

(19) AUSTRALIAN PATENT OFFICE

(54) Title
Prostaglandin derivatives

(51)⁶ International Patent Classification(s)
C07C 405/00 8BMEP **A61P**
(2006.01) 25/20
A61P 25/20 (2006.01) 20060101ALI2006052
C07C 405/00 1BMWO
20060101AFI2005100 PCT/JP2003/008864

(21) Application No: 2003280977 (22) Application Date: 2003 .07 .11

(87) WIPO No: W004/007442

(30) Priority Data

(31) Number	(32) Date	(33) Country
2002-204908	2002 .07 .12	JP

(43) Publication Date : 2004 .02 .02
(43) Publication Journal Date : 2004 .03 .18

(71) Applicant(s)
Fumie Sato, Taisho Pharmaceutical Co., Ltd.

(72) Inventor(s)
Yagi, Makoto, Sato, Fumie, Ono, Naoya, Tanami, Tohru

(74) Agent/Attorney
Phillips Ormonde & Fitzpatrick, Level 22 367 Collins Street, Melbourne, VIC, 3000

(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局



(43) 国際公開日
2004 年 1 月 22 日 (22.01.2004)

PCT

(10) 国際公開番号
WO 2004/007442 A1

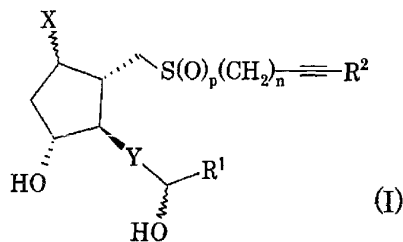
- (51) 国際特許分類: C07C 405/00, 170-8633 東京都 豊島区 高田 3 丁目 2 4 番 1 号 大正製薬株式会社内 Tokyo (JP)
A61K 31/5575, A61P 25/20
- (21) 国際出願番号: PCT/JP2003/008864 (74) 代理人: 佐島 宗一, 外(SATORI, Soichi et al.); 〒170-8633 東京都 豊島区 高田 3 丁目 2 4 番 1 号 大正製薬株式会社 知的財産部 Tokyo (JP).
- (22) 国際出願日: 2003 年 7 月 11 日 (11.07.2003)
- (25) 国際出願の言語: 日本語 (81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (26) 国際公開の言語: 日本語 (84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NI, SN, TD, TG).
- (30) 優先権データ: 特願2002-204908 2002 年 7 月 12 日 (12.07.2002) JP
- (71) 出願人 (米国を除く全ての指定国について): 大正製薬株式会社 (TAISHO PHARMACEUTICAL CO., LTD.) [JP/JP]; 〒170-8633 東京都 豊島区 高田 3 丁目 2 4 番 1 号 Tokyo (JP).
- (72) 発明者: 佐藤 史衛 (SATO, Fumie) [JP/JP]; 〒251-0026 神奈川県 藤沢市 鶴沼東 2-1-9 O 1 Kanagawa (JP).
- (72) 発明者: および
- (75) 発明者/出願人 (米国についてのみ): 田名見 亨 (TANAMI, Tohru) [JP/JP]; 〒170-8633 東京都 豊島区 高田 3 丁目 2 4 番 1 号 大正製薬株式会社内 Tokyo (JP), 八木 慎 (YAGI, Makoto) [JP/JP]; 〒170-8633 東京都 豊島区 高田 3 丁目 2 4 番 1 号 大正製薬株式会社内 Tokyo (JP), 小野 直哉 (ONO, Naoya) [JP/JP]; 〒

添付公開書類:
— 国際調査報告書

2 文字コード及び他の略語については、定期発行される各 PCT ガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: PROSTAGLANDIN DERIVATIVES

(54) 発明の名称: プロスタグランジン誘導体



(57) Abstract: Prostaglandin derivatives represented by the general formula (I), pharmaceutically acceptable salts thereof, or hydrates of the salts: (I) wherein X is halogeno of α or β configuration; Y is ethylene, vinylene, or ethynylene; R¹ is C₃₋₁₀ cycloalkyl which may be substituted with a linear or branched C₁₋₄ alkyl group, or C₄₋₁₃ cycloalkylalkyl; R² is hydrogen or CO₂R³; R³ is hydrogen, linear or branched C₁₋₄ alkyl, or linear or branched C₂₋₄ alkenyl; n is an integer of 1 to 4; and p is 0, 1, or 2.

(続葉有)

DESCRIPTION
PROSTAGLANDIN DERIVATIVES

Technical Field

5 The present invention relates to a novel
prostaglandin derivative, a pharmaceutically acceptable salt
thereof or a hydrate thereof and a sleep-inducing agent
containing the same as the effective ingredient.

Background Art

10 Since prostaglandins (hereinafter referred to as
"PG(s)") exhibit various important physiological actions in
trace amounts, the syntheses of natural PGs and a great
number of their derivatives as well as their biological
activities have been investigated with the intention of
15 practical use as medicines, and have been reported in many
types of literature.

 Particularly, while various central nervous
actions of PGs have been reported, their intracerebral
contents, biosynthesis, metabolic pathways, intracerebral
20 localizations and changes with growth or aging have been
revealed. Interest has been maintained on their relations
with sleep or arousal by PGs. Particularly, PGD₂ has been
known as an intracerebral humoral factor that regulates the
occurrence or maintenance of sleep; and it became clear that
25 the sleep induced by PGD₂ in monkeys is indistinguishable
from their spontaneous natural sleep in brain wave or
behavior (Proc. Natl. Acad. Sci. USA, Vol. 85, pp.4082-4086,

1988). PGD₂ was, therefore, expected to be a new compound possessing sleep-inducing action. However, PGD₂ derivatives including PGD₂ have not been put in practical use because of problems on their brain penetration and stability.

5 W099/61419 discloses a compound having an ethynylene group at its α -chain. This compound is difficult to crystallize and presents the problem of formulation.

The discussion of documents, acts, materials, devices, articles and the like is included in this
10 specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed
15 before the priority date of each claim of this application.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as
20 specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

Disclosure of the Invention

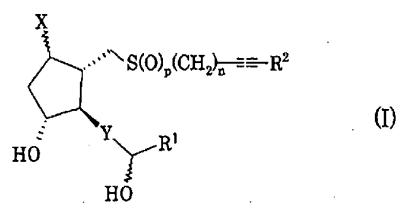
25 An aspect of the present invention is to provide PG derivatives possessing an excellent sleep-inducing action.

As a result of continued extensive studies, the present inventors found that prostaglandin derivatives
30 represented by Formula (I) described below possess the excellent sleep-inducing action, upon which the present invention has been accomplished.

Specifically, according to one embodiment of the

2a

present invention, the invention is directed to a prostaglandin derivative represented by Formula (I):



wherein X is a halogen atom in the α - or β -substitution, Y is an ethylene group, a vinylene group or an ethynylene group, R¹ is a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkyl group substituted with a C₁₋₄ straight or branched chain alkyl group or a C₄₋₁₃ cycloalkylalkyl group, R² is a hydrogen atom or a CO₂R³ group (R³ is a hydrogen atom, a C₁₋₄ straight or branched chain alkyl group, or a C₂₋₄ straight or branched chain alkenyl group), n is an integer of 1 to 4 and p is 0, 1 or 2, a pharmaceutically acceptable salt thereof or a hydrate thereof.

According to another embodiment of the present invention, the invention is directed to a prostaglandin derivative represented by Formula (I) as described above wherein R¹ is a C₃₋₁₀ cycloalkyl group or a C₄₋₁₃ cycloalkylalkyl group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

According to a further embodiment of the present invention, the invention is directed to a prostaglandin derivative represented by Formula (I) as described above wherein X is a chlorine atom or a bromine atom in the α - or β -substitution, a pharmaceutically acceptable salt thereof or a hydrate thereof.

According to a still further embodiment of the present invention, the invention is directed to a prostaglandin derivative represented by Formula (I) as

described above wherein Y is an ethynylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

5 According to a still further embodiment of the present invention, the invention is directed to a prostaglandin derivative represented by Formula (I) as described above wherein R^2 is a CO_2R^3 group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

10 According to a still further embodiment of the present invention, the invention is directed to a prostaglandin derivative represented by Formula (I) as described above wherein $p=0$, a pharmaceutically acceptable salt thereof or a hydrate thereof.

15 According to a still further embodiment of the present invention, the invention is directed to a prostaglandin derivative represented by Formula (I) as described above wherein $n=1$ or 2 , a pharmaceutically acceptable salt thereof or a hydrate thereof.

20 According to a still further embodiment of the present invention, the invention is directed to a pharmaceutical composition comprising the aforementioned prostaglandin derivative, a pharmaceutically acceptable salt thereof or a hydrate thereof.

25 Best Mode for Carrying out the Invention

In the present invention, the halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom or an

iodine atom.

Examples of the C₃₋₁₀ cycloalkyl group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group.

Examples of the C₃₋₁₀ cycloalkyl group substituted with a C₁₋₄ straight or branched chain alkyl group include a methylcyclopropyl group, a methylcyclohexyl group, an ethylcyclohexyl group.

The C₄₋₁₃ cycloalkylalkyl group refers to an alkyl group substituted with a cycloalkyl group, and preferably a C₃₋₁₀ cycloalkyl-C₁₋₃ alkyl group. The examples include a cyclopropylmethyl group, a cyclobutylmethyl group, a cyclopentylmethyl group, a cyclopentylethyl group, a cyclohexylmethyl group, a cyclohexylethyl group and a cycloheptylmethyl group.

Examples of the C₁₋₄ straight or branched chain alkyl group include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group and a tert-butyl group.

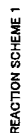
Examples of the C₂₋₄ straight or branched chain alkenyl group include an allyl group, a crotyl group and a 2-methyl-2-propenyl group.

Examples of the pharmaceutically acceptable salts include salts with alkali metals (e.g., sodium and potassium), salts with alkaline earth metals (e.g., calcium and magnesium), ammonia, methylamine, dimethylamine,

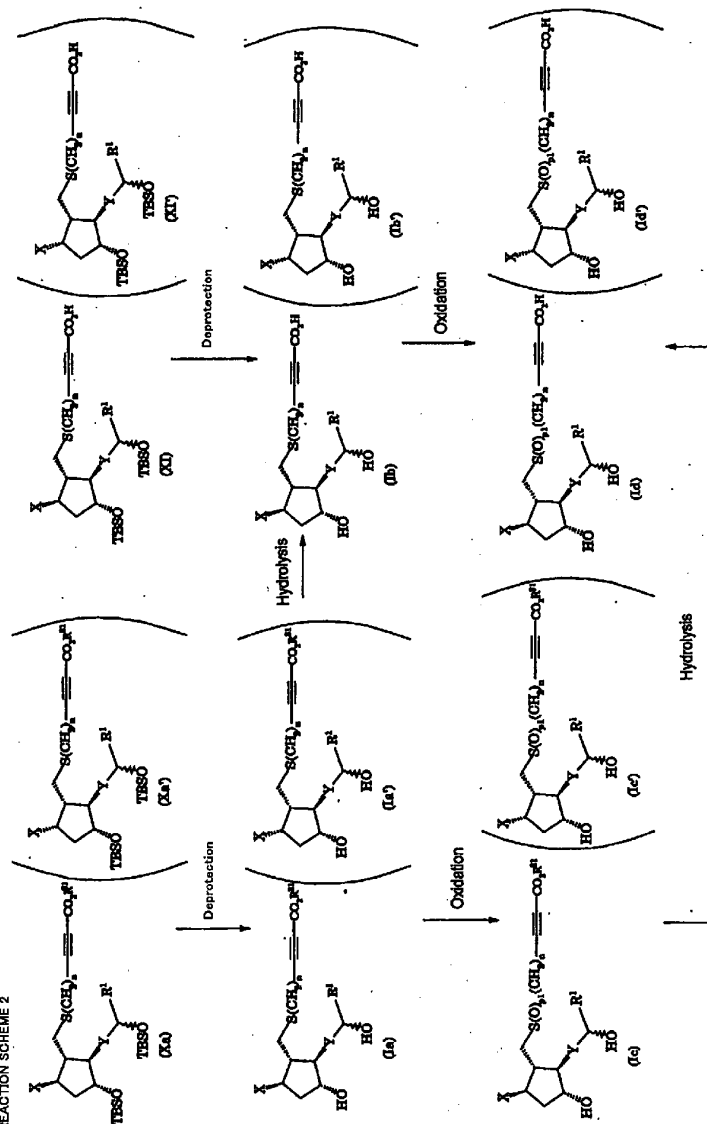
cyclopentylamine, benzylamine, piperidine, monoethanolamine, diethanolamine, monomethylmonoethanolamine, tromethamine, lysine and tris(hydroxymethyl)aminomethane.

Although n represents an integer of from 1 to 4,
5 n=1 or n=2 is preferable in terms of crystallinity.

The compounds of Formula (I) may be prepared, for example, by the methods summarized in the following reaction schemes:



REACTION SCHEME 2



In the reaction schemes, TBS is a tert-butyltrimethylsilyl group, Y' is an ethylene group or a vinylene group, R³¹ is a C₁₋₄ alkyl group or a C₂₋₄ alkenyl group, p₁ is 1 or 2, Z is a halogen atom and X, Y, R¹ and n are as previously defined.

The aforementioned reaction schemes are illustrated below.

(1) At first, the known compound of Formula (II) is reacted with 0.8 to 2.0 equivalents of a compound represented by Formula (III) or (III') in an inert solvent (e.g., benzene, toluene, tetrahydrofuran, diethyl ether, methylene chloride or n-hexane) at -78 to 30 °C according to the method of Sato et al. (Journal of Organic Chemistry, Vol. 53, p. 5590 (1988)) to stereospecifically give a compound of Formula (IV). Here, the compound wherein Y is an ethylene group or a vinylene group (i.e., the compound wherein Y is Y') can be obtained by a reaction using a compound of Formula (III') at -78 to 0 °C, and the compound wherein Y is an ethynylene group can be obtained by a reaction using a compound of Formula (III) at 0 to 30 °C.

(2) The compound of Formula (IV) is reacted with 1 to 6 equivalents of a compound represented by Formula (V) and 0.05 to 2 equivalents of a radical generating agent (e.g., azobisisobutyronitrile, azobiscyclohexanecarbonitrile, benzoyl peroxide or triethyl borane), if necessary, further with 1 to 5 equivalents of a radical reducing agent (e.g., tributyltin hydride, triphenyltin hydride, dibutyltin

hydride or diphenyltin hydride) in an organic solvent (e.g., benzene, toluene, xylene, n-hexane, n-pentane or acetone) at -78 to 100 °C to give a compound of Formula (VI). Depending on the situation, the compound of Formula (VI) can also be
5 obtained by a reaction using 0.05 to 2 equivalents of a base (e.g., an organic amine such as triethylamine, diisopropylamine, pyridine or dimethylaniline, or a base resin such as polyvinylpyrrolidone, diisopropylaminomethylpolystyrene or (piperidinomethyl)polystyrene) in an organic
10 solvent (e.g., benzene, toluene, xylene, n-hexane, n-pentane or acetone) at -78 to 100 °C.

(3) The compound of Formula (VI) is reacted with 0.5 to 5 equivalents of a reducing agent (e.g., potassium borohydride, sodium borohydride, sodium cyanoborohydride,
15 lithium tri-sec-butylborohydride or diisobutylaluminum hydride-BHT(2,6-di-tert-butyl-p-cresol)) in an organic solvent (e.g., tetrahydrofuran, diethyl ether, ethyl alcohol or methyl alcohol or toluene) at -78 to 40 °C to give compounds of Formula (VII) and (VII'). These compounds of
20 Formula (VII) and (VII') can be purified by a conventional separation method such as column chromatography.

(4) The compound of Formula (VII) or Formula (VII') is mesylated or tosylated, for example, with 1 to 6 equivalents of methanesulfonyl chloride or p-toluenesulfonyl
25 chloride in a suitable solvent such as pyridine, if necessary, in the presence of 0.8 to 6 equivalents of 4-dimethylaminopyridine at -20 to 40 °C, followed by

chlorination with 1 to 16 equivalents of tetra-n-butylammonium chloride to give a compound of Formula (VIII) or (VIII') wherein X is a chlorine atom. Here, bromination or fluorination can also be carried out in an ordinary manner. For example, bromination can be carried out by a reaction using 1 to 10 equivalents of carbon tetrabromide in the presence of 1 to 10 equivalents of triphenylphosphine and 1 to 10 equivalents of pyridine in acetonitrile. Fluorination can be carried out, for example, by a reaction with 5 to 20 equivalents of diethylaminosulfur trifluoride (DAST).

(5) The compound of Formula (VIII) or Formula (VIII') is reacted with a base (e.g., an alkylolithium such as n-butyllithium) in a suitable inert solvent (e.g., tetrahydrofuran or diethyl ether) at from -78 °C to room temperature, followed by reaction with a compound of Formula (IX) at from -78 to 40 °C to give a compound of Formula (Xa) or Formula (Xa'). Reaction with carbon dioxide instead of the compound of Formula (IX) can yield a compound of Formula (XI) or Formula (XI').

(6) The protecting group of a hydroxyl group of the compound of Formula (Xa) or Formula (Xa'), i.e., the tert-butyldimethylsilyl group is removed by using hydrofluoric acid, pyridium poly(hydrogenfluoride) or hydrochloric acid under conventional conditions in methanol, ethanol, acetonitrile or a mixed solvent of these, or a mixed solvent of the foregoing with water to give a PG

derivative of Formula (Ia) or Formula (Ia').

(7) The compound of Formula (Ia) or Formula (Ia') is hydrolyzed by a reaction with an enzyme in a buffer solution such as phosphate buffer or Tris-hydrochloride buffer, if necessary, by using an organic solvent (e.g., a water-miscible solvent such as acetone, methanol or ethanol) to give a PG derivative of Formula (Ib) or (Ib') according to the present invention. For the enzyme, there are mentioned enzymes produced by microorganisms (e.g., those produced by the microorganisms belonging to *Candida* sp. or *Pseudomonas* sp.) and enzymes prepared from animal organs (e.g., pig liver or pig pancreas). Examples of the commercially available enzymes include lipase VII (derived from a microorganism belonging to *Candida* sp.: Sigma Co., Ltd.), lipase AY (derived from a microorganism belonging to *Candida* sp.: Amano Pharmaceutical Co., Ltd.), lipase PS (derived from a microorganism belonging to *Pseudomonas* sp.: Amano Pharmaceutical Co., Ltd.), lipase MF (derived from a microorganism belonging to *Pseudomonas* sp.: Amano Pharmaceutical Co., Ltd.), PLE (prepared from pig liver: Sigma Co., Ltd.), lipase II (prepared from pig pancreas: Sigma Co., Ltd.) and lipoprotein lipase (prepared from pig pancreas: Tokyo Kasei Kogyo Co., Ltd.).

The amount of the enzyme to be used may appropriately be determined, depending on the potency of the enzyme and the amount of the substrate (the compound of Formula (Ia) or (Ia')). It is usually 0.1 to 20 parts by

weight based on the substrate. The reaction temperature is from 25 to 50 °C, preferably 30 to 40 °C.

Alternatively, the compound of Formula (Ia) or (Ia') is hydrolyzed using a base in a solvent ordinarily used for hydrolysis to give the PG derivative of Formula (Ib) or (Ib') according to the present invention. Examples of the base to be used here are lithium hydroxide and potassium carbonate. Examples of the solvent are acetonitrile, acetone, methanol, ethanol, water and a mixture of any of the foregoing.

The compound of Formula (XI) or (XI') is deprotected similarly to the above (6) to give the PG derivative of Formula (Ib) or (Ib') according to the present invention.

(8) The compound of Formula (Ia) or (Ia') is reacted with an oxidizing agent such as sodium metaperiodate, hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid or tert-butyl hydroxyperoxide in diethyl ether, methanol, ethanol, methylene chloride, water or a mixture of any of the foregoing at from -20 to 50 °C to give a PG derivative of Formula (Ic) or (Ic').

(9) The compound of Formula (Ic) or (Ic') is hydrolyzed similarly to the above (7) to give a PG derivative of Formula (Id) or (Id') according to the present invention. In addition, the compound of Formula (Ib) or (Ib') is used and oxidized similarly to the above (8) to give the PG derivative of Formula (Id) or (Id').

$S(O)_p$ in the α -chain represents the formulae:



when $p=1$; and



5 when $p=2$

Representative compounds of Formula (I) according to the present invention are illustrated below.

TABLE 1

Compound	X	Y	n	p	R ¹	R ²	15-position ^{*)}
1	β -Cl	CH ₂ CH ₂	2	0	cyclopentyl	CO ₂ Me	α
2	β -Cl	CH ₂ CH ₂	2	0	cyclohexyl	CO ₂ H	α
3	α -Cl	CH ₂ CH ₂	2	0	cyclohexyl	H	α
4	β -Br	CH ₂ CH ₂	3	0	4-methylcyclohexyl	CO ₂ H	α
5	β -Br	CH ₂ CH ₂	1	1	cycloheptyl	CO ₂ -allyl	α
6	β -Cl	(E)CH=CH	2	0	cyclopentylmethyl	CO ₂ Et	α
7	β -Cl	(E)CH=CH	3	0	cyclohexyl	CO ₂ H	β
8	F	(E)CH=CH	2	0	cyclohexylethyl	CO ₂ -tBu	α
9	β -Br	(E)CH=CH	4	2	cyclooctyl	CO ₂ H	α
10	β -Cl	(Z)CH=CH	2	0	cyclopentylmethyl	CO ₂ H	α
11	β -Cl	C $\equiv$ C	2	0	cyclopentyl	CO ₂ H	α
12	β -Cl	C $\equiv$ C	2	0	cyclohexyl	H	α
13	β -Cl	C $\equiv$ C	1	0	cyclohexyl	CO ₂ Me	α
14	β -Cl	C $\equiv$ C	1	0	cyclohexyl	CO ₂ H	α
15	α -Cl	C $\equiv$ C	1	0	cyclohexyl	CO ₂ H	α
16	β -Cl	C $\equiv$ C	2	0	cyclohexyl	CO ₂ H	α
17	β -Br	C $\equiv$ C	2	0	cyclohexyl	CO ₂ H	α
18	F	C $\equiv$ C	2	0	cyclohexyl	CO ₂ H	α
19	β -Cl	C $\equiv$ C	3	0	cyclohexyl	CO ₂ Me	α
20	α -Br	C $\equiv$ C	3	0	cyclohexyl	CO ₂ Me	β
21	F	C $\equiv$ C	3	0	cyclohexyl	CO ₂ Me	α
22	β -Cl	C $\equiv$ C	3	0	cyclohexyl	CO ₂ H	α
23	β -Cl	C $\equiv$ C	2	0	cyclohexylmethyl	CO ₂ H	α
24	β -Cl	C $\equiv$ C	2	0	cycloheptyl	CO ₂ H	α
25	β -Cl	C $\equiv$ C	2	0	cyclooctyl	CO ₂ H	α

(E) CH=CH: trans-vinylene, (Z) CH=CH: cis-vinylene,

*) Bonding between the carbon atom adjacent to R¹ and the OH group

The compounds of the present invention can be administered systemically or topically, or orally or parenterally such as intravenously or nasally. They can be, for example, administered orally in the form of tablets, dusting powders, granules, powders, capsules, solutions, emulsions, suspensions or the like, any of which may be prepared according to conventional methods. As the dosage forms for intravenous administration, there are used aqueous or non-aqueous solutions, emulsions, suspensions or solid preparations to be dissolved in solvents for injection immediately before use. Nasal administration can be performed by quantitatively spraying a solution or a powder (hard capsule) containing the drug into the nasal cavity by the use of a dedicated nasal dropper or sprayer. Further, the compounds of the present invention can be formulated into the forms of inclusion compounds with α -, β -, or γ -cyclodextrin or methylated cyclodextrin. In addition, the compounds of the present invention can be administered by injection in the form of aqueous or non-aqueous solutions, emulsions, suspensions or the like. Although the dose may be varied according to the age, body weight, etc., it is from 1 ng to 1 mg/day per adult and may be administered once a day or several times a day in divided doses.

The present invention will be described in more details by way of the following test example and examples, but the invention is in no way limited to the descriptions of these examples.

Test Example (Sleep-inducing test by cisternal administration)

Method:

5 Four male cynomolgus monkeys weighing 2.0-3.5 kg
were individually placed in cages. The behaviors of the
respective animals were recorded by videotape from one hour
before drug administration to three hours after drug
administration. Compound 16 was dissolved in physiological
10 saline solution and sterilized using a Minipore filter. The
drug was cisternally infused into the monkeys anesthetized
with isoflurane inhalation. The dose was 10 μ g/0.1 ml per
monkey and 100 μ g/0.1 ml per monkey. The same dose of the
vehicle was infused cisternally to the control group. The
15 test schedule was carried out according to the following
protocol.

Week 1: Group treated with vehicle

Week 2: Group treated with 10 μ g of Compound
16/monkey

20 Week 3: Group treated with 100 μ g of Compound
16/monkey

The sleep times at three hours after
administration were determined by playing back the recorded
videotape and measuring the times (second) during which the
25 animals relaxed with their both eyes closed, which are shown
in Table 2.

Table 2

	Sleep time (sec)	Number of slept animals
Vehicle-treated group	0	0/4
10 μ g/monkey treated group	293	3/4
100 μ g/monkey treated group	1734	4/4

Example 1

9-Deoxy-9 β -chloro-16,17,18,19,20-pentanor-15-cyclohexyl-
 5 2,2,3,3,13,14-hexadehydro-6-thia-PGF₁ α (Compound 16)
 (1) (3S)-3-(tert-Butyldimethylsiloxy)-3-cyclohexylprop-1-yne (6.58 g) was dissolved in toluene (80 ml), and n-butyl lithium (3.0 M, hexane solution, 8.0 ml) was added at 0 °C, followed by stirring at the same
 10 temperature for 30 minutes. To the solution was added diethylaluminum chloride (0.95 M, hexane solution 29.0 ml) at 0 °C, followed by stirring until the solution reached room temperature for 30 minutes. To the solution was added
 15 (4R)-2-(N,N-diethylamino)methyl-4-(tert-butyldimethylsiloxy)-cyclopent-2-en-1-one (0.25 M, toluene solution, 80.0 ml) at room temperature, followed by stirring for 15 minutes. The reaction solution, while stirring, was added to a mixture of hexane (190 ml), a saturated aqueous ammonium chloride solution (190 ml) and an aqueous
 20 hydrochloric acid solution (3 M, 56 ml), and the organic layer was separated and washed with a saturated aqueous sodium bicarbonate solution (50 ml). The resulting organic layer was dried over anhydrous magnesium sulfate, filtered

and concentrated. The resulting residue was purified by silica gel column chromatography (developing solvent; hexane:ether=10:1) to give (3R,4R)-2-methylene-3-[(3S)-3-(tert-butyltrimethylsiloxy)-3-cyclohexylprop-1-ynyl]-4-(tert-butyltrimethylsiloxy)cyclopentan-1-one (7.92 g).

¹H-NMR (CDCl₃, 200 MHz) δ ppm: 0.07, 0.08, 0.12 (3s, 12H), 0.88 (s, 18H), 0.92-1.92 (m, 11H), 2.32 (dd, J=17.8, 7.4 Hz, 1H), 2.71 (dd, J=17.8, 6.5 Hz, 1H), 3.48-3.58 (m, 1H), 4.11 (dd, J=6.2, 1.4 Hz, 1H), 4.20-4.32 (m, 1H), 5.55 (d, J=2.6 Hz, 1H), 6.13 (d, J=3.0 Hz, 1H).

IR (neat): 2930, 2850, 1735, 1640, 1470, 1380, 1255, 830, 770 cm⁻¹.

(2) A toluene solution (6 ml) of the compound obtained in the above (1) (2.63 g) and 4-mercapto-1-butyne (4.63 g, 9.8% xylene solution) was stirred at room temperature for 3 days. The reaction solution was concentrated under reduced pressure, and then the resulting residue was purified by silica gel column chromatography (developing solvent; n-hexane:ethyl acetate=40:1) to give 2-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-2,2,3,3,13,14-hexahydro-6-thia-PGE₁ 11,15-bis(tert-butyltrimethylsilyl ether) (1.52 g).

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.13 (s, 3H), 0.82-1.92 (m, 11H), 0.89 (s, 9H), 0.90 (s, 9H), 2.02 (t, J=2.6 Hz, 1H), 2.17-2.55 (m, 4H), 2.67-2.81 (m, 1H), 2.71 (t, J=7.2 Hz, 2H), 2.91 (d, J=5.9 Hz, 1H), 3.08-3.19 (m, 1H), 4.09 (dd, J=6.2, 1.7 Hz, 1H), 4.30-

4.39 (m, 1H).

IR (neat): 3312, 2929, 2856, 1750, 1472, 1463, 1451, 1362, 1252, 1105, 1064, 1006, 940, 898, 837, 778, 669, 637 cm^{-1}

(3) To a toluene solution (6.3 ml) of BHT (2,6-di-
 5 tert-butyl-p-cresol) (1.13 g) was added dropwise
 diisobutylaluminum hydride (0.9 M, hexane solution, 5.2 ml)
 at $-78\text{ }^{\circ}\text{C}$, followed by stirring at $-10\text{ }^{\circ}\text{C}$ for 1 hour. To
 the solution was added dropwise a toluene solution (21.3 ml)
 of the compound obtained in the above (2) (1.20 g), followed
 10 by stirring at $-25\text{ }^{\circ}\text{C}$ for 1 hour. Saturated ammonium
 chloride solution was added to the reaction solution and the
 solution was made weakly acidic with a 1 M aqueous
 hydrochloric acid solution, followed by extraction with
 ethyl acetate. The organic layer was washed with a 1 M
 15 aqueous hydrochloric acid solution and a saturated aqueous
 sodium chloride solution, dried over anhydrous magnesium
 sulfate and filtered. The filtrate was concentrated under
 reduced pressure, and then the resulting residue was
 purified by silica gel column chromatography (developing
 20 solvent; n-hexane:ethyl acetate=20:1 to 5:1) to give 2-
 decarboxy-16,17,18,19,20- pentanor-15-cyclohexyl-
 2,2,3,3,13,14-hexadehydro-6-thia-PGF $_{1\alpha}$ 11,15-bis(tert-
 butyldimethylsilyl ether) (930 mg) and 2-decarboxy-
 16,17,18,19,20-pentanor-15-cyclohexyl-2,2,3,3,13,14-
 25 hexadehydro-6-thia-PGF $_{1\beta}$ 11,15-bis(tert-butyldimethylsilyl
 ether) (38 mg).

2-Decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-

2,2,3,3,13,14-hexadehydro-6-thia-PGF₁α 11,15-bis(tert-butyltrimethylsilyl ether)

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (s, 3H),
0.10 (s, 6H), 0.80-2.18 (m, 14H), 0.88 (s, 9H), 0.90 (s, 9H),
5 2.03 (t, J=2.6 Hz, 1H), 2.46-2.61 (m, 2H), 2.51 (dt, J=2.6,
7.5 Hz, 2H), 2.66-2.92 (m, 4H), 4.08 (dd, J=6.2, 1.7 Hz, 1H),
4.17-4.32 (m, 2H).
IR (neat): 3468, 3313, 2929, 2856, 2232, 2120, 1472, 1463,
1451, 1388, 1362, 1338, 1253, 1101, 1062, 1006, 964, 898,
10 837, 778, 668, 637 cm⁻¹.

2-Decarboxy-16,17,18,19,20-pentano-15-cyclohexyl-
2,2,3,3,13,14-hexadehydro-6-thia-PGF₁β 11,15-bis(tert-butyltrimethylsilyl ether)

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.07 (s, 3H), 0.08 (s, 6H),
15 0.11 (s, 3H), 0.76-2.07 (m, 14H), 0.88 (s, 9H), 0.90 (s, 9H),
2.05 (t, J=2.6 Hz, 1H), 2.34 (ddd, J=10.7, 6.4, 1.7 Hz, 1H),
2.41-2.59 (m, 4H), 2.71-2.79 (m, 2H), 3.05 (dd, J=13.4, 4.3
Hz, 1H), 4.03-4.28 (m, 2H), 4.08 (dd, J=6.1, 1.7 Hz, 1H).
IR (neat): 3436, 3313, 2929, 2856, 2234, 2121, 1472, 1463,
20 1451, 1388, 1362, 1338, 1252, 1101, 1066, 1006, 898, 837,
777, 669, 637 cm⁻¹

(4) To a pyridine solution (16 ml) of 2-decarboxy-
16,17,18,19,20-pentano-15-cyclohexyl-2,2,3,3,13,14-
hexadehydro-6-thia-PGF₁α 11,15-bis(tert-butyltrimethylsilyl
25 ether) (925 mg) obtained in the above (3) was added
methanesulfonyl chloride (0.253 ml) under an argon stream at
0 °C, followed by stirring at room temperature for 3.5 hours.

To the solution were added tetra-n-butyl ammonium chloride (3.64 g) and toluene (16 ml), followed by stirring at 45 °C overnight. After addition of water and hexane, the solution was made weakly acidic with a 6 M aqueous hydrochloric acid solution and extracted with n-hexane. The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (developing solvent; n-hexane:ethyl acetate=20:1) to give 9-deoxy-9 β -chloro-2-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-2,2,3,3,13,14-hexadehydro-6-thia-PGF $_1\alpha$ 11,15-bis(tert-butyldimethylsilyl ether) (850 mg).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ ppm: 0.07 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.11 (s, 3H), 0.78-1.90 (m, 11H), 0.88 (s, 9H), 0.90 (s, 9H), 2.03 (t, $J=2.6$ Hz, 1H), 2.11-2.37 (m, 3H), 2.50 (dt, $J=2.6, 7.2$ Hz, 2H), 2.57 (ddd, $J=9.3, 5.4, 1.6$ Hz, 1H), 2.74 (t, $J=7.2$ Hz, 2H), 2.87 (d, $J=5.4$ Hz, 2H), 4.09 (dd, $J=6.1, 1.6$ Hz, 1H), 4.13-4.33 (m, 2H).
 IR (neat): 3313, 2953, 2929, 2856, 2234, 2121, 1472, 1463, 1451, 1387, 1362, 1339, 1281, 1253, 1155, 1101, 1006, 962, 927, 898, 837, 778, 668, 638 cm^{-1} .

(5) To a tetrahydrofuran solution (28.8 ml) of the compound (840 mg) obtained in the above (4) was added n-butyllithium (1.59 M, hexane solution, 0.95 ml) under an argon stream at -78 °C, followed by stirring at the same temperature for 1.5 hours. Dry ice was added to the

reaction solution and the solution was allowed to reach room temperature. The reaction was then poured to a saturated ammonium chloride solution and the solution was made weakly acidic with a 2 M aqueous hydrochloric acid solution and
 5 extracted with ethyl acetate. The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography
 10 (developing solvent; n-hexane:ethyl acetate=10:1 to 1:2) to give 9-deoxy-9 β -chloro-16,17,18,19,20-pentanor-15-cyclohexyl-2,2,3,3,13,14-hexadehydro-6-thia-PGF $_1\alpha$ 11,15-bis(tert-butyldimethylsilyl ether) (728 mg).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (2s, 6H),
 15 0.11 (s, 3H), 0.74-1.92 (m, 12H), 0.88 (s, 9H), 0.90 (s, 9H), 2.13-2.36 (m, 3H), 2.55 (ddd, $J=9.1, 5.2, 1.6$ Hz, 1H), 2.59-2.83 (m, 4H), 2.88 (d, $J=5.4$ Hz, 2H), 4.05-4.32 (m, 2H), 4.09 (dd, $J=6.3, 1.6$ Hz, 1H).
 IR (neat): 3400, 2929, 2856, 2241, 1691, 1472, 1464, 1451,
 20 1411, 1385, 1362, 1279, 1255, 1156, 1087, 1006, 962, 898, 837, 778, 670, 590, 504 cm^{-1}

(6) To a methyl alcohol solution (22.8 ml) of the compound obtained in the above (5) (720 mg) was added conc. hydrochloric acid (0.114 ml) at room temperature, followed
 25 by stirring for 4 hours. The reaction solution was added to a mixture of ethyl acetate and a saturated aqueous sodium bicarbonate solution, and the organic layer was separated.

The aqueous layer was extracted with ethyl acetate, and the organic layers were combined, washed with a saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (developing solvent; chloroform:methanol=20:1) to give the title compound (312 mg).

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.84-1.90 (m, 11H), 2.20-2.44 (m, 3H), 2.59-3.50 (m, 8H), 2.90 (dd, J=13.6, 5.0 Hz, 1H), 2.97 (dd, J=13.6, 5.5 Hz, 1H), 4.07-4.23 (m, 2H), 4.35-4.45 (m, 1H).

IR (neat): 3368, 2928, 2853, 2624, 2239, 1696, 1450, 1417, 1278, 1156, 1082, 1005, 893, 828, 795, 755, 592 cm⁻¹.
m.p. 77-78 °C

Example 2

9-Deoxy-9β-chloro-2-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-2,2,3,3,13,14-hexadehydro-6-thia-PGF_{1α} (Compound 12)

Following the substantially same manner as in Example 1(6) but using the compound (112 mg) obtained in Example 1(4), the title compound was obtained.

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.82-2.98 (m, 16H), 2.05 (t, J=2.6Hz, 1H), 2.51 (dt, J=2.6, 7.2 Hz, 2H), 2.61 (ddd, J=10.1, 6.6, 1.9 Hz, 1H), 2.76 (t, J=7.2 Hz, 2H), 2.87 (dd, J=13.8, 5.0 Hz, 1H), 2.93 (dd, J=13.8, 5.1 Hz, 1H), 4.07-4.25 (m, 2H), 4.34-4.45 (m, 1H).

IR (neat): 3368, 3304, 2926, 2852, 2236, 2118, 1450, 1384,

1284, 1228, 1153, 1083, 1008, 893, 832, 641 cm^{-1} .

Example 3

9-Deoxy-9 β -chloro-2,16,17,18,19,20-hexanor-15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF $_1\alpha$ (Compound 14)

5 (1) Following the substantially same manner as in Example 1(2) but using 3-mercapto-1-propyne instead of 4-mercapto-1-butyne, 2-decarboxy-2,16,17,18,19,20-hexanor-15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGE $_1$ 11,15-bis(tert-butyltrimethylsilyl ether) was obtained.

10 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.13 (s, 3H), 0.80-1.90 (m, 11H), 0.89 (s, 9H), 0.90 (s, 9H), 2.24 (dd, $J=18.0$, 6.4 Hz, 1H), 2.25 (t, $J=2.6$ Hz, 1H), 2.50-2.60 (m, 1H), 2.73 (ddd, $J=18.0$, 6.3, 1.0 Hz, 1H), 2.99 (dd, $J=13.7$, 7.2 Hz, 1H), 3.08 (dd, $J=13.7$, 5.1 Hz, 1H), 3.08-3.16 (m, 1H), 3.27 (d, $J=2.6$ Hz, 2H), 4.08 (dd, $J=6.4$, 1.7 Hz, 1H), 4.32-4.40 (m, 1H)

15 IR (neat): 3311, 2929, 2856, 2236, 1750, 1472, 1386, 1362, 1253, 1106, 1065, 1006, 940, 898, 837, 778, 669 cm^{-1} .

(2) Following the substantially same manner as in
20 Example 1(3) but using the compound obtained in the above (1), 2-decarboxy-2,16,17,18,19,20-hexanor-15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF $_1\alpha$ 11,15-bis(tert-butyltrimethylsilyl ether) and 2-decarboxy-2,16,17,18,19,20-hexanor-15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF $_1$
25 β 11,15-bis(tert-butyltrimethylsilyl ether) were obtained.

2-Decarboxy-2,16,17,18,19,20-hexanor-15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF $_1\alpha$ 11,15-

bis(tert-butyltrimethylsilyl ether)

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (s, 3H),
0.11 (s, 6H), 0.82-1.90 (m, 12H), 0.89 (s, 9H), 0.90 (s, 9H),
2.02-2.16 (m, 2H), 2.23 (t, J=2.6 Hz, 1H), 2.59-2.63 (m, 2H),
5 2.98 (d, J=7.8 Hz, 2H), 3.23-3.37 (m, 2H), 4.07 (dd, J=6.3,
1.8 Hz, 1H), 4.20-4.33 (m, 2H).

IR (neat): 3468, 3313, 2929, 2856, 2232, 1472, 1451, 1388,
1362, 1338, 1253, 1101, 1062, 1005, 926, 898, 837, 777, 668,
634 cm⁻¹.

10 2-Decarboxy-2,16,17,18,19,20-hexanor-15-

cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF₁β 11,15-
bis(tert-butyltrimethylsilyl ether)

¹H-NMR(CDCl₃, 300 MHz) δ ppm: 0.07 (s, 3H), 0.08 (s, 6H),
0.12 (s, 3H), 0.78-2.12 (m, 13H), 0.88 (s, 9H), 0.90 (s, 9H),
15 1.97 (t, J=6.6 Hz, 2H), 2.27 (t, J=2.0 Hz, 1H), 2.37 (ddd,
J=9.6, 6.1, 1.5 Hz, 1H), 2.68 (dd, J=13.4, 9.7 Hz, 1H), 3.16
(dd, J=13.4, 4.5 Hz, 1H), 3.22-3.39 (m, 2H), 4.02-4.29 (m,
2H), 4.08 (dd, J=6.2, 1.5 Hz, 1H).
IR (neat): 3400, 3313, 2929, 2856, 2233, 1472, 1463, 1451,
20 1386, 1362, 1338, 1252, 1101, 1066, 1006, 898, 837, 777, 669,
636 cm⁻¹.

(3) Following the substantially same manner as in
Example 1(4) but using 2-decarboxy-2,16,17,18,19,20-hexanor-
15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF₁α 11,15-
25 bis(tert-butyltrimethylsilyl ether), 9-deoxy-9β-chloro- 2-
decarboxy-2,16,17,18,19,20-hexanor-15-cyclohexyl-
3,3,4,4,13,14-hexadehydro-6-thia-PGF₁α 11,15-bis(tert-

butyldimethylsilyl ether) was obtained.

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (2s, 6H), 0.09 (s, 3H), 0.12 (s, 3H), 0.82-1.90 (m, 11H), 0.88 (s, 9H), 0.90 (s, 9H), 2.14-2.29 (m, 2H), 2.26 (t, J=2.6 Hz, 1H), 2.31-2.43 (m, 1H), 2.56 (ddd, J=8.8, 4.9, 1.7 Hz, 1H), 2.95 (dd, J=13.6, 6.1 Hz, 1H), 3.02 (dd, J=13.6, 5.8 Hz, 1H), 3.31 (d, J=2.6 Hz, 2H), 4.08 (dd, J=6.2, 1.7 Hz, 1H), 4.12-4.32 (m, 2H). IR (neat): 3313, 2952, 2929, 2856, 2234, 1472, 1464, 1451, 1408, 1389, 1362, 1253, 1100, 1006, 962, 927, 898, 837, 778, 668, 637 cm⁻¹.

(4) Following the substantially same manner as in Example 1(5) but using the compound obtained in the above (3), 9-deoxy-9β-chloro-2,16,17,18,19,20-hexanor-15-cyclohexyl-3,3,4,4,13,14-hexadehydro-6-thia-PGF_{1α} 11,15-bis(tert-butyldimethylsilyl ether) was obtained.

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (2s, 6H), 0.12 (s, 3H), 0.76-1.91 (m, 12H), 0.88 (s, 9H), 0.91 (s, 9H), 2.14-2.40 (m, 3H), 2.54 (ddd, J=9.1, 5.0, 1.5 Hz, 1H), 2.96 (dd, J=13.6, 5.8 Hz, 1H), 3.04 (dd, J=13.6, 5.4 Hz, 1H), 3.37-3.51 (m, 2H), 4.01-4.33 (m, 2H), 4.09 (dd, J=6.3, 1.5 Hz, 1H). IR (neat): 2929, 2856, 2240, 1692, 1472, 1451, 1409, 1362, 1279, 1256, 1100, 1006, 962, 898, 837, 778, 670, 602 cm⁻¹.

(5) Following the substantially same manner as in Example 1(6) but using the compound obtained in the above (4), the titled compound was obtained.

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.93-1.92 (m, 11H), 2.22-

2.46 (m, 3H), 2.67-2.81 (m, 1H), 2.87-3.58 (m, 3H), 2.93 (dd, J=13.8, 4.8 Hz, 1H), 3.15 (dd, J=13.8, 5.4 Hz, 1H), 3.44 (s, 2H), 4.09-4.25 (m, 2H), 4.34-4.47 (m, 1H).

IR (KBr): 3402, 2929, 2854, 2239, 1694, 1576, 1451, 1380,
5 1275, 1162, 1083, 1007, 894, 880, 782, 758, 666, 588, 499,
471 cm^{-1} .

Example 4

1a-Homo-9-deoxy-9 β -chloro-16,17,18,19,20-pentanol-15-
cyclohexyl-1a,1a,2,2,13,14-hexadecyloxy-6-thia-PGF $_{1\alpha}$ methyl
10 ester (Compound 19)

(1) Following the substantially same manner as in
Example 1(2) but using 5-mercapto-1-pentyne instead of 4-
mercapto-1-butyne, 1a-homo-1a-decarboxy-16,17,18,19,20-
pentanol-15-cyclohexyl-1a,1a,2,2,13,14-hexadecyloxy-6-thia-
15 PGE $_1$ 11,15-bis(tert-butyldimethylsilyl ether) was obtained.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (s, 3H),
0.10 (s, 3H), 0.13 (s, 3H), 0.80-1.92 (m, 13H), 0.89 (s, 9H),
0.90 (s, 9H), 1.96 (t, J=2.6 Hz, 1H), 2.23 (dd, J=18.0, 5.8
Hz, 1H), 2.31 (dt, J=2.6, 7.0 Hz, 2H), 2.43-2.52 (m, 1H),
20 2.64 (t, J=7.2 Hz, 2H), 2.71 (dd, J=18.0, 7.3 Hz, 1H), 2.81-
2.94 (m, 2H), 3.10-3.20 (m, 1H), 4.08 (dd, J=6.3, 1.6 Hz, 1H),
4.30-4.39 (m, 1H).

IR (neat): 3314, 2929, 2856, 2236, 1751, 1472, 1463, 1451,
1386, 1362, 1253, 1106, 1065, 1006, 940, 898, 837, 778, 669,
25 634 cm^{-1} .

(2) Following the substantially same manner as in
Example 1(3) but using the compound obtained in the above

(1), 1a-homo-1a-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁α 11,15-bis(tert-butyldimethylsilyl ether) and 1a-homo-1a-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁β 11,15-bis(tert-butyldimethylsilyl ether) were obtained.

1a-Homo-1a-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁α 11,15-bis(tert-butyldimethylsilyl) ether

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (s, 3H), 0.09 (s, 3H), 0.11 (s, 6H), 0.78-1.91 (m, 14H), 0.89 (s, 9H), 0.90 (s, 9H), 1.93-2.18 (m, 2H), 1.96 (t, J=2.6 Hz, 1H), 2.33 (dt, J=2.6, 6.9 Hz, 2H), 2.50-2.61 (m, 2H), 2.68 (t, J=7.1 Hz, 2H), 2.81 (d, J=7.6 Hz, 2H), 4.08 (dd, J=6.2, 1.6 Hz, 1H), 4.20-4.33 (m, 2H).

IR (neat): 3468, 3313, 2929, 2855, 2232, 1472, 1451, 1388, 1362, 1338, 1252, 1101, 1062, 1005, 918, 898, 837, 777, 668, 633 cm⁻¹.

1a-Homo-1a-decarboxy-16,17,18,19,20-pentanor-15-cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁β 11,15-bis(tert-butyldimethylsilyl ether)

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.06 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.74-2.10 (m, 17H), 0.88 (s, 9H), 0.90 (s, 9H), 2.21-2.37 (m, 1H), 2.33 (dt, J=2.5 7.0 Hz, 2H), 2.47 (dd, J=13.3, 10.4 Hz, 1H), 2.53-2.63 (m, 1H), 2.69 (t, J=7.2 Hz, 2H), 3.00 (dd, J=13.3, 4.1 Hz, 1H), 4.00-4.28 (m, 2H), 4.08 (dd, J=6.1, 1.3 Hz, 1H).

IR (neat): 3400, 3314, 2929, 2856, 2232, 1472, 1463, 1451, 1385, 1362, 1253, 1101, 1067, 1006, 898, 836, 777, 669, 634 cm^{-1} .

(3) Following the substantially same manner as in Example 1(4) but using 1a-homo-1a-decarboxy-16,17,18,19,20-pentano-15-cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁ α 11,15-bis(tert-butyltrimethylsilyl ether), 1a-homo-1a-decarboxy-9-deoxy-9 β -chloro-16,17,18,19,20-pentano-15-cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁ α 11,15-bis(tert-butyltrimethylsilyl ether) was obtained.

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.08 (2s, 6H), 0.09 (s, 3H), 0.12 (s, 3H), 0.81-1.90 (m, 13H), 0.88 (s, 9H), 0.91 (s, 9H), 1.97 (t, J=2.6 Hz, 1H), 2.11-2.44 (m, 5H), 2.53-2.62 (m, 1H), 2.68 (t, J=7.1 Hz, 2H), 2.82(d, J=5.4 Hz, 2H), 4.04-4.32 (m, 3H).

IR (neat): 3313, 2929, 2856, 2234, 1472, 1463, 1451, 1388, 1362, 1281, 1253, 1100, 1006, 962, 927, 898, 837, 778, 668, 635 cm^{-1} .

(4) To a tetrahydrofuran solution (3.3 ml) of the compound (395 mg) obtained in the above (3) was added n-butyllithium (1.59 M, hexane solution, 447 μ l) at -78 °C, followed by stirring at the same temperature for 1 hour. To the solution was then added dropwise a tetrahydrofuran solution (3.3 ml) of methyl chloroformate (75 mg) at the same temperature, followed by stirring at room temperature overnight. The reaction solution was poured into a saturated aqueous sodium chloride solution and the solution

was made weakly acidic with a 1 M aqueous hydrochloric acid solution and extracted with n-hexane. The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford a crude product. To a methanol solution (8.0 ml) of the crude product was added conc. hydrochloric acid (0.04 ml) at room temperature, followed by stirring for 4 hours. The reaction solution was added to a mixture of ethyl acetate and saturated sodium bicarbonate solution and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with a saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (developing solvent; n-hexane:ethyl acetate=1:1) to give the title compound (130 mg).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ ppm: 0.95-1.39 (m, 6H), 1.46-2.00 (m, 9H), 2.18-2.44 (m, 3H), 2.46-2.56 (m, 2H), 2.62 (ddd, $J=10.1, 6.5, 1.9$ Hz, 1H), 2.65-2.76 (m, 2H), 2.80 (dd, $J=13.7, 5.0$ Hz, 1H), 2.88 (dd, $J=13.7, 5.1$ Hz, 1H), 3.77 (s, 3H), 4.06-4.27 (m, 2H), 4.34-4.45 (m, 1H).
 IR (neat): 3368, 2928, 2853, 2237, 1716, 1435, 1384, 1326, 1257, 1154, 1078, 1011, 894, 832, 753 cm^{-1} .

Example 5

1a-Homo-9-deoxy-9 β -chloro-16,17,18,19,20-pentanor-15-

cyclohexyl-1a,1a,2,2,13,14-hexadehydro-6-thia-PGF₁α
(Compound 22)

To a water suspension (16 ml) of lipase PS (2.3 g) was added an acetone solution (4.8 ml) of the compound (100 mg) obtained in Example 4. To this were then added phosphate buffer (0.2 M, pH=7.0, 2.5 ml) and water (32 ml), followed by stirring at 30 °C overnight. After filtration, ammonium sulfate was added to the mixture for salting out and it was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (developing solvent; ethyl acetate) to give the title compound (85 mg).

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 0.86-1.40 (m, 6H), 1.46-2.00 (m, 7H), 2.10-4.05 (m, 12H), 2.95 (dd, J=14.1, 4.8 Hz, 1H), 4.10-4.55 (m, 3H).

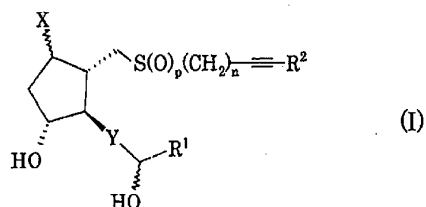
IR (neat): 3368, 2927, 2853, 2237, 1695, 1574, 1450, 1418, 1384, 1347, 1279, 1258, 1157, 1082, 1008, 957, 893, 834, 756, 592 cm⁻¹.

Industrial Applicability

The compounds of the present invention possess a sufficient sleep-inducing action; therefore, they are useful as a drug intended for sleep induction.

The Claims Defining The Invention Are As Follows

1. A prostaglandin derivative represented by
Formula (I):



- wherein X is a halogen atom in the α - or β -substitution, Y is an ethylene group, a vinylene group or an ethynylene group, R^1 is a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkyl group substituted with a C_{1-4} straight or branched chain alkyl group or a C_{4-13} cycloalkylalkyl group, R^2 is a hydrogen atom or a CO_2R^3 group (R^3 is a hydrogen atom, a C_{1-4} straight or branched chain alkyl group or a C_{2-4} straight or branched chain alkenyl group), n is an integer of 1 to 4 and p is 0, 1 or 2,
- a pharmaceutically acceptable salt thereof or a hydrate thereof.

2. The prostaglandin derivative represented by Formula (I) according to claim 1, wherein R^1 is a C_{3-10} cycloalkyl group or a C_{4-13} cycloalkylalkyl group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

3. The prostaglandin derivative represented by Formula (I) according to claim 1 or 2, wherein X is a chlorine atom or a bromine atom in the α - or β -substitution.

4. The prostaglandin derivative represented by

W:\SEW\736095 (GYC)\Response to a 1st report\736095_Spec-200008.doc

Formula (I) according to any one of claims 1-3, wherein Y is an ethynylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

5 5. The prostaglandin derivative represented by Formula (I) according to any one of claims 1-4, wherein R^2 is a CO_2R^3 group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

10 6. The prostaglandin derivative represented by Formula (I) according to any one of claims 1-5, wherein $p=0$, a pharmaceutically acceptable salt thereof or a hydrate thereof.

15 7. The prostaglandin derivative represented by Formula (I) according to any one of claims 1-6, wherein $n=1$ or 2, a pharmaceutically acceptable salt thereof or a hydrate thereof.

20 8. A pharmaceutical composition comprising the prostaglandin derivative according to any one of claims 1-7, a pharmaceutically acceptable salt thereof or a hydrate thereof.