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**Process for production of 1-(3-(2-(1-benzothiophen-5-YL)- ethoxy)propyl)azetidin-3-ol or salts thereof**
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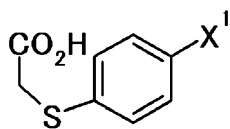
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のガイダンスノート」を参照。(54) Title: PROCESS FOR PRODUCTION OF 1-(3-(2-(1-BENZOTHIOPHEN-5-YL)-ETHOXY)PROPYL)AZETIDIN-3-OL  
OR SALTS THEREOF(54) 発明の名称: 1 - (3 - (2 - (1 - ベンゾチオフェン - 5 - イル) エトキシ) プロピル) アゼチジン - 3 -  
オールまたはその塩の製造法

(1)

(57) Abstract: A process for the production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol or salts thereof which comprises using as a starting compound a (phenylthio)acetic acid derivative represented by the general formula [1] or a salt thereof: [Chemical Formula 1] (wherein X<sup>1</sup> is halogeno) is useful as a safe process for mass production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol or salts thereof which are useful as remedies for central nervous system diseases and peripheral nerve diseases.(57) 要約: 一般式【化 1】「式中、X<sup>1</sup>は、ハロゲン原子を示す。」で表される (フェニルチオ) 酢酸誘導体またはその塩を出発原料とする 1 - (3 - (2 - (1 - ベンゾチオフェン - 5 - イル) エトキシ) プロピル) アゼチジン - 3 - オールまたはその塩の製造法は、中枢および末梢神経の疾病の治療薬として有用な 1 - (3 - (2 - (1 - ベンゾチオフェン - 5 - イル) エトキシ) プロピル) アゼチジン - 3 - オールまたはその塩を大量製造する安全な方法として有用である。

DESCRIPTION

PROCESS FOR PRODUCTION OF 1-(3-(2-(1-  
BENZOTHIOPHEN-5-YL)ETHOXY)PROPYL)  
AZETIDIN-3-OL OR SALTS THEREOF

FIELD OF THE INVENTION

[0001]

The present invention relates to a new  
process for production of 1-(3-(2-(1-benzothiophen-5-  
5 yl)ethoxy)propyl)azetidin-3-ol or salts thereof which  
is useful as remedies for central nervous system and  
peripheral nerve diseases.

BACKGROUND ART

10 [0002]

1-(3-(2-(1-benzothiophen-5-  
yl)ethoxy)propyl)azetidin-3-ol or salts thereof has  
nerve protective action, nerve regeneration promotion  
action and neurite outgrowth action, and is a useful  
15 compound as remedies for central nervous system and  
peripheral nerve diseases.

As processes for production of this compound,  
for example, (1) a process of reacting 5-(2-(3-  
chloropropoxy)ethyl)-1-benzothiophene with 3-azetidinol  
20 or salts thereof, (2) a process of subjecting 1-(3-(2-  
(1-benzothiophen-5-yl)ethoxy) propionyl)azetidin-3-ol  
obtained from 3-(2-(1-benzothiophen-5-

yl)ethoxy)propionic acid or its salts thereof to  
reduction reaction with borane-tetrahydrofuran complex  
or subjecting it to reduction reaction with sodium  
borohydride in the presence of boron trifluoride  
5 complex tetrahydrofuran complex, and so forth are known  
(patent document 1).

However, the process of (1) has the following  
defects, (A) the yield is low, (B) complicated  
procedures of purification such as silica gel column  
10 chromatography are necessary, (C) therefore, a lot of  
waste is egested, and so forth.

In addition, the process of (2) cannot be  
satisfied as an industrial manufacturing process,  
because the process has the following defects, (A) the  
15 process uses reagents of borane-tetrahydrofuran complex  
and boron trifluoride tetrahydrofuran and so forth,  
which are harmful to human body, highly flammable,  
highly toxic and having problems of stability, (B)  
therefore, attention is necessary to handle and store  
20 it and special equipments are required, and so forth.  
[0003]

In addition, as a process for production of  
3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or  
salts thereof used in (2) mentioned above, for example,  
25 the following processes are known, (3) a process of  
subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael  
addition reaction with tert-butyl acrylate,  
subsequently subjecting it to de-tert-butylation, (4) a

process of subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael addition reaction with acrylonitrile, subsequently subjecting it to hydrolysis with acid, and so forth (patent document 1).

5                   However, the processes of (3) and (4) cannot be satisfied as industrial manufacturing processes, because these processes have the following defects, the process of (3): (A) by-products form because of the occurrence of trans-esterification of acrylic acid, (B)  
10 special equipments and treatments are required because of the occurrence of a large quantity of combustible isobutene gas in de-tert-butylation reaction, the process of (4): the yield of hydrolysis with acid is low, and so forth.

15 [0004]

As a process for production of 2-(1-benzothiophen-5-yl)ethanol used in (3) and (4) mentioned above, for example, the following processes are known, (5) a process of subjecting 5-methyl-1-  
20 benzothiophene to bromination with N-bromosuccinimide and to reaction with cyano compounds to obtain (1-benzothiophen-5-yl)acetonitrile, subsequently subjecting it to hydrolysis, subsequently subjecting it to reduction reaction (non-patent document 1, 2 , 3),  
25 (6) a process of reacting 5-bromo-1-benzothiophene with magnesium to obtain Grignard reagent, subsequently subjecting it to reaction with ethylene oxide (patent document 2), (7) a process of subjecting 5-(1-

benzothiophene)carbaldehyde to Wittig reaction with methoxymethylene ylide, subsequently subjecting it to hydrolysis to obtain (1-benzothiophen-5-yl)acetaldehyde, subsequently subjecting it to  
5 reduction reaction, and so forth (patent document 3).

However, the processes of (5) to (7) cannot be satisfied as industrial manufacturing processes, because these processes have the following defects, (A) intermediates have a stimulatory property, (B) a highly  
10 toxic reagent(cyano compounds) is used, (C) a carcinogenic reagent(ethylene oxide) is used, (D) highly ignitable reagents(butyllithium, Grignard reagent) are used, (E) procedures of the reaction are complicated, and so forth.

15 [0005]

On the other hand, as processes for production of benzothiopheneacetic acid derivative or salts thereof, for example, the following processes are known, (8) a process of subjecting the hydroxyl group  
20 of benzothiophenemethanol to halogenation, subsequently subjecting it to reaction with cyano compounds to obtain benzothiopheneacetonitrile, subsequently subjecting it to hydrolysis (non-patent document 3),  
(9) a process of subjecting 7-oxo-4,5,6,7-  
25 tetrahydrobenzothiophene produced from 3-bromothiophene to Reformatsky reaction with ethyl bromoacetate, subsequently subjecting it to aromatization by dehydrogenation by use of sulfur, and subjecting it to

hydrolysis, and so forth (non-patent document 4).

However, the processes of (8) and (9) cannot be satisfied as industrial manufacturing processes, because these processes have the following defects, (A) intermediates have a stimulatory property, (B) a highly toxic reagent (cyano compounds) is used, (C) therefore, complicated treatments of waste are required, (D) there are many steps of the process (E) the yield is low, (F) the reaction temperature is high, (G) procedures of the reaction are complicated, and so forth.

[0006]

In addition, as a process for production of 5-halogeno-1-benzothiophene derivative, for example, the following processes are known, (10) a process of reacting 4-halogenothiophenol with 2-halogenoacetaldehyde dimethylacetal in the presence of base to obtain 2-(4-halogenophenylthio)acetaldehyde dimethylacetal, subsequently subjecting it to intramolecular ring closure reaction in the presence of polyphosphoric acid, and so forth (non-patent document 5, patent document 4, patent document 5).

However, the process of (10) cannot be satisfied as an industrial manufacturing process, because the process has the following defects, (A) complicated procedures such as distillation or silica gel column chromatography and so forth are necessary to isolate because the production intermediates are oily substances, (B) treatments of the process are

complicated in ring closure reaction by use of  
phosphate compound because complicated by-products  
form, (C) complicated procedures such as distillation  
or silica gel column chromatography and so forth are  
5 necessary to separate 5-halogeno-1-benzothiophene  
derivatives from formed by-products because their  
derivatives have low melting points, (D) a large  
quantities of liquid waste is formed, which contains  
phosphorus compounds that require complicated  
10 procedures for treatment, and so forth.  
[0007]

As 4-halogenothiophenol used in (10)  
mentioned above, for example, (11) a process of  
subjecting thioanisole to halogenation with chlorine or  
15 bromine, subsequently subjecting it to demethylation  
with large excess of chlorine (patent document 6), (12)  
a process of reacting (4-halogenophenylthio)acetic acid  
with sodium sulfide in the presence of sodium hydroxide  
(patent document 7), (13) a process of reacting  
20 monohalogenobenzene with sulfur monochloride in the  
presence of zinc chloride to obtain dihalogenodiphenyl  
polysulfide, subsequently subjecting it to reduction  
reaction with hydrochloric acid-zinc (patent document  
8), (14) a process of reacting 1,4-dihalogenobenzene  
25 with sodium hydrosulfide in 1-methyl-2-pyrrolidone  
(patent document 9), and so forth are known.

However, the processes of (11) to (14) cannot  
be satisfied as industrial manufacturing processes,

because these processes have the following defects, (A) the yield is low, (B) isomers form, (C) high reaction temperature is required, (D) reagents that bear large environment loads such as chlorine or sulfide are used,  
5 and so forth.

[0008]

Further, as a process for production of a benzothiophene derivative from a (phenylthio) acetic acid derivative or salts thereof, for example, the  
10 following processes are known, (15) a process of subjecting it to intramolecular ring closure reaction in the presence of Lewis acid, subsequently subjecting it to reduction reaction, subsequently subjecting it to dehydration reaction, and so forth (patent document  
15 10).

However, in this process, the structure of produced compound is limited.

[0009]

[patent document 1]

20 International publication No. 03/035,647  
pamphlet

[patent document 2]

EP0129478 bulletin

[patent document 3]

25 International publication No. 99/31,056  
pamphlet

[patent document 4]

International publication No. 02/100,850

pamphlet

[patent document 5]

International publication No. 2,005/012,291

pamphlet

5 [patent document 6]

Japanese Patent Laid-Open No. H08-143533

bulletin

[patent document 7]

Japanese Patent Laid-Open No. H05-178816

10 bulletin

[patent document 8]

Japanese Patent Laid-Open No. H05-140086

bulletin

[patent document 9]

15 Japanese Patent Laid-Open No. H04-182463

bulletin

[patent document 10]

International publication No. 98/43,967

pamphlet

20 [non-patent document 1]

Journal of Medicinal Chemistry (J. Med.

Chem.), 1991, Vol. 34, p. 65-73

[non-patent document 2]

Journal of Medicinal Chemistry (J. Med.

25 Chem.), 1997, Vol. 40, p 1049-1062

[non-patent document 3]

Nippon Kagaku Zashi, 1967, Vol. 88, p. 445-

447

[non-patent document 4]

Journal of Heterocyclic Chemistry (J. Heterocyclic Chem.), 1965, Vol. 2, p. 44-48

[non-patent document 5]

5 Journal of Medicinal Chemistry (J. Med. Chem.), 2003, Vol. 46, p 2446-2455

#### DISCLOSURE OF THE INVENTION

#### PROBLEM TO BE SOLVED BY THE INVENTION

10 [0010]

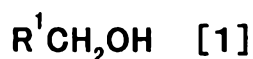
A new process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol and salts thereof, process which has safety to human body, low environmental loads and a possibility of mass  
15 production, is strongly expected.

#### MEANS TO SOLVE THE PROBLEM

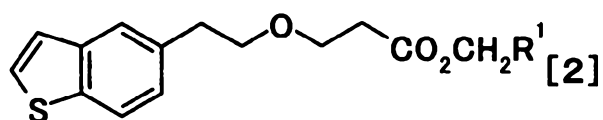
[0011]

Under the circumstances, the present  
20 inventors have studied zealously and consequently, and found that in a process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol or salts thereof from 2-(1-benzothiophen-5-yl)ethanol, a process for production of 3-(2-(1-benzothiophen-5-  
25 yl)ethoxy)propionic acid or salts thereof characterized by subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael addition reaction with acrylonitrile in the presence of base, subsequently subjecting it to

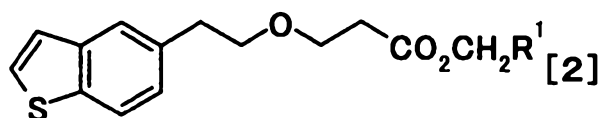
reaction with an alcohol represented by the general formula [1]:



wherein  $R^1$  represents a hydrogen atom or an unsubstituted or substituted alkyl, cycloalkyl or aryl group,  
5 in the presence of acid to obtain a propionic acid ester derivative represented by the general formula [2]:



wherein  $R^1$  has the same meanings as the above,  
10 subsequently subjecting the propionic acid ester derivative to hydrolysis reaction in the presence of base;  
the propionic acid ester derivative represented by the general formula [2]:



15 wherein  $R^1$  has the same meanings as the above,  
being important intermediates in the production of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salts thereof;

a process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy) propionyl)azetidin-3-ol or salts thereof characterized by deriving 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salts thereof to a reactive derivative, subsequently reacting the reactive derivative with 3-azetidinol or salts thereof in the presence of base, and subsequently crystallizing the crystals from the reaction mixture;

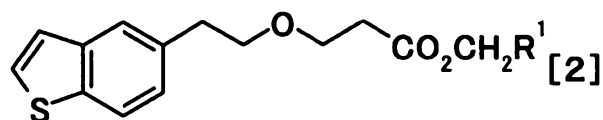
a process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl) azetidin-3-ol or salts thereof characterized by subjecting 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol to reduction reaction with an addition of activator in the presence of alkali metal borohydride; and

a process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol or salts thereof characterized by subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael addition reaction with acrylonitrile in the presence of base, subsequently subjecting it to reaction with an alcohol represented by the general formula [1]:



wherein  $R^1$  has the same meanings as the above, in the presence of acid to obtain a propionic acid ester derivative represented by the general formula

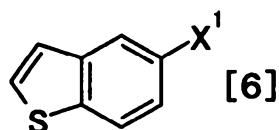
[2]:



wherein  $R^1$  has the same meanings as the above,  
 subsequently subjecting the propionic acid ester  
 derivatives to hydrolysis reaction in the presence of  
 base to obtain 3-(2-(1-benzothiophen-5-  
 5 yl)ethoxy)propionic acid or salts thereof, subsequently  
 converting it to a reactive derivative, subsequently  
 reacting the reactive derivative with 3-azetidinol or  
 salts thereof in the presence of base to obtain 1-(3-  
 (2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-  
 10 ol, subsequently subjecting it to reduction reaction  
 with an addition of activator in the presence of alkali  
 metal borohydride.

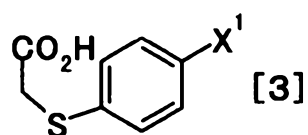
[0012]

In addition, the present inventors have found  
 15 that in the process of 2-(1-benzothiophen-5-yl)ethanol  
 which is a starting material, a process for production  
 of a 5-halogeno-1-benzothiophene derivative represented  
 by the general formula [6]:

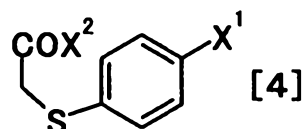


wherein  $X^1$  represents a halogen atom,  
 20 characterized by reacting a (phenylthio)acetic acid

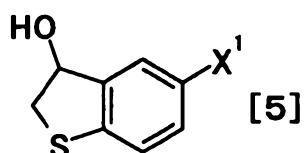
derivative or salts thereof represented by the general formula [3]:



wherein X<sup>1</sup> has the same meanings as the above,  
with a halogenating agent to obtain an acid halide  
5 represented by the general formula [4]:

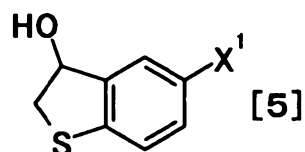


wherein X<sup>2</sup> represents a halogen atom; X<sup>1</sup> has the same meanings as the above,  
subsequently subjecting the acid halide to  
intramolecular ring closure reaction in the presence of  
10 Lewis acid, subsequently subjecting it to reduction  
reaction to obtain a dihydrobenzothiophene derivative  
represented by the general formula [5]:

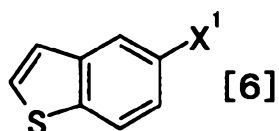


wherein X<sup>1</sup> has the same meanings as the above,  
and subjecting the dihydrobenzothiophene derivative to  
15 dehydration reaction in the presence of acid catalyst;

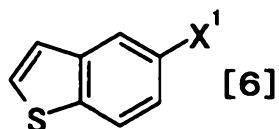
the dihydrobenzothiophene derivative represented by the general formula [5]:



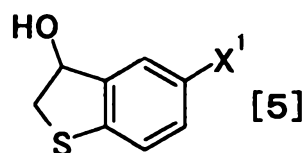
wherein  $X^1$  has the same meanings as the above,  
being important intermediates in the process for  
5 production of a 5-halogeno-1-benzothiophene derivative  
represented by the general formula [6]:



wherein  $X^1$  has the same meanings as the above;  
the 5-halogeno-1-benzothiophene derivative represented  
by the general formula [6]:

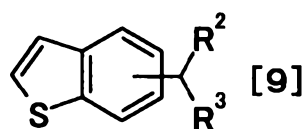


10 wherein  $X^1$  has the same meanings as the above,  
can be produced at simple procedures with a high purity  
by crystallizing and isolating crystals of the  
dihydrobenzothiophene derivative represented by the  
general formula [5]:

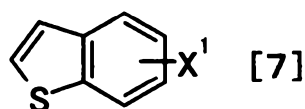


wherein  $X^1$  has the same meanings as the above,  
subsequently subjecting the crystals to dehydration  
reaction;

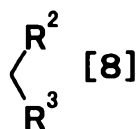
a process for production of benzothiophene derivative  
5 or salts thereof represented by the general formula  
[9]:



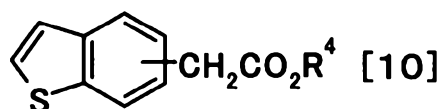
wherein  $R^2$  and  $R^3$  represent identically or differently  
an unsubstituted or substituted alkyloxycarbonyl,  
cycloalkyloxycarbonyl or aralkyloxycarbonyl group or  
10 cyano group,  
characterized by coupling a benzothiophene derivative  
represented by the general formula [7]:



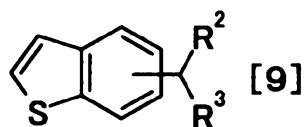
wherein  $X^1$  has the same meanings as the above,  
in the presence of base and palladium catalyst with a  
15 malonic acid derivative or salts thereof represented by  
the general formula [8]



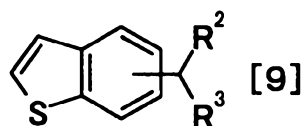
wherein  $\text{R}^2$  and  $\text{R}^3$  have the same meanings as the above;  
 a process for production of benzothiopheneacetic acid  
 derivative or salts thereof represented by the general  
 formula [10]:



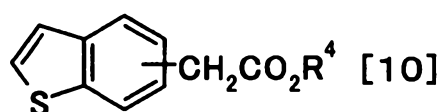
5 wherein  $\text{R}^4$  represents a hydrogen atom or unsubstituted  
 or substituted alkyl, cycloalkyl or aralkyl group,  
 characterized by reacting a benzothiophene derivative  
 or salts thereof represented by the general formula [9]



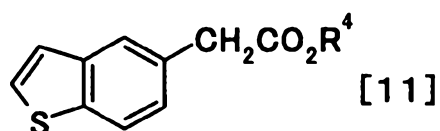
wherein  $\text{R}^2$  and  $\text{R}^3$  have the same meanings as the above,  
 10 with acid or base, subjecting the benzothiophene  
 derivative or salts thereof to decarboxylation reaction  
 if necessary;  
 the benzothiophene derivative represented by the  
 general formula [9]:



wherein  $R^2$  and  $R^3$  have the same meanings as the above, being important intermediates in the process for production of benzothiopheneacetic acid derivative or salts thereof represented by the general formula [10]:

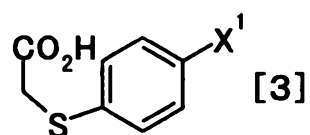


5 wherein  $R^4$  has the same meanings as the above;  
a process for production of 2-(1-benzothiophen-5-yl)ethanol characterized by subjecting a benzothiopheneacetic acid derivative or salts thereof represented by the general formula [11]:

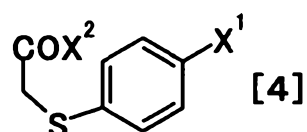


10 wherein  $R^4$  has the same meanings as the above,  
to hydrolysis reaction if necessary, subsequently  
subjecting it to reductive reaction with an addition of  
activator in the presence of alkali metal borohydride;  
and  
15 a process for production of 2-(1-benzothiophen-5-yl)ethanol characterized by reacting a

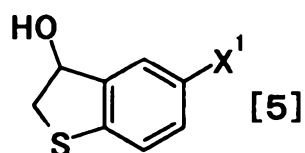
(phenylthio)acetic acid derivative or salts thereof  
represented by the general formula [3]:



wherein  $X^1$  has the same meanings as the above,  
with a halogenating agent to obtain an acid halide  
5 represented by the general formula [4]:

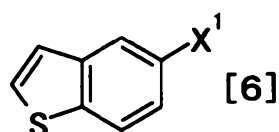


wherein  $X^1$  and  $X^2$  have the same meanings as the above,  
subsequently subjecting the acid halide to  
intramolecular ring closure reaction in the presence of  
Lewis acid, subsequently subjecting it to reduction  
10 reaction to obtain a dihydrobenzothiophene derivative  
represented by the general formula [5]:

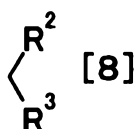


wherein  $X^1$  has the same meanings as the above,  
subsequently subjecting the dihydrobenzothiophene  
derivative to dehydration reaction in the presence of

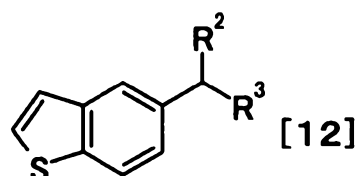
acid catalyst to obtain a 5-halogeno-1-benzothiophene derivative represented by the general formula [6]:



wherein  $X^1$  has the same meanings as the above,  
subsequently coupling the 5-halogeno-1-benzothiophene  
5 derivative with a malonic acid derivative or salts  
thereof represented by the general formula [8]:

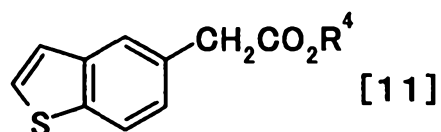


wherein  $R^2$  and  $R^3$  have the same meanings as the above,  
in the presence of base and palladium catalyst to  
obtain a benzothiophene derivative or salts thereof  
10 represented by the general formula [12]:



wherein  $R^2$  and  $R^3$  have the same meanings as the above,  
subsequently reacting the benzothiophene derivative or  
salts thereof with acid or base, subjecting it to  
decarboxylation reaction if necessary, to obtain a

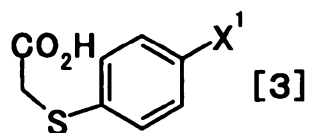
benzothiopheneacetic acid derivative or salts thereof represented by the general formula [11]:



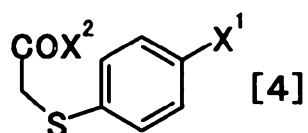
wherein R<sup>4</sup> has the same meanings as the above,  
subsequently subjecting, the benzothiopheneacetic acid  
5 derivative or salts thereof to hydrolysis reaction if  
necessary, subsequently subjecting it to reduction  
reaction with an addition of activator in the presence  
of alkali metal borohydride.

[0013]

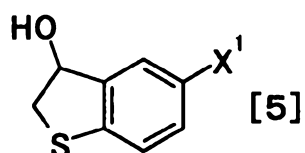
10 Further, the present inventors have found  
that  
a process for production of 1-(3-(2-(1-benzothiophen-5-  
yl)ethoxy)propyl)azetidin-3-ol or salts thereof  
characterized by reacting a (phenylthio)acetic acid  
15 derivative or salts thereof represented by the general  
formula [3]:



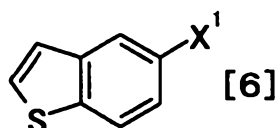
wherein X<sup>1</sup> has the same meanings as the above,  
with a halogenating agent to obtain an acid halide  
represented by the general formula [4]:



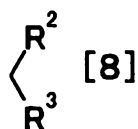
wherein  $X^1$  and  $X^2$  have the same meanings as the above,  
subsequently subjecting the acid halide to  
intramolecular ring closure reaction in the presence of  
Lewis acid, subsequently subjecting it to reduction  
5 reaction to obtain a dihydrobenzothiophene derivative  
represented by the general formula [5]:



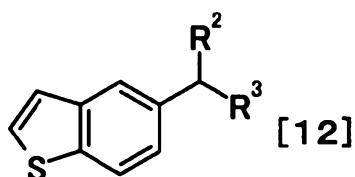
wherein  $X^1$  has same the meanings as the above,  
subsequently subjecting the dihydrobenzothiophene  
derivative to dehydration reaction in the presence of  
10 acid catalyst to obtain a 5-halogeno-1-benzothiophene  
derivative represented by the general formula [6]:



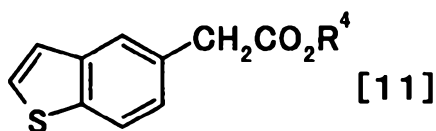
wherein  $X^1$  has the same meanings as the above,  
subsequently coupling the 5-halogeno-1-benzothiophene  
derivative with a malonic acid derivative or salts  
15 thereof represented by the general formula [8]:



wherein  $R^2$  and  $R^3$  have same meanings as the above,  
in the presence of base and palladium catalyst to  
obtain a benzothiophene derivative or salts thereof  
represented by the general formula [12]:

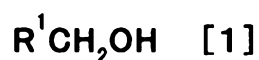


5 wherein  $R^2$  and  $R^3$  have the same meanings as the above,  
subsequently reacting the benzothiophene derivative or  
salts thereof with acid or base, subjecting it to  
decarboxylation reaction if necessary, to obtain a  
benzothiopheneacetic acid derivative or salts thereof  
10 represented by the general formula [11]:

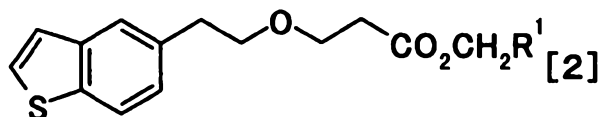


wherein  $R^4$  have the same meanings as the above,  
subsequently subjecting the benzothiopheneacetic acid  
derivative or salts thereof to hydrolysis reaction if  
necessary, subsequently subjecting it to reduction  
15 reaction with an addition of activator in the presence

of alkali metal borohydride to obtain 2-(1-benzothiophen-5-yl)ethanol, subsequently subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael addition reaction with acrylonitrile in the presence of base, subsequently subjecting it to reaction with an alcohol represented by the general formula [1]:



wherein  $R^1$  has the same meanings as the above, in the presence of acid to obtain a propionic acid ester derivative represented by the general formula [2]:



wherein  $R^1$  has the same meanings as the above, subsequently subjecting the propionic acid ester derivative to hydrolysis reaction in the presence of base to obtain 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salts thereof, subsequently converting 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salts thereof to a reactive derivative, subsequently reacting the reactive derivative with 3-azetidinol or salts thereof in the presence of base to obtain 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol, and subsequently

subjecting 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol to reduction reaction with an addition of activator in the presence of alkali metal borohydride, and have completed the present  
5 invention.

#### EFFECT OF THE INVENTION

[0014]

The process for production of 1-(3-(2-(1-  
10 benzothiophen-5-yl)ethoxy)propyl)-3-azetidinol or salts thereof of the present invention has the following characteristics, (1) the yield is high, (2) silica gel column chromatography is not required, (3) therefore, the amount of wastes is small, (4) reagents which have  
15 harmfulness and problems of stability are not used, and so forth, and the process is useful as industrial manufacturing process.

[0015]

The process for production of 3-(2-(1-  
20 benzothiophen-5-yl)ethoxy)propionic acid or salts thereof of the present invention has the following characteristics, (1) by-products are small, (2) inflammable gases do not occur, (3) the yield is high, and so forth, and the process is useful as  
25 industrial manufacturing process.

[0016]

The process for production of  
benzothiopheneacetic acid derivative or salts thereof

represented by the general formula [10] of the present invention has the following characteristics, (1) stimulative intermediates are not used during the process, (2) highly toxic reagents (cyano compounds) are not used, (3) complicated treatments of waste are not required, (4) the number of steps of the process is few, (5) the yield is high, (6) high reaction temperature is not required, (7) reaction procedures are simple, and so forth, and the process is useful as industrial manufacturing process.

[0017]

The process for production of 5-halogeno-1-benzothiophene derivatives represented by the general formula [6] of the present invention has the following characteristics, (1) by-products are few, (2) purification can be performed by simple procedure such as extraction and crystallization, (3) therefore, complicated refining procedures such as distillation or silica gel column chromatography are not required, and so forth, and the process is useful as industrial manufacturing process.

#### BEST MODE FOR CARRYING OUT THE INVENTION

[0018]

The present invention is explained below in detail.

In the present specification, unless otherwise specified, the term "halogen atom" means

fluorine atom, chlorine atom, bromine atom or iodine atom;

the term "alkyl group" means a straight or branched chain C<sub>1-12</sub>alkyl group, for example, methyl, ethyl, 5 propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl, octyl or the like;

the term "cycloalkyl group" means a C<sub>3-8</sub>cycloalkyl group, for example, cyclopropyl, cyclobutyl, 10 cyclopentyl, cyclohexyl or the like;

the term "aralkyl group" means an arC<sub>1-6</sub>alkyl group, for example, benzyl, diphenylmethyl, trityl, phenethyl, naphthylmethyl or the like;

the term "alkoxy group" means a straight or branched 15 chain C<sub>1-6</sub>alkyloxy group, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy or the like;

the term "alkyloxycarbonyl group" means a straight or branched chain C<sub>1-12</sub>alkyloxycarbonyl group, for example, 20 methoxycarbonyl, ethoxycarbonyl, 1,1-

dimethylpropoxycarbonyl, isopropoxycarbonyl, 2-ethylhexyloxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl or the like;

the term "cycloalkyloxycarbonyl group" means a C<sub>3-</sub> 25 <sub>8</sub>cycloalkyloxycarbonyl group, for example, cyclopropoxycarbonyl, cyclobutoxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl or the like;

the term "aralkyloxycarbonyl group" means an arC<sub>1</sub>-alkyloxycarbonyl group, for example, benzyloxycarbonyl, phenethyloxycarbonyl or the like;

the terms "aryl group" means group, for example,  
5 phenyl, naphthyl or the like;

the term "alkenyl group" means a C<sub>2-12</sub>alkenyl group, for example, vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl or the like, respectively.

[0019]

10           The alkyl, cycloalkyl and aryl group of R<sup>1</sup> may be substituted with at least one group selected from a halogen atom, a hydroxyl group, a nitro group, an alkyl group, a cycloalkyl group, an alkoxy group, an alkenyl group and an aryl group or the like.

15           The alkyloxycarbonyl, cycloalkyloxycarbonyl and aralkyloxycarbonyl group of R<sup>2</sup> and R<sup>3</sup> may be substituted with at least one group selected from a halogen atom, a hydroxyl group, a nitro group, an alkyl group, a cycloalkyl group, an alkoxy group, an alkenyl  
20 group and an aryl group or the like.

          The alkyl, cycloalkyl and aralkyl group of R<sup>4</sup> may be substituted with at least one group selected from a halogen atom, a hydroxyl group, a nitro group, an alkyl group, a cycloalkyl group, an alkoxy group, an  
25 alkenyl group and an aryl group or the like.

[0020]

          In the present invention, the following processes are given for preferable manufacturing

processes.

[0021]

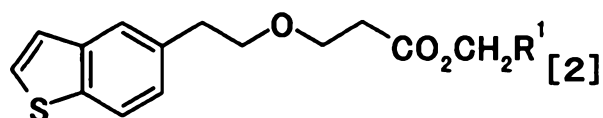
For the production of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salts thereof, in the process for production by subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael addition reaction in the presence of base with acrylonitrile, subsequently reacting it with an alcohol represented by the general formula [1]:

10



wherein  $\text{R}^1$  has the same meanings as the above, in the presence of acid to obtain a propionic acid ester derivative represented by the general formula [2]:

15



20 wherein  $\text{R}^1$  has the same meanings as the above, and subjecting the propionic acid ester derivative to hydrolysis reaction in the presence of base, the process for production in which  $\text{R}^1$  is a hydrogen atom or an alkyl group is preferable, the process for production in which  $\text{R}^1$  is a hydrogen atom, methyl group, ethyl group or propyl group is more preferable, and the process for production in which  $\text{R}^1$  is a hydrogen atom or

25

ethyl group is further more preferable.

The process for production in which the acid used is an inorganic acid is preferable, and the process for production in which the acid used is  
5 sulfuric acid or hydrogen chloride is more preferable.

In the case that the acid is hydrogen chloride, the process for production in which R<sup>1</sup> is hydrogen atom is preferable.

In the case that the acid is sulfuric acid,  
10 the process for production in which R<sup>1</sup> is ethyl group is preferable.

[0022]

In the process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol or salts  
15 thereof by subjecting 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol to reduction reaction with an addition of activator in the presence of alkali metal borohydride, the process for production in which the alkali metal borohydride used is sodium borohydride  
20 is preferable.

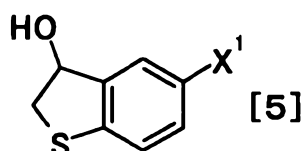
The process for production in which the activator used is a protonic acid such as sulfuric acid and hydrogen chloride and so forth is preferable, and the process for production in which the activator used  
25 is sulfuric acid is more preferable.

In the case that the activator is sulfuric acid, the process for production in which the volume of sulfuric acid used is 0.5-0.6 times mole per mole of

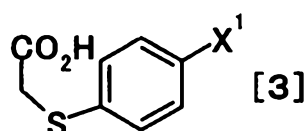
the alkali metal borohydride, the addition of sulfuric acid at 0 to 30°C for 10 minutes to 6 hours and the subsequent reaction at 30 to 70°C is preferable.

[0023]

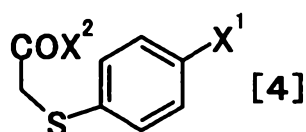
- 5 For the production of a dihydrobenzothiophene derivative represented by the general formula [5]:



- 10 wherein X¹ has the same meanings as the above,  
in the process for production by reacting a  
(phenylthio)acetic acid derivative or salts thereof  
represented by the general formula [3]:



- wherein X¹ has the same meanings as the above,  
15 with a halogenating agent to obtain an acid halide  
represented by the general formula [4]:

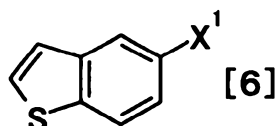


- 20 wherein X¹ and X² have the same meanings as the above,  
subsequently subjecting the acid halide to

intramolecular ring closure reaction in the presence of Lewis acid, subsequently subjecting it to reduction reaction, the process for production in which  $X^1$  is a chlorine atom, a bromine atom or an iodine atom is preferable, the process for production in which  $X^1$  is a bromine atom or an iodine atom is more preferable, and the process for production in which  $X^1$  is a bromine atom is further more preferable.

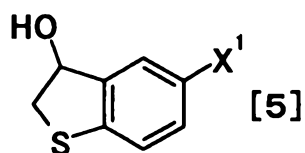
[0024]

10 For the production of a 5-halogeno-1-benzothiophene derivative represented by the general formula [6]:



15

wherein  $X^1$  has the same meanings as the above, in the process for production by subjecting a dihydrobenzothiophene derivative represented by the general formula [5]:



20 wherein  $X^1$  has the same meanings as the above, to dehydration reaction in the presence of acid catalyst, the process for production in which  $X^1$  is a

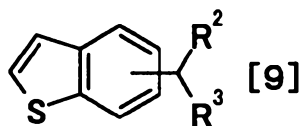
chlorine atom, a bromine atom or an iodine atom is preferable, the process for production in which  $X^1$  is a bromine atom or an iodine atom is more preferable, and the process for production in which  $X^1$  is a bromine atom  
5 is further more preferable.

[0025]

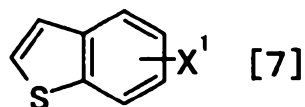
In the process for isolation by crystallizing crystals of a dihydrobenzothiophene derivative represented by the general formula [5], the process for  
10 isolation by crystallizing it from an aliphatic hydrocarbon such as hexane and cyclohexane and so forth is preferable, the process for isolation by crystallizing it from hexane or cyclohexane is more preferable, and the process for isolation by  
15 crystallizing it from cyclohexane is further more preferable.

[0026]

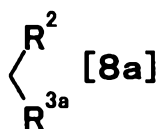
In the production of benzothiophene derivative or salts thereof represented by the general  
20 formula [9]:



wherein  $R^2$  and  $R^3$  have the same meanings as the above,  
25 the process for production by subjecting a benzothiophene derivative represented by the general formula [7]:



wherein  $X^1$  has the same meanings as the above,  
 5 to coupling reaction with a malonic acid derivative or  
 salts thereof represented by the general formula [8a]  
 in the presence of the palladium catalyst and base:



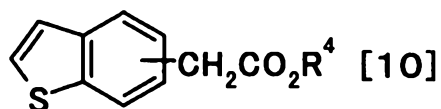
wherein  $R^{3a}$  represents an unsubstituted or substituted  
 alkyloxycarbonyl, cycloalkyloxycarbonyl or  
 10 aralkyloxycarbonyl group;  $R^2$  has same meanings as the  
 above,  
 is preferable, the process for production in which  $R^2$  is  
 an alkyloxycarbonyl group, an aralkyloxycarbonyl group  
 or a cyano group;  $R^{3a}$  is an alkyloxycarbonyl group or an  
 15 aralkyloxycarbonyl group is more preferable, the  
 process for production in which  $R^2$  is a  $C_{1-4}$ -  
 alkyloxycarbonyl group, an  $arC_{1-4}$ alkyloxycarbonyl group  
 or a cyano group;  $R^{3a}$  is a  $C_{1-4}$ alkyloxycarbonyl group or  
 an  $arC_{1-4}$ alkyloxycarbonyl group is further preferable.  
 20 The process for production in which  $X^1$  is a  
 chlorine atom, a bromine atom or an iodine atom is  
 preferable, and the process for production in which  $X^1$   
 is a bromine atom or an iodine atom is further

preferable.

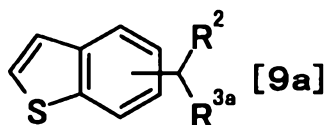
The process for production in which X<sup>1</sup> bonds to 4- or 5-position of the benzothiophene ring is preferable, and the process for production in which X<sup>1</sup> bonds 5-position of the benzothiophene ring is further preferable.

[0027]

In the process for production of a benzothiopheneacetic acid derivative or salts thereof represented by the general formula [10]:



wherein R<sup>4</sup> has the same meanings as the above, the process for production by reacting a benzothiophene derivative or salts thereof represented by the general formula [9a]:

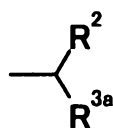


wherein R<sup>2</sup> and R<sup>3a</sup> have the same meanings as the above, with acid or base, subjecting it to decarboxylation reaction if necessary, is preferable, the process for production in which R<sup>2</sup> is an alkyloxycarbonyl group, an aralkyloxycarbonyl group or a cyano group; R<sup>3a</sup> is an alkyloxycarbonyl group or an aralkyloxycarbonyl group

is more preferable, and the process for production in which  $R^2$  is a  $C_{1-4}$ alkyloxycarbonyl group, an  $arC_{1-4}$ alkyloxycarbonyl group or a cyano group;  $R^{3a}$  is a  $C_{1-4}$ alkyloxycarbonyl group or an  $arC_{1-4}$ alkyloxycarbonyl group is further preferable.

[0028]

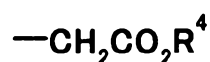
The process for production in which the group represented by the general formula:



wherein  $R^2$  and  $R^{3a}$  have the same meanings as the above, bonds to 4- or 5-position of the benzothiophene ring is preferable, and the process for production in which the group bonds to 5-position of the benzothiophene ring is further preferable.

[0029]

The process for production in which the group represented by the general formula:

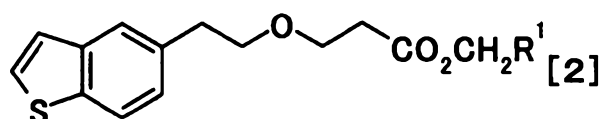


wherein  $R^4$  has the same meanings as the above, bonds to 4- or 5-position of the benzothiophene ring is preferable, and the process for production in which the group bonds to 5-position of the benzothiophene ring is further preferable.

The process for production in which  $R^4$  is a hydrogen atom or an unsubstituted or substituted alkyl, cycloalkyl or aralkyl group is preferable, the process for production in which  $R^4$  is a hydrogen atom, an alkyl group or an aralkyl group is preferable, and the process for production in which  $R^4$  is a hydrogen atom, a  $C_{1-4}$ alkyl group or an  $arC_{1-4}$  alkyl group is further preferable.

[0030]

10 In the propionic acid ester derivative represented by the general formula [2]:

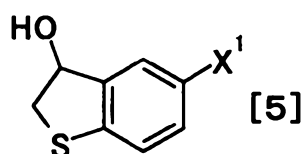


wherein  $R^1$  has the same meanings as the above, the following compounds are given for a preferable compound.

15 The compound of which  $R^1$  is a hydrogen atom or an alkyl group is preferable, the compound of which  $R^1$  is a hydrogen atom, a methyl group, an ethyl group or a propyl group is more preferable, and the compound of which  $R^1$  is a hydrogen atom or an ethyl group is further preferable.

[0031]

In a dihydrobenzothiophene derivative represented by the general formula [5]:

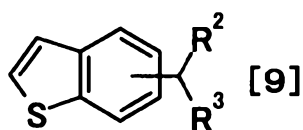


wherein  $X^1$  has the same meanings as the above,  
5 the following compounds are given for a preferable compound.

The compound of which  $X^1$  is a chlorine atom, a bromine atom or an iodine atom is preferable, the compound of which  $X^1$  is a bromine atom or an iodine atom  
10 is more preferable, and the compound of which  $X^1$  is a bromine atom is further preferable.

[0032]

In a benzothiophene derivative or salts thereof represented by the general formula [9]:



15 wherein  $R^2$  and  $R^3$  have the same meanings as the above, the following compounds are given for a preferable compound.

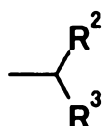
The compound of which  $R^2$  is an alkyloxycarbonyl, cycloalkyloxycarbonyl or  
20 aralkyloxycarbonyl group or a cyano group is preferable, the compound of which  $R^2$  is an alkyloxycarbonyl group, an aralkyloxycarbonyl group or

a cyano group is more preferable, and the compound of which  $R^2$  is a  $C_{1-4}$ alkyloxycarbonyl group, an  $arC_{1-4}$ alkyloxycarbonyl group or a cyano group is further preferable.

5           The compound of which  $R^3$  is an alkyloxycarbonyl, cycloalkyloxycarbonyl or aralkyloxycarbonyl group is preferable, the compound of which  $R^3$  is an alkyloxycarbonyl group or an aralkyloxycarbonyl group is more preferable, and the  
10 compound of which  $R^3$  is a  $C_{1-4}$ alkyloxycarbonyl group or  $arC_{1-4}$ alkyloxycarbonyl group is further preferable.

[0033]

The compound of which the group represented by the general formula:



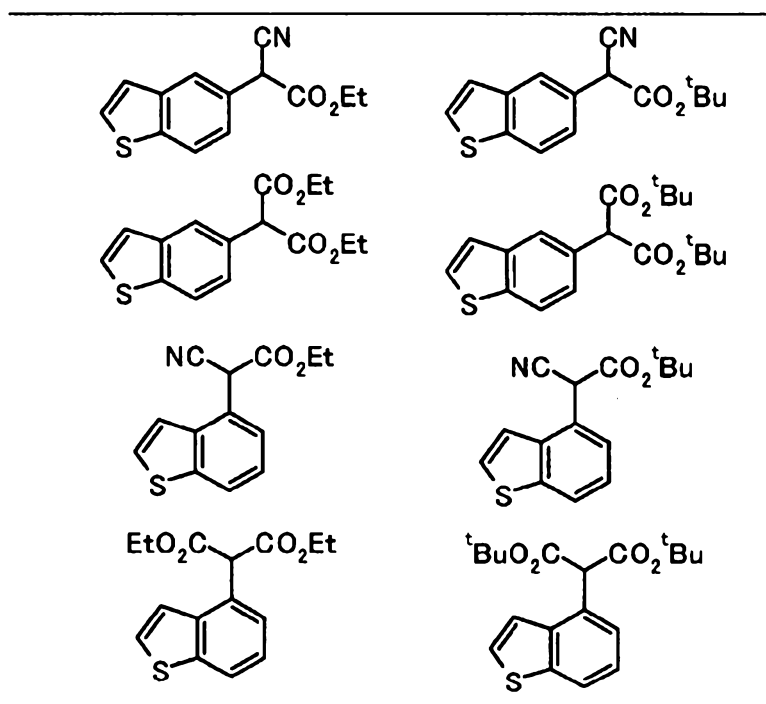
15 wherein  $R^2$  and  $R^3$  have the same meanings as the above, bonds to 4- or 5-position of the benzothiophene ring is preferable, and, the compound of which the group bonds to 5-position of the benzothiophene ring is further preferable.

20           As the representative compound of the general formula [9] or salts thereof of the present invention, for example, the following compounds are given.

In a table, Et represents an ethyl group,  $^t$ Bu represents a tert-butyl group.

[0034]

[TABLE 1]



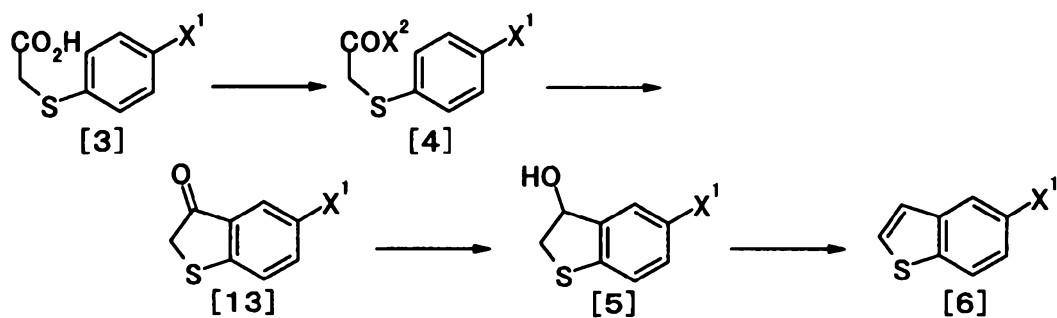
5

[0035]

Next, the process for production of the present invention is explained.

[0036]

10 [Production process 1]



wherein  $X^1$  and  $X^2$  have the same meanings as the above.

[0037]

The compound of the general formula [5] can be produced by deriving the compound of the general formula [3] or salts thereof to an acid halide, subsequently subjecting the acid halide to intramolecular ring closure reaction in the presence of Lewis acid, subsequently subjecting it to reduction reaction.

The compound of the general formula [5] can be derived to the compound of general formula [6] easily by subjecting it to dehydration reaction in the presence of acid catalyst.

[0038]

The compound of the general formula [3] or salts thereof, for example, can be obtained easily and with good yield by reacting thiophenol with chloroacetic acid in the presence of base to obtain (phenylthio)acetic acid, subsequently subjecting (phenylthio)acetic acid to halogenating reaction, or reacting 4-halogenothiophenol with chloroacetic acid in the presence base.

In addition, the salt of the compound of general formula [3], if it is usually known for a salt in acidic group such as carboxyl group, is not particularly limited, but for example, salts with alkali metal such as sodium, potassium, cesium and the like; salts with alkali earth metal such as calcium,

magnesium and the like;

ammonium salts;

and salts with nitrogen containing organic base such as trimethylamine, triethylamine, tributylamine, N,N-

5 diisopropylethylamine, pyridine, N-methylpiperidine, N-methylmorpholine, diethylamine, dicyclohexylamine and the like; are given.

[0039]

The present process for production is  
10 explained below in detail.

Intramolecular ring closure reaction:

The compound of the general formula [13] can be produced by reacting the compound of the general formula [3] or salts thereof with a halogenating agent  
15 to obtain an acid halide, subsequently subjecting the acid halide to intramolecular ring closure reaction in the presence of Lewis acid.

[0040]

This reaction is usually carried out in the  
20 presence of solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, for example, aliphatic halogenated hydrocarbons such as dichloromethane, chloroform, dichloroethane and the like;  
25 nitro compounds such as nitromethane, nitrobenzene and the like;  
and carbon disulfide and the like; are given, and these solvents may be used in admixture.

As a preferable solvent, aliphatic halogenated hydrocarbons is given, and dichloromethane is more preferable.

The amount of the solvent used is not particularly limited, but is preferably 1 to 50 times volume per weight (v/w) of the compound of the general formula [3] or salts thereof, and is more preferably 3 to 15 times (v/w).

[0041]

As the halogenating agent used in this reaction, for example, phosphorus oxychloride, phosphorus oxybromide, phosphorus trichloride, phosphorous pentachloride, thionyl chloride, thionyl bromide and oxalyl chloride are given, and thionyl chloride is preferable.

The amount of the halogenating agent used is different in the kind of the halogenating agent, but for example, in the case of thionyl chloride, it may be equal to or more than 0.5 times mole per mole of the compound of the general formula [3] or salts thereof, and is preferably 1 to 2 times mole.

[0042]

As Lewis acid used in this reaction, for example, aluminum chloride, aluminum bromide, boron trifluoride, titanium tetrachloride, iron chloride, tin chloride, mercuric chloride, sulfuric acid and the like are given, and aluminum chloride is preferable.

The amount of Lewis acid used may be equal to

or more than 1 time mole per mole of the compound of general formula [3] or salts thereof, and is preferably 1 to 5 times mole.

[0043]

5           The reaction temperature is not particularly limited, but is from -20°C to equal to or less than the boiling point of solvent, and is preferably 0 to 70°C.

          The reaction time is not particularly limited, but is for 10 minutes to 50 hours, and is  
10 preferably for 30 minutes to 20 hours.

[0044]

          The compound of the general formula [13] obtained in this way can be isolated and purified, but it is preferable to proceed to the next reaction  
15 without isolation.

[0045]

#### Reduction reaction:

The compound of the general formula [5] can be produced by subjecting the compound of the general formula [13]  
20 to reduction reaction. This reaction is usually carried out in the presence of solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, but for example, aliphatic halogenated hydrocarbons such as  
25 dichloromethane, chloroform, dichloroethane and the like;  
ethers such as tetrahydrofuran, 1,2-dimethoxyethane, bis(2-methoxyethyl)ether, dioxane and the like;

amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; alcohols such as methanol, ethanol, propanol, 2-propanol, butanol and the like; nitriles such as acetonitrile and the like; esters such as methyl acetate, ethyl acetate and the like; nitro compounds such as nitromethane, nitrobenzene and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and water and the like; are given, and these solvents may be used in admixture.

As a preferable solvent, a mixed solvent of aliphatic halogenated hydrocarbons and alcohols are given, a mixed solvent of dichloromethane and methanol is more preferable.

The amount of the solvent used is not particularly limited, but preferably 1 to 50 times volume per weight of the compound of the general formula [13], and is more preferably 3 to 15 times (v/w).

[0046]

As the reducing agent used in this reaction, for example, alkali metal such as lithium, sodium, potassium and the like; alkali earth metal such as magnesium, calcium and the

like;

metal such as zinc, aluminium, chrome, titanium, iron, samarium, selenium, sodium hydrosulfite and the like, and salts of these metals;

- 5 metal hydride such as diisobutylaluminium hydride, trialkylaluminium hydride, stannyl hydride compound, hydrosilane and the like;  
complex compound of borohydride such as sodium borohydride, lithium borohydride, potassium borohydride

10 and the like;

complex compound of aluminium hydride such as lithium aluminum hydride and the like;

and borane and alkyl borane and the like; are given.

- As a preferable reducing agent, complex  
15 compound of borohydride is given, and sodium borohydride is more preferable.

The amount of the reducing agent used is different in the kind of the reducing agent, but for example, in the case of the complex compound of  
20 borohydride, it may be equal to or more than 0.25 times mole per mole of the compound of the general formula [13], and is preferably 0.25 to 2 times mole.

[0047]

- The reaction temperature is not particularly  
25 limited, but is from -20°C to equal to or less than the boiling point of solvent, and is preferably 0 to 70°C.

The reaction time is not particularly limited, but is for 10 minutes to 50 hours, and is

preferably for 30 minutes to 20 hours.

[0048]

The compound of the general formula [5] obtained in this way may be used as it is in the next  
5 reaction without isolation, but it is preferable to isolate it by crystallizing the crystal.

The process of crystallization from aliphatic hydrocarbons such as hexane, cyclohexane and the like is preferable, the process of crystallization from  
10 hexane or cyclohexane is more preferable, and the process of crystallization from cyclohexane is further preferable.

[0049]

Dehydration reaction:

15 The compound of the general formula [6] can be produced by subjecting the compound of the general formula [5] to dehydration reaction in the presence of acid catalyst.

[0050]

20 This reaction is usually carried out in the presence of solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, but for example, aliphatic hydrocarbons such as hexane, cyclohexane and the like;  
25 aromatic hydrocarbons such as benzene, toluene, xylene and the like;  
aliphatic halogenated hydrocarbons such as dichloromethane, chloroform, dichloroethane and the

like;  
ethers such as tetrahydrofuran, 1,2-dimethoxyethane,  
bis(2-methoxyethyl)ether, dioxane and the like;  
amides such as N,N-dimethylformamide, N,N-  
5 dimethylacetamide, 1-methyl-2-pyrrolidone and the like;  
sulfoxides such as dimethyl sulfoxide and the like;  
esters such as methyl acetate, ethyl acetate and the  
like;  
ketones such as acetone, 2-butanone and the like;  
10 alcohols such as methanol, ethanol, propanol, 2-  
propanol, butanol and the like;  
nitriles such as acetonitrile and the like;  
aliphatic carboxylic acid such as acetic acid,  
propionic acid and the like;  
15 and water and the like; are given, and these may be  
used in admixture.

As a preferable solvent, ketone is given, and  
acetone is more preferable.

The amount of the solvent used is not  
20 particularly limited, but is preferably 1 to 50 times  
volume per weight of the compound of the general  
formula [5], and is preferably 1 to 10 times(v/w).  
[0051]

As the acid catalyst used in this reaction,  
25 for example, Broensted acids such as hydrochloric acid,  
sulfuric acid, methanesulfonic acid,  
trifluoromethanesulfonic acid, p-toluenesulfonic acid,  
dichloroacetic acid and the like;

and Lewis acid such as aluminum chloride, boron trifluoride, boron trichloride and the like; are given, and p-toluenesulfonic acid is preferable.

The amount of the acid catalyst used may be equal to or more than 0.0001 times mole per mole of the compound of the general formula [5], and is 0.001 to 1 times mole.

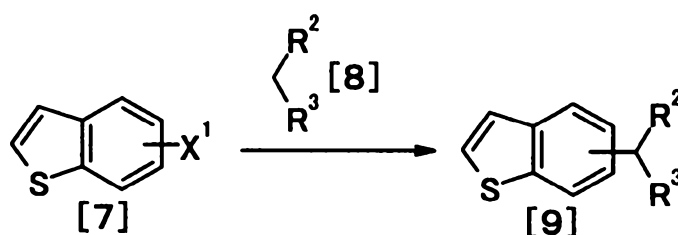
[0052]

The reaction temperature is not particularly limited, but is from -20°C to equal to or less than the boiling point of solvent, and is preferably 0 to 70°C.

The reaction time is not particularly limited, but is for 10 minutes to 50 hours, and is preferably for 30 minutes to 20 hours.

[0053]

[Production process 2]



wherein R<sup>2</sup>, R<sup>3</sup> and X<sup>1</sup> have the same meanings as the above.

[0054]

As the compound of the general formula [8] or salts thereof, for example, diethyl malonate, di(tert-butyl) malonate, ethyl cyano acetate, tert-butyl cyano

acetate, malononitrile and the like; are marketed.

[0055]

The compound of the general formula [9] or salts thereof can be produced by subjecting the  
5 compound of the general formula [7] to coupling reaction with the compound of the general formula [8] or salts thereof in the presence of base and palladium catalyst, in the presence or absence of ligand, in the presence or absence of reducing agent.

10 This reaction is usually carried out in the presence of solvent, the solvent used, if it does not affect a bad influence on the reaction, is not particularly limited, but for example, aliphatic hydrocarbons such as hexane, cyclohexane and the like;  
15 halogenated hydrocarbons such as dichloromethane, chloroform, dichloroethane and the like; ethers such as tetrahydrofuran, 1,2-dimethoxyethane, bis(2-methoxyethyl)ether, dioxane and the like; aromatic hydrocarbons such as benzene, toluene, xylene  
20 and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; esters such as ethyl acetate, butyl acetate and the  
25 like; ketones such as acetone, 2-butanone and the like; alcohols such as methanol, ethanol, propanol, butanol, 2-propanol, 2-methyl-2-propanol and the like;

and nitriles such as acetonitrile and the like; are given, and these may be used in admixture.

The amount of the solvent used is not particularly limited, but is preferably 1 to 20 times  
5 volume per weight of the compound of the general formula [7], and is preferably 1 to 10 times (v/w).

As the base used in this reaction, for example, metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and sodium  
10 tert-butoxide and the like;  
inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, barium carbonate, sodium phosphate, potassium phosphate, sodium hydride and potassium  
15 hydride and the like;  
organic base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like; are given.

The amount of the base used may be equal to  
20 or more than 1 time mole per mole of the compound of the general formula [7], is preferably 2 to 10 times mole, and is more preferably 2 to 4 times mole.

[0056]

As the palladium catalyst used in this  
25 reaction, for example, metal palladium such as palladium-carbon, palladium black and the like;  
inorganic palladium salt such as palladium chloride;  
organic palladium salt such as palladium acetate;

organopalladium complex such as  
tetrakis(triphenylphosphine) palladium (0),  
bis(triphenylphosphine)palladium (II) chloride, 1,1'-  
bis(diphenylphosphino)ferrocene palladium (II)  
5 chloride, tris(dibenzylideneacetone)dipalladium (0) and  
the like;  
and polymer fixed organopalladium complex such as  
bis(acetate)triphenylphosphine palladium (II) carried  
in polymer, di(acetate)dicyclohexylphosphine palladium  
10 (II) carried in polymer and the like; are given.

The amount of the palladium catalyst used is  
not particularly limited, but is preferably 0.0001 to 1  
times mole per mole of the compound of general formula  
[7], and is more preferably is 0.005 to 0.1 times mole.  
15 [0057]

As the ligand used, if desired, in this  
reaction, for example, trialkylphosphines such as  
trimethylphosphine, tri(tert-butyl)phosphine and the  
like;  
20 tricycloalkylphosphines such as tricyclohexylphosphine  
and the like;  
triarylphosphines such as triphenylphosphine,  
tritolylphosphine and the like;  
trialkyl phosphites such as trimethyl phosphite,  
25 triethyl phosphite, tributyl phosphite and the like;  
tricycloalkyl phosphites such as tricyclohexyl  
phosphite and the like;  
triaryl phosphites such as triphenyl phosphite and the

like;

imidazolium salt such as 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and the like;

diketones such as acetylacetone,

5 octafluoroacetylacetone and the like;

amines such as trimethylamine, triethylamine, tripropylamine, triisopropylamine and the like;

1,1'-bis(diphenylphosphino)ferrocene;

and 2,2-bis(diphenylphosphino)-1,1'-binaphthyl and the

10 like; are given.

The amount of the ligand used is not particularly limited, but is preferably 0.0001 to 2 times mole per mole of the compound of general formula [7], and is more preferably 0.005 to 0.2 times mole.

15 [0058]

As the reducing agent used, if desired, in this reaction, for example, complex compound of borohydride such as lithium borohydride, sodium borohydride, calcium borohydride, triacetoxy sodium borohydride, sodium cyano borohydride and the like; is  
20 given.

The amount of the reducing agent used is not particularly limited, but is preferably 0.0001 to 1 times mole per mole of the compound of general formula  
25 [7], and is more preferably 0.01 to 0.1 times mole.

The amount of the compound of general formula [8] is 1 to 5 times mole per mole of the compound of general formula [7], and is preferably 1 to 2 times

mole.

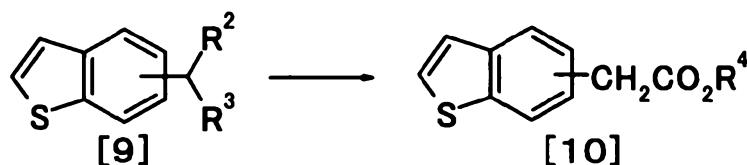
This reaction may be carried out at 0 to 200°C, and preferably at 50 to 150°C for 1 minute to 24 hours.

5 [0059]

The compound of general formula [9] or salts thereof obtained in this way may be used as it is in the next reaction without isolation.

[0060]

10 [Production process 3]



wherein  $R^2$ ,  $R^3$  and  $R^4$  have the same meanings as the  
15 above.

[0061]

The compound of the general formula [10] or salts thereof can be produced by reacting the compound of the general formula [9] or salts thereof with acid  
20 or base in the presence or absence of water, in the presence or absence of alcohol, subjecting it to decarboxylation reaction if necessary.

This reaction is usually carried out in the presence of solvent, the solvent used, if it does not  
25 affect a bad influence on the reaction, is not particularly limited, but for example, aliphatic

hydrocarbons such as hexane, cyclohexane and the like;  
halogenated hydrocarbons such as dichloromethane,  
chloroform, dichloroethane and the like;  
ethers such as tetrahydrofuran, 1,2-dimethoxyethane,  
5 bis(2-methoxyethyl)ether, dioxane and the like;  
aromatic hydrocarbons such as benzene, toluene, xylene  
and the like;  
amides such as N,N-dimethylformamide, N,N-  
dimethylacetamide, 1-methyl-2-pyrrolidone and the like;  
10 sulfoxides such as dimethyl sulfoxide and the like;  
esters such as ethyl acetate, butyl acetate and the  
like;  
ketones such as acetone, 2-butanone and the like;  
alcohols such as methanol, ethanol, propanol, butanol,  
15 2-propanol, 2-methyl-2-propanol and the like;  
glycols such as ethylene glycol, propylene glycol,  
diethylene glycol and the like;  
nitriles such as acetonitrile and the like;  
and water and the like; are given, and these may be  
20 used in admixture.

The amount of the solvent used is not particularly limited, but is preferably 1 to 50 times volume per weight of the compound of the general formula [9] or salts thereof, and is more preferably 1  
25 to 15 times(v/w).

[0062]

As the acid used in this reaction, inorganic acid such as hydrochloric acid, sulfuric acid,

phosphoric acid, hydrogen chloride, hydrogen bromide and the like;

organic carboxylic acid such as acetic acid, trichloroacetic acid, trifluoroacetic acid and the

5 like;

and organic sulfonic acid such as methanesulfonic acid, p-toluenesulfonic acid and the like; are given.

The amount of the acid used may be equal to or more than 0.001 times mole per mole of the compound  
10 of the general formula [9] or salts thereof, and is preferably 0.01 to 5 times mole.

In addition, the acid may be used as solvent.

In addition, as the base used in this reaction, for example, metal alkoxide such as sodium  
15 methoxide, sodium ethoxide, potassium tert-butoxide and sodium tert-butoxide and the like;

inorganic base such as sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate and the like;

20 and organic base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like; are given.

The amount of base used is 2 to 10 times mole per mole of the compound of general formula [9] or  
25 salts thereof, and is preferably 2 to 5 times mole.

The amount of water used, if desired, in this reaction, is not particularly limited, but is preferably 0.5 to 5 times volume per weight of the

compound of general formula [9] or salts thereof in order to make it have the function of solvent.

As the alcohol used, if desired, in this reaction, for example, primary alcohols such as  
5 methanol, ethanol, propanol, butanol and the like;  
and glycols such as ethylene glycol, propylene glycol,  
diethylene glycol and the like; are given.

The amount of the alcohol used is not particularly limited, but is preferably 0.5 to 5 times  
10 volume per weight of the compound of general formula  
[9] or salts thereof in order to make it have the  
function of solvent.

This reaction may be carried out at 0 to 200°C, and preferably at 20 to 150°C for 1 minute to 24  
15 hours.

[0063]

Decarboxylation reaction which may be performed if necessary is carried out by heating  
As the acid used, if desired, in this reaction, for  
20 example, inorganic acid such as hydrochloric acid,  
sulfuric acid, phosphoric acid, hydrogen chloride,  
hydrogen bromide and the like;  
organic carboxylic acid such as acetic acid,  
trichloroacetic acid, trifluoroacetic acid and the  
25 like;  
and organic sulfonic acid such as methanesulfonic acid,  
p-toluene sulfonic acid and the like; are given.

The amount of the acid used may be equal to

or more than 0.001 times mole per mole of the compound of general formula [9] or salts thereof, and is preferably 0.01 to 5 times mole.

In addition, the acid may be used as solvent.

5 [0064]

This reaction may be carried out if necessary in coexistent of solvent.

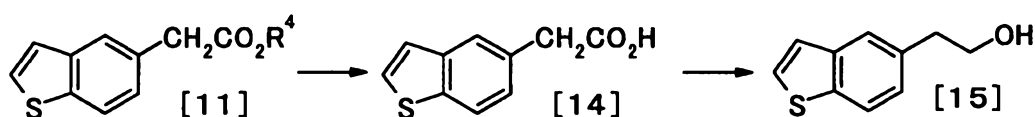
The solvent used, if it does not affect a bad influence on the reaction, is not particularly limited, but for example, aliphatic hydrocarbons such as hexane, cyclohexane and the like;  
halogenated hydrocarbon such as dichloromethane, chloroform, dichloroethane and the like;  
ethers such as tetrahydrofuran, 1,2-dimethoxyethane, bis(2-methoxyethyl)ether, dioxane and the like;  
aromatic hydrocarbons such as benzene, toluene, xylene and the like;  
amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like;  
20 sulfoxides such as dimethyl sulfoxide and the like;  
esters such as ethyl acetate, butyl acetate and the like;  
ketones such as acetone, 2-butanone and the like;  
alcohols such as methanol, ethanol, propanol, butanol, 2-propanol, 2-methyl-2-propanol and the like;  
25 glycols such as ethylene glycol, propylene glycol, diethylene glycol and the like;  
nitriles such as acetonitrile and the like;

and water and the like; are given, and these may be used in admixture.

This reaction may be carried out at 50 to 200°C, and preferably at 50 to 150°C for 1 minute to 24 hours.

[0065]

[Production process 4]



wherein  $R^4$  has the same meanings as the above.

[0066]

2-(1-benzothiophen-5-yl)ethanol of the compound of the formula [15] can be produced by subjecting the compound of the general formula [11] or salts thereof to hydrolysis reaction if necessary, and deriving it to (1-benzothiophen-5-yl)acetic acid or salts thereof of the compound of the formula [14], subsequently subjecting (1-benzothiophen-5-yl)acetic acid or salts thereof to reduction reaction with an addition of activator in the presence of alkali metal borohydride.

This reaction is usually carried out in the presence of solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, but for example, ethers such as tetrahydrofuran, 1,2-dimethoxyethane, bis(2-

methoxyethyl)ether, dioxane and the like; is given, and tetrahydrofuran is preferable.

In addition, these solvents may be mixed with a solvent of halogenated hydrocarbons such as

5 dichloromethane, chloroform and the like;  
aromatic hydrocarbons such as benzene, toluene, xylene  
and the like;  
and aliphatic hydrocarbons such as hexane, cyclohexane,  
octane and the like; and the mixed solvent may be used.

10 The amount of the solvent used is not  
particularly limited, but is preferably 1 to 20 times  
volume per weight of the compound of the formula [14]  
or salts thereof, and is preferably 2 to 10 times (v/w).  
[0067]

15 As the alkali metal borohydride used in this  
reaction, for example, sodium borohydride, lithium  
borohydride, potassium borohydride and the like; are  
given, and sodium borohydride is preferable.

The amount of the alkali metal borohydride  
20 used may be equal to or more than 1 time mole per mole  
of the compound of the formula [14] or salts thereof,  
is preferably 1 to 10 times mole, and is more  
preferably 1 to 2 times mole.  
[0068]

25 As the activator used in this reaction, for  
example, protonic acid such as sulfuric acid, hydrogen  
chloride, trifluoroacetic acid and the like is given,  
and sulfuric acid and hydrogen chloride are preferable.

The amount of the activator used is different in the kind of the activator, but for example, but in the case of sulfuric acid it is preferably 0.5 to 1 times mole per mole of the alkali metal borohydride,  
5 and is more preferably 0.5 to 0.6 times mole.

In addition, the addition time of the activator is different in the kind of the activator, but in the case of sulfuric acid it is preferably for 10 minutes to 6 hours, and is more preferably for 30  
10 minutes to 2 hours.

In addition, the activator may be dissolved in solvent appropriately, and the dissolved solvent may be added.

[0069]

15 The reaction temperature is not particularly limited, but may be -20 to 150°C, and is preferably 0 to 80°C.

Further, the process by the addition of the activator at 0 to 30°C and the subsequent reaction at 40  
20 to 80°C is more preferable, because generation of by-products can be suppressed.

In addition, the reaction time is not particularly limited, but is for 10 minutes to 50 hours, and is preferably for 1 to 20 hours.

25 [0070]

In addition, the hydrolysis reaction of the compound of the general formula [11] or salts thereof which may be carried out if necessary may be performed

by a reaction in a manner per se, for example, the compound of the formula [14] or salts thereof can be derived by subjecting it to hydrolysis reaction in the presence of base.

5           This reaction is usually carried out in the presence solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, but for example, aliphatic hydrocarbons such as hexane, cyclohexane and the like; 10 aromatic hydrocarbons such as benzene, toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran, 1,2-dimethoxyethane, 15 bis(2-methoxyethyl)ether, dioxane and the like; sulfoxides such as dimethyl sulfoxide and the like; alcohols such as methanol, ethanol, propanol, butanol, 2-propanol, tert-butanol and the like; and water and the like; are given, and these solvents 20 may be used in admixture.

As a preferable solvent, a mixed solvent of aromatic hydrocarbons such as benzene, toluene and xylene and alcohols, and a mixed solvent of alcohols and water; are given, and a mixed solvent of toluene 25 and methanol and a mixed solvent of methanol and water are preferable.

The amount of the solvent used is not particularly limited, but is preferably 0.5 to 10 times volume per

weight of the compound of the general formula [11] or salts thereof, and is more preferably 0.5 to 5 times (v/w).

As the base used in this reaction, for example, metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium tert-butoxide and the like; and inorganic base such as sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate and the like; are given.

As a preferable base, inorganic base is given, and sodium hydroxide and potassium hydroxide are preferable.

The amount of base used may be equal to or more than 1 time mole per mole of the compound of the general formula [11] or salts thereof, and is preferably 1 to 3 times mole.

This reaction is preferably performed by an addition of water.

The amount of water added may be equal to or more than 1 time mole per mole of the compound of the general formula [11] or salts thereof, is preferably 0.1 to 10 times (v/w), and is more preferably 0.3 to 2 times (v/w) in order to make it have the function of solvent.

The reaction temperature is not particularly limited, but it may be from 0°C to equal to or less than the boiling point of solvent, and is preferably 10 to

40°C.

The reaction time is not particularly limited, but may be for 10 minutes to 50 hours, and is preferably for 1 to 24 hours.

5 [0071]

The compound of the formula [14] or salts thereof obtained in this way can be isolated from the reaction mixture after the termination of the reaction in the usual manner.

10 For example, after the termination of the reaction, it can be isolated by acidification with a diluted hydrochloric acid, extraction with organic solvent such as toluene, and subsequent removal of solvent.

15 In addition, it can be isolated as a salt by the way of an addition of base into the extract.

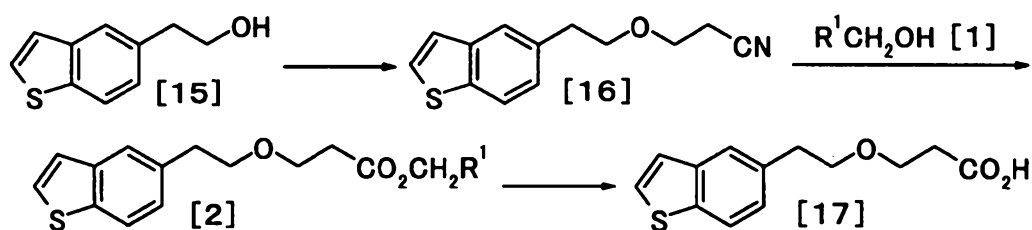
As the salt of the compound of the formula [14], the salt, if it is usually known for a salt in acidic group such as carboxyl group, is not particularly limited, but for examples, salts with alkali metal such as sodium, potassium, cesium and the like;  
salts with alkali earth metal such as calcium, magnesium and the like;  
25 ammonium salts,  
and salts with nitrogen containing organic base such as trimethyl amine, triethylamine, tributylamine, N,N-diisopropylethylamine, pyridine, N-methylpiperidine, N-

methylmorpholine, diethylamine, dicyclohexylamine and the like; are given.

As a preferable salt, a salt with alkali metal such as sodium and potassium is given, and a sodium salt is  
5 preferable.

[0072]

[Production process 5]



wherein  $R^1$  has the same meanings as the above.

[0073]

10                    3-(2-(1-benzothiophen-5-yl)ethoxy)propionic  
acid of the compound of the formula [17] or salts  
thereof can be produced by subjecting the compound of  
the formula [15] to Michael addition reaction with  
acrylonitrile in the presence of base to obtain the  
15 compound of the formula [16], subsequently subjecting  
the compound of the formula [16] to reaction with the  
alcohol of the general formula [1] in the presence of  
acid, subsequently deriving it to the compound of  
general formula [2], and subjecting the compound of  
20 general formula [2] to hydrolysis reaction in the  
presence of base.

[0074]

The present process for production is explained below in detail.

Michael addition reaction:

The compound of the formula [16] can be produced by  
5   subjecting the compound of the formula [15] to Michael  
addition reaction with acrylonitrile in the presence of  
base.

This reaction is usually carried out in the  
presence of solvent, the solvent used, if it does not  
10   affect an influence on the reaction, is not  
particularly limited, but for example, aliphatic  
hydrocarbons such as hexane, cyclohexane and the like;  
aromatic hydrocarbons such as benzene, toluene, xylene  
and the like;  
15   halogenated hydrocarbons such as dichloromethane,  
chloroform and the like;  
ethers such as tetrahydrofuran, 1,2-dimethoxyethane,  
bis(2-methoxyethyl)ether, dioxane and the like;  
sulfoxides such as dimethyl sulfoxide and the like;  
20   and tertiary alcohols such as tert-butanol, tert-amyl  
alcohol and the like; are given, and these may be used  
in admixture.

As a preferable solvent, a sole solvent of  
aromatic hydrocarbons and a mixed solvent of aromatic  
25   hydrocarbons, ethers and tertiary alcohols are given, a  
sole solvent of aromatic hydrocarbons, a mixed solvent  
of aromatic hydrocarbons and ethers, and a mixed  
solvent of aromatic hydrocarbons and tertiary alcohols

are preferable, toluene, a mixed solvent of toluene and tetrahydrofuran, a mixed solvent of toluene and tert-butanol, and a mixed solvent of toluene and tert-amyl alcohol are more preferable.

5           The amount of the solvent used is not particularly limited, but is preferably 0.5 to 10 times volume per weight of the compound of the formula [15], and is more preferably 0.5 to 3 times(v/w).

          In addition, as an additive to these  
10 solvents, primary alcohols such as small amount of methanol and ethanol and the like;  
secondary alcohols such as 2-propanol and the like;  
and water and the like; these may be mixed.

          The amount of the additive used is equal to  
15 or less than 0.5 times volume per weight of the compound of the formula [15], and is preferably equal to or less than 0.1 times(v/w).

[0075]

          As the base used in this reaction, for  
20 example, organic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU),  
tetramethylammonium hydroxide, benzyltrimethylammonium hydroxide and the like;  
metal alkoxide such as sodium methoxide, sodium  
25 ethoxide, potassium tert-butoxide, sodium tert-butoxide  
and the like;  
inorganic base such as sodium hydroxide, potassium hydroxide, sodium hydride and the like; are given.

As a preferable base, organic base and metal alkoxide are given, benzyltrimethylammonium hydroxide and potassium tert-butoxide are more preferable.

The amount of the base used may be equal to  
5 or more than 0.0001 times mole per mole of the compound of the formula [15], and is preferably 0.01 to 0.1 times mole.

[0076]

In addition, this reaction may be carried out  
10 in the presence of catalyst.

As the catalyst used, if desired, quaternary ammonium salt which is usually known is given, tetrabutylammonium bromide, benzyltrimethylammonium chloride and benzyltrimethylammonium bromide are  
15 preferable.

The amount of the catalyst used may be equal to or more than 0.0001 times mole per mole of the compound of the formula [15], and is preferably 0.01 to 0.1 times mole.

20 As the base, for example, in the case that inorganic base such as sodium hydroxide and potassium hydroxide and the like are used, it is preferable to perform this reaction in the presence of catalyst.

The amount of acrylonitrile used in this  
25 reaction may be equal to or more than 1 time mole per mole of the compound of the formula [15], and is preferably 1 to 2 times mole.

The reaction temperature is not particularly

limited, but may be from 0°C to equal to or less than the boiling point of solvent, and is preferably 0 to 35°C.

The reaction time is not particularly limited, but may be for 1 minute to 24 hours, and is preferably for 30 minutes to 4 hours.

The compound of the formula [16] obtained in this way may be used as it is in the next reaction without isolation.

10 [0077]

Esterification reaction:

The compound of the general formula [2] can be produced by subjecting the compound of formula [16] to reaction with the alcohol of the general formula [1] in the presence acid.

As the acid used in this reaction, for example, inorganic acid such as hydrochloric acid, sulfuric acid, hydrogen chloride, hydrogen bromide and the like; and organic sulfonic acid such as methanesulfonic acid, p-toluenesulfonic acid and the like; are given.

As a preferable acid, inorganic acid is given, and sulfuric acid and hydrogen chloride are more preferable.

25 The amount of the acid used is different in the amount of the solvent used, but may be equal to or more than 1 time mole per mole of the compound of the formula [16], and is preferably 2 to 10 times mole.

As the alcohol of general formula [1] used in this reaction, a straight chain alkyl alcohols such as methanol, ethanol, propanol, butanol, pentanol and the like;

5 branched chain alkyl alcohols such as isobutanol and the like;  
substituted alkyl alcohols such as methoxy ethanol, chloroethanol, cyclohexanethanol and the like;  
and aralkyl alcohols such as benzyl alcohol, phenethyl  
10 alcohol and the like; are given.

As a preferable alcohol, straight chain alkyl alcohols are given, and methanol, ethanol, propanol and butanol are more preferable.

The amount of the alcohol used may be equal  
15 to or more than 1 time mole pre mole of the compound of the formula [16], is preferable 0.5 to 10 times(v/w), and is more preferably 0.5 to 5 times(v/w) in order to make it have the function of solvent.

[0078]

20 In this reaction, in the case that inorganic acid such as sulfuric acid and hydrogen chloride and the like;  
and organic sulfonic acid such as methanesulfonic acid and the like; are used, it is preferable to perform the  
25 reaction with an addition of water.

The amount of water added may be equal to or more than 1 time mole per mole of the compound of the formula [16], is preferably 1 to 10 times mole, and is

more preferably 1 to 6 times mole.

This reaction may be performed in the presence of solvent.

As the solvent used, it is not particularly limited, but the same as Michael addition reaction is given.

The reaction temperature is not particularly limited, but may be from 0°C to equal to or less than the boiling point of solvent, and is preferably 20 to 150°C.

The reaction time is not particularly limited, but may be for 10 minutes to 50 hours, and is preferably for 1 to 24 hours.

The compound of the general formula [2] obtained in this way may be used as it is to the next reaction without isolation.

[0079]

#### Hydrolysis reaction:

The compound of the general formula [17] or salts thereof can be produced by hydrolyzing the compound of formula [2] in the presence of base.

This reaction is usually carried out in the presence of solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, but for example, aliphatic hydrocarbons such as hexane, cyclohexane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like;

halogenated hydrocarbons such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran, 1,2-dimethoxyethane, dioxane and the like;

5 sulfoxides such as dimethyl sulfoxide and the like; alcohols such as methanol, ethanol, propanol, butanol, 2-propanol, tert-butanol and the like; and water and the like; are given, and these solvents may be used in admixture.

10 As a preferable solvent, a mixed solvent of the solvent used in the esterification reaction and alcohols, and a mixed solvent of alcohols water are given, and a mixed solvent of toluene and methanol, and a mixed solvent of methanol and water are more preferable.

15 The amount of the solvent used is not particularly limited, but is preferably 0.5 to 10 times volume per weight of the compound of the general formula [2], and is more preferably 0.5 to 3 times(v/w).

20 As the base used in this reaction, for example, metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium tert-butoxide and the like; and inorganic base such as sodium hydroxide, potassium  
25 hydroxide, barium hydroxide, sodium carbonate, potassium carbonate and the like; are given.

As a preferable base, inorganic base is given, and sodium hydroxide and potassium hydroxide are

preferable.

The amount of the base used may be equal to or more than 1 time mole per mole of the compound of the general formula [2], and is preferably 1 to 3 times  
5 mole.

This reaction is preferably performed with an addition of water.

The amount of water added may be equal to or more than 1 time mole per mole of the compound of the  
10 general formula [2], is preferably 0.1 to 10 times(v/w), and is more preferably 0.3 to 2 times(v/w) in order to make it have the function of solvent.

The reaction temperature is not particularly limited, but may be from 0°C to equal to or less than  
15 the boiling point of solvent, and is preferably 10 to 40°C.

The reaction time is not particularly limited, but may be for 10 minutes to 50 hours, and is preferably 1 to 24 hours.

20 [0080]

The compound of the formula [17] or salts thereof obtained in this way can be isolated from the reaction mixture after the termination of the reaction in the usual manner.

25 For example, after the termination of the reaction, it can be isolated by acidification with diluted hydrochloric acid, subsequent extraction with organic solvent such as toluene and removal of solvent.

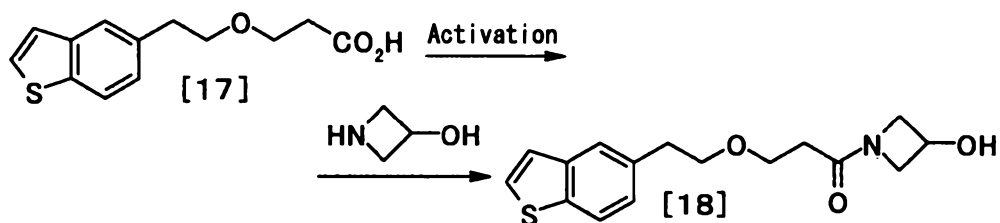
In addition, it can be isolated as a salt by an addition of base into the extract.

As the salt of the compound of the formula [17], the salt, if it is usually known for a salt in  
5 acidic group such as carboxyl group, is not particularly limited, but for example, salts with alkali metal such as sodium, potassium, cesium and the like;  
salts with alkali earth metal such as calcium,  
10 magnesium and the like;  
ammonium salt,  
and salts with nitrogen containing organic base such as trimethyl amine, triethylamine, tributylamine, N,N-diisopropylethylamine, pyridine, N-methylpiperidine, N-  
15 methylmorpholine, diethylamine, dicyclohexylamine and the like; are given.

As a preferable salt, a salt with alkali metal such as sodium and potassium and the like is given, and a sodium salt is more preferable.

20 [0081]

[Production processes 6]



25 1-(3-(2-(1-benzothiophen-5-

yl)ethoxy)propionyl)azetidin-3-ol of the compound of the formula [18] can be produced by deriving the compound of the formula [17] or salts thereof to a reactive derivative, subsequently subjecting the  
5 reactive derivative to amidation reaction with 3-azetidinol or salts thereof in the presence of base.  
[0082]

The present process for production is explained below in detail.

10 [0083]

Derivation to reactive derivative:

The compound of formula [17] or salts thereof can be derived to a reactive derivative by reacting it with an activator.

15 As the reactive derivative, for example, an acid halide, an acid anhydride, an activated amide and an activated ester and the like; are given, and an acid halide is preferable.

As the process of deriving it to the reactive  
20 derivative, for example, the derivation to the acid halide with the use of a halogenating agent such as thionyl chloride, oxalyl chloride, phosphorus trichloride, phosphorous pentachloride and the like; the derivation to the acid anhydride by condensation  
25 with an acid halide such as ethyl chloroformate, isobutyl chloroformate, pivaloyl chloride and the like; the derivation to the activated amide by use of imidazole condensation and an activated amidation agent

such as carbonyldiimidazole and the like;  
and the derivation to the activated ester by  
condensation with p-nitrophenol, 2-  
mercaptobenzothiazole and the like; are given.

5           As the derivation to the reactive derivative,  
the derivation to the acid halide by use of a  
halogenating agent is preferable, and the derivation to  
the acid chloride by use of thionyl chloride is more  
preferable.

10           The amount of the activator used in this  
derivation is different in the kind of the activator,  
but for example, in the case of thionyl chloride, it  
may be equal to or more than 0.5 times mole per mole of  
the compound of the formula [17] or salts thereof, and  
15 is preferably 1 to 2 times mole.

          This reaction is usually carried out in the  
presence of solvent, the solvent used, if it does not  
affect an influence on the reaction, is not  
particularly limited, but for example, aliphatic  
20 hydrocarbons such as hexane, cyclohexane and the like;  
aromatic hydrocarbons such as benzene, toluene, xylene  
and the like;  
halogenated hydrocarbons such as dichloromethane,  
chloroform and the like;  
25 ethers such as tetrahydrofuran, 1,2-dimethoxyethane,  
bis(2-methoxyethyl)ether, dioxane and the like;  
amides such as N,N-dimethylformamide, N,N-  
dimethylacetamide, 1-methyl-2-pyrrolidone and the like;

sulfoxides such as dimethyl sulfoxide and the like;  
esters such as methyl acetate, ethyl acetate and the  
like;

ketones such as acetone, 2-butanone and the like;

5 and nitriles such as acetonitrile and the like; are  
given, and these may be used in admixture.

As a preferable solvent, aromatic  
hydrocarbons such as benzene, toluene and xylene and  
the like and ethers such as tetrahydrofuran, 1,2-  
10 dimethoxyethane, bis(2-methoxyethyl)ether, dioxane and  
the like are given, and toluene and 1,2-dimethoxyethane  
are preferable.

The amount of the solvent used is not  
particularly limited, but is preferably 1 to 20 times  
15 volume per weight of the compound of the formula [17]  
or salts thereof, and is more preferably 1 to 10  
times (v/w).

The reaction temperature is not particularly  
limited, but is preferably -60 to 150°C, and is more  
20 preferably -30 to 120°C.

The reaction time is not particularly  
limited, but is for 10 minutes to 50 hours, and is  
preferably 30 minutes to 20 hours.

The reactive derivative of the compound of  
25 the formula [17] or salts thereof derived in this way  
can be isolated and purified, but it is preferable to  
proceed to the next reaction without isolation.

[0084]

Amidation reaction:

The compound of the formula [18] can be produced by reacting the solution of the reactive derivative of the compound of the formula [17] or salts thereof described  
5 above with 3-azetidinol or salts thereof in the presence of base.

As the base used in this reaction, for example, organic base such as triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-  
10 ene(DBU), pyridine and the like; and inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate and the like; are given.

15 As a preferable base, inorganic base is given, and sodium hydroxide is more preferably.

The amount of the base used may be equal to or more than 1 time mole per mole of the compound of the formula [17] or salts thereof, and is preferably 1  
20 to 10 times mole.

The amount of 3-azetidinol or salts thereof may be equal to or more than 1 time mole per mole of the compound of the formula [17] or salts thereof, and is preferably 1 to 2 times mole.

25 In addition, it is preferable to use 3-azetidinol or salts thereof in aqueous solution.

The amount of water having 3-azetidinol or salts thereof dissolved is not particularly limited,

but is preferably 1 to 20 times volume per weight of the compound of the formula [17] or salts thereof, and is preferably 1 to 10 times (v/w).

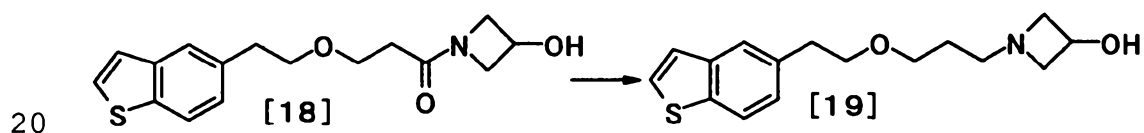
The reaction temperature is not particularly limited, but is preferably -60 to 100°C, and is more preferably -30 to 50°C.

The reaction time is not particularly limited, but is for 10 minutes to 50 hours, and is preferably for 30 minutes to 20 hours.

After the termination of the reaction, the compound of the formula [18] obtained in this way can be isolated and purified by crystallization from the reaction mixture by performing treatments such as neutralization of the reaction mixture and dilution with water if necessary, and subsequent operation of warming and cooling.

[0085]

[Production process 7]



1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol of the compound of the formula [19] or salts thereof can be produced by subjecting the compound of the formula [18] to reduction reaction with an addition of activator such as a protonic acid, a methylating agent and a silylating agent and the like in the presence of

alkali metal borohydride.

This reaction is usually carried out in the presence of solvent, the solvent used, if it does not affect an influence on the reaction, is not particularly limited, but for example, ethers such as tetrahydrofuran, 1,2-dimethoxyethane, bis(2-methoxyethyl)ether, dioxane and the like; is given, and tetrahydrofuran is more preferable.

In addition, these solvents may be used in admixture of halogenated hydrocarbons such as dichloromethane, chloroform and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; and aliphatic hydrocarbons such as hexane, cyclohexane, octane and the like.

The amount of the solvent used is preferably 1 to 20 times volume per weight of the compound of the formula [18], and is more preferably 3 to 10 times (v/w).

[0086]

As the alkali metal borohydride used in this reaction, for example, sodium borohydride, lithium borohydride, potassium borohydride and the like; are given, and sodium borohydride is preferable.

The amount of the alkali metal borohydride is preferably 1 to 10 times mole per mole of the compound of the formula [18], and is more preferably 2 to 3 times mole.

[0087]

As the activator used in this reaction, for example, protonic acid such as sulfuric acid, hydrogen chloride, trifluoroacetic acid and the like;

5 methylating agent such as dimethyl sulfate and the like;

and silylating agent such as trimethylsilyl chloride and the like; are given.

As a preferable activator, protonic acid such  
10 as sulfuric acid, hydrogen chloride and the like; is given, and sulfuric acid is more preferable.

The amount of the activator used is different in the kind of the activator, but for example, in the case of sulfuric acid, it is preferably 0.5 to 1 times  
15 mole per mole of alkali metal borohydride, and is more preferably 0.5 to 0.6 times mole.

In addition, the addition time of the activator is different in the kind of the activator, but in the case of sulfuric acid, it is preferably for  
20 10 minutes to 6 hours, and is more preferably for 30 minutes to 4 hours.

In addition, the activator may be dissolved in solvent appropriately, and the dissolved solvent may be added.

25 [0088]

Further, in the case that the amount of the alkali metal borohydride is 2.0 to 2.2 times mole per mole of the compound of the formula [18] and the amount

of sulfuric acid is 0.5 to 0.6 times mole per mole of the alkali metal borohydride and the dropping time of the sulfuric acid is 1 to 4 hours, the compound of the formula [19] or salts thereof having high purity can be  
5 obtained because of the further suppression of the formation of by-products  
[0089]

The reaction temperature is not particularly limited, but may be -20 to 150°C, and is preferably 0 to  
10 70°C.

After an addition of activator at 0 to 30°C, it is preferable to react at 30 to 70°C, and after an addition of activator at 0 to 30°C, it is more preferable to react at 40 to 60°C.

15 The reaction time is not particularly limited, but may be for 10 minutes to 50 hours, is preferably for 1 to 20 hours.  
[0090]

In the present invention, as a preferable  
20 process for production, the following process is given,  
the process by suspending the compound of the formula [18] in ether (3-10 times(v/w)), adding alkali metal borohydride(2 to 3 times mole), adding activator at 0 to 30°C, and subsequently reacting at 30 to 70°C  
25 for 1 to 20 hours is preferable, the process by suspending the compound of the formula [18] in ether (3 to 10 times(v/w)), adding sodium borohydride (2 to 3 times mole), adding protonic acid (0.5 to 1 times mole

per mole of sodium borohydride) at 0 to 30°C, and subsequently reacting at 30 to 70°C for 1 to 20 hours is more preferable, and the process by suspending the compound of formula [18] in tetrahydrofuran (3 to 10  
5 times(v/w)), adding sodium borohydride (2.0 to 2.2 times mole), adding sulfuric acid (0.5 to 0.6 times mole per mole of sodium borohydride), adding sulfuric acid at 0 to 30°C for 1 to 4 hours, and subsequently reacting at 40 to 60°C for 1 to 20 hours is further  
10 preferable.

[0091]

After the termination of the reaction, the compound of the formula [19] or salts thereof obtained in this way can be isolate in usual manner.

15 For example, after the termination of the reaction, it can be isolated by adding 6.0mol/L hydrochloric acid to decompose an excessive reducing agent, cooling to room temperature, subsequently making the reaction mixture alkaline with aqueous sodium  
20 hydroxide, extracting with organic solvent such as ethyl acetate, and subsequently removing the solvent from the extract.

In addition, it can be isolated as a salt by an addition of acid into the extract.

25 [0092]

As the salt of the compound of the formula [19], the salt, if it is usually known for a salt in basic group such as amino group, is not particularly

limited, but for example, salts with mineral acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and the like;

salts with organic carboxylic acid such as formic acid,  
5 acetic acid, citric acid, oxalic acid, fumaric acid, maleic acid, succinic acid, malic acid, tartaric acid, aspartic acid, trichloroacetic acid, trifluoroacetic acid and the like;

and salts with sulfonic acid such as methanesulfonic  
10 acid, benzenesulfonic acid, toluenesulfonic acid, mesitylene sulfonic acid, naphthalenesulfonic acid and the like; are given.

As a preferable salt, a pharmacologically acceptable salt is given, and a salt with maleic acid  
15 is more preferable.

[0093]

In the compound of the present invention, if isomer (for example, optical isomer), hydrate, solvate and various kinds of crystalline forms exist, the  
20 present invention includes these all.

In addition, in the compound used by the process for production described above, if isomer (for example, optical isomer), hydrate, solvate and various kinds of crystal form exist, all these can be used in  
25 the process for production of the present invention.

#### Examples

[0094]

Next, the present invention will be described in the following reference examples and examples. However, the present invention is not intended to be limited thereto.

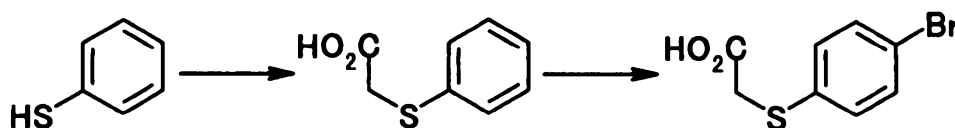
5 The mixing ratios in the eluents are by volume. A case without description in particular, the carrier in silica gel column chromatography is B.W. silica gel, BW-127ZH or PSQ100B(product of Fuji Silysia Chemical Ltd.).

10 The abbreviations in examples mean the following:  
Me: methyl, Et: ethyl, Pr: propyl, Bu: butyl, <sup>t</sup>Bu: tert-butyl  
DMSO-d<sub>6</sub>: dimethylsulfoxide-d<sub>6</sub>

[0095]

#### Reference Example 1

15



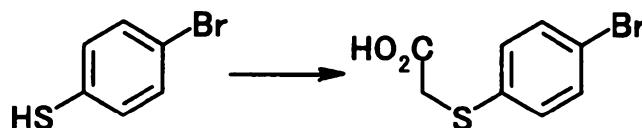
To water(275mL) suspension of 546g of thiophenol was dropwise added water(550mL) solution of  
20 585g of potassium hydroxide at no more than 20°C. Next, thereto was dropwise added a water(825mL) solution of 492g of chloroacetic acid, which was then stirred at 80 to 90°C for 3 hours. After cooling the reaction mixture, the pH was adjusted to 1.5 with hydrochloric  
25 acid, and thereto were added 1650mL of dichloromethane and 550mL of water. The organic layer was separated, and anhydrous magnesium sulfate was added. Insoluble

matter was filtered off, and to the filtrate was added 5.95g of iron(III) chloride, and dropwise added 832g of Bromine at 5 to 10°C, which was then stirred at room temperature for 5 hours. After cooling the reaction solution to 5°C, thereto was dropwise added water(825mL) solution of 187g of sodium sulfite, and the pH was adjusted 1.2 with hydrochloric acid. After stirring at 5 to 10°C for 1 hour, the precipitate was collected by filtration to provide solid matter. To this solid matter was added 2000mL of toluene, from which water was removed by heating and azeotropic distillation. The reaction mixture was cooled to 5°C over a period of 2 hours. After stirring at the same temperature for 1 hour, crystals precipitate was collected by filtration to provide 1108g of (4-bromophenylthio)acetic acid as white solid form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value: 3.65(2H,s), 7.25-7.35(2H,m), 7.40-7.50(1H,m)

[0096]

Reference Example 2

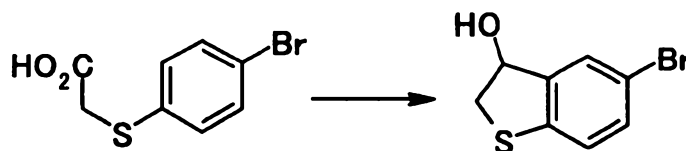


To water(600mL) solution of 88.9g of sodium hydroxide was added 200g of 4-bromothiophenol and dropwise added water(300mL) solution of 105g of chloroacetic acid, which was then stirred at 60 to 70°C

for 1 hour. After cooling the reaction mixture to 40°C, thereto were added 140mL of hydrochloric acid and 600mL of toluene, which was then heated to 80°C. The organic layer was separated and slowly cooled to 5°C. After  
5 stirring at the same temperature for 1 hour, the crystals precipitate was collected by filtration to provide 243g of (4-bromophenylthio)acetic acid as white solid form.

The Chemical shift values of <sup>1</sup>H-NMR spectral  
10 in CDCl<sub>3</sub> agreed with the values of reference example 1.  
[0097]

Example 1-1



15

To dichloromethane(750mL) suspension of 250g of (4-bromophenylthio)acetic acid were added 2.5mL of N, N-dimethylformamide and 132g of thionyl chloride, which was then refluxed for 1 hour. After cooling the  
20 reaction mixture to 20°C, thereto was dropwise added dichloromethane(1500mL) suspension of 148g of aluminum chloride at 5 to 15°C, which was then stirred at 15 to 25°C for 1.5 hours. Next, this reaction mixture was added dropwise to a mixed solution of 1310mL of water  
25 and 188mL of hydrochloric acid under cooling. The organic layer was separated, thereto was added 1250mL of water, and the pH was adjusted to 3.0 with 5%

potassium carbonate aqueous solution. The organic layer was separated and cooled to 5°C. Thereto were added 15.3g of sodium borohydride and 500mL of methanol, which was then stirred at 10 to 20°C for 2  
5 hours. To the reaction solution was added 750mL of water, followed by adjustment to pH7.0 using acetic acid and left unattended in room temperature overnight. To the reaction solution was added 200mL of 5% potassium hydroxide aqueous solution, and the organic  
10 layer was separated. To the organic layer was 25.0g of activated carbon, which was then stirred at room temperature. Insoluble matter was filtered off, and the solvent of filtrate was distilled off. To the resultant residue was added cyclohexane, the crystals  
15 precipitated were collected by filtration to provide 194g of 5-bromo-2,3-dihydro-1-benzothiophen-3-ol as pale red solid form.

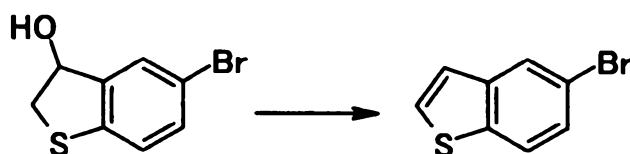
$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

2.18 (1H, d, J=8.3Hz), 3.30 (1H, dd, J=12.0, 4.4Hz), 3.61 (1H, dd,  
20 J=12.0, 6.3Hz), 5.30-5.40 (1H, m), 7.11 (1H, d, J=8.3Hz),  
7.35 (1H, dd, J=8.3, 2.0Hz), 7.50 (1H, d, J=2.0Hz)

[0098]

Example 1-2

25



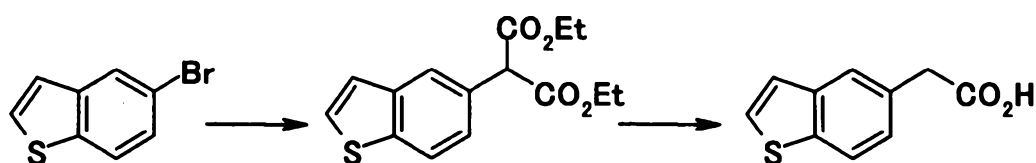
To acetone(600mL) solution of 300g of 5-bromo-2,3-dihydro-1-benzothiophen-3-ol was added 12.4g of p-toluenesulfonic acid monohydrate, which was then refluxed for 2 hours. To the reaction solution was added 15.0g of activated carbon, which was then stirred. Insoluble matter was filtered off and washed with 300mL of acetone. The filtrate and washings were combined, to which was dropwise added 2700mL of water at 5 to 15°C. The precipitate was collected by filtration to provide 268g of 5-bromo-1-benzothiophene as pale purple solid form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

7.27 (1H, d, J=5.4Hz), 7.44 (1H, dd, J=8.5, 1.9Hz), 7.48 (1H, d, J=5.4Hz), 7.74 (1H, d, J=8.5Hz), 7.97 (1H, d, J=1.9Hz)

[0099]

Example 2-1



(1) To 1,2-dimethoxyethane(10mL) suspension of 0.02g of tris(dibenzylideneacetone)dipalladium(0) were added 0.11g of 10%(w/w)tri(tert-butyl)phosphine/hexane, 1.76g of cesium carbonate, 0.50g of 5-bromobenzothiophene and 0.45g of diethyl malonate, which was then refluxed for 2 hours. To the reaction mixture were added water and ethyl acetate, followed by adjustment to pH2 using 2mol/L hydrochloric acid. The

organic layer was separated, and dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The resultant residue was purified using silica gel column chromatography

5 (eluent; hexane:ethyl acetate = 10:1) to provide 0.69 g of diethyl 2-(1-benzothiophen-5-yl)malonate as white solid form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

1.27(6H,t,J=7.1Hz), 4.1-4.3(4H,m), 4.73(1H,s), 7.33  
10 (1H,d,J=5.4Hz), 7.40(1H,dd,J=8.3,2.0Hz), 7.45(1H,d,J=5.4Hz), 7.87(1H,d,J=8.3Hz), 7.87(1H,d,J=2.0Hz)

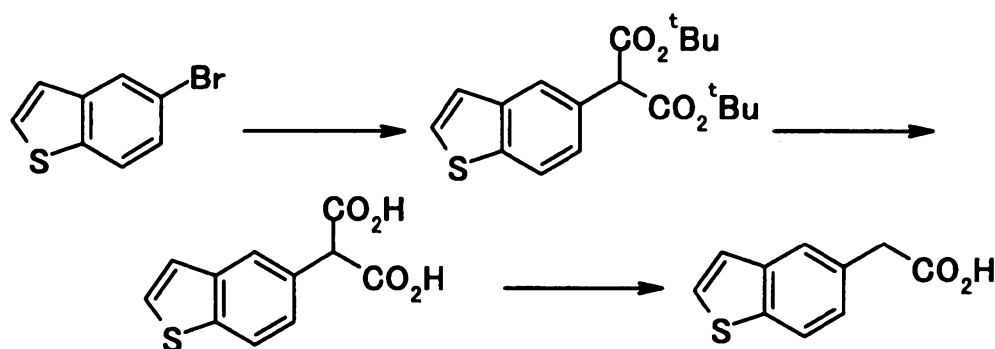
(2) To ethylene glycol(1.0mL) suspension of 0.25g of diethyl 2-(1-benzothiophen-5-yl)malonate were added 1.0mL of 40%(w/w) potassium hydroxide aqueous solution  
15 and 0.3mL of water, which was then refluxed for 2 hours. To the reaction mixture were added water and toluene, and the aqueous layer was separated. The pH was adjusted to 2 with 6mol/L hydrochloric acid, and thereto was added ethyl acetate. The organic layer was  
20 separated, and dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The resultant residue was suspended to 5mL of xylene, and thereto was added 0.01g of p-toluenesulfonic acid monohydrate, which was then  
25 refluxed for 30 minutes. The solvent was distilled off under reduced pressure, and to the resultant residue were added toluene and cyclohexane. The precipitate was collected by filtration to provide 0.02g of 2-(1-

benzothiophen-5-yl)acetic acid as pale yellow solid form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

3.76(2H,s), 7.2-7.3(1H,m), 7.29(1H,d,  $J=5.4\text{Hz}$ ),  
 5 7.44(1H,d,  $J=5.4\text{Hz}$ ), 7.73(1H,s), 7.83(1H,d,  $J=8.1\text{Hz}$ )  
 [0100]

Example 2-2



10

(1) To 1,2-dimethoxyethane(10mL) solution of 0.11g of 10%(w/w)tri(tert-butyl)phosphine/hexane were added 0.02g of tris(dibenzylideneacetone)dipalladium(0), 1.76g of cesium carbonate, 0.50g of 5-bromobenzothiophene and 0.61g of tert-butyl malonate, which was then refluxed for 2 hours. Next, thereto were added 0.02g of tris(dibenzylideneacetone)dipalladium(0) and 0.11g of 10%(w/w)tri(tert-butyl)phosphine/hexane, which was then  
 15 refluxed for 1 hour. This reaction mixture was added to a mixed solution of 30mL of water and 20mL of ethyl acetate, and the pH was adjusted to 3 with 6mol/L hydrochloric acid. The organic layer was separated,  
 20

and dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The resultant residue was purified using silica gel column chromatography (eluent; hexane: ethyl acetate = 20:1)

5 to provide 0.49 g of di(tert-butyl) 2-(1-benzothiophen-5-yl)malonate as white solid form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

1.47(18H,s), 4.55(1H,s), 7.32(1H,d,J=5.4Hz), 7.39(1H,dd,J=8.5,1.7Hz), 7.43(1H,d,J=5.4Hz), 7.84(1H,d,J=1.7Hz), 7.86(1  
10 H,d,J=8.5Hz)

(2) To toluene(2.5mL) solution of 0.25g of di(tert-butyl) 2-(1-benzothiophen-5-yl)malonate was added 0.01g of p-toluenesulfonic acid monohydrate, which was then refluxed for 1 hour. After cooling the  
15 reaction mixture, the precipitate was collected by filtration to provide 0.14g of 2-(1-benzothiophen-5-yl)malonic acid as white solid form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

4.80(1H,s), 7.3-7.5(1H,m), 7.47(1H,d,J=5.5Hz),  
20 7.77(1H,d,J=5.5Hz), 7.89(1H,s), 7.97(1H,d,J=8.3Hz)

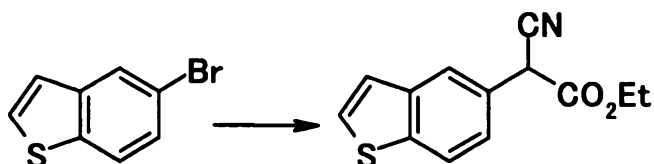
(3) To xylene(2mL) suspension of 0.10g of 2-(1-benzothiophen-5-yl)malonic acid was added 4mg of p-toluenesulfonic acid monohydrate, which was then refluxed for 1 hour. The solvent was distilled off  
25 under reduced pressure, and to the resultant residue was added cyclohexane. The precipitate was collected by filtration to provide 0.08g of 2-(1-benzothiophen-5-yl)acetic acid as white solid form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 2-1(2).

[0101]

Example 2-3

5



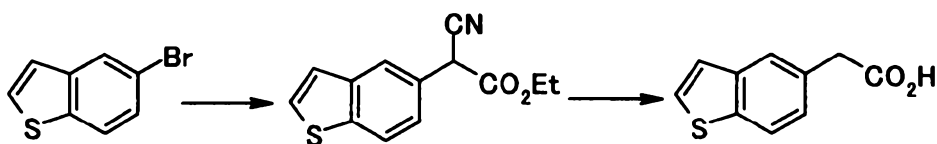
To toluene (3mL) solution of 0.21g of ethyl cyanoacetate were added 0.41g of potassium tert-butoxide, 0.30g of 5-bromobenzothiophene and 0.02g of tetrakis(triphenylphosphine)palladium(0), which was then refluxed for 7.5 hours. To the reaction mixture was added water, and the pH was adjusted to 2 with hydrochloric acid. Thereto was added ethyl acetate, and insoluble matter was filtered off. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The resultant residue was purified using silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to provide 0.16g of ethyl 2-(1-benzothiophen-5-yl)-2-cyanoacetate as pale yellow solid form.

$^1\text{H}$ -NMR( $\text{CDCl}_3$ )  $\delta$  value:

1.29 (3H, t,  $J=7.1\text{Hz}$ ), 4.25 (2H, m), 4.84 (1H, s), 7.37 (1H, d,  $J=5.4\text{Hz}$ ), 7.41 (1H, dd,  $J=8.5, 1.7\text{Hz}$ ), 7.54 (1H, d,  $J=5.4\text{Hz}$ ), 7.92 (1H, d,  $J=8.5\text{Hz}$ ), 7.94 (1H, d,  $J=1.7\text{Hz}$ )

[0102]

## Example 2-4



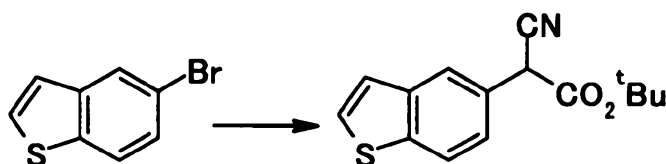
To toluene (25mL) suspension of 0.16g of dichlorobis(triphenylphosphine)palladium(II) were added  
5 0.12g of triphenylphosphine, 0.01g of sodium borohydride, 5.79g of potassium tert-butoxide and 2.92g of ethyl cyanoacetate, which was then stirred at room temperature for 10 minutes. Thereto were added 5.00g of 5-bromobenzothiophene and 25mL of toluene, which was  
10 then refluxed for 4 hours. Thereto was added 0.14g of tetrakis(triphenylphosphine)palladium(0), which was then refluxed for 2 hours. Next, to the reaction solution were added 25mL of ethanol, 2.82g of sodium hydroxide and 5mL of water, which was then refluxed for  
15 6 hours. Thereto was added 2.82g of sodium hydroxide, which was then refluxed for 5 hours. To the reaction mixture were added 15mL of water and 0.5g of activated carbon, and insoluble matter was filtered off. The aqueous layer was separated, and to the solution was  
20 added 35mL of ethanol. The pH was adjusted to 2 with 15mL of hydrochloric acid. Thereto was added 15mL of water, which was then stirred at 40°C. Thereto was added 30mL of water, which was stirred. After that, it was cooled. The precipitate was collected by

filtration to provide 3.38g of 2-(1-benzothiophen-5-yl)acetic acid as pale yellow solid form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 2-1(2).

5 [0103]

Example 2-5



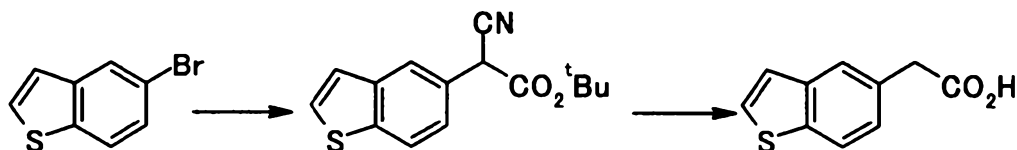
To 1,2-dimethoxyethane(25mL) suspension of 0.16g of dichlorobis(triphenylphosphine)palladium(II) were added 0.12g of triphenylphosphine, 0.01g of sodium borohydride, 5.53g of potassium tert-butoxide and 3.48g of tert-butyl cyanoacetate, which was then stirred at room temperature for 10 minutes. Thereto was added 5.00g of 5-bromobenzothiophene, which was then refluxed for 2 hours. After to the reaction mixture was added 15 15mL of water, the pH was adjusted to 1 with 2mL of hydrochloric acid. The precipitate was collected by filtration to provide 5.69g of tert-butyl 2-(1-benzothiophen-5-yl)-2-cyanoacetate as pale yellow solid form.

20  $^1\text{H}$ -NMR( $\text{CDCl}_3$ )  $\delta$  value:

1.45(9H,s), 4.73(1H,s), 7.36(1H,d,J=5.6Hz), 7.39(1H,dd,J=8.5,2.0Hz), 7.52(1H,d,J=5.6Hz), 7.91(1H,d,J=8.5Hz), 7.9-8.0(1H,m)

[0104]

## Example 2-6

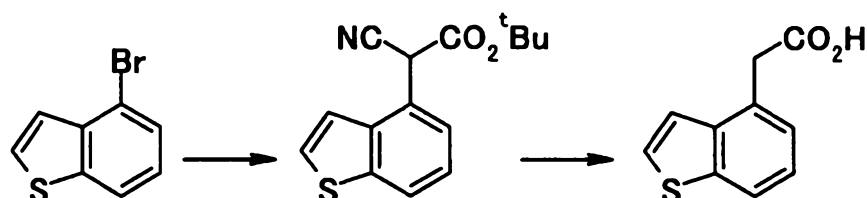


To 1,2-dimethoxyethane(1.00L) solution of 250g of 5-bromobenzothiophene were added 276g of potassium tert-butoxide and 174g of tert-butyl cyanoacetate. Thereto were added 8.23g of dichlorobis(triphenylphosphine)palladium(II) and 6.15g of triphenylphosphine at 80 to 85°C, which was then refluxed for 2 hours. Next, to the reaction mixture were added 500mL of ethylene glycol, 250mL of water and 263g of potassium hydroxide, which was then refluxed for 4 hours. To the reaction mixture were added 1.50L of water and 12.5g of kieselguhr (cellpure, product of Advanced Minerals Company). After insoluble matter was filtered off, to the filtrate was added 250mL of toluene, and the aqueous layer was separated. To the aqueous layer were added 375mL of toluene and 375mL of ethyl acetate, the pH was adjusted to 1 with 505mL of hydrochloric acid, and the organic layer was separated. The organic layer was treated with 12.5g of activated carbon. The solvent was distilled off under reduced pressure, to which was added toluene. The precipitate was collected by filtration to provide 176g of 2-(1-benzothiophen-5-yl)acetic acid as white solid form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 2-1(2).

[0105]

Example 2-7



5 To 1,2-dimethoxyethane(3mL) solution of 0.30g of 4-bromobenzothiophene were added 0.33g of potassium tert-butoxide, 0.21g of tert-butyl cyanoacetate, 0.01g of dichlorobis(triphenylphosphine)palladium(II) and 0.01g of triphenylphosphine, which was then refluxed  
10 for 40 minutes. Thereto were added 0.33g of potassium tert-butoxide, 0.01g of dichlorobis(triphenylphosphine) palladium(II) and 0.01g of triphenylphosphine, which was then refluxed for 30 minutes. The reaction mixture was added to a mixed solution of water and ethyl  
15 acetate, and the pH was adjusted to 1 with 6mol/L hydrochloric acid. The organic layer was separated, and dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure. The resultant residue was purified using silica gel column  
20 chromatography (eluent; hexane:ethyl acetate = 5:1) to provide 0.26g of tert-butyl 2-(1-benzothiophen-4-yl)-2-cyanoacetate as pale brown oily form.

$^1\text{H}$ -NMR( $\text{CDCl}_3$ )  $\delta$  value:

1.42 (9H, s), 5.03 (1H, s), 7.39 (1H, t, J=7.8Hz), 7.49 (1H, d, J=7.8Hz), 7.54 (1H, d, J=5.6Hz), 7.59 (1H, d, J=5.6Hz), 7.92 (1H, d, J=7.8Hz)

(2) To ethylene glycol (1.0mL) solution of 0.25g  
5 of tert-butyl 2-(1-benzothiophen-4-yl)-2-cyanoacetate  
were added 1.0mL of aqueous solution of  
40% (w/w) potassium hydroxide and 0.3mL of water, which  
was then stirred at 95 to 105°C for 1 hour. To the  
reaction mixture were added water and toluene, and the  
10 aqueous layer was separated. The pH was adjusted to 2  
with 6mol/L hydrochloric acid, to which was added ethyl  
acetate. The organic layer was separated, and dried  
over anhydrous magnesium sulfate, followed by  
distilling off the solvent under reduced pressure. To  
15 the resultant residue was added cyclohexane. The  
precipitate was collected by filtration to provide  
0.15g of 2-(1-benzothiophen-4-yl)acetic acid as white  
solid form.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ value:

20 3.95 (2H, s), 7.2-7.4 (2H, m), 7.41 (1H, d, J=5.5Hz),  
7.47 (1H, d, J=5.5Hz), 7.82 (1H, d, J=7.8Hz)

[0106]

Example 3-1



To 340mL of tetrahydrofuran was suspended

50.2g of sodium borohydride, to which were dropped tetrahydrofuran(340mL) solution of 170g of (1-benzothiophen-5-yl)acetic acid, and 65.1g of sulfuric acid successively, which was then stirred at room temperature for 2.5 hours. To this reaction mixture was dropwise added 85mL of acetone, which was then stirred for 30 minutes. Thereto were added 510mL of water and 680mL of toluene. The organic layer was separated, to which was added 510mL of water, and the pH was adjusted to 12 with 48mL of 20%(w/w)sodium hydroxide aqueous solution. The organic layer was separated, and washed with water, followed by distilling off the solvent. Thereto were added cyclohexane and toluene. The precipitate was collected by filtration to provide 135g of 2-(1-benzothiophen-5-yl)ethanol as white solid form.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ value:

1.41(1H,t,J=6.0Hz),2.99(2H,t,J=6.5Hz),3.8-4.0(2H,m),  
7.22(1H,dd,J=8.3,1.7Hz),7.30(1H,d,J=5.4Hz),7.44(1H,d,J=5.4Hz),7.6-7.7(1H,m),7.83(1H,d,J=8.3Hz)

[0107]

#### Example 3-2

To 5mL of 1,2-dimethoxyethane was suspended 2.95g of sodium borohydride, to which were dropwise added 1,2-dimethoxyethane(25mL) solution of 10g of (1-benzothiophen-5-yl)acetic acid, and 11mL of 6.9mol/L hydrochloride/1,2-dimethoxyethane solution, which was then stirred at room temperature for 1 hour. To this

reaction mixture was dropwise added 5mL of acetone,  
which was then stirred for 30 minutes. Thereto were  
added 20mL of water, 30mL of toluene and 2mL of 2mol/L  
hydrochloric acid. Next, after the pH was adjusted to  
5 9.5 with 20mL of 2mol/L sodium hydroxide aqueous  
solution, the organic layer was separated. The organic  
layer was dried over anhydrous magnesium sulfate,  
followed by distilling off the solvent. Thereto were  
added cyclohexane and toluene. The precipitate was  
10 collected by filtration to provide 7.84g of 2-(1-  
benzothiophen-5-yl)ethanol as white solid form.

[0108]

#### Example 3-3

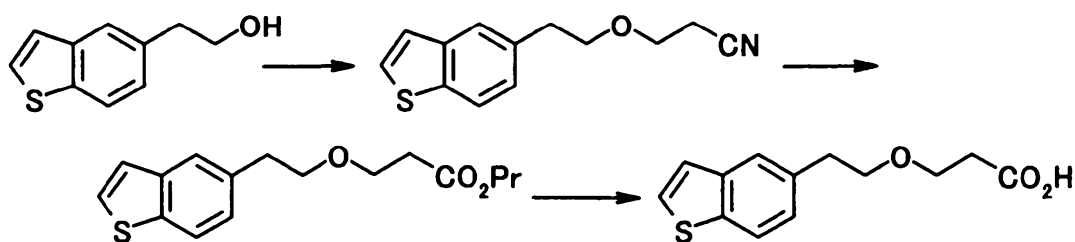
To 40mL of tetrahydrofuran was suspended  
15 4.72g of sodium borohydride, to this solution were  
dropwise added tetrahydrofuran(60mL) solution of 20g of  
(1-benzothiophen-5-yl)acetic acid, and 6.12g of  
sulfuric acid. The solution was heated to 66°C,  
followed by distilling off about 40mL of the solvent  
20 under normal pressure, which was then stirred at same  
temperature for 1 hour. After cooling, to this  
reaction mixture was dropwise added 10mL of acetone,  
which was then stirred for 30 minutes. Thereto were  
added 90mL of water and 80mL of toluene. The organic  
25 layer was separated, to which was added 60mL of water,  
and the pH was adjusted to 13.6 with 5mL of 5mol/L  
sodium hydroxide aqueous solution. The organic layer  
was separated, washed with water, followed by

distilling off the solvent, and thereto were added cyclohexane and toluene. The precipitate was collected by filtration to provide 16.5g of 2-(1-benzothiophen-5-yl)ethanol as white solid form.

5 The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 3-1.

[0109]

Example 4-1



(1) To toluene(5mL) suspension of 0.23g of  
10 40%(w/w)benzyltrimethylammonium hydroxide aqueous solution was added 5.00g of 2-(1-benzothiophen-5-yl)ethanol, and dropwise added 2.20mL of acrylonitrile at 0 to 5°C, which was then stirred at 0 to 20°C for 1 hour. To this reaction mixture was added 0.125mL of  
15 hydrochloric acid. Thereto were added 10mL of propanol, 1.0mL of water and 3.1mL of sulfuric acid, which was then refluxed for 6.5 hours. After cooling, to the reaction mixture were added 10mL of water and 10mL of toluene. The organic layer was separated, and  
20 dried over anhydrous magnesium sulfate. After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. The resultant residue was purified using silica gel column

chromatography (eluent; hexane:ethyl acetate = 15:1 to 7:1) to provide 7.21g of propyl 3-(2-(1-benzothiophen-5-yl)ethoxy)propionate as colorless oily form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

5 0.91 (3H, t, J=7.4Hz), 1.57-1.67 (2H, m), 2.58 (2H, t, J=6.4Hz),  
2.99 (2H, t, J=7.1Hz), 3.71 (2H, t, J=7.1Hz), 3.74 (2H, t, J=6.4Hz),  
, 4.02 (2H, t, J=6.7Hz), 7.20 (1H, dd, J=8.2, 1.6Hz), 7.28 (1H, d,  
J=5.6Hz), 7.41 (1H, d, J=5.6Hz), 7.60-7.70 (1H, m), 7.78  
(1H, d, J=8.2Hz)

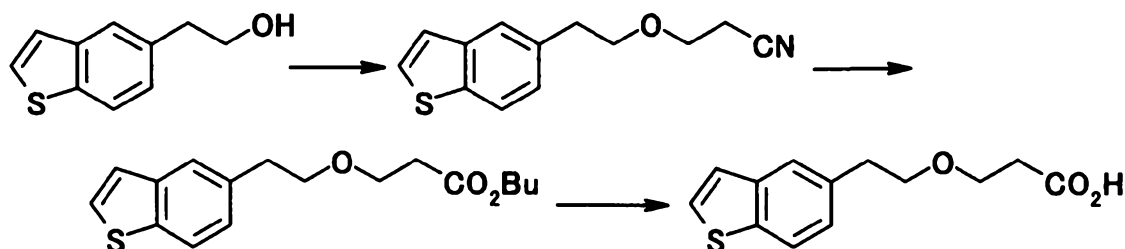
10 (2) To methanol(12mL) solution of 12.0g of propyl  
3-(2-(1-benzothiophen-5-yl)ethoxy)propionate was added  
water(12mL) solution of 2.76g of potassium hydroxide,  
which was then stirred at room temperature for 1.5  
hours. This reaction mixture was distilled off under  
15 reduced pressure, to which were added 36mL of toluene  
and 36mL of water. The pH was adjusted to 1.9 with 8mL  
of 6mol/L hydrochloric acid. The organic layer was  
separated, followed by distilling off the solvent under  
reduced pressure. Thereto were added 12mL of toluene  
20 and 24mL of cyclohexane. The precipitate was collected  
by filtration to provide 8.91g of 3-(2-(1-  
benzothiophen-5-yl)ethoxy)propionic acid as white solid  
form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

25 2.63 (2H, t, J=6.2Hz), 3.00 (2H, t, J=7.1Hz), 3.72 (2H, t, J=7.1Hz),  
, 3.74 (2H, t, J=6.2Hz), 7.20 (1H, dd, J=8.4, 1.6Hz), 7.27 (1H, dd,  
J=5.5, 0.6Hz), 7.40 (1H, d, J=5.5Hz), 7.65-7.70 (1H, m), 7.78  
(1H, d, J=8.4Hz)

[0110]

## Example 4-2



- (1) To toluene(5mL) suspension of 5.00g of 2-(1-benzothiophen-5-yl)ethanol were added 0.23g of
- 5 40%(w/w)benzyltrimethylammonium hydroxide aqueous solution and 2.28mL of tetrahydrofuran, and dropwise added 2.20mL of acrylonitrile at 0 to 10°C, which was then stirred at same temperature for 1.5 hours. To this reaction mixture were added 0.1mL of hydrochloric
- 10 acid, 10mL of butanol and 5mL of 50%(w/w) sulfuric acid, which was then refluxed for 15 hours. After cooling, to the reaction mixture was added 15mL of water. The organic layer was separated, and dried over anhydrous magnesium sulfate. After insoluble matter
- 15 was filtered off, the solvent was distilled off under reduced pressure. The resultant residue was purified using silica gel column chromatography(eluent; hexane:ethyl acetate = 10:1) to provide 6.65g of butyl 3-(2-(1-benzothiophen-5-yl)ethoxy)propionate as
- 20 colorless oily form.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  value:

0.92 (3H,t,J=7.4Hz), 1.30-1.45 (2H,m), 1.50-1.65 (2H,m), 2.57 (2H,t,J=6.3Hz), 2.99 (2H,t,J=7.1Hz), 3.71 (2H,t,J=7.1Hz), 3.

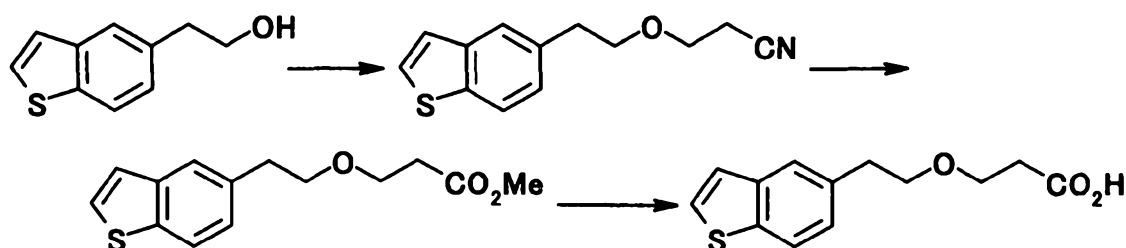
74 (2H, t, J=6.3Hz), 4.06 (2H, t, J=6.7Hz), 7.21 (1H, dd, J=8.3, 1.7Hz), 7.28 (1H, dd, J=5.4, 0.7Hz), 7.41 (1H, d, J=5.4Hz), 7.65-7.70 (1H, m), 7.78 (1H, d, J=8.3Hz)

(2) To methanol (5mL) solution of 5.00g of butyl 3-(2-(1-benzothiophen-5-yl)ethoxy)propionate was added water (5mL) solution of 1.10g of potassium hydroxide, which was then stirred at room temperature for 2 hours. This reaction mixture was distilled off under reduced pressure, to which were added 30mL of toluene and 30mL of water. The pH was adjusted to 1.6 with 3.5mL of 6mol/L hydrochloric acid. The organic layer was separated, followed by distilling off the solvent under reduced pressure. Thereto were added 15mL of toluene and 30mL of cyclohexane. The precipitate was collected by filtration to provide 3.60g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid as white solid form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 4-1(2).

[0111]

Example 4-3



(1) To toluene (5mL) suspension of 5.00g of 2-(1-benzothiophen-5-yl)ethanol were added 0.23g of

40% (w/w) benzyltrimethylammonium hydroxide aqueous solution and 2.28 mL of tetrahydrofuran, and dropwise added 2.22 mL of acrylonitrile at 5°C, which was then stirred at 0 to 15°C for 1.5 hours. To this reaction mixture were added 0.13 mL of hydrochloric acid, 10 mL of methanol and 1.52 g of water. Thereto was introduced 9.47 g of hydrogen chloride, which was then refluxed for 4 hours. After cooling, to the reaction mixture were added 15 mL of water and 10 mL of toluene. The organic layer was separated, and dried over anhydrous magnesium sulfate. After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. The resultant residue was purified using silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to provide 7.36 g of methyl 3-(2-(1-benzothiophen-5-yl)ethoxy)propionate as colorless oily form.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ value:

2.58 (2H, t, J=6.4 Hz), 2.99 (2H, t, J=7.1 Hz), 3.65 (3H, s), 3.71 (2H, t, J=7.1 Hz), 3.74 (2H, t, J=6.4 Hz), 7.20 (1H, dd, J=8.3, 1.7 Hz), 7.28 (1H, d, J=5.4 Hz), 7.41 (1H, d, J=5.4 Hz), 7.65-7.70 (1H, m), 7.78 (1H, d, J=8.3 Hz)

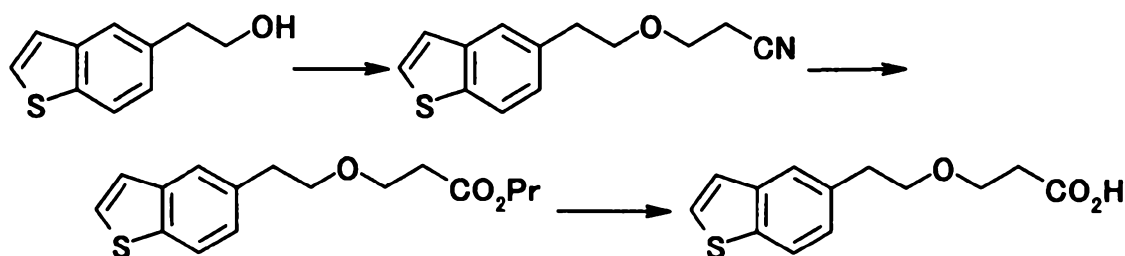
(2) To methanol (5 mL) solution of 5.00 g of methyl 3-(2-(1-benzothiophen-5-yl)ethoxy)propionate was added water (5 mL) solution of 1.27 g of potassium hydroxide, which was then stirred at room temperature for 2 hours. This reaction mixture was distilled off under reduced pressure, to which were added 30 mL of toluene and 30 mL of water. The pH was adjusted to 1.0 with 5 mL of

6mol/L hydrochloric acid. The organic layer was separated, followed by distilling off the solvent under reduced pressure. Thereto were added 11mL of toluene and 30mL of cyclohexane. The precipitate was collected by filtration to provide 4.51g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid as white solid form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 4-1(2).

[0112]

#### Example 4-4

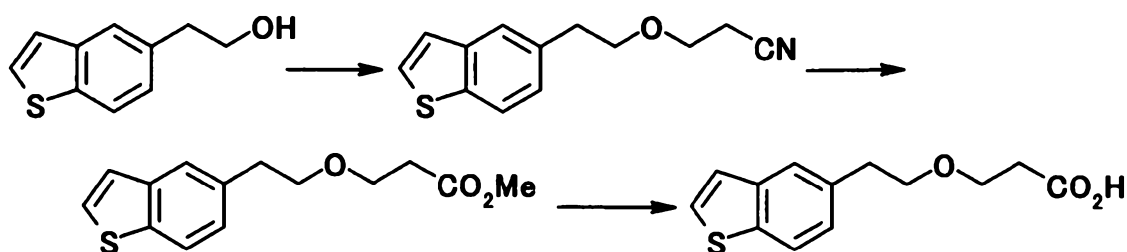


To toluene(50mL) suspension of 50.0g of 2-(1-benzothiophen-5-yl)ethanol was added 2.35g of 40%(w/w)benzyltrimethylammonium hydroxide aqueous solution, and dropwise added 17.9g of acrylonitrile at 8 to 15°C, which was then stirred at 10 to 20°C for 1.5 hours. To this reaction mixture were added 1.25mL of hydrochloric acid, 100mL of propanol and 5.05g of water. Thereto was dropwise added 55.0g of sulfuric acid, which was then refluxed for 6 hours. After cooling, to the reaction mixture was added 100mL of water. The organic layer was separated. Thereto was

added 50mL of methanol and dropwise added water (50mL) solution of 31.5g of potassium hydroxide, which was then stirred at room temperature for 1.5 hours. To this reaction mixture were added 75mL of toluene and 5 75mL of water. The aqueous layer was separated, thereto was added 100mL of toluene, the pH was adjusted to 0.9 with 6mol/L hydrochloric acid, and the organic layer was separated. After the solvent was distilled off under reduced pressure, thereto were added 50mL of 10 toluene and 125mL of cyclohexane. The precipitate was collected by filtration to provide 59.6g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid as white solid form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral 15 in  $\text{CDCl}_3$  agreed with the values of example 4-1(2).  
[0113]

#### Example 4-5



To toluene (260mL) suspension of 260g of 2-(1-benzothiophen-5-yl)ethanol were added 43.8g of 2- 20 propanol and 1.64g of potassium tert-butoxide, which was then stirred for 0.5 hours. After cooling the reaction mixture to 15°C, thereto was dropwise added 116g of acrylonitrile, which was then stirred at 15 to

25°C for 1 hour. To this reaction mixture were added 6.5mL of hydrochloric acid, 520mL of methanol and 78.9g of water. Thereto was introduced 310g of hydrogen chloride at 10 to 25°C, which was then refluxed for 3  
5 hours. After cooling, to the reaction mixture were added 780mL of water and 520mL of toluene, and the organic layer was separated. To the organic layer were dropwise added 260mL of methanol and water(260mL) solution of 164g of potassium hydroxide, which was then  
10 stirred at 30 to 35°C for 2 hours. To this reaction mixture was added 260mL of water, and the aqueous layer was separated. To the aqueous layer were added 520mL of toluene and 260mL of water and dropwise added 234mL of hydrochloric acid, and the organic layer was  
15 separated. After 390mL of solvent was distilled off under reduced pressure from the organic layer, thereto was added 1040mL of cyclohexane. The precipitate was collected by filtration to provide 326g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid as white solid  
20 form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 4-1(2).

[0114]

#### Example 4-6

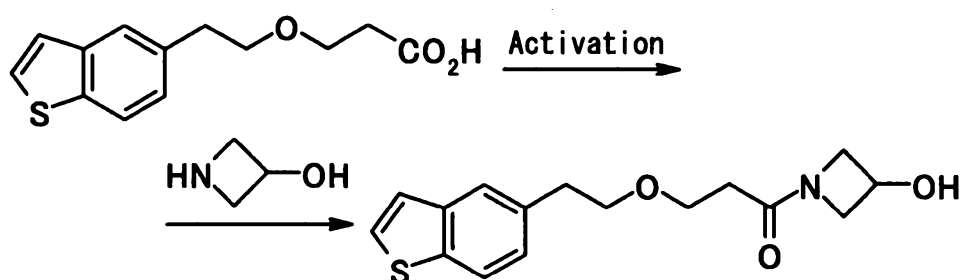
25 To toluene(360mL) suspension of 180g of 2-(1-benzothiophen-5-yl)ethanol was added 4.22g of aqueous solution of 40%(w/w)benzyltrimethylammonium hydroxide, and dropwise added 8.04g of acrylonitrile at 30°C.

After cooling the reaction mixture to 20°C, thereto was dropwise added 53.6g of acrylonitrile, which was then stirred at 15 to 25°C for 2 hours. To this reaction mixture were added 27mL of hydrochloric acid and 180mL of methanol. Thereto was introduced 97g of hydrogen chloride at 10 to 25°C, which was then stirred at 30 to 40°C for 30 minutes and refluxed for 3 hours. After cooling, to the reaction mixture was added 360mL of water, and the organic layer was separated. To the organic layer were dropwise added 180mL of methanol, and water(180mL) solution of 113g of potassium hydroxide, which was then stirred at 30 to 35°C for 2 hours. To the reaction mixture was added 360mL of water, and the aqueous layer was separated. To this aqueous layer was added 360mL of toluene and dropwise added 151mL of hydrochloric acid, and the organic layer was separated. After 126mL of solvent was distilled off under normal pressure from the organic layer, thereto was added 1080mL of cyclohexane. The precipitate was collected by filtration to provide 222g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid as white solid form.

The Chemical shift values of <sup>1</sup>H-NMR spectral in CDCl<sub>3</sub> agreed with the values of example 4-1(2).

[0115]

Example 5-1



In 15mL of 1,2-dimethoxyethane was dissolved  
 5 10.0g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic  
 acid. Thereto were added 0.1mL of N,N-  
 dimethylformamide and 5.23g of thionyl chloride, which  
 was then stirred at room temperature for 1.5 hours.  
 This reaction solution was dropwise added to a mixed  
 10 solution of 50mL of water, 7.19g of sodium hydroxide  
 and 7.69g of 3-azetidinol 1/2 tartrate at 5 to 15°C,  
 which was then stirred at same temperature for 2 hours.  
 Thereto was added 90mL of water. The precipitate was  
 collected by filtration to provide 11.0g of 1-(3-(2-(1-  
 15 benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol as  
 white solid form.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ value:

2.25-2.35 (2H,m), 2.96 (2H,t,J=7.0Hz), 3.65-3.80  
 (5H,m), 3.85-3.95 (1H,m), 4.05-4.15 (1H,m), 4.15-  
 20 4.25 (1H,m), 4.40-4.50 (1H,m), 7.19 (1H,dd,J=8.3,1.5Hz),  
 7.27 (1H,d,J=5.4Hz), 7.40 (1H,d,J=5.4Hz), 7.62-7.66 (1H,m),  
 7.78 (1H,d,J=8.3Hz)

[0116]

Example 5-2

25 To 116mL of toluene was suspended 29.0g of 3-

(2-(1-benzothiophen-5-yl)ethoxy)propionic acid.

Thereto were added 0.6mL of N,N-dimethylformamide and 14.5g of thionyl chloride, which was then stirred at room temperature for 2 hours. After that, 62mL of solvent was distilled off under reduced pressure. This reaction solution was dropwise added to a mixed solution of 87mL of water, 13.9g of sodium hydroxide and 25.7g of 3-azetidinol 1/2 tartrate at 10 to 20°C, which was then stirred at 20 to 25°C for 1 hour and left unattended overnight. After cooling the reaction solution, the pH was adjusted to 6 with 7mL of acetic acid. After stirring at 10 to 15°C for 1 hour, the precipitate was collected by filtration to provide 31.9g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol as white solid form.

The Chemical shift values of <sup>1</sup>H-NMR spectral in CDCl<sub>3</sub> agreed with the values of example 5-1.

[0117]

#### Example 5-3

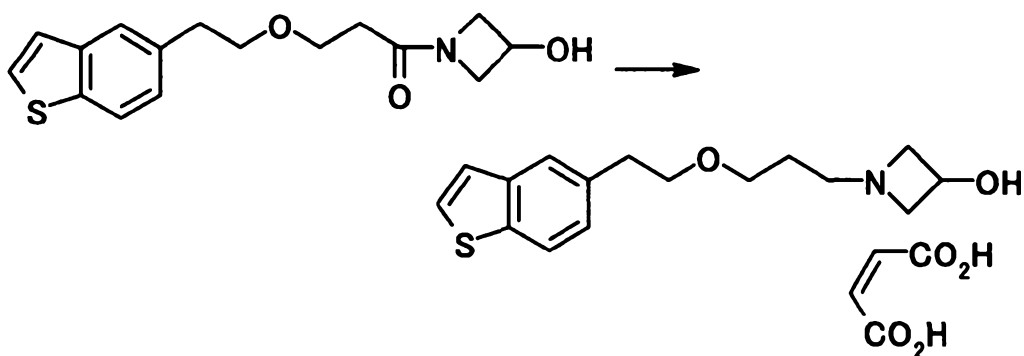
In 75mL of 1,2-dimethoxyethane was dissolved 50.0g of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid. Thereto was added 26.1g of thionyl chloride, which was then refluxed for 2 hours. After cooling, this reaction solution was dropwise added to a mixed solution of 125mL of water, 20.0g of sodium hydroxide and 25.2g of 3-azetidinol hydrochloride at -5 to 10°C, which was then stirred at 0 to 15°C for 30 minutes. Thereto was added 75mL of water, which was heated to

40°C and dissolved. After cooling, the precipitate was collected by filtration to provide 56.5g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol as white solid form.

5 The Chemical shift values of  $^1\text{H}$ -NMR spectral in  $\text{CDCl}_3$  agreed with the values of example 5-1.

[0118]

Example 6-1



To bis(2-methoxyethyl) ether(5mL) suspension  
10 of 1.00g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 0.37g of sodium borohydride, which was then cooled to 10°C. Thereto was dropwise added 2.49mL of chlorotrimethylsilane at 5 to 10°C for 20 minutes, which  
15 was then stirred at room temperature for 2.5h and at 40°C for 4 hours. After cooling, thereto was dropwise added 3.27mL of 6.0mol/L hydrochloric acid, which was then stirred at 70 to 75°C for 30 minutes. To the reaction mixture were added water and ethyl acetate,  
20 and the pH was adjusted to 10.0 with 2.0mol/L sodium

hydroxide aqueous solution. The organic layer was separated, washed sequentially with water and saturated sodium chloride aqueous solution. Thereto were added anhydrous magnesium sulfate and activated carbon.

5 After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 0.36g of maleic acid, which was solidified from a mixed solvent(5mL) of ethyl acetate:2-propanol(4:1) to provide 0.72g of 1-(3-(2-(1-  
10 benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ value:

1.65-1.75(2H,m), 2.93(2H,t, J=6.9Hz), 3.14(2H,t, J=7.4Hz),  
3.44(2H,t, J=6.0Hz), 3.63(2H,t, J=6.9Hz), 3.75-3.85(2H,m),  
15 4.15-4.25(2H,m), 4.40-4.50(1H,m), 6.06(2H,s), 7.26  
(1H,dd, J=8.3, 1.5Hz), 7.41(1H,d, J=5.4Hz), 7.73(1H,d, J=5.4H  
z), 7.70-7.75(1H,m), 7.91(1H,d, J=8.3Hz)

[0119]

#### Example 6-2

20 To 1,2-dimethoxyethane(5mL) suspension of 1.00g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 0.37g of sodium borohydride, which was then cooled to 10°C. Thereto was dropwise added 2.49mL of  
25 chlorotrimethylsilane at 5 to 10°C, which was then stirred at room temperature for 2.5h and at 40°C for 4 hours. After cooling, thereto was dropwise added 3.27mL of 6.0mol/L hydrochloric acid, which was then

stirred at 70 to 75°C for 30 minutes. To the reaction mixture were added water and ethyl acetate, and the pH was adjusted to 10.0 with 2.0mol/L sodium hydroxide aqueous solution. The organic layer was separated, washed sequentially with water and saturated sodium chloride aqueous solution. Thereto were added anhydrous magnesium sulfate and activated carbon. After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 0.36g of maleic acid, which was solidified from a mixed solvent(5mL) of ethyl acetate:2-propanol(4:1) to provide 0.71g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in DMSO- $\text{d}_6$  agreed with the values of example 6-1.

[0120]

#### Example 6-3

To tetrahydrofuran(5mL) suspension of 1.00g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 0.37g of sodium borohydride, and dropwise added tetrahydrofuran(1mL) solution of 0.75mL of trifluoroacetic acid for 30 minutes, which was then refluxed for 2 hours. After cooling, thereto was dropwise added 3.27mL of 6.0mol/L hydrochloric acid, which was then refluxed for 1.5 hours. To the reaction mixture were added water and ethyl acetate, and the

aqueous layer was separated. To the aqueous layer was added ethyl acetate, and the pH was adjusted to 10.0 with 20% (w/w) sodium hydroxide aqueous solution. The organic layer was separated, washed sequentially with  
5 water and saturated sodium chloride aqueous solution, and dried over anhydrous magnesium sulfate. After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 0.36g of maleic acid, which was  
10 solidified from a mixed solvent (5mL) of ethyl acetate:2-propanol (4:1) to provide 0.62g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral  
15 in DMSO- $d_6$  agreed with the values of example 6-1.  
[0121]

#### Example 6-4

To tetrahydrofuran (3mL) suspension of 0.50g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)  
20 azetidin-3-ol was added 0.19g of sodium borohydride, which was then heated to 50°C. Thereto was dropwise added tetrahydrofuran (1mL) solution of 0.46mL of dimethyl sulfate at 50 to 55°C for 10 minutes, which was then stirred at same temperature for 2.5 hours. After  
25 cooling, thereto was dropwise added 1.64mL of 6.0mol/L hydrochloric acid, which was then refluxed for 1.5 hours. To the reaction mixture was added ethyl acetate, and the pH was adjusted to 10.0 with

20% (w/w) sodium hydroxide aqueous solution. The organic layer was separated, washed sequentially with water and saturated sodium chloride aqueous solution, and dried over anhydrous magnesium sulfate. After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 0.18g of maleic acid, which was solidified from a mixed solvent (3.75mL) of ethyl acetate:2-propanol (4:1) to provide 0.49g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

The Chemical shift values of  $^1\text{H}$ -NMR spectral in DMSO- $d_6$  agreed with the values of example 6-1.

[0122]

#### 15 Example 6-5

To bis(2-methoxyethyl) ether (5mL) suspension of 1.00g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 0.37g of sodium borohydride, which was then cooled to 10°C.

20 Thereto was dropwise added 2.46mL of 4.0mol/L hydrogen chloride/dioxane at 5 to 15°C for 12 minutes, which was then stirred at same temperature for 30 minutes, at room temperature for 3 hours and at 35 to 40°C for 6 hours. After cooling, thereto was dropwise added  
25 3.27mL of 6.0mol/L hydrochloric acid, which was then stirred at 65 to 70°C for 1.5 hours. To the reaction mixture were added water and ethyl acetate, and the pH was adjusted to 10.0 with 2.0mol/L sodium hydroxide

aqueous solution. The organic layer was separated, washed sequentially with water and saturated sodium chloride aqueous solution. Thereto were added anhydrous magnesium sulfate and activated carbon.

- 5 After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 0.36g of maleic acid, which was solidified from a mixed solvent(5mL) of ethyl acetate:2-propanol(4:1) to provide 0.86g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate  
10 as colorless crystal form.

<sup>1</sup>H-NMR in DMSO-d<sub>6</sub> agreed with the values of example 6-1.

[0123]

15 Example 6-6

To 1,2-dimethoxyethane(5mL) suspension of 1.00g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 0.37g of sodium borohydride, which was then cooled to 10°C.

- 20 Thereto was dropwise added 2.46mL of 4.0mol/L hydrogen chloride/dioxane at 5 to 15°C for 10 minutes, which was then stirred at same temperature for 1 hour, at room temperature for 3.5 hours and at 35 to 40°C for 6 hours. After cooling, thereto was dropwise added 3.27mL of  
25 6.0mol/L hydrochloric acid, which was then stirred at 65 to 70°C for 1.5 hours. To the reaction mixture were added water and ethyl acetate, and the pH was adjusted to 10.0 with 2.0mol/L sodium hydroxide aqueous

solution. The organic layer was separated, washed sequentially with water and saturated sodium chloride aqueous solution. Thereto were added anhydrous magnesium sulfate and activated carbon. After  
5 insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 0.36g of maleic acid, which was solidified from a mixed solvent (5mL) of ethyl acetate:2-propanol (4:1) to provide 0.93g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate  
10 as colorless crystal form.

<sup>1</sup>H-NMR in DMSO-d<sub>6</sub> agreed with the values of example 6-1.  
[0124]

#### Example 6-7

15 To 1,2-dimethoxyethane (70mL) suspension of 20.0g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 5.46g of sodium borohydride, which was then cooled to 15°C. Thereto was dropwise added 20.6mL of 7.0mol/L hydrogen  
20 chloride/1,2-dimethoxyethane at 15 to 20°C for 40 minutes, which was then stirred at room temperature for 1.5 hours and at 53 to 57°C for 4 hours. After cooling, thereto was dropwise added 65.5mL of 6.0mol/L hydrochloric acid, which was then stirred at 65 to 70°C  
25 for 1 hour. The reaction mixture was concentrated under reduced pressure, thereto were added 100mL of water and 100mL of ethyl acetate, and the pH was adjusted to 10.0 with 5.0mol/L sodium hydroxide aqueous

solution. After the organic layer was separated, washed with 50mL of water, and the pH was adjusted to 1.0 with 6.0mol/L hydrochloric acid. The aqueous layer was separated, to which was added 50mL of ethyl acetate. The pH was adjusted to 10.0 with 5.0mol/L sodium hydroxide aqueous solution. The organic layer was separated, to which was added anhydrous magnesium sulfate. After insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 7.22g of maleic acid, which was solidified from a mixed solvent(100mL) of ethyl acetate:2-propanol(4:1) to provide 19.2g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

[0125]

#### Example 6-8

To tetrahydrofuran(35.0mL) suspension of 5.00g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 1.61g of sodium borohydride, and dropwise added tetrahydrofuran(15mL) solution of 2.09g of sulfuric acid at room temperature for 30 minutes, which was then stirred at 48 to 52°C for 7.5 hours. After cooling, thereto was dropwise added 16.4mL of 6.0mol/L hydrochloric acid, which was then refluxed for 1 hour. The reaction mixture was concentrated under reduced pressure, thereto were added water and ethyl acetate, and the pH was adjusted to 9.5 with 5.0mol/L sodium

hydroxide aqueous solution. The organic layer was separated, and washed with saturated sodium chloride aqueous solution. Thereto were added anhydrous magnesium sulfate and activated carbon. After  
5 insoluble matter was filtered off, the solvent was distilled off under reduced pressure. To the resultant residue was added 1.81g of maleic acid, which was solidified from a mixed solvent(25mL) of ethyl acetate:2-propanol(4:1) to provide 4.82g of 1-(3-(2-(1-  
10 benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

<sup>1</sup>H-NMR in DMSO-d<sub>6</sub> agreed with the values of example 6-1.

[0126]

15 Example 6-9

To tetrahydrofuran(2.38L) suspension of 340g of 1-(3-(2-(1-benzothiophen-5-  
yl)ethoxy)propionyl)azetidin-3-ol was added 110g of sodium borohydride, and dropwise added  
20 tetrahydrofuran(1.02L) solution of 142g of sulfuric acid at room temperature for 1 hour, which was then stirred at 45 to 55°C for 5 hours. After cooling, thereto was added 170mL of acetone and dropwise added 204mL of 36% hydrochloric acid, which was then stirred  
25 at room temperature for 3 hours and left unattended overnight. To the reaction mixture was added 1.02L of water, and 3.34L of the solvent was distilled off under reduced pressure. After cooling, thereto was added

0.68L of ethyl acetate, and dropwise added water(0.68L) solution of 147g of sodium hydroxide at 14 to 22°C, which was then stirred at 7 to 15°C for 30 minutes. Insoluble matter was filtered off, washed with 0.34L of ethyl acetate. The filtrate and washings were combined, and the organic layer was separated, washed with 0.68L of water. After to the organic layer was added 2.04L of 2-propanol, 3.01L of the solvent was distilled off under reduced pressure. Thereto were added 1.02L of ethyl acetate and 34g of activated carbon, which was stirred for 20 minutes. Insoluble matter was filtered off and washed with 0.34L of ethyl acetate. The filtrate and washings were combined, thereto was added 116g of maleic acid. After this reaction mixture was heated and dissolved, it was slowly cooled. The precipitate was collected by filtration to provide 376g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

<sup>1</sup>H-NMR in DMSO-d<sub>6</sub> agreed with the values of example 6-1.

[0127]

#### Example 6-10

To tetrahydrofuran(250mL) suspension of 50.0g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propionyl)azetidin-3-ol was added 13.6g of sodium borohydride, and dropwise added 18.5g of sulfuric acid at room temperature for 3 hours, which

was then stirred at 45 to 55°C for 4.5 hours. After cooling, thereto was added 15mL of acetone and dropwise added 120mL of 6.0mol/L hydrochloric acid, which was then refluxed for 1 hour. To the reaction mixture was added 150mL of water, and the solvent was distilled off under reduced pressure. Thereto was added 200mL of ethyl acetate, and dropwise added water(100mL) solution of 43.9g of sodium hydroxide at 10 to 21°C. The organic layer was separated, washed with 20% sodium chloride aqueous solution. Thereto were added 50.0g of zeolite and 5.0g of activated carbon, which was then stirred for 20 minutes. Insoluble matter was filtered off and washed with 100mL of ethyl acetate. The filtrate and washings were combined, thereto were added 63mL of ethyl acetate, 75mL of 2-propanol and 17.1g of maleic acid. After this reaction mixture was heated and dissolved, it was slowly cooled. The precipitate was collected by filtration to provide 56.7g of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol maleate as colorless crystal form.

<sup>1</sup>H-NMR in DMSO-d<sub>6</sub> agreed with the values of example 6-1.

#### INDUSTRIAL APPLICABILITY

[0128]

The process for production of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol and salts thereof of the present invention has the following characteristics, (1) safety to human body,

(2) low environmental loads and (3) a possibility of mass production, and so forth, therefore, the process of 1-(3-(2-(1-benzothiophen-5-yl)ethoxy)propyl)azetidin-3-ol and salts thereof is  
5 useful as industrial manufacturing process.

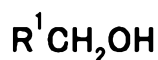
It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in  
10 Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as  
15 "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

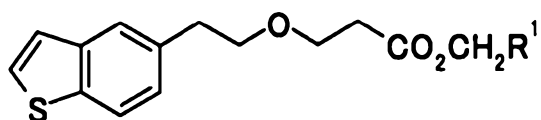
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for production of 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salts thereof, whereby the process comprises subjecting 2-(1-benzothiophen-5-yl)ethanol to Michael addition reaction with acrylonitrile in the presence of base, subsequently subjecting it to reaction with an alcohol represented by the general formula:



wherein  $R^1$  represents a hydrogen atom or an unsubstituted or substituted alkyl, cycloalkyl or aryl group, in the presence of acid to obtain a propionic acid ester derivative represented by the general formula:



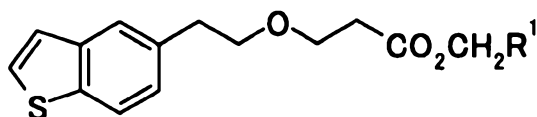
wherein  $R^1$  has the same meanings as the above, subsequently subjecting the propionic acid ester derivative to hydrolysis reaction in the presence of base.

2. The process of claim 1, wherein the acid used is sulfuric acid or hydrogen chloride.

3. The process of claim 1 or claim 2, wherein the acid used is hydrogen chloride and  $R^1$  is a hydrogen atom.

4. The process of claim 1 or claim 2, wherein the acid used is sulfuric acid and  $R^1$  is ethyl group.

5. A propionic acid ester derivative represented by the general formula:



wherein  $R^1$  represents a hydrogen atom or an unsubstituted or substituted alkyl, cycloalkyl or aryl group.

6. A 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salt thereof produced by the process according to any one of claims 1 to 4.

7. A process for producing 3-(2-(1-benzothiophen-5-yl)ethoxy)propionic acid or salt thereof, or use of a propionic derivative as defined in claim 5, substantially as herein described with reference to the Examples.