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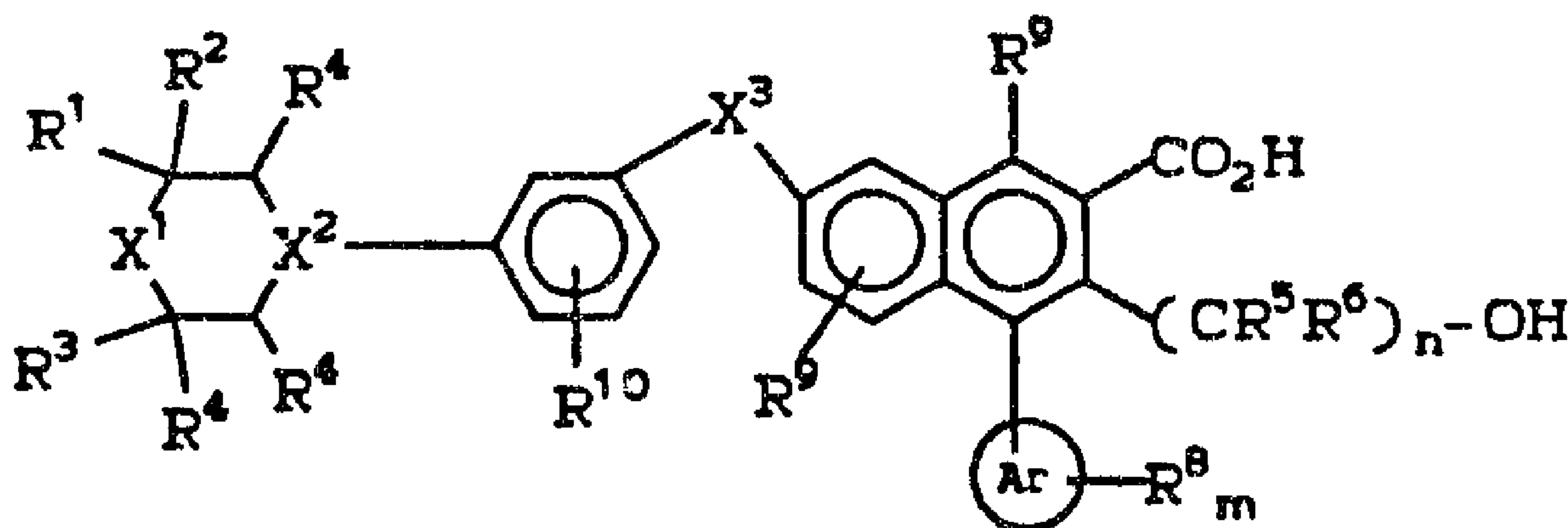
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(54) Titre : ACIDES PYRANYLPHENYLHYDROXYALKYLNAPHTHOIQUE, INHIBITEURS DE LA BIOSYNTHESE DE LEUCOTRIENE

(54) Title: PYRANYLPHENYL HYDROXYALKYLNAPHTHOIC ACIDS AS INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS



I

(57) Abrégé/Abstract:

Compounds having the formula I: (see formula I) are inhibitors of leukotriene biosynthesis. These compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis and allograft rejection and in preventing the formation of atherosclerotic plaques.

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TITLE OF THE INVENTION

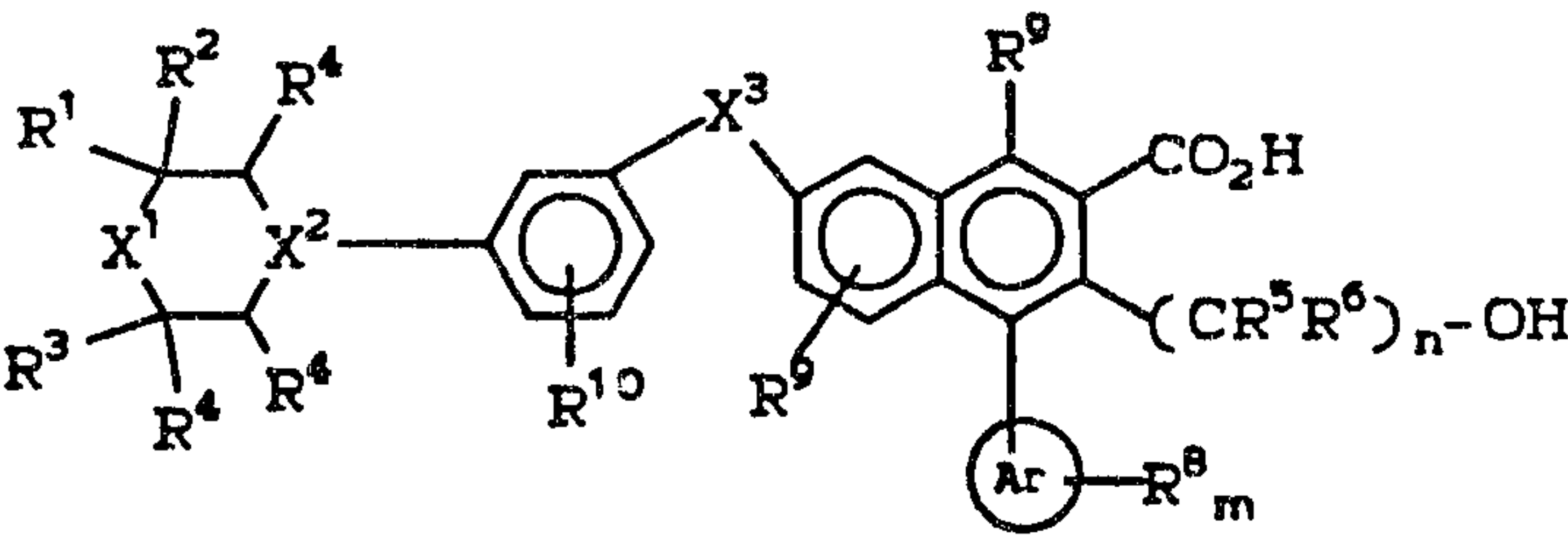
10 PYRANYLPHENYL HYDROXYALKYLNAPHTHOIC ACIDS AS
INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

ABSTRACT OF THE DISCLOSURE

Compounds having the formula I:

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I

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are inhibitors of leukotriene biosynthesis. These compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis and allograft rejection and in preventing the formation of atherosclerotic plaques.

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PYRANYLPHENYL HYDROXYALKYLNAPHTHOIC ACIDS AS
INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

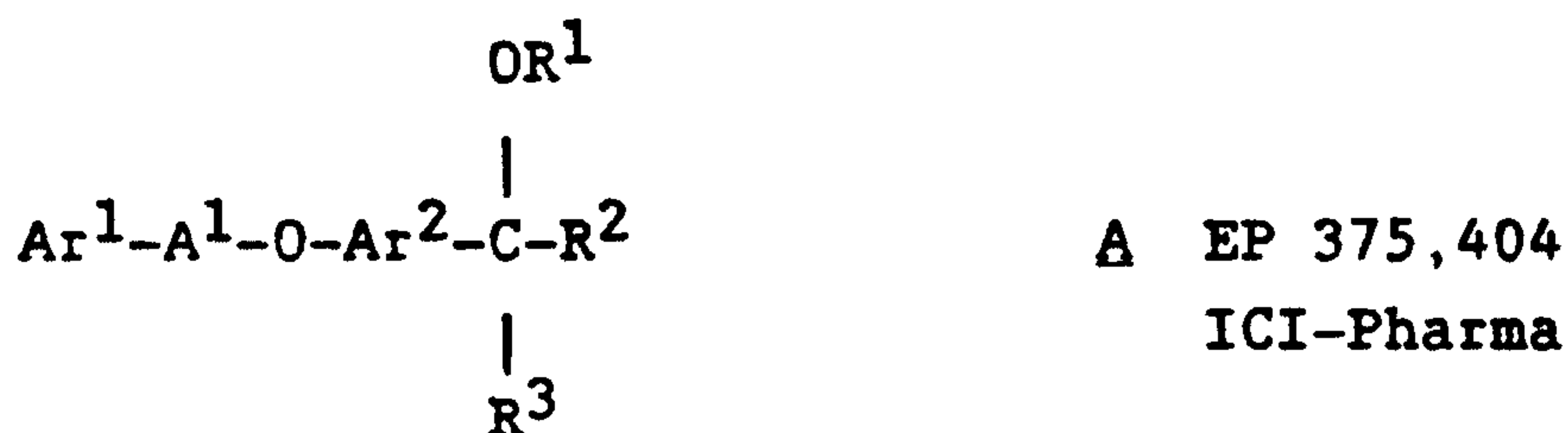
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BACKGROUND OF THE INVENTION

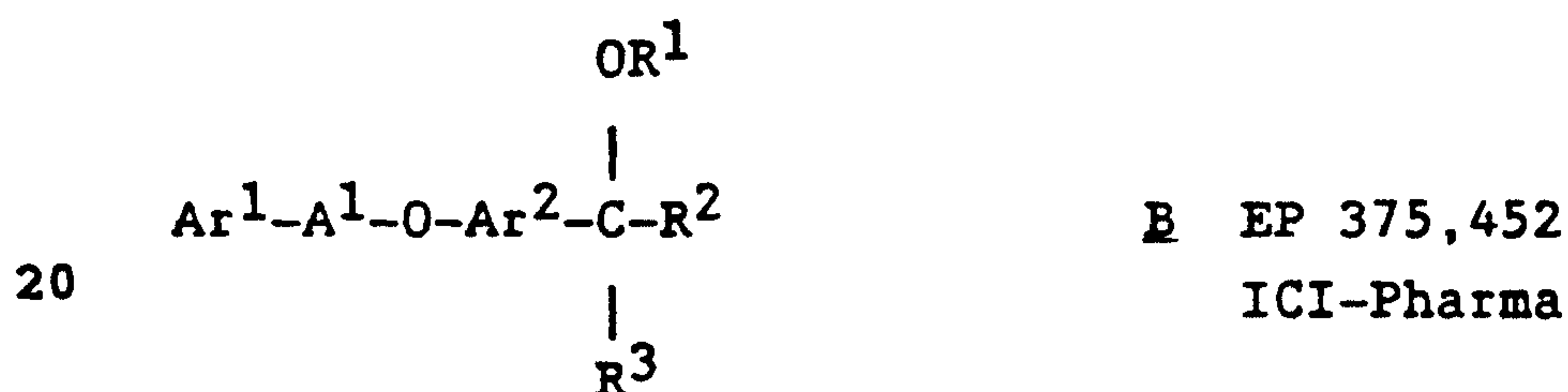
20 The leukotrienes constitute a group of
locally acting hormones, produced in living systems
from arachidonic acid. The major leukotrienes are
Leukotriene B₄ (abbreviated as LTB₄), LTC₄, LTD₄ and
LTE₄. The biosynthesis of these leukotrienes begins
with the action of the enzyme 5-lipoxygenase on
25 arachidonic acid to produce the epoxide known as
Leukotriene A₄ (LTA₄), which is converted to the
other leukotrienes by subsequent enzymatic steps.
Further details of the biosynthesis as well as the
metabolism of the leukotrienes are to be found in the
30 book Leukotrienes and Lipoxygenases, ed. J. Rokach,
Elsevier, Amsterdam (1989). The actions of the
leukotrienes in living systems and their contribution
to various diseases states are also discussed in the
book by Rokach.

EP 375,404 (27 June 1990) describes certain naphthalene-containing heterocyclic ethers of structure A which are inhibitors of the enzyme 5-lipoxygenase. EP 375,452 (27 June 1990) describes naphthalene-containing hydrocarbon ethers of structure B which are reported to possess the same activity. Both of these series of compounds differ significantly from the present invention in that they lack the major aryl substituent.

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SUMMARY OF THE INVENTION

The present invention relates to pyranylphenyl hydroxyalkylnaphthoic acids having activity as leukotriene biosynthesis inhibitors, to methods for their preparation, and to methods and pharmaceutical formulations for using these compounds in mammals (especially humans).

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Because of their activity as leukotriene biosynthesis inhibitors, the compounds of the present invention are useful as anti-asthmatic, anti-allergic,

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wherein:

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$\mathbf{x}^1$ is $\mathbf{O}$, $\mathbf{S}$, $\mathbf{S}(\mathbf{O})$, $\mathbf{S}(\mathbf{O})_2$, or $\mathbf{CH}_2$;

x^2 is N, N(O), C(OR⁷), or C(R⁷);

x^3 is CH₂O, OCH₂, or CH₂CH₂;

(Ar) is phenyl or 1- or 2-naphthyl;

m is 0, 1, or 2;

5 n is 1 or 2;

or the pharmaceutically acceptable salts thereof.

10 It will be obvious to one skilled in the art that if R⁵ is OH or lower alkoxy on the same carbon atom as the OH group of I, the elements of water or an alcohol may be lost to give an aldehyde or ketone.

Definitions

15 The following abbreviations have the indicated meanings:

	Ac	=	acetyl
	Bn	=	benzyl
	i-Pr	=	isopropyl
20	n-Pr	=	normal propyl
	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
25	Et	=	ethyl
	Me	=	methyl
	Ph	=	phenyl
	RIA	=	radio immuno assay
	TFAA	=	trifluoroacetic anhydride
30	AIBN	=	azoisobutyronitrile
	LDA	=	lithium diisopropylamide

	DMSO	=	dimethylsulfoxide
	Ts	=	p-toluenesulfonate = tosylate
	Ms	=	methanesulfonate = mesylate
	Et ₃ N	=	triethylamine
5	DMF	=	N,N-dimethylformamide
	Tf	=	trifluoromethanesulfonyl
	DHP	=	dihydropyran
	DIPHOS	=	1,2-bis(diphenylphosphino)-ethane
10	DMAP	=	4-dimethylaminopyridine
	NBS	=	N-bromosuccinimide
	THP	=	tetrahydropyran
	PCC	=	pyridinium chlorochromate

15 Alkyl is intended to include linear and branched structures and combinations thereof.

"Alkyl" includes "lower alkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, 20 nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl-4-propylnonyl, and the like.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups 25 include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, and the like.

"Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups 30 include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

Halogen means F, Cl, Br, and I.

It is intended that the definitions of any substituent (e.g., R^4 , R^7 , etc.) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, $-(CR^5R^6)_2-$ represents CH_2CH_2 , $CH(CH_3)CH_2$, $C(CH_3)_2CH(CH_3)$, etc.

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium

salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

The ability of the compounds of Formula I to inhibit biosynthesis of the leukotrienes makes them
5 useful for preventing or reversing the symptoms induced by the leukotrienes in a human subject. This inhibition of the mammalian biosynthesis of leukotrienes indicates that the compounds and pharmaceutical compositions thereof are useful to treat,
10 prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjunctivitis, and the like, 3)
15 inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, atopic eczema, and the like, 6) cardiovascular disorders such as angina, formation of atherosclerotic plaques, myocardial ischemia, hypertension,
20 platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology and 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from
25 chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as
30 Interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small- and large-airway diseases, 15) cholecystitis, and 16) multiple sclerosis.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion; dysmenorrhea; ischemia; noxious agent-induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also act as inhibitors of tumor metastasis and exhibit cytoprotective action.

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay and are described in EP 140,684.

Dose Ranges

5 The magnitude of prophylactic or therapeutic
dose of a compound of Formula I will, of course, vary
with the nature of the severity of the condition to
be treated and with the particular compound of
Formula I and its route of administration. It will
also vary according to the age, weight and response
of the individual patient. In general, the daily
10 dose range for anti-asthmatic, anti-allergic or
anti-inflammatory use and generally, uses other than
cytoprotection, lie within the range of from about
0.001 mg to about 100 mg per kg body weight of a
mammal, preferably 0.01 mg to about 10 mg per kg, and
15 most preferably 0.1 to 1 mg per kg, in single or
divided doses. On the other hand, it may be
necessary to use dosages outside these limits in some
cases.

20 For use where a composition for intravenous
administration is employed, a suitable dosage range
for anti-asthmatic, anti-inflammatory or
anti-allergic use is from about 0.001 mg to about 25
mg (preferably from 0.01 mg to about 1 mg) of a
compound of Formula I per kg of body weight per day
25 and for cytoprotective use from about 0.1 mg to about
100 mg (preferably from about 1 mg to about 100 mg
and more preferably from about 1 mg to about 10 mg)
of a compound of Formula I per kg of body weight per
day.

30 In the case where an oral composition is
employed, a suitable dosage range for anti-asthmatic,
anti-inflammatory or anti-allergic use is, e.g. from

about 0.01 mg to about 100 mg of a compound of
Formula I per kg of body weight per day, preferably
from about 0.1 mg to about 10 mg per kg and for
cytoprotective use from 0.1 mg to about 100 mg
5 (preferably from about 1 mg to about 100 mg and more
preferably from about 10 mg to about 100 mg) of a
compound of Formula I per kg of body weight per day.

For the treatment of diseases of the eye,
ophthalmic preparations for ocular administration
10 comprising 0.001-1% by weight solutions or
suspensions of the compounds of Formula I in an
acceptable ophthalmic formulation may be used.

The exact amount of a compound of the
Formula I to be used as a cytoprotective agent will
15 depend on, inter alia, whether it is being
administered to heal damaged cells or to avoid future
damage, on the nature of the damaged cells (e.g.,
gastrointestinal ulcerations vs. nephrotic necrosis),
and on the nature of the causative agent. An example
20 of the use of a compound of the Formula I in avoiding
future damage would be co-administration of a
compound of the Formula I with a non-steroidal
anti-inflammatory drug that might otherwise cause
such damage (for example, indomethacin). For such
25 use, the compound of Formula I is administered from
30 minutes prior up to 30 minutes after
administration of the NSAID. Preferably it is
administered prior to or simultaneously with the
NSAID, (for example, in a combination dosage form).

Pharmaceutical Compositions

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers.

5 The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI)
10 aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

Suitable topical formulations of a compound of Formula I include transdermal devices, aerosols,
15 creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to
20 conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral
25 dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for
30 example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline

cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosures of which are hereby incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with

liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally
5 with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or
10 dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 2.5 mg to about 500 mg of the active ingredient and
15 each cachet or capsule contains from about 2.5 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

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<u>Injectable Suspension (I.M.)</u>	<u>mg/ml</u>
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
25 Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to a total volume of 1 ml	

30

	<u>Tablet</u>	<u>mg/tablet</u>
	Compound of Formula I	25
	Microcrystalline Cellulose	415
	Providone	14.0
5	Pregelatinized Starch	43.5
	Magnesium Stearate	<u>2.5</u>
		500
	<u>Capsule</u>	<u>mg/capsule</u>
10	Compound of Formula I	25
	Lactose Powder	573.5
	Magnesium Stearate	<u>1.5</u>
		600
15	<u>Aerosol</u>	<u>Per canister</u>
	Compound of Formula I	24 mg
	Lecithin, NF Liquid Concentrate	1.2 mg
	Trichlorofluoromethane, NF	4.025 gm
	Dichlorodifluoromethane, NF	12.15 gm

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Combinations with Other Drugs

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a

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compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200.

5 Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

- 10 (1) the propionic acid derivatives;
(2) the acetic acid derivatives;
(3) the fenamic acid derivatives;
(4) the biphenylcarboxylic acid derivatives;

and

- 15 (5) the oxicams;

or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, 20 flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, prano-profen, suprofen, tiaprofenic acid, and tioxaprofen. Structurally related propionic acid derivatives having similar analgesic and 25 anti-inflammatory properties are also intended to be included in this group.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free 30 $-\text{CH}(\text{CH}_3)\text{COOH}$ or $-\text{CH}_2\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-\text{CH}(\text{CH}_3)\text{COO}^-\text{Na}^+$ or $-\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+$),

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typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

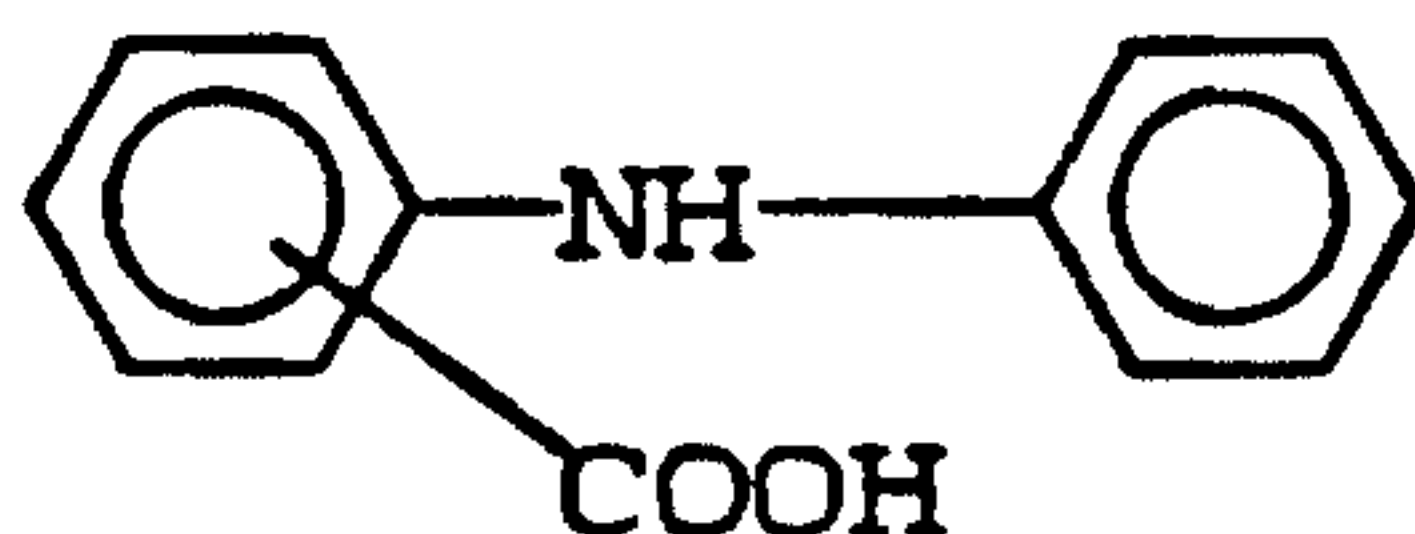
5 The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, acetaminophen, alclofenac, clidac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac. Structurally
10 related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal
15 anti-inflammatory drugs having a free $-\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic
20 ring system.

The fenamic acid derivatives which may be used comprise: flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having
25 similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic
30 structure:

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which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO⁻Na⁺.

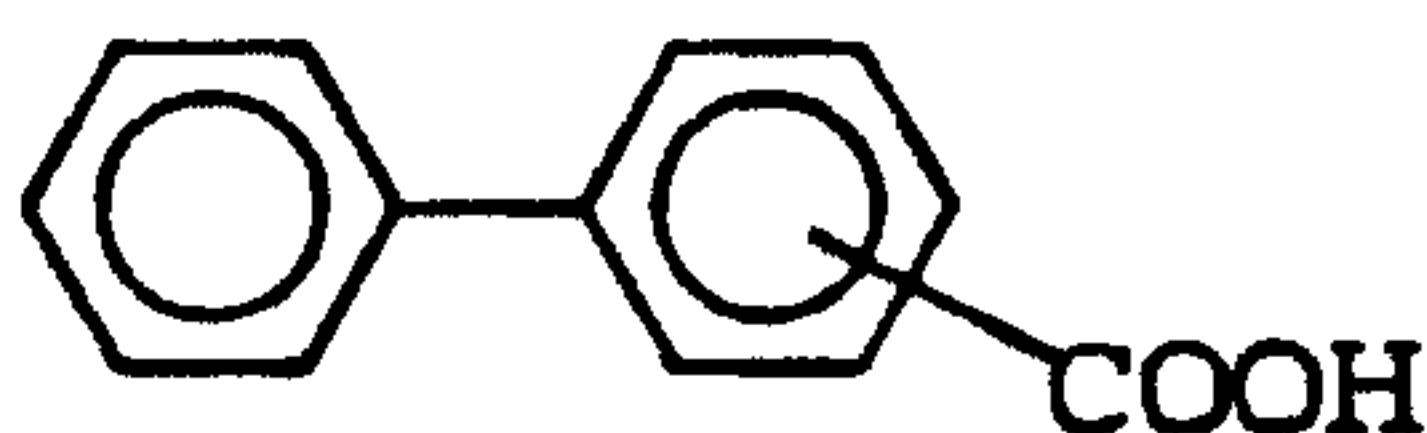
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The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

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Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

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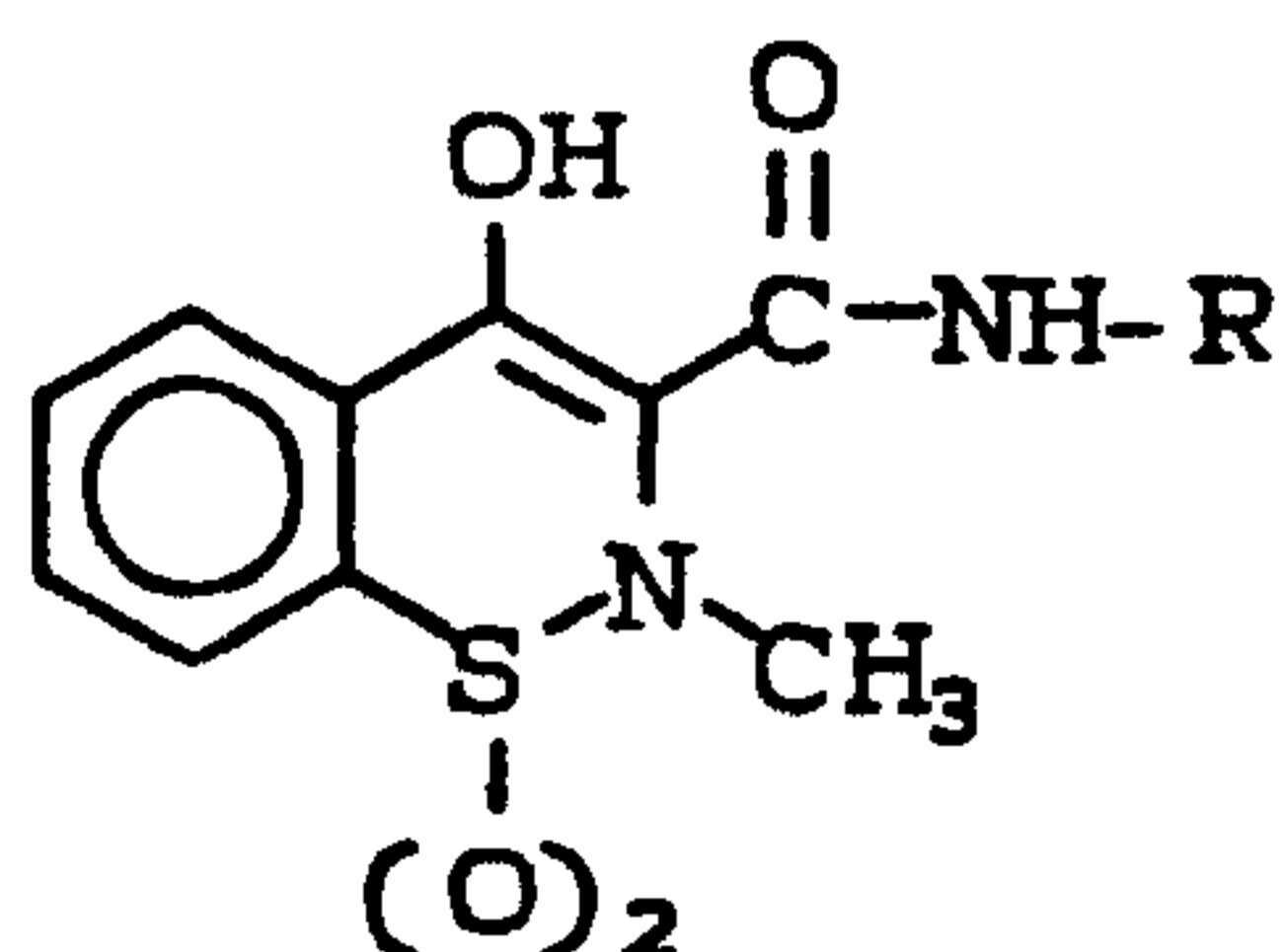


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which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO⁻Na⁺.

The oxicams which can be used in the present invention comprise: isoxicam, piroxicam, sudoxicam and tenoxican. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:



wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used:

amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydanine, beprozin, broperamole, bufezolac, cinmetacin, ciproquazone, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclorac, fendosal, fenflumizole, feprazone, floctafenine, flunixin, flunoxaprofen, fluproquazone, fopirtoline, fosfosal, furclopofen, glucametacin, guaimesal, ibuproxam, isofezolac, isonixim,

isoprofen, isoxicam, lefetamine HCl, leflunomide,
lofemizole, lonazolac calcium, lotifazole,
loxoprofen, lysin clonixinate, meclofenamate sodium,
mesecclazone, nabumetone, nictindole, nimesulide,
5 orpanoxin, oxametacin, oxapadol, perisoxal citrate,
pimeprofen, pimetacin, piroxan, pirazolac,
pirfenidone, proglumetacin maleate, proquazone,
pyridoxiprofen, sudoxicam, talmetacin, talniflumate,
tenoxicam, thiazolinobutazone, thielavin B, tiaramide
10 HCl, tiflamizole, timegadine, tolpadol, tryptamid and
ufenamate.

The following NSAIDs, designated by company
code number (see e.g., Pharmaprojects), may also be
used:

15 480156S, AA861, AD1590, AFP802, AFP860, AI77B, AP504,
AU8001, BPPC, BW540C, CHINOIN 127, CN100, EB382,
EL508, F1044, GV3658, ITF182, KCNTEI6090, KME4,
LA2851, MR714, MR897, MY309, ONO3144, PR823, PV102,
PV108, R830, RS2131, SCR152, SH440, SIR133, SPAS510,
20 SQ27239, ST281, SY6001, TA60, TAI-901 (4-benzoyl-1-
indancarboxylic acid), TVX2706, U60257, UR2301, and
WY41770.

Finally, NSAIDs which may also be used
include the salicylates, specifically acetyl
25 salicylic acid and the phenylbutazones, and
pharmaceutically acceptable salts thereof.

In addition to indomethacin, other preferred
NSAIDs are acetyl salicylic acid, diclofenac,
fenbufen, fenoprofen, flurbiprofen, ibuprofen,
30 ketoprofen, naproxen, phenylbutazone, piroxicam,
sulindac, and tolmetin.

Pharmaceutical compositions comprising the Formula I compounds may also contain inhibitors of the biosynthesis of the leukotrienes such as are disclosed in EP 138,481 (April 24, 1985), EP 115,394 (August 8, 1984), EP 136,893 (April 10, 1985), and EP 140,709 (May 8, 1985), which are hereby incorporated herein by reference.

The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP 106,565 (April 25, 1984) and EP 104,885 (April 4, 1984) which are hereby incorporated herein by reference and others known in the art such as those disclosed in EP Application Nos. 56,172 (July 21, 1982) and 61,800 (June 10, 1982); and in U.K. Patent Specification No. 2,058,785 (April 15, 1981), which are hereby incorporated herein by reference.

Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, prostaglandin antagonists such as those disclosed in EP 11,067 (May 28, 1980) or thromboxane antagonists such as those disclosed in U.S. Pat. 4,237,160. They may also contain histidine decarboxylase inhibitors such as α -fluoromethyl-histidine, described in U.S. Pat. 4,325,961. The compounds of the Formula I may also be advantageously combined with an H₁- or H₂-receptor antagonist, such as for instance acetamazole, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981), benadryl, cimetidine, famotidine, framamine, histadyl, phenergan, ranitidine, terfenadine and like compounds, such as those disclosed in U.S. Patent

Nos. 4,283,408; 4,362,736; and 4,394,508. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Compounds of
5 Formula I may also be usefully combined with most cell stabilizing agents, such as 1,3-bis(2-carboxy-chromon-5-yloxy)-2-hydroxypropane and related compounds described in British Patent Specifications 1,144,905 and 1,144,906. Another useful
10 pharmaceutical composition comprises the Formula I compounds in combination with serotonin antagonists such as methysergide, the serotonin antagonists described in Nature, Vol. 316, pages 126-131, 1985, and the like. Each of the references referred to in
15 this paragraph is hereby incorporated herein by reference.

Other advantageous pharmaceutical compositions comprise the Formula I compounds in combination with anti-cholinergics such as
20 ipratropium bromide, bronchodilators such as the beta agonist salbutamol, metaproterenol, terbutaline, fenoterol and the like, and the anti-asthmatic drugs theophylline, choline theophyllinate and enprofylline, the calcium antagonists nifedipine,
25 diltiazem, nitrendipine, verapamil, nimodipine, felodipine, etc. and the corticosteroids, hydrocortisone, methylprednisolone, betamethasone, dexamethasone, beclomethasone, and the like.

30

Methods of Synthesis

Compounds of the formula I of the present invention may be prepared according to the synthetic routes outlined in the Schemes I to VII and by following the methods described herein.

SCHEME I

The lactone intermediate IX of Scheme I may be prepared, in a multistep sequence, from 3-benzyl-oxy benzaldehyde (II). The aldehyde II is firstly converted to the dibromide product III by treatment with CBr_4 and triphenylphosphine in an organic solvent such as CH_2Cl_2 . Subsequent treatment of III with base such as n-butyllithium in an organic solvent such as THF followed by quenching with CO_2 leads to the acid IV. Conversion of IV to the ester V via the acyl chloride is achieved by treatment of IV with oxalyl chloride in an organic solvent such as toluene and DMF followed by addition of a 3-aryl-2-propyn-1-ol and a base such as Et_3N in an organic solvent such as THF. The intramolecular cyclisation of the ester V to provide VI is achieved by heating in an organic acid such as acetic acid. From this reaction, two side-products (VII and VIII) may also be isolated in varying amounts. The debenzylation process is achieved under acidic conditions such as HCl in hot acetic acid leading to the lactone intermediate IX.

SCHEME II

5 The lactone intermediate IX may also be prepared from a 2-bromo-5-benzyloxy benzaldehyde dimethyl acetal X as outlined in Scheme II. The bromo derivative X is converted to the alcohol XI by treatment with a base such as n-butyl lithium in an organic solvent such as hexane followed by the addition of an aryl carboxaldehyde such as benzaldehyde in an organic solvent such as THF. The 10 Diels-Alder reaction is achieved by heating the alcohol XI in the presence of maleic anhydride in an organic solvent such as toluene, providing the anhydride XII. The reduction of the anhydride XII by treatment with a reducing agent such as $\text{Zn}(\text{BH}_4)_2$ in 15 an organic solvent such as DMF provides the lactone VI. The debenzylation process to provide the lactone IX is described in Scheme I.

SCHEME III

20 An alternate route may also be used to prepare the lactone intermediate IX as outlined in Scheme III. The 2-bromo-5-benzyloxybenzaldehyde XIV is firstly converted to the thioacetal XV by treatment with 1,3-propanedithiol in the presence of 25 a Lewis acid such as $\text{BF}_3/\text{Et}_2\text{O}$ in an organic solvent such as CH_2Cl_2 . The bromothioacetal XV is converted to the alcohol XVI under treatment with a base such as n-butyllithium in an organic solvent such as hexane followed by the addition of an aryl carbox- 30 aldehyde such as benzaldehyde in an organic solvent such as THF. Heating the alcohol XVI in the presence of maleic anhydride in an organic solvent such as

toluene, provides the Diels-Alder adduct XII. The final conversion of the anhydride XII to the lactone intermediate IX via the benzylated lactone VI is described above.

5

SCHEME IV

Another route which may be used to provide the lactone intermediate IX is outlined in Scheme IV. The bromoacetal X is firstly converted to the
10 ketoacetal XVII by treatment with a base such as n-butyllithium in an organic solvent such as hexane in the presence of CuBr/SMe₂ followed by the addition of an aroyl halide such as benzoyl chloride in an organic solvent such as THF. The ketoacetal XVII is
15 hydrolysed to the ketoaldehyde XVIII by acidic treatment such as HCl in acetone-water. The Diels-Alder reaction is achieved by heating the ketone XVIII in the presence of an N-arylmaleimide such as N-phenylmaleimide and triethylphosphite in an
20 organic solvent such as benzene, providing the imide XIX. The imide XIX is hydrolysed to the dicarboxylic acid XX under basic conditions such as NaOH in water, then after acidification with acid, such as HCl in water, and treatment with trifluoroacetic anhydride,
25 the anhydride XII is isolated. The final conversion of XII to the lactone intermediate IX is described in Scheme II.

SCHEME V

30

The preparation of compounds of Formula I (wherein X³ = -CH₂O-) is described in Scheme V. Coupling of the phenol lactone IX with the appropriate

benzyl halide XXI such as 3-[4-(4-methoxy)tetrahydro-
pyranyl]benzyl bromide in an organic solvent such as
DMF using an inorganic base such as K_2CO_3 provides
the lactone XXII.

5

SCHEME VI

The synthesis of compounds of Formula I
(wherein $X^3 = -OCH_2-$) is described in Scheme VI. The
phenol lactone IX is converted to the triflate XXIII
10 by treatment with trifluoromethanesulfonic anhydride
in the presence of an organic base such as pyridine
in a solvent such as CH_2Cl_2 . Subsequent treatment of
XXIII in a solvent such as DMSO/methanol with an
organic base such as triethylamine, a phosphine such
15 as 1,1'-bis(diphenylphosphino)ferrocene, a
palladium(II) salt such as palladium(II)acetate under
an atmosphere of carbon monoxide leads to the ester
XXIV. The hydrolysis of the ester XXIV is achieved
using an inorganic base such as lithium hydroxide in
20 water and the resulting acid XXV is reduced to the
alcohol XXVI by treatment with a chloroformate such
as isopropyl chloroformate in the presence of an
organic base such as triethylamine in an organic
solvent such as THF, followed by addition of a
25 reducing agent such as sodium borohydride in water.
The alcohol XXVI is then converted to the halide
XXVII by treatment with triphenylphosphine, imidazole
and CBr_4 in an organic solvent such as CH_2Cl_2 .
Coupling of halide XXVII with the appropriate
30 phenol XXVIII such as 3-[4-(4-methoxy)tetrahydro-
pyranyl]phenol in an organic solvent such as DMF
using an inorganic base such as K_2CO_3 provides the
lactone XXIX.

SCHEME VII

Scheme VII illustrates the conversion of lactone XXII (Scheme V) and lactone XXIX (Scheme VI) to lactone XXXI. Lactones XXII and XXIX can be alkylated at the methylene group as shown by treatment with a strong base such as lithium diisopropylamide in an organic solvent such as THF, followed by quenching with an alkyl halide such as methyl iodide. A second alkylation may be achieved by using the same conditions. Conversion of lactones XXII and XXIX to lactone XXXI (wherein $R^5 = OH$, $R^6 = H$) may be achieved by an hydrolysis process using an inorganic base such as NaOH in a solvent such as EtOH/H₂O to provide the carboxylate salt XXX, followed by an oxidation step using an oxidizing agent such as pyridinium chlorochromate in an organic solvent such as CH₂Cl₂.

The hydrolysis of lactones XXII (Scheme V), XXIX (Scheme IV) and XXXI (Scheme VII) using an inorganic base such as NaOH in a solvent such as EtOH/H₂O provides compounds of Formula I of the present invention. It will be evident to one skilled in the art that a variety of cationic salt forms of I can be prepared in this way or by cation exchange processes.

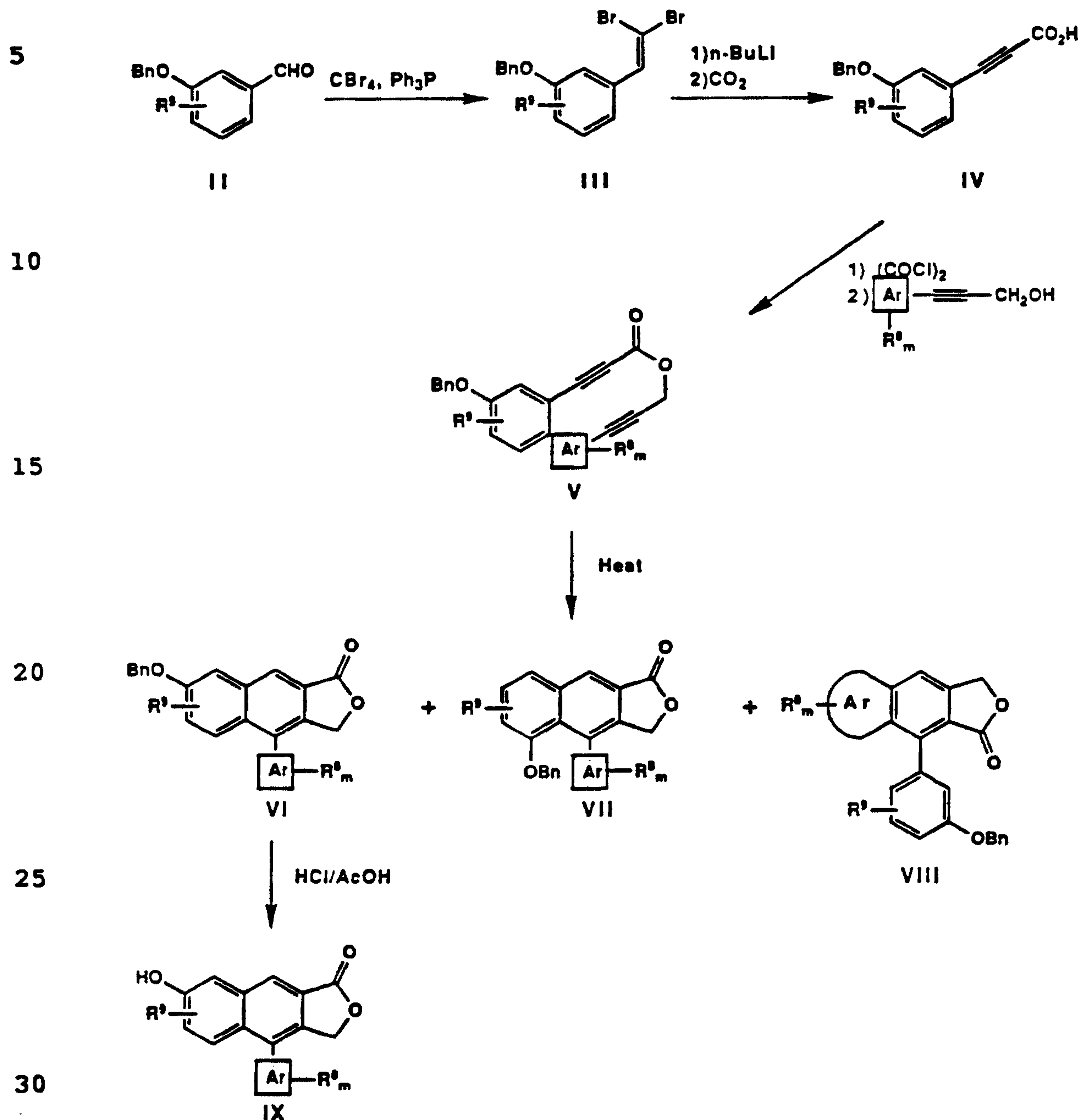
Lactone XXXI ($R^5 = OH$, $R^6 = H$) may be reacted with a lower alkyl Grignard or lithium reagent to prepare XXXI, wherein $R^5 = \text{lower alkyl}$, $R^6 = H$.

SCHEME VIII

Another alternative route which may be used to prepare the lactone IX is outlined in Scheme VIII. The aryl carboxaldehyde XXIX is converted to the thioacetal XXX by treatment with thiophenol in the presence of a Lewis-Acid such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in an organic solvent such as isopropyl acetate. The thioacetal XXX is then converted to the lactone XXXII by treatment with a base such as n-butyl lithium in an organic solvent such as THF followed by the successive additions of 2-(5H) furanone and the benzyloxyaryl carboxaldehyde XXXI in an organic solvent such as THF and after quenching with an acid such as HOAc. The cyclization, dehydration and debenzylation are achieved simultaneously by heating the lactone XXXII in the presence of an acid such as trifluoroacetic acid, and using thioanisole as organic solvent providing the lactone IX.

SCHEME I

PREPARATION OF LACTONE INTERMEDIATES (METHOD A)



SCHEME II

PREPARATION OF LACTONE INTERMEDIATES (METHOD B)

5

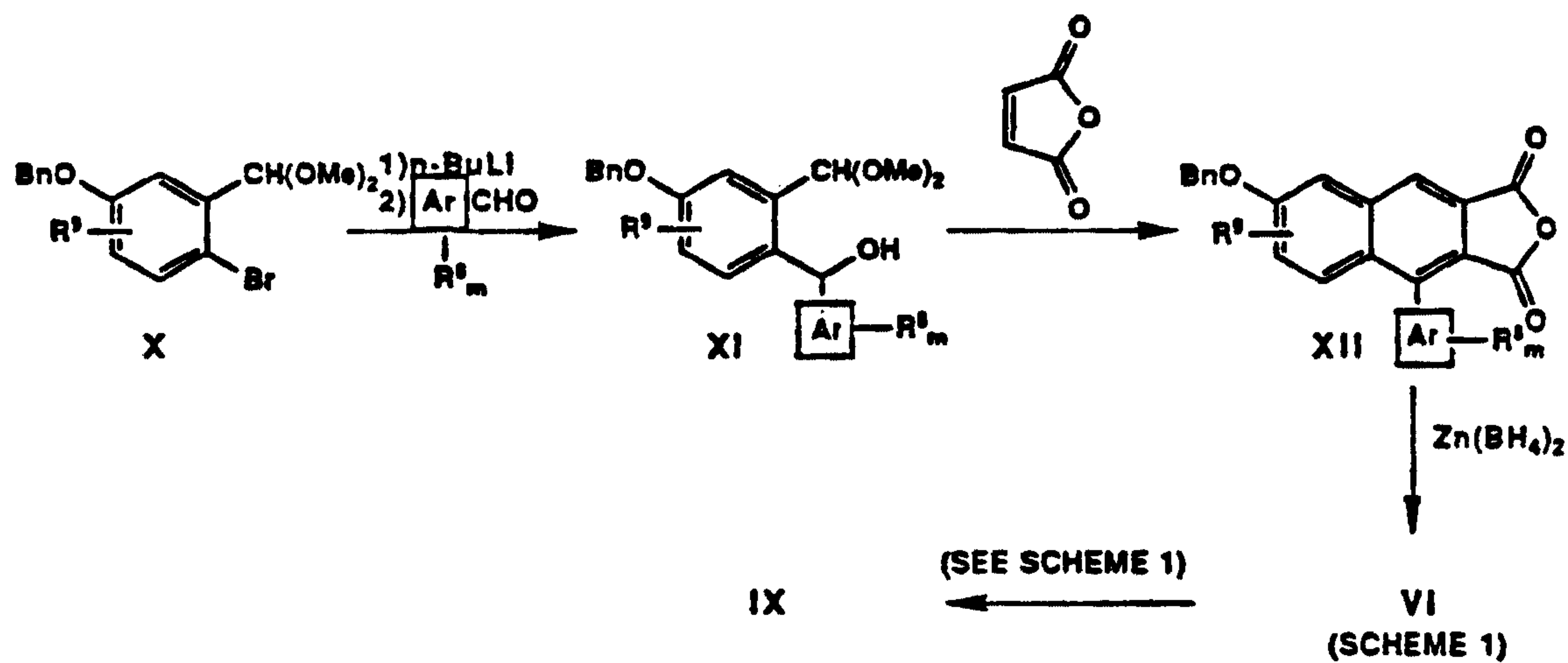
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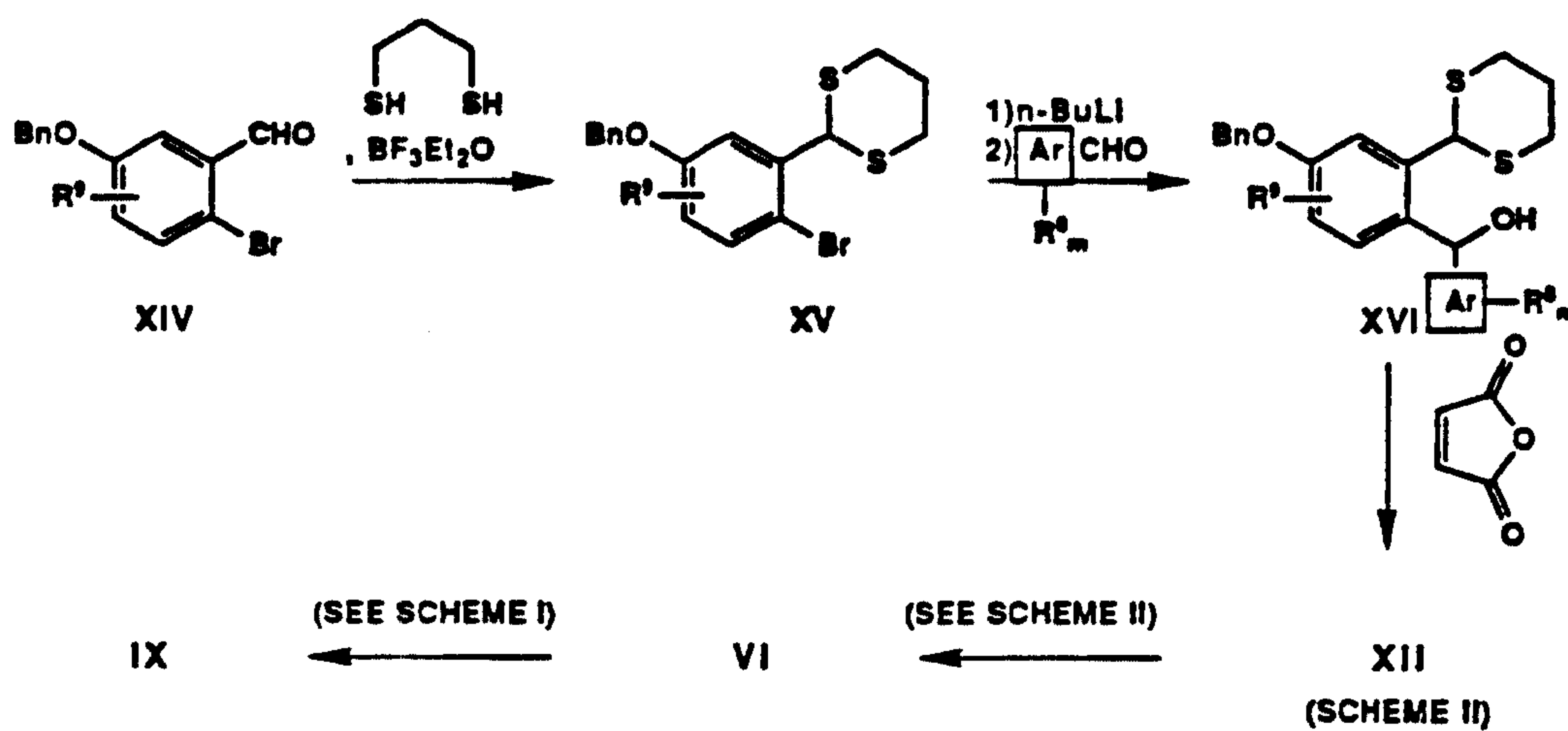
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SCHEME III

PREPARATION OF LACTONE INTERMEDIATES (METHOD C)



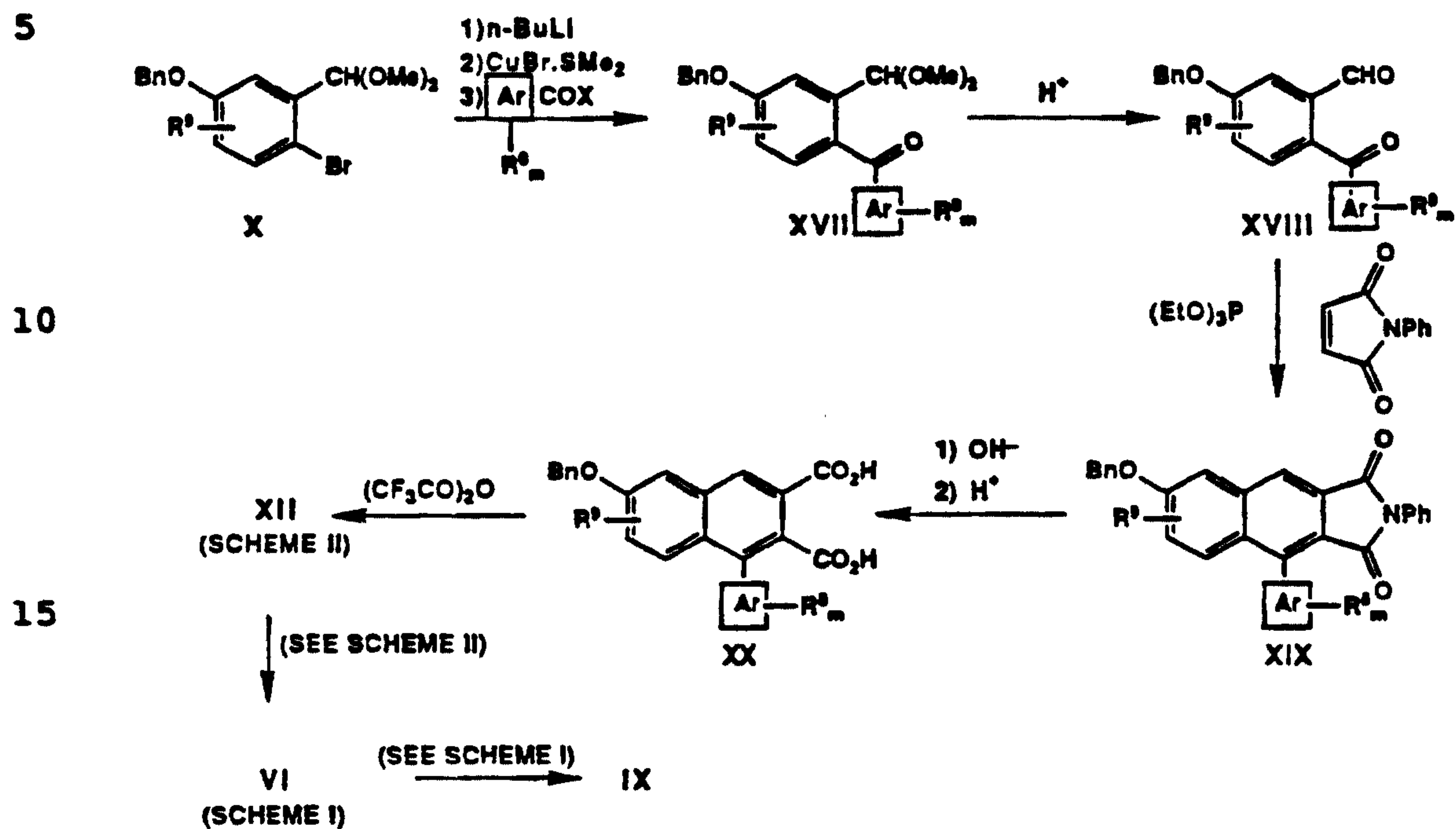
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SCHEME IV

PREPARATION OF LACTONE INTERMEDIATES (METHOD D)



SCHEME V

PREPARATION OF FINAL PRODUCTS

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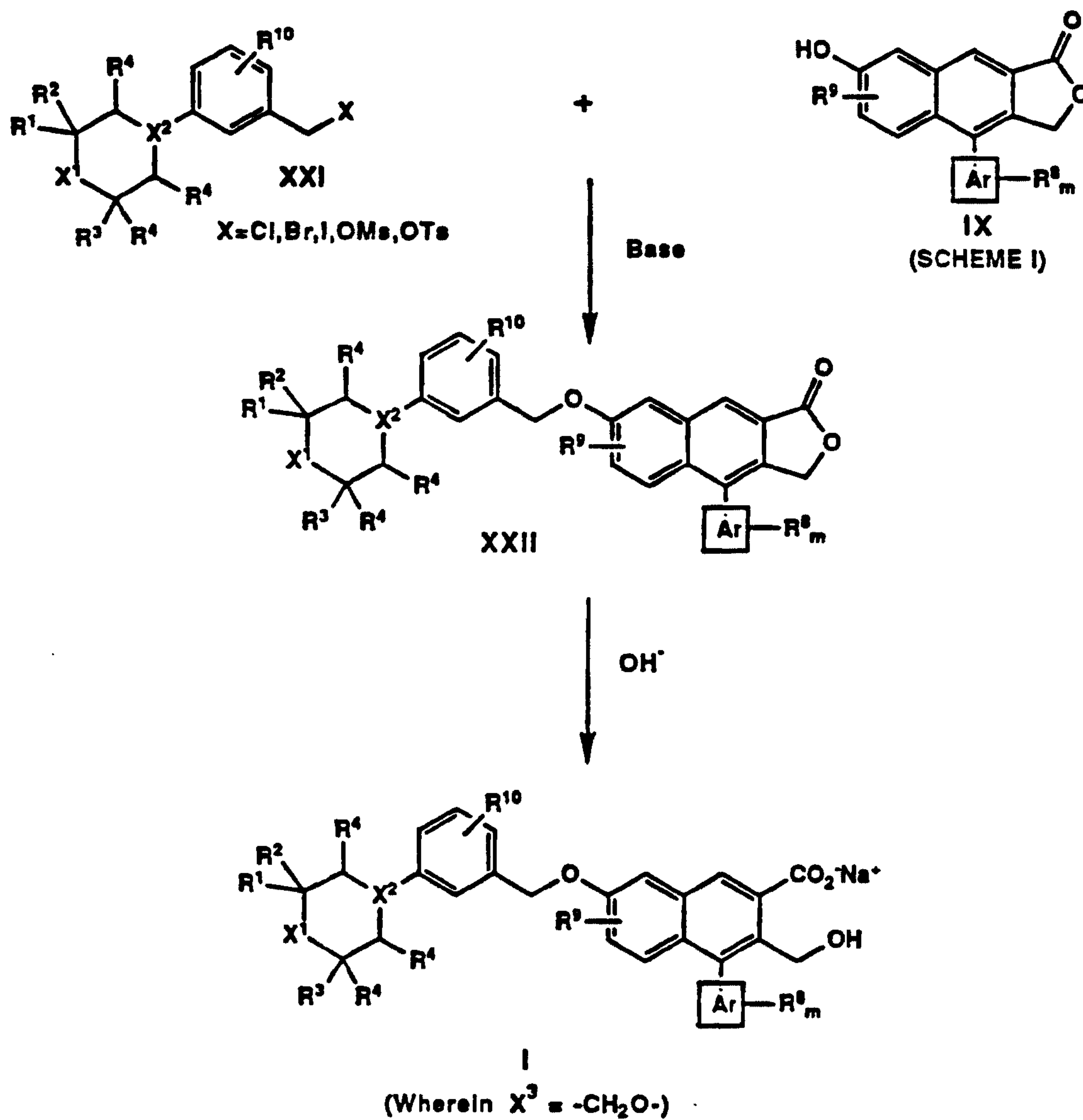
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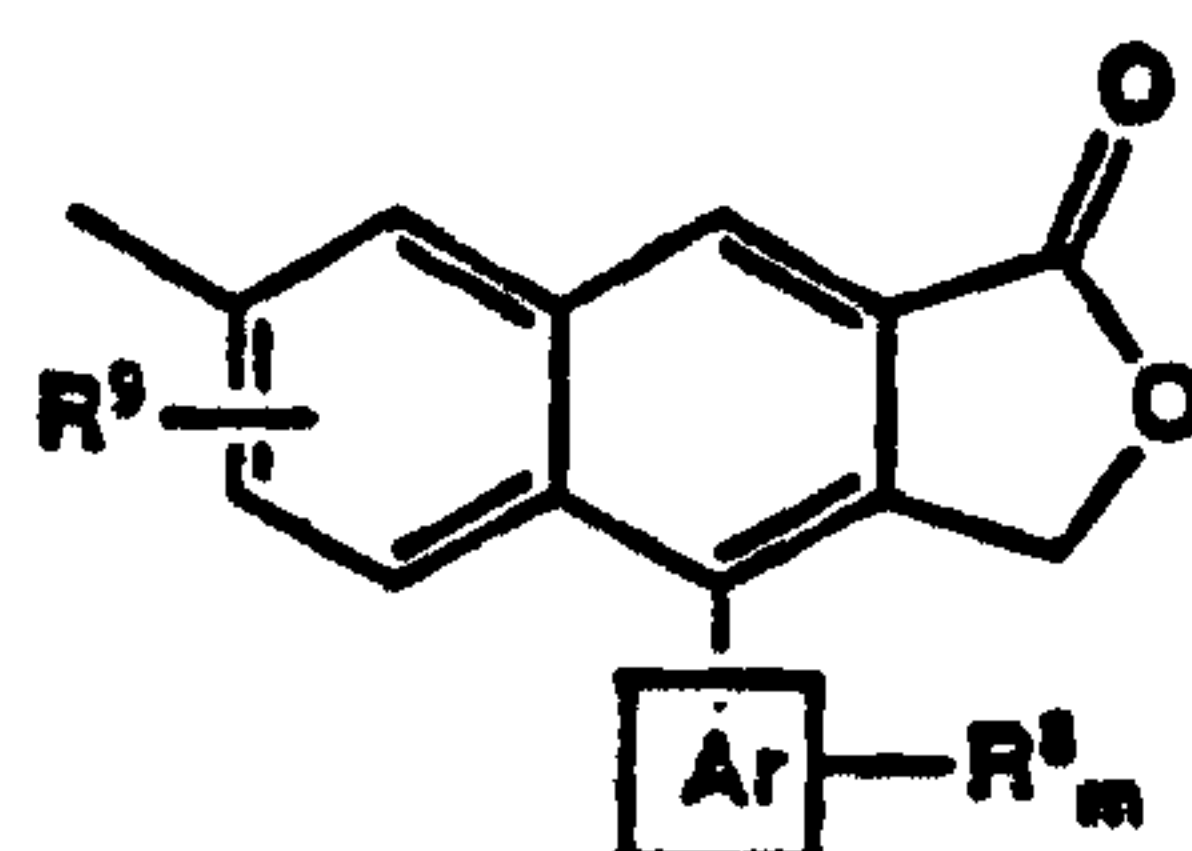
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SCHEME VI

PREPARATION OF FINAL PRODUCTS

5



= NAPH below

10

HO-NAPH

IX
(SCHEME I)

TIO-NAPH

XXIII

MeO₂C-NAPH

XXIV

15

BrCH₂-NAPH

XXVII

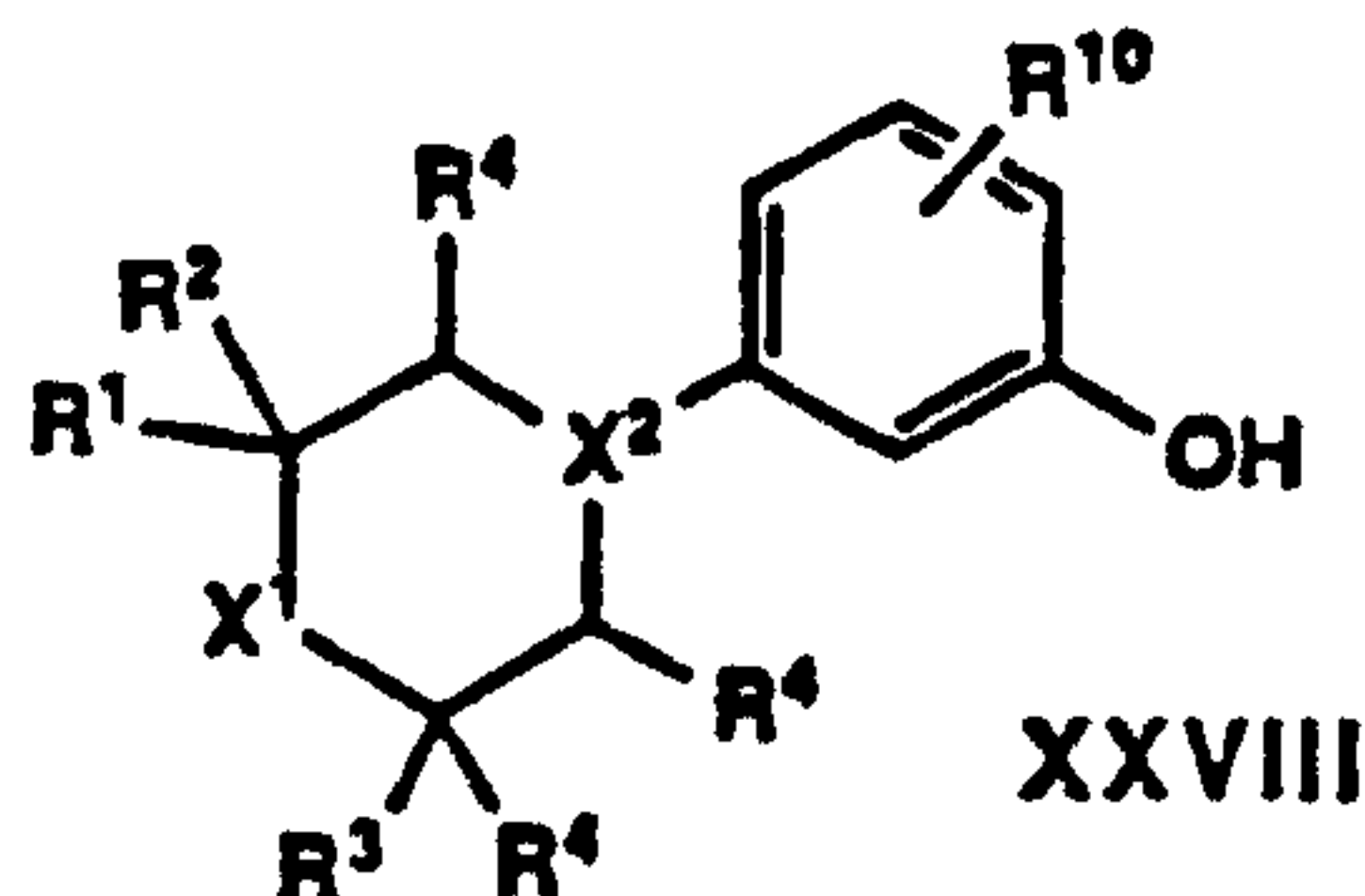
HOCH₂-NAPH

XXVI

HO₂C-NAPH

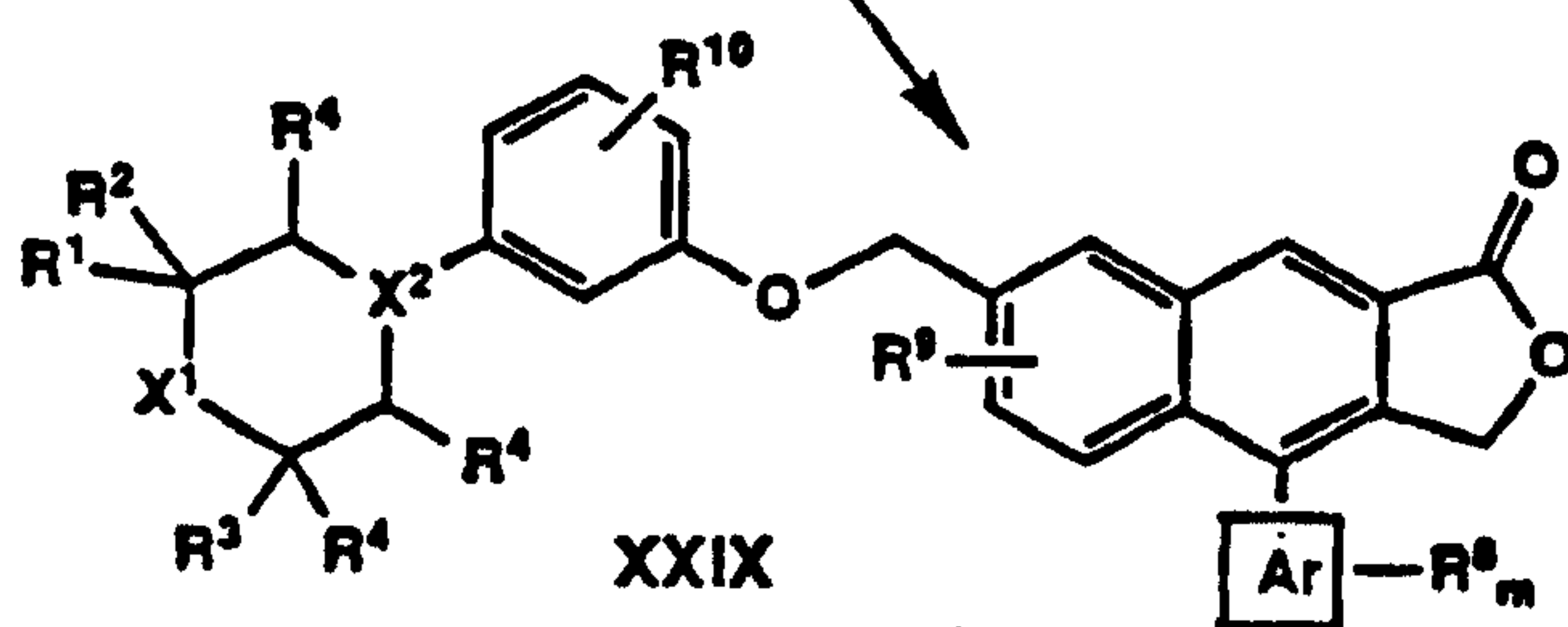
XXV

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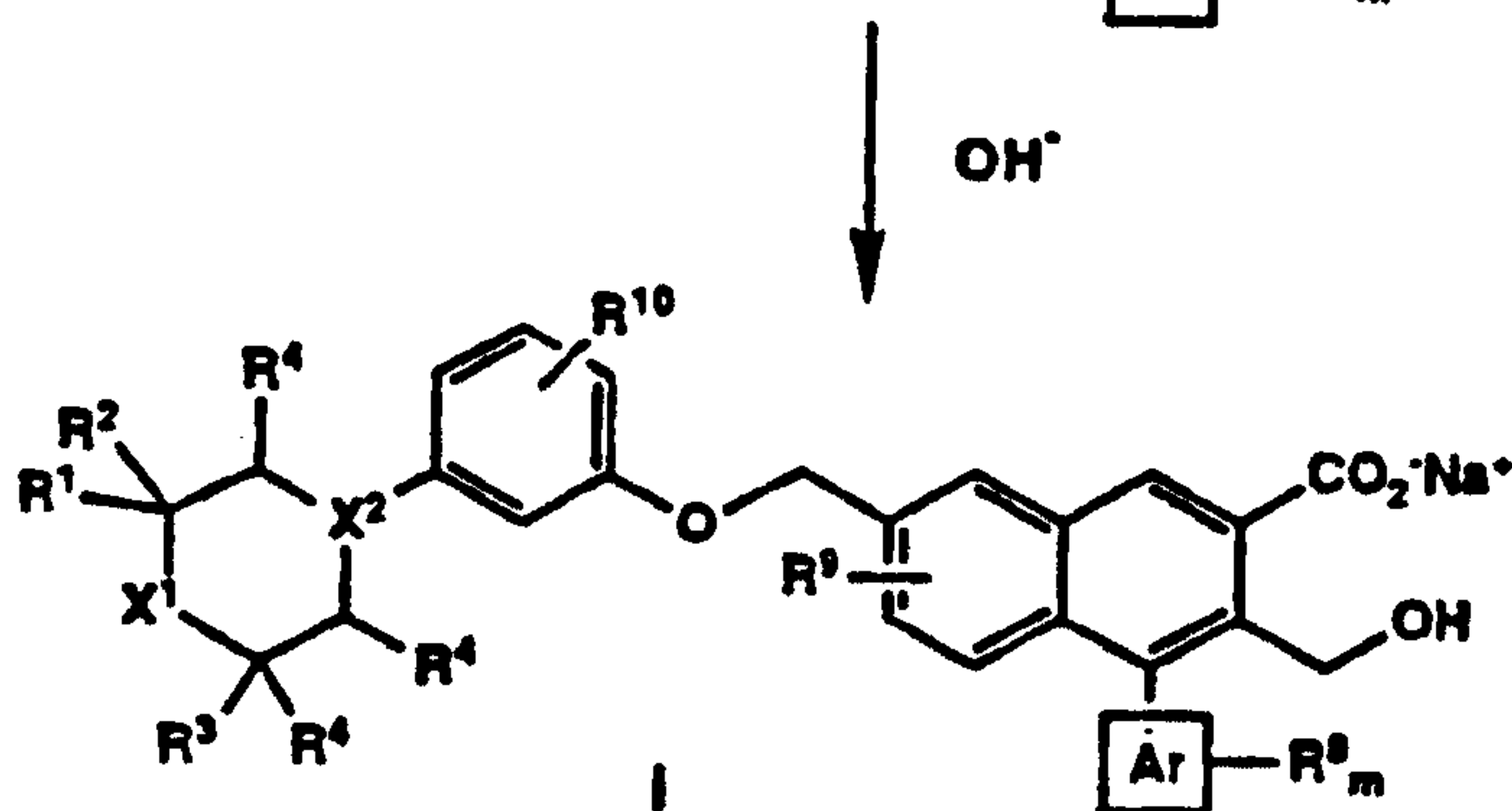
XXVIII

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XXIX

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(Wherein X³ = -OCH₂-)

SCHEME VII

PREPARATION OF FINAL PRODUCTS

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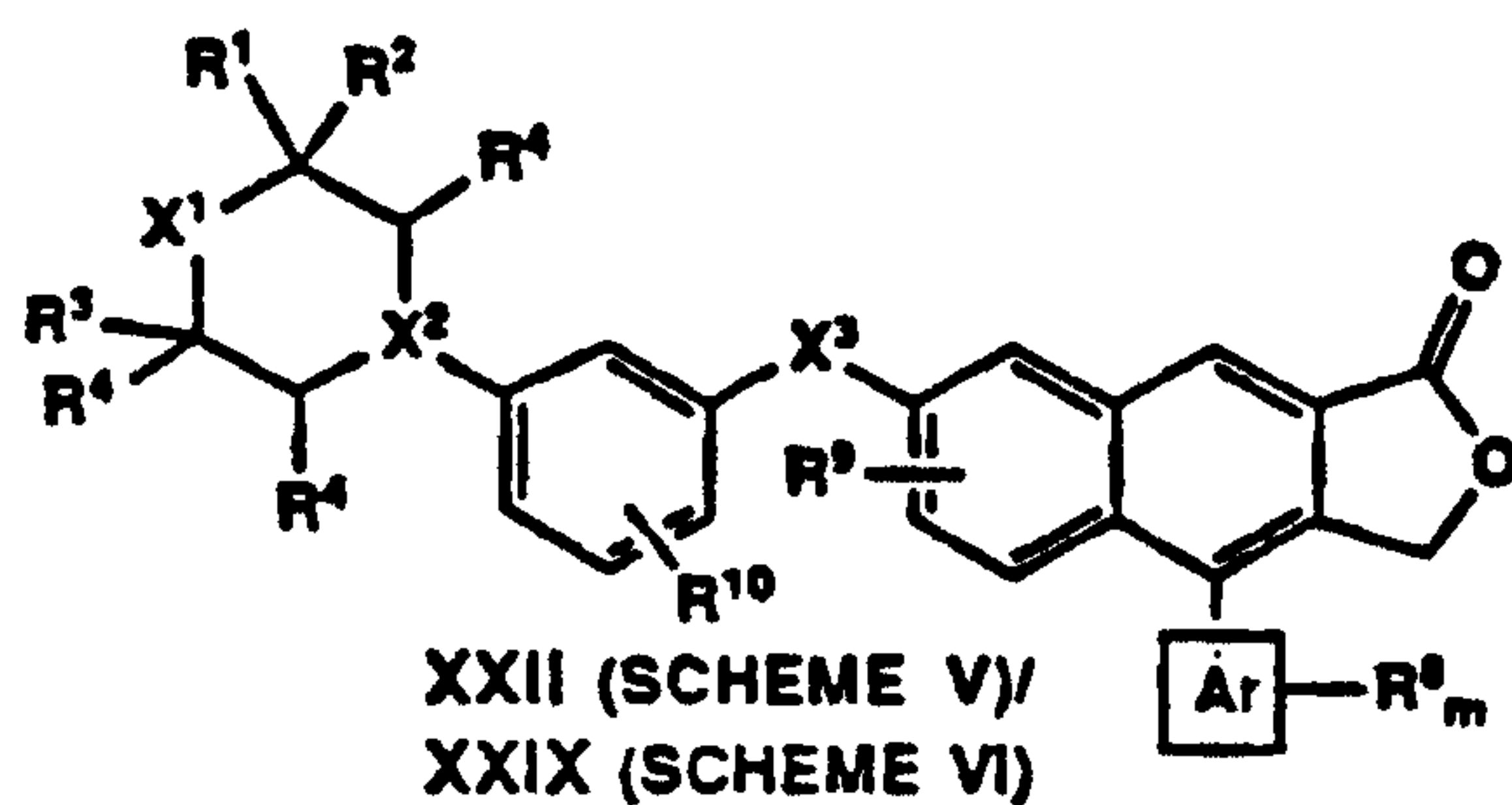
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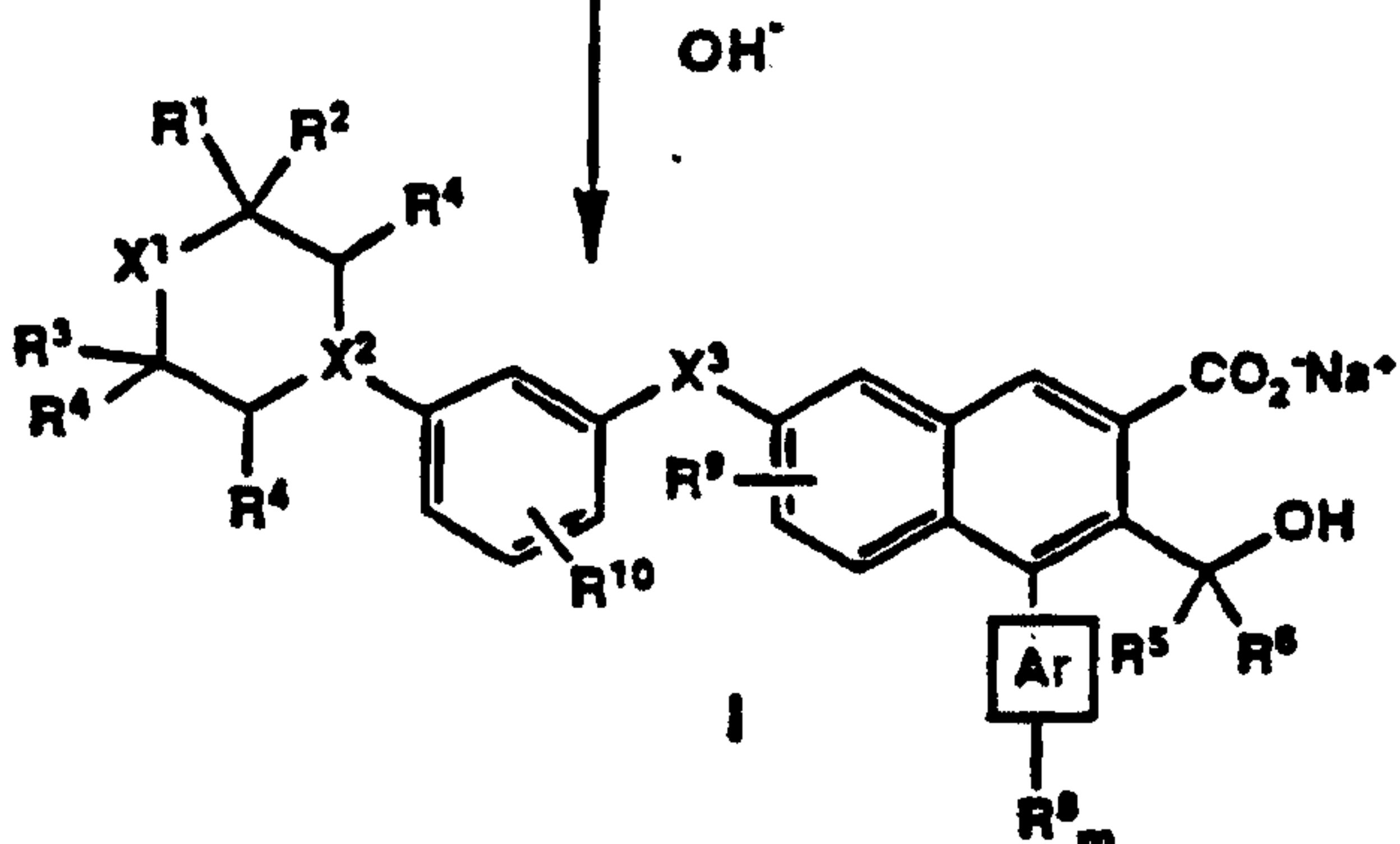
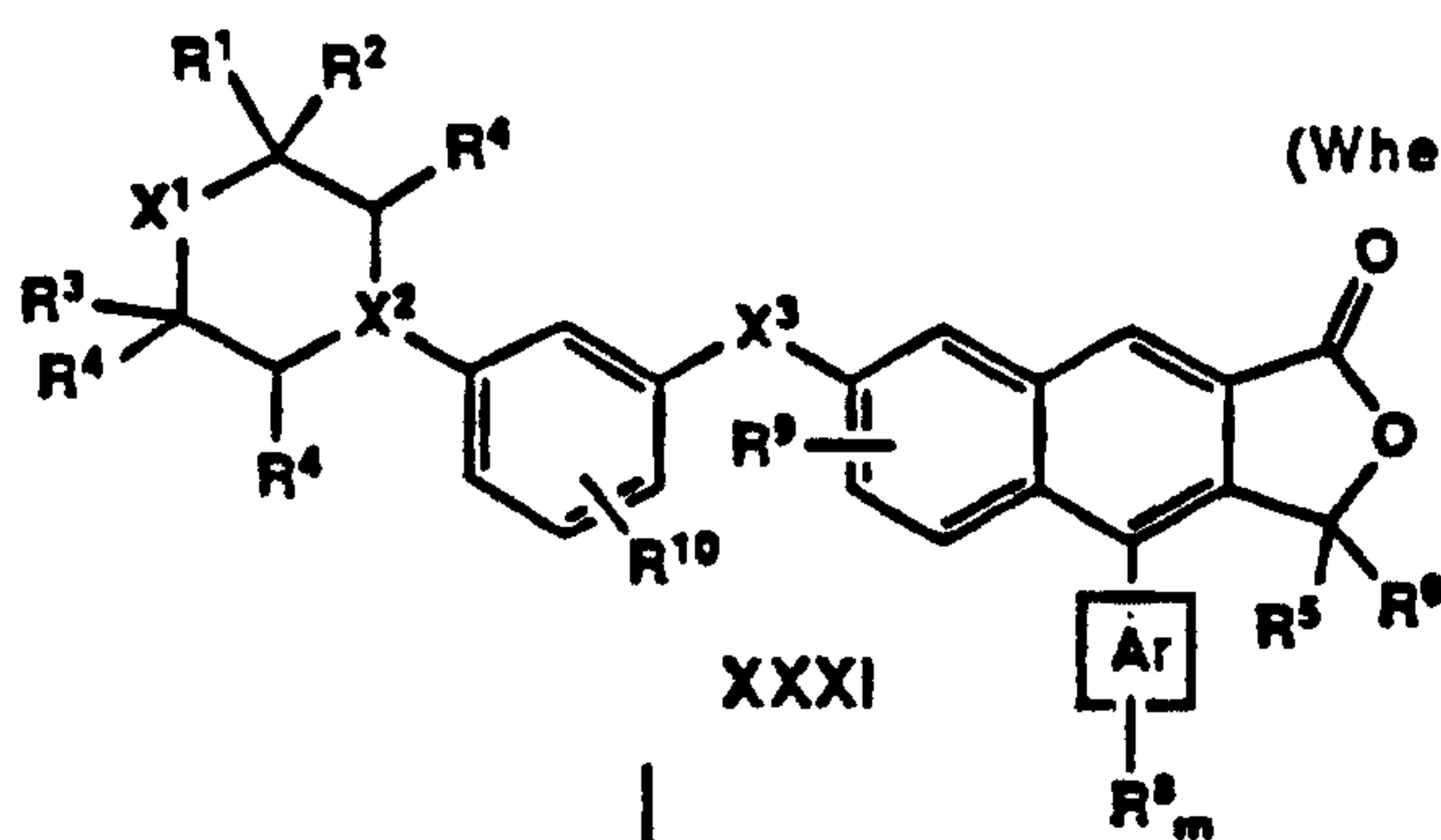
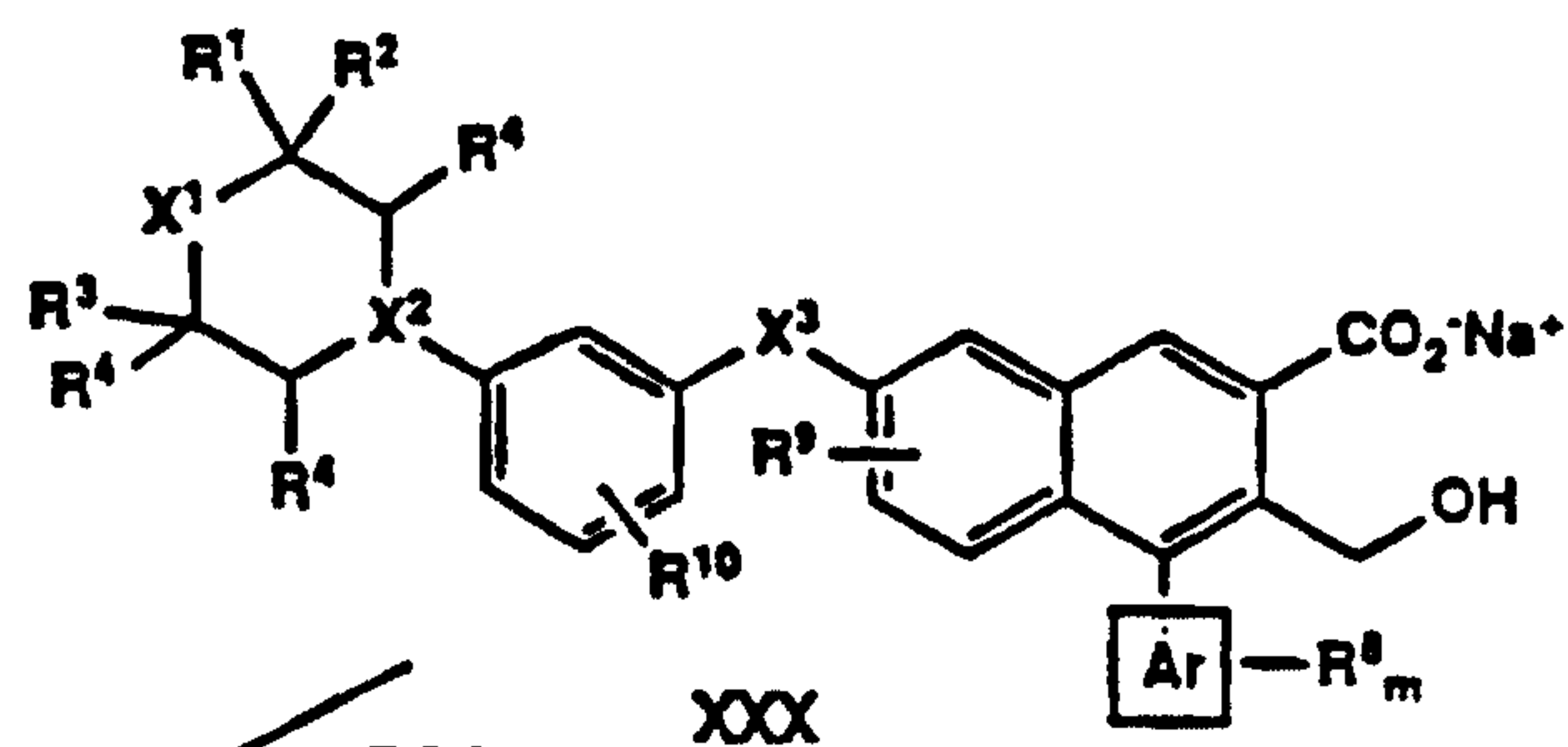
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1) Base
2) R⁵X/R⁶X

(Wherein R⁵/R⁶ is lower alkyl)

OH⁻

PCC

(Wherein R⁵ is hydroxyl)
(and R⁶ is H)

SCHEME VIII

PREPARATION OF LACTONE INTERMEDIATES (METHOD E)

5

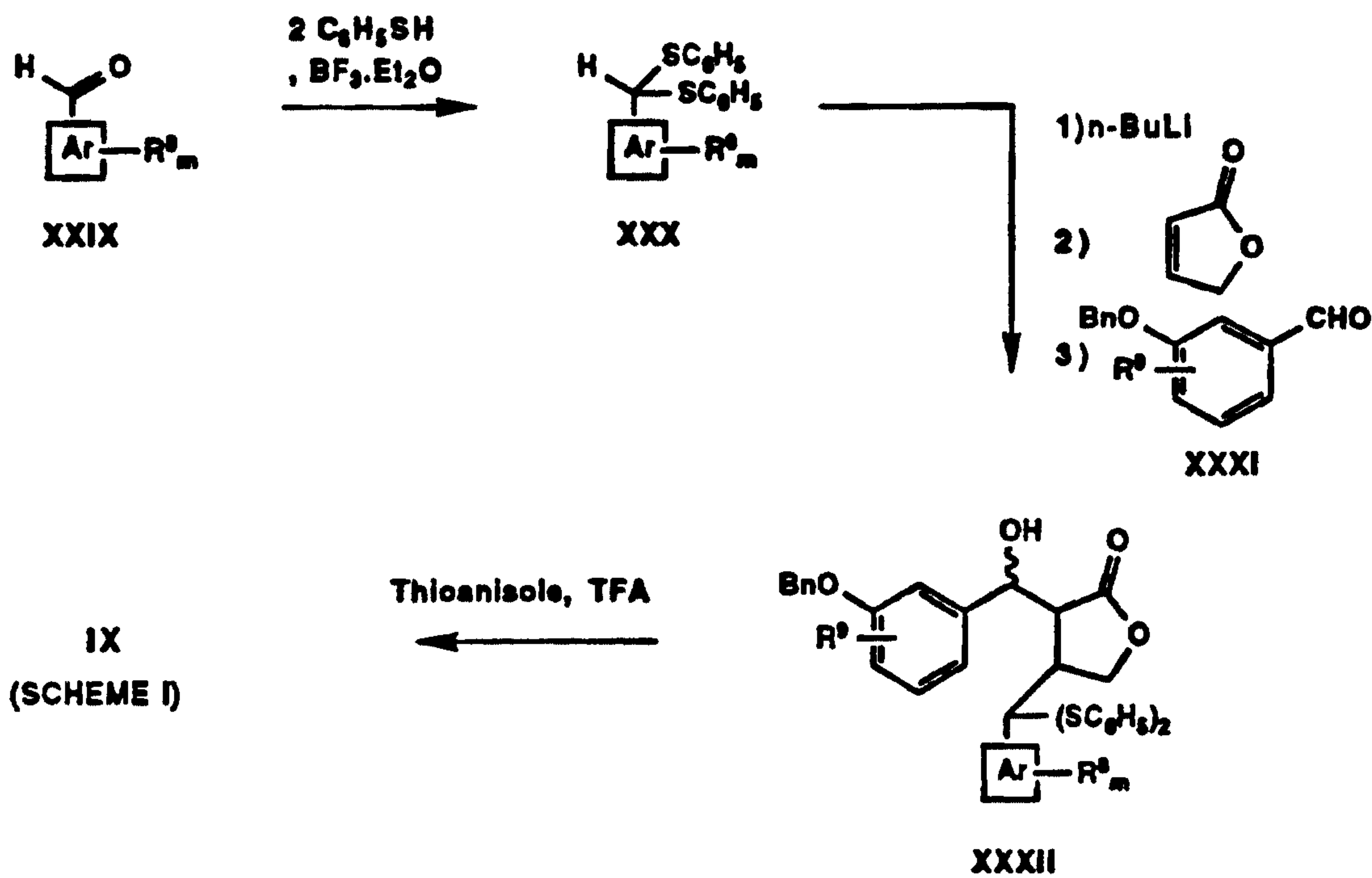
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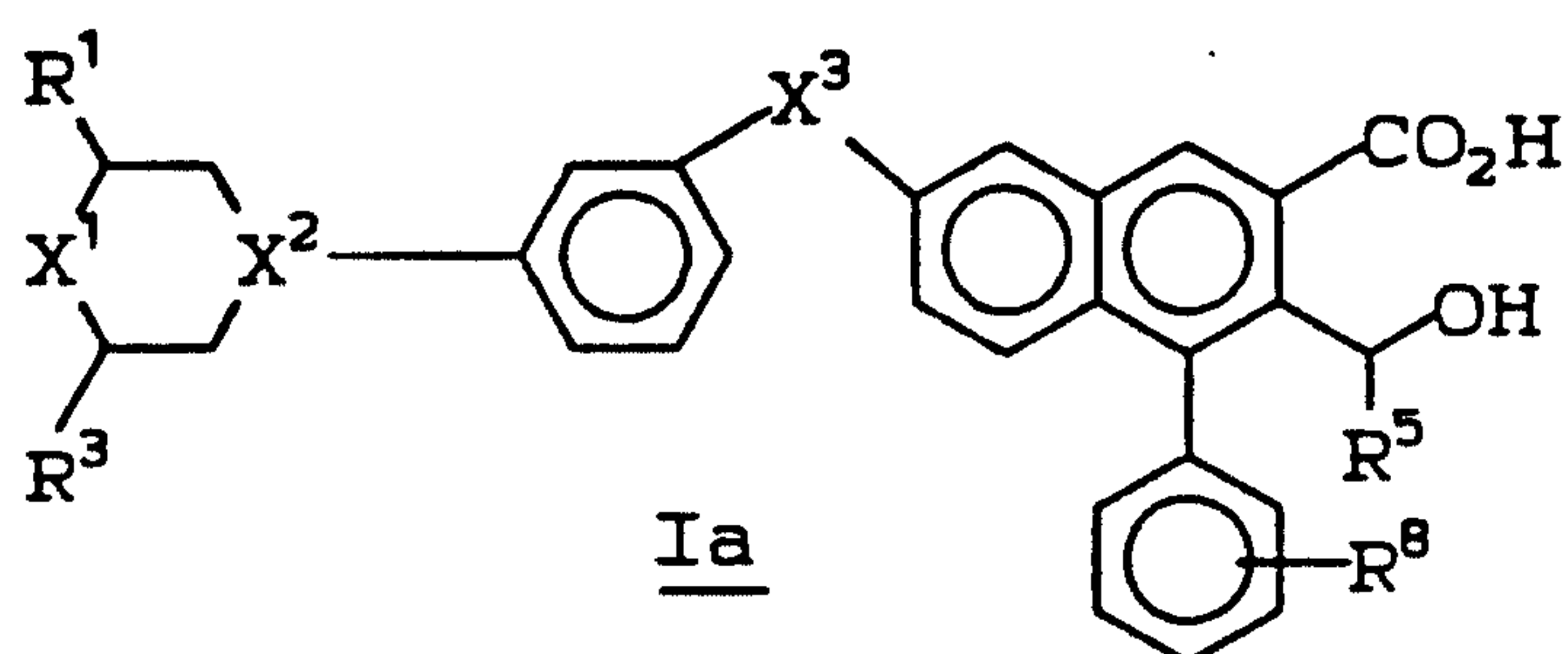
Representative Compounds

Tables 1 and 2 illustrate compounds of Formulas Ia and Ib, which are representative of the present invention.

5

TABLE 1

10



15

Ex.	R ¹	R ³	R ⁵	R ⁸	X ¹	X ²	X ³
1	H	H	H	H	O	C(OMe)	CH ₂ O
2	H	H	H	H	O	C(OMe)	OCH ₂
3	H	H	H	4-F	O	C(OMe)	CH ₂ O
4	H	H	H	H	O	C(OH)	CH ₂ O
5	H	H	H	H	O	C(OEt)	CH ₂ O
6	H	H	H	H	CH ₂	C(OMe)	CH ₂ O
7	H	H	H	H	O	N	CH ₂ O
8	H	H	H	H	O	N(O)	CH ₂ O
9	H	H	OH	H	O	C(OMe)	CH ₂ O
10	OH	H	H	H	O	C(OMe)	CH ₂ O
11	OH	H	H	H	O	C(OH)	CH ₂ O
12	H	H	OH	H	O	C(OH)	CH ₂ O
13	OH	H	OH	H	O	C(OH)	CH ₂ O
14	H	H	Me	H	O	C(OMe)	CH ₂ O
15	OH	H	OH	H	O	C(OMe)	CH ₂ O
16*	Me	Me	H	H	O	C(OH)	CH ₂ O
17*	Me	Me	H	H	O	C(OH)	CH ₂ O

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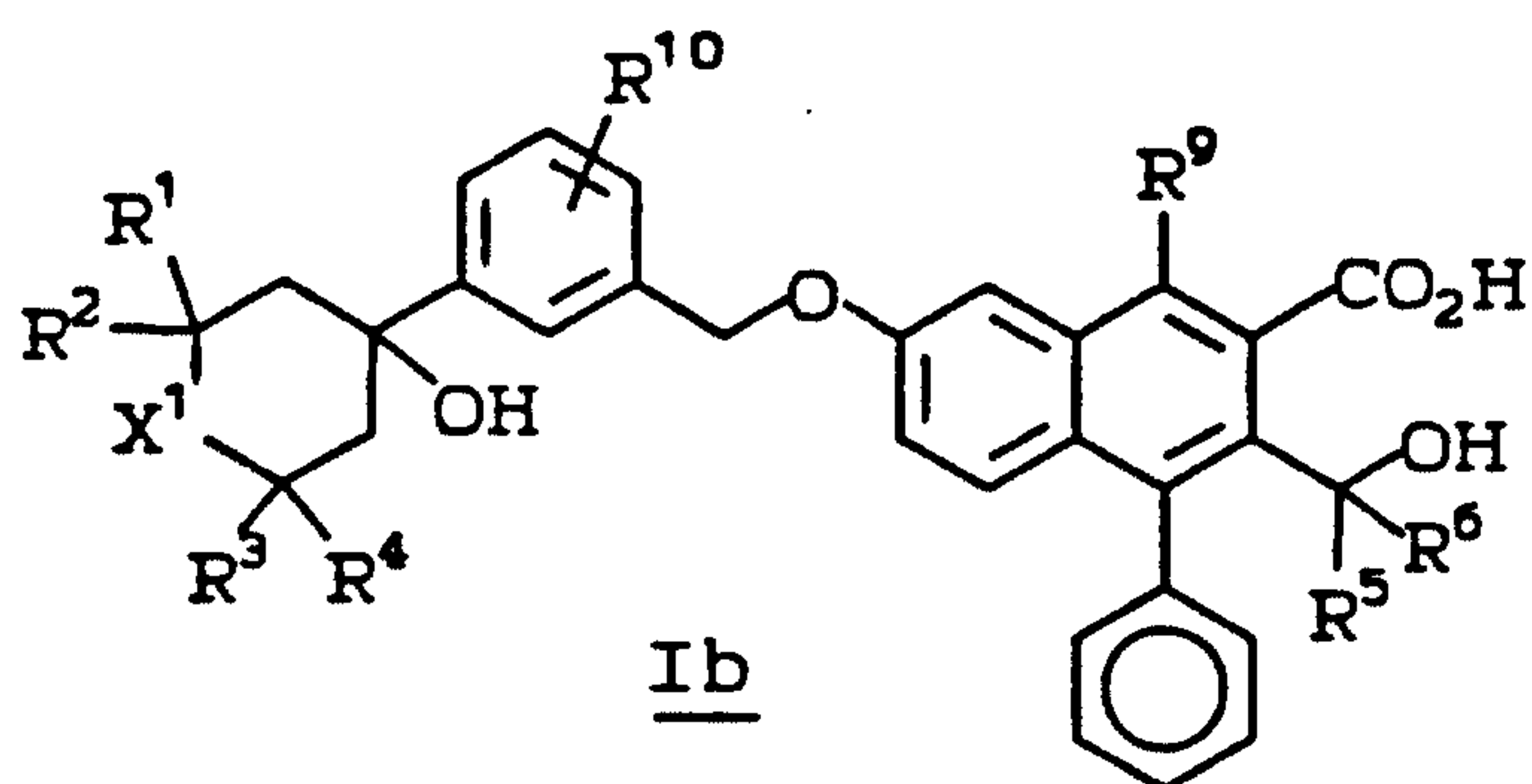
*cis and trans isomers

Table 1 (cont.)

5	Ex.	R ¹	R ³	R ⁵	R ⁸	X ¹	X ²	X ³
10	18	H	H	H	4-Cl	O	C(OH)	CH ₂ O
	19	H	H	H	4-OMe	O	C(OH)	CH ₂ O
	20	Me	Me	H	H	O	C(OMe)	CH ₂ O
	21	H	H	H	H	S	C(OH)	CH ₂ O
	22	H	H	H	H	S(O)	C(OH)	CH ₂ O
	23	H	H	H	H	S(O) ₂	C(OH)	CH ₂ O
	24**	OMe	H	H	H	O	C(OH)	CH ₂ O
	25**	OMe	H	H	H	O	C(OH)	CH ₂ O
	26	H	H	H	H	O	C(Me)	CH ₂ O
	27	H	H	Me	H	O	C(OH)	CH ₂ O
20	28	H	H	H	4-F	O	C(OH)	CH ₂ O
	29	H	H	H	H	O	C(Et)	CH ₂ O
	30	H	H	H	2-F	O	C(OH)	CH ₂ O
	31	H	H	H	2-Cl	O	C(OH)	CH ₂ O
	32	H	H	H	3-OMe	O	C(OH)	CH ₂ O
25	33**	OCH(Me) ₂	H	H	H	O	C(OH)	CH ₂ O
	34**	OCH(Me) ₂	H	H	H	O	C(OH)	CH ₂ O
	35	(R ¹ R ³)=	-CH=CH-	H	H	O	C(OH)	CH ₂ O
	36	(R ¹ R ³)=	-CH ₂ CH ₂ -	H	H	O	C(OH)	CH ₂ O

**axial and equatorial isomers

TABLE 2



Ex.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁹	R ¹⁰	X ¹
15	37	H	H	H	H	H	H	4-Ome	O
	38	H	H	H	Me	Me	H	H	O
	39	H	H	H	H	H	1-OMe	H	O
	40	Me	Me	Me	H	H	H	H	S
	41	(R ¹ R ²)=	=O	H	H	H	H	H	O

Assays for Determining Biological Activity

Compounds of Formula I can be tested using the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity.

5

Human 5-Lipoxygenase Inhibitor Screen

Objective of the Assay: The objective of the assay is to select agents which specifically inhibit the activity of human 5-lipoxygenase using a 100,000x g supernatant fraction prepared from insect cells infected with recombinant baculovirus containing the coding sequence for human 5-lipoxygenase. Enzyme activity is measured spectrophotometrically from the optimal rate of conjugated diene formation (A_{234}) measured after the incubation of the enzyme with arachidonic acid in the presence of ATP, calcium ions and phosphatidylcholine.

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Description of Procedure: The activity of 5-lipoxygenase is measured using a spectrophotometric assay and recombinant human 5-lipoxygenase as a source of enzyme. The 100,000x g fraction from S19 cells infected with the recombinant baculovirus rvH5LO(8-1) containing the coding region sequence for human 5-lipoxygenase is prepared as described below. The enzymatic activity is measured, using a spectrophotometric assay from the optimal rate of conjugated diene formation (A_{234}) using the procedure described by Riendeau *et al.* (Biochem. Pharmacol., 38, 2323-2321, 1989) with minor modifications. The incubation mixture contains 50 mM sodium phosphate pH 7.4, 0.2 mM ATP, 0.2 mM $CaCl_2$, 20 μ M arachidonic acid

(5 μ l from a 100-fold concentrated solution in ethanol), 12 μ g/ml phosphatidylcholine, an aliquot of the 100,000x g fraction (2-10 μ l) and inhibitor (0.5 ml final volume). Inhibitors are added as 500-fold concentrated solutions in DMSO. Reactions are initiated by the addition of an aliquot of the enzyme preparation and the rate of conjugated diene formation is followed for 2 minutes at room temperature. The reactions are performed in semi-micro cuvettes (0.7 ml capacity, 10 mm path length and 4 mm internal width) and the absorbance changes are recorded with a Hewlett-Packard diode array spectrophotometer (HP 8452A) connected to the ChemStation using UV/VIS Kinetics Software. Enzymatic activity is calculated from the optimal rate of the reaction by a linear fit of the variation of A_{234} during the first twenty seconds using the least square method for the equation $A_{234} = V_0 t + A_0$ where V_0 is the rate, t is the time, and A_0 is the absorbance at zero time. The results are expressed as percentages of inhibition of the reaction rate relative to controls (typically between 0.15-0.21 AU/min) containing the DMSO vehicle.

Preparation of Lysates from Infected Cells:
S19 cells are grown at 27°C in 100 ml spinner flasks to a cell density of $1.5-2 \times 10^6$ cells/ml and infected for 44-48 hours with rvH5L0(8-1). The cells are then collected by centrifugation (900x g for 10 min, at 20°C), washed twice with Dulbacco's phosphate-buffered saline (pH 7.4) ($25 \text{ ml}/2 \times 10^8$ cells) and resuspended at 1.2×10^7 cells/ml in a

homogenization buffer containing 50 mM potassium phosphate (pH 7.9) 2 mM EDTA, 1mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride and 60 µg/ml soybean trypsin inhibitor. The cells are then lysed by
5 sonication at 4°C using a Cole Parmer (4710 Series) Ultrasonic homogeniser (3 to 5 bursts of 10 sec. with 30-sec. lags, pulse mode, 70% duty cycle, and output setting at 3). The preparations are examined under the microscope to achieve efficient cell lysis (>
10 90%) with minimal sonication. The lysate is then centrifuged at 100,000x g for 1 hour (Beckman L5-65, 60 Ti rotor) at 4°C and the resulting supernatant (S-100 fraction) brought to 24 µg/ml PC by the addition of a 250-fold concentrated solution in
15 ethanol. The S-100 fraction (1-3 mg/ml) is stable for several hours at 4°C and can be stored for several months at -70°C in 20% ethylene glycol with about 50% recovery of activity.

20 Rat Peritoneal Polymorphonuclear (PMN) Leukocyte Assay

Rats under ether anesthesia are injected (i.p.) with 8 mL of a suspension of sodium caseinate (6 grams in ca. 50 mL water). After 15-24 hr. the rats are sacrificed (CO₂) and the cells from the
25 peritoneal cavity are recovered by lavage with 20 mL of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350x g, 5 min.), resuspended in buffer with vigorous shaking, filtered through lens paper, recentrifuged
30 and finally suspended in buffer at a concentration of 10 cells/mL. A 500 mL aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37°C,

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5 followed by the addition of 10 mM A-23187. The
suspension is stirred for an additional 4 minutes
then bioassayed for LTB₄ content by adding an aliquot
to a second 500 mL portion of the PMN at 37°C. The
10 LTB₄ produced in the first incubation causes
aggregation of the second PMN, which is measured as a
change in light transmission. The size of the assay
aliquot is chosen to give a submaximal transmission
change (usually -70%) for the untreated control. The
percentage inhibition of LTB₄ formation is calculated
from the ratio of transmission change in the sample
to the transmission change in the compound-free
control.

15 Human Polymorphonuclear (PMN) Leukocyte LTB₄ Assay

A. Preparation of Human PMN. Human blood is
obtained by antecubital venepuncture from consenting
volunteers who have not taken medication within the
20 previous 7 days. The blood is immediately added to
10% (v/v) trisodium citrate (0.13 M) or 5% (v/v)
sodium heparin (1000 IU/mL). PMNs are isolated from
anticoagulated blood by dextran sedimentation of
erythrocytes followed by centrifugation through
25 Ficoll-Hypaque (specific gravity 1.077), as described
by Boyum.¹ Contaminating erythrocytes are removed by
lysis following exposure to ammonium chloride (0.16
M) in Tris buffer (pH 7.65), and the PMNs resuspended
at 5 x 10⁵ cells/mL in HEPES (15 mM)-buffered Hanks
30 balanced salt solution containing Ca²⁺ (1.4 mM) and
Mg²⁺ (0.7 mM), pH 7.4.

B. Generation and Radioimmunoassay of LTB₄.

PMNs (0.5 mL; 2.5×10^5 cells) are placed in plastic tubes and incubated (37°C, 2 min) with test compounds at the desired concentration or vehicle (DMSO, final concentration 0.2%) as control. The synthesis of LTB₄ is initiated by the addition of calcium ionophore A23187 (final concentration 10 mM) or vehicle in control samples and allowed to proceed for 5 minutes at 37°C. The reactions are then terminated by the addition of cold methanol (0.25 mL) and samples of the entire PMN reaction mixture removed for radioimmunoassay of LTB₄.

Samples (50 mL) of authentic LTB₄ of known concentration in radioimmunoassay buffer (RIA) buffer (potassium phosphate 1 mM; disodium EDTA 0.1 mM; Thimerosal 0.025 mM; gelatin 0.1%, pH 7.3) or PMN reaction mixture diluted 1:1 with RIA buffer are added to reaction tubes. Thereafter [³H]-LTB₄ (10 nCi in 100 mL RIA buffer) and LTB₄-antiserum (100 mL of a 1:3000 dilution in RIA buffer) are added and the tubes vortexed. Reactants are allowed to equilibrate by incubation overnight at 4°C. To separate antibody-bound from free LTB₄, aliquots (50 mL) of activated charcoal (3% activated charcoal in RIA buffer containing 0.25% Dextran T-70) are added, the tubes vortexed, and allowed to stand at room temperature for 10 minutes prior to centrifugation

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(1) Boyum, A. Scand. J. Clin. Lab. Invest., 1968, 21 (Supp 97), 77.

(1500x g; 10 min; 4°C). The supernatants containing antibody-bound LTB₄ are decanted into vials and Aquasol 2 (4 mL) added. Radioactivity is quantified by liquid scintillation spectrometry. The
5 specificity of the antiserum and the sensitivity of the procedure have been described by Rokach et al.² The amount of LTB₄ produced in the test and control samples is calculated. Inhibitory dose-response curves are constructed using a four-parameter
10 algorithm and from these the IC₅₀ values determined.

Human Whole Blood Assay in Vitro for LTB₄ Production

A. Blood

15 Blood (60 ml) is collected from male volunteers directly into 10 ml heparinized vacutainers for assay; one volunteer per assay.

B. Test Compounds

20 Stock solution: Most concentrated working solution (final) multiplied by the dilution factor (volume of compound vs blood volume); e.g., 60 µM dose X 500 (DMSO 1/500) = 30 mM stock solution. To calculate the amount of compound needed to make stock
25 solution: mol. wt. of drug x 1/1000 x stock concentration; e.g., 618 x 1/1000 x 30 mM = 18.54 mg for 1 ml vehicle either DMSO or methanol.

30 (2) Rokach, J.; Hayes, E.C.; Girard, Y.; Lombardo, D.L.; Maycock, A.L.; Rosenthal, A.S.; Young, R.N.; Zamboni, R.; Zweerink, H.J. Prostaglandins Leukotrienes and Medicine, 1984, 13, 21.

Working Solutions: Serial dilutions of stock with appropriate vehicle. If methanol is used to dissolve compound, then use methanol/BSA solution to dilute the stock. Methanol/BSA = 1 ml 100% methanol = 9 ml BSA 1 mg/ml saline.

Effective conc. in the assay depends upon the test compound (may be 60 μ M to 0.1 μ M). 1/500 dilution for DMSO vehicle = 1 μ l for 500 μ l blood. 1/50 dilution for MeOH/BSA = 10 μ l for 500 μ l blood.

C. A23187

50 mM stock solution: 50 mg A23187 for 1.9 ml DMSO in 50 μ l aliquots (stored at -20°C).

Working Solution: 40 μ l of 50 mM stock + 760 μ l homologous plasma = 2.5 mM solution vehicle = plasma.

Effective conc. in assay should be 25 μ M (1/100 dilution).

D. Assay

Add 1 μ l (DMSO) of 10 μ l (MeOH/BSA) of either test compound or vehicle (use 10 μ l hamilton syringe to deliver 1-10 μ l) to properly labelled 1.5 ml Eppendorf tubes. 500 μ l of blood is dispensed into each tube, which is then vortexed, transferred to a plastic box with lid, washed outside with methanol and incubated 15 min. at 37°C . Meanwhile, centrifuge ~2 ml blood in microfuge at 12,000x g for 5 minutes to obtain plasma for the A23187 solution. At the end of the 15 minutes incubations, add 5 μ l of the 2.5 mM A23187 working solution or 5 μ l of plasma (blanks)

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The challenge and subsequent respiratory recordings are carried out in a clear plastic box with internal dimensions 10x6x4 inches. The top of the box is removable; in use, it is held firmly in place by four clamps and an airtight seal is maintained by a soft rubber gasket. Through the center of each end of the chamber a DeVilbiss nebulizer (No. 40) is inserted via an airtight seal and each end of the box also has an outlet. A Fleisch No. 0000 pneumotachograph is inserted into one end of the box and coupled to a Grass volumetric pressure transducer (PT5-A) which is then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the outlets are open and the pneumotachograph is isolated from the chamber. The outlets are closed and the pneumotachograph and the chamber are connected during the recording of the respiratory patterns. For challenge, 2 mL of a 3% solution of antigen in saline is placed into each nebulizer and the aerosol is generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minute.

Rats are sensitized by injecting (subcutaneously) 1 mL of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. They are used between days 12 and 24 postsensitization. In order to eliminate the serotonin component of the response, rats are pretreated intravenously 5 minutes prior to aerosol challenge with 3.0 mgm/kg of methysergide. Rats are then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their

respiratory profiles are recorded for a further 30 minutes. The duration of continuous dyspnea is measured from the respiratory recordings.

5 Compounds are generally administered either orally 1-4 hours prior to challenge or intravenously 2 minutes prior to challenge. They are either dissolved in saline or 1% methocel or suspended in 1% methocel. The volume injected is 1 mL/kg (intravenously) or 10 mL/kg (orally). Prior to oral
10 treatment rats are starved overnight. Their activity is determined in terms of their ability to decrease the duration of symptoms of dyspnea in comparison with a group of vehicle-treated controls. Usually, a compound is evaluated at a series of doses and an
15 ED₅₀ is determined. This is defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

20 Pulmonary Mechanics in Trained Conscious Squirrel Monkeys

The test procedure involves placing trained squirrel monkeys in chairs in aerosol exposure chambers. For control purposes, pulmonary mechanics measurements of respiratory parameters are recorded
25 for a period of about 30 minutes to establish each monkey's normal control values for that day. For oral administration, compounds are dissolved or suspended in a 1% methocel solution (methylcellulose, 65HG, 400 cps) and given in a volume of 1 ml/kg body
30 weight. For aerosol administration of compounds, a DeVilbiss ultrasonic nebulizer is utilized. Pretreatment periods vary from 5 minutes to 4 hours before the monkeys are challenged with aerosol doses of Ascaris antigen.

Following challenge, each minute of data is calculated by computer as a percent change from control values for each respiratory parameter including airway resistance (R_L) and dynamic compliance (C_{dyn}). The results for each test compound are subsequently obtained for a minimum period of 60 minutes post challenge which are then compared to previously obtained historical baseline control values for that monkey. In addition, the overall values for 60 minutes post-challenge for each monkey (historical baseline values and test values) are averaged separately and are used to calculate the overall percent inhibition of Ascaris antigen response by the test compound. For statistical analysis, paired t-test is used. (References: McFarlane, C.S. et al., Prostaglandins, 28:173-182, 1984, McFarlane, C.S. et al., Agents Actions 22:63-68, 1987.)

Prevention of Induced Bronchoconstriction in Allergic Sheep

A. Rationale. Certain allergic sheep with known sensitivity to a specific antigen (Ascaris suum) respond to inhalation challenge with acute and late bronchial responses. The time course of both the acute and the late bronchial responses approximates the time course observed in asthmatics and the pharmacological modification of both responses is similar to that found in man. The effects of antigen in these sheep are largely observed in the large airways and are conveniently monitored as changes in lung resistance or specific lung resistance.

B. Methods. Animal Preparation: Adult sheep with a mean weight of 35 kg (range, 18 to 50 kg) are used. All animals used meet two criteria: a) they
5 have a natural cutaneous reaction to 1:1,000 or 1:10,000 dilutions of Ascaris suum extract (Greer Diagnostics, Lenois, NC) and b) they have previously responded to inhalation challenge with Ascaris suum with both an acute bronchoconstriction and a late
10 bronchial obstruction (Abraham, W.M. Delehunt, J.C., Yerger, L. and Merchette, B., Am. Rev. Resp. Dis., 1983, 128, 839-44).

Measurement of Airway Mechanics: The unsedated sheep are restrained in a cart in the prone
15 position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine solution, a balloon catheter is advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube
20 through the other nostril using a flexible fiberoptic bronchoscope as a guide. Pleural pressure is estimated with the esophageal balloon catheter (filled with one ml of air), which is positioned such that inspiration produces a negative pressure
25 deflection with clearly discernible cardiogenic oscillations. Lateral pressure in the trachea is measured with a sidehole catheter (inner dimension, 2.5 mm) advanced through and positioned distal to the tip of the nasotracheal tube. Transpulmonary
30 pressure, the difference between tracheal pressure and pleural pressure, is measured with a differential pressure transducer (DP45; Validyne Corp.,

Northridge, CA). For the measurement of pulmonary resistance (R_L), the maximal end of the nasotracheal tube is connected to a pneumotachograph (Fleisch, Dyna Sciences, Blue Bell, PA). The signals of flow and transpulmonary pressure are recorded on an oscilloscope (Model DR-12; Electronics for Medicine, White Plains, NY) which is linked to a PDP-11 Digital computer (Digital Equipment Corp., Maynard, MA) for on-line calculation of R_L from transpulmonary pressure, respiratory volume obtained by integration and flow. Analysis of 10-15 breaths is used for the determination of R_L . Thoracic gas volume (V_{tg}) is measured in a body plethysmograph, to obtain specific pulmonary resistance ($SR_L = R_L \cdot V_{tg}$).

Aerosol Delivery Systems: Aerosols of Ascaris suum extract (1:20) are generated using a disposable medical nebulizer (Raindrop®, Puritan Bennett), which produces an aerosol with a mass median aerodynamic diameter of 6.2 μ M (geometric standard deviation, 2.1) as determined by an electric size analyzer (Model 3030; Thermal Systems, St. Paul, MN). The output from the nebulizer is directed into a plastic t-piece, one end of which is attached to the nasotracheal tube, the other end of which is connected to the inspiratory part of a Harvard respirator. The aerosol is delivered at a tidal volume of 500 ml of a rate of 20 per minute. Thus, each sheep receives an equivalent dose of antigen in both placebo and drug trials.

Experimental Protocol: Prior to antigen challenge baseline measurements of SR_L are obtained, infusion of the test compound is started 1 hr prior

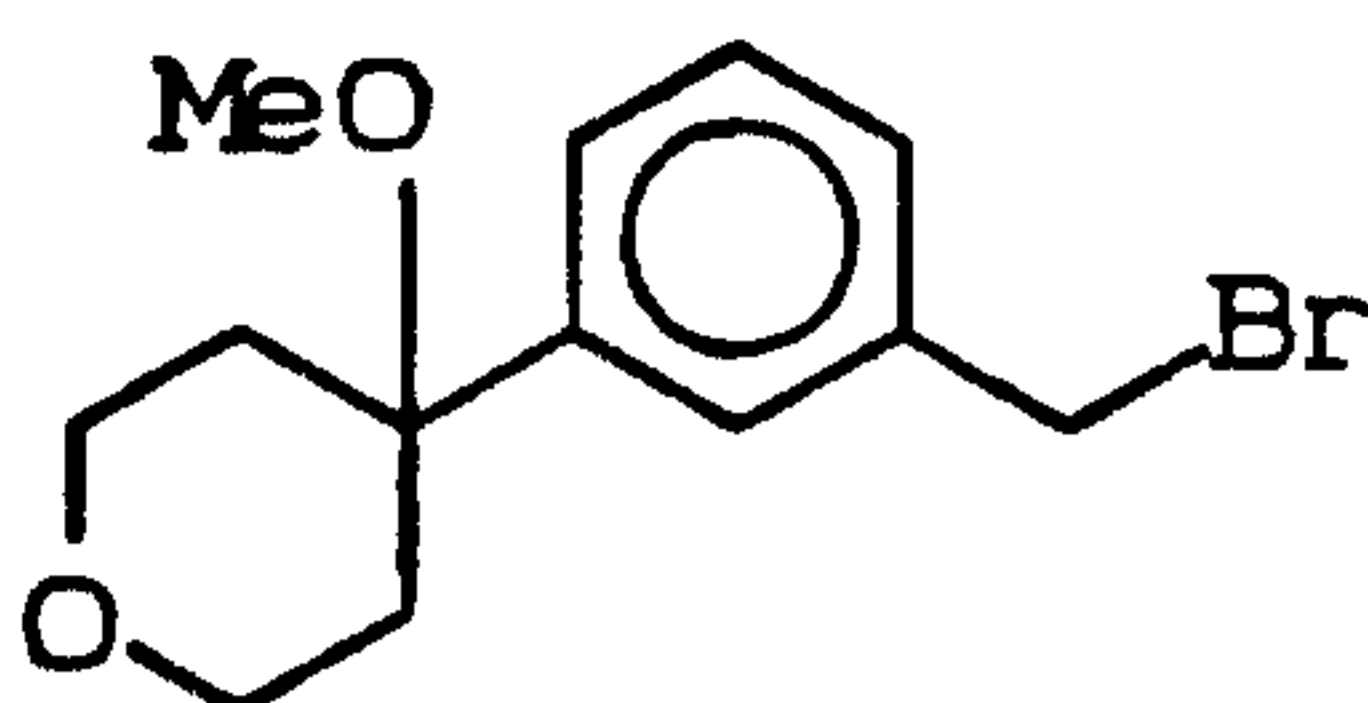
to challenge, the measurement of SR_L repeated and then the sheep undergoes inhalation challenge with Ascaris suum antigen. Measurements of SR_L are obtained immediately after antigen challenge and at
5 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, and 8 hrs after antigen challenge. Placebo and drug tests are separated by at least 14 days. In a further study, sheep are given a bolus dose of the test compound followed by an infusion of the test compound for
10 0.5-1 hr prior to Ascaris challenge and for 8 hrs after Ascaris as described above.

Statistical Analysis: A Kruskal-Wallis one way ANOVA test is used to compare the acute immediate responses to antigen and the peak late response in
15 the controls and the drug treated animals.

PREPARATION OF BENZYL HALIDES

20 Halide 1: 3-[4-(4-Methoxy)tetrahydropyranyl]benzyl
bromide

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Step 1: 3-[4-(4-Hydroxy)tetrahydropyranyl]toluene

To a solution of 3-bromotoluene (24.3 mL; Aldrich) in THF (250 mL) stirred at -78°C was added a solution of n-butyl lithium in hexane (1.75M; 114 mL;

5 Aldrich). After 45 min., the resulting white suspension was treated with a solution of tetrahydropyran-4-one (18.5 mL; Aldrich) in THF (125 mL). After 45 min. at -78°C , the mixture was stirred for 1.5 h at room temperature. Saturated aqueous NH_4Cl was then added and the organic phase separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (MgSO_4) and evaporated. Flash chromatography of the residue (silica gel; hexane/EtOAc (1:1)) followed by crystalli-
10 zation in hexane/EtOAc afforded the title compound as a white solid.

15 Step 2: 3-[4-(4-Methoxy)tetrahydropyranyl]toluene

To a 0°C solution of the alcohol (38 g; Step 1) in DMF (300 mL) were added NaH (60% in mineral oil; 16 g) and methyl iodide (31 mL). The mixture was stirred under nitrogen at room temperature for 15
20 hours before water (1 L) was added. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried (MgSO_4) and evaporated. Flash chromatography of the residue (silica gel; hexane/EtOAc (4:1)) yielded the title
25 ether as a colorless liquid.

Step 3: 3-[4-(4-Methoxy)tetrahydropyranyl]benzyl bromide

30 A mixture of the toluene (16 g) from Step 2, N-bromosuccinimide (14.6 g) and azoisobutyronitrile (AIBN) (127 mg) in CCl_4 (250 mL) was refluxed for 1.5

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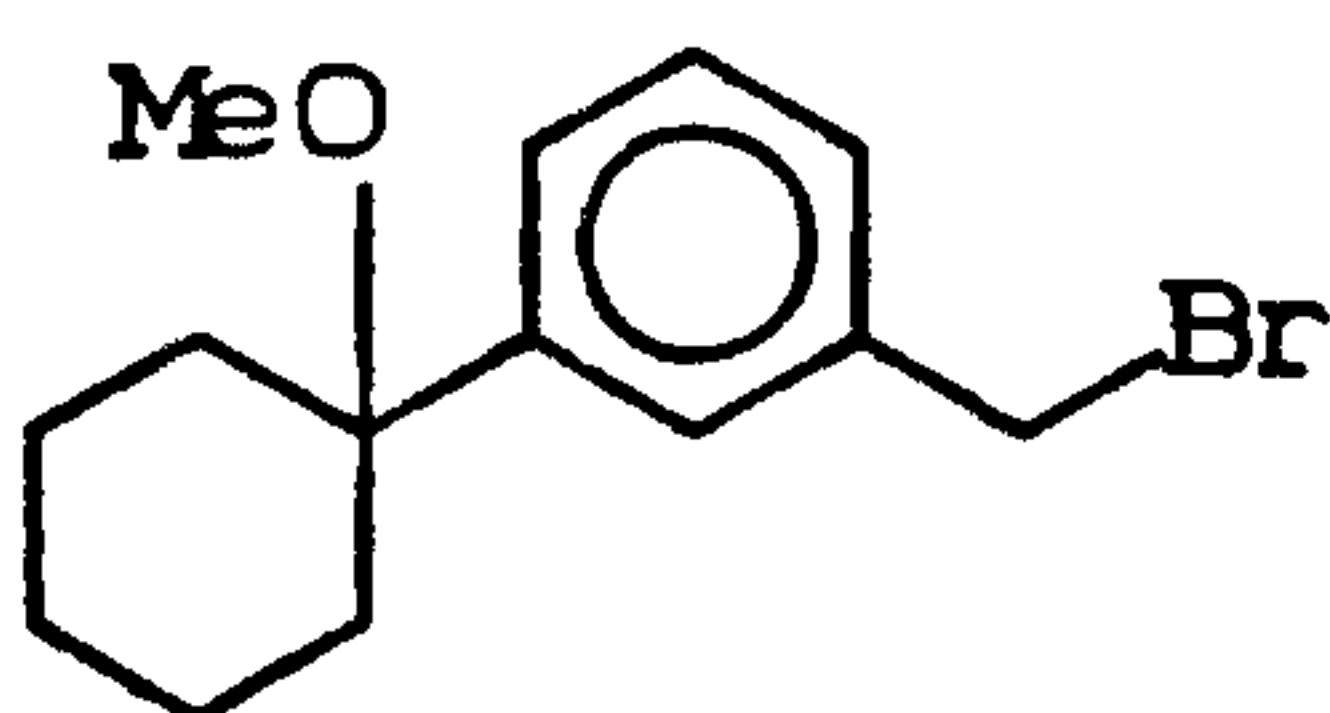
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ethyl iodide (0.38 mL). After the mixture had been stirred at room temperature for 22 hours, ether (25 mL) was added. The organic phase was then washed with water (2x 25 mL) and brine, dried (MgSO₄), and evaporated. Flash chromatography of the residue (silica gel; hexane/EtOAc, (85:15)) afforded the title product as a colorless liquid.

Step 2: 3-[4-(4-Ethoxy)tetrahydropyranyl]benzyl bromide

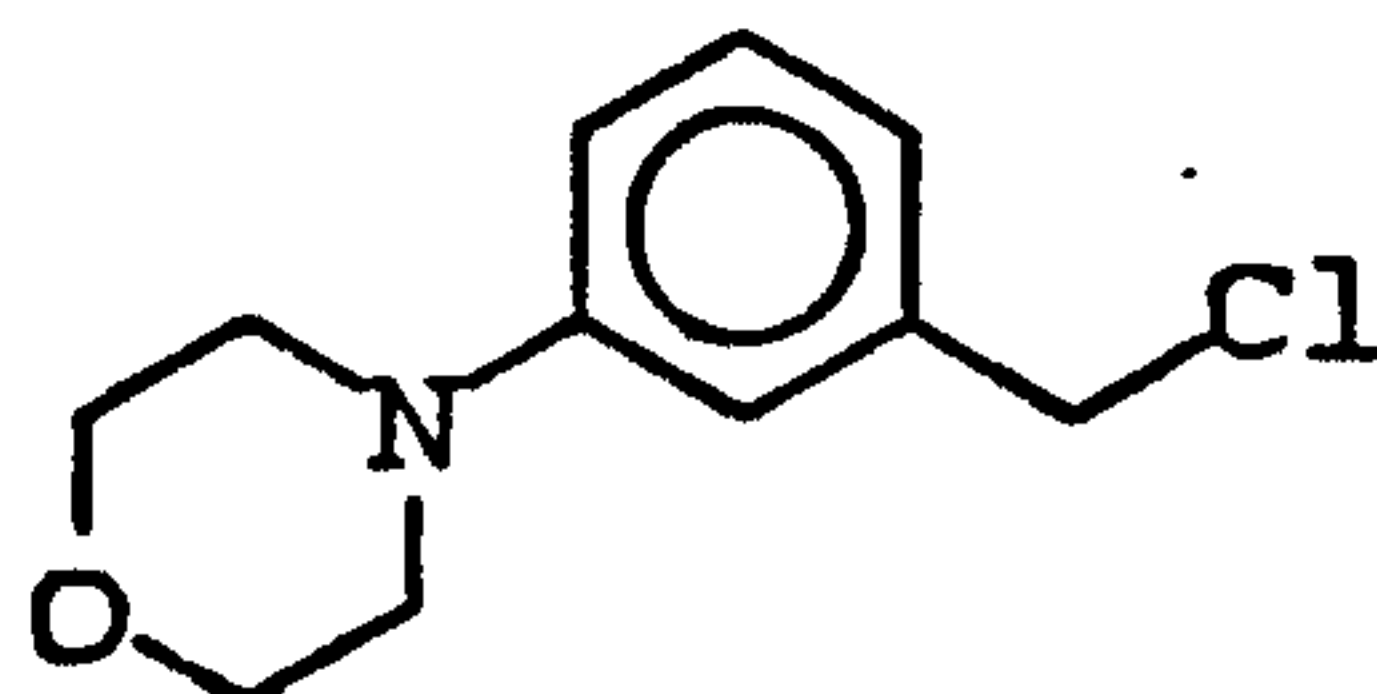
Following the procedure described in Halide 1, Step 3, but substituting the toluene from Halide 3, Step 1 for 3-[4-(4-methoxy)tetrahydropyranyl]-toluene, the title benzyl bromide was obtained as an oil.

Halide 4: 3-(1-Methoxycyclohexyl)benzyl bromide



Following the procedure described in Halide 1, Steps 1-3 but substituting cyclohexanone for tetrahydropyran-4-one, the title product was obtained as a liquid.

Halide 5: 3-(N-Morpholino)benzyl chloride



10 Step 1: Ethyl 3-(N-morpholino)benzoate

15 In a glass pressure vessel containing a magnetic stirrer was placed morpholine (8.7 g; 100 mmol), ethyl 3-bromobenzoate (20.6 g; 90 mmol), cupric oxide (0.79 g; 10 mmol), potassium carbonate (13.8 g; 100 mmol) and pyridine (20 mL). The vessel was closed and heated under pressure at 175°C for 18 hrs. The mixture was cooled and stirred with water and diethyl ether. The organic layer was separated, washed with water, 1N hydrochloric acid, dried (MgSO₄), filtered and concentrated. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane to obtain the title compound in low yield as an oil.

25 Step 2: 3-(N-Morpholino)benzyl alcohol

30 To a solution of ethyl 3-(N-morpholino)benzoate (432 mg; 1.8 mmol) in THF (15 mL) at 0-5°C was added lithium aluminum hydride (209 mg; 5.5 mmol) in portions under a nitrogen atmosphere. After stirring for 30 min., excess water was added dropwise.

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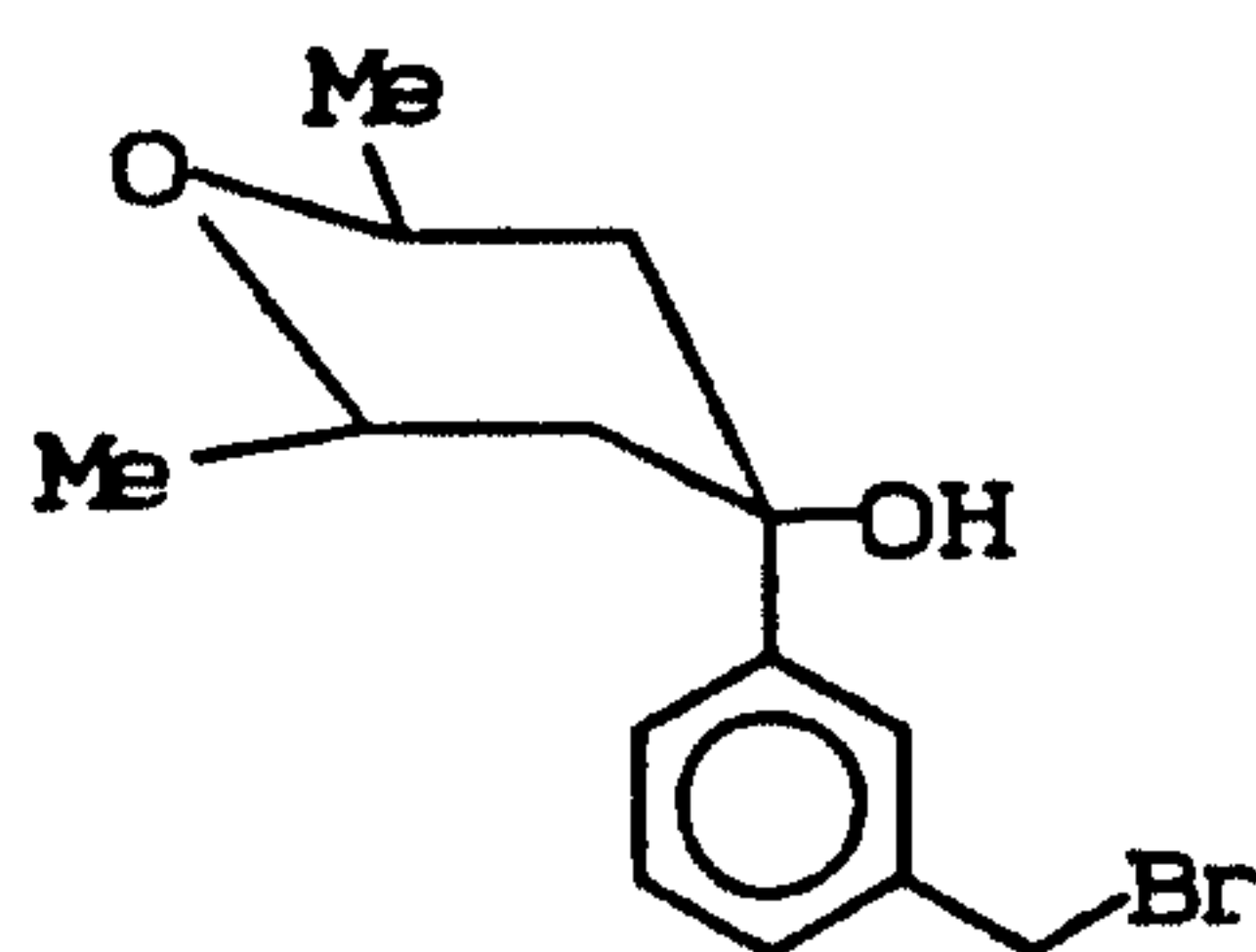
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Diethyl ether and 1N sodium hydroxide were then added. The organic layer was separated, dried (MgSO_4), filtered and concentrated to obtain the title compound as an oil which was used as such in the next reaction.

Step 3: 3-(N-Morpholino)benzyl chloride

To a solution of 3-(N-morpholino)benzyl alcohol (265 mg; 1.3 mmol) and hexamethyl phosphorus triamide (502 μL ; 2.7 mmol) in dichloromethane (10 mL) was added at room temperature carbon tetrachloride (280 μL ; 2.7 mmol). The mixture was stirred for 15 minutes and then concentrated. Diethyl ether was added to the residue and the mixture filtered through celite. The filtrate was concentrated and the residue chromatographed on silica gel using 30% ethyl acetate in hexane to obtain the title compound. m.p. 52-55°C.

Halide 6: 3-[4-(4 β -Hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyl bromide



Step 1: 3-Bromo-0-tetrahydropyranylbenzyl alcohol

5 To a solution of 3-bromobenzyl alcohol (11.5 g; Aldrich) dissolved in CH_2Cl_2 (100 mL) at 0°C and p-toluenesulfonic acid monohydrate (116 mg) was added 6.2 mL of DHP. The resulting solution was stirred at r.t. for 3 hr. then was quenched with NH_4OAc . The aqueous phase was extracted with CH_2Cl_2 . The combined organic phases were washed with brine, dried
10 (MgSO_4) and evaporated. Flash chromatography of the residue (silica gel; hexane/ EtOAc , 9:1) afforded the title compound as an oil.

Step 2: 2,6-Dimethyltetrahydropyran-4-one

15 A solution of 2,6-dimethyl- γ -pyrone (17 g) in 300 mL of EtOH 95% was hydrogenated for 3 days under 70 psi. After filtration over celite, without extraction, the solvent was evaporated and replaced
20 by CH_2Cl_2 . The solution was then treated with 30 g of celite and 48.5 g of pyridinium chlorochromate. The suspension was stirred for 3 hr. and the reaction was diluted with 300 mL of Et_2O and then filtered over a pad of celite. The filtrate was evaporated to
25 dryness and the residual solution was then chromatographed using hexane/ether (1:1) to give the title compound.

Step 3: 3-[4-(4B-Hydroxy-2,6-dimethyl)tetrahydro-
pyranyl]-O-tetrahydropyranylbenzyl alcohol

5 Following the procedure described in Halide 1,
Step 1, but substituting 3-bromo-O-tetrahydropyranyl-
benzyl alcohol from Halide 6, Step 1 for 3-bromo-
toluene and substituting 2,6-dimethyltetrahydropyran-
4-one from Halide 6, Step 2 for tetrahydropyran-4-one,
10 the title compound was obtained as a mixture of α
and β isomers (30:70). Both isomers could be
isolated from a flash column (hexane/EtOAc, 6:4).
The β -hydroxy isomer is more polar than the
 α -hydroxy isomer.

15 Step 4: 3-[4-(4B-Hydroxy-2,6-dimethyl)tetrahydro-
pyranyl]benzyl alcohol

20 The β -hydroxy-THP derivative (1.0 g) obtained in
Halide 6, Step 3, was dissolved in 10 mL of EtOH and
treated with 30 mg of p-toluenesulfonic acid. The
reaction was stirred at r.t. for 90 min. The EtOH
was evaporated and the resulting syrup was flash
chromatographed to give the title compound.

25 Step 5: 3-[4-(4B-Hydroxy-2,6-dimethyl)tetrahydro-
pyranyl]benzyl bromide

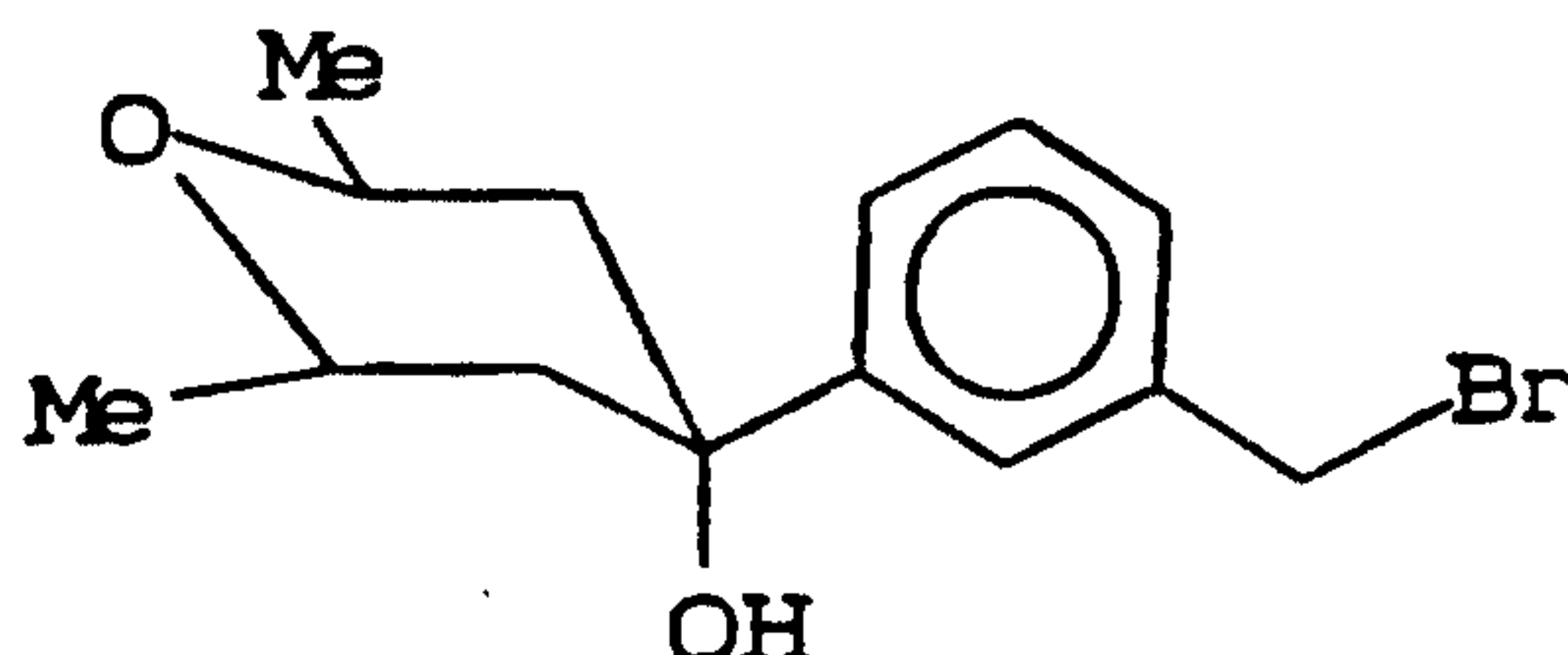
30 To a solution of alcohol (183 mg) from Halide 6,
Step 4, in CH_2Cl_2 (9 mL) was added 269 mg of CBr_4 .
The reaction was then cooled at -30°C and 298 mg of
DIPHOS was added in portions. After 10 min., the
reaction was quenched with a solution (10 mL) of 10%

EtOAc in hexane and without evaporation, the solvent was poured onto a silica gel column and eluted with EtOAc/hexane (3:7). The title compound was isolated and used immediately in the next step.

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Halide 7: 3-[4-(4 α -Hydroxy-2,6-dimethyl)tetrahydro-pyranyl]benzyl bromide

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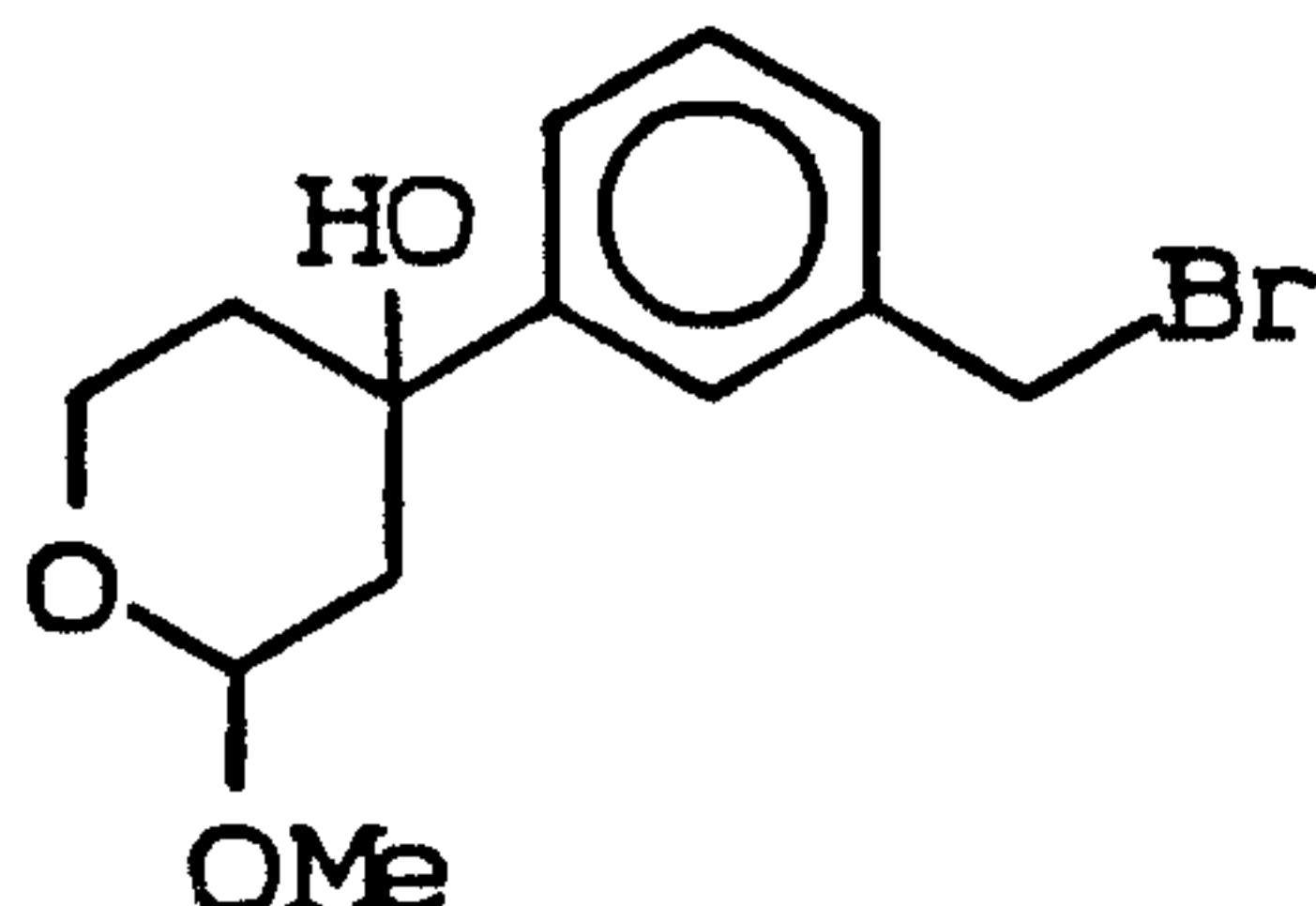
Step 1: 3-[4-(4 α -Hydroxy-2,6-dimethyl)tetrahydro-pyranyl]benzyl alcohol

Following the procedure described in Halide 6, Step 4, but substituting α -hydroxy-THP derivative from Halide 6, Step 3, for β -hydroxy-THP derivative, the title product was obtained.

Step 2: 3-[4-(4 α -Hydroxy-2,6-dimethyl)tetrahydro-pyranyl]benzyl bromide

Following the procedure described in Halide 6, Step 5, but substituting the α -hydroxy alcohol derivative from Halide 7, Step 1 for the β -hydroxy alcohol derivative, the title compound was obtained.

Halide 8: 3-[4-(4-Hydroxy-2-methoxy)tetrahydro-
pyranyl]benzyl bromide



Step 1: 3-[4-(4-Hydroxy-2,3-dihydropyranyl)toluene

Following the procedure described in Halide
1, Step 1, but substituting 2,3-dihydro-4H-pyran-4-one
15 (J. Org. Chem., 49, 1955 (1984)) for tetrahydropyran-
4-one, the title compound was obtained as an oil.

Step 2: 3-[4-(3-Bromo-4-hydroxy-2-methoxy)tetrahydro-
pyranyl]toluene

20 To a cold (10°C) solution of the alcohol
(1.45 g) from Step 1 in MeOH (15 mL) was added NBS
(1.36 g) and the resulting mixture stirred for 40
minutes. A phosphate buffer solution (pH 7, 50 mL)
25 was added to the reaction mixture and extracted with
CH₂Cl₂ (3x 25 mL). The organic layers were dried
over MgSO₄ and evaporated to dryness. Flash
chromatography of the residue (silica gel; hexane/
EtOAc, 80:20) afforded the title product as an oil.
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Step 3: 3-[4-(4-Hydroxy-2-methoxy)tetrahydropyranyl]-
toluene

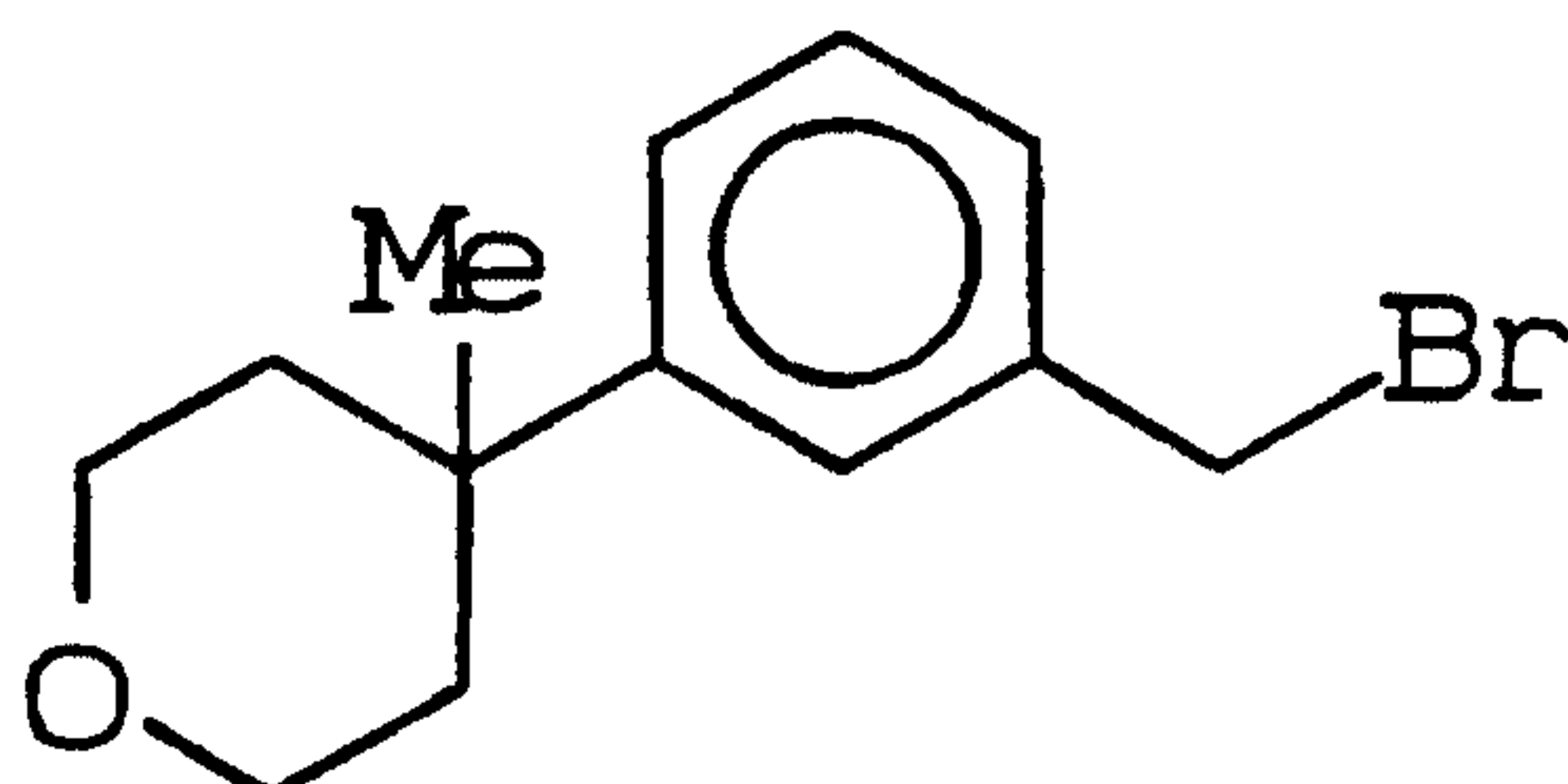
5 A mixture of the bromo alcohol (480 mg) from
Step 2, tributyltinhydride (0.43 mL) and AIBN (2 mg)
in toluene (3 mL) was refluxed under nitrogen for 2
hours. After evaporation, the resulting residue was
dissolved in CH₃CN (20 mL) and washed with hexane (3x
10 mL). The acetonitrile layer was evaporated to
dryness and the resulting residue was purified by
flash chromatography (silica gel; hexane/EtOAc,
85:15) to afford the title compound as an oil.

15 Step 4: 3-[4-(4-Hydroxy-2-methoxy)tetrahydropyranyl]-
benzyl bromide

Following the procedure described for Halide 1,
Step 3, but substituting 3-[4-(4-hydroxy-2-methoxy)-
20 tetrahydropyranyl]toluene from Step 3 for 3-[4-(4-
methoxy)tetrahydropyranyl]toluene, the title product
was obtained as an oil.

25 Halide 9: 3-[4-(4-Methyl)tetrahydropyranyl]benzyl
bromide

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Step 1: 3-[4-(4-Chloro)tetrahydropyranyl]toluene

5 A solution of 3-[4-(4-hydroxy)tetrahydro-
pyranyl]toluene (Halide 1, Step 1) (0.57 g in CHCl_3
(10 mL)) was added to a slurry of P_2Cl_5 (1.92 g) and
 K_2CO_3 (0.41 g) in CHCl_3 (10 mL) and stirred at 0°C
for 35 min. The reaction mixture was filtered.
Evaporation of the filtrate afforded the title
compound as a yellow semi-solid.

10

Step 2: 3-[4-(4-Methyl)tetrahydropyranyl]toluene

15 To a 0°C solution of the chloride (452 mg;
Step 1) in CH_2Cl_2 (7 mL) was added a solution of
trimethylaluminum in hexane (2.0 M; 2.2 mL;
Aldrich). The mixture was stirred at room
temperature for 19 hours before saturated NaHCO_3 was
added. The aqueous phase was extracted twice with
 CH_2Cl_2 and the combined organic phases were dried
20 (MgSO_4) and evaporated. Flash chromatography of the
residue (silica gel; hexane/EtOAc, 9:1) yielded the
title compound as a colorless liquid.

25 Step 3: 3-[4-(4-Methyl)tetrahydropyranyl]benzyl
bromide

Following the procedure described in Halide
1 Step 3, but substituting the toluene from Halide 8,
Step 2, for 3-[4-(4-methoxy)tetrahydropyranyl]toluene,
30 the title product was obtained as an oil.

5



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Step 1: 3-[4-(4 α -Hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]-O-tetrahydropyranylbenzyl alcohol

5 Following the procedure described in Halide
1 Step 1, but substituting 3-bromo-O-tetrahydro-
pyranylbenzyl alcohol (Halide 6, Step 1) for
3-bromotoluene and tetrahydro-2,2,6,6-tetramethyl-
thiopyran-4-one (J. Org. Chem. 43, 331 (1978)) for
10 tetrahydropyran-4-one, the title compound was
obtained.

Step 2: 3-[4-(4 α -Hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]benzyl alcohol

15 A solution of the THP derivative (1.5 g)
from Step 1, in 20 mL of EtOH and pyridinium
p-toluenesulfonate (39 mg) was heated at 55°C for 3
hours. Evaporation of the solvent followed by a
20 flash column (hexane/EtOAc, 7:3) gave the title
compound.

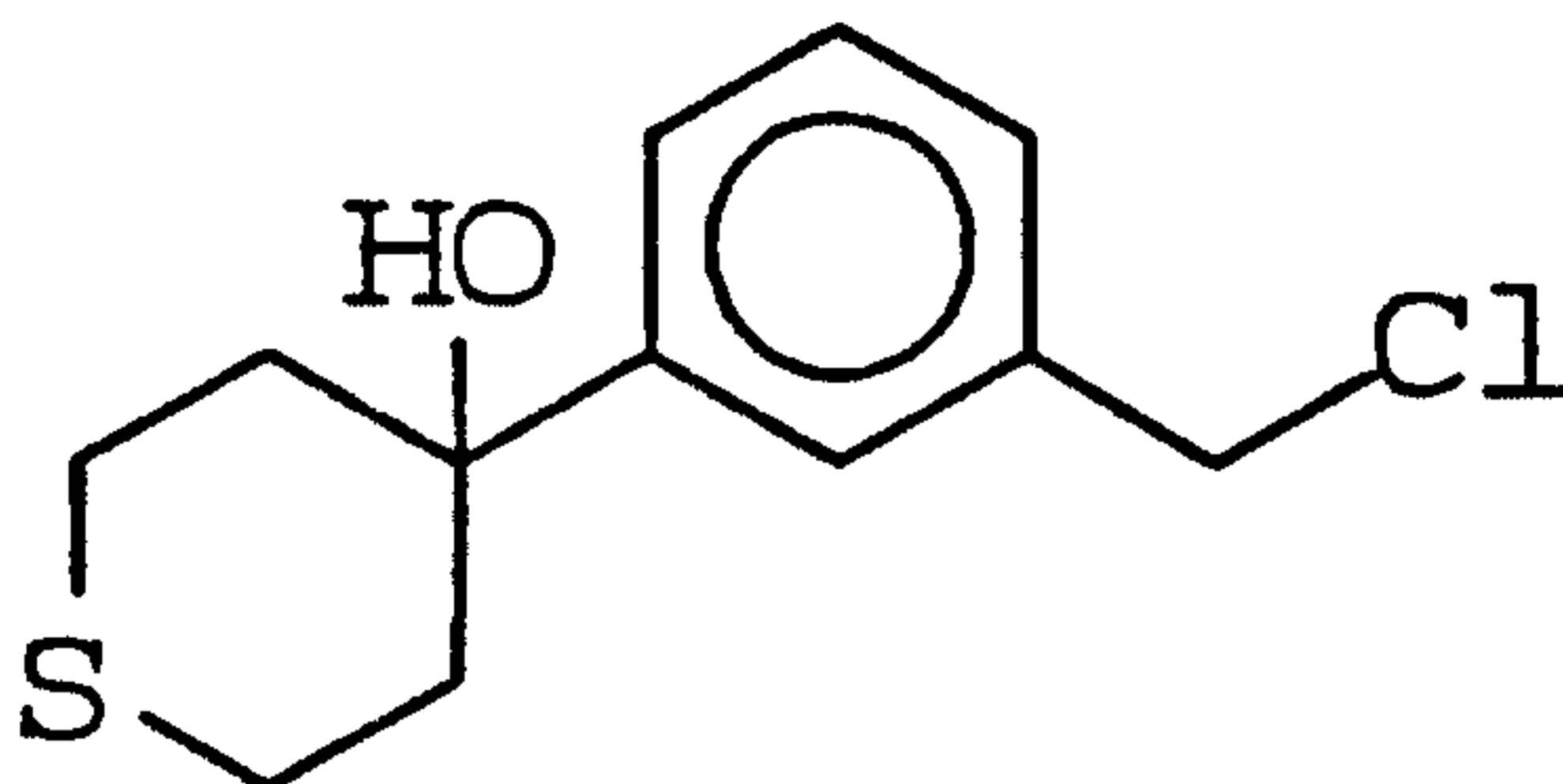
Step 3: 3-[4-(4 α -Hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]benzyl chloride

25 To a solution of the alcohol (500 mg) from
Step 2, in CH₂Cl₂ (20 ml) and CCl₄ (250 μ L) was added
Ph₃P (515 mg). The reaction was heated overnight at
70°C. Then the reaction was diluted with 10% EtOAc
30 in hexane and flash chromatographed directly to give
the title compound.

Halide 12: 3-[4-(4-Hydroxy)tetrahydrothiopyranyl]-
benzyl chloride

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Step 1: 3-[4-(4-Hydroxy)tetrahydrothiopyranyl]-0-
tetrahydropyranylbenzyl alcohol

15

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Following the procedure described in Halide 1 Step 1, but substituting 3-bromo-0-tetrahydropyranylbenzyl alcohol from Halide 6, Step 1, for 3-bromotoluene and substituting tetrahydrothiopyran-4-one (Aldrich) for tetrahydropyran-4-one, the title compound was obtained.

Step 2: 3-[4-(4-Hydroxy)tetrahydrothiopyranyl]benzyl
alcohol

25

Following the procedure described in Halide 6, Step 4, but substituting the THP derivative from Step 1 for the β -hydroxy-THP derivative, the title product was obtained.

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Step 3: 3-[4-(4-Hydroxy)tetrahydrothiopyranyl]benzyl chloride

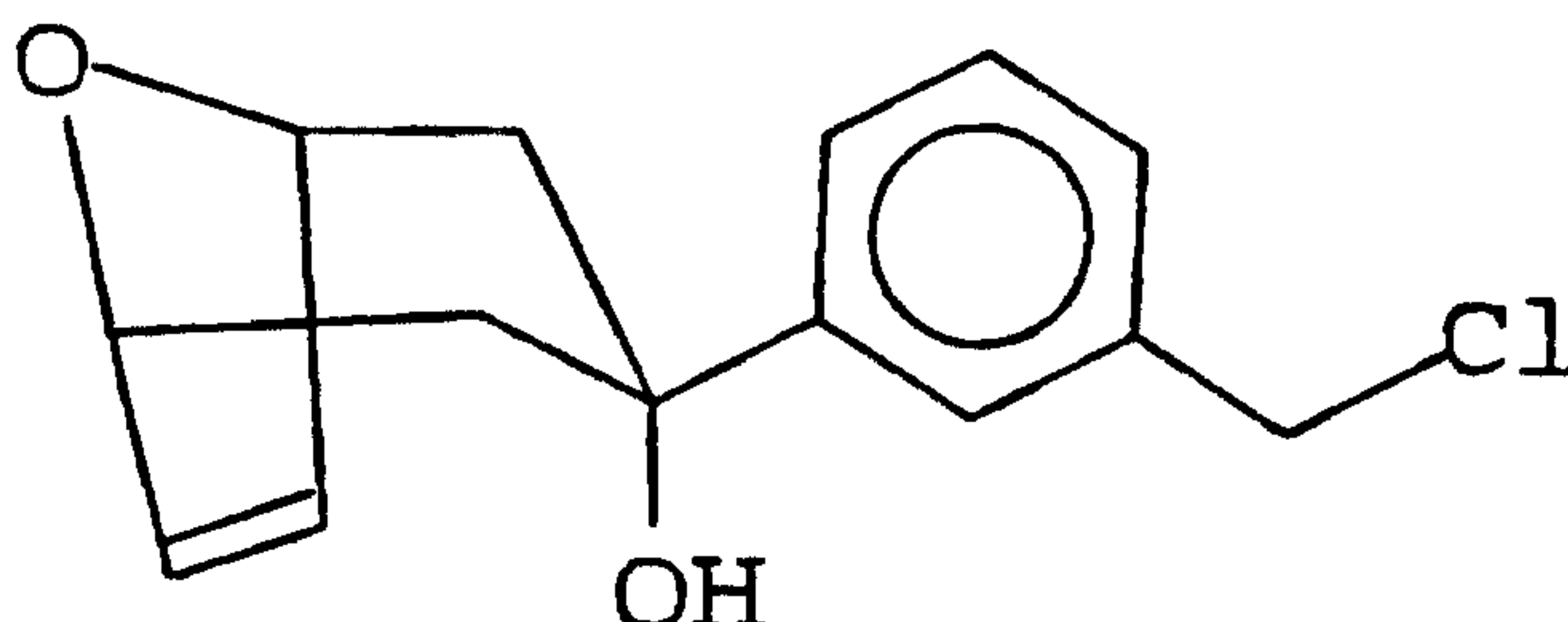
5 To a solution of the alcohol (572 mg, 2.3 mmol) from Step 2, in CH₂Cl₂ (20 mL) and CCl₄ (273 μL) was added Ph₃P (681 mg). The reaction was heated overnight at 70°C. Then the reaction was diluted with 10% EtOAc in hexane and flash chromatographed directly to give the title compound.

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Halide 13: 3-[3-(8-oxabicyclo[3.2.1]oct-6-en-3α-ol)-benzyl chloride

15

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Step 1: 3-[3-(8-Oxabicyclo[3.2.1]oct-6-en-3α-ol)-O-tetrahydropyranylbenzyl alcohol

25

Following the procedure described in Halide 1, Step 1, but substituting 3-bromo-O-tetrahydropyranylbenzyl alcohol from Halide 6, Step 1, for 3-bromotoluene and substituting 8-oxabicyclo[3.2.1]-oct-6-en-3-one (J. Amer. Chem. Soc. 100, 1765 (1978)) for tetrahydropyran-4-one, the title compound was obtained.

30

Step 2: 3-[3-(8-Oxabicyclo[3.2.1]oct-6-en-3 α -ol)-
benzyl alcohol]

5 Following the procedure described in Halide
11 Step 2, but using the THP derivative from Step 1,
the title product was obtained.

Step 3: 3-[3-(8-Oxabicyclo[3.2.1]oct-6-en-3 α -ol)-
benzyl chloride]

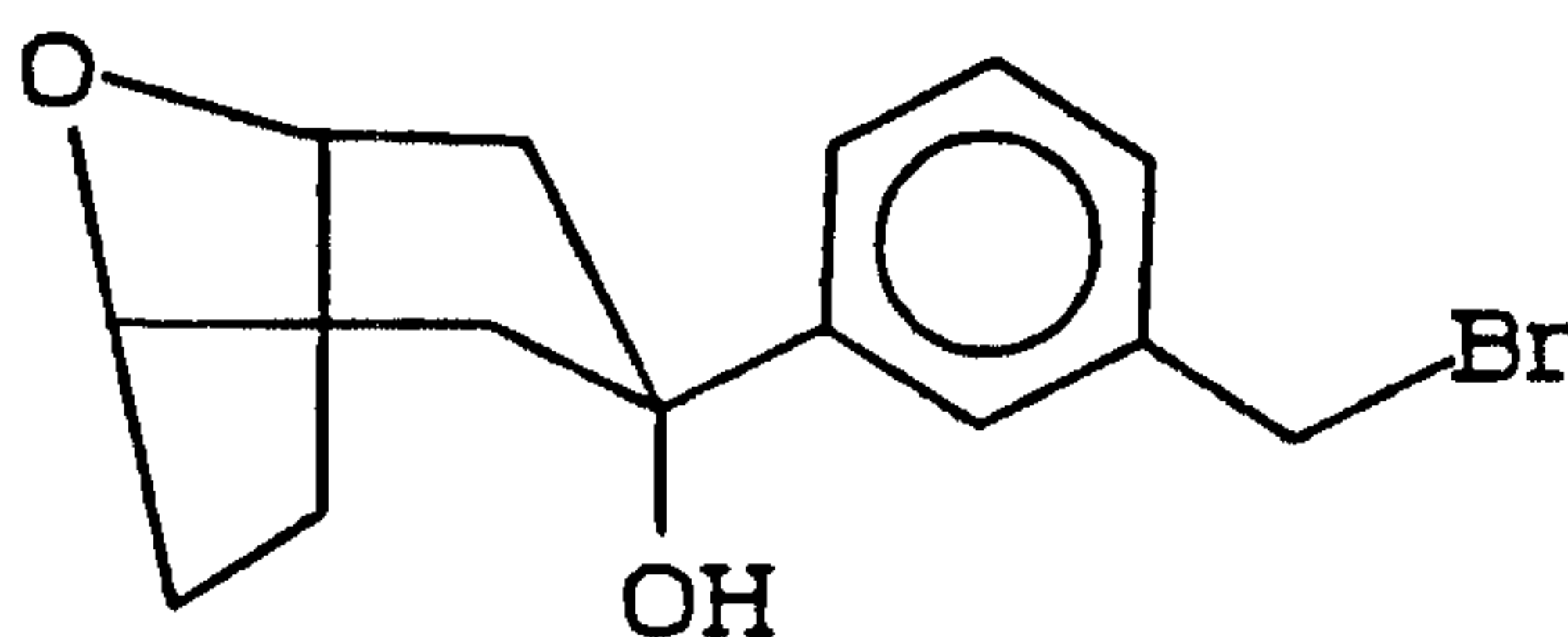
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To a solution of the alcohol (300 mg, 1.3
mmol) obtained from Step 2, in CH₂Cl₂ (5 mL) and CCl₄
(144 μ L) was added Ph₃P (407 mg). The reaction was
heated overnight at 70°C. The reaction was diluted
15 with 10% EtOAc in hexane and flash chromatographed
directly to give the title compound.

Halide 14: 3-[3-(8-Oxabicyclo[3.2.1]octan-3 α -ol)-
benzyl bromide]

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Step 1: 3-[3-(8-Oxabicyclo[3.2.1]oct-6-en-3 α -ol)]-
toluene

5 Following the procedure described in Halide
1, Step 1, but substituting 8-oxabicyclo[3.2.1]oct-
6-en-3-one (J. Amer. Chem. Soc. 100, 1765 (1978)) for
tetrahydropyran-4-one, the title compound was
obtained..

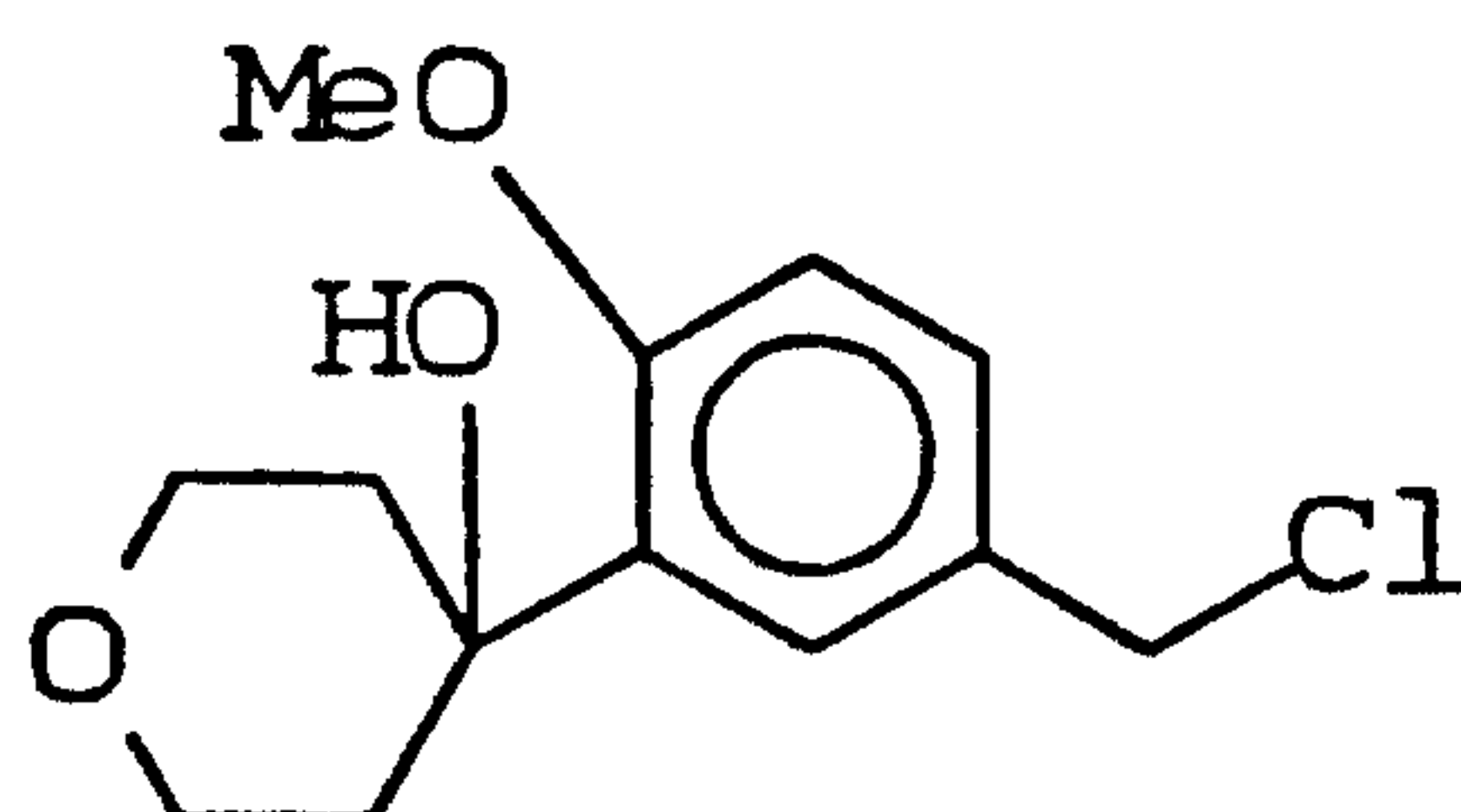
10 Step 2: 3-[3-(8-Oxabicyclo[3.2.1]octan-3 α -ol)]-
toluene

15 A mixture of the bicyclic alkene (1.50 g)
from Step 1 and 10% Pd/C on carbon (0.5 g) in EtOAc
(150 mL) and MeOH (15 mL) was stirred under hydrogen
at r.t. for 18 hours. The reaction mixture was then
filtered over celite and evaporation of the filtrate
afforded a yellow waxy solid. Trituration in ether
followed by filtration and evaporation of the
20 filtrate then gave a white solid. Purification by
flash chromatography (silica gel; hexane/EtOAc, 3:1)
yielded the title toluene.

25 Step 3: 3-[3-(8-Oxabicyclo[3.2.1]octan-3 α -ol)]benzyl
bromide

30 A mixture of the toluene (0.39 g) from Step
2, NBS (0.33 g) and benzoyl peroxide (10 mg) in CCl₄
(10 mL) was refluxed and irradiated with visible
light for 1.5 hours. Filtration and evaporation of
the filtrate gave the title benzyl bromide.

Halide 15: 3-[4-(4-Hydroxy)tetrahydropyranyl]-4-methoxybenzyl chloride



Step 1: 3-Bromo-4-methoxybenzyl alcohol

15 To a solution of 9.8 g (42 mmol) of 3-bromo-4-methoxybenzoic acid in THF (100 mL) was added 1M solution of borane in THF (130 mL) at r.t. under nitrogen. The resulting solution was then heated at 75°C for 30 min. The reaction mixture was then cooled to r.t. and MeOH (0.5 mL) was slowly added. The mixture was concentrated and successively treated

20 with MeOH (0.5 mL), evaporated (2x) and finally triturated with Et₂O and filtered to yield the title product as a solid, m.p.: 49-54°C.

25 Step 2: 3-[4-(4-Hydroxy)tetrahydropyranyl]-4-methoxybenzyl alcohol

30 To a solution of 9.1 g (42 mmol) of 3-bromo-4-methoxybenzyl alcohol from Step 1 in THF (250 mL) cooled at -78°C was added n-BuLi (1.6 M, 58 mL) and the resulting solution was stirred for 20 min., then tetrahydropyran-4-one (4.6 g) was added dropwise. The mixture was then allowed to warm to

r.t., diluted with brine and extracted with Et₂O.
The organic phase was dried over anhydrous MgSO₄ and
evaporated. The resulting product was purified by
flash chromatography using EtOAc as eluant to give
the title product.

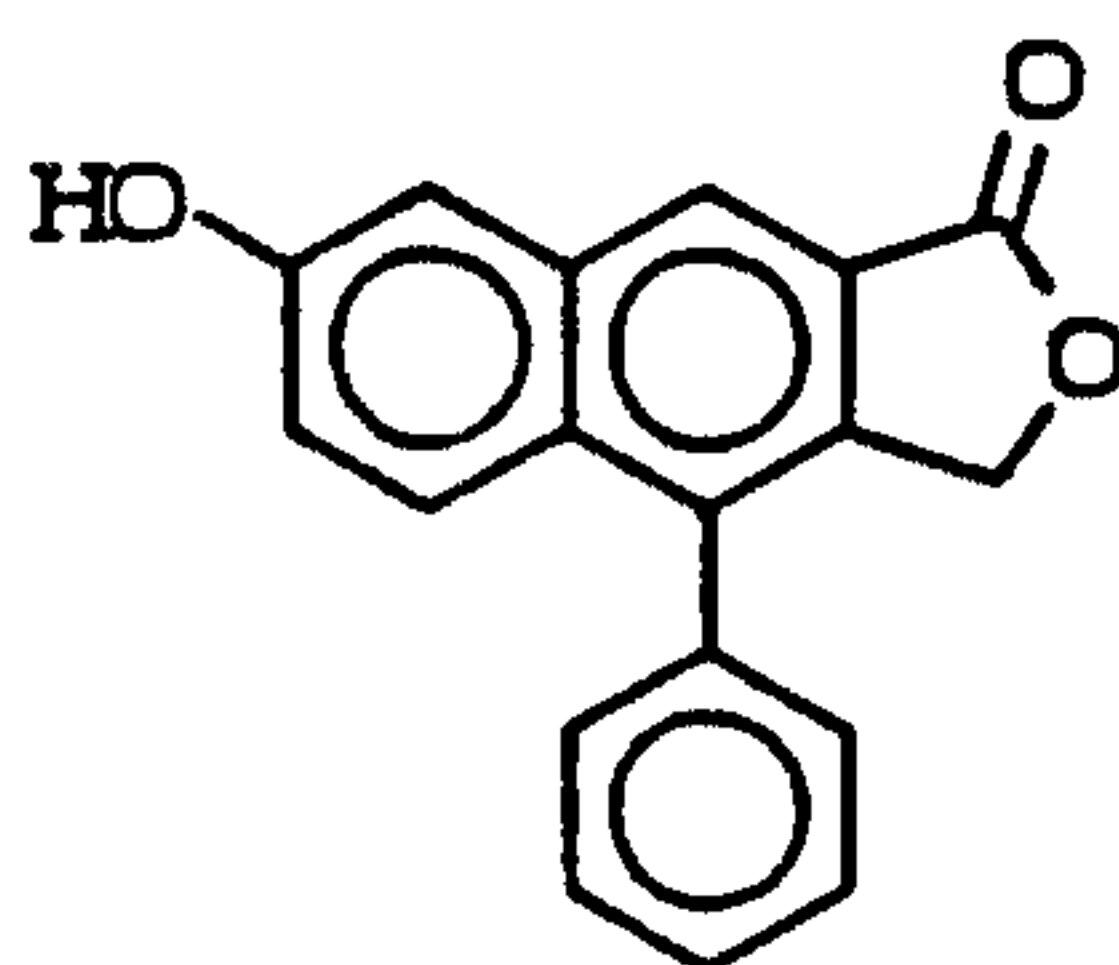
Step 3: 3-[4-(4-Hydroxy)tetrahydropyranyl]-4-methoxy-
benzyl chloride

To a solution of 4.0 g (16.8 mmol) of the
corresponding diol from Step 2 in THF (80 mL) was
added NaH (887 mg) by portion at r.t. The resulting
mixture was stirred for 1 hr then cooled to 5°C and
TsCl (3.8 g) was added. The reaction mixture was
then stirred at r.t. and LiCl (3 g) was added and
stirred for 1 hr. The resulting mixture was then
transferred to a solution of 20% citric acid and
extracted with Et₂O. The organic layer was washed
with brine, dried over anhydrous MgSO₄, filtered and
concentrated. Purification by flash chromatography
using 50% EtOAc in hexane gave 900 mg (21%) of the
title product, m.p.: 96-99°C.

PREPARATION OF LACTONES

Lactone 1: 7-Hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

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10

Method A:

15

Step 1: 3-Benzyloxy- β,β -dibromostyrene

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To a solution of triphenylphosphine (119.6 g) in methylene chloride (420 mL) at 0°C was added a solution of carbon tetrabromide (75.72 g) in methylene chloride (90 mL). After completion of the addition, the mixture was stirred for 10 min. Then a solution of 3-(benzyloxy)benzaldehyde (J.A.C.S., 99, 2571 (1977)) (40 g) in methylene chloride (150 ml) was added. The mixture was stirred for 16 hrs at -5°C. After warming to room temperature, the organic layer was washed with saturated sodium bicarbonate (2x 150 ml) and brine (1x 150 ml), then dried over magnesium sulfate, filtered and the mixture was concentrated. Ether (300 ml) was added, causing the formation of a precipitate which was filtered. The filtrate was concentrated and the process repeated 2

times. Finally, the filtrate was concentrated and chromatographed using 10% ethyl acetate in hexane, affording the title compound as a solid.

5 Step 2: 3-Benzyloxyphenylpropionic acid

 To a solution of the dibromide from Step 1 (15g) in tetrahydrofuran (150 ml) at -78°C was added slowly n-BuLi (53.4 ml, 1.6 M). Then the mixture was
10 left to warm to 0°C and stirred at that temperature for 1 hour. Carbon dioxide was bubbled for 10 min. through the mixture which was then diluted with water (150 ml) and 10N NaOH (20 ml). The aqueous layer was washed with ether (2x 100 ml), acidified with 6N HCl,
15 and extracted with ethyl acetate (300 ml). The organic layer was washed with brine (2x 150 ml), dried over magnesium sulfate, filtered and the solvent evaporated affording the title compound as a solid.

20

Step 3: 3-Phenylpropargyl 3-benzyloxyphenylpropiolate

 To a solution of acid (7.5 g) from Step 2
25 in toluene (123.8 ml) and N,N-dimethylformamide (10 ml) at 0°C was slowly added oxalyl chloride (2.84 ml). The mixture was stirred for 15 min., then slowly transferred into a solution of
3-phenyl-2-propyn-1-ol (J.O.C., 41, 4089 (1976))
30 (3.93 g) in tetrahydrofuran (82 ml) and triethylamine (9.94 ml) at 0°C. The mixture was stirred for 20

min. then saturated sodium bicarbonate (80 ml) was added, followed by ether (200 ml). The organic layer was washed with brine (2x 100 ml), dried over magnesium sulfate, filtered and the solvent
5 evaporated. Purification by chromatography afforded the title compound as a solid.

Step 4: 7-Benzyloxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form
10

A solution of the ester (6 g) from Step 3 in acetic acid (300 ml) was heated to reflux for 6 hours. Then the acetic acid was evaporated. Chromatography on silica gel, eluting with a mixture
15 of EtOAc/CH₂Cl₂/hexane (5:15:80), afforded the title product, m.p. 180-181°C.

Two side-products were isolated from this reaction: 3-hydroxymethyl-4-phenyl-5-benzyloxy-2-naphthoic acid, lactone form and 3-hydroxymethyl-
20 1-(3-benzyloxyphenyl)-2-naphthoic acid, lactone form.

Step 5: 7-Hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

A solution of the lactone from Step 4 (2.8 g; 7.6 mmol) in acetic acid (80 ml) and 6N hydrochloric acid (15 mL) was refluxed for 7 hours. The mixture was concentrated and then chromatographed
25 using 10% ethyl acetate in toluene to obtain the
30 title compound, m.p. 266-269°C.

Method B:

Step 1: 2-(α -Hydroxybenzyl)-5-benzyloxybenzaldehyde dimethylacetal

5

To a solution of 2-bromo-5-benzyloxy benzaldehyde dimethylacetal (Tet. Lett., 22, 5027 (1981)) (130 g) in THF (2.0 L), cooled to -78°C , was added dropwise a solution of n-BuLi (210 ml, 1.91 M) in hexane. After 15 min., a solution of benzalde48 mL) in THF (50 ml) was added dropwise. The cooling bath was removed, then the reaction mixture was warmed slowly (40 min.) to -10°C and quenched with a saturated NH_4Cl solution. The reaction mixture was diluted with Et_2O (2.0 L). The organic phase decanted, washed with H_2O (3x), brine, dried over MgSO_4 and the solvents evaporated. The residue was chromatographed on silica gel (hexane/ EtOAc 95:5 to 85:15) to give the title product as a foam.

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Step 2: 7-Benzyloxy-4-phenylnaphthalene-2,3-dicarboxylic anhydride

To a solution of the alcohol (112 g) from Step 1 in toluene (1.1 L) was added maleic anhydride (150 g). The reaction mixture was heated to reflux for 24 hours. After cooling to room temperature, the toluene was evaporated. The residue was triturated in EtOAc at 0°C , filtered and washed with Et_2O to afford the title product as a white solid.

25
30

Use of the title product is described in Method A, Step 5.

Method C:

Step 1: 2-Bromo-5-benzyloxybenzaldehydepropane
dithioacetal

To a solution of 2-bromo-5-benzyloxy benzaldehyde (Tet. Lett., 22, 5027 (1981)) (51.8 g) in CH₂Cl₂ (400 mL) was added 1,3-propanedithiol (17.5 mL), then BF₃•Et₂O (3 mL). The reaction mixture was stirred at room temperature for 16 hours then quenched with a saturated solution of NH₄Cl. The organic phase was extracted and washed with a saturated solution of sodium bicarbonate, H₂O, brine,

dried over MgSO_4 and evaporated. The solid residue was recrystallized from hexane/EtOAc to afford the title compound.

5 Step 2: 7-Benzoyloxy-4-phenylnaphthalene-2,3-
 dicarboxylic anhydride

 Following the procedures described in
Method B, Steps 1 and 2, but substituting the
10 thioacetal from Method C, Step 1 for 2-bromo-5-
 benzyloxy benzaldehyde dimethylacetal, the title
 compound was obtained as a foam.

 Use of the title product is described in
Method B, Step 3 and Method A, Step 5.

15

Method D:

Step 1: 2-Benzoyl-5-benzyloxybenzaldehyde
 dimethylacetal

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 To a solution of 2-bromo-5-benzyloxy
benzaldehyde dimethyl acetal (Tet. Lett., 22, 5027
(1981)) (52.2 g) in THF (600 mL), cooled to -78°C ,
was added dropwise a solution of n-BuLi (78 ml, 2.1
25 M) in hexane. After 15 min. $\text{CuBr}\cdot\text{SMe}_2$ (32 g) was
added in 3 portions. The reaction mixture was
stirred at -78°C until $\text{CuBr}\cdot\text{SMe}_2$ was dissolved
(approx. 1 hr.), then benzoyl chloride (20 mL) was
added dropwise. The cooling bath was removed and the
30 reaction mixture was stirred at room temperature over
night and was quenched with a saturated NH_4Cl
solution. The organic phase was diluted with Et_2O .

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washed with H₂O (3x), brine, dried (MgSO₄) and evaporated to afford the title compound which was used as such for the next step.

5 Step 2: 2-Benzoyl-5-benzyloxybenzaldehyde

10 A solution of crude ketone from Step 1 in acetone (250 mL) and HCl 10% (25 mL) was stirred for 6 hours, diluted with Et₂O, washed with a saturated NH₄Cl solution, H₂O (3x), brine and dried (MgSO₄). After evaporation of the solvent, the residue was saturated with hexane and filtered to afford the title compound as pale yellow solid.

15 Step 3: 7-Benzyloxy-4-phenylnaphthalene-2,3-dicarboxylic N-phenylimide

20 A solution of the keto aldehyde from Step 2 (27.9 g), N-phenyl maleimide (23 g) and triethyl phosphite (24 mL) in benzene (500 mL) was heated at reflux for 3 hours then stirred at room temperature overnight. The reaction mixture was filtered and the solid washed with Et₂O to give the title compound as a pale yellow solid.

25 Step 4: 7-Benzyloxy-4-phenylnaphthalene-2,3-dicarboxylic acid

30 A solution of the imide from Step 3 (5.3 g) in triglyme (30 mL) and NaOH (10N, 20 mL) was stirred at 120°C for 48 hours. The reaction mixture was cooled, extracted with H₂O (2x), and the water

phase acidified to pH 3 with conc. HCl, and filtered. The solid residue was dissolved in CHCl₃ and washed with H₂O, brine, dried (MgSO₄) and evaporated to afford the title compound which was used as such for the next step.

Step 5: 7-Benzyloxy-4-phenylnaphthalene-2,3-carboxylic anhydride

To a solution of the crude acid from Step 4 in THF (20 mL) at 0°C was added trifluoroacetic anhydride (TFAA) (5 mL) dropwise. The reaction mixture was stirred at 0°C for 1 hour then at room temperature overnight. After evaporation of the solution, the residue was triturated with Et₂O and filtered to afford the title compound as a white solid.

Use of the title product is described in Method B, Step 3 and Method A, Step 5.

Method E:

Step 1: Benzaldehyde phenyl dithioacetal

To a solution of benzaldehyde (31.8 g) and thiophenol (69.2 g) in isopropyl acetate (300 mL), cooled in an ice-water bath, there was slowly added BF₃•Et₂O (42.6 g). The resulting mixture was stirred in the cold for an additional hour. There was slowly added 10% aqueous K₂CO₃ (200 mL) and the phases were separated. The aqueous phase was extracted with EtOAc and the combined organic layers were washed

with 10% aq. K_2CO_3 , then with H_2O (3x), dried and evaporated down to an oil which solidified. This solid was stirred in pentane (250 mL) at r.t. for 5 hr. and filtered to afford the desired dithioacetal.

5

Step 2: 3-[α,α -bis(Phenylthio)benzyl]-2-(3-benzyl-oxy- α -hydroxybenzyl)butyrolactone

To a solution of the dithioacetal from Step 1 (23.5 g) in THF (250 mL), at $-70^\circ C$ there was slowly added 2.1M n-BuLi in hexanes (37 mL). The resulting yellow suspension was stirred for a further 20 min at $-70^\circ C$, then there was added dropwise 2-(5H)furanone (Omega Inc., 7.64 g) and, 30 min later, a solution of 3-benzyloxybenzaldehyde (Aldrich, 16.5 g) in THF (75 mL). The mixture was stirred a further hour at $-70^\circ C$, then there was slowly added glacial HOAc (9.0 g). The mixture was allowed to warm up to r.t., diluted with Et_2O (300 mL), washed with brine (4x), dried and evaporated. The residue was used as such in the next step.

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Step 3: 7-Hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

25

The crude product from Step 2 was dissolved in thioanisole (75 mL). There was added TFA (190 mL) and the mixture was heated to $60^\circ C$ for 1 hr. After cooling, the TFA was evaporated, the residue was diluted with Et_2O (200 mL), and after 20 min, the insoluble solid was filtered to afford the desired title compound.

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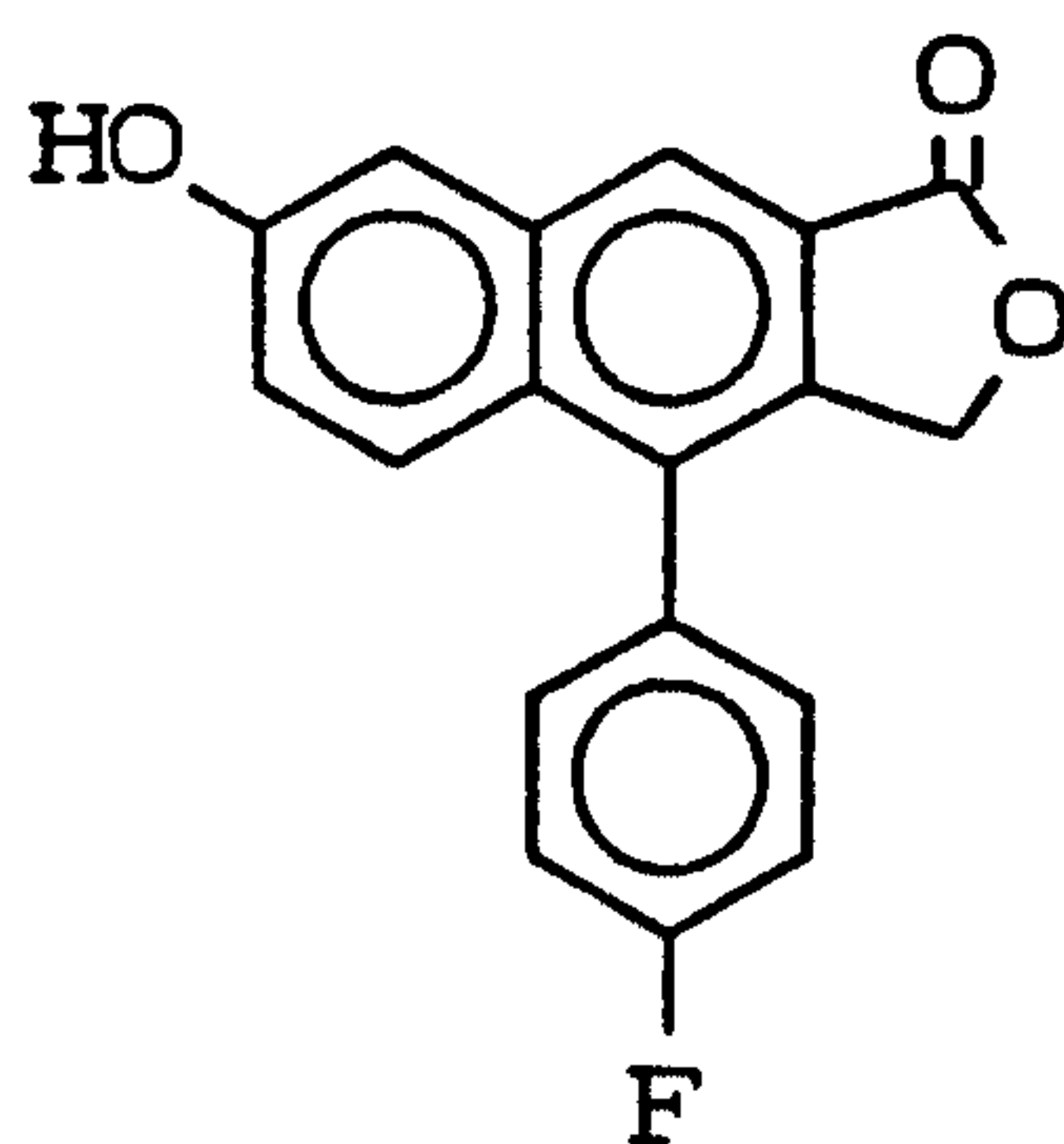
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Lactone 2: 7-Hydroxy-3-hydroxymethyl-4-(4-fluoro-phenyl)-2-naphthoic acid, lactone form

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5 Following the procedures described in
Lactone 1, Method A, Steps 3-5, but substituting
3-(4-fluorophenyl)-2-propyn-1-ol for 3-phenyl-2-
propyn-1-ol, the title product was obtained as a
solid.

Lactone 3: 7-Hydroxy-3-hydroxymethyl-4-(4-chloro-
phenyl)-2-naphthoic acid, lactone form

10 Following the procedure described in Lactone
1, Method B, Steps 1-3, followed by Method A, Step 5,
but substituting 4-chlorobenzaldehyde for
benzaldehyde, the title compound was obtained as a
solid.

15 Lactone 4: 7-Hydroxy-3-hydroxymethyl-4-(4-methoxy-
phenyl)-2-naphthoic acid, lactone form

20 Following the procedure described in Lactone
1, Method B, Steps 1-3, and followed by Method A,
Step 5, but substituting 4-methoxybenzaldehyde for
benzaldehyde, the title compound was obtained as a
solid.

25 Lactone 5: 7-Hydroxy-3-hydroxymethyl-4-(2-fluoro-
phenyl)-2-naphthoic acid, lactone form

30 Following the procedure described in Lactone
1, Method B, Steps 1-3, and followed by Method A,
Step 5, but substituting 2-fluorobenzaldehyde for
benzaldehyde, the title product was obtained as a
white solid.

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Lactone 6: 7-Hydroxy-3-hydroxymethyl-4-(2-chloro-
phenyl)-2-naphthoic acid, lactone form

5 Following the procedure described in Lactone
1, Method B, Steps 1-3, and followed by Method A,
Step 5, but substituting 2-chlorobenzaldehyde for
benzaldehyde, the title product was obtained as a
white solid.

10 Lactone 7: 7-Hydroxy-3-hydroxymethyl-4-(3-methoxy-
phenyl)-2-naphthoic acid, lactone form

15 Following the procedure described in Lactone
1, Method E, but substituting m-anisaldehyde for
benzaldehyde, the title compound was obtained as a
white solid.

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EXAMPLES

5 The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting. All temperatures are in degrees Celsius.

EXAMPLE 1

10 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranylbenzyloxy]}-2-naphthoic acid, sodium salt

15 Step 1: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone form

A mixture of 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, (Halide 1), (1.04 g), 7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid lactone form (Lactone 1) (0.60 g), and potassium carbonate (0.78 g) in DMF (15 mL) was stirred at room temperature. After 17 hours, water was added and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with 1N NaOH, water and brine before being dried (MgSO₄) and evaporated. The resulting solid was crystallized in EtOAc to afford the title compound as a pale yellow solid, m.p. 191-192°C.

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Step 2: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt

5 A suspension of the lactone from Step 1 (0.50 g) in absolute ethanol (15 mL) was treated with 1N aqueous NaOH (1.2 mL) and refluxed for 21 hours. The resulting yellow solution was evaporated to dryness and gave the title salt as a yellow solid.

10

^1H NMR (250 MHz, DMSO- d_6): δ 1.92 (m, 4H), 2.86 (s, 3H), 3.69 (m, 4H) 4.18 (d, 2H), 5.23 (s, 2H), 7.0-7.6 (m, 12 H), 7.82 (t, 1H), 8.07 (s, 1H).

15

EXAMPLE 2

3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]phenoxymethyl}-2-naphthoic acid, sodium salt

20

Step 1: 3-Hydroxymethyl-4-phenyl-7-trifluoromethanesulfonyloxy-2-naphthoic acid, lactone form

25

To a solution of Lactone 1 (141 mg) in CH_2Cl_2 (25 mL) and pyridine (400 μL) at -78°C was added trifluoromethanesulfonic anhydride (150 μL) dropwise. The reaction mixture was stirred at room temperature for 30 min. diluted with Et_2O , quenched with a saturated NH_4Cl solution, washed successively with HCl (10%, 2x), H_2O , brine and dried (MgSO_4). Purification by flash chromatography (hexane/ EtOAc , 95% to 85%) gave the title compound.

30

Step 2: 7-Carbomethoxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

5 To a solution of the triflate ester from Step 1 (160 mg) in DMSO (5 mL) was added. MeOH (3 mL, Et₃N (110 μ L), 1,1-bis(diphenylphosphino)ferrocene (50 mg) and Pd(OAc)₂ (10 mg). The reaction mixture was saturated with carbon monoxide (bubbling for 10 min) then heated at 75°C under a CO atmosphere for 15
10 min. The reaction was cooled, diluted with Et₂O, washed with saturated NH₄Cl solution, H₂O, brine and dried (MgSO₄). Evaporation and purification of the residue by flash chromatography (hexane/EtOAc/CHCl₃ 75:15:10) afforded the title compound as a pale
15 yellow solid.

Step 3: 7-Carboxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

20 To a solution of the lactone from Step 2 (110 mg) in THF/H₂O (4:1, 10 mL) was added LiOH•H₂O (50 mg). After 30 min., the reaction mixture was acidified to pH 2-3, and the water phase saturated with NaCl. The organic phase was decanted, dried
25 (MgSO₄) and evaporated. The residue was purified by flash chromatography (CHCl₃/MeOH, 85:15) to afford the title compound.

Step 4 3,7-Dihydroxymethyl-4-phenyl-2-naphthoic
 acid, lactone form

5 To a solution of the acid from Step 3 (94
mg) in THF (10 mL) at -70°C was added Et₃N (65 µL),
then isopropyl chloroformate (48 µL). After 20 min.,
NaBH₄ (25 mg) in H₂O (2 mL) was added and the
reaction mixture was stirred at room temperature for
30 min. The reaction was diluted with EtOAc and
10 saturated NH₄Cl solution, washed with H₂O, brine and
dried (MgSO₄). After evaporation, the residue was
purified by flash chromatography (CHCl₃/MeOH, 99:1 to
97:3) to give the title compound.

15 Step 5: 7-Bromomethyl-3-hydroxymethyl-4-phenyl-2-
 naphthoic acid, lactone form

 To a solution of the alcohol from Step 4 (76
mg) in CH₂Cl₂ (10 mL) at 0°C was added Ph₃P (76 mg),
20 imidazole (20 mg) and CBr₄ (90 mg). The reaction
mixture was stirred 30 min. at 0°C then diluted with
H₂O, brine and dried (MgSO₄). After evaporation, the
residue was purified by flash chromatography
(hexane/EtOAc, 85:15) to give the title compound.

25 Step 6: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-
 methoxy)tetrahydropyranyl]phenoxymethyl}-
 2-naphthoic acid, lactone form

30 Following the procedure described in Example
1 but substituting 3-[4-(4-methoxy)tetrahydro-
pyranyl]phenol (EP-A-351,194) for 7-hydroxy-3-

hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form, and substituting 7-bromomethyl-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form, from Step 5 for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, the title product was obtained as a cream colored solid, m.p. 165-166°C.

Step 7: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]phenoxymethyl}-2-naphthoic acid, sodium salt

Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 6 for 3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)-tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 3

3-Hydroxymethyl-4-(4-fluorophenyl)-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt

Step 1: 3-Hydroxymethyl-4-(4-fluorophenyl)-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone form

Following the procedure described in Example 1 but substituting 7-hydroxy-3-hydroxymethyl-4-(4-fluorophenyl)-2-naphthoic acid, lactone form, (Lactone 2), for 7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form, the title compound was obtained as a white solid, m.p. 140-141°C.

Step 2: 3-Hydroxymethyl-4-(4-fluorophenyl)-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)-tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone form, the title product is obtained.

10

EXAMPLE 4

3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt

15

Step 1: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone form

20 Following the procedure described in Example 1 but substituting 3-[4-(4-hydroxy)tetrahydropyranyl]-benzyl bromide (Halide 2) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, the title product was obtained as a white solid, m.p. 191-192°C.

25

Step 2: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt

30 Following the procedure of Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-{3-[4-methoxy)tetrahydro-

pyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product was obtained as a yellow solid. ¹H NMR(250 MHz, DMSO-d₆): δ 1.56 (m, 2H), 1.98 (m, 2H), 3.75 (m, 4H) 4.17 (d, 2H), 5.09 (s, 1H), 5.21 (s, 2H) 7.0-7.6 (m, 11 H), 7.65 (s, 1H), 7.95 (br s, 1H), 8.05 (s, 1H).

EXAMPLE 5

10 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-ethoxy)-tetrahydro-
pyranyl]benzyloxy}-2-naphthoic acid, sodium salt

15 Step 1: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-ethoxy)-
tetrahydropyranyl]benzyloxy}-2-naphthoic
acid, lactone form

20 Following the procedure described in Example 1 but substituting 3-[4-(4-ethoxy)tetrahydro-
pyranyl]benzyl bromide (Halide 3) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, the title
compound was obtained as a white solid, m.p. 153-155°C.

25 Step 2: 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-ethoxy)-
tetrahydropyranyl]benzyloxy}-2-naphthoic
acid, sodium salt

30 Following the procedure of Example 1, Step 2, but substituting the lactone from Step 1 for
3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone
form, the title product was obtained as a yellow solid.

¹H-NMR (250 MHz, DMSO-d₆): δ 1.02 (t, 3H), 1.90 (m, 4H), 2.99 (q, 2H), 3.70 (m, 4H), 4.18 (d, 2H), 5.24 (s, 2H), 7.0-7.6 (m, 12H), 7.82 (t, 1H), 8.06 (s, 1H).

5

EXAMPLE 6

3-Hydroxymethyl-4-phenyl-7-{3-(1-methoxycyclohexyl)-benzyloxy}-2-naphthoic acid, sodium salt

10

Step 1: 3-Hydroxymethyl-4-phenyl-7-{3-(1-methoxycyclohexyl)benzyloxy}-2-naphthoic acid, lactone form

15

Following the procedure described in Example 1 but substituting 3-(1-methoxycyclohexyl)-benzyl bromide (Halide 4) for 3-[4-(4-methoxy)-tetrahydropyranyl]benzyl bromide, the title compound was obtained as a white solid, m.p. 174-176°C.

20

Step 2: 3-Hydroxymethyl-4-phenyl-7-{3-(1-methoxycyclohexyl)benzyloxy}-2-naphthoic acid, sodium salt

25

Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)-tetrahydropyranyl]benzyloxy}-2-naphthoic acid, lactone form, the title product is obtained.

30

EXAMPLE 7

3-Hydroxymethyl-4-phenyl-7-{3-(N-morpholino)benzyl-
oxy}-2-naphthoic acid, sodium salt

5

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-(N-morpholi-
no)benzyloxy]-2-naphthoic acid, lactone form

Following the procedure described in Example
10 1 but substituting 3-(N-morpholino)benzyl chloride
(Halide 5) for 3-[4-(4-methoxy)tetrahydropyranyl]-
benzyl bromide, the title product was obtained as a
white solid, m.p. 194-196°C.

15 Step 2: 3-Hydroxymethyl-4-phenyl-7-{3-(N-morpho-
lino)benzyloxy}-2-naphthoic acid, sodium
salt

Following the procedure described in Example
20 1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)-
tetrahydropyranyl]benzyloxy}-2-naphthoic acid,
lactone form, the title product is obtained.

25

30

EXAMPLE 8

3-Hydroxymethyl-4-phenyl-7-{3-(N-oxomorpholino)-
benzyloxy}-2-naphthoic acid, sodium salt

5

Step 1: 3-Hydroxymethyl-4-phenyl-7-{3-(N-oxomor-
pholino)benzyloxy}-2-naphthoic acid, lactone
form

10

To a solution of 3-hydroxymethyl-4-
phenyl-7-[3-(N-morpholino)benzyloxy]-2-naphthoic
acid, lactone form (from Example 7, Step 1) (40 mg;
0.08 mmol) in dichloromethane (5 mL) was added 85%
meta-chloroperbenzoic acid (28 mg; 0.11 mmol). The
mixture was stirred for one hour at room temperature
and then excess calcium hydroxide added. After
stirring for 15 minutes the mixture was filtered
through celite and the filtrate concentrated. The
residue was chromatographed using 10% methanol in
dichloromethane to obtain the title compound, m.p.
199-200°C.

15

20

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-(N-oxomorpho-
lino)benzyloxy]-2-naphthoic acid, sodium
salt

25

Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)-
tetrahydropyranyl]benzyloxy}-2-naphthoic acid,
lactone form, the title product is obtained.

30

EXAMPLE 9

3-Formyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydro-
pyranyl]benzyloxy}-2-naphthoic acid, sodium salt

5

Step 1: 3-Formyl-4-phenyl-7-{3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy}-2-naphthoic acid,
lactone form

10

A suspension of 3-hydroxymethyl-4-phenyl-
7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-
naphthoic acid sodium salt (9 mg) from Example 1 in
CH₂Cl₂ (0.5 mL) was treated with pyridinium
chlorochromate (5 mg) at room temperature for 40
minutes. The mixture was then eluted through a short
column of silica gel with 5% methanol in chloroform.
Preparative thin layer chromatography of the residue
gave the title compound as a colorless gum.

15

20

¹H NMR (250 MHz, CDCl₃): δ 2.00 (m, 4H), 2.99 (s,
3H), 3.85 (m, 4H), 5.25 (s, 2H), 6.63 (s, 1H),
7.25-7.55 (m, 12H), 7.69 (d, 1H) and 8.33 (s, 1H).

25

Step 2: 3-Formyl-4-phenyl-7-{3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy}-2-naphthoic acid,
sodium salt

30

Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)-
tetrahydropyranyl]benzyloxy}-2-naphthoic acid,
lactone form, the title product is obtained.

EXAMPLE 11

3-Hydroxymethyl-4-phenyl-7-[3-[4-(2,4-dihydroxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
2-methoxy)tetrahydropyranyl]benzyloxy]-2-
naphthoic acid, lactone form

10

Following the procedure described in Example 1 but substituting 3-[4-(4-hydroxy-2-methoxy)tetrahydropyranyl]benzyl bromide (Halide 8) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, the title compound was obtained as a yellow gum.

15

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(2,4-
dihydroxy)tetrahydropyranyl]benzyloxy]-2-
naphthoic acid, lactone form

20

To a solution of the methoxy alcohol (85 mg) from Step 1 in THF (1.5 mL) was added 10% aqueous HCl (1 mL) and the resulting solution was stirred at r.t. for 3 hr. The reaction mixture was basified with a solution of NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and evaporated to dryness. The residue was purified by preparative TLC (silica gel; CHCl₃/EtOAc, 40:60) to afford the title product as a white solid. ¹H NMR (250 MHz, CDCl₃): δ 1.83 (m, 1H), 2.05 (m, 2H), 2.31 (dt, 1H), 3.81 (m, 1H), 3.82 (s, 1H), 4.37 (d, 1H), 4.43 (dt, 1H), 5.22 (s, 2H), 5.24 (s, 2H), 5.41 (m, 1H), 7.29-7.59 (m, 10H), 7.67 (s, 1H), 7.73 (d, 1H) and 8.36 (s, 1H).

30

Step 3: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(2,4-dihydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 2 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

10

EXAMPLE 12

3-Formyl-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

15

Step 1: 3-Formyl-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

20

Following the procedure described in Example 9, Steps 1-2, but substituting the lactone from Example 4 for the lactone from Example 1, the title compound was obtained as a white solid, m.p. 214-218°C.

25

Step 2: 3-Formyl-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

30

Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 16

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,6-dimethyl)tetrahydropyranyl]-benzyloxy]-2-naphthoic acid, lactone form

Following the procedure described in Example 1 but substituting 3-[4-(4 α -hydroxy-2,6-dimethyl)-tetrahydropyranyl]benzyl bromide (Halide 7) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide (Halide 1) and substituting Cs₂CO₃ for K₂CO₃, the title compound was obtained as a white solid.

15 ¹H NMR (250 MHz, CDCl₃): δ 1.2 (d, 6H); 1.5-1.7 (m, 4H); 2.4 (broad s, 1H); 4.0 (m, 2H); 5.2-5.3 (2s, 4H); 7.2-7.6 (m, 11H); 7.75 (d, 1H); 8.4 (s, 1H).

20 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,6-dimethyl)tetrahydropyranyl]-benzyloxy]-2-naphthoic acid, sodium salt

25 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product was obtained.

30 ¹H NMR (250 MHz, DMSO-d₆): δ 1.1 (d, 6H); 1.4-1.7 (m, 4H); 3.8 (m, 2H); 4.2 (d, 2H); 5.0-5.1 (m, 1H); 5.2 (s, 2H); 7.1 (q, 1H); 7.2 (d, 1H); 7.3-7.7 (m, 8H); 7.9 (d, 1H); 8.0 (s, 1H); 8.5 (s, 1H).

EXAMPLE 17

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4B-hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4B-hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

15 Following the procedure described in Example 1 but substituting 3-[4-(4B-hydroxy-2,6-dimethyl)-tetrahydropyranyl]benzyl bromide (Halide 6) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide (Halide 1) and substituting Cs₂CO₃ for K₂CO₃, the title compound was obtained as a white solid.

20 ¹H NMR (250 MHz, CDCl₃): δ 1.2 (d, 6H); 1.65 (t, 2H); 1.9 (broad s, 1H); 2.4 (d, 2H); 3.4 (m, 2H); 5.25 (s, 4H); 7.2-7.6 (m, 11H); 7.75 (d, 1H); 8.4 (s, 1H).

25 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4B-hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

30 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 18

2061706

5 3-Hydroxymethyl-4-(4-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-(4-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

15 A mixture of Lactone 3 (450 mg, 1.45 mmol), Halide 2 (434 mg, 1.6 mmol) and Cs₂CO₃ (520 mg, 1.6 mmol) in DMF (10 mL) was stirred at r.t. for two hr. The mixture was diluted with H₂O and extracted twice
20 with EtOAc. The extracts were washed twice with brine, dried, and evaporated. The residue was chromatographed on silica gel, eluting with a 60:40 mixture of hexane and EtOAc, to afford the title compound. This was stirred at r.t. in a small volume
of Et₂O for 1 hr and filtered to afford the purified desired product; m.p. 125- 127°C.

25 Step 2: 3-Hydroxymethyl-4-(4-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

30 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]- 2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 19

2061706

5 3-Hydroxymethyl-4-(4-methoxyphenyl)-7-[3-[4-hydroxy)-
tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium
salt

10 Step 1: 3-Hydroxymethyl-4-(4-methoxyphenyl)-7-[3-
[4-hydroxy)tetrahydropyranyl]benzyloxy]-2-
naphthoic acid, lactone form

15 Following the procedure described in Example
18, but substituting 7-hydroxy-3-hydroxymethyl-4-(4-
methoxyphenyl)-2-naphthoic acid, lactone form
(Lactone 4) for 7-hydroxy-3-hydroxymethyl-4-(4-
chlorophenyl)-2-naphthoic acid, lactone form (Lactone
3), the title compound was obtained as a solid; m.p.
220-225°C.

20 Step 2: 3-Hydroxymethyl-4-(4-methoxyphenyl)-7-[3-[4-
hydroxy)tetrahydropyranyl]benzyloxy]-2-
naphthoic acid, sodium salt

25 Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, lactone
form, the title product is obtained.

30

EXAMPLE 20

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -methoxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -methoxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

15 A mixture of 3-hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid lactone form (from Example 17) (50 mg) in DMF (1 mL) was stirred at r.t. with excess of NaH and MeI. A solution of NH₄Cl was added and the reaction mixture was extracted with EtOAc and the combined organic phase was dried and evaporated. Flash column of the residue with 30% EtOAc in hexane afforded the title compound as a solid; m.p. 195°C.

20

25 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -methoxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

30 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

2061706

EXAMPLE 21

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy)-tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, lactone form

15 Following the procedure described in Example 1, but substituting 3-[4-(hydroxy)tetrahydrothiopyranyl]benzyl chloride (Halide 12) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide (Halide 1) and substituting Cs_2CO_3 for K_2CO_3 , the title compound was obtained as a white solid; m.p. 203-205°C.

20 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy)-tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt

25 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product was obtained.

30 ^1H NMR (250 MHz, DMSO-d_6): δ 2.1-1.8 (m, 4H); 2.4 (d, 2H); 3.1 (dd, 2H); 4.2 (d, 2H); 5.0-5.2 (m, 1H); 5.2 (s, 2H); 7.1 (q, 1H); 7.2 (d, 1H); 7.3-7.8 (m, 8H); 7.9 (s, 1H); 8.2 (s, 1H); 8.5 (s, 1H).

EXAMPLE 22

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-S-oxo)-
tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid,
sodium salt

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-S-oxo)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, lactone form

To a solution at -78°C of 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, lactone form (from Example 21) (50 mg; 0.1 mmol) in CH_2Cl_2 (1 mL) and THF (1 mL) was added 85% meta-chloroperbenzoic acid (21 mg; 0.12 mmol). The mixture was stirred for one hr. at -78°C and then filtered through celite and the filtrate concentrated. The residue was chromatographed using 5% MeOH in CHCl_3 to obtain the title compound as a foam.

^1H NMR (250 MHz, CDCl_3): δ 1.8 (d, 2H); 2.7-3.4 (m, 7H); 5.2-5.3 (2s, 4H); 7.2-7.8 (m, 12H); 8.3 (s, 1H).

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-S-oxo)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt

Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 23

2061703

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-S,S-di-
oxo)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic
acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
S,S-dioxo)tetrahydrothiopyranyl]benzyloxy]-2-
naphthoic acid, lactone form

15 Using 3.0 eq. of meta-chloroperbenzoic acid,
the procedure described in Example 22 was followed.
Aqueous work-up was done using EtOAc/NH₄OAc
extraction (3x). The combined organic layer was
dried and evaporated to give, after flash
chromatography, the title compound as a solid; m.p.
247-249°C.

20 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
S,S-dioxo)tetrahydrothiopyranyl]benzyloxy]-2-
naphthoic acid, sodium salt

25 Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, lactone
form, the title product is obtained.

30

EXAMPLE 24

2051706

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 α -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 α -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, and 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 β -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

15 To a solution of the diol (77 mg) from Example 11 in MeOH (3 mL) and THF (3 mL) was added p-TSA (2 mg) and the resulting solution was stirred at r.t. 21 hr. The solvents were then evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel; CHCl₃/EtOAc, 75:25 to 60:40) to afford first the α -glycoside as a white solid, (m.p. 179-180°C) followed by the β -glycoside as a white solid.

20 ¹H NMR (250 MHz, CDCl₃): δ 1.69 (m, 1H), 1.82 (s, 1H), 1.94-2.13 (m, 3H), 3.54 (s, 3H), 4.00-4.04 (m, 2H), 4.79 (dd, 1H), 5.20 (s, 2H), 5.23 (s, 2H), 7.28-7.64 (m, 11H), 7.72 (d, 1H), 8.35 (s, 1H).

30

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 α -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the α -glycoside lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic
10 ^1H NMR (250 MHz, DMSO- d_6): δ 1.56 (d, 1H); 1.77 (d, 1H); 2.12 (m, 2H); 3.30 (s, 3H); 3.53 (m, 1H); 4.06 (td, 1H); 4.17 (s, 2H); 4.73 (s, 1H); 5.20 (s, 2H); 7.03-7.55 (m, 11H); 7.65 (s, 1H); 8.07 (s, 1H).

15

EXAMPLE 25

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 β -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid,
20 sodium salt

25 Following the procedure described in Example 1, Step 2, but substituting the β -glycoside lactone from Example 24, Step 1, for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

30

2061706

EXAMPLE 26

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-methyl)tetrahydro-
pyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-methyl)-
tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, lactone form

10

Following the procedure described in Example 1 but substituting 3-[4-(4-methyl)tetrahydropyranyl]benzyl bromide (Halide 9) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, the title lactone was obtained as a white solid.

15

¹H NMR (250 MHz, CDCl₃): δ 1.32 (s, 3H), 1.72-1.85 (m, 2H), 2.08-2.20 (m, 2H), 3.63-3.85 (m, 4H), 5.23 (s, 2H), 5.26 (s, 2H), 7.30-7.60 (m, 11H), 7.74 (d, 1H), 8.39 (s, 1H).

20

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-methyl)-
tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt

25

Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

30

EXAMPLE 27

3-(1-Hydroxyethyl)-[3-[4-hydroxy)tetrahydropyranyl]-
benzyloxy]-4-phenyl-2-naphthoic acid, sodium salt

5

Step 1: 7-benzyloxy-2,3-bis(hydroxymethyl)-4-phenyl-
naphthalene

10

To a suspension of LAH (3 g) in THF (50 mL) at 0°C, was added the anhydride from Lactone 1, Method B, Step 2 (6 g) in small portions. The resulting reaction mixture was stirred at r.t. 2 hr. then heated to reflux for 55 hr. After cooling to 0°C, an aqueous solution of 6N HCl was added dropwise until the aluminum salts dissolved. The mixture was diluted with EtOAc, washed with H₂O (3x), brine, dried over MgSO₄, and the solvent evaporated. The residue was swished in ether for 1 hr, then filtered to afford the title diol as a white solid.

15

20

Step 2: 7-Benzyloxy-2-(tert-butyldiphenylsilyloxy-
methyl)-3-hydroxymethyl-4-phenylnaphthalene

25

To a solution of diol (1.02 g) from Step 1 in DMF (15 mL) was added imidazole (410 mg) and t-BuPh₂SiCl (790 µL) at r.t. After 1 hr. the reaction mixture was diluted with Et₂O, washed with H₂O (3x), brine, dried over MgSO₄, and the solvent evaporated. The residue was purified by chromatography on silica gel using hexane/EtOAc 95:5 to give the title product.

30

Step 3: 7-Benzyloxy-2-(tert-butyldiphenylsilyloxy-methyl)-3-formyl-4-phenylnaphthalene

5 To a solution of alcohol (1.2 g) from Step 2 in CH₂Cl₂ (25 mL) was added molecular sieves powder (1 g, flame dried) and PCC (1 g). After 40 min, the reaction mixture was poured on a plug of SiO₂ (wet with Et₂O), and eluted with Et₂O. The solvent was evaporated to give the title product.

10

Step 4: 7-Benzyloxy-2-(tert-butyldiphenylsilyloxy-methyl)-3-(1-hydroxyethyl)-4-phenylnaphthalene

15 To a solution of aldehyde (1.1 g) from Step 3 in THF (15 mL) at -78°C, was added MeMgBr (1.4M PhMe-THF, 2.8 mL) dropwise. After 10 min, the bath was removed and the reaction mixture quenched with a saturated solution of NH₄Cl. The reaction was diluted with Et₂O, washed with saturated NH₄Cl solution, H₂O, brine, dried over MgSO₄, and the solvent evaporated to afford the title product as a foam.

20

Step 5: 3-(1-Acetoxyethyl)-7-benzyloxy-2(tert-butyl-diphenylsilyloxymethyl)-4-phenylnaphthalene

25

30 To a solution alcohol (300 mg) from Step 4 in Ac₂O (2 mL) was added pyridine (300 mL) and DMAP (2 mg). After 2 hr, the reaction mixture was diluted with Et₂O, washed with H₂O, a solution of CuSO₄, and the solvent evaporated to give the title product which was used as such for the next step.

Step 6: 3-(1-Acetoxyethyl)-7-benzyloxy-2-hydroxy-
methyl-4-phenylnaphthalene

5 To a solution of the crude ether from Step 5
in THF (10 mL) at 0°C was added HOAc (4 drops)
followed by n-Bu₄NF (1M, THF, 1.4 mL). The reaction
mixture was stirred 2 hr. at 0°C then quenched with a
saturated solution of NH₄Cl and diluted with Et₂O.
10 The organic phase was washed with H₂O, brine, dried
over MgSO₄, and the solvent evaporated. The residue
was purified by chromatography on silica gel using
hexane/EtOAc, 7:3, to give the title product.

15 Step 7: 3-(1-Acetoxyethyl)-7-benzyloxy-4-phenyl-2-
naphthoic acid

To a solution of alcohol (110 mg) from Step 6 in
t-BuOH (6 mL) was added a KH₂PO₄ buffer solution (pH
7, 4 mL) and a solution of KMnO₄ (90 mg/2mL H₂O).
20 After 3 hr. at r.t., the reaction mixture was diluted
with EtOAc and an aqueous solution of Na₂SO₃. The
mixture was then acidified to pH 2, the organic phase
was separated, washed with H₂O, brine, dried over
MgSO₄ and evaporated to give the title product which
25 was used as such for the next step.

Step 8: 7-Benzyloxy-3-(1-hydroxyethyl)-4-phenyl-2-
naphthoic acid, lactone form

30 To a solution of the crude acid (100 mg)
from Step 7 in MeOH (3 mL) was added NaOMe (cat.).
After 24 hr, the solvent was evaporated to dryness.

The residue was dissolved in EtOAc (3 mL) and HCl 6N (2 drops). The reaction mixture was stirred 20 min, washed with H₂O (3x), brine, dried over MgSO₄, and the solvent evaporated to afford the title compound.

5

Step 9: 7-Hydroxy-3-(1-hydroxyethyl-4-phenyl-2-naphthoic acid, lactone form

10 To a solution of the lactone (90 mg) from Step 8 in EtOAc was added 10% Pd/C (11 mg) and the reaction mixture was stirred under H₂ for 24 hr. The solution was filtered and the solvent evaporated to afford the title product.

15 Step 10: 3-(1-Hydroxyethyl)-[3-[4-hydroxy)tetrahydro-pyranyl]benzyloxy]-4-phenyl-2-naphthoic acid, lactone form

20 Following the procedure described in Example 1 but substituting 7-hydroxy-3-(2-hydroxyethyl)-4-phenyl-2-naphthoic acid, lactone form, for 7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form, the title product was obtained as a glassy solid after purification by chromatography on silica gel using hexane/EtOAc/CH₂Cl₂ (7:3:5).

25 ¹H NMR (250 MHz, CDCl₃): δ 1.15 (d, 3H), 1.7 (m, 2H), 2.2 (m, 2H), 3.9 (m, 4H), 5.25 (s, 2H), 5.7 (q, 1H), 7.27-7.7 (m, 12H), 8.35(s, 1H).

30

Step 11: 3-(1-Hydroxyethyl)-[3-[4-hydroxy)tetrahydro-
pyranyl]benzyloxy]-4-phenyl-2-naphthoic
acid, sodium salt

5 Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 10
for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, lactone
form, the title product is obtained.

10

EXAMPLE 28

3-Hydroxymethyl-4-(4-fluorophenyl)-7-[3-[4-(4-
hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic
15 acid, sodium salt

Step 1: 3-Hydroxymethyl-4-(4-fluorophenyl)-7-[3-[4-
(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-
naphthoic acid, lactone form

20

Following the procedure described in Example
18, but substituting 7-hydroxy-3-hydroxymethyl-4-(4-
fluorophenyl)-2-naphthoic acid, lactone form (Lactone
2) for 7-hydroxy-3-hydroxymethyl-4-(4-chlorophenyl)-
25 2-naphthoic acid, lactone form (Lactone 3), the title
compound was obtained as a solid; m.p. 167-169°C
(dec).

30

Step 2: 3-Hydroxymethyl-4-(4-fluorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product was obtained.

10 ¹H NMR (300 MHz, DMSO-d₆): δ 1.53 (d, 2H), 2.0 (m, 2H), 3.65-3.85 (m, 4H), 4.18 (s, 2H), 5.08 (s, 1H), 5.22 (s, 2H), 7.10 (m, 2H), 7.23-7.50 (m, 8H), 7.66 (s, 1H), 7.90 (broad s, 1H), 8.06 (s, 1H).

15 EXAMPLE 29

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-ethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

20 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-ethyl)-tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

25 Following the procedure described in Example 1 but substituting 3-[4-(4-ethyl)tetrahydropyranyl]-benzyl bromide (Halide 10) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, the title lactone was obtained as a white solid; m.p. 157-159°C.

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-ethyl)-
tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt

5 Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, lactone
form, the title product is obtained.

10

EXAMPLE 30

3-Hydroxymethyl-4-(fluorophenyl)-7-[3-[4-(4-hydroxy)-
tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium
15 salt

Step 1: 3-Hydroxymethyl-4-(fluorophenyl)-7-[3-[4-(4-
hydroxy)tetrahydropyranyl]benzyloxy]-2-
naphthoic acid, lactone form

20

Following the procedure described in Example
18, but substituting 7-hydroxy-3-hydroxymethyl-4-(2-
fluorophenyl)-2-naphthoic acid, lactone form (Lactone
5) for 7-hydroxy-3-hydroxymethyl-4-(4-chlorophenyl)-
25 2-naphthoic acid, lactone form (Lactone 3), the title
compound was obtained as a solid; m.p. 194-196°C.

30

Step 2: 3-Hydroxymethyl-4-(fluorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

10

EXAMPLE 31

3-Hydroxymethyl-4-(2-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

15

Step 1: 3-Hydroxymethyl-4-(2-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

20

Following the procedure described in Example 18, but substituting 7-hydroxy-3-hydroxymethyl-4-(2-chlorophenyl)-2-naphthoic acid, lactone form (Lactone 6) for 7-hydroxy-3-hydroxymethyl-4-(4-chlorophenyl)-2-naphthoic acid, lactone form (Lactone 3), the title compound was obtained as a solid; m.p. 198-200°C (dec).

25

30

Step 2: 3-Hydroxymethyl-4-(2-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

10

EXAMPLE 32

3-Hydroxymethyl-4-(3-methoxyphenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

15

Step 1: 3-Hydroxymethyl-4-(3-methoxyphenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

20

Following the procedure described in Example 18, but substituting 7-hydroxy-3-hydroxymethyl-4-(3-methoxyphenyl)-2-naphthoic acid, lactone form (Lactone 7) for 7-hydroxy-3-hydroxymethyl-4-(4-chlorophenyl)-2-naphthoic acid, lactone form (Lactone 3), the title compound was obtained as a solid; m.p. 182-184°C (dec).

25

30

Step 2: 3-Hydroxymethyl-4-(3-methoxyphenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product was obtained.

10 ¹H NMR (300 MHz, DMSO-d₆): δ 1.53 (d, 2H), 1.98 (m, 2H), 3.65-3.85 (m, 4H), 3.80 (s, 3H), 4.18 (d, 2H), 5.09 (broad s, 1H), 5.21 (s, 2H), 6.80 (m, 2H), 6.98-7.12 (m, 2H), 7.18 (d, 1H), 7.43-7.52 (m, 5H), 7.66 (s, 1H), 7.95 (t, 1H), 8.05 (s, 1H).

15 EXAMPLE 33

20 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2α-isopropoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

25 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2α-isopropoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, and 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2β-isopropoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form

30 Following the procedure described in Examples 24 and 25, but substituting i-PrOH for MeOH, afforded the title compounds as a mixture. The two compounds were separated by flash chromatography

(silica gel; CHCl₃/EtOAc, 90:10 to 80:20), affording first the α - then the β -glycoside, both as white solids.

5 α -Glycoside:

¹H NMR (250 MHz, CDCl₃): δ 1.19 (d, 3H), 1.33 (d, 3H), 1.74 (d, 1H), 1.93 (d, 1H), 2.17 (dd, 1H), 2.29 (dd, 1H), 3.77 (dd, 1H), 4.04 (m, 1H), 4.25 (td, 1H), 5.10 (s, 1H), 5.18 (d, 1H), 5.23 (s, 2H), 5.25 (s, 2H), 7.30-7.75(m, 12H) 8.38 (s, 1H).

β -Glycoside:

¹H NMR (250 MHz, CDCl₃): δ 1.19 (d, 3H), 1.26 (d, 3H), 1.68 (d, 1H), 1.99-2.13 (m, 4H), 3.98-4.13 (m, 3H), 4.98 (dd, 1H), 5.20 (s, 2H), 5.24 (s, 2H), 7.28-7.75 (m, 12H), 8.36 (s, 1H).

20 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 α -isopropoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt

25 Following the procedure described in Example 1, Step 2, but substituting the α -glycoside lactone from Step 1, for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

30

EXAMPLE 34

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 β -isopropoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt

10 Following the procedure described in Example 1, Step 2, but substituting the β -glycoside lactone from Example 33, Step 1, for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 35

15 3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabicyclo[3,2,1]oct-6-en-3 α -ol)]benzyloxy]-2-naphthoic acid, sodium salt

20 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabicyclo[3,2,1]oct-6-en-3 α -ol)]benzyloxy]-2-naphthoic acid, lactone form

25 Following the procedure described in Example 1, but substituting Halide 13 for 3-[4-(4-methoxy)-tetrahydropyranyl]benzyl bromide, the title lactone was obtained as a white solid.

30 ^1H NMR (250 MHz, CDCl_3): δ 1.92 (d, 2H), 2.55 (dd, 2H), 3.10 (s, 1H), 4.94 (d, 2H), 5.22 (s, 2H), 5.26 (s, 2H), 6.62 (s, 2H), 7.29-7.60 (m, 10H), 7.65 (s, 1H), 7.72 (s, 1H), 8.39 (s, 1H).

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabicyclo[3,2,1]oct-6-en-3 α -ol)]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

10

EXAMPLE 36

3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabicyclo[3.2.1]octan-3 α -ol)]benzyloxy]-2-naphthoic acid,
15 sodium salt

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabicyclo[3.2.1]octan-3 α -ol)]benzyloxy]-2-naphthoic acid, lactone form

20

Following the procedure described in Example 1 but substituting Halide 14 for 3-[4-(4-methoxy)-tetrahydropyranyl]benzyl bromide, the title compound was obtained as an off-white solid.

25 ^1H NMR (250 MHz, CDCl_3): δ 1.81 (m, 2H), 1.98 (m, 3H), 2.40 (m, 4H), 4.52 (m, 2H), 5.18 (s, 2H), 5.23 (s, 2H), 7.27-7.74 (m, 12H), 8.35 (s, 1H).

30

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Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabicyclo[3.2.1]octan-3 α -ol)]benzyloxy]-2-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1, for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product was obtained.

10 ¹H NMR (250 MHz, DMSO-d₆): δ 1.75 (m, 4H); 2.10 (dd, 2H); 2.33 (d, 2H); 4.17 (d, 2H); 4.37 (broad s, 2H); 4.99 (s, 1H); 5.19 (s, 2H); 7.03-7.54 (m, 12H); 7.87 (t, 1H); 8.06 (s, 1H).

15

EXAMPLE 37

3-Hydroxymethyl-4-phenyl-7-[3-[4-(hydroxy)tetrahydropyranyl]-4-methoxybenzyloxy]-2-naphthoic acid, sodium salt

20

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(hydroxy)tetrahydropyranyl]-4-methoxybenzyloxy]-2-naphthoic acid, lactone form

25

Following the procedure described in Example 18 but substituting 3-[4-(4-hydroxy)tetrahydropyranyl]-4-methoxybenzyl bromide (Halide 15) for 3-[4-(4-hydroxy)tetrahydropyranyl]benzyl bromide (Halide 2) and 7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid lactone form (Lactone 1) for 7-hydroxy-3-hydroxymethyl-4-(4-chlorophenyl)-2-naphthoic acid lactone form (Lactone 3), the title product was obtained as a white solid.

30

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¹H NMR (250 MHz, CDCl₃): δ 1.95 (m, 2H); 2.2 (dt, 2H); 2.85 (m, 2H); 3.95 (s, 3H); 4.0 (m, 2H); 5.15 (s, 2H); 5.25 (s, 2H); 7.0 (d, 1H); 7.3 (dd, 1H); 7.4 (m, 5H); 7.55 (m, 3H); 7.75 (d, 1H); 8.4 (s, 1H).

5

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(hydroxy)-tetrahydropyranyl]-4-methoxybenzyloxy]-2-naphthoic acid, sodium salt

10

Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

15

EXAMPLE 38

20

3-(1-Hydroxy-1-methylethyl)-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-1-naphthoic acid, sodium salt

Step 1: 3-Acetyl-7-benzyloxy-2-hydroxymethyl-4-phenylnaphthalene

25

To a heterogeneous solution of 500 mg of 7-benzyloxy-2-hydroxymethyl-4-phenyl-3-naphthoic acid, lactone form (minor isomer obtained from Lactone 1, Method B, Step 3) in THF at -78°C was added MeLi (1M, Et₂O, 2 mL). The reaction mixture was warmed slowly until the solution became homogeneous then quenched with a saturated NH₄Cl solution. The organic phase was diluted with Et₂O.

30

washed with H₂O, brine, dried over MgSO₄ and the solvent evaporated to afford the title compound used as such in the next step.

5 Step 2: 3-Acetyl-7-benzyloxy-4-phenyl-2-naphthoic acid

Following the procedure described in Example 27, Step 7, substituting 3-(2-acetoxyethyl)-7-benzyloxy-2-hydroxymethyl-4-phenylnaphthalene for 3-acetyl-7-benzyloxy-2-hydroxymethyl-4-phenylnaphthalene, the title product was obtained and used as such in the next step.

15 Step 3: 7-Benzyloxy-3-(1-hydroxy-1-methylethyl)-4-phenyl-2-naphthoic acid, lactone form

To a solution of the acid (150 mg) from Step 2 in THF at -8°C was added MeMgBr (1.4M, 0.8 mL) dropwise. After 2 hr, the reaction mixture was quenched with 10% HCl and diluted with Et₂O. After another 2 hr, the organic phase was extracted, washed with H₂O, brine, dried over MgSO₄, and the solvent evaporated. The residue was purified by chromatography on silica gel using hexane/EtOAc/CH₂Cl₂ (85:15:30) to give the title product.

Step 4: 7-Hydroxy-3-(1-hydroxy-1-methylethyl)-4-phenyl-2-naphthoic acid, lactone form

5 Following the procedure described in Lactone
1, Method A, Step 5, but substituting 7-benzyloxy-3-(1-hydroxy-1-methylethyl)-4-phenyl-2-naphthoic acid, lactone form, for 7-benzyloxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form, the title
10 product was obtained and used as such in the next step.

Step 5: 3-(1-Hydroxy-1-methylethyl)-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-1-naphthoic acid, lactone form

15

 Following the procedure described in Example 1, but substituting 7-hydroxy-3-(1-hydroxy-1-methylethyl)-4-phenyl-2-naphthoic acid, lactone form, for 7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form, the title product was obtained as a
20 white foam. After purification on flash chromatography (hexane/EtOAc, 1:1), the title compound was obtained.

25 ¹H NMR (250 MHz, CDCl₃): δ 1.49 (s, 6H), 1.7 (m, 2H), 2.22 (m, 2H), 3.93 (m, 4H), 5.23 (s, 2H), 7.21-7.58 (m, 11H), 7.67 (s, 1H), 8.35 (s, 1H).

30

Step 6: 3-(1-Hydroxy-1-methylethyl)-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-1-naphthoic acid, sodium salt

5 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 5 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

10

EXAMPLE 39

3-Hydroxymethyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-1-methoxy-4-phenyl-2-naphthoic acid,
15 sodium salt

Step 1: 3-[α,α -bis(Phenylthio)benzyl]-2-(3-benzyloxybenzoyl)butyrolactone

20 To a solution of the crude alcohol (10.8 g) from Lactone 1, Method E, Step 2, in CH_2Cl_2 (150 mL) at 0°C was added molecular sieves powder (flame dried, 10 g) followed by PCC (10.5 g) portion. The reaction mixture was stirred at r.t. for 1 hr then
25 poured on a SiO_2 plug (prewashed with Et_2O), and eluted with Et_2O . The solvent was evaporated and the residue purified by flash chromatography on silica gel using hexane/ EtOAc , 80:20, to give the title
30 product.

Step 2: 2-[α -Acetoxy(3-benzyloxybenzylidene)]-3[α,α -bis(phenylthio)benzyl]butyrolactone

5 To a solution of the ketone from Step 1
(1.91 g) in CH_2Cl_2 (20 mL) was added Ac_2O (1.5 mL),
 Et_3N (2.3 mL) and DMAP (40 mg). The reaction mixture
was stirred at r.t. for 18 hr then diluted with Et_2O
and a saturated solution of NH_4Cl . The organic phase
10 was extracted, washed with H_2O , brine, dried over
 MgSO_4 , and the solvent evaporated to afford the title
product as a foam which was used as such in the next
step.

15 Step 3: 1-Acetoxy-7-benzyloxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

To a solution of acetoxy derivative (1.8 g)
from Step 2, in TFA (8 mL) and thioanisole (2 mL) was
stirred at 0°C for 2 hr. The reaction mixture was
20 diluted with Et_2O , washed with H_2O (3x), pH 7 buffer
solution, brine, dried over MgSO_4 , and the solvent
evaporated. The residue was purified by
chromatography on silica gel using hexane/ EtOAc /
 CH_2Cl_2 (85:15:50) to give the title product.
25

Step 4: 7-Benzyloxy-1-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

5 To a solution of the lactone (320 mg) from Step 3, in MeOH/THF (5:1, 12 mL) was added a solution of NaOMe in MeOH (2 drops). After 18 hr the reaction mixture was acidified to pH 4 and the solvent evaporated. The residue was triturated in Et₂O and filtered to afford the title product as a white solid.

10

Step 5: 7-Benzyloxy-1-(t-butyldiphenylsilyloxy)-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

15

To a solution of alcohol (160 mg) from Step 4, in CH₂Cl₂ (10 mL) was added imidazole (60 mg) and t-BuPh₂SiCl (150 µL). The reaction mixture was stirred overnight then diluted with Et₂O, washed with H₂O and brine, and dried over MgSO₄, and the solvent

20

Step 6: 1-(t-Butyldiphenylsilyloxy)-7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form

25

To a solution of the lactone (120 mg) from Step 5, in EtOAc/CH₂Cl₂ (4:1) was added Pd(OH)₂/C 20% (30 mg). The reaction mixture was stirred under H₂ (balloon) for 36 hr. then filtered and the solvent evaporated. The residue was triturated in Et₂O and filtered to afford the title product as a white solid.

30

Step 7: 1-(t-Butyldiphenylsilyloxy)-3-hydroxymethyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-4-phenyl-2-naphthoic acid, lactone form

5 Following the procedure described in Example 7 but substituting 1-(t-butyldiphenylsilyloxy)-7-hydroxy-3-hydroxy methyl-4-phenyl-2-naphthoic acid, lactone form, from Step 6 for 7-hydroxy-3-hydroxy-methyl-4-phenyl-2-naphthoic acid, lactone form, the
10 title product was obtained after purification on flash chromatography (hexane/EtOAc/CH₂Cl₂, 85:15:40 to 65:35:40).

Step 8: 1-Hydroxy-3-hydroxymethyl-7-[3-[4-(4-hydroxy)tetrahydro-pyranyl]benzyloxy]-4-phenyl-2-naphthoic acid, lactone form
15

To a solution of lactone (44 mg) from Step 7, in THF (5 mL) at 0°C was added a n-Bu₄NF solution
20 (1M, 85 µl). The reaction mixture was stirred at r.t. for 1 hr then diluted with Et₂O and H₂O. The organic phase was extracted, washed with H₂O, brine, dried over MgSO₄, and the solvent evaporated. The residue was triturated in Et₂O and filtered to afford
25 the title product as a pale yellow solid.

Step 9: 3-Hydroxymethyl-7-[3-[4-(4-hydroxy)tetra-
hydropyranyl]benzyloxy]-1-methoxy-4-phenyl-
2-naphthoic acid, lactone form

5 To a solution of phenol (13 mg) from Step 8,
in THF (2 mL) at 0°C was added NaH (~1.5 mg) followed
by MeI (10 µL). The reaction mixture was stirred at
r.t. overnight then quenched with a pH 7 buffer
10 solution and diluted with Et₂O. The organic phase
was washed with H₂O, brine, dried over MgSO₄, and the
solvent evaporated. The residue was purified by
chromatography on silica gel using hexane/EtOAc/
CH₂Cl₂ (7:3:5) to give the title product as a white
foam.

15 ¹H NMR (250 MHz, CDCl₃): δ 1.65 (m, 2H), 2.15 (m,
2H), 3.85 (s, 3H), 3.92 (m, 4H), 5.2 (s, 2H), 5.65
(s, 2H), 7.2 (dd, 1H), 7.32-7.63 (m, 10H), 7.7 (s,
1H).

20 Step 10: 3-Hydroxymethyl-7-[3-[4-(4-hydroxy)tetra-
hydropyranyl]benzyloxy]-1-methoxy-4-phenyl-2-
naphthoic acid, sodium salt

25 Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 9
for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, lactone
form, the title product is obtained.

30

EXAMPLE 40

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt

10 Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, lactone form

15 Following the procedure described in Example 1, but substituting 3-[4-(4 α -hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]benzyl chloride, (Halide 11) for 3-[4-(4-methoxy)tetrahydropyranyl]benzyl bromide, and substituting Cs₂CO₃ for K₂CO₃, the title compound was obtained as a white foam.

20 ¹H NMR (250 MHz, CDCl₃): δ 1.3 (s, 6H); 1.7 (s, 6H); 2.0 (m, 5H); 5.2-5.3 (2s, 4H); 7.2-7.7 (m, 12H); 8.4 (s, 1H).

25 Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt

30 Following the procedure described in Example 1, Step 2, but substituting the lactone from Step 1 for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, lactone form, the title product is obtained.

EXAMPLE 41

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2-oxo)-
tetrahydropyranyl]benzyloxy-2-naphthoic acid, sodium
salt

Step 1: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
2-oxo)tetrahydropyranyl]benzyloxy-2-naphthoic
acid, lactone form

A mixture of the diol (152 mg) from Example
11 and Ag_2CO_3 on celite (1.60 g; prepared as
described in Tetrahedron, 31, 171 (1975)) in benzene
(25 mL) was refluxed for 4 hr. Filtration and
evaporation of the filtrate followed by flash
chromatography (silica gel; $\text{CHCl}_3/\text{EtOAc}$, 3:2) yielded
the title compound as a white solid.

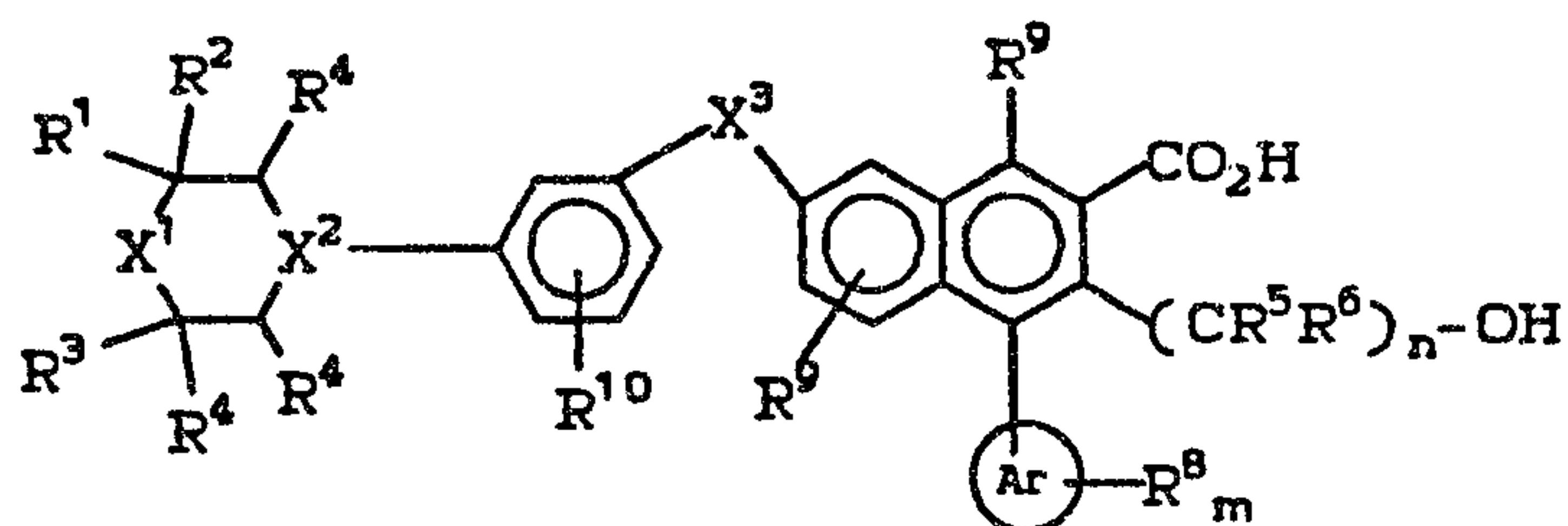
^1H NMR (250 MHz, CDCl_3): δ 2.13-2.20 (m, 1H), 2.15
(s, 1H), 2.32-2.45 (m, 1H), 2.87-3.05 (m, 2H), 4.42
(m, 1H), 4.75 (td, 1H), 5.24 (s, 2H), 5.25 (s, 2H),
7.29-7.60 (m, 10H), 7.63 (s, 1H), 7.74 (d, 1H), 8.37 (s,
1H).

Step 2: 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
2-oxo)tetrahydropyranyl]benzyloxy-2-naphthoic
acid, sodium salt

Following the procedure described in Example
1, Step 2, but substituting the lactone from Step 1
for 3-hydroxymethyl-4-phenyl-7-[3-[4-(4-methoxy)tetra-
hydropyranyl]benzyloxy]-2-naphthoic acid, lactone
form, the title product is obtained.

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

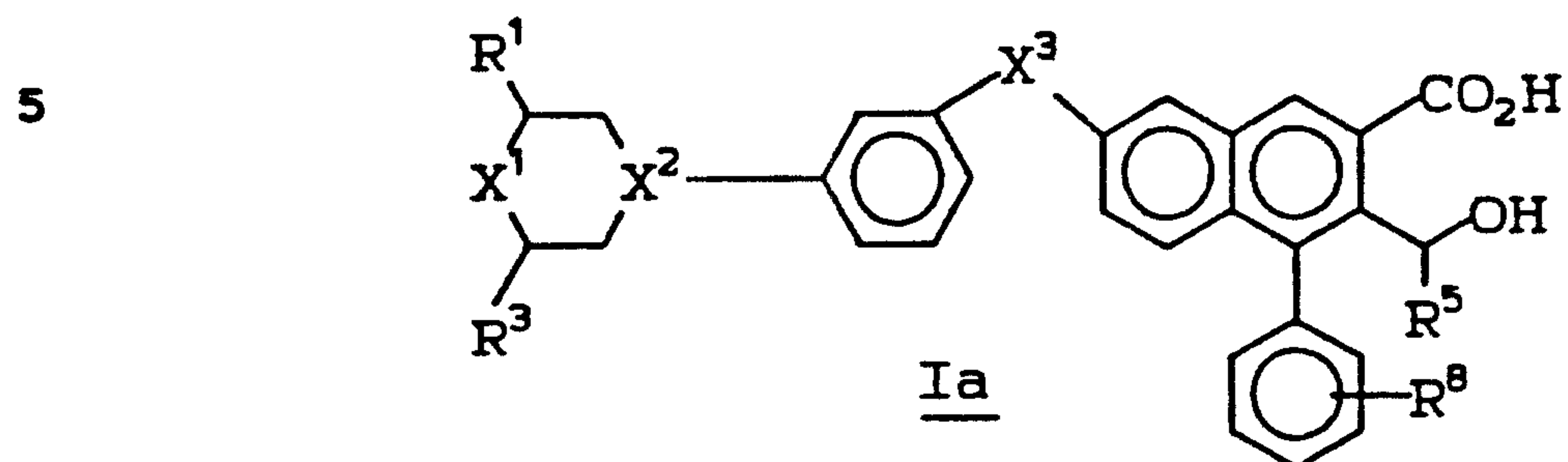
- 15 R^1 and R^5 are independently H, OH, lower alkyl, or lower alkoxy;
 R^2 is H, lower alkyl or together with R^1 forms a double bonded oxygen (=O);
 R^3 is H, lower alkyl or together with R^1 forms a
 20 carbon bridge of 2 or 3 carbon atoms, said bridge optionally containing a double bond;
 each R^4 , R^6 and R^7 is independently H or lower alkyl;
 R^8 is halogen, lower alkyl, or lower alkoxy;
 each R^9 is independently H, halogen, lower alkyl, or lower alkoxy;
 25 R^{10} is H, halogen, lower alkyl, or lower alkoxy;
 X^1 is O, S, S(O), S(O)₂, or CH₂;
 X^2 is N, N(O), C(OR⁷), or C(R⁷);
 X^3 is CH₂O, OCH₂, or CH₂CH₂;
 30 (Ar) is phenyl or 1- or 2-naphthyl;
 m is 0, 1, or 2;
 n is 1 or 2;
 or the pharmaceutically acceptable salts thereof.

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2. A compound of Claim 1 of the formula:



10 wherein the substituents are:

Ex.	R ¹	R ³	R ⁵	R ⁸	X ¹	X ²	X ³
15	1	H	H	H	0	C(OMe)	CH ₂ O
	2	H	H	H	0	C(OMe)	OCH ₂
	3	H	H	H	0	C(OMe)	CH ₂ O
	4	H	H	H	0	C(OH)	CH ₂ O
	5	H	H	H	0	C(OEt)	CH ₂ O
20	6	H	H	H	CH ₂	C(OMe)	CH ₂ O
	7	H	H	H	0	N	CH ₂ O
	8	H	H	H	0	N(O)	CH ₂ O
	9	H	H	OH	0	C(OMe)	CH ₂ O
	10	OH	H	H	0	C(OMe)	CH ₂ O
25	11	OH	H	H	0	C(OH)	CH ₂ O
	12	H	H	OH	0	C(OH)	CH ₂ O
	13	OH	H	OH	0	C(OH)	CH ₂ O
	14	H	H	Me	0	C(OMe)	CH ₂ O
	15	OH	H	OH	0	C(OMe)	CH ₂ O
30	16*	Me	Me	H	0	C(OH)	CH ₂ O
	17*	Me	Me	H	0	C(OH)	CH ₂ O

*cis and trans isomers

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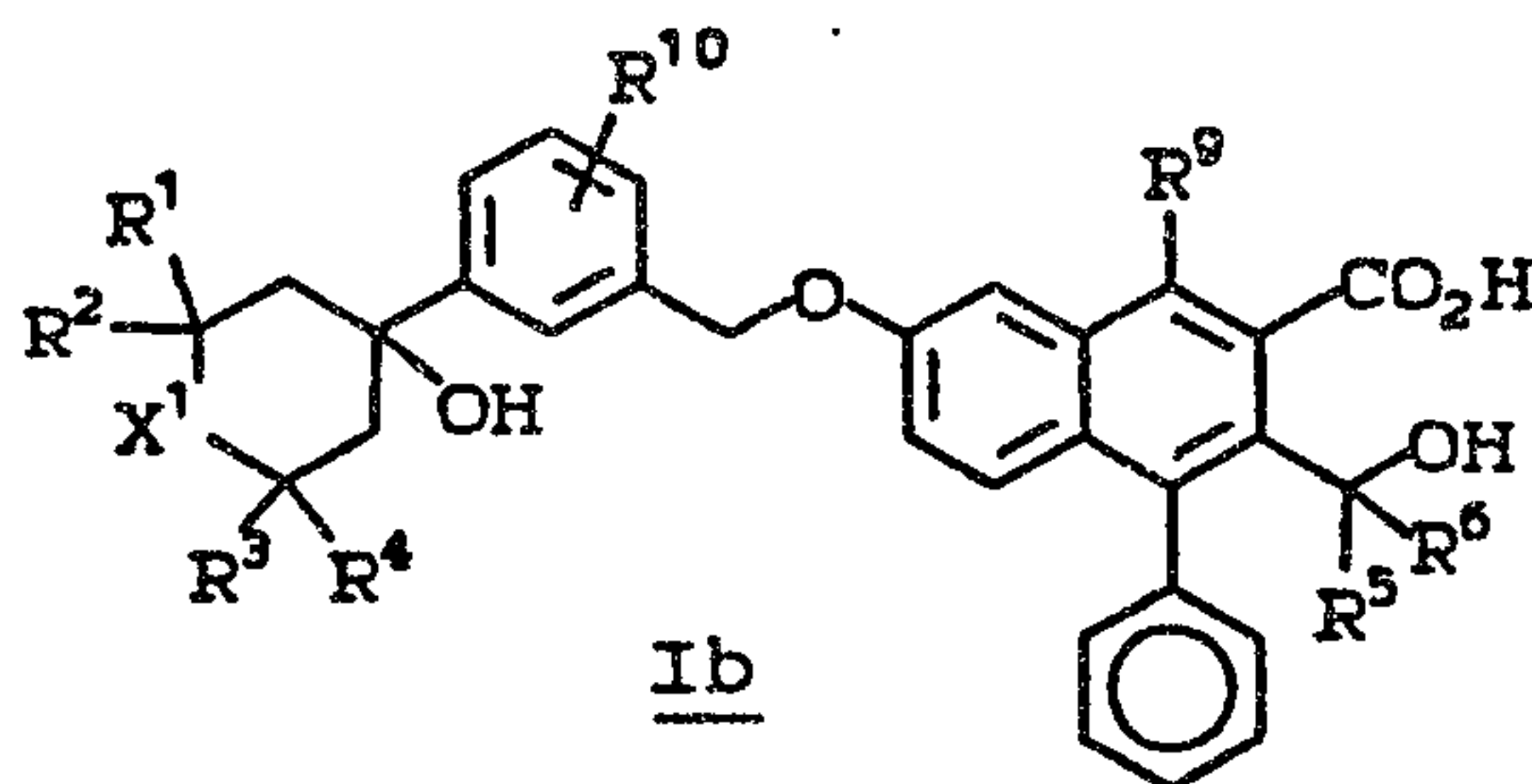
Ex.	R ¹	R ³	R ⁵	R ⁸	X ¹	X ²	X ³
5	18	H	H	H	4-Cl	O	C(OH) CH ₂ O
	19	H	H	H	4-OMe	O	C(OH) CH ₂ O
	20	Me	Me	H	H	O	C(OMe) CH ₂ O
	21	H	H	H	H	S	C(OH) CH ₂ O
	22	H	H	H	H	S(O)	C(OH) CH ₂ O
10	23	H	H	H	H	S(O) ₂	C(OH) CH ₂ O
	24 ^{**}	OMe	H	H	H	O	C(OH) CH ₂ O
	25 ^{**}	OMe	H	H	H	O	C(OH) CH ₂ O
	26	H	H	H	H	O	C(Me) CH ₂ O
	27	H	H	Me	H	O	C(OH) CH ₂ O
15	28	H	H	H	4-F	O	C(OH) CH ₂ O
	29	H	H	H	H	O	C(Et) CH ₂ O
	30	H	H	H	2-F	O	C(OH) CH ₂ O
	31	H	H	H	2-Cl	O	C(OH) CH ₂ O
	32	H	H	H	3-OMe	O	C(OH) CH ₂ O
20	33 ^{**}	OCH(Me) ₂	H	H	H	O	C(OH) CH ₂ O
	34 ^{**}	OCH(Me) ₂	H	H	H	O	C(OH) CH ₂ O
	35	(R ¹ R ³)=	-CH=CH-	H	H	O	C(OH) CH ₂ O
	36	(R ¹ R ³)=	-CH ₂ CH ₂ -	H	H	O	C(OH) CH ₂ O

^{**}axial and equatorial isomers.

25

30

3. A compound of Claim 1 of the formula:



wherein the substituents are:

15

Ex.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁹	R ¹⁰	X ¹
37	H	H	H	H	H	H	H	4-Ome	O
38	H	H	H	H	Me	Me	H	H	O
39	H	H	H	H	H	H	1-OMe	H	O
20 40	Me	Me	Me	Me	H	H	H	H	S
41	(R ¹ R ²)=	=O	H	H	H	H	H	H	O

4. A following compounds of Claim 1:

25

3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranylbenzyloxy]-2-naphthoic acid, sodium salt;

30

3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]phenoxymethyl}-2-naphthoic acid, sodium salt;

- 3-Hydroxymethyl-4-(4-fluorophenyl)-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt;
- 5 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt;
- 3-Hydroxymethyl-4-phenyl-7-{3-[4-(4-ethoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt;
- 10 3-Hydroxymethyl-4-phenyl-7-{3-(1-methoxycyclohexyl)benzyloxy}-2-naphthoic acid, sodium salt;
- 3-Hydroxymethyl-4-phenyl-7-{3-(N-morpholino)benzyloxy}-2-naphthoic acid, sodium salt;
- 15 3-Hydroxymethyl-4-phenyl-7-{3-(N-oxomorpholino)benzyloxy}-2-naphthoic acid, sodium salt;
- 3-Formyl-4-phenyl-7-{3-[4-(4-methoxy)tetrahydropyranyl]benzyloxy}-2-naphthoic acid, sodium salt;
- 3-Hydroxymethyl-4-phenyl-7-[3-[4-(2,4-dihydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;
- 20 3-Formyl-4-phenyl-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;
- 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;
- 25 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 β -hydroxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;
- 3-Hydroxymethyl-4-(4-chlorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;
- 30

3-Hydroxymethyl-4-(4-methoxyphenyl)-7-[3-[4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -methoxy-2,6-dimethyl)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy)-tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

10 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-S-oxo)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

15 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-S,S-dioxo)tetrahydrothiopyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 α -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

20 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-2 β -methoxytetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-methyl)-tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

25 3-(1-Hydroxyethyl)-[3-[4-hydroxy)tetrahydropyranyl]benzyloxy]-4-phenyl-2-naphthoic acid, sodium salt;

30 3-Hydroxymethyl-4-(4-fluorophenyl)-7-[3-[4-(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium salt;

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-ethyl)-
tetrahydropyranyl]benzyloxy]-2-naphthoic acid, sodium
salt;

5 3-Hydroxymethyl-4-(fluorophenyl)-7-[3-[4-(4-
hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt;

3-Hydroxymethyl-4-(2-chlorophenyl)-7-[3-[4-
(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt;

10 3-Hydroxymethyl-4-(3-methoxyphenyl)-7-[3-[4-
(4-hydroxy)tetrahydropyranyl]benzyloxy]-2-naphthoic
acid, sodium salt;

15 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
2 α -isopropoxy)tetrahydropyranyl]benzyloxy]-2-naph-
thoic acid, sodium salt;

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
2 β -isopropoxy)tetrahydropyranyl]benzyloxy]-2-naph-
thoic acid, sodium salt;

20 3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabi-
cyclo[3,2,1]oct-6-en-3 α -ol)]benzyloxy]-2-naphthoic
acid, sodium salt;

3-Hydroxymethyl-4-phenyl-7-[3-[3-(8-oxabi-
cyclo[3.2.1]octan-3 α -ol)]benzyloxy]-2-naphthoic
acid, sodium salt;

25 3-Hydroxymethyl-4-phenyl-7-[3-[4-(hydroxy)-
tetrahydropyranyl]-4-methoxybenzyloxy]-2-naphthoic
acid, sodium salt;

30 3-(1-Hydroxy-1-methylethyl)-4-phenyl-7-[3-[4-
(4-hydroxy)tetrahydropyranyl]benzyloxy]-1-naphthoic
acid, sodium salt;

3-Hydroxymethyl-7-[3-[4-(4-hydroxy)tetrahydro-
pyranyl]benzyloxy]-1-methoxy-4-phenyl-2-naphthoic
acid, sodium salt;

5 3-Hydroxymethyl-4-phenyl-7-[3-[4-(4 α -
hydroxy-2,2,6,6-tetramethyl)tetrahydrothiopyranyl]-
benzyloxy]-2-naphthoic acid, sodium salt; or

3-Hydroxymethyl-4-phenyl-7-[3-[4-(4-hydroxy-
2-oxo)tetrahydropyranyl]benzyloxy]-2-naphthoic acid,
sodium salt.

10

5. A pharmaceutical composition comprising
a therapeutically effective amount of a compound of
Claim 1 and a pharmaceutically acceptable carrier.

15

6. The pharmaceutical composition of Claim
5 additionally comprising an effective amount of a
second active ingredient selected from the group
consisting of non-steroidal anti-inflammatory drugs;
peripheral analgesic agents; cyclooxygenase
20 inhibitors; leukotriene antagonists; leukotriene
biosynthesis inhibitors; H₁- or H₂-receptor
antagonists; antihistaminic agents; prostaglandin
antagonists; and ACE antagonists.

25

7. A pharmaceutical composition of Claim
30 6, wherein the weight ratio of said compound of Claim
1 to said second active ingredient ranges from about
1000:1 to 1:1000.

8. The use of a compound of claim 1, 2, 3 or 4 for preventing the synthesis, the action, or the release of SRS-A or leukotrienes in a mammal.

5 9. The use of a compound of claim 1, 2, 3 or 4 for treating asthma in a mammal.

10 10. The use of a compound of claim 1, 2, 3 or 4 for treating inflammatory diseases of the eye in a mammal.

