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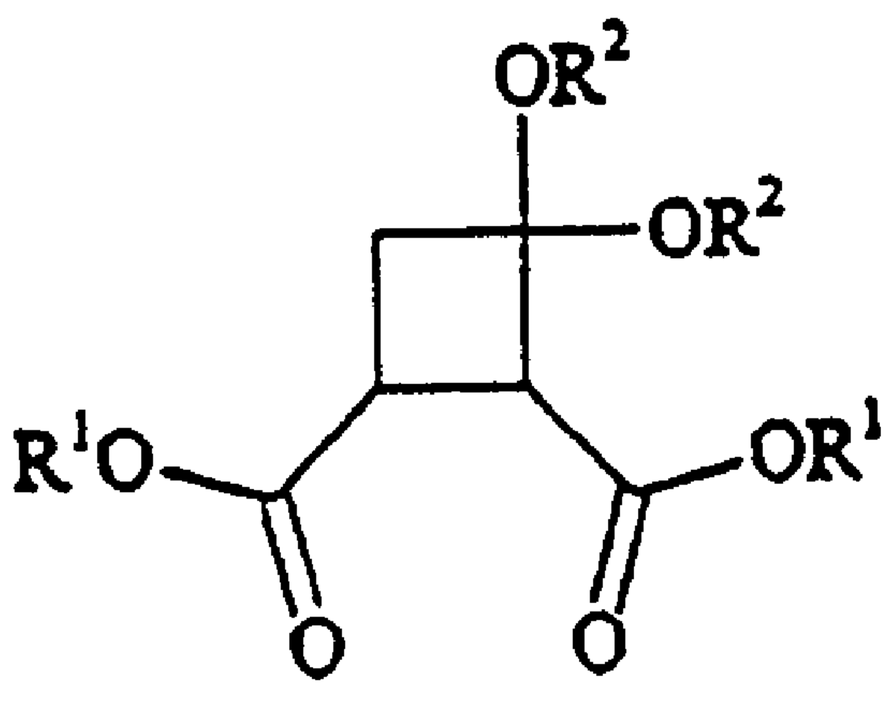
(54) Titre : METHODE POUR PREPARER DES ESTERS D'ACIDE CYCLOBUTANE-1,2-DICARBOXYLIQUE
(54) Title: PROCESS FOR PREPARING CYCLOBUTANE-1,2-DICARBOXYLIC ESTERS



(I)

(57) Abrégé/Abstract:
Cyclobutane-1,2-dicarboxylic esters of the formula: (see formula I) in which R^1 is a C_{1-8}-alkyl group, an optionally substituted mono- or bicyclic cycloaliphatic group having 3 to 10 ring carbon atoms, an optionally substituted aryl or arylalkyl group or an optionally substituted saturated heterocyclic group and R^2 is either C_{1-4}-alkyl or both radicals R^2 together form a group of the formula $-(CH_2)_n-$ (n = 2 to 4), are prepared from the corresponding maleic or fumaric ester and ketene acetal in the presence of a Lewis acid and a sterically hindered base. The reaction is stereoselective when an optically active maleic or fumaric ester is employed. The cyclobutane-1,2-dicarboxylic esters (I), in particular those having trans configuration, are intermediates in the synthesis of pharmaceutically active compounds.

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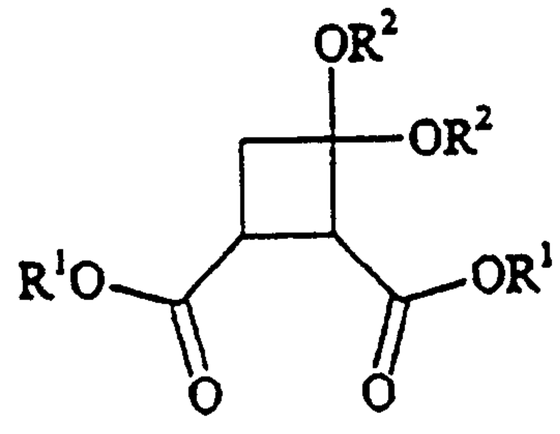
Abstract

Cyclobutane-1,2-dicarboxylic esters of the formula:



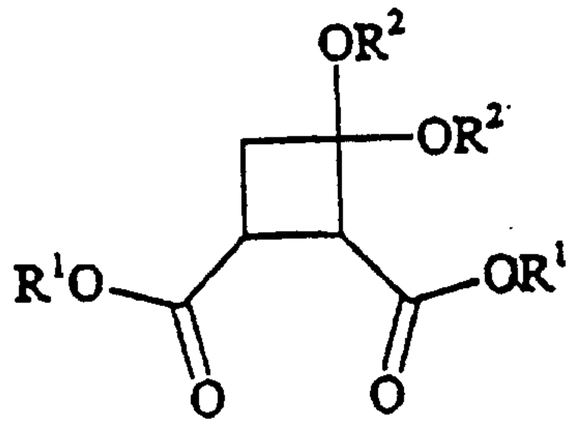
(I)

in which R^1 is a C_{1-8}-alkyl group, an optionally substituted mono- or bicyclic cycloaliphatic group having 3 to 10 ring carbon atoms, an optionally substituted aryl or arylalkyl group or an optionally substituted saturated heterocyclic group and R^2 is either C_{1-4}-alkyl or both radicals R^2 together form a group of the formula $-(CH_2)_n-$ (n = 2 to 4), are prepared from the corresponding maleic or fumaric ester and ketene acetal in the presence of a Lewis acid and a sterically hindered base. The reaction is stereoselective when an optically active maleic or fumaric ester is employed. The cyclobutane-1,2-dicarboxylic esters (I), in particular those having *trans* configuration, are intermediates in the synthesis of pharmaceutically active compounds.

Process for preparing cyclobutane-1,2-dicarboxylic esters

The present invention relates to a process for preparing cyclobutane-1,2-dicarboxylic esters (I) by [2+2]cycloaddition of ketene acetals and fumaric or maleic esters.

The compounds preparable according to the invention are of the general formula:



(I)

in which R^1 is a C_{1-8}-alkyl group, an optionally substituted mono- or bicyclic cycloaliphatic group having 3 to 10 ring carbon atoms, an optionally substituted aryl or arylalkyl group or an optionally substituted saturated heterocyclic group and R^2 is C_{1-4}-alkyl or both radicals R^2 together are $-(CH_2)_n-$ where n = 2 to 4.

As referred to herein, C_{1-4}- or C_{1-8}-alkyl groups are in each case all straight-chain or branched primary, secondary or tertiary alkyl groups having 1 to 4 and 1 to 8 carbon atoms, respectively, i.e. C_{1-4}-alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl or *tert*-butyl and C_{1-8}-alkyl additionally includes, for example, pentyl, isopentyl, neopentyl, hexyl and octyl. Mono- or bicyclic cycloaliphatic groups having 3 to 10 carbon atoms are, for example, groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornan-x-yl, norcaran-x-yl or norpinan-x-yl, where the "x" represents any position of attachment desired. These groups may also carry one or more substituents, for example C_{1-4}-alkyl groups. These substituted cycloaliphatic groups include, for example, menthan-x-yl, bornan-x-yl, caran-x-yl, pinan-x-yl or thujan-x-yl. Aryl groups are aromatic hydrocarbon radicals having one or more rings, for

example phenyl, x-naphthyl, anthracen-x-yl, phenanthren-x-yl, fluoren-x-yl or biphenyl-x-yl. The rings in radicals having a plurality of rings may also be partially hydrogenated, such as tetrahydronaphthalen-x-yl, indan-x-yl or acenaphthen-x-yl. Examples of arylalkyl groups include benzyl, 1-phenylethyl, 2-phenylethyl (phenethyl) and diphenylmethyl (benzhydryl). Saturated heterocyclic groups include, for example, tetrahydrofuryl and tetrahydropyranyl. These aryl, arylalkyl and saturated heterocyclic groups may optionally carry one or more identical or different substituents, such as C_{1-4}-alkyl groups, C_{1-4}-alkoxy groups or halogen atoms, for example.

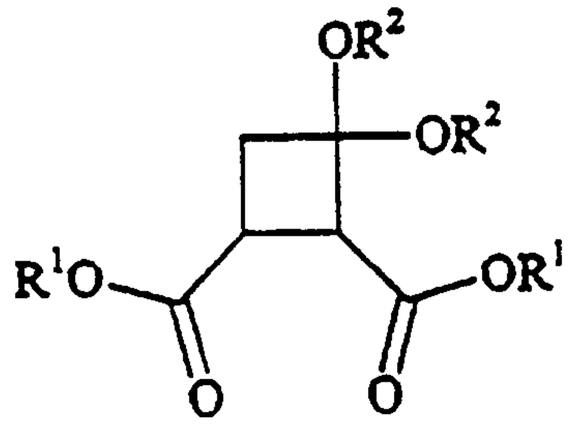
The compounds which are preparable according to the invention, in particular those having *trans* configuration at the cyclobutane ring, are intermediates in the synthesis of pharmaceutically active compounds, for example antiviral nucleoside analogues (EP-A-0 458 643).

It is known that 3,3-dialkoxycyclobutane-1,2-dicarboxylic esters can be prepared from fumaric or maleic esters and ketene acetals by [2+2]-cycloaddition. Since the cycloaddition proceeds in a stereospecific manner, fumaric esters give products having *trans* configuration at the cyclobutane ring, usually in the form of a racemate. Furthermore, it is known that if esters of fumaric acid in combination with optically active alcohols are employed, mixtures of diastereomers are obtained in which one of the two stereoisomers (depending on the nature and the configuration of the alcohol component either that having (1*S*) or that having (1*R*) configuration at the cyclobutane ring) prevails (EP-A-0 458 643, Example 1; S. Ahmad, *Tetrahedron Lett.* **1991**, *32*, 6997-7000). The process requires the use of at least two equivalents of dialkylaluminium chloride. A further disadvantage of this process consists in the fact that it has to be carried out at low temperatures of, for example, -75°C to obtain good yields. On an industrial scale, however, such low temperatures can only be achieved at considerable cost.

Accordingly, it is an object of the present invention

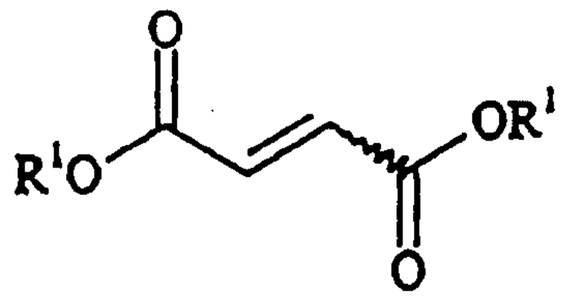
to provide a process which does not require a large excess of expensive dialkylaluminium chloride and which can be carried out at temperatures which are relatively higher.

According to the present invention, there is provided a process for preparing a cyclobutane-1,2-dicarboxylic ester of the general formula:



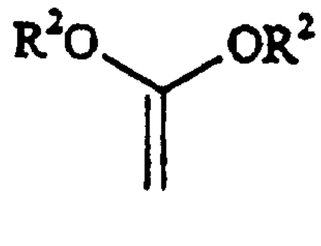
(I)

in which R^1 is a C_{1-8}-alkyl group, an optionally substituted mono- or bicyclic cycloaliphatic group having 3 to 10 ring carbon atoms, an optionally substituted aryl or arylalkyl group or an optionally substituted saturated heterocyclic group and R^2 is either C_{1-4}-alkyl or both radicals R^2 together form a group of the general formula $-(CH_2)_n-$ where *n* is an integer from 2 to 4, which comprises reacting a dicarboxylic ester of the general formula:



(II)

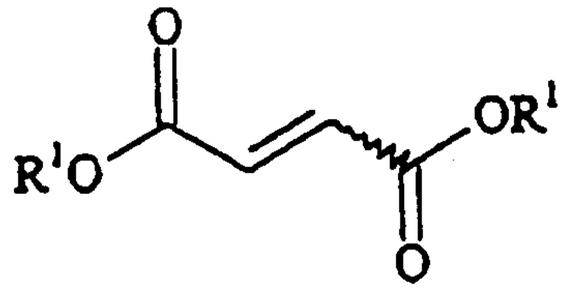
in which R^1 is as defined above, with a ketene acetal of the general formula:



(III)

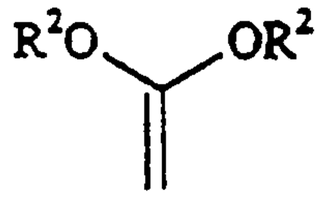
in which R^2 is as defined above, in the presence of a Lewis acid, and in the presence of a sterically hindered base.

Surprisingly, it has been found that when a dicarboxylic ester of the general formula:



(II)

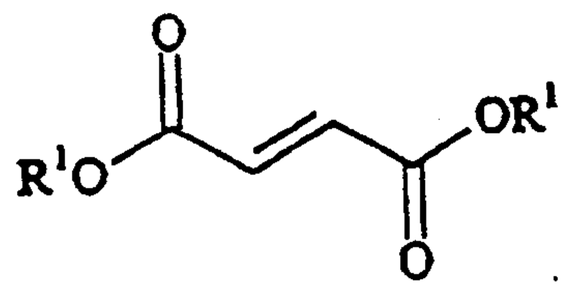
in which R^1 is as defined above, is reacted with a ketene acetal of the general formula:



(III)

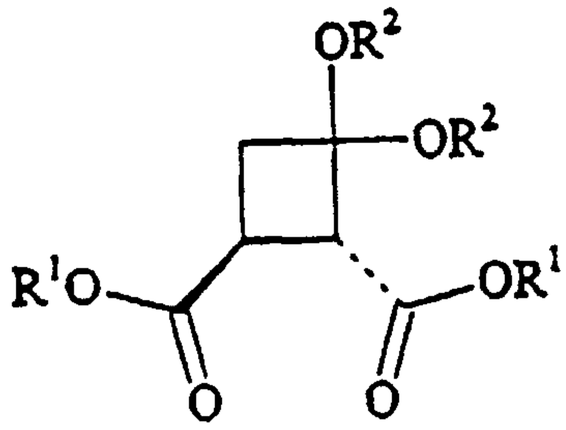
in the presence of a Lewis acid by addition of a sterically hindered base to the reaction mixture, it is possible not only to obtain an improved yield, but it is also possible to carry out the reaction with a reduced excess of Lewis acid (for example dialkylaluminium chloride) and at a higher temperature (up to approximately +20°C and above).

In a preferred embodiment of the process according to the invention, the dicarboxylic ester (II) employed is a fumaric ester of the general formula:



(IIa)

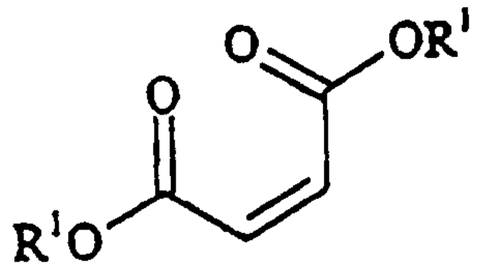
in which R^1 is as defined above, and a cyclobutane-*trans*-1,2-dicarboxylic ester of the general formula:



(Ia)

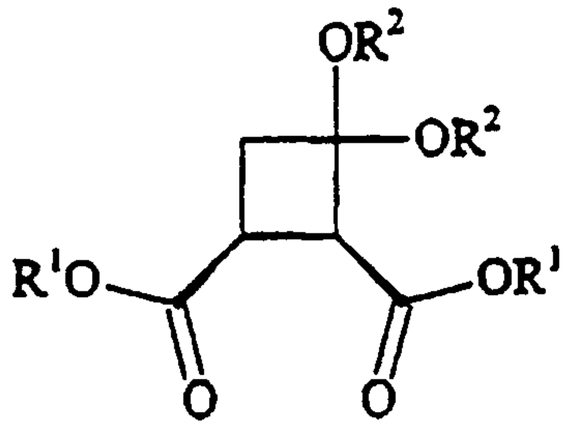
and/or the mirror image,
in which R^1 and R^2 are as defined above, is obtained.

In another embodiment, the dicarboxylic ester (II) employed is a maleic ester of the general formula:



(IIb)

in which R^1 is as defined above, and a cyclobutane-*cis*-1,2-dicarboxylic ester of the general formula:



(Ib)

and/or the mirror image,
in which R^1 and R^2 are as defined above, is obtained.

Preference is given to using those dicarboxylic esters (II) in which R^1 contains at least one chiral element, namely in non-racemic form. Particularly preferably, these non-racemic dicarboxylic esters (II) are essentially optically pure. The cyclobutane-1,2-dicarboxylic ester stereoisomers (I) obtained from chiral dicarboxylic esters (II) are not enantiomers, but are diastereomers which differ in their physical properties and which can be separated more or less easily. With these dicarboxylic esters (II), the [2+2]-cycloaddition proceeds stereoselectively with respect to the absolute configuration of the resulting cyclobutane ring, so that one diastereomer is preferentially formed.

Chiral radicals R^1 which are preferably used are radicals such as 1-phenylethyl, menthyl and its stereoisomers, bornyl and its stereoisomers, dihydro-4,4-dimethylfuran-2(3*H*)-on-3-yl (derived from pantolactone), 1-(methoxycarbonyl)ethyl or 1-(ethoxycarbonyl)ethyl (derived from methyl lactate or ethyl lactate). Particular preference is given to menthyl. Using optically pure dimenthyl fumarates, very good diastereoselectivities can be achieved, and it is possible to obtain cyclobutane-*trans*-1,2-dicarboxylic esters (Ia) having *de* values (*de* =

diastereomeric excess, defined as quotient |A-B| : (A+B), where A and B represent the amounts of the two diastereomers) of up to 90% and more, which are virtually stereoisomerically pure after a simple purification step (for example recrystallization).

In particular, (1*R*)-menthyl fumarates (IIa, R^1 = (1*R*)-menthyl) yield predominantly cyclobutane-*trans*-1,2-dicarboxylic esters (Ia) in the (1*S*) configuration of the cyclobutane ring.

Ketene acetals (III) which are preferably used are those in which R^2 is methyl or ethyl or both radicals R^2 together denote $-(CH_2)_4-$. Specifically, these are ketene dimethyl acetal, ketene diethyl acetal and 2-methylene-1,3-dioxepane.

Suitable Lewis acids are, for example, organoaluminium and organotitanium compounds of the general formulae R_2AlCl, $RAlCl_2$, $Al(OR)_3$, $Ti(OR)_2Cl_2$ and $Ti(OR)_4$ in which the radicals R are identical or different and each represents a C_{1-8}-alkyl group, and also halides such as $AlCl_3$, $TiCl_4$, BF_3, $ZnCl_2$, $ZnBr_2$, $ZrCl_4$ and $SnCl_4$. The Lewis acid which is preferably used is a dialkylaluminium chloride of the general formula R_2AlCl. Particular preference is given to those dialkylaluminium chlorides in which R is ethyl or isobutyl.

Suitable sterically hindered bases are in particular tertiary amines, such as, for example, 2,6-di-*tert*-butylpyridine, 2,6-di-*tert*-butylpyridine bound to a polymeric support, 2,6-di-*tert*-butyl-4-methylpyridine, triethylamine, diethylisopropylamine, triisopropylamine and *N*-ethyldicyclohexylamine. Particular preference is given to ethyldiisopropylamine ("Hünigs base").

The following Examples illustrate the practice of the process according to the invention without limiting it.

Example 1

Di-(1*R*)-menthyl (1*S*,2*R*)-3,3-diethoxy-1,2-cyclobutane-dicarboxylate

At room temperature and under argon, 30.0 g (76.5 mmol) of di-(1*R*)-menthyl fumarate were dissolved in 250 ml of toluene in a double-jacket flask cooled by a circulation cryostat. The solution was cooled to -21°C and admixed with 16.5 ml (84.5 mmol) of diisobutylaluminium chloride over a period of 15 minutes. After a further 5 minutes, 5.2 ml (30.4 mmol) of ethyldiisopropylamine were added. The mixture was stirred for another 5 minutes and then, with enhanced cooling (coolant temperature: -24°C), admixed with 11.1 ml (84.1 mmol) of ketene diethyl acetal over a period of 15 minutes, the internal temperature rising to -19°C. The dark reaction mixture was stirred for another 40 minutes at -22 to -20°C and then poured onto a mixture of 200 ml of *n*-hexane, 200 ml of saturated aqueous sodium bicarbonate solution and a little ice. The resulting orange emulsion was stirred until it had reached room temperature. The phases were subsequently separated and the aqueous phase was extracted with 2 × 200 ml of hexane. The combined organic phases were washed two times each with saturated sodium bicarbonate solution and saturated sodium chloride solution, filtered through Celite® and dried over sodium sulphate. The solvent was distilled off under reduced pressure and the residue was dried under high vacuum. The crude product obtained in this manner (40.38 g, orange solid) contained, according to NMR, no unreacted starting material and consisted, according to GC, of a mixture of the (1*S*,2*R*)- and (1*R*,2*S*)-diastereomers in a ratio of 93.5:6.5 (87% *de*). For purification, 39.1 g of the crude product were dissolved in 1.2 l of methanol/water (95:5), cooled to room temperature with stirring and left to stand at 0°C overnight. The yellowish crystals which had precipitated were filtered off, washed with a little methanol/water and dried under high vacuum.

Yield: 27.9 g (74%, based on dimenthyl fumarate), diastereomerically pure.

Example 2

Di-(1*R*)-menthyl (1*S*,2*R*)-3,3-dimethoxy-1,2-cyclobutanedicarboxylate

Following the method of Example 1, di-(1*R*)-menthyl fumarate was reacted at -40°C with ketene dimethyl acetal in the presence of 0.2 equivalent of ethyldiisopropylamine and 2 equivalents of diethylaluminium chloride. ^{1}H NMR analysis of the reaction mixture showed that the yield was quantitative and the *de* value was >80%.

Comparative Example 1

Di-(1*R*)-menthyl (1*S*,2*R*)-3,3-dimethoxy-1,2-cyclobutanedicarboxylate

Example 2 was repeated, but without addition of ethyldiisopropylamine. ^{1}H NMR analysis of the reaction mixture showed that the yield was 37% and the *de* value was >80%.

Example 3

Di-(1*R*)-menthyl (1*S*,2*R*)-5,10-dioxaspiro[3.6]decane-1,2-dicarboxylate

[I,R^1 = (1*R*)-menthyl, $2R^2$ = $-(CH_2)_4-$]

Following the method of Example 1, di-(1*R*)-menthyl fumarate was reacted at -20°C with 2-methylene-1,3-dioxepane (ketene tetramethylene acetal) in the presence of 0.2 equivalent of ethyldiisopropylamine and 2 equivalents of diethylaluminium chloride. ^{1}H NMR analysis of the reaction mixture showed that the yield was 93%, and only one diastereomer could be detected. A repetition of the experiment at a reaction temperature of 0°C gave the same result.

Comparative Example 2

Di-(1*R*)-menthyl (1*S*,2*R*)-5,10-dioxaspiro[3.6]decane-1,2-dicarboxylate

Example 3 was repeated, but without addition of ethyldiisopropylamine. At a reaction temperature of -40°C, a yield of 73% was obtained, at 0°C only 33%.

Example 4

Diethyl (±)-3,3-diethoxy-*trans*-1,2-cyclobutanedicarboxylate

Following the method of Example 1, diethyl fumarate was reacted at -40°C with 2 equivalents of ketene diethyl acetal in the presence of 0.2 equivalent of ethyldiisopropylamine and 2 equivalents of diisobutylaluminium chloride. ^{1}H NMR analysis of the reaction mixture showed that the yield was quantitative.

Examples 5-14, Comparative Examples 3-4

Di-(1*R*)-menthyl (1*S*,2*R*)-3,3-diethoxy-1,2-cyclobutanedicarboxylate

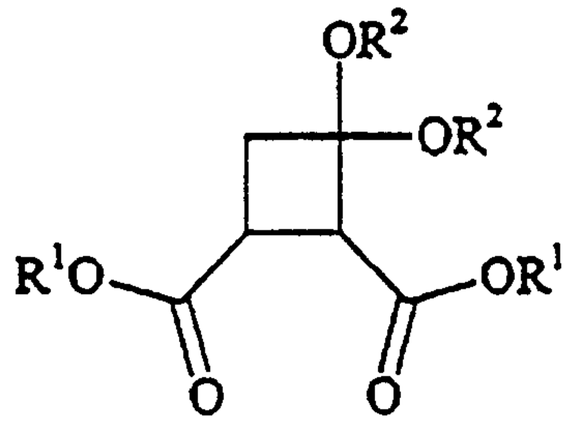
Example 1 was repeated, but the amounts of ketene diethyl acetal, ethyldiisopropylamine and dialkylaluminium chloride, and also the reaction temperature, the solvent and the alkyl radical in the dialkylaluminium chloride were varied. The conditions and the yields and *de* values determined by GC are summarized in Table 1 below.

Table 1

Ex. No.	Acetal [Eq.]	Amine [Eq.]	Temp. [°C]	R	R_2AlCl [Eq.]	Solvent	Yield [%]	*de* [%]
5	1.1	0.4	-20	Et	2.0	toluene	≈100	86.6
6	1.1	0.4	-20	Bu	2.0	toluene	≈100	90.7
7	1.1	0.4	0	Et	2.0	toluene	95	78.9
8	1.1	0.4	0	Bu	2.0	toluene	≈100	84.7
9	1.1	0.4	+20	Bu	2.0	toluene	≈100	73
10	1.1	0.4	-20	Bu	1.1	toluene	≈100	90.9
11	1.1	0.4	-40	Bu	1.1	toluene	≈100	94.8
12	1.1	0.4	-20	Et	2.0	CH_2Cl_2	≈100	83.2
13	1.1	0.4	-20	Bu	2.0	CH_2Cl_2	≈100	83.1
14	1.1	0.4	-20	Bu	1.1	$C_2H_4Cl_2$	≈100	90.9
C 3	1.5	-	-78	Et	2.0	toluene	<10	n.d.
C 4	1.5	-	-40	Et	2.0	toluene	29	n.d.

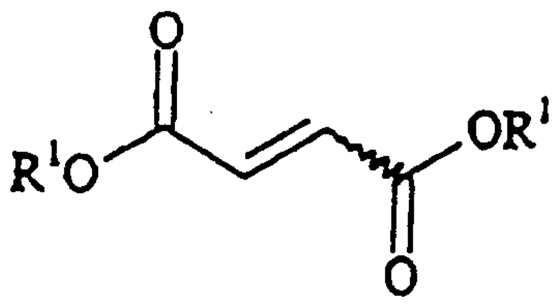
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for preparing a cyclobutane-1,2-dicarboxylic ester of the general formula:



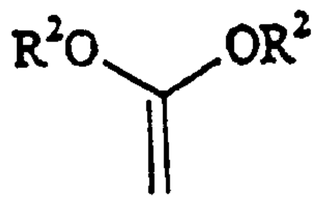
(I)

in which R^1 is a C_{1-8}-alkyl group, an optionally substituted mono- or bicyclic cycloaliphatic group having 3 to 10 ring carbon atoms, an optionally substituted aryl or arylalkyl group or an optionally substituted saturated heterocyclic group and R^2 is either C_{1-4}-alkyl or both radicals R^2 together form a group of the general formula $-(CH_2)_n-$ where *n* is an integer from 2 to 4, which comprises reacting a dicarboxylic ester of the general formula:



(II)

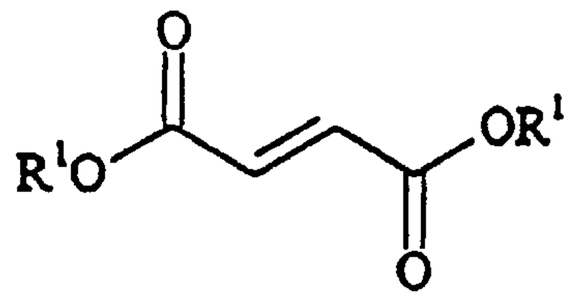
in which R^1 is as defined above, with a ketene acetal of the general formula:



(III)

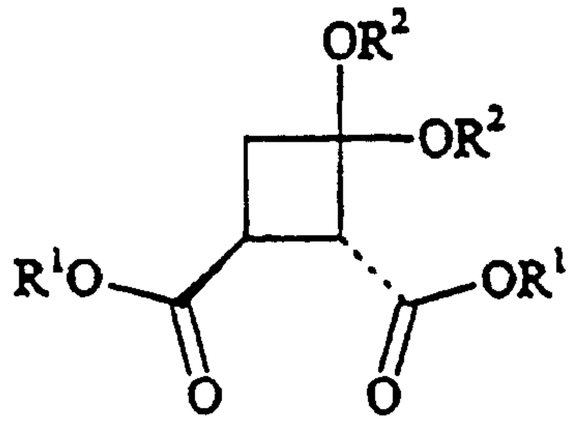
in which R^2 is as defined above, in the presence of a Lewis acid, and in the presence of a sterically hindered base.

2. A process according to claim 1, wherein the dicarboxylic ester (II) is a fumaric ester of the general formula:



(IIa)

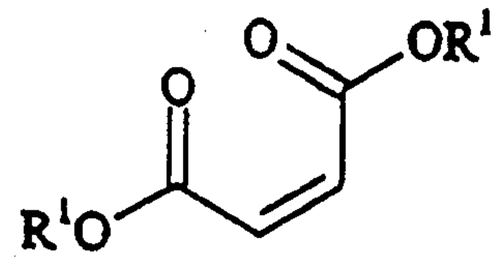
in which R^1 is as defined in claim 1, whereby a cyclobutane-*trans*-1,2-dicarboxylic ester of the general formula:



(Ia)

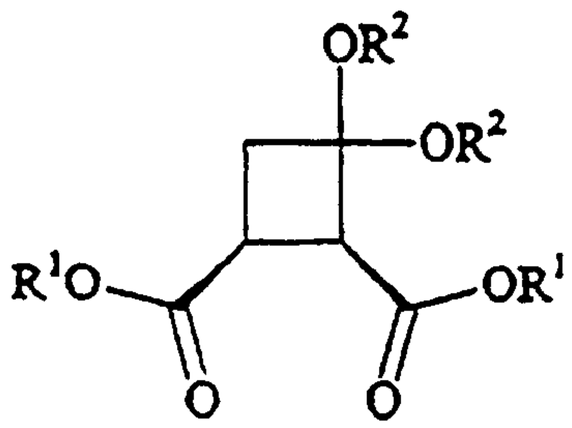
and/or the mirror image,
in which R^1 and R^2 are as defined in claim 1, is obtained.

3. A process according to claim 1, wherein the dicarboxylic ester (II) is a maleic ester of the general formula:



(IIb)

in which R^1 is as defined in claim 1, whereby a cyclobutane-*cis*-1,2-dicarboxylic ester of the general formula:



(Ib)

and/or the mirror image,
in which R^1 and R^2 are as defined in claim 1, is obtained.

4. A process according to any one of claims 1 to 3, wherein R^1 contains at least one chiral element and the dicarboxylic ester (II) is present in non-racemic form.

5. A process according to claim 4, wherein R^1 is selected from the group consisting of 1-phenylethyl, menthyl and bornyl and their stereoisomers, dihydro-4, 4-dimethylfuran-2 (*3H*) -on-3-yl, 1- (methoxycarbonyl) ethyl and 1-(ethoxycarbonyl) ethyl.

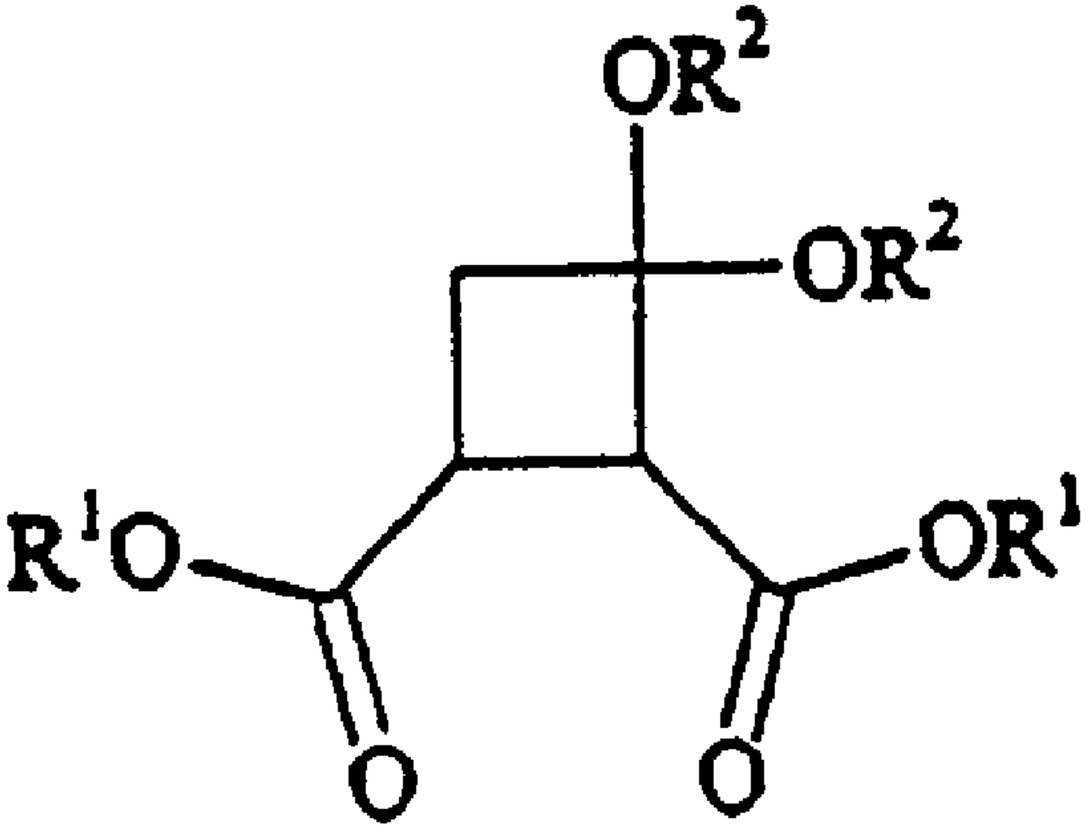
6. A process according to claims 2 and 5, wherein R^1 is (1*R*)-menthyl and the cyclobutane-*trans*-1, 2-dicarboxylic ester (Ia) is obtained predominantly in the (I*S*) configuration.

7. A process according to any one of claims 1 to 6, wherein R^2 is methyl or ethyl or both radicals R^2 together are $-(CH_2)_4-$.

8. A process according to any one of claims 1 to 7, wherein the Lewis acid employed is a dialkylaluminium chloride of the general formula R_2AlCl, in which each R is a C_{1-8}-alkyl group.

9. A process according to claim 8, wherein R is ethyl or isobutyl.

10. A process according to any one of claims 1 to 9, wherein the sterically hindered base employed is ethyldiisopropylamine.



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