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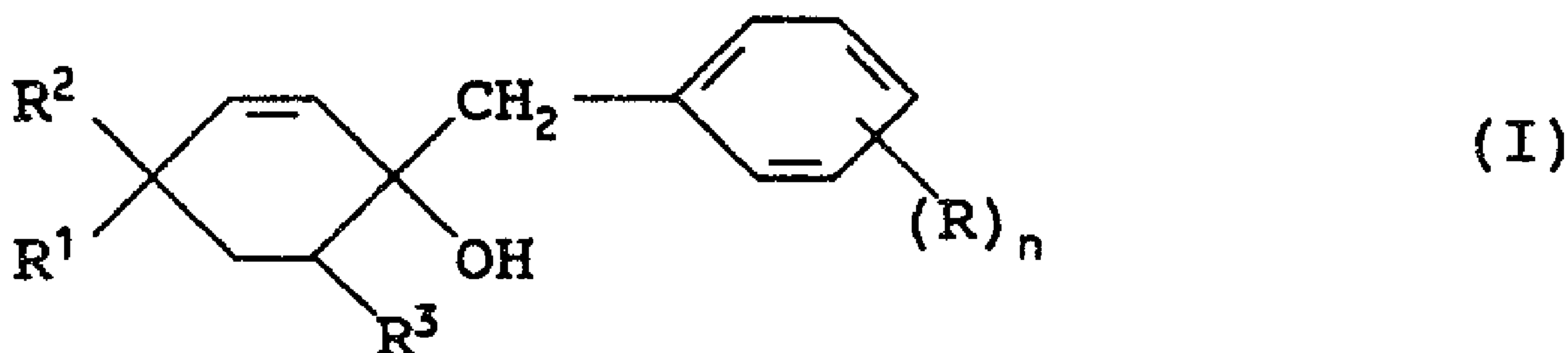
(72) Inventeur/Inventor:
Briner, Paul H., GB

(73) Propriétaire/Owner:
SHELL INTERNATIONALE RESEARCH
MAATSCHAPPIJ B.V., NL

(74) Agent: SWABEY OGILVY RENAULT

(54) Titre : DERIVES DE CYCLOHEXENOL

(54) Title: CYCLOHEXENOL DERIVATIVES



(57) Abrégé/Abstract:

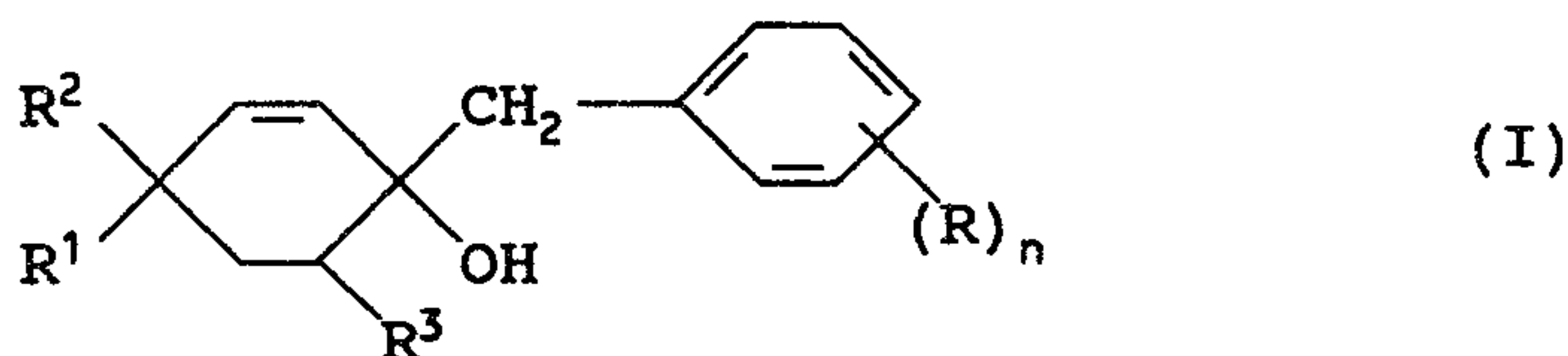
The invention provides cyclohexenol derivatives of the general formula (see formula I) in which n represents an integer from 0 to 5: each R represents a halogen atom, nitro, cyano, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylamido, cycloalkyl or phenyl group; and R¹, R² and R³ independently represent a hydrogen atom or an alkyl group, with the provisos that when R¹, R² and R³ all represent a hydrogen atom then n is not 0 and, when R¹, R² and R³ all represent a hydrogen atom and n is 1, R does not represent a fluorine atom substituted at the 4-position of the phenyl ring; and a process for their preparation. Compounds of formula I are useful as intermediates in the preparation of certain fungicidally active cyclopentane derivatives.



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ABSTRACT
CYCLOHEXENOL DERIVATIVES

The invention provides cyclohexenol derivatives of the general formula



in which n represents an integer from 0 to 5; each R
5 represents a halogen atom, nitro, cyano, hydroxyl,
alkyl, haloalkyl, alkoxy, haloalkoxy, amino,
alkylamino, dialkylamino, alkoxycarbonyl, carboxyl,
alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl,
carbamoyl, alkylamido, cycloalkyl or phenyl group; and
10 R¹, R² and R³ independently represent a hydrogen atom
or an alkyl group, with the provisos that when R¹, R²
and R³ all represent a hydrogen atom then n is not 0
and, when R¹, R² and R³ all represent a hydrogen atom
and n is 1, R does not represent a fluorine atom
15 substituted at the 4-position of the phenyl ring;
and a process for their preparation. Compounds of
formula I are useful as intermediates in the
preparation of certain fungicidally active
cyclopentane derivatives.

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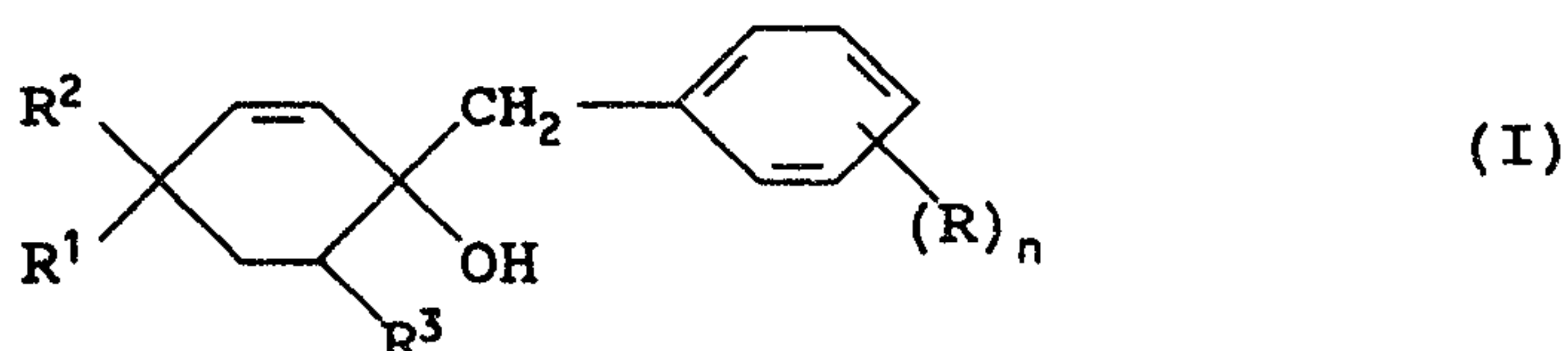
CYCLOHEXENOL DERIVATIVES

This invention relates to certain cyclohexenol derivatives, which are useful as intermediates in the preparation of fungicidally active cyclopentane derivatives, and a process for their preparation.

5 Tetrahedron Letters, 26, No. 8, pp 1093-1096, (1985) discloses 1-benzylcyclohex-2-en-1-ol and 1-(4-fluorobenzyl)cyclohex-2-en-1-ol.

10 It has now been discovered that certain cyclohexenol derivatives are useful as intermediates in a highly stereospecific route to certain fungicidally active cyclopentane derivatives.

According to the present invention there is therefore provided a compound of the general formula



15 in which n represents an integer from 0 to 5; each R represents a halogen atom, nitro, cyano, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl,

carbamoyl, alkylamido, cycloalkyl or phenyl group; and R^1 , R^2 and R^3 independently represent a hydrogen atom or an alkyl group; with the provisos that when R^1 , R^2 and R^3 all represent a hydrogen atom then n is not 0 and, when R^1 , R^2 and R^3 all represent a hydrogen atom and n is 1, R does not represent a fluorine atom substituted at the 4- position of the phenyl ring.

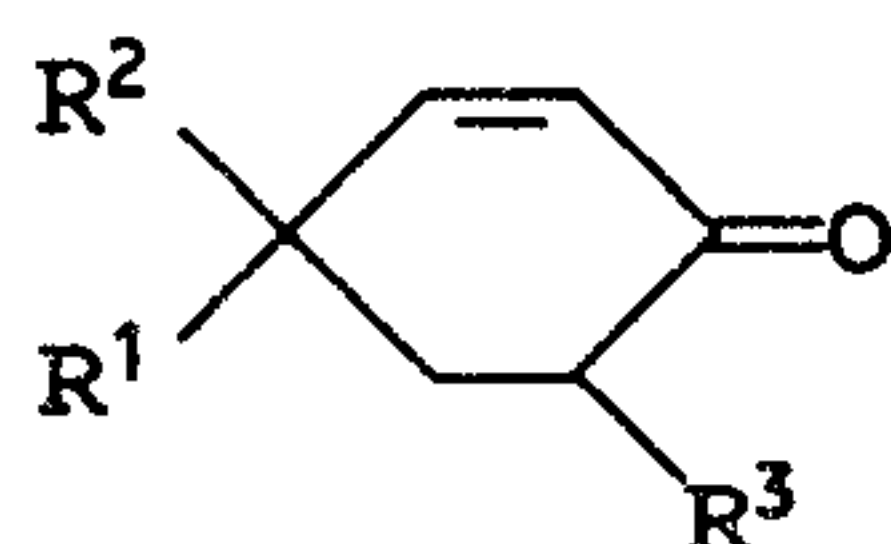
When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, and especially up to 4, carbon atoms. A cycloalkyl substituent group may contain 3 to 8, preferably 3 to 6, carbon atoms.

It is preferred that R^1 , R^2 and R^3 independently represent a hydrogen atom or a C_{1-4} alkyl, particularly a methyl, group.

Preferably, R represents a halogen, especially a chlorine atom.

A particularly preferred sub-group of compounds of formula I is that in which n is 1, R represents a chlorine atom, preferably substituted at the 4- position of the phenyl ring, R^1 and R^2 both represent a hydrogen atom or both represent a methyl group and R^3 represents a hydrogen atom or methyl group.

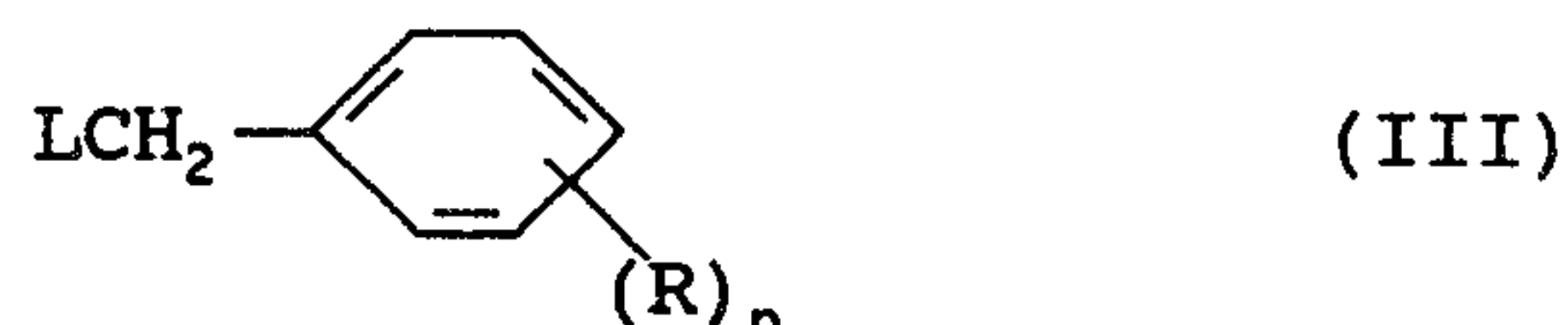
The present invention also provides a process for the preparation of a compound of formula I as defined above which comprises reacting a compound of the general formula



(II)

- 3 -

in which R^1 , R^2 and R^3 are as defined above, with a compound of the general formula



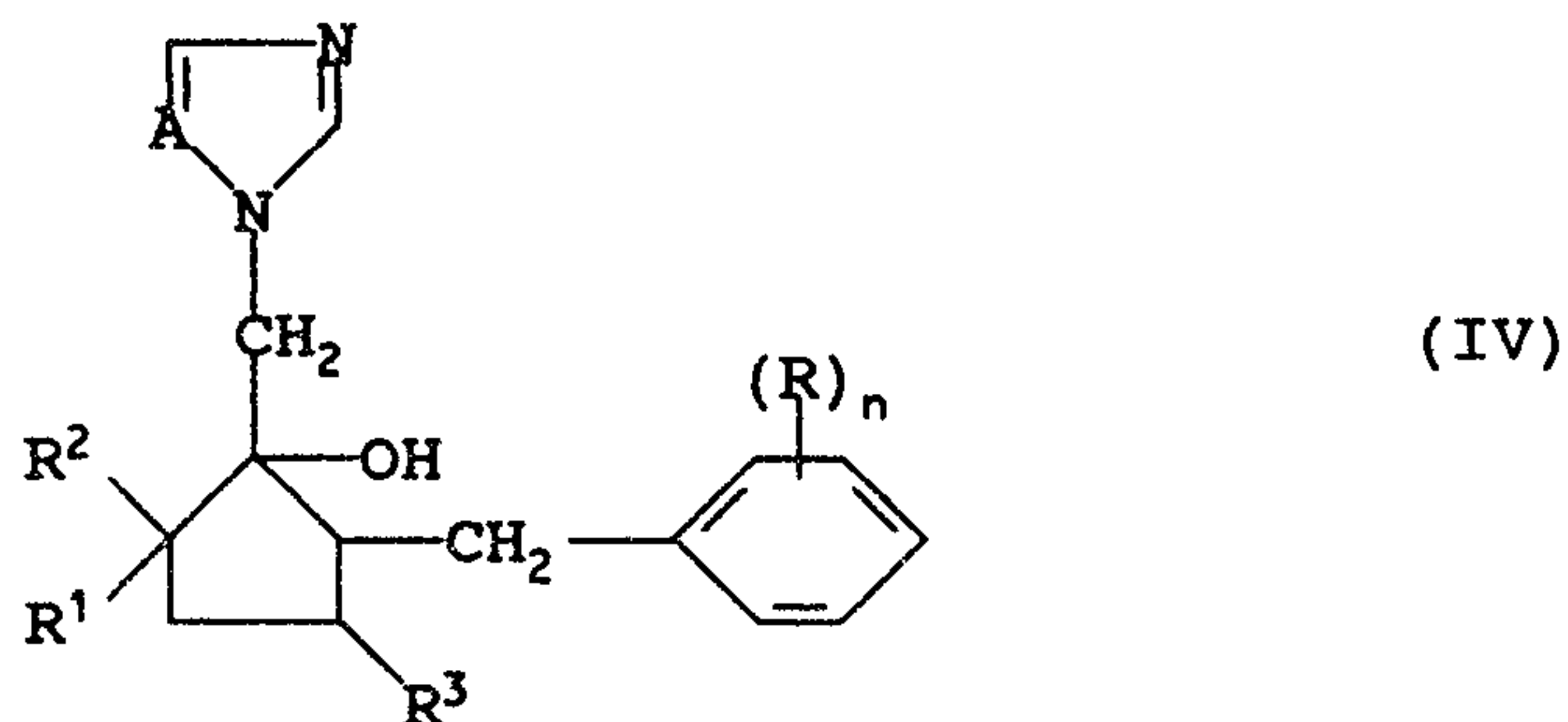
in which R and n are as defined above and L represents an organometallic group. Suitable organometallic groups include lithium and the group $-MgHal$ where Hal represents a chlorine or bromine atom.

The process is conveniently carried out in the presence of a solvent. Suitable solvents include ethers, such as diethyl ether and methyl t-butyl ether.

The reaction is suitably carried out at a temperature in the range from $0^{\circ}C$ to the reflux temperature of the solvent, if present.

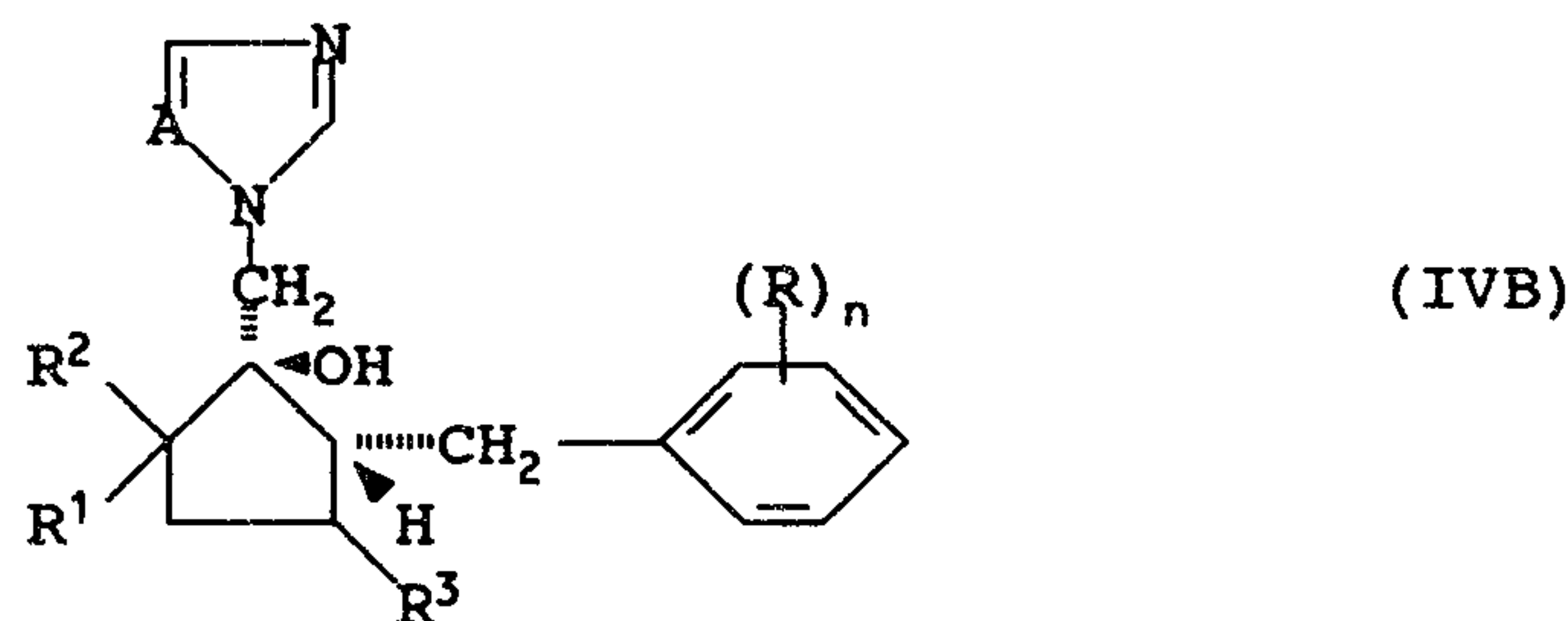
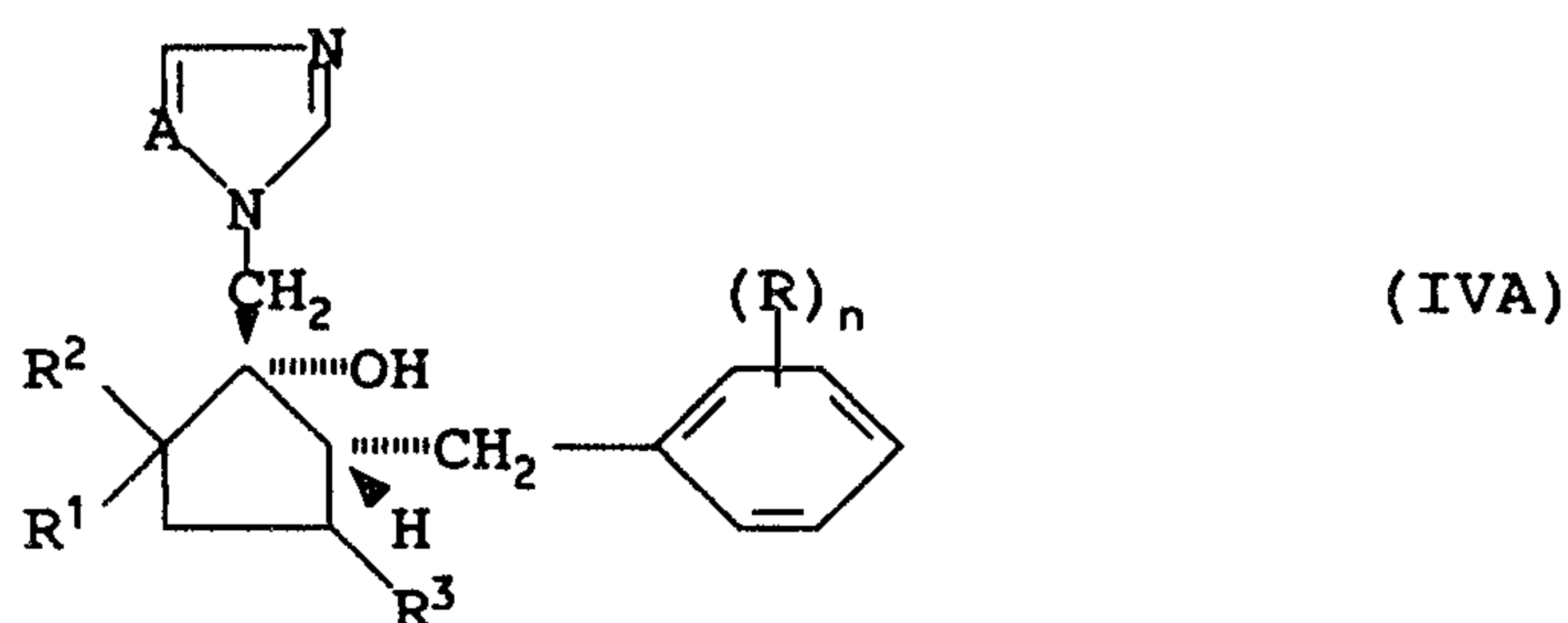
Compounds of formula II and III are known compounds or can be prepared by processes analogous to known processes.

The compounds of formula I are useful as intermediates in the preparation of fungicidally active cyclopentane derivatives of the general formula



in which n , R , R^1 , R^2 and R^3 are as defined above and A represents a nitrogen atom or a CH group. Certain compounds of formula IV are the subject of co-pending patent applications GB-A1-2180236 and EP-A2-0267778.

5 The compounds disclosed in EP-A2-0267778 and GB-A1-2180236 exist in two stereoisomeric forms which have the following structures:-

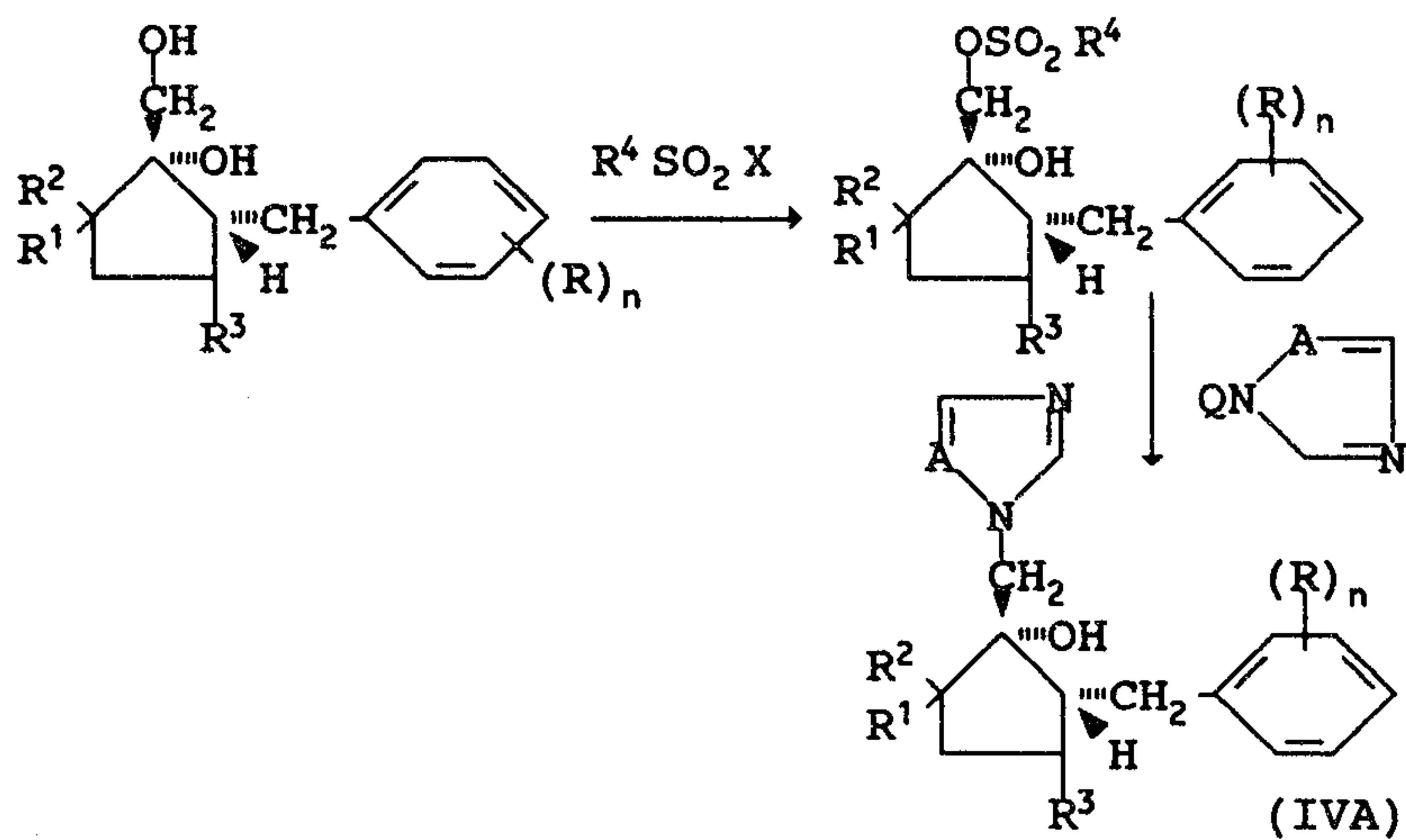
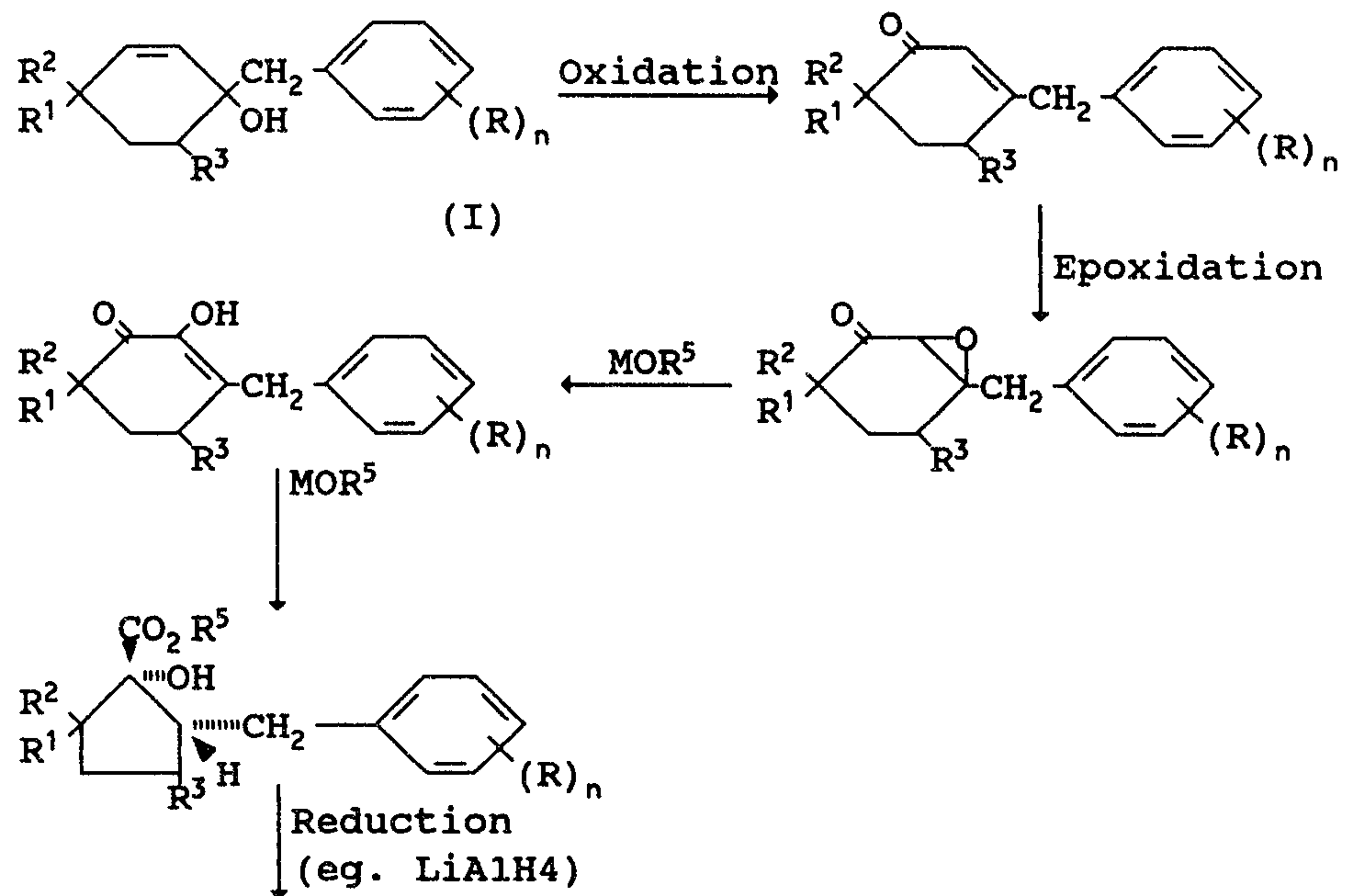


10 The letters A and B will be used hereinafter to denote compounds having the same stereochemical configuration as isomers A and B above.

Isomers A and B can be separated by, for instance, chromatography and exhibit different fungicidal activity. Generally, isomers of formula IVA exhibit greater fungicidal activity than isomers of formula IVB. The process used to synthesise compounds of formula IVA from compounds of formula I

15

is set out in the following reaction scheme:-



- 6 -

In the above reaction scheme, n, R, R¹, R², R³ and A are as previously defined, R⁴ represents an optionally substituted alkyl or aryl group, preferably a C₁₋₄ alkyl or a phenyl group each optionally substituted by one or more substituents selected from halogen atoms, nitro, cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, amino, C₁₋₄ alkylamino, di-C₁₋₄ alkylamino, C₁₋₄ alkoxycarbonyl, carboxyl, C₁₋₄ alkanoyl, C₁₋₄ alkylthio, C₁₋₄ alkylsulphinyl, C₁₋₄ alkylsulphonyl, carbamoyl, C₁₋₄ alkylamido, C₃₋₈ cycloalkyl and phenyl groups, R⁵ represents a hydrogen atom or an alkyl, preferably C₁₋₆ alkyl, or cycloalkyl group, X represents a halogen, preferably a chlorine or bromine, atom, M represents an alkali metal, preferably a sodium or potassium, atom and Q represents a hydrogen or alkali metal, preferably sodium or potassium, atom.

The invention is further illustrated by the following Examples.

Example 1

Preparation of 1-(4-chlorobenzyl)-4,4-

dimethylcyclohex-2-en-1-ol

(n=1, R=4-Cl, R¹=R²=CH₃, R³=H)

A solution of 4-chlorobenzyl chloride (266g, 1.65mol) in diethyl ether (200ml) was added slowly to a stirred mixture of magnesium (42g, 1.73mol) in diethyl ether (700ml) to maintain the mixture at

reflux. The mixture was warmed for a further 20 minutes after addition was complete. A solution of 4,4-dimethylcyclohex-2-en-1-one (226g, 1.82 mol) in diethyl ether (60ml) was then added dropwise over a period of 30 minutes so as to maintain the mixture at reflux and the mixture stirred overnight. The mixture was then quenched with water (250ml) and hydrochloric acid (5M, 500ml), extracted with diethyl ether (3x400ml), backwashed once with sodium bicarbonate solution (5%w/v) and once with water and then dried with anhydrous magnesium sulphate. The solvent was then flashed off to give 369g 1-(4-chlorobenzyl)-4,4-dimethylcyclohex-2-en-1-ol as an oil.

NMR (in CDCl_3 solvent, tetramethylsilane as reference)
Characteristic peaks at:-

δ (ppm) 0.90, 0.99 (3H, singlet), 2.78 (2H, singlet), 5.40 (1H, doublet, $J=11\text{Hz}$), 5.50 (1H, doublet, $J=11\text{Hz}$), 7.17 (2H, doublet, $J=8\text{Hz}$), 7.26 (2H, doublet, $J=8\text{Hz}$).

Example 2

Preparation of 1-(4-chlorobenzyl)-4,4,6-trimethylcyclohex-2-en-1-ol ($n=1$, $R=4\text{-Cl}$, $R^1=R^2=R^3=\text{CH}_3$)

To a slurry of magnesium turnings (66g, 2.73 g.atoms) in diethyl ether (300ml) was added a solution of 4-chlorobenzyl chloride (418g, 2.6 moles) in diethyl ether (1500ml) at such a rate as to maintain gentle reflux. After a further 30 minutes, a solution of 4,4,6-trimethylcyclohex-2-en-1-one (340g, 2.46 moles) in diethyl ether (350ml) was added, again maintaining a gentle reflux. After 1 hour the mixture was added into saturated aqueous ammonium chloride (4 litres) and the phases separated. The ether phase was back-washed with water (1 litre) and used directly in

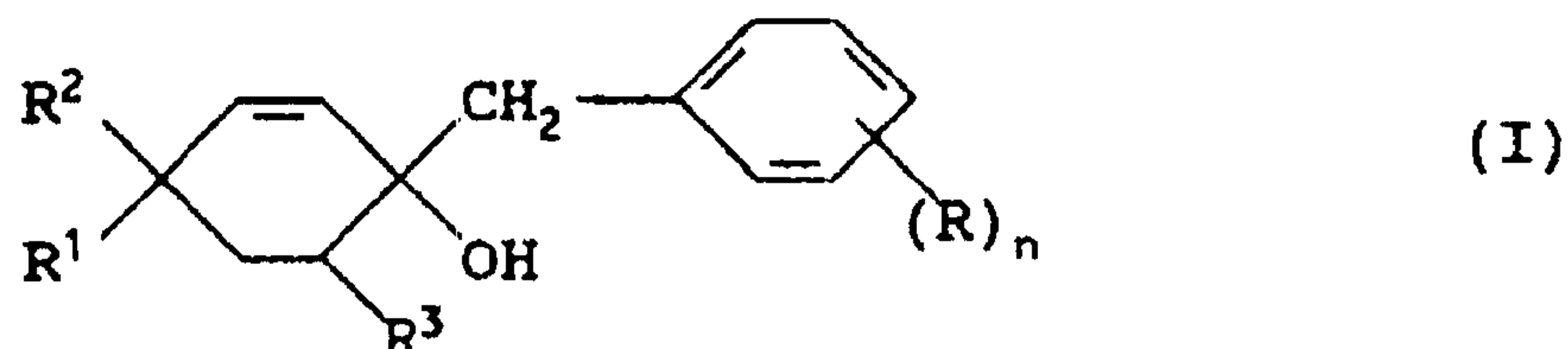
the next reaction. A small portion of
1-(4-chlorobenzyl)-4,4,6-trimethylcyclohex-2-en-1-ol
was isolated for characterisation (gas chromatography
analysis showed two isomers in approximately equal
amounts).

NMR (in CDCl_3 solvent, tetramethylsilane as
reference). Characteristics peak at:-

δ (ppm) 0.75, 0.95, 1.00, 1.02, 1.05, 1.07,
1.09 (total 9H), 2.00 (1H, multiplet),
2.57, 2.79 (2H, AB, $J=12\text{Hz}$), 2.69, 2.94
(2H, AB, $J=12\text{Hz}$), 4.94 (1H, doublet,
 $J=10\text{Hz}$), 5.34 (1H, doublet, $J=10\text{Hz}$),
7.1-7.4 (4H).

CLAIMS

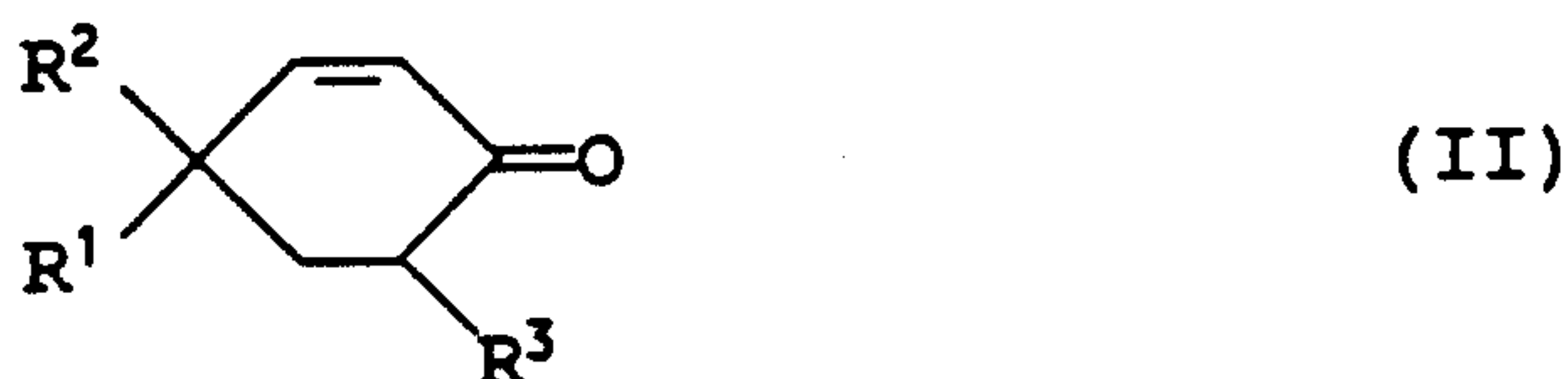
1. A compound of the general formula



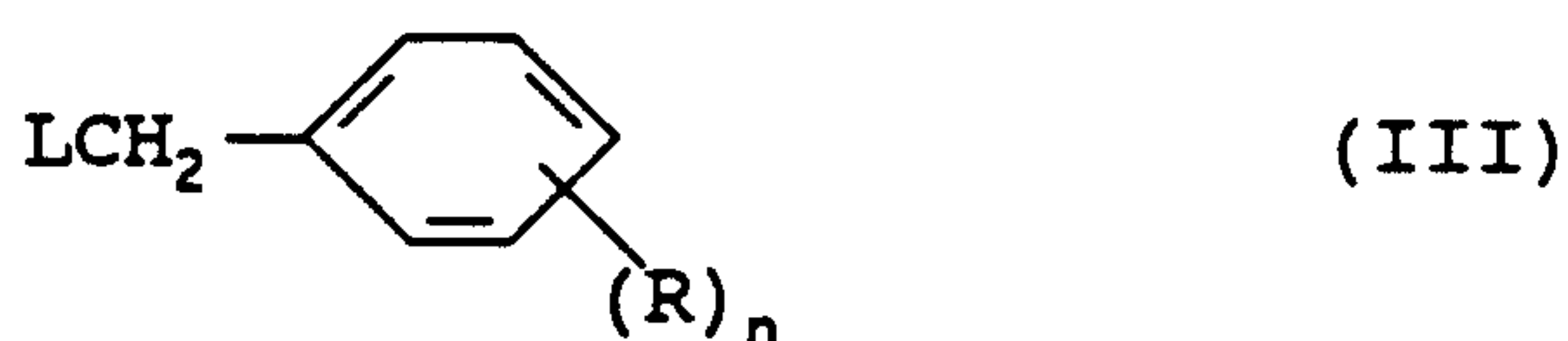
in which n represents an integer from 0 to 5; each R represents a halogen atom, nitro, cyano, hydroxyl, C_1 - C_{12} alkyl, C_1 - C_{12} haloalkyl, C_1 - C_{12} alkoxy, C_1 - C_{12} haloalkoxy, amino, C_1 - C_{12} alkylamino, di- C_1 - C_{12} alkylamino, C_1 - C_{12} alkoxycarbonyl, carboxyl, C_1 - C_{12} alkancyl, C_1 - C_{12} alkylthio, C_1 - C_{12} alkylsulphanyl, C_1 - C_{12} alkylsulphonyl, carbamoyl, C_1 - C_{12} alkylamido, C_3 - C_8 cycloalkyl or phenyl group; and R^1 , R^2 and R^3 independently represent a hydrogen atom or an alkyl group; with the provisos that when R^1 , R^2 and R^3 all represent a hydrogen atom then n is not 0 and, when R^1 , R^2 and R^3 all represent a hydrogen atom and n is 1, R does not represent a fluorine atom substituted at the 4-position of the phenyl ring.

2. A compound according to claim 1 in which R^1 , R^2 and R^3 independently represent a hydrogen atom or a C_{1-4} alkyl group.

3. A compound according to claim 1 or 2, in which R^1 , R^2 and R^3 independently represent a hydrogen atom or a methyl group.
4. A compound according to any one of claims 1 to 3, in which R represents a halogen atom.
5. A compound according to claim 1, 2, 3 or 4, in which n is 1, R represents a chlorine atom, R^1 and R^2 both represent a hydrogen atom or both represent a methyl group and R^3 represents a hydrogen atom or a methyl group.
6. A process for the preparation of a compound of formula I, as defined in any one of claims 1 to 5, which comprises reacting a compound of the general formula:

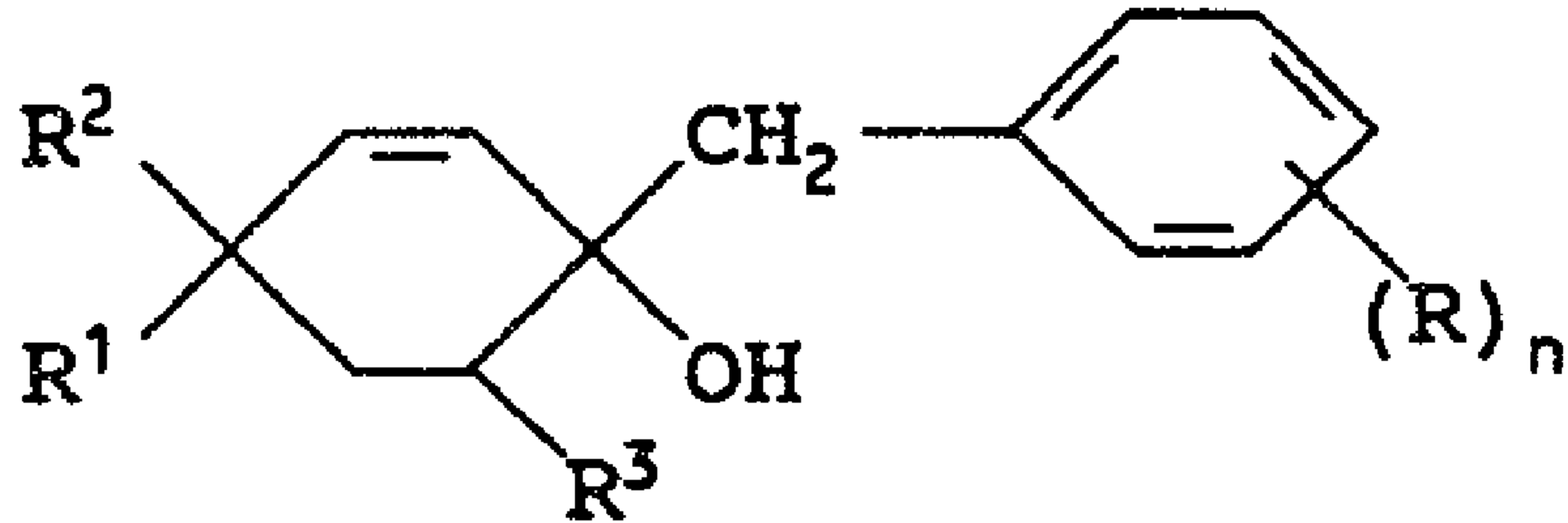


in which R^1 , R^2 and R^3 are as defined in claim 1, with a compound of the general formula:



in which R and n are as defined in claim 1 and L represents an organometallic group.

7. A process according to claim 6, in which the organometallic group L is a group $-MgHal$ where Hal represents a chlorine or bromine atom.
8. 1-(4-Chlorobenzyl)-4,4-dimethylcyclohex-2-en-1-ol.
9. 1-(4-Chlorobenzyl)-4,4,6-trimethylcyclohex-2-en-1-ol.



(I)