

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00016012

Solicitud de Patente en nombre de

THE PROCTER & GAMBLE COMPANY

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Santafé de Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad THE PROCTER & GAMBLE COMPANY solicitante de la patente de la referencia, anexo al presente memorial el siguiente documento:

Copia certificada de la solicitud de Patente Número 60/122,924 presentada en los Estados Unidos de América el día 5 de marzo de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

Señor Superintendente,



JIMENA ESCOBAR URIBE

C.C.39.779.452 de usaquén

T.P. 68228

Cód. 5376

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**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

Febrero 11, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/122,924

Fecha de Presentación: Marzo 05, 1999

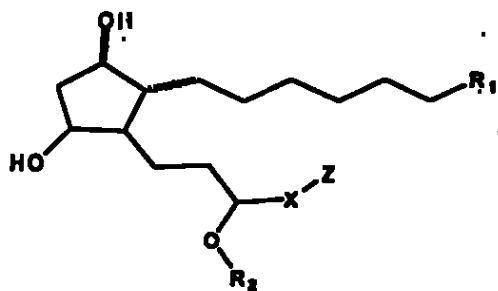
**Por la autoridad del
Comisionado de Patentes y Marcas**

**(fdo) N. WOODSON
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América.**

LO QUE SE REIVINDICA ES :

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1. Un compuesto que tiene la estructura:



donde

(a) R₁ es CO₂H, C(O)NHOH, CO₂R₃, CH₂OH, S(O)₂R₃, C(O)NHR₃, C(O)NHS(O)₂R₄ y tetrazol ; donde R₃ es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico, anillo heteroaromático monocíclico;

(b) R₂ es H o alquilo inferior;

(c) X es

(1) C≡C ó

(2) un enlace covalente;

(d) Z es un anillo aromático o un anillo heteroaromático a condición que cuando Z sea un anillo heteroaromático y X un enlace covalente, Z esté unido a C₁₅ mediante un átomo miembro carbono; y

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- () cualquier isómero óptico, diastereómero, enantiómero de la estructura anterior o una sal farmacéuticamente aceptable o amida biohidrolizable, éster o imida de ellos.
2. El compuesto de la Reivindicación 1 donde X es $C \equiv C$.
 3. El compuesto de la Reivindicación 2 donde R_1 es CO_2H , $C(O)NHOH$, CO_2CH_3 , $C(O)NHS(O)_2R_4$ o tetrazol.
 4. El compuesto de la Reivindicación 3 donde Z es monocíclico.
 5. El compuesto de la Reivindicación 4 donde Z es seleccionado del grupo consistente de: fenilo, tienilo y furanilo.
 6. El compuesto de acuerdo con la Reivindicación 5 donde Z es sustituido con un sustituyente, dicho sustituyente siendo seleccionado del grupo consistente de: alquilo inferior, halo y haloalquilo.
 7. El compuesto de la Reivindicación 5 donde R_2 es H.
 8. El compuesto de la Reivindicación 7 donde R_1 es CO_2H o CO_2R_3 .
 9. El compuesto de la Reivindicación 1 donde X es un enlace covalente.
 10. El compuesto de la Reivindicación 9 donde R_1 es CO_2H , $C(O)NHOH$, CO_2R_3 , $C(O)NHS(O)_2R_4$ o tetrazol.

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11. El compuesto de la Reivindicación 10 donde Z es un anillo heteroaromático bicíclico.

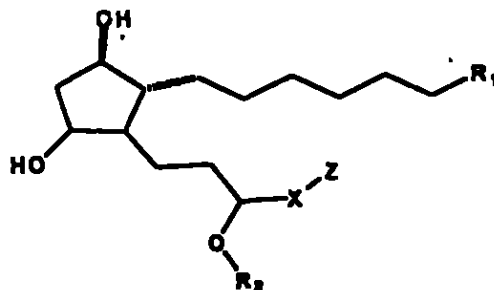
12. El compuesto de la Reivindicación 11 donde Z es seleccionado del grupo consistente de: benzo[β]tiazolilo, benzo[β]tiofenilo y benzoxazolilo.

13. El compuesto de la Reivindicación 12 donde Z es sustituido con un sustituyente, dicho un sustituyente siendo seleccionado del grupo consistente de: alquilo inferior, halo y haloalquilo.

14. El compuesto de la Reivindicación 12 donde R_2 es H.

15. El compuesto de la Reivindicación 14 donde R_1 es CO_2H ó CO_2R_3 .

16. Un método de tratamiento para un humano u otro sujeto animal que tiene un desorden óseo, dicho método comprende la administración a dicho sujeto de un compuesto de acuerdo con la estructura:



donde

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(a) R_1 es seleccionado del grupo consistente de: CO_2H , $C(O)NHOH$, CO_2R_3 , CH_2OH , $S(O)_2R_3$, $C(O)NHR_3$, $C(O)NHS(O)_2R_4$ y tetrazol; donde R_3 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico; y R_4 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico;

(b) R_2 es H o alquilo inferior;

(c) X es:

(1) $C \equiv C$ ó

(2) un enlace covalente;

(d) Z es un anillo aromático o un anillo heteroaromático a condición que cuando Z sea un anillo heteroaromático y X un enlace covalente, Z esté unida a C_{15} mediante un átomo miembro de carbono; y

(e) cualquier isómero óptico, diastereómero, enantiómero de la estructura anterior o una sal farmacéuticamente aceptable o amida biohidrolizable, éster o imida de ellos.

17. El método de la Reivindicación 16 donde dicho desorden óseo es osteoporosis.

18. El método de la Reivindicación 17 donde la osteoporosis es post menopáusica.

19. El método de la Reivindicación 17 donde la osteoporosis es cortico esteroide inducida.

20. El método de la Reivindicación 16 donde dicho desorden óseo es osteopenia.

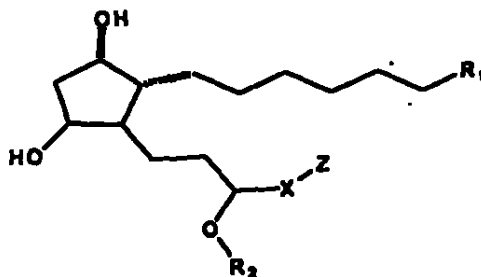
21. El método de la Reivindicación 16 donde dicho desorden óseo es una fractura de hueso.

22. El método de la Reivindicación 16 donde dicho compuesto es administrado oralmente.

23. El método de la Reivindicación 16 donde dicho compuesto es administrado transdérmicamente.

24. El método de la Reivindicación 16 donde dicho compuesto es administrado intranasalmente.

25. Un método de tratamiento de glaucoma, dicho método comprende la administración a dicho humano u otro animal una cantidad segura y efectiva de un compuesto de acuerdo con la estructura:



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d nd

(a) R_1 es seleccionada del grupo consistente de: CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_3 , CH_2OH , $\text{S}(\text{O})_2\text{R}_3$, $\text{C}(\text{O})\text{NHR}_3$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_4$ y tetrazol; donde R_3 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico; y R_4 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico;

(b) R_2 es H o alquilo inferior;

(c) X es:

(1) $\text{C}\equiv\text{C}$ ó

(2) un enlace covalente;

(d) Z es un anillo aromático o un anillo heteroaromático a condición que cuando Z sea un anillo heteroaromático y X un enlace covalente, Z esté unida a C_{15} mediante un átomo miembro de carbono; y

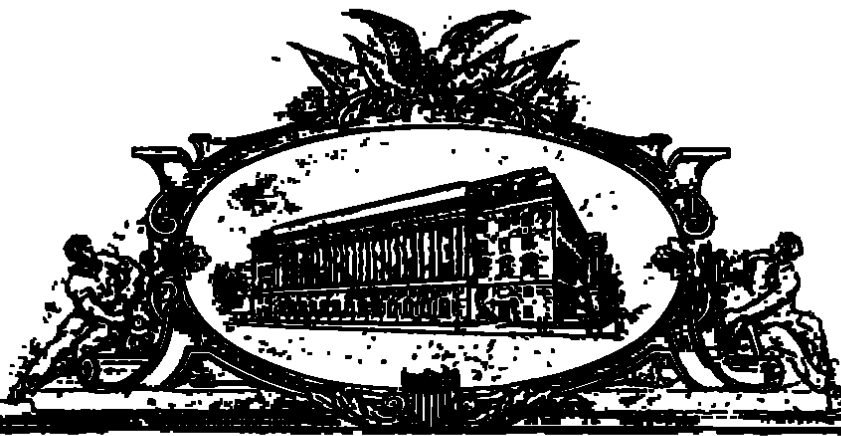
(e) cualquier isómero óptico, diastereómero, enantiómero de la estructura anterior o una sal farmacéuticamente aceptable o amida biohidrolizable, éster o imida de ellos.

26. El método de la R ivindicación 25, donde dicho compuesto es administrad tópicamente.

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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 11, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/122,924

FILING DATE: March 05, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

N. Woodson
N. WOODSON

Certifying Officer

Provisional Patent Application Form

Date of Deposit: March 5, 1999

I hereby certify that this application is being deposited with the United States Patent Service (USPS) Post Office to Addressed Service under 37 CFR 1.53 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

James C. Kellerman
Applicant

Signature of Applicant

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(c).

Docket Number 7462P Type a plus sign (+) inside this box +

INVENTOR(s) / APPLICANT(s)

FAMILY NAME OR SURNAME	GIVEN NAME (first name)	MIDDLE INITIAL (if any)	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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Wes	John	A.	Cincinnati, OH
De	Eleonora		Cincinnati, OH
Super	David	L.	Moravia, OH

TITLE OF THE INVENTION (200 characters max)

C₁₂ Unsaturated FP-Selective Prostaglandins Analogs

CORRESPONDENCE ADDRESS

James C. Kellerman
The Procter & Gamble Company
Health Care Research Center
8700 Mason Montgomery Road
Mason

STATE OH ZIP CODE 45040-8006 COUNTRY USA

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages: 37 + Abstract ☐ Small Entity Statement
☐ Drawing(s) Number of Sheets: ☐ Other (specify):

METHOD OF PAYMENT (check one)

☐ A check or money order is enclosed to cover the Provisional filing fee
☒ The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 162492 PROVISIONAL FILING FEE AMOUNT(\$): \$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of United States Government.

☒ No

☐ Yes, the name of the U. S. Government agency and the Government contract number are:

Respectfully submitted

SIGNATURE James C. Kellerman Date March 5, 1999

TYPED or PRINTED NAME James C. Kellerman REGISTRATION NO. P43.708 (if appropriate)

Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL PATENT APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual cases. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0037), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Patent Application; Assistant Commissioner for Patents, Washington, D.C. 20231.

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C₁₆ UNSATURATED FP-SELECTIVE PROSTAGLANDINS ANALOGS

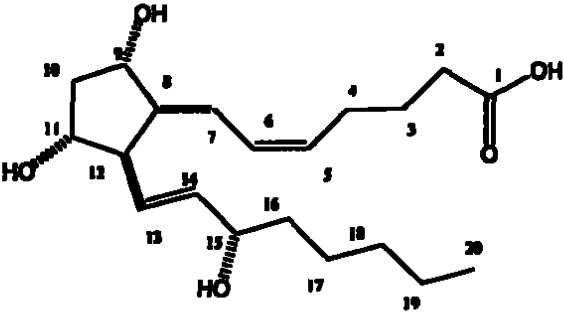
Mitchell deLong
John Wos
Blawanath De
David Soper

TECHNICAL FIELD

The subject invention relates to certain novel analogs of the naturally occurring prostaglandins. Specifically, the subject invention relates to novel Prostaglandin F analogs. The subject invention further relates to methods of using said novel Prostaglandin F analogs. Preferred uses include methods of treating bone disorders and glaucoma.

BACKGROUND OF THE INVENTION

Naturally occurring prostaglandins (PGA, PGB, PGE, PGF, and PGI) are C-20 unsaturated fatty acids. PGF_{2α}, the naturally occurring Prostaglandin F in humans, is characterized by hydroxyl groups at the C₉ and C₁₁ positions on the allcyclic ring, a cis-double bond between C₅ and C₆, and a trans-double bond between C₁₃ and C₁₄. Thus PGF_{2α} has the following formula:



PGF_{2α}

Analog of naturally occurring Prostaglandin F have been disclosed in the art. For example, see U.S. Patent No. 4,024,179 issued to Bindra and Johnson on May 17, 1977; German Patent No. DT-002,460,990 issued to Beck, Lerch, Seeger, and Teufel published on July 1, 1976; U.S. Patent No. 4,128,720 issued to Hayashi, Kori, and Miyake on December 5, 1978; U.S. Patent No. 4,011,282 issued to Hess, Johnson, Bindra, and Schaef on March 8, 1977; U.S. Patent No. 3,776,938 issued to Bergstrom and Sjoval on December 4, 1973; P.W. Collins

and S. W. Djuric, "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chem. Rev. Vol. 83 (1983), pp. 1533-1564; G. L. Bundy and F. H. Lincoln, "Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins: I. The PG₁ Series", Prostaglandins, Vol. 9 No. 1 (1975), pp. 1-4; W. Bartman, G. Beck, U. Lerch, H. Teufel, and B. Scholkens, "Luteolytic Prostaglandins: Synthesis and Biological Activity", Prostaglandins, Vol. 17 No. 2 (1979), pp. 301-311; C. Liljebris, G. Selen, B. Rasul, J. Sternschantz, and U. Hackzell, "Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin F₂ α Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry, Vol. 38 No. 2 (1995), pp. 289-304.

10 Naturally occurring prostaglandins are known to possess a wide range of pharmacological properties. For example, prostaglandins have been shown to: relax smooth muscle, which results in vasodilatation and bronchodilatation, to inhibit gastric acid secretion, to inhibit platelet aggregation, to reduce intraocular pressure, and to induce labor. Although naturally occurring prostaglandins are
15 characterized by their activity against a particular prostaglandin receptor, they generally are not specific for any one prostaglandin receptor. Therefore, naturally-occurring prostaglandins are known to cause side effects such as inflammation, as well as surface irritation when administered systemically. It is generally believed that the rapid metabolism of the naturally occurring
20 prostaglandins following their release in the body limits the effects of the prostaglandin to a local area. This effectively prevents the prostaglandin from stimulating prostaglandin receptors throughout the body and causing the effects seen with the systemic administration of naturally occurring prostaglandins.

Prostaglandins, especially prostaglandins of the E series (PGE), are
25 known to be potent stimulators of bone resorption. PGF_{2 α} has also been shown to be a stimulator of bone resorption but not as potent as PGE₂. Also, it has been demonstrated the PGF_{2 α} has little effect on bone formation as compared to PGE₂. It has been suggested that some of the effects of PGF_{2 α} on bone resorption, formation and cell replication may be mediated by an increase in
30 endogenous PGE₂ production.

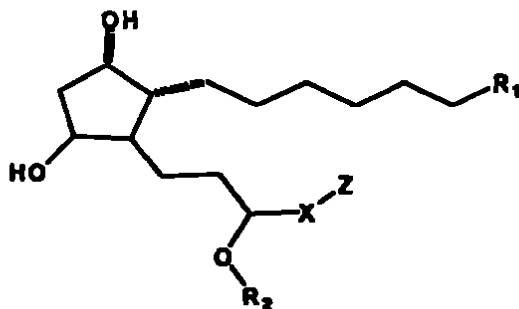
In view of both the wide range of pharmacological properties of naturally occurring prostaglandins and of the side effects seen with the systemic administration of these naturally occurring prostaglandins, attempts have been made to prepare analogs to the naturally occurring prostaglandins that are
35 selective for a specific receptor or receptors. A number of such analogs have been disclosed in the art. Though a variety of prostaglandin analogs have been disclosed, there is a continuing need for potent, selective prostaglandin analogs for the treatment of a variety diseases and conditions.

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SUMMARY OF THE INVENTION

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to the following formula:



Formula A

wherein R₁, R₂, X, and Z are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using these compounds or the compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

Terms and Definitions

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or two branches, preferably one branch. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted alkyl are mono-, di-, or trisubstituted. The substituents may be lower alkyl, halo, hydroxy, aryloxy (e.g., phenoxy), acyloxy (e.g., acetoxy), carboxy, monocyclic aromatic ring (e.g., phenyl), monocyclic heteroaromatic ring, monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, and amino.

התאחדות המורים

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"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double

bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or trisubstituted. The substituents may be lower alkyl, halo, hydroxy, aryloxy (e.g., phenoxy), acyloxy (e.g., acetoxy), carboxy, monocyclic aromatic ring (e.g., phenyl), monocyclic heteroaromatic ring, monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, and amino.

"Lower heteroalkyl" is a heteroalkyl chain comprised of 1 to 6, preferably 1 to 3 member atoms.

"Heteroaromatic ring" is an aromatic ring containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings include ring systems wherein only one ring in the system is aromatic. Preferred bicyclic heteroaromatic rings are ring systems wherein both rings in the system are aromatic. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. The substituents may be halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Preferred substituents include halo, haloalkyl, and phenyl. Preferred monocyclic heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred monocyclic heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred monocyclic heteroaromatic ring is thienyl. Preferred bicyclic heteroaromatic rings include benzo[β]thiazolyl, benzo[β]thiophenyl, quinoxalyl, quinoxalyl, benzo[β]furanyl, benzimidazolyl, benzoxazolyl, indolyl, and anthranilyl. More preferred bicyclic heteroaromatic rings include benzo[β]thiazolyl, benzo[β]thiophenyl, and benzoxazolyl.

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

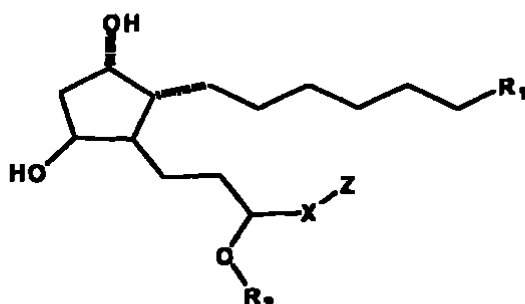
"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic. Heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7 member atoms, and most preferably from 5 to 6 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the

ring. The substituents may be halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholynyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

5 "Phenyl" is a monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be fused but not bridged and may be substituted at the *ortho*, *meta* or *para* position on the phenyl ring, or any combination thereof. The substituents may be halo, acyl, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination
10 thereof. Preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo. The preferred substitution pattern on the phenyl ring is *ortho* or *meta*. The most preferred substitution pattern on the phenyl ring is *meta*.

15 **Compounds**

The subject invention involves compounds having the following structure:



Formula A

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In the above structure, R₁ is CO₂H, C(O)NHOH, CO₂R₃, CH₂OH, S(O)₂R₃, C(O)NHR₃, C(O)NHS(O)₂R₄, or tetrazole; wherein R₃ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring; and R₄ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring. Preferred R₃ is methyl, ethyl, and isopropyl. Preferred R₁ is CO₂H, C(O)NHOH, CO₂R₃, C(O)NHS(O)₂R₄, and tetrazole. Most preferred R₁ is CO₂H and CO₂R₃.

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In the above structure, R₂ is H or lower alkyl. The most preferred R₂ is H.

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In the above structure, X is C=C or a covalent bond.

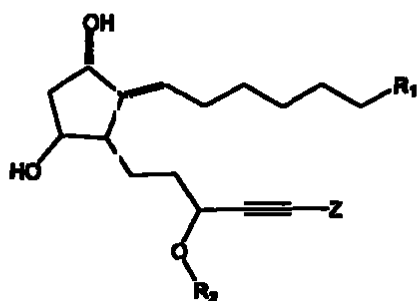
In the above structure, Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring and X is a covalent bond, Z is attached to C₁₁ via a Carbon member atom. When X is C=C, preferred Z is

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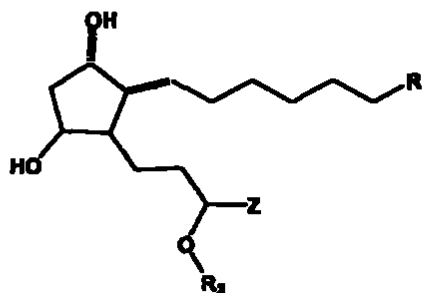
monocyclic aromatic ring. When X is C≡C, more preferred Z is furanyl, thienyl, and phenyl. When X is a covalent bond, preferred Z is a bicyclic heteroaromatic ring.

The invention also includes optical isomers, diastereomers and enantiomers of the above structure. Thus, at all stereocenters where stereochemistry is not defined (C₁₁, C₁₃, and C₁₅), both epimers are envisioned. Preferred stereochemistry at all such stereocenters of the compounds of the invention mimic that of naturally occurring PGF_{2α}.

As can be readily seen from the description above, the invention can be placed into two subgenres based upon the functional group "X." Formula A1 (X is C≡C) and Formula A2 (X is a covalent bond) below depict these two subgenres:



Formula A1



Formula A2

It has been discovered that the novel PGF analogs of the subject invention are useful for treating bone disorders, especially those that require a significant increase in bone mass, bone volume, or bone strength. Surprisingly, the compounds of the subject invention have been found to provide the following advantages over known bone disorder therapies: (1) An increase trabecular number through formation of new trabeculae; (2) An increase in bone mass and bone volume while maintaining a more normal bone turnover rate; and/or (3) An increase in bone formation at the endosteal surface without increasing cortical porosity.

In order to determine and assess pharmacological activity, testing of the subject compounds in animals is carried out using various assays known to those skilled in the art. For example, the bone activity of the subject compounds can be conveniently demonstrated using an assay designed to test the ability of the subject compounds to increase bone volume, mass, or density. An example of such assays is the ovariectomized rat assay.

In the ovariectomized rat assay, six-month old rats are ovariectomized, aged 2 months, and then dosed once a day subcutaneously with a test

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compound. Upon completion of the study, bone mass and/or density can be measured by dual energy x-ray absorptometry (DXA) or peripheral quantitative computed tomography (pQCT), or micro computed tomography (mCT). Alternatively, static and dynamic histomorphometry can be used to measure the increase in bone volume or formation.

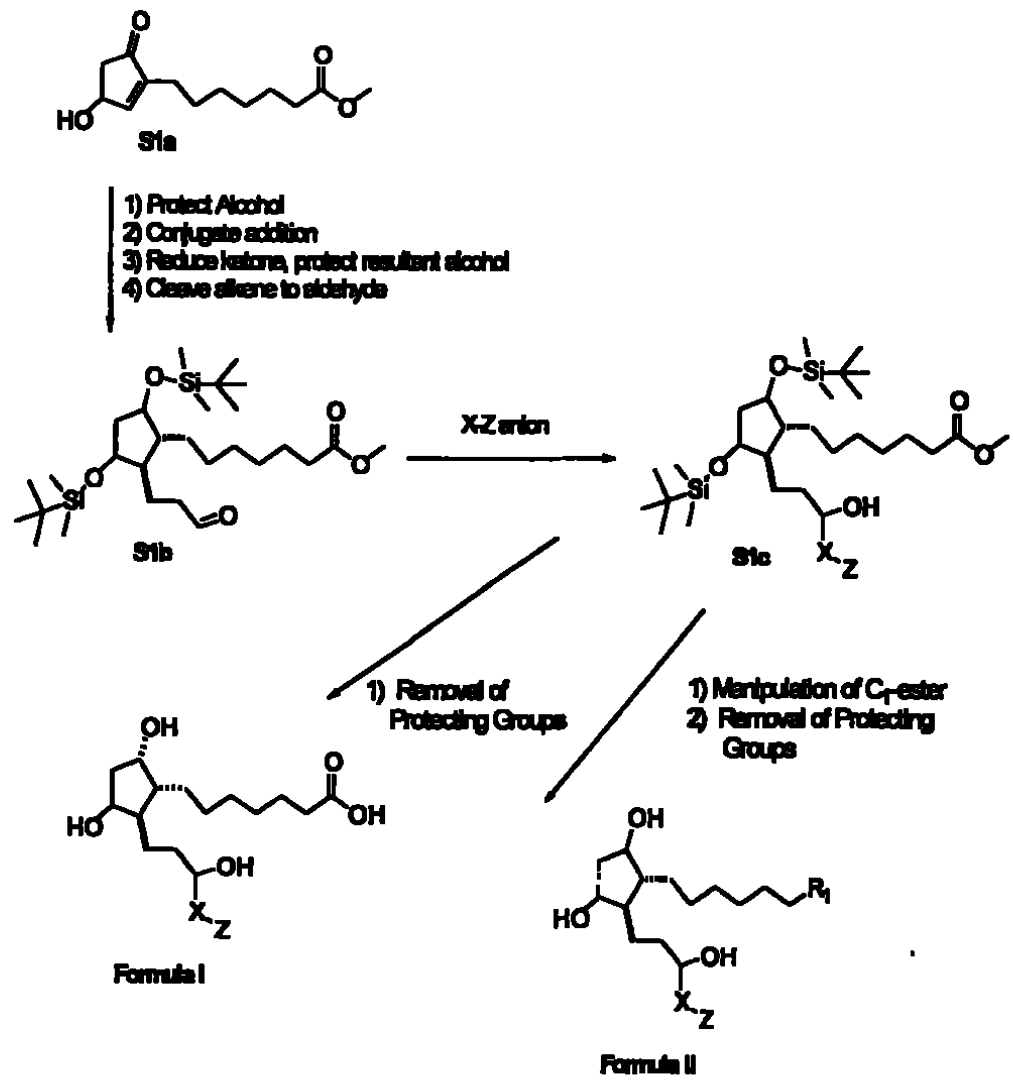
Pharmacological activity for glaucoma can be demonstrated using assays designed to test the ability of the subject compounds to decrease intraocular pressure. Examples of such assays are described in the following reference, incorporated herein: C. Liljebris, G. Selen, B. Resul, J. Stenmachantz, and U. Hackzell, "Derivatives of 17- Phenyl-18,19,20-trinorprostaglandin F₂ α Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry, Vol. 38 No. 2 (1995), pp. 289-304.

Compounds useful in the subject invention can be made using conventional organic syntheses. A particularly preferred synthesis is the following general reaction scheme:

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Scheme 1



5 In Scheme 1, R₁, R₂, X, and Z are as defined above. The methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (S1a) depicted as starting material for Scheme 1 is commercially available (such as from Sumitomo Chemical or Cayman Chemical).

10 The C₁₁ alcohol of methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (S1a) is protected with a suitable protecting group. The most preferred protecting group is a silyl group. In the above Scheme 1, methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (S1a) is reacted with a silylating agent and base in a solvent that will allow the silylation to proceed. Preferred silylating agents include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulphonate. The most preferred silylating agent is tert-butyldimethylsilyl trifluoromethanesulphonate. Preferred bases include

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triethylamine, trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature preferably
5 between -100°C and 100°C, more preferably between -80°C and 80°C, and most preferably between -70°C and 23°C.

The resulting silylated compound is isolated by methods known to those of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the
10 silyl ether is purified after isolation by distillation under vacuum.

The silylated compound is then reacted with the cuprate generated via Grignard formation of the appropriate alkenyl bromide as disclosed, for example, in the following references: H.O. House et. al., "The Chemistry of Carbanions: A Convenient Precursor for the Generation of Lithium Organocuprates", J. Org. Chem. Vol. 40 (1975) pp. 1480-69 ; and P. Knochel et. al., "Zinc and Copper Carbenoids as Efficient and Selective α/δ Multicoupling Reagents", J. Amer. Chem. Soc. Vol. 111 (1989) p. 8474-76. Preferred alkenyl bromides include 4-bromo-1-butene, 4-bromo-1-butyne, 4-bromo-2-methyl-1-butene, and 4-bromo-2-ethyl-1-butene. The most preferred alkenyl bromide is 4-bromo-1-butene.
15 Preferred solvents include ethereal solvents, of which diethyl ether and tetrahydrofuran are preferred. The most preferred solvent is tetrahydrofuran. The Grignard reagent is allowed to form at a temperature between 100°C and 23°C, more preferably between 85°C and 30°C, and most preferably between 75°C and 65°C. The reaction time is preferably between 1 hour and 6 hours,
20 with a more preferred reaction time being between 2 hours and 5 hours, and the most preferred reaction time being between 3 hours and 4 hours.

Once the Grignard reagent is formed, the cuprate is generated from the alkenyl magnesium species. The temperature range for cuprate formation is between -100°C and 0°C. The preferred temperature range is between -80°C
30 and -20°C. The more preferred temperature range is between -75°C and -50°C. The preferred reaction time is between 30 minutes and 6 hours. The more preferred reaction time is between 45 minutes and 3 hours. The most preferred reaction time is between 1 hours and 1.5 hours.

The alkene thus formed is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the alkene is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 10% EtOAc/hexanes as the eluent. The alkene is then reacted with a hydride reducing agent and a polar, protic solvent to give the C-9 alcohol. Preferred
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The key intermediate aldehyde depicted as S1b can be reacted with a variety unsaturated carbon nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin F₁α derivatives depicted as S1c.

With alkyne nucleophiles, the reaction is carried out preferably at between -80°C and 0°C, more preferably between -80°C and -20°C, and most preferably between -80°C and -40°C. Preferred bases for the reaction include *n*-butyl lithium, *s*-butyl lithium, *t*-butyl lithium, and lithium diisopropyl amide (LDA). Preferred solvents for the reaction are ether solvents. Preferred solvents include diethyl ether, and tetrahydrofuran. The most preferred solvent is tetrahydrofuran. With heterocyclic nucleophiles, preferred solvents include ethereal solvents. More preferred ethereal solvents include diethyl ether, dibutyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran.

The resulting compounds depicted as S1c can then be deprotected using techniques known to one of ordinary skill in the art, and isolated yielding the 13,14-dihydro-15-substituted-15-pentanor prostaglandin F_{1α} derivatives depicted by Formula I. Compounds depicted by Formula I are exemplified in Examples 1-43.

Compounds depicted by Formula II can be made directly from the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin F_{1α} derivatives depicted as S1c by methods known to one of ordinary skill in the art. For example, the condensation of methyl esters of S1c with amines or hydroxylamine provides compounds depicted by Formula II. Compounds depicted by Formula II are exemplified in Examples 44-47. These compounds are isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization.

The following non-limiting examples illustrate the compounds, compositions, and uses of the present invention.

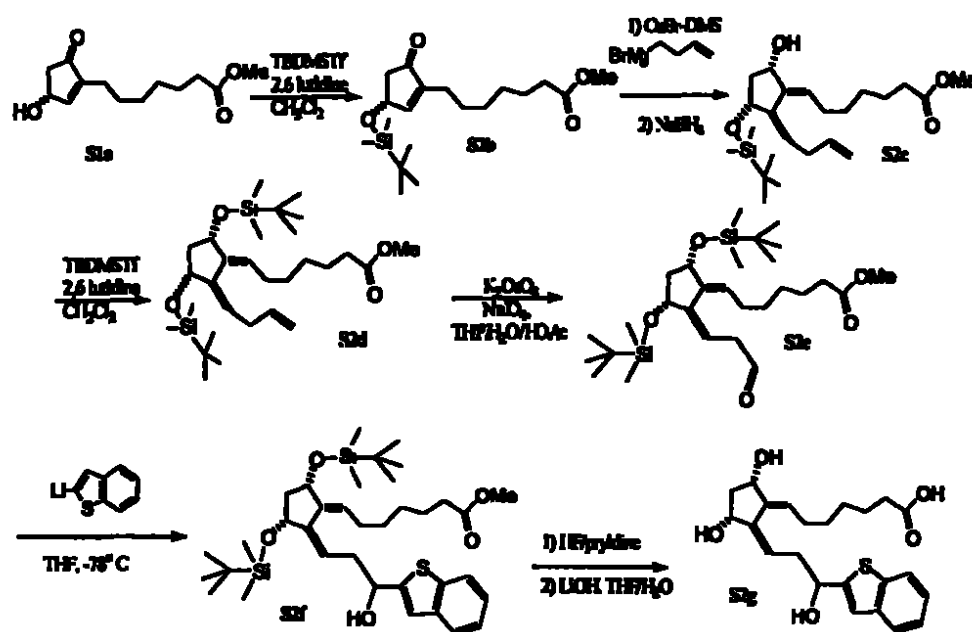
Examples

Compounds are analyzed using ¹H and ¹³C NMR, Elemental analysis, mass spectra, high resolution mass spectra and/or IR spectra as appropriate.

Typically, inert solvents are used, preferably in dried form. For example, tetrahydrofuran (THF) is distilled from sodium and benzophenone, diisopropylamine is distilled from calcium hydride and all other solvents are purchased as the appropriate grade. Chromatography is performed on silica gel (70-230 mesh; Aldrich) or (230-400 mesh; Merck) as appropriate. Thin layer chromatography analysis is performed on glass mounted silica gel plates (200-300 mesh; J.T. Baker) and visualized using *uv* light, 5% phosphomolybdic acid in EtOH, or ammonium molybdate/ceric sulfate in 10% aqueous H₂SO₄.

EXAMPLE 1

Preparation of 13,14-dihydro-15-(thianaphthyl) pentanoic prostaglandin F_{1α} :



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a. **Methyl 7-(2-oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopent-1-enyl) heptanoate S2b:** To a solution of Methyl-7-[3-(R)-hydroxy-5-oxo-1-cyclopenten-1-yl] heptanoate S2a (1 equiv.) in CH₂Cl₂ at -78°C is added 2,6-Lutidine (1.3 equiv.) dropwise over 15 minutes. The solution is kept at -78°C, and TBDMS Triflate (1.2 equiv.) in CH₂Cl₂ is added dropwise over 15 minutes. The reaction is warmed gradually to room temperature and stirred at room temperature for 15 hours. Aqueous 10% HCl is added and the layers are separated. The water layer is extracted with CH₂Cl₂ and the organic layers are combined. The organic layer is washed with brine, dried (Na₂SO₄) and concentrated. The residue is distilled under vacuum (10 mm Hg) to provide the silyl ether S2b.

b. **Methyl 7-(5-but-3-enyl-2-hydroxy-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopentyl) heptanoate S2c:** To a slurry of Mg⁰ powder (2 equiv.) in THF at room temperature is added one crystal of iodine (catalytic I₂) and 1-bromobutene (2 equiv.) dropwise over 10 minutes. The reaction proceeds to exotherm as the addition continues. After the addition is complete, the reaction is refluxed for 3 hours and cooled to room temperature. The Grignard is diluted with THF and added via cannula to a 3-necked flask equipped with mechanical stirring and charged with CuBr·DMS (2 equiv.) in a 1:1 solution

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of THF/DMS at -78°C . After the addition of the Grignard (~20 min), the reaction is stirred for 1 hour at -78°C . The color of the reaction is dark red at this point. A solution of the ketone S2b (1 equiv.) in THF is then added dropwise over 25 minutes. The reaction is stirred at -78°C for 15 minutes, then allowed to warm slowly to room temperature over 2 hours. The reaction is quenched with aqueous NH_4Cl and the excess DMS is allowed to evaporate overnight. The reaction is partitioned between brine/ CH_2Cl_2 and the layers are separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers are combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue is chromatographed on SiO_2 (10 % hexane/EtOAc) to give the ketone precursor to S2c.

The ketone precursor to S2c (1 equiv.) is dissolved in MeOH and cooled to -40°C . Sodium borohydride (0.9 equiv.) is added portionwise over 10 minutes. After the addition is complete, the reaction is stirred for 13 hours at -40°C and then for 12 hours at -78°C . The reaction is quenched with water, partitioned between brine and CH_2Cl_2 , and the layers separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers are combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue chromatographed on SiO_2 (30 % EtOAc/hexanes) to give the alcohol S2c.

c. Methyl 7-(5-but-3-enyl -2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate S2d: The alcohol S2c (1 equiv.) is dissolved in CH_2Cl_2 and cooled to 0°C and added is 2,6 lutidine (1.3 equiv.) dropwise over 15 minutes. The solution is kept at -78°C , and TBDMS Triflate (1.2 equiv.) in CH_2Cl_2 is added dropwise over 15 minutes. The reaction is warmed gradually to room temperature and stirred at room temperature for 15 hours. Aqueous 10% HCl is added and the layers are separated. The water layer is extracted with CH_2Cl_2 and the organic layers are combined. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. The residue is chromatographed (10% EtOAc in hexanes) to provide the silyl ether S2d.

d. Methyl 7-(5-(3-oxopropanyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate S2e: In a 50 mL round-bottomed flask, Sodium periodate (2 equiv.) and 10 mL of water are added. This is stirred until the periodate has completely dissolved. Then an equal portion of glacial acetic acid is added, followed by two portions of tetrahydrofuran. Finally, a few mole percent of potassium osmate are added, followed by the alkene S2d (1 equiv.). The reaction is stirred at room temperature under nitrogen with TLC being used to monitor the reaction. When no starting material is evident by TLC, The reaction

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is quenched with brine and is extracted with ethyl acetate and hexanes in a 4:1 ratio. The organic layer is washed with brine to neutral pH, dried over sodium sulfate, and concentrated. After column chromatography, (7:3, Hexane: Ethyl Acetate) S2a is obtained.

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e. Methyl 7-(5-(3-hydroxy-3-thianaphthyl-propenyl)-2,4-di(1,1,2,2-tetramethyl-1-ellapropoxy) cyclopentyl) heptanoate S2f: The aldehyde S2e is dissolved in a few mL of dry THF and is added dropwise to a -78 °C THF solution of the lithium anion of thianaphthylene (prepared by combining *n*-butyl lithium and thianaphthylene at -78°C.) in a 50 mL round-bottomed flask. This is stirred until the reaction has ceased to progress as evidenced by TLC. Then the reaction is quenched at -78 °C with a saturated solution of ammonium chloride and is extracted with ethyl acetate and hexanes in a 4:1 ratio. The organic layer is washed with brine to neutral pH, dried over sodium sulfate, and concentrated. After column chromatography, (7:3, Hexane: Ethyl Acetate) S2f is obtained.

f. 13,14-dihydro-15-(thianaphthyl)-15-pentanor prostaglandin F_{1α} (S2g): To a small round-bottomed flask, is added methyl ester S2f and 3 mL of CH₃CN and 0.1 mL of HF/Pyridine (0.1 mmol, 1 equiv.) are added while the flask is warmed from 0°C to room temperature. After 3 hours at 21°C, the reaction is quenched with saturated aqueous NaCl. The aqueous layer is extracted three times with CH₂Cl₂. The organic layers are combined and washed three times with 1N HCl, brine, and dried (Na₂SO₄). After column chromatography, (7:3, Hexane: Ethyl Acetate) a clear oil is obtained. This oil is added to a few mL of a 3:1 THF: water solution, and the flask is cooled to 0°C. An excess amount (2.5 equiv.) of lithium hydroxide is added, the ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, the aqueous layer is washed 3 times with methylene chloride, the organic layers are combined and washed with brine, dried (Na₂SO₄), concentrated *in vacuo*, and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide S2g.

Examples 2-22

Examples 2-22 are prepared using substantially the same procedures as those described in Example 1, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All

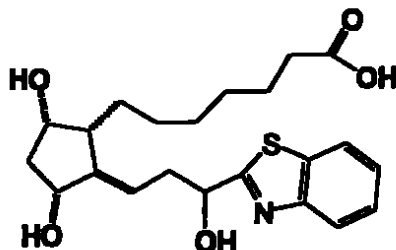
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such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

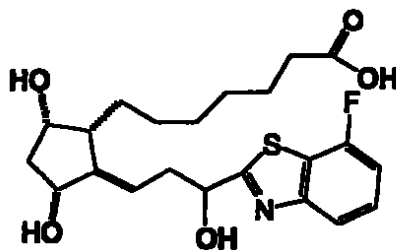
Example 2

5 **13,14-dihydro-15-(2-benzathiazolyl)-15-pentanor Prostaglandin F_{1α}**



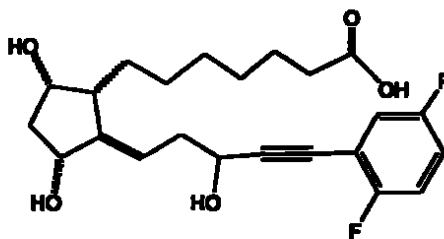
Example 3

10 **13,14-dihydro-15-(7-fluorobenzathiazolyl)-15-pentanor Prostaglandin F_{1α}**



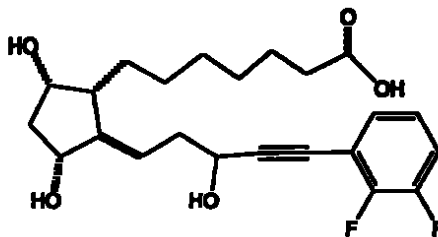
Example 4

15 **13,14-dihydro-16-ynyl-17-(2,5-difluorophenyl)-17-trinor Prostaglandin F_{1α}**



Example 5

20 **13,14-dihydro-16-ynyl-17-(2,3-difluorophenyl)-17-trinor Prostaglandin F_{1α}**



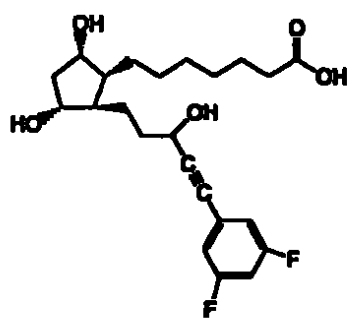
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Example 6

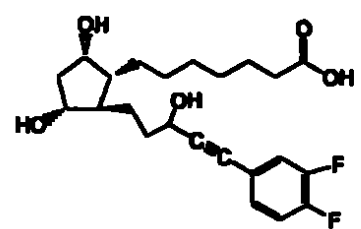
13,14-dihydro-16-ynyl-17-(3,5-difluorophenyl)-17-trinor Prostaglandin F_{1α}



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Example 7

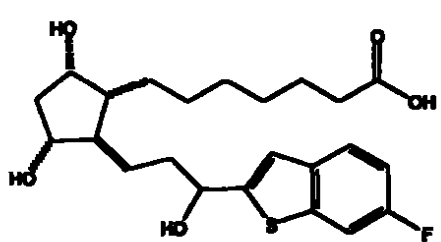
13,14-dihydro-16-ynyl-17-(3,4-difluorophenyl)-17-trinor Prostaglandin F_{1α}



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Example 8

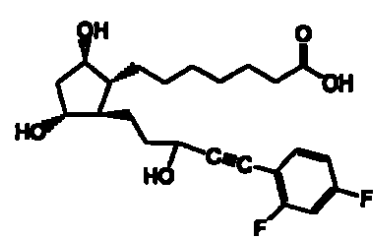
13,14-dihydro-16-(6-fluorothianaphthyl)-15-pentanor Prostaglandin F_{1α}



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Example 9

13,14-dihydro-16-ynyl-17-(2,4-difluorophenyl)-17-trinor Prostaglandin F_{1α}



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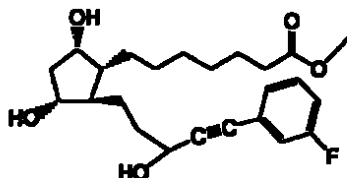
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Example 10

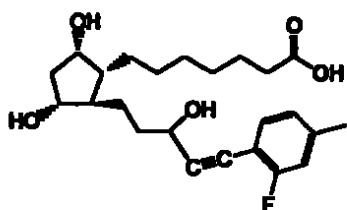
13,14-dihydro-16-ynyl-17-(3-fluorophenyl)-17-trinor Prostaglandin F1 α methyl ester



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Example 11

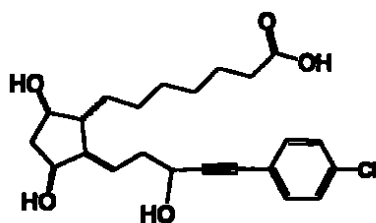
13,14-dihydro-16-ynyl-17-(2-fluoro-4-methylphenyl)-17-trinor Prostaglandin F1 α



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Example 12

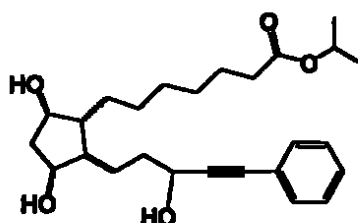
13,14-dihydro-16-ynyl-17-(4-chlorophenyl)-17-trinor Prostaglandin F1 α



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Example 13

13,14-dihydro-16-ynyl-17-phenyl-17-trinor Prostaglandin F1 α isopropyl ester



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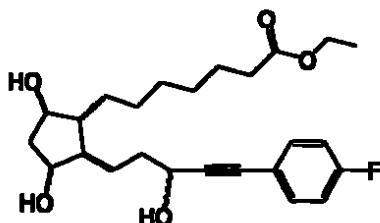
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Example 14

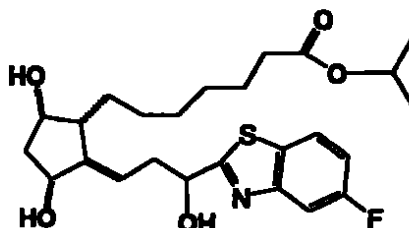
13,14-dihydro-16-ynyl-17-(4-fluorophenyl)-17-trinor Prostaglandin F1 α ethyl ester



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Example 15

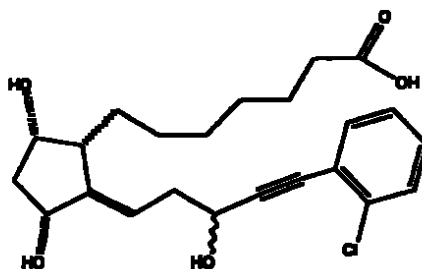
13,14-dihydro-15-(5-fluorobenzothiazolyl)-15-pentanor Prostaglandin F1 α isopropyl ester



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Example 16

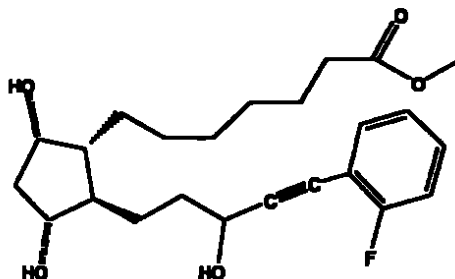
13,14-dihydro-16-ynyl-17-(2-chlorophenyl)-17-trinor Prostaglandin F1 α



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Example 17

13,14-dihydro-16-ynyl-17-(2-fluorophenyl)-17-trinor Prostaglandin F1 α methyl ester

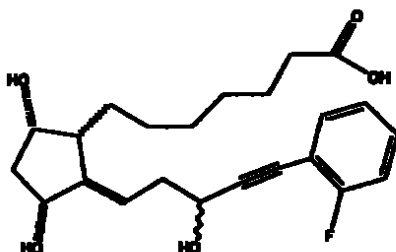


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Example 18

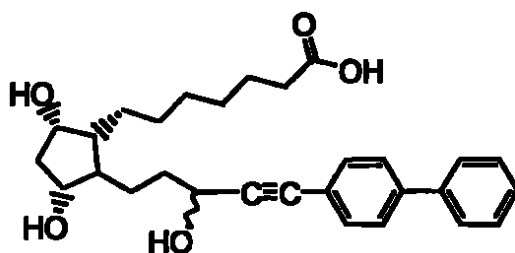
13,14-dihydro-16-ynyl-17-(2-fluorophenyl)-17-trinor Prostaglandin F1 α



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Example 19

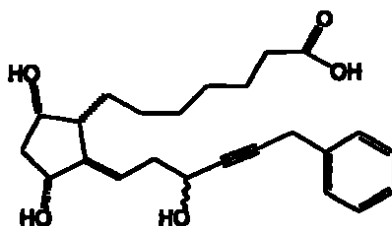
13,14-dihydro-16-ynyl-17-(4-phenylphenyl)-17-trinor Prostaglandin F1 α



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Example 20

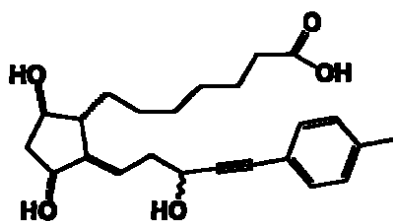
13,14-dihydro-16-ynyl-18-phenyl-18-dinor Prostaglandin F1 α



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Example 21

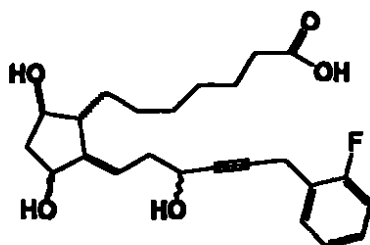
13,14-dihydro-16-ynyl-17-(4-methylphenyl)-17-trinor Prostaglandin F1 α



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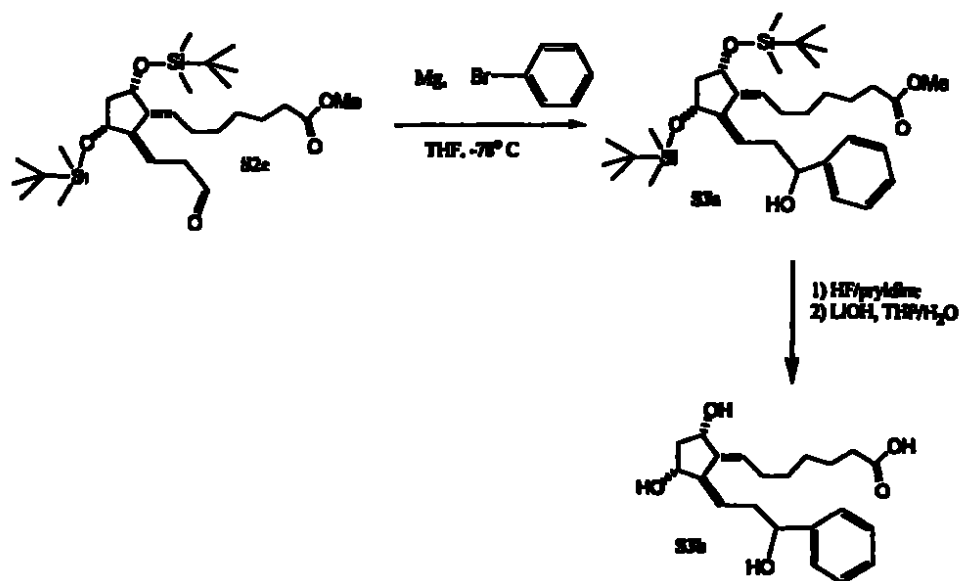
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13,14-dihydro-16-ynyl-18-(2-fluorophenyl)-18-dinor Prostaglandin F1 α



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Preparation of 13,14-dihydro-15-phenyl-15-pentanor prostaglandin F_{1α} :



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a. Methyl 7-(5-(3-hydroxy,3-phenyl-propanyl)-2,4-dl(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate S3a: The aldehyde S2e from Example 1 is dissolved in a few mL of dry THF and is added dropwise to a -78 °C THF solution of the Grignard species (prepared by combining Magnesium and bromobenzene at 0°C.) a 50 mL round-bottomed flask. This is stirred until the reaction has ceased to progress as evidenced by TLC. Then the reaction is quenched at -78 °C with a saturated solution of ammonium chloride and is extracted with ethyl acetate and hexanes in a 4:1 ratio. The organic layer is washed with brine to neutral pH, dried over sodium sulfate, and concentrated. After column chromatography, (7:3, Hexane: Ethyl Acetate) S3a is obtained.

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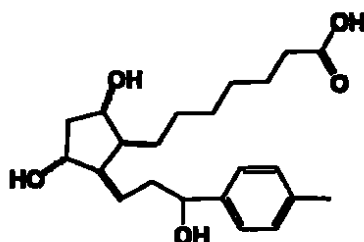
- b. 13,14-dihydro-15-phenyl-15-pentanor prostaglandin F_{1α} (S3b): To a small round-bottomed flask, is added methyl ester S3a and 3 mL of CH₃CN and 0.1 mL of HF/Pyridine (0.1 mmol, 1 equiv.) are added while the flask is warmed from 0°C to room temperature. After 3 hours at 21°C, the reaction is quenched with saturated aqueous NaCl. The aqueous layer is extracted three times with CH₂Cl₂. The organic layers are combined and washed three times with 1N HCl, brine, and dried (Na₂SO₄). After column chromatography, (97:3, dichloromethane:methanol) a clear oil is obtained. This oil is added to a few mL of a 3:1 THF: water solution, and the flask is cooled to 0°C. An excess amount (2.5 equiv.) of lithium hydroxide is added, the ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, the aqueous layer is washed 3 times with methylene chloride, the organic layers are combined and washed with brine, dried (Na₂SO₄), concentrated *in vacuo*, and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide S3b.

Examples 24-35

- Examples 24-35 are prepared using substantially the same procedures as those described in Example 23, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

Example 24

13,14-dihydro-15-(4-methylphenyl)-15-pentanor Prostaglandin F_{1α}

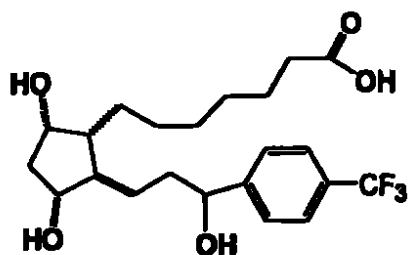


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Example 25

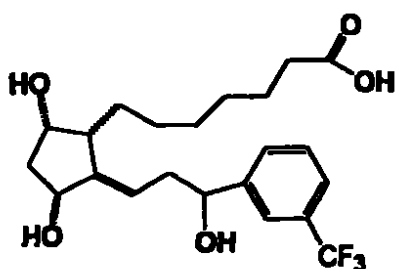
13,14-dihydro-15-(4-trifluoromethylphenyl)-15-pentanor Prostaglandin F_{1α}



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Example 26

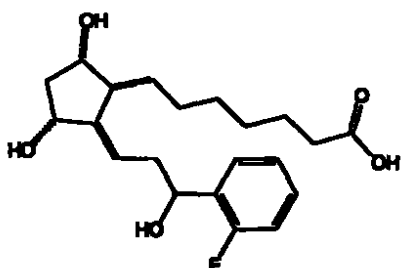
13,14-dihydro-15-(3-trifluoromethylphenyl)-15-pentanor Prostaglandin F_{1α}



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Example 27

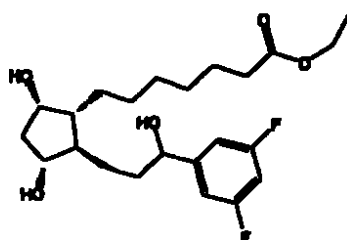
13,14-dihydro-15-(2-fluorophenyl)-15-pentanor Prostaglandin F_{1α}



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Example 28

13,14-dihydro-15-(3,5 difluorophenyl)-15-pentanor Prostaglandin F_{1α} ethyl ester

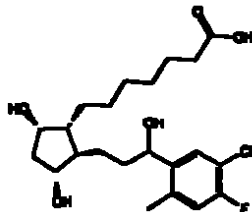


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Example 29

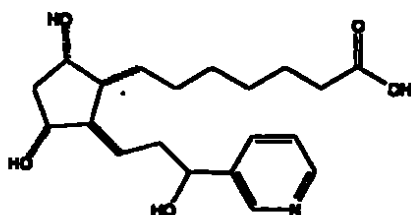
13,14-dihydro-15-(3-chloro-4-fluoro-6-methylphenyl)-15-pentanor
Prostaglandin F_{1α}



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Example 30

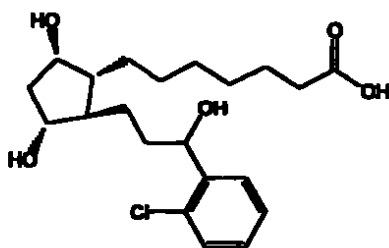
13,14-dihydro-15-(3-pyridinyl)-15-pentanor Prostaglandin F_{1α}



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Example 31

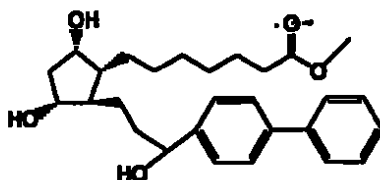
13,14-dihydro-15-(2-chlorophenyl)-15-pentanor Prostaglandin F_{1α}



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Example 32

13,14-dihydro-15-(4-phenylphenyl)-15-pentanor Prostaglandin F_{1α}



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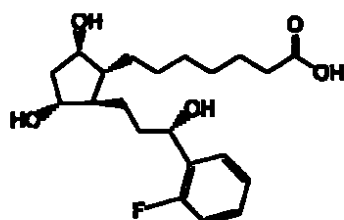
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Example 33

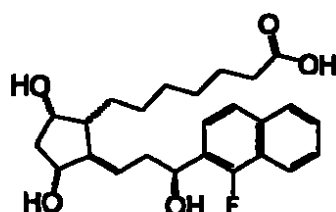
13,14-dihydro-15-S- (2-fluorophenyl)-15-pentanor Prostaglandin F_{1α}



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Example 34

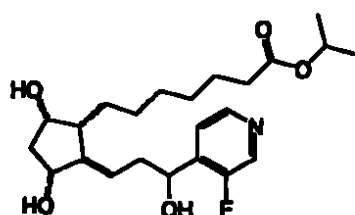
13,14-dihydro-15-S- (2-fluoronaphthyl)-15-pentanor Prostaglandin F_{1α}



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Example 35

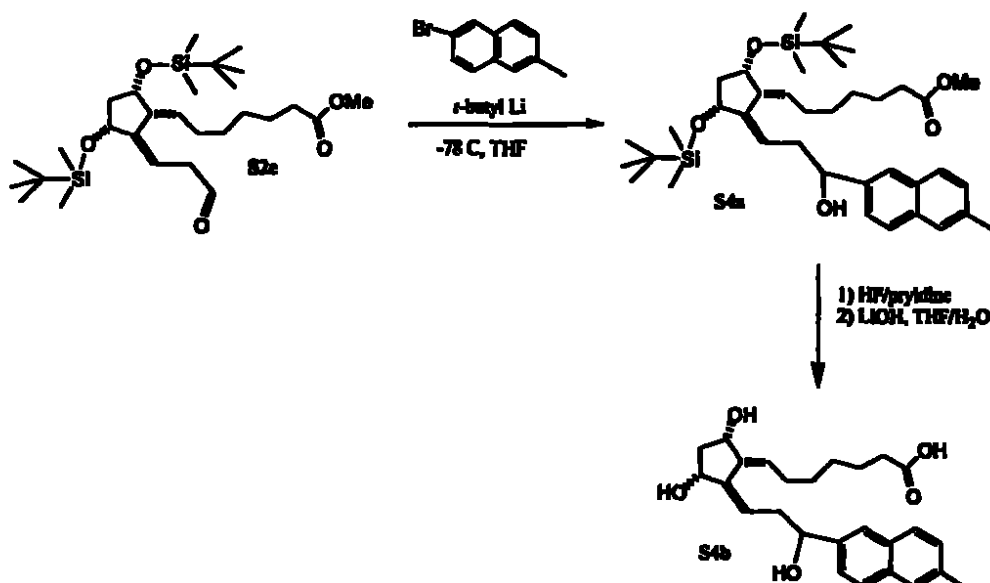
**13,14-dihydro-15- (2-fluoro-4-pyridyl)-15-pentanor Prostaglandin F_{1α}
isopropyl ester**



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Example 36

Preparation of 13,14-dihydro-15-(6-methylnaphth-2-yl)-15-pentanor
prostaglandin F_{1α} :



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- a. Methyl 7-(5-(3-hydroxy,(4-methyl-2-naphthyl)-propanyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate S4a: The aldehyde S2e from Example 1 is dissolved in a few mL of dry THF and is added dropwise to a -78 °C THF solution of naphthyl anion (prepared by t-butyl Lithium and the naphthyl bromide at -78°C.) a 50 mL round-bottomed flask. This is stirred until the reaction has ceased to progress as evidenced by TLC. Then the reaction is quenched at -78 °C with a saturated solution of ammonium chloride and is extracted with ethyl acetate and hexanes in a 4:1 ratio. The organic layer is washed with brine to neutral pH, dried over sodium sulfate, and concentrated. After column chromatography, (7:3, Hexane: Ethyl Acetate) S4a is obtained.
- b. 13,14-dihydro-15,17-dehydro-15-(6-methyl-2-naphthyl)-15-pentanor prostaglandin F_{1α} (S4b): To a small round-bottomed flask, is added methyl ester S4a and 3 mL of CH₃CN and 0.1 mL of HF/Pyridine (0.1 mmol, 1 equiv.) are added while the flask is warmed from 0°C to room temperature. After 3 hours at 21°C, the reaction is quenched with saturated aqueous NaCl. The aqueous layer is extracted three times with CH₂Cl₂. The organic layers are combined and washed three time with 1N HCl, brine, and dried (Na₂SO₄). After

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column chromatography, (97:3,dichlormethane:methanol) a clear oil is obtained. This oil is added to a few mL of a 3:1 THF: water solution, and the flask is cooled to 0°C. An excess amount (2.5 equiv.) of lithium hydroxide is added, the ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, the aqueous layer is washed 3 times with methylene chloride, the organic layers are combined and washed with brine, dried (Na₂SO₄), concentrated *in vacuo*, and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide S4b.

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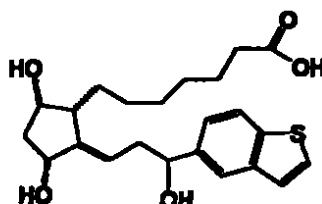
Examples 37-42

Examples 37-42 are prepared using substantially the same procedures as those described in Example 36, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

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Example 37

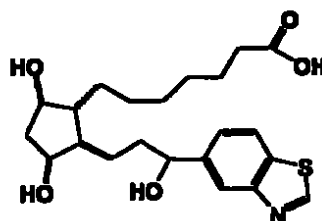
13,14-dihydro-15-(benzo[b]thiophen-5-yl)-15-pentanor prostaglandin F_{1α}



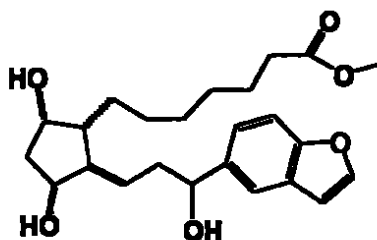
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Example 38

13,14-dihydro-15-(6-benzothiazol-5-yl)-15-pentanor prostaglandin F_{1α}

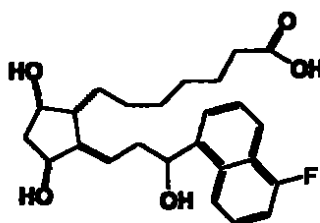


13,14-dihydro-15-(benzo[b]furan-5-yl)-15-pentanor prostaglandin F_{1α} methyl ester



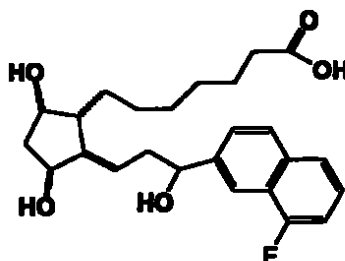
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13,14-dihydro-15-(5-fluoronaphthyl)-16-pentanor prostaglandin F_{1α}



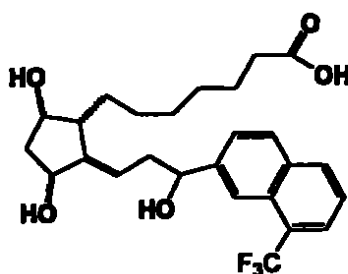
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13,14-dihydro-15-(8-fluoro-2-naphthyl)-15-pentanor prostaglandin F_{1α}



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**13,14-dihydro-15-(8-trifluoromethyl -2-naphthyl)-15-pentanor prostaglandin
F_{1α}**



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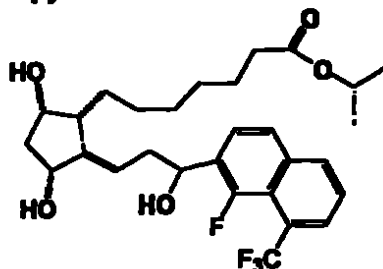
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Example 43

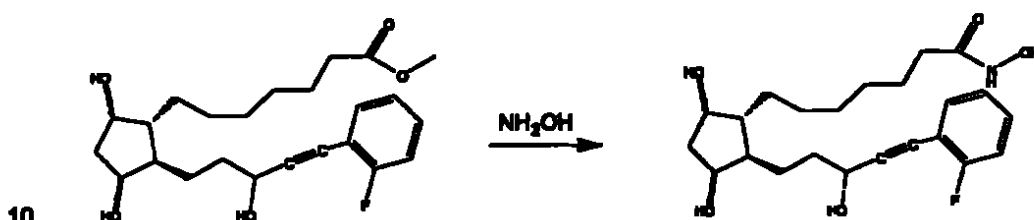
**13,14-dihydro-15-(1-fluoro-3-trifluoromethyl-2-naphthyl)-15-pentanor
prostaglandin F_{1α} isopropyl ester**



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Example 44

**Preparation of 13,14-dihydro-16-ynyl-17-(2-fluorophenyl)-17-trinor
Prostaglandin F_{1α} 1-hydroxamic acid:**



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In a flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar is placed 13,14-dihydro-16,17-didehydro-17-o-fluorophenyl trinor Prostaglandin F_{1α} methyl ester (Example 17) (1.0 equiv.) in methanol. To this solution is added hydroxylamine in methanol (1.25 equiv.). The solution stirred for a few minutes. The solution is then treated with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by chromatography to give 13,14-dihydro-16,17-didehydro-17-o-fluorophenyl trinor Prostaglandin F_{1α} 1-hydroxamic acid.

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Examples 45-47

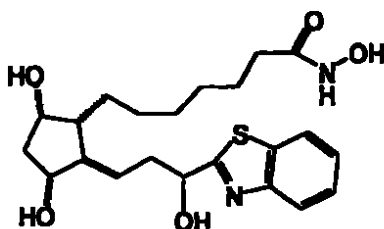
Examples 45-47 are prepared using substantially the same procedures as those described in Example 44, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

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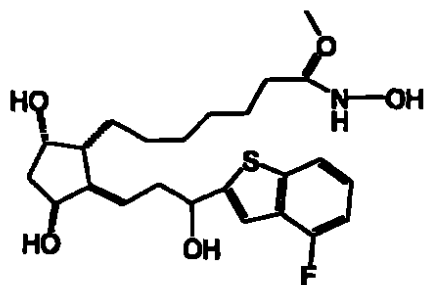
החברות המצטרפות הן:

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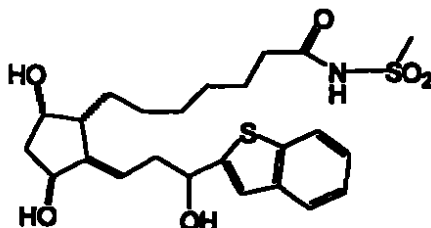
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Compositions of the subject invention comprise a safe and effective amount of the subject compounds, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of a compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular

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pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a subject. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the subject being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents, excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a compound is basically determined by the way the compound is to be administered. The compounds of the present invention may be administered systemically. Routes of administration include transdermal; oral; parenterally, including subcutaneous or intravenous injection; topical; and/or intranasal.

The appropriate amount of the compound to be used may be determined by routine experimentation with animal models. Such models include, but are not limited to the intact and ovariectomized rat models, the ferret, canine, and non human primate models as well as disease models.

Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Suitable carriers for injection or surgical implants

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The compounds of the present invention are also useful in decreasing intraocular pressure. Thus, these compounds are useful in the treatment of glaucoma. The preferred route of administration for treating glaucoma is topically.

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Composition and Method Examples

The following non-limiting examples illustrate the subject invention. The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions and methods of the invention. In each case other compounds within the invention may be substituted for the example compound shown below with similar results. The skilled practitioner will appreciate that the examples provide guidance and may be varied based on the condition being treated and the patient.

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Example A

Pharmaceutical compositions in the form of tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

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<u>Ingredient</u>	<u>Quantity (mg per tablet)</u>
Compound of Example 1	5
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

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When administered orally once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

Example B

Pharmaceutical compositions in liquid form are prepared by conventional methods, formulated as follows:

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<u>Ingredient</u>	<u>Quantity</u>
Compound of Example 32	1 mg
Phosphate buffered physiological saline	10 ml
Methyl Paraben	0.05ml

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When 1.0 ml of the above composition is administered subcutaneously once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

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Example C

Topical pharmaceutical compositions for lowering intraocular pressure are prepared by conventional methods and formulated as follows:

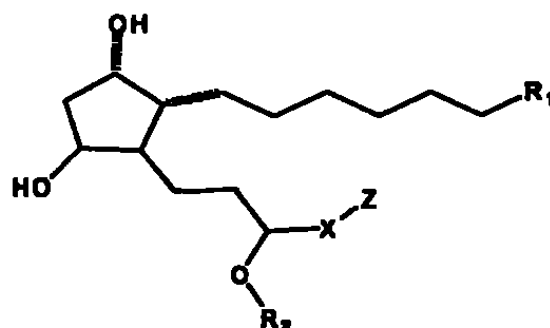
	<u>Ingredient</u>	<u>Amount (wt %)</u>
5	Compound of Example 1	0.004
	Dextran 70	0.1
	Hydroxypropyl methylcellulose	0.3
	Sodium Chloride	0.77
	Potassium chloride	0.12
10	Disodium EDTA (Edetate disodium)	0.05
	Benzalkonium chloride	0.01
	HCL and/or NaOH	pH 7.2-7.5
	Purified water	q.s. to 100%

15 While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this
20 invention.

WHAT IS CLAIMED IS:

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- 1. A compound having the structure:**

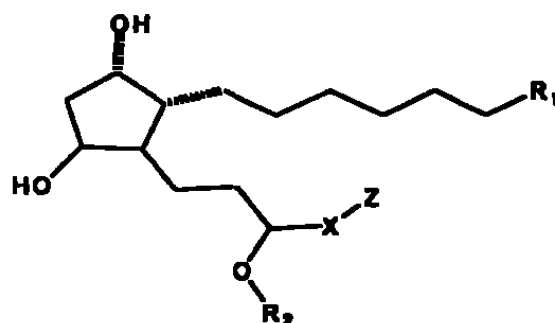


wherein

- 5 (a) R_1 is selected from the group consisting of CO_2H , $C(O)NHOH$, CO_2R_3 , CH_2OH , $S(O)_2R_3$, $C(O)NHR_3$, $C(O)NHS(O)_2R_4$, and tetrazole; wherein R_3 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring; and R_4 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring,
10 monocyclic aromatic ring, or monocyclic heteroaromatic ring;
- (b) R_2 is H or lower alkyl;
- (c) X is:
- (1) $C\equiv C$, or
- (2) a covalent bond;
- 15 (d) Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring and X is a covalent bond, Z is attached to C_{15} via a Carbon member atom; and
- (e) any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or
20 imide thereof.
2. The compound of Claim 1 wherein X is $C\equiv C$.
3. The compound of Claim 2 wherein R_1 is CO_2H , $C(O)NHOH$, CO_2R_3 , $C(O)NHS(O)_2R_4$, or tetrazole.
- 25 4. The compound of Claim 3 wherein Z is monocyclic.
5. The compound of Claim 4 wherein Z is selected from the group consisting of: phenyl, thienyl, and furanyl.
6. The compound of Claim 5 wherein Z substituted with one substituent, said one substituent being selected from the group consisting of: lower alkyl, halo, and haloalkyl.
- 30 7. The compound of Claim 5 wherein R_2 is H.
8. The compound of Claim 7 wherein R_1 is CO_2H or CO_2R_3 .
9. The compound of Claim 1 wherein X is a covalent bond.

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10. The compound of Claim 9 wherein R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_3 , $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_4$, or tetrazole.
11. The compound of Claim 10 wherein Z is a bicyclic heteroaromatic ring.
12. The compound of Claim 11 wherein Z is selected from the group consisting of: benzo[β]thiazolyl, benzo[β]thiophenyl, and benzoxazolyl.
13. The compound of Claim 12 wherein Z substituted with one substituent, said one substituent being selected from the group consisting of: lower alkyl, halo, and haloalkyl.
14. The compound of Claim 12 wherein R_2 is H.
15. The compound of Claim 14 wherein R_1 is CO_2H or CO_2R_3 .
16. A method of treating a human or other animal subject having a bone disorder, said method comprising administering to said subject a compound according to the structure:



wherein

- (a) R_1 is selected from the group consisting of CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_3 , CH_2OH , $\text{S}(\text{O})_2\text{R}_3$, $\text{C}(\text{O})\text{NHR}_3$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_4$, and tetrazole; wherein R_3 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring; and R_4 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring;

(b) R_2 is H or lower alkyl;

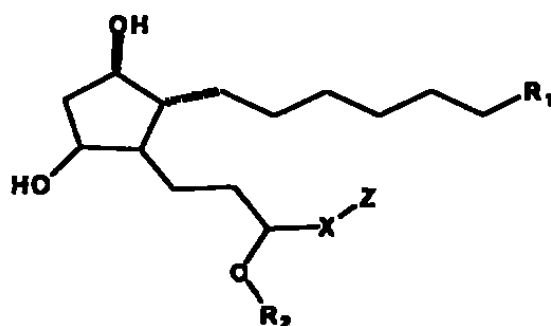
(c) X is:

- (1) $\text{C}=\text{C}$, or
(2) a covalent bond;

(d) Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring and X is a covalent bond, Z is attached to C_{15} via a Carbon member atom; and

(e) any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

17. The method of Claim 16 wherein said bone disorder is osteoporosis.
 18. The method of claim 17 wherein in osteoporosis is post-menopausal.
 19. The method of claim 17 wherein in osteoporosis is cortico-steroid induced.
 20. The method of claim 16 wherein said bone disorder is osteopenia.
 5 21. The method of claim 16 wherein said bone disorder is a bone fracture.
 22. The method of claim 16 wherein said compound is administered orally.
 23. The method of claim 16 wherein said compound is administered transdermally.
 24. The method of claim 16 wherein said compound is administered intranasally.
 10 25. A method of treating glaucoma, said method comprising administering to a human or other animal a safe and effective amount of a compound according to the structure:



15 wherein

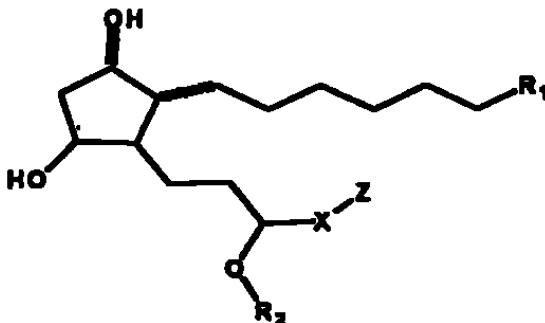
- (a) R_1 is selected from the group consisting of CO_2H , $C(O)NHOH$, CO_2R_3 , CH_2OH , $S(O)_2R_3$, $C(O)NHR_3$, $C(O)NHS(O)_2R_4$, and tetrazole; wherein R_3 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring; and R_4 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring;
 20 (b) R_2 is H or lower alkyl;
 (c) X is:
 (1) $C\equiv C$, or
 25 (2) a covalent bond;
 (d) Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring and X is a covalent bond, Z is attached to C_{13} via a Carbon member atom; and
 (e) any optical isomer, diastereomer, enantiomer of the above structure or a
 30 pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.
 26. The method of Claim 25 wherein said compound is administered topically.

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C₁₆ UNSATURATED FP-SELECTIVE PROSTAGLANDINS ANALOGS

Abstract Of The Invention

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to the following formula:



wherein R₁, R₂, X, and Z are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, bihydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders using these compounds or the compositions containing them.

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"Express Mail" mailing label number 8-000000000000

Date of Deposit March 8, 1999

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 39 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20521

James C. Sullivan 758 278

Attorney-in-fact 758 278

Signature of Attorney-in-fact

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 137

Radicación no 00-16012

Concepto Técnico no 276

Clasificación Internacional de Patentes A61K 31/557

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 488 se determinó que esta solicitud de Patente de Invención:

- | | | |
|--|--|--|
| SI ☒ | NO ☐ | Contiene un resumen de la invención (Art.26-e). |
| SI ☒ | NO ☐ | Contiene el título o nombre de la invención (Art.27-d). |
| SI ☒ | NO ☐ | Contiene la descripción de la invención (Art.28-b). |
| SI ☒ | NO ☐ | NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d) |
| SI ☒ | NO ☐ | Contiene una o más reivindicaciones. (Art.28-c). |
| SI ☐ | NO ☐ | NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 28- h). |
| SI ☐ | NO ☐ | NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes. (Art.28-i). |
| SI ☐ | NO ☒ | La invención se refiere a un producto relativo a un material biológico. (Art.28-j). |
| SI ☒ | NO ☐ | La prioridad coincide con la materia reivindicada. |
| SI ☒ | NO ☐ | CUMPLE LOS REQUISITOS TÉCNICOS |

OBSERVACIONES Y OTROS: SI ☒ NO ☐ ver hoja(s) anexa(s)

1. Se anexa artes 12x12cm y 6x6cm folios 73-75
2. Se anexa tarjetos de archivo temático y de Propietarios folios 76 y 77.

EXAMINADOR TÉCNICO

202038

Bogotá D. C., febrero 28/02

Folio 138

2020
Bogotá, D.C.

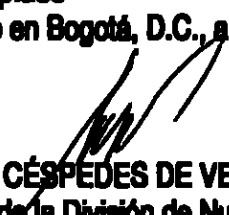
Doctor(a)
JIMENA ESCOBAR URIBE
Apoderado(a)

REFERENCIA:	Radicación No.	00-16012
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	410
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la comunidad andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá, D.C., a los

11 MAR. 2002


ALIX CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, D.C., *Sept-2001* El extracto de esta solicitud fue publicado en el número 516 de la Gaceta de Propiedad Industrial, de fecha *30-05-2002*. El término hábil señalado por la ley expiró el *29-08-02* y SI NO *X* se presentaron oposiciones por parte de terceros.

202038

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: info@slc.gov.co
Bogotá, D.C., Colombia

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-10012

EDICTO No. 18262

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió Resolución No. 29809 de 30-NOV-2004. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

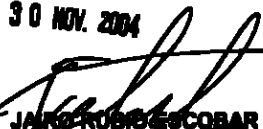
ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Jimena Escobar Uribe, o a quien haga sus veces, quien actúa como apoderada de The Procter & Gamble Company., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los

30 NOV. 2004

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 14-DIC-2004
Secretaría General Ad-Hoc
EDICTO No. 18262

Este edicto se desfija hoy 27-DIC-2004 a las cinco (5:00 p.m.)



