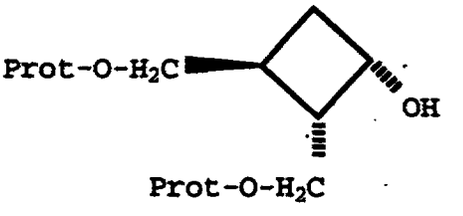
Process for Preparing Diprotected 2,3-Hydroxymethyl Cyclobutanol

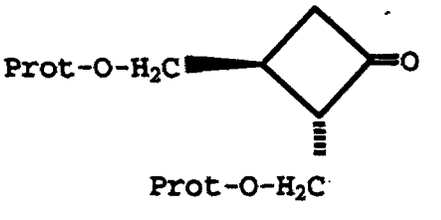
This invention relates to an improved process for the preparation of the diprotected 2,3-hydroxymethyl cyclobutanol of the formula

(I)



wherein Prot is a protecting group by treating the cyclobutanone of the formula

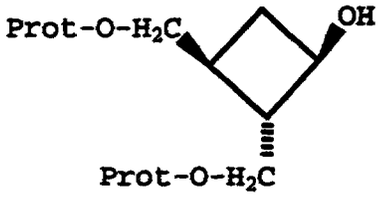
(II)



with a reducing agent selected from dialkylaluminum chlorides, alkylaluminum dichlorides, trialkylaluminum compounds, hydrogen in the presence of the catalysts ruthenium black or ruthenium on alumina, diphenylsilane in the presence of tris(triphenyl-

phosphine)rhodium(I)chloride, and iridium tetrachloride in the presence of phosphorous acid to give the desired cyclobutanol of formula I in predominance to the undesired isomeric compound of the formula

(III)



The process of this invention can utilize the cyclobutanone of formula II in its optically active (2S-trans) form, also referred to as [2S,3S]. In this situation, the desired cyclobutanol of formula I will also be optically active, i.e., [1S-(1α,2β,3β)]. This optically active cyclobutanol can then be converted to an optically active antiviral agent such as [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one.

The process of this invention can also utilize the cyclobutanone of formula II as the racemic compound in which situation the desired cyclobutanol of formula I will also be optically inactive, i.e., (1α,2β,3β). This racemic cyclobutanol can then be converted to an antiviral agent in racemic form such as (±)-(1α,2β,3α)-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one.

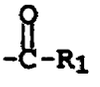
In the diprotected 2,3-hydroxymethyl cyclobutanol of formula I, the relative stereochemistry of the substituents on the cyclobutyl ring are drawn to indicate that the hydroxy substituent is

cis to the vicinal $-CH_2-O-Prot$ substituent and that the two $-CH_2-O-Prot$ substituents are trans to each other.

By treating the cyclobutanone of formula II with a reducing agent selected from dialkylaluminum chlorides such as diisobutylaluminum chloride, alkylaluminum dichlorides such as isobutylaluminum dichloride, trialkylaluminum compounds such as triisobutylaluminum, hydrogen in the presence of the catalysts ruthenium black or ruthenium on alumina, diphenylsilane in the presence of tris(triphenylphosphine)rhodium(I)chloride, and iridium tetrachloride in the presence of phosphorous acid, the desired diprotected 2,3-hydroxymethyl cyclobutanol of formula I is obtained in predominance to the undesired isomeric compound of formula (III).

The term "alkyl" refers to straight or branched chain groups of 1 to 20 carbons, preferably 3 to 10 carbons.

Prot is a hydroxy protecting group. Suitable protecting groups include hindered silyl groups such as t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl and triisopropylsilyl. Suitable protecting groups also include benzyl and substituted benzyl groups such as p-methoxybenzyl, and acyl groups of the formula



wherein R_1 is a straight or branched chain lower alkyl of 1 to 6 carbons, or phenyl, with benzoyl, i.e. R_1 is phenyl, the preferred acyl protecting group.

When the reducing agent employed in the process of this invention is a dialkylaluminum chloride suitable solvents for the reaction include unreactive aprotic solvents such as methylene chloride, toluene, and the like. The reaction can be run at a temperature of from about -90°C. to the boiling point of solvent, preferably at from about -90°C. to about 0°C., most preferably at about -40°C.

When the reducing agent employed in the process of this invention is an alkylaluminum dichloride such as isobutylaluminum dichloride or a trialkylaluminum compound such as triisobutyl-aluminum suitable solvents for the reaction include unreactive aprotic solvents such as methylene chloride, toluene and the like: The reaction can be run at a temperature of from about -90°C. to the boiling point of the solvent, preferably from about -90°C. to about 0°C. When the reducing agent employed is a trialkylaluminum compound then the protecting group Prot cannot be benzoyl.

When the reducing agent employed in the process of this invention is iridium tetrachloride in the presence of phosphorous acid, suitable solvents for the reaction include hydroxylic solvents such as water, methanol, propanol, isopropanol and the like or mixtures thereof such as water-isopropanol. The reaction can be run at a temperature of from about 50°C. to about 100°C., most preferably at about 80°C.

When the reducing agent employed in the process of this invention is hydrogen in the presence of the catalyst ruthenium black, suitable solvents for the reaction include hydroxylic

solvents such as methanol, isopropanol, or mixtures thereof, preferably methanol. The reaction can be run at a temperature of from about -90°C. to the boiling point of the solvent, preferably at about 0°C. to about 50°C., most preferably at about 25°C.

When the reducing agent employed in the process of this invention is hydrogen in the presence of the catalyst ruthenium on alumina, suitable solvents for the reaction include hydroxylic solvents such as methanol, which is preferred, ethanol and the like but not isopropanol. The reaction can be run at a temperature of from about -90°C. to the boiling point of the solvent, preferably at 0°C. to 50°C., most preferably at about 25°C.

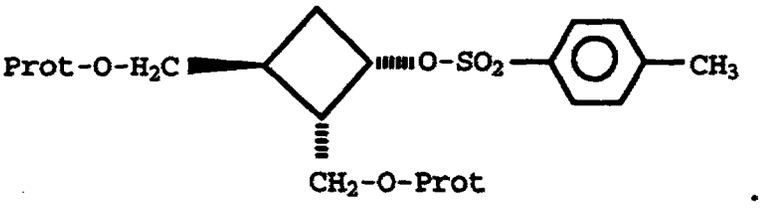
When the reducing agent employed in the process of this invention is diphenylsilane in the presence of tris(triphenylphosphine)rhodium (I) chloride, suitable solvents for the reaction include benzene, toluene, hexane, cyclohexane, and the like, preferably toluene or, alternatively, the reaction can be run in the absence of solvent. If the reaction is run in the presence of a solvent, then the reaction is carried out at a temperature of from about 0°C. to the boiling point of the solvent, preferably at about 25°C. If the reaction is performed without a solvent, then the reaction is carried out at a temperature from about 0°C. to about 120°C.

In the preferred process of this invention the reducing agent is a dialkylaluminum chloride, most preferably diisobutylaluminum chloride,

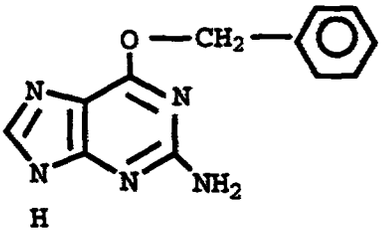
the protecting group Prot is benzoyl, and the cyclobutanone starting material of formula II is in the optically active (2S-trans) form.

The optically active (2S-trans) diprotected 2,3-hydroxymethyl cyclobutanone of formula I can be prepared as described by Bisacchi et al. in U.S. Patent 5,064,961, by Norbeck et al. in European Patent Application 366,059, by Ichikawa et al. in European Patent Application 358,154, by Pariza et al. in European Patent Application 452,729, or by Ahmad in European Patent Application 458,643. The racemic (trans)-diprotected 2,3-hydroxymethyl cyclobutanone of formula I can be prepared as described by Slusarchyk et al. in European Patent Application 335,355, as well, as in the European Patent Applications of Norbeck et al. and Ichikawa et al. mentioned above. Another method for preparing the optically active cyclobutanone of formula II is described by Godfrey et al. in U.S. Patent 5,185,463.

As taught by Bisacchi et al. in U.S. Patent 5,064,961 the optically active [1S-(1α,2β,3β)] diprotected 2,3-hydroxymethyl cyclobutanol of formula I can be treated with tosyl chloride to give the cyclobutane compound of the formula (IV)

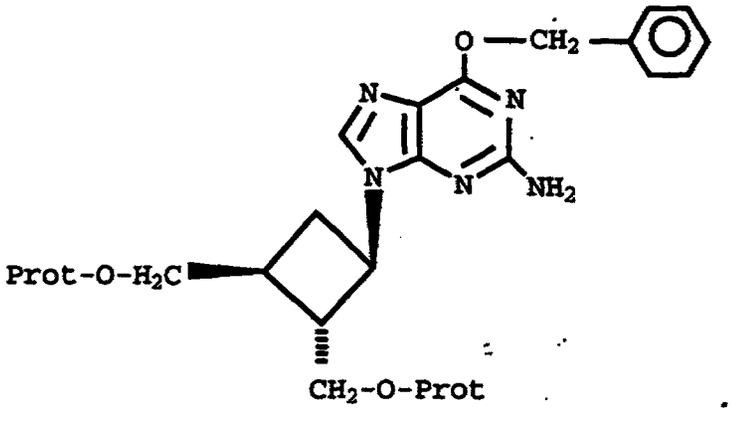


The tosyl compound of formula IV is then treated with the benzyloxy guanine of the formula (V)



to give a compound of the formula

(VI)



Removal of the protecting groups from the compound of formula VI yields the antiviral agent [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis-(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one.

The following examples are illustrative of the process of this invention.

EXAMPLE 1

[1S-(1α,2β,3β)]-3-Hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester

A 3 l. three-necked flask equipped with a mechanical stirrer, an internal digital thermometer, an addition funnel, and nitrogen inlet was charged with 2385 ml. of anhydrous methylene chloride. After cooling to -40°C., diisobutylaluminum chloride (156.6 g., 886 mmole, 1.27 moleq.) was added. To this cold solution was added, dropwise via addition funnel over 63 minutes,a solution of (2S-trans)-2,3-bis[(benzoyloxy)methyl]cyclobutanone (235 g., 699 mmole) in methylene chloride (600 ml.). The reaction was maintained at -40°C. for an additional 70 minutes. The reaction was quenched by the slow addition of methanol (502 ml.). During quench the temperature rose from about -40°C.to -32°C. over one hour. The cold bath was removed and a saturated aqueous solution of ammonium chloride (502 ml.) was added. After stirring for 18 hours, the mixture was filtered through anhydrous magnesium sulfate (502 g.) and the filter cake was washed thoroughly with methylene chloride. The filtrate was concentrated at reduced pressure and the residue was dried under pump vacuum at 35°C. to give 287.3 g. of crude product. The slightly wet solid was crystallized from about 2 l. of methanol and about 400 ml. of water to give 160.6 g. (yield 68%) of [1S-(1α,2β,3β)]-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester; m.p. 75 - 77°C. TLC(silica gel; 40% ethyl acetate/hexane) R_f = 0.39.

$[\alpha]_D$ = -15.3° (c = 1.1, chloroform). HPLC:HI (215 nm, Zorabax-cyano column, water-acetonitrile gradient) 99.95%.

Anal. calc'd. for: $C_{20}H_{20}O_5$

C, 70.38; H, 5.94; H_2O, 0.27

Found: C, 69.92; H, 5.87; H_2O, 0.27.

EXAMPLE 2

[1S-(1α,2β,3β)]-3-Hydroxy-1,2-cyclobutane-dimethanol, dibenzyl ether

A solution of (2S-trans)-2,3-bis[(benzyloxy)-methyl]cyclobutanone (0.5 g., 1.61 mmole) in toluene (1 ml.) was added dropwise to a solution of isobutylaluminum dichloride (0.71 M in hexane, 3.41 ml., 2.42 mmole) at -78°C. The mixture was allowed to warm slowly to room temperature over 2 hours. After stirring for 30 minutes at room temperature, the mixture was allowed to stand at 0°C. overnight. After dilution with ethyl acetate, the reaction mixture was quenched with 10% hydrochloric acid. The organic phase was washed with brine, dried (magnesium sulfate) and the solvent evaporated to give [1S-(1α,2β,3β)]-3-hydroxy-1,2-cyclobutane-dimethanol, dibenzyl ether; TLC (50% ethyl acetate/hexane) R_f = 0.53.

EXAMPLE 3

[1S-(1α,2β,3β)]-3-Hydroxy-1,2-cyclobutane-dimethanol, dibenzyl ether

A solution of (2S-trans)-2,3-bis[(benzyloxy)-methyl]cyclobutanone (0.2 g., 0.645 mmole) in toluene (4 ml.) was added dropwise over 10 minutes to a solution of triisobutylaluminum (0.91 M in hexane, 0.9 ml., 0.816 mmole) in toluene (2 ml.) at -40°C. The mixture was stirred at -50°C. for 4 hours and at -40°C for one hour. A solution of

triisobutylaluminum (1 ml., 0.91 mmole) was added to the reaction mixture. After stirring for 30 minutes the reaction was quenched by adding 10% hydrochloric acid (2 ml.) at -40°C. The organic phase was washed with brine, dried (magnesium sulfate), and the solvent was evaporated to give [1S-(1α,2β,3β)]-3-hydroxy-1,2-cyclobutane-dimethanol, dibenzyl ether; TLC (30% ethyl acetate/hexane) R_f = 0.3. The product contained about 5% of the isomeric compound; TLC (30% ethyl acetate/hexane) R_f = 0.2.

EXAMPLE 4

[1S-(1α,2β,3β)]-3-Hydroxy-1,2-cyclobutane-dimethanol, dibenzyl ether

A mixture of (2S-trans)-2,3-bis[(benzyloxy)-methyl]cyclobutanone (0.25 g., 0.806 mmole), iridium tetrachloride (0.016 g., 0.0483 mmole), phosphorous acid (0.397 g., 4.84 mmole) and water (0.3 ml.) in isopropanol (3 ml.) was refluxed overnight. The solvent was evaporated on a rotary evaporator. The residue was taken up in ethyl acetate and washed successively with 10% hydrochloric acid, brine, and 5% sodium bicarbonate. The organic layer was dried (magnesium sulfate) and the solvent was evaporated to give [1S-(1α,2β,3β)]-3-hydroxy-1,2-cyclobutane-dimethanol, dibenzyl ether; TLC (40% ethyl acetate/hexane) R_f = 0.51.

EXAMPLE 5

(1α,2β,3β)-3-Hydroxy-1,2-cyclobutanedi-methanol,dibenzoate ester

A suspension of ruthenium black (20 mg.) in isopropanol (1 ml.) was pre-hydrogenated under 1 atmosphere of hydrogen for one hour at room

temperature. To this mixture, (trans)-2,3-bis[(benzoyloxy)methyl]cyclobutanone (200 mg.) in isopropanol (11 ml.) was added and the combined mixture was stirred under 1 atmosphere of hydrogen at room temperature. After 21 hours, HPLC indicated the presence of (1α,2β,3β)-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester along with the isomeric compound (1α,2β,3α)-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester in a 84:16 ratio.

EXAMPLE 6

(1α,2β,3β)-3-Hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester

A mixture of (trans)-2,3-bis[(benzoyloxy)-methyl]cyclobutanone (50 mg.) and 5% ruthenium on alumina (10 mg.) in methanol (2 ml.) was stirred under 1 atmosphere of hydrogen at room temperature. After 46 hours, HPLC indicated the presence of (1α,2β,3β)-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester along with the isomeric compound (1α,2β,3α)-3-hydroxy-1,2-cyclobutanedimethnaol, dibenzoate ester in a 73:27 ratio.

EXAMPLE 7

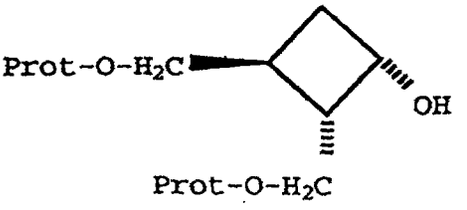
(1α,2β,3β)-3-Hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester

Diphenylsilane (27.4 µl., 0.148 mmole) was added dropwise to a stirred solution of (trans)-2,3-bis[(benzoyloxy)methyl]cyclobutanone (50 mg., 0.148 mmole) and tris-(triphenylphosphine)-rhodium (I) chloride (1.4 mg., 0.0015 mmole) in toluene (0.75 ml.) and kept for 15 minutes at room temperature under an argon atmosphere. The reaction mixture was then concentrated to an oil which was then stirred at room temperature for 1

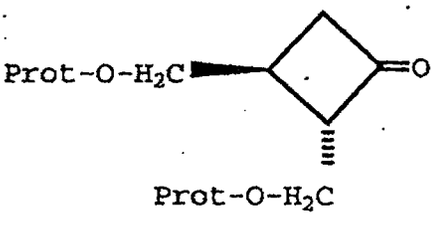
hour with 10% aqueous methanol (1 ml.) containing a catalytic quantity of p-toluenesulfonic acid. The mixture was concentrated to an oil which was then partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and the solvent removed to afford 55 mg. of a clear oil. HPLC of this oil indicated the presence of (1α,2β,3β)-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester along with the isomeric compound (1α,2β,3α)-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester in a 82:18 ratio.

CLAIMS

1. A process for preparing a compound of the ɔrmula



ıerein the hydroxy substituent is cis to the .cinal -CH_2-O-Prot substituent and two -CH_2-O-Prot bstituents are trans to each other, which mprises treating a compound of the formula

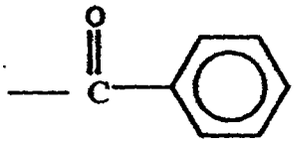


:h a reducing agent selected from ılkylaluminum chlorides, alkyl- ıminum dichlorides, trialkylaluminum compounds, ıydrogen in the presence of the catalyst ruthenium ıck or ruthenium on alumina, diphenylsilane in ; presence of tris(triphenylphosphine)rhodium (I) .oride, and iridium tetrachloride in the presence phosphorous acid wherein alkyl is straight or .nched chain of 1 to 20 carbons, Prot is a .dered silyl group, benzyl, substituted benzyl or

R_1 wherein R_1 is straight or branched lower alkyl

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of 1 to 6 carbons or phenyl provided that when the reducing agent is a trialkylaluminum compound Prot



cannot be .

2. A process of Claim 1 wherein the reducing agent is a dialkylaluminum chloride, the term alkyl refers to a straight or branched chain group of 3 to 10 carbons, and Prot is a hindered silyl selected from t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl, and triisopropylsilyl, or Prot is benzyl, p-methoxybenzyl, or benzoyl.

3. A process of Claim 2 wherein the reaction is performed in the presence of an aprotic solvent selected from methylene chloride and toluene at a temperature of from about -90°C. to the boiling point of the solvent, the reducing agent is diisobutylaluminum chloride, and Prot is benzoyl.

4. A process of Claim 1 wherein the reducing agent is an alkylaluminum dichloride, the term alkyl refers to a straight or branched chain group of 3 to 10 carbons, and Prot is a hindered silyl selected from t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl, and triisopropylsilyl, or Prot is benzyl, p-methoxybenzyl, or benzoyl.

5. A process of Claim 4 wherein the reaction is performed in the presence of an aprotic solvent selected from methylene chloride and toluene at a temperature of from about

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-90°C. to the boiling point of the solvent, and the reducing agent is isobutylaluminum dichloride.

6. A process of Claim 1 wherein the reducing agent is a trialkylaluminum compound, the term alkyl refers to a straight or branched chain group of 3 to 10 carbons, and Prot is a hindered silyl selected from t-butyldi- methylsilyl, t-butyldiphenylsilyl, (triphenyl-methyl)dimethylsilyl, methyldiisopropylsilyl, and triisopropylsilyl, or Prot is benzyl, or p-methoxybenzyl.

7. A process of Claim 6 wherein the reaction is performed in the presence of an aprotic solvent selected from methylene chloride and toluene at a temperature of from about -90°C. to the boiling point of the solvent, and the reducing agent is triisobutylaluminum.

8. A process of Claim 1 wherein the reducing agent is hydrogen in the presence of ruthenium black, Prot is a hindered silyl selected from t-butyldimethylsilyl, t- butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl, and triisopropylsilyl, or Prot is benzyl, p-methoxybenzyl, or benzoyl, and the reaction is performed in a solvent selected from methanol, isopropanol, and mixtures thereof at a temperature of from about -90°C. to the boiling point of the solvent or a process of Claim 1 wherein the reducing agent is hydrogen in the presence of ruthenium on aluminum, Prot is a hindered silyl selected from t-butyldimethylsilyl, t- butyldiphenylsilyl, (triphenylmethyl)dimethyl-silyl, methyldiisopropylsilyl, and triisopropyl-

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silyl, or Prot is benzoyl, and the reaction is performed in a solvent selected from methanol and ethanol at a temperature of about -90°C. to the boiling point of the solvent.

9. A process of Claim 1 wherein the reducing agent is diphenylsilane in the presence of tris-(triphenylphosphine) rhodium (I) chloride, Prot is a hindered silyl selected from t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldi-isopropylsilyl, and triisopropylsilyl, or Prot is benzyl, p-methoxybenzyl, or benzoyl, and the reaction is performed in a solvent selected from benzene, toluene, hexane, and cyclohexane at a temperature of from about 0°C. to the boiling point of the solvent or the reaction is performed in the absence of a solvent at a temperature of from about 0°C. to about 120°C.

10. A process of Claim 1 wherein the reducing agent is iridium tetrachloride in the presence of phosphorous acid, Prot is a hindered silyl selected from t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethyl-silyl, methyldiisopropylsilyl, and triisopropylsilyl, or Prot is benzyl, p-methoxybenzyl, or benzoyl, and the reaction is performed in the presence of a solvent selected from water, methanol, propanol, isopropanol, and mixtures thereof at a temperature of from about 50°C. to about 100°C.

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