SUBSTITUTED GAMMA LACTAMS AS THERAPEUTIC AGENTS

By Inventors David W. Old and Danny T. Dinh

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Application serial number 61/047,501, filed April 24, 2007, which is hereby incorporated by reference in its entirety.

DESCRIPTION OF RELATED ART

[0002] Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

[0003] Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

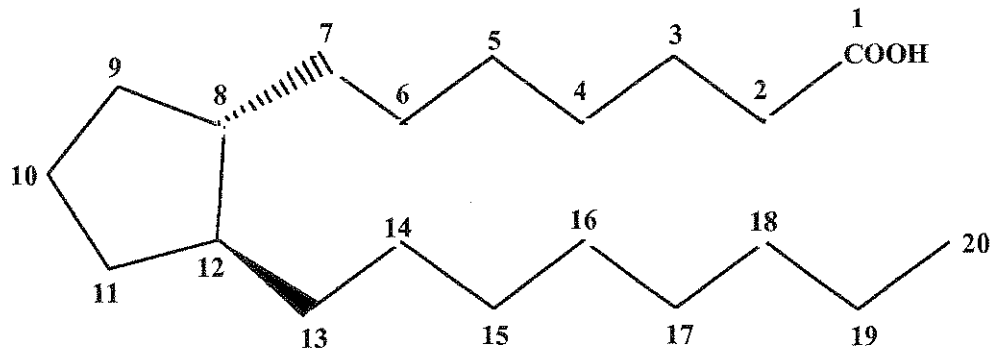
[0004] The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

[0005] Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors,

enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

[0006] Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

[0007] Certain eicosanoids and their derivatives are currently commercially available for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



[0008] Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

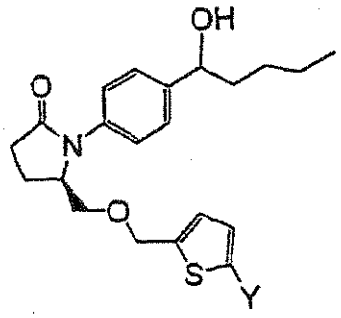
[0009] Prostaglandin EP_2 selective agonists are believed to have several medical uses. For example, U.S. Patent No. 6,437,146 teaches the use of prostaglandin EP_2 selective agonists "for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g.,

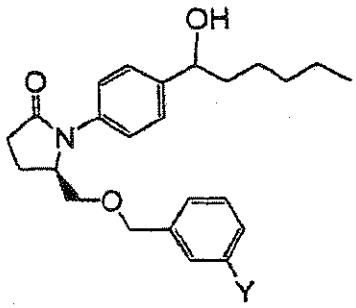
aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus crythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc.), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel disease, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodonritis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid carcinoma, mesangial proliferative glomerulonephritis, edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like."

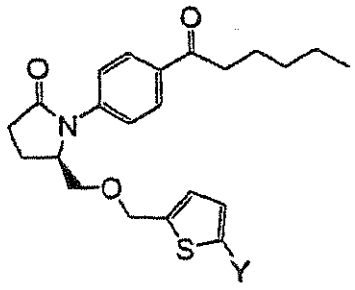
[0010] United State Patent No 6,710,072 teaches the use of EP2 agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation...various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris."

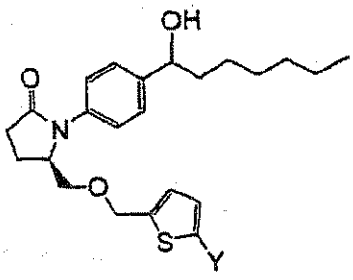
SUMMARY OF THE INVENTION

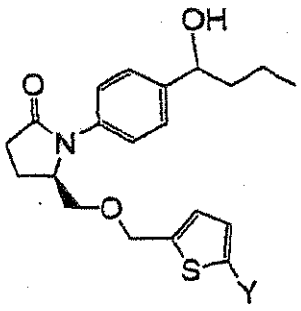
[0010a] In one aspect, there is provided a compound represented by one of the following formulae or a pharmaceutically-acceptable salt thereof:

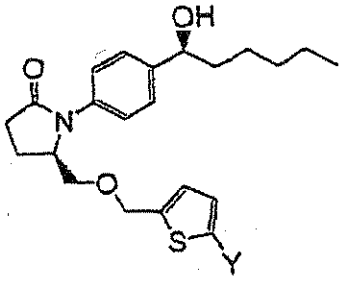


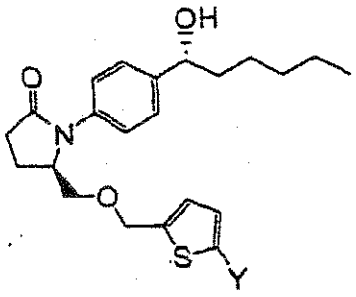
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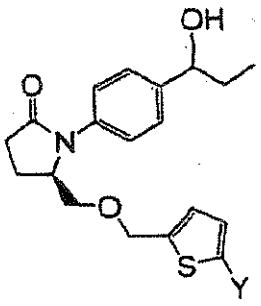
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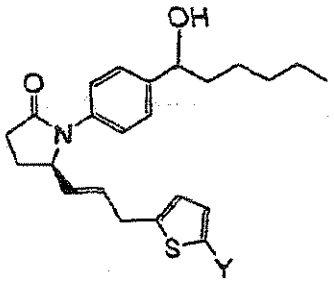
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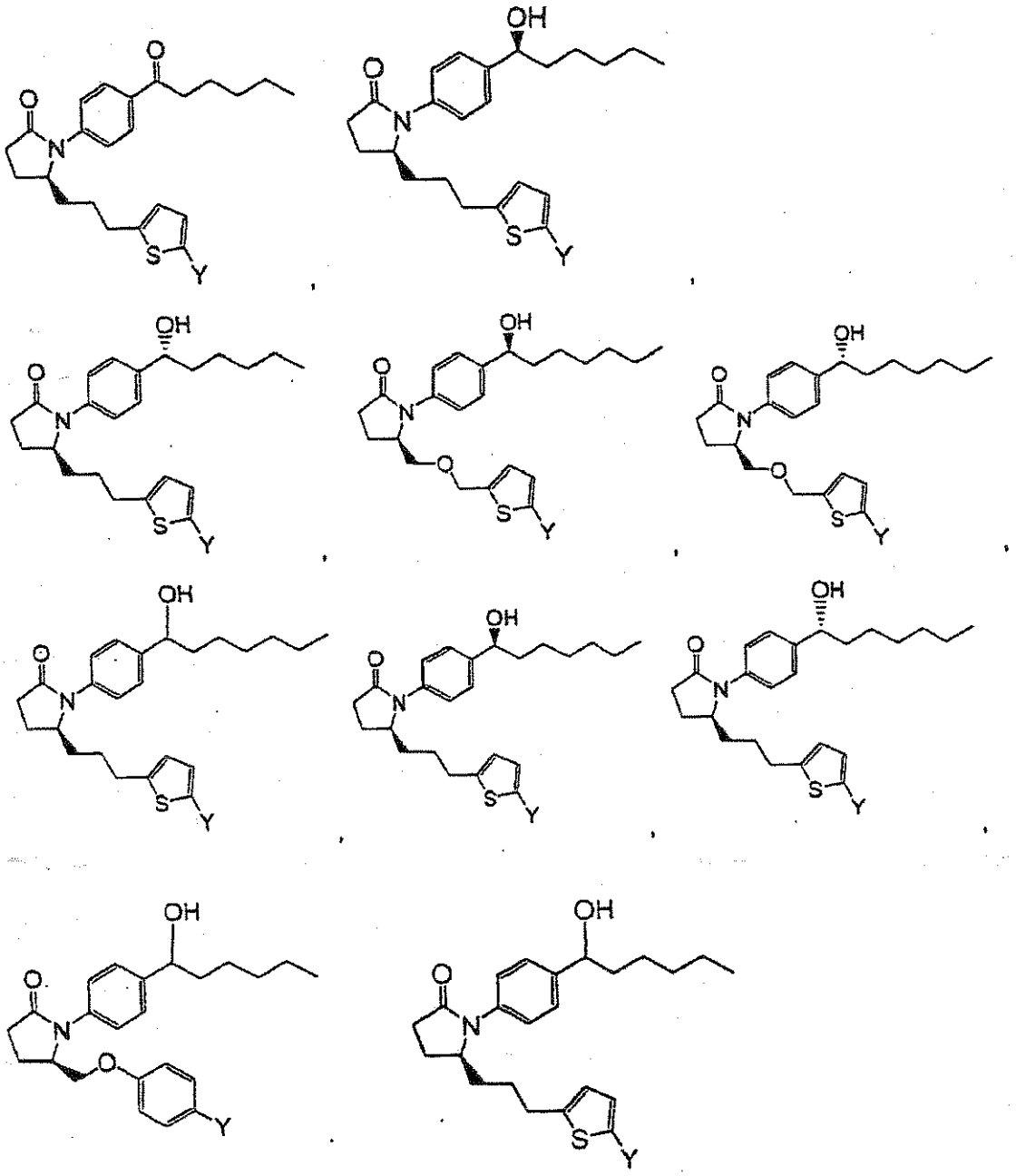
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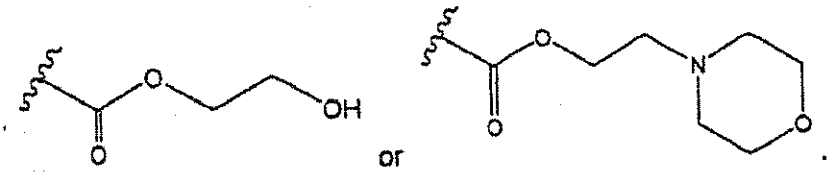
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wherein Y is

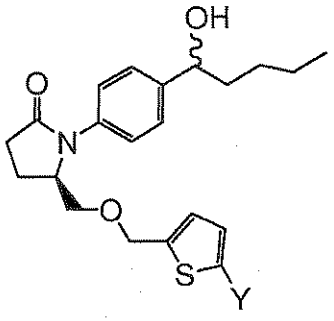


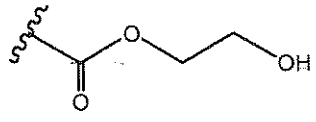
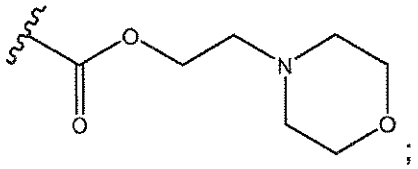
[0010b] In other aspect, there is provided a compound as defined above for use in treating baldness.

[0011] Disclosed herein are compounds useful in treating glaucoma, inflammatory bowel disease, the stimulation of hair growth, and the stimulation of the conversion of vellus hair to terminal hair. The compounds themselves are disclosed below.

DESCRIPTION OF THE INVENTION

[0012] One embodiment is a compound according to the formula



wherein Y is  or ;

or a pharmaceutically acceptable salt or a prodrug thereof.

[0013] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

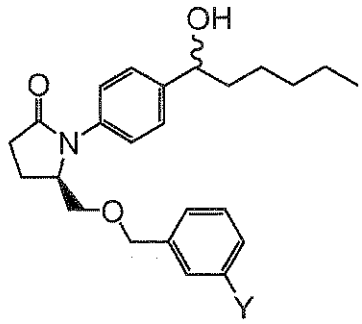
[0014] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

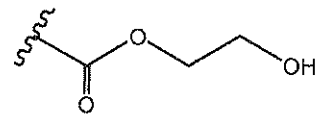
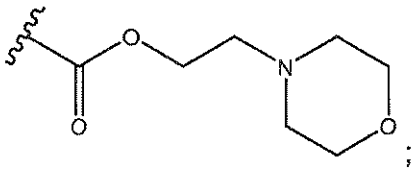
[0015] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0016] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0017] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0018] Another embodiment is a compound according to the formula



wherein Y is  or ;

or a pharmaceutically acceptable salt or a prodrug thereof.

[0019] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

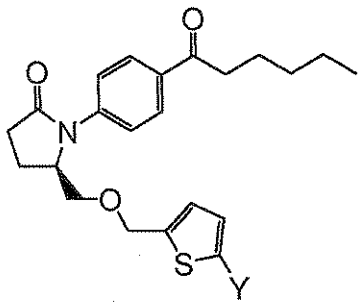
[0020] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

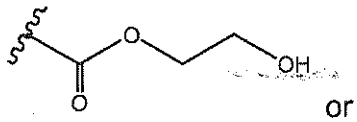
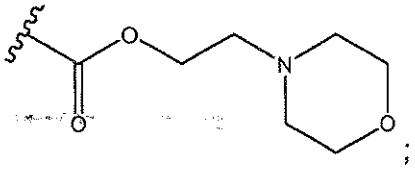
[0021] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0022] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0023] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0024] Another embodiment is a compound according to the formula



wherein Y is  or ;

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[0025] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

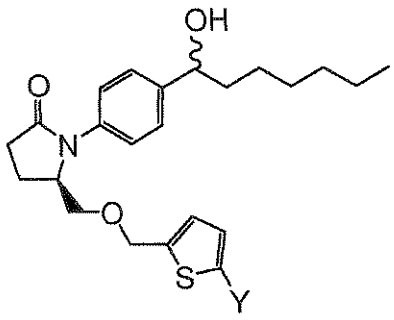
[0026] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

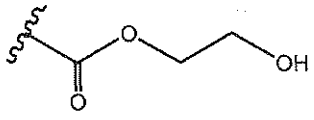
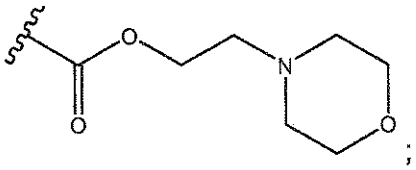
[0027] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0028] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0029] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0030] Another embodiment is a compound according to the formula



wherein Y is  or ;

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[0031] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

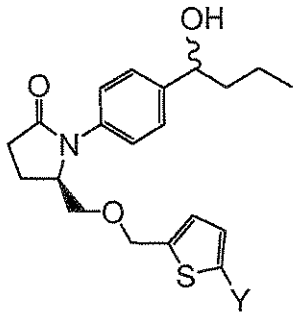
[0032] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

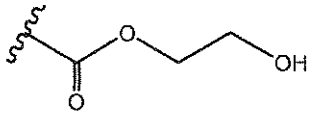
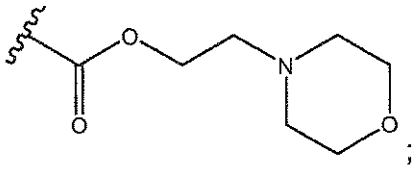
[0033] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0034] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0035] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0036] Another embodiment is a compound according to the formula



wherein Y is  or ;

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[0037] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

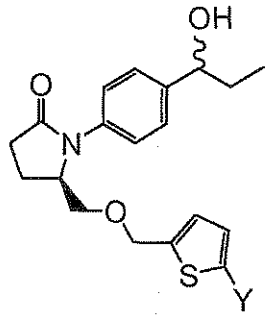
[0038] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

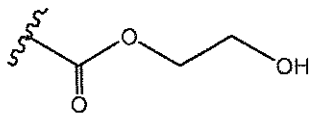
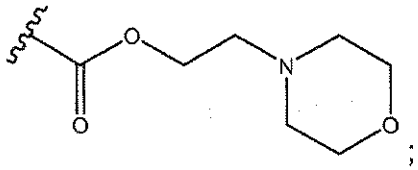
[0039] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0040] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0041] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0042] Another embodiment is a compound according to the formula



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[0043] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

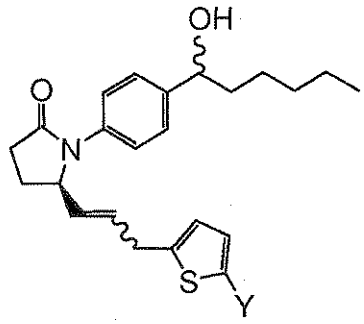
[0044] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

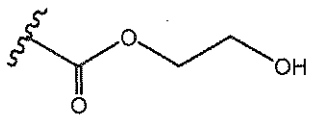
[0045] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

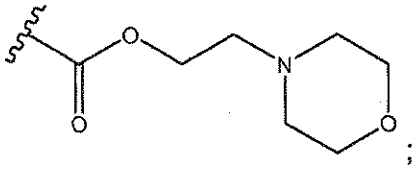
[0046] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0047] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0048] Another embodiment is a compound according to the formula



wherein Y is 

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[0049] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

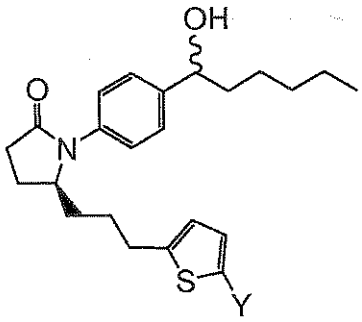
[0050] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

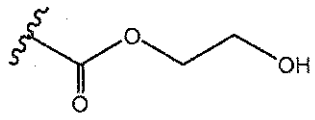
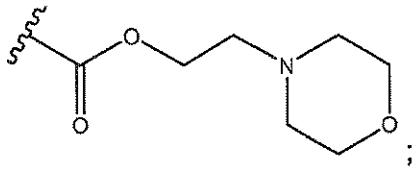
[0051] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0052] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0053] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

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or a pharmaceutically acceptable salt or a prodrug thereof.

[0055] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

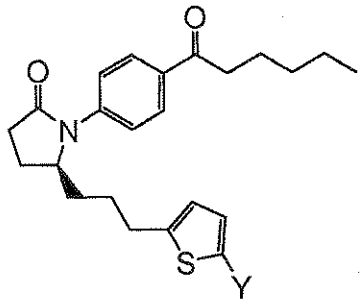
[0056] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

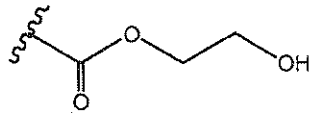
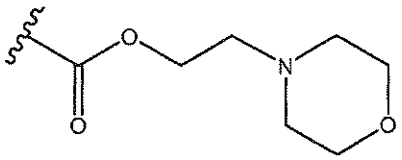
[0057] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0058] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0059] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0060] Another embodiment is a compound according to the formula



Y is  or  ;

or a pharmaceutically acceptable salt or a prodrug thereof.

[0061] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

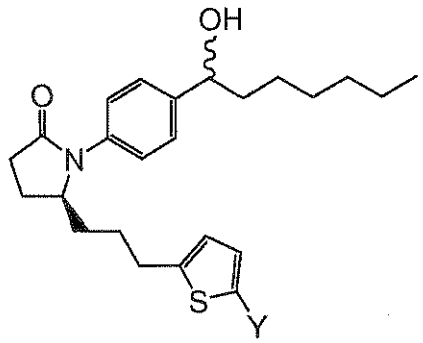
[0062] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

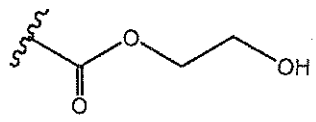
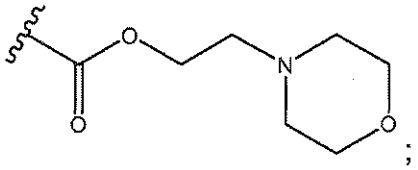
[0063] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0064] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0065] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0066] Another embodiment is a compound according to the formula



Y is  or  ;

or a pharmaceutically acceptable salt or a prodrug thereof.

[0067] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

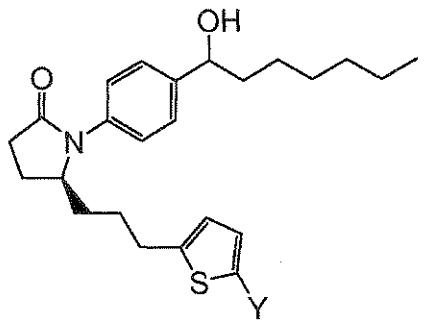
[0068] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

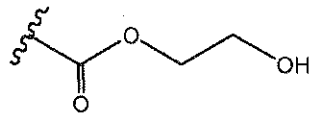
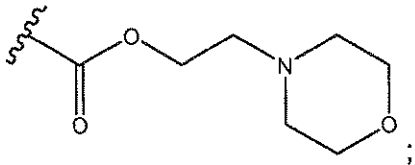
[0069] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0070] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0071] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0072] Another embodiment is a compound according to the formula



Y is  or  ;

or a pharmaceutically acceptable salt or a prodrug thereof.

[0073] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

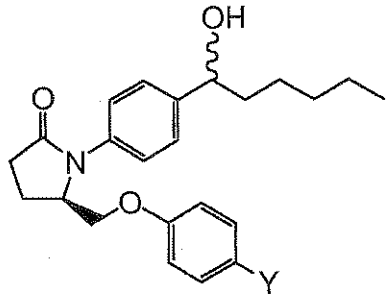
[0074] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

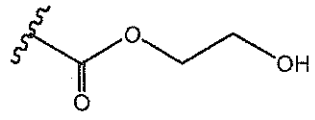
[0075] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

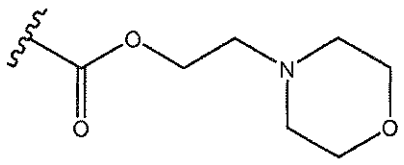
[0076] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0077] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0078] Another embodiment is a compound according to the formula



Y is 

or 

;

or a pharmaceutically acceptable salt or a prodrug thereof.

[0079] In another embodiment, said compound, salt thereof, and/or prodrug thereof is used to treat and/or prevent glaucoma and/or ocular hypertension in a mammal.

[0080] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment and/or prevention of glaucoma and/or ocular hypertension in a mammal.

[0081] In another embodiment, said compound, and/or salt thereof, and/or prodrug thereof is used in the manufacture of a medicament for the treatment of baldness in a mammal.

[0082] Another embodiment is a composition comprising said compound, and/or salt thereof, and/or prodrug thereof, wherein said composition is ophthalmically acceptable.

[0083] Use of this compound in the treatment and/or prevention, and/or in the manufacture of a medicament for the treatment and/or prevention, of any disease and/or condition mentioned herein as related to prostaglandin EP2 activity is also contemplated.

[0084] The compounds disclosed herein are useful for the prevention or treatment of glaucoma or ocular hypertension in mammals, or for the manufacture of a medicament for the treatment of glaucoma or ocular hypertension. They are also useful for the treatment of those diseases disclosed in the art as being amenable to treatment by prostaglandin EP_2 agonist, such as the ones listed previously.

[0085] A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

[0086] Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions, lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

[0087] A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted. Ester prodrugs of the compounds disclosed herein are specifically contemplated. An ester may be derived from a carboxylic acid of C1 (i.e. the terminal carboxylic acid of a natural prostaglandin), or an ester may be derived from a carboxylic acid functional group on another part of the molecule, such as on a phenyl ring. While not intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. C_{1-6} alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

[0088] A metabolite is broadly defined as a compound which is formed in vivo from the disclosed compound.

[0089] Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

[0090] For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distcarate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

[0091] Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients

are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

[0092] The amount of the presently useful compound or compounds administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 or about 1 to about 100 mg/kg/day.

[0093] A liquid which is ophthalmically acceptable is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0094] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0095] Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0096] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0097] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0098] In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0099] Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[00100] The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

Applications for Stimulating Hair Growth

[00101] In one embodiment, the compounds disclosed herein can be useful in the treatment of baldness and/or hair loss. Alopecia (baldness) is a deficiency of either normal or abnormal hair, and is primarily a cosmetic problem in humans. It is a deficiency of terminal hair, the broad diameter, colored hair that is readily seen. However, in the so called bald person, although there is a noticeable absence of

terminal hair, the skin does contain vellus hair, which is a fine colorless hair which may require microscopic examination to determine its presence. This vellus hair is a precursor to terminal hair.

[00102] The compounds described herein can be used to stimulate, such as the conversion of vellus hair to growth as terminal hair, as well as increasing the rate of growth of terminal hair. The utility of the compounds described herein for the simulation of hair growth was discovered as follows.

[00103] In the course of treating patients having glaucoma, treatment may only be appropriate in one eye. Within the course of daily practice, it was discovered that a patient who had been treated with bimatoprost, a prostaglandin analogue, developed lashed that were longer, thicker, and fuller in the treated eye than in the non-treated eye. On examination, the difference was found to be very striking. The lashes were longer and had a fuller, denser appearance in the treated eye. The lash appearance on the lids of the treated eyes would have appeared quite attractive if it represented a bilateral phenomenon. As a result of its asymmetric nature, the long lashes on one side could be construed as disturbing from a cosmetic standpoint. A systemic examination was preformed as a result of the asymmetric phenomenon. It soon became apparent that this altered appearance was not an isolated finding. Comparison of the lids of patients who were taking bimatoprost in only one eye revealed subtle changes in the lashed and adjacent hairs of the bimatoprost-treated side in several patients. Definite differences could be identified to varying degrees in the lashes and adjacent hairs of all patients who were taking the drug on a unilateral basis for longer than 6 months.

[00104] The changes in the lashes were apparent on gross inspection in several patients once attention was focused on the issue. In those with light colored hair and lashes, the differences were only seen easily with the aid of the high magnification and lighting capabilities of the slit lamp biomicroscope. In the course of glaucoma follow-up examination, attention is generally immediately focused on the eye itself. As a result of the high power magnification needed only one eye is seen at a time and the eye is seen at a high enough power that the lashes are not in focus. At these higher powers, any lash asymmetry between the two eyes is not likely to be noticed except by careful systematic comparison of the lashes and adjacent hairs of the eyelids of the two eyes.

[00105] Observed parameters leading to the conclusion that more robust hair growth occurred in the treatment area following administration of the prostaglandin analogue were multiple. They included increased length of lashed, increased number of lashes along the normal lash line, increased thickness and luster of lashes, increased auxiliary lash-like terminal hair in transitional areas adjacent to areas of normal lash growth, increased auxiliary lash-like terminal hairs at the medial and lateral canthal area, increased pigmentation of the lashes, increased numbers, increased length, as well as increased luster, and thickness of fine hair on the skin of the adjacent lid, and finally, increased perpendicular angulation of lashes and lash-like terminal hairs. The conclusion that hair growth is stimulated by prostaglandin analogues such as bimatoprost is thus supported not by evidence of a difference in a single parameter, but is based on multiple parameters of hair appearance in treated versus control areas in many subjects.

[00106] The compounds described herein are prostaglandin analogues and therefore have similar activities as bimatoprost, contain structural similarities, and therefore are expected to stimulate hair growth and stimulation of the conversion of vellus hair to terminal hair. In one embodiment, the compounds described herein and their prodrugs can be used for the stimulation of hair growth. As used herein, hair growth includes hair associated with the scalp, eyebrows, eyelids, beard, and other areas of the skin of animals.

[00107] In one embodiment, the compound is mixed with a dermatologically compatible vehicle or carrier. The vehicle, which may be employed for preparing compositions as described herein, may comprise, for example, aqueous solutions such as e.g., physiological salines, oil solutions, or ointments. The vehicle furthermore may contain dermatologically compatible preservatives such as e.g., benzalkonium chloride, surfactants like e.g., polysorbate 80, liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

[00108] In one embodiment, dermatological compositions can be formulated for topical treatment for the stimulation of hair growth which comprises an effective hair growth simulating amount of one or more compounds as defined above and a dermatologically compatible carrier. Effective amounts of the active compounds may

be determined by one of ordinary skill in the art, but will vary depending on the compound employed, frequency of application and desired result. The compound will generally range from about 0.0000001 to about 50% by weight of the dermatological composition. Preferably, the compound will range from about 0.001 to about 50% by weight of total dermatological composition, more preferably from about 0.1 to about 30% by weight of the composition.

[00109] In one embodiment, the application of the present compounds for stimulation of hair growth finds applications in mammalian species, including both humans and animals. In humans, the compounds described herein can be applied for example, to the scalp, face beard, head, pubic area, upper lip, eyebrows, and eyelids. In animal raised for their pelts, e.g., mink, the compounds described herein can be applied over the entire surface of the body to improve the overall pelt for commercial reasons. The process can also be used for cosmetic reasons in animals, e.g., applied to the skin of dogs and cats having bald patches due to mange or other diseases causing a degree of alopecia.

[00110] The pharmaceutical compositions contemplated for the stimulation of hair growth include pharmaceutical compositions suited for topical and local action. The term "topical" as employed herein relates to the use of a compound, as described herein, incorporated in a suitable pharmaceutical carrier, and applied at the site of thinning hair or baldness for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contact with the skin to be treated. Conventional pharmaceutical forms for this purpose include ointments, liniments, creams, shampoos, lotions, pastes, jellies, sprays, aerosols, and the like, and may be applied in patches or impregnated dressings depending on the part of the body to be treated. The term "ointment" embraces formulations (including creams) having oleaginous, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

[00111] Typically, the compounds can be applied repeatedly for the sustained period of time topically on the part of the body to be treated, for example, the eyelids, eyebrows, skin or scalp. The preferred dosage regimen will generally involve regular, such as daily, administration for a period of treatment of at least one month, more preferably at least three months, and most preferably, at least six months.

[00112] For topical use on the eyelids or eyebrows, the active compounds can be formulated in aqueous solutions, creams, ointments, or oils exhibiting physologicla acceptable osmolarity by addition of pharmaceutically acceptable buffers and salts. such formulations may or may not, depending on the dispenser, contain preservatives such as benzalkonium chloride, chlorhexidine, chlorobutanol, parahydroxybenzoic acids and phenylmercuric salts such as nitrate, chloride, acetate, and borate, or antioxidants, as well as additives like EDTA, sorbitol, boric acid and the like as additives. Furthermore, particularly aqueous solutions may contain viscosity increasing agents such as polysaccharides, e.g., methylcellulose, mucopolysaccharides, e.g., hyaluronic acid and chondroitin sulfate, or poly alcohol, e.g., polyvinylalcohol. Various slow releasing gels and matricies may also be employed as well as soluble and insoluble ocular inserts, for instance, based on substances forming *in situ* gels. Depending on the actual formation and compound to be used, various amounts of the drug and different dose regimens may be employed. Typically, the daily amount of compound for treatment of the eyelid may be about 0.1 ng to about 100 mg per eyelid.

[00113] For topical use on the skin and scalp, the compound can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matricies for the slow release delivery may also be used. Typically, the dose to be applied on the scalp is in the range of about 0.1 ng to about 100 mg per day, more preferably about 1 ng to about 10 mg per day, and most preferably about 10 ng to about 1 mg per day depending on the compound and the formulation. To achieve the daily amount of medication depending on the formulation, the compound may be administered once or several times daily with or without antioxidants.

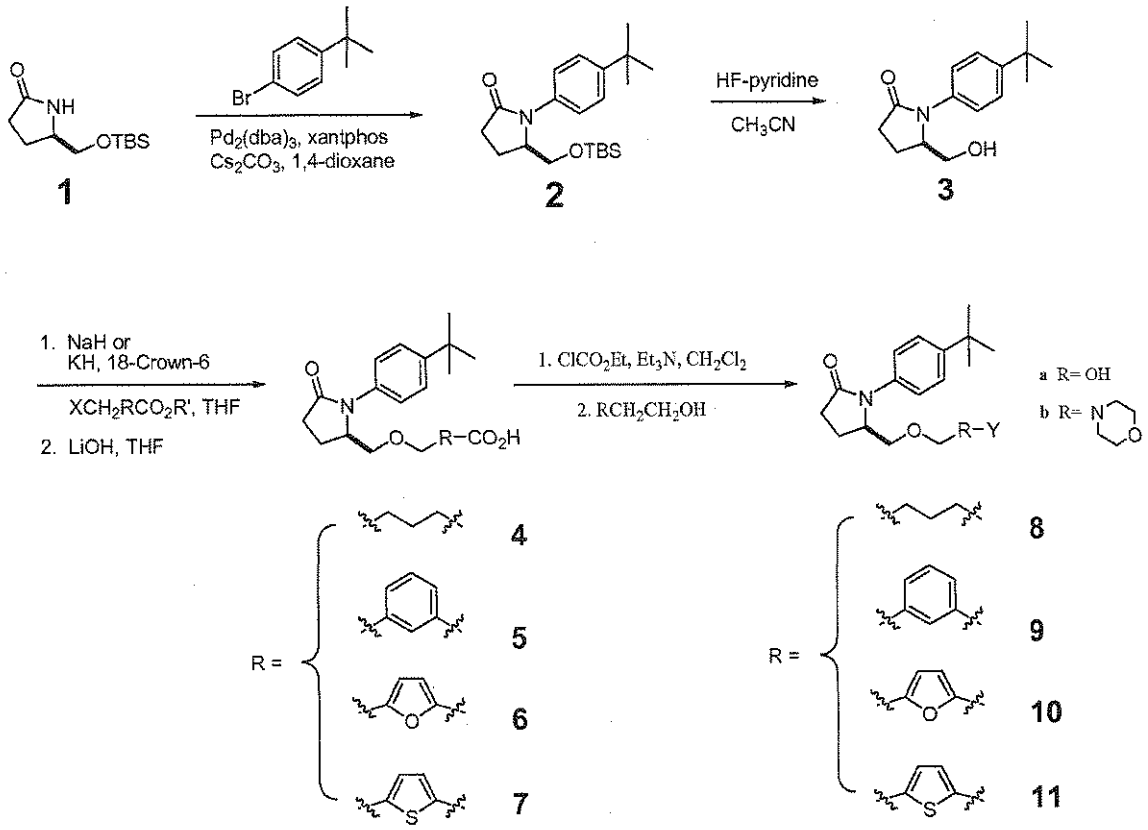
[00114] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

[00115] The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

[00116] The compounds disclosed herein are also useful in combination with other drugs useful for the treatment of glaucoma or other conditions.

Examples

Scheme 1



Example 1

Step 1. Arylation of **1** to give **2**

[00117] A solution of amide **1** (3.30 g, 14.4 mmol) in 1,4-dioxane (25 mL) was added to a mixture of 4,5-bis(triphenylphosphino)-9,9-dimethylxanthene (xantphos, 600 mg, 1.04 mmol), $Pd_2(dba)_3$ (317 mg, 0.35 mmol) and Cs_2CO_3 (6.46 g, 19.8 mmol). 1-Bromo-4-*tert*-butylbenzene (2.40 mL, 13.8 mmol) was added and the reaction mixture was purged with nitrogen. The mixture was heated at reflux for 19 h, then cooled to rt. The reaction mixture was then filtered through celite, washing with CH_2Cl_2, and the filtrate

was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% → 20% EtOAc/Hexane, gradient) afforded 3.53 g (71%) of the desired product **2**.

Step 2. Deprotection of **2** to give **3**

[00118] HF-pyridine (5 mL) was added to a solution of silyl ether **2** (3.53 g, 9.76 mmol) in MeCN (20 mL) in a plastic bottle. The reaction was stirred at rt for 5 h, then was quenched with saturated aqueous $NaHCO_3$ (250 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (150 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo to yield 2.14 g (89%) of the desired product **3**.

Step 3. Alkylation of **3** to give the ester of **4**

[00119] Sodium hydride (11 mg, 0.46 mmol) was added to a solution of alcohol **3** (100 mg, 0.40 mmol) in THF (3 mL) at 0 °C under nitrogen. After 1 h at 0 °C, methyl 5-bromovalerate (67 µL, 0.47 mmol) was added and the reaction was allowed to warm to rt. After 3 h, tlc analysis showed mostly starting alcohol remaining and another portion of bromide (67 µL, 0.47 mmol) was added. After 22 h total reaction time, the reaction was quenched with 1 N HCl and extracted with EtOAc (3 x 25 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (40% EtOAc/Hexane → EtOAc, gradient) afforded 19 mg (13%) of the desired ester.

Step 4. Saponification to give **4**

[00120] Aqueous lithium hydroxide (1 N, 0.5 mL) was added to a solution of ester from step 3 above (12.3 mg, 0.034 mmol) in THF (0.7 mL). After 2.5 h at rt, the reaction was acidified with 0.25 M HCl (5 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 10.2 mg (86%) of compound **4**.

Step 5. Compounds **8a** and **8b**

[00121] Triethylamine and ethyl chloroformate are added sequentially to a solution of compound **4** in CH_2Cl_2 at room temperature. After 2.5 h, triethylamine and ethylene glycol are added. After stirring overnight at room temperature, the reaction mixture is partitioned between H_2O and CH_2Cl_2. The phases are separated and the aqueous phase is extracted with CH_2Cl_2 (2x). The combined organic phase is washed with 1 N

HCl then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% CH_3OH / CH_2Cl_2) affords compound **8a**.

[00122] Triethylamine and ethyl chloroformate are added sequentially to a solution of compound **4** in CH_2Cl_2 at room temperature. After 2.5 h, triethylamine and 4-(2-hydroxyethyl)-morphine are added. After stirring overnight at room temperature, the reaction mixture is partitioned between H_2O and CH_2Cl_2. The phases are separated and the aqueous phase is extracted with CH_2Cl_2 (2x). The combined organic phase is washed with 1 N HCl then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% CH_3OH / CH_2Cl_2) affords compound **8b**.

Example 2

Step 1. Alkylation of **3** to give the ester of **5**

[00123] Potassium hydride (23.4 mg, 0.58 mmol) and 18-crown-6 (167 mg, 0.63 mmol) were added sequentially to a solution of alcohol **3** (130 mg, 0.53 mmol) in THF (3 mL) at 0 °C. After 1 h at 0 °C, a solution of methyl 3-(chloromethyl)benzoate (prepared from the corresponding acid chloride, pyridine and methanol: see *J. Org. Chem.* **1988**, *53*, 2548-2552; 116 mg, 0.63 mmol) in THF (1.5 mL) was added via cannula and the reaction was allowed to warm to rt. After 22.5 h, the reaction was quenched with 0.1 N HCl (10 mL) and extracted with EtOAc (3 x 15 mL). Combined extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% → 50% EtOAc/Hexane, gradient) afforded 66 mg (32%) of the desired ester.

Step 2. Saponification to give **5**

[00124] Aqueous lithium hydroxide (1 N, 0.4 mL) was added to a solution of ester from step 1 above (33.5 mg, 0.085 mmol) in THF (0.75 mL). After 3.5 h at rt, the reaction was acidified with 0.25 M HCl (5 mL) then extracted with CH_2Cl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (2%

MeOH/CH_2Cl_2), followed by preparative thin layer chromatography (10% MeOH/CH_2Cl_2) afforded 6.6 mg (20%) of compound **5**.

Step 3. Compounds **9a** and **9b**

[00125] Compounds **9a** and **9b** are prepared from compound **5** according to Example 1, step 5.

Example 3

Step 1. Alkylation of **3** to give the ester of **6**

[00126] Potassium hydride (27 mg, 0.67 mmol) and 18-crown-6 (193 mg, 0.73 mmol) were added sequentially to a solution of alcohol **3** (150 mg, 0.61 mmol) in THF (4 mL) at 0 °C. After 1 h at 0 °C, a solution of ethyl 5-chloromethylfuran-2-carboxylate (commercially available from Aldrich Chemical Company, 138 mg, 0.73 mmol) in THF (1 mL) was added via cannula and the reaction was allowed to warm to rt. After 18.5 h, the reaction was quenched with 0.25 N HCl (10 mL) and extracted with EtOAc (3 x 15 mL). Combined extracts were washed with brine (20 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 50% EtOAc/Hexane, gradient) afforded 78 mg (32%) of the desired ester.

Step 2. Saponification to give **6**

[00127] Aqueous lithium hydroxide (1 N, 0.5 mL) was added to a solution of ester from step 1 above (66.7 mg, 0.17 mmol) in THF (0.5 mL). After 3 h at rt, the reaction was acidified with 1 N HCl (2 mL) then extracted with CH_2Cl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 54.4 mg (88%) of compound **6**.

Step 3. Compounds **10a** and **10b**

[00128] Compounds **10a** and **10b** are prepared from compound **6** according to Example 1, step 5.

Example 4

Step 1. Alkylation of **3** to give the ester of **7**

[00129] Potassium hydride (25.2 mg, 0.63 mmol) and 18-crown-6 (181 mg, 0.68 mmol) were added sequentially to a solution of alcohol **3** (140 mg, 0.57 mmol) in THF (4 mL) at 0 °C. After 1.5 h at 0 °C, a solution of methyl 5-chloromethylthiophene-2-

carboxylate (prepared according to the procedures described in WO2004/037808; 130 mg, 0.68 mmol) in THF (1.5 mL) was added via cannula and the reaction was allowed to warm to rt. After 20 h, the reaction was quenched with 0.25 N HCl (15 mL) and extracted with EtOAc (3 x 20 mL). Combined extracts were washed with brine (30 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 50% EtOAc/Hexane, gradient) afforded 40.7 mg (18%) of the desired ester.

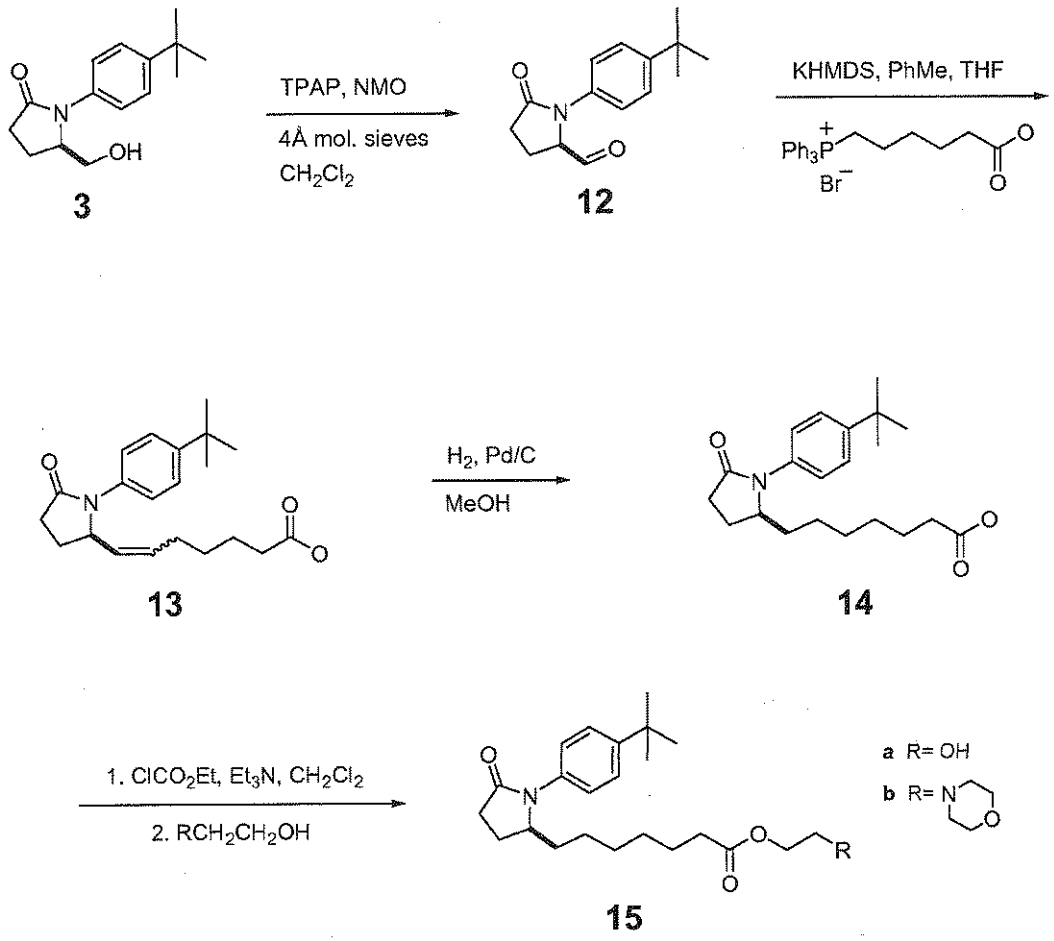
Step 2. Saponification to give **7**

[00130] Aqueous lithium hydroxide (1 N, 0.4 mL) was added to a solution of ester from step 1 above (37 mg, 0.092 mmol) in THF (0.75 mL). After 18 h at rt, the reaction was acidified with 1 N HCl (7 mL) then extracted with CH_2Cl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 22.3 mg (62%) of compound **7**.

Step 3. Compounds **11a** and **11b**

[00131] Compounds **11a** and **11b** are prepared from compound **7** according to Example 1, step 5.

Scheme 2



Example 5

Step 1. Oxidation of **3** to give aldehyde **12**

[00132] Molecular sieves (4Å, 300 mg), 4-methylmorpholine *N*-oxide (427 mg, 3.64 mmol) and tetrapropylammonium perruthenate (250 mg, 0.71 mmol) were added sequentially to a solution of alcohol **3** (600 mg, 2.43 mmol) in CH_2Cl_2 (15 mL) at rt. After 23 h, the reaction mixture was filtered through celite, washing with CH_2Cl_2 (10 mL). The filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 10% EtOAc/CH_2Cl_2, gradient) afforded 92 mg (15%) of the desired aldehyde **12**.

Step 2. Wittig reaction of **12** to give **13**

[00133] Potassium bis(trimethylsilyl)amide (0.5 M in PhMe, 1.92 mL, 0.96 mmol) was added to a solution of aldehyde **12** (86 mg, 0.35 mmol) in THF (2 mL) at rt. After 15 min at rt, the reaction mixture was cooled to – 55 °C for 10 min before a solution of 5-carboxypentyltriphenylphosphonium bromide (207 mg, 0.45 mmol) was added via cannula. After 10 min at – 55 °C, the reaction was allowed to warm to rt. After 18 h at

rt, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). Combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 10.5 mg (9%) of desired alkene **13**.

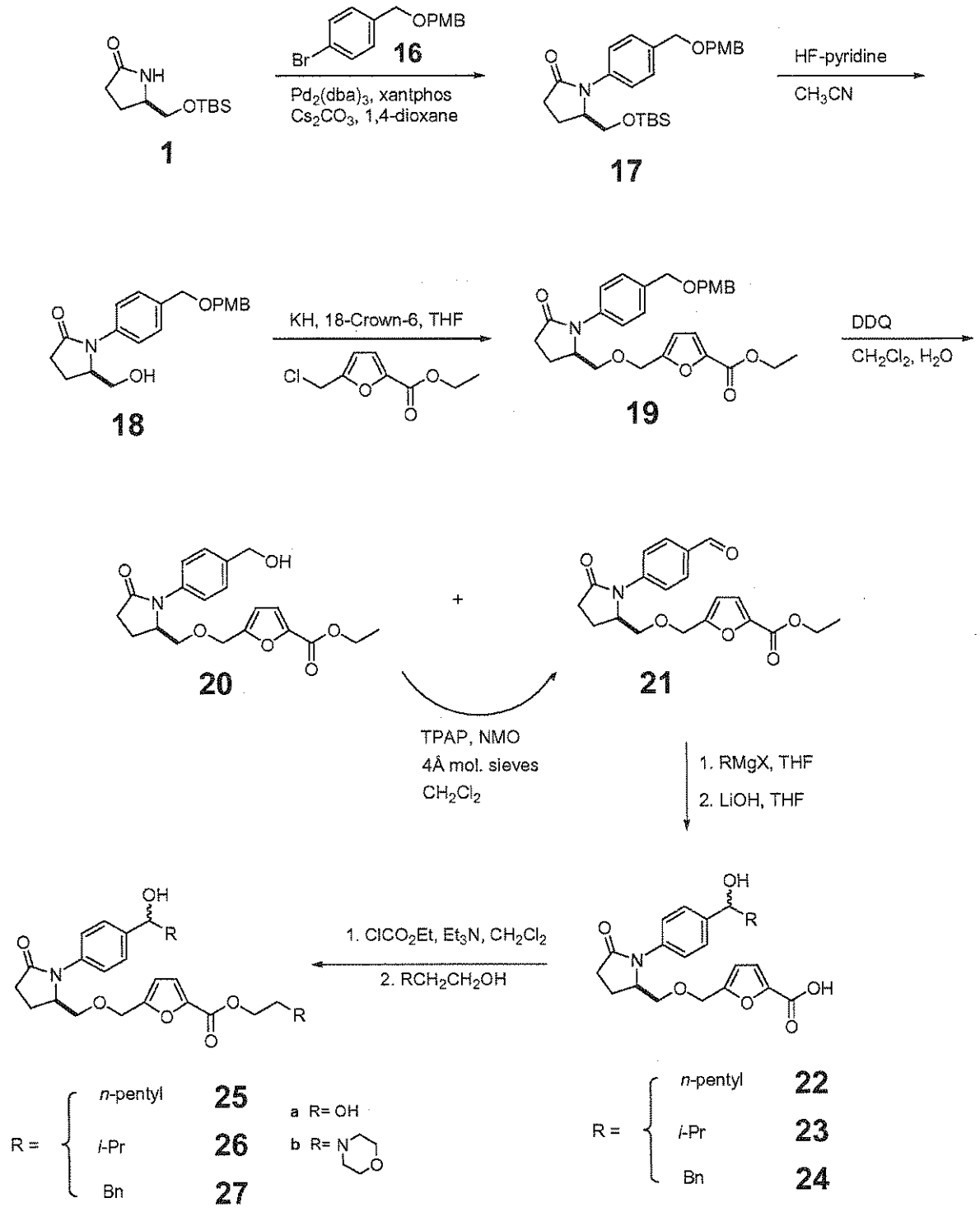
Step 3. Hydrogenation of **13** to give **14**

[00134] Palladium on carbon (10 wt. %, 2 mg) was added to a solution of alkene **13** (5.8 mg, 0.017 mmol) in MeOH (1 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 18 h. The reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo to afford 4.1 mg (70%) of compound **14**.

Step 4. Compounds **15a** and **15b**

[00135] Compounds **15a** and **15b** are prepared from compound **14** according to Example 1, step 5.

Scheme 3



Example 6

Step 1. Arylation of **1** to give **17**

[00136] A solution of amide **1** (2.89 g, 12.60 mmol) in 1,4-dioxane (20 mL) followed by a solution of 1-(4-methoxybenzyloxymethyl)-4-bromobenzene (**16**: for synthesis, see U.S. Patent No. 7,091,231, incorporated herein by reference; 3.88 g, 12.63 mmol) were added sequentially to a mixture of xantphos (877 mg, 1.52 mmol), $Pd_2(dba)_3$ (463 mg, 0.51 mmol) and Cs_2CO_3 (3.2 g, 9.82 mmol) via cannula. The reaction mixture was purged with nitrogen and then heated at reflux for 22 h. The reaction mixture was allowed to cool to rt then filtered through celite, washing with CH_2Cl_2, and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% → 25% EtOAc/Hexane, gradient) afforded 1.70 g (30%) of desired product **17**.

Step 2. Deprotection of **17** to give **18**

[00137] HF-pyridine (5 mL) was added to a solution of silyl ether **17** (1.38 g, 3.03 mmol) in MeCN (15 mL) in a plastic bottle at 0 °C. The reaction was stirred at 0 °C for 3 h, then was quenched with saturated aqueous $NaHCO_3$ (250 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (100 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (1% → 3% MeOH/CH_2Cl_2, gradient) afforded 464 mg (45%) of desired alcohol **18**.

Step 3. Alkylation of alcohol **18** to give **19**

[00138] Potassium hydride (44 mg, 1.10 mmol) and 18-crown-6 (365 mg, 1.38 mmol) were added sequentially to a solution of alcohol **18** (315 mg, 0.92 mmol) in THF (4 mL) at 0 °C. After 1 h at 0 °C, ethyl 5-chloromethylfuran-2-carboxylate (0.28 mL, 1.82 mmol) was added and the reaction was allowed to warm to rt. After 22 h, the reaction was quenched with 0.5 N HCl (20 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (50 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% EtOAc/Hexane → EtOAc, gradient) afforded 148 mg (32%) of desired product **19**.

Step 4. Oxidative deprotection of **19** to give **20** and **21**

[00139] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 82 mg, 0.36 mmol) was added to a mixture of **19** (143 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) and water (0.2 mL). After 3 h, tlc indicated that starting material remained and another portion of DDQ (82 mg, 0.36 mmol) was added. After a further 1.25 h, the reaction was quenched with

saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (20 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2, gradient) afforded 38 mg (35%) of the desired alcohol **20** and 61 mg of impure aldehyde **21**. Aldehyde **21** was further purified by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) to afford 48.7 mg (45%) of aldehyde **21**.

Step 5. Oxidation of **20** to give **21**

[00140] Molecular sieves (4Å, 3 mg), 4-methylmorpholine *N*-oxide (12.6 mg, 0.11 mmol) and tetrapropylammonium perruthenate (2.5 mg, 0.007 mmol) were added sequentially to a solution of alcohol **20** (26.8 mg, 0.072 mmol) in CH_2Cl_2 (1.5 mL) at rt. After 20 min, the reaction mixture was filtered through celite, washing with CH_2Cl_2 (5 mL). The filtrate was concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 9.6 mg (36%) of the desired aldehyde **21**.

Step 6. Grignard reaction with **21** to give the ester of **22**

[00141] Pentyl magnesium bromide (2.0 M in Et_2O, 32 L, 0.064 mmol) was added to a solution of aldehyde **21** (21.7 mg, 0.058 mmol) in THF (0.4 mL) at – 40 °C under nitrogen. After 25 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 10.6 mg (41%) of the desired ester.

Step 7. Saponification to give **22**

[00142] Aqueous lithium hydroxide (1 N, 0.1 mL) was added to a solution of ester from step 6 above (8.8 mg, 0.02 mmol) in THF (0.2 mL). After 1 h at rt, the reaction was acidified with 0.5 N HCl (1 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 8.2 mg (99%) of compound **22**.

Step 8. Compounds **25a** and **25b**

[00143] Compounds **25a** and **25b** are prepared from compound **22** according to Example 1, step 5.

Example 7

Step 1. Grignard reaction with **21** to give the ester of **23**

[00144] Isopropyl magnesium chloride (2.0 M in THF, 31 L, 0.062 mmol) was added to a solution of aldehyde **21** (20.5 mg, 0.055 mmol) in THF (0.4 mL) at – 40 °C under nitrogen. After 35 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 5 mg (22%) of the desired ester.

Step 2. Saponification to give **23**

[00145] Aqueous lithium hydroxide (1 N, 0.05 mL) was added to a solution of the ester from step 1 above (3.1 mg, 0.007 mmol) in THF (0.15 mL). After 1 h at rt, the reaction was acidified with 0.2 N HCl (1 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2.5 mg (86%) of compound **23**.

Step 3. Compounds **26a** and **26b**

[00146] Compounds **26a** and **26b** are prepared from compound **23** according to Example 1, step 5.

Example 8

Step 1. Grignard reaction with **21** to give the ester of **24**

[00147] Benzyl magnesium chloride (2.0 M in THF, 14 µL, 0.028 mmol) was added to a solution of aldehyde **21** (9.6 mg, 0.026 mmol) in THF (0.3 mL) at – 40 °C under nitrogen. After 45 min, the reaction was warmed to 0 °C. After 25 min at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (7% MeOH/CH_2Cl_2) afforded 3.3 mg (28%) of the desired ester.

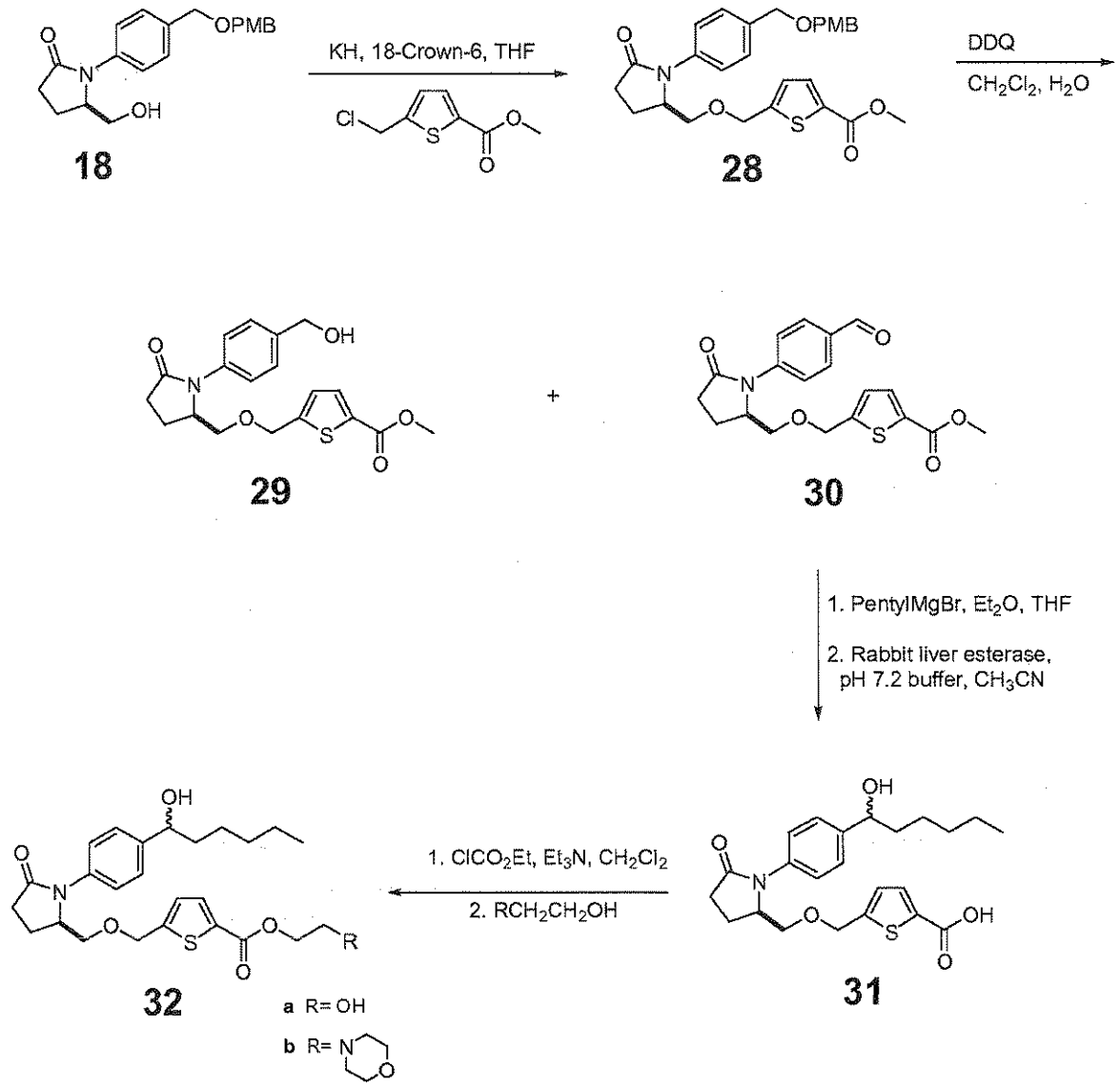
Step 2. Saponification to give **24**

[00148] Aqueous lithium hydroxide (1 N, 0.05 mL) was added to a solution of the ester from step 1 above (2.4 mg, 0.005 mmol) in THF (0.15 mL). After 2.5 h at rt, the reaction was acidified with 0.2 N HCl (1 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2.2 mg (98%) of compound **24**.

Step 3. Compounds **27a** and **27b**

[00149] Compounds **27a** and **27b** are prepared from compound **24** according to Example 1, step 5.

Scheme 4



Example 9

Step 1. Alkylation of **18** to give **28**

[00150] Potassium hydride (55.5 mg, 1.38 mmol) and 18-crown-6 (456 mg, 1.73 mmol) were added sequentially to a solution of alcohol **18** (394 mg, 1.15 mmol) in THF (5 mL) at 0 °C. After 1 h at 0 °C, a solution of methyl 5-chloromethylthiophene-2-carboxylate (439 mg, 2.30 mmol) in THF (2 mL) was added via cannula and the reaction was allowed to warm to rt. After 19 h, tlc analysis showed starting material remained. Another portion of KH (20 mg, 0.50 mmol) was added and the reaction was

heated at 50 °C. After 2 h at 50 °C, the reaction was cooled and quenched with 0.5 N HCl (20 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (50 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (15% EtOAc/Hexane → EtOAc, gradient) afforded 108 mg (19%) of desired product **28**.

Step 2. Oxidative deprotection of **28** to give **29** and **30**

[00151] DDQ (91 mg, 0.40 mmol) was added to a mixture of **28** (98 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) and water (0.15 mL). After 4.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (40 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 14.4 mg (19%) of alcohol **29** and 16.2 mg (22%) of aldehyde **30**.

Step 3. Grignard reaction with **30** to give the ester of **31**

[00152] Pentyl magnesium bromide (2.0 M in Et_2O, 22 µL, 0.044 mmol) was added to a solution of aldehyde **30** (11 mg, 0.029 mmol) in THF (0.2 mL) at – 40 °C under nitrogen. After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 4.8 mg (37%) of the desired ester.

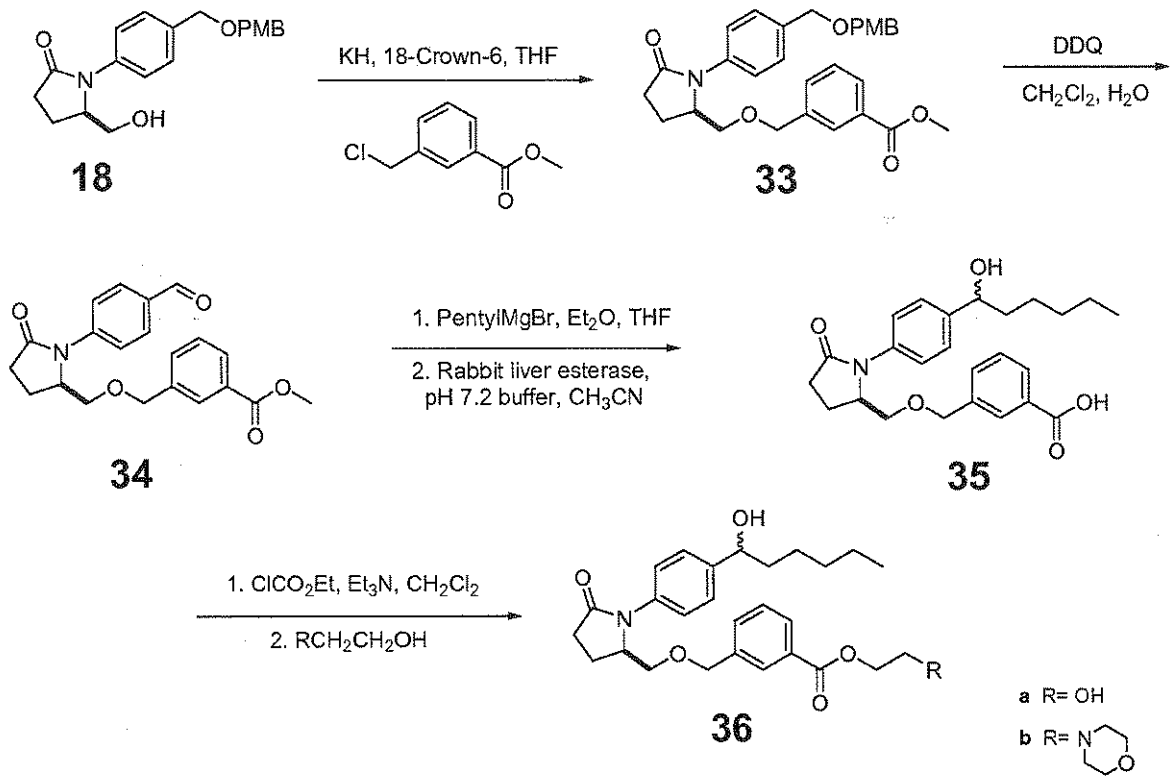
Step 4. Saponification to give **31**

[00153] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 3 above (3.6 mg, 0.008 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (2.5 mL). After 16.5 h at rt, the reaction was diluted with MeCN (7 mL) and concentrated in vacuo. The residue was suspended in CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 2.0 mg (57%) of compound **31**.

Step 5. Compounds **32a** and **32b**

[00154] Compounds **32a** and **32b** are prepared from compound **31** according to Example 1, step 5.

Scheme 5



Example 10

Step 1. Alkylation of **18** to give **33**

[00155] Potassium hydride (16 mg, 0.39 mmol) was added to a solution of alcohol **18** (112 mg, 0.33 mmol) in THF (1.0 mL) at 0 °C. After 1 h at 0 °C, 18-crown-6 (114 mg, 0.43 mmol), potassium iodide (5 mg, 0.03 mmol) and a solution of methyl 3-chloromethylbenzoate (121 mg, 0.66 mmol) in THF (0.5 mL) were added sequentially. The reaction was allowed to warm to rt. After 19 h, the reaction was quenched with 0.1 N HCl (10 mL) and extracted with EtOAc (3 x 10 mL). Combined extracts were washed with brine (15 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% EtOAc/Hexane → EtOAc, gradient) afforded 23 mg (14%) of desired product **33**.

Step 2. Oxidative deprotection of **33** to give **34**

[00156] DDQ (23 mg, 0.10 mmol) was added to a mixture of **33** (23 mg, 0.047 mmol) in CH_2Cl_2 and water (20:1, 0.25 mL). After 3.75 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 7 mL). Combined extracts were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (80% EtOAc/Hex) afforded 13 mg (58%) of aldehyde **34**.

Step 3. Grignard reaction with **34** to give the ester of **35**

[00157] Pentyl magnesium bromide (2.0 M in Et_2O, 50 µL, 0.10 mmol) was added to a solution of aldehyde **34** (12.4 mg, 0.034 mmol) in THF (0.1 mL) at – 40 °C under nitrogen. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (7 mL) and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 8.6 mg (58%) of the desired ester.

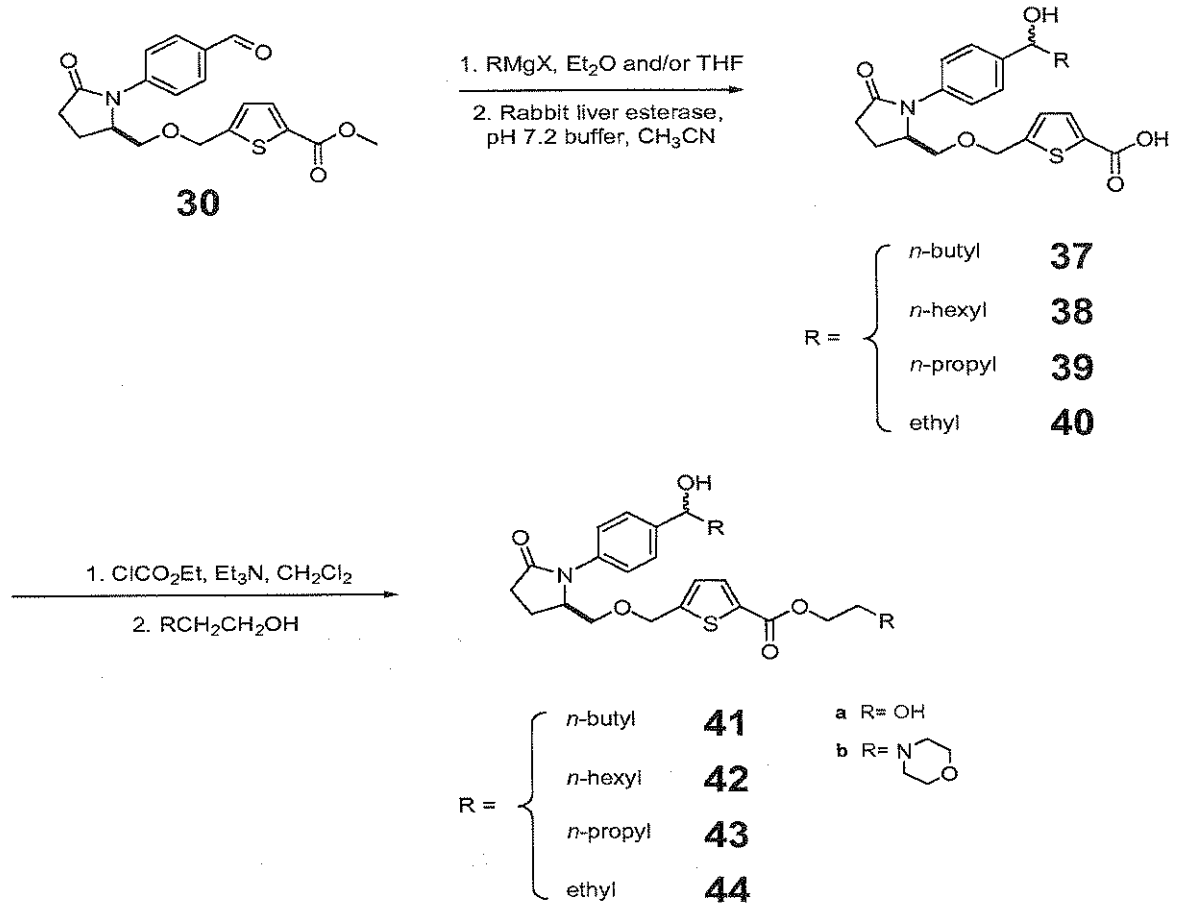
Step 4. Saponification to give **35**

[00158] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 3 above (7.4 mg, 0.017 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (2.5 mL). After 18 h at rt, the reaction was diluted with MeCN (7 mL) and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 1.5 mg (21%) of compound **35**.

Step 5. Compounds **36a** and **36b**

[00159] Compounds **36a** and **36b** are prepared from compound **35** according to Example 1, step 5.

Scheme 6



Example 11

Step 1. Grignard reaction with **30** to give the ester of **37**

[00160] *n*-Butyl magnesium chloride (2.0 M in THF, 41 µL, 0.082 mmol) was added to a solution of aldehyde **30** (20.2 mg, 0.054 mmol) in THF (0.1 mL) at – 40 °C under nitrogen. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 12.3 mg (53%) of the desired ester.

Step 2. Saponification to give **37**

[00161] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 1 above (11.2 mg, 0.026 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (3.0 mL). After 19 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was suspended in 5% MeOH/CH_2Cl_2 and filtered through a

cotton plug. The filtrate was concentrated in vacuo to afford 10.7 mg (99%) of compound **37**.

Step 3. Compounds **41a** and **41b**

[00162] Compounds **41a** and **41b** are prepared from compound **37** according to Example 1, step 5.

Example 12

Step 1. Grignard reaction with **30** to give the ester of **38**

[00163] *n*-Hexyl magnesium bromide (2.0 M in Et_2O, 100 L, 0.20 mmol) was added to a solution of aldehyde **30** (24.6 mg, 0.054 mmol) in THF (0.12 mL) at – 40 °C under nitrogen. After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 16.3 mg (54%) of the desired ester.

Step 2. Saponification to give **38**

[00164] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 1 above (13 mg, 0.028 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (3.0 mL). After 18 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was suspended in 5% MeOH/CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 11 mg (87%) of compound **38**.

Step 3. Compounds **42a** and **42b**

[00165] Compounds **42a** and **42b** are prepared from compound **38** according to Example 1, step 5.

Example 13

Step 1. Grignard reaction with **30** to give the ester of **39**

[00166] *n*-Propyl magnesium chloride (2.0 M in Et_2O, 92 µL, 0.18 mmol) was added to a solution of aldehyde **30** (22.9 mg, 0.061 mmol) in THF (0.12 mL) at – 40 °C under nitrogen. After 1.75 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 13 mg (51%) of the desired ester.

Step 2. Saponification to give **39**

Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 1 above (10.8 mg, 0.026 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (3.0 mL). After 17 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was suspended in 5% MeOH/CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 10.4 mg (99%) of compound **39**.

Step 3. Compounds **43a** and **43b**

[00167] Compounds **43a** and **43b** are prepared from compound **39** according to Example 1, step 5.

Example 14

Step 1. Grignard reaction with **30** to give the ester of **40**

[00168] Ethyl magnesium chloride (2.0 M in Et_2O, 24 µL, 0.048 mmol) was added to a solution of aldehyde **30** (5.8 mg, 0.016 mmol) in THF (0.1 mL) at – 40 °C under nitrogen. After 1.25 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 2.5 mg (40%) of the desired ester.

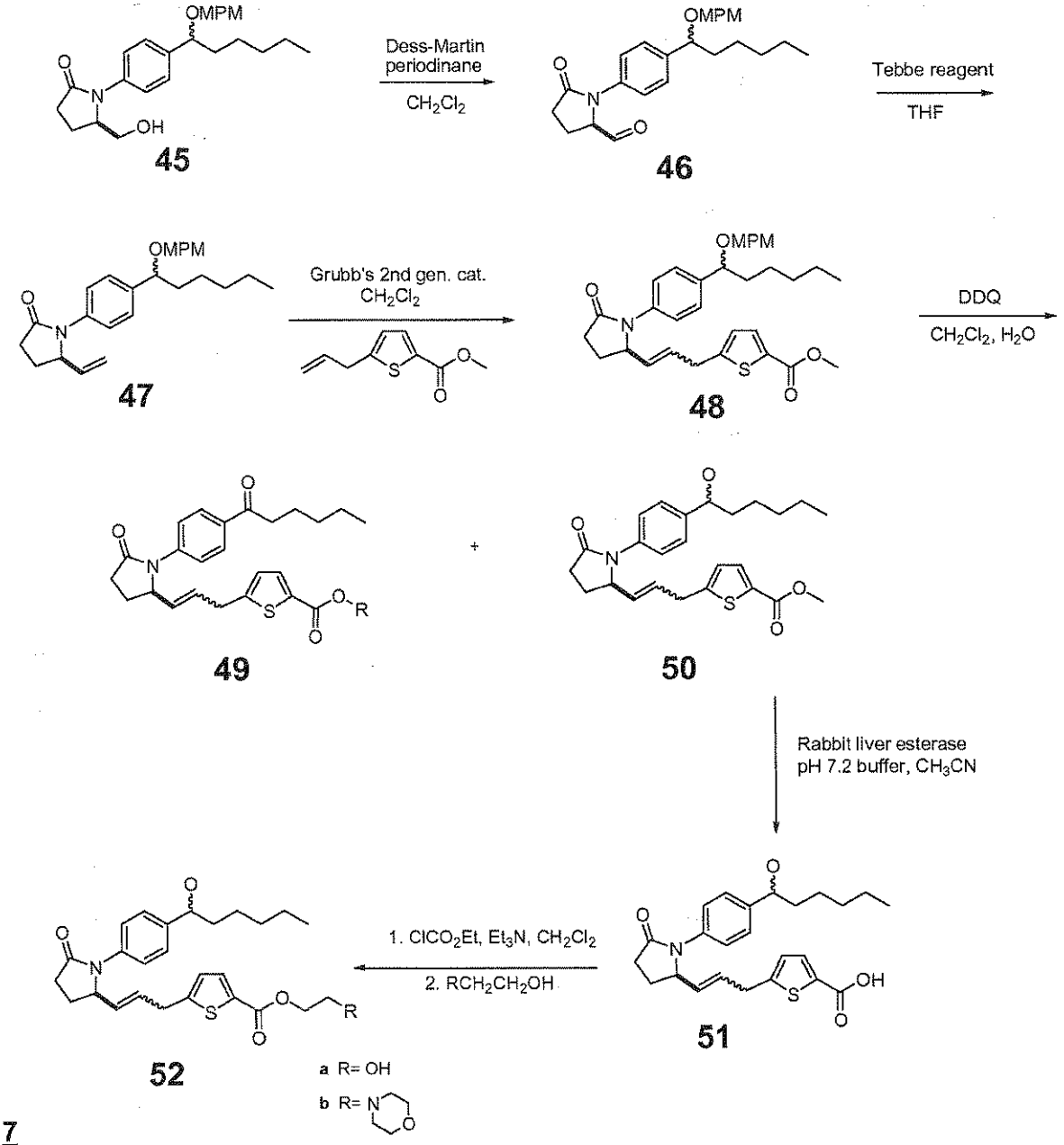
Step 2. Saponification to give **40**

[00169] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 1 above (2.8 mg, 0.007 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (2.5 mL). After 17 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was suspended in 5% MeOH/CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 2.7 mg (99%) of compound **40**.

Step 3. Compounds **44a** and **44b**

[00170] Compounds **44a** and **44b** are prepared from compound **40** according to Example 1, step 5.

Scheme



7

Example 15

Step 1. Oxidation of **45** to give aldehyde **46**

[00171] Dess-Martin periodinane (1.63 g, 3.83 mmol) was added to a solution of alcohol **45** (1.43 g, 3.48 mmol) in CH_2Cl_2 (12 mL) at rt under nitrogen. After 1 h at rt the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $NaHSO_3$ (1:1, 100 mL). The mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification

of the residue by flash column chromatography on silica (2% MeOH/CH_2Cl_2) afforded 915 mg (64%) of the desired aldehyde **46**.

Step 2. Methylenation of **46** to give alkene **47**

[00172] The Tebbe reagent (0.5 M in THF, 4.86 mL, 2.43 mmol) was added to a solution of aldehyde **46** (677 mg, 1.65 mmol) in THF (11 mL) at – 40 °C under nitrogen. After 1 h at – 40 °C the reaction was quenched by addition of aqueous 2 N NaOH (1.65 mL) and stirred vigorously overnight with the addition of THF (15 mL). The mixture was filtered through celite, washing with excess EtOAc. The filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica (30% → 50% EtOAc/Hex) afforded 254 mg (38%) of the desired alkene **47**.

Step 3. Metathesis reaction of **47** to give alkene **48**

[00173] Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)-ruthenium (Grubbs' catalyst, 2nd generation, 48 mg, 0.057 mmol) was added to a solution of alkene **47** (230 mg, 0.56 mmol) and methyl 5-allylthiophene-2-carboxylate (preparation 3, 206 mg, 1.13 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was heated at reflux for 4 h. The reaction mixture was cooled to rt and more catalyst (48 mg, 0.057 mmol) and methyl 5-allylthiophene-2-carboxylate (100 mg, 0.55 mmol) were added. The mixture was heated for 18 h longer at reflux then cooled and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (5% → 50% EtOAc/Hex, gradient) afforded 100 mg (32%) of the desired alkene **48** along with 130 mg (57%) of the starting alkene **47**.

Step 4. Oxidative deprotection of **48** to give **49** and **50**

[00174] DDQ (58 mg, 0.26 mmol) was added to a mixture of **48** (130 mg, 0.23 mmol) in CH_2Cl_2 (3.1 mL) and water (0.16 mL) at 0 °C under nitrogen. After 45 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (40 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were washed with brine (25 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (50% → 75% EtOAc/Hex, gradient) afforded 28 mg of an inseparable mixture of starting material **48** and ketone **49**, and 63 mg (62%) of the desired alcohol **50**.

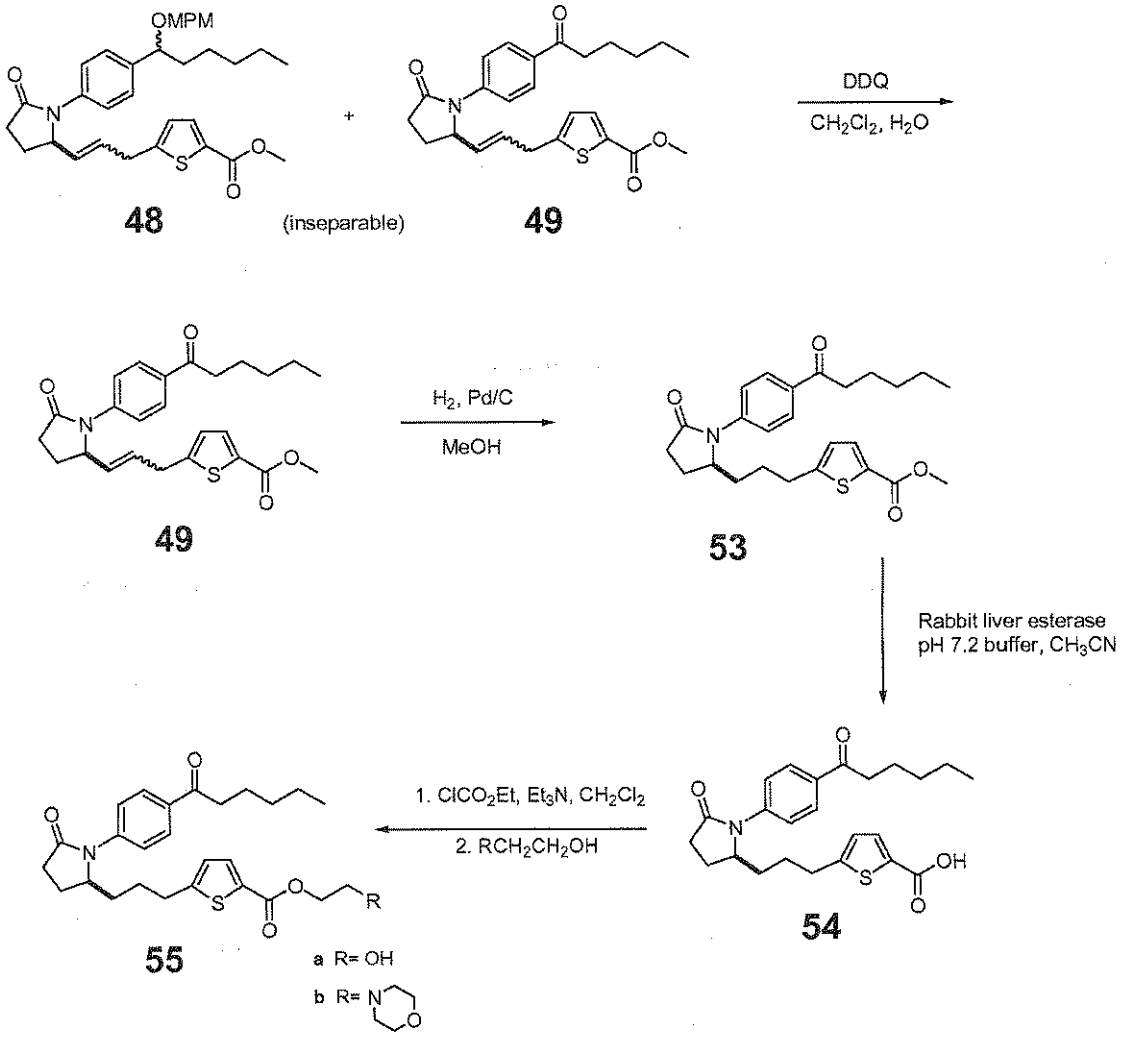
Step 5. Saponification of **50** to give **51**

[00175] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of ester **50** (3.7 mg, 0.008 mmol) in MeCN (0.2 mL) and pH 7.2 buffer (2.5 mL). After 15.5 h at rt, the reaction was diluted with MeCN (8 mL) and concentrated in vacuo. The residue was suspended in 10% MeOH/CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 3.0 mg (84%) of compound **51**.

Step 6. Compounds **52a** and **52b**

[00176] Compounds **52a** and **52b** are prepared from compound **51** according to Example 1, step 5.

Scheme 8



Example 16

Step 1. Oxidation of **38/39** afford **39**

[00177] DDQ (5.5 mg, 0.024 mmol) was added to the mixture of ether **48** and ketone **49** (6.8 mg, 0.012 mmol) in CH_2Cl_2 and water (20:1, 0.25 mL) at room temperature under nitrogen. After 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine (5 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (60% EtOAc/Hex) afforded 1.5 mg (28%) of desired ketone **49**.

Step 2. Hydrogenation of **49** to give ester **53**

[00178] Palladium on carbon (10 wt. %, 1 mg) was added to a solution of alkene **49** (1.5 mg, 0.0034 mmol) in methanol (0.5 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen. After 2 h at rt, the reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo to afford 1.3 mg (86%) of desired ester **53**.

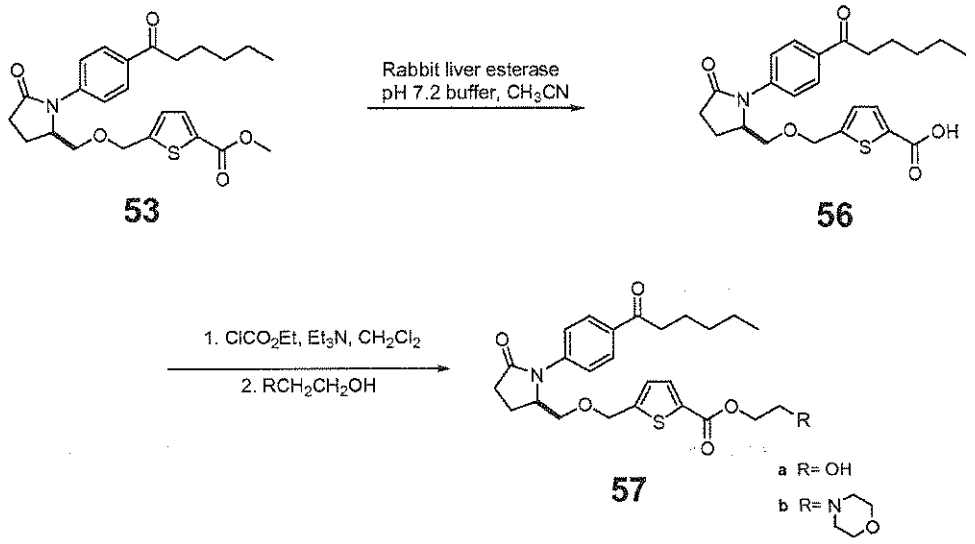
Step 3. Saponification of **53** to give **54**

[00179] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of ester **53** (1.3 mg, 0.0029 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (2.5 mL). After 23 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was suspended in 10% MeOH/CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 1.2 mg (95%) of compound **54**.

Step 4. Compounds **55a** and **55b**

[00180] Compounds **55a** and **55b** are prepared from compound **54** according to Example 1, step 5.

Scheme 9

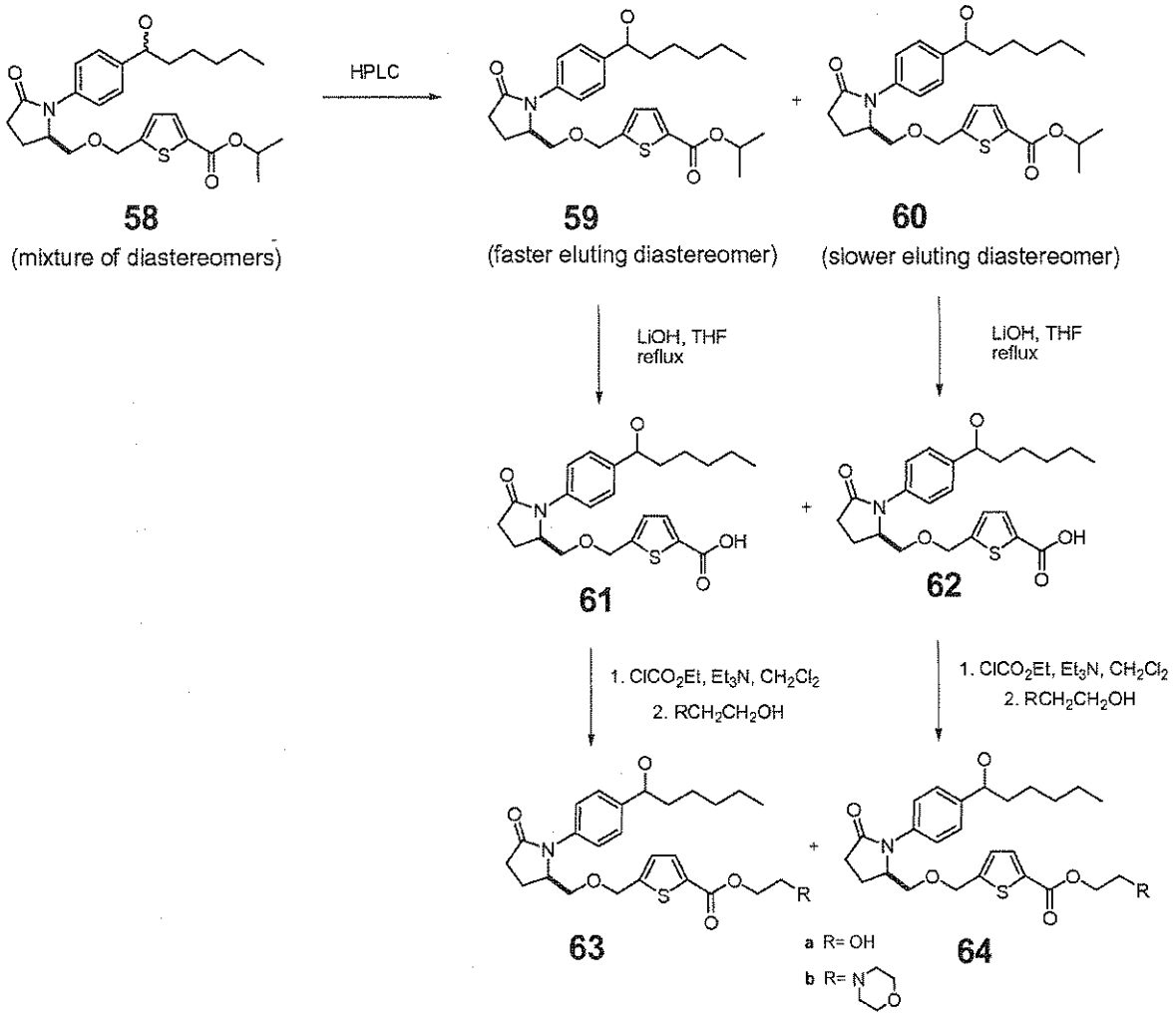


53 56 57

Example 17

[00181] Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of ester **53** (0.6 mg, 0.014 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (2.5 mL). After 17 h at rt, the reaction was diluted with MeCN (8 mL) and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (4% MeOH/CH_2Cl_2) afforded 1 mg (17%) of compound **56**. Compounds **57a** and **57b** are prepared from compound **56** according to Example 1, step 5.

Scheme 10



Examples 18

[00182] The two diastereomers (**58**, ~100 mg) were separated on a Waters 600 HPLC instrument employing a Waters 2996 PDA detector and a Whatman Partisil® 10 M20/50 column, 22 mm x 500 mm (Cat. No. 4232-220, Q.A. No. 3TA02D80). Using 60% EtOAc/Hex as the eluent and a flow rate of 15 mL/min, the first diastereomer (**59**, 32.8 mg total isolated) eluted at 55-60 min, and the second diastereomer (**60**, 52.6 mg total isolated) eluted at 61-70 min.

Example 19

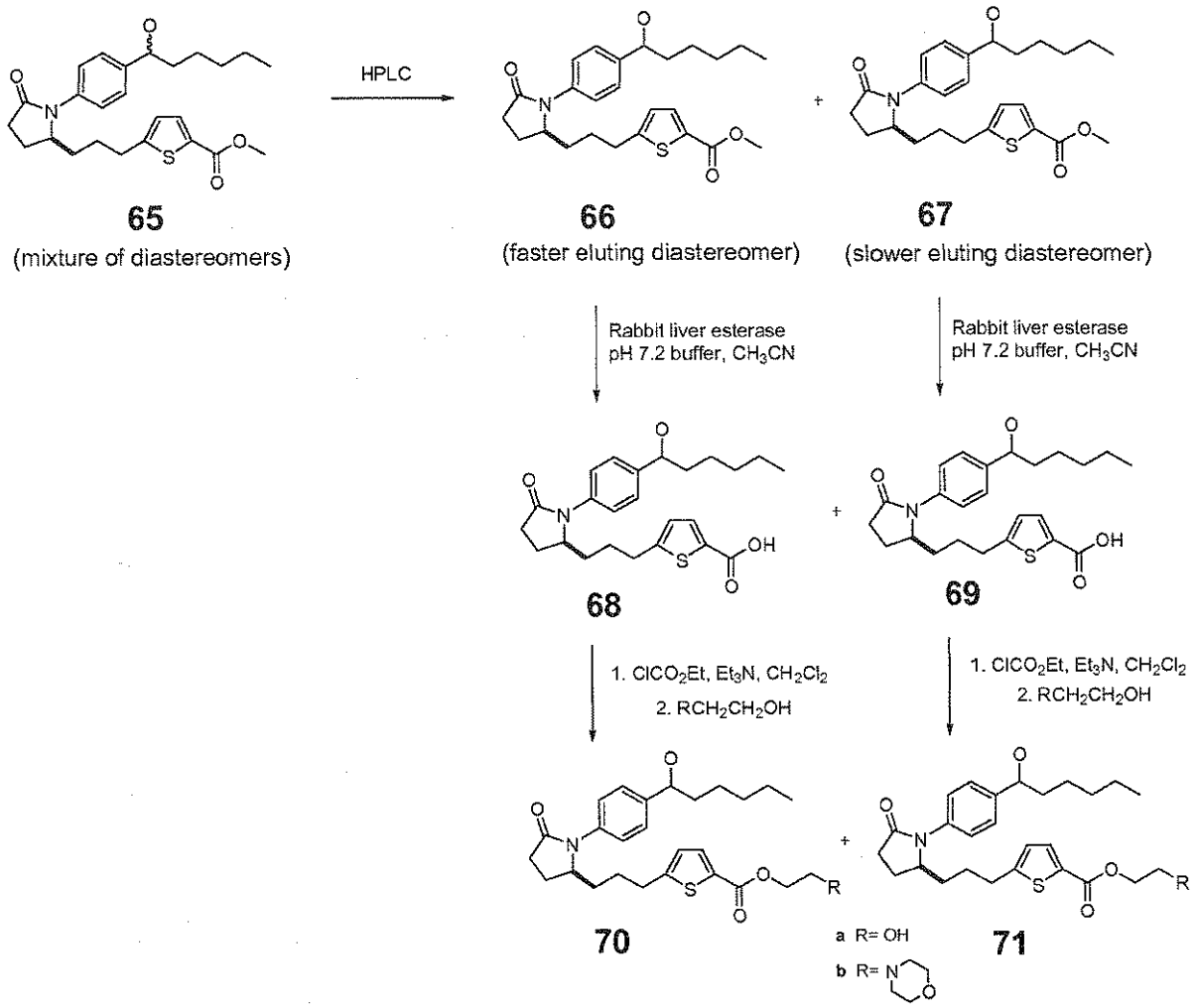
[00183] Aqueous 1 N lithium hydroxide (0.05 mL, 0.05 mmol) was added to a solution of faster eluting ester diastereomer **59** (2.7 mg, 0.0057 mmol) in THF (0.1 mL) and the mixture was heated at reflux overnight. After 17 h, the reaction was cooled to

rt, acidified with 0.05 N aqueous HCl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2.5 mg (100%) of compound **61**. Compounds **63a** and **63b** are prepared from compound **61** according to Example 1, step 5.

Example 20

[00184] Aqueous 1 N lithium hydroxide (0.05 mL, 0.05 mmol) was added to a solution of slower eluting ester diastereomer **60** (2.8 mg, 0.0059 mmol) in THF (0.1 mL) and the mixture was heated at reflux overnight. After 23 h, the reaction was cooled to rt, acidified with 0.05 N aqueous HCl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 1.7 mg (67%) of compound **62**. Compounds **64a** and **64b** are prepared from compound **62** according to Example 1, step 5.

Scheme 11



Examples 21

[00185] The two diastereomers (**65**, ~43 mg) were separated on a Waters 600 HPLC instrument employing a Waters 2996 PDA detector and a Whatman Partisil® 10 M20/50 column, 22 mm x 500 mm (Cat. No. 4232-220, Q.A. No. 3TA02D80). Using 55% EtOAc/Hex as the eluent and a flow rate of 15 mL/min, the first diastereomer (**66**, 16 mg) eluted at 69-75 min, and the second diastereomer (**67**, 19 mg) eluted at 80-88 min.

Example 22

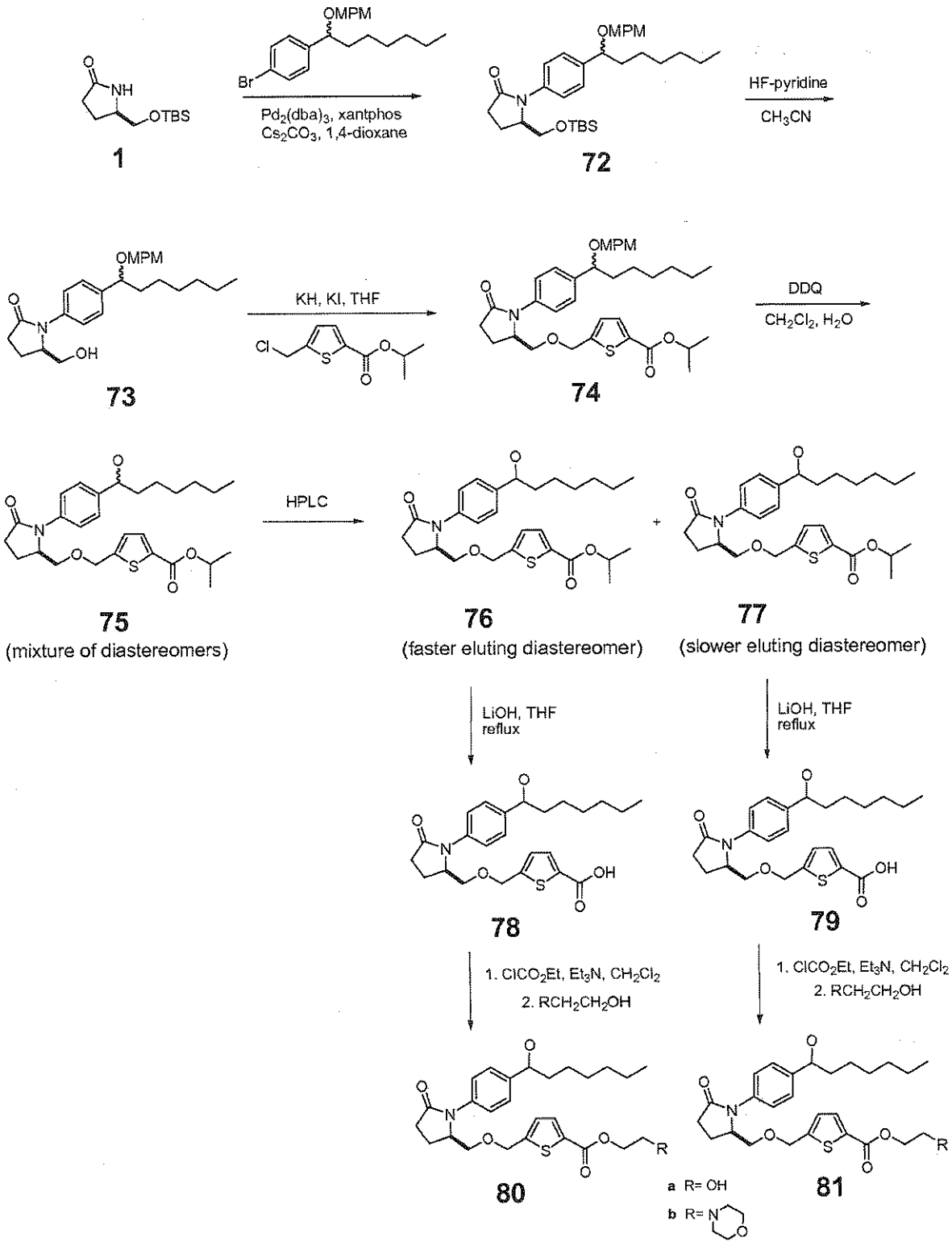
[00186] Rabbit liver esterase (134 units/mg, 2 mg) was added to a solution of faster eluting ester diastereomer **66** (16 mg, 0.036 mmol) in MeCN (0.2 mL) and pH 7.2 buffer (3.0 mL). After 18 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was diluted with CH_2Cl_2 (5 mL), filtered through a plug of glass

wool and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (EtOAc → 25% MeOH/EtOAc, gradient) afforded 12 mg (77%) of compound **68**. Compounds **70a** and **70b** are prepared from compound **68** according to Example 1, step 5.

Example 23

[00187] Rabbit liver esterase (134 units/mg, 2 mg) was added to a solution of slower eluting ester diastereomer **67** (19 mg, 0.043 mmol) in MeCN (0.2 mL) and pH 7.2 buffer (3.0 mL). After 18 h at rt, the reaction was diluted with MeCN (10 mL) and concentrated in vacuo. The residue was diluted with CH_2Cl_2 (5 mL), filtered through a plug of glass wool and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (EtOAc → 25% MeOH/EtOAc, gradient) afforded 10.5 mg (57%) of compound **69**. Compounds **71a** and **71b** are prepared from compound **69** according to Example 1, step 5.

Scheme 12



1

72

73

74

75
(mixture of diastereomers)

76
(faster eluting diastereomer)

77
(slower eluting diastereomer)

78

79

80

81

Example 24

Step 1. Arylation of **1** to give **72**

[00188] $Pd_2(dba)_3$ (550 mg, 0.60 mmol), xantphos (1.04 g, 180 mmol) and Cs_2CO_3 (5.87 g, 18.0 mmol) were added sequentially to a solution of amide **1** (3.45 g, 15.0 mmol) in 1,4-dioxane (100 mL). A solution of 1-(1-(4-methoxybenzyloxyheptyl)-4-bromobenzene (preparation 4, 5.30 g, 13.54 mmol) in 1,4-dioxane (50 mL) was added via cannula. The reaction mixture was purged with nitrogen then heated at reflux overnight. After 17 h, the reaction was cooled to rt and filtered through celite, washing with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (5% → 35% EtOAc/Hexane, gradient) to afford 5.26 g (72%) of the desired product **72**.

Step 2. Deprotection of **72** to give **73**

[00189] HF-pyridine (8.8 mL) was added to a solution of silyl ether **72** (5.26 g, 9.74 mmol) in MeCN (50 mL) in a plastic bottle at 0 °C. After 45 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (400 mL). The mixture was extracted with EtOAc (3 x 200 mL). The combined extracts were washed with brine (200 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (CH_2Cl_2 → 5% MeOH/CH_2Cl_2, gradient) afforded 3.9 g (94%) of the desired alcohol **73** as a pale yellow solid.

Step 3. Alkylation of **73** to give **74**

[00190] A round bottom flask was charged with potassium hydride (30 wt% in oil, 138 mg, 1.03 mmol). The material was washed with hexanes (3 x 1 mL), then suspended in THF (1 mL). The mixture was cooled to 0 °C and a solution of alcohol **73** (339 mg, 0.80 mmol) in THF (1.5 mL) was added via cannula. After 1 h at 0 °C, a solution of isopropyl 5-chloromethylthiophene-2-carboxylate (preparation 2, 174 mg, 0.80 mmol) in THF (1.5 mL) was added via cannula. Potassium iodide (14 mg, 0.08 mmol) was added and the reaction was allowed to warm to rt. After 18 h, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (15 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 75% EtOAc/Hexane, gradient), followed by preparative thin layer chromatography (65% EtOAc/Hexane) afforded 65 mg (14%) of desired product **74.**

Step 4. Oxidative deprotection of **74** to give **75**

[00191] DDQ (26 mg, 0.12 mmol) was added to a solution of **74** (65 mg, 0.11 mmol) in CH_2Cl_2 (1.4 mL) and water (0.07 mL) at 0 °C under nitrogen. After 40 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 20 mL). Combined extracts were washed with brine (15 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (50% → 75% EtOAc/Hexane, gradient), followed by preparative thin layer chromatography (60% EtOAc/Hexane) afforded 36 mg (69%) of compound **75**.

Examples 25

[00192] The two diastereomers (**75**, ~36 mg) were separated on a Waters 600 HPLC instrument employing a Waters 2996 PDA detector and a Whatman Partisil® 10 M20/50 column, 22 mm x 500 mm (Cat. No. 4232-220, Q.A. No. 3TA02D80). Using 60% EtOAc/Hex as the eluent and a flow rate of 15 mL/min, the first diastereomer (**76**, 14.8 mg) eluted at 50-56.5 min, and the second diastereomer (**77**, 16.4 mg) eluted at 56.5-70 min.

Example 26

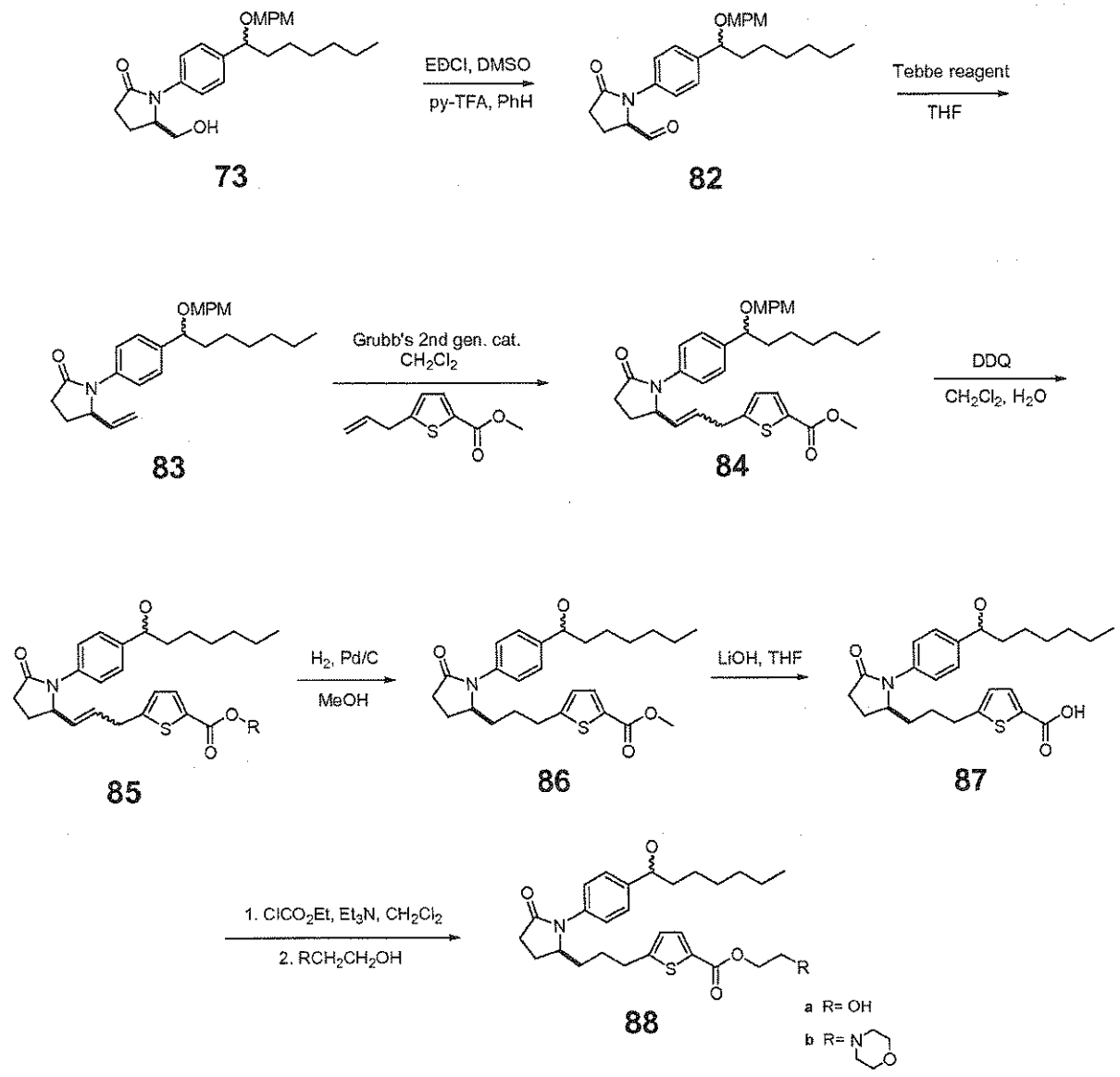
[00193] Aqueous 1 N lithium hydroxide (0.05 mL, 0.05 mmol) was added to a solution of faster eluting ester diastereomer **76** (3.5 mg, 0.0072 mmol) in THF (0.1 mL) and the mixture was heated at reflux overnight. After 18 h, the reaction was cooled to rt, diluted with water (2 mL), acidified with 1.0 N aqueous HCl (1 mL) and extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford 3.0 mg (94%) of compound **78**. Compounds **80a** and **80b** are prepared from compound **78** according to Example 1, step 5.

Example 27

[00194] Aqueous 1 N lithium hydroxide (0.05 mL, 0.05 mmol) was added to a solution of slower eluting ester diastereomer **77** (3.5 mg, 0.0072 mmol) in THF (0.1 mL) and the mixture was heated at reflux overnight. After 18 h, the reaction was cooled to rt, diluted with water (2 mL), acidified with 1.0 N aqueous HCl (1 mL) and extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford 3.2 mg (99%) of compound **79**.

Compounds **81a** and **81b** are prepared from compound **79** according to Example 1, step 5.

Scheme 13



73 **82** **83** **84** **85** **86** **87** **88**

Example 28

Step 1. Oxidation of **73** to give aldehyde **82**

[00195] 1-(3-(Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.43 g, 7.45 mmol) and DMSO (0.70 mL, 9.86 mmol) were added sequentially to a solution of alcohol **73** (1.06 g, 2.48 mmol) in benzene (25 mL) at rt under nitrogen. After 10 min at rt, pyridinium trifluoroacetate (527 mg, 2.73 mmol) was added. After 3 h at rt, the solution was decanted from the oily residue and the residue was washed with benzene (3 x 15 mL). The combined benzene phases were concentrated in vacuo. Purification of the residue by flash column chromatography on silica ($CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2, gradient) afforded 1.0 g (95%) of the desired aldehyde **82**.

Step 2. Methylenation of **82** to give alkene **83**

[00196] The Tebbe reagent (0.5 M in THF, 7.0 mL, 3.5 mmol) was added to a solution of aldehyde **82** (1.0 g, 2.36 mmol) in THF (16 mL) at – 40 °C under nitrogen. After 1 h at – 40 °C the reaction was quenched by addition of aqueous 2 N NaOH (5.25 mL) and stirred vigorously overnight with the addition of THF (20 mL). The mixture was filtered through celite, washing with excess EtOAc. The filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica (40% EtOAc/Hex) afforded 195 mg (20%) of the desired alkene **83**.

Step 3. Metathesis reaction of **83** to give alkene **84**

[00197] Grubbs' second generation catalyst (38 mg, 0.045 mmol) was added to a solution of alkene **83** (190 mg, 0.45 mmol) and methyl 5-allylthiophene-2-carboxylate (preparation 3, 173 mg, 0.95 mmol) in CH_2Cl_2 (2.4 mL). The reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to rt and more catalyst (9 mg, 0.011 mmol) and methyl 5-allylthiophene-2-carboxylate (165 mg, 0.91 mmol) were added. The mixture was heated for 22 h longer at reflux then cooled and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (2 times, first using 5% → 50% EtOAc/Hex, gradient then second using $CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2, gradient) afforded 180 mg (69%) of the desired alkene **84**.

Step 4. Oxidative deprotection of **84** to give **85**

[00198] DDQ (78 mg, 0.34 mmol) was added to a mixture of **84** (180 mg, 0.31 mmol) in CH_2Cl_2 (4.1 mL) and water (0.21 mL) at 0 °C under nitrogen. After 45 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine

(50 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (50% → 66% EtOAc/Hex, gradient) afforded 50 mg (35%) of the desired alcohol **85**.

Step 5. Hydrogenation of **85** to give ester **86**

[00199] Palladium on carbon (10 wt. %, 12 mg) was added to a solution of alkene **85** (50 mg, 0.11 mmol) in methanol (2.3 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen. After 20 h at rt, the reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo to afford 50 mg (99%) of the desired ester **86**.

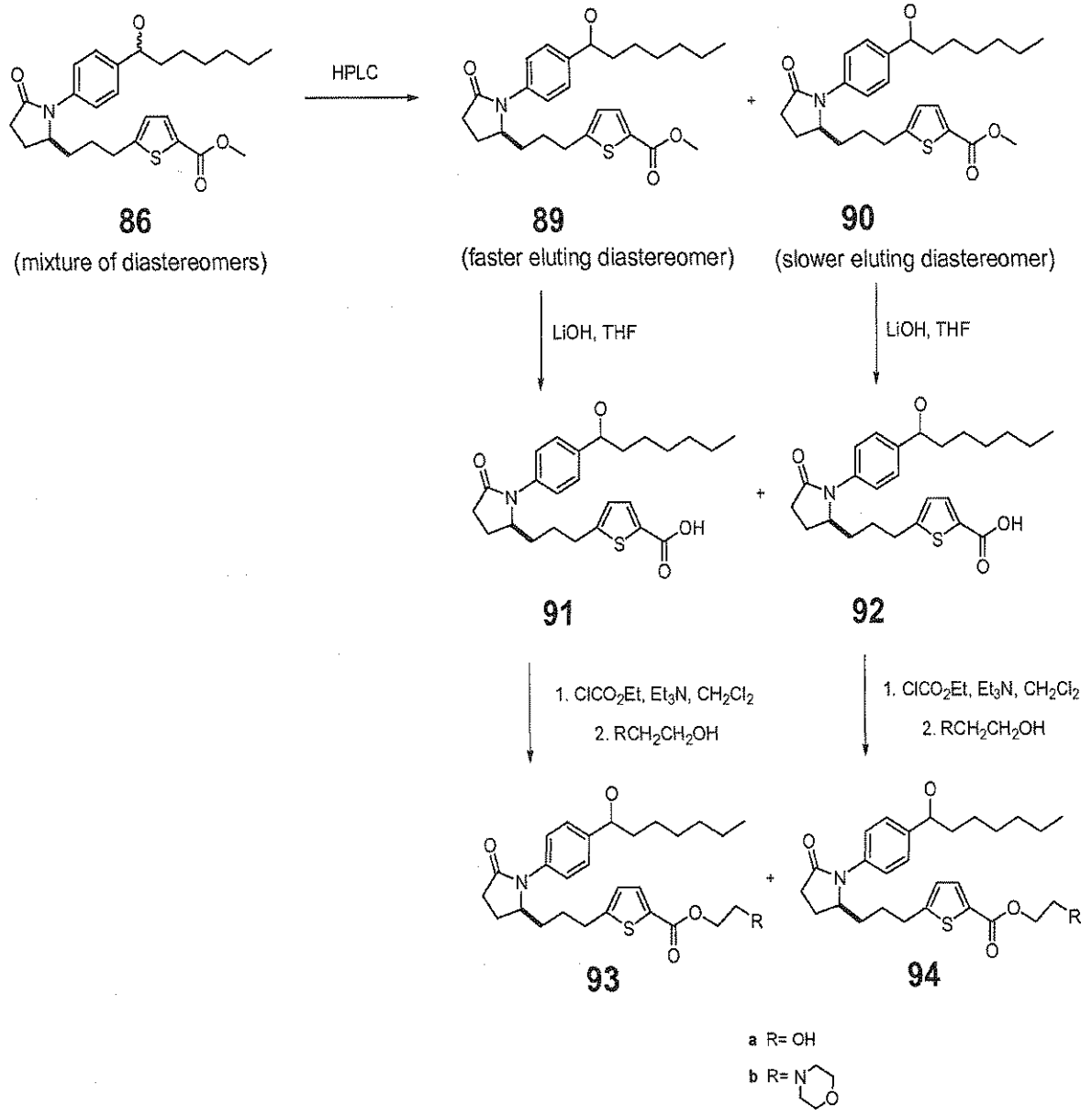
Step 6. Saponification of **86** to give **87**

[00200] Aqueous 1 N lithium hydroxide (0.19 mL, 0.19 mmol) was added to a solution of ester **86** (17 mg, 0.038 mmol) in THF (0.4 mL). After 18 h at rt, H_2O (1.0 mL) was added and the mixture was acidified with 1 N aqueous HCl (1.0 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (15% MeOH/CH_2Cl_2) afforded 5.6 mg (34%) of compound **87**.

Step 7. Compounds **88a** and **88b**

[00201] Compounds **88a** and **88b** are prepared from compound **87** according to Example 1, step 5.

Scheme 14


HPLC
86
(mixture of diastereomers)
89
(faster eluting diastereomer)
90
(slower eluting diastereomer)
LiOH, THF
LiOH, THF
91
92
1. ClCO2Et, Et3N, CH2Cl2
2. RCH2CH2OH
1. ClCO2Et, Et3N, CH2Cl2
2. RCH2CH2OH
93
94
a R= OH
b R= N O

Examples 29

[00202] The two diastereomers **86** (~34 mg) were separated on a Waters 600 HPLC instrument employing a Waters 2996 PDA detector and a Whatman Partisil® 10 M20/50 column, 22 mm x 500 mm (Cat. No. 4232-220, Q.A. No. 3TA02D80). Using 55% EtOAc/Hex as the eluent and a flow rate of 15 mL/min, the first diastereomer (**89**, 10.7 mg) eluted at 78-87.5 min, and the second diastereomer (**90**, 7.0 mg) eluted at 91-101 min.

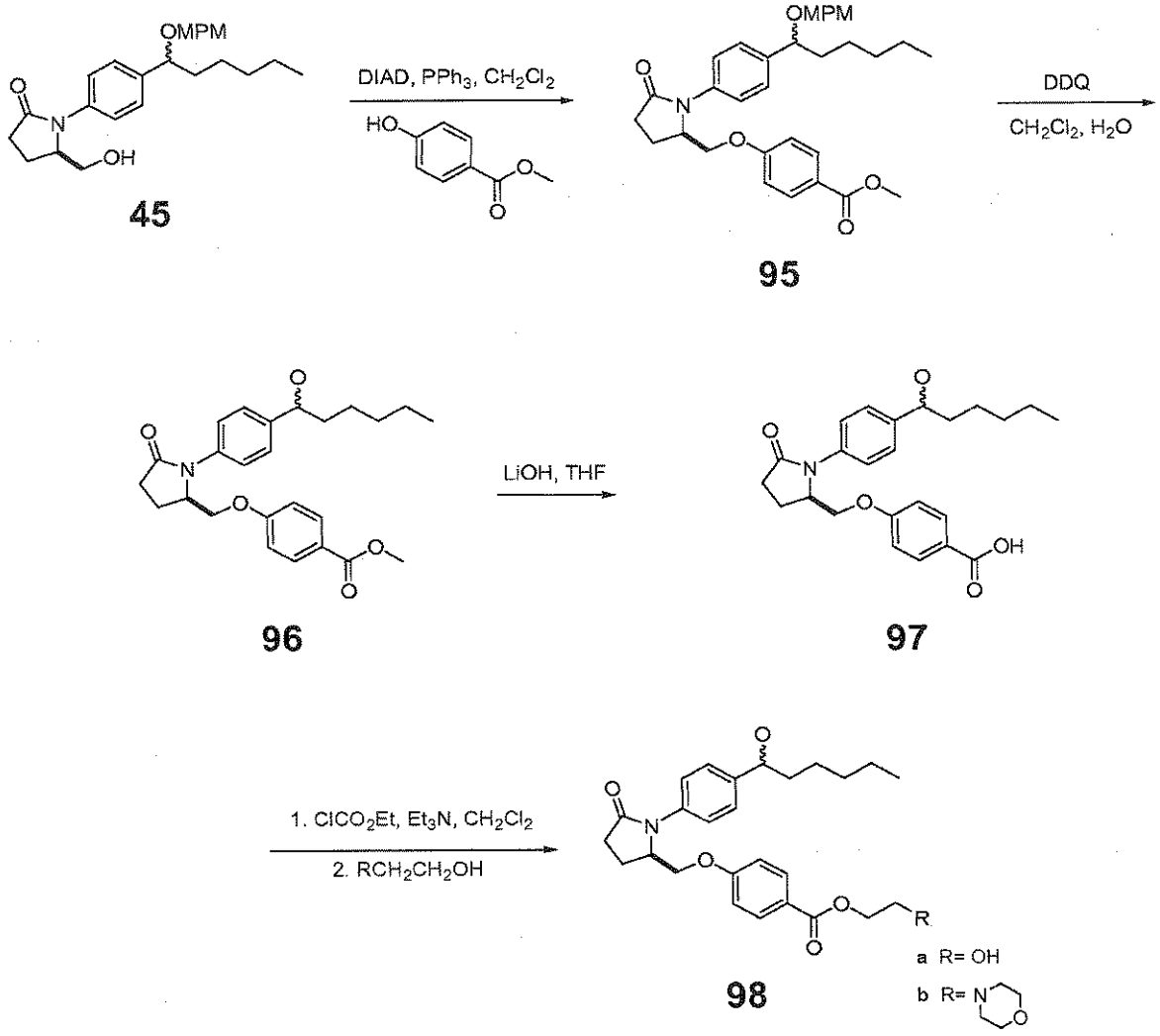
Example 30

[00203] Aqueous 1 N lithium hydroxide (0.12 mL, 0.12 mmol) was added to a solution of faster eluting ester diastereomer **89** (10.7 mg, 0.023 mmol) in THF (0.3 mL). After 66 h at rt, H_2O (1.0 mL) was added and the mixture was acidified with 1 N aqueous HCl (1.0 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (5 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo to afford 10 mg (96%) of compound **91**. Compounds **93a** and **93b** are prepared from compound **91** according to Example 1, step 5.

Example 31

[00204] Aqueous 1 N lithium hydroxide (0.08 mL, 0.08 mmol) was added to a solution of slower eluting ester diastereomer **90** (7.0 mg, 0.015 mmol) in THF (0.2 mL). After 66 h at rt, H_2O (1.0 mL) was added and the mixture was acidified with 1 N aqueous HCl (1.0 mL) and extracted with EtOAc (3 x 8 mL). The combined extracts were washed with brine (5 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo to afford 6.5 mg (96%) of compound **92**. Compounds **94a** and **94b** are prepared from compound **92** according to Example 1, step 5.

Scheme 14


OMPM
OH
45
DIAD, PPh3, CH2Cl2
HO
OMPM
95
DDQ
CH2Cl2, H2O
96
LiOH, THF
OH
97
1. ClCO2Et, Et3N, CH2Cl2
2. RCH2CH2OH
R
a R= OH
b R= N
O
98

Example 32

Step 1. Mitsunobu reaction of **45** and methyl 4-hydroxybenzoate to give **95**

[00205] Diisopropyl azodicarboxylate (DIAD, 194 µL, 1.0 mmol) was added to a solution of alcohol **45** (200 mg, 0.49 mmol), triphenylphosphine (191 mg, 0.73 mmol) and methyl 4-hydroxybenzoate (87 mg, 0.57 mmol) in CH_2Cl_2 (2.5 mL). After stirring 18 h at rt, the solvent was removed under a stream of nitrogen and the residue was suspended in EtOAc (75 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (3 x 25 mL) and brine (25 mL) then the organic phase was dried (Na_2SO_4) filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (50% EtOAc/hexane → EtOAc, gradient) afforded 81mg (31%) of the desired ether **95**.

Step 2. Oxidative deprotection of **95** to give **96**

[00206] DDQ (37 mg, 0.16 mmol) was added to a mixture of **95** (81 mg, 0.15 mmol) in CH_2Cl_2 (2.0 mL) and water (0.1 mL) at 0 °C under nitrogen. After 45 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The mixture was extracted with EtOAc (3 x 25 mL). The combined extracts were washed with brine (25 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (85% EtOAc/Hex → EtOAc, gradient) afforded 31 mg (49%) of the desired alcohol **96**.

Step 3. Saponification of **96** to give **97**

[00207] Aqueous 1 N lithium hydroxide (0.35 mL, 0.35 mmol) was added to a solution of ester **96** (30 mg, 0.071 mmol) in THF (0.7 mL). After 20 h at rt, water (2.0 mL) was added and the mixture was acidified with 1 N aqueous HCl (1.5 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (EtOAc → 10% MeOH/EtOAc, gradient) afforded 11.5 mg (38%) of starting ester **96** and 8.5 mg (29%) of compound **97**.

Step 4. Compounds **98a** and **98b**

[00208] Compounds **98a** and **98b** are prepared from compound **97** according to Example 1, step 5.

Preparation 1

1-(1-(4-Methoxybenzyloxy-hexyl)-4-bromobenzene

Step 1. Pentyl grignard addition to 4-bromobenzaldehyde

[00209] n-Pentyl magnesium bromide (2.0 M in THF, 27 mL, 54 mmol) was added to a solution of 4-bromobenzaldehyde (5.0 g, 27 mmol) in THF (20 mL) at 0 °C under nitrogen. After 1 h, the reaction was quenched with 3 N HCl and extracted with Et_2O (3 x 120 mL). Combined extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% EtOAc/Hex) afforded 5.1 g (74%) of 1-(4-bromophenyl)-hexan-1-ol.

Step 2. Protection of the alcohol as its MPM ether

[00210] Sodium hydride (60% wt. in oil, 0.95 g, 23.8 mmol) was added to a solution of the alcohol from step 1 (5.11 g, 19.9 mmol) in THF and DMF (2:1, 20 mL) at 0 °C under nitrogen. After 1 h at 0 °C, 4-methoxybenzyl chloride (3.23 mL, 23.8 mmol) and the reaction was allowed to warm to rt. The reaction was then heated at 80 °C. After 17 h, the reaction was allowed to cool to rt, quenched with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (2% EtOAc/Hex) afforded 7.02 g (94%) of the title compound.

Preparation 2

Isopropyl 5-chloromethylthiophene-2-carboxylate

Step 1. Preparation of the bis-isopropyl ester

[00211] DBU (31.3 mL, 209 mmol) and 2-iodopropane (20.9 mL, 209 mmol) were added to a solution of thiophene-2,5-dicarboxylic acid (6.0 g, 34.9 mmol) in acetone (60 mL) at rt under nitrogen. After 21 h at rt, the reaction was quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford 7.59g (85%) of the diester.

Step 2. Reduction to the hydroxymethyl ester

[00212] Sodium borohydride (3.36 g, 88.8 mmol) was added to a solution of the diester (7.59 g, 29.6 mmol) in CH_2Cl_2/MeOH (1:1, 100 mL) at 0 °C under nitrogen. The ice bath was removed and the reaction was allowed to stir at rt overnight. After 20.5 h at rt the reaction was concentrated in vacuo then aqueous 0.5 N HCl (100 mL) was

added. The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (5% → 60% EtOAc/Hex, gradient) afforded 738 mg (12%) of the alcohol.

Step 3. Conversion of the alcohol to the chloride

[00213] Methanesulfonyl chloride (0.67 mL, 8.1 mmol) and triethylamine (1.7 mL, 12.2 mmol) were added sequentially and dropwise to a solution of the alcohol (696 mg, 3.48 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C under nitrogen. The ice bath was removed and the reaction was allowed to stir overnight at rt. After 17 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica (5% EtOAc/Hex) afforded 664 mg (87%) of the title compound.

Preparation 3

Methyl 5-allylthiophene-2-carboxylate

Step 1. Preparation of the methyl ester

[00214] Acetyl chloride (6.9 mL, 96.6 mmol) was added to a solution of 5-bromo-2-thiophenecarboxylic acid (4.0 g, 19.3 mmol) in methanol (30 mL) at rt. After 17 h at rt, the reaction was heated at reflux for 1.5 h to drive it to completion. The reaction was then cooled to rt and concentrated in vacuo to remove methanol. Saturated aqueous NH_4Cl (120 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 3.57 g (84%) of the desired methyl ester as an off white solid.

Step 2. Allylation of the bromothiophene

[00215] Isopropyl magnesium chloride (2.0 M in Et_2O, 8.9 mL, 17.8 mmol) was added to a solution of the bromide from step 1 (3.56 g, 16.1 mmol) in THF (10 mL) at – 40 °C under nitrogen. The reaction mixture was stirred at – 40 °C for 1 h, then copper (I) cyanide (144 mg, 1.61 mmol) and allyl bromide (3.0 mL, 35.4 mmol) were added sequentially. The reaction mixture was stirred at – 40 °C for 1 h then was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on

silica gel (5% EtOAc/Hex) afforded 2.45 g (83%) of the title compound as a pale yellow oil that solidified on standing.

Preparation 4

1-(1-(4-Methoxybenzyloxy-heptyl)-4-bromobenzene

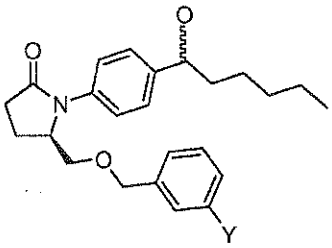
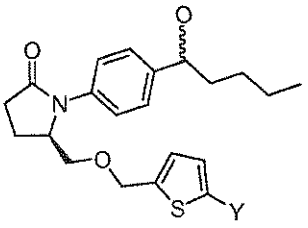
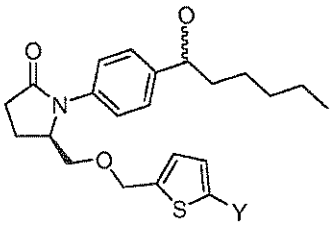
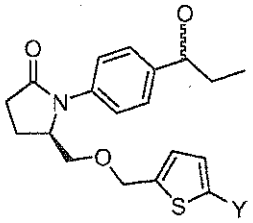
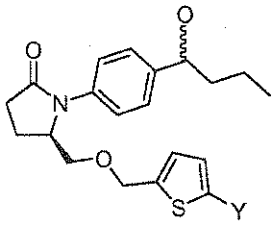
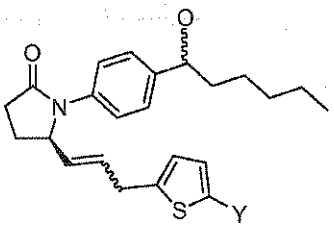
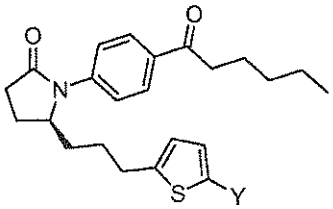
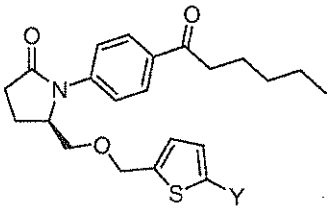
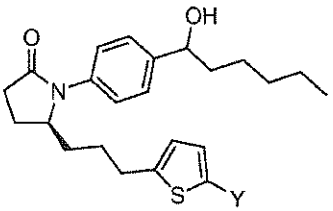
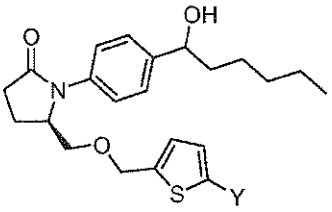
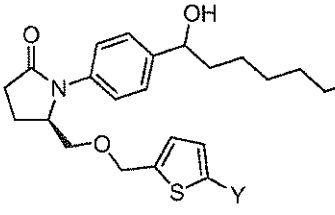
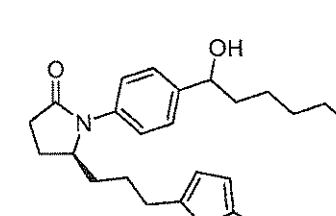
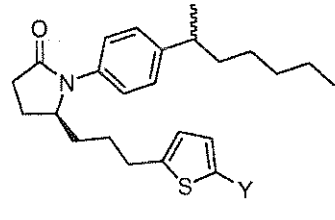
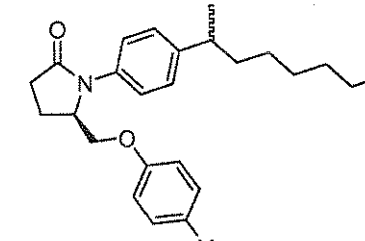
Step 1. Hexyl grignard addition to 4-bromobenzaldehyde

[00216] n-Hexyl magnesium bromide (2.0 M in Et_2O, 27 mL, 54 mmol) was added to a solution of 4-bromobenzaldehyde (5.0 g, 27 mmol) in THF (20 mL) at 0 °C under nitrogen. After 1.5 h at 0 °C, the reaction was quenched slowly with 3 N HCl (20 mL) and concentrated in vacuo. The residue was diluted with water (30 mL) and extracted with Et_2O (3 x 150 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% → 10% EtOAc/Hex) afforded 5.6 g (76%) of 1-(4-bromophenyl)-heptan-1-ol.

Step 2. Protection of the alcohol as its MPM ether

[00217] Sodium hydride (60% wt. in oil, 0.991 g, 24.8 mmol) was added to a solution of the alcohol from step 1 (5.6 g, 20.6 mmol) in THF and DMF (2:1, 30 mL) at 0 °C under nitrogen. After 5 min at 0 °C, the reaction was allowed to warm to rt and 4-methoxybenzyl chloride (3.4 mL, 25.0 mmol) was added.. The reaction was then heated at 80 °C. After 18 h at 80 °C, the reaction was allowed to cool to rt, quenched with saturated aqueous NH_4Cl (50 mL) and concentrated in vacuo. The remainder was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water (2 x 100 mL) and brine (75 mL), then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (2% EtOAc/Hex) afforded 7.5 g (93%) of the title compound.

[00218] Exemplary, non-limiting examples of compounds useful according to the present disclosure include the following compounds.

Composition Example:

[00219] A composition comprising a compound listed above, wherein said composition is a liquid which is ophthalmically acceptable.

Medicament Examples:

[00220] Use of a compound listed above in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal.

[00221] Use of a compound listed above in the manufacture of a medicament for the treatment of baldness in a mammal.

[00222] A medicament comprising a compound listed above, wherein said composition is a liquid which is ophthalmically acceptable.

Method Example:

[00223] A method comprising administering a compound listed above to a mammal for the treatment of glaucoma or ocular hypertension.

[00224] A method comprising administering a compound listed above to a mammal for the treatment of baldness.

Kit Example:

[00225] A kit comprising a composition comprising a compound listed above, a container, and instructions for administration of said composition to a mammal for the treatment of glaucoma or ocular hypertension.

[00226] A kit comprising a composition comprising a compound listed above, a container, and instructions for administration of said composition to a mammal for the treatment of baldness.

[00227] A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

[00228] Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions lithium, sodium, potassium, calcium,

and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

[00229] A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted. Ester prodrugs of the compounds disclosed herein are specifically contemplated. An ester may be derived from a carboxylic acid of C1 (i.e. the terminal carboxylic acid of a natural prostaglandin), or an ester may be derived from a carboxylic acid functional group on another part of the molecule, such as on a phenyl ring. While not intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. C_{1-6} alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

[00230] Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

[00231] For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the

gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

[00232] Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

[00233] The amount of the presently useful compound or compounds administered is dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds may be in the range of about 0.5 or about 1 to about 100 mg/kg/day.

[00234] A liquid which is ophthalmically acceptable is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[00235] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[00236] Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[00237] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[00238] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[00239] In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[00240] Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[00241] The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

Applications for Stimulating Hair Growth

[00242] In one embodiment, the compounds disclosed herein can be useful in the treatment of baldness and/or hair loss. Alopecia (baldness) is a deficiency of either normal or abnormal hair, and is primarily a cosmetic problem in humans. It is a deficiency of terminal hair, the broad diameter, colored hair that is readily seen. However, in the so called bald person, although there is a noticeable absence of terminal hair, the skin does contain vellus hair, which is a fine colorless hair which may require microscopic examination to determine its presence. This vellus hair is a precursor to terminal hair.

[00243] The compounds described herein can be used to stimulate, such as the conversion of vellus hair to growth as terminal hair, as well as increasing the rate of growth of terminal hair. The utility of the compounds described herein for the simulation of hair growth was discovered as follows.

[00244] In the course of treating patients having glaucoma, treatment may only be appropriate in one eye. Within the course of daily practice, it was discovered that a patient who had been treated with bimatoprost, a prostaglandin analogue, developed

lashed that were longer, thicker, and fuller in the treated eye than in the non-treated eye. On examination, the difference was found to be very striking. The lashes were longer and had a fuller, denser appearance in the treated eye. The lash appearance on the lids of the treated eyes would have appeared quite attractive if it represented a bilateral phenomenon. As a result of its asymmetric nature, the long lashes on one side could be construed as disturbing from a cosmetic standpoint. A systemic examination was preformed as a result of the asymmetric phenomenon. It soon became apparent that this altered appearance was not an isolated finding. Comparison of the lids of patients who were taking bimatoprost in only one eye revealed subtle changes in the lashed and adjacent hairs of the bimatoprost-treated side in several patients. Definite differences could be identified to varying degrees in the lashes and adjacent hairs of all patients who were taking the drug on a unilateral basis for longer than 6 months.

[00245] The changes in the lashes were apparent on gross inspection in several patients once attention was focused on the issue. In those with light colored hair and lashes, the differences were only seen easily with the aid of the high magnification and lighting capabilities of the slit lamp biomicroscope. In the course of glaucoma follow-up examination, attention is generally immediately focused on the eye itself. As a result of the high power magnification needed only one eye is seen at a time and the eye is seen at a high enough power that the lashes are not in focus. At these higher powers, any lash asymmetry between the two eyes is not likely to be noticed except by careful systematic comparison of the lashes and adjacent hairs of the eyelids of the two eyes.

[00246] Observed parameters leading to the conclusion that more robust hair growth occurred in the treatment area following administration of the prostaglandin analogue were multiple. They included increased length of lashed, increased number of lashes along the normal lash line, increased thickness and luster of lashes, increased auxiliary lash-like terminal hair in transitional areas adjacent to areas of normal lash growth, increased auxiliary lash-like terminal hairs at the medial and lateral canthal area, increased pigmentation of the lashes, increased numbers, increased length, as well as increased luster, and thickness of fine hair on the skin of the adjacent lid, and finally, increased perpendicular angulation of lashes and lash-like terminal hairs. The conclusion that hair growth is stimulated by prostaglandin analogues such as bimatoprost is thus supported not by evidence of a difference in a single parameter, but

is based on multiple parameters of hair appearance in treated versus control areas in many subjects.

[00247] The compounds described herein are prostaglandin analogues and therefore have similar activities as bimatoprost, contain structural similarities, and therefore are expected to stimulate hair growth and stimulation of the conversion of vellus hair to terminal hair. In one embodiment, the compounds described herein and their prodrugs can be used for the stimulation of hair growth. As used herein, hair growth includes hair associated with the scalp, eyebrows, eyelids, beard, and other areas of the skin of animals.

[00248] In one embodiment, the compound is mixed with a dermatologically compatible vehicle or carrier. The vehicle, which may be employed for preparing compositions as described herein, may comprise, for example, aqueous solutions such as e.g., physiological salines, oil solutions, or ointments. The vehicle furthermore may contain dermatologically compatible preservatives such as e.g., benzalkonium chloride, surfactants like e.g., polysorbate 80, liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

[00249] In one embodiment, dermatological compositions can be formulated for topical treatment for the stimulation of hair growth which comprises an effective hair growth simulating amount of one or more compounds as defined above and a dermatologically compatible carrier. Effective amounts of the active compounds may be determined by one of ordinary skill in the art, but will vary depending on the compound employed, frequency of application and desired result. The compound will generally range from about 0.0000001 to about 50% by weight of the dermatological composition. Preferably, the compound will range from about 0.001 to about 50% by weight of total dermatological composition, more preferably from about 0.1 to about 30% by weight of the composition.

[00250] In one embodiment, the application of the present compounds for stimulation of hair growth finds applications in mammalian species, including both humans and animals. In humans, the compounds described herein can be applied for example, to the scalp, face beard, head, pubic area, upper lip, eyebrows, and eyelids.

In animal raised for their pelts, e.g., mink, the compounds described herein can be applied over the entire surface of the body to improve the overall pelt for commercial reasons. The process can also be used for cosmetic reasons in animals, e.g., applied to the skin of dogs and cats having bald patches due to mange or other diseases causing a degree of alopecia.

[00251] The pharmaceutical compositions contemplated for the stimulation of hair growth include pharmaceutical compositions suited for topical and local action. The term "topical" as employed herein relates to the use of a compound, as described herein, incorporated in a suitable pharmaceutical carrier, and applied at the site of thinning hair or baldness for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contact with the skin to be treated. Conventional pharmaceutical forms for this purpose include ointments, liniments, creams, shampoos, lotions, pastes, jellies, sprays, aerosols, and the like, and may be applied in patches or impregnated dressings depending on the part of the body to be treated. The term "ointment" embraces formulations (including creams) having oleaginous, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

[00252] Typically, the compounds can be applied repeatedly for the sustained period of time topically on the part of the body to be treated, for example, the eyelids, eyebrows, skin or scalp. The preferred dosage regimen will generally involve regular, such as daily, administration for a period of treatment of at least one month, more preferably at least three months, and most preferably, at least six months.

[00253] For topical use on the eyelids or eyebrows, the active compounds can be formulated in aqueous solutions, creams, ointments, or oils exhibiting physologicla acceptable osmolarity by addition of pharmaceutically acceptable buffers and salts. such formulations may or may not, depending on the dispenser, contain preservatives such as benzalkonium chloride, chlorhexidine, chlorobutanol, parahydroxybenzoic acids and phenylmercuric salts such as nitrate, chloride, acetate, and borate, or antioxidants, as well as additives like EDTA, sorbitol, boric acid and the like as additives. Furthermore, particularly aqueous solutions may contain viscosity increasing agents such as polysaccharides, e.g., methylcellulose, mucopolysaccharides, e.g., hyaluronic acid and chondroitin sulfate, or poly alcohol, e.g., polyvinylalcohol. Various slow

releasing gels and matricies may also be employed as well as soluble and insoluble ocular inserts, for instance, based on substances forming *in situ* gels. Depending on the actual formation and compound to be used, various amounts of the drug and different dose regimens may be employed. Typically, the daily amount of compound for treatment of the eyelid may be about 0.1 ng to about 100 mg per eyelid.

[00254] For topical use on the skin and scalp, the compound can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matricies for the slow release delivery may also be used. Typically, the dose to be applied on the scalp is in the range of about 0.1 ng to about 100 mg per day, more preferably about 1 ng to about 10 mg per day, and most preferably about 10 ng to about 1 mg per day depending on the compound and the formulation. To achieve the daily amount of medication depending on the formulation, the compound may be administered once or several times daily with or without antioxidants.

[00255] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

[00256] The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

[00257] The compounds disclosed herein are also useful in combination with other drugs useful for the treatment of glaucoma or other conditions.

[00258] For the treatment of glaucoma, combination treatment with the following classes of drugs are contemplated:

β-Blockers (or β-adrenergic antagonists) including carteolol, levobunolol, metiparanolol, timolol hemihydrate, timolol maleate, β1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;
Adrenergic Agonists including

non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α_2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including

direct acting cholinergic agonists such as carbachol, pilocarpine hydrochloride, pilocarbine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

chlolinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Glutamate Antagonists and other neuroprotective agents such as Ca^{2+} channel blockers such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil, emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil, ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedimpine, nimodipine, barnidipine, verapamil, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, isopropyl unoprostone, latanoprost and the like.

Cannabinoids including CB1 agonists such as WIN-55212-2 and CP-55940 and the like, or pharmaceutically acceptable salts or prodrugs thereof.

[00259] For treatment of diseases affecting the eye including glaucoma, these compounds can be administered topically, periocularly, intraocularly, or by any other effective means known in the art.

[00260] In addition to the treatment of glaucoma, prostaglandin EP_2 selective agonists are believed to have several medical uses. For example, U.S. Patent No.

6,437,146 teaches the use of prostaglandin EP_2 selective agonists "for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus crythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc.), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel disease, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodonritis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid carcinoma, mesangial proliferative glomerulonephritis, edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like."

[00261] United State Patent No 6,710,072 teaches the use of EP2 agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation...various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris."

[00262] These compounds can also be used to treat or prevent conditions affecting the posterior part of the eye including maculopathies/ retinal degeneration such as non-exudative age related macular degeneration (ARMD), exudative age related macular degeneration (ARMD), choroidal neovascularization, diabetic retinopathy, acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; uveitis/ retinitis/ choroiditis such as acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome; vasuclar diseases/ exudative diseases such as retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes such as

retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigement epitheliitis. Preferably, the disease or condition is retinitis pigmentosa, proliferative vitreal retinopathy (PVR), age-related macular degeneration (ARMD), diabetic retinopathy, diabetic macular edema, retinal detachment, retinal tear, uveitus, or cytomegalovirus retinitis.

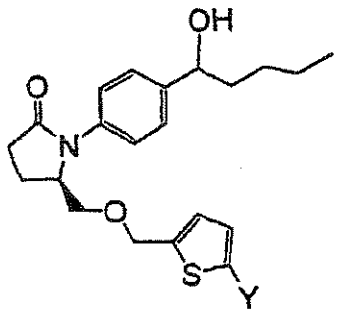
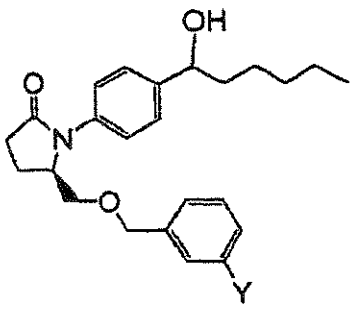
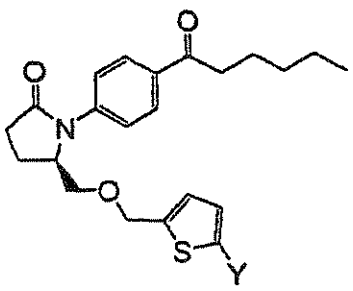
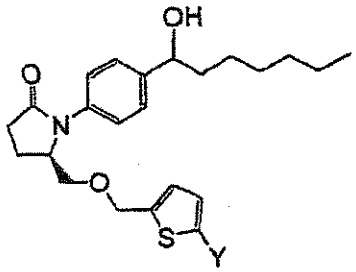
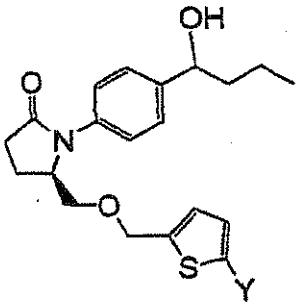
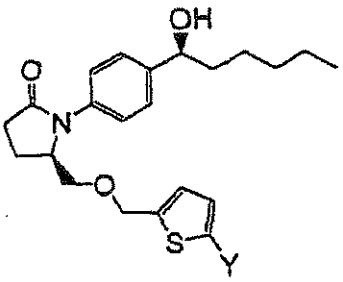
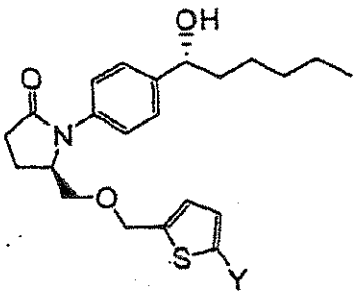
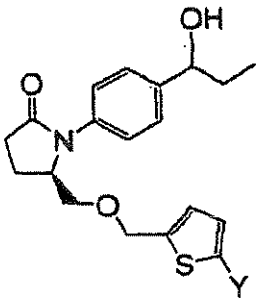
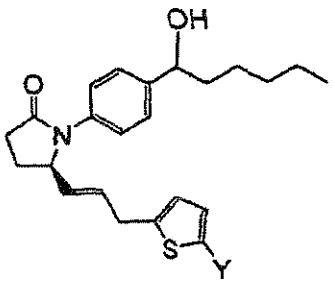
[00263] These compounds are also useful in treating asthma.

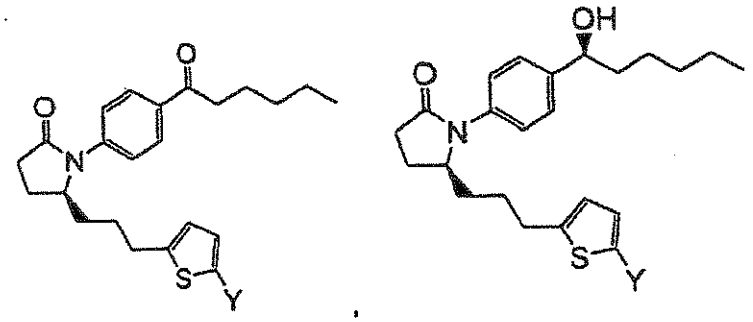
[00264] A person of ordinary skill in the art understands the meaning of the stereochemistry associated with the hatched wedge/solid wedge structural features. For example, an introductory organic chemistry textbook (Francis A. Carey, Organic Chemistry, New York: McGraw-Hill Book Company 1987, p. 63) states "a wedge indicates a bond coming from the plane of the paper toward the viewer" and the hatched wedge, indicated as a "dashed line", "represents a bond receding from the viewer." Unless stereochemistry is explicitly depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture. Unless stereochemistry is explicitly depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture.

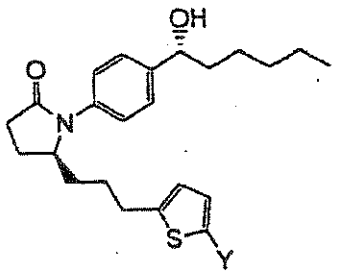
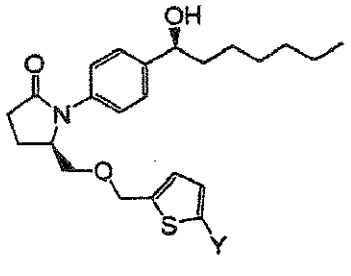
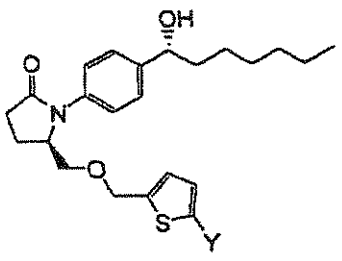
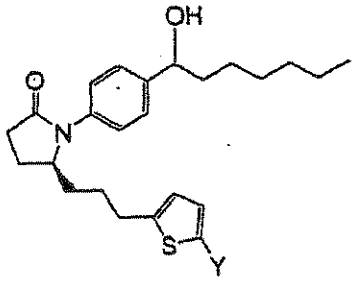
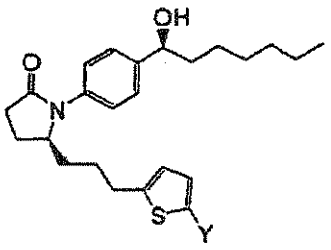
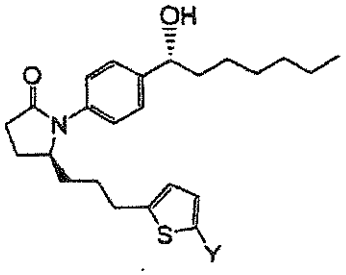
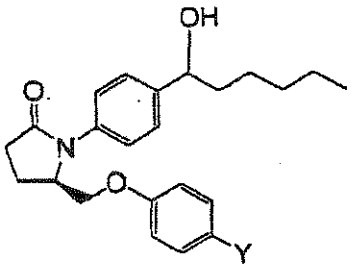
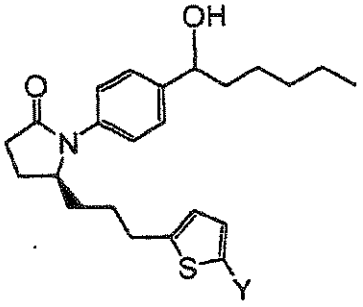
[00265] The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

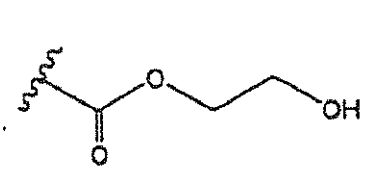
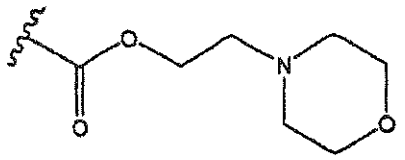
1. A compound represented by one of the following formulae or a pharmaceutically-acceptable salt thereof:

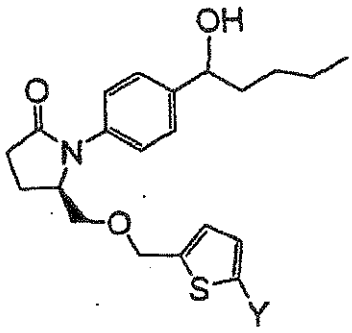
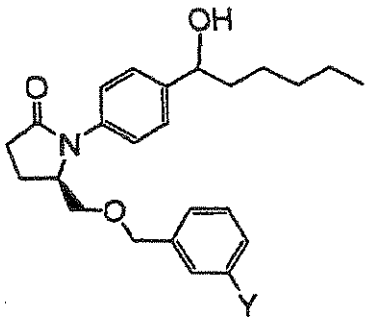
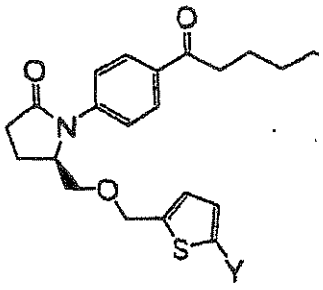


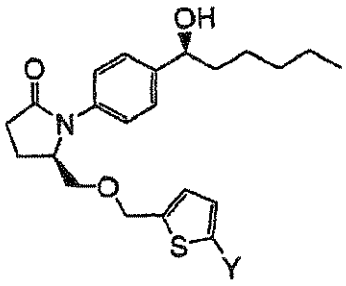
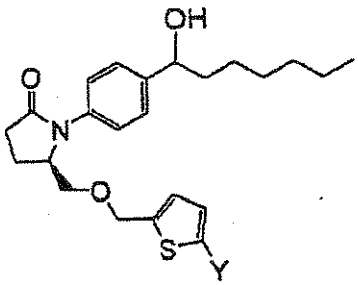
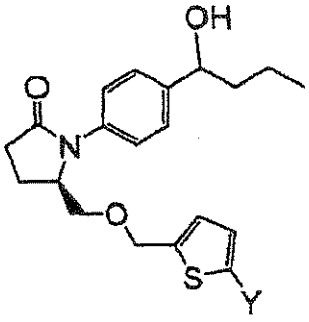
wherein Y is


or


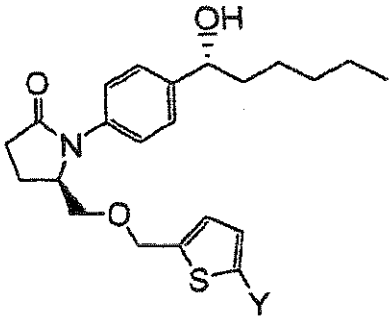
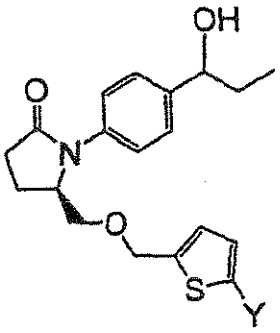
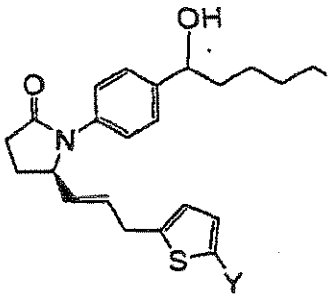
2. A compound according to Claim 1, which is represented by one of the following formulae or is a pharmaceutically-acceptable salt thereof:

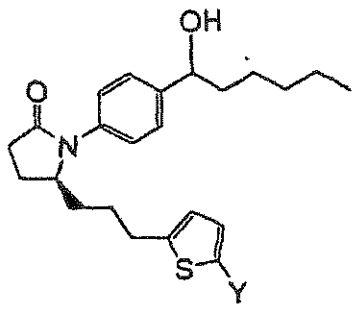
3. A compound according to Claim 1, which is represented by one of the following formulae or is a pharmaceutically-acceptable salt thereof:

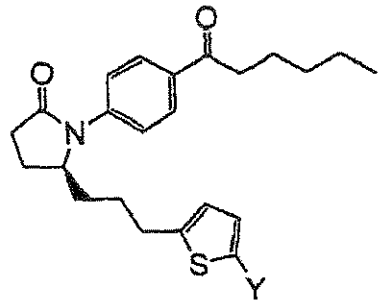
4. A compound according to Claim 1, which is represented by one of the following formulae or is a pharmaceutically-acceptable salt thereof:

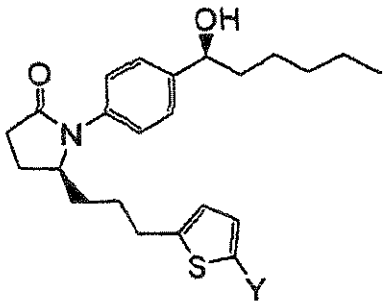
5. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



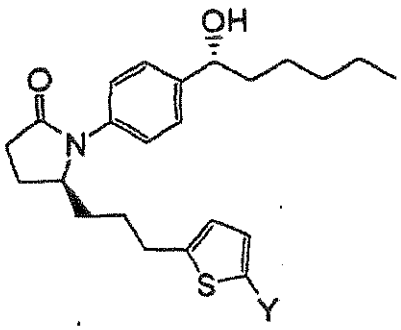
6. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



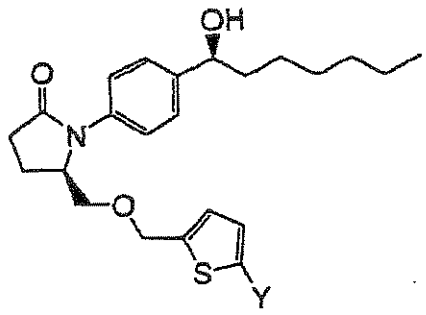
7. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



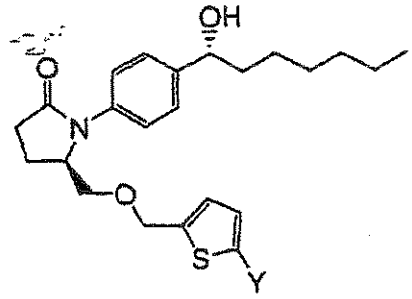
8. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



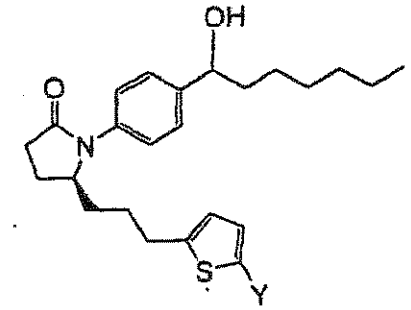
9. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



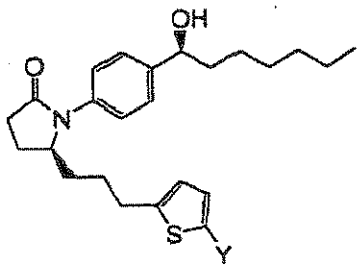
10. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



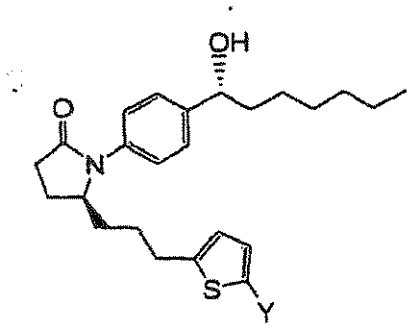
11. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



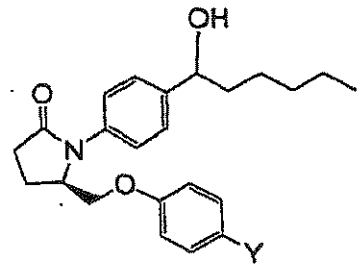
12. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



13. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



14. A compound according to Claim 1, which is represented by the following formula or is a pharmaceutically-acceptable salt thereof:



15. A compound according to Claim 1 for use in treating baldness.