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1988,GASTON, PA US pages 7538 - 7539; YUN GAO: ‘Vicinal Diol Cyclic Sulfates:Like Epoxides Only More Reactive’

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1. FIELD OF THE INVENTION

The present invention relates to a method for the stereoselective transformation of a diol into an alcohol via a cyclic sulfite moiety. In particular, the present invention relates to the formation of a cyclic sulfite moiety from a 1,2- or 1,3-diol, the ring-opening displacement of the cyclic sulfite by a suitable nucleophile and the subsequent removal of the attached nucleophile under reducing conditions. The present invention is stereoselective in that any optical activity present in the initial diol substrate is preserved in the product alcohol.

The disclosed method is particularly suitable for the preparation of the D- or L-isomers of malic acid.

2. BACKGROUND OF THE INVENTION

2.1. Stereochemistry

The study of the spatial arrangement of atoms in a compound and their relation to the properties of the compound is called stereochemistry. Stereoisomers are molecules which possess identical chemical formulas with the same atoms bonded to one another, however they differ in the manner in which these atoms are arranged in three dimensional space. Optical isomers or enantiomers are molecules that are mirror images but are nonetheless nonsuperimposable. Such molecules can rotate the plane of plane-polarized light. Molecules that exhibit this phenomenon are said to be optically active. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). A chiral center is usually an asymmetric carbon atom, that is, one with four different groups attached to it. The prefixes (+) and (-) or d and l are employed to designate the sign of rotation of plane-polarized light by the compound. A compound with the prefix (+) or l is levorotatory. A levorotatory compound rotates plane-polarized light to the left (counterclockwise). A compound prefixed with (+) or d is dextrorotatory. A dextrorotatory compound rotates plane polarized light to the right (clockwise). As mentioned above, a specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric or racemic mixture.

The property of optical activity is due to molecular asymmetry about carbon atoms that are linked to four different atoms. Where there is only one asymmetric carbon atom, or chiral center as it is sometimes called, there are two possible stereoisomers. Where there are n asymmetric carbons or chiral centers, the number of potential stereoisomers increases to \(2^n\). Thus, a molecule with three chiral centers would have eight possible stereoisomers.

While the structural differences between stereoisomers are subtle and of little consequence in ordinary chemical reactions, they may be profound where biological systems are concerned, i.e., if the compounds are utilized in enzyme-catalyzed reactions. Thus, the L-amino acids are metabolized in humans but the corresponding D-analogs are not, and only D-glucose can be phosphorylated and processed into glycogen or degraded by the glycolytic and oxidative pathways or intermediary metabolism. Similarly, beta blockers, pheromones, prostaglandins, steroids, flavoring and fragrance agents, pharmaceuticals, pesticides, herbicides and many other compounds exhibit critical stereospecificity. In the field of pesticides, Tessier (Chemistry and Industry, 1984, March 19, 199) has shown that only two of the eight stereoisomers of deltamethrin, a pyrethroid insecticide, have any biological activity. The same statement concerning the concentration of bioactivity in a single isomer can be made about many other pesticides, including the phenoxypropionate and haloxypropionate derivatives, each containing one chiral center and existing in the form of two optical isomers.
Stereocchemical purity is of equal importance in the field of pharmaceuticals, where 12 of the 20 most prescribed drugs exhibit chirality. A case in point is provided by naproxen, or (+)-S-2-(6-methoxy-2- naphthyl)propionic acid, which is one of the two most important members of a class of 2-arylpropanoic acids with non-steroidal anti-inflammatory activity used, for instance, in the management of arthritis. In this case, the S(+) enantiomer of the drug is known to be 28 times more therapeutically potent than its R(-) counterpart. Still another example of chiral pharmaceuticals is provided by the family of beta-blockers; the L-form of propranolol is known to be 100 times more potent than the D-enantiomer.

Synthesis of compounds with asymmetric centers by standard organic synthetic techniques generally leads to a racemic mixture which, in the aggregate, may have a relatively low specific bioactivity since certain of the stereoisomers in the mixture are likely to be biologically or functionally inactive. As a result, larger quantities of the material must be used to obtain an effective dose, and manufacturing costs are increased due to the co-production of stereocchemically "incorrect" and hence, inactive ingredients.

Thus, optical purity or enantiomeric excess is a very important consideration in the design of chemical syntheses of optically active compounds.

2.2. Previous Methods for the Preparation of Malic Acid

Malic acid is an extremely valuable chiral starting material for synthesis of chiral complex natural products, agrochemicals and pharmaceuticals.

While the natural L- (+) or R-malic acid, also known as apple acid, is readily available, the unnatural D- (+) or S-isomer is more difficult to obtain. Due to its usefulness, extensive efforts have been directed to the preparation of optically pure malic acid and its derivatives. Several methods including enzymatic processes, catalytic asymmetric synthesis and asymmetric transformations of readily available chiral natural products have been developed.

For example, Chibata et al., (Pure and Appl. Chem. 1978, 50, 667) have utilized fumaric acid and immobilized fumarase to obtain a mixture of products containing 80% of the natural L-malic acid. However, this method cannot furnish the unnatural D-isomer due to the stereospecificity of the enzyme. Wynberg et al., (J. Am. Chem. Soc. 1982, 104, 166) have developed an asymmetric synthesis of D- and L-malic acid using chiral alkaloid-catalyzed cyclization of ketene and chloral, followed by stereoselective hydrolysis of the cyclized product. For example, L-malic acid can be obtained in three steps in 79% yield and 98% enantiomeric excess (ee) using quinidine as the catalyst. However, the unnatural D-malic acid can only be prepared in 76% ee using quinine as the catalyst.

Another strategy for the preparation of optically pure malic acid and its derivatives involves stereoselective transformations of readily available, inexpensive chiral natural products such as L-amino acid and optically pure tartaric acid and its derivatives. For example, Henrot et al., (Synth. Commun. 1986, 16, 183) are able to prepare L-and D-malic acid from L- and D-aspartic acid, respectively, in three steps and 66% yield. However, the synthesis of D-malic acid involves the use of less accessible and expensive D-aspartic acid.

Because of its abundance, tartaric acid, especially the natural L-isomer, has been widely used for the preparation of optically pure malic acid and its derivatives. From the naturally-occurring L-tartaric acid, the unnatural D-malic acid is produced. For examples, Hungerbühl et al., (Angew. Chem. Int. Ed. Engl. 1979, 18, 958) prepared D-dimethyl maleate from L-dimethyl tartrate via the reduction of the corresponding β- bromo maleate by tributyltin hydride in four steps and 44% yield. Alpegiani et al., (J. Org. Chem. 1987, 52, 278) obtained D-dimethyl maleate from L-dimethyl tartrate via the reduction of the corresponding thionocarbonate derivative by tributyltin hydride in two steps and 67% yield. Gao et al., (J. Am. Chem. Soc. 1988, 110, 7538) have developed a general method for the preparation of D-maleate from L-tartrate via the reduction of the corresponding tartrate cyclic sulfone by sodium cyanoborohydride. For example, D-diospropyl maleate is prepared in 50% overall yield from L-diospropyl tartrate. More recently Kusuda et al., (Tetrahedron Lett. 1989, 30, 2945) prepared D-diospropyl maleate from L-(+)-diospropyl tartrate directly by the reduction of the latter with samarium iodide in 99% yield. However, methods described above involve the use of expensive and hazardous reagents for the preparation of the intermediates and in subsequent reductions. Therefore, they are not amenable to the large-scale production of optically pure malic acid and its derivatives.

3. SUMMARY OF THE INVENTION

The present invention is directed to a process of transforming a compound of the formula I to a compound of the formula II.
in which \( n = 0 \) or 1, \( R_1, R_2, R_3 \) and \( R_4 \) represent independently a hydrogen atom, an aliphatic group, an aromatic group, an aromatic heterocyclic group, an aliphatic heterocyclic group or a carbonyl-containing group of the formula COY in which Y represents a hydrogen atom, a halogen atom, any of the groups recited previously for \( R_1-\) \( R_4 \), or a group of the formula W(R\(_6\))\(_m\) in which W represents a nitrogen atom, an oxygen atom or a sulfur atom and \( R_6 \) represents a hydrogen atom or any of the groups recited previously for \( R_1-\) \( R_4 \) provided that when W represents a nitrogen atom, \( m \) is equal to 2 and when W represents an oxygen atom or a sulfur atom, \( m \) is equal to 1 and \( R_6 \) may not be a hydrogen atom.

The principal steps of the process include: (a) allowing a compound of the formula I to react with a thionyl halide under conditions effective to form a cyclic sulfite; (b) allowing said cyclic sulfite to react with a suitable halide salt under conditions effective to form a halo-substituted acyclic sulfite; and (c) allowing said halide-substituted acyclic sulfite to react with a suitable reducing agent under conditions effective to provide a compound of the formula II.

In a particular embodiment of the present invention, a process is disclosed for the preparation of malic acid and its derivatives in which a tartaric acid derivative is transformed to the corresponding cyclic sulfite by reaction with a thionyl halide such as thionyl chloride or thionyl bromide. The resulting cyclic sulfite is then treated with an inorganic halide, followed by reduction of the resulting \( \beta \)-halo malic acid derivative with reducing metal or by noble-metal-catalyzed hydrogenation with hydrogen gas to give a malic acid derivative after workup. Malic acid is then obtained by a subsequent transformation of the malic acid derivative (e.g., by hydrolysis of the corresponding ester of malic acid). The intermediates can be isolated or more conveniently used without isolation, thus permitting the entire process to be performed in one reactor. The present invention can be more easily understood with reference to the general equation (exemplified by the preparation of D-malic acid derivative) shown below:
Equation 1:

It is, therefore, an object of the present invention to provide a process for the stereoselective transformation of a diol to an alcohol.

It is, likewise, an object of the present invention to provide a practical process for the preparation of malic acid and its derivatives in high yield and high optical purity from L- or D-tartaric acid and its derivatives. In particular, the present invention contemplates the preparation of the unnatural D-malic acid and its derivatives from natural L-tartaric acid and its derivatives using inexpensive reagents and simple procedures.

It is a further object of this invention to provide a practical route to L- or D-malic acid where a malic acid derivative is prepared by a practical process followed by hydrolysis of said malic acid derivative to malic acid.

4. NOMENCLATURE

Unless otherwise indicated, the term aliphatic group encompasses linear, branched or cyclic hydrocarbons, including those that may possess a combination of such structural features. In addition, such hydrocarbons may also contain various substituents in which one or more hydrogen atoms has been replaced by functional group (that is, the aliphatic group may also be substituted). Thus, groups of chemicals such as alkanes, alkenes and alkynes fall within the meaning of this term.

Unless otherwise indicated, the term aromatic group means a hydrocarbon ring bearing a system of conjugated double bonds, usually comprising six or more even number of \( \pi \) (pi) electrons, including those present as unshared pairs of electrons (i.e., lone pairs). Likewise, these aromatic groups may also be substituted with a variety of functional groups. Examples, of aromatic and substituted aromatic groups include, but are not limited to, phenyl, naphthyl, anisyl, tolyl, \( p \)-nitrophenyl and the like.

Aliphatic groups may also be substituted with aromatic groups (e.g., benzyl) and vice-versa (e.g., xylenyl). Heteroatoms, such as nitrogen, oxygen or sulfur, may also be present, particularly in cyclic structures, thus, giving rise to heterocycles, both aliphatic (e.g., tetrahydrofuranyl, tetrahydropyranyl, morpholino, piperidinyl, pyrrolidino and the like) and aromatic (e.g., imidazolino, furanyl, thiencyl, thiazolyl,
pyridinyl, pyrazinyl and the like).

5. DETAILED DISCUSSION OF THE INVENTION

In a general embodiment of the present invention, an efficient process for the replacement of one of two neighboring hydroxyl groups by hydrogen atom while retaining the stereochemistry of the diol substrate is disclosed. Thus, compounds of formula I, may be transformed readily and inexpensively to compounds of the formula II:

\[
\begin{align*}
\text{I} & : \quad R_1 \quad \text{OH} \quad \text{CH}_2 \quad R_2 \quad \text{OH} \quad R_4 \\
\text{II} & : \quad R_1 \quad \text{OH} \quad \text{H} \quad R_4
\end{align*}
\]

in which \( n = 0 \) or 1, \( R_1, R_2, R_3 \) and \( R_4 \) represent independently a hydrogen atom, an aliphatic group, an aromatic group, an aromatic heterocyclic group, an aliphatic heterocyclic group or a carbonyl-containing group of the formula \( COY \) in which \( Y \) represents a hydrogen atom, a halogen atom, any of the groups recited previously for \( R_1-R_4 \) or a group of the formula \( WR_6 \) in which \( W \) represents a nitrogen atom, an oxygen atom or a sulfur atom and \( R_6 \) represents a hydrogen atom or any of the groups recited previously for \( R_1-R_4 \) provided that when \( W \) represents a nitrogen atom, \( m \) is equal to 2 and when \( W \) represents an oxygen atom or a sulfur atom, \( m \) is equal to 1 and \( R_6 \) may not be a hydrogen atom.

In one embodiment of the present invention, \( R_1 \) and \( R_2, R_3, R_4, R_5, R_6, R_7 \) or \( R_2, R_3 \) of the diol of the formula (I) represent the same atom or group and are used as starting materials for the formulation of cyclic sulfoxide intermediates useful in the preparation of malic acid and its derivatives.

The cyclic sulfoxide is formed by the reaction of a compound of formula (I) with a thionyl halide such as thionyl chloride or bromide without solvent or in an inert solvent such as methylene chloride, ethyl acetate and dimethoxyethane (DME) at about 20-100°C in the presence of catalytic amount of N,N-dimethylformamide (DMF). The hydrogen halide formed during the reaction can be swept away with an inert gas and trapped with a basic solution or recycled. A stoichiometric amount of thionyl halide can be used. In practice, a slight excess (1.1-1.2 equivalents) of thionyl halide is used to ensure a complete reaction. The cyclic sulfoxide, which comprises a five-membered or a six-membered ring depending on the choice of compound I, can be isolated and purified if desired; however, it can be used directly, simply by removing the solvent.

The cyclic sulfoxide thus obtained is then treated with a suitable halide salt in a polar solvent at about 40-100°C in a separate or same reactor. The halides are inorganic halide salts, such as ammonium halide salts, alkali metal halide salts or alkaline-earth metal halide salts, for example, ammonium bromide, lithium bromide, lithium chloride, barium chloride, magnesium bromide, sodium iodide, sodium bromide, calcium chloride and the like. The suitable halide salt may also be an organic halide salt such as a tetra-alkyl substituted ammonium halide. A stoichiometric amount of halide salt is needed, but in practice 1.5-2.0 equivalents of halide salt are used to insure complete conversion. The resulting \( \beta \)-halo acyclic sulfoxide derivatives can be isolated, but more conveniently they are used without isolation.

Reduction of the \( \beta \)-halo acyclic sulfoxide derivatives, produced upon reaction of the cyclic sulfites with halide salt, may be performed either by treatment with finely divided active metal such as zinc, iron and tin or by catalytic hydrogenation in the presence of noble metals. For instance, reduction can be carried out with hydrogen in the presence of catalytic amounts of palladium on carbon or Raney nickel. After the \( \beta \)-halo acyclic sulfoxide is completely consumed, the desired compound of formula II can be obtained by filtration and extractive workup.

5.1. Preferred Embodiment

In a preferred embodiment of the present invention, dialkyl, or diaryl esters or amides of L- or D-tartaric acid are used as the starting materials for the formation of cyclic sulfoxide intermediates useful in the preparation of malic acid and its derivatives. Examples of esters include dimethyl, diethyl, and disopropyl tartrates, which can be made by reaction of tartaric acid with the corresponding alcohol in the presence of
an acid catalyst (e.g., H$_2$SO$_4$ or HCl). Other dialkyl esters or diaryl esters may be prepared likewise.

The cyclic sulfite is formed by the reaction of a tartrate or tartramide with a thionyl halide such as thionyl chloride or bromide without solvent or in an inert solvent such as methylene chloride, ethyl acetate and dimethoxyethane at 20°C to 100°C in the presence of catalytic amount of N,N-dimethylformamide (DMF). The hydrogen halide formed during the reaction is swept away with an inert gas and trapped with a basic solution or recycled. A stoichiometric amount of thionyl halide can be used. In practice, a slight excess (1.1-1.2 equivalents) of thionyl halide is used to ensure a complete reaction. The reaction is normally complete in less than 10 hours. After the reaction, the excess thionyl halide is removed by distillation if isolation of the resulting cyclic sulfite is desired; this is done by distillation under vacuum. More conveniently the cyclic sulfite can be used directly, simply by removing the solvent without isolation and further purification. In some cases the solvent is used for the next reaction without removal.

The cyclic sulfite thus obtained is then treated with a suitable halide salt in a polar solvent (preferably a polar aprotic one) at 20°C to 100°C in a separate reactor or the same reactor according to Equation 1. The halides are either organic halide salts such as ammonium or tetra-alkylammonium halide or inorganic halide salts such as alkali metal or alkaline-earth metal salts, for example, lithium bromide, lithium chloride, magnesium bromide, calcium chloride, sodium iodide and the like. A stoichiometric amount of halide is needed, but in practice 1.5-2.0 equivalents of halide are used to ensure complete conversion. Useful solvents include acetone, tetrahydrofuran (THF), dimethyl-formamide (DMF) and dimethoxyethane (DME) and the like. The concentration of the solution is about 0.5 M and above. The reaction can be monitored by thin layer chromatography on silica gel and is usually complete in less than 12 hours. The resulting β-halo malic acid derivatives can be isolated, but more conveniently they are used without isolation. The β-halo malic acid derivatives are known and can also be obtained from a different route involving the reaction of tartaric acid derivatives such as dialkyl tartrate with phosphorus pentachloride or phosphorus tribromide (Beilstein’s Handbuch der Organischen Chemie, Band III, 419).

Reduction of the β-halo malic acid derivatives produced upon the reaction of the cyclic sulfites with halide is performed either by an active metal such as zinc, iron, and tin or by catalytic hydrogenation with noble metals such as palladium, Raney nickel and the like. For example, after the cyclic sulfite is completely consumed, zinc dust, pre-washed with dilute hydrochloric acid, is added. If the cyclic sulfite is formed in situ from tartrate, a catalytic amount of water is added to the reaction mixture after the addition of zinc. If the cyclic sulfite is first isolated for use as the starting material, water is used as a co-solvent in an amount equal to that of the organic solvent. The reaction mixture is kept at the same temperature as the ring opening step and vigorously stirred. Preferably, the amount of zinc present is about 2-3 equivalents of the cyclic sulfite. The reaction is usually completed in less than 10 hours. The desired malic acid derivative can be obtained by filtration and extractive workup.

The alternative process for reduction of the β-halo malic acid derivatives by catalytic hydrogenation is performed under 15-50 psi of hydrogen pressure and at ambient temperature. Useful catalysts include palladium on carbon, Raney nickel, and the like. Effective solvents are usually aqueous-organic mixtures produced by the addition of water to the mixture resulting from the reaction of the cyclic sulfite with halide. Hydrogenation may also be carried out in the presence of an alcohol or an aromatic solvent. To ensure complete and fast reaction, a base is added to the reaction to neutralize the resulting hydrogen halide. The base is usually a metal oxide such as magnesium oxide, a hydroxide such as calcium hydroxide or potassium hydroxide, other base such as sodium acetate, or a tertiary amine such as triethylamine. The desired malic acid derivative is obtained by filtration and usual workup.

A typical workup procedure is as follows: the reaction mixture from the reduction step is filtered to remove the zinc residue or noble metal catalyst, which can be recovered. The filtrate is then acidified with dilute hydrochloric acid and extracted with an organic solvent such as ethyl acetate, ether, or methylene chloride. The combined extracts are then washed with saturated sodium chloride and sodium bicarbonate solutions and dried over anhydrous magnesium sulfate or sodium sulfate. The crude product after removal of the solvent is then purified, e.g., by distillation or chromatography on silica gel.

The overall yield of the reaction from tartrate as shown in Equation 1 is usually in the range of 65-82%. The optical purity of the malic acid derivative product is determined by 1H NMR analysis of the ester produced by the reaction of the malate compound with (S)α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride. The optical purity of the malic acid derivatives typically produced in the disclosed method is substantially 100% indicating that no racemization has occurred during the various reactions and that the reactions proceed with high stereoselectivity.

Known methods can be employed to produce malic acid from the malate derivatives of the present invention. For example, malate esters can be hydrolyzed with base, e.g., aqueous alcohol sodium hydroxide under refluxing conditions. In addition, known methods can be used to produce tartaric acid derivatives from
tartaric acid, with said derivatives subsequently used as starting material.

5.2. EXAMPLES

In order to more fully illustrate the nature of the invention and the manner of practicing the same, the following examples are provided, which are not to be construed as limiting the remainder of the disclosure in any way whatsoever.

5.3. General Experimental Conditions

Reactions are performed in a three-neck round-bottomed flask equipped with a reflux condenser, a thermometer and a magnetic stirring bar, either under nitrogen atmosphere or under dry air using a drying tube. Catalytic hydrogenations are performed in a Parr hydrogenation apparatus. All solvents are anhydrous or are dried before use.

Analytical thin-layer chromatography (TLC) is performed on glass silica gel plates (0.25 mm thick E. Merck silica gel 60-F254). Flash chromatography is performed on E. Merck 40-63-μm normal phase silica gel eluting with 15% to 20% or 50% ethyl acetate in hexane.

All proton NMR spectra are run on a Varian EM 360 60 MHz spectrometer using CDCl₃ as the solvent and tetramethylsilane as an internal standard. Optical purities of the maleate products are determined by ¹H NMR analysis of the derived esters from the reaction of the maleates with (S)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid on a Bruker 300 MHz spectrometer in CDCl₃ which in all cases showed 100% enantiomeric excess. Infrared spectra are taken on a Nicolet 5DX FT-IR spectrometer. Optical rotations are obtained on a Perkin-Elmer 243 polarimeter.

All reagents are obtained from commercial sources and used without further purification unless otherwise stated. Zinc dust is treated briefly with 10% HCl solution and then is washed with distilled water and acetone and is dried under vacuum.

The tartrate cyclic sulfites are prepared in ≥98% yield according to the known procedure (E. Schiller, Berichte 1909, 42, 2017) with small modifications by reaction of tartrates with thionyl chloride without solvent or in minimum amount of solvent. From L-(+)-tartrates, (−)-tartrate cyclic sulfites are obtained. They are either used without isolation or isolated by removing the solvent and then used without further purification.

5.4. Preparation of D-(+)-diisopropyl malate

LiBr (1.3 g, 15 mmol) is added slowly to a cold (ice-water bath) solution of (−)-diisopropyl tartrate cyclic sulfite (2.8 g, 10 mmol) in 10 mL of DME. After addition, the mixture is heated to ca. 60-70 °C and is stirred for 2 hrs. Thin Layer Chromatography (TLC) shows the starting cyclic sulfite is consumed. Water (10 mL) is added, followed by zinc dust (2.0 g, 30 mmol). The mixture stirs vigorously at the same temperature for 2 hrs. and is cooled. The mixture is filtered through Celite. The solid residue is washed thoroughly with water (2×10 mL) and ethyl acetate (2×10 mL). The aqueous phase is separated, acidified with conc. HCl and extracted with 3×20 mL of ethyl acetate. The combined organic phase is then washed with brine and saturated NaHCO₃ and is dried over MgSO₄. After removal of the solvent, the crude product is purified by flash chromatography on silica gel eluting with 15% EtOAc in hexane to afford 1.8 g (82%) of the title compound as a colorless liquid. [α]D₂₀ +12.2° (c 1.02, EtOH). ¹H NMR: δ 4.9-5.4 (m, 2H), 4.5 (d, d, J = 5 Hz, 6 Hz, 1H), 3.3 (d, J = 5 Hz, 1H), 2.8 (d, J = 6 Hz, 2 H), 1.3 (d, d, J = 6 Hz, 12 H); IR (neat) 3500, 2981, 1743, 1456, 1378, 1223, 1109, 960, 826 cm⁻¹.

5.5. Preparation of D-(−)-diisopropyl malate

LiBr (2.6 g, 30 mmol) is added slowly to a cold (ice water bath) solution of (−)-diisopropyl tartrate cyclic sulfite (5.6 g, 20 mmol) in 20 mL of THF. After addition, the mixture is heated to ca. 60 °C and is stirred for 16 hrs. Water (20 mL) is added, followed by zinc dust (2.6 g, 40 mmol). The mixture is stirred vigorously at the same temperature for 2 hrs. and is cooled. The reaction is worked up and the product is purified as Example 5.4 to give the title compound (3.8 g, 82%). [α]D₂₀ +9.6° (c 2.24, EtOH).
5.6. Preparation of methyl 2-ethyl-3-methyl-3-hydroxypropionate

LiBr (1.3 g, 15 mmol) is added to a cold solution (icebath) of three-methyl 2-ethyl-3-methyl-2,3-dihydroxyglycidate cyclic sulfite (2.1 g, 10 mmol) in 10 mL of DME. After addition, the mixture is heated to ca 60-70 °C and stirred for 5 h. Water (10 mL) is added, followed by zinc dust (2.0 g, 30 mmol). The mixture is stirred vigorously at the same temperature for 2 h. The reaction is worked up as in Example 5.4 and the crude product is purified by chromatography on silica gel eluting with 25% EtOAc in hexane to give the title compound.

5.7. Preparation of D-(+)-diisopropyl malate

LiCl (1.7 g, 40 mmol) is added slowly to a solution of (-)-diisopropyl tartrate cyclic sulfite (5.6 g, 20 mmol) in 20 mL of DMF at room temperature. After addition, the mixture is heated to ca. 70 °C and is stirred for 3 hrs. TLC shows the starting cyclic sulfite is consumed. Water (20 mL) is added, followed by zinc dust (3.9 g, 60 mmol). The mixture is stirred vigorously at the same temperature for 3 hrs. and cooled. The reaction is worked up and the product is purified as Example 5.4 to afford the title compound (2.94 g, 67%). [α]25D +10.8° (c 2.24, EtOH).

5.8. Preparation of methyl 3-hydroxy-3-isopropyl propionate

LiBr (1.3 g, 15 mmol) is added to a cold solution (icebath) of methyl 3-isopropyl 2,3-dihydroxyglycidate cyclic sulfite (2.1 g, 10 mmol) in 10 mL of DME. After addition, the mixture is heated to ca 60-70 °C and stirred for 5 h. Water (10 mL) is added, followed by zinc dust (2.0 g, 30 mmol). The mixture is stirred vigorously at the same temperature for 2 h. The reaction is worked up as in Example 5.4 and the crude product is purified by chromatography on silica gel eluting with 25% EtOAc in hexane to give the title compound.

5.9. Preparation of D-(+)-diisopropyl malate from L-(+)-diisopropyl tartrate

Thionyl Chloride (8.1 mL, 110 mmol) is added dropwise to L-(+)-diisopropyl tartrate (23.4 g, 100 mmol), followed by 10 drops of DMF. The solution is slowly heated to ca. 50 °C and is stirred while the HCl which evolves is swept away by nitrogen and is trapped with a NaOH solution. After 30 minutes, the solution is cooled and acetone (200 mL) is added. The solution is cooled to ca. 5 °C and LiBr (13 g, 150 mmol) is added in portions. During addition, the temperature rises to ca 10 °C. The resulting mixture is refluxed at 50 °C for 12 hrs. The mixture cools and is transferred to a hydrogenation flask containing 10% Pd/C (3.5 g) and MgO (14 g, 350 mmol) in the presence of 150 mL of water. The mixture is hydrogenated at 25 °C under 15 psi of H2 for 5.5 hrs. The mixture is filtered through Celite and the filtrate is concentrated to remove acetone and is worked up as Example 5.4 using CH2Cl2 as the extraction solvent. The crude product is distilled at 78-80 °C/0.4 mmHg to afford the title compound (17.4 g, 80%). [α]25D +11.6° (c 2.56, EtOH).

5.10. Preparation of methyl 2-methyl-3-ethyl-3-hydroxypropionate

LiBr (1.3 g, 15 mmol) is added to a cold solution (icebath) of three-methyl 2-methyl-3-ethyl 2,3-dihydroxyglycidate cyclic sulfite (2.1 g, 10 mmol) in 10 mL of DME. After addition, the mixture is heated to ca 60-70 °C and stirred for 5 h. Water (10 mL) is added, followed by zinc dust (2.0 g, 30 mmol). The mixture is stirred vigorously at the same temperature for 2 h. The reaction is worked up as in Example 5.4 and the crude product is purified by chromatography on silica gel eluting with 25% EtOAc in hexane to give the title compound.

5.11. Preparation of D-(+)-diethyl malate

LiBr (13 g, 150 mmol) is added slowly to a cold (ice-water bath) solution of (-)-diethyl tartrate cyclic sulfite (25.2 g, 100 mmol) in 100 mL of DME. After addition, the mixture is heated to ca. 80 °C and is stirred for 2 hrs. TLC shows the starting cyclic sulfite is consumed. Water (100 mL) is added, followed by zinc dust (20 g, 300 mmol). The mixture is stirred vigorously at the same temperature for 1 hr. and cooled. The reaction is worked up as Example 5.4 and the product is purified by distillation at 86-90 °C/14 mm Hg to give the title compound as a colorless liquid (15.7 g, 82%). [α]25D +10.7° (c 2.29, EtOH). 1H NMR: δ 4.5
5.12. Preparation of D-(+)-N,N,N',N'-tetraethyl malamide from L-(+)-N,N,N', N'-tetraethyl tartramide

Thionyl chloride (8.1 mL, 110 mmol) is added dropwise to L-(+)-N,N,N',N'-tetraethyl tartramide (26.0 g, 100 mmol) in ca. 30 mL of DME. The mixture is slowly heated to ca. 50-60 °C and stirred while the evolved HCl gas is swept away by nitrogen. After all the tartramide is consumed, the mixture is cooled to ambient temperature and DME (170 mL) is added. The solution is cooled to ca. 5 °C and LiBr (13 g, 150 mmol) is added in portions. The resulting mixture is then heated at 60-70 °C for 12 h. Zinc dust (16.4 g, 250 mmol) is added followed by ca. 1 mL of water. The mixture is stirred at the same temperature for 2 h. The reaction is then worked up as Example 5.4 and the crude product is distilled to give the title compound.

5.13. Preparation of D-(+)-diethyl malate from L-(+)-diethyl tartrate

Thionyl Chloride (8.1 mL, 110 mmol) is added dropwise to L-(+)-diethyl tartrate (20.6 g, 100 mmol), followed by 10 drops of DMF. The solution is slowly heated to ca. 50 °C and stirred while the HCl which evolves is swept away by nitrogen and is trapped with a NaOH solution. After one hour, the solution cools and acetone (100 mL) is added. The solution is cooled to ca. 0 °C and LiBr (17.4 g, 200 mmol) is added in portions. During addition, the temperature raised to ca. 10 °C. The resulting mixture is refluxed at 45-50 °C for 7 hrs. Zinc (16.4 g, 250 mmol) is added, followed by 0.5 mL of water. The mixture is stirred at the same temperature for 2 hrs. The reaction is worked up as Example 5.4 and the crude product is distilled to give the title compound (13.3 g, 70%). \([\text{a}]_{D}^{25} +10.5^\circ (c 2.05, \text{EtOH})\).

5.14. Preparation of D-(+)-diethyl malate

LiBr (2.6 g, 30 mmol) is added slowly to a cold (ice water bath) solution of (-)-diethyl tartrate cyclic sulfite (5.1 g, 20 mmol) in 20 mL of DME. After addition, the mixture is heated to ca. 50 °C and stirred for 5 hrs. TLC showed the starting cyclic sulfite is consumed. The mixture is cooled and transferred with the aid of 20 mL of DME to a hydrogenation flask containing 10% Pd/C (1.5 g) and MgO (2.4 g, 60 mmol) in 100 mL of water. The mixture is hydrogenated at 25 °C under 50 psi of H₂ for 30 minutes. The mixture is filtered and worked up as Example 5.9. The crude product is purified by flash chromatography eluting with 15% EtOAc in hexane to provide the title compound (2.45 g, 64%). \([\text{a}]_{D}^{25} +10.3^\circ (c 2.23, \text{EtOH})\).

5.15. Preparation of D-(+)-diphenyl malate from L-(+)-diphenyl tartrate

Thionyl chloride (8.1 mL, 110 mmol) is added dropwise to L-(+)-diphenyl tartrate (30.2 g, 100 mmol) in ca. 30 mL of EtOAc. The mixture is slowly heated to ca. 50-60 °C and stirred while the evolved HCl gas is swept away by nitrogen. After all the tartrate is consumed, the mixture is cooled to ca. 5 °C and LiBr (13.0 g, 50 mmol) is added in portion. The resulting mixture is then refluxed for 12 h. The mixture is cooled to ambient temperature and transferred to a hydrogenation flask containing 10% Pd on carbon (3.5 g) and MgO (14 g, 350 mmol) in the presence of 150 mL of water. The mixture is hydrogenated at ambient temperature under 15-50 psi of hydrogen until completion. The mixture is then filtered and worked up as Example 5.9. The crude product can be purified by chromatography on silica gel eluting with 25% EtOAc in hexane to give the title compound.

5.16. Preparation of D-(+)-diethyl malate

LiBr (2.6 g, 30 mmol) is added slowly to a cold (ice water bath) solution of (-)-diethyl tartrate cyclic sulfite (5.1 g, 20 mmol) in 20 mL of DME. After addition the mixture is heated to ca. 70 °C and stirred for 12 hrs. TLC showed the starting cyclic sulfite is consumed. The mixture is cooled and transferred to a hydrogenation flask containing active Raney nickel (10 g, 50% slurry in water, pH > 9) in 150 mL of MeOH. The mixture is hydrogenated at 25 °C under 50 psi of H₂ pressure for 5 hrs. The mixture is filtered, the filtrate is concentrated and worked up as Example 5.9. The crude product is purified by flash chromatography eluting with 15% and 20% EtOAc in hexane to provide the title compound (2.67 g, 70%). \([\text{a}]_{D}^{25} +9.9^\circ (c 2.22, \text{EtOH})\).
5.17. Preparation of D-(+)-diethyl maleate

LiBr (2.6 g, 30 mmol) is added slowly to a solution of (−)-diethyl tartrate cyclic sulfite (5.1 g, 20 mmol) in 20 mL of acetone at 0°C. During addition, the temperature is warmed up to 10°C. After addition, the mixture is refluxed at ca. 50°C and stirred for 6 hrs. TLC showed the starting cyclic sulfite is consumed. The mixture is cooled and transferred to a hydrogenation flask containing 10% Pd/C (1.0 g) and MgO (2.4 g, 60 mmol) in 100 mL of water. The mixture is hydrogenated at 25°C under 15-40 psi of H2 pressure for 2 hrs. The mixture is filtered and worked up as Example 5.9. The crude product is purified by flash chromatography eluting with 15% and 20% EtOAc in hexane to provide the title compound (2.83 g, 74%).

[α]D20 +10.6° (c 2.22, EtOH).

5.18. Preparation of D-(+)-dimethyl maleate from L-(+)-dimethyl tartrate

Thionyl chloride (8.1 mL, 110 mmol) is added dropwise to a suspension of L-(+)-dimethyl tartrate (17.8 g, 100 mmol) in 25 mL of EtOAc. The mixture is heated at 60°C for 15 hrs. The resulting solution is diluted with 100 mL of DME and then is cooled to 0°C. LiBr (17.4 g, 200 mmol) is added in portions. The resulting mixture is heated at 70°C and stirred for 2 hrs. Zinc dust (16.4 g, 250 mmol) is added and the mixture is refluxed at 80°C for 5 hrs. The mixture is cooled and worked up as Example 5.4. Because the product is water soluble, low recovery results. The crude product is purified by chromatography diluting with 20% and 50% EtOAc in hexane to give the title compound as a colorless liquid (6.17 g, 38%). [α]D20 +9.1° (c 2.15, EtOH). 1H NMR: δ 4.5 (t, J = 6 Hz, 1 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.5 (bs, 1 H), 2.8 (d, J = 6 Hz, 2 H); IR (neat) 3494, 3008, 2959, 1743, 1440, 1370, 1279, 1222, 1173, 1110, 1046, 1004, 850 cm⁻¹.

5.19. Preparation of D-(+)-diisopropyl maleate

CaCl2 (2.22 g, 20 mmol) is added to a solution of (−)-diisopropyl tartrate cyclic sulfite (2.8 g, 10 mmol) in 10 mL of DMF. After addition, the mixture is heated to ca 60°C and stirred for 16 h. Water (10 mL) is added, followed by zinc dust (2.0 g, 30 mmol). The mixture is stirred vigorously at 70°C for 5 h. The reaction is worked up as in Example 5.4 and the crude product is purified by chromatography on silica gel eluting with 25% EtOAc in hexane to give the title compound as a colorless oil (0.86 g, 40% yield).

The preceding examples are given as an illustration of specific embodiments of the present invention. These examples are, thus, not to be construed as limiting the scope of the invention in any way. Indeed, other embodiments of the present invention are readily apparent to those of ordinary skill from a reading of the present disclosure. These embodiments are considered to fall within the scope and spirit of the present invention, boundaries of which are defined solely by the following claims.

**Claims**

1. A method of transforming a compound of the formula I to a compound of the formula II

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\begin{array}{c}
\text{OH} \\
R_1 \\
(\text{CH}_2)_n \\
R_2 \\
\text{OH} \\
R_3 \\
R_4 \\
\end{array} & \quad \begin{array}{c}
\text{OH} \\
R_1 \\
(\text{CH}_2)_n \\
R_2 \\
\text{H} \\
R_3 \\
R_4 \\
\end{array}
\end{align*}
\]

in which n = 0 or 1, R1, R2, R3 and R4 represent independently a hydrogen atom, an aliphatic group, an aromatic group, an aromatic heterocyclic group, an aliphatic heterocyclic group or a carbonyl-containing group of the formula COY in which Y represents a hydrogen atom, a halogen atom, any of the groups recited previously for R1-R4 or a group of the formula W(R6)m in which W represents a nitrogen atom, an oxygen atom or a sulfur atom and R6 represents a hydrogen atom or any of the groups recited previously for R1-R4 provided that when W represents a nitrogen atom, m is equal to 2 and when W represents an oxygen atom or a sulfur atom, m is equal to 1 and R6 may not be hydrogen atom, comprising:

(a) allowing a compound of the formula I to react with a thionyl halide to form a cyclic sulfite;
(b) allowing said cyclic sulfite to react with a halide salt to form a halo-substituted acyclic sulfite; and
(c) allowing said halo-substituted acyclic sulfite to react with a suitable reducing agent to provide a compound of the formula II.

2. The method of claim 1 in which thionyl halide is thionyl chloride.

3. The method of claim 1 in which said thionyl halide is thionyl bromide.

4. The method of claim 1 in which said suitable halide salt is selected from the group consisting of an inorganic halide salt.

5. The method of claim 4 in which said inorganic halide salt is an alkali metal halide salt selected from the group consisting of LiBr, LiCl, NaBr or NaI.

6. The method of claim 4 in which said inorganic halide salt is an alkaline-earth metal halide salt selected from the group consisting of CaCl₂, BaCl₂ or MgBr₂.

7. The method of claim 1 in which said suitable halide salt is an organic halide salt.

8. The method of claim 1 in which the conditions of step (a), (b) or (c) includes the use of an inert solvent.

9. The method of claim 1 in which said reducing agent comprises finely divided active metal.

10. The method of claim 9 in which said metal is selected from the group consisting of zinc, iron or tin.

11. The method of claim 1 in which said reducing agent comprises hydrogen in the presence of a noble metal.

12. The method of claim 1 in which said reducing agent comprises hydrogen in the presence of palladium on carbon.

13. The method of claim 1 in which said reducing agent comprises hydrogen in the presence of Raney nickel.

14. The method of claim 1 in which step (a), (b) or (c) includes the use of an inert solvent.

15. The method of claim 14 in which said inert solvent of step (a) is selected from the group consisting of methylene chloride, ethyl acetate or dimethoxyethane.

16. The method of claim 14 in which said inert solvent of step (b) is a polar aprotic solvent selected from the group consisting of acetone, dimethylformamide, tetrahydrofuran or dimethoxyethane.

17. The method of claim 14 in which said inert solvent of step (c) is an aliphatic alcohol or an aromatic solvent.

18. The method of claim 1 in which step (a), (b) or (c) includes a reaction temperature falling in the range of about 20 to about 100 °C.

19. The method of claim 1 in which the compound of the formula I is optically active and the compound of formula II is optically active.

20. The method of claim 1 in which R₁ and R₃ represent the same atom or group.

21. The method of claim 1 in which R₁ and R₄ represent the same atom or group.

22. The method of claim 1 in which R₂ and R₄ represent the same atom or group.

23. The method of claim 1 in which R₂ and R₅ represent the same atom or group.
24. The method of claim 1 in which the compound of the formula I is a derivative of tartaric acid having no free acid or thioacid groups.

25. The method of claim 1 in which the compound of the formula I is a diester or a diamide of L-tartaric acid.

26. The method of claim 1 in which the compound of the formula I is a diester or a diamide of D-tartaric acid.

27. The method of claim 1 in which the compound of formula II is a derivative of malic acid having no free acid or thioacid groups.

28. The method of claim 1 in which the compound of the formula II is a derivative of L-malic acid having no free acid or thioacid groups.

29. The method of claim 1 in which the compound of the formula II is a derivative of D-malic acid having no free acid or thioacid groups.

30. The method of claim 1 which is a method of transforming a tartaric acid derivative having no free acid or thioacid groups to a malic acid derivative having no free acid or thioacid groups, comprising:
   (a) allowing a derivative of tartaric acid having no free acid or thioacid groups to react with a thionyl halide to form a cyclic tartrate sulfite;
   (b) allowing said cyclic tartrate sulfite to react with a suitable halide salt to form a β-halo malic acid sulfite; and
   (c) allowing said β-halo malic acid sulfite to react with a reducing agent to provide a derivative of malic acid having no free acid or thioacid groups.

31. The method of claim 30 in which the tartaric acid derivative is the L-isomer thereof and the malic acid derivative is the D-isomer thereof.

32. The method of claim 31 in which the malic acid derivative is an ester of D-malic acid.

33. The method of claim 30 which further comprises transforming the derivative of malic acid to free malic acid or a salt thereof.

34. The method of claim 33 in which the free malic acid or salt thereof is the D-isomer thereof.

Patentansprüche

1. Ein Verfahren zur Transformation einer Verbindung mit der Strukturformel I in eine Verbindung mit der Strukturformel II,

   ![Diagram](image)

   worin \( n = 0 \) or 1 ist, \( R_1, R_2, R_3 \) und \( R_4 \) unabhängig voneinander für ein Wasserstoffatom, eine aliphatische Gruppe, eine aromatische Gruppe, eine aromatische heterozyklische Gruppe, eine aliphatische heterozyklische Gruppe oder eine carbonyllhaltige Gruppe der Formel COY stehen, in welcher Y für ein Wasserstoffatom, ein Halogenatom, eine beliebige der oben für \( R_1-R_4 \) genannten Gruppen oder eine Gruppe der Formel \( W(R_6) \) steht, worin W für ein Stickstoffatom, ein Sauerstoffatom oder ein Schwefelatom und \( R_6 \) für ein Wasserstoffatom oder eine beliebige der oben für \( R_1-R_4 \) genannten Gruppen steht, unter der Bedingung, daß wenn W für ein Stickstoffatom steht, \( m \) gleich 2 ist, und daß wenn W für ein Sauerstoffatom oder Schwefelatom steht, \( m \) gleich 1 ist und \( R_6 \) kein Wasserstoffatom sein darf, wobei das Verfahren die nachgenannten Verfahrensschritte beinhaltet:
(a) Herbeiführen einer Reaktion zwischen einer Verbindung mit der Strukturformel I und einem Thionylhalogenid zwecks Bildung eines zyklischen Sulfitis;
(b) Herbeiführen einer Reaktion zwischen dem besagten zyklischen Sulfit und einem Halogenidsalz zwecks Bildung eines halo-substituierten zyklischen Sulfitis; und
(c) Herbeiführen einer Reaktion zwischen dem besagten halo-substituierten zyklischen Sulfit und einem geeigneten Reduktionsmittel zwecks Lieferung einer Verbindung mit der Strukturformel II.

2. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei dein Thionylhalogenid um Thionylchlorid handelt.

3. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Thionylhalogenid um Thionylbromid handelt.

4. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß das besagte geeignete Halogenidsalz ausgewählt wird aus der Gruppe bestehend aus einem anorganischen Halogenidsalz.

5. Das Verfahren gemäß Anspruch 4, dadurch gekennzeichnet, daß es sich bei dem anorganischen Halogenidsalz um ein Alkalimetallhalogenidsalz handelt, ausgewählt aus der Gruppe bestehend aus LiBr, LiCl, NaBr oder Nal.

6. Das Verfahren gemäß Anspruch 4, dadurch gekennzeichnet, daß es sich bei dem anorganischen Halogenidsalz um ein Erdalkalimetallhalogenidsalz handelt, ausgewählt aus der Gruppe bestehend aus CaCl₂, BaCl₂ oder MgBr₂.

7. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem besagten geeigneten Halogenidsalz um ein organisches Halogenidsalz handelt.

8. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß die Bedingungen in Verfahrensschritt (a), (b) oder (c) die Verwendung eines inerten Lösungsmittels beinhalten.

9. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß das besagte Reduktionsmittel feingeteiltes aktives Metall enthält.

10. Das Verfahren gemäß Anspruch 9, dadurch gekennzeichnet, daß das besagte Metall ausgewählt wird aus der Gruppe bestehend aus Zink, Eisen oder Zinn.

11. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß das besagte Reduktionsmittel Wasserstoff in Gegenwart eines Edelmetalls enthält.

12. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß das besagte Reduktionsmittel Wasserstoff in Gegenwart von Palladium auf Kohlenstoff enthält.


14. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß der Verfahrensschritt (a), (b) oder (c) die Verwendung eines inerten Lösungsmittels beinhaltet.

15. Das Verfahren gemäß Anspruch 14, dadurch gekennzeichnet, daß das besagte innere Lösungsmittel nach Verfahrensschritt (a) ausgewählt wird aus der Gruppe bestehend aus Methylenclorid, Ethylacetat oder Dimethoxyethan.

16. Das Verfahren gemäß Anspruch 14, dadurch gekennzeichnet, daß es sich bei dem besagten inerten Lösungsmittel nach Verfahrensschritt (b) um ein polares aprotisches Lösungsmittel handelt, ausgewählt aus der Gruppe bestehend aus Aceton, Dimethylformamid, Tetrahydrofuran oder Dimethoxyethan.

17. Das Verfahren gemäß Anspruch 14, dadurch gekennzeichnet, daß es sich bei dem besagten inerten Lösungsmittel nach Verfahrensschritt (c) um einen aliphatischen Alkohol oder ein aromatisches Lö-
sungsmittel handelt.

18. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß Verfahrensschritt (a), (b) oder (c) eine Reaktionstemperatur beinhaltet, die in dem Bereich zwischen ca. 20 °C und ca. 100 °C liegt.

19. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß die Verbindung mit der Strukturformel I optisch aktiv ist und daß die Verbindung mit der Strukturformel II optisch aktiv ist.

20. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß R₁ und R₅ für dasselbe Atom oder dieselbe Gruppe stehen.

21. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß R₁ und R₄ für dasselbe Atom oder dieselbe Gruppe stehen.

22. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß R₂ und R₅ für dasselbe Atom oder dieselbe Gruppe stehen.

23. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß R₂ und R₄ für dasselbe Atom oder dieselbe Gruppe stehen.

24. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei der Verbindung mit der Strukturformel I um ein Weinsäurederivat handelt, das keine freie Säure oder Thiosäuregruppen enthält.

25. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei der Verbindung mit der Strukturformel I um einen Diester oder ein Diamid von L-Weinsäure handelt.


27. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei der Verbindung mit der Strukturformel II um ein Hydroxybernsteinsäurederivat handelt, das keine freie Säure oder Thiosäuregruppen enthält.

28. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei der Verbindung mit der Strukturformel II um ein L-Hydroxybernsteinsäurederivat handelt, das keine freie Säure oder Thiosäuregruppen enthält.

29. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß es sich bei der Verbindung mit der Strukturformel II um ein D-Hydroxybernsteinsäurederivat handelt, das keine freie Säure oder Thiosäuregruppen enthält.

30. Das Verfahren gemäß Anspruch 1, bei dem es sich um ein Verfahren zur Transformierung eines Weinsäurederivats, das keine freie Säure oder Thiosäuregruppen enthält, in ein Hydroxybernsteinsäurederivat, das keine freie Säure oder Thiosäuregruppen enthält, handelt, umfassend die nachfolgenden Verfahrensschritte:
   (a) Herbeiführen einer Reaktion zwischen einem Weinsäurederivat, das keine freie Säure oder Thiosäuregruppen enthält und einem Thionylhalogenid zwecks Bildung eines zyklischen Weinsäure-
       sulfits;
   (b) Herbeiführen einer Reaktion zwischen dem besagten zyklischen Weinsäuresulfit und einem geeigneten Halogenidsalz zwecks Bildung eines β-halo-Hydroxybernsteinsäuresulfits; und
   (c) Herbeiführen einer Reaktion zwischen dem besagten β-halo-Hydroxybernsteinsäuresulfit und einem Reduktionsmittel zwecks Lieferung eines Hydroxybernsteinsäurederivats das keine freie Säure oder Thiosäuregruppen enthält.

32. Das Verfahren gemäß Anspruch 31, dadurch gekennzeichnet, daß es sich bei dem Hydroxybernstein-
säurederivat um einen Ester von D-Hydroxybernsteinsäure handelt.

33. Das Verfahren gemäß Anspruch 30, gekennzeichnet durch den weiteren Verfahrensschritt der Transfor-
mierung des Hydroxybernsteinsäurederivats in freie Hydroxybernsteinsäure oder ein Salz derselben.

34. Das Verfahren gemäß Anspruch 33, dadurch gekennzeichnet, daß es sich bei der freien Hydroxybern-
steinsäure oder dem Salz derselben um das D-Isomer derselben handelt.

**Revendications**

1. Un procédé de transformation d’un composé de formule I en un composé de formule II

\[
\begin{align*}
\text{R}_1 & \quad \text{OH} & \quad \text{OH} \\
\text{R}_2 & \quad (\text{CH}_2)_n & \quad \text{R}_3 \\
\text{R}_4 & \quad \text{R}_4 & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{R}_6 & \quad \text{R}_5
\end{align*}
\]

dans lesquelles n = 0 ou 1, R₁, R₂, R₃ et R₄ représentent indépendamment un atome d’hydrogène, un groupe aliphatique, un groupe aromatique, un groupe aromatique hétérocyclique, un groupe hétérocyclique aliphatique ou un groupe carbonyl de formule COY dans laquelle Y représente un atome d’hydrogène, un atome d’halogène, l’un quelconque des groupes cités précédemment pour R₁-R₄ ou un groupe de formule W(R₅), dans laquelle W représente un atome d’azote, un atome d’oxygène ou un atome de soufre, R₅ représente un atome d’hydrogène ou l’un quelconque des groupes cités précédemment pour R₁-R₄, sous réserve que lorsque W représente un atome d’azote, m est égal à 2, et lorsque W représente un atome d’oxygène ou un atome de soufre, m est égal à 1 et R₆ n’est pas un atome d’hydrogène, consistant à:

(a) faire réagir un composé de formule 1 avec un halogénure de thionyle dans des conditions efficaces permettant la formation d’un sulfite cyclique;

(b) faire réagir ledit sulfite cyclique avec un halogénure approprié dans des conditions efficaces permettant de former le sulfite cyclique halogéné; et

(c) faire réagir ledit sulfite acyclique halogéné avec un agent réducteur approprié dans des conditions efficaces pour permettre l’obtention d’un composé de formule II.

2. Le procédé selon la revendication 1, dans lequel l’halogénure de thionyle est le chlorure de thionyle.

3. Le procédé selon la revendication 1, dans lequel ledit halogénure de thionyle est le bromure de thionyle.

4. Le procédé selon la revendication 1, dans lequel ledit halogénure approprié est sélectionné parmi le groupe consistant en halogénures inorganiques.

5. Le procédé selon la revendication 4, dans lequel ledit halogénure inorganique est un halogénure de métal alcalin sélectionné parmi le groupe consistant en LiBr, LiCl, NaBr ou NaI.

6. Le procédé selon la revendication 4, dans lequel ledit halogénure inorganique est un halogénure de métal alcalino-terreux sélectionné dans le groupe consistant en CaCl₂, BaCl₂ ou MgBr₂.

7. Le procédé selon la revendication 1, dans lequel ledit halogénure approprié est un halogénure organique.

8. Le procédé selon la revendication 1, dans lequel les conditions des étapes (a), (b), ou (c) incluent l’utilisation d’un solvant inerte.
9. Le procédé selon la revendication 1, dans lequel ledit agent réducteur comprend un métal actif finement divisé.

10. Le procédé selon la revendication 9, dans lequel ledit métal est sélectionné dans le groupe consistant en zinc, fer ou étain.

11. Le procédé selon la revendication 1, dans lequel ledit agent réducteur comprend de l’hydrogène en présence d’un métal noble.

12. Le procédé selon la revendication 1, dans lequel ledit agent réducteur comprend de l’hydrogène en présence de palladium sur du carbone.

13. Le procédé selon la revendication 1, dans lequel ledit agent réducteur comprend de l’hydrogène en présence de nickel de Raney.

14. Le procédé selon la revendication 1, dans lequel l’étape (a), (b) ou (c) incluent l’utilisation d’un solvant inerte.

15. Le procédé selon la revendication 14, dans lequel ledit solvant inerte de l’étape (a) est sélectionné parmi le groupe consistant en chlorure de méthylène, acétate d’éthyle, ou diméthoxyéthane.

16. Le procédé selon la revendication 14, dans lequel ledit solvant inerte de l’étape (b) est un solvant polaire aprotique sélectionné parmi le groupe consistant en acétone, diméthylformamide, tétrahydrofuranne ou diméthoxyéthane.

17. Le procédé selon la revendication 14, dans lequel ledit solvant inerte de l’étape (c) est un alcool aliphatique ou un solvant aromatique.

18. Le procédé selon la revendication 1, dans lequel l’étape (a), (b) ou (c) comporte une température réactionnelle de l’ordre d’environ 20 à environ 100 °C.

19. Le procédé selon la revendication 1, dans lequel le dérivé de formule I est optiquement actif et le dérivé de formule II est optiquement actif.

20. Le procédé selon la revendication 1, dans lequel R₁ et R₃ représentent le même atome ou le même groupe.

21. Le procédé selon la revendication 1, dans lequel R₁ et R₄ représentent le même atome ou le même groupe.

22. Le procédé selon la revendication 1, dans lequel R₂ et R₄ représentent le même atome ou le même groupe.

23. Le procédé selon la revendication 1, dans lequel R₂ et R₃ représentent le même atome ou le même groupe.

24. Le procédé selon la revendication 1, dans lequel le dérivé de formule I est un dérivé de l’acide tartrique ne comportant ni groupe acide libre ni groupe thioacide libre.

25. Le procédé selon la revendication 1, dans lequel le dérivé de formule I est un diester ou un diamide de l’acide L-tartrique.

26. Le procédé selon la revendication 1, dans lequel le dérivé de formule I est un diester ou un diamide de l’acide D-tartrique.

27. Le procédé selon la revendication 1, dans lequel le dérivé de formule II est un dérivé de l’acide malique ne comportant groupe acide libre ni groupe thioacide libre.
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28. Le procédé selon la revendication 1, dans lequel le dérivé de formule II est un dérivé d'acide L-malique ne comportant ni groupe acide libre ni groupe thioacide libre.

29. Le procédé selon la revendication 1, dans lequel le dérivé de formule II est un dérivé d'acide D-malique ne comportant ni groupe acide libre ni groupe thioacide libre.

30. Le procédé selon la revendication 1, qui est un procédé de transformation d'un dérivé d'acide tartrique sans groupe acide libre ni groupe thioacide libre en un dérivé d'acide malique ne comportant ni groupe acide libre ni groupe thioacide libre, consistant à:
   (a) faire réagir un dérivé de l'acide tartrique ne comportant ni groupe acide libre ni groupe thioacide libre, avec un halogénure de thionyle pour former un sulfite de tartrate cyclique;
   (b) faire réagir ledit sulfite de tartrate cyclique avec un halogénure approprié pour former un sulfite d'acide malique β-halogéné; et
   (c) faire réagir ledit sulfite d'acide malique β-halogéné avec un agent réducteur pour obtenir un dérivé d'acide malique ne comportant pas de groupe acide libre ni de groupe thioacide libre.

31. Le procédé selon la revendication 30, dans lequel le dérivé d'acide tartrique est son isomère-L et le dérivé d'acide malique en est son isomère-D.

32. Le procédé selon la revendication 31, dans lequel le dérivé d'acide malique est un ester de l'acide D-malique.

33. Le procédé selon la revendication 30, qui comprend de plus la transformation du dérivé d'acide malique en acide malique libre, ou en un sel dudit acide malique.

34. Le procédé selon la revendication 33, dans lequel l'acide malique libre ou son sel est l'isomère D dudit acide malique ou dudit sel.