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(54) Titre : PROCEDE POUR LA PREPARATION D'ACIDE SHIKIMIQUE ET DE SES DERIVES
(54) Title: PROCESS FOR THE PREPARATION OF SHIKIMIC ACID AND ITS DERIVATIVES

(57) Abrégé/Abstract:
The present invention relates to a process for the preparation of shikimic acid [3R-(3α,4α,5β)]-(3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid) and its derivatives from quinic acid [1R-(1α,3α,4α,5β)]-(1,3,4,5-tetrahydroxycyclohexanecarboxylic acid) and derivatives of quinic acid, by dehydration with Vilsmeier reagent.

Abstract

The present invention relates to a process for the preparation of shikimic acid [3R-(3α,4α,5β)]-(3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid) and its derivatives from quinic acid [1R-(1α,3α,4α,5β)]-(1,3,4,5-tetrahydroxycyclohexanecarboxylic acid) and derivatives of quinic acid, by dehydration with Vilsmeier reagent.

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Ref. 20097

The present invention relates to a process for the preparation of shikimic acid [3R-(3α,4α,5β)]-(3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid) and its derivatives from quinic acid [1R-(1α,3α,4α,5β)]-(1,3,4,5-tetrahydroxy-cyclohexanecarboxylic acid) and corresponding derivatives.

Shikimic acid and its derivatives are compounds well known in the art and can be prepared according to known methods from corresponding quinic acid derivatives by dehydration using, e.g., $POCl_3$ in pyridine (Bestmann, H.J. et al., Angew. Chemie 83, 329 [1971]; Snyder, C.D. et al., J. Am. Chem. Soc. 95, 7821 [1973]; Grewe R. et al., Chem. Ber. 98, 104 [1965]) or SO_2Cl_2 in pyridine (Snyder, loc. cit.; WO 98/07685).

It has now surprisingly been found that higher regioselectivity of the dehydration than described in the state of the art can be achieved by using $ClCH=N^+(CH_3)_2Cl^-$ (Vilsmeier reagent) as dehydration reagent. The degree of regioselectivity is very high, e.g., in the range of 50:1 and can be as high as 100:1 for the desired stereoisomer.

The present invention, therefore, relates to the use of Vilsmeier reagent in the preparation of shikimic acid and its derivatives from quinic acid and derivatives.

The present invention, furthermore, relates to a process for the preparation of shikimic acid and its derivatives by dehydration of quinic acid and its derivatives using Vilsmeier reagent and, finally, to the intermediates built in the reaction.

Derivatives of quinic acid comprise all derivatives obtainable by modification of one, several or all functional groups except the hydroxy group in 1-position, especially those quinic acid derivatives with a protected carboxylic group and/or at least one of the three adjoining hydroxy groups being in protected form and corresponding salts. If two adjoining hydroxy groups are protected they can be protected separately by the same or by

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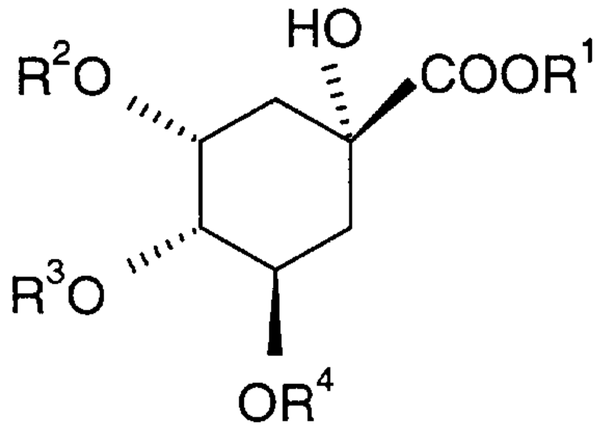
different protecting groups or jointly by a 1,2-diol protecting group. Either the hydroxy groups in 3- and 4-position or in 4- and 5-position can be protected by a 1,2-diol protecting group, the hydroxy group in 5- or 3-position respectively being not protected or by a different protecting group.

In a specific embodiment of the present invention a compound of formula



I

wherein

R^1 is hydrogen or a carboxylic acid protecting group,

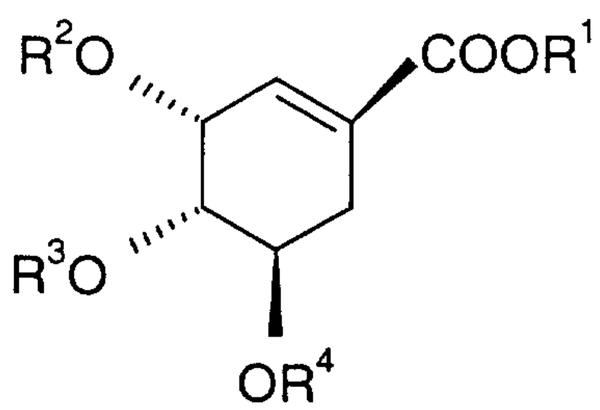
R^2 is hydrogen or a hydroxy protecting group,

R^3 is hydrogen or a hydroxy protecting group or

R^2 and R^3 taken together are a 1,2-diol protecting group,

R^4 is hydrogen or a hydroxy protecting group,

or a salt thereof is dehydrated with Vilsmeier reagent to form a corresponding compound of formula



II

A very large number of carboxylic acid and hydroxy protecting groups (including 1,2-diol protecting groups) and corresponding chemical cleavage reactions are known to the person skilled in the art and described, e.g., in "Protective Groups in Organic Chemistry", Theodora W. Greene et al. (John Wiley & Sons, Inc., New York, 1991) or in "Protecting Groups", Philip J. Kocienski (Georg Thieme Verlag Stuttgart, New York, 1994).

Typically a carboxylic acid group is protected in form of an ester group. In this situation R^1 is alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms, any one of which alkyl, alkenyl, or alkynyl may be substituted with 0-3 groups as defined, e.g., in WO 98/07685. More typically a carboxylic acid protecting group R^1 is alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, or alkynyl of 2 to 6 carbon atoms, any one of which alkyl, alkenyl, or alkynyl may be substituted with 0-3 groups as defined in the above mentioned WO. Still more typically, such protecting group R^1 is alkyl of 1 to 8 carbon atoms substituted with 0-2 groups as defined in the above mentioned WO. Even more typically, R^1 is alkyl of 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. Most typically a carboxylic acid protecting group R^1 is methyl, ethyl, 1-propyl or 2-propyl.

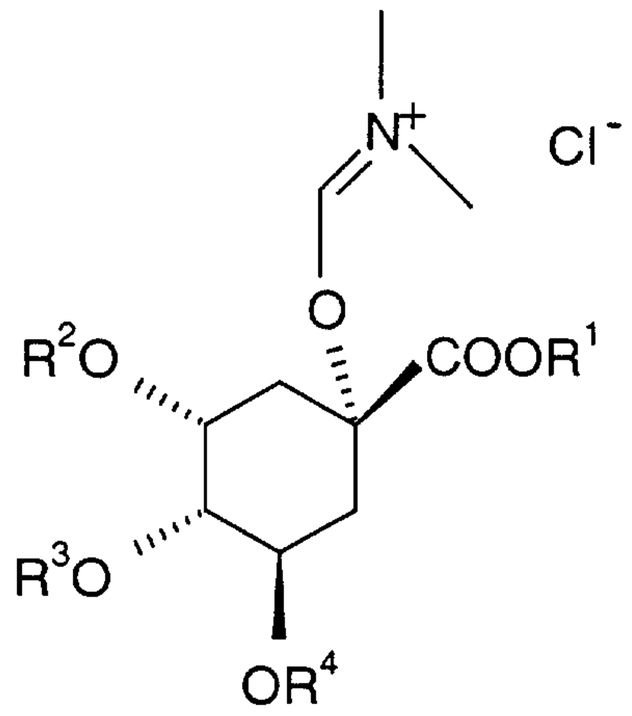
Typically a hydroxy group is protected in form of an ether or ester. Therefore, a R^2, R^3 or R^4 hydroxy protecting group is, e.g., methyl, substituted methyl, ethyl, substituted ethyl, benzyl, substituted benzyl or substituted silyl, such as trialkyl silyl. Examples of suitable esters are formates, benzoylformates, acetates, chloroacetates, dichloroacetates, trichloroacetates, trifluoroacetates, methoxyacetates, benzoates, carbonates and sulfonates, such as sulfates, methanesulfonates (mesylates), benzylsulfonates and tosylates.

Typical 1,2-diol protecting groups are described in Greene and mentioned in WO 98/07685 and include groups forming cyclic acetals and ketals (e.g. methylene, ethylidene, 1-t-butylethylidene, 1-phenylethylidene, (4-methoxy-phenyl)-ethylidene, 2,2,2-trichloroethylidene, isopropylidene, cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, p-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, 2-nitrobenzylidene); cyclic ortho esters (e.g. methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidene, 1,2-dimethoxyethylidene, α-methoxybenzylidene), silyl derivatives (e.g. di-t-butylsilylene), cyclic carbonates, cyclic boronates, ethyl boronate and phenyl boronate. Preferred 1,2-diol protecting groups are alkylidene, esp. with 1-6 C atoms, isopropylidene being most preferred.

In preferred specific embodiments of the present invention compounds of formula I are dehydrated wherein R^1 is hydrogen or alkyl; or R^2, R^3 and R^4 are hydrogen; or at least one of R^2, R^3 and R^4 is a hydroxy protecting group; or the protecting group(s) is(are) an acyl and/or alkyl group(s); or R^2 and R^3 together represent an alkylidene group; or R^2 and R^3 together represent an alkylidene

group and R^4 is an acyl group; or R^4 is a sulfonic acid residue; or R^1 is ethyl, R^2 and R^3 are isopropylidene and R^4 is mesyl.

Typically the dehydrating process comprises treating quinic acid or a derivative thereof with the Vilsmeier reagent in a suitable solvent, preferably a polar aprotic solvent, such as ethyl acetate or dimethylformamide (DMF), at a temperature between room temperature and about 100°C, preferably at 50-100°C, more preferably at 50-80°C, during several hours. In case of ethyl acetate the reaction mixture is preferably heated under reflux. The Vilsmeier reagent is a commercially available product and can be introduced into the reaction as such. Alternatively the Vilsmeier reagent can be produced in situ from $POCl_3$, oxalyl dichloride or phosgene in DMF. In the latter case a solution of quinic acid or its derivative in DMF is reacted with an excess of $POCl_3$, oxalyl dichloride or phosgene, preferably 1.1-1.5 equivalents, at room temperature for about one hour. The reaction mixture is then heated for several hours to a temperature of about 70°C. During the reaction at room temperature the Vilsmeier reagent reacts with the tertiary hydroxy group to form an intermediate compound which in case of a starting material of formula I is represented by general formula



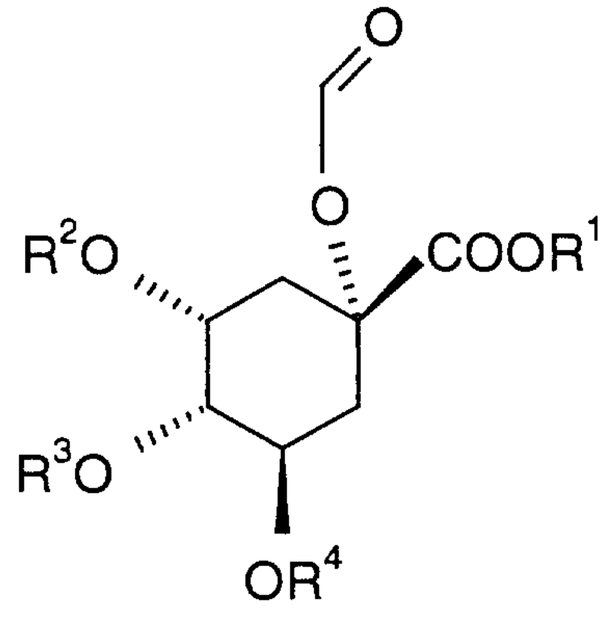
III

wherein R^1-R^4 are as defined above.

During further heating of up to 70°C the intermediate compound by elimination of DMF is converted into the corresponding shikimic acid or derivative which after neutralization of the reaction mixture can then be isolated and purified using methods well known in the art.

Treatment of the intermediate compounds mentioned above with an aqueous solvent yield corresponding quinic acid derivatives wherein the tertiary hydroxy group is formylated. These compounds are also an

embodiment of the present invention. In case of starting compounds of formula I there can be obtained compounds of formula



IV

wherein R^1-R^4 are as defined above,
via compounds of formula III.

Depending on the specific protecting groups present in the starting material, viz. the quinic acid derivative, and the specific reaction conditions used in the dehydrating reaction, protecting groups may be eliminated or transformed and shikimic acid in unprotected or in partially protected form may be obtained. It is within the general knowledge of the person skilled in the art to manipulate the reaction conditions in the desired direction or to transform a specific shikimic acid derivative of formula II obtained into a different derivative of formula II.

Shikimic acid and its derivatives are intermediates in the synthesis of known valuable compounds with known industrial applicability, especially of pharmaceutically active compounds (e.g. WO 96/26933 and WO 98/07685).

The following Examples illustrate and describe in more detail the present invention without limiting it.

Example 1

In a dried and nitrogen purged reactor 61.4 g of commercially available Vilsmeier reagent (480 mmol, 1.2 equiv.) are suspended in 112 ml of ethyl acetate. A solution of 135.3 g of 1-hydroxy-3,4-isopropylidenedioxy-5-mesyloxy-cyclohexanecarboxylic acid ethyl ester (= 3,4-isopropylidene-5-mesyl-quinic acid ethyl ester; 400 mmol, 1.0 equiv.) in 458 ml ethyl acetate is added at room temperature. The resulting mixture is heated to 70-75°C until the reaction is finished (about 3 hrs). After cooling the solution is quenched with a mixture of 330.5 g of aqueous sodium hydroxide solution (28%) and 460 g of ice. The

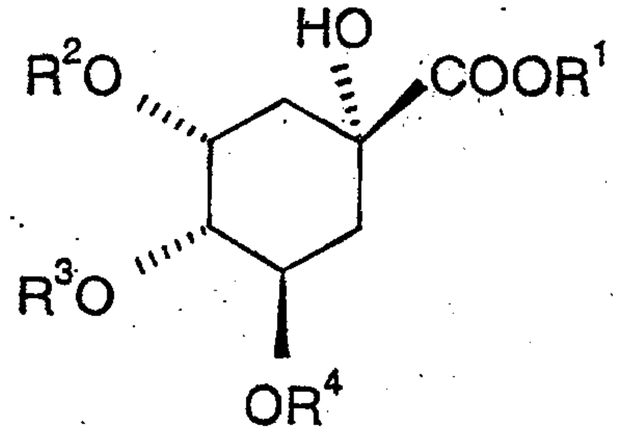
organic layer is washed with sodium hydrogen carbonate and water. The combined water layers are back-extracted with ethyl acetate. The combined organic layers are then concentrated under reduced pressure and the residue is crystallized from hot methanol. 75 g (59%) of 3,4-isopropylidene-5-mesyl-shikimic acid ethyl ester are obtained, m.p. 103°C.

Example 2

In a dried and nitrogen purged reactor 80.0 g of 3,4-isopropylidene-5-mesyl-quinic acid ethyl ester (236 mmol, 1.0 equiv.) are dissolved in 320 ml of dimethylformamide (DMF). Under cooling 47.1 g of phosphorus oxychloride ($POCl_3$; 307 mmol, 1.3 equiv.) are added. The resulting clear solution is stirred for additional 60 minutes at room temperature and then heated to 60-63°C until the reaction is finished (about 6 hrs). After cooling the solution is quenched with a mixture of 480 ml tert-butyl methyl ether (TBME), 120 ml methylene chloride, and 500 ml of aqueous 2.5N sodium hydroxide solution. The pH-value is adjusted to neutral. The aqueous layer is extracted with a mixture of TBME and methylene chloride. The combined organic layers are washed with sodium hydrogen carbonate and water. The organic layer is concentrated under reduced pressure and the product is crystallized from hot TBME. 42 g (55%) of 3,4-isopropylidene-5-mesyl-shikimic acid ethyl ester are obtained, m.p. 103°C.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for the preparation of shikimic acid and its derivatives by dehydration of a compound of formula



I

wherein

R^1 is hydrogen or a carboxylic acid protecting group,
R^2 is hydrogen or a hydroxy protecting group,
R^3 is hydrogen or a hydroxy protecting group or
R^2 and R^3 taken together are a 1,2-diol protecting group,
R^4 is hydrogen or a hydroxy protecting group,
or a salt thereof;
with Vilsmeier reagent.

2. A process as claimed in claim 1 characterized in that a compound of formula I wherein R^1 is hydrogen or alkyl is dehydrated.

3. A process as claimed in any one of claims 1-2 characterized in that a compound of formula I wherein R^2, R^3 and R^4 are hydrogen is dehydrated.

4. A process as claimed in any one of claims 1-2 characterized in that a compound of formula I wherein at least one of R^2, R^3 and R^4 is a hydroxy protecting group is dehydrated.

5. A process as claimed in claim 4 characterized in that the protecting group(s) is(are) an acyl and/or alkyl group(s).

6. A process as claimed in claim 4 characterized in that R^2 and R^3 together represent an alkylidene group and R^4 is an acyl group.

7. A process as claimed in claim 6 characterized in that R^4 is a sulfonic acid residue.

8. A process as claimed in any one of claims 1-2 and 4-7 characterized in that the compound of formula I is 3,4 isopropylidene-5-mesyl-quinic acid ethyl ester.

9. A process as claimed in any one of claims 1-8 characterized in that the reaction with Vilsmeier reagent is carried out in ethyl acetate.

10. A process as claimed in any one of claims 1-8 characterized in that the Vilsmeier reagent is formed in situ with $POCl_3$, oxalyl dichloride or phosgene in dimethylformamide.