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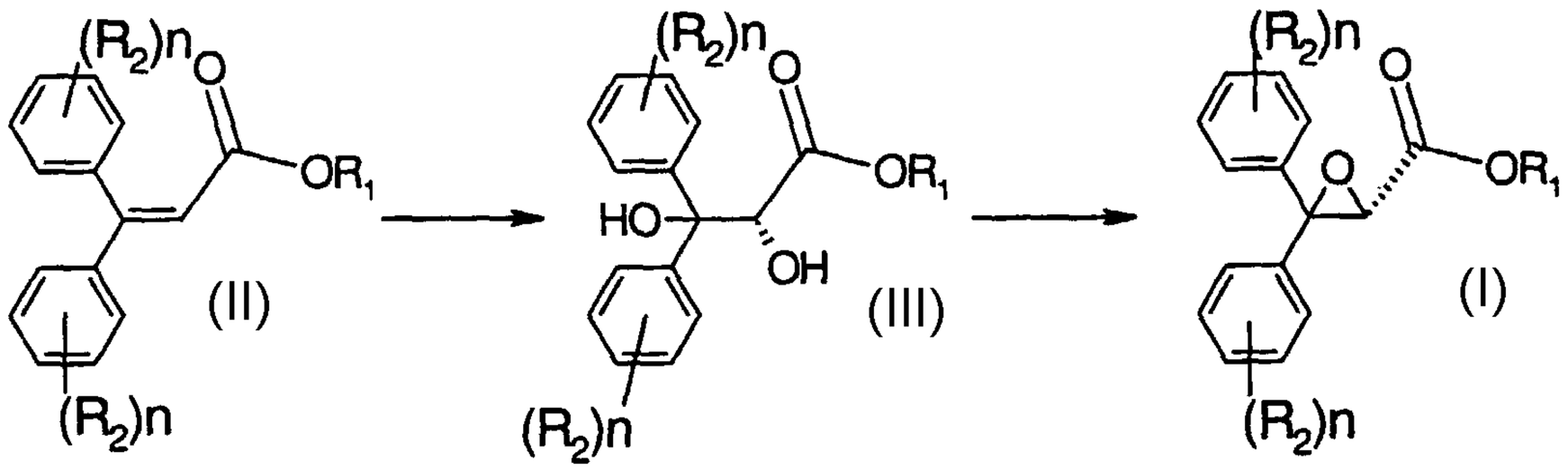
(54) Titre : PROCEDE DE PREPARATION ENANTIOSELECTIVE D'ESTERS D'ACIDE 3,3-DIPHENYL-2,3-EPOXYPROPIONIQUE

(54) Title: METHOD FOR THE ENANTIOSELECTIVE PREPARATION OF 3,3-DIPHENYL-2,3-EPOXY PROPIONIC ACID ESTERS



(57) Abrégé/Abstract:
The invention relates to a method for the enantioselective preparation of the glycide ester (I) by (a) dihydroxylating a corresponding 3-phenyl cinnamic acid ester (II) by osmium (VIII) oxide catalysis in the presence of a Sharpless ligand and an oxidant to give a dihydroxy ester (III), (b) selectively converting the hydroxy function in the 2 position of the dihydroxy ester (III) to a leaving group, (c) intramolecularly substituting the leaving group by the hydroxy function in the 3 position to the glycide ester (I). In formulae (I), (II), and (III), R_1 represents C_1-C_{10} alkyl, aryl or arylalkyl, which can optionally be substituted, and R_2 represents C_1-C_{10} alkyl, aryl, arylalkyl, halogen, C_1-C_{10} alkoxy, acyloxy or amide, which can be optionally substituted, and n is 0 to 5.

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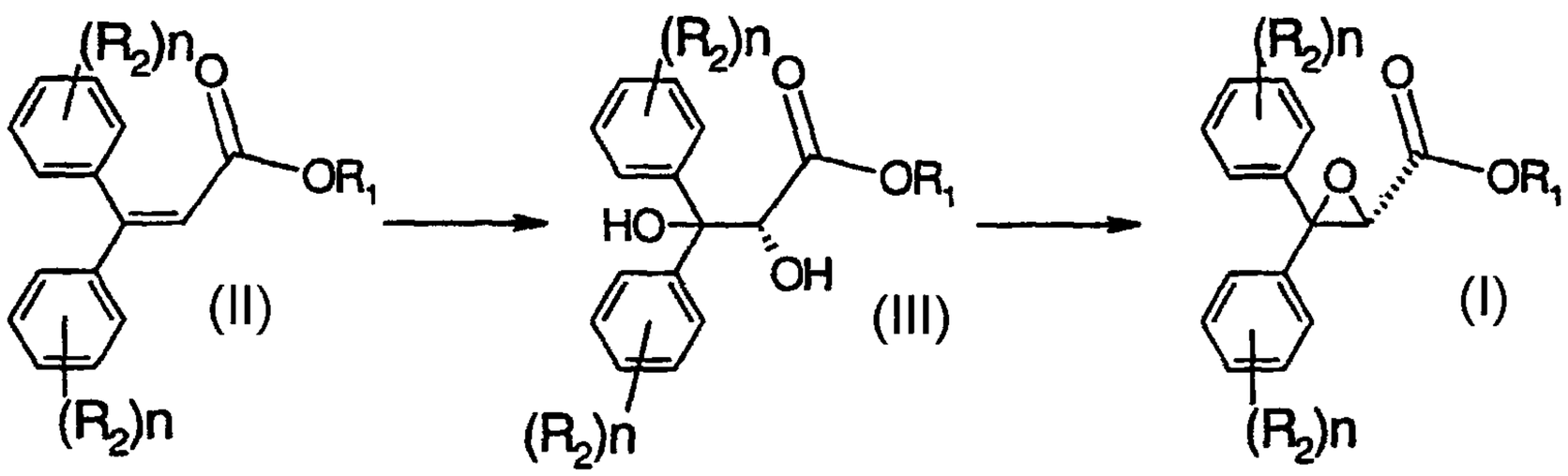
[Fortsetzung auf der nächsten Seite]

(54) Title: METHOD FOR THE ENANTIOSELECTIVE PREPARATION OF 3,3-DIPHENYL-2,3-EPOXY PROPIONIC ACID ESTERS

(54) Bezeichnung: VERFAHREN ZUR ENANTIOSELEKTIVEN HERSTELLUNG VON 3,3-DIPHENYL-2,3-EPOXYPROPIONSÄUREESTERN



(57) Abstract: The invention relates to a method for the enantioselective preparation of the glycide ester (I) by (a) dihydroxylating a corresponding 3-phenyl cinnamic acid ester (II) by osmium (VIII) oxide catalysis in the presence of a Sharpless ligand and an oxidant to give a dihydroxy ester (III), (b) selectively converting the hydroxy function in the 2 position of the dihydroxy ester (III) to a leaving group, (c) intramolecularly substituting the leaving group by the hydroxy function in the 3 position to the glycide ester (I). In formulae (I), (II), and (III), R_1 represents C_1-C_{10} alkyl, aryl or arylalkyl, which can optionally be substituted, and R_2 represents C_1-C_{10} alkyl, aryl, arylalkyl, halogen, C_1-C_{10} alkoxy, acyloxy or amide, which can be optionally substituted, and n is 0 to 5.

(57) Zusammenfassung: Die Erfindung betrifft ein Verfahren zur enantioselektiven Herstellung des Glycidesters (I) durch (a) Dihydroxylierung eines entsprechenden 3-Phenylzimtsäureesters (II) durch Osmium (VIII) oxid-Katalyse in Gegenwart eines Sharpless-Liganden und einem Oxidationsmittel zum Dihydroxyester (III), (b) selektive Überführung der Hydroxyfunktion in 2-Position des Dihydroxyesters (III) in eine Abgangsgruppe, (c) intramolekulare Substitution der Abgangsgruppe durch die Hydroxyfunktion in der 3-Position zum Glycidester (I), (II), (III), wobei R_1 C_1-C_{10}-Alkyl, Aryl oder Arylalkyl, das gegebenenfalls substituiert sein kann, und R_2 C_1-C_{10}-Alkyl, Aryl, arylalkyl, Halogen, C_1-C_{10}-Alkoxy, Acyloxy oder Amid, das gegebenenfalls substituiert sein kann, n 0 bis 5 bedeutet.

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Veröffentlicht:

— *mit internationalem Recherchenbericht*

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

0050/51096

METHOD FOR THE ENANTIOSELECTIVE PREPARATION OF 3,3-DIPHENYL-2,3-EPOXY PROPIONIC ACID ESTERS

Description

The present invention relates to a process for the transformation of 3-phenyl cinnamate to enantiomerically pure 3,3-diphenyl-2,3-epoxy propionate.

3,3-Diphenyl-2,3-epoxy propionates are important intermediate products for the synthesis of biologically active substances, such as are described in, for example, Patent Applications WO 96/11914, WO 97/38981, DE 1963046.3 and DE 19944049.2. Said references describe the production of these active substances via racemic and enantiomerically pure glycide esters. In the racemic process the glycide ester is provided by Darzen´s synthesis of glycide ester. The racemic process suffers from the drawback that in a subsequent stage the undesirable enantiomer must be separated, which gives rise to a loss in total yield.

In said process for the preparation of enantiomerically pure glycide esters, 3-phenyl cinnamates are used as starting materials, which are transformed by Jacobsen epoxidation. This variant has however the drawback that the enantiomeric purities attained are only *ca* 85 % e.e. and clean-up of the products is very elaborate. Thus these known processes are only useful to a limited extent in manufacturing processes intended for use on an industrial scale.

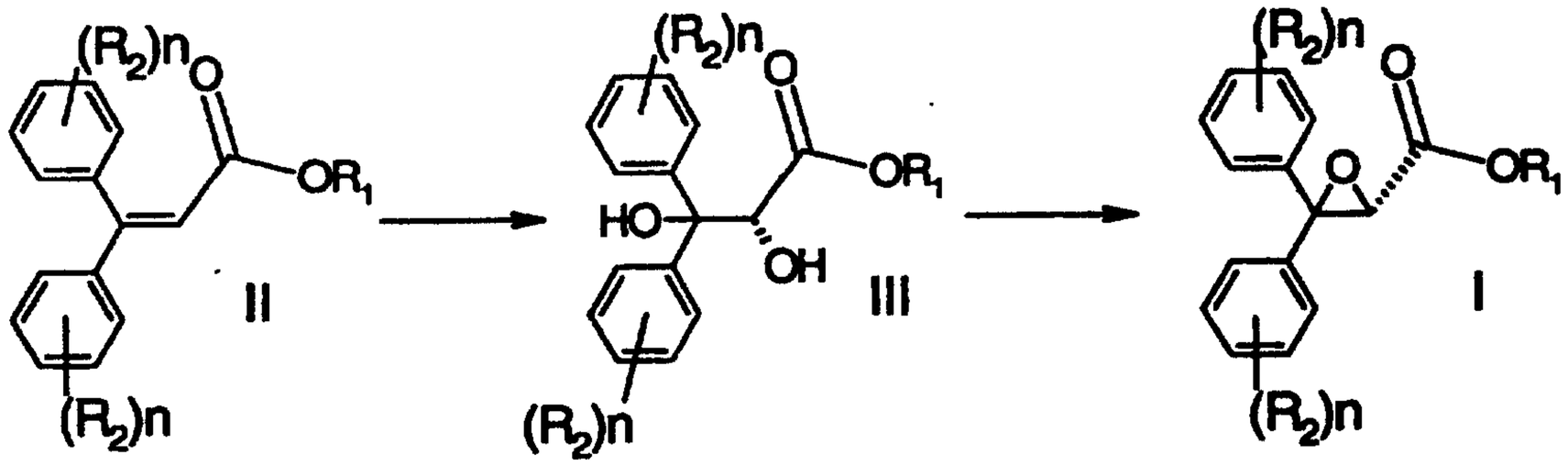
It is thus an object of the present invention to provide a process to the production of 3,3-diphenyl-2,3-epoxy propionate, which guarantees high enantiomeric purity and can be used on an industrial scale.

We have found a process for the enantioselective production of glycide ester by

(a) dihydroxylation of a corresponding 3-phenyl cinnamate (II) by osmium (VIII) oxide catalysis in the presence of a Sharpless ligand and an oxidizing agent to form the dihydroxy ester (III),

(b) selective conversion of the hydroxy function in position 2 of the dihydroxy ester (III) to a leaving group,

(c) intramolecular substitution of the leaving group through the hydroxy function in position 3 to produce the glycide ester (I),



in which

R_1 denotes C_1-C_{10} alkyl, aryl or arylalkyl, which may be substituted,

R_2 denotes C_1-C_{10} alkyl, aryl, arylalkyl, halogen, C_1-C_{10} alkoxy, hydroxy, acyloxy, amide, or amine, which may be substituted,

n is 0 to 5.

The reaction step (a) is an asymmetrical dihydroxylation such as has been described, for example, by Sharpless. Sharpless dihydroxylation and the use thereof have been described in detail by H.C. Kolb, M.S. Van Niewenhze, and K.B. Sharpless, in Chem. Rev. 1994, 94, 2483, the contents of which are included herein by reference. An article by L. Ahrgren and L. Sutin in Organic Process Research & Development 1997, 1, 425-427 has shown that the reaction should basically be executable on a greater scale (upscaleable).

By an osmium (VIII) oxide catalyst is meant an oxygen compound of osmium showing a level of oxidation of + VIII; OsO_4 and $K_2OsO_2(OH)_4$ are preferred.

The osmium (VIII) oxide need not be used in a stoichiometric amount relatively to the substrate of formula (II) but can, as catalyst, be employed in very much smaller

quantities, the spent catalyst being regenerated by an oxidizing agent.

The osmium (VIII) oxide catalyst is usually used in amounts of from 0.1 to 5 mol % and preferably from 0.1 to 2.5 mol %, based on the substrate of formula (II).

By Sharpless ligands are meant compounds which are chiral, possess a nitrogen-containing six-membered heterocycle, bind to OsO_4, and accelerate OsO_4-dependent dihydroxylation.

Such Sharpless ligands are preferably hydroquinine and hydroquinidine derivatives as disclosed, for example, in the above literature. Preference is given to hydroquinine-(1,4-phthalazine-diyl diether) (DHQ)2PHAL or hydroquinidine-(1,4-phthalazine-diyl diether) (DHQD)2PHAL or hydroquinine-(2,5-diphenyl-4,6-pyrimidine-diyl diether) (DHQ)2PYR or hydroquinidine-(2,5-diphenyl-4,6-pyrimidine-diyl diether) (DHQD)2PYR.

The choice of Sharpless ligand is naturally governed by the desired enantiomer (III). Depending on the side from which the attack by (II) on the double bond to be hydroxylated is to take place, a corresponding Sharpless ligand must be selected according to the known mechanistic rules of Sharpless.

Suitable oxidizing agents for step (a) are those materials which are capable of reconverting the osmium oxide reduced during dihydroxylation of the double bond to its active level of oxidation of + VIII, *ie* materials which permit reactivation of the dihydroxylation catalyst. Such oxidizing agents can be readily found by considering their electrochemical potential. Well suited oxidizing agents are, for example, oxygen, hydrogen peroxide, *N*-methylmorpholine-*N*-oxide (NMO), potassium hexacyanoferrate, the AD-mix described by Sharpless (J. Org. Chem., 1992, 57, 2768), or alternatively electochemical processes.

Further oxidizing agents are described, for example, by M. Schröder, Chem. Rev. 1980, 80, 187-213.

The oxidizing agents used are preferably oxygen, hydrogen peroxide,

N–methylmorpholine-*N*-oxide, potassium hexacyanoferrate, and electrochemical processes.

A particularly suitable mixture for use in an industrial reaction according to (a) has been found to be a mixture of from 0.1 to 1.5 mol % of $K_2OsO_2(OH)_4$, from 0.1 to 3 mol % of hydroquinine-(1,4-phthalazine-diyl diether) (DHQ)2PHAL or hydroquinidine-(1,4-phthalazine-diyl diether) (DHQD)2PHAL or hydroquinine-(2,5-diphenyl-4,6-pyrimidine-diyl diether) (DHQ)2PYR or hydroquinidine-(2,5-diphenyl-4,6-pyrimidine-diyl diether) (DHQD)2PYR and from 100 to 300 mol % of NMO, always based on the amount of 3-phenyl cinnamate (II).

Suitable solvents used are mixtures of water with an organic solvent.

Particularly suitable mixtures have been found to be mixtures of water with alcohols, acetonitrile, and acetone in a ratio of from 0.1 to 5:1 w/w.

The reaction temperature is in the range of -20 °C to 100 °C, temperatures below 75 °C being preferred.

In order to transform the diol to an epoxide, there are added to the diol from 1 to 10 equivalents of a base and from 1 to 3 equivalents of a sulfonyl chloride, an azodioic derivative, or a carbodiimide. In particular, preferred bases are tertiary amines, and sulfonyl chlorides are preferred for generation of a leaving group.

To introduce the leaving group in reaction step (b) use is preferably made of sulfonyl chlorides such as methanesulfonyl chloride and toluenesulfonyl chloride.

The reaction can be carried out as a one-pot process without isolation of an intermediate stage or as a two-stage process with isolation of the precursor of the epoxide. A preferred embodiment is the one-pot process.

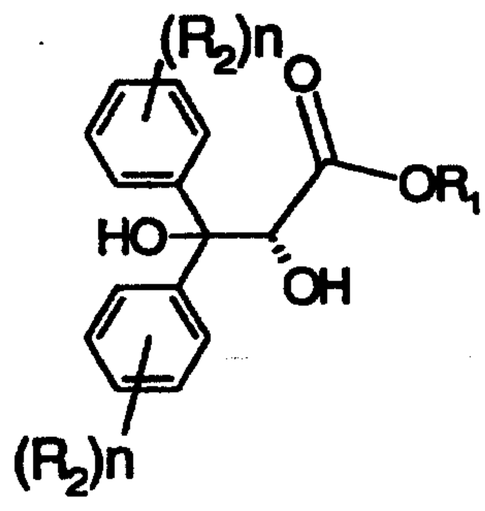
Solvents for (b) or (c) are preferably aprotic solvents of medium polarity such as toluene or dichloromethane.

The reaction takes place at temperatures ranging from -70 °C to 100 °C. Preference is given to reaction temperatures between -10 °C and 35 °C.

The production of the corresponding 3-phenyl cinnamates (II) is known to the person skilled in the art from standard works of organic literature.

The conversion of 1,2-diols to epoxides is well-known and is described, for example, in the textbook by J. March, Advanced Organic Chemistry, 1985, Wiley, pages 270 and 345.

The invention also relates to the enantiomerically pure dihydroxy esters (III) obtained in the aforementioned process and forming valuable intermediate products for pharmaceutically active substances:



III

in which

R_1 denotres C_1-C_{10} alkyl, aryl, or arylalkyl, particularly alkyl or benzyl,

R_2 denotes C_1-C_{10} alkyl, aryl, arylalkyl, halogen, C_1-C_{10} alkoxy, acyloxy or amide, and

n is 0 to 5, particularly 0.

The invention is illustrated below with reference to the following examples.

General working instructions:

1.) Synthesis of 2,3-dihydroxy-3,3-diphenyl propionate

a) AD-mix variant:

In a flask there were placed 27.2 g of AD mix alpha, and 100 mL of water were added, 80 mL of 2-methylpropan-2-ol were added, and to this mixture there were added 5.6 g of *tert*-butyl 3-phenyl cinnamate dissolved in 20 mL of *tert*-butanol. The reaction was complete after 3 days at room temperature. To the two-phase system there were added 30 g of sodium sulfite dissolved in water and the mixture was stirred for half an hour. The organic phase was separated and the aqueous phase extracted with dichloromethane, and the combined organic phases were rewashed with water. The mixture was then dried over magnesium sulfate and the solvent removed by distillation. 4.8 g of a flocculent solid were isolated (HPLC purity 95 %, the incorrect enantiomer was not considered).

b) *N*-methylmorpholine-*N*-oxide variant (slow addition of substrate):

In a flask there were placed 250 mg of $K_2OsO_2(OH)_4$, 750 mg of hydroquinidine-1,4-phthalazine-diy-ethyl ether and 30 mL of 50 % strength *N*-methylmorpholine-*N*-oxide solution in 120 mL of *tert*-BuOH, and 90 mL of water, and the mixture was stirred until all was dissolved. 24 g of ethyl 3-phenylcinnamate were topped up with *tert*-butanol to a volume of 48 mL and passed directly into the solution at a rate of 1 mL/h. After *ca* 1 hour the solution changed color from violet to yellow, and after three hours solid matter began to precipitate. Following a period of 28 hours a solid paste had formed, and following a period of 50 hours a sodium sulfite solution was added thereto and the mixture was stirred for a period of 30 minutes. Dichloromethane and 1N HCl were then added, and the organic phase was separated and the solvent removed by distillation. The crude product was recrystallized from heptane and there were isolated 17 g of product as a white flocculate (98 % purity, 61 % yield).

c) *N*-methylmorpholine-*N*-oxide variant (direct addition of substrate):

In a flask there were placed 30 mg of $K_2OsO_2(OH)_4$, 95 mg the (DHQ)2PHAL and 4.2 mL of 50 % strength *N*-methylmorpholine-*N*-oxide solution in 90 mL of isopropanol and 30 mL of water, and the mixture was stirred over a period of 2 hours. To the solution there were added 10 g of ethyl 3-phenylcinnamate, and the mixture was stirred for 48 hours at 0 °C. Workup was effected by adding sodium sulfite solution and stirring over a period of 30 minutes. 50 mL of dichloromethane and 50 mL 1N HCl were then added, and the organic phase was separated and the solvent removed by distillation. The crude product was recrystallized from MTB/heptane and there were isolated 7 g of product as a white flocculate.

R-ethyl 2,3-dihydroxy-3,3-diphenylpropionate [alpha] 20 = -149 (methanol, c = 1.589 nm).

2.) Formation of the glycide ester

Ethyl 2,3-dihydroxy-3,3-diphenylpropionate (12.4 g, 43 mmol) was used as initial batch in 260 mL of CH_2Cl_2 and, at 0 °C, first triethylamine (17.5 g, 101 mmol) and then methanesulfonyl chloride (10 g, 86 mmol) were added. The solution was stirred over a period of 48 hours at room temperature. Workup was effected by washing the methylene chloride phase with 100 mL of 1N HCl and an $NaHCO_3$ solution. Following azeotropic distillation of residues of water with dichloromethane the glycide ester can be caused to react further in solution. In order to determine the yield, the solvent was removed by distillation and there were isolated 13 g of an oil, which had a purity of 94 % as determined by HPLC.

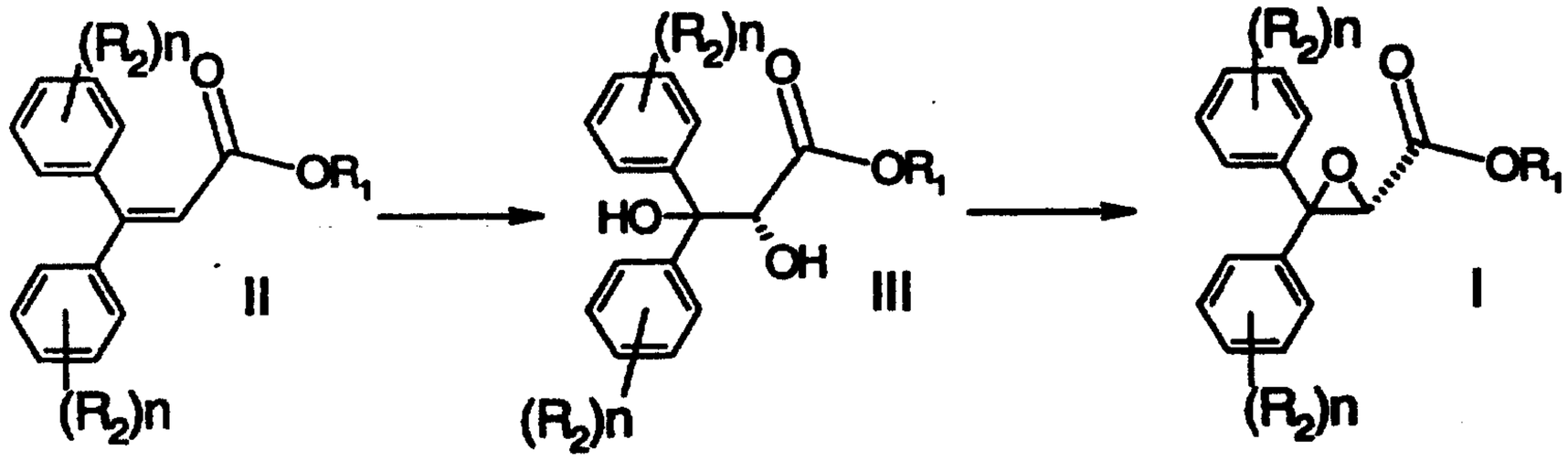
Patent Claims

1. A process for enantioselective production of glycide ester (I) by

(a) dihydroxylation of a corresponding 3-phenyl cinnamate (II) by osmium (VIII) oxide catalysis in the presence of a Sharpless ligand and an oxidizing agent to form the dihydroxy ester (III),

(b) selective conversion of the hydroxy function in the 2 position of the dihydroxy ester (III) to a leaving group,

(c) intramolecular substitution of the leaving group through the hydroxy function in the 3 position to form the glycide ester (I),



in which

R_1 denotes C_1-C_{10} alkyl, aryl, or arylalkyl, which may be substituted,

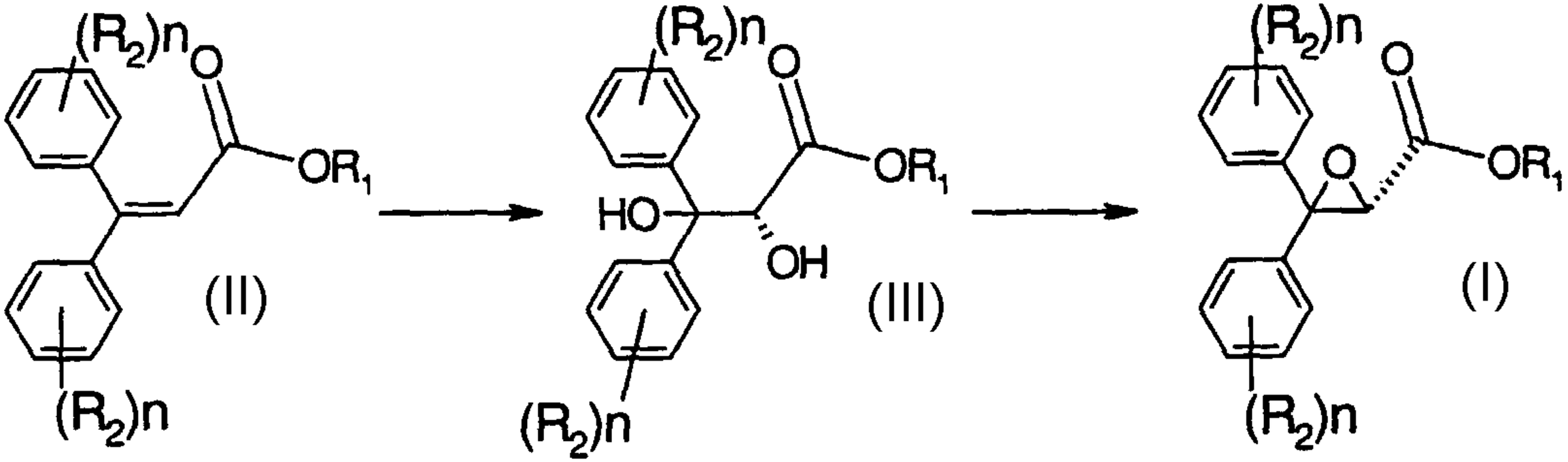
R_2 denotes C_1-C_{10} alkyl, aryl, arylalkyl, halogen, C_1-C_{10} alkoxy, acyloxy, or amide, which may be substituted, and

n is 0 to 5.

2. A process as defined in claim 1, wherein the transformation of dihydroxy ester (III) to glycide ester (I) is carried out in a one-pot process without isolation of the intermediate stage.

3. A process as defined in claim 1, wherein the compound (III) used is a cinnamic derivative in which R^1 denotes alkyl or benzyl, and R^2 denotes H.

4. An enantiomerically pure dihydroxy ester of formula (III), in which R_1 denotes C_1-C_{10} alkyl or benzyl and n is 0.


(R2)n
O
OR1
(II)
(R2)n
HO
OH
(III)
(I)