cause side effects such as inflammation, surface irritation, smooth muscle contraction, pain, and bronchoconstriction. Therefore, it is an object of this invention to provide methods for using prostaglandin analogs to grow hair and to provide compositions that promote hair growth in humans and lower animals. It is a further object of this invention to provide a selection of appropriate prostaglandin analogs that will promote hair growth and that do not cause significant undesirable side effects.

SUMMARY OF THE INVENTION

This invention relates to compositions and methods for treating hair loss. The methods comprise administering the compositions comprising specific prostaglandin analogs that interact strongly with hair-selective receptors, such as the FP receptor. The choice of prostaglandin analog is important because the prostaglandin analogs must selectively activate the FP receptor and not activate any other receptors that would negate the effect of activating the FP receptor. The compositions comprise: component A) the prostaglandin analog, component B) a carrier, and optionally component C) an activity enhancer.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compositions and methods using prostaglandin F analogs ("PGF's") to treat hair loss in mammals. "Treating hair loss" includes arresting hair loss or reversing hair loss, or both, and promoting hair growth.

Publications and patents are referred to throughout this disclosure. All U.S. Patents cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

Definition and Usage of Terms

The following is a list of definitions for terms, as used herein:

"Activate" means binding and signal transduction of a receptor.

"Acyl group" means a monovalent group suitable for acylating a nitrogen atom to form an amide or carbamate, an alcohol to form a carbonate, 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.

"Aromatic group" means a monovalent group having a monocyclic ring structure or fused bicyclic ring structure. Monocyclic aromatic groups contain 5 to 10 carbon atoms, preferably 5 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Bicyclic aromatic groups contain 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic groups are unsubstituted. The most preferred aromatic group is phenyl. Bicyclic aromatic groups include ring systems wherein one ring in the system is aromatic. Preferred bicyclic aromatic groups are ring systems wherein both rings in the system are aromatic. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Carbocyclic group" means a monovalent saturated or unsaturated hydrocarbon ring. Carbocyclic groups are monocyclic. Carbocyclic groups contain 4 to 10 carbon atoms, preferably 4 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Carbocyclic groups are unsubstituted. Preferred carbocyclic groups include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic groups include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic group is cycloheptyl. Carbocyclic groups are not aromatic.

"FP agonist" means a compound that activates the FP receptor.

"FP receptor" means known human FP receptors, their splice variants, and undescribed receptors that have similar binding and activation profiles as the known human FP receptors. "FP" means the receptor is of the class which has the highest affinity for $PGF_{2\alpha}$ of all the naturally occurring prostaglandins. FP refers to a known protein.

"Halogen atom" means F, Cl, Br, or I. Preferably, the halogen atom is F, Cl, or Br; more preferably Cl or F; and most preferably F.

"Halogenated heterogenous group" means a substituted heterogenous group or a substituted heterocyclic group, wherein at least one substituent is a halogen atom. Halogenated heterogenous groups can have a straight, branched, or cyclic structure. Preferred halogenated heterogenous groups have 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, and most preferably 1 to 3 carbon atoms. Preferred halogen atom substituents are Cl and F.

"Halogenated hydrocarbon group" means a substituted monovalent hydrocarbon group or a substituted carbocyclic group, wherein at least one substituent is a halogen atom. Halogenated hydrocarbon groups can have a straight, branched, or cyclic structure. Preferred halogenated hydrocarbon groups have 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, and most preferably 1 to 3 carbon atoms. Preferred halogen atom substituents are Cl and F. The most preferred halogenated hydrocarbon group is trifluoromethyl.

"Heteroaromatic group" means an aromatic ring containing carbon and 1 to 4 heteroatoms in the ring. Heteroaromatic groups are monocyclic or fused bicyclic rings. Monocyclic heteroaromatic groups contain 5 to 10 member atoms (i.e., carbon and heteroatoms), preferably 5 to 7, and more preferably 5 to 6 in the ring. Bicyclic heteroaromatic rings contain 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic groups are unsubstituted. Bicyclic heteroaromatic groups include ring systems in which only one ring is aromatic. Preferred bicyclic heteroaromatic groups are ring systems in which both rings are aromatic. Preferred monocyclic heteroaromatic groups include thienyl, thiazolyl, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred monocyclic heteroaromatic groups include thienyl, furanyl, and pyridyl. The most preferred monocyclic heteroaromatic group is thienyl. Preferred bicyclic heteroaromatic rings include benzothiazolyl, benzothiophenyl, quinolinyl, quinoxalinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, indolyl, and anthranilyl. More preferred bicyclic heteroaromatic rings include benzothiazolyl, benzothiophenyl, and benzoxazolyl.

"Heteroatom" means an atom other than carbon in the ring of a heterocyclic group or the chain of a heterogeneous group. Preferably, heteroatoms are selected from the group consisting of nitrogen, sulfur, and oxygen atoms. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic group" means a saturated or unsaturated ring structure containing carbon and 1 to 4 heteroatoms in the ring. No two heteroatoms are adjacent in the ring, and no carbon in the ring that has a heteroatom bonded to it also has a hydroxyl, amino, or thiol group bonded to it. Heterocyclic groups are not aromatic. Heterocyclic groups are monocyclic. Heterocyclic groups contain 4 to 10 member atoms (i.e., including both carbon atoms and at least 1 heteroatom), preferably 4 to 7, and more preferably 5 to 6 in the ring. Hetero-

cyclic groups are unsubstituted. Preferred heterocyclic groups include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and piperdyl.

"Heterogeneous group" means a saturated or unsaturated chain containing 1 to 18 member atoms (i.e., including both carbon and at least one heteroatom). No two heteroatoms are adjacent. Preferably, the chain contains 1 to 12 member atoms, more preferably 1 to 6. "Lower heterogeneous" means a heterogeneous group having 1 to 6, preferably 1 to 3, member atoms. The chain may be straight or branched. Preferred branched heterogeneous groups have one or two branches, preferably one branch. Preferred heterogeneous groups are saturated. Unsaturated heterogeneous groups have one or more double bonds, one or more triple bonds, or both. Preferred unsaturated heterogeneous groups have one or two double bonds or one triple bond. More preferably, the unsaturated heterogeneous group has one double bond. Heterogeneous groups are unsubstituted.

"Monovalent hydrocarbon group" means a chain of 1 to 18, preferably 1 to 12, carbon atoms. "Lower monovalent hydrocarbon group" means a monovalent hydrocarbon group having 1 to 6, preferably 1 to 3, carbon atoms. Monovalent hydrocarbon groups may have a straight chain or branched chain structure. Preferred monovalent hydrocarbon groups have one or two branches, preferably 1 branch. Preferred monovalent hydrocarbon groups are saturated. Unsaturated monovalent hydrocarbon groups have one or more double bonds, one or more triple bonds, or combinations thereof. Preferred unsaturated monovalent hydrocarbon groups have one or two double bonds or one triple bond; more preferred unsaturated monovalent hydrocarbon groups have one double bond.

"Pharmaceutically acceptable" means suitable for use in a human or other mammal.

"Prostaglandin" means a fatty acid derivative which has a variety of potent biological activities of a hormonal or regulatory nature.

"Protecting group" is a group that replaces the active hydrogen of a hydroxyl moiety thus preventing undesired side reaction at the hydroxyl moiety. Use of protecting groups in organic synthesis is well known in the art. Examples of protecting groups are found in Chapter 2 *Protecting Groups in Organic Synthesis* by Greene, T. W. and Wuts, P. G. M., 2nd ed., Wiley & Sons, Inc., 1991. Preferred protecting groups include silyl ethers, alkoxymethyl ethers, tetrahydropyranyl, tetrahydrofuranyl, esters, and substituted or unsubstituted benzyl ethers.

"Safe and effective amount" means a quantity of a prostaglandin high enough to provide a significant positive modification of the subject's condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio).

"Selective" means having a binding or activation preference for a specific receptor over other receptors which can be quantitated based upon receptor binding or activation assays.

"Subject" means a living, vertebrate, hair- or fur-bearing animal such as a mammal (preferably human) in need of treatment.

"Substituted aromatic group" means an aromatic group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated monovalent hydrocarbon groups, phenyl groups, and phenoxy groups. Preferred substituted aromatic groups include naphthyl. The substituents may be substituted at the ortho, meta, or para position on the ring, or any combination thereof. The preferred substitution pattern on the ring is ortho or meta. The most preferred substitution pattern is ortho.

"Substituted carbocyclic group" means a carbocyclic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, monovalent heterogeneous groups, substituted monovalent hydrocarbon groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated monovalent hydrocarbon groups, phenyl groups, and phenoxy groups.

"Substituted heteroaromatic group" means a heteroaromatic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. The substituents include halogen atoms, acyl groups, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, heteroaromatic groups, substituted heteroaromatic groups, and any combination thereof. Preferred substituents include halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, phenyl groups, phenoxy groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated hydrocarbon groups, monovalent hydrocarbon groups, halogenated heterogenous groups, and phenyl groups.

"Substituted heterocyclic group" means a heterocyclic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterogeneous groups, substituted heterogeneous groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated hydrocarbon groups, phenyl groups, phenoxy groups, or any combination thereof. Substituted heterocyclic groups are not aromatic.

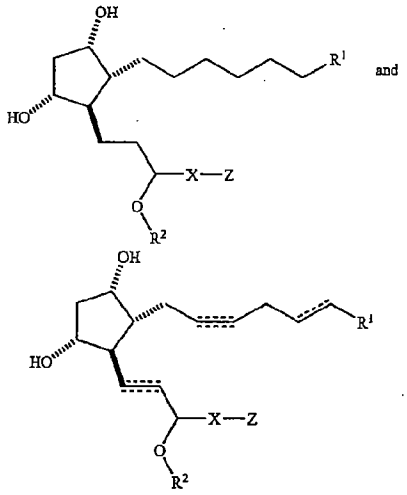
"Substituted heterogeneous group" means a heterogeneous group, wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the chain have been replaced with other substituents. Preferably substituted heterogeneous groups are mono, di, or trisubstituted. Preferred substituents include halogen atoms, hydroxy groups, carboxy groups, aryloxy groups (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, and acyloxyphenoxy), acyloxy groups (e.g., propionyloxy, benzoyloxy, and acetoxy), aromatic groups (e.g., phenyl and tolyl), substituted aromatic groups (e.g., alkoxyphenyl, alkoxycarbonylphenyl, and halophenyl), heterocyclic groups, heteroaromatic groups, substituted heterocyclic groups, and amino groups (e.g., amino, mono- and di-alkylamino having 1 to 3 carbon atoms, methylphenylamino, methylbenzylamino, alkanylamido groups of 1 to 3 carbon atoms, carbamamido, ureido, and guanidino).

"Substituted monovalent hydrocarbon group" means a monovalent hydrocarbon group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the chain have been replaced with other substituents. Preferred substituted monovalent hydrocarbon groups are mono, di, or trisubstituted. Preferred substituents include halogen atoms; lower

monovalent hydrocarbon groups; hydroxy groups; aryloxy groups (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, and acyloxyphenoxy); acyloxy groups (e.g., propionyloxy, benzoyloxy, and acetoxy); carboxy groups; monocyclic aromatic groups; monocyclic heteroaromatic groups; monocyclic carbocyclic groups, monocyclic heterocyclic groups, and amino groups (e.g., amino, mono- and di-alkanylamino groups of 1 to 3 carbon atoms, methylphenylamino, methylbenzylamino, alkanylamido groups of 1 to 3 carbon atoms, carbamamido, ureido, and guanidino).

Prostaglandins Used in the Invention

This invention relates to the use of prostaglandin F analogs (PGF's) to treat hair loss. Suitable PGF's can have a structure selected from the group consisting of:



and

The PGF can also be selected from the group consisting of pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; and optical isomers, diastereomers, and enantiomers of the structures above. 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 $PGF_{2\alpha}$. A combination of two or more PGF's can also be used.

R^1 is selected from the group consisting of C(O)OH, C(O)NHOH, $C(O)OR^3$, CH_2OH, $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms. Preferably, R^1 is selected from the group consisting of CO_2H, C(O)NHOH, CO_2R^3, $C(O)NHS(O)_2R^4$, and tetrazole. More preferably, R^1 is selected from the group consisting of CO_2H and CO_2R^3.

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and lower monovalent hydrocarbon groups. Preferably, R^2 is a hydrogen atom.

$R^3$is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group. Preferably, R^3 is selected from the group consisting of methyl, ethyl, and isopropyl

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group. Preferably, R^4 is a phenyl group.

X is divalent. X is selected from the group consisting of —C≡C—, a covalent bond, —CH=C=CH—, —CH=CH—, —CH=N—, —C(O)—, —C(O)Y—, $—(CH_2)_n—$, wherein n is 2 to 4, $—CH_2NH—$, $—CH_2S—$, and $—CH_2O—$.

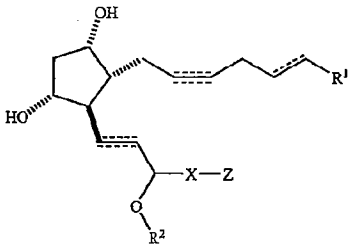
Y is selected from the group consisting of O, S, and NH.

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group.

Preferably, when X is a covalent bond, Z is selected from the group consisting of an aromatic group, a heteroaromatic group, a substituted aromatic group, and a substituted heteroaromatic group. More preferably, when X is a covalent bond, Z is a bicyclic heteroaromatic group.

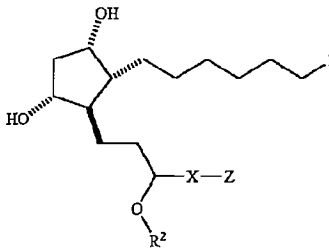
Preferably, when X is —C≡C—, Z is a monocyclic aromatic group. More preferably, when X is —C≡C—, Z is selected from the group consistng of furanyl, thienyl, and phenyl.

Bonds shown as dashed lines in the second structure above indicate that those bonds may optionally be double or triple bonds. For example, when R^1 is C(O)OH in the structure:



The bond at the C2-C3 position may be a single bond or a double bond. The bond at the C5-C6 position may be a single, double, or triple bond. The bond at the C13-C14 position may be a single, double, or triple bond.

Examples of PGF's' having the structure:



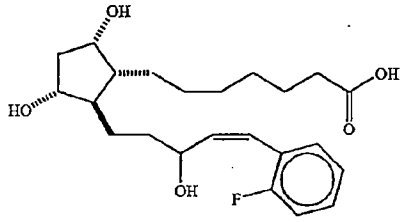
and

which are suitable for component A) are shown below in Tables 1 and 2.

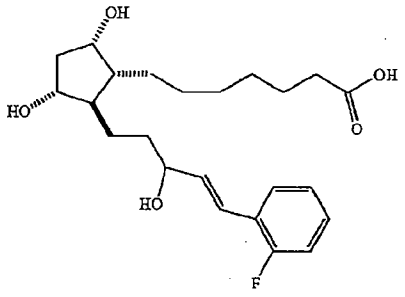
TABLE 1

Examples of Suitable PGF's for Component A)

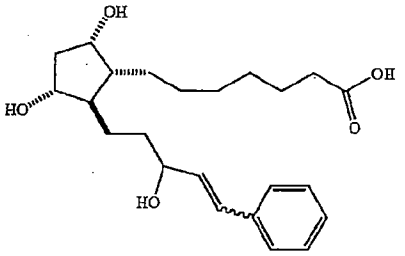
13,14-dihydro-16,17-Z-didehyro-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-E-didehyro-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-E-16,17-didehyro-17-phenyl-17-trinor $PGF_{1\alpha}$



13,14-dihydro-E-16,17-didehyro-17-(2, 4-dichlorophenyl)-17-trinor $PGF_{1\alpha}$

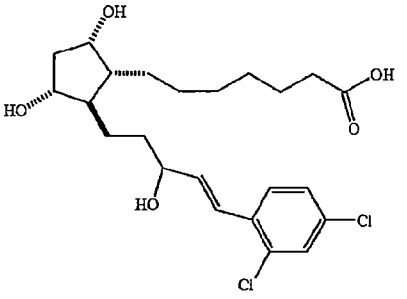
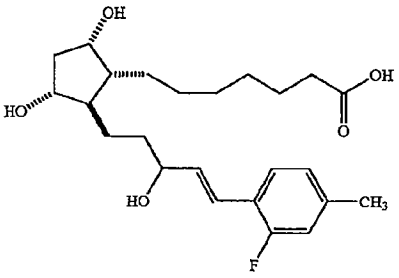


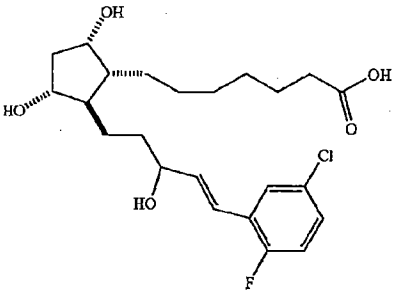
TABLE 1-continued

Examples of Suitable PGF's for Component A)

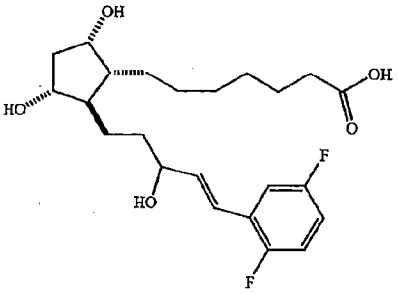
13,14-dihydro-E-16,17-didehyro-17-(2-fluoro-4-methylphenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-E-16,17-didehyro-17-(2-fluoro-5-chlorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-E-16,17-didehyro-17-(2, 5-difluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-E-16,17-didehyro-17-(2-fluoro-3-chlorophenyl)-17-trinor $PGF_{1\alpha}$

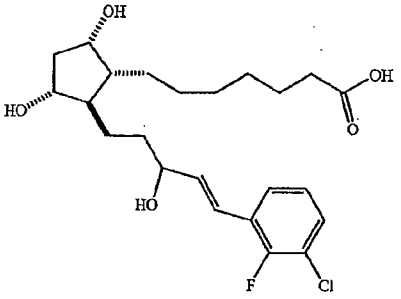
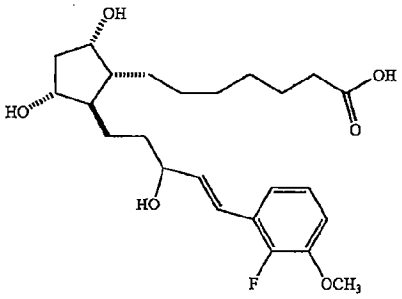


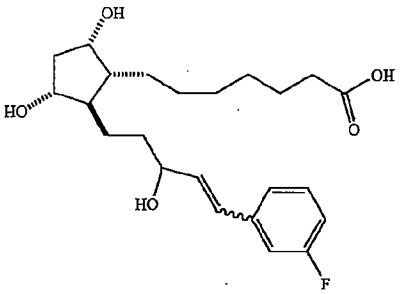
TABLE 1-continued

Examples of Suitable PGF's for Component A)

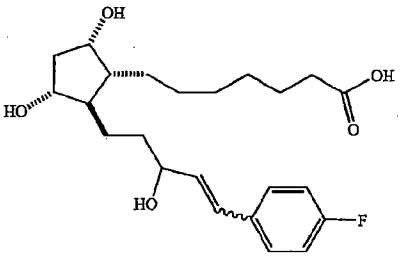
13,14-dihydro-E-16,17-didehyro-17-(2-fluoro-3-methoxyphenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehyro-17-(3-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehyro-17-(4-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-E-16,17-didehyro-17-(3-trifluoromethylphenyl)-17-trinor $PGF_{1\alpha}$

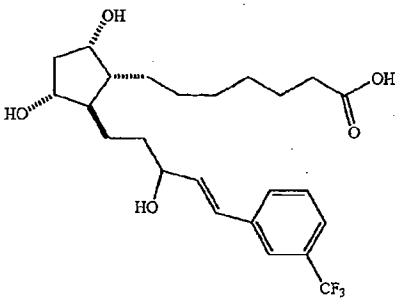
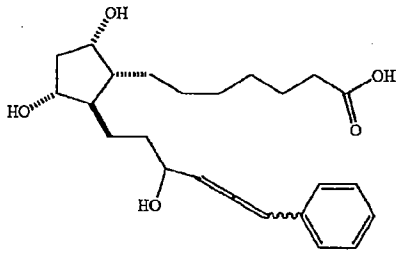


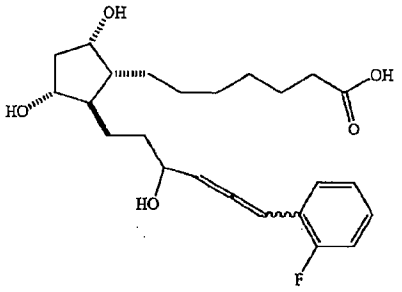
TABLE 1-continued

Examples of Suitable PGF's for Component A)

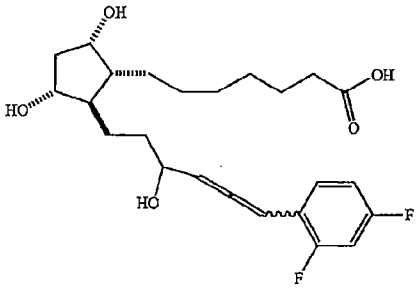
13,14-dihydro-16,17,17,18-dienyl-18-phenyl-18-dinor $PGF_{1\alpha}$



13,14-dihydro-16,17,17,18-dienyl-18-(2-fluorophenyl)-18-dinor $PGF_{1\alpha}$



13,14-dihydro-16,17,17,18-dienyl-18-(2, 4-difluorophenyl)-18-dinor $PGF_{1\alpha}$



13,14-dihydro-16,17,17,18-dienyl-18-(3-trifluoromethylphenyl)-18-dinor $PGF_{1\alpha}$

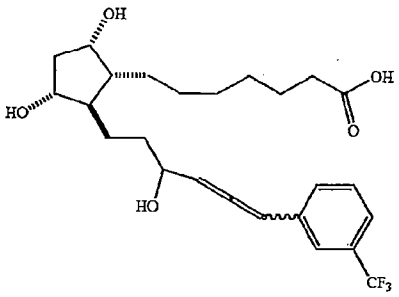
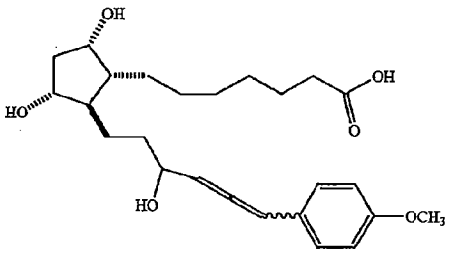


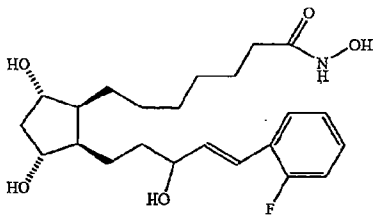
TABLE 1-continued

Examples of Suitable PGF's for Component A)

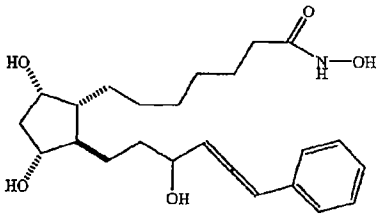
13,14-dihydro-16,17,17,18-dienyl-18-(4-methoxyphenyl)-18-dinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehydro-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$ 1-hydroxamic acid



13,14-dihydro-16,17,17,18-dienyl-18-phenyl-18-dinor$PGF_{2\alpha}$ 1-hydroxamic acid



13,14-dihydro-16,17-didehydro-17-3-fluorophenyl-17-trinor $PGF_{1\alpha}$ 1-N-methanesulfonamide

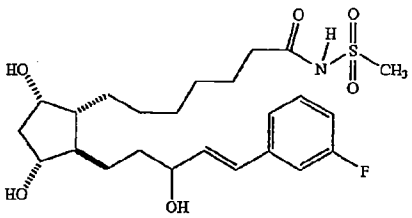
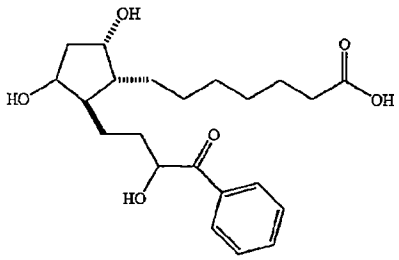


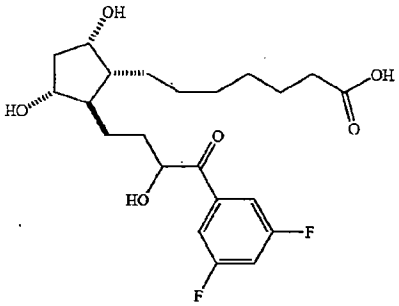
TABLE 1-continued

Examples of Suitable PGF's for Component A)

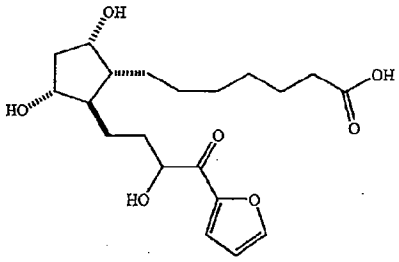
13,14-dihydro-16-oxo-16-phenyl-16-tetranor$PGF_{1\alpha}$



13,14-dihydro-16-oxo-16-(3, 5-difluorophenyl)-16-tetranor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-16-(2-furanyl)-16-tetranor $PGF_{1\alpha}$



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

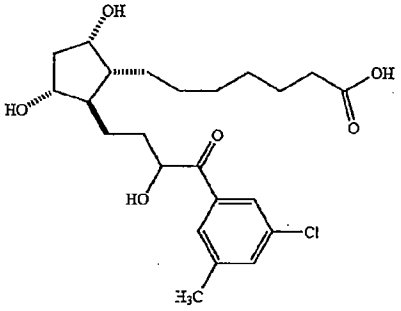
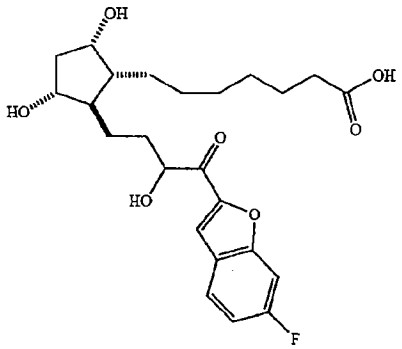


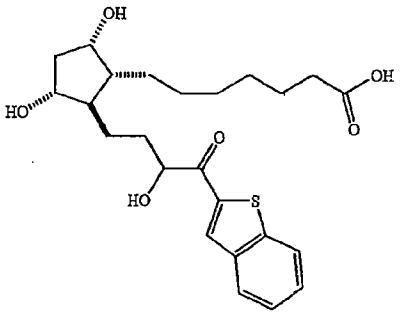
TABLE 1-continued

Examples of Suitable PGF's for Component A)

13,14-dihydro-16-oxo-16-(6-fluorobenzo-[b]-furanyl-16-(tetranor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-16-(2-benzo[b]thienyl)-16-tetranor $PGF_{1\alpha}$



13,14-dihydro-16-oxo16-(2-benzothiazolyl)-16-tetranor $PGF_{1\alpha}$

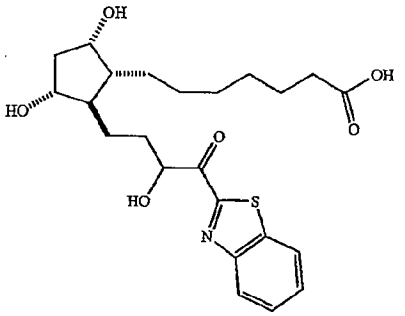
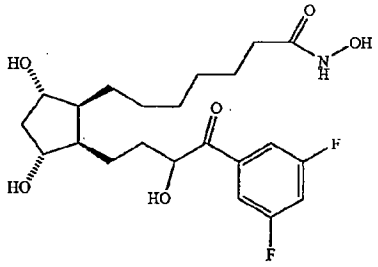


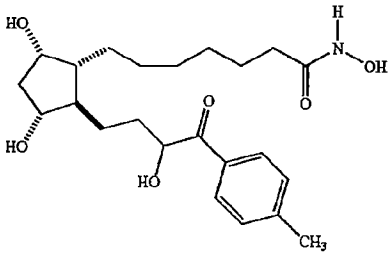
TABLE 1-continued

Examples of Suitable PGF's for Component A)

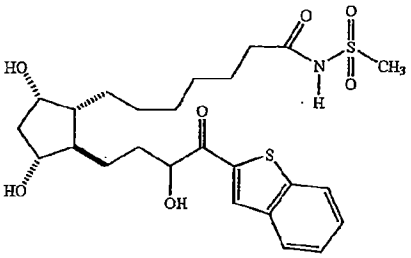
13,14-dihydro-16-oxo-16-(3, 5-difluorophenyl)-16-tetranor $PGF_{1\alpha}$ 1-hydroxamic acid



13,14-dihydro-16-oxo-16-(4-methylphenyl)-16-tetranor $PGF_{1\alpha}$ 1-hydroxamic acid



13,14-dihydro–16-oxo-16-(2-benzo[b]thienyl)-16-tetranor $PGF_{1\alpha}$ 1-N-methanesulfonamide



13,14-dihydro-16-oxo-17-aza-17-phenyl-17-trinor $PGF_{1\alpha}$

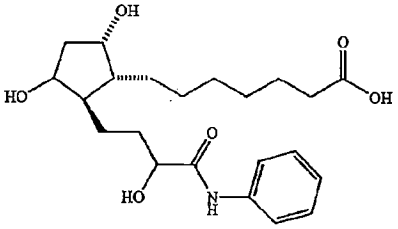
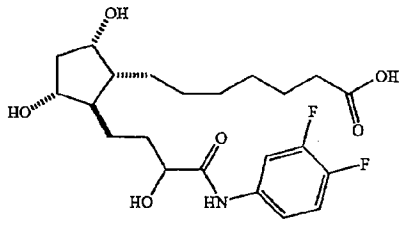


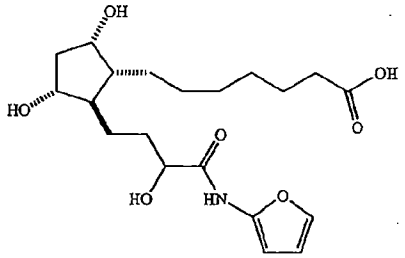
TABLE 1-continued

Examples of Suitable PGF's for Component A)

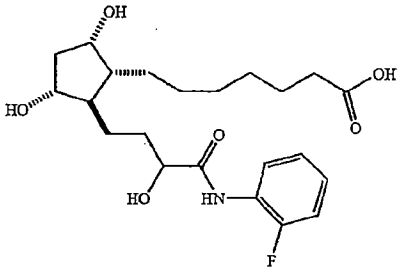
13,14-dihydro-16-oxo-17-aza-17-(3,4-difluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-17-aza-17-(2-furyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-17-aza-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-16-phenoxy-16-tetranor $PGF_{1\alpha}$

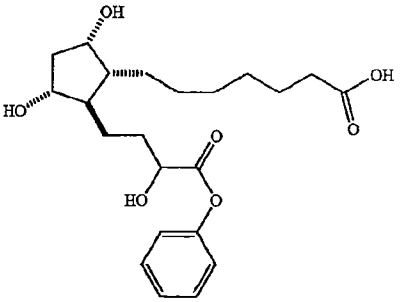
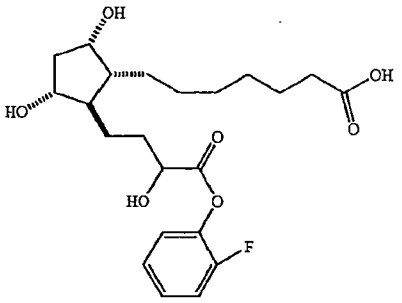


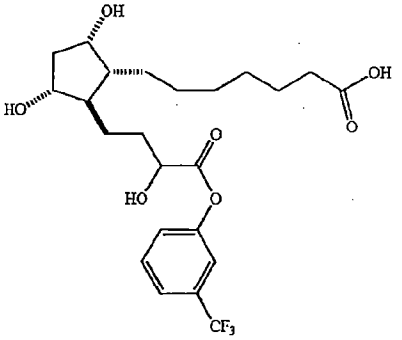
TABLE 1-continued

Examples of Suitable PGF's for Component A)

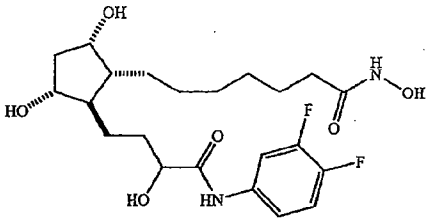
13,14-dihydro-16-oxo-16-(2-fluorophenoxy)-16-tetranor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-16-(3-trifluoromethylphenoxy)-16-tetranor $PGF_{1\alpha}$



13,14-dihydro-16-oxo-17-aza-17-(3,4-difluorophenyl)-17-trinor $PGF_{1\alpha}$ 1-hydroxamic acid



13,14-dihydro-16-oxo-17-amino-17-(3-chlorophenyl)-17-trinor $PGF_{1\alpha}$ 1-hydroxamic acid:

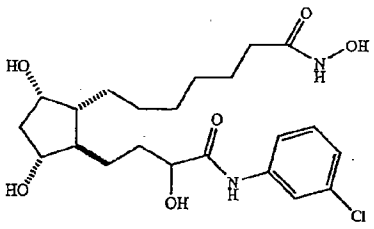
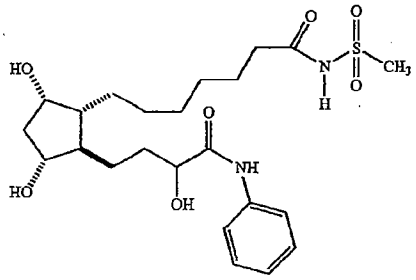


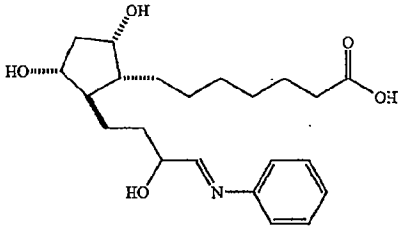
TABLE 1-continued

Examples of Suitable PGF's for Component A)

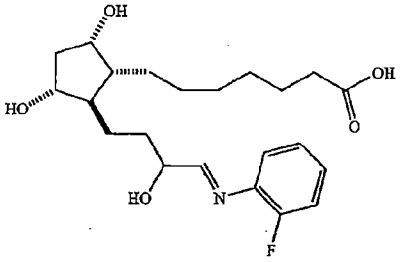
13,14-dihydro-16-oxo-17-amino-17-phenyl-17-trinor $PGF_{1\alpha}$ 1-methane sulfonamide



13,14-dihydro-16,17-didehydro-17-aza-17-phenyl-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehydro-17-aza-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehydro-17-aza-17-(2-furanyl)-17-trinor $PGF_{1\alpha}$

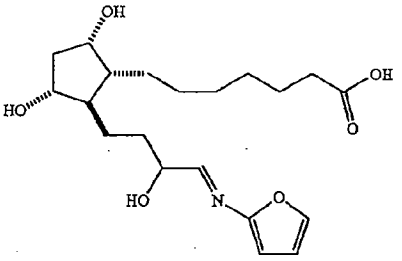
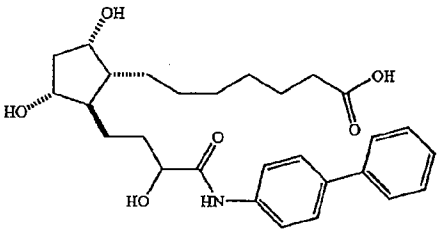


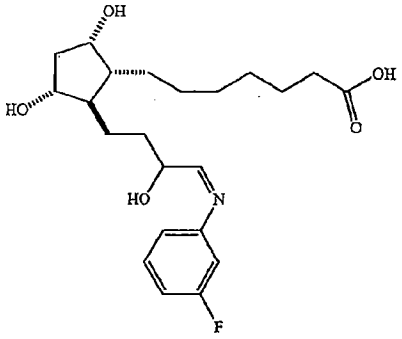
TABLE 1-continued

Examples of Suitable PGF's for Component A)

13,14-dihydro-16-oxo-17-aza--17-(4-phenylphenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehydro-17-aza-17-(3-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-didehydro-17-aza-17-(2-furanyl)-17-trinor $PGF_{1\alpha}$ 1-hydroxamic acid

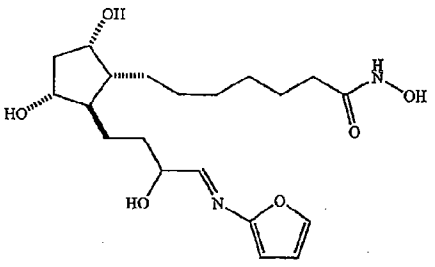


TABLE 1-continued

Examples of Suitable PGF's for Component A)
13,14-dihydro-16,17-didehydro-17-aza-17-(3 -chlorophenyl)-17-trinor $PGF_{1\alpha}$ 1-hydroxamic acid

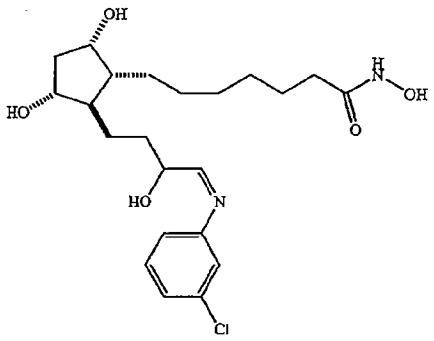
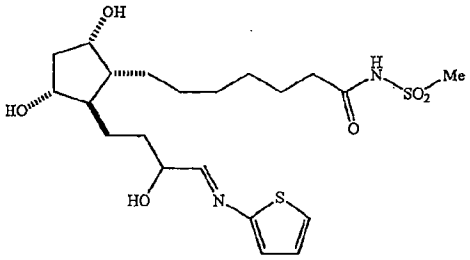


TABLE 1-continued

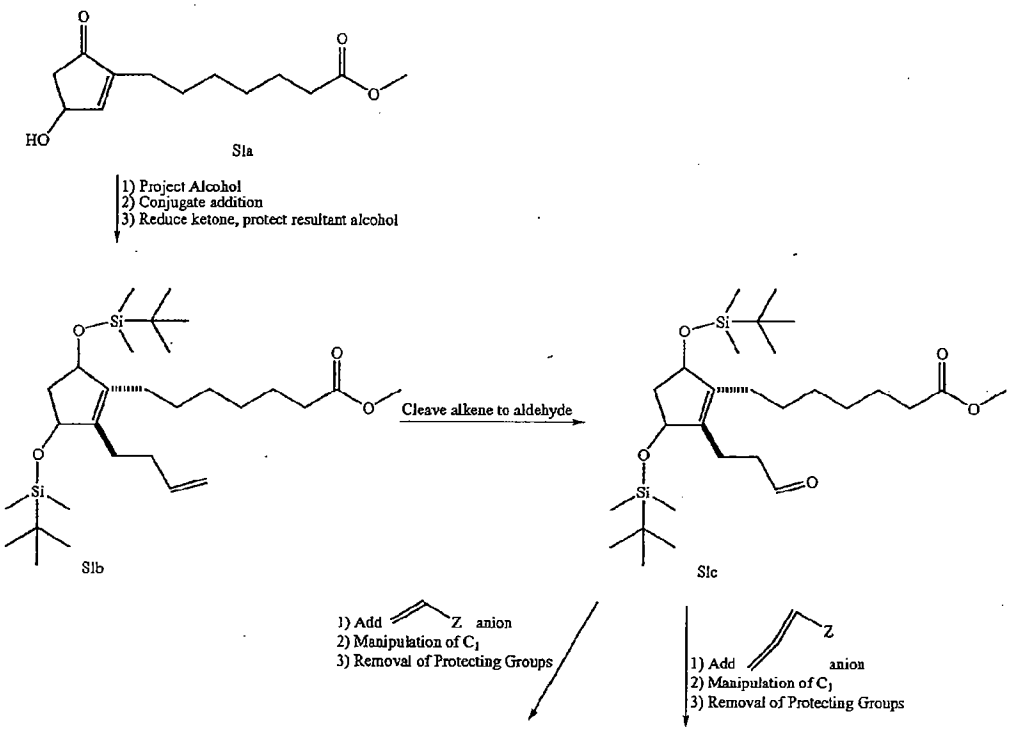
Examples of Suitable PGF's for Component A)
13,14-dihydro-16,17-didehydro-17-aza-17-(2-thienyl)-17-trinor $PGF_{1\alpha}$ 1-methanesulfonamide



Where Me in the table above represents a methyl group.

The PGF's in Table 1 can be prepared using conventional organic syntheses. Preferred syntheses are carried out using reaction schemes 1, 2, and 3. Scheme 1 describes a general reaction scheme for making PGFs wherein X is —CH=CH—(Formula I) or —CH=C=CH—(Formula II). Scheme 2 describes a general reaction scheme for making PGFs wherein X is —C(O)—(Formula III) or —C(O)Y—(Formula IV). Scheme 3 describes a general reaction scheme for making PGFs wherein X is —CH=N—(Formula V).

Scheme 1



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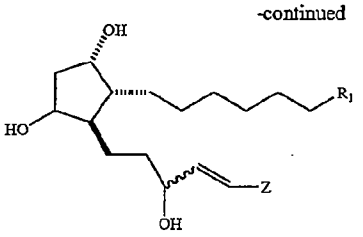
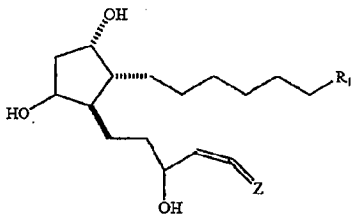


Formula I



Formula II

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 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 halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably −100° C. to 100° C., more preferably −80° C. to 80° C., and most preferably −70° C. to 23° C.

The resulting silylated compound is isolated by methods known to one of ordinary skill in the art. Such methods include 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 of 100° C. to 23° C., more preferably 85° C. to 30° C., and most preferably 75° C. to 65° C. The reaction time is preferably 1 to 6 hours, more preferably 2 to 5 hours, and most preferably 3 to 4 hours.

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

The alkene thus formed is isolated by methods known to one of ordinary skill in the art. Such methods include 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. (EtOAc represents ethyl acetate.)

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 of 31 100° C. to 23° C. The preferred temperature range is −60° C. to 0° C. The most preferred temperature range is −45° C. to −20° C.

The resulting alcohol is isolated by methods known to one of ordinary skill in the art. Such methods include 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 halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably −100° C. to 100° C., more preferably −80° C. to 80° C., and most preferably −70° C. to 23° C.

The resulting silylated compound, S1b is isolated by methods known to one of ordinary skill in the art. Such methods include 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 in which both are soluble. Preferred forms of osmium include osmium tetraoxide 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. (THF represents tetrahydrofuran.) The result of this treatment is the aldehyde, S1c.

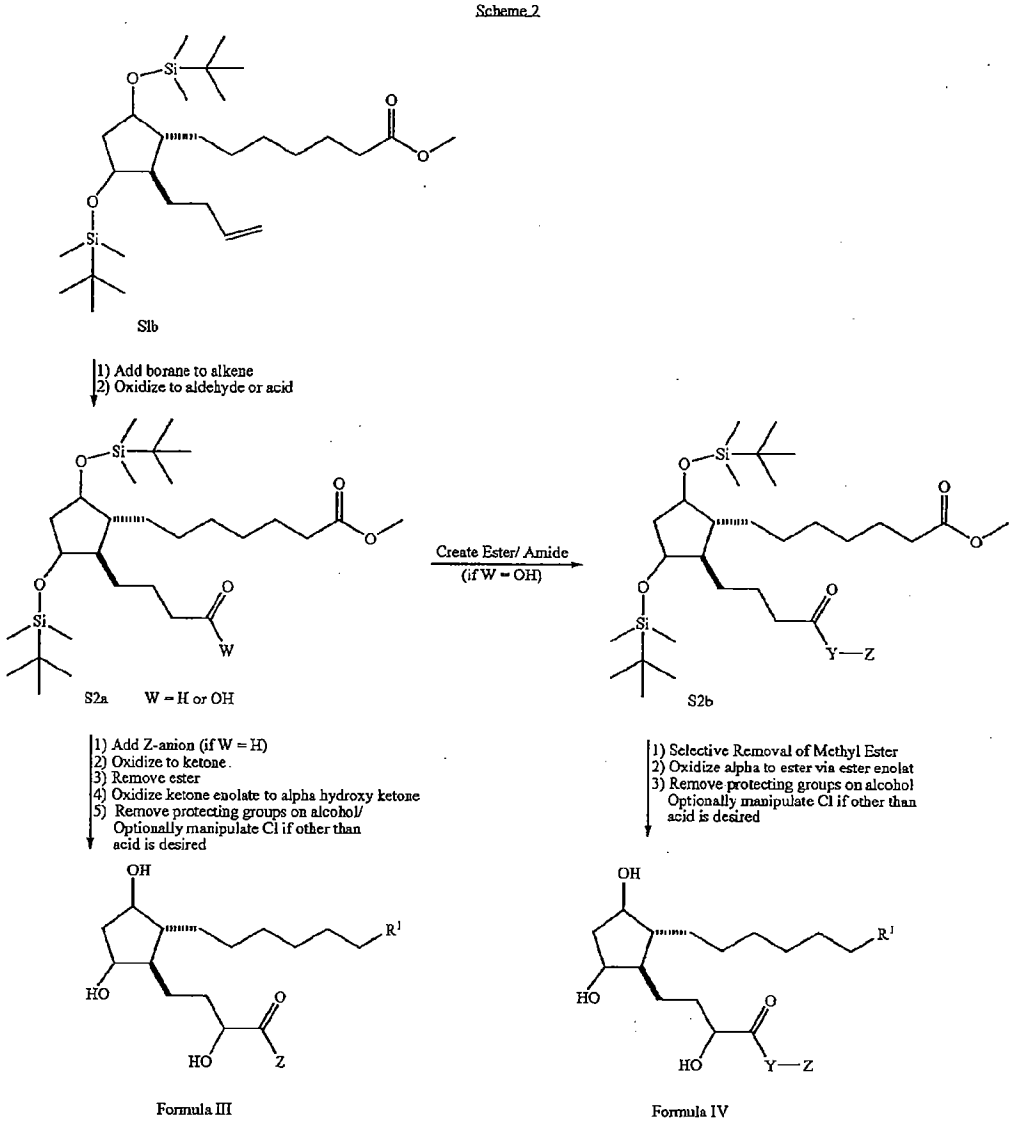
The compound S1c is isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization. Preferably, S1c is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

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 $F_{1\alpha}$ 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 R^1. 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 $F_{1\alpha}$ derivative, Formula I.

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 −80° C. to 0° C., more preferably −80° C. to −20° C., and most preferably −80° C. to −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 tetrahydrofuiran. 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.

Scheme 2



Formula III Formula IV

In Scheme 2, R^1, 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 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 about −20° C. to about +30° C. The preferred temperature range is about 0° C. to about +20° C. The hydroborated product of this reaction may then be oxidatively removed to the alcohol using alkaline hydrogen peroxide (See *Boranes in Organic Chemistry*, H. C. Brown, Cornell University Press, Ithaca, N.Y. 1972, pp. 321-325), which may then be oxidized to either the aldehyde (W=H) or to the acid (W=OH) using methods known to one of ordinary skill in the art. Alternatively, the hydroborated product may be directly oxidized to the aldehyde or acid by treatment with chromic acid or a Cr(VI) salt. 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 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.

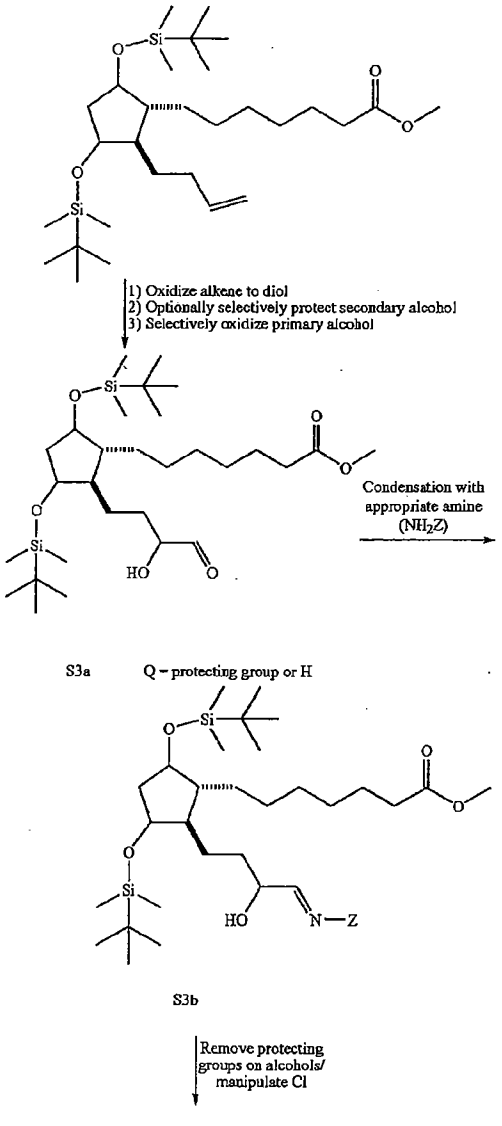
The key intermediate aldehyde depicted as S2a can be reacted with a variety unsaturated carbon nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin $F_{1\alpha}$ derivatives of Formula III.

With aromatic and heteroaromatic nucleophiles, the reaction is carried out preferably at −80° C. to 0° C., more preferably −80° C. to −20° C., and most preferably −80° C. to −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, N.Y. 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 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 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 dicyclohexylcarbodiimide ("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, N.Y. 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.

Scheme 3



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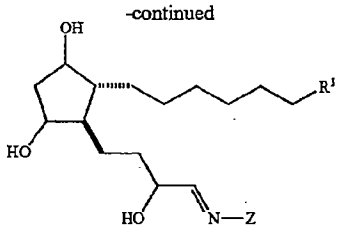


Formula V

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 several ways. For example, a selective oxidant such as DMSO-oxalyl chloride may be used. ("DMSO" represents dimethylsulfoxide.) 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 reagents. This technique yields compounds of the type S3a, wherein Q=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 of Formula V.

TABLE 2

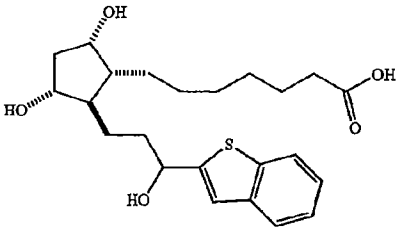
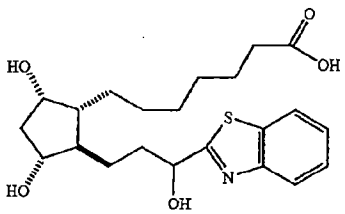
Examples of Suitable PGF's
13,14-dihydro-15-(2-benzothienyl)-15-pentanor $PGF_{1\alpha}$

13,14-dihydro-15-(2-benzothiazolyl)-15-pentanor $PGF_{1\alpha}$


TABLE 2-continued

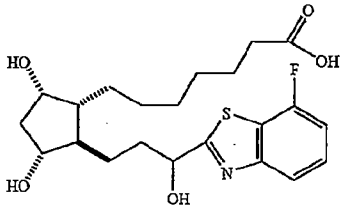
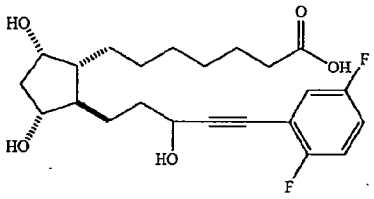
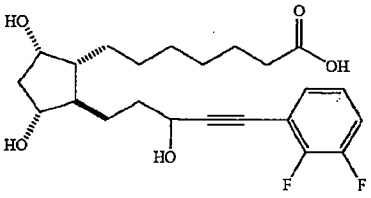
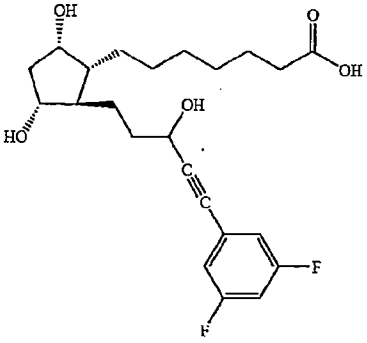
Examples of Suitable PGF's
13,14-dihydro-15-(8-fluoro-2-benzothiazolyl)-15-pentanor $PGF_{1\alpha}$

13,14-dihydro-16,17-ynyl17-(2,5-difluorophenyl)-17-trinor $PGF_{1\alpha}$

13,14-dihydro-16,17-ynyl-17-(2,3-difluorophenyl)-17-trinor $PGF_{1\alpha}$

13,14-dihydro-16,17-ynyl-17-(3,5-difluorophenyl)-17-trinor $PGF_{1\alpha}$


TABLE 2-continued

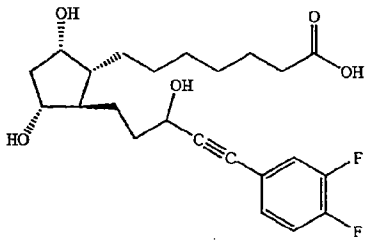
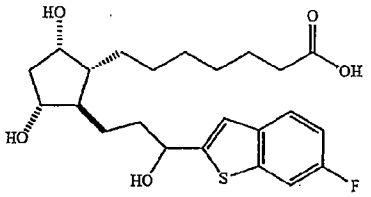
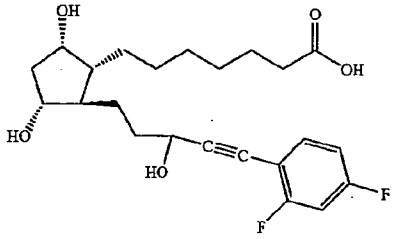
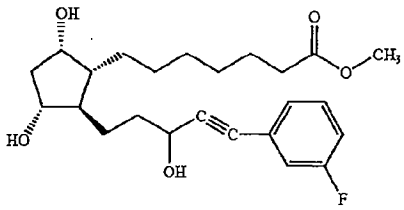
Examples of Suitable PGF's
13,14-dihydro-16,17-ynyl-17-(3,4-difluorophenyl)-17-trinor $PGF_{1\alpha}$ 
13,14-dihydro-15-(6-fluoro-2-benzothienyl)-15-pentanor $PGF_{1\alpha}$ 
3,14-dihydro-16,17-ynyl-17-(2,4-difluorophenyl)-17-trinor $PGF_{1\alpha}$ 
13,14-dihydro-16,17-ynyl-17-(3-fluorophenyl)-17-trinor $PGF_{1\alpha}$ methyl ester 

TABLE 2-continued

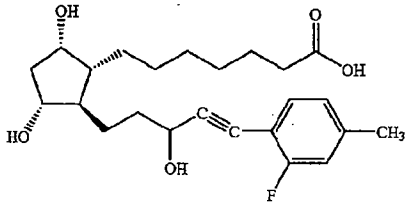
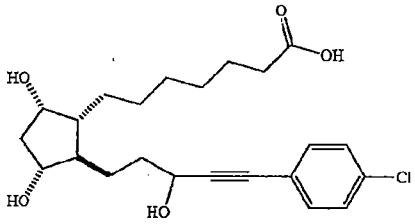
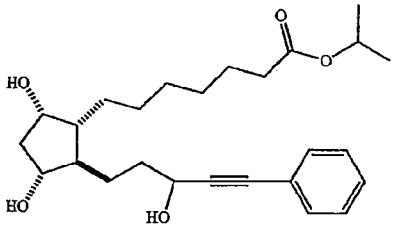
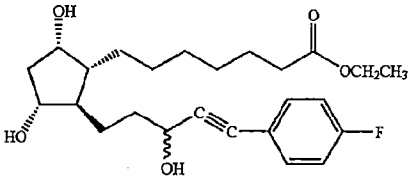
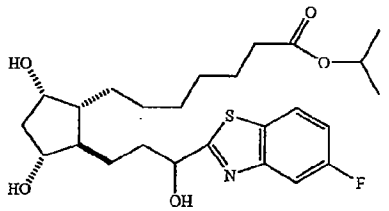
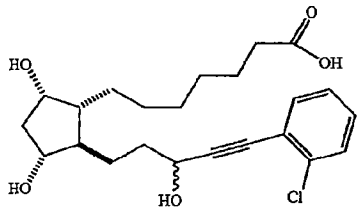
Examples of Suitable PGF's
13,14-dihydro-16,17-ynyl-17-(2-fluoro-4-methylphenyl)-17-trinor $PGF_{1\alpha}$ 
13,14-dihydro-16,17-ynyl-17-(4-chlorophenyl)-17-trinor $PGF_{1\alpha}$ 
13,14-dihydro-16,17-ynyl-17-phenyl-17-trinor $PGF_{1\alpha}$ isopropyl ester 
13,14-dihydro-16,17-ynyl-17-(4-fluorophenyl)-17-trinor $PGF_{1\alpha}$ ethyl ester 
13,14-dihydro-15-(5-fluoro-2-benzothiazolyl)-15-pentanor $PGF_{1\alpha}$ isopropyl ester 

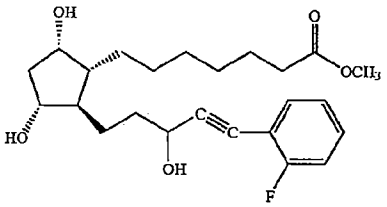
TABLE 2-continued

Examples of Suitable PGF's

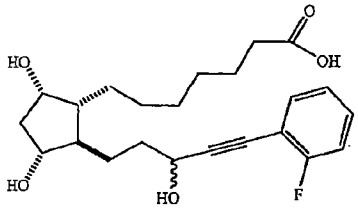
13,14-dihydro-16,17-ynyl-17-(2-chlorophenyl)-17-trinor $PGF_{1\alpha}$



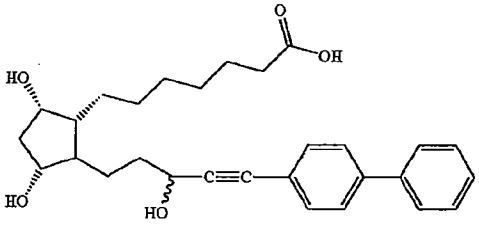
13,14-dihydro-16,17-ynyl-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$ methyl ester



13,14-dihydro-16,17-ynyl-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$



13,14-dihydro-16,17-ynyl-17-(4-phenyl-phenyl)-17-trinor $PGF_{1\alpha}$



13,14 dihydro-16,17-ynyl-18-phenyl-18-dinor $PGF_{1\alpha}$

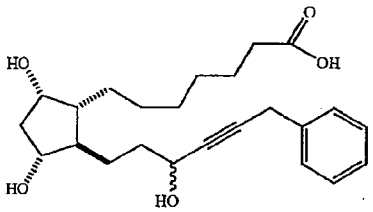
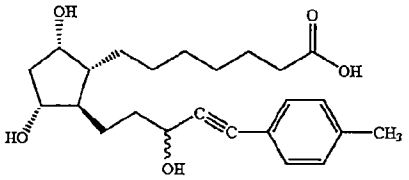


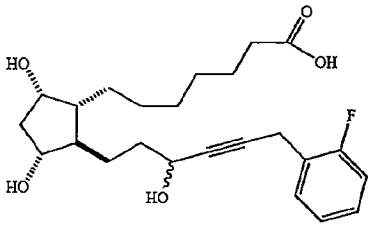
TABLE 2-continued

Examples of Suitable PGF's

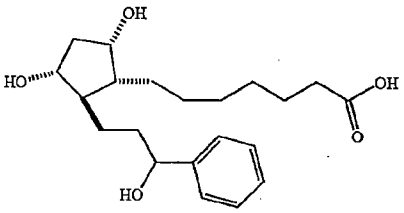
13,14-dihydro-16,17-ynyl-17-(4-methylphenyl)-17-trinor $PGF_{1\alpha}$



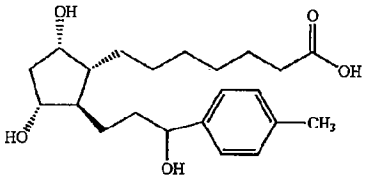
13,14-dihydro-16,17-ynyl-18-(2-fluorophenyl)-18-dinor $PGF_{1\alpha}$



13,14-dihydro-15-phenyl-15-pentenor $PGF_{1\alpha}$



13,14-dihydro-15-(4-methylphenyl)-15-pentanor $PGF_{1\alpha}$



13,14-dihydro-15-(4-trifluoromethylphenyl)-15-pentanor $PGF_{1\alpha}$

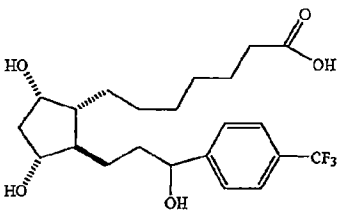


TABLE 2-continued

Examples of Suitable PGF's

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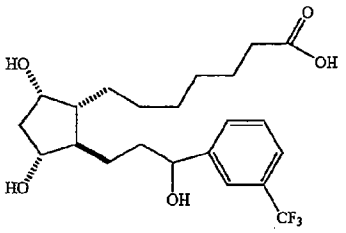
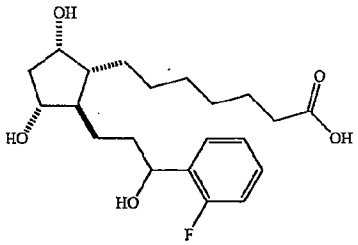
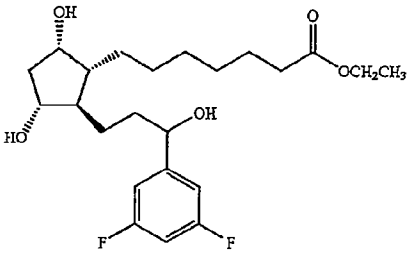


13,14-dihydro-15-(2-fluorophenyl)-15-pentanor $PGF_{1\alpha}$



13,14-dihydro-15-(3,5 difluorophenyl)-15-pentanor $PGF_{1\alpha}$ ethyl ester



13,14-dihydro-15-(3-chloro-4-fluoro-6-methylphenyl)-15pentanor $PGF_{1\alpha}$

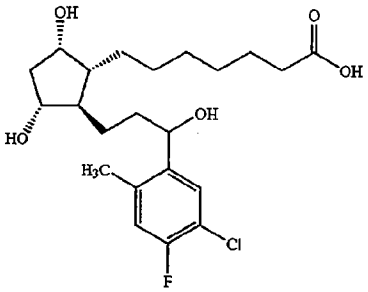


TABLE 2-continued

Examples of Suitable PGF's

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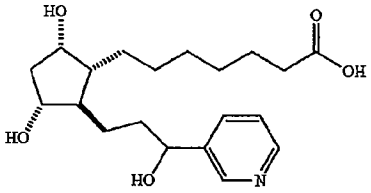
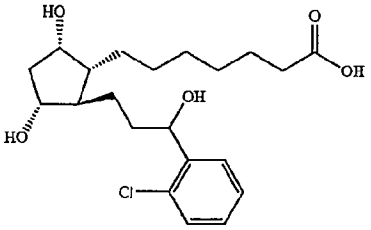
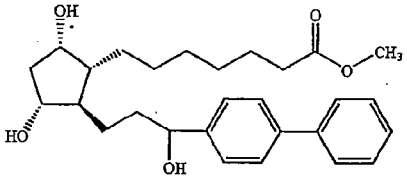


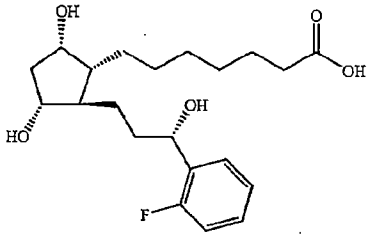
13,14-dihydro-15-(2-chlorophenyl)-15-pentanor $PGF_{1\alpha}$



13,14-dihydro-15-(4-phenylphenyl)-15-pentanor $PGF_{1\alpha}$ methyl ester



13,14-dihydro-15-S-(2-fluorophenyl)-15-peatanor $PGF_{1\alpha}$



13,14-dihydro-15-S-(2-fluoronaphthyl)-15-pentanor $PGF_{1\alpha}$

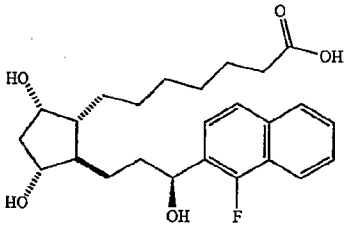


TABLE 2-continued

Examples of Suitable PGF's
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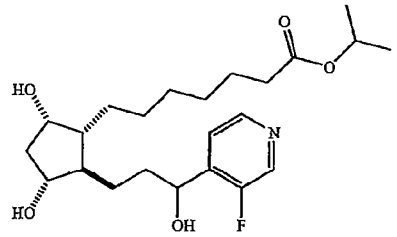
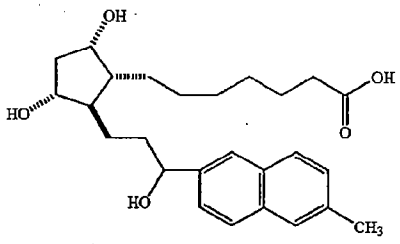
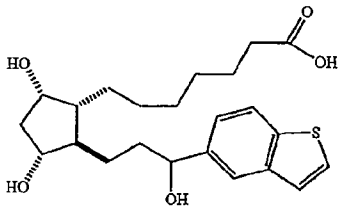
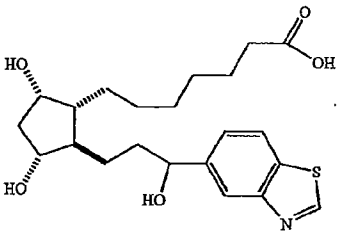

13,14-dihydro-15-(6-methylnaphth-2-yl)-15-pentanor $PGF_{1\alpha}$

13,14-dihydro-15-(benzo(b)thiophen-5-yl)-15-pentanor $PGF_{1\alpha}$

13,14-dihydro-15-(6-benzothiazol-5-yl)-15-pentanor $PGF_{1\alpha}$


TABLE 2-continued

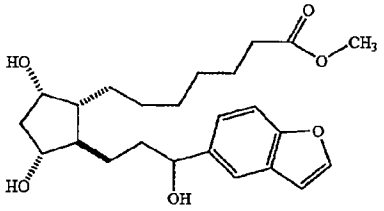
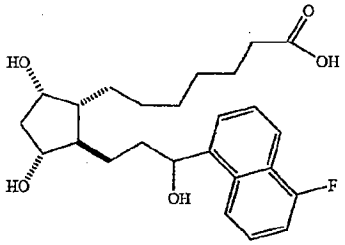
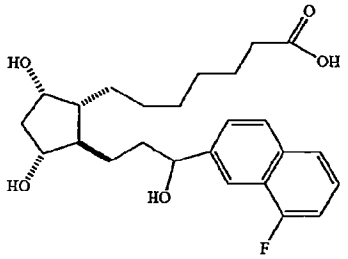
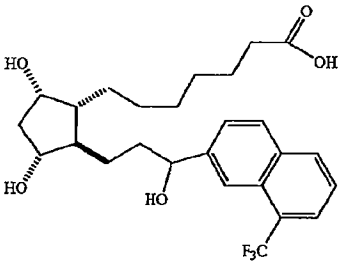
Examples of Suitable PGF's
13,14-dihydro-15-(benzofuran-5-yl)-15-pentanor $PGF_{1\alpha}$ methyl ester

13,14-dihydro-15-(5-fluoronaphth-1-yl)-15-pentanor $PGF_{1\alpha}$

13,14-dihydro-15-(8-fluoro-2-naphthyl)-15-pentanor $PGF_{1\alpha}$

13,14-dihydro-15-(8-trifluoromethyl-2-naphthyl)-15-pentanor $PGF_{1\alpha}$


TABLE 2-continued

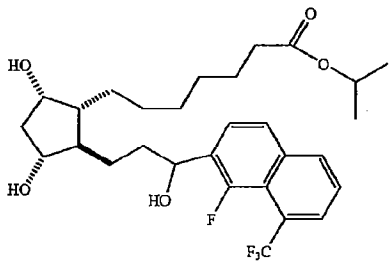
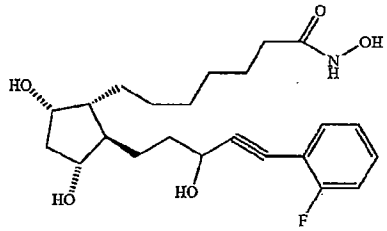
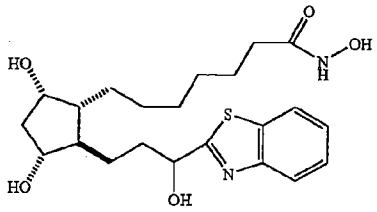
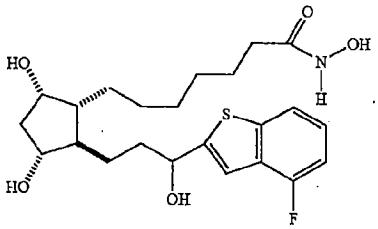
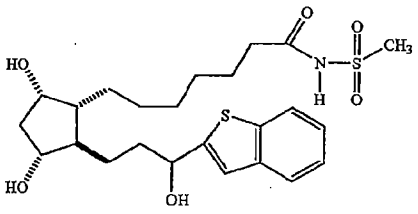
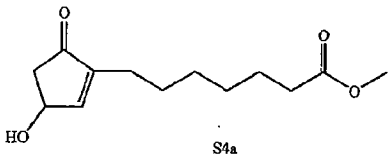
Examples of Suitable PGF's
13,14-dihydro-15-(1-fluoro-3-trifluoromethyl-2-naphthyl)-15-pentanor $PGF_{1\alpha}$ isopropyl ester

13,14-dihydro-16,17-ynyl-17-(2-fluorophenyl)-17-trinor $PGF_{1\alpha}$ hydroxamic acid


TABLE 2-continued

Examples of Suitable PGF's
13,14-dihydro-15-(benzothiazolyl)-15-pentanor $PGF_{1\alpha}$ 1-hydroxamic acid

13,14-dihydro-15-(4-fluoro-2-benzothienyl)-15-pentanor $PGF_{1\alpha}$ 1-hydroxamic acid

13,14-dihydro-15-(2-benzothienyl)-15-pentanor $PGF_{1\alpha}$ 1-N-methanesulfonamide


The PGF's in Table 2 can be prepared by conventional organic syntheses. A preferred synthesis is reaction scheme 4.

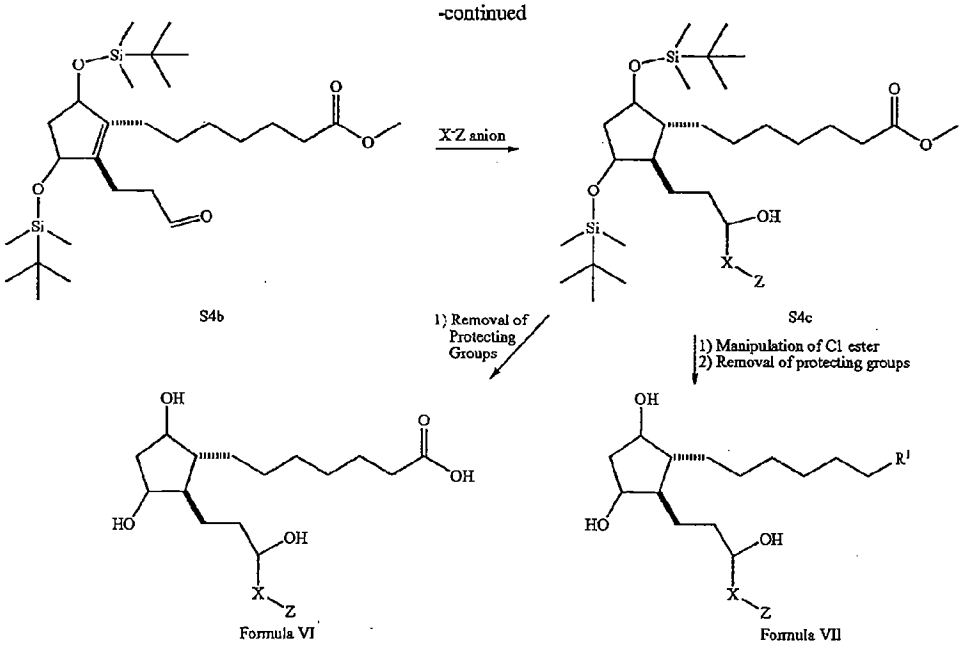
Scheme 4



S4a

1) Project alcohol
2) Conjugate addition
3) Reduce ketone, protect resultant alcohol
4) Cleave alkene to aldehyde

-continued



In Scheme 4, R^1, R^2, X, and Z are as defined above. The methyl 7(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (S4a) depicted as starting material for Scheme 4 is commercially available (such as from Sumitomo Chemical or Cayman Chemical).

The C_{11}, alcohol of methyl 7-(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (S4a) is protected with a suitable protecting group. The most preferred protecting group is a silyl group. In the above Scheme 4, methyl7-(3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl) heptanoate (S4a) 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 halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably −100° C. to 100° C., more preferably −80° C. to 80° C., and most preferably −70° C. to 23° C.

The resulting silylated compound is isolated by methods known to those of ordinary skill in the art. Such methods include 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, pp. 1460-69 (1975); and P. Knochel et. al., "Zinc and Copper Carbenoids as Efficient and Selective a'/d' Multicoupling Reagents", *J. Amer. Chem. Soc.*, Vol. 111, p. 6474-76 (1989). 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 of 100° C. to 23° C., more preferably 85° C. to 30° C., and most preferably 75° C. to 65° C. The reaction time is preferably 1 to 6 hours, more preferably 2 to 5 hours, and most preferably 3 to 4 hours.

Once the Grignard reagent is formed, the cuprate is generated from the alkenyl magnesium species. The temperature range for cuprate formation is −100° C. and 0° C. The preferred temperature range is −80° C. to −20° C., more preferably −75° C. to −50° C. The preferred reaction time is 30 minutes to 6 hours, more preferably 45 minutes to 3 hours, and most preferably 1 to 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 −60° C. to 0° C. The most preferred temperature range is −45° C. to −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 halogenated hydrocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature of preferably −100° C. to 100° C., more preferably −80° C. to 80° C., and most preferably −70° C. to 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 protected or 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 tetraoxide 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, S4b.

The compound S4b 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, S4b is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

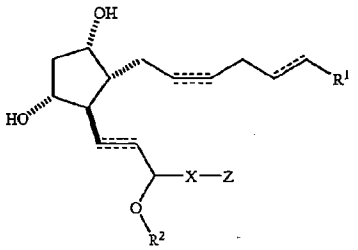
The key intermediate aldehyde depicted as S4b can be reacted with a variety unsaturated carbon nucleophiles to provide the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin $F_{1\alpha}$ derivatives depicted as S4c.

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

The resulting compounds depicted as S4c can then be deprotected using techniques known to one of ordinary skill in the art, and isolated yielding the 13,14-dihydro-15-substituted-15-pentanor prostaglandin $F_{1\alpha}$ derivatives depicted by Formula VI.

Compounds depicted by Formula VII can be made directly from the C-9 and C-11-protected 13,14-dihydro-16-tetranor prostaglandin $F_{1\alpha}$ derivatives depicted as S4c by methods known to one of ordinary skill in the art. For example, the condensation of methyl esters of S4c with amines or hydroxylamine provides compounds depicted by Formula VII. These compounds are isolated by methods known to one of ordinary skill in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization.

Examples of PGF's having the structure:



which are suitable for component A) include: cloprostenol (estrumate), fluprostenol (equimate), tiaprost, alfaprostol, delprostenate, froxiprost, 9-alpha, 11-alpha, 15-alpha-trihydroxy-16-(3-chlorophenoxy)-omega-tetranor-prosta-4-cis-13-trans-dienoic acid, latanoprost and their analogs; and 13,14-dihydro-16-((3-trifluoromethyl)phenoxy)-16-tetranor prostaglandin $F_{1\alpha}$, 17-((3-trifluoromethyl)phenyl)-17-trinor-prostaglandin $F_{2\alpha}$ and its analogs, 13,14-dihydro-18-thienyl-18-dinor prostaglandin $F_{1\alpha}$ and their analogs. Additional PGF's are also disclosed in *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids*, Volume I, Chemical and Biochemical Aspects, Part B. Ed. by Anthony L. Willis, CRC Press, Boca Raton, Table Four, pp. 80-97 (1987) and references therein.

Preferred PGF's of the present invention are further selective for the FP receptor over an excitatory prostaglandin receptor in a ratio of 1:10, preferably from 1:20, more preferably from 1:50.

Compositions of the Invention

This invention further relates to a composition for treating hair loss. "Treating hair loss" means arresting hair loss, reversing hair loss, or both, and promoting hair growth. The composition comprises component A) the PGF described above and component B) a carrier. The composition may further comprise component C) one or more optional activity enhancers.

The composition can be a pharmaceutical or cosmetic composition, administered for treatment or prophylaxis of hair loss. Standard pharmaceutical formulation techniques are used, such as those disclosed in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa. (1990).

The composition further comprises component B) a carrier. "Carrier" means one or more compatible substances that are suitable for administration to a mammal. Carrier includes solid or liquid diluents, hydrotopes, surface-active agents, and encapsulating substances. "Compatible" means that the components of the composition are capable of being commingled with the PGF's, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the mammal being treated. The carrier can be inert, or it can possess pharmaceutical benefits, cosmetic benefits, or both.

The choice of carrier for component B) depends on the route by which A) the PGF will be administered and the form of the composition. The composition may be in a variety of

forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, or parenteral) or topical administration (e.g., local application on the skin, ocular, liposome delivery systems, or iontophoresis). Topical administration directly to the locus of desired hair growth is preferred.

Carriers for systemic administration typically comprise one or more ingredients selected from the group consisting of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, j) preservatives, k) glidants, m) solvents, n) suspending agents, o) surfactants, combinations thereof, and others.

Ingredient a) is a diluent. Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; polyols such as propylene glycol; calcium carbonate; sodium carbonate; glycerin; mannitol; sorbitol; and maltodextrin.

Ingredient b) is a lubricant. Suitable lubricants are exemplified by solid lubricants including silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma.

Ingredient c) is a binder. Suitable binders include polyvinylpyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethylcellulose, methylcellulose, microcrystalline cellulose, and hydroxypropylmethylcellulose; carbomer; providone; acacia; guar gum; and xanthan gum.

Ingredient d) is a disintegrant. Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmelose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins.

Ingredient e) is a colorant such as an FD&C dye.

Ingredient f) is a flavor such as menthol, peppermint, and fruit flavors.

Ingredient g) is a sweetener such as saccharin and aspartame.

Ingredient h) is an antioxidant such as butylated hydroxyanisole, butylated hydroxytoluene, and vitamin E.

Ingredient j) is a preservative such as phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chorbutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben, and sodium benzoate.

Ingredient k) is a glidant such as silicon dioxide.

Ingredient m) is a solvent, such as water, isotonic saline, ethyl oleate, alcohols such as ethanol, glycerin, glycols (e.g., polypropylene glycol and polyethylene glycol), and buffer solutions (e.g., phosphate, potassium acetate, boric carbonic, phosphoric, succinic, malic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric and glutamic).

Ingredient n) is a suspending agent. Suitable suspending agents include AVICEL® RC-591 from FMC Corporation of Philadelphia, Pa. and sodium alginate.

Ingredient o) is a surfactant such as lecithin, polysorbate 80, sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters, lanolin esters, and lanolin ethers. Suitable surfactants are known in the art and commercially available, e.g., the TWEENS® from Atlas Powder Company of Wilmington, Del.

Compositions for parenteral administration typically comprise A) 0.1 to 10% of a PGF and B) 90 to 99.9% of a carrier comprising a) a diluent, and m) a solvent. Preferably, component a) is propylene glycol and m) is ethanol or ethyl oleate.

Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms comprise a safe and effective amount, usually at least 5%, and preferably from 25% to 50%, of A) the PGF. The oral dosage compositions further comprise B) 50 to 95% of a carrier, preferably 50 to 75%.

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically comprise A) the PGF, and B) a carrier comprising ingredients selected from the group consisting of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, k) glidants, and combinations thereof. Preferred diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Preferred binders include starch, gelatin, and sucrose. Preferred disintegrants include alginic acid, and croscarmelose. Preferred lubricants include magnesium stearate, stearic acid, and talc. Preferred colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain g) sweeteners such as aspartame and saccharin, or f) flavors such as menthol, peppermint, and fruit flavors.

Capsules (including time release and sustained release formulations) typically comprise A) the PGF, and B) a carrier comprising one or more a) diluents disclosed above in a capsule comprising gelatin. Granules typically comprise A) the PGF, and preferably further comprise k) glidants such as silicon dioxide to improve flow characteristics.

The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention. One skilled in the art can optimize appropriate ingredients without undue experimentation.

The solid compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that A) the PGF is released in the gastrointestinal tract at various times to extend the desired action. The coatings typically comprise one or more components selected from the group consisting of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, acrylic resins such as EUDRAGIT® coatings (available from Rohm & Haas G.M.B.H. of Darmstadt, Germany), waxes, shellac, polyvinylpyrrolidone, and other commercially available film-coating preparations such as Dri-Klear, manufactured by Crompton & Knowles Corp., Mahwah, N.J. or OPADRY® manufactured by Colorcon, Inc., of West Point, Pa.

Compositions for oral administration can also have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically comprise A) the PGF and B) a carrier comprising ingredients selected from the group consisting of a) diluents, e) colorants, and f) flavors, g) sweeteners, j) preservatives, m) solvents, n) suspending agents, and o) surfactants. Peroral liquid compositions preferably comprise one or more ingredients selected from the group consisting of e) colorants, f) flavors, and g) sweeteners.

Other compositions usefuil for attaining systemic delivery of the subject compounds include sublingual, buccal and

nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as a) diluents including sucrose, sorbitol and mannitol; and c) binders such as acacia, microcrystalline cellulose, carboxymethylcellulose, and hydroxypropylmethylcellulose. Such compositions may further comprise b) lubricants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, and k) glidants.

The compositions may further comprise component C) an optional activity enhancer. Component C) is preferably selected from the group consisting of i) hair growth stimulants (other than the PGF) and ii) penetration enhancers.

Component i) is an optional hair growth stimulant. Component i) is exemplified by vasodilators, antiandrogens, cyclosporins, cyclosporin analogs, antimicrobials, anti-inflammatories, thyroid hormones, thyroid hormone derivatives, and thyroid hormone analogs, non-selective prostaglandin agonists or antagonists, retinoids, triterpenes, combinations thereof, and others. "Non-selective prostaglandin" agonists and antagonists differ from component A) in that they do not selectively activate the FP receptor, and they may activate other receptors.

Vasodilators such as potassium channel agonists including minoxidil and minoxidil derivatives such as aminexil and those described in U.S. Pat. Nos. 3,382,247, 5,756,092, 5,772,990, 5,760,043, 5,466,694, 5,438,058, 4,973,474, and cromakalin and diazoxide can be used as optional hair growth stimulants in the composition.

Examples of suitable antiandrogens include 5-α-reductase inhibitors such as finasteride and those described in U.S. Pat. No. 5,516,779, and in Nane et al., *Cancer Research* 58, "Effects of Some Novel Inhibitors of C17,20-Lyase and 5α-Reductase in vitro and in vivo and Their Potential Role in the Treatment of Prostate Cancer," as well as cyproterone acetate, azelaic acid and its derivatives and those compounds described in U.S. Pat. No. 5,480,913, flutamide, and those compounds described in U.S. Pat. Nos. 5,411,981, 5,565,467, and 4,910,226.

Antimicrobials include selenium sulfide, ketoconazole, triclocarbon, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680, 745, clinacycin hydrochloride, benzoyl peroxide, benzyl peroxide and minocyclin.

Examples of suitable anti-inflammatories include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories including cyclooxygenase or lipoxygenase inhibitors such as those described in U.S. Pat. No. 5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published Mar. 31, 1994, and FR 2,268,523, published Nov. 21, 1975.

3,5,3'-Triiodothyronine is an example of a suitable thyroid hormone.

Examples of suitable non-selective prostaglandins agonists and antagonists include compounds such as those described in WO 98/33497, Johnstone, published Aug. 6, 1998, WO 95/11003, Stjernschantz, published Apr. 27, 1995, JP 97-100091, Ueno and JP 96-134242, Nakamura.

Suitable retinoids include isotretinoin, acitretin, and tazarotene.

Other optional hair growth stimulants for component i) include benzalkonium chloride, benzethonium chloride, phenol, estradiol, chlorpheniramine maleate, chlorophyllin derivatives, cholesterol, salicylic acid, cysteine, methionine, red pepper tincture, benzyl nicotinate, D,L - menthol, peppermint oil, calcium pantothenate, panthenol, castor oil, prednisolone, resorcinol, chemical activators of protein kinase C, glycosaminoglycan chain cellular uptake inhibitors, inhibitors of glycosidase activity, glycosaminoglycanase inhibitors, esters of pyroglutamic acid, hexosaccharic acids or acylated hexosaccharic acids, aryl-substituted ethylenes, N-acylated amino acids, flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Pat. Nos. 5,529,769, 5,468,888, 5,631,282, and 5,679,705, JP 10017431, WO 95/35103, JP 09067253, WO 92/09262, JP 62093215, and JP 08193094; saponins such as those described in EP 0,558,509 to Bonte et al., published Sep. 8, 1993 and WO 97/01346 to Bonte et al, published Jan. 16, 1997, proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Pat. Nos. 5,015,470, 5,300,284, and 5,185,325, estrogen agonists and antagonists, pseudoterins, cytokine and growth factor promoters, analogs or inhibitors such as interleukin-1 inhibitors, interleukin-6 inhibitors, interleukin-10 promoters, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthenol, interferon agonists and antagonists, hydroxyacids such as those described in U.S. Pat. No. 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin, and combinations thereof.

Other additional hair growth stimulants are described in JP 09-157,139 to Tsuji et al., published Jun. 17, 1997; EP 0277455 A1 to Mirabeau, published Aug. 10, 1988; WO 97/05887 to Cabo Soler et al., published Feb. 20, 1997; WO 92/16186 to Bonte et al., published Mar. 13, 1992; JP 62-93215 to Okazaki et al., published Apr. 28, 1987; U.S. Pat. No. 4,987,150 to Kurono et al., issued Jan. 22, 1991; JP 290811 to Ohba et al., published Oct. 15, 1992; JP 05-286,835 to Tanaka et al., published Nov. 2, 1993, FR 2,723,313 to Greff, published Aug. 2, 1994, U.S. Pat. No. 5,015,470 to Gibson, issued May 14, 1991, U.S. Pat. No. 5,559,092, issued Sep. 24, 1996, U.S. Pat. No. 5,536,751, issued Jul. 16, 1996, U.S. Pat. No. 5,714,515, issued Feb. 3, 1998, EPA 0,319,991, published Jun. 14, 1989, EPA 0,357,630, published Oct. 6, 1988, EPA 0,573,253, published Dec. 8, 1993, JP 61-260010, published Nov. 18, 1986, U.S. Pat. No. 5,772,990, issued Jun. 30, 1998, U.S. Pat. No. 5,053, 410, issued Oct. 1, 1991, and U.S. Pat. No. 4,761,401, issued Aug. 2, 1988.

The most preferred activity enhancers are minoxidil and finasteride, most preferably minoxidil.

Component ii) is a penetration enhancer that can be added to all of the compositions for systemic administration. The amount of component ii), when present in the composition, is typically 1 to 5%. Examples of penetration enhancers include 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, polyoxyethylene(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, polyoxyethylene(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, polyoxyethylene ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, isopropyl palmitate, ethyl laurate, 2-ethylhexyl pelargonate, isopropyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyr-

rolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, 1-dodecylazacycloheptan-2-one, omega three fatty acids and fish oils, and combinations thereof.

In a preferred embodiment of the invention, the PGF's are topically administered. Topical compositions that can be applied locally to the skin may be in any form including solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions comprise: component A) the PGF described above and component B) a carrier. The carrier of the topical composition preferably aids penetration of the PGF's into the skin to reach the environment of the hair follicle. Topical compositions preferably further comprise C) one or more of the optional activity enhancers described above.

The exact amounts of each component in the topical composition depend on various factors. The amount of component A) depends on the IC_{50} of the PGF selected. "IC_{50}" means inhibitory concentration 50th percentile. The amount of component A) added to the topical composition is:

$$IC_{50}\times 10^{-2} \cong \%\text{ of component } A) \cong IC_{50}\times 10^{-3},$$

where IC_{50} is expressed in nanomolar units. For example, if the IC_{50} of the PGF is 1 nM, the amount of component A) will be 0.001 to 0.01%. If the IC_{50} of the PGF is 10 nM, the amount of component A) will be 0.01 to 0.1%. If the IC_{50} of the PGF is 100 nM, the amount of component A) will be 0.1 to 1.0%. If the IC_{50} of the PGF is 1000 nM, the amount of component A) will be 1.0 to 10%, preferably 1.0 to 5%. If the amount of component A) is outside the ranges specified above (i.e., either higher or lower), efficacy of the treatment may be reduced. IC_{50} can be calculated according to the method in Reference Example 1, below. One skilled in the art can calculate IC_{50} without undue experimentation.

The topical composition preferably further comprises 1 to 20% component C), and a sufficient amount of component B) such that the amounts of components A), B), and C), combined equal 100%. The amount of B) the carrier employed in conjunction with the PGF is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: *Modern Pharmaceutics*, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., *Pharmaceutical Dosage Forms: Tablets* (1981); and Ansel, *Introduction to Pharmaceutical Dosage Forms*, 2nd Ed., (1976).

Component B) the carrier may comprise a single ingredient or a combination of two or more ingredients. In the topical compositions, component B) is a topical carrier. Preferred topical carriers comprise one or more ingredients selected from the group consisting of water, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, polypropylene glycol-2 myristyl propionate, dimethyl isosorbide, combinations thereof, and the like. More preferred carriers include propylene glycol, dimethyl isosorbide, and water.

The topical carrier may comprise one or more ingredients selected from the group consisting of q) emollients, r) propellants, s) solvents, t) humectants, u) thickeners, v) powders, and w) fragrances in addition to, or instead of, the preferred topical carrier ingredients listed above. One skilled in the art would be able to optimize carrier ingredients for the topical compositions without undue experimentation.

Ingredient q) is an emollient. The amount of ingredient q) in the topical composition is typically 5 to 95%. Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petrolatum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, polydimethylsiloxane, and combinations thereof. Preferred emollients include stearyl alcohol and polydimethylsiloxane.

Ingredient r) is a propellant. The amount of ingredient r) in the topical composition is typically 5 to 95%. Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof.

Ingredient s) is a solvent. The amount of ingredient s) in the topical composition is typically 5 to 95%. Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Preferred solvents include ethyl alcohol.

Ingredient t) is a humectant. The amount of ingredient t) in the topical composition is typically 5 to 95%. Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Preferred humectants include glycerin.

Ingredient u) is a thickener. The amount of ingredient u) in the topical composition is typically 0 to 95%.

Ingredient v) is a powder. The amount of ingredient v) in the topical composition is typically 0 to 95%. Suitable powders include chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminum silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof.

Ingredient w) is a fragrance. The amount of ingredient w) in the topical composition is typically 0.001 to 0.5%, preferably 0.001 to 0.1%.

Component C) the optional activity enhancer is as described above. Any of the i) hair growth stimulants and ii) penetration enhancers may be added to the topical compositions. Preferably, the topical composition comprises 0.01 to 15% of component i) the optional hair growth stimulant. More preferably, the composition comprises 0.1 to 10%, and most preferably 0.5 to 5% of component i). Preferably, the topical composition comprises 1 to 5% of component ii).

In an alternative embodiment of the invention, topical pharmaceutical compositions for ocular administration are prepared by conventional methods. Topical pharmaceutical compositions for ocular administration typically comprise A) a PGF, B) a carrier, such as purified water, and one or more ingredients selected from the group consisting of y) sugars such as dextrans, particularly dextran 70, z) cellulose or a derivative thereof, aa) a salt, bb) disodium EDTA (Edetate disodium), and cc) a pH adjusting additive.

Examples of z) cellulose derivatives suitable for use in the topical pharmaceutical composition for ocular administration include sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and hydroxypropylmethylcellulose. Hydroxypropylmethylcellulose is preferred.

Examples of aa) salts suitable for use in the for use in the topical pharmaceutical composition for ocular administration include sodium chloride, potassium chloride, and combinations thereof.

Examples of cc) pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of the topical pharmaceutical composition for ocular administration to 7.2-7.5.

This invention further relates to a method for darkening hair, thickening hair, and reversing hair graying. The method comprises applying the topical composition for treating hair loss to hair, to skin in the locus of hair, or both. For example, the topical composition may be applied to hair growing on the scalp or eyelashes. The topical composition can be, for example, a cosmetic composition prepared as described above. An example of a composition that may be applied to eyelashes is a mascara. The PGF may be added to mascara compositions known in the art, such as the mascara described in U.S. Pat. No. 5,874,072, which is hereby incorporated by reference. The mascara further comprises dd) a water-insoluble material, ee) a water-soluble, film-forming polymer, ff) a wax, o) a surfactant, gg) a pigment, and s) a solvent.

Ingredient dd) is a water-insoluble material selected from the group consisting of acrylate copolymers; styrene/acrylate/methacrylate copolymers; acrylic latex; styrene/acrylic ester copolymer latex; polyvinylacetate latex; vinyl acetate/ethylene copolymer latex; styrene/butadiene copolymer latex; polyurethane latex; butadiene/acrylonitrile copolymer latex; styrene/acrylate/acrylonitrile copolymer latex; and mixtures thereof, wherein the acrylate copolymers, and the styrene/acrylate/methacrylate copolymers additionally comprise ammonia, propylene glycol, a preservative and a surfactant.

Ingredient ee) is a water-soluble, film-forming polymer. Ingredient ee) is selected from the group consisting of vinyl alcohol/poly(alkyleneoxy)acrylate, vinyl alcohol/vinyl acetate/poly-(alkyleneoxy)acrylate, polyethylene oxide, polypropylene oxide, acrylates/octyl-acrylamide copolymers and mixtures thereof.

Ingredient ff) is a wax. "Wax" means a lower-melting organic mixture or compound of high molecular weight, solid at room temperature and generally similar in composition to fats and oils except that they contain no glycerides. Some are hydrocarbons, others are esters of fatty acids and alcohols. Waxes useful in this invention are selected from the group consisting of animal waxes, vegetable waxes, mineral waxes, various fractions of natural waxes, synthetic waxes, petroleum waxes, ethylenic polymers, hydrocarbon types such as Fischer-Tropsch waxes, silicone waxes, and mixtures thereof wherein the waxes have a melting point between 55 and 100° C.

Ingredient o) is surfactant, as described above. Ingredient o) in the mascara is preferably a surfactant having an HLB from 3 to 15. Suitable surfactants include those disclosed in the *C.T.F.A. Cosmetic Ingredient Handbook*, pp. 587-592 (1992); *Remington's Pharmaceutical Sciences*, 15th ed., pp. 335-337 (1975); and *McCutcheon's Volume 1, Emulsifiers & Detergents*, North American Edition, pp. 236-239 (1994).

Ingredient gg) is a pigment. Suitable pigments include inorganic pigments, organic lake pigments, pearlescent pigments, and mixtures thereof. Inorganic pigments useful in this invention include those selected from the group consisting of rutile or anatase titanium dioxide, coded in the Color Index under the reference CI 77,891; black, yellow, red and brown iron oxides, coded under references CI 77,499, 77,492 and, 77,491; manganese violet (CI 77,742); ultramarine blue (CI 77,007); chromium oxide (CI 77,288); chromium hydrate (CI 77,289); and ferric blue (CI 77,510); and mixtures thereof.

The organic pigments and lakes useful in this invention include those selected from the group consisting of D&C Red No. 19 (CI 45,170), D&C Red No. 9 (CI 15,585), D&C Red No. 21 (CI 45,380), D&C Orange No. 4 (CI 15,510), D&C Orange No. 5 (CI 45,370), D&C Red No. 27 (CI 45,410), D&C Red No. 13 (CI 15,630), D&C Red No. 7 (CI 15,850), D&C Red No. 6 (CI 15,850), D&C Yellow No. 5 (CI 19,140), D&C Red No. 36 (CI 12,085), D&C Orange No. 10 (CI 45,425), D&C Yellow No. 6 (CI 15,985), D&C Red No. 30 (CI 73,360), D&C Red No. 3 (CI 45,430), and the dye or lakes based on Cochineal Carmine (CI 75,570), and mixtures thereof.

The pearlescent pigments useful in this invention include those selected from the group consisting of the white pearlescent pigments such as mica coated with titanium oxide, bismuth oxychloride, colored pearlescent pigments such as titanium mica with iron oxides, titanium mica with ferric blue, chromium oxide and the like, titanium mica with an organic pigment of the above-mentioned type as well as those based on bismuth oxychloride and mixtures thereof.

Ingredient s) is a solvent described above, preferably water.

The amount of A) the PGF added to the mascara is as described above for topical compositions.

The PGF's may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds uses liposomes as described in Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An in vitro Study Using Hairless Mouse Skin", *S.T.P. Pharma Sciences*, Vol. 3, pp. 404-407 (1993); Wallach and Philippot, "New Type of Lipid Vesicle: Novasomeo®", *Liposome Technology*, Vol. 1, pp. 141-156 (1993); Wallach, U.S. Pat. No. 4,911,928, assigned to Micro-Pak, Inc., issued Mar. 27, 1990; and Weiner et al., U.S. Pat. No. 5,834,014, assigned to The University of Michigan and Micro-Pak, Inc., issued Nov. 10, 1998 (with respect to Weiner et al., with a compound as described herein administered in lieu of, or in addition to, minoxidil).

The PGF's may also be administered by iontophoresis. See, e.g., Internet site www.unipr.it/arpa/dipfarm/erasmus/erasm14.html; Banga et al., "Hydrogel-based Iontotherapeutic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", *Pharm. Res.*, Vol. 10 (5), pp. 697-702 (1993); Ferry, "Theoretical Model of Iontophoresis Utilized in Transdermal Drug Delivery", *Pharmaceutical Acta Helvetiae*, Vol 70, pp. 279-287 (1995); Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", *Int. J. Pharm.*, Vol. 123, pp. 159-171 (1995); Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin in vitro", *Pharm Res.*, Vol 8, pp. 1121-1127 (1991); Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", *Int. J. Pharm.*, Vol. 120, pp. 221-8 (1995); O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", *Drugs*, Vol. 37, pp. 233-309 (1989); Parry et al., "Acyclovir Biovailability in Human Skin", *J. Invest. Dermatol.*, Vol. 98 (6), pp. 856-63 (1992); Santi et al., "Drug Reservoir

Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", *Pharm Res.*, Vol 14 (1), pp. 63-66 (1997); Santi et al., "Reverse Iontophoresis-Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", *J. Control. Release*, Vol. 38, pp. 159-165 (1996); Santi et al., "Reverse Iontophoresis-Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", *J. Control. Release*, Vol. 42, pp. 29-36 (1996); Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring in vivo in Humans", *Pharm Res.*, Vol. 12 (12), pp. 1869-1873 (1995); Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", *J. Pharm. Pharmacol.*, Vol. 46, pp. 725-730 (1994); and Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through Nude Mouse Skin by Electrorepulsion and Electroosmosis", *Pharm Res.*, Vol. 12 (11), pp. 1623-1627 (1995).

The PGF's may be included in kits comprising a PGF, a systemic or topical composition described above, or both; and information, instructions, or both that use of the kit will provide treatment for hair loss in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may comprise a PGF, a composition, or both; and information, instructions, or both, regarding methods of application of the PGF or composition, preferably with the benefit of treating hair loss in mammals.

Methods of the Invention

This invention further relates to a method for treating hair loss in mammals. The method comprises administering to a mammal (preferably a human) suffering from hair loss, a PGF described above. For example, a mammal diagnosed with alopecia including male pattern baldness and female pattern baldness can be treated by the methods of this invention. Preferably, a systemic or topical composition comprising A) the PGF and B) a carrier is administered to the mammal. More preferably, the composition is a topical composition comprising A) the PGF, B) the carrier, and C) an optional activity enhancer.

The dosage of the PGF administered depends on the method of administration. For systemic administration, (e.g., oral, rectal, nasal, sublingual, buccal, or parenteral), typically, 0.5 mg to 300 mg, preferably 0.5 mg to 100 mg, more preferably 0.1 mg to 10 mg, of a PGF described above is administered per day. These dosage ranges are merely exemplary, and daily administration can be adjusted depending on various factors. The specific dosage of the PGF to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific PGF used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

For topical administration (e.g., local application on the skin, ocular, liposome delivery systems, or iontophoresis), the topical composition is typically administered once per day. The topical compositions are administered daily for a relatively short amount of time (i.e., on the order of weeks). Generally, 6 to 12 weeks is sufficient. The topical compositions are preferably leave-on compositions. In general, the topical composition should not be removed for at least several hours after administration.

In addition to the benefits in treating hair loss, the inventors have surprisingly found that the PGF's in the compositions and methods of this invention also darken and thicken hair and may reverse hair graying. This invention further relates to a method for darkening and thickening hair. The method comprises applying the topical composition for treating hair loss to growing hair and skin in the locus of the growing hair. In a preferred embodiment of the invention, the topical composition, such as the mascara composition described above, is applied to eyelashes.

EXAMPLES

These examples are intended to illustrate the invention to those skilled in the art and should not be interpreted as limiting the scope of the invention set forth in the claims.

Reference Example 1

Radioligand Binding Assay

IC_{50} of a PGF can be determined relative to $PGF_{2\alpha}$ using the Radioligand Binding Assay. As a control, the IC_{50} for $PGF_{2\alpha}$ a itself should be no lower than 1.0 nM and no higher than 5.0 nM.

In this assay, COS-7 cells are transiently transfected with the hFP recombinant plasmid using LipofectAMINE Reagent. Forty-eight hours later, the tranfected cells are washed with Hank's Balanced Salt Solution (HBSS, without $CaCl_2$, $MgCl_2$, $MgSO_4$, or phenol red). The cells are detached with versene, and HBSS is added. The mixture is centrifuged at 200 g for 10 minutes, at 4° C. to pellet the cells. The pellet is resuspended in Phosphate-Buffered Saline-EDTA buffer (PBS; 1 mM EDTA; pH 7.4; 4° C.). The cells are disrupted by nitrogen cavitation (Parr model 4639), at 800 psi, for 15 minutes at 4° C. The mixture is centrifuged at 1000 g for 10 minutes at 4° C. The supernatant is centrifuged at 100,000 g for 60 minutes at 4° C. The pellet is resuspended to 1 mg protein/mL TME buffer (50 mM Tris; 10 mM MgCl2; 1 mM EDTA; pH 6.0; 4° C.) based on protein levels measured using the Pierce BCA Protein Assay kit. The homogenate is mixed for 10 seconds using a Kinematica POLYTRON® (available from KINEMATICA AG, Luzernerstrasse147A CH-6014 Littau, Switzerland). The membrane preparations are then stored at −80° C., until thawed for assay use.

The receptor competition binding assays are developed in a 96 well format. Each well contains 100 g of hFP membrane, 5 nM (3H) PGF2, and the various competing compounds in a total volume of 200 L. The plates are incubated at 23° C. for 1 hour. The incubation is terminated by rapid filtration using the Packard Filtermate 196 harvester through Packard UNIFILTER® GF/B filters (available from Packard Instrument Co., Inc. of Downers Grove Ill.) pre-wetted with TME buffer. The filter is washed four times with TME buffer. Packard Microscint 20, a high efficiency liquid scintillation cocktail, is added to the filter plate wells and the plates remain at room temperature for three hours prior to counting. The plates are read on a Packard TOPCOUNT® Microplate Scintillation Counter (also available from Packard Instrument Co., Inc.)

Reference Example 2

Telogen Conversion Assay

PGF's are tested for their potential to grow hair using the Telogen Conversion Assay. The Telogen Conversion Assay measures the potential of a PGF to convert mice in the resting stage of the hair growth cycle ("telogen"), to the growth stage of the hair growth cycle ("anagen").

Without intending to be limited by theory, there are three principal phases of the hair growth cycle: anagen, catagen, and telogen. It is believed that there is a longer telogen period in C3H mice (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) from approximately 40 days of age until about 75 days of age, when hair growth is synchronized. It is believed that after 75 days of age, hair growth is no longer synchronized. Wherein about 40 day-old mice with dark fur (brown or black) are used in hair growth experiments, melanogenesis occurs along with hair (fur) growth wherein the topical application of hair growth inducers are evaluated. The Telogen Conversion Assay herein is used to screen PGF's for potential hair growth by measuring melanogenesis.

Three groups of 44 day-old C3H mice are used: a vehicle control group, a positive control group, and a test PGF group, wherein the test PGF group is administered a PGF used in the method of this invention. The length of the assay is 24 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. A typical study design is shown in Table 3 below. Typical dosage concentrations are set forth in Table 3, however the skilled artisan will readily understand that such concentrations may be modified.

TABLE 3

Assay Parameters

Group #	Animal #	Compound	Concentration	Application volume	Length of Study
1	1-10	Test Compound	0.01% in vehicle**	400 μL topical	26 days
2	11-20	Positive Control (T3)*	0.01% in vehicle**	400 μL topical	26 days
3	21-30	Vehicle**	N/A	400 μL topical	26 days

*T3 is 3,5,3'-triiodothyronine.
**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide (commercially available from Sigma Chemical Co., St. Louis, MO).

The mice are treated topically Monday through Friday on their lower back (base of tail to the lower rib). A pipettor and tip are used to deliver 400 μL to each mouse's back. The 400 μL application is applied slowly while moving hair on the mouse to allow the application to reach the skin.

While each treatment is being applied to the mouse topically, a visual grade of from 0 to 4 will be given to the skin color in the application area of each animal. As a mouse converts from telogen to anagen, its skin color will become more bluish-black. As indicated in Table 4, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black.

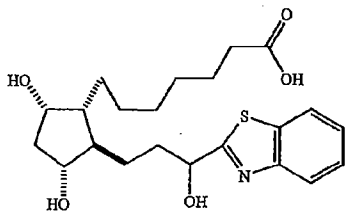
TABLE 4

Evaluation Criteria

Visual Observation	Grade
Whitish Skin Color	0
Skin is light gray (indication of initiation of anagen)	1
Appearance of Blue Spots	2
Blue Spots are aggregating to form one large blue area	3
Skin is dark blue (almost black) with color covering majority of treatment area (indication of mouse in full anagen)	4

Example 1

13,14-dihydro-15-(2-benzathiozolyl) pentanor Prostaglandin $F_1\alpha$, having the structure:

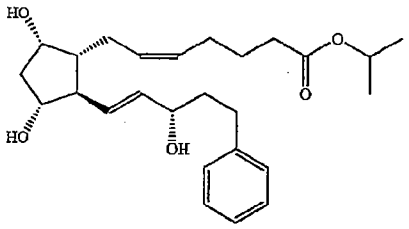


was tested according to the method Reference Example 1. 13,14-dihydro-15-(2-benzathiozolyl) pentanor Prostaglandin $F_1\alpha$ grew hair and had IC_{50} of 45nM.

Comparative Example 1

Latanoprost, having the structure:

Latanoprost



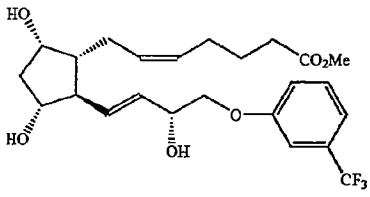
was tested according to the method Reference Example 1. Latanoprost was active at 0.01% and 0.1%. Grades representing the average animal score on day 26 are reported in Table 5.

However, latanoprost is nonselective. Although latanoprost does not negate the effect of activating the FP receptor, latanoprost also activates the EP_1 receptor, which which results in the side effect of causing pain.

Example 2

Fluprostenol Methyl Ester having the structure:

Fluprostenol Methyl Ester



was tested according to the method Reference Example 1. Fluprostenol grew hair at 0.01% and 0.1%. Grades representing the average animal score on day, 26 are reported in Table 5.

TABLE 5

Example	PGF	Grades 0.01%	0.1%
Comparative Example 1	latanaprost	0.71	2.9
Example 2	fluprostenol methyl ester	3.9	2.6

Comparative Example 2

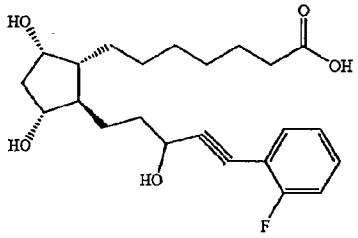
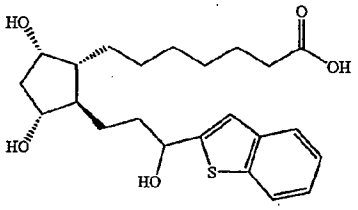
A composition containing 0.01% of a T3 compound was prepared and tested according to the method of Reference Example 1. The T3 compound grew hair.

Example 3

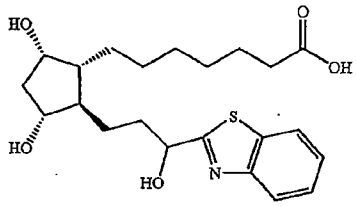
Compositions for topical administration are made, comprising:

Component	3-1	3-2	3-3
PGF (wt %)	0.019	0.027	0.045
IC_{50} the PGF (nM)	19	27	45
Ethanol (wt %)	59.988	59.983	59.973
Propylene Glycol (wt %)	19.996	19.995	19.991
Dimethyl Isosorbide (wt %)	19.996	19.995	19.991

The PGFs in the compositions are as follows:

Sample	PGF
3-1	
3-2	

-continued

Sample	PGF
3-3	

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, one of the above compositions is daily administered topically to the subject to induce hair growth.

Example 4

A composition for topical administration is made according to the method of Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An in vitro Study Using Hairless Mouse Skin", *S.T.P. Pharma Sciences*, Vol. 3, pp. 404-407 (1993), using a PGF in lieu of cyclosporin A and using the NOVASOME® 1 (available from Micro-Pak, Inc. of Wilmington, Del.) for the non-ionic liposomal formulation.

A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

Example 5

Shampoos are made, comprising:

Component	Ex. 5-1	Ex. 5-2	Ex. 5-3	Ex. 5-4
Ammonium Lauryl Sulfate	11.5%	11.5%	9.5%	7.5%
Ammonium Laureth Sulfate	4%	3%	2%	2%
Cocamide MEA	2%	2%	2%	2%
Ethylene Glycol Distearate	2%	2%	2%	2%
Cetyl Alcohol	2%	2%	2%	2%
Stearyl Alcohol	1.2%	1.2%	1.2%	1.2%
Glycerin	1%	1%	1%	1%
Polyquaternium 10	0.5%	0.25%	—	—
Polyquaternium 24	—	—	0.5%	0.25%
Sodium Chloride	0.1%	0.1%	0.1%	0.1%
Sucrose Polyesters of Cottonate Fatty Acid	3%	3%	—	—
Sucrose Polyesters of Behenate Fatty Acid	2%	3%	—	—
Polydimethyl Siloxane	—	—	3%	2%
Cocaminopropyl Betaine	—	1%	3%	3%
Lauryl Dimethyl Amine Oxide	1.5%	1.5%	1.5%	1.5%
Decyl Polyglucose	—	—	1%	1%
DMDM Hydantoin	0.15%	0.15%	0.15%	0.15%
PGF having IC_{50} of 19 nM	—	0.019%	0.019%	—
PGF having IC_{50} of 45 nM	0.045%	—	—	0.045%
Minoxidil			3%	2%
Phenoxyethanol	0.5%	0.5%	0.5%	0.5%
Fragrance	0.5%	0.5%	0.5%	0.5%
Water	q.s.	q.s.	q.s.	q.s.

The PGF having IC_{50} of 19 nM is the same as that in Example 3-1.

The PGF having IC_{50} of 45 nM is the same as that in Example 3-3.

A human subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, a shampoo described above is used daily by the subject.

Example 6

A mascara composition is prepared. The composition comprises:

Component	% W/W
WATER, DEIONIZED, USP	q.s
BLACK 1080 MICRONIZED TYPE	10.000
GLYCERYL MONOSTEARATE (2400 TYPE)	8.500
C18–36 ACID TRIGLYCERIDE	5.500
STEARIC ACID, TRIPLE PRESSED, LIQUID	4.000
ETHYL ALCOHOL SD 40-B, 190 PROOF/SERIAL #:	4.000
BEESWAX WHITE, FLAKES	3.250
SHELLAC, NF	3.000
LECITHIN, GRANULAR (TYPE 6450)	2.500
TRIETHANOLAMINE 99% - TANK	2.470
PARAFFIN WAX	2.250
PARAFFIN WAX 118/125	2.250
CARNAUBA WAX, NF	2.000
POTASSIUM CETYL PHOSPHATE	1.000
PHENOXYETHANOL	0.800
OLEIC ACID NF	0.750
DL-PANTHENOL	0.350
PVP/VA COPOLYMER	0.250
METHYLPARABEN, NF	0.200
DIAZOLIDINYL UREA	0.200
SIMETHICONE	0.200
ETHYLPARABEN NF	0.150
PENTAERYTHRITYL HYDROGENATED ROSINATE	0.150
PROPYLPARABEN, NF	0.100
TRISODIUM EDTA	0.100
PGF having IC_{50} of 19 nM	0.019

The PGF is the same as that used in Example 3-1.

A human female subject applies the composition each day. Specifically, for 6 weeks, the above composition is administered topically to the subject to darken and thicken eyelashes.

Example 7

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

Ingredient	Quantity (mg per tablet)
PGF	0.5
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

The PGF is the same as that used in Example 3-3.

The above composition is administered orally to a subject once daily for 6 to 12 weeks to promote hair growth.

Example 8

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

Ingredient	Quantity
PGF	0.1 mg
Phosphate buffered physiological saline	10 ml
Methyl Paraben	0.05 ml

The PGF is the same as that used in Example 3-3.

1.0 ml of the above composition is administered subcutaneously once daily at the site of hair loss for 6 to 12 weeks to promote hair growth.

Example 9

A topical pharmaceutical composition is prepared by conventional methods and formulated as follows:

Ingredient	Amount (wt %)
PGF	0.004
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
HCL and/or NaOH	pH 7.2–7.5
Purified water	q.s. to 100%

The PGF is the same as that used in Example 3-3.

The above composition is administered ocularly to a subject once per day for 6 to 12 weeks to promote eyelash growth.

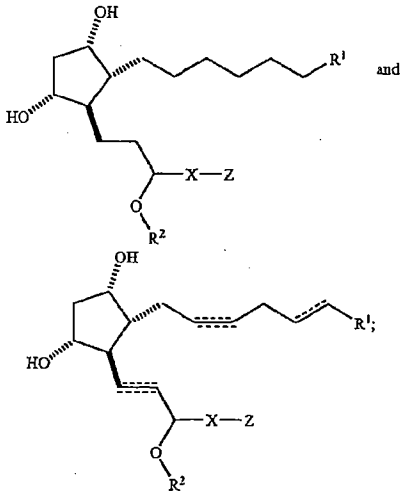
Effects of the Invention

The compositions and methods herein provide a cosmetic benefit with respect to hair growth and appearance in subjects desiring such treatment.

What is claimed is:

1. A method of treating hair loss comprising administering to a mammal a composition comprising:

A) an active ingredient selected from the group consisting of a prostaglandin F analog having a structure selected from the group consisting of



and

pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; optical isomers, diastereomers, and enantiomers of the structures above; and combinations thereof;

wherein R^1 is selected from the group consisting of C(O)OH, C(O)NHOH, C(O)OR^3, CH_2OH, $S(O)_2R^3$, C(O)NHR^3, C(O)$NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogenous group, and a lower monovalent hydrocarbon group;

R^3 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of —C≡C—, a covalent bond, —CH═C═CH—, —CH═CH—, —CH═N—, —C(O)—, —C(O)Y—, $—(CH_2)_n—$, wherein n is 2 to 4, $—CH_2NH—$, $—CH_2S—$, and $—CH_2O—$;

Y is selected from the group consisting of a sulfur atom, an oxygen atom, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

with the proviso that when the bond at the C2-C3 position is a single bond, the bond at the C5-C6 position is a double bond, R^1 is C(O)OR^3 and R^3 is a monovalent hydrocarbon group or substituted monovalent hydrocarbon group, then R^2 is not hydrogen.

2. The method of claim 1, wherein R^1 is selected from the group consisting of CO_2H, C(O)NHOH, CO_2R^3, C(O)$NHS(O)_2R^4$, and tetrazole.

3. The method of claim 1, wherein R^2 is a hydrogen atom.

4. The method of claim 1, wherein R^3 is selected from the group consisting of methyl, ethyl, and isopropyl.

5. The method of claim 1, wherein R^4 is a phenyl group.

6. The method of claim 1, wherein X is a covalent bond and Z is selected from the group consisting of an aromatic ring, a heteroaromatic ring, a substituted aromatic ring, and a substituted heteroaromatic ring.

7. The method of claim 1, wherein X is —C≡C—, and Z is a monocyclic aromatic ring.

8. The method of claim 1, wherein the composition is administered by a route selected from the group consisting of systemic and topical routes.

9. The method of claim 8, wherein the composition is a topical composition in a form selected from the group consisting of solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, and skin patches.

10. The method of claim 8, wherein the composition is a topical composition further comprising B) a carrier, wherein the carrier is selected from the group consisting of water, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, dimethyl isosorbide, polypropylene glycol-2 myristyl propionate, and combinations thereof.

11. The method of claim 8, wherein the composition further comprises C) an activity enhancer selected from the group consisting of i) a hair growth stimulant, ii) a penetration enhancer, and combinations thereof.

12. The method of claim 11, wherein component i) is selected from the group vasodilator, an antiandrogen, a cyclosporin, a cyclosporin analog, an antimicrobial, an anti-inflammatory, a thyroid hormone, a thyroid hormone derivative, and a thyroid hormone analog, a non-selective prostaglandin agonist, a non-selective prostaglandin antagonist, a retinoid, a triterpene, and combinations thereof.

13. The method of claim 11, wherein component ii) is selected from the group consisting of 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropancate, hexan-2,5-diol, polyoxyethylene(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, polyoxyethylene(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, polyoxyethylene ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, isopropyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, isopropyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, 1-dodecylazacycloheptan-2-one, and combinations thereof.

14. The method of claim 8, wherein the composition is a topical composition locally administered on the skin once per day.

15. The method of claim 14, wherein the composition is administered once per day for 6 to 12 weeks.

16. The method of claim 1, wherein R^1 is selected from the group consisting of C(O)NHOH, C(O)OR^3, CH_2OH, $S(O)_2R^3$, C(O)NHR^3, C(O)$NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms; and

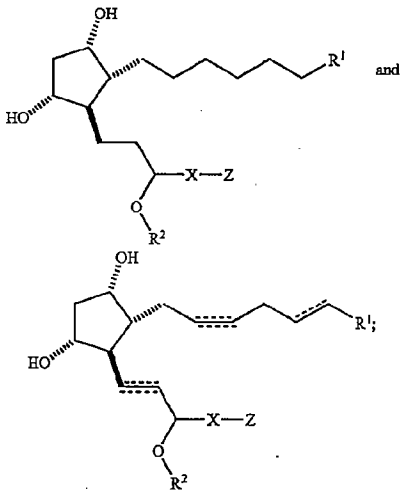
R^3 is selected from the group consisting of a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group.

17. The method of claim 16, wherein R^3 is selected from the group consisting of a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaro-

matic group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group.

18. A method of treating hair loss comprising administering to a mammal a composition comprising:

A) an active ingredient selected from the group consisting of a prostaglandin F analog having a structure selected from the group consisting of



and

pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; optical isomers, diastereomers, and enantiomers of the structures above; and combinations thereof;

wherein R^1 is selected from the group consisting of C(O)OH, C(O)NHOH, $C(O)OR^3$, CH_2OH, $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogeneous group, and a lower monovalent hydrocarbon group;

R^3 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of -C≡C-, a covalent bond, -CH=C=-CH-, -CH=CH-, -CH=N-, -C(O)-, -C(O)Y-, $-(CH_2)n-$, wherein n is 2 to 4, $-CN_2NH-$, $-CH_2S-$, and $-CH_2)-$;

Y is selected from the group consisting of a sulfur atom, an oxygen atom, and NH; and

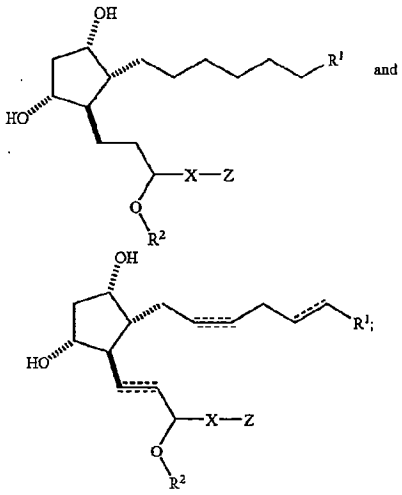
Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

with the proviso that when the bond at the C2-C3 position is a single bond, the bond at the C5-C6 position is a double bond, R^1 is C(O)OH or $C(O)OR^3$ and R^3 is a monovalent hydrocarbon group or substituted monovalent hydrocarbon group, then X is selected from the group consisting of -C≡C-, -CH=C=CH-, -CH=CH- and -CH=N-.

19. The method of claim 18, wherein the composition is administered by a route selected from the group consisting of systemic and topical routes.

20. A method of treating hair loss comprising administering to a mammal a composition comprising:

A) an active ingredient selected from the group consisting of a prostaglandin F analog having a structure selected from the group consisting of



and

pharmaceutically acceptable salts and hydrates of the structures above; biohydrolyzable amides, esters, and imides of the structures above; optical isomers, diastereomers, and enantiomers of the structures above; and combinations thereof;

wherein R^1 is selected from the group consisting of C(O)OH, C(O)NHOH, $C(O)OR^3$, CH_2OH, $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms;

R^2 is selected from the group consisting of a hydrogen atom, a lower heterogeneous group, and a lower monovalent hydrocarbon group;

R^3 is selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a sub-

stituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

R^4 selected from the group consisting of a monovalent hydrocarbon group, a heterogeneous group, a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted monovalent hydrocarbon group, a substituted heterogeneous group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group;

X is selected from the group consisting of -C≡C-, a covalent bond, -CH=C=CH-, -CH=CH-, -CH=N-, -C(O)-, -C(O)Y-, $-(CH_2)_n-$, wherein n is 2 to 4, $-CH_2NH-$, $-CH_2S-$, and $-CH_2)-$;

Y is selected from the group consisting of a sulfur atom, an oxygen atom, and NH; and

Z is selected from the group consisting of a carbocyclic group, a heterocyclic group, an aromatic group, a heteroaromatic group, a substituted carbocyclic group, a substituted heterocyclic group, a substituted aromatic group, and a substituted heteroaromatic group,

with the proviso that when the bond at the C2-C3 position is a single bond, the bond at the C5-C6 position is a double bond, R^1 is C(O)OH or $C(O)OR^3$ and R^3 is a monovalent hydrocarbon group or substituted monovalent hydrocarbon group, then Z is selected from the group consisting of a heterocyclic group, a substituted heterocyclic group and a substituted heteroaromatic group.

* * * * *

Exhibit E

LICENSE AGREEMENT

THIS Agreement is entered into this 18 day of December, 2007 ("Effective Date") between DUKE UNIVERSITY, a nonprofit educational and research institution organized under the laws of North Carolina ("DUKE"), having a place of business at Durham, North Carolina 27710, and Allergan, Inc., a Delaware Corporation and Allergan Sales LLC, a Delaware Limited Liability Company (collectively "Licensee"), with each having its principal place of business at 2525 Dupont Drive, Irvine, California 92612 (hereinafter "Agreement").

RECITALS

A. Patent Rights (defined below) were donated to DUKE by Proctor & Gamble under a donation agreement, and DUKE now owns the Patent Rights and has the right to grant licenses under the Patent Rights. Such Patent Rights are described in DUKE Office of Licensing & Ventures File #2357, titled "Hair Loss Drug Development Project." The Duke employees who were assigned as inventors ("Inventors" defined below), have continued research on this project at DUKE and will share in revenues as Inventors under the Duke Patent Policy.

B. DUKE desires to have its Patent Rights developed and commercialized to benefit the public and is willing to grant a license to the Licensee for that purpose.

C. Licensee desires to obtain a license under the Patent Rights upon the terms and conditions set forth in this Agreement.

NOW, THEREFORE, in consideration of the premises and the mutual covenants set forth herein, and for good and valuable consideration, the receipt and sufficiency of which is acknowledged, the parties hereto, intending to be legally bound, agree as follows:

TERMS AND CONDITIONS:

ARTICLE 1 – DEFINITIONS

For the purposes of this Agreement, the terms and phrases below have the following definitions:

1.01 "Affiliate" means any corporation or non-corporate entity that controls, is controlled by or is under the common control with a party. A corporation or a non-corporate entity, as applicable, is deemed to be in control of another corporation if (a) it owns or directly or indirectly controls at least 50% of the voting stock of the other corporation or (b) in the absence of ownership of at least 50% of the voting stock of a corporation, or in the case of a non

corporate entity, if it possesses directly or indirectly, the power to direct or cause the direction of the management and policies of such corporation or non-cooperate entity, as applicable.

1.02. "Field of Use" means treating the loss or promoting the growth of eyelashes and/or eyebrows (excluding hair loss or growth on the scalp or elsewhere on the body other than on eyebrows and eyelashes).

1.03 "Patent Rights" means (a) the patents and patent applications listed in Appendix A (hereafter referred to as "Patent Applications"); (b) any patent (US or foreign) issuing on any such Patent Applications; and (c) all divisions, continuations, continuations-in-part (but only to the extent that the subject matter of each such continuation-in-part application is described in and enabled by the disclosure of the Patent Applications), re-examinations, reissues, substitutions, or extensions thereof and patent issuing from those things described in (a) or (b) above. Notwithstanding the foregoing, Patent Rights does not include those patents and/or patent applications that, during the term of this Agreement, cease to be Patent Rights pursuant to Article 6.04.

1.04 "Licensed Product" means an approved pharmaceutical product labeled for use in the Field of Use, or a cosmetic product which:

(a) is covered in whole or in part by an issued, unexpired claim or pending claim contained in the Patent Rights in the Field of Use in the country in which any such product or part thereof is made, used or sold; or
(b) uses a process, is manufactured by using a process or is employed to practice a process which is covered in whole or in part by an issued, unexpired claim or pending claim contained in the Patent Rights in the Field of Use in the country in which such product or part thereof is used or sold; or
(c) provides a service that is (1) provided by Licensee to a Third Party and (2) that utilizes Licensed Product.

1.05 "Net Sales" means, in the case of Licensed Products, billings made by or on behalf of Licensee or sublicensees for Licensed Products;

less the sum of the following:

(a) discounts, allowances and credits actually allowed or actually paid to customers in amounts customary in the trade;
(b) sales, VAT taxes, tariff duties and/or use taxes directly imposed and with reference to particular sales and that are paid by Licensee;
(c) amounts actually granted or credited on returns, price adjustments and billing errors;
(d) distribution service agreement fees allowed or paid to third party distributors;

(e) transportation costs;
(f) governmental and other rebates granted to managed health care organizations, pharmacy benefit managers, federal, state/provincial, local and other governments, their agencies and purchasers and reimbursers or to trade customers; or
(g) any other items that reduce gross sales amounts as required by United States Generally Accepted Accounting Principles ("GAAP") applied on a consistent basis

No deductions from the amounts defined by 1.06 (a) - (e) may be made for commissions paid to individuals whether those individuals are associated with independent sales agencies or regularly employed by Licensee, nor may deductions be made for cost of collections. Licensed Products are considered "sold" when billed out or invoiced or, in the event such Licensed Products are services that are not billed out or invoiced, when the consideration for provision of such is received by the Licensee.

1.06 "Territory" means worldwide.

1.07 "Inventors" means Elise Olsen, David Epstein, and Eric Toone.

1.08 "Third Party" means any individual or entity that is not a party to this Agreement.

1.09 Words denoting a singular number include the plural and vice versa.

1.10 Certain other defined terms have the meanings given them elsewhere in this Agreement.

1.11 "Valid Claim" means a claim of the Patent Rights in the Field of Use which has not been held invalid or unenforceable in a decision which is not appealable or is not appealed within the time allowed. A claim that has been pending for more than five (5) years shall not be considered a Valid Claim until granted.

ARTICLE 2 - LICENSE

2.01 Subject to the terms and conditions of this Agreement, DUKE grants to Licensee and Licensee accepts from DUKE an exclusive, sublicenseable license for the Field of Use in the Territory to:

(a) practice under the Patent Rights,
(b) make, have made, use, lease, import, export and/or sell Licensed Products,

The rights granted in this Article 2.01 begin on the Effective Date and last until the end of the term for which the Patent Rights are granted unless this Agreement is sooner terminated according to its terms.

2.02 Any sublicenses granted under authority of this Agreement are subject to the terms and conditions of this Agreement, must be consistent with this Agreement, and may not be further sublicensed without the express written approval of DUKE, such approval not to be unreasonably withheld or delayed. Running royalties payable to DUKE for Net Sales of Licensed Products covered by a Valid Claim by sublicensees will be equal to 1.5% of Net Sales. Further, Licensee is responsible for paying DUKE such running royalties and must use commercially reasonable efforts to enforce the terms of the sublicense agreements. In addition, and with respect to any other financial considerations associated with any particular sublicense granted by Licensee under this Agreement, and notwithstanding anything to the contrary in this Agreement, DUKE will receive the following:

(a) all Performance Milestone Fees set forth in Article 3.02 for milestones met by sublicensee. For purposes of clarity, this Article 2.02(a) does not alter Licensee's obligation to pay milestone fees as described in Article 3.02; and

(b) 10% of all cash payments (other than running royalties on Net Sales and reimbursement of expenses directly relating to pursuit, maintenance, and defense of Patent Rights) received by Licensee in consideration for grant or for pending grant of each said sublicense, including, but not limited to, upfront license fees, annual license maintenance fees, milestone payments, and the like. It is agreed that Licensee shall not receive from sublicensees anything of value in lieu of cash payments in consideration for any sublicense under this Agreement without the express prior written approval of DUKE, such approval not to be unreasonably withheld or delayed.

Licensee further agrees to provide DUKE with a copy of any and all sublicenses of rights granted under this Agreement within thirty (30) days of execution of each subject sublicense agreement.

2.03 Notwithstanding anything to the contrary in this Agreement, DUKE retains the right to practice under the Patent Rights for its own non-commercial educational, research and clinical purposes and without payment of royalties or other fees, including the right (a) to provide the Patent Rights to governmental laboratories and to other non-profit or not-for-profit institutions for non-commercial purposes only and (b) to perform research for non-commercial purposes without payment of royalties or other fees. In doing so, DUKE will not knowingly grant any for-profit party any rights to Patent Rights in the Field of Use, which are licensed to Licensee under this Agreement. It is understood and acknowledged that nothing in this Agreement may be construed to restrict DUKE from using Patent Rights outside the Field of Use and/or Territory as it sees fit (which shall include, but shall not be limited to, the transferring of Patent Rights to any Third Party).

2.04 Except as expressly provided herein, the license granted hereunder does not confer any other rights upon Licensee by implication, estoppel or otherwise as to any technology or intellectual property (including, but not limited to, know-how, patent applications, patents, and the like) held by DUKE.

2.05 During the term of this Agreement, DUKE hereby grants Licensee and its permitted sublicensees, transferees and assignees a covenant not to sue under any patents owned or controlled by DUKE which would otherwise prevent Licensee and/or its permitted sublicensees, transferees or assignees from using the license to the Patent Rights granted herein within the Field of Use both before and after expiration of the licensed Patent Rights.

ARTICLE 3 - LICENSE FEE and ROYALTIES

3.01 Within ten (10) days of the Effective Date, Licensee must pay to DUKE a non-refundable, non-creditable lump sum license fee of four million US Dollars ($4,000,000 US).

3.02 Licensee must pay to DUKE the non-refundable, non-creditable milestone payments set forth in Appendix B (hereafter, "Performance Milestone Fees"). Each Performance Milestone Fee is due and payable within thirty (30) days of achievement of the relevant milestone. Performance Milestone Fees are payable once and only once upon the achievement of a MILESTONE EVENT as set forth in Appendix B.

3.03 At the times and in the manner set forth in this Agreement, Licensee must pay to DUKE a non-refundable, non-creditable running royalty on Licensee's Net Sales of Licensed Product covered by a Valid Claim of two percent (2.0%).

In the event that Licensee determines that it is necessary to obtain licenses for patent rights owned by one or more Third Parties in order to make, have made, use, lease, import, export and/or sell Licensed Products under this Agreement, then the amount of running royalty obligation paid to all such parties will be decreased proportionately so that such proportionate reduction of running royalties payable to DUKE ("DUKE Reduction") shall apply only if a proportionate royalty reduction on terms that are similar in all material respects to DUKE Reduction also applies to all such Third Party licensors, and provided further that the running royalty rate payable to DUKE shall in no event be reduced to less than 1.5% of Net Sales. Nothing herein, however shall be construed as reducing any payment other than running royalty on Net Sales. The above terms regarding the requirement for proportionality in Third Party licenses shall apply only to agreements with Third Parties that are executed by the final signature after the Effective Date of this Agreement.

3.04 Licensee's obligation to pay minimum annual royalties begins on January 1 of the first year following the year in which the Licensed Product is first sold. Licensee's minimum annual royalties will be one hundred thousand US Dollars (US$100,000) per year.

3.05 By the end of the third year of commercial sales of Licensed Product, or by January 1, 2014, whichever comes first, fifty percent (50%) of the minimum royalty paid by Licensee in accordance with Article 3.04 must come from running royalties on Net Sales. If this requirement is not met, DUKE may, at its sole discretion, terminate this Agreement in accordance with Article 10.03(b) or convert it to non-exclusive.

3.06 Notwithstanding reports, correspondence or other communications from Licensee, it is understood that DUKE will apply any amounts received from Licensee in accordance with its policies and procedures in effect at the time of receipt.

3.07 In the event that Licensee reasonably demonstrates to Duke that any payments Licensee owes DUKE or its assignee under this Agreement become subject to withholding taxes under the laws of any jurisdiction, Licensee may withhold from the payment the amount of such taxes due. Licensee will timely pay to the proper governmental authority the amount of any taxes withheld and will provide DUKE with an official tax certificate or other evidence of tax obligating, together with proof of payment from the relevant governmental authority sufficient to enable DUKE to claim such payment of taxes.

3.08 Licensee must make all payments due to DUKE under this Agreement on or before the date set forth by the terms of this Agreement, or within thirty (30) days of any invoice date on invoices received from DUKE. If Licensee fails to pay any amount due to DUKE during the aforementioned time period, then the payments set forth in this Agreement will bear interest until payment is made in full. Interest will be calculated on the balance due at a per annum rate of 4% above the prime rate in effect at the Wachovia Bank (N.A.) (or its successors, as the case may be) on the due date of the payment(s) in question. Amounts due are compounded monthly until the Licensee meets the full financial obligation due at the time of the next payment or invoice due date. However, in no event may any interest calculation hereunder exceed 18% per annum (or 1.5 % per month). The payment of such interest does not foreclose DUKE from exercising any other rights it may have as a consequence of the lateness of the payment, including termination in accordance with Article 10.03 herein.

3.09 All payments due to DUKE under this Agreement must be paid in United States Dollars in Durham, North Carolina, or at such place as DUKE may reasonably designate consistent with the laws and regulations controlling in any foreign country. If any currency conversion is required in connection with such payments due, such conversion must be made by using the exchange rate used by Licensee in preparing its financial statements pursuant to GAAP, for the reporting period to which such payments relate.

3.10 All payments due to DUKE under this Agreement must cite "DUKE File # 2357", and must be made payable to "Duke University." If payments are made by wire, the wiring instructions below must be followed. Payments made by check, as well as reports due to DUKE in accordance with Articles 5.02 and 5.03 must be sent to DUKE at the following address:

For delivery via the U.S. Postal Service:

DUKE UNIVERSITY
Office of Licensing & Ventures
Duke University & Medical Center
Attn: Agreements Admin
Box 90083
Durham, NC 27708

For delivery via nationally/internationally recognized courier:

DUKE UNIVERSITY
Office of Licensing & Ventures
Duke University & Medical Center
Attn: Agreements Admin
2812 Erwin Road, Suite 306
Durham, NC 27705

Wiring Instructions:

Bank:	Wachovia Bank NA Charlotte, NC USA
ABA#:	053000219 (Domestic wires only)
Swift Code:	PNBPUS33 (Foreign wires only)
Beneficiary:	Duke University Concentration Account
Account No:	202374-0253053
Attention:	Office of Licensing & Ventures, 401-1222

Note: All bank fees are the responsibility of the sender.

ARTICLE 4 – DEVELOPMENT AND COMMERCIALIZATION

4.01 Licensee must use commercially reasonable efforts to develop and sell Licensed Products. The parties agree that the development and commercialization schedule established in attached Appendix C is reasonable. Modifications to Appendix C must be expressly approved by DUKE in writing, such approval not to be unreasonably withheld.

4.02 During the term of this Agreement, Licensee will submit annual progress reports to DUKE by February 28th of each year. The progress reports will discuss the progress and results, as well as ongoing plans, with respect to the development and commercialization of Patent Rights. DUKE has the right to one meeting per year with Licensee to discuss such

information at a mutually acceptable time and place. Should DUKE's personnel be required by Licensee to consult with Licensee outside of Durham, North Carolina, Licensee will reimburse reasonable travel and living expenses incident to such consulting.

4.03 Subject to the terms of Article 10, if Licensee fails to meet the terms of the Development Schedule set forth in Appendix C, Licensee shall have the right to extend the period applicable to such obligation for ninety (90) day periods upon payment of $100,000 for each such ninety (90) day periods. In the event Licensee fails to meet any obligation after the expiration of any three (3) consecutive ninety (90) day periods, and after any notice to cure from DUKE has expired/lapsed, DUKE may terminate this Agreement in accordance with Article 10.03 or convert the license to a non-exclusive license, unless such variations are expressly approved by DUKE in writing.

ARTICLE 5 – REPORTS AND RECORDS

5.01 Licensee must keep full, true and accurate books of accounts and other records containing all particulars necessary to properly ascertain and verify the amounts payable to DUKE hereunder. These books of account must be kept at Licensee's principal place of business or the principal place of business of the appropriate division of Licensee to which this Agreement relates. These books and the supporting data must be open and available for inspection by DUKE or its designee(s) at all reasonable times for a minimum of three (3) years following the end of the calendar year to which they pertain.

5.02 DUKE shall have the right, at its expense, from time to time and at reasonable times during normal business hours, through an independent certified public accountant reasonably acceptable to Licensee, to examine the records of Licensee, including, but not limited to, sales invoice registers, sales analysis reports, original invoices, inventory records, price lists, sublicense and distributor agreements, accounting general ledgers, and sales tax returns, in order to verify the calculation of any royalties and/or fees payable under this Agreement. Such examination and verification shall not occur more than once each calendar year. If any such examination and verification reveals an underpayment by Licensee to DUKE of more than 5% for any quarter examined, Licensee shall within sixty (60) days, pay DUKE the amount of such overall underpayment plus interest (in accordance with Article 3.08) and shall reimburse DUKE for all expenses incurred in the examination and verification of the records by the independent certified public accountant.

5.03 After the first commercial sale of a Licensed Product and in addition to the reports required under Article 4, Licensee must render to DUKE prior to February 28th and August 31st of each year a written account of the Net Sales of Licensed Products made during the prior six-month period ending December 31st and June 30th, respectively. Licensee must simultaneously with the submission of the reports pay to DUKE the royalties due on such Net Sales in United States dollars. Reports tendered must include the calculation of royalties by product by country in substantially the format provided in Appendix D. Minimum annual royalties, if any, which are

due DUKE for any calendar year must be paid by Licensee along with the written report due on February 28th of each year.

ARTICLE 6 - PATENTS

6.01 DUKE will apply for, prosecute, and maintain during the term of this Agreement, the Patent Rights in the United States and in the foreign countries listed in Appendix A hereto, subject to this Article 6.

6.02 Licensee will be given reasonable advance opportunities to advise DUKE in the filing, prosecution, and maintenance of Patent Rights and will cooperate with DUKE in such filing, prosecution, and maintenance. At Licensee's expense, Licensee shall be provided with copes of all prosecution documents relating to Patent Rights so that Licensee may have the opportunity to offer comments and remarks thereon, such comments and remarks to be given due consideration by DUKE. However, notwithstanding anything to the contrary in this Agreement, all decisions with respect to the filing, prosecution, and maintenance of Patent Rights are reserved solely to DUKE.

6.03 As of the Effective Date and during the term of this Agreement, payment of all fees and costs relating to the filing, prosecution, and maintenance of the Patent Rights are the responsibility of Licensee. Licensee must pay all such fees and costs within sixty (60) days of receipt of an invoice for the same, and failure to pay such invoice within such sixty (60)-day period is a default hereunder for which DUKE may terminate this Agreement in accordance with Article 10.03(b).

6.04 If Licensee provides DUKE with written notification that it will no longer support the filing, prosecution, or maintenance of a specified patent(s) and/or patent application(s) within the Patent Rights, then Licensee's responsibility for fees and costs related to the filing, prosecution, and maintenance of such subject Patent Rights will terminate sixty (60) days after DUKE's receipt of such written notification. However, in such instances, sixty (60) days after DUKE's receipt of written notification, such patents and/or patent applications will no longer be included in Patent Rights (and Appendix A is deemed to be so amended accordingly), and Licensee surrenders all rights under this Agreement to such patents, patent applications, and any patents issuing therefrom.

6.05 To the extent reasonably practical, Licensee must mark any Licensed Product, sold in the United States and/or their containers, labels, and/or other packaging with all applicable United States patent numbers. All Licensed Products shipped to or sold in other countries must be marked in such a manner as to conform with the patent laws and practices of the country of manufacture or sale.

ARTICLE 7 - INFRINGEMENT OF THIRD-PARTY RIGHTS

7.01 If DUKE or Licensee is charged with infringement of a patent by a Third Party or is made a party in a civil action as a result of Licensee's or a sub-Licensee's practice of the Patent Rights under this Agreement, Licensee:

(a) must defend and/or settle any such claim of infringement or civil action;

(b) must assume all costs, expenses, damages, and other obligations for payments incurred as a consequence of such charges of infringement and/or civil action;

(c) must indemnify and hold DUKE harmless from any and all damages, losses, liability, and costs resulting from a charge of infringement or civil brought against DUKE and attributable to either (i) technology added to, incorporated into or sold with a Licensed Product by Licensee or a sub-Licensee or (ii) a manufacturing processes utilized by Licensee or a sub-Licensee; and

(d) may, if such claim of infringement or civil action is based on patent claims contained in any pending or issued patent included in the Patent Rights, terminate this Agreement effective immediately upon DUKE's receipt of written notice of termination. Thereafter, Licensee has no further liability for claims and/or damages arising subsequent to said date of termination unless Licensee is exercising its license under Article 10.08, in which case Licensee's liability and obligations under this Article shall continue as long as the license granted in Section 10.08 is in effect.

(e) must use their commercially reasonable efforts to secure from any such Third Party a covenant not to sue DUKE, or any of its faculty, students, employees or agents, for any historic and/or ongoing research, educational, or clinical efforts conducted at DUKE that relate to the Patent Rights.

7.02 DUKE will give Licensee assistance, at Licensee's expense, in the defense of any such infringement charge or lawsuit, as may be reasonably required.

ARTICLE 8 - INFRINGEMENT OF DUKE's PATENT RIGHTS BY THIRD PARTIES

8.01 Each Party to this Agreement is obligated to inform the other promptly in writing of any alleged infringement of which it becomes aware and of any available evidence of infringement by a third party of any patents within the Patent Rights in the Field of Use.

8.02 If during the term of this Agreement, Licensee becomes aware of any alleged infringement of the Patent Rights in the Field of Use by a third party, Licensee shall have the right, but not the obligation, to either:

(a) settle the infringement suit by sub-licensing the alleged infringer or by other means; or

(b) prosecute at its own expense any infringement of the Patent Rights. In the event Licensee prosecutes such infringement, Licensee may, for such purposes, request to use the name of DUKE as party plaintiff. If DUKE is a necessary party to an infringement lawsuit, then DUKE agrees to join the lawsuit as a party plantiff, and all costs associated therewith shall be borne by Licensee.

8.03 In the event that Licensee undertakes the enforcement and/or defense of the Patent Rights by litigation, including any declaratory judgment action, the total cost of any such action commenced or defended solely by Licensee shall be borne by Licensee. Any recovery of damages by Licensee as a result of such action shall be applied first in satisfaction of any unreimbursed expenses and attorneys' fees of Licensee relating to the action, and second in satisfaction of unreimbursed legal expenses and attorneys' fees of DUKE, if any, relating to the action. If applicable, Licensee shall receive an amount equal to its lost profits or a reasonable royalty on sales of the infringer (whichever measure of damages the court shall have applied), less a reasonable approximation of the royalties that Licensee would have owed to DUKE on Net Sales that were lost to the infringer, which amount shall be promptly paid by Licensee to DUKE. Any balance remaining from such recovery shall be distributed between Licensee and DUKE with Licensee receiving seventy-five percent (75%) and DUKE receiving twenty-five percent (25%).

8.04 In the event Licensee does not undertake action to prevent the infringing activity within three (3) months of having been made aware and notified thereof, DUKE shall have the right, but not the obligation, to prosecute at its own expense any such infringements of the Patent Rights and, in furtherance of such right, DUKE may use the name of Licensee as a party plaintiff in any such suit without expense to Licensee. The total cost of any such infringement action commenced or defended solely by DUKE shall be borne by DUKE. Any recovery of damages by DUKE for any infringement shall be applied first in satisfaction of any unreimbursed expenses and attorneys' fees of DUKE relating to the suit, and second toward reimbursement of Licensee's reasonable expenses, including reasonable attorneys' fees, relating to the suit. Any balance

remaining from such recovery shall be distributed with DUKE receiving one-hundred percent (100%).

8.05 In any infringement suit instituted by either party to enforce the Patent Rights in the Territory pursuant to this Agreement, the other party hereto shall, at the request and expense of the party initiating such suit, reasonably cooperate in all respects and, to the extent reasonably possible, have its employees testify when requested and make available relevant records, papers, information, samples, specimens, and the like.

8.06 Licensee has the sole right in accordance with the terms and conditions herein to sub-license any alleged infringer under the Patent Rights in the Field of Use in the Territory for future infringements.

8.07 Any of the foregoing notwithstanding, if at any time during the term of this Agreement any of the Patent Rights are held invalid or unenforceable in a decision which is not appealable or is not appealed within the time allowed, Licensee shall have no further obligations to DUKE with respect to its future use or sale of any Licensed Product covered solely by such Patent Rights, including the obligation of paying royalties. For avoidance of doubt it is understood and agreed that in such event, Licensee shall not have any damage claim or any claim for refund or reimbursement against DUKE for any amounts previously paid to DUKE under this Agreement.

ARTICLE 9 - GOVERNMENT CLEARANCE, PUBLICATION, EXPORT

9.01 To the extent such clearance is required, Licensee must use commercially reasonable efforts to have the Licensed Products cleared for marketing in those countries in which Licensee intends to sell Licensed Products by timely filing or have filed any necessary data with appropriate government agencies.

9.02 It is understood and agreed that the right of publication of the Patent Rights resides in the inventor and other staff and students of DUKE. Licensee may also publish and/or co-author any publication on the Patent Rights in accordance with academic custom.

9.03 This Agreement is subject to all of the United States laws and regulations controlling the export of technical data, computer software, laboratory prototypes and other commodities and technology. It is understood that DUKE is subject to United States laws and regulations controlling the export of technical data, computer software, laboratory prototypes and other commodities (including the Arms Export Control Act, as amended and the Export Administration Act of 1979), and that its obligations under this Agreement are contingent on compliance with applicable United States export laws and regulations. The transfer of certain technical data and commodities may require a license from the cognizant agency of the United States Government and/or written assurances by Licensee that Licensee will not export data or commodities to certain foreign countries without prior approval of such agency. DUKE makes no promise or representation that a license is not required nor that, if required, it will be issued.

ARTICLE 10 - DURATION AND TERMINATION

10.01 This Agreement is effective upon the Effective Date, and unless sooner terminated in accordance with any of its provisions, it remains in full force and effect on a country-by-country basis for the life of the last-to-expire of the patents included in the Patent Rights, except that Licensee may earlier terminate this Agreement and the license granted herein in accordance with its terms, by providing written notice of same to Licensor. If Licensee terminates license for any reason other than (i) as provided in Article 7.01(d), (ii) a decision of invalidity of all of the claims of the Patent Rights in the Field of Use (iii) cessation of development of Licensed Product or (iv) the termination of sales of Licenced Products by Licensee or its sublicensee, then Licensee must pay DUKE an early termination fee of fifty million dollars ($50,000,000). This will not impair or prejudice any other right of remedy that DUKE might have under this Agreement.

10.02 Subject to Article 10.01, Licensee may terminate this Agreement by giving DUKE written notice at least three (3) months prior to such termination. It is understood that Licensee remains responsible for the timely payment of all amounts due DUKE under this Agreement through the effective date of the termination.

10.03

(a) By giving written notice of termination to the other party, either party may immediately terminate this Agreement for fraud, willful misconduct, or illegal conduct by the other party.

(b) Except for the types of breaches described in 10.03(a), if either party fails to fulfill any of its material obligations under this Agreement the non-breaching party may terminate this Agreement by giving written notice to the breaching party as described in 10.03 (c).

(c) Any notice of termination must contain a reasonably adequate description of the event or occurrence constituting a breach of the Agreement. For breaches described in 10.03(b), the party receiving notice of the breach will have the opportunity to cure that breach within forty-five (45) days of receipt of notice. If the breach is not cured within that time, the termination will be effective as of the forty-sixth 46st day after receipt of notice. A party's ability to cure a breach will apply only to the first 2 breaches properly noticed under the terms of this Agreement, regardless of the nature of those breaches. Any subsequent breach or any uncured breach by that party will entitle the other party to terminate this Agreement upon proper notice.

10.04 If (a) an order for relief is entered against Licensee under the Federal Bankruptcy Code, (b) an order appointing a receiver for substantially all of Licensee's assets is entered by a court of competent jurisdiction, (c) Licensee makes an assignment for the benefit of creditors, or (d) a levy of execution is made upon substantially all of the assets of Licensee and such levy is

not quashed or dismissed within thirty (30) days, this Agreement automatically terminates effective on the date of such order or assignment or, in the case of such levy or ceasing of active business, the expiration of such thirty (30) day period. If Licensee shall cease to exist as an active business, this Agreement terminates immediately. Nothwithstanding the foregoing, terminations in accordance with this Article 10.04 will not impair or prejudice any other right of remedy that DUKE might have under this Agreement.

10.05 If at any time prior to the first commercial sale of a Licensed Product under this Agreement Licensee shall cease to pursue commercial development of Licensed Product as contemplated herein, this Agreement may be terminated by DUKE in accordance with Article 10.03(b) without obligation on the part of DUKE to refund any of the fees or royalties which may have been paid by Licensee prior to such termination. Licensee must notify Duke immediately in writing if they cease to pursue commercial development of the Patent Rights as contemplated herein.

10.06 If Licensee commences a declaratory judgement action or any legal proceeding that challenges the Patent Rights (or any part thereof) or the scope of the Patent Rights in the Field of Use, DUKE shall have the right to terminate this Agreement, without obligation on the part of DUKE to refund any of the fees or royalties which may have been paid by Licensee prior to such termination. Further, once any one of the following events have occurred, Licensee agrees that, for the term of this Agreement, it will not commence a declaratory judgement action or any legal proceeding that challenges the Patent Rights (or any part thereof) or the scope of the Patent Rights:

(a) Licensee has had any commercial sales of a Licensed Product, or
(b) Licensee has asserted the Patent Rights against a third party, or
(c) This Agreement has been in effect for three years and no charge of infringement has been filed against Duke or Licensee for the practice of the Patent Rights.

10.07 Neither expiration nor termination of this Agreement removes or diminishes any financial obligations to DUKE that Licensee has incurred under this Agreement prior to and as of the effective date of termination or expiration.

10.08 Upon the termination of this Agreement pursuant to this Article 10, Licensee may notify DUKE of the amount of Licensed Products that Licensee has on hand and Licensee may then sell that amount of Licensed Products, but no more; provided, however, that Licensee pay DUKE any fees, royalties or other financial consideration as provided for in this Agreement.

10.09 Upon termination of this Agreement, any and all rights granted to Patent Rights under sublicenses will terminate immediately, effective on the date of termination of this Agreement. However, termination of any such rights under sublicensing agreement does not remove or diminish any financial obligations to DUKE, which sublicensee incurred prior to and as of the effective date of termination. Any such obligations are payable directly to DUKE and any sublicense executed by Licensee must contain language to this effect.

10.10 Subject to completion of all obligations hereunder, and upon expiration of the Agreement on the last to expire of the patents included in the Patent Rights in the Field of Use, Licensee shall have a paid-up license hereunder.

ARTICLE 11 - CONFIDENTIALITY

11.01 DUKE and Licensee will treat any confidential information disclosed to it by the other party with reasonable care and will not disclose such information to any other person, firm or corporation, except Affiliates bound by the obligations of confidentiality and restricted use set forth in this Article 11. The receiving party may not use the disclosing party's confidential information other than for the benefit of the parties hereto and for the performance of this Agreement. These obligations of non-disclosure and restricted use remain effect for each subject disclosure of confidential information for five (5) years from the date of disclosure. However, neither party is obligated, with respect to confidential information disclosed to it, or any part thereof, which:

(a) is already known to the receiving party at the time of the disclosure;
(b) becomes publicly known without the wrongful act or breach of this Agreement by the receiving party;
(c) is rightfully received by the receiving party from a Third Party on a non-confidential basis;
(d) is subsequently and independently developed by employees of the receiving party who had no knowledge of the information, as verified by written records;
(e) is approved for release by prior written authorization of the disclosing party; or
(f) is disclosed pursuant to the requirements of applicable law or pursuant to any judicial or government requirement or order, provided that the party so disclosing takes reasonable steps to provide the other party sufficient prior notice in order to contest such request, requirement or order and provided that such disclosed confidential information otherwise remains subject to the obligations of confidentiality set forth in this Article 11.

11.02 DUKE and Licensee agree that any information to be treated as confidential information under this Article 11 must be disclosed in writing or in another tangible medium and must be clearly marked "CONFIDENTIAL". Information disclosed orally must be summarized and reduced to writing and communicated to the other party within 30 days of such disclosure.

11.03 Notwithstanding the foregoing, Licensee may use and disclose any confidential information related to the Patent Rights to investors, prospective investors, employees, consultants and agents with a need to know, collaborators, prospective collaborators,

governmental authorities and other third parties in the chain of manufacturing and distribution, but if and only if Licensee obtains from each such recipient other than governmental authorities, a written confidentiality agreement, the provisions of which are at least as protective of DUKE's confidential information as those provided in this Article 11.

11.04 Notwithstanding anything to the contrary in this Agreement, all information relating to filing, prosecution, maintenance, defense, infringement, and the like regarding the Patent Rights (no matter how disclosed) is the confidential information of DUKE and subject to the provisions of this Article 11.

11.05 Subject to this Article 11, the parties agree to keep the terms of this agreement confidential.

ARTICLE 12 - NOTICES

12.01 It is a sufficient giving of any notice, request, report, statement, disclosure or other communication hereunder if the party giving the same:

(a) hand delivers such communication; or
(b) mails such communication, postage prepaid, first class, certified mail; or
(c) sends such communication, shipping prepaid, by national/international courier service

to the other party at the address given below or as given in Article 3.10, in the case of payments and reports due in accordance with Article 3.01, 3.02, 3.03, 5.02, 5.03, and 6.03.

DUKE

For delivery via the U.S. Postal Service:

DUKE UNIVERSITY
Office of Licensing & Ventures
Duke University & Medical Center
Attn: Agreements Admin
Box 90083
Durham, NC 27708

Licensee

ALLERGAN, INC.
2525 Dupont Drive
Irvine, CA 92612
Attn: General Counsel

ALLERGAN SALES, LLC
2525 Dupont Drive
Irvine, CA 92612
Attn: S.V.P. Corporate Development

For delivery via nationally/internationally recognized courier:

DUKE UNIVERSITY
Office of Licensing & Ventures
Duke University & Medical Center
Attn: Agreements Admin
2812 Erwin Road, Suite 306
Durham, NC 27705

ALLERGAN, INC.
2525 Dupont Drive
Irvine, CA 92612
Attn: General Counsel

ALLERGAN SALES, LLC
2525 Dupont Drive Irvine, CA 92612
Attn: S.V.P. Corporate Development

12.02 The date of giving any such notice, request, report, statement, disclosure or other communications, and the date of making any payment hereunder required (provided such payment is received), is the date of the U.S. postmark of such envelope if marked or the actual date of receipt if not marked or if delivered otherwise.

ARTICLE 13 - ASSIGNMENT

13.01 This Agreement is binding upon and inures to the benefit of the respective successors and assigns of the parties hereto. This Agreement may not be assigned by Licensee except to an Affiliate or in connection with the merger, sale or other transfer of Licensee's entire business or that part of Licensee's business to which this Agreement relates. Licensee shall give DUKE thirty (30) days prior written notice of such assignment or transfer. Any other assignment of this Agreement without the prior written consent of DUKE shall be void.

13.02 Prior to any such assignment, the following conditions must be met:

(a) Licensee must give Duke thirty (30) days prior written notice of the assignment, including the new assignee's contact information; and
(b) The new assignee must agree in writing to DUKE to be bound by this Agreement.

13.03 During the term of this Agreement, Duke agrees to inform Licensee of any assignment of the Patent Rights at least sixty (60) days prior to such transfer.

ARTICLE 14 - INDEMNITY, INSURANCE, REPRESENTATIONS, STATUS

14.01 DUKE, and its trustees, officers, employees, students, and agents (collectively, "DUKE Indemnitees") will be indemnified, defended by counsel acceptable to DUKE, and held harmless by Licensee from and against any claim, liability, cost, expense, damage, deficiency, loss or obligation, of any kind or nature (including, without limitation, reasonable attorneys' fees and other costs and expenses of defense) (hereinafter referred to as "Claim" or "Claims") based upon, arising out of, or otherwise relating to Licensee's activities under this Agreement, including, but not limited to, any cause of action relating to product liability, Licensee's use of the Patent Rights, and/or Licensee's exercise of the license(s) granted herein. The previous sentence will not apply to any Claim that is determined with finality by a court of competent jurisdiction to result solely from the gross negligence or willful misconduct of a DUKE Indemnitee.

14.02 Licensee must maintain in force at its sole cost and expense, with licensed and reputable insurance companies, general liability insurance and products liability insurance coverage in amounts reasonably sufficient to protect against liability under Article 14.01 above. DUKE has the right to ascertain from time to time that such coverage exists, such right to be exercised in a reasonable manner. Licensee shall provide DUKE with written evidence of such insurance upon request of DUKE. Licensee shall provide DUKE with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance; if Licensee does not obtain replacement insurance providing comparable coverage prior to the expiration of such fifteen (15) day period, DUKE shall have the right to terminate this Agreement in accordance with Article 10.03(b).

14.03 DUKE MAKES NO WARRANTIES OF ANY KIND. IN PARTICULAR, THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE NOR IS THERE A WARRANTY THAT THE USE OF THE PATENT RIGHTS WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK OR OTHER RIGHTS. IN ADDITION, NOTHING IN THIS AGREEMENT MAY BE DEEMED TO BE A REPRESENTATION OR WARRANTY BY DUKE OF THE VALIDITY OF ANY OF THE PATENTS OR THE ACCURACY, SAFETY, EFFICACY, OR USEFULNESS, FOR ANY PURPOSE, OF THE PATENT RIGHTS. DUKE HAS NO OBLIGATION, EXPRESS OR IMPLIED, TO SUPERVISE, MONITOR, REVIEW OR OTHERWISE ASSUME RESPONSIBILITY FOR THE PRODUCTION, MANUFACTURE, TESTING, MARKETING OR SALE OF ANY LICENSED PRODUCT OR LICENSED SERVICE. DUKE HAS NO LIABILITY WHATSOEVER TO LICENSEE OR ANY THIRD PARTIES FOR OR ON ACCOUNT OF ANY INJURY, LOSS, OR DAMAGE, OF ANY KIND OR NATURE, SUSTAINED BY, OR ANY DAMAGE ASSESSED OR ASSERTED AGAINST, OR ANY OTHER LIABILITY INCURRED BY OR IMPOSED UPON LICENSEE OR ANY OTHER PERSON OR ENTITY, ARISING OUT OF OR IN CONNECTION WITH OR RESULTING FROM:

(a) the production, use, practice, lease, or sale of any Licensed Product;
(b) the use of the Patent Rights; or
(c) any advertising or other promotional activities with respect to any of the foregoing.

14.04 Notwithstanding anything to the contrary in this Agreement, it is understood and agreed that it shall be the responsibility of Licensee to secure rights under any Third Party intellectual property rights that may be required to practice the Patent Rights and to exercise any and all of the rights granted under Article 2.

14.05 Neither party is an agent of the other party for any purpose whatsoever.

14.06 DUKE represents to the best of our knowledge, that it has the right to enter into this Agreement.

ARTICLE 15 - USE OF A PARTY'S NAME

15.01 Neither party may, without the prior written consent of the other party:

(a) use in any publication, advertising, publicity, press release, promotional activity or otherwise, any trade-name, personal name, trademark, trade device, service mark, symbol, image, icon, or any abbreviation, contraction or simulation thereof owned by the other party; or
(b) use the name or image of any employee or agent of the other party in any publication, publicity, advertising, press release, promotional activity or otherwise; or
(c) represent, either directly or indirectly, that any product or service of the other party is a product or service of the representing party or that it is made in accordance with or utilizes the information or documents of the other party.

ARTICLE 16 – SEVERANCE AND WAIVER

16.01 Each clause of this Agreement is a distinct and severable clause and if any clause is deemed illegal, void or unenforceable, the validity, legality or enforceability of any other clause or portion of this Agreement will not be affected.

16.02 The failure of a party in any instance to insist upon the strict performance of the terms of this Agreement is not a waiver or relinquishment of any of the terms of this Agreement,

either at the time of the party's failure to insist upon strict performance or at any time in the future, and such terms will continue in full force and effect.

ARTICLE 17 - TITLES

17.01 All titles and article headings contained in this Agreement are inserted only as a matter of convenience and reference. They do not define, limit, extend or describe the scope of this Agreement or the intent of any of its provisions.

ARTICLE 18 – SURVIVAL OF TERMS

18.01 The provisions of Articles 1, 3, 5, 6.05, 7, 9.03, 10.01,10.05, 10.06, 10.07, 10.10, 11, 12, 14, 15, 16, 17, 18 and 19, and any other terms which by their nature survive, shall survive the expiration or termination of this Agreement.

ARTICLE 19 – GOVERNING LAW

19.01 This Agreement is entered into in the State of New York and must be interpreted in accordance with and its performance governed by the laws of the State of New York, without reference to its choice of law provisions. The parties hereby submit to the jurisdiction of the courts of New York in all matters concerning this Agreement.

ARTICLE 20 - ENTIRE UNDERSTANDING

20.01 This Agreement represents the entire understanding between the parties, and supersedes all other agreements, express or implied, between the parties concerning the subject matter hereof, and is not subject to any change or modification except by the execution of a written instrument subscribed to by authorized representatives of the parties.

IN WITNESS WHEREOF, the parties have executed this Agreement on the dates set forth below.

DUKE UNIVERSITY

By: _____
Name: Rose Ritts, Ph D
Title: Executive Director
Office of Licensing & Ventures
Duke University & DUMC
Date: December 18, 2007

ALLERGAN, INC.

By: _____
approved MV Law Department
Name: Douglas S. Ingram
Title: Executive Vice President, Chief Adminstrative Officer, General Counsel, Secretary
Date: December 18, 2007

ALLERGAN SALES, LLC

By: _____
approved MV Law Department
Name: David M. Lawrence
Title: Vice President
Date: December 18, 2007

APPENDICES

APPENDIX A—PATENT RIGHTS

APPENDIX B—PERFORMANCE MILESTONE FEES

APPENDIX C—DEVELOPMENT SCHEDULE

APPENDIX D—ROYALTY REPORT FORM

APPENDIX A—PATENT RIGHTS

Title/ Country	Client Ref.	Case No./ Subcase	Case Type/ Status	Appl. No./ Filing Date	Patent No./ Issue Date
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS Canada	2357	028193-9012	Patent Cooperation Treaty Granted	2401731 3/30/2001	2401731 5/29/2007
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS China (Peoples Republic)	2357	028193-9012	Patent Cooperation Treaty Pending	01807355.7 3/30/2001	
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS Germany	2357	028193-9012	European Patent - PCT Originated Granted	01926506.5 3/30/2001	60115000.7 11/16/2005
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS European Patent Convention	2357	028193-9012	Patent Cooperation Treaty Granted	01926506.5 3/30/2001	1267807 11/16/2005
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS Spain	2357	028193-9012	European Patent - PCT Originated Granted	01926506.5 3/30/2001	1267807 11/16/2005
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS France	2357	028193-9012	European Patent - PCT Originated Granted	01926506.5 3/30/2001	1267807 11/16/2005
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS United Kingdom	2357	028193-9012	European Patent - PCT Originated Granted	01926506.5 3/30/2001	1267807 11/16/2005
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS Italy	2357	028193-9012	European Patent - PCT Originated Granted	01926506.5 3/30/2001	1267807 11/16/2005
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS Japan	2357	028193-9012	Patent Cooperation Treaty Published	2001-572061 3/30/2001	
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS United States of America	2357	028193-9012	Provisional Abandoned	60/193645 3/31/2000	
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS United States of America	2357	028193-9012 01'	Utility Patent Filing Abandoned	09/774557 1/31/2001	

APPENDIX A—PATENT RIGHTS (Cont.)

Title/ Country	Client Ref.	Case No./ Subcase	Case Type/ Status	Appl. No./ Filing Date	Patent No./ Issue Date
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS United States of America	2357	028193-9012 02	Divisional Filing Allowed	11/138097 5/26/2005	
COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS Patent Cooperation Treaty	2357	028193-9012	Utility Patent Filing Nationalized	PCTUS0110370 3/30/2001	

APPENDIX B— PERFORMANCE MILESTONE FEES

MILESTONE EVENT: Patent Issuance
Four Million US Dollars ($4,000,000) - To be paid upon issuance of any one or more claims contained in the U.S. Patent Rights in the Field of Use.

MILESTONE EVENT: Regulatory

- Six and one-half million US Dollars ($6,500,000) upon First Marketing Approval in the U.S. of a Licensed Product
- Six million US Dollars ($6,000,000) upon First Marketing Approval in any country in the European Union of a Licensed Product
- Five million US Dollars ($5,000,000)upon First Marketing Approval in Japan of a Licensed Product
- "First Marketing Approval" means receipt by Licensee of written approval to sell a Licensed Product, in the indicated country or region, including, where applicable, pricing approval and any other governmental approvals that may be necessary to sell Licensed Products. A copy of such approval will be promptly sent to Duke upon receipt by or on behalf of Licensee.

MILESTONE EVENT: Sales

- Eight million US Dollars ($8,000,000) upon the first instance where Net Sales of Licensed Product exceed two hundred million dollars ($200,000,000) in a calendar year.

Note: Each Performance Milestone Fee will be payable once and only once upon the occurrence of the first instance of each Milestone Event.

APPENDIX C—DEVELOPMENT SCHEDULE

- Initiate a Phase III clinical trial with a LICENSED PRODUCT within one (1) year following the EFFECTIVE DATE, and

- Sell LICENSED PRODUCT in the U.S. within six (6) months of receipt of U.S. regulatory approval.

APPENDIX D—ROYALTY REPORT FORM

ROYALTY REPORT for period ending _____

Duke File #

Country	Product	Sales in 1st Quarter	Sales in 2nd Quarter	Sales in 3rd Quarter	Sales in 4th Quarter			TOTAL GROSS SALES	Reductions to Sales**	TOTAL NET SALES	% Royalty Due	TOTAL ROYALTY DUE
SubTOTAL x Country												
SubTOTAL x Country												
GRAND TOTAL												

Royalty Credits Taken		
	(eg)3rd-party Royalties pd--max. of 50% of royalties due	
TOTAL Royalty Credits		

Min. Annual Royalty Due		
	ROYALTIES PAID	

**Note that Reductions to Sales are limited to those items in Section 1.05 of the License Agreement.

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

NOTICE OF ASSIGNMENT TO UNITED STATES MAGISTRATE JUDGE FOR DISCOVERY

This case has been assigned to District Judge Cormac J. Carney and the assigned discovery Magistrate Judge is Arthur Nakazato.

The case number on all documents filed with the Court should read as follows:

SACV09- 328 CJC (ANx)

Pursuant to General Order 05-07 of the United States District Court for the Central District of California, the Magistrate Judge has been designated to hear discovery related motions.

All discovery related motions should be noticed on the calendar of the Magistrate Judge

---

NOTICE TO COUNSEL

A copy of this notice must be served with the summons and complaint on all defendants (if a removal action is filed, a copy of this notice must be served on all plaintiffs).

Subsequent documents must be filed at the following location:

[ ] **Western Division**
312 N. Spring St., Rm. G-8
Los Angeles, CA 90012

[X] **Southern Division**
411 West Fourth St., Rm. 1-053
Santa Ana, CA 92701-4516

[ ] **Eastern Division**
3470 Twelfth St., Rm. 134
Riverside, CA 92501

Failure to file at the proper location will result in your documents being returned to you.

COPY

JEFFREY T. THOMAS, SBN 106409
JTthomas@gibsondunn.com
T. KEVIN ROOSEVELT, SBN 205485
KRoosevelt@gibsondunn.com
GIBSON, DUNN & CRUTCHER LLP
3161 Michelson Drive
Irvine, California 92612-4412
Telephone: (949) 451-3800
Facsimile: (949) 451-4220

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

ALLERGAN, INC.; MURRAY A. JOHNSTONE, M.D.; and DUKE UNIVERSITY,

PLAINTIFF(S),

v.

ATHENA COSMETICS, INC.; PHARMA TECH INTERNATIONAL, INC.; DIMENSIONAL MERCHANDISING, INC.; STELLA INTERNATIONAL, LLC; PRODUCT INNOVATIONS, LLC; METICS, LLC; NUTRA-LUXE M.D., LLC; SKIN RESEARCH LABORATORIES, INC.; LIFETECH RESOURCES LLC; ROCASUBA, INC.; LA CANADA VENTURES, INC.; SUSAN F. LIN, M.D.; PETER THOMAS ROTH LABS LLC; and PETER THOMAS ROTH, INC.,

DEFENDANT(S).

CASE NUMBER

SACV09 -328 CJC (ANx)

SUMMONS

TO: DEFENDANT(S): _____

A lawsuit has been filed against you.

Within 20 days after service of this summons on you (not counting the day you received it), you must serve on the plaintiff an answer to the attached ☒ complaint ☐ _____ amended complaint ☐ counterclaim ☐ cross-claim or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff's attorney, JEFFREY T. THOMAS / T. KEVIN ROOSEVELT, whose address is 3161 Michelson Drive, Irvine, California 92612-4412. If you fail to do so, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

Clerk, U.S. District Court

Dated: MAR 16 2009

By: DODJIE GARGANTOS
Deputy Clerk

SEAL

(Seal of the Court)

[Use 60 days if the defendant is the United States or a United States agency, or is an officer or employee of the United States. Allowed 60 days by Rule 12(a)(3)].

UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA
CIVIL COVER SHEET

I (a) PLAINTIFFS (Check box if you are representing yourself ☐)

ALLERGAN, INC.; MURRAY A. JOHNSTONE, M.D.; and DUKE UNIVERSITY

DEFENDANTS ATHENA COSMETICS, INC.; PHARMA TECH INTERNATIONAL, INC.; DIMENSIONAL MERCHANDISING, INC.; STELLA INTERNATIONAL, LLC; PRODUCT INNOVATIONS, LLC; METICS, LLC; NUTRA-LUXE M.D., LLC; SKIN RESEARCH LABORATORIES, INC.; LIFETECH RESOURCES LLC; ROCASUBA, INC.; LA CANADA VENTURES, INC.; SUSAN F. LIN, M.D.; PETER THOMAS ROTH LABS LLC; and PETER THOMAS ROTH, INC.

(b) Attorneys (Firm Name, Address and Telephone Number. If you are representing yourself, provide same.)

JEFFREY T. THOMAS, SBN 106409; JTthomas@gibsondunn.com
T. KEVIN ROOSEVELT, SBN 205485; KRoosevelt@gibsondunn.com
GIBSON, DUNN & CRUTCHER LLP
3161 Michelson Drive, Irvine, California 92612-4412
Telephone: (949) 451-3800 / Facsimile: (949) 451-4220

Attorneys (If Known)

Counsel for Athena Cosmetics, Inc.:
PHILIP J. GRAVES / PGraves@gravesiawpc.com
GRAVES LAW OFFICE, P.C.
12121 Wilshire Blvd., Suite 775, Los Angeles, CA 90025
Telephone: (310) 295-6500 / Facsimile: (310) 295-6501

II. BASIS OF JURISDICTION (Place an X in one box only.)

☐ 1 U.S. Government Plaintiff ☒ 3 Federal Question (U.S. Government Not a Party)
☐ 2 U.S. Government Defendant ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES - For Diversity Cases Only (Place an X in one box for plaintiff and one for defendant.)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated or Principal Place of Business in this State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated and Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. ORIGIN (Place an X in one box only.)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify): ☐ 6 Multi-District Litigation ☐ 7 Appeal to District Judge from Magistrate Judge

V. REQUESTED IN COMPLAINT: JURY DEMAND: ☒ Yes ☐ No (Check 'Yes' only if demanded in complaint.)

CLASS ACTION under F.R.C.P. 23: ☐ Yes ☒ No ☒ MONEY DEMANDED IN COMPLAINT: $ To be determined at trial

VI. CAUSE OF ACTION (Cite the U.S. Civil Statute under which you are filing and write a brief statement of cause. Do not cite jurisdictional statutes unless diversity.)

This is a civil action for patent infringement arising under the Patent Laws of the United States, Title 35, United States Code

VII. NATURE OF SUIT (Place an X in one box only.)

OTHER STATUTES
☐ 400 State Reapportionment
☐ 410 Antitrust
☐ 430 Banks and Banking
☐ 450 Commerce/ICC Rates/etc.
☐ 460 Deportation
☐ 470 Racketeer Influenced and Corrupt Organizations
☐ 480 Consumer Credit
☐ 490 Cable/Sat TV
☐ 810 Selective Service
☐ 850 Securities/Commodities/ Exchange
☐ 875 Customer Challenge 12 USC 3410
☐ 890 Other Statutory Actions
☐ 891 Agricultural Act
☐ 892 Economic Stabilization Act
☐ 893 Environmental Matters
☐ 894 Energy Allocation Act
☐ 895 Freedom of Info. Act
☐ 900 Appeal of Fee Determination Under Equal Access to Justice
☐ 950 Constitutionality of State Statutes

CONTRACT
☐ 110 Insurance
☐ 120 Marine
☐ 130 Miller Act
☐ 140 Negotiable Instrument
☐ 150 Recovery of Overpayment & Enforcement of Judgment
☐ 151 Medicare Act
☐ 152 Recovery of Defaulted Student Loan (Excl. Veterans)
☐ 153 Recovery of Overpayment of Veteran's Benefits
☐ 160 Stockholders' Suits
☐ 190 Other Contract
☐ 195 Contract Product Liability
☐ 196 Franchise

REAL PROPERTY
☐ 210 Land Condemnation
☐ 220 Foreclosure
☐ 230 Rent Lease & Ejectment
☐ 240 Torts to Land
☐ 245 Tort Product Liability
☐ 290 All Other Real Property

TORTS
PERSONAL INJURY
☐ 310 Airplane
☐ 315 Airplane Product Liability
☐ 320 Assault, Libel & Slander
☐ 330 Fed. Employers' Liability
☐ 340 Marine
☐ 345 Marine Product Liability
☐ 350 Motor Vehicle
☐ 355 Motor Vehicle Product Liability
☐ 360 Other Personal Injury
☐ 362 Personal Injury-Med Malpractice
☐ 365 Personal Injury-Product Liability
☐ 368 Asbestos Personal Injury Product Liability

IMMIGRATION
☐ 462 Naturalization Application
☐ 463 Habeas Corpus-Alien Detainee
☐ 465 Other Immigration Actions

TORTS
PERSONAL PROPERTY
☐ 370 Other Fraud
☐ 371 Truth in Lending
☐ 380 Other Personal Property Damage
☐ 385 Property Damage Product Liability

BANKRUPTCY
☐ 422 Appeal 28 USC 158
☐ 423 Withdrawal 28 USC 157

CIVIL RIGHTS
☐ 441 Voting
☐ 442 Employment
☐ 443 Housing/Accommodations
☐ 444 Welfare
☐ 445 American with Disabilities - Employment
☐ 446 American with Disabilities - Other
☐ 440 Other Civil Rights

PRISONER PETITIONS
☐ 510 Motions to Vacate Sentence Habeas Corpus
☐ 530 General
☐ 535 Death Penalty
☐ 540 Mandamus/ Other
☐ 550 Civil Rights
☐ 555 Prison Condition

FORFEITURE/ PENALTY
☐ 610 Agriculture
☐ 620 Other Food & Drug
☐ 625 Drug Related Seizure of Property 21 USC 881
☐ 630 Liquor Laws
☐ 640 R.R. & Truck
☐ 650 Airline Regs
☐ 660 Occupational Safety /Health
☐ 690 Other

LABOR
☐ 710 Fair Labor Standards Act
☐ 720 Labor/Mgmt. Relations
☐ 730 Labor/Mgmt. Reporting & Disclosure Act
☐ 740 Railway Labor Act
☐ 790 Other Labor Litigation
☐ 791 Empl. Ret. Inc. Security Act

PROPERTY RIGHTS
☐ 820 Copyrights
☒ 830 Patent
☐ 840 Trademark

SOCIAL SECURITY
☐ 861 HIA (1395ff)
☐ 862 Black Lung (923)
☐ 863 DIWC/DIWW (405(g))
☐ 864 SSID Title XVI
☐ 865 RSI (405(g))

FEDERAL TAX SUITS
☐ 870 Taxes (U.S. Plaintiff or Defendant)
☐ 871 IRS-Third Party 26 USC 7609

SACV09 -328 CJC (ANx)

FOR OFFICE USE ONLY: Case Number: _____

AFTER COMPLETING THE FRONT SIDE OF FORM CV-71, COMPLETE THE INFORMATION REQUESTED BELOW.