

PROCESS FOR THE PRODUCTION OF ESTERS FROM EPOXIDES

Field of the Invention

The present invention relates to processes for the production of vicinal diesters.

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Background of the Invention

Various silicone containing monomers have found utility as starting materials in the production of medical devices, such as ophthalmic devices and particularly, soft contact lenses having improved permeability to oxygen. One class of suitable monomers includes tris and bis(trimethylsilyloxy)silylalkylglycerol methacrylates ("SiAGMA"). During the synthesis of SiAGMA certain diester acrylate impurities are also generated. The diester acrylates or free radical reactive difunctional groups act as crosslinkers during the polymerization of the SiAGMAs with other polymer forming components. Accordingly, the concentration of the diester acrylates must be controlled to ensure that the mechanical properties of the resulting medical device do not vary to an unacceptable degree.

Classical methods for preparing 1,2-diester involve the treatment of 1,2-diols with acid chlorides or anhydrides in the presence of a base. However, functional groups such as trimethylsilyl ethers are sensitive to such conditions and additional purification is required to obtain the desired product(s) in high purity. One method for the production of vicinal diesters uses an amine to catalyze the nucleophilic opening of the epoxide in the presence of an anhydride and methacrylic acid to form a partially acylated mixture of compounds containing a vicinal methacrylate. The difunctional free radical impurities that are made during the course of producing the monofunctional free radical reactive monomer have to be controlled using either a different synthetic pathway or the use of various purification steps. The free radical reactive functional groups in the monomeric materials are made and then rely heavily on various modes of post synthesis purification methodology.

Accordingly, there remains a need in the art for a process which can produce vicinal diesters in high yield and purity.

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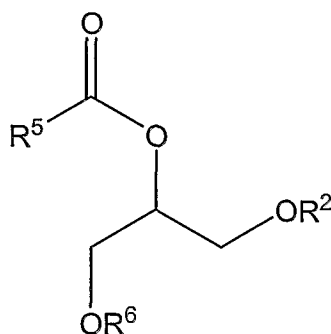
Summary of the Invention

The present invention relates to a process comprising the steps of reacting, in the presence of an epoxide opening catalyst, a substituted epoxide, and preferably a silicone containing substituted epoxide with at least one carboxylic acid and at least one protecting agent to form a vicinal dialkyl ester or a vicinal disilyl ester. More

5 specifically, the present invention relates to a process comprising the steps of reacting a substituted epoxide with at least one epoxide opening catalyst, at least one carboxylic acid, at least one protecting agent and at least one inhibitor at a temperature above about 60°C for at least about 4 hours to form a compound of Formula VI or VII:

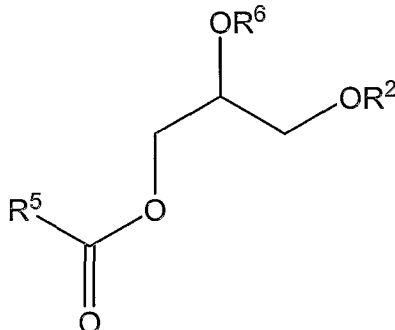
Formula VI

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Formula VII

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wherein R² is any group which reacts more slowly with an oxygen containing nucleophile as compared to said epoxide, R⁵ is a straight or branched alkyl and alkenyl groups having 1 to 10 carbon atoms and R⁶ is a residue of said protecting group which is capable of forming an ester or ether linkage. The vicinal dialkyl ester or a vicinal disilyl ester which are formed by the process of the present invention are useful as polymerization components for biomedical devices, and particularly for ophthalmic devices such as contact lenses.

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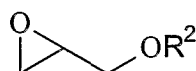
Description of the Invention

Suitable substituted epoxides include those of Formula I, below:

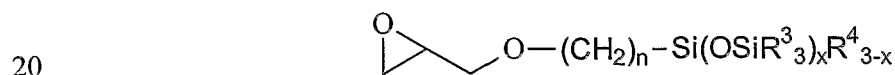


Wherein R¹ is any substituent which reacts more slowly with an oxygen containing nucleophile as compared to the epoxide moiety. Preferred substituted epoxides include those shown in Formula II

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Wherein R² is any group which reacts more slowly with an oxygen containing nucleophile as compared to the epoxide moiety. Examples of suitable R² groups include esters, amides, substituted and unsubstituted alkyls, siloxanes, ethers and the like. Specific, non-limiting examples include C1 to 3 alkyls substituted with at least one Si containing substituent and preferably at least one silicone linkage. Specific examples of suitable substituted epoxides include those of formula III:



Wherein R³ and R⁴ are independently selected from alkyl groups having 1 to 3 carbon atoms, n is 1 to 3 and x is 0 to 3. Even more specifically, the substituted epoxide may be glycidoxypentyl heptamethyltrisiloxane.

25 Epoxides may be formed in a number of ways including, but not limited to, oxidation of alkenes with peroxyacids, formation by an intramolecular S_N2 reaction in which there is a trans halohydrin moiety, addition of a nucleophilic oxidizing agent (such as a basic solution of hydrogen peroxide) to an α,β-unsaturated carbonyl compound, and the reaction of a sulfonium ylide with a carbonyl compound. Alternatively, epoxides

substituted with a Si containing group may be prepared by the hydrosilylation of an already formed epoxide containing an allyl functionality. Such methods are well known to those skilled in the art and this list of synthetic routes to epoxides and epoxides substituted with a Si containing group, in no way limits the scope of this invention to these preparations.

According to the process of the present invention the substituted epoxide is reacted with at least one soluble carboxylate salt, R^5CO_2X , at least one carboxylic acid R^5CO_2H and at least protecting agent which can block reaction of free radical reactive species with a hydroxyl group. Suitable protecting agents include anhydrides, trimethylsilylchloride, allyl halide and the like. Anhydrides are preferred protecting agents. Suitable anhydrides include those having the formula $R^5CO_2OCR^5$. R^5 may be the same or different, and may be selected from straight or branched alkyl and alkenyl groups having 1 to 10 carbon atoms. Preferably R^5 is selected from alkenyl groups having 1-5 carbon atoms, and more preferably vinyl, styryl, allyl. Preferably R^5 is the same in the carboxylate salt, carboxylic acid and protecting agents.

The protecting agent reacts with the hydroxyl group after the carboxylate salt has opened the oxirane ring, keeping the metal alkoxide group from displacing the carboxy group from the carboxylic acid, and limits the OH reaction with other reactive species present in the reaction mixture. Thus, the use of a protecting agent allows for the production of the desired product in purities in excess of 80%, prior to any purification.

The epoxide opening catalyst used in the first step of the present invention may be any catalyst which is known in the art to open the epoxide ring. Suitable epoxide opening catalysts include Lewis acids, Lewis bases, Bronsted acids and porphyrin complexes, combinations thereof and the like. A preferred class of epoxide opening catalysts include carboxylate salts. For the carboxylate salt, suitable cations include alkali metals, such as Li, Na, K and ammonium. Preferably said cation is Li or Na, and preferred carboxylate salts include Li methacrylate and Na methacrylate. The epoxide opening catalyst should be soluble in the selected reaction solvent and at that the selected reaction temperature. The epoxide opening catalyst is added in an amount sufficient to catalyze the reaction, and preferably in an amount up to about 0.5 equivalents, based upon the epoxide.

In a preferred embodiment the carboxylic acid is methacrylic acid, the protecting agent is an anhydride and preferably methacrylic acid anhydride and the epoxide opening catalyst is an alkali metal methacrylate.

5 The carboxylic acid is used in an amount between about 0.01 and about 0.2 molar equivalents and preferably between about 0.05 and about 0.15 about based upon the amount of epoxide.

The protecting agent is used in a slight excess, preferably in an amount between about 1 and 1.5 molar equivalents and preferably between about 1 and about 1.1 molar equivalents based upon the amount of epoxide.

10 The reaction mixture may also include an inhibitor. Any free radical inhibitor may be used and suitable non-limiting examples include MEHQ, BHT, phenothiazine, hydroquinones, mixtures thereof and the like. The initiator may be used in amounts between about 1 and about 1000 ppm, and more preferably between about 1 and about 750 ppm.

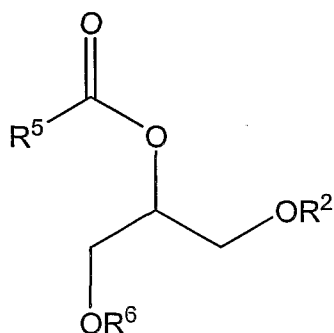
15 The carboxylic acid may be used in a slight excess as the solvent or any non-reactive solvent may be used. Suitable non-reactive solvents are those that do not contribute or detract from the desired reaction at the selected reaction conditions, and include, but are not limited to non-nucleophilic solvents such as DMF, benzene, THF, mixtures thereof and the like.

20 The reaction is conducted at elevated temperatures, preferably greater than about 60°C and more preferably between about 80°C and about 120°C.

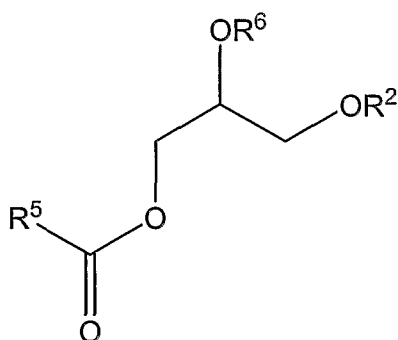
Suitable reaction times include at least about 4 hours, preferably at least about six hours and more preferably between about 6 and about 15 hours. It will be appreciated by those of skill in the art the temperature and reaction time are inversely proportional, and that
25 higher reaction temperatures may allow for decreased reaction times and vice versa. Also, other reaction conditions, which effect the reaction, such as catalyst concentration, may also be varied to vary the reaction time and temperature of the process of the present invention.

The product of the reaction is a compound of Formula VI or VII, below:

Formula VI



Formula VII



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wherein R^2 , R^5 are as defined above and R^6 is a residue of the protecting group which is capable of forming an ester or an ether linkage.

In one embodiment the protecting agent is an anhydride and the product of the process of the present invention is a diester which contains siloxane moieties and has a purity of at least about 80%. The purity of the diester is further increased by treating a solution in hexanes with flash grade silica gel. The silica gel slurry is agitated (trituated) for a few hours and filtered to remove significant quantities of impurities that are more polar than the desired product. Alternatively, the purity of the vicinal diester may be increased by other purification such as supercritical fluid extraction.

Thus, the process of the present invention provides a one-pot tandem chemical transformation where an epoxide is first opened by reaction with a carboxylate and the resulting alcohol is rapidly trapped by the anhydride to form the desired vicinal diester. Many of the side reactions that occur due to the presence of hydroxyl groups and silicone moieties in the reaction mixture are avoided because the hydroxyl groups in the reaction mixture are short lived.

In order to illustrate the invention the following examples are included. These examples do not limit the invention. They are meant only to suggest a method of practicing the invention. Those knowledgeable in contact lenses as well as other specialties may find other methods of practicing the invention. However, those methods
5 are deemed to be within the scope of this invention.

Example 1

The following reactants were charged to a dry 100mL, 3 neck round bottom flask equipped with a magnetic stirrer, thermocouple, and a drying tube in the order and amounts
10 listed below:

1.47g	lithium methacrylate (0.016 mole)
12.9mg	butylated hydroxytoluene
16.17g	methacrylic anhydride (0.105 mole)
15 17.20g	methacrylic acid (0.2 mole)
33.60g	glycidoxypentyl heptamethyltrisiloxane (0.1 mole)

The mixture was stirred vigorously, and heated to 100° C for 7.5 hours. Once the reaction was complete, it was allowed to cool to ambient conditions, and transferred to a
20 500 mL separatory funnel.

The organics were diluted with 100mL of hexanes, washed with 3x200mL of 0.5N aqueous NaOH, followed with 3x100mL of 2.5% aqueous NaCl. The organics were dried with 5.0g of sodium sulfate, and the material was filtered over a fritted glass funnel.

The filtrate was treated with 15g of silica gel, and the system was trituated for 3
25 hours. The organics were filtered over a fritted glass funnel, and the trituration was repeated using an additional 15g of silica gel for another 3 hours. The desired product was isolated after filtration over a fritted glass funnel, followed by evaporation of volatile components at 55°C under a vacuum pf <10mbar. The purity of vicinal diester before and after trituration is shown in Table 1, below.

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Examples 2-6

The reaction described in Example 1 was repeated; but the conditions were varied as shown in Table 1. The purity of the vicinal diester before & after trituration is also shown in Table 1.

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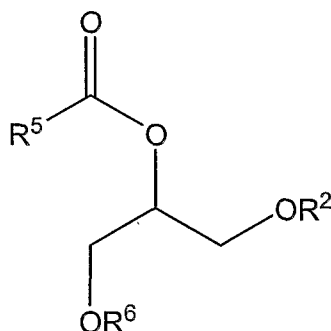
Table 1

Ex. #	Temp. (°C)	Methacrylic anhydride/epoxide	Purity of Crude Material	Purity - 1 trituration	Purity -2 tritutations	Purity - 4 tritutations	Silica gel/epoxide per trituation	Epoxide scale (g)
1	100	1.05	83.2		89.9		0.45	33.6
2	90	1.05	82.2		89.6		0.45	33.6
3	90	1.1	82.5		89.4		0.45	33.6
4	90	1.05		82.4	86.3	89.2	0.25	
5	90	1.05	81.1		87.8		0.45	1000
6	100				88.60		0.45	500

WE CLAIM

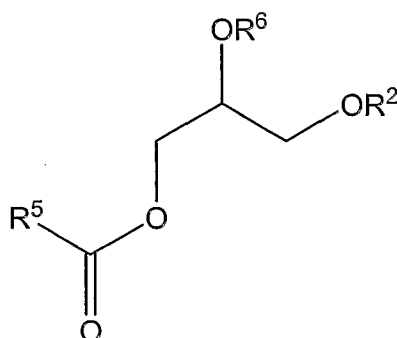
1. A process comprising the steps of reacting a substituted epoxide with at least one epoxide opening catalyst, at least one carboxylic acid, at least one protecting agent and at least one inhibitor at a temperature above about 60°C for at least about 4 hours to form a compound of Formula VI or VII:

Formula VI



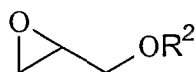
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Formula VII



- 15 wherein R² is any group which reacts more slowly with an oxygen containing nucleophile as compared to said epoxide, R⁵ is a straight or branched alkyl and alkenyl groups having 1 to 10 carbon atoms and R⁶ is a residue of said protecting group which is capable of forming an ester or ether linkage.

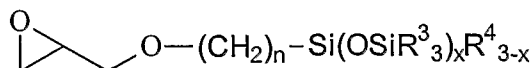
2. The process of claim 1 wherein said substituted epoxide is a compound of Formula II



wherein R^2 is selected from the group consisting of esters, amides, substituted and unsubstituted alkyls, siloxanes and ethers.

3. The process of claim 2 wherein R^2 is selected from the group consisting of C1 to 3 alkyls substituted with at least one Si containing substituent.

4. The process of claim 1 wherein said substituted epoxide is a compound of formula III:



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wherein R^3 and R^4 are independently selected from alkyl groups having 1 to 3 carbon atoms, n is 1 to 3 and x is 0 to 3.

5. The process of claim 1 wherein said protecting agent is selected from the group consisting of anhydrides, trimethylsilylchloride and allyl halide.

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6. The process of claim 5 wherein said protecting agent is an anhydride having the formula $R^5\text{CO}_2\text{OCR}^5$, wherein R^5 may be the same or different, and is selected from the group consisting of straight or branched alkyl and alkenyl groups having 1 to 10 carbon atoms.

7. The process of claim 5 wherein R^5 is selected from alkenyl groups having 1-5 carbon atoms.

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8. The process of claim 5 wherein R^5 is selected from vinyl, styryl and allyl.

9. The process of claim 1 wherein said carboxylic acid $R^5\text{CO}_2\text{H}$, wherein R^5 is selected from the group consisting of straight or branched alkyl and alkenyl groups having 1 to 10 carbon atoms.

10. The process of claim 9 wherein R^5 is selected from alkenyl groups having 1-5 carbon atoms.

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11. The process of claim 9 wherein R^5 is selected from vinyl, styryl and allyl.

12. The process of claim 1 wherein said epoxide opening catalyst is selected from the group consisting of Lewis acids, Lewis bases, Bronsted acids and porphyrin complexes.

13. The process of claim 1 wherein said epoxide opening catalyst comprises an alkali metal salt.

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14. The process of claim 13 wherein said alkali metal salt comprises at least one cation selected from the group consisting of Li, Na, K and ammonium.

15. The process of claim 13 wherein said alkali metal salt comprises Li methacrylate or Na methacrylate.

5 16. The process of claim 1 wherein said epoxide opening catalyst is added in an amount up to about 0.5 equivalents, based upon the epoxide.

17. The process of claim 1 wherein said carboxylic acid is used in an amount between about 0.01 and about 0.2 molar equivalents based upon the amount of epoxide.

10 18. The process of claim 1 wherein said protecting agent is used in an amount between about 1 and 1.5 molar equivalents based upon the amount of epoxide.

19. The process of claim 1 wherein said inhibitor is selected from the group consisting of MEHQ, BHT, phenothiazine, hydroquinones and mixtures thereof.

20. The process of claim 1 wherein said initiator is used in amounts between about 1 and about 1000 ppm.

15 21. A process comprising the step of reacting glycidoxypentyl
heptamethyltrisiloxane with at least one carboxylate salt, at least one carboxylic acid, at
least one protecting agent and at least one inhibitor at a temperature above about 60°C for
at least about 4 hours to form bis(trimethylsilyloxy)silylalkylglycerol methacrylate.

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