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United States Patent [19]
Wos et al.[11] **Patent Number:** **5,977,173**
[45] **Date of Patent:** **Nov. 2, 1999**[54] **AROMATIC C₁₆-C₂₀-SUBSTITUTED
TETRAHYDRO PROSTAGLANDINS USEFUL
AS FPAGONISTS**[76] Inventors: **John August Wos; Mitchell Anthony deLong; Jack S. Amburgey, Jr.; Biswanath De**, all of The Procter Gamble Company 8700 Mason-Montgomery Rd., Mason, Ohio 45040-9462; **Haiyan George Dai**, 47-2 Revere Rd., Drexel Hill, Pa. 19026; **Yili Wang**, 8700 Mason-Montgomery Rd., Mason, Ohio 45040-9462[21] Appl. No.: **09/148,006**[22] Filed: **Sep. 4, 1998****Related U.S. Application Data**

[60] Provisional application No. 60/058,217, Sep. 9, 1997.

[51] **Int. Cl.⁶** **C07C 405/00; A01K 31/557**[52] **U.S. Cl.** **514/530; 514/562; 514/567; 514/570; 549/66; 560/12; 560/16; 560/17; 560/43; 562/429; 562/431; 562/457; 562/64; 564/99**[58] **Field of Search** 560/121, 12, 16, 560/17, 43; 562/431, 429, 457, 621; 514/530, 562, 567, 570; 549/66; 564/99[56] **References Cited****U.S. PATENT DOCUMENTS**

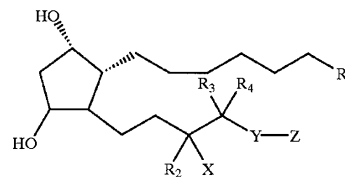
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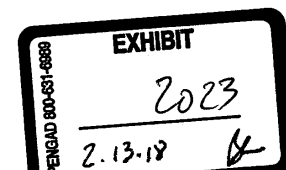
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Attorney, Agent, or Firm—James C. Kellerman; Carl J. roof; Mary Pat McMahon[57] **ABSTRACT**

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

wherein R₁, R₂, R₃, R₄, X, Y, 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.

28 Claims, No Drawings

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**AROMATIC C₁₆-C₂₀-SUBSTITUTED
TETRAHYDRO PROSTAGLANDINS USEFUL
AS FPAGONISTS**

CROSS REFERENCE

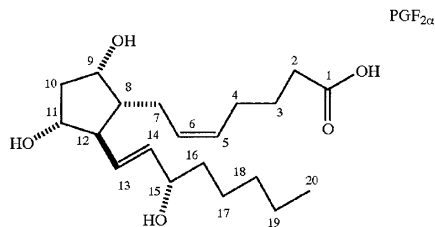
This application claims priority under Title 35, United States Code 119(e) from Provisional Application Ser. No. 60/058,217, filed Sep. 9, 1997.

TECHNICAL FIELD

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

BACKGROUND OF THE INVENTION

Naturally occurring prostaglandin (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:



Analog of naturally occurring Prostaglandin F have been disclosed in the art. For example, see U.S. Pat. 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 Jul. 1, 1976; U.S. Pat. No. 4,128, 720 issued to Hayashi, Kori, and Miyake on Dec. 5, 1978; U.S. Pat. No. 4,011,262 issued to Hess, Johnson, Bindra, and Schaaf on Mar. 8, 1977; U.S. Pat. No. 3,776,938 issued to Bergstrom and Sjovall on Dec. 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. I. Bundy and F. H. Lincoln, "Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins: I. The PG₁ Series", *Prostaglandin*, Vol. 9 No. 1 (1975), pp. 1-4; W. Bartman, G. Beck, U. Lerch, H. Teufel, and B. Scholkens, "Luteolytic Prostaglandin: Synthesis and Biological Activity", *Prostaglandin*, Vol. 17 No. 2 (1979), pp. 301-311; C. Iljebri, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-18, 19,20-trinorprostaglandin F_{2α} Isopropyl Ester: Potential Antiglaucoma Agents", *Journal of Medicinal Chemistry*, Vol. 38 No. 2 (1995), pp. 289-304.

Naturally occurring prostaglandin are known to possess a wide range of pharmacological properties. For example, prostaglandin 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

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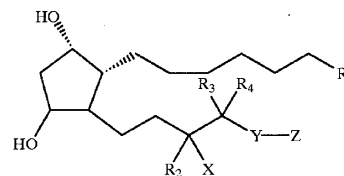
naturally occurring prostaglandin are characterized by their activity against a particular prostaglandin receptor, they generally are not specific for any one prostaglandin receptor. Therefore, naturally-occurring prostaglandin are known to cause side effects such as inflammation, as well as surface irritation when administered systemically. It is generally believed that the rapid metabolism of the naturally occurring prostaglandin following their release in the body limits some of 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 prostaglandin.

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

In view of both the wide range of pharmacological properties of naturally occurring prostaglandin and of the side effects seen with the systemic administration of these naturally occurring prostaglandin, attempts have been made to prepare analogs to the naturally occurring prostaglandin that are 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 of 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:



wherein R₁, R₂, R₃, R₄, X, Y, and Z are defined below.

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

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

DETAILED DESCRIPTION OF THE
INVENTION

Terms and Definitions

"Acyl" is a group suitable for acylating a nitrogen atom to form an amide or carbamate or an oxygen atom to form an ester group. Preferred acyl groups include benzoyl, acetyl,

tert-butyl acetyl, para-phenyl benzoyl, and trifluoroacetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

"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 about 4 substituents. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

"Aromatic ring" is an aromatic hydrocarbon ring system. 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. Aromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Bone disorder" means the need for bone repair or replacement. Conditions in which the need for bone repair or replacement may arise include: osteoporosis (including post menopausal osteoporosis, male and female senile osteoporosis and corticosteroid induced osteoporosis), osteoarthritis, Paget's disease, osteomalacia, multiple myeloma and other forms of cancer, prolonged bed rest, chronic disuse of a limb, anorexia, microgravity, exogenous and endogenous gonadal insufficiency, bone fracture, non-union, defect, prosthesis implantation and the like.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. 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. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More 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. The most preferred carbocyclic aliphatic ring is cycloheptyl.

"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 C_1-C_{12} ; more preferred are C_1-C_6 ; more preferred still are C_1-C_3 . 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 about 4 substituents. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionylloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), amino (e.g., amino, mono- and di- C_1-C_3 alkanylamino, methylphenylamino, methylbenzylamino, C_1-C_3 alkanylamido, carbamamido, ureido, guanidino).

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

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heterocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to about 4

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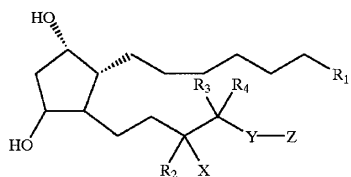
substituents on the ring. Preferred heteroaromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain radical comprised of 1 to 6, preferably 1 to 4 carbon atoms.

"Phenyl" is a six-membered monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the ortho, meta or para position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More 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 ortho.

Compounds

The subject invention involves compounds having the following structure:



In the above structure, R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_5 , CH_2OH , $\text{S}(\text{O})_2\text{R}_5$, $\text{C}(\text{O})\text{NHR}_5$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_5$, or tetrazole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_5 is CH_3 , C_2H_5 , C_3H_7 . Preferred R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2CH_3 , $\text{CO}_2\text{C}_2\text{H}_5$, $\text{CO}_2\text{C}_3\text{H}_7$, $\text{CO}_2\text{C}_4\text{H}_9$, $\text{CO}_2\text{C}_3\text{H}_7\text{O}_2$, and $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_5$. More preferred R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2CH_3 , and $\text{CO}_2\text{C}_3\text{H}_5$. Most preferred R_1 is CO_2H and CO_2CH_3 .

In the above structure, R_2 is H or lower alkyl. Preferred R_2 is H and CH_3 . Most preferred R_2 is H.

In the above structure, X is NR_6R_7 , OR_8 , SR_9 , $\text{S}(\text{O})\text{R}_9$, or $\text{S}(\text{O})_2\text{R}_9$; wherein R_6 , R_7 , and R_8 are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and wherein R_9 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_6 and R_7 are H, CH_3 and C_2H_5 . Preferred R_8 is H, CH_3 , C_2H_5 and C_3H_7 . Preferred R_9 is CH_3 and C_2H_5 . Preferred X is NR_6R_7 and OR_8 . Most preferred X is OH.

In the above structure, R_3 and R_4 are independently selected from the group consisting of H, CH_3 , and C_2H_5 . Preferred R_3 and R_4 are H.

In the above structure, Y is NR_{10} , S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$; wherein R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic

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aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_{10} is H and CH_3 . Preferred Y is NH and S.

In the above structure, Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred Z is monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, monocyclic aromatic ring, and monocyclic heteroaromatic ring. More preferred Z is monocyclic aromatic ring or monocyclic heteroaromatic ring. The most preferred Z is thienyl or 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} , C_{15} , and C_{16}), both epimers are envisioned. Preferred stereochemistry at all such stereocenters of the compounds of the invention mimic that of naturally occurring $\text{PGF}_{2\alpha}$.

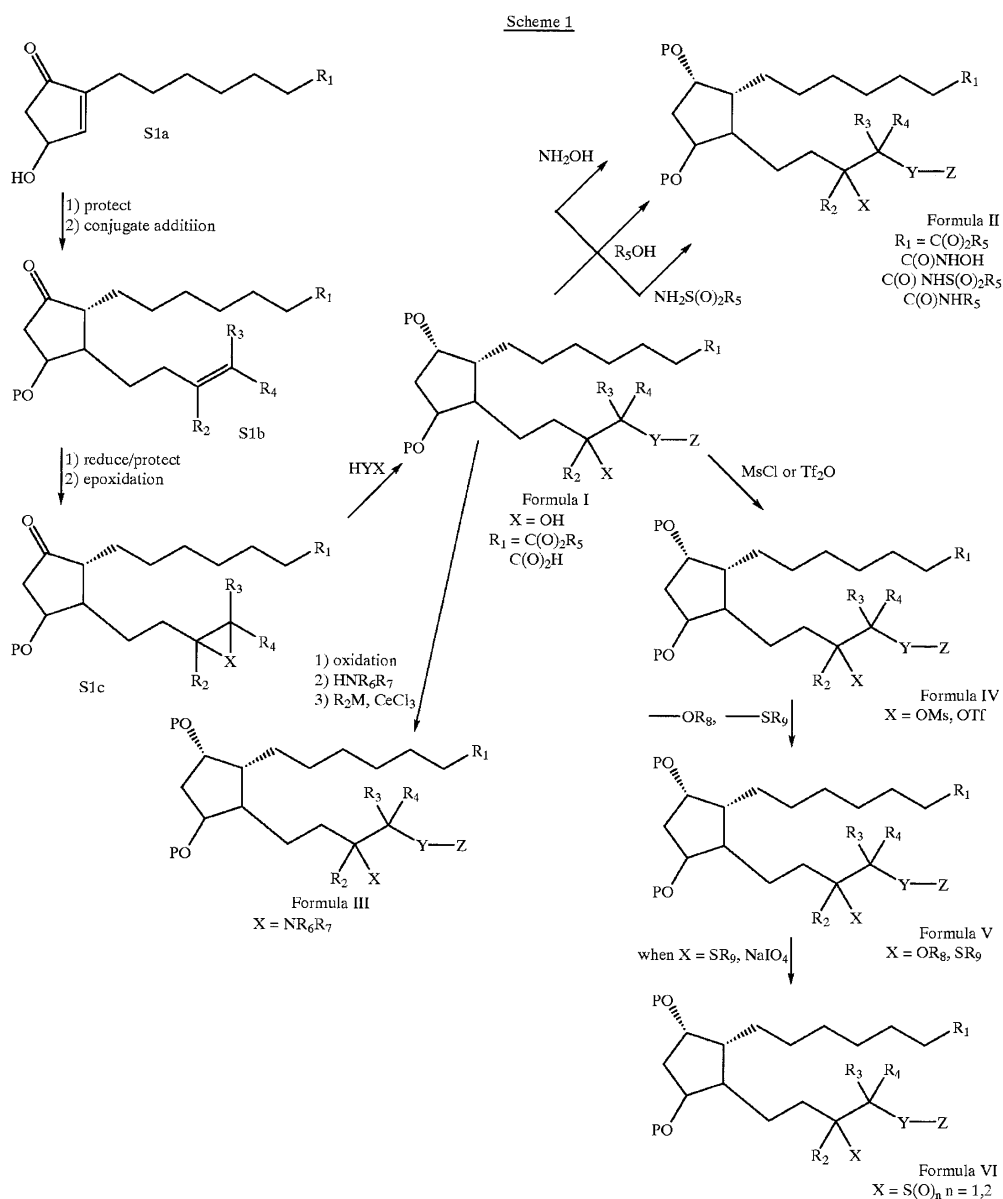
It has been discovered that the novel PGF analogs of the subject invention are useful for treating bone disorders, especially those that require a significant increase in bone mass, bone volume, or bone strength. Surprisingly, the compounds of the subject invention have been found to provide the following 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 (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. Iijebri, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $\text{F}_2\alpha$ 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. A particularly preferred synthesis is the following general reaction scheme:



In Scheme 1, R_1 , R_2 , R_3 , R_4 , X , Y , 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 those 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

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