PROSTAGLANDIN E₁, F₁, AND A₁ ANALOGS
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ABSTRACT OF THE DISCLOSURE
This invention is a group of prostaglandin E₁, F₁, and A₁ analogs which differ from the natural compounds in having one or more alkyl or fluoro substituents near the end of the terminal alkyl portion. These compounds are useful in the same pharmacological purposes as the natural compounds.

CROSS REFERENCE TO RELATED APPLICATION
This application is a continuation-in-part of my co-pending application Ser. No. 748,158, filed July 29, 1968, now abandoned.

DESCRIPTION OF THE INVENTION
This invention relates to compositions of matter and to methods for making and using them. In particular, this invention relates to novel analogs of PGE₁, PGF₁α, PGF₁β, PGA₁, and their salts and esters.

PGE₁ has the following structure:

PGE₁, PGF₁α, PGF₁β, and PGA₁ are derivatives of prostanoic acid which has the following structure and atom numbering:

Various isomers of PGE₁, PGF₁α, PGF₁β, and PGA₁ are known. For example, the compound of the following structure is known as 8β-PGE₁, although 15R-PGE₁, and 15-epi-PGE₁ are alternative names for this compound.

In formulas I—VII as well as the formulas given hereinafter, broken line attachments to the cyclopentane ring indicate substituents in alpha configuration, i.e., below the plane of the cyclopentane ring. Heavy solid line attachments to the cyclopentane ring indicate substituents in beta configuration, i.e., above the plane of the cyclopentane ring. The configuration of the hydroxy at C-15 in PGE₁, PGF₁α, PGF₁β, and PGA₁, is S although alpha is preferred as a designation for that configuration. The configuration of the hydroxy at C-15 in the compound of formula VII is R although beta is preferred as a designation for that configuration. See Nature 212, 38 (1966) for discussion of the configuration of the prostaglandins.

Each of the novel PGE₁, PGF₁α, PGF₁β, and PGA₁ analogs of this invention is encompassed by one of the following formulas:
Compounds of formulas VIII, XI, and XIV are of the PGE₁-type. Compounds of formulas IX, XII, and XV are of the PGF₂α-type. Compounds of formulas X, XIII, and XVI are of the PGA₁-type.

In formulas VIII to XVI, R₁ is hydrogen, alkyl of one to 8 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, phenyl substituted with one to 3 chloro or alkyl of one to 4 carbon atoms, inclusive, or ethyl substituted in the β-position with 3 chloro, 2 or 3 bromo, or one, 2, or 3 iodo. Also in formulas VIII to XVI, α indicates attachment of the group to the ring in alpha or beta configuration, α is zero to 4, and n is 4 to 8. In formulas VIII, IX, and X, Y is isobutyl, tert-butyl, 3,3-difluorobutyl, 4,4-difluorobutyl, or 4,4,4-trifluorobutyl. In formulas XI, XII, and XIII, G is isobutyl or tert-butyl. In formulas XIV, XV, and XVI, Z is 3,3-difluorobutyl, 4,4,4-trifluorobutyl, 3,3,4,4-tetrafluorobutyl, or 3,3,4,4,4-pentafluorobutyl. Thus, all of the compounds XI, XII, and XIII compounds are encompassed by formulas VIII, IX, and X, respectively. All of the compounds of formulas XIV, XV, and XVI except

those wherein Z is 3,3,4,4-tetrafluorobutyl and 3,3,4,4,4-pentafluorobutyl are also encompassed by formulas VIII, IX, and X, respectively. Also included among the novel PGE₁, PGF₂α, PGF₁α, and PGA₁ analogs of this invention are the pharmaceutically acceptable salts of the compounds of formulas VIII to XVI wherein R₁ is hydrogen.

The PGE₁-type compounds of formulas VIII, XI, and XIV are useful for pharmacological and medicinal purposes as will be described hereinafter. These same compounds are also useful as intermediates for the preparation of the corresponding compounds of the PGF₂α-type, the PGF₁α-type, and the PGA₁-type.

Formulas VIII to XVI are intended to include compounds wherein the side chain hydroxy has the same configuration as in PGE₁, i.e., α, α, α, α, α, α, and compounds wherein the side chain hydroxy has the opposite configuration, i.e., β (R or opt). In all of these compounds, the carbon-carbon double bond in the side chain is in the trans configuration and that side chain is attached to the cyclopentane ring in beta configuration, both as shown in those formulas.

With regard to the novel PGE₁-type, PGF₂α-type, PGF₁α-type, and PGA₁-type analogs of formulas VIII to XVI, examples of alkyl of one to 8 carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomeric forms thereof, e.g., isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, 2-methylpentyl, 3-methylhexyl, 2,4-dimethylpentyl, and the like. Examples of cycloalkyl of 3 to 10 carbon atoms, inclusive, which includes alkyl-substituted cycloalkyl, are cyclopentyl, 2-methylcyclopentyl, 2,2-dimethylcyclopentyl, 2,3,4-trimethylcyclohexyl, 2,3,4-trimethylcyclopentyl, 2,2-dimethylcyclopentyl, 3-pentylcyclopentyl, 3-tert-butylocyclohexyl, cyclohexyl, 4-tert-butylocyclohexyl, 3-isopropylcyclohexyl, 2,2-dimethylcyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl. Examples of aralkyl of 7 to 12 carbon atoms, inclusive, are benzyl, phenethyl, 1-phenylethyl, 2-phenylethyl, 4-phenylbutyl, 3-phenylbutyl, 2-(1-naphthylethyl), and 1-(2-naphthylethyl). Examples of phenyl substituted by one to 3 chloro or alkyl of one to 4 carbon atoms, inclusive, are p-chlorophenyl, m-chlorophenyl, o-chlorophenyl, 2,4-dichlorophenyl, 2,4,6-trichlorophenyl, p-toly1, m-toly1, o-toly1, p-ethylphenyl, p-t-butylphenyl, 2,5-dimethylphenyl, 4-chloro-2-methylphenyl, and 2,4-dichloro-3-methylphenyl.

PGE₁, PGF₂α, PGF₁α, and PGA₁, and their esters and pharmacologically acceptable salts, are extremely potent in causing various biological responses. For that reason, these compounds are useful for pharmacological purposes. See, for example, Bergstrom et al., Pharmacol. Rev. 20, 1 (1968), and references cited therein. A few of those biological responses are systemic arterial blood pressure lowering in the case of PGE₁, PGF₂α, and PGA₁, as measured, for example, in anesthetized (pentobarbital sodium) pentolinium-treated rats with indwelling aortic and right heart canulas; pressor activity, similarly measured, for PGF₂α; stimulation of smooth muscle as shown, for example, by tests on strips of guinea pig ileum, rabbit duodenum, or gerbil colon; potentiation of other smooth muscle stimulants; antipolytic activity as shown by antagonism of epinephrine-induced mobilization of free fatty acids or inhibition of the spontaneous release of glycerol from isolated rat fat pads; inhibition of gastric secretion in the case of PGE₁ and PGA₁ as shown in dogs with secretion stimulated by food or histamine infusion; activity on the central nervous system; decrease of blood platelet adhesiveness as shown by platelet-to-glass adhesiveness, and inhibition of blood platelet aggregation and thrombus formation induced by various physical stimuli, e.g., arterial injury, and various biochemical stimuli, e.g., ATP, ADP, serotonin, thrombin, and collagen.
Because of these biological responses, these known prostaglandins are useful to study, prevent, control, or alleviate diseases and undesirable physiological conditions in birds and mammals, including humans, domestic animals, pets, and zoological specimens, and in laboratory animals, for example, mice, rats, rabbits, and monkeys.

For example, these compounds, and especially PGE₂, are useful in mammals, including man, as smooth muscle stimulants, for example, to reduce and control excessive gastric secretion, thereby reducing or avoiding gastrointestinal ulcer formation, and accelerating the healing of such ulcers already present in the gastrointestinal tract. For this purpose, the compounds are injected or infused intravenously, subcutaneously, or intramuscularly in an infusion dose range about 0.1 μg to about 500 μg per kg of body weight per minute, or in a total daily dose by injection or infusion in the range about 0.1 to about 20 mg per kg of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

PGE₁, PGA₁, PGF₁α, and PGE₂ are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and to remove or prevent the formation of thrombi in mammals, including man, rabbits, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative thrombosis, to promote potency of vascular grafts following surgery, and to treat conditions such as atherosclerosis, arteriosclerosis, blood clotting defects due to leipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred. Doses in the range about 0.004 to about 20 mg per kg of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

PGE₁, PGA₁, and PGE₂ are especially useful as additives to blood, blood products, blood substitutes, and other fluids which are used in artificial extracorporeal circulation and perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. During these circulations and perfusions, aggregated platelets tend to block the blood vessels and portions of the circulation apparatus. This blocking is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of those at a total steady state dose of about 0.001 to 10 mg per liter of circulating fluid. It is especially useful to use these compounds in laboratory animals, e.g., cats, dogs, rabbits, monkeys, and rats, for these purposes in order to develop new methods and techniques for organ and body parts, including humans.

PGE₁ is extremely potent in causing stimulation of smooth muscle, and is also highly active in potentiating other known smooth muscle stimulators, for example, oxytocic agents, e.g., oxytocin, and the various ergot alkaloids including derivatives and analogs thereof. Therefore PGE₁ is useful in place of or in combination with less than usual amounts of these known smooth muscle stimulators, for example, to relieve the symptoms of paralytic ileus, or to control or prevent atomic uterine bleeding after abortion or delivery, to aid in expulsion of the placenta, and during the puerperium. For the latter purpose, PGE₁ is administered by intravenous infusion immediately after abortion or delivery at a dose in the range about 0.01 to about 50 μg per kg of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, subcutaneous, or intramuscular injection or infusion during puerperium in the range about 0.01 to 2 μg per kg of body weight per day, the exact dose depending on the age, sex, weight, and condition of the patient or animal.

PGE₁, PGA₁, and PGF₁α are useful as hypotensive agents to reduce blood pressure in mammals, including man. For this purpose, the compounds are administered by intravenous infusion at the rate about 0.01 to about 50 μg per kg of body weight per minute or in single or multiple doses of about 25 to 500 μg per kg of body weight total per day.

As mentioned above, PGE₁ is a potent antagonist of epinephrine-induced mobilization of free fatty acids. For this purpose, this compound is useful in the administration of medicine for both in vitro and in vivo studies in mammals, including man, rabbits, and rats, intended to lead to the understanding, prevention, symptom alleviation, and cure of diseases involving abnormal lipid mobilization and high free fatty acid levels, e.g., diabetes mellitus, vascular diseases, and hyperthyroidism.

The PGE₁, PGE₂, and PGA₁ compounds are useful in the treatment of asthma. For example, these compounds are useful as bronchodilators or as inhibitors of mediators, such as SRS-A, and histamine which are released from cells activated by an antigen-antibody complex. Thus, these compounds control spasm and facilitate breathing in conditions such as bronchial asthma, bronchitis, bronchectasis, pneumonia and emphysema. For these purposes, these compounds are administered in a variety of dosage forms, e.g., orally in the form of tablets, capsules, or liquids; rectally in the form of suppositories; parenterally, subcutaneously, or intramuscularly, with intravenous administration being preferred in emergency situations; by inhalation in the form of aerosols or solutions for nebulizers; or by insufflation in the form of powder. Doses in the range of about 0.01 to 5 mg per kg of body weight are used 1 to 4 times a day, the exact dose depending on the age, weight, and condition of the patient and on the frequency and route of administration. For the above use these prostaglandins can be combined advantageously with other anti-asthmatic agents, such as sympathomimetics (isoproterenol, phenylephrine, ephedrine, etc.); xanthine derivatives (theophylline and aminophyllin); and corticosteroids (ACTH and prednisolone). Regarding use of these compounds, see South African Pat. No. 681,055.

The PGE₁, PGA₁, and PGE₂ compounds also increase the flow of blood in the mammalian kidney, thereby increasing volume and electrolyte content of the urine. Therefore, these compounds are useful in managing cases of renal dysfunction, especially those involving blockage of the renal vascular bed. Illustratively, the compounds are useful to alleviate and correct edema resulting, for example, from massive surface burns, and in the management of shock. For these purposes, the compounds are preferably first administered by intravenous injection at a dose in the range 10 to 1000 μg per kg of body weight or by intravenous infusion at a dose in the range 0.1 to 20 μg per kg of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, intramuscular, or subcutaneous injection or infusion in the range 0.05 to 2 mg per kg of body weight per day.

The PGE₁, PGE₂, and PGA₁ compounds are useful for controlling the reproductive cycle in ovulating female mammals, including humans and animals such as...
monkeys, rats, rabbits, dogs, cattle, and the like. For that purpose, PGF, for example, is administered systemically or subcutaneously at a dose level in the range 0.01 mg. to about 20 mg. per kg. of body weight of the female mammal, advantageously during a span of time starting approximately at the time of ovulation and ending approximately at the time of menses or just prior to menses. Additionally, expulsion of an embryo or fetus is accomplished by similar administration of the compound during the first third of the normal mammalian gestation period.

The novel compounds of this invention encompassed by formulas VIII to XVI each cause the same biological responses described above for the known prostaglandins. Each of these compounds is accordingly useful for the above-described pharmacological uses, and is used for those purposes as described above. However, it is preferred not to use the compounds of formulas VIII to XVI wherein R₁ is ethyl substituted in the β-position with chloro, bromo, or iodo for these pharmacological purposes. Those compounds are more useful for other purposes as will be described hereinafter.

The natural prostaglandins, PGE₁, PGF₁₅, and PGA₁, and the PGE₂ reduction product PGF₁₅, are all potent in causing multiple biological responses even at low doses. For example, PGE₂ is extremely potent in causing vasodilation, and smooth muscle stimulation, and is also potent as an antilipolytic agent. In striking contrast, the novel formulas VII to XVI compounds are substantially more specific with regard to potency in causing prostaglandin-like biological responses. Therefore, each of the formulas VII to XVI compounds is surprisingly and unexpectedly more useful than one of the corresponding known prostaglandins for at least one of the pharmacological purposes indicated for the latter, and is surprisingly and unexpectedly more useful for that purpose because it has a different and narrower spectrum of activity than the natural prostaglandin, and therefore is more specific in its activity and causes smaller and fewer undesired side effects than when the natural prostaglandin is used for the same purpose. Moreover, some of these novel prostaglandin analogs have greater potency in causing one or more of the above-described biological responses than the corresponding natural compound.

Further, these novel formulas VII to XVI prostaglandin analogs are especially useful because they have a substantially longer duration of activity than the corresponding known compounds, and because they can be administered sublingually intravaginally, or rectally, as well as by the usual intravenous, intramuscular, or subcutaneous injection or infusion as indicated above for the uses of the known prostaglandins. These qualities are advantageous because they facilitate maintaining uniform levels of these compounds in the body with fewer, shorter, or smaller doses, and make possible self-administration by the patient.

Especially preferred compounds for the above-described pharmacological purposes are those within the scope of formulas VIII to XVI wherein n is 6, 6, hexamethylene. With regard to formulas XI, XII, and XIII, another preference is that a be 2 or 3. Without regard to formulas XIV, XV, and XVI, another preference is that a be one or two. Two other preferences regarding formulas VIII to XVI are that the —(CH₂)₆—COOR₁ side chain be attached to the ring in alpha configuration and that the side-chain hydroxyl have the same configuration as in PGE₂, formula I, i.e., the alpha configuration.

The novel prostaglandin analogs of formulas VIII to XVI, including the preferred compounds defined above, are used for the above-described pharmacological purposes in the free acid form, i.e., when R₂ is hydrogen, in the ester form, or in pharmaceutically acceptable salt form. When the ester form is used, the ester can be any of those within the above definition of R₁, except that as men-

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type compounds. For example, carbonyl reduction of a formula VIII PGE$_2$-type compound gives a mixture of the corresponding formula IX PGF$_{1a}$-type and PGF$_{1b}$-type compounds. Similarly, carbonyl reduction of a formula XI PGE$_1$-type compound gives a mixture of the corresponding formula XII PGF$_{1a}$-type and PGF$_{1b}$-type compounds, and carbonyl reduction of a formula XIV PGE$_1$-type compound gives a mixture of the corresponding formula XV PGF$_{1a}$-type and PGF$_{1b}$-type compounds.

These ring carbonyl reductions are carried out by methods known in the art for ring carbonyl reductions of known prostanoic acid derivatives. See, for example, Bergstrom et al., Arkiv Kemi 19, 563 (1963), Acta Chem. Scand. 16, 969 (1962), and British Specification No. 1,097,533. Any reducing agent is used which does not react with carbon-carbon double bonds or ester groups. Preferred reagents are lithium(tri-tert-butoxy)aluminum hydride, the metal borohydrides, especially sodium, potassium and zinc borohydrides, the metal trialkoxy borohydrides, e.g., sodium trimethoxyborohydride. The mixtures of alpha and beta hydroxy reduction products are separated into the individual alpha and beta isomers by methods known in the art for the separation of analogous pairs of known isomeric prostanoic acid derivatives. See, for example, Bergstrom et al., cited above, Granstrom et al., J. Biol. Chem. 240, 457 (1965), and Greén et al., J. Lipid Research 5, 117 (1964). Especially preferred as separation methods are partition chromatographic procedures, both normal and reversed phase, preparative thin layer chromatography, and countercurrent distribution procedures.

The PGE$_1$-type compounds are prepared by acidic dehydration of the corresponding PGE$_2$-type compounds. For example, acidic dehydration of a formula VIII PGE$_2$-type compound gives the corresponding formula X PGE$_1$-type compound. Similarly, acidic dehydration of a formula XI PGE$_1$-type compound gives the corresponding formula XIII PGA$_1$-type compound and acidic dehydration of a formula XIV PGE$_1$-type compound gives the corresponding formula XVI PGA$_1$-type compound.

These acidic dehydrations are carried out by methods known in the art for acidic dehydrations of known prostanoic acid derivatives. See, for example, Pike et al., Proc. Nobel Symposium II, Stockholm (1966), Interscience Publishers, New York, pp. 162–163 (1967); and British Specification 1,097,533. Alkanoic acids of 2 to 6 carbon atoms, inclusive, especially acetic acid, are preferred acids for this acidic dehydration. Dilute aqueous solutions of mineral acids, e.g., hydrochloric acid, especially in the presence of a solubilizing diluent, e.g., tetrahydrofuran, are also useful as reagents for this acidic dehydration, although these reagents may cause partial hydrolysis of an ester reactant.

These carbonyl reductions and acidic dehydrations are shown in Chart A for formula VIII PGE$_2$-type reactants and formula IX PGF$_{1a}$-type and PGF$_{1b}$-type and formula X PGA$_1$-type

![Chart A](image_url)

products. Similar processes are used for transformation of formula XI and XIV PGE$_2$-type reactants to be corresponding PGE$_1$-type, PGF$_{1a}$-type, and PGA$_1$-type products. In Chart A, R$_1$, R$_2$, Y, n, a, and ~ are as defined above.

The PGE$_1$-type esters encompassed by formula VIII are prepared by the sequence of reactions shown in Chart B. Similar reaction sequences are used to prepare the PGE$_1$-type esters of formulas XI and XIV. In Chart B, a and Y are as defined above, and R$_2$ has the same definition as R$_1$ except that hydrogen is not included in the definition of R$_2$. R$_3$ is alkyl of one to 5 carbon atoms, inclusive, and ~ indicates alpha or beta attachment of

$$-(CH_2)_2-COOR_3$$

to the cyclopentane ring and exo or endo configuration with respect to the group attached to the cyclopropane ring. The PGE$_1$-type acids of formula VIII (R$_2$ is hydrogen) are not prepared by this Chart B sequence, but rather from certain of the formula VIIIIA esters by methods described below.

Exo-bicyclo[3.1.0]hexane olefins of formula XVII have the formula:

![Chart XVIIA](image_url)
These olefins are known in the art or are prepared by methods known in the art. See, for example, Belgian Pat. No. 702,477; reprinted in Farmdoc Complete Specifications, Book 714, No. 30,905, page 313, Mar. 12, 1968. See also Just et al., J. Am. Chem. Soc. 91, 5364 (1969).

In that Belgian patent, the reaction sequence leading to exo olefin XVIIIA is as follows: The hydroxy of 3-cyclopentenol is protected, for example, with a tetrahydropyranyl group. Then a diazoacetate acid ester is added to the double bond to give an exo-endo mixture of a bicyclo[3.1.0]hexane substituted at 3 with the protected hydroxy and at 6 with an esterified carbonyl. The exo-endo mixture is treated with a base to isomerize the endo isomer in the mixture to more of the exo isomer. Next, the carboxylate ester group at 6 is transformed to an aldehyde group. Then, said aldehyde group is transformed by the Wittig reaction to a moiety of the formula:

\[ \text{CH=CH-(CH)}_{2}\text{Y} \]

This moiety is in exo configuration relative to the bicyclo ring structure. Next, the protective group is removed to regenerate the 3-hydroxy which is then oxidized, for example, by the Jones reagent, to give an intermediate of the formula:

**CHART B**

**XVII**

**O**

\[ (\text{CH})_{2}\text{COOR}_{2} \]

**CH=CH-(\text{CH})_{2}\text{Y} \]

**XVIII**

**O**

\[ (\text{CH})_{2}\text{COOR}_{2} \]

**CH\text{OH}-CH\text{(OH)}-(\text{CH})_{2}\text{Y} \]

**XIX**

**O**

\[ (\text{CH})_{2}\text{COOR}_{2} \]

**CH\text{OH-(O SOR)\text{-(CH)}-Y} \]

**VIIIA**

Finally, this formula XX intermediate is alkylated with an \( \omega \) iodo or \( \omega \)-bromo ester of the formula:

\[ \text{I-(CH}_{2})_{n}\text{COOR}_{2} \]

or Br-(CH\text{2})\text{n-COR}_{2} to give a mixture of the \( \alpha \) and \( \beta \) isomers of the formula XVIIIA olefin. These \( \alpha \) and \( \beta \) isomers are separated by chromatography as described in said Belgian patent.

Endo-bicyclo[3.1.0]hexane olefins of formula XVII have the formula:

**CHART B XVI**

**O**

\[ (\text{CH})_{2}\text{COOR}_{2} \]

**CH=CH-(CH\text{2})_{n}\text{-Y} \]

These are prepared by reacting endo-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester with diborane in a mixture of tetrahydrofuran and diethyl ether to give a mixture of the methyl esters of endo-bicyclo[3.1.0]hexan-3-ol-6-carboxylic acid and endo-bicyclo[3.1.0]hexan-2-ol-6-carboxylic acid. This mixture is reacted with dihydroxypropyl to give the corresponding mixture of tetrahydropropyl ethers. The carboxylate group at 6 in this mixture of ethers is then transformed to an aldehyde group which in turn is transformed by the Wittig reaction to a moiety of the formula:

\[ \text{CH=CH-(CH}_{2})_{n}\text{-Y} \]

This moiety is in endo configuration relative to the bicyclo ring structure. Next, the tetrahydropropyl group is removed, and the resulting hydroxy group is oxidized, for example, by the Jones reagent, to give an intermediate of the formula:

**CHART B XVIIIB**

**O**

\[ (\text{CH})_{2}\text{COOR}_{2} \]

**CH=CH-(CH\text{2})_{n}\text{-Y} \]

Mixed with this formula XXI intermediate is some of the corresponding 2-keto isomer. These are separated by silica gel chromatography, and the formula XXI compound is alkylated with a compound of the formula:

\[ \text{I-(CH}_{2})_{n}\text{COOR}_{2} \]

or Br-(CH\text{2})\text{n-COR}_{2} The resulting \( \alpha \) and \( \beta \) isomers of formula XVIIIB are then separated as described above for the formula XVIIIA exo olefins.

Four stereoisomers are possible for each of the exo and endo olefins encompassed by formulas XVIIIA and XVIIIB. The \( \text{CH=CH-} \) moiety can exist in cis or trans form, and the \( \text{-(CH}_{2})_{n}\text{COOR}_{2} \) chain can be attached to the cyclopentane ring in alpha or beta configuration.

The Wittig reaction leading to the intermediates of formulas XX and XXI produces mixtures of cis and trans isomers, with the cis isomer usually predominant. These isomers can be separated, for example, by silica gel chromatography, and alkylated separately to give cis and trans forms of the formula XVIIIA and XVIIIB olefins. However, these cis and trans olefins are equally useful as intermediates in the processes of Chart B, and there is usually no need to carry out this separation.

The alklylation reactions leading from exo intermediate XX to exo olefin XVIIIA and from endo intermediate XXI to endo olefin XVIIIB produce mixtures of alpha and beta isomers. The processes of Chart B usually do not change this alpha or beta configuration of the

\[ \text{-(CH}_{2})_{n}\text{COOR}_{2} \]

moiety, and when the pure alpha or pure beta isomers of the formula VIIIA PGE-type product is de-
sired, it is necessary to separate alpha and beta isomers at some stage, i.e., olefin XVII, glycol XVIII, bis-sulfonate XIX, and αβ, βα, VIIIA. Separation of alpha and beta isomers of olefin XVII is preferred. This separation is carried out by silica gel chromatography as described in our previous work and exemplified below.

With regard to the Wittig reagents necessary to prepare the intermediates of formulas XX and XXI, these are triphenylphosphonium bromides prepared as known in the art from the corresponding alky or fluoroalkyl bromides, all of which are known in the art or can be prepared by methods known in the art. To illustrate, the necessary alkyl bromides have the formulas

\[
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{(CH}_3\text{)}\text{CHBr}
\]

and \(\text{(CH}_3\text{)}_2\text{CCH}_2\text{CHBr}\), wherein \(a\) is zero to 4. For the compounds wherein \(a\) is zero, the alcohols

\[
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{CHOH}
\]

and \(\text{(CH}_3\text{)}_2\text{CCH}_2\text{CHOH}\), and the corresponding bromides are prepared by reacting said alcohols with phosphorous tribromide. The bromides where

\(a\) is one to 4 are prepared by extending the chains of the above two bromides by reacting them with sodium cyanide, hydrolyzing the resulting nitriles to the corresponding carboxylic acids, reducing those acids to primary alcohols, and reacting the alcohols with phosphorous tribromide. This reaction sequence is repeated as often as necessary to prepare all of the required alkyl bromides. The necessary fluoroalkyl bromides have the formulas

\[
\text{CH}_2\text{CF}_2\text{CH}_2\text{(CH}_3\text{)}\text{CHBr}, \\
\text{CH}_2\text{CF}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{CHBr}, \\
\text{CF}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{CHBr}, \\
\text{CF}_2\text{CF}_2\text{CH}_2\text{(CH}_3\text{)}\text{CHBr}, \\
\text{CF}_2\text{CF}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{CHBr}
\]

and \(\text{CF}_2\text{CF}_2\text{CH}_2\text{CH}_2\text{CHOH}\), wherein \(a\) is zero to 4. The bromides of the first group are prepared from ketocarboxylic acids

\[
\text{CH}_2\text{COCH}_2\text{CH}_2\text{(CH}_3\text{)}\text{COOH}
\]

all of which are known. The methyl esters of those acids are brominated and reacted with sulfur tetrafluoride to give \(\text{CH}_2\text{CF}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{COOH}\), which are reduced using lithium aluminum hydride to give primary alcohols, which in turn are reacted with phosphorous tribromide to give the desired bromides. The second group of fluoroalkyl bromides are prepared from the known carboxylic acids \(\text{HOOCCH}_2\text{CH}_2\text{(CH}_3\text{)}\text{COOH}\). These are esterified to dimethyl esters and then half saponified with barium hydroxide. The free carboxyl group is changed by known methods to a carboxaldehyde group, and the resulting aldehyde is reacted with sulfur tetrafluoride to give \(\text{CH}_2\text{CF}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{COOCH}_3\). Successive treatment of that with lithium aluminum hydride and phosphorous tribromide gives the desired fluoroalkyl bromide. The third group of fluoroalkyl bromides is prepared from aldehydes \(\text{OCH}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{COOH}\) prepared as above. Successive reaction of those with sodium borohydride and phosphorous tribromide gives

\[
\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{(CH}_3\text{)}\text{COOCH}_3
\]

Saponification of that ester and reaction of the acid with sulfur tetrafluoride gives the desired third group of fluoroalkyl bromides. The fourth and fifth groups of fluoroalkyl bromides are prepared starting with the known alcohols \(\text{CH}_2\text{CF}_2\text{CH}_2\text{CHOH}\) and \(\text{CF}_2\text{CF}_2\text{CH}_2\text{CHOH}\). Those are transformed to bromides by reaction with phosphorous tribromide. Then the carbon chain of those bromides is extended one methylene at a time until the desired fluoroalkyl bromide is obtained. This chain extension is accomplished as above by replacement of bromine with

\[
\text{CN, hydrolysis of } -\text{CN to } -\text{COOH, reduction of } -\text{COOH to } -\text{CH}_2\text{OH, and transformation of } -\text{CH}_2\text{OH to } -\text{CH}_2\text{Br}.
\]

The esters of the various α-iodo or α-bromo alkanolic acids necessary for the alkylation of exo and endo intermediates XX and XXI are also known in the art or are prepared by methods known in the art.

Referring again to Chart B, the glycol intermediates of formula XVIII are prepared by hydroxylolation of olefins XVII. Hydroxylation reagents and procedures for this purpose are known in the art. See, for example, Gunstone, in Advances in Organic Chemistry, Vol. I, pp. 103–147 (1960), Interscience Publishers, New York, N.Y. Especially useful hydroxylation reagents for this purpose are osmium tetroxide and performic acid (formic acid plus hydrogen peroxide). Various mixtures of glycols isomeric with respect to the \(-\text{CH(OH)}-\text{CH(OH)}-\) moiety are obtained by these olefin hydroxylations depending on the nature of the hydroxylation reagent and the cis and trans content of the formula XVII olefin. These glycol isomers can be separated by silica gel chromatography. However, these separations are usually not necessary since all isomers of a particular glycol are equally useful as intermediates to produce the desired formula VIIIA product.

Referring again to Chart B, the glycol intermediates of formula XVIII are transformed to bis-alkanesulfonates of formula XIX by reaction of the glycol with an alkane-sulfonic chloride or bromide, the alkanesulfonic chloride containing one to 5 carbon atoms, inclusive. The reaction is carried out in the presence of a base to neutralize the by-product acid. Especially suitable bases are tertiary amines, e.g., dimethylaniline or pyridine. It is usually sufficient merely to mix the two reactants and the base, and maintain the mixture in the range 0° to 25° C. for several hours. The formula XIX bis-sulfonic acid esters are then isolated by procedures known to the art and exemplified below. It is usually not necessary to purify the bis-sulfonic acid esters prior to transformations to the desired PGE₆-type esters.

Referring again to Chart B, the bis-sulfonic acid esters of formula XIX are transformed to the desired PGE₆-type esters of Formula VIIIA by reacting the bis-sulfonic acid ester with water. This reaction is carried out by mixing the bis-sulfonic acid ester with water in the range about 0° to about 60° C. In making dl-19-ethyl-methyl-PGE₆, methyl ester, 25° C. is a suitable reaction temperature, the reaction then proceeding to completion in about 20 hours. It is advantageous to have a homogeneous reaction mixture. This is accomplished by adding sufficient amounts of a water-soluble organic diluent which does not enter into the reaction. Acetone is a suitable diluent. The desired product is isolated by evaporation of excess water and diluent if one is used. The residue contains a mixture of formula VIIIA isomers which differ in the configuration of the side chain hydroxy, being either α (S) or β (R). These are separated from byproducts and from each other by silica gel chromatography.

For this transformation of a formula XIX bis-sulfonate to a formula VIIIA PGE₆-type product, it is preferred to use the bis-mesyl esters, i.e., compounds of formula XIX wherein both R₅ are methyl.

As mentioned above, the processes of Chart B lead to esters of PGE₆-type compounds. For some of the pharmacological uses described above, it is preferred that the PGE₆-type compound be in free acid form, or in salt form which requires the free acid as starting material. Moreover, for some of the pharmacological uses described above, formula IX, XII, or XV PGE₆-type compounds or formula X, XIII, or XVI PGE₆-type compounds in free acid form or salt form are preferred. Formula IX, XII, and XV PGE₆-type esters are easily saponified to free acids by procedures known in the art. However, it is difficult to hydrolyze or saponify the PGE₆-type esters or the PGE₆-type esters to free acids without unwanted structural changes in the desired acids. When formula VIII, XI, or XIV PGE₆-type free acid (R₁ is hydrogen) is desired, an ester wherein R₅ (R₂) is ethyl substituted in the beta-position with 3 chloro, 2 or 3 bromo, or one, 2, or 3 iodo is used as a starting material. Such esters, for ex-
ample, wherein R_1 (R_2) is \(-\text{CH}_2\text{Cl}_3\), are transformed to free acids by treatment with zinc metal and an alkanoic acid of 2 to 6 carbon atoms, preferably acetic acid. Zinc dust is preferred as the physical form of the zinc. Mixing the halo ester with the zinc dust at about 25°C for several hours in the presence of the alkanoic acid causes replacement of the haloethyl moiety with hydrogen. The free acid is then isolated from the reaction mixture by procedures known in the art and exemplified below. For preparation of the free acids of formulas VIII, XI, and XIV in this manner, the \(\beta,\beta,\beta\)-trichloroethyl esters are preferred. This same procedure is also used to prepare PGE_{1a}, PGE_{1b}, and PGA_{1a} type free acids (R_1 is hydrogen), starting with the corresponding haloethyl ester. However, as mentioned above, this procedure is not necessary to prepare PGE_{1a} type acids.

These formulas VIII, XI, and XIV haloethyl esters, i.e., wherein R_1 is ethyl substituted in the beta-position with 3 chloro, 2 or 3 bromo, or one, 2, or 3 iodo, are prepared in several ways. Some of these are outlined in Chart C. The haloethyl esters are also prepared by alkylation of a formula XX exo intermediate or a formula XXI endo intermediate with the haloethyl esters of the \(\omega\)-bromo or \(\omega\)-iodo alkanoic acid.

Chart C described the transformation of a formula XVII on other than a haloethyl ester to haloethyl ester of a formula XVIII glycol. Thus, Chart C relates only to PGE_{1a} type products of formula VIII, as does Chart B. However, as for Chart B, similar reactions are available leading to the PGE_{1b} type products of formula XI and XIV. In Chart C, formula XVIIA is the same as formula XVII (Chart B) except that haloethyl esters are not included in XVIIA. In other words, R_4 has the same definition as R_3 except that R_4 does not include ethyl substituted in the beta-position with 3 chloro, 2 or 3 iodo, or one, 2, or 3 iodo. Also in Chart C, \(\sim\) and \(n\) are as defined above, and A is \(-\text{C}(\text{HO})_n\text{-}\text{Y}\) wherein \(n\) and \(Y\) are as defined above.

To make the desired formula XVIIA haloester, it is necessary at some stage to saponify the \(-\text{COO}\text{R}_4\) moiety to \(-\text{COOH}\) and then esterify that with the appropriate haloethanol, e.g., \text{C}_{4}\text{H}_{9}\text{CH}_{2}\text{OH}. Formula XVIIA olefin esters and formula XVIIIA glycol esters each have a ring carbonyl group adjacent to the point of attachment of \(-\text{CH}_2\text{COO}\text{R}_4\) to the ring. Saponification of such a keto ester is likely to lead to isomerization such that an alpha-attached chain will change partly to a beta-attached chain, and a beta partly to an alpha. Therefore, keto ester XVIIA is reduced, for example, with sodium borohydride according to known procedures described above and exemplified below, to hydroxy ester XVII. This hydroxy ester is then saponified to hydroxy acid XXIII, also by known procedures.

Three reactions are necessary to transform hydroxy acid XXIII to keto glycol haloester XVIIIA. The ring hydroxy group is oxidized back to a ring carbonyl, the carbonyl is esterified with a haloethanol, and the \(-\text{CH}_2\text{OH}\) is hydroxylated to \(-\text{CH}(\text{OH})\text{-CH}(\text{OH})\). As shown in Chart C, these three reactions are carried out in any of three sequences, i.e., XXIII to XXIV to XXV to XVIIA, XXIII to XXIV to XXV to XVIIA, and XXIII to XXV to XXVII to XVIIA. Of these, XXIII to XXVII to XVIIA. Of these, XXIII to XXV to XXVII to XVIIA.

For the oxidation of XXIII to XXVI or XXIV to XXV, an especially useful reagent is the Jones reagent, i.e., acidic chromic acid. See J. Chem. Soc. 39 (1946). Acetone is a suitable diluent for this purpose, and a slight excess of oxidant and temperatures at least as low as about 0°C, preferably about \(-10^\circ\) to about \(-20^\circ\). Should be used. The oxidation proceeds rapidly and is usually complete in about 5 to about 30 minutes. Excess oxidant is destroyed, for example, by addition of a lower alkanol, advantageously isopropyl alcohol, and the aldehyde is isolated by conventional methods, for example, by extraction with a suitable solvent, e.g., diethyl ether. Other oxidizing agents can also be used. Examples are mixtures of chromium trioxide and pyridine or mixtures of dicyclohexylcarbodiimide and dimethyl sulfoxide. See, for example, J. Am. Chem. Soc. 87, 5661 (1965).

For the esterification to haloethyl esters XXIV, XXV, or XVIIIA, the acid is reacted with the appropriate haloethanol, e.g., \(\beta,\beta,\beta\)-trichloroethanol, in the presence of a carbodiimide, e.g., dicyclohexylcarbodiimide, and a base, e.g., pyridine, preferably in the presence of an inert liquid diluent, e.g., dichloromethane, for several hours at about 2°C.

The PGE_{1a}, PGE_{1b}, PGE_{1c}, and PGA_{1a} type free acids of formulas VIII to XVI are transformed to pharmaceutically acceptable salts by neutralization with appropriate amounts of the corresponding inorganic or organic base, examples of which correspond to the cations and amines listed above. These transformations are carried out by a variety of procedures known in the art to be generally useful for the preparation of inorganic, i.e., metal or ammonium, salts, amine acid addition salts, and quaternary ammonium salts. The choice of procedure depends in part on the solubility characteristics of the particular salt to be prepared. In the case of the inorganic salts, it is usually suitable to dissolve the acid in water containing the stoichiometric amount of a hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. For example, such use of sodium hydroxide, sodium carbonate, or sodium bicarbonate gives a solution of the sodium salt. Evaporation of the water or addition of a water-miscible solvent of moderate polarity, for example, a lower alkalin or a lower alkanone, gives the solid inorganic salt if that form is desired.

To produce an amine salt, the acid is dissolved in a suitable solvent of either moderate or low polarity. Examples of the former are ethanol, acetone, and ethyl acetate. Examples of the latter are diethyl ether and benzene.
At least a stoichiometric amount of the amine corresponding to the desired cation is then added to that solution. If the resulting salt does not precipitate, it is usually obtained in solid form by addition of a miscible diluent of low polarity or by evaporation. If the amine is relatively volatile, any excess can easily be removed by evaporation. It is preferred to use stoichiometric amounts of the less volatile amines.

Salts wherein the cation is quaternary ammonium are produced by mixing the acid with the stoichiometric amount of the corresponding quaternary ammonium hydroxide in water solution, followed by evaporation of the water.

Molecules of each of the compounds encompassed by formulas I to IV, VI to XIX, and XXII to XXVII each have at least one center of symmetry, and each can exist in racemic form and in either enantiomeric form, i.e., d and l. A formula accurately defining the d form would be the mirror image of the formula which defined the l form. Both formulas are necessary to define accurately the corresponding racemic form. For convenience, the various formulas herein and in the claims are to be construed as including racemic (dl), d, and l compounds. However, for the above-described pharmacological purposes, preferred compounds are the racemic compounds of formulas VIII to XVI and the optically active enantiomers of those compounds with the same absolute configuration as the PGE$_1$ obtained from certain mammalian tissues, for example, sheep vesicular glands and human seminal plasma, or compounds obtained by carbonyl reduction or acid dehydration of a compound so obtained. The specific compounds shown in formulas I, II, III, and IV are intended to represent intended that absolute configuration. See Nature 212, 38 (1966).

Hereinafter, names of specific final products of formulas VIII to XVI will be based on relationship to the optically active compound of formula I, i.e., PGE$_1$. Substituents and structural variations will be based on the numbering of formula V, i.e., prostanoid acid; thus, 19-methyl-PGE$_1$, or 19,19-difluoro-PGA$_2$. An alpha or S configuration of the hydroxy at C-15 will be assumed unless otherwise appears before the name. An alpha configuration at C-8 will also be assumed unless otherwise appears before the name. An optically active compound with the same absolute configuration of PGE$_1$ will be assumed unless dl (racemic) or ent (optically inactive unnatural configuration) appear before the name.

When an optically active (d or l) final compound is desired, that is made by resolution of the racemic compound or one of the asymmetric racemates hereinafter. These resolutions are carried out by procedures known in the art. For example, when a final compound or an asymmetric intermediate is a free acid, the di form thereof is resolved into the d and l forms by reacting said free acid by known general procedures with an optically active base, e. g., brucine or strychnine, to give a mixture of two diastereoisomers which are separated by known general procedures, e. g., fractional crystallization, to give the separate diastereoisomeric salts. The optically active acid is then obtained by treatment of the salt with an acid by known general procedures.

Alternatively, for example, hexadecylbenzene is hexan-3-ol to give a mixture of analogues of which is separated into the d and l diastereoisomers, each of which is then hydrolyzed with an acid, e. g., oxalic acid, to give the original keto compound, now in optically active form. These reactions involving optically active glycals and ketals for resolution purposes are generally known in the art. For example, Chem. Ind. 1664 (1961) and J. Am. Chem. Soc. 84, 2938 (1962). Dithiols may be used instead of glycals.

The invention can be more fully understood by the following examples and preparations.

All temperatures are in degrees centigrade.

The collection of chromatographic eluate fractions starts when the eluant front reaches the bottom of the column.

**PREPARATION 1**

**Endo-Bicyclo[3.1.0]Hexan-3-ol-6-Carboxylic Acid Methyl Ester**

A mixture of endo-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester (103 g) and antimony di-ethyl ether (650 ml) is stirred under nitrogen and cooled to −5° C. A one molar solution (284 ml) of diborane in tetrahydrofuran is added dropwise during 30 minutes while keeping the temperature below 0° C. The resulting mixture is then stirred and allowed to warm to 25° C. during 3 hours. Evaporation under reduced pressure gives a residue which is dissolved in 650 ml of anhydrous diethyl ether. The solution is cooled to 0° C, and 3 normal aqueous sodium hydroxide solution (172 ml) is added dropwise under nitrogen and with vigorous stirring during 15 minutes, keeping the temperature at 0° to 5° C. Next, 30% aqueous hydrogen peroxide (94 ml) is added dropwise with stirring during 30 minutes at 0° to 5° C. The resulting mixture is stirred an hour while warming to 25° C. Then, 500 ml of saturated aqueous sodium chloride solution is added, and the diethyl ether layer is separated. The aqueous layer is washed with four 200 ml portions of ethyl acetate, the washings being added to the diethyl ether layer, which is then washed with saturated aqueous sodium chloride solution, dried, and evaporated to give 115 g of a residue. This residue is distilled under reduced pressure to give 68 g of a mixture of the methyl esters of endo-bicyclo[3.1.0]hexan-3-ol-6-carboxylic acid and endo-bicyclo[3.1.0]hexan-2-ol-6-carboxylic acid; b.p. 86–95° C. at 0.5 mm.

**PREPARATION 2**

**Endo-Bicyclo[3.1.0]Hexan-3-ol-6-Carboxylic Acid Methyl Ester Tetrahydropropyl Ether**

The 2-ol and 3-ol mixture (66 g) obtained according to Preparation 1 in 66 ml of dihydropropyln is stirred and cooled at 15–20° C. during addition of 3 ml of anhydrous diethyl ether saturated with hydrogen chloride. The temperature of the mixture is then kept in the range 20° to 30° C. for one hour with cooling, and is then kept at 23° C. for 15 hours. Evaporation gives a residue which is distilled under reduced pressure to give 66 g of a mixture of the methyl esters-tetrahydropropyln ethers of endo-bicyclo[3.1.0]hexan-3-ol-6-carboxylic acid and endo-bicyclo[3.1.0]hexan-2-ol-6-carboxylic acid; b.p. 96–104° C. at 0.1 mm.

**PREPARATION 3**

**Endo-6-Hydroxyethylmethylbicyclo[3.1.0]Hexan-3-ol 3-Tetrahydropropyl Ether**

A solution of the mixture (66 g) of products obtained according to Preparation 2 in 300 ml of anhydrous diethyl ether is added dropwise during 45 minutes to a stirred and cooled mixture of lithium aluminum hydride (21 g) in 1300 ml of anhydrous diethyl ether under nitrogen. The resulting mixture is stirred 2 hours at 25° C., and is then cooled to 0° C. Ethyl acetate (71 ml) is added, and the mixture is stirred 15 minutes. Water (235 ml) is then added, and the diethyl ether layer is separated. The water layer is washed twice with diethyl ether and twice with ethyl acetate. A solution of Rochelle salts is added to the aqueous layer, which is then concentrated to dryness and cooled. Evaporation gives a residue which is extracted with chloroform and extracted twice with ethyl acetate. All diethyl ether and ethyl acetate solutions are combined, washed
with saturated aqueous sodium chloride solution, dried, and evaporated to give 61 g. of a mixture of the 3-tetrahydropyranyl ethers of endo-6-hydroxymethylbicyclo[3.1.0]hexan-3-ol and endo - 6 - hydroxymethylbicyclo[3.1.0]hexan-2-ol.

PREPARATION 4

Endo-Bicyclo[3.1.0]Hexan-3-ol-6-Carboxylic acid-3-Tetrahydropyranyl Ether

A solution of the mixture (34 g.) of products obtained according to Preparation 3 in 1000 ml. of acetone is cooled to 10° C. Jones reagent (75 ml. of a solution of 21 g. of chromic acid, 60 ml. of water, and 17 ml. of concentrated sulfuric acid), precooled to 0° C., is added dropwise with stirring during 10 minutes at 10°C. After 10 minutes of additional stirring at -10° C, isopropyl alcohol (35 ml.) is added during 5 minutes, and stirring is continued for 10 minutes. The reaction mixture is then poured into 8 l. of an ice and water mixture. The resulting mixture is extracted 6 times with dichloromethane. The combined extracts are washed with aqueous sodium bicarbonate solution, dried, and evaporated to give 27 g. of a mixture of the tetrahydropyranyl ethers of endo-6-carboxylic acid-3-ol - 6-carboxylic acid-3-ol and endo-bicyclo[3.1.0]hexan-2-ol-carboxylic acid.

EXAMPLE 1

dl 20,20-Dimethyl-PGE1, Methyl Esters and dl 15β,20,20-Dimethyl-PGE1, Methyl Esters

A. A solution of 6-methyl-1-bromohexane (131 g.) and triphenylphosphine (180 g.) in 350 ml. of toluene is heated at reflux for 16 hours under nitrogen. The mixture is cooled, and the solid product is removed by filtration, washed with toluene, and dried to give 220 g. of (6-methyl-heptyl)-(triphenylphosphin) bromide.

B. A suspension of (6-methyl-heptyl)-(triphenylphosphin) bromide (305 g.) in 3 l. of benzene is mixed with 400 ml. of 15% butyllithium in hexane during 15 minutes. The mixture is stirred one hour at 35° C, and then cooled to 20°C. To this mixture is added a solution of a mixture of aldehydes (100 g.) obtained according to Preparation 4 in 200 ml. of benzene. The mixture is heated at 70°C for 2.5 hours, and then cooled and filtered. The filtrate is washed with water, dried with sodium sulfate, and evaporated to give an olefin mixture.

C. The olefin mixture (340 g.) is dissolved in 4 l. of methanol containing 8.4 g. of oxalic acid. This solution is heated at reflux for 1.5 hours. The methanol is then removed under reduced pressure, and the residue is mixed with water and extracted repeatedly with dichloromethane. The dichloromethane extracts are combined, washed successively with aqueous sodium bicarbonate and brine, dried with sodium sulfate, and evaporated. The residue (120 g.) is chromatographed on 1.5 kg. of silica gel. Elution with 10-15% ethyl acetate in Skellysolve B (a mixture of isomeric hexanes) gives 75.5 g. of a mixture of alcohols; infrared absorption at 3300, 1460, 1440, 1180, 1120, 745, 725, and 697 cm.-1.

D. Jones reagent (133 ml.; see Preparation 4) is added dropwise to a solution of the above-described alcohol mixture (75.5 g.) in 2 l. of acetonitrile at -10° C. After 10 minutes at -10°C, 75 ml. of isopropyl alcohol is added, and the mixture is poured into 8 l. of water. This mixture is extracted repeatedly with dichloromethane. The combined extracts are washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate, and brine, and then dried with sodium sulfate. Evaporation under reduced pressure gives 65 g. of a residue which is chromatographed on 2.5 kg. of silica gel. Elution with 5% ethyl acetate in Skellysolve B gives 30.3 g. of 6-endo-(7-methyl-1-octenyl)-3-oxobicyclo[3.1.0]hexan-2-one (19.5 g.) and methyl 7-lodohexanoate (110.4 g.) in 100 ml. of tetrahydrofuran. Then, 100 ml. of 2.5 M hydrochloric acid is added to the mixture, and the mixture is poured into brine and extracted repeatedly with diethyl ether. The combined extracts are washed successively with aqueous sodium thiosulfate, aqueous sodium bicarbonate, and brine, dried with sodium sulfate, and evaporated under reduced pressure. The residue (150 g.) is chromatographed on 5 kg. of silica gel, eluting with 2.5–5% ethyl acetate in Skellysolve B to remove unreacted starting materials, elution with additional 5% ethyl acetate in Skellysolve B gives 19.5 g. of methyl 6-endo-(7-methyl-1-octenyl)-3-oxobicyclo[3.1.0]hexane-2,6-heptanoate; infrared absorption at 1740, 1460, 1430, 1360, 1200, and 1160 cm.-1. Further elution with 5–10% ethyl acetate in Skellysolve B gives methyl 6-endo-(7-methyl-1-octenyl)-3-oxobicyclo[3.1.0]hexane-2,6-heptanoate.

F. A solution of 1.0 g. of methyl 6-endo-(7-methyl-1-octenyl)-3-oxobicyclo[3.1.0]hexane-2,6-heptanoate in 13.5 ml. of tetrahydrofuran is warmed to 50°C, and a warm solution of 330 mg. of potassium carbonate and 35 mg. of ammonium tetroxide in 6.5 ml. of water is added with stirring. The mixture is stirred for 5 hours at 50°C; then it is concentrated under reduced pressure to remove the tetrahydrofuran. The mixture is dissolved in diethyl ether, and the solution is diluted with the extraction mixture and extracted with 3 portions of dichloromethane. The dichloromethane extracts are combined, washed with water, dried over sodium sulfate, and evaporated under reduced pressure to give 1.0 g. of oil. The oil is chromatographed over 120 g. of silica gel. The column is eluted with 500 ml. of 10%, 1000 ml. of 25%, 1000 ml. of 35%, 1000 ml. of 45%, 1000 ml. of 50%, and 1000 ml. of 60% ethyl acetate in Skellysolve B. The 35% ethyl acetate eluate is concentrated to give 255 mg. of the less polar form of methyl 6-endo-(7-methyl-1,2-dihydroxyoctyl)-3-oxobicyclo[3.1.0]hexane-2,6-heptanoate. The only 50% ethyl acetate eluate is concentrated to give 248 mg. of a more polar form.

G. A solution of 0.255 g. of methyl 6-endo-(7-methyl-1,2-dihydroxyoctyl)-3-oxobicyclo[3.1.0]hexane-2-heptanoate (less polar glycol, obtained as above) in 7 ml. of pyridine is stirred under nitrogen in ice bath, and 0.7 ml. of methanesulfonyl chloride is added. Stirring is continued for 2.5 hours. The solution is diluted with 30 ml. of ice and water, and stirred for 10 minutes; then it is transferred to a separatory funnel containing washed and extracted with 5 100-ml. portions of ethyl acetate. The ethyl acetate extracts are combined, washed with cold 10% sulfuric acid, cold 10% sodium carbonate, and ice water, then dried over sodium sulfate, and evaporated to give 338 mg. of dimesyate as an oil. This oil is dissolved in 8 ml. of acetone, diluted with 4 ml. of water, and allowed to stand at 25°C for about 20 hours. The reaction mixture is then diluted with 25 ml. of water and concentrated under reduced pressure to remove acetone; then 50 ml. of water is added and the mixture is extracted three times with ethyl acetate. The ethyl acetate extracts are combined, washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give 258 mg. of an oil.

Following the above procedure, but starting with the more polar glycol (248 mg., obtained as above), there is obtained 270 mg. of an oil identified by thin layer chromatographic analysis to the oil obtained above from the less polar glycol. These two oils are combined (528 mg.) and chromatographed over 70 g. of silica gel. The column is eluted with 0.6 l. of 20%, 1 l. of 35%, 1 l. of 40%, 1 l. of 50%, and 3 l. of 70% ethyl acetate in Skellysolve B, then with 1 l. of ethyl acetate, and 1 l. of 5% MeOH in ethyl acetate, taking 75-ml. fractions. Eluate fractions...
67 to 73 are evaporated and combined to give 64 mg of dl 15β,20,20-dimethyl-PEG3 methyl ester; infrared absorption at 3430, 1740, 1250, 1200, 1165, 1075 and 970 cm⁻¹.

Elute fractions 88 to 104 are evaporated and combined to give 111 mg of dl 20,20-dimethyl-PEG1 methyl ester. This is crystallized from a mixture of ether and Skellysolve B to give dl 20,20-dimethyl-PEG1; m.p. 75–76°C; mass spectrum peaks at 378, 360, 347, 297, 278 and 218; infrared absorption null at 3315, 1735, 1325, 1310, 1290, 1275, 1260, 1225, 1195, 1150, 1105, 1055 and 975 cm⁻¹.

**EXAMPLE 2**

dl 8α,20,20-Dimethyl-PEG3 Methyl Ester and dl 8β,15α,20,20-Dimethyl-PEG3 Methyl Ester

Following the procedures of Example 1, parts F and G, methyl 6-endo-(7-methyl-1-octenyl) - 3 - oxobicyclo[3.1.0]hexane-2β-carboxylic acid is transformed to dl 8α,20,20-dimethyl-PEG3 methyl ester; mass spectral peaks at 396, 378, 360, 347, 297, 279, and 218; Rf 0.47 on TLC with the A-IX solvent system; and dl 8α,15β,20-20-dimethyl-PEG3 methyl ester; mass spectral peaks at 396, 378, 360, 347, 297, 279, and 218; Rf 0.36 on TLC with the A-IX solvent system.

**EXAMPLE 3**

dl 19,19-Dimethyl-PEG3 Methyl Ester and dl 15α,20,20-Dimethyl-PEG3 Methyl Ester

A. Following the procedures of Example 1, parts A, B, C, D, and E, but starting with 5,5-dimethyl-1-bromohexane rather than 6-methyl-1-bromohexane, there are obtained methyl 6-endo-(6,6-dimethyl-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2α-carboxylic acid; infrared absorption at 1730, 1470, 1445, 1370, 1250, and 1700 cm⁻¹; and the more polar methyl 6-endo-(6,6-dimethyl-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2β-carboxylic acid.

B. A solution of 12.0 g. of methyl 6-endo-(6,6-dimethyl-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2α-carboxylic acid, as above, in 150 ml of tetrahydrofuran is warmed to 50°C and stirred under nitrogen; then 1 g of solid osmium tetroxide is added to the solution followed immediately by a warm solution of 6.5 g. of potassium chloride in 76 ml of water, added in one portion. The reaction mixture is stirred for 5 hours at 50°C under nitrogen; then it is concentrated to dryness under reduced pressure to remove the tetrahydrofuran. The mixture is diluted with water and extracted three times with dichloromethane. The dichloromethane extracts are combined, washed with water, dried over sodium sulfate, and evaporated under reduced pressure to give 14.0 g. of oil. The oil is chromatographed over 2.0 kg. of silica gel. The column is eluted with 8 l. of 15%, 12 l. of 25%, 16 l. of 35%, 16 l. of 45% and 8 l. of 60% ethyl acetate in Skellysolve B, taking 600 ml. fractions. Fractions 22 to 66 are evaporated and combined to give 9.0 g. of methyl 6-endo-(6,6-dimethyl-1,2-dihydroxyheptyl)-3-oxobicyclo[3.1.0]hexane-2α-carboxylic acid. C. A solution of 9.0 g. of methyl 6-endo-(6,6-dimethyl-1,2-dihydroxyheptyl) - 3 - oxobicyclo[3.1.0]hexane-2α-carboxylic acid, obtained as above, in 110 ml of pyridine is stirred under nitrogen and cooled in an ice bath while 10.7 ml of methanesulfon chloride is added dropwise over a period of 15 minutes. The mixture is stirred for 2.5 hours at 0°C, then cooled to −10°C to −15°C with a Dry Ice-acetone bath and 10 ml of ice and water is added slowly, with good stirring, while keeping the temperature below 0°C. The mixture is poured into 500 ml of ice and water. Then 200 ml of cold 1:3 dichloromethane-ether mixture and 440 ml of cold 3 N hydrochloric acid are added, and the mixture is separated rapidly. The mixture is extracted three more times with 200-ml portions of cold 1:3 dichloromethane-ether mixture. The dichloromethane-diethyl ether extracts are combined, washed with cold 2% sulfuric acid, cold 10% aqueous sodium carbonate, and cold saturated aqueous sodium chloride, then dried over sodium sulfate and potassium carbonate and evaporated to give 14.0 g of oil. This oil is dissolved in 450 ml of 2:1 acetone-water and allowed to stand at about 25°C. After about 24 hours, the reaction mixture is diluted with 200 ml of water and concentrated under reduced pressure to remove acetone. Then, 100 ml of water is added and the mixture is extracted 4 times with ethyl acetate. The ethyl acetate extracts are washed with aqueous sodium bicarbonate and aqueous sodium chloride, dried over sodium sulfate, and evaporated to give 9.5 g. of oil. This oil is chromatographed over 1.6 kg. of silica gel. The column is eluted with 4 l. of 20%, 8 l. of 30%, 8 l. of 40%, 20 l. of 60%; and 20 l. of 80% ethyl acetate in Skellysolve B, then 20 l. of ethyl acetate and 4 l. of methanol in ethyl acetate, taking 600-ml fractions. Elute fractions 66 to 72 are evaporated and combined to give 1,253 g. of dl 15β,19,19-dimethyl-PEG3 methyl ester; infrared absorption at 3420, 1740, 1245, 1200, 1165, 1075, 1020, and 970 cm⁻¹.

Elute fractions 90 to 111 are evaporated and combined to give 1,228 g. of dl 19,19-dimethyl-PEG3 methyl ester. This is crystallized from a mixture of ether and Skellysolve B to give 19,19-dimethylprostaglandin E1 methyl ester, m.p. 53–55°C; infrared absorption (null) at 3450, 3390, 3280, 1740, 1675 (weak), 1510, 1290, 1275, 1235, 1195, 1165, 1090, 1065, 1020 and 985 cm⁻¹; infrared absorption at 390, 386, 378, 372, 358 and 343.

**EXAMPLE 4**

dl 8β,19,19-Dimethyl-PEG3 Methyl Ester and dl 8α,15β,19,19-Dimethyl-PEG3 Methyl Ester

Following the procedure of Example 3, parts B and C, methyl 6-endo-(6,6-dimethyl-1-heptenyl) - 3 - oxobicyclo[3.1.0]hexane-2α-carboxylic acid is transformed to dl 8α,19,19-dimethyl-PEG3 methyl ester and dl 8β,15β,19,19-dimethyl-PEG3 methyl ester.

**EXAMPLE 5**

dl 19-Methyl-PEG3 Methyl Ester and dl 15α,19-Methyl-PEG3 Methyl Ester

A. Following the procedure of Example 1, parts A, B, C, D, and E, but starting with 5-methyl-1-bromohexane rather than 6-methyl-1-bromohexane, there are obtained methyl 6-endo-(6-methyl-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2α-carboxylic acid; infrared absorption (null) at 3430, 3290, 1740, 1675, 1300, 1275, 1225, 1200, 1170, 1065, and 990 cm⁻¹; and dl 15β,19-methyl-PEG3 methyl ester; infrared absorption at 3420, 1740, 1250, 1200, 1165, 1075 and 1055 cm⁻¹.

**EXAMPLE 6**

dl 8α,19-Methyl-PEG3 Methyl Ester and dl 8β,15β,19-Methyl-PEG3 Methyl Ester

Following the procedure of Example 1, parts F and G, but using methyl 6-endo-(6,6-dimethyl-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2α-carboxylic acid as a reactant, there are obtained dl 19,19-dimethyl-PEG3 methyl ester and dl 8α,15β,19-methyl-PEG3 methyl ester.

**EXAMPLE 7**

dl 19,19,20,20,20-Pentafluoro-PEG3 Methyl Ester and dl 15β,19,19,20,20,20-Pentafluoro-PEG3 Methyl Ester

A. Following the procedure of Example 1, parts A, B, C, D, and E, but starting with 1,1,1,2,2,2-pentafluoro-6-iodohexane rather than 6-methyl-1-bromohexane, there are obtained methyl 6-endo-(6,6,7,7,7-pentafluoro-1-heptenyl) - 3 - oxobicyclo[3.1.0]hexane-2α-carboxylic acid and methyl 6-endo-(6,6,7,7,7-pentafluoro-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2β-carboxylic acid.
Following the procedure of Example 1, parts F and G, but using methyl 6-endo-(6,6,7,7,7-pentafluoro-1-heptenyl)-3-oxobicyclo[3.1.0]hexane-2a-heptanoate as a reactant, there are obtained dl 19,19,20,20,20-pentafluoro-PGE₁ methyl ester; infrared absorption at 3430, 2920, 2850, 1715, 1105, 1110, 1075, 1010, 980 and 970 cm⁻¹; and dl 15β-19,19,20,20,20-pentafluoro-PGE₁ methyl ester; infrared absorption at 3430, 1735, 1435, 1345, 1320, 1270, 1195, 1125, 1110, 1070, 1005, 975, and 715 cm⁻¹.

**EXAMPLE 8**

dl 8β-19,19,20,20,20-Pentafluoro-PGE₁ Methyl Ester and dl 8β,15α-19,19,20,20,20-Pentafluoro-PGE₁ Methyl Ester

Following the procedures of Example 1–8 but using exo reactants rather than endo reactants, the same PGE₁ type methyl esters are obtained.

Also following the procedures of Examples 1–8 but using separately as reactants the ethyl, 2-ethylhexyl, phenyl, benzyl, cyclohexyl, and β,β,β-trichloroethyl esters of 7-ido-heptanoic acid in place of methyl 7-ido-heptanoate, there are obtained the 8α-15α, 8α-15β, 8β-15α, and 8β-15β forms of the corresponding esters of dl 20,20-dimethyl-PGE₁, dl 19,19-dimethyl-PGE₁, dl 19,19,20,20,20-pentafluoro-PGE₁, and dl 19,19,20,20,20-pentafluoro-PGE₁.

Also following the procedures of Examples 1–8 but using separately as reactants both optically active enantiomers of the methyl, ethyl, 2-ethylhexyl, phenyl, benzyl, cyclohexyl, and β,β,β-trichloroethyl esters of the various 6-endo-(substituted - 1 - alkenyl)-3-oxobicyclo[3.1.0]hexane-2-heptanoic acid reactants defined in those examples, there are obtained the 8α-15α, 8α-15β, 8β-15α, and 8β-15β forms of the corresponding esters of dl 20,20-dimethyl-PGE₁, ent 20,20-dimethyl-PGE₁, 19,19-dimethyl-PGE₁, ent 19,19,20,20,20-pentafluoro-PGE₁, 19,19,20,20,20-pentafluoro-PGE₁, and ent 19,19,20,20,20-pentafluoro-PGE₁.

Also following the procedures of Example 1 but using as pairs of reactants in place of the 6-methyl-1-bromohexane and the methyl 7-ido-heptanoate, the following pairs of alkyl bromide or fluoroalkyl bromide and α-ido-alkanoate ester, the corresponding PGE₁-type esters are produced:

- (CH₃)₂-COOR ———— (CH₃)₂-CF₂(CH₂)₄Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂(CH₃)₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂(CH₂)₃Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂(CH₂)₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂(CH₂)Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br
- (CH₃)₂-COOR ———— (CH₂)₄-CF₂Br

wherein R₃ is methyl, ethyl, 2-ethylhexyl, phenyl, benzyl, cyclohexyl, or β,β,β-trichloroethyl.

**EXAMPLE 9**
dl 20,20-Dimethyl-PGE₁

A solution of the β,β,β-trichloro-ethyl ester of dl 20,20-dimethyl-PGE₁ (30 mg.) in 5 ml. of 90% acetic acid is stirred with 400 mg. of zinc dust for 2 hours at 25°C.

**EXAMPLE 10**
dl 19-Methyl-PGA₁ Methyl Ester

A solution of 200 mg. of dl 19-methyl-PGE₁ methyl ester in a mixture of 2 ml. of tetrahydrofuran and 2 ml. of 0.5 N hydrochloric acid is stirred under nitrogen at 25°C for 5 days. The reaction mixture is then diluted with saturated aqueous sodium chloride and extracted with ethyl acetate. The ethyl acetate extract is washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give 159 mg. of an oil. The oil is chromatographed over 25 g. of silica gel and eluted with 350 ml. of 20%, 400 ml. of 30%, 500 ml. of 40%, 1000 ml. of 50%, and 500 ml. of 60% ethyl acetate in Skellysolve B, then with 500 ml. of ethyl acetate, taking 25 ml. fractions. Eluates fractions 17–22 are concentrated and combined to give 45 mg. of dl 19-methyl-PGA₁, methyl ester; ultraviolet absorption maximum (ethanol) at 217 μm, with shoulder at 204 μm.

Following the procedure of Example 10, dl 15β-19,19-dimethyl-PGA₁ methyl ester, dl 8β-19,19-dimethyl-PGA₁ methyl ester, dl 8β,15β-19,19-dimethyl-PGA₁ methyl ester, and both optically active forms of each of those are obtained from the corresponding PGE₁-type compounds.

Also following the procedure of Example 10, the ethyl, 2-ethylhexyl, phenyl, benzyl, and cyclohexyl esters of the 8α-15α, 8α-15β, 8β-15α, and 8β-15β forms of the racemic and both optically active forms of 19-methyl-PGA₁ are obtained from the corresponding PGE₁-type compounds.

Also following the procedure of Example 10, the methyl, ethyl, 2-ethylhexyl, phenyl, benzyl, and cyclohexyl esters of the 8α-15α, 8α-15β, 8β-15α, and 8β-15β forms of the racemic and both optically active forms of 19,19-dimethyl-PGA₁, 20,20-dimethyl-PGA₁, and 19,19,20,20,20-pentafluoro-PGA₁ are obtained from the corresponding PGE₁-type acids.

Also following the procedure of Example 10, each of the PGE₁-type esters described after Example 8 and each of the PGE₁-type acids described after Example 9 is debrominated to the corresponding PGE₁-type ester and acid.

**EXAMPLE 11**
dl 19,19-Dimethyl-PGE₁, and dl 19,19-Dimethyl-PGF₁, and Their Methyl Esters

A solution of dl 19,19-dimethyl-PGE₁ methyl ester...
(500 mg.) in 25 ml. of isopropyl alcohol is stirred at 0°C. under nitrogen, and a cold solution of 250 mg. of sodium borohydride in 5 ml. of water is added. The mixture is stirred at 0°C. for 2.5 hours, then 1 ml. of acetone is added and the mixture is stirred for 10 minutes at 0°C. The mixture is made slightly acidic (pH 5-6) with acetic acid, and is then concentrated under reduced pressure to remove the acetone and isopropyl alcohol. This mixture is poured into saturated aqueous sodium chloride and extracted 3 times with ethyl acetate. The ethyl acetate extracts are combined, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give 507 mg. of a mixture of dl 19,19-dimethyl-PGF\(_2\)\(_a\), methyl ester and dl 19,19-dimethyl-PGF\(_2\)\(_a\), methyl ester as a white solid. This mixture (503 mg.) is dissolved in 15 ml. of methanol, cooled to about 5°C. and stirred under nitrogen while 2 ml. of 50% aqueous potassium hydroxide is added. The mixture is then stirred, under nitrogen, for 4 hours at 25°C. The mixture is diluted with 100 ml. of water and extracted once with ethyl acetate. The aqueous phase is acidified with dilute hydrochloric acid and extracted 4 times with ethyl acetate. The ethyl acetate extracts are combined, washed 3 times with water and once with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give 506 mg. of white crystalline material. This crystalline material is chromatographed over 150 g. of silica gel. The column is eluted with 500 ml. of 50% and 500 ml. of 75% ethyl acetate in cyclohexane, and then with 4000 ml. of ethyl acetate followed by 500 ml. of 10% and 500 ml. of 25% methanol in ethyl acetate. The ethyl acetate-cyclohexane eluates are discarded, then 50 ml. eluate fractions are taken beginning with the ethyl acetate eluate. Fractions 16 to 35 are evaporated and combined to give 135 mg. of residue which is recrystallized from a mixture of ethyl acetate and Skellysolve B to give dl 19,19-dimethyl-PGF\(_2\)\(_a\); m.p. 107-109°C.; infrared absorption at 3320, 2700, 1710, 1425, 1305, 1290, 1275, 1040, 1210, 1200, 1095, 1050, 1020, 985, 975 and 945 cm\(^{-1}\); mass spectrum peaks at 384, 366, 348 and 294.

Fractions 46 to 84 are evaporated and combined to give 211 mg. of residue which is recrystallized from a mixture of ethyl acetate and Skellysolve B to give dl 19,19-dimethyl-PGF\(_2\)\(_a\); methyl ester and dl 19,19-dimethyl-PGF\(_2\)\(_a\), methyl ester is separated by chromatography on neutral silica gel, eluting with a gradient of 20-100% ethyl acetate in Skellysolve B, to give the separate alpha and beta isomers of these esters.

Following the procedure of Example 11, dl 15a,19,19-dimethyl-PGE\(_2\), methyl ester, dl 8a,15a,19,19-dimethyl-PGE\(_1\), methyl ester, dl 8a,15p,19,19-dimethyl-PGE\(_1\), methyl ester, and both optically active forms of each of which are each transformed to the corresponding PGE\(_{1a}\)-type and PGE\(_{2a}\)-type acids and esters.

Also following the procedure of Example 11, the ethyl 2-ethylhexyl, phenyl, benzyl, and cyclohexyl esters of the 8a-15a, 8a-15p, 8p-15a, and 8p-15p forms of the racemic and both optically active forms of 19,19-dimethyl-PGF\(_2\)\(_a\), and 19,19-dimethyl-PGF\(_2\)\(_b\) are obtained from the corresponding PGE\(_1\)-type compounds.

Also following the procedure of Example 11, and the methyl, ethyl, 2-ethylhexyl, phenyl, benzyl, and cyclohexyl esters of the 8a-15a, 8a-15p, 8p-15a, and 8p-15p forms of both the racemic and both optically active forms of 19,19-dimethyl-PGF\(_2\)\(_a\), 20,20-dimethyl-PGF\(_2\)\(_a\), and 19,19,20,20-tetrafluoro-PGF\(_2\)\(_a\) are each transformed to the corresponding PGE\(_{1a}\)-type and PGE\(_{2a}\)-type acids and esters.

Also following the procedure of Example 11, each of the PGE\(_1\)-type esters described after Example 8 and each of the PGE\(_2\)-type acids described after Example 9 is reduced to the corresponding PGE\(_{1a}\)-type and PGE\(_{2a}\)-type ester and acid.

What is claimed is:

1. An optically active compound of the absolute configuration of natural PGE\(_1\) or a racemic compound of the formula:

2. A compound according to claim 1 wherein R\(_1\) is hydrogen or alkyl of one to 4 carbon atoms, inclusive, and pharmacologically acceptable salts thereof when R\(_1\) is hydrogen.

3. A compound according to claim 2 wherein the formula is VI.

4. A compound according to claim 3 wherein the compound according to claim 4 wherein the sidechain hydroxyl is in alpha configuration.

5. A compound according to claim 4 wherein the sidechain hydroxyl is in beta configuration.

6. A compound according to claim 5 wherein n is 6.

7. A compound according to claim 6 wherein n is 6.

8. A compound according to claim 7 wherein R is 3,3,4,4,4-pentafluorobutyryl, and a is 1.

9. A compound according to claim 8 wherein Z is 3,3,4,4,4-pentafluorobutyryl, and a is 1.

10. A compound according to claim 9 wherein the compound according to claim 10 wherein the sidechain hydroxyl is in alpha configuration.

11. A compound according to claim 10 wherein the sidechain hydroxyl is in beta configuration.

12. A compound according to claim 11 wherein the sidechain hydroxyl is in alpha configuration.

13. A compound according to claim 12 wherein the ring hydroxyl is in alpha configuration.

14. A compound according to claim 12 wherein the ring hydroxyl is in beta configuration.
27. A compound according to claim 13 wherein the side-chain hydroxy is in alpha configuration.

28. A compound according to claim 26 wherein Z is 3,3,4,4,4-pentafluorobutyl, and a is 1.

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ROBERT GERSTL, Primary Examiner

U.S. Cl. X.R.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 3,833,640
DATED: September 3, 1974
INVENTOR(S): John E. Pike

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 2, lines 1-4, Formula V, that portion of the formula reading

should read

Column 2, line 36, "and PGA₁₀₀, is S" should read -- and PGA₁₀₀, is S --. Column 7, line 35, "potency" should read -- potency --. Column 8, lines 39-40, "gelactamine," should read -- galactamine, --; lines 60-62, "simple compounds of formulas IX, XII, and XV, and PGA₁-type solutions," should read -- simple solutions --. Column 11, line 54, "carbonyl." should read -- carboxyl. --.
Column 12, lines 74-75 and Column 13, line 1, "product is de-
CH₂(CH₂)₆Br sired," should read -- product is desired --. Column 19, line 37, "in 3.1 of benzene" should read -- in 3.1 of benzene --. Column 20, line 41, "The only 50% ethyl acetate" should read -- The 50% ethyl acetate --. Column 21, line 23, "and 21 8;" should read -- and 218 8; --.

Signed and Sealed this
Thirteenth Day of September 1977

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

LUTRELLE F. PARKER
Acting Commissioner of Patents and Trademarks