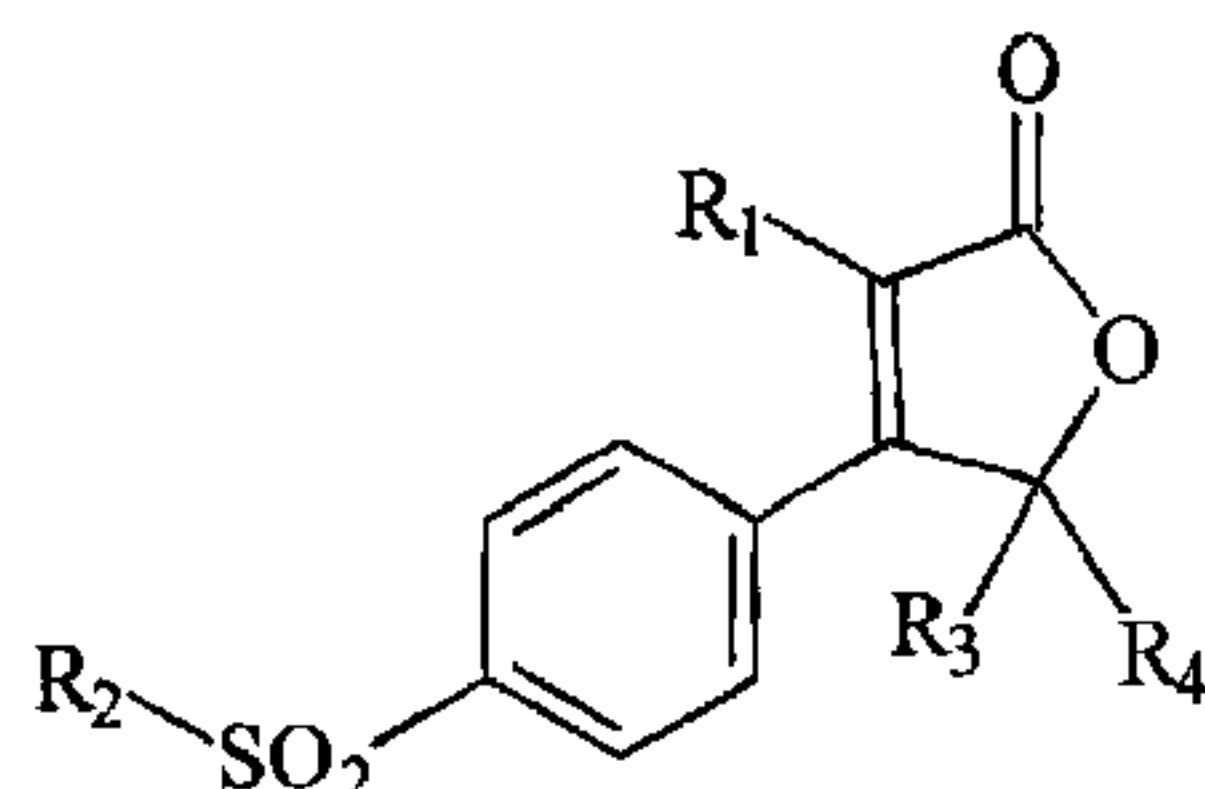




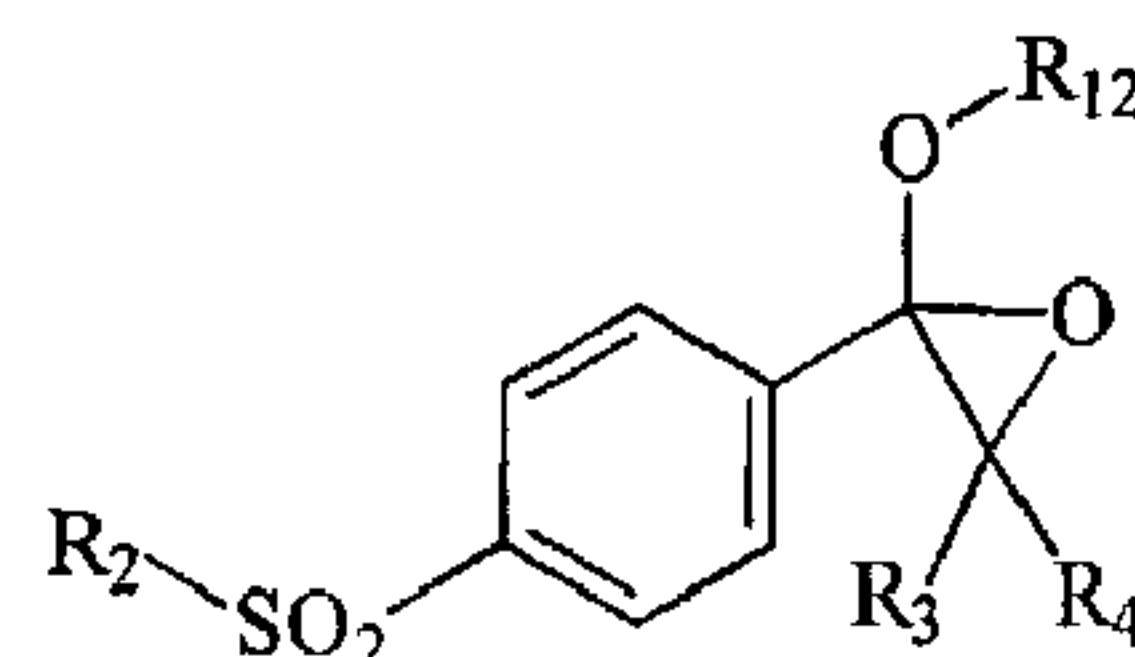
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(54) Titre : PROCEDE DE PREPARATION D'INHIBITEURS COX-2
(54) Title: METHOD OF PREPARING COX-2 INHIBITORS



(I)



(II)

(57) **Abrégé/Abstract:**

The invention relates to a method for producing compounds of general formula (I) wherein R_1 is selected from the following groups: (a) OR_5 and (b) mono-, di-, or tri-substituted phenyl; and R_2 represents a group (C_1-C_6) alkyl. The method is characterized in that it comprises the following steps: a) reacting a compound of general formula (II) with an acid of general formula R_1CH_2COOH (III) in a water-free medium; b) reacting the resulting compound with a strong base in an aprotic solvent in order to obtain an intermediate cyclic compound which forms a compound of general formula (I) after dehydration; and c) isolating said resulting compound of general formula (I).



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ABSTRACT

The invention relates to a method for producing compounds of general formula (I) wherein R_1 is selected from the following groups: (a) OR_5 and (b) mono-, di-, or tri-substituted phenyl; and R_2 represents a group (C_1-C_6) alkyl.

5 The method is characterized in that it comprises the following steps: a) reacting a compound of general formula (II) with an acid of general formula R_1CH_2COOH (III) in a water-free medium; b) reacting the resulting compound

10 with a strong base in an aprotic solvent in order to obtain an intermediate cyclic compound which forms a compound of general formula (I) after dehydration; and c) isolating said resulting compound of general formula (I).

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METHOD OF PREPARING COX-2 INHIBITORS

BACKGROUND OF THE INVENTION

The invention concerns a method of preparing (4-alkylsulphonyl)-phenyl-2-(5H)-furanones, which are
5 compounds inhibiting cyclooxygenase-2 (COX-2); as well as novel intermediate compounds useful for preparing these compounds.

(4-Alkylsulphonyl)-phenyl-2-(5H)-furanone compounds useful as COX-2 inhibitors and their
10 pharmacological applications as anti-inflammatories are known and described in the following documents: WO 97/44027, WO 97/28121, WO 98/41516, WO 96/19469, WO 97/16435 and WO 97/14691.

The synthesis of these compounds involves a method
15 in several steps involving an intermediary of the 4-alkylsulphonyl- α -bromoisobutyrophenone type.

Thus WO 97/45420 describes a method of preparing (methyl-4-sulphonyl)-phenyl-2-(5H)-furanones from thioanisole involving five steps.

20 The second step of this method consists of brominating 4-thiomethyl-isobutyrophenone in order to obtain 4-thiomethyl- α -bromoisobutyrophenone.

In the following step the 4-thiomethyl- α -bromoisobutyrophenone is oxidised to 4-methylsulphonyl- α -
25 bromoisobutyrophenone, which is a highly allergenic compound, and this compound is then esterified with a carboxylic acid in order to form a 2-methyl-1-(4'-methylsulphonylphenyl)-1-oxo-prop-2-yl ester.

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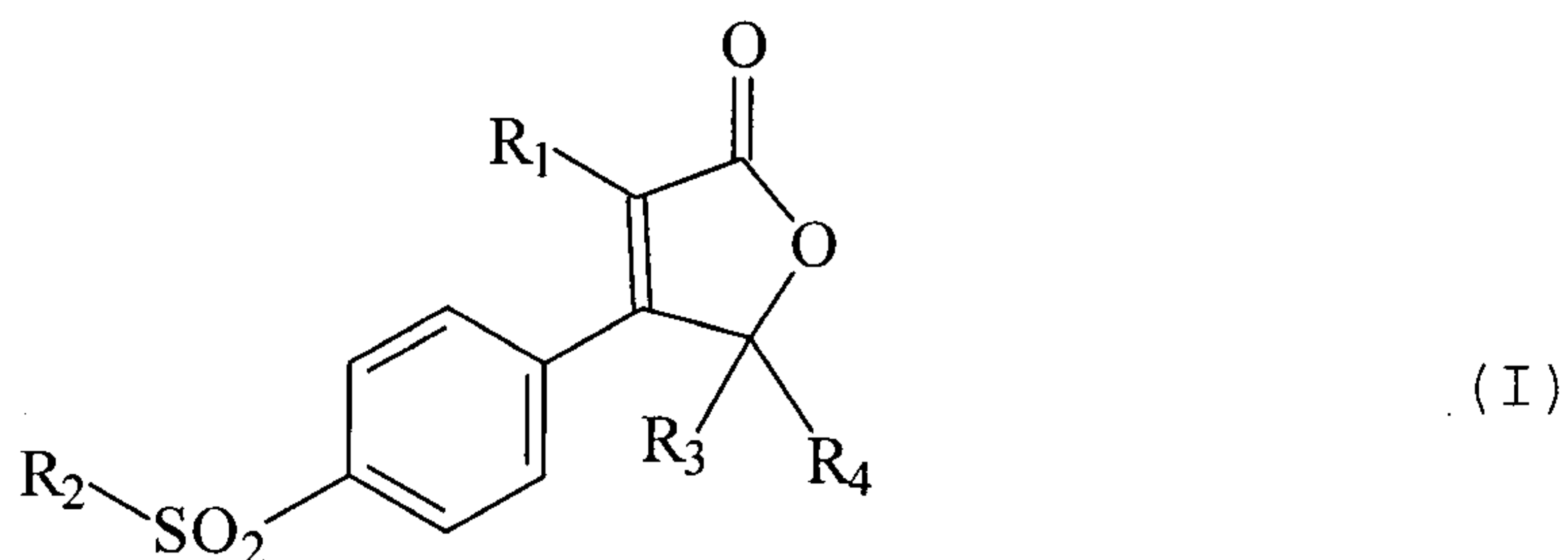
This reaction is also accompanied by a certain number of by-products, including an elimination product, 4-(4'-methylsulphonylphenyl)-2-methyl-propenone.

The aim of the invention is to propose an alternative to the method described in WO 97/45420 and in particular a general method of preparing substituted (4-alkylsulphonylphenyl)-2-(5H)-furanone compounds which avoids the problem posed by the α -bromoisobutyrophenone-type intermediary, is easy to implement, avoids the formation of the elimination by-product and provides an acceptable yield of final product.

SUMMARY AND DESCRIPTION OF THE INVENTION

The work carried out by the inventors has now made it possible to propose a method meeting these expectations, and which in particular avoids passing through a toxic bromosulphone derivative and the formation of the aforementioned by-product.

The object of the invention is thus a method of preparing compounds of general formula (I):



in which

25 R_1 is chosen from amongst the groups:

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(a) OR₅ where R₅ represents a group chosen from amongst:

(1) a C₁-C₆ branched linear or ring alkyl group;

5 (2) a mono-, di- or tri-substituted phenyl or naphthyl group in which the substituents are chosen from amongst:

hydrogen;

halogen;

10 (C₁-C₃) alkoxy;

CN;

(C₁-C₃) fluoroalkyl;

(C₁-C₃) alkyl;

-COOH; and

15 (b) mono-, di- or tri-substituted phenyl in which the substituents are chosen from amongst:

hydrogen;

halogen;

(C₁-C₃) alkoxy;

20 CN;

(C₁-C₃) fluoroalkyl;

(C₁-C₃) alkyl;

-COOH;

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R₂ represents a (C₁-C₆)alkyl group;

R₃ and R₄ represent independently of one another a hydrogen atom or a CHR₆R₇ group;

in which R₆ and R₇ are independently of each other chosen
5 from amongst:

hydrogen;

(C₁-C₁₀)alkyl;

(C₁-C₁₀)alkoxy;

OH;

10 CN;

CH₂CN;

OCOR₈;

(C₁-C₆)fluoroalkyl;

halogen;

15 CON(R₈)₂;

mono-, di- or tri-substituted phenyl;

mono-, di- or tri-substituted heteroaryl;

the substituents being chosen from amongst:

hydrogen;

20 halogen;

(C₁-C₆)alkyl;

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(C₁-C₁₀) alkoxy;

CN;

CF₃;N₃;

5

C(R₉)(R₁₀)-OH;C(R₉)(R₁₀)-O-(C₁-C₄) alkyl;(C₁-C₆) fluoroalkyl;R₈ is chosen from amongst:

hydrogen;

10

(C₁-C₆) alkyl;

mono-, di- or tri-substituted phenyl, the substituents being chosen from amongst hydrogen, halogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, (C₁-C₆) alkylthio, CN or CF₃; and

15

mono-, di- or tri-substituted benzyl, the substituents being chosen from amongst hydrogen, halogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, (C₁-C₆) alkylthio, CN or CF₃;

or two R₈ groups form together with the nitrogen atom to which they are attached a ring with 5 to 7 atoms, and possibly comprising a heteroatom chosen from amongst O,

20

S or NR₉;

R₉ and R₁₀ are independently of one another chosen from amongst:

hydrogen; and

(C₁-C₁₀) alkyl; or

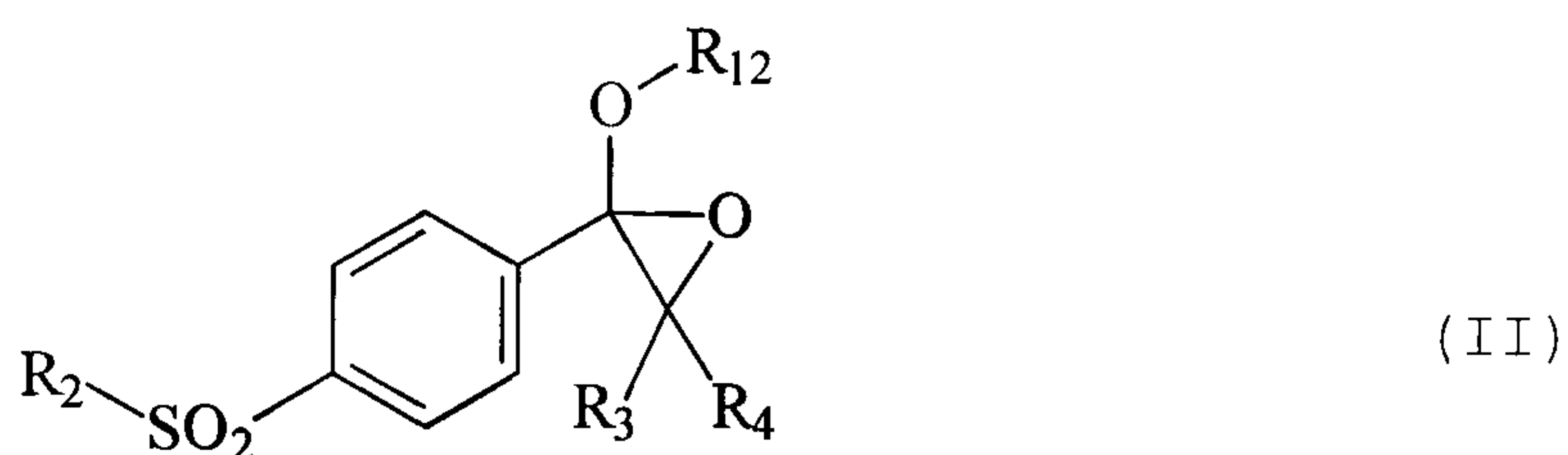
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form, together with the atom to which they are attached, a ring with 3 to 7 carbon atoms and where applicable a nitrogen atom;

wherein it comprises the following steps:

5 a) reaction of a compound of general formula (II):



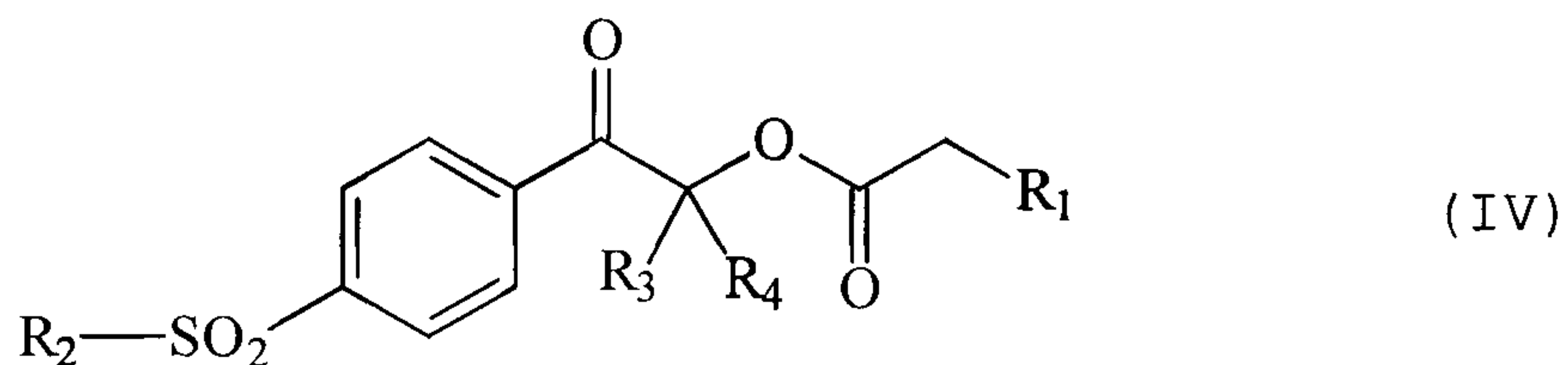
10 in which R_2 , R_3 and R_4 are as defined above and R_{12} represents a (C_1-C_6) alkyl group,

with an acid of general formula (III):



15

in which R_1 is as defined previously, in an anhydrous medium, in order to form a compound of formula (IV):



20

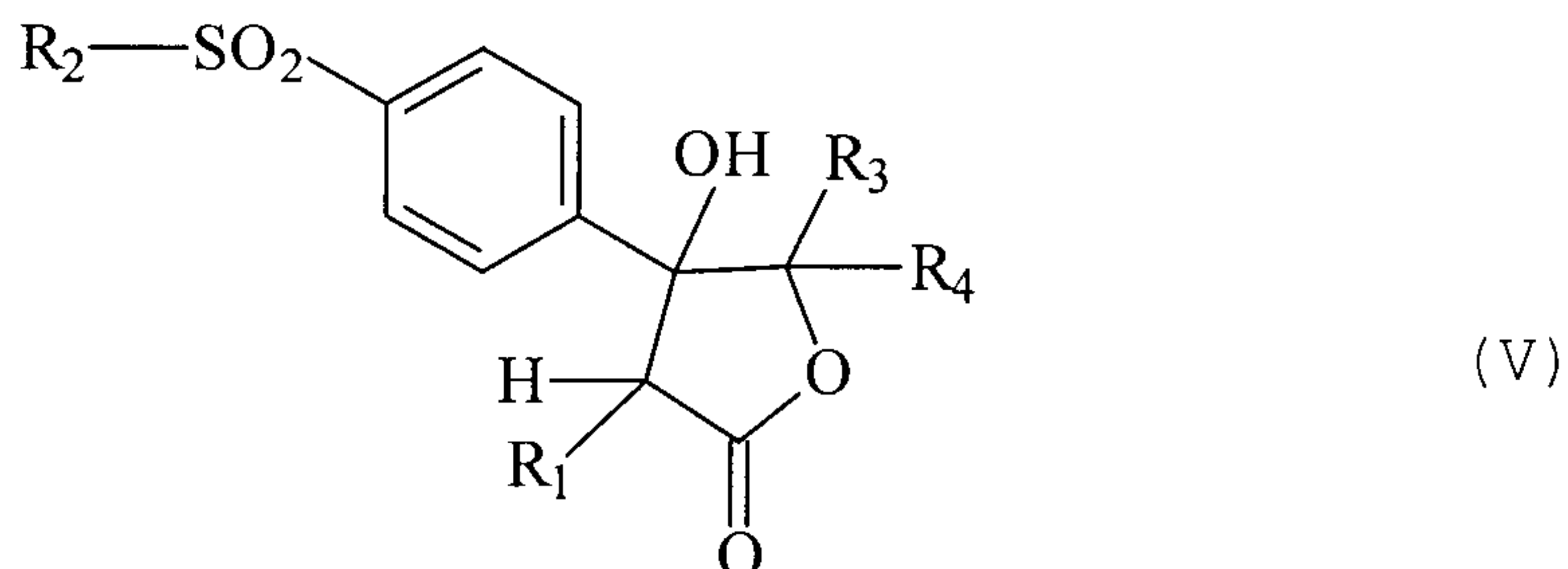
R_1 , R_2 , R_3 and R_4 being as defined above;

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b) reaction of the compound of formula (IV) with a strong base in an aprotic solvent in order to obtain an intermediate ring compound of formula (V):

5



which, after elimination of a water molecule, forms a compound of general formula (I); and

10

c) isolation of the compound of general formula (I) thus obtained.

The reaction of step a) takes place in an anhydrous solvent, preferably an ether, for example diethylether, or methyltertbutylether. The reaction temperature is advantageously between -20 and 40°C. At the end of step a), a compound of general formula (IV) is obtained as well as secondary products in minor quantities. However, the aforementioned elimination product does not form.

20

For the reaction of step b), the strong base is advantageously chosen from amongst 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).

25

The elimination of a water molecule is achieved in a manner known per se, advantageously by thermal dehydration in the presence of a dehydration agent.

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The dehydration agent can be chosen in particular from amongst trifluoroacetic acid esters, for example isopropyl trifluoroacetate, trichloroacetic acid esters and alkyl or arylsulphonic acid esters.

5 The reaction preferably takes place in an aprotic solvent such as acetonitrile, N,N-dimethylformamide, N-methylsulphoxide, propionitrile or nitromethane.

The dehydration is achieved by heating to reflux.

10 The molar ratio of the ester of formula (IV) to the strong base is generally between 1:1 and 1:2, a ratio of 1:1.5 being preferred.

The molar ratio of the ring ester of formula (V) to the dehydration agent is generally 1:1 to 1:2, a ratio 1:1.2 being preferred.

15 The reaction is carried out at a temperature preferably between 0°C and the reflux temperature of the solvent.

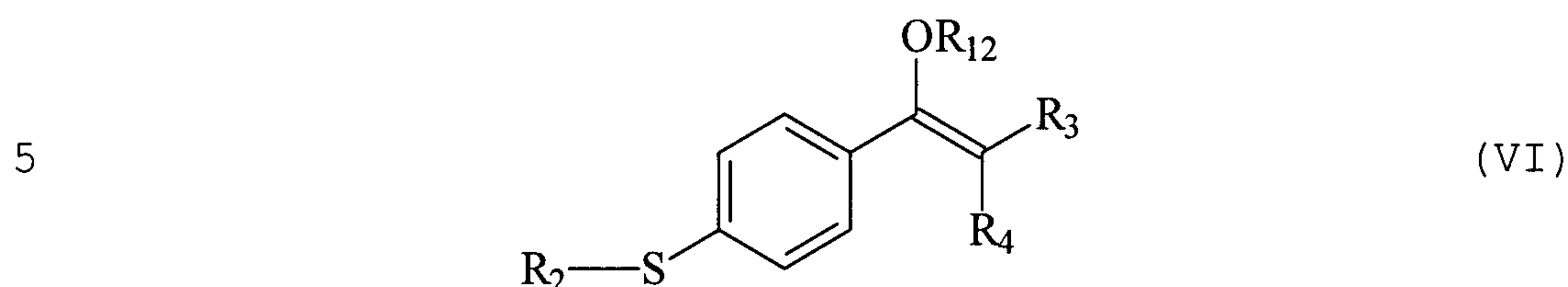
20 Particularly advantageous reaction conditions are achieved by the use of a mixture of 1.2 equivalents of isopropyl trifluoroacetate and 1.5 equivalents of DBU in acetonitrile at reflux. Under these conditions, the reaction is terminated after 24 hours and the product crystallises by the addition of water after partial elimination of the acetonitrile. For more information,
25 reference should be made to the description of the patent application WO 97/45420.

Step c) is carried out in a manner known per se, in particular by elimination of the solvent, precipitation of the product, recrystallisation, etc.

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The epoxy compound of general formula (II) can be obtained by the reaction of a compound of general formula (VI):

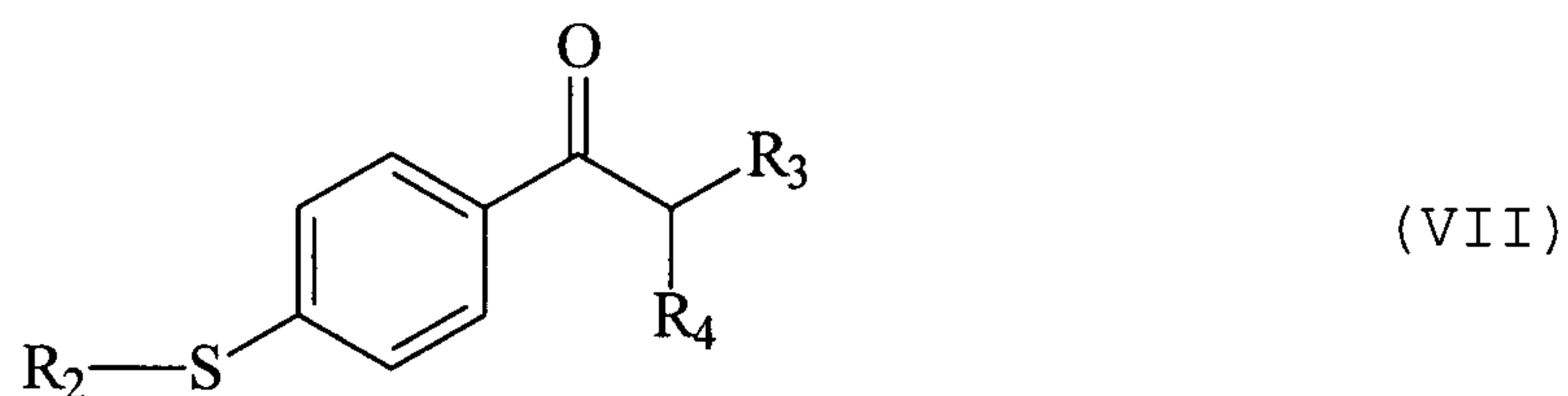


in which R_2 , R_3 , R_4 and R_{12} are as defined above, with an oxidising agent.

10 Oxidising agents can in particular include organic peracids, such as meta-chloroperbenzoic acid and peracetic acid or dioxiranes such as dimethyldioxirane, generated in situ or not. The reaction temperature is advantageously between -40°C and 30°C .

15 The oxidising agent is used in excess with respect to the compound of general formula (II) (3 to 40 equivalents), so as to oxidise on the one hand the olefin function into epoxide and on the other hand the sulphide function into sulphone.

20 The compound of general formula (VI) can be obtained by reaction of a compound of general formula (VII):



25 in which R_2 , R_3 and R_4 are as defined above, with an alcohol of general formula (VIII):



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R_{12} being as defined above, in the presence of a catalytic quantity of acid and a dehydrating agent.

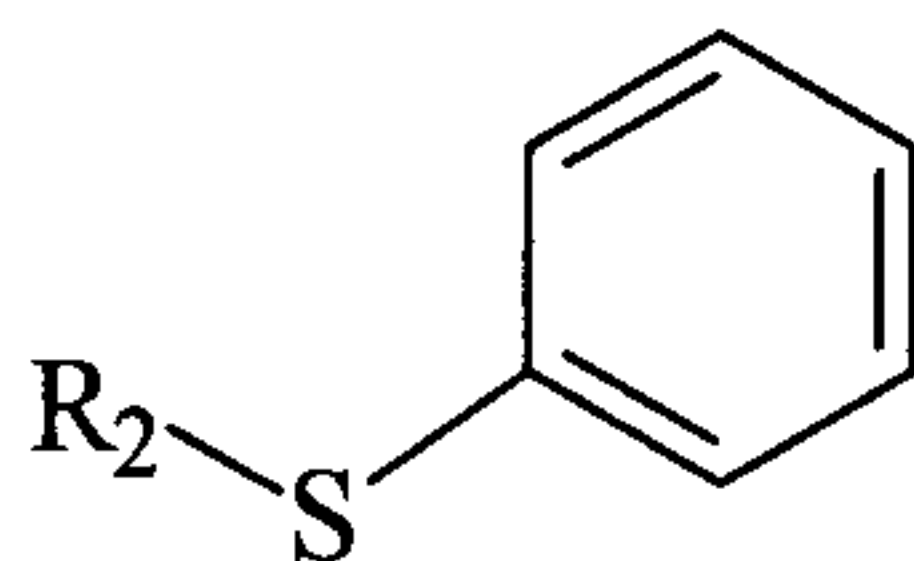
Advantageously, the acid is chosen from amongst the sulphonic acids, for example p-toluene sulphonic acid, or the mineral acids, for example hydrochloric acid. By way of dehydrating agent, (C_1-C_6) alkyl orthoformates are preferred.

The reaction is carried out in an excess of alcohol of general formula (VIII), this serving as a reactive solvent.

In the compound of general formula (VIII), R_{12} is advantageously a methyl group, the alcohol being methanol.

Another object of the invention is a method of preparing a compound of general formula (I) as defined above, wherein it comprises the following steps:

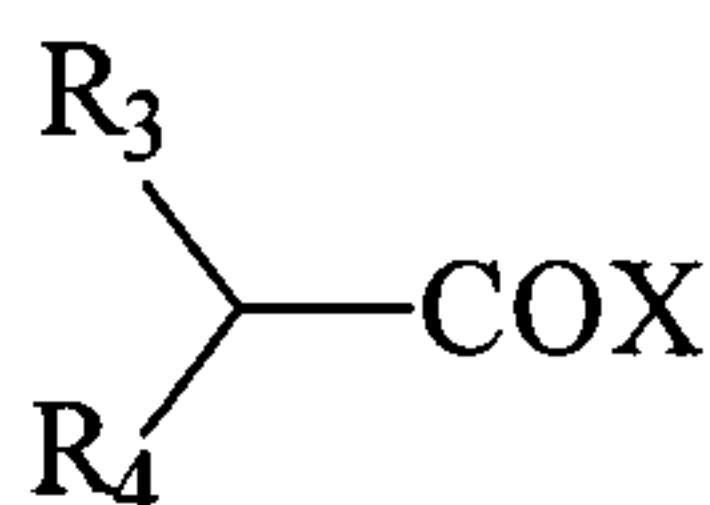
(1) reaction of a compound of general formula (IX):



(IX)

20

in which R_2 is as defined above, in a solvent which is inert in the presence of a Lewis acid with a compound of general formula (X):



(X)

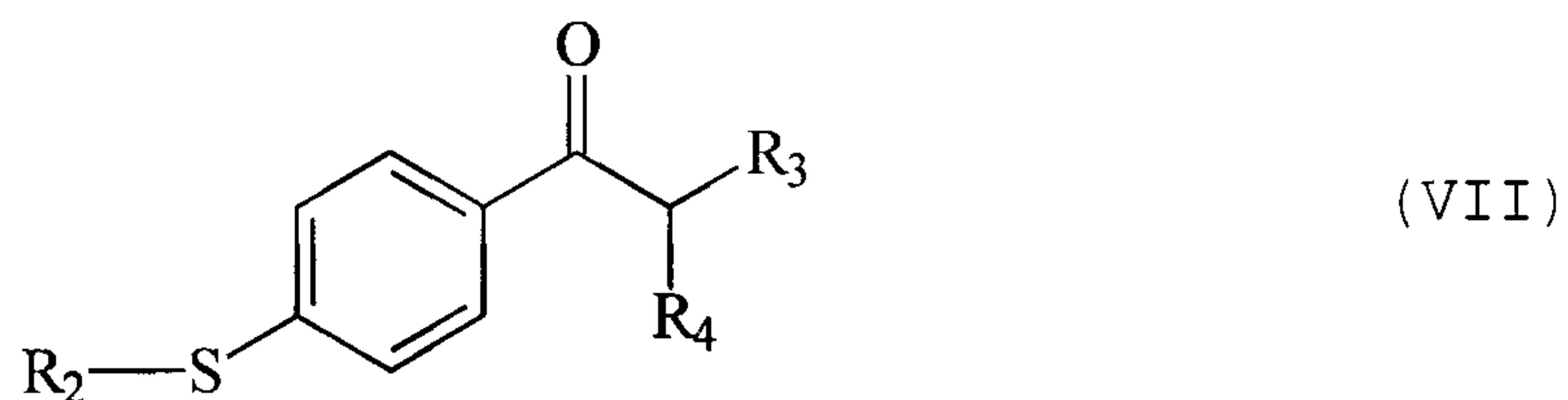
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in which X is a starting group, preferably a chlorine atom,
in order to form a compound of general formula (VII):

5

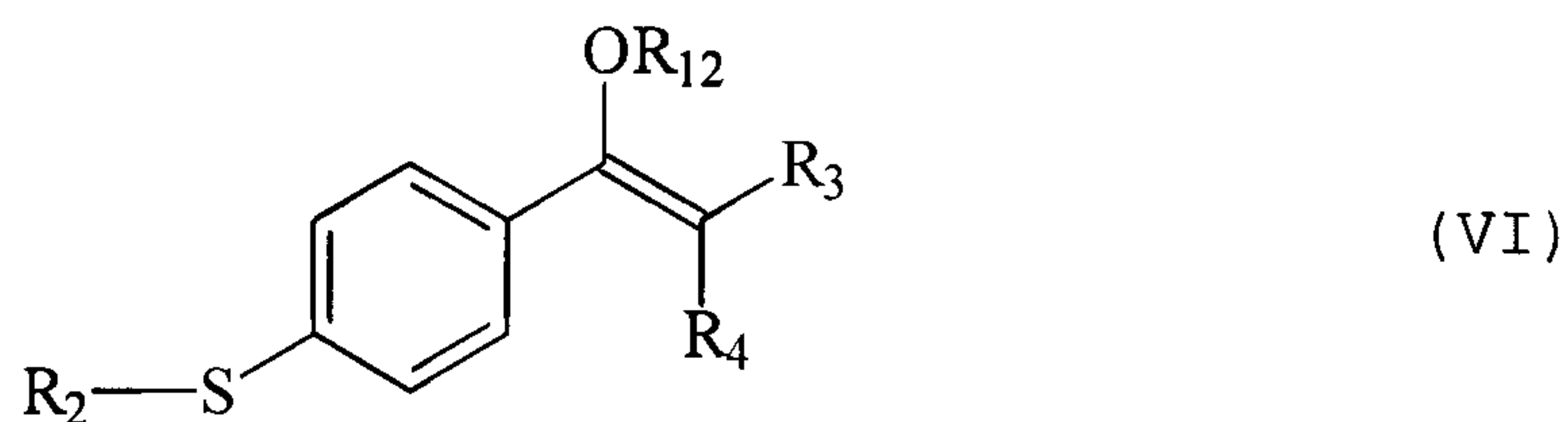


in which R₂, R₃ and R₄ are as defined previously,

(2) reaction of a compound of general
formula (VII) with an alcohol of general formula (VIII):



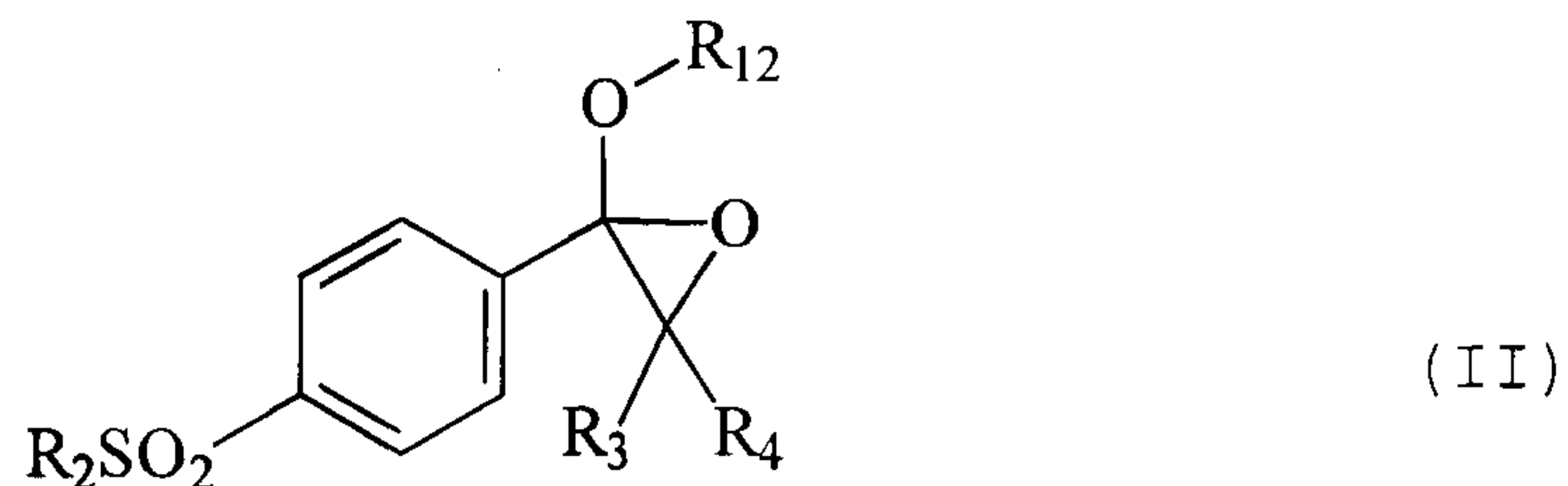
10 in which R₁₂ represents a (C₁-C₆)alkyl group in order to form
a compound of general formula (VI):



15 in which R₂, R₃, R₄ and R₁₂ are as defined above,

(3) reaction of the compound of general
formula (VI) with an oxidising agent in order to obtain a
compound of general formula (II):

20



in which R₂, R₃, R₄ and R₁₂ are as defined previously;

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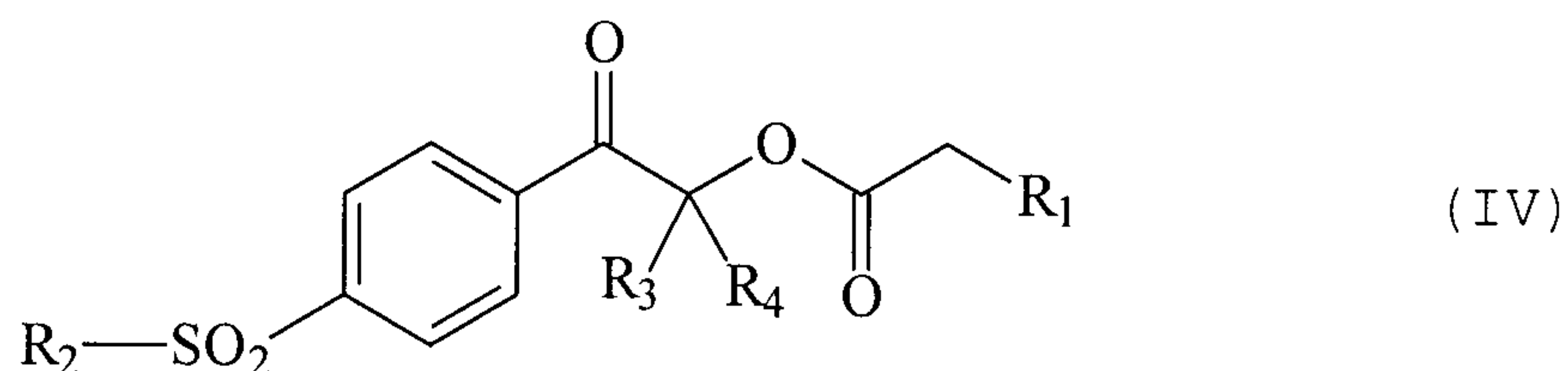
(4) reaction of the compound of general formula (II) as defined at step (3) with an acid of general formula (III):

5



in which R₁ is as defined previously, in an anhydrous medium, in order to form a compound of formula (IV):

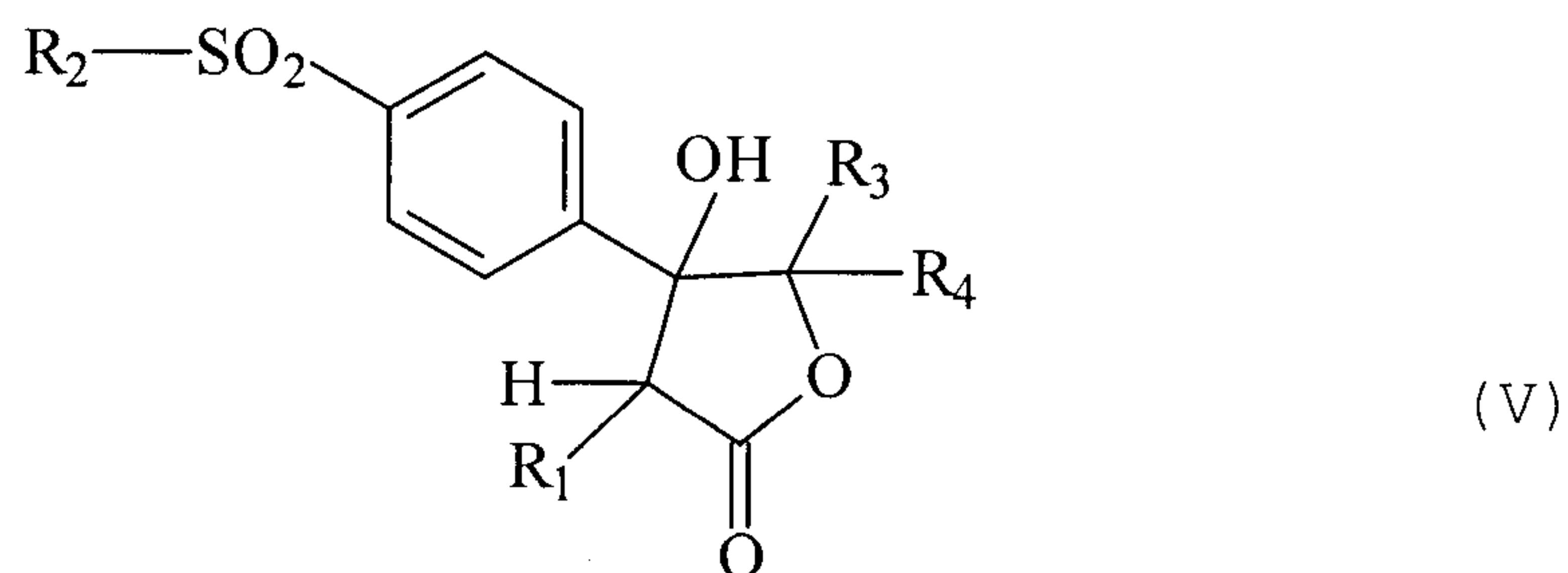
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R₁, R₂, R₃ and R₄ being as defined above;

(5) reaction of the compound of formula (IV) with a strong base in an aprotic solvent in order to obtain an intermediate ring compound of formula (V):

15



20 which, after elimination of a water molecule, forms a compound of general formula (I); and

(6) isolation of the compound of general formula (I) thus obtained.

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For the reaction of step (1), the Lewis acid is advantageously chosen from amongst AlCl_3 , FeCl_3 , TiCl_4 and SnCl_4 without however being limited to these. The non-reactive solvents comprise halogenated and polyhalogenated hydrocarbons such as the mono- or dihalo(C_1 - C_4)alkyls, for example dichloromethane; the aromatic solvents such as nitrobenzene or halogenated aromatic compounds, as well as branched linear or ring C_6 - C_{10} hydrocarbons comprising notably hexane, cyclohexane, methylcyclohexane or CS_2 . For this step, cyclohexane or dichlorobenzene can in particular be chosen. The molar ratio of the compound of general formula (IX) to the compound of general formula (X) is generally between 1:1.5 and 1.5:1, a ratio of 1:1 to 1:1.5 being preferred.

The reaction is generally carried out with an excess of the compound of general formula (X). Generally the molar ratio of the compound of general formula (IX) to the Lewis acid is between 1:1.5 and 1.5:1. Preferably, the molar ratio of the compound of general formula (IX) to the Lewis acid is between 1:1 and 1:1.5. The reaction can advantageously be carried out in a temperature range of between 0 and 25°C, preferably 5 and 15°C. The reagents are set to react until the reaction is completed, which occurs after an interval of time ranging from 8 to 4 hours, generally 1 to 2 hours. The reaction is preferably carried out in a nitrogen atmosphere. Steps (2) to (6) are carried out under conditions as described previously.

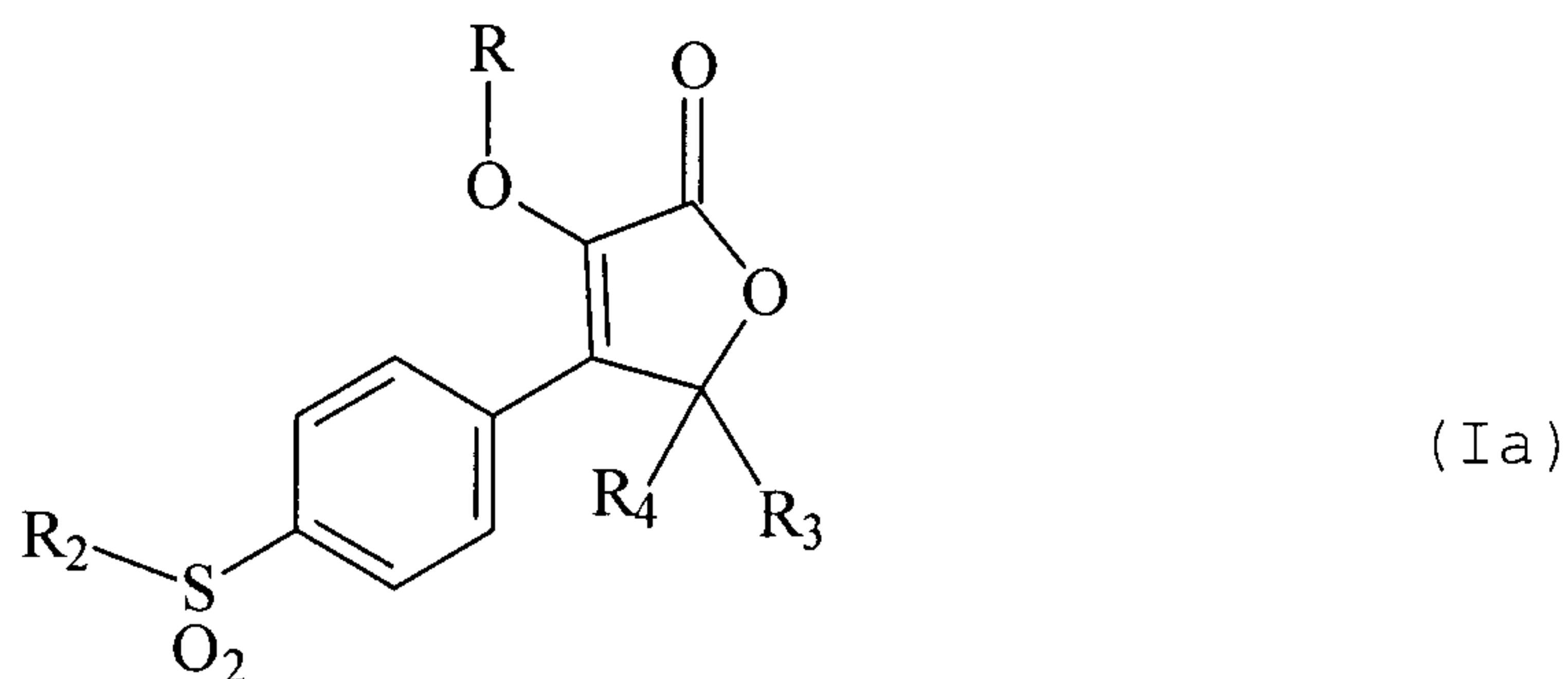
The compounds of general formula (IX) and (X) are commercially available compounds or ones which can easily be prepared by a person skilled in the art using well known routine methods.

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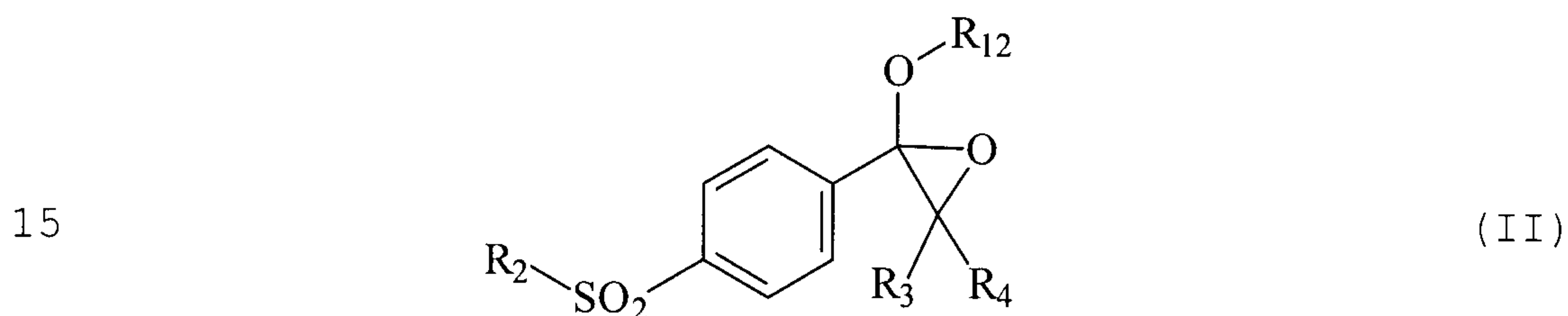
In a first embodiment of the method of the invention, R_1 is an RO group, R being as defined previously for R_5 .

The compound of general formula (I) then becomes a
5 compound of general formula (Ia):

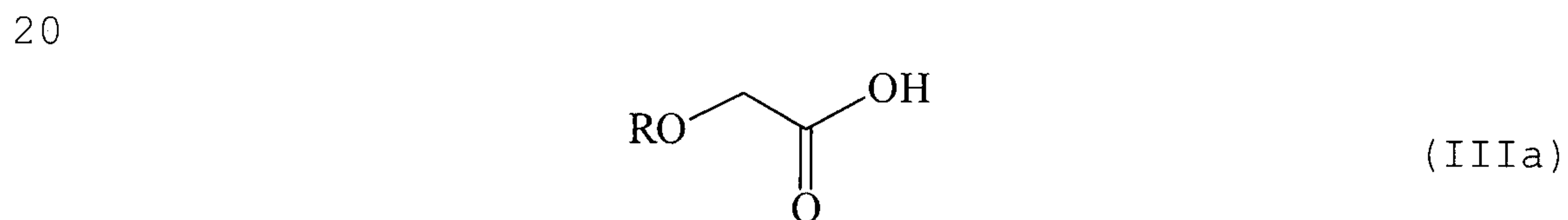


10 The method according to the invention in this case comprises the following steps:

a) reaction of a compound of general formula (II):



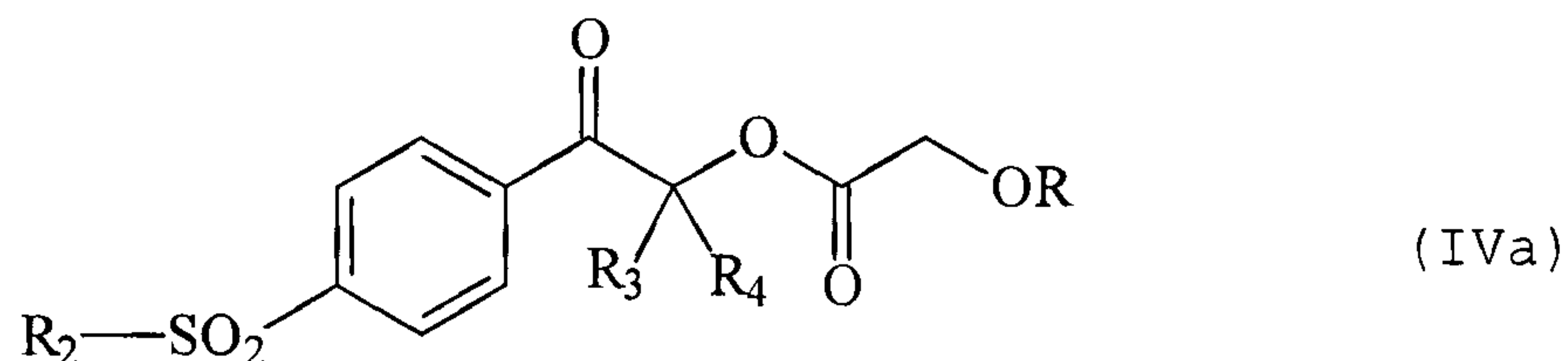
in which R_2 , R_3 and R_4 are as defined previously and R_{12} represents a (C_1-C_6) alkyl group, with an acid of general formula (IIIa):



in which R is as defined above, in an anhydrous medium, in order to form a compound of general formula (IVa):

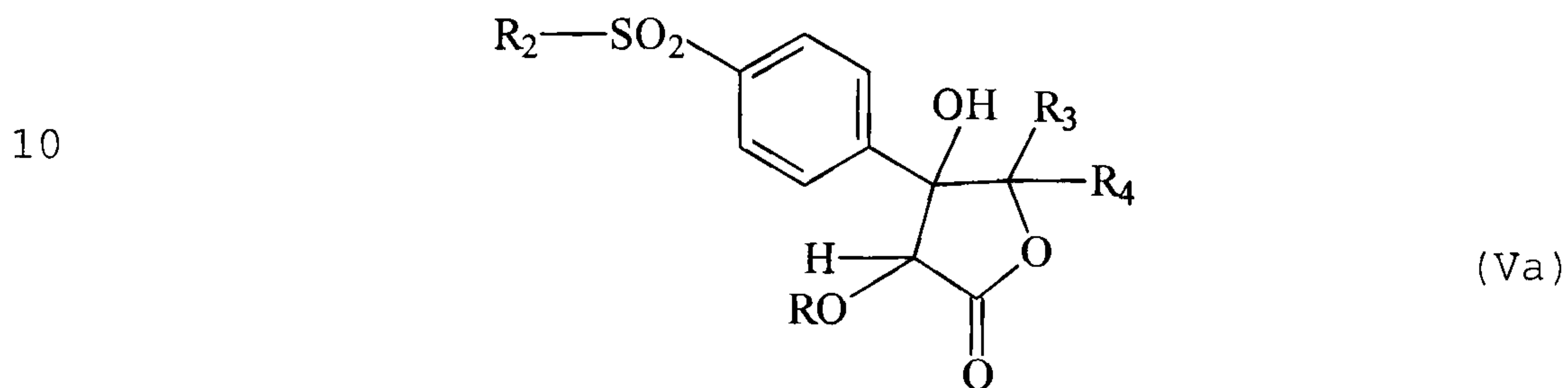
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5 in which R, R₂, R₃ and R₄ are as defined previously;

b) reaction of the compound of formula (IVa) with a strong base in an aprotic solvent in order to obtain an intermediate ring compound of formula (Va):



which, after elimination of a water molecule, forms a compound of general formula (Ia); and

15 c) isolation of the compound of general formula (Ia) thus obtained.

Preference is particularly given to the compounds of general formula (Ia) in which:

R represents the cyclopropylmethyl group, and

20 R₂, R₃ and R₄ represent the methyl group.

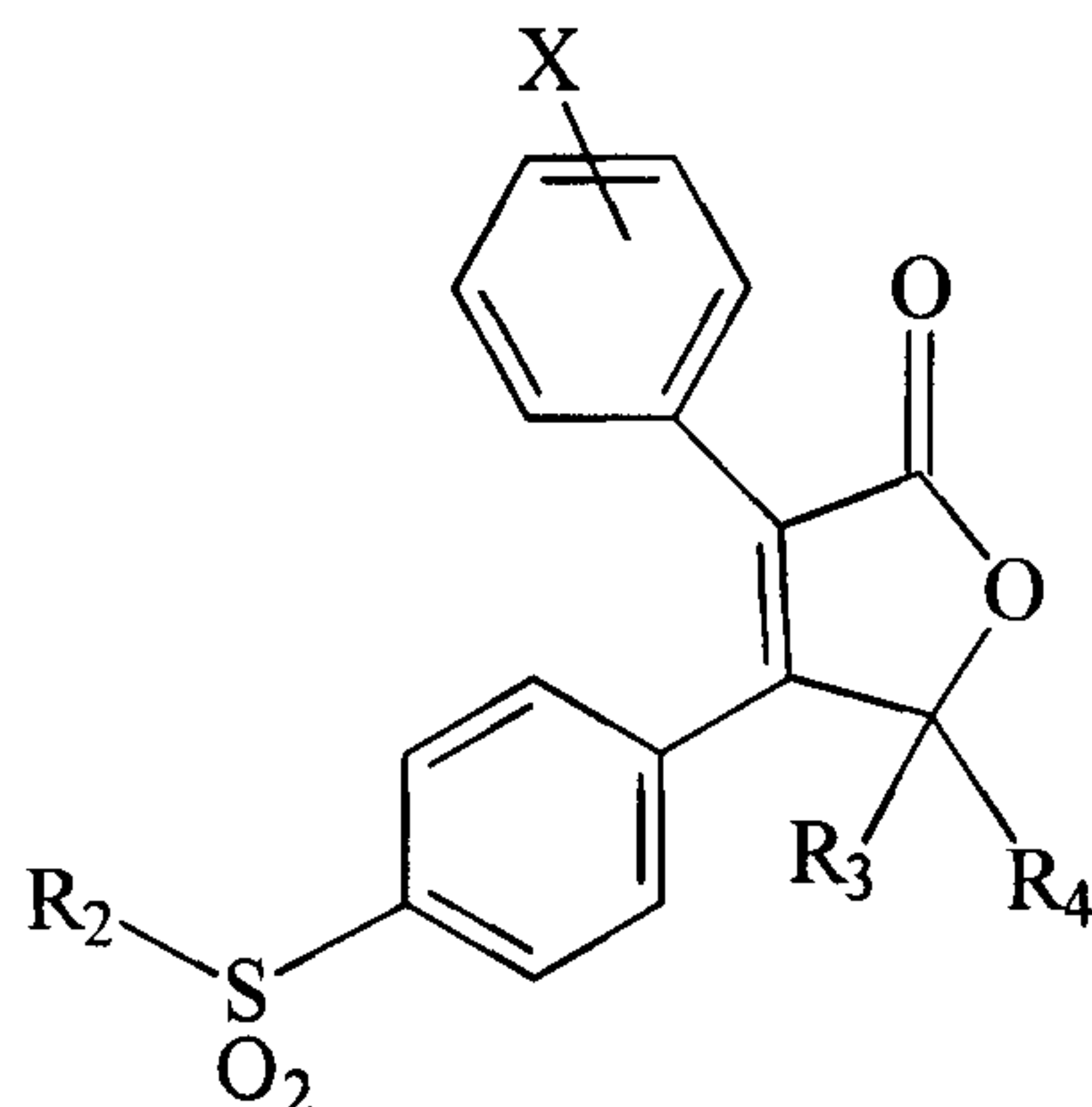
In a second embodiment of the invention, the group R₁ is a substituted phenyl ring.

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The compound of general formula (I) then becomes a compound of general formula (Ib):

5



(Ib)

in which R_2 is as defined previously and X is chosen from amongst:

10

hydrogen;

halogen;

 (C_1-C_3) alkoxy;

CN;

 (C_1-C_3) fluoroalkyl;

15

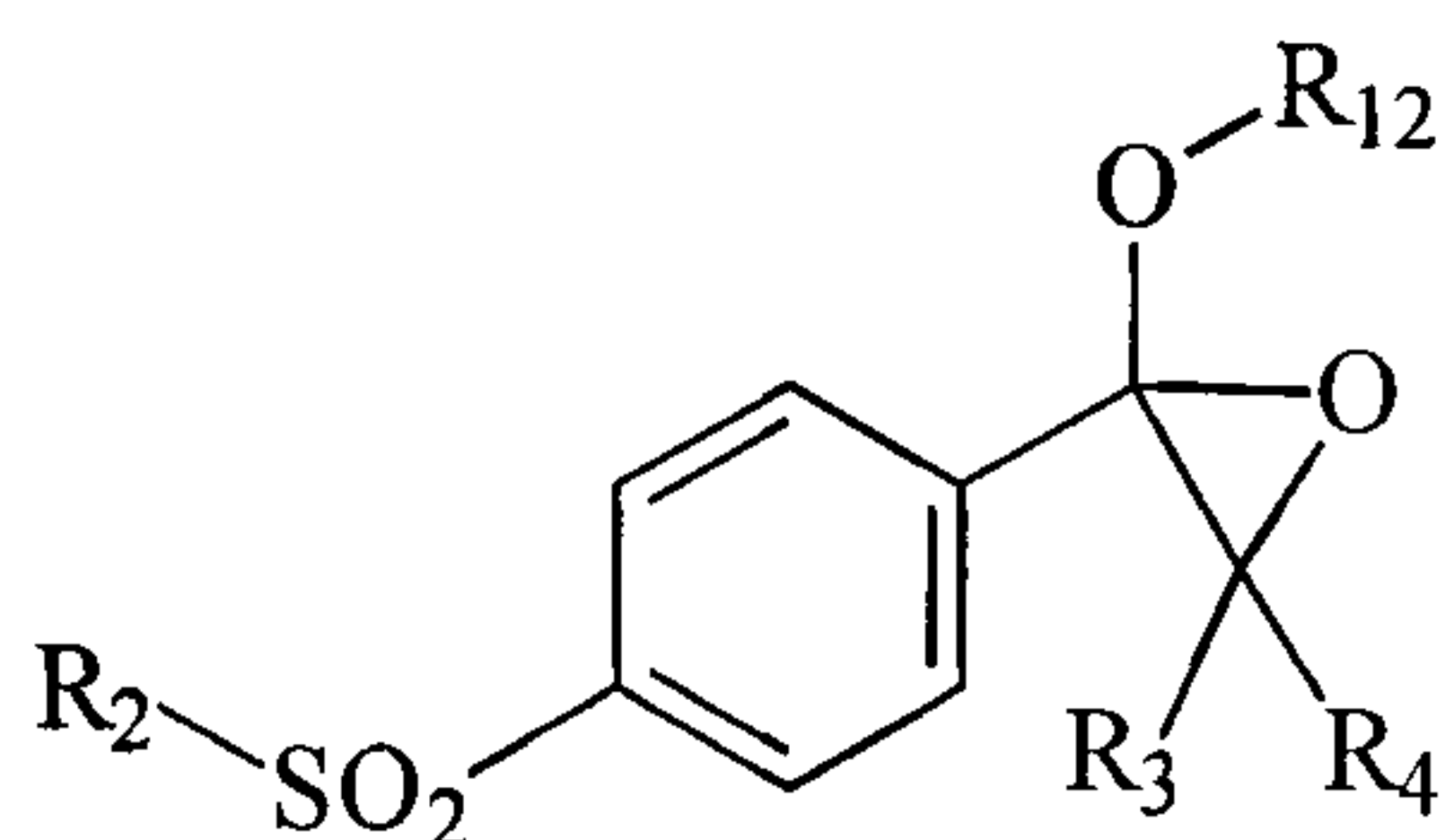
 (C_1-C_3) alkyl;

-COOH.

The method of the invention then comprises the following steps:

a) reaction of a compound of general formula (II):

20



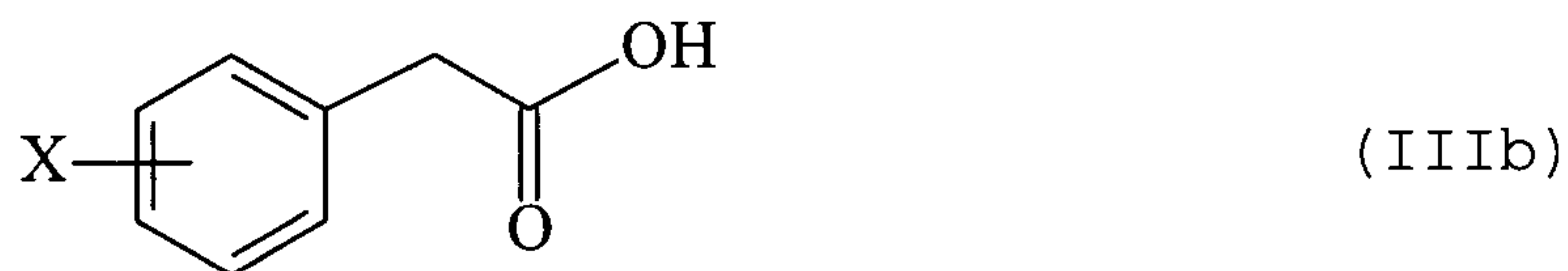
(II)

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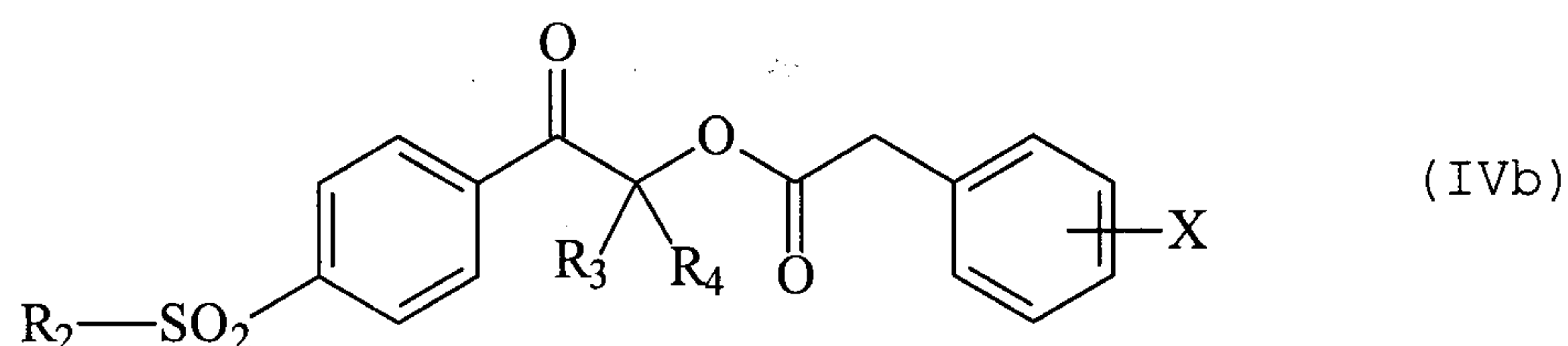
in which R_2 , R_3 and R_4 are as defined previously and R_{12} represents a (C_1-C_6) alkyl group, with an acid of general formula (IIIb):

5



in which X is as defined previously, in an anhydrous medium, in order to form a compound of general formula (IVb):

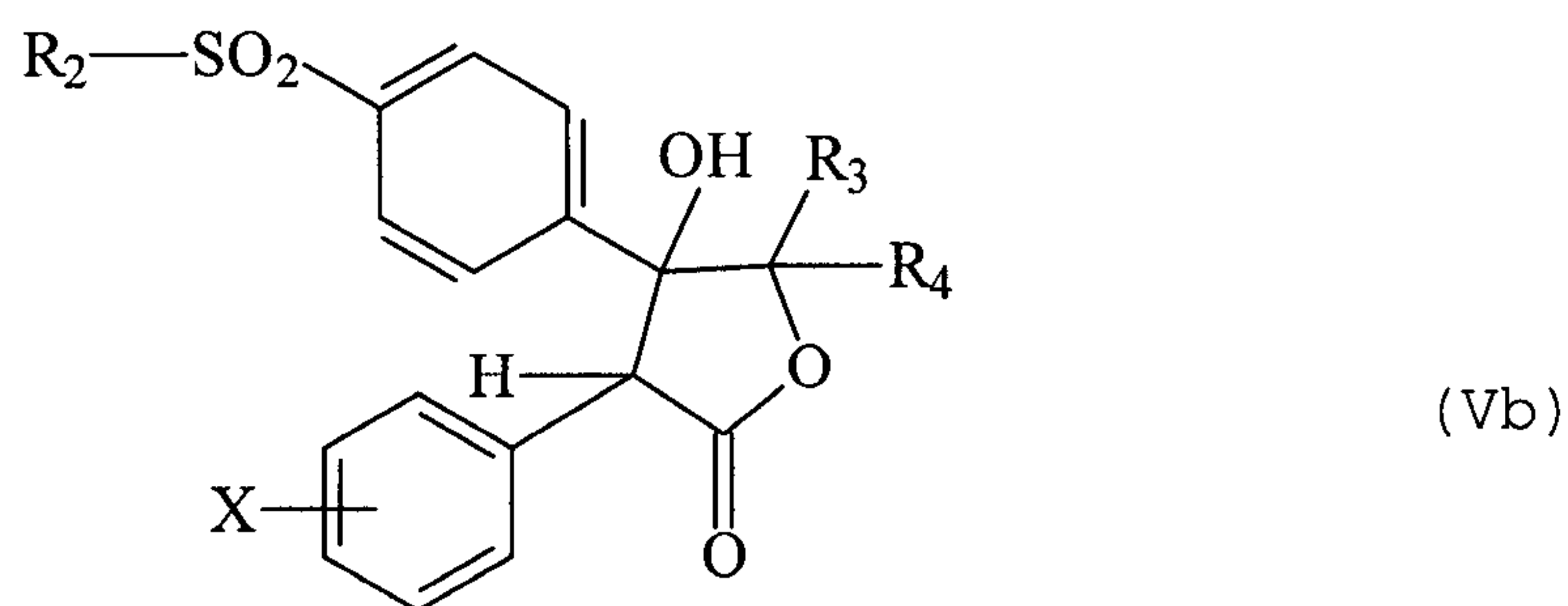
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R_2 , R_3 and R_4 being as defined above;

b) reaction of the compound of formula (IVb) with a strong base in an aprotic solvent in order to obtain an intermediate ring compound of formula (Vb):

15



20 which, after elimination of a water molecule, forms a compound of general formula (Ib);

c) isolation of the compound of general formula (Ib) thus obtained.

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The intermediate compound of general formula (VI) is novel and constitutes another object of the invention.

In particular the compounds of general formula (VI) in which R_2 , R_3 and R_4 represent the methyl group and R_{12} is as defined above are preferred.

A particularly preferred compound of this type is the one in which R_{12} represents methyl.

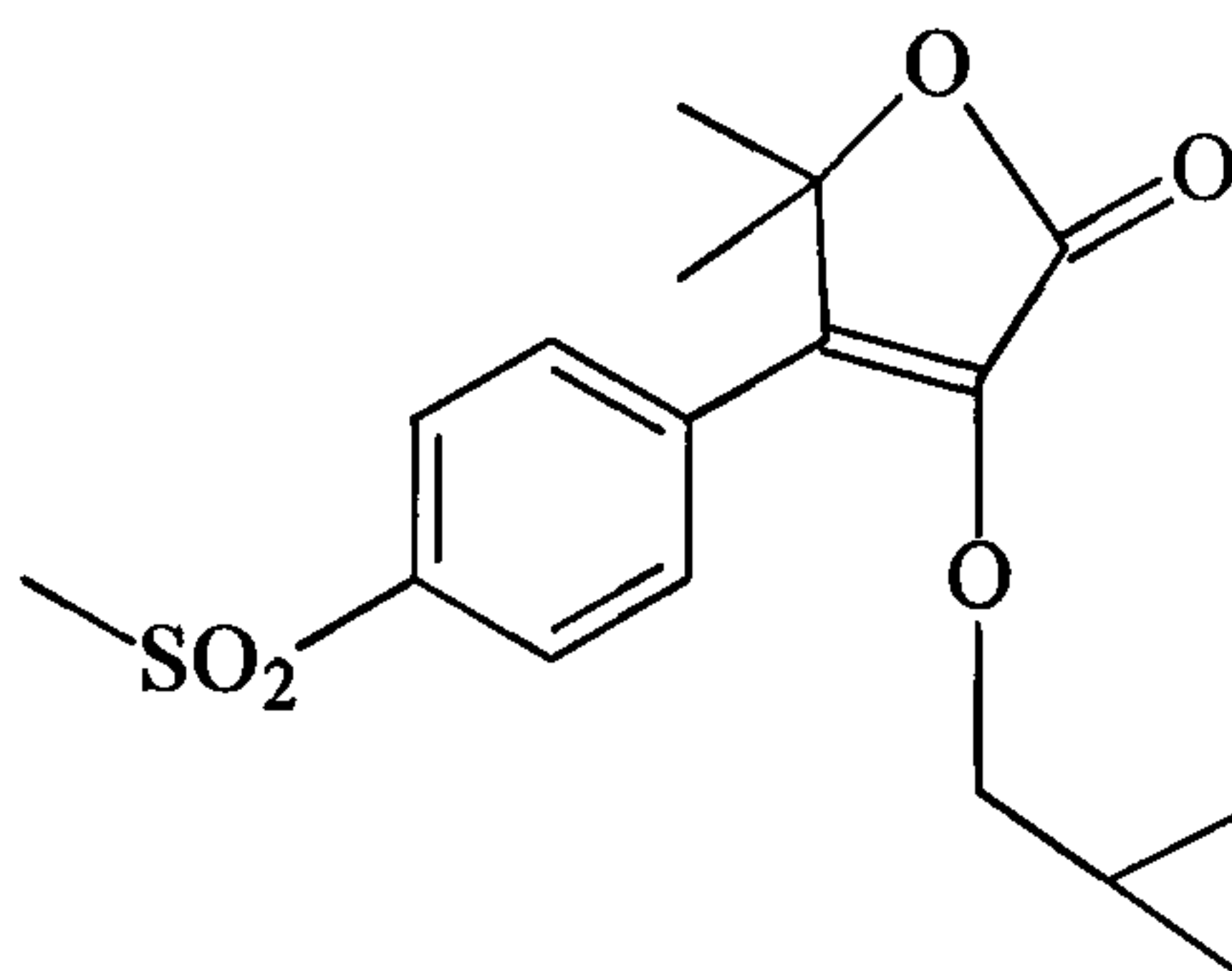
The method of the invention is illustrated by means of the following example:

10

EXAMPLE

Preparation of 3-(cyclopropylmethoxy)-[4-(4-methylsulphonyl)phenyl]-5,5-dimethyl-5-H-furan-2-one.

15



Preparation of 1-methoxy-2-methyl-1-(4'-methylthiophenyl)prop-1-ene:

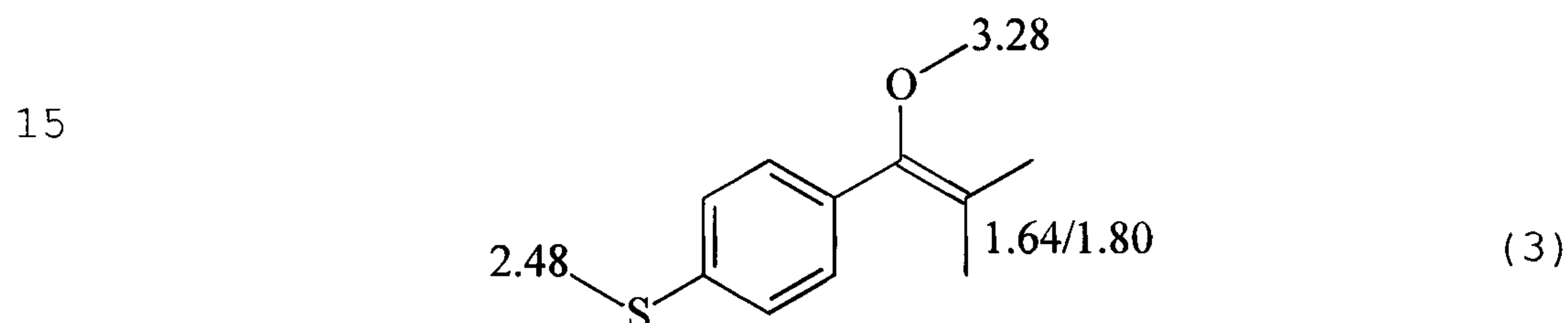
p-Toluene sulphonic acid (1.2 g, 6.3 mmol 0.12 equiv) is added to a solution of 2-methyl-1-(4'-methylthiophenyl)propan-1-one or (4-thiomethyl-isobutyrophenone (compound 2; 10.11 g, 52 mmol, 1 equiv) obtained as described in Example 1 from WO 97/45420) by reaction of thioanisole in the presence of a Lewis acid with isobutyryl chloride in a mixture of methanol (40 ml)/methyl

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orthoformate (40 ml). This solution is heated for 1.5 hours to reflux and then the methanol is distilled. The reactional mass is then heated for 41 hours at 115°C. After return to room temperature, the reactional mixture is
 5 diluted with dichloromethane (50 ml), washed with a saturated aqueous solution of potassium carbonate (50 ml) and then with brine (50 ml) and dried on sodium sulphate. Evaporation of the solvents supplies a mixture of the expected 1-methoxy-2-methyl-1-(4'-methylthiophenyl)prop-
 10 1-ene and 1,1-dimethoxy-2-methyl-1-(4'-methylthiophenyl)propane in a molar ratio of 83/17 (10.0 g).

RMN-¹H (200 MHz, CDCl₃) ppm:



GC/IR/MS:

m/z: 208;

20 IR (cm⁻¹): aromatic C-H 3073; O-CH₃ 2872, 2840; C=C 1668, C-O-C 1143.

2) Preparation of 3,3-dimethyl-2-methoxy-2-(4'-methylsulphonylphenyl)oxirane:

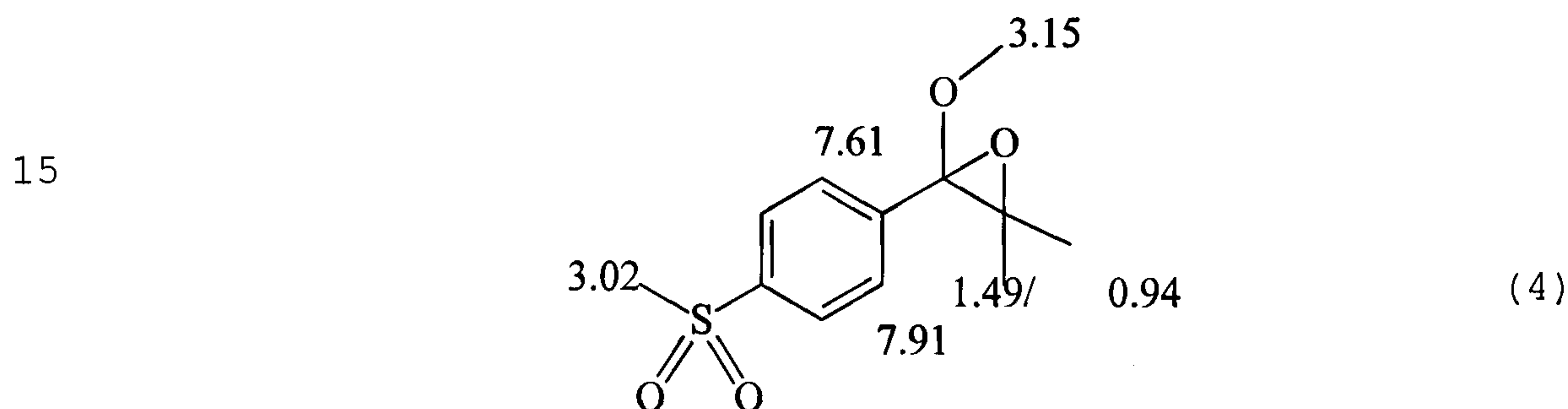
Oxone® (dimethyldioxirane) (78.9 g, 128.3 mmol, 6.3 equiv) is added to a suspension of sodium
 25 hydrogenocarbonate (38.14 g, 454.0 mmol) in a mixture of

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acetone (126 ml)/water (167 ml) at 0°C in 5 portions at intervals of 3 minutes. A solution of raw 1-methoxy-2-methyl-1-(4'-methylthiophenyl)prop-1-ene (4.24 g, 20.3 mmol) in dichloromethane (10 ml) is added to the reaction mixture. The ice bath is removed and the mixture is stirred for 3.5 hours at room temperature. The reaction medium is then filtered and the filtrate is extracted with dichloromethane (5x60 ml). The assembled organic phases are dried on sodium sulphate and concentrated in order to supply expected 3,3-dimethyl-2-methoxy-2-(4'-methylsulphonylphenyl)oxirane expected (compound 4; 3.80 g).

RMN-¹H (200 MHz, CDCl₃) ppm:



GC/IR/MS:

m/z: 241 (M-15); 183;

20 IR (cm⁻¹): O-CH₃ 2845; SO₂ 1348, 1164.

3) Preparation of [2-methyl-1-(4'-methylsulphonylphenyl)-1-oxo-prop-2-yl]-2-(cyclopropylmethoxy)acetate:

A solution of raw 3,3-dimethyl-2-methoxy-2-(4'-methylsulphonylphenyl)oxirane (3.6 g, 14.1 mmol) and 2-(cyclopropylmethoxy)acetic acid (2.17 g, 16.7 mmol, 1.2 equiv) in anhydrous tert-butylmethylether (10 ml) is

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stirred at room temperature for 2 days. The reaction mixture is then concentrated in order to supply a yellow solid (5.24 g) containing 65% p/p of [2-methyl-1-(4'-methylsulphonylphenyl)-1-oxo-prop-2-yl]-2-(cyclopropylmethoxy)acetate. The concatenated yield from the 2-methyl-1-(4'-methylthiophenyl)propan-1-one is 46% pure/pure.

GC/IR/MS:

m/z: 238; 183;

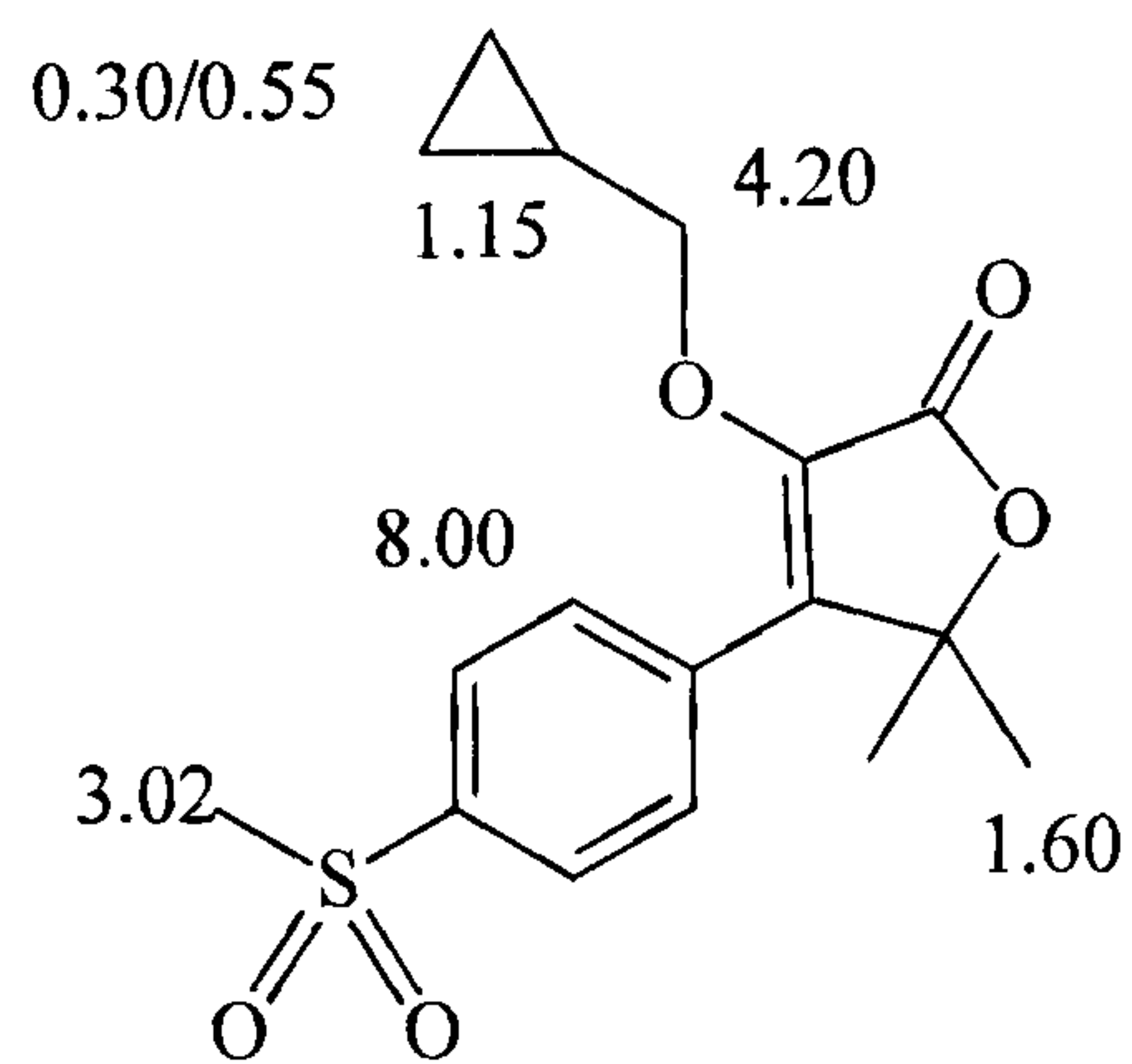
10 IR (cm⁻¹): C=O 1752, 1711, SO₂ 1349, 1166;
C-O-C 1124.

4) Preparation of 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4'-methylsulphonylphenyl)-5H-furan-2-one
(title compound)

15 A solution of isopropyl trifluoroacetate (1.58 g, 10.1 mmol, 1.2 equiv) and 1,8-diazabicyclo-[5.4.0]-undec-7-ene (2.6 g, 13.5 mmol, 1.6 equiv) in anhydrous acetonitrile (20 ml) is stirred for 15 minutes at room temperature. [2-methyl-1-(4'-methylsulphonylphenyl)-1-oxo-prop-2-yl]-2-(cyclopropylmethoxy)acetate (3.00 g, 8.4 mmol)
20 is then added and the reaction mixture is heated to reflux for 18 hours. After returning the temperature to 40°C, the acetonitrile is partially evaporated and then water (20 ml) is added to the reaction medium. After returning to room
25 temperature and a few hours of crystallisation, the mixture is filtered in order to recover the expected 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4'-methylsulphonyl)-5H-furan-2-one. The yield of isolated product is 85%.

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RMN-¹H (200 MHz, CD₃COCD₃) ppm:

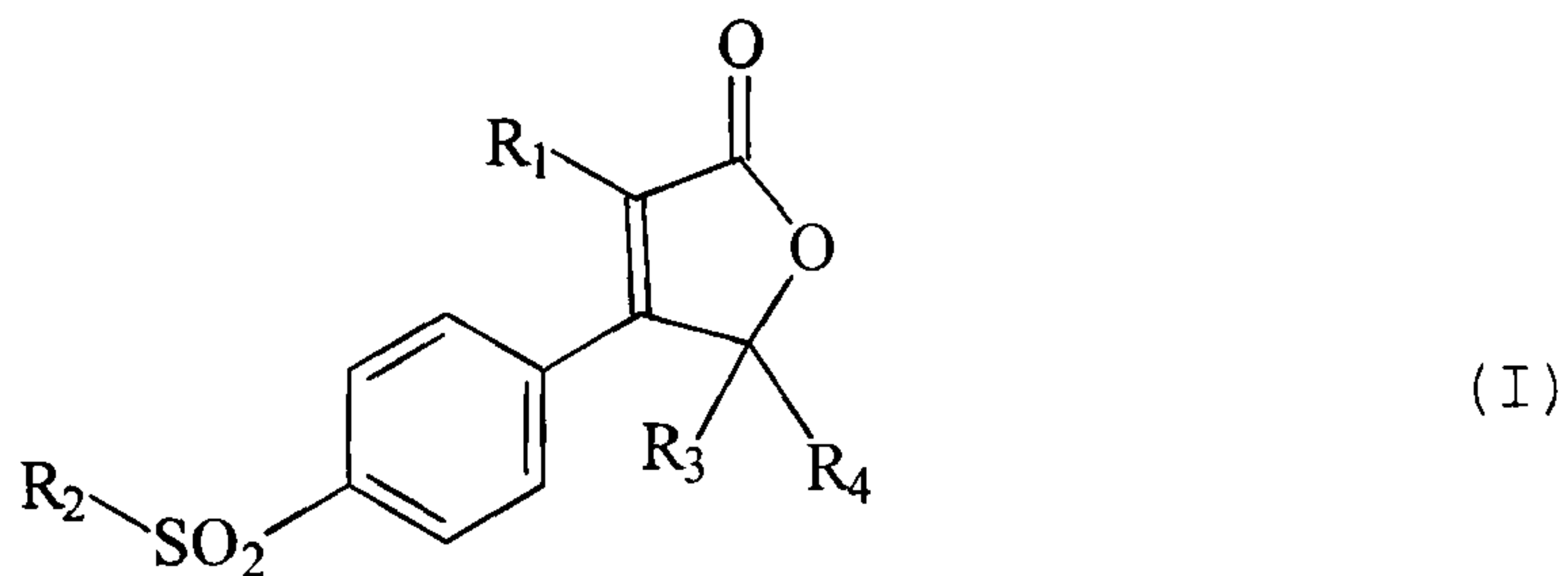
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CLAIMS:

1. Process for the preparation of compounds of general formula (I):

5



in which

R_1 is chosen from the groups:

10

(a) OR_5 where R_5 represents a group chosen from:

(1) a linear, branched or cyclic (C_1-C_6) alkyl group;

(2) a mono-, di- or tri-substituted phenyl or naphthyl group in which the substituents are chosen from:

15

hydrogen;

halogen;

(C_1-C_3) alkoxy;

CN;

(C_1-C_3) fluoroalkyl;

20

(C_1-C_3) alkyl;

-COOH; and

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(b) mono-, di- or tri-substituted phenyl in which the substituents are chosen from:

hydrogen;

halogen;

5 (C₁-C₃)alkoxy;

CN;

(C₁-C₃)fluoroalkyl;

(C₁-C₃)alkyl;

-COOH;

10 R₂ represents a (C₁-C₆)alkyl group;

R₃ and R₄ independently of one another represent a hydrogen atom or a CHR₆R₇ group in which R₆ and R₇ independently of one another are chosen from:

hydrogen;

15 (C₁-C₁₀)alkyl;

(C₁-C₁₀)alkoxy;

OH;

CN;

CH₂CN;

20 OCOR₈;

(C₁-C₆)fluoroalkyl;

halogen;

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25

 $\text{CON}(\text{R}_8)_2$;

mono-, di- or tri-substituted phenyl;

mono-, di- or tri-substituted heteroaryl;

the substituents being chosen from:

5

hydrogen;

halogen;

 $(\text{C}_1\text{-C}_6)$ alkyl; $(\text{C}_1\text{-C}_{10})$ alkoxy;

CN;

10

 CF_3 ; N_3 ; $\text{C}(\text{R}_9)(\text{R}_{10})\text{-OH}$; $\text{C}(\text{R}_9)(\text{R}_{10})\text{-O-}(\text{C}_1\text{-C}_4)$ alkyl; $(\text{C}_1\text{-C}_6)$ fluoroalkyl;15 R_8 is chosen from:

hydrogen;

 $(\text{C}_1\text{-C}_6)$ alkyl;mono-, di- or tri-substituted phenyl, the
substituents being chosen from hydrogen, halogen,20 $(\text{C}_1\text{-C}_6)$ alkyl; $(\text{C}_1\text{-C}_6)$ alkoxy; $(\text{C}_1\text{-C}_6)$ alkylthio; CN or CF_3 ; andmono-, di- or tri-substituted benzyl, the
substituents being chosen from hydrogen, halogen,
 $(\text{C}_1\text{-C}_6)$ alkyl; $(\text{C}_1\text{-C}_6)$ alkoxy; $(\text{C}_1\text{-C}_6)$ alkylthio, CN or CF_3 ;

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or two R_8 groups form together with the nitrogen atom to which they are attached a ring having 5 to 7 atoms and optionally comprising a heteroatom chosen from O, S or NR_9 ;

R_9 and R_{10} independently of one another are chosen from:

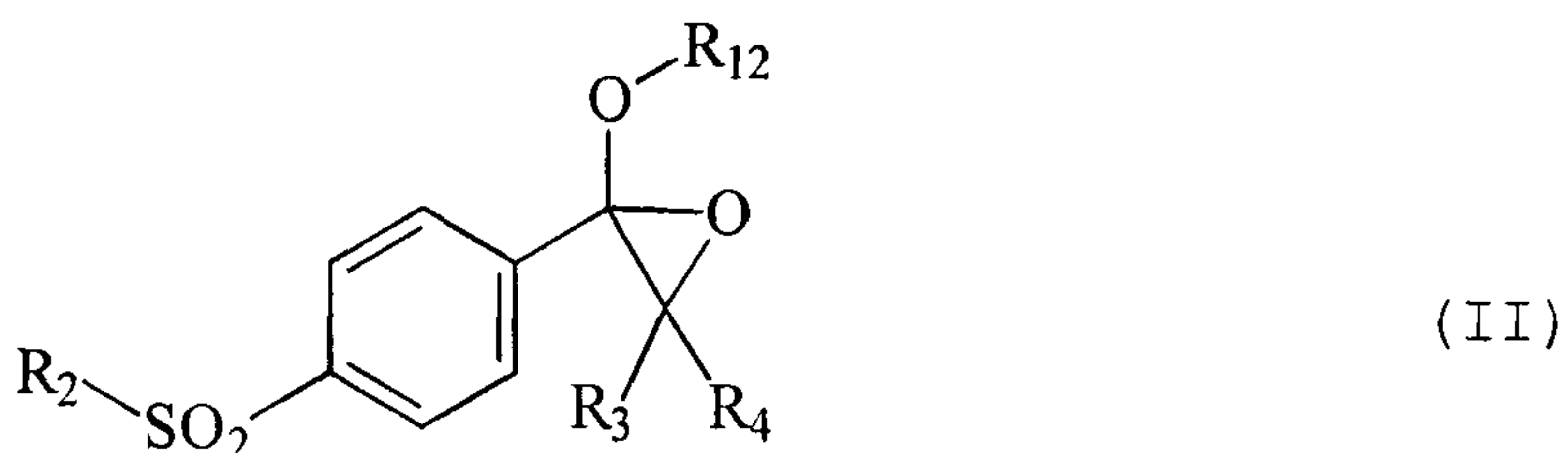
5 hydrogen; and

(C_1 - C_{10})alkyl; or

form, together with the atom to which they are attached, a ring having 3 to 7 carbon atoms and, if appropriate, a nitrogen atom;

10 which comprises the following stages:

a) reaction of a compound of general formula (II):



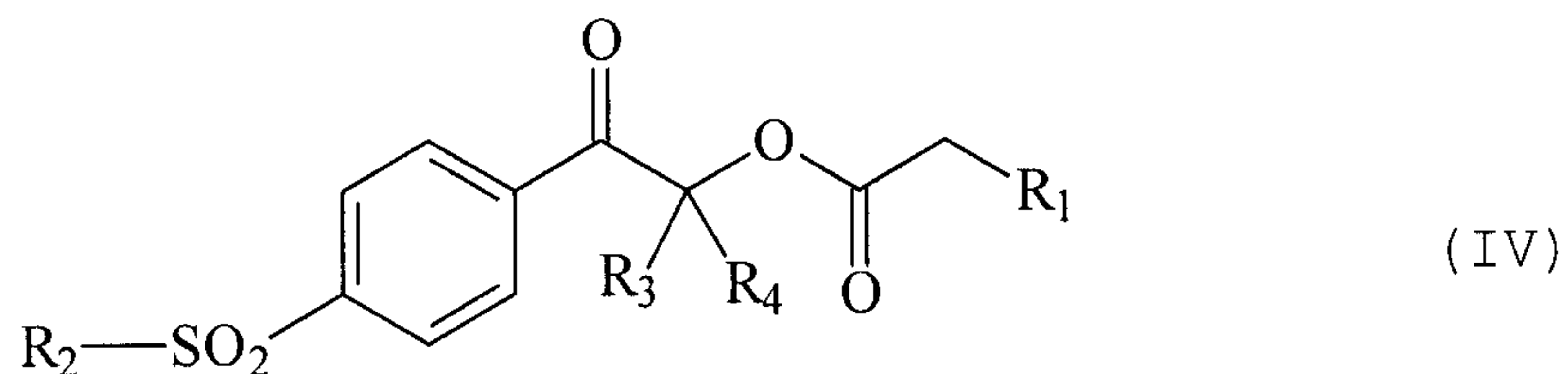
15 in which R_2 , R_3 , and R_4 are as defined previously and R_{12} represents a (C_1 - C_6)alkyl group, with an acid of general formula (III):



20 in which R_1 is as defined previously, in anhydrous medium, in order to form a compound of formula (IV):

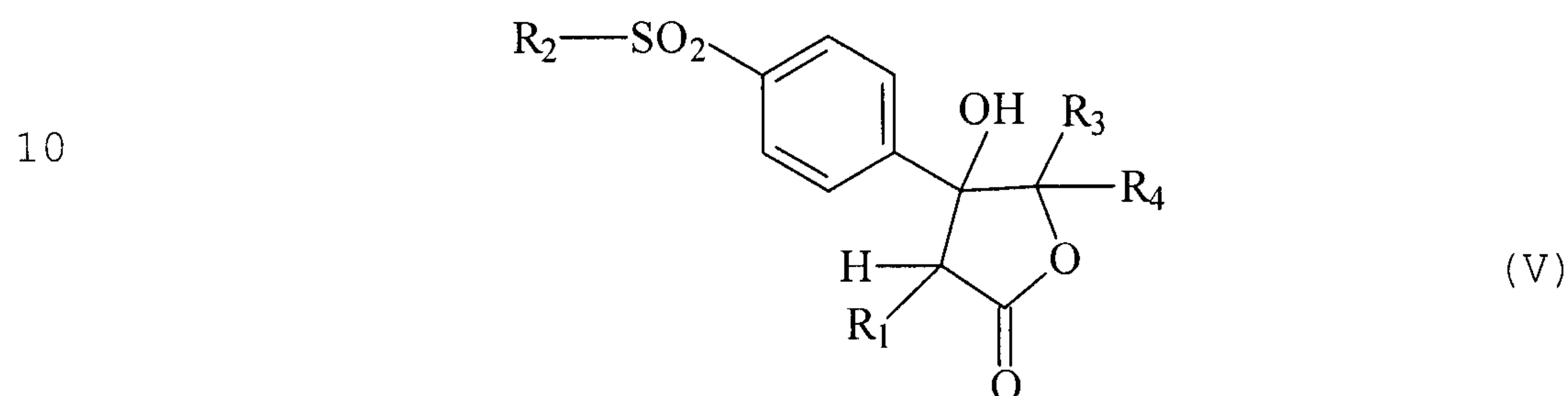
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5 R_1 , R_2 , R_3 , and R_4 being as defined above;

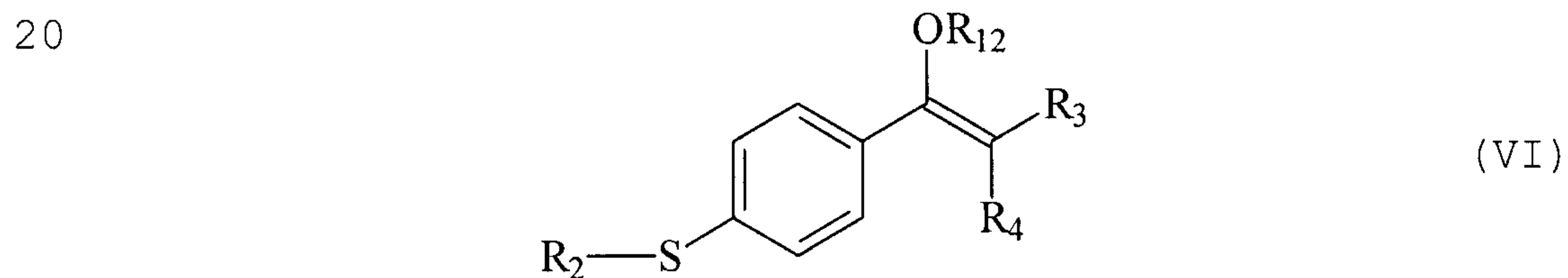
b) reaction of the compound of formula (IV) with a strong base in an aprotic solvent in order to obtain an intermediate cyclic compound of formula (V):



which, after elimination of a water molecule forms a compound of general formula (I);

15 c) isolation of the compound of general formula (I) thus obtained.

2. Process according to claim 1, wherein the compound of general formula (II) is prepared by reaction of a compound of general formula (VI):

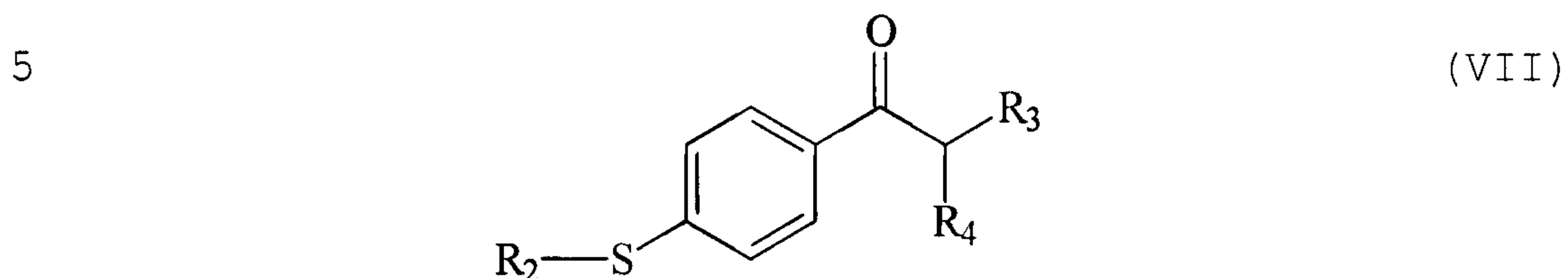


in which R_2 , R_3 , R_4 and R_{12} are as defined in claim 1, with an oxidizing agent.

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3. Process according to claim 2, wherein the compound of general formula (VI) as defined in claim 2 is prepared by reaction of a compound of general formula (VII):



in which R_2 , R_3 , and R_4 are as defined in claim 1, with an alcohol of general formula (VIII):

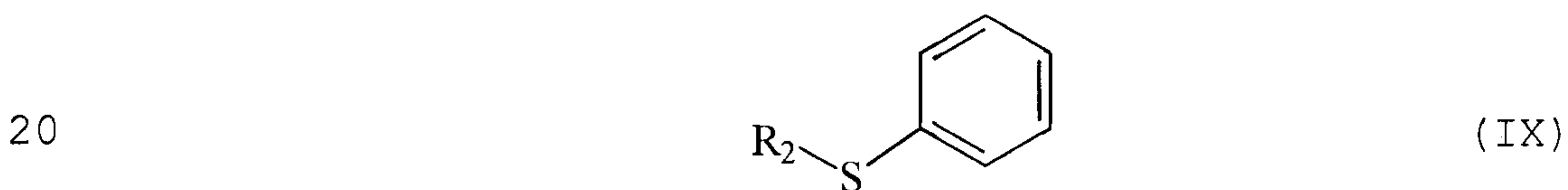


10 R_{12} being as defined above, in the presence of a catalytic quantity of acid and a dehydrating agent.

4. Process according to claim 3, wherein R_{12} is methyl and the compound of general formula (VIII) is methanol.

5. Process for the preparation of compounds of general formula (I) as defined in claim 1, which comprises the following stages:

(1) reaction of a compound of general formula (IX):



in which R_2 is as defined in claim 1, in an inert solvent in the presence of a Lewis acid with a compound of general formula (X):

25

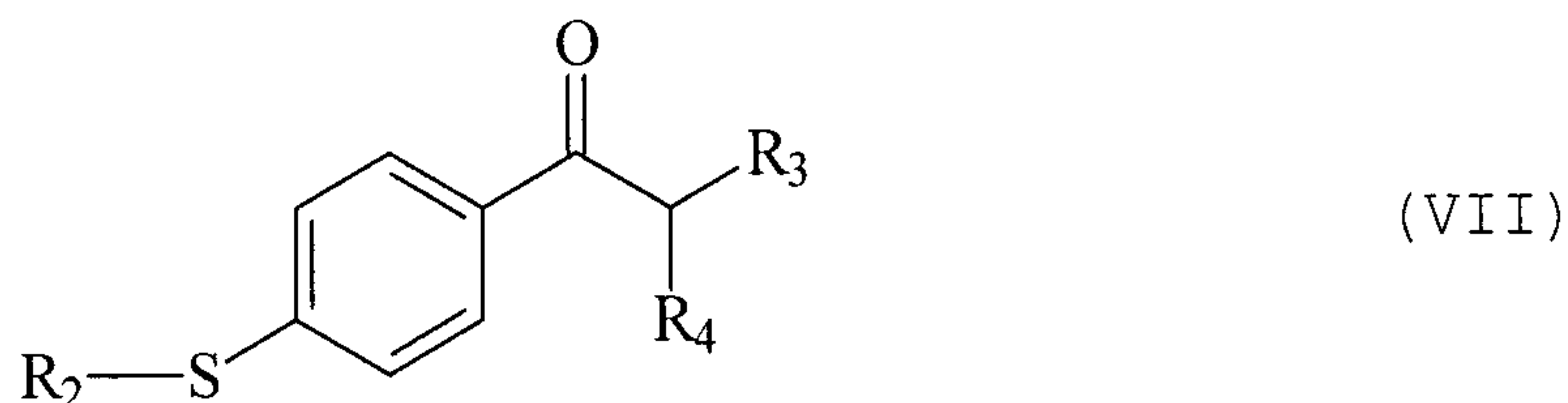
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in which X is a leaving group, preferably a chlorine atom in order to form a compound of general formula (VII):

5



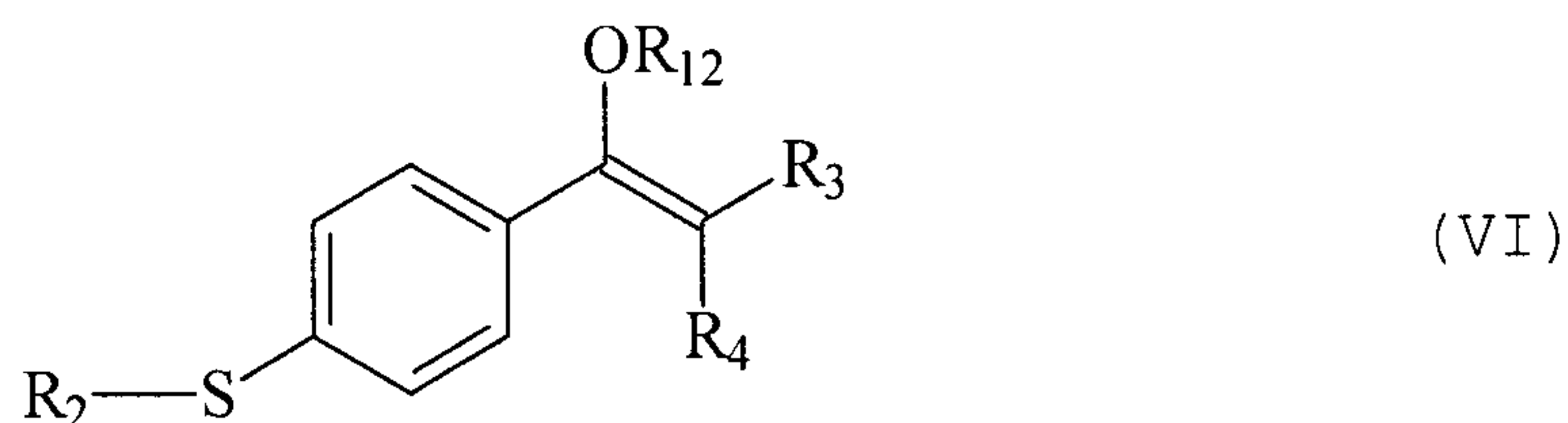
in which R_2 , R_3 , and R_4 are as defined in claim 1,

(2) reaction of the compound of general formula (VII) with an alcohol of general formula (VIII):



in which R_{12} represents a $(\text{C}_1\text{---C}_6)$ alkyl group in order to form a compound of general formula (VI):

15



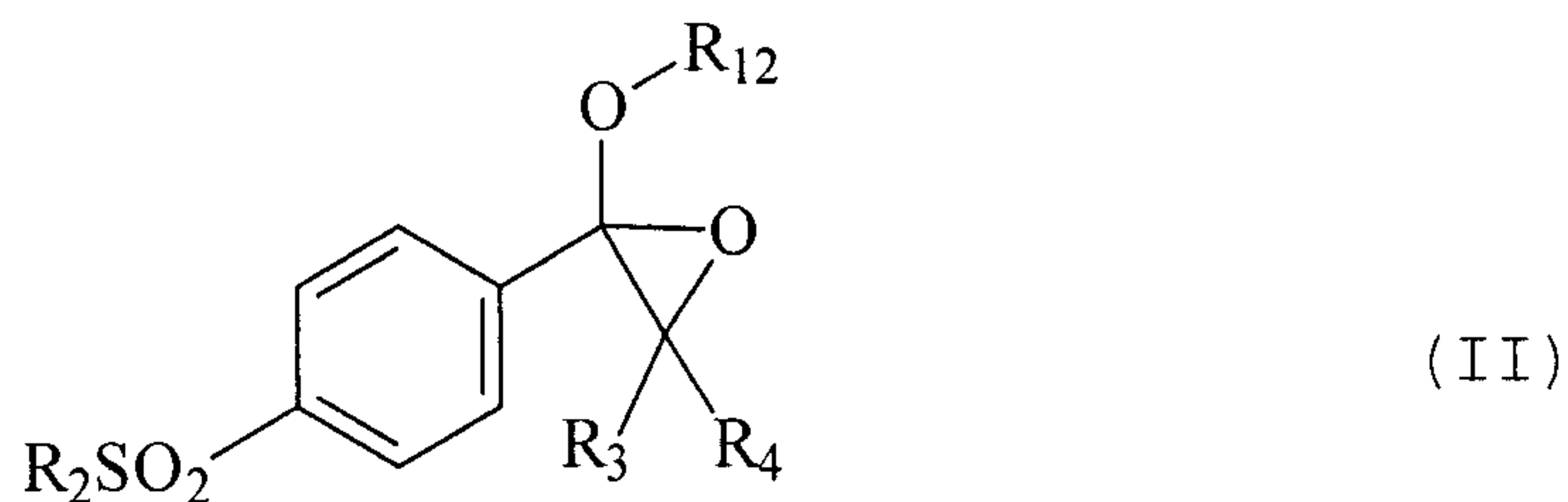
in which R_2 , R_3 , R_4 and R_{12} are as defined previously,

(3) reaction of the compound of general formula (VI) with an oxidizing agent in order to obtain a compound of general formula (II):

20

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5 in which R_2 , R_3 , R_4 and R_{12} are as defined previously,

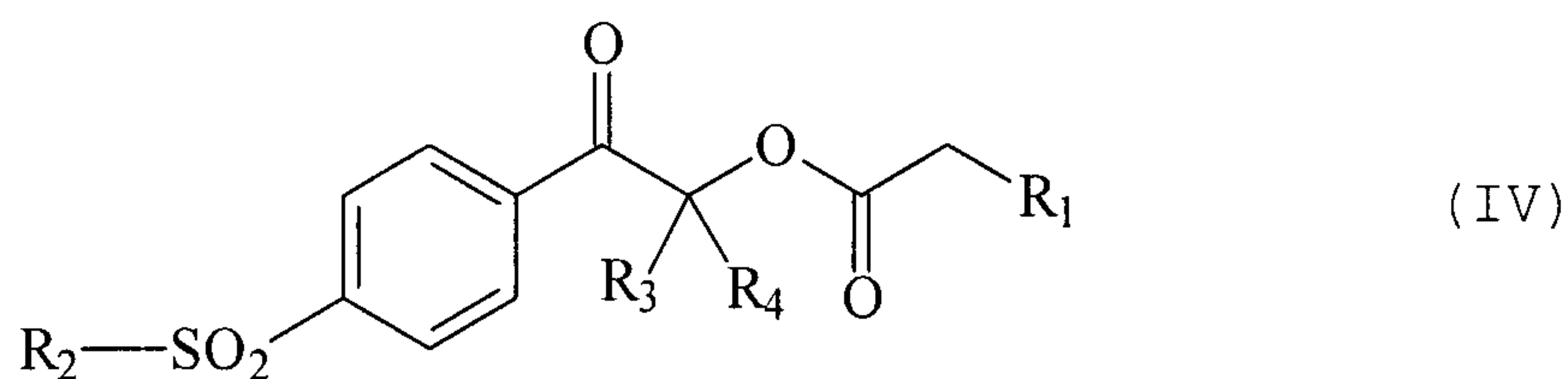
(4) reaction of the compound of general formula (II) as defined at Stage (3) with an acid of general formula (III):

10



in which R_1 is as defined previously, in an anhydrous medium, in order to form a compound of formula (IV):

15



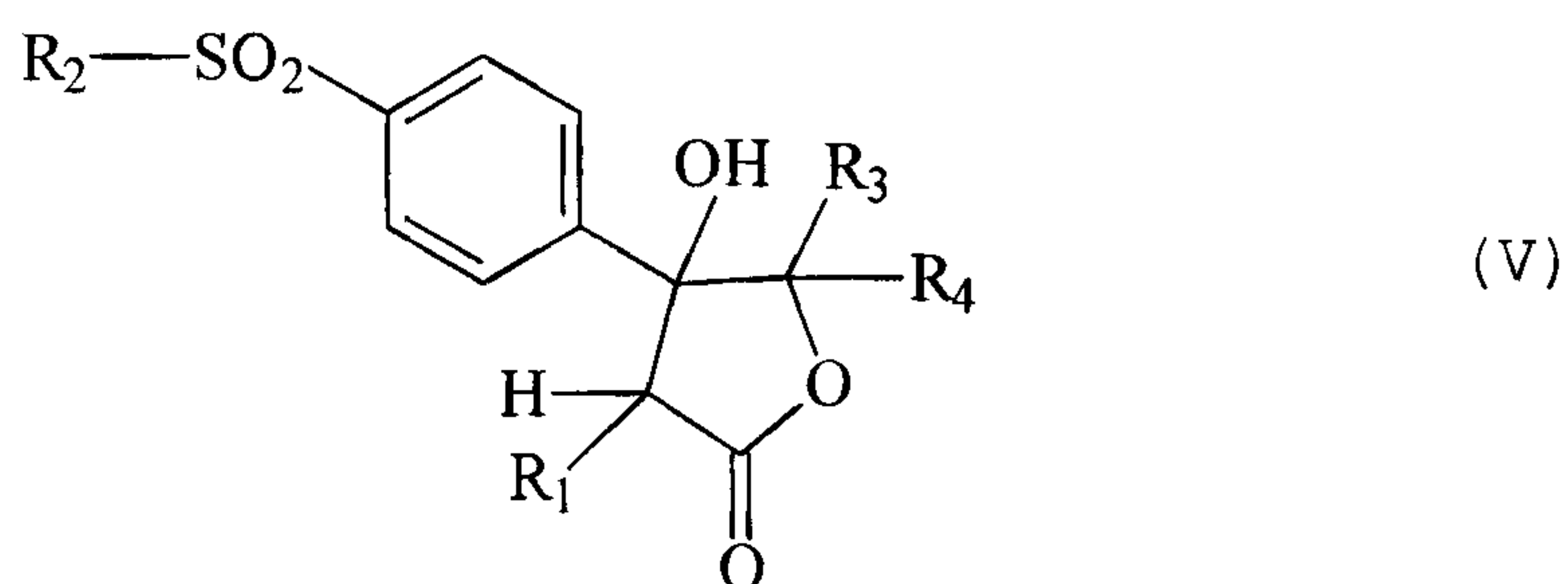
R_1 , R_2 , R_3 and R_4 being as defined above,

(5) reaction of the compound of formula (IV) with a strong base in an aprotic solvent in order to obtain an intermediate cyclic compound of formula (V):

20

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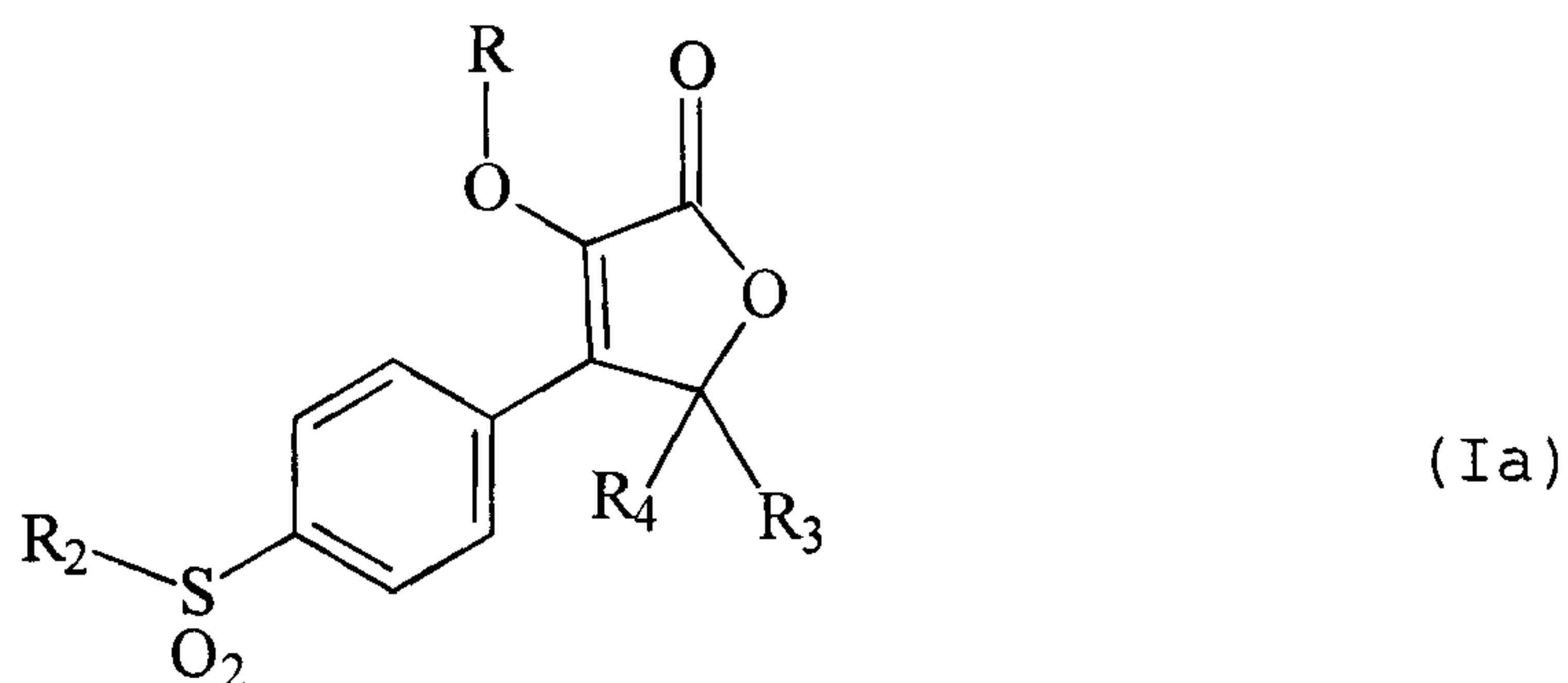


5

which, after elimination of a water molecule, forms a compound of general formula (I); and

(6) isolation of the compound of general formula (I) thus obtained.

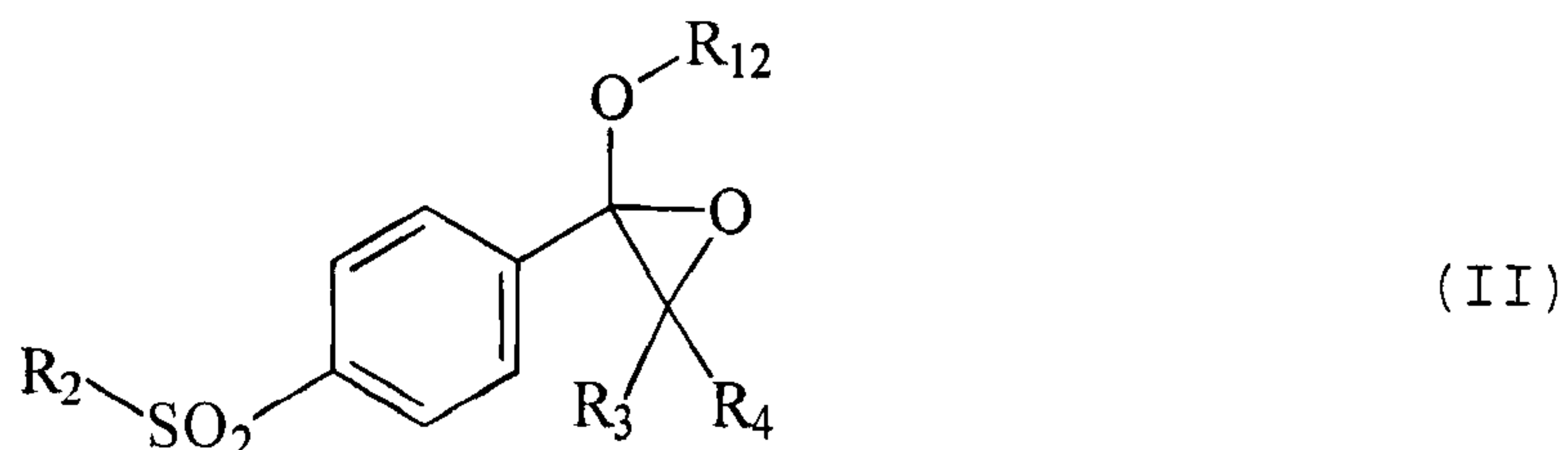
10 6. Process according to claim 1 for the preparation of a compound of general formula (Ia):



15

in which R represents an R_5 group as defined in claim 1 and R_2 , R_3 , and R_4 are as defined in claim 1, which comprises the following stages:

a) reaction of a compound of general formula (II):

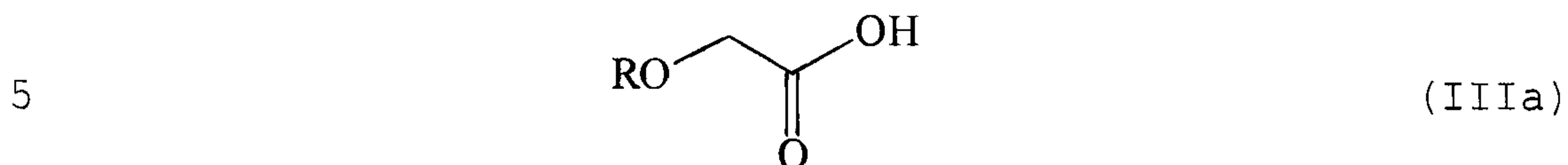


20

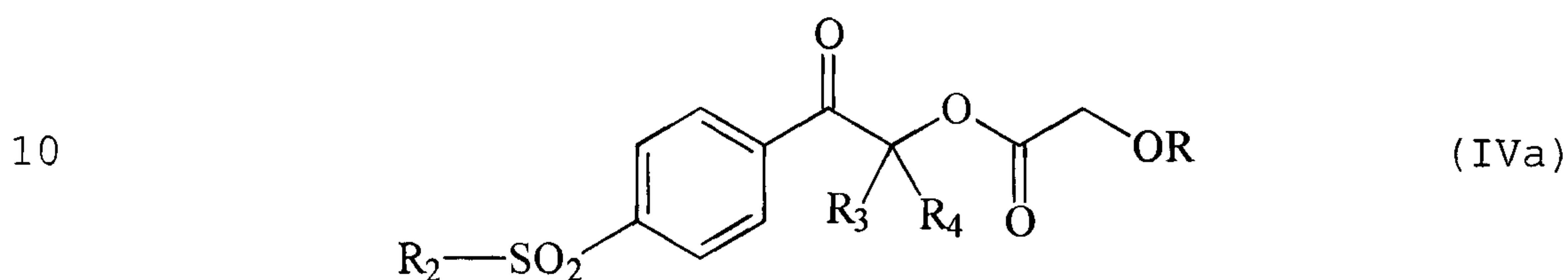
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in which R_2 , R_3 , and R_4 are as defined previously and R_{12} represents a (C_1-C_6) alkyl group, with an acid of general formula (IIIa):



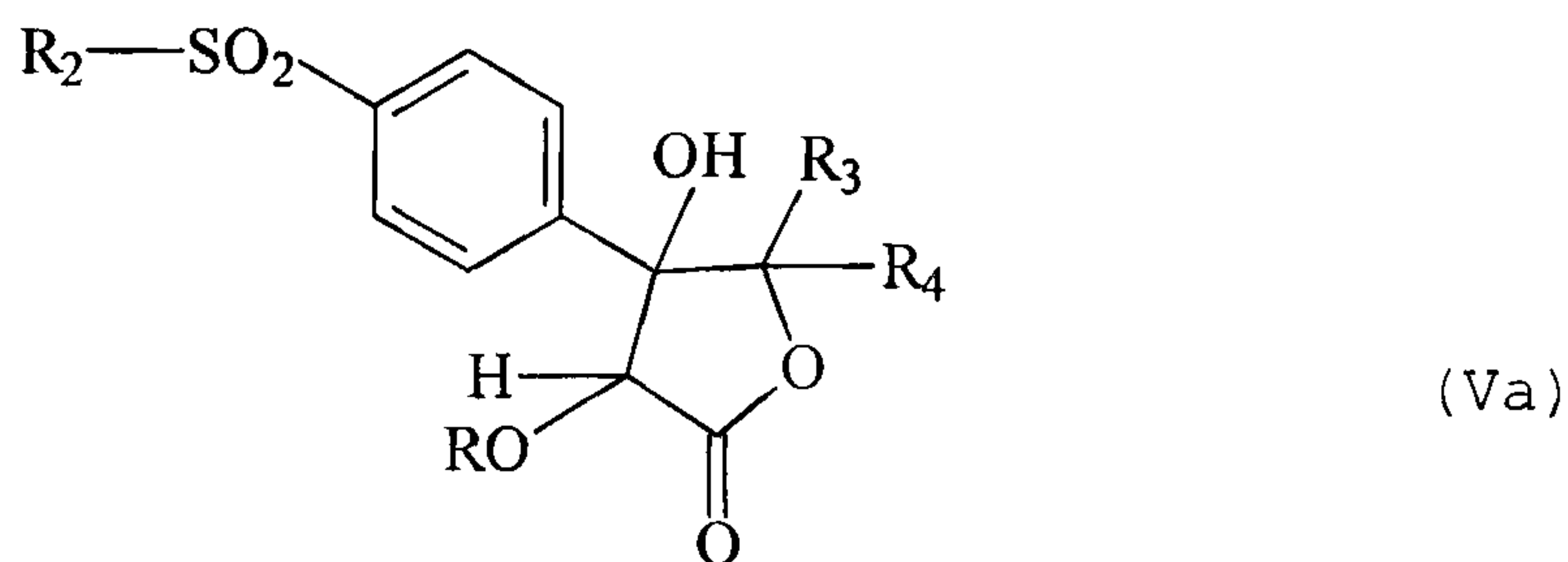
in which R is as defined above, in anhydrous medium in order to form a compound of general formula (IVa):



in which R, R_2 , R_3 , and R_4 are as defined previously;

b) reaction of the compound of formula (IVa) with a strong base in an aprotic solvent in order to obtain an intermediate cyclic compound of formula (Va):

15



20 which, after elimination of a water molecule forms a compound of general formula (Ia);

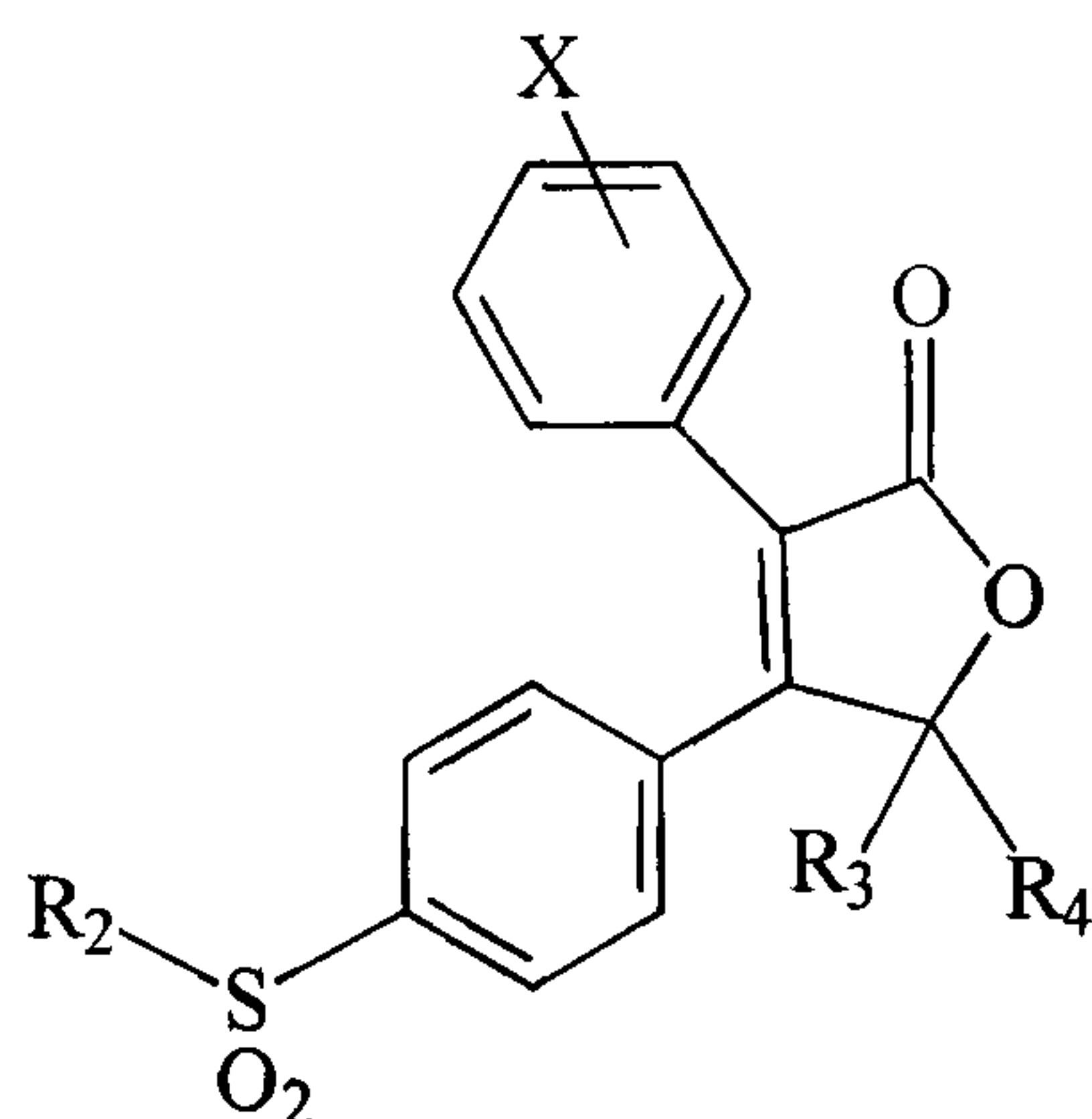
c) isolation of the compound of formula (Ia) thus obtained.

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7. Process according to claim 1 for the preparation of a compound of general formula (Ib):

5



(Ib)

in which R_2 is as defined in claim 1 and X is chosen from:

hydrogen;

10

halogen;

(C_1 - C_3) alkoxy;

CN;

(C_1 - C_3) fluoroalkyl;

(C_1 - C_3) alkyl;

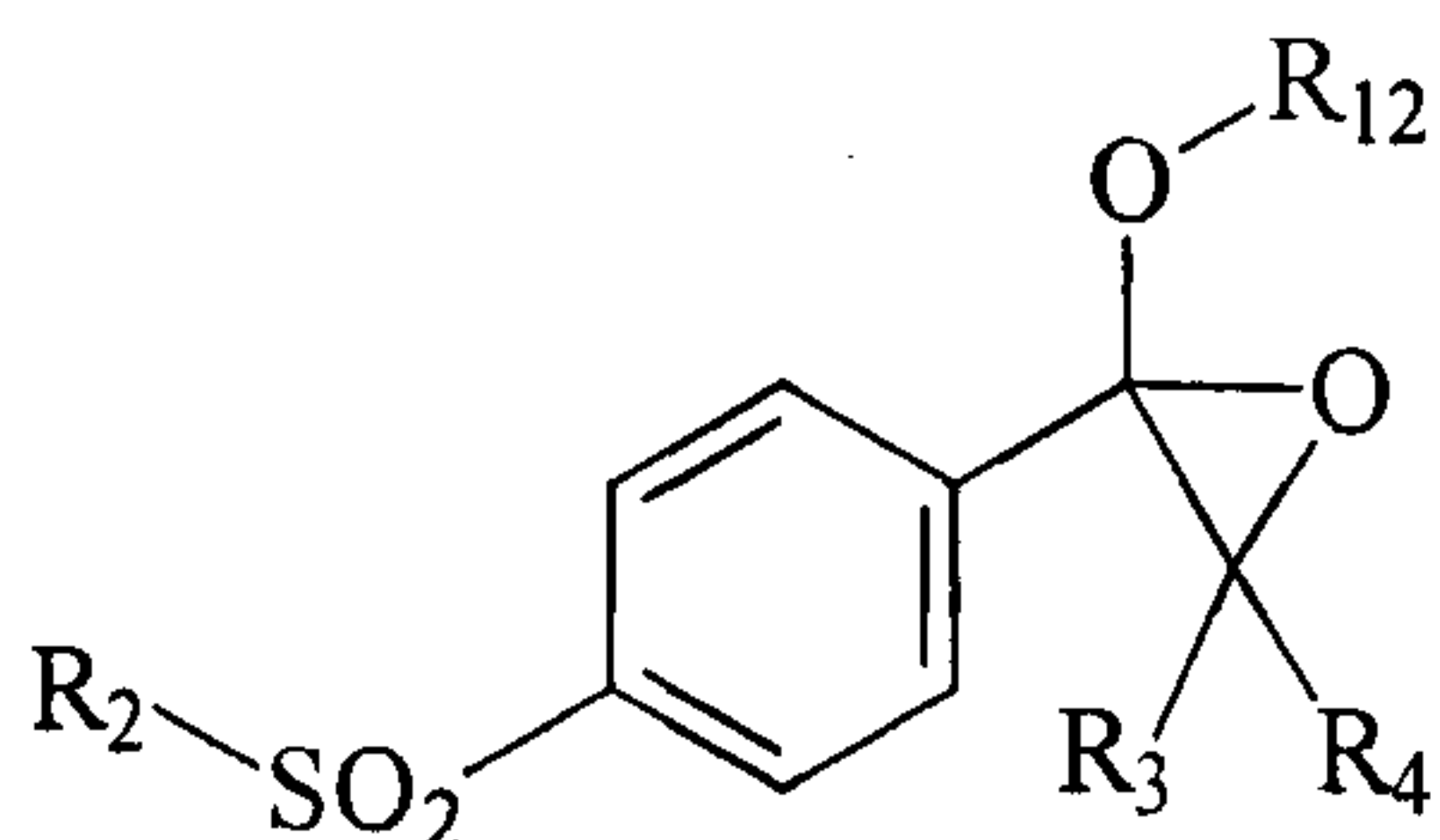
15

-COOH;

which comprises the following stages:

a) reaction of the compound of general formula (II):

20

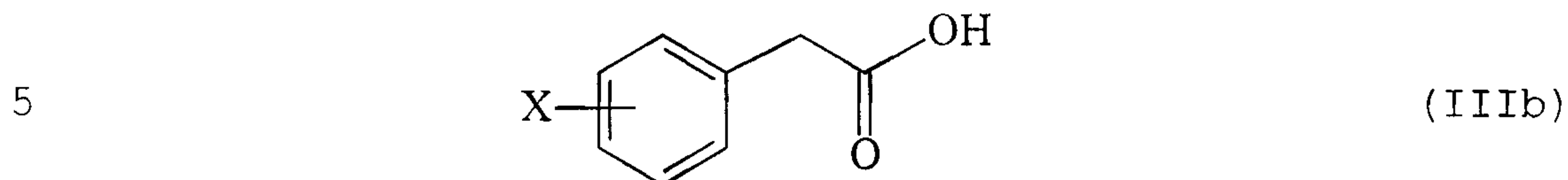


(II)

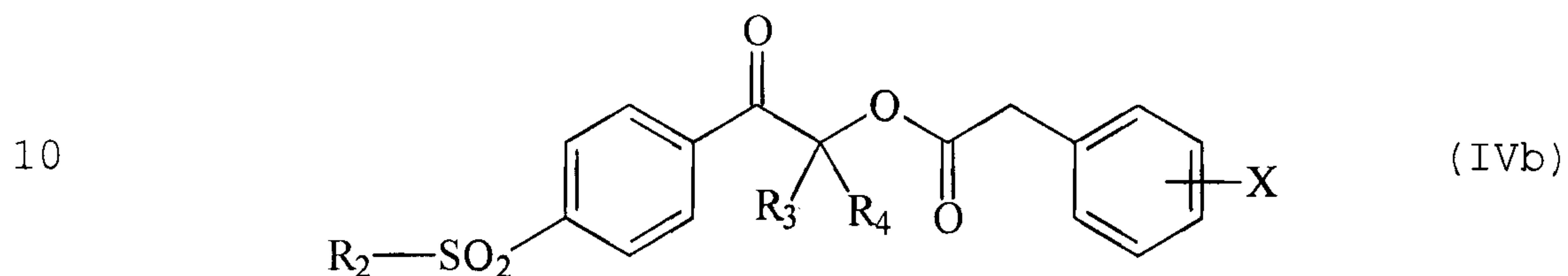
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in which R_2 , R_3 , and R_4 are as defined previously and R_{12} represents a (C_1-C_6) alkyl group, with an acid of general formula (IIIb):

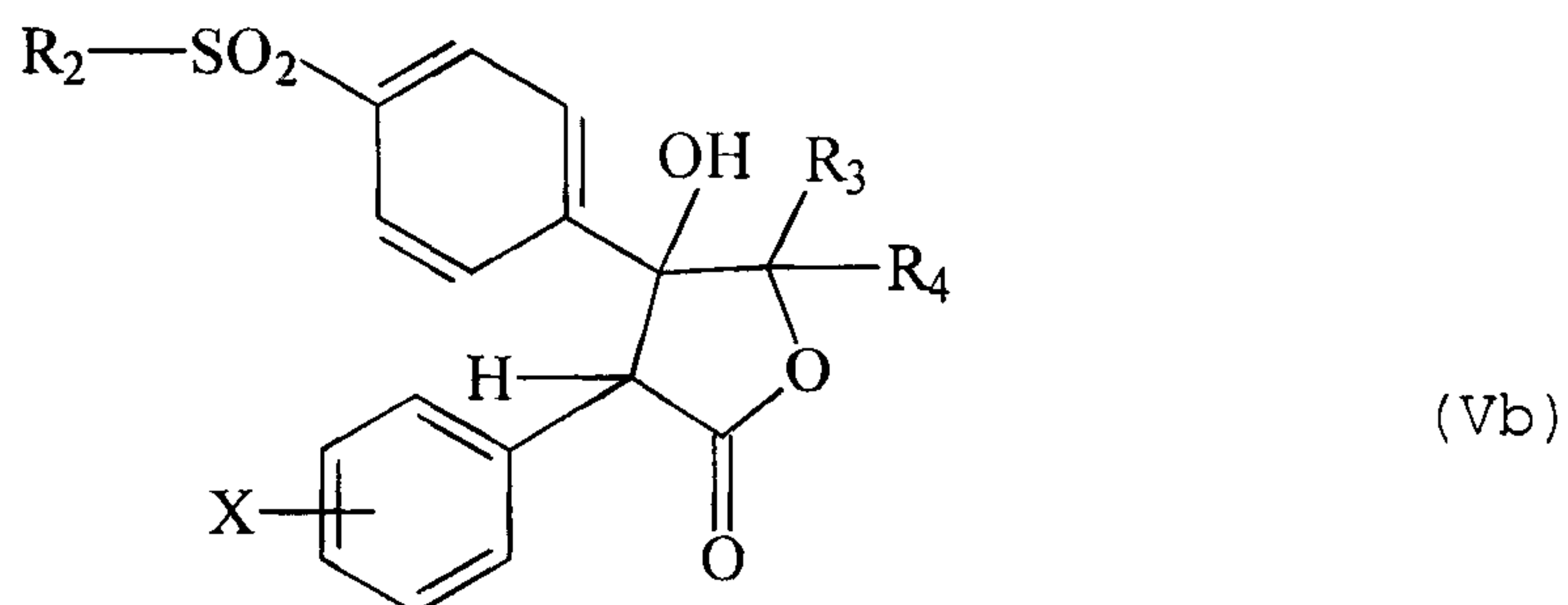


in which X is as defined previously, in anhydrous medium in order to form a compound of general formula (IVb):



R_2 , R_3 , and R_4 being as defined above;

b) reaction of the compound of formula (IVb) with a strong base in an aprotic solvent in order to obtain an intermediate cyclic compound of formula (Vb):



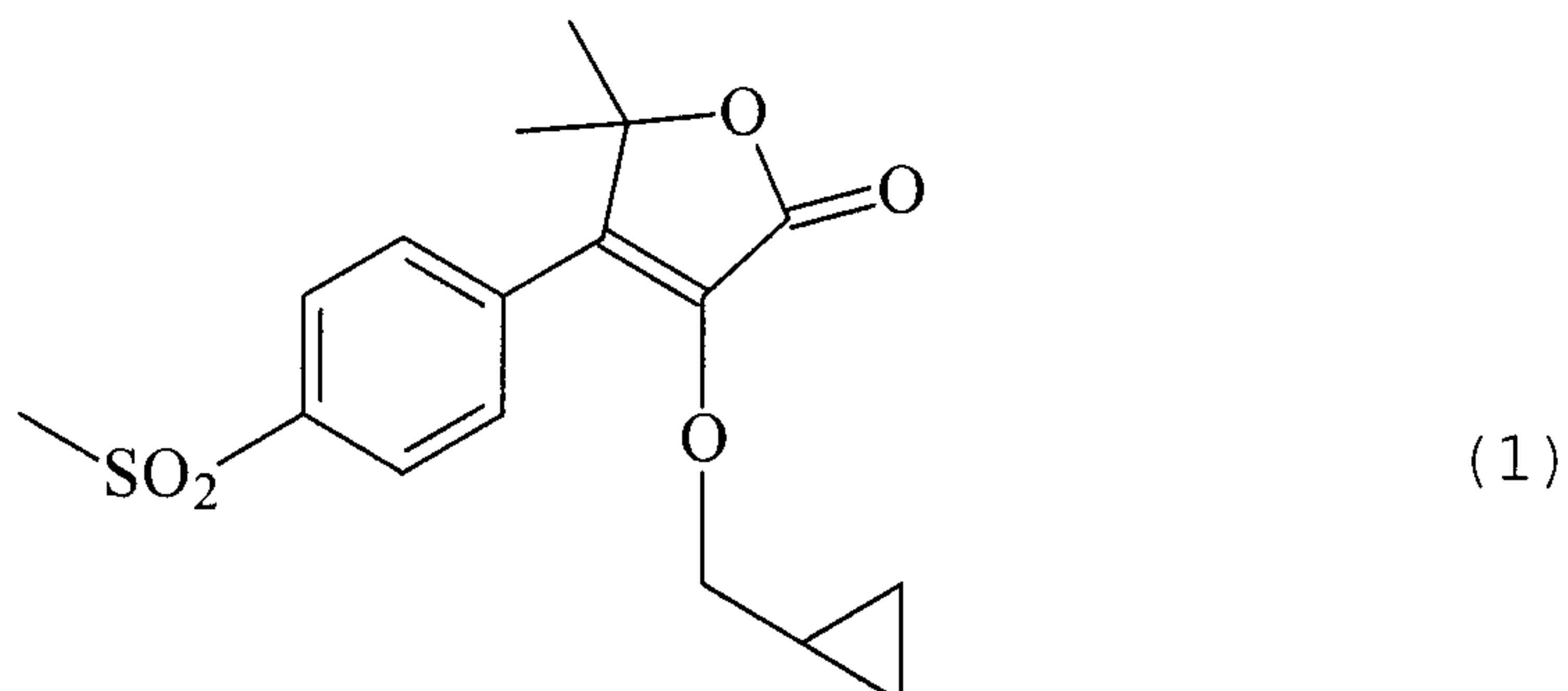
20 which, after elimination of a water molecule forms a compound of general formula (Ib);

c) isolation of the compound of formula (Ib) thus obtained.

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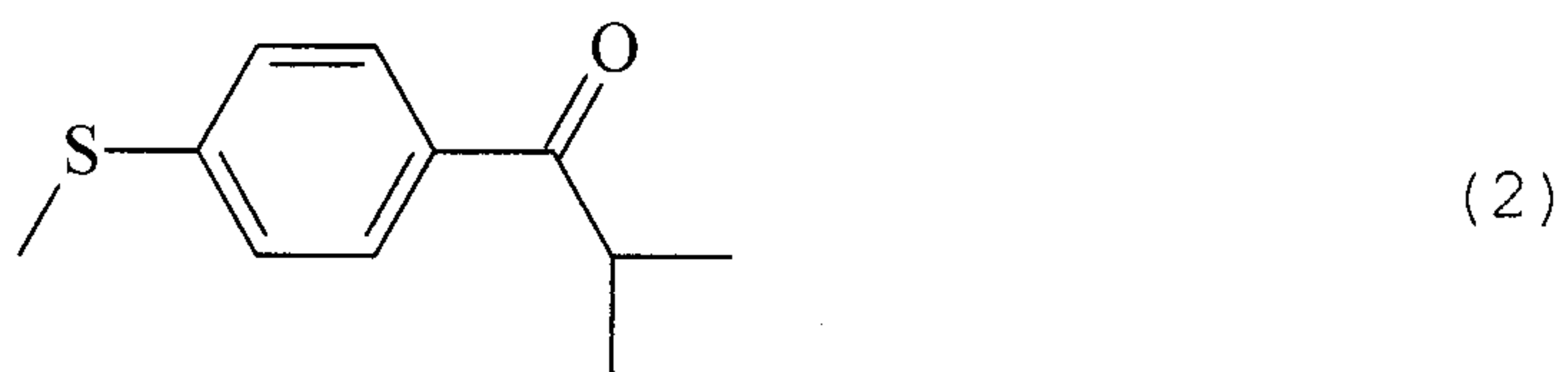
8. Process for the preparation of the compound of formula (1):



comprising the following stages:

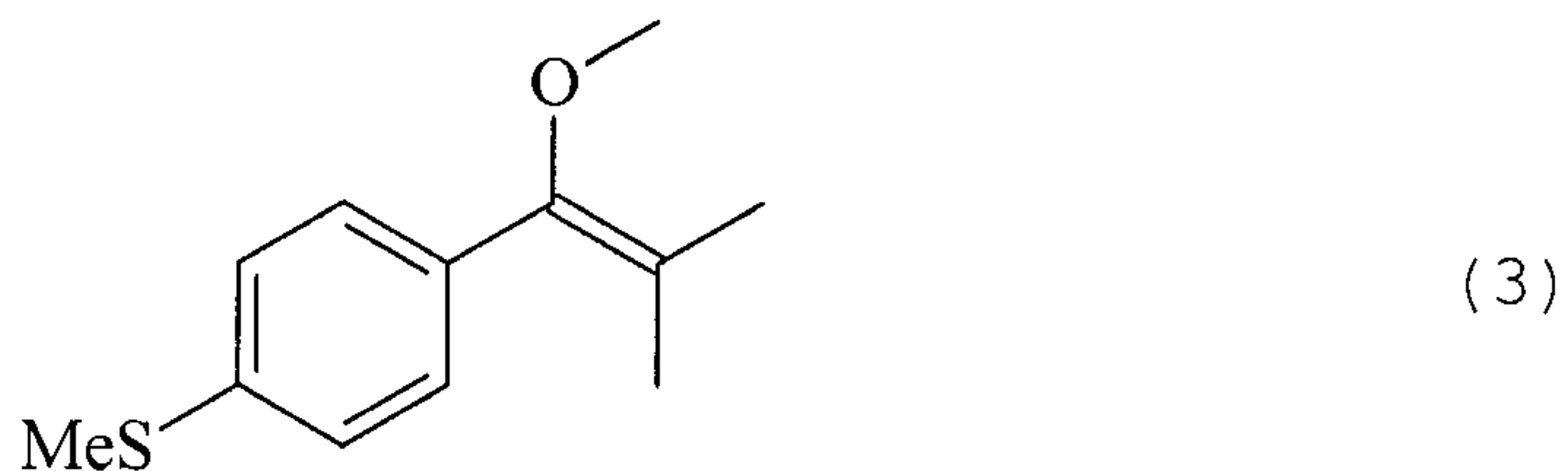
reaction of thioanisole in the presence of a Lewis acid with isobutyryl chloride in order to obtain the compound of formula (2):

10



reaction of the compound of formula (2) with methanol in the presence of para-toluene sulphonic acid and methyl orthoformate in order to form the compound of formula (3):

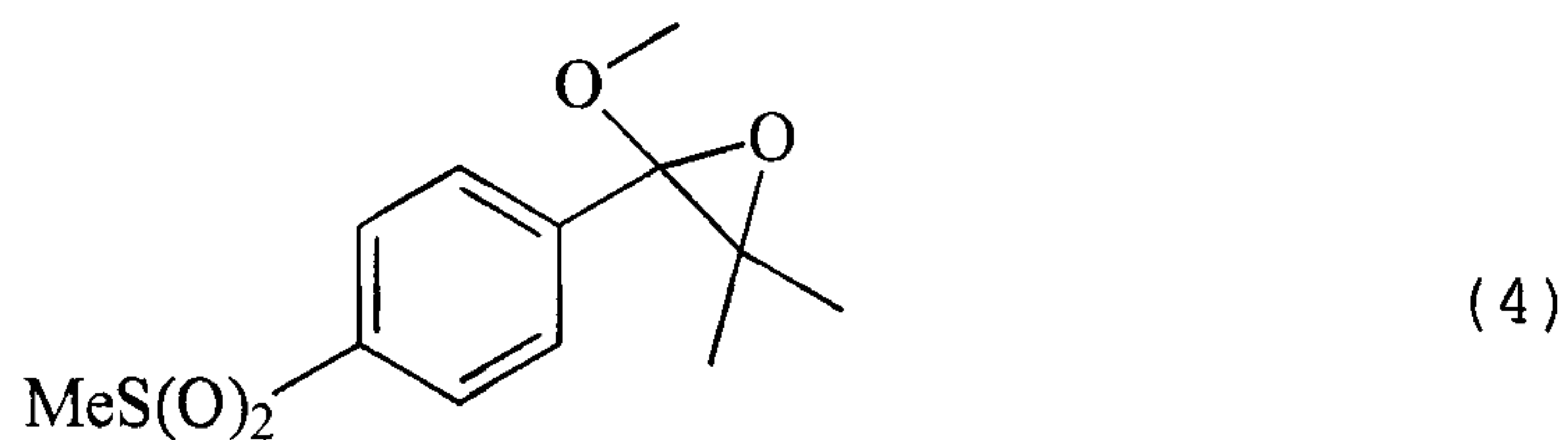
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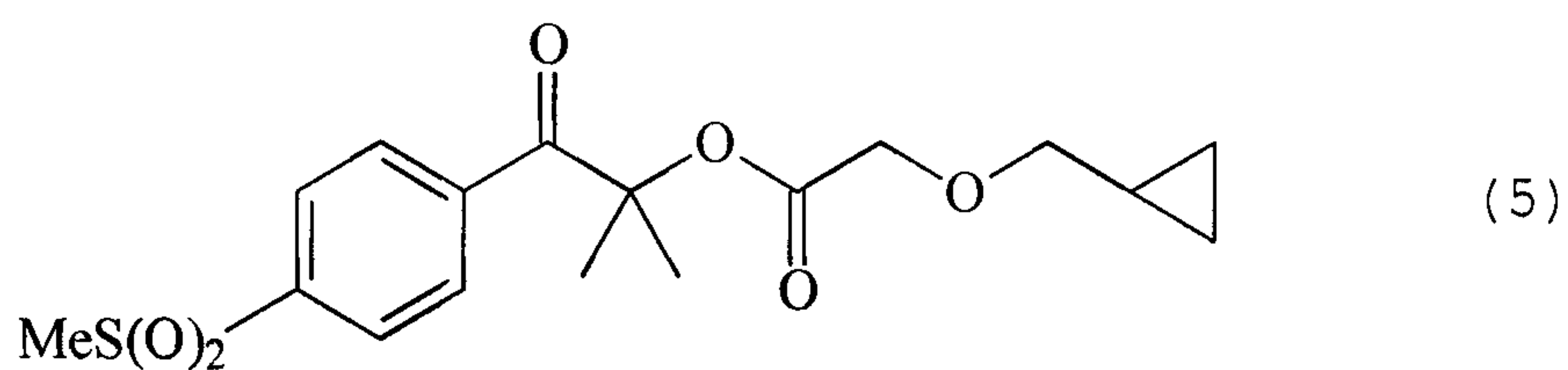
reaction of compound (3) with dimethyldioxirane in order to form the compound of formula (4):

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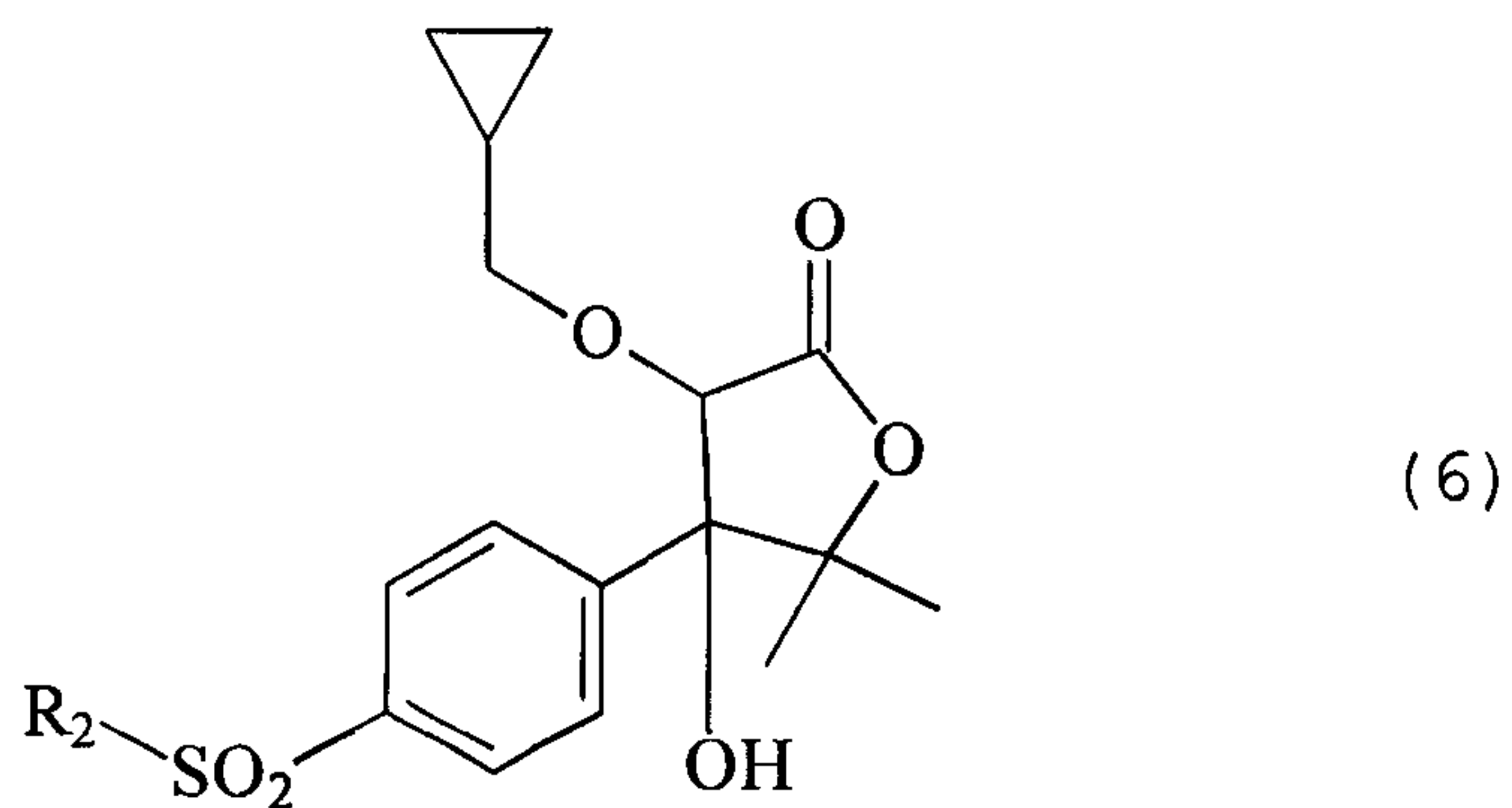
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5 reaction of compound (4) with cyclopropylmethyloxy acetic acid in an anhydrous solvent in order to obtain compound (5):



10 reaction of compound (5) in an aprotic solvent with a strong base in order to obtain an intermediate cyclic compound (6):



15 which, after dehydration in the presence of a
20 dehydrating agent forms compound (1).

9. Process according to claim 2 or 5, wherein the oxidizing agent is chosen from organic peracids, and dioxiranes.

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10. Process according to claim 2, 5 or 9, wherein the temperature of the oxidation reaction is comprised between -40° and 30°C .

11. Process according to claim 2, 5, 9 or 10, wherein
5 the oxidizing agent is used in excess relative to the compound of general formula (II).

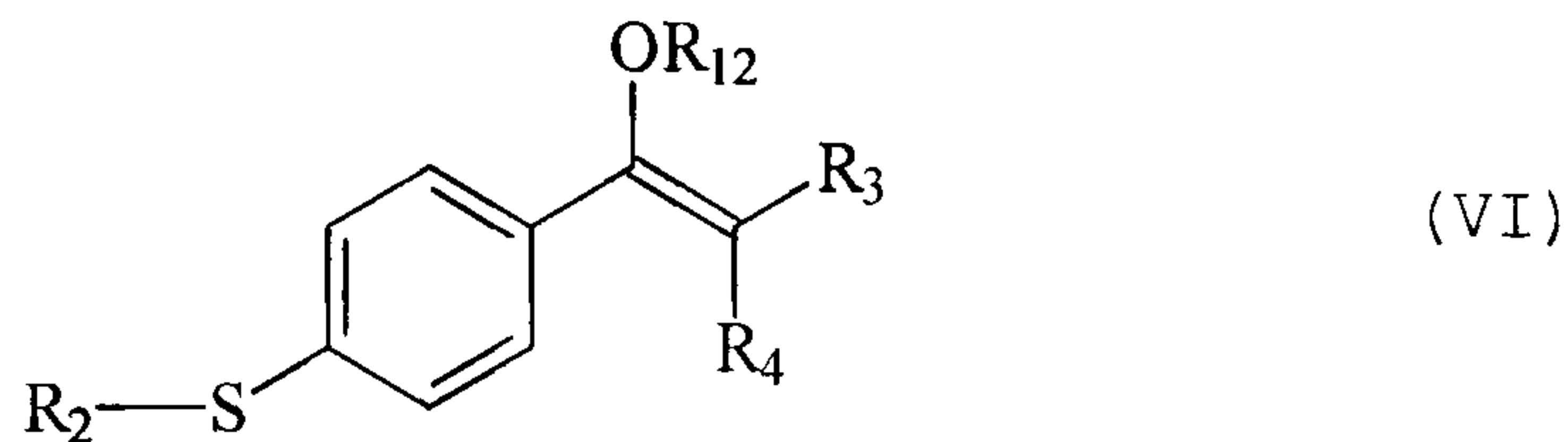
12. Process according to claim 3, wherein the acid is chosen from the sulphonic acids and the mineral acids.

13. Process according to claim 3, wherein a
10 $(\text{C}_1\text{-C}_6)$ alkyl orthoformate is used as dehydrating agent.

14. Process according to claim 3 or 5, wherein the reaction is carried out in an excess of alcohol of general formula (VIII), serving as reagent solvent.

15. Compound of general formula (VI):

15



in which

R_2 represents a $(\text{C}_1\text{-C}_6)$ alkyl group;

20 R_3 and R_4 represent independently of one another a hydrogen atom or a CHR_6R_7 group in which R_6 and R_7 independently of one another are chosen from:

hydrogen;

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 (C_1-C_{10}) alkyl; (C_1-C_{10}) alkoxy;

OH;

CN;

5

 CH_2CN ; $OCOR_8$; (C_1-C_6) fluoroalkyl;

halogen;

 $CON(R_8)_2$;

10

mono-, di- or tri-substituted phenyl;

mono-, di- or tri-substituted heteroaryl;

the substituents being chosen from:

hydrogen;

halogen;

15

 (C_1-C_6) alkyl; (C_1-C_{10}) alkoxy;

CN;

 CF_3 ; N_3 ;

20

 $C(R_9)(R_{10})-OH$; $C(R_9)(R_{10})-O-(C_1-C_4)$ alkyl;

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(C₁-C₆)fluoroalkyl;R₈ is chosen from:

hydrogen;

(C₁-C₆)alkyl;

5 mono-, di- or tri-substituted phenyl, the substituents being chosen from hydrogen, halogen, (C₁-C₆)alkyl; (C₁-C₆)alkoxy; (C₁-C₆)alkylthio, CN or CF₃; and

mono-, di- or tri-substituted benzyl, the substituents being chosen from hydrogen, halogen,
 10 (C₁-C₆)alkyl; (C₁-C₆)alkoxy; (C₁-C₆)alkylthio, CN or CF₃;

or two R₈ groups form together with the nitrogen atom to which they are attached a ring having 5 to 7 atoms and optionally comprising a heteroatom chosen from O, S or NR₉;

R₉ and R₁₀ independently of one another are chosen from:

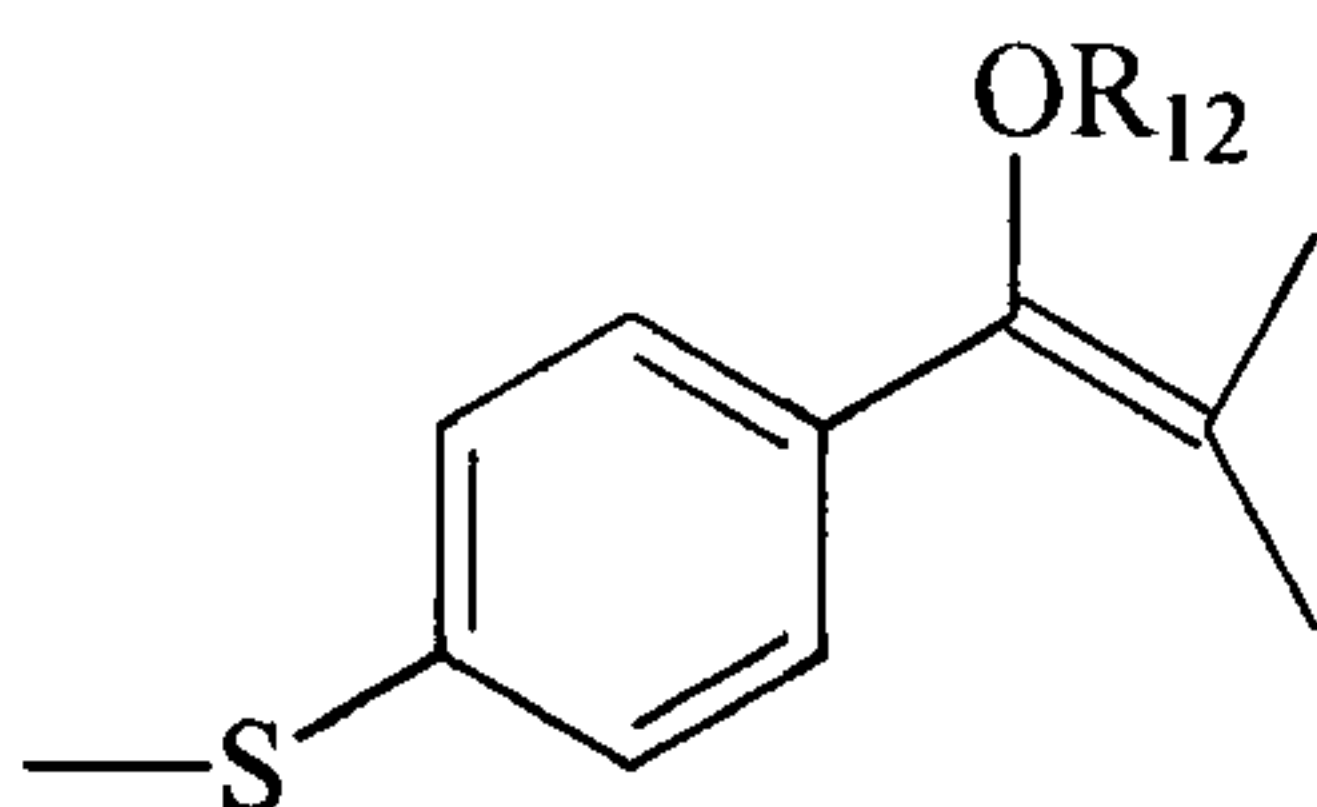
15 hydrogen; and

(C₁-C₁₀)alkyl; or

form, together with the atom to which they are attached, a ring having 3 to 7 carbon atoms and, if appropriate, a nitrogen atom;

20 and R₁₂ represents a (C₁-C₆)alkyl group.

16. Compound of formula



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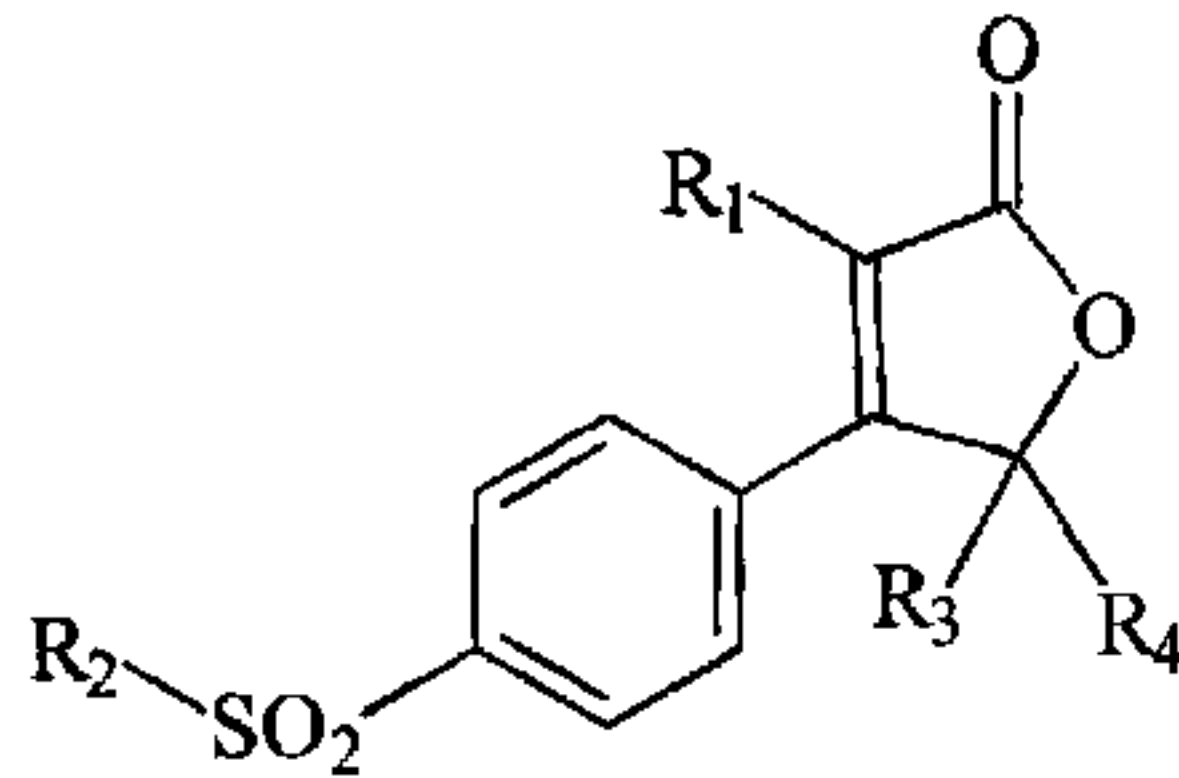
in which R_{12} is as defined in claim 15.

17. The compound according to claim 16, wherein R_{12} is methyl.

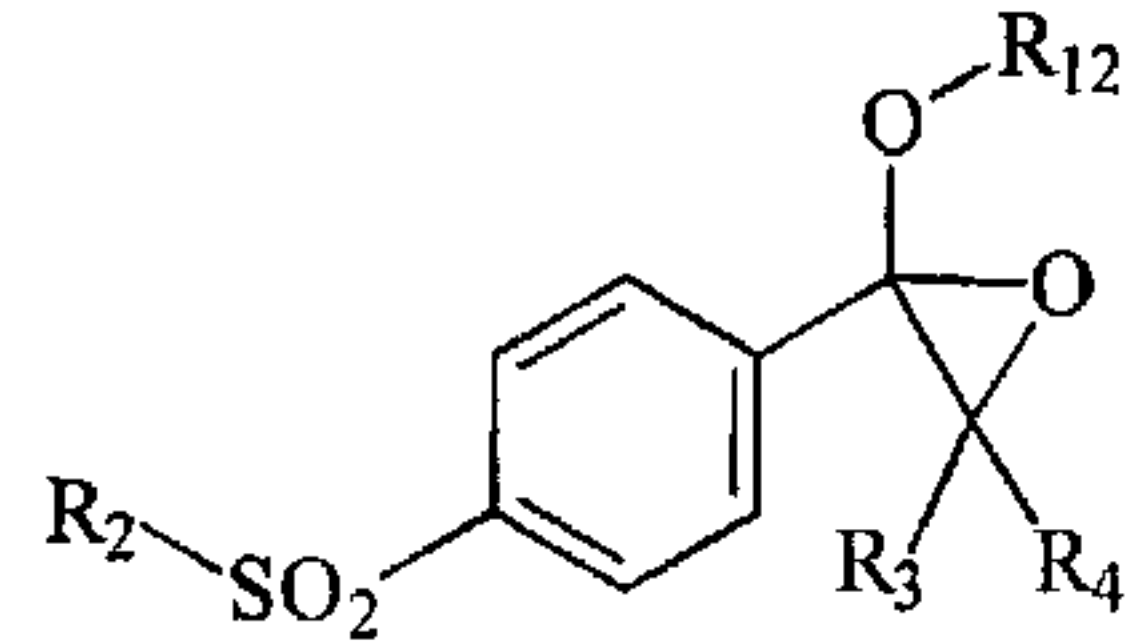
FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS



(I)



(II)