THE SYNTHESIS AND BIOLOGY OF FLUORINATED PROSTACYCLINS

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I. INTRODUCTION

A. Prostacyclin (PGI_2)

An unstable substance designated PGX was first isolated in 1975 as the transformation product of the prostaglandin endoperoxides PGH_2 and PGG_2 by blood vessel microsomes.[1] The structure of PGX was elucidated in 1976 from its hydrolysis product 6-keto $PGF_{1\alpha}$[2] and renamed PGI_2[3], also referred to as prostacyclin because of its bicyclic structure (Figure 1).

PGI_2 is a potent vasodilator and the most potent inhibitor of platelet aggregation know, properties opposite those of thromboxane A_2[4] (TXA_2), another major metabolite of the endoperoxides.[5] The enzyme which produces prostacyclin predominates in vascular tissue, thus, in vivo prostacyclin prevents the attachment of platelet aggregates to the blood vessel walls, and at higher levels the formation of platelet aggregates and also causes hypotension. Further, it has been postulated that the opposing actions of PGI_2 and TXA_2 play a crucial role in the maintenance of the integrity of the cardiovascular system.[6] These and other properties of prostacyclin have been discussed extensively.[7]

As a potential therapeutic agent, prostacyclin could find application in a wide variety of important areas. Its antiaggregating properties would be useful in the treatment of acute disorders like myocardial infarction, as well as solving chronic problems associated with dialysis and cardiopulmonary by-pass. As a vasodilator, prostacyclin could be utilized in treating shock by maintaining blood flow to key areas. Aside from these properties, PGI_2 has been shown to be an inhibitor of gastric secretion and a cytoprotective agent. Application as an antiulcer compound is, thus, also under study.[6,7]

The development of prostacyclin as a potential therapeutic agent faces a number of significant problems, however. PGI_2 is chemically very unstable and, thus, the lifetime of its activity is limited. Also, while it is both a potent inhibitor of platelet aggregation and a vasodilator, its actions are not selective. Furthermore, like the primary prostaglandins, PGI_2 is subject to metabolic deactivation as well.[7] Thus, a large number of analogs of prostacyclin have been prepared with the aim of overcoming these problems of stability as well as to separate its various actions.[5] It is the purpsoe of this review to examine the use of fluorination in meeting this challenge.

To begin the discussion, a more specific definition of the problems and objectives as well as alternate solutions will first be considered. Next the fluorination of biological molecules, in general, will be discussed, guiding principles for the introduction of fluorine, the effects which might be expected, and limitations. Then, a brief review of fluoro prostaglandins will be presented, the effects of substitution of fluorine on

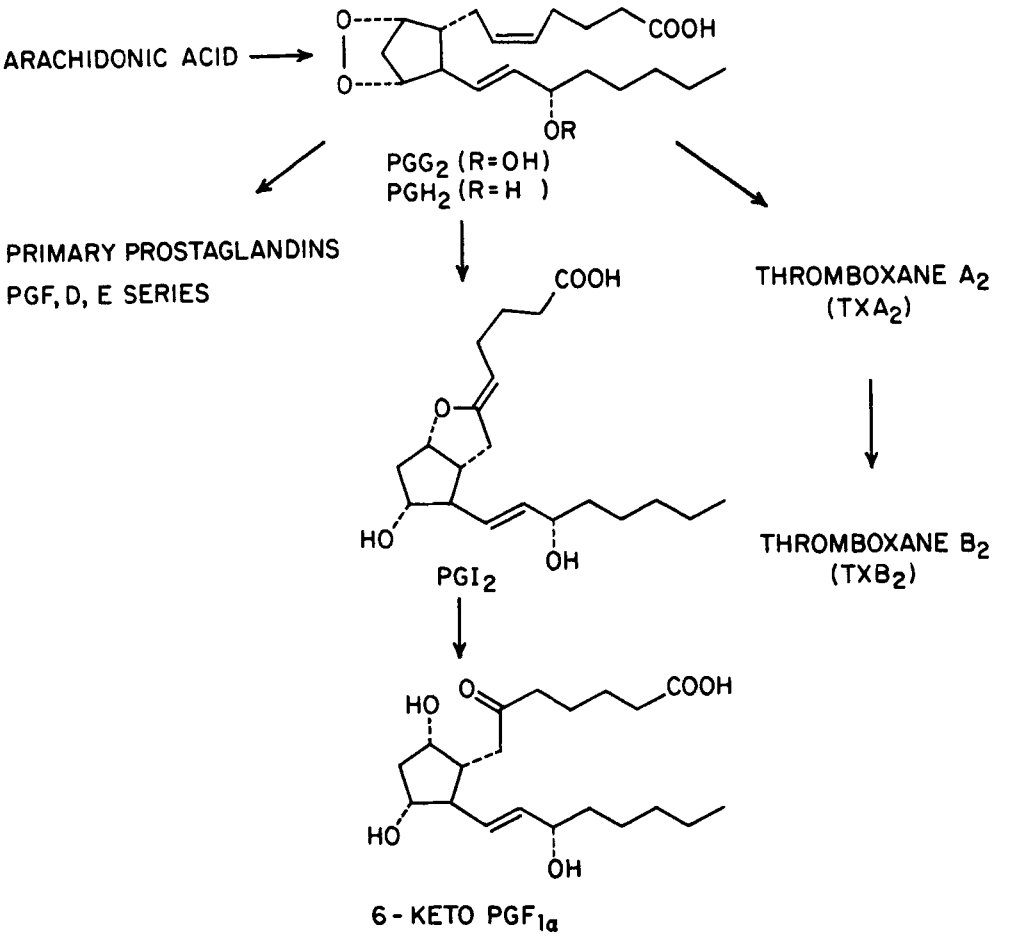


FIGURE 1. Biosynthesis of prostanoids.

chemistry and biology, and conclusions as to the role played by fluorine. Finally, the fluoro prostacyclins will be discussed, their design, preparation, and biology, as well as conclusions as to the achievement of objectives and some remarks on future work.

As the discussion proceeds to the design and preparation of fluorinated prostacyclins, these ideas should be kept in mind.

B. The Objectives for the Design of Prostacyclin Analogs

The chemical instability of prostacyclin arises from the presence of a labile enol ether group. Thus, PGI_2 is rapidly hydrolyzed under acidic or neutral conditions to 6-keto $PGF_{1\alpha}$.[8] The short half-life ($t_{\frac{1}{2}} = 3$ min, 37°, physiological pH[9]) in the body, thus, greatly limits the duration of its action. Metabolically, PGI_2 is degraded in similar fashion as the primary prostaglandins, although not in the same tissues. While prostacyclin is not oxidized in the lungs by 15-prostaglandin dehydrogenase (15-PGDH) to the inactive 15-keto form,[10] the major deactivation pathway for the primary prostaglandins,[11] it is rapidly removed from circulation by the liver through 15-PGDH and β-oxidation of the upper side chain.[12] With regard to its selectivity of action, it is not possible to substantially inhibit platelet aggregation without producing significant and unwanted cardiovascular effects[13] (vasodilation, decrease in blood pressure).

As with similar problems faced in other areas, chemists world-wide have met this challenge with the preparation of a large number of analogs of prostacyclin. The objective is clear: to synthesize derivatives which are chemically and metabolically stable but which still possess comparable levels of activity and ideally separate the features of antiaggregating ability and vasodilation. The approaches to these problems are widely varied due to lack of knowledge of structure activity relationships at the outset as well as lack of a detailed mechanism of action for PGI_2 itself and prostaglandins in general.

To overcome problems of chemical stability, analogs where the enol ether has been stabilized by delocalization (Figure 2) (**1** and **2**),[14,15] replaced by a simple ether and more stable allylic ether function (**3** and **4**),[16,17] or where the 6,9-oxygen has been substituted by a heteroatom (**5** and **6**)[18,19] or carbon (**7**),[20] just to name a few, have been prepared. While many of these derivatives show only a trace of the activity of PGI_2, a few demonstrate activity at comparable levels.[18-20]

Solutions to problems of metabolism developed for the primary prostaglandins which suffer similar biological degradation (15-hydroxy and β-oxidation) were naturally applied to prostacyclin. These include the preparation of the 15-methyl,[21] 16-methyl,[22] 16,16-dimethyl,[22] and 13-dehydro derivatives.[23] It has been well demonstrated for the primary prostaglandins that such modifications render the materials inert to 15-prostaglandin hydroxy dehydrogenase.[21-24] The 13-dehydro PGI_2 (**8**)[25] prepared by Fried is probably one of the best examples in this regard with respect to available information. The derivative possesses potency similar to PGI_2 in inhibiting platelet aggregation but is metabolized more slowly than PGI_2 itself.[25] Similarly, as the carboxamides of primary prostaglandins exhibit the same activity profiles as the natural materials but with increased duration of activity due to resistance to β-oxidation,[26] amide derivatives of prostacyclin have been prepared.[27]

The 6a-carba[20] and 13-dehydro PGI_2[25] analogs (**7** and **8**) also illustrate a basic point. Although 6a-carba PGI_2 (7) is chemically stable indefinitely while possessing comparable potency to PGI_2 itself (approximately one tenth as potent), nevertheless, in vivo, its duration of activity is similar to prostacyclin and little selectivity is observed.[28] On the other hand, 13-dehydro PGI_2 (**8**),[25] while metabolically more stable, is chemically as unstable as PGI_2 and again is not selective.[25] Thus, the key to the design of a pharmaceutically useful agent rests not with the individual consideration of the problems of stability, activity, and selectivity separately. Instead, all factors must be addressed simultaneously.

C. The Fluorination of Biologically Active Molecules

Fluorination has been used extensively in the area of biologically active molecules.[29-33] Mild reagents for the selective introduction of fluorine have been developed and the subject has recently been reviewed.[34,35] As with any other analoging program, the objectives of introducing fluorine include enhancing activity and / or selectivity and increasing chemical or metabolic stability. Sterically fluorine, with its small van der Waals radius (1.35 Å), closely resembles hydrogen (1.20 Å) and, upon substitution, causes minimal spatial disturbances to the overall molecule. Because of the high carbon fluorine bond energy, replacement of fluorine for hydrogen can render a position resistant to metabolic oxidation. Its strong inductive effect, a consequence of its high electronegativity (4 vs. 2.1 for hydrogen), can alter the electron distribution in a molecule affecting dipole moments, polarizability, and reactivity and stability of functional groups. Substitution of fluorine for hydrogen also increases a molecule's lipophilicity, thus, affecting absorption and transport. Physiochemically, fluorine most closely resembles oxygen (van der Waals radius = 1.35 vs. 1.40 and bond length C—F = 1.39 vs. C—O 1.43), again a consequence of its high electronegativity (4 vs. 3.5 for oxygen), and can function as a hydrogen bond

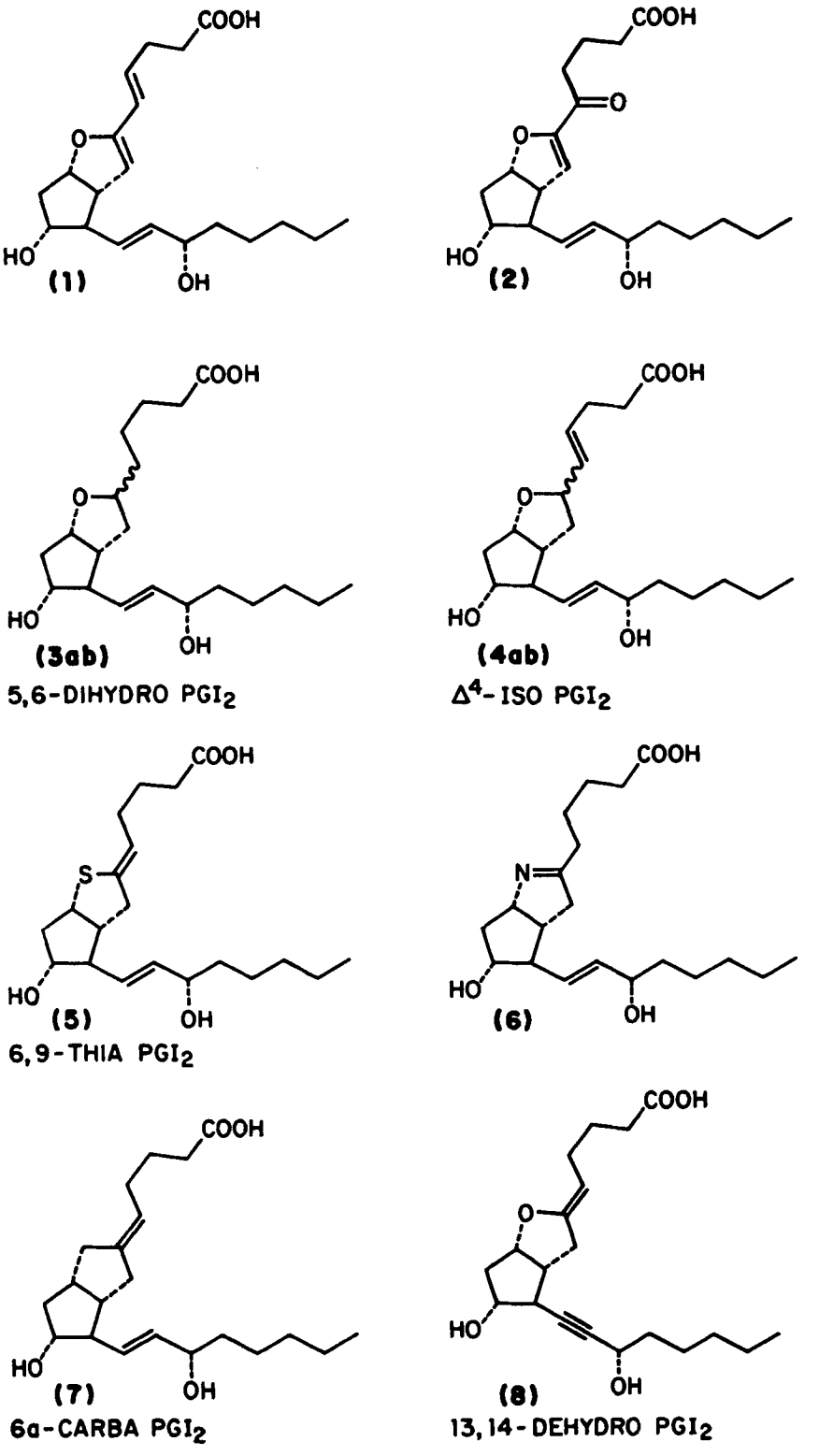


FIGURE 2. Analogs of prostacyclin.

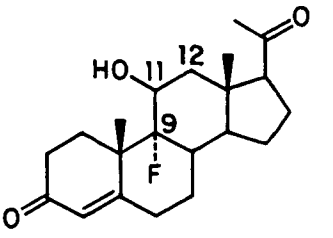


FIGURE 3. 9α-Fluoro-11β-hydroxyprogesterone.

acceptor,[36] thus, acting as a suitable replacement for hydroxyl and alkoxyl groups in some systems.[37]

To illustrate the use of fluorine as a replacement for hydrogen and its affect on functional groups, consider its application to the steroid field.[38-42] In some of the earliest work it was demonstrated that the corticoid activity of 11β-hydroxy steroids increases with the acidity of the 11β-hydroxyl group.[43] Thus, a 9α-fluoro substituent enhanced to a significant degree the activity due to its inductive effect (Figure 3). Structure activity relationships indicated fluorine (vs. Cl, Br, I, OCH_3, OH, H) had a maximum effect due to its high electronegativity combined with its small size causing minimal steric problems. Similar effects were observed for the 12α-fluoro derivatives and it was noted that since the 11β-hydroxyl group is essential for activity, the effect was not due to the presence of fluorine alone.

While it has been known for a relatively long time that fluorine can function as a hydrogen bond acceptor,[36] the use of fluorine as a substitute for oxygen in biological systems has been much less studied than as a hydrogen replacement.[29-33] Perhaps the most extensive use in this area has been in carbohydrate chemistry.[37,44-46] In general, substitution in sugars as in steroids assumes a minimal effect on overall stereochemistry, and this has been confirmed by X-ray structural analysis.[46] To illustrate this application, consider the problem of the mapping of the binding of carbohydrates to their carrier proteins. In studies of the transport of galactose in the intestine[37] it was determined that 6-fluoro-6-deoxygalactose undergoes active transport while 6-deoxy galactose does not. By systematic substitution of hydrogen and fluorine for hydroxyl, it was, thus, possible to identify which positions of galactose interact with the protein as hydrogen bond donors and acceptors (Figure 4). The results suggested transport to involve hydrogen bonding to the substituents at 3 and 6, while the 5 position was unimportant and the substituent at carbon 2 either functioned as a donor or was involved in the formation of a covalent bond.

In summary, the substitution of fluorine into a biologically active molecule can have a dramatic effect on potency, stability, and selectivity. By establishing structure activity relationships it is sometimes possible to draw conclusions as to the role played by fluorine in effecting these changes. However, more often it is not possible to explain all modifications of activity simply by identifying any single alteration in the chemical and physiochemical properties of a fluorinated molecule. Furthermore, although some of the alterations in the chemistry of functional groups can be anticipated and even measured, their effects on the biochemical interactions with a protein or enzyme are not clear and cannot always be reasonably predicted.[39]

D. Fluorinated Prostaglandins

The introduction of fluorine into the steroid molecule represents the most extensive use of fluorination in the area of biologically active compounds. Enhancement of biological activity and improved selectivity along with reduction of undesired properties

FIGURE 4. Galactose and 6-deoxy-6-fluoro galactose.

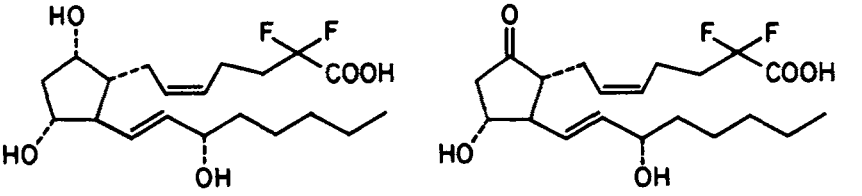


FIGURE 5. 2,2-Difluoro $PGF_{2\alpha}$ and 2,2-difluoro PGE_2.

and side effects have been achieved and a number of fluorinated steroids are marketed today.[40] Thus, considering the intense chemical and biological interest in prostaglandins and prostaglandin derivatives over the past 15 years, with similar problems of stability, selectivity, and side effects, it is not surprising that fluorination has again found considerable application. As many of these materials were utilized as precursors of the first fluoro prostacyclins, a brief summary of the area and discussion of the rationale behind the application of fluorination is in order. This is especially true in terms of addressing problems of metabolism and selectivity since these are common both to the primary prostaglandins and prostacyclin itself.

1. Prostaglandins Fluorinated at the 2-Position

The 2,2-difluoro derivatives of $PGF_{2\alpha}$ and PGE_2 have been prepared[47] and it is reported[47] that these materials exhibit the same biological properties as the parent materials but show a longer duration of action and, thus, equal responses can be achieved at reduced dosages (Figure 5). β-Oxidation is a major pathway of prostaglandin metabolism to the inactive desoxy forms,[11] thus, it appears that fluorination effectively blocks side-chain oxidation.

2. Prostaglandins Fluorinated at the 9-, 11-, and 15-Position

A series of 9α- and β-fluoro, 9α or β- and 11α or β-difluoro, 11α- and β-fluoro, 11, 11-difluoro,[48] and 15-fluoro $PGF_{2\alpha}$[49] derivatives have been reported. While some derivatives demonstrated activity comparable to the natural materials, others did not demonstrate any significant levels of response. In general, no basic explanation for the observed structure activity relationships was advanced. While it may appear in some cases that fluorine is acting as a physiochemical replacement for oxygen, the overall situation seems to be more complex.

3. Prostaglandins Fluorinated at the 10-Position

Both the 10-α- and 10-β-fluoroderivatives of $PGF_{2\alpha}$ have been prepared.[50,51] Assumably the idea was to probe the inductive effect of fluorination at this position on the 9α-and 11α-hydroxyl groups with the resulting effects on activity and, ideally, to

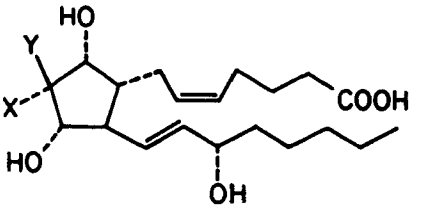


FIGURE 6. (X = F, Y = H) 10α-Fluoro $PGF_{2\alpha}$ (X = H, Y = F) 10β-fluoro $PGF_{2\alpha}$.

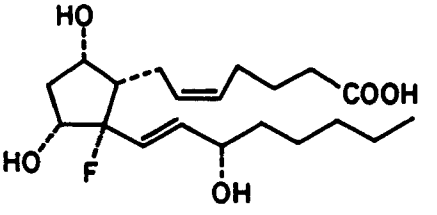


FIGURE 7. 12-Fluoro $PGF_{2\alpha}$.

achieve some selectivity. This is similar to the strategy for the preparation of the 9α- and 12α-fluoro corticoid steroid derivatives previously discussed.[43] No biological data, however, were reported as to the consequences of substitution (Figure 6).

4. Prostaglandins Fluorinated at the 12-Position

An effort to enhance the antifertility activity of $PGF_{2\alpha}$ over smooth muscle-stimulating activity resulted in the preparation of 12-fluoro $PGF_{2\alpha}$[52] (Figure 7). It was assumed that fluorine would cause minimal disturbance to the conformation of the $PGF_{2\alpha}$ derivative while providing some protection from metabolism. Indeed, 12-fluoro $PGF_{2\alpha}$ demonstrated more than a tenfold increase in activity over $PGF_{2\alpha}$ in the antifertility assay while its effect on smooth muscle was significantly decreased. Further, the derivative was not susceptible to oxidation by 15-hydroxyprostaglandin dehydrogenase.[53] No explanation was offered to account for the observed selectivity imparted by fluorine and whether there is any connection between selectivity or resistance to metabolism. As for the protection from 15-HPDH it was suggested that the 12-fluoro substituent altered the conformation of the 14-hydrogen relative to the 15-hydroxyl group affecting the overall conformation of the molecule from its natural form and, thus, inhibiting binding to the enzyme.[54] As an alternative explanation consider the observation that fluorination at the 6α or 6β position of steroid enones[55] shifts the equilibrium toward the reduced form by increasing the electrophilicity of the enone toward reduction in the reversible enzyme-catalyzed reaction. Just how selectivity is related to metabolic stability is unclear (Figure 9).

5. Prostaglandins Fluorinated at the 14-Position

The successful enhancement of antifertility activity and selectivity and the inhibition of metabolism achieved with the substitution of fluorine at the 12-position of $PGF_{2\alpha}$[52,53] led to the preparation of 14-fluoro $PGF_{2\alpha}$[56] (Figure 8). Again by analogy to steroidal systems,[55] substitution of an electron withdrawing group on the olefin favors the reduced form in the enzyme-catalyzed reversible conversion of the allylic alcohol to the enone. However, as the antifertility activity of 14-fluoro $PGF_{2\alpha}$ is significantly reduced relative to $PGF_{2\alpha}$ or 12-fluoro $PGF_{2\alpha}$,[56] and no studies of the ability of 14-fluoro $PGF_{2\alpha}$ to act as

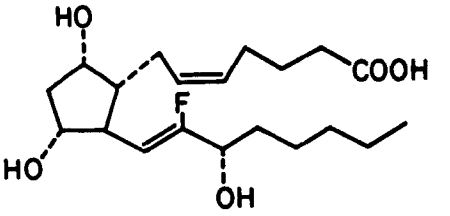


FIGURE 8. 14-Fluoro $PGF_{2\alpha}$.

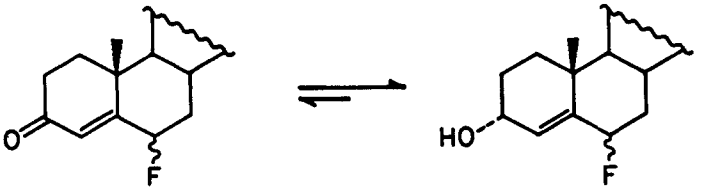


FIGURE 9. 6α- and 6β-Fluoro steroids.

a substrate for 15-hydroxy prostaglandin dehydrogenase were reported, it is difficult to draw any conclusion as to the effect of the 14-fluoro substituent on oxidation. Similar results were reported for 14-chloro $PGF_{2\alpha}$[57] which showed only weak antifertility activity relative to $PGF_{2\alpha}$.

6. Prostaglandins Fluorinated at the 16-Position

It was established early on that one of the primary reasons for the short duration of action of the natural prostaglandins was oxidation of the allylic alcohol to the inactive enone form by 15-hydroxy prostaglandin dehydrogenase.[11] Thus, a number of derivatives were designed to inhibit or eliminate this deactivation pathway. These included the 15-alkyl,[21] 16-alkyl,[22] and 13-dehydroprostaglandins[23] already discussed, but also the 16-fluoro and 16,16-difluoro prostaglandins.[47,58,59] 16-Fluoro-$PGF_{2\alpha}$ and PGE_2 undergo oxidation at the 15-position at significantly reduced rates than the parent compounds.[58] The 16, 16-difluoro derivatives (Figure 10) are completely resistant to oxidation in vitro.[58,59] This inhibition of enzymatic oxidation is again believed to be the result of destabilization of the carbonyl group by the α-fluorine substituents causing a shift in equilibrium favoring the reduced form. This effect was previously cited in the case of 12- and 14-fluoro prostaglandins by analogy to β- and γ-fluoro steroid enone systems.[55] It has also been demonstrated for α-fluoro keto steroids as well.[55] 16, 16-Difluoro $PGF_{2\alpha}$ demonstrates comparable activity to $PGF_{2\alpha}$ in stimulating smooth muscle. Both 16, 16-difluoro $PGF_{2\alpha}$ and PGE_2 possessed significantly greater antifertility activity (approximately tenfold greater potency) compared to the natural products. Also, increased selectivity of action again seems to be associated with resistance to metabolism.

II. FLUORINATED PROSTACYCLINS

A. Strategy and Synthesis

Fluorinated derivatives of prostacyclin can be readily divided into three major classes: PGI_2 derivatives possessing an unstabilized enol ether linkage prepared from available fluoro prostaglandins, PGI_2 derivatives possessing the enol ether where fluorine has been introduced specifically to stabilize this function, and fluoro derivatives of hydrolytically

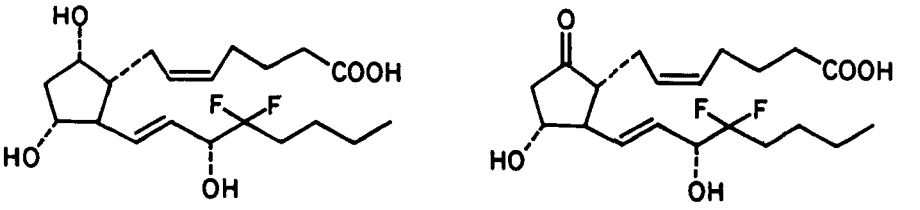


FIGURE 10. 16,16-Difluoro $PGF_{2\alpha}$ and 16,16-difluoro PGE_2.

stable prostacyclin analogs. The following discussion will concentrate on the strategy and objectives for preparing these derivatives and the synthesis of individual compounds in some detail from the point of initial introduction of fluorine. The next section (II.B) will discuss the biological activity of selected compounds and the overall achievement of objectives.

The general approach to fluoro prostaglandins involves the introduction of fluorine early on in the synthesis prior to the completion of the prostanoid skeleton and unmasking of the ring hydroxyl groups or already incorporated into the reagents for introduction of the side chains. This is in contrast to the general approach to fluorinated steroids where fluorine can be introduced into the steroid nucleus itself.[38-42] However, prostaglandins are much more sensitive compounds and despite the improvements made in the area of mild and selective fluorinating agents,[34,35] fluorine is best introduced into intermediates at convenient points along the synthetic route.

Since most of the literature on fluoro prostaglandins is in the form of preliminary communications or patents, in many cases a detailed experimental is not reported as well as general analytical and spectral data and reaction yields. Furthermore, in many patents it is difficult to distinguish between case examples and compounds which have actually been prepared.

1. Fluorinated PGI_2 Derivatives Possessing an Unstabilized Enol Ether Prepared from Fluorinated Prostaglandins

It is not surprising that the first fluorinated PGI_2 derivatives were prepared from available fluoro prostaglandins. The strategy was simple, advantages including enhanced stability, or selectivity imparted to fluoro prostaglandins by fluorination might also be translated to prostacyclin. The synthetic approach involved the use of fluoro $PGF_{2\alpha}$ derivatives which are readily converted to the corresponding prostacyclins.

a. 12-Fluoro PGI_2

Substitution of a fluorine at the 12-position of $PGF_{2\alpha}$ significantly enhanced antifertility activity relative to smooth muscle stimulation while also inhibiting oxidative deactivation by 15-hydroxy dehydrogenase[52,53] (Section I.D.4). In the hope that a 12-fluoro substituent would favorably enhance the activity and metabolic stability of prostacyclin, 12-fluoro PGI_2 (**9**) was prepared[60] from 12-fluoro $PGF_{2\alpha}$ (**10**)[52] using the now well-known approach of cyclization (I_2, K_2CO_3) followed by E_2 elimination of iodide (DBU) to form the cyclic enol ether[61] (Scheme 1). (The regiochemistry of cyclization and the stereospecific formation of the Z-enol ether have been extensively discussed.[16,61]) The synthesis of 12-fluoro $PGF_{2\alpha}$[52] (**10**) began with the optically active bicyclic ketal ester **11**.[62] Treatment of the enolate (LDA) of **11** with perchloryl fluoride[63] afforded the tertiary fluoro compound **12**. Conversion of **12** to the lactone intermediate **13** with introduction of the upper and lower side chains to complete the synthesis essentially followed the Corey approach.[64] It was not expected that the fluoro substituent would have a stabilizing effect on the enol ether and none was observed.

b. 14-Fluoro PGI_2

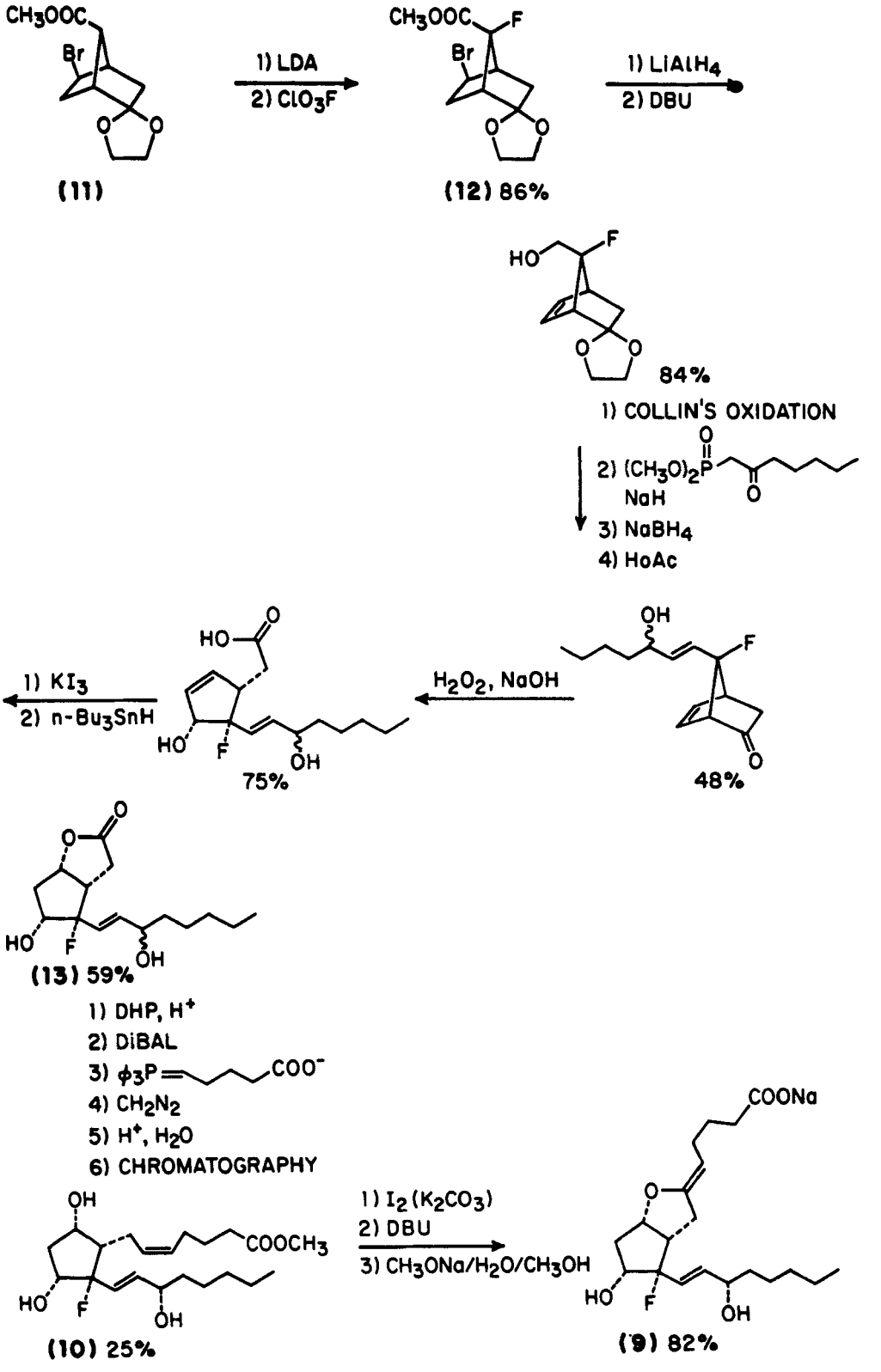
Although the introduction of fluorine at the 14-position of $PGF_{2\alpha}$ significantly reduced antifertility activity relative to $PGF_{2\alpha}$ and 12-fluoro $PGF_{2\alpha}$ (**10**) (Section I.D.5), it was hoped that the anticipated protection offered by the 14-fluoro group to oxidation of the 15-hydroxyl group could be realized and, thus, offer some enhancement to the activity of the corresponding PGI_2 derivative. 14-fluoro $PGF_{2\alpha}$ (**14**)[56] was prepared (Scheme 2) starting with the bicyclic aldehyde **15** available from the ester **11** (Scheme 1)[62] by the described sequence utilizing the corresponding unfluorinated derivatives. Introduction of the lower side chain utilized the standard approach[64] with the requistie fluoro phosphonate **16** prepared by fluorination of the sodium salt of dimethyl-2-oxoheptylphosphonate (**17**) (NaH, $FClO_3$).[56] However, the presence of the fluorine resulted in the formation of the *cis* enone **18** rather than the required *trans* system. Isomerization was accomplished by reduction of the enone ($NaBH_4$) to the allylic alcohol and formation of the sulfenate[65] (*p*-toluenesulfenyl chloride) which underwent a 2,3-sigmatropic shift to the sulfoxide **19**. A second 2,3-sigmatropic shift induced by trimethylphosphite[66] afforded the desired epimeric *trans* allylic alcohols **20**. Conversion of **20** to 14-fluoro $PGF_{2\alpha}$ methyl ester (**14**) and finally to 14-fluoro PGI_2 (**21**) followed the sequence described in Scheme 1. Again, no enhancement of chemical stability was observed.

c. 15-Fluoro-15-Deoxy PGI_2

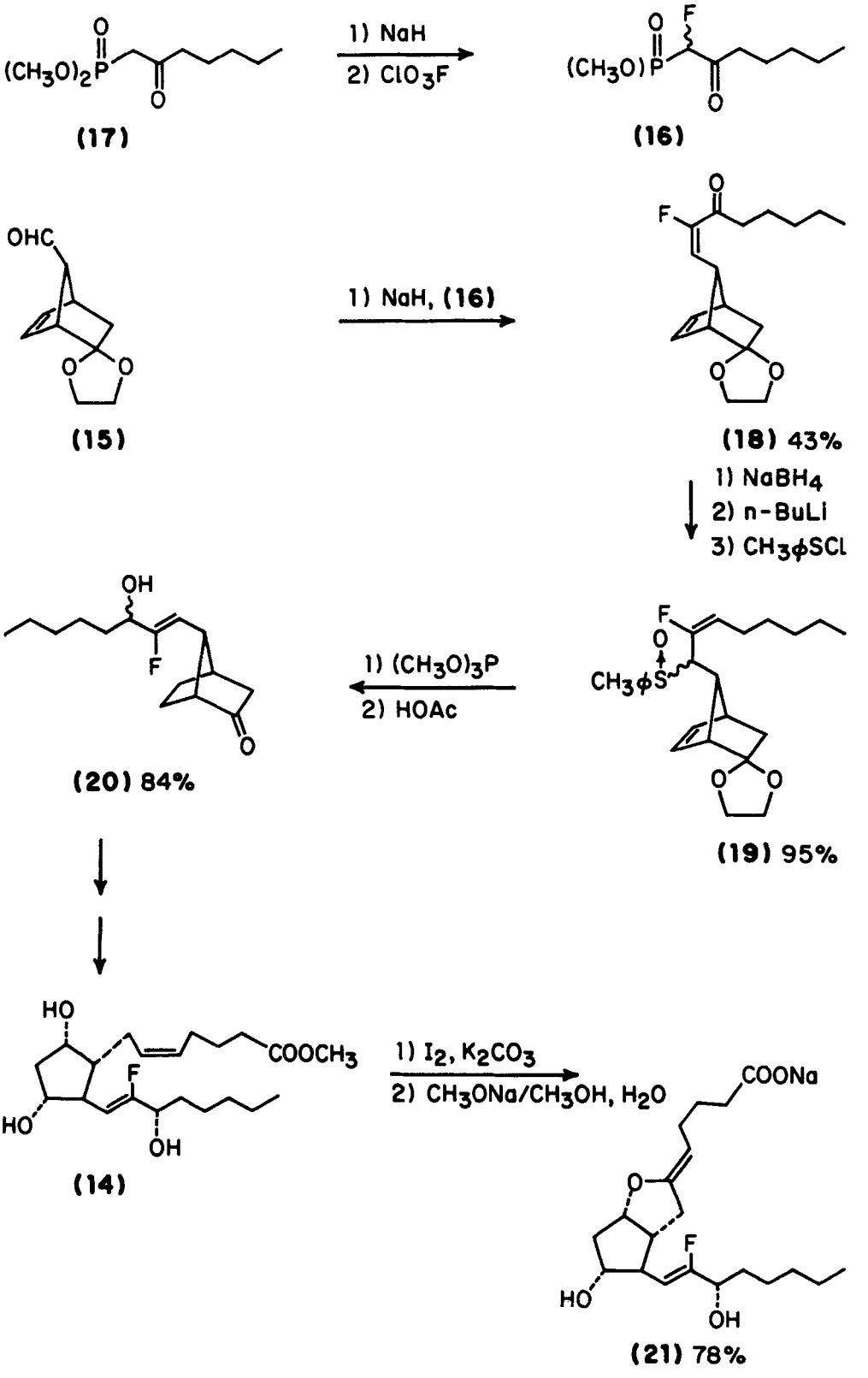
While no general conclusions could be drawn as to the role of fluorine in biologically active 9- and 11-fluoro $PGF_{2\alpha}$ derivatives,[48] and information on the activity of 15-fluoro prostaglandins[49] is presently unavailable, it can be assumed that the strategy behind the substitution of fluorine at the 15-position of PGI_2 was to utilize fluorine as a physiochemical mimic for the hydroxyl group. Thus, it was hoped that 15-fluoro-15-deoxy PGI_2 (**22**)[67] (Scheme 3) would retain significant levels of activity while possessing a longer duration of action due to loss of susceptibility to deactivation by 15-hydroxy dehydrogenase. Readily available PGA_2 methyl ester[68] (**23**) was converted to the epimeric mixture of fluorides **24** (morpholino sulfur trifluoride).[69] This material was then elaborated to the corresponding $PGF_{2\alpha}$ derivative **25** by the sequence developed by Upjohn.[70] The well-known iodine cyclization-elimination sequence[61] afforded the sodium salt of 15-fluoro-15-deoxy PGI_2 (**22**) as a mixture of epimers. Although hydrolytic stability is not discussed, **22** would not be expected to be any more stable than PGI_2 itself.

2. Prostacyclins Containing a Fluorine-Stabilized Enol Ether Function

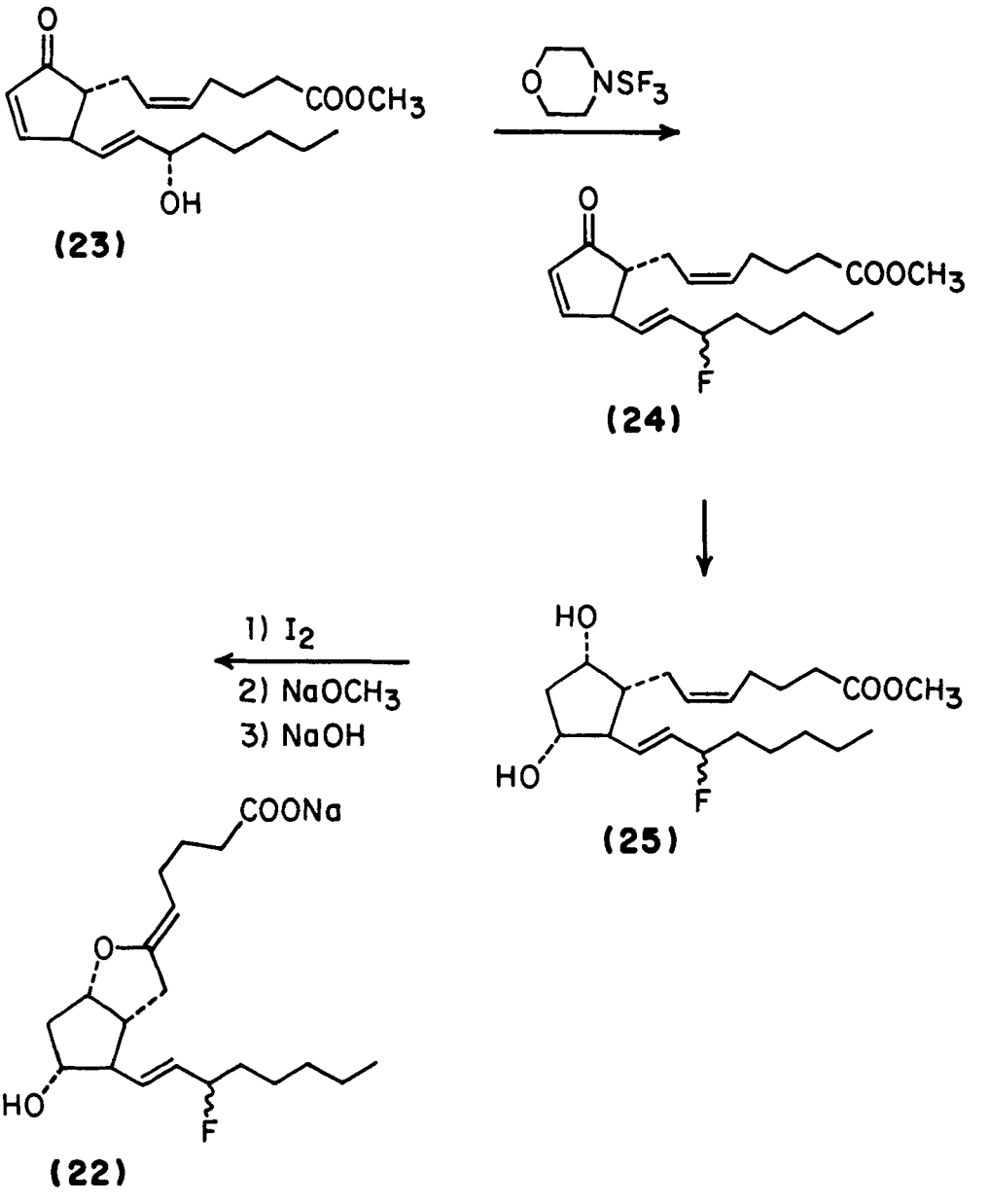
Fried[71] has reported the synthesis of a series of prostacyclins where fluorine has been systematically introduced at sites where, because of its high electronegativity, it can inductively stabilize the enol ether function toward hydrolysis. This has been demonstrated for enol ethers substituted by trifluoromethyl groups.[72] The placement of electron withdrawing groups in conjugation with or in close proximity to the enol ether can reduce the electron density of the system and decrease the susceptibility of the linkage to protonation which is mechanistically the first step of hydrolysis.[73] This approach using substituents other than fluorine has been shown to be successful in stabilizing the enol ether group but has also resulted in significant reductions in activity due to conformational and steric effects.[14,15] It was assumed at the outset of these studies that fluorine used as a replacement for hydrogen would have a minimal effect on the overall molecule, as has been demonstrated in other systems.[29-33] In addition to fluorine substitution, in most of derivatives reported the *trans* allylic alcohol system of the lower side chain has been replaced by the propargylic system. Fried has demonstrated that such



SCHEME 1. 12-Fluoro PGI_2.



SCHEME 2. 14-Fluoro PGI_2.

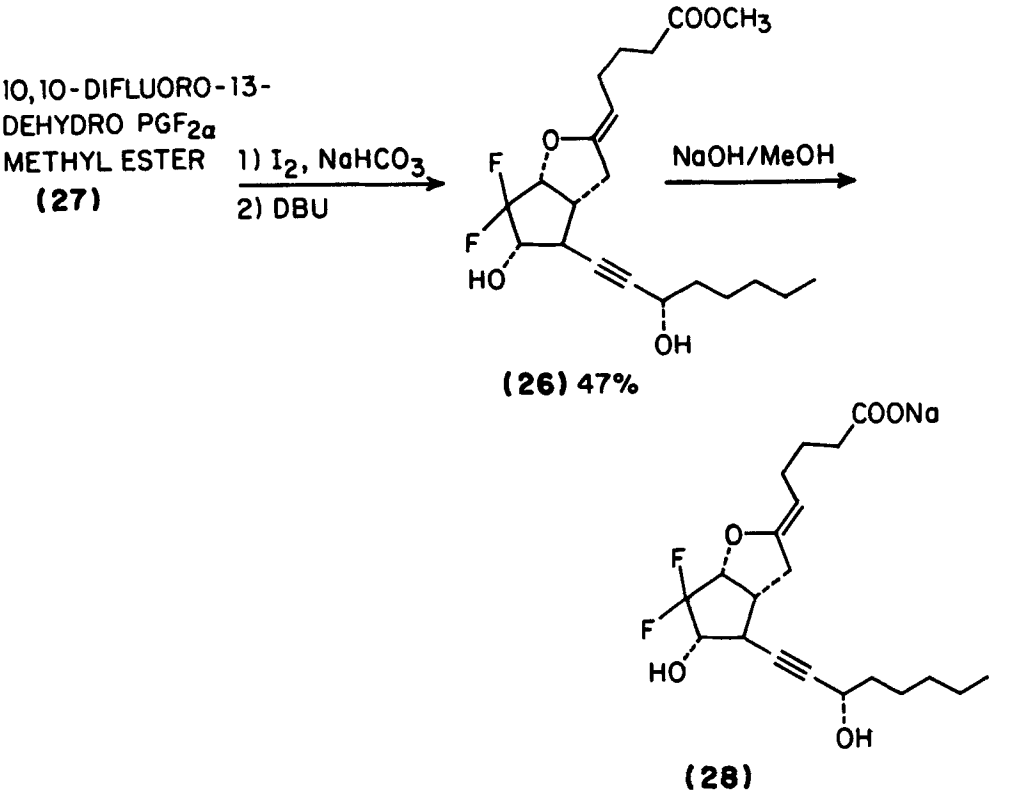


SCHEME 3. 15-Fluoro-15-deoxy PGI_2.

13-dehydroprostaglandins and dehydroprostacyclin **8** are resistant to oxidation by 15-hydroxy dehydrogenase.[24,25] Thus, the two major contributors to the problem of the lability of prostacyclin, chemical and metabolic stability, are addressed. The general synthetic approach follows that reported by Fried for the total synthesis of 13-dehydro prostaglandins.[23] Yields are reported wherever specific information is available.

a. 10,10-Difluoro-13-Dehydro-PGI_2 and 10,10-Difluoro-PGI_2

10,10-Difluoro-13-dehydro PGI_2 methyl ester (**26**)[74] (Scheme 4A) was prepared from 10,10-difluoro-13-dehydro $PGF_{2\alpha}$ (**27**) (Scheme 4B) following the standard method[16,61]



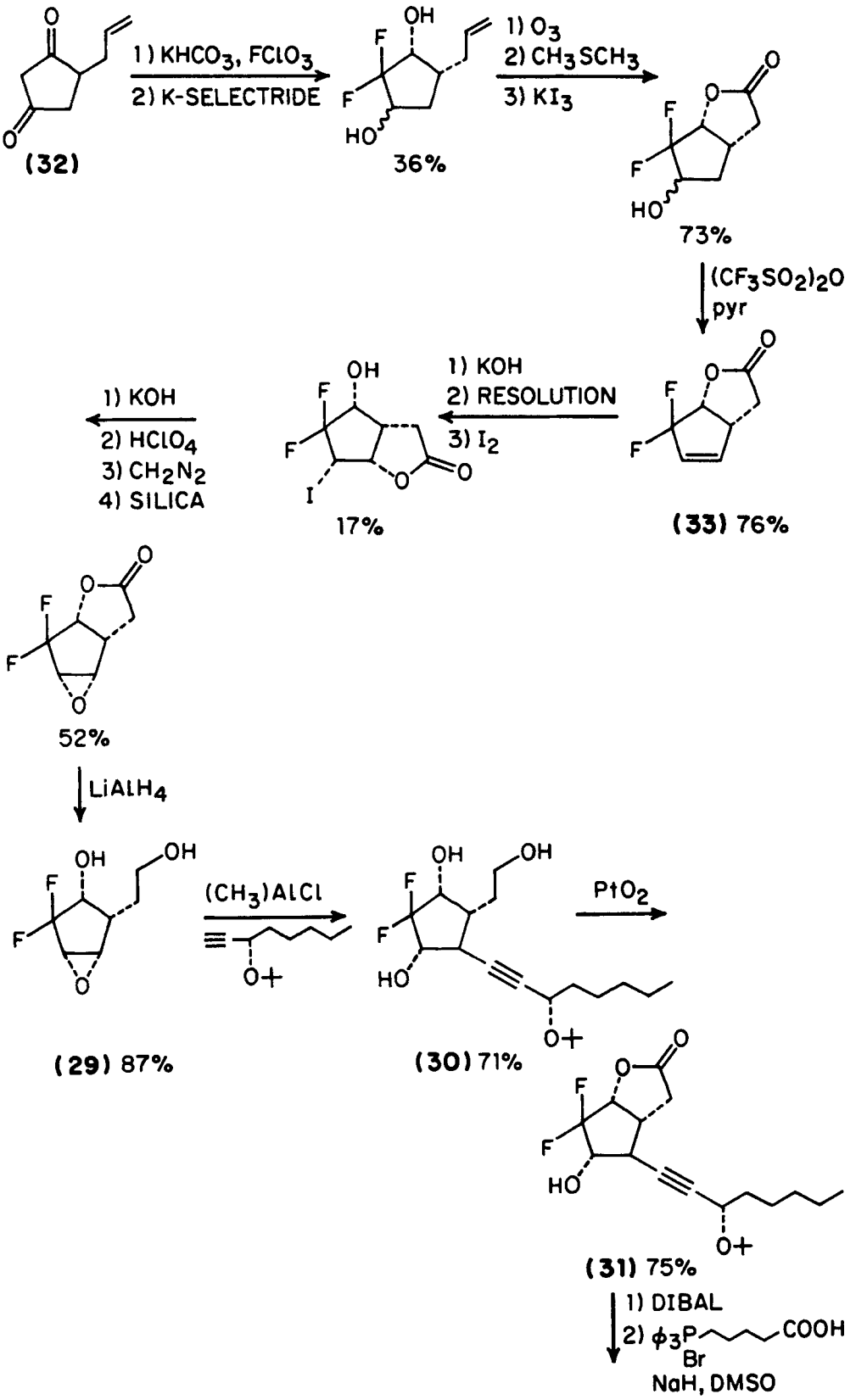
A

SCHEME 4. (A) 10,10-Difluoro-13-dehydro PGI_2; (B) 10,10-difluoro-13-dehydro $PGF_{2\alpha}$; (C) 10,10-difluoro PGI_2.

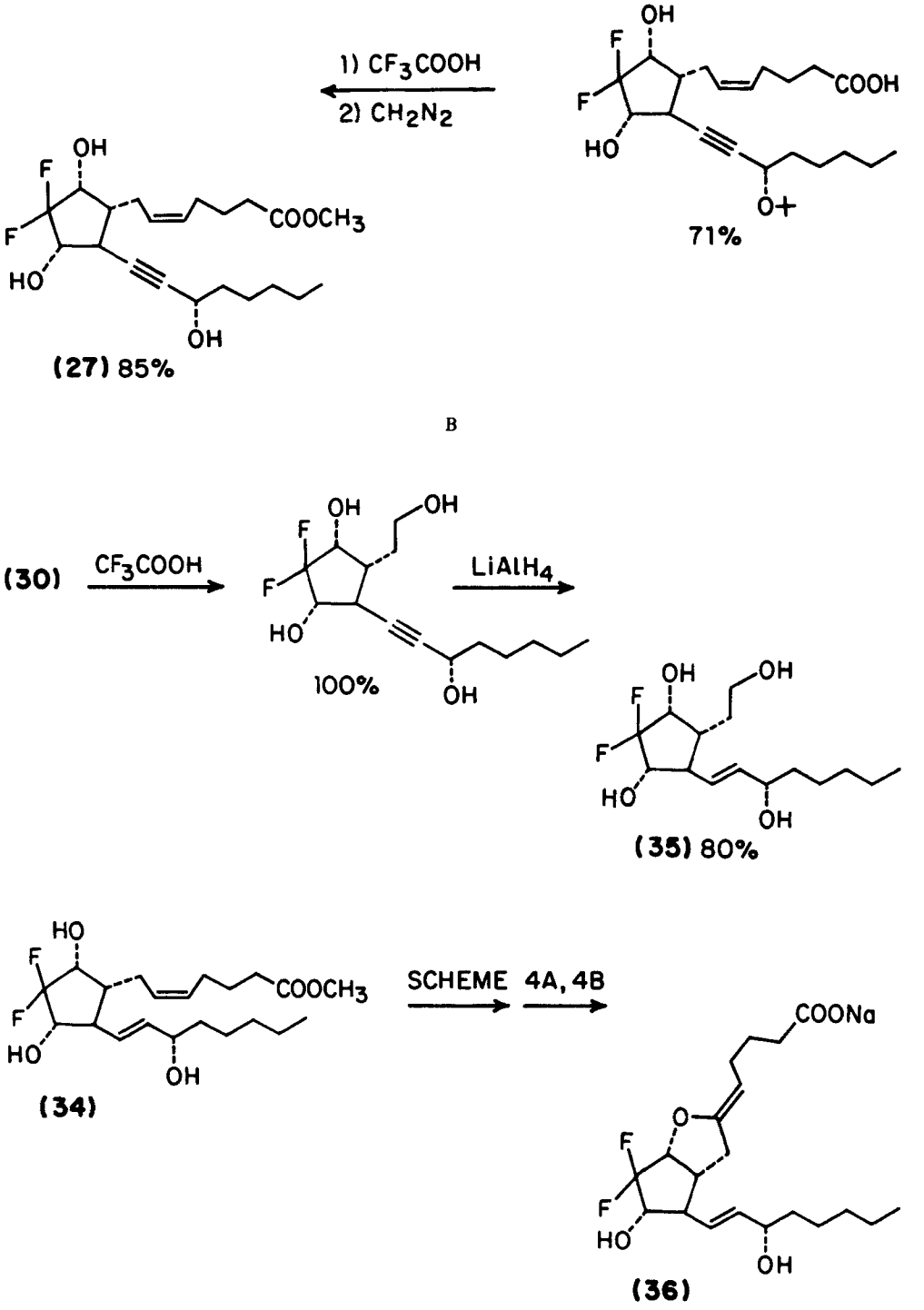
of cyclization with iodine followed by base-induced E_2 elimination of HI affording the Z-enol ether (Scheme 4A). Basic hydrolysis then yielded the sodium salt **28**.

The synthesis of 10,10-difluoro-13-dehydro $PGF_{2\alpha}$ (**27**)[71,74] (Scheme 4B) parallels that reported by Fried for the corresponding $PGF_{2\alpha}$ itself[75,76] from the point of introduction of the lower side chain. Thus, regioselective ring opening[75] of diol epoxide **29** with S-3-t-butyloxy-1-octynyldimethylalane[76] yielded triol **30**. Selective oxidation of the primary alcohol (PtO_2)[75] resulted in formation of the lactone **31**. The upper side chain was introduced using the approach developed by Corey.[64] Removal of the t-butoxy protecting group (CF_3COOH) and esterification (CH_2N_2) gave the desired compound **27**. The difluoro diol epoxide **29** was available in optically active form by a multistep sequence (Scheme 4B) starting with 1,3-cyclopentanedione. Fluorine was introduced by treatment of allyldione (**32**) with perchloryl fluoride[63] in the presence of base (K_2CO_3). Lactone **33** was resolved as its acid salt [(R) − (+)-2-(1-naphthyl)ethylamine]. The acid was then converted to the intermediate diol epoxide **29** for introduction of the side chains.

10,10-Difluoro PGI_2 was similarly prepared from 10,10-difluoro $PGF_{2\alpha}$ (**34**) (Scheme 4C). Deprotection of the dehydro intermediate **30** (Scheme 4B) propargylic alcohol (CF_3COOH) and reduction of the tetraol to the corresponding *trans* allylic compound **35** ($LiAlH_4$) followed by introduction of the upper side chain and cyclization as in Scheme 4A provided 10,10-difluoro PGI_2 sodium salt **36** itself.



SCHEME 4B



SCHEME 4C

The methyl esters of 10,10-difluoro PGI_2 (**36**) and 10,10-difluoro-13-dehydro PGI_2 (**28**) showed enhanced stability relative to PGI_2 and are both chromatographable on silica without noticeable decomposition. Solutions of **28** could be acidified (pH 3), the

free acid extracted and isolated as the methyl ester **26** (CH_2N_2) with only minor hydrolysis observed, whereas only 6-keto $PGF_{1\alpha}$ was isolated upon similar treatment of PGI_2. The half-life of the difluoro dehydro derivative **28** was approximately 24 hr (pH 7.4, 37°C), while for PGI_2 itself 50% loss of activity was observed after only 10 min.[74]

b. 7,7-Difluoro-13-Dehydro PGI_2 and 7,7,10,10-Tetrafluoro-13-Dehydro PGI_2

The key intermediate for the synthesis of 7,7-difluoro-13-dehydro PGI_2 (**37**)[71] is the difluoro bicyclic lactone **38** (Scheme 5A) prepared by cycloaddition of chloroketene to cyclopentadiene[77] followed by a two-step conversion to the dichlorolactone (**39**).[78] Halogen exchange (KF, diethylene glycol)[79] afforded the corresponding difluoride **38** which was then elaborated to 7,7-difluoro-13-dehydro PGI_2 (**37**) as in Schemes 4A and 4B.

Purportedly, 7,7,10,10-tetrafluoro-13-dehydro PGI_2 (**40**) (Scheme 5B) can be prepared from the tetrafluoro lactone **41** again as in Schemes 4A and 4B. The problem arises with the preparation of the lactone from 1,1-difluorocyclopentadiene (Scheme 5B). 1,1-Difluorocyclopentadiene is not known in the literature and, thus, it would seem that the inclusion of this compound was as an example for patent purposes.

Reduction of the 7,7- and 7,7,10,10-fluoro derivatives of the tetraol (Scheme 4C) would allow preparation of the PGI_2 derivatives.

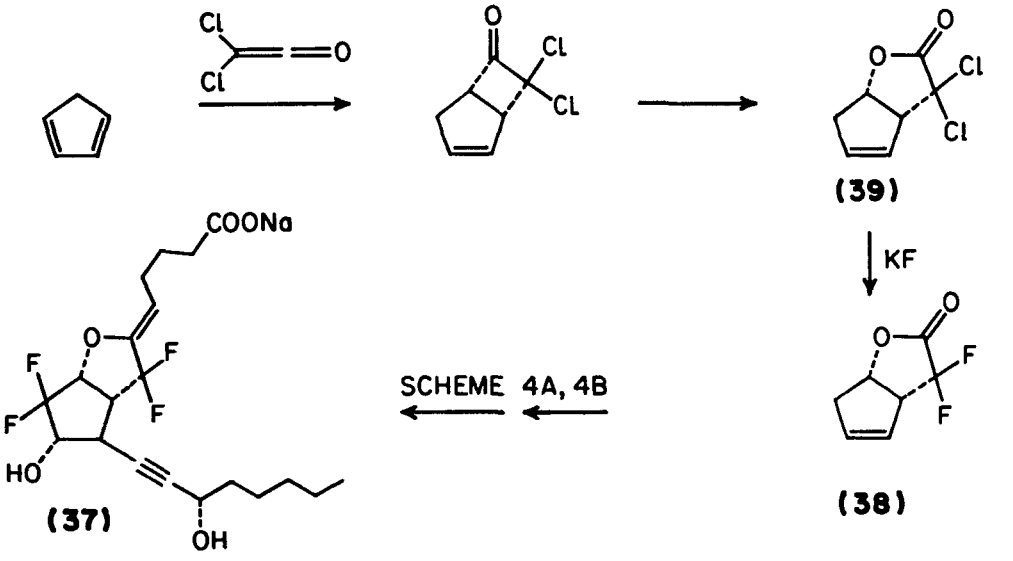
No specific comments on the hydrolytic stability of **37** or, not surprisingly, **40** relative to 10,10-difluoro-13-dehydro PGI_2 **28** or PGI_2 were discussed, however. Reported yields for **37** are similar to those obtained in the synthesis of 10,10-difluoro-13-dehydro PGI_2 (**28**) and 10,10-difluoro PGI_2 (**36**).

c. 5-Fluoro PGI_2 Derivatives

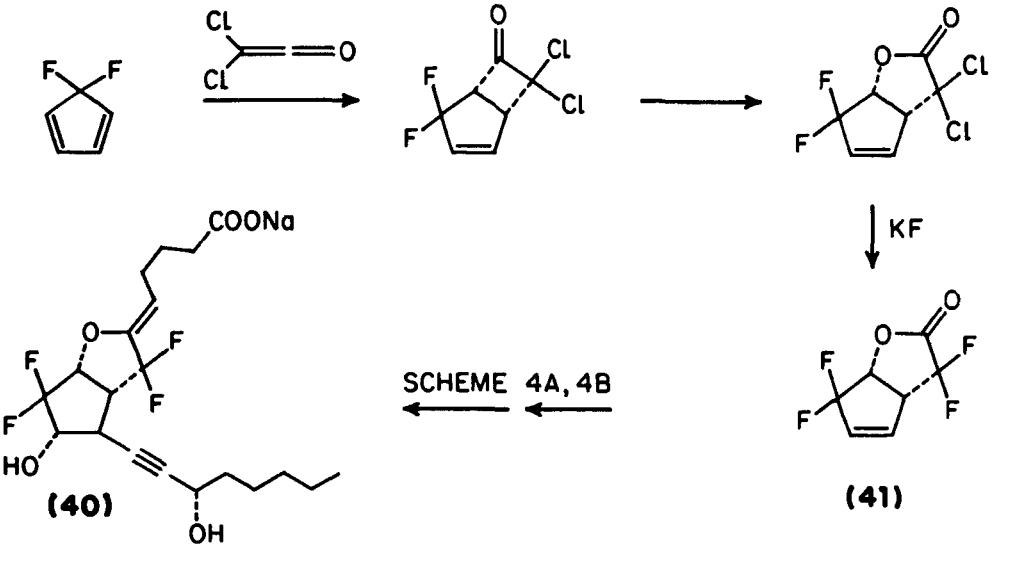
The incorporation of fluorine into the enol ether system of prostacyclin itself might be expected to have a maximum effect on hydrolytic stability, thus, suggesting the preparation of 5-fluoro PGI_2 derivatives. Although the preparation of 5-fluoro-13-dehydro prostacyclin derivatives are claimed[71] no specific experimental is described. In general terms it was stated that such derivatives could be prepared from the corresponding $PGF_{2\alpha}$ derivatives available as in Scheme 4B with the 5-fluorine introduced into the upper side chain utilizing the modified Wittig reagent, 1-fluoro-4-carboxybutyltriphenylphosphine ylid (Scheme 6). Fluorination of ylids with perchloryl fluoride and subsequent preparation of fluoro olefins has been described.[80] However, although it is well known that use of such reagents leads to a mixture of *cis/trans* isomers,[80] this question was not addressed in the general discussion. The use of a C-5 olefinic mixture of $PGF_{2\alpha}$ derivatives would complicate the iodine cyclization elimination sequence[16] for the preparation of the enol ether leading to a mixture of E and Z isomers. Also, no mention is made of any increased stability resulting from the addition of the 5-fluoro substituent. However, in a recent paper[81] which described the synthesis of 5-chloro PGI_2, it was reported that the chlorine substituent significantly increased stability toward hydrolysis in acid media ($t\frac{1}{2}$ = 1.5 hr for 5-chloro PGI_2 vs. 22 sec for PGI_2, pH 4.7).

d. 4,4-Difluoro-13-Dehydro PGI_2

The same rationale for the preparation of the 10,10-difluoro- and 7,7-difluoro-13-dehydro PGI_2 derivatives **28** and **37** was applied in the case of the 4,4-difluoro derivative **42** (Scheme 7).[71] Thus, it was expected that fluorine substitution α to the enol ether would inductively stabilize the system to hydrolysis.[72] The synthesis (Scheme 7) involves a reversal of the usual procedure for attachment of the upper prostaglandin side chain. The prostanoid phosphonium salt **43** was coupled with the fluoro aldehyde **44** affording



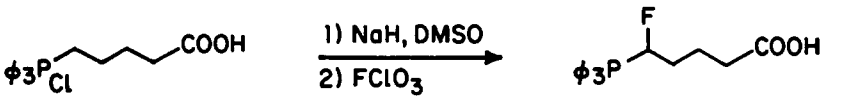
A



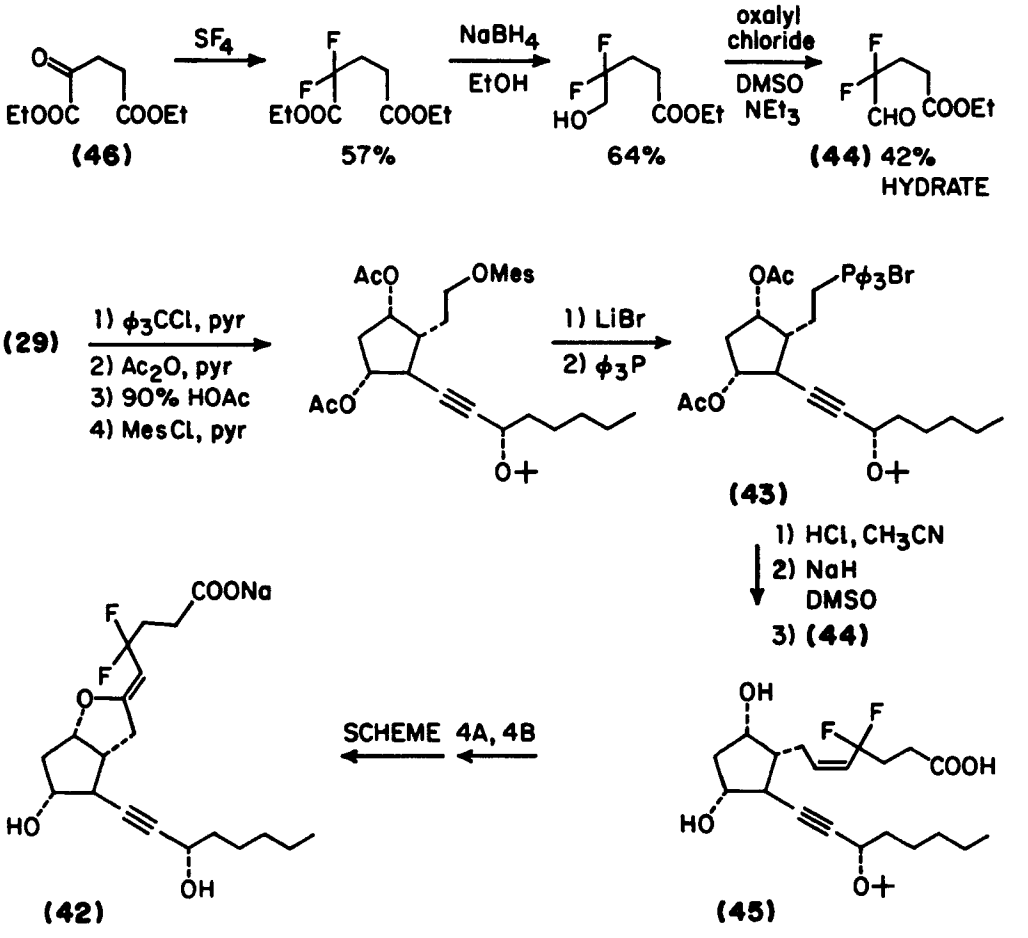
B

SCHEME 5. (A) 7,7-Difluoro-13-dehydro PGI_2; (B) 7,7,10,10-tetrafluoro-13-dehydro PGI_2.

4,4-difluoro-13-dehydro $PGF_{2\alpha}$ (**45**). This intermediate was then converted to the desired 4,4-difluoro-13-dehydro PGI_2 sodium salt (**42**) as previously described (Scheme 4A). The phosphonium salt is available from the triol **29** (Scheme 4B) through selective protection of the primary and secondary hydroxyl groups (ϕ_3CCl, pyr). The difluoro aldehyde **44** was synthesized (Scheme 7) from readily available diethyl-2-keto succinate **46** and existed mainly as the hydrate. Again, no specific comments on the relative stability of **42** were presented, however.



SCHEME 6. 5-Fluoro PGI_2 derivatives.



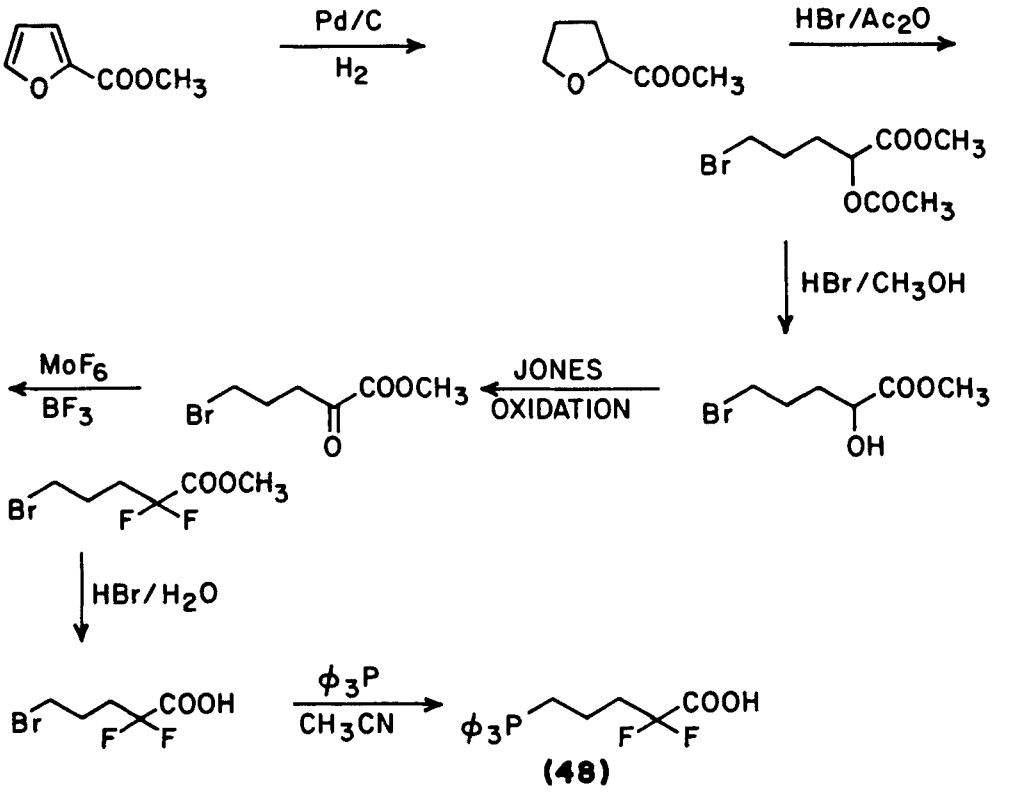
SCHEME 7. 4,4-Difluoro-13-dehydro PGI_2.

3. Fluorinated Derivatives of Stable PGI_2 Analogs

It is generally accepted that a pharmaceutically useful prostacyclin would combine the features of chemical and metabolical stability with some selectivity with respect to antiaggregating and cardiovascular activity.[6] Thus, as previously discussed, a large number of derivatives have been prepared. Included in this number are derivatives where the enol ether linkage has been replaced by a more or less structurally similar but chemically more stable system, along with fluorination at key sites previously demonstrated with the primary prostaglandins to increase metabolic stability and, in some cases, selectivity.

a. 2,2-Difluoro- and 16,16-Difluoro-5,6-Dihydro PGI_2

6α And 6β-5,6-dihydro PGI_2 (**3ab**)[16] were among the first chemically stable analogs of



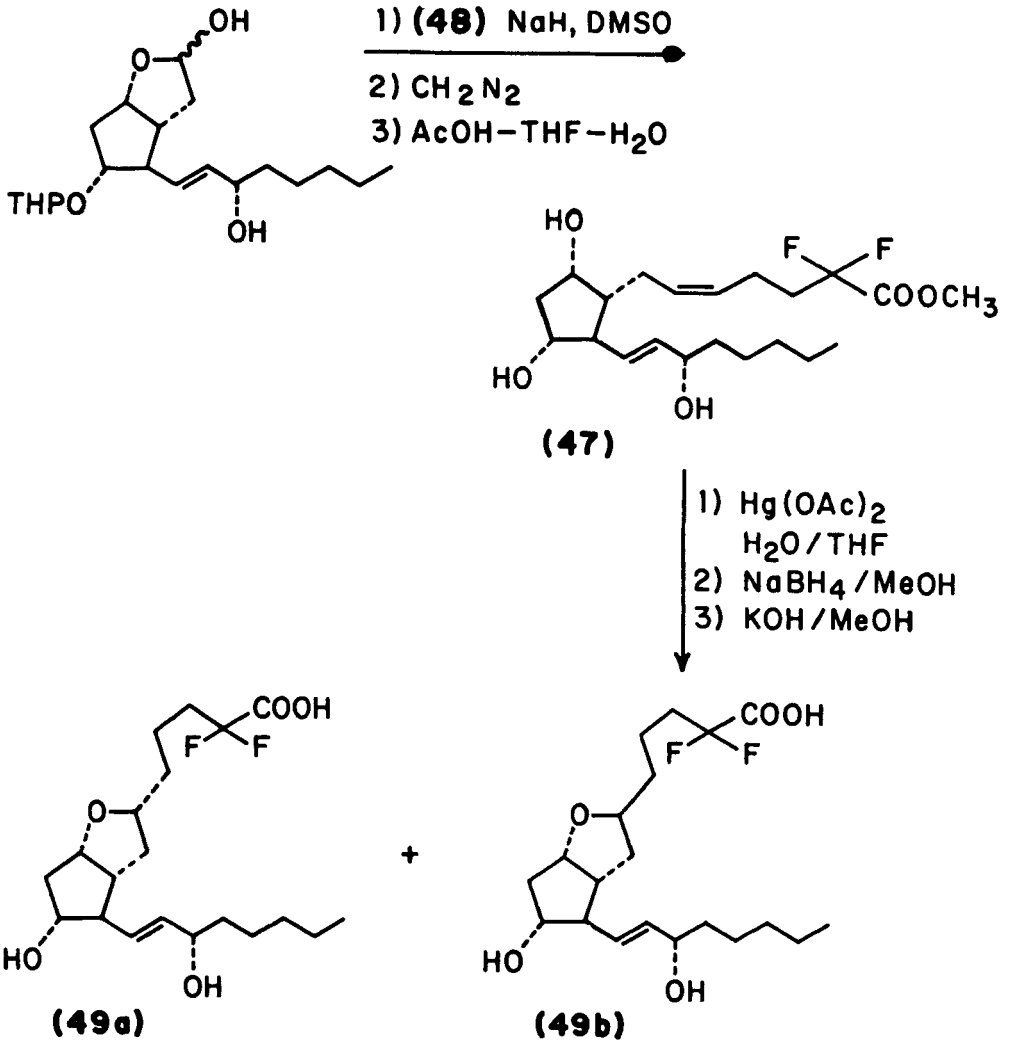
SCHEME 8. 4,4-Difluoro-4-carboxybutyl triphenylphosphonium bromide.

prostacyclin prepared. Reduction of the enol ether function rendered these materials completely resistant to hydrolysis but also drastically reduced activity (more than 500 times less active in inhibiting platelet aggregation). Further, although chemically stable, as with PGI_2 itself and the primary prostaglandins these materials are subject to metabolic oxidation. With the aim of increasing the levels of activity through reduction of metabolic inactivation the 2,2- and 16,16-difluoro derivatives were prepared.[82] As was demonstrated with the primary prostaglandins (Section I.D.1 and I.D.6) fluorination at these positions effectively blocked β-oxidation of the upper side chain or deactivation by 15-hydroxydehydrogenase and significantly increased potency.

The 2,2-difluoro derivatives were prepared (Scheme 9) by the mercury-catalyzed cyclization-reduction sequence, described by the Upjohn group,[16b] utilizing 2,2-difluoro $PGF_{2\alpha}$ (**47**)[47] as starting material. 2,2-Difluoro $PGF_{2\alpha}$ (**47**) was synthesized following the Corey approach[64] introducing the fluorines as part of the upper side-chain Wittig reagent. The modified phosphonium salt **48** was prepared as shown (Scheme 8). The epimeric prostacyclins (C6, endo, and exo) are readily separated by chromatography.

Similarly, the 16,16-difluoro $PGF_{2\alpha}$ **52**[47] was prepared by condensing the difluoro keto phosphonate **50**[47] with the Corey lactone **51** (Scheme 10) and further elaboration to **52** using standard methods.[64] Iodine cyclization afforded the epimeric iodo ethers (**53ab**), which upon reduction (n-Bu_3SnH) and deprotection yielded the endo and exo ethers (**54ab**) separable by chromatography.[16b] The conditions for cyclization, regiochemistry, and assignment of isomers has been discussed in detail.[16b]

Finally, the corresponding tetrafluoro derivatives are easily synthesized from the corresponding $PGF_{2\alpha}$ derivatives utilizing both modified Wittig reagents and either of the above cyclization-reduction methods.

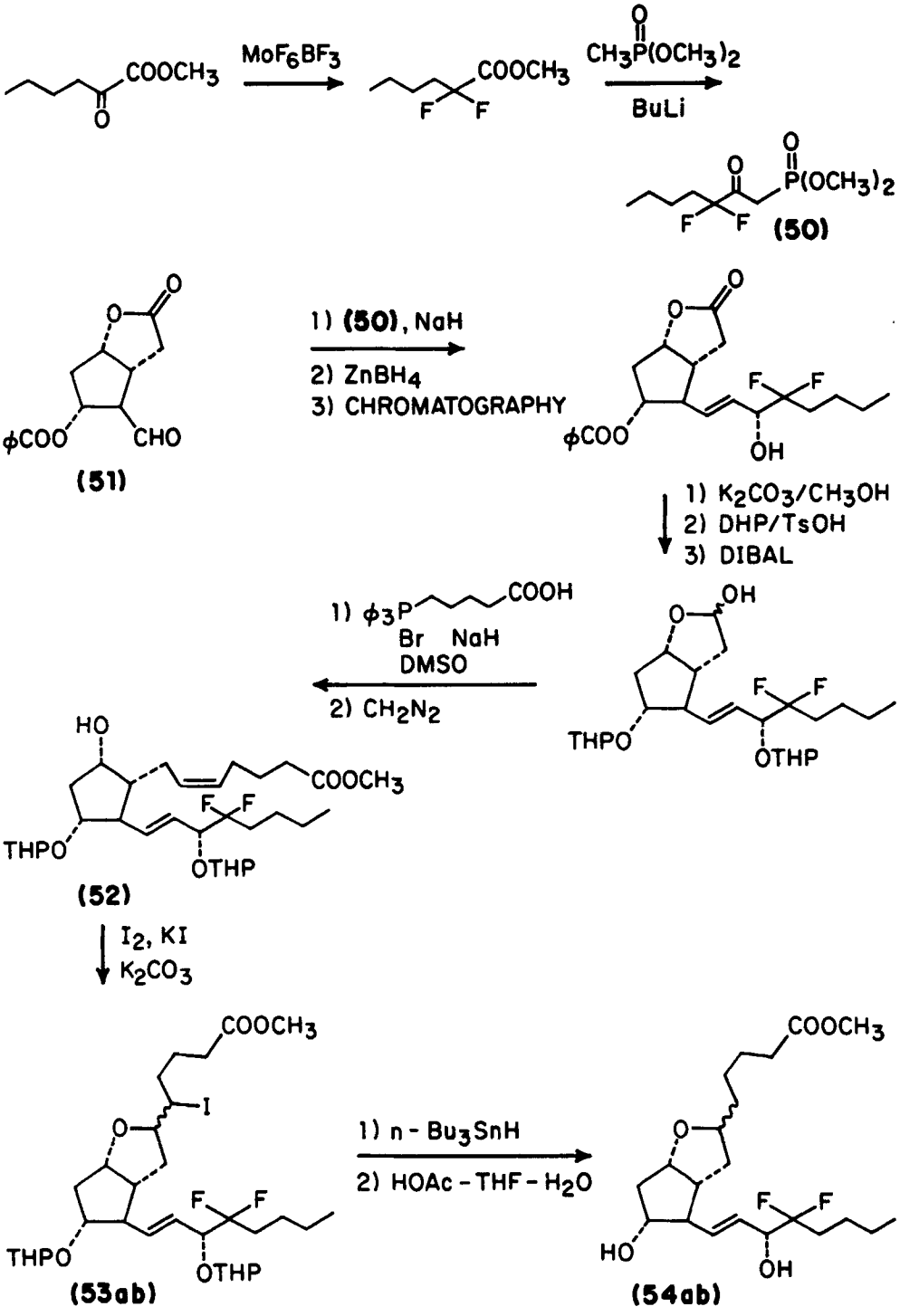


SCHEME 9. 2,2-Difluoro-5,6-dihydro PGI_2.

b. 12-Fluoro-5,6-Dihydro PGI_2 and 12-Fluoro-Δ^4-Iso PGI_2

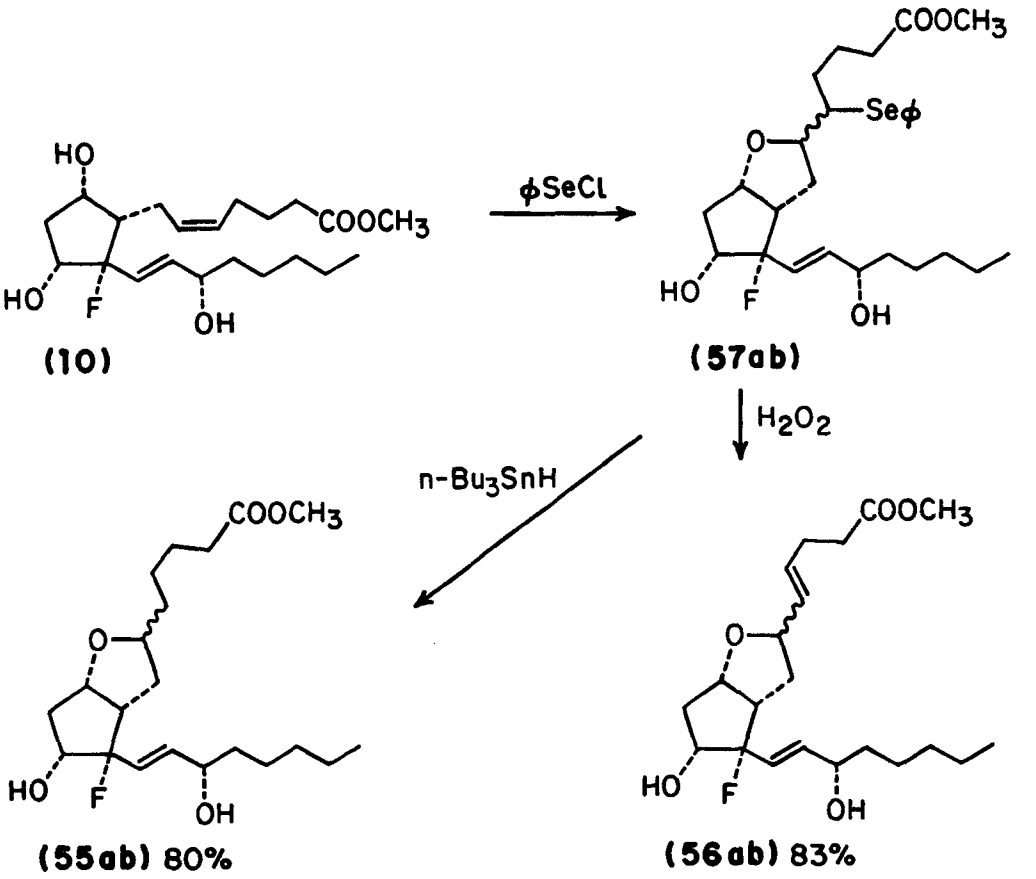
The ability of a 12-fluoro substituent on $PGF_{2\alpha}$ to significantly increase antifertility activity over effects on smooth muscle[52,53] led to the preparation of the corresponding dihydro- and iso-PGI_2 derivatives **55ab** and **56ab** respectively.[60] As previously discussed (Section I.D.4), the 12-fluoro substituent reduces the susceptibility to oxidation by 15-hydroxydehydrogenase. Thus, selenium-induced cyclization (ϕSeCl)[17,83] of 12-fluoro $PGF_{2\alpha}$ (**10**) (Scheme 11) afforded an epimeric mixture of selenoethers (**57ab**). Reductive removal of selenium (n-Bu_3SnH)[84] or oxidative elimination (H_2O_2)[85] yielded the dihydro- and iso-PGI_2 derivatives, respectively. Unlike their unfluorinated counterparts, however, the isomers were not separable by preparative layer chromatography and were hydrolyzed to their corresponding acids and studied as mixtures.

The inability to resolve the epimers of **55ab** and **56ab** by preparative layer chromatography while the corresponding unfluorinated compounds are readily separated[17] suggests hydrogen bonding of the 11-hydroxyl group with the 12-fluoro substituent. In the unfluorinated derivatives it is believed that the ability to separate the



SCHEME 10. 16,16-Difluoro-5,6-dihydro PGI_2.

exo from the endo isomer is a result of hydrogen bonding between the 6,9-oxygen and the 11-hydroxyl group in the exo isomer which is reduced or prevented in the endo isomer for steric reasons. It has also been suggested that since the 11-hydroxyl group is in close



SCHEME 11. 12-Fluoro-5,6-dihydro PGI_2 and 12-fluoro-Δ^4-iso PGI_2.

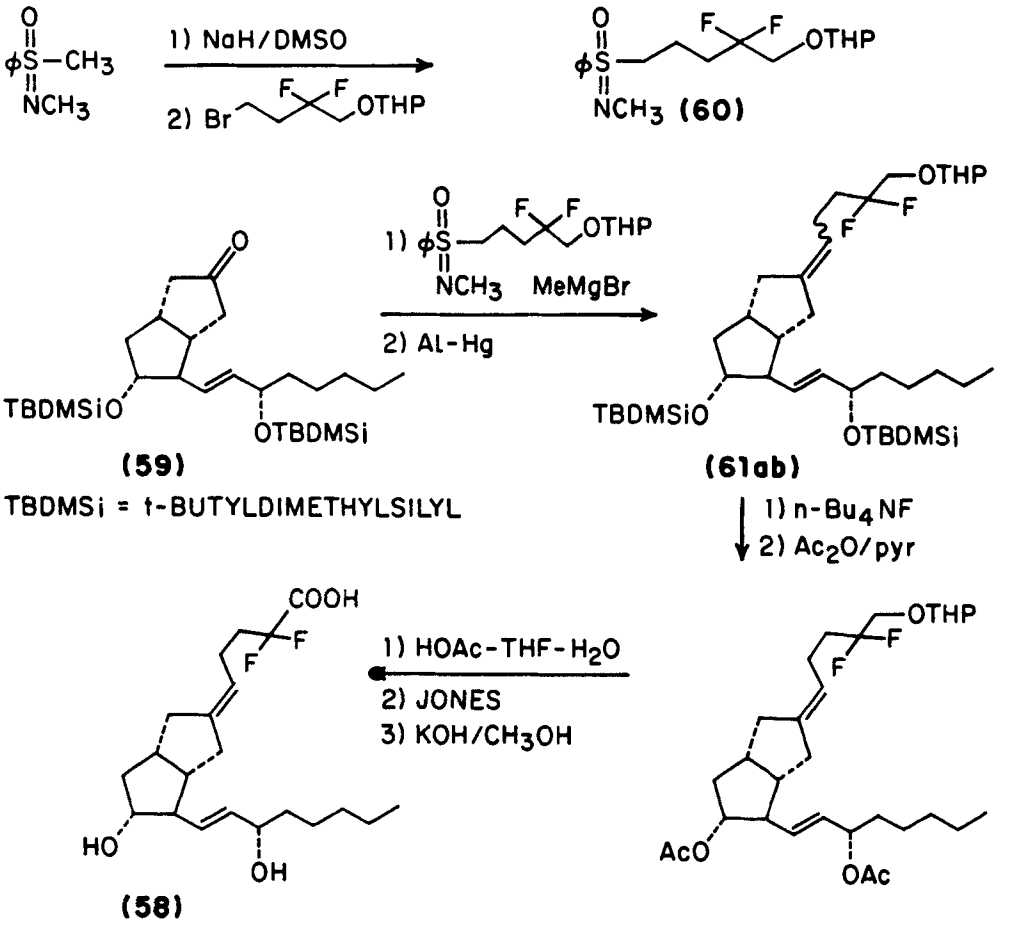
proximity to the enol ether in PGI_2 as demonstrated by the ease of internal ketal formation,[86] it might serve to stabilize the linkage by the withdrawal of electron density from the system. Hydrogen bonding to the fluoro substituent would interrupt this interaction and, thus, the 12-fluorine would actually reduce the hydrolytic stability of 12-fluoro PGI_2. No effort was made, however, to determine if this was the case.[87]

c. 2,2-Difluoro- and 16,16-Difluoro-6a-Carba PGI_2

6a-Carba PGI_2 (7)[20] is a chemically stable analog of prostacyclin completely resistant to hydrolysis under physiological conditions, but, of equal importance, possessing comparable potency and a similar activity profile to PGI_2 itself (= one tenth as active).[20] While it might seem that carba prostacyclin (7) would be the ideal candidate for pharmaceutical development, it has been demonstrated that, while hydrolytically stable, the material is metabolically unstable possessing a similar duration of activity as PGI_2 itself.[28] Like prostacyclin, 6a-carba PGI_2 (7) is a substrate for 15-hydroxy prostaglandin dehydrogenase[28] and is rapidly inactivated in vivo.

As the problem of metabolic oxidation had been successfully addressed with the primary prostaglandins with the preparation of the 2,2-difluoro and 16,16-difluoro derivatives (Sections I.D.1 and I.D.6), the same approach was naturally applied to 6a-carba PGI_2 (7) as it had been to other stable prostacyclin analogs.

2,2-Difluoro-6a-carba PGI_2 (58)[88] (Scheme 12) was prepared from the bicyclic ketone 59, a common intermediate in many of the reported syntheses of carba PGI_2 (7) itself.[20]



SCHEME 12. 2,2-Difluoro-6a-carba PGI_2.

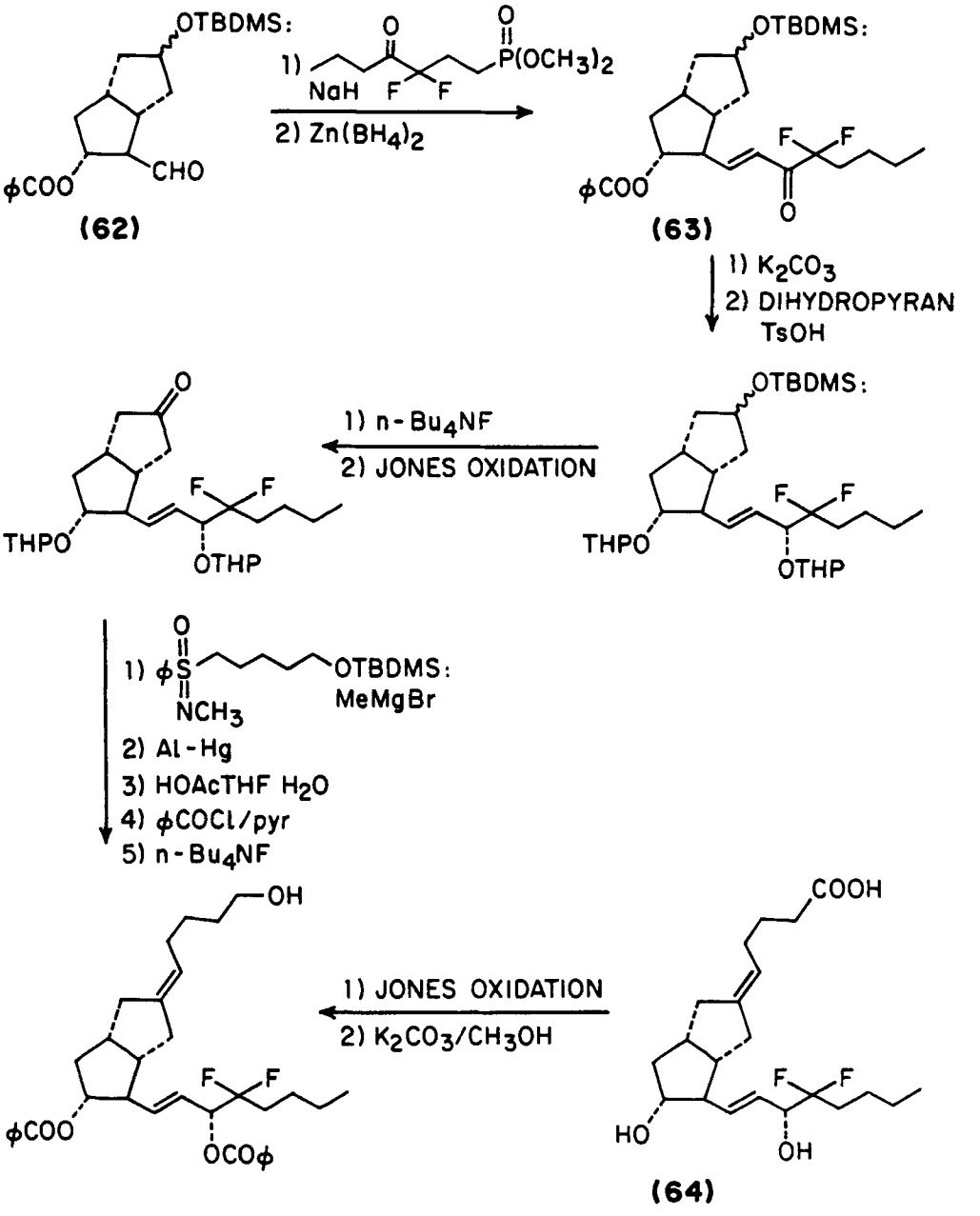
Thus, (Scheme 12) addition of the difluoro sulfoximine carbanion **60** to **59** and reductive elimination[89] yielded the isomeric olefins **61ab**. The E-Z isomers were separated chromatographically and the compound of correct configuration converted to 2,2-difluoro-6a-carba PGI_2 (**58**). The required sulfoxime reagent was prepared (Scheme 12) as shown with the bromide available from the difluoro ester of Scheme 8 by reduction and tetrahydro pyranylation.[88]

Desilylation of **59** (Scheme 12) followed by benzoylation, reduction, and silylation of the ketone, and ozonolysis provided the aldehyde **62** (Scheme 13). Condensation of **62** with dimethyl-(2-keto-3,3-difluoro)-phosphonate (**50**)[47] (Scheme 10) afforded the 16,16-difluoro-15-keto intermediate **63** which was elaborated to 16,16-difluoro-6a-carba PGI_2 (**64**) by methods utilized for the preparation of the parent compound.[20]

The assignment of the stereochemistry of the C-5,6 olefins was based upon the observed greater activity of one isomer (natural PGI_2 configuration) over the other.

d. 5-Fluoro-6a-Carba PGI_2

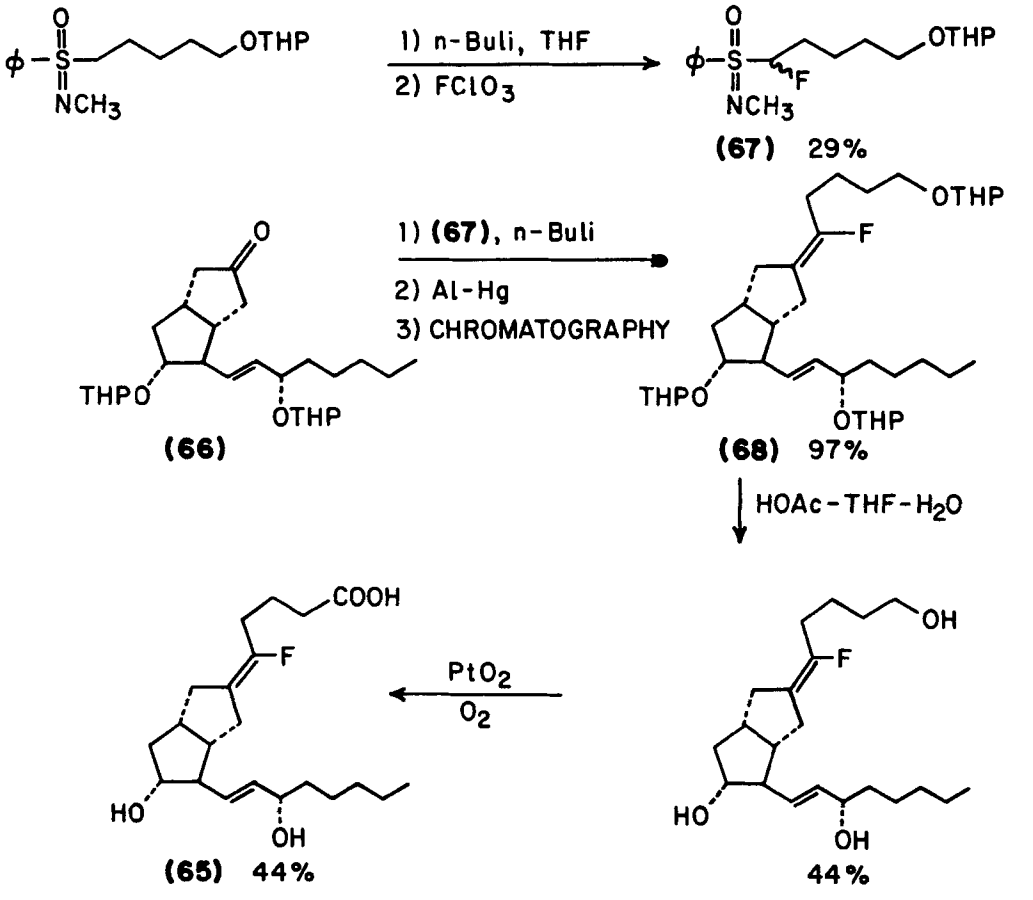
Although the reasons behind the preparation of 5-fluoro-6a-carba PGI_2 (**65**)[90] (Scheme 14) were not discussed, it can be assumed that it was of interest to determine the effect of substituting electronegative fluorine for hydrogen on activity. The C-5,6-olefin in the natural configuration is crucial to activity. As this double bond is somewhat



SCHEME 13. 16,16-Difluoro-6a-carba PGI_2.

polarized in an enol ether, perhaps the object was to simulate this polarization by fluorine substitution and, thus, hopefully to enhance activity.

The bicyclic ketone **66** (Scheme 14) is again a common intermediate in the synthesis of 6a-carbon PGI_2.[20] Protection of the hydroxyl groups, coupling with the sulfoximine **67**, and chromatographic separation of isomers afforded **68** which required only deprotection and selective oxidation (PtO_2,O_2)[75] of the primary alcohol to the carboxylic acid affording 5-fluoro-6a-carba PGI_2 (**65**). The requisite fluoro sulfoximine is prepared by fluorination of the parent sulfoximine anion with perchloryl fluoride (Scheme 14).[63]



SCHEME 14. 5-Fluoro-6a-carba PGI_2.

As in the previous cases (Section II.A.3.c) the assignment of the C5,6 E and Z isomers was based on bioassay.

B. Biology of Fluorinated Prostacyclins

Disappointingly, the literature describing the biology of the fluorinated prostacyclins is extremely limited. In most cases, the reports contain only preliminary results of initial testing. In too many cases no data are reported. For many of the analogs discussed in the previous section, marked improvements in chemical and metabolic stability were noted or would be expected. Thus, it would seem that further investigations of the biology of these materials would be in order. The following summarizes the available information on the activity of fluorinated prostacyclins.

1. Fluorinated PGI_2 Derivatives Possessing an Unstabilized Enol Ether Prepared from Fluorinated Prostaglandins

a. 12-Fluoro PGI_2

Enantiomerically pure 12-fluoro PGI_2 (**9**)[60] was found to be equipotent to PGI_2 itself in its ability to inhibit ADP-induced platelet aggregation (ADP in vitro induced) as well as in its ability to dilate smooth muscle (isolated perfused cat coronary arteries) in vitro. While substitution of fluorine at the 12-position of $PGF_{2\alpha}$ significantly increased potency relative to $PGF_{2\alpha}$ itself and improved selectivity (Section I.D.4), no selectively of action for 12-fluoro $PGI_{2\alpha}$ (**9**) was observed. Furthermore, any increased duration of activity

due to inhibition of metabolic oxidation would be expected to be minimal due to the chemical instability of the material and none was reported. These findings were the results of preliminary testing included in the original communication of the synthesis. No follow-up has since appeared.

b. 14-Fluoro PGI_2

Racemic 14-fluoro PGI_2 (**21**) exhibited potency equal the optically pure PGI_2 in inhibiting platelet aggregation (ADP in vitro induced) and dilating smooth muscle (isolated perfused cat coronary artery) in vitro.[56] It was suggested in the report that the enantiomerically pure 14-fluoro derivative **21** might be expected to be more active than natural PGI_2 itself based on these results. These observations contrast with the results obtained for 14-fluoro $PGF_{2\alpha}$ where substitution of fluorine reduced significantly antifertility activity relative to $PGF_{2\alpha}$ (Section I.D.5). For 14-fluoro PGI_2 (**21**)[52] it was hoped that substitution at the 14-position would reduce susceptibility to oxidation by 15-hydroxy prostaglandin dehydrogenase and this would account for the proposed higher potency of this material.[56] Similarly, it was observed that 13-dehydro PGI_2 (**8**)[25] possessed a somewhat increased duration of activity relative to PGI_2, which was attributed to the lack of susceptibility of the propargylic side chain to oxidation despite its lack of increased chemical stability. However, no reports beyond this preliminary communication have since appeared to confirm these results and allow a conclusion to be drawn.

c. 15-Fluoro-15-Deoxy PGI_2

As the communication describing the synthesis of 15-fluoro-15-deoxy PGI_2 (**22**)[67] did not contain any information concerning biological activity and no further information has appeared, no conclusion can be drawn as to whether fluorine can effectively function as a hydroxyl replacement in this system.

d. 16,16-Difluoro PGI_2 and 2,2,16,16-Tetrafluoro PGI_2

During a conference on Prostaglandins and Cancer,[91] it was reported that the 16,16-difluoro PGI_2 and 2,2,16,16-tetrafluoro PGI_2 (Figure 11) both exhibited an increased duration of action relative to prostacyclin in their ability to inhibit platelet aggregation (8 min vs. 5 and 12 min vs. 5) and lowering blood pressure (14 min vs. 5 and 30 min vs. 5), respectively. These effects can be attributed to resistance to metabolic deactiviation by 15-hydroxydehydrogenase and β-oxidation as was demonstrated for the corresponding $PGF_{2\alpha}$ derivatives (Section I.D.1 and I.D.6). While the syntheses of these materials have not been formally reported they would be readily prepared from the corresponding $PGF_{2\alpha}$ derivatives (Section II.A.3.a) by reported methods.

2. Prostacyclins Containing a Fluorine Stabilized Enol Ether Function

a. 10,10-Difluoro-13-Dehydro PGI_2

The most extensive information on the biological activity of any fluoro prostacyclins exists for 10,10-difluoro-13-dehydro PGI_2 (**28**).[71,74] As previously discussed, substitution of fluorine at the 10-position inductively stabilizes the enol ether function increasing the hydrolytic stability of the molecule (Section II.A.2).[74] Furthermore, substitution of a propargylic alcohol in the lower side chain, while not reducing activity relative to PGI_2, renders the compound resistant to 15-hydroxy prostaglandin dehydrogenase.[25]

In in vitro vascular relaxation studies, 10,10-difluoro-13-dehydro PGI_2 (**28**) was three to four times more active than PGI_2 in relaxing canine mesenteric artery and bovine coronary strips than natural prostacyclin.[92] Dose response curves for both materials were very similar except that the 10,10-difluoro derivative **28** exhibited a longer induction period before onset of action for unknown reasons.

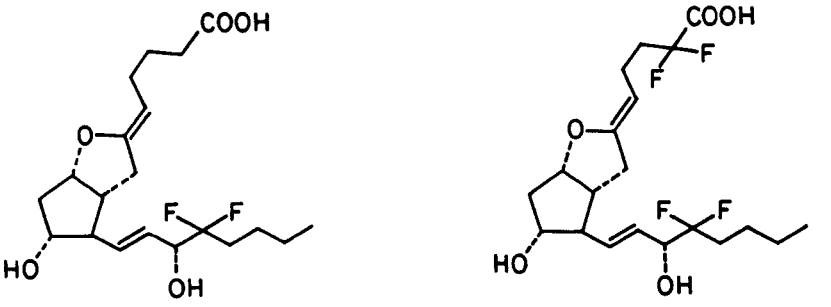


FIGURE 11. 16,16-Difluoro PGI_2 and 2,2,16,16-tetrafluoro PGI_2.

In the inhibition of platelet aggregation **28** was ten times less potent than PGI_2 in preventing arachidonic acid-induced aggregation.

In vivo,[92] difluoro PGI_2 **28** showed parallel activity to prostacyclin in reducing blood pressure and in increasing blood flow to the kidneys. Due to experimental limitations, quantitative results were not reported.

While the stability of 10,10-difluoro PGI_2 (**28**) in vitro ($t\frac{1}{2}$ = 23.5 hr vs. 10 min for PGI_2, Kreb's bicarbonate buffer, pH 7.4, 37° C) was discussed previously (Section II.A.2.a), later reports[92] indicated that although PGI_2 lost activity completely after in vitro incubation with blood in a short time, the difluoro derivative showed no loss of activity after 4 hr. However, further studies[92] in vivo demonstrated that despite increased chemical and metabolic stability, the duration of action of 10,10-difluoro PGI_2 was not much greater than that of natural prostacylin, a surprising and disappointing result. To explain these observations it has been suggested that in addition to hydrolysis and oxidation, the major modes of chemical deactivation, transport of the material away from the site of action, may also be involved. This has been demonstrated in in vivo studies using radioactivity labeled PGI_2.[93]

In the most recent studies,[94] 10,10-difluoro PGI_2 has been shown, like prostacyclin, to be a stimulator of adenylate cyclase causing a dose-related increase in cyclic AMP levels in platelets. The level of activity was intermediate between that of PGI_2 itself and PGE (28-, 20-, and 7-fold increase, respectively, at the highest dose level). Inhibition of platelet aggregation results from the increased levels of cyclic AMP in the platelets, and the ability of PGI_2 and PGE to induce this elevation has been previously reported.[95] Thus, the response induced by 10,10-difluoro PGI_2 was anticipated.

3. Fluorinated Derivatives of Stable PGI_2 Analogs

a. 12-Fluoro-5,6-Dihydro PGI_2 and 12-Fluoro-Δ^4-Iso-PGI_2

Of the large number of PGI_2 analogs prepared to date, it is clear that the most active compounds possess a double bond at C-6. Thus, 5,6-dihydro[16] and Δ^4-iso PGI_2[17] (**3ab**) and (**4ab**), while hydrolytically stable, are significantly less active (<500 times) than PGI_2 itself. It is not surprising then that both 12-fluoro-5,6-dihydro PGI_2 (**55ab**) and 12-fluoro Δ^4-iso PGI_2 (**56ab**) were found to possess only extremely weak prostacyclin activity at high concentrations.[60]

b. 2,2-Difluoro-6a-Carba PGI_2

6a-Carba PGI_2 (**7**)[20] is one of the more promising of the stable prostacyclin analogs synthesized to date possessing comparable potency and a similar activity profile.[28] Thus, it is unfortunate that the only available biological datum on any of the previously

discussed fluoro derivatives of **7** (Sections II.A.3.c and II.A.3.d) was a brief comment during a conference on prostaglandins and cancer.[91] It was reported that fluorine substitution at the 2-position of 6a-carba PGI_2 (**7**) did not increase the duration of action of 2,2-difluoro-6a-carba PGI_2 (**58**) relative to PGI_2 or 6a-carba PGI_2 (**7**) either in the inhibition of platelet aggregation or the reduction of blood pressure. Although no conclusions were discussed, this result would seem to indicate that inactivation of (**7**) by β-oxidation of the upper side chain is much less important than oxidation by 15-hydroxydehydrogenase in the metabolic deactivation of prostacyclins or, as with 10,10-difluoro-13-dehydro PGI_2 (**28**),[92] transport away from the site of action is of key importance.[93]

C. Concluding Remarks

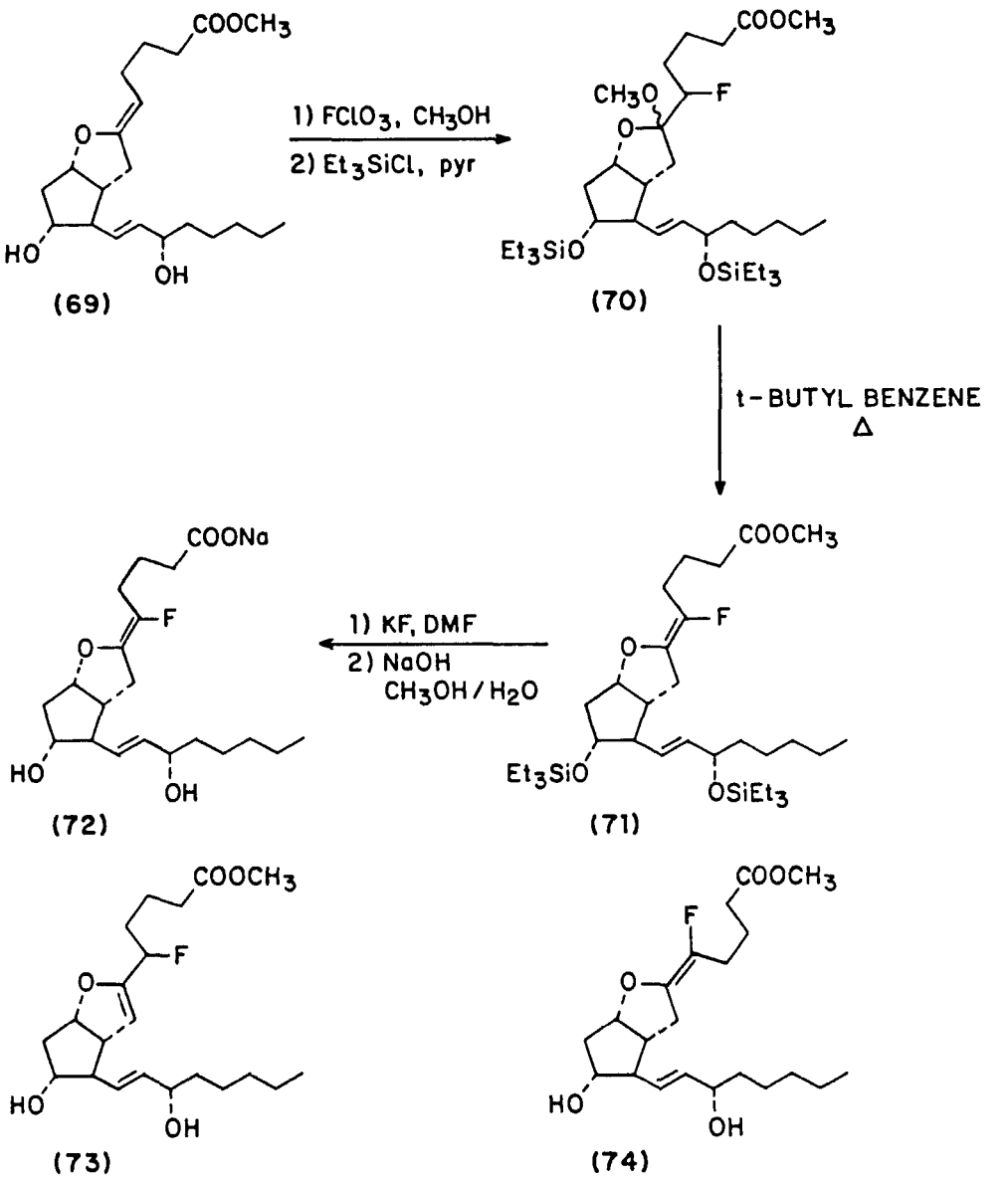
The objectives of this review have been to trace the use of fluorination in the preparation of prostacyclin analogs and now to draw some conclusions as to the success of this approach toward the realization of a useful therapeutic agent and increasing understanding of the relative importance of the factors of stability and selectivity.

In summary, the discussion began with an overview of the use of fluorine as a substitute for hydrogen (steroids) and hydroxyl (carbohydrates) in biologically active molecules. Examples of the resulting effects on nearby functional groups and the protection of key sites from chemical degradation, all with minimal steric effects on the overall system, were considered. The use of fluorination to reduce metabolic inactivation, thus, increasing the duration of action and to enhance the selectivity of the primary prostaglandins was discussed. It was these prostaglandin derivatives that then became the precursors for the first fluorine containing prostacyclins. It was later that fluorination was utilized specifically to increase the hydrolytic stability of prostacyclin, a problem not commonly shared with the primary prostaglandins. Also, the techniques for enhancing metabolic stability established for the primary prostaglandins were applied to chemically stable prostacyclin analogs.

As with any analoging program, the aim of the preparation of fluoro prostacyclins was to achieve the optimum combination of stability, activity, and selectivity. Ideally, a therapeutically useful prostacyclin analog would be one with a reasonable biological half-life and comparable potency to PGI_2 itself but possessing some selectivity of action with respect to inhibition of platelet aggregation and cardiovascular effects. While the biological studies of the fluoro prostacyclins are limited, some conclusions as to the success of the three classes (Sections II.A.1 to II.A.3) of fluoro derivatives in addressing these needs can be drawn. In general, fluorinated prostacyclins prepared from fluorinated prostaglandins possessing an unstabilized enol ether function do not address the fundamental problem of chemical stability thereby having a built-in limited usefulness. On the other hand, derivatives like 10,10-difluoro-13-dehydro PGI_2 (**28**) and 2,2-difluoro-6a-carba PGI_2 (**58**) combine the key features of increased chemical and metabolic stability with potency and an activity profile similar to prostacyclin itself. However, despite the success in these areas, even these derivatives lack a significantly increased duration of action and are not selective. Duration of action appears not to be simply a function of stability and resistance to metabolism alone and factors affecting selectivity as with prostaglandins, in general, remain unclear. The solution to these problems lies with a better understanding of the mechanism of action of prostacyclin itself as well as the transport system for its removal from the site of action.

As for the role of fluorinated prostacyclins in ultimately achieving these goals and in the eventual design and preparation of a therapeutically useful agent, while there is no reason to assume that fluorination alone will solve these problems, fluoro analogs like 10,10-difluoro-13-dehydro PGI_2 (**28**) and 2,2-difluoro-6a-carba PGI_2 (**58**) might serve as

the tools in increasing the knowledge in these areas. Thus, the techniques utilized here might eventually become a part of the solution to the overall problem. Of the continued interest in the area of prostaglandins, in general,[96] there is no doubt as evidenced by the awarding of the 1982 Nobel Prize in medicine.



SCHEME 15. 5-Fluoro PGI_2

III. ADDENDUM

A recently released European patent application describes the synthesis of 5-fluoro PGI_2.[97] As with 10,10-difluoro-13-dehydro-PGI_2 (**28**) substitution of fluorine at the enol ether would be expected to reduce the basicity of the linkage resulting in increased resistance to protonation and consequently greater stability to hydrolysis. This was well stated by the inventors. The synthesis itself (Scheme **15**) utilized PGI_2 methyl ester (**69**) as starting material. Taking advantage of the electrophilic properties of perchlorylfluoride[63] as a source of positive fluorine, **69** was converted to the internal fluoro ketal **70**. Protection of the hydroxyl groups of **70** as the silyl ethers followed by pyrolytic elimination of methanol afforded the prostacyclin **71**. Deprotection and ester hydrolysis then yielded 5-fluoro-PGI_2 sodium salt (**72**). The actual experiment is reasonably detailed although no spectral data is reported. The pyrolysis of **70** reportedly results in the formation of an unspecified amount of Δ-6 prostacyclin **73**. The stereoselectivity of the elimination is also not discussed. It would be reasonable to assume that some of the isomeric Z-fluoro PGI_2 **74** was formed.

As anticipated, the 5-fluoro substituent imparts the desired increased stability to the enol ether and the methyl ester of **72** could be chromatographed without significant decomposition. While no quantitative data on biological activity was provided, it was stated that the sodium salt **72** demonstrated comparable antiaggregating activity to PGI_2 itself and for a longer period of time. More importantly, however, the hypotensive activity was found to be only a small percentage (unspecified) of that of prostacyclin. Thus it would seem that the selectivity of action which is not found in most of the stable prostacyclin derivatives including 10,10-difluoro-13-dehydroprostacyclin (**28**) is effectively provided by substitution of fluorine for hydrogen at C-5. The effect of this substitution on additional factors like metabolism and transport was also unfortunately not discussed for this important and interesting analog.

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