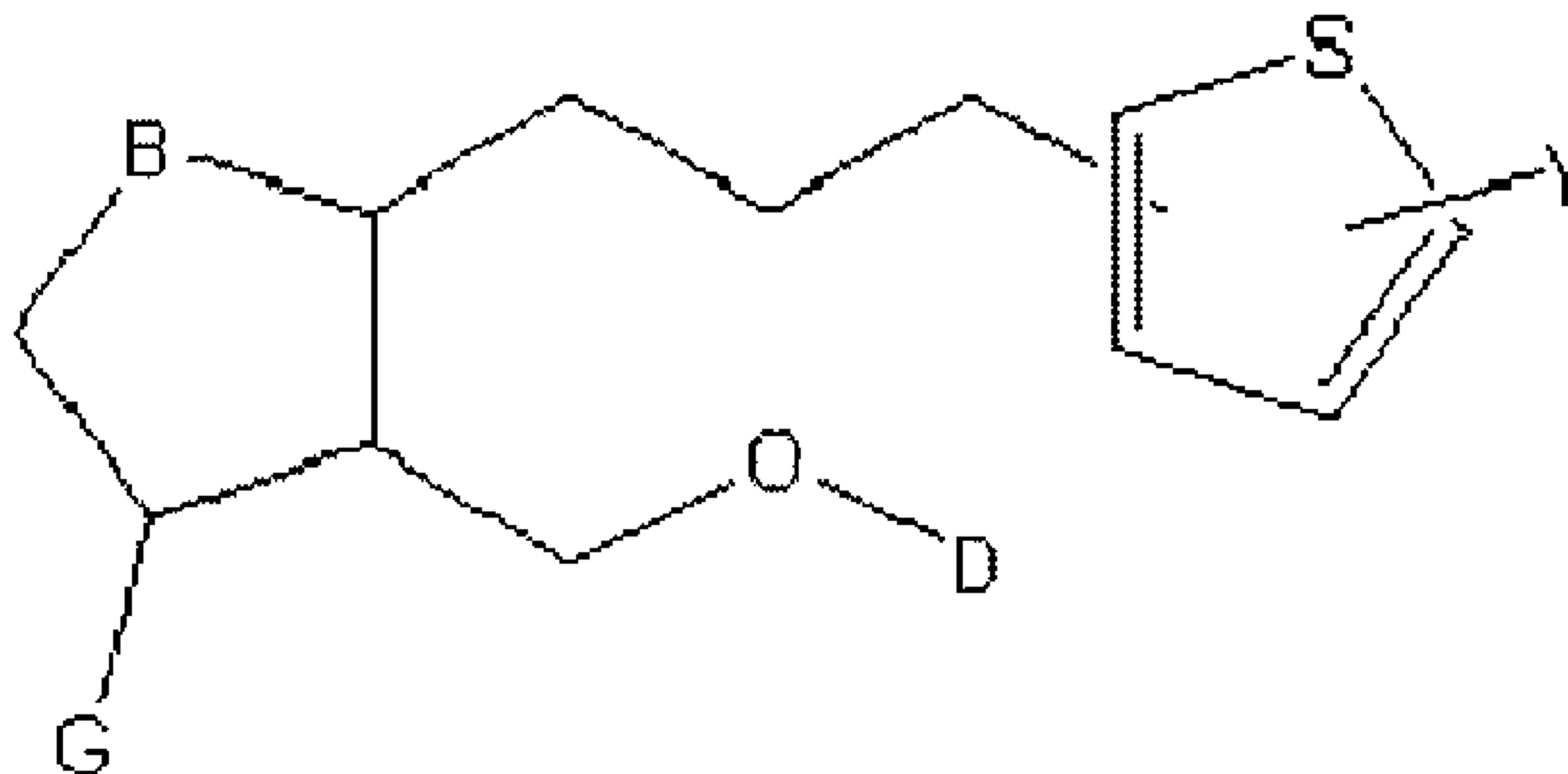




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(72) **Inventeurs/Inventors:**
OLD, DAVID W., US;
NGO, VINH X., US
(73) **Propriétaire/Owner:**
ALLERGAN, INC., US
(74) **Agent:** GOWLING WLG (CANADA) LLP

(54) **Titre : DERIVES DU THIOPHENE UTILES EN TANT QU'AGENTS HYPOTENSIFS OCULAIRES**
(54) **Title: THIOPHENE DERIVATIVES USEFUL AS OCULAR HYPOTENSIVE AGENTS**



(I)

(57) **Abrégé/Abstract:**

Compounds comprising (formula I), or a pharmaceutically acceptable salt or a prodrug thereof, are disclosed, wherein G, B, D, and Y are as described. Methods, compositions, and medicaments related thereto are also disclosed.



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(71) **Applicant** (for all designated States except US): **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, T2-7H, Irvine, CA 92612 (US).

(72) Inventors; and

(75) **Inventors/Applicants** (for US only): **OLD, David, W.** [US/US]; 13771 Typee Way, Irvine, CA 92620 (US).
NGO, Vinh, X. [US/US]; 20701 Aquatic Lane, Huntington Beach, CA 92646 (US).

(74) **Agents**: **FORRESTAL, Kevin** et al.; Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).

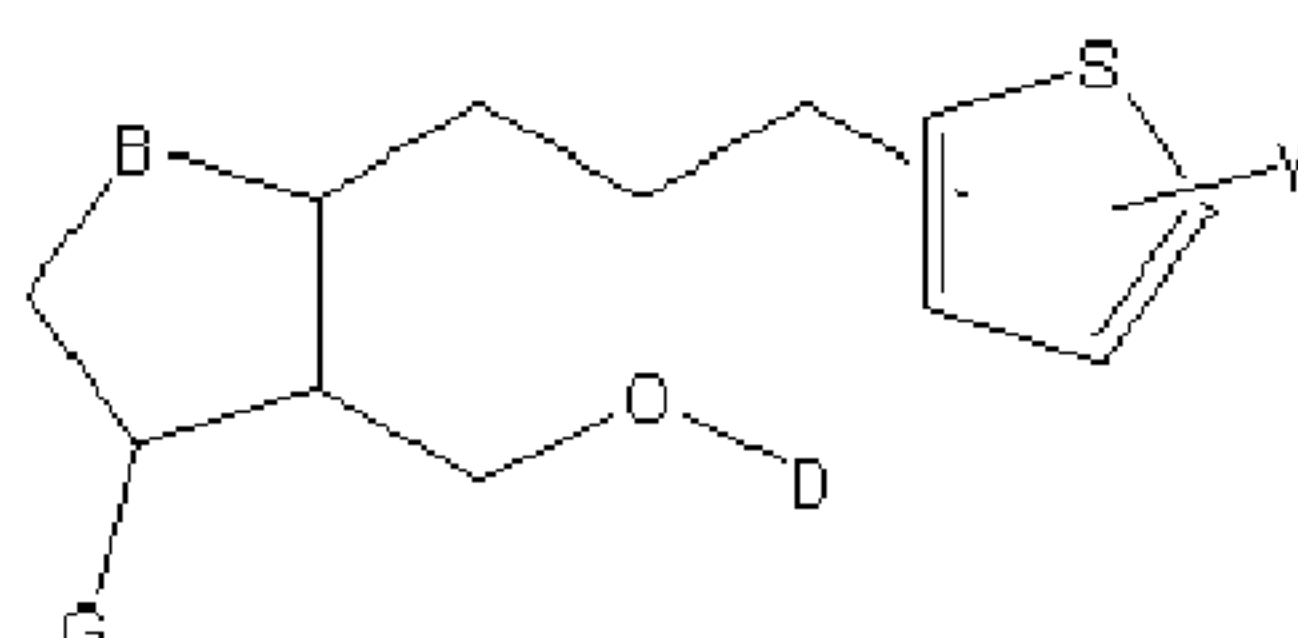
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(I)

(57) **Abstract**: Compounds comprising (formula I), or a pharmaceutically acceptable salt or a prodrug thereof, are disclosed, wherein G, B, D, and Y are as described. Methods, compositions, and medicaments related thereto are also disclosed.

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THIOPHENE DERIVATIVES USEFUL AS OCULAR HYPOTENSIVE AGENTS

By Inventors David W. Old and Vinh X. Ngo

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.

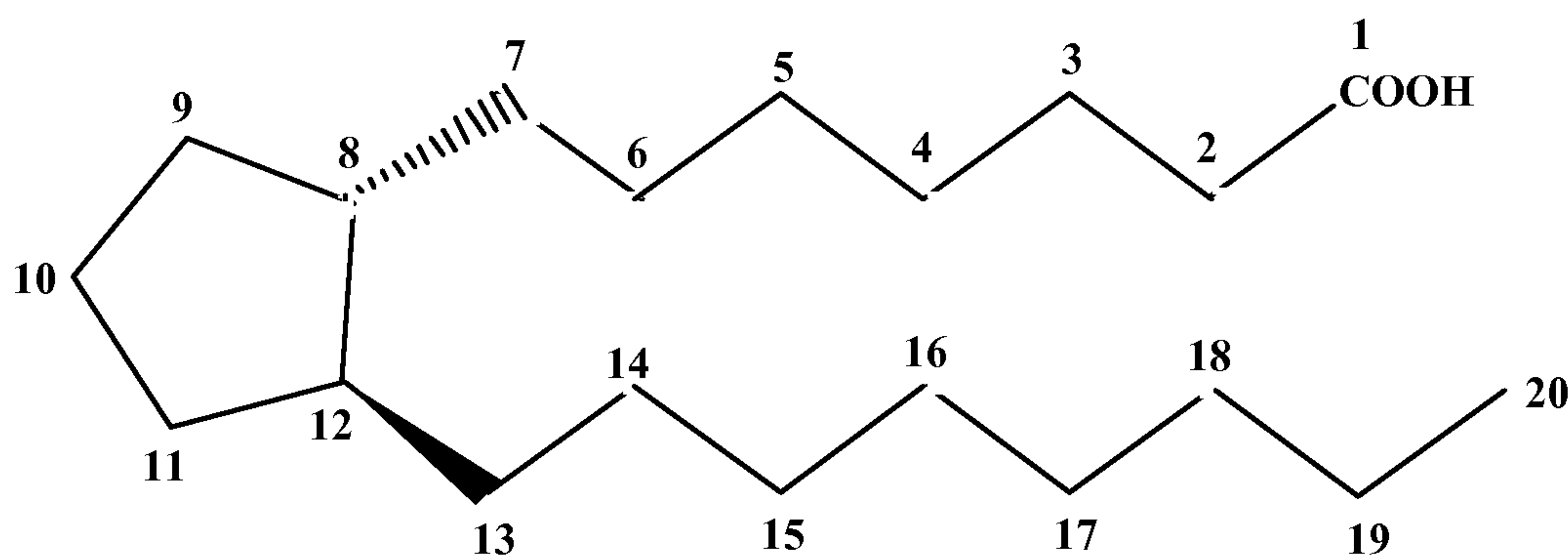
[0004] The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute 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 pupillary 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 E₁ (PGE₁), prostaglandin E₂ (PGE₂)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin F₂ α (PGF₂ β)].

[0009] Prostaglandin EP₂ selective agonists are believed to have several medical uses. For example, U.S. Patent No. 6,437,146 teaches the use of prostaglandin EP₂ 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 erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neuropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's 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, periodontitis, 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."

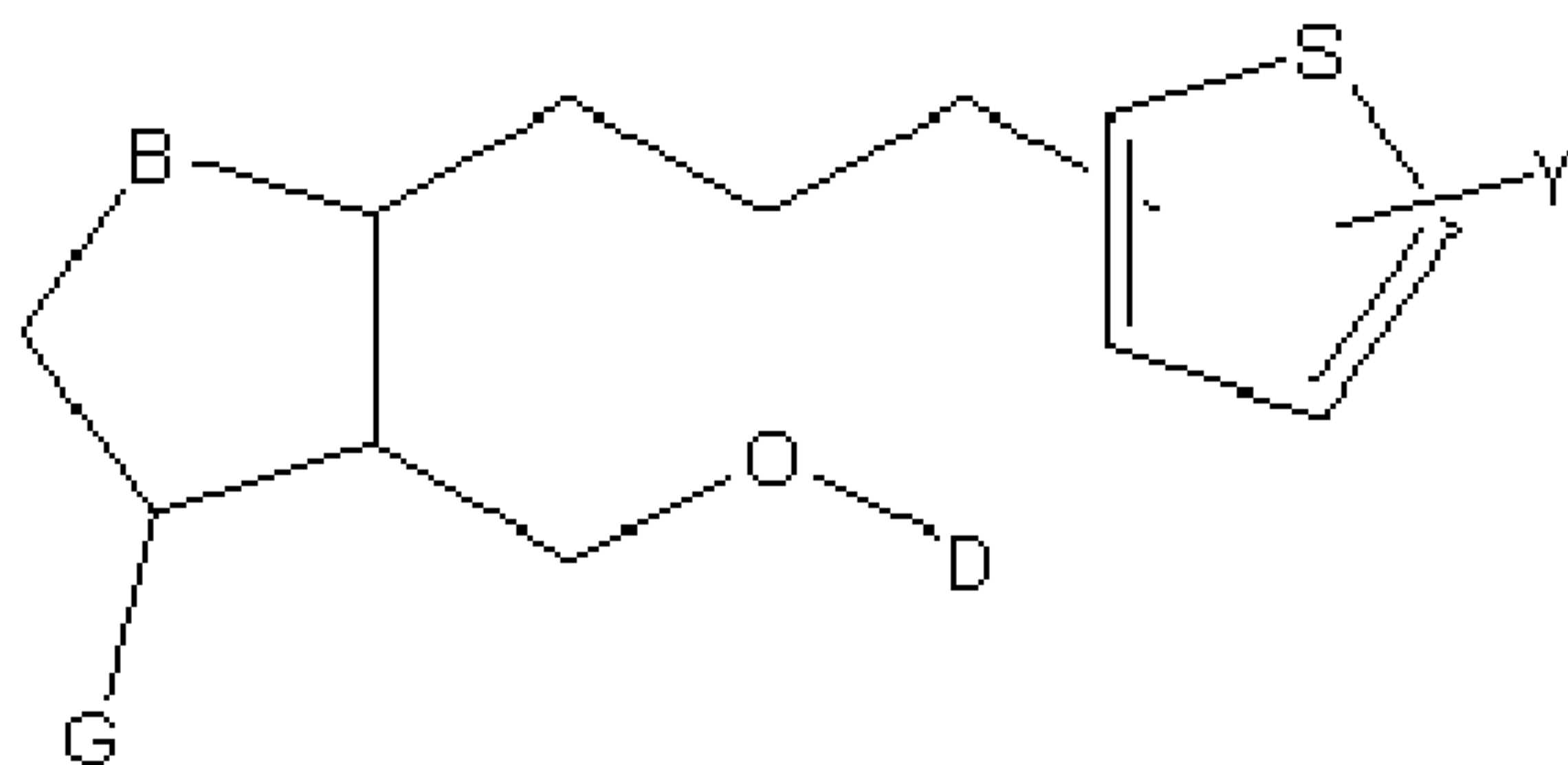
[0010] United State Patent No 6,710,072 teaches the use of EP2 agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation...various pathophysiological diseases including acute myocardial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

SUMMARY OF THE INVENTION

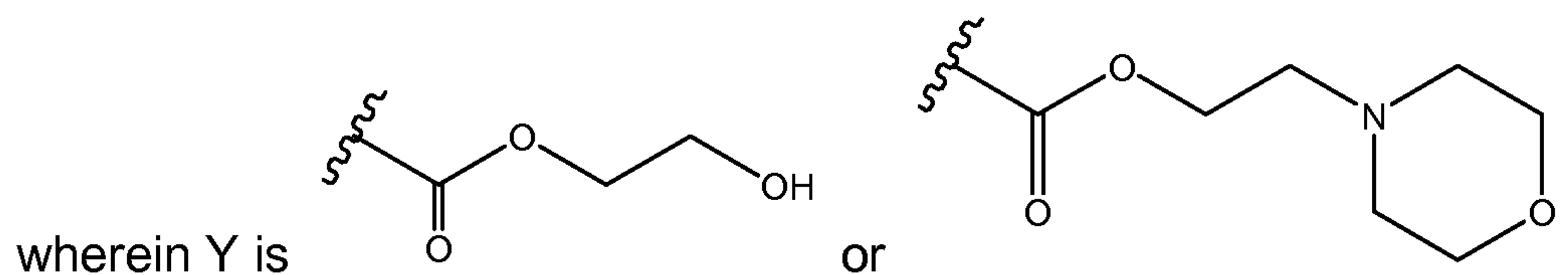
[0011] Disclosed herein are compounds useful in treating glaucoma, inflammatory bowel disease, the stimulation of hair growth, and the stimulation of the conversion of vellus hair to terminal hair. The compounds themselves are disclosed below.

DESCRIPTION OF THE INVENTION

[0012] Disclosed herein is a compound of the formula



or a pharmaceutically acceptable salt or a prodrug thereof;

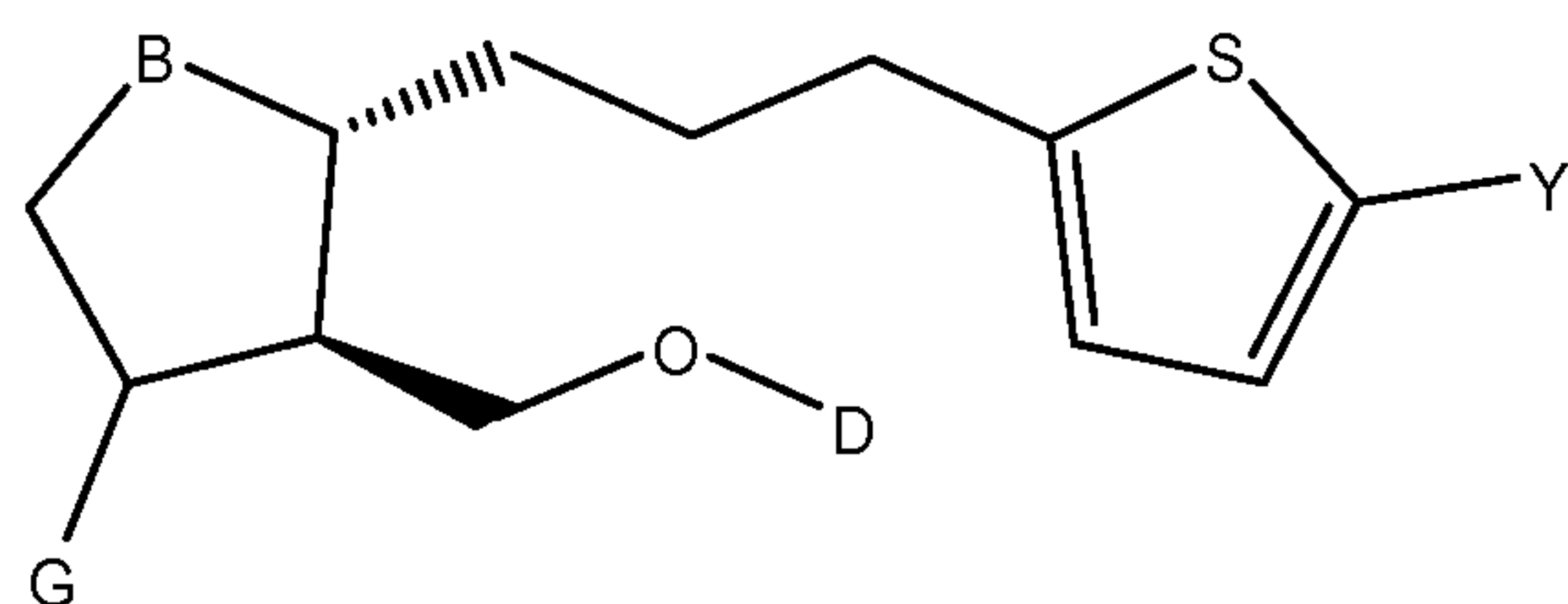
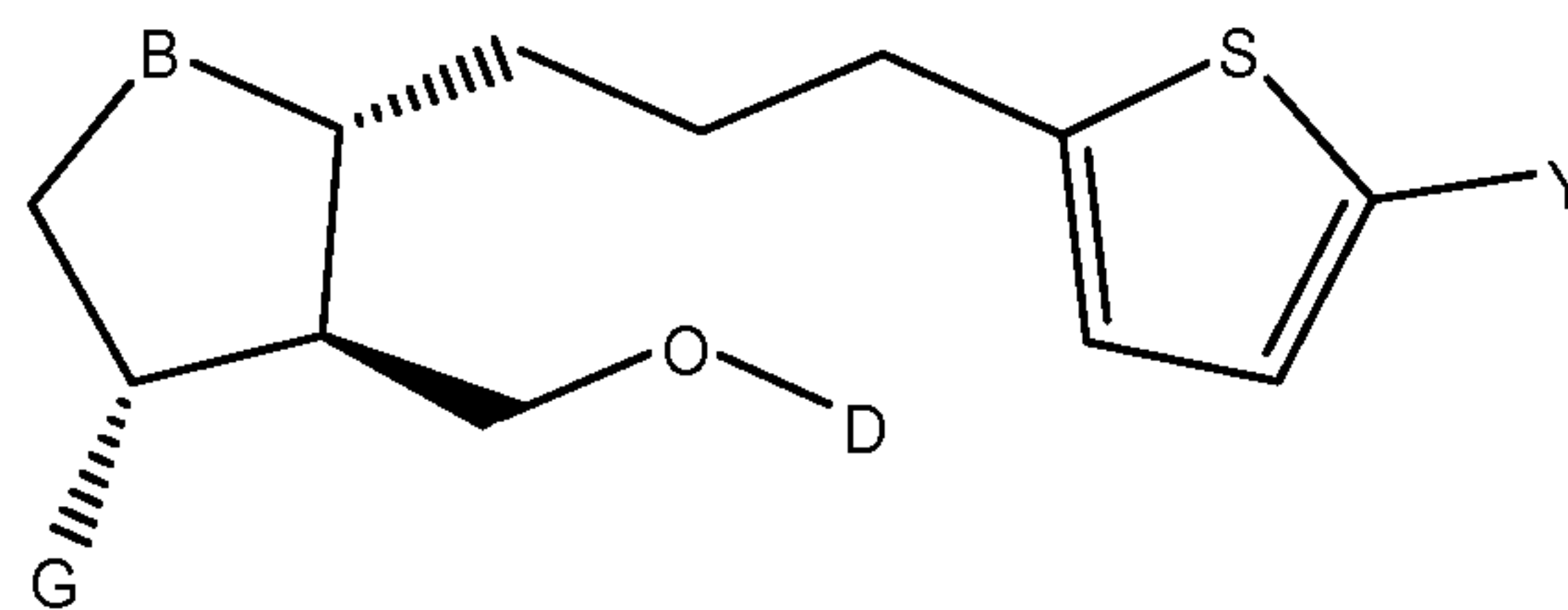


B is C=O, CH₂, CHOH, CHCl, CHF, CHBr, or CHCN;

G is OH or H; and

D is substituted phenyl.

[0013] These compounds have several chiral centers. While all stereoisomers are contemplated herein, those shown below are believed to be particularly useful.



[0014] As used herein, substituted phenyl refers to phenyl having one or more substituents. The substituents of phenyl have from 0 to 6 carbon atoms, from 0 to 3 atoms independently selected from O, S, N, F, Cl, Br, or I, and from 0 to 15 hydrogen atoms. If a substituent is a salt, such as a carboxylic acid, and it is associated with a counterion, the counterion is not counted as an atom of the substituent. For example, CO₂⁻Na⁺ is treated as having 1 carbon and 2 oxygen atoms. Substituents must be sufficiently stable to be stored in a bottle at room temperature under a normal atmosphere for at least 12 hours, or stable enough to be useful for any purpose disclosed herein. Examples of substituents include, but are not limited to:

hydrocarbyl, including alkyl, alkenyl, alkynyl, which are linear, branched, or cyclic, such as methyl, ethyl, propyl isomers, butyl isomers, and the like;

hydrocarbyloxy, including alkoxy, alkenoxy, alkynoxy; such as -OCH₃, OEthyl, O-*i*Propyl; and the like;

acyl, i.e.



acyloxy, i.e. -O-acyl, including formate, acetate, propanoate, and the like;

amino, i.e. NH_2 , $\text{NH}(\text{hydrocarbyl})$, or $\text{N}(\text{hydrocarbyl})_2$;

hydroxylalkyl, meaning alkyl having one or more hydroxyl groups, such as CH_2OH , $\text{CH}_2\text{CH}_2\text{OH}$, and the like;

CF_3 ;

F;

Cl;

Br;

I;

CN;

NO_2 ;

SO_3H , and/or

OH.

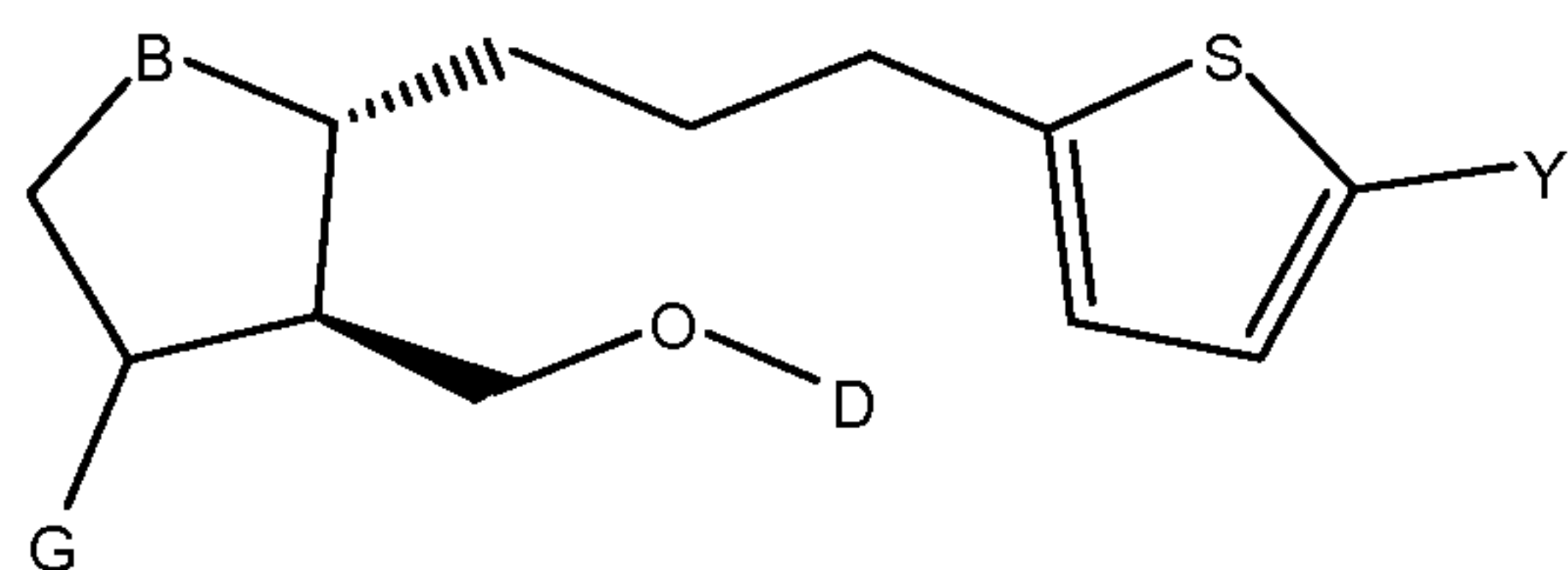
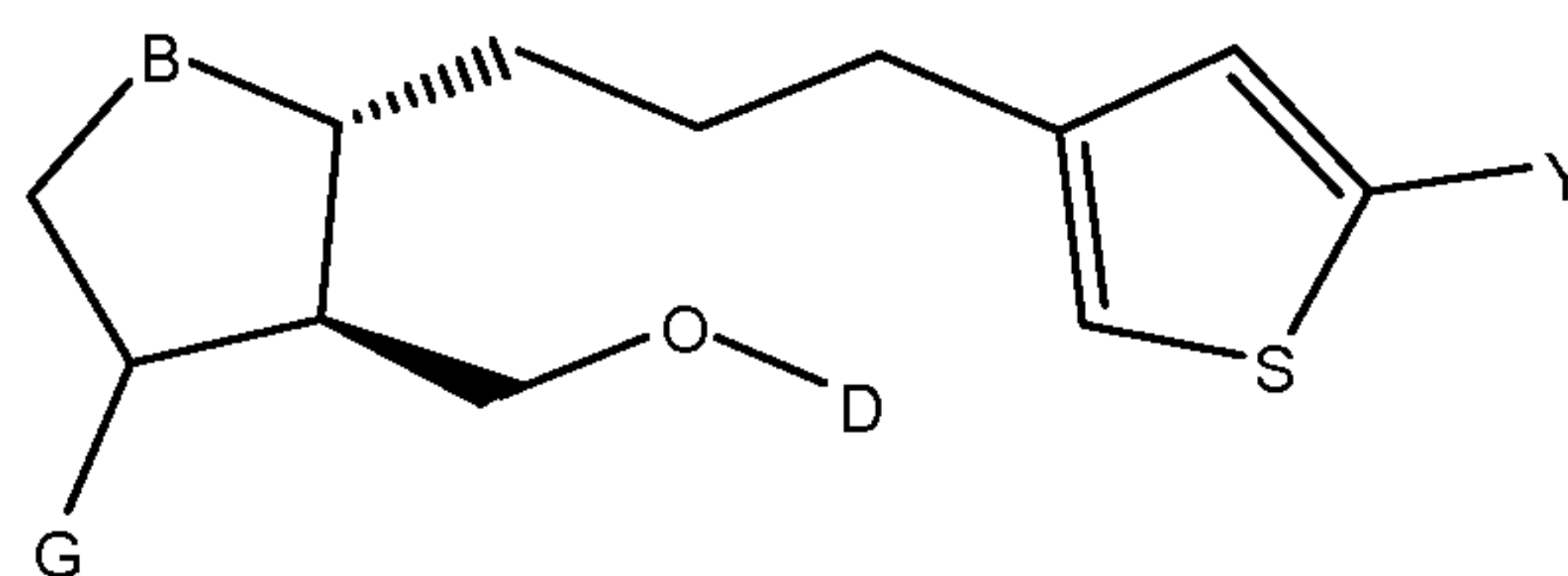
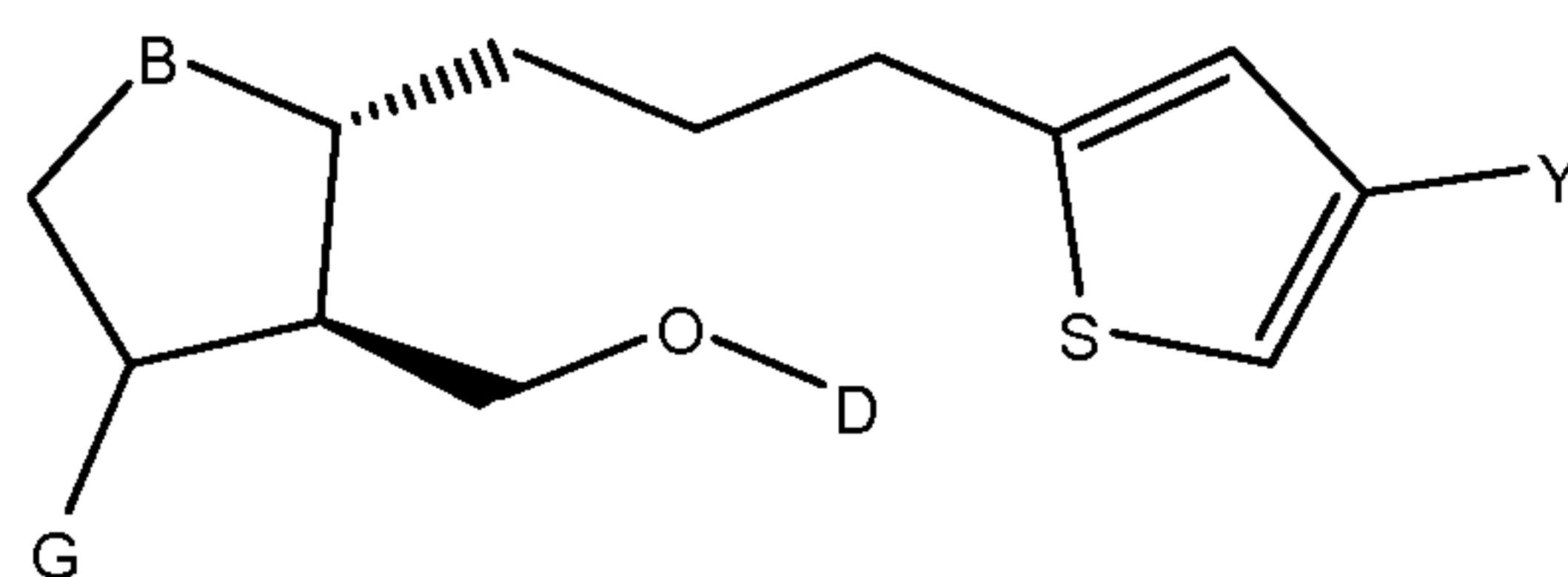
[0015] Substituents on phenyl may be the same or different.

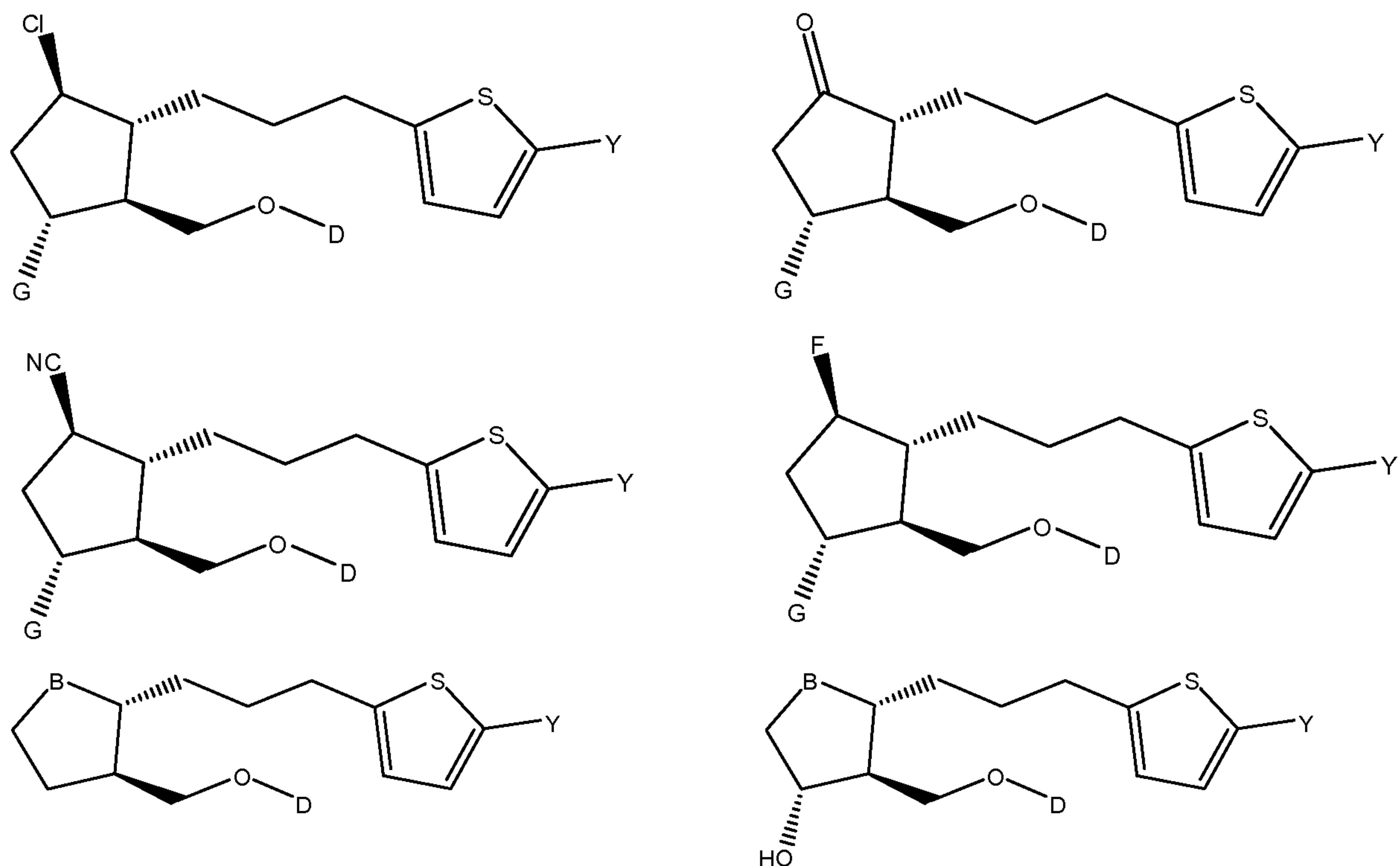
[0016] In one embodiment, phenyl has 1, 2, or 3 substituents.

[0017] In another embodiment, at least one substituent is C_{1-3} alkyl, Cl, or F.

[0018] In another embodiment, all substituents are C_{1-3} alkyl, Cl, F, or hydroxyalkyl.

[0019] Compounds of the following structures are specifically contemplated as individual embodiments.





[0020] These compounds are useful for treating glaucoma and elevated intraocular pressure.

[0021] For the purposes of this disclosure, “treat,” “treating,” or “treatment” refer to the use of a compound, composition, therapeutically active agent, or drug in the diagnosis, cure, mitigation, treatment, prevention of disease or other undesirable condition.

Applications for Stimulating Hair Growth

[0022] 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.

[0023] 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 stimulation of hair growth was discovered as follows.

[0024] 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 lashes 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 performed 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 lashes 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.

[0025] 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.

[0026] 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 lashes, 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.

[0027] 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.

[0028] 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.

[0029] In one embodiment, dermatological compositions can be formulated for topical treatment for the stimulation of hair growth which comprises an effective hair growth stimulating 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.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] For topical use on the eyelids or eyebrows, the active compounds can be formulated in aqueous solutions, creams, ointments, or oils exhibiting physiologicla 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 matrices 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.

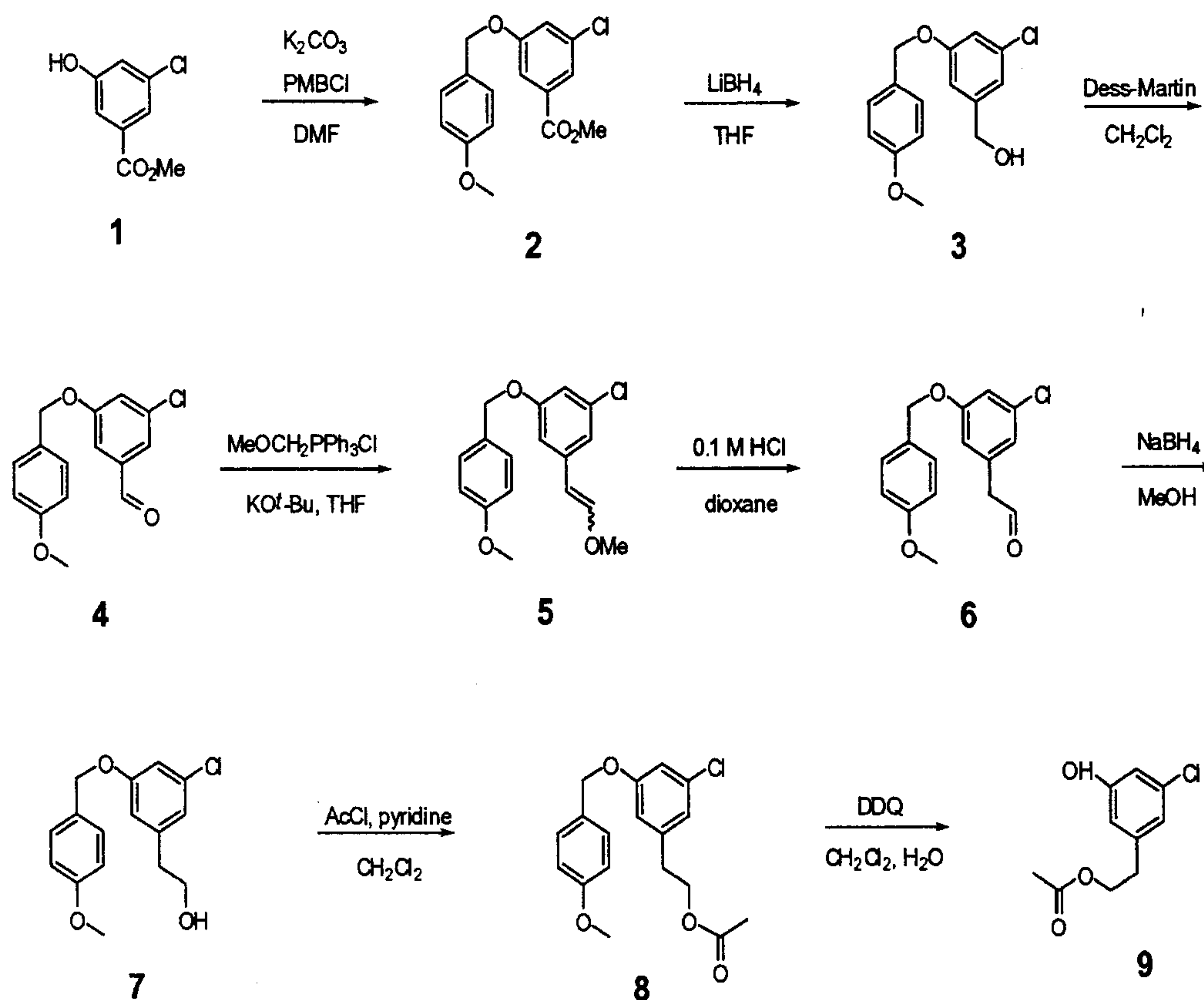
[0034] For topical use on the skin and scalp, the compound can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matrices 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.

[0035] 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.

[0036] 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.

Synthetic Methods

Scheme 1



Step 1. Protection of phenol **1** to give ether **2**

[0037] Potassium carbonate (4.3 g, 31.1 mmol) and 4-methoxybenzyl chloride (2.02 mL, 14.9 mmol) were added to a solution of phenol **1** (see US Provisional Patent Application No. 60/757,696, filed January 10, 2006, 2.30 g, 12.3 mmol) in DMF (100 mL). The mixture was heated at 100 °C. After 3 hours the mixture was allowed to cool to room temperature and then partitioned between water (150 mL) and EtOAc (200 mL). The phases were separated and the organic phase was washed with additional water (100 mL) and brine (50 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% EtOAc/hexane) afforded 3.25 g (86%) of ether **2**.

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

[0038] A solution of ester **2** (3.25 g, 10.6 mmol) in THF (17 mL) was added via syringe to a solution of $LiBH_4$ (0.346 g, 15.9 mmol) in THF (5 mL) at 0 °C. The mixture

was heated at 80 °C overnight. The reaction mixture was allowed to cool to room temperature, quenched with water, diluted with 5% aqueous citric acid (100 mL) and extracted with EtOAc (75 mL). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 2.91 g (99%) of alcohol **3**.

Step 3. Oxidation of **3** to give **4**

[0039] A solution of alcohol **3** (2.50 g, 8.97 mmol) in CH₂Cl₂ (125 mL) was added to a solution of Dess-Martin periodinane (4.57 g, 10.8 mmol) in CH₂Cl₂ (125 mL). After 2 hours at room temperature the reaction was partitioned between water (500 mL) and CH₂Cl₂ (300 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 250 mL). The combined organic phase was washed with brine (200 mL) then dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 2.42 g (97%) of aldehyde **4**.

Step 4. Wittig reaction of **4** to give **5**

[0040] Potassium tert-butoxide (2.54 g, 22.6 mmol) was added to a solution of methoxymethyltriphenylphosphonium chloride (3.72 g, 10.8 mmol) in THF (60 mL) at 0 °C. After 30 minutes at 0 °C, a solution of aldehyde **4** (2.5 g, 9.03 mmol) in THF (30 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched at 0 °C by the slow addition of H₂O then was partitioned between 10% aqueous HCl (95 mL) and EtOAc (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (20 mL) then dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (40% EtOAc/hexane) afforded 2.70 g (98%) of enol ether **5**.

Step 5. Hydrolysis of **5** to give **6**

[0041] M aqueous HCl (2.84 mL, 0.28 mmol) was added to a solution of enol ether **5** (2.70 g, 8.86 mmol) in dioxane (90 mL). After 1 hour at room temperature, the mixture was heated at 60 °C for 2.5 hours then cooled to room temperature. The reaction mixture was partitioned between saturated aqueous NaHCO₃ (300 mL) and CH₂Cl₂ (300 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 300 mL). The combined organic phase was washed with H₂O and brine then dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by flash

column chromatography on silica gel (30% EtOAc/hexane) afforded 812 mg (32%) of aldehyde **6**.

Step 6. Reduction of **6** to give **7**

[0042] Sodium borohydride (159 mg, 4.20 mmol) was added to a solution of aldehyde **6** (812 mg, 2.79 mmol) in MeOH (34 mL) at 0 °C. The mixture was allowed to warm to room temperature. After 20 minutes at room temperature, the reaction was cooled to 0 °C and quenched by the slow addition of water. The mixture was then diluted with water (200 mL) and extracted with EtOAc (2 x 300 mL). The combined organic phase was washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (50% EtOAc/hexane) afforded 816 mg (99%) of alcohol **7**.

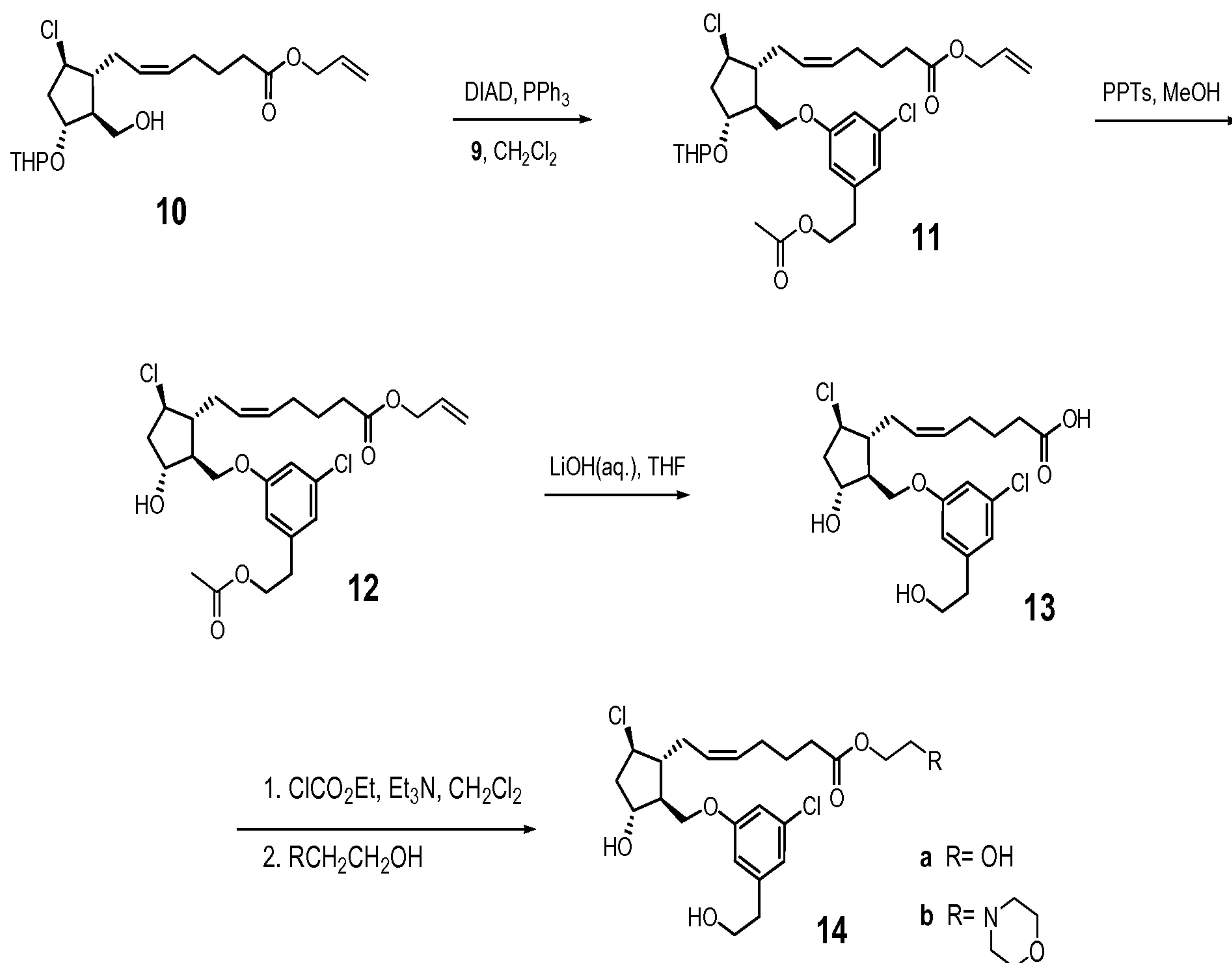
Step 7. Protection of **7** to give **8**

[0043] Pyridine (247 µL, 3.05 mmol) and acetyl chloride (216 µL, 3.04 mmol) were added sequentially to a solution of alcohol **7** (816 mg, 2.79 mmol) in CH₂Cl₂ (15 mL). After 5 min, the reaction mixture was partitioned between saturated aqueous NaHCO₃ (150 mL) and CH₂Cl₂ (150 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 150 mL). The combined organic phases were washed with brine (150 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (10% EtOAc/hexane) afforded 850 mg (91%) of acetate **8**.

Step 8. Deprotection of **8** to give **9**

[0044] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 814 mg, 3.59 mmol) was added to a mixture of ether **8** (400 mg, 1.19 mmol) in CH₂Cl₂ (9 mL) and H₂O (0.45 mL) at 0 °C. After 1 hour at 0 °C the reaction was allowed to warm to room temperature. After 4 hours at room temperature, the reaction was quenched with saturated aqueous NaHCO₃ (100 mL). The mixture was extracted with CH₂Cl₂ (3x100 mL). The combined extracts were washed with water and brine then dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 80 mg (31%) of compound **9**.

Scheme 2



Step 1. Mitsunobu reaction of **9** and **10** to give **11**

[0045] Triphenylphosphine (98 mg, 0.37 mmol) and diisopropyl azodicarboxylate (DIAD, 58 μL , 0.30 mmol) were added sequentially to a solution of alcohol **10** (see US Provisional Patent Application No. 60/757,696, filed January 10, 2006; 100 mg, 0.25 mmol) and phenol **9** (preparation 1, 80 mg, 0.37 mmol) in CH_2Cl_2 (1.0 mL). After stirring 18 hours at room temperature, the reaction mixture was partitioned between saturated aqueous NaHCO_3 (20 mL) and CH_2Cl_2 (15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phase was washed with brine (15 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% EtOAc/hexane) afforded 108 mg (72%) of aryl ether **11**.

Step 2: Deprotection of **11** to give **12**.

[0046] Pyridinium *p*-toluenesulfonate (PPTs, 4.7 mg, 0.019 mmol) was added to a solution of **11** (108 mg, 0.18 mmol) in methanol (2.0 mL) at room temperature under nitrogen. The solution was heated at 40 $^\circ\text{C}$ for 5 h, then cooled and concentrated in

vacuo. Purification of the crude residue by flash column chromatography on silica gel (50% EtOAc/hexane) afforded 53 mg (57%) of alcohol **12**.

Step 3: Hydrolysis of **12** to give **13**

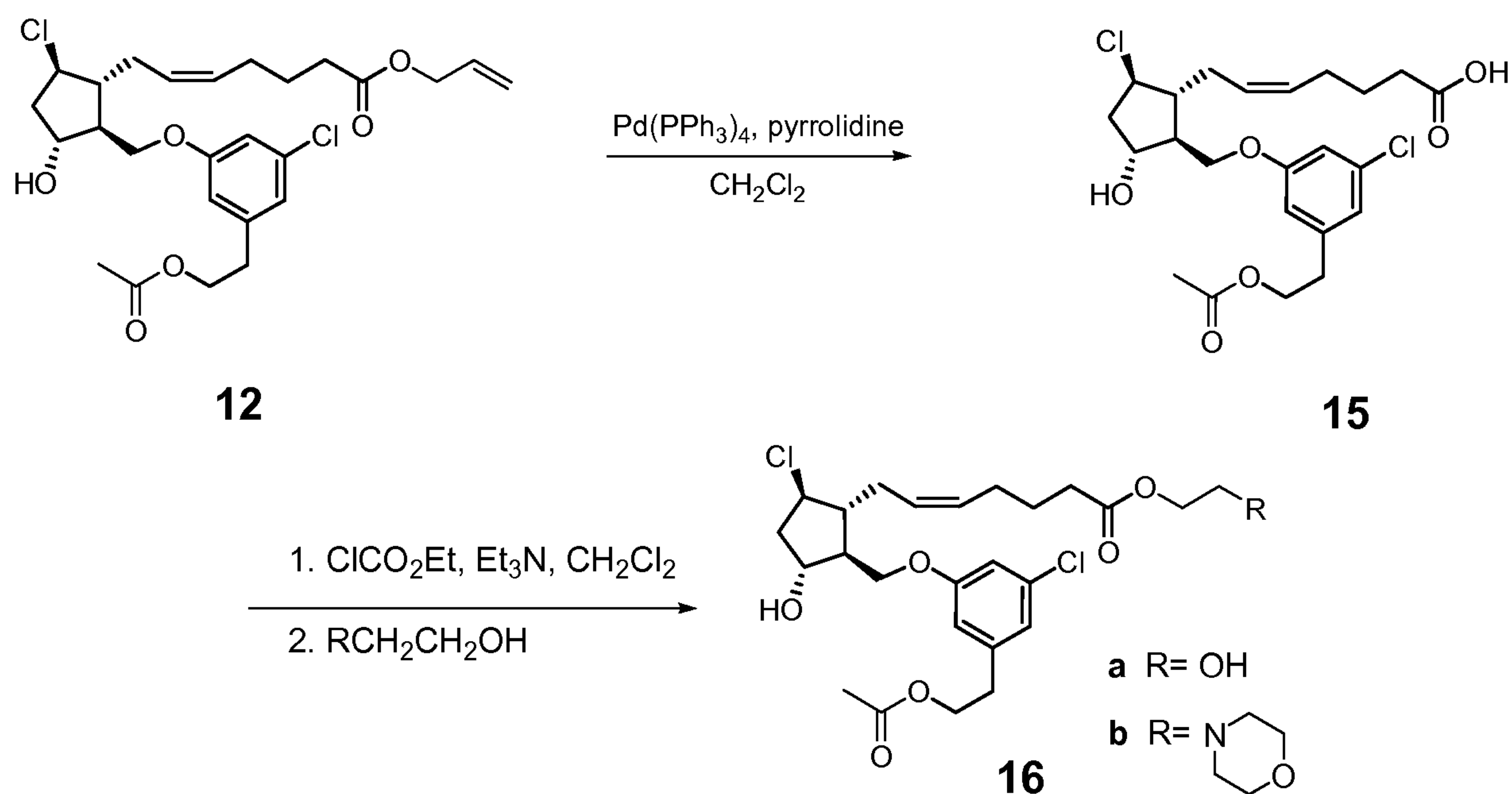
[0047] Lithium hydroxide (0.15 mL of a 1.0 M aqueous solution, 0.15 mmol) was added to a solution of ester **12** (13 mg, 0.025 mmol) in THF (0.13 mL). After 2 hours room temperature, the reaction was partitioned between 10% aqueous HCl (3 mL) and EtOAc (7 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 7 mL). The combined organic phase was washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to afford 11 mg (quant.) of compound **13**.

Step 4: **13** to give **14a** and **14b**

[0048] Compound **14a**. Triethylamine and ethyl chloroformate are added sequentially to a solution of compound **13** in CH₂Cl₂ 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 H₂O and CH₂Cl₂. The phases are separated and the aqueous phase is extracted with CH₂Cl₂ (2x). The combined organic phase is washed with 1 N HCl then dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% CH₃OH / CH₂Cl₂) affords compound **14a**.

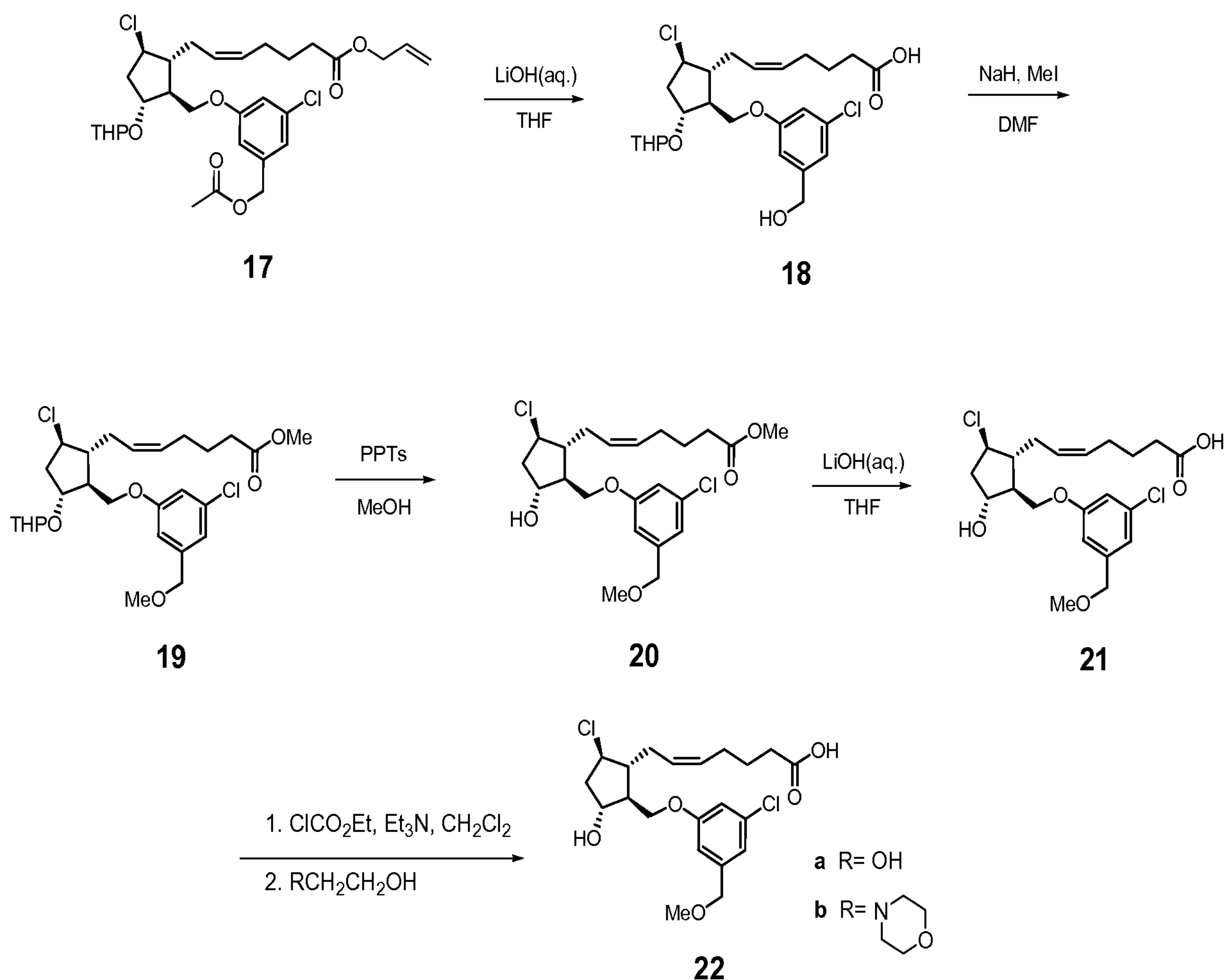
[0049] Compound **14b**. Triethylamine and ethyl chloroformate are added sequentially to a solution of compound **13** in CH₂Cl₂ at room temperature. After 2.5 h, triethylamine and 4-(2-hydroxyethyl)-morphine are added. After stirring overnight at room temperature, the reaction mixture is partitioned between H₂O and CH₂Cl₂. The phases are separated and the aqueous phase is extracted with CH₂Cl₂ (2x). The combined organic phase is washed with 1 N HCl then dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% CH₃OH / CH₂Cl₂) affords compound **14b**.

Scheme 3



[0050] Tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol) and pyrrolidine (14 μL , 0.17 mmol) were added sequentially to a solution of allyl ester **12** (30 mg, 0.058 mmol) in CH_2Cl_2 (1.0 mL). After 5 min the reaction mixture was partitioned between 1.0 M aqueous HCl (5 mL) and CH_2Cl_2 (15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (60% EtOAc/hexane) afforded 9 mg (33%) of compound **15**. Compound **16a** and **16b** can be made according to Step 4 of Scheme 2.

Scheme 4



Step 1. Hydrolysis of **17** to give **18**

[0051] Ester **17** (see US Provisional Patent Application No. 60/757,696, filed January 10, 2006; 200 mg, 0.343 mmol) was converted into 140 mg (57%) of hydroxy-acid **18** in accordance with the procedure of Scheme 2, step 3.

Step 2. Dimethylation of **18** to give **19**

A solution of hydroxy-acid **18** (54 mg, 0.11 mmol) in DMF (0.5 mL) was added to a suspension of sodium hydride (11 mg of a 60 wt. % suspension, 0.28 mmol) in DMF (0.5 mL). Iodomethane (67 μ L, 1.08 mmol) was then added. The reaction mixture was partitioned between water (5 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (hexanes $\rightarrow$ EtOAc, gradient) afforded 50 mg (88%) of **19**.

Step 3. Deprotection of **19** to give **20**

[0052] Acetal **19** (50 mg, 0.094 mmol) was converted into 23 mg (55%) of alcohol **20** in accordance with the procedure of Scheme 2, step 2.

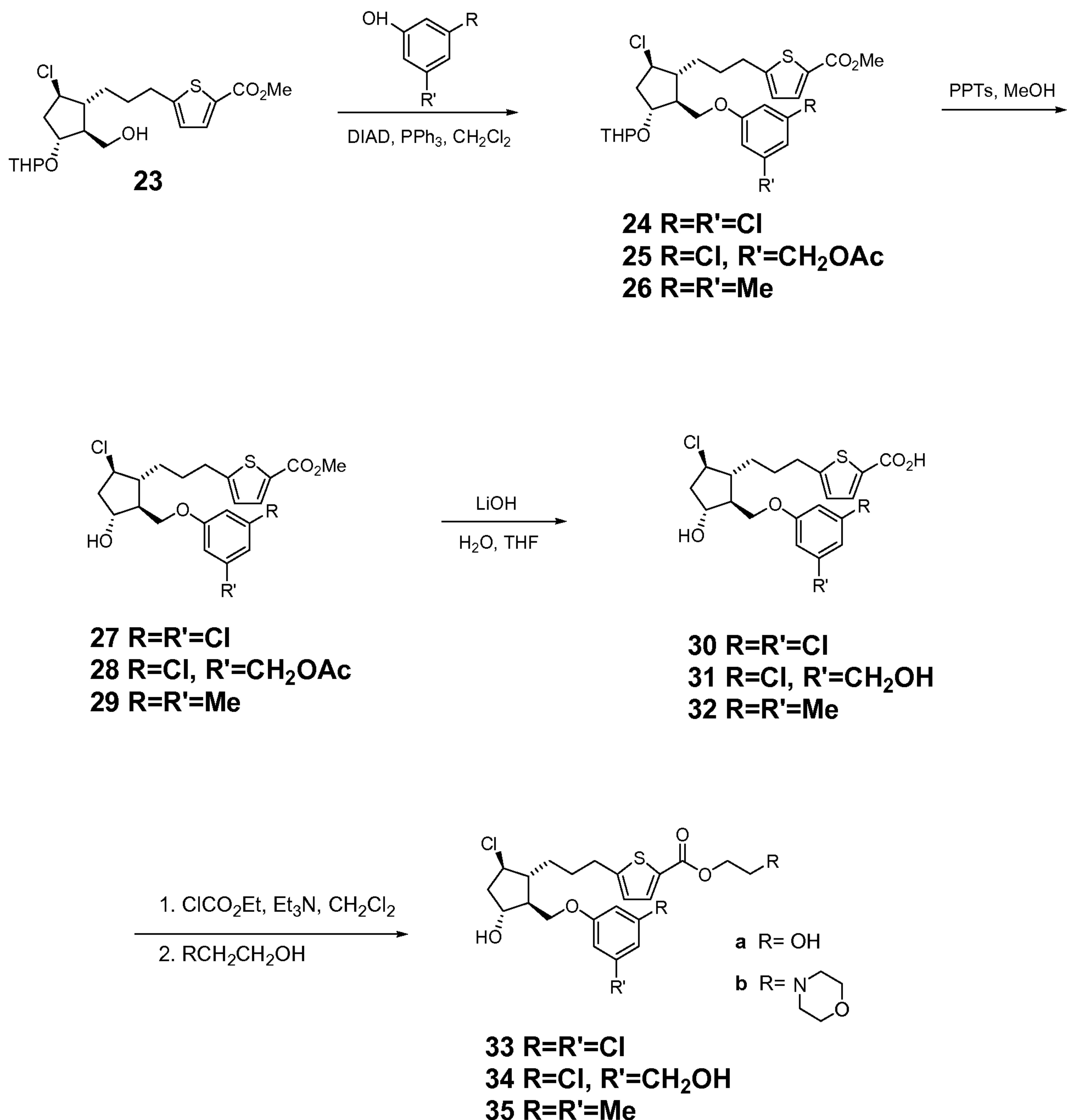
Step 4. Hydrolysis of **20** to give **21**

[0053] Ester **20** (23 mg, 0.052 mmol) was converted into 13 mg (58%) of compound **21** in accordance with the procedure of Scheme 2, step 3.

Step 5. **21** to give **22a** and **22b**

[0054] Compound **21** can be converted to compounds **16a** and **16b** according to Step 4 of Scheme 2.

Scheme 5



Step 1. Mitsunobu reaction of **23** to give **24**

[0055] Triphenylphosphine (38 mg, 0.14 mmol) and DIAD (23 μ L, 0.12 mmol) were added to a solution of alcohol **23** (see US Provisional Patent Application No. 60/805,285, filed June 20, 2006; 40 mg, 0.096 mmol) and 3,5-dichlorophenol (23 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL). After stirring 18 hours at room temperature, the mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous NaHCO_3 (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phase was washed with brine (10 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 20 mg (37%) of **24**.

[0056] Pyridinium *p*-toluenesulfonate (PPTs, 1 mg, 0.004 mmol) was added to a solution of **24** (20 mg, 0.036 mmol) in methanol (0.35 mL) at room temperature. The solution was heated at 40 $^\circ\text{C}$ overnight, then cooled and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 10 mg (59%) of **27**.

Step 3. Hydrolysis of **27** to give **30**

[0057] Ester **27** (10 mg, 0.021 mmol) was converted into 3 mg (31%) of compound **30** in accordance with the procedure of Scheme 2, step 3 with the following modifications: the reaction was stirred for 18 hours at room temperature, and the crude product was purified by flash column chromatography on silica gel (10% MeOH/ CH_2Cl_2).

Step 4. **30** to give **33a** and **33b**

[0058] Compound **30** can be converted to compounds **33a** and **33b** according to Step 4 of Scheme 2.

Step 1.

[0059] Ester **28** (see US Provisional Patent Application No. 60/805,285, filed June 20, 2006; 30 mg, 0.058 mmol) was converted into 13 mg (49%) of compound **31** in accordance with the procedure of Scheme 5, step 3 (above).

Step 2. **31** to give **34a** and **34b**

[0060] Compound **31** can be converted to compounds **34a** and **34b** according to Step 4 of Scheme 2.

Step 1. Mitsunobu reaction of **23** to give **26**

[0061] Triphenylphosphine (47 mg, 0.18 mmol) and DIAD (27 μ L, 0.14 mmol) were added to a solution of alcohol **23** (see US Provisional Patent Application No. 60/805,285, filed June 20, 2006; 50 mg, 0.12 mmol) and 3,5-dimethylphenol (17 mg, 0.14 mmol) in CH_2Cl_2 (0.6 mL). After stirring 18 hours at room temperature, the mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous NaHCO_3 (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phase was washed with brine (10 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 53 mg (85%) of **26**.

Step 2. Deprotection of **26** to give **29**

[0062] Acetal **26** (53 mg, 0.10 mmol) was converted into 37 mg (83%) of alcohol **29** in accordance with the procedure of Scheme 5, step 2 (above).

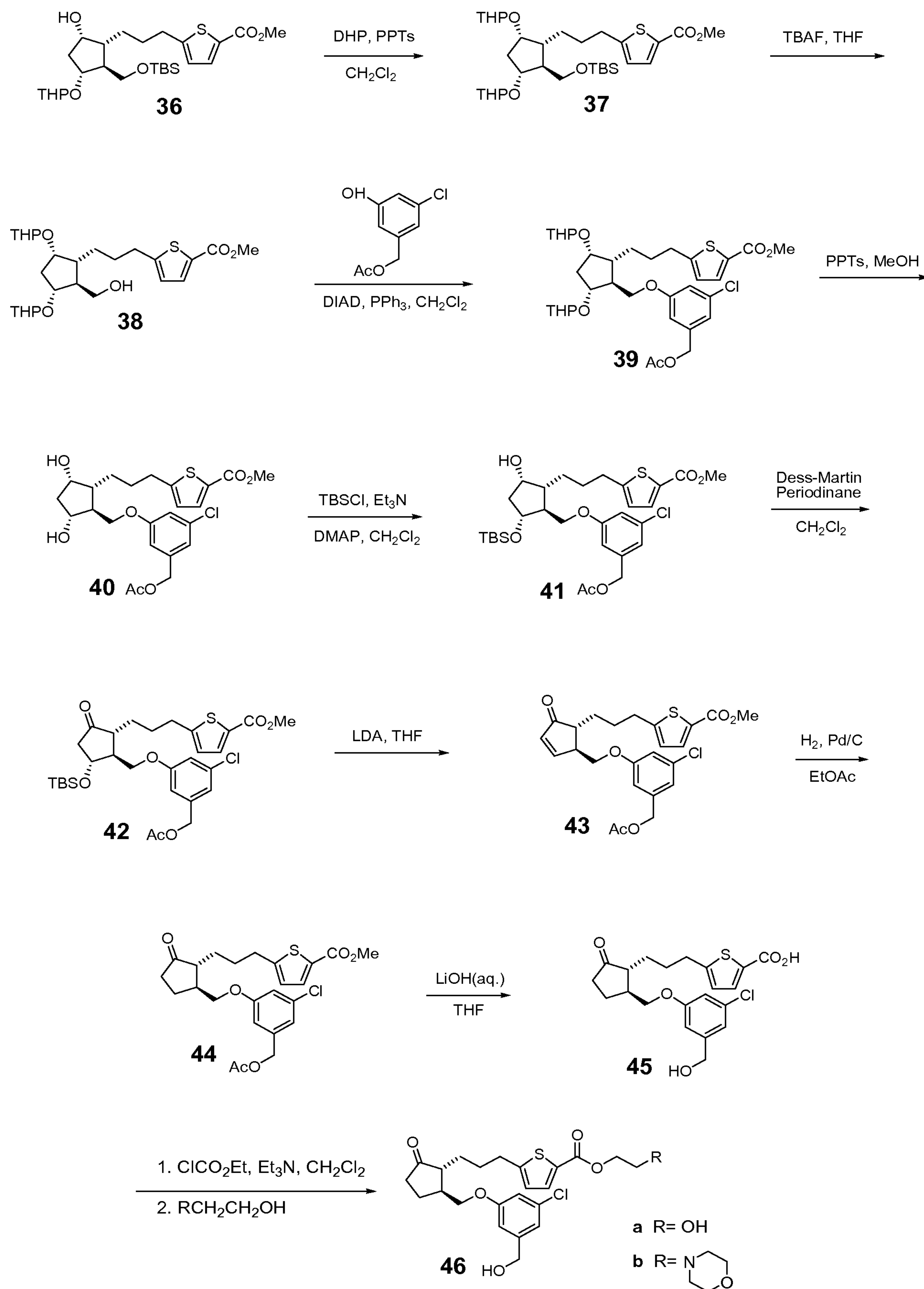
Step 3. Hydrolysis of **29** to give **32**

[0063] Ester **29** (37 mg, 0.085 mmol) was converted into 15 mg (42%) of compound **32** in accordance with the procedure of Scheme 2, step 3 with the following modifications: the reaction was stirred for 18 hours at 40 $^\circ\text{C}$, and the crude product was purified by flash column chromatography on silica gel (10% MeOH/ CH_2Cl_2).

Step 4. **32** to give **35a** and **35b**

[0064] Compound **32** can be converted to compounds **35a** and **35b** according to Step 4 of Scheme 2.

Scheme 6

Step 1. Protection of **36** to give **37**

[0065] Dihydropyran (391 μ L, 4.29 mmol) and PPTs (50 mg, 0.20 mmol) were added to a solution of alcohol **37** (see US Provisional Patent Application No. 60/805,285, filed June 20, 2006; 550 mg, 1.07 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was heated at 40 °C overnight, then cooled and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 550 mg (86%) of **37**.

Step 2. Desilylation of **37** to give **38**

[0066] Tetrabutylammonium fluoride (2.51 mL of a 1.0 M THF solution, 2.51 mmol) was added to a solution of **37** (500 mg, 0.84 mmol) in THF (7.6 mL). After 18 hours at room temperature, the reaction mixture was partitioned between water (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine then dried (MgSO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 393 mg (97%) of **38**.

Step 3. Mitsunobu of **38** to give **39**

[0067] Alcohol **38** (437 mg, 0.91 mmol) and 3-chloro-5-hydroxybenzyl acetate (see US Provisional Patent Application No. 60/757,696, filed January 10, 2006; 218 mg, 1.09 mmol) were converted into 350 mg (58%) of aryl ether **39** in accordance with the procedure of Scheme 5, step 1.

Step 4. Deprotection of **39** to give **40**

[0068] Bis-acetal **39** (350 mg, 0.53 mmol) was converted into 150 mg (57%) of diol **40** in accordance with the procedure of Scheme 5, step 2.

Step 5. Monosilylation of **40** to give **41**

[0069] Triethylamine (63 μ L, 0.45 mmol), dimethylaminopyridine (7 mg, 0.057 mmol), and *tert*-butyldimethylsilyl chloride (50 mg, 0.33 mmol) were sequentially added to a solution of **41** (150 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL). After stirring 18 hours at room temperature, the mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous NaHCO_3 (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phase was washed with brine (10 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 90 mg (49%) of **41**.

Step 6. Oxidation of **41** to give **42**

[0070] Dess-Martin periodinane (75 mg, 0.18 mmol) was added to a solution of **41** (90 mg, 0.15 mmol) in CH₂Cl₂ (7.35 mL) at 0 °C and the mixture was allowed to warm to room temperature. After 2 hours at room temperature, the mixture was partitioned between CH₂Cl₂ (10 mL) and water (10 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic phase was washed with brine (5 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane → EtOAc, gradient) afforded 80 mg (89%) of ketone **42**.

Step 7. Elimination of **42** to give **43**

[0071] A solution of lithium diisopropylamide (0.41 mL of a 2.0 M solution in heptane-THF-ethylbenzene, 0.82 mmol) was added to a solution of **42** (80 mg, 0.13 mmol) in THF (2.3 mL) at – 78 °C. After 90 minutes at – 78 °C, the mixture was allowed to warm to room temperature. After 15 minutes at room temperature, the reaction was quenched by the addition of 0.1 N aqueous HCl (15 mL), and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane → EtOAc, gradient) afforded 40 mg (64%) of enone **43**.

Step 8. Hydrogenation of **43** to give **44**

[0072] Palladium on carbon (10 wt.%, 8 mg) was added to a solution of enone **43** (40 mg, 0.084 mmol) in EtOAc (1.6 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (5x) and the reaction mixture was stirred under a balloon of hydrogen for 18 hours. The reaction mixture was filtered through celite™, washing with EtOAc, and the filtrate was concentrated in vacuo to afford 31 mg (77%) of saturated ketone **44**.

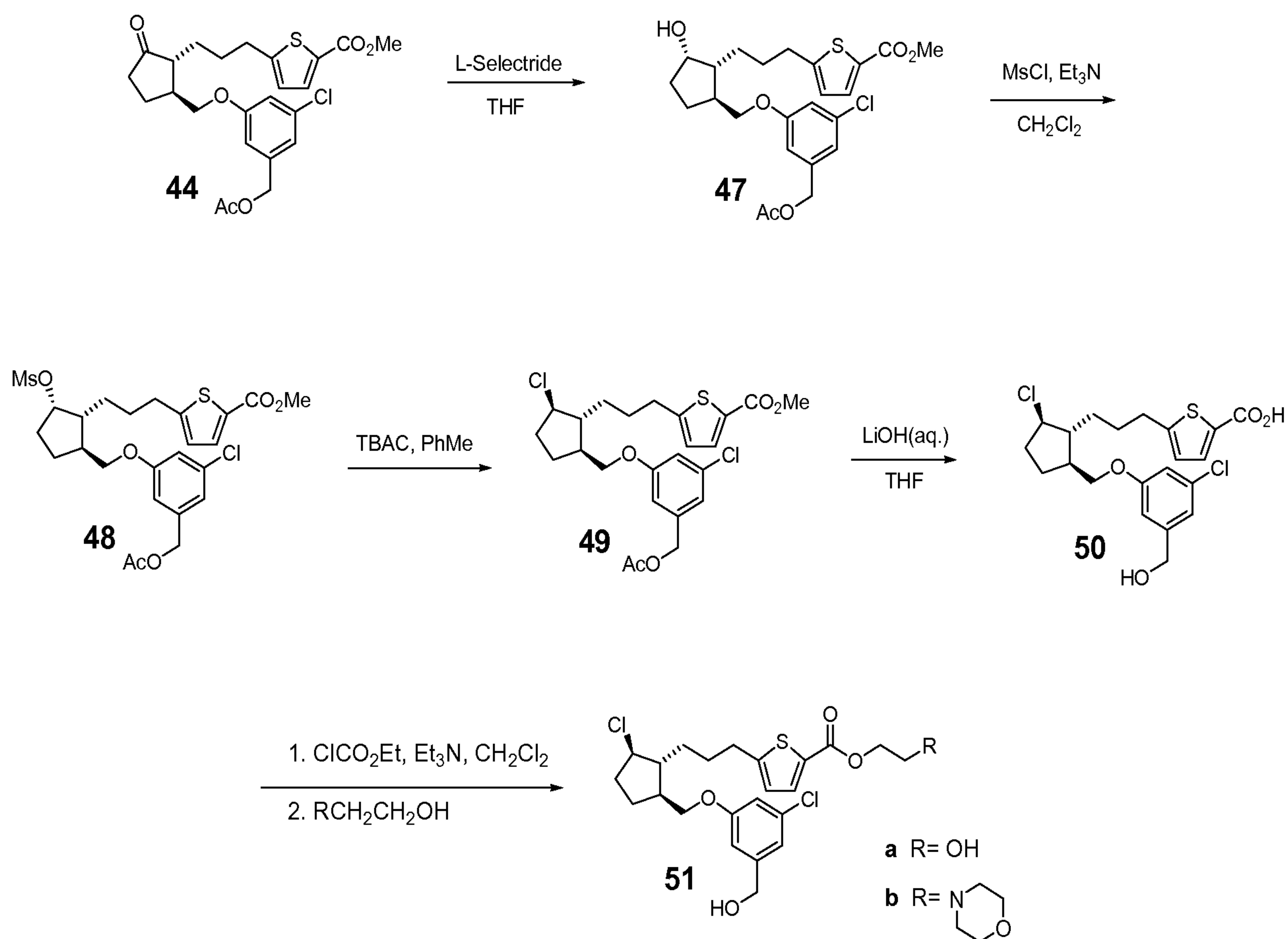
Step 9. Hydrolysis of **44** to give **45**

[0073] Ester **44** (5 mg, 0.010 mmol) was converted into 3.5 mg (79%) of compound **45** in accordance with the procedure of Scheme 5, step 3.

Step 10. **45** to give **46a** and **46b**

[0074] Compound **45** can be converted to compounds **46a** and **46b** according to Step 4 of Scheme 2.

Scheme 7

Step 1. Reduction of **44** to give **47**

[0075] A solution of L-selectride (74 μL of a 1.0 M solution in THF, 0.074 mmol) was added to a solution of **44** (26 mg, 0.054 mmol) in THF (1.8 mL) at -78°C . After 1 hour at -78°C , additional L-selectride (108 μL , 0.108 mmol) was added. After 5 hours at -78°C , the reaction was quenched by the addition of 3% aqueous H_2O_2 (1.5 mL) and the mixture was allowed to warm to room temperature. Water (5 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The combined extracts were dried (MgSO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 13 mg (50%) of alcohol **47**.

Step 2. Mesylation of **47** to give **48**

[0076] Triethylamine (5.6 μL , 0.040 mmol) and methanesulfonyl chloride (2.6 μL , 0.033 mmol) were added sequentially to a solution of **47** (13 mg, 0.027 mmol) in CH_2Cl_2 (0.2 mL) at 0°C , and reaction was allowed to warm to room temperature. After 18 hours at room temperature, saturated aqueous NaHCO_3 (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed

with brine (2 mL), dried (MgSO_4), filtered and concentrated in vacuo to afford 15 mg (99%) of mesylate **48**.

Step 3. Conversion of **48** to chloride **49**

[0077] Tetrabutylammonium chloride (38 mg, 0.14 mmol) was added to a solution of **48** (15 mg, 0.027 mmol) in toluene (0.27 mL). The reaction mixture was heated at 50 °C for 18 hours. The cooled mixture was diluted with brine (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 5 mg (37%) of chloride **49**.

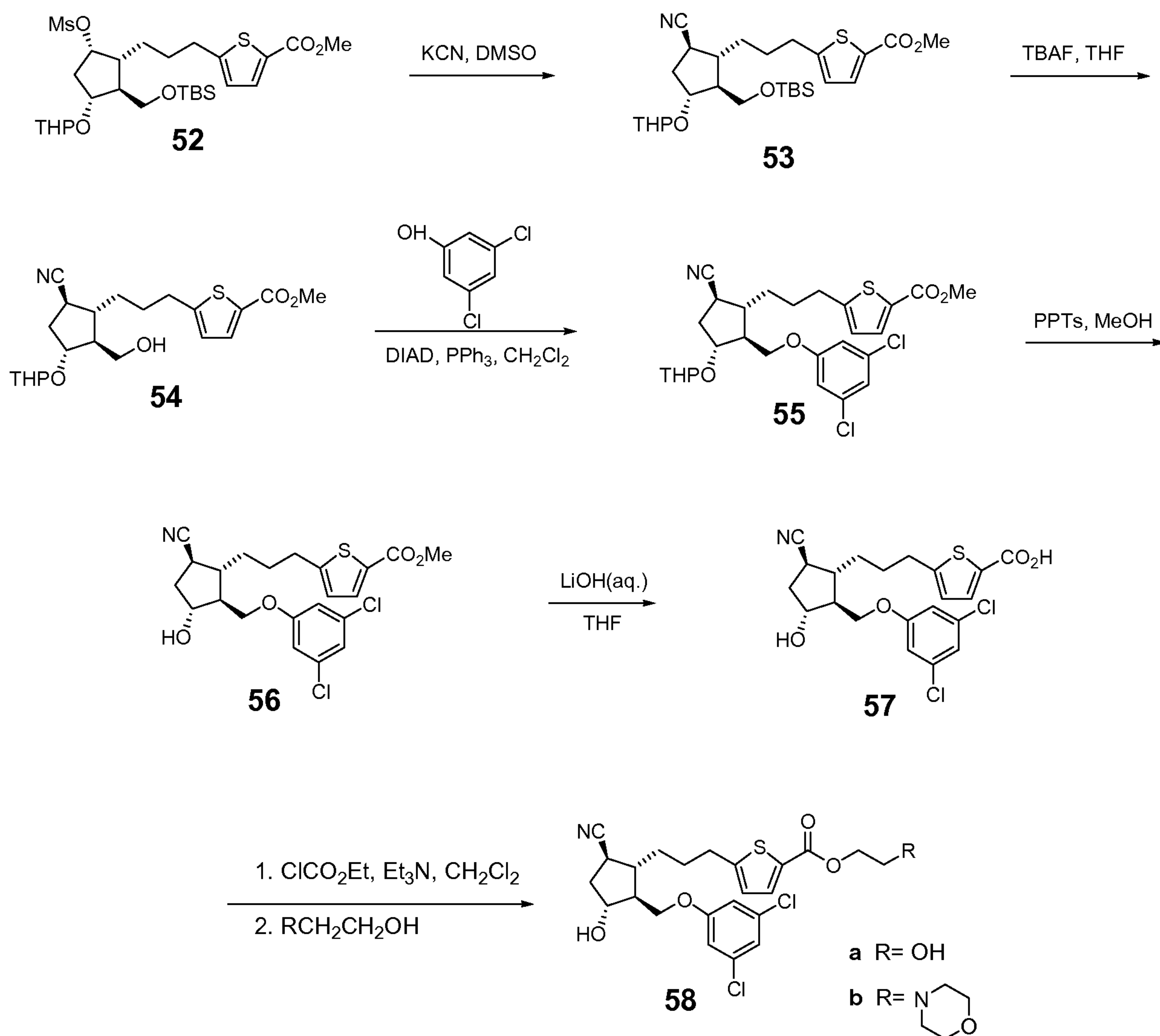
Step 4. Hydrolysis of **49** to give **50**

[0078] Ester **49** (5 mg, 0.010 mmol) was converted into 1 mg (23%) of compound **50** in accordance with the procedure of Scheme 5, step 3.

Step 5. **50** to give **51a** and **51b**

[0079] Compound **50** can be converted to compounds **51a** and **51b** according to Step 4 of Scheme 2.

Scheme 8



Step 1. Conversion of **52** to give nitrile **53**

[0080] Potassium cyanide (569 mg, 8.74 mmol) was added to a solution of mesylate **52** (see US Provisional Patent Application No. 60/805,285, filed June 20, 2006; 2.10 g, 3.55 mmol) in DMSO (97 mL). The mixture was heated at 65 °C for 18 hours then cooled to room temperature. The mixture was diluted with water (100 mL) and brine (100 mL) and extracted with CH₂Cl₂ (3 x 200 mL). The combined organic phase was dried (MgSO₄) filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane → EtOAc, gradient) afforded 270 mg (15%) of nitrile **53**.

Step 2. Desilylation of **53** to give **54**

[0081] Silyl ether **53** (270 mg, 0.52 mmol) was converted into 150 mg (71%) of alcohol **54** in accordance with the procedure of Scheme 6, step 2.

Step 3. Mitsunobu of **54** to give **55**

[0082] Alcohol **54** (50 mg, 0.12 mmol) and 3,5-dichlorophenol (24 mg, 0.15 mmol) were converted into 50 mg (74%) of aryl ether **55** in accordance with the procedure of Scheme 5, step 1.

Step 4. Deprotection of **55** to give **56**

[0083] Acetal **55** (50 mg, 0.090 mmol) was converted into 20 mg (47%) of alcohol **56** in accordance with the procedure of Scheme 5, step 2.

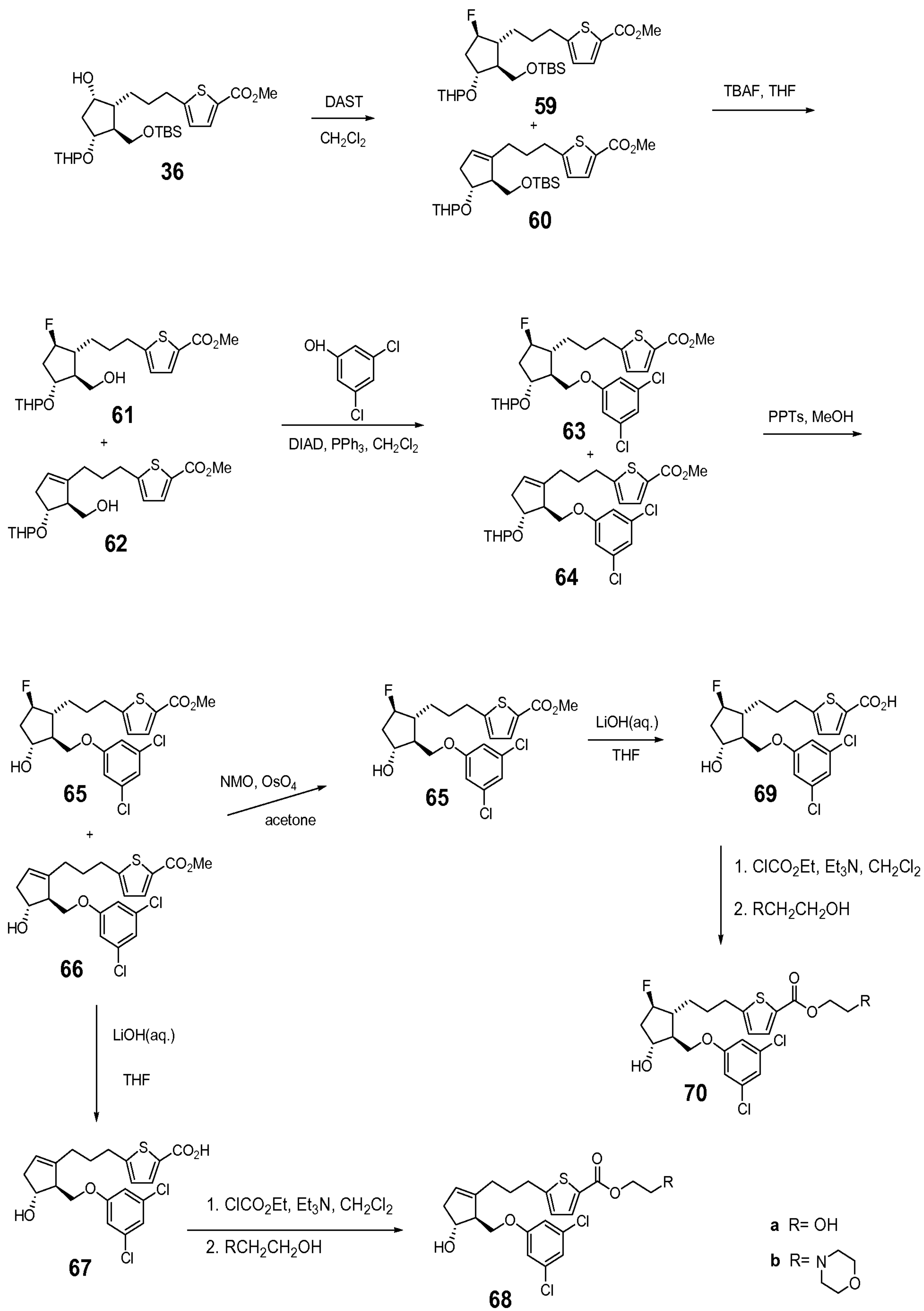
Step 5. Hydrolysis of **56** to give **57**

[0084] Ester **56** (15 mg, 0.032 mmol) was converted into 8 mg (55%) of compound **57** in accordance with the procedure of Scheme 2, step 3 with the following modifications: the concentration was 0.4 M in THF, the reaction was stirred for 18 hours at 40 °C, and the crude product was purified by flash column chromatography on silica gel (10% MeOH/CH₂Cl₂).

Step 6. **57** to give **58a** and **58b**

[0085] Compound **57** can be converted to compounds **58a** and **58b** according to Step 4 of Scheme 2.

Scheme 9



Step 1. Conversion of **36** to fluoride **59** and alkene **60**

[0086] (Diethylamino)sulfur trifluoride (DAST, 104 μ L, 0.79 mmol) was added to a solution of alcohol **36** (see US Provisional Patent Application No. 60/805,285, filed June 20, 2006; 200 mg, 0.39 mmol) in CH_2Cl_2 (92 mL) at -78°C . After 30 minutes at room temperature, the reaction was quenched with saturated aqueous NaHCO_3 (25 mL). The mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phase was dried (MgSO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane $\rightarrow$ EtOAc, gradient) afforded 42 mg (~20%) of an inseparable mixture of **59** and **60**.

Step 2. Disilylation of **59/60** to **61/62**

[0087] Silyl ethers **59/60** (42 mg, ~0.08 mmol) were converted into 25 mg (~77%) of inseparable alcohols **61/62** in accordance with the procedure of Scheme 6, step 2.

Step 3. Mitsunobu of **61/62** to **63/64**

[0088] Alcohols **61/62** (25 mg, ~0.06 mmol) and 3,5-dichlorophenol (9 mg, 0.055 mmol) were converted into 24 mg (~70%) of inseparable aryl ethers **63/64** in accordance with the procedure of Scheme 5, step 1.

Step 4. Deprotection of **63/64** to **65** and **66**

[0089] Acetals **63/64** (24 mg, ~0.45 mmol) were converted into 1 mg (~5%) of hydroxyl alkene **57** and 20 mg (~83%) of a mixture of **65** and **66** in accordance with the procedure of Scheme 5, step 2.

Step 5. Hydrolysis of **66** to **67**

[0090] Ester **66** (1 mg, 0.022 mmol) was converted into 1 mg (quant.) of compound **67** in accordance with the procedure of Scheme 5, step 3.

Step 6. **67** to give **68a** and **68b**

[0091] Compound **67** can be converted to compounds **68a** and **68b** according to Step 4 of Scheme 2.

Step 1. Oxidation of **66** to afford pure **65**

[0092] Osmium tetroxide (160 μ L of a 4 wt. % solution in water, 0.026 mmol) was added to a solution of 4-methylmorpholine N-oxide (NMO, 11.4 mg, 0.097 mmol) and the mixture of **65** and **66** (Scheme 9, step 4, 20 mg, ~0.044 mmol) in acetone (1.1 mL) at 0°C and the reaction was allowed to warm to room temperature. After 1 h, the reaction was quenched with 5% aqueous NaHCO_3 (5 mL) and extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (MgSO_4), filtered

and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane → EtOAc, gradient) afforded 5 mg (~24%) of fluoride **65**.

Step 2. Hydrolysis of **65** to give **69**

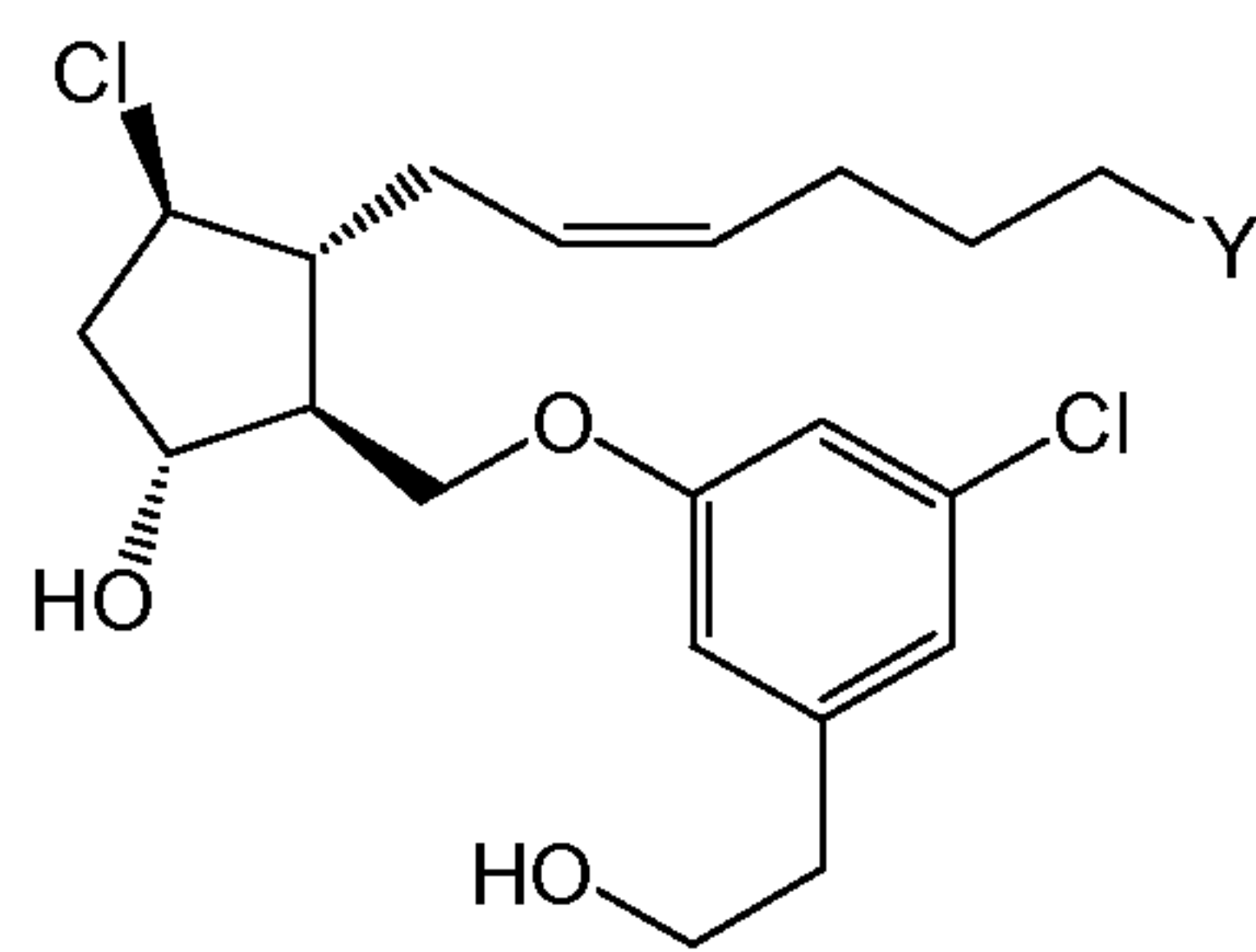
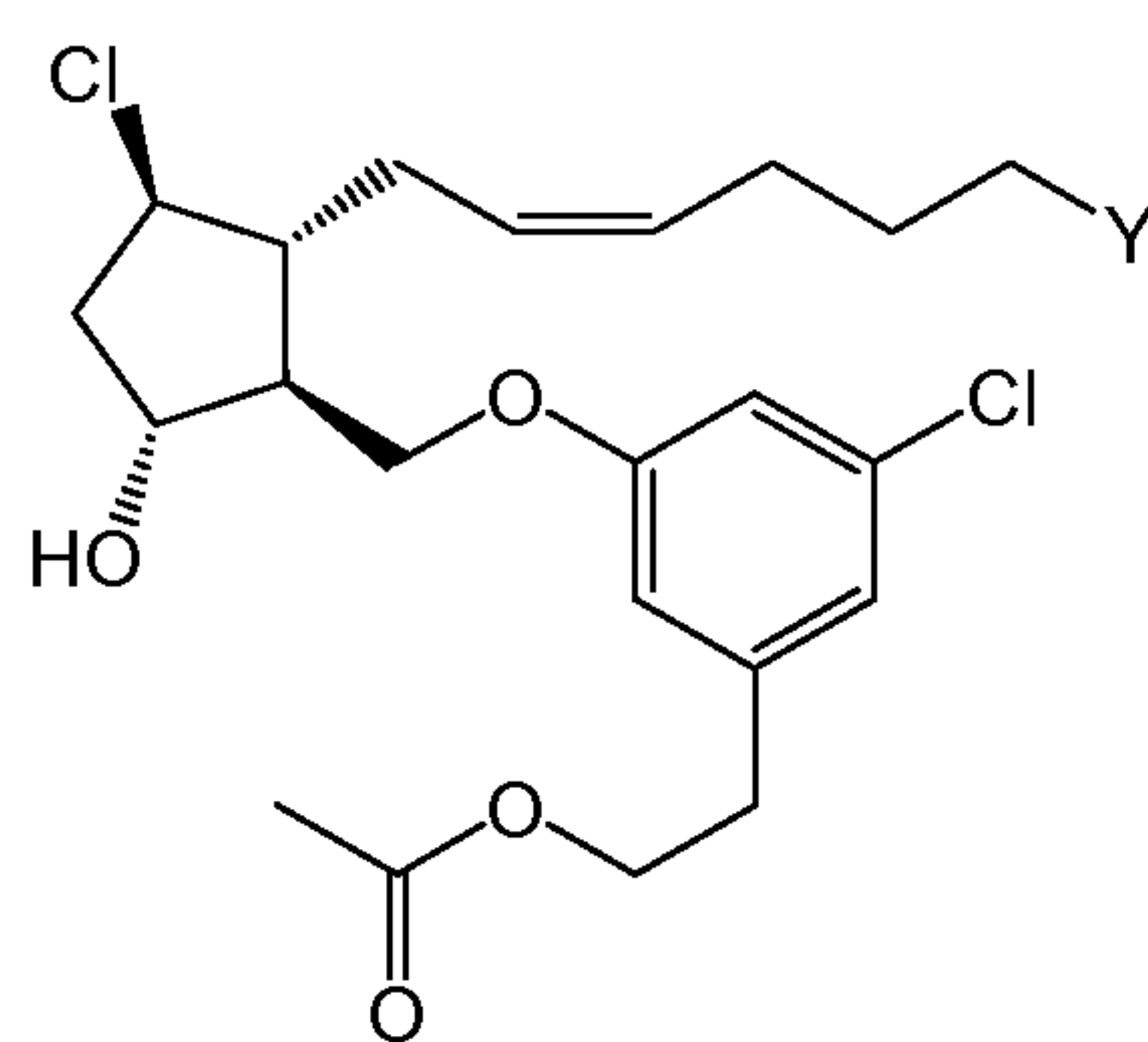
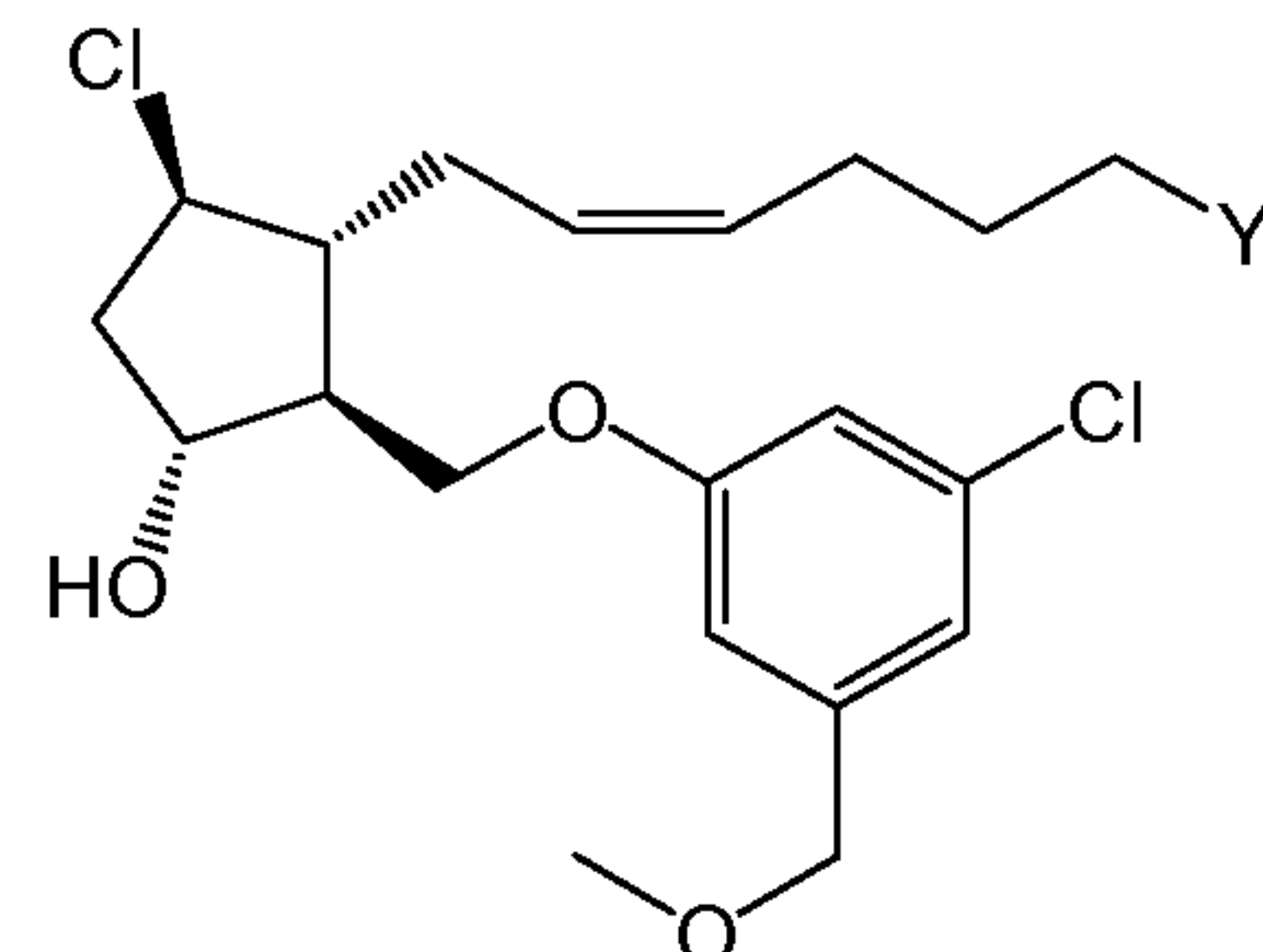
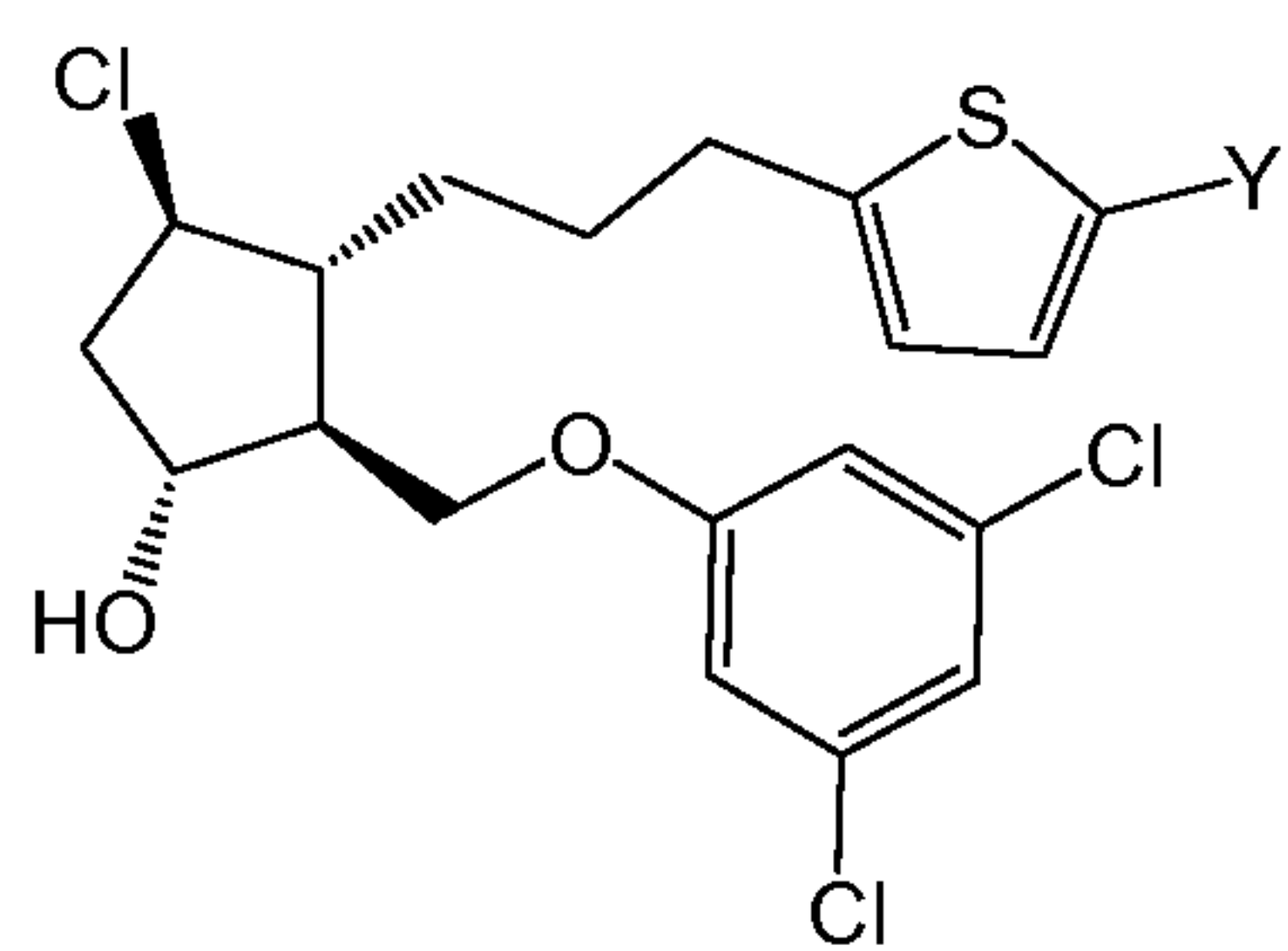
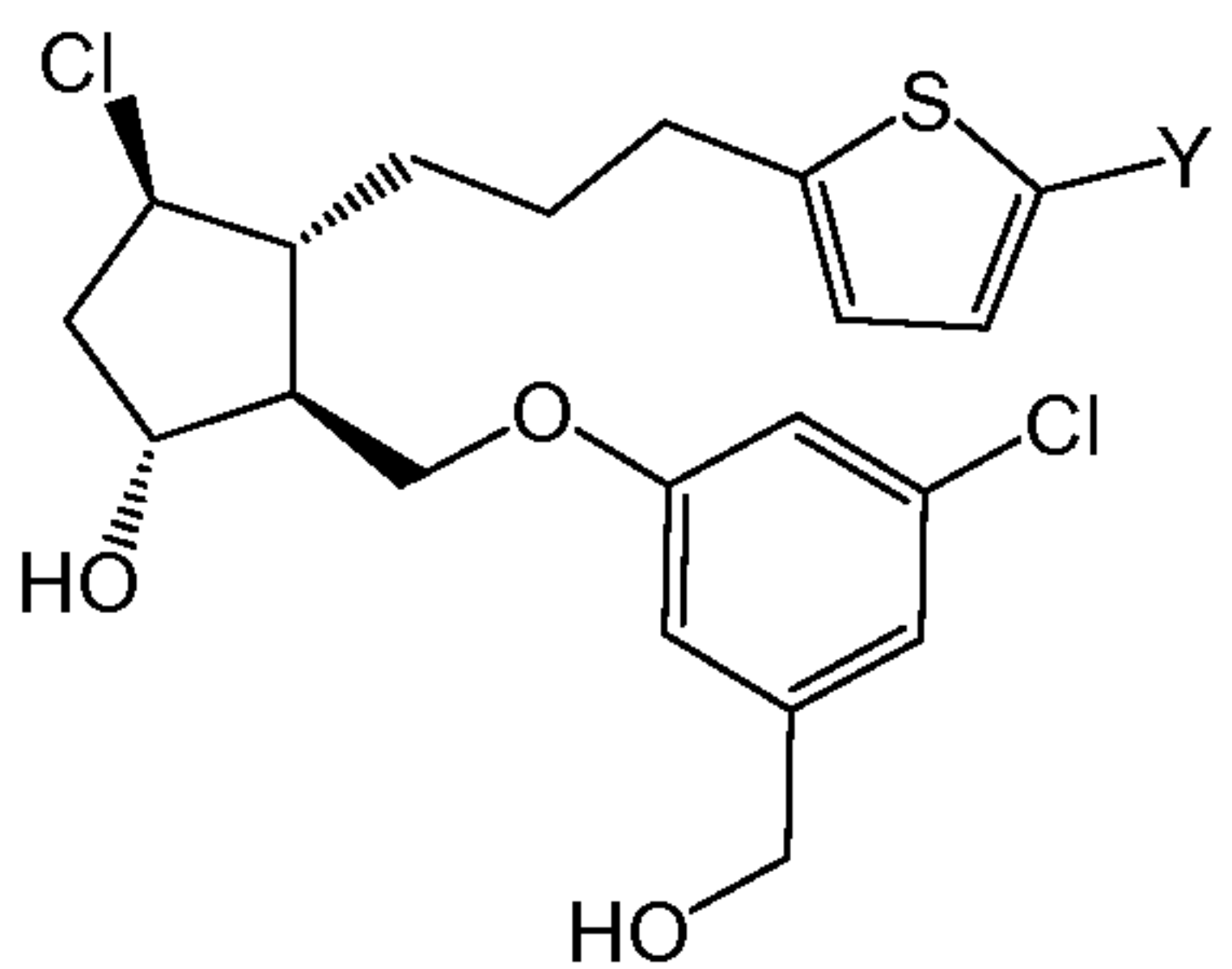
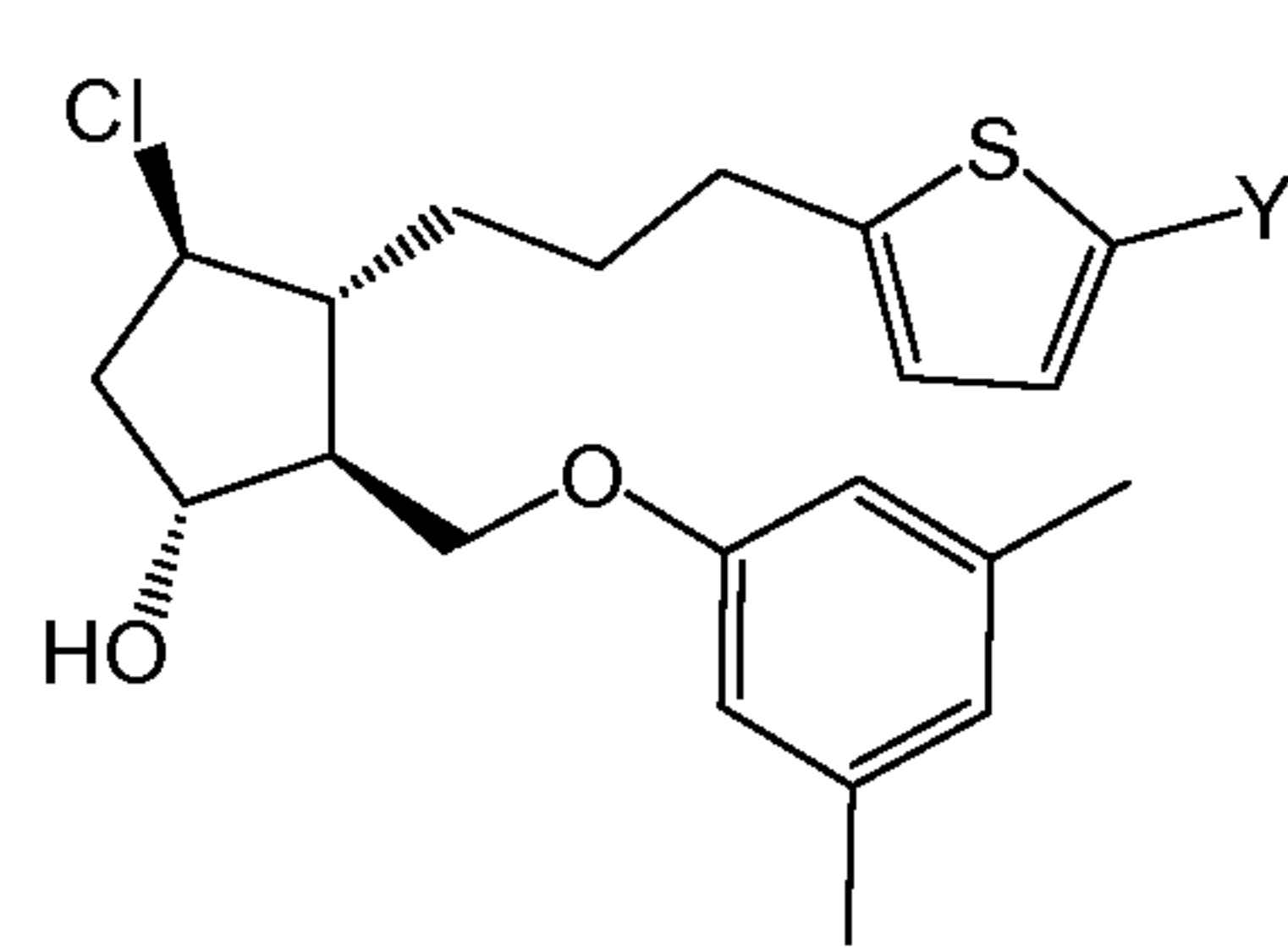
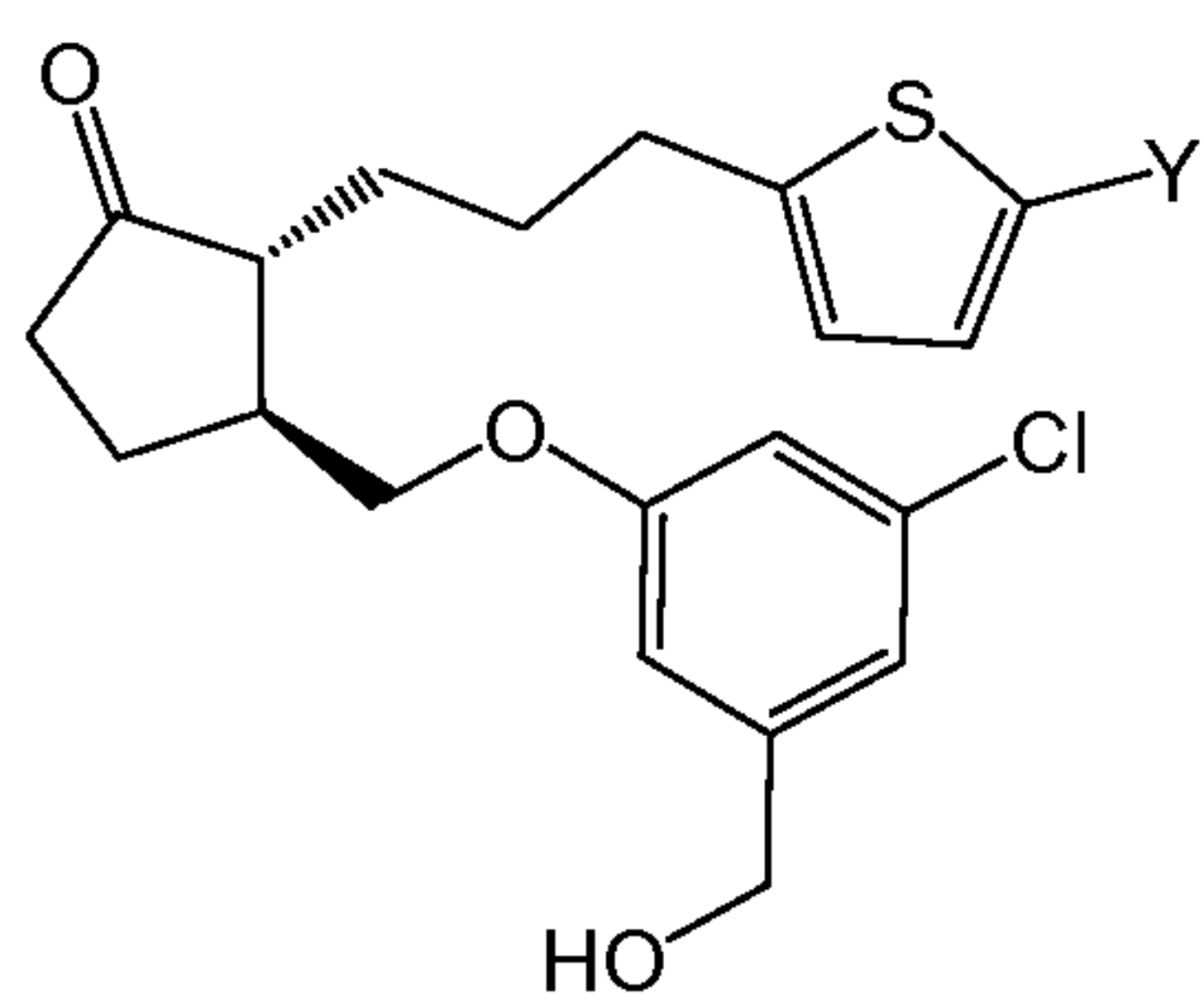
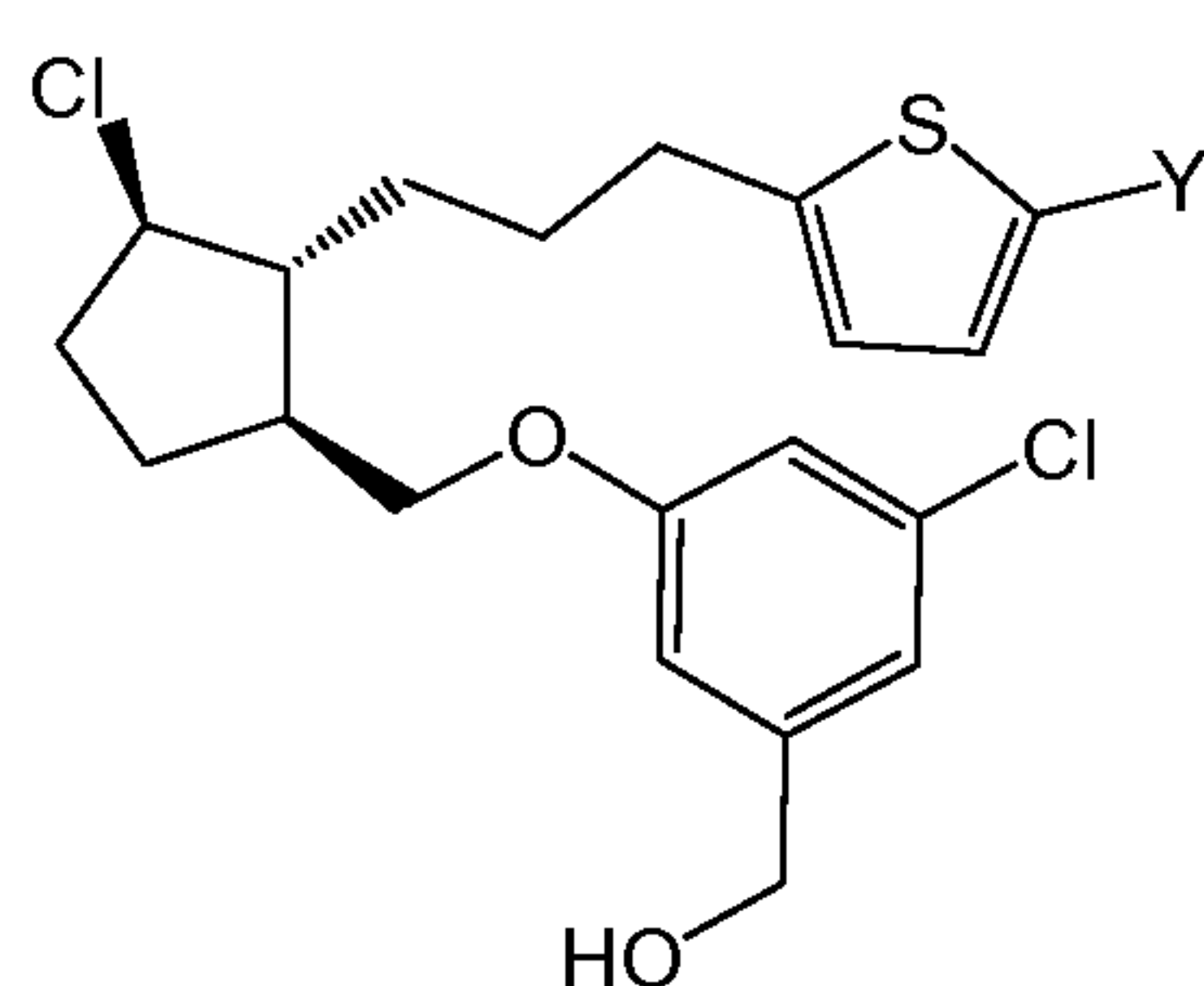
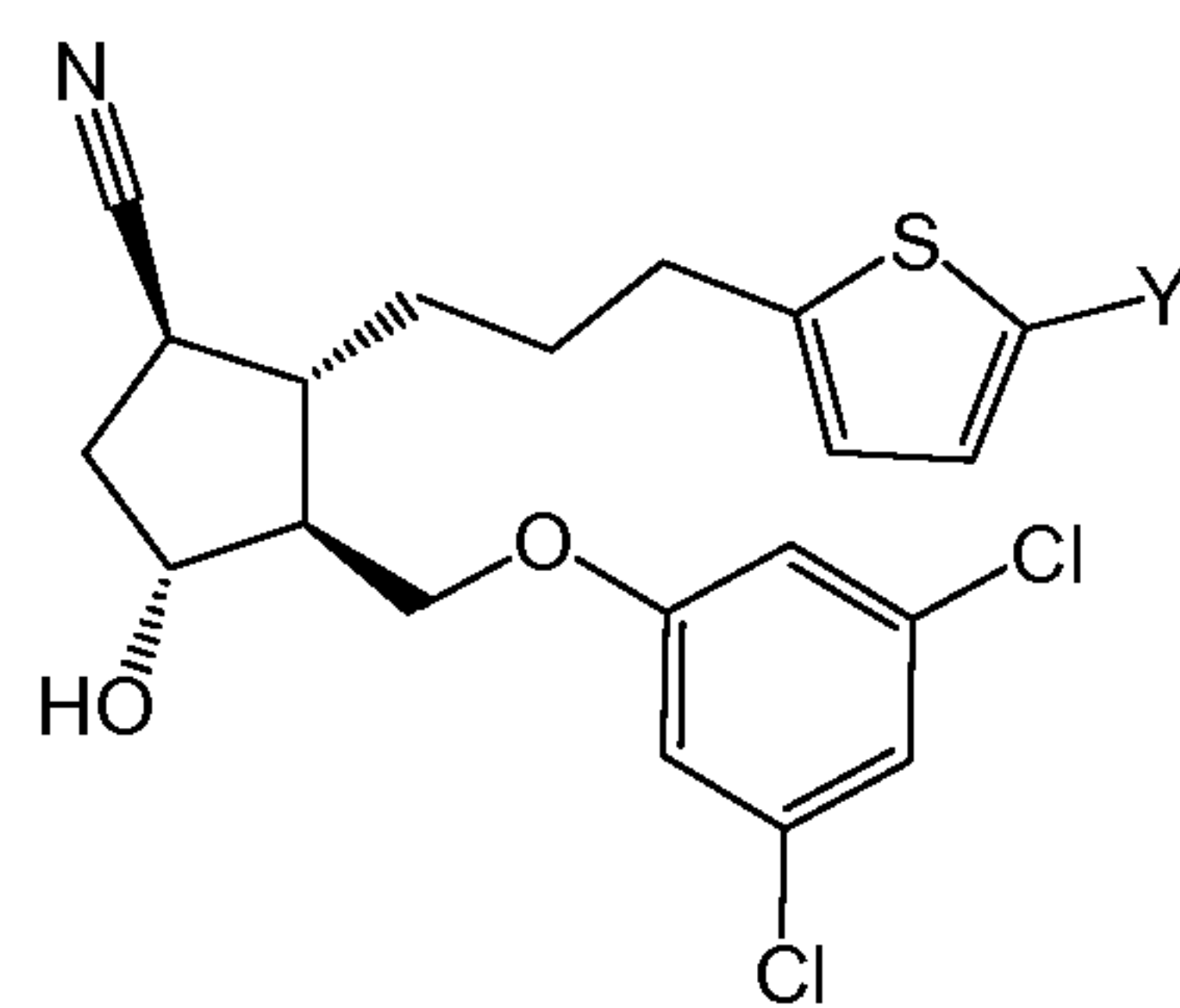
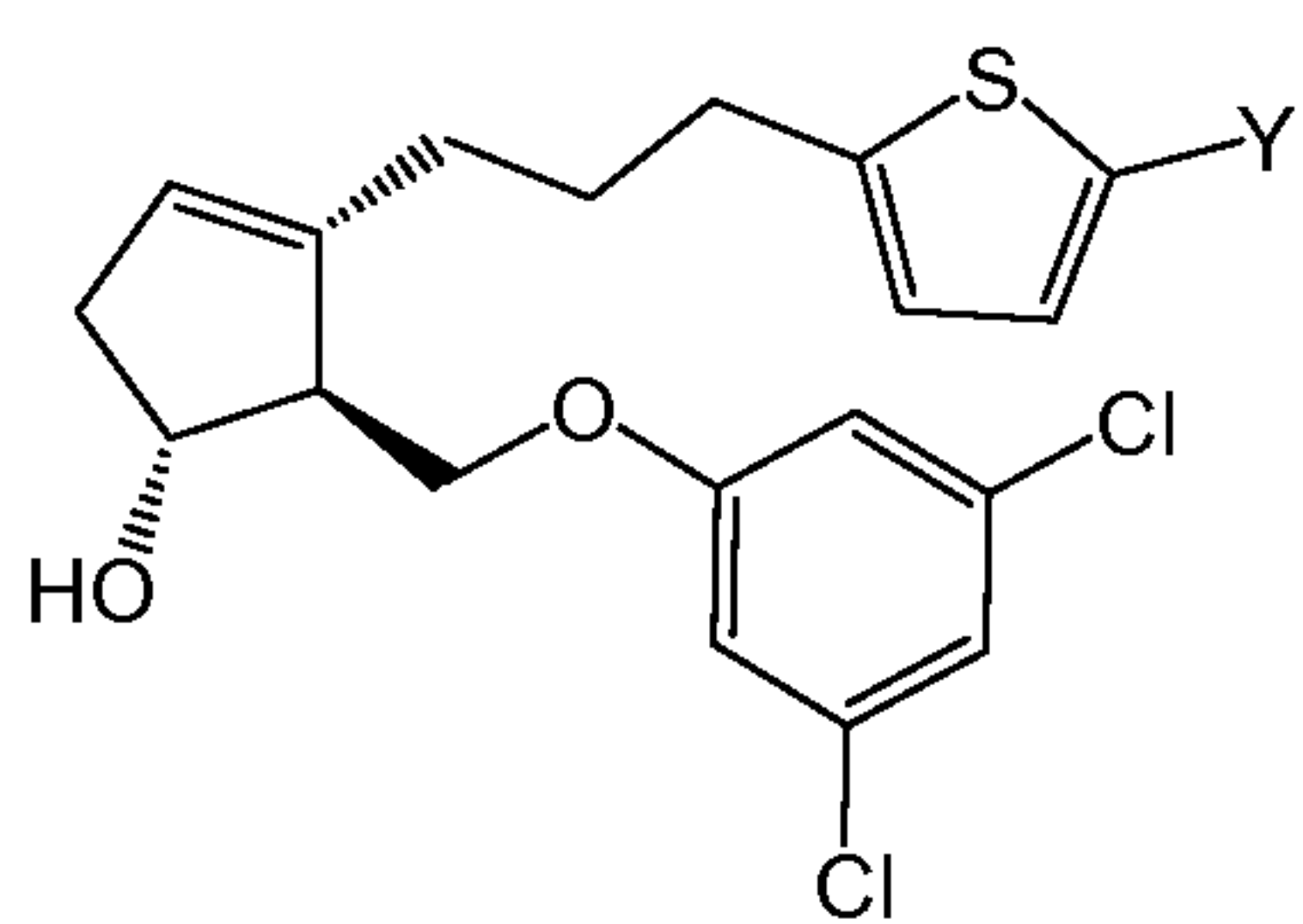
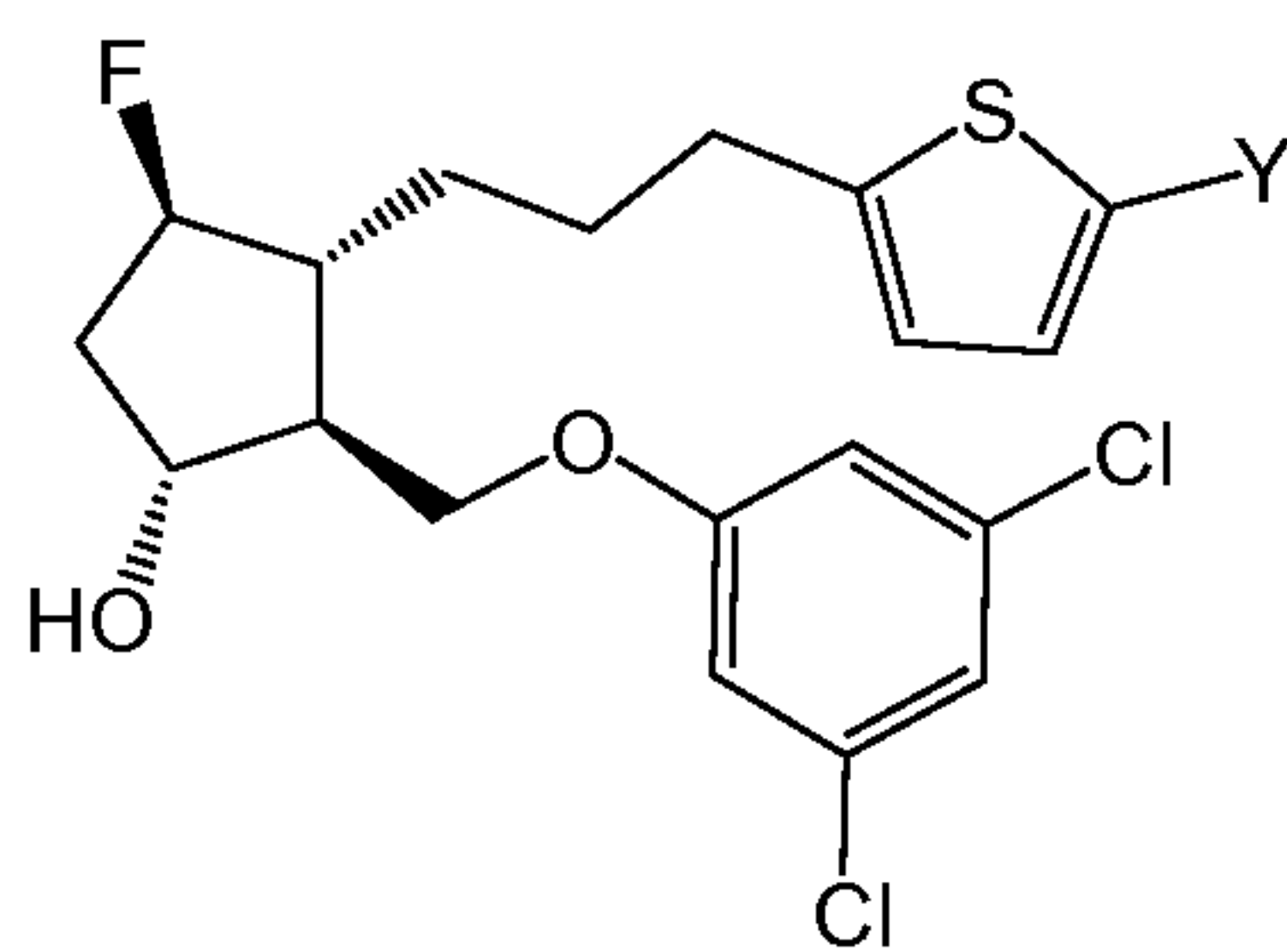
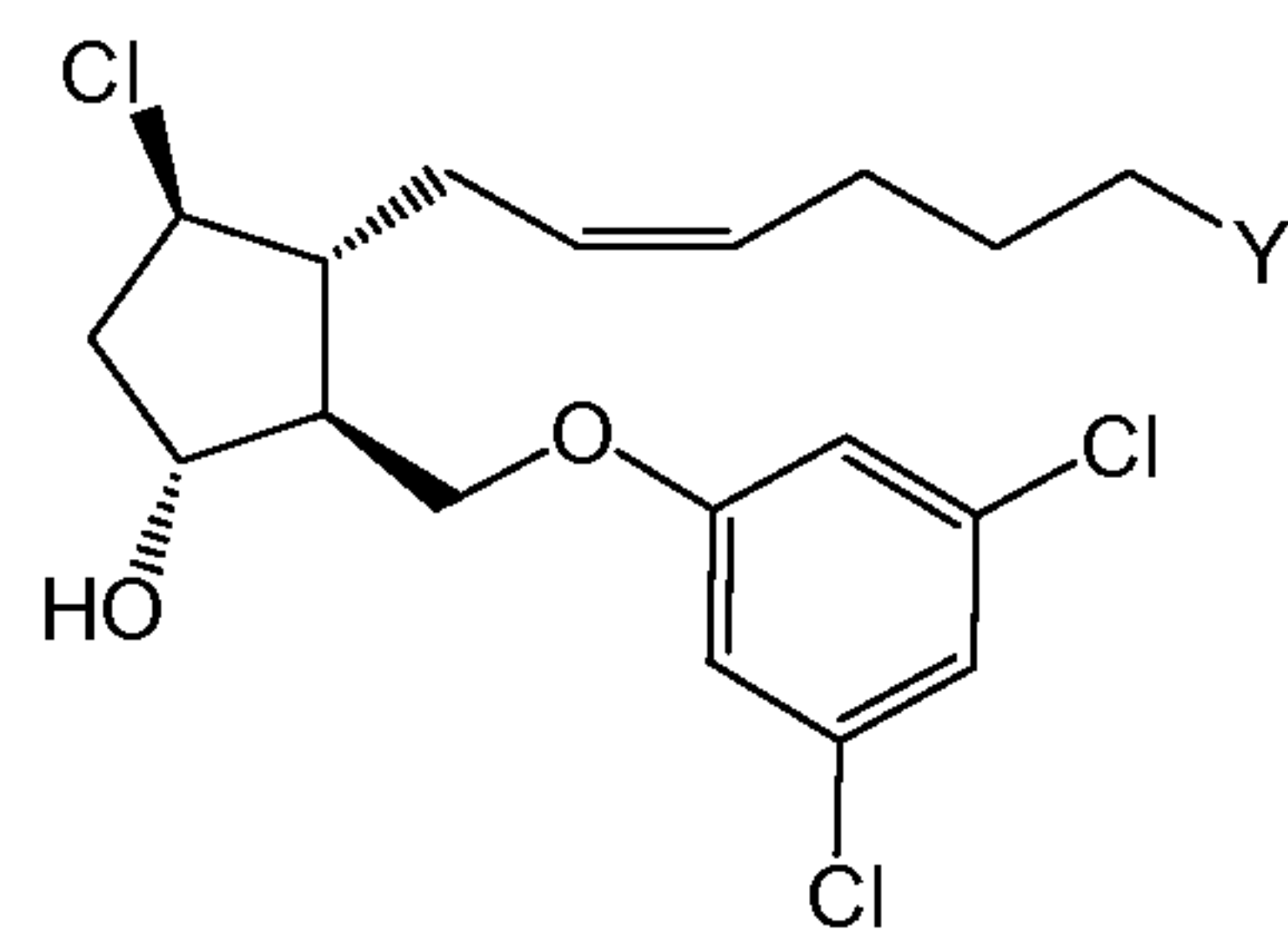
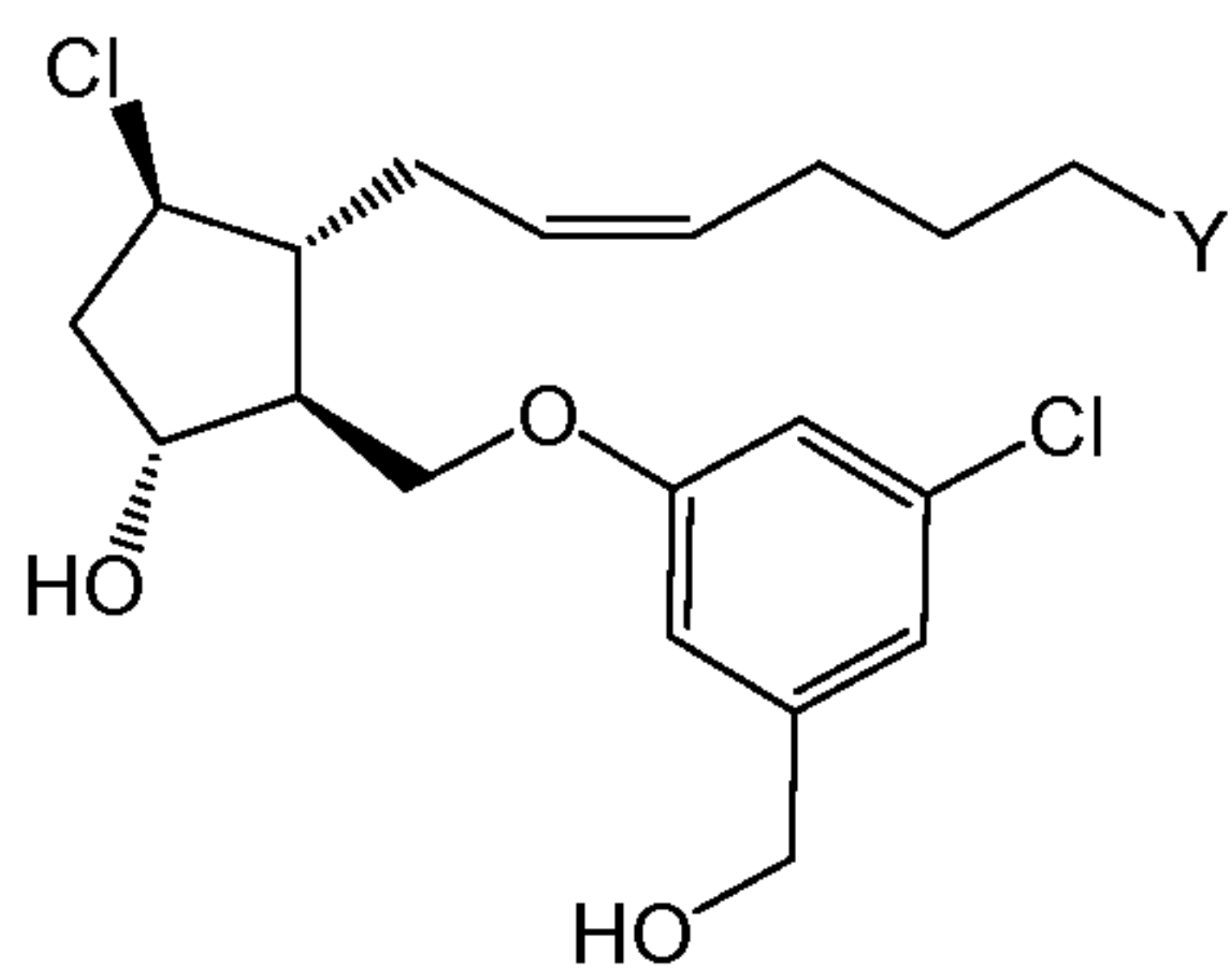
[0093] Ester **65** (5 mg, 0.011 mmol) was converted into 2 mg (41%) of compound **69** in accordance with the procedure of Scheme 5, step 3.

Step 3. **69** to give **70a** and **70b**

[0094] Compound **69** can be converted to compounds **70a** and **70b** according to Step 4 of Scheme 2.

[0095] 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.

[0096] The following non-limiting examples are compounds that are contemplated according to the present description.



In vivo testing

[0097] United States Patent No. 7,091,231 describes the methods used for these *in vivo* tests.

[0098] Compounds such as those described in the above are tested *in vivo* to measure its ability to reduce intraocular pressure. Compound **14a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[0099] Compound **14b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00100] Compound **16a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00101] Compound **16b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00102] Compound **22a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00103] Compound **22b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00104] Compound **33a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00105] Compound **33b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00106] Compound **34a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00107] Compound **34b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00108] Compound **35a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00109] Compound **35b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00110] Compound **46a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00111] Compound **46b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00112] Compound **51a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00113] Compound **51b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00114] Compound **58a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00115] Compound **58b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00116] Compound **68a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00117] Compound **68b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

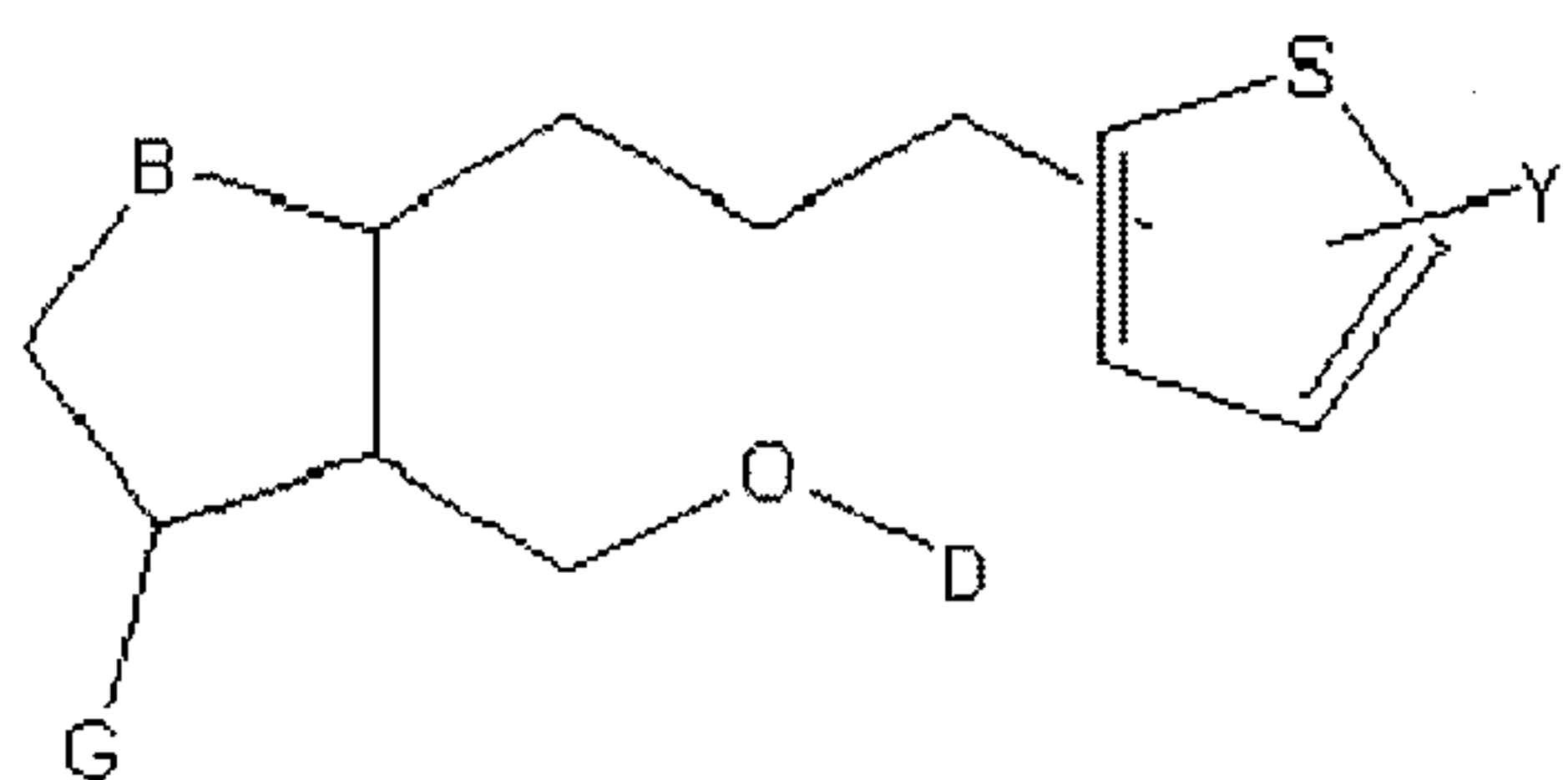
[00118] Compound **70a** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

[00119] Compound **70b** is tested in normotensive dogs. The intraocular pressure (IOP) decreases from baseline. This compound is also tested in laser-induced hypertensive monkeys, the IOP decreases from baseline.

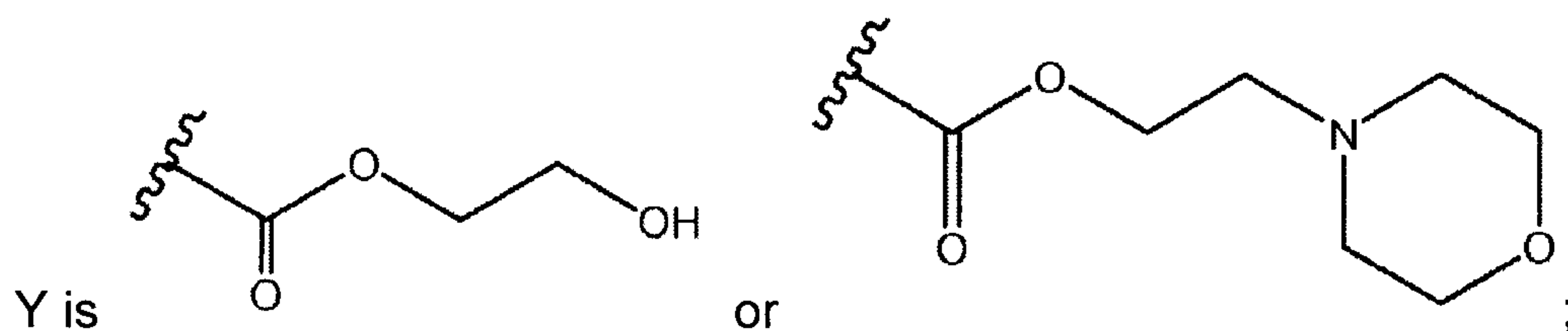
[00120] The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties 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 claims.

What is claimed is:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof;



B is C=O, CH₂, CHOH, CHCl, CHF, CHBr, or CHCN;

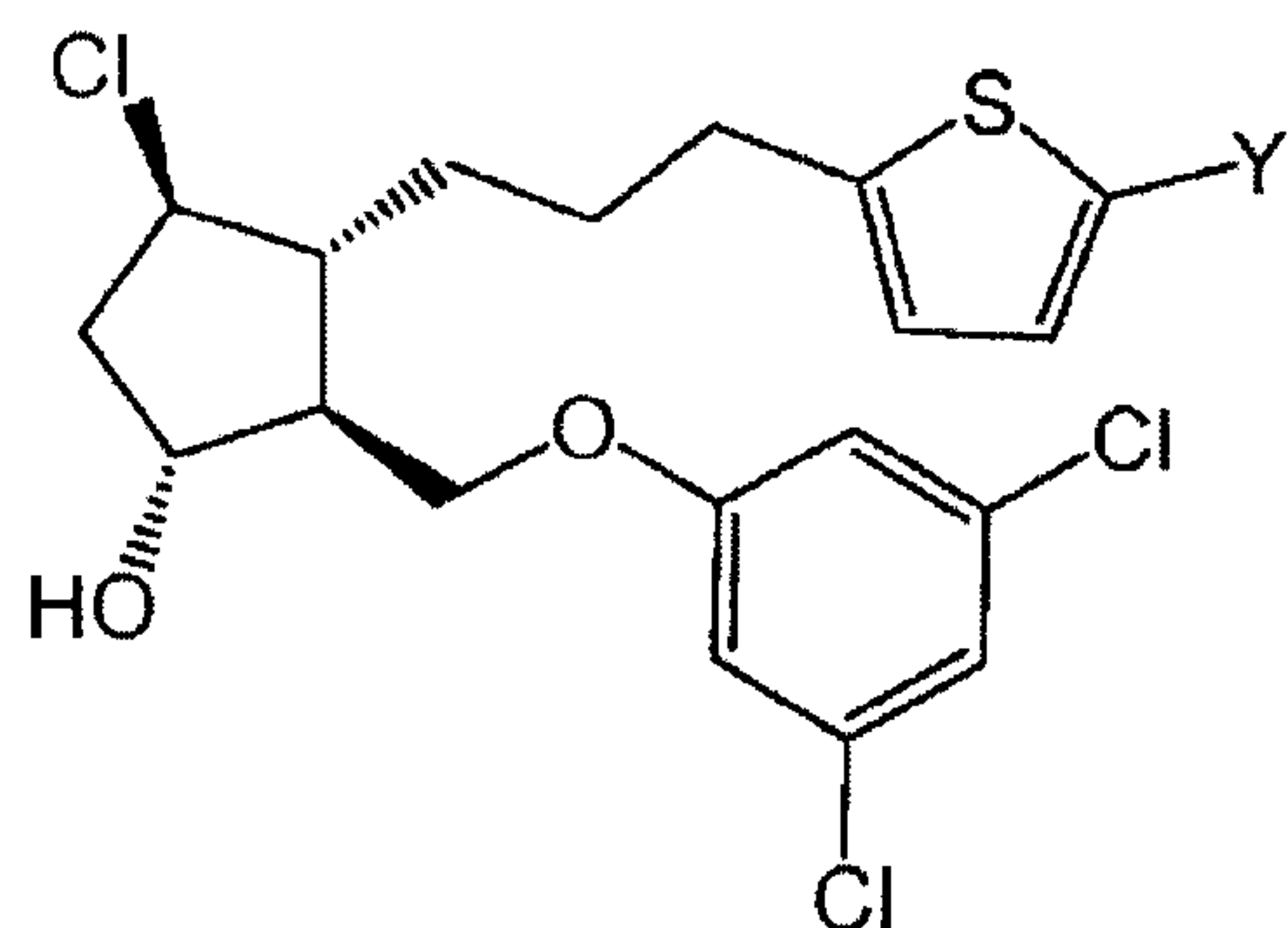
G is OH or H; and

D is substituted phenyl.

2. The compound of claim 1 wherein D is a dichloro substituted phenyl.

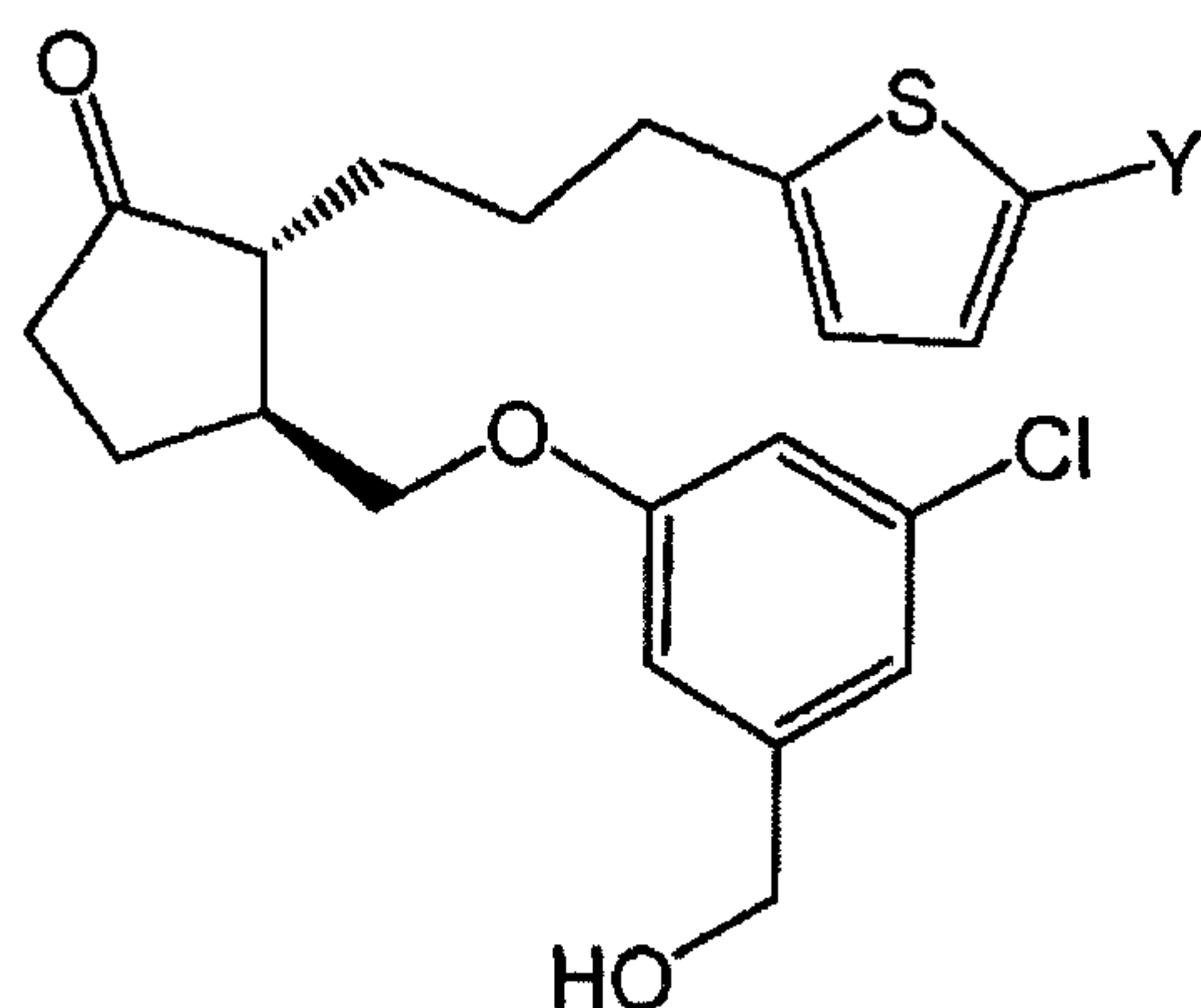
3. The compound of claim 1 wherein G is a hydroxyl.

4. The compound of claim 1 having the formula



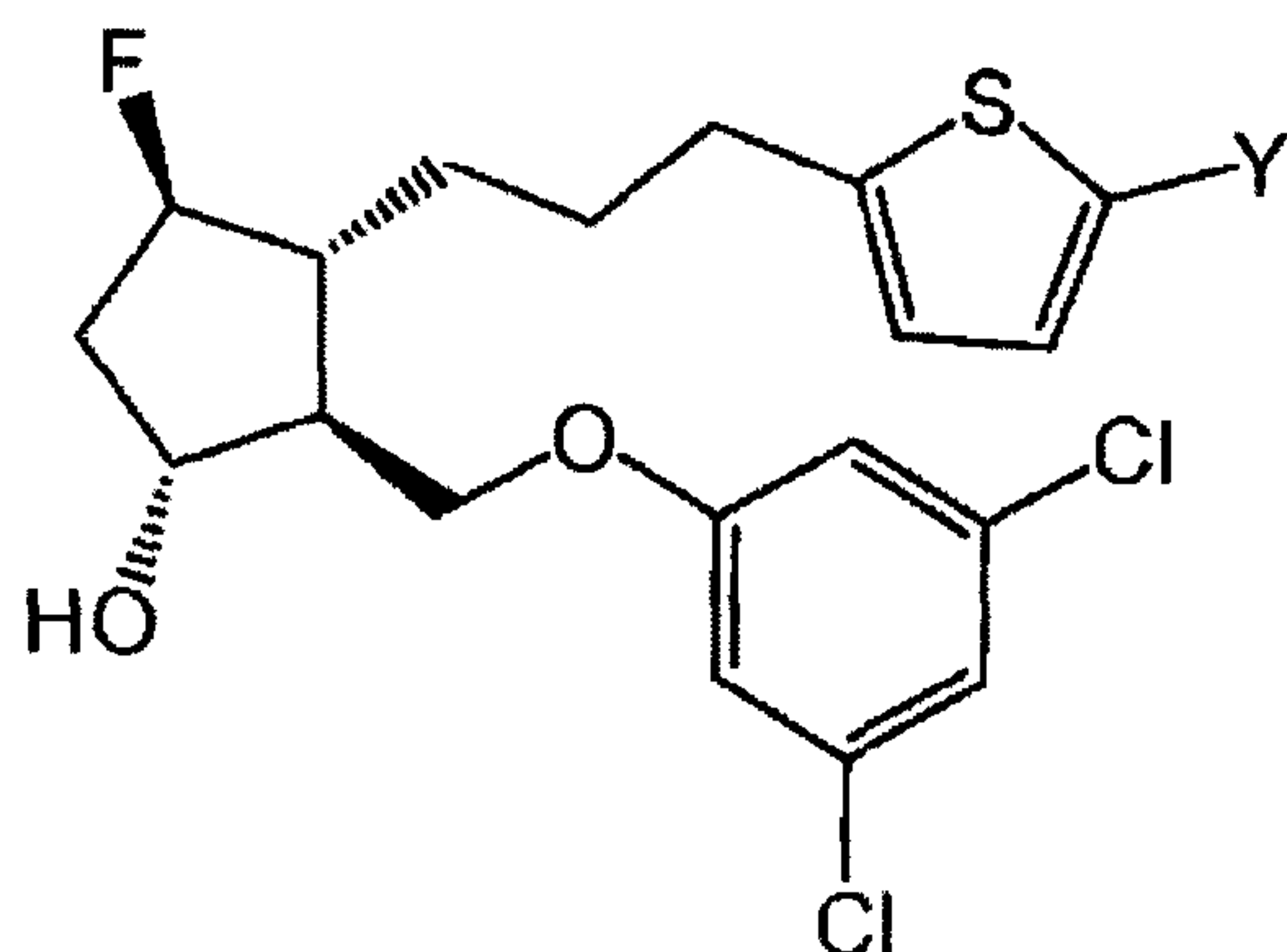
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 having the formula



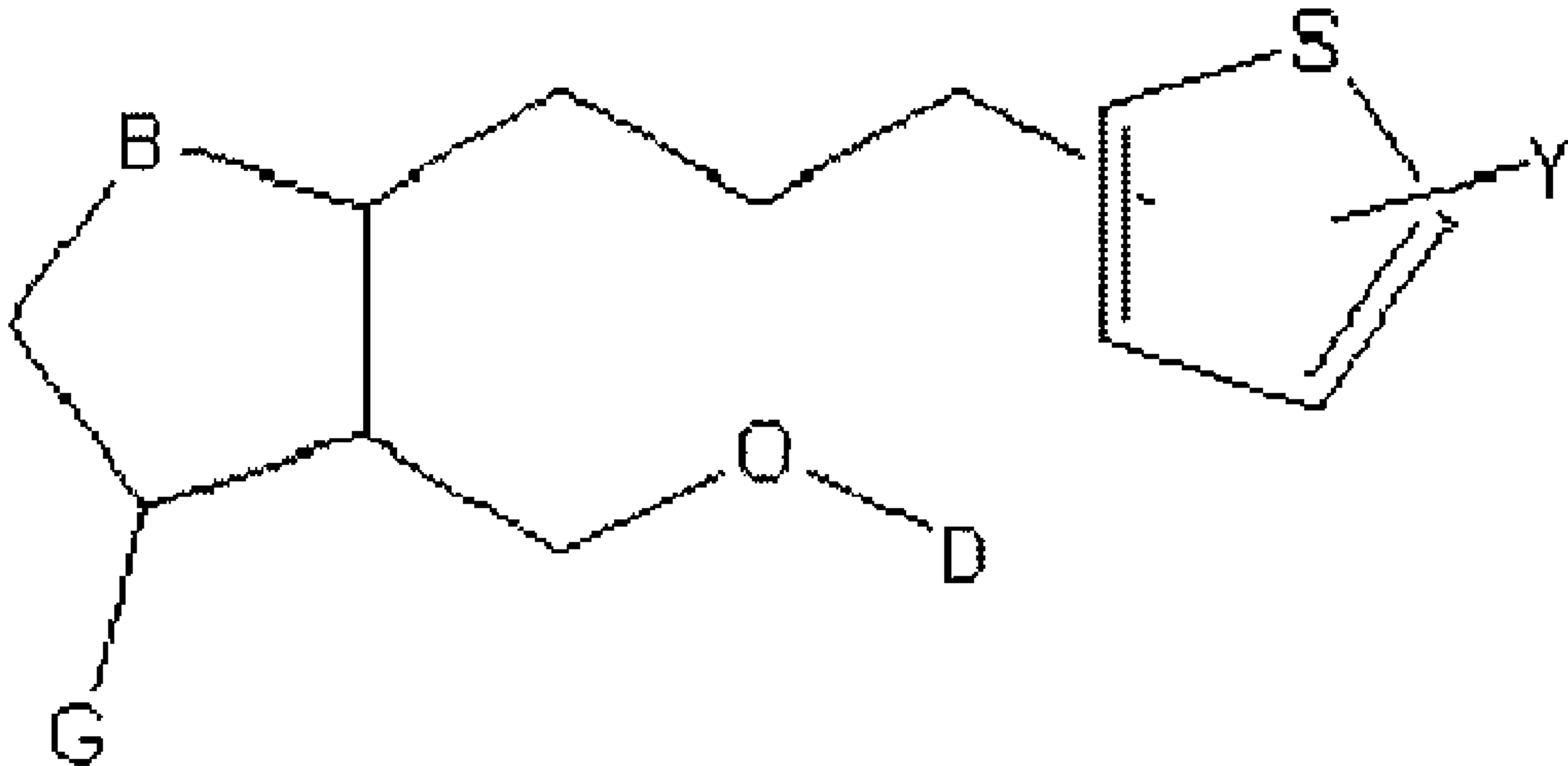
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 having the formula



or a pharmaceutically acceptable salt thereof.

7. Use of the compound defined by any one of claims 1 to 6 for treating baldness in a subject.
8. Use of the compound defined by any one of claims 1 to 6 for the production of a medicament for treating baldness in a subject.



(I)