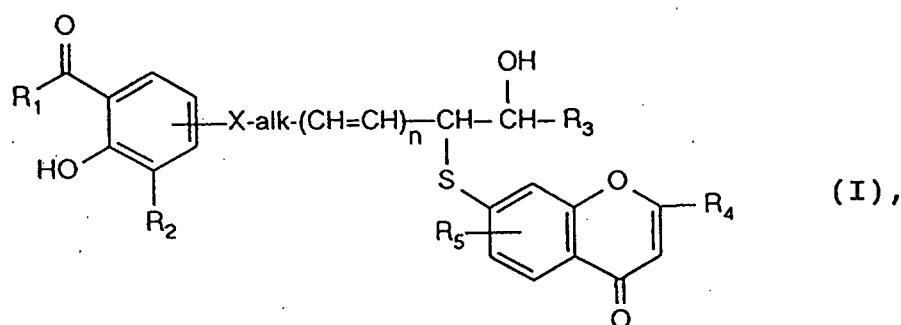


EP-A-228 045 discloses asymmetric alpha-hydroxythio ethers that are effective as leucotriene antagonists and are suitable for the treatment of allergic conditions. The documents EP-A-017 332, EP-A-079 637, US-A-4 546 194, EP-A-139 809 and EP-A-150 447 describe SRS-A or leucotriene antagonists that contain as a common structural feature an alkanophenone radical which is bonded via a chain to a 4-oxo-4H-1-benzopyrane group.

The invention relates to novel substituted alkanophenones of general formula I



in which R_1 is lower alkyl or mono-, di- or poly-fluoro-lower alkyl, R_2 is hydrogen, lower alkyl, lower alkenyl or mono-, di- or poly-fluoro-lower alkyl, X is C_1 - C_3 -alkylene, oxy or thio, alk is lower alkylene, n is 1 or 2, R_3 is phenyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy, halogen, carboxy, lower alkoxy-carbonyl, amino, N-mono- or N,N-di-lower alkyl-amino, carbamoyl, N-mono- or N,N-di-lower alkyl-carbamoyl and/or by trifluoromethyl, or is lower alkyl, mono-, di- or tri-fluoro-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, R_4 is carboxy, lower alkoxy-carbonyl, 5-tetrazolyl, carbamoyl, N-mono- or N,N-di-lower alkyl-carbamoyl, or N-(benzene-sulfonyl)-carbamoyl that is unsubstituted or is substi-

tuted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or by trifluoromethyl, and R_5 is hydrogen or lower alkyl; radicals designated "lower" having not more than 7 carbon atoms; and salts thereof, to processes for their preparation, to pharmaceutical preparations comprising them as active ingredient, and to their use as active ingredients in medicaments.

The spatial arrangement shown in the above formula I for the preferred compounds in which the O atom of the hydroxy group is in the relative trans-configuration with the S atom is to be understood as follows: the symbols in the first line lie above the plane of the drawing and the symbols in the third line therefore lie below the plane of the drawing (or vice versa), which for the formula shown corresponds to the opposite configuration, (RS)-(SR), according to the Kahn-Ingold-Prelog convention at the carbon atom bonded to the sulfur atom, (C-S-), and the carbon atom carrying the hydroxy group, (C-OH). When n is 2, the enantiomers having the S(C-S-), R(C-OH)-configuration and, when n is 1, the enantiomers having the R(C-S-), S(C-OH)-configuration are especially preferred. In a vinylene or buta-1,3-dienylene radical represented by the symbol $-(CH=CH)_n$, the double bond or the double bond of the butadienylene radical originating from the carbon atom bonded to the radical alk is preferably, but not necessarily, in the cis-configuration, usually designated (Z), the other double bond then preferably, but again not necessarily, having the trans-configuration, usually designated (E).

N-(Benzenesulfonyl)-carbamoyl that is unsubstituted or substituted in the phenyl moiety as indicated is, for example, unsubstituted or monosubstituted, preferably in

the ortho-position.

Hereinbefore and hereinafter "lower" radicals and compounds are to be understood as being those radicals and compounds containing no more than 7 and, unless otherwise indicated, preferably no more than 4 carbon atoms (C atoms).

Lower alkyl is, for example, C₁-C₇alkyl, especially straight-chain C₁-C₄alkyl, such as methyl, ethyl, propyl, isopropyl, butyl or sec-butyl, but may also be a branched-chain C₁-C₄alkyl, such as isobutyl or tert-butyl, or a pentyl, hexyl or heptyl radical. Lower alkyl R₁, R₅ and as a substituent of phenyl or N-(benzene-sulfonyl)-carbamoyl is preferably C₁-C₄alkyl, for example methyl; lower alkyl R₂ is preferably C₂-C₅alkyl, for example propyl, and lower alkyl R₃ is preferably C₃-C₇alkyl, for example propyl, butyl or pentyl.

Mono-, di- or poly-fluoro-lower alkyl has, for example, up to and including 5 fluorine atoms and is, for example, mono-, di- or tri-fluoro-C₁-C₇alkyl, especially ω -fluoro- or ω,ω,ω -trifluoro-C₁-C₄alkyl, such as trifluoromethyl, 2,2,2-trifluoroethyl or 3,3,3-trifluoropropyl. Fluorinated lower alkyl R₁ and as a substituent of phenyl R₃ is especially trifluoromethyl, and fluorinated lower alkyl R₃ is preferably ω,ω,ω -trifluoro-C₂-C₄alkyl, for example 3,3,3-trifluoropropyl.

Lower alkenyl R₂ is, for example, C₂-C₄alkenyl, such as vinyl, prop-1-enyl or especially prop-2-enyl (allyl).

Lower alkylene is, for example, straight-chain C₁-C₇alkylene, and in the case of X especially C₁-C₃alkylene,

such as methylene or ethylene, and in the case of alk especially C₂-C₆alkylene, such as ethylene, 1,3-propylene, 1,4-butylene, also 1,5-pentylene or 1,6-hexylene.

Lower alkoxy is, for example, C₁-C₄alkoxy, such as methoxy.

Lower alkoxy-carbonyl is, for example, C₁-C₄alkoxy-carbonyl, such as methoxy-, ethoxy-, propoxy- or butoxy-carbonyl.

Lower alkylamino is, for example, C₁-C₄alkylamino, such as methyl-, ethyl-, propyl- or isopropyl-amino.

Di-lower alkylamino is, for example, di-C₁-C₄alkylamino, such as dimethylamino, diethylamino or N-ethyl-N-methyl-amino.

N-mono- or N,N-di-lower alkylcarbamoyl is, for example, N-C₁-C₄alkyl- or N,N-di-C₁-C₄alkyl-carbamoyl, such as N-methyl-, N-ethyl- or N,N-dimethyl-carbamoyl.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as fluorine, chlorine or bromine.

Most of the compounds of formula I can, depending upon their individual character, also be in the form of salts. Those compounds which have sufficient acidity, such as, especially, those having carboxy, tetrazolyl or sulfamoyl groups, can form salts with bases, such as, especially, inorganic bases, preferably physiologically tolerable alkali metal salts, especially sodium and potassium salts. However, ammonium salts with ammonia or physiolo-

gically tolerable organic amines, such as mono-, di- or tri-lower alkylamines, for example diethylamine, mono-, di- or tri-(hydroxyalkyl)-amines, such as tris(hydroxymethyl)-methylanine, or D-glucosamine, also come into consideration.

The compounds of formula I and their salts exhibit advantageous pharmacological properties, especially a pronounced leucotriene-antagonism.

For example, in vitro in a concentration range of approximately from 0.001 to 1.0 $\mu\text{mol/l}$, they inhibit the contraction of a smooth muscle induced by leucotriene- D_4 (LTD_4). This so-called LTD_4 -antagonism is detected experimentally, for example, as follows: in segments which have been removed from the ileum of a guinea pig weighing 300-400 g and which have been incubated in an organ bath in Tyrode's solution at 38°C and while being gassed with a mixture of 95 % oxygen and 5 % carbon dioxide at a load of 1 g, contractions are induced with synthetic leucotriene D_4 (in potassium salt form) and are registered isotonically. The extent of the inhibition by the test compound is detected after a preliminary incubation of 2 minutes and is evaluated as IC_{50} , that is to say the concentration which reduces the test contraction by 50 %. The compounds of formula I also have excellent activity in vivo. In addition, they have a relatively long duration of action which is a very significant advantage both specifically and therapeutically. For example, in an in vivo bronchoconstriction standard test on guinea pigs, with aerosol administration of a solution comprising from 0.0001 to 1 % by weight of the test compound, a marked LTD_4 -antagonistic effect was demonstrated. (A description of the test method can be

found in the appendix after the Examples).

Surprisingly, many compounds of formula I also exert a pronounced inhibitory action on other physiologically important enzyme systems. For example, the inhibition of phospholipase A₂ obtained from human leucocytes was observed in the tested concentration range of approximately 0.5-50 $\mu\text{mol/l}$. (The experimental procedure for this determination is described in more detail in the appendix after the Examples.) Likewise, the inhibition of phospholipase C obtained from human thrombocytes was observed in the tested concentration range of approximately 1-100 $\mu\text{mol/l}$.

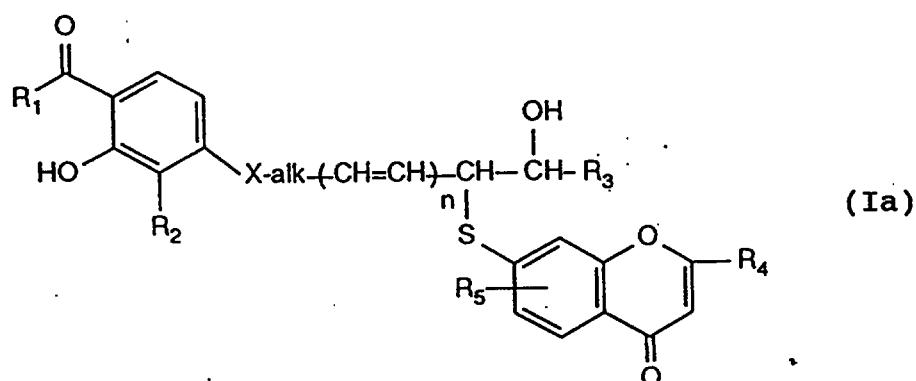
Owing to these valuable pharmacological properties, the compounds of formula I according to the invention can be used therapeutically in all cases where the action of leucotrienes results in pathological conditions, and alleviate or eliminate these conditions. Accordingly, they can be used, for example, for the treatment of allergic conditions and diseases, such as, especially, asthma, but also hay fever and obstructive pulmonary diseases, including cystic fibrosis. Owing to their anti-inflammatory activity, they are also suitable as inflammation-inhibiting agents, especially as external (topical) skin phlogistatics for the treatment of inflammatory dermatoses of any origin, as in mild skin irritations, contact dermatitis, exanthemas and burns, and also as mucous membrane phlogistatics for the treatment of inflammation of the mucosa, for example of the eyes, nose, lips, mouth and genital or anal region. They can also be used as sun screens. The high inhibitory effect on various blood factors also points to the possibility of the therapeutic use of the compounds of

formula I where thrombosis and blood coagulation are indicated.

The invention relates preferably to compounds of formula I in which R_1 is C_1 - C_4 alkyl or ω,ω,ω -trifluoro- C_1 - C_4 alkyl, R_2 is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl or ω,ω,ω -trifluoro- C_1 - C_4 alkyl, X is C_1 - C_3 alkylene, oxy or thio, alk is straight-chain C_2 - C_6 alkylene, n is 1 or 2, R_3 is phenyl that is unsubstituted or is substituted by C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, carboxy and/or by C_1 - C_4 alkoxycarbonyl, or is C_1 - C_7 alkyl, ω,ω,ω -trifluoro- C_2 - C_5 alkyl, carboxy- C_2 - C_5 alkyl or C_1 - C_4 alkoxy-carbonyl- C_2 - C_5 alkyl, R_4 is carboxy or N-(benzene-sulfonyl)-carbamoyl, and R_5 is hydrogen, and salts thereof, especially the pharmaceutically acceptable salts thereof.

Of the above-mentioned compounds of formula I preference is given especially to those wherein R_1 is C_1 - C_4 alkyl or ω,ω,ω -trifluoro- C_1 - C_4 alkyl, R_2 is C_1 - C_4 alkyl, C_2 - C_4 alkenyl or ω,ω,ω -trifluoro- C_1 - C_4 alkyl, and the group X is bonded in the para-position with respect to the R_1 -C(=O) group, and salts thereof, especially the pharmaceutically acceptable salts thereof.

Special preference is given to the compounds of the formula Ia



in which R_1 is C_1 - C_4 alkyl, R_2 is C_1 - C_4 alkyl, C_2 - C_4 alkenyl or ω,ω,ω -trifluoro- C_1 - C_4 alkyl, X is C_1 - C_3 alkylene, oxy or thio, alk is straight-chain C_2 - C_6 alkylene, n is 1 or 2, R_3 is a group of formula $-A-R_3'$ in which $-A-$ is C_1 - C_4 -alkylene, phenylene or a direct bond and R_3' is C_1 - C_4 -alkyl, trifluoromethyl, carboxy or C_1 - C_4 alkoxycarbonyl, R_4 is carboxy or N-(benzenesulfonyl)-carbamoyl, and R_5 is hydrogen, and salts thereof, especially the pharmaceutically acceptable salts thereof.

The invention relates preferably to the compounds of formula Ia in which R_1 is C_1 - C_4 alkyl, R_2 is C_1 - C_4 alkyl, X is oxy, alk is C_2 - C_6 alkylene, n is 1 or 2, R_3 is phenyl substituted by C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl or by C_1 - C_4 alkoxycarbonyl, or is C_2 - C_8 alkyl, ω,ω,ω -trifluoro- C_3 - C_5 alkyl or C_1 - C_4 alkoxycarbonyl- C_1 - C_4 alkyl, R_4 is carboxy, and R_5 is hydrogen, and salts thereof, especially the pharmaceutically acceptable salts thereof.

The invention relates especially to the compounds of formula Ia in which R_1 is C_1 - C_4 alkyl, R_2 is C_1 - C_4 alkyl, X is oxy, alk is C_2 - C_6 alkylene, n is 2, R_3 is a group of the formula $-A-R_3'$ in which $-A-$ is C_1 - C_4 alkylene or phenylene, and R_3' is C_1 - C_4 alkyl, trifluoromethyl or

C₁-C₄alkoxycarbonyl, R₄ is carboxy or N-(benzene-sulfonyl)-carbamoyl, and R₅ is hydrogen, and salts thereof, especially the pharmaceutically acceptable salts thereof.

Preference is given generally to compounds of formula I or Ia in which X is oxy, and salts thereof, especially the pharmaceutically acceptable salts thereof:

Preference is also given generally to compounds of formula I or Ia in which n is 2, and salts thereof, especially the pharmaceutically acceptable salts thereof.

Preference is given generally also to compounds of formula I or Ia in which R₃ is m-C₁-C₄alkylphenyl or m-trifluoromethylphenyl, R₄ is carboxy and R₅ is hydrogen, and salts thereof, especially the pharmaceutically acceptable salts thereof.

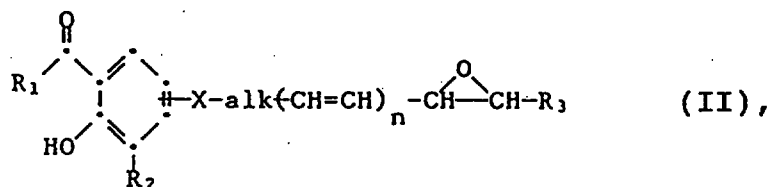
Preference is given generally also to compounds of formula I or Ia in which in the radical $-(CH=CH)_n-$ the double bond adjacent to the radical alk is in the (Z)-, that is to say the cis-configuration, and the additional double bond which may be present in the radical $-(CH=CH)_n-$ is in the (E)-, that is to say the trans-configuration, and salts thereof, especially the pharmaceutically acceptable salts thereof.

Finally, preference is given generally to compounds of formula I or Ia in which the chain carbon atom bonded to the sulfur atom has the (S)-configuration and the chain carbon atom carrying the hydroxy group has the (R)-configuration, and salts thereof, especially the pharmaceutically acceptable salts thereof.

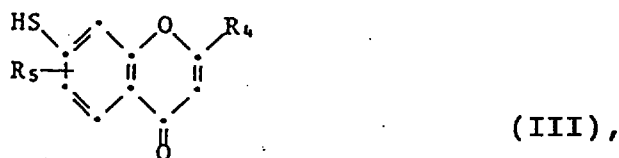
The invention relates specifically to the compounds of formula I mentioned in the Examples and to their salts, especially pharmaceutically acceptable salts.

The process according to the invention for the preparation of compounds of formula I and their salts is based on methods known per se and is carried out as follows:

an epoxide of formula II



in which R_1 , R_2 , X , alk, n and R_3 are as defined above,
is reacted with a thiol of formula III



in which R₄ and R₅ are as defined above, or with a salt thereof, and, if desired, a compound obtainable in accordance with the process is converted into a different compound of formula I, a stereoisomeric mixture obtainable in accordance with the process is separated into the components, and/or a free compound obtainable in accordance with the process is converted into a salt, or a salt obtainable in accordance with the process is converted into the free compound or into a different salt.

In the reaction of epoxides II with thiols III, the

configuration at the carbon atom bonding with the thio group is reversed and the configuration at the carbon atom carrying the hydroxy group is retained. In order to obtain the preferred compounds having the opposite configuration at these two carbon atoms, it is therefore preferable to use the corresponding trans-epoxides II as starting materials. Starting from R,R-epoxides II there are obtained compounds I having the S(C-S-), R(C-OH)-configuration, and starting from S,S-epoxides II there are obtained compounds I having the R(C-S-), S(C-OH)-configuration. The reaction is effected under conditions known per se at a temperature of from approximately -20°C to approximately $+50^{\circ}\text{C}$, preferably at room temperature, that is to say from 18°C to 25°C , and especially in a basic medium, for example in the presence of an amine, especially a tertiary aliphatic, arylaliphatic or saturated heterocyclic amine, such as a trialkylamine (for example triethylamine or ethyldiisopropylamine), a dialkylbenzylamine (for example N,N-dimethylbenzylamine), an N,N-dialkylaniline (for example N,N-dimethylaniline) or N-methyl- or N-ethyl-piperidine or N,N'-dimethyl-piperazine. The reaction is usually carried out in an inert organic solvent, such as a lower alkanol, for example methanol or ethanol.

In a preferred form, components II and III in which R_4 is esterified carboxy or tetrazolyl and R_3 is as defined above and is, for example, esterified carboxy or unsubstituted or fluorinated lower alkyl are used as starting materials and R_4 is hydrolysed (optionally selectively) to carboxy, which is then converted, if desired, into amidated carboxy.

Starting materials for the process according to the

invention are either known per se or can be obtained in a manner known per se by known analogy processes.

The epoxide of the above-defined formula II used as starting material can be prepared especially by means of the same processes as those used in the synthesis of leucotrienes. In a typical general method of synthesis for compounds II in which n is 1, for example, an aldehyde of formula



in which A and R_3 are as defined above, is used as starting material, a free carboxy group R_3 which may be present being protected in the form of an ester, for example a lower alkyl ester. This compound is condensed with formylmethylenetriphenylphosphorane (or an equivalent reagent), the corresponding trans-3- R_3 -prop-2-enal of formula

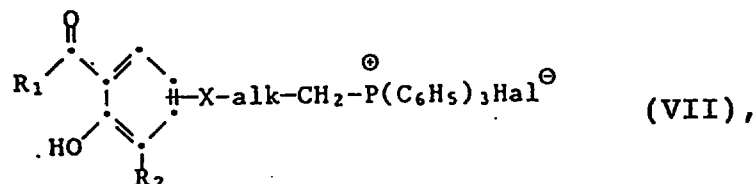


being formed. This compound is then epoxidised in a manner known per se, preferably under weakly alkaline conditions (for example in the presence of alkali metal carbonates), with aqueous hydrogen peroxide, to produce a trans-, that is to say 2(RS),3(RS)-epoxy-3- R_3 -propanal of formula



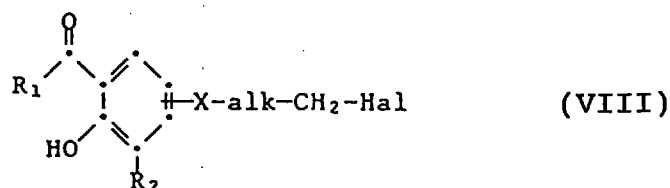
The epoxyaldehyde VI can then be reacted to form the corresponding epoxide II in which R_4 is esterified

carboxy and n is 1 by condensation with a phosphonium halide

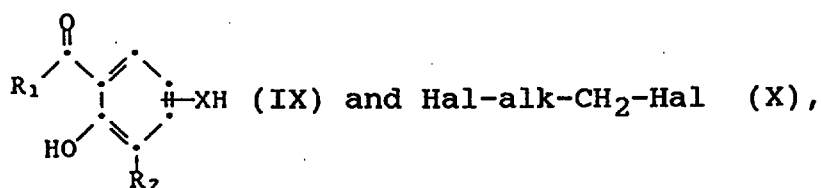


in which R_1 , R_2 and alk are as defined above and Hal is a halogen atom, preferably bromine, and with a base, for example sodium amide, in tetrahydrofuran.

Compounds VII are prepared especially by reaction of a corresponding compound of formula

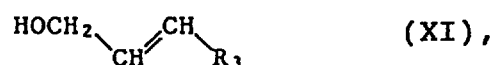


with triphenylphosphine in customary manner. Compounds VIII in which X is oxy or thio are obtained, for example, by condensing with one another corresponding compounds of formulae

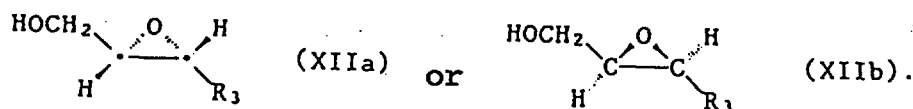


in customary manner.

In another method of preparing compounds II, trans-3- R_3 -prop-2-enol of formula



in which R_3 is as defined above, but free carboxy as a substituent of R_3 is preferably in an ester form, is epoxidised, for example, by means of tert-butyl hydroperoxide in the presence of titanium tetraisopropanolate and a D- or L-tartaric acid di-lower alkyl ester, and when a D-tartaric acid ester is used there is obtained predominantly 2R,3R-epoxy-3- R_3 -propanol XIIa, and when an L-tartaric acid ester is used there is obtained predominantly the corresponding 2S,3S-epoxy-3- R_3 -propanol XIIb

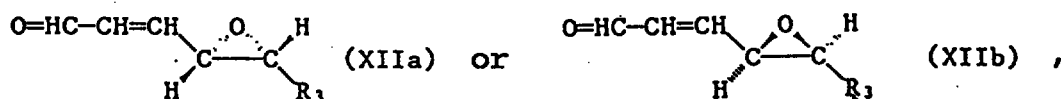


This compound is then oxidised, for example by treatment with oxalyl chloride/dimethyl sulfoxide and then with triethylamine, to the corresponding epoxyaldehyde VI which can then be reacted with the corresponding phosphonium salt VII to form the corresponding epoxide II in which R_3 is esterified carboxy and n is 1.

In that reaction there are obtained predominantly epoxides II in which the double bond has the preferred cis-stereoconfiguration. If a D-tartaric acid ester is used, then, as mentioned above, there are obtained predominantly compounds II in which the epoxy group has the R,R-configuration, or S,S-enantiomers when the reaction is carried out in the presence of L-tartaric acid esters.

For the preparation of epoxides II in which n is 2, for example the epoxy alcohol XIIa or XIIb is first converted by treatment with N,N'-dicyclohexylcarbodiimide and dimethyl sulfoxide in the presence of trifluoroacetic

acid and pyridine and then with triphenylphosphoranyl-
ideneacetaldehyde into the corresponding 4R,5R- or 4S,5S-
4,5-epoxy-5-R₃-pent-2-enal of formula XIIIa or XIIIb,
respectively



which is then reacted further with the phosphonium halide
VII to form the corresponding epoxide II in which n is 2.
It is preferable to obtain those epoxides in which the
double bond joined to the radical alk has cis-stereo-
configuration and the double bond joined to the oxirane
ring has trans-stereo-configuration.

Compounds obtainable in accordance with the process can,
if desired, be converted into other compounds of
formula I.

For example, esterified or amidated carboxy groups can be
hydrolysed to free hydroxy, preferably under basic condi-
tions, for example in the presence of sodium hydroxide
solution, and preferably in a water-miscible organic
solvent, such as tetrahydrofuran, dioxane or a lower
alkanol, such as methanol or ethanol. Starting from
compounds I in which R₄ is esterified carboxy, such as
lower alkoxycarbonyl, and R₃ contains such a group as
substituent, the hydrolysis can be controlled in such a
manner that selectively only R₄ or both R₄ and the lower
alkoxycarbonyl substituent of R₃ are hydrolysed to
carboxy. If an equimolar sodium hydroxide solution is
used and mild reaction conditions are chosen, for example
stirring at room temperature for about 0.5 to 2 hours,
virtually only alkoxycarbonyl R₄ is hydrolysed, whilst

under extreme conditions, for example with prolonged reaction periods or with heating, both R_4 and the alkoxycarbonyl group in R_3 are hydrolysed to carboxy.

Conversely, carboxy R_4 and a carboxy substituent of R_3 can be esterified in customary manner.

Furthermore, free or esterified carboxy R_4 and such a group as a substituent of R_3 can be amidated in customary manner, for example by treatment with ammonia or with a mono- or di-lower alkylamine. For example, carboxy R_4 can be converted in customary manner, for example in the presence of a carbodiimide salt, for example N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride, and 4-dimethylaminopyridine, with an unsubstituted or substituted benzenesulfonamide into the corresponding N-benzenesulfamidoylcarbamoyl groups.

Of course, it is also possible to separate resulting diastereoisomeric mixtures into the individual components on the basis of the different physical properties of the components and/or to separate resulting mixtures of enantiomers into the individual enantiomers according to customary racemate separation processes.

If individual diastereoisomers are desired, then advantageously an individual diastereoisomer of a starting material can be used at any stage or one diastereoisomer can be formed preferentially from a starting material in diastereoisomer form by means of stereoselective reaction conditions or optically active reagents, or racemic diastereoisomeric mixtures can be separated into the individual diastereoisomers by physical separation methods, optionally using optically active auxiliaries.

From the stereochemical standpoint, however, both the condensation according to the invention of components II and III and the preparation of the starting materials are preferably carried out using starting materials that are uniform in stereo-configuration in each case, where possible carrying out the reactions stereoselectively, for example by the use of configuratively uniform, optically active reagents and/or auxiliaries, and isolating configuratively uniform products from reaction mixtures immediately after the reaction. For example, in the preparation of the unsaturated starting materials, cis- and trans-isomers which may be formed are separated from one another immediately, for which purpose the customary physical separation methods, such as, especially, chromatography, are suitable. In the main reaction there is used especially the stereoisomeric epoxide II having the stereoconfiguration of the double bond(s) that is preferred in the end product and in racemic form (which is often formed in the variant of the epoxidisation of the compound V with hydrogen peroxide) or preferably in the form of an individual diastereoisomer in which the configuration at the oxirane carbon atom making a bond with the S atom is opposite to the configuration at the (C-S-) carbon atom preferred in the end product I.

Likewise, resulting salts can be converted, for example by treatment with an acid, into the free acids, and resulting free acids can be converted by treatment with a base into salts.

As a result of the close relationship between the novel compounds in free form and in the form of their salts,

hereinbefore and hereinafter the free compounds and their salts should be understood, where appropriate, as meaning also the corresponding salts and free compounds, respectively.

The invention relates also to those forms of the process according to which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material is used in the form of a salt or is formed under the reaction conditions.

The invention relates also to the novel starting materials and intermediates occurring in the processes according to the invention and their preliminary stages.

Preferably, the starting materials used and the reaction conditions chosen are such that the compounds listed above as being especially preferred are obtained.

The present invention relates also to pharmaceutical preparations and medicaments that comprise one of the compounds of formula I according to the invention or a pharmaceutically acceptable salt thereof. The pharmaceutical preparations according to the invention are especially those which are intended for local administration and especially for administration by inhalation, for example in the form of an aerosol, a micronised powder or a fine spray solution, to mammals, especially humans, and which comprise the active ingredient on its own or together with a pharmaceutically acceptable carrier.

Pharmaceutical preparations for topical and local use are, for example, for the treatment of the skin, lotions

and creams which comprise a liquid or semi-solid oil-in-water or water-in-oil emulsion, and ointments (which preferably comprise a preservative). Suitable for the treatment of the eyes are eye drops which comprise the active ingredient in aqueous or oily solution, and eye ointments which are preferably manufactured in sterile form. Suitable for the treatment of the nose are aerosols and sprays (similar to those described below for the treatment of the respiratory tract), coarse powders which are administered by rapid inhalation through the nostrils, and especially nose drops which comprise the active ingredient in aqueous or oily solution; suitable for local treatment of the buccal cavity are lozenges which comprise the active ingredient in a mass generally formed of sugar and gum arabic or tragacanth, to which flavourings may be added, and pastilles which comprise the active ingredient in an inert mass, for example of gelatine and glycerine or sugar and gum arabic.

Pharmaceutical preparations suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compound of formula I according to the invention with a suitable pharmaceutically acceptable solvent, such as, especially, ethanol and water, or a mixture of such solvents. They may, as necessary, comprise other pharmaceutical adjuncts, such as non-ionic or anionic surface-active agents, emulsifiers and stabilisers, and also active ingredients of other kinds, and especially advantageously they can be mixed with a propellant gas, such as an inert gas under elevated pressure or especially with a readily volatile liquid, preferably a liquid that boils under normal atmospheric pressure below customary room temperature (for example from approximately -30 to $+10^{\circ}\text{C}$), such

as an at least partially fluorinated polyhalogenated lower alkane, or a mixture of such liquids. Such pharmaceutical preparations, which are used predominantly as intermediates or stock mixtures for the preparation of the corresponding medicaments in finished form, comprise the active ingredient customarily in a concentration of from approximately 0.1 to approximately 10 % by weight, especially from approximately 0.3 to approximately 3 % by weight. For the preparation of medicaments in finished form, such a pharmaceutical preparation is introduced into suitable containers, such as flacons and pressurised bottles, which are provided with a spray device or valve suitable for such purposes. The valve is preferably constructed in the form of a metering valve which on operation releases a predetermined amount of liquid, corresponding to a predetermined dose of the active ingredient. In the preparation of the finished medicament form, it is also possible for corresponding amounts of the pharmaceutical preparation in stock solution form and of the propellant to be introduced separately into the containers and to be mixed with one another only at that stage. The dosage of the compound of formula I to be administered and the frequency of administration depend upon the effectiveness and the duration of action of each individual compound, upon the severity of the disease to be treated and its symptoms, and upon the sex, age, weight and individual responsiveness of the mammal to be treated. On average, the recommended daily dose of a compound of formula I according to the invention for a mammal (especially a human) weighing 75 kg might be in the region of from approximately 10 to approximately 500 mg, preferably from approximately 25 to approximately 250 mg, which can advantageously be administered in several doses per day, as necessary.

The following Examples illustrate the present invention in more detail but do not limit the scope thereof. All temperatures are given in degrees Celsius.

Example 1: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

A solution of 0.93 g of (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene in 25 ml of methanol is stirred under argon with 0.80 g of triethylamine and 0.62 g of 7-mercaptochromone-2-carboxylic acid methyl ester for 20 hours at room temperature and concentrated by evaporation. The residue is dissolved in ethyl acetate and filtered over silica gel. The filtrate is washed once with 2N hydrochloric acid and 3 times with brine, dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by chromatography on silica gel with hexane/ethyl acetate (1:1) yields the title compound having a melting point of 62-63°; $[\alpha]_D^{20}$ (methanol, 0.135 %) = 103 ± 7.4°; UV (methanol): $\lambda_{\max}$ (ϵ) = 216 (50,000), 235/sh, 271 (27,940), 285/sh; 325 (12900).

The starting material is prepared, for example, as follows:

a) (2R,3R)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanol
Under totally anhydrous conditions and an argon atmosphere, a solution of 4.62 ml of tetraisopropyl orthotitanate in 100 ml of methylene chloride is cooled to -70°, and 3.2 ml of D(-)-tartaric acid diethyl ester and

5.45 g of 3-(3-trifluoromethylphenyl)-prop-2(E)-enol in a small amount of methylene chloride are added. After stirring for 10 minutes at -70° , 21.5 ml of 3-molar tert-butyl hydroperoxide solution in toluene are added, the temperature rising to -60°C . The temperature is allowed to rise to 0° within a period of 2 hours, and the resulting yellow solution is poured slowly into a solution of 14.5 g of iron(II) sulfate and 5.8 g of L(+)-tartaric acid in 60 ml of water (cooling!, exothermic) and the mixture is stirred for 30 minutes at $5-10^{\circ}$. The aqueous phase is separated off and extracted with ether. The combined organic extracts are dried over sodium sulfate and concentrated by evaporation. The residue is dissolved in 90 ml of ether, cooled to $0-5^{\circ}$, and a suspension of 2.32 g of sodium hydroxide in 60 ml of brine is added and the mixture is stirred for 1 hour at $0-5^{\circ}$. The aqueous phase is separated off and extracted with ether. The combined ether phases are dried over sodium sulfate and concentrated by evaporation. The residue is purified by chromatography on silica gel with hexane/ethyl acetate (3:2). The title compound is thus obtained in the form of a colourless oil;

IR (CH_2Cl_2): 3550, 3430, 2950, 2880, 2830, 1310, 1150, 1110, 1050 cm^{-1} ; $[\alpha]_{\text{D}}^{20}$ (methanol, 0.175 %) = $42.3 \pm 5.7^{\circ}$; $R_f = 0.30$ (hexane/ethyl acetate 3:2).

b) (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal

A solution of 4.5 g of (2R,3R)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanol in 105 ml of dimethyl sulfoxide is stirred under argon with 1.7 ml of pyridine, 0.77 ml of trifluoroacetic acid and 12.75 g of N,N-dicyclohexylcarbodiimide for 6 hours at room temperature. After the addition of 8.25 g of formylmethylenetriphenylphos-

phorane, stirring is continued for a further 20 hours at room temperature; 320 ml of ethyl acetate are added and after 10 minutes the mixture is poured onto 320 ml of brine. The resulting suspension is stirred for 5 minutes and filtered. In the filtrate the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed 3 times with brine, dried over sodium sulfate and concentrated by evaporation. The residue is filtered over silica gel with ether/hexane = (4:1). The filtrate is concentrated by evaporation and the residue is purified by chromatography on silica gel with hexane/ethyl acetate (3:1). The title compound is thus obtained in the form of a light-yellow oil; IR (CH_2Cl_2): 2780, 2695, 1670, 1620, 1305, 1145, 1105 cm^{-1} ; $R_f = 0.31$ (hexane/ethyl acetate 3:1) $[\alpha]_D^{20}$ (chloroform, 0.245 %) = $144.5 \pm 4.1^\circ$.

c) 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide

A solution of 27 g of 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl bromide in 50 ml of toluene is heated at reflux with 21.85 g of triphenylphosphine for 20 hours. The resulting suspension is cooled to room temperature; 200 ml of ether are added and the mixture is stirred for 1 hour. The colourless precipitate is filtered off with suction, washed with ether and dried. The title compound has a melting point of 211-212°.

d) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

A suspension of 5.55 g of 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide in 80 ml of tetrahydrofuran is stirred under argon with 0.78 g of

NaNH_2 and 60 mg of potassium tert-butanolate for 1 hour at room temperature, then cooled to $0-5^\circ$; 1.7 g of (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal in 20 ml of tetrahydrofuran are added within a period of 5 minutes and the mixture is then stirred for 2 hours at room temperature. The resulting suspension is poured onto phosphate buffer (pH 7) and extracted with ether. The combined ether extracts are washed with phosphate buffer pH 7, dried over sodium sulfate and concentrated by evaporation. The residue is taken up in hexane/ethyl acetate/triethylamine (24:71:5) and filtered over silica gel that has been prewashed with that solvent mixture. The filtrate is concentrated by evaporation and yields the title compound in the form of a light-yellow oil; $R_f = 0.75$ (hexane/ethyl acetate 3:2).

Example 2: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

0.7 g of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester is dissolved under argon in 20 ml of tetrahydrofuran; 5.1 ml of 0.2N sodium hydroxide solution are added and the mixture is stirred for 1 hour at room temperature. Concentration by evaporation and purification of the residue by chromatography on a "Reversed Phase" silica gel column (for example Merck Lichroprep® RP-8) with methanol/water (3:1) yield the title compound, m.p. $207-209^\circ$, $[\alpha]_D^{20}$ (0.54 %, methanol) = $96.3 \pm 1.9^\circ$ UV (methanol): λ_{max} (ϵ) = 220 (488840), 235/sh, 267 (25940), 285 (22900), 324/sh.

Example 3: (1S,2R)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; m.p. 68-69°.

The starting material is prepared, for example, as follows:

a) (2S,3S)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanol

The title compound is prepared as described in Example 1a) but using L(+)-tartaric acid diethyl ester; colourless oil; IR (CH₂Cl₂): 3590, 3480, 2920, 2870, 1330, 1165, 1125, 1070 cm⁻¹; $[\alpha]_D^{20}$ (methanol, 0.175 %) = -41.7 ± 5.7°; R_f = 0.34 (hexane/ethyl acetate 1:1).

b) (4S,5S)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from the epoxy alcohol according to a); light-yellow oil; IR (CH₂Cl₂): 2780, 2695, 1670, 1620, 1305, 1145, 1110 cm⁻¹; $[\alpha]_D^{20}$ (chloroform, 0.15 %) = -158.0 ± 6.7°; R_f = 0.4 (hexane/ethyl acetate 4:1).

c) (1S,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to b); light-brown oil; R_f = 0.61 (hexane/ethyl acetate 3:2).

Example 4: Sodium salt of (1S,2R)-1-hydroxy-1-(3-tri-fluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 3; m.p. 210-212°, $[\alpha]_D^{20}$ (MeOH, 0.18 %) = $-86.1 \pm 5.6^\circ$
UV (MeOH): $\lambda_{\max}(\epsilon)$ = 220 (42820); 235/sh; 267 (26660); 285 (23760); 320 (15800).

Example 5: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene; light-yellow viscous oil; $[\alpha]_D^{20}$ (MeOH, 0.115 %) = $57.4 \pm 8.7^\circ$;
UV (MeOH): $\lambda_{\max}(\epsilon)$ = 220/sh; 271 (5280); 285/sh; 320 (2800).

The starting material is prepared, for example, as follows:

a) (2S,3R)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanal

A solution of 1.1 g of oxalyl chloride in 15 ml of methylene chloride is cooled to -65-70° under argon and within a period of 2 minutes 1.5 g of dimethyl sulfoxide in 5 ml of methylene dichloride are added. After stirring for 10 minutes at -65-70°, 1.7 g of (2R,3R)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanol in 15 ml of methylene chloride are added dropwise. After stirring for a further 30 minutes, 4 g of triethylamine are added dropwise, the temperature rising to -40°. The tempera-

ture is allowed to rise to 0° and the reaction mixture is poured onto phosphate buffer (pH 8). The organic phase is separated off and the aqueous phase is extracted with methylene chloride. The combined organic extracts are washed twice with brine, dried over sodium sulfate and concentrated by evaporation. Chromatography of the residue on silica gel with hexane/ethyl acetate (7:3) yields the title compound in the form of a colourless oil; IR (methylene chloride): 2820, 1730, 1330, 1165, 1125, 1070 cm^{-1} . $R_f = 0.36$ (hexane/ethyl acetate 3:2). $[\alpha]_D^{20}$ (chloroform, 0.20 %) = $-17.5 \pm 5^\circ$.

b) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to a); light-yellow oil; $R_f = 0.69$ (hexane/ethyl acetate 3:2).

Example 6: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 5; m.p. 222-224°; $[\alpha]_D^{20}$ (MeOH, 0.135 %) = $62.2 \pm 7.4^\circ$. UV (MeOH): $\lambda_{\text{max}}(\epsilon) = 267$ (22060); 285 (21140); 318/sh.

Example 7: (1S,2R)-1-hydroxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene; colour-

less powder having a melting point of 69-71°.

The starting material is prepared, for example, as follows:

a) (2R,3S)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanal

The title compound is prepared analogously to Example 5a) from (2S,3S)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanol. Light-yellow liquid; IR (CH₂Cl₂): 2820, 1730, 1330, 1165, 1130, 1070 cm⁻¹; $[\alpha]_D^{20}$ (chloroform, 0.20 %) = 0.0 ± 5°; $[\alpha]_{365}^{20}$ (chloroform, 0.20 %) = 475.0 ± 5.0°; R_f = 0.44 (hexane/ethyl acetate 7:3).

b) (1S,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to a). Light-yellow oil; R_f = 0.43 (hexane/ethyl acetate 3:2).

Example 8: Sodium salt of (1S,2R)-1-hydroxy-1-(3-trifluoromethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 7; m.p. 239-241°; $[\alpha]_D^{20}$ (methanol, 0.15 %) = -60.7 ± 6.7°; UV (methanol): $\lambda_{\max}(\epsilon)$ = 216 (44080); 268 (22520); 285 (21640); 320/sh.

Example 9: (1R,2S)-1-hydroxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1

from (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; light-yellow powder having a melting point of 71-72°; $[\alpha]_D^{20} = 81.7 \pm 8.7^\circ$ (MeOH, 0.115 %); UV (MeOH): $\lambda_{\max}(\epsilon) = 217$ (53680); 235/sh; 271 (29120); 285/sh; 325 (13200).

The starting material is prepared, for example, as follows:

a) (2R,3R)-2,3-epoxy-3-(3-methylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(3-methylphenyl)-prop-2(E)-enol; colourless, viscous oil; IR (CH₂Cl₂): 3560, 3410, 2880, 2830, 1590, 1050 cm⁻¹; R_f = 0.39 (hexane/ethyl acetate 1:1); $[\alpha]_D^{20} = 38.9 \pm 5.3^\circ$ (chloroform, 0.19 %).

b) (4R,5R)-4,5-epoxy-5-(3-methylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from the epoxy alcohol according to a); light-yellow powder, m.p. 60-61°; IR (CH₂Cl₂): 2920, 2820, 2740, 1690, 1640, 1610, 1155, 1130 cm⁻¹; R_f = 0.34 (hexane/ethyl acetate 4:1).

c) (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to a); light-yellow oil; R_f = 0.63 (hexane/ethyl acetate 3:2).

Example 10: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 9; beige powder having a melting point of 217° (decomp.); $[\alpha]_D^{20}$ (methanol, 0.15 %) = 71.3 ± 6.7°; UV (methanol): $\lambda_{\max}(\epsilon)$ = 219 (51520); 234/sh; 267 (26460); 284 (23280); 322/sh.

Example 11: (1S,2R)-1-hydroxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(m-tolyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; $[\alpha]_D^{20}$ (MeOH, 0.148 %) = -75.7 ± 6.8°; UV (MeOH): $\lambda_{\max}(\epsilon)$ = 217 (51760); 240/sh; 271 (27860); 290/sh; 328 (12600).

The starting material is prepared, for example, as follows:

a) (2S,3S)-2,3-epoxy-3-(3-methylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(3-methylphenyl)-prop-2(E)-enol but using L(+)-tartaric acid diethyl ester; colourless oil; IR (CH₂Cl₂): 3550, 3470, 2940, 2880, 2830, 1590, 1050 cm⁻¹; R_f = 0.31 (hexane/ethyl acetate 3:2).

b) (4S,5S)-4,5-epoxy-5-(3-methylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b)

from the epoxy alcohol according to a); light-yellow oil;
IR (CH₂Cl₂): 2920, 2820, 2740, 1690, 1640, 1610, 1155,
1130, 1085 cm⁻¹; R_f = 0.29 (hexane/ethyl acetate 4:1).

c) (1S,2S)-1,2-epoxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to b); light-yellow oil; R_f = 0.51 (hexane/ethyl acetate 7:3).

Example 12: Sodium salt of (1S,2R)-1-hydroxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 1 from the corresponding methyl ester according to Example 11; m.p. 197-198°; $[\alpha]_D^{20}$ (0.14 %, methanol) = -72.1 ± 7.1°; UV (MeOH): $\lambda_{\max}(\epsilon)$ = 218 (50700); 235/sh; 267 (25780); 285 (22600); 321 (15000).

Example 13: (1R,2S)-1-hydroxy-1-(3-methylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-tolyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene; colourless powder having a melting point of 136-138°; $[\alpha]_D^{20}$ = 28.1 ± 7.4° (methanol, 0.135 %); UV (methanol): $\lambda_{\max}(\epsilon)$ = 271 (26020); 282/sh; 323 (13700).

The starting material is prepared, for example, as follows:

a) (2S,3R)-2,3-epoxy-3-(3-methylphenyl)-propanal

The title compound is prepared analogously to Example 5a) from (2R,3R)-2,3-epoxy-3-(3-methylphenyl)-propanol; light-yellow oil. IR (methylene chloride): 2920, 2820, 1730, 1610, 1140, 1070 cm^{-1} ; $R_f = 0.49$ (hexane/ethyl acetate 3:2).

b) (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to a); light-yellow oil; $R_f = 0.73$ (hexane/ethyl acetate 3:2).

Example 14: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 13; beige powder having a melting point of 238-240°; $[\alpha]_D^{20}$ (methanol 0.135 %) = $31.1 \pm 7.4^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 268$ (21800); 285 (20860); 322/sh.

Example 15: (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; $[\alpha]_D^{20}$ (methanol, 0.14 %) = $27.9 \pm 7.1^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 221$ (53560); 234/sh; 270 (28980); 285/sh; 326

(13860).

The starting material is prepared, for example, as follows:

a) (2R,3R)-2,3-epoxy-3-(3-methoxycarbonylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from (E)-3-methoxycarbonylcinnamic alcohol; slightly yellowish oil; $R_f = 0.3$ (hexane/ethyl acetate 1:1).

b) (4R,5R)-4,5-epoxy-5-(3-methoxycarbonylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from the corresponding epoxy alcohol; light-yellow oil; $R_f = 0.35$ (hexane/ethyl acetate 3:2).

c) (1R,2R)-1,2-epoxy-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to b); viscous yellow oil; $R_f = 0.50$ (hexane/ethyl acetate 3:2).

Example 16: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester according to Example 15; light-brown powder having a melting point of 181° (decomp.); $[\alpha]_D^{20}$ (methanol,

0.15 %) = $32.0 \pm 6.7^\circ$; UV (methanol): $\lambda_{\max}(\epsilon) = 222$ (51600); 232/sh; 267 (24160); 284 (22940); 320/sh; 400/sh.

Example 17: (1S,2R)-1-hydroxy-1-(3-methoxycarbonyl-phenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from the (1S,2S)-1,2-epoxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; m.p. $77-78^\circ$ (colourless powder); $[\alpha]_D^{20}$ (methanol, 0.15 %) = $-52.7 \pm 6.7^\circ$; UV (methanol): $\lambda_{\max}(\epsilon) = 221$ (57420); 235/sh; 271 (29980); 288/sh; 326 (14320).

The starting material is prepared, for example, as follows:

a) (2S,3S)-2,3-epoxy-3-(3-methoxycarbonylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from (E)-3-methoxycarbonylcinnamic alcohol but using L(+)-tartaric acid diethyl ester; colourless oil; $R_f = 0.48$ (hexane/ethyl acetate 1:1).

b) (4S,5S)-4,5-epoxy-5-(3-methoxycarbonylphenyl)-pent-2-(E)-enal

The title compound is prepared analogously to Example 1b) from the corresponding epoxy alcohol; colourless oil; IR (methylene chloride): 3050, 2990, 2945, 2820, 2730, 1725, 1695, 1640, 1290, 1255 cm^{-1} ; $R_f = 0.34$ (hexane/-ethyl acetate 3:2).

c) (1S,2S)-1,2-epoxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to b); light-yellow oil; $R_f = 0.54$ (hexane/ethyl acetate 3:2).

Example 18: Sodium salt of (1S,2R)-1-hydroxy-1-(3-methoxycarbonylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 17; beige powder having a melting point of 174-176°; $[\alpha]_D^{20}$ (methanol, 0.155 %) = $-80.6 \pm 6.5^\circ$; UV (methanol): $\lambda_{\max}(\epsilon) = 223$ (59300); 235 sh; 267 (27300); 284 (24800); 321 (16200).

Example 19: (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene; colourless oil; $[\alpha]_D^{20}$ (methanol, 0.11 %) = $24.5 \pm 9.1^\circ$; UV (methanol): $\lambda_{\max}(\epsilon) = 270$ (22400); 322 (12000).

The starting material is prepared, for example, as follows:

a) (2S,3R)-2,3-epoxy-3-(3-methoxycarbonylphenyl)-propanal

The title compound is prepared analogously to Example 5a)

from (2R,3R)-2,3-epoxy-3-(3-methoxycarbonylphenyl)-propanol; light-yellow oil; IR (methylene chloride): 2950, 2820, 1725, 1610, 1590, 1430, 1290, 1255 cm^{-1} ; $R_f = 0.33$ (hexane/ethyl acetate 3:2).

b) (1R,2R)-1,2-epoxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to a); light-yellow oil; $R_f = 0.39$ (hexane/ethyl acetate 3:2).

Example 20: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid (A), and disodium salt of (1R,2S)-1-hydroxy-1-(3-carboxyphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid (B)

A solution of 0.5 g of (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester according to Example 19 in 20 ml of tetrahydrofuran is stirred under argon for 40 hours with 7.5 ml of 0.2N sodium hydroxide solution at room temperature and is then concentrated by evaporation. The residue is purified by chromatography on Lichroprep[®] RP-8, Merck, with methanol/water (3:1) and yields in fractions 2-5 title compound B; m.p. 262-264°; $[\alpha]_D^{20}$ (methanol, 0.105 %) = $17.1 \pm 9.5^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 268$ (19680); 284 (19060); 325/sh; and in fractions 8-12 title compound A; m.p. 155° (decomp.); $[\alpha]_D^{20}$ (methanol, 0.12 %) = $22.5 \pm 8.3^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 268$

(26200); 286 (29220); 325/sh.

Example 21: (1S,2R)-1-hydroxy-1-(3-methoxycarbonyl-phenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(3-carboxymethylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene; colourless oil which hardens in the refrigerator, m.p. 90-91°; $[\alpha]_D^{20} = -41.5 \pm 7.7^\circ$ (0.13 % methanol); UV (methanol): $\lambda_{\max}(\epsilon) = 271$ (25120); 322 (13280).

The starting material is prepared, for example, as follows:

a) (2R,3S)-2,3-epoxy-3-(3-methoxycarbonylphenyl)-propanal

The title compound is prepared analogously to Example 5 from (2S,3S)-2,3-epoxy-3-(3-methoxycarbonylphenyl)-propanol; colourless oil; IR (methylene chloride): 2910, 2780, 1705, 1590, 1570, 1415, 1270, 1235 cm^{-1} ; $R_f = 0.36$ (hexane/ethyl acetate 3:2).

b) (1S,2S)-1,2-epoxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-ene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to a); colourless oil, not characterised in more detail.

Example 22: Sodium salt of (1S,2R)-1-hydroxy-1-(3-methoxycarbonylphenyl)-6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hex-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 21; beige powder having a melting point of 208-210°; $[\alpha]_D^{20}$ (methanol, 0.12 %) = $-41.7 \pm 8.3^\circ$; UV (methanol): $\lambda_{\max}(\epsilon)$ = 268 (21060); 285 (21540); 325/sh.

Example 23: (4R,5S)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4R,5R)-4,5-epoxy-1,1,1-trifluoro-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-diene; beige powder having a melting point of 64-66°, $[\alpha]_D^{20}$ (methanol, 0.15 %) = $147.3 \pm 6.7^\circ$. UV (methanol): $\lambda_{\max}(\epsilon)$ = 220 (48960); 270 (28500); 283/sh; 325 (13400).

The starting material is prepared, for example, as follows:

a) (2R,3R)-2,3-epoxy-6,6,6-trifluoro-hexanol

The title compound is prepared analogously to Example 1a) from 6,6,6-trifluoro-hex-2(E)-enol; colourless oil; $[\alpha]_D^{20}$ (chloroform, 0.17 %) = $35.9 \pm 5.9^\circ$; IR (methylene chloride): 3550, 3420, 2950, 2890, 2830, 1125 cm^{-1} .

b) (4R,5R)-4,5-epoxy-8,8,8-trifluoro-oct-2(E)-enal

The title compound is prepared analogously to Example 1b) from the corresponding epoxy alcohol according to a);

light-yellow oil; IR (CH₂Cl₂): 3050, 2980, 2930, 2820, 2730, 1695, 1645, 1450, 1150, 1100 cm⁻¹; R_f = 0.41 (hexane/ethyl acetate = 3:2).

c) (4R,5R)-4,5-epoxy-1,1,1-trifluoro-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-diene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to b); light-yellow oil; R_f = 0.48 (hexane/ethyl acetate 3:2).

Example 24: Sodium salt of (4R,5S)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 23; beige powder having a melting point of 198-200°; $[\alpha]_D^{20}$ (methanol, 0.15 %) = 127.3 ± 6.7°; UV (methanol): $\lambda_{\max}(\epsilon)$ = 221 (48820); 230/sh; 267 (25440); 285 (23080); 322/sh.

Example 25: (4S,5R)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4S,5S)-4,5-epoxy-1,1,1-trifluoro-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-diene; colourless powder having a melting point of 69-71°; $[\alpha]_D^{20}$ = -153.3 ± 6.7° (methanol, 0.15 %). UV (methanol): $\lambda_{\max}(\epsilon)$ = 220 (49560); 235/sh; 270 (29220); 285/sh; 325 (12990).

The starting material is prepared, for example, as follows:

a) (2S,3S)-2,3-epoxy-6,6,6-trifluoro-hexanol

The title compound is prepared analogously to Example 1a) from 6,6,6-trifluoro-hex-2(E)-enol but using L(+)-tartaric acid diethyl ester; colourless oil; $[\alpha]_D^{20}$ (chloroform, 0.17 %) = $-25.9 \pm 5.9^\circ$; IR (methylene chloride): 3550, 3430, 2940, 2880, 2830, 1125 cm^{-1} .

b) (4S,5S)-4,5-epoxy-8,8,8-trifluoro-oct-2(E)-enal

The title compound is prepared analogously to Example 1b) from the corresponding epoxy alcohol according to a); light-yellow oil; IR (methylene chloride): 3050, 2990, 2930, 2820, 2730, 1695, 1645, 1450, 1150, 1100 cm^{-1} ; $R_f = 0.36$ (hexane/ethyl acetate 3:2).

c) (4S,5S)-4,5-epoxy-1,1,1-trifluoro-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-diene

The title compound is prepared analogously to Example 1d) from the corresponding epoxyaldehyde according to b); light-yellow oil.

Example 26: Sodium salt of (4S,5R)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 25; beige powder having a melting point of $201-203^\circ$; $[\alpha]_D^{20}$ (methanol, 0.15 %) = $-117.3 \pm 6.7^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 222$ (48320); 233/sh; 267 (26440); 285 (24440); 330/sh.

Example 27: (4R,5S)-1,1,1-trifluoro-4-hydroxy-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-non-6(Z)-en-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4R,5R)-4,5-epoxy-1,1,1-trifluoro-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-non-6(Z)-ene; colourless, viscous oil; IR (methylene chloride): 3530, 2920, 2890, 2820, 1720, 1640, 1605, 1585 cm^{-1} .

The starting material is prepared, for example, as follows:

a) (2S,3R)-2,3-epoxy-6,6,6-trifluoro-hexanal

The title compound is prepared analogously to Example 5a) from (2R,3R)-2,3-epoxy-6,6,6-trifluoro-hexanol; colourless liquid having a boiling point of 80-81°/26 mbar.; $[\alpha]_D^{20}$ (chloroform, 0.15 %) = $-10.7 \pm 6.7^\circ$.

b) (4R,5R)-4,5-epoxy-1,1,1-trifluoro-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-non-6(Z)-ene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to a); light-yellow oil.

Example 28: Sodium salt of (4R,5S)-1,1,1-trifluoro-4-hydroxy-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-non-6(Z)-en-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 27; light-yellow powder having a melting point of 204-206°; $[\alpha]_D^{20}$ (methanol, 0.15 %) = $42.7 \pm 6.7^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon)$ = 218 (36920); 268 (20280); 285 (20180); 325/sh.

Example 29: (5R,6S)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5R,6R)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-ene; light-yellow oil; $R_f = 0.37$ (hexane/ethyl acetate 1:1).

The starting material is prepared, for example, as follows:

a) 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-tri-phenylphosphonium bromide

The title compound is prepared as in Example 1c) from 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl bromide; colourless crystals having a melting point of 82-85°.

b) (2S,3R)-2,3-epoxy-heptanal

The title compound is prepared analogously to Example 5a) from (2R,3R)-2,3-epoxy-heptanol; $[\alpha]_D^{20} = -99.4 \pm 0.1^\circ$.

c) (5R,6R)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-ene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to a), light-yellow oil.

Example 30: Sodium salt of (5R,6S)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example

29; m.p. 192-194°; $[\alpha]_D^{20}$ (methanol, 0.125 %) = +5.6 ± 8.0°; UV (methanol): $\lambda_{\max}(\epsilon)$ = 218 (38000); 268 (22040); 285 (21120); 325 sh.

Example 31: (5S,6R)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5S,6S)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-ene; light-yellow oil; R_f = 0.41 (hexane/ethyl acetate 1:1).

The starting material is prepared, for example, as follows:

a) (2R,3S)-2,3-epoxy-heptanal

The title compound is prepared analogously to Example 5a) from (2S,3S)-2,3-epoxy-heptanol; $[\alpha]_D^{20}$ = +104.3 ± 0.4°.

b) (5S,6S)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-ene

The title compound is prepared analogously to Example 1d) from the epoxyaldehyde according to a); light-yellow oil, R_f = 0.42 (hexane/ethyl acetate 3:2).

Example 32: Sodium salt of (5S,6R)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 31; m.p. 192-194°; $[\alpha]_D^{20}$ (methanol, 0.145 %) = 0 ± 6.9°;

UV (methanol): $\lambda_{\max}(\epsilon) = 218 (37060); 268 (21760); 286 (20520); 325 \text{ sh.}$

Example 33: (4R,5S)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undec-6(Z)-en-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4R,5R)-4,5-epoxy-1,1,1-trifluoro-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undec-6(Z)-ene, light-yellow oil; $R_f = 0.47$ (hexane/ethyl acetate 1:1).

The starting material is prepared, for example, analogously to Example 1d) from (2S,3R)-2,3-epoxy-6,6,6-trifluoro-hexanal; light-yellow oil.

Example 34: Sodium salt of (4R,5S)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undec-6(Z)-en-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 33; m.p. $193-195^\circ$; $[\alpha]_D^{20}$ (methanol, 0.135 %) = $+16.3 \pm 7.4^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 218 (37380); 267 (21380); 286 (21020); 325/\text{sh.}$

Example 35: (5R,6S)-5-hydroxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5R,6R)-5,6-epoxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-ene, light-yellow oil; $[\alpha]_D^{20}$ (methanol, 0.135 %) = $+48.9 \pm 7.4^\circ$; UV (methanol): $\lambda_{\max}(\epsilon) = 216$

(38140); 271 (24040); 285 sh, 322 (12700).

The starting material is prepared, for example, analogously to Example 1d) from (2S,3R)-2,3-epoxy-heptanal; light-yellow oil. $R_f = 0.45$ (hexane/ethyl acetate = 7:3).

Example 36: (5R,6S)-5-hydroxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 35 and is converted into the free acid with hydrochloric acid; m.p. 58-60°; $[\alpha]_D^{20}$ (methanol, 0.130 %) = +36.2 ± 7.7°; UV (methanol): $\lambda_{\max}(\epsilon) = 218$ (35240); 269 (20760); 283 (19800); 330 sh.

Example 37: (5S,6R)-5-hydroxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5S,6S)-5,6-epoxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-ene, light-yellow oil; $[\alpha]_D^{20}$ (methanol, 0.115 %) = -50.4 ± 8.7°; UV (MeOH): $\lambda_{\max}(\epsilon) = 217$ (38000); 271 (24100); 285 sh, 321 (12800).

The starting material is prepared, for example, analogously to Example 1d) from (2R,3S)-2,3-epoxy-heptanal; light-brown oil; $R_f = 0.52$ (hexane/ethyl acetate 7:3).

Example 38: Sodium salt of (5S,6R)-5-hydroxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester according to Example 37; m.p. 224-226°, $[\alpha]_D^{20}$ (methanol, 0.145 %) = -29.0 ± 6.9°; UV (methanol): $\lambda_{\max}(\epsilon)$ = 219 (38760); 268 (21880); 285 (21260); 325 sh.

Example 39: (5S,6R)-5-hydroxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-(N-benzenesulfonamidyl)-carboxamide

A solution of 0.20 g of (5S,6R)-5-hydroxy-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-dec-7(Z)-en-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid in 10 ml of methylene chloride is stirred under argon at room temperature with 60 mg of benzenesulfonamide, 44 mg of 4-dimethylaminopyridine and 70 mg of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride for 24 hours. The resulting solution is diluted with 30 ml of methylene chloride, washed twice with 1N hydrochloric acid and twice with brine, dried over magnesium sulfate and concentrated by evaporation. Chromatography of the residue on silica gel with methylene chloride/methanol (9:1) yields the title compound having a melting point of 140-142°.

Example 40: (4RS,5SR)-1-methoxycarbonyl-4-hydroxy-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-non-6(Z)-en-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4RS,5RS)-4,5-epoxy-1-methoxycarbonyl-9-(4-acetyl-3-

hydroxy-2-propylphenoxy)-non-6(Z)-ene; colourless oil;
 $[\alpha]_D^{20}$ (methanol, 0.125 %) = $0.0 \pm 8.0^\circ$; UV (methanol):
 $\lambda_{\max}(\epsilon) = 270$ (24000); 340 (13200).

The starting material is prepared, for example, analogously to Example 1d) from 5,6-epoxy-6-formylhexanoic acid methyl ester; light-yellow oil; $R_f = 0.35$ (hexane/ethyl acetate 3:2).

Example 41: Disodium salt of (4RS,5SR)-1-carboxy-4-hydroxy-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-non-6(Z)-en-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

0.24 g of the methyl ester according to Example 40 is dissolved under argon in 15 ml of tetrahydrofuran; 3.8 ml of 0.2N sodium hydroxide solution are added and the mixture is stirred for 20 hours at room temperature. Concentration by evaporation and purification of the residue by chromatography on a "Reversed Phase" silica gel column (for example Merck Lichroprep[®] RP-8) with methanol/water (7:3) yield the title compound having a melting point of 248-250° (decomp.); UV (methanol): $\lambda_{\max}(\epsilon) = 218$ (33900); 268 (18580); 284 (18240); 330 sh.

Example 42: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene; light-yellow oil. $[\alpha]_D^{20}$ (CHCl₃, 0.363 %) = $46.6 \pm 2.8^\circ$; UV (CHCl₃): $\lambda_{\max}(\epsilon) = 270$ (26500); 285 (24240); 322

(15200).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyltriphenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal (Example 1b); light-brown oil; $[\alpha]_D^{20}$ (CHCl₃, 0.224 %) = 70.8 ± 10°; R_f = 0.50 (hexane/ethyl acetate = 1:1); IR (CH₂Cl₂): 2960, 2930, 2865, 1735, 1625, 1330, 1125 cm⁻¹.

Example 43: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 42); m.p. 217-219°; $[\alpha]_D^{20}$ (MeOH, 0.160 %) = 145.6 ± 6.3°; UV (MeOH): $\lambda_{max}(\epsilon)$ = 220 (50480), 230 (sh), 267 (26240), 284 (23000), 320 sh.

Example 44: (1R,2S)-1-hydroxy-1-(3-methylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene;

m.p. 59-60°; $[\alpha]_D^{20}$ (CHCl₃, 0.163 %) = 31.9 ± 6.1°;
UV (CHCl₃): $\lambda_{\max}(\epsilon)$ = 241 (31420); 286 (23060).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyltriphenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-5-(3-methylphenyl)-pent-2(E)-enal (Example 9b); light-yellow oil; $[\alpha]_D^{20}$ (CHCl₃, 0.273 %) = 118.7 ± 3.7°.
 R_f = 0.62 (hexane/ethyl acetate = 3:2).

Example 45: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 44);
m.p. 208-210°; $[\alpha]_D^{20}$ (MeOH, 0.30 %) = 50.7 ± 3.3°.
UV (MeOH): $\lambda_{\max}(\epsilon)$ = 219 (52420), 230 (sh), 267 (26620), 285 (23520), 325 (sh).

Example 46: (1S,2R)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-10-(4-

acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene;
viscous mass; $R_f = 0.48$ (hexane/ethyl acetate = 1:1).

The starting material is prepared, for example, as follows:

a) (1S,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyltri-phenylphosphonium bromide (Example 29a) and (4S,5S)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal (Example 3b); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.454 % = $-86.8 \pm 2.2^\circ$; $R_f = 0.46$ (hexane/ethyl acetate = 1:1). IR (methylene chloride): 2960, 2930, 1730, 1625, 1330, 1130 cm^{-1} .

Example 47: Sodium salt of (1S,2R)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 46); m.p. 168-170°; $[\alpha]_D^{20}$ (methanol, 0.150 %) = $-66.7 \pm 6.7^\circ$; UV (MeOH): $\lambda_{\text{max}}(\epsilon) = 220$ (49640), 230 (sh), 266 (25640), 285 (22140), 320 (sh).

Example 48: (1R,2S)-1-hydroxy-1-(3-trifluoromethyl-phenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-diene; light-yellow oil; $R_f = 0.34$ (hexane/ethyl acetate = 1:1).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-propyltriphenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal (Example 1b); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.406 %) = $-58.6 \pm 2.5^\circ$; $R_f = 0.45$ (hexane/ethyl acetate = 7:3). IR (methylene chloride): 2945, 1670, 1610, 1310, 1055 cm^{-1} .

b) 3-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-propyl-triphenylphosphonium bromide

The title compound is prepared analogously to Example 1c) from 3-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-propyl bromide. M.p. 184-185°.

Example 49: Sodium salt of (1R,2S)-1-hydroxy-1-(3-tri-fluoromethylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 48);

m.p. 238-240°; $[\alpha]_D^{20}$ (methanol, 0.150 %) = $208 \pm 6.6^\circ$;
UV (MeOH): $\lambda_{\max}(\epsilon)$ = 216 (50040), 230 (sh), 267 (28960), 280 (sh), 320 (16020).

Example 50: (1R,2S)-1-hydroxy-1-(3-methylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-diene; light-yellow, viscous oil; R_f = 0.41 (hexane/ethyl acetate = 1:1). $[\alpha]_D^{20}$ (chloroform, 0.155 %) = $32.3 \pm 6.5^\circ$. UV (chloroform): $\lambda_{\max}(\epsilon)$ = 271 (32320), 318 (16100).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-methylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-propyltriphenylphosphonium bromide (Example 48b) and (4R,5R)-4,5-epoxy-5-(3-methylphenyl)-pent-2(E)-enal

(Example 9b), light-yellow oil; $R_f = 0.38$ (hexane/ethyl acetate = 3:2).

Example 51: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methylphenyl)-8-[4-acetyl-3-hydroxy-2-(3,3,3-trifluoropropyl)-phenoxy]-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 50);
m.p. 233-235°; $[\alpha]_D^{20}$ (methanol, 0.195 %) = $69.7 \pm 5.1^\circ$;
UV (MeOH): $\lambda_{\max}(\epsilon) = 218$ (52320), 230 (sh), 267 (29040), 280 (sh), 320 (16000).

Example 52: (1R,2S)-1-hydroxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene;
m.p. 66-68°; $R_f = 0.23$ (hexane/ethyl acetate = 3:2).
 $[\alpha]_D^{20}$ (methanol, 0.150 %) = $22.0 \pm 6.7^\circ$; UV (MeOH):
 $\lambda_{\max}(\epsilon) = 216$ (50000), 238 (sh), 271 (27860), 285 (sh), 324 (13900).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d)

from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyltri-phenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-epoxy-5-(2-trifluoromethylphenyl)-pent-2(E)-enal; light-brown oil; $[\alpha]_D^{20}$ (chloroform, 0.207 %) = $-5.8 \pm 4.8^\circ$
 $R_f = 0.25$ (hexane/ethyl acetate = 4:1).

b) (4R,5R)-4,5-epoxy-5-(2-trifluoromethylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-3-(2-trifluoromethylphenyl)-propanol; yellow crystals; $R_f = 0.36$ (hexane/ethyl acetate = 4:1). $[\alpha]_D^{20}$ (methanol, 0.165 %) = 23.0 ± 6.1 ;
UV (MeOH): $\lambda_{\max}(\epsilon) = 216$ (14400), 235 (17240).

c) (2R,3R)-2,3-epoxy-3-(2-trifluoromethylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(2-trifluoromethylphenyl)-prop-2(E)-enol; colourless crystals; $R_f = 0.38$ (hexane/ethyl acetate = 3:2);
IR (methylene chloride): 3600, 3050, 2990, 2920, 2870, 1610, 1585, 1320, 1170, 1125 cm^{-1} .

Example 53: Sodium salt of (1R,2S)-1-hydroxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 52);
m.p. 155-157°; $[\alpha]_D^{20}$ (methanol, 0.180 %) = $12.8 \pm 5.6^\circ$;
UV (MeOH): $\lambda_{\max}(\epsilon) = 219$ (48400), 230 (sh), 266 (25480), 284 (22540), 325 (sh).

Example 54: (1S,2R)-1-hydroxy-1-(2-trifluoromethyl-phenyl)-8-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; m.p. 71-73°; $R_f = 0.25$ (hexane/ethyl acetate = 3:2). $[\alpha]_D^{20}$ (methanol, 0.170 %) = $-27.1 \pm 5.9^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 216$ (51040), 235 (sh), 271 (28140), 285 (sh), 324 (13500).

The starting material is prepared, for example, as follows:

a) (1S,2S)-1,2-epoxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide (Example 1c) and (4S,5S)-4,5-epoxy-5-(2-trifluoromethylphenyl)-pent-2(E)-enal; reddish oil; $[\alpha]_D^{20}$ (chloroform, 0.207 %) = $5.4 \pm 4.8^\circ$; $R_f = 0.29$ (hexane/ethyl acetate = 4:1).

b) (4S,5S)-4,5-epoxy-5-(2-trifluoromethylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2S,3S)-2,3-epoxy-3-(2-trifluoromethylphenyl)-propanol; yellow crystals; $R_f = 0.38$ (hexane/ethyl acetate = 4:1); $[\alpha]_D^{20}$ (methanol, 0.180 %) = $-25.0 \pm 5.6^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 215$ (13960), 236 (17060).

c) (2S,3S)-2,3-epoxy-3-(2-trifluoromethylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(2-trifluoromethylphenyl)-prop-2(E)-enol; colourless crystals; $R_f = 0.35$ (hexane/ethyl acetate = 3:2). IR (methylene chloride): 3600, 3050, 2990, 2920, 2870, 1610, 1585, 1320, 1170, 1125 cm^{-1} .

Example 55: Sodium salt of (1S,2R)-1-hydroxy-1-(2-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 54); m.p. 182-184°; $[\alpha]_D^{20}$ (methanol, 0.205 %) = $-16.6 \pm 4.9^\circ$; UV (MeOH): $\lambda_{\text{max}}(\epsilon) = 219$ (47680), 235 (sh), 266 (24960), 284 (22100), 330 (sh).

Example 56: (1R,2S)-1-hydroxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; m.p. 68-70°; $R_f = 0.16$ (hexane/ethyl acetate = 3:2). $[\alpha]_D^{20}$ (methanol, 0.155 %) = $110.3 \pm 6.5^\circ$; UV (MeOH): $\lambda_{\text{max}}(\epsilon) = 217$ (52880), 236 (sh), 270 (28880), 285 (sh), 326 (13700).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyltriphenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-epoxy-5-(4-trifluoromethylphenyl)-pent-2(E)-enal; yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.220 %) = $6.5 \pm 4.5^\circ$; $R_f = 0.35$ (hexane/ethyl acetate = 4:1).

b) (4R,5R)-4,5-epoxy-5-(4-trifluoromethylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-3-(4-trifluoromethylphenyl)-propanol; yellow crystals; m.p. $67-70^\circ$; $R_f = 0.24$ (hexane/ethyl acetate = 4:1). $[\alpha]_D^{20}$ (methanol, 0.150 %) = $171.3 \pm 6.7^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 237$ (19660).

c) (2R,3R)-2,3-epoxy-3-(4-trifluoromethylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(4-trifluoromethylphenyl)-prop-2(E)-enol; colourless crystals; $R_f = 0.25$ (hexane/ethyl acetate = 3:2). IR (methylene chloride): 3550, 3010, 2950, 2880, 2830, 1605, 1310, 1150, 1110, 1050 cm^{-1} .

Example 57: Sodium salt of (1R,2S)-1-hydroxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 56); m.p. $229-231^\circ$; $[\alpha]_D^{20}$ (methanol, 0.160 %) = $118.8 \pm 6.3^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 220$ (53060), 235 (sh), 267 (27280),

284 (23880), 320 (16300).

Example 58: (1S,2R)-1-hydroxy-1-(4-trifluoromethyl-phenyl)-8-(4-acetyl-3-hydroxy-3-propyl-phenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1S,2S)-1,2-epoxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; m.p. 67-69°; $R_f = 0.13$ (hexane/ethyl acetate = 3:2); $[\alpha]_D^{20}$ (methanol, 0.155 %) = $-109.7 \pm 6.5^\circ$; UV (MeOH): $\lambda_{max}(\epsilon) = 217$ (52640), 235 (sh), 270 (28660), 285 (sh), 326 (13680).

The starting material is prepared, for example, as follows:

a) (1S,2S)-1,2-epoxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide (Example 1c) and (4S,5S)-4,5-epoxy-5-(4-trifluoromethylphenyl)-pent-2(E)-enal; reddish oil; $[\alpha]_D^{20}$ (chloroform, 0.199 %) = $-5.4 \pm 5.0^\circ$; $R_f = 0.23$ (hexane/ethyl acetate = 4:1).

b) (4S,5S)-4,5-epoxy-5-(4-trifluoromethylphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2S,3S)-2,3-epoxy-3-(4-trifluoromethylphenyl)-propanol; yellow crystals; m.p. 67-69°. $R_f = 0.18$ (hexane/ethyl acetate = 4:1). $[\alpha]_D^{20}$ (methanol, 0.150 %) =

$-180.0 \pm 6.7^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 236$ (19740).

c) (2S,3S)-2,3-epoxy-3-(4-trifluoromethylphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(4-trifluoromethylphenyl)-prop-2(E)-enol; colourless crystals; $R_f = 0.23$ (hexane/ethyl acetate = 3:2). IR (methylene chloride): 3550, 3010, 2950, 2880, 2830, 1605, 1310, 1150, 1110, 1050 cm^{-1} .

Example 59: Sodium salt of (1S,2R)-1-hydroxy-1-(4-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 58); m.p. 228-230°; $[\alpha]_D^{20}$ (methanol, 0.175 %) = $-99.4 \pm 5.7^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 220$ (49800), 235 (sh), 267 (25320), 284 (22200), 320 (15600).

Example 60: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(Z)-ene; colourless oil; $R_f = 0.41$ (hexane/ethyl acetate = 1:1); $[\alpha]_D^{20}$ (chloroform, 0.150 %) = $46.7 \pm 6.7^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 271$ (22760), 288 (20060), 270 (28880), 324 (14460).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(Z)-ene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-triphenylphosphonium bromide (Example 29a) and (2S,3R)-2,3-epoxy-3-(3-trifluoromethylphenyl)-propanal (Example 5a); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.221 %) = $25.3 \pm 4.5^\circ$; $R_f = 0.56$ (hexane/ethyl acetate = 3:2).

Example 61: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(Z)-en-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 60); m.p. 231-233°; $[\alpha]_D^{20}$ (methanol, 0.190 %) = $51.1 \pm 5.3^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon) = 215$ (42320), 267 (22220), 286 (20800), 320 (sh).

Example 62: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-diene; light-yellow viscous oil; $[\alpha]_D^{20}$ (chloroform, 0.155 %) = $44.5 \pm 6.5^\circ$; $R_f = 0.50$ (hexane/ethyl acetate = 1:1); UV (CHCl₃): $\lambda_{\max}(\epsilon) = 270$ (26800), 284 (23100), 323 (14480).

The starting material is prepared, for example, as follows:

a) 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-butyl-tri-phenylphosphonium bromide

The title compound is prepared analogously to Example 1c) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-butyl bromide; m.p. 167-169°.

b) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-butyl-tri-phenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal (Example 1b); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.308 %) = $40.7 \pm 3.2^\circ$; $R_f = 0.70$ (hexane/ethyl acetate = 3:2); IR (methylene chloride): 2950, 2860, 1625, 1325, 1120 cm^{-1} .

Example 63: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 62); m.p. 204-206°; $[\alpha]_D^{20}$ (chloroform, 0.289 %) = $8.0 \pm 3.5^\circ$; $[\alpha]_D^{20} = 55.5 \pm 6.5^\circ$ (methanol, 0.155 %); UV (methanol): $\lambda_{\text{max}}(\epsilon) = 219$ (49320), 232 (sh), 266 (25800), 285 (22060), 330 (sh).

Example 64: (1R,2S)-1-hydroxy-1-(3-trifluoromethyl-phenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-diene; light-yellow viscous oil; $[\alpha]_D^{20}$ (chloroform, 0.160 %) = $48.1 \pm 6.3^\circ$; R_f = 0.50 (hexane/ethyl acetate = 1:1). UV (CHCl₃): $\lambda_{\max}(\epsilon)$ = 270 (27120), 286 (23300), 323 (14740).

The starting material is prepared, for example, as follows:

a) 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-hexyl-tri-phenylphosphonium bromide

The title compound is prepared analogously to Example 1c) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-hexyl bromide; the compound crystallises very slowly.

b) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d from 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-hexyl-tri-phenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal (Example 1b); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.450 %) = $41.1 \pm 2.2^\circ$; R_f = 0.66 (hexane/ethyl acetate = 3:2); IR (methylene chloride): 2960, 2860, 1625, 1325, 1120 cm⁻¹.

Example 65: Sodium salt of (1R,2S)-1-hydroxy-1-(3-tri-fluoromethylphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 64);
m.p. 216-218°; $[\alpha]_D^{20}$ (chloroform, 0.258 %) = $34.9 \pm 3.9^\circ$;
 $[\alpha]_D^{20}$ = $73.8 \pm 6.3^\circ$ (methanol, 0.160 %); UV (methanol):
 $\lambda_{\max}(\epsilon)$ = 219 (50140), 232 (sh), 266 (26120), 286 (22460), 320 (15600).

Example 66: (1R,2S)-1-hydroxy-1-phenyl-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-phenyl-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; light-yellow foam;
 R_f = 0.41 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{20}$ = $47.3 \pm 2.6^\circ$ (chloroform, 0.385 %).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-phenyl-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-tri-phenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-epoxy-5-phenyl-pent-2(E)-enal; light-yellow oil; R_f = 0.60 (hexane/ethyl acetate = 3:2).

b) (4R,5R)-4,5-epoxy-5-phenyl-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-3-phenyl-propanol; yellow oil which crystallises on standing; $R_f = 0.38$ (hexane/ethyl acetate = 3:2); $[\alpha]_D^{20} = 185 \pm 5.0^\circ$ (chloroform, 0.200 %).

c) (2R,3R)-2,3-epoxy-3-phenyl-propanol

The title compound is prepared analogously to Example 1a) from 3-phenyl-prop-2(E)-enol; colourless oil which crystallises at low temperature. $R_f = 0.49$ (hexane/ethyl acetate = 1:1); IR (methylene chloride): 3590, 3040, 2980, 2920, 2870, 1605, 1080, 1070 cm^{-1} . $[\alpha]_D^{20}$ (chloroform, 0.279 %) = $47.7 \pm 3.6^\circ$.

Example 67: Sodium salt of (1R,2S)-1-hydroxy-1-phenyl-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 66); m.p. 219-221°; $[\alpha]_D^{20}$ (chloroform, 0.160 %) = $103.1 \pm 6.3^\circ$; UV (methanol): $\max(\epsilon) = 221$ (51180), 232 (sh), 267 (27040), 284 (23840), 321 (16200); UV (chloroform): $\lambda_{\max}(\epsilon) = 274$ (26080), 286 (sh), 330 (sh).

Example 68: (1R,2S)-1-hydroxy-1-(3-trifluoromethyl-phenyl)-8-(3-acetyl-4-hydroxy-5-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(3-acetyl-4-hydroxy-5-propylphenoxy)-octa-3(E),5(Z)-diene; $R_f = 0.21$ (hexane/ethyl acetate, 3:2).

The starting material is prepared, for example, as follows:

a) 3-(3-acetyl-4-hydroxy-5-propylphenoxy)-propyl bromide

6.2 g of potassium carbonate and 0.5 g of potassium iodide are added to a solution of 5.8 g of 2,5-dihydroxy-3-propyl-acetophenone and 6.1 ml of 1,3-dibromopropane in 60 ml of methyl ethyl ketone. The reaction mixture is heated at reflux for 24 hours, and then poured onto 300 ml of ice-water, rendered acidic with hydrochloric acid and extracted with dichloromethane (3 x 150 ml). The combined extracts are washed with 50 ml of water and dried over sodium sulfate. After filtration and concentration by evaporation *in vacuo*, the residue is chromatographed on 400 g of silica gel with dichloromethane. In the first fraction the title compound is eluted which, after concentration by evaporation, is obtained in the form of light-yellow crystals having a melting point of 69-70°.

b) 3-(3-acetyl-4-hydroxy-5-propylphenoxy)-propyl-triphenylphosphonium bromide

The title compound is prepared analogously to Example 1c) from 3-(3-acetyl-4-hydroxy-5-propylphenoxy)-propyl bromide and triphenylphosphine; m.p. 103-105°.

c) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(3-acetyl-4-hydroxy-5-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(3-acetyl-4-hydroxy-5-propylphenoxy)-propyl-triphenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal; $R_f = 0.54$

(hexane/ethyl acetate 2:1).

Example 69: Sodium salt of (1R,2S)-1-hydroxy-1-(3-tri-fluoromethylphenyl)-8-(3-acetyl-4-hydroxy-5-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(3-acetyl-4-hydroxy-5-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester; yellow foam; $^1\text{H-NMR}$ (CD_3OD): $\delta = 7.91, 7.76-7.56, 7.50, 7.36, 7.05, 6.82, 6.41, 6.00, 5.75, 5.47, 5.12, 4.45, 3.78, 2.65-2.35, 1.88, 1.58, 0.94$ ppm.

Example 70: (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-chlorophenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; m.p. $76-77^\circ$; $[\alpha]_{\text{D}}^{20}$ (chloroform, 0.215 %) = $51.2 \pm 4.7^\circ$; UV (chloroform): $\lambda_{\text{max}}(\epsilon) = 271 (28160), 285 (\text{sh}), 321 (15380)$.

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-chlorophenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-

epoxy-5-(3-chlorophenyl)-pent-2(E)-enal; light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.541 %) = $63.9 \pm 1.8^\circ$.

b) (4R,5R)-4,5-epoxy-5-(3-chlorophenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-3-(3-chlorophenyl)-propanol; dark-yellow oil; $R_f = 0.23$ (hexane/ethyl acetate = 4:1).

$[\alpha]_D^{20}$ (chloroform, 0.30 %) = 184.7 ± 3.3 .

c) (2R,3R)-2,3-epoxy-3-(3-chlorophenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(3-chlorophenyl)-prop-2(E)-enol; light-yellow oil; $R_f = 0.22$ (hexane/ethyl acetate = 7:3). IR (methylene chloride): 3580, 3040, 2980, 2910, 2860, 1600, 1570, 1070 cm^{-1} . $[\alpha]_D^{20}$ (chloroform, 0.334 %) = $47.3 \pm 3.0^\circ$.

Example 71: Sodium salt of (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 70);

m.p. $217-219^\circ$; $[\alpha]_D^{20}$ (methanol, 0.160 %) = $107.5 \pm 6.3^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 219$ (55060), 235 (sh), 267 (27340), 284 (23920), 320 (16500).

Example 72: (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-chlorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene;

m.p. 61-62°. $[\alpha]_D^{20}$ (chloroform, 0.170 %) = $52.9 \pm 5.9^\circ$;
UV (chloroform): $\lambda_{\max}(\epsilon)$ = 271 (27120), 286 (24800), 322 (15400).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-chlorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-tri-phenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-5-(3-chlorophenyl)-pent-2(E)-enal (Example 70b); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.391 %) = $61.4 \pm 2.5^\circ$.

Example 73: Sodium salt of (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 72); m.p. 204-206°; $[\alpha]_D^{20}$ (methanol, 0.205 %) = $58.5 \pm 4.9^\circ$; UV (MeOH): $\lambda_{\max}(\epsilon)$ = 218 (27940), 267 (13140), 285 (11600), 320 (sh).

Example 74: (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-methoxyphenyl)-8-(4-acetyl-3-

hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene;

m.p. 65-67°; UV (chloroform): $\lambda_{\max}(\epsilon) = 271 (30360), 285$
(sh), 323 (16600).

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-methoxyphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-epoxy-5-(3-methoxyphenyl)-pent-2(E)-enal; light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.315 %) = 78.4 ± 3.2 .

b) (4R,5R)-4,5-epoxy-5-(3-methoxyphenyl)-pent-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-3-(3-methoxyphenyl)-propanol; yellow oil; $R_f = 0.41$ (hexane/ethyl acetate = 3:2); $[\alpha]_D^{20}$ (chloroform, 0.567 %) = $168.9 \pm 1.8^\circ$.

c) (2R,3R)-2,3-epoxy-3-(3-methoxyphenyl)-propanol

The title compound is prepared analogously to Example 1a) from 3-(3-methoxyphenyl)-prop-2(E)-enol; light-yellow oil; $R_f = 0.31$ (hexane/ethyl acetate = 3:2).

IR (methylene chloride): 3550, 2890, 1580, 1565, 1465, 1445, 1130 cm^{-1} .

Example 75: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2

from the corresponding methyl ester (Example 74);
m.p. 206-208°; $[\alpha]_D^{20}$ (methanol, 0.293 %) = $99.7 \pm 3.4^\circ$;
UV (methanol): $\lambda_{\max}(\epsilon)$ = 221 (57840), 235 (sh), 268
(29360), 282 (26400), 320 (16800).

Example 76: (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-methoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene; m.p. 53° (partly sublimes); UV (chloroform): $\lambda_{\max}(\epsilon)$ = 272 (29920), 285 (sh), 323 (15540); $[\alpha]_D^{20}$ (chloroform, 0.180 %) = $44.4 \pm 5.6^\circ$.

The starting material is prepared, for example, as follows:

a) (1R,2R)-1,2-epoxy-1-(3-methoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-triphenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-5-(3-methoxyphenyl)-pent-2(E)-enal (Example 74b); light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.375 %) = 72.5 ± 2.7 .

Example 77: Sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2

from the corresponding methyl ester (Example 76);
m.p. 187-188°; $[\alpha]_D^{20}$ (methanol, 0.150 %) = $72.0 \pm 6.7^\circ$;
UV (methanol): $\lambda_{\max}(\epsilon)$ = 222 (55780), 268 (27820), 282
(25200), 321 (16200).

Example 78: (1R,2S)-1-hydroxy-1-(3-trifluoromethyl-
phenyl)-8-(4-trifluoroacetyl-3-hydroxy-
phenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-
oxo-4H-1-benzopyrane-2-carboxylic acid
methyl ester

The title compound is prepared analogously to Example 1
from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-
trifluoroacetyl-3-hydroxyphenoxy)-octa-3(E),5(Z)-diene;
 R_f = 0.23 (hexane/ethyl acetate 3:2).

The starting material is prepared, for example, as
follows:

a) 3-(4-trifluoroacetyl-3-hydroxyphenoxy)-propyl bromide

The title compound is prepared analogously to Example
68a) from 2,4-dihydroxytrifluoroacetophenone and is
obtained in the form of a light-yellow oil; IR (dichloro-
methane): 3150, 2940, 1645, 1625, 1380, 1210, 1150, 1125,
1020, 940 cm^{-1} .

b) 3-(4-trifluoroacetyl-3-hydroxyphenoxy)-propyl-tri-
phenylphosphonium bromide

The title compound is prepared analogously to Example 1c)
from 3-(4-trifluoroacetyl-3-hydroxyphenoxy)-propyl
bromide and triphenylphosphine; m.p. 125-130°C.

c) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-trifluoroacetyl-3-hydroxyphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-trifluoroacetyl-3-hydroxyphenoxy)-propyl-triphenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal; $R_f = 0.56$ (hexane/ethyl acetate 2:1).

Example 79: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-trifluoroacetyl-3-hydroxyphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

10 ml of 0.1N aqueous sodium hydroxide solution are added to a solution, cooled to 10°C, of 708 mg of the methyl ester of the title compound (see Example 78) in 25 ml of tetrahydrofuran. The reaction mixture is stirred at room temperature for 24 hours, freed of solvent in vacuo and the residue is taken up in water. After filtration until clear, the solution is lyophilised. The title compound is obtained in the form of an olive-green amorphous powder. $^1\text{H-NMR}$ (CD_3OD): $\delta = 7.94, 7.78-7.46, 7.36, 6.90, 6.36, 6.04, 5.74, 5.42, 5.12, 4.42, 3.86$ ppm.

Example 80: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene; $R_f = 0.18$ (toluene/ethyl acetate 5:1).

The starting material is prepared, for example, as follows:

a) 3-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-propyl bromide

The title compound is prepared analogously to Example 68a) from 2,4-dihydroxy-3-propyl-trifluoroacetophenone and is obtained in the form of a yellow oil; IR (dichloromethane): 3150, 2950, 2860, 1640, 1620, 1500, 1295, 1210, 1150, 1120, 1070 cm^{-1} .

b) 3-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide

The title compound is prepared analogously to Example 1c) from 3-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-propyl bromide and triphenylphosphine; m.p. 170-190°C.

c) (1R,2R)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal; R_f = 0.55 (hexane/ethyl acetate 2:1).

Example 81: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-trifluoroacetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

6.6 ml of 0.1N aqueous sodium hydroxide solution are added to a solution, cooled to 10°C, of 500 mg of the

methyl ester of the title compound (see Example 80) in 20 ml of tetrahydrofuran. The reaction mixture is stirred for 1 hour at 10°C, freed of tetrahydrofuran in vacuo and the solution that remains is lyophilised. The title compound is obtained in the form of a yellowish-green amorphous powder; ¹H-NMR (CD₃OD): δ = 7.93, 7.77-7.60, 7.50, 7.36, 6.92, 6.43, 6.04, 5.73, 5.47, 5.13, 4.47, 4.00, 2.50, 2.38, 0.72 ppm.

Example 82: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenylthio)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenylthio)-octa-3(E),5(Z)-diene; R_f = 0.19 (hexane/ethyl acetate 3:2).

The starting material is prepared, for example, as follows:

a) 3-(4-acetyl-3-hydroxy-2-propylphenylthio)-propyl bromide

The title compound is prepared analogously to Example 68a) from 2-hydroxy-4-mercapto-acetophenone; light-yellow oil.

b) 3-(4-acetyl-3-hydroxy-2-propylphenylthio)-propyl-triphenylphosphonium bromide

The title compound is prepared analogously to Example 1 from 3-(4-acetyl-3-hydroxy-2-propylphenylthio)-propyl bromide and triphenylphosphine.

c) (1R,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenylthio)-octa-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenylthio)-propyl-triphenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enal.

Example 83: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenylthio)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 82).

Example 84: (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenylthio)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (1R,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenylthio)-deca-3(E),5(Z)-diene; $R_f = 0.17$ (hexane/ethyl acetate 3:2).

The starting material can be prepared, for example, as follows:

a) 5-(4-acetyl-3-hydroxy-2-propylphenylthio)-pentyl bromide

The title compound is prepared analogously to Example 68a) from 2-hydroxy-4-mercapto-acetophenone; light-yellow oil.

b) 5-(4-acetyl-3-hydroxy-2-propylphenylthio)-pentyl-triphenylphosphonium bromide

The title compound is prepared analogously to Example 1 from 5-(4-acetyl-3-hydroxy-2-propylphenylthio)-pentyl bromide and triphenylphosphine.

c) (1R,2S)-1,2-epoxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenylthio)-deca-3(E),5(Z)-diene

The title compound is prepared analogously to Example 1d) from 5-(4-acetyl-3-hydroxy-2-propylphenylthio)-pentyl-triphenylphosphonium bromide and (4R,5R)-4,5-epoxy-5-(3-trifluoromethylphenyl)-pent-2(E)-enol.

Example 85: Sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenylthio)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 84).

Example 86: (5R,6S)-1,1,1-trifluoro-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5R,6R)-5,6-epoxy-1,1,1-trifluoro-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-diene; light-yellow foam; $R_f = 0.24$ (hexane/ethyl acetate = 3:2).

The starting material is prepared, for example, as follows:

a) (2R,3R)-2,3-epoxy-7,7,7-trifluoro-heptanol

The title compound is prepared analogously to Example 1a) from 7,7,7-trifluoro-hept-2(E)-enol; light-yellow oil; $R_f = 0.38$ (hexane/ethyl acetate = 3:2). $[\alpha]_D^{20}$ (chloroform, 0.490 %) = $15.3 \pm 2.0^\circ$. IR (methylene chloride): 3550, 3430, 2900, 1180, 1125 cm^{-1} .

b) (4R,5R)-4,5-epoxy-9,9,9-trifluoro-non-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-7,7,7-trifluoro-heptanol; oil, which crystallises in the refrigerator. $R_f = 0.63$ (hexane/ethyl acetate = 1:1). $[\alpha]_D^{20}$ (chloroform, 0.210 %) = $19.5 \pm 4.8^\circ$.

c) (5R,6R)-5,6-epoxy-1,1,1-trifluoro-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyltriphenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-epoxy-9,9,9-trifluoro-non-2(E)-enal; yellow oil; $R_f = 0.56$ (hexane/ethyl acetate = 3:2).

Example 87: Sodium salt of (5R,6S)-1,1,1-trifluoro-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 86); m.p. $190-191^\circ$; $[\alpha]_D^{20}$ (methanol, 0.268 %) = $105.2 \pm 3.7^\circ$; UV (methanol): $\lambda_{\text{max}}(\epsilon) = 222$ (48800), 235 (sh), 267 (25920), 285 (22920), 320 (16000).

Example 88: (4R,5S)-1,1,1-trifluoro-4-hydroxy-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4R,5R)-4,5-epoxy-1,1,1-trifluoro-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-6(E),8(Z)-diene; yellow oil.

The starting material is prepared, for example, as follows:

a) (4R,5R)-4,5-epoxy-8,8,8-trifluoro-oct-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-6,6,6-trifluoro-hexanol; light-yellow oil which crystallises in the refrigerator; $R_f = 0.53$ (hexane/ethyl acetate = 3:2). $[\alpha]_D^{20}$ (chloroform, 0.290 %) = $21.7 \pm 3.4^\circ$. IR (methylene chloride): 3050, 2980, 2930, 2810, 2730, 1690, 1640, 1145 cm^{-1} .

b) (4R,5R)-4,5-epoxy-1,1,1-trifluoro-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-6(E),8(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-triphenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-8,8,8-trifluoro-oct-2(E)-enal; yellow oil; $R_f = 0.69$ (hexane/ethyl acetate = 3:2).

Example 89: Sodium salt of (4R,5R)-1,1,1-trifluoro-4-hydroxy-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 88);

m.p. 150-152°; $[\alpha]_D^{20}$ (methanol, 0.265 %) = $72.5 \pm 3.8^\circ$;
UV (methanol): $\lambda_{\max}(\epsilon)$ = 221 (44680), 231 (sh), 266
(22560), 285 (20560), 330 (sh).

Example 90: (4R,5S)-1,1,1-trifluoro-4-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (4R,5R)-4,5-epoxy-1,1,1-trifluoro-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-6(E),8(Z)-diene; yellow oil; R_f = 0.31 (hexane/ethyl acetate = 3:2).

The starting material is prepared, for example, as follows:

a) (4R,5R)-4,5-epoxy-1,1,1-trifluoro-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-6(E),8(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-butyl-triphenylphosphonium bromide (Example 62b) and (4R,5R)-4,5-epoxy-8,8,8-trifluoro-oct-2(E)-enal (Example 88a); yellow oil; R_f = 0.64 (hexane/ethyl acetate = 3:2).

Example 91: Sodium salt of (4R,5S)-1,1,1-trifluoro-4-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 90);

m.p. 180-182°; $[\alpha]_D^{20}$ (methanol, 0.292 %) = $77.1 \pm 3.4^\circ$;
UV (methanol): $\lambda_{\max}(\epsilon)$ = 222 (47480), 231 (sh), 267
(24840), 285 (22120), 321 (15800).

Example 92: (5R,6S)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5R,6R)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-diene; light-yellow foam; $R_f = 0.43$ (hexane/ethyl acetate = 1:1); $[\alpha]_D^{20}$ (methanol, 0.150 %) = $22.0 \pm 6.7^\circ$; IR (methylene chloride): 3580, 2950, 1745, 1655, 1625, 1600 cm^{-1} .

The starting material is prepared, for example, as follows:

a) (4R,5R)-4,5-epoxy-non-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2R,3R)-2,3-epoxy-heptanol; yellow oil; $R_f = 0.29$ (hexane/ethyl acetate = 4:1); $[\alpha]_D^{20}$ (chloroform, 0.390 %) = $21.3 \pm 2.6^\circ$; IR (methylene chloride): 2950, 2920, 2860, 1690, 1640, 1100, 970 cm^{-1} .

b) (5R,6R)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyl-triphenylphosphonium bromide (Example 1c) and (4R,5R)-4,5-epoxy-non-2(E)-enal; light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.650 %) = $23.7 \pm 1.5^\circ$.

Example 93: Sodium salt of (5R,6S)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 92);
m.p. 205-207°; $[\alpha]_D^{20}$ (methanol, 0.278 %) = $115.1 \pm 3.6^\circ$;
UV (methanol): $\lambda_{\max}(\epsilon)$ = 222 (50960), 232 (sh), 267 (27400), 285 (24000), 321 (16400).

Example 94: (5R,6S)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5S,6S)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-diene; colourless foam;
 $[\alpha]_D^{20}$ (methanol, 0.260 %) = $136.2 \pm 3.8^\circ$; UV (methanol):
 $\lambda_{\max}(\epsilon)$ = 221 (48040), 271 (28320), 327 (13200).

The starting material is prepared, for example, as follows:

a) (4S,5S)-4,5-epoxy-non-2(E)-enal

The title compound is prepared analogously to Example 1b) from (2S,3S)-2,3-epoxy-heptanol; yellow oil; R_f = 0.27 (hexane/ethyl acetate = 5:1); $[\alpha]_D^{20}$ (chloroform, 0.325 %) = $23.1 \pm 3.0^\circ$.

b) (5S,6S)-5,6-epoxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propyltriphenylphosphonium bromide (Example 1c) and (4S,5S)-4,5-

epoxy-non-2(E)-enal; light-yellow oil; $[\alpha]_D^{20}$ (chloroform, 0.600 %) = $24.8 \pm 1.6^\circ$.

Example 95: Sodium salt of (5S,6R)-5-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 94);

m.p. 204-206°; $[\alpha]_D^{20}$ (methanol, 0.570 %) = $121.1 \pm 1.8^\circ$;
UV (methanol): $\lambda_{\max}(\epsilon)$ = 222 (51240), 235 (sh), 267 (27360), 284 (21400), 320 (16400).

Example 96: (5R,6S)-5-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5R,6R)-5,6-epoxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-diene; light-yellow viscous

oil; $[\alpha]_D^{20}$ (chloroform, 0.424 %) = $66.5 \pm 2.4^\circ$;
UV (chloroform): $\lambda_{\max}(\epsilon)$ = 270 (28560), 288 (sh), 325 (15240).

The starting material is prepared, for example, as follows:

a) (5R,6R)-5,6-epoxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-triphenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-non-2(E)-enal (Example 92a); light-yellow oil;

$[\alpha]_D^{20}$ (chloroform, 0.441 %) = $20.6 \pm 2.3^\circ$.

Example 97: Sodium salt of (5R,6S)-5-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 96);

m.p. 193-195°; $[\alpha]_D^{20}$ (methanol, 0.284 %) = $71.1 \pm 3.5^\circ$.

UV (methanol): $\lambda_{\max}(\epsilon)$ = 222 (49320), 232 (sh), 267 (25520), 286 (22680), 321 (16000).

Example 98: (5S,6R)-5-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5S,6S)-5,6-epoxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-diene; light-yellow viscous

mass; $[\alpha]_D^{20}$ (chloroform, 0.463 %) = $79.0 \pm 2.2^\circ$;

UV (chloroform): $\lambda_{\max}(\epsilon)$ = 270 (27120), 288 (sh), 326 (14960).

The starting material is prepared, for example, as follows:

a) (5S,6S)-5,6-epoxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-triphenylphosphonium bromide (Example 29a) and (4S,5S)-4,5-epoxy-non-2(E)-enal (Example 94a); light-yellow oil;

$[\alpha]_D^{20}$ (chloroform, 0.472 %) = $18.8 \pm 2.1^\circ$.

Example 99: Sodium salt of (5S,6R)-5-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 98);

m.p. 193-195°; $[\alpha]_D^{20}$ (methanol, 0.296 %) = $65.9 \pm 3.4^\circ$.

UV (methanol): $\lambda_{\max}(\epsilon)$ = 222 (49760), 232 (sh), 267 (25800), 285 (22520), 320 (16000).

Example 100: (5R,6S)-1,1,1-trifluoro-5-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid methyl ester

The title compound is prepared analogously to Example 1 from (5R,6R)-5,6-epoxy-1,1,1-trifluoro-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-diene; light-yellow oil; R_f = 0.32 (hexane/ethyl acetate = 3:2).

The starting material is prepared, for example, as follows:

a) (5R,6R)-5,6-epoxy-1,1,1-trifluoro-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-diene

The title compound is prepared analogously to Example 1d) from 3-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl-triphenylphosphonium bromide (Example 29a) and (4R,5R)-4,5-epoxy-9,9,9-trifluoro-non-2(E)-enal (Example 86b); yellow oil; R_f = 0.72 (hexane/ethyl acetate = 3:2).

Example 101: Sodium salt of (5R,6S)-1,1,1-trifluoro-5-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid

The title compound is prepared analogously to Example 2 from the corresponding methyl ester (Example 100);

UV (methanol): $\lambda_{\max}(\epsilon) = 222 (48800), 235 (sh), 267 (25920), 285 (22920), 320 (16000).$

Example 102: In a manner analogous to that described in Examples 1 to 77 it is also possible to prepare:

the sodium salt of (1R,2S)-1-hydroxy-1-phenyl-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-phenyl-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-phenyl-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic

acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-fluorophenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-fluorophenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-fluorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-fluorophenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (1R,2S)-1-hydroxy-1-(3-carboxyphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-

3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (1R,2S)-1-hydroxy-1-(3-carboxyphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (1R,2S)-1-hydroxy-1-(3-carboxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (1R,2S)-1-hydroxy-1-(3-carboxyphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3,4-dichloro-

phenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(2,4-dichlorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3,4-dimethoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(2,4-dimethoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(2,4-dimethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-dimethylamino-phenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid.

Example 103: In a manner analogous to that described in Examples 1 to 101 it is also possible to prepare the following compounds:

the sodium salt of (1R,2S)-1-hydroxy-1-(3-bromophenyl)-8-

(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-bromophenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-bromophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (1R,2S)-1-hydroxy-1-(3-bromophenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (5R,6S)-1,1,1-trifluoro-5-hydroxy-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (5R,6S)-1,1,1-trifluoro-5-hydroxy-15-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentadeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (5R,6S)-5-hydroxy-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the sodium salt of (5R,6S)-5-hydroxy-15-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentadeca-7(E),9(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (4R,5S)-1-carboxy-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-dien-6-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (4R,5S)-1-carboxy-4-hydroxy-12-(4-acetyl-3-hydroxy-2-propylphenoxy)-dodeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (4R,5S)-1-carboxy-4-hydroxy-13-(4-acetyl-3-hydroxy-2-propylphenoxy)-trideca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid;

the disodium salt of (4R,5S)-1-carboxy-4-hydroxy-14-(4-acetyl-3-hydroxy-2-propylphenoxy)-tetradeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid.

Examples of pharmaceutical preparations

and corresponding finished medicament forms

In the following the term "active ingredient" is to be understood as being a compound of formula I according to the invention, especially a compound described as a product in Examples 1 to 9, for example the sodium salt of (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid.

Example A: An inhalation suspension, comprising propellant and forming a solid aerosol, comprising 0.1 % by weight active ingredient

<u>Composition:</u>	% by weight
active ingredient, micronised	0.1
sorbitan trioleate	0.5
Propellant A (trichlorotrifluoroethane)	4.4
Propellant B (dichlorodifluoromethane and 1,2-dichlorotetrafluoroethane)	15.0 80.0

Preparation: In the absence of moisture, the active ingredient is suspended in trichlorotrifluoroethane using a customary homogeniser and with the addition of the sorbitan trioleate, the suspension is introduced into an aerosol container provided with a metering valve; the container is sealed and filled up with propellant B under pressure.

Example B: An approximately 2 % aqueous solution, suitable for inhalation, of an active ingredient in the form of its sodium or potassium salt.

<u>Composition:</u>	
active ingredient (K or Na salt)	2000 mg
disodium salt of ethylenediaminetetraacetic acid	10 mg
benzalkonium chloride	10 mg
water, freshly distilled	ad 100 ml

Preparation: The active ingredient is dissolved in approximately 60 ml of freshly distilled water, and the stabiliser (disodium salt of ethylenediaminetetraacetic acid) and the preservative (benzalkonium chloride) are added. When all the components have completely dissolved, the resulting solution is made up to 100 ml

and introduced into small pressurised bottles which are then sealed in gas-tight manner. The propellant is added, as required, in gaseous form under pressure or in liquid form.

APPENDIX - PHARMACOLOGICAL TEST METHODS

Bronchoconstriction test on guinea pigs (in vivo, aerosol):

Male guinea pigs weighing 400-700 g are anaesthetised intraperitoneally with 1.4 g/kg of urethane and a polyethylene cannula is inserted into the jugular vein. A second polyethylene cannula is inserted into the trachea. The pressure in the oesophagus is recorded by means of a cannula that is inserted into the oesophagus and that is connected to a Statham pressure transducer. The animal is placed in an airtight plexiglass chamber which is connected to a Fleisch's tube No. 000 and a Validyne transducer MP 45-1. This arrangement is used to measure the flow.

After the surgical preparation of the test animals, a certain period of time is allowed to elapse to enable the pulmonary functions to stabilise. The test compound is then administered in accordance with the following procedure: The test animals are exposed for one minute to a 1 % aerosol solution of the test compound (weight/volume) or to distilled water (for control purposes). For all the test compounds that are administered by inhalation, a Monaghan ultrasound spray apparatus (model 670) of which the particle size varies between 1 and 8 microns, the majority being 3 microns, is used.

Aqueous solutions are freshly prepared each time and are introduced into the chamber of the spray device using an On-stream drug vial. The spray mist produced is administered to the experimental animals via a glass chamber of 65 ml capacity which is connected to the trachea by a cannula. When the treatment period has elapsed, LTD₄ (0.3 µg/ml) is administered over a period of 2 minutes using a second Monaghan ultrasound spray device (model 670) and via a similar glass chamber.

The reduction in compliance in the third minute after the LTD₄ administration is read off and the average value of three animals is compared with the average value of three control animals and the percentage inhibition of compliance is calculated in accordance with the following formula:

$$\% \text{ inhibition} = 100 - \frac{(100 - \text{compliance preparation}) \times 100}{(100 - \text{compliance control})}$$

If different concentrations of active ingredient are tested, the percentage inhibition for each concentration is recorded, the log concentration on the abscissa being plotted against the percentage inhibition on the ordinate. The IC₅₀ is then determined by linear regression analysis.

In vitro test to determine the inhibition of phospholipase A₂ obtained from human leucocytes

Neutrophilic polymorpho-nuclear human leucocytes are isolated from "Buffy coats" by multi-step fractional sedimentation and are deep-frozen. The phospholipase A₂

is extracted from the cell suspension by homogenisation with the addition of ice-cold 0.36N H_2SO_4 in 2N NaCl and the supernatant obtained after centrifugation at 10,000 x g is dialysed against sodium acetate buffer pH 4.5.

In order to determine the enzyme activity, enzyme (10-30 μg of protein) is incubated at 37° for 1 hour in 0.1M tris/HCl buffer pH 7 with the addition of 1 mmol of CaCl_2 and substrate consisting of phospholipids (2 μm) of *Escherichia coli* radioactively labelled biosynthetically with ^{14}C -oleic acid. The reaction is stopped by the addition of Dole reagent (isopropanol/heptane/1N H_2SO_4 40:10:1, v/v) and the ^{14}C -oleic acid freed selectively by phospholipase A_2 is extracted. Substrate extracted therewith is completely removed by filtration of the extract through a column of silica gel. The determination of ^{14}C -oleic acid in the eluate is effected by radiometry.

In order to detect an inhibitory action of test substances on phospholipase A_2 , the test substances are added to the incubation mixture in the form of solutions in water, dimethyl sulfoxide (final concentration in the batch up to 5 %, v/v) or ethanol (final concentration in the batch up to 2.5 %, v/v). The degree of action of the test substances is expressed by the IC_{50} , that is to say the concentration which effects inhibition of 50 % of the control activity. The IC_{50} is determined graphically by plotting the percentage inhibition on the ordinate against the log of the concentration (μm) on the abscissa.

Under the described test conditions mepacrin inhibits

phospholipase A₂ with an IC₅₀ of 1600 μ m.

In vitro test to determine the inhibition of phospholipase C obtained from human thrombocytes

Human thrombocytes are obtained from "Buffy coats" by fractional centrifugation and are then deep-frozen. The phospholipase C is freed by ultrasound treatment of the cell suspension and after ultracentrifugation (150,000 x g for 1 hour) is present in soluble form in the supernatant.

In order to determine the enzyme activity, enzyme (20-100 μ g of protein) is incubated at 37° for 5 minutes in 0.025M tris/maleate buffer pH 6 with the addition of 0.2 mmol of CaCl₂ and 0.02 mmol of radioactively labelled substrate, phosphatidyl-[¹⁴C]-inositol. The reaction is stopped by shaking with CHCl₃/CH₃OH 2:1 (v/v), in the course of which unused substrate is extracted into the organic phase, while the reaction product, ¹⁴C-inositol phosphate, remains in the aqueous phase and can be measured by radiometry of an aliquot.

In order to detect an inhibitory action of test substances on phospholipase C, the test substances are added to the incubation mixture in the form of solutions in water, dimethyl sulfoxide (final concentration in the batch up to 5 %, v/v) or ethanol (final concentration in the batch up to 2.5 %, v/v). The degree of action of the test substances is expressed by the IC₅₀, that is to say the concentration which effects inhibition of 50 % of the control activity. The IC₅₀ is determined graphically by plotting the percentage inhibition on the ordinate against the log of the concentration (μ m) on the

abscissa.

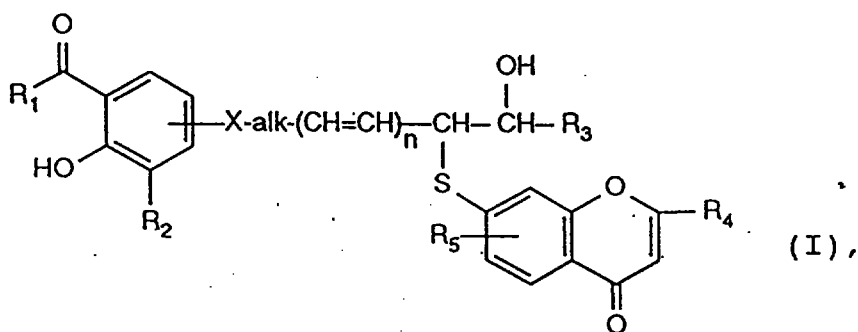
Under the described test conditions mepacrin inhibits phospholipase C with an IC_{50} of 20 μm .



Patent claims

for the contracting states AT, BE, CH,
DE, FR, GB, IT, LI, LU, NL, SE:

1. A compound of formula I



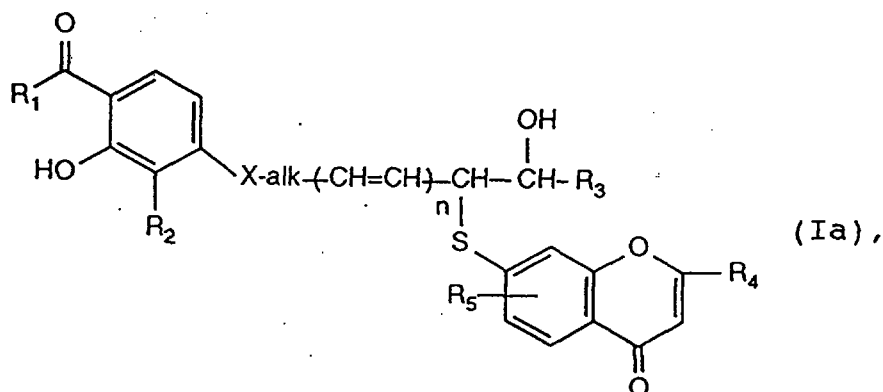
in which R_1 is lower alkyl or mono-, di- or poly-fluoro-lower alkyl, R_2 is hydrogen, lower alkyl, lower alkenyl or mono-, di- or poly-fluoro-lower alkyl, X is C_1 - C_3 -alkylene, oxy or thio, alk is lower alkylene, n is 1 or 2, R_3 is phenyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy, halogen, carboxy, lower alkoxy-carbonyl, amino, N-mono- or N,N-di-lower alkyl-amino, carbamoyl, N-mono- or N,N-di-lower alkyl-carbamoyl and/or by trifluoromethyl, or is lower alkyl, mono-, di- or tri-fluoro-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, R_4 is carboxy, lower alkoxy-carbonyl, 5-tetrazolyl, carbamoyl, N-mono- or N,N-di-lower alkyl-carbamoyl, or N-(benzene-sulfonyl)-carbamoyl that is unsubstituted or is substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or by trifluoromethyl, and R_5 is hydrogen or lower alkyl; radicals designated "lower" having not more than 7 carbon atoms; or a salt thereof.

2. A compound according to claim 1, of formula I, in which R_1 is C_1 - C_4 alkyl or ω, ω, ω -trifluoro- C_1 - C_4 alkyl, R_2 is hydrogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl or ω, ω, ω -trifluoro- C_1 - C_4 alkyl, X is C_1 - C_3 alkylene, oxy or thio,

alk is straight-chain C₂-C₆alkylene, n is 1 or 2, R₃ is phenyl that is unsubstituted or is substituted by C₁-C₄alkyl, C₁-C₄alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl, carboxy and/or by C₁-C₄alkoxycarbonyl, or is C₁-C₇alkyl, ω,ω,ω-trifluoro-C₂-C₅alkyl, carboxy-C₂-C₅alkyl or C₁-C₄alkoxycarbonyl-C₂-C₅alkyl, R₄ is carboxy or N-(benzenesulfonyl)-carbamoyl, and R₅ is hydrogen, or a salt thereof.

3. A compound according to either claim 1 or claim 2, of formula I, in which R₁ is C₁-C₄alkyl or ω,ω,ω-trifluoro-C₁-C₄alkyl, R₂ is C₁-C₄alkyl, C₂-C₄alkenyl or ω,ω,ω-trifluoro-C₁-C₄alkyl, and the group X is bonded in the para-position with respect to the R₁-C(=O) group, or a salt thereof.

4. A compound of formula Ia



in which R₁ is C₁-C₄alkyl, R₂ is C₁-C₄alkyl, C₂-C₄alkenyl or ω,ω,ω-trifluoro-C₁-C₄alkyl, X is C₁-C₃alkylene, oxy or thio, alk is straight-chain C₂-C₆alkylene, n is 1 or 2, R₃ is a group of formula -A-R₃' in which -A- is C₁-C₄alkylene, phenylene or a direct bond and R₃' is C₁-C₄alkyl, trifluoromethyl, carboxy or C₁-C₄alkoxycarbonyl, R₄ is carboxy or N-(benzenesulfonyl)-carbamoyl, and R₅ is hydrogen, or a salt thereof.



5. A compound according to claim 4, of formula Ia, in which R_1 is C_1 - C_4 alkyl, R_2 is C_1 - C_4 alkyl, X is oxy, alk is C_2 - C_6 alkylene, n is 1 or 2, R_3 is phenyl substituted by C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen having an atomic number of up to and including 35, trifluoromethyl or by C_1 - C_4 alkoxycarbonyl, or is C_2 - C_8 alkyl, ω, ω, ω -trifluoro- C_3 - C_5 alkyl or C_1 - C_4 alkoxycarbonyl- C_1 - C_4 alkyl, R_4 is carboxy, and R_5 is hydrogen, or a salt thereof.

6. A compound according to claim 4, of formula Ia, in which R_1 is C_1 - C_4 alkyl, R_2 is C_1 - C_4 alkyl, X is oxy, alk is C_2 - C_6 alkylene, n is 2, R_3 is a group of formula -A- R_3' in which -A- is C_1 - C_4 alkylene or phenylene, and R_3' is C_1 - C_4 alkyl, trifluoromethyl or C_1 - C_4 alkoxycarbonyl, R_4 is carboxy or N-(benzenesulfonyl)-carbamoyl, and R_5 is hydrogen, or a salt thereof.

7. A compound according to any one of claims 1 to 4, of formula I or Ia, in which X is oxy, or a salt thereof.

8. A compound according to any one of claims 1 to 5, of formula I or Ia, in which n is 2, or a salt thereof.

9. A compound according to any one of claims 1 to 8, of formula I or Ia, in which R_3 is m- C_1 - C_4 alkylphenyl or m-trifluoromethylphenyl, R_4 is carboxy and R_5 is hydrogen, or a salt thereof.

10. A compound according to any one of claims 1 to 9, of formula I or Ia, in which in the radical $-(CH=CH)_n-$ the double bond adjacent to the radical alk is in the (Z)-, that is to say the cis-configuration, and the additional double bond which may be present in the radical $-(CH=CH)_n-$ is in the (E)-, that is to say the trans-configuration, or a salt thereof.



11. A compound according to any one of claims 1 to 10, of formula I or Ia, in which the chain carbon atom bonded to the sulfur atom has the (S)-configuration and the chain carbon atom carrying the hydroxy group has the (R)-configuration, or a salt thereof.

12. (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

13. (1R,2S)-1-hydroxy-1-(3-methylphenyl)-8-(4-acetyl-3-hydroxy-2-propylphenoxy)-octa-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

14. (1R,2S)-1-hydroxy-1-phenyl-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

15. (4R,5S)-1,1,1-trifluoro-4-hydroxy-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-6(E),8(Z)-dien-5-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

16. (1R,2S)-1-hydroxy-1-(3-fluorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

17. (1R,2S)-1-hydroxy-1-(3-bromophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.



18. (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

19. (1R,2S)-1-hydroxy-1-(3-methylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

20. (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-9-(4-acetyl-3-hydroxy-2-propylphenoxy)-nona-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

21. (1R,2S)-1-hydroxy-1-(3-trifluoromethylphenyl)-11-(4-acetyl-3-hydroxy-2-propylphenoxy)-undeca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

22. (1R,2S)-1-hydroxy-1-(3-chlorophenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

23. (1R,2S)-1-hydroxy-1-(3-methoxyphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

24. (1R,2S)-1-hydroxy-1-(3-methoxycarbonylphenyl)-10-(4-acetyl-3-hydroxy-2-propylphenoxy)-deca-3(E),5(Z)-dien-2-yl-7-thio-4-oxo-4H-1-benzopyrane-2-carboxylic acid or the sodium salt thereof.

25. A compound according to any one of claims 1 to 24

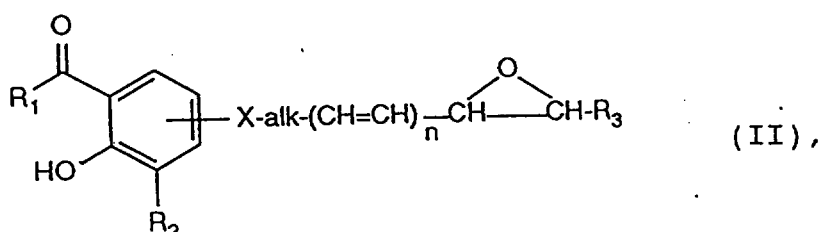
for use in a method for the therapeutic treatment of the human or animal body.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 24 and at least one pharmaceutically acceptable carrier.

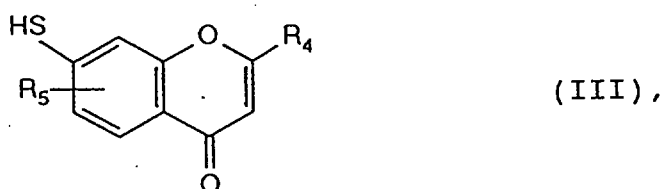
27. A pharmaceutical composition comprising a compound according to claim 14 and at least one pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising a compound according to claim 18 and at least one pharmaceutically acceptable carrier.

29. A process for the preparation of a compound of formula I according to claim 1, or a salt thereof, which process comprises reacting an epoxide of formula II



in which R_1 , R_2 , X , alk, n and R_3 are as defined for formula I, with a thiol of formula III



in which R_4 and R_5 are as defined for formula I, or with a salt thereof, and, if desired, converting a compound obtainable in accordance with the process into a different compound of formula I, separating a stereoisomeric mixture obtainable in accordance with the



process into the components and/or converting a free compound obtainable in accordance with the process into a salt, or converting a salt obtainable in accordance with the process into the free compound or into a different salt.

30. The use of a compound according to any one of claims 1 to 24 for the preparation of a pharmaceutical composition.

31. The use of a compound according to any one of claims 1 to 24 for the preparation of an anti-allergic medication.