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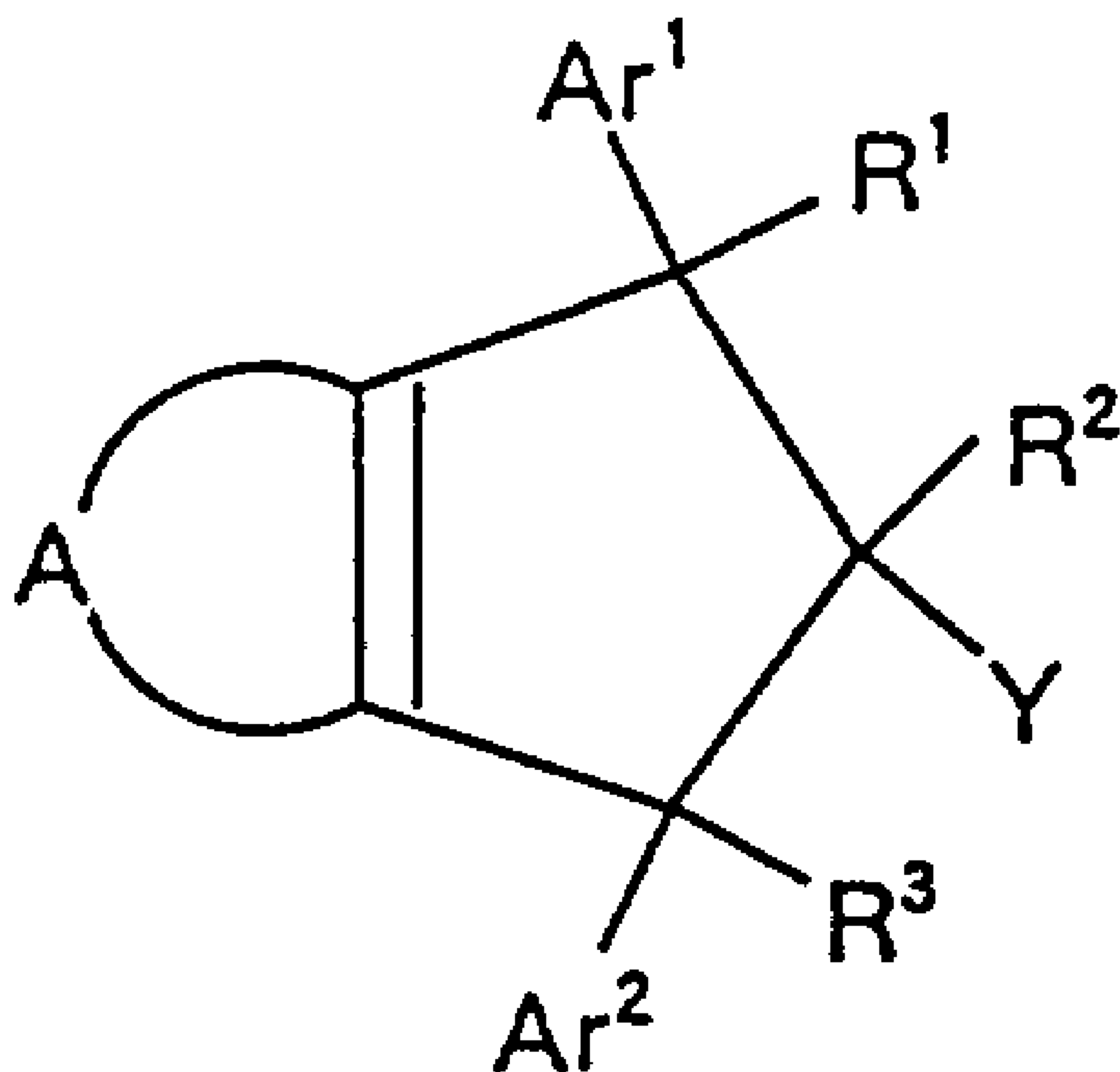
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(54) Titre : DERIVES HETEROATOMIQUES DU CYCLOPENTENE A NOYAUX CONDENSES, ANTAGONISTES DE
L'ENDOTHELINE

(54) Title: ENDOTHELIN ANTAGONISTIC HETEROAROMATIC RING-FUSED CYCLOPENTENE DERIVATIVES



(I)

(57) Abrégé/Abstract:

A heteroaromatic ring-fused cyclopentene derivative of the formula: (see formula I) wherein each of Ar¹ and Ar² is independently a phenyl group, a thienyl group, a pyridyl group, an indolyl group, a benzofuranyl group or a dihydrobenzofuranyl group wherein an optional hydrogen atom(s) on the aromatic ring may be replaced with 1 to 4 groups selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a carboxyl group, a C₁-C₆ alkoxy carbonyl group, a mono- or di- C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a tetrazol-5-yl group, a methylenedioxy group, a C₁-C₆ alkoxy group, a C₂-C₆ alkenyloxy group, a mono- or di- C₁-C₆ alkylamino group, a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group and a C₂-C₆ alkynyl group

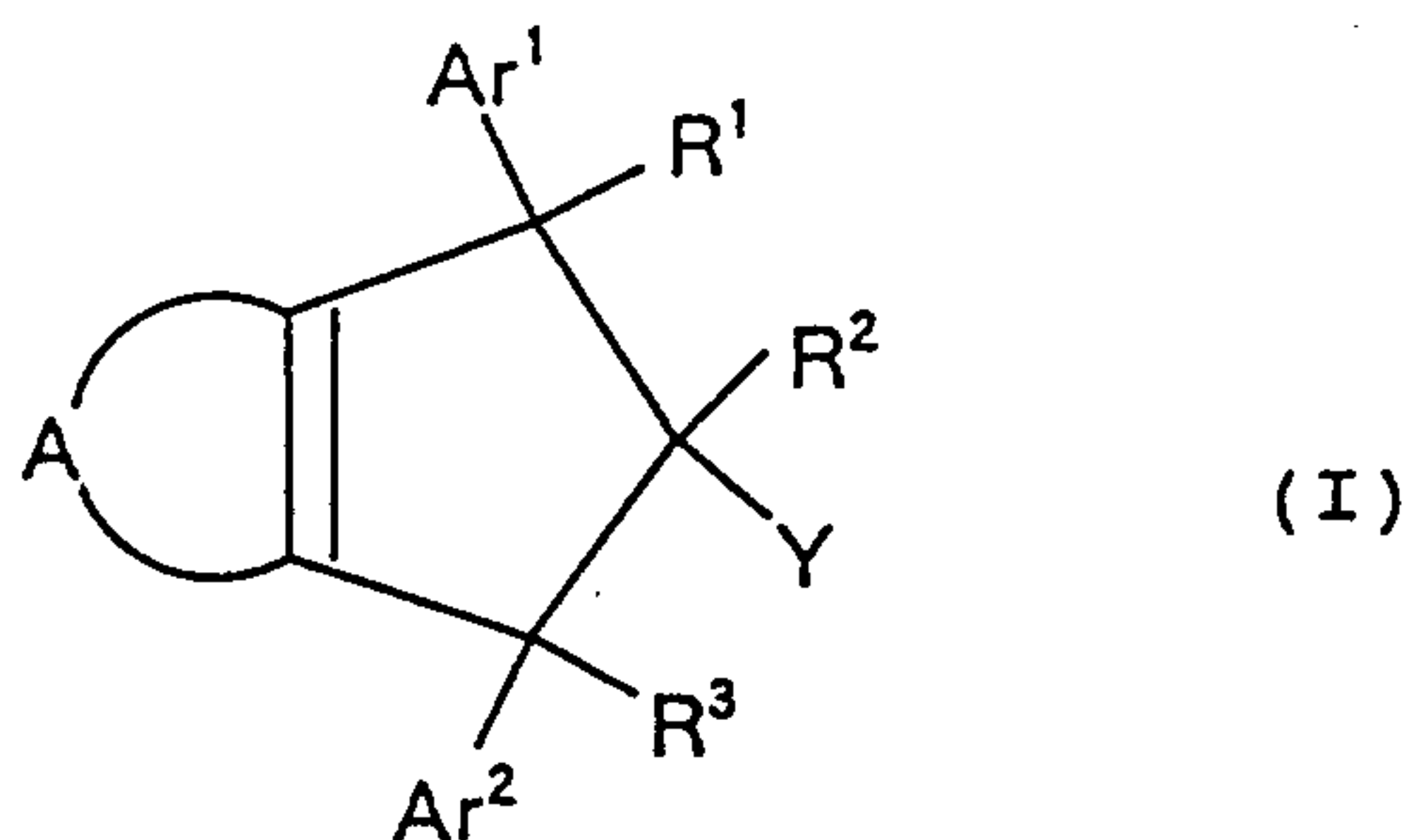
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(57) **Abrégé(suite)/Abstract(continued)**:

(provided that the C₁-C₆ alkoxy group, C₂-C₆ alkenyloxy group, mono- or di- C₁-C₆ alkylamino group, C₁-C₆ alkyl group, C₂-C₆ alkenyl group and C₂-C₆ alkynyl group may be substituted by 1 to 3 groups selected from the group consisting of a phenyl group, a pyridyl group, an imidazolyl group, a hydroxyl group, a C₁-C₆ alkoxy group, an amino group, a mono- or di- C₁-C₆ alkylamino group, a hydroxy C₁-C₆ alkylcarbonyl group, a C₁-C₆ acyloxy C₁-C₆ alkylcarbonyl group, a carboxy C₁-C₆ alkoxycarbonyl group, a carboxy C₁-C₆ alkoxycarbonyl C₁-C₆ alkoxycarbonyl group, a C₁-C₆ alkoxycarbonyl group, a mono- or di- C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a C₁-C₆ alkylsulfonylaminocarbonyl group, a tetrazol-5-ylaminocarbonyl group, a carboxyl group, SO₃H, PO₃H₂, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl group (provided that when a hydroxyl group and a carboxyl group are selected as substituents, they may together form a lactone ring)); each of R¹, R² and R³ is independently a hydrogen atom, a hydroxyl group or a C₁-C₆ alkyl group, or R¹ and R², or R² and R³ together form a single bond; Y is a group of -CO-R⁴ (wherein R⁴ is a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a mono- or di- C₁-C₆ alkylamino group, a C₁-C₆ alkylsulfonylamino group, or an arylsulfonylamino group or an aryl C₁-C₆ alkylsulfonylamino group wherein an optional hydrogen atom(s) on the aryl ring may be replaced with a C₁-C₆ alkyl group), SO₃H, PO₃H₂, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group or a 5-oxo-4H-1,2,4-oxadiazol-3-yl group; and A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6-membered heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (provided that optional 1 or 2 hydrogen atoms on the heteroaromatic ring may be replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a halogen atom, a cyano group, a nitro group, a mono- or di- C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, a C₃-C₈ cycloalkyl C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(aroyl)amino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group at the alkylene moiety, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a formyl group, a C₂-C₆ alkanoyl group, an aroyl group, or a C₁-C₆ alkyl group, C₃-C₈ cycloalkyl group, C₃-C₈ cycloalkyl C₁-C₆ alkyl group, C₂-C₆ alkenyl group or C₂-C₆ alkynyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group, a C₁-C₆ alkoxy group and a mono- or di- C₁-C₆ alkylamino group, and when the heteroaromatic ring includes one or more nitrogen atoms, the nitrogen atom(s) may be oxidized to form an N-oxide group); or a pharmaceutically acceptable salt thereof.

ABSTRACT

A heteroaromatic ring-fused cyclopentene derivative of the formula:



10 wherein

each of Ar¹ and Ar² is independently a phenyl group, a thienyl group, a pyridyl group, an indolyl group, a benzofuranyl group or a dihydrobenzofuranyl group wherein an optional hydrogen atom(s) on the aromatic ring may be replaced with 1 to 4 groups selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a mono- or di- C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a tetrazol-5-yl group, a methylenedioxy group, a C₁-C₆ alkoxy group, a C₂-C₆ alkenyloxy group, a mono- or di- C₁-C₆ alkylamino group, a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group and a C₂-C₆ alkynyl group (provided that the C₁-C₆ alkoxy group, C₂-C₆ alkenyloxy group, mono- or di- C₁-C₆ alkylamino group, C₁-C₆ alkyl group, C₂-C₆ alkenyl group and C₂-C₆ alkynyl group may be substituted by 1 to 3 groups selected from the group consisting of a

phenyl group, a pyridyl group, an imidazolyl group, a hydroxyl group, a C_1-C_6 alkoxy group, an amino group, a mono- or di- C_1-C_6 alkylamino group, a hydroxy C_1-C_6 alkylcarbonyl group, a C_1-C_6 acyloxy C_1-C_6 alkylcarbonyl group, a carboxy C_1-C_6 alkoxycarbonyl group, a carboxy C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkoxycarbonyl group, a mono- or di- C_1-C_6 alkylaminocarbonyl group, a carbamoyl group, a C_1-C_6 alkylsulfonylaminocarbonyl group, a tetrazol-5-ylamino-carbonyl group, a carboxyl group, SO_3H , PO_3H_2 , a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl group (provided that when a hydroxyl group and a carboxyl group are selected as substituents, they may together form a lactone ring));

each of R^1 , R^2 and R^3 is independently a hydrogen atom, a hydroxyl group or a C_1-C_6 alkyl group, or R^1 and R^2 , or R^2 and R^3 together form a single bond;

Y is a group of $-CO-R^4$ (wherein R^4 is a hydroxyl group, an amino group, a C_1-C_6 alkoxy group, a mono- or di- C_1-C_6 alkylamino group, a C_1-C_6 alkylsulfonylamino group, or an arylsulfonylamino group or an aryl C_1-C_6 alkylsulfonylamino group wherein an optional hydrogen atom(s) on the aryl ring may be replaced with a C_1-C_6 alkyl group), SO_3H , PO_3H_2 , a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group or a 5-oxo-4H-1,2,4-oxadiazol-3-yl group; and

A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6- membered heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (provided that optional 1 or 2 hydrogen atoms on the heteroaromatic ring may be replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a halogen atom, a cyano group, a nitro group, a mono- or di- C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, a C₃-C₈ cycloalkyl C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(aroyl)amino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group at the alkylene moiety, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a formyl group, a C₂-C₆ alkanoyl group, an aroyl group, or a C₁-C₆ alkyl group, C₃-C₈ cycloalkyl group, C₃-C₈ cycloalkyl C₁-C₆ alkyl group, C₂-C₆ alkenyl group or C₂-C₆ alkynyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a

hydroxyl group, an amino group, a C₁-C₆ alkoxy group and
a mono- or di- C₁-C₆ alkylamino group, and when the
heteroaromatic ring includes one or more nitrogen atoms,
the nitrogen atom(s) may be oxidized to form an N-oxide
5 group); or a pharmaceutically acceptable salt thereof.

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SPECIFICATION

ENDOTHELIN ANTAGONISTIC HETEROAROMATIC RING - FUSED
CYCLOPENTENE DERIVATIVES

5 Technological Field

The present invention relates to novel compounds having antagonism against three endothelin isopeptides (endothelin-1, endothelin-2 and endothelin-3), which are physiologically highly active
10 endogenous peptides, processes for their preparation and their use as a drug.

Two endothelin receptor subtypes ET_A and ET_B are known so far. The compounds of the present invention possess high affinity to at least one of two receptor
15 subtypes, so that they show the dilative actions of smooth muscles, such as vessel and trachea. The compounds of the present invention provide a new therapeutic potential, particularly for the treatment of hypertension, pulmonary hypertension, Raynaud's disease,
20 acute renal failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatauxe endotoxin shock, endotoxin-induced multiple organ failure or disseminated
25 intravascular coagulation, and/or cyclosporin-induced renal failure or hypertension.

Background Technology

Endothelin is a polypeptide composed of 21 amino acids, and it is produced by vascular endothelial cells of human or pig. Endothelin has a potent vasoconstrictor effect and a sustained and potent pressor action (Nature, 332, 411-415 (1988)).

Three endothelin isopeptides (endothelin-1, endothelin-2 and endothelin-3), which resemble one another in structure, exist in the bodies of animals including human, and these peptides have vasoconstriction and pressor effects (Proc. Natl. Acad. Sci. USA, 86, 2863-2867 (1989)).

As reported, the endothelin levels are clearly elevated in the blood of patients with essential hypertension, acute myocardial infarction, pulmonary hypertension, Raynaud's disease, diabetes or atherosclerosis, or in the washing fluids of the respiratory tract or the blood of patients with asthmatics as compared with normal levels (Japan, J. Hypertension, 12, 79, (1989), J. Vascular Medicine Biology, 2, 207 (1990), Diabetologia, 33, 306-310 (1990), J. Am. Med. Association, 264, 2868 (1990), and The Lancet, ii, 747-748 (1989) and ii, 1144-1147 (1990)).

Further, an increased sensitivity of the cerebral blood vessel to endothelin in an experimental model of cerebral vasospasm (Japan. Soc. Cereb. Blood Flow & Metabol., 1, 73 (1989)), an improved renal function by the endothelin antibody in an acute renal

failure model (J. Clin, Invest., 83, 1762-1767 (1989),
and inhibition of gastric ulcer development with an
endothelin antibody in a gastric ulcer model (Extract of
Japanese Society of Experimental Gastric Ulcer, 50
5 (1991)) have been reported. Therefore, endothelin is
assumed to be one of mediators causing acute renal
failure or cerebral vasospasm following subarachnoid
hemorrhage.

Further, endothelin is secreted not only by
10 endothelial cells but also by tracheal epithelial cells
or from kidney cells (FEBS Letters, 255, 129-132 (1989),
and FEBS Letters, 249, 42-46 (1989)).

Endothelin was also found to control the
release of physiologically active endogenous substances
15 such as renin, atrial natriuretic peptide, endothe-
lium-derived relaxing factor (EDRF), thromboxane A₂,
prostacyclin, noradrenaline, angiotensin II and
substance P (Biochem. Biophys, Res. Commun., 157,
1164-1168 (1988); Biochem. Biophys, Res. Commun., 155,
20 167-172 (1989); Proc. Natl. Acad. Sci. USA, 85,
9797-9800 (1989); J. Cardiovasc. Pharmacol., 13, S89-S92
(1989); Japan. J. Hypertension, 12, 76 (1989) and
Neuroscience Letters, 102, 179-184 (1989)). Further,
endothelin causes contraction of the smooth muscle of
25 gastrointestinal tract and the uterine smooth muscle
(FEBS Letters, 247, 337-340 (1989); Eur. J. Pharmacol.,
154, 227-228 (1988); and Biochem. Biophys. Res. Commun.,

159, 317-323 (1989)). Further, endothelin was found to promote proliferation of rat vascular smooth muscle cells, suggesting a possible relevance to the arterial hypertrophy (Atherosclerosis, 78, 225-228 (1989)).

5 Furthermore, since the endothelin receptors are present in a high density not only in the peripheral tissues but also in the central nervous system, and the cerebral administration of endothelin induces a behavioral change in animals, endothelin is likely to play an important
10 role for controlling nervous functions (Neuroscience Letters, 97, 276-279 (1989)). Particularly, endothelin is suggested to be one of mediators for pain (Life Sciences, 49, PL61-PL65 (1991)).

Internal hyperplastic response was induced by
15 rat carotid artery balloon endothelial denudation. Endothelin causes a significant worsening of the internal hyperplasia(J. Cardiovasc. Pharmacol. , 22, 355 - 359 & 371 - 373(1993)). These data support a role of endothelin in the pathogenesis of vascular restenosis.
20 Recently, it has been reported that both ET_A and ET_B receptors exist in the human prostate and endothelin produces a potent contraction of it. These results suggest the possibility that endothelin is involved in the pathophysiology of benign prostatic hyperplasia(J.
25 Urology, 151, 763 - 766(1994), Molecular Pharmacol., 45, 306 - 311(1994)).

On the other hand, endotoxin is one of

potential candidates to promote the release of endothelin. Remarkable elevation of the endothelin levels in the blood or in the culture supernatant of endothelial cells was observed when endotoxin was exogenously administered to animals or added to the culture endothelial cells, respectively. These findings suggest that endothelin is one of important mediators for endotoxin-induced diseases (Biochem. Biophys. Res. Commun., 161, 1220-1227 (1989); and Acta Physiol. Scand., 137, 317-318 (1989)).

Further, it was reported that cyclosporin remarkably increased endothelin secretion in the renal cell culture (LLC-PK1 cells) (Eur. J. Pharmacol., 180, 191-192 (1990)). Further, dosing of cyclosporin to rats reduced the glomerular filtration rate and increased the blood pressure in association with a remarkable increase in the circulating endothelin level. This cyclosporin-induced renal failure can be suppressed by the administration of endothelin antibody (Kidney Int., 37, 1487-1491 (1990)). Thus, it is assumed that endothelin is significantly involved in the pathogenesis of the cyclosporin-induced diseases.

Such various effects of endothelin are caused by the binding of endothelin to endothelin receptors widely distributed in many tissues (Am. J. Physiol., 256, R856-R866 (1989)).

It is known that vasoconstriction by the

endothelins is caused via at least two subtypes of endothelin receptors (J. Cardiovasc. Pharmacol., 17(Suppl.7), S119-S121 (1991)). One of endothelin receptors is ET_A receptor selective to ET-1 rather than
5 ET-3, and the other is ET_B receptor equally active to ET-1 and ET-3. These receptor proteins are reported to be different from each other (Nature, 348, 730-735 (1990)).

These two subtypes of endothelin receptors are
10 differently distributed in tissues. It is known that the ET_A receptor is present mainly in cardiovascular tissues, whereas the ET_B receptor is widely distributed in various tissues such as brain, kidney, lung, heart and vascular tissues.

15 Substances which specifically inhibit the binding of endothelin to the endothelin receptors are believed to antagonize various pharmacological activities of endothelin and to be useful as a drug in a wide field. Since, the action of the endothelins is
20 caused via not only the ET_A receptor but also the ET_B receptor, novel non-peptidic substances with ET receptor antagonistic activity to either receptor subtype are desired to block activities of the endothelins effectively in various diseases.

25 Disclosure of the Invention

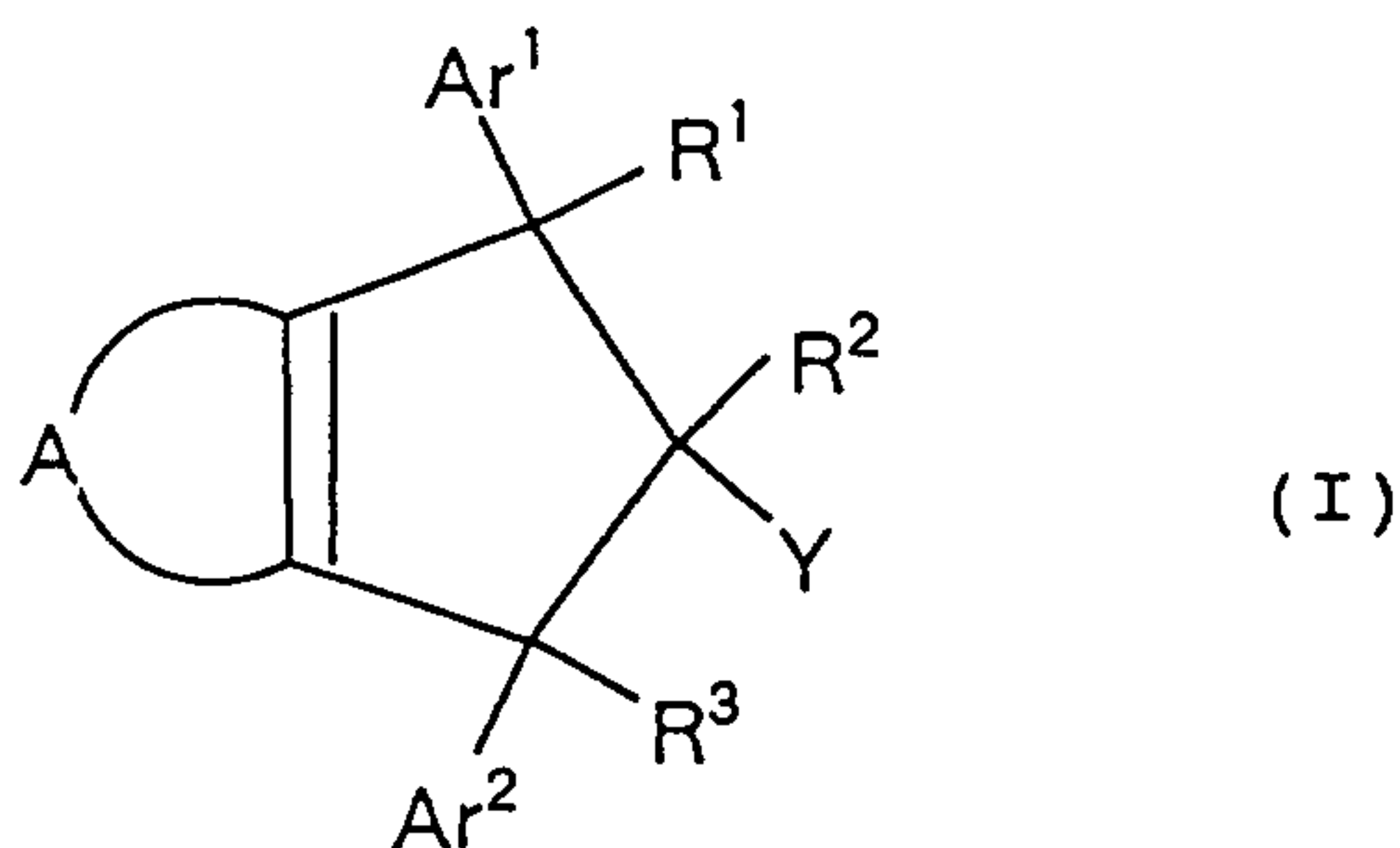
Endothelin is an endogenous substance which directly or indirectly (by controlling liberation of

various endogenous substances) induces sustained contraction or relaxation of vascular or non-vascular smooth muscles, and its excess production or excess secretion is believed to be one of pathogeneses for hypertension, pulmonary hypertension, Raynaud's disease, bronchial asthma, gastric ulcer, diabetes, arteriosclerosis, restenosis, acute renal failure, myocardial infarction, angina pectoris, cerebral vasospasm and cerebral infarction. Further, it is suggested that endothelin serves as an important mediator involved in diseases such as restenosis, prostatauxe, endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular coagulation, and cyclosporin-induced renal failure or hypertension. Two endothelin receptors ET_A and ET_B are known so far. An antagonistic agent against the ET_B receptor as well as the ET_A receptor is useful as a drug. In the field of anti-endothelin agents, some non-peptidic compounds possessing antagonistic activity against endothelin receptors were already disclosed in patents (for example, EP 0526708 A1, WO 93/08799 A1). Accordingly, it is an object of the present invention to provide a novel therapeutics for the treatment of the above-mentioned various diseases by an invention of a novel and potent non-peptidic antagonist against either ET_A or ET_B receptor.

In order to accomplish the above object, the

present inventors have synthesized various non-peptidic derivatives and have investigated their endothelin antagonistic activities, and as a result have found that novel heteroaromatic ring-fused cyclopentene derivatives represented by the following formula (I) and their pharmaceutically acceptable salts have potent affinity to at least one of these ET_A and ET_B receptor subtypes. The present invention has been accomplished on the basis of this discovery.

Thus, the present invention provides a non-peptidic derivative of the formula:



wherein each of Ar^1 and Ar^2 is independently a phenyl group, a thienyl group, a pyridyl group, an indolyl group, a benzofuranyl group or a dihydrobenzofuranyl group wherein an optional hydrogen atom(s) on the aromatic ring may be replaced with 1 to 4 groups selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a carboxyl group, a C_1-C_6 alkoxycarbonyl group, a mono- or di- C_1-C_6 alkylaminocarbonyl group, a carbamoyl group, a tetrazol-5-yl group, a methylenedioxy group, a C_1-C_6

alkoxy group, a C₂-C₆ alkenyloxy group, a mono- or di-
C₁-C₆ alkylamino group, a C₁-C₆ alkyl group, a C₂-C₆
alkenyl group and a C₂-C₆ alkynyl group (provided that
the C₁-C₆ alkoxy group, C₂-C₆ alkenyloxy group, mono- or
5 di- C₁-C₆ alkylamino group, C₁-C₆ alkyl group, C₂-C₆
alkenyl group and C₂-C₆ alkynyl group may be substituted
by 1 to 3 groups selected from the group consisting of a
phenyl group, a pyridyl group, an imidazolyl group, a
hydroxyl group, a C₁-C₆ alkoxy group, an amino group, a
10 mono- or di- C₁-C₆ alkylamino group, a hydroxy C₁-C₆
alkylcarbonyl group, a C₁-C₆ acyloxy C₁-C₆ alkylcarbonyl
group, a carboxy C₁-C₆ alkoxycarbonyl group, a carboxy
C₁-C₆ alkoxycarbonyl C₁-C₆ alkoxycarbonyl group, a C₁-C₆
alkoxycarbonyl group, a mono- or di- C₁-C₆ alkyl-
15 aminocarbonyl group, a carbamoyl group, a C₁-C₆
alkylsulfonylaminocarbonyl group, a tetrazol-5-ylamino-
carbonyl group, a carboxyl group, SO₃H, PO₃H₂, a
tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathia-
diazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl
20 group (provided that when a hydroxyl group and a
carboxyl group are selected as substituents, they may
together form a lactone ring)); each of R¹, R² and R³ is
independently a hydrogen atom, a hydroxyl group or a
C₁-C₆ alkyl group, or R¹ and R², or R² and R³ together
25 form a single bond; Y is a group of -CO-R⁴ (wherein R⁴
is a hydroxyl group, an amino group, a C₁-C₆ alkoxy
group, a mono- or di- C₁-C₆ alkylamino group,

a C₁-C₆ alkylsulfonylamino group, or an arylsulfonylamino group or aryl C₁-C₆ alkylsulfonylamino group wherein an optional hydrogen atom(s) on the aryl ring may be replaced with a C₁-C₆ alkyl group), SO₃H, PO₃H₂,
5 a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group or a 5-oxo-4H-1,2,4-oxadiazol-3-yl group; and A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6- membered heteroaromatic ring including 1 to 4 hetero atoms
10 selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (provided that optional 1 or 2 hydrogen atoms on the heteroaromatic ring may be replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a halogen atom, a
15 cyano group, a nitro group, a mono- or di- C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, a C₃-C₈ cycloalkyl C₁-C₆
20 alkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(aroyl)amino group which
25 may be substituted by a hydroxyl group at the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group at the alkylene moiety,

a carboxyl group, a C₁-C₆ alkoxy carbonyl group, a formyl group, a C₂-C₆ alkanoyl group, an aroyl group, or a C₁-C₆ alkyl group, C₃-C₈ cycloalkyl group, C₃-C₈ cycloalkyl C₁-C₆ alkyl group, C₂-C₆ alkenyl group or
5 C₂-C₆ alkynyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group, a C₁-C₆ alkoxy group and a mono- or di- C₁-C₆ alkylamino group, and when the heteroaromatic ring includes one or more nitrogen atoms,
10 the nitrogen atom(s) may be oxidized to form an N-oxide group); or a pharmaceutically acceptable salt thereof.

Now, the present invention will be described in further detail with reference to the preferred embodiments.

15 Now, the meanings of various abbreviations used in this specification will be given.

<u>Abbreviation</u>	<u>Meaning of Abbreviation</u>
Et	ethyl
Me	methyl
20 ⁿ Pr	n-propyl
ⁱ Pr	isopropyl
ⁿ Bu	n-butyl
^t Bu	tert-butyl
Ph	phenyl
25 Bzl	benzyl
c-Pent	cyclopentyl
CDI	1,1'-carbonyldiimidazole

	DCC	N,N'-dicyclohexylcarbodiimide
	DMAP	4-(dimethylamino)pyridine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
5	HMPA	hexamethylphosphoric triamide
	mCPBA	m-chloroperbenzoic acid
	NMP	N-methylpyrrolidone
	NMM	N-methylmorpholine
	EDCI · HCl	1-ethyl-3-(3-dimethylaminopropyl)-
10		carbodiimide · hydrochloride
	HOBT · H ₂ O	1-hydroxy-1H-benzotriazole monohydrate
	HOSu	N-hydroxysuccinimide
	TEA	triethylamine
	TFA	trifluoro acetic acid
15	THF	tetrahydrofuran
	TsOH	p-toluene sulfonic acid
	Ts	p-toluenesulfonyl
	Z	benzyloxycarbonyl
	MOPS	3-morpholinopropane sulfonic acid
20	HEPES	2-[4-(2-hydroxyethyl)-1-piperazinyl]-
		ethane sulfonic acid
	Tris	tris(hydroxymethyl)aminomethane
	PMSF	phenylmethanesulfonyl fluoride

25 Now, the definitions of the various terms mentioned in this specification will be explained.

 In this specification, the halogen atom means a

fluorine, chlorine, bromine or iodine atom.

The C_1-C_6 alkoxycarbonyl group means an alkoxycarbonyl group having a linear or branched C_1-C_6 alkoxy group such as a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, tert - butyloxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl or hexyloxycarbonyl group.

The mono - or di - C_1-C_6 alkylaminocarbonyl group means an alkylaminocarbonyl group having 1 or 2 linear or branched C_1-C_6 alkyl groups at the nitrogen atom such as a methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl, isobutylaminocarbonyl, tert - butylaminocarbonyl, pentyaminocarbonyl, isopentyaminocarbonyl group, hexylaminocarbonyl, dimethylaminocarbonyl group, ethylmethylaminocarbonyl group, diethylaminocarbonyl, isopropylmethylaminocarbonyl, dipropylaminocarbonyl, ethylisopropylaminocarbonyl, diisopropylaminocarbonyl, dibutylaminocarbonyl, diisobutylaminocarbonyl, di - tert - butylaminocarbonyl, dipentyaminocarbonyl, ethylpentyaminocarbonyl, diisopentyaminocarbonyl or ethylhexylaminocarbonyl group.

The C_1-C_6 alkoxy group means a linear or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy or

hexyloxy group.

The C_2-C_6 alkenyloxy group means an alkenyloxy group having a linear or branched C_2-C_6 alkenyl group such as a vinyloxy, allyloxy, 1 - propenyloxy, isopropenyloxy, 2 - butenyloxy, 3 - butenyloxy, 2 - pentenyloxy, 3 - methyl - 3 - butenyloxy or 2 - hexenyloxy group.

The mono - or di - C_1-C_6 alkylamino group means an alkylamino group having 1 or 2 linear or branched C_1-C_6 alkyl groups at the nitrogen atom such as a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, isopentylamino, hexylamino, dimethylamino, ethylmethylamino, diethylamino, dipropylamino, propylmethylamino, ethylpropylamino, diisopropylamino, diisobutylamino, ethylisobutylamino, di - tert-butylamino, di pentylamino, diisopentylamino, isopentylmethylamino or dihexylamino group.

The C_1-C_6 alkyl group means a linear or branched alkyl group having 1 to 6 carbon atoms such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl,

1-ethyl-2-methylpropyl or 1-ethyl-1-methylpropyl group.

The C_2-C_6 alkenyl group means a linear or branched alkenyl group having 2 to 6 carbon atoms such as a vinyl, allyl, 2-propenyl, isopropenyl, 3-butenyl, 2-butenyl, 1-butenyl, 1-methyl-2-propenyl, 1-methyl-1-propenyl, 1-ethyl-1-ethenyl, 2-methyl-2-propenyl, 2-methyl-1-propenyl or 4-pentenyl group.

The C_2-C_6 alkynyl group means a linear or branched alkynyl group having 2 to 6 carbon atoms such as a ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-methyl-2-propynyl or 1-pentyne group.

The hydroxy C_1-C_6 alkylcarbonyl group means a linear or branched hydroxyalkylcarbonyl group having 2 to 7 carbon atoms such as a hydroxymethylcarbonyl, 1-hydroxyethylcarbonyl, 1-hydroxypropylcarbonyl, 1-hydroxybutylcarbonyl, 1-hydroxypentylcarbonyl, 1-hydroxyhexylcarbonyl, 2-hydroxyethylcarbonyl, 3-hydroxypropylcarbonyl, 2-hydroxybutylcarbonyl, 4-hydroxypentylcarbonyl, 3-hydroxyhexylcarbonyl or 2-hydroxy-2-methylpropylcarbonyl group.

The C_1-C_6 acyloxy C_1-C_6 alkylcarbonyl group means an acyloxy C_1-C_6 alkylcarbonyl group having an aliphatic or aromatic acyloxy group such as an acetyloxymethylcarbonyl, 1-acetyloxyethylcarbonyl, 2-acetyloxyethylcarbonyl, 1-acetyloxypropylcarbonyl, 1-

acetyloxybutylcarbonyl, 1 - acetyloxypentylcarbonyl, 1 -
 acetyloxyhexylcarbonyl, 2 - acetyloxypropylcarbonyl,
 propionyloxymethylcarbonyl, 1 - propionyloxye-
 thylcarbonyl, butylyloxymethylcarbonyl, pentanoyloxy-
 5 methylcarbonyl, hexanoyloxymethylcarbonyl,
 benzoyloxymethylcarbonyl, 1 - benzoyloxyethylcarbonyl, 2
 - benzoyloxyethylcarbonyl, thienylcarbonylox-
 ymethylcarbonyl, furfuryloxymethylcarbonyl, pyridylcar-
 bonyloxymethylcarbonyl or
 10 imidazolylcarbonyloxymethylcarbonyl group.

The carboxy C_1-C_6 alkoxycarbonyl group means a
 linear or branched carboxy C_1-C_6 alkoxycarbonyl group
 having 3 to 10 carbon atoms such as a carboxyme-
 thoxycarbonyl, 1 - carboxyethoxycarbonyl, 1 - carboxy-
 15 propoxycarbonyl, 1 - carboxybutoxycarbonyl, 2 -
 carboxyethoxycarbonyl, 2 - carboxybutoxycarbonyl, 2 -
 carboxypentoxycarbonyl, 3 - carboxypropoxycarbonyl, 3 -
 carboxybutoxycarbonyl, 4 - carboxypentoxycarbonyl, 3 -
 carboxyhexyloxycarbonyl or 2 - carboxy - 2 - methylpropy-
 20 loxycarbonyl group.

The carboxy C_1-C_6 alkoxycarbonyl C_1-C_6
 alkoxycarbonyl group means a linear or branched carboxy
 C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxycarbonyl group such as
 a carboxymethoxycarbonylmethoxycarbonyl,
 25 1 - carboxyethoxycarbonylmethoxycarbonyl,
 1 - carboxypropoxycarbonylmethoxycarbonyl,
 1 - carboxybuoxycarbonylmethoxycarbonyl,

2 - carboxyethoxycarbonylmethoxycarbonyl,
2 - carboxybutoxycarbonylethoxycarbonyl,
2 - carboxypentoxycarbonylethoxycarbonyl,
3 - carboxypropoxycarbonylethoxycarbonyl,
5 3 - carboxybutoxycarbonylethoxycarbonyl,
4 - carboxypentoxycarbonylethoxycarbonyl,
3 - carboxyhexyloxycarbonylmethoxycarbonyl or
2 - carboxy - 2 - methylpropyloxycarbonylmethoxycarbonyl
group.

10 The C_1 - C_6 alkylsulfonylaminocarbonyl group means
an alkylsulfonylaminocarbonyl group having a linear or
branched C_1 - C_6 alkyl group such as a methylsulfonyl-
aminocarbonyl, ethylsulfonylaminocarbonyl, propylsulfo-
nylaminocarbonyl, isopropylsulfonylaminocarbonyl,
15 butylsulfonylaminocarbonyl, isobutylsulfonyl-
aminocarbonyl, tert - butylsulfonylaminocarbonyl, pen-
tylsulfonylaminocarbonyl, isopentylsulfonylaminocarbonyl
or hexylsulfonylaminocarbonyl group.

 The C_1 - C_6 alkylsulfonylamino group means an
20 alkylsulfonylamino group having a linear or branched
 C_1 - C_6 alkyl group such as a methylsulfonylamino,
ethylsulfonylamino, propylsulfonylamino, isopropylsul-
fonylamino, butylsulfonylamino, isobutylsulfonylamino,
tert - butylsulfonylamino, pentylsulfonylamino, isopen-
25 tylsulfonylamino or hexylsulfonylamino group.

 The arylsulfonylamino group means an arylsulfo-
nylamino group having a C_6 - C_{14} aromatic hydrocarbon

ring or heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom such as a phenylsulfonylamino, naphthylsulfonylamino, thienylsul-
5 fonylamino, pyridylsulfonylamino or furylsulfonylamino group.

The aryl C_1-C_6 alkylsulfonylamino group means an aryl C_1-C_6 alkylsulfonylamino group having a $C_6 - C_{14}$ aromatic hydrocarbon ring or heteroaromatic ring
10 including 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom at the alkyl moiety of the above - defined C_1-C_6 alkylsulfonylamino group such as a benzylsulfonylamino, phenylethylsulfonylamino, phenylpropylsulfonylamino, 1 - methyl - 2 - phenylethylsulfonylamino,
15 phenylbutylsulfonylamino, phenylpentylsulfonylamino, phenylhexylsulfonylamino, naphthylmethylsulfonylamino, naphthylethylsulfonylamino, naphthylpropylsulfonylamino, thienylmethylsulfonylamino, pyridylmethylsulfonylamino, furylmethylsulfonylamino, thienylethylsulfonylamino,
20 pyridylethylsulfonylamino, furylethylsulfonylamino, thienylpropylsulfonylamino, pyridylbutylsulfonylamino, furylpentylsulfonylamino or thienylhexylsulfonylamino group.

25 The C_1-C_6 alkylthio group means a linear or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio, ethylthio, propylthio, isopropylthio,

butylthio, isobutylthio, sec - isobutylthio, tert - butylthio, pentylthio or hexylthio group.

The $C_3 - C_8$ cycloalkylamino group means a cycloalkylamino group having 3 to 8 carbon atoms such as
5 a cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cyclooctylamino, 2 - methylcyclopropylamino, 1 - methylcyclobutylamino, 2 - methylcyclopentylamino or 2,2 - dimethylcyclohexylamino group.

The $C_3 - C_8$ cycloalkyl C_1-C_6 alkylamino group
10 means a cycloalkylalkylamino group having a $C_3 - C_8$ cycloalkyl at the alkyl moiety of the above - defined C_1-C_6 alkylamino group such as a cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino,
15 cyclooctylmethylamino, 1 - cyclopropylethylamino, 2 - cyclopropylethylamino or 3 - cyclopropylpropylamino group.

The N - (C_1-C_6 alkyl) - N - ($C_3 - C_8$ cycloalkyl)amino group means an N - (C_1-C_6 alkyl) - N - ($C_3 - C_8$
20 cycloalkyl)amino group having 4 to 15 carbon atoms such as an N - methyl - N - cyclopropylamino, N - methyl - N - cyclobutylamino, N - methyl - N - cyclopentylamino, N - methyl - N - cyclohexylamino, N - methyl - N - cyclooctylamino, N - ethyl - N - cyclopropylamino, N - butyl - N
25 - cyclopropylamino, N - pentyl - N - cyclopropylamino, N - hexyl - N - cyclopropylamino, N - ethyl - N - cyclobutylamino, N - ethyl - N - cyclopentylamino, N - propyl -

N - cyclobutylamino, N - pentyl - N - cyclopentylamino group.

The N - (C₁-C₆ alkyl) - N - (aroyl)amino group means an N - (C₁-C₆ alkyl) - N - (aroyl)amino group having
5 6 to 12 carbon atoms such as an N - methyl - N - benzoylamino, N - (1 - ethyl) - N - benzoylamino, N - (1 - propyl) - N - benzoylamino, N - (1 - butyl) - N - benzoylamino, N - (1 - pentyl) - N - benzoylamino, N - (2 - ethyl - N - benzoylamino, N - (2 - propyl) - N - benzoylamino,
10 N - (3 - butyl) - N - benzoylamino, N - (4 - pentyl) - N - benzoylamino, N - methyl - N - naphthoylamino, N - methyl - N - thienylcarbonylamino, N - methyl - N - furylcarbonylamino, N - methyl - N - pyridylcarbonylamino or N - methyl - N - imidazolylcarbonylamino group.

15 The C₄ - C₇ cyclic imino group means a cyclic imino group having 4 to 7 carbon atoms such as a 1 - pyrrolidinyl, 2 - methylpyrrolidino, 2,5 - dimethylpyrrolidino, piperidino, 2 - methylpiperidino, 2,6 - dimethylpiperidino, morpholino, thiomorpholino, piperazino,
20 4 - methylpiperazino or hexamethyleneimino group.

The C₂ - C₆ alkanoyl group means a linear or branched alkanoyl group having 2 to 6 carbon atoms such as an acetyl, propanoyl, butyl, isobutyl, isopropanoyl, isobutyl, pentanoyl or hexanoyl group.

25 The aroyl group means an aroyl group including mono - , bi - or tri - cyclic aromatic hydrocarbon ring or heteroaromatic ring including 1 to 4 hetero atoms

selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, such as a benzoyl, naphthoyl, pyridylcarbonyl, thienylcarbonyl, furylcarbonyl, thiazolylcarbonyl, oxazolylcarbonyl, imidazolylcarbonyl or quinolylcarbonyl group.

The $C_3 - C_8$ cycloalkyl group means a cycloalkyl group having 3 to 8 carbon atoms such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group.

The $C_3 - C_8$ cycloalkyl $C_1 - C_6$ alkyl group means a $C_1 - C_6$ alkyl group substituted by a $C_3 - C_8$ cycloalkyl group such as a cyclopropylmethyl, 1 - cyclopropylethyl, 2 - cyclopropylethyl, 2 - cyclopropylpropyl, 3 - cyclopropylpropyl, 4 - cyclopropylbutyl, 5 - cyclopropylpentyl, 6 - cyclopropylhexyl, cyclobutylmethyl, 1 - cyclobutylethyl, 2 - cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl or cyclooctylmethyl group.

Now, this invention will be described in more detail with reference to specific examples for the various symbols used in the formula (I).

Each of Ar^1 and Ar^2 is independently a phenyl group, a thienyl group, a pyridyl group, an indolyl group, a benzofuranyl group or a dihydrobenzofuranyl group wherein an optional hydrogen atom(s) on the aromatic ring may be replaced with 1 to 4 groups selected from the group consisting of a halogen atom, a

hydroxyl group, an amino group, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a mono- or di- C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a tetrazol-5-yl group, a methylenedioxy group, a C₁-C₆ alkoxy group, a C₂-C₆ alkenyloxy group, a mono- or di- C₁-C₆ alkylamino group, a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group and a C₂-C₆ alkynyl group (provided that the C₁-C₆ alkoxy group, C₂-C₆ alkenyloxy group, mono- or di- C₁-C₆ alkylamino group, C₁-C₆ alkyl group, C₂-C₆ alkenyl group and C₂-C₆ alkynyl group may be substituted by 1 to 3 groups selected from the group consisting of a phenyl group, a pyridyl group, an imidazolyl group, a hydroxyl group, a C₁-C₆ alkoxy group, an amino group, a mono- or di- C₁-C₆ alkylamino group, a hydroxy C₁-C₆ alkylcarbonyl group, a C₁-C₆ acyloxy C₁-C₆ alkylcarbonyl group, a carboxy C₁-C₆ alkoxycarbonyl group, a carboxy C₁-C₆ alkoxycarbonyl C₁-C₆ alkoxycarbonyl group, a C₁-C₆ alkoxycarbonyl group, a mono- or di- C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a C₁-C₆ alkylsulfonylaminocarbonyl group, a tetrazol-5-ylaminocarbonyl group, a carboxyl group, SO₃H, PO₃H₂, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl group (provided that when a hydroxyl group and a carboxyl group are selected as substituents, they may together form a lactone ring)).

The halogen atom means a fluorine, chlorine,

bromine or iodine atom.

The C_1-C_6 alkoxycarbonyl group means an alkoxycarbonyl group having a linear or branched C_1-C_6 alkoxy group such as a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, tert-butylloxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl or hexyloxycarbonyl group.

The mono- or di- C_1-C_6 alkylaminocarbonyl group means an alkylaminocarbonyl group having 1 or 2 linear or branched C_1-C_6 alkyl groups at the nitrogen atom such as a methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, pentylaminocarbonyl, isopentylaminocarbonyl group, hexylaminocarbonyl, dimethylaminocarbonyl group, ethylmethylaminocarbonyl group, diethylaminocarbonyl, isopropylmethylaminocarbonyl, dipropylaminocarbonyl, ethylisopropylaminocarbonyl, diisopropylaminocarbonyl, dibutylaminocarbonyl, diisobutylaminocarbonyl, di-tert-butylaminocarbonyl, dipentylaminocarbonyl, ethylpentylaminocarbonyl, diisopentylaminocarbonyl or ethylhexylaminocarbonyl group.

The C_1-C_6 alkoxy group means a linear or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy or

hexyloxy group.

The C_2-C_6 alkenyloxy group means an alkenyloxy group having a linear or branched C_2-C_6 alkenyl group such as a vinyloxy, allyloxy, 1-propenyloxy, isopropenyloxy, 2-butenyloxy, 3-butenyloxy, 2-pentenyloxy, 3-methyl-3-butenyloxy or 2-hexenyloxy group.

The mono- or di- C_1-C_6 alkylamino group means an alkylamino group having 1 or 2 linear or branched C_1-C_6 alkyl groups at the nitrogen atom such as a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, isopentylamino, hexylamino, dimethylamino, ethylmethylamino, diethylamino, dipropylamino, propylmethylamino, ethylpropylamino, diisopropylamino, diisobutylamino, ethylisobutylamino, di-tert-butylamino, dipentylamino, diisopentylamino, isopentylmethylamino or dihexylamino group,

The C_1-C_6 alkyl group means a linear or branched alkyl group having 1 to 6 carbon atoms such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl or 1-ethyl-1-methylpropyl group.

The C_2-C_6 alkenyl group means a linear or branched alkenyl group having 2 to 6 carbon atoms such as a vinyl, allyl, 2-propenyl, isopropenyl, 3-butenyl, 2-butenyl, 1-butenyl, 1-methyl-2-propenyl, 1-methyl-1-propenyl, 1-ethyl-1-ethenyl, 2-methyl-2-propenyl, 2-methyl-1-propenyl or 4-pentenyl group.

The C_2-C_6 alkynyl group means a linear or branched alkynyl group having 2 to 6 carbon atoms such as an ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-methyl-2-propynyl or 1-pentyne group.

The hydroxy C_1-C_6 alkylcarbonyl group means a linear or branched hydroxyalkylcarbonyl group having 2 to 7 carbon atoms such as a hydroxymethylcarbonyl, 1-hydroxyethylcarbonyl, 1-hydroxypropylcarbonyl, 1-hydroxybutylcarbonyl, 1-hydroxypentylcarbonyl, 1-hydroxyhexylcarbonyl, 2-hydroxyethylcarbonyl, 3-hydroxypropylcarbonyl, 2-hydroxybutylcarbonyl, 4-hydroxypentylcarbonyl, 3-hydroxyhexylcarbonyl or 2-hydroxy-2-methylpropylcarbonyl group.

The C_1-C_6 acyloxy C_1-C_6 alkylcarbonyl group means an acyloxy C_1-C_6 alkylcarbonyl group having an aliphatic or aromatic acyloxy group such as an acetyloxymethylcarbonyl, 1-acetyloxyethylcarbonyl, 2-acetyloxyethylcarbonyl, 1-acetyloxypropylcarbonyl, 1-acetyloxybutylcarbonyl, 1-acetyloxypentylcarbonyl, 1-

acetyloxyhexylcarbonyl, 2 - acetyloxypropylcarbonyl, propionylloxymethylcarbonyl, 1 - propionylloxyethylcarbonyl, butylloxymethylcarbonyl, pentanoyloxymethylcarbonyl, hexanoyloxymethylcarbonyl, benzoyloxymethylcarbonyl, 1 - benzoyloxyethylcarbonyl, 2 - benzoyloxyethylcarbonyl, thienylcarbonyloxymethylcarbonyl, furfuryloxymethylcarbonyl, pyridylcarbonyloxymethylcarbonyl or imidazolylcarbonyloxymethylcarbonyl group.

The carboxy C_1-C_6 alkoxycarbonyl group means a linear or branched carboxy C_1-C_6 alkoxycarbonyl group having 3 to 10 carbon atoms such as a carboxymethoxycarbonyl, 1 - carboxyethoxycarbonyl, 1 - carboxypropoxycarbonyl, 1 - carboxybutoxycarbonyl, 2 - carboxyethoxycarbonyl, 2 - carboxybutoxycarbonyl, 2 - carboxypentoxycarbonyl, 3 - carboxypropoxycarbonyl, 3 - carboxybutoxycarbonyl, 4 - carboxypentoxycarbonyl, 3 - carboxyhexyloxycarbonyl or 2 - carboxy - 2 - methylpropyloxycarbonyl group.

The carboxy C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxycarbonyl group means a linear or branched carboxy C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxycarbonyl group having 3 to 16 carbon atoms such as a carboxymethoxycarbonylmethoxycarbonyl, 1 - carboxyethoxycarbonylmethoxycarbonyl, 1 - carboxypropoxycarbonylmethoxycarbonyl, 1 - carboxybutoxycarbonylmethoxycarbonyl, 2 - carboxyethoxycarbonylmethoxycarbonyl,

2 - carboxybutoxycarbonylethoxycarbonyl,
2 - carboxypentoxycarbonylethoxycarbonyl,
3 - carboxypropoxycarbonylethoxycarbonyl,
3 - carboxybutoxycarbonylethoxycarbonyl,
5 4 - carboxypentoxycarbonylethoxycarbonyl,
3 - carboxyhexyloxycarbonylmethoxycarbonyl or
2 - carboxy - 2 - methylpropyloxycarbonylmethoxycarbonyl
group.

The C_1-C_6 alkylsulfonylaminocarbonyl group means
10 an alkylsulfonylaminocarbonyl group having a linear or
branched C_1-C_6 alkyl group such as a methylsulfonyl-
aminocarbonyl, ethylsulfonylaminocarbonyl, propylsulfo-
nylaminocarbonyl, isopropylsulfonylaminocarbonyl,
butylsulfonylaminocarbonyl, isobutylsulfonyl-
15 laminocarbonyl, tert - butylsulfonylaminocarbonyl, pen-
tylsulfonylaminocarbonyl, isopentylsulfonylaminocarbonyl
or hexylsulfonylaminocarbonyl group.

Preferred compounds are those wherein Ar^1 and
 Ar^2 are independently a phenyl group, a thienyl group or
20 a dihydrobenzofuranyl group wherein an optional hydrogen
atom(s) on the aromatic ring may be replaced with 1 to 4
groups selected from the group consisting of a halogen
atom, a hydroxyl group, an amino group, a methylenedioxy
group, a C_1-C_6 alkoxy group, a C_2-C_6 alkenyloxy group, a
25 mono- or di- C_1-C_6 alkylamino group, a C_1-C_6 alkyl
group, a C_2-C_6 alkenyl group and a C_2-C_6 alkynyl group
(provided that the said C_1-C_6 alkoxy group, C_2-C_6

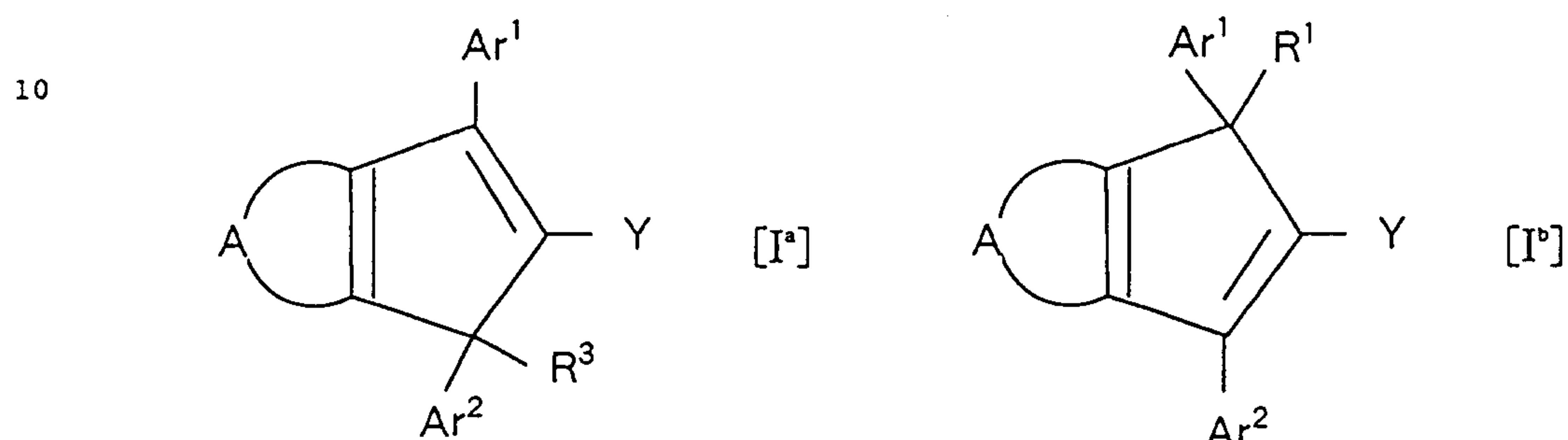
alkenyloxy group, mono- or di- C_1-C_6 alkylamino group, C_1-C_6 alkyl group, C_2-C_6 alkenyl group and C_2-C_6 alkynyl group may be substituted by 1 to 3 groups selected from the group consisting of a phenyl group, a pyridyl group, an imidazolyl group, a hydroxyl group, a C_1-C_6 alkoxy group, an amino group, a mono- or di- C_1-C_6 alkylamino group, a hydroxy C_1-C_6 alkylcarbonyl group, a C_1-C_6 acyloxy C_1-C_6 alkylcarbonyl group, a carboxy C_1-C_6 alkoxycarbonyl group, a carboxy C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkoxycarbonyl group, a mono- or di- C_1-C_6 alkylaminocarbonyl group, a carbamoyl group, a C_1-C_6 alkylsulfonylaminocarbonyl group, a tetrazol-5-ylaminocarbonyl group, a carboxyl group, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl group (provided that when a hydroxyl group and a carboxyl group are selected as the substituents, they may together form a lactone ring)).

Each of R^1 , R^2 and R^3 is independently a hydrogen atom, a hydroxyl group or a C_1-C_6 alkyl group, or R^1 and R^2 , or R^2 and R^3 together form a single bond.

The C_1-C_6 alkyl group means a linear or branched alkyl group having 1 to 6 carbon atoms such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl,

1-ethylpropyl, hexyl, isohexyl, 1-methylpentyl,
 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl,
 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl,
 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl,
 5 1-ethyl-2-methylpropyl or 1-ethyl-1-methylpropyl group.

When R^1 and R^2 , or R^2 and R^3 together form a
 single bond, compounds of the general formula(I) are
 compounds of the general formula (I^a) or (I^b).



15 Ar^1 , Ar^2 , A, R^1 and R^3 are as defined above.

Y is a group of $-CO-R^4$ (wherein R^4 is a hydroxyl
 group, an amino group, a C_1-C_6 alkoxy group, a mono- or
 di- C_1-C_6 alkylamino group, a C_1-C_6 alkylsulfonylamino
 group, or an arylsulfonylamino group or aryl C_1-C_6
 20 alkylsulfonylamino group wherein an optional hydrogen
 atom(s) on the aryl ring may be replaced with a C_1-C_6
 alkyl group), SO_3H , PO_3H_2 , a tetrazol-5-yl group, a
 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group or a
 5-oxo-4H-1,2,4-oxadiazol-3-yl group.

25 The C_1-C_6 alkoxy group means a linear or
 branched alkoxy group having 1 to 6 carbon atoms such as
 a methoxy, ethoxy, propoxy, isopropoxy, butoxy,

isobutoxy, sec-butoxy, tert-butoxy, pentyloxy or hexyloxy group.

The mono - or di - C_1 - C_6 alkylamino group means an alkylamino group having 1 or 2 linear or branched C_1 - C_6 alkyl groups at the nitrogen atom such as a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, isopentylamino, hexylamino, dimethylamino, ethylmethylamino, diethylamino, dipropylamino, propylmethylamino, ethylpropylamino, diisopropylamino, diisobutylamino, ethylisobutylamino, di - tert-butylamino, di pentylamino, diisopentylamino, isopentylmethylamino or dihexylamino group,

The C_1 - C_6 alkylsulfonylamino group means an alkylsulfonylamino group having a linear or branched C_1 - C_6 alkyl group such as a methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino, butylsulfonylamino, isobutylsulfonylamino, tert - butylsulfonylamino, pentylsulfonylamino, isopentylsulfonylamino or hexylsulfonylamino group.

The arylsulfonylamino group wherein an optional hydrogen atom(s) on the aryl ring may be replaced with a C_1 - C_6 alkyl group means an arylsulfonylamino group having a C_6 - C_{14} aromatic hydrocarbon ring or heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, wherein an optional

hydrogen atom(s) on the aryl ring may be replaced with a
C₁ - C₆ alkyl group, such as a phenylsulfonylamino,
naphthylsulfonylamino, thienylsulfonylamino, pyridylsul-
fonylamino or furylsulfonylamino group, or said groups
5 having a C₁ - C₆ alkyl group on the aromatic ring.

The aryl C₁ - C₆ alkylsulfonylamino group
wherein an optional hydrogen atom(s) on the aryl ring
may be replaced with a C₁ - C₆ alkyl group means an
arylalkylsulfonylamino group having, at the alkyl moiety
10 of the above - defined C₁ - C₆ alkylsulfonylamino group,
a C₆ - C₁₄ aromatic hydrocarbon ring or heteroaromatic
ring including 1 to 4 hetero atoms selected from the
group consisting of an oxygen atom, a nitrogen atom and
a sulfur atom, wherein an optional hydrogen atom(s) on
15 the aryl ring may be replaced with a C₁ - C₆ alkyl
group, such as a benzylsulfonylamino, phenylethyl-
sulfonylamino, phenylpropylsulfonylamino, 1 - methyl - 2
- phenylethylsulfonylamino, phenylbutylsulfonylamino,
phenylpentylsulfonylamino, phenylhexylsulfonylamino,
20 naphthylmethylsulfonylamino, naphthylethylsulfonylamino,
naphthylpropylsulfonylamino, thienylmethylsulfonylamino,
pyridylmethylsulfonylamino, furylmethylsulfonylamino,
thienylethylsulfonylamino, pyridylethylsulfonylamino,
furylethylsulfonylamino, thienylpropylsulfonylamino,
25 pyridylbutylsulfonylamino, furylpentylsulfonylamino or
thienylhexylsulfonylamino group, or said groups having a
C₁ - C₆ alkyl group on the aromatic ring.

A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6- membered heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (provided that optional 1 or 2 hydrogen atoms on the heteroaromatic ring may be replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a halogen atom, a cyano group, a nitro group, a mono- or di- C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, a C₃-C₈ cycloalkyl C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(aroyl)amino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group at the alkylene moiety, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a formyl group, a C₂-C₆ alkanoyl group, an aroyl group, or a C₁-C₆ alkyl group, C₃-C₈ cycloalkyl group, C₃-C₈ cycloalkyl C₁-C₆ alkyl group, C₂-C₆ alkenyl group or C₂-C₆ alkynyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a

hydroxyl group, an amino group, a C_1-C_6 alkoxy group and a mono- or di- C_1-C_6 alkylamino group, and when the heteroaromatic ring includes one or more nitrogen atoms, the nitrogen atom(s) may be oxidized to form an N-oxide group).

The C_1-C_6 alkoxy group means a linear or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy or hexyloxy group.

The C_1-C_6 alkylthio group means a linear or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec - isobutylthio, tert - butylthio, pentylthio or hexylthio group.

The halogen atom means a fluorine, chlorine, bromine or iodine atom.

The mono - or di - alkylamino group wherein an optional hydrogen atom(s) at the alkyl moiety may be replaced with a hydroxyl group means a linear or branched alkylamino group having, at the nitrogen atom, 1 or 2 linear or branched alkyl groups which may be substituted by a hydroxyl group, such as a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, isopentylamino, hexylamino, dimethylamino, ethylmethylamino, diethylamino, dipropylamino, propylmethylamino, ethyl-

propylamino, diisopropylamino, diisobutylamino, ethylisobutylamino, di - tert-butylamino, dipentylamino, diisopentylamino, isopentylmethylamino or dihexylamino group.

5 The $C_3 - C_8$ cycloalkylamino group wherein an optional hydrogen atom(s) at the alkyl or alkylene moiety may be replaced with a hydroxyl group means a $C_3 - C_8$ cycloalkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, such
10 as a cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cyclooctylamino, 2 - methylcyclopropylamino, 1 - methylcyclobutylamino, 2 - methylcyclopentylamino or 2,2 - dimethylcyclohexylamino.

 The $C_3 - C_8$ cycloalkyl C_1-C_6 alkylamino group
15 wherein an optional hydrogen atom(s) at the alkyl or alkylene moiety may be replaced with a hydroxyl group means a $C_3 - C_8$ cycloalkyl C_1-C_6 alkylamino group which has 4 to 14 carbon atoms and may be substituted by a hydroxyl group at the alkyl or alkylene moiety, such as
20 a cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, cyclohexylmethylamino, cycloheptylmethylamino, cyclooctylmethylamino, 1 - cyclopropylethylamino, 2 - cyclopropylethylamino , 3 - cyclopropylpropylamino , 2 - cyclobutylethylamino or 2 -
25 cyclopentylethylamino group.

 The $N - (C_1-C_6 \text{ alkyl}) - N - (C_3 - C_8 \text{ cycloalkyl})$ amino group wherein an optional hydrogen atom(s) at

the alkyl or alkylene moiety may be replaced with a hydroxyl group means an N - (C₁-C₆ alkyl) - N - (C₃ - C₈ cycloalkyl)amino group which has 4 to 15 carbon atoms and may be substituted by a hydroxyl group at the

5 alkyl or alkylene moiety, such as an N - methyl - N - cyclopropylamino, N - methyl - N - cyclobutylamino, N - methyl - N - cyclopentylamino, N - methyl - N - cyclohexylamino, N - methyl - N - cyclooctylamino, N - ethyl - N - cyclopropylamino, N - butyl - N - cyclopropylamino, N -

10 pentyl - N - cyclopropylamino, N - hexyl - N - cyclopropylamino, N - ethyl - N - cyclobutylamino, N - ethyl - N - cyclopentylamino, N - propyl - N - cyclobutylamino, N - pentyl - N - cyclopentylamino group.

The N - (C₁-C₆ alkyl) - N - (aroyl)amino group

15 wherein an optional hydrogen atom(s) at the alkyl moiety may be replaced with a hydroxyl group means an N - (C₁-C₆ alkyl) - N - (aroyl)amino group which has 6 to 12 carbon atoms and may be substituted by a hydroxyl group at the alkyl moiety, such as an N - methyl - N -

20 benzoylamino, N - (1 - ethyl) - N - benzoylamino, N - (1 - propyl) - N - benzoylamino, N - (1 - butyl) - N - benzoylamino, N - (1 - pentyl - N - benzoylamino, N - (2 - ethyl) - N - benzoylamino, N - (2 - propyl) - N - benzoylamino, N - (3 - butyl - N - benzoylamino, N - (4 - pentyl) - N -

25 benzoylamino, N - methyl - N - naphthoylamino, N - methyl - N - thienylcarbonylamino, N - methyl - N - furylamino, N - methyl - N - pyridylamino or N - methyl - N -

imidazoylamino group.

The $C_4 - C_7$ cyclic imino group wherein an optional hydrogen atom(s) may be replaced with a hydroxyl group means a cyclic imino group which has 4 to 7 carbon atoms and may be substituted by a hydroxyl group at the alkylene moiety, such as a 1 - pyrrolidinyl, 2 - methylpyrrolidino, 2,5 - dimethylpyrrolidino, piperidino, 2 - methylpiperidino, 2,6 - dimethylpiperidino, morpholino, thiomorpholino, piperazino, 4 - methylpiperazino or hexamethyleneimino group.

The $C_1 - C_6$ alkoxycarbonyl group means an alkoxycarbonyl group having a linear or branched $C_1 - C_6$ alkoxy group such as a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, tert - butyloxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl or hexyloxycarbonyl group.

The $C_2 - C_6$ alkanoyl group means a linear or branched alkanoyl group having 2 to 6 carbon atoms such as an acetyl, propanoyl, butyl, isobutyl, isopropanoyl, isobutyl, pentanoyl or hexanoyl group.

The aroyl group means an aroyl group having mono - , bi - or tri - cyclic aromatic hydrocarbon ring or heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, such as a benzoyl, naphthoyl, pyridylcarbonyl, thienylcarbonyl, furylcar-

bonyl, thiazolylcarbonyl, oxazolylcarbonyl, imidazolylcarbonyl or quinolylcarbonyl group.

The C_1 - C_6 alkyl group means a linear or branched alkyl group having 1 to 6 carbon atoms such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl or 1-ethyl-1-methylpropyl group.

The C_3 - C_8 cycloalkyl group means a cycloalkyl group having 3 to 8 carbon atoms such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group.

The C_2 - C_6 alkenyl group means a linear or branched alkenyl group having 2 to 6 carbon atoms such as a vinyl, allyl, 2-propenyl, isopropenyl, 3-butenyl, 2-butenyl, 1-butenyl, 1-methyl-2-propenyl, 1-methyl-1-propenyl, 1-ethyl-1-ethenyl, 2-methyl-2-propenyl, 2-methyl-1-propenyl or 4-pentenyl group.

The C_3 - C_8 cycloalkyl C_1 - C_6 alkyl group means a C_1 - C_6 alkyl group substituted by a C_3 - C_8 cycloalkyl group such as a cyclopropylmethyl, 1 - cyclopropylethyl, 2 - cyclopropylethyl, 2 - cyclopropylpropyl, 3

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- 38 -

-cyclopropylpropyl, 4-cyclopropylbutyl, 5-cyclopropylpenyl, 6-cyclopropylhexyl, cyclobutylmethyl, 1-cyclobutylethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl or cyclooctylmethyl group.

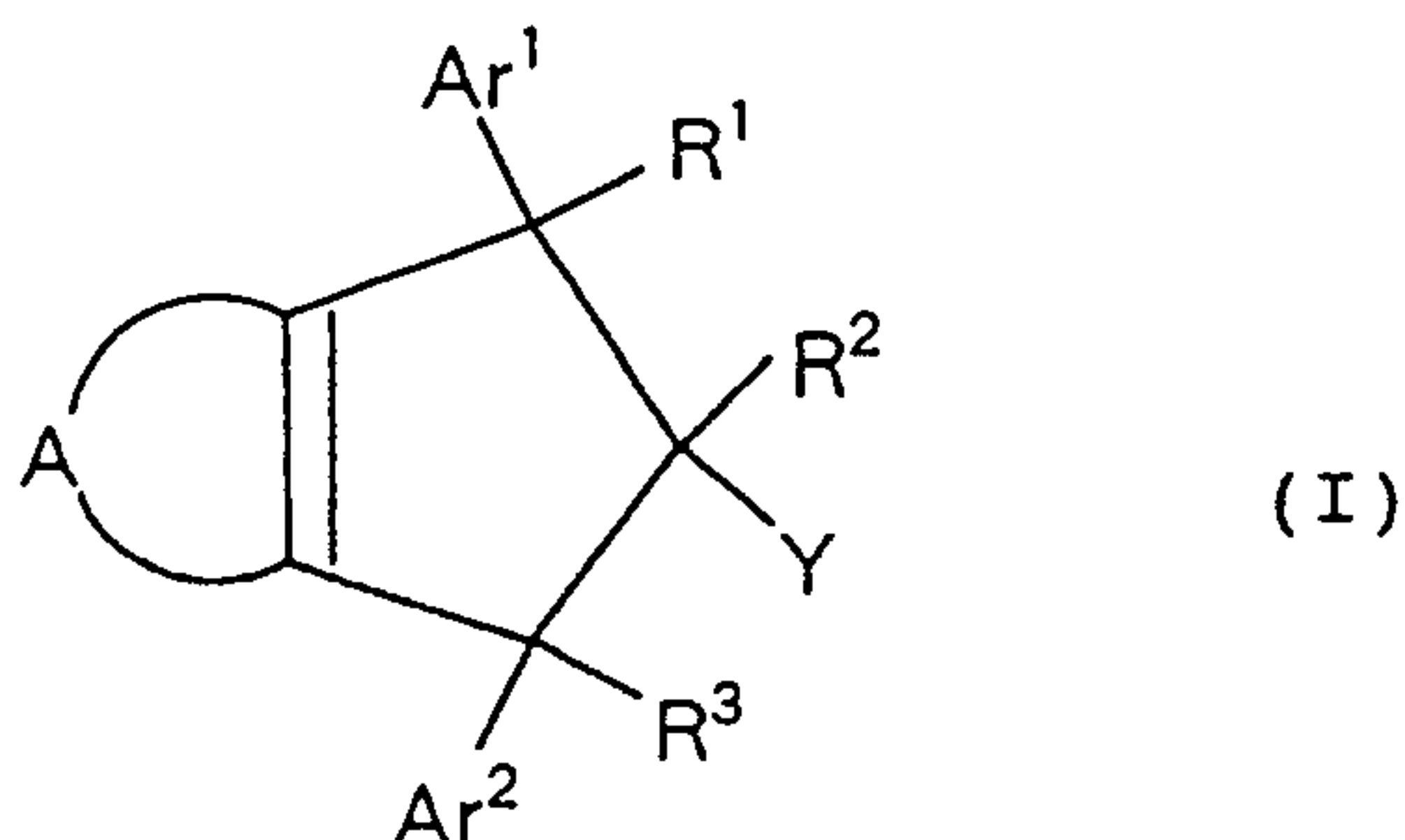
5 The C₂-C₆ alkynyl group means a linear or branched alkynyl group having 2 to 6 carbon atoms such as a ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl or 1-pentynyl group.

10 A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6-membered heteroaromatic ring including 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and examples of the 5- or 6-membered heteroaromatic ring are a furan ring, a pyrrole ring, a thiophene ring, a diazole
15 ring, a thiazole ring, an oxazole ring, a pyridine ring, a diazine ring, a triazine ring, etc..

20 Preferred compounds are those wherein A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6-membered nitrogen-containing aromatic ring (more preferably pyridine, pyrimidine, pyridazine, pyrazine or thiazole ring) or the corresponding N-oxide ring (provided that optional 1 or 2 hydrogen atoms on the heteroaromatic ring may be replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a mono- or di-C₁-C₆
25 alkylamino

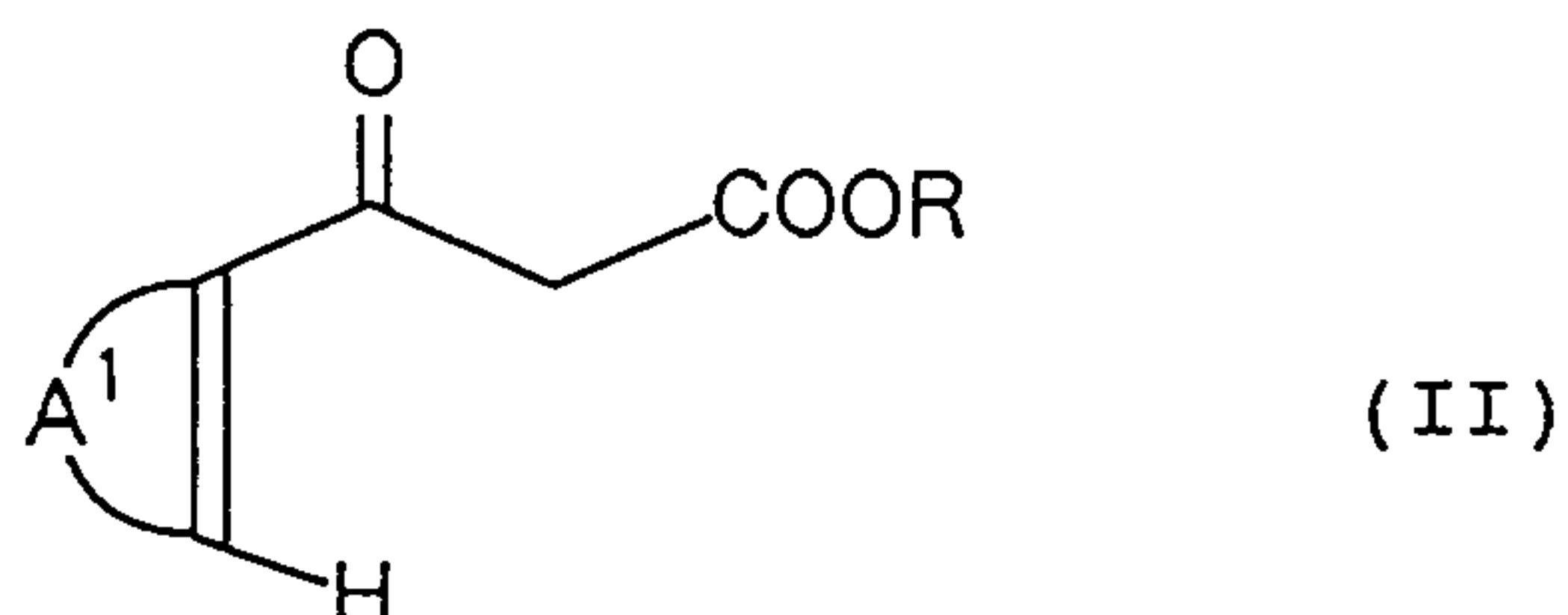
group which may be substituted by a hydroxyl group at the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, a C₃-C₈ cycloalkyl C₁-C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N-(C₁-C₆ alkyl)-N-(aroyl)amino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group at the alkylene moiety, or a C₁-C₆ alkyl group, C₃-C₈ cycloalkyl group, C₃-C₈ cycloalkyl C₁-C₆ alkyl group, C₂-C₆ alkenyl group or C₂-C₆ alkynyl group which may be substituted by 1 to 3 groups selected from the group consisting of a hydroxyl group, an amino group, a C₁-C₆ alkoxy group and a mono- or di- C₁-C₆ alkylamino group).

The present invention provides novel heteroaromatic ring-fused cyclopentene derivatives of Formula (I) above



which can be prepared by a process which comprises:

1) reacting a β -keto ester derivative of Formula (II):



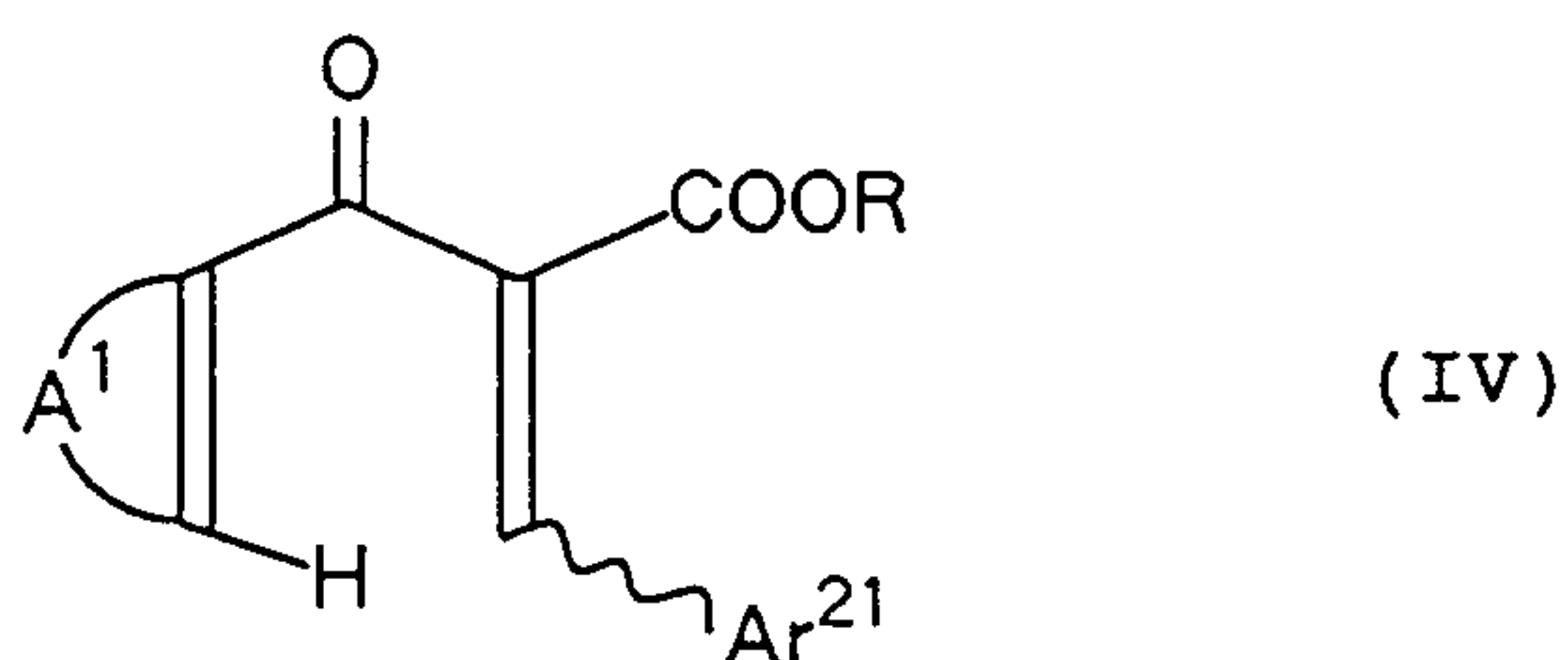
wherein R is a C_1 - C_6 alkyl group, and A^1 is A or its synthetic equivalents, with an aldehyde of Formula (III):

10



wherein Ar^{21} is Ar^2 or its synthetic equivalents, in a suitable solvent such as benzene or toluene with a catalyst such as piperidinium acetate at $-20^\circ C$ to reflux temperature of a solvent to provide a 2-propenate derivative of Formula (IV):

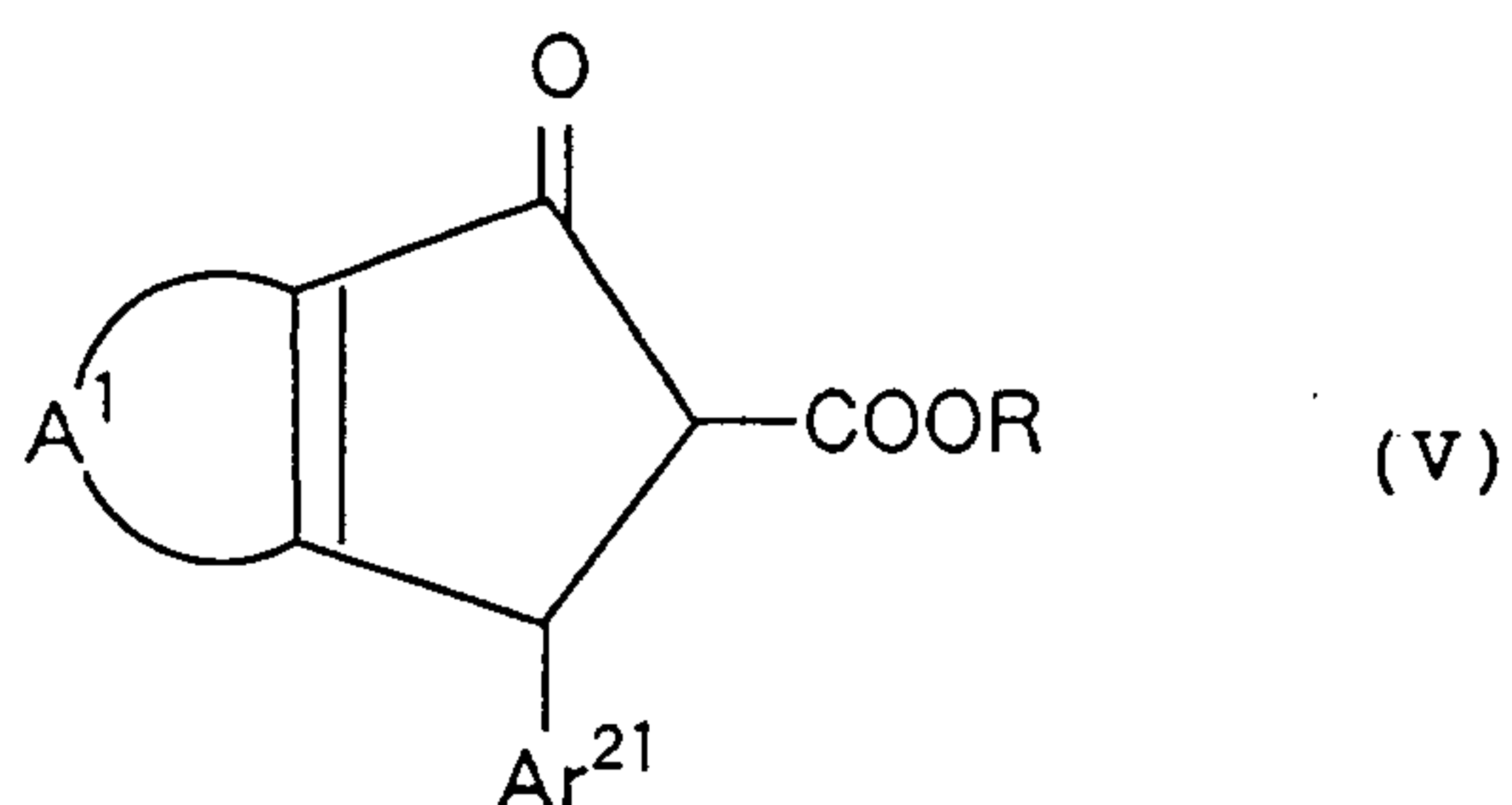
15



wherein Ar^{21} , A^1 and R are as defined before.

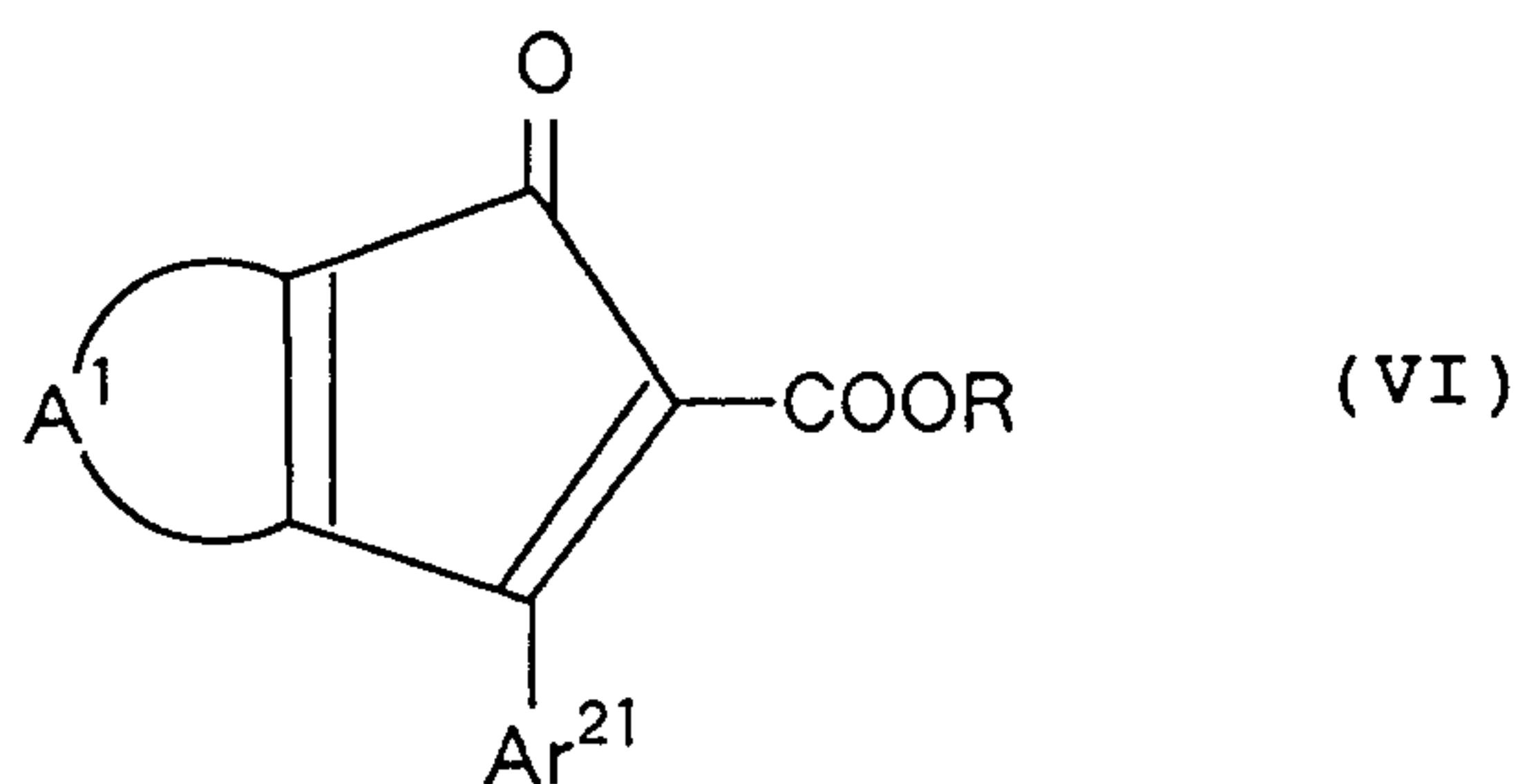
25 Cyclization of Compound (IV) in the presence of a suitable Lewis acid such as titanium tetrachloride, tin tetrachloride or aluminum chloride, or alternatively a

protic acid such as trifluoroacetic acid, conc. H_2SO_4 , perchloric acid or polyphosphoric acid in a suitable solvent such as benzene or toluene at -20°C to reflux temperature of a solvent, provides a cyclopentene derivative of Formula (V):



wherein Ar^{21} , A^1 and R are as defined before.

Dehydrogenation of Compound (V) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) or alternative bromination of Compound (V) followed by dehydrobromination provides a cyclopentadienone derivative of Formula (VI):



wherein Ar^{21} , A^1 and R are as defined before.

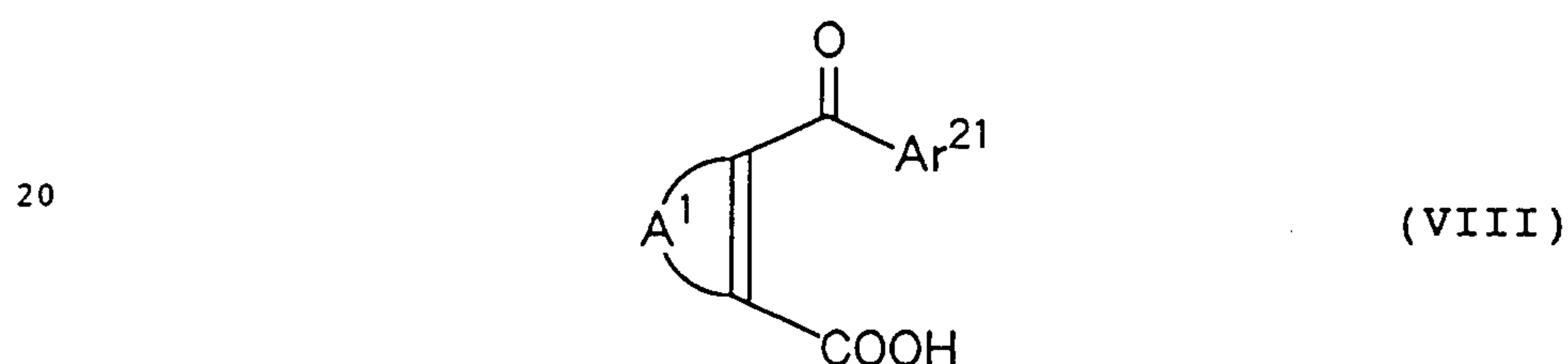
2) Alternatively, a compound of Formula (VI) can be prepared as follows:

a compound of Formula (VII):



5

wherein Met is metal and A¹ is as defined before, which was prepared by halogen-metal exchange reaction of the corresponding β -halocarboxylic acid with 2 equivalents of a metal reagent such as butyllithium, or by direct
 10 metallation of a β -hydrogen of the corresponding carboxylic acid with 2 equivalents of a strong base such as n - butyllithium, sec - butyllithium, tert-butyl-
 lithium, sodium or lithium, was treated with aroyl halide or arynitrile in an aprotic solvent such as THF,
 15 Et₂O or dimethoxyethane at -100 °C to room temperature to provide a carboxylic acid derivative of Formula (VIII):

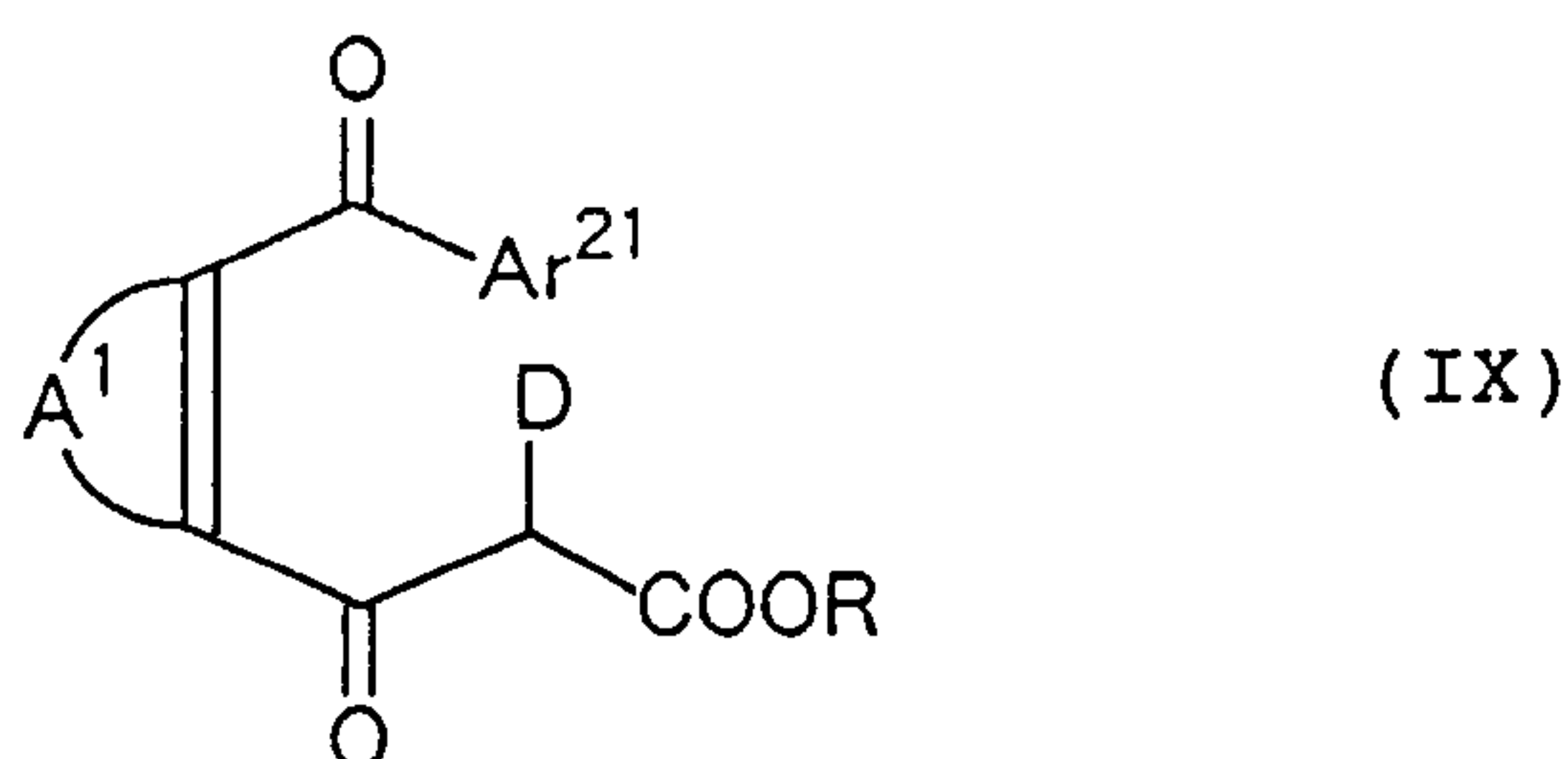


20

wherein Ar²¹ and A¹ are as defined before.

To activate the carboxyl group, Compound (VIII) can
 25 be treated with a halogenated agent such as thionyl chloride or oxalyl chloride at -40 °C to 100 °C or with CDI in an aprotic solvent such as CHCl₃, THF or DMF at

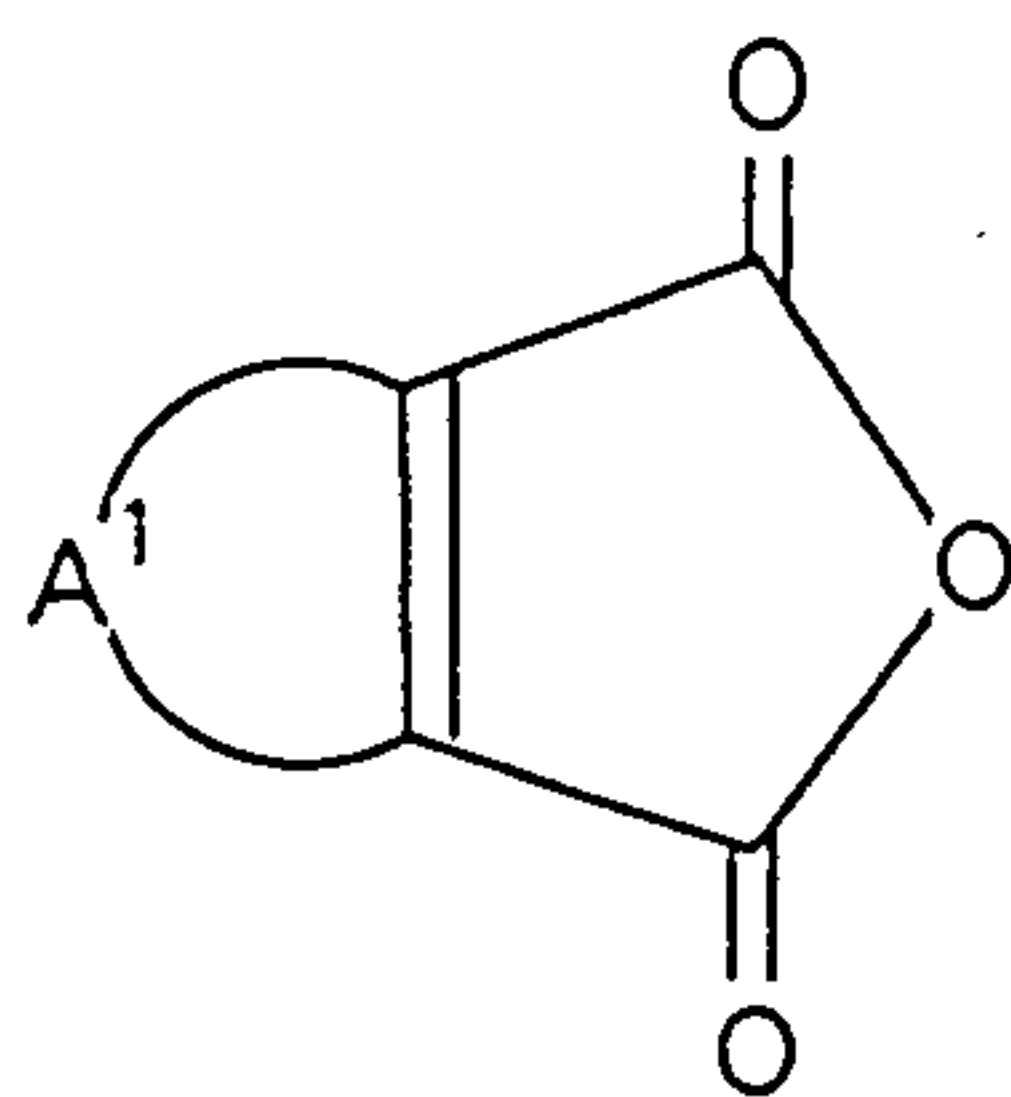
-20 °C to room temperature. The resulting activated carboxylic acid derivative, that is, acid chloride or imidazolide or activated ester, can then be treated with 1 to 5 equivalents of diethyl magnesium malonate, magnesium salt of malonic acid half ester or lithium enolate of acetic acid ester in a suitable solvent such as ether or THF at -100 °C to 50 °C to give a compound of Formula (IX):



15 wherein D is H, -COOR, -COOMet or -COOH, and Ar²¹, A¹, R and Met are as defined before.

Treatment of Compound (IX) with an aqueous inorganic base such as sodium carbonate under heating, or with an acid such as 1N HCl, acetic acid or SiO₂ at 0 °C to
20 room temperature gives a compound of Formula (VI).

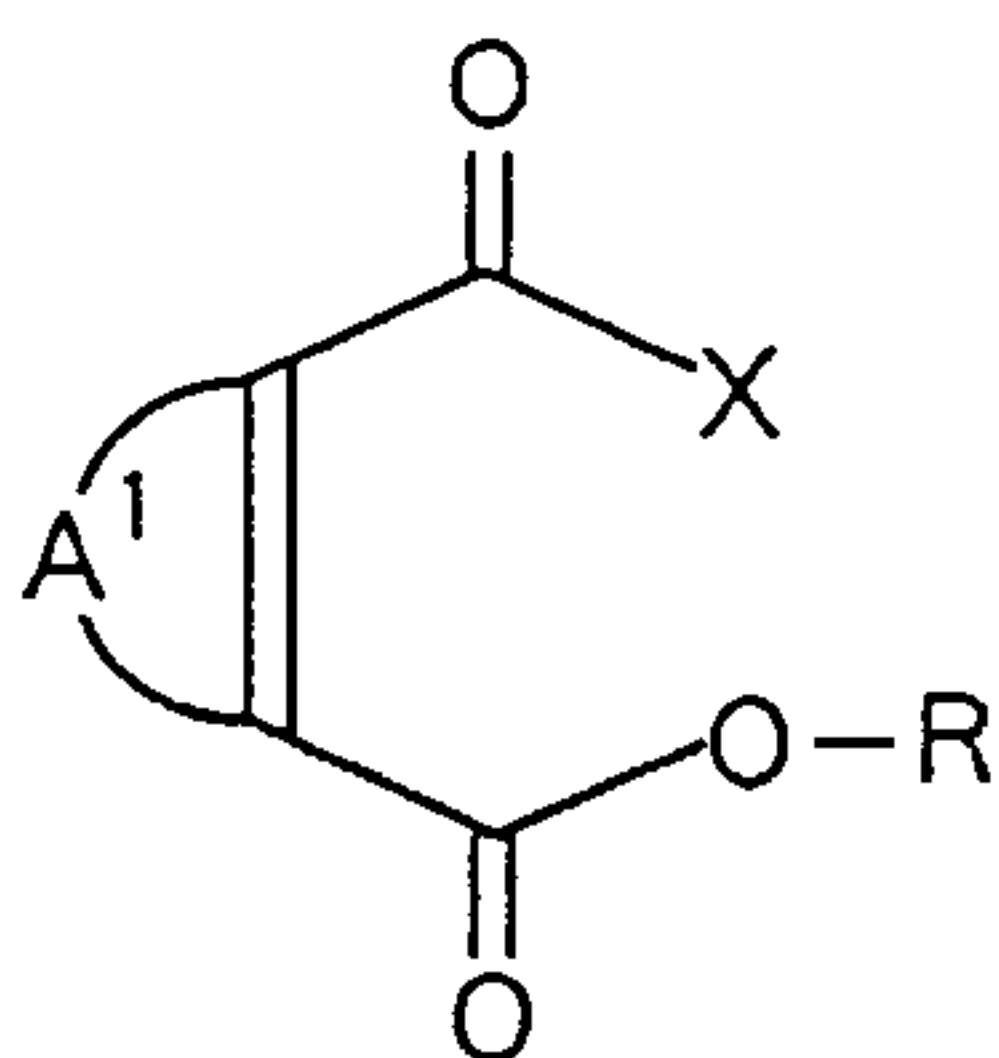
Alternatively, Compound (VIII) can be prepared by reaction of a dicarboxylic acid anhydride of Formula (X):



(X)

5

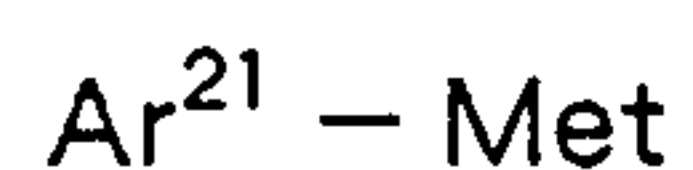
wherein A¹ is as defined before, or a dicarboxylic acid mono ester of Formula (XI):



(XI)

10

wherein X is a leaving group, and A¹ and R are as defined before, with an organometallic reagent of Formula (XII):



(XII)

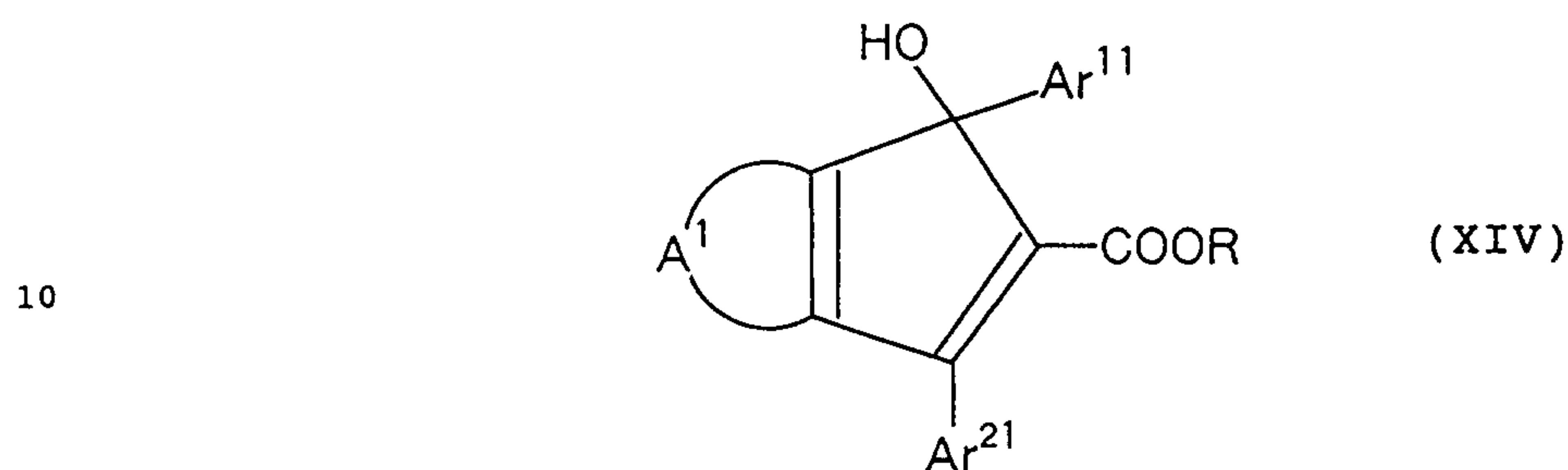
wherein Ar²¹ and Met are as defined before, in an aprotic solvent such as THF or ether at -100 °C to room temperature. Preferred organometallic reagents are organomagnesium reagents such as Grignard reagents, organolithium reagents or organozinc reagents.

3) Treatment of Compound (VI) with an organometallic reagent such as Grignard reagent of Formula (XIII):

25



wherein Ar^{11} is Ar^1 or its synthetic equivalents and
 Met is as defined before, in a suitable solvent such as
 5 THF, Et_2O or dimethoxyethane at -100°C to room
 temperature provides compounds of Formula (XIV):

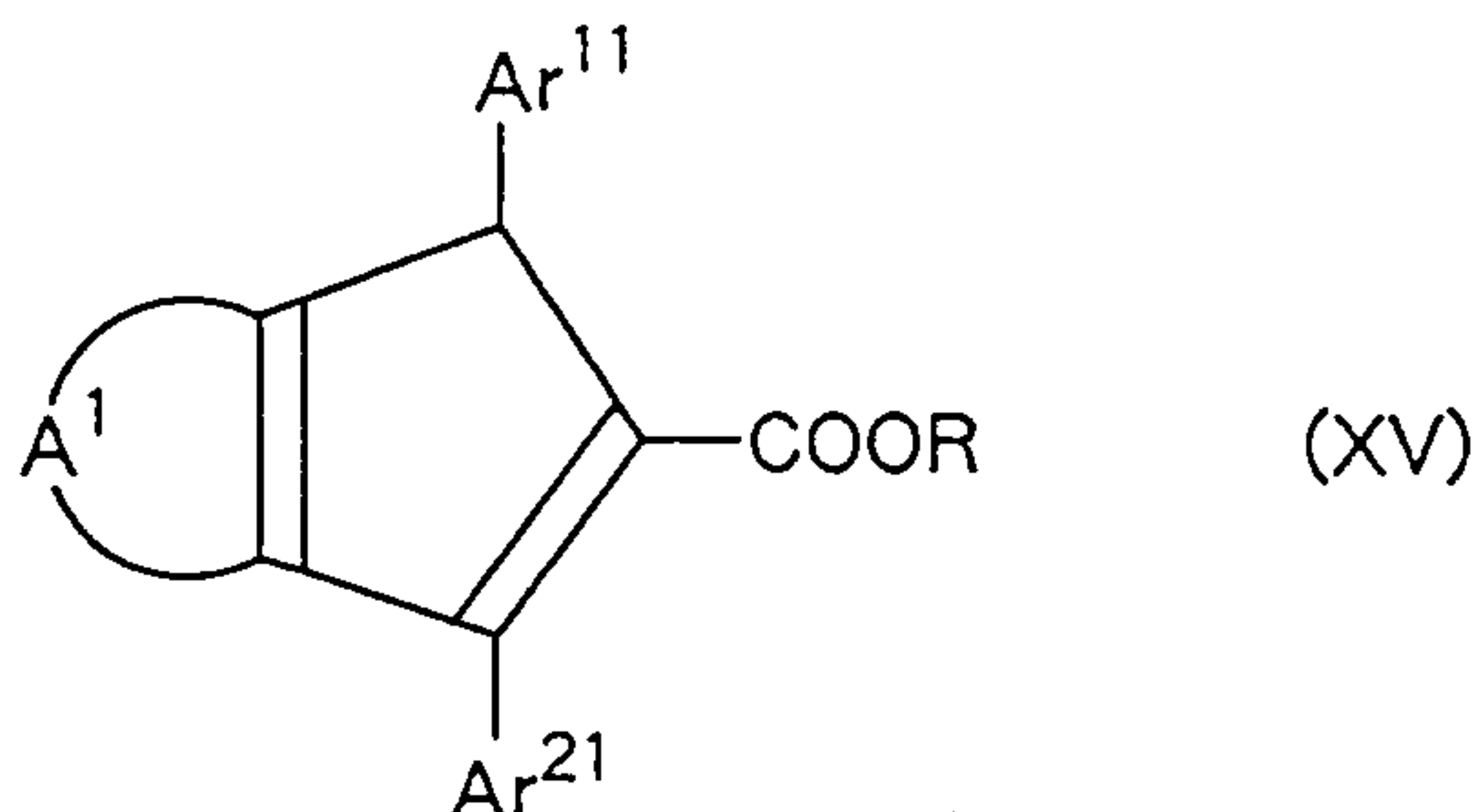


wherein Ar^{11} , Ar^{21} , A^1 and R are as defined before.

Hydrolysis of an ester group(s) of Compound (XIV)
 15 using an inorganic base such as NaOH or KOH or an acid
 such as HCl or TFA in an aqueous solvent such as
 methanol, ethanol, dioxane or acetonitrile, as the case
 is required, combined with the following procedures: i)
 appropriate conversion(s) of a synthetic equivalent(s)
 20 to a desired group(s), ii) deprotection of a protective
 group(s), affords compounds of the present invention
 which have a hydroxy group as R^1 in Formula (I).

Reduction of Compound (XIV) with a reductant such as
 triethylsilane in the presence of a Lewis acid such as
 25 boron trifluoride etherate or metal powder such as zinc
 and iron in the presence of acetic acid or HCl etc.; or
 hydrolysis of an ester group(s) of Compound (XIV)

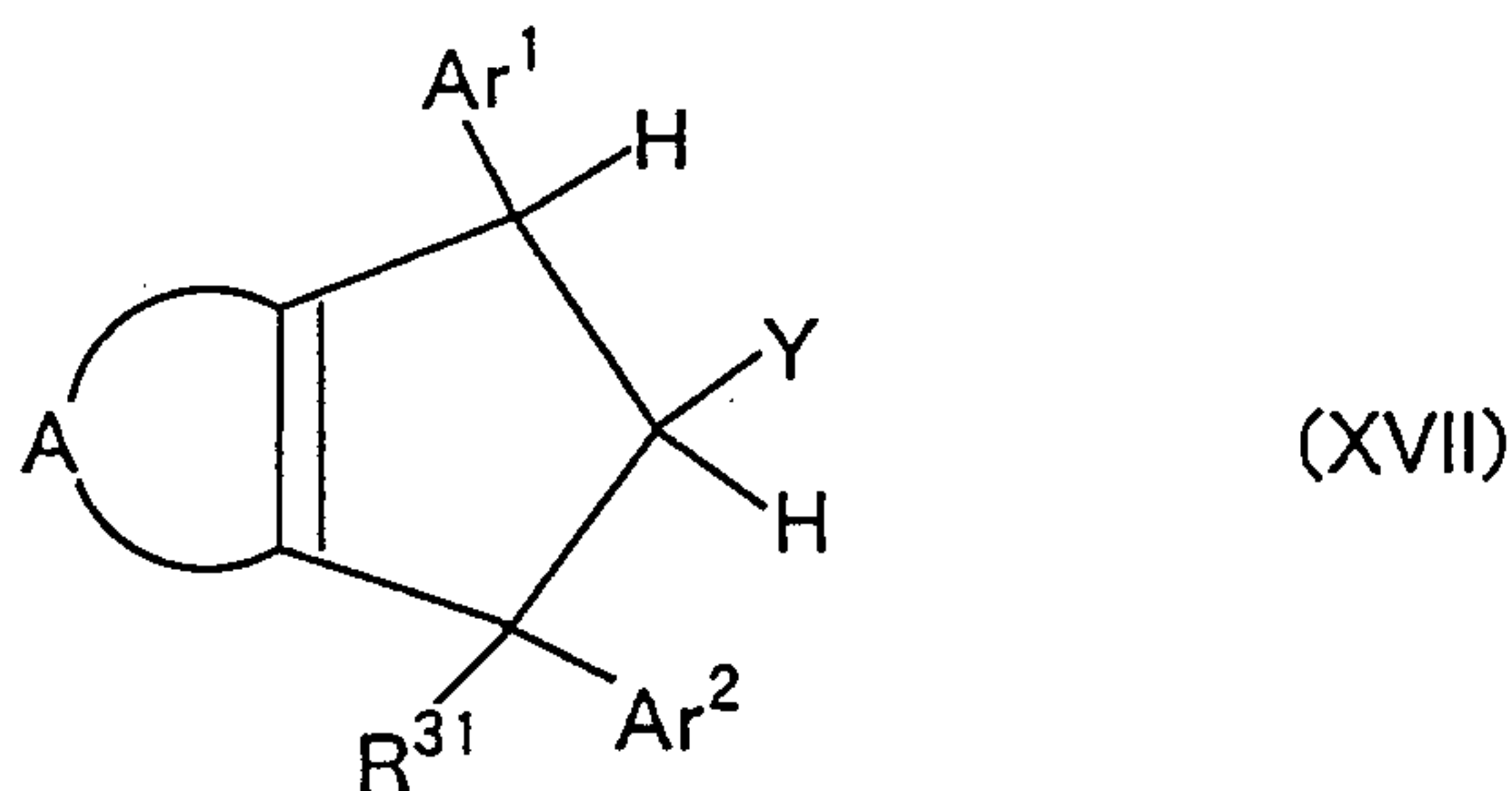
followed by reduction of a hydroxyl group and re-esterification of a carboxyl group affords an α, β -unsaturated ester of Formula (XV):



10 wherein Ar^{11} , Ar^{21} , A^1 and R are as defined before. Conjugate addition of an organometallic reagent of Formula (XVI):



15 wherein R^{31} is a C_1 - C_6 alkyl group, and Met is as defined before, to Compound (XV), followed by appropriate conversion(s) of a synthetic equivalent(s) to a desired group(s) and/or deprotection of a protective group(s), hydrolysis of an ester group(s), as
20 the case is required, affords compounds of the present invention which are shown in Formula (XVII):

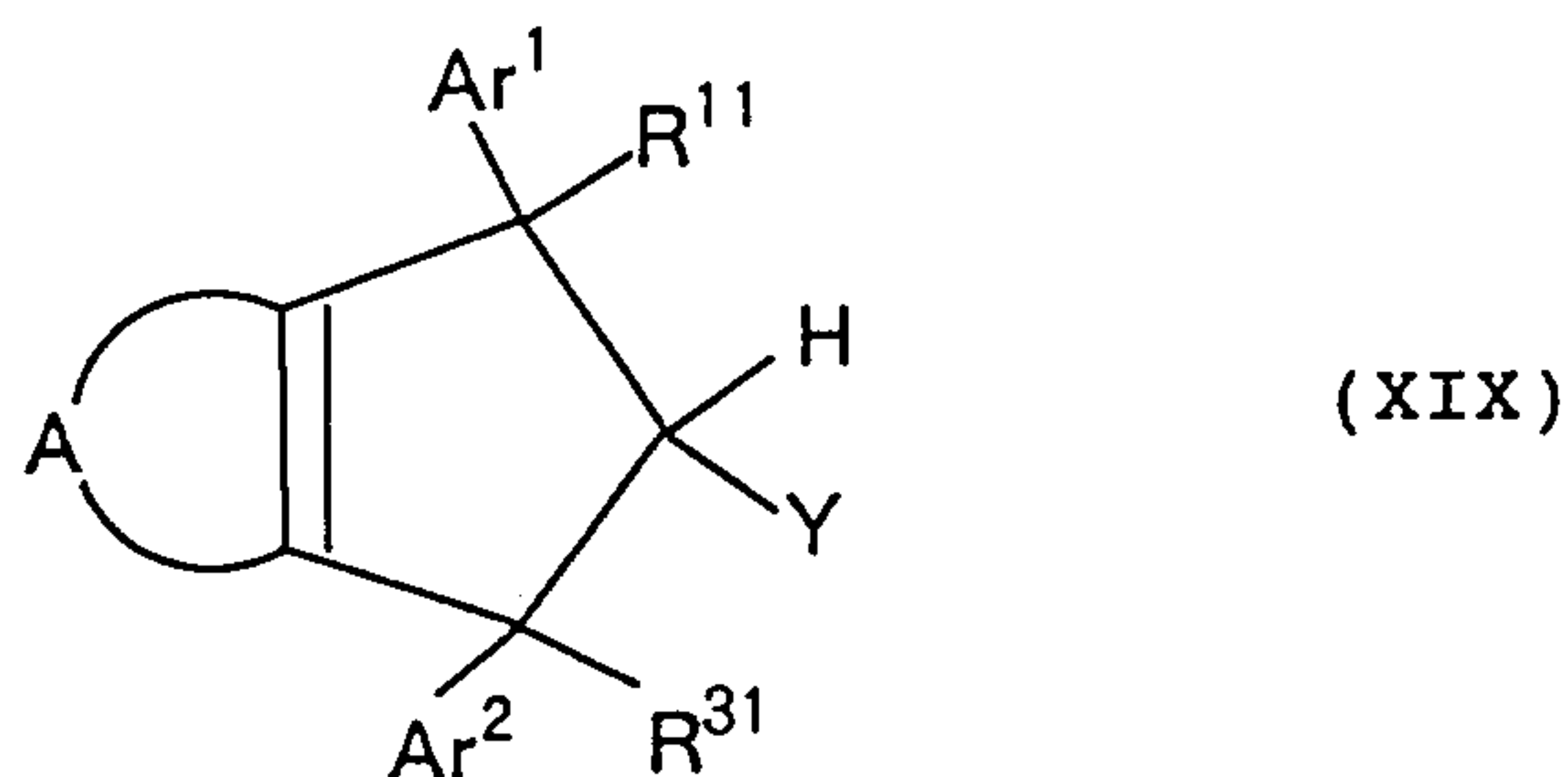


wherein Ar^1 , Ar^2 , A , R^{31} and Y are as defined before.

Re-introduction of a double bond into an ester ,
 which was obtained by reacting Compounds (XV) with
 10 Compounds (XVI), by appropriate methods such as DDQ
 oxidation or bromination - dehydrobromination followed
 by conjugate addition of another organometallic reagent
 of Formula (XVIII):

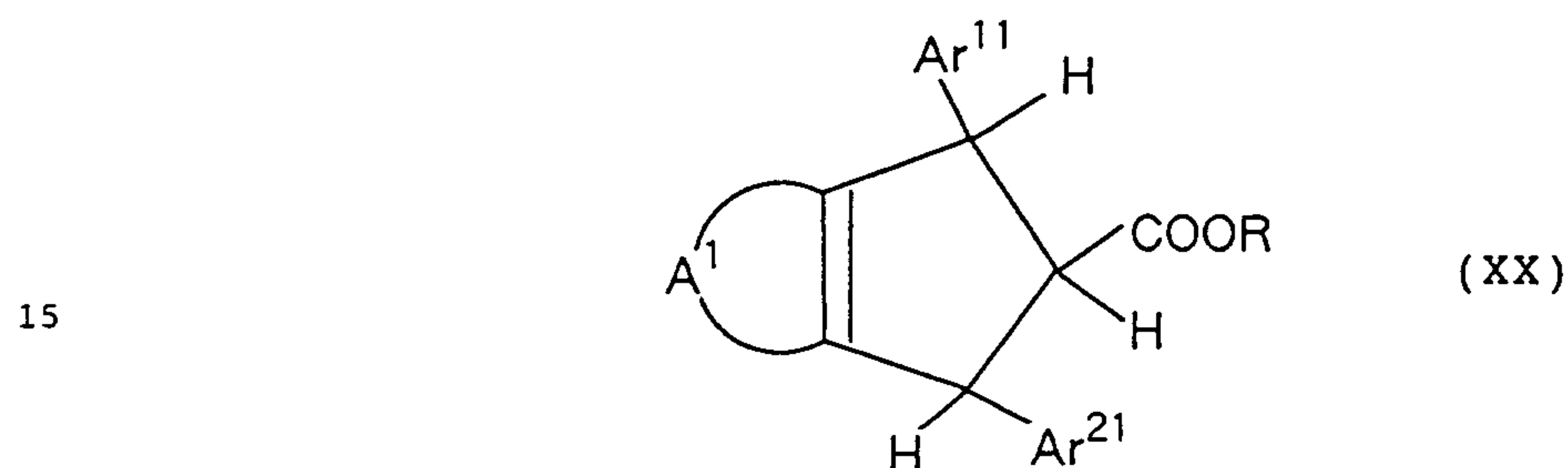


15 wherein R^{11} is a C_1 - C_6 alkyl group, and Met is as
 defined before, and subsequent appropriate conversion
 affords compounds of the present invention of Formula
 (XIX):

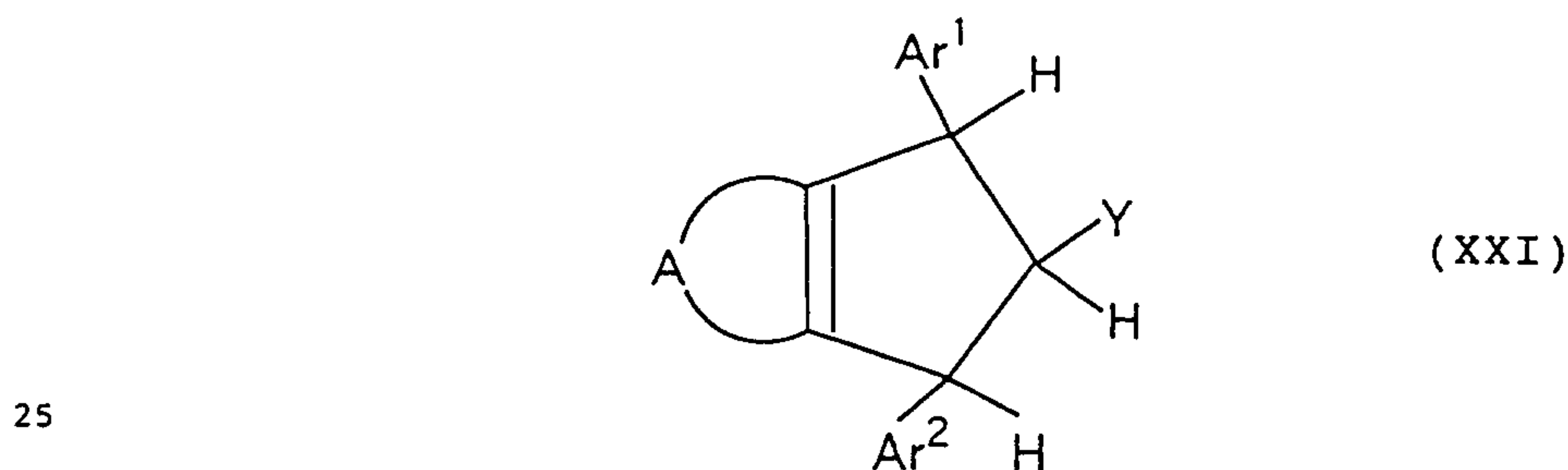


20
 25 wherein Ar^1 , Ar^2 , A , R^{11} , R^{31} and Y are as defined
 before.

Hydrogenation of Compound (XIV) with hydrogen gas under pressure at approximately 1-5 kg/cm² at room temperature to 50°C in the presence of a suitable acid such as acetic acid, conc-H₂SO₄ or perchloric acid using
 5 a suitable catalyst such as palladium on charcoal, or reduction of Compound(XIV) with metal such as zinc powder and iron powder and acid such as acetic acid and HCl at - 78°C to room temperature in a mixture of
 10 etheric solvent of etheric solvent such as THF, ether, dioxane and alcoholic solvent such as methanol, ethanol, tert - butanol affords compounds of Formula (XX):



wherein Ar¹¹, Ar²¹, A¹ and R are as defined before, which are converted to compounds of the present
 20 invention of Formula (XXI):



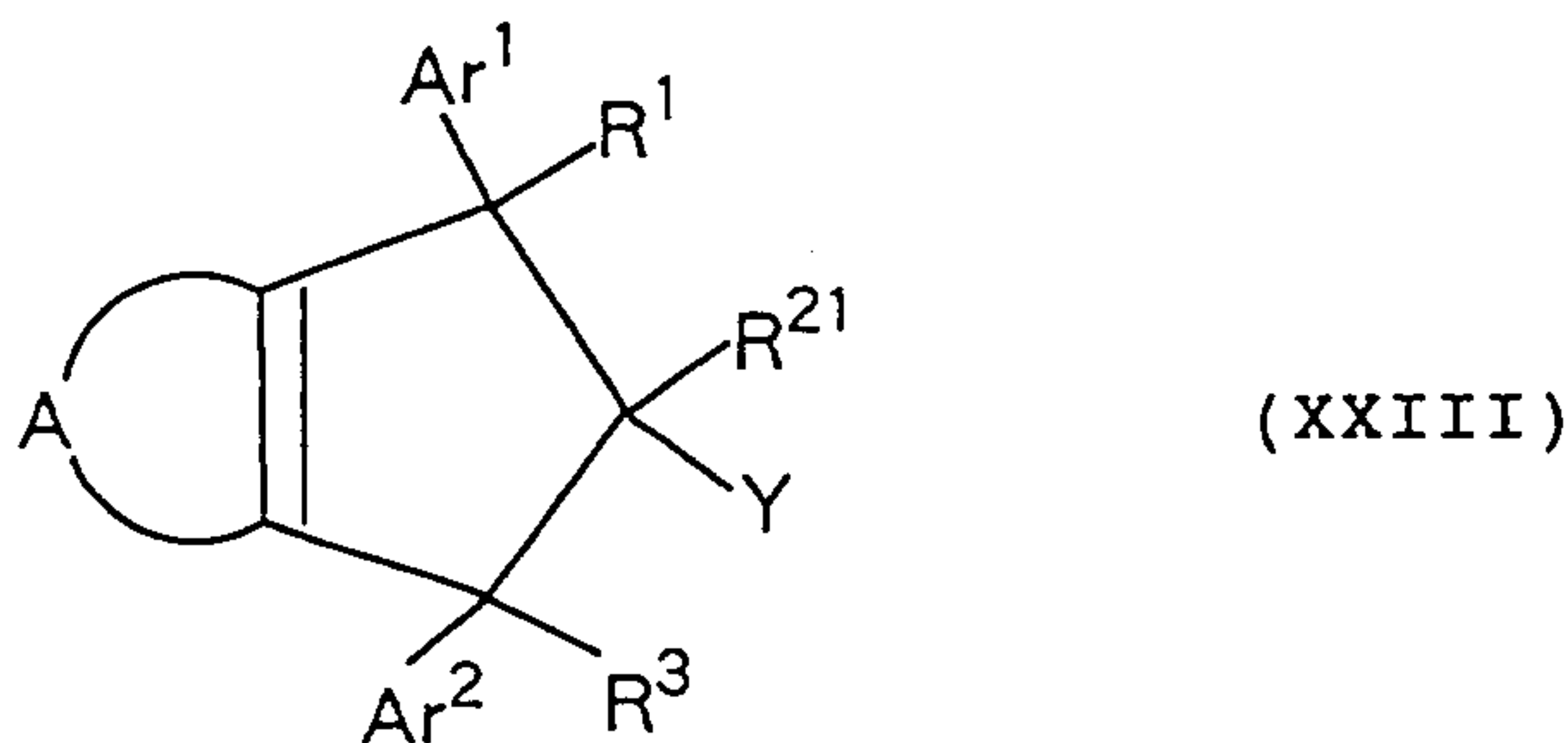
wherein Ar¹, Ar², A and Y are as defined before, by

appropriate reaction(s) such as hydrolysis of an ester group(s), conversion of a synthetic equivalent(s) to a desired functional group(s), or deprotection of a protective group(s).

5 Treatment of Compounds (XVII), (XIX) and their synthetic precursors, or Compound (XX) with a compound of Formula (XXII):



10 wherein R^{21} is a C_1-C_6 alkyl group and X is a leaving group, in the presence of a base such as BuLi, LDA or NaH in a suitable solvent such as THF, Et_2O , DMF or DMSO at $-100^\circ C$ to $100^\circ C$ followed by appropriate conversion(s) affords compounds of the present invention
15 of Formula (XXIII):



20 wherein Ar^1 , Ar^2 , A, R^1 , R^{21} , R^3 and Y are as defined before.

4) Treatment of Compound (V) with a sulfonic acid
25 anhydride such as trifluoromethanesulfonic acid anhydride in the presence of a strong base such as BuLi or LDA, an organic base such as TEA, or a metal hydride

such as NaH, in a suitable solvent such as THF, Et₂O, dimethoxyethane, DMF or DMSO at -78 °C to room temperature affords the corresponding sulfonyloxy-cyclopentadiene derivatives, which was allowed to react
 5 with an organometallic reagent of Formula (XXIV):

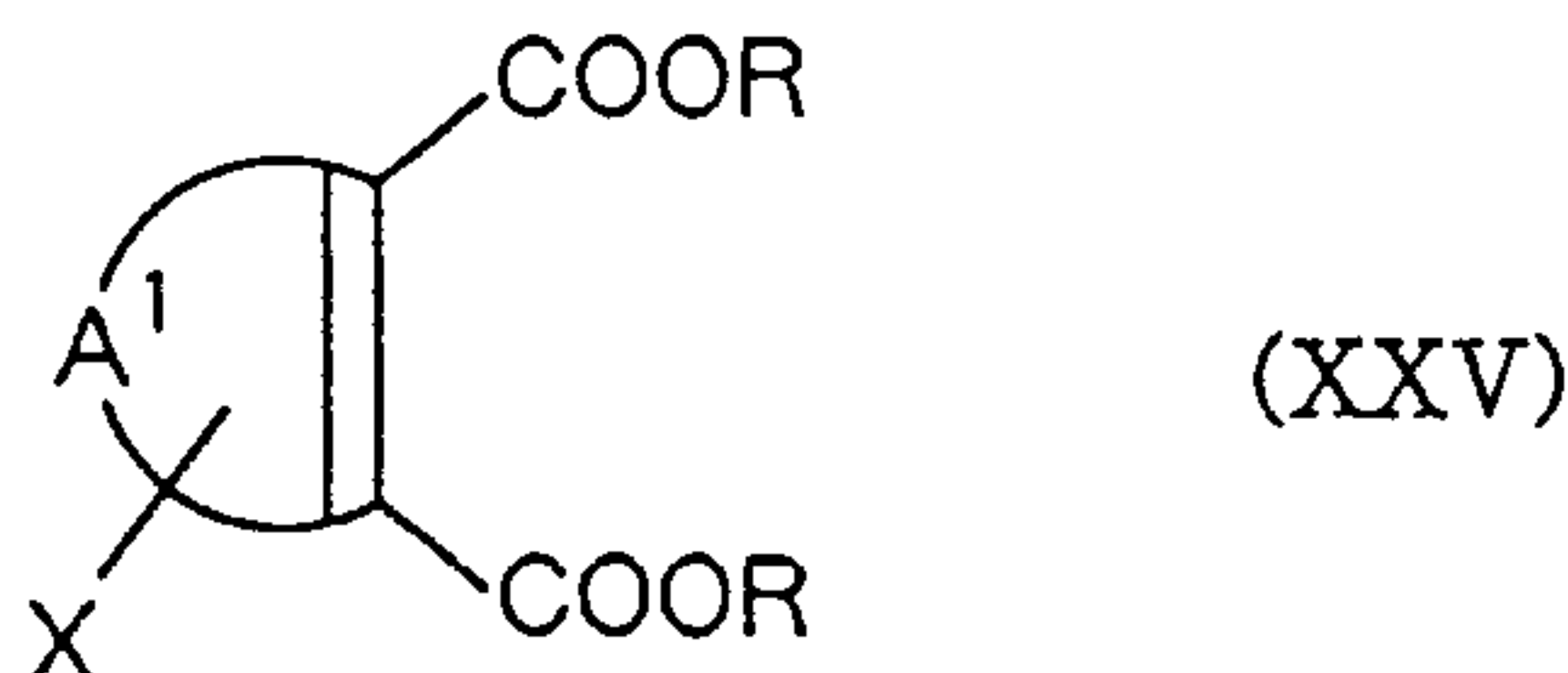


wherein Ar¹¹ and Met are as defined before, followed by an appropriate conversion(s) to give compounds of the
 10 present invention of Formula (XXI).

5) Among the compounds of the present invention the compounds, which have an above - defined substituent(s) on the heteroaromatic ring formed by combination of A and the adjacent carbon - carbon double bond, are
 15 prepared by the above - described methods 1) to 4) using a raw material(s) of Formula(II), (VII) or (X) having corresponding substituent(s) on the heteroaromatic ring .

They are also prepared by the following methods.

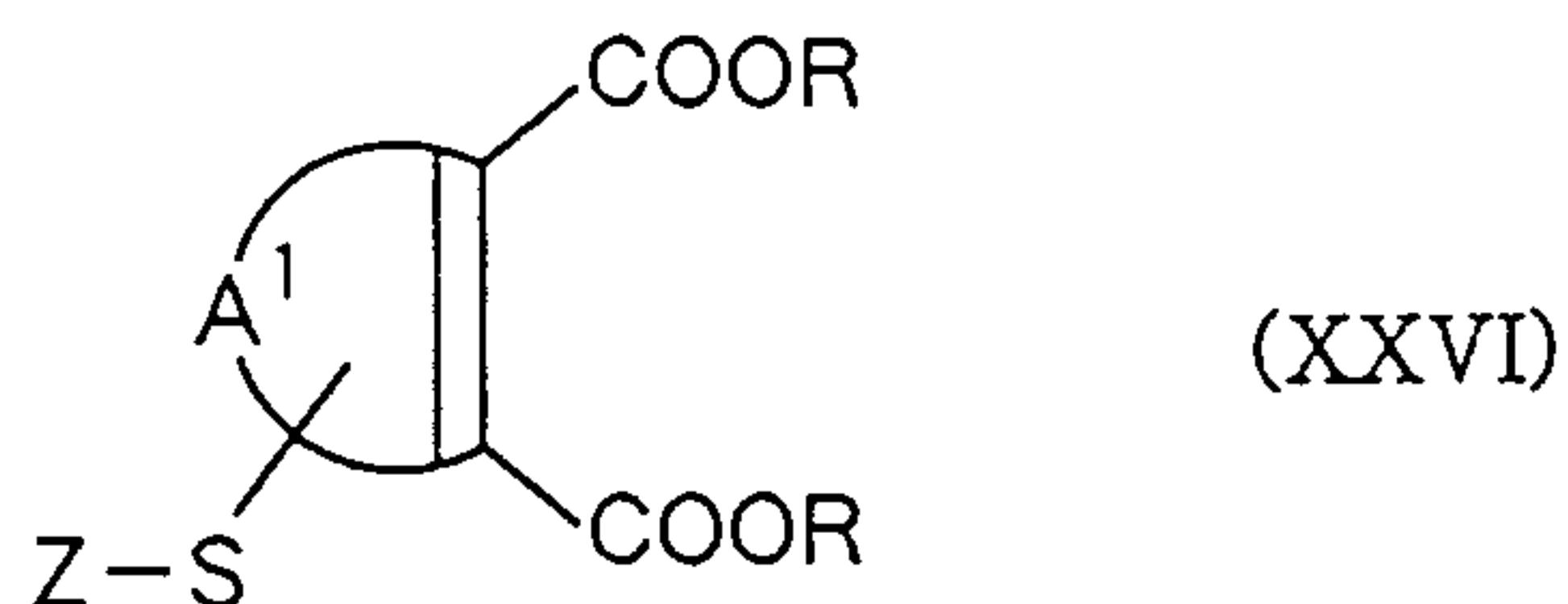
20 Treatment of the compounds of Formula(XXV):



25

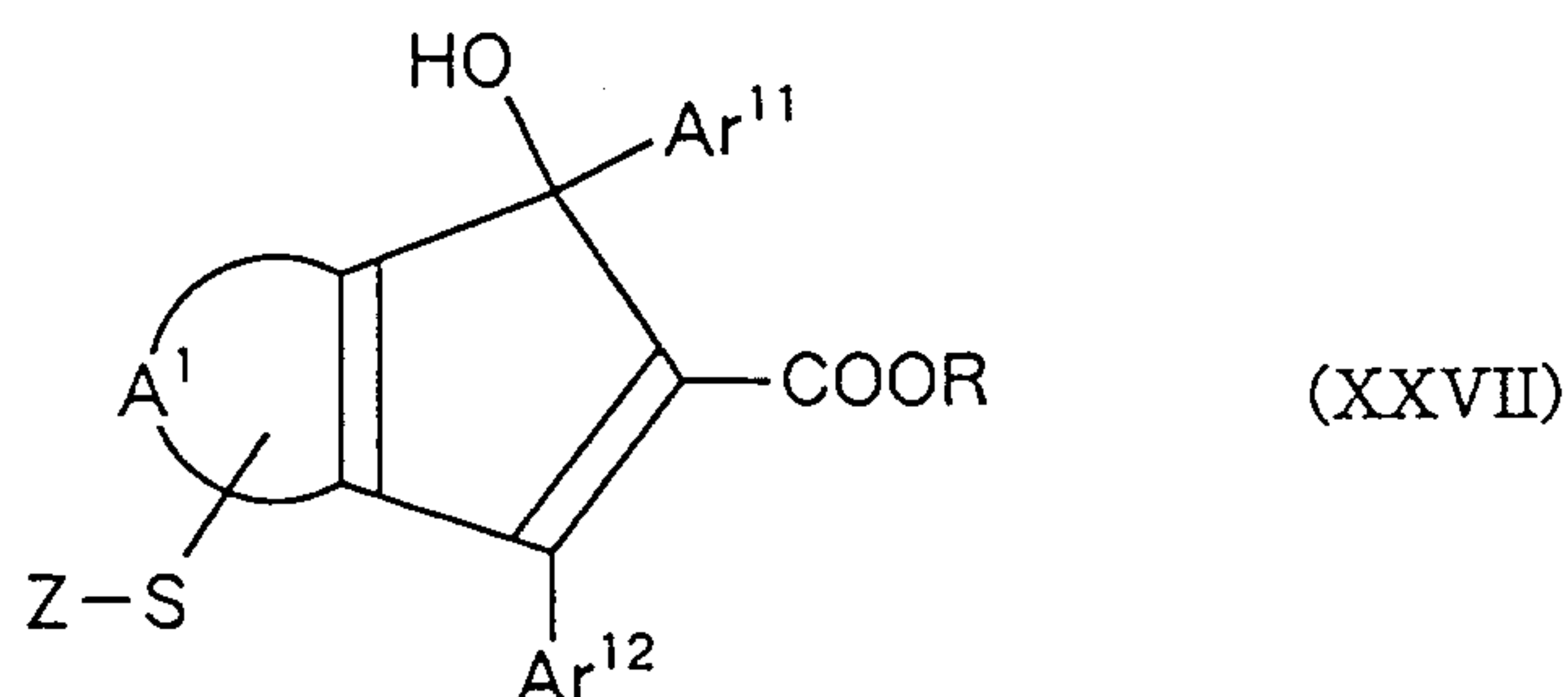
wherein X is a leaving group and A¹ and R are as defined

before, with an arylmercaptide such as an alkylmercaptide or a phenylmercaptide under an inert gas such as nitrogen or argon in an inert solvent such as methanol, THF, ether, benzene, toluene to give the sulfide compounds of Formula(XXVI):



wherein Z is a C₁ - C₆ alkyl group or an aryl group and A¹ and R are as defined before.

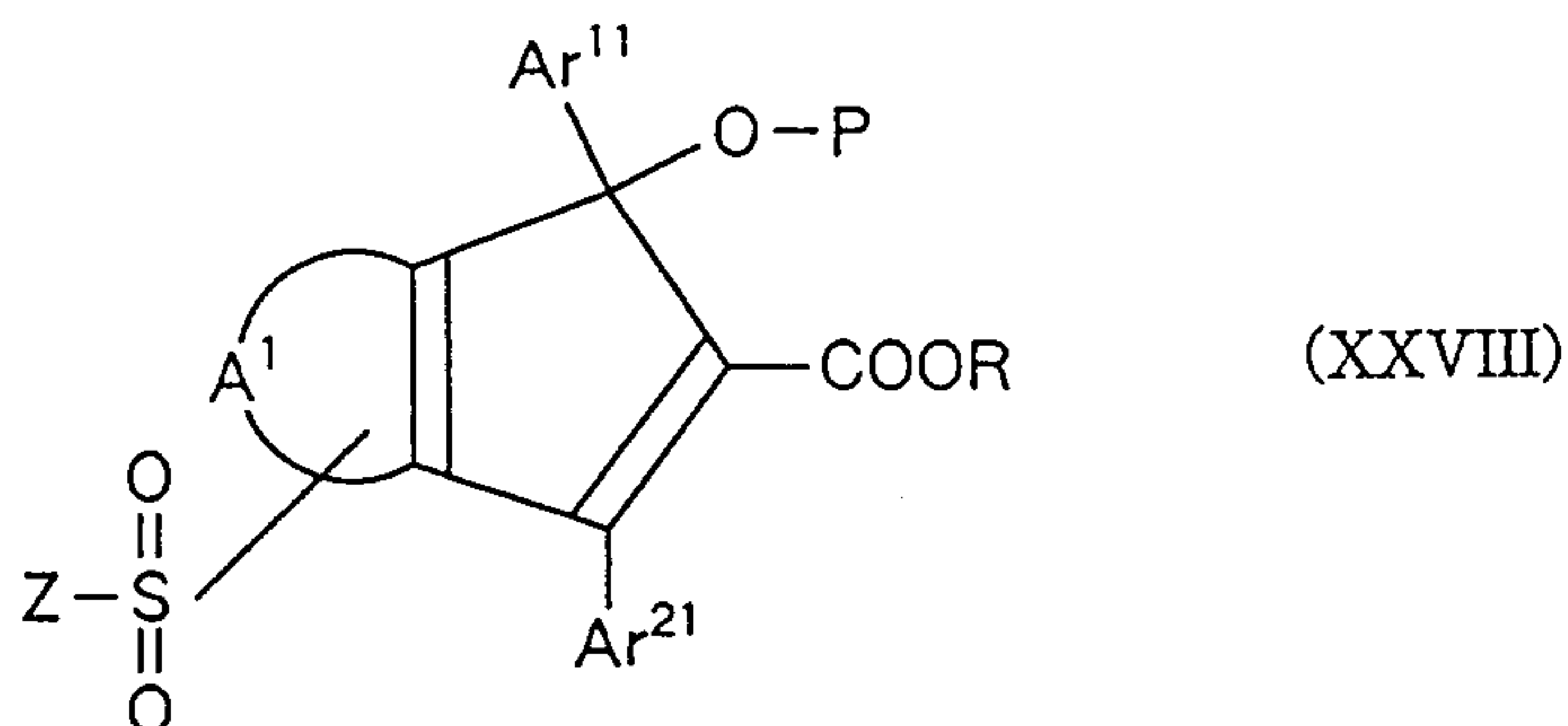
The diester compounds(XXVI) are converted to the anhydride compounds(X), followed by conversion by the above - described methods to give the alcohol compounds of Formula(XXVII):



wherein A¹, Ar¹¹, Ar¹², R and Z are as defined before.

A hydroxyl group of the alcohol compounds(XXVII) is protected by an appropriate protective group such as trimethylsilylethoxymethyl group, followed by oxidation

of a sulfur atom bonded to the heteroaromatic ring with an appropriate oxidant such mCPBA as to give the sulfonyl compounds of Formula(XXVIII):



10 wherein P is a protective group, and A¹, Ar¹¹, Ar²¹, R and Z as defined before.

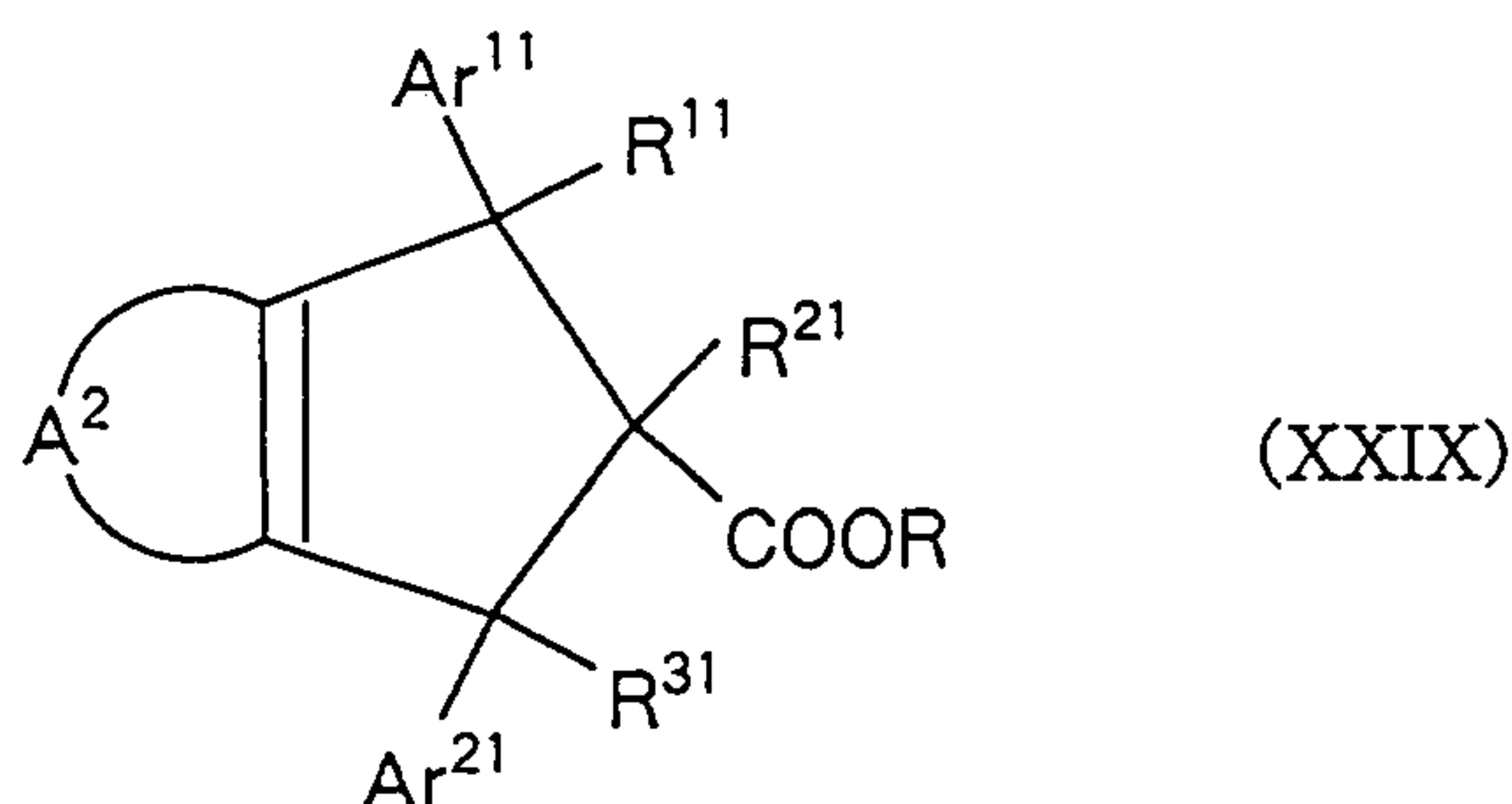
Treatment of the compounds(XXVIII) with a nucleophilic reagent such as an organolithium reagent, lithium amide, a mercaptide or an alkoxide at - 110°C to room
 15 temperature in an inert solvent such as THF or ether to replace the sulfonyl group on the heteroaromatic ring with a nucleophilic group, followed by the above - mentioned method(s) to give the compounds of the present invention.

20 6) Among the compounds of the present invention presented by Formula(I) the compounds, which have an amino group, a mono - or di - C₁ - C₆ alkylamino group which may be substituted by a hydroxyl group at the alkyl moiety, a C₃ - C₈ cycloalkylamino group which may
 25 be substituted by a hydroxyl group at the alkyl or alkylene moiety, a C₃ - C₈ cycloalkyl C₁ - C₆ alkylamino group which may be substituted by a hydroxyl group at

the alkyl or alkylene moiety, an N - (C₁ - C₆ alkyl) - N - (C₃ - C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group at the alkyl or alkylene moiety, an N - (C₁ - C₆ alkyl) - N - (aroyl)amino group which may be substituted by a hydroxyl group at the alkylene moiety or a C₄ - C₇ cyclic imino group which may be substituted by a hydroxyl group at the alkylene moiety on the heteroaromatic ring formed by combination of A and the adjacent double bond containing at least one nitrogen atom, can be prepared by the above - described methods 1) to 5).

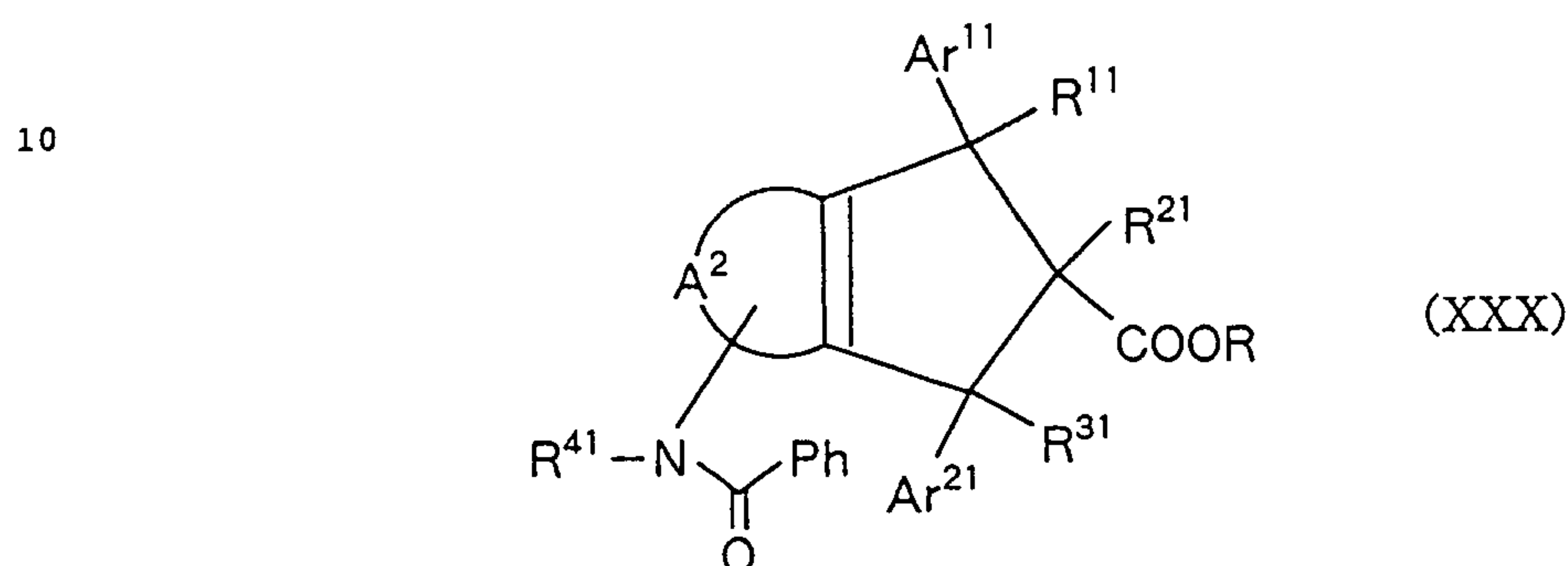
They can also be prepared by the following method.

The compounds of Formula:



wherein A² is A or its synthetic equivalents, the heteroaromatic ring which is formed by combination of A² and the adjacent double bond has at least one nitrogen atom and Ar¹¹, Ar²¹, R¹¹, R²¹, R³¹ and R are as defined before, are treated with an oxidizing agent such as m - chloroperbenzoic acid or sodium periodate at - 40°C to room temperature in a solvent such as dichloromethane or chloroform to give the corresponding heteroaromatic ring

N - oxide and the N - oxides were reacted at room temperature to boiling point of the solvent in a solvent such as methylene chloride, chloroform, 1,2 - dichloroethane, DMF with an imidoyl halide prepared by
 5 treating an N - benzoyl derivative of a primary amine with thionyl chloride or phosphorus pentachloride without solvent or in an inert solvent such as benzene or toluene to give the compounds of Formula(XXX):



15 wherein R^{41} is a $C^1 - C^6$ alkyl group which may be substituted by a protected hydroxyl group, A^2 , Ar^{11} , Ar^{21} , R^{11} , R^{21} , R^{31} and R are as defined before, when primary amines, raw materials of the imidoyl halide, have a hydroxyl group as a substituent, it is preferable
 20 to protect the hydroxyl group with an appropriate protective group such as an acetyl group, a benzyl group or a benzoyl group. The imidoyl halide can be preferably reacted with the N - oxide in 5 to 30 equimolecular amounts to the N - oxide in the presence of 10 to 50
 25 equimolecular amounts of inorganic base such as sodium hydrogencarbonate or cesium fluoride. Treatment of the compounds(XXX) with a base such as sodium hydroxide in a

solvent such as methanol, 1,4 - dioxane to remove the N - benzoyl group, followed by deprotection of the hydroxyl group at R⁴¹, intramolecular or intermolecular nucleophilic substitution reaction, intramolecular or intermolecular reductive alkylation of the NH group, aroylation of the NH group or above - described reactions give the compounds of the present invention represented by Formula(I). The nucleophilic substitution reaction can be preferably carried out by reacting with an alkyl halide such as an alkylbromide or an alkyl iodide using a bulky strong base such as lithium hexamethylene disilazide, LDA at - 78 °C to room temperature in a solvent such as THF or ether. The intramolecular substitution reaction can be carried out by converting a desired hydroxyl group to the leaving group such as a halide, followed by the above - described nucleophilic substitution reaction. The reductive alkylation can be carried out by reacting with formalin or acetaldehyde etc. in the presence of reducing agent such as formic acid or sodium cyanoborohydride, preferably at - 20°C to boiling point of the solvent. The intramolecular reductive alkylation can be carried out by oxidizing a desired hydroxyl group to the aldehyde, followed by subjecting to the same reaction as the above - described intermolecular reaction.

With appropriate manipulation and protection of any

chemical functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

5 All reaction intermediates and products so far described can be purified by well-known methods such as recrystallization, reprecipitation, partition procedures, normal- or reverse-phase chromatography and ion-exchange chromatography.

10 Now, the endothelin antagonistic properties of the heteroaromatic ring-fused cyclopentene derivatives of the present invention will be described.

Endothelin binding inhibition test to ET_A receptor

The smooth muscle tissue of porcine aorta was
15 homogenized in a buffer solution of 10 mM MOPS, pH 7.4, at 4 °C by a polytron. To the homogenate, sucrose was added to a concentration of 20%, and the mixture was centrifuged at 1,000 x g for 15 minutes, and the supernatant was further centrifuged at 10,000 x g for 15
20 minutes. The supernatant thereof was further centrifuged at 90,000 x g for 40 minutes. The membrane precipitate thereby obtained was suspended in a buffer solution of 5 mM HEPES/Tris, pH 7.4, at a concentration of 25 mg/ml.

25 Then, 16 μ l of this membrane suspension was added to 340 μ l of 50 mM tris/HCl buffer, pH 7.4, containing 10 μ l calcium chloride, 10 μ M magnesium chloride, 0.1

mM PMSF, 1 μ M pepstatin A, 2 μ M leupeptin, 1 mM 1,10-phenanthroline and 0.1% bovine serum albumin. To this suspension, 4 μ l of (A) endothelin-1 (for nonspecific binding; 0.2 μ M as the final concentration), (B) buffer solution A (for total control binding), or (C) a test compound (1.1 μ M as the final concentration), was added. Further, to each suspension, 40 μ l of ^{125} I-endothelin-1 (12000-18000 cpm) was added. These mixtures were incubated at 25 °C for 4 hours, then subjected to filtration on a glass filter GF/C and then washed with 5 mM HEPES/Tris, pH 7.4, containing 0.3% bovine serum albumin. Then, the radioactivity trapped by the glass filter was measured, and the ^{125} I-endothelin-1 binding inhibition D (%) at 1.1 μ M of the test compound was determined by the following equation.

$$D(\%) = 100 - \frac{(C) - (A)}{(B) - (A)} \times 100$$

Each test was performed in triplicate.

Compound 2-enantiomer A, a representative compound of the present invention, was found to be very potent inhibitor of endothelin binding to ET_A (99% inhibition at 1.1 μ M).

Endothelin binding inhibition test to ET_B receptor

The cerebellum of porcine was homogenized in a buffer solution of 10 mM MOPS, pH 7.4, at 4 °C by a

polytron. To the homogenate, sucrose was added to a concentration of 20%, and the mixture was centrifuged at 1,000 x g for 15 minutes, and the supernatant was further centrifuged at 10,000 x g for 15 minutes. The supernatant thereof was further centrifuged at 90,000 x g for 40 minutes. The membrane precipitate thereby obtained was suspended in a buffer solution of 5 mM HEPES/Tris, pH 7.4, at a concentration of 3.3 mg/ml.

Then, 16 μ l of this membrane suspension was added to 340 μ l of 50 mM tris/HCl buffer, pH 7.4, containing 10 μ l calcium chloride, 10 μ M magnesium chloride, 0.1 mM PMSF, 1 μ M pepstatin A, 2 μ M leupeptin, 1 mM 1,10-phenanthroline and 0.1% bovine serum albumin. To this suspension, 4 μ l of (A) endothelin-1 (for nonspecific binding; 0.2 μ M as the final concentration), (B) buffer solution A (for total control binding), or (C) a test compound (1.1 μ M as the final concentration), was added. Further, to each suspension, 40 μ l of ^{125} I-endothelin-1 (12000-18000 cpm) was added. These mixtures were incubated at 25 °C for 4 hours, then subjected to filtration on a glass filter GF/C and then washed with 5 mM HEPES/Tris, pH 7.4, containing 0.3% bovine serum albumin. Then, the radioactivity trapped by the glass filter was measured, and the ^{125} I-endothelin-1 binding inhibition D (%) at 1.1 μ M of the test compound was determined by the following equation.

$$D(\%) = 100 - \frac{(C) - (A)}{(B) - (A)} \times 100$$

Each test was performed in triplicate.

5 Compound 2-enantiomer A, a representative compound of the present invention, was found to be very potent inhibitor of endothelin binding to ET_B (80% inhibition at 1.1 μM).

10 Activities against endothelin-induced contraction of isolated porcine coronary arteries

 The coronary artery of pig was extracted, and a spiral preparation having a width of 1 mm and a length of 10 mm was prepared therefrom. The preparation having the endothelial cells denuded, was hanged in a 5 ml
15 organ bath filled with a Krebs-Heneseleit solution saturated with a gas mixture of 95% O₂ and 5% CO₂, and a change in the tension was isometrically measured and recorded.

 Endothelin-1 was added into the organ bath in a
20 cumulatively increasing manner, whereby the influence of a compound of the present invention to the concentration-response curve for endothelin-1 was examined. The compound was added into the organ bath 20 minutes prior to the addition of endothelin-1.

25 Compound 2 (10 μM), a representative compound of the present invention, remarkably shifted the concentration-response curves of endothelin-1 to the right and

did not affect the maximum response. Further, the compound showed no effects to the isolated coronary artery when applied alone. As is evident from the above, the compound showed remarkable antagonistic activities against endothelin-induced concentration of isolated porcine coronary artery.

Endothelin binding inhibition test to human ET receptor

The human neuroblastoma SK-N-MC cells or the human Girardi heart cells purchased from Dainippon Seiyaku (Japan) were cultured in minimal essential medium supplemented with fetal calf serum. The cells were collected and homogenized in 10 mM MOPS buffer (pH 7.4) containing 154 mM NaCl, 10 mM KCl, 0.8 mM CaCl₂ and 20% sucrose at 4 °C using a polytron homogenizer. The homogenate was then centrifuged at 1,000×g for 15 minutes. The supernatant was centrifuged at 100,000×g for 1 hour at 4 °C. Then the pellet was washed with 5 mM Hepes/Tris buffer (pH 7.4). The resulting membranes were incubated with [¹²⁵I]endothelin-1 in the presence of each test compound or vehicle (1% dimethyl sulfoxide) in 50 mM Tris/HCl buffer (pH 7.4) containing 0.1 mM phenylmethanesulfonyl fluoride, 1 μM pepstatin, 2 μM leupeptin, 1 mM 1,10-phenanthroline, 1 mM EDTA, 10 μM CaCl₂, 10 μM MgCl₂ and 0.1% BSA in a total volume of 0.4 ml. After 4 hours incubation, cold 5 mM Hepes/Tris buffer (pH 7.4) containing 0.3% BSA (Buffer A) was added to the mixture. Free and bound [¹²⁵I]endothelin-1 were

separated by filtration using Whatman GF/C glass fiber filters. After the filtration, the filters were washed with buffer A, and the radioactivity on the filters was measured in a γ counter. Nonspecific binding was determined in the presence of 200 nM endothelin-1. Percent (%) inhibition of [^{125} I]ET-1 specific binding by 1.1 μ M of the test compound was determined.

Compound 2-enantiomer A, a representative compound of the present invention, was found to be very potent inhibitor of endothelin binding to ET_A (99% inhibition) and ET_B (80% inhibition) receptors, respectively.

Activities against endothelin-induced contraction of isolated rabbit iliac arteries

The iliac artery of rabbit was isolated, and a spiral preparation having a width of 1 mm and a length of 10 mm was prepared therefrom. The preparation having the endothelial cells denuded, was placed in a 5 ml organ bath filled with a Krebs-Henseleit solution saturated with a gas mixture of 95% O₂ and 5% CO₂, and a change in the tension was isometrically measured and recorded.

Endothelin-1 was added into the organ bath in a cumulatively increasing manner, whereby the influence of a compound of the present invention to the concentration-response curve for endothelin-1 was examined. The compound was added into the organ bath 20 minutes prior to the addition of endothelin-1.

Compound 2 (0.1 to 10 μ M) remarkably shifted the concentration-response curves of endothelin-1 to the right and did not affect the maximum response. Further, the compound showed no effects to the isolated iliac artery when applied alone. As is evident from the above, the compound showed remarkable antagonistic activities against endothelin-induced contraction of isolated rabbit iliac artery.

Plasma concentrations after oral dosing in rats

10 Male SD strain rats (8 weeks, n=3) with a cervical artery cannula were used in this experiment under a fasted condition. Compound 2, which is a representative of the invention, was suspended in 0.5% methylcellulose and administered orally in the stomach with a gavage at
15 a dose of 10 mg/kg. The blood (120 μ l) was drained from the cannula just before dosing, and 1 and 8 h after dosing. The plasma was separated by centrifugation (6000 rpm, 10 min, at 4 °C), and a portion (10 μ l) was mixed with 40 μ l of ethanol and the mixture was
20 centrifugated (10000 rpm, 10 min, at 4 °C) to obtain supernatant. The supernatant (40 μ l) was mixed with an equivalent volume of 0.2% trifluoroacetic acid (TFA), and the mixture was subjected to an HPLC assay to determine concentration of Compound 2-enantiomer A which
25 is the active species.

Analytical conditions

analytical column: Chiralcel OD-R (Daicel

Chemical, ϕ 4.6 mm $\times$ 250 mm)

mobile phase: 0.1% TFA-water/

0.1% TFA-acetonitrile=75:25

flow rate: 1.0 ml/min

5 oven temperature: 40 °C

injection volume: 50 μ l

detection: absorbance at 276 nm

Plasma concentrations of enantiomer A, the active
10 species, were 8.77 ± 3.52 μ g/ml and 2.11 ± 0.37 μ g/ml at
1 and 8 h, respectively, after oral dosing of Compound
2.

Consequently, the compounds of the present invention
were found to be highly orally absorbable and long
15 lasting in the plasma.

Thus, the compounds of the present invention have
excellent endothelin antagonistic activities and are
useful as vasodilators or bronchodilators in the field
of medicines, and they can be drugs for treating
20 hypertension, pulmonary hypertension, Raynaud's disease,
acute renal failure, myocardial infarction, angina
pectoris, cerebral infarction, cerebral vasospasm,
arteriosclerosis, asthma, gastric ulcer, diabetes,
restenosis, prostatauxe, endotoxin shock endo-
25 toxin-induced multiple organ failure or disseminated
intravascular coagulation, and/or cyclosporin-induced
renal failure or hypertension. When used as drugs for

treating such diseases, the compounds of the present invention can be used alone or in combination with other drugs for treatment.

The compounds of the present invention may be used
5 in the form of drug formulations suitable for parenteral administration, oral administration or external administration by mixing them with solid or liquid excipient carriers known in this field. The drug formulations include a liquid formulation such as an
10 injection formulation, an inhalant formulation, a syrup formulation or an emulsion, a solid formulation such as tablets, capsules or granules, and an external drug such as an ointment or a suppository. Further, these drug formulations may contain additives which are commonly
15 employed, such as an adjuvant, a stabilizer, a wetting agent, an emulsifier, an absorption-promoting agent or a surfactant, as the case requires. As the additives, distilled water for injection, physiological saline, Ringer's solution, glucose, sugar syrup, gelatin,
20 vegetable oil, cacao butter, ethylene glycol, hydroxypropyl cellulose, lactose, sucrose, corn starch, magnesium stearate and talc may be mentioned.

The dose of a compound of the present invention as an endothelin antagonist varies depending upon the
25 manner of administration, the age and body weight of the patient and the condition of the patient to be treated. However, a typical administration method for an adult is

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oral administration or parenteral administration. The daily dose in the case of oral administration to an adult patient is from 0.1 to 100 mg/kg body weight, and the daily dose in the case of parenteral administration is from 0.01 to 10 mg/kg body weight.

The following Examples illustrate the present invention more specifically. It should be understood that the present invention is not limited to these examples alone.

10 Example 1

6-Ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine
(Compound 1)

(1) 2-(4-Methoxyphenylcarbonyl)-3-pyridine carboxylic acid

To a THF (15 ml) solution of pyridine-2,3-dicarboxylic acid anhydride (1.0 g, 6.7 mmol) was added dropwise a THF solution of 4-methoxyphenylmagnesium bromide (0.89M, 8.0 ml, 7.1 mmol) at -78 °C. The reaction mixture was stirred at the same temperature for 1 h and then a saturated aqueous solution of NH₄Cl (20 ml) was added to quench the reaction. The reaction mixture was diluted with 1N HCl and extracted with AcOEt. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (E. Merck, Kieselgel* 60/chloroform:methanol=10:1) to

*Trade-mark

give 2-(4-methoxyphenylcarbonyl)-3-pyridine carboxylic acid (479 mg) as a colorless solid.

(2) 2-(4-Methoxyphenylcarbonyl)-3-pyridylcarbonylmalonic acid diethyl ester

5 A mixture of 2-(4-methoxyphenylcarbonyl)-3-pyridine carboxylic acid (475 mg, 1.85 mmol) and thionyl chloride (11.0 ml) was stirred at 90 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in anhydrous THF. This solution
10 was concentrated under reduced pressure and the residue was dried in vacuo. The resulting residue was dissolved in a mixed solvent of anhydrous THF (6.0 ml) and anhydrous Et₂O (1.0 ml). To the solution was added diethyl magnesiummalonate (2.0M ether solution, 1.0 ml)
15 which was prepared according to a method described in a literature (J. Am. Chem. Soc., 1946, 68, 1386-1388) and the mixture was stirred at 45 °C for 1.5 h. 1N HCl (10 ml) was added to quench the reaction. The mixture was diluted with water and extracted with AcOEt. The
20 organic layer was dried over MgSO₄, filtered, and concentrated to give 2-(4-methoxyphenyl-carbonyl)-3-pyridylcarbonylmalonic acid diethyl ester which was used in the next step without further purification.

25 (3) 6-Ethoxycarbonyl-5-oxo-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine

To 2-(4-methoxyphenylcarbonyl)-3-pyridylcarbonyl-

malonic acid diethyl ester which is prepared in (2) was added a 5% aqueous solution of Na_2CO_3 (10 ml) and the mixture was refluxed for 10 min. After cooling, the supernatant solution was removed by decantation. The aqueous solution was diluted with water and extracted with AcOEt. The residue was suspended in water and the suspension was refluxed. After cooling, the suspension was diluted with brine and extracted with AcOEt. Combined AcOEt layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (E. Merck, Kieselgel 60/hexane:

AcOEt=3:1 to 2:1 to 1:1) to give 6-ethoxycarbonyl-5-oxo-7-(4-methoxyphenyl)cyclopent-1,3-dieno-[2,1-b]pyridine (215 mg) as an orange oil.

(4) 6-Ethoxycarbonyl-5-hydroxy-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno-[2,1-b]pyridine

To a THF (5.0 ml) solution of 6-ethoxycarbonyl-5-oxo-7-(4-methoxyphenyl)cyclopent-1,3-dieno-[2,1-b]pyridine (208 mg, 0.67 mmol) was added dropwise 3,4-methylenedioxyphenylmagnesium bromide (1.08M THF solution, 0.8 ml, 0.86 mmol) under ice - cooling and the mixture was stirred at the same temperature for 30 min. To the mixture was added 1N HCl (10 ml) to quench the reaction. The mixture was extracted AcOEt and the organic layer was washed with brine, dried over MgSO_4 ,

filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (E. Merck, Kieselgel 60/hexane:AcOEt=2:1) to give
6-ethoxycarbonyl-5-hydroxy-5-(3,4-methylenedioxyphenyl)
- 7 - (4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyri-
dine (160 mg) as a yellow foam.

(5) 6-Ethoxycarbonyl-5-(3,4-methyl-enedioxyphenyl)-
7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

To a ethanol (4.0 ml) solution of 6-ethoxy-
carbonyl-5-hydroxy-5-(3,4-methylenedioxyphenyl)-7-(4-me-
thoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine (130 mg)
were added conc. H₂SO₄ (2 drops) and 10% Pd-C (60 mg).
The mixture was vigorously stirred at room temperature
under an atmospheric pressure of hydrogen. After the
reaction completed, the catalyst was removed by
Celite-filtration. Combined filtrate and washings were
washed with a saturated aqueous solution of NaHCO₃ and
brine, dried over Na₂SO₄, filtered and concentrated
under reduced pressure. The residue was purified by
preparative TLC (E. Merck, Kieselgel 60 F₂₅₄/hexane:
AcOEt=1:1) to give 6-ethoxycarbonyl-5-(3,4-methylene-
dioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]-
pyridine (23 mg) as a pale yellow oil.

FAB-MS(m/e): 418(M+H)⁺

¹H-NMR(300MHz, CDCl₃, δ ppm):

0.69(3H, t, J=7.2Hz), 3.46(2H, q, J=7.2Hz), 3.78(3H, s),
3.88(1H, t, J=7.6Hz), 4.70(1H, d, J=7.6Hz),

4.79 (1H, d, J=7.6Hz), 5.94 (1H, d, J=1.5Hz),
5.95 (1H, d, J=1.5Hz), 6.76-6.88 (5H, m),
7.17 (1H, dd, J=4.8Hz, 7.6Hz), 7.34 (2H, d, J=8.9Hz),
7.52 (1H, d, J=7.6Hz), 8.51 (1H, d, J=4.8Hz)

5 Rf Value: 0.45 (E. Merck, Kieselgel 60 F₂₅₄/
hexane:AcOEt=1:1)

Example 2

(5RS,6SR,7SR)-6-Carboxy-5-(3,4-methylenedioxy-
phenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine
10 (Compound 2)

To a methanol (1.0 ml) solution of 6-ethoxy-
carbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphe-
nyl)cyclopenteno[1,2-b]pyridine (20 mg, 0.048 mmol)
which was prepared in Example 1-(5) was added a 4N
15 aqueous solution of NaOH (0.2 ml) and the mixture was
stirred at room temperature for 18 h. The reaction
mixture was diluted with water, washed with Et₂O and
AcOEt, and acidified with 1N HCl. The acidic solution
was extracted with AcOEt. The organic layer was washed
20 with brine, dried over Na₂SO₄, filtered, and
concentrated under reduced pressure to give
(5RS,6SR,7SR) -6-carboxy-5-(3,4-methylenedioxyphenyl)
-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine (16 mg)
as a pale yellow solid.

25 mp: 230-233 °C(dec.)

FAB-MS(m/e): 390 (M+H)⁺

¹H-NMR (300MHz, DMSO-d₆, δ ppm):

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3.15(1H,t,J=10.1Hz),3.73(3H,s),
4.52(1H,d,J=10.1Hz),4.53(1H,d,J=10.1Hz),6.01(2H,s),
6.77(1H,dd,J=1.7Hz,7.7Hz),6.84-6.91(4H,m),
7.15-7.26(4H,m),8.33(1H,d,J=4.1Hz)

5 Rf Value: 0.22 (E. Merck, Kieselgel* 60 F₂₅₄/
chloroform:methanol=10:1)

Compound 2 is a 1:1 mixture of each enantiomer
(racemate). These enantiomers can be separated by
reverse phase HPLC using a chiral column (Daicel
10 Chemical Chiralcel* OD-R, ϕ 4.6mm $\times$ 250mm, flow rate: 1.0
ml/min, 0.1% TFA-water/0.1% TFA-acetonitrile=75/25,
column temperature: 40 °C).

Retention Time

Compound 2-enantiomer A: 9.8 min

15 Compound 2-enantiomer B: 12.1 min

Each Compound in the following Examples 3-18 was
prepared in the same manner as in Examples 1 and 2.

Example 3

20 6-Ethoxycarbonyl-5,7-diphenylcyclopenteno[1,2-b]-
pyridine

Example 4

(5RS,6SR,7SR)-6-Carboxy-5,7-diphenylcyclopenteno-
[1,2-b]pyridine

Example 5

25 6-Ethoxycarbonyl-5,7-di(4-methoxyphenyl)cyclo-
penteno[1,2-b]pyridine

Example 6

*Trade-mark

(5RS,6SR,7SR)-6-Carboxy-5,7-di(4-methoxyphenyl)-
cyclopenteno[1,2-b]pyridine

High Resolution FAB-MS(m/e, (C₂₃H₂₁O₄N+H)⁺):

Calcd: 376.1549

5 Found: 376.1536

¹H-NMR(300MHz, CDCl₃, δ ppm):

3.33(1H, dd, J=9.6Hz, 10.0Hz), 3.79(3H, s), 3.82(3H, s),
4.63(1H, d, J=9.6Hz), 4.71(1H, d, J=9.6Hz),
6.89(2H, d, J=8.8Hz), 6.90(2H, d, J=8.8Hz),
10 7.12(1H, dd, J=4.6Hz, 8.6Hz), 7.19(2H, d, J=8.8Hz),
7.20(2H, d, J=8.8Hz), 7.21-7.30(1H, m),
8.46(1H, dd, J=1.4Hz, 4.6Hz)

Rf Value: 0.29 (E. Merck, Kieselgel 60 F₂₅₄/
chloroform:methanol=10:1)

15 Example 7

6-Ethoxycarbonyl-5,7-di(3,4-methylenedioxyphenyl)-
cyclopenteno[1,2-b]pyridine

Example 8

(5RS,6SR,7SR)-6-Carboxy-5,7-di(3,4-methylenedioxy-
20 phenyl)cyclopenteno[1,2-b]pyridine

Example 9

6-Ethoxycarbonyl-7-(3,4-methylenedioxyphenyl)-5-(4
-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopen-
teno[1,2-b]pyridine

25 Example 10

(5RS,6SR,7SR)-6-Carboxy-7-(3,4-methylenedioxypheny
l)-5-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

mp: 195-205 °C

High Resolution FAB-MS(m/e, (C₂₃H₁₉NO₅+H)⁺):

Calcd: 390.1341

Found: 390.1338

5 ¹H-NMR(300MHz, CDCl₃, δ ppm):

3.30(1H, dd, J=9.8Hz, 10.1Hz), 3.82(3H, s),

4.61(1H, d, J=9.7Hz), 4.68(1H, d, J=10.1Hz), 5.92(2H, s),

6.68(1H, d, J=1.3Hz), 6.74(1H, dd, J=1.3Hz, 7.9Hz),

6.79(1H, d, J=7.9Hz), 6.90(2H, d, J=8.8Hz),

10 7.13(1H, dd, J=4.9Hz, 7.7Hz), 7.19(2H, d, J=8.8Hz),

7.28(1H, dd, J=1.6Hz, 7.7Hz), 8.48(1H, dd, J=1.6Hz, 4.9Hz)

Rf Value: 0.25 (E. Merck, Kieselgel 60 F₂₅₄/

chloroform:methanol=20:1)

Example 11

15 6-Ethoxycarbonyl-5-phenyl-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

Example 12

(5RS,6SR,7SR)-6-Carboxy-5-phenyl-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

20 High Resolution FAB-MS(m/e, (C₂₂H₁₉NO₃+H)⁺):

Calcd: 346.1443

Found: 346.1444

¹H-NMR(300MHz, CDCl₃, δ ppm):

3.38(1H, t, J=9.8Hz), 3.78(3H, s), 4.68(1H, d, J=9.8Hz),

25 4.73(1H, d, J=9.8Hz), 6.89(2H, d, J=8.8Hz),

7.12(1H, dd, J=4.9Hz, 8.6Hz), 7.19(2H, d, J=8.8Hz),

7.20-7.40(6H, m), 8.47(1H, dd, J=1.5Hz, 4.9Hz)

Rf Value: 0.36 (E. Merck, Kieselgel 60 F₂₅₄/
chloroform:methanol=10:1)

Example 13

6-Ethoxycarbonyl-7-phenyl-5-(4-methoxyphenyl)cyclo-
5 penteno[1,2-b]pyridine

Example 14

(5RS,6SR,7SR)-6-Carboxy-7-phenyl-5-(4-methoxypheny
l)cyclopenteno[1,2-b]pyridine

Example 15

10 6-Ethoxycarbonyl-5-phenyl-7-(3,4-methylenedioxyph
enyl)cyclopenteno[1,2-b]pyridine

Example 16

(5RS,6SR,7SR)-6-Carboxy-5-phenyl-7-(3,4-methylened
ioxyphenyl)cyclopenteno[1,2-b]pyridine

15 Example 17

6-Ethoxycarbonyl-7-phenyl-5-(3,4-methylenedioxyph
enyl)cyclopenteno[1,2-b]pyridine

Example 18

20 (5RS,6SR,7SR)-6-Carboxy-7-phenyl-5-(3,4-methylened
ioxyphenyl)cyclopenteno[1,2-b]pyridine

High Resolution FAB-MS(m/e, (C₂₂H₁₇NO₄+H)⁺):

Calcd: 360.1236

Found: 360.1225

¹H-NMR(300MHz, CDCl₃, δ ppm):

25 3.35(1H,t,J=9.7Hz), 4.63(1H,d,J=9.7Hz),
4.75(1H,d,J=9.7Hz), 5.97(2H,s), 6.72(1H,d,J=1.7Hz),
6.77(1H,dd,J=1.7Hz,8.0Hz), 6.81(1H,d,J=8.0Hz),

7.14(1H,dd,J=5.5Hz,8.3Hz),7.20-7.40(6H,m),

8.48(1H,dd,J=1.7Hz,5.5Hz)

Rf Value: 0.47 (E. Merck, Kieselgel 60 F₂₅₄/
chloroform:methanol=10:1)

5 Each Compound in the following Examples 19 and 20
was prepared using pyridine-3,4-dicarboxylic acid
anhydride instead of pyridine-2,3-dicarboxylic acid
anhydride as a starting material in the same manner as
in Examples 1 and 2.

10 Example 19

(5RS,6SR,7SR)-6-Carboxy-7-(3,4-methylenedioxypheny
l)-5-(4-methoxyphenyl)cyclopenteno[1,2-c]pyridine

mp: 190-192 °C

High Resolution FAB-MS(m/e,(C₂₃H₁₉NO₅+H)⁺):

15 Calcd: 390.1341

Found: 390.1354

¹H-NMR(300MHz,DMSO-d₆, δ ppm):

3.18(1H,t,J=10.2Hz),3.75(3H,s),

4.54(1H,d,J=10.2Hz),4.60(1H,d,J=10.2Hz),

20 6.02(2H,s),6.79-6.82(2H,m),6.89(1H,s),

6.89-6.94(1H,m),6.93(2H,d,J=8.4Hz),

7.23(2H,d,J=8.4Hz),8.00(1H,s),8.38(1H,d,J=4.8Hz),

12.41(1H,s)

Rf Value: 0.49 (E. Merck, Kieselgel 60 F₂₅₄/

25 methylene chloride:methanol=8:1)

Example 20

(5RS,6SR,7SR)-6-Carboxy-5-(3,4-methylenedioxypheny

1)-7-(4-methoxyphenyl)cyclopenteno[1,2-c]pyridine

mp: 187 °C(dec)

High Resolution FAB-MS(m/e, (C₂₃H₁₉NO₅+H)⁺):

Calcd: 390.1341

5 Found: 390.1347

¹H-NMR(300MHz, DMSO-d₆, δ ppm):

3.18(1H, t, J=10.6Hz), 3.76(3H, s),

4.55(1H, d, J=10.6Hz), 4.59(1H, d, J=10.6Hz),

6.01(2H, s), 6.79(1H, dd, J=1.7Hz, 8.1Hz),

10 6.82-6.90(3H, m), 6.93(2H, d, J=8.5Hz),

7.26(2H, d, J=8.5Hz), 7.96(1H, s), 8.38(1H, d, J=4.6Hz)

Each Compound in the following Examples 21-24 was prepared using the corresponding 6-substituted pyridine-2,3-dicarboxylic acid anhydride as a starting material
15 in the same manner as in Examples 1 and 2.

Example 21

(5RS, 6SR, 7SR)-6-Carboxy-2-propoxy-5-(3,4-methylene
dioxyphe nyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]-
pyridine

20 High Resolution FAB-MS(m/e, (C₂₆H₂₅NO₆+H)⁺):

Calcd: 448.1760

Found: 448.1778

¹H-NMR(300MHz, CDCl₃, δ ppm):

0.94(3H, t, J=7.2Hz), 1.68(2H, sext, J=7.2Hz),

25 3.21(1H, t, J=9.3Hz), 3.81(3H, s), 4.00-4.18(2H, m),

4.51(1H, d, J=9.3Hz), 4.64(1H, d, J=9.3Hz), 5.94(2H, s),

6.56(1H, d, J=8.0Hz), 6.70(1H, s), 6.71-6.80(2H, m),

6.87(2H,d,J=8.7Hz),7.17(1H,d,J=8.0Hz),

7.19(2H,d,J=8.7Hz)

Rf Value: 0.44 (E. Merck, Kieselgel 60 F₂₅₄/

chloroform:methanol=20:1)

5 Example 22

(5RS,6SR,7SR)-6-Carboxy-2-methyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

mp: 192-194 °C

10 FAB-MS(m/e, (C₂₄H₂₁NO₅+H)⁺):404

¹H-NMR(300MHz,DMSO-d₆, δ ppm):

2.35(3H,s),3.08(1H,t,J=10.0Hz),3.74(3H,s),

4.46(2H,t,J=10.0Hz),6.00(2H,s),

6.75(1H,dd,J=1.6Hz,8.0Hz),6.81(1H,d,J=1.6Hz),

15 6.87-6.91(3H,m),7.04(1H,d,J=7.8Hz),7.11-7.17(3H,m)

Rf Value: 0.29 (E. Merck, Kieselgel 60 F₂₅₄/

chloroform:methanol=20:1)

Example 23

(5RS,6SR,7SR)-6-Carboxy-2-butyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

Example 24

(5RS,6SR,7SR)-6-Carboxy-2-ethylaminomethyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

Example 25

(5RS,6SR,7SR)-6-Carboxy-5-(3,4-methylenedioxypheny

1)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine N-oxide

To a chloroform-methanol (10:1) solution (2.8 ml) of (5RS,6SR,7SR)-6-carboxy-5-(3,4-methylenedioxyphenyl) 1)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine (27.3 mg, 0.0701 mmol) which was prepared in Example 2 was added mCPBA (24.1 mg, 0.14 mmol) at room temperature and the mixture was stirred at the same temperature for 9 h.

The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative TLC (E. Merck Kieselgel 60 F₂₅₄/chloroform:methanol:acetic acid=30:1:1) to give a solid, which was partitioned between dichloromethane (20 ml) and water (2 ml). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give (5RS,6SR,7SR)-6-carboxy-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine N-oxide (21.9 mg) as a pale purple powder.

mp: 130-134 °C

FAB-MS(m/e, (C₂₃H₁₉NO₆+H)⁺): 406

¹H-NMR(300MHz, CDCl₃, δ ppm):

3.24(1H, t, J=5.1Hz), 3.77(3H, s), 4.87(1H, d, J=5.1Hz),
5.01(1H, d, J=5.1Hz), 5.91(2H, s), 6.65-6.61(2H, m),
6.67-6.73(1H, m), 6.82-6.88(2H, m), 7.10-7.16(2H, m),
7.23(1H, d, J=7.8Hz), 7.31(1H, dd, J=6.4Hz, 7.8Hz),
8.20(1H, d, J=6.4Hz)

Rf Value: 0.28 (E. Merck, Kieselgel 60 F₂₅₄/

chloroform:methanol:acetic acid=30:1:1)

Example 26

(5RS,6SR,7SR)-6-Carbamoyl-5-(3,4-methylenedioxy
phenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

5 (5RS,6SR,7SR)-6-carboxy-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine (27.3 mg, 0.0701 mmol) which was prepared in Example 2, HOBT·H₂O (10.7 mg, 0.0700 mmol) and ammonium chloride (7.5 mg, 0.14 mmol) were suspended in DMF (0.70 ml). To
10 the suspension were added EDCI·HCl (16.1 mg, 0.084 mmol) and TEA (20 μl, 0.14 mmol) under ice - cooling. The resulting mixture was stirred at room temperature for 3.5 h. Dichloromethane (0.70 ml) was added to the suspension and the mixture was additionally stirred at
15 room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in AcOEt. The solution was washed with water (2 ml) and brine (2 ml), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue
20 was purified by preparative TLC (E. Merck Kieselgel 60 F₂₅₄/chloroform:methanol=10:1) to give (5RS,6SR,7SR)-6-carbamoyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine (25.5 mg) as a colorless powder.

25 mp: 200-203 °C

FAB-MS(m/e, (C₂₃H₂₀N₂O₄+H)⁺): 389

¹H-NMR(300MHz, CDCl₃, δ ppm):

3.01(1H,t,J=10.1Hz),3.80(3H,s),
4.67(1H,d,J=10.1Hz),4.69(1H,d,J=10.1Hz),
4.91(1H,brs),5.23(1H,brs),5.94-6.00(2H,m),
6.72-6.74(1H,m),6.79-6.82(2H,m),6.88-6.94(2H,m),
5 7.09-7.15(1H,m),7.18-7.23(2H,m),7.28-7.34(1H,m),
8.44-8.48(1H,m)

Rf Value: 0.66 (E. Merck, Kieselgel 60 F₂₅₄/
chloroform:methanol=10:1)

Example 27

10 (5RS,6SR,7SR)-6-Methanesulfonylaminocarbonyl-5-(3,
4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopente-
no[1,2-b]pyridine

(5RS,6SR,7SR)-6-carboxy-5-(3,4-methylenedioxyphenyl)
-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine (23.4
15 mg, 0.0601 mmol) which was prepared in Example 2,
methanesulfonic amide (14.4 mg, 0.151 mmol), and DMAP
(8.8 mg, 0.72 mmol) were dissolved in DMF (0.60 ml). To
the solution was added EDCI·HCl (40.4 mg, 0.21 mmol)
under ice - cooling. The resulting mixture was stirred
20 at room temperature for 78 h. The solvent was removed
in vacuo and the residue was partitioned between AcOEt
and water. The aqueous layer was extracted with AcOEt.
The combined organic layer was dried over Na₂SO₄,
filtered, and concentrated under reduced pressure. The
25 residue was purified by preparative TLC (E. Merck
Kieselgel 60 F₂₅₄/chloroform:methanol=10:1) to give
(5RS,6SR,7SR)-6-methanesulfonylaminocarbonyl-5-(3,4-me-

thylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno
[1,2-b]pyridine (17.0 mg) as a colorless powder.

mp: 113-118 °C

FAB-MS(m/e, (C₂₄H₂₂N₂O₆S+H)⁺): 467

5 ¹H-NMR(300MHz, CDCl₃, δ ppm):

3.06(1H, t, J=10.1Hz), 3.21(3H, s), 3.81(3H, s),

4.69(2H, d, J=10.0Hz), 5.95-6.05(2H, m),

6.68-6.86(3H, m), 6.90-6.98(2H, m), 7.12-7.16(1H, m),

7.16-7.22(2H, m), 7.28-7.34(1H, m), 8.44-8.50(1H, m)

10 Rf Value: 0.58 (E. Merck, Kieselgel 60 F₂₅₄/
chloroform:methanol=10:1)

Example 28

(5RS,6SR,7SR)-6-(4-Isopropylbenzenesulfonylaminoca
rbonyl)-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphe-
15 nyl)cyclopenteno[1,2-b]pyridine

This compound was prepared using 4-isopropylbenzene-
sulfonamide in the same manner as in Example 27.

mp: 104-110 °C

FAB-MS(m/e, (C₃₂H₃₀N₂O₆S+H)⁺): 571

20 ¹H-NMR(300MHz, CDCl₃, δ ppm):

1.31(6H, d, J=6.9Hz), 2.94(1H, t, J=10.2Hz),

3.04(1H, sept, J=6.9Hz), 3.82(3H, s),

4.51(1H, d, J=10.2Hz), 4.54(1H, d, J=10.2Hz),

5.95-6.02(2H, m), 6.57(1H, d, J=1.7Hz),

25 6.62(1H, dd, J=1.7Hz, 8.0Hz), 6.77(1H, d, J=8.0Hz),

6.84-6.92(2H, m), 6.96-7.04(2H, m), 7.08-7.14(1H, m),

7.24-7.30(1H, m), 7.40-7.46(2H, m), 7.87-7.93(2H, m),

8.42-8.46 (1H, m)

Rf Value: 0.69 (E. Merck, Kieselgel 60 F₂₅₄/

chloroform:methanol=10:1)

Example 29

5 6-Carboxy-5-hydroxy-5-(3,4-methylenedioxyphenyl)-7-
-(4-methoxyphenyl)cyclopent-1,4-dieno[1,2-b]pyridine

The title compound was prepared using 6-ethoxy-carbonyl-5-hydroxy-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine which was
10 prepared in Example 1-(4) in the same manner as in Example 2.

¹H-NMR (300MHz, CDCl₃, δ ppm):

3.88 (3H, s), 5.90-5.95 (2H, m), 6.74 (1H, d, J=8.1Hz),
6.97 (1H, d, J=2.2Hz), 7.00-7.05 (3H, m),
15 7.16 (1H, dd, J=4.9Hz, 7.6Hz),
7.57 (1H, dd, J=1.5Hz, 7.6Hz),
8.55 (1H, dd, J=1.5Hz, 4.9Hz)

Example 30

(5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethoxy-4-
20 methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno-
[1,2-b]pyridine
(1) 2-(2-Benzylloxy-4-methoxyphenylcarbonyl)-3-pyridine
carboxylic acid

To a THF (20 ml) solution of pyridine-2,3-
25 dicarboxylic acid anhydride (1.92 g, 12.9 mmol) was added a THF solution of 2-benzylloxy-4-methoxyphenyllithium (10 ml), which was prepared from

2-benzyloxy-4-methoxyphenyl bromide (3.77 g, 12.9 mmol) and BuLi (1.6M hexane solution, 8.85 ml, 14.2 mmol) at -78 °C, at -78 °C over a period of 5 min. The temperature of the mixture was raised to room temperature and the mixture was additionally stirred at the same temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between 1N HCl and AcOEt. The organic layer was washed with 1N HCl, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in 1N NaOH and the solution was washed with AcOEt and chloroform. The aqueous layer was acidified with conc. HCl and extracted with AcOEt. The AcOEt layer was washed with 1N HCl and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was recrystallized from chloroform and chloroform-ether to give 2-(2-benzyloxy-4-methoxyphenylcarbonyl)-3-pyridine carboxylic acid (2.03 g) as a colorless solid.

(2) 6-Ethoxycarbonyl-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

The title compound was prepared using 2-(2-benzyloxy-4-methoxyphenylcarbonyl)-3-pyridine carboxylic acid which was prepared in (1), in the same manner as in Example 1-(2)-(5).

(3) 6-Ethoxycarbonyl-7-(2-ethoxycarbonylmethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclo-

penteno[1,2-b]pyridine

To a DMF (1 ml) solution of 6-ethoxycarbonyl-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (15 mg, 0.035 mmol) was added a DMF (1.0 ml) suspension of NaH (1.60 mg, 0.040 mmol) under ice - cooling. The mixture was stirred under ice - cooling for 30 min, and at room temperature for 30 min. To the solution was added ethyl bromoacetate (5.74 μ l, 0.052 mmol). The mixture was stirred at room temperature for 12 h and then at 50 °C for 3.5 h. 1N HCl was added to the solution and the mixture was partitioned between chloroform and water. The organic layer was washed with 1N HCl, a saturated aqueous solution of NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (E. Merck Kieselgel 60 F₂₅₄/hexane: AcOEt=1:1) to give 6-ethoxycarbonyl-7-(2-ethoxycarbonylmethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)-cyclopenteno[1,2-b]pyridine (8.8 mg) as a pale yellow solid.

(4) To a methanol (0.5 ml) solution of 6-ethoxycarbonyl-7-(2-ethoxycarbonylmethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (8.8 mg, 0.017 mmol) was added 4N NaOH (41.4 μ l, 0.17 mmol) and the solution was stirred at room temperature for 3 days. The reaction mixture was diluted with water

and washed with AcOEt. The pH value of the aqueous layer was turned to 2-3 and the aqueous layer was extracted with AcOEt. The organic layer was washed with 1N HCl and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was dried in vacuo to give (5RS,6SR,7SR)-6-carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (4.9 mg) as an orange powder.

mp: 154-156 °C

High Resolution FAB-MS(m/e, (C₂₅H₂₁NO₈+H)⁺):

Calcd: 464.1345

Found: 464.1356

¹H-NMR(300MHz, CDCl₃/CD₃OD=4/1, δ ppm):

3.66(1H, t, J=10.3Hz), 3.80(3H, s),
4.60(2H, ABq, J=16.4Hz, Δν=47.0Hz),
4.67(1H, d, J=10.3Hz), 5.10(1H, d, J=10.3Hz),
5.97(2H, s), 6.50(1H, d, J=2.5Hz),
6.55(1H, dd, J=2.5Hz, 8.3Hz), 6.76(1H, s), 6.80(2H, s),
7.18(1H, d, J=8.3Hz), 7.28(1H, dd, J=5.5Hz, 7.7Hz),
7.48(1H, td, J=1.4Hz, 7.7Hz), 8.32(1H, dd, J=1.4Hz, 5.5Hz)

Rf Value: 0.24 (E. Merck, Kieselgel 60 F₂₅₄/

chloroform:methanol:acetic acid=10:1:1)

Example 31

(5RS,6SR,7RS)-6-carboxy-5-(2-carboxymethoxy-4-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopenteno-
[1,2-c]pyridine

The title compound was prepared using pyridine-3,4-dicarboxylic acid anhydride in the same manner as in Example 30.

Example 32

5 (5RS,6SR,7SR)-6-carboxy-7-(2-hydroxy-4-methoxy-phenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno-[1,2-b]pyridine

The title compound was prepared using 6-ethoxycarbonyl-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylene-
10 dioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example 30-(2) in the same manner as in Example 2.

Example 33

15 (5RS,6SR,7SR)-6-carboxy-7-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno-[1,2-b]pyridine

The title compound was prepared using 2-(tert-butyldimethylsiloxy)ethylbromide in the same manner as in Examples 30-(3) and (4).

20 Example 34

(5RS,6SR,7SR)-6-carboxy-7-[2-(2-methylaminoethoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

25 6-Ethoxycarbonyl-7-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example 33 was converted to the corresponding tosylate according to a

conventional method and the tosylate was treated with methylamine. The resulting methylamino derivative was hydrolyzed in the same manner as in Example 2 to give
5 (5RS,6SR,7SR)-6-carboxy-7-[2-(2-methylaminoethoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine.

Each Compound in the following Examples 35-45 was prepared by the procedures given above.

Example 35

10 (5RS,6SR,7SR)-6-Carboxy-2-ethoxymethyl-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

Example 36

15 (5RS,6SR,7SR)-6-Carboxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)-2-propylcyclopenteno[1,2-b]pyridine

Example 37

20 (5RS,6SR,7SR)-6-Carboxy-2-isobutyl-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

Example 38

6-Carboxy-7-hydroxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopent-1,3-dieno[1,2-b]pyridine

Example 39

25 6-Carboxy-5-hydroxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)-2-propylcyclopent-1,3-dieno[2,1-b]pyridine

Example 40

(5RS,6SR,7RS)-6-Carboxy-5-hydroxy-7-(4-methoxy-phenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]-pyridine

5 Example 41

(5RS,6SR,7SR)-6-Carboxy-7-(4-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

Example 42

10 (5RS,6SR,7RS)-6-Carboxy-7-[4-(2-hydroxyethoxy)-phenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]-pyridine

Example 43

15 (5RS,6SR,7SR)-6-Carboxy-7-[4-(2-methylaminoethoxy)-phenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]-pyridine

Example 44

(5RS,6SR,7SR)-6-Carboxy-7-(4-hydroxymethylphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

Example 45

20 (5RS,6SR,7SR)-6-Carboxy-5-(3,4-methylenedioxyphenyl)-7-(3-thienyl)cyclopenteno[1,2-b]pyridine

Example 46

25 (5RS,6SR,7RS)-7-(4-Methoxyphenyl)-5-(3,4-methylene-dioxyphenyl)-6-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)-cyclopenteno[1,2-b]pyridine

The title compound was prepared using
(5RS,6SR,7SR)-6-carbamoyl-7-(4-methoxyphenyl)-5-(3,4-

methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example 26 as a starting material by the method described in the literature (J, Med. Chem. 1993, 36, 2485-2493).

5 Example 47

(5RS,6SR,7SR) - 6 - (5 - Oxo - 4H - 1,2,4 - oxadiazol - 3 - yl) - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared using (5RS,6SR,7SR) - 6 - carbamoyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 26 as a starting material by the method described in the literature (J. Med. Chem., 1993, 36, 3691 - 3698).

15 mp: 251 - 255 °C

High Resolution FAB - MS(m/e, (C₂₄H₁₉N₃O₅+H)⁺):

Calcd: 430.1403

Found: 430.1400

¹H - NMR(300MHz, DMSO - d₆, δ ppm): 3.32(1H, t, J=10.8Hz),
20 3.74(3H, s), 4.53(1H, d, J=10.8Hz), 4.60(1H, d, J=10.8Hz), 6.02(2H, s), 6.77(1H, dd, J=2.3Hz, 7.8Hz), 6.89(2H, d, J=8.7Hz), 6.90(1H, d, J=7.8Hz), 6.91(1H, d, J=2.3Hz), 7.18(2H, d, J=8.7Hz), 7.25(1H, dd, J=4.7Hz, 7.7Hz), 7.31(1H, d, J=7.7Hz),
25 7.7Hz), 8.39(1H, d, J=4.7Hz), 12.56(1H, brs)

Rf Value: 0.21 (E. Merck, Kieselgel 60F₂₅₄/dichloro-methane:methanol=20:1)

Example 48

(5RS,6SR,7SR)-6-(Tetrazol-5-yl)-5-(3,4-methylene-
dioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]py-
ridine

5 The title compound was prepared using (5RS,6SR,7SR)-
6-carbamoyl-5-(3,4-methylenedioxyphenyl)-7-(4-methox-
yphenyl)cyclopenteno[1,2-b]pyridine which was prepared
in Example 26 as a starting material by the method
described in the literature(J.Org.Chem.,1991,56,2400 -
10 2404).

mp:264 - 266 °C

High Resolution FAB - MS(m/e, (C₂₃H₁₉N₅O₃+H)⁺):

Calcd: 414.1566

Found: 414.1561

15 ¹H - NMR(300MHz, DMSO- d₆, δ ppm):3.71(3H, s), 3.86(1H, t,
J=10.9Hz), 4.63(1H, d, J=10.9Hz), 4.71(1H, d,
J=10.9Hz), 6.00(2H, s), 6.66(1H, dd, J=1.7Hz,
8.0Hz), 6.85(1H, d, J=1.7Hz), 6.85(2H, d, J=8.6Hz),
6.85(1H, d, J=8.0Hz), 7.11(2H, d, J=8.6Hz),
20 7.25(1H, dd, J=4.6Hz, 7.7Hz), 7.30(1H, dd, J=1.8Hz,
7.7Hz), 8.40(1H, dd, J=1.8Hz, 4.6Hz)

Rf Value:0.23(E. Merck, Kieselgel 60F₂₅₄/dichloro-
methane:methanol=10:1)

Example 49

25 (5RS,6SR,7SR)-5-(3,4-methylenedioxyphenyl)-6-me-
thoxycarbonyl-7-(4-methoxyphenyl)cyclopenteno[1,2-
b]pyridine

To a DMF solution (1ml) of sodium salt of (5RS,6SR,7SR) - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 2 was added methanol(15
5 1).EDCI·HCl(21mg) and DMPA(2mg) were added to the solution and the reaction solution was stirred at room temperature for 12h, and partitioned between AcOEt and 10% citric acid. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine, dried
10 over MgSO₄ and concentrated under reduced prssure to give the title compound(20.2mg) as a colorless powder.

mp:140 - 141.5 °C

High ResolutionFAB - MS(m/e, (C₂₄H₂₁NO₆+H)⁺):

Calcd: 404.1498

15 Found: 404.1510

¹H - NMR(300MHz, CDCl₃, δ ppm):3.27(1H, t, J=10.0Hz),
3.64(3H, s), 3.80(3H, s), 4.59(1H, d, J=10.0Hz),
4.67(1H, d, J=10.0Hz), 5.92 - 6.01(2H, m), 6.66 -
6.83(3H, m), 6.90(2H, d, J=8.5Hz), 7.09 - 7.20(1H,
20 m), 7.16(2H, d, J=8.5Hz), 7.29(1H, d, J=7.9Hz),
8.46(1H, d, J=4.6Hz)

Rf Value:0.42(E. Merck, Kieselgel 60F₂₅₄/hexane:AcOEt=
1:1)

Example 50

25 (5RS,6SR,7SR) - 7 - (2 - Ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

(1) 5 - Oxo - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine

To a DMF(110mg) suspension of 2 - (2 - benzyloxy - 4 - methoxyphenylcarbonyl) - 3 - pyridine carboxylic acid which
5 was prepared in Example 30 - (1) was added CDI(10.3g) under ice - cooling . The mixture was stirred under ice - cooling for 1.5 h and at room temperature for 1 h, and partitioned between AcOEt and water. The aqueous layer was extracted with AcOEt, the combined organic layer was
10 washed with water and brine, dried over MgSO₄ and evaporated to give a solid residue. The residue was dissolved in THF(350ml), then cooled at - 78°C. To the solution was added dropwise THF solution of lithium enolate of acetic acid tert - butyl ester which was
15 prepared from acetic acid tert - butyl ester(14ml) and LDA(1.7M,61ml). The reaction solution was stirred at - 78°C for 15 min, and 1N HCl(500ml) was added. The mixture was extracted with AcOEt, washed with a saturated aqueous solution of NaHCO₃ and brine, dried
20 over MgSO₄, and concentrated under reduced pressure. To a dichloromethane solution of the residue was added SiO₂ (Wako gel C - 200, 140g), and the mixture was stirred at room temperature, filtrated to remove SiO₂, then washed with dichloromethane and AcOEt. Filtrate and washings
25 were combined and concentrated. The residue was purified by silica gel column chromatography(E. Merck Kieselgel 60/dichloromethane:acetone=100:1 to 50:1) to give 5 - oxo

- 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(9.83g) as a reddish orange solid.

(2) 5 - Hydroxy - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine

To a THF(100ml) solution of 5 - oxo - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(10.8g,25.5mg) was added a THF solution(1.0M,28.0ml) of 3,4 - methylenedioxyphenylmagnesium bromide dropwise at -78°C. The solution was stirred at -78°C for 45 min and the temperature of the solution was raised at room temperature after addition of a saturated aqueous solution of NH₄Cl(300ml). The reaction solution was partitioned between AcOEt and water, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was recrystallized from AcOEt - hexane to give 5 - hydroxy - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(11.1g) as a reddish orange solid.

(3) (5RS,6RS,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a THF(100ml) - ethanol(100ml) solution of 5 - hydroxy - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(11.4g, 20.1mmol) was added zinc
5 powders(9.87g) under ice - cooling. A HCl - dioxane solution(4N,45.3ml) was added dropwise to this suspension, and then a saturated aqueous solution of NaHCO₃(300ml) and ethyl acetate were added to quench the reaction. Resulting precipitates were removed off by
10 filtration, washed and extracted with AcOEt. The filtrate, washings and extracts were combined, washed with brine, dried over MgSO₄ and concentrated. The residue was crystallized from AcOEt - hexane to give
15 (5RS,6RS,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine as a light yellow solid.

(4) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

20 To a t - BuOH(60ml) - 1,4 - dioxane(60ml) solution of (5RS,6RS,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(6.96g,12.6mmol) solution was added potassium tert - butoxide(0.15g). The solution was
25 stirred at 60°C for 8 h and partitioned between water and AcOEt. The aqueous layer was extracted with AcOEt, and the organic layers were combined, washed with brine

and dried over MgSO_4 . After removal of the solvent under reduced pressure the residue was crystallized from ether and hexane to give (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(6.07g) as a colorless crystal.

(5) (5RS,6SR,7SR) - 7 - (2 - Hydroxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a THF(25ml) - 1,4 - dioxane(25ml) solution of (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyl - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(2.68g,4.86mmol) was added a water suspension(5ml) of Pd black under argon atmosphere. The reaction mixture was stirred under hydrogen atmosphere at roomtemperature for 12 h, filtrated to remove the catalyst and concentrated under reduced pressure. The residue was recrystallized from AcOEt - hexane to give (5RS,6SR,7SR) - 7 - (2 - hydroxy - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(2.11g) as a colorless crystal.

(6) (5RS,6SR,7SR) - 7 - (2 - Ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 30 - (3) using (5RS,6RS,7SR) - 7 - (2 - Hydroxy

- 4-methoxyphenyl)- 6- tert- butoxycarbonyl- 5- (3,4- methy-
lendioxyphenyl)cyclopenteno[1,2 - b]pyridine.

(7) (5RS,6SR,7SR)- 7- (2- Ethoxycarbonylmethoxy- 4- methox-
yphenyl) - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl)cyclo-
5 penteno[1,2 - b]pyridine

(5RS,6SR,7SR)- 7- (2- Ethoxycarbonylmethoxy- 4- methox-
yphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylen-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(15mg,0.027mmol)
was treated with TFA(1ml) under ice - cooling and stirred
10 at room temperature for 1.5 h. The title compound was
prepared by removing TFA under reduced pressure as a
light yellow solid.

High ResolutionFAB - MS(m/e, (C₂₇H₂₅NO₈+H)⁺):

Calcd: 492.1659

15 Found: 492.1651

¹H - NMR(300MHz, CDCl₃, δ ppm):1.20(3H, t, J=7.1Hz),
3.77(3H, s), 3.84(1H, t, J=10.3Hz), 4.01 - 4.18(2H,
m), 4.36(1H, d, J=15.5Hz), 4.46(1H, d, J=15.5Hz),
4.70(1H, d, J=10.3Hz), 5.02(1H, d, J=10.3Hz),
20 5.95(1H, d, J=1.4Hz), 5.97(1H, d, J=1.4Hz),
6.33(1H, d, J=2.2Hz), 6.48(1H, dd, J=2.2Hz, 8.2Hz),
6.78(1H, d, J=8.5Hz), 6.84(1H, s), 6.84(1H, d,
J=8.5Hz), 7.22(1H, d, J=8.2Hz), 7.53(1H, dd,
J=5.7Hz, 7.7Hz), 7.81(1H, d, J=7.7Hz), 8.39(1H, d,
25 J=5.7Hz)

Rf Value:0.32(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol=10:1)

Example 51

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (tetrazol - 5 - ylamino - carbonylmethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

5 (1) (5RS,6SR,7SR) - 7 - (2 - Carboxymethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a methanol solution(4ml) of (5RS,6SR,7SR) - 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 6 - tert - butoxy -
10 carbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(263mg,0.480mmol) which was prepared in Example 50 - (6) was added 6N NaOH(500 μ l) at 0°C. The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was
15 acidified with 3N HCl, and extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give (5RS,6SR,7SR) - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(248mg).
20

(2) (5RS,6SR,7SR) - 7 - [2 - Tetrazol - 5 - ylamino - carbonylmethoxy) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

25 To a THF(1ml) solution of (5RS,6SR,7SR) - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-

dine(64mg,0.123mmol) was added CDI(20mg) at room temperature and the mixture was stirred for 1 h. 5 - Aminotetrazole(11mg) was added to the solution at room temperature and the mixture was stirred at room temperature for 16 h. The reaction solution was diluted with AcOEt, washed with 1N HCl and brine, and dried over Na₂SO₄. After removal of the solvent under reduced pressure the residue was purified by preparative TLC(E. Merck Kieselgel 60F₂₅₄/chloroform: methanol:acetic acid=20:1:1) to give (5RS,6SR,7SR) - 7 - [2 - (tetrazol - 5 - ylamino-carbonylmethoxy) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(73.1mg).

(3) A solution of (5RS,6SR,7SR) - 7 - [2 - (tetrazol - 5 - ylamino-carbonylmethoxy) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(61mg) and thioanisole(0.15ml) in TFA(3ml) was stirred at room temperature for 1 h. After removal of the solvent the residue was crystallized from ether to give the title compound(39.2mg) as a colorless powder.

mp:>220 °C (dec.)

High Resolution FAB - MS(m/e, (C₂₆H₂₂N₆O₇+H)⁺):

Calcd: 531.1628

Found: 531.1654

¹H - NMR(300MHz, DMSO - d₆, δ ppm):3.57(1H, t, J=10.2Hz), 3.72(3H, s), 4.56(1H, d, J=10.2Hz), 4.82(1H, d,

J=14.8Hz), 4.93(1H, d, J=10.2Hz), 4.97(1H, d, J=14.8Hz), 5.98(2H, d, J=2.6Hz), 6.50 - 6.60(2H, m), 6.75 - 6.90(3H, m), 7.15 - 7.33(3H, m), 8.56(1H, brs), 12.43(1H, brs)

5 Rf Value:0.29(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 52

(5RS,6SR,7SR) - 7 - (2 - Carbamoylmethoxy - 4 - methoxyphenyl)
- 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2
10 - b]pyridine

(5RS,6SR,7SR) - 7 - (2 - Carboxymethoxy - 4 - methoxyphenyl)
- 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 51 - (1) was condensed with ammonium chloride in the
15 same manner as in Example 26 and the tert - butyl group was cleaved with TFA to give the title compound.

mp:138 - 139.5 °C

High Resolution FAB - MS(m/e, (C₂₅H₂₂N₂O₇+H)⁺):

Calcd: 463.1505

20 Found: 463.1501

¹H - NMR(300MHz, DMSO - d₆, δ ppm):3.37(1H, t, J=10.0Hz), 3.74(3H, s), 4.40(2H, s), 4.53(1H, d, J=10.0Hz), 4.90(1H, d, J=10.0Hz), 6.00(2H, s), 6.51(1H, d, J=2.9Hz), 6.52(1H, dd, J=2.9Hz, 8.2Hz), 6.77(1H, dd, J=1.6Hz, 7.8Hz), 6.83(1H, d, J=1.6Hz), 6.89(1H, d, J=7.8Hz), 7.10(1H, d, J=8.2Hz), 7.17(1H, dd, J=4.6Hz, 7.5Hz), 7.23(1H, dd, J=1.9Hz, 7.5Hz),

25

7.26(1H, brs), 7.41(1H, brs), 8.25(1H, dd, J=1.9Hz, 4.6Hz)

Rf Value:0.37(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

5 Example 53

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2 - methanesulfonyl - aminocarbonylmethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

(5RS,6SR,7SR)- 7- (2- Carboxymethoxy- 4- methoxyphenyl)
10 - 6- tert- butylcarbonyl- 5- (3,4- methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 51 - (1) was condensed with methanesulfoneamide in the same manner as in Example 27 and the tert- butyl group was cleaved with TFA to give the title compound.

15 mp:143.5 - 145 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₄N₂O₉S+H)⁺):

Calcd: 541.1280

Found: 541.1282

¹H - NMR(300MHz, DMSO- d₆, δ ppm):3.10(3H, s), 3.49(1H, t, J=10.2Hz), 3.73(3H, s), 4.49(2H, ABq, J=16.3Hz, Δν=61.3Hz), 4.51(1H, d, J=10.2Hz), 4.77(1H, d, J=10.2Hz), 5.99(2H, s), 6.47(1H, d, J=2.4Hz), 6.53(1H, dd, J=2.4Hz, 8.4Hz), 6.79(1H, dd, J=1.9Hz, 8.0Hz), 6.86(1H, d, J=1.9Hz), 6.87(1H, d, J=8.0Hz),
20 7.12(1H, d, J=8.4Hz), 7.14 - 7.24(2H, m), 8.31(1H, d, J=4.9Hz)
25

Rf Value:0.27(E. Merck, Kieselgel 60F₂₅₄/chloro-

roform:methanol=4:1)

Example 54

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (tetrazol - 5 - ylme-
thoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
5 dioxyphenyl)cyclopenteno[1,2 - b]pyridine

(1) (5RS,6SR,7SR) - 7 - (2 - Cyanomethoxy - 4 - methoxyphenyl)
- 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cy-
clopenteno[1,2 - b]pyridine

(5RS,6SR,7SR) - 7 - (2 - Hydroxy - 4 - methoxyphenyl) - 6 -
10 tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine which was prepared in Example 50
- (5) was reacted with bromoacetonitrile in the same
manner as in Example 50 - (6) to give (5RS,6SR,7SR) - 7 - (2
- cyanomethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl
15 - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-
dine.

(2) (5RS,6SR,7SR) - 7 - [2 - (tetrazol - 5 - ylmethoxy) - 4 -
methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylene
dioxyphenyl)cyclopenteno[1,2 - b]pyridine

20 This compound was prepared in the same manner as in
Example 48 using (5RS,6SR,7SR) - 7 - (2 - cyanomethoxy - 4 -
methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylene
dioxyphenyl)cyclopenteno[1,2 - b]pyridine.

25 (3) The title compound was prepared by reacting
(5RS,6SR,7SR) - 7 - [2 - (tetrazol - 5 - ylmethoxy) - 4 - methoxy-
phenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylene

dioxyphenyl)cyclopenteno[1,2 - b]pyridine in THF at room temperature for 1.5 h.

mp:155 - 158 °C

High Resolution FAB - MS(m/e, (C₂₅H₂₁N₅O₆+H)⁺):

5 Calcd: 488.1570

Found: 488.1567

¹H - NMR(300MHz, CDCl₃, δ ppm):3.60(1H, dd, J=9.5Hz, 10.6Hz), 3.67(3H, s), 4.65(1H, d, J=9.5Hz), 5.36(1H, d, J=10.6Hz), 5.45(1H, d, J=15.3Hz), 10 5.68(1H, d, J=15.3Hz), 6.00(2H, s), 6.41(1H, d, J=1.9Hz), 6.44(1H, dd, J=1.9Hz, 8.5Hz), 6.71(1H, d, J=1.6Hz), 6.73(1H, dd, J=1.6Hz, 7.9Hz), 6.83(1H, d, J=7.9Hz), 7.08(1H, d, J=8.5Hz), 7.27(1H, dd, J=4.9Hz, 7.6Hz), 7.46(1H, d, J=7.6Hz), 8.54(1H, d, 15 J=4.9Hz)

Rf Value:0.26(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 55

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - methoxycarbonylpropoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine
20 (1) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - [2 - (1 - methoxycarbonylpropoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

25 To a methylethylketone(1.5ml) solution of (5RS,6SR,7SR) - 7 - (2 - hydroxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-

penteno[1,2 - b]pyridine(98.2mg, 0.213mmol), K_2CO_3 (48.8mg) and KI(1.6mg) was added 2 - bromobutylic acid methyl ester(33 μ l) and the solution was heated under reflux for 19.5 h. The reaction solution was partitioned
5 between water and AcOEt, and organic layer was washed with brine and dried over Na_2SO_4 . After removal of the solvent the residue was purified by silica gel column chromatography(E. Merck Kieselgel 60F₂₅₄/dichloromethane:AcOEt=3:1) and by preparative TLC(E. Merck
10 Kieselgel 60F₂₅₄ dichloromethane:acetone=30:1) to give each of diastereomers (5RS,6SR,7SR) - 6 - tert - butoxy-carbonyl - 7 - [2 - (1 - methoxycarbonylpropoxy) - 4 - methoxy-phenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 -
15 b]pyridine as a colorless amorphous solid. The yield of one of diastereomers is 56.2mg and the other 38.8mg.
(2) One of the diastereomers(56.2mg,0.100mmol)which was prepared in (1) was dissolved under ice - cooling in TFA(2ml) and the solution was stirred under ice - cooling to room temperature for 3.5 h. After removal of TFA the
20 residue was neutrallized with a saturated aqueous solution of $NaHCO_3$, and the pH of suspension was adjusted at approximately 5. The suspension was extracted with AcOEt, washed with brine and dried over Na_2SO_4 . After removal of the solvent the residue was
25 purified by preparative TLC(E. Merck Kieselgel 60F₂₅₄ dichloromethane:acetone=4:1) to give one of diastereomers of title compound(45.3mg) as a colorless

amorphous solid.

mp: 85 - 123 °C

High Resolution FAB - MS(m/e, (C₂₈H₂₇NO₈+H)⁺):

Calcd: 506.1815

5 Found: 506.1803

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.56(3H, t, J=7.4Hz), 1.34
- 1.76(2H, m), 3.67(3H, s), 3.76(3H, s), 4.05(1H, t,
J=10.5Hz), 4.51(1H, dd, J=5.1Hz, 8.1Hz), 4.60(1H,
d, J=10.5Hz), 4.72(1H, d, J=10.5Hz), 5.96(2H, s),
10 6.33(1H, d, J=2.3Hz), 6.51(1H, dd, J=2.3Hz, 8.3Hz),
6.79(1H, d, J=7.7Hz), 6.83(1H, d, J=1.6Hz),
6.84(1H, dd, J=1.6Hz, 7.7Hz), 7.07(1H, dd, J=4.9Hz,
7.6Hz), 7.22(1H, d, J=8.3Hz), 7.25(1H, d, J=7.6Hz),
8.39(1H, d, J=4.9Hz)

15 Rf Value: 0.25 (E. Merck, Kieselgel 60F₂₅₄/dichloro-
methane:acetone=3:1)

Example 56

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - methoxycar-
bonylpropoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
20 dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other
diastereomer)

The other diastereomer(38.8mg, 0.0691mmol) which was
prepared in Example 55 - (2) was subjected to the same
reaction as in Example 55 - (2) to give the other
25 diastereomer of title compound(31.5mg) as a colorless
amorphous solid.

mp: 94 - 102 °C

High Resolution FAB - MS(m/e, (C₂₈H₂₇NO₈+H)⁺):

Calcd: 506.1815

Found: 506.1790

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.99(3H, t, J=7.4Hz), 1.85
5 - 2.01(2H, m), 3.22(1H, t, J=10.0Hz), 3.71(3H, s),
3.75(3H, s), 4.61(1H, t, J=6.6Hz), 4.69(1H, d,
J=10.0Hz), 5.09(1H, d, J=10.0Hz), 5.94(1H, d,
J=2.0Hz), 5.95(1H, d, J=2.0Hz), 6.27(1H, d,
J=2.1Hz), 6.50(1H, dd, J=2.1Hz, 8.3Hz), 6.71(1H,
10 s), 6.77(2H, s), 7.04(1H, d, J=8.3Hz), 7.13(1H, dd,
J=5.1Hz, 7.4Hz), 7.33(1H, d, J=7.4Hz), 8.48(1H, d,
J=5.1Hz)

Rf Value: 0.26 (E. Merck, Kieselgel 60F₂₅₄/dichloro-
methane:acetone=4:1)

15 Example 57

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxypropoxy)
- 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
pentino[1,2 - b]pyridine(one of diastereomers)

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - methoxycar-
20 bonylpropoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopentino[1,2 - b]pyridine(one of
diastereomers) which was prepared in Example 55 was
subjected to the same reaction as in Example 30 - (4) to
give the title compound.

25 mp: 151 - 154 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₈+H)⁺):

Calcd: 492.1658

Found: 492.1646

¹H - NMR(300MHz, CDCl₃, δ ppm): 1.02(3H, t, J=7.4Hz), 1.92
- 2.08(2H, m), 3.78(3H, s), 3.81(1H, dd, J=9.9Hz,
11.4Hz), 4.72(1H, d, J=9.9Hz), 4.90(1H, dd,
5 J=5.8Hz, 6.3Hz), 5.24(1H, d, J=11.4Hz), 6.00(2H,
s), 6.51(1H, dd, J=2.3Hz, 8.6Hz), 6.58(1H, d,
J=2.3Hz), 6.70(1H, d, J=1.7Hz), 6.77(1H, dd,
J=1.7Hz, 7.9Hz), 6.84(1H, d, J=7.9Hz), 7.20(1H, dd,
J=4.8Hz, 7.5Hz), 7.23(1H, d, J=8.6Hz), 7.38(1H, d,
10 J=7.5Hz), 8.24(1H, d, J=4.8Hz)

Rf Value: 0.32(E. Merck, Kieselgel 60F₂₅₄/dichloro-
methane:methanol:acetic acid=10:1:1)

Example 58

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxypropoxy)
15 - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine(the other diastereomer)

The title compound was prepared in the same manner
as in Example 57.

mp: 141 - 144 °C

20 High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₈+H)⁺):

Calcd: 492.1658

Found: 492.1639

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.88(3H, t, J=7.5Hz), 1.51
- 1.83(2H, m), 3.33(1H, t, J=10.8Hz), 3.76(3H, s),
25 4.62(1H, d, J=10.8Hz), 4.68(1H, dd, J=5.4Hz,
6.9Hz), 4.96(1H, d, J=10.8Hz), 5.95(1H, d,
J=1.6Hz), 5.97(1H, d, J=1.6Hz), 6.38(1H, d, J=

2.0Hz), 6.52(1H, dd, J=2.0Hz, 8.4Hz), 6.64(1H, d, J=1.7Hz), 6.73(1H, dd, J=1.7Hz, 7.9Hz), 6.79(1H, d, J=7.9Hz), 7.09(1H, d, J=8.4Hz), 7.18(1H, dd, J=4.8Hz, 7.7Hz), 7.36(1H, d, J=7.7Hz), 8.41(1H, d, J=4.8Hz)

Rf Value:0.25(E. Merck, Kieselgel 60F₂₅₄/dichloromethane:methanol:acetic acid=10:1:1)

Example 59

(5RS,6SR,7SR)-7-[2-(1-ethoxycarbonylethoxy)-4-methoxyphenyl]-6-carboxy-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

The title compound was prepared in the same manner as in Example 55 as a colorless solid(diastereomer ratio=2:1)

High Resolution FAB-MS(m/e, (C₂₈H₂₇NO₈+H)⁺):

Calcd: 506.1815

Found: 506.1817

¹H-NMR(300MHz, CDCl₃, δ ppm):1.01, 1.53(3H, 2d, J=6.5Hz, J=6.6Hz), 1.18(3H, t, J=7.3Hz), 3.24, 3.93(1H, 2t, J=10.0Hz, J=10.5Hz), 3.74(3H, s), 4.08-4.24(2H, m), 4.52-4.78, 5.08(3H, m, d, J=10.0Hz), 5.95(2H, s), 6.30(1H, d, J=2.1Hz), 6.50(1H, dd, J=2.1Hz, 8.2Hz), 6.69-6.90(3H, m), 6.97-7.38(3H, m), 8.37, 8.47(1H, 2d, J=5.1Hz, J=4.6Hz)

Rf Value:0.36(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 60

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxyethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner
5 as in Example 57 using (5RS,6SR,7SR) - 7 - [2 - (1 - ethoxycarbonylethoxy) - 4 - methoxyphenyl] - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(2:1 diastereomer mixture) as a colorless solid(diastereomer ratio=2:1).

10 High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₈+H)⁺):

Calcd: 478.1502

Found: 478.1521

¹H - NMR(300MHz, CDCl₃, δ ppm):1.26, 1.62(3H, 2d, J=7.0Hz), 3.38, 3.75(1H, t+dd, J=10.5Hz, J=9.9Hz, 11.2Hz), 3.75, 3.77(3H, 2s), 4.60, 4.71(1H, 2d, J=10.5Hz, J=9.9Hz), 4.83, 5.03(1H, 2q, J=7.0Hz), 4.92, 5.25(1H, 2d, J=10.5Hz, J=11.2Hz), 5.95, 5.96, 6.00(2H, d, J=1.9Hz, d, J=1.9Hz, s), 6.38 - 6.87(5H, m), 7.08 - 7.41(3H, m), 8.40, 8.28(1H, 2d, J=4.9Hz)

20 Rf Value:0.27, 0.17(E. Merck, Kieselgel 60F₂₅₄
/chloroform:methanol:acetic

Example 61 - 63

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxyethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(Example 61)

25 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - [2 - (2 - carboxyethoxycarbonyl)ethoxy] - 4 - methoxyphenyl] - 5 - (3,4 - methylene-

dioxyphenyl)cyclopenteno[1,2-b]pyridine(Example 62)

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - [2 - [2 - (2 - carboxye-
thoxycarbonyl)ethoxycarbonyl]ethoxy] - 4 - methoxyphenyl] -
5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-
dine(Example 63)

These three compounds were prepared by reacting
(5RS,6SR,7SR) - 7 - (2 - hydroxy - 4 - methoxyphenyl) - 6 - tert -
butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine with β - propiolactone, followed
by purification by preparative TLC(E. Merck Kieselgel
60F₂₅₄/chloroform:methanol:acetic acid=20:1:1).

Example 61

High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₈+H)⁺):

Calcd: 478.1502

Found: 478.1491

¹H - NMR(300MHz, CDCl₃, δ ppm):2.53- 2.77(2H, m), 3.23(1H,
t, J=9.6Hz), 3.77(3H, s), 4.10 - 4.21(2H, m), 4.63,
5.08(1H $\times$ 2, d $\times$ 2, J=9.6Hz), 5.91- 5.96(2H, m), 6.42
- 6.52(2H, m), 6.63 - 6.80(3H, m), 6.94(1H, d,
J=8.8Hz), 7.14(1H, dd, J=4.8Hz, 7.7Hz), 7.34(1H, d,
J=7.7Hz), 8.46(1H, d, J=4.8Hz)

Rf Value:0.44(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol:acetic acid=20:1:1)

Example 62

High Resolution FAB - MS(m/e, (C₂₉H₂₇NO₁₀+H)⁺):

Calcd: 550.1713

Found: 550.1696

¹H - NMR(300MHz, CDCl₃, δ ppm): 2.45-2.76(4H, m), 3.16(1H, t, J=9.4Hz), 3.77(3H, s), 4.08-4.31(3H, m), 4.53-4.70(1H, m), 4.66, 5.16(1H × 2, d × 2, J=9.4Hz), 5.92-5.96(2H, m), 6.43-6.51(2H, m), 6.65-6.81(3H, m), 6.84(1H, d, J=8.9Hz), 7.18(1H, dd, J=5.0Hz, 7.6Hz), 7.38(1H, d, J=7.6Hz), 8.44(1H, d, J=5.0Hz)

Rf Value: 0.47(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 63

High Resolution FAB - MS(m/e, (C₃₂H₃₁NO₁₂+H)⁺):

Calcd: 622.1925

Found: 622.1938

¹H - NMR(300MHz, CDCl₃, δ ppm): 2.50-2.90(6H, m), 3.03(1H, t, J=9.3Hz), 3.78(3H, s), 4.09-4.54(6H, m), 4.63, 5.16(1H × 2, d × 2, J=9.3Hz), 5.92-5.96(2H, m), 6.44-6.53(2H, m), 6.64(1H, s), 6.66-6.80(2H, m), 6.91(1H, d, J=9.2Hz), 7.15(1H, dd, J=4.9Hz, 7.6Hz), 7.33(1H, d, J=7.6Hz), 8.53(1H, d, J=4.9Hz)

Rf Value: 0.54(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 64

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

(1) (5RS,6SR,7SR) - 7 - [2 - (2 - Benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl -

5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-
dine

(5RS,6SR,7SR) - 7 - (2 - Hydroxy - 4 - methoxyphenyl) - 6 -
tert-butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
5 penteno[1,2 - b]pyridine which was prepared in Example 50
- (5) was allowed to react with 2 - bromo - 3 - (benzy-
loxy)propionic acid methyl ester which was prepared from
O - benzylserine according to the method described in a
literature(J. Med. Chem., 1985,28,1447 - 1453)in the same
10 manner as in Example 55 - (1) and the crude product was
purified by silica gel column chromatography(E. Merck
Kieselgel 60/hexane:AcOEt=3:1 to 2:1 to 1:1) to give
each of the diastereomers of (5RS,6SR,7SR) - 7 - [2 - (2 -
benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 6
15 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine and (5RS,6SR,7SR) - 7 - [2 - (1 -
methoxycarbonylethenyloxy) - 4 - methoxyphenyl] - 6 - tert - bu-
toxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine.

20 (2) The title compound was prepared in the same manner
as in Example 55 - (2) using one of the diastereomers of
(5RS,6SR,7SR) - 7 - [2 - (2 - benzyloxy - 1 - methoxycar-
bonylethoxy) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl -
5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-
25 dine.

mp:73 - 76 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):3.37(1H, t, J=10.0Hz),

3.69(3H, s), 3.75(3H, s), 3.87(2H, d, J=5.0Hz),
4.51(1H, d, J=12.1Hz), 4.56(1H, d, J=12.1Hz),
4.65(1H, d, J=10.0Hz), 4.88(1H, t, J=5.0Hz),
5.04(1H, d, J=10.0Hz), 5.92(1H, d, J=1.3Hz),
5.94(1H, d, J=1.3Hz), 6.36(1H, d, J=2.3Hz),
6.53(1H, dd, J=2.3Hz, 8.4Hz), 6.72 - 6.80(3H, m),
7.07(1H, d, J=8.4Hz), 7.10(1H, dd, J=4.5Hz, 7.7Hz),
7.18 - 7.40(6H, m), 8.46(1H, d, J=4.5Hz)

Rf Value:0.35(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 65

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other diastereomer)

The title compound was prepared in the same manner as in Example 64 - (2) using the other diastereomer of (5RS,6SR,7SR) - 7 - [2 - (2 - benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 64 - (1)(the other diastereomer).

mp:75 - 78 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):3.37(1H, dd, J=3.6Hz, 9.9Hz), 3.55(1H, dd, J=5.4Hz, 9.9Hz), 3.70(1H, t, J=10.4Hz), 3.70(3H, s), 3.75(3H, s), 4.35(1H, d, J=12.2Hz), 4.42(1H, d, J=12.2Hz), 4.59(1H, d,

J=10.4Hz), 4.77(1H, dd, J=3.6Hz, 5.4Hz), 4.85(1H, d, J=10.4Hz), 5.92(2H, s), 6.32(1H, d, J=2.3Hz), 6.52(1H, dd, J=2.3Hz, 8.5Hz), 6.72(1H, d, J=7.9Hz), 6.83(1H, d, J=7.9Hz), 6.88(1H, s), 7.03(1H, dd, J=4.8Hz, 7.5Hz), 7.17 - 7.38(7H, m), 8.36(1H, d, J=4.8Hz)

Rf Value:0.39(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 66

10 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - methoxycarbonylethenyloxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 64 - (2) using (5RS,6SR,7SR) - 7 - [2 - (1 - methoxycarbonylethenyloxy) - 4 - methoxyphenyl] - 6 - tert-butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 64 - (1).

mp:147 - 150 °C

20 H - NMR(300MHz, CDCl₃, δ ppm):3.60(1H, t, J=10.0Hz), 3.67(3H, s), 3.72(3H, s), 4.57(1H, d, J=10.0Hz), 4.80(1H, d, J=10.0Hz), 5.01(1H, d, J=2.1Hz), 5.66(1H, d, J=2.1Hz), 5.94(1H, d, J=1.4Hz), 5.95(1H, d, J=1.4Hz), 6.47(1H, d, J=2.5Hz), 6.65(1H, dd, J=2.5Hz, 8.5Hz), 6.71 - 6.79(3H, m), 7.09(1H, dd, J=4.9Hz, 7.6Hz), 7.21(1H, d, J=8.5Hz), 7.25(1H, d, J=7.6Hz), 8.40(1H, d, J=4.9Hz)

Rf Value:0.22(E. Merck, Kieselgel 60F/chloroform:methanol=95:5)

Each Compound in the following Examples 67 and 68 was prepared by hydrogenation of the corresponding benzyl ether compound using palladium black as a catalyst.

Example 67

(5RS,6SR,7SR)-6-Carboxy-7-[2-(2-hydroxy-1-methoxycarbonylethoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

mp:108 - 110 °C

High Resolution FAB-MS(m/e, (C₂₇H₂₅NO₉+H)⁺):

Calcd: 508.1607

Found: 508.1602

¹H-NMR(300MHz, CDCl₃, δ ppm):3.31(1H, t, J=9.6Hz), 3.75(3H, s), 3.76(3H, s), 3.99(1H, dd, J=4.2Hz, 12.3Hz), 4.10(1H, dd, J=2.2Hz, 12.3Hz), 4.63(1H, d, J=9.6Hz), 4.79(1H, dd, J=2.2Hz, 4.2Hz), 5.29(1H, d, J=9.6Hz), 5.96(2H, s), 6.28(1H, d, J=2.3Hz), 6.52(1H, dd, J=2.3Hz, 8.5Hz), 6.70(1H, s), 6.74(1H, d, J=7.9Hz), 6.78(1H, d, J=7.9Hz), 7.07(1H, d, J=8.5Hz), 7.14(1H, dd, J=4.9Hz, 7.6Hz), 7.35(1H, d, J=7.6Hz), 8.43(1H, d, J=4.9Hz)

Rf Value:0.47(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 68

(5RS,6SR,7SR)-6-Carboxy-7-[2-(2-hydroxy-1-methox-

ycarbonylethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other dias-
tereomer)

High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₉+H)⁺):

5 Calcd: 508.1608

Found: 508.1579

¹H - NMR(300MHz, CDCl₃, δ ppm):3.48(1H, t, J=9.9Hz), 3.66
- 3.80(2H, m), 3.69(3H, s), 3.75(3H, s), 4.55(1H, d,
J=9.9Hz), 4.77(1H, dd, J=3.0Hz, 6.3Hz), 5.07(1H, d,
10 J=9.9Hz), 5.94(2H, s), 6.31(1H, d, J=2.0Hz),
6.52(1H, dd, J=2.0Hz, 8.5Hz), 6.73 - 6.76(3H, m),
7.10(1H, d, J=8.5Hz), 7.13(1H, dd, J=5.0Hz, 7.7Hz),
7.29(1H, d, J=7.7Hz), 8.45(1H, d, J=5.0Hz)

Rf Value:0.41(E. Merck, Kieselgel 60F₂₅₄/chlo-
15 roform:methanol=10:1)

Each compound in the following Examples 69 - 71 was
prepared by hydrolyzing the corresponding methyl ester
compounds with base.

Example 69

20 (5RS,6SR,7SR)- 6- Carboxy- 7- [2- (1- carboxy- 2- hydrox-
yethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
diastereomers)

mp:158 - 163 °C

25 High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₉+H)⁺):

Calcd: 494.1451

Found: 494.1452

¹H - NMR(300MHz, acetone - d₆, δ ppm): 3.79(3H, s),
3.898(1H, dd, J=10.2Hz, 11.3Hz), 3.900(1H, dd,
J=4.6Hz, 12.0Hz), 3.99(1H, dd, J=3.0Hz, 12.0Hz),
4.68(1H, d, J=10.2Hz), 5.03(1H, dd, J=3.0Hz,
5 4.6Hz), 5.28(1H, d, J=11.3Hz), 6.03(2H, s), 6.58
(1H, dd, J=2.3Hz, 8.4Hz), 6.62(1H, d, J=2.3Hz),
6.86 - 6.92(3H, m), 7.31(1H, dd, J=5.0Hz, 7.6Hz),
7.39 - 7.42(2H, m), 8.24(1H, d, J=5.0Hz)

Rf Value: 0.25(E. Merck, Kieselgel 60F₂₅₄/chloro-
10 roform:methanol:acetic acid=10:1:1)

Example 70

(5RS,6SR,7SR)-6-Carboxy-7-[2-(1-carboxy-2-hydrox-
yethoxy)-4-methoxyphenyl]-5-(3,4-methylene-
dioxyphenyl)cyclopenteno[1,2-b]pyridine(the other
15 diastereomer)

mp: 139 - 142 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₉+H)⁺):

Calcd: 494.1451

Found: 494.1454

20 ¹H - NMR(300MHz, acetone-d₆, δ ppm): 3.58(1H, t, J=9.7Hz),
3.75 - 3.81(1H, dd, J=5.6Hz, 11.9Hz), 3.78(3H, s),
3.97(1H, dd, J=3.0Hz, 11.9Hz), 4.67(1H, d,
J=9.7Hz), 5.03(1H, dd, J=3.0Hz, 5.6Hz), 5.17(1H, d,
J=9.7Hz), 6.01(2H, s), 6.55(1H, dd, J=2.4Hz,
25 8.4Hz), 6.61(1H, d, J=2.4Hz), 6.82 - 6.89(3H, m),
7.18(1H, d, J=8.4Hz), 7.25(1H, dd, J=5.0Hz, 7.6Hz),
7.39(1H, d, J=7.6Hz), 8.32(1H, d, J=5.0Hz)

Rf Value:0.20(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 71

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxyethenyloxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:144 - 147 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₁NO₈+H)⁺):

Calcd: 476.1345

10 Found: 476.1360

¹H - NMR(300MHz, CDCl₃, δ ppm):3.72(1H, t, J=10.4Hz),
3.75(3H, s), 4.68(1H, d, J=10.4Hz), 5.23(1H, d,
J=10.4Hz), 5.41(1H, s), 5.99(2H, s), 6.09(1H, s),
6.58(1H, d, J=2.4Hz), 6.61(1H, dd, J=2.4Hz, 8.1Hz),
15 6.70(1H, d, J=1.6Hz), 6.76(1H, dd, J=1.6Hz, 7.9Hz),
6.82(1H, d, J=7.9Hz), 7.216(1H, d, J=8.1Hz),
7.225(1H, dd, J=5.1Hz, 7.7Hz), 7.41(1H, d,
J=7.7Hz), 8.31(1H, d, J=5.1Hz)

20 Rf Value:0.46(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 72

(5RS,6SR,7SR) - 6 - Carboxy - 2 - hydroxymethyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

25 (1) 6 - Methyl - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid methyl ester

6 - Methyl - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyri-

dine - 2 - carboxylic acid which was prepared in the same manner as in Example 1 - (1) was treated with HCl - methanol by a conventional method to give the methyl ester.

5 (2) 6 - Methyl - 3 - (3,4 - methylenedioxyphenylcarbonyl) - 2 - methoxycarbonylpyridine N - oxide

To a dichloromethane(20ml) solution of 6 - methyl - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid methyl ester(1.75g,5.85mmol) was added
10 mCPBA(1.73g) under ice - cooling. The mixture was stirred at room temperature for 20 h and an aqueous solution of sodium thiosulfate was added to the mixture to quench the reaction. The mixture was neutralized with a saturated aqueous solution of NaHCO₃ and extracted with
15 dichloromethane. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduce pressure to give 6 - methyl - 3 - (3,4 - methylenedioxyphenylcarbonyl) - 2 - methoxycarbonylpyridine N - oxide(1.57g).

20 (3) 6 - Hydroxymethyl - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid methyl ester

To a DMF(15ml) solution of 6 - methyl - 3 - (3,4 - methylenedioxyphenylcarbonyl) - 2 - methoxycarbonylpyridine N - oxide(1.56g,4.95mmol) was added anhydrous trifluoro
25 acetic acid(7ml) under ice - cooling, and the mixture was stirred at room temperature for 18 h. After removal of the excess anhydrous trifluoro acetic acid the residue

was partitioned between water and AcOEt. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine, dried over MgSO₄ and concentrated under reduced pressure to give 6-hydroxymethyl-3-(3,4-methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid methyl ester(1.72g).

(4) 6 - (Trimethylsilylethoxymethoxymethyl) - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid methyl ester

10 To a dichloromethane(9ml) solution of 6 - hydroxymethyl-3-(3,4-methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid methyl ester(1.71g,4.50mmol) were added ethyldiisopropylamine(3.9ml) and 2-trimethylsilylethoxymethyl chloride(2.4ml) at room temperature. The
15 mixture was stirred at room temperature for 17 h, partitioned between AcOEt and water, The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by MPLC(E.
20 Merck lohar column Kieselgel 60/hexane:AcOEt=3:1 to 1:1) to give 6-(2-trimethylsilylethoxymethoxymethyl)-3-(3,4-methylenedioxyphenylcarbonyl)pyridine - carboxylic acid methyl ester(1.44g).

(5) 6 - (2 - Trimethylsilylethoxymethoxymethyl) - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid

25 6 - (2 - Trimethylsilylethoxymethoxymethyl) - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - carboxylic acid

methyl ester was subjected to alkaline hydrolysis in methanol to give 6 - (2 - trimethylsilylethoxymethoxymethyl) - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid.

5 (6) 6 - Ethoxycarbonyl - 7 - oxo - 2 - (2 - trimethylsilylethoxymethoxymethyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine

To a THF(10ml) solution of 6 - (2 - trimethylsilylethoxymethoxymethyl) - 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid(1.27g,2.94mmol) was added CDI(950ml) under ice - cooling. The mixture was stirred at room temperature for 5 h and treated with magnesium ethyl malonate(2.6g) under ice - cooling. The mixture was stirred at room temperature for 63 h, treated with 3N HCl(10ml) under ice - cooling, and then stirred at room temperature for 30 min. The mixture was extracted with dichloromethane and the organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in dichloromethane (20ml), treated with Wako gel C - 200(10g) and stirred at room temperature for 4 h. The gel was removed by filtration and washed with AcOEt. The filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=3:1) to give 6 - ethoxycarbonyl - 7 - oxo - 2 - (2 - trimethylsilyle-

thoxymethoxymethyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine(556mg) as a reddish orange solid.

(7) (5RS,6RS,7SR) - 6 - Ethoxycarbonyl - 2 - (2 - trimethylsilyl -
5 lethoxymethoxymethyl) - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4
- methoxyphenyl)cyclopenteno[1,2 - b]pyridine

(5RS,6RS,7SR) - 6 - Ethoxycarbonyl - 2 - (2 - trimethylsilyl -
lethoxymethoxymethyl) - 5 - (3,4 - methylenedioxyphenyl) - 7 -
(4 - methoxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine
10 was prepared in the same manner as in Example 50 -
(2),(3) using 6 - ethoxycarbonyl - 7 - oxo - 2 - (2 - trimethyl -
silylethoxymethoxymethyl) - 5 - (3,4 - methylene -
dioxyphenyl)cyclopenteno[1,2 - b]pyridine.

(8) (5RS,6RS,7SR) - 6 - Ethoxycarbonyl - 2 - hydroxymethyl - 5
15 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclo -
penteno[1,2 - b]pyridine

A solution of (5RS,6RS,7SR) - 6 - ethoxycarbonyl - 2 - (2
- trimethylsilylethoxymethoxymethyl) - 5 - (3,4 - methylene -
dioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]py -
20 ridine (34mg,0.059mmol) in 10% HCl - MeOH was stirred at
room temperature for 15 h. After removal of the solvent
the residue was partitioned between brine and AcOEt. The
organic layer was washed a saturated aqueous solution of
NaHCO₃ and brine, dried over Na₂SO₄ and concentrated
25 under reduced pressure. The residue was purified by
preparaive TLC(E. Merck Kieselgel 60F₂₅₄/hex -
ane:AcOEt=1:1) to give (5RS,6RS,7SR) - 6 - ethoxycarbonyl -

2-hydroxymethyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine(17mg).

(9) The title compound was prepared in the same manner as in Example 2 using (5RS,6RS,7SR)-6-ethoxycarbonyl-2-
5 - hydroxymethyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine.

High Resolution FAB-MS(m/e, (C₂₄H₂₁NO₆+H)⁺):

Calcd: 420.1447

Found: 420.1457

10 ¹H-NMR(300MHz, CDCl₃, δ ppm):3.30(1H, t, J=9.5Hz),
3.81(3H, s), 4.60(1H, d, J=9.5Hz), 4.70(2H, s),
4.71(1H, d, J=9.5Hz), 5.97(2H, s), 6.70(1H, brs),
6.75(1H, d, J=7.9Hz), 6.80(1H, d, J=7.9Hz),
6.89(2H, d, J=8.7Hz), 7.09(1H, d, J=7.8Hz),
15 7.17(2H, d, J=8.7Hz), 7.31(1H, d, J=7.8Hz)

Rf Value:0.28(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 73

20 (5RS,6SR,7SR)-2-Ethoxymethyl-6-carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(1) (5RS,6RS,7SR)-2-Ethoxycarbonyl-2-hydroxymethyl-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

25 (5RS,6RS,7SR)-2-Ethoxycarbonyl-2-hydroxymethyl-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine was prepared in

the same manner as in Example 72 - (7), (8) using 6 - ethoxycarbonyl - 7 - oxo - 2 - (2 - trimethylsilylethoxymethoxymethyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine prepared in Example
5 72 - (6) and 4 - methoxy - 2 - methoxymethoxyphenyl bromide.

(2) (5RS,6RS,7SR) - 2 - Ethoxycarbonyl - 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - hydroxymethyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

(5RS,6RS,7SR) - 2 - Ethoxycarbonyl - 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - hydroxymethyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine was prepared in the same manner as in Example 30 - (3) using
10 (5RS,6RS,7SR) - 2 - ethoxycarbonyl - 2 - hydroxymethyl - 7 - (2 - hydroxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was
15 prepared in (1).

(3) (5RS,6RS,7SR) - 2 - Ethoxycarbonyl - 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - chloromethyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a chloroform solution(1ml) of (5RS,6RS,7SR) - 2 - ethoxycarbonyl - 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - hydroxymethyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(17mg,0.031mmol)
20 was added thionyl chloride(20 μ l) under ice - cooling and the mixture was stirred at room temperature for 2 h.
25 After removal of the solvent the residue was dried under reduced pressure to give (5RS,6RS,7SR) - 2 - ethoxycarbonyl

- 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - chloromethyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(14mg).

(4) (5RS,6RS,7SR) - 2 - Ethoxycarbonyl - 7 - (2 - ethoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - chloromethyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine (14mg,0.025mmol) which was prepared in (3) was dissolved in an ethanol solution of sodium ethoxide(1.1M,10ml), stirred at room temperature for 16 h, treated with water, and then stirred at room temperature 18 h. The reaction solution was treated with 1N HCl and extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound(8.4mg).

High Resolution FAB - MS(m/e, (C₂₈H₂₇NO₉+H)⁺):

Calcd: 522.1764

Found: 522.1785

¹H - NMR(300MHz, acetone- d₆, δ ppm):1.18(3H, t, J=7.1Hz), 3.54(2H, q, J=7.1Hz), 3.68(1H, t, J=10.0Hz), 3.79(3H, s), 4.45 - 4.55(3H, m), 4.63(1H, d, J=10.0Hz), 4.74(1H, d, J=16.2Hz), 4.95(1H, d, J=10.0Hz), 6.00(2H, s), 6.57(1H, dd, J=2.4Hz, 8.3Hz), 6.61(1H, d, J=2.4Hz), 6.82 - 6.93(3H, m), 7.22(1H, d, J=8.3Hz), 7.34 - 7.40(2H, m)

Rf Value:0.60(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 74

(5RS,6SR,7SR)-7-(2-Ethylaminocarbonylmethoxy-4-methoxyphenyl)-2-ethylaminomethyl-6-carboxy-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(1) (5RS,6RS,7SR)-2-Ethoxycarbonyl-7-(2-ethoxycarbonylmethoxy-4-methoxyphenyl)-2-chloromethyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example 73-(3) was dissolved in a THF solution of ethylamine(21%,4ml) and stirred at room temperature for 6 h. After removal of the solvent the residue was purified by preparative TLC(E. Merck Kieselgel 60F₂₅₄/chloroform:methanol=10:1) to give (5RS,6RS,7SR)-7-(2-ethylaminocarbonylmethoxy-4-methoxyphenyl)-2-ethylaminomethyl-6-ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(17.1mg) and (5RS,6RS,7SR)-2-ethylaminomethyl-6-ethoxycarbonyl-7-(2-ethoxycarbonylmethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(1.2mg).

(2) The title compound was prepared in the same manner as in Example 2 using (5RS,6RS,7SR)-7-(2-ethylaminocarbonylmethoxy-4-methoxyphenyl)-2-ethylaminomethyl-6-ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in (1).

High Resolution FAB-MS(m/e, (C₃₀H₃₃N₃O₇+H)⁺):

Calcd: 548.2397

Found: 548.2396

¹H-NMR(300MHz, CD₃OD, δ ppm):1.13(3H, t, J=7.3Hz),

1.23(3H, t, J=7.2Hz), 3.04(2H, q, J=7.2Hz),
 3.17(1H, t, J=9.9Hz), 3.23 - 3.33(2H, m), 3.76(3H,
 s), 4.23(2H, s), 4.36(1H, d, J=14.6Hz), 4.44(1H, d,
 J=14.6Hz), 4.60(1H, d, J=9.9Hz), 5.04(1H, d,
 5 J=9.9Hz), 5.90(2H, s), 6.48(1H, d, J=2.3Hz),
 6.55(1H, dd, J=2.3Hz, 8.1Hz), 6.70(1H, s), 6.74 -
 6.80(2H, m), 6.99(1H, d, J=8.1Hz), 7.24(1H, d,
 J=7.9Hz), 7.35 - 7.40(1H, m)

Rf Value: 0.43(E. Merck, Kieselgel 60F₂₅₄/chloro-
 10 form:methanol:acetic acid=10:1:1)

Example 75

(5RS,6SR,7SR) - 2 - Ethylaminomethyl - 6 - carboxy - 7 - (2
- carboxymethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine

15 The title compound was prepared in the same manner
 as in Example 2 using (5RS,6RS,7SR) - 2 - ethylaminomethyl -
 6 - ethoxycarbonyl - 7 - (2 - ethoxycarbonylmethoxy - 4 - methox-
 yphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 -
 b]pyridine which was prepared in Example 74 - (1).

20 High Resolution FAB - MS(m/e, (C₂₈H₂₈N₂O₈+H)⁺):

Calcd: 521.1924

Found: 521.1939

¹H - NMR(300MHz, CD₃OD, δ ppm): 1.25(3H, t, J=7.2Hz),
 3.06(2H, q, J=7.2Hz), 3.56(1H, t, J=10.0Hz),
 25 3.75(3H, s), 4.17(1H, d, J=15.4Hz), 4.19(2H, s),
 4.28(1H, d, J=15.4Hz), 4.56(1H, d, J=10.0Hz),
 4.71(1H, d, J=10.0Hz), 5.92(2H, s), 6.42(1H, d,

J=2.2Hz), 6.49(1H, dd, J=2.2Hz, 8.2Hz), 6.71(1H, s), 6.75 - 6.81(2H, m), 7.13(1H, d, J=8.2Hz), 7.17(1H, d, J=7.6Hz), 7.27 - 7.31(1H, m)

Rf Value:0.22(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 76

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2 - carboxylmethoxy - 4 - methoxyphenyl) - 2 - propoxy - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 30 - (1), Example 50 - (1) - (6) and Example 30 - (4) using 6 - propoxypyridine - 2,3 - dicarboxylic acid anhydride.

High Resolution FAB - MS(m/e, (C₂₈H₂₇NO₉+H)⁺):

Calcd: 522.1764

Found: 522.1769

¹H - NMR(300MHz, CDCl₃, δ ppm):0.97(3H, t, J=7.2Hz), 1.72(2H, sext, J=7.2Hz), 2.96(1H, t, J=9.6Hz), 3.81(3H, s), 4.02 - 4.22(2H, m), 4.52(1H, d, J=16.1Hz), 4.61(1H, d, J=9.6Hz), 4.67(1H, d, J=16.1Hz), 5.22(1H, d, J=9.6Hz), 5.92, 5.94(1H × 2, d × 2, J=1.9Hz), 6.37(1H, d, J=2.3Hz), 6.53(1H, dd, J=2.3Hz, 8.6Hz), 6.59(1H, d, J=8.4Hz), 6.63 - 6.79(3H, m), 7.06(1H, d, J=8.4Hz), 7.20(1H, d, J=8.6Hz)

Rf Value:0.31(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 77

(5RS,6SR,7SR)-2-Ethyl-6-carboxy-5-(3,4-methylene-
dioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]py-
ridine

5 (1) 6-Phenylthiopyridine-2,3-dicarboxylic acid dime-
thyl ester

To an anhydrous DMF suspensin of K_2CO_3 (8.29g) was added thiophenol (3.08ml) under nitrogen atmospher and the mixture was stirred at room temperature for 10 min.
10 A DMF (10ml) solution of 6-chloropyridine-2,3-dicarboxylic acid dimethyl ester was added to the mixture. The mixture was stirred at 80°C for 30 min and at 100°C for 1 h, then cooled. The reaction solution was partitioned between water and AcOEt, and the organic
15 layer was washed with water and then dried over $MgSO_4$. After evaporation of the solvent the residue was purified by dry flash column chromatography (E. Merck Kieselgel 60/hexane:dichloromethane=1:1 to dichloromethane) to give 6-phenylthiopyridine-2,3-dicarboxylic
20 acid dimethyl ester (6.07g) as a colorless powder.

(2) 5-Hydroxy-2-phenylthio-6-tert-butoxycarbonyl-5-
(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclop-
ent-1,3-dieno[2,1-b]pyridine

6-phenylthiopyridine-2,3-dicarboxylic acid dime-
25 thyl ester which was prepared in (1) was converted to the acid anhydride in a conventional manner and subjected to the same reactions as in Example 30 - (1),

Example 50 - (1), (2) to give 5 - hydroxy - 2 - phenylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine.

(3) 5 - (2 - Trimethylsilylethoxymethoxy) - 2 - phenylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine

To a dichloromethane(1ml) solution of 5 - hydroxy - 2 - phenylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(647mg, 1.14mmol) which was prepared in (2) was added ethyldiisopropylamine(0.99ml). The mixture was cooled in an ice - bath and trimethylsilylethoxymethyl chloride(0.61ml) was added dropwise to the mixture. The mixture was stirred at room temperature for 2 h, diluted with dichloromethane, washed with a saturated aqueous solution of NaHCO₃ and dried over MgSO₄. After removal of the solvent under reduced pressure the resulting residue was purified by column chromatography(E. Merck Kieselgel 60/hexane:dichloromethane=1:3 to 1:10) to give 5 - (2 - trimethylsilylethoxymethoxy) - 2 - phenylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(594mg) as a pale yellow oil.

(4) 5 - (2 - Trimethylsilylethoxymethoxy) - 2 - phenylsulfonyl - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine

To a chloroform(40ml) solution of 5-(2-trimethylsilylethoxymethoxy)-2-phenylthio-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine (593mg,0.850mmol) which was prepared in (3) was added MCPBA(323mg) and the solution was stirred at room temperature for 12 h. The reaction solution was partitioned between chloroform and 5% aqueous solution of NaHCO₃. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and dried over MgSO₄. After removal of the solvent under reduced pressure the residue was purified by dry flash chromatography(E. Merck Kieselgel 60/dichloromethane) to give 5-(2-trimethylsilylethoxymethoxy)-2-phenylsulfonyl-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine (554mg) as a pale yellow powder.

(5) 2-Ethyl-5-(2-trimethylsilylethoxymethoxy)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine

To a THF(2.5ml) solution of 5-(2-trimethylsilylethoxymethoxy)-2-phenylsulfonyl-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine (100mg,0.137mmol) which was prepared in (4) was added a THF solution(0.10M,1.64ml) of ethyllithium dropwise at -78°C and the solution was stirred at -78°C for 1.5 h. To the

reaction solution was added 10% citric acid at -78°C and the solution was extracted with AcOEt. The organic layer was washed with brine and dried over MgSO_4 . After removal of the solvent under reduced pressure the
5 resulting residue was purified by preparative TLC(E. Merck Kieselgel 60/hexane:AcOEt=3:1) to give 2-ethyl-5-(2-trimethylsilylethoxymethoxy)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine(25.6mg).

10 (6) 2-Ethyl-5-hydroxy-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine

To a methanol(2ml) solution of 2-ethyl-5-(2-trimethylsilylethoxymethoxy)-6-tert-butoxycarbonyl-5-
15 (3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine (52mg,0.084mmol) which was prepared in (5) was added 10%HCl-methanol(0.2ml) dropwise under ice-cooling and the mixture was stirred at room temperature for 2 h. To the reaction solution
20 was added a saturated aqueous solution of NaHCO_3 and the solution was extracted with AcOEt. The organic layer was washed with brine and dried over MgSO_4 . The solvent was evaporated to give 2-ethyl-5-hydroxy-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine
25 (45mg).

(7) The title compound was prepared in the same manner

as in Example 50 - (3), (4), (7) using 2-ethyl-5-hydroxy-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine which was prepared in (6).

5 High Resolution FAB-MS(m/e, (C₂₅H₂₃NO₅+H)⁺):

Calcd: 418.1654

Found: 418.1636

¹H-NMR(300MHz, CDCl₃, δ ppm): 1.21(3H, t, J=7.6Hz), 2.65
- 2.86(2H, m), 3.15(1H, t, J=9.2Hz), 3.73(3H, s),
10 4.52, 4.75(1H × 2, d × 2, J=9.2Hz), 5.94(2H, s),
6.71(1H, s), 6.64 - 6.87(2H, m), 6.81(2H, d, J=8.4Hz),
7.01(1H, d, J=7.9Hz), 7.13(2H, d, J=8.4Hz), 7.24(1H, d, J=7.9Hz)

Rf Value: 0.26(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=20:1)
15

Each compound in the following Examples 78-81 was prepared in the same manner as in Example 77.

Example 78

(5RS,6SR,7SR)-6-Carboxy-2-cyclopropyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine
20

mp: 98 - 100 °C

High Resolution FAB-MS(m/e, (C₂₆H₂₃NO₅+H)⁺):

Calcd: 430.1654

25 Found: 430.1640

¹H-NMR(300MHz, CDCl₃, δ ppm): 0.75 - 0.95(4H, m), 1.95 -
2.05(1H, m), 3.19(1H, t, J=9.5Hz), 3.80(3H, s),

4.53(1H, d, J=9.5Hz), 4.67(1H, d, J=9.5Hz),
 5.95(2H, ABq, J=1.5Hz), 6.69(1H, d, J=1.6Hz),
 6.73(1H, dd, J=1.6Hz, 7.8Hz), 6.78(1H, d, J=7.8Hz),
 6.86(2H, d, J=9.1Hz), 6.89(1H, d, J=8.0Hz),
 5 7.15(1H, d, J=8.0Hz), 7.16(2H, d, J=9.1Hz)

Rf Value:0.51(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 79

10 (5RS,6SR,7SR) - 6 - Carboxy - 2 - pentyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

High Resolution FAB - MS(m/e, (C₂₈H₂₉NO₅+H)⁺):

Calcd: 460.2124

Found: 460.2127

15 ¹H - NMR(300MHz, CDCl₃, δ ppm):0.86(3H, t, J=6.8Hz), 1.24
 - 1.38(4H, m), 1.57 - 1.70(2H, m), 2.69 - 2.77(2H, m),
 3.17(1H, t, J=9.4Hz), 3.78(3H, s), 4.54(1H, d,
 J=9.4Hz), 4.73(1H, d, J=9.4Hz), 5.95(2H, ABq,
 J=1.4Hz), 6.69(1H, d, J=1.5Hz), 6.75(1H, dd,
 20 J=1.5Hz, 7.8Hz), 6.78(1H, d, J=7.8Hz), 6.85(2H, d,
 J=8.7Hz), 6.99(1H, d, J=7.7Hz), 7.14(2H, d,
 J=8.7Hz), 7.21(1H, d, J=7.7Hz)

Rf Value:0.47(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

25 Example 80

6 - Carboxy - 5 - hydroxy - 2 - (3 - butenyl) - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - die-

no[2,1-b]pyridineHigh Resolution FAB - MS(m/e, (C₂₇H₂₃NO₆+H)⁺):

Calcd: 458.1604

Found: 458.1618

5 ¹H - NMR(300MHz, CDCl₃, δ ppm): 2.47(2H, q, J=7.3Hz),
2.86(2H, t, J=7.3Hz), 3.88(3H, s), 4.90 - 5.10(2H,
m), 5.75 - 6.00(3H, m), 6.71(1H, d, J=7.6Hz), 6.89 -
7.10(5H, m), 7.45(1H, d, J=7.6Hz), 7.76(2H, d,
J=7.8Hz)

10 Rf Value: 0.42(E. Merck, Kieselgel 60F₂₅₄/chloro-
form:methanol=10:1)

Example 81

(5RS,6SR,7SR) - 6 - Carboxy - 2 - (3 - butenyl) - 5 - (3,4 - me-
thylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclo-
15 penteno[1,2-b]pyridine

High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₅+H)⁺):

Calcd: 444.1811

Found: 444.1805

¹H - NMR(300MHz, CDCl₃, δ ppm): 2.34 - 2.48(2H, m), 2.74 -
20 2.93(2H, m), 3.19(1H, t, J=9.6Hz), 4.55, 4.73(1H ×
2, d × 2, J=9.6Hz), 3.79(3H, s), 4.90 - 5.06(2H, m),
5.71 - 5.90(1H, m), 5.91 - 6.00(2H, m), 6.69(1H, s),
6.71 - 6.81(2H, m), 6.86(2H, d, J=8.6Hz), 6.99(1H, d,
J=8.0Hz), 7.15(2H, d, J=8.6Hz), 7.24(1H, d,
25 J=8.0Hz)

Rf Value: 0.25(E. Merck, Kieselgel 60F₂₅₄/chloro-
form:methanol=20:1)

Example 82

(5RS,6SR,7SR) - 6 - Carboxy - 2 - propylthio - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

5 (1) 5 - (2 - Trimethylsilylethoxymethoxy) - 2 - propylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine

A benzene(1ml) solution of 5 - (2 - trimethylsilylethoxymethoxy) - 2 - phenylsulfonyl - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(100mg,0.14mmol) which was prepared in Example 77 - (4) and 18 - Crown - 6(7.1mg) was added to a benzene solution(1ml) of sodium propylmercaptide which was prepared from sodium hydride(7.3mg) and propanethiol(19 μ l) and the mixture was stirred at room temperature under nitrogen atmosphere for 19 h. To the solution was added a saturated aqueous solution of NaHCO₃ and the solution was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=9:1 to 3:1) to give 5 - (2 - trimethylsilylethoxymethoxy) - 2 - propylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine(19mg) as a brown solid.

(2) The title compound was prepared in the same manner as in Example 77 - (5),(6) using 5 - (2 - trimethylsilylethoxymethoxy) - 2 - propylthio - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - b]pyridine which was prepared in (1).

mp: 62 - 65 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₅S+H)⁺):

Calcd: 464.1532

10 Found: 464.1541

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.84(3H, t, J=7.4Hz), 1.55(2H, sext, J=7.4Hz), 2.80(1H, dt, J=13.7Hz, 7.4Hz), 3.08(1H, dt, J=13.7Hz, 7.4Hz), 3.27(1H, t, J=8.8Hz), 3.79(3H, s), 4.53(1H, d, J=8.8Hz), 4.65(1H, d, J=8.8Hz), 5.94(2H, brs), 6.68(1H, s), 6.73(1H, d, J=7.8Hz), 6.77(1H, d, J=7.8Hz), 6.86(2H, d, J=8.3Hz), 6.99(1H, d, J=8.2Hz), 7.07(1H, d, J=8.2Hz), 7.18(2H, d, J=8.3Hz)

15 Rf Value: 0.32(E. Merck, Kieselgel 60F₂₅₄/hexane:AcOEt= 1:1)

Each compound in the following Example 83 and 84 was prepared in the same manner as in Example 77 using lithium amide instead of lithium alkyl.

Example 83

25 (5RS,6SR,7SR) - 6 - carboxy - 2 - propylamino - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

mp: 92 - 100 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₆N₂O₅+H)⁺):

Calcd: 447.1920

Found: 447.1902

5 ¹H - NMR(300MHz, CDCl₃, δ ppm): 0.94(3H, t, J=7.2Hz),
1.61(2H, sext, J=7.2Hz), 2.97(1H, t, J=8.3Hz),
3.08(2H, t, J=7.2Hz), 3.64(3H, s), 4.33(1H, d,
J=8.3Hz), 4.63(1H, d, J=8.3Hz), 5.93(2H, s),
6.33(1H, d, J=8.7Hz), 6.63 - 6.76(3H, m), 6.79(2H, d,
10 J=8.5Hz), 7.15(2H, d, J=8.5Hz), 7.21(1H, d,
J=8.7Hz)

Rf Value: 0.56 (E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 84

15 (5RS,6SR,7SR) - 6 - Carboxy - 2 - piperidino - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

mp: 48 - 50 °C

High Resolution FAB - MS(m/e, (C₂₈H₂₈N₂O₅+H)⁺):

20 Calcd: 473.2077

Found: 473.2078

¹H - NMR(300MHz, CDCl₃, δ ppm): 1.50 - 1.70(6H, m), 3.15(1H, dd, J=9.1Hz, 9.5Hz), 3.30 - 3.50(4H, m), 3.81(3H, s),
4.48(1H, d, J=9.1Hz), 4.60(1H, d, J=9.5Hz),
25 5.94(2H, ABq, J=1.4Hz), 6.59(1H, d, J=8.6Hz),
6.71(1H, s), 6.76(2H, s), 7.07(1H, d, J=8.6Hz),
7.21(2H, d, J=8.8Hz), 6.87(2H, d, J=8.8Hz)

Rf Value: 0.23 (E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=20:1)

Each compound in the following Example 85 and 86 was prepared in the same manner as in Example 77 - (4), (5), Example 50 - (3) to (6) and Example 30 - (4) using 6-ethoxycarbonyl-5-(trimethylsilylethoxymethoxy)-2-phenylsulfonyl-7-(2-benzyloxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine instead of 5-(trimethylsilylethoxymethoxy)-2-phenylsulfonyl-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-b]pyridine.

Example 85

(5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-2-butyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

mp: 123 - 128 °C

High Resolution FAB-MS (m/e, (C₂₉H₂₉NO₈+H)⁺):

Calcd: 520.1971

Found: 520.1968

¹H-NMR (300MHz, CD₃OD, δ ppm): 0.91 (3H, t, J=7.3Hz), 1.28 - 1.40 (2H, m), 1.55 - 1.65 (2H, m), 2.78 (2H, dd, J=7.7Hz, 7.8Hz), 3.53 (1H, t, J=9.9Hz), 3.77 (3H, s), 4.33 (1H, d, J=16.0Hz), 4.53 (1H, d, J=16.0Hz), 4.55 (1H, d, J=9.9Hz), 4.91 (1H, d, J=9.9Hz), 5.92 (2H, s), 6.50 (1H, d, J=2.4Hz), 6.56 (1H, dd, J=2.4Hz, 8.4Hz), 6.76 - 6.83 (3H, m), 7.13 (1H, d,

J=8.4Hz), 7.21(1H, d, J=7.9Hz), 7.40(1H, d, J=7.9Hz)

Rf Value:0.18(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

5 Example 86

(5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-2-propylamino-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

mp:166 - 168.5 °C

10 High Resolution FAB-MS(m/e, (C₂₈H₂₈N₂O₈+H)⁺):

Calcd: 521.1924

Found: 521.1945

H-NMR(300MHz, acetone-d, δ ppm):0.91(3H, t, J=7.4Hz),
1.58(2H, sept, J=7.4Hz), 3.00 - 3.32(1H, br),
15 3.18(2H, brt.dt - like, J=7.4Hz), 3.51(1H, t, J=9.0Hz),
3.77(3H, s), 4.52(1H, d, J=9.0Hz),
4.67(2H, ABq, J=16.1Hz, Δν=54.0Hz), 5.03(1H, d, J=9.0Hz),
5.99(2H, s), 6.50(1H, d, J=8.4Hz),
6.54(1H, dd, J=2.3Hz, 8.5Hz), 6.61(1H, d, J=2.3Hz),
20 6.82(2H, s), 6.84(1H, s), 7.17(1H, d, J=8.4Hz),
7.19(1H, d, J=8.5Hz)

Rf Value:0.68(E. Merck, Kieselgel 60F/chloroform:methanol:acetic acid=10:1:1)

Example 87

25 (5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethylamino-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(1) 6 - Ethoxycarbonyl - 7 - oxo - 5 - (3,4 - methylene-dioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine

6 - Ethoxycarbonyl - 7 - oxo - 5 - (3,4 - methylene-dioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine was prepared in the same manner as in Example 72 - (6) using 3 - (3,4 - methylenedioxyphenylcarbonyl)pyridine - 2 - carboxylic acid.

(2) 6 - Ethoxycarbonyl - 7 - (2 - nitro - 4 - methoxyphenyl) - 7 - hydroxy - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine

To a solution of 4 - methoxy - 3 - nitrophenyl bromide(472mg) in THF(24ml) was added a solution of phenyl lithium in cyclohexane - ether(7:3,1.8M,1.11ml) dropwise at -100°C. To the solution was added a solution of 6 - ethoxycarbonyl - 7 - oxo - 5 - (3,4 - methylene-dioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine(500mg,1.55mmol) in THF(24ml). The temperature of the reaction solution was raised to -78°C over 1 h. After adding water the solution was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography(E. Merck Kieselgel 60/hexane:AcOEt=1:1 to 2:3 to 1:2) to give 6 - ethoxycarbonyl - 7 - (2 - nitro - 4 - methoxyphenyl) - 7 - hydroxy - 5 - (3,4 - methylenedioxyphenyl)cyclopent - 1,3 - dieno[1,2 - b]pyridine(758mg).

(3) 7 - Acetoxy - 6 - ethoxycarbonyl - 7 - (2 - nitro - 4 - methoxy-

phenyl)-5-(3,4-methylenedioxyphenyl)cyclopent-1,3-dieno[1,2-b]pyridine

To a AcOEt(2ml) suspension of 6-ethoxycarbonyl-7-(2-nitro-4-methoxyphenyl)-7-hydroxy-5-(3,4-methylenedioxyphenyl)cyclopent-1,3-dieno[1,2-b]pyridine which was prepared in (2) was added TEA(1.25ml), Ac₂O(0.85ml) and DMAP(110mg) at 0°C. The reaction solution was stirred at room temperature for 15 min and at 50°C for 2 h, diluted with water, adjusted at pH4 with HCl and extracted with AcOEt. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and dried over MgSO₄. After removal of the solvent the residue was purified by dry column flash chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1 to 1:1 to 2:3) to give 7-acetoxy-6-ethoxycarbonyl-7-(2-nitro-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopent-1,3-dieno[1,2-b]pyridine(753mg).

(4) 7-(2-Amino-4-methoxyphenyl)-6-ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

To a THF(25ml)-EtOH(25ml) suspension of 7-acetoxy-6-ethoxycarbonyl-7-(2-nitro-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopent-1,3-dieno[1,2-b]pyridine which was prepared in (3) and zinc(1.43g) was added 4N HCl-dioxane(10.9ml) dropwise at -78°C. The reaction solution was stirred at -78°C for 1 h and the temperature of the solution was raised to room temperature over 2 h. After adding a saturated aqueous

solution of Na_2CO_3 the resulting insoluble material was removed by filtration and washed with AcOEt. The filtrate and washings were partitioned between water and AcOEt. The organic layer was washed with brine and dried over MgSO_4 . After removal of the solvent the residue was purified by silica gel column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1 to 1:1 to 2:3) to give 7 - (2 - amino - 4 - methoxyphenyl) - 6 - ethoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(355mg).

(5) 6 - Ethoxycarbonyl - 7 - (2 - tert - butoxycarbonyl-methylaminophenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a THF(3ml) solution of 7 - (2 - amino - 4 - methoxyphenyl) - 6 - ethoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(150mg,0.35mmol) which was prepared in (4) was added TEA(1.75ml) and tert - butyl bromoacetate(1.75ml) and the solution was stirred under reflux for 16 h. After cooling the reaction solution was diluted with water and made weak acid with HCl and extracted with AcOEt. The organic layer was washed with brine and dried over MgSO_4 . After removal of the solvent the residue was purified by preparative TLC(E. Merck Kieselgel 60F₂₅₄/hexane:AcOEt=2:1) to give (5RS,7SR) - 6 - ethoxycarbonyl - 7 - (2 - tert - butoxycarbonyl-methylaminophenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(33mg) and (5RS,7RS) - 6 -

ethoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethylaminophenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(20mg).

(6) To a methanol(0.4ml) and dioxane(0.4ml) solution
5 of (5RS,7SR) - 6 - ethoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethylaminophenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(33mg,0.06mmol) which was prepared in (5) was added 6N NaOH(0.1ml) and the solution was stirred at room temperature for 16 h. After
10 removal of the solvent the residue was partitioned between water and AcOEt and the aqueous layer was made at pH4 with HCl and extracted with AcOEt. The organic layer was washed with brine and dried over MgSO₄. After removal of the solvent the residue was reprecipitated
15 from AcOEt and hexane to give the title compound(15.3mg) as a colorless solid.

mp:152 - 155 °C

High Resolution FAB - MS(m/e, (C₂₅H₂₂N₂O₇+H)⁺):

Calcd: 463.1506

20 Found: 463.1512

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm):3.47(1H, t, J=9.4Hz), 3.78(3H, s), 3.80 - 3.95(2H, m), 4.62(1H, d, J=9.4Hz), 4.92(1H, d, J=9.4Hz), 5.95(2H, s), 6.16(1H, d, J=2.2Hz), 6.32(1H, dd, J=2.2Hz, 8.4Hz),
25 6.78 - 6.82(3H, m), 6.88(1H, d, J=8.4Hz), 7.22(1H, dd, J=5.0Hz, 7.8Hz), 7.42(1H, d, J=7.8Hz), 8.36(1H, d, J=5.0Hz)

Rf Value:0.13(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 88

(5RS,7SR)-6-Ethoxycarbonyl-7-(2-carboxymethylamino-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(5RS,7SR)-6-Ethoxycarbonyl-7-(2-tert-butoxycarbonylmethylaminophenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example 87 - (5) was hydrolized under ice-cooling to give the title compound.

mp:113 - 117 °C

¹H-NMR(300MHz, CDCl₃, δ ppm):1.04(3H, t, J=7.2Hz), 3.69 - 3.92(1H, m), 3.76(3H, s), 3.86(2H, q, J=7.2Hz), 3.94 - 4.89(2H, m), 4.86(1H, d, J=9.6Hz), 5.21(1H, d, J=9.9Hz), 5.92 - 5.93(2H, m), 6.22(1H, d, J=2.5Hz), 6.32(1H, dd, J=2.5Hz, 8.5Hz), 6.47(1H, d, J=1.8Hz), 6.54(1H, dd, J=1.8Hz, 8.0Hz), 6.72(1H, d, J=8.0Hz), 6.84(1H, d, J=8.5Hz), 7.21(1H, dd, J=5.0Hz, 7.3Hz), 7.52(1H, d, J=7.3Hz), 8.43(1H, d-like, J=5.0Hz)

Rf Value:0.44(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=5:1)

Each compound in the following Examples 89 to 93 was prepared in the same manner as in Example 76 using pyridine-2,3-dicarboxylic acid anhydride.

Example 89

(5RS,6SR,7SR)-6-Carboxy-7-(2-pyridyl)-5-(3,4-me-

thylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

¹H - NMR(300MHz, CDCl₃, δ ppm):3.48(1H, t, J=9.4Hz),
4.88(1H, d, J=9.4Hz), 5.04(1H, d, J=9.4Hz),
5.91(1H, d, J=1.4Hz), 5.91(1H, d, J=1.4Hz),
5 6.67(1H, d, J=1.7Hz), 6.74(1H, d, J=8.0Hz),
6.80(1H, dd, J=1.7Hz, 8.0Hz), 7.24(1H, dd, J=4.9Hz,
7.8Hz), 7.37(1H, dd, J=5.2Hz, 7.8Hz), 7.42(1H, d,
J=7.8Hz), 7.89(1H, t, J=7.8Hz), 8.54(1H, d,
J=7.8Hz), 8.56(1H, d, J=5.2Hz), 8.62(1H, d,
10 J=4.9Hz)

Rf Value:0.25(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 90

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3 - fluorophenyl) - 7 - (4
15 - methoxyphenyl)cyclopenteno[1,2-b]pyridine

mp:211 - 212 °C

High Resolution FAB - MS(m/e, (C₂₂H₁₈FNO₃+H)⁺):

Calcd: 364.1350

Found: 364.1347

20 ¹H - NMR(300MHz, CD₃OD, δ ppm):3.21(1H, t, J=9.9Hz),
3.78(3H, s), 4.69(2H, d, J=9.9Hz), 6.92(2H, d,
J=8.8Hz), 7.00 - 7.45(4H, m), 7.12(1H, td, J=1.3Hz,
7.9Hz), 7.16(2H, d, J=8.8Hz), 7.28(1H, dd, J=4.8Hz,
7.5Hz), 8.34(1H, d, J=4.8Hz)

25 Rf Value:0.51(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 91

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3 - methoxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:193 - 195 °C

High Resolution FAB - MS(m/e, (C₂₃H₂₁NO₄+H)⁺):

5 Calcd: 376.1550

Found: 376.1541

¹H - NMR(300MHz, CDCl₃, δ ppm):3.36(1H, t, J=9.6Hz),
3.77(3H, s), 3.79(3H, s), 4.65(1H, d, J=9.6Hz),
4.72(1H, d, J=9.6Hz), 6.80 - 6.90(3H, m), 6.88(2H, d,
10 J=8.8Hz), 7.11 - 7.15(1H, m), 7.17(2H, d, J=8.8Hz),
7.23 - 7.33(2H, m), 8.47(1H, td, J=1.3Hz, 4.8Hz)

Rf Value:0.54(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 92

15 (5RS,6SR,7SR) - 6 - Carboxy - 7 - (4 - fluorophenyl) - 5 - (3,4 - methylenedioxyphenyl) - cyclopenteno[1,2 - b]pyridine

mp:234 - 236 °C

High Resolution FAB - MS(m/e, (C₂₂H₁₆FNO₄+H)⁺):

Calcd: 378.1142

20 Found: 378.1139

¹H - NMR(300MHz, CDCl₃, δ ppm):3.29(1H, t, J=10.0Hz),
4.62(1H, d, J=10.0Hz), 4.75(1H, d, J=10.0Hz),
5.98(2H, s), 6.71(1H, d, J=1.3Hz), 6.77(1H, dd,
J=1.3Hz, 7.9Hz), 6.81(1H, d, J=7.9Hz), 7.03 -
25 7.25(5H, m), 7.33(1H, d, J=7.6Hz), 8.49(1H, d-like,
J=4.7Hz)

Rf Value:0.42(E. Merck, Kieselgel 60F₂₅₄/chloro-

roform:methanol=10:1)

Example 93

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (2 - methoxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

5 mp:194 - 197 °C

High Resolution FAB - MS(m/e, (C₂₃H₂₁NO₄+H)⁺):

Calcd: 376.1549

Found: 376.1547

¹H - NMR(300MHz, CDCl₃, δ ppm):3.48(1H, t, J=9.6Hz),
10 3.67(3H, s), 3.75(3H, s), 4.73(1H, d, J=9.6Hz),
4.94(1H, d, J=9.6Hz), 6.82 - 6.97(4H, m), 7.06 -
7.19(4H, m), 7.24 - 7.31(2H, m), 8.43(1H, d - like,
J=5.0Hz)

Rf Value:0.38(E. Merck, Kieselgel 60F₂₅₄/chlo-
15 roform:methanol=10:1)

Example 94

(5RS,6SR,7SR) - 7 - [2 - (5 - Oxo - 4H - 1,2,4 - oxadiazol - 3 - ylmethoxy) - 4 - methoxyphenyl] - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

20 mp:161 - 163 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₁N₃O₈+H)⁺):

Calcd: 504.1407

Found: 504.1380

¹H - NMR(300MHz, DMSO - d₆, δ ppm):3.28(1H, t, J=10.1Hz),
25 3.76(3H, s), 4.51(1H, d, J=10.1Hz), 4.79(1H, d,
J=13.1Hz), 4.85(1H, d, J=10.1Hz), 5.09(1H, d,
J=13.1Hz), 6.00(2H, s), 6.58(1H, dd, J=2.4Hz,

8.4Hz), 6.69(1H, dd, J=1.7Hz, 8.0Hz), 6.75(1H, d, J=2.4Hz), 6.79(1H, d, J=1.7Hz), 6.86(1H, d, J=8.0 Hz), 7.11(1H, d, J=8.4Hz), 7.15(1H, dd, J=4.9Hz, 7.3Hz), 7.21(1H, d, J=7.3Hz), 8.29(1H, d, J=4.9Hz)

5 Rf Value:0.18(E. Merck, Kieselgel 60F₂₅₄/dichloro-methane:methanol=10:1)

Example 95

6 - Carboxy - 5 - hydroxy - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - d]pyrim-
10 idine

(1) 4 - (4 - Methoxyphenylcarbonyl)pyrimidine - 5 - carboxylic acid ethyl ester

To a THF solution(30ml) of pyrimidine - 4,5 - dicarboxylic acid diethyl ester(1.46g,6.52mmol) which
15 was prepared by the method described in the literature(Chem. Pharm. Bull.,1972,20,1513 - 1521) was added a THF solution of 4 - methoxyphenyl magnesium bromide (1.25M,5.47ml) dropwise at - 78°C. The reaction solution was stirred at - 78°C for 30 min, treated with
20 1N HCl and extracted with AcOEt. The organic layer was washed with brine and dried over MgSO₄. After removal of the solvent under reduced pressure the residue was purified by silica gel column chromatography(E. Merck Kieselgel 60/chloroform) to give 4 - (4 - methoxyphe-
25 nylcarbonyl)pyrimidine - 5 - carboxylic acid ethyl ester(1.57g) as a pale yellow oil.

(2) 4 - (4 - Methoxyphenylcarbonyl)pyrimidine - 5 - carboxylic

acid

To a methanol solution(15ml) of 4 - (4 - methoxyphenylcarbonyl)pyrimidine - 5 - carboxylic acid ethyl ester was added 4N NaOH(4ml). The solution was stirred at room temperature for 15 h. Water was added to the reaction solution to dissolve the resulting solid. After removal of methanol the aqueous layer was washed with AcOEt, made pH2 with 2N HCl and extracted with AcOEt. The organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent the residue was recrystallized from AcOEt and hexane(1:1) to give 4 - (4 - methoxyphenylcarbonyl)pyrimidine - 5 - carboxylic acid(1.06g) as a yellow solid.

(3) 6-Ethoxycarbonyl-5-oxo-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-d]pyrimidine

6-Ethoxycarbonyl-5-oxo-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-d]pyrimidine was prepared in the same manner as in Example 72 - (6) using 4 - (4 - methoxyphenylcarbonyl)pyrimidine - 5 - carboxylic acid which was prepared in (2).

(4) The title compound was prepared in the same manner as in Example 1 - (4) and Example 29 using 6 - ethoxycarbonyl-5-oxo-7-(4-methoxyphenyl)cyclopent-1,3-dieno[2,1-d]pyrimidine which was prepared in (3).

High Resolution FAB - MS(m/e, (C₂₂H₁₆N₂O₆+H)⁺):

Calcd: 405.1087

Found: 405.1083

¹H - NMR(300MHz, CDCl₃, δ ppm):3.89(3H, s), 5.95(1H, d, J=1.4Hz), 5.96(1H, d, J=1.4Hz), 6.76(1H, d, J=8.1Hz), 6.99(1H, d, J=1.7Hz), 7.02(1H, dd, J=1.7Hz, 8.1Hz), 7.05(2H, d, J=8.8Hz), 7.72(2H, d, J=8.8Hz), 8.58(1H, s), 9.18(1H, s)

Rf Value:0.86(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 96

6 - Carboxy - 5 - hydroxy - 2 - butyl - 5 - (3,4 - methylene-dioxyphenyl) - 7 - (methoxyphenyl)cyclopent - 1,3 - dieno[2,1 - d]pyrimidine

The title compound was prepared in the same manner as in Example 95 using 2 - butylpyrimidine - 4,5 - dicarboxylic acid diethyl ester.

High Resolution FAB - MS(m/e, (C₂₆H₂₄N₂O₆+H)⁺):

Calcd: 461.1713

Found: 461.1709

¹H - NMR(300MHz, CDCl₃, δ ppm):0.91(3H, t, J=7.3Hz), 1.36(2H, sext, J=7.3Hz), 1.74(2H, quint, J=7.3Hz), 2.93(2H, t, J=7.3Hz), 3.89(3H, s), 5.94(2H, d, J=2.2Hz), 6.74(1H, d, J=8.0Hz), 6.97(1H, s), 7.00(1H, d, J=8.0Hz), 7.02(2H, d, J=8.9Hz), 7.76(2H, d, J=8.9Hz), 8.48(1H, s)

Rf Value:0.82(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Each compound in the following Example 97 and 98 was prepared in the same manner as in Example 57.

Example 97

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxypentyloxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

5 mp:135 - 138 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):0.84(3H, t, J=7.2Hz), 1.20
- 1.53(4H, m), 1.82 - 2.07(2H, m), 3.77(3H, s),
3.81(1H, t, J=10.9Hz), 4.73(1H, d, J=10.9Hz),
4.93(1H, dd, J=5.3Hz, 6.7Hz), 5.23(1H, d,
10 J=10.9Hz), 6.00(2H, s), 6.51(1H, dd, J=2.3Hz,
8.6Hz), 6.58(1H, d, J=2.3Hz), 6.71(1H, d, J=1.6Hz),
6.77(1H, dd, J=1.6Hz, 7.9Hz), 6.84(1H, d, J=7.9Hz),
7.21(1H, dd, J=4.9Hz, 7.7Hz), 7.24(1H, d, J=8.6Hz),
7.39(1H, d, J=7.7Hz), 8.26(1H, d, J=4.9Hz)

15 Rf Value:0.67(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 98

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxypentyloxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other diastereomer)

20 mp:130 - 133 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):0.83(3H, t, J=6.7Hz), 1.10
- 1.80(6H, m), 3.36(1H, t, J=10.4Hz), 3.74(3H, s),
4.61(1H, d, J=10.4Hz), 4.71(1H, dd, J=4.7Hz,
25 7.1Hz), 4.96(1H, d, J=10.4Hz), 5.95 - 6.05(2H, m),
6.39(1H, s), 6.50(1H, d, J=8.0Hz), 6.65(1H, s),
6.73(1H, d, J=8.9Hz), 6.79(1H, d, J=8.9Hz),

7.09(1H, d, J=8.0Hz), 7.17-7.27(1H, m), 7.40(1H, d, J=7.3Hz), 8.38-8.43(1H, m)

Rf Value:0.45(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

5 Example 99

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - [(E) - 2 - carboxyethenyl] - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

(1) (5RS,6SR,7SR) - 7 - (2 - trifluoromethanesulfonyloxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

10

To a dichloromethane solution(3.5ml) of (5RS,6SR,7SR) - 7 - (2 - hydroxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 50 - (5), DMPA(7.9mg) and TEA(0.45ml) was added a dichloromethane solution(3ml) of N - phenyltrifluoromethanesulfoneimide(695mg) dropwise under ice - cooling. The solution was stirred at the same temperature for 5 min and at room temperature for 1 h. After concentration under reduced pressure the residue was purified by silica gel column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1) to give (5RS,6SR,7SR) - 7 - (2 - trifluoromethanesulfonyloxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(410mg) as a colorless amorphous solid.

15

20

25

(2) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) 7 - [(2 - [(E) - 2 - methoxycarbonylethenyl] - 4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

A DMF(6ml) - TEA(8ml) solution of (5RS,6SR,7SR) - 7 - (2
5 - trifluoromethanesulfonyloxy - 4 - methoxyphenyl) - 6 - tert -
butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine(411mg,0.650mmol) which was
prepared in (1), palladium(II) acetate(15mg), 1,3 -
bis(diphenylphosphino)propane(28mg) and acrylic acid
10 methyl ester(1.8ml) was heated under reflux for 24 h
under argon atmosphere. The catalyst was removed by
filtration and washed with AcOEt. The filtrate and
washings were combined and concentrated under reduced
pressure. The residue was purified by silica gel column
15 chromatography(E. Merck Kieselgel 60F/hexane:AcOEt=2:1)
to give (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 5 - (3,4 -
methylenedioxyphenyl) - 7 - [2 - [(E) - 2 - methoxycar-
bonylethenyl] - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyri-
dine(147mg) as a pale brown amorphous solid.

20 (3) To (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 5 - (3,4 -
methylenedioxyphenyl) - 7 - [2 - [(E) - 2 - methoxycar-
bonylethenyl] - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyri-
dine(107mg,0.202mmol) was added TFA(5ml) under ice -
cooling and the solution was stirred at room temperature
25 for 2 h. After concentration of the solution the residue
was dissolved in 0.5N NaOH and washed with ether. The
aqueous layer was adjusted at pH5 to 6 with 1N HCl and

extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (77.5mg) as a pale yellow powder.

5 mp: 180 °C (dec.)

^1H -NMR (300MHz, CDCl_3 , δ ppm): 3.03 (1H, t, $J=10.2\text{Hz}$), 3.83 (3H, s), 4.77 (1H, d, $J=10.2\text{Hz}$), 5.27 (1H, d, $J=10.2\text{Hz}$), 5.95 (1H, d, $J=1.9\text{Hz}$), 5.96 (1H, d, $J=1.9\text{Hz}$), 6.29 (1H, d, $J=15.4\text{Hz}$), 6.68 (1H, d, $J=1.8\text{Hz}$), 6.76 (1H, dd, $J=1.8\text{Hz}$, 7.9Hz), 6.79 (1H, d, $J=7.9\text{Hz}$), 7.00 (1H, dd, $J=2.3\text{Hz}$, 8.9Hz), 7.03 (1H, d, $J=8.9\text{Hz}$), 7.12 (1H, d, $J=2.3\text{Hz}$), 7.20 (1H, dd, $J=4.9\text{Hz}$, 7.9Hz), 7.38 (1H, d, $J=7.9\text{Hz}$), 8.32 (1H, d, $J=15.4\text{Hz}$), 8.54 (1H, d, $J=4.9\text{Hz}$)

15 Rf Value: 0.37 (E. Merck, Kieselgel 60F₂₅₄/dichloromethane:methanol:acetic acid=10:1:1)

Example 100

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (2-methoxycarbonylethyl) - 4-methoxyphenyl]cyclopenteno[1,2-b]pyridine

20 (1) (5RS,6SR,7SR) - 6 - Tert-butoxycarbonyl - 5 - (3,4-methylenedioxyphenyl) - 7 - [2 - (2-methoxycarbonylethyl) - 4-methoxyphenyl]cyclopenteno[1,2-b]pyridine

To a solution of (5RS,6SR,7SR) - 6 - tert-butoxycarbonyl - 5 - (3,4-methylenedioxyphenyl) - 7 - [[(E) - 2-methoxycarbonylethenyl] - 4-methoxyphenyl]cyclopenteno[1,2-b]pyridine (60mg, 0.11mmol) in AcOEt (1.5ml) was added 10%

Pd - carbon(61mg) and the solution was stirred at room temperature under hydrogen atmosphere. After the reaction was completed, the catalyst was removed by filtration and washed with AcOEt. The filtrate and washings were combined and concentrated under reduced pressure to give (5RS,6SR,7SR)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonyl)ethyl]-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine(59mg) as a pale brown amorphous solid.

(2) The title compound was prepared in the same manner as in Example 50 - (7).

mp:95 - 103 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):2.52 - 2.80(2H, m), 2.83 - 3.22(2H, m), 3.38(1H, t, J=9.9Hz), 3.63(3H, s), 3.77(3H, s), 4.62(1H, d, J=9.9Hz), 4.96(1H, d, J=9.9Hz), 5.97(1H, d, J=2.4Hz), 5.98(1H, d, J=2.4Hz), 6.74 - 6.80(5H, m), 6.84 - 7.00(1H, m), 7.11(1H, dd, J=4.7Hz, 7.6Hz), 7.30(1H, d, J=7.6Hz), 8.43(1H, d, J=4.7Hz)

Rf Value:0.36(E. Merck, Kieselgel 60F₂₅₄/hexane:acetone=1:1)

Example 101

(5RS,6SR,7SR)-6-Carboxy-7-[2-(2-carboxyethyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

The title compound was prepared in the same manner as in Example 2 using (5RS,6SR,7SR)-6-carboxy-5-(3,4-

methylenedioxyphenyl)-7-[2-(2-methoxycarbonylethyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine which was prepared in Example 100.

mp:130 - 139 °C

5 ¹H - NMR(300MHz, CDCl₃, δ ppm):2.60 - 2.80(2H, m), 2.98 - 3.26(2H, m), 3.43(1H, t, J=9.9Hz), 3.76(3H, s), 4.64(1H, d, J=9.9Hz), 5.04(1H, d, J=9.9Hz), 5.98(1H, d, J=2.3Hz), 5.99(1H, d, J=2.3Hz), 6.72 - 6.83(5H, m), 6.90(1H, d, J=8.2Hz), 7.19(1H, dd, J=5.0Hz, 8.1Hz), 7.39(1H, dt, J=1.9Hz, 8.1Hz), 8.38(1H, dt, J=1.9Hz, 5.0Hz)

Rf Value:0.43(E. Merck, Kieselgel 60F₂₅₄/dichloro-methane:methanol:acetic acid=10:1:1)

Example 102

15 (5RS,6SR,7SR) - 6 - Carboxy - 5 - (3,4 - methylene-dioxyphenyl) - 7 - [2 - (2-methoxycarbonylpropyl) - 4-methoxyphenyl]cyclopenteno[1,2 - b]pyridine(one of diastereomers)

(1) (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (2 - methoxycarbonylpropenyl) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine

(5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (2 - methoxycarbonylpropenyl) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine was prepared as a mixture of 1-propenyl isomer and 2-propenyl isomer in the same manner as in Example 99 - (2) using methacrylic acid methyl ester instead of acrylic acid

methyl ester.

(2) (5RS,6SR,7SR)-6-Tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine

5 (5RS,6SR,7SR)-6-Tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine was prepared in the same manner as in Example 100 - (1) using the mixture of 1-propenyl isomer and 2-propenyl isomer of
10 (5RS,6SR,7SR)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropenyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine which was prepared in (1).

(3) The title compound was prepared in the same manner
15 as in Example 100 - (2) using (5RS,6SR,7SR)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine which was prepared in (2).

mp: 86 - 88 °C

20 High Resolution FAB-MS(m/e, (C₂₈H₂₇NO₇+H)⁺):

Calcd: 490.1866

Found: 490.1856

¹H-NMR(300MHz, CDCl₃, δ ppm): 1.16(3H, d, J=6.3Hz), 2.73
- 2.86(2H, m), 3.03 - 3.17(1H, m), 3.32(1H, t,
25 J=9.9Hz), 3.59(3H, s), 3.74(3H, s), 4.60(1H, d,
J=9.9Hz), 4.95(1H, d, J=9.9Hz), 5.96(1H, d,
J=1.4Hz), 5.97(1H, d, J=1.4Hz), 6.72 - 6.81(5H, m),

6.90(1H, d, J=7.9Hz), 7.12(1H, dd, J=4.9Hz, 7.6Hz),
7.31(1H, d, J=7.6Hz), 8.45(1H, d, J=4.9Hz)

Rf Value:0.44(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

5 Example 103

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) -
4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine(one of diastereomers)

The title compound was prepared in the same manner
10 as in Example 2 using (5RS,6SR,7SR) - 6 - carboxy - 5 - (3,4 -
methylenedioxyphenyl) - 7 - [2 - (2 - methoxycarbonylpropyl) -
4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine which was
prepared in 102 - (3).

mp:138 - 141 °C

15 High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₇+H)⁺):

Calcd: 476.1709

Found: 476.1717

¹H - NMR(300MHz, CDCl₃, δ ppm):1.30(3H, d, J=6.1Hz),
2.68(1H, dd, J=12.2Hz, 13.2Hz), 2.93(1H, ddq,
20 J=5.7Hz, 12.2Hz, 6.1Hz), 3.29(1H, dd, J=5.7Hz,
13.2Hz), 3.65(1H, t, J=9.7Hz), 3.76(3H, s),
4.65(1H, d, J=9.7Hz), 5.02(1H, d, J=9.7Hz),
6.01(2H, s), 6.73 - 6.84(5H, m), 6.95(1H, d,
J=8.6Hz), 7.23(1H, dd, J=5.1Hz, 7.7Hz), 7.44(1H, d,
25 J=7.7Hz), 8.30(1H, d, J=5.1Hz)

Rf Value:0.59(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 104

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3,4 - methylene-
dioxyphenyl) - 7 - [2 - (2 - carboxy - 2 - propenyl) - 4 - methoxy-
phenyl]cyclopenteno[1,2 - b]pyridine

5 The title compound was prepared in the same manner
as in Example 100 - (2) using 2 - propenyl isomer prepared
by isolation and purification of (5RS,6SR,7SR) - 6 - tert -
butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (2 -
methoxycarbonylpropenyl) - 4 - methoxyphenyl]cyclo-
10 penteno[1,2 - b]pyridine(a mixture of 1 - propenyl isomer
and 2 - propenyl isomer) which was prepared in Example
102 - (1).

mp:97 - 100 °C

High Resolution FAB - MS(m/e, (C₂₈H₂₅NO₇+H)⁺):

15 Calcd: 488.1710

Found: 488.1717

¹H - NMR(300MHz, CDCl₃, δ ppm):3.27 - 3.42(1H, m), 3.65 -
3.85(2H, m), 3.65(3H, s), 3.75(3H, s), 4.58(1H, d,
J=10.0Hz), 4.86(1H, d, J=10.0Hz), 5.45(1H, s),
20 5.96(2H, s), 6.23(1H, s), 6.68 - 7.01(6H, m),
7.12(1H, dd, J=4.7Hz, 7.6Hz), 7.30(1H, d, J=7.6Hz),
8.44(1H, d, J=4.7Hz)

Rf Value:0.12(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol=95:5)

25 Example 105

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 2 - pro-
penyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-

dioxyphenyl)cyclopenteno[1,2-b]pyridine

The title compound was prepared in the same manner as in Example 2 using (5RS,6SR,7SR) - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (2 - methoxycarbonyl - 2 - propenyl) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine which was prepared in Example 104.

mp:150 - 153 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₃NO₇+H)⁺):

Calcd: 474.1553

10 Found: 474.1538

¹H - NMR(300MHz, CDCl₃, δ ppm):3.28(1H, t, J=9.6Hz),
3.65(1H, d, J=17.2Hz), 3.75(3H, s), 3.93(1H, d,
J=17.2Hz), 4.56(1H, d, J=9.6Hz), 5.06(1H, d,
J=9.6Hz), 5.46(1H, s), 5.96(2H, s), 6.24(1H, s),
15 6.65 - 6.94(6H, m), 7.16(1H, dd, J=4.9Hz, 7.6Hz),
7.36(1H, d, J=7.6Hz), 8.50(1H, d, J=4.9Hz)

Rf Value:0.58(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 106

20 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2 - dihydroxy - 2 - methoxycarbonyl)ethyl] - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

(1) (5RS,6SR,7SR) - 7 - [2 - (1,2 - dihydroxy - 2 - methoxycarbonyl)ethyl] - 4 - methoxyphenyl] - 6 - tert - butoxycarboxy - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

25 To a acetone(1.0ml) - water(0.5ml) solution of

(5RS,6SR,7SR) - 6 - tert - butoxycarboxy - 5 - (3,4 - methylene-dioxyphenyl) - 7 - [[(E) - 2 - methoxycarbonylethenyl] - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine (108mg, 0.204mmol) which was prepared in Example 99 - (2) was added N - methylmorpholine N - oxide (45mg) and a solution of osmium tetroxide in tert - butanol (0.079mmol/ml, 0.50ml). The solution was stirred at room temperature under nitrogen atmosphere for 22.5 h, treated with 1.5N sodium sulfite, stirred at room temperature for 30 min, diluted with water and extracted with AcOEt. The organic layer was washed with 10% aqueous solution of citric acid and brine and dried over Na₂SO₄. After removal of the solvent the resulting residue was purified by preparative TLC (E. Merck Kieselgel 60F₂₅₄/chloroform:methanol=95:5) to give (5RS,6SR,7SR) - 7 - [2 - (1,2 - dihydroxy - 2 - methoxycarbonylethyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine (21mg, the other diastereomer).

(2) The title compound was prepared in the same manner as in Example 50 - (7) using one of diastereomer of (5RS,6SR,7SR) - 7 - [2 - (1,2 - dihydroxy - 2 - methoxycarbonylethyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in (1).

mp: 133 - 136 °C

High Resolution FAB - MS (m/e, (C₂₇H₂₅NO₉+H)⁺):

Calcd: 508.1607

Found: 508.1602

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm): 3.52(1H, t, J=9.5Hz), 3.82(6H, s), 4.54(1H, brs), 4.67(1H, d, J=9.5Hz), 5.15(1H, d, J=9.5Hz), 5.50(1H, brs), 5.99(2H, s), 6.77(1H, s), 6.78 - 6.87(3H, m), 6.97(1H, d, J=8.5Hz), 7.17(1H, dd, J=5.0Hz, 7.6Hz), 7.37(1H, d, J=2.7Hz), 7.39(1H, d, J=7.6Hz), 8.27(1H, d, J=5.0Hz)

Rf Value: 0.53(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 107

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2 - dihydroxy - 2 - methoxycarbonyl ethyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine (the other-diastereomer)

The title compound was prepared in the same manner as in Example 106 using the other diastereomer which was prepared in Example 106 - (1).

mp: 134 - 137 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₉+H)⁺):

Calcd: 508.1607

Found: 508.1590

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm): 3.35(1H, t, J=9.9Hz), 3.81(3H, s), 3.83(3H, s), 4.53(1H, d, J=2.0Hz), 4.65(1H, d, J=9.9Hz), 5.03(1H, d, J=9.9Hz), 5.63(1H, brs), 5.98(1H, d, J=1.4Hz),

5.99(1H, d, J=1.4Hz), 6.76(1H, s), 6.78 - 6.86(3H, m), 6.89(1H, d, J=8.6Hz), 7.20(1H, dd, J=4.9Hz, 7.7Hz), 7.21(1H, d, J=2.6Hz), 7.40(1H, d, J=7.7Hz), 8.30(1H, d, J=4.9Hz)

5 Rf Value:0.41(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Each compound in the following Examples 108 and 109 was prepared in the same manner as in Example 2 using compounds of Examples of 106 and 107.

10 Example 108

(5RS,6SR,7SR)-6-Carboxy-7-[2-(2-carboxy-1,2-dihydroxyethyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

15 mp:189 - 191 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₉+H)⁺):

Calcd: 494.1451

Found: 494.1440

¹H - NMR(300MHz, DMSO - d₆, δ ppm):3.47(1H, t, J=10.1Hz),
20 3.74(3H, s), 4.22(1H, brs), 4.55(1H, d, J=10.1Hz),
4.93(1H, d, J=10.1Hz), 5.41(1H, brs), 6.02(2H, s),
6.76(1H, dd, J=2.9Hz, 8.6Hz), 6.83(1H, dd, J=1.5Hz, 8.0Hz), 6.86 - 6.97(2H, m), 7.09(1H, d, J=8.6Hz),
7.14 - 7.20(2H, m), 7.24(1H, d, J=7.3Hz), 8.27(1H, d,
25 J=4.9Hz)

Rf Value:0.07(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 109

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 1,2 - dihydroxyethyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other
 5 diastereomer)

mp:168 - 170 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₉+H)⁺):

Calcd: 494.1451

Found: 494.1446

10 ¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm):3.36(1H, t, J=9.9Hz), 3.84(3H, s), 4.46(1H, d, J=2.4Hz), 4.65(1H, d, J=9.9Hz), 5.05(1H, d, J=9.9Hz), 5.68(1H, brs), 5.98(1H, d, J=1.4Hz), 5.99(1H, d, J=1.4Hz), 6.75(1H, s), 6.80(1H, d, J=8.6Hz),
 15 6.83(1H, d, J=8.6Hz), 6.84(1H, dd, J=2.9Hz, 8.6Hz), 6.89(1H, d, J=8.6Hz), 7.23(1H, dd, J=5.3Hz, 7.8Hz), 7.26(1H, d, J=2.9Hz), 7.42(1H, d, J=7.8Hz), 8.30(1H, d, J=5.3Hz)

Rf Value:0.03(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)
 20

Example 110

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (3 - hydroxy - 1 - propynyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine
 25 (1) 3 - (Tetrahydropyranyloxy) - 1 - tributylstanyl - 1 - propyne

To an ether(20ml) solution of 3 - (tetrahydro-

pyranyloxy) - 1 - propyne(2.00g,14.3mmol) which was prepared by the method described in the literature[see J. Chem. Soc. Perkin I,1089(1992)] was added a butyl lithium-hexane solution(1.66M,8.60ml) dropwise at -78°C and the solution was stirred at the same temperature for 30 min. To the solution was added tributylstanyl chloride(3.87ml) dropwise at -78°C and the solution was stirred at the same temperature for 1 h. After adding water at -78°C to quench the reaction the temperature of the mixture was raised to room temperature. The organic layer was separated, washed with brine and dried over MgSO₄. The solvent was evaporated to give 3 - (tetrahydropyranyloxy) - 1 - tributylstanyl - 1 - propyne(6.13g).

(2) (5RS,6SR,7SR) - 7 - [2 - (3 - Tetrahydropyranyloxy - 1 - propynyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a DMF(1ml) solution of (5RS,6SR,7SR) - 7 - (2 - trifluoromethanesulfonyl - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(30mg,0.0505mmol) which was prepared in Example 99 - (1) and 3 - (tetrahydropyranyloxy) - 1 - tributylstanyl - 1 - propyne which was prepared in (1) were added lithium chloride(7mg) and palladium(II) chloride bis - triphenylphosphine complex(2mg) at room temperature under nitrogen atmosphere. The mixture was stirred at 100°C for 2 h and cooled to room temperature.

After removal of DMF the residue was dissolved in AcOEt, treated with a 40% aqueous KF solution(1ml) and stirred at room temperature for 30 min. The resulting tributylstanyl fluoride was removed by Celite -
5 filtration. The filtrate and washings were combined , washed with brine and dried over MgSO₄. After removal of the solvent the residue was purified by preparative TLC (E. Merck Kieselgel 60F₂₅₄/AcOEt:hexane=1:1) to give
10 (5RS,6SR,7SR) - 7 - [2 - (3 - tetrahydropyranyloxy - 1 - propynyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-
dine(17.2mg).

(3) (5RS,6SR,7SR) - 7 - [2 - (3 - Hydroxy - 1 - propynyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methyle-
15 nedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a ethanol solution(0.5ml) of (5RS,6SR,7SR) - 7 - [2 - (3 - tetrahydropyranyloxy - 1 - propynyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(31.0mg,0.0532mmol) which was
20 prepared in (2) was added pyridium p - toluene sulfonate(13mg) and the mixture was subjected to react at room temperature to give (5RS,6SR,7SR) - 7 - [2 - (3 - hydroxy - 1 - propynyl) - 4 - methoxyphenyl] - 6 - tert - butoxy-
carbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 -
25 b]pyridine(18.4mg).

(4) The title compound was prepared in the same manner as in Example 50 - (7) using (5RS,6SR,7SR) - 7 - [2 - (3 -

hydroxy - 1 - propynyl) - 4 - methoxyphenyl] - 6 - tert - butoxy -
carbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 -
b]pyridine which was prepared in (3).

mp: -200 °C (dec.)

5 High Resolution FAB - MS(m/e, (C₂₆H₂₁NO₆+H)⁺):

Calcd: 444.1447

Found: 444.1458

¹H - NMR(300MHz, CD₃OD, δ ppm): 3.30(1H, t, J=9.9Hz),
3.79(3H, s), 4.19(2H, s), 4.62(1H, d, J=9.9Hz),
10 5.08(1H, d, J=9.9Hz), 5.94(2H, s), 6.77 - 6.82(3H,
m), 6.92(1H, dd, J=2.6Hz, 8.6Hz), 7.02(1H, d,
J=2.6Hz), 7.07(1H, d, J=8.6Hz), 7.25(1H, dd,
J=4.9Hz, 7.5Hz), 7.38(1H, dt, J=1.9Hz, 7.5Hz),
8.29(1H, dt, J=1.9Hz, 4.9Hz)

15 Rf Value: 0.1(E. Merck, Kieselgel 60F₂₅₄/AcOEt:hex-
ane=1:1)

Example 111

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - [(Z) - (3 - hydroxy - 1 -
- propenyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
20 dioxyphenyl)cyclopenteno[1,2 - b]pyridine

(1) (5RS,6SR,7SR) - 7 - [2 - (3 - Tetrahydropyranyloxy - 1 -
propenyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 -
(3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The mixture of (3 - tetrahydropyranyloxy - 1 - pro-
25 penyl)tributyltin(320mg) which was prepared by the
method described in the literature[J. Org. Chem., 40,
2265(1975)] , (5RS,6SR,7SR) - 7 - (2 - trifluorometha-

nesulfonyloxy-4-methoxy)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(264mg,0.445mmol) which was prepared in Example 99-(1), palladium (II) dichloride bis-triphenylphosphine complex(25.8mg), lithium chloride(57.0mg), 2,6-di-tert-butyl-4-methylphenol(20mg) and DMF(2.2ml) in a schlenk reactor was heated under nitrogen atmosphere at 110°C in an oil bath for 17 h with stirring. The reaction solution was cooled and concentrated under reduced pressure. The residue was treated with ether(4ml) and a 40% aqueous KF solution(2ml) and the mixture was stirred at room temperature for 30 min. The insoluble material was removed by Celite-filtration. The filtrate and washings were combined, washed with a 40% aqueous KF solution, water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1) to give (Z)-1-propenyl isomer(42.8mg), (E)-1-propenyl isomer(57.7mg) and the mixture (150.5mg,Z/E=1/2.4) of (5RS,6SR,7SR)-7-[2-(3-tetrahydropyranyloxy-1-propenyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine.

(2) The title compound was prepared in the same manner as in Example 110-(3) and (4) using (5RS,6SR,7SR)-7-[2-(3-tetrahydropyranyloxy-1-propenyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine.

clopento[1,2-b]pyridine which was prepared in (1).

High Resolution FAB-MS(m/e, (C₂₆H₂₃NO₆+H)⁺):

Calcd: 446.1604

Found: 446.1581

5 ¹H-NMR(300MHz, DMSO-d₆, δ ppm):3.10(1H, t, J=10.0Hz),
3.73(3H, s), 3.97(1H, ddd, J=1.2Hz, 6.5Hz, 13.3Hz),
4.03(1H, ddd, J=1.2Hz, 6.5Hz, 13.3Hz), 4.50(1H, d,
J=10.0Hz), 4.74(1H, d, J=10.0Hz), 5.78(1H, td,
J=6.5Hz, 11.3Hz), 6.00(2H, s), 6.44-6.54(1H, m),
10 6.65(1H, d, J=2.7Hz), 6.74(1H, dd, J=1.6Hz, 8.0Hz),
6.79(1H, d, J=1.6Hz), 6.80(1H, dd, J=2.7Hz, 8.5Hz),
6.88(1H, d, J=8.0Hz), 6.99(1H, d, J=8.5Hz),
7.16(1H, dd, J=4.6Hz, 7.7Hz), 7.23(1H, d, J=7.7Hz),
8.29(1H, d, J=4.6Hz)

15 Rf Value:0.24(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=15:1)

Example 112

(5RS,6SR,7SR)-6-Carboxy-7-[2-[(E)-(3-hydroxy-1
-propenyl)]-4-methoxyphenyl]-5-(3,4-methylene-
20 dioxyphenyl)cyclopento[1,2-b]pyridine

The title compound was prepared in the same manner as in Example 110-(3) and (4) using (E)-propenyl isomer of (5RS,6SR,7SR)-7-[2-(3-tetrahydropyranyloxy-1-propenyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-
25 -methylenedioxyphenyl)cyclopento[1,2-b]pyridine which was prepared in Example 111-(1).

mp:218-221 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₃NO₆+H)⁺):

Calcd: 446.1604

Found: 446.1621

¹H - NMR(300MHz, CDCl₃, δ ppm): 3.18(1H, t, J=9.5Hz),
 5 3.79(3H, s), 4.12 - 4.26(2H, m), 4.54(1H, d,
 J=9.5Hz), 5.10(1H, d, J=9.5Hz), 5.94(1H, d,
 J=1.4Hz), 5.95(1H, d, J=1.4Hz), 6.07(1H, td,
 J=5.7Hz, 15.5Hz), 6.67(1H, brs), 6.71(1H, d,
 J=8.0Hz), 6.76(1H, d, J=8.0Hz), 6.66 - 6.86(1H, m),
 10 6.81(1H, dd, J=2.7Hz, 8.5Hz), 6.91(1H, d, J=2.7Hz),
 6.93(1H, d, J=8.5Hz), 7.15(1H, dd, J=4.8Hz, 7.7Hz),
 7.33(1H, d, J=7.7Hz), 8.47(1H, d, J=4.8Hz)

Rf Value: 0.33(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

15 Example 113

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (3 - hydroxypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared by hydrogenation of
 20 a mixture of E/Z - isomers of (5RS,6SR,7SR) - 7 - [2 - (3 - tetrahydropyranyloxy - 1 - propenyl) - 4 - methoxyphenyl] - 6 - tert-butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in Example 111 - (1) using palladium black as a catalyst, followed
 25 by the same reactions as in Example 110 - (3) and (4).

mp: 222 - 226 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₆+H)⁺):

Calcd: 448.1760

Found: 448.1770

¹H - NMR(300MHz, DMSO-*d*₆, δ ppm): 1.62 - 1.78(2H, m), 2.48 -
2.86(2H, m), 3.19(1H, t, J=10.2Hz), 3.33 - 3.50(2H,
5 m), 3.72(3H, s), 4.53(1H, d, J=10.2Hz), 4.83(1H, d,
J=10.2Hz), 6.01(2H, s), 6.70(1H, dd, J=2.7Hz,
8.4Hz), 6.74(1H, d, J=2.7Hz), 6.78(1H, dd, J=1.6Hz,
8.0Hz), 6.86(1H, d, J=1.6Hz), 6.90(1H, d, J=8.0Hz),
6.95(1H, d, J=8.4Hz), 7.16(1H, dd, J=4.6Hz, 7.4Hz),
10 7.23(1H, td, J=1.4Hz, 7.4Hz), 8.30(1H, td, J=1.4Hz,
4.6Hz)

Rf Value: 0.12(E. Merck, Kieselgel 60F₂₅₄/chloro-
form:methanol=15:1)

Each compound in the following Examples 114 and 115
15 was prepared in the same manner as in Example 111 - (1)
and Example 106 using vinyltributyl tin.

Example 114

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2 - dihydroxyethyl)
- 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
20 penteno[1,2 - b]pyridine(one of diastereomers)

mp: 140 - 144 °C

High Resolution FAB - MS(m/e, (C₂₅H₂₃NO₇+H)⁺):

Calcd: 450.1553

Found: 450.1558

¹H - NMR(300MHz, acetone-*d*₆, δ ppm): 3.47(1H, t, J=9.9Hz),
3.56(1H, dd, J=8.0Hz, 11.6Hz), 3.79(3H, s),
3.89(1H, dd, J=4.4Hz, 11.6Hz), 4.64(1H, d,

J=9.9Hz), 5.09(1H, d, J=9.9Hz), 5.26(1H, brs),
6.02(2H, s), 6.79(1H, dd, J=2.5Hz, 8.6Hz), 6.85 -
6.93(3H, m), 7.04(1H, d, J=8.6Hz), 7.20 - 7.26(2H,
m), 7.35(1H, d, J=7.1Hz), 8.33(1H, d, J=4.5Hz)

5 Rf Value:0.30(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 115

(5RS,6SR,7SR)-6-Carboxy-7-[2-(1,2-dihydroxyethyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(the other diastereomer)

mp:132 - 135 °C

High Resolution FAB - MS(m/e, (C₂₅H₂₃NO₇+H)⁺):

Calcd: 450.1553

Found: 450.1563

15 ¹H - NMR(300MHz, acetone - d₆, δ ppm):3.50 - 3.80(3H, m),
3.78(3H, s), 4.67(1H, d, J=9.2Hz), 5.05 - 5.20(2H,
m), 6.01(2H, s), 6.80(1H, dd, J=3.1Hz, 8.5Hz),
6.87(3H, s), 7.09 - 7.16(2H, m), 7.19(1H, dd,
J=4.8Hz, 7.5Hz), 7.33(1H, d, J=7.5Hz), 8.32(1H, d,
20 J=4.8Hz)

Rf Value:0.27(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

A Z/E mixture of (5RS,6SR,7SR)-7-[2-(3-tetrahydropyranyloxy-1-propenyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine was treated with a solution of diboran in dimethylsulfide and THF under ice - cooling to room

temperature and treated with an aqueous 35% hydrogen peroxide solution to give a mixture of hydroxy isomers. The tetrahydropyranyl group of the hydroxyl isomers was removed and the resulting material was separated to each of isomers by preparative TLC(E. Merck Kieselgel 60/
5 chloroform:AcOEt=5:2, then AcOEt only) in the same manner as in Example 110 - (3) and followed by the same treatment as in Example 110 - (4) to give each compound in the following Examples 116 - 119.

10 Example 116

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,3 - dihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
diastereomers)

15 mp:115 - 120 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₇+H)⁺):

Calcd: 464.1709

Found: 464.1716

¹H - NMR(300MHz, CD₃OD, δ ppm):1.88- 2.17(2H, m), 3.27(1H,
20 t, J=9.8Hz), 3.65 - 3.75(2H, m), 3.79(3H, s),
4.59(1H, d, J=9.8Hz), 5.09(1H, d, J=9.8Hz), 5.28 -
5.40(1H, m), 5.94(2H, s), 6.74 - 6.84(4H, m),
6.89(1H, d, J=8.5Hz), 7.15(1H, d, J=2.7Hz),
7.25(1H, dd, J=4.8Hz, 7.5Hz), 7.39(1H, d, J=7.5Hz),
25 8.29(1H, d, J=4.8Hz)

Rf Value:0.07(E. Merck, Kieselgel 60F₂₅₄/chloro-
form:methanol=10:1)

Example 117

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,3 - dihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other
s diastereomer)

mp:104 - 108 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₇+H)⁺):

Calcd: 464.1709

Found: 464.1725

10 ¹H - NMR(300MHz, CDCl₃, δ ppm):1.78 - 1.94(1H, m), 1.94 -
2.13(1H, m), 3.45(1H, t, J=9.3Hz), 3.67 - 3.92(2H,
m), 3.76(3H, s), 4.67(1H, d, J=9.3Hz), 5.36(1H, m),
5.47(1H, d, J=9.3Hz), 5.97(2H, s), 6.63 - 6.84(5H,
m), 7.04(1H, brs), 7.41(1H, dd, J=5.5Hz, 7.4Hz),
15 7.68(1H, d, J=7.4Hz), 8.41(1H, d, J=5.5Hz)

Rf Value:0.10(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol=10:1)

Example 118

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2,3 - dihydrox-
20 ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(on of
diastereomers)

mp:115 - 120 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₇+H)⁺):

25 Calcd: 464.1709

Found: 464.1699

¹H - NMR(300MHz, CDCl₃, δ ppm):2.73(1H, m), 3.06(1H, dd,

- 174 -

J=9.5Hz, 13.3Hz), 3.30(1H, t, J=9.4Hz), 3.44 -
 3.76(2H, m), 3.72(3H, s), 3.80 - 3.97(1H, m),
 4.52(1H, d, J=9.4Hz), 5.20(1H, d, J=9.4Hz),
 5.96(2H, s), 6.66 - 6.80(5H, m), 6.84(1H, d,
 5 J=8.3Hz), 7.21(1H, dd, J=5.3Hz, 7.6Hz), 7.39(1H, d,
 J=7.6Hz), 8.34(1H, d, J=5.3Hz)

Rf Value:0.13(E. Merck, Kieselgel 60F₂₅₄/chlo-
 roform:methanol=10:1)

Example 119

10 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2,3 - dihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other
diastereomer)

mp:208 - 212 °C

15 High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₇+H)⁺):

Calcd: 464.1709

Found: 464.1722

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm):2.40 - 2.75(1H, m),
 3.18(1H, dd, J=4.2Hz, 13.8Hz), 3.34(1H, t,
 20 J=9.7Hz), 3.57(1H, dd, J=6.7Hz, 11.3Hz), 3.67(1H,
 dd, J=3.8Hz, 11.3Hz), 3.80(3H, s), 3.89 - 4.00(1H,
 m), 4.62(1H, d, J=9.7Hz), 4.99(1H, d, J=9.7Hz),
 5.97(1H, d, J=1.4Hz), 5.98(1H, d, J=1.4Hz),
 6.75(1H, brs), 6.76 - 6.84(4H, m), 6.88(1H, d,
 25 J=8.2Hz), 7.17(1H, dd, J=5.0Hz, 7.6Hz), 7.38(1H, d,
 J=7.6Hz), 8.31(1H, d, J=5.0Hz)

Rf Value:0.13(E. Merck, Kieselgel 60F₂₅₄/chlo-

roform:methanol=10:1)

Each compound in the following Examples 120 - 123 was prepared in the same manner as in Example 106 - (1) and Example 111 - (3) , (4) using (E) - propenyl isomer (Examples 120 and 121) and (Z) - isomer (Examples 123 and 123) of (5RS,6SR,7SR) - 7 - [2 - (3 - tetrahydropyranyloxy - 1 - propenyl) - 4 - methoxyphenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine.

Example 120

10 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2,3 - trihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
diastereomers derived from (E) - propenyl isomer)

mp:127 - 129 °C

15 High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₈+H)⁺):

Calcd: 480.1658

Found: 480.1652

¹H - NMR(300MHz, CDCl₃, δ ppm):3.32(1H, dd, J=9.2Hz,
10.6Hz), 3.40 - 3.55(2H, m), 3.64(3H, s), 3.95 -
20 4.05(1H, m), 4.49(1H, d, J=9.2Hz), 5.02 - 5.11(1H,
m), 5.25(1H, d, J=10.6Hz), 5.94(2H, s), 6.61 -
6.68(2H, m), 6.72 - 6.81(2H, m), 6.88(1H, d, J=
8.9Hz), 6.97(1H, d, J=2.0Hz), 7.06(1H, dd, J=5.3Hz,
7.6Hz), 7.32(1H, d, J=7.6Hz), 8.22(1H, d, J=5.3Hz)

25 Rf Value:0.19(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol:acetic acid=10:1:1)

Example 121

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2,3 - trihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other
diastereomer derived from (E) - propenyl isomer)

5 mp:143 - 146 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₈+H)⁺):

Calcd: 480.1658

Found: 480.1660

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm):3.34(1H, t,
10 J=9.8Hz), 3.63(1H, dd, J=5.3Hz, 11.6Hz), 3.70(1H,
dd, J=4.7Hz, 11.6Hz), 3.83(3H, s), 3.91(1H, ddd,
J=4.7Hz, 5.2Hz, 5.3Hz), 4.63(1H, d, J=9.8Hz),
5.11(1H, d, J=9.8Hz), 5.21(1H, d, J=5.2Hz),
5.98(1H, d, J=1.4Hz), 5.99(1H, d, J=1.4Hz),
15 6.76(1H, s), 6.77 - 6.88(3H, m), 6.89(1H, d,
J=8.6Hz), 7.13(1H, d, J=2.6Hz), 7.20(1H, dd,
J=5.1Hz, 7.7Hz), 7.40(1H, td, J=1.4Hz, 7.7Hz),
8.30(1H, td, J=1.4Hz, 5.1Hz)

Rf Value:0.19(E. Merck, Kieselgel 60F₂₅₄/chlo-
20 roform:methanol:acetic acid=10:1:1)

Example 122

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2,3 - trihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
25 diastereomers derived from (Z) - propenyl isomer)

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₈+H)⁺):

Calcd: 480.1658

- 177 -

Found: 480.1630

¹H - NMR(300MHz, CD₃OD, δ ppm): 3.49(1H, t, J=10.0Hz),
 3.72 - 3.94(3H, m), 3.82(3H, s), 4.69(1H, d,
 J=10.0Hz), 5.22(1H, d, J=6.3Hz), 5.38(1H, d,
 J=10.0Hz), 5.96(2H, s), 6.80 - 6.88(3H, m), 6.89(1H,
 dd, J=2.8Hz, 8.6Hz), 7.04(1H, d, J=8.6Hz), 7.25(1H,
 d, J=2.8Hz), 7.53(1H, dd, J=5.5Hz, 7.7Hz), 7.72(1H,
 d, J=7.7Hz), 8.37(1H, d, J=5.5Hz)

Rf Value: 0.23(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 123

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1,2,3 - trihydrox-
ypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other
diastereomer derived from (Z) - propenyl isomer)

High Resolution FAB - MS(m/e, (C₂₆H₂₅NO₈+H)⁺):

Calcd: 480.1658

Found: 480.1667

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm): 3.54(1H, t,
 J=9.6Hz), 3.75 - 3.95(3H, m), 3.82(3H, s), 4.73(1H,
 d, J=9.6Hz), 5.05(1H, d, J=7.6Hz), 5.43(1H, d,
 J=9.6Hz), 6.00(2H, s), 6.78(1H, brs), 6.81(1H, dd,
 J=1.5Hz, 8.0Hz), 6.85(1H, d, J=8.0Hz), 6.87(1H, dd,
 J=2.7Hz, 8.6Hz), 6.95(1H, d, J=8.6Hz), 7.15(1H, d,
 J=2.7Hz), 7.45(1H, dd, J=5.5Hz, 7.6Hz), 7.67(1H, d,
 J=7.6Hz), 8.42(1H, d, J=5.5Hz)

Rf Value: 0.26(E. Merck, Kieselgel 60F₂₅₄/chloro-

roform:methanol:acetic acid=10:1:1)

Example 124

(5RS,6SR,7SR)-6-Carboxy-7-[2-(1-carboxy-2-hydrox-
yethoxy)-4-methoxyphenyl]-2-propylamino-5-(3,4-methy-
5 lenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of
diastereomers)

(1) (5RS,6SR,7SR)-6-Tert-butoxycarbonyl-7-(2-benzy-
loxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cy-
clopenteno[1,2-b]pyridine N-oxide

10 To a dichloromethane(4ml) solution of (5RS,6SR,7SR)-
6-tert-butoxycarbonyl-7-(2-benzyloxy-4-methoxyphenyl)-
-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyri-
dine (386mg,0.70mmol) which was prepared in Example 50-
(4) was added mCPBA(190mg) at 0 °C over 5 min. The
15 mixture was stirred at 0 °C 1.5 h and at room
temperature for 4 h, diluted with dichloromethane,
washed with a saturated aqueous solution of NaHCO₃ and
brine and dried over MgSO₄. After removal of the solvent
the residue was purified by dry column flash
20 chromatography(E. Merck Kieselgel 60/chloroform:meth-
anol=50:1 to 30:1) to give (5RS,6SR,7SR)-6-tert-
butoxycarbonyl-7-(2-benzyloxy-4-methoxyphenyl)-5-(3,4-
-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine N-
oxide(345mg).

25 (2) (5RS,6SR,7SR)-6-Tert-butoxycarbonyl-7-(2-benzy-
loxy-4-methoxyphenyl)-2-[(N-benzoyl)propylamino]-5-
(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine N - oxide(224mg, 0.395mmol) and CsF(1.82g) were dried under reduced pressure. To the mixture were added dichloromethane(4.0ml) under nitrogen atmosphere and N - propylbenzimidoyl chloride(210mg) which was prepared from benzoic acid N - propylamide and thionyl chloride. The solution was stirred vigorously under heating at reflux, treated with an aqueous saturated solution of NaHCO₃ and water, stirred at room temperature to make the solution homogeneous and extracted with dichloromethane. The organic layer was washed with brine and dried over MgSO₄. After removal of the solvent the residue was purified by MPL(E. Merck Kieselgel 60 lobar column/dichloromethane:acetone=100:1 to 50:1 to 30:1) to give (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(138mg).

(3) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - [2 - (2 - benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

Each of diastereomers of (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - [2 - (2 - benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 -

b]pyridine and (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (1 - methoxycarbonylethenyloxy) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine were prepared in the same manner as in Example 64 - (1) using (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - benzyloxy - 4 - methoxyphenyl) - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in (2).

(4) One of diastereomers of (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - [2 - (2 - benzyloxy - 1 - methoxycarbonylethoxy) - 4 - methoxyphenyl] - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in (3) was subjected to debenylation using palladium black as a catalyst, de - tert - butylation with TFA, demethylation and debenzoylation with 4N NaOH to give the title compound.

mp: 183 - 188 °C

High Resolution FAB - MS (m/e, (C₂₉H₃₀N₂O₉ + H)⁺):

Calcd: 551.2030

Found: 551.2057

¹H - NMR (300 MHz, CDCl₃, δ ppm): 0.86 (3H, t, J = 7.3 Hz), 1.54 (2H, sext, J = 7.3 Hz), 2.99 - 3.13 (2H, m), 3.62 (1H, t, J = 8.7 Hz), 3.67 (3H, s), 3.93 - 4.07 (2H, m), 4.63 (1H, d, J = 8.7 Hz), 4.83 - 4.93 (1H, m), 5.43 (1H, d, J = 8.7 Hz), 5.97 (2H, s), 6.36 - 6.52 (2H, m), 6.62 - 6.72 (2H, m), 6.78 (1H, d, J = 8.4 Hz), 7.08 (1H, d, J =

8.6Hz), 7.36(1H, d, J=8.9Hz), 7.74(1H, brs)

Rf Value:0.47(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 125

5 (5RS,6SR,7SR)-6-Carboxy-7-[2-(1-carboxy-2-hydroxyethoxy)-4-methoxyphenyl]-2-propylamino-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(the other diastereomer)

10 The title compound was prepared in the same manner as in Example 124 - (4) using the other diastereomer of (5RS,6SR,7SR)-6-tert-butoxycarbonyl-7-[2-(2-benzyloxy-1-methoxycarbonylethoxy)-4-methoxyphenyl]-2-[(N-benzoyl)propylamino]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example
15 124 - (3).

mp:165 - 175 °C

High Resolution FAB - MS(m/e, (C₂₉H₃₀N₂O₅+H)⁺):

Calcd: 551.2030

Found: 551.2046

20 ¹H - NMR(300MHz, Acetone-d₆, δ ppm):0.90(3H, t, J=7.4Hz), 1.56(2H, sext, J=7.4Hz), 3.11 - 3.21(2H, m), 3.26(1H, t, J=8.2Hz), 3.76(3H, s), 3.83 - 4.04(2H, m), 4.47(1H, d, J=8.2Hz), 4.91 - 4.99(1H, m), 5.06(1H, d, J=8.2Hz), 5.97(2H, s), 6.41(1H, d, J=8.5Hz), 6.48 -
25 6.58(2H, m), 6.80(3H, s), 7.08(1H, d, J=7.9Hz), 7.10(1H, d, J=7.6Hz)

Rf Value:0.27(E. Merck, Kieselgel 60F₂₅₄/chloro-

roform:methanol:acetic acid=10:1:1)

Example 126

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (1 - carboxyethenyloxy) - 4 - methoxyphenyl] - 2 - propylamino - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

(5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 2 - [(N - benzoyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (1 - methoxycarbonylethenyloxy) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine which was prepared in Example 124 - (3) was subjected to de - tert - butylation with TFA, demethylation and debenzoylation with 4N NaOH to give the title compound.

mp:165 - 169 °C

High Resolution FAB - MS(m/e, (C₂₃H₂₈N₂O₈+H)⁺):

Calcd: 533.1924

Found: 533.1940

¹H - NMR(300MHz, CDCl₃, δ ppm):0.86(3H, t, J=7.4Hz), 1.55(2H, sext, J=7.4Hz), 3.03 - 3.17(2H, m), 3.69(3H, s), 3.70(1H, t, J=8.0Hz), 4.59(1H, d, J=8.0Hz), 5.31(1H, brs), 5.34(1H, d, J=8.0Hz), 5.98(2H, s), 6.06(1H, brs), 6.42 - 6.52(2H, m), 6.59(1H, d, J=2.2Hz), 6.69 - 6.83(3H, m), 7.11(1H, d, J=8.6Hz), 7.33(1H, d, J=8.9Hz), 7.63(1H, brs)

Rf Value:0.35(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 127

(5RS,6SR,7SR) - 7 - (2 - Ethoxycarbonylmethoxy - 4 - methox-

yphenyl)-6-carboxy-2-(N-propyl-N-methylamino)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(1) (5RS,6SR,7SR)-6-Tert-butoxycarbonyl-2-propylamino-7-[2-benzyloxy-4-methoxyphenyl]-5-(3,4-methylene-
5 dioxyphenyl)cyclopenteno[1,2-b]pyridine

To a dioxane solution(3ml) of (5RS,6SR,7SR)-6-tert-butoxycarbonyl-7-(2-benzyloxy-4-methoxyphenyl)-2-[(N-benzoyl)propylamino]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(215mg,0.301mmol) which was
10 prepared in Example 124 - (2) was added 4N NaOH(3ml) and tetrabutylammonium bromide(97mg) and the mixture was stirred at 110°C for 22 h. The reaction solution was made acid with 3N HCl and extracted with AcOEt. The organic layer was washed with water, a saturated aqueous
15 solution of NaHCO₃ and brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure the residue was purified by dry flash column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=1:1) to give
(5RS,6SR,7SR)-6-tert-butoxycarbonyl-2-propylamino-7-(2-benzyloxy-4-methoxyphenyl)-5-(3,4-methylene-
20 dioxyphenyl)cyclopenteno[1,2-b]pyridine(167mg).

(2) (5RS,6SR,7SR)-6-Tert-butoxycarbonyl-2-(N-propyl-N-methylamino-7-(2-benzyloxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

25 To a THF solution(3ml) of (5RS,6SR,7SR)-6-tert-butoxycarbonyl-2-propylamino-7-(2-benzyloxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-

b]pyridine(163mg,0.267mmol) which was prepared in (1) was added 1M lithium hexamethyldisilazide - THF solution(290 μ l) at - 78°C. The mixture was stirred at the same temperature for 10 min and at room temperature for 5 30 min. The reaction solution was treated with methyl iodide(18 μ l) at room temperature, stirred at room temperature for 1 h, cooled at 0°C and treated with 3N HCl to quench the reaction. The reaction solution was extracted with AcOEt and the organic layer was washed 10 with water, a saturated aqueous solution of NaHCO₃ and brine and dried over Na₂SO₄. After removal of the solvent under reduced pressure the residue was purified by dry flash column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1) to give (5RS,6SR,7SR) - 6 - Tert - 15 butoxycarbonyl - 2 - (N-propyl - N-methylamino - 7 - (2-benzyloxy - 4-methoxyphenyl) - 5 - (3,4-methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(152mg).

(3) The title compound was prepared in the same manner as in Example 50 - (5),(6),(7) using (5RS,6SR,7SR) - 6 - 20 tert-butoxycarbonyl - 2 - (N-propyl - N-methylamino - 7 - (2-benzyloxy - 4-methoxyphenyl) - 5 - (3,4-methylene-dioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in (2).

mp:55 - 57 °C

25 High Resolution FAB - MS(m/e, (C₃₁H₃₄N₂O₈+H)⁺):

Calcd: 563.2393

Found: 563.2417

¹H - NMR(300MHz, CDCl₃, δ ppm):0.82(3H, t, J=7.4Hz),
1.21(3H, t, J=7.1Hz), 1.46 - 1.59(2H, m), 2.95(3H,
s), 3.15(1H, t, J=9.2Hz), 3.15 - 3.27(1H, m), 3.50 -
3.59(1H, m), 3.77(3H, s), 4.18(2H, q, J=7.1Hz),
5 4.46(1H, d, J=15.9Hz), 4.53(1H, d, J=9.2Hz),
4.57(1H, d, J=15.9Hz), 4.90(1H, d, J=9.2Hz), 5.91 -
5.92(2H, m), 6.29(1H, d, J=8.6Hz), 6.35(1H, d,
J=2.3Hz), 6.50(1H, dd, J=2.3Hz, 8.4Hz), 6.71 -
6.77(3H, m), 7.06(1H, d, J=8.6Hz), 7.11(1H, d,
10 J=8.4Hz)

Rf Value:0.66(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1).

Example 128

(5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-2-(N-propyl-N-methylamino)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

The title compound was prepared in the same manner as in Example 2 using (5RS,6SR,7SR)-7-(2-ethoxycarbonylmethoxy-4-methoxyphenyl)-6-carboxy-2-(N-propyl-N-methylamino)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in Example 127.

mp:120 - 123 °C

High Resolution FAB-MS(m/e, (C₂₉H₃₀N₂O₈+H)⁺):

25 Calcd: 535.2080

Found: 535.2110

¹H - NMR(300MHz, CDCl₃, δ ppm):0.83(3H, t, J=7.4Hz), 1.49

- 1.61(2H, m), 2.92(1H, t, J=9.0Hz), 2.99(3H, s),
 3.19 - 3.29(1H, m), 3.50 - 3.60(1H, m), 3.77(3H, s),
 4.45 - 4.60(3H, m), 5.17(1H, d, J=9.0Hz), 5.90 -
 5.91(2H, m), 6.35 - 6.37(2H, m), 6.47(1H, d,
 5 J=2.3Hz), 6.66(1H, s), 6.68 - 6.74(2H, m), 7.05(1H,
 d, J=8.6Hz), 7.11(1H, d, J=8.6Hz)

Rf Value:0.30(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Each compound in the following Examples 129 and 130
 10 was prepared in the same manner as in Examples 127 and 128.

Example 129

(5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-2-methylamino-5-(3,4-methylene-
 15 dioxyphenyl)cyclopenteno[1,2-b]pyridine

mp:194 - 196 °C

High Resolution FAB-MS(m/e, (C₂₆H₂₄N₂O₈+H)⁺):

Calcd: 493.1611

Found: 493.1622

20 ¹H - NMR(300MHz, DMSO - d₆, δ ppm):2.62(3H, d, J=4.8Hz),
 3.04(1H, t, J=8.5Hz), 3.71(3H, s), 4.30(1H, d,
 J=8.5Hz), 4.36(1H, d, J=16.4Hz), 4.56(1H, d,
 J=16.4Hz), 4.61(1H, d, J=8.5Hz), 5.96(2H, s),
 6.21(1H, d, J=8.3Hz), 6.34(1H, d, J=4.8Hz), 6.46 -
 25 6.49(2H, m), 6.68(1H, d, J=8.2Hz), 6.71(1H, s),
 6.82(1H, d, J=7.6Hz), 6.90 - 6.96(2H, m)

Rf Value:0.46(E. Merck, Kieselgel 60F₂₅₄/chloro-

roform:methanol:acetic acid=10:1:1)

Example 130

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 2 - (N,N - dimethylamino) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:153 - 156 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₆N₂O₈+H)⁺):

Calcd: 507.1767

Found: 507.1759

¹H - NMR(300MHz, CD₃OD, δ ppm):3.03(6H, s), 3.19-3.25(1H, m), 3.76(3H, s), 4.38 - 4.55(3H, m), 4.86(1H, m), 5.89(2H, s), 6.47(1H, d, J=2.1Hz), 6.53(1H, dd, J=2.1Hz, 8.5Hz), 6.61(1H, d, J=8.9Hz), 6.72(1H, s), 6.75(2H, s), 7.03(1H, d, J=8.5Hz), 7.19(1H, d, J=8.9Hz)

Rf Value:0.57(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=5:1:1)

Example 131

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2 - carboxymethoxy - 5 - tert-butyl - 4 - methoxyphenyl) - 2 - methylamino - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a tert - butyl acetate solution(10ml) of (5RS,6SR,7SR) - 6 - carboxy - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 2 - methylamino - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(64.1mg,0.13mmol) which was prepared in Example 129 was added 70% perchloric acid to make acid(pH1 - 2), and the mixture was stirred at room

temperature for 66 h, neutralized with a saturated aqueous solution of NaHCO_3 and extracted with AcOEt and dried over Na_2SO_4 . After removal of the solvent under reduced pressure the residue was purified by preparative
 5 TLC(E. Merck Kieselgel 60/chloroform:methanol=10:1) to give mono tert-butyl esters of 7-(2-carboxymethoxy-5-tert-butyl-4-methoxyphenyl) compounds(yields:49mg,10mg), followed by removing the tert-butyl ester with TFA to give the title compound.

10 mp:190 - 192 °C

High Resolution FAB-MS(m/e, $(\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_8+\text{H})^+$):

Calcd: 549.2237

Found: 549.2253

^1H -NMR(400MHz, CD_3OD , δ ppm):1.27(9H, s), 2.95(3H, s),
 15 3.57(1H, t, $J=8.4\text{Hz}$), 3.84(3H, s), 4.59(1H, d, $J=8.4\text{Hz}$), 4.64(1H, d, $J=16.4\text{Hz}$), 4.80(1H, d, $J=16.4\text{Hz}$), 5.17(1H, d, $J=8.4\text{Hz}$), 5.95(2H, s), 6.62(1H, s), 6.75 - 6.84(4H, m), 7.09(1H, s), 7.55(1H, d, $J=8.8\text{Hz}$)

20 Rf Value:0.55(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 132

(5RS,6SR,7SR) - 2 - Amino - 6 - carboxy - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphe-
 25 nyl)cyclopenteno[1,2-b]pyridine
 (1) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methyle-

nedioxyphenyl)cyclopenteno[1,2 - b]pyridine N - oxide

(5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine N - oxide was
5 prepared in the same manner as in Example 124 - (1) using
(5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was
prepared in the same manner as in Example 50 - (6) using
10 tert - butyl bromoacetate.

(2) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - [(N - benzoyl)benzylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

15 (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine N - oxide which
was prepared in (1) was reacted with N - benzylbenzimidoyl chloride which was prepared from N - benzylbenzamide in the same manner as in Example 124 - (2) to give
20 (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - [(N - benzoyl)benzylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine.

25 (3) (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 7 - (2 - tert - butoxycarbonylmethoxy - 4 - methoxyphenyl) - 2 - (benzoylamino) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 -

b]pyridine

(5RS,6SR,7SR)-6-Tert-butoxycarbonyl-7-(2-tert-butoxycarbonylmethoxy-4-methoxyphenyl)-2-[(N-benzoyl)benzylamino]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in (2) was subjected to hydrogenation under hydrogen atmosphere at 50 to 60 psi using palladium black as a catalyst to give (5RS,6SR,7SR)-6-tert-butoxycarbonyl-7-(2-tert-butoxycarbonylmethoxy-4-methoxyphenyl)-2-(benzoylamino)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine.

(4) (5RS,6SR,7SR)-6-tert-butoxycarbonyl-7-(2-tert-butoxycarbonylmethoxy-4-methoxyphenyl)-2-(benzoylamino)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine was subjected to the same reaction as in Example 124-(4) to give the title compound.

mp:204 - 206 °C

High Resolution FAB-MS(m/e, (C₂₅H₂₂N₂O₈+H)⁺):

Calcd: 479.1454

Found: 479.1458

¹H-NMR(300MHz, CD₃OD, δ ppm):3.70(1H, t, J=9.2Hz), 3.77(3H, s), 4.55(1H, d, J=9.2Hz), 4.61(1H, d, J=16.2Hz), 4.78(1H, d, J=16.2Hz), 5.22(1H, d, J=9.2Hz), 5.95(2H, s), 6.54(1H, dd, J=2.2Hz, 8.4Hz), 6.58(1H, d, J=2.2Hz), 6.72 - 6.78(3H, m), 6.83(1H, d, J=8.4Hz), 7.23(1H, d, J=8.3Hz), 7.40(1H, d, J=8.9Hz)

Rf Value:0.48(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Each compound in the following Examples 133 to 135 was prepared in the same manner as in Example 132 using
5 N - (3 - benzyloxypropyl) - or N - (2 - benzyloxyethyl) - benzimidoyl chloride.

Example 133

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 2 - [(N - benzoyl) - 3 - hydroxypropylamino] - 5 -
10 (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:127 - 132 °C

High Resolution FAB - MS(m/e, (C₃₅H₃₂N₂O₁₀+H)⁺):

Calcd: 641.2135

Found: 641.2131

15 ¹H - NMR(300MHz, CD₃OD, δ ppm):1.71- 1.89(2H, m), 3.52(1H, t, J=9.6Hz), 3.52 - 3.58(2H, m), 3.79(3H, s), 4.00(2H, t, J=6.9Hz), 4.42(1H, d, J=16.2Hz), 4.48(1H, d, J=9.6Hz), 4.58(1H, d, J=16.2Hz), 4.77(1H, d, J=9.6Hz), 5.89(2H, s), 6.46(1H, d, J=2.3Hz),
20 J=2.3Hz), 6.53(1H, dd, J=2.3Hz, 8.4Hz), 6.68(1H, d, J=7.9Hz), 6.71 - 6.75(3H, m), 7.00(1H, d, J=8.4Hz), 7.06(1H, dd, J=1.4Hz, 7.9Hz), 7.22 - 7.37(5H, m)

Rf Value:0.39(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=30:1:1)

25 Example 134

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2 - carboxymethoxy - 4 - methoxyphenyl) - 2 - (3 - hydroxypropylamino) - 5 - (3,4 - methyle-

nedioxyphenyl)cyclopenteno[1,2-b]pyridine

mp:166 - 169 °C

High Resolution FAB - MS(m/e, (C₂₈H₂₈N₂O₉+H)⁺):

Calcd: 537.1873

5 Found: 537.1864

¹H - NMR(300MHz, CD₃OD, δ ppm):1.81(2H, quint, J=6.3Hz),
3.39(2H, t, J=6.3Hz), 3.60 - 3.70(3H, m), 3.78(3H,
s), 4.56(1H, d, J=9.2Hz), 4.61(1H, d, J=13.8Hz),
4.76(1H, d, J=13.8Hz), 5.20(1H, d, J=10.0Hz),
10 5.96(2H, s), 6.53 - 6.57(2H, m), 6.78 - 6.86(4H, m),
7.22(1H, d, J=8.5Hz), 7.47(1H, d, J=8.9Hz)

Rf Value:0.33(E. Merck, Kieselgel 60F₂₅₄/chloro-
roform:methanol:acetic acid=30:1:1)

Example 135

15 (5RS,6SR,7SR)-6-Carboxy-7-(2-carboxymethoxy-4-me-
thoxyphenyl)-2-(2-hydroxyethylamino]-5-(3,4-methyle-
nedioxyphenyl)cyclopenteno[1,2-b]pyridine

mp:200 °C (dec.)

High Resolution FAB - MS(m/e, (C₂₇H₂₆N₂O₉+H)⁺):

20 Calcd: 523.1717

Found: 523.1687

¹H - NMR(300MHz, CD₃OD, δ ppm):3.35(2H, t, J=5.2Hz),
3.43(1H, t, J=9.6Hz), 3.67(2H, t, J=5.2Hz),
3.75(3H, s), 4.48(1H, d, J=9.6Hz), 4.49(1H, d,
25 J=15.8Hz), 4.61(1H, d, J=15.8Hz), 5.09(1H, d,
J=9.6Hz), 5.91(2H, s), 6.51(1H, dd, J=2.4Hz,
8.3Hz), 6.53(1H, d, J=2.4Hz), 6.67(1H, d, J=8.6Hz),

6.74 - 6.77(3H, m), 7.19(1H, d, J=8.3Hz), 7.31(1H, d, J=8.6Hz)

Rf Value:0.53(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=3:1)

5 Each compound in the following Examples 136 to 144 was prepared in the same manner as in Example 89 using corresponding aryl Grignard reagent or aryl lithium reagent.

Example 136

10 (5RS,6SR,7SR) - 6 - Carboxy - 5 - (3,5 - dimethoxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:212 - 214 °C

High Resolution FAB - MS(m/e, (C₂₄H₂₃NO₅+H)⁺):

Calcd: 406.1654

15 Found: 406.1658

¹H - NMR(300MHz, CDCl₃, δ ppm):3.35(1H, t, J=9.5Hz),
3.76(3H, s), 3.77(6H, s), 4.61(1H, d, J=9.5Hz),
4.70(1H, d, J=9.5Hz), 6.40(3H, s), 6.87(2H, d, J=8.7Hz),
7.14(1H, dd, J=4.9Hz, 7.7Hz), 7.16(2H, d, J=8.7Hz),
20 7.35(1H, td, J=1.4Hz, 7.7Hz), 8.47(1H, td, J=1.4Hz, 4.9Hz)

Rf Value:0.33(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=15:1)

Example 137

25 (5RS,6SR,7SR) - 6 - Carboxy - 5 - (3 - propoxy - 5 - methoxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:205 - 206 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₇NO₅+H)⁺):

Calcd: 434.1968

Found: 434.1953

¹H - NMR(300MHz, CDCl₃, δ ppm): 1.02(3H, t, J=7.2Hz),
 5 1.79(2H, sext, J=7.2Hz), 3.37(1H, t, J=9.7Hz),
 3.77(3H, s), 3.78(3H, s), 3.87(2H, t, J=7.2Hz),
 4.61(1H, d, J=9.7Hz), 4.70(1H, d, J=9.7Hz),
 6.40(3H, s), 6.88(2H, d, J=8.4Hz), 7.13(1H, dd,
 J=4.9Hz, 7.7Hz), 7.18(2H, d, J=8.4Hz), 7.35(1H, d,
 10 J=7.7Hz), 8.47(1H, d, J=4.9Hz)

Rf Value: 0.42(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 138

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3,4 - methylenedioxy - 5
 15 - methoxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 -
b]pyridine

mp: 220 °C (dec.)

High Resolution FAB - MS(m/e, (C₂₄H₂₁NO₆+H)⁺):

Calcd: 420.1447

20 Found: 420.1466

¹H - NMR(300MHz, CDCl₃, δ ppm): 3.32(1H, t, J=9.6Hz),
 3.80(3H, s), 3.89(3H, s), 4.60(1H, d, J=9.6Hz),
 4.69(1H, d, J=9.6Hz), 5.98(2H, s), 6.42(1H, d,
 J=1.1Hz), 6.46(1H, d, J=1.1Hz), 6.90(2H, d,
 25 J=8.6Hz), 7.14(1H, dd, J=4.5Hz, 7.4Hz), 7.19(2H, d,
 J=8.6Hz), 7.33(1H, d, J=7.4Hz), 8.48(1H, d,
 J=4.5Hz)

Rf Value: 0.47 (E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 139

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3 - benzyloxy - 4 - methoxy - phenyl) - 7 - (4 - methoxyphenyl) cyclopenteno[1,2 - b]pyridine

mp: 79 - 80 °C

High Resolution FAB - MS (m/e, (C₃₀H₂₇NO₅+H)⁺):

Calcd: 482.1967

Found: 482.1989

¹H - NMR (300MHz, CDCl₃, δ ppm): 3.22 (1H, t, J=9.3Hz),
3.75 (3H, s), 3.89 (3H, s), 4.55 (1H, d, J=9.3Hz),
4.71 (1H, d, J=9.3Hz), 5.07 (1H, d, J=13.1Hz),
5.12 (1H, d, J=13.1Hz), 6.68 (1H, d, J=1.9Hz), 6.77 -
6.88 (2H, m), 7.10 (2H, d, J=8.6Hz), 7.12 - 7.37 (9H,
m), 8.47 (1H, d, J=4.8Hz)

Rf Value: 0.21 (E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=20:1)

Example 140

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3 - hydroxy - 4 - methoxy - phenyl) - 7 - (4 - methoxyphenyl) cyclopenteno[1,2 - b]pyridine

mp: 127 - 129 °C

High Resolution FAB - MS (m/e, (C₂₃H₂₁NO₅+H)⁺):

Calcd: 392.1498

Found: 392.1520

¹H - NMR (300MHz, CDCl₃, δ ppm): 3.31 (1H, t, J=9.8Hz),
3.77 (3H, s), 3.89 (3H, s), 4.57 (1H, d, J=9.8Hz),
4.70 (1H, d, J=9.8Hz), 6.77 (1H, dd, J=2.0Hz, 8.1Hz),

6.80(1H, d, J=2.0Hz), 6.84(1H, d, J=8.1Hz),
6.87(2H, d, J=8.8Hz), 7.12(1H, dd, J=4.9Hz, 7.0Hz),
7.16(2H, d, J=8.8Hz), 7.30(1H, td, J=1.3Hz, 7.0Hz),
8.45(1H, td, J=1.3Hz, 4.9Hz)

5 Rf Value:0.30(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 141

(5RS,6SR,7SR) - 5 - (4 - Indolyl) - 6 - carboxy - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

10 mp:144 - 148 °C

High Resolution FAB - MS(m/e, (C₂₄H₂₀N₂O₃+H)⁺):

Calcd: 385.1552

Found: 385.1540

¹H - NMR(300MHz, CD₃OD, δ ppm):3.51(1H, t, J=10.1Hz),
15 3.79(3H, s), 4.75(1H, d, J=10.1Hz), 5.04(1H, d, J=10.1Hz), 6.12 - 6.18(1H, m), 6.90 - 6.96(3H, m),
7.10(1H, dd, J=7.3Hz, 8.1Hz), 7.16 - 7.25(4H, m),
7.30 - 7.34(1H, m), 7.36(1H, dd, J=1.0Hz, 8.1Hz),
8.32 - 8.36(1H, m)

20 Rf Value:0.42(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 142

(5RS,6SR,7SR) - 5 - (6 - Indolyl) - 6 - carboxy - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

25 mp:128 - 134 °C

High Resolution FAB - MS(m/e, (C₂₄H₂₀N₂O₃+H)⁺):

Calcd: 385.1552

Found: 385.1570

^1H -NMR(300MHz, CD_3OD , δ ppm): 3.27- 3.35(1H, m), 3.79(3H, s), 4.69(1H, d, $J=9.8\text{Hz}$), 4.73(1H, d, $J=9.6\text{Hz}$), 6.43(1H, dd, $J=0.9\text{Hz}$, 3.2Hz), 6.90(1H, dd, $J=1.6\text{Hz}$, 8.1Hz), 6.85 - 6.96(2H, m), 7.15 - 7.21(2H, m), 7.22 - 7.28(1H, m), 7.22(1H, d, $J=3.2\text{Hz}$), 7.37 - 7.43(1H, m), 7.55(1H, d, $J=8.1\text{Hz}$), 8.30 - 8.34(1H, m)

Rf Value: 0.29(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

10 Example 143

(5RS,6SR,7SR)-7-(5-Indolyl)-6-carboxy-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

mp: -250 °C (dec.)

High Resolution FAB-MS(m/e , $(\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_4+\text{H})^+$):

15 Calcd: 399.1345

Found: 399.1330

^1H -NMR(300MHz, methanol - d_4 , δ ppm): 3.26(1H, t, $J=9.9\text{Hz}$), 4.60(1H, d, $J=9.9\text{Hz}$), 4.77(1H, d, $J=9.9\text{Hz}$), 5.94(2H, s), 6.40(1H, dd, $J=0.85\text{Hz}$, 3.1Hz), 6.75(1H, brs), 6.79(1H, d, $J=7.9\text{Hz}$), 6.83(1H, dd, $J=0.8\text{Hz}$, 7.9Hz), 6.92(1H, dd, $J=1.7\text{Hz}$, 8.4Hz), 7.21(1H, d, $J=3.1\text{Hz}$), 7.27(1H, dd, $J=4.9\text{Hz}$, 7.6Hz), 7.36(1H, d, $J=8.4\text{Hz}$), 7.42(1H, td, $J=1.4\text{Hz}$, 7.6Hz), 7.43(1H, brs), 8.30(1H, td, $J=1.4\text{Hz}$, 4.9Hz)

25 Rf Value: 0.42(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 144

(5RS,6SR,7SR)-7-(4-Ethoxyphenyl)-6-carboxy-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

mp:215 - 217 °C

High Resolution FAB-MS(m/e, (C₂₄H₂₁NO₅+H)⁺):

5 Calcd: 404.1497

Found: 404.1519

¹H-NMR(300MHz, CDCl₃, δ ppm):1.39(3H, t, J=7.0Hz),
 3.30(1H, t, J=10.0Hz), 4.00(2H, q, J=7.0Hz),
 4.60(1H, d, J=10.0Hz), 4.69(1H, d, J=10.0Hz),
 10 5.96(1H, d, J=1.4Hz), 5.97(1H, d, J=1.4Hz),
 6.71(1H, d, J=1.2Hz), 6.76(1H, dd, J=1.2Hz, 8.2Hz),
 6.81(1H, d, J=8.2Hz), 6.88(2H, d, J=8.8Hz), 7.11 -
 7.13(1H, m), 7.16(2H, d, J=8.8Hz), 7.31(1H, d,
 J=7.6Hz), 8.48(1H, d, J=5.0Hz)

15 Rf Value:0.80(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 145

(5RS,6SR,7SR)-7-[2-(4-imidazolylmethoxy)-4-methoxyphenyl)-6-carboxy-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

20 The ^{im}N-trityl-tert-butyl ester of (5RS,6SR,7SR)-7-[2-hydroxy-4-methoxyphenyl)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine was prepared in the same manner as in Example 50 -
 25 (6) using (5RS,6SR,7SR)-7-[2-hydroxy-4-methoxyphenyl)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine which was prepared in

Example 50 - (5) and 4 - chloromethyl - 1 - tritylimidazole.
The ^{im}N - trityl - tert - butyl ester was treated with 4N
HCl - dioxane to give the di - HCl salt of the title
compound.

5 mp: 172 - 175 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₃N₃O₆+H)⁺):

Calcd: 486.1665

Found: 486.1678

¹H - NMR(300MHz, CD₃OD, δ ppm): 3.59(1H, t, J=10.3Hz),
10 3.86(3H, s), 4.70(1H, d, J=10.3Hz), 4.98(1H, d,
J=11.9Hz), 5.14(1H, d, J=10.3Hz), 5.23(1H, d,
J=11.9Hz), 5.98 - 6.03(2H, m), 6.18(1H, brs),
6.65(1H, dd, J=1.6Hz, 7.9Hz), 6.73(1H, dd, J=2.3Hz,
8.4Hz), 6.84(1H, d, J=7.9Hz), 6.85(1H, d, J=2.3Hz),
15 7.35(1H, d, J=8.4Hz), 7.50(1H, brs), 7.80(1H, dd,
J=5.7Hz, 7.6Hz), 7.88(1H, d, J=7.6Hz), 8.55(1H, d,
J=5.7Hz), 8.96(1H, brs)

Each compound in the following Examples 146 and 147
was prepared in the same manners as in Examples 55 and
20 56 using α - bromo - γ - butyrolactone.

Example 146

(5RS,6SR,7SR) - 7 - [2 - (2 - Oxo - 4,5 - dihydrofuryloxy) -
4 - methoxyphenyl] - 6 - carboxy - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diaster-
25 eomers)

mp: 172 - 175 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₃NO₈+H)⁺):

Calcd: 490.1502

Found: 490.1499

¹H - NMR(300MHz, Acetone - d₆, δ ppm): 1.80 - 1.96(1H, m),
 2.48 - 2.60(1H, m), 3.61(1H, t, J=10.2Hz), 3.80(3H,
 5 s), 4.18 - 4.30(2H, m), 4.63(1H, d, J=10.2Hz),
 4.87(1H, d, J=10.2Hz), 5.19(1H, t, J=8.3Hz),
 6.00(2H, s), 6.60(1H, dd, J=2.4Hz, 8.4Hz), 6.83(1H,
 d, J=8.0Hz), 6.84(1H, d, J=2.4Hz), 6.90(1H, dd,
 J=1.7Hz, 8.0Hz), 6.93(1H, d, J=1.7Hz), 7.20(1H, d,
 10 J=8.4Hz), 7.33(1H, dd, J=5.0Hz, 7.6Hz), 7.43(1H,
 td, J=1.4Hz, 7.6Hz), 8.42(1H, td, J=1.4Hz, 5.0Hz)

Rf Value: 0.34(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 147

15 (5RS,6SR,7SR) - 7 - [2 - (2 - Oxo - 4,5 - dihydrofuryloxy) -
4 - methoxyphenyl] - 6 - carboxy - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other dias-
tereomer)

mp: 170 - 173 °C

20 High Resolution FAB - MS(m/e, (C₂₇H₂₃NO₈+H)⁺):

Calcd: 490.1502

Found: 490.1500

¹H - NMR(300MHz, Acetone - d₆, δ ppm): 2.24 - 2.39(1H, m),
 2.81 - 2.92(1H, m), 3.50(1H, t, J=10.2Hz), 3.79(3H,
 25 s), 4.29 - 4.42(2H, m), 4.67(1H, d, J=10.2Hz),
 5.01(1H, d, J=10.2Hz), 5.21(1H, t, J=7.9Hz),
 6.01(2H, s), 6.57(1H, dd, J=2.4Hz, 8.4Hz), 6.79 -

6.87(4H, m), 7.18(1H, d, J=8.4Hz), 7.39(1H, dd, J=5.2Hz, 7.7Hz), 7.54(1H, td, J=1.3Hz, 7.7Hz), 8.43(1H, td, J=1.3Hz, 5.2Hz)

Rf Value:0.36(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Each compound in the following Examples 148 and 149 was prepared by hydrolyzing the corresponding compounds of Examples 146 and 147 with base.

Example 148

10 (5RS,6SR,7SR)-6-Carboxy-7-[2-(1-carboxy-3-hydroxypropoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

High Resolution FAB-MS(m/e, (C₂₇H₂₅NO₉+H)⁺):

15 Calcd: 508.1608

Found: 508.1613

Rf Value:0.26(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 149

20 (5RS,6SR,7SR)-6-Carboxy-7-[2-(1-carboxy-3-hydroxypropoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(the other diastereomer)

High Resolution FAB-MS(m/e, (C₂₇H₂₅NO₉+H)⁺):

25 Calcd: 508.1608

Found: 508.1602

Rf Value:0.25(E. Merck, Kieselgel 60F₂₅₄/chloro-

roform:methanol:acetic acid=10:1:1)

Example 150

(5RS,6SR,7SR) - 7 - (2 - Acetoxymethylcarbonylmethoxy - 4 - methoxyphenyl - 6 - carboxy - 5 - (3,4 - methylene-
 5 dioxyphenyl)cyclopenteno[1,2 - b]pyridine

(1) (5RS,6SR,7SR) - 7 - (2 - Diazomethylcarbonylmethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylene-
nedioxyphenyl)cyclopenteno[1,2 - b]pyridine

To a DMF suspension (2ml) of CsCO₃(79.5mg) and
 10 (5RS,6SR,7SR) - 7 - (2 - hydroxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(98.0mg,0.212mmol) which was prepared in Example 50 - (5) was added a DMF(1ml) solution of diazomethylbromomethylketone(43mg) which was
 15 prepared by the method described in the literature[Biochemistry, 16, 1964 - 1970(1977)] at 0°C. The mixture was stirred at 0°C to room temperature for 12 h, treated with 10% citric acid and extracted with AcOEt. The organic layer was washed brine, dried over Na₂SO₄
 20 and concentrated under reduced pressure. The residue was purified by preparative TLC(E. Merck Kieselgel 60F₂₅₄/hexane:AcOEt=2:3) to give (5RS,6SR,7SR) - 7 - (2 - diazomethylcarbonylmethoxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(64.4mg).
 25

(2) An AcOH suspension(2.5ml) of (5RS,6SR,7SR) - 7 - (2 - diazomethylcarbonylmethoxy - 4 - methoxyphenyl) - 6 - tert - bu-

toxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine(13.5mg,0.0249mmol) which was
prepared in (1) was heated at 110°C for 30 min with
stirring. The reaction solution was concentrated under
5 reduced pressure and the residue was purified by
preparative TLC(E. Merck Kieselgel 60F₂₅₄/hex-
ane:AcOEt=1:2) to give (5RS,6SR,7SR) - 7 - (2 - acetoxyme-
thylcarbonylmethoxy - 4 - methoxyphenyl) - 6 - tert -
butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
10 penteno[1,2 - b]pyridine(8.6mg). The title compound was
prepared by treating the ester with 4N HCl - dioxane.

mp:80 - 84 °C

High Resolution FAB - MS(m/e, (C₂₈H₂₅NO₉+H)⁺):

Calcd: 520.1608

15 Found: 520.1640

¹H - NMR(300MHz, Acetone- d₆, δ ppm):2.08(3H, s), 3.46(1H,
t, J=10.1Hz), 3.79(3H, s), 4.64(1H, d, J=10.1Hz),
4.65(1H, d, J=16.6Hz), 4.80(1H, d, J=16.6Hz),
4.84(2H, s), 4.97(1H, d, J=10.1Hz), 5.99(1H, d,
20 J=1.5Hz), 6.00(1H, d, J=1.5Hz), 6.56 - 6.59(2H, m),
6.81 - 6.87(3H, m), 7.14(1H, d, J=8.8Hz), 7.17(1H,
dd, J=4.9Hz, 7.6Hz), 7.30(1H, td, J=1.3Hz, 7.6Hz),
8.35(1H, td, J=1.3Hz, 4.9Hz)

Rf Value:0.55(E. Merck, Kieselgel 60F₂₅₄/chlo-
25 roform:methanol=10:1)

Each compound in the following Examples 151 and 152
was prepared in the same manner as in Example 83.

Example 151

(5RS,6SR,7SR) - 2 - Isopropylamino - 6 - carboxy - 5 - (3,4 - methylenedioxyphenyl - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

5 mp:100 - 101 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₆N₂O₅+H)⁺):

Calcd: 447.1919

Found: 447.1927

¹H - NMR(300MHz, CDCl₃, δ ppm):1.17(3H, d, J=6.3Hz),
10 1.20(3H, d, J=6.3Hz), 3.03(1H, t, J=8.6Hz),
3.64(1H, sept, J=6.3Hz), 3.70(3H, s), 4.40(1H, d,
J=8.6Hz), 4.59(1H, d, J=8.6Hz), 4.62(1H, brs),
5.93(2H, ABq, J=1.4Hz, Δν=2.3Hz), 6.28(1H, d,
J=8.4Hz), 6.717(1H, d, J=6.1Hz), 6.723(1H, d,
15 J=6.1Hz), 6.74(1H, s), 6.82(2H, d, J=8.6Hz),
7.14(1H, d, J=8.4Hz), 7.17(2H, d, J=8.6Hz)

Rf Value:0.30(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=20:1)

Example 152

20 6 - Carboxy - 5 - (3,4 - methylenedioxyphenyl - 7 - (4 - methoxyphenyl)cyclopent - 1,2 - dieno[1,2 - b]pyridine and 6 - Carboxy - 5 - (3,4 - methylenedioxyphenyl - 7 - (4 - methoxyphenyl)cyclopent - 1,2 - dieno[2,1 - b]pyridine(1:2 mixture)

High Resolution FAB - MS(m/e, (C₂₆H₂₄N₂O₅+H)⁺):

25 Calcd: 445.1763

Found: 445.1746

¹H - NMR(300MHz, CDCl₃, δ ppm):1.17(3H, d, J=6.5Hz),

1.19(3H, d, J=6.5Hz), 3.72(1H, sept, J=6.5Hz),
3.76+3.86(3H, s × 2), 4.62+5.08(1H, brs × 2),
4.79+5.90(1H, s × 2), 6.02(2H, s), 6.22+6.26(1H, d ×
2, J=8.7Hz, J=8.6Hz), 6.79(2H, ddd, J=0.8Hz, 2.1Hz,
8.8Hz), 6.91(1H, d, J=8.6Hz), 6.98(1H, dd, J=2.0Hz,
8.6Hz), 6.99(1H, d, J=2.0Hz), 7.09(2H, ddd,
J=0.8Hz, 2.1Hz, 8.8Hz), 7.35+7.70(1H, d × 2,
J=8.7Hz, J=8.6Hz)

Rf Value: 0.36, 0.33 (E. Merck, Kieselgel 60F₂₅₄)

/chloroform:methanol=20:1)

Example 153

(5RS,6SR,7SR) - 6 - Carboxy - 2,7 - dimethyl - 5 - (3,4 - methylenedioxyphenyl - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 77 using an excess amount of methyl lithium ether solution.

mp: 226 - 227 °C

High Resolution FAB - MS(m/e, (C₂₅H₂₃NO₅+H)⁺):

Calcd: 418.1654

Found: 418.1652

¹H - NMR(300MHz, CDCl₃+CD₃OD, δ ppm): 1.66(3H, s),
2.49(3H, s), 3.40(1H, d, J=10.3Hz), 3.81(3H, s),
4.73(1H, d, J=10.3Hz), 5.95(2H, s), 6.72(1H, s),
6.73 - 6.90(2H, m), 6.89(2H, d, J=8.4Hz), 7.06(1H, d,
J=6.3Hz), 7.22(2H, d, J=8.4Hz), 7.31(1H, d,
J=6.3Hz)

Rf Value:0.54(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 154

(5RS,6SR,7SR) - 6 - Carboxy - 2 - pyrrolidino - 5 - (3,4 - methylenedioxyphenyl - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 83.

High Resolution FAB - MS(m/e, (C₂₇H₂₆N₂O₅+H)⁺):

Calcd: 459.1920

Found: 459.1910

¹H - NMR(300MHz, CDCl₃, δ ppm):1.84-2.03(4H, m), 3.15(1H, dd, J=8.6Hz, 9.6Hz), 3.28-3.44(4H, m), 3.80(3H, s), 4.49(1H, d, J=8.6Hz), 4.62(1H, d, J=9.6Hz), 5.95(2H, ABq, J=1.4Hz, Δν=3.3Hz), 6.20(1H, d, J=8.6Hz), 6.72(1H, s), 6.76(2H, s), 6.86(2H, d, J=8.7Hz), 7.05(1H, d, J=8.6Hz), 7.24(2H, d, J=8.7Hz)

Rf Value:0.40(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 155

(5RS,6SR,7SR) - 6 - Carboxy - 7 - (2,3 - dihydro - 5 - benzofuranyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 114 using 2,3 - dihydro - 5 - benzofuranyl magnesium bromide which was prepared by the method

described in the literature[Synthesis, 950 - 953(1988)].

mp:235 - 237 °C

High Resolution FAB - MS(m/e, (C₂₄H₁₉NO₅+H)⁺):

Calcd: 402.1341

5 Found: 402.1325

¹H - NMR(300MHz, DMSO-d₆, δ ppm):3.08 - 3.21(3H, m), 4.42 -
4.56(4H, m), 6.01(2H, s), 6.65 - 7.25(8H, m),
8.33(1H, d, J=3.6Hz), 12.39(1H, brs)

Rf Value:0.41(E. Merck, Kieselgel 60F₂₅₄/chlo-
10 roform:methanol=10:1)

Example 156

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - hydroxyethoxy) -
4 - methoxyphenyl] - 2 - (3 - hydroxypropylamino) - 5 - (3,4 - me-
thylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

15 (1) (5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - [2 - (2 -
benzyloxyethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine

(5RS,6SR,7SR) - 7 - (2 - Hydroxy - 4 - methoxyphenyl) - 6 -
tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
20 penteno[1,2 - b]pyridine which was prepared in Example 50
- (5) was allowed to react with 2 - benzyloxyethyl bromide
in DMF in the presence of CsCO₃ to give (5RS,6SR,7SR) - 6
- tert - butoxycarbonyl - 7 - [2 - (2 - benzyloxyethoxy) - 4 - me-
thoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
25 penteno[1,2 - b]pyridine

(2) The title compound was prepared in the same manner
as in Example 124 - (1), (2) and (4) using (5RS,6SR,7SR) - 6

- tert - butoxycarbonyl - 7 - [2 - (2 - benzyloxyethoxy) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine and N - (3 - benzyloxypropyl)benzimidoyl chloride.

5 mp:168 - 173 °C

High Resolution FAB - MS(m/e, (C₂₈H₃₀N₂O₈+H)⁺):

Calcd: 523.2080

Found: 523.2084

¹H - NMR(300MHz, CD₃OD, δ ppm):1.70(2H, quint, J=6.2Hz),
 10 3.07(1H, t, J=8.7Hz), 3.20 - 3.37(2H, m), 3.55(2H, t, J=5.0Hz), 3.65 - 3.80(2H, m), 3.76(3H, s), 3.91(1H, td, J=5.0Hz, 10.0Hz), 4.06(1H, td, J=5.0Hz, 10.0Hz), 4.40(1H, d, J=8.7Hz), 4.83(1H, d, J=8.7Hz), 5.88(2H, s), 6.37(1H, dd, J=0.9Hz, 8.5Hz),
 15 6.48(1H, dd, J=2.4Hz, 8.3Hz), 6.53(1H, d, J=2.4Hz), 6.70 - 6.78(3H, m), 6.98(1H, d, J=8.3Hz), 7.05(1H, d, J=8.5Hz)

Rf Value:0.32(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

20 Example 157

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - hydroxyethoxy) - 4 - methoxyphenyl] - 2 - (N - methyl - 3 - hydroxypropylamino) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

25 The intermediate of Example 156 was N - methylated in the same manner as in Example 127 - (2) and then subjected to the same reaction as in Example 156 - (2) to

give the title compound.

mp:92 - 95 °C

High Resolution FAB - MS(m/e, (C₂₉H₃₂N₂O₈+H)⁺):

Calcd: 537.2237

5 Found: 537.2223

¹H - NMR(300MHz, CD₃OD, δ ppm):1.55- 1.78(2H, m), 2.95(3H, s), 3.13(1H, t, J=9.2Hz), 3.33 - 3.47(3H, m), 3.60 - 3.72(1H, m), 3.67(2H, t, J=5.1Hz), 3.78(3H, s), 3.86(1H, td, J=5.1Hz, 10.1Hz), 4.08(1H, td, J=5.1Hz, 10.1Hz), 4.40(1H, d, J=9.2Hz), 4.78(1H, d, J=9.2Hz), 5.91(2H, s), 6.49(1H, dd, J=1.0Hz, 8.7Hz), 6.50(1H, dd, J=2.4Hz, 8.4Hz), 6.55(1H, d, J=2.4Hz), 6.72 - 6.77(3H, m), 7.01(1H, d, J=8.4Hz), 7.10(1H, dd, J=0.9Hz, 8.7Hz)

15 Rf Value:0.40(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 158

(5RS,6SR,7SR) - 6 - Carboxy - 2 - cyclopropylamino - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 83.

mp:136 - 138.5 °C

High Resolution FAB - MS(m/e, (C₂₆H₂₄N₂O₅+H)⁺):

25 Calcd: 445.1763

Found: 445.1754

¹H - NMR(300MHz, CDCl₃, δ ppm):0.48 - 0.56(2H, m), 0.68 -

2169737

0.76(2H, m), 2.37 - 2.46(1H, m), 2.95(1H, t, J=8.3Hz), 3.63(3H, s), 4.32(1H, d, J=8.3Hz), 4.59(1H, d, J=8.3Hz), 5.93(2H, ABq, J=1.5Hz, $\Delta \nu$ =2.1Hz), 6.65 - 6.82(4H, m), 6.77(2H, d, J=8.7Hz),
5 7.12(2H, d, J=8.7Hz), 7.22(1H, dd, J=0.9Hz, 8.5Hz)

Rf Value:0.22(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=30:1)

Example 159

(5RS,6SR,7SR)-6-Carboxy-2-(N-methylisopropylamino)
10 -5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine

The precursor of the compound of Example 151, tert-butyl ester, was N-methylated by heating at 100°C in a mixture of formic acid and formaline. The tert-butyl
15 ester was cleaved to give the title compound.

mp:94 - 96 °C

High Resolution FAB-MS(m/e, (C₂₇H₂₈N₂O₅+H)⁺):

Calcd: 461.2078

Found: 461.2078

20 ¹H-NMR(300MHz, CDCl₃, δ ppm):1.05(3H, d, J=6.7Hz),
1.11(3H, d, J=6.7Hz), 2.77(3H, s), 3.14(1H, t, J=9.2Hz), 3.81(3H, s), 4.48(1H, d, J=9.2Hz),
4.60(1H, d, J=9.2Hz), 4.69(1H, sept, J=6.7Hz),
5.94(1H, d, J=1.4Hz), 5.95(1H, d, J=1.4Hz),
25 6.34(1H, d, J=8.6Hz), 6.71-6.76(3H, m), 6.86(2H, d, J=8.8Hz), 7.06(1H, d, J=8.6Hz), 7.23(2H, d, J=8.8Hz)

Rf Value:0.14(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=30:1)

Example 160

(5RS,6SR,7SR) - 6 - Carboxy - 2 - (N - methylcyclopropylamino) - 5 - (3,4 - methylenedioxyphenyl) - 7 - (4 - methoxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner as in Example 159.

mp:94 - 98 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₆N₂O₅+H)⁺):

Calcd: 459.1920

Found: 459.1934

¹H - NMR(300MHz, CDCl₃, δ ppm):0.53 - 0.70(2H, m), 0.70 - 0.90(2H, m), 2.38 - 2.47(1H, m), 2.99(3H, s), 3.17(1H, dd, J=8.9Hz, 9.5Hz), 3.80(3H, s), 4.49(1H, d, J=8.9Hz), 4.61(1H, d, J=9.5Hz), 5.94(2H, ABq, J=1.5Hz, Δν=2.6Hz), 6.72(1H, d, J=1.1Hz), 6.764(1H, d, J=1.1Hz), 6.766(1H, s), 6.83(1H, dd, J=0.9Hz, 8.6Hz), 6.86(2H, d, J=8.7Hz), 7.09(1H, dd, J=0.9Hz, 8.6Hz), 7.22(2H, d, J=8.7Hz)

Rf Value:0.32(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=30:1)

Example 161

(5RS,6SR,7SR) - 2 - Ethylamino - 6 - carboxy - 7 - [2 - (2 - carboxyethyl - 4 - methoxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner

as in Example 124 - (1), (2) and (4) using (5RS,6SR,7SR) - tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylethyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine.

5 mp: 225 - 228 °C

High Resolution FAB-MS(m/e, (C₂₈H₂₈N₂O₇+H)⁺):

Calcd: 505.1975

Found: 505.1985

10 ¹H-NMR(300MHz, DMSO-d₆, δ ppm): 0.99(3H, t, J=7.2Hz),
2.35 - 3.43(6H, m), 2.99(1H, t, J=8.9Hz), 3.71(3H, s),
4.32(1H, d, J=8.9Hz), 4.61(1H, d, J=8.9Hz),
6.00(2H, s), 6.22(1H, d, J=8.3Hz), 6.35(1H, t, J=5.6Hz),
6.68 - 7.02(7H, m), 12.22(2H, brs)

15 Rf Value: 0.50(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Example 162

(5RS,6SR,7SR) - 6-Carboxy - 7 - [2 - (2-carboxy - 2-propenyl) - 4-methoxyphenyl] - 2-propylamino - 5 - (3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

20 The title compound was prepared in the same manner as in Example 124 - (1), (2) and (3) using 2-propenyl compound of (5RS,6SR,7SR)-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropenyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine.
25

mp: 144 - 148 °C

High Resolution FAB-MS(m/e, (C₃₀H₃₀N₂O₇+H)⁺):

Calcd: 531.2131

Found: 531.2112

¹H - NMR(300MHz, CD₃OD, δ ppm): 0.91(3H, t, J=7.3Hz),
1.56(2H, sext, J=7.3Hz), 3.06 - 3.19(3H, m), 3.44 -
3.94(2H, m), 3.74(3H, s), 4.42(1H, d, J=8.6Hz),
4.85(1H, m), 5.44(1H, brs), 5.92(2H, s), 6.14(1H,
brs), 6.46(1H, d, J=8.4Hz), 6.73 - 6.80(5H, m),
6.99(1H, d, J=7.9Hz), 7.16(1H, d, J=8.6Hz)

Rf Value: 0.28(E. Merck, Kieselgel 60F₂₅₄/chloro-
form:methanol:acetic acid=20:1:1)

Each compound in the following Examples 163 and 164
was prepared by hydrogenation of (5RS,6SR,7SR) - 6 -
carboxy- 7 - [2 - (2 - carboxy- 2 - propenyl) - 4 - methoxyphenyl]
- 2 - propylamino - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine which was prepared in Example
162 using palladium black as a catalyst.

Example 163

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) -
4 - methoxyphenyl] - 2 - propylamino - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diaster-
eomer)

mp: 138 - 140 °C

High Resolution FAB - MS(m/e, (C₃₀H₃₂N₂O₇+H)⁺):

Calcd: 533.2288

Found: 533.2281

¹H - NMR(300MHz, CD₃OD, δ ppm): 0.91(3H, t, J=7.3Hz),
1.22(3H, d, J=6.0Hz), 1.55(2H, sext, J=7.3Hz), 2.77

- 2.92(2H, m), 3.05 - 3.11(1H, m), 3.13(2H, t, J=7.3Hz), 3.15(1H, t, J=9.1Hz), 3.75(3H, s), 4.44(1H, d, J=9.1Hz), 4.86(1H, t, J=9.1Hz), 5.93(2H, s), 6.48(1H, d, J=8.6Hz), 6.73 - 6.80(5H, m), 6.96(1H, d, J=8.5Hz), 7.18(1H, d, J=8.6Hz)

Rf Value:0.50(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 164

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - propylamino - 5 - (3,4 - methylenedioxypenteno[1,2 - b]pyridine(the other diastereomer)

mp:93 - 96 °C

High Resolution FAB - MS(m/e, (C₃₀H₃₂N₂O₇+H)⁺):

Calcd: 533.2288

Found: 533.2314

¹H - NMR(300MHz, CD₃OD, δ ppm):0.91(3H, t, J=7.3Hz), 1.33(3H, d, J=8.6Hz), 1.48(2H, sext, J=7.3Hz), 2.56 - 2.70(1H, m), 2.74 - 2.90(1H, m), 3.05 - 3.20(4H, m), 3.75(3H, s), 4.44(1H, d, J=8.9Hz), 4.75 - 4.95(1H, m), 5.92(2H, s), 6.46(1H, d, J=8.9Hz), 6.74 - 6.78(5H, m), 6.93(1H, d, J=7.6Hz), 7.16(1H, d, J=8.6Hz)

Rf Value:0.35(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 165

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) -

4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine(the other diastereomer)

The title compound was prepared in the same manner
as in Example 102 - (3) and 103 using (5RS,6SR,7SR) - 6 -
5 tert-butoxycarbonyl- 5 - (3,4 - methylenedioxyphenyl) - 7 - [2
- (2 - methoxycarbonylpropyl) - 4 - methoxyphenyl]cyclo-
penteno[1,2 - b]pyridine(the other diastereomer) which
was prepared in Example 102 - (2).

mp:125 - 127 °C

10 High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₇+H)⁺):

Calcd: 476.1709

Found: 476.1719

¹H - NMR(300MHz, CDCl₃, δ ppm):1.14(3H, d, J=6.9Hz),
2.60(1H, dd, J=9.3Hz, 12.7Hz), 2.75 - 2.90(1H, m),
15 3.18 - 3.26(2H, m), 3.76(3H, s), 4.64(1H, d,
J=9.5Hz), 5.03(1H, d, J=9.5Hz), 5.95(1H, d,
J=1.4Hz), 5.96(1H, d, J=1.4Hz), 6.69 - 6.88(6H, m),
7.15(1H, dd, J=4.9Hz, 7.8Hz), 7.35(1H, d, J=7.8Hz),
8.44(1H, d, J=4.9Hz)

20 Rf Value:0.40(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol:acetic acid=10:1:1)

Example 166

(5RS,6SR,7SR) - 6 - Carboxy - 5 - (3,4 - methylene-
dioxyphenyl) - 7 - [2 - (3 - methoxypropyl) - 4 - methoxy-
25 phenyl]cyclopenteno[1,2 - b]pyridine

The title compound was prepared in the same manner
as in Example 113 using 3 - methoxypropen - 1 - yltributyl

tin.

mp: 78 - 82 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₇NO₆+H)⁺):

Calcd: 462.1917

5 Found: 462.1924

¹H - NMR(300MHz, CDCl₃, δ ppm): 1.80 - 2.00(2H, m), 2.20 -
3.00(2H, m), 3.20(3H, s), 3.29 - 3.48(3H, m),
3.79(3H, s), 4.63(1H, d, J=9.9Hz), 4.97(1H, d,
J=9.9Hz), 5.97(1H, d, J=1.4Hz), 5.98(1H, d,
10 J=1.4Hz), 6.74(1H, brs), 6.75(1H, d, J=8.1Hz),
6.76(1H, brs), 6.78(1H, dd, J=1.6Hz, 7.9Hz),
6.80(1H, d, J=7.9Hz), 6.89 - 6.95(1H, m), 7.11(1H,
dd, J=4.9Hz, 7.6Hz), 7.30(1H, d, J=7.6Hz), 8.44(1H,
d, J=4.9Hz)

15 Rf Value: 0.40(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=15:1)

Example 167

(5RS,6SR,7SR) - 7 - [2 - (2 - Acetoxymethylcarbonyl)ethyl - 4 - methoxyphenyl] - 6 - carboxy - 5 - (3,4 - methylene-
20 dioxyphenyl)cyclopenteno[1,2-b]pyridine

(1) (5RS,6SR,7SR) - 7 - [2 - (2 - Carboxylethyl) - 4 - methoxy-
phenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2-b]pyridine

(5RS,6SR,7SR) - 7 - [2 - (2 - Carboxylethyl) - 4 - methoxy-
25 phenyl] - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2-b]pyridine was prepared in
the same manner as in Example 2 using (5RS,6SR,7SR) - 6 -

tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylethyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine which was prepared in Example 100-(1).

5 (2) (5RS,6SR,7SR)-7-[2-(2-Diazomethylcarbonylethyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

To a THF solution(1.5ml) of (5RS,6SR,7SR)-7-[2-(2-carboxyethyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine (151mg,0.292mmol) which was prepared in (1) were added a THF solution(1ml) of TEA(45 μ l) at -10°C and then a THF(1ml) solution of propyl chloroformate(39 μ l). The mixture was stirred at 0°C for 1 h, treated with 2% diazomethane-ether solution(4ml) and stirred for 10 h. Acetic acid(0.5ml) was added to the reaction solution. After removal of the solvent under reduced pressure the residue was purified by dry column flash chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1 to 1:1) to give (5RS,6SR,7SR)-7-[2-(2-diazomethylcarbonylethyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(78.3mg).

(3) The title compound was prepared in the same manner as in Example 150-(2) using (5RS,6SR,7SR)-7-[2-(2-diazomethylcarbonylethyl)-4-methoxyphenyl]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclo-

penteno[1,2-b]pyridine which was prepared in (2).

mp: 94 - 100 °C

High Resolution FAB - MS(m/e, (C₂₉H₂₇NO₈+H)⁺):

Calcd: 518.1815

5 Found: 518.1837

¹H - NMR(300MHz, Acetone - d₆, δ ppm): 2.06(3H, s), 2.65 -
3.25(4H, m), 3.42(1H, t, J=9.8Hz), 3.77(3H, s),
4.63(1H, d, J=9.8Hz), 4.69(2H, s), 4.95(1H, d,
J=9.8Hz), 6.01(2H, s), 6.75(1H, dd, J=2.6Hz,
10 8.5Hz), 6.83(1H, d, J=2.6Hz), 6.84 - 6.90(3H, m),
7.05(1H, d, J=8.5Hz), 7.18(1H, dd, J=4.8Hz, 7.5Hz),
7.31(1H, td, J=1.6Hz, 7.5Hz), 8.35(1H, td, J=1.6Hz,
4.8Hz)

Rf Value: 0.55(E. Merck, Kieselgel 60F₂₅₄/chloro-
15 roform:methanol=10:1)

Example 168

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - hydroxymethyl-
carbonylethyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphe
nyl)cyclopenteno[1,2-b]pyridine

20 The title compound was prepared by treating
(5RS,6SR,7SR) - 7 - [2 - (2 - acetoxymethylcarbonylethyl) - 4 -
methoxyphenyl] - 6 - carboxy - 5 - (3,4 - methylene-
dioxyphe
nyl)cyclopenteno[1,2-b]pyridine with 4N K₂CO₃
in dioxane.

25 mp: 116 - 125 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₇+H)⁺):

Calcd: 476.1709

Found: 476.1701

¹H - NMR(300MHz, Acetone - d₆, δ ppm): 2.65 - 3.00(3H, m),
3.05 - 3.25(1H, m), 3.41(1H, t, J=9.9Hz), 3.77(3H,
s), 4.10(1H, d, J=8.6Hz), 4.13(1H, d, J=8.6Hz),
5 4.63(1H, d, J=9.9Hz), 4.96(1H, d, J=9.9Hz),
6.02(2H, s), 6.75(1H, dd, J=2.8Hz, 8.5Hz), 6.82(1H,
d, J=2.8Hz), 6.84 - 6.90(3H, m), 7.05(1H, d,
J=8.5Hz), 7.20(1H, dd, J=4.7Hz, 7.7Hz), 7.32(1H,
td, J=1.4Hz, 7.7Hz), 8.35(1H, td, J=1.4Hz, 4.7Hz)

10 Rf Value: 0.33(E. Merck, Kieselgel 60F₂₅₄/chloro-
form:methanol=10:1)

Example 169

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (3 - carboxypropyl) -
4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclo-
15 penteno[1,2 - b]pyridine

To a methanol solution of (5RS,6SR,7SR) - 7 - [2 - (2 -
diazomethylcarbonyl)ethyl] - 4 - methoxyphenyl] - 6 - tert - bu-
toxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclo-
penteno[1,2 - b]pyridine which was prepared in Example
20 167 - (2) was added a triethylamine solution of benzoic
acid silver salt at 100 °C. The product was treated with
TFA and hydrolyzed with base to give the title compound.

mp: 110 - 113 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₇NO₇+H)⁺):

25 Calcd: 490.1866

Found: 490.1895

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.96(3H, d, J=6.3Hz),

2.12(1H, dd, J=9.4Hz, 13.8Hz), 2.37 - 2.42(1H, m),
2.49(1H, dd, J=10.2Hz, 13.8Hz), 2.56(1H, dd,
J=9.2Hz, 13.6Hz), 2.88(1H, dd, J=5.8Hz, 13.6Hz),
3.44(1H, d, J=9.8Hz), 3.77(3H, s), 4.66(1H, d,
5 J=9.8Hz), 5.01(1H, d, J=9.8Hz), 5.98(1H, d,
J=1.3Hz), 5.994(1H, d, J=1.3Hz), 6.69 - 6.96(6H, m),
7.13(1H, dd, J=4.9Hz, 7.8Hz), 7.34(1H, d, J=7.8Hz),
8.42(1H, d, J=4.9Hz)

Rf Value:0.47(E. Merck, Kieselgel 60F₂₅₄/chlo-
10 roform:methanol:acetic acid=10:1:1)

Example 170

(5RS,6SR,7SR)- 6- Carboxy- 7- [2- (3- carboxy- 2- propyl-
methyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine

15 Title compound was prepared in the same manner as in
Example 167 - (1),(2) and Example 169 using (5RS,6SR,7SR)
- 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphe
nyl) -
7 - [2 - (2 - methoxycarbonylpropyl) - 4 - methoxyphenyl]cyclo-
penteno[1,2 - b]pyridine.

20 mp:98 - 101 °C

High Resolution FAB - MS(m/e, (C₂₇H₂₅NO₇+H)⁺):

Calcd: 476.1709

Found: 476.1707

¹H - NMR(300MHz, CDCl₃, δ ppm):1.84 - 2.10(2H, m), 2.35 -
25 2.48(2H, m), 2.70 - 2.91(2H, m), 3.34(1H, dd, J=7.9Hz,
9.6Hz), 3.77(3H, s), 4.64(1H, d, J=9.6Hz), 5.06(1H,
d, J=9.9Hz), 5.97(2H, s), 6.71 - 6.89(6H, m),

7.13(1H, dd, J=4.9Hz, 7.7Hz), 7.33(1H, d, J=7.7Hz),
8.45(1H, d, J=4.9Hz)

Rf Value:0.40(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

5 Each compound in the following Examples 171 - 175 was prepared in the same manner as in Example 161.

Example 171

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - isopropylamino - 5 - (3,4 - methylene-
10 dioxyphenyl)cyclopenteno[1,2 - b]pyridine

mp:149 - 152 °C

¹H - NMR(300MHz, acetone- d₆, δ ppm):1.10(3H, d, J=6.3Hz),
1.13(3H, d, J=6.3Hz), 1.22(3H, d, J=6.5Hz), 2.80 -
3.00(2H, m), 3.10 - 3.17(1H, m), 3.29(1H, dd,
15 J=8.9Hz, 9.5Hz), 3.75(3H, s), 3.75 - 3.87(1H, m),
4.47(1H, d, J=8.9Hz), 4.90(1H, d, J=9.5Hz),
5.20(1H, brs), 6.00(2H, s), 6.38(1H, d, J=8.5Hz),
6.72 - 6.88(5H, m), 7.05(1H, d, J=8.3Hz), 7.08(1H, d,
J=8.5Hz)

20 Rf Value:0.40(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 172

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 3 - hydrox-
ypropyl) - 4 - methoxyphenyl] - 2 - propylamino - 5 - (3,4 - methy-
25 lenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
diastereomers)

mp:176 °C (dec.)

High Resolution FAB - MS(m/e, (C₃₀H₃₂N₂O₈+H)⁺):

Calcd: 549.2237

Found: 549.2217

¹H - NMR(300MHz, CD₃OD, δ ppm): 0.92(3H, t, J=7.2Hz),
 1.57(2H, sext, J=7.2Hz), 2.58 - 3.38(4H, m), 3.14(2H,
 t, J=7.2Hz), 3.74(3H, s), 3.66 - 3.88(2H, m), 4.40 -
 4.50(1H, m), 4.91 - 5.04(1H, m), 5.91(2H, s),
 6.52(1H, d, J=7.8Hz), 6.68 - 6.83(5H, m), 6.98(1H, d,
 J=8.4Hz), 7.25(1H, d, J=8.6Hz)

Rf Value: 0.44(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=5:1)

Example 173

(5RS,6SR,7SR) - 2-Ethylamino-6-carboxy-7-[2-(2-carboxypropyl) - 4-methoxyphenyl] - 5-(3,4-methylene-dioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

Example 174

(5RS,6SR,7SR) - 2-Isobutylamino-6-carboxy-7-[2-(2-carboxypropyl) - 4-methoxyphenyl] - 5-(3,4-methylene-dioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.91(6H, d, J=6.6Hz),
 1.31(3H, d, J=6.3Hz), 1.72 - 1.88(1H, m), 2.62(1H, t, J=12.5Hz), 2.87(2H, d, J=6.6Hz), 2.88 - 3.02(1H, m),
 3.29 - 3.40(1H, m), 3.49(1H, t, J=9.2Hz), 3.75(3H, s), 4.49(1H, d, J=9.2Hz), 4.86(1H, d, J=9.2Hz),
 5.99(2H, s), 6.28(1H, d, J=8.8Hz), 6.68(1H, d,

J=2.5Hz), 6.75 - 6.87(4H, m), 6.99(1H, d, J=8.8Hz),

7.18(1H, d, J=8.8Hz)

Rf Value:0.67(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

5 Example 175

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - cyclopentylamino - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

10 mp:154-156 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):1.30(3H, d, J=6.3Hz), 1.35 - 2.03(8H, m), 2.55 - 2.70(1H, m), 2.85 - 3.01(1H, m), 3.21 - 3.35(1H, m), 3.47(1H, t, J=9.2Hz), 3.63 - 3.75(1H, m), 3.75(3H, s), 4.48(1H, d, J=9.2Hz), 4.85(1H, d, J=9.2Hz), 5.98(2H, s), 6.32(1H, d, J=8.6Hz), 6.67(1H, d, J=2.4Hz), 6.75 - 6.85(4H, m), 6.98(1H, d, J=8.6Hz), 7.18(1H, d, J=8.6Hz)

Rf Value:0.48(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

20 Example 176

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

25 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - propylamino - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine was treated

with diazomethane in methanol to give the dimethyl ester, which was subjected to the same reaction as in Example 160 to give the title compound.

Each compound in the following Examples 177 - 179 was prepared in the same manner as in Example 176.

mp: 90 - 95 °C

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.77(3H, t, J=7.4Hz), 1.22(3H, d, J=6.6Hz), 1.47(2H, sext, J=7.4Hz), 2.80 - 3.13(3H, m), 2.90(3H, s), 3.18(1H, t, J=8.7Hz), 3.30(2H, t, J=7.4Hz), 3.76(3H, s), 4.53(1H, d, J=8.7Hz), 4.97(1H, d, J=8.7Hz), 5.94(2H, s), 6.29(1H, d, J=8.6Hz), 6.69 - 6.80(5H, m), 6.92(1H, d, J=9.2Hz), 7.06(1H, d, J=8.6Hz)

Rf Value: 0.54(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=20:1:1)

Example 177

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)isopropylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

Example 178

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)ethylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

Example 179

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 2 - hydrox-

ypropyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)propylamino] -
5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyri-
dine(one of diastereomers)

mp:158 - 162 °C

5 ¹H - NMR(300MHz, CD₃OD, δ ppm):0.76(3H, t, J=7.4Hz),
1.46(2H, sext, J=7.4Hz), 2.90(3H, s), 2.80 - 3.80(8H,
m), 3.75(3H, s), 4.45(1H, d, J=8.0Hz), 4.68 -
5.02(1H,m), 5.90(2H, s), 6.38(1H, d, J=8.6Hz),
6.68 - 6.86(5H, m), 6.90(1H, d, J=8.6Hz), 7.05(1H, d,
10 J=8.5Hz)

Rf Value:0.49(E. Merck, Kieselgel 60F₂₅₄/chlo-
roform:methanol=5:1)

Example 180

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxyethyl) - 4
15 - methoxyphenyl] - 2 - (N,N - diethylamino) - 5 - (3,4 - methyle-
nedioxyphenyl)cyclopenteno[1,2 - b]pyridine

(5RS,6SR,7SR) - 2 - Ethylamino - 6 - carboxy - 7 - [2 - (2 - car-
boxyethyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine which was
20 prepared in Example 161 was treated with a diazomethane
- ether solution in methanol to give the dimethy ester
compound, which was treated with acetoaldehyde and
sodium cyanoborohydride in acetonitrile to give the
title compound.

25 High Resolution FAB - MS(m/e, (C₃₀H₃₂N₂O₇+H)⁺):

Calcd: 533.2288

Found: 533.2281

¹H - NMR(300MHz, CDCl₃, δ ppm): 1.05(6H, t, J=6.9Hz), 2.58
- 2.85(2H, m), 3.06 - 3.22(2H, m), 3.17(1H, t,
J=8.3Hz), 3.29 - 3.48(4H, m), 3.78(3H, s), 4.53(1H,
d, J=8.3Hz), 4.96(1H, d, J=8.3Hz), 5.94(2H, s),
5 6.31(1H, d, J=8.6Hz), 6.68 - 6.81(5H, m), 6.93(1H, d,
J=8.5Hz), 7.07(1H, d, J=8.6Hz)

Rf Value: 0.61(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)

Each compound in the following Examples 181 - 183 was
10 prepared in the same manner as in Example 180.

Example 181

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxyethyl) - 4
- methoxyphenyl] - 2 - [N - (ethyl)propylamino] - 5 - (3,4 - me-
thylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

15 High Resolution FAB - MS(m/e, (C₃₁H₃₄N₂O₇+H)⁺):

Calcd: 547.2444

Found: 547.2463

¹H - NMR(300MHz, CDCl₃, δ ppm): 0.78(3H, t, J=7.4Hz),
1.02(3H, t, J=6.9Hz), 1.48(2H, sext, J=7.4Hz), 2.57
20 - 2.86(2H, m), 3.07 - 3.47(7H, m), 3.77(3H, s),
4.53(1H, d, J=8.6Hz), 4.94(1H, d, J=8.6Hz),
5.94(2H, s), 6.27(1H, d, J=8.6Hz), 6.67 - 6.82(5H,
m), 6.93(1H, d, J=8.3Hz), 7.05(1H, d, J=8.6Hz)

Rf Value: 0.66(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol:acetic acid=10:1:1)
25

Example 182

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) -

4-methoxyphenyl]-2-(N,N-diethylamino)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

Example 183

5 (5RS,6SR,7SR)-6-Carboxy-7-[2-(2-carboxypropyl)-4-methoxyphenyl]-2-[N-(ethyl)propylamino]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

Example 184

10 (5RS,6SR,7SR)-6-Carboxy-7-[2-(2-carboxypropyl)-4-methoxyphenyl]-2-pyrrolidino-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

(1) (5RS,6SR,7SR)-2-(4-Hydroxybutylamino)-5-(3,4-methylenedioxyphenyl)-6-methoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine

15

(5RS,6SR,7SR)-6-Tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine which was prepared in Example 102 - (2) was reacted with N-(4-benzoyloxybutyl)bezimidoyl chloride in the same manner as in Example 133 and subjected to the same reaction as in Example 134 to give the corresponding dibasic acid.

20

25 The dibasic acid was treated with diazomethane to give (5RS,6SR,7SR)-2-(4-hydroxybutylamino)-5-(3,4-methylenedioxyphenyl)-6-methoxycarbonyl-7-[2-(2-methoxycar-

bonylpropyl) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine.

(2) (5RS,6SR,7SR) - 2 - (4 - Hydroxybutylamino) - 5 - (3,4 - methylenedioxyphenyl) - 6 - methoxycarbonyl - 7 - [2 - (2 - methoxycarbonylpropyl - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine which was prepared in (1) was reacted with ruthenium(II) chloride tris(triphenylphosphine) complex in dioxane at 150 - 200 °C in a sealed tube to give 2 - pyrrolidino compound. The pyrrolidino compound was hydrolyzed with base to give the title compound.

mp:121 - 133 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):1.20 - 1.30(3H, m), 1.82 - 1.96(4H, m), 2.65(1H, dd, J=9.4Hz, 13.5Hz), 2.92 - 2.99(1H, m), 3.25(1H, t, J=9.1Hz), 3.24 - 3.37(4H, m), 3.43(1H, dd, J=6.3Hz, 13.5Hz), 3.75(3H, s), 4.48(1H, d, J=9.1Hz), 4.98(1H, d, J=9.1Hz), 5.96(2H, s), 6.29(1H, d, J=8.6Hz), 6.67(1H, d, J=2.6Hz), 6.73 - 6.80(4H, m), 6.94(1H, d, J=8.6Hz), 7.12(1H, d, J=8.6Hz)

Rf Value:0.44(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 185

(5RS,6SR,7SR) - 2 - Isobutyl - 6 - carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

The title compound was prepared in the same manner

as in Example 102 and 103 using 2 - isobutyl - 6 - ethoxycarbonyl- 7- (2- benzyloxy- 4- methoxyphenyl)- 5- (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine which was prepared in example 85.

¹H - NMR(300MHz, CDCl₃, δ ppm):0.80(3H, d, J=6.6Hz),
0.81(3H, d, J=6.6Hz), 1.31(3H, d, J=6.3Hz), 1.70 -
1.85(1H, m), 2.55(2H, d, J=7.3Hz), 2.62(1H, dd,
J=12.5Hz, 13.3Hz), 2.88 - 3.03(1H, m), 3.37(1H, dd,
J=5.7Hz, 13.3Hz), 3.61(1H, t, J=9.7Hz), 3.76(3H,
s), 4.59(1H, d, J=9.7Hz), 4.99(1H, d, J=9.7Hz),
6.00(2H, s), 6.71(1H, d, J=2.7Hz), 6.76 - 6.87(4H,
m), 6.93(1H, d, J=8.6Hz), 7.03(1H, d, J=7.9Hz),
7.33(1H, dd, J=1.1Hz, 7.9Hz)

Rf Value:0.50(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Each compound in the following Examples 186 and 187 was prepared in the same manner as in Example 185.

Example 186

(5RS,6SR,7SR) - 2 - Butyl - 6 - carboxy - 7 - [2 - (2 - carboxy - propyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene - dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

mp:107 - 110 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):0.84(3H, t, J=7.3Hz), 1.18 - 1.35(2H, m), 1.31(3H, d, J=6.3Hz), 1.40 - 1.56(2H, m), 2.55 - 2.72(3H, m), 2.88 - 3.02(1H, m), 3.36(1H, dd, J=5.6Hz, 13.1Hz), 3.60(1H, t, J=9.7Hz),

3.75(3H, s), 4.58(1H, d, J=9.7Hz), 4.99(1H, d, J=9.7Hz), 6.00(2H, brs), 6.70(1H, d, J=2.7Hz), 6.775(1H, d, J=1.4Hz), 6.785(1H, dd, J=2.7Hz, 8.6Hz), 6.81(1H, dd, J=1.4Hz, 7.9Hz), 6.84(1H, d, J=7.9Hz), 6.94(1H, d, J=8.6Hz), 7.06(1H, d, J=7.9Hz), 7.33(1H, d, J=7.9Hz)

Rf Value:0.40(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 187

10 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - cyclopentyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

Example 188

15 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)isopropylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

20 The title compound was prepared in the same manner as in Example 176.

Example 189

25 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 2 - [N - (ethyl)isopropylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diastereomers)

The title compound was prepared in the same manner as in Example 180.

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Example 190

(5RS,6SR,7SR) - 7 - [2 - (2 - Carboxypropyl) - 4 - methoxy-phenyl] - 5 - (3,4 - methylenedioxyphenyl) - 6 - methoxycarbonylcyclopenteno[1,2 - b]pyridine(one of diastereomers)

5 The methoxycarbonyl group of (5RS,6SR,7SR) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl) - 7 - [2 - (2 - methoxycarbonylpropyl) - 4 - methoxyphenyl]cyclopenteno[1,2 - b]pyridine which was prepared in Example 120 - (2) was hydrolyzed with base and benzylated to convert it to the
10 benzyloxycarbonyl group. The tert - butoxycarbonyl group was cleaved with TFA and treated with CsCO₃ and methyl iodide to convert it to the methoxycarbonyl group. And the product was subjected to catalytic hydrogenation to give the tilte compound.

15 mp:85 - 87 °C

¹H - NMR(300MHz, CDCl₃, δ ppm):1.32(3H, d, J=6.4Hz),
2.66(1H, t, J=12.9Hz), 2.89 - 3.01(1H, m), 3.32(1H, dd, J=5.5Hz, 12.9Hz), 3.62(1H, t, J=9.8Hz),
3.65(3H, s), 3.77(3H, s), 4.63(1H, d, J=9.8Hz),
20 5.03(1H, d, J=9.8Hz), 6.01(2H, s), 6.73 - 6.96(6H, m), 7.23(1H, dd, J=5.0Hz, 7.7Hz), 7.44(1H, td, J=1.3Hz, 7.7Hz), 8.28(1H, d, J=5.0Hz)

Rf Value:0.72(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

25 Example 191

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 3 - hydroxypropyl) - 4 - methoxyphenyl] - 2 - propylamino - 5 - (3,4 - methy-

lenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other diastereomer)

The title compound was prepared in the same manner as in Example 172.

5 mp:192 °C (dec.)

High Resolution FAB - MS(m/e, (C₃₀H₃₂N₂O₆+H)⁺):

Calcd: 549.2237

Found: 549.2252

1H - NMR(300MHz, CD₃OD, δ ppm):0.92(3H, t, J=7.2Hz),
10 1.56(2H, sext, J=7.2Hz), 2.68 - 3.38(4H, m), 3.06 -
3.19(2H, m), 3.74(3H, s), 3.51 - 3.90(2H, m), 4.40 -
4.52(1H, m), 4.69 - 5.05(1H, m), 5.90(2H, s), 6.36 -
6.51(1H, m), 6.66 - 7.00(6H, m), 7.12 - 7.23(1H, m)

Rf Value:0.42(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=5:1)
15

Example 192

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 3 - hydroxypropyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)propylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(the other diastereomer)
20

The title compound was prepared in the same manner as in Example 179.

Example 193

(5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxyethyl) - 4 - methoxyphenyl] - 2 - [N - (methyl)ethylamino] - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine
25

The title compound was prepared in the same manner

as in Example 176.

mp:119 - 124 °C

High Resolution FAB - MS(m/e, (C₂₉H₃₀N₂O₇+H)⁺):

Calcd: 519.2131

5 Found: 519.2122

¹H - NMR(300MHz, CDCl₃, δ ppm):1.01(3H, t, J=7.0Hz), 2.58
- 2.87(2H, m), 2.91(3H, s), 3.01 - 3.24(2H, m),
3.17(1H, t, J=8.6Hz), 3.42(2H, q, J=7.0Hz),
3.77(3H, s), 4.53(1H, d, J=8.6Hz), 4.96(1H, d,
10 J=8.6Hz), 5.94(2H, s), 6.32(1H, d, J=8.6Hz), 6.68 -
6.80(5H, m), 6.91(1H, d, J=8.6Hz), 7.09(1H, d, J=8.6
Hz)

Rf Value:0.23(E. Merck, Kieselgel 60F₂₅₄/chloro-
roform:methanol:acetic acid=20:1:1)

15 Example 194

(5RS,6SR,7SR) - 2 - Sec - butylamino - 6 - carboxy - 7 - [2 -
(2 - carboxypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylene-
dioxyphehyl)cyclopenteno[1,2 - b]pyridine(one of diaster-
eomers derived from the carboxypropyl group)

20 The title compound was prepared in the same manner
as in Example 161 using corresponding racemate of sec -
butylamine compound.

mp:147 - 153 °C

¹H - NMR(300MHz, acetone - d₆, δ ppm):0.82+0.87(3H, t × 2,
25 J=7.5Hz), 1.06+1.10(3H, d × 2, J=7.4Hz), 1.21(3H, d,
J=6.3Hz), 1.13-1.61(2H, m), 2.82-3.01(2H, m), 3.08-
3.16(1H, m), 3.275+3.284(1H, t × 2, J=9.2Hz), 3.58 -

3.70(1H, m), 3.75(3H, s), 4.47(1H, d, J=9.2Hz),
4.89(1H, d, J=9.2Hz), 5.23(1H, brs), 6.00(2H, s),
6.40(1H, d, J=8.2Hz), 6.73-6.89(5H, m), 7.05(1H, d,
J=7.5Hz), 7.08(1H, d, J=8.2Hz)

5 Rf Value:0.45(E. Merck, Kieselgel 60F₂₅₄/chloroform:methanol=10:1)

Example 195

(5RS,6SR,7SR)-6-Carboxy-7-[2-(3-carboxy-2-methylpropyl)-4-methoxyphenyl]-2-propylamino-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine(one of diastereomers)

10 (1) (5RS,6SR,7SR)-7-[2-(3-Carboxypropyl)-4-methoxyphenyl]-2-[N-(benzoyl)propylamino]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine

(5RS,6SR,7SR)-6-tert-Butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-b]pyridine which was prepared in Example 102 - (2) was subjected to the same
20 reaction as in Example 124 - (1) and (2) to give the corresponding N-benzoyl diester compound. The N-benzoyl diester compound was reacted with 4N NaOH in dioxane at room temperature to give (5RS,6SR,7SR)-7-[2-(3-carboxypropyl)-4-methoxyphenyl]-2-[N-(benzoyl)propylamino]-6-tert-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine
25

(2) The title compound was prepared in the same manner

as in Example 169 using (5RS,6SR,7SR) - 7 - [2 - (3 - carboxypropyl) - 4 - methoxyphenyl] - 2 - [N - (benzoyl)propylamino] - 6 - tert - butoxycarbonylcyclopenteno[1,2 - b]pyridine.

5 Example 196

(5RS,6SR,7SR) - 6 - Tert - butoxycarbonyl - 7 - [2 - (2 - methoxycarbonyl - 2 - propenyl) - 4 - methoxyphenyl] - 5 - (3,4 - methylenedioxyphenyl) - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine

10 (5RS,6SR,7SR) - 7 - (2 - Trifluoromethanesulfonyloxy - 4 - methoxyphenyl) - 6 - tert - butoxycarbonyl - 5 - (3,4 - methylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(100mg,0.169mmol) which was prepared in Example 99 - (1) and LiCl(21mg) were added in a Schlenk reactor under
15 nitrogen atmospher. To the mixture were added a DMF solution(1.5ml) of (2 - methoxycarbonyl - 2 - propenyl)tributyl tin(131mg) which was prepared by the method described in the literature[J. Chem. Soc. Chem. Commun., 1339 - 1340(1986), Tetrahedron, 47, 5901(1991)], palla-
20 dium(II) chloride bis - triphenylphosphine complex(6mg) and the mixture was heated at 100°C for 15 h. To the reaction solution were added AcOEt(3ml) and a 40% aqueous KF solution(1ml) and the mixture was stirred vigorously for 10 min. The resulting precipitate was
25 removed by Celite - filtration and the filtrate and washings were combined and washed with water dried over MgSO₄. After removal of the solvent the residue was

purified by silica gel column chromatography(E. Merck Kieselgel 60/hexane:AcOEt=2:1) to give the title compound(85.7mg)

Example 197

5 (5RS,6SR,7SR) - 2 - (1-Ethylpropylamino) - 6 - carboxy - 7
- [2 - (2 - carboxypropyl) - 4 - methoxyphenyl] - 5 - (3,4 - methy-
lenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
diastereomers)

10 The title compound was prepared in the same manner
as in Example 171.

Each compound in the following Examples 198 - 200 was prepared in the same manners as in Examples 162 and 163.

Example 198

15 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) -
4 - methoxyphenyl] - 2 - tert - butylamino - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diaster-
eomers)

Example 199

20 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxy - 2 - pro-
penyl) - 4 - methoxyphenyl] - 2 - isopropylamino - 5 - (3,4 - me-
thylenedioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of
diastereomers)

Example 200

25 (5RS,6SR,7SR) - 6 - Carboxy - 7 - [2 - (2 - carboxypropyl) -
4 - methoxyphenyl] - 2 - cyclohexylamino - 5 - (3,4 - methylene-
dioxyphenyl)cyclopenteno[1,2 - b]pyridine(one of diaster-
eomers)

Utilizability in Industry

The heteroaromatic ring fused compounds of the present invention possess high antagonistic activity to endotheline, endogenous biologically active peptide, so
5 that they are useful as drugs which possess high antagonistic activity to endotheline related vasoconstriction and bronchoconstriction. The compounds of the present invention provide a new therapeutic potential, particularly for the treatment of hypertension,
10 pulmonary hypertension, Raynaud's disease, acute renal failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatauxe endotoxin shock, endotoxin-induced multiple
15 organ failure or disseminated intravascular coagulation, and/or cyclosporin-induced renal failure or hypertension.

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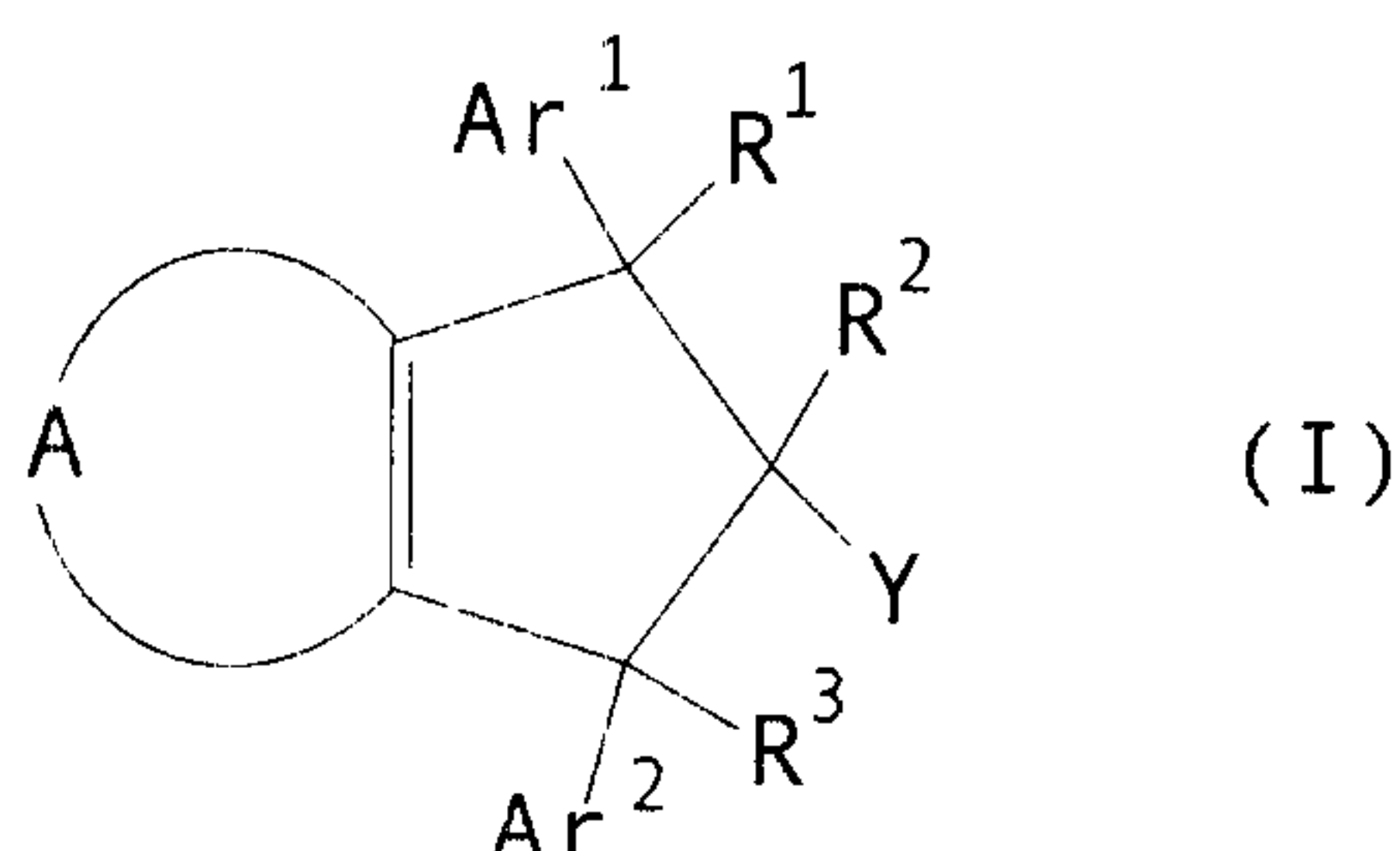
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CLAIMS:

1. A heteroaromatic ring-fused cyclopentene derivative of the formula:



wherein:

5 each of Ar¹ and Ar² is independently a phenyl group, a thienyl group, a pyridyl group, an indolyl group, a benzofuranyl group or a dihydrobenzofuranyl group, each being unsubstituted or substituted with 1 to 4 groups each independently selected from the group consisting of a halogen

10 atom, a hydroxyl group, an amino group, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a mono- or di-C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a tetrazol-5-yl group, a methylenedioxy group, a C₁-C₆ alkoxy group, a C₂-C₆ alkenyloxy group, a mono- or di-C₁-C₆ alkylamino group, a C₁-C₆

15 alkyl group, a C₂-C₆ alkenyl group and a C₂-C₆ alkynyl group (wherein the C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, mono- or di-C₁-C₆ alkylamino, C₁-C₆ alkyl, C₂-C₆ alkenyl and C₂-C₆ alkynyl groups may be further substituted by 1 to 3 groups each independently selected from the group consisting of a phenyl group, a pyridyl

20 group, an imidazolyl group, a hydroxyl group, a C₁-C₆ alkoxy group, an amino group, a mono- or di-C₁-C₆ alkylamino group, a hydroxy-C₁-C₆ alkylcarbonyl group, a C₁-C₆ acyloxy-C₁-C₆ alkylcarbonyl group, a carboxy-C₁-C₆ alkoxycarbonyl group, a carboxy C₁-C₆ alkoxycarbonyl-C₁-C₆ alkoxycarbonyl group, a C₁-C₆

25 alkoxycarbonyl group, a mono- or di-C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a C₁-C₆ alkylsufonaminocarbonyl group, a tetrazol-5-ylaminoacarbonyl group, a carboxyl group,

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SO₃H, PO₃H₂, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl group (where, when the hydroxyl group and the carboxyl group are selected as substituents, they may together form a lactone ring));

each of R¹, R² and R³ is independently a hydrogen atom, a hydroxyl group or a C₁-C₆ alkyl group, or R¹ and R², or R² and R³ together form a single bond;

Y is a group of -CO-R⁴ (wherein R⁴ is a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a mono- or di-C₁-C₆ alkylamino group, a C₁-C₆ alkylsulfonylamino group, or an arylsulfonylamino group or an aryl-C₁-C₆ alkylsulfonylamino group wherein the aryl moiety of the arylsulfonylamino and aryl-C₁-C₆ alkylsulfonylamino groups may be substituted with a C₁-C₆ alkyl group), SO₃H, PO₃H₂, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group or a 5-oxo-4H-1,2,4-oxadiazol-3-yl group; and

A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6-membered heteroaromatic ring containing 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, (wherein the heteroaromatic ring may have 1 or 2 hydrogen atoms replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a halogen atom, a cyano group, a nitro group, a mono- or di-C₁-C₆ alkylamino group which may be substituted by a hydroxyl group in the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group in the cycloalkyl moiety, a C₃-C₈ cycloalkyl-C₁-C₆ alkylamino group which may be substituted by a hydroxyl group in the cycloalkyl or alkyl moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group in the alkyl or cycloalkyl moiety, an N-(C₁-C₆ alkyl)-N-

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(aroyl)amino group which may be substituted by a hydroxyl group in the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group in the cyclic moiety, a carboxyl group, a C₁-C₆ alkoxycarbonyl group, a formyl group, a C₂-C₆ alkanoyl group, an aroyl group, or a C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl-C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group, a C₁-C₆ alkoxy group and a mono- or di-C₁-C₆ alkylamino group, and when the heteroaromatic ring includes one or more nitrogen atoms, the nitrogen atom or atoms may be oxidized to form an N-oxide group); or

a pharmaceutically acceptable salt thereof.

2. The heteroaromatic ring-fused cyclopentene derivative or salt of Claim 1, wherein:

A is a group which forms together with the adjacent carbon-carbon double bond a 5- or 6-membered nitrogen-containing aromatic ring or a corresponding N-oxide ring (wherein the aromatic ring may have 1 or 2 hydrogen atoms replaced with a hydroxyl group, an amino group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylamino group, a C₁-C₆ alkylthio group, a mono- or di-C₁-C₆ alkylamino group which may be substituted by a hydroxyl group in the alkyl moiety, a C₃-C₈ cycloalkylamino group which may be substituted by a hydroxyl group in the cycloalkyl moiety, a C₃-C₈ cycloalkyl-C₁-C₆ alkylamino group which may be substituted by a hydroxyl group in the cycloalkyl or alkyl moiety, an N-(C₁-C₆ alkyl)-N-(C₃-C₈ cycloalkyl)amino group which may be substituted by a hydroxyl group in the alkyl or cycloalkyl moiety, an N-(C₁-C₆ alkyl)-N-(aroyl)amino group which may be substituted by a hydroxyl group in the alkyl moiety, a C₄-C₇ cyclic imino group which may be substituted by a hydroxyl group in the cyclic moiety, or a C₁-C₆ alkyl, C₃-C₈

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cycloalkyl, C₃-C₈ cycloalkyl-alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group which may be substituted by 1 to 3 groups selected from the group consisting of a hydroxyl group, an amino group, a C₁-C₆ alkoxy group and a mono- or di-C₁-C₆ alkylamino group).

3. The heteroaromatic ring-fused cyclopentene derivative or salt of Claim 1, wherein:

A is a group which forms together with the adjacent carbon-carbon double bond a pyridine, pyrimidine, pyridazine, pyrazine or thiazole ring;

each of Ar¹ and Ar² is independently a phenyl group, a thienyl group or a dihydrobenzofuranyl group, each of which may have 1 to 4 substituents each independently selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a methylenedioxy group, a C₁-C₆ alkoxy group, a C₂-C₆ alkenyloxy group, a mono- or di-C₁-C₆ alkylamino group, a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group and a C₂-C₆ alkynyl group (where the C₁-C₆ alkoxy group, C₂-C₆ alkenyl group and C₂-C₆ alkynyl group may be further substituted by 1 to 3 substituents selected from the group consisting of a phenyl group, a pyridyl group, an imidazolyl group, a hydroxyl group, a C₁-C₆ alkoxy group, an amino group, a mono- or di-C₁-C₆ alkylamino group, a hydroxy C₁-C₆ alkylcarbonyl group, a C₁-C₆ acyloxy-C₁-C₆ alkylcarbonyl group, a carboxy-C₁-C₆ alkoxycarbonyl group, a carboxy-C₁-C₆ alkoxycarbonyl-C₁-C₆ alkoxycarbonyl group, a C₁-C₆ alkoxycarbonyl group, a mono- or di-C₁-C₆ alkylaminocarbonyl group, a carbamoyl group, a C₁-C₆ alkylsufonaminocarbonyl group, a tetrazol-5-ylaminocarbonyl group, a carboxyl group, a tetrazol-5-yl group, a 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl group and a 5-oxo-4H-1,2,4-oxadiazol-3-yl group (provided that when the hydroxyl group and the carboxyl group are selected as

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the further substituents, they may together form a lactone ring)).

4. The heteroaromatic ring-fused cyclopentene derivative or salt of Claim 1, 2, or 3, wherein A is a group which forms together with the adjacent carbon-carbon double bond a pyridine ring.
5. The heteroaromatic ring-fused cyclopentene derivative or salt of any one of Claims 1 to 4, wherein Y is a group of the formula $-\text{CO}-\text{R}^4$ in which R^4 is as defined in Claim 1.
- 10 6. The heteroaromatic ring-fused cyclopentene derivative or salt of Claim 5, wherein R^4 is a hydroxyl group, an amino group, a C_1 - C_6 alkoxy group or a mono- or di- C_1 - C_6 alkylamino group.
7. The heteroaromatic ring-fused cyclopentene derivative or salt of any one of Claims 1 to 6, wherein R^1 , R^2 and R^3 are each a hydrogen atom.
8. The compound (5RS, 6SR, 7SR)-6-carboxy-5-(3,4-methylenedioxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-b]pyridine or a pharmaceutically acceptable salt thereof.
- 20 9. The compound according to Claim 8, which is a first enantiomer separated from a second enantiomer, the first enantiomer having a shorter retention time than the second enantiomer when a racemate of the enantiomers is subjected to a reverse phase HPLC using a chiral column (Diciel Chemical Chiralcel* OD-R, having a diameter of 4.6 mm and a length of 25 250 mm) at a flow rate of 1.0 ml/min. of 0.1% TFA-water/0.1% TFA-acetonitrile = 75/25 at a column temperature of 40°C.
10. A drug for the treatment of a disorder selected from the group consisting of hypertension, pulmonary hypertension,
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Raynaud's disease, acute renal failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatauxe, endotoxin shock, endotoxin-induced multiple organ
5 failure or disseminated intravascular coagulation, and cyclosporin-induced renal failure or hypertension, which comprises:

the heteroaromatic ring-fused cyclopentene derivative or salt as defined in any one of Claims 1 to 7, in an amount
10 effective to treat the disorder, and

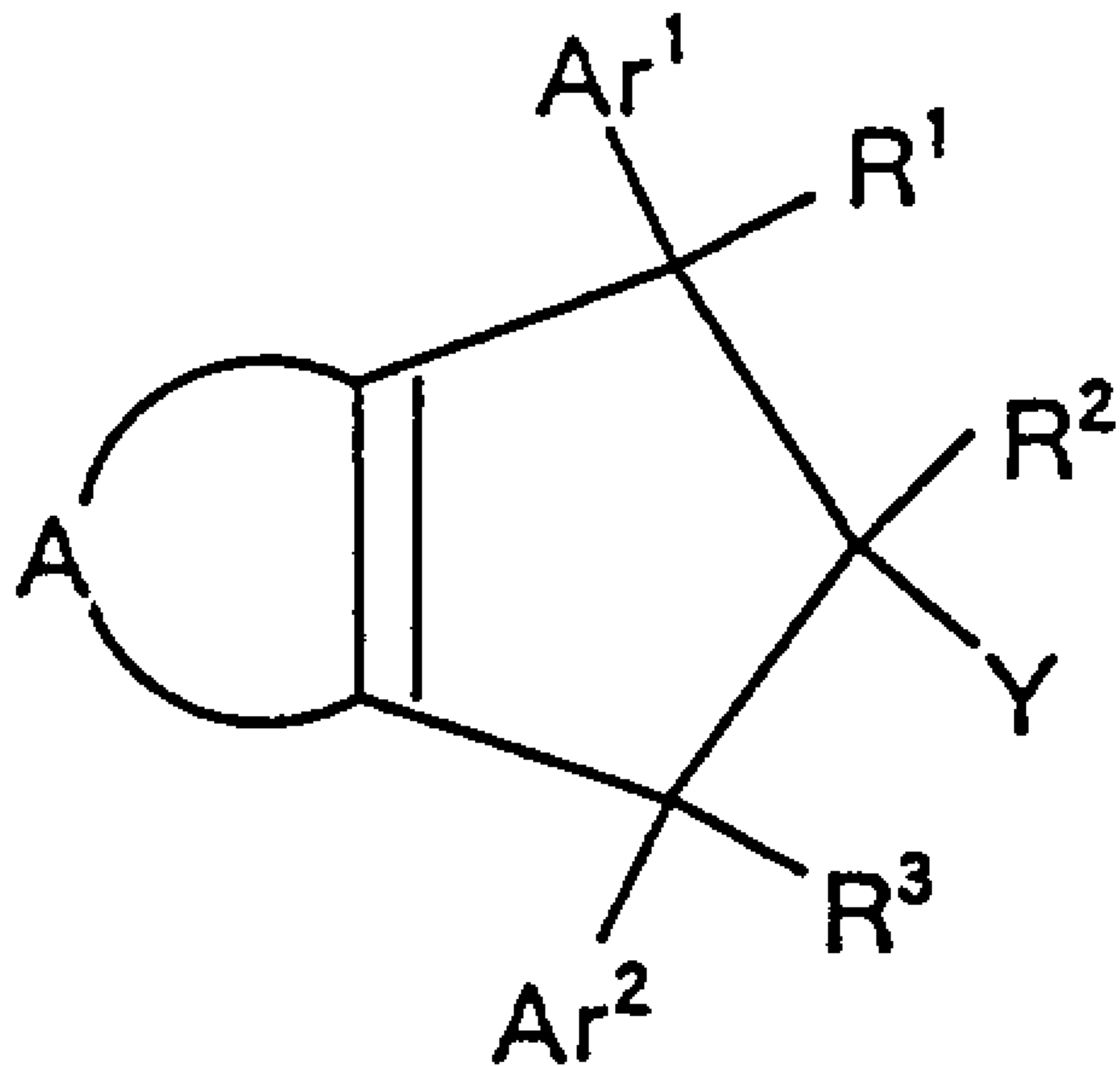
a pharmaceutically acceptable solid or liquid excipient carrier.

11. A drug for the treatment of a disorder selected from the group consisting of hypertension, pulmonary hypertension,
15 Raynaud's disease, acute renal failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatauxe, endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular coagulation, and
20 cyclosporin-induced renal failure or hypertension, which comprises:

the compound or salt as defined in Claim 8 or 9 in an amount effective to treat the disorder, and

a pharmaceutically acceptable solid or liquid
25 excipient carrier.

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