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ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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SUPERINDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00016015
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 60/122,929 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: 60/122,929

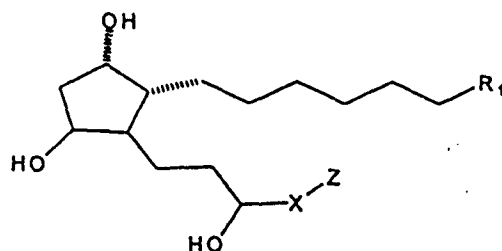
Fecha de Presentación: Marzo 05, 1999

Por la autoridad del
Comisionado de Patentes y Marcas

(fdo) L. EDELEN
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América.

LO QUE SE REIVINDICA ES :

1. Un compuesto que tiene la estructura :



donde

(a) R_1 es seleccionado del grupo consistente de CO_2H , C(O)NHOH , CO_2R_2 , CH_2OH , $\text{S(O)}_2\text{R}_2$, C(O)NHR_2 , $\text{C(O)NHS(O)}_2\text{R}_2$ o tetrazol ; donde R_2 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico y R_3 es alquilo inferior, heteroalquilo inferior o haloalquilo. El R_2 preferido es metilo, etilo e isopropilo ;

(b) X es :

(1) $\text{CH}=\text{C}=\text{CH}$

(2) $\text{CH}=\text{CH}$

(3) $\text{CH}=\text{N}$

(4) C(O)

(5) C(O)Y ; donde Y es seleccionada del grupo consistente de O, S y NH ;

(c) Z es un anillo aromático o un anillo heteroaromático a condición que cuando Z es un anillo heteroaromático, Z esté unida mediante un miembro átomo de Carbono ; y

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

2. El compuesto de la Reivindicación 2, donde R_1 es CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_2 , $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_2$ o tetrazol.

3. El compuesto de la Reivindicación 2, donde X es $\text{CH}=\text{C}=\text{CH}$ ó $\text{C}(\text{O})\text{Y}$.

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 la Reivindicación 5, donde Z es sustituido con un sustituyente, siendo dicho sustituyente seleccionado del grupo consistente de : alquilo inferior, halo y haloalquilo.

7. El compuesto de la Reivindicación 7, donde R_1 es CO_2H ó CO_2R_2 .

8. El compuesto de la Reivindicación 2, donde X es $\text{CH}=\text{CH}$, $\text{CH}=\text{N}$ ó $\text{C}(\text{O})$.

9. El compuesto de la Reivindicación 8, donde Z es bicíclico.

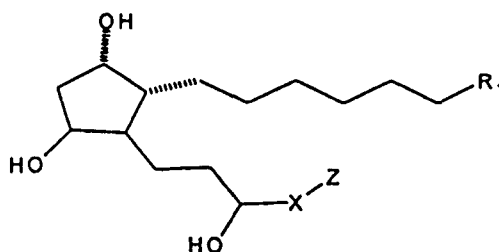
10. El compuesto de la Reivindicación 9, donde Z es un anillo heteroaromático bicíclico.

11. El compuesto de la Reivindicación 10, donde Z es seleccionado del grupo consistente de: benzo[β]tiazolilo, benzo[β]tiofenilo y benzoxazolilo.

12. El compuesto de la Reivindicación 11, donde Z es sustituido con un sustituyente, siendo dicho sustituyente seleccionado del grupo consistente de: alquilo inferior, halo y haloalquilo.

13. El compuesto de la Reivindicación 12, donde R_1 es CO_2H ó CO_2R .

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



donde

(a) R_1 es seleccionado del grupo consistente de CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_2 , CH_2OH , $\text{S}(\text{O})_2\text{R}_2$, $\text{C}(\text{O})\text{NHR}_2$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_2$ o tetrazol; donde R_2 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo

heteroaromático monocíclico y R_3 es alquilo inferior, heteroalquilo inferior o haloalquilo. El R_2 preferido es metilo, etilo e isopropilo ;

(b) X es :

(1) $CH=C=CH$

(2) $CH=CH$

(3) $CH=N$

(4) $C(O)$

(5) $C(O)Y$; donde Y es seleccionada del grupo consistente de O, S y NH ;

(c) Z es un anillo aromático o un anillo heteroaromático a condición que cuando Z es un anillo heteroaromático, Z esté unida mediante un miembro átomo de Carbono ; y

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

15. El método de la Reivindicación 14, donde dicho desorden óseo es osteoporosis.

16. El método de la Reivindicación 15, donde es en osteoporosis post menopáusica.

17. El método de la Reivindicación 15, donde es en osteoporosis cortico esteroide inducida.

18. El método de la Reivindicación 14, donde dicho desorden óseo es osteopenia.

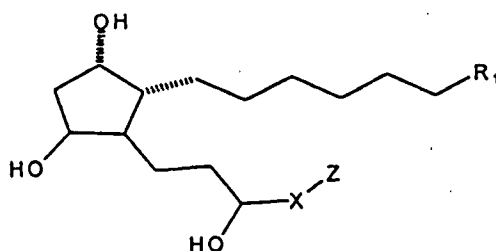
19. El método de la Reivindicación 14, donde dicho desorden óseo es una fractura de huesos.

20. El método de la Reivindicación 14, donde dicho compuesto es administrado oralmente.

21. El método de la Reivindicación 14, donde dicho compuesto es administrado transdérmicamente.

22. El método de la Reivindicación 14, donde dicho compuesto es administrado intranasalmente.

23. Un método para tratar glaucoma, dicho método comprende administrar a un humano u otro animal una cantidad segura y efectiva de un compuesto de acuerdo con la estructura :



donde

(a) R_1 es seleccionado del grupo consistente de CO_2H , C(O)NHOH , CO_2R_2 , CH_2OH , $\text{S(O)}_2\text{R}_2$, C(O)NHR_2 , $\text{C(O)NHS(O)}_2\text{R}_2$ o tetrazol ; donde R_2 es alquilo, heteroalquilo, anillo alifático carbocíclico, anillo alifático heterocíclico, anillo aromático monocíclico o anillo heteroaromático monocíclico y R_3 es alquilo inferior, heteroalquilo inferior o haloalquilo. El R_2 preferido es metilo, etilo e isopropilo ;

(b) X es :

(1) $\text{CH}=\text{C}=\text{CH}$

(2) $\text{CH}=\text{CH}$

(3) $\text{CH}=\text{N}$

(4) C(O)

(5) C(O)Y ; donde Y es seleccionada del grupo consistente de O, S y NH ;

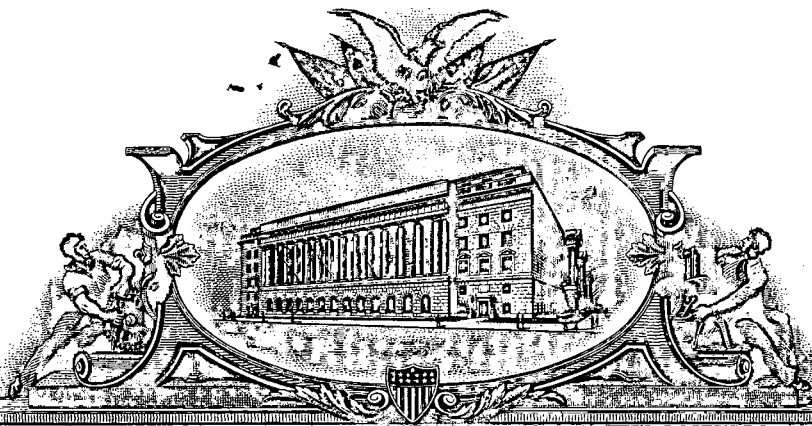
(c) Z es un anillo aromático o un anillo heteroaromático a condición que cuando Z es un anillo heteroaromático, Z esté unida mediante un miembro átomo de Carbono ; y

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

26. El método de la Reivindicación 25, donde dicho compuesto es administrado tópicamente.

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PA 203258



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: 60/122,929

FILING DATE: *March 05, 1999*



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

Date of Deposit March 5, 1999

I hereby certify that this paper/fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

James C. Kellerman
Attorney mailing application

Signature of Attorney mailing application

PTO/SB/16 (2/98)
Approved for use through 01/31/2001. OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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

Docket Number		7463P		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)	
deLong		Mitchell		A.		West Chester, OH	
Wos		John		A.		Cincinnati, OH	
De		Biswanath				Cincinnati, OH	
Soper		David		L.		Monroe, OH	
TITLE OF THE INVENTION (280 characters max)							
C ₁₆ 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: 47		☒ + 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 fees						PROVISIONAL FILING FEE AMOUNT(S)	
☒ The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number: 16-2480						\$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.

C₁₆ UNSATURATED FP-SELECTIVE PROSTAGLANDINS ANALOGS

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Mitchell deLong
John Wos
Biswanath De
David Soper

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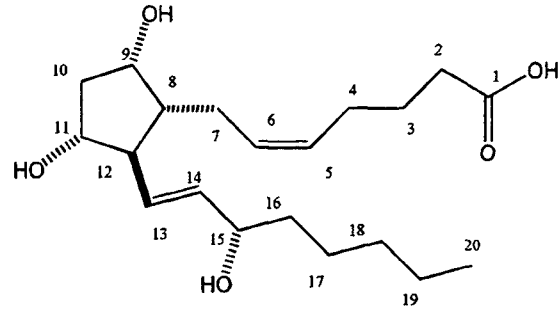
TECHNICAL FIELD

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

20

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 alicyclic 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:



25

PGF_{2α}

Analogues 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. 4,011,262 issued to Hess, Johnson, Bindra, and Schaaf 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. 93 (1993), 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. Resul, J. Sternschantz, and U. Hacksell, "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.

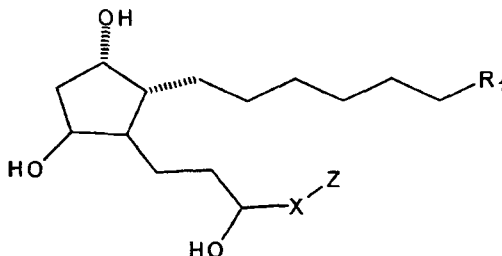
10 Naturally occurring prostaglandins are known to possess a wide range of pharmacological properties. For example, prostaglandins have been shown to: relax smooth muscle, which results in vasodilatation and bronchodilatation, to inhibit gastric acid secretion, to inhibit platelet aggregation, to reduce 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.

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:



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wherein R_1 , 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

20 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.

"Lower alkyl" is an alkyl chain comprised of 1 to 6, preferably 1 to 3 carbon atoms.

"Aromatic ring" is an aromatic hydrocarbon ring. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring system. Bicyclic aromatic rings include ring systems wherein one ring in the system is aromatic. Preferred bicyclic aromatic rings are ring systems wherein both rings in the system are aromatic. Aromatic 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 aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic. Carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Carbocyclic 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 carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic aliphatic rings include cyclohexyl, cycloheptyl, and cyclooctyl.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C₁-C₁₂; more preferred are C₁-C₆; more preferred still are C₁-C₃. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"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
5 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
10 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
15 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
20 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, quinolinyl, quinoxaliny, benzo[β]furanyl, benzimidazolyl, benzoxazolyl, indolyl, and anthranilyl. More preferred bicyclic heteroaromatic
25 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
30 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 radical attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic. Heterocyclic aliphatic rings contain from about 4 to about 10
35 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

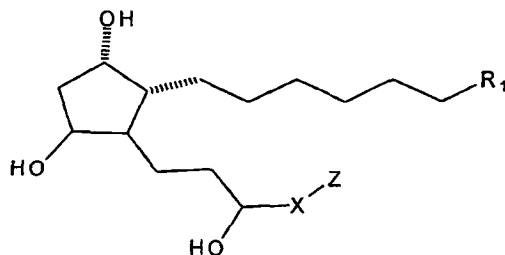
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haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"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 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*.

Compounds

The subject invention involves compounds having the following structure:



Formula A

In the above structure, R_1 is CO_2H , $C(O)NHOH$, CO_2R_2 , CH_2OH , $S(O)_2R_2$, $C(O)NHR_2$, $C(O)NHS(O)_2R_2$, or tetrazole; wherein R_2 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring and R_3 is lower alkyl, lower heteroalkyl, or haloalkyl. Preferred R_2 is methyl, ethyl, and isopropyl. Preferred R_1 is CO_2H , $C(O)NHOH$, CO_2R_2 , $C(O)NHS(O)_2R_2$, and tetrazole. Most preferred R_1 is CO_2H and CO_2R_2 .

In the above structure, X is $CH=C=CH$, $CH=CH$, $CH=N$, $C(O)$, or $C(O)Y$; wherein Y is O , S , or NH . Preferred X is $CH=C=CH$, $CH=N$, $C(O)$, and $C(O)Y$. X is not part of an aromatic or heteroaromatic ring system.

In the above structure, Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring Z is attached via a Carbon member atom. Preferred Z is monocyclic aromatic ring. More preferred Z is furanyl, thienyl, and phenyl.

The invention also includes optical isomers, diastereomers and enantiomers of the above structure. Thus, at all stereocenters where

stereochemistry is not defined (C_{11} , C_{12} , and C_{15}), both epimers are envisioned. Preferred stereochemistry at all such stereocenters of the compounds of the invention mimic that of naturally occurring $PGF_{2\alpha}$.

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 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.

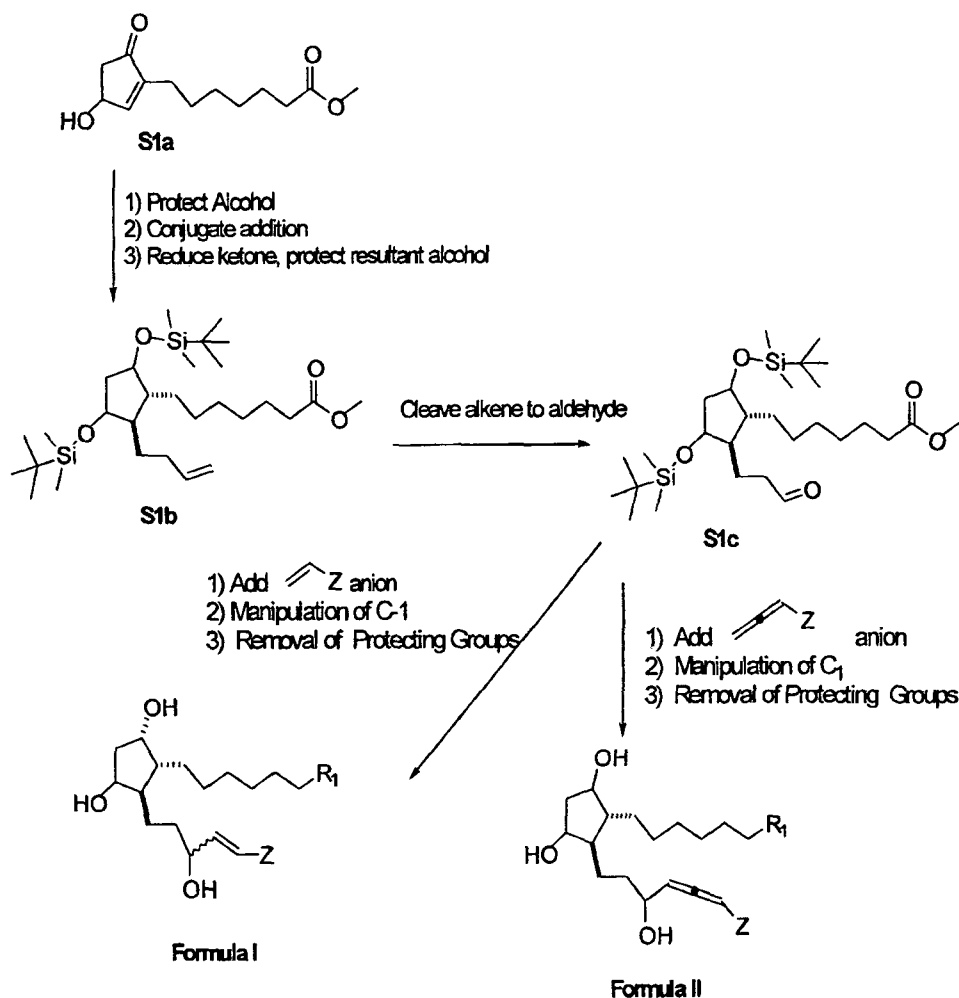
Pharmacological activity for glaucoma can be demonstrated using assays designed to test the ability of the subject compounds to decrease intraocular pressure. Examples of such assays are described in the following reference, incorporated herein: C. Iljebri, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17- Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ 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. Particularly preferred syntheses are carried out using the following general reaction schemes, **Schemes I, II, and III**. **Scheme I** describes a general reaction scheme for making compounds of the invention wherein X is $CH=CH$ (**Formula I**) or $CH=C=CH$ (**Formula II**). **Scheme II** describes a general reaction scheme for making compounds of the invention wherein X is $C(O)$ (**Formula III**) or $C(O)Y$ (**Formula IV**). **Scheme III** describes a

general reaction scheme for making compounds of the invention wherein X is CH=N (Formula V).

Scheme 1

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In Scheme 1, R_1 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).

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 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 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 one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the 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. 1460-69 ; and P. Knochel et. al., "Zinc and Copper Carbenoids as Efficient and Selective a/d' Multicoupling Reagents", J. Amer. Chem. Soc. Vol. 111 (1989) p. 6474-76. 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. 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, 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 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 reducing agents include lithium aluminum hydride, sodium borohydride, and L-

selectride. More preferred reducing agents include sodium borohydride, and L-selectride. The most preferred reducing agent is sodium borohydride. Preferred solvents include methanol, ethanol, and butanol. The most preferred solvent is methanol. The reduction is carried out at a temperature between -100°C and 23°C. The preferred temperature range is between -60°C and 0°C. The most preferred temperature range is between -45°C and -20°C.

The resulting alcohol 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 alcohol is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

The resultant alcohol can be protected as described previously herein. Preferred silylating agents in this case also include *tert*-butyldimethylsilyl chloride and *tert*-butyldimethylsilyl trifluoromethanesulfonate. The most preferred silylating agent is *tert*-butyldimethylsilyl trifluoromethanesulfonate. Preferred bases include 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 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, **S1b** 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 silyl ether is purified after isolation by distillation under vacuum, giving compound **S1b**.

The protected alcohol is then treated with a form of osmium and sodium periodate in a solvent where they are both soluble. Preferred forms of osmium include osmium tetroxide and potassium osmate. Preferred solvent systems include 1:1 mixtures of acetic acid and water and 1:1:2 mixtures of water, acetic acid and THF. The result of this treatment is the aldehyde, **S1c**.

The compound **S1c** 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, **S1c** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

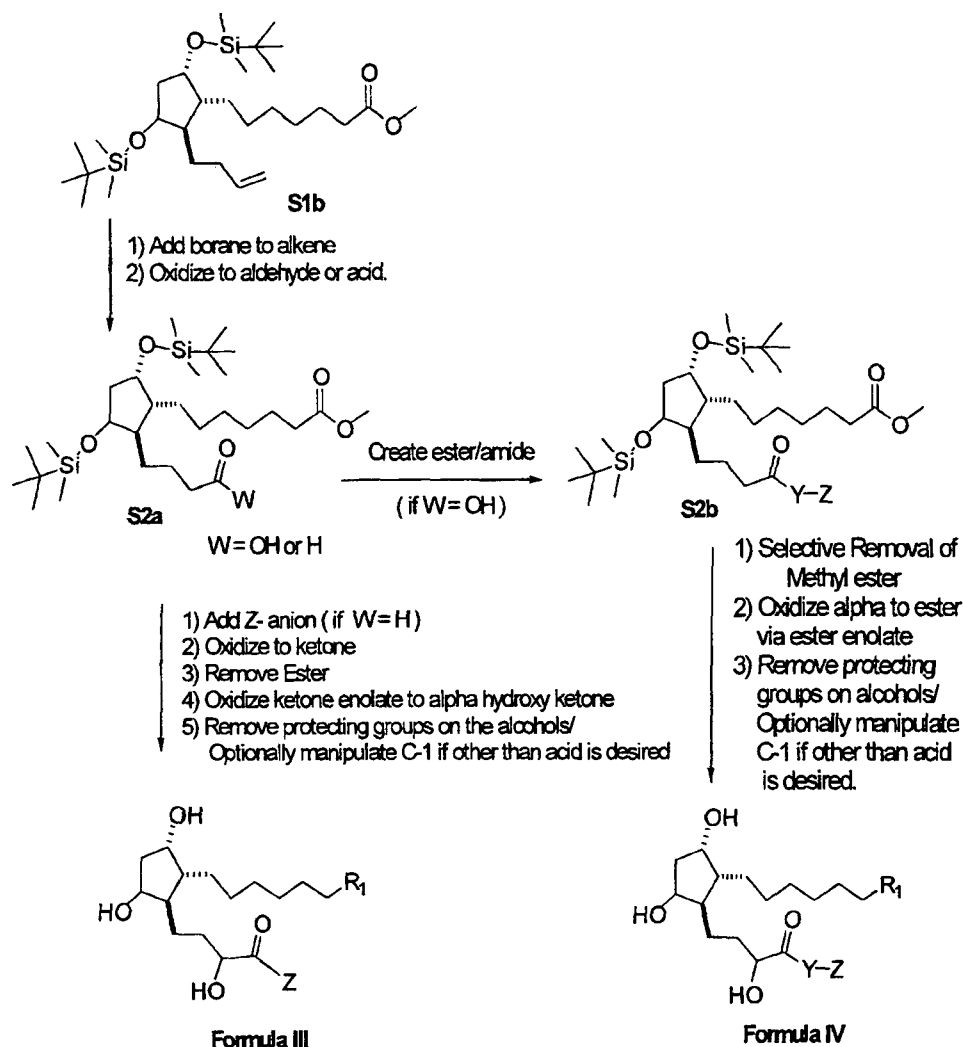
The key intermediate aldehyde depicted as **S1c** can be reacted with a variety of unsaturated alkenyl anion nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-prostaglandin F_{1α} derivatives.

The resulting compounds can be isolated, but are generally deprotected using techniques known to one of ordinary skill in the art, and optionally, manipulated at C-1 to provide the desired acid derivative at R₁. For example, the condensation of a methyl ester with an amine or a hydroxylamine provides an amide or a hydroxamic acid compound, respectively. After any such manipulation at C-1, the compounds are isolated as the final 13,14-dihydro-15-substituted-15-pentanor prostaglandin F_{1α} derivative, **Formula I**. Compounds depicted by **Formula I** are exemplified in **Examples 1-12, 18, and 20**.

Compounds depicted by **Formula II** can be made directly from intermediate **S1c** in a manner similar to that for compounds depicted by **Formula I** substituting the appropriate allene anion. With allene 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, and *t*-butyl lithium. The most preferred base is *n*-butyl lithium. 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. After isolation, similar C-1 manipulations and/or deprotection of the functional groups ensues using techniques known to one of ordinary skill in the art. Compounds depicted by **Formula II** are exemplified in **Examples 13-17 and 19**.

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Scheme II



- 5 In **Scheme 2**, R₁, Y, and Z are as defined above. The protected alcohol **S1b** (from **Scheme 1**) is treated with a hydroborating reagent in an ethereal solvent, followed by oxidative removal of the boron reagent with a suitable oxidant to give a compound of the type **S2a**. Preferred hydroborating reagents include monochloroborane-dimethylsulfide, diborane, borane-tetrahydrofuran and
- 10 borane-dimethylsulfide. The most preferred hydroborating reagent is borane-dimethylsulfide. Preferred ethereal solvents include THF and diethyl ether. The most preferred solvent is THF. The reaction is carried out from about 1 to about 24 hours at a temperature of from about -20 °C to about +30 °C. The preferred temperature range is from about 0 °C to about +20 °C. The hydroborated product of this reaction may then be oxidatively removed to the alcohol using alkaline
- 15 hydrogen peroxide (See *Boranes in Organic Chemistry*, H. C. Brown, Cornell

[illegible]

- Such salts include pyridinium chlorochromate (PCC) and dichlorochromate. See Brown, H. C.; Kulkarni, Rao, and Patil, *Tetrahedron*, 1986, 45515. The preferred method is treatment of the hydroborated product with PCC in dichloromethane at room temperature. The result of these manipulations is a compound of the type **S2a**.
- The compound **S2a** 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, **S2a** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent with 0.1% acetic acid added if W = OH.
- The key intermediate aldehyde depicted as **S2a** can be reacted with a variety unsaturated carbon nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin $F_{1\alpha}$ derivatives of **Formula III**.
- With aromatic and heteroaromatic 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, lithium diisopropylamide, and *t*-butyl lithium. The most preferred base is *n*-butyl lithium. 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 alcohol can be isolated, but is generally oxidized as a crude isolate. The oxidation of benzylic alcohols to benzylic ketones is well known in the art. The preferred reagents to effect this reaction include $KMnO_4$, MnO_2 , chromic acid, Jones' reagent, Collins' reagent, and PCC. The most preferred method is oxidation at room temperature in dichloromethane with PCC for about 4 hours. The ketones are isolated by column chromatography using 20% hexanes/ethyl acetate as solvent. The ester is then removed using standard conditions. See Greene and Wuts, *Protecting Groups in Organic Synthesis*, Wiley Interscience, NY pp.224-276. The free acid is then treated with 2.1 equivalents of a strong nitrogen base to effect deprotonation both of the acid and adjacent to the benzylic ketone. Such bases include LDA. This enolate is reacted with a peroxidizing agent which has the effect of oxidizing the compound to deliver the alpha-hydroxy ketone. Such

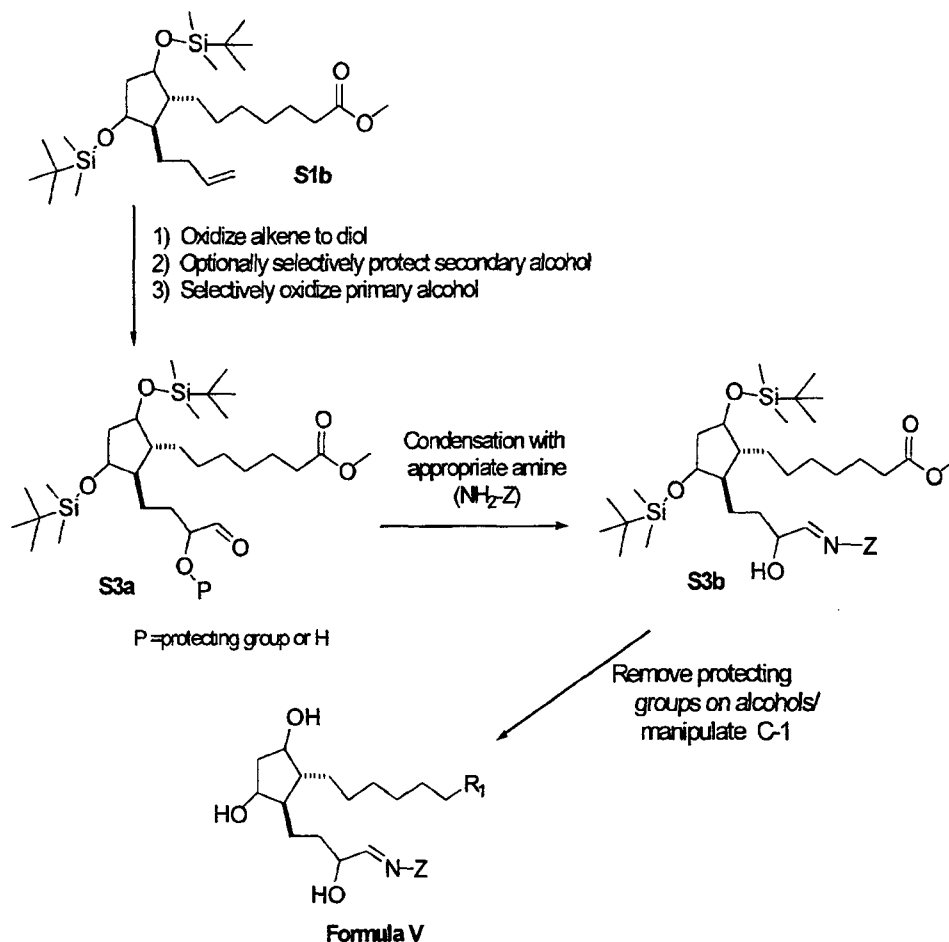
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reagents include *meta* -chloroperoxybenzoic acid, dimethyl dioxirane, Davis' reagent and peracetic acid. The crude product may be isolated or the remaining protecting groups may be removed. At this point manipulation of the acid at C-1 may take place. For example, re-esterifying, making the amide, the hydroxamic acid or the sulfonamide using methods known to one of ordinary skill in the art may be performed to yield compounds according to **Formula III**. Compounds depicted by **Formula III** are exemplified in **Examples 21-30**.

Compounds depicted by **Formula IV** can be made from intermediate **S2b**. In this case, condensation of the free acid is readily achieved with a variety of alcohols and amines, either by the use of coupling agents such as DCC, or by activating the acid with, for example, oxalyl chloride. Following this is the selective removal of the methyl esters as described in Greene and Wuts, *Protecting Groups in Organic Synthesis*, Wiley Interscience, NY pp.224-276, and the oxidation of the ester enolates using the same technique described above for the ketone intermediates. Similarly, as described above, the remaining protecting groups are removed and the desired manipulation of C-1 is effected, yielding compounds of **Formula IV**. Compounds depicted by **Formula IV** are exemplified in **Examples 31-40**.

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Scheme III



- 5 In **Scheme 3**, R_1 and Z are as defined above. The alkene **S1b** (from **Scheme 1**) is treated with an osmium salt and with an optional catalyst reoxidant, preferably *N*-methyl morpholine *N*-oxide (NMO), to give the diol. This diol is isolated by extraction and purified by silica gel chromatography. The diol is then oxidized selectively to the *alpha* hydroxy aldehyde. This may be accomplished in
- 10 several ways. For example, a selective oxidant such as DMSO-oxalyl chloride may be used. Alternatively, the primary alcohol may be selectively protected, then the secondary alcohol protected, then the protection on the primary alcohol may then be removed and the alcohol oxidized as described above in **Scheme II**. However, the preferred method is the addition of a *o*-bromo-benzyl bromide protecting group, which can be removed with concomitant oxidation by tributyl tin hydride and like
- 15 reagents. This technique yields compounds of the type **S3a**, wherein $\text{P} = \text{H}$. From this step follows the condensation of the aldehyde with an amine to form an imine of the type **S3b**. Appropriate removal of protecting groups and manipulation of C-1

as stated above in **Schemes I and II** yields compounds according the **Formula V**.
Compounds depicted by **Formula V** are exemplified in **Examples 41-48**.

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

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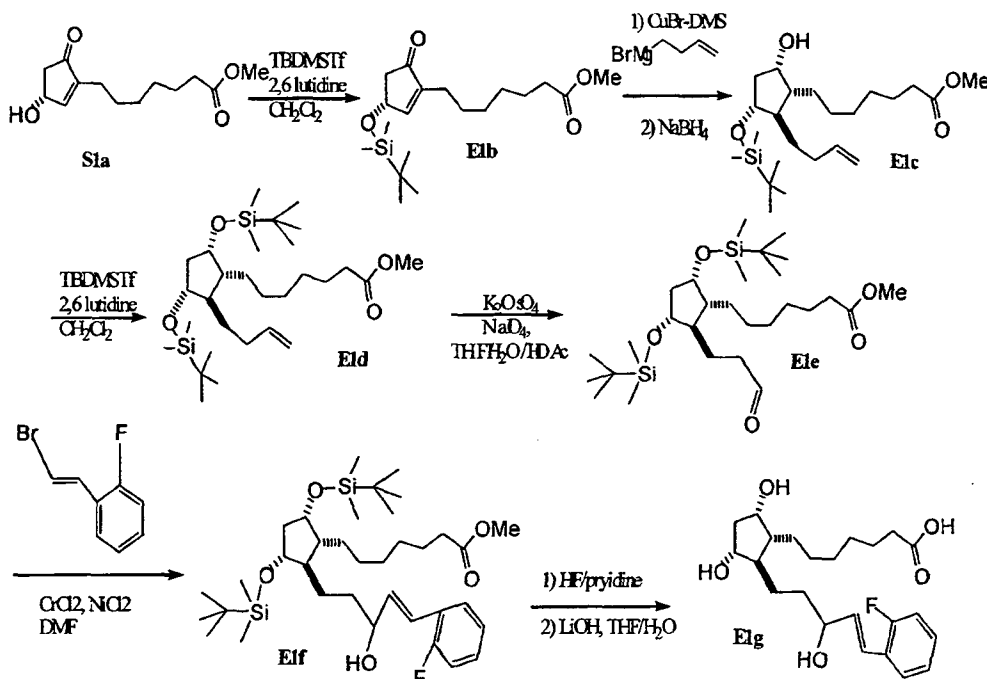
Examples

Compounds are analyzed using ^1H and ^{13}C 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,
10 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-
15 300 mesh; J.T. Baker) and visualized using *uv* light, 5% phosphomolybdic acid in EtOH, or ammonium molybdate/ceric sulfate in 10% aqueous H_2SO_4 .

EXAMPLE 1

20 **Preparation of 13,14-dihydro-16-17-Z-didehydro-17-(2-fluorophenyl) prostaglandin $\text{F}_{1\alpha}$:**



a. **Methyl 7-(2-oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopent-1-enyl) heptanoate (E1b):** To a solution of Methyl-7-[3-(R)-hydroxy-5-oxo-1-cyclopenten-1-yl] heptanoate **S1a** (1 equiv.) in CH_2Cl_2 at -78°C is added 2,6 Lutidine (1.3 equiv.) dropwise over 15 minutes. The solution is kept at -78°C .
 5 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
 10 concentrated. The residue is distilled under vacuum (10 mm Hg) to provide the silyl ether **E1b**.

b. **Methyl 7-(5-but-3-enyl)- 2-hydroxy-4- (1,1,2,2-tetramethyl-1-silapropoxy)cyclopentyl) heptanoate (E1c):** To a slurry of Mg^0 powder (2 equiv.) in THF at room temperature is added one crystal of iodine (catalytic I_2) 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
 15 mechanical stirring and charged with $\text{CuBr}\cdot\text{DMS}$ (2 equiv.) in a 1:1 solution of THF/DMS at -78°C . After the addition of the Grignard (~20 minutes), 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 **E1b** (1 equiv.) in THF is then added dropwise over 25 minutes. The reaction is stirred at -78°C for 15 minutes, then allowed to
 20 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
 25 chromatographed on SiO_2 (10 % hexane/EtOAc) to give the ketone precursor to **E1c**.
 30

The ketone precursor to **E1c** (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
 35 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 **E1c**.

c. **Methyl 7-(5-but-3-enyl -2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E1d):** The alcohol **E1c** (1 equiv.) is dissolved in CH_2Cl_2 and cooled to 0°C and 2,6 lutidine (1.3 equiv.) is added 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 **E1d**.

d. **Methyl 7-(5-(3-oxopropanyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E1e):** 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 **E1d** (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 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) **E1e** is obtained.

e. **9,11-(1,1,2,2-tetramethyl-1-silapropoxy)-13,14-dihydro-16-17-didehydro-17-(o-fluoro-phenyl) prostaglandin $\text{F}_{1\alpha}$ (E1f):** In a Round bottom flask is added chromium(II) chloride (2eq) and Nickel (II) chloride (.02 eq). DMF is added and the solution is stirred. To this is added alpha bromo-(o-fluro)styrene (2eq) and the aldehyde (1eq). The reaction is monitored by TLC and then quenched with ammonium chloride when starting material is no longer present. The mixture is extracted into ethyl ether and washed with brine to neutral pH, dried with Magnesium sulfate, and concentrated. After column chromatography, (7:3, hexane: ethyl acetate) **E1f** is obtained.

f. **13,14-dihydro-16-17-Z-didehydro-17-(2-fluorophenyl) prostaglandin $\text{F}_{1\alpha}$ (E1g):** To a small round-bottomed flask, is added methyl ester **E1f** and 3 mL of CH_3CN . Then 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

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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 E1g.

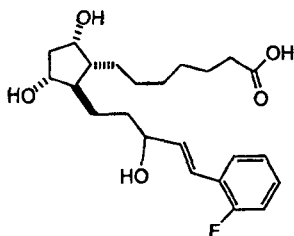
Examples 2-17

Examples 2-17 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 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

13,14-dihydro-16-17-*E*-didehydro-17-(2-fluoro-phenyl)-17-trinor prostaglandin

F_{1α}

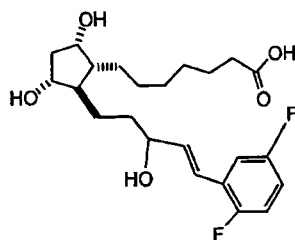


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Example 7

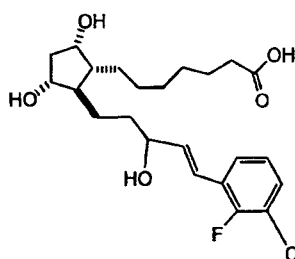
13,14-dihydro-*E*-16-17-didehydro-17-(2,5-difluoro-phenyl)-17-trinor
prostaglandin $F_{1\alpha}$



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Example 8

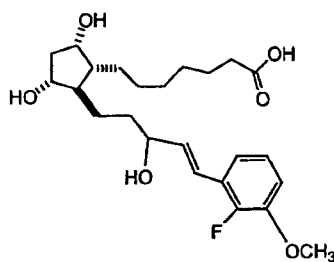
13,14-dihydro-*E*-16-17-didehydro-17-(2-fluoro-3-chloro-phenyl)-17-trinor
prostaglandin $F_{1\alpha}$



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Example 9

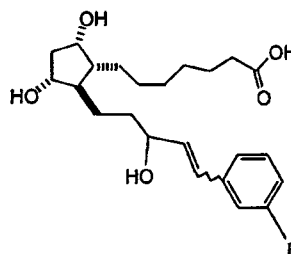
13,14-dihydro-*E*-16-17-didehydro-17-(2-fluoro-3-methoxy-phenyl)-17-trinor
prostaglandin $F_{1\alpha}$



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Example 10

13,14-dihydro-16-17-didehydro-17-(3-fluoro-phenyl)-17-trinor prostaglandin
 $F_{1\alpha}$



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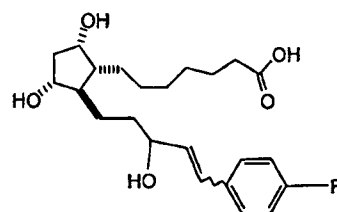
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Example 11

13,14-dihydro-16-17-didehydro-17-(4-fluoro-phenyl)-17-trinor prostaglandin

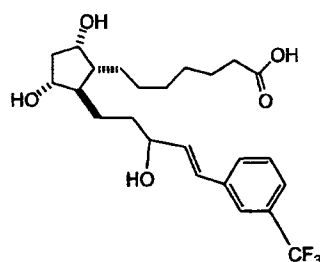
F_{1α}



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Example 12

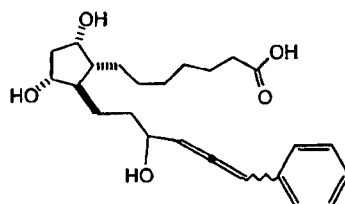
13,14-dihydro-*E*-16-17-didehydro-17-(3-trifluoromethyl-phenyl)-17-trinor prostaglandin F_{1α}



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Example 13

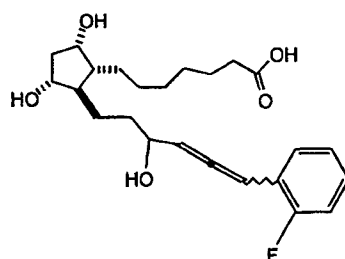
13,14-dihydro-16-17-dienyl-18-(phenyl)-18-dinor prostaglandin F_{1α}



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Example 14

13,14-dihydro-16-17-dienyl-18-(2-fluoro-phenyl)-18-dinor prostaglandin F_{1α}



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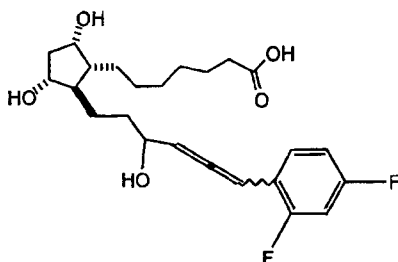
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Example 15

13,14-dihydro-16-17-dienyl-18-(2,4-difluoro-phenyl)-18-dinor prostaglandin

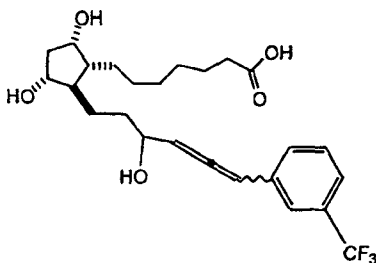
F_{1α}



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Example 16

13,14-dihydro-16-17-dienyl-18-(3-trifluoromethyl-phenyl)-18-dinor prostaglandin F_{1α}

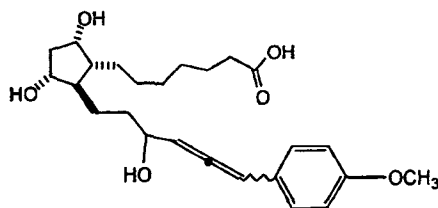


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Example 17

13,14-dihydro-16-17-dienyl-18-(4-methoxy-phenyl)-18-dinor prostaglandin

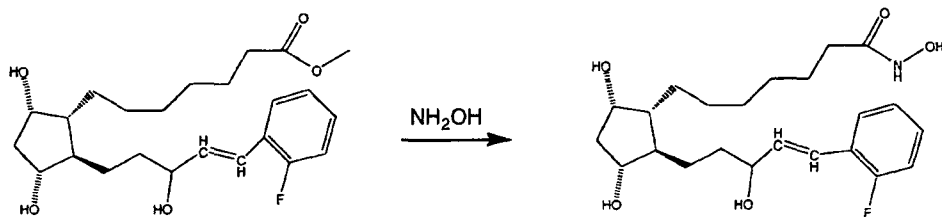
F_{1α}



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Example 18

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



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In a flame-dried round-bottomed flask equipped with a magnetic stir bar is placed 13,14-dihydro-16,17-alkenyl-17-(2-fluorophenyl) trinor Prostaglandin F_{1α} methyl ester (**Example 1**) (1.0 equiv.) in methanol. To this solution is added hydroxylamine in methanol (1.25 equiv.). The solution stirred for a few minutes.

- 5 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-alkenyl-17-(2-fluorophenyl) trinor Prostaglandin F_{1α} 1-hydroxamic acid.

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Examples 19-20

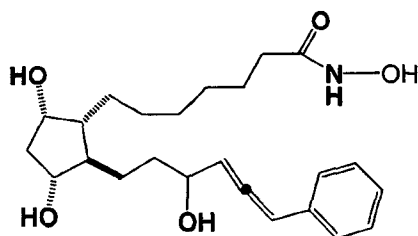
Examples 19-20 are prepared using substantially the same procedures as those described in **Example 18**, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or

- 15 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 19

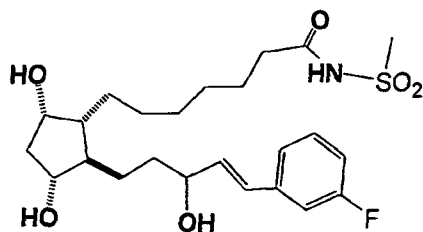
13,14-dihydro-15,16-dienyl-17-phenyl-17-trinor Prostaglandin F_{1α} 1-hydroxamic acid



25

Example 20

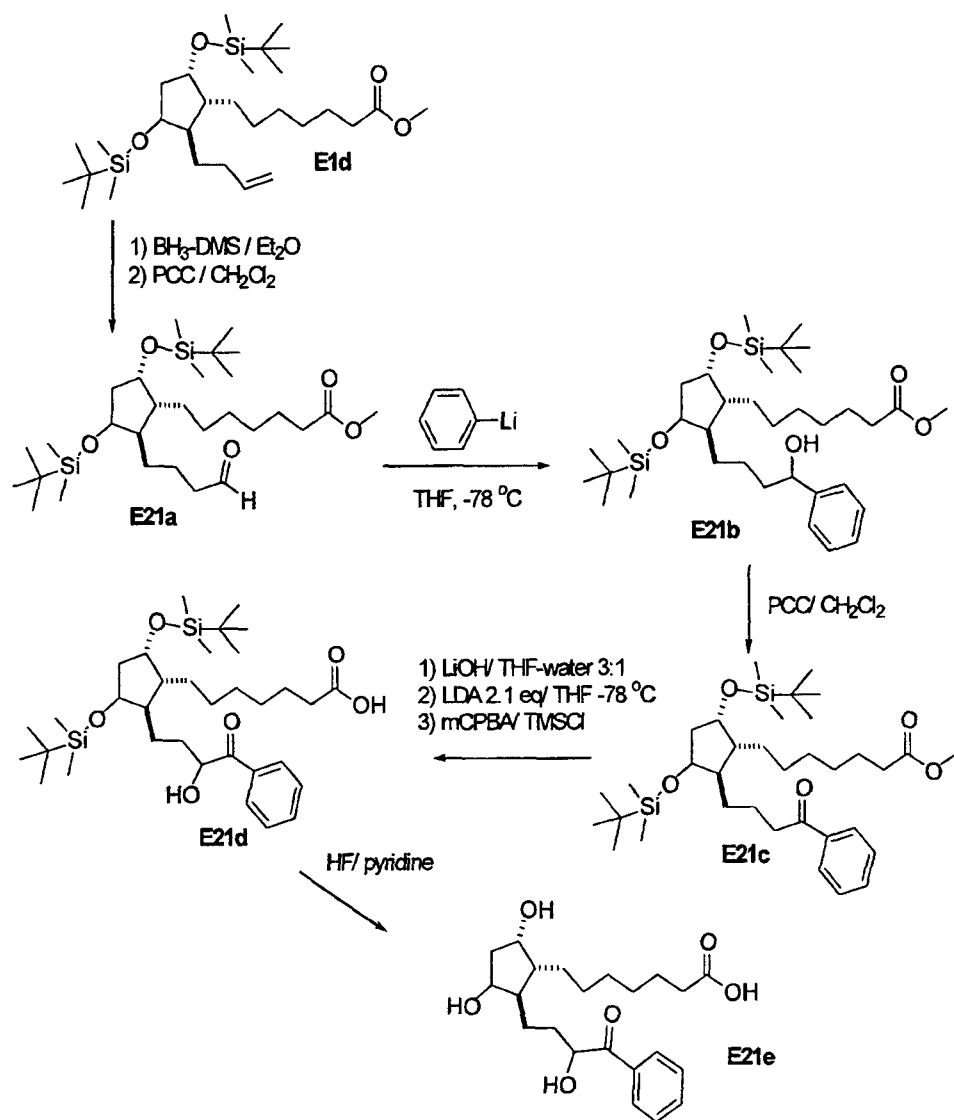
13,14-dihydro-16,17-alkenyl-17-(3-fluorophenyl)-17-trinor Prostaglandin F_{1α} 1-N-methanesulfonamide



H3
110

Example 21

13,14-dihydro-16-keto-17-phenyl-17-trinor Prostaglandin F_{1α}



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- a. **Methyl 7-(5-(4-oxobutyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E21a):** In a 50 mL round-bottomed flask, Borane-dimethyl sulfide adduct (2 equiv.) and 10 mL of ethyl ether are added. This is stirred until the borane reagent has completely dissolved. The flask is cooled to 0°C and the alkene is added in portions. When the reaction is complete by TLC, the mixture is poured into a well-stirred solution of pyridinium chlorochromate (PCC) in dichloromethane. The reaction is stirred at room temperature under nitrogen with TLC monitoring of the reaction. When no starting material is evident by TLC, the reaction is quenched with a saturated ammonium chloride

solution 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, (1:1.5, Hexane: Ethyl Acetate) **E21a** is obtained.

5

b. **Methyl 7-(5-(4-hydroxy-4-phenylbutyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E21b)**: To a 50 mL round bottom flask is added phenyl lithium (1 equiv.) in THF and it is cooled to -78°C. To this flask is then added **E21a** in THF and is stirred for 30 minutes. The reaction was monitored by TLC and then quenched with ammonium chloride when starting material was no longer present. The mixture is extracted into ethyl ether and washed with brine to neutral pH, dried over magnesium sulfate, and concentrated. After column chromatography, (7:3, hexane: ethyl acetate) **E21b** is obtained.

15

c. **Methyl 7-(5-(4-oxo-4-phenylbutyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E21c)**: To a small round-bottomed flask is added methyl ester **E21b** and a portion of dichloromethane. Added slowly is PCC and activated sieves. The solution is stirred at room temperature and monitored by TLC until further oxidation ceases. At this point, the crude material is filtered through Fluorosil, concentrated and chromatographed to separate the ketone from the residual alcohol. After column chromatography, (7:3, hexane: ethyl acetate) **E21c** is obtained.

d. **7-(5-(3-hydroxy-4-oxo-4-phenylbutyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoic acid (E21d)**: The oil **E21c** 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 the free acid which is then dissolved in THF and cooled to -78°C. A THF solution containing 2.1 equivalents of LDA is added, followed by 2.2 equivalents of TMSCl. This is followed by 1.1 equivalents of *m*CPBA and the entire reaction is allowed to warm to room temperature. An acidic workup ensues, followed by extraction into a 3:1 mixture of ethyl acetate/hexane, yielding the hydroxy ketone **E21d**.

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e. **13,14-dihydro-16-keto-17-phenyl-17-trinor Prostaglandin $F_{1\alpha}$ (E21e)**: To a small round-bottomed flask, are added acid **E21d** and a portion of CH_3CN and $HF/Pyridine$ (0.1 mmol, 1 equiv.) while the flask is slowly warmed from $0^\circ C$ to room temperature. After 3 hours at $21^\circ C$, the reaction is quenched with saturated aqueous $NaCl$. The aqueous layer is extracted three times with CH_2Cl_2 . The organic layers are combined and washed three times with 0.1N HCl , brine, and dried (Na_2SO_4), and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide the final product.

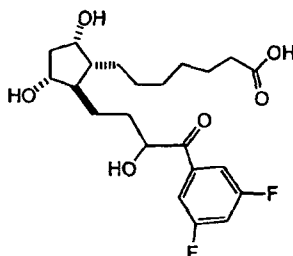
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Examples 22-27

Examples 22-27 are prepared using substantially the same procedures as those described in **Example 21**, 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.

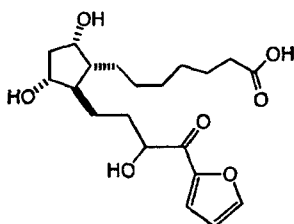
Example 22

20 **13,14-dihydro-16-keto-16-(3,5-difluorophenyl)-16-tetranor prostaglandin $F_{1\alpha}$**



Example 23

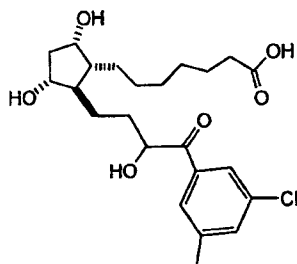
25 **13,14-dihydro-16-oxo-16-(2-furanyl)-16-tetranor prostaglandin $F_{1\alpha}$**



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Example 24

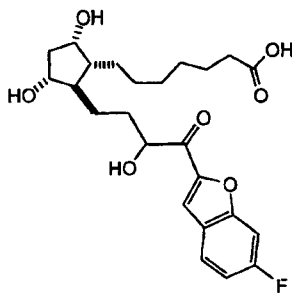
13,14-dihydro-16-oxo, 16-(3-chloro-5-methylphenyl)-16-tetranor
prostaglandin $F_{1\alpha}$



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Example 25

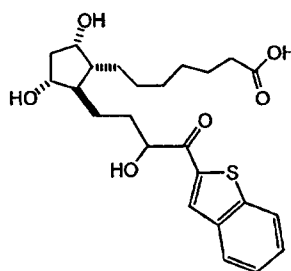
13,14-dihydro-16-keto-16-(4-fluorobenzo[b]furan-2-yl)-16-tetranor
prostaglandin $F_{1\alpha}$



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Example 26

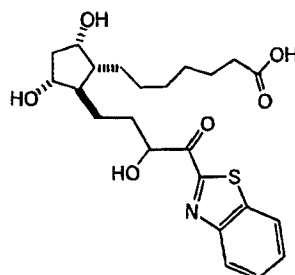
13,14-dihydro-16-oxo-16-(2-thianaphthyl)-16-tetranor prostaglandin $F_{1\alpha}$



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Example 27

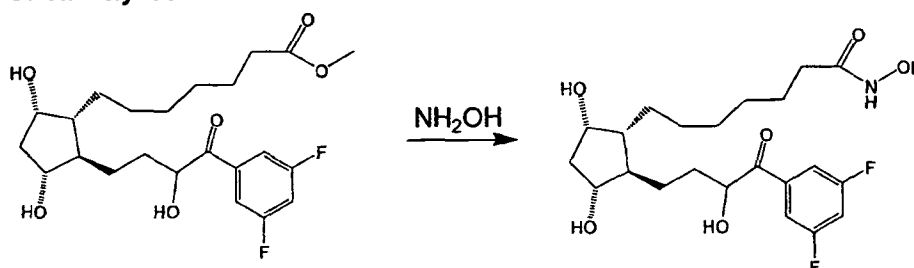
13,14-dihydro-16-oxo-17-(2-benzothiazolyl)-16-tetranor prostaglandin F_{1α}



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Example 28

Preparation of 13,14-dihydro-16-oxo-16-(2,4-difluorophenyl)-16-tetranor PGF_{1α} 1-hydroxamic acid:



10 In a flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar is 13,14-dihydro-16,17-alkenyl-17-*o*-fluorophenyl trinor PGF_{1α} methyl ester (**Example 22**) (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 1.0 N hydrochloric acid (HCl) and extracted twice with portions of 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 is 13,14-dihydro-16,17-alkenyl-17-(2-fluorophenyl) trinor PGF_{1α} 1-hydroxamic acid.

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Examples 29-30

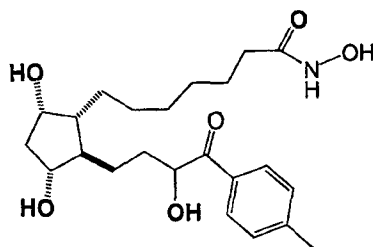
Examples 29-30 are prepared using substantially the same procedures as those described in **Example 28**, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan 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 29

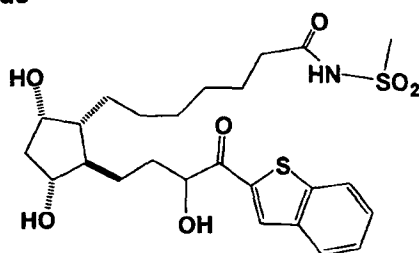
13,14-dihydro-16-oxo-16-(4-methylphenyl)-16-tetranor Prostaglandin F_{1α} 1-hydroxamic acid



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Example 30

13,14-dihydro-16-oxo,16-(2-thianaphthyl)-16-tetranor Prostaglandin F_{1α} 1-N-methanesulfonamide



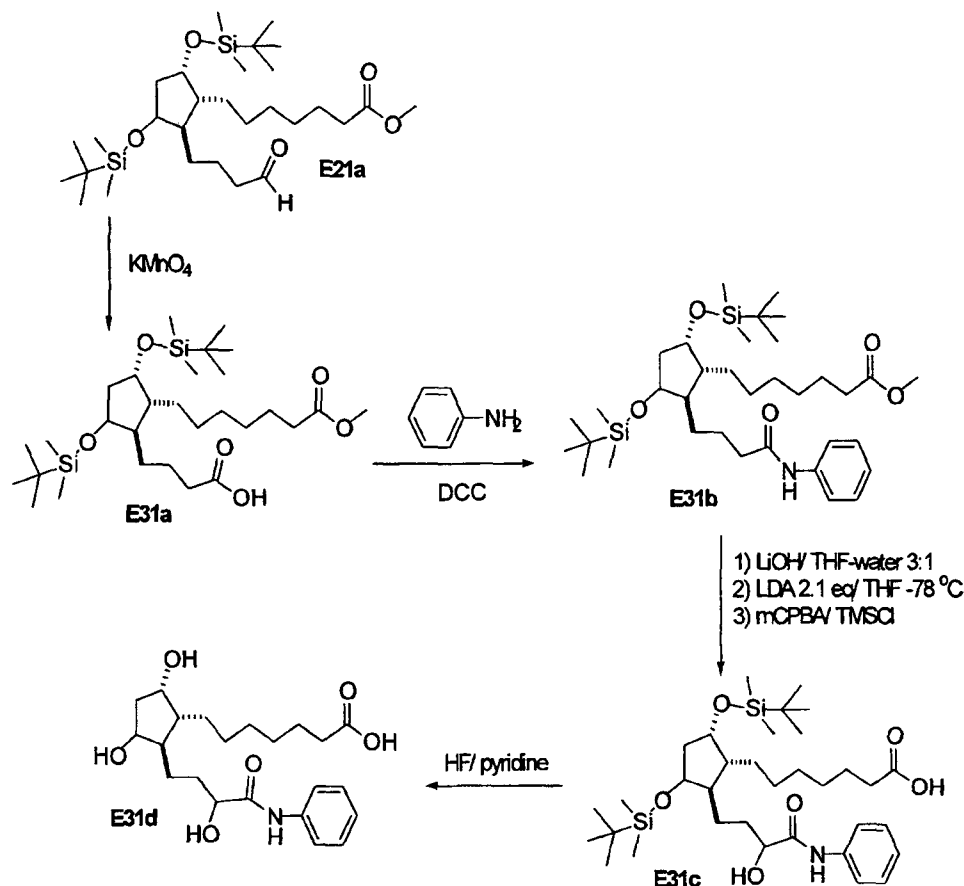
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Example 31

13,14-dihydro-15-(N-phenylcarbamoyl)-15-pentanor Prostaglandin F₁α



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a. Methyl 7-(5-(4-carboxybutyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E31a): In a 50 mL round-bottomed flask, compound E21a is added. There follows a titration with a neutral solution of potassium permanganate (KMnO₄). When the reaction is complete by TLC, the mixture is washed with saturated sodium citrate and extracted three times with dichloromethane. The organic layer is separated, dried over sodium sulfate, and concentrated. After column chromatography, (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), E31a is obtained.

10

b. Methyl 7-(5-(3-N-phenylcarbamyl-propyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E31b): To a 50 mL round bottom flask is added aniline (1 equiv.) in THF, then dicyclohexylcarbodiimide (DCC) is added in excess. To this flask is then added E31a in THF and is stirred for 30 minutes. The reaction is monitored by TLC and slight heat is applied if necessary, then quenched with ammonium chloride when starting material is no longer present.

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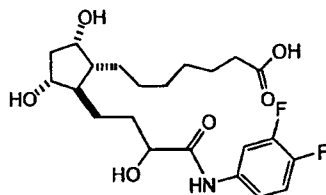
Examples 32-37 are prepared using substantially the same procedures as those described in **Example 31**, substituting the appropriate starting materials. The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan 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 32

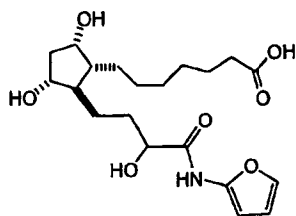
13,14-dihydro-15-(*N*-3,4-difluorophenylcarbamoyl)-15-pentanor
prostaglandin $F_{1\alpha}$



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Example 33

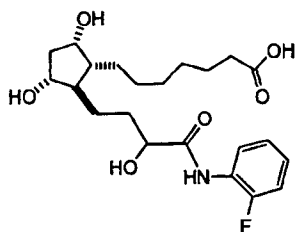
13,14-dihydro-15-(*N*-2-furanylcabamoyl)-15-pentanor prostaglandin $F_{1\alpha}$



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Example 34

13,14-dihydro-15-(*N*-2-fluorophenylcarbamoyl)-15-pentanor prostaglandin
 $F_{1\alpha}$



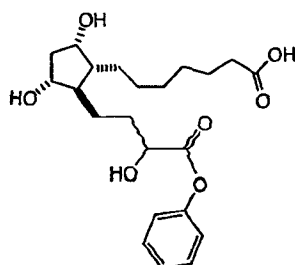
15

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Example 35

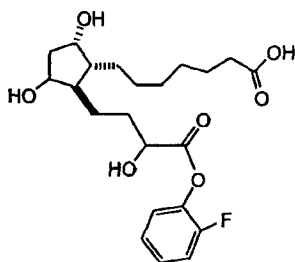
13,14-dihydro-15-(phenoxycarbonyl)-15-pentanor prostaglandin F_{1α}



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Example 36

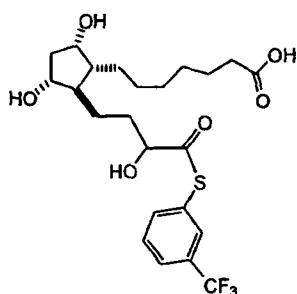
13,14-dihydro-15-(2-fluorophenoxycarbonyl)-15-pentanor prostaglandin F_{1α}



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Example 37

13,14-dihydro-15-(3-trifluoromethylthiaphenoxycarbonyl)-15-pentanor prostaglandin F_{1α}



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Examples 38-40

Examples 38-40 are prepared using substantially the same procedures as those described in **Example 28**, 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.

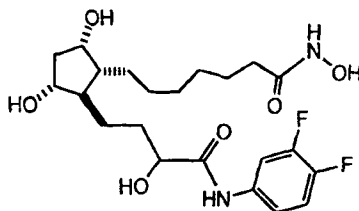
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Example 38

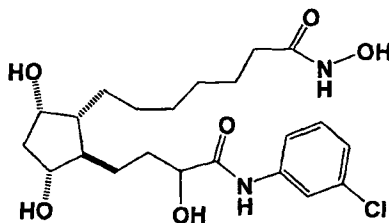
Preparation of 13,14-dihydro-15-(*N*-3,4-difluorophenylcarbamoyl)-15-pentanor PGF_{1α} 1-hydroxamic acid:



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Example 39

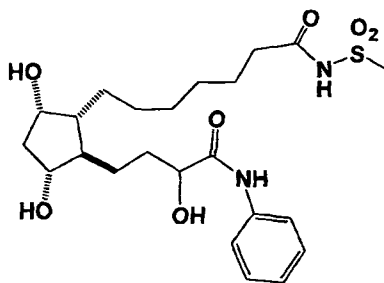
Preparation of 13,14-dihydro-15-(*N*-3-chlorophenylcarbamoyl)-15-pentanor PGF_{1α} 1-hydroxamic acid:



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Example 40

Preparation of 13,14-dihydro-15-(*N*-phenylcarbamoyl)-15-pentanor PGF_{1α} 1-*N* methane sulfonamide:

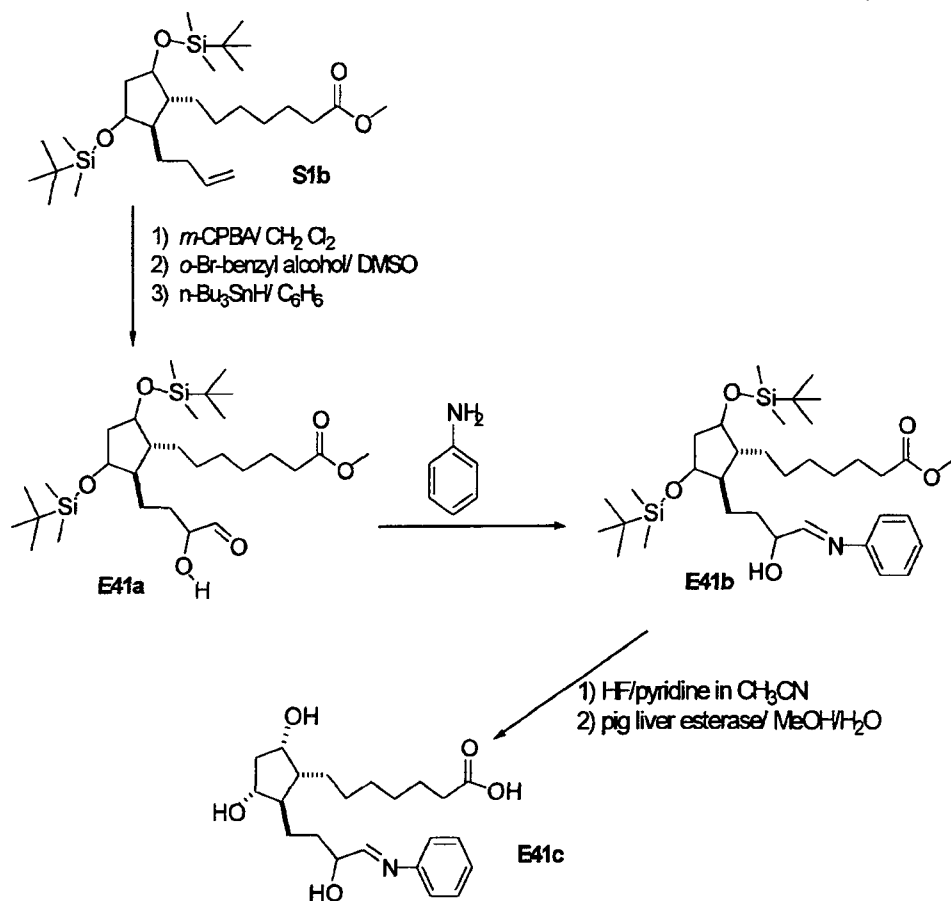


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Example 41

Preparation of 13,14-dihydro-17-aza-16-enyl-17-phenyl-17-trinor PGF_{1α}:



- 5 a. **Methyl 7-(5-(3-hydroxy-4-oxobutyl)butyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E41a):** In a 50 mL round-bottomed flask, compound **E21a** is added, followed by a portion of methylene chloride (CH₂Cl₂). There follows addition of a slight molar excess of *meta*-chloroperoxybenzoic acid (*m*-CPBA) (Aldrich). When the reaction is complete by
- 10 TLC, the mixture is washed with sodium sulfite solution, the organic layer is separated, is dried over sodium sulfate, and is concentrated. After column chromatography (20% EtOAc in hexanes), the epoxide as a clear oil is obtained. This oil is dissolved in DMSO and an equivalent of *o*-bromo-benzyl alcohol is added. This is heated to effect the nucleophilic opening of the epoxide by the
- 15 alcohol. The material is added to a portion of brine and extracted exhaustively with a 3:1 mixture of ethyl acetate and hexanes. This material is chromatographed (10% EtOAc in hexanes) to provide the benzyl ether as an oil. The benzyl ether is then dissolved in benzene and a dilute solution of tri-*n*-butyl tin hydride is slowly added at the temperature increased to reflux. More hydride

is added if needed to ensure complete reaction. The aldehyde thus recovered, **E41a**, is carefully chromatographed on silica gel (20% EtOAc in hexanes).

5 **b. Methyl 7-(5-(5-aza-3-hydroxypent-4-enyl)-2,4-di(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl) heptanoate (E41b):** To a 50 mL round bottom flask is added aniline (1 equiv.) in C₆H₆, then **E41a**. The mixture is then heated and the water formed is removed by azetropic distillation with a Dean-Stark trap. The reaction is monitored by TLC. The product is isolated by removal of the benzene *in vacuo*, and column chromatography, (1:1, hexane: ethyl acetate) yields **E41b**.

10

15 **c. 13,14-dihydro-17-aza-16-enyl-17-phenyl-17-trinor PGF_{1α} (E41c):** To a small round-bottomed flask, is added methyl ester **E41b** and a portion CH₃CN and HF/Pyridine (0.1 mmol, 1 equiv.) while the flask is slowly warmed from 0°C to room temperature. After 3 hours at 21°C, the reaction mixture is added to a silica gel chromatography column and chromatographed with 5% methanol in CH₂Cl₂ to yield the dihydroxy ester. This ester is saponified by adding it dropwise in methanol to a gently stirred aqueous solution of pig liver esterase (Sigma) buffered at pH =7. Care must be taken to ensure that the total concentration of the MeOH remains below 10% (v/v). When the reaction is complete by TLC, the solution is acidified with citric acid, and is extracted three times with CH₂Cl₂. The organic layers are combined and washed with brine, and dried (Na₂SO₄), and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide the final product.

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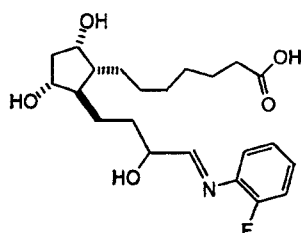
Examples 42-45

30 **Examples 42-45** are prepared using substantially the same procedures as those described in **Example 41**, 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 42

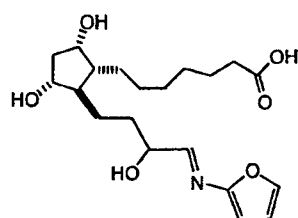
13,14-dihydro-17-aza-16-enyl-17-(2-fluorophenyl)-17-trinor PGF_{1α}



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Example 43

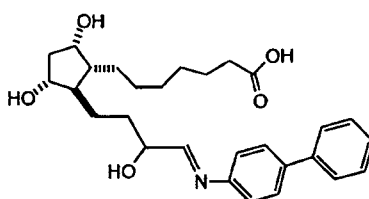
13,14-dihydro-17-aza-16-enyl-17-(2-furanyl)-17-trinor prostaglandin F_{1α}



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Example 44

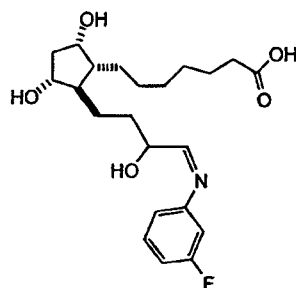
13,14-dihydro-17-aza-16-enyl-17-(4-phenylphenyl)-17-trinor prostaglandin F_{1α}



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Example 45

13,14-dihydro-17-aza-16-enyl-17-(3-fluorophenyl)-17-trinor prostaglandin F_{1α}



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Examples 46-48

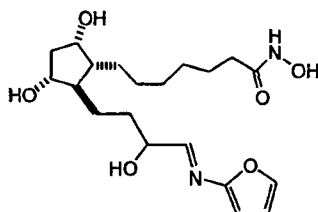
Examples 46-48 are prepared using substantially the same procedures as those described in Example 28, substituting the appropriate starting materials.

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 46

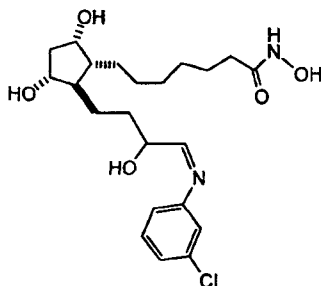
Preparation of 13,14-dihydro-17-aza-16-enyl-17-(2-furanyl)-17-trinor prostaglandin F_{1α} 1-hydroxamic acid



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Example 47

Preparation of 13,14-dihydro-17-aza-16-enyl-17-(3-chlorophenyl)-17-trinor prostaglandin F_{1α} 1-hydroxamic acid

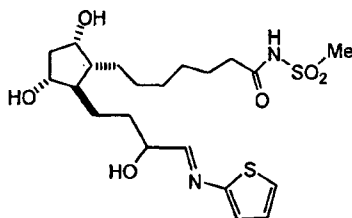


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Example 48

Preparation of 13,14-dihydro-17-aza-16-enyl-17-(-2-thiofuranyl)-17-trinor
prostaglandin F_{1α} 1-N-methanesulfonamide



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Compositions

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 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

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Methods of Use

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The compounds of the present invention are useful in increasing bone volume and trabecular number through formation of new trabeculae, bone mass while maintaining a normalized bone turnover rate, and formation at the

endosteal surface without removing bone from the existing cortex. Thus, these compounds are useful in the treatment and prevention of bone disorders.

The preferred routes of administration for treating bone disorders are transdermal and intranasal. Other preferred routes of administration include 5 rectal, sublingual, and oral.

The dosage range of the compound for systemic administration is from about 0.01 to about 1000 $\mu\text{g/kg}$ body weight, preferably from about 0.1 to about 100 $\mu\text{g/kg}$ per body weight, most preferably from about 1 to about 50 $\mu\text{g/kg}$ body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range of 0.01 to 100 nanograms/ml, more preferably from 0.05 to 50 ng/ml, and most preferably from 0.1 to 10 ng/ml. While these dosages are based upon a daily administration rate, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements.

Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.

20 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.

25 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.

Example A

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

5	<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:

15	<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.

Example C

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

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

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and

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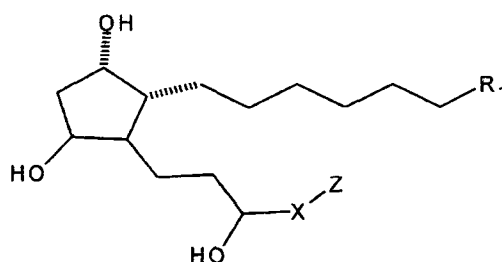
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modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

5 WHAT IS CLAIMED IS:

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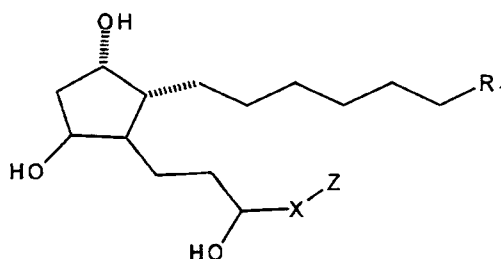
1. A compound having the structure:



wherein

- 5 (a) R_1 is selected from the group consisting of CO_2H , $C(O)NHOH$, CO_2R_2 , CH_2OH , $S(O)_2R_2$, $C(O)NHR_2$, $C(O)NHS(O)_2R_2$, or tetrazole; wherein R_2 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring and R_3 is lower alkyl, lower heteroalkyl, or haloalkyl. Preferred R_2 is methyl, ethyl, and isopropyl;
- 10 (b) X is:
- (1) $CH=C=CH$
 - (2) $CH=CH$
 - (3) $CH=N$
 - 15 (4) $C(O)$
 - (5) $C(O)Y$; wherein Y is selected from the group consisting of O, S, and NH;
- (c) Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring Z is attached via a Carbon member atom; and
- 20 (d) any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.
2. The compound of Claim 2 wherein R_1 is CO_2H , $C(O)NHOH$, CO_2R_2 , $C(O)NHS(O)_2R_2$, or tetrazole.
- 25 3. The compound of Claim 2 wherein X is $CH=C=CH$ or $C(O)Y$.
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 7 wherein R_1 is CO_2H or CO_2R_2 .
8. The compound of Claim 2 wherein X is $CH=CH$, $CH=N$, or $C(O)$.
9. The compound of Claim 8 wherein Z is bicyclic.

10. The compound of Claim 9 wherein Z is a bicyclic heteroaromatic ring.
11. The compound of Claim 10 wherein Z is selected from the group consisting of: benzo[β]thiazolyl, benzo[β]thiophenyl, and benzoxazolyl.
12. The compound of Claim 11 wherein Z substituted with one substituent, said one substituent being selected from the group consisting of: lower alkyl, halo, and haloalkyl.
13. The compound of Claim 12 wherein R_1 is CO_2H or CO_2R_2 .
14. 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:

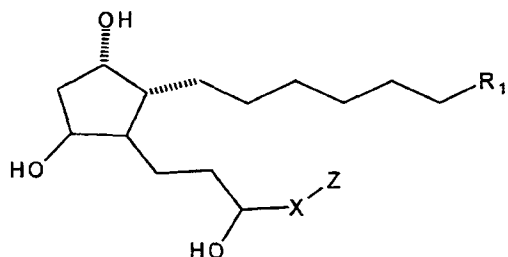


wherein

- (a) R_1 is selected from the group consisting of CO_2H , $C(O)NHOH$, CO_2R_2 , CH_2OH , $S(O)_2R_2$, $C(O)NHR_2$, $C(O)NHS(O)_2R_2$, or tetrazole; wherein R_2 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic aromatic ring, or monocyclic heteroaromatic ring and R_3 is lower alkyl, lower heteroalkyl, or haloalkyl. Preferred R_2 is methyl, ethyl, and isopropyl;
- (b) X is:
 - (1) $CH=C=CH$
 - (2) $CH=CH$
 - (3) $CH=N$
 - (4) $C(O)$
 - (5) $C(O)Y$; wherein Y is selected from the group consisting of O, S, and NH;
- (c) Z is an aromatic ring or a heteroaromatic ring provided that when Z is a heteroaromatic ring Z is attached via a Carbon member atom; and
- (d) any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.
15. The method of Claim 14 wherein said bone disorder is osteoporosis.
16. The method of claim 15 wherein in osteoporosis is post-menopausal.
17. The method of claim 15 wherein in osteoporosis is cortico-steroid induced.

18. The method of claim 14 wherein said bone disorder is osteopenia.
19. The method of claim 14 wherein said bone disorder is a bone fracture.
20. The method of claim 14 wherein said compound is administered orally.
21. The method of claim 14 wherein said compound is administered
5 transdermally.
22. The method of claim 14 wherein said compound is administered intranasally.
23. 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:

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wherein

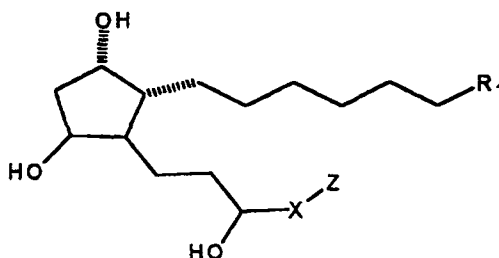
- (a) R_1 is selected from the group consisting of CO_2H , $C(O)NHOH$, CO_2R_2 ,
15 CH_2OH , $S(O)_2R_2$, $C(O)NHR_2$, $C(O)NHS(O)_2R_2$, or tetrazole; wherein R_2 is
alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring,
monocyclic aromatic ring, or monocyclic heteroaromatic ring and R_3 is
lower alkyl, lower heteroalkyl, or haloalkyl. Preferred R_2 is methyl, ethyl,
and isopropyl;
(b) X is:
20 (1) $CH=C=CH$
(2) $CH=CH$
(3) $CH=N$
(4) $C(O)$
(5) $C(O)Y$; wherein Y is selected from the group consisting of O , S ,
25 and NH ;
(c) Z is an aromatic ring or a heteroaromatic ring provided that when Z is a
heteroaromatic ring Z is attached via a Carbon member atom; and
(d) any optical isomer, diastereomer, enantiomer of the above structure or a
pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or
30 imide thereof.

26. The method of Claim 25 wherein said compound is administered topically.

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, 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. 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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