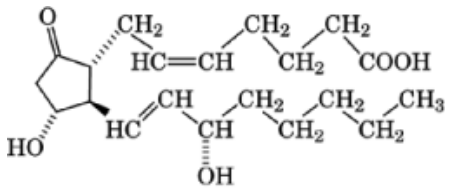
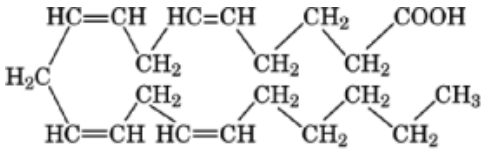
Kirk-Othmer Encyclopedia of Chemical Technology.

PROSTAGLANDINS

Prostaglandins, typified by prostaglandin E_2 **(1)**, are a family of naturally occurring substances found in animals and humans. They play important and diverse roles in both health and disease. Some plant species also contain prostaglandins and the coral species *Plexaura homomalla* is one of the richest known sources (1.5–3% of dryweight) (1). Prostaglandins are biosynthesized from 20 carbon polyunsaturated fatty acids. In humans, the predominant precursor of prostaglandins (PGs) is arachidonic acid [506-32-1] **(2)** which is available either from the diet or by anabolic conversion of linoleic acid, an essential fatty acid.

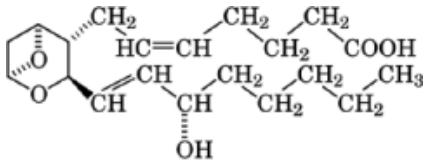


(1)



(2)

The enzyme system responsible for the biosynthesis of PGs is widely distributed in mammalian tissues and has been extensively studied (2). It is referred to as prostaglandin H synthase (PGHS) and exhibits both cyclooxygenase and peroxidase activity. In addition to the classical PGs two other prostanoid products, thromboxane A_2 [57576-52-0] (TxA_2) **(3)** and prostacyclin [35121-78-9] (PGI_2) **(4)** are also derived from the action of the enzyme system on arachidonic acid (Fig. 1).



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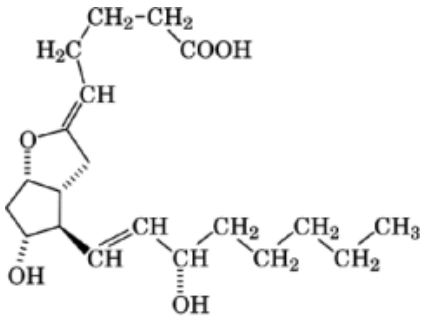
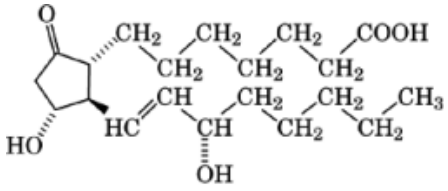


(4)

Prostaglandins were discovered in the 1930s when it was noted (3) that fresh human semen caused strips of human uterine tissue to either relax or contract depending on whether or not the tissue donor had borne children. In 1935 extracts of human seminal fluid were observed to cause a fall in blood pressure in laboratory animals, and contraction of a variety of smooth muscle tissues (4, 5). This factor was differentiated from known agents having similar activities, eg, adrenaline and acetylcholine, and named prostaglandin in the belief that it originated from prostate glands (5). The name is somewhat of a misnomer because PGs occur much more ubiquitously. Later work (6) led to the isolation and structural elucidation of prostaglandin E_1 [745-65-3] (PGE_1) **(9)** and prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) **(10)**.



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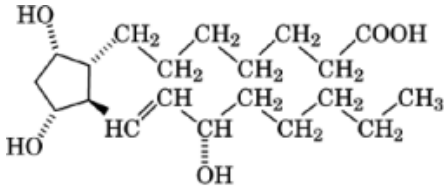


(10)

Additional compounds having similar biological activities and structural components were isolated resulting in the recognition of PGs as a family of closely related compounds. Structural and stereochemical assignments of PGE_1 and $PGF_{1\alpha}$ were confirmed by x-ray crystallographic analysis of their bromo- and iodobenzoates (7, 8) (see X-ray technology). The absolute stereochemical configuration of PGs is based on the configuration of L-2-hydroxyheptanoic acid, obtained by oxidative ozonolysis of acetylated PGE_1 methyl ester (9). In 1983 Bergström and Samuelsson shared (with John Vane) the Nobel Prize for their contributions to this field (10). Thromboxane A_2 **(3)** and prostacyclin **(4)** were discovered in the mid-1970s (11). Both substances are highly unstable making identification and structural determinations elusive and difficult.

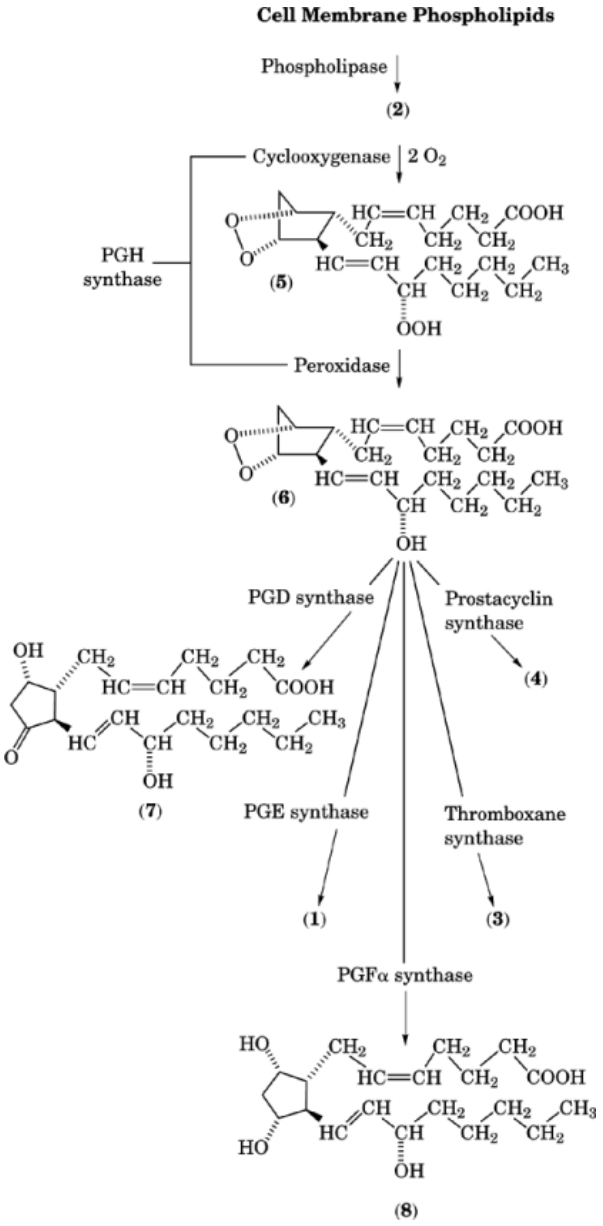
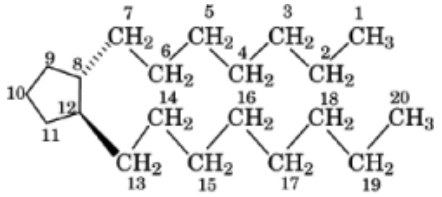


Fig. 1. Biosynthesis of prostanoids, where structures (**5**)–(**8**) are PGG_2, PGH_2, PGD_2, and $PGF_{2\alpha}$, respectively.

The PGs TxA_2 and PGI_2, commonly referred to as prostanoids, may be thought of as hormone-like substances which are produced on demand rather than stored and which modulate cellular functions at or near their site of generation (see Hormones). Unlike typical circulating hormones which are released from one principal tissue site, prostanoids are synthesized and released by virtually all tissues. They are extremely potent and exert regulatory influences on the endocrine, reproductive, nervous, gastrointestinal, cardiovascular, renal, and immunological systems. They are also short lived because of rapid metabolism to inactive species.

Their effects are generally considered to be beneficial and homeostatic in nature. In some cases, however, their biological effects can be detrimental and disease producing; for example, PGs can exert inflammatory actions and produce fever, and TxA_2 is a pro-aggregatory factor for platelets.

The nomenclature of prostaglandins and prostacyclins is based on the basic prostane skeleton **(11)**, whereas thromboxane **(12)** is the parent for the thromboxanes.



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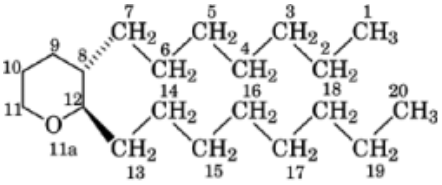


(12)

Implicit in the base names are the absolute configurations at carbons 8 and 12 and the indicated numbering systems. Derivatives of these parent structures are named according to terpene and steroid nomenclature rules (see Steroids; Terpenoids). The lengthy and awkward nature of the chemical abstract systematic nomenclature (12) for these compounds has resulted in the development (13) and use of simplified nomenclature based on common names.

The PGs are grouped into several basic families which differ from each other in the nature of the five-membered ring functionalities (Fig. 2). The principal families are designated as PGA through PGJ. The letters E and F originated from the finding that PGE and PGF compounds partition differently. The compound that was more soluble in ethyl ether was called prostaglandin E and the one that was more soluble in phosphate buffer (*fosfate* in Swedish) was termed prostaglandin F **(10)**. The letters A and B refer to the formation of these derivatives from PGE compounds by treatment with acid and base, respectively. As indicated in the general structures of Figure 2, the carboxylic acid side chain is referred to as the alpha chain R_α, and the hydroxy-bearing chain as the omega chain, R_ω. The number of double bonds in the molecule are denoted by subscript numerals appearing after the name; for example, PGE_1 contains one double bond at C_{13}; PGE_2 has an additional double bond at C_5. The stereochemistry of substituents on the cyclopentane ring is designated α- or β- depending on whether the substituent is above or below the plane of the paper.

1. Biosynthesis and Metabolism

Detailed accounts of the biosynthesis of the prostanoids have been published (14–17). Under normal circumstances arachidonic acid (AA) is the most abundant C-20 fatty acid *in vivo* (18–21) which accounts for the predominance of the prostanoids containing two double bonds eg, PGE_2 (see Fig. 1). Prostanoids of the one and three series are biosynthesized from dihomo-8-linolenic and eicosapentaenoic acids, respectively.

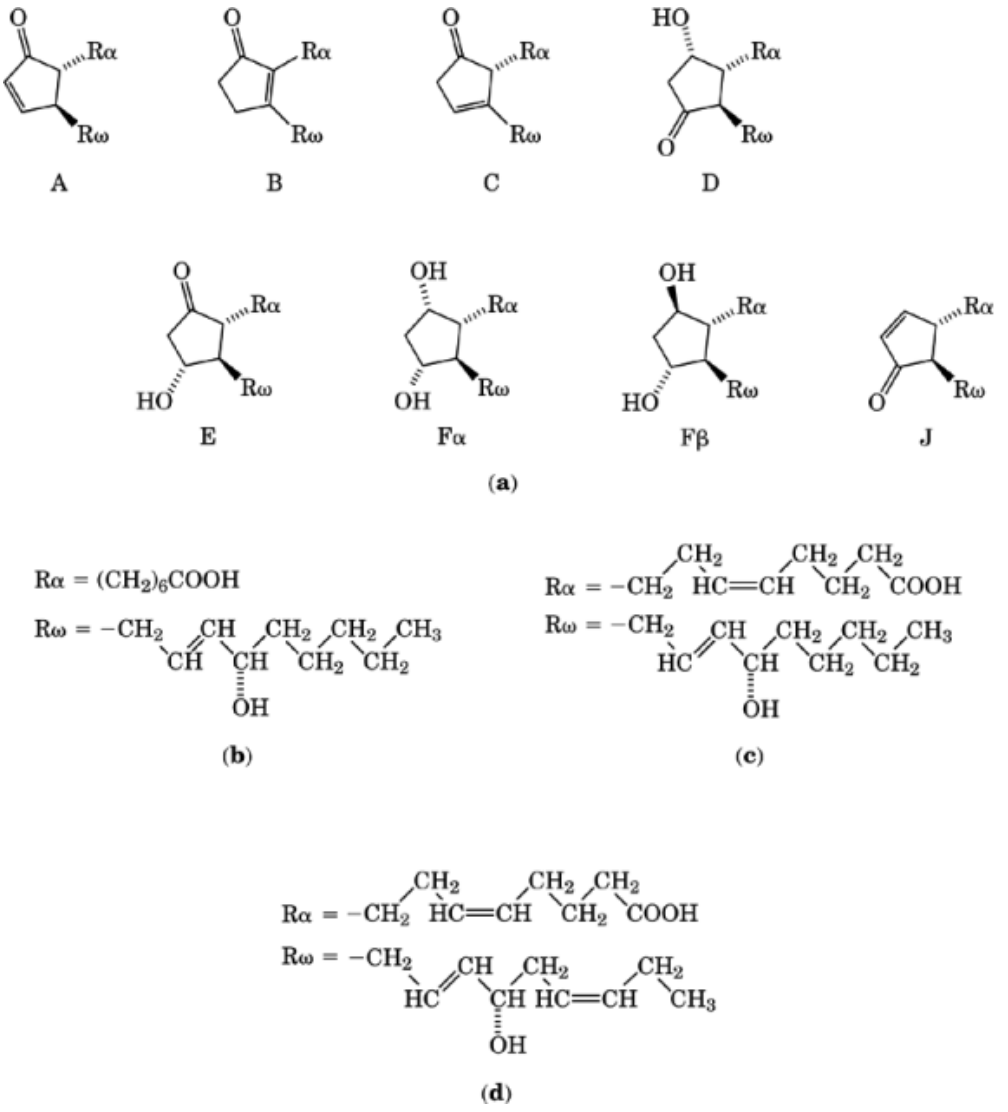
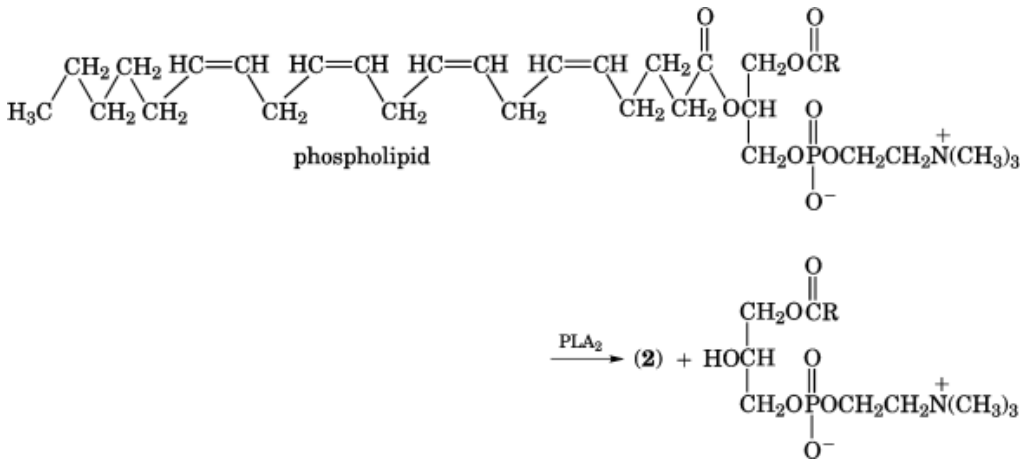


Fig. 2. (**a**) The basis for prostaglandin nomenclature, where the letters A–F and J define principal families; (**b**) defines the side chains for PG_1 derived from dihomo-γ-linolenic acid; (**c**) PG_2 derived from arachidonic acid; and (**d**), PG_3 derived from eicosapentaenoic acid.

Concentrations in human tissue of the one-series precursor, dihomo-8-linolenic acid, are about one-fourth those of AA (22) and the presence of PGE_1 has been noted in a variety of tissues (23). The biosynthesis of the two-series prostaglandins from AA is shown in Figure 1. These reactions make up a portion of what is known as the arachidonic acid cascade. Other lipid products of the cascade include the leukotrienes, lipoxins, and the hydroxyeicosatetraenoic acids (HETEs). Collectively, these substances are termed eicosanoids.

Prostanoid synthesis is initiated by the interaction of a stimulus with the cell surface which results in the activation of cellular phospholipases. Arachidonic acid is generally present in phospholipids esterified at position two. It is released by the action of phospholipase A_2 (PLA_2) which is specific for fatty acid

deesterification at that position of the phospholipid molecule. Other pathways for AA mobilization also exist but are less prevalent. Once AA is released, it can be acted upon by prostaglandin H synthase (EC 1.14.99.1) (PGHS) (2), a membrane-bound enzyme which is present in an active form, primarily in the endoplasmic reticulum. This enzyme exhibits two different catalytic activities (Fig. 1): a cyclooxygenase (bis-oxygenase) which catalyzes the formation of prostaglandin G_2 [51982-36-6] (PGG_2) (**5**) from AA, and a peroxidase (or hydroperoxidase) which facilitates the reduction of PGG_2 to prostaglandin H_2 [42935-17-1] (PGH_2) (**6**).



The initial step in the action of the cyclooxygenase is the stereospecific removal of the 13-pro-(*S*)-hydrogen from AA. As shown in Figure 3 (2, 24), the enzyme is thought to orient an AA molecule by inducing a kink in the carbon chain at C-10. Abstraction of the 13-pro-(*S*)-hydrogen and subsequent isomerization leads to a carbon-centered radical at C-11 which is attacked by molecular oxygen from the solvent side. The resulting 11-hydroperoxyl radical adds to the double bond at C-9; intramolecular rearrangement yields another carbon-centered radical. Reaction of this radical with another molecule of oxygen at C-15 yields PGG_2. Newly formed PGG_2 can undergo a two-electron reduction to PGH_2 catalyzed by the peroxidase activity of PGH synthase. In order for the cyclooxygenase to function, a source of hydroperoxide (R–O–O–H) appears to be required. The hydroperoxide oxidizes a heme prosthetic group at the peroxidase active site of PGH synthase. This in turn leads to the oxidation of a tyrosine residue producing a tyrosine radical which is apparently involved in the abstraction of the 13-pro-(*S*)-hydrogen of AA (25). The cyclooxygenase is inactivated during catalysis by the nonproductive breakdown of an active enzyme intermediate. This suicide inactivation occurs, on average, every 1400 catalytic turnovers.

The endoperoxides PGG_2 and PGH_2 are extremely important intermediates in the metabolism of AA. In addition to having pronounced biological activity, eg, aggregation of blood platelets and constriction of vascular tissue, they serve as intermediates in the biosynthesis of a variety of prostanoids. PGH_2 is a substrate for a number of enzymes in the cascade including PGE synthase (EC 5.3.99.3), PGD synthase (EC 5.3.99.2), and PGF_α synthase (EC 1.1.1.188) which catalyze the synthesis of the classical prostaglandins, PGE_2, PGD_2, and $PGF_{2\alpha}$. The formation of PGI_2 and TxA_2 from PGH_2 is catalyzed by PGI synthase (EC 5.3.99.4), and TxA synthase (EC 5.3.99.5).

PGE synthases are unique in that each requires reduced glutathione (GSH) as a cofactor. GSH appears to facilitate cleavage of the endoperoxide group and formation of the C-9 keto group (2). Synthesis of $PGF_{2\alpha}$ involves a net two-electron reduction of PGH_2; a PGF_α synthase utilizing NADPH catalyzes this reaction. All other prostanoids are formed via isomerization reactions involving no net change in the oxidation state of PGH_2. PGI synthase and TxA synthase are hemoproteins having molecular weights of 50,000–55,000. Both enzymes,

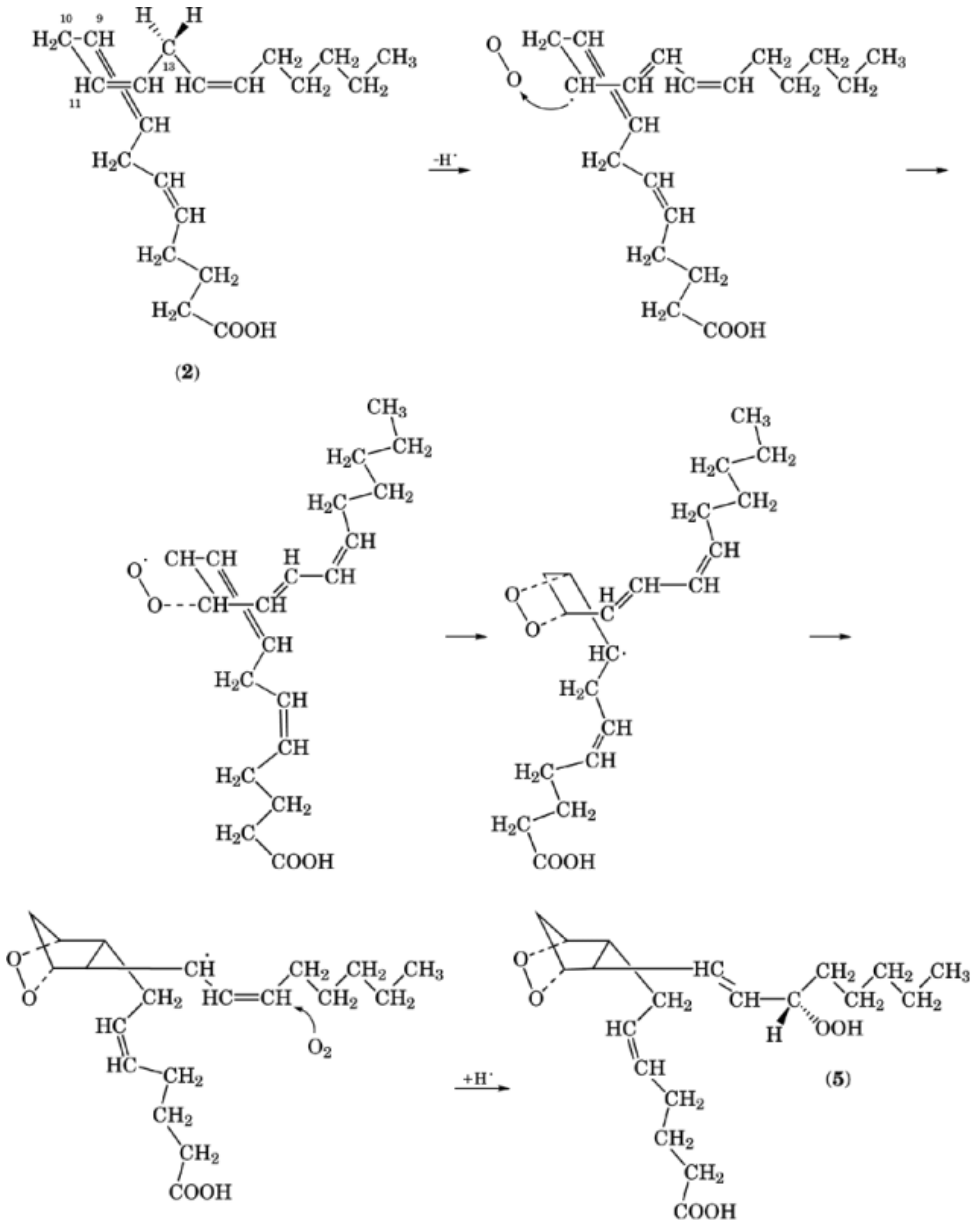


Fig. 3. Putative mechanism of PGH synthase action on arachidonic acid.

like PGH synthase, undergo suicide inactivation during catalysis. Although all the principal prostanoids are depicted in Figure 1 as being formed by a single cell, prostanoid synthesis appears to be cell specific (2). For example, platelets form mainly TxA_2, endothelial cells form PGI_2 as their primary prostanoid, and PGE_2 is the primary prostanoid produced by renal collecting tubule cells. TxA synthase is found in abundance in platelets and lung. PGI synthase is localized to endothelial cells and vascular and nonvascular smooth muscle. PGE

synthase activities are present in several different tissues, but there are differences among these proteins from different tissues.

The primary prostaglandins are believed to be mediators of inflammation and their synthesis can be inhibited by both nonsteroidal antiinflammatory drugs (NSAIDS) and antiinflammatory steroids. The best known of the NSAIDS is aspirin (see Analgesics, antipyretics, and antiinflammatory agents; Salicylic acid and related compounds). Aspirin competes with arachidonic acid (AA) for binding to the cyclooxygenase active site, but the binding of AA is about 10,000 times more efficient than that of aspirin. However, once bound, aspirin can acetylate a specific serine residue of PGH synthase: Ser^{530}. Acetylation of Ser^{530} causes irreversible cyclooxygenase inactivation (see Enzyme inhibitors). It was initially thought that the hydroxyl group of Ser^{530} was required for catalysis. However, studies using site-directed mutagenesis have shown that replacement of Ser^{530} with an alanine residue yields an active enzyme, whereas replacement with an asparagine, which is about the same size as an acetylated serine, yields an inactive enzyme. Apparently, acetylation of Ser^{530} by aspirin results in steric hindrance at this position: the bulky acetyl group protrudes into the cyclooxygenase active site and prevents AA from binding (2).

There are many nonsteroidal antiinflammatory drugs. In fact, this is by far the largest portion of the pharmaceutical market, with 1990s worldwide sales exceeding $4 billion. Most other NSAIDS also act by inhibiting the cyclooxygenase activity of PGH synthase. However, unlike aspirin, most of these drugs cause reversible enzyme inhibition by competing with AA for binding. Well-known examples of reversible NSAIDS are ibuprofen (Advil, Whitehall), indomethacin (Indocin, Merck) and naproxen (Naprosyn, Syntex). Antiinflammatory steroids were once thought to attenuate prostanoid synthesis by inhibiting stimulus-induced AA release. However, research in the 1990s has suggested that antiinflammatory steroids may function principally by inhibiting transcription of the PGH synthase gene. Presumably, these steroids interact with a receptor which binds to a negative regulatory element in the promoter region of the PGH synthase gene (26).

There are two isozymes of PGH synthase (27). PGHS-1 (or COX-1) is constitutively expressed in most tissues (28), and is responsible for the production of PGs involved in cellular housekeeping functions such as coordinating the actions of circulating hormones (29) and regulating vascular, gastric, intestinal, and renal homeostasis. PGHS-2 (COX-2), which shares about 59% amino acid homology with PGHS-1, only is expressed following cell activation. Its expression is stimulated by inflammatory mediators (30) and inhibited by antiinflammatory steroids (31). All of the available nonsteroidal antiinflammatory drugs inhibit both forms of the enzyme. As a result they produce side effects in tissues which are dependent on homeostatic levels of PGs. The gastrointestinal tract and kidney are particularly sensitive to PG synthesis inhibition. NSAIDS can cause damage and ulceration in the stomach and intestinal tract and can compromise kidney function especially in people with pre-existing renal impairment. Many pharmaceutical companies are involved in research to identify compounds which would selectively inhibit only the PGHS-2 enzyme and thereby be potentially free of the undesirable side effects of conventional NSAIDS. The x-ray structure of PGHS-1 has been reported (32).

Acetylation of PGH synthase by aspirin has important pharmacological consequences. Besides the analgesic, antipyretic, and antiinflammatory actions of aspirin, low dose aspirin treatment is a useful antiplatelet cardiovascular therapy (33) (see Cardiovascular agents). TxA_2 is a potent stimulator of platelet aggregation; low dosage aspirin treatment leads to selective inhibition of platelet TxA_2 formation without appreciably affecting the synthesis of prostanoids in other cells. Aspirin causes irreversible inactivation PGH synthase. Since platelets, unlike most other cells, are unable to synthesize new enzyme, new PGH synthase activity must come from new platelets. The replacement time for platelets is 5–10 days, thus considerable time is required for the circulating platelet pool to regain its original complement of active PGH synthase. PGH synthase inactivation also occurs in other cell types, but these cell types can resynthesize PGH synthase relatively quickly.

Once prostanoids are formed they exit the cell, probably via carrier-mediated transport. They act very near their sites of synthesis, then are rapidly inactivated by metabolic enzymes and excreted. The prostanoids are subject to four principal metabolic transformations, as illustrated in Figure 4 for PGE_2: oxidation catalyzed by C-15 prostaglandin dehydrogenase (15-PGDH) (EC 1.1.1.196); reduction by 13,14-reductase; β-oxidation

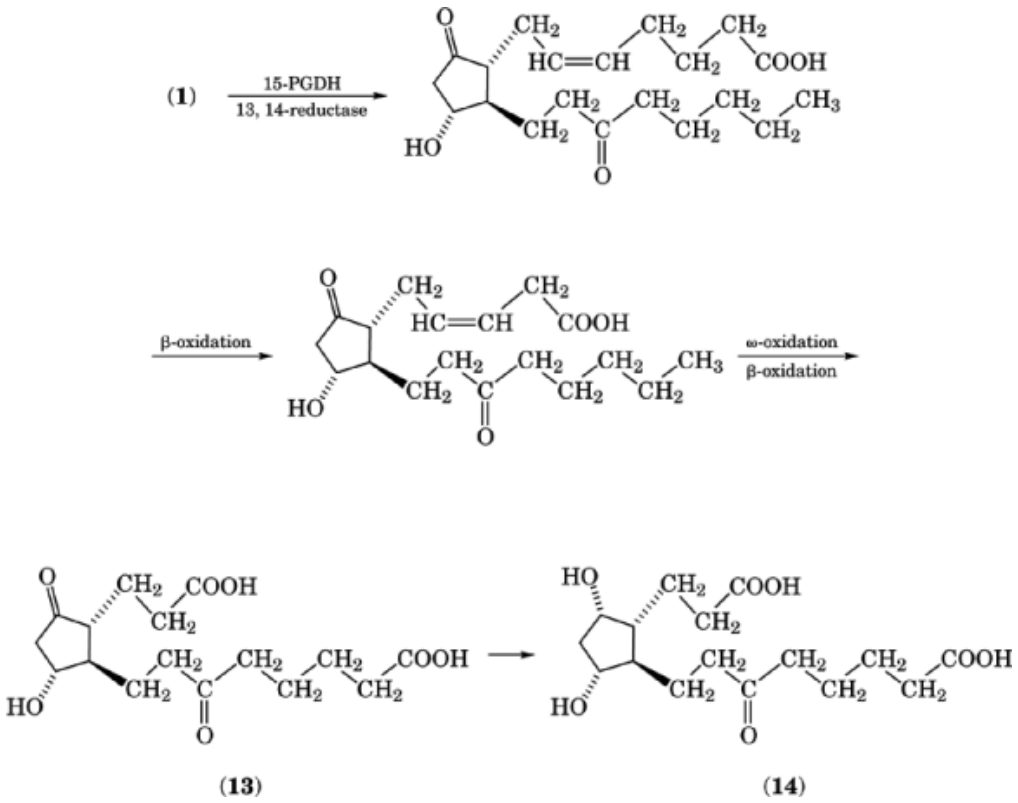


Fig. 4. Metabolism of natural prostaglandins.

of the carboxylic acid side chain; and ω- and (ω–1)-oxidation of the aliphatic side chain (34). The 15-PGDH step occurs most rapidly in humans and most other mammals, and it converts the parent PG molecule into its corresponding C-15 ketone structure. The lung is especially enriched in 15-PGDH, and this enzymatic transformation is so rapid that 90–95% of a circulating PG is transformed into its biologically inactive C-15 ketone metabolite on a single pass through the lungs. Reduction of the C-15 ketone metabolite by the 13,14-reductase enzyme produces the saturated metabolite shown. β-Oxidation, a reaction common to fatty acids in general, involves a sequence of dehydrogenation at C-2 and C-3, followed by oxidation to the 3-ketone and finally cleavage to produce the dinor (-2 carbon atoms) metabolite and acetic acid. A second oxidation sequence usually occurs to generate the tetranor (-4 carbon atoms) metabolite. Another point of attack is the ω-chain terminus. Oxidation occurs either at C-20 to give the alcohol and subsequently the acid (**13**) or at C-19 to produce the 19-hydroxy metabolite. The primary urinary metabolite of natural PGs is (**14**) which is the final keto product of all of these processes plus the reduction of the C-9 carbonyl group.

2. Physical and Chemical Properties

The melting points, optical rotations, and uv spectral data for selected prostanoids are provided in Table 1. Additional physical properties for the primary PGs have been summarized in the literature and the physical methods have been reviewed (47). The molecular conformations of PGE_2 and PGA_1 have been determined in

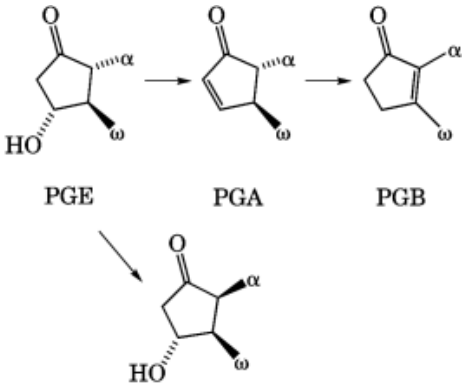
Table 1. Physical Properties of Selected Prostanoids Derived from Arachidonic Acid

Compound	CAS Registry Number	Mp, °C	$[\alpha]_D$ (Solvent), deg	Refs.
PGA_2[a]	[13345-50-1]	pale yellow oil	145 (chloroform)	35
PGB_2[b]	[13367-85-6]	30–34	16–18	36
PGC_2[c]	[49825-91-4]	oil		37
PGC_2, methyl ester[d]	[51172-26-0]	oil		38
PGD_2	[41598-07-6]	62.8–63.3	13 (chloroform)	39
PGE_2	[363-24-6]	65–66	−61 (tetrahydrofuran)	40
		62–64	−52 (tetrahydrofuran)	41
		65.0–67.5		35
$PGF_{2\alpha}$	[551-11-1]	30–35	26 (ethanol)	(35, 42)
			23.8 (tetrahydrofuran)	40
PGI_2				
sodium salt	[61849-14-7]	166–168	88 (chloroform)	43
		116–124	97 (ethanol)	43
methyl ester	[61799-74-4]	30–33	78 (chloroform)	43
6-*oxo*-$PGF_{1\alpha}$	[58962-34-8]	75–78		43
TXB_2	[54397-85-2]	91–93	57.4 (ethyl acetate)	44
		92–94		45
		89–90		46

[a] In C_2H_5OH, λ_{max} is 217 nm and $\epsilon = 10{,}300\ (M{\cdot}\mathrm{cm})^{-1}$.
[b] In C_2H_5OH, λ_{max} is 278 nm and $\epsilon = 26{,}000\ (M{\cdot}\mathrm{cm})^{-1}$.
[c] In CH_3OH, λ_{max} is 234 nm and $\epsilon = 17{,}000\ (M{\cdot}\mathrm{cm})^{-1}$.
[d] In CH_3OH, λ_{max} is 229 (sh) and 234 nm.

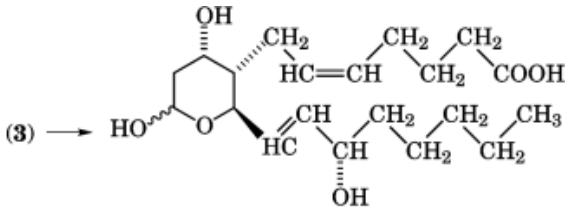
the solid state by x-ray diffraction, and special ^1H and ^{13}C nuclear magnetic resonance (nmr) spectral studies of several PGs have been reported (11, 48–53). Mass spectral data have also been compiled (54) (see Mass spectrometry; Spectroscopy).

The E- and D-type PGs are inherently unstable compounds. Their instability is primarily due to the lability of the β-hydroxyketone system in the cyclopentane ring. Under acidic or alkaline conditions ($<$ pH3 and $>$ pH7) there is a strong driving force for elimination of the 11-hydroxy group of PGE structures to give the more stable α,β-unsaturated ketone of PGA. In an analogous manner, PGD structures give rise to PGJ compounds. The A-form can isomerize to the PGB derivative under the same conditions. In general, esters or similar derivatives are more stable than their acids which are sufficiently acidic to catalyze their own dehydration. E-type PGs also are susceptible to epimerization of the C-8 side chain under alkaline or thermal conditions. In more acidic media three other processes become significant: C-15-epimerization, allyl transposition of the C-15 hydroxyl group, and dehydration of the C-15 hydroxyl group.



All the bis- and tri-unsaturated prostanoids display sensitivity to atmospheric oxygen similar to that of polyunsaturated fatty acids and lipids. As a result, exposure to the air causes gradual decomposition although the crystalline prostanoids are less prone to oxygenation reactions than PG oils or solutions.

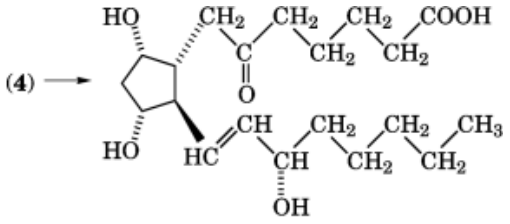
Both thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) are extremely unstable compounds. The instability of TxA_2 **(3)** is due to the strained bicyclic acetal system. Hydrolysis of the acetal to give TxB_2 **(15)** releases the strain.



(15)

TxB_2 **(15)** is a stable but biologically inactive compound and its isolation and characterization were essential to the discovery of TxA_2. Measurement of the half-life of TxA_2 has been based on the decay of biological activity and the rate of appearance of *O*-methyl-TxB_2 from methanolysis of TxA_2. All methods gave values of 30–41 seconds at 37°C in aqueous media free of proteins (55, 56). TxA_2 has never been isolated and characterized directly. Its structural assignment was based on TxB_2 and its more stable synthetic analogues. However, confirmation of the structure of TxA_2 by chemical synthesis has been achieved (57).

PGI_2 **(4)** contains an acid-labile enol ether which is readily hydrolyzed to generate 6-keto-$PGF_{1\alpha}$ **(16)**.



(16)

As with TxA_2, the reactivity of PGI_2 ($t_{1/2}$ = 3 min at pH 7.6 and 37°C) made isolation of the natural substance difficult, and a pure chemical sample was obtained only through chemical synthesis. PGI_2 is stable under more alkaline conditions and can be isolated and stored as a salt. Additional information on the chemistry and stability of TxA_2 and PGI_2 has been summarized (58).

3. Biological Properties

The PGs, PGI_2 and TxA_2 collectively exhibit a wide variety of biochemical and pharmacological activities and are involved in both physiological and pathophysiological processes. However, the individual compounds show different overall activity profiles sometimes in opposing directions. Excellent reviews are available (59–64). A survey of some of the more important biological actions of the prostanoids follow.

3.1. Cardiovascular System

In most species and vascular beds PGEs and PGAs are potent vasodilators, whereas responses to $PGF_{2\alpha}$ vary. Prostacyclin, PGI_2, is a potent vasodilator with five times the potency of PGE_2 and causes prominent hypotension in animals and humans following intravenous administration. Its hydrolysis product, 6-keto-$PGF_{1\alpha}$, is essentially inactive. In contrast, TxA_2 is a powerful vasoconstrictor. PGE_1 and D_2 are inhibitors of platelet aggregation, whereas PGE_2 has variable effects depending on its concentration. PGI_2 is 30–50-fold more potent than PGE_1, inhibiting aggregation at concentrations between 1 and 10 n*M*. TxA_2 is a powerful aggregatory substance. The opposing effects of PGI_2 and TxA_2 on vascular tone and platelet aggregatory state are believed to be important in vascular homeostasis, and disruption of this balance can lead to cardiovascular disease (see Cardiovascular agents). Aspirin is used prophylactically to prevent heart attacks because it can selectively reduce TxA_2 levels relative to PGI_2 levels. TxA_2 is produced by platelets which cannot synthesize more PGHS, whereas vascular endothelial cells, which generate PGI_2, can rapidly produce fresh enzyme. The PG endoperoxides are vasoconstrictory and platelet aggregators, although less active than TxA_2.

3.2. Pulmonary System

In general PGFs contract and PGEs relax bronchial and tracheal muscle. Asthmatics are particularly sensitive to PGs and $PGF_{2\alpha}$ can cause severe bronchospasm in these patients. In contrast, PGE_1 and -E_2 are potent bronchodilators when given by aerosol to asthmatic patients (65) (see Antiasthmatic agents). Prostaglandin endoperoxides and TxA_2 are constrictors whereas PGI_2 induces slight bronchodilation and antagonizes bronchoconstriction produced by other agents in asthmatics (66).

3.3. Reproductive System

The primary PGs are intimately involved in reproductive physiology (67). PGE_2 and $PGF_{2\alpha}$ are potent contractors of the pregnant uterus and intravenous infusion of either of these compounds to pregnant humans produces a dose-dependent increase in frequency and force of uterine contraction. PGI_2 and TxA_2 have mild relaxant and stimulatory effects, respectively, on uterine tissue. The primary PGs also play a role in parturition, ovulation, luteolysis, and lactation and have been implicated in male infertility.

3.4. Gastrointestinal System

PGEs, PGAs, and PGI_2 inhibit gastric acid secretion stimulated by feeding, histamine, or gastrin. The volume of secretion, acidity, and content of pepsin are all reduced, probably by an action exerted directly on the

secretory cells. In addition, these PGs are vasodilators in the gastric mucosa, and are likely to be involved in the local regulation of blood flow. PGs cause increased mucus secretion in the stomach and small intestine and substantial movement of water and electrolytes into the intestinal lumen. Such effects contribute to the diarrhea noted in animals and humans following the oral or parenteral administration of PGs. In contrast, PGI_2 does not induce diarrhea in animals or humans; it prevents that provoked by other PGs, and inhibits the toxin-induced accumulation of intestinal fluid in experimental models.

3.5. Nervous System

PGEs produce sedation and catatonia when injected into the cerebral ventricles of cats (67) (see Hypnotics, sedatives, anticonvulsants, and anxiolytics; Psychopharmacological agents). A number of studies using microiontophoretic techniques, ie, the electrolytic injection of substances into tissues, have been carried out to study the effects of PGs on brain function (68); perhaps the most interesting effect observed is fever production following intraventricular injection of PGEs. This finding prompted the hypothesis that pyrogen-induced fever is due to release of PGE_2 in the brain. The antipyretic activity of aspirin and other NSAIDS is thus hypothesized to be due to inhibition of PG synthesis in the brain. Although this is a satisfying explanation, there is considerable contradictory evidence (69). In humans, PGEs cause pain when injected intradermally or applied to facial skin. They also potentiate the pain-producing effects of bradykinin and histamine (see Histamine and histamine antagonists).

3.6. Kidney Function

Prostanoids influence a variety of kidney functions including renal blood flow, secretion of renin, glomerular filtration rate, and salt and water excretion. They do not have a critical role in modulating normal kidney function but play an important role when the kidney is under stress. For example, PGE_2 and $-I_2$ are renal vasodilators (70, 71) and both are released as a result of various vasoconstrictor stimuli. They thus counterbalance the vasoconstrictor effects of the stimulus and prevent renal ischemia. The renal side effects of NSAIDS are primarily observed when normal kidney function is compromised.

3.7. Metabolic and Endocrine Effects

The role of PGs in these systems is complex and generally modulatory in nature. PGE_2 is synthesized by adipocytes and is a potent inhibitor of lipolysis. It is also a potent inducer of bone resorption and of calcium release from bone. Under certain circumstances, however, PGEs can stimulate lipolysis and bone growth (72). PGE_2 increases circulating levels of adrenocorticotropic hormone (ACTH), growth hormone, prolactin, and the gonadotropin hormones (see Growth regulators; Hormones, human growth hormone). Other endocrine effects have been reviewed (73). The effect of PGEs on insulin and glucose levels is also complex and regulatory in nature (74) (see Insulin and other antidiabetic drugs).

3.8. Inflammatory and Immune Responses

The role of prostanoids in inflammation is controversial and good evidence exists on both sides of the argument as to whether they are pro- or antiinflammatory (75). PGE_2 and PGI_2 are present in inflamed tissues in sufficient concentrations to account for the erythema and increased sensitivity characteristic of acute inflammation (76, 77). PGEs are vasodilatory and hyperalgesic, ie, increase sensitivity to pain, and in concert with other mediators such as bradykinin and histamine, PGEs increase vascular permeability. It is also generally accepted that NSAIDS act, at least in part, by inhibiting prostanoid production (78). However, PGEs suppress the secretion of inflammatory mediators by mast cells and the release of lysosomal enzymes from human neutrophils. Possibly

the state of the tissue governs the nature of the response to prostanoids (79). Prostanoids also moderate the humoral and cellular immune systems, but their effects are complicated and involve both inhibition and stimulation (80). Thus PGE_2 can inhibit T-cell function and proliferation, but under some circumstances PGEs also stimulate the development of mature T-cells from immature thymocytes and stimulate mitogenic activity of low density T-cells. These dual excitatory/suppressive effects are also observed on B-cells, natural killer cells, and macrophages.

3.9. Cytoprotection

One of the most intriguing properties of prostanoids is their ability to protect cells and tissues from various damaging agents. This phenomenon was first discovered by the observation that natural PGs would prevent damage of the gastric mucosa when administered prior to various chemical irritants such as ethanol, acid, and alkali (81, 82). Exogenously administered PGs were also found to prevent the gastric and duodenal damage caused by NSAIDS. The mechanisms underlying the protective properties of prostanoids remain unknown. In the stomach the prostanoids exert actions such as stimulation of mucus and bicarbonate, prevention of mucosal barrier disruption, enhancement of mucosal blood flow, and acceleration of mucosal repair following damage, but none of these are adequate explanations (83). Rather it appears that additional, unidentified cellular protective mechanisms exist. The fact that PGs are protective to tissues other than the gastric mucosa supports this hypothesis. Protective effects of PGs have been documented in the colon (84), liver (85), kidney (86), and pancreas (87), and for injury caused by radiation and chemotherapeutic agents (88, 89) (see Chemotherapeutics, anticancer; Radioprotective agents). A comprehensive review of the biological protective properties of prostanoids has been published (90).

3.10. Health and Safety

The prostanoids are extremely potent substances with a wide variety of biological effects. Therefore utmost caution should be used in their handling to avoid adverse effects. As an example, PGE_1, if ingested, may cause fever, diarrhea, abdominal pain, low blood pressure, nausea, vomiting, headache, and dizziness. If inhaled, bronchodilatation and respiratory tract irritation may occur. Skin exposure, especially with esters of PGE_1, can result in reddening and increased pain sensitivity of the skin, particularly the face. Prostaglandins of the E- and F-types have uterine stimulating properties and therefore can endanger pregnancy. The LD_{50} (the dose lethal to 50% of the treated population) for PGE_1 in rats is 228 mg/kg of body weight by oral administration and 19.2 mg/kg intravenously. Material Safety Data Sheets (MSDS) are available for some of the natural compounds, for example, PGE_1, PGD_2, and TxB_2, from MDL Information Systems, Inc. (San Leandro, California). Other sources of MSDS are Sigma-Aldrich Corp. (Milwaukee, Wisconsin) or the individual manufacturers of marketed prostanoids. Prostanoids that are marketed as drugs, for example misoprostol (Cytotec), are regulated by the U.S. FDA and corresponding agencies in other countries.

4. Prostanoid Receptors

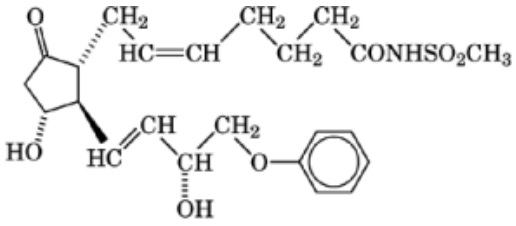
Characterization of prostanoid receptors and quantification of the action of ligands at these receptors have been hampered by lack of selectivity of the natural prostanoids and most synthetic agonists and antagonists for specific receptors, the ability of the prostanoids to induce opposing actions in the same tissue, and the multiplicity of prostanoid receptor subtypes in most tissues. The development of a classification system of prostanoid receptors (91) (Table 2) provides a working framework toward understanding these interactions. PGE receptors are pharmacologically divided into three subtypes, EP_1, EP_2, and EP_3, which differ in their mode of signal transduction; binding at these receptors is believed to lead to elevation of intracellular calcium

Table 2. Prostaglandin Receptor Subtypes

Receptor subtype	Most potent natural PG agonist	Usual response on smooth muscle
EP_1	PGE_2	contraction
EP_2	PGE_2	relaxation
EP_3	PGE_2	inhibition
DP	PGD_2	relaxation
FP	$PGF_{2\alpha}$	contraction
IP	PGI_2	relaxation
TP	TxA_2	contraction

levels, stimulation of adenylate cyclase, and inhibition of adenylate cyclase, respectively (92). PGE_2 increases cyclic adenosine monophosphate (cAMP) levels in many tissues suggesting that the EP_2 subtype is ubiquitously distributed and mediates various PGE_2 actions in many tissues and cells. EP_2 receptors mediate relaxation of tracheal and ileum circular muscle, vasodilation of various blood vessels, and stimulation of sodium and water reabsorption in kidney tubules. EP_1 receptors, in contrast, mediate contraction of tracheal and gastrointestinal smooth muscle. EP_3 receptors are involved in modulation of neurotransmitter release (see Neuroregulators), inhibition of gastric acid secretion, stimulation and relaxation of smooth muscle, and stimulation of lipolysis in adipose tissue. Two excellent reviews on the prostanoid receptors and their biological actions have been published (93). The cloning and expression of complementary deoxyribonucleic acids (cDNAs) for various animal and human prostanoid receptors have been described (94–99) (see Biotechnology; Genetic engineering).

The paucity of selective ligands to activate and antagonize the EP-receptors continues to make characterizations extremely difficult. Sulprostone [60325-46-4] **(17)** is reported to activate EP_1 and EP_3 but not EP_2 receptors, whereas butaprost **(18)** selectively but weakly activates EP_2 receptors (100). A potent and highly selective agonist at EP_3 receptors, SC-46275 **(19)**, has been described (101). Only two selective EP_1 antagonists, SC-19220 **(20)** and AH-6809 **(21)**, are known and no selective antagonists of the EP_2 and EP_3 receptors have been reported. A number of structurally diverse TxA_2 antagonists have been described (102).



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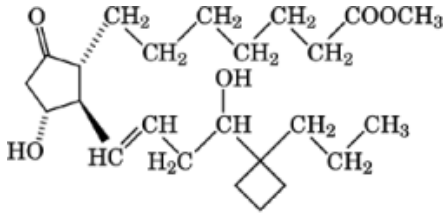

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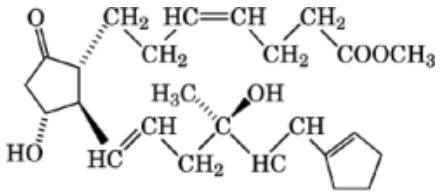

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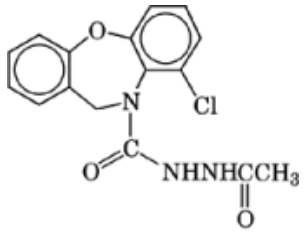

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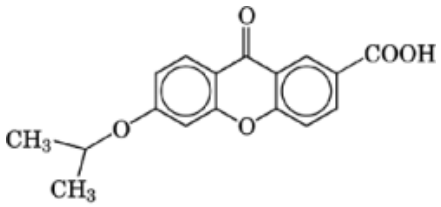


(21)

5. Synthesis of Naturally Occurring Prostanoids and Analogues

Following the rebirth of prostanoid research in the early 1960s, intensive efforts were made in numerous academic and industrial laboratories to develop total chemical syntheses of the natural compounds and, subsequently, their analogues. The driving forces behind this plethora of research were the challenges presented by the stereochemical and functional group complexities of the substances, the wide array of their biological activities, and their extraordinary therapeutic potential in a host of diseases. Likewise, the discovery of prostacyclin and thromboxane in the late 1970s also created a burst of activity. Comprehensive reviews of the total synthesis of the natural prostanoids and their structural analogues are given (6, 103–107) (see Pharmaceuticals, chiral).

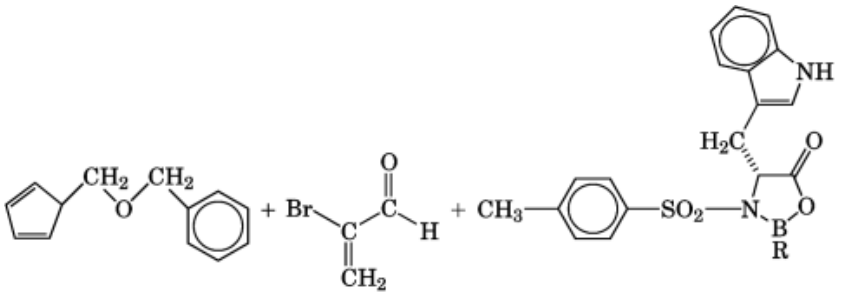
5.1. Classical Prostaglandins

Prostanoids of the A to F series are known as the classical prostaglandins to distinguish them from those discovered and characterized at later dates. Although the bulk of the synthetic activity occurred in the 1970s, various improvements and new approaches are still appearing in the literature in the 1990s. The numerous syntheses of the classical prostaglandins may be grouped into three basic strategies: cleavage of polycyclic intermediates, the conjugate addition approach, and the cyclization of aliphatic precursors (108). The bulk of the efforts have been devoted to the biologically more important E and F compounds, but direct synthesis of PGAs, -Cs, and -Ds have been reported.

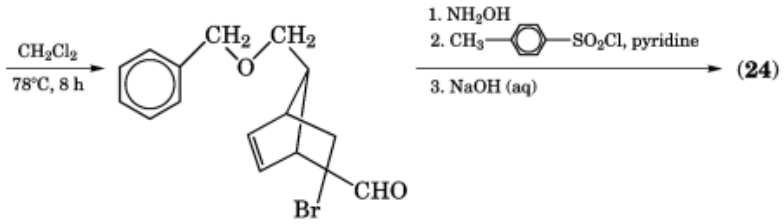
5.1.1. Cleavage of Polycyclic Intermediates

Polycyclic intermediates are constructed so that subsequent cleavage generates cyclopentane derivatives containing the proper functional groups and relative configurations. The synthesis of PGE_2 and $PGF_{2\alpha}$ (Fig. 5) developed by Corey is an elegant example of this approach and is one of the most widely utilized procedures for both laboratory synthesis and commercial production (6). In addition to providing the natural products PGE_2 and $PGF_{2\alpha}$, various intermediates in this process, eg, lactone aldehyde (**29**) and lactone diol (**33**), are extensively used in the synthesis of PG analogues. This stereocontrolled synthesis starts from thallous cyclopentadienide (**22**), which is alkylated with benzyl chloromethyl ether to give the substituted cyclopentadiene (**23**). This reactive and somewhat unstable diene is subjected to a Diels-Alder cycloaddition with α-chloroacrylonitrile, and the resulting cycloadduct is treated with base to generate the ketone function in (**24**). The rigid bicyclic structure of (**24**) has the desired trans relationship between the groups which become the side chains at carbons 8 and 12 of the prostaglandins. Baeyer-Villiger oxidation of ketone (**24**) using MCPBA gives the lactone (**25**), which is hydrolyzed with base to generate a racemic acid. This acid is resolved via its (+)-amphetamine salt to provide the enantiomer (**26**) which has the proper absolute configurations at C-8, -11, and -12. Reaction of (**26**) with potassium iodide and iodine results in the formation of iodolactone (**27**), which has the absolute configurations of $PGF_{2\alpha}$ at C-8, -9, -11, and -12. The hydroxy function at C-11 is acylated with *p*-phenylbenzoyl chloride, the iodine atom at C-10 is removed by reaction with tributyltin hydride, and the benzyl ether is reductively cleaved to afford lactone alcohol (**28**). This alcohol is oxidized, by a modified Collins oxidation, to produce the lactone aldehyde (**29**) which is commonly referred to as the Corey aldehyde. The lower side chain is stereospecifically attached using the Wadsworth-Emmons modification of the Wittig reaction to give the trans-enone (**30**); the ketone group of this side chain is stereoselectively reduced with lithium diisopinocamphenyl-*tert*-butylborohydride to a 2:1 mixture of the 15(*S*):15(*R*) alcohols (**31**) and (**32**). The (*R*)-isomer (**32**), which is separated from (**31**) by silica gel chromatography (qv), is efficiently recycled to (**30**) by manganese dioxide oxidation; the natural (*S*)-isomer (**31**) is hydrolyzed to the lactone diol (**33**). The hydroxyl functions of (**33**) are protected as tetrahydropyranyl (THP) ethers, the lactone is reduced to the corresponding lactol, and Wittig reaction of this lactol with the ylid derived from (4-carboxybutyl)triphenylphosphonium bromide affords bis-protected $PGF_{2\alpha}$ (**34**). Deprotection of (**34**) with aqueous acetic acid generates $PGF_{2\alpha}$ (**8**), whereas oxidation of (**34**) with chromic acid followed by aqueous acetic acid deprotection leads to PGE_2 **(1)**.

Because the Corey synthesis has been extensively used in prostaglandin research, improvements on the various steps in the procedure have been made. These variations include improved procedures for the preparation of norbornenone (**24**), alternative methods for the resolution of acid (**26**), stereoselective preparations of (**26**), improved procedures for the deiodination of iodolactone (**27**), alternative methods for the synthesis of Corey aldehyde (**29**) or its equivalent, and improved procedures for the stereoselective reduction of enone (**30**) (108–120)(121–147)(148–168). For example, a catalytic enantioselective Diels-Alder reaction has been used in a highly efficient synthesis of key intermediate (**24**) in 92% ee (169).



(**35**) R = H or C_4H_9



(**36**)

Diels-Alder reaction of 2-bromoacrolein and 5-[(benzyloxy)methyl]cyclopentadiene in the presence of 5 mol % of the catalyst **(35)** afforded the adduct **(36)** in 83–85% yield, 95:5 exo/endo ratio, and greater than 96:4 enantioselectivity. Treatment of the aldehyde **(36)** with aqueous hydroxylamine, led to oxime formation and bromide solvolysis. Tosylation and elimination to the cyanohydrin followed by basic hydrolysis gave (**24**).

The Corey process is also useful for the synthesis of PGs of the 1 and 3 series. Catalytic hydrogenation of (**34**) (see Fig. 5) with 5% Pd/C at $-15 - 20^{\circ}C$ results in selective reduction of the 5,6-double bond. Subsequent transformations analogous to those in Figure 5 lead to PGE_1 **(9)** and $PGF_{1\alpha}$ **(10)**. The key step for synthesis of the PG_3 series is the Wittig reaction of (**29**) with the appropriate unsaturated ω-chain ylide (170).

Another commercially important total synthesis of PGs is based on the stereoselective cleavage of a bicyclo[3.1.0]hexane structure (Fig. 6). This approach was used in the first published synthesis of a classical PG (171), and was subsequently improved (172, 173). The synthesis started with norbornadiene (**37**), which was monoepoxidized, rearranged under acidic conditions, and treated with 6 to afford the bicyclo[3.1.0]hexene (**38**). This intermediate was converted to cyclobutanone (**39**) by means of a ketene–cycloaddition reaction, followed by dechlorination with Zn dust. Compound (**39**) was resolved by diastereomeric oxazolidine formation with *l*-ephedrine. Treatment of (**39**) with *m*-chloroperbenzoic acid (MCPBA) and hydrolysis of the acetal group gave (**40**); condensation of (**40**) with 1-cyano-1,1-dibromohexane afforded glycidonitrile (**41**). Solvolysis of (**41**) generated enone (**42**) with the desired C-11 hydroxyl and ω-chain allylic alcohol functions. In the solvolysis of (**41**), the hydroxyl ion is sterically directed to the α-face of C-11 and formation of the trans double bond is favored by the spacial disposition of the substituents during the ring-opening sequence. The enone (**42**) was acylated at C-11 to produce the lactone enone (**30**) from the Corey process (see Fig. 5). This synthesis has produced the equivalent of more than 50 kg/yr of $PGF_{2\alpha}$ and has effectively reduced the cost of synthesizing PGs to less than one-hundredth of the cost of bioconversion of arachidonic acid (174).

A third procedure involving cleavage of polycyclic intermediates has been reported (175). This synthesis exploits the stereochemical properties of the bicyclo[3.2.0]heptan-6-one ring system (Fig. 7). Compound (**43**)

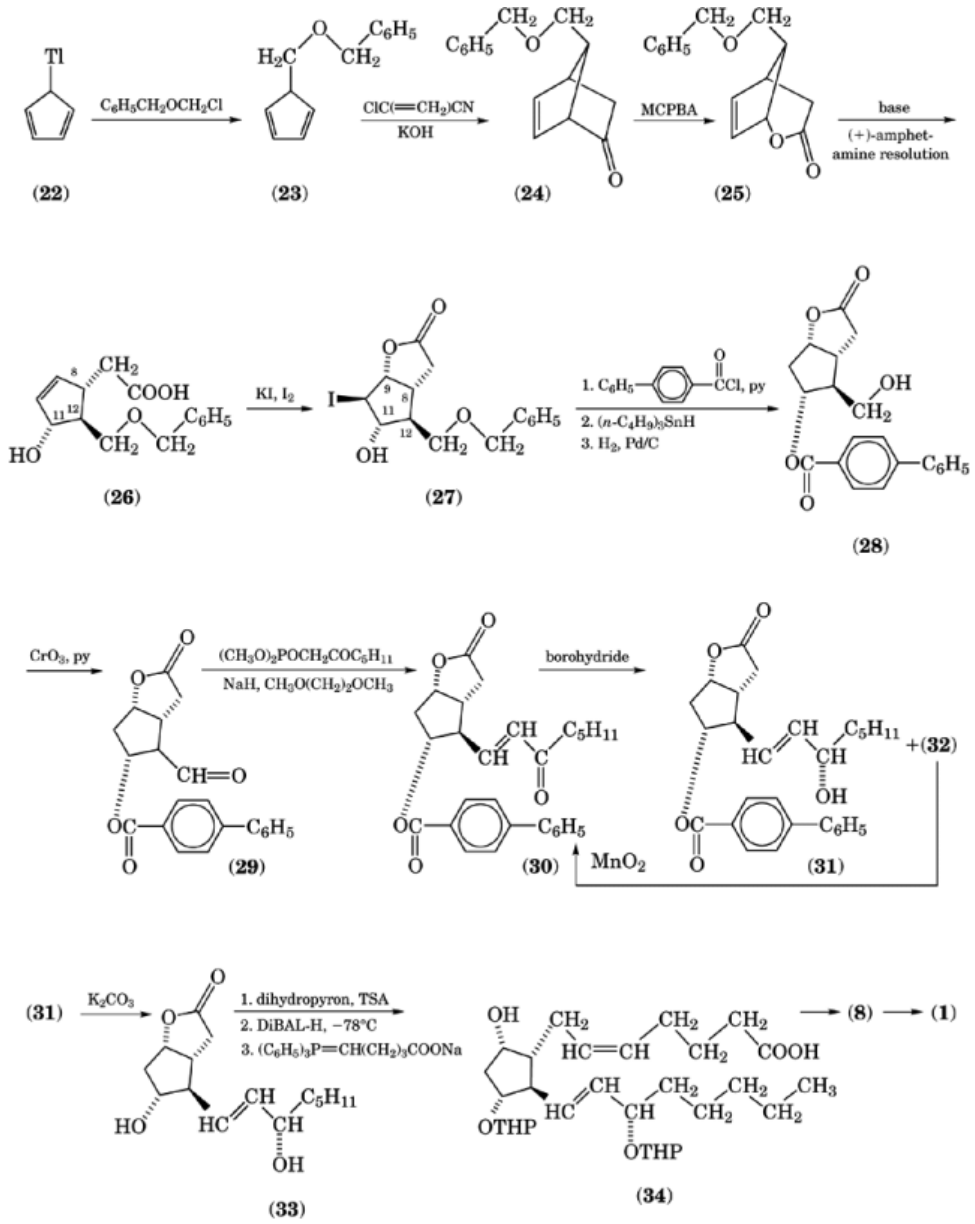


Fig. 5. Corey synthesis of PGE_2 and $PGF_{2\alpha}$ where DiBAL–H=diisobutylaluminumhydride; MCPBA=*m*–chloroperbenzoic acid; py=pyridine; THP=tetrahydropyran; and TSA=*p*–toluenesulfonic acid (6).

was reduced with Baker's yeast to give a mixture of the chiral endo and exo (*S*)-alcohols (**44**) and (**45**) which were readily separated by distillation (qv) or chromatography. Treatment of these intermediates with *N*-bromoacetamide provided the corresponding bromohydrins (**46**) and (**47**) with concomitant oxidation of the cyclobutane alcohol group. Both isomers were converted to the lactone diol intermediate (**33**) by different processes. With (**46**), protection of the C-11 hydroxyl group as a silyl ether followed by treatment with potassium

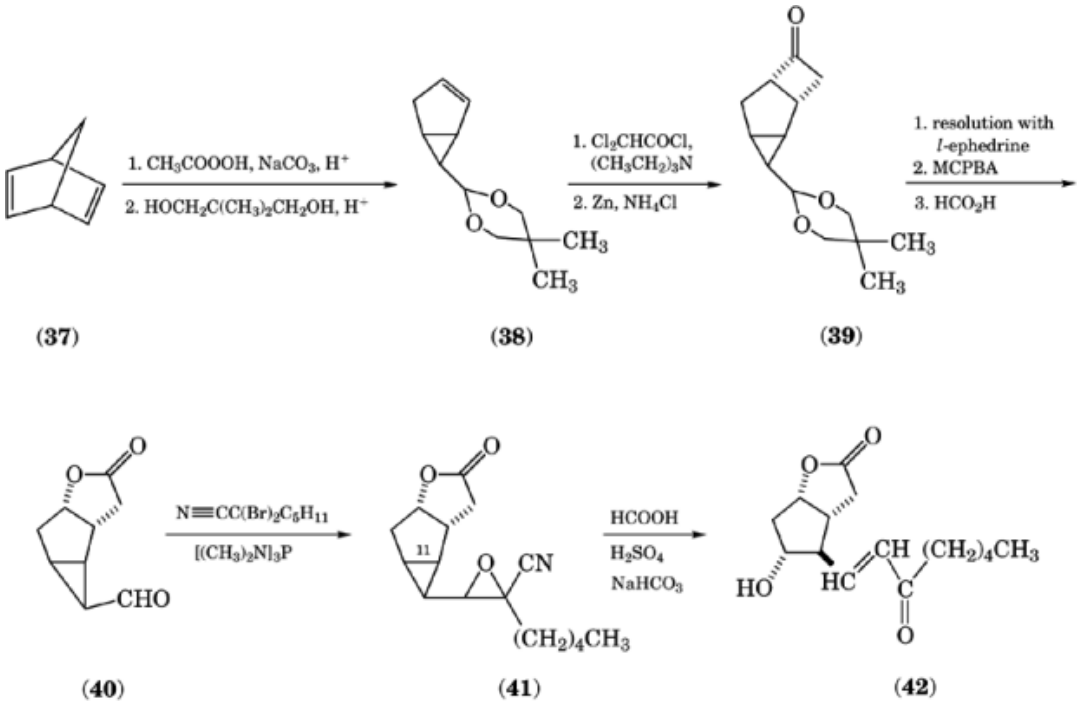
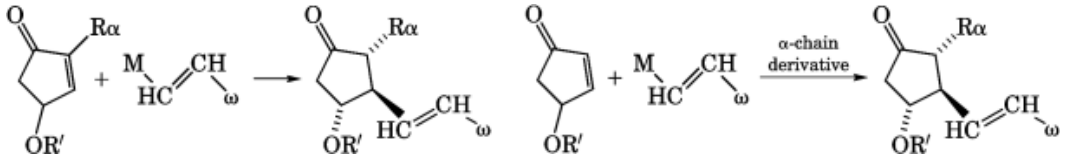


Fig. 6. Synthesis of prostaglandins via a bicyclo[3.1.0]hexane intermediate where MCPBA=*m*–chloroperbenzoic acid.

t-butoxide generated the isolatable intermediate (**48**) (176, 177). Regiospecific cleavage of the cyclopropyl ring of (**48**) with an ω-chain organocuprate reagent provided (**50**) which was subjected to Baeyer-Villiger oxidation, hydrolysis of the silyl ethers, and reverse lactonization to give (**33**). With the other isomer (**47**), an epoxide cleavage route was employed. Thus (**47**) was ketalized and an epoxide formed by base treatment to give (**49**). Cleavage of the strained ketal–epoxide of (**49**) with the ω-chain cuprate reagent gave a 4:1 ratio of (**51**) and its undesired regioisomer. The Corey intermediate (**33**) was generated by hydrolysis and Baeyer-Villiger oxidation of (**51**). A number of other synthetic approaches to Corey intermediates have been developed and reviewed (107, 108).

5.1.2. Conjugate Addition Approach

The use of conjugate addition for prostaglandin synthesis has been widely researched (6, 108, 178–184). It has been applied to both classical PGs and their analogues and is the basis for the commercial production of several marketed PG analogues (107, 185). The approach involves the conjugate addition of an organometallic derivative of the omega chain, $M(HC{=}CH-\omega)$, where M is a metal, to a protected hydroxycyclopentenone which generally already contains the appropriate R^{α}, wherein R′ = protecting group.



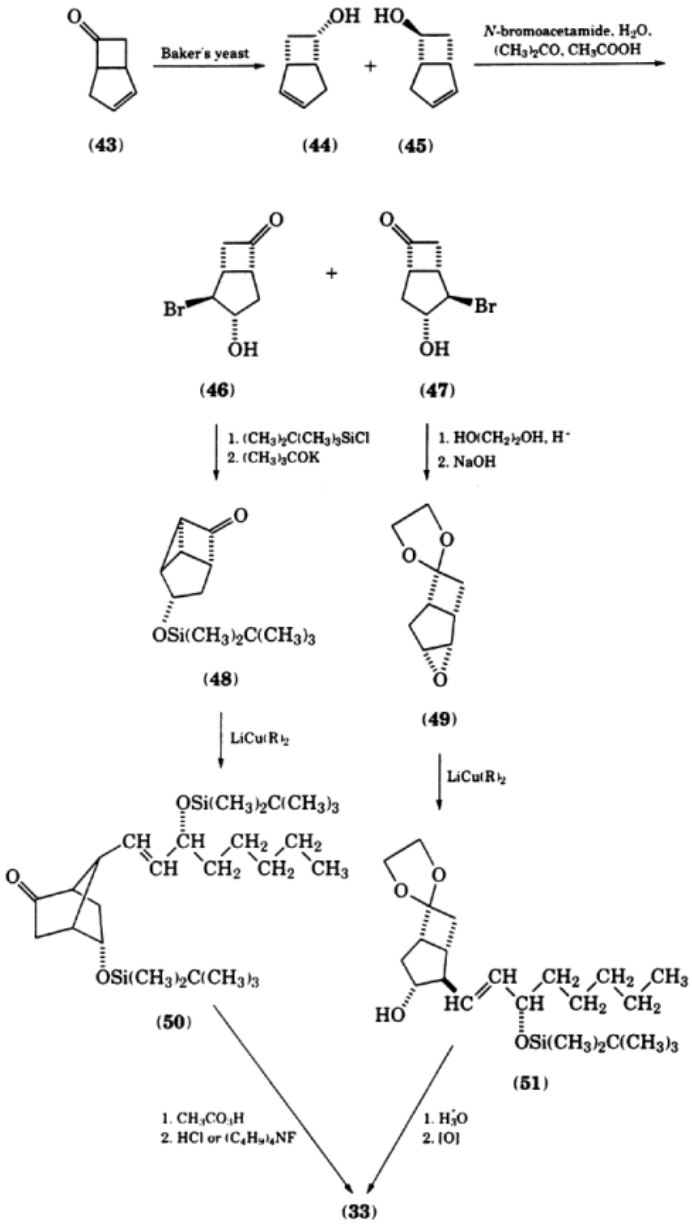
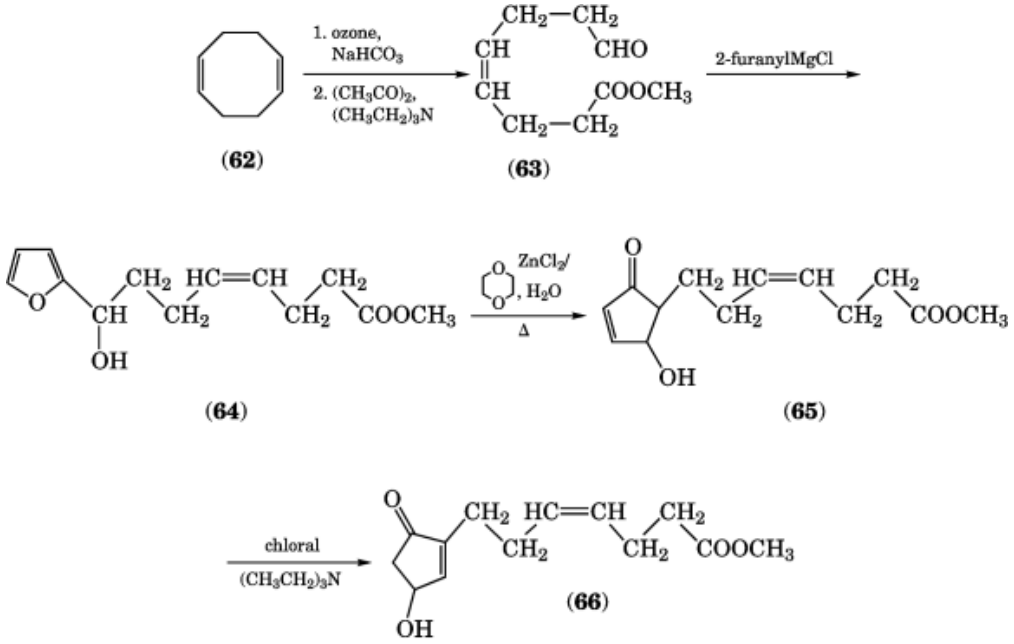


Fig. 7. Synthesis of prostaglandins via cleavage of polycyclic intermediates where $R{=}HC{=}CHCH(OSi(CH_3)_2C(CH_3)_3)C_5H_{11}$.

An alternative three-component coupling procedure, in which the α-chain is incorporated by reaction with the enolate arising from the initial conjugate addition reaction, has been elegantly researched and refined (186). The advantage of this overall approach is its convergency, versatility for preparing analogues, and the stereoselectivity of the addition reaction. The stereoselectivity arises from enolate quenching under thermodynamic conditions to generate the more stable all-trans product. Thus, fixation of the single asymmetric center in the enone dictates the eventual stereochemical outcome at C-8 and C-12. Although a variety of organometal-

lic reagents have been studied, organocuprates have been the most extensively applied to PG synthesis. The first applications of organocuprate chemistry to PG synthesis were reported in 1972 (187–189). The original synthesis of PGE_1 **(9)** using conjugate addition is shown in Figure 8 (189). The diastereomeric product (**54**) was removed by chromatography. The cuprate species (**53**) was prepared as shown. The enone (**60**), a precursor of (**52**), was prepared from cyclopentadiene. Quantitative alkylation of (**57**) using ethyl 7-bromoheptanoate gave the diene (**58**). Cycloaddition with chemically generated singlet oxygen afforded a mixture of hydroxycyclopentenones (**59**) and (**60**), in which the desired isomer (**60**) was a minor proportion of the product. However, oxidation of the isomeric mixture with Jones reagent to the dione (**61**), followed by reduction of the sterically more accessible ketone function, improved the isomer ratio to 2:1 in favor of the 4-hydroxycyclopentenone (**60**). In a later synthesis, using a resolved enone, PGE_1 was produced exclusively (190).

Since this original synthesis, a great number of improvements (191–201) have been made in the stereoselective preparation and derivatization of the ω-chain precursor, in cuprate reagent composition and preparation, in protecting group utilization, and in the preparation and resolution of hydroxycyclopentenones. Illustration of some of the many improvements are seen in a synthesis (202) of enisoprost, a PGE_1 analogue. The improvements consist of a much more efficient route to the enone as well as modifications in the cuprate reactions. Preparation of the racemic enone is as follows:



(*Z,Z*)-1,5-Cyclooctadiene **(62)** was ozonolyzed to about 65–70% of completion and quenched with triethylamine and acetic anhydride to give the aldehyde ester **(63)** in 40–50% yield along with about 2–5% of the corresponding dialdehyde. Reaction of crude **(63)** with 2-furanylmagnesium chloride provided the furanylcarbinol **(64)** which was treated with zinc chloride to produce **(65)**. Treatment of **(65)** with a catalytic amount of anhydrous chloral in the presence of triethylamine gave the desired enone **(66)**. For preparation of the cuprate reagent, zirconocene chloride hydride followed by iodine was used to generate exclusively the (*E*)-vinyl iodide **(68)** from **(67)**. Treatment of **(68)** with n-C_4H_9Li generated the vinyllithium species which was then converted to the dilithiocyanocuprate reagent **(69)** by addition of lithium methylcyanocuprate, prepared freshly from methyllithium and copper cyanide.

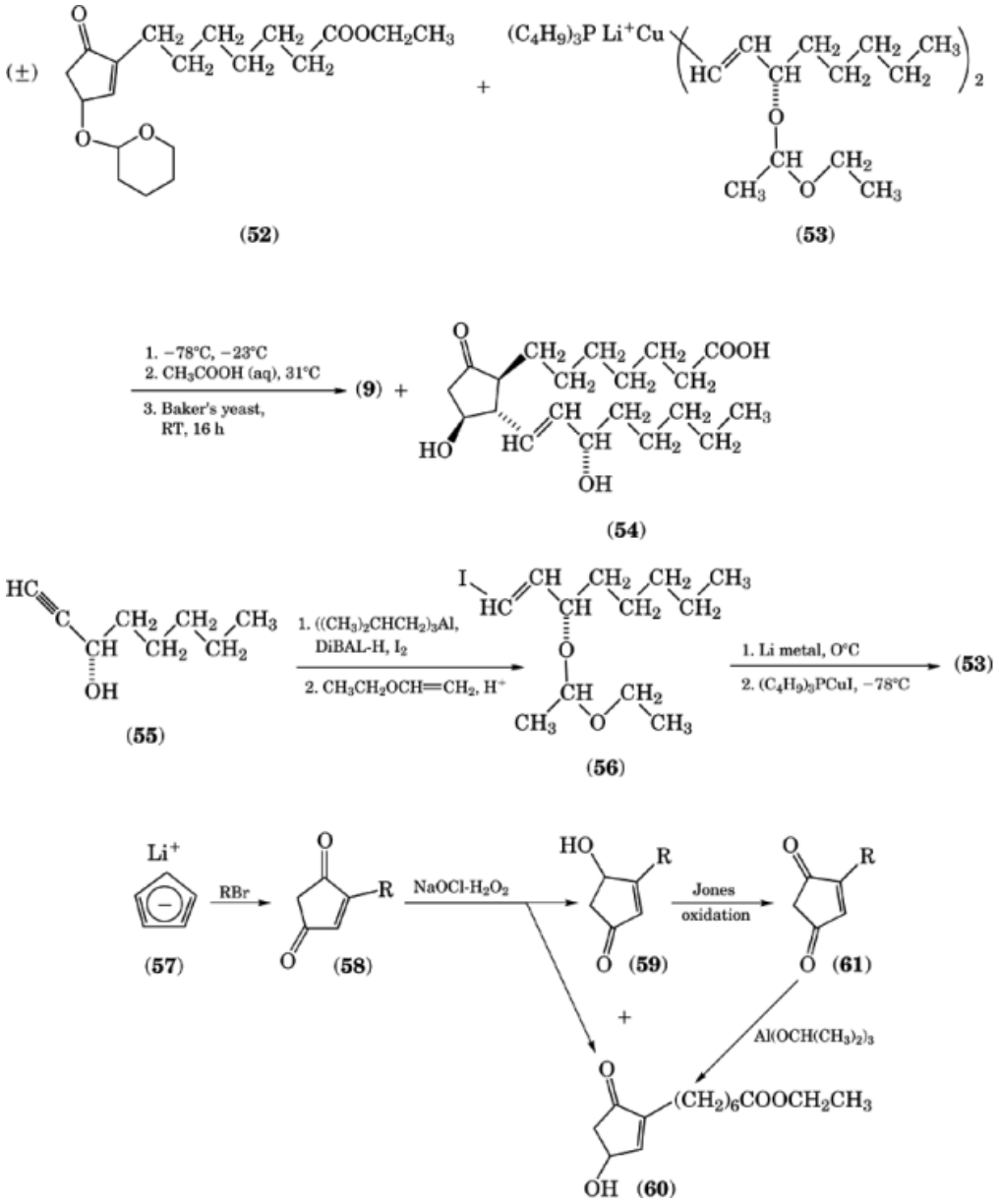
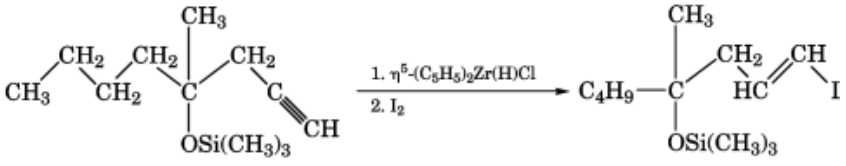
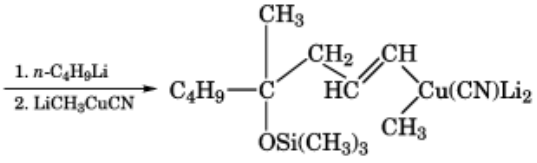


Fig. 8. Synthesis of PGE_1 using an organocuprate reagent where DiBAL-H is diisobutylaluminumhydride and $R=(CH_2)_6COOCH_2CH_3$.



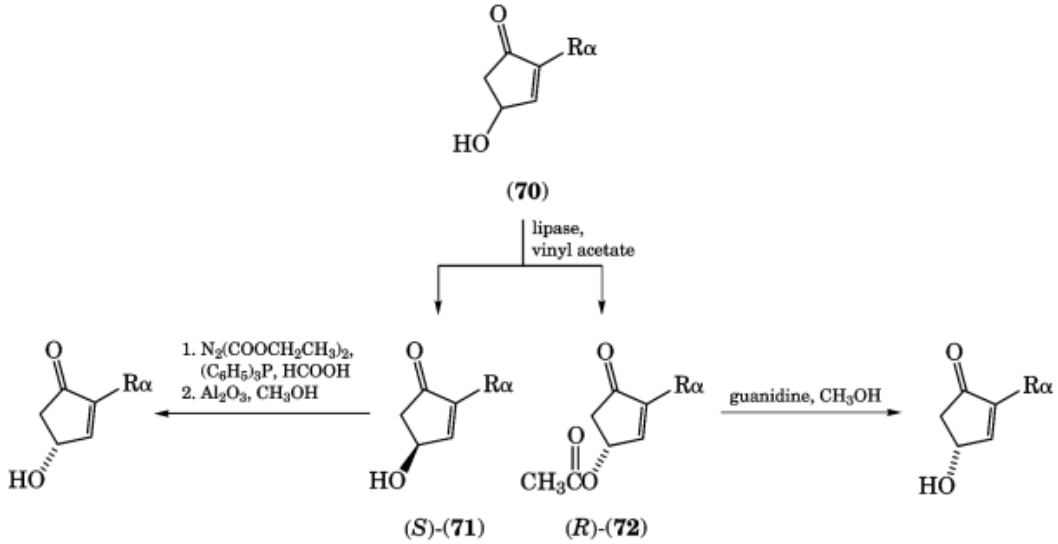
(67) (68)



(69)

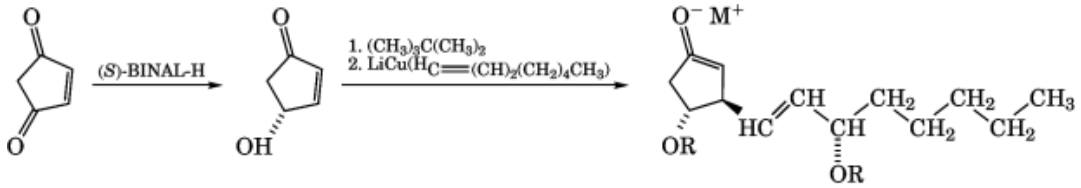
A further improvement in the cuprate-based methodology for producing PGs utilizes a one-pot procedure (203). The ω-chain precursor **(67)** was first functionalized with zirconocene chloride hydride in THF. The vinylzirconium intermediate was transmetalated directly by treatment with two equivalents of *n*-butyllithium or methyllithium at -30 to $-70^{\circ}\mathrm{C}$. Sequential addition of copper cyanide and methyllithium elicited the *in situ* generation of the higher order cyanocuprate which was then reacted with the protected enone to give the PG.

The primary disadvantage of the conjugate addition approach is the necessity of performing two chiral operations (resolution or asymmetric synthesis) in order to obtain exclusively the stereochemically desired end product. However, the advent of enzymatic resolutions and stereoselective reducing agents has resulted in new methods to efficiently produce chiral enones and ω-chain synthons, respectively (see Enzymes, industrial; Enzymes in organic synthesis). For example, treatment of the racemic hydroxy enone **(70)** with commercially available porcine pancreatic lipase (PPL) in vinyl acetate gave a separable mixture of (*S*)-hydroxyenone **(71)** and (*R*)-acetate **(72)** with enantiomeric excess (ee) of 90% or better (204).

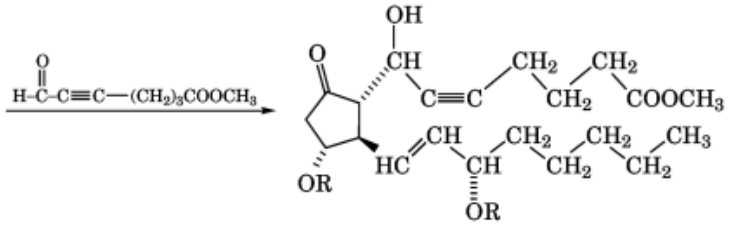


(*S*)-(**71**) (*R*)-(**72**)

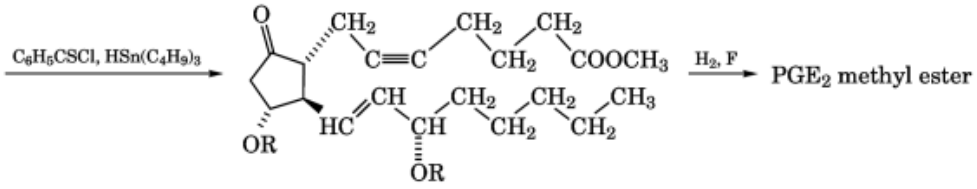
The (*S*)-**(71)** material could be inverted via Mitsunobu chemistry to the desired (*R*)-isomer without loss of stereochemical integrity, whereas the (*R*)-**(72)** product was readily cleaved to the (*R*)-alcohol with guanidine in methanol. The (*R*)-alcohol could also be recycled to improve its enantiomeric purity. Chiral ω-chain alcohols can be produced with a high ee from the corresponding ketones using stereoselective reducing agents such as (*S*)-bi-2-naphthol aluminum hydride ((*S*)-BINAL-H) (191) and alpine-borane (192). A three-component coupling procedure has been devised in which conjugate addition to the chiral cyclopentenone **(74)** is followed by *in situ* quenching of the enolate with an α-chain derivative. A typical synthesis using this methodology is as follows:



(**73**) (**74**) (**75**, R = –Si(CH$_3$)$_2$C(CH$_3$)$_3$)



(**76**)

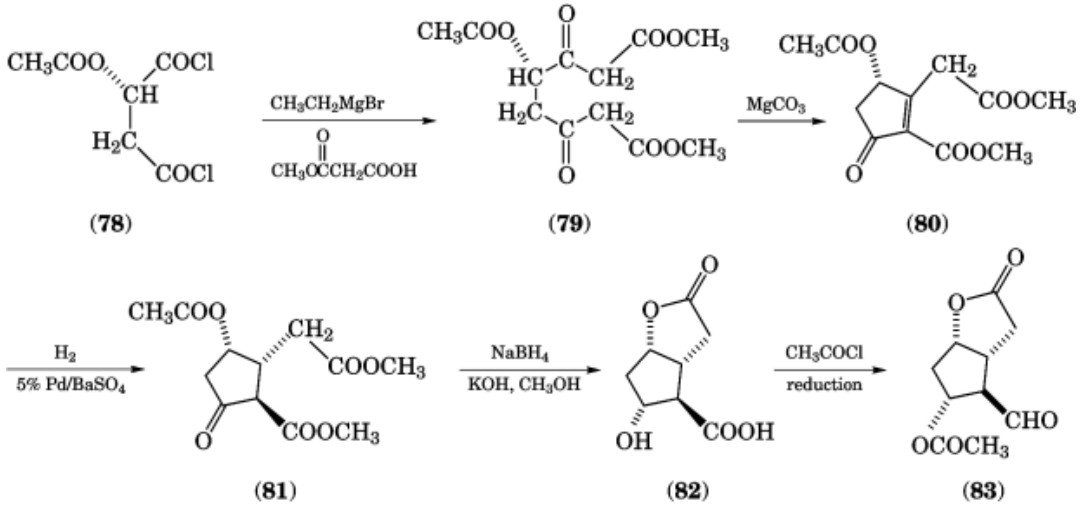


(**77**)

PGE$_2$ methyl ester was obtained by reduction of the triple bond to the (*Z*)-olefin and removal of silyl-protecting groups using fluoride. The primary drawback to this approach is the instability of the enolate leading to elimination of the 11-hydroxy group. Although reactive trapping species such as aldehydes, alkyl halides, Michael acceptors, and allylic halides provide reasonable yields of product, simply alkyl halides fail. In addition, the use of reactive α-chain derivatives often requires further manipulations to generate the desired PG structure. A number of strategies (205–211) have been implemented to avoid or minimize this problem. With propargyl halides as trapping agents, the addition of triphenyltin chloride to the enolate aids the alkylation presumably by enolate metal exchange (186). One improvement (205) of this procedure utilized a vinyl zincate rather than a cuprate.

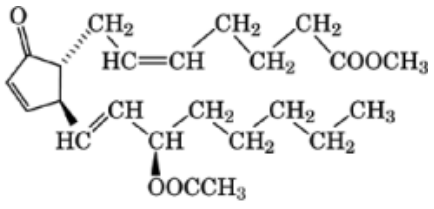
5.1.3. Cyclization of Aliphatic Precursors

This strategy consists of assembling the key functional groups in an aliphatic format, cyclizing to a cyclopentane intermediate, and completing the synthesis by further elaboration of the side chains. One application of this strategy is as follows:



Reaction of (*S*)-(-)-2-acetoxysuccinyl chloride **(78)**, prepared from (*S*)-malic acid, using the magnesio-bromide salt of monomethyl malonate afforded the dioxosuberate **(79)** which was cyclized with magnesium carbonate to a 4:1 mixture of cyclopentenone **(80)** and the 5-acetoxy isomer. Catalytic hydrogenation of **(80)** gave **(81)** having the thermodynamically favored all-trans stereochemistry. Ketone reduction and hydrolysis produced the bicyclic lactone acid **(82)** which was converted to the Corey aldehyde equivalent **(83)**. A number of other approaches have been described (108).

The discovery (1) that the "unnatural" isomer (15*R*)-PGA_2 [23602-72-4] and its 15-acetate, methyl ester **(84)** were present in unusually large quantities (1.5–3.0% of dry weight) in the coral species *Plexaura homomalla* provided a stimulus to utilize these materials as sources for synthesis of PGE_2 **(1)** and $PGF_{2\alpha}$ (**8**). (15*S*)-PGA_2 was also shown to be present in certain types of *P. homomalla* coral (212, 213), making access to PGE_2 and $PGF_{2\alpha}$ more direct and efficient. However, modern day total synthesis methods have rendered this source unnecessary.



(84)

5.2. Synthesis of Other Prostanoids

The other classical prostaglandins, PGAs, Bs, Cs, Ds, and Js, can be prepared from the PGEs and Fs. Dehydration of PGE_2 under acidic conditions (CH_3COOH/H_2O, heat) generates PGA_2, whereas alkaline conditions

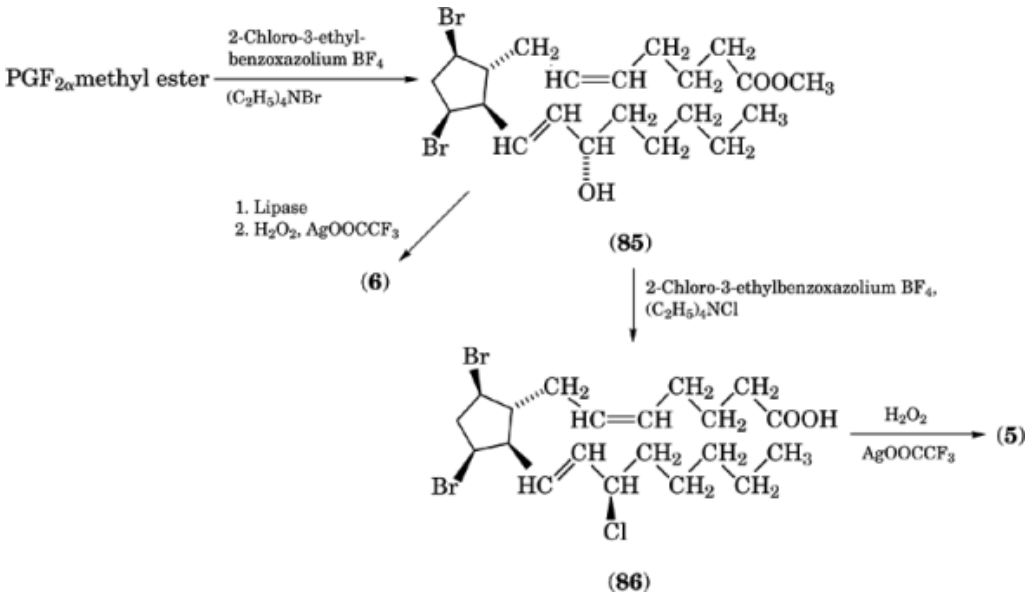


Fig. 9. Synthesis of prostaglandin endoperoxides.

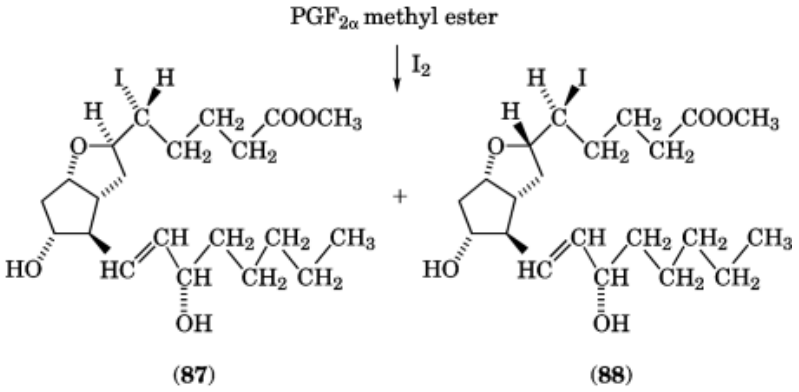
(NaOH, CH_3OH) produce PGB_2. PGJ_2 can be formed by dehydration of PGD_2. Total synthetic procedures for these PGs have been given (6).

5.2.1. Prostaglandin Endoperoxides

The naturally occurring endoperoxides, PGG_1, PGG_2, PGH_1, and PGH_2, as well as a number of their analogues, having variations in the α- and ω-chains, have been prepared by biosynthesis using seminal vesicles (sheep) as the enzyme source, from the corresponding fatty acids (58). The isolation of these products, demonstrating that they have an adequate degree of chemical stability, prompted efforts to prepare them by total synthesis. A practical and efficient synthesis of PGH_2 (**6**) and PGG_2 (**5**) is depicted in Figure 9 (214, 215).

5.2.2. Prostacyclin

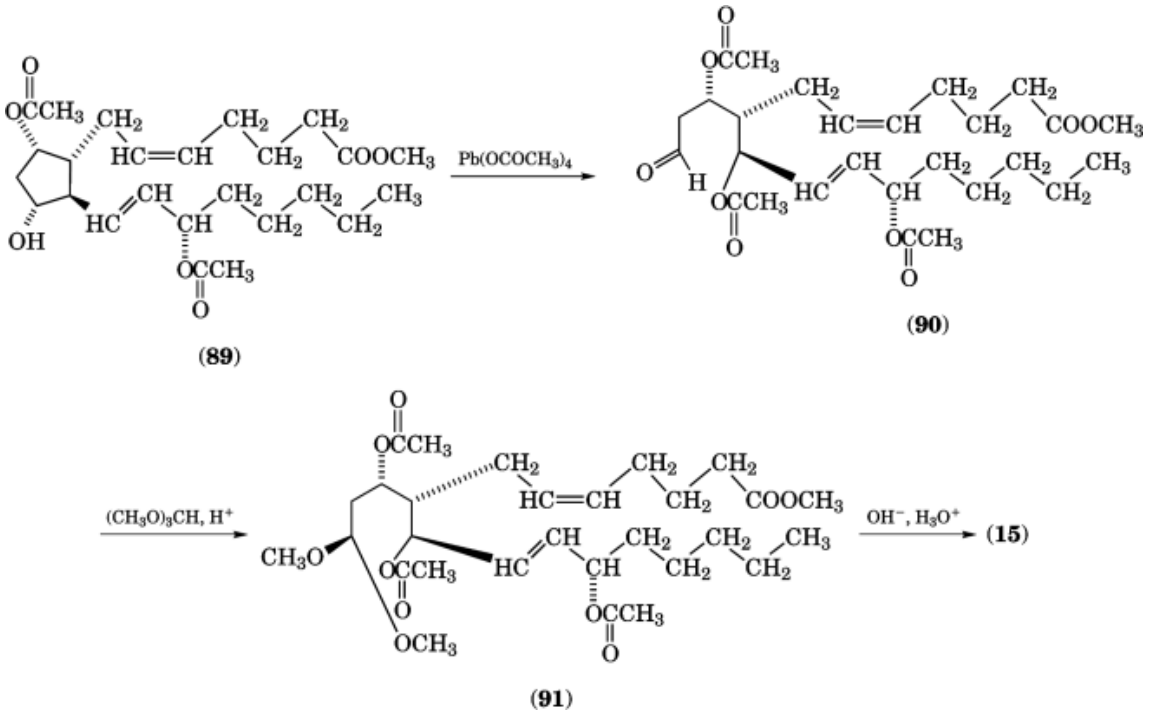
The total syntheses of PGI_2 (**4**) have been extensively reviewed (58, 103). The first synthesis of PGI_2 as its methyl ester and sodium salt (epoprostenol) (216–218) was pivotal in the chemical characterization of this unstable molecule (58). The key feature of this synthesis was the iodocyclization reaction to produce a pair of diastereomers **(87)** and **(88)**.



Subsequent dehydrohalogenation afforded exclusively the desired (*Z*)-olefin of the PGI_2 methyl ester. Conversion to the sodium salt was achieved by treatment with sodium hydroxide. The sodium salt is crystalline and, when protected from atmospheric moisture and carbon dioxide, is indefinitely stable. A variation of this synthesis started with a C-5 acetylenic PGF derivative and used a mercury salt catalyzed cyclization reaction (219). Although natural PGI_1 has not been identified, the syntheses of both (6*R*)- and (6*S*)-PGI_1, [62777-90-6] and [62770-50-7], respectively, have been described, as has that of PGI_3 (104, 216).

5.2.3. Thromboxanes

Because of its highly unstable nature, TxA_2 **(3)** eluded total synthesis until 1985. However, following the disclosure in 1975 of its proposed structure and pharmacological importance, a great deal of effort was expended to develop syntheses of its stable metabolite, TxB_2 **(15)**. A practical, short synthesis (220) from the 9,15-diacetate of $PGF_{2\alpha}$ **(89)** follows.



Treatment of **(89)** with lead tetraacetate generates the unstable open-ring aldehyde **(90)** which is quickly converted to a dimethylacetal **(91)**. Following basic hydrolysis of the methyl ester and acetates, the acetal is cleaved with aqueous acid to produce TxB_2. A number of other approaches, including one starting from the Corey aldehyde, have been described (58).

The definitive synthesis of TxA_2 **(3)** (57) is outlined in Figure 10. A lactone **(91)** was formed from TxB_2. Dehydration to the enol ether followed by bromohydrin formation gave intermediate (**92**) which was cyclized to the bromooxetane (**93**) by use of a modified Mitsunobu reaction. Debromination with tri-*n*-butyltin hydride cleanly yielded the desired 1,15-lactone form of TxA_2, (**94**). Lactone (**94**) was unstable to chromatographic purification but could be obtained free of tin by-products by use of a polymer-bound tin hydride. X-ray crystallography confirmed the structure of (**94**). The macrolactone was saponified in a 1:1 mixture of CD_3OD–D_2O containing 10 equivalents of NaOD to give the sodium salt of TxA_2. This material possessed the appropriate H^1-nmr features of the bicyclic oxetane nucleus and reproduced the biological activities of natural platelet-derived TxA_2 in a variety of assays. The lactone (**94**) was inactive in these assays.

6. Design of Synthetic Analogues

The natural prostanoids have myriad biological effects and held great promise as potential therapeutic agents in numerous diseases. The natural prostanoids, however, also have three notable drawbacks which medicinal chemists have tried to overcome by molecular modification in order to produce acceptable drug candidates. These drawbacks are rapid metabolism which results in lack of activity if taken orally and a short duration of action, numerous side effects due to their multiplicity of biological activities, and poor chemical stability, a characteristic especially pronounced in PGE, -D, and -I structures.

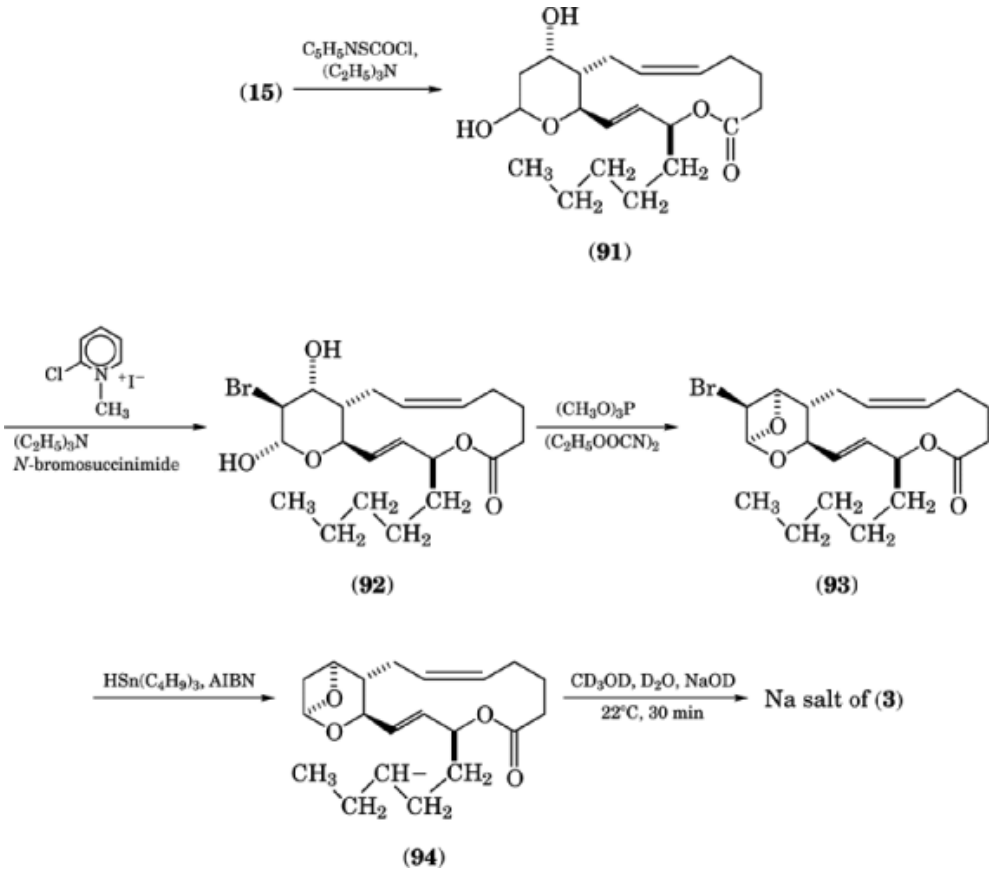


Fig. 10. Synthesis of TxA_2 **(3)**, where AIBN=azobisisobutyronitrile.

Table 3. Therapeutically Useful Prostaglandin Analogues

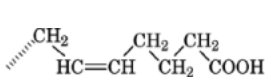
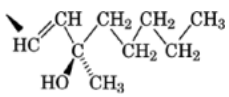
[a]Compound generic name (Trade name)	Structure		CAS Registry Number	Company
	Rα	Rω		
arbaprostil (Arbacet)			[55028-70-1]	Upjohn

Table 3. ***Continued***

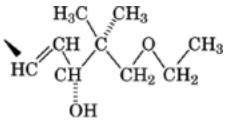
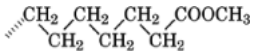
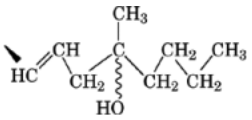
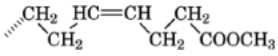
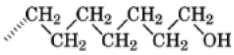
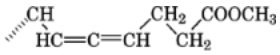
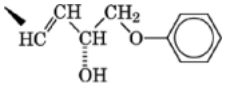
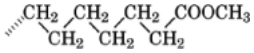
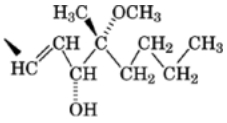
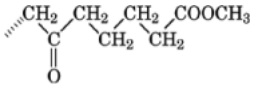
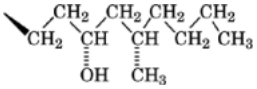
[a]Compound generic name (Trade name)	Structure		CAS Registry Number	Company
	Rα	Rω		
HR-260 dimoxaprost	same		[90243-98-4]	Hoechst-Roussel
SC-29333 misoprostol (Cytotec)			[59122-46-2]	Searle
SC-34301 enisoprost		same	[81026-63-3]	Searle
TR-4698 rioprostol		same	[77287-05-9]	Miles/Ortho and Bayer AG
RS-84,135 enprostil (Gardrin)			[73121-56-9]	Syntex
MDL-646 mexiprostil			[88980-20-5]	Lepetit
ONO-1308 ornoprostol (Ronak)			[70667-26-4]	ONO

Table 3. ***Continued***

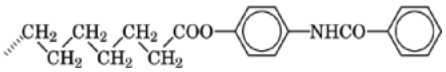
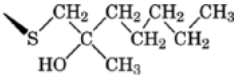
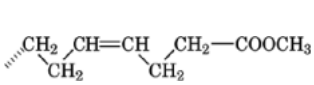
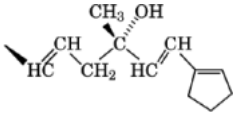
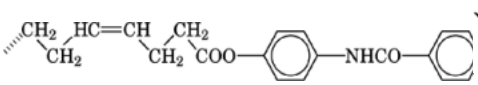
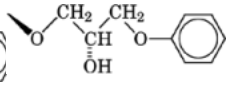
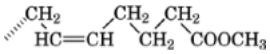
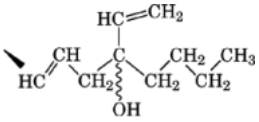
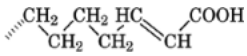
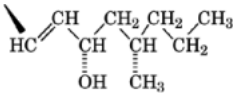
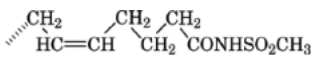
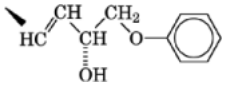
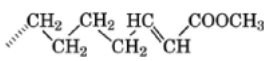
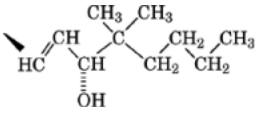
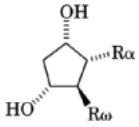
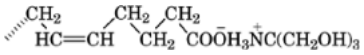
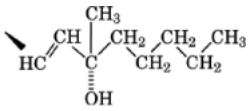
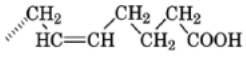
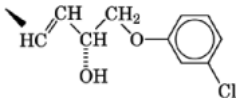
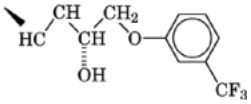
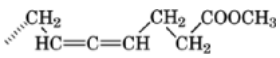
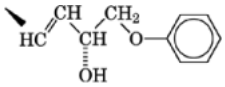
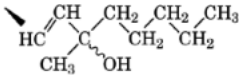
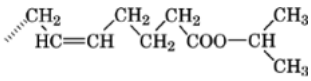
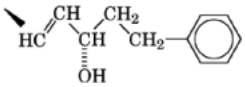
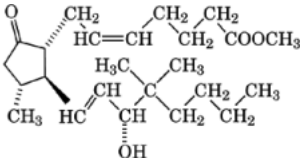
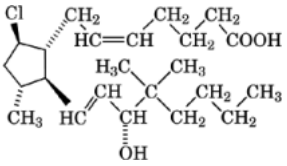
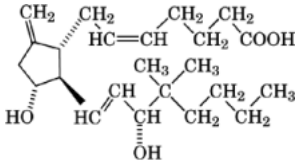
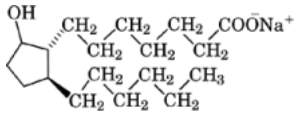
[a]Compound generic name (Trade name)	Structure		CAS Registry Number	Company
	Rα	Rω		
EMD-33290 tiprostanide[b]			[67040-53-3]	Merck AG
SC-46275 remiprostol			[110845-89-1]	Searle
GR-63799X			[106342-69-2]	Glaxo
CL-115,347 viprostol[c]			[73647-73-1]	Lederle
ONO-1206 limaprost (Opalmon)[c]			[74397-12-9]	ONO
CP-34089 sulprostone (Nalador)[d]			[54348-10-6]	Pfizer/Schering AG
ONO-802 gemeprost (Cervagem)[d]			[64318-79-2]	ONO

Table 3. ***Continued***

[a]Compound generic name (Trade name)	Structure		CAS Registry Number	Company
				
Carboprost (Prostin 15M)[d]			[58551-69-2]	Upjohn
ICI 80,996 cloprostenol (Estrumate)[e]			[62561-03-9]	ICI
ICI 80,008 fluprostenol (Equimate)[e]	same		[59685-93-7]	ICI
RS-84043 fenprostalene[e]			[69381-94-8], [73175-12-9]	Syntex
RS-9390 prostalene (Synchrocept)[e]	same		[54120-61-5]	Syntex
PhXA41 latanoprost[f]			[130209-82-4]	Kabi Pharmacia

Structure as given

Table 3. ***Continued***

[a]Compound generic name (Trade name)	Structure Rα	Rω	CAS Registry Number	Company
RO-21,6937 trimoprostil			[69900-72-7]	Roche
ZK-94726 nocloprost			[79360-43-3]	Schering AG
meteneprost[d]			[61263-35-2]	Upjohn
rosaprostol			[56695-65-9]	IBI

[a] The therapeutic indication (TI) is antiulcer, unless otherwise noted.
[b] TI is antiulcer and antihypertensive.
[c] TI is antihypertensive.
[d] TI is fertility control and labor induction.
[e] TI is veterinary use and synchronization of estrus.
[f] TI is antiglaucoma.

6.1. Analogues of the Classical Prostaglandins

A list of the more prominent prostaglandin analogues which are either marketed or have reached some stage of development is given in Table 3. Two reviews (107, 221) detail the syntheses of these compounds and the strategies associated with their design. One significant strategy in analogue conception has been directed at impeding the rapid metabolic degradation of the natural compounds. Placement of methyl groups at C-15 or C-16 to block C-15 dehydrogenation has been effective and is exemplified by arbaprostil and trimoprostil. Blockage of β-oxidation of the α-chain has been attempted by placement of double bonds at C-2,3 and C-

4,5 and heteroatoms at C-3. Enisoprost, enprostil, and limaprost are examples. Strategies to prevent ω-chain oxidation have also been employed and are seen in enprostil, dimoxaprost, remiprostol, and sulprostone, among others. To improve selectivity, a number of strategies have been attempted, but the task has proven difficult and side effects remain a principal hindrance to the therapeutic use of prostaglandins. Perhaps the most successful modification has been the translocation of the 15-hydroxy group of natural PGEs to the adjacent C-16 position. Analogues such as misoprostol, enisoprost, rioprostol, and remiprostol are examples of this approach. Misoprostol, for example, shows improved separation of therapeutic action from undesired effects such as diarrhea production and cardiovascular effects in comparison with its 15-hydroxy counterparts (222). Replacement of the C-13,14 double bond with a heteroatom as in GR-63779X and tiprostanide has also provided improved selectivity. Modifications to improve chemical stability are evident in trimoprostol, nocloprost, and metenoprost. The propensity for β-elimination of the 11-hydroxy group has been eliminated in each of these analogues. The use of bulky aromatic esters, as found in tiprostanide and GR-63779X, to induce or enhance crystallinity has also been a strategy to improve stability.

6.2. Prostacyclin Analogues

Problems of poor chemical stability, rapid metabolic disposition, and lack of selectivity coupled with its high therapeutic potential for treatment of cardiovascular diseases led to an extensive exploration of structural variants of prostacyclin. A list of prominent analogues is given in Table 4, and the synthetic details for these compounds are available (107, 223). One of the obvious strategies has been to alleviate the chemical instability inherent in the cyclic enol ether of PGI_2. The replacement of oxygen with carbon to give carbacyclic analogues has been a favorite and successful endeavor. Other modifications have been made to the α- and ω-chains to reduce metabolic susceptibility.

Table 4. Therapeutically Useful Prostacyclin Analogues

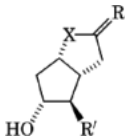
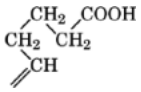
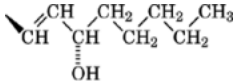
Compound generic name (Trade name)	Structure			CAS Registry Number	Company[a]
	R	R′	X		
					
epoprostenol (Flolan)			O	[73873-87-7]	Upjohn/Wellcome

Table 4. ***Continued***

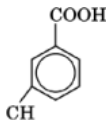
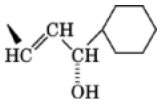
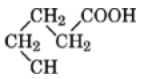
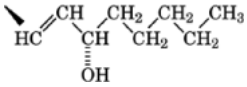
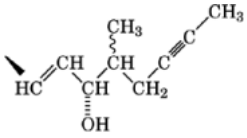
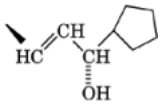
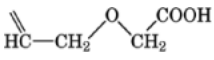
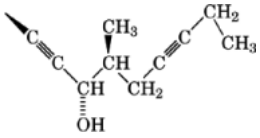
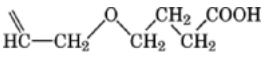
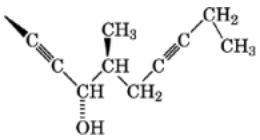
Compound generic name (Trade name)	Structure R	Structure R′	X	CAS Registry Number	Company[a]
ZK-34798 taprostene[b]			O	[108945-35-3]	Gruenenthal
carbacyclin[c]			CH_2	[69552-46-1]	Upjohn/Wellcome
ZK-97951 iloprost	same		CH_2	[78919-13-8]	Schering AG
OP41483 at-aprost	same		CH_2	[83997-19-7]	Ono/Dainippon
ZK-96480 ci-caprost			CH_2	[94079-80-8]	Schering AG
U-61431 eptaloprost[d]			CH_2	[90693-76-8]	Schering AG

Table 4. ***Continued***

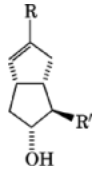
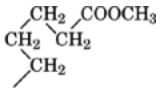
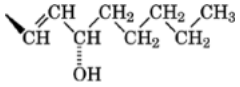
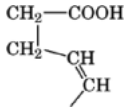
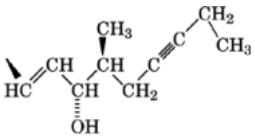
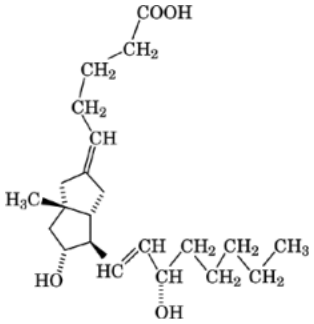
Compound generic name (Trade name)	Structure R	Structure R′	Structure X	CAS Registry Number	Company[a]
					
TTC-909 lipoiso-carba-cyclin				[88931-51-5]	Teijin/Taisho
KP-10614				[130273-99-3]	Mitsubishi/Kasei
		Structures as given			
CG-4203 ciprostene				[81845-44-5]	Upjohn/Wellcome

Table 4. ***Continued***

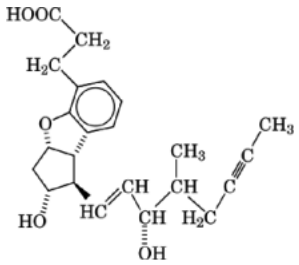
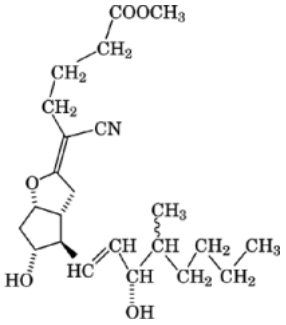
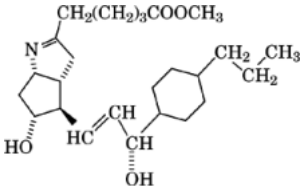
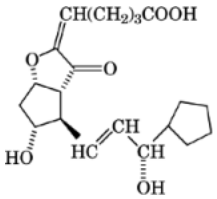
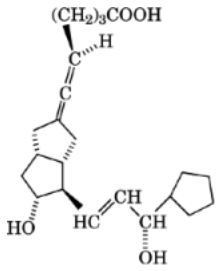
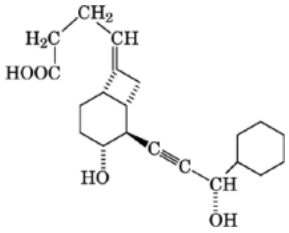
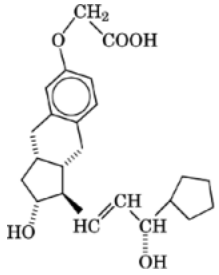
Compound generic name (Trade name)	Structure R	Structure R′	Structure X	CAS Registry Number	Company[a]
beraprost				[88430-50-6]	Toray/Kaken
ZK-34798 nileprost[e]				[71097-83-1]	Schering AG
OP-2507[f]				[101758-79-6]	Ono
CH-5084				[111319-88-1]	Chinoin

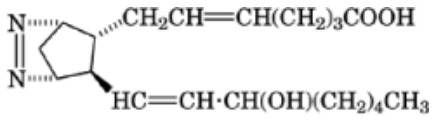
Table 4. ***Continued***

Compound generic name (Trade name)	Structure R	Structure R′	X	CAS Registry Number	Company[a]
SC-43350				[106138-20-9]	Searle
RS-93427				[105284-21-7]	Syntex
U-68,215[e]				[99570-57-7]	Upjohn

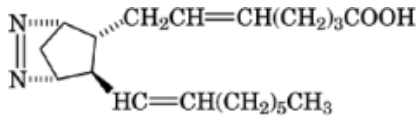
[a] The therapeutic indication (TI) is antithrombotic, unless otherwise noted.
[b] TI is antithrombotic and sudden hearing loss.
[c] TI is peripheral vascular disease.
[d] TI is antithrombotic and antimetastatic.
[e] TI is antiulcer.
[f] TI is antihypoxic.

6.3. Endoperoxide Analogues

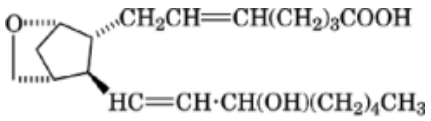
The endoperoxide analogues that have been synthesized and biologically evaluated have been summarized (103, 104, 224). In general, these analogues were designed to be more chemically stable than the naturally occurring substances PGG_2 and PGH_2, which have labile 2,3-dioxabicyclo[2.2.1]heptane ring systems. The following compounds are notable among the many analogues that have been synthesized. The azo analogue **(95)** and the epoxymethano analogues **(97)** and **(98)** appear to mimic the biological actions of the native compounds, whereas the 15-deoxy analogues **(96)**, **(99)**, and **(100)** inhibit PGH_2-induced human platelet aggregation (225, 226).



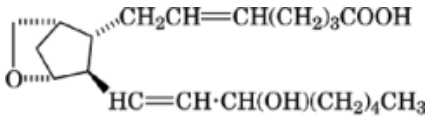
(95)



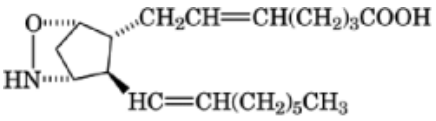
(96)



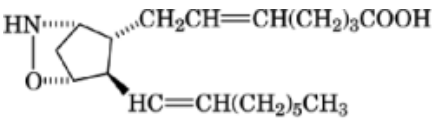
(97)



(98)



(99)



(100)

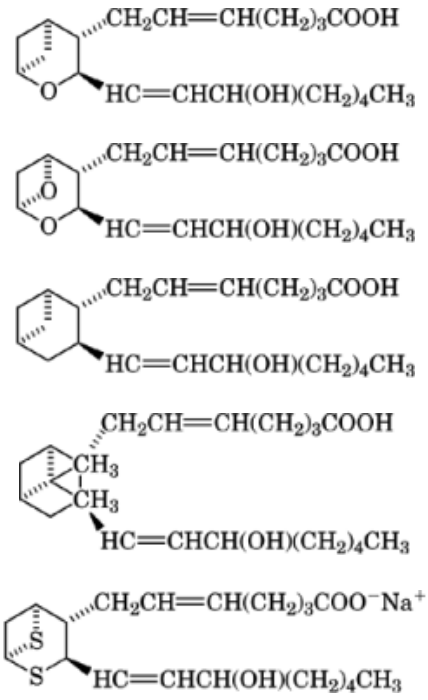
R = $CH_2CH{=}CH\,(CH_2)_3\,COOH$

$$R' = HC{=}CH{\cdot}CH(OH)(CH_2)_4CH_3$$

$$R'' = HC{=}CH(CH_2)_5CH_3$$

6.4. Thromboxane A_2 Analogues

The thrust of molecular modification in this arena has been to make chemically stable mimics of TxA_2 for biological studies and, secondly, to identify antagonists of TxA_2 as potential therapeutic agents. The synthesis and biological properties of some of these analogues, as well as those of numerous other analogues have been described (224).



$$R = CH_2CH{=}CH(CH_2)_3COOH$$

$$R' = HC{=}CHCH(OH)(CH_2)_4CH_3$$

$$R'' = CH_2CH{=}CH(CH_2)_3COO^-Na^+$$

7. Therapeutic Role of Prostanoids

The early promise and anticipation of a large and varied therapeutic role for the prostanoids and their analogues has gone, for the most part, unfulfilled. In spite of the potential for therapeutic usefulness in many diseases and a massive effort by many pharmaceutical companies to identify appropriate analogues, only a few compounds have actually been marketed, and the therapeutic applications have, thus far, been limited to the treatment of peptic ulcer disease, gynecological needs (labor induction and fertility control), synchronization of estrus in farm animals, cardiovascular indications (antihypertension and ischemic conditions), and likely, with latanoprost, treatment of glaucoma (see Contraceptive drugs; Gastrointestinal agents; Pharmaceuticals). Even the use of prostanoids (PGEs and PGIs) in peptic ulcer disease, an application intensely pursued with many analogues (see Tables 3 and 4) has been only modestly successful. While these perform about as well as the more widely used histamine blocker agents (cimetidine, etc) in curing ulcers, they are not competitive because of their side effects, most notably diarrhea and abdominal discomfort, and their contraindication in pregnant patients. The most widely approved analogue, misoprostol, has found a niche market in the prevention and treatment of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. This rather disappointing overall scenario for prostanoid use in therapy may be changing, however. As the tools and knowledge of science have advanced, so have approaches and techniques for studying prostaglandins, resulting in the discovery of potential applications as well as the revisitation of possible use in previously studied diseases. Of special note for PGE analogues has been the examination of their cytoprotective properties in cancer treatment and their role in inflammatory and allergic diseases. Several PG analogues have been found to protect a number of tissues against the effects of radiation and chemotherapeutic agents (88, 89, 227); these analogues may be useful in preventing side effects, such as mucositis, hair loss, and skin damage, of cancer treatments. The effectiveness of PGEs in animal models of inflammatory diseases (228, 229) has been noted and there are anecdotal reports of therapeutic benefit in human patients. Inhaled PGE_2 has been reported to be effective in preventing late-phase response to allergen-induced asthma (230) and misoprostol has prevented the late-phase response to antigens in the skin (231). Thus this renewal of interest and increased breadth of investigation may signal a renaissance for the participation of prostanoids in drug therapy.

The potential of thromboxane-based drugs in cardiovascular disease is also promising. The early attempts to produce effective therapeutics based on inhibition of TxA_2 synthesis failed because of poor efficacy. The lack of effectiveness of these agents was attributed to the accumulation of the TxA_2 precursor, PGH_2, which is itself a thromboxane receptor activator (232). However, a more recent and effective approach has been to combine within one molecule both synthesis-inhibiting properties and receptor antagonism (233, 234) and molecules of this type are being pursued (235).

8. Commercial Sources

Many of the natural prostanoids as well as some of their analogues and related products are available in research quantities from several companies. These include Biomol Research Laboratories (Plymouth Meeting, Pennsylvania), Cayman Chemical (Ann Arbor, Michigan), and Cascade Biochem, Ltd. (Berkshire, England).

BIBLIOGRAPHY

"Prostaglandins" in *ECT* 3rd ed., Suppl. Vol., pp. 711–752, by D. R. Morton, Jr., The Upjohn Co.

Cited Publications

1. A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Lett.*, 5185 (1969); W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Am. Chem. Soc.* **94**, 2122 (1972).
2. W. L. Smith and L. J. Marnett, *Biochem. Biophysic. Acta* **1083**, 1 (1991); W. L. Smith, L. J. Marnett, and D. L. Dewitt, *Pharm. Ther.* **49**, 153 (1991).
3. R. Kurzrok and C. Lieb, *Proc. Soc. Exp. Biol. N.Y.* **28**, 268 (1930).
4. M. W. Goldblatt, *J. Soc. Chem. Ind., London* **52**, 1056 (1933).
5. U. S. Von Euler, *Naunyn-Schmiedeberg's Arch. Exp. Path. Pharmak.* **175**, 78 (1934).
6. J. S. Bindra and R. Bindra, *Prostaglandin Synthesis*, Academic Press, Inc., New York, 1977, p. 7; S. Bergström, *Prog. Lipid Res.* **20**, 7 (1982).
7. S. Abrahamsson, *Acta Crystallogr.* **16**, 409 (1963).
8. S. Abrahamsson, S. Bergström, and B. Samuelsson, *Proc. Chem. Soc.*, 332 (1962).
9. D. H. Nugteren, D. A. van Dorp, S. Bergström, M. Hamberg, and B. Samuelsson, *Nature* **212**, 38 (1966).
10. *Chem. Brit.*, 847 (Dec. 1982).
11. N. H. Anderson, C. J. Hartzell, and B. De, in J. E. Pike and D. R. Morton, eds., *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Vol. **14**, Raven Press, New York, 1985, p. 1; S. Moncada and J. R. Vane, in J. R. Vane and S. Bergström, eds., *Prostacyclin*, Raven Press, New York, 1979, p. 5.
12. J. H. Fletcher, O. C. Dermer, and R. B. Fox, *Nomenclature of Organic Compounds*, American Chemical Society Advances in Chemistry Series, Vol. **126**, Washington, D.C., 1974; *Selection of Index Names for Chemical Substances, Chem. Abstracts 82*, Index Guide, American Chemical Society, Washington, D.C., 1982.
13. N. A. Nelson, *J. Med. Chem.* **17**, 911 (1974).
14. S. Moncada and J. R. Vane, *J. Med. Chem.* **23**, 591 (1980).
15. B. Samuelsson, M. Goldyne, E. Granström, M. Hamberg, S. Hammarström, and C. Malmsten, *Annu. Rev. Biochem.* **47**, 997 (1978).
16. B. Samuelsson, G. Folco, E. Granström, H. Kindahl, and C. Malmsten, in F. Coceani and P. M. Olley, eds., *Advances in Prostaglandin and Thromboxane Research*, Vol. **4**, Raven Press, New York, 1978, 1–25.
17. S. Hammarström, *Arch. Biochem. Biophys.* **214**, 431 (1982).
18. A. J. Marcus, H. L. Ullman, and L. B. Safier, *J. Lipid Res.* **10**, 108 (1969).
19. T. K. Bills and M. J. Silver, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **34**, 322 (1975).
20. E. J. Christ and D. H. Nugteren, *Biochim. Biophys. Acta* **218**, 296 (1970).
21. P. Cohen and A. Derksen, *Br. J. Haematol.* **17**, 359 (1969).
22. D. F. Horrobin, *Prostaglandins, Leukot. Essent. Fatty Acids* **31**, 181 (1989).
23. R. T. Holman, L. Smythe, and S. Johnson, *Am. J. Clin. Nutr.* **32**, 2390 (1979).
24. M. Hamberg and B. Samuelsson, *J. Biol. Chem.* **242**, 5344 (1967).
25. W. L. Smith and co-workers, in B. Samuelsson, S.-E. Dahlén, J. Fritsch, and P. Hedqvist, eds., *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Vol. **20**, Raven Press, New York, 1990, p. 14.
26. D. L. DeWitt, *Biochem. Biophys. Acta* **1083**, 121 (1991).
27. W. Xie, D. L. Robertson, and D. L. Simmons, *Drug Dev. Res.* **25**, 249 (1992).
28. D. L. Simmons, W. Xie, J. G. Chipman, and G. E. Evett in J. M. Bailey, ed., *Prostaglandins, Leukotrienes, Lipoxins and PAF*, Plenum Press, New York, 1991, p. 67.
29. W. L. Smith, *Biochem. J.* **259**, 315 (1989).
30. J. A. Mitchell, P. Akarasereenont, C. Thiemermann, R. J. Flower, and J. R. Vane, *Proc. Natl. Acad. Sci., USA* **90**, 11693 (1993).
31. J. L. Masferrer, K. Seibert, B. Zweifel, and P. Needleman, *Proc. Natl. Acad. Sci., USA* **89**, 3917 (1992).
32. D. Picot, P. J. Loll, and R. M. Garavito, *Nature* (*London*) **367**, 243 (1994).
33. J. R. Vane, R. J. Flower, and R. M. Botting, *Stroke* **21** (Suppl. IV), 12 (1990).

34. L. R. Roberts, A. R. Brash, and J. A. Oates, in J. A. Oates, ed., *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*, Vol. **10**, Raven Press, New York, 1982, p. 211.
35. W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Am. Chem. Soc.* **99** 1222 (1977).
36. W. P. Schneider, *J. Chem. Soc. Chem. Commun.*, 304 (1969).
37. E. J. Corey and C. R. Cyr, *Tetrahedron Lett.*, 1761 (1974).
38. R. C. Kelly, I. Schletter, and R. L. Jones, *Prostaglandins* **4**, 653 (1973).
39. E. E. Nishizawa and co-workers, *Prostaglandins* **9**, 109 (1975).
40. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.* **92**, 397 (1970).
41. C. J. Sih and co-workers, *J. Am. Chem. Soc.* **97**, 865 (1975).
42. J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.* **34**, 3552 (1969).
43. R. A. Johnson and co-workers, *J. Am. Chem. Soc.* **100**, 7690 (1978).
44. S. Hanessian and P. Lavalle, *Can. J. Chem.* **55**, 562 (1977).
45. W. P. Schneider and R. A. Morge, *Tetrahedron Lett.*, 3283 (1976).
46. N. A. Nelson and R. W. Jackson, *Tetrahedron Lett.*, 3275 (1976).
47. P. W. Ramwell and co-workers, *Prog. Chem. Fats Other Lipids* **9**, 231 (1968); C. Hensby, in P. Crabbe, ed., *Prostaglandin Research*, Academic Press, Inc., New York, 1977, p. 89.
48. W. L. Duax and J. W. Edmonds, *Prostaglandins* **3**, 201 (1973).
49. J. W. Edmonds and W. L. Duax, *Prostaglandins* **5**, 275 (1974).
50. G. Kotovych, G. H. M. Aarts, T. T. Nakashima, and G. Bigam, *Can. J. Chem.* **58**, 974 (1980).
51. G. Kotovych and G. H. M. Aarts, *Org. Magn. Reson.* **18**, 77 (1982).
52. C. Chachaty, Z. Wolkowski, F. Piriou, and G. Lukacs, *J. Chem. Soc. Chem. Commun.*, 951 (1973).
53. G. F. Cooper and J. Fried, *Proc. Natl. Acad. Sci., USA* **70**, 1579 (1973); G. F. Cooper and J. Fried, *Proceedings of the First International Conference on Stable Isotopes in Chemistry, Biology and Medicine*, 1973, 72–83; S. A. Mizsak and G. Slomp, *Prostaglandins* **10**, 807 (1975).
54. C. R. Pace-Asciak, *Advances in Prostaglandins, Thromboxane and Leukotriene Research*, Vol. **18**, Raven Press, New York, 1989.
55. M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci.* **72**, 2994 (1975).
56. M. Hamberg, J. Svensson, and B. Samuelsson, *Adv. Prostaglandin Thromboxane Res.* **1**, 19 (1976).
57. S. S. Bhagwat, P. R. Hamann, and C. Still, *J. Am. Chem. Soc.* **107**, 6372 (1985).
58. R. A. Johnson, in Ref. 11, p. 131.
59. B. Samuelsson, *The Harvey Lectures, 1979–1980*, Academic Press, Inc., New York, 1981, 1–40.
60. R. P. Robertson, ed., *Med. Clin. North Am.* **65**, 711 (1981).
61. P. W. Ramwell and co-workers, *Prog. Chem. Fats Other Lipids* **9**, 231 (1968).
62. B. Samuelsson and R. Paoletti, eds., *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Vol. **9**, Raven Press, New York, 1982.
63. N. H. Andersen and P. W. Ramwell, *Arch. Intern. Med.* **133**, 30 (1974).
64. E. W. Horton, in S. M. Roberts and F. Scheinmann, eds., *Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids*, Pergamon Press, Oxford, U.K., 1979, p. 1.
65. M. F. Cuthbert, in M. F. Cuthbert, ed., *The Prostaglandins: Pharmacological and Therapeutic Advances*, J. B. Lippincott Co., Philadelphia, Pa., 1973, p. 253.
66. S. Bianco, M. Robuschi, R. Ceserani, and C. Gandolfi, *Int. Res. Commun. Syst. Med. Sci.* **6**, 256 (1978).
67. E. W. Horton, *Brit. J. Pharmacol. Chemother.* **22**, 189 (1964).
68. E. W. Horton, *Prostaglandins: Monographs on Endocrinology*, Springer-Verlag, Berlin, 1972, p. 141.
69. L. S. Wolfe, *J. Neurochem.* **38**, 1 (1982).
70. D. J. Levenson, C. E. Simmons, and B. M. Brenner, *Am. J. Med.* **72**, 354 (1982).
71. J. Tannenbaum, J. A. Splawinski, J. A. Oates, and A. S. Nies, *Circ. Res.* **36**, 197 (1975).
72. K. Ueda and co-workers, *J. Pediatrics* **97**, 834 (1980).
73. S. C. Willey and B. Chernow, in W. D. Watkins, M. B. Peterson, and J. R. Fletcher, eds., *Prostaglandins in Clinical Practice*, Raven Press, New York, 1989, p. 227.
74. R. P. Robertson, *Annu. Rev. Med.* **34**, 1 (1983).
75. J. S. Goodwin, *J. Rheumatol.* **18**(Suppl 28), 26 (1991).
76. L. M. Solomon, L. Juhlin, and M. B. Kirschenbaum, *J. Invest. Derm.* **51**, 280 (1968).

77. G. L. Larsen and P. M. Henson, *Annu. Rev. Immunol.* **1**, 335 (1983).
78. J. R. Vane, *Nature* **231**, 232 (1971).
79. P. Hedqvist, J. Raud, and S.-E. Dahlén, in B. Samuelsson, P. Y.-K. Wong, and F. F. Sun, eds., *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Vol. **19**, Raven Press, New York, 1989, p. 539.
80. J. S. Goodwin and J. L. Ceuppens, *J. Clin. Immunol.* **3**, 295 (1983); J. S. Goodwin and D. R. Webb, in J. S. Goodwin, ed., *Suppressor Cells in Human Disease*, Marcel Dekker, New York, 1981, p. 99.
81. A. Robert, *Gastroenterology* **69**, 1045 (1975).
82. A. Robert, J. E. Nezamis, C. Lancaster, and A. J. Hanchar, *Gastroenterology* **77**, 433 (1979).
83. T. A. Miller, *Am. J. Physiol.* **245**, 6601 (1983); J. L. Wallace, *Gastroenterol. Clin. N. Am.* **21**, 631 (1992).
84. J. L. Wallace, B. J. R. Whittle, and N. K. Boughton-Smith, *Dig. Dis. Sci.* **30**, 866 (1985).
85. J. Stachura, A. Tarnawski, and J. Szezudrawa, *Folia Histochem. Cytochem.* **18**, 311 (1980).
86. M. S. Paller, *Transplan. P.* **20**, 634 (1988).
87. T. Manabe and M. L. Steer, *Gastroenterology* **78**, 777 (1980).
88. W. R. Hanson and K. DeLaurentis, *Prostaglandins* **33**(Suppl.), 93 (1987).
89. F. D. Malkinson, L. Geng, and W. R. Hanson, *J. Invest. Dermatol.* **101**, 1355 (1993).
90. M. M. Cohen, *Biological Protection with Prostaglandins*, Vols. **1** and **2**, CRC Press, Boca Raton, Fla., 1985.
91. I. Kennedy, R. A. Coleman, P. P. A. Humphrey, G. P. Levy, and P. Lumley, *Prostaglandins* **24**, 667 (1982).
92. R. A. Coleman, I. Kennedy, P. P. A. Humphrey, K. Bunce, and P. Lumley, in C. Hansch, P. G. Sammes, J. B. Taylor, and J. C. Emmeth, eds., *Comprehensive Medicinal Chemistry*, Vol. **3**, Pergamon Press, Oxford, U.K., 1989, p. 643.
93. M. Negishi, Y. Sugimoto, and A. Ichikawa, *Prog. Lipid Res.* **32**, 417 (1993); R. A. Coleman, W. L. Smith, and S. Narumiya, *Biol. Rev.* **46**, 205 (1994).
94. A. Honda and co-workers, *J. Biol. Chem.* **268**, 7759 (1993).
95. Y. Sugimoto and co-workers, *J. Biol. Chem.* **267**, 6463 (1992).
96. S. An, J. Yang, M. Xia, and E. J. Goetzl, *Biochem. Biophys. Res. Comm.* **197**, 263 (1993).
97. M. Hirata and co-workers, *Nature* **349**, 617 (1991).
98. R. M. Breyer and co-workers, *J. Biol. Chem.* **269**, 6163 (1994).
99. M. Adam and co-workers, *FEBS Lett.* **338**, 170 (1994).
100. P. J. Gardiner, in Ref. 25, p. 110.
101. M. A. Savage, C. Moummi, P. J. Karabatsos, and T. H. Lanthorn, *Prostaglandins, Leukot. Essent. Fatty Acids* **49**, 939 (1993).
102. J. E. Pike and D. R. Morton, eds., *Advances in Prostaglandin, Thromboxane and Leukotriene Research*, Vol. **14**, Raven Press, New York, 1985.
103. S. M. Roberts and F. Scheinmann, eds., *New Synthetic Routes to Prostaglandins and Thromboxanes*, Academic Press, Inc., New York, 1982.
104. K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, *Angew. Chem. Int. Ed. Engl.* **17**, 293 (1978).
105. M. P. L. Caton and K. Crowshaw, in G. P. Ellis and G. B. West, eds., *Progress in Medicinal Chemistry*, Vol. **15**, Elsevier/North-Holland, Inc., New York, 1978, 357–423.
106. P. R. Marcham, in F. D. Gunstone, ed., *Aliphatic and Related Natural Product Chemistry*, Vol. **1**, The Chemical Society, London, 1979, 170–235.
107. P. W. Collins and S. W. Djuric, *Chem. Rev.* **93**, 1533 (1993).
108. M. P. L. Caton and T. W. Hart, in Ref. 106, p. 73.
109. E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Am. Chem. Soc.* **93**, 4326 (1971).
110. E. J. Corey and P. L. Fuchs, *J. Am. Chem. Soc.* **94**, 4014 (1972).
111. N. M. Weinshenker, *Prostaglandins* **3**, 219 (1973).
112. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Tetrahedron Lett.*, 1215 (1975).
113. B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.* **97**, 3528 (1975).
114. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.* **97**, 6908 (1975).
115. P. A. Bartlett, F. R. Green, and T. R. Webb, *Tetrahedron Lett.*, 331 (1977).
116. H. E. Ensley, C. A. Parnell, and E. J. Corey, *J. Org. Chem.* **43**, 1610 (1978).
117. J. S. Bindra and R. Bindra, *Prostaglandin Synthesis*, Academic Press, Inc., New York, 1977, 187–245.
118. N. Inukai and co-workers, *Chem. Pharm. Bull.* **24**, 2566 (1976).
119. N. M. Weinshenker, G. A. Crosby, and J. Y. Wong, *J. Org. Chem.* **40**, 1966 (1975).

120. E. J. Corey and J. W. Suggs, *J. Org. Chem.* **40**, 2554 (1975).
121. M. Vandewalle, V. Sipido, and H. DeWilde, *Bull. Soc. Chim. Belg.* **79**, 403 (1970).
122. E. J. Corey, Z. Arnold, and J. Hutton, *Tetrahedron Lett.*, 307 (1970).
123. E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971).
124. D. Brewster and co-workers, *J. Chem. Soc. Chem. Commun.*, 1235 (1972).
125. G. Jones, R. A. Raphael, and S. Wright, *J. Chem. Soc. Chem. Commun.*, 609 (1972).
126. F. Kienzle, G. W. Holland, J. L. Jernow, S. Kwok, and P. Rosen, *J. Org. Chem.* **38**, 3440 (1973).
127. E. J. Corey and B. B. Snider, *Tetrahedron Lett.*, 3091 (1973).
128. D. Brewster and co-workers, *J. Chem. Soc. Perkin Trans. 1*, 2796 (1973).
129. R. B. Woodward and co-workers, *J. Am. Chem. Soc.* **95**, 6853 (1973).
130. J. S. Bindra, A. Grodski, and T. K. Schaaf, *J. Am. Chem. Soc.* **95**, 7522 (1973).
131. E. J. Corey and C. U. Kim, *J. Org. Chem.* **38**, 1233 (1973).
132. J. Van Hooland, P. De Clercq, and M. Vanderwalle, *Tetrahedron Lett.*, 4343 (1974).
133. P. de Clercq and M. Vanderwalle, *Bull. Soc. Chim. Belg.* **83**, 305 (1974).
134. P. de Clercq, D. Van Haver, D. Tavernier, and M. Vandewalle, *Tetrahedron* **30**, 55 (1974).
135. G. Jones, R. A. Raphael, and S. Wright, *J. Chem. Soc. Perkin Trans. 1*, 1676 (1974).
136. E. J. Corey and B. B. Snider, *J. Org. Chem.* **39**, 256 (1974).
137. E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, *J. Chem. Soc. Chem. Commun.*, 642 (1974).
138. E. J. Corey, K. C. Nicolaou, and D. J. Beames, *Tetrahedron Lett.*, 2439 (1974).
139. R. Peel and J. K. Sutherland, *J. Chem. Soc. Chem. Commun.*, 151 (1974).
140. R. Coen, P. De Clercq, D. Van Haver, and M. Vandewalle, *Bull. Soc. Chim. Belg.* **84**, 203 (1975).
141. W. Van Brussel, J. Van Hooland, P. De Clercq, and M. Vandewalle, *Bull. Soc. Chim. Belg.* **84**, 813 (1975).
142. M. Samson, P. De Clercq, and M. Vandewalle, *Tetrahedron* **31**, 1233 (1975).
143. H. Shimomura, J. Katsube, and M. Matsui, *Agric. Biol. Chem.* **39**, 657 (1975).
144. A. Fischli, M. Klau, H. Mayer, P. Schonholzer, and R. Ruegg, *Helv. Chem. Acta* **58**, 564 (1975).
145. G. A. Crosby, N. M. Weinshenker, and H.-S. Uh, *J. Am. Chem. Soc.* **97**, 2232 (1975).
146. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Tetrahedron Lett.*, 1215 (1975).
147. P. De Clercq, M. De Smet, K. Legein, F. Vanhulle, and M. Vandewalle, *Bull. Soc. Chim. Belg.* **85**, 503 (1976).
148. P. De Clercq, R. Coen, E. Van Hoff, and M. Vandewalle, *Tetrahedron* **32**, 2747 (1976).
149. I. Tomoskozi, L. Gruber, G. Kovacs, I. Szekely, and V. Simonidesz, *Tetrahedron Lett.*, 4639 (1976).
150. K. G. Paul, F. Johnson, and D. Favara, *J. Am. Chem. Soc.* **98**, 1285 (1976).
151. I. Ernest, *Angew Chem. Int. Ed. Engl.* **15**, 207 (1976).
152. S. Takano, N. Kubodera, and K. Ogasawara, *J. Org. Chem.* **42**, 786 (1977).
153. E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, *J. Chem. Soc. Perkin Trans. 1*, 1507 (1978).
154. M. Naruto, K. Ohno, and N. Naruse, *Chem. Lett.*, 1419 (1978).
155. L. A. Paquette, G. D. Crouse, and A. K. Sharma, *J. Am. Chem. Soc.* **102**, 3972 (1980).
156. S. Goldstein and co-workers, *J. Am. Chem. Soc.* **103**, 4616 (1981).
157. L. A. Paquette and G. D. Crouse, *Tetrahedron* **37**(Suppl. 1), 281 (1981).
158. I. Fleming and B.-W. Au-Yeung, *Tetrahedron* **37**(Suppl. 1), 13 (1981).
159. E. J. Corey, K. B. Becker, and R. K. Varma, *J. Am. Chem. Soc.* **94**, 8616 (1972).
160. J. Bowler, K. B. Mallion, and R. A. Raphael, *Synth. Commun.* **4**, 211 (1974).
161. E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).
162. J. Hutton, M. Senior, and N. C. A. Wright, *Synth. Commun.* **9**, 799 (1979).
163. K. B. Mallion and E. R. H. Walker, *Synth. Commun.* **5**, 221 (1975).
164. R. Noyori, *Pure Appl. Chem.* **53**, 2315 (1981).
165. S. Iguchi, H. Nakai, M. Hayashi, and H. Yamamoto, *J. Org. Chem.* **44**, 1363 (1979).
166. S. Iguchi, H. Nakai, M. Hayashi, H. Yamamoto, and K. Maruoka, *Bull. Chem. Soc. Jpn.* **54**, 3033 (1981).
167. A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.* **103**, 5454 (1981).
168. E. J. Corey, N. Imai, and S. Pikul, *Tetrahedron Lett.* **32**, 7517 (1991).
169. E. J. Corey and T.-P. Loh, *J. Am. Chem. Soc.* **113**, 8966 (1991).
170. E. J. Corey and co-workers, *J. Am. Chem. Soc.* **93**, 1490 (1970).
171. G. Just and C. Simonovitch, *Tetrahedron Lett.*, 2093 (1967).

172. R. C. Kelly, V. Van Rheenen, I. Schletter, and M. D. Pillai, *J. Am. Chem. Soc.* **95**, 2746 (1973), and references cited therein.
173. D. R. White, *Tetrahedron Lett.*, 1753 (1976).
174. N. A. Nelson, R. C. Kelly, and R. A. Johnson, *Chem. Eng. News*, 30 (Aug. 16, 1982).
175. R. F. Newton and S. M. Roberts, *Tetrahedron* **36**, 2163 (1980), and references cited therein.
176. S. M. Roberts, *J. Chem. Soc. Chem. Commun.*, 948 (1974).
177. T. V. Lee, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., [Perkins I]* 1179 (1978).
178. M. P. L. Caton, in S. M. Roberts and F. Scheinmann eds., *New Synthetic Routes to Prostaglandin and Thromboxanes*, Academic Press, London, 1982, p. 105.
179. F. Scheinmann, in S. M. Roberts and R. F. Newton, eds., *Prostaglandins and Thromboxanes*, Butterworth, London, 1982, p. 62.
180. J. P. Marino, R. F. de la Pradilla, and E. Laborde, *J. Org. Chem.* **52**, 4898 (1987).
181. C. R. Johnson and T. D. Penning, *J. Am. Chem. Soc.* **110**, 4726 (1988).
182. E. J. Corey, K. Niimura, Y. Konishi, S. Hashimoto, and Y. Hamada, *Tetrahedron Lett.* **27**, 2199 (1986).
183. R. K. Haynes, D. E. Lambert, P. A. Schober, and S. G. Turner, *Aust. J. Chem.* **40**, 1211 (1987).
184. T. Toru, Y. Yamada, T. Ueno, E. Mackawa, and Y. Ueno, *J. Am. Chem. Soc.* **110**, 4815 (1988).
185. P. W. Collins, *J. Med. Chem.* **29**, 437 (1986).
186. R. Noyori and M. Suzuki, *Angew Chem., Int. Ed. Engl.* **23**, 847 (1984); T. Tanaka and co-workers, *Tetrahedron* **43**, 813 (1987).
187. C. J. Sih and co-workers, *J. Am. Chem. Soc.* **94**, 3643 (1972).
188. A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.* **94**, 7827 (1972); F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.* **94**, 7823 (1972).
189. R. Pappo and P. W. Collins, *Tetrahedron Lett.*, 2627 (1972).
190. C. J. Sih and co-workers, *J. Am. Chem. Soc.* **97**, 865 (1975).
191. R. Noyori, L. Tomino, and M. Nishizawa, *J. Am. Chem. Soc.* **101**, 5843 (1979).
192. M. Midland and A. Kasubski, *J. Org. Chem.* **47**, 2814 (1982).
193. E. J. Corey and R. H. Wollenberg, *J. Org. Chem.* **40**, 2265 (1975).
194. P. W. Collins, "Misoprostol," in D. Lednicer, ed., *Chronicles of Drug Discovery*, American Chemical Society, Washington, D.C., 1993.
195. J. R. Behling, P. W. Collins, and J. S. Ng, in L. S. Liebeskind, ed., *Advances in Metal-Organic Chemistry*, Vol. **4**, JAI Press, Greenwich, Conn., 1994.
196. P. W. Collins and co-workers, *J. Med. Chem.* **29**, 1195 (1986).
197. M. B. Floyd, in S. M. Roberts and F. Scheinmann, eds., *Chemistry, Biochemistry and Pharmacological Activity of Prostanoids*, Pergamon Press, Oxford, U.K., 1979, p. 161.
198. G. Piancatelli and A. Scettri, *Synthesis*, 116 (1977).
199. R. Pappo, P. Collins, and C. Jung, *Tetrahedron Lett.*, 943 (1973).
200. M. Gill, P. Bainton, and R. W. Rickards, *Tetrahedron Lett.* **22**, 1437 (1981).
201. G. Stork and T. Takahashi, *J. Am. Chem. Soc.* **99**, 1275 (1977).
202. J. H. Dygos and co-workers, *J. Org. Chem.* **56**, 2549 (1991).
203. K. A. Babiak and co-workers, *J. Am. Chem. Soc.* **112**, 7441 (1990); B. H. Lipschutz and E. L. Ellsworth, *J. Am. Chem. Soc.* **112**, 7440 (1990).
204. K. A. Babiak and co-workers, *J. Organic Chem.* **55**, 3377 (1990).
205. Y. Morita, M. Suzuki, and R. Noyori, *J. Org. Chem.* **54**, 1784 (1989).
206. T. Takahashi, M. Nakazawa, M. Kanoh, and K. Yamamoto, *Tetrahedron Lett.* **31**, 7349 (1990).
207. S. J. Danishefsky, M. P. Cabal, and K. Chow, *J. Am. Chem. Soc.* **111**, 3456 (1989); K. Chow and S. J. Danishefsky, *J. Org. Chem.* **54**, 6016 (1989).
208. C. R. Johnson and Y.-F. Chen, *J. Org. Chem.* **56**, 3344, 3352 (1991).
209. G. Stork and M. Isobe, *J. Am. Chem. Soc.* **97**, 4765, 6260 (1975).
210. T. Yoshino, S. Okamoto, and F. Sato, *J. Org. Chem.* **56**, 3205 (1991).
211. R. E. Donaldson, J. C. Saddler, S. Byrn, A. T. McKenzie, and P. L. Fuchs, *J. Org. Chem.* **48**, 2167 (1983).
212. G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Am. Chem. Soc.* **94**, 2123 (1972).
213. W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Am. Chem. Soc.* **99**, 1222 (1977).

214. N. A. Porter, J. D. Byers, A. E. Ali, and T. E. Eling, *J. Am. Chem. Soc.* **102**, 1183 (1980).
215. N. A. Porter, J. D. Byers, K. M. Holden, and D. B. Menzel, *J. Am. Chem. Soc.* **101**, 4319 (1979).
216. R. A. Johnson and co-workers, *J. Am. Chem. Soc.* **100**, 7690 (1978).
217. R. A. Johnson and co-workers, *J. Am. Chem. Soc.* **99**, 4182 (1977).
218. N. Wittaker, *Tetrahedron Lett.* **32**, 2805 (1977).
219. M. Suzuki, A. Yanagisawa, and R. Noyori, *Tetrahedron Lett.* **24**, 1187 (1983).
220. W. P. Schneider and R. A. Morge, *Tetrahedron Lett.*, 3283 (1976).
221. B. Radüchel and H. Vorbrüggen, in Ref. 102, p. 263.
222. P. W. Collins, *Med. Res. Rev.* **10**, 149 (1990).
223. P. A. Aristoff, in Ref. 102, p. 309.
224. N. H. Wilson and R. L. Jones, in Ref. 102, p. 393.
225. E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. Samuelsson, *Proc. Natl. Acad. Sci. USA* **72**, 3355 (1975).
226. G. L. Bundy, *Tetrahedron Lett.*, 1957 (1975).
227. W. R. Hanson and E. J. Ainsworth, *Radiat. Res.* **103**, 196 (1985).
228. R. N. Fedorak, L. R. Empey, C. MacArthur, and L. D. Jewell, *Gastroenterology* **98**, 149 (1990).
229. H. Allgayer, K. Deschryver, and W. F. Stenson, *Gastroenterology* **96**, 1290 (1989).
230. I. D. Pavord, C. S. Wong, J. Williams, and A. E. Tattersfield, *Am. Rev. Respir. Dis.* **148**, 87 (1993).
231. R. Alam and co-workers, *Am. Rev. Respir. Dis.* **148**, 1066 (1993).
232. T. A. Morinelli and P. V. Halushka, *Trends Cardiovasc. Med.* **1**, 157 (1991).
233. P. Gresele, E. Van Houtte, J. Arnout, H. Deckmyn, and J. Vermylen, *Thromb. Haemostasis* **52**, 364 (1984).
234. P. Gresele and co-workers, *J. Clin. Invest.* **80**, 1435 (1987).
235. R. Soyka and co-workers, *J. Med. Chem.* **37**, 26 (1994).

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