(54) Cyclopropane derivatives and method of preparing the same
Cyclopropanderivate und Verfahren zu ihrer Herstellung
Dérivés de cyclopropane et procédé pour sa préparation

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The present invention relates to cyclopropane derivatives useful in preparation of antiviral agents and the like, and to methods of preparing such derivatives and also to the intermediates useful in preparation of such derivatives.

Compounds represented by formula (a) shown below are known to have potent antiviral activity (JP-A-5/78357).

However, the method described in the above publication is a time-consuming process involving the protection of an intermediate and the deprotection, and is not suitable for industrial-scale production.

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The present inventors have found that cyclopropane derivatives of formula (I) are useful for preparing the compounds of formula (a) shown above simply and conveniently at a high yield.

wherein B represents a purine residue selected from a guanine residue, adenine residue, 2-amino-6-chloropurine residue, xanthine residue, hypoxanthine residue, 2,6-diaminopurine residue or 2-aminopurine residue, and preferably guanin-9-yl, 2-amino-6-chloropurin-9-yl, 2-acetoamino-6-chloropurin-9-yl, 2-acetoamino-6-(N,N-diphenylcarbamoyl) oxypurin-9-yl, 2-amino-6-benzylloxypurin-9-yl, 2-amino-6-(methoxyethoxy)purin-9-yl or adenin-9-yl.

Compounds of formula (I) according to the present invention may be prepared, for example, as follows:
wherein $X$ represents a leaving group and $B$ is defined as above.

Precisely, the hydroxyl group of compound (1) is converted into a leaving group such as halogen or sulfonate to form compound (2), which is then reacted with a purine derivative in the presence of a base such as potassium carbonate to obtain a compound according to the present invention.

When compound (1) is halogenated, it may be reacted with carbon tetrabromide, carbon tetrachloride, bromine or N-bromosuccinimide in the presence of a trialkylphosphine or triphenylphosphine or it is halogenated using a halogenating agent such as thionyl chloride or phosphorus tribromide. Typically, when triphenylphosphine and carbon tetrachloride are employed, 1.1 to 3, preferably 1.2 to 2 equivalents of triphenylphosphine and 1.1 to 100, preferably 1.5 to 5 equivalents of carbon tetrachloride are employed and reacted in a solvent such as dichloromethane, dichloroethane and dimethylformamide at a temperature of -20 to 40°C, preferably 0 to 30°C for the period of 5 minutes to 3 hours. In such a process, 0.1 to 2 equivalents of a base such as triethylamine and pyridine may be present. When thionyl chloride is used as a halogenating agent, a reaction may be conducted in the presence of 1 to 2 equivalents of a base such as triethylamine and pyridine using 1 to 2 equivalents of thionyl chloride in a solvent such as dichloromethane at a temperature of 0 to 50°C for a period of 5 minutes to 3 hours.

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In the case of conversion into sulfonyloxy group, a reaction may be conducted in the presence of 1 to 2 equivalents of a base such as triethylamine and pyridine using 1 to 2 equivalents of methanesulfonyl chloride or p-toluenesulfonyl chloride in a solvent such as dichloromethane and ethyl acetate at a temperature of 0 to 50°C for a period of 5 minutes to 10 hours.

The reaction of compound (2) with a purine derivative may be conducted by adding compound (2) to the purine derivative in the presence of a base such as sodium carbonate, potassium carbonate and sodium hydride in an amount of 1 to 3, preferably 1 to 1.1 equivalents based on the amount of the purine derivative in a polar solvent such as dimethylformamide, acetonitrile and tetrahydrofuran at a temperature of 0 to 80°C for a period of 1 to 72 hours. In this reaction process, a crown ether such as 18-crown-6 may be added to facilitate the reaction.

The starting material in the reaction mentioned above, namely, (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol (compound (1)) is a novel compound, and may be prepared by the method shown below:

![Diagram](image-url)

wherein $R^1$ represents a lower alkyl group, and $R^2$ represents a lower alkyl or an aryl group.

Compound (4) may be obtained by reacting dialkyl malonate with epichlorohydrin in the presence of a base such as sodium alkoxide according to a known method (Helv. Chim. Acta, 72, 1301 (1989)). In such a reaction, by using an optically active epichlorohydrin, an optically active compound (4) is obtained and its absolute structure can be retained in compound (1) and compound (3).

Compound (4) can readily be converted into compound (5) by saponifying with an alkali such as sodium hydroxide and potassium hydroxide followed by cyclization into a lactone using a suitable acid such as hydrochloric acid and sulfuric acid.

Compound (5) thus obtained leads directly to a target compound (1) through a reaction with 0.8 to 1.2 equivalents of a reducing agent such as diborane in a polar solvent such as tetrahydrofuran. Alternatively, compound (5) is converted into compound (6) through a reaction with 1 to 10 equivalents of thionyl chloride and then into compound (1) through reaction with 0.5 to 2 equivalents of a reducing agent such as sodium borohydride in a polar solvent such as dioxane and diglyme. Further, alternatively, compound (5) may be converted into compound (7) through a reaction with 1 to 2 equivalents of chloroformate in the presence of 1 to 2 equivalents of a base such as triethylamine and...
pyridine in a solvent such as tetrahydrofuran and then into compound (1) through reaction with 0.5 to 5 equivalents of a reducing agent such as sodium borohydride.

[0017] Another process can be used to obtain compound (1) as shown below:

wherein $R^1$ is defined as above, and $R^3$ and $R^4$ are each hydrogen or an alkyl group.

[0018] Compound (4) is reacted with 1 to 10 equivalents of an amine such as ammonia in a solvent such as ethanol and methanol to obtain compound (8), to which 0.5 to 20 equivalents of a reducing agent such as sodium borohydride were added to obtain compound (9). Then the amide is hydrolyzed with a suitable acid such as hydrochloric acid and sulfuric acid to cyclize the lactone ring, thereby obtaining compound (1).

[0019] As still another alternative method of preparing compound (1), the process shown below may be suggested.

wherein $R^1$ is defined as above and $M$ represents an alkaline metal or an alkaline earth metal.

[0020] Compound (4) is reacted with 0.8 to 1.2 equivalents of a base such as sodium hydroxide in a solvent such as ethanol and methanol to obtain compound (10), with which 0.5 to 20 equivalents of a reducing agent such as sodium borohydride are reacted to obtain compound (11). Then a suitable acid such as hydrochloric acid and sulfuric acid is added to cyclize the lactone ring to obtain compound (1).

[0021] A cyclopropane derivative represented by formula (I) according to the present invention (compound (3)) can be converted into a compound represented by formula (a) (compound (12)) which has potent antiviral activity through a reaction with 0.5 to 20 equivalents of a reducing agent such as sodium borohydride in a suitable solvent such as ethanol, methanol, water or the like.
wherein B is defined as above.

[0022] When B is 2-amino-6-chloropurine, 2-acetoamino-6-chloropurine, 2-acetoamino-6-(N,N-diphenylcarbamoyl) oxypurine, 2-amino-6-benzyloxypurine or 2-amino-6-(methoxyethoxy)purine and the like, the base moiety can be converted into guanine by an appropriate means such as acid hydrolysis, alkaline hydrolysis and reduction. Conversion into guanine is preferably conducted before the reduction of the lactone ring.

[0023] The cyclopropane derivatives of formula (1) and its precursor (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol include their racemates, optical isomers and stereoisomers. As described above, by using an optically active epichlorohydrin, any of the optical isomers can be prepared similarly as described above. Alternatively, any of the intermediates or the final product may be resolved by optical resolution column chromatography or by fractional crystallization using diastereomeric salts.

Examples

[0024] Embodiments of the present invention are further described in the following examples. With regard to the relative configuration in the examples, the cyclopropane moiety is considered to be on a flat plane and the substituents positioned below the plane are represented by "α" while those positioned above the same by "β".

Example 1:

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol

Process 1:

Preparation of ethyl 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carboxylate

[0025] 2.42 g (105 mmol) of metallic sodium was dissolved in 200 ml of ethanol at 0°C in an argon atmosphere. 16.7 g (110 mmol) of diethyl malonate was added and then 7.8 ml (100 mmol) of epichlorohydrin dissolved in 5 ml of ethanol was added dropwise at room temperature. The solution thus obtained was heated at 75°C for 20 hours and then cooled to 0°C, and the precipitation formed was filtered off. The filtrate was concentrated under reduced pressure, and water was added to the residue, which was then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel chromatography (hexane: ethyl acetate=5:1 to 1:1) to yield 12.0 g (70 mmol, 70%) of the entitled compound.

Colorless oil

$^1$H-NMR(CDC$_3$): 1.31(t, J=7.1Hz, 3H), 1.37(dd, J=4.8, 5.4Hz, 1H), 2.08(dd, J=4.8, 8.0Hz, 1H), 2.72(m, 1H), 4.18(d, J=9.6Hz, 1H), 4.27(q, J=7.1Hz, 2H), 4.36(dd, J=4.5, 9.6Hz, 1H)

FD Mass spectrum: 170 (M+)

Process 2:

Preparation of 3-oxa-2-oxabicyclo[3.1,0]hexan-1-carboxylic acid

[0026] 5.10 g (30.0 mmol) of ethyl 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carboxylate was dissolved in 80 ml of 1N aqueous solution of sodium hydroxide and stirred at a room temperature for 4 hours. After the solvent was concentrated to a volume of about 40 ml under reduced pressure, 10 ml of concentrated hydrochloric acid was added to adjust the pH to 1 or lower and the mixture was adsorbed to a resin (SEPABEADS SP-207, Mitsubishi Kasei) equilibrated with 0.1N hydrochloric acid. After washing the resin with 120 ml of 0.1N hydrochloric acid and 80 ml of water, the product was eluted with 300 ml of 20% aqueous solution of methanol to yield 3.85 g (27.0 mmol, 90%) of the entitled compound. White solid

$^1$H-NMR(CDC$_3$): 1.56(dd, J=4.5, 5.6Hz, 1H), 2.15(dd, 4.5, 7.8Hz, 1H), 2.96-3.03(m, 1H), 4.31(d, J=9.6Hz, 1H), 4.47
**Process 3:**

Preparation of 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carbonyl chloride

[0027] 134.7 mg (0.948 mmol) of 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carboxylic acid was dissolved in 1.13 g of thionyl chloride, and stirred at 65°C for 100 minutes. After cooling to room temperature, thionyl chloride was distilled off under reduced pressure to obtain 152.2 mg (0.984 mmol, 100%) of the entitled compound.

White solid

1H-NMR(CDCl3): 1.68(t, J=5.4Hz, 1H), 2.41(dd, J=5.4, 8.4Hz, 1H), 3.04-3.11(m, 1H), 4.24(d, J=9.9Hz, 1H), 4.44(dd, J=4.7, 9.9Hz, 1H)

FAB Mass spectrum: 161 (MH+)

**Process 4:**

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol

[0028] 76.1 mg (0.474 mmol) of 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carbonyl chloride was dissolved in 2 ml of 1,4-dioxane and 10.8 mg (0.284 mmol) of sodium borohydride was added. After stirring for 3 hours at room temperature, phosphate buffer (pH 7) was added and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=19:1) to yield 15.7 mg (0.123 mmol, 26%) of the entitled compound.

Colorless oil

1H-NMR(CDCl3): 1.01(t, J=4.8Hz, 1H), 1.32(dd, J=4.8, 7.7Hz, 1H), 2.26-2.33(m, 1H), 3.69(d, 12.6Hz, 1H), 4.05(d, J=12.6Hz, 1H), 4.18(d, J=9.3Hz, 1H), 4.34(dd, J=4.7, 9.3Hz, 1H)

FAB Mass spectrum: 129 (MH+)

**Example 2:**

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol

[0029] 72.5 mg (0.510 mmol) of 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carboxylic acid and 77.4 mg (0.764 mmol) of triethylamine were dissolved in 1.0 ml of tetrahydrofuran and cooled to -18°C, and then 83.0 mg (0.764 mmol) of ethyl chloroformate in 0.5 ml of tetrahydrofuran was added. After stirring for 30 minutes at -18°C, 57.9 mg (1.53 mmol) of sodium borohydride in 0.75 ml of water was added. After further stirring for 20 minutes at -18°C, 2 ml of 2N hydrochloric acid were added. Tetrahydrofuran was distilled off under reduced pressure, and the residue was extracted with dichloromethane. After drying the organic layer over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=19:1) to yield 35.9 mg (0.281 mmol, 55%) of the entitled compound. This compound had physical data similar to that of Example 1.

**Example 3:**

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol

**Process 1:**

Preparation of 1β-ethoxycarbonyl-2α-hydroxymethylcyclopropan-1-carboxamide

[0030] 1.73 g (10.2 mmol) of ethyl 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carboxylate was dissolved in 2 M NH₄/methanol solution. After stirring at room temperature for 15 minutes, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to obtain 1.12 g (6.62 mmol, 65%) of the entitled compound.

White solid

1H-NMR(CDCl3): 1.25(t, J=7.1Hz, 1H), 1.80(dd, 4.5, 9.7Hz, 1H), 1.88(dd, 4.5, 8.OHz, 1H), 2.19-2.30(m, 1H), 3.67-3.78 (m, 1H), 3.90-3.99(m, 1H), 4.15(q, J=7.1Hz, 2H), 5.96(bs, 1H), 8.25(bs, 1H)
FAB mass spectrum: 188 (MH⁺)

Process 2:

Preparation of 1β,2α-bis(hydroxymethyl)cyclopropan-1-carboxyamide

[0031] 94.9 mg (0.558 mmol) of 1β-ethoxycarbonyl-2α-hydroxymethylcyclopropan-1-carboxyamide was dissolved in 1.2 ml of t-butyl alcohol and 42.2 mg (0.558 mmol) of sodium borohydride was added. After heating to 83°C, 0.2 ml of methanol was added and the mixture was heated under reflux for 1 hour. After cooling to room temperature, 0.279 ml of 2N hydrochloric acid was added and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 9 : 1) to yield 70.3 mg (0.485 mmol, 87%) of the entitled compound. Colorless oil

1H-NMR(CD3OD): 0.88(dd, J=4.9, 8.9Hz, 1H), 1.24(dd, J=4.9, 6.3Hz, 1H), 1.40-1.50(m, 1H), 3.50(d, J=12.0Hz, 1H), 3.61(dd, J=7.4, 11.7Hz, 1H), 3.66(dd, J=6.9, 11.7Hz, 1H), 3.76(d, J=12.0Hz, 1H)

FAB mass spectrum: 146 (MH⁺)

Process 3:

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol

[0032] 31.0 mg (0.214 mmol) of 1β,2α-bis(hydroxymethyl)cyclopropan-1-carboxyamide was admixed with 2.1 ml of 2N hydrochloric acid. After stirring at room temperature for 18 hours, 8.4 ml of water was added and the mixture was extracted with ethyl acetate. After drying the organic layer over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 19:1) to yield 23.1 mg (0.166 mmol, 78%) of the entitled compound. This compound had physical data similar to that of Example 1.

Example 4:

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol

[0033] 258.7 mg (1.52 mmol) of ethyl 3-oxa-2-oxobicyclo[3.1.0]hexan-1-carboxylate was dissolved in 5 ml of ethanol and 60.8 mg (1.52 mmol) of sodium hydroxide in 5 ml of ethanol was added. After stirring for 16 hours, 287.5 mg (7.60 mmol) of sodium borohydride was added and the mixture was heated under reflux for 3 hours. After cooling to room temperature, 4.56 ml of 2N hydrochloric acid was added. After distilling ethanol off under reduced pressure, 10 ml of 2N hydrochloric acid was further added. After stirring for 18 hours, the mixture was extracted with ethyl acetate. After drying the organic layer over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=19:1) to yield 106.2 mg (0.829 mmol, 55%) of the entitled compound. This compound had physical data similar to that of Example 1.

Example 5:

Preparation of 2-amino-6-chloro-9-(3‘-oxa-2‘-oxobicyclo[3.1.0]hexan-1‘-yl)methylpurine

Process 1:

Preparation of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methyl bromide

[0034] 15.7 mg (0.123 mmol) of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol, 6.2 mg (0.062 mmol) of triethylamine and 58.1 mg (0.221 mmol) of triphenylphosphine were dissolved in 1.5 ml of dichloromethane, and the mixture was cooled to 0°C and then 73.4 mg (0.221 mmol) of carbon tetrabromide was added. After stirring for 100 minutes, phosphate buffer (pH 7) was added and the mixture was extracted with dichloromethane. After drying the organic layer over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to yield 13.3 mg (70 μmol, 57%) of the entitled compound. White solid

1H-NMR(CDCl3): 1.28(t, J=5.1Hz, 1H), 1.49(dd, J=5.1, 7.8Hz, 1H), 2.33-2.40(m, 1H), 3.30(d, J=11.3Hz, 1H), 4.12(d, J=11.3Hz, 1H), 4.17(d, J=9.3Hz, 1H), 4.36(dd, J=4.7, 9.3Hz, 1H)
Process 2:

Preparation of 2-amino-6-chloro-9-(3’-oxa-2’-oxabicyclo[3.1.0]hexan-1’-yl)methylpurine

[0035] 13.3 mg (69.6 μmol) of (3-oxa-2-oxabicyclo[3.1.0]hexan-1-yl)methyl bromide was dissolved in 1.4 ml of N,N-dimethylformamide and 11.8 mg (69.6 μmol) of 2-amino-6-chloropurine and 9.6 mg (69.6 μmol) of potassium carbonate were added. After stirring for 17 hours at room temperature, insoluble materials were filtered off, and the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: methanol=49:1) to yield 11.4 mg (41.1 μmol) of the entitled compound. White solid

\[^{1}\text{H-NMR (CD}_3\text{OD)}: 1.16(t, J=4.8Hz, 1H), 1.65(dd, J=4.8, 7.8Hz, 1H), 2.70-2.76(m, 1H), 4.20(d, J=9.3Hz, 1H), 4.29(dd, J=4.5, 9.3Hz, 1H), 4.37(d, J=15.0Hz, 1H), 4.69(d, J=15.0Hz, 1H), 8.17(s, 1H)]

FAB mass spectrum: 280 (MH\(^+\))

Example 6:

Preparation of 2-amino-6-chloro-9-(3’-oxa-2’-oxabicyclo[3.1.0]hexan-1’-yl)methylpurine

Process 1:

Preparation of (3-oxa-2-oxabicyclo[3.1.0]hexan-1-yl)methyl chloride

[0036] 31.3 mg (0.244 mmol) of (3-oxa-2-oxabicyclo[3.1.0]hexan-1-yl)methanol and 37.0 mg (0.366 mmol) of triethylamine were dissolved in 1 ml of dichloromethane, and then 43.5 mg (0.366 mmol) of thionyl chloride in 1 ml of dichloromethane was added. After stirring for 90 minutes, phosphate buffer (pH 7) was added and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to yield 29.5 mg (0.200 mmol, 82%) of the entitled compound. White solid

\[^{1}\text{H-NMR (CDCl}_3\text{): 1.16(t, J=5.1Hz, 1H), 1.47(dd, J=5.1, 8.0Hz, 1H), 2.35-2.42(m, 1H), 3.48(d, J=12.0Hz, 1H), 4.19(d, J=9.3Hz, 1H), 4.27(d, J=12.0Hz, 1H), 4.36(dd, J=4.5, 9.3Hz, 1H)]

Process 2:

Preparation of 2-amino-6-chloro-9-(3’-oxa-2’-oxabicyclo[3.1.0]hexan-1’-yl)methylpurine

[0037] 27.8 mg (0.190 mmol) of (3-oxa-2-oxabicyclo[3.1.0]hexan-1-yl)methyl chloride was dissolved in 1.9 ml of N,N-dimethylformamide and 32.2 mg (0.19 mmol) of 2-amino-6-chloropurine and 26.3 mg (0.190 mmol) of potassium carbonate were added. After stirring for 21 hours at room temperature, stirring was further continued at 55°C for 20 hours. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol=49:1) to yield 41.5 mg (0.148 mmol, 78%) of the entitled compound. This compound had physical data similar to that of Example 5.

Example 7:

Preparation of 2-amino-6-chloro-9-(3’-oxa-2’-oxabicyclo[3.1.0]hexan-1’-yl)methylpurine

Process 1:

Preparation of (3-oxa-2-oxabicyclo[3.1.0]hexan-1-yl)methyl methanesulfonate

[0038] 33.0 mg (0.258 mmol) of (3-oxa-2-oxabicyclo[3.1.0]hexan-1-yl)methanol and 39.1 mg (0.386 mmol) of triethylamine were dissolved in 1 ml of dichloromethane and cooled to 0°C, and then 35.5 mg (0.310 mmol) of methanesulfonyl chloride in 1 ml of dichloromethane was added. After stirring for 21 hours, phosphate buffer (pH 7) was added and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to yield 41.5 mg (0.148 mmol, 78%) of the entitled compound. White solid

\[^{1}\text{H-NMR (CDCl}_3\text{): 1.16(t, J=5.1Hz, 1H), 1.44(dd, J=5.1, 8.0Hz, 1H), 2.47-2.54(m, 1H), 3.08(s, 3H), 4.13(d, J=11.9Hz, 1H)]

**Process 2:**

Preparation of 2-amino-6-chloro-9-(3'-oxa-2'-oxobicyclo[3.1.0]hexan-1'-yl) methylpurine

**[0039]** 35.5 mg (0.172 mmol) of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methyl methanesulfonate was dissolved in 1.7 ml of N,N-dimethylformamide and 29.2 mg (0.172 mmol) of 2-amino-6-chloropurine and 23.8 mg (0.172 mmol) of potassium carbonate were added. After stirring for 20 hours at room temperature, insoluble materials were filtered off, and the filtrate was distilled under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 49:1) to yield 37.5 mg (0.134 mmol, 78%) of the entitled compound. This compound had physical data similar to that of Example 5.

**Example 8:**

Preparation of 9-(3'-oxa-2'-oxobicyclo[3.1.0]hexan-1'-yl)methylguanine

**[0040]** 11.7 mg (41.8 μmol) of 2-amino-6-chloro-9-(3'-oxa-2'-oxobicyclo[3.1.0]hexan-1'-yl)methylpurine was dissolved in 0.5 ml of 80% formic acid and the solution was heated at 100 °C for 2 hours. After cooling to room temperature, the solvent was distilled off under reduced pressure. After adjustment of the pH to 4 with potassium carbonate followed by purification by reverse C18 silica gel chromatography (water:methanol=3:1), 10.9 mg (41.8 μmol, 100%) of the entitled compound were obtained.

White solid

1H-NMR (DMSO-d6): δ: 1.05(t, J=4.8Hz, 1H), 1.42(dd, J=4.8, 7.8Hz, 1H), 2.57-2.64(m, 1H), 4.11(d, J=9.3Hz, 1H), 4.13(d, J=14.9Hz, 1H), 4.25(dd, J=4.5, 9.3Hz, 1H), 4.44(d, J=14.9Hz, 1H), 6.41(bs, 2H), 7.66(s, 1H)

High resolution mass spectrum (C11H12O3N5, M+H):

Calculated value: 262.0940
Found value: 262.0942

**Example 9:**

Preparation of 9-[1'a, 2'a-bis(hydroxymethyl)cyclopropan-1'-yl]methylguanine

**[0041]** Preparation of 9-[1'a, 2'a-bis(hydroxymethyl)cyclopropan-1'-yl]methylguanine

**[0042]** 20.9 mg (80.0 μmol) of 9-(3'-oxa-2'-oxobicyclo[3.1.0]hexan-1'-yl)methylguanine was dissolved in 1 ml of ethanol, and 15.1 mg (0.400 mmol) of sodium borohydride was added. After stirring at 80°C for 90 minutes, 0.25 ml of 2N hydrochloric acid was added and ethanol was distilled off under reduced pressure. After adjustment of the pH to 4 with potassium carbonate followed by purification by reverse C18 silica gel chromatography (water:methanol=4:1), 19.7 mg (74.4 μmol, 93%) of the entitled compound were obtained.

White solid

1H-NMR (DMSO-d6): δ: 0.40(t, J=5.1Hz, 1H), 0.88(dd, J=4.8, 8.7Hz, 1H), 1.23(m, 1H), 3.24-3.37(m, 2H), 3.41(dd, J=6.0, 12.0Hz, 1H), 3.58(dt, J=12.0, 6.0Hz, 1H), 3.81(d, J=14.1Hz, 1H), 4.00(d, J=14.1Hz, 1H), 4.49(m, 1H), 4.64(m, 1H), 6.38(bs, 2H), 7.71(s, 1H), 10.49(bs, 1H)

High resolution mass spectrum (C11H16O3N5, M+H):

Calculated value: 266.1253
Found value: 266.1263

**Example 10:**

Preparation of 9-(3'-oxa-2'-oxobicyclo[3.1.0]hexan-1'-yl)methyladenine

**[0043]** 40.0 mg (1.00 mmol) of 60% sodium hydride which had previously been washed with hexane were suspended in 10 ml of N,N-dimethylformamide, and 210.5 mg (1.02 mmol) of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methyl methanesulfonate and 135.1 mg (1.00 mmol) of adenine were added. After stirring at 60°C for 3 hours, insoluble materials were filtered off, and the filtrate was distilled under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=19:1) to yield 153.0 mg (0.624 mmol, 62%) of the entitled compound.

White solid

1H-NMR (DMSO-d6): δ: 1.06(t, J=4.7Hz, 1H), 1.54(dd, J=4.7, 7.8Hz, 1H), 2.59-2.67(m, 1H), 4.10(d, J=9.3Hz, 1H), 4.22(dd, J=5.0, 9.3Hz, 1H), 4.37(d, J=15.0Hz, 1H), 4.63(d, J=15.0Hz, 1H), 7.20(bs, 2H), 8.10(s, 1H), 8.14(s, 1H)

High resolution mass spectrum (C11H12O2N5, M+H):
Example 11:
Preparation of 9-[1'α,2'α-bis(hydroxymethyl)cyclopropan-1'-yl]methyladenine

[0044] 36.1 mg (0.147 mmol) of 9-(3'-oxa-2'-oxobicyclo[3.1.0]hexan-1'-yl)methyladenine was dissolved in 1.5 ml of ethanol, and 27.8 mg (0.736 mmol) of sodium borohydride was added. After stirring at room temperature for 14 hours, 0.37 ml of 2N hydrochloric acid was added and ethanol was distilled off under reduced pressure. After adjustment of the pH to 4 followed by the purification by reverse C18 silica gel chromatography (water:methanol=4:1), 33.3 mg (0.134 mmol, 91%) of the entitled compound were obtained.

White solid

\[ ^1H-NMR(DMSO-d_6) \delta: 0.41(t, J=5.1Hz, 1H), 0.93(dd, J=5.1, 8.7Hz, 1H), 1.32(m, 1H), 3.23-3.44(m, 3H), 3.58(m, 1H), 4.02(d, J=14.2Hz, 1H), 4.19(d, J=14.2Hz, 1H), 4.56(d, J=5.2Hz, 1H), 4.74(d, J=5.2Hz, 1H), 7.20(bs, 2H), 8.13(s, 1H), 8.16(s, 1H) \]

High resolution mass spectrum (C_{11}H_{16}O_2N_5, M^+H):
Calculated value: 250.1304
Found value: 250.1310

Claims

1. A cyclopropane derivative represented by the formula (I):

\[
\text{(I)}
\]

wherein B represents a hypoxanthine residue, guanine residue, adenine residue, 2-amino-6-chloropurine residue, xanthine residue, 2,6-diaminopurine residue or 2-aminopurine residue.

2. A cyclopropane derivative according to claim 1, wherein B is guanin-9-yl, 2-amino-6-chloropurin-9-yl, 2-acetamino-6-chloropurin-9-yl, 2-acetamino-6-(N,N-diphenylcarbamoyl)oxypurin-9-yl, 2-amino-6-benzyloxypurin-9-yl, 2-amino-6-(methoxyethoxy)purin-9-yl or adenin-9-yl.

3. A method of preparing a compound of formula (a):

\[
\text{(a)}
\]

wherein B is as defined in claim 1 by reducing a cyclopropane derivative represented by formula (I) set out in claim 1.

4. (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol represented by formula (II):
5. A method of preparing a cyclopropane derivative of formula (I) as set out in claim 1, comprising conversion of the hydroxyl group of (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol into a leaving group susceptible to substitution by a purine in the presence of a base and subsequent reaction with a purine derivative.

6. A compound of formula:

![Formula 2](image)

wherein X represents a leaving group susceptible to substitution by a purine in the presence of a base.

7. A method for the preparation of the cyclopropane derivative of formula (I) as set out in claim 1 comprising reaction of a compound of claim 5 with a purine derivative.

8. An intermediate for the production of a compound of claim 4 selected from compounds (6)-(11) as shown below, wherein R¹ represents a lower alkyl group, R² represents a lower alkyl or an aryl group, R³ and R⁴ are each, independently, hydrogen or an alkyl group and M is an alkali metal or alkaline earth metal:

![Formulas 6-11](images)

9. A method for the production of the compound of claim 4 comprising:
(a) reduction to an alcohol

(i) of the carboxylic acid group of a compound of formula:

![Diagram of a carboxylic acid group]

or

(ii) of the acyl chloride group of a compound of formula:

![Diagram of an acyl chloride group]

or

(iii) of the acyl carbonate group of a compound of formula:

![Diagram of an acyl carbonate group]

wherein \( R^2 \) represents a lower alkyl or an aryl group;

or

(b) acid hydrolysis of a compound of formula:
wherein $R^3$ and $R^4$ are each, independently, hydrogen or an alkyl group; or

(c) acid catalysed cyclisation of a compound of formula:

wherein $M$ is an alkali metal or alkaline earth metal.

**Patentansprüche**

1. Cyclopropanderivat, das durch die Formel (I) dargestellt ist


3. Verfahren zur Herstellung einer Verbindung der Formel (a)

4. (3-Oxa-oxobicyclo[3.1.0]hexan-1-yl)methanol, dargestellt durch Formel (II)
5. Verfahren zur Herstellung eines Cyclopropanderivats der in Anspruch 1 angegebenen Formel (I), welches die Umwandlung der Hydroxylgruppe von (3-Oxa-2-oxobicyclo[3.1.0]hexan-1-yl)methanol in eine Austrittsgruppe, welche befähigt ist, in Gegenwart einer Base durch ein Purin ersetzt zu werden und die nachfolgende Reaktion mit einem Purinderivat umfaßt.

6. Verbindung der Formel

in der X eine Austrittsgruppe darstellt, die befähigt ist, in Gegenwart einer Base durch ein Purin ersetzt zu werden.

7. Verfahren zur Herstellung des Cyclopropanderivats der in Anspruch 1 angegebenen Formel (I), welches die Umsetzung einer Verbindung gemäß Anspruch 5 mit einem Purinderivat umfaßt.

8. Zwischenprodukt für die Herstellung einer Verbindung gemäß Anspruch 4, das unter den nachstehend gezeigten Verbindungen (6) bis (11) ausgewählt ist, worin $R^1$ eine niedere Alkylgruppe darstellt, $R^2$ eine niedere Alkyl- oder Arylgruppe darstellt, $R^3$ und $R^4$ jeweils unabhängig Wasserstoff oder eine Alkylgruppe bedeuten und $M$ ein Alkalimetall oder Erdalkalimetall ist:

9. Verfahren zur Herstellung der Verbindung gemäß Anspruch 4, welches folgende Stufen umfaßt:

   (a) die Reduktion zu einem Alkohol

   (i) der Carboxylgruppe eine Verbindung der Formel
oder
(ii) der Acylchloridgruppe einer Verbindung der Formel

oder
(iii) der Acylcarbonatgruppe einer Verbindung der Formel

worin $R^2$ eine niedere Alkyl- oder eine Arylgruppe darstellt,

oder
(b) die Säurehydrolyse einer Verbindung der Formel

worin $R^3$ und $R^4$ jeweils unabhängig Wasserstoff oder eine Alkylgruppe darstellen oder
(c) die säurekatalysierte Cyclisierung einer Verbindung der Formel

worin $M$ ein Alkalimetall oder Erdalkalimetall ist.
Revendications

1. Dérivé de cyclopropane représenté par la formule (I) :

\[
\text{(I)}
\]

où B représente un résidu hypoxanthine, un résidu guanine, un résidu adénine, un résidu 2-amino-6-chloropurine, un résidu xanthine, un résidu 2,6-diaminopurine ou un résidu 2-aminopurine.


3. Procédé de préparation d’un composé de la formule (a) :

\[
\text{(a)}
\]

où B est comme défini dans la revendication 1 par réduction d’un dérivé de cyclopropane représenté par la formule (I) défini dans la revendication 1.

4. (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yle)méthanol représenté par la formule (II) :

\[
\text{(II)}
\]

5. Procédé de préparation d’un dérivé de cyclopropane de la formule (I) défini dans la revendication 1 comprenant la transformation du groupe hydroxyle de (3-oxa-2-oxobicyclo[3.1.0]hexan-1-yle)méthanol en un groupe qui se éloigne susceptible d’être substitué par une purine en présence d’une base et la réaction subséquente avec un dérivé de purine.

6. Composé de la formule :
où X représente un groupe qui s'éloigne susceptible d'être substitué par une purine en présence d'une base.

7. Procédé pour la préparation du dérivé de cyclopropane de la formule (I) définie dans la revendication 1 comprenant la réaction d'un composé de la revendication 5 avec un dérivé purine.

8. Intermédiaire pour la production d'un composé selon la revendication 4 choisi parmi les composés (6)-(11) représentés ci-dessous où R₁ représente un groupe alkyle inférieur, R₂ représente un groupe alkyle inférieur ou un groupe aryle, R₃ et R₄ sont chacun indépendamment un atome d'hydrogène ou un groupe alkyle et M est un métal alcalin ou un métal alcalino-terreux :

9. Procédé pour la production du composé selon la revendication 4 comprenant :

   (a) la réduction en un alcool,

   (i) du groupe d'acide carboxylique d'un composé de la formule : 
ou

(ii) du groupe de chlorure d'acyle d'un composé de la formule :

ou

(iii) du groupe de carbonate d'acyle d'un composé de la formule :

ou

(b) l'hydrolyse acide d'un composé de la formule :

(c) la cyclisation catalysée par un acide d'un composé de la formule :

où R² représente un groupe alkyle inférieur ou un groupe aryle; ou

où R³ et R⁴ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle; ou

(c) la cyclisation catalysée par un acide d'un composé de la formule :
où M est un métal alcalin ou un métal alcalino-terreux.