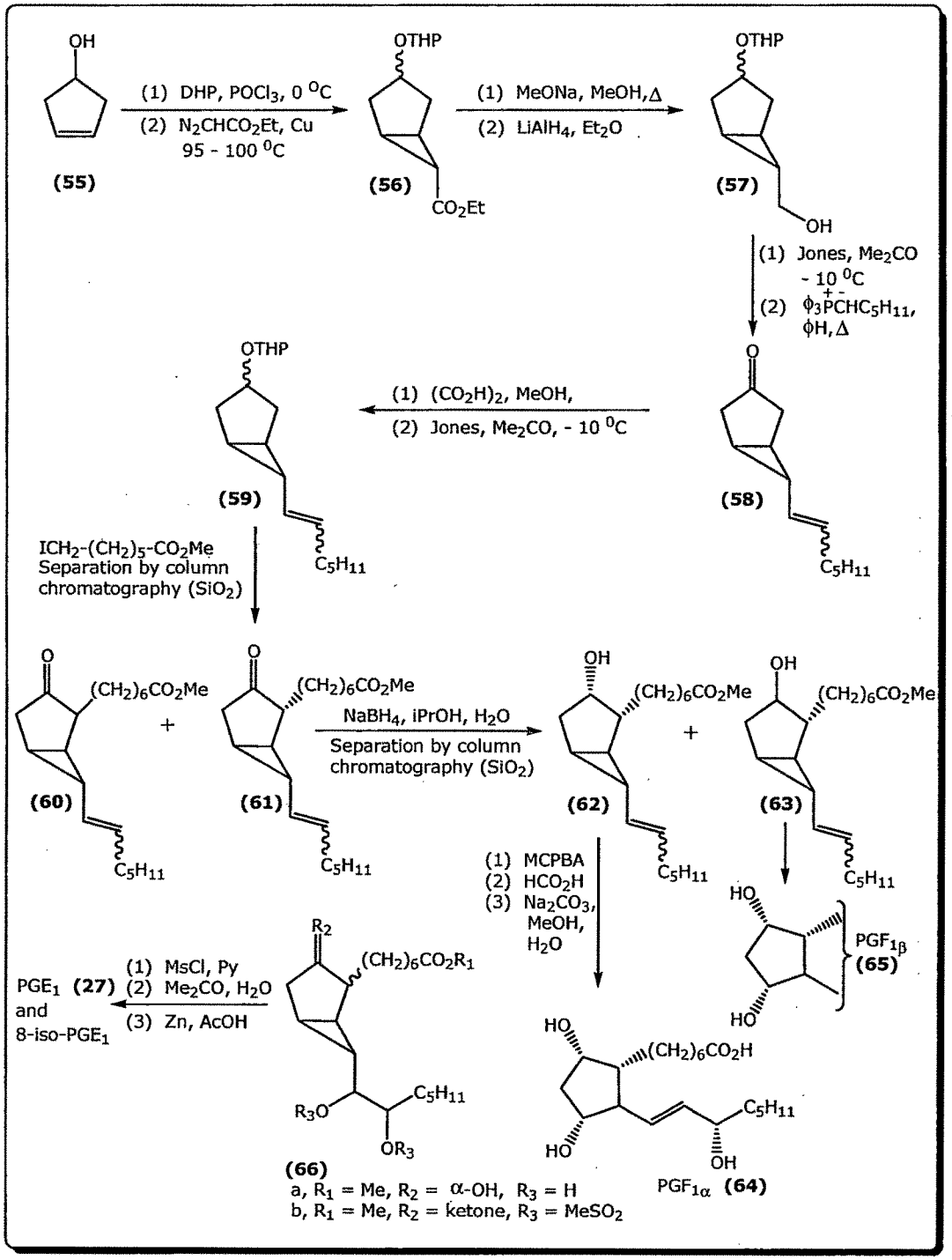


Figure I.7

Since PG may be considered as products of such rearrangement occurring at position 11 and 12, this solvolysis has been used for the synthesis of the lower part of the PG molecule.

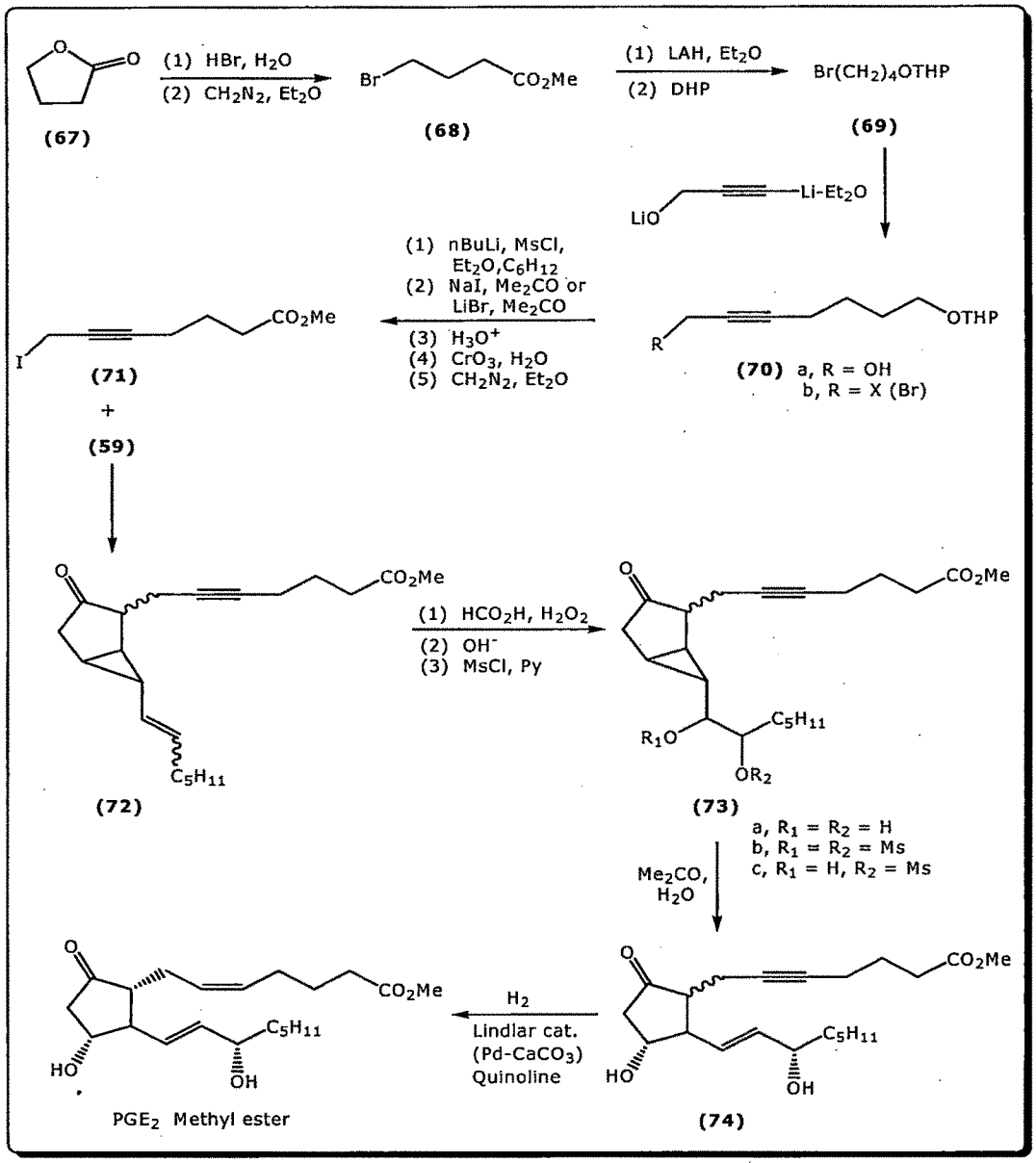
Scheme 7 outlines the total synthesis of $PGF_{1\alpha}$ (**64**).[82,83] The bicyclo[3.1.0] hexane system was prepared from 3-cyclopentenol (**55**) by copper-catalyzed addition of carbethoxycarbene to the THP derivative. After base equilibration to give the *exo*-isomer (**56**), lithium aluminium hydride reduction afforded the primary alcohol (**57**). Oxidation to the corresponding aldehyde was followed by a Wittig reaction, which furnished a mixture of olefins (**58**). Acid hydrolysis of the THP protecting group, followed by Jones oxidation gave the ketone (**59**). Treatment of this intermediate with methyl-7-iodoheptanoate in the presence of potassium tert-butoxide afforded the alkylated

cyclopentanones (**60**) and (**61**), separated by column chromatography. Reduction of the carbonyl group provided the mixture of alcohols (**62**) and (**63**).



Scheme 7

After separation and epoxidation with MCPBA, the corresponding epoxides were solvolyzed. Alkaline hydrolysis of the resulting formats gave PGF_{1_α} (**64**), PGF_{1_β} (**65**), 8-epi-F_{1_α}, and 8-epi-F_{1_β} as their methyl esters.[54,82,83] Unfortunately, the yields in the conversion of the intermediate (**63**) to PGF_{1_α} (**64**) were low, since the nonrearranged glycols (**66a**) constituted the major compounds in these reactions. PGE_1 along with 8-iso-PGE_1 were prepared by solvolysis of the 9-keto-13,14-dimesylates (**66b**).[83]

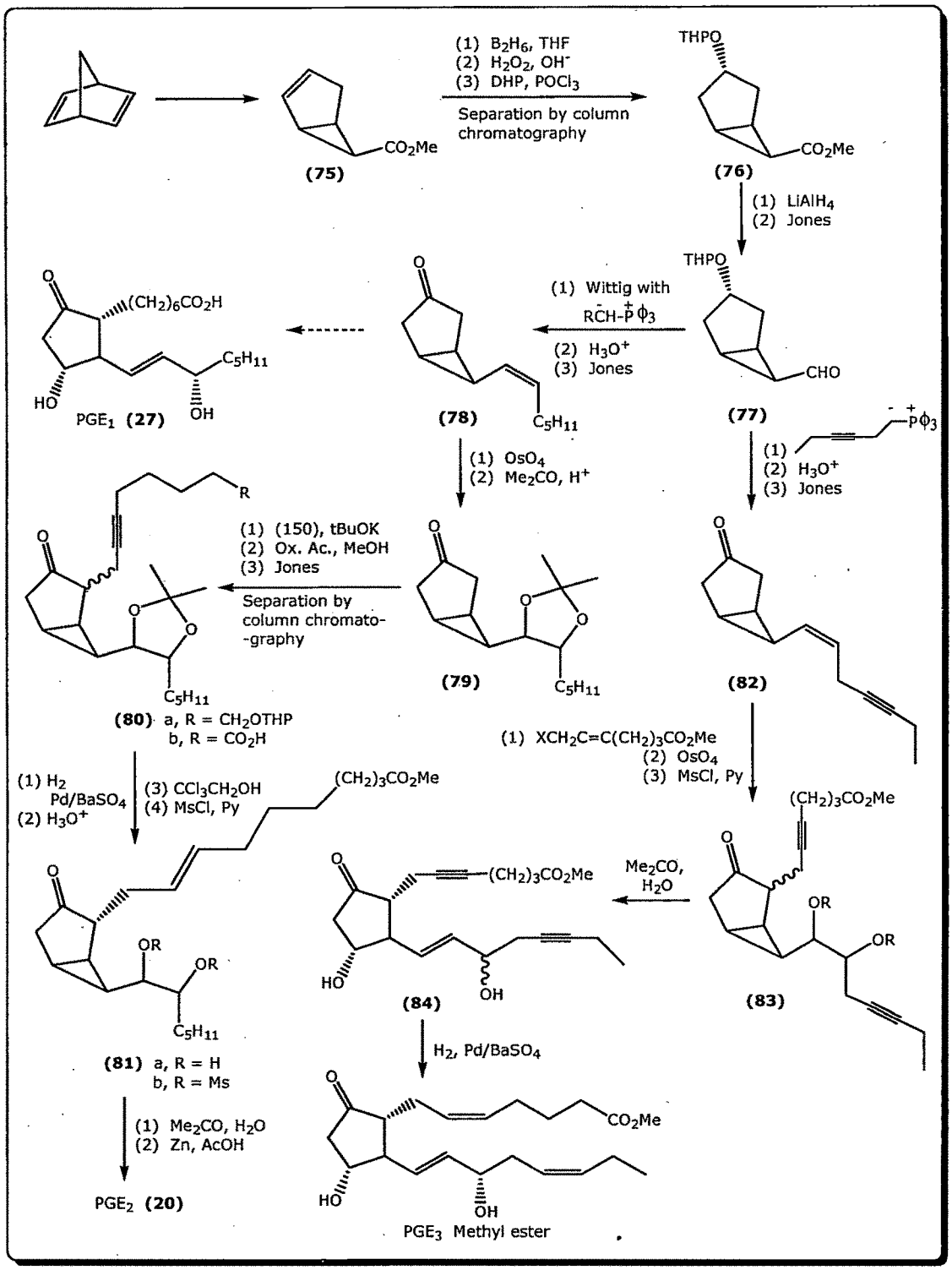


Scheme 8

An appropriate modification of the route described above PGE_2 as its methyl ester [84]. The iodoester (**71**) was obtained from butyrolactone (**67**) by the reaction sequences shown in **Scheme 8**. Alkylation of the key intermediate (**59**) with the iodo ester (**71**) gave the monoalkylated compound (**72**). Hydrocylation of the double bond with performic acid followed by saponification, afforded the glycol (**73a**), which was transformed to the dimethyl derivative (**73b**) and then solvolyzed to give the 5,6-dehydro-PGE_2 derivative (**74**). Selective hydrogenation of the triple bond with Lindlar catalyst yielded PGE_2 methyl ester.

Although the above reaction sequence gives generally good yields, it presents two troublesome steps: the alkylation reaction and the solvolysis. The latter has been thoroughly investigated. It is now established that this solvolytic rearrangement is not a completely concerted process as initially thought and the yields of the rearranged products are always higher with the 8β-isomers. Additionally the isomers with an *endo*-chain give much higher yields than their exo-analogues. These observations induced the Upjohn laboratories to design a second synthesis, shown in **Scheme 9**, which gave much better yields than the initial approach.[85] The known methyl ester (**75**) [86] was converted by hydroboration and oxidation of a mixture of alcohols. The desired ester-alcohol, protected as its THP derivative (**76**), was then transformed to the aldehyde (**77**), which was alkylated to give, after oxidation, the ketone (**78**). This, in turn, was submitted to the reaction sequence described above to afford PGE_1.[85]

Appropriate modifications were necessary to prepare PGE of the 2- and 3-series.[85] For the synthesis of PGE_2 (**20**), the double bond of the intermediate (**78**) was hydroxylated and protected as an acetonide (**79**). Alkylation with the propargyl bromide (**70b, Scheme 8**) gave the substituted cyclopentanone (**80**), which was then transformed to PGE_2 by the classic reaction sequence. For the preparation of PGE_3 methyl ester, the aldehyde (**77**) was submitted to a Wittig reaction with the appropriate acetylenic ylid thus furnishing the ene-yne keto intermediate (**82**). Alkylation at position 8 as above, followed by solvolysis of the proper 13,14-dimesylate (**83**) and catalytic reduction of the triple bonds afforded PGE_3 methyl ester.


(1) B_2H_6, THF
(2) H_2O_2, OH^-
(3) DHP, $POCl_3$
Separation by column chromatography
(75)
(76)
(1) $LiAlH_4$
(2) Jones
(1) Wittig with $R\bar{C}H\text{-}\overset{+}{P}\phi_3$
(2) H_3O^+
(3) Jones
(77)
(78)
PGE1 (27)
(1) OsO_4
(2) Me_2CO, H^+
(1) (150), tBuOK
(2) Ox. Ac., MeOH
(3) Jones
Separation by column chromato--graphy
(79)
(80) a, R = CH_2OTHP
b, R = CO_2H
(82)
(1) $XCH_2C{=}C(CH_2)_3CO_2Me$
(2) OsO_4
(3) MsCl, Py
(1) H_2 $Pd/BaSO_4$
(2) H_3O^+
(3) CCl_3CH_2OH
(4) MsCl, Py
(81) a, R = H
b, R = Ms
Me_2CO, H_2O
(84)
(83)
H_2, $Pd/BaSO_4$
(1) Me_2CO, H_2O
(2) Zn, AcOH
PGE2 (20)
PGE3 Methyl ester

Scheme 9

I.5 (4) THE CYCLOPENTANE EPOXIDE ROUTE

Theoretically, the *trans* configuration between the C-11-hydroxy and C-12 chain in PG of the E and F families should be obtained by opening the cyclopentane epoxide **(a', Figure I.8)** with an appropriate nucleophile to give **(b')**.

The above approach poses some problem. The method cannot be applied directly to the preparation of PG belonging to the E family, due to competition with the internal opening of the epoxide. Additionally, the stereochemistry of the epoxide group and seven-carbon chain or a precursor located at C-8 must be as indicated in formulas **(a')** and **(c')** (i.e., *cis*). Finally and perhaps most importantly the epoxide opening must be highly regioselective, due to the absence of symmetry in the starting epoxide **(a')**. This difficulty is obvious if one considers that the required compound **(g')** (attack at C-12) is the less probable from steric considerations. The developments of new synthetic approaches to PG that are stereoselective, simple, and efficient depend to a large extent on the availability of good methods for the appropriate elaboration of the 3-hydroxy-*trans*-1-octenyl side chain at position 12.

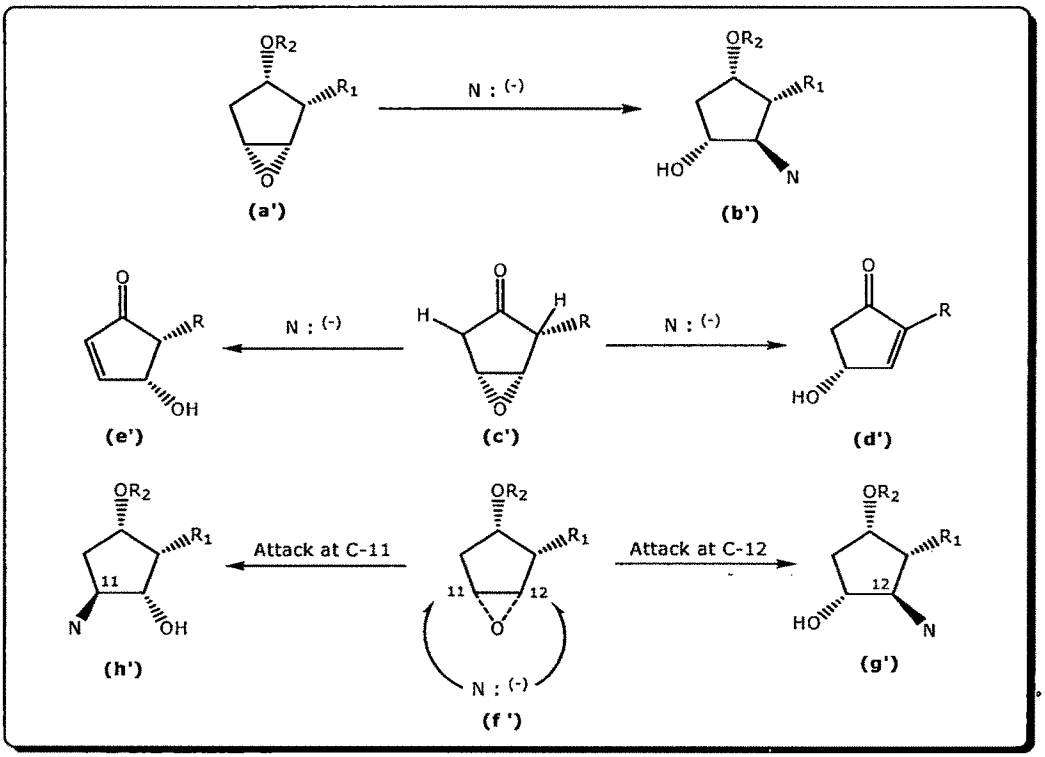
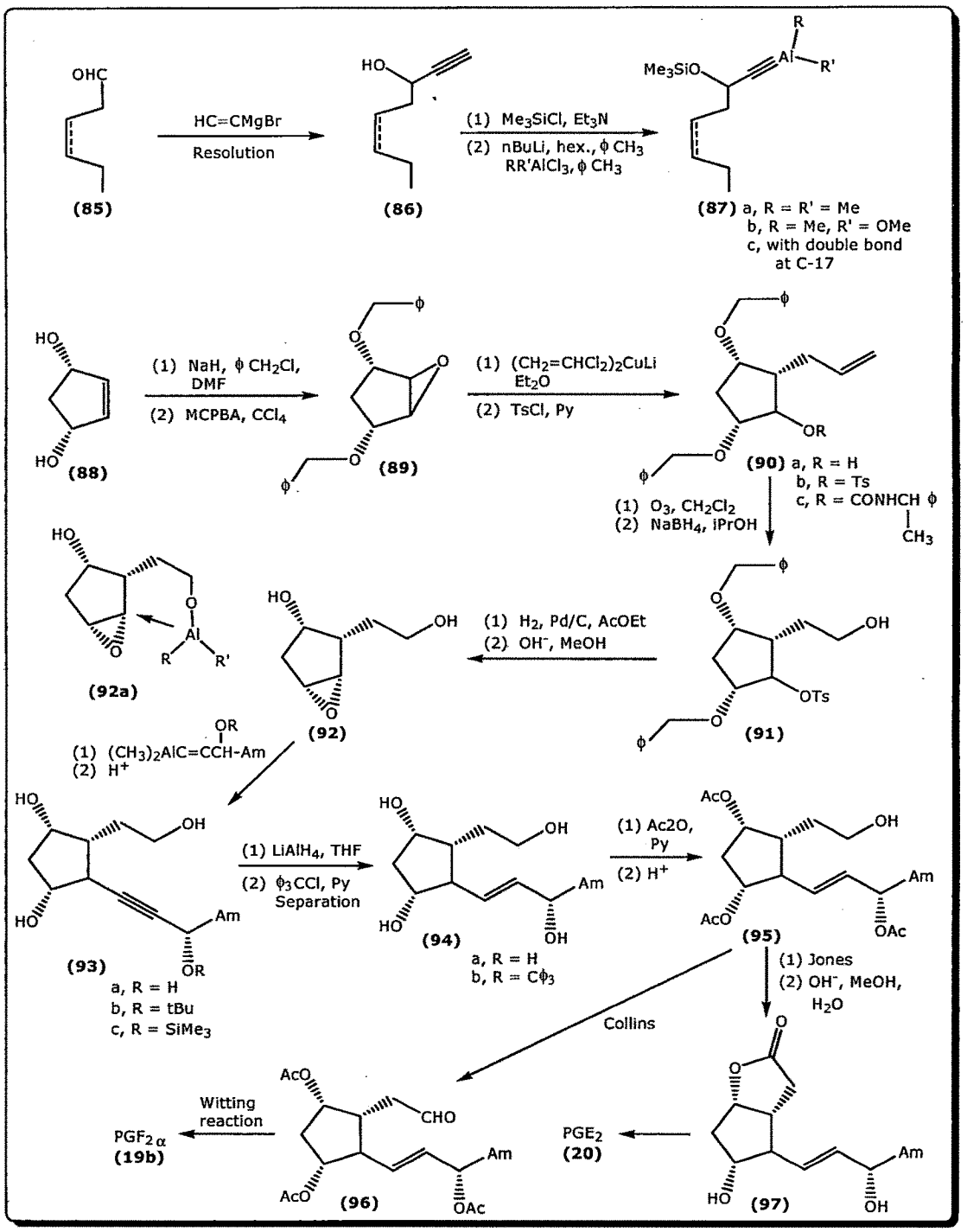


Figure I.8

Although, *a priori* a large range of nucleophiles may be considered for opening the epoxide, reagents such as alanes [87], alkyllithiums, and alkylcuprates [88] were chosen. Perhaps it may be worth noting that Fried and co-workers at the University of Chicago have made the most fundamental contributions in this area. [87, 89]

As shown in **Scheme 10**, the required *cis* relationship between the epoxide ring and the precursor of the seven-carbon chain at C-8 was obtained by an interesting reaction sequence. The protection of the hydroxyl groups in the *cis*-cyclopentene-3,5-diol **(88)** as the dibenzyl ether, followed by epoxidation gave the crucial intermediate **(89)**. The epoxide opening with lithium diallycopper,followed by tosylation afforded compound **(90a)** in high yield. Reaction of the olefin **(90b)** with ozone, followed by reductive work up of the ozonide, catalytic debenzylation and mild alkaline treatment provided the key cyclopentane epoxide **(92)**. Regiospecific epoxide opening with the alkynyl alane **(87a)**, prepared from the aldehyde **(85)**, as shown in **Scheme 10**, gave the intermediate **(93a)**, after acid removal of the protecting group. Reduction of the triple bond of the propargylic system of tetrol **(93a)** with lithium aluminum hydride furnished the allylic alcohol **(94a)** with the correct *trans* configuration. Monotritylation of tetrol **(94a)**, effected with low selectivity [90], gave the trihydroxytrityl ether **(94b)**, which was acetylated and hydrolyzed with acid to afford the free primary hydroxyl derivative **(95)**. Collins oxidation to the aldehyde **(96)**, followed by reaction in DMSO with excess Wittig reagent generated from (4-carboxybutyl) triphenylphosphonium bromide and dimsylsodium, followed by base hydrolysis yielded PGF_{2_α} **(19b)**. For the synthesis of PGE_2 **(20)**, the intermediate **(95)** was converted to the known bicyclic lactone intermediate **(97)**. The conversion of lactone **(97)** to PGE_2 **(20)** and then to PGE_1 and PGF_{1_α}. Prostaglandins of 3-series have also been prepared by this route, using the appropriate alkynyl alane **(87c)** with the *cis*-double bond.[89] The identification of the reagent responsible for the regiospecific alkylation of the epoxide **(92)** has been established. It has been shown to be a methoxy-methyl alkynylalane of type **(87b)**.[91] The resolution was performed at an early stage of the synthesis [92] on the alcohol **(90a)**. Its (+)-phenethyl urethane **(90c)** was hydrolyzed with base to afford the alcohol **(90a)** in the optically active form, which in turn was converted to the natural PG. Another way to prepare optically active material was to couple (*S*)-(-)-alkynylalane **(87)** with the racemic

epoxydiol (**92**). After separation of the resulting diastereoisomers and completion of the synthesis, the natural PG was obtained.



Scheme 10

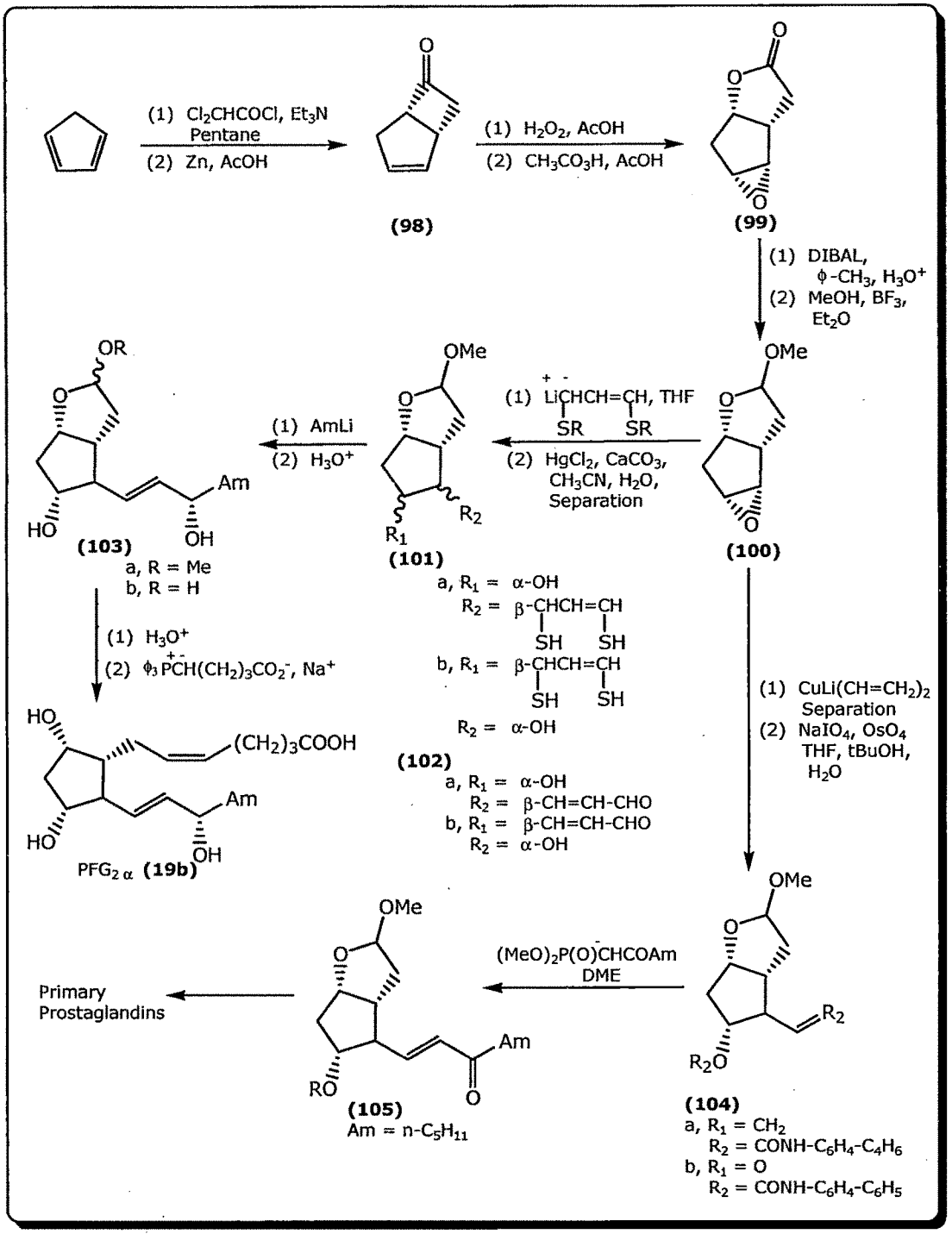
In the synthesis outlined in **Scheme 27** the *cis*-epoxylactone **(99)** was prepare in high yield from cyclopentadiene by addition of dichloroketene, followed by dechlorination with zinc, Baeyer-Villiger oxidation and epoxidation.[93] In order to protect the lactone **(99)** from nucleophilic attack, it was transformed quantitatively to the mixed acetal **(100)** by DIBAL reduction followed by reaction with methanol in the presence of boron trifluoride etherate.[93,94] The intermediate **(100)**, which presents the required *cis* relationship between the epoxide and the precursor of the seven-carbon chain at C-8, was treated with the functionalized allyllithium (i = RS-$\bar{C}$H-CH=CH-SR, Li^+) to provide a mixture of regio isomers **(101a)** and **(101b)**. Hydrolysis with a mercuric salt and chromatographic separation gave the corresponding conjugated aldehydes **(102a)** and **(102b)**. The desired isomer **(102a)** was treated with n-amyllithium to afford a mixture of alcohols from which the 15(*S*)-isomer **(103a)** was separated by chromatography. Acid hydrolysis and the classical alkylation of the hemiacetal **(103b)** with the appropriate Wittig reagent then gave $PGF_{2\alpha}$ **(19b)**.

When the epoxide opening was performed with lithium divinylcopper, the alkylation was much more regioselective, yielding mainly the desired isomer, which was separated through its p-phenylphenylurethane **(104a)**. The conversion of the vinyl group into an aldehyde was performed by sodium periodate treatment in the presence of a catalytic amount of osmium tetroxide. The aldehyde was then alkylated to provide the known enone intermediate **(105)** [95,96], which was further converted to the primary PG. [93]

Some particular features of this synthesis are worth discussing. The *cis* relationship between the epoxide and the lactone group in compound **(99)** was carefully established. [93] Hence, the epoxidation of the unsaturated lactone with peroxyacetic acid is higly stereoelective, perhaps due to the vicinal assistance of the lactone group.

The most novel aspect of this synthesis **(Scheme 11)** is probably the high regioselective observed during the opening of the epoxide **(100)** with lithium divinylcopper. It should be mentioned that the ketal **(100)** has been obtained in the optically active form [98], so that this route constitutes an appropriate approach to the synthesis of natural PG.

Finally, an elegant new approach to PG synthesis via a methylenecyclopentanone has been reported by Stock and Isobe. [97]


(1) Cl2CHCOCl, Et3N
Pentane
(2) Zn, AcOH
(98)
(1) H2O2, AcOH
(2) CH3CO3H, AcOH
(99)
(1) DIBAL, ϕ-CH3, H3O+
(2) MeOH, BF3, Et2O
(100)
(1) LiCHCH=CH, THF
SR SR
(2) HgCl2, CaCO3, CH3CN, H2O, Separation
(101)
a, R1 = α-OH
R2 = β-CHCH=CH
SH SH
b, R1 = β-CHCH=CH
SH SH
R2 = α-OH
(102)
a, R1 = α-OH
R2 = β-CH=CH-CHO
b, R1 = β-CH=CH-CHO
R2 = α-OH
(1) AmLi
(2) H3O+
(103)
a, R = Me
b, R = H
(1) H3O+
(2) ϕ3P+CH(CH2)3CO2-, Na+
PFG2α (19b)
(1) CuLi(CH=CH2)2
Separation
(2) NaIO4, OsO4
THF, tBuOH, H2O
(104)
a, R1 = CH2
R2 = CONH-C6H4-C4H6
b, R1 = O
R2 = CONH-C6H4-C6H5
(MeO)2P(O)CHCOAm
DME
(105)
Am = n-C5H11
Primary Prostaglandins

Scheme 11

I.5 (5) THE 1,4-ADDITION ROUTE

The fact that PG of the E family can be converted more easily to those belonging to other families than vice versa has made PGE the objective of most Synthesis. There are essentially two ways to introduce the seven-carbon chain at C-8 and the eight-carbon chain at C-12 for PG of the E family. On the one hand, the most direct route consists in the alkylation of the enolate (**i', Figure I.9**) of ketone (**h'**), which affords the alkylated cyclopentanone (**j'**). This is then converted to an appropriate entity for the introduction of the lower chain.

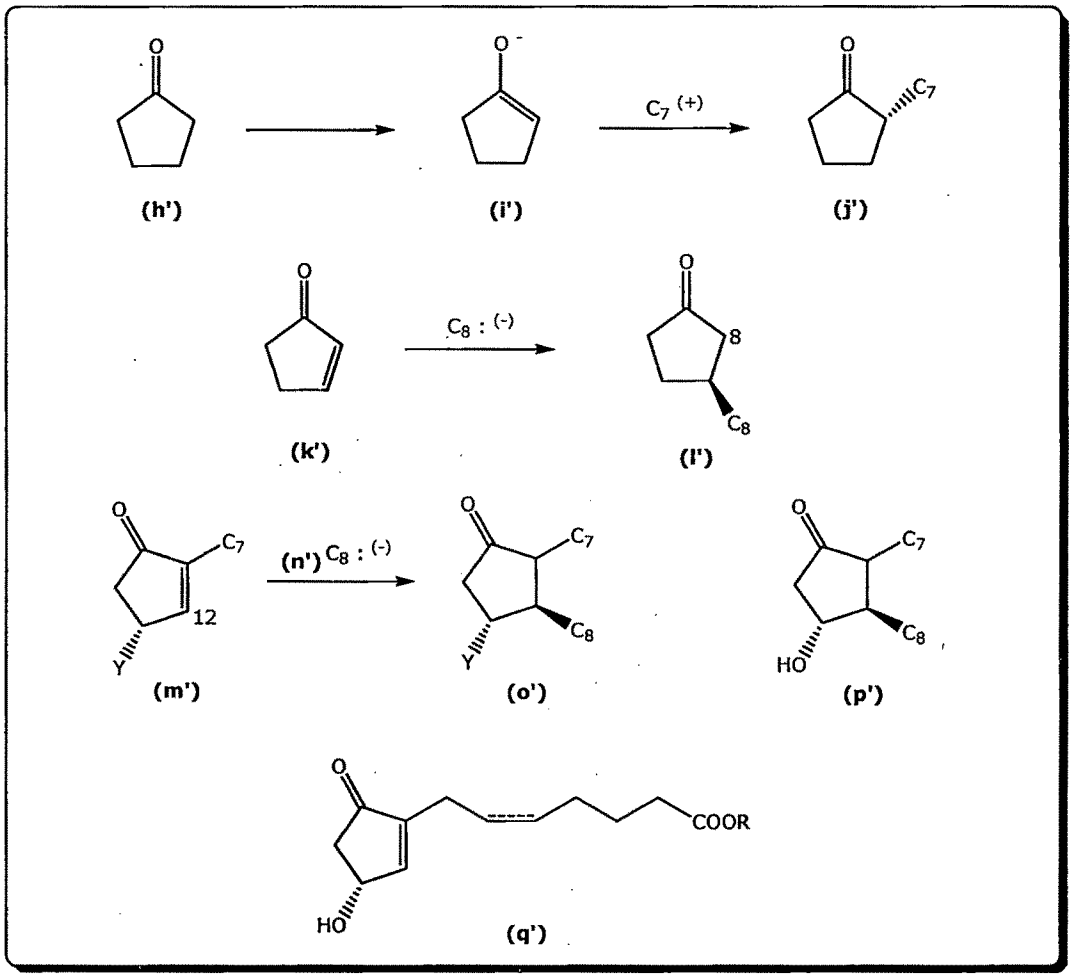


Figure I.9

On the other hand, Michael addition to a cyclopentenone (**k'**) permits the introduction of the lower chain of the PG molecule or a precursor thereof. This is then followed by appropriate alkylation at position 8.

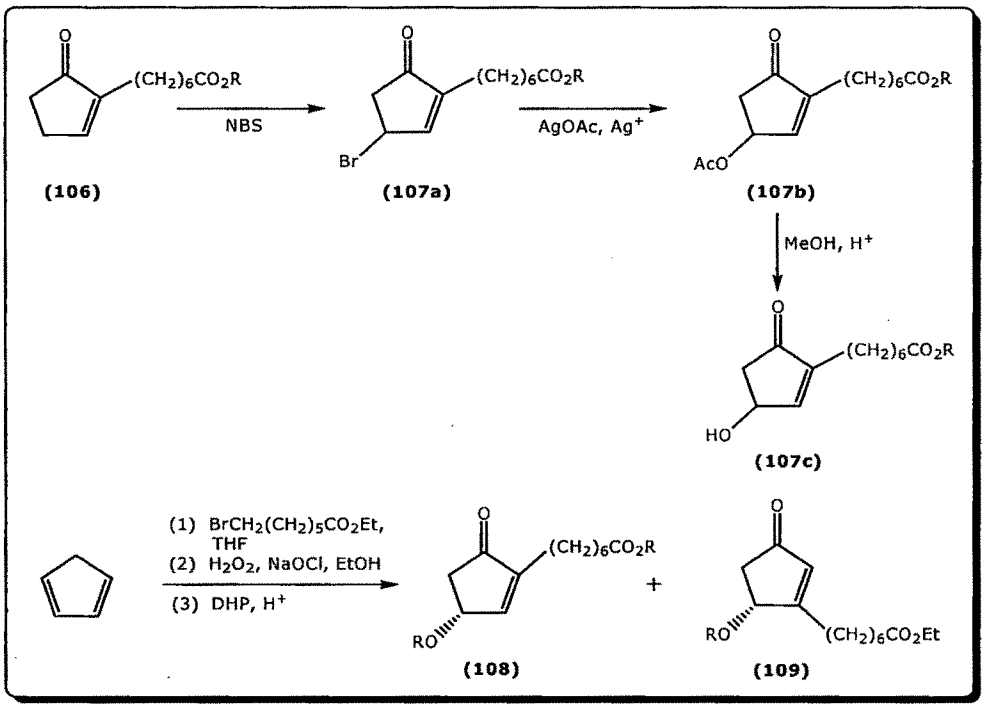
The first approach has already been commented on in connection with other Synthesis. The general scheme for the Michael addition type synthesis consists in preparing the appropriate cyclopentenone **(m')** with the C-7 chain, to which the eight-carbon fragment **(n')**, or a precursor, can be added. The methodology used for the preparation of fragments **(m')** and **(n')**, as well as the characteristics that **(m')** and **(n')** should present, differentiate the various Synthesis of this discussion.

The *trans* relationship among the cyclopentanone substituents will only be obtained if the fragment **(n')** attacks the enone **(m')** at position 12 *trans* with respect to the substituent Y. This is generally the case for steric reasons. Moreover, since Michael addition conditions produce the enolate, at the C-8 position, the stereochemistry of the final product has usually the thermodynamically more stable all-*trans* configuration. Granted these premises, the choice of a hydroxyl as Y group in formula **(m')** was obvious. In fact, most of the Synthesis used 4-hydroxycyclopentenones of type **(q')**.

I.5 (5a) Synthesis of Hydroxycyclopentenones

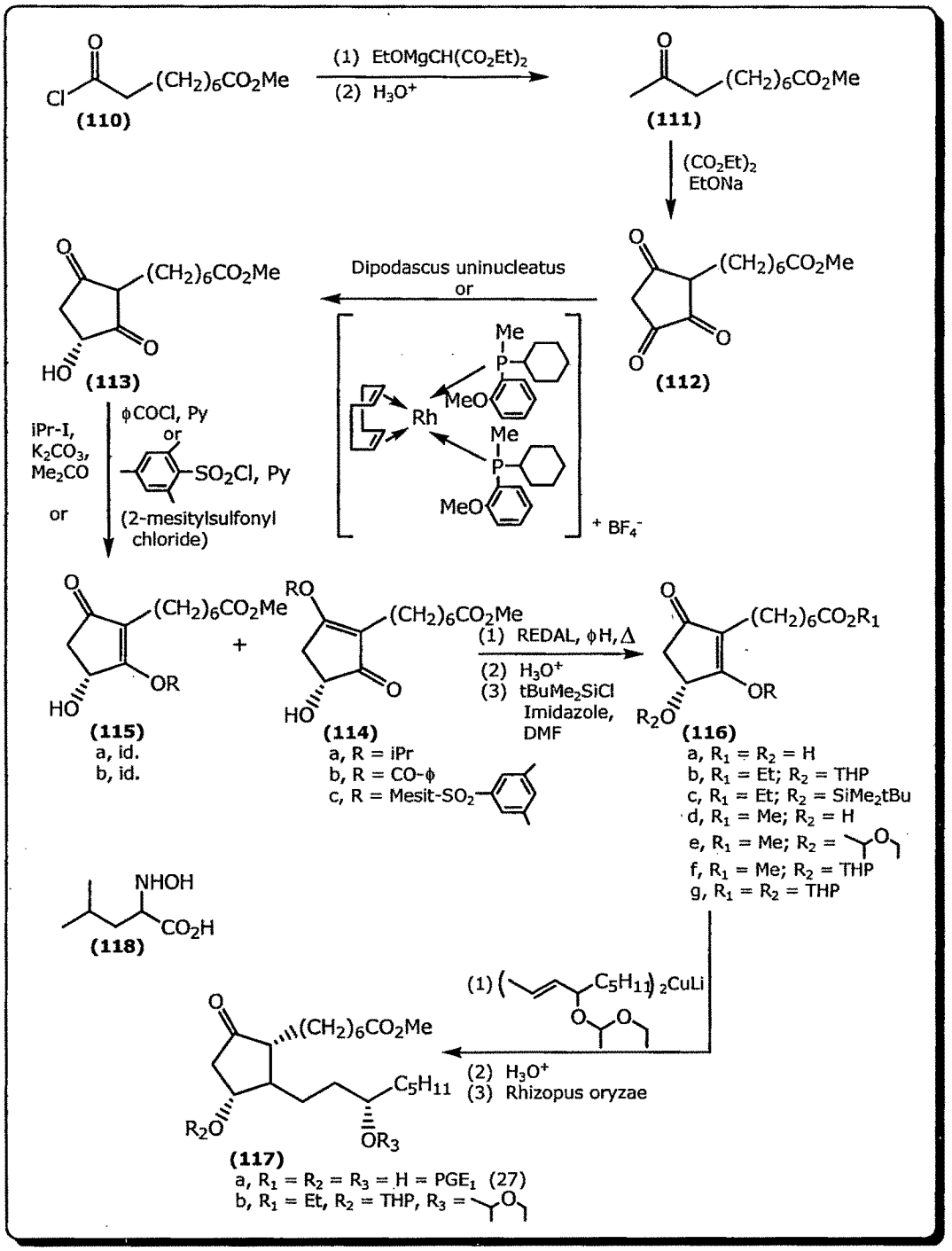
The method used by DePuy [99] for the preparation of 4-hydroxycyclopentenone has been applied to the synthesis of cyclopentenone **(106)**. As shown in **Scheme 12**, treatment of cyclopentenone **(106)** with N-bromosuccinimide (NBS) gave the bromo compound **(107a)**. Acetolysis in the presence of silver salts afforded the acetate **(107b)**, which by acid catalyzed hydrolysis provided the 4-hydroxycyclopentenone **(107c)** in moderate yields. Microbiological hydroxylation of cyclopentenone **(106)** with *Aspergillusniger* not only afforded 4-hydroxycyclopentenone **(107c)** in reasonable yields, but also effected partial asymmetric induction [100], making this technique particularly interesting and useful. Both (*R*)- and (*S*)-4-hydroxy-2-cyclopentenones **(107c)** have been prepared from D- and L-tartaric acids, respectively.[101]

Another very short synthesis of a hydroxylated cyclopentenone was reported by Sih and co-workers [102] who alkylated cyclopentadiene with ethyl-7-bromoheptanoate, and then oxidized the adduct with singlet oxygen. This furnished a mixture of isomeric cyclopentenones **(108)** and **(109)**, which were separated by column chromatography. A more synthesis afforded intermediate **(108)** in the optically active form by selective asymmetric reduction.[103, 104]



Scheme 12

In **Scheme 13**, the acid chloride **(110)** was transformed to the methyl ketone **(111)** by Bowman's method [105] (treatment of the acid chloride with the ethoxymangnesium salt of diethyl malonate), followed by hydrolysis and decarboxylation. The trione **(112)** was then prepared by a known procedure.[106] The selective asymmetric reduction of trione **(112)** was achieved both microbiologically and catalytically.[103,104] On the one hand, treatment of the triketone **(112)** with *Dipodascus uninucleatus* gave stereospecifically the 11-(*R*)-alcohol **(113)** in high yield. On the other hand, catalytic hydrogenation of compound **(112)** in the presence of (1,5-cyclooctadiene)bis(O-anisylcyclohexymethylhphosphine) rodiumx (I) tetrafluoroborate yielded the same alcohol **(113)**. The conversion of the 1,3-dione system **(113)** to the enone **(116)** could be achieved without racemization of the alcohol group both by a known sequence [107] as well as by modification. The method consisted of the formation of the enol ether **(114a)** of the 1,3-dicarbonyl system, followed by reduction with an appropriate hydride and acid hydrolysis. In the modification, the enol benzoate **(114b)** was used instead of the enol ester **(114a)**.



Scheme 13

The selective observed in the transformation of the diketone **(113)** to its enol **(114)** is noteworthy. The preferred formation of enol **(114)** instead of its isomer **(115)**

seems to be attributable to steric factors. One should be able still to improve the selectivity by increasing the size of the group R in the enol (**114**), as evidence with the mesityl sulfonyl ester, which was a considerable improvement.[103, 104]

A similar synthesis has been reported [108], in which in place of a microbiological reduction, a resolution of the hydroxycyclopentenone (**116**) was achieved via the (*R*)-2-aminoxy-4-methylvaleric acid (**118**) derivative. Regeneration of the carbonyl group was effected by reduction of the oximino derivative with titanium trichloride.

I.5 (5b) 1,4-Dialkylcopper Addition

Although theoretically a large variety of reagents can be added to the aforementioned cyclopentenones in a Michael reaction, only a few of them fulfill the requirements for the construction of PG. Lithium dialkylcopper and Grignard reagents in the presence of copper salts [109] have been widely used in PG synthesis. Since the building of the lower chain through the coupling of an aldehyde group at position 12 and a fragment containing seven carbon atoms has been so fruitful, the intermediate objective of several groups has been to prepare an aldehyde of type (**s', Figure I.10**) from (**r'**). The synthesis is then usually completed by one of the known methods.

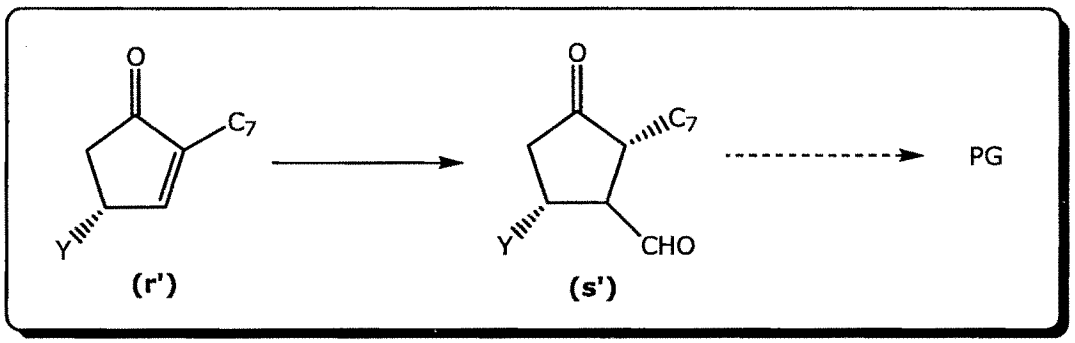
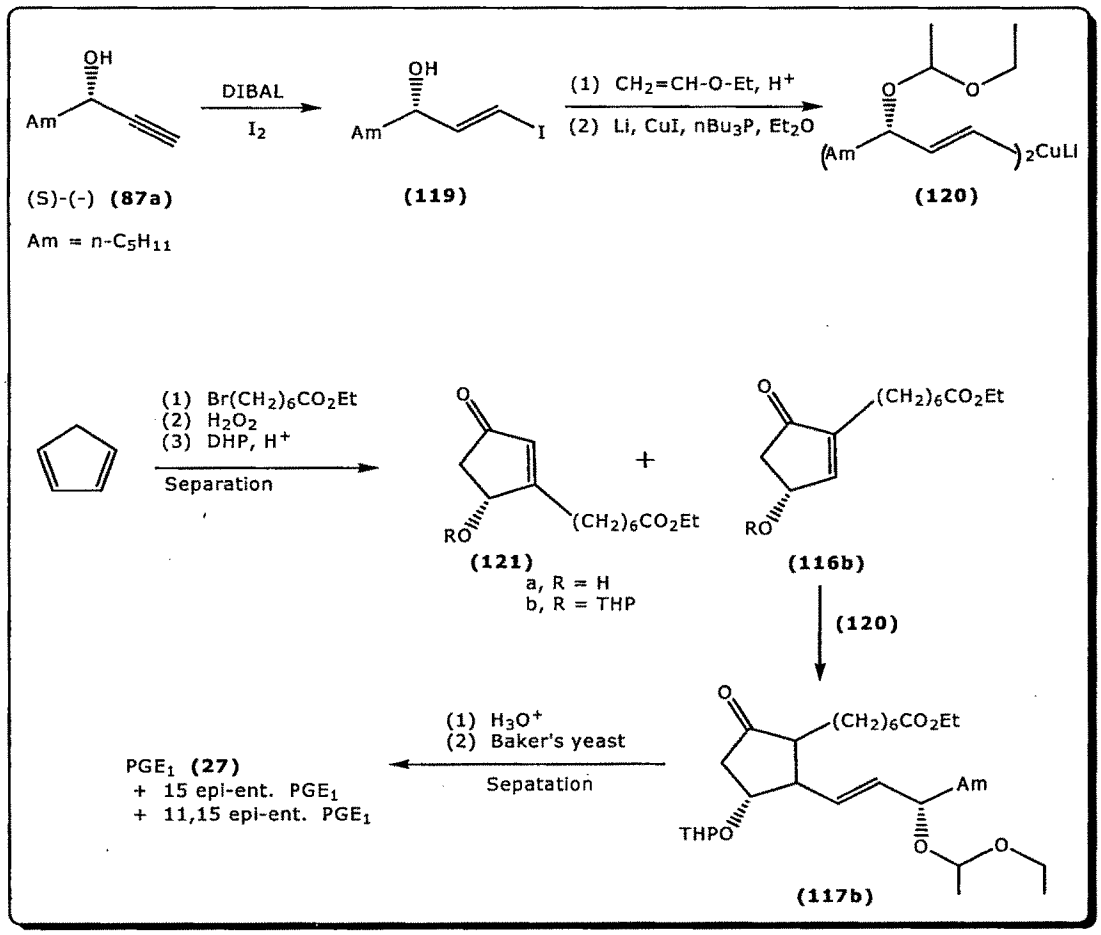


Figure I.10

However, in agreement with the general theory on total synthesis [92], the above process should be less efficient than the introduction of the complete lower chain by 1,4-addition. The first direct PG synthesis using a 1,4 Michael addition reaction was reported by Sih *et al.*, [110] using cuprate (**120**) and hydroxyenone (**116b**) (**see Scheme 13**) to prepare PGE_1, as outlined in **Scheme 14**. The cuprate (**120**) was prepared from (*S*)-(-)-octynyl alcohol (**87a**) (**Scheme 10**)[87,89], which by hydroalumination, followed by

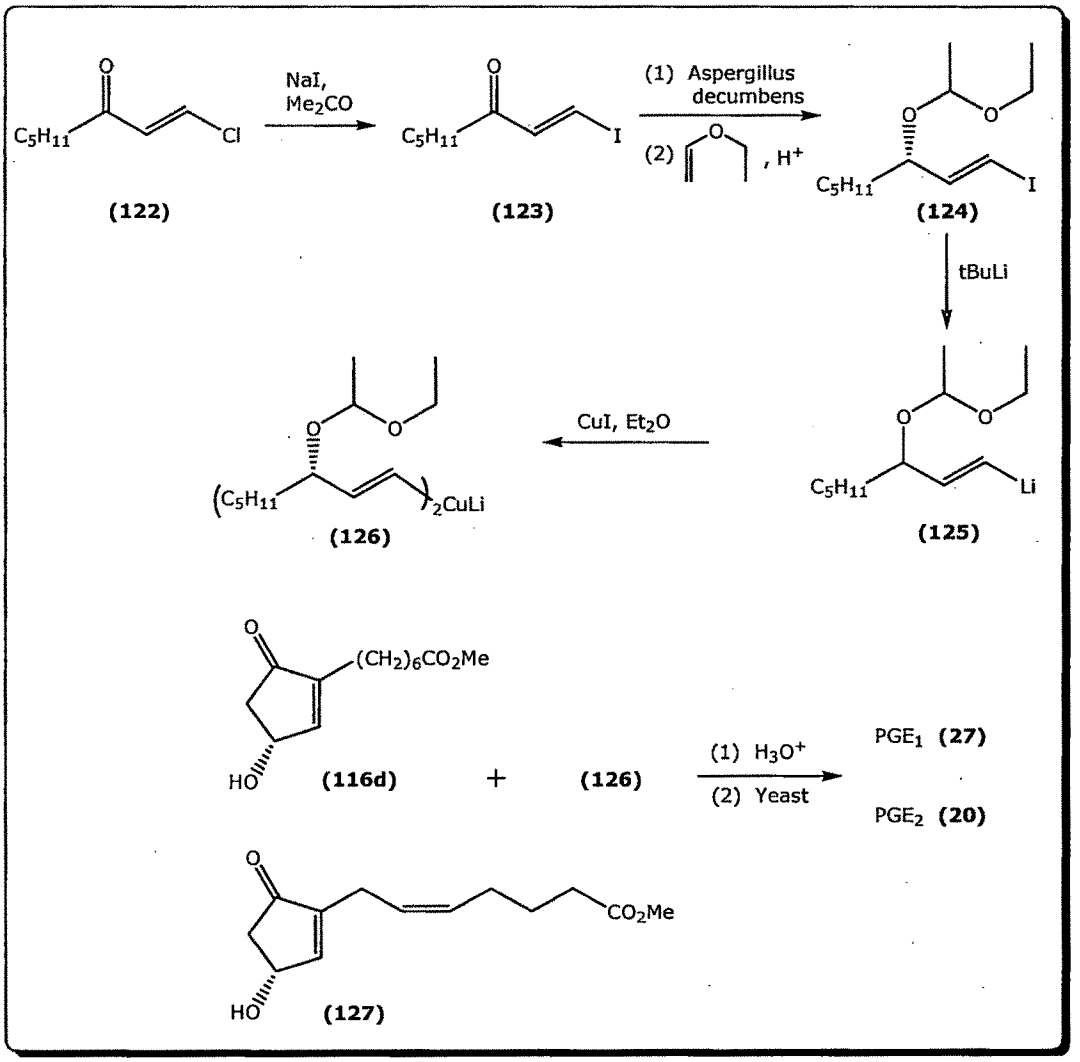
treatment of the vinylalane with iodine gave the intermediate (**119**). Since the hydroalumination reaction is a *cis* addition and the substitution of the dialkylalane group by iodine occurs with retention of configuration, a *trans* geometry is obtained for the double bond. Protection of the alcohol group (**119**) as its α-ethoxyethyl ether, followed by reaction with metallic lithium gave the corresponding lithium derivative, which could be transformed to the required cuprate with the cuprous iodide-tri-n-butyl phosphine complex in ether. Coupling of the optically active cuprate (**120**) with the racemic enone (**116b**), gave compound (**117b**). Acid cleavage of the ether protecting groups, seponification of the ester with baker's yeast, and chromatographic separation of the resulting mixture gave PGE_1, along with the enantiomer of 15-epi-PGE_1 and the enantiomer of 11,15-diepi-PGE_1.



Scheme 14

Later, the total Synthesis of PGE_1 **(27)** and PGE_2 **(20)** by completely asymmetric methods were reported.[103,104,111] This achieved by the coupling of the optically active fragments **(116b)** and **(120)**.

Another route, shown in **Scheme 15**, used the known chlorovinylketone **(112)**, which was transformed to its iodo analogue **(123)**.[112] Whereas asymmetric microbiological reduction of the enone **(123)** with *Penicillium decumbens* produced the (*S*)-(+)-alcohol **(124)**, with *Aspergullus ustus* the (*R*)-(-)-isomer was obtained in low yield. The noteworthy feature of these reactions is that they constitute the first cases of microbiological reduction of an enone to the corresponding allylic alcohol.



Scheme 15

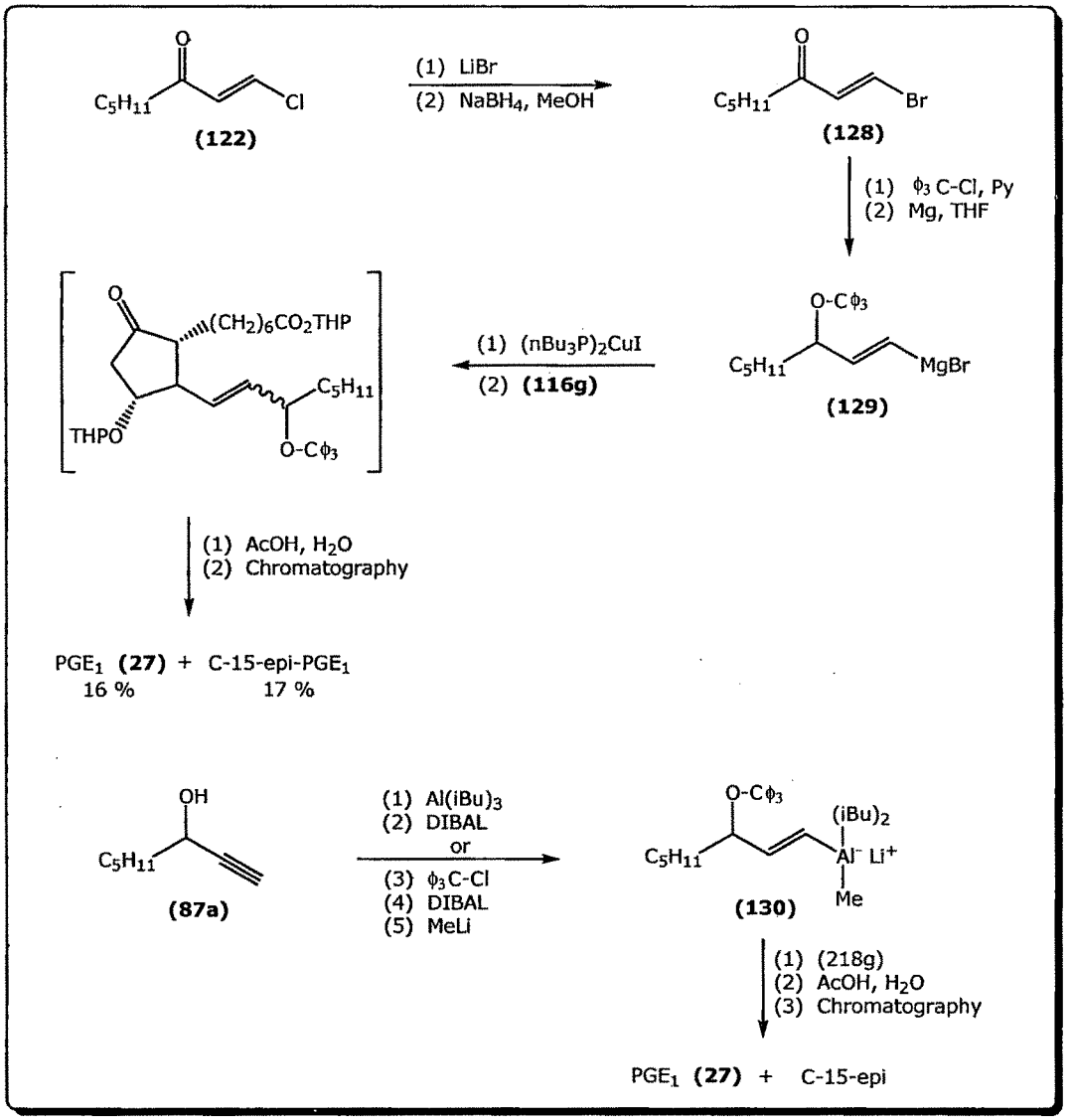
The (*S*)-(+)-derivative (**124**), protected as its α-ethoxyether, was then converted to the lithium derivative (**125**) by treatment with tert-butyllithium. The corresponding lithium dialkylcopper reagent (**126**) was then prepared and used with the eneones (**116d**) and (**127**), leading to optically active PGE_1 (**27**) and PGE_2 (**20**), respectively.[112] Although the yields need to be improved, this synthetic approach is likely to be one of the best ways to prepare a number of PGs.

I.5 (5c) Copper-catalyzed Grignard Reactions

A copper-catalyzed 1,4-addition has also been used for the synthesis PGE_1 (**27**) [113]. As shown in **Scheme 16**, other than the use of Grignard reagent, this synthesis is very similar to those discussed above. The addition of the Grignard reagent (**129**), prepared from the chloroketone (**122**) (**Scheme 15**), by treatment of (**128**) with magnesium in tetrahydrofuran, was performed in the presence of the cuprous iodide-tri-n-butyl phosphine. After removal of the protecting groups, the resulting mixture of epimers at C-15 was separated chromatographically. A drawback of the synthesis is the partial isomerization of the double bond during the preparation of the Grignard reagent (**129**).

I.5 (5d) Conjugate Addition of Alanes

This method, also shown in **Scheme 16**, consists of the addition of the alane (**130**) to the enone (**116g**).[114] The organometallic reagent (**130**) was obtained by treatment of the hydroalumination product from the propargyl alcohol (**87a**) (**Scheme 10**) with methyllithium, as reported previously.[104] However, the trityl ether protecting group (**130**) was used in this work to prevent coordination of the oxygen with aluminium, which would assist an intramolecular attack by hydride and lead to the undesired *cis*-olefin. [114] This claim is in contrast with an earlier report by Sih *et al.*, [110] who failed to detect the *cis* compound. An alternative route to the required vinylalane (**130**) consisted of adding the vinyllithium derivative to trimethylaluminium.[115] Michael addition of the alane (**130**) to the protected cyclopentenone (**116g**) provided, after the usual reaction sequence, PGE_1 (**117a**) in low yield.



Scheme 16

I.5 (5e) Conjugate Addition of Nitroalkanes

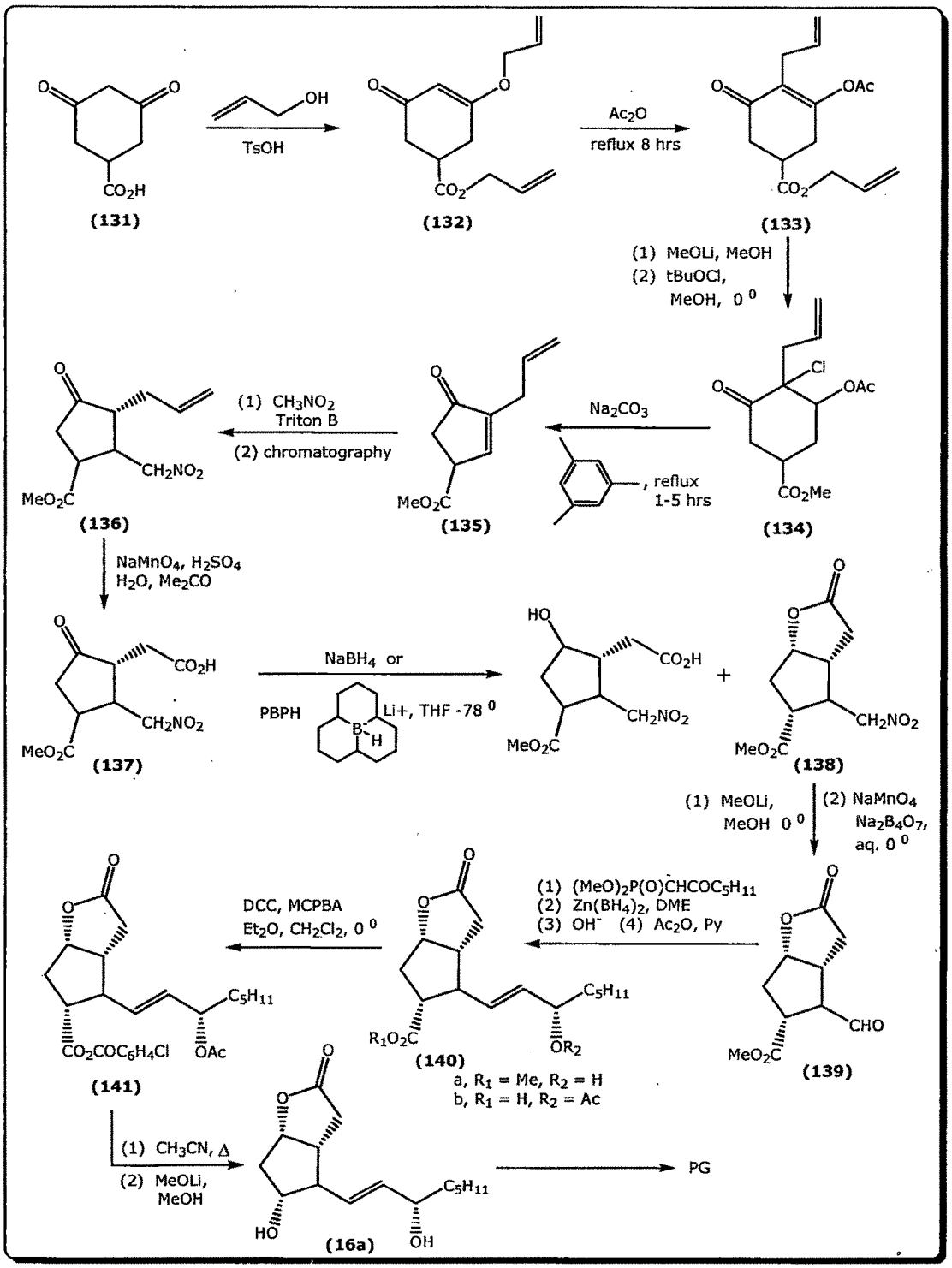
This approach is slightly different from the methods discussed previously. First, it is the only conjugate addition synthesis that does not use a cyclooentenone of type **(q')** mentioned at the beginning of this section. Second, the eight-carbon chain at C-12 is introduced by the Hoener-Emmons reaction [71] on the appropriate aldehyde, generated from a nitro precursor introduced by a 1,4-addition reaction. Finally, the synthetic

objective was the bicyclic lactone intermediate of the Corey synthesis. Hence, although longer than most other approaches in this section, this last synthesis is quite versatile. [116] The key concept in the preparation of the necessary cyclopentenone is that a properly oriented carbomethoxy group (-$COOCH_3$) could serve as the hydroxy synthon at position 11.[117]

The required cyclopentenone **(135)** was prepared by a ring contraction first reported by Buchi and Egger [118] in another context. The enol ether **(132)** was formed by reaction of the β-diketone **(131, Scheme 17)** with allyl alcohol in acidic medium. Claisen rearrangement of the ether **(132)** provided the alkylated compound **(133)**. *Trans*-esterification with lithium methoxide and basic aprotic chlorination provided the chloroketone **(134)**, which was smoothly converted to the required cyclopentenone **(135)** by treatment with sodium carbonate in refluxing mesitylene.[118] Michael addition of nitromethane to the enone **(135)** produced the nitro derivative **(136)**, oxidized to the keto acid **(137)** with sodium permanganate in acidic medium. Reduction of the keto-group with PBPH gave the lactone **(138)**.[116]

For the construction of the lower chain, the nitromethyl group was converted to the aldehyde **(139)** by sodium permanganate oxidation buffered with a borate salt. The classical Horner-Emmons reaction, followed by normal sequence, then completed the synthesis of the eight-carbon chain.

The transformation of the ester group to the required alcohol at position 11 was achieved by saponification, followed by acetylation to produce the acetate acid **(140b)**. Treatment of the acid **(140b)** with *N,N'*-dicyclohexylcarbodiimide (DCC) and MCPBA produced the mixed peranhydride **(141)**, which, when refluxed in acetonitrile underwent a carboxy inversion with retention of configuration. *Trans*-esterification with lithium methoxide afforded the known hydroxylactone intermediate **(16a)**.[116] The conversion of lactone **(16a)** to PG has been described as in **Scheme 2.**


(131)
TsOH
(132)
Ac2O
reflux 8 hrs
(133)
(1) MeOLi, MeOH
(2) tBuOCl,
MeOH, 0 0
(134)
Na2CO3
, reflux
1-5 hrs
(135)
(1) CH3NO2
Triton B
(2) chromatography
(136)
NaMnO4, H2SO4
H2O, Me2CO
(137)
NaBH4 or
PBPH
Li+, THF -78 0
(138)
(1) MeOLi,
MeOH 0 0
(2) NaMnO4
Na2B4O7,
aq. 0 0
(139)
(1) (MeO)2P(O)CHCOC5H11
(2) Zn(BH4)2, DME
(3) OH- (4) Ac2O, Py
DCC, MCPBA
Et2O, CH2Cl2, 0 0
(140)
a, R1 = Me, R2 = H
b, R1 = H, R2 = Ac
(141)
(1) CH3CN, Δ
(2) MeOLi,
MeOH
(16a)
PG

Scheme 17

I.6 (6) THE INTRAMOLECULAR CONDENSATION ROUTE

The ease of obtaining cyclopentenones through intramolecular cyclization reactions [119] has induced PG investigators to use sometimes this type of transformation. Two reactions that have been employed in PG Synthesis are Aldol type and Dieckmann condensation.

I.6 (6a) Aldol Condensation

The distribution of functional groups in the PG ring should permit its synthesis through an intramolecular condensation.[120] Thus, for the synthesis of PG belonging to the E or F family it is necessary to prepare ketol (**t', Figure I.11**) or (**u'**).

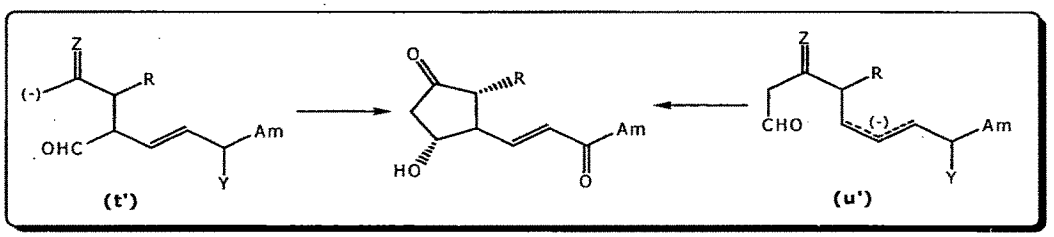
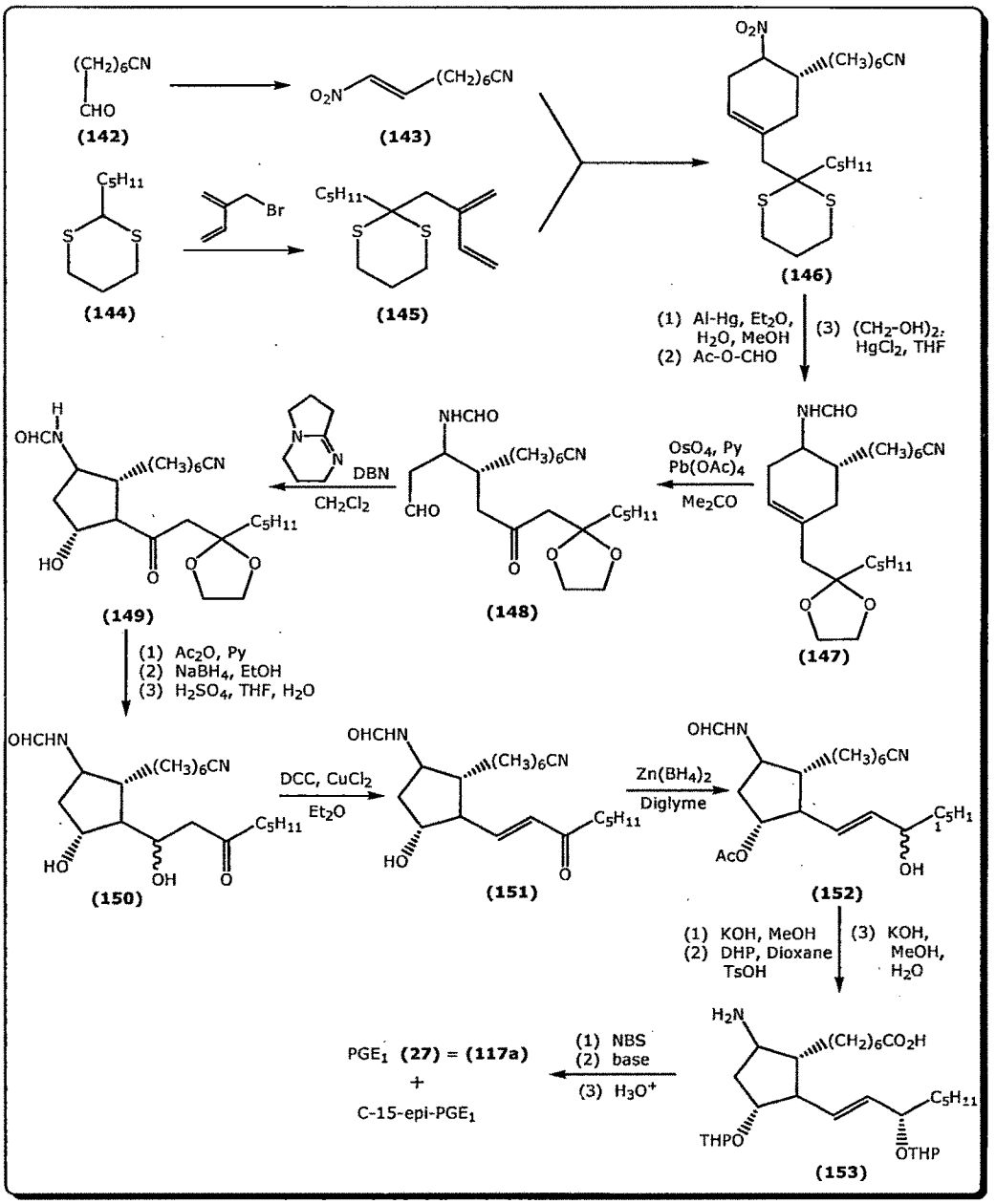


Figure I.11

So far no PG synthesis has used an intermediate such as (**t'**). In contrast, two approaches utilizing intermediates of type (**u'**) have been reported, in which Z is an amide and Y a ketal. Although both routes are similar, they differ in the elaboration of the intermediates used in the cyclization, as well as in the nature of the activating group necessary for the ring formation.

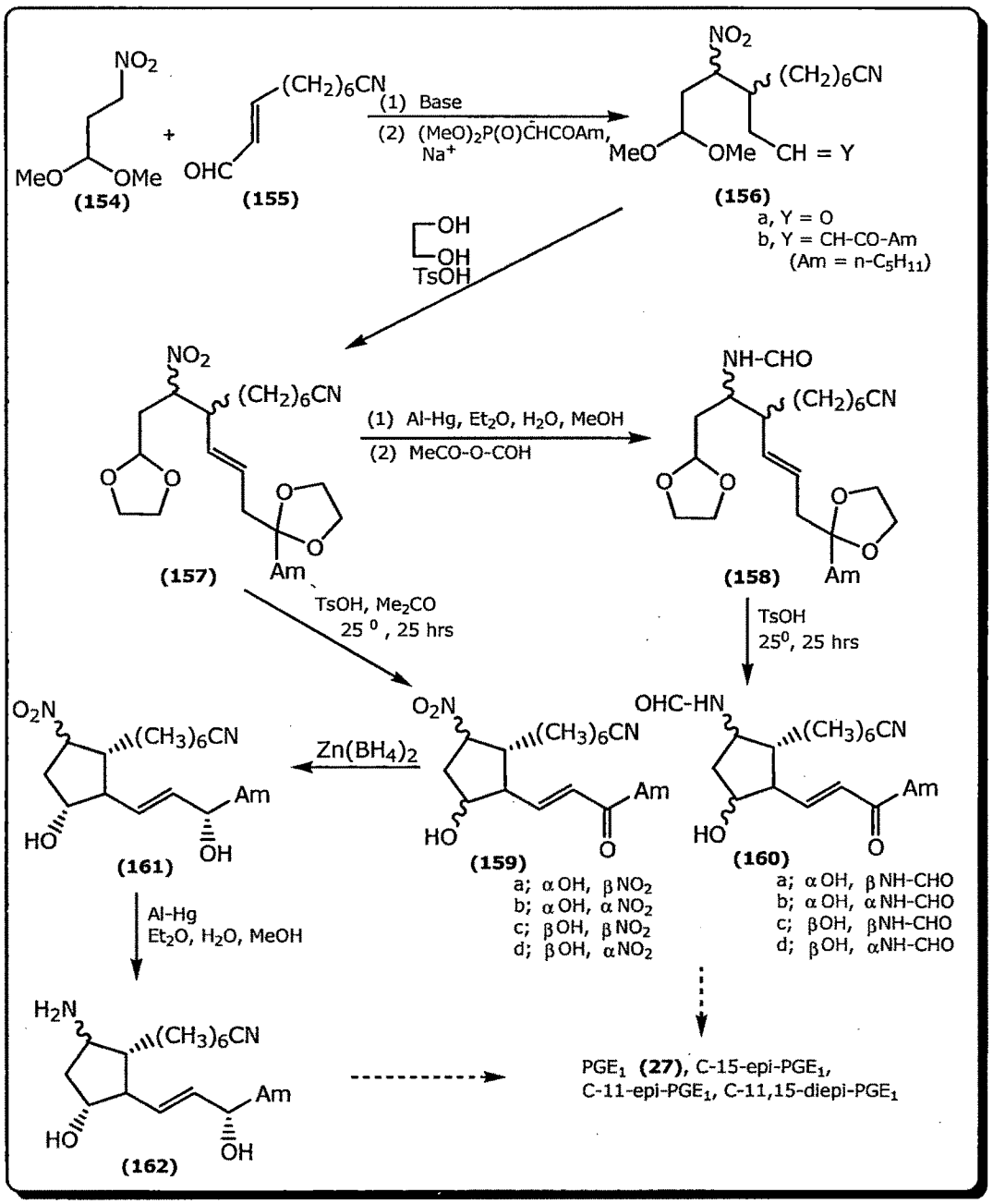
Scheme 18 outlines the first route in which the cyclohexene intermediate (**146**) was obtained by Diels-Alder addition of the nitroethylene (**143**) with diene (**145**).[121] After reduction of the nitro group of compound (**146**) to an amine, followed by protection as its formamide derivatives, the thioketal was transformed to the ketal (**147**) by exchange with ethyleneglycol. Cleavage of the double bond gave the keto-aldehyde (**148**) which underwent an aldonization in the presence of 1,5-diazabicyclononene (DBN) to produce the intermediate (**149**). Acetylation of the hydroxyl at C-11, followed by reduction with sodium borohydride and acid hydrolysis afforded the ketol (**150**). The required enone (**151**) was then obtained by a new dehydration method using DCC and cupric chloride as the catalyst, which provided the mixture of epimeric alcohols at C-15 (**152**) by zinc

borohydride reduction. After saponification of the ester at position 11 and protection of the alcohols as THP ethers, the amide and cyano groups were hydrolyzed with potassium hydroxide to give the amino derivative **(153)**. Ruschig reaction then converted the amine to a ketone and acid hydrolysis of the protecting groups yielded PGE_1 **(117a = 27)** and its 15-epimer.[121]



Scheme 18

In another synthesis, also from the Harvard team, shown in **Scheme 19**, Michael addition of the dimethyl acetal of 3-nitropropionaldehyde (**154**) to the conjugated aldehyde (**155**) produced the adduct (**156a**), readily converted to the conjugated ketone (**156b**) by the Horner-Emmons reaction [71] with the sodium salt of dimethyl 2-oxoheptylphosphonate.[122]



Scheme 19

Ketalization of the keto acetal (**156b**) afforded the diketal (**157**) in which the nitro group was reduced with aluminum amalgam and then formylated (**158**). Acid-catalyzed cyclization of the nitro derivative (**157**) and the amide (**158**) provided the vinylogous aldols (**159**) and (**160**), respectively, as mixtures of stereoisomers. After chromatographic separation both intermediates (**159**) and (**160**) were transformed to PGE_1 (**27**) by essentially the same sequence, as shown in **Scheme 18**.[122] In practice the nitro compound (**157**) allowed a better separation of the stereoisomers formed in the cyclization than did the formamide derivative (**158**).

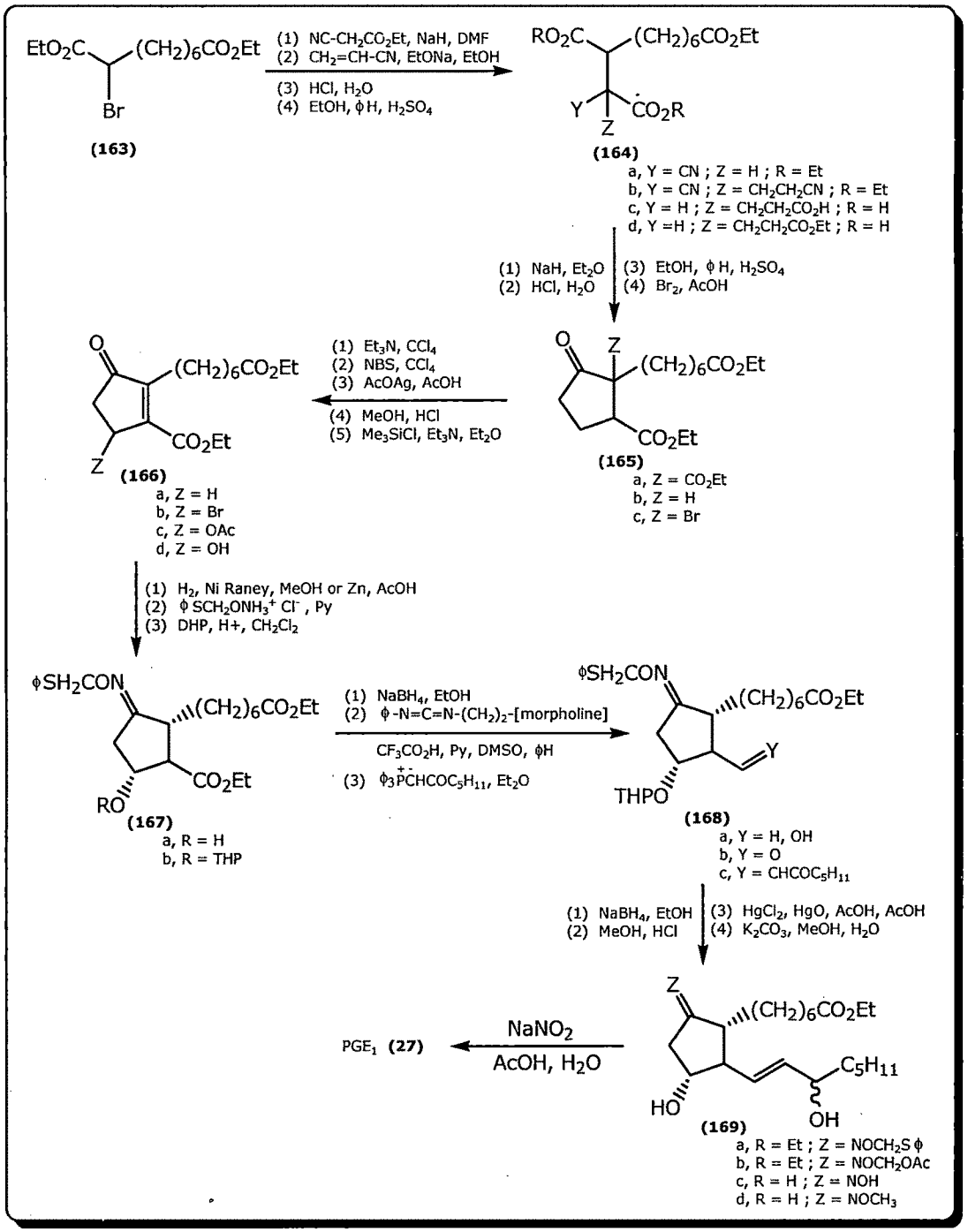
Although the cyclization reaction was initially performed with p-toluenesulfonic acid (PTSA) in acetone, it was observed that the ratio of the cyclized stereoisomers can be altered by appropriate modification of the acid catalyst. Thus, with sulfuric acid in aqueous tetrahydrofuran (THF), the undesired stereoisomers (**159c**) and (**159d**) were mainly obtained, whereas by cyclization of the intermediate (**157**) with stannic chloride, the epimers (**159a**) and (**159b**) with the correct stereochemistry at position 11 were secured almost exclusively.[122] Additionally, since the amine (**162**) could be resolved with (-)-α-bromocamphorsulfonic acid, the above synthesis constitutes a stereoselective route to natural PGE_1 (**27**), except for the generation of the hydroxyl at position 15. In spite of satisfactory yields and relatively few numbers of steps, this route does not seem to have been sufficiently optimized for commercial applications.

I.6 (6b) Dieckmann Reaction

The intramolecular version of the Claisen condensation, the Dieckmann reaction [123], is also frequently used for the obtention of cyclopentanones. In applying this reaction to PG synthesis a regiospecific cyclization is obviously necessary, since the intermediate (**v'**) can in principle lead either to (**w'**) or (**x'**), or both.

In addition, group Y cannot be a hydroxyl because it would not withstand the basic medium in which this reaction takes place. Its β relationship to one of the esters would lead to a retro Claisen reaction and/or dehydration and therefore Y must be a potential hydroxyl. Alternatively, the introduction of the hydroxyl group could occur at a later stage, as shown in the PG Synthesis discussed in sequence.

Scheme 20 outlines the original approach of Finch and co-workers [124], reported as early as 1969, which made use of unusual protecting groups for that time.



Scheme 20

The cyano triester (**164a**), prepared from ethyl 2-bromoazelate (**163**) and ethyl cyanoacetate, was used as starting material. Cyanoethylation of compound (**164a**) in the presence of sodium ethoxide afforded the dicyano triester (**164b**) in high yield. Acid hydrolysis gave the tetra acid (**164d**), which was esterified and submitted to Dieckmann condensation conditions to provide the cyclopentanone (**165a**). Hydrolysis and decarboxylation in acid medium, followed by reesterification yielded the diester (**165b**). The following steps concerned the introduction of the oxygen functionality at position 11. This was achieved by the method of DePuy [99] i.e., bromination followed by dehydrobromination furnished the cyclopentenone (**166a**). Allylic bromination then gave the bromo derivative (**166b**), which was subjected to acetolysis with silver acetate, followed by acid methanolysis to produce the acetate (**166c**). Catalytic hydrogenation of the trimethylsilyl derivative (**y'**, **Figure I.12**) gave unexpectedly, a mixture of the isomers (**z'**) and (**z''**).

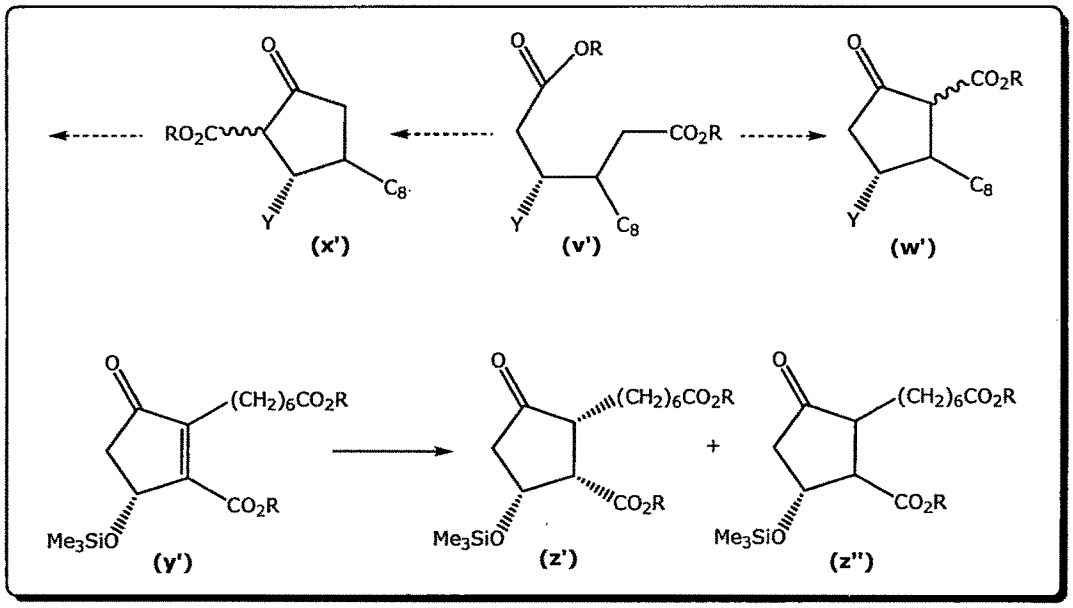


Figure I.12

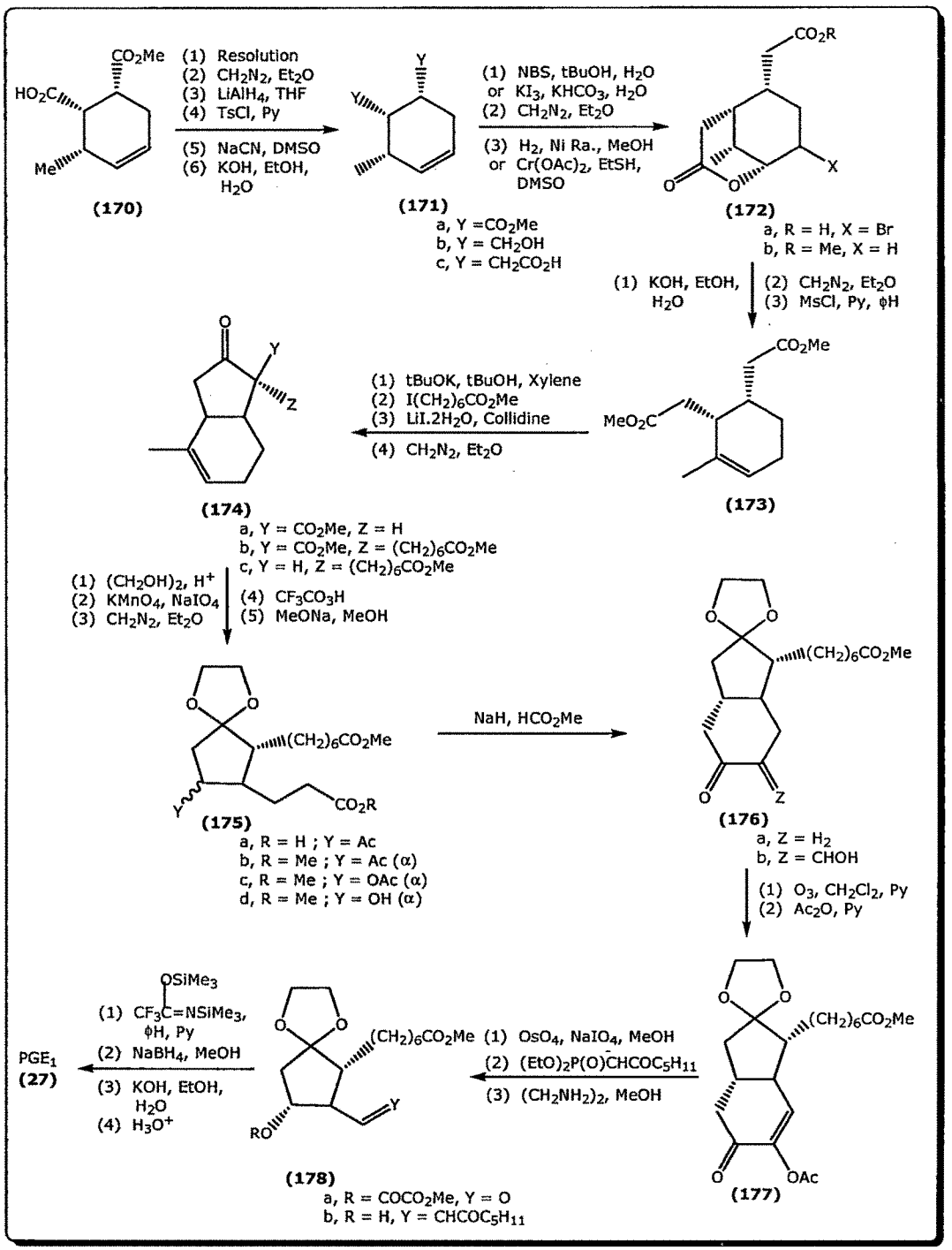
Hence, the catalytic reduction was performed on the free alcohol (**166d**) and the mixture of isomers was converted to the phenylthiomethoxylamine derivatives, followed by alkaline epimerization at position 12 and fractional crystallization, which produced the expected 12 β-isomer (**167b**). Later the equilibration step could be avoided when the reduction was achieved with zinc in acetic acid.[124] Protection of the alcohol group as

THP (**167b**) and selective reduction of the ester on the ring with sodium borohydride afforded the corresponding primary alcohol (**168a**). The conversion of this intermediate to the phenylthiomethoxylamino derivative of PGE_1 (**169a**) was effected by the classic route. The cleavage of the phenylthiomethoxylamino protecting group was achieved by treatment with mercuric salts, and PGE_1 (**27**) was obtained after saponification and nitrosation.[124]

This route gives generally high yields, except for the selective ester reduction and the elimination of the carbonyl protecting group at C-9. Furthermore, the reactions are generally simple and can be performed on a large scale. Additionally, new developments have led to other protecting groups that are easier to remove.

Merck Sharp and Dohme Laboratories developed their own PG Synthesis, which will be sequence.[125-127] These approaches are also based on Dieckmann cyclization reaction [125,126] although, the diester required for the cyclization was prepared by a Diels-Alder addition. In the first synthesis [125], the adduct (**171a**) was obtained from a reaction between piperylene and maleic anhydride, followed by methanolysis. Resolution of this compound through its dehydroabietylammonium salt, followed by bishomologation of the appropriate enantiomer produced the diacid (**171c**). Iodolactonization of the intermediate (**171c**) gave exclusively the bicyclic lactone (**172a**), which by esterification and dehalogenation afforded the ester (**172b**), whose free acid could also be resolved through its dehydroabiethylammonium salt. Saponification of (**172b**) followed by elimination through the mesylate yielded the substituted cyclohexene (**173**), which cyclized regiospecifically to give the bicyclic ketone (**174a, Scheme 21**). This was alkylated to give the intermediate (**174b**), which in turn was decarbocylated to afford the monoester (**174c**). Ketalization followed by cleavage of the olefin by the Lemieux-von Rudloff method [128] provided the cyclopentane derivative (**175a**). Esterification, equilibration to the thermodynamically more stable *trans*-isomer (**175b**), and Baeyer-Villiger oxidation furnished the acetate (**175c**). Basic methanolysis led to the lactone (**176a**), which was then formylated (**176b**). Ozonolysis of this product followed by reductive decomposition of the ozonide and acetylation produced the enol acetate (**177**), which was cleaved by the Lemieux-Johnson procedure[129] to provide the aldehyde

(178a).[125] The conversion of this intermediate to PGE_1 (27) was realized by the well-established techniques.



Scheme 21

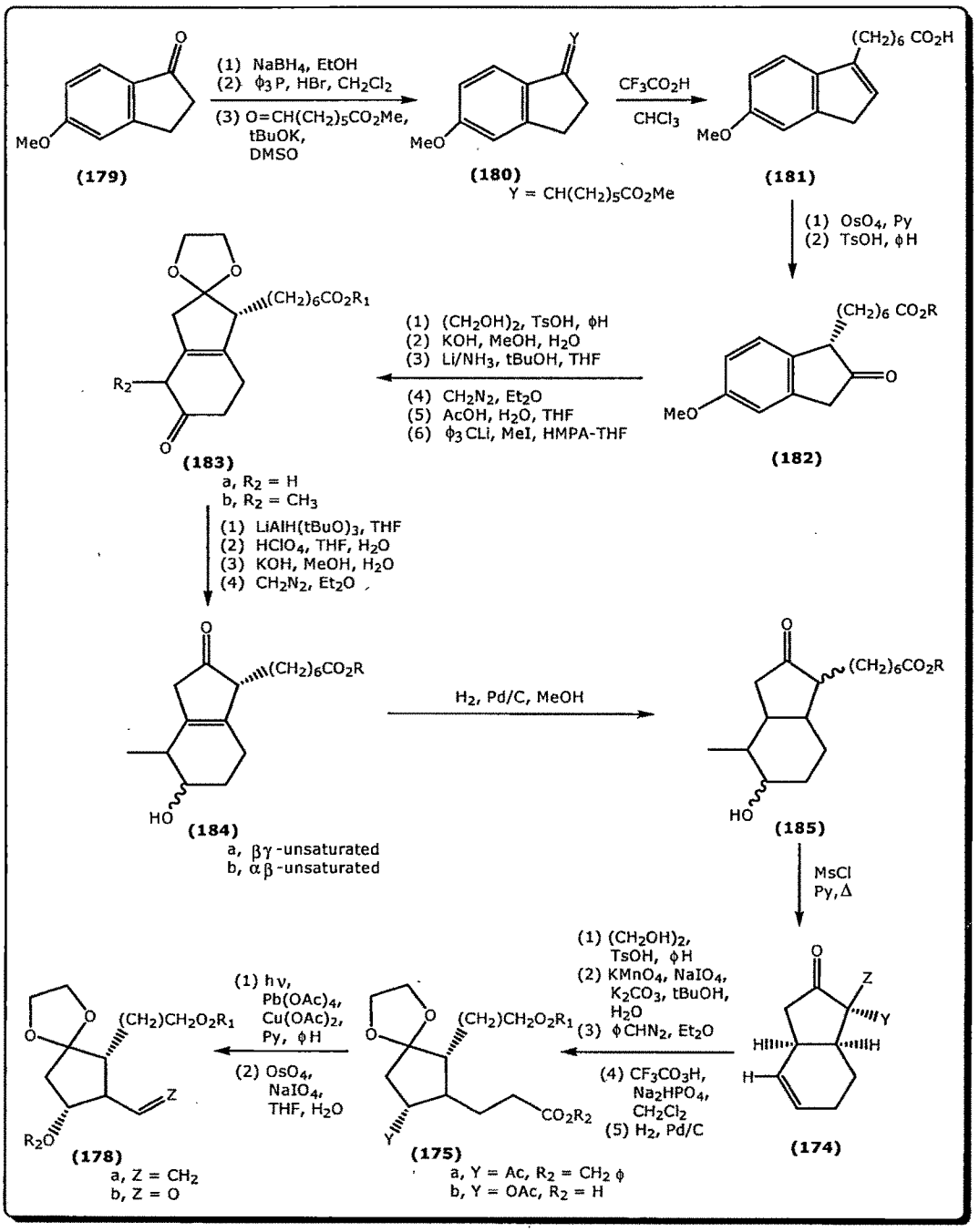
I.7 (7) MISCELLANEOUS APPROACHES

This includes the Synthesis which did not fit in the classes mentioned previously.

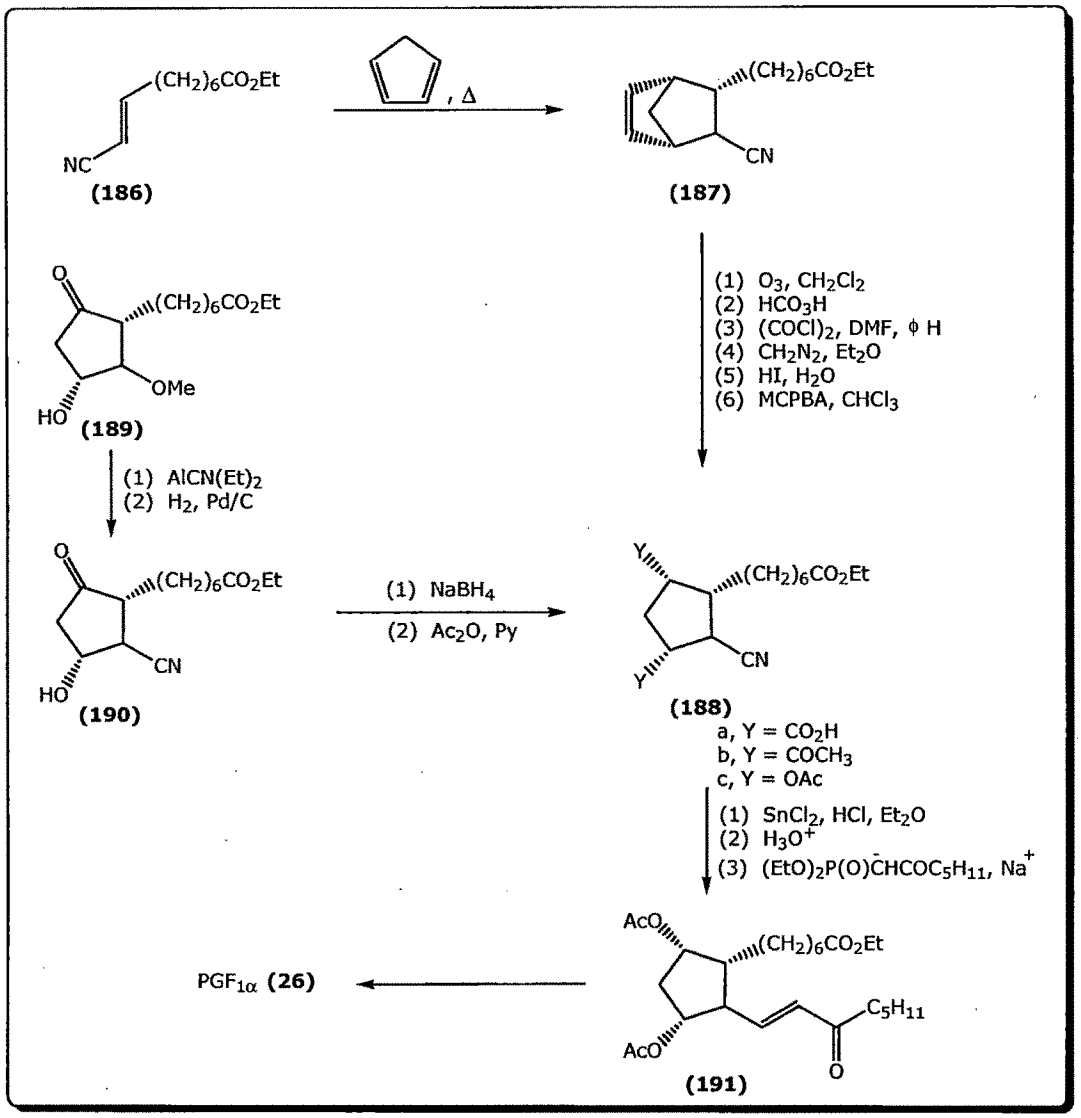
I.7 (7a) Synthesis of Primary PG

In the route shown in **Scheme 22**, 5-methoxyindanone (**179**) was converted to the *exo*-cyclic olefin (**180**) through a Wittig reaction with methyl-6-formyl-hexanonate. Acid isomerization produced the *endo*-cyclic olefin (**181**), which was hydroxylated with osmium tetroxide, and the resulting diol was rearranged in acid medium to give the alkylated methoxy-β-indanone (**182**). Ketalization and saponification, followed by Birch reduction afforded theβ,γ-unsaturated ketone (**183a**), after esterification and hydrolysis of the enol ether.[127] Monomethylation of ketone (**183a**) furnished the alkylated compound (**183b**). After reduction of the cyclohexanone and acid hydrolysis to regenerate the five membered keto group (**184a**), the double bond was put into conjugation (**184b**) and the material was reesterified. Catalytic hydrogenation produced the cyclopentanone (**185**), converted to the known olefin (**174**) by elimination of the corresponding mesylate. By a similar reaction sequence described in **Scheme 21**, the PG molecule was obtained [125,127], although some other modifications were introduced.

Another PG synthesis involving a Diels-Alder addition is shown in **Scheme 23**.[130] Reaction of 9-carbethoxy-2-*trans*-nonenonitrile (**186**) with cyclopentadiene furnished a mixture of *endo*-nitrile-isomers in a ¼ ratio. After separation, the *exo*-isomer (**187**) was converted to the diacid (**188a**) by ozonolysis and oxidative decomposition of the resulting ozonide. The 9,11-dicarboxy compound (**188a**) was transformed to the diacetyl intermediate (**188b**), which in turn was submitted to a Baeyer-Villiger reaction to give the corresponding acetate (**188c**). The alternative route to compound (**188c**), also shown in **Scheme 23**, called for an addition of cyanide by reaction of diethylaluminum cyanide on the enol ether (**189**), followed by catalytic hydrogeneation of the double bond, reduction of the carbonyl and acetylation.[130] Conversion of the cyano group to the corresponding aldehyde which has presumably the correct configuration at position 12 was achieved by a Stephen reduction. Horner-Emmons alkylation to the 15-ketone (**191**) and reduction to am mixture of epimeric alcohols at position 15, afforded PGF_{1_α} (**26**).[130]


(1) NaBH4, EtOH
(2) ϕ3P, HBr, CH2Cl2
(3) O=CH(CH2)5CO2Me, tBuOK, DMSO
CF3CO2H
CHCl3
(179)
(180)
Y = CH(CH2)5CO2Me
(181)
(1) OsO4, Py
(2) TsOH, ϕH
(1) (CH2OH)2, TsOH, ϕH
(2) KOH, MeOH, H2O
(3) Li/NH3, tBuOH, THF
(4) CH2N2, Et2O
(5) AcOH, H2O, THF
(6) ϕ3CLi, MeI, HMPA-THF
(182)
(183)
a, R2 = H
b, R2 = CH3
(1) LiAlH(tBuO)3, THF
(2) HClO4, THF, H2O
(3) KOH, MeOH, H2O
(4) CH2N2, Et2O
H2, Pd/C, MeOH
(184)
a, βγ-unsaturated
b, αβ-unsaturated
(185)
MsCl
Py, Δ
(1) (CH2OH)2, TsOH, ϕH
(2) KMnO4, NaIO4, K2CO3, tBuOH, H2O
(3) ϕCHN2, Et2O
(4) CF3CO3H, Na2HPO4, CH2Cl2
(5) H2, Pd/C
(174)
(1) hν, Pb(OAc)4, Cu(OAc)2, Py, ϕH
(2) OsO4, NaIO4, THF, H2O
(175)
a, Y = Ac, R2 = CH2ϕ
b, Y = OAc, R2 = H
(178)
a, Z = CH2
b, Z = O

Scheme 22

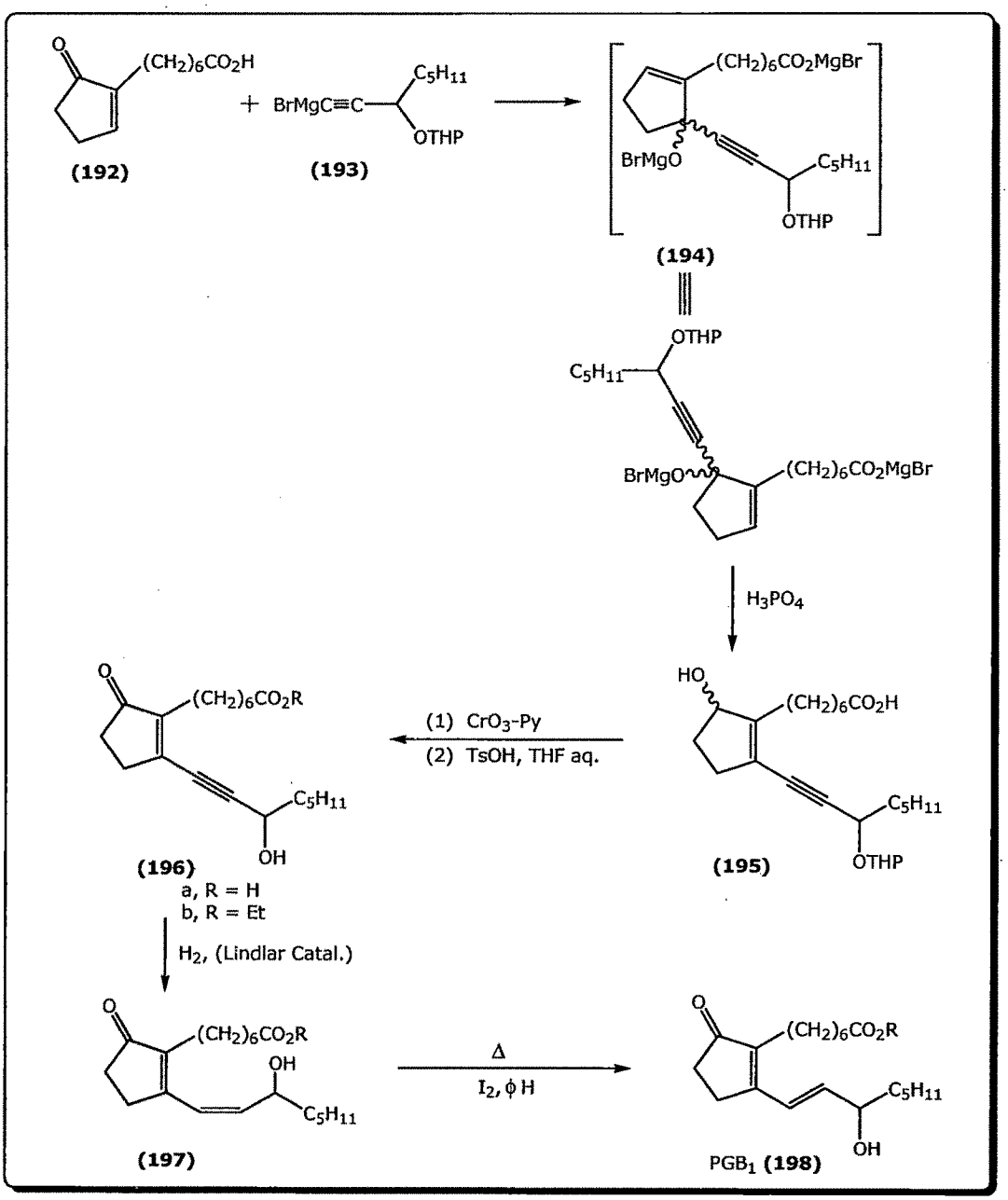


Scheme 23

I.7 (7b) Synthesis of Secondary PG

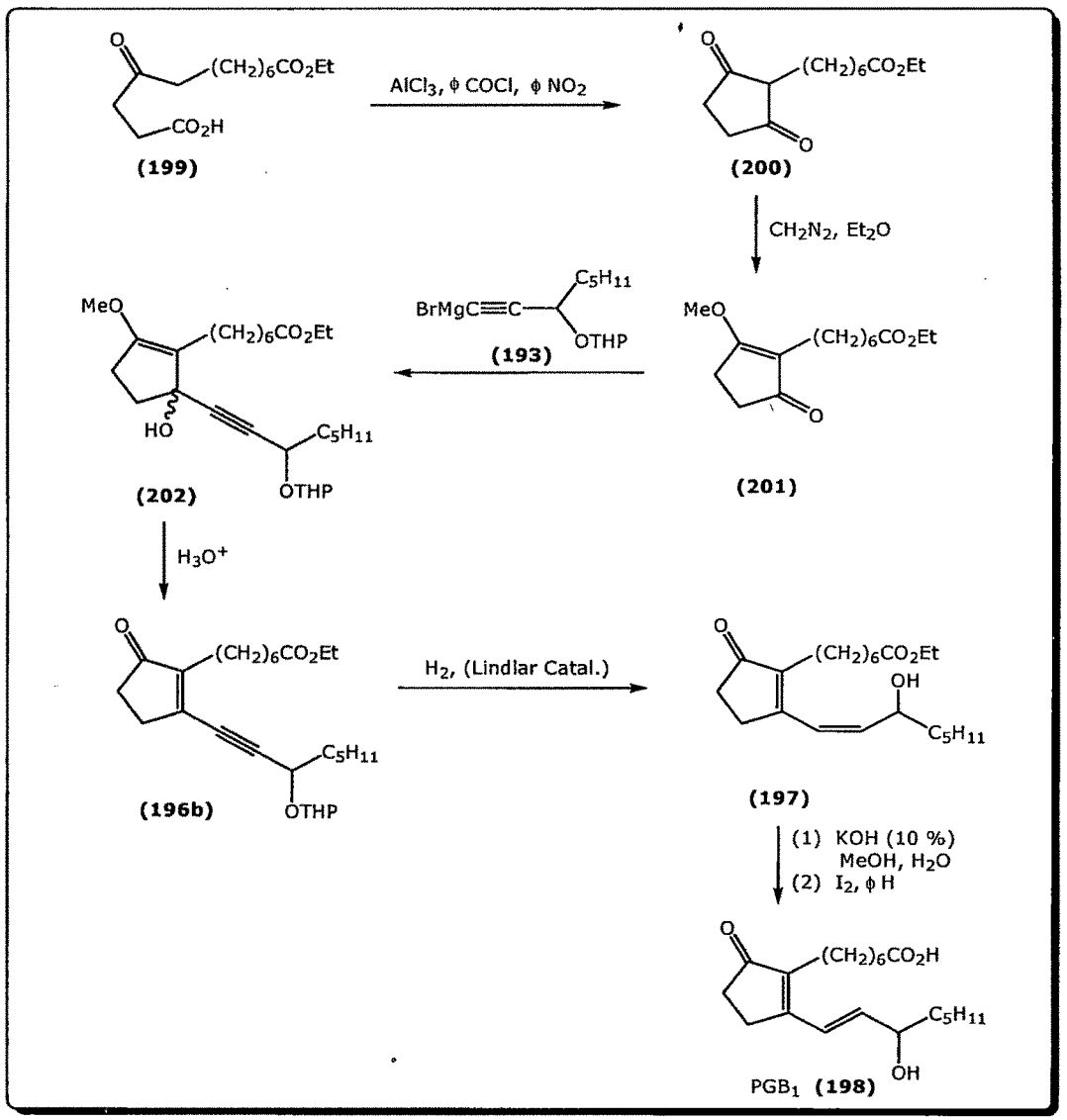
Most synthesis of this group lead to PGB derivatives. Two synthesis of PGB_1 have several features in common.[131] One of them used the keto acid (**192**) as the starting material. Reaction of enone (**192**) with the alkyne Grignard (**193**) gave the 1,2-addition product (**194**), which was rearranged in acid medium to give the acid alcohol (**195**). Oxidation followed by hydrolysis furnished the intermediate (**196a**). Finally, catalytic

hydrogenation gave the *cis*-olefin, which was isomerized to the *trans*-isomer with iodine, thus completing the synthesis of PGB_1 **(198)**, as shown on **Scheme 24**.[131]



Scheme 24

Scheme 25 outlines a similar approach, which started from the keto acid (**199**).[132] Cyclization with aluminum chloride furnished the cyclopentane dione (**200**) which was transformed to the enol ether (**201**) by treatment with diazomethane. Addition of the alkyne chain (**193, Scheme 24**) to the keto group gave the 1,2-addition compound (**202**), which was converted to the enone (**196b**). Catalytic reduction of the triple bond with Lindlar catalyst furnished the *cis*-olefin (**197**), which was isomerized to provide PGB_1 (**198**), after alkaline hydrolysis.[132]



Scheme 25

I.7 (7c) Biogenetic Type Synthesis

Among the total Synthesis of natural products, those which mimic biogenetic pathways are often unusually short and efficient. These include "biomimetic" or "biogenetically modeled" routes, initially developed in the alkaloid field and later extended particularly to terpenes and steroids.[133] Hence, it is not surprising that biogenetic type Synthesis have been suggested for prostanoids.

The biosynthesis of PG is due mainly to the work of van Drop [134] and Samuelsson [135] who have shown that PG are formed from unsaturated fatty acid precursors (**a''**). Enzymatic cyclization through a series of isomerization and peroxidation reactions (**b''**) leads to the PG precursors (**c''**), which already possess the appropriate oxygenated pattern of the PG molecule. Usual biogenetic reactions such as reductions, oxidations, dehydrogenations, etc., then produce the PG of the various series and families. From the simplified scheme shown below it is obvious that the cyclization of an intermediate (**b''**) to form the five-member ring (**c''**) is the crucial step in the biogenetic process.

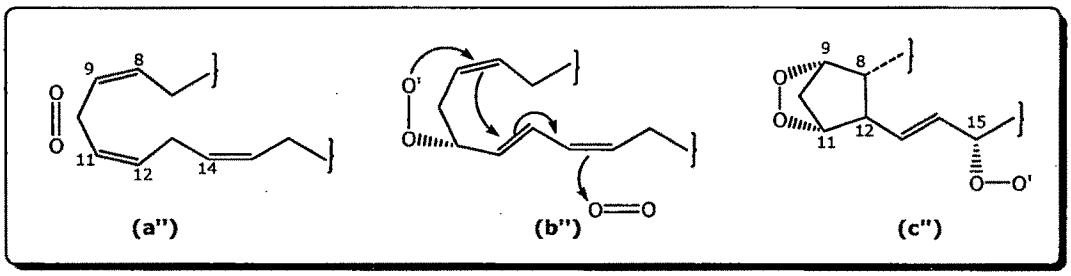
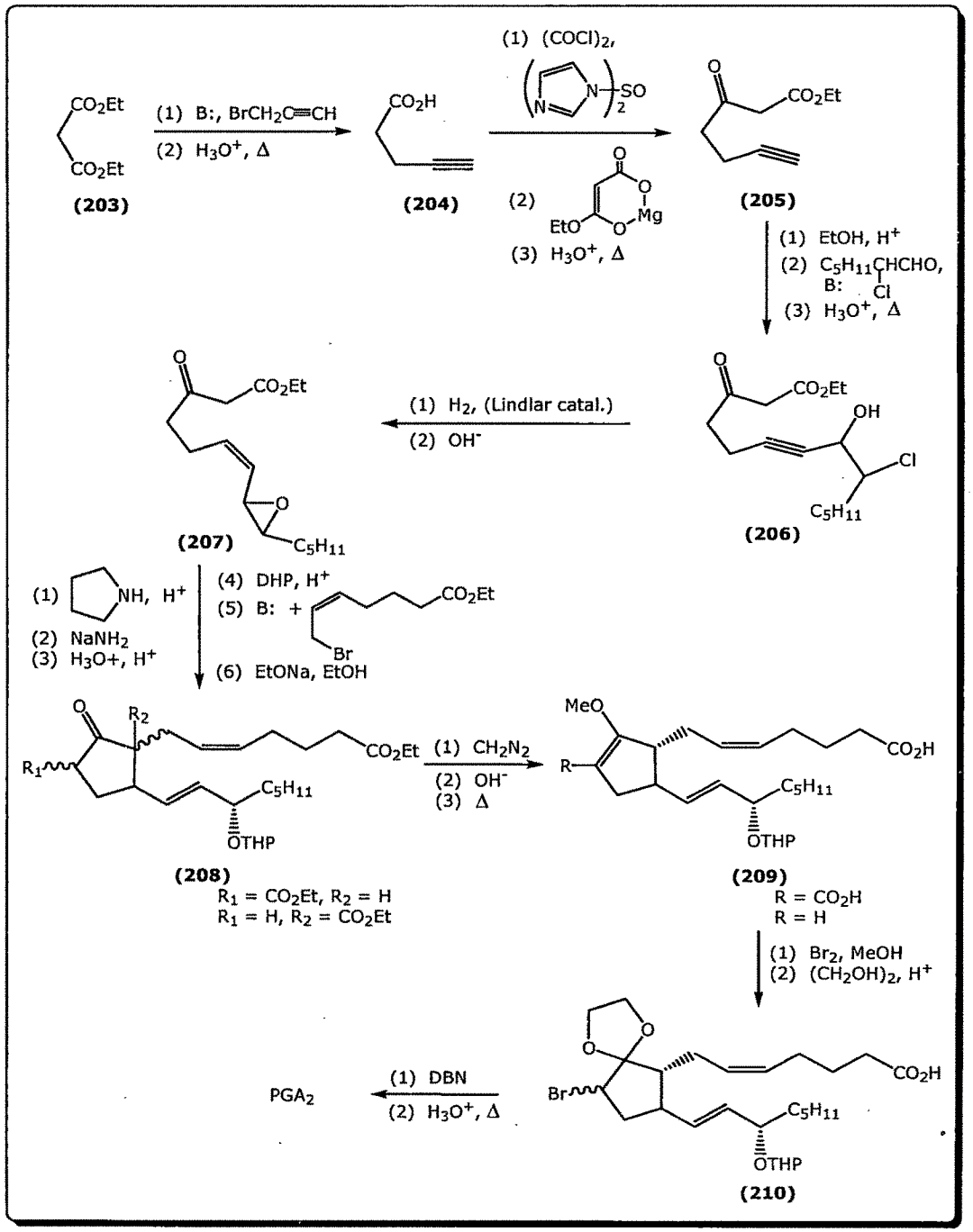


Figure I.13

Scheme 26 summarizes a report on the synthesis of PGA_2 based on this concept.[136] Although few reagents were mentioned in the original publication [136], **Scheme 26** suggests specific reaction conditions. Alkylation of malonic ester (**203**) with propargyl chloride afforded the acetylenic acid (**204**) after acid hydrolysis and decarboxylation. Conversion to the β-keto ester (**205**) was achieved through the acyl imidazole derivative by reaction with the magnesium enolate of the hemiester of malonic acid, followed by decarboxylation. The transformation to the enol ether and subsequent alkylation with 2-chloroheptanal produced the erythro-chlorohydrin (**206**) after acid hydrolysis. Partial catalytic hydrogenation to give the cis-double bond, followed by mild base treatment formed the epoxide (**207**), which was to act as the electrophilic site in a

biogenetic type cyclization. Treatment of the pyrrolidine enamine with sodamide in THF and acid hydrolysis provided the cyclopentanone **(208)** with the correct configuration at position 12 and 15. The chain at position 8 was introduced by alkylation with the appropriate bromoolefin.



Scheme 26

Isomerization of the carboethoxy group from position 8 to 10 was effected by opening and closure of the ring. After hydrolysis and decarboxylation of the ester at C-10, the double bond was introduced in the ring by bromination and dehydrobromination, affording PGA_2 after cleavage of the protecting groups. [136]

This synthetic approach to PG is of theoretical interest because of the cyclization step. However, it is obvious that this route is not very practical. Hence, although elegant, the crucial steps raise a number of experimental problems and clearly, a greater measure of efficacy in the cyclization process would be desirable.

I.7 (8) Some unconventional PGs

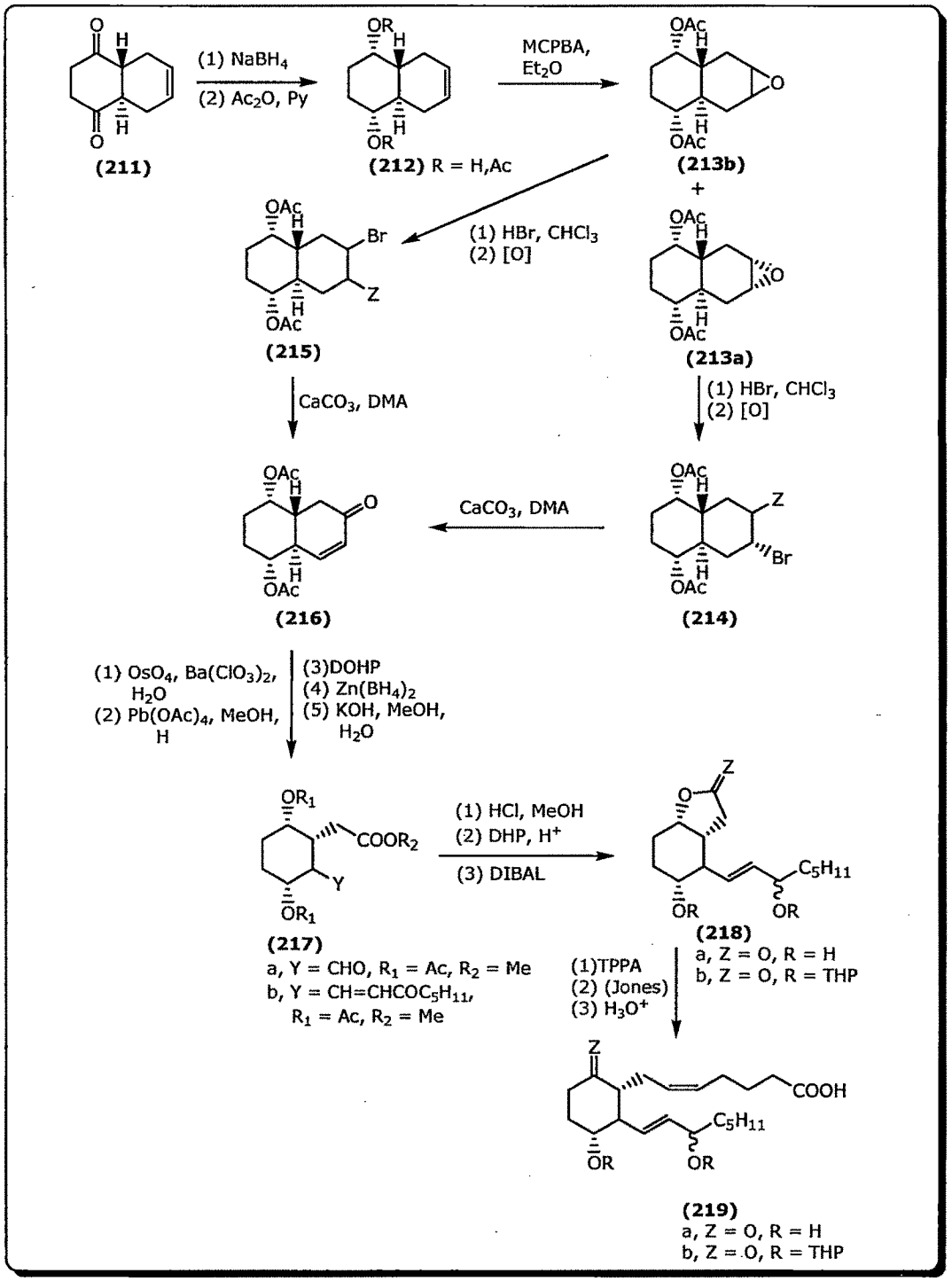
This includes the Synthesis of some PG analogues, which are different from the Primary and secondary classes PGs. skeleton of natural PG

Scheme 27 describes the synthesis of six-membered PG analogues **(219)** from the bicyclic compound **(211)**.[137] This approach is similar to those discussed in **Scheme 21** and **22**, but differs in that the starting material belongs to the decaline series, where as in the previously mention schemes passed through hydrindane-type intermediates. In the **Scheme 27** involves well established chemical sequences.[137]

The ready availability of PGA_2 derivative **(220)** from the marine coral (Plexaura homomalla)[12], has stimulated research programs aimed at the partial synthesis of numerous modified PGs. Indeed, the use of PGA_2 derivative **(220)** as starting material presents the important advantage of providing the complete skeleton with appropriate stereochemistry and functionality. Moreover, it eliminates the need of resolution step, an advantage over total synthesis schemes. Thus a number of alkylated PGs, preparing up to three structural modifications when compared to natural PGs, have been prepared from PGA_2 **(220)**.[138]

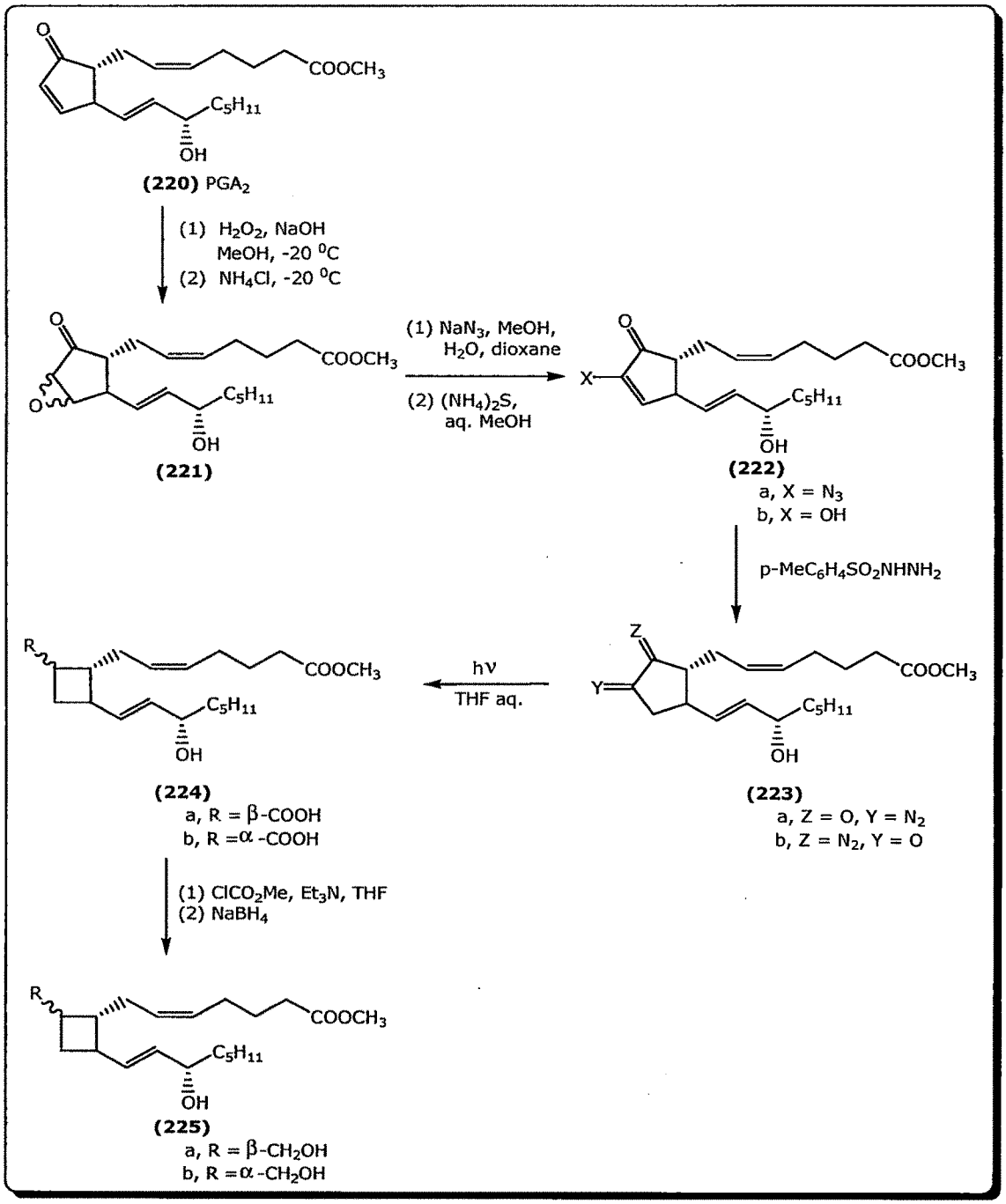
By gaining the above mentioned advantages, Scheme 1 outlines the preparation of a four-membered PG by the ring contraction procedure developed in the steroid filed.[139] The mixture of epoxides **(221)** obtained from PGA_2 methyl ester **(220)**, was treated with sodium azide to give the azido intermediate **(222a)**. Hydrolysis with ammonium sulfide provided the enolized *a*-diketone **(222b)** that when heated with *p*-

toluenesulfonylhydrazine furnished the diazoketones (**223**).[140] Photolysis in aqueous THF then afforded a mixture of the isomeric carboxylic acids (**224a**) and (**224b**), which were



Scheme 27

then converted to the hydroxymethyl cyclobutano-PG (**225a**) and (**225b**), respectively, by reduction of their mixed ethylcarbonic anhydrides with sodium borohydride.[140]



Scheme 28

I.8 OBJECTIVE

In spite of the fact that the total synthesis of PG constitutes a challenge for organic chemists, numerous conceptually different synthetic routes have been explored with considerable success.

In spite of the little biological information yet available on structurally modified novel PG, it is already apparent that a desired activity can be enhanced in certain entities, sometimes with reduction of side effects, in agreement with expectations. Hence, one can be confident that future research in this field will lead to a better understanding of the complex relationships between PG and human organs and to useful applications of modified PG in human therapy.

It is clearly seen from the various routes that we have described herein for the synthesis of PGs, majority of methods proceed via bicyclic lactone intermediate and are multi step sequences. It was therefore desired to design and develop a general, short procedure for the rapid acquisition of natural PG framework via [2+2] cycloaddition and oxidative decarboxylation of the resulting diacid using cheap and easily available starting materials like Citric acid and Methyl oleate or Methyl ricinoleate. Our efforts in this direction are discussed in the next chapter.

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