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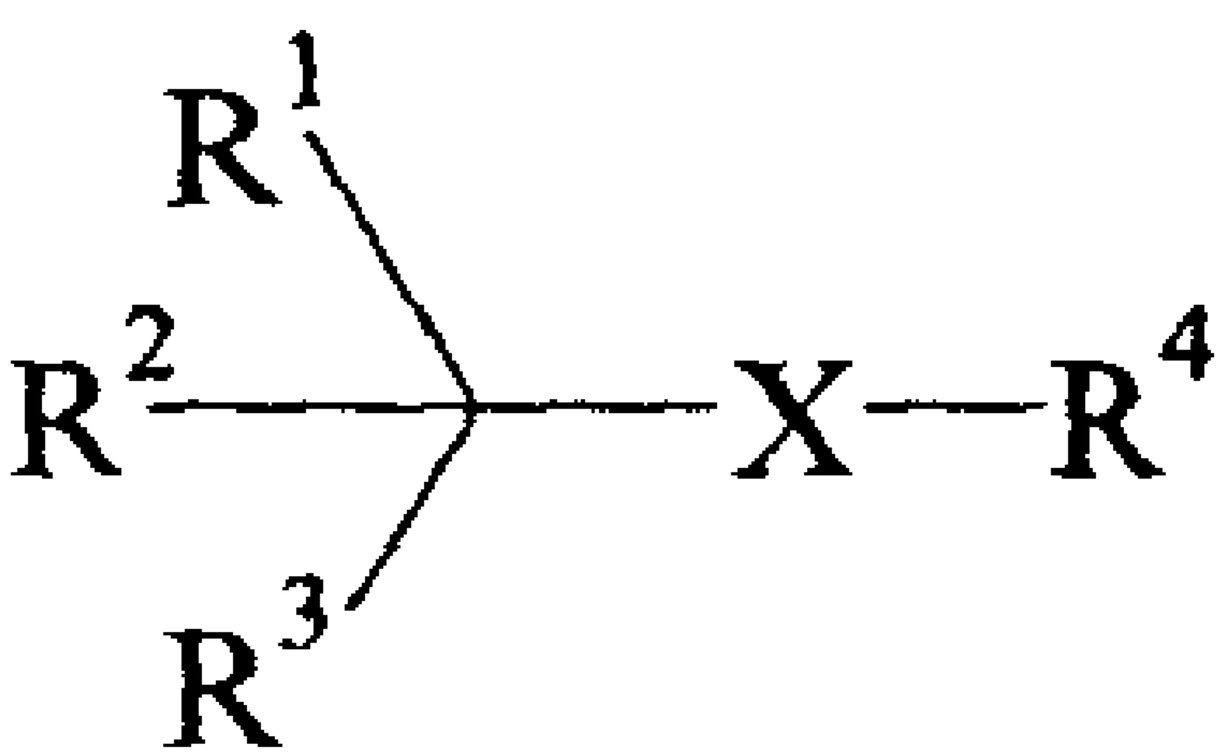

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(57) Abrégé/Abstract:
Provided are novel compounds having an inhibitory activity against production or secretion of β-amyloid protein. They embrace compounds represented by the following formula (1): (see formula 1) and capable of being replaced with a variety of substituents; and salts thereof, and solvates of any one of them.

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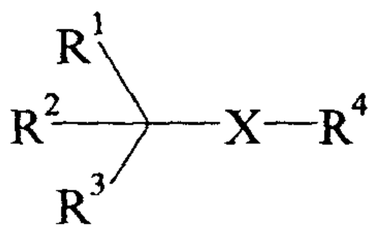
ABSTRACT

Provided are novel compounds having an inhibitory activity against production or secretion of β-amyloid protein. They embrace compounds represented by the following formula (1):



(1)

and capable of being replaced with a variety of substituents; and salts thereof, and solvates of any one of them.

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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β-AMYLOID PROTEIN PRODUCTION·SECRETION INHIBITOR

Technical Field

The present invention relates to novel compounds having an inhibitory activity against production or secretion of β-amyloid protein; and a medicament to treat for various diseases caused by abnormal production or secretion of β-amyloid protein such as Alzheimer disease, Down syndrome and the other diseases associated with amyloid deposition.

Background Art

Alzheimer disease is a neurodegenerative disease having pathological features such as degeneration or loss of nerve cells, formation of senile plaques and neurofibrillary tangles. Alzheimer disease causes symptoms of dementia such as gradual loss of memory, recognition, thinking, judgment or the like, and it eventually leads to death. No effective method for treating or preventing this disease has hitherto been known.

The main protein constituting a senile plaque deposited in the brain is β-amyloid protein which is composed of from 39 to 43 amino acids. β-Amyloid protein exhibits cytotoxicity, which is presumed to induce Alzheimer disease (Science, 259, 514(1993)). β-Amyloid

protein secreted from cells is a polypeptide composed mainly of 40 or 42 amino acids and particularly, that composed of 42 amino acids is known to deposit in the brain quickly because of strong aggregation property and in addition, have strong cytotoxicity (Journal of Biological Chemistry, 270, 7013(1995)). β-Amyloid protein is produced ubiquitously in vivo, but its function remains unknown.

β-Amyloid protein is produced by processing of a β-amyloid precursor protein (APP) which is a membrane protein. Mutation of an APP gene is observed from patients suffering from familial Alzheimer disease. An increase in the production or secretion amount of β-amyloid protein is known to occur in the cells having this mutated gene introduced therein. This suggests that a medicament inhibiting the production or secretion of β-amyloid protein is effective for the prevention or treatment of Alzheimer disease.

In the processing of APP, BACE (β-site APP Cleaving Enzyme) (Science, 286, 735(1999)) or Asp1 (Molecular and Cellular Neuroscience, 16, 609(2000)), each an aspartic protease, is reported as a β secretase for cleaving the N terminal of β-amyloid protein. It is suggested strongly that presenilin participates in C-terminal cleavage events by γ-secretase (Nature, 398, 513(1999)). Inhibitors of the secretase have been reported (Journal of Medicinal

Chemistry, 44, 2039(2001)), but most of the inhibitors are peptide compounds.

In WO00/50391, SMITH, et al., disclose compounds having a sulfonamide skeleton and capable of controlling production of β-amyloid protein. In WO01/70677 (GB 026827) BELANGER, et al., disclose compounds having a bicycloalkylsulfonamide skeleton and inhibiting γ-secretase.

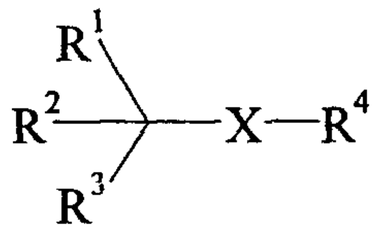
An object of the present invention is to provide compounds having a structure different from that of the above-described known compounds, having excellent inhibitory action against production or secretion of β-amyloid protein and having desirable properties as pharmaceuticals.

Disclosure of the Invention

The present inventors have carried out various investigations. As a result, it has been found that thiomethane, sulfinylmethane or sulfonylmethane compounds represented by the below-described formula (1) have excellent inhibitory action against production or secretion of β-amyloid protein and are therefore useful as a medicament for treatment of various diseases resulting from the abnormal production or secretion of β-amyloid protein, leading to the completion of the present invention.

In the present invention, there is thus provided a

compound represented by the following formula (1):



(1)

{wherein:

X represents -S-, -SO- or $-SO_2-$;

R^1 represents:

$-C(R^5)(R^6)(R^7)$

[in which, R^5, R^6 and R^7 each independently represents a halogen atom, cyano group, nitro group or $-Q^{51}-Q^{52}-Q^{53}-Q^{54}$

[in which, Q^{51} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{52} represents a single bond, -O-, $-O-N(A^{51})-$, $-O-N(COA^{51})-$, $-N(A^{51})-$, $-N(COA^{51})-$, $-N(COOA^{51})-$, $-N(CON(A^{51})(A^{52})-$, $-N(OA^{51})-$, $-N(NA^{51}A^{52})-$, $-N(A^{51})-N(A^{52})-$, $-N(COA^{51})-N(A^{52})-$, $-N(A^{51})-O-$, $-N(COA^{51})-O-$, -S-, -N=N-, $-C(A^{51})=N-$, $-C(A^{51})=N-O-$, $-C(A^{51})=N-N(A^{52})-$, $-N=C(A^{51})-$, $-O-N=C(A^{51})-$, $-(NA^{51})-N=C(A^{52})-$ or $-C(=NA^{51})-N(A^{52})-$

(in which, A^{51} and A^{52} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{53} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{54} represents $-A^{53}$, $-OA^{53}$, $-N(A^{53})(A^{54})$, $-SA^{53}$, $-NA^{54}-OA^{53}$,

$-NA^{55}-N(A^{53})(A^{54})$ or $-O-N(A^{53})(A^{54})$

(in which, A^{53}, A^{54} and A^{55} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)], or

R^5 and R^6 may be coupled together to form a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent (when the cyclic hydrocarbon group or heterocyclic group formed by coupling of R^5 and R^6 is unsaturated, R^7 may represent the corresponding unsaturated bond)],

$-N(R^8)(R^9)$

[in which, R^8 and R^9 each independently represents $-Q^{81}-Q^{82}-Q^{83}-Q^{84}$

[in which, Q^{81} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{82} represents a single bond, -O-, $-O-N(A^{81})-$, $-O-N(COA^{81})-$, $-N(A^{81})-$, $-N(COA^{81})-$, $-N(COOA^{81})-$, $-N(CON(A^{81})(A^{82}))-$, $-N(OA^{81})-$, $-N(NA^{81}A^{82})-$, $-N(A^{81})-N(A^{82})-$, $-N(COA^{81})-N(A^{82})-$, $-N(A^{81})-O-$, $-N(COA^{81})-O-$, -S-, -N=N-, $-C(A^{81})=N-$, $-C(A^{81})=N-O-$, $-C(A^{81})=N-N(A^{82})-$, $-N=C(A^{81})-$, $-O-N=C(A^{81})-$, $-(NA^{81})-N=C(A^{82})-$ or $-C(=NA^{81})-N(A^{82})-$

(in which, A^{81} and A^{82} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a

substituent),

Q^{83} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{84} represents $-A^{83}$, $-OA^{83}$, $-N(A^{83})(A^{84})$, $-SA^{83}$, $-NA^{84}-OA^{83}$, $-NA^{85}-N(A^{83})(A^{84})$ or $-O-N(A^{83})(A^{84})$

(in which, A^{83}, A^{84} and A^{85} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)]],

$-X^1R^{10}$

[in which, X^1 represents -O- or -S- and R^{10} represents -$Q^{101}-Q^{102}-Q^{103}-Q^{104}$,

[in which, Q^{101} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{102} represents a single bond, -O-, $-O-N(A^{101})-$, $-O-N(COA^{101})-$, $-N(A^{101})-$, $-N(COA^{101})-$, $-N(COOA^{101})-$, $-N(CON(A^{101})(A^{102}))-$, $-N(OA^{101})-$, $-N(NA^{101}A^{102})-$, $-N(A^{101})-N(A^{102})-$, $-N(COA^{101})-N(A^{102})-$, $-N(A^{101})-O-$, $-N(COA^{101})-O-$, -S-, -N=N-, $-C(A^{101})=N-$, $-C(A^{101})=N-O-$, $-C(A^{101})=N-N(A^{102})-$, $-N=C(A^{101})-$, $-O-N=C(A^{101})-$, $-(NA^{101})-N=C(A^{102})-$ or $-C(=NA^{101})-N(A^{102})-$

(in which, A^{101} and A^{102} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{103} represents a single bond, -CO-, -CS-, -SO-, -SO_2-, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{104} represents -A^{103}, -OA^{103}, -$N(A^{103})(A^{104})$, -SA^{103}, -NA^{104}-OA^{103}, -NA^{105}-$N(A^{103})(A^{104})$ or -O-$N(A^{103})(A^{104})$

(in which, A^{103}, A^{104} and A^{105} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)]], or

-X^2R^{11}

[in which, X^2 represents -SO- or -SO_2- and R^{11} represents -Q^{111}-Q^{112}-Q^{113}-Q^{114},

[in which, Q^{111} represents a single bond, -CO-, -CS-, -SO-, -SO_2-, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{112} represents a single bond, -O-, -O-$N(A^{111})$-, -O-$N(COA^{111})$-, -$N(A^{111})$-, -$N(COA^{111})$ -, -$N(COOA^{111})$-, -$N(CON(A^{111})(A^{112}))$-, -$N(OA^{111})$-, -$N(NA^{111}A^{112})$-, -$N(A^{111})$-$N(A^{112})$-, -$N(COA^{111})$-$N(A^{112})$-, -$N(A^{111})$-O-, -$N(COA^{111})$-O-, -S-, -N=N-, -$C(A^{111})$=N-, -$C(A^{111})$=N-O-, -$C(A^{111})$=N-$N(A^{112})$-, -N=$C(A^{111})$-, -O-N=$C(A^{111})$-, -(NA^{111})-N=$C(A^{112})$- or -$C(=NA^{111})$-$N(A^{112})$-

(in which, A^{111} and A^{112} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{113} represents a single bond, -CO-, -CS-, -SO-, -SO_2-, -

CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{114} represents $-A^{113}$, $-OA^{113}$, $-N(A^{113})(A^{114})$, $-SA^{113}$, $-NA^{114}-OA^{113}$, $-NA^{115}-N(A^{113})(A^{114})$ or $-O-N(A^{113})(A^{114})$

(in which, A^{113}, A^{114} and A^{115} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)]];

R^2 represents $-Q^{21}-Q^{22}-Q^{23}-Q^{24}$

[in which, Q^{21} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{22} represents a single bond, -O-, $-O-N(A^{21})-$, $-O-N(COA^{21})-$, $-N(A^{21})-$, $-N(COA^{21})-$, $-N(COOA^{21})-$, $-N(CON(A^{21})(A^{22}))-$, $-N(OA^{21})-$, $-N(NA^{21}A^{22})-$, $-N(A^{21})-N(A^{22})-$, $-N(COA^{21})-N(A^{22})-$, $-N(A^{21})-O-$, $-N(COA^{21})-O-$, -S-, -N=N-, $-C(A^{21})=N-$, $-C(A^{21})=N-O-$, $-C(A^{21})=N-N(A^{22})-$, $-N=C(A^{21})-$, $-O-N=C(A^{21})-$, $-(NA^{21})-N=C(A^{22})-$ or $-C(=NA^{21})-N(A^{22})-$

(in which, A^{21} and A^{22} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{23} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{24} represents $-A^{23}$, $-OA^{23}$, $-N(A^{23})(A^{24})$, $-SA^{23}$, $-NA^{24}-OA^{23}$, $-NA^{25}-N(A^{23})(A^{24})$ or $-NA^{25}-N(A^{23})(A^{24})$

(in which, A^{23}, A^{24} and A^{25} each independently represents

a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)]; or

R^1 and R^2 may be coupled together to form a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent, or may be coupled together to form $=CR^{12}R^{13}$

[in which, R^{12} and R^{13} each independently represents a halogen atom, cyano group, nitro group or $-Q^{121}-Q^{122}-Q^{123}-Q^{124}$,

[in which, Q^{121} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{122} represents a single bond, -O-, $-O-N(A^{121})-$, $-O-N(COA^{121})-$, $-N(A^{121})-$, $-N(COA^{121})-$, $-N(COOA^{121})-$, $-N(CON(A^{121})(A^{122}))-$, $-N(OA^{121})-$, $-N(NA^{121}A^{122})-$, $-N(A^{121})-N(A^{122})-$, $-N(COA^{121})-N(A^{122})-$, $-N(A^{121})-O-$, $-N(COA^{121})-O-$, -S-, -N=N-, $-C(A^{121})=N-$, $-C(A^{121})=N-O-$, $-C(A^{121})=N-N(A^{122})-$, $-N=C(A^{121})-$, $-O-N=C(A^{121})-$, $-(NA^{121})-N=C(A^{122})-$ or $-C(=NA^{121})-N(A^{122})-$

(in which, A^{121} and A^{122} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{123} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{124} represents $-A^{123}$, $-OA^{123}$, $-N(A^{123})(A^{124})$, $-SA^{123}$, $-NA^{124}-OA^{123}$, $-NA^{125}-N(A^{123})(A^{124})$ or $-O-N(A^{123})(A^{124})$

(in which, A^{123}, A^{124} and A^{125} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)]];

R^3 represents $-Q^{31}-Q^{32}-Q^{33}-Q^{34}$,

[in which, Q^{31} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{32} represents a single bond, -O-, $-O-N(A^{31})-$, $-O-N(COA^{31})-$, $-N(A^{31})-$, $-N(COA^{31})-$, $-N(COOA^{31})-$, $-N(CON(A^{31})(A^{32}))-$, $-N(OA^{31})-$, $-N(NA^{31}A^{32})-$, $-N(A^{31})-N(A^{32})-$, $-N(COA^{31})-N(A^{32})-$, $-N(A^{31})-O-$, $-N(COA^{31})-O-$, -S-, -N=N-, $-C(A^{31})=N-$, $-C(A^{31})=N-O-$, $-C(A^{31})=N-N(A^{32})-$, $-N=C(A^{31})-$, $-O-N=C(A^{31})-$, $-(NA^{31})-N=C(A^{32})-$ or $-C(=NA^{31})-N(A^{32})-$

(in which, A^{31} and A^{32} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{33} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{34} represents $-A^{33}$, $-OA^{33}$, $-N(A^{33})(A^{34})$, $-SA^{33}$, $-NA^{34}-OA^{33}$, $-NA^{35}-N(A^{33})(A^{34})$ or $-O-N(A^{33})(A^{34})$

(in which, A^{33}, A^{34} and A^{35} each independently represents a hydrogen atom, a hydrocarbon group which may have a

substituent or a heterocyclic group which may have a substituent)];

R^4 represents $-Q^{41}-Q^{42}-Q^{43}-Q^{44}$,

[in which, Q^{41} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{42} represents a single bond, -O-, $-O-N(A^{41})-$, $-O-N(COA^{41})-$, $-N(A^{41})-$, $-N(COA^{41})-$, $-N(COOA^{41})-$, $-N(CON(A^{41})(A^{42}))-$, $-N(OA^{41})-$, $-N(NA^{41}A^{42})-$, $-N(A^{41})-N(A^{42})-$, $-N(COA^{41})-N(A^{42})-$, $-N(A^{41})-O-$, $-N(COA^{41})-O-$, -S-, -N=N-, $-C(A^{41})=N-$, $-C(A^{41})=N-O-$, $-C(A^{41})=N-N(A^{42})-$, $-N=C(A^{41})-$, $-O-N=C(A^{41})-$, $-(NA^{41})-N=C(A^{42})-$ or $-C(=NA^{41})-N(A^{42})-$

(in which, A^{41} and A^{42} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent),

Q^{43} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$, -CO-CO-, -CO-CS-, -CS-CO- or -CS-CS-,

Q^{44} represents $-A^{43}$, $-OA^{43}$, $-N(A^{43})(A^{44})$, $-SA^{43}$, $-NA^{44}-OA^{43}$, $-NA^{45}-N(A^{43})(A^{44})$ or $-O-N(A^{43})(A^{44})$

(in which, A^{43}, A^{44} and A^{45} each independently represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent)]; or

R^3 and R^4 may be coupled together to form a cyclic hydrocarbon group which may have a substituent or a

heterocyclic group which may have a substituent}, N-oxide or S-oxide of the compound, salt thereof, or solvate of the above-described compound.

In the present invention, there is also provided a medicament containing, as an effective ingredient, the compound represented by the formula (1), N-oxide or S-oxide thereof, or salt thereof, or solvate of thereof.

In the present invention, there is also provided a pharmaceutical composition containing the compound represented by the formula (1), N-oxide or S-oxide thereof, or salt thereof, or solvate of thereof; and a pharmaceutically acceptable carrier.

In the present invention, there is also provided use of the compound represented by the formula (1), N-oxide or S-oxide thereof, or salt thereof, or solvate of thereof for the preparation of a medicament.

In the present invention, there is also provided a method of treating a disease resulting from abnormal production or secretion of β-amyloid protein, which comprises administering an effective amount of the compound represented by the formula (1), N-oxide or S-oxide thereof, or salt thereof, or solvate of thereof.

Best Mode for Carrying out the Invention

A description will next be made of the compound

represented by the formula (1).

The term "hydrocarbon group" as used herein means a group composed only of carbon and hydrogen atoms. The group may be any one of linear, branched and cyclic, or a combination of any two or three of them and it may be either one of saturated and unsaturated groups.

Typical examples of the linear or branched hydrocarbon group include alkyl, alkenyl and alkynyl groups, and combinations thereof. These linear or branched hydrocarbon groups embrace those having a plurality of double bonds or triple bonds, or those having both a double bond and triple bond.

As the alkyl group, linear or branched alkyl groups having from 1 to 18 carbon atoms, especially linear or branched alkyl groups having from 1 to 12 carbon atoms are preferred. Specific examples of such an alkyl group include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylpentyl, 2-ethylpentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-decyl groups.

As the alkenyl group, linear or branched alkenyl groups having from 2 to 18 carbon atoms, especially linear or branched alkenyl groups having from 2 to 12 carbon atoms are preferred. Specific examples of such an alkenyl group include vinyl, allyl, propenyl, butenyl and pentenyl groups.

As the alkynyl group, linear or branched alkynyl groups having from 2 to 18 carbon atoms, especially linear or branched alkynyl groups having from 2 to 12 carbon atoms are preferred. Specific examples of such an alkynyl group include ethynyl, 2-butynyl and 3-pentynyl groups.

Typical cyclic hydrocarbon groups include cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, spiro-hydrocarbon, crosslinked cyclic hydrocarbon, and condensed polycyclic hydrocarbon groups. A combination thereof is also usable. The cyclic hydrocarbons groups embrace those having a plurality of double bonds or triple bonds and those having both a double bond and a triple bond.

Examples of the cycloalkyl group include cycloalkyl groups having from 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Examples of the cycloalkenyl group include cycloalkenyl groups having from 4 to 7 carbon atoms such as cyclopentenyl and cyclohexenyl. Examples of the cycloalkynyl group include cycloalkynyl groups having from 4 to 7 carbon atoms.

Examples of the aryl group include monocyclic or polycyclic aromatic hydrocarbon groups having from 6 to 14 carbon atoms. Specific examples include phenyl, indenyl, naphthyl, anthracenyl and biphenyl.

Examples of the spiro-hydrocarbon group include

spiro-hydrocarbon groups having from 7 to 11 carbon atoms such as spiro[3.4]octanyl and spiro[4.5]deca-1,6-dienyl groups.

Examples of the crosslinked cyclic hydrocarbon group include crosslinked cyclic hydrocarbon groups having from 7 to 10 carbon atoms such as bicyclo[2.2.1]heptanyl, adamantyl, bicyclo[3.2.1]octanyl, bicyclo[2.2.1]hept-2-enyl, tricyclo[2.2.1.$0^{2,6}$]heptanyl and bicyclo[4.3.1]decanyl groups.

Examples of the condensed polycyclic hydrocarbon group include condensed polycyclic hydrocarbon groups having from 8 to 14 carbon atoms such as indanyl, tetrahydronaphthalenyl, hexahydroindanyl and octahydronaphthalenyl groups.

The term "heterocyclic group" as used herein means a cyclic group having one or more hetero atoms (N, O, S, etc.) as a component of its cyclic structure and it may be any one of a saturated ring, an unsaturated ring or aromatic ring, or may be either one of a monocylic or polycyclic group. It also embraces a group introduced from a heterocyclic spiro compound or a heterocyclic compound having a crosslinked cyclic structure.

Examples of the saturated monocyclic heterocyclic group include from 3- to 7-membered groups each having from 1 to 4 atoms selected from nitrogen, oxygen and sulfur

atoms. Specific examples include pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, thioranyl, dioxanyl, aziridinyl, imidazolidinyl, pyrazolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroxazolyl, tetrahydrothiazolyl, tetrahydroisoxazolyl, tetrahydroisothiazolyl, dioxolanyl and oxathioranyl groups.

Examples of the unsaturated monocyclic heterocyclic group include from 4- to 7-membered groups having 1 to 4 atoms selected from nitrogen, oxygen and sulfur atoms. Specific examples include pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiadiazolyl, oxadiazolyl, dihydroxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyrazinyl, pyridazinyl, pyranyl, dihydropyridinyl, dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl and dihydropyridazinyl groups.

Examples of the polycyclic heterocyclic group include from 7- to 14-membered groups having 1 to 4 atoms selected from nitrogen, oxygen and sulfur atoms. Specific examples

include benzofuranyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, benzothiophenyl, benzisothiazolyl, benzisoxazolyl, chromenyl, chromanyl, isochromenyl, isochromanyl, indolinyl, indazolyl, indolizinyl, isoindolyl, isoindolinyl, quinolizinyl, quinoxalinyl, quinazolyl, cinnolinyl, phthalazinyl, naphthyridinyl, purinyl, carbazolyl, xanthenyl, acridinyl, phenazinyl, phenoxazinyl, phenothiazinyl and quinuclidinyl groups.

Examples of the combination of cycloalkyl and alkyl groups include cycloalkyl-alkyl groups, with (C_{3-7} cycloalkyl)-(C_{1-12} alkyl) groups being especially preferred.

As the combination of aryl and alkyl groups, (C_{6-10} aryl)-(C_{1-12} alkyl) groups are preferred.

Examples of the substituent for these hydrocarbon groups and heterocyclic groups include $-Q^{201}-Q^{202}-Q^{203}-Q^{204}-Q^{205}-Q^{206}-Q^{207}$, in which Q^{201} represents a single bond, an alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms or heterocyclic group; Q^{202} represents a single bond, -O-, -NH-, -CH=-N-, -C(alkyl)=N-, -N(alkyl)- or -S-; Q^{203} represents a single bond, -CO-, -CS-, -SO-, $-SO_2-$ or -CONH-; Q^{204} represents a single bond, an alkyl group from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, a cycloalkyl

group, a cycloalkenyl group, an aromatic hydrocarbon group or a heterocyclic group; Q^{205} represents a single bond, -O-, -NH- or -N(alkyl)-; Q^{206} represents a single bond, -CO-, -CS-, $-SO_2-$, -SO- or -S-; and Q^{207} represents a hydrogen atom, a halogen atom, a hydroxy group, an oxo group, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-8} cycloalkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group, an azide group, a cyano group, an amino group, a C_{1-6} alkylamino group, a di(C_{1-6} alkyl)amino group, a C_{2-6} alkanoylamino group, di(C_{2-6} alkanoyl)amino group, a carboxyamino group, a C_{1-6} alkoxycarbonylamino group, a di(C_{1-6} alkoxy)carbonylamino group, a heterocyclic group, an aromatic hydrocarbon group, a cycloalkenyl group, a heterocyclic oxy group, or an aromatic hydrocarbon-oxy group. The alkyl group having from 1 to 6 carbon atoms, alkenyl group having from 2 to 6 carbon atoms, cycloalkyl group, cycloalkenyl group, heterocyclic group, heterocyclic-oxy group, aromatic hydrocarbon group or aromatic hydrocarbon-oxy group may be substituted with 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{2-6} alkenyl groups, carboxyamino(C_{1-6} alkyl) groups, (C_{1-6} alkoxy)carbonylamino(C_{1-6} alkyl) groups, formyl group, C_{2-6} alkanoyl groups, oxo group, nitro group, cyano group, azide group, amidino group, C_{2-6} alkenyloxy groups, hydroxy group, carboxyl group, C_{7-16} aralkyl groups, thioxo group, C_{2-7}

alkanoyl groups, C_{2-7} thioalkanoyl groups, thioformyl group, amino group, C_{1-6} alkylamino groups, di(C_{1-6} alkyl)amino groups, C_{1-6} alkoxycarbonyl groups, carbamoyl group, C_{1-6} alkylcarbamoyl groups, di(C_{1-6} alkyl)carbamoyl groups, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl groups, di(C_{1-6} alkyl)thiocarbamoyl groups, C_{1-6} alkoxycarbamoylamino groups, C_{1-6} alkoxycarbamoyl(C_{1-6} alkyl)amino groups, C_{2-7} alkanoylamino groups, (C_{2-7} alkanoyl)(C_{1-6} alkyl)amino groups, thio(C_{2-7} alkanoyl)amino groups, thio(C_{2-7} alkanoyl)(C_{1-6} alkyl)amino groups, formylamino group, formyl(C_{1-6} alkyl)amino groups, thioformylamino group, thioformyl(C_{1-6} alkyl)amino groups, C_{2-7} alkanoyloxy groups, formyloxy group, C_{1-6} alkoxycarbonyloxy groups, carbamoyloxy group, C_{1-6} alkylcarbamoyloxy groups, di(C_{1-6} alkyl)carbamoyloxy groups, aminocarbonylamino group, (C_{1-6} alkyl)aminocarbonylamino groups, di(C_{1-6} alkyl)aminocarbonylamino groups, aminocarbonyl(C_{1-6} alkyl)amino groups, (C_{1-6} alkyl)aminocarbonyl(C_{1-6} alkyl)amino groups, di(C_{1-6} alkyl)aminocarbonyl(C_{1-6} alkyl)amino groups, mercapto group, C_{1-6} alkylthio groups, C_{1-6} alkylsulfinyl groups, C_{1-6} alkylsulfonyl groups, aminosulfonyl group, C_{1-6} alkylaminosulfonyl groups, di(C_{1-6} alkyl)aminosulfonyl groups, C_{1-6} alkylsulfonylamino groups, (C_{1-6} alkylsulfonyl(C_{1-6} alkyl)amino groups, aminosulfonylamino group, C_{1-6} alkylaminosulfonylamino groups, di(C_{1-6}

alkyl)aminosulfonylamino groups, aminosulfonyl(C_{1-6} alkyl)amino groups, C_{1-6} alkylaminosulfonyl(C_{1-6} alkyl)amino groups, and di(C_{1-6} alkyl)aminosulfonyl(C_{1-6} alkyl)amino groups.

Examples of the aromatic hydrocarbon groups include C_{6-14} aromatic hydrocarbon groups, for example, phenyl, naphthyl, indenyl, anthracenyl and biphenyl groups. Of these, phenyl and naphthyl groups are especially preferred. The heterocyclic groups include the above-described saturated or unsaturated, monocyclic or polycyclic heterocyclic groups, for example, pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, thiolanyl, dioxanyl, pyrrolyl, aziridinyl, imidazolidinyl, pyrazolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrooxazolyl, tetrahydrothiazolyl, tetrahydroisoxazolyl, tetrahydroisothiazolyl, dioxolanyl, oxathiolanyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, dihydroxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiadiazolyl, oxadiazolyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyrazinyl, pyridazinyl, pyranyl, dihydropyridinyl,

dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridazinyl, benzofuranyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, benzothiophenyl, benzisothiazolyl, benzisoxazolyl, chromenyl, chromanyl, isochromenyl, isochromanyl, indolinyl, indazolyl, indolizinyl, isoindolyl, isoindolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, purinyl, carbazolyl, xanthenyl, acridinyl, phenazinyl, phenoxazinyl, phenothiazinyl and quinuclidinyl groups. Of these pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, dioxanyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxadiazolyl, thiadiazolyl, pyrazinyl, pyridazinyl, dihydropyridinyl, dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridazinyl, tetrahydrooxazolyl,

chromenyl, chromanyl, isochromenyl, and isochromanyl groups are preferred, with pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxolanyl, pyridyl, furyl and thienyl groups being especially preferred.

In the formula (1), X represents any one of -S-, -SO- and $-SO_2-$. Of these, -SO- are $-SO_2-$ are preferred, with $-SO_2-$ being especially preferred.

In the formula (1), R^1 represents any one of $-C(R^5)(R^6)(R^7)$, $-N(R^8)(R^9)$, $-X^1R^{10}$, and $-X^2R^{11}$. Of these, R^1 representing $-C(R^5)(R^6)(R^7)$ is preferred. Especially, R^1 representing $-C(R^5)(R^6)(R^7)$ in which R^5 and R^6 may be coupled together to form a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent is preferred.

In the formula (1), R^2 represents $-Q^{21}-Q^{22}-Q^{23}-Q^{24}$, with R^2 representing $-Q^{21}-Q^{22}-Q^{23}-Q^{24}$ in which Q^{21}, Q^{22}, and Q^{23} each represents a single bond and Q^{24} represents A^{23} in which A^{23} represents a hydrogen atom or an alkyl group being preferred.

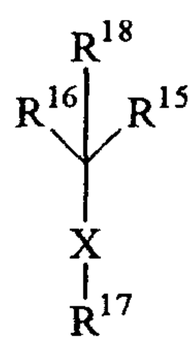
Or, R^1 and R^2 may be coupled together to form a cyclic hydrocarbon group which may have a substituent, a heterocyclic group which may have a substituent, or $=C(R^{12})(R^{13})$.

In the formula (1), R^3 represents $-Q^{31}-Q^{32}-Q^{33}-Q^{34}$, with R^3 representing $-A^{33}$, $-CO-A^{33}$ or $-COOA^{33}$ in which A^{33}

represents a hydrogen atom, a hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent being preferred.

R^4 represents $-Q^{41}-Q^{42}-Q^{43}-Q^{44}-$, with R^4 representing A^{43} in which A^{43} represents a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent being preferred.

In the present invention, compounds of the formula (1) in which R^1 represents a heterocyclic group which may have a substituent, R^2 represents a hydrogen atom or a C_{1-6} alkyl group, R^3 represents a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent, and R^4 represents a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent are especially preferred. These compounds are represented by the following formula (3):



(3)

(wherein, R^{15} represents a heterocyclic group which may have a substituent, R^{16} represents a cyclic hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent, R^{17} represents a cyclic

hydrocarbon group which may have a substituent or a heterocyclic group which may have a substituent, R^{18} represents a hydrogen atom or a C_{1-6} alkyl group and X represents -S-, -SO- or $-SO_2-$).

As the heterocyclic group represented by R^{15}, R^{16} or R^{17}, the above-described heterocyclic groups can be given as examples. As the cyclic hydrocarbon group represented by R^{16} or R^{17}, the above-described cyclic hydrocarbon groups can be given as examples. As the substituents on these groups, the above-described ones can be given as examples. As X, -SO- or $-SO_2-$ is preferred, with $-SO_2-$ being especially preferred.

As the heterocyclic group represented by R^{15}, R^{16} or R^{17}, from 3- to 7-membered saturated or from 4- to 7-membered unsaturated monocylic heterocyclic groups having from 1 to 4 atoms selected from nitrogen atom, oxygen atom and sulfur atom, and from 7- to 14-membered polycyclic heterocyclic groups having from 1 to 4 atoms selected from nitrogen atom, oxygen atom and sulfur atom are preferred.

As the cyclic hydrocarbon group represented by R^{16} or R^{17}, cycloalkyl groups having from 3 to 7 carbon atoms, cycloalkenyl groups having from 4 to 7 carbon atoms, monocylic or polycyclic aromatic hydrocarbon groups having from 6 to 14 carbon atoms, spirohydrocarbon groups having from 7 to 11 carbon atoms, crosslinked cyclic hydrocarbon

groups having from 7 to 10 carbon atoms and condensed polycyclic hydrocarbon groups having from 8 to 14 carbon atoms are preferred.

As the substituent for the cyclic hydrocarbon group or heterocyclic group of R^{15}, R^{16} or R^{17}, groups represented by the above-described $-Q^{201}-Q^{202}-Q^{203}-Q^{204}-Q^{205}-Q^{206}-Q^{207}$ can be given as examples.

As the cyclic hydrocarbon group represented by R^{16} or R^{17}, monocylic or polycyclic aromatic hydrocarbon groups having from 6 to 14 carbon atoms are preferred, with phenyl, naphthyl, indenyl and anthracenyl groups being more preferred, and a phenyl group being especially preferred.

These hydrocarbon groups may have 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{2-6} alkenyl groups, formyl group, C_{2-6} alkanoyl groups, carboxyl group, carboxyamino C_{1-6} alkyl groups, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl groups, oxo group, nitro group, cyano group, amidino group, C_{2-7} alkenyloxy groups, hydroxy group, thioxo group, amino group, C_{1-6} alkylamino groups, di(C_{1-6} alkyl)amino groups, C_{1-6} alkoxycarbonyl groups, carbamoyl group, C_{1-6} alkylcarbamoyl groups, di(C_{1-6} alkyl)carbamoyl groups, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl groups, di(C_{1-6} alkyl)thiocarbamoyl groups, mercapto group, C_{1-6} alkylthio groups, C_{1-6} alkylsulfinyl groups and C_{1-6} alkylsulfonyl groups.

Examples of the heterocyclic group represented by R^{16} or R^{17} include pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, thiolanyl, dioxanyl, pyrrolyl, aziridinyl, imidazolidinyl, pyrazolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrooxazolyl, tetrahydrothiazolyl, tetrahydroisoxazolyl, tetrahydroisothiazolyl, dioxolanyl, oxathiolanyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, dihydroxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiadiazolyl, oxadiazolyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyrazinyl, pyridazinyl, pyranyl, dihydropyridinyl, dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridazinyl, benzofuranyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, benzothiophenyl, benzisothiazolyl, benzisoxazolyl, chromenyl, chromanyl, isochromenyl, isochromanyl, indolinyl, indazolyl, indolizinyl, isoindolyl, isoindolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl,

naphthyridinyl, purinyl, carbazolyl, xanthenyl, acridinyl, phenazinyl, phenoxazinyl, phenothiazinyl and quinuclidinyl groups. Of these pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, dioxanyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxadiazolyl, thiadiazolyl, pyrazinyl, pyridazinyl, dihydropyridinyl, dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridazinyl, tetrahydrooxazolyl, chromenyl, chromanyl, isochromenyl, and isochromanyl groups are preferred, with tetrahydropyranyl, piperidinyl, pyridyl and pyrimidinyl groups being especially preferred.
These heterocyclic groups may have 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{2-6} alkenyl groups, formyl group, C_{2-6} alkanoyl groups, carboxyl group, carboxyamino C_{1-6} alkyl groups, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl groups, oxo group, nitro group, cyano group, amidino group, C_{2-7} alkenyloxy groups,

hydroxy group, thioxo group, amino group, C_{1-6} alkylamino groups, di(C_{1-6} alkyl)amino groups, C_{1-6} alkoxycarbonyl groups, carbamoyl groups, C_{1-6} alkylcarbamoyl groups, di(C_{1-6} alkyl)carbamoyl groups, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl groups, di(C_{1-6} alkyl)thiocarbamoyl groups, mercapto group, C_{1-6} alkylthio groups, C_{1-6} alkylsulfinyl groups and C_{1-6} alkylsulfonyl groups.

Examples of the heterocyclic group represented by R^{15} include pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, thiolanyl, dioxanyl, pyrrolyl, aziridinyl, imidazolidinyl, pyrazolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrooxazolyl, tetrahydrothiazolyl, tetrahydroisoxazolyl, tetrahydroisothiazolyl, dioxolanyl, oxathiolanyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, dihydroxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiadiazolyl, oxadiazolyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, pyrazinyl, pyridazinyl, pyranyl, dihydropyridinyl, dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridazinyl,

benzofuranyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, benzothiophenyl, benzisothiazolyl, benzisoxazolyl, chromenyl, chromanyl, isochromenyl, isochromanyl, indolinyl, indazolyl, indolizinyl, isoindolyl, isoindolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, purinyl, carbazolyl, xanthenyl, acridinyl, phenazinyl, phenoxazinyl, phenothiazinyl and quinuclidinyl groups which may be substituted with the above-described -Q^{201}-Q^{202}-Q^{203}-Q^{204}-Q^{205}-Q^{206}-Q^{207}. Of these groups, pyrrolidinyl, tetrahydrofuranyl, oxetanyl, tetrahydrothienyl, piperidinyl, dihydrooxazolyl, dihydrothiazolyl, dihydroisoxazolyl, dihydroisothiazolyl, piperazinyl, morpholinyl, thiomorpholinyl, oxiranyl, dioxanyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazinyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, quinolyl, isoquinolyl, benzopyranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzodioxanyl, dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxadiazolyl, thiadiazolyl, pyperizinyl, pyridazinyl, dihydropyridinyl, dihydropyrrolyl, dihydroquinolyl, dihydroimidazolyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridazinyl, tetrahydrooxazolyl, chromenyl, chromanyl, isochromenyl, and

isochromanyl groups are preferred, with tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, benzimidazolyl and chromenyl groups being especially preferred. The heterocyclic group may be substituted with a halogen atom, C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{2-6} alkenyl group, C_{2-6} alkenyloxy group, hydroxy group, carboxyl group, carboxy C_{1-6} alkyl group, C_{1-6} alkoxycarbonyl C_{1-6} alkyl group, C_{1-6} alkoxycarbonyl-C_{2-6} alkenyl group, hydroxyl C_{1-6} alkyl group, (C_{6-14} aromatic hydrocarbon)-sulfonyl C_{1-6} alkyl group, heterocyclic-C_{1-6} alkylamino group, heterocyclic group, heterocyclic-C_{1-6} alkyl group, C_{6-14} aromatic hydrocarbon group, (C_{6-14} aromatic hydrocarbon)(C_{1-6} alkyl) group, (C_{6-14} aromatic hydrocarbon)thio C_{1-6} alkyl group, azido-C_{1-6} alkyl group, amino C_{1-6} alkyl group, C_{1-6} alkylamino C_{1-6} alkyl group, di C_{1-6} alkylamino C_{1-6} alkyl group, hydroxy(C_{1-6} alkylamino)(C_{1-8} alkyl) group, C_{1-6} alkoxy(C_{1-6} alkyl)amino C_{1-6} alkyl group, (hydroxy C_{1-6} alkyl)(C_{1-6} alkoxy C_{1-6} alkyl)amino C_{1-6} alkyl group, C_{2-6} alkanoylamino C_{1-6} alkyl group, (C_{6-14} aromatic hydrocarbon) sulfonylamino C_{1-6} alkyl group, (C_{1-6} alkoxy)carbonylamino C_{1-6} alkyl group, carbamoylamino C_{1-6} alkyl group, N-alkylcarbamoylamino C_{1-6} alkyl group, N,N-dialkylcarbamoylamino C_{1-6} alkyl group, aminosulfonylamino C_{1-6} alkyl group, N-alkylsulfonylamino C_{1-6} alkyl group, N,N-dialkylsulfonylamino C_{1-6} alkyl group, (C_{6-14} aromatic

hydrocarbon)(C_{1-6} alkyl)amino group, heterocyclic C_{1-6} alkylamino group, carbamoyloxy C_{1-6} alkyl group, N-alkylcarbamoyloxy C_{1-6} alkyl group, N,N-dialkylcarbamoyloxy C_{1-6} alkyl group, (C_{6-14} aromatic hydrocarbon)-(C_{1-6} alkyl)carbamoyloxy C_{1-6} alkyl group, C_{1-6} alkoxycarbonyloxy-C_{1-6} alkyl group, (C_{6-14} aromatic hydrocarbon)oxycarbonyloxy C_{1-6} alkyl group, (C_{6-14} aromatic hydrocarbon)sulfonylamino-(C_{1-6} alkanoyl)amino C_{1-6} alkyl group, C_{1-6} alkoxycarbonylamino C_{1-6} alkylamino group, amino C_{1-6} alkylamino group, C_{1-6} alkylamino C_{1-6} alkylamino group, di(C_{1-6} alkyl)amino C_{1-6} alkylamino group, carboxyamino(C_{1-6} alkyl) group, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl group, C_{1-6} alkylsulfonylamino C_{1-6} alkyl group, amino C_{1-6} alkylcarbonylamino C_{1-6} alkyl group, N-(C_{1-6} alkyl)amino C_{1-6} alkylcarbonylamino C_{1-6} alkyl group, N,N-di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonylamino C_{1-6} alkyl group, heterocyclic carbonyl group, heterocyclic carbonylamino group, (C_{6-14} aromatic hydrocarbon)carbonyl group, C_{6-14} aromatic carbonylamino group, heterocyclic C_{1-6} alkylcarbonylamino C_{1-6} alkyl group, heterocyclic C_{2-6} alkenylcarbonylamino C_{1-6} alkyl group, C_{6-14} aromatic hydrocarbon alkenylcarbonylamino C_{1-6} alkyl group, C_{6-14} aromatic hydrocarbon carbonylamino C_{1-6} alkyl group, heterocyclic carbonylamino C_{1-6} alkyl group, C_{1-6} alkoxyoxalylamino C_{1-6} alkyl group, carbamoyl group, N-(C_{1-6} alkyl)carbamoyl group, N,N-di(C_{1-6} alkyl)carbamoyl

group, C_{1-6} alkyl-C_{3-8} cycloalkylcarbamoyl group, C_{3-8} cycloalkyl-C_{1-6} alkylcarbamoyl group, heterocyclic carbamoyl group, C_{1-6} aromatic carbamoyl group, heterocyclic carbonylhydrazonomethyl group, C_{6-14} aromatic hydrocarbon carbonylhydrazonomethyl group, C_{1-6} alkylthio C_{1-6} alkylcarbamoyl group, C_{1-6} alkylsulfinyl C_{1-6} alkylcarbamoyl group, C_{1-6} alkylsulfonyl C_{1-6} alkylcarbamoyl group, hydroxyaminocarbonyl group, hydrazinocarbonyl group or N-C_{1-6} alkylhydrazinocarbonyl group, thioformylamino-(C_{6-14} aromatic hydrocarbon)-thiocarbonylamino C_{1-6} alkyl group, thioformyl-C_{1-6} alkylamino-C_{6-14} aromatic hydrocarbon-thiocarbonylamino C_{1-6} alkyl group, formylamino-(C_{6-14} aromatic hydrocarbon)-carbonylamino(C_{1-6} alkyl) group, formyl-C_{1-6} alkylamino-(C_{6-14} aromatic hydrocarbon)-carbonylamino C_{1-6} alkyl group, C_{1-6} alkanoyl-heterocycle-carbonylamino C_{1-6} alkyl group, di(C_{2-6} alkanoyl)amino C_{1-6} alkyl group, di(C_{1-6} alkoxycarbonyl)amino C_{1-6} alkyl group, C_{1-6} alkyl-heterocycle-carbonyl group, C_{3-7} cycloalkyl C_{1-6} alkylaminocarbonyl group, C_{1-6} alkoxyaminocarbonyl group, (hydroxy)(C_{1-6} alkyl)aminocarbonyl group, (C_{1-6} alkoxy)(C_{1-6} alkyl)aminocarbonyl group, N'-C_{1-6} alkylhydrazinocarbonyl group, N',N'-di(C_{1-6} alkyl)hydrazinocarbonyl group, N,N'-di(C_{1-6} alkyl)hydrazinocarbonyl group, N,N',N'-tri(C_{1-6} alkyl)hydrazinocarbonyl group, N'-(heterocycle-carbonyl)-hydrazinocarbonyl group, formyl group, hydroxyimino group,

C_{1-6} alkoxyimino group, bis(C_{1-6} alkoxy C_{1-6} alky)amino C_{1-6} alkyl group, hydroxy-C_{1-6} alkyl-heterocyclic group, C_{1-6} alkoxy-C_{1-6} alkyl-heterocyclic group, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl-heterocyclic group, amino(C_{1-6} alkyl)-heterocyclic group, N-C_{1-6} alkylamino C_{1-6} alkyl-heterocyclic group, N,N-di(C_{1-6} alkyl)amino C_{1-6} alkyl-heterocyclic group, hydroxy-heterocyclic group, C_{1-6} alkoxy-heterocyclic group, carboxy-C_{2-5} alkenyl group, or oxo group (wherein, the above-described C_{6-14} aromatic hydrocarbon group or heterocyclic group may be substituted with a halogen atom, C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{2-6} alkenyl group, formyl group, C_{2-6} alkanoyl group, carboxyl group, carboxyamino(C_{1-6} alkyl) group, C_{1-6} alkoxycarbonylamino(C_{1-6} alkyl) group, oxo group, nitro group, cyano group, amidino group, C_{2-6} alkenyloxy group, hydroxy group, thioxo group, amino group, C_{1-6} alkylamino group, di(C_{1-6} alkyl)amino group, amino(C_{1-6} alkyl) group, C_{1-6} alkoxycarbonyl group, carbamoyl group, C_{1-6} alkylcarbamoyl group, di(C_{1-6} alkyl)carbamoyl group, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl group, di(C_{1-6} alkyl)thiocarbamoyl group, C_{2-7} alkanoylamino group, C_{2-7} alkanoyl(C_{1-6} alkyl)amino group, thio C_{2-7} alkanoylamino group, thio C_{2-7} alkanoyl (C_{1-6} alkyl)amino group, formylamino group, formyl(C_{1-6} alkyl)amino group, thioformylamino group, thioformyl(C_{1-6} alkyl)amino group,

C

C_{2-7} alkanoyloxy group, formyloxy group, mercapto group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, aminosulfonyl group, C_{1-6} alkylaminosulfonyl group, di C_{1-6} alkylaminosulfonyl group, C_{1-6} alkylsulfonylamino group or C_{1-6} alkylsulfonyl(C_{1-6} alkyl)amino group.

The compounds of the present invention represented by the formula (1) may have a stereoisomer or an enantiomer derived from an asymmetric hydrocarbon. Any one of the stereoisomer and enantiomer, and mixture thereof are all embraced in the present invention. The S-oxide of the invention compound exists when the heterocyclic group contains a sulfur atom. Either one of a monoxide or dioxide is embraced in the S-oxide.

No particular limitation is imposed on the salt of the compound of the present invention represented by the formula (1) insofar as it is a pharmaceutically acceptable salt. Specific examples of the salt include mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate and sulfate, benzoates, organic sulfonates such as methanesulfonate, 2-hydroxyethanesulfonate and p-toluenesulfonate, and organic carboxylates such as acetate, propanoate, oxalate, malonate, succinate, glutarate, adipate, tartrate, maleate, malate and mandelate.

When the compound represented by the formula (1) has

an acid group, the salt may be a salt of an alkali metal ion or alkaline earth metal ion. No particular limitation is imposed on the solvate insofar as it is pharmaceutically acceptable. Specific examples of it include hydrates and ethanol solvates.

Preparation processes of the compounds of the present invention represented by the formula (1) will next be described.

The compounds of the present invention represented by the formula (1) or salts thereof, or solvates thereof can be prepared using generally known chemical preparation processes in combination. Typical synthesis processes will next be described.

Upon synthesis of each invention compound, a substituent such as nitrogen atom, hydroxyl group or carboxyl group which needs protection may be protected by a generally known protecting group which can be removed as needed. The protecting group can be eliminated by the general organic chemical method if necessary.

The sulfide compound (1) having S as X can be prepared by the substitution of a thiol compound with carbon or addition of carbon to the thiol compound (below-descried formulas 2, 4 and 5).

The sulfinyl compound (1) having SO as X can be prepared by oxidizing a sulfide compound (below-described

formula 2).

The sulfonyl compound (1) having SO_2 as X may be prepared by condensing a sulfonyl compound (R^1 and/or R^2 and/or R^3 = H) with a substituent (R^1 and/or R^2 and/or R^3), or by oxidizing the sulfide compound (X represents S) or sulfinyl compound (X represents SO) (the below-described formulas 1 and 2). It can also be prepared by substituting a sulfinic acid compound with carbon or adding carbon to the sulfinic acid compound (the below-described formulas 3, 4 and 5). Use of these processes in combination may also be employed for the preparation.

The substituent portion of the compound (1) thus prepared can be converted and have another structure. Described specifically, R^1 and/or R^2 and/or R^3 and/or R^4 can be substituted with another substituent in a known manner.

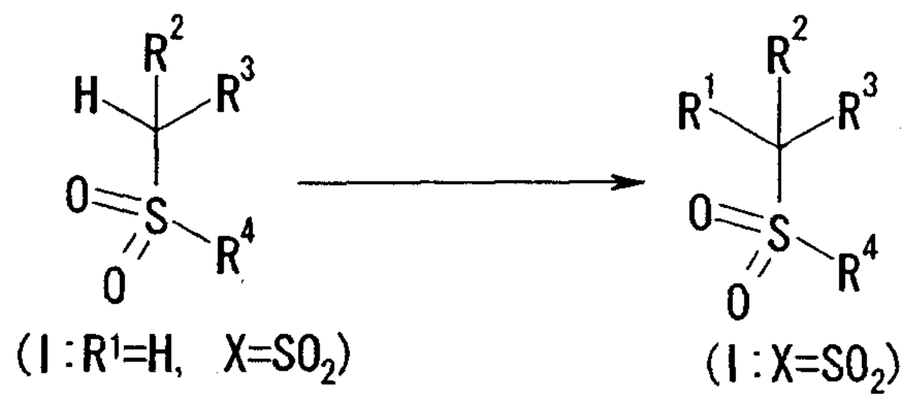
For example, the compound (1) having, as R^1 and/or R^2 and/or R^3 and/or R^4, an alkyl group having a hydroxyl group protected with a vinyl or silyl group can be converted into the corresponding hydroxyalkyl group by deprotection in a conventional manner. Moreover, the hydroxyl group portion can be introduced into a functional group such as ester, carbonate, carbamate, halogen or sulfonate in a known manner. Or, some of them can be introduced into a substituent such as hydrocarbon, alkoxy, amine, amide or sulfide or into a functional group in a conventional manner.

Alternatively, a cyclic portion can be formed with the other R^1, R^2, R^3 or R^4.

Various functional groups besides a hydroxyl group can be obtained by such conversion and the conversion method can be performed based on the known technique. The reagent, solvent and reaction conditions known *per se* in the art may be employed for these conversion steps.

Preparation process of the sulfonyl compound (1: $X=SO_2$):

Reaction scheme 1



Reaction scheme 1

For example, various compounds (1) different in R^1 can be prepared by reacting a compound (1) having a hydrogen atom as R^1 and SO_2 as X, which compound is known or can be prepared in a known manner, with an electrophilic reagent in the presence of a base in an inert solvent. In this reaction, R^1 can be introduced as an independent substituent by utilizing an intramolecular reaction with the electrophilic reagent, but alternatively, a cyclic structure can be formed together with R^2 by an intermolecular reaction with R^2 having an electrophilic functional group on its side chain.

Described specifically, the reaction is effected by adding the compound (1: R^1=H, X=SO_2) and at least an equivalent amount of a base with at least an equivalent amount of an electrophilic reagent in an inert solvent.

The reaction temperature is usually from -78°C to 200°C.

The reaction time is usually from 0.5 hour to 1 day.

Examples of the inert solvent which can be used in the above-described reaction include ether solvents, halogen solvents, aromatic solvents, nitrile solvents and amide solvents. They may be used either singly or in combination of two or more. Of these, tetrahydrofuran, dimethoxyethane, diethyl ether, dimethylformamide and toluene and so on are preferred.

Examples of the electrophilic reagent usable in the above reaction include R^1-Y [in which, Y represents an eliminating group], carbonyl compounds (such as aldehyde, ketone, ester and amide), and epoxy compounds. Alternatively, R^2 containing Y, carbonyl group or epoxy group may be used as the electrophilic functional group.

Examples of the eliminating group represented by Y include halogen atoms (such as chlorine, bromine and iodine), alkylsulfonyloxy groups having from 1 to 6 carbon atoms, which groups may be halogenated (such as methanesulfonyloxy, ethanesulfonyloxy and

trifluoromethanesulfonyloxy), and arylsulfonyloxy groups which have from 6 to 10 carbon atoms and may have a substituent. Substituents for the arylsulfonyloxy group include 1 to 3 halogen atoms, alkyl groups which have from 1 to 6 carbon atoms and may be halogenated, and alkoxy groups having from 1 to 6 carbon atoms.

Specific examples of the eliminating group include benzenesulfonyloxy, p-toluenesulfonyloxy, 1-naphthalenesulfonyloxy and 2-naphthalensulfonyloxy groups.

Examples of the base which can be used for the above reaction include alkyl lithiums (such as n-butyl lithium, sec-butyl lithium and t-butyl lithium), hydrides of an alkali metal or alkaline earth metal (such as lithium hydride, sodium hydride, potassium hydride and calcium hydride), amides of an alkali metal or alkaline earth metal (such as lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide), lower alkoxides of an alkali metal or alkaline earth metal (such as sodium methoxide, sodium ethoxide, and potassium t-butoxide), hydroxides of an alkali metal, alkaline earth metal or silver (such as silver hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide and barium hydroxide), carbonates of an alkali metal, alkaline earth

metal or silver (sodium carbonate, potassium carbonate, cesium carbonate and silver carbonate), bicarbonates of an alkali metal (such as sodium bicarbonate and potassium bicarbonate), and silver oxide.

The sulfonyl compound (1: X=SO_2) can also be prepared by reacting the compound (1) which has a hydrogen atom as R^1 and SO_2 as X and is known or can be prepared in a known manner with 1 to 3 equivalents of R^1-OH in the presence of a condensing agent in an inert solvent.

The reaction temperature is usually from -20°C to 200°C, preferably from 0°C to 150°C.

The reaction time is usually from 0.5 hour to 3 days.

Examples of the inert solvent which can be used in the above-described reaction include ether solvents, halogen solvents and aromatic solvents. They may be used either singly or in combination of two or more. Of these, tetrahydrofuran and toluene are preferred.

Examples of the condensing agent which can be used in the above reaction include any one of cyanomethylene trialkylphosphoranes (such as cyanomethylene trimethylphosphorane and cyanomethylene tri-n-butylphosphorane), triarylphosphines (such as triphenylphosphine) and trialkylphosphines (such as tributylphosphine), and azodicarboxylic acid compounds (such as diethyl azodicarboxylate, diisopropyl

azodicarboxylate, dipiperizineamide azodicarboxylate and bisdimethylamide azodicarboxylate).

Preparation process of a sulfonyl compound (1:X=SO_2) having SR^{10} as R^1

The sulfonyl compound (1: X=SO_2) having SR^{10} as R^1 is available by reacting a compound (1), which has a hydrogen atom as R^1 and SO_2 as X and is known or can be prepared in a known manner, with from 1 to 3 equivalents or $R^{10}S$-Y (Y has the same meaning as described above) in the presence of from 1 to 3 equivalents of a base (such as sodium hydride) in an inert solvent.

The reaction temperature is usually from -20°C to 150°C.

The reaction time is usually from 0.5 hour to 1 day.

Examples of the inert solvent which can be used in the above-described reaction include ether solvents, halogen solvents, aromatic solvents, and amide solvents. They may be used either singly or in combination of two or more. Of these, dimethylformamide is preferred.

Preparation process of a sulfonyl compound (1: X=SO_2) in which R^1 and R^2 have been coupled together to form =$CR^{12}R^{13}$

The sulfonyl compound (1:X=SO_2) in which R^1 and R^2 have been coupled together to form =$CR^{12}R^{13}$ can be prepared by acting a base on a compound (1) having a hydrogen atom as R^1, SO_2 as X and -$CYR^{12}R^{13}$ [Y has the same meaning as

described above] as R^2.

More specifically, the compound which has a hydrogen atom as R^1, SO_2 as X and $-CYR^{12}R^{13}$ as R^2 [Y has the same meaning as described above] and is known or available in a conventional manner is treated with at least an equivalent amount of a base in an inert solvent.

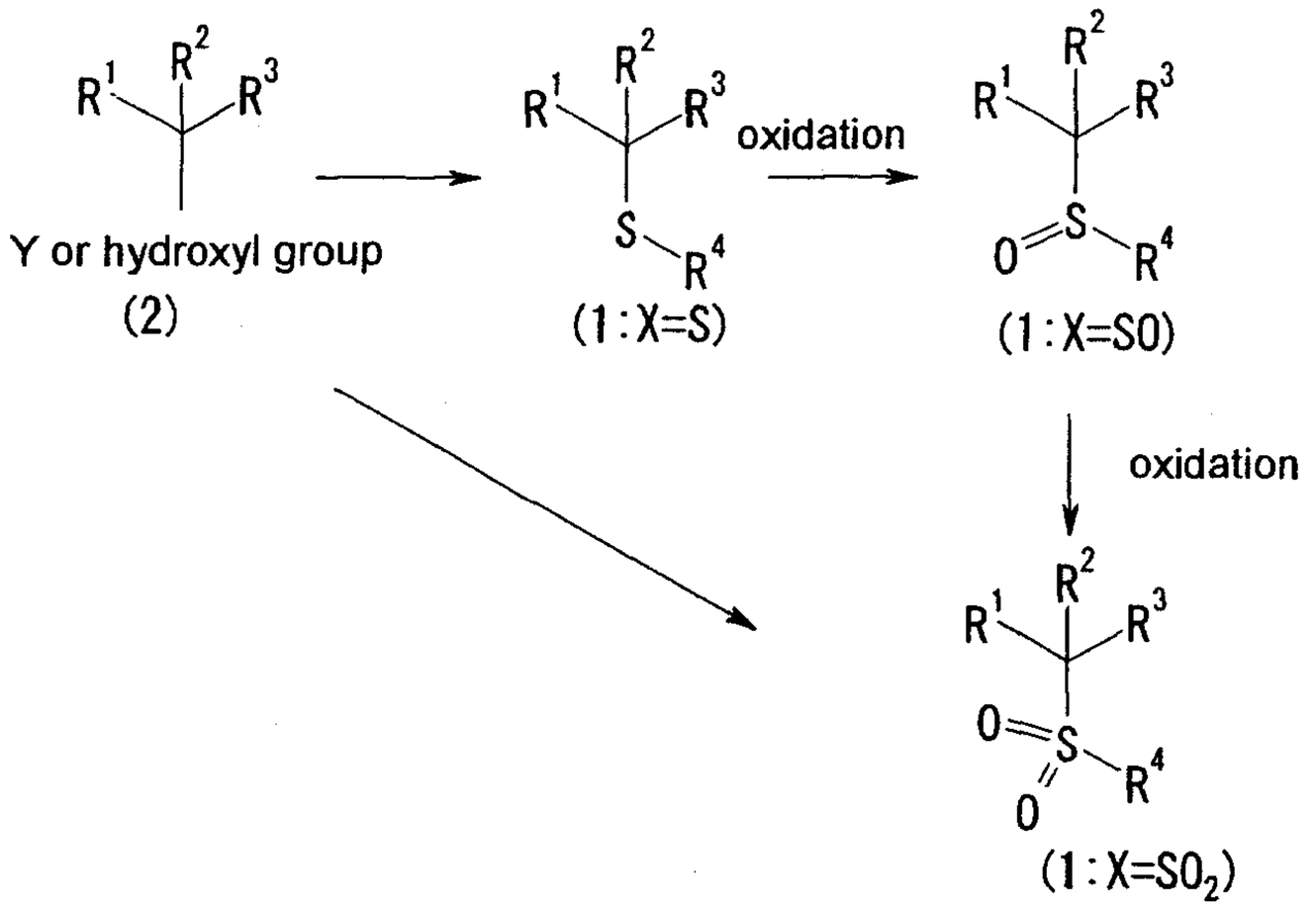
The reaction temperature is usually from -78°C to 150°C, preferably from -78°C to 50°C. The reaction time is usually from 0.5 hour to 1 day.

Examples of the inert solvent which can be used in the above-described reaction include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents and water. They may be used either singly or in combination of two or more. Of these, methylene chloride, tetrahydrofuran and diethyl ether and so on are preferred.

Examples of the base which can be used for the above reaction include hydrides of an alkali metal or alkaline earth metal (such as lithium hydride, sodium hydride, potassium hydride and calcium hydride); amides of an alkali metal or alkaline earth metal (such as lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide);

lower alkoxides of an alkali metal or alkaline earth metal (such as sodium methoxide, sodium ethoxide, and potassium t-butoxide); hydroxides of an alkali metal, alkaline earth metal or silver (such as silver hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide and barium hydroxide); carbonates of an alkali metal, alkaline earth metal or silver (sodium carbonate, potassium carbonate, cesium carbonate and silver carbonate); bicarbonates of an alkali metal (such as sodium bicarbonate and potassium bicarbonate); alkyl lithiums (such as n-butyl lithium) or alkyl Grignards (such as methyl magnesium bromide); inorganic bases such as silver oxide or amines (such as triethylamine, diisopropylethylamine and N-methylmorpholine); and organic bases, for example, basic heterocyclic compounds (such as dimethylaminopyridine, pyridine, imidazole, 2,6-lutidine, collidine, 1,8-diazabicyclo[5.4.0]undece-7-en, 1,5-diazabicyclo[4.3.0]non-5-en, and 1,4-diazabicyclo[2.2.2]octane).

Preparation process of a sulfide compound (1:X=S), a sulfinyl compound (1:X=SO), a sulfonyl compound (1:X=SO_2)



Reaction scheme 2

1) Preparation process of the sulfide compound (1: X=S)

The compound (1) having S as X is available by reacting the compound (2) with a thiol compound in the presence of a base in an inert solvent.

The compound (2) having a hydroxyl group can be prepared in a known manner. Various processes are known and one example will next be described. The compound (2) having a hydroxyl group is available by adding an organometal reagent (as a metal, lithium or magnesium representative of a Grignard reagent is usually employed) in an amount of from equivalent to excess to an aldehyde or ketone represented by $R^1(C=O)R^2$ in an inert solvent such as tetrahydrofuran or diethyl ether to react them. The organometal reagent represented by R^3-M can be prepared, for example when R^3 represents an aromatic ring or aromatic

heterocycle, by adding an alkyl lithium reagent or alkyl Grignard reagent to an aryl halide to cause metal exchange, as reported in the paper of H. Gilman, et. al., J. Org. Chem. 1951, 16, 1788-1791, or in the paper of F. Trecourt, et al., Tetrahedron 2000, 56, 1349-1460. The compound (2) having an eliminating group Y can be prepared by converting the hydroxyl group of the hydroxyl-containing compound (2) to an eliminating group in a known manner.

The compound (1) having S as X is also obtainable by reacting the compound (2) with an alkali metal or alkaline earth metal salt (such as lithium, sodium or potassium) of a thiol compound in an inert solvent.

The reaction temperature is usually from -20°C to 200°C, preferably from room temperature to 100°C. When the R substituent of the compound is a bulky one, reaction at a temperature higher than the above one or reaction in a sealed tube is sometimes preferred.

The reaction time usually ranges from 0.5 hour to 1 hour.

Examples of the base which can be used in the above-described reaction include hydrides of an alkali metal or alkaline earth metal (such as lithium hydride, sodium hydride, potassium hydride and calcium hydride), amides of an alkali metal or alkaline earth metal (such as lithium amide, sodium amide, lithium diisopropylamide, lithium

dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide), lower alkoxides of an alkali metal or alkaline earth metal (such as sodium methoxide, sodium ethoxide, and potassium t-butoxide), hydroxides of an alkali metal, alkaline earth metal or silver (such as silver hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide and barium hydroxide), carbonates of an alkali metal, alkaline earth metal or silver (sodium carbonate, potassium carbonate, cesium carbonate and silver carbonate), bicarbonates of an alkali metal (such as sodium bicarbonate and potassium bicarbonate), alkyl lithiums (such as n-butyl lithium) or alkyl Grignard reagents (such as methyl magnesium bromide), inorganic bases such as silver oxide, or amines (such as triethylamine, diisopropylethylamine and N-methylmorpholine), and organic bases, for example, basic heterocyclic compounds (such as dimethylaminopyridine, pyridine, imidazole, 2,6-lutidine, collidine, 1,8-diazabicyclo[5.4.0]undece-7-en, 1,5-diazabicyclo[4.3.0]non-5-en, and 1,4-diazabicyclo[2.2.2]octane).

Examples of the inert solvent which can be used in the above-described reaction include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents and water. They may be used either

singly or in combination of two or more. Of these, methylene chloride, tetrahydrofuran and diethyl ether are preferred.

The compound (2) has a hydroxyl group instead of the eliminating group Y, a condensate can be prepared by the Mitsunobu reaction.

The compound (1) can be prepared by reacting the hydroxyl-containing compound (2) which is known or can be prepared in a known manner with 1 to 3 equivalents of a thiophenol compound in the presence of both 1 to 3 equivalents of a triarylphosphine (such as triphenylphosphine) or trialkylphosphine (such as tributylphosphine) and 1 to 2 equivalents of an azodicarboxylic acid compound (such as diethyl azodicarboxylate, diisopropyl azodicarboxylate, dipiperidineamide dicarboxylate or bisdimethylamide azodicarboxylate) in an inert solvent.

The reaction temperature is usually from -20°C to 150°C, preferably from room temperature to 80°C. When the R substituent of the compound is a bulky one, reaction at a high temperature or reaction in a sealed tube is sometimes preferred.

The reaction time usually ranges from 0.5 hour to 1 day.

Examples of the inert solvent which can be used in

the above-described reaction include ether solvents, halogen solvents, and aromatic solvents. Two or more of these solvents may be used as a mixture. Of these, tetrahydrofuran is preferred.

2) Preparation process of the sulfinyl compound (1: X=SO)

The sulfinyl compound (1:X=SO) can be synthesized by oxidizing the sulfide compound (1:X=S), more specifically, reacting the sulfide compound (1) in the presence of an oxidizing agent in an inert solvent.

The reaction temperature usually ranges from -20°C to 200°C, preferably from 0°C to 100°C.

Examples of the inert solvent which can be used in the above reaction include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide compounds and water. Two or more of these solvents may be used in combination. Of these, methylene chloride, chloroform, methanol and ethanol are preferred.

Examples of the oxidizing agent which can be used in the above reaction include hydrogen peroxide, organic peracid compounds (such as peracetic acid and meta-chloroperbenzoic acid), metaperiodates (such as sodium metaperiodate), acyl nitrate, dinitrogen tetroxide, halogen, N-halogen compounds (such as N-chlorosuccinimide and N-bromosuccinimide), hydroperoxides (such as t-

butylhydroperoxide), iodobenzene diacetate, iodobenzene dichloride, t-butyl hypochlorite, sulfuryl chloride, singlet oxygen, ozone, selenium oxide, and seleninic acid. An optically active sulfoxide (1:X=SO) can be prepared by using titanium tetraisopropoxide/diethyl tartrate/t-butylhydroperoxide, titanium tetraisopropoxide/diethyl tartrate/peracetic acid or the like.

Described specifically, the sulfide compound (1:X=S) and from 1 to 2 equivalents of an oxidizing agent such as meta-chloroperbenzoic acid, sodium periodate or hydrogen peroxide may be stirred in an inert solvent such as methylene chloride, tetrahydrofuran-water, methanol or the like at 0 to 100°C for from about 1 hour to 2 days.

3) Preparation process of the sulfonyl compound (1: $X=SO_2$)

The sulfonyl compound (1: $X=SO_2$) can be synthesized by oxidizing the sulfide compound (1: X=S) or sulfinyl compound (1: $X=SO_2$), more specifically, by reacting the sulfide compound (1: X=S) or sulfinyl compound (1: X=SO) with an oxidizing agent in an inert solvent.

The reaction temperature usually ranges from -20°C to 150°C, preferably from 0°C to 80°C.

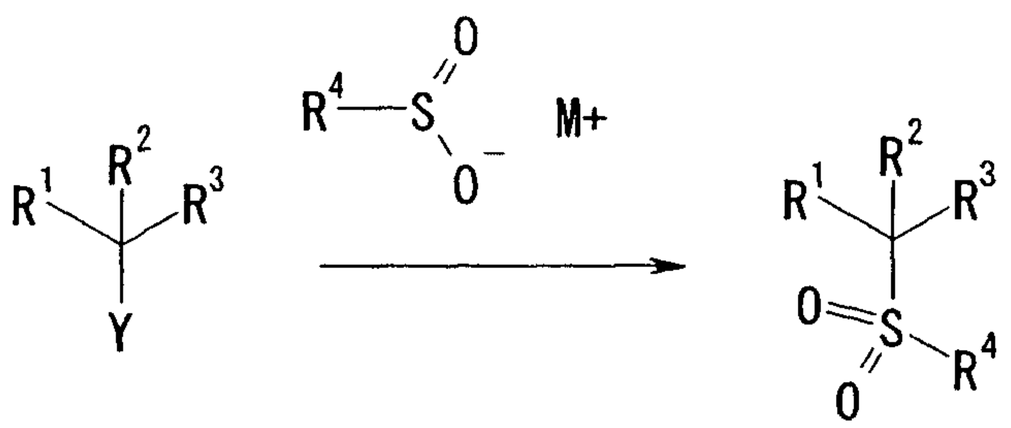
Examples of the inert solvent which can be used in the above-described reaction include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, carboxylic acid solvents, nitrile solvents, amide solvents,

ketone solvents, sulfoxide solvents and water. Two or more of these solvents may be used as a mixture. Of these, methylene chloride, chloroform, methanol, ethanol and acetic acid are preferred.

Examples of the oxidizing agent which can be used in the above reaction include hydrogen peroxide, hydrogen peroxide - transition metal catalyst (such as ammonium molybdate or iron (III) chloride), organic peracid compounds (such as peracetic acid and meta-chloroperbenzoic acid), metaperiodates (such as sodium metaperiodate), potassium peroxysulfate, permanganates (such as potassium permanganate), sodium perborate, halogen, N-halogen compounds (such as N-chlorosuccinimide and N-bromosuccinimide), hydroperoxides (such as t-butylhydroperoxide), iodobenzene diacetate, iodobenzene dichloride, hypochlorites (such as sodium hypochlorite, or t-butyl hypochlorite), singlet oxygen, ozone, selenium oxide, and seleninic acid. The preferred example of the reaction conditions include reaction of the sulfide compound (1: X=S) with from 2 to 5 equivalents of an oxidizing agent (such as meta-chloroperbenzoic acid, sodium periodate, hydrogen peroxide or hydrogen peroxide-ammonium molybdate) in methylene chloride, tetrahydrofuran-water or methanol at from 0 to 100°C for from about 1 hour to 2 days.

Preparation process of the sulfonyl compound (1: X=SO_2):

Reaction scheme 3



(2) (1 : X=SO_2)

Reaction scheme 3

The sulfonyl compound (1: X=SO_2) can be synthesized by introducing a sulfonyl group into the compound (2), more specifically, by reacting the compound (2) with an alkali metal, alkaline earth metal or tetrabutylammonium salt of sulfinic acid.

Described specifically, the compound (2) is reacted with from an equivalent to excess amount of sulfinic acid or salt thereof in an inert solvent.

The reaction temperature usually ranges from -20°C to 200°C, preferably from room temperature to 100°C. When the R substituent of the compound is a bulky one, reaction at higher reaction temperature than that described above or reaction in a sealed tube is sometimes preferred.

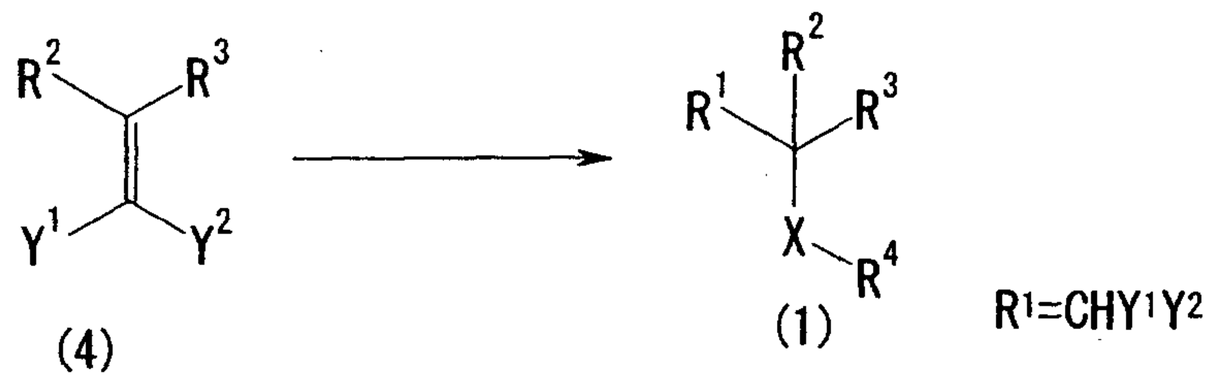
The reaction time usually ranges from 0.5 hour to 1 day.

Examples of the inert solvent which can be used in the above reaction include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, nitrile solvents,

amide solvents, ketone solvents, sulfoxide solvents and water. Two or more of these solvents may be used as a mixture. Of these, butanol and dimethoxyethane are preferred.

Preparation process of the sulfide compound (1: X=S):

Reaction scheme 4



Reaction scheme 4

Preparation process of the sulfide compound (1: X=S)

(1) when Y^1 or Y^2 is an electron attractive group

The compound (1) can be prepared by subjecting the compound (4) which is known or is available in a known manner to the Michael reaction, more specifically, by reacting the compound (4) with a thiol (R^4SH) in the presence of a base.

Described specifically, the compound (4) is reacted with from an equivalent to excess amount of a thiol in an inert solvent in the presence of from a catalytic amount to equivalent amount of a base.

The reaction temperature usually ranges from -20°C to 100°C, preferably at room temperature.

The reaction time usually ranges from 0.5 hour to 1

day.

Examples of the electron attractive group include carbonyl groups (such as acyl, ester, carboxylic acid, and amide), cyano group, nitro group, sulfinyl group and sulfonyl group. Examples of the inert solvent which can be used in the above-described reaction include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents and water. Two or more of these solvents may be used as a mixture. Of these, methanol, methylene chloride, and tetrahydrofuran and so on are preferred.

(2) When R^2 represents an alkoxy group or a sulfide group:

The compound (1) can be prepared by treating the compound (4), which is known or can be prepared in a known manner, in the presence of an acid catalyst, more specifically, by reacting the compound (4) with a thiol in the presence of an acid.

Described specifically, the compound (4) is reacted with from an equivalent to excess amount of a thiol in an inert solvent in the presence of from a catalytic amount to equivalent amount of an acid catalyst.

The reaction temperature usually ranges from -20°C to 100°C, preferably at room temperature.

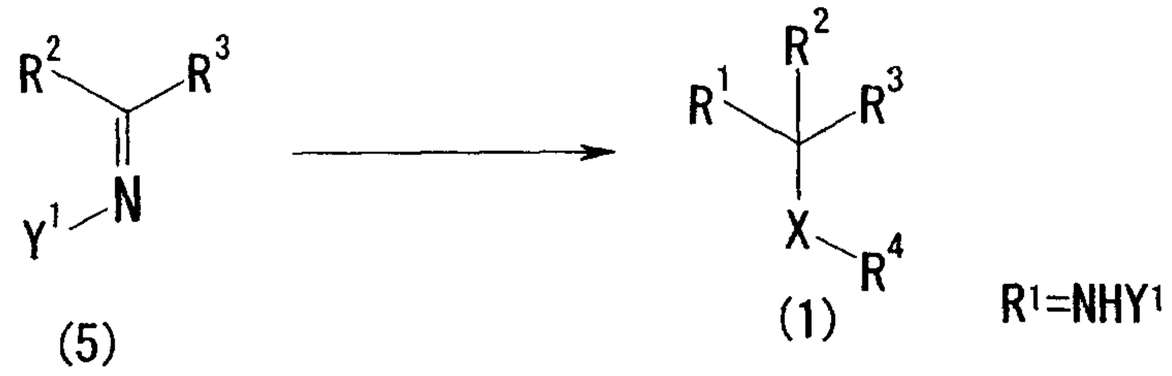
The reaction time usually ranges from 0.5 hour to 1

day.

Examples of the acid which can be used in the above reaction include water-free acid such as para-toluenesulfonic acid, camphor-sulfonic acid, hydrogen chloride and acid ion exchange resin; and Lewis acid catalysts such as trimethylsilyl trifluoromethanesulfonate and boron trifluoride.

Examples of the inert solvent which can be used in the above reaction include ether solvents, halogen solvents, aromatic solvents, nitrile solvents, and amide solvents. Two or more of thee solvents may be used as a mixture. Of these, methylene chloride is preferred.

Preparation process of the sulfide compound (1: X=S) and the sulfonyl compound (1: X=SO_2): Reaction scheme 5



Reaction scheme 5

1) Preparation process of the sulfide compound (1: X=S)

The compound (1) can be prepared by subjecting an imine to the nucleophilic substitution reaction, more specifically, reacting an imine or iminium salt, which is the compound (5), with from an equivalent to an excess amount of a thiol in the presence of from a catalytic

amount to excess amount of a base or an acid. The compound (5) can be prepared by mixing a carbonyl compound (R^2COR^3) with a primary or secondary amine or amide in a proper solvent.

The reaction temperature usually ranges from 0 to 100°C, preferably at room temperature.

The reaction time usually ranges from 0.5 hour to 1 day.

Examples of the base which can be used in the above reaction include hydrides of an alkali metal or alkaline earth metal (such as lithium hydride, sodium hydride, potassium hydride and calcium hydride); amides of an alkali metal or alkaline earth metal (such as lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide); lower alkoxides of an alkali metal or alkaline earth metal (such as sodium methoxide, sodium ethoxide, and potassium t-butoxide); hydroxides of an alkali metal, alkaline earth metal or silver (such as silver hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide and barium hydroxide); carbonates of an alkali metal, alkaline earth metal or silver (sodium carbonate, potassium carbonate, cesium carbonate and silver carbonate); bicarbonates of an alkali metal (such as sodium bicarbonate and potassium

bicarbonate); alkyl lithiums (such as n-butyl lithium) or alkyl Grignard reagents (such as methyl magnesium bromide); inorganic bases such as silver oxide, or amines (such as triethylamine, diisopropylethylamine and N-methylmorpholine); and organic bases, for example, basic heterocyclic compounds (such as dimethylaminopyridine, pyridine, imidazole, 2,6-lutidine, collidine, 1,8-diazabicyclo[5.4.0]undece-7-en, 1,5-diazabicyclo[4.3.0]non-5-en, and 1,4-diazabicyclo[2.2.2]octane).

Examples of the acid which can be used in the above reaction include formic acid, acetic acid, benzoic acid, para-toluenesulfonic acid and hydrochloric acid.

Examples of the inert solvent which can be used in the above reaction include alcohol solvents, ether solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents and water. Two or more of thee solvents may be used as a mixture. Of these, a mixed solvent of water and tetrahydrofuran is preferred.

2) Preparation process of the sulfonyl compound (1: $X=SO_2$)

The compound (1) can be prepared by subjecting an imine to the nucleophilic substitution reaction, more specifically, by reacting the imine or iminium salt, which is the compound (5), with from an equivalent amount to an excess amount of a sulfinic acid in the presence of from a catalytic amount to excess amount of an acid.

The reaction temperature usually ranges from 0 to 100°C, preferably at room temperature.

The reaction time usually ranges from 0.5 hour to 1 day.

Examples of the acid which can be used in the above reaction include formic acid, acetic acid, benzoic acid, para-toluenesulfonic acid and hydrochloric acid.

The compound (5) can be prepared by mixing a carbonyl compound (R^2COR^3) with a primary or secondary amine or amide in a proper solvent.

The compound (1) is also available without isolation of the compound (5). For example, it is available only by reacting an aldehyde with an equivalent amount of amide or sulfinic acid in the presence of an excess amount of an acid in an inert solvent.

The reaction time usually ranges from 0 to 100°C, preferably at room temperature.

The reaction time ranges from 1 hour to 1 day.

Examples of the inert solvent which can be used in the above reaction include alcohol solvents, ether solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents and water. Two or more of these solvents may be used as a mixture. Of these, a mixed solvent of water and tetrahydrofuran is preferred.

The compounds (1) of the present invention,

particularly the compounds of the formula (3) strongly inhibit production or secretion of β-amyloid protein so that they are useful as a medicament for prevention or treatment for diseases resulting from abnormal production or secretion of β-amyloid protein, such as Alzheimer disease and Down syndrome or diseases associated with amyloid deposition.

When the compound of the present invention is used as a pharmaceutical for human, the dose ranges from 1 mg to 1 g daily for adult, preferably from 10 mg to 300 mg. When it is administered to animals, the dose varies, depending on the purpose of administration (treatment or prevention), kind or size of the animal to be treated, the kind or degree of bacteria with which the animal has been infected, but daily dose usually ranges from 0.1 mg to 200 mg, preferably from 0.5 mg to 100 mg per kg of the weight of the animal. The daily dose is administered once a day or from two to four portions a day. The daily dose may exceed the above-described amount, if necessary.

The pharmaceutical composition containing the compound of the present invention can be formulated into a desired form selected in accordance with the administration route by using various ordinarily employed preparation processes. Examples of the form of the pharmaceutical composition having the invention compound as a main

ingredient include oral administrable preparations such as tablets, powders, granules, capsules, liquids, syrups, elixirs, oily or aqueous suspensions.

Injections may contain therein a stabilizer, antiseptic, solubilizing agent or the like. It is also possible to reconstitute a solid preparation, which has been obtained by filling a vessel with a solution which may contain such an agent and then lyophilizing it, upon use. An amount to be administered once may be filled in one vessel or an amount to be administered plural times may be filled in one container.

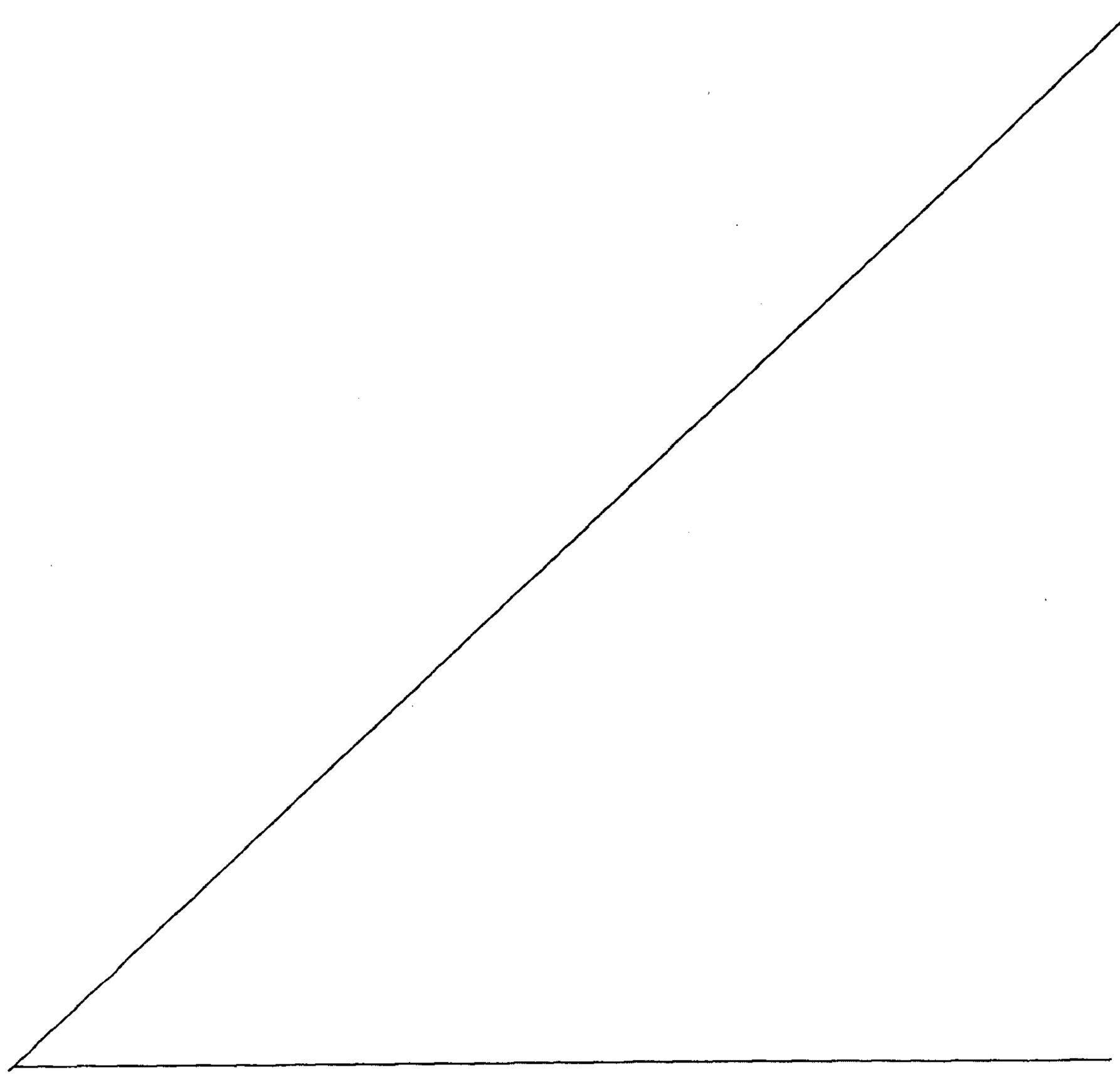
Examples of the preparation for external use include liquids, suspensions, emulsions, ointments, gels, creams, lotions, sprays and plasters.

The solid preparation contains, together with the invention compound, pharmaceutically acceptable additives. It can be prepared by mixing the invention compound with additives selected from fillers, extenders, binders, disintegrants, solubilizing promoters, humetants and lubricants as needed.

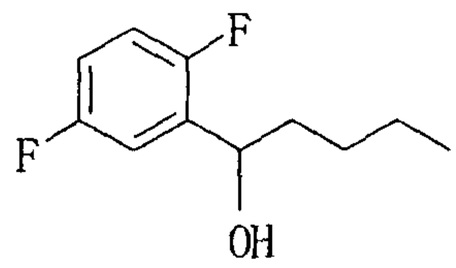
Examples of the liquid preparations include solutions, suspensions and emulsions. They may contain a suspending agent or emulsifier as an additive.

Examples

The present invention will be described hereinafter in detail with reference to embodiments of the present invention, but should not be construed as limited to the embodiments set forth herein. Also, all the compounds exemplified hereinafter should be construed as belonging either to E type or Z type unless specifically indicated.



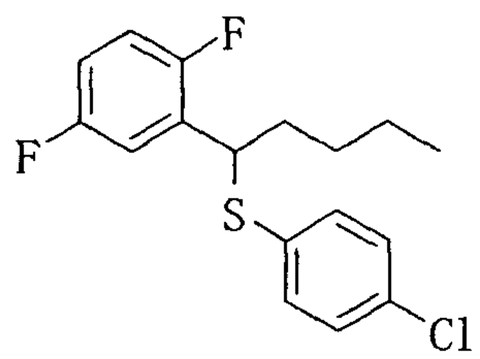
Referential Example1: 1-(2,5-Difluorophenyl)-1-pentanol



At -78°C under an argon atmosphere, n-butyl lithium (a 1.52M hexane solution, 14.5 ml, 22.0 mmol) was added dropwise to a solution of 1,4-difluorobenzaldehyde (2.84 g, 20.0 mmol) in tetrahydrofuran (40 ml). While stirring, the temperature of the reaction mixture was raised to -20°C over 2 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by chromatography on a silica gel column (9% ethyl acetate-hexane), whereby the title compound (2.62 g, 66%) was obtained as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90(3H,t,J=7.3Hz), 1.28-1.50(4H,m), 1.70-1.82(2H,m), 1.91-1.95(1H,br m), 4.98(1H,dd,J=11.7,5.9Hz), 6.88-7.00(2H,m), 7.18(1H,ddd,J=8.8,5.6,3.2Hz).

Example 1: 2-[1-[(4-Chlorophenyl)thio]pentyl]-1,4-difluorobenzene



At 0°C, 4-chlorobenzenethiol (435 mg, 3.00 mmol), triphenylphosphine (798 mg, 3.00 mmol), and diisopropyl azodicarboxylate (588 µl, 3.00 mmol) were successively added to a solution of 1-(2,5-difluorophenyl)-1-pentanol (300 mg, 1.50 mmol) in methylene chloride (6 ml). The reaction mixture was stirred at room temperature for 15 hours, diluted with methylene chloride, and then washed successively with a 1N aqueous solution of sodium hydroxide and brine. After drying over $MgSO_4$, the mixture was concentrated. The residue thus obtained was purified twice by medium-pressure chromatography on a silica gel column (first time with 1% ethyl acetate-hexane, and second time with hexane), whereby the title compound (266 mg, 54%) was obtained as a colorless oil.

IR (ATR) ν: 2958, 2931, 1624, 1595, 1574, 1493, 1475, 1425, 1389, 1234, 1215, 1171, 1095, 1012, 874, 814 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.86(3H,t,J=7.3Hz), 1.22-1.41(4H,m), 1.78-1.88(1H,m), 1.89-1.99(1H,m), 4.48(1H,ddd,J=8.6,6.6,1.7Hz), 6.81-6.86(1H,m), 6.90(1H,td,J=9.0,4.6Hz), 7.06(1H,ddd,J=9.0,5.8,3.2Hz), 7.17(4H,s).

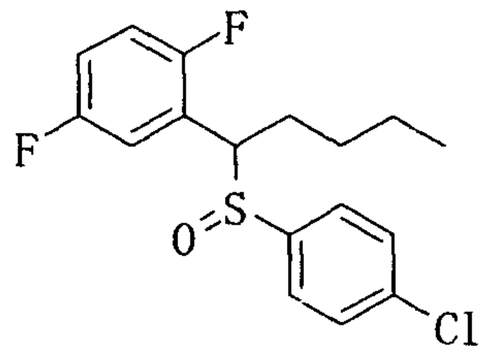
MS (m/z): 326 (M^+).

HRMS (EI): as $C_{17}H_{17}ClF_2S$ (M^+)

Calculated: 326.0708

Found: 326.0696

Example 2: 2-[1-[(4-Chlorophenyl)sulfinyl]pentyl]-1,4-difluorobenzene (Isomer 2-A and Isomer 2-B)



After addition of 3-chloroperbenzoic acid (301 mg, 1.74 mmol) to a solution of 2-[1-[(4-chlorophenyl)thio]pentyl]-1,4-difluorobenzene (515 mg, 1.58 mmol) in methylene chloride (10 ml) at 0°C, the mixture was stirred for 18 hours at room temperature. After further addition of 3-chloroperbenzoic acid (100 mg, 0.578 mmol), the mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with methylene chloride, washed successively with a 1N aqueous solution of sodium hydroxide, water, and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane), whereby the title Isomer 2-A (low-polarity) and the title Isomer 2-B (high-polarity) (230 mg, 43%) were obtained each as a colorless oil. The resulting

title Isomer 2-A was then recrystallized from hexane and obtained as colorless needle crystals (79.8 mg, 15%).

Isomer 2-A

Melting point: 108.5-109.0°C.

IR (ATR) ν: 2929, 2854, 1493, 1275, 1132, 1174, 1086, 1043, 1011, 962, 862, 823, 735, 503 cm^{-1}.

^{1}H-NMR (400MHz,$CDCl_3$) δ: 0.90(3H,t,J=7.1Hz), 1.30-1.50(4H,m), 1.96-2.06(1H,m), 2.27-2.36(1H,m), 4.03(1H,ddd,J=9.6,6.1,1.2Hz), 6.71(1H,td,J=9.1,4.4Hz), 6.85-6.92(1H,m), 7.07-7.12(1H,m), 7.10(2H,d,J=8.6Hz), 7.28(2H,d,J=8.6Hz).

MS (m/z) 343 (M^++H).

Elemental Analysis for $C_{17}H_{17}ClF_2OS$

Calculated: C 59.56%; H 5.00%; Cl 10.34%; F 11.08%; S 9.35%.

Found: C 59.27%; H 4.91%;Cl 10.42%; F 11.05%; S 9.45%.

Isomer 2-B

IR (ATR) ν: 3078, 2958, 2931, 2862, 1574, 1495, 1425, 1390, 1213, 1090, 1051, 1012, 818, 741 cm^{-1}.

^{1}H-NMR (400MHz,$CDCl_3$) δ: 0.83(3H,t,J=7.1Hz), 1.17-1.40(4H,m), 1.94-2.05(1H,m), 2.24-2.34(1H,m), 4.03(1H,dd,J=12.0,3.2Hz), 6.87-6.99(3H,m), 7.26(2H,d,J=8.3Hz), 7.35(2H,d,J=8.3Hz).

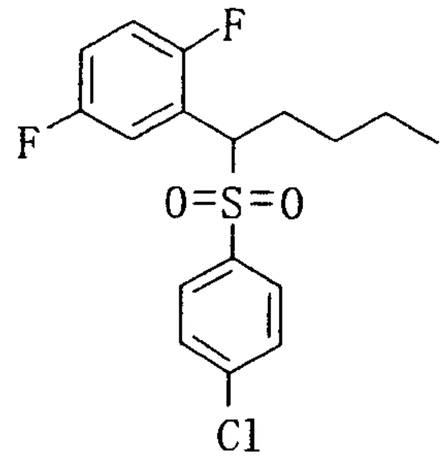
MS (m/z): 343(M^++H).

HRMS (FAB) for $C_{17}H_{18}OClF_2S$ (M^++H)

Calculated: 343.0735

Found: 343.0750

Example 3: 2-[1-[(4-Chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene



After addition of 3-chloroperbenzoic acid (98.8 mg, 0.571 mmol) to a solution of 2-[1-[(4-chlorophenyl)sulfinyl]pentyl]-1,4-difluorobenzene (Isomer 2-B) (150 mg, 0.439 mmol) in methylene chloride (5 ml), the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with methylene chloride, washed successively with a 1N aqueous solution of sodium hydroxide, water and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane), whereby the title compound (122 mg, 77%) was obtained as a colorless oil.

IR (ATR) ν: 3089, 2958, 2933, 2873, 1583, 1496, 1475, 1427, 1394, 1321, 1279, 1219, 1176, 1149, 1086, 1014, 829, 754 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 0.85(3H,t,J=7.3Hz), 1.15-

1.40(4H,m), 2.03-2.14(1H,m), 2.38-2.47(1H,m),

4.51(1H,dd,J=10.5,3.7Hz), 6.83(1H,td,J=9.0,4.6Hz), 6.94-

7.01(1H,m), 7.25(1H,ddd,J=8.8,5.4,3.2Hz),

7.38(2H,d,J=8.5Hz), 7.53(2H,d,J=8.5Hz).

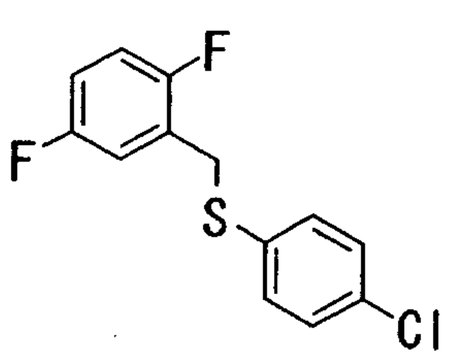
MS (m/z): 359 (M^++H).

HRMS (FAB) for $C_{17}H_{18}ClF_2O_2S$ (M^++H)

Calculated: 359.0684

Found: 359.0688

Example 4: 2-[(4-Chlorophenyl)thiomethyl]-1,4-difluorobenzene



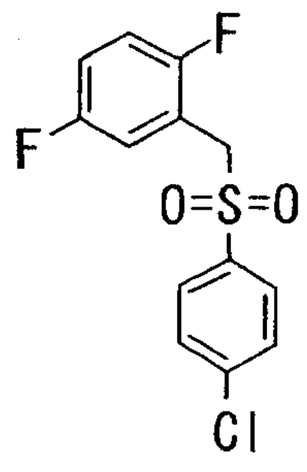
Process 1: At 0°C, 4-chlorobenzenethiol (5.45 g, 38.2 mmol), triphenylphosphine (11.1 g, 41.6mmol),and diisopropyl azodicarboxylate (8.16 ml, 41.6 mmol) were added successively to a solution of 2,5-difluorobenzyl alcohol (5.00 g, 34.7 mmol) in tetrahydrofuran (150 ml). The reaction mixture was stirred at room temperature for 4 days, followed by concentration. The residue thus obtained was purified by chromatography on a silica gel column (1% ethyl acetate-hexane), whereby the title compound (2.68 g, 29%) was obtained as a colorless oil.

Process 2: After addition of potassium carbonate (4.00 g,

29.0 mmol) and 2-bromomethyl-1,4-difluorobenzene (5.00 g, 24.2 mmol) to a solution of 4-chlorobenzenethiol (3.86 g, 26.6 mmol) in N,N-dimethylformamide (120 ml), the mixture was stirred for 3 hours at room temperature. To the reaction mixture were added saturated ammonium chloride (50 ml) and water (20 ml), followed by extraction with diethyl ether. The extracts were combined, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was purified by chromatography on a silica gel column (1% ethyl acetate-hexane), whereby the title compound (6.41 g, 98%) was obtained as a colorless oil.

^{1}H-NMR (400MHz,$CDCl_3$) δ: 4.04(2H,s), 6.85-7.00(3H,m), 7.23(4H,s).

Example 5: 2-[(4-Chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene



Process 1: At 0°C, 3-chloroperbenzoic acid (225 mg, 1.30 mmol) was added to a solution of 2-[(4-chlorophenyl)thiomethyl]-1,4-difluorobenzene (271 mg, 1.00 mmol) in methylene chloride (5 ml). The mixture was then stirred at room temperature for 15 hours. The reaction

mixture was diluted with methylene chloride, washed with a saturated aqueous solution of potassium bicarbonate and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was dissolved in methylene chloride (5 ml). After cooling to 0°C, 3-chloroperbenzoic acid (450 mg, 2.60 mmol) was added to the solution and then the mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with methylene chloride, washed with a saturated aqueous solution of potassium bicarbonate and brine, dried over $MgSO_4$, then concentrated. The residue thus obtained was purified by chromatography on a silica gel column (9% ethyl acetate-hexane), whereby the title compound (210 mg, 69%) was obtained as a colorless solid.

Process 2: After addition of H_2O (16.4 ml), 30% H_2O_2 (16.4 ml, 145 mmol) and hexaammonium heptamolybdate tetrahydrate (425 mg, 0.344 mmol) to a solution of 2-[(4-chlorophenyl)thiomethyl]-1,4-difluorobenzene (6.54 g, 24.1 mmol) in methanol (100 ml) at 0°C, the mixture was stirred for 1 hour and then stirred further for 15 hours at room temperature. The solid thus precipitated was collected by filtration and the filtrate was concentrated to about half of its amount. The resulting aqueous solution was extracted with methylene chloride. The solid was then dissolved in the extract. The resulting solution was washed successively with water and brine, dried over $MgSO_4$,

and concentrated. The residue thus obtained was recrystallized from hexane, whereby the title compound (6.34 g, 87%) was obtained as colorless needle crystals.

Process 3: After addition of 2-bromomethyl-1,4-difluorobenzene (12.3 ml, 95.5 mmol) to a suspension of sodium 4-chlorobenzenesulfinate (19.0 g, 95.5 mmol) in butanol (200 ml), the mixture was heated under reflux for 5 hours. The solid thus precipitated was collected by filtration and dissolved in methylene chloride. The resulting solution was washed with brine, dried over $MgSO_4$, and concentrated. The solid thus obtained was recrystallized from hexane, whereby the title compound (12.3 g, 43%) was obtained as colorless needle crystals.

IR (ATR) ν: 3089, 2991, 2943, 1581, 1496, 1315, 1279, 1213, 1149, 1090, 1080, 1012, 958, 816, 779, 756, 729, 708, 646, 517, 469 cm^{-1}.

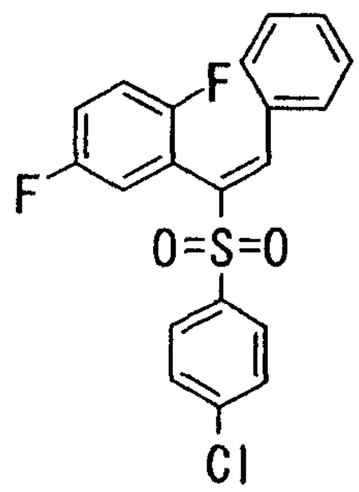
^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.36(2H,s), 6.91(1H,td,J=9.0,4.4Hz), 6.99-7.06(1H,m),

7.11(1H,ddd,J=8.3,5.6,3.2Hz), 7.45(2H,d,J=8.8Hz),

7.62(2H,d,J=8.8Hz).

MS (m/z): 303 (M^++H).

Example 6: E-2-[1-[(4-Chlorophenyl)sulfonyl]-2-phenylethenyl]-1,4-difluorobenzene



Under a nitrogen atmosphere and at 0°C, potassium hexamethyldisilazide (a 0.5M toluene solution, 2.20 ml, 1.10 mmol) was added to a tetrahydrofuran (5 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (303 mg, 1.00 mmol) obtained in Example 5 was added. The resulting mixture was stirred at 0°C for 1 hour. After addition of benzaldehyde (127 mg, 1.20 mmol), the mixture was stirred at room temperature for 15 hours. The reaction mixture was added with a saturated aqueous solution of ammonium chloride, followed by extraction with ethyl acetate. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane), whereby the title compound (220 mg,

56%) was obtained as a colorless solid. The solid was recrystallized from methanol to yield a colorless solid (111 mg, 28%). Based on the observation test of NOE (Nuclear Overhauser Effect), the olefin of the title compound was determined as an E-form.

Melting point: 144.5-145.0°C.

IR (KBr) ν: 3068, 1637, 1581, 1489, 1450, 1419, 1315, 1246, 1155, 1086, 887, 814, 752, 725, 690, 648, 627, 613, 534, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 6.88(1H,td,J=9.1,4.4Hz), 7.06-7.18(4H,m), 7.22-7.28(2H,m), 7.30-7.36(1H,m), 7.39(2H,d,J=8.8Hz), 7.60(2H,d,J=8.8Hz), 8.09(1H,s).

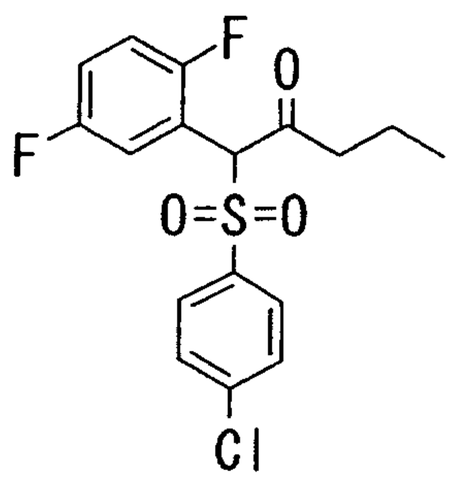
MS (m/z): 391 (M^++H).

Elemental Analysis for $C_{20}H_{13}ClF_2O_2S$

Calculated: C 61.46%; H 3.35%; Cl 9.07%; F 9.72%; S 8.20%.

Found: C 61.39%; H 3.28%; Cl 8.95%; F 9.82%; S 8.30%.

Example 7: 1-[(4-Chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-2-pentanone



In an argon gas stream and at -78°C, n-butyl lithium

(a 1.57M hexane solution, 1.27 ml, 2.00 mmol) was added to a tetrahydrofuran (10 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (606 mg, 2.00 mmol) obtained in Example 5. The temperature of the resulting mixture was then raised to room temperature. After cooling to -78°C, butyryl chloride (0.218 ml, 2.10 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at -78°C for 1.5 hours, and added with 1N hydrochloric acid (2.0 ml). The temperature of the mixture was then raised to room temperature. The reaction mixture was extracted with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane). The solid thus obtained was recrystallized from hexane, whereby the title compound (330 mg, 44%) was obtained as colorless needle crystals.

Melting point: 85.5-86.0°C.

IR (ATR) ν: 2968, 1724, 1581, 1491, 1394, 1335, 1323, 1155, 1088, 1034, 1011, 906, 829, 816, 758, 725, 615, 546, 469 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.90(3H,t,J=7.6Hz), 1.52-1.68(2H,m), 2.62(1H,ddd,J=18.1,7.6,6.8Hz), 2.84(1H,ddd,J=18.1,7.6,6.8Hz), 5.66(1H,s),

6.95(1H,td,J=9.0,4.4Hz), 7.02-7.08(1H,m), 7.39-7.43(1H,m), 7.43(2H,d,J=8.5Hz), 7.56(2H,d,J=8.5Hz).

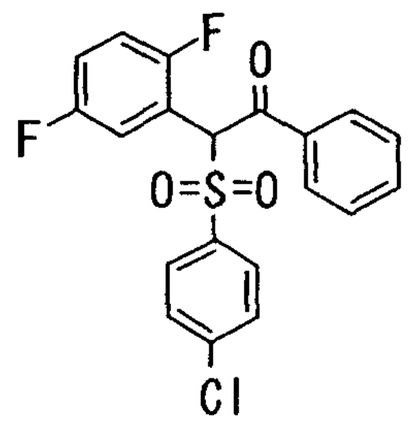
MS (m/z) 372 (M^+).

Elemental Analysis for $C_{17}H_{15}ClF_2O_3S$

Calculated: C 54.77%; H 4.06%; Cl 9.51%; F 10.19%; S 8.60%.

Found: C 54.47%; H 3.92%; Cl 9.68%; F 10.26%; S 8.76%.

Example 8: 2-[(4-Chlorophenyl)sulfonyl]-2-(2,5-difluorophenyl)-1-phenyl-1-ethanone



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.701 ml, 1.10 mmol) was added to a tetrahydrofuran (5 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (303 mg, 1.00 mmol) obtained in Example 5. The temperature of the resulting mixture was raised to room temperature and then stirred for 10 minutes. After cooling the reaction mixture to -78°C, benzoyl chloride (0.140 ml, 1.20 mmol) was added thereto dropwise. The reaction mixture was stirred at -78°C for 30 minutes. The temperature of the mixture was then raised to 0°C over 3 hours. After addition of 1N hydrochloric acid (2.0 ml), the mixture was extracted with

ethyl acetate. The extracts were combined, washed successively with water, a saturated aqueous solution of sodium bicarbonate, and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane). The solid thus obtained was washed with hexane, whereby the title compound (200 mg, 49%) was obtained as a colorless solid.

Melting point: 179.5-180.0°C.

IR (ATR) ν: 1682, 1595, 1579, 1495, 1475, 1315, 1284, 1240, 1209, 1153, 1082, 991, 874, 766, 708, 687, 607, 547, 509, 453 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 6.54(1H,s), 7.01-7.10(2H,m), 7.34-7.38(1H,m), 7.44-7.50(4H,m), 7.58-7.65(1H,m), 7.67(2H,d,J=8.8Hz), 7.88-7.93(2H,m).

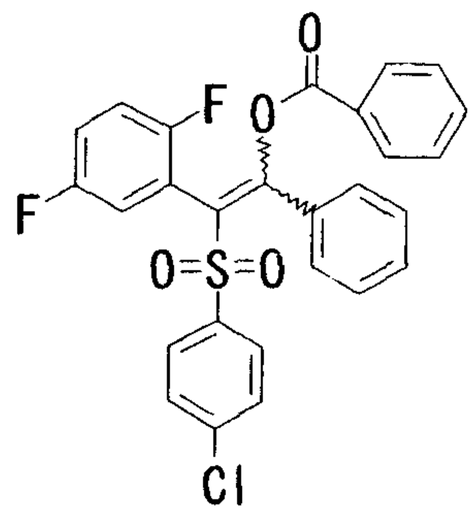
MS (m/z): 406 (M^+).

HRMS (EI): as $C_{20}H_{13}ClF_2O_3S$ (M^+)

Calculated: 406.0242

Found: 406.0230

Example 9: <u>2-[(4-Chlorophenyl)sulfonyl]-2-(2,5-difluorophenyl)-1-phenylethenyl benzoate</u>



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.701 ml, 1.10 mmol) was added to a dimethoxyethane (5 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (303 mg, 1.00 mmol) obtained in Example 5. The temperature of the mixture was then raised to room temperature, followed by stirring for 10 minutes. After cooling to -78°C, benzoyl chloride (0.140 ml, 1.20 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at -78°C for 30 minutes. The temperature of the mixture was then raised to 0°C over 3 hours. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane). The solid thus obtained was recrystallized from ethyl acetate, whereby the title compound (80.0 mg, 26%) was obtained as a

colorless solid.

Melting point: 224.5-227.0°C.

IR (ATR) ν: 1756, 1610, 1491, 1450, 1325, 1228, 1155, 1092, 1072, 1011, 808, 756, 694, 606, 553, 462 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 6.97(1H,ddd,J=8.8,4.4Hz), 7.02-7.09(1H,m), 7.15-7.21(3H,m), 7.23-7.30(3H,m), 7.34(2H,d,J=8.5Hz), 7.51-7.57(2H,m), 7.77(2H,d,J=8.5Hz), 8.02-8.06(2H,m).

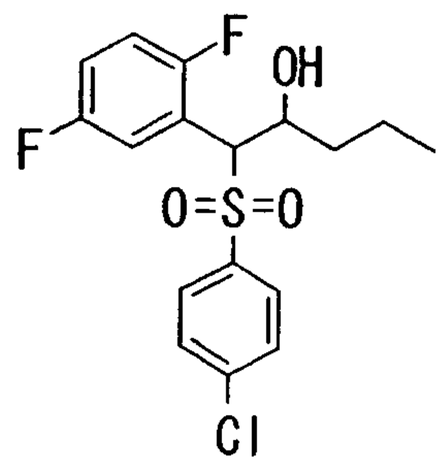
MS (m/z): 528 (M^++NH_4).

Elemental Analysis for $C_{27}H_{17}ClF_2O_4S$

Calculated: C 63.47%; H 3.35%; Cl 6.94%; F 7.44%; S 6.28%.

Analyzed: C 63.04%; H 3.24%; Cl 6.92%; F 7.39%; S 6.44%.

Example 10: 1-[(4-Chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-2-pentanol



Under a nitrogen atmosphere and at -78°C, n-butyl lithium (a 1.60M hexane solution, 0.688 ml, 1.10mmol) was added to a tetrahydrofuran (5 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (303 mg, 1.00 mmol) obtained in Example 5. The mixture was stirred

at -78°C for 1 hour. After addition of butanal (0.108 ml, 1.20 mmol), the mixture was stirred at -78°C for 2 hours. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane) as a low-polarity isomer to yield by a colorless solid. The solid thus obtained was washed with hexane, whereby the title compound (30.5 mg, 8%) was obtained as a colorless solid.

Melting point: 134.5-135.0°C.

IR (ATR) ν: 3502, 2966, 2931, 2873, 1585, 1491, 1309, 1277, 1227, 1173, 1147, 1084, 1083, 1014, 810, 756, 721, 613, 542, 445 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.87(3H,t,J=7.1Hz), 1.20-1.65(4H,m), 3.06(1H,d,J=2.2Hz), 4.48(1H,s), 4.85-4.90(1H,m), 6.84(1H,td,J=9.1,4.7Hz), 6.96-7.02(1H,m), 7.40(2H,d,J=8.6Hz), 7.58(2H,d,J=8.6Hz), 7.85(1H,ddd,J=9.1,5.4,3.4Hz).

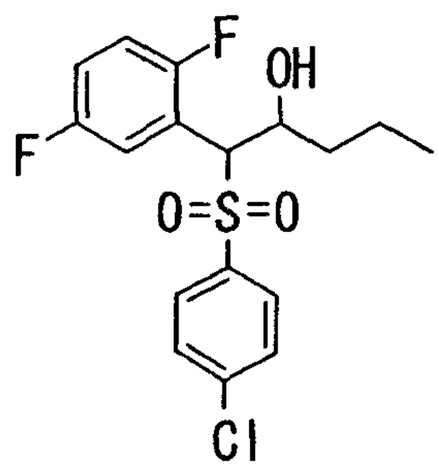
MS (m/z): 374 (M^+).

HRMS (EI) m/z as $C_{17}H_{17}O_3ClF_2S$ (M^+):

Calculated: 374.0555

Found: 374.0540

Example 11: 1-[(4-Chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-2-pentanol



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 7.01 ml, 11.0 mmol) was added to a tetrahydrofuran (50 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (3.03 g, 10.0mmol) obtained in Example 5 and the mixture was stirred at -78°C for 1 hour. Butanal (1.08 ml, 12.0 mmol) was added dropwise to the reaction mixture. The mixture was stirred for 15 hours while elevating its temperature to room temperature. After cooling to 0°C and addition of a saturated aqueous ammonium chloride solution, the mixture was extracted with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The solid thus precipitated was collected by filtration and washed with hexane. The filtrate and washing with hexane were combined, followed by concentration. The residue was purified by medium-pressure chromatography on a silica gel column (10% ethyl acetate-hexane) as a high-polarity isomer to yield a

colorless solid. The resulting colorless solid was recrystallized from hexane, whereby the title compound (396 mg, 11%) was obtained as colorless needle crystals.

Melting point: 76.5-78.0°C.

IR (ATR) ν: 3533, 2960, 1581, 1498, 1394, 1329, 1306, 1242, 1178, 1146, 1082, 987, 887, 754, 712, 644, 594, 515 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.82(3H,t,J=7.3Hz), 1.22-1.53(4H,m), 3.78(1H,br s), 4.55-4.80(2H,br m), 6.84(1H,td,J=9.0,4.4Hz), 6.96-7.04(1H,m), 7.15-7.26(1H,br s), 7.39(2H,d,J=8.3Hz), 7.52(2H,d,J=8.3Hz).

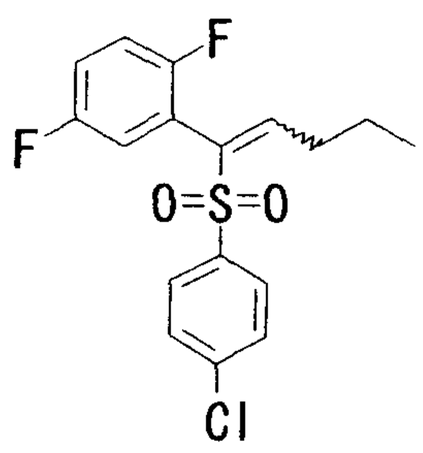
MS (m/z): 374 (M^+).

Elemental Analysis for $C_{17}H_{17}ClF_2O_3S$

Calculated: C 54.47%; H 4.57%; Cl 9.46%; F 10.14%; S 8.55%.

Found: C 54.27%; H 4.51%; Cl 9.44%; F 10.20%; S 8.70%.

Example 12: 2-[1-[(4-Chlorophenyl)sulfonyl]-1-penten-1-yl]-1,4-difluorobenzene



At 0°C, triethylamine (0.131 ml, 0.942mmol) and methanesulfonyl chloride (0.0665 ml, 0.856 mmol) were added to a solution of 1-[(4-chlorophenyl)sulfonyl]-1-(2,5-

difluorophenyl)-2-pentanol (204 mg, 0.544 mmol) in methylene chloride (10 ml). After stirring at 0°C for 1 hour, the reaction mixture was diluted with methylene chloride, washed successively with a saturated aqueous ammonium chloride solution, water and brine, dried over $MgSO_4$, and then concentrated. The residue was dissolved in tetrahydrofuran (5 ml). After cooling the solution to 0°C, potassium hexamethyldisilazide (a 0.5M toluene solution, 1.30 ml, 0.650 mmol) was added thereto. The resulting mixture was stirred at 0°C for 3 hours, and saturated ammonium chloride was added thereto. The resulting mixture was extracted with ethyl acetate, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (15% ethyl acetate-hexane). The resulting solid was recrystallized from hexane, whereby the title compound (33.0 mg, 17%) was obtained as colorless needle crystals.

Melting point: 95.5-97.0°C.

IR (ATR) ν: 2960, 1645, 1579, 1489, 1421, 1311, 1252, 1198, 1165, 1140, 1086, 1012, 818, 769, 752, 640, 606, 552, 467 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 0.89 (3H,t,J=7.3Hz), 1.45-1.56(2H,m), 2.00(2H,br s), 6.89(1H,td,J=8.3,4.4Hz), 7.01-7.08(2H,m), 7.31(1H,t,J=8.3Hz), 7.38(2H,d,J=8.5Hz),

7.55(2H,d,J=8.5Hz).

MS (m/z): 356 (M^+).

HRMS (EI): as $C_{17}H_{15}ClF_2O_2S$ (M^+)

Calculated: 356.0449

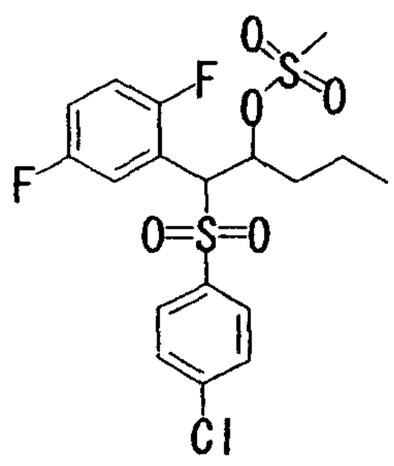
Found: 356.0450

Elemental Analysis for $C_{17}H_{15}ClF_2O_2S$

Calculated: C 57.22%; H 4.24%; Cl 9.94%; F 10.65%; S 8.99%.

Found: C 56.80%; H 4.21%; Cl 10.04%; F 10.65%; S 9.11%.

Example 13: 1-[(4-Chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-2-pentyl methanesulfonate



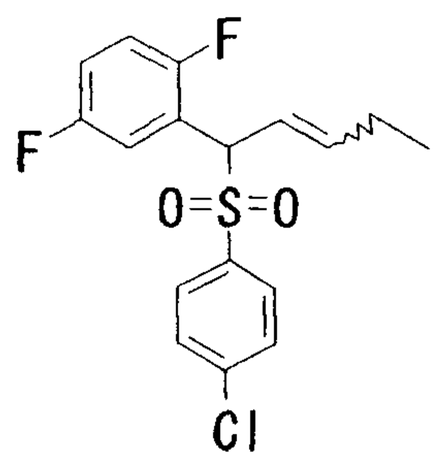
At 0°C, triethylamine (0.300 ml, 2.16mmol) and methanesulfonyl chloride (0.150 ml, 1.93 mmol) were added to a methylene chloride (10 ml) solution of the 1-[(4-chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-2-pentanol (449 mg, 1.20 mmol) obtained in Example 11. The resulting mixture was then stirred at 0°C for 2 hours. The reaction mixture was diluted with methylene chloride, washed successively with a saturated aqueous solution of ammonium chloride, water and brine, dried over $MgSO_4$, then

concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (15% ethyl acetate-hexane), whereby the title compound (503 mg, 93%) was obtained as a colorless solid.

IR (ATR) ν: 2966, 1498, 1350, 1176, 1149, 1086, 928, 879, 789, 752, 636, 592, 550, 525, 455 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.86(3H,t,J=7.1Hz), 1.33-1.61(3H,m), 1.88-1.96(1H,m), 3.21(3H,d,J=0.7Hz), 5.03(1H,d,J=7.7Hz), 5.58-5.66(1H,m), 6.83(1H,td,J=9.0,4.4Hz), 6.97-7.05(1H,m), 7.33-7.40(1H,m,including 2H,d,J=8.3Hz at 7.35ppm), 7.54(2H,d,J=8.3Hz).

Example 14: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-penten-1-yl]-1,4-difluorobenzene



To a solution of 1-[(4-chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-2-pentyl=methanesulfonato (200 mg, 0.442 mmol) in methylene chloride (4 ml) was added 1,8-diazabicyclo[5,4,0]undec-7-ene (69.1 μl, 0.464mmol) at room temperature. The mixture was stirred for 15 hours. The reaction mixture was concentrated. The residue was

purified by medium-pressure chromatography on a silica gel column (8% ethyl acetate-hexane), whereby the title compound (72.0 mg, 46%) was obtained as a colorless solid. The resulting solid was recrystallized from hexane to yield a colorless solid (60.0 mg).

Melting point: 99.0-100.0°C.

IR (ATR) ν: 1581, 1496, 1392, 1309, 1279, 1232, 1173, 1149, 1084, 978, 837, 816, 806, 758, 731, 710, 644, 598, 561, 521 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.99(3H,t,J=7.3Hz), 2.12(2H,m), 5.06(2H,d,J=7.3Hz), 5.74-5.85(2H,m), 6.92(1H,td,J=9.0,4.4Hz), 6.97-7.04(1H,m), 7.32(1H,ddd,J=8.5,5.4,3.2Hz), 7.43(2H,d,J=8.5Hz), 7.64(2H,d,J=8.5Hz).

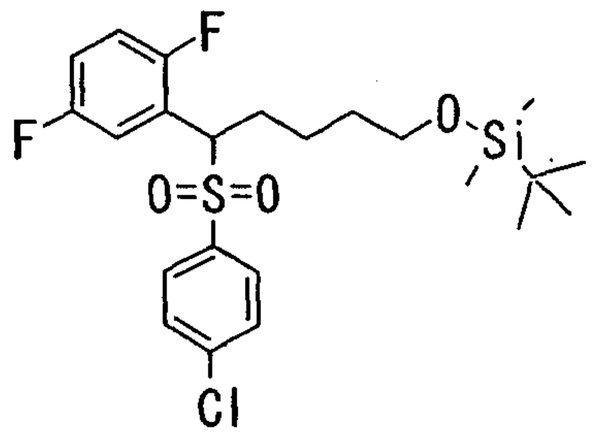
MS (m/z): 374 (M^++NH_4).

Elemental Analysis for $C_{17}H_{15}ClF_2O_2S$

Calculated: C 57.22%; H 4.24%; Cl 9.94%; F 10.65%; S 8.99%.

Analyzed: C 57.15%; H 4.18%; Cl 9.90%; F 10.74%; S 9.09%.

Example 15: 2-[5-(t-Butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.701 ml, 1.10 mmol) was added to a dimethoxyethane (5 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (303 mg, 1.00 mmol) obtained in Example 5. The mixture was stirred at -78°C for 1 hour and then, at room temperature for 30 minutes. The reaction mixture was cooled to -78°C, followed by the dropwise addition of 4-(t-butyldimethylsilyloxy)-1-iodobutane (0.260 ml, 1.00 mmol). While elevating the temperature of the reaction mixture to room temperature, stirring was conducted for 15 hours. Water was added to the reaction mixture, followed by extraction with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (8% ethyl acetate-hexane), whereby the title compound (401 mg, 82%) was obtained as a colorless solid. The resulting solid was recrystallized from hexane to yield colorless needle crystals.

IR (ATR) ν: 2945, 2927, 2854, 1583, 1496, 1427, 1392, 1321, 1248, 1144, 1082, 1038, 1012, 941, 822, 775, 748, 708, 623, 542, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: -0.02(3H,s), -0.02(3H,s), 0.82(9H,s), 1.23-1.33(2H,m), 1.42-1.58(2H,m), 2.06-2.18(1H,m), 2.39-2.48(1H,m), 3.53(2H,t,*J*=6.3Hz), 4.52(1H,dd,J=11.6,2.6Hz), 6.83(1H,td,J=9.0,4.4Hz), 6.94-7.00(1H,m), 7.22-7.26(1H,m), 7.38(2H,d,J=8.5Hz), 7.53(2H,d,J=8.5Hz).

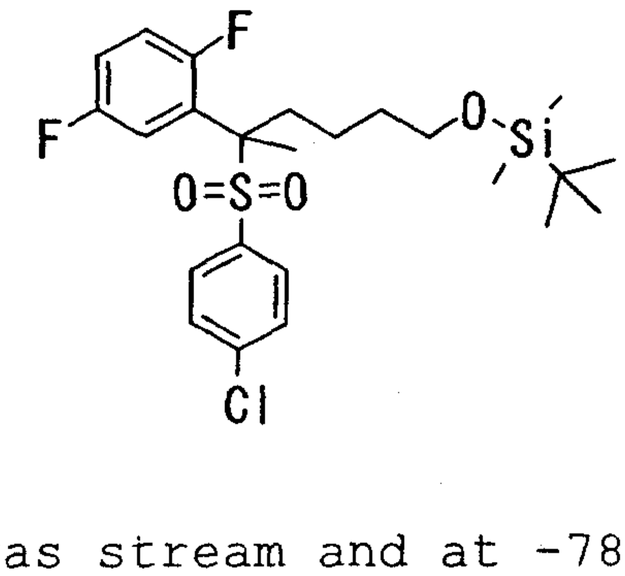
MS (m/z): 489 (M^++H).

Elemental Analysis for $C_{23}H_{31}ClF_2O_3SSi$

Calculated: C 56.48%; H 6.39%; Cl 7.25%; F 7.77%; S 6.56%.

Analyzed: C 56.29%; H 6.28%; Cl 7.29%; F 7.75%; S 6.70%.

Example 16: 2-[5-(t-Butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-1-methylpentyl]-1,4-difluorobenzene



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.294 ml, 0.461 mmol) was added to a solution of 2-[5-(t-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene (205 mg,

0.419 mmol) in tetrahydrofuran (4 ml). The mixture was stirred at room temperature for 1 hour. After cooling to -78°C, iodomethane (0.339 ml, 0.545 mmol) was added dropwise to the reaction mixture and the mixture was stirred at room temperature for 4 hours. Water was added to the reaction mixture, followed by extraction with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (6% ethyl acetate-hexane), whereby the title compound (168 mg, 80%) was obtained as a colorless oil.

IR (ATR) ν: 2952, 2929, 2856, 1583, 1496, 1473, 1392, 1311, 1255, 1192, 1149, 1090, 1014, 833, 760, 710, 629, 552 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: -0.01(3H,s), 0.00(3H,s), 0.84(9H,s), 1.05-1.18(1H,m), 1.29-1.41(1H,m), 1.52-1.60(2H,m), 1.81(3H,d,J=2.9Hz), 1.95-2.05(1H,m), 2.61-2.71(1H,m), 3.57(2H,t,J=6.1Hz), 6.82-6.88(1H,m), 6.98-7.07(2H,m), 7.38(2H,d,J=9.1Hz), 7.40(2H,d,J=9.1Hz).

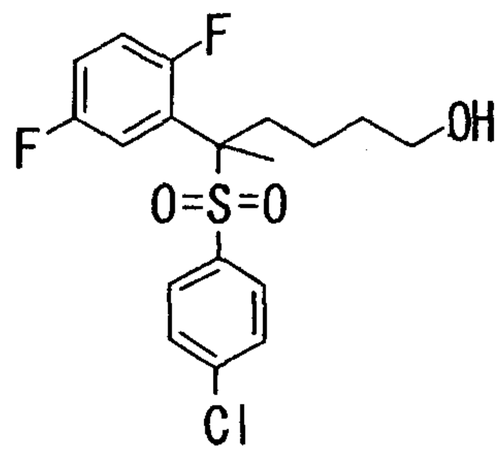
MS (m/z): 503 (M^+).

HRMS (FAB) for $C_{24}H_{34}ClF_2O_3SSi$ (M^++H)

Calculated: 503.1655

Analyzed: 503.1704

Example 17: 5-(4-Chlorophenylsulfonyl)-5-(2,5-difluorophenyl)-1-hexanol



After addition of tetrabutylammonium fluoride (a 1M tetrahydrofuran solution, 0.978 ml, 0.978 mmol) to a solution of 2-[5-(t-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-1-methylpentyl]-1,4-difluorobenzene (164 mg, 0.326 mmol) in tetrahydrofuran (4 ml), the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with diethyl ether, washed successively with saturated ammonium chloride, water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (50% ethyl acetate-hexane), whereby the title compound (122 mg, 96%) was obtained as a colorless oil.

IR (ATR) ν: 3516, 3089, 2939, 2870, 1583, 1495, 1475, 1412, 1394, 1306, 1279, 1188, 1146, 1088, 1070, 1012, 823, 758, 710, 679, 649, 602, 546, 474 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 2.09-2.20(1H,m), 1.23(1H,br s), 1.34-1.46(1H,m), 1.63(1H,quint,J=7.1Hz), 1.82(3H,d,J=2.7Hz), 1.98-2.07(1H,m), 2.71(1H,td,J=13.0,3.4Hz), 3.63(2H,t,J=6.4Hz), 6.83-6.90(1H,m), 6.99-7.06(2H,m),

7.38(4H,s).

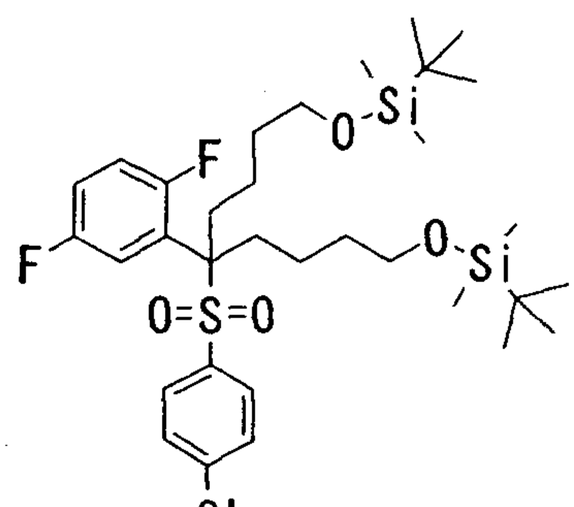
MS (m/z): 389 (M^++H).

HRMS (FAB) for $C_{18}H_{20}ClF_2O_3S$ (M^++H)

Calculated: 389.0790

Analyzed: 389.0795

Example 18: 2-[5-(t-Butyldimethylsilyloxy)-1-[4-(t-butyldimethylsilyloxy)butyl]-1-(4-chlorophenylsulfonyl)pentyl]-1,4-difluorobenzene



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.358 ml, 0.562 mmol) was added to a tetrahydrofuran (4 ml) solution of the 2-[5-(t-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene (250 mg, 0.511 mmol) obtained in Example 15. The temperature of the resulting mixture was raised to room temperature. After cooling to -78°C, 4-(t-butyldimethylsilyloxy)-1-iodobutane (0.146 ml, 0.562 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 3 days. Water was added to the reaction mixture, followed by extraction

with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (6% ethyl acetate-hexane), whereby the title compound (167 mg, 48%) was obtained as a colorless solid.

IR (ATR) ν: 3082, 2927, 2856, 1583, 1495, 1462, 1308, 1250, 1146, 1080, 1012, 833, 758, 675, 646, 607, 579, 544, 455 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.03(12H,s), 0.87(18H,s), 1.25-1.70(8H,m), 2.23-2.34(2H,m), 2.40-2.48(2H,m), 3.58-3.68(4H,m), 6.74-6.82(1H,m), 6.97-7.06(2H,m), 7.30(2H,d,J=8.8Hz), 7.34(2H,d,J=8.8Hz).

MS (m/z): 675 (M^++H).

HRMS (FAB) for $C_{33}H_{54}ClF_2O_4SSi_2$ (M^++H)

Calculated: 675.2938

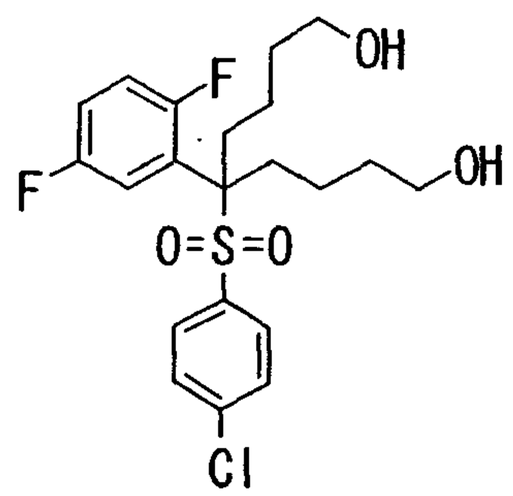
Analyzed: 675.2900

Elemental Analysis for $C_{33}H_{53}ClF_2O_4SSi_2$

Calculated: C 58.68%; H 7.91%; Cl 5.25%; F 5.63%.

Analyzed: C 58.63%; H 7.91%; Cl 5.32%; F 5.69%.

Example 19: 5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-1,9-nonanediol



To a solution of 2-[5-(t-butyldimethylsilyloxy)-1-[4-(t-butyldimethylsilyloxy)butyl]-1-(4-chlorophenylsulfonyl)pentyl]-1,4-difluorobenzene (158 mg, 0.234 mmol) in tetrahydrofuran (4 ml) was added tetrabutylammonium fluoride (a 1M tetrahydrofuran solution, 0.702 ml, 0.702 mmol). The resulting mixture was stirred at room temperature for 24 hours. After concentration of the reaction mixture, the residue was dissolved in diethyl ether, followed by successive washing with water and brine, drying over $MgSO_4$, and concentration. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (5% methanol-methylene chloride) to yield a colorless solid. The resulting solid was recrystallized from ethyl acetate-hexane, whereby the title compound (97.0 mg, 93%) was obtained as a colorless solid.

Melting point: 107.0-108.5°C.

IR (ATR) ν: 3275, 2939, 1572, 1495, 1414, 1306, 1261, 1140, 1078, 1066, 847, 812, 754, 710, 679, 644, 606, 544, 474, 449 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.36-1.82(10H,m), 2.24-2.35(2H,m),

2.47-2.57(2H,m), 3.70(4H,t,J=5.9Hz),

6.79(1H,ddd,J=12.4,8.3,4.6Hz), 6.97-7.08(2H,m),

7.29(2H,d,J=8.8Hz), 7.34(2H,d,J=8.8Hz).

MS (m/z): 447 (M^++H).

HRMS (FAB) for $C_{21}H_{26}ClF_2O_4S$ (M^++H)

Calculated: 447.1208

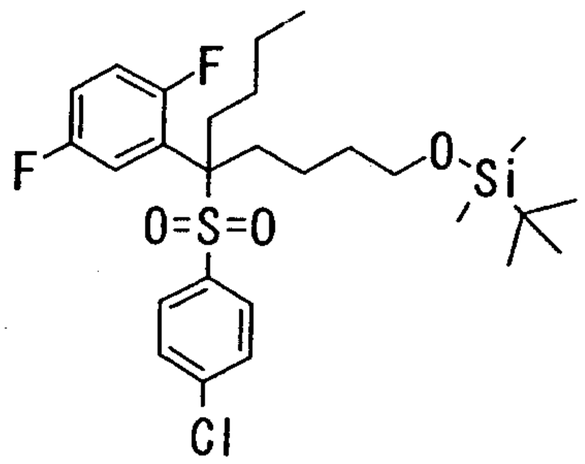
Found: 447.1227

Elemental Analysis for $C_{21}H_{25}ClF_2O_4S \cdot 0.25H_2O$

Calculated: C 55.87%; H 5.69%; Cl 7.85%; F 8.42%; S 7.10%.

Analyzed: C 55.62%; H 5.40%; Cl 7.89%; F 8.58%; S 7.26%.

Example 20: 2-[5-(t-Butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-1-butylpentyl]-1,4-difluorobenzene



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.287 ml, 0.450 mmol) was added to a tetrahydrofuran (4 ml) solution of the 2-[5-(t-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene (200 mg, 0.409 mmol) obtained in Example 15. The temperature of the resulting mixture was raised to room temperature. After cooling to -78°C,

hexamethylphosphoric triamide (0.214 ml, 1.23 mmol) and iodobutane (51.1 µl, 0.450 mmol) were added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 20 hours. Isopropanol (0.5 ml) was added to the reaction mixture, followed by concentration. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (5% ethyl acetate-hexane), whereby the title compound (163 mg, 73%) was obtained as a colorless oil.

IR (ATR) ν: 2954, 2929, 2858, 1583, 1495, 1473, 1412, 1394, 1311, 1255, 1192, 1147, 1090, 1014, 833, 756, 710, 677, 606 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.03(6H,s), 0.87(9H,s), 0.95(3H,t,J=7.4Hz), 1.20-1.45(5H,m), 1.52-1.70(3H,m), 2.21-2.32(2H,m), 2.40-2.49(2H,m), 3.64(2H,t,J=6.1Hz), 6.74-6.82(1H,m), 6.97-7.07(2H,m), 7.29(2H,d,J=8.8Hz), 7.34(2H,d,J=8.8Hz).

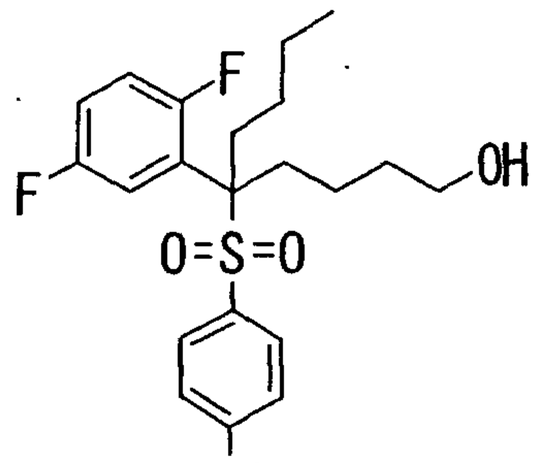
MS (m/z): 545 (M^+).

HRMS (FAB) for $C_{27}H_{40}ClF_2O_3SSi$ (M^++H)

Calculated: 545.2124

Analyzed: 545.2087

Example 21: 5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-1-nonanol



Cl

After addition of tetrabutylammonium fluoride (a 1M tetrahydrofuran solution, 0.532 ml, 0.532 mmol) to a solution of 2-[5-(t-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-1-butylpentyl]-1,4-difluorobenzene (154 mg, 0.283 mmol) in tetrahydrofuran (4 ml), the mixture was stirred at room temperature for 18 hours. The reaction mixture was then concentrated. The residue thus obtained was dissolved in diethyl ether, followed by successive washing with water and brine, drying over $MgSO_4$, and concentration. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (50% ethyl acetate-hexane), whereby the title compound (122 mg, 0.283 mmol) was obtained as a colorless oil.

IR (ATR) ν: 3539, 2958, 2873, 1583, 1495, 1412, 1308, 1277, 1192, 1146, 1090, 1014, 829, 758, 710, 675, 606, 548, 463 cm^{-1}.

^1H-NMR (400 MHz, $CDCl_3$) δ: 0.95(3H,t,J=7.3Hz), 1.19-1.77(9H,m), 2.21-2.34(2H,m), 2.38-2.53(2H,m), 3.70(2H,br s), 6.75-6.83(1H,m), 6.98-7.08(2H,m), 7.29(2H,d,J=8.8Hz),

7.34(2H,d,J=8.8Hz).

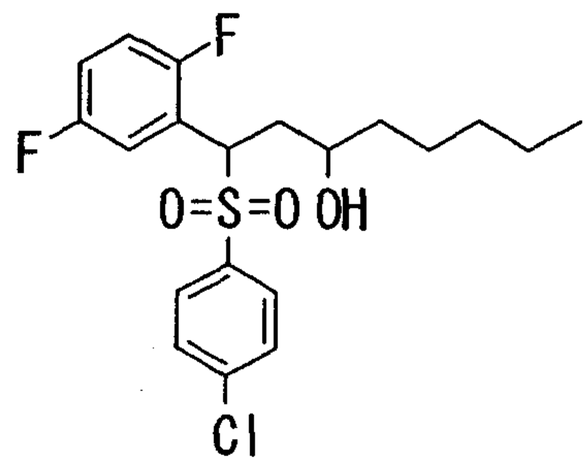
MS (m/z): 431 (M^++H).

HRMS (EI): as $C_{21}H_{26}ClF_2O_3S$ (M^++H)

Calculated: 431.1259

Found: 431.1237

Example 22: 1-[(4-Chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-3-octanol (Isomer 22-A and Isomer 22-B)



In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.701 ml, 1.10 mmol) was added to a tetrahydrofuran (5 ml) solution of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (303 mg, 1.00 mmol) obtained in Example 5. The temperature of the resulting mixture was raised to room temperature. After cooling to -78°C, a trifluoroborane-ether complex (0.133 ml, 1.05 mmol) and 1,2-epoxyheptane (0.163 ml, 1.20 mmol) were added dropwise to the reaction mixture. The mixture was stirred at room temperature for 2 days. Water was added to the reaction mixture, followed by extraction with diethyl ether. The extracts were combined, washed successively with a saturated aqueous solution of sodium bicarbonate,

water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (20% ethyl acetate-hexane), whereby a low-polarity isomer, an isomer mixture and a high-polarity isomer were obtained as a first fraction, a second fraction and a third fraction, respectively, each as a colorless solid. The low-polarity isomer and high-polarity isomer were recrystallized from hexane to yield the title Isomer 22-A (low-polarity) (98.0 mg, 24%), and the title Isomer 22-B (high-polarity) (199 mg, 48%), each as colorless needle crystals.

Isomer 22-A

Melting point: 84.0-84.5°C.

IR (ATR) ν: 3533, 2933, 2860, 1574, 1495, 1429, 1278, 1240, 1182, 1142, 1092, 1080, 1014, 962, 885, 829, 766, 737, 710, 681, 619, 526, 476 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 0.88(3H,t,J=6.8Hz), 1.20-1.50(8H,m), 1.57(1H,d,J=5.1Hz), 2.07(1H,ddd,J=14.7,8.1,6.8Hz), 2.70(1H,ddd,J=14.7,6.8,4.6Hz), 3.93-4.01(1H,m), 4.85(1H,t,J=6.8Hz), 6.77(1H,td,J=9.0,4.4Hz), 6.91-6.98(1H,m), 7.24-7.30(1H,m), 7.36(2H,d,J=8.5Hz), 7.51(2H,d,J=8.5Hz).

MS (m/z): 417 (M^++H).

HRMS (FAB) for $C_{20}H_{24}ClF_2O_3S$ (M^++H)

Calculated: 417.1103

Analyzed: 417.1102

Elemental Analysis for $C_{20}H_{23}ClF_2O_3S \cdot 0.25H_2O$

Calculated: C 57.00%; H 5.62%; Cl 8.41%; F 9.02%; S 7.61%.

Analyzed: C 57.18%; H 5.38%; Cl 8.57%; F 9.22%; S 7.79%.

Isomer 22-B

Melting point: 123.0-123.5°C.

IR (ATR) ν: 3502, 2925, 2858, 1583, 1496, 1410, 1304, 1275, 1213, 1184, 1149, 1086, 1045, 1014, 958, 910, 829, 796, 752, 725, 710, 627, 552, 503, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.87 (3H,t,J=7.1Hz), 1.20-1.60(9H,m), 2.21-2.30(1H,m), 2.41(1H,ddd, J=13.9,10.5,3.4Hz), 3.23-3.32(1H,m), 4.94(1H,dd,J=11.7,2.9Hz), 6.85(1H,td,J=9.0,4.4Hz), 6.96-7.03(1H,m), 7.23-7.29(1H,m), 7.39(2H,d,J=8.5Hz), 7.55(2H,d,J=8.5Hz).

MS (m/z) 417 (M^++H).

HRMS (FAB) for $C_{20}H_{24}ClF_2O_3S$ (M^++H)

Calculated: 417.1103

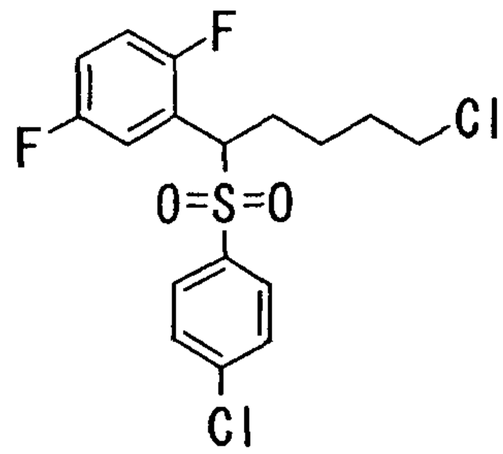
Analyzed: 417.1122

Elemental Analysis for $C_{20}H_{23}ClF_2O_3S \cdot 0.25H_2O$

Calculated: C 57.00%; H 5.62%; Cl 8.41%; F 9.02%; S 7.61%.

Analyzed: C 57.16%; H 5.34%; Cl 8.55%; F 9.18%; S 7.82%.

Example 23: 2-[5-Chloro-1-[(4-chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene



Under an argon atmosphere and at -78°C, n-butyl lithium (a 1.57M hexane solution, 3.52 ml) was added to a dimethoxyethane solution (30 ml) of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (1.52 g, 5.02 mmol) obtained in Example 5. The temperature of the reaction mixture was elevated to room temperature, at which stirring was conducted for 15 minutes. After cooling the reaction mixture to -78°C, 4-chloro-1-iodobutane (672 µl, 5.52 mmol) was added thereto and the mixture was stirred at room temperature for 24 hours. A saturated ammonium chloride solution was added to the reaction mixture, followed by extraction with diethyl ether. The extracts were combined, washed successively with water, a saturated aqueous solution of sodium thiosulfate and brine, dried over $MgSO_4$, and then distilled under reduced pressure to remove the solvent. The residue thus obtained was recrystallized from hexane, whereby the title compound (1.64 g, 83%) was obtained as colorless needle crystals.

IR (ATR) ν: 2945, 1583, 1495, 1475, 1311, 1277, 1230, 1149, 1142, 1082, 1014, 872, 822, 793, 752, 708, 629, 557, 532, 465 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.33-1.48(2H,m), 1.72-1.87(2H,m), 2.08-2.18(1H,m), 2.43-2.52(1H,m), 3.44-3.53(2H,m), 4.52(1H,ddd,J=11.5,3.9,1.2Hz), 6.84(1H,td,J=9.0,4.4Hz), 6.96-7.02(1H,m), 7.23-7.28(1H,m), 7.39(2H,d,J=8.8Hz), 7.53(2H,d,J=8.8Hz).

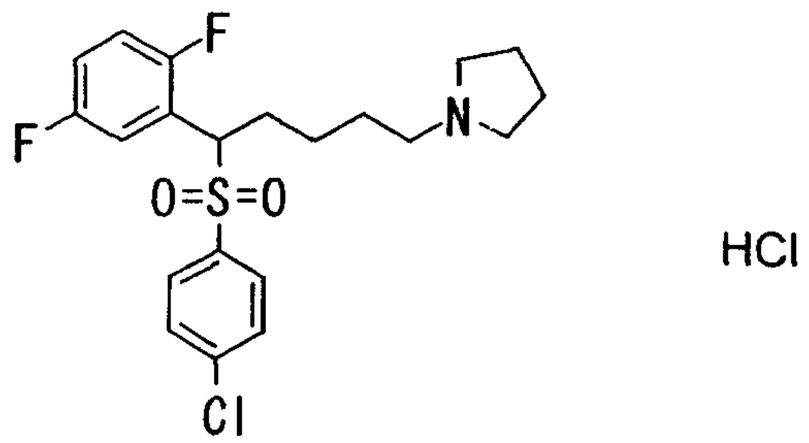
MS (m/z): 393 (M^++H).

Elemental Analysis for $C_{17}H_{16}Cl_2F_2O_2S$

Calculated: C 51.92%; H 4.10%; Cl 18.03%; F 9.66%; S 8.15%.

Found: C 51.33%; H 4.07%; Cl 17.64%; F 9.72%; S 8.25%.

Example 24: 1-[5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)pentyl]pyrrolidine hydrochloride



To a solution of 2-[5-chloro-1-[(4-chlorophenyl)sulfonyl]pentyl]-1,4-difluorobenzene (200 mg, 0.509 mmol) in acetonitrile (6 ml) were added pyrrolidine (213 μl, 2.55 mmol), potassium carbonate (73.7 mg, 0.534 mmol) and potassium iodide (15 mg). The resulting mixture

was heated at 70°C for 18 hours. The temperature of the reaction mixture was cooled back to room temperature. The residue thus obtained was partitioned between water and methylene chloride. After separation of the organic layer, the water layer was extracted with methylene chloride. The organic layer and the extract were combined, washed with water and brine, dried over $MgSO_4$, and then concentrated. The crude product thus obtained was subjected to a short column (SiO_2, methylene chloride-methanol, 10:1). The resulting oil was dissolved in ethanol. After addition of 1N hydrochloric acid-ethanol (2 ml) to the resulting solution, the mixture was concentrated. The solid substance thus obtained was recrystallized from ethyl acetate, whereby the title compound (128 mg, 54%) was obtained as a pale yellow solid.

Melting point: 167.0-170.5°C.

IR (ATR) ν: 2960, 2565, 2453, 1583, 1495, 1321, 1277, 1211, 1173, 1145, 1084, 1011, 879, 820, 787, 754, 721, 708, 627, 557, 540, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.31-1.47(2H,m), 1.93-2.30(6H,m), 2.42-2.51(1H,m), 2.66-2.78(2H,m), 2.87-3.03(2H,m), 3.76(2H,br s), 4.51(1H,dd,J=10.7,4.4Hz), 6.85(1H,td,J=8.8,4.4Hz), 6.96-7.03(1H,m), 7.22(1H,ddd,J=8.8,5.4,3.2Hz), 7.40(2H,d,J=8.3Hz), 7.54(2H,d,J=8.3Hz), 12.54(1H,br s).

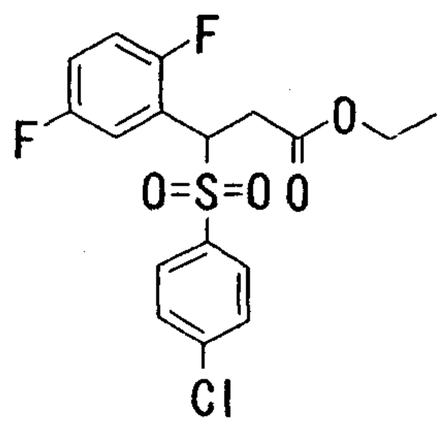
MS (m/z): 428 (M^++H).

Elemental Analysis for $C_{21}H_{24}ClF_2NO_2S \cdot HCl$

Calculated: C 54.31%; H 5.43%; Cl 15.27%; F 8.18%; N 3.02%; S 6.90%.

Analyzed: C 54.19%; H 5.37%; Cl 15.07%; F 8.10%;N 3.21%; S 6.98%.

Example 25: Ethyl 3-[(4-chlorophenyl)sulfonyl]-3-(2,5-difluorophenyl)propionate



Under an argon atmosphere and at -78°C, n-butyl lithium (a 1.57M hexane solution, 7.01 ml) was added to a dimethoxyethane solution (50 ml) of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (3.03 g, 10.0 mmol) obtained in Example 5. The temperature of the reaction mixture was raised to room temperature, at which stirring was conducted for 15 minutes. After cooling to -78°C, bromoethyl acetate (1.33 ml, 12.0 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 3 hours. To the reaction mixture was added a saturated ammonium chloride solution, followed by extraction with diethyl ether. The extracts were combined, washed successively with water, a saturated aqueous

solution of sodium thiosulfate, and brine, dried over $MgSO_4$, and then distilled under reduced pressure to remove the solvent. The residue thus obtained was recrystallized from hexane, whereby the title compound (1.95 g, 50%) was obtained as colorless needle crystals.

Melting point: 99.5-100.5°C.

IR (ATR) ν: 3078, 2952, 1734, 1587, 1493, 1419, 1377, 1327, 1279, 1213, 1149, 1047, 1014, 829, 779, 754, 727, 611, 542, 453 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.15(3H,t,J=7.1Hz), 3.08(1H,dd,J=16.6,10.3Hz), 3.46(1H,dd,J=16.6,4.6Hz), 3.99-4.12(2H,m), 5.06(1H,dd,J=10.3,4.6Hz), 6.85(1H,td,J=9.0,4.4Hz), 6.96-7.02(1H,m), 7.19(1H,ddd,J=8.6,5.4,3.2Hz), 7.42(2H,d,J=8.8Hz), 7.56(2H,d,J=8.8Hz).

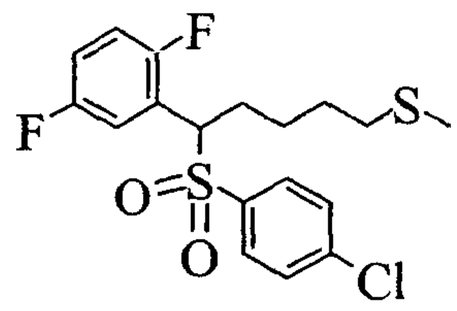
MS (m/z): 389 (M^++H).

Elemental Analysis for $C_{17}H_{15}ClF_2O_4S$

Calculated: C 52.51%; H 3.89%; Cl 9.12%; F 9.77%; S 8.25%.

Found: C 52.33%; H 3.86%; Cl 9.10%; F 9.88%; S 8.37%.

Example 26: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylthio)pentyl]-1,4-difluorobenzene



The 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (0.94 g, 3.1 mmol) obtained in Example 5 was dissolved in toluene (15 ml). After addition of 4-(methylthio)-1-butanol (0.25 ml, 2.1 mmol) and cyanomethylenetri-n-butylphosphorane (1.0 g, 4.1 mmol), the resulting mixture was heated under reflux for 14 hours under an argon atmosphere. The reaction mixture was allowed to cool down. Then, 4-(methylthio)-1-butanol (0.25 ml, 2.1 mmol) was added, followed by heating under reflux for 6 hours under an argon atmosphere. The reaction mixture was allowed to cool down and then, concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate = 10:1) to yield a colorless oil. The resulting colorless oil was solidified with hexane, whereby the title compound (0.55 g, 44%) was obtained as a white powder.

Melting point: 103-106°C.

IR (ATR) ν: 3066, 2960, 2935, 1583, 1493, 1147, 1082, 1012, 893, 829, 752, 625, 542, 465 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.23-1.45(2H,m), 1.50-1.75(2H,m), 2.04(3H,s), 2.04-2.20(1H,m), 2.35-2.60(3H,m),

4.52(1H,dd,J=11.5,2.4Hz), 6.78-6.88(1H,m), 6.95-7.01(1H,m), 7.20-7.30(1H,m), 7.38(2H,dm,J=8.4Hz), 7.53(2H,dm,J=8.4Hz).

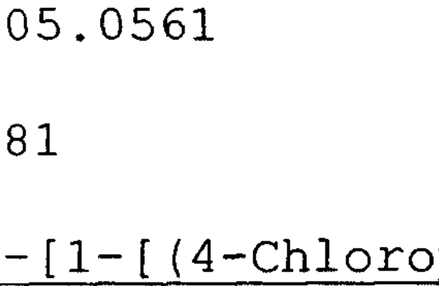
MS (m/z): 405, 407 (M^++H).

HRMS (FAB) for $C_{18}H_{20}ClF_2O_2S_2$ (M^++H)

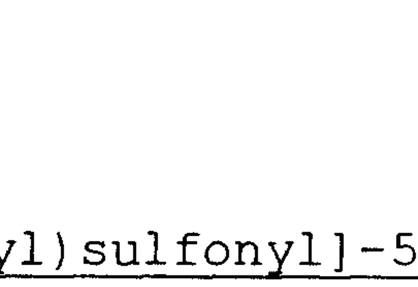
Calculated: 405.0561

Found: 405.0581

Example 27: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]-1,4-difluorobenzene (Compound A) and 2-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfinyl)pentyl]-1,4-difluorobenzene (Compound B)



Compound A



Compound B

In methylene chloride (30 ml) was dissolved 2-[1-[(4-chlorophenyl)sulfonyl]-5-(methylthio)pentyl]-1,4-difluorobenzene (500 mg, 1.23 mmol). Under ice cooling, 3-chloroperbenzoic acid (340 mg, 1.97 mmol) was added to the resulting solution. The mixture was stirred at room temperature for 14 hours. After concentration of the reaction mixture under reduced pressure, the residue was subjected to silica gel chromatography. From the fraction eluted with hexane:ethyl acetate=10:1, a white solid was

obtained. The solid was then washed with diethyl ether/methylene chloride to yield the title compound A (211 mg, 39%) as a white powder. Further, from the fraction eluted with the methylene chloride:methanol=40:1, a white solid was obtained. The solid was washed with diethyl ether/methylene chloride, whereby the title compound B (144 mg, 39%) was obtained as a white powder.

Compound A

Melting point: 145-148°C.

IR (ATR) ν: 1496, 1317, 1292, 1273, 1149, 1124, 1086, 829, 756, 631, 544, 523, 499, 478, 465 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.38-1.70(2H,m), 1.80-2.00(2H,m), 2.05-2.22(1H,m), 2.45-2.60(1H,m), 2.88(3H,s), 2.96(2H,tm,J=7.0Hz), 4.51(1H,dm,J=7.6Hz), 6.80-6.90(1H,m), 6.95-7.05(1H,m), 7.20-7.35(1H,m), 7.39(2H,d,J=8.7Hz), 7.53(2H,d,J=8.7Hz).

MS (m/z): 437, 439(M^++H).

Elemental Analysis for $C_{18}H_{19}ClF_2O_4S_2$

Calculated: C 49.48%; H 4.38%; Cl 8.11%;F 8.70%; S 14.68%.

Found: C 49.50%; H 4.28%; Cl 8.05%; F 8.77%; S 14.70%.

Compound B

Melting point: 126-129°C.

IR (ATR) ν: 1495, 1475, 1277, 1147, 1086, 1012, 833, 752, 625, 540, 465 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.32-1.70(2H,m), 1.75-1.93(2H,m), 2.08-2.22(1H,m), 2.46-2.75(3H,m), 2.54(3H,S), 4.52(1H,dd,J=11.4,2.4Hz), 6.80-6.90(1H,m), 6.94-7.04(1H,m), 7.20-7.30(1H,m), 7.39(2H,dd,J=8.5,1.8Hz), 7.53(2H,dd,J=8.5,2.7Hz).

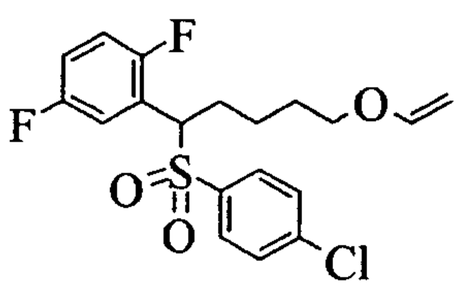
MS (m/z): 421, 423 (M^++H).

Elemental Analysis for $C_{18}H_{19}ClF_2O_3S_2$

Calculated: C 51.36%; H 4.55%; Cl 8.42%; F 9.03%; S 15.24%.

Found: C 51.36%; H 4.49%; Cl 8.35%; F 9.00%; S 15.24%.

Example 28: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-vinyloxypentyl]-1,4-difluorobenzene



The 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (0.94 g, 3.1 mmol) obtained in Example 5 was dissolved in toluene (30 ml). After addition of 4-vinyloxy-1-butanol (0.51 ml, 4.2 mmol) and cyanomethylenetri-n-butylphosphorane (1.0 g, 4.1 mmol), the resulting mixture was heated under reflux for 3 days under an argon atmosphere. The reaction mixture was allowed to cool down and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=10:1) to yield a white

solid. The resulting white solid was washed with hexane, whereby the title compound (0.97 g, 78%) was obtained as a white powder.

Melting point: 54-56°C.

IR (ATR) ν: 2943, 1618, 1495, 1475, 1308, 1198, 1147, 1080, 1012, 962, 899, 829, 750, 623, 559, 544, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.25-1.45(2H,m), 1.55-1.80(2H,m), 2.05-2.22(1H,m), 2.40-2.55(1H,m), 3.62(2H,t,J=6.2Hz), 3.96(1H,dd,J=6.8,2.1Hz), 4.12(1H,dd,J=14.4,2.1Hz), 4.53(1H,dd,J=11.5,2.7Hz), 6.39(1H,dd,J=14.4,6.8Hz), 6.80-6.90(1H,m), 6.95-7.04(1H,m), 7.20-7.30(1H,m), 7.39(2H,d,J=8.6Hz), 7.54(2H,d,J=8.6Hz).

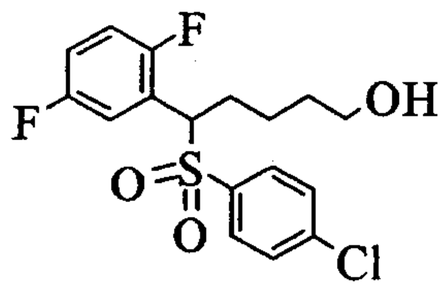
MS (m/z): 418, 420 (M^++NH_4).

Elemental Analysis for $C_{19}H_{19}ClF_2O_3S$

Calculated: C 56.93%; H 4.78%; Cl 8.84%; F 9.48%; S 8.00%.

Found: C 56.98%; H 4.83%; Cl 8.78%; F 9.51%; S 8.13%.

Example 29: 5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-1-pentanol



In methanol (30 ml) was dissolved 2-[1-[(4-chlorophenyl)sulfonyl]-5-vinyloxypentyl]-1,4-difluorobenzene (0.90 g, 2.3 mmol). After addition of p-

toluenesulfonic acid monohydrate (20 mg, 0.11 mmol), the resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=3:2) to yield a white solid. The resulting white solid was washed with diisopropyl ether, whereby the title compound (0.73 g, 85%) was obtained as a white powder.

Melting point: 84-86°C.

IR (ATR) ν: 3325, 2941, 2866, 1583, 1496, 1313, 1151, 1084, 825, 752, 629, 534 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.18-1.29(1H,m), 1.29-1.40(2H,m), 1.40-1.70(2H,m), 2.08-2.22(1H,m), 2.42-2.55(1H,m), 3.55-3.67(2H,m), 4.53(1H,dd,J=11.4,3.8Hz), 6.78-6.88(1H,m), 6.93-7.03(1H,m), 7.20-7.30(1H,m), 7.39(2H,d,J=8.5Hz), 7.53(2H,d,J=8.5Hz).

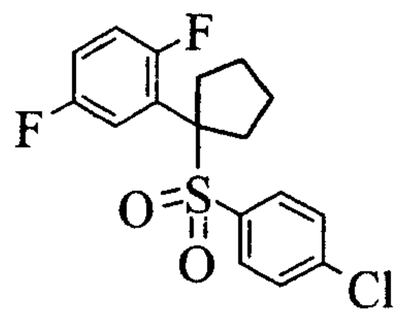
MS (m/z): 375, 377 (M^++H).

Elemental Analysis for $C_{17}H_{17}ClF_2O_3S \cdot 0.25H_2O$

Calculated: C 53.83%; H 4.65%; Cl 9.35%; F 10.02%; S 8.45%.

Found: C 53.73%; H 4.63%; Cl 9.35%; F 10.03%; S 8.55%.

Example 30: 2-[1-[(4-Chlorophenyl)sulfonyl]cyclopentyl]-1,4-difluorobenzene



In toluene (10 ml) was dissolved 5-[(4-chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-1-pentanol (100 mg, 0.267 mmol). After addition of cyanomethylenetri-n-butylphosphorane (130 mg, 0.539 mmol), the mixture was heated under reflux for 2 days under an argon atmosphere. The reaction mixture was allowed to cool down and then, added with cyanomethylenetri-n-butylphosphorane (130 mg, 0.539 mmol). The mixture was heated under reflux for 3 days under an argon atmosphere. The reaction mixture was allowed to cool down and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=15:1) to yield a white solid. The resulting white solid was washed with hexane, whereby the title compound (35 mg, 37%) was obtained as a white powder.

Melting point: 153-155°C.

IR (ATR) ν: 2968, 1581, 1489, 1304, 1277, 1138, 1082, 827, 752, 606, 569, 519, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.70-1.85 (2H,m), 2.05-2.20 (2H,m), 2.22-2.35(2H,m), 2.88-3.00(2H,m), 6.75-6.83(1H,m), 6.95-7.05(2H,m), 7.35(4H,s).

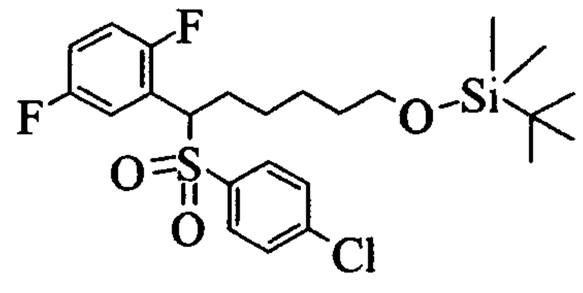
MS (m/z): 374, 376(M^++NH_4).

Elemental Analysis for $C_{17}H_{15}ClF_2O_2S$

Calculated: C 57.22%; H 4.24%; Cl 9.94%; F 10.65%; S 8.99%.

Found: C 56.87%; H 4.14%; Cl 10.28%; F 10.44%; S 9.05%.

Example 31: 2-[6-(t-Butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]hexyl]-1,4-difluorobenzene



In toluene (30 ml) was dissolved the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (0.94 g, 3.1 mmol) obtained in Example 5, followed by the addition of 5-(t-butyldimethylsilyloxy)-1-pentanol (1.1 ml, 4.6 mmol) and cyanomethylenetri-n-butylphosphorane (1.0 g, 4.1 mmol). The resulting mixture was heated under reflux for 14 hours under an argon atmosphere. The reaction mixture was allowed to cool down and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=15:1), whereby the title compound (1.4 g, 87%) was obtained as a colorless oil.

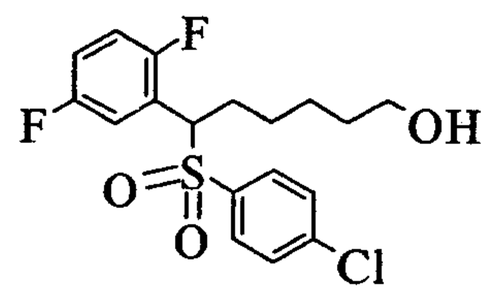
IR (ATR) ν: 2929, 2856, 1583, 1496, 1325, 1151, 1088, 835, 775, 754, 629 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.01(6H,s), 0.86(9H,s), 1.18-

1.60(6H,m), 2.04-2.17(1H,m), 2.38-2.50(1H,m), 3.54(2H,t,J=6.1Hz), 4.53(1H,dd,J=11.5,2.7Hz), 6.78-6.88(1H,m), 6.93-7.03(1H,m), 7.20-7.30(1H,m), 7.38(2H,d,J=8.5Hz), 7.53(2H,d,J=8.5Hz).

MS (m/z): 503, 505 (M^++H).

Example 32: 6-[(4-Chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-1-hexanol



In tetrahydrofuran (30 ml) was dissolved 2-[6-(t-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]hexyl]-1,4-difluorobenzene (0.70 g, 1.4 mmol). Under ice cooling, a tetrahydrofuran solution (1.0M, 4.2 ml, 4.2 mmol) of tetrabutylammonium fluoride was added and the mixture was stirred at room temperature for 1 hour. After addition of water (1.0 ml) to the reaction mixture, the mixture was concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=3:2) to yield a white solid. The resulting white solid was washed with hexane, whereby the title compound (0.47 g, 86%) was obtained as a white powder.

Melting point: 98-99°C.

IR (ATR) ν: 3575, 2929, 1495, 1279, 1146, 1082, 1014, 833,

752, 627, 541, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.18-1.62(7H,m), 2.04-2.18(1H,m), 2.40-2.53(1H,m), 3.59(2H,dd,J=11.5,6.4Hz), 4.52(1H,dd,J=11.5,2.7Hz), 6.78-6.88(1H,m), 6.94-7.04(1H,m), 7.20-7.30(1H,m), 7.38(2H,d,J=8.4Hz), 7.53(2H,d,J=8.4Hz).

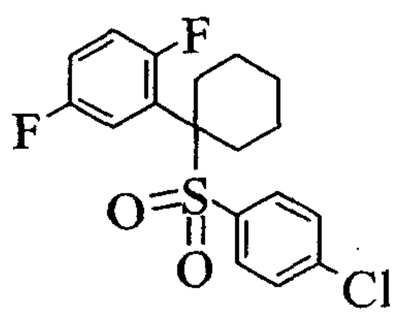
MS (m/z): 389, 391 (M^++H).

Elemental Analysis for $C_{18}H_{19}ClF_2O_3S$

Calculated: C 55.60%; H 4.92%; Cl 9.12%; F 9.77%; S 8.25%.

Found: C 55.38%; H 4.75%; Cl 9.09%; F 9.81%; S 8.34%.

Example 33: 2-[1-[(4-Chlorophenyl)sulfonyl]cyclohexyl]-1,4-difluorobenzene



In toluene (20 ml) was dissolved 6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-1-hexanol (200 mg, 0.514 mmol). After addition of cyanomethylenetri-n-butylphosphorane (500 mg, 2.07 mmol), the resulting mixture was heated under reflux for 4 days under an argon atmosphere. The reaction mixture was allowed to cool down and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=20:1) to yield a white solid. The resulting solid was washed with hexane/methylene chloride,

whereby the title compound (97 mg, 51%) was obtained as a white powder.

Melting point: 137-139°C.

IR (ATR) ν: cm^{-1}. 2933, 2862, 1495, 1309, 1144, 1082, 885, 814, 750, 619, 559, 464 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.10-1.45(3H,m), 1.61(1H,dm,J=12.0Hz), 1.81(2H,br d,J=13.4Hz), 2.09(2H,br t,J=13.0Hz), 2.55-2.95(2H,m), 6.84(1H,ddd,J=12.2,9.0,4.9Hz), 7.00-7.11(2H,m), 7.36(2H,s), 7.36(2H,s).

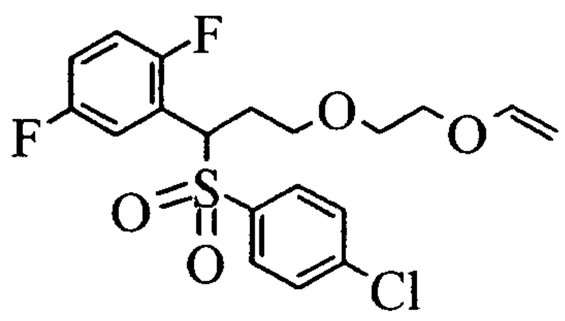
MS (m/z): 388, 390 (M^++NH_4).

Elemental Analysis for $C_{18}H_{17}ClF_2O_3S$

Calculated: C 58.30%; H 4.62%; Cl 9.56%; F 10.25%; S 8.65%.

Found: C 58.01%; H 4.49%; Cl 9.58%; F 10.35%; S 8.82%.

Example 34: 2-[1-[(4-Chlorophenyl)sulfonyl]-3-(2-vinyloxyethoxy)propyl]-1,4-difluorobenzene



In toluene (30 ml) was dissolved the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (520 mg, 1.72 mmol) obtained in Example 5. After addition of 2,2-(2-vinyloxyethoxy)ethanol (0.270 ml, 2.10 mmol) and cyanomethylenetri-n-butylphosphorane (500 mg, 2.07 mmol), the mixture was heated under reflux for 24 hours under an

argon atmosphere. The reaction mixture was then allowed to cool down. After addition of 2-(2-vinyloxyethoxy)-ethanol (0.170 ml, 1.25 mmol) and cyanomethylenetri-n-butylphosphorane (300 mg, 1.24 mmol), the mixture was heated under reflux for 12 hours under an argon atmosphere. The reaction mixture was allowed to cool down and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=7:1) to yield a white solid. The resulting white solid was washed with hexane, whereby the title compound (140 mg, 20%) was obtained as a white powder.

Melting point: 55-56°C.

IR (ATR) ν: 2927, 2877, 1621, 1496, 1323, 1198, 1144, 1084, 1012, 829, 752, 633, 542, 469 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.20-2.35(1H,m), 2.70-2.85 (1H,m), 3.28(1H,td,J=9.5,4.6Hz), 3.40-3.50(1H,m), 3.54-3.68(2H,m), 3.71(2H,t,J=4.6Hz), 3.99(1H,dd,J=6.7,2.1Hz), 4.14(1H,dd,J=14.3,2.1Hz), 4.81(1H,dd,J=10.9,4.0Hz), 6.41(1H,dd,J=14.3,6.7Hz), 6.84(1H,td,J=9.0,4.4Hz), 6.94-7.04(1H,m), 7.18-7.30(1H,m), 7.39(2H,dm,J=8.3Hz), 7.56(2H,dm,J=8.3Hz).

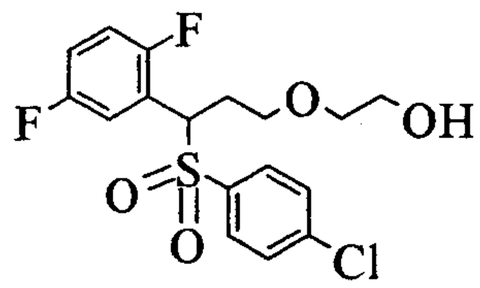
MS (m/z): 417, 419 (M^++H).

Elemental Analysis for $C_{19}H_{19}ClF_2O_4S$

Calculated: C 54.74%; H 4.59%; Cl 8.50%; F 9.11%; S 7.69%.

Found: C 54.54%; H 4.46%; Cl 8.46%; F 9.02%; S 7.81%.

Example 35: 2-[3-[(4-Chlorophenyl)sulfonyl]-3-(2,5-difluorophenyl)propoxy]ethanol



In methanol (10 ml) was dissolved 2-[1-[(4-chlorophenyl)sulfonyl]-3-(2-vinyloxyethoxy)propyl]-1,4-difluorobenzene (123 mg, 0.295 mmol). P-toluenesulfonic acid monohydrate (2.0 mg, 0.011 mmol) was added and the mixture was stirred at room temperature for 4 hours. After concentration under reduced pressure, the residue was purified by silica gel chromatography (methylene chloride:methanol=50:1) to yield a white solid. The resulting white solid was washed with hexane, whereby the title compound (80 mg, 70%) was obtained as a white powder.

Melting point: 41-46°C.

IR (ATR) ν: 3467, 2943, 1495, 1315, 1149, 1086, 1061, 829, 762, 521 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.78-1.80(1H,m), 2.22-2.36(1H,m), 2.75-2.88(1H,m), 3.20-3.40(2H,m), 3.42-3.52(1H,m), 3.57-3.73(3H,m), 4.81(1H,dd,J=10.9,3.8Hz), 6.84(1H,td,J=9.0,4.4Hz), 6.94-7.04(1H,m), 7.22-7.30(1H,m), 7.39(2H,dm,J=8.4Hz), 7.55(2H,dm,J=8.4Hz).

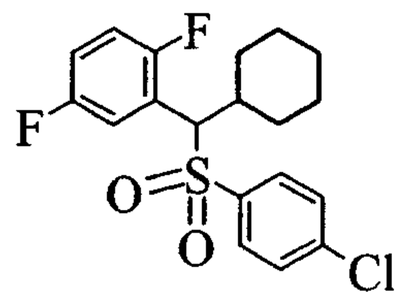
MS (m/z): 391, 393 (M^++H).

Elemental Analysis for $C_{17}H_{17}ClF_2O_4S$

Calculated: C 52.24%; H 4.38%; Cl 9.07%; F 9.72%; S 8.20%.

Found: C 52.12%; H 4.36%; Cl 9.11%; F 9.86%; S 8.32%.

Example 36: 2-[[(4-Chlorophenyl)sulfonyl](cylcohexyl)methyl]-1,4-difluorobenzene



The 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (240 mg, 0.793 mmol) obtained in Example 5 was dissolved in toluene (20 ml). To the resulting solution were added cyclohexanol (0.11 ml, 1.0 mmol) and cyanomethylenetri-n-butylphosphorane (250 mg, 1.0 mmol). The resulting mixture was heated under reflux for 14 hours under an argon atmosphere. The reaction mixture was allowed to cool down and then, added with cyclohexanol (0.22 ml, 2.1 mmol) and cyanomethylenetri-n-butylphosphorane (500 mg, 2.08 mmol). The mixture was heated under reflux for 14 hours under an argon atmosphere. After the reaction mixture was allowed to cool down and concentrated under reduced pressure, the residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=30:1) to yield a white solid. The

resulting white solid was washed with hexane, whereby the title compound (188 mg, 62%) was obtained as a white powder.

Melting point: 107-109°C.

IR (ATR) ν: 2927, 2858, 1495, 1240, 1138, 1080, 874, 831, 796, 750, 708, 615, 548, 507, 469, 444 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.92-1.08(1H,m), 1.08-1.22(1H,m), 1.22-1.50(3H,m), 1.60-1.75(3H,m), 1.75-1.88(1H,m), 2.37(1H,br d,J=12.5Hz), 2.48-2.62(1H,m), 4.44(1H,d,J=7.6Hz), 6.68-6.80(1H,m), 6.86-6.95(1H,m), 7.30(2H,dm,J=8.6Hz), 7.38-7.52(1H,m), 7.49(2H,dm,J=8.6Hz).

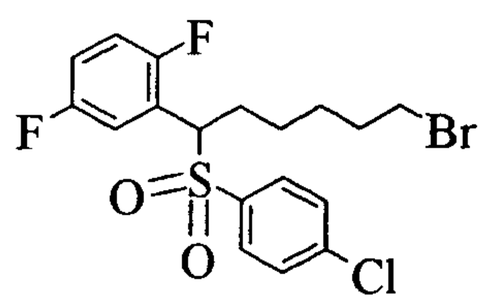
MS (m/z): 402, 404 (M^++NH_4).

Elemental Analysis for $C_{19}H_{19}ClF_2O_2S$

Calculated: C 59.29%; H 4.98%; Cl 9.21%; F 9.87%; S 8.33%.

Found: C 59.11%; H 4.93%; Cl 9.18%; F 9.82%; S 8.49%.

Example 37: 2-[6-Bromo-1-[(4-chlorophenyl)sulfonyl]hexyl]-1,4-difluorobenzene



Sodium hydride (60% dispersion in oil, 15 mg, 0.38 mmol) was added to tetrahydrofuran (10 ml). Under ice cooling, the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (100 mg, 0.330 mmol) obtained in Example 5 was added. After stirring the reaction mixture at room

temperature for 30 minutes, 1,5-dibromopentane (0.10 ml, 0.74 mmol) was added. The reaction mixture was stirred at room temperature for 3 days, followed by the addition of sodium hydride (60% dispersion in oil, 15 mg, 0.38 mmol) under ice cooling. The resulting mixture was stirred at room temperature for 15 minutes and then added with 1,5-dibromopentane (0.10 ml, 0.74 mmol). The mixture was stirred at room temperature for 14 hours and then concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=10:1) to yield a white solid. The resulting white solid was washed with hexane, whereby the title compound (51 mg, 30%) was obtained as a white powder.

Melting point: 77-79°C.

IR (ATR) ν: 2937, 1495, 1147, 1084, 1014, 893, 833, 795, 752, 708, 627, 559, 536, 465 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.20-1.35(2H,m), 1.37-1.55(2H,m), 1.74-1.88(2H,m), 2.05-2.20(1H,m), 2.40-2.53(1H,m), 3.34(2H,td,J=6.6,1.3Hz), 4.51(1H,dd,J=11.5,2.7Hz), 6.83(1H,td,J=9.0,4.6Hz), 6.94-7.04(1H,m), 7.20-7.30(1H,m), 7.38(2H,d,J=8.7Hz), 7.53(2H,d,J=8.7Hz).

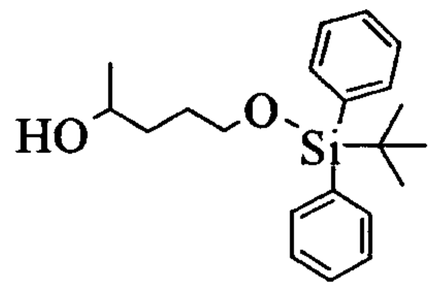
MS (m/z): 468, 470 (M^++NH_4).

Elemental Analysis for $C_{18}H_{18}BrClF_2O_2S$

Calculated: C 47.86%; H 4.02%; Br 17.69%; Cl 7.85%; F 8.41%; S 7.10%.

Found: C 47.80%; H 3.83%; Br 17.67%; Cl 7.86%; F 8.65%; S 7.25%.

Referential Example 2: 4-(t-Butyldiphenylsilyloxy)-1-methyl-1-butanol



In N,N-dimethylformamide (200 ml) were dissolved 1,4-pentanediol (10.0 g, 96.0 mmol) and imidazole (6.6 g, 96.9 mmol). Under ice cooling, t-butyl chlorodiphenylsilane (25.2 ml, 96.4 mmol) was added dropwise. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 2 days. To the reaction mixture was added diethyl ether, followed by washing with water. The organic layer was dried over anhydrous magnesium sulfate. After filtration, the residue obtained by concentrating the filtrate under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=5:1), whereby the title compound (32.0 g, 97%) was obtained as a colorless oil.

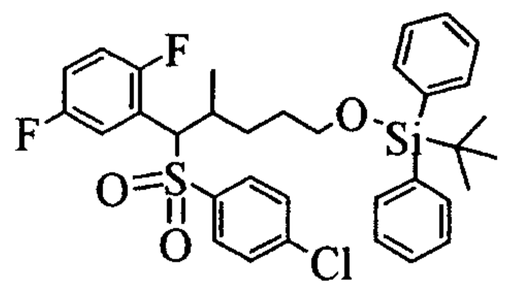
IR (ATR) ν: 3350, 2929, 2856, 1427, 1105, 822, 739, 698, 609, 501 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.05(9H,S), 1.19(3H,d,J=6.3Hz), 1.46-1.72(4H,m), 2.02-2.08(1H,m), 3.69(2H,t,J=6.0Hz), 3.78-

3.90(1H,m), 7.30-7.50(6H,m), 7.62-7.88(4H,m).

MS (m/z): 343 (M^++H).

Example 38: 2-[5-(t-Butyldiphenylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene (Isomer 38-A and Isomer 38-B)



The 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (0.94 g, 3.1 mmol) obtained in Example 5 was dissolved in toluene (30 ml), followed by the addition of 4-(t-butyldiphenylsilyloxy)-1-methyl-1-butanol (1.40 g, 4.1 mmol) and cyanomethylenetri-n-butylphosphorane (1.0 g, 4.1 mmol). The resulting mixture was heated under reflux for 2 days under an argon atmosphere. The reaction mixture was allowed to cool down and then, cyanomethylenetri-n-butylphosphorane (1.0 g, 4.1 mmol) was added thereto. Under an argon atmosphere, the resulting mixture was heated under reflux for 3 days. After the reaction mixture was allowed to cool down, the residue obtained by concentrating the mixture under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=60:1), whereby the title Isomer 38-A (low-polarity) (0.71 g, 37%) and the title isomer 38-B (high-polarity) (0.45 g, 23%) were

obtained, each as a colorless oil.

Isomer 38-A

IR (ATR) ν: 2931, 2858, 1495, 1322, 1149, 1109, 1088, 1012, 822, 752, 700, 613, 503, 488, 469 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.02(9H,s), 1.09(3H,d,J=6.8Hz), 1.26-1.42(1H,m), 1.50-1.80(3H,m), 2.74-2.86(1H,m), 3.64(2H,t,J=5.7Hz), 4.51(1H,d,J=5.6Hz), 6.78(1H,td,J=9.1,4.6Hz), 6.90-7.00(1H,m), 7.30-7.48(8H,m), 7.50-7.58(3H,m), 7.60-7.70(4H,m).

MS (m/z): 627 (M^++H).

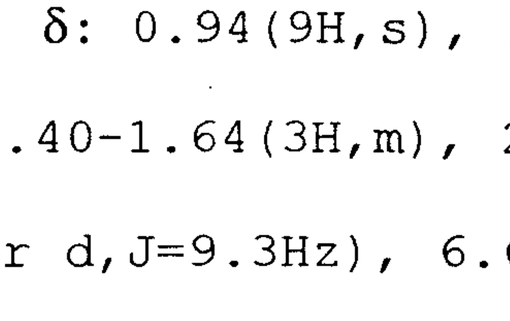
Isomer 38-B

IR (ATR) ν: 2931, 2858, 1495, 1147, 1107, 1088, 822, 752, 729, 700, 613, 559, 503, 471 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.94(9H,s), 1.00-1.20(1H,m), 1.37(3H,d,J=6.8Hz), 1.40-1.64(3H,m), 2.60-2.74(1H,m), 3.48-3.60(2H,m), 4.43(1H,br d,J=9.3Hz), 6.69(1H,td,J=9.0,4.4Hz), 6.84-6.93(1H,m), 7.24-7.45(9H,m), 7.48(2H,d,J=8.6Hz), 7.52-7.62(4H,m).

MS (m/z): 627 (M^++H).

Example 39: <u>5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-4-methyl-1-pentanol</u>



The 2-[5-(t-butyldiphenylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene (Isomer 38-A) (710 mg, 1.13 mmol) obtained in Example 38 was dissolved in methylene chloride (20 ml). Under ice cooling, hydrogen fluoride-pyridine (0.64 ml) was added dropwise. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 14 hours. To the reaction mixture was added a saturated aqueous solution (20 ml) of sodium bicarbonate, followed by extraction with diethyl ether. The organic layer was washed successively with 1N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=2:1) to yield a colorless oil. The resulting colorless oil was solidified with hexane, whereby the title compound (283 mg, 64%) was obtained as a white powder.

Melting point: 84-86°C.

IR (ATR) ν: 3367, 2937, 1496, 1138, 1084, 1051, 1012, 829, 754, 729, 708, 621, 561, 532, 471 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.07(3H,d,J=6.8Hz), 1.40-1.85(5H,m), 2.75-2.90(1H,m), 3.64-3.75(2H,m), 4.54(1H,d,J=6.6Hz), 6.77(1H,td,J=9.0,4.4Hz), 6.90-

7.00(1H,m), 7.33(2H,d,J=8.4Hz), 7.43-7.60(1H,m), 7.51(2H,d,J=8.4Hz).

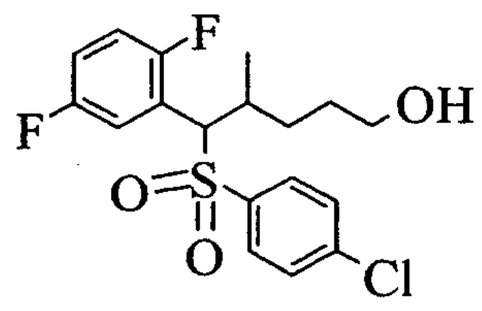
MS (m/z): 389, 391 (M^++H).

Elemental Analysis for $C_{18}H_{19}ClF_2O_3S$

Calculated: C 55.60%; H 4.92%; Cl 9.12%; F 9.77%; S 8.25%.

Found: C 55.42%; H 4.83%; Cl 9.10%; F 9.85%; S 8.30%.

Example 40: 5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-4-methyl-1-pentanol



The 2-[5-(t-butyldiphenylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene (Isomer 38-B) (450 mg, 0.717 mmol) obtained in Example 38 was dissolved in methylene chloride (10 ml). Under ice cooling, hydrogen fluoride-pyridine (0.41 ml) was added dropwise. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 14 hours. To the reaction mixture was added a saturated aqueous solution (20 ml) of sodium bicarbonate, followed by extraction with diethyl ether. The organic layer was washed successively with 1N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. After filtration, the

residue obtained by concentrating the filtrate under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=2:1) to yield a colorless oil. The resulting colorless oil was solidified with hexane, whereby the title compound (194 mg, 70%) was obtained as a white powder.

Melting point: 67-69°C.

IR (ATR) ν: 3537, 2933, 2868, 1481, 1308, 1279, 1240, 1144, 1078, 822, 802, 754, 712, 665, 613, 544, 469 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.08-1.22(1H,m), 1.23(1H,t,J=5.2Hz), 1.36(3H,d,J=6.8Hz), 1.45-1.70(3H,m), 2.67-2.80(1H,m), 3.50-3.65(2H,m), 4.45(1H,d,J=8.3Hz), 6.73(1H,td,J=9.0,4.6Hz), 6.88-6.97(1H,m), 7.31(2H,d,J=8.8Hz), 7.34-7.48(1H,m), 7.49(2H,d,J=8.8Hz).

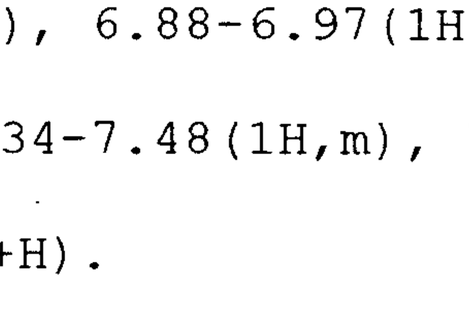
MS (m/z): 389, 391 (M^++H).

Elemental Analysis for $C_{18}H_{19}ClF_2O_3S$

Calculated: C 55.60%; H 4.92%; Cl 9.12%; F 9.77%; S 8.25%.

Found: C 55.48%; H 4.84%; Cl 9.01%; F 9.76%; S 8.32%.

Example 41: 2-[5-Bromo-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene



The 5-[(4-chlorophenyl)sulfonyl]-5-(2,5-

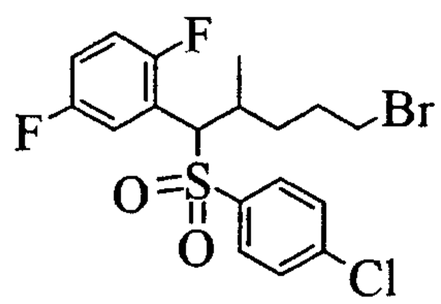
difluorophenyl)-4-methyl-1-pentanol (290 mg, 0.746 mmol) obtained in Example 39 and carbon tetrabromide (290 mg, 0.874 mmol) were dissolved in methylene chloride (8 ml). While stirring under ice cooling, a solution obtained by dissolving triphenylphosphine (230 mg, 0.877 mmol) in methylene chloride (2 ml) was added dropwise to the resulting solution. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 3 days. To the reaction mixture were added carbon tetrabromide (290 mg, 0.874 mmol) and triphenylphosphine (230 mg, 0.877 mmol) under ice cooling, followed by stirring at room temperature for 6 hours. The residue obtained by concentrating the reaction mixture under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=15:1), whereby the title compound (331 mg, 98%) was obtained as a colorless oil.

IR (ATR) ν: 2966, 1495, 1321, 1238, 1147, 1088, 1012, 789, 752, 729, 712, 613, 559, 536, 471 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.07(3H,d,J=6.8Hz), 1.46-1.60(1H,m), 1.77-2.11(3H,m), 2.74-2.90(1H,m), 3.41(2H,t,J=6.7Hz), 4.49(1H,d,J=6.6Hz), 6.78(1H,td,J=9.1,4.6Hz), 6.90-7.00(1H,m), 7.33(2H,d,J=8.7Hz), 7.45-7.60(1H,m), 7.52(2H,d,J=8.7Hz).

MS(m/z): 451, 453 (M^++H).

Example 42: 2-[5-Bromo-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene



The 5-[(4-chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-4-methyl-1-pentanol (170 mg, 0.437 mmol) obtained in Example 40 and carbon tetrabromide (170 mg, 0.648 mmol) were dissolved in methylene chloride (8 ml). While stirring under ice cooling, triphenylphosphine (135 mg, 0.515 mmol) was added to the resulting solution, followed by stirring at room temperature for 14 hours. To the reaction mixture were added carbon tetrabromide (170 mg, 0.437 mmol) and triphenylphosphine (135 mg, 0.515 mmol) under ice cooling. The reaction mixture was stirred at room temperature for 6 hours. The residue obtained by concentrating the reaction mixture under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=10:1), whereby the title compound (192 mg, 97%) was obtained as a colorless oil.

IR (ATR) ν: 3091, 2966, 1496, 1296, 1246, 1142, 1080, 889, 839, 754, 710, 627, 553, 513, 471 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.18-1.31(1H,m), 1.37(3H,d,J=6.8Hz), 1.50-1.70(1H,m), 1.78-1.92(2H,m), 2.62-

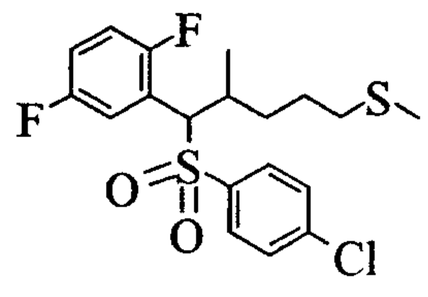
2.80(1H,m), 3.20-3.40(2H,m), 4.44(1H,d,J=8.5Hz),

6.73(1H,td,J=9.0,4.5Hz), 6.88-6.98(1H,m),

7.30(2H,d,J=8.6Hz), 7.30-7.50(1H,m), 7.49(2H,d,J=8.6Hz).

MS (m/z): 451, 453 (M^++H).

Example 43: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-methyl-5-(methylthio)pentyl]-1,4-difluorobenzene (Isomer 43-A and Isomer 43-B)



The 2-[5-bromo-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene (325 mg, 0.719 mmol) obtained in Example 41 and the 2-[5-bromo-1-[(4-chlorophenyl)sulfonyl]-2-methylpentyl]-1,4-difluorobenzene (185 mg, 0.410 mmol) obtained in Example 42 were dissolved in tetrahydrofuran (25 ml). To the resulting solution was added sodium thiomethoxide (160 mg, 2.28 mmol) under ice cooling. After stirring at room temperature for 14 hours, sodium thiomethoxide (190 mg, 2.71 mmol) was added to the resulting mixture under ice cooling. The residue obtained by concentrating the reaction mixture under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=30:1), whereby the title Isomer 43-A (low-polarity) (185 mg, 39%) and the title Isomer 43-B

(high-polarity) (186 mg, 39%) were obtained, each as a colorless oil.

Isomer 43-A

IR (ATR) ν: 2916, 1493, 1321, 1238, 1146, 1088, 1012, 789, 752, 712, 613, 559, 536, 469 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.08(3H,d,J=6.9Hz), 1.40-1.54(1H,m), 1.55-1.85(3H,m), 2.10(3H,s), 2.50(2H,t,J=7.2Hz), 2.75-2.90(1H,m), 4.51(1H,d,J=6.1Hz), 6.78(1H,td,J=9.1,4.4Hz), 6.90-7.00(1H,m), 7.33(2H,d,J=8.6Hz), 7.45-7.60(1H,m), 7.52(2H,d,J=8.6Hz).

MS (m/z): 419, 421(M^++H).

HRMS (FAB) for $C_{19}H_{22}ClF_2O_2S_2$ (M^++H)

Calculated: 419.0718

Found: 419.0733

Isomer 43-B

IR (ATR) ν: 2952, 2920, 1493, 1308, 1232, 1176, 1149, 1090, 827, 750, 629, 590, 557, 532, 472 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.10-1.30(1H,m), 1.37(3H,d,J=6.6Hz), 1.50-1.65(3H,m), 2.03(3H,s), 2.30-2.50(2H,m), 2.64-2.78(1H,m), 4.44(1H,d,J=8.6Hz), 6.73(1H,td,J=9.0,4.5Hz), 6.86-6.98(1H,m), 7.30(2H,d,J=8.6Hz), 7.34-7.46(1H,m), 7.48(2H,d,J=8.6Hz).

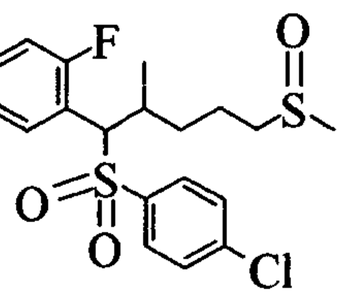
MS (m/z): 419, 421(M^++H).

HRMS (FAB) for $C_{19}H_{22}ClF_2O_2S_2$ (M^++H)

Calculated: 419.0718

Found: 419.0715

Example 44: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-methyl-5-(methylsulfinyl)pentyl]-1,4-difluorobenzene



The 2-[1-[(4-chlorophenyl)sulfonyl]-2-methyl-5-(methylthio)pentyl]-1,4-difluorobenzene (Isomer 43-A) (180 mg, 0.430 mmol) obtained in Example 43 was dissolved in methylene chloride (10 ml). Under ice cooling, 3-chloroperbenzoic acid (89 mg, 0.52 mmol) was added, followed by stirring at room temperature for 14 hours. The residue obtained by concentrating the reaction mixture under reduced pressure was purified by silica gel chromatography (methylene chloride:methanol=40:1), whereby the title compound (172 mg, 92%) was obtained a colorless oil.

IR (ATR) ν: 2920, 1495, 1317, 1279, 1238, 1146, 1086, 1036, 829, 789, 752, 712, 615, 559, 471 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.00-1.10(3H,m), 1.50-1.75(1H,m), 1.78-2.10(3H,m), 2.60(1.5H,s), 2.60(1.5H,s), 2.65-2.90(3H,m), 4.50(1H,d,J=7.6Hz), 6.77(1H,td,J=9.2,4.4Hz), 6.90-7.00(1H,m), 7.32(2H,d,J=8.5Hz), 7.40-7.60(1H,m), 7.50(2H,d,J=8.5Hz).

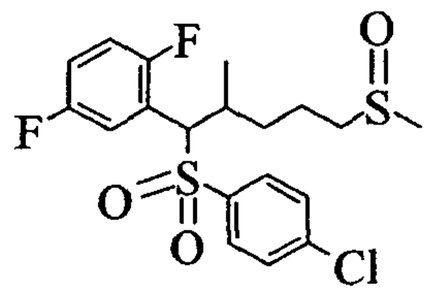
MS (m/z): 435, 437 (M^++H).

HRMS (FAB) for $C_{19}H_{22}ClF_2O_3S_2$ (M^++H)

Calculated: 435.0667

Found: 435.0655

Example 45: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-methyl-5-(methylsulfinyl)pentyl]-1,4-difluorobenzene



The 2-[1-[(4-chlorophenyl)sulfonyl]-2-methyl-5-(methylthio)pentyl]-1,4-difluorobenzene (Isomer 43-B) (175 mg, 0.418 mmol) obtained in Example 43 was dissolved in methylene chloride (10 ml). Under ice cooling, 3-chloroperbenzoic acid (87 mg, 0.50 mmol) was added. The resulting mixture was stirred at room temperature for 14 hours. The residue obtained by concentrating the reaction mixture under reduced pressure was purified silica gel chromatography (methylene chloride:methanol=40:1) to yield a white solid. The resulting solid was washed with diethyl ether, whereby the title compound (118 mg, 65%) was obtained as a white powder.

Melting point: 107-112°C.

IR (ATR) ν: 3087, 2943, 1496, 1315, 1242, 1178, 1149, 1088, 1028, 829, 731, 623, 584, 538, 457 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.15-1.40(4H,m), 1.45-2.00(3H,m), 2.50-2.85(3H,m), 2.54(3H,s), 4.46(1H,d,J=8.1Hz), 6.78(1H,td,J=9.0,4.7Hz), 6.90-7.00(1H,m), 7.32(2H,d,J=8.4Hz), 7.35-7.50(1H,m), 7.49(2H,d,J=8.4Hz).

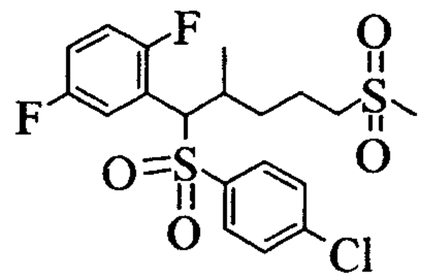
MS (m/z): 435, 437 (M^++H).

Elemental Analysis for $C_{19}H_{21}ClF_2O_3S_2$

Calculated: C 52.47%; H 4.87%; Cl 8.15%; F 8.74%; S 14.74%.

Found: C 52.44%; H 4.85%; Cl 8.17%; F 8.79%; S 14.63%.

Example 46: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-methyl-5-(methylsulfonyl)pentyl]-1,4-difluorobenzene



The 2-[1-[(4-chlorophenyl)sulfonyl]-2-methyl-5-(methylsulfinyl)pentyl]-1,4-difluorobenzene (76 mg, 0.18 mmol) obtained in Example 44 was dissolved in methylene chloride (5 ml). Under ice cooling, 3-chloroperbenzoic acid (36 mg, 0.21 mmol) was added. The resulting mixture was stirred at room temperature for 2 hours. The residue obtained by concentrating the reaction mixture was purified by silica gel chromatography (methylene chloride:methanol=100:1) to yield a pale yellowish brown oil. The resulting pale yellowish brown oil was solidified with diethyl ether/methylene chloride, whereby the title

compound (61 mg, 77%) was obtained as a white powder.

Melting point: 115-117°C.

IR (ATR) ν: 3078, 2937, 1493, 1311, 1286, 1230, 1151, 1136, 1086, 831, 754, 729, 712, 623, 542, 519, 471, 459 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.03(3H,d,J=7.1Hz), 1.60-1.80(1H,m), 1.85-2.20(3H,m), 2.70-2.90(1H,m), 2.94(3H,s), 3.07(2H,t,J=7.8Hz), 4.49(1H,d,J=7.8Hz), 6.76(1H,td,J=9.1,4.5Hz), 6.90-7.00(1H,m), 7.32(2H,d,J=8.5Hz), 7.35-7.60(1H,m), 7.49(2H,d,J=8.5Hz).

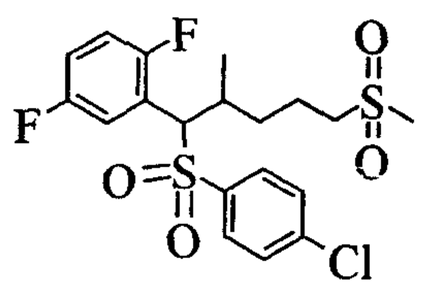
MS (m/z): 451, 453 (M^++H).

Elemental Analysis for $C_{19}H_{21}ClF_2O_4S_2$

Calculated: C 50.61%; H 4.96%; Cl 7.86%; F 8.43%; S 14.22%.

Found: C 50.57%; H 4.74%; Cl 7.85%; F 8.58%; S 14.25%.

Example 47: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-methyl-5-(methylsulfonyl)pentyl]-1,4-difluorobenzene



The 2-[1-[(4-chlorophenyl)sulfonyl]-2-methyl-5-(methylsulfinyl)pentyl]-1,4-difluorobenzene (66 mg, 0.15 mmol) obtained in Example45 was dissolved in methylene chloride (5 ml). Under ice cooling, 3-chloroperbenzoic acid (32 mg, 0.19 mmol) was added. The resulting mixture was stirred at room temperature for 3 hours. The residue

obtained by concentrating the reaction mixture under reduced pressure was purified by silica gel chromatography (methylene chloride:methanol=100:1) to yield a white solid. The resulting white solid was washed with diethyl ether/methylene chloride, whereby the title compound (52 mg, 76%) was obtained as a white powder.

Melting point: 142-144°C.

IR (ATR) ν: 3082, 2937, 1495, 1317, 1290, 1234, 1151, 1130, 1092, 831, 769, 754, 731, 712, 625, 544, 525, 503, 472, 449, 417 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.15-1.40(1H,m), 1.32(3H,d,J=6.6Hz), 1.40-2.05(3H,m), 2.65-3.10(3H,m), 2.88(3H,s), 4.46(1H,d,J=7.1Hz), 6.77(1H,td,J=9.1,4.6Hz), 6.90-7.00(1H,m), 7.32(2H,d,J=8.4Hz), 7.35-7.50(1H,m), 7.49(2H,d,J=8.4Hz).

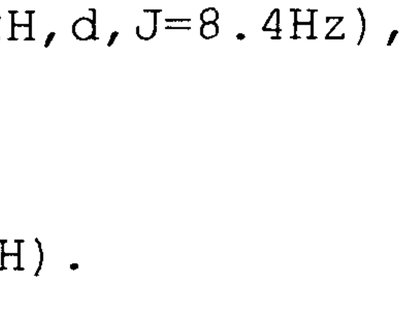
MS (m/z): 451, 453 (M^++H).

Elemental Analysis for $C_{19}H_{21}ClF_2O_4S_2$

Calculated: C 50.61%; H 4.69%; Cl 7.86%; F 8.43%; S 14.22%.

Found: C 50.48%; H 4.59%; Cl 7.93%; F 8.57%; S 14.09%.

Example 48: 4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)tetrahydropyrane



The 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (1.0 g, 3.30 mmol) obtained in Example 5 was dissolved in tetrahydrofuran (70 ml). At -78°C, a hexane solution (1.57M, 5.3 ml, 8.3 mmol) of n-butyl lithium was added dropwise. After completion of the dropwise addition, the reaction mixture was stirred at -78°C for 10 minutes and then stirred for another 30 minutes under ice cooling. At -78°C, 2-bromoethyl ether (0.55 ml, 3.9 mmol) was added dropwise to the reaction mixture. After completion of the dropwise addition, the temperature of the reaction mixture was elevated to room temperature over 14 hours. Water (2.0 ml) was added to the reaction mixture. The residue obtained by concentrating the resulting mixture under reduced pressure was purified by silica gel chromatography (hexane:ethyl acetate=5:1) to yield a white solid. The resulting white solid was washed with diisopropyl ether/methylene chloride, whereby the title compound (317 mg, 26%) was obtained as a white powder.

Melting point: 157-160°C.

IR (ATR) ν: 2966, 2862, 1496, 1309, 1188, 1149, 1086, 1012, 899, 841, 808. 750, 710, 629, 592, 569, 536, 515, 471 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.40-2.80(4H,m), 3.32(2H,t,J=12.5Hz), 4.02(2H,dt,J=11.8,3.3Hz), 6.82-6.95(1H,m), 7.05-7.17(2H,m), 7.38(2H,s), 7.39(2H,s).

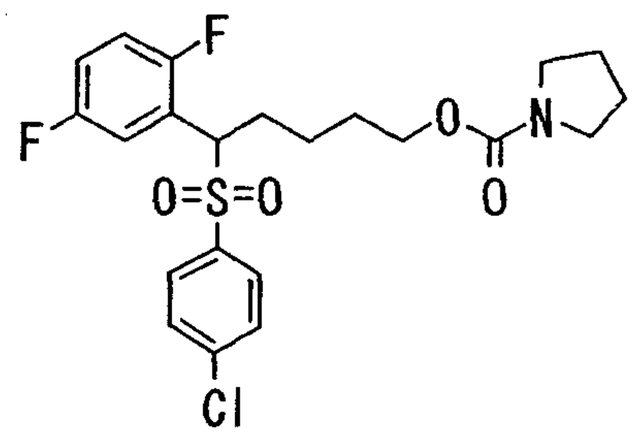
MS (m/z): 373, 375 (M^++H).

Elemental Analysis for $C_{17}H_{15}ClF_2O_3S$

Calculated: C 54.77%; H 4.06%; Cl 9.51%; F 10.19%; S 8.60%.

Found: C 54.55%; H 4.00%; Cl 9.69%; F 10.33%; S 8.64%.

Example 49: 5-[(4-Chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)pentyl=1-pyrrolidinecarboxylato



To a methylene chloride (6 ml) solution of the 5-[(4-chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)-1-pentanol (390 mg, 1.04 mmol) obtained in Example 29 were added triethylamine (152 µl, 1.09 mmol) and 4-nitrophenyl chloroformate (220 mg, 1.09 mmol). The resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated, whereby crude 5-[(4-chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)pentyl=4-nitrophenyl=carbonato (759 mg) was obtained. The resulting crude 5-[(4-chlorophenyl)sulfonyl]-5-(2,5-difluorophenyl)pentyl=4-nitrophenyl=carbonato (268 mg) was dissolved in methylene chloride (4 ml), followed by the addition of triethylamine (76.7 µl, 0.551 mmol) and pyrrolidine (46.0 µl, 0.551 mmol). The mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated and the residue was dissolved in diethyl ether.

The resulting solution was washed successively with a saturated aqueous solution of potassium bicarbonate, a saturated aqueous solution of ammonium chloride, water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (40% ethyl acetate-hexane), whereby the title compound (128 mg, 74%) was obtained as a pale brown oil.

IR (ATR) ν: 3086, 2954, 2875, 1689, 1583, 1496, 1423, 1321, 1176, 1147, 1084, 1012, 874, 752, 536, 467 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 1.26-1.38(2H,m), 1.54-1.73(2H,m), 1.78-1.90(4H,m), 2.09-2.20(1H,m), 2.42-2.52(1H,m), 3.19-3.40(4H,m), 3.96-4.05(2H,m), 4.52(1H,dd,J=11.5,2.7Hz), 6.83(1H,td,J=9.1,4.4Hz), 6.94-7.01(1H,m), 7.21-7.28(1H,m), 7.38(2H,d,J=8.6Hz), 7.52(2H,d,J=8.6Hz).

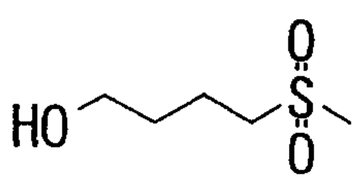
MS (m/z) 472 (M^++H).

HRMS (FAB) for $C_{22}H_{24}ClF_2NO_4S$ (M^++H)

Calculated: 472.1161

Analyzed: 472.1124

Referential Example 3: <u>4-(Methylsulfonyl)-1-butanol</u>



While stirring under ice cooling, 3-chloroperbenzoic acid (3.04 g, 17.6 mmol) was added to a methylene chloride (100ml) solution of 4-(methylthio)-1-butanol (1.01 g, 8.40

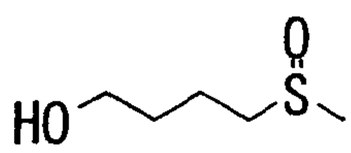
mmol). At room temperature, the mixture was stirred for 20 hours. After completion of the reaction was confirmed, the solvent was concentrated under reduced pressure. To the residue were added diethyl ether and water to separate the water layer. The resulting water layer was concentrated under reduced pressure. Methylene chloride was added to the residue. The mixture was dried over anhydrous sodium sulfate, and then the solvent was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. From the fraction eluted with methanol:methylene chloride(=1:20), the title compound (1.21 g, 95%) was obtained as a pale yellow oil.

IR (ATR) ν: 3494, 2931, 2877, 1457, 1413, 1282, 1122, 1054, 1029, 966, 827, 765, 518, 462 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.55-1.91(3H,m), 1.91-2.11(2H,m), 2.92(3H,s), 3.09(2H,t,J=7.9Hz), 3.72(2H,t,J=6.1Hz).

MS (m/z): 153 (M^++H).

Referential Example 4: <u>4-(Methylsulfinyl)-1-butanol</u>



While stirring under ice cooling, sodium periodate (1.24 g, 5.80 mmol) was added to a mixed solution of 4-(methylthio)-1-butanol (465 mg, 3.87 mmol) in tetrahydrofuran (15 ml) and water (3 ml). At room temperature, the resulting mixture was stirred for 21.5

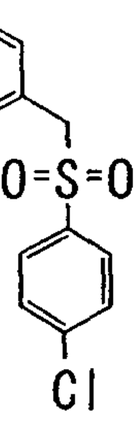
hours. After completion of the reaction was confirmed, the reaction mixture was diluted with methylene chloride and then subjected to Celite filtration. The filtrate was concentrated under reduced pressure. To the residue was added methylene chloride. The resulting mixture was dried over anhydrous sodium sulfate and then, the solvent was concentrated under reduced pressure. The residue thus obtained was subjected to chromatography on a silica gel column, whereby from the fraction eluted with methanol:methylene chloride(=1:10), the title compound (160 mg, 30%) was obtained as a pale yellow oil.

IR (ATR) ν: 3369, 2937, 2867, 1658, 1452, 1411, 1054, 1006, 941, 694 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.40-1.55(1H,br), 1.68-1.83(2H,m), 1.93-2.08(2H,m), 2.92(3H,s), 3.09(2H,t,J=7.9Hz), 3.72(2H,t,J=5.5Hz).

MS (m/z): 137 (M^++H).

Example 50: 1-Chloro-4-(benzylsulfonyl)benzene



Sodium 4-chlorobenzenesulfinate (306 mg, 1.54 mmol) and benzyl bromide (0.18 ml, 1.54 mmol) were added to n-

butanol (15 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. To the residue were added ethyl acetate. The resulting mixture was washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate (=8:1), the title compound (299 mg, 73%) was obtained as a white solid.

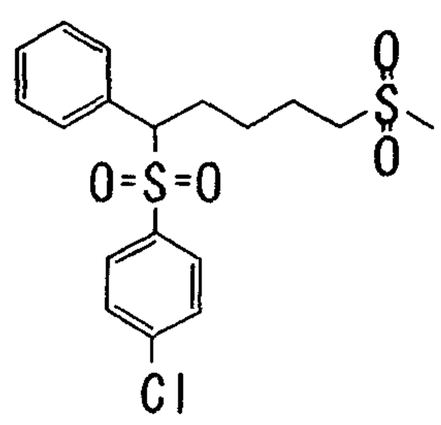
Melting point: 147.5-148.5°C.

IR (ATR) ν: 3060, 3029, 2994, 2942, 1583, 1571, 1492, 1475, 1454, 1396, 1311, 1294, 1274, 1147, 1087, 1014, 977, 917, 831, 773, 757, 696, 642, 532, 462 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.31(2H,s), 7.23-7.38(4H,m), 7.38-7.46(2H,m), 7.49-7.58(2H,m).

MS (m/z): 267 (M^++H).

Example 51: 1-Chloro-4-(5-methylsulfonyl-1-phenylpentyl)sulfonylbenzene



Under an argon atmosphere, a toluene (20 ml) solution of 1-chloro-4-(benzylsulfonyl)benzene (90 mg, 0.337 mmol),

the 4-(methylsulfonyl)-1-butanol (69 mg, 0.453 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (233 mg, 0.965 mmol) was heated under reflux for 21 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the fraction eluted with hexane:ethyl acetate(=2:1), the title compound (44 mg, 33%) was obtained as a white solid.

Melting point: 151-152°C.

IR (ATR) ν: 2937, 2867, 1577, 1467, 1396, 1319, 1270, 1203, 1147, 1087, 1058, 1014, 962, 842, 802, 755, 696, 632, 565, 530, 474, 420 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.34-1.52(2H,m), 1.79-1.97(2H,m), 2.13-2.28(2H,m), 2.45-2.58(1H,m), 2.86(3H,s), 2.89-3.00(2H,m), 4.01(1H,dd,J=11.2,3.9Hz), 7.08(1H,d,J=8.1Hz), 7.22-7.47(8H,m).

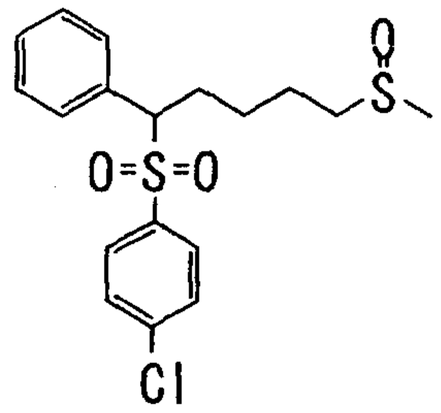
MS (m/z): 401 (M^++H).

Elemental Analysis for $C_{18}H_{21}ClO_4S_2$

Calculated: C 53.92%; H 5.28%; Cl 8.84%; S 16.00%.

Found: C 53.92%; H 5.21%; Cl 9.05%; S 15.88%.

Example 52: 1-Chloro-4-(5-methylsulfinyl-1-phenylpentyl)sulfonylbenzene



A toluene (15 ml) solution of the 4-chloro-1-(benzylsulfonyl)benzene (122 mg, 0.457 mmol) obtained in Example 50, the 4-(methylsulfinyl)-1-butanol (81 mg, 0.595 mmol) obtained in Referential Example 4 and cyanomethylenetri-n-butylphosphorane (221 mg, 0.916 mmol) was heated under reflux for 2 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with methylene chloride:methanol(=100:1), a white solid was obtained. The resulting white solid was recrystallized from diethyl ether to give the title compound (20 mg, 11%) as white needle crystals.

Melting point: 98.5-99.5°C.

IR (ATR) ν: 2935, 2856, 1575, 1473, 1455, 1392, 1309, 1276, 1143, 1081, 1016, 946, 829, 794, 755, 694, 624, 563, 520, 464 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 32-1.50(2H,m), 1.70-1.90(2H,m), 2.15-2.28(1H,m), 2.45-2.70(2H,m), 2.52(3H,s), 4.02(1H,dd,J=11.4,3.8Hz), 7.05-7.12(1H,m), 7.20-7.47(8H,m).

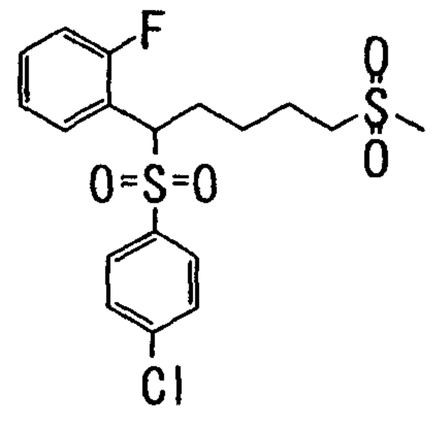
MS (m/z): 385 (M^++H).

Elemental Analysis for $C_{18}H_{21}ClO_3S_2$

Calculated: C 56.16%; H 5.50%; Cl 9.21%; S 16.66%.

Found: C 56.03%; H 5.37%; Cl 9.29%; S 16.69%.

Example 53: 1-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]-2-fluorobenzene



To sodium 4-chlorobenzenesulfinate (203 mg, 1.02 mmol) and 2-fluorobenzyl bromide (124 μL, 1.02 mmol) were added n-butanol (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. To the residue was added methylene chloride and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether to yield white powder (111 mg).

A toluene (10 ml) solution of the resulting white powder (35 mg), the 4-(methylsulfonyl)-1-butanol (38 mg, 0.250 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (60 mg, 0.246 mmol) was heated under reflux for 17.5 hours under an argon

atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the fraction eluted with hexane:ethyl acetate(=1:1), the title compound was obtained as a white solid (46 mg).

Melting point: 167-168°C.

IR (ATR) ν: 2948, 2867, 1614, 1579, 1488, 1455, 1396, 1319, 1290, 1268, 1230, 1199, 1149, 1126, 1085, 1014, 962, 829, 792, 767, 752, 713, 628, 572, 532, 495, 458, 430 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.38-1.52(2H,m), 1.80-1.98(2H,m), 2.16-2.29(1H,m), 2.48-2.60(1H,m), 2.87(3H,s), 2.96(2H,t,J=7.9Hz), 4.55(1H,dd,J=11.0,4.2Hz), 6.85(1H,td,J=9.1,1.1Hz), 7.17-7.39(4H,m), 7.43-7.58(3H,m).

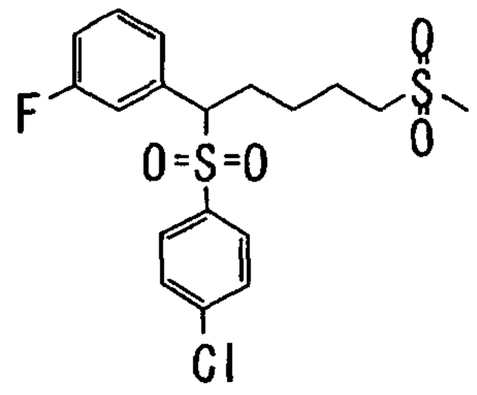
MS (m/z): 419 (M^++H).

Elemental Analysis for $C_{18}H_{20}ClFO_4S_2$

Calculated: C 51.61%; H 4.81%; Cl 8.46%; F 4.53%; S 15.31%.

Found: C 51.65%; H 4.74%; Cl 8.33%; F 4.50%; S 15.20%.

Example 54: <u>1-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]-3-fluorobenzene</u>



Sodium 4-chlorobenzenesulfinate (216 mg, 1.09 mmol) and 3-fluorobenzyl bromide (136 μL, 1.09 mmol) were added to n-butanol (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. To the residue was added methylene chloride and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue thus obtained was washed with diisopropyl ether to yield a white powder (208 mg).

Then, a toluene (10 ml) solution of the resulting white powder (59 mg), the 4-(methylsulfonyl)-1-butanol (65 mg, 0.427 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (100 mg, 0.414 mmol) was heated under reflux for 29.5 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=2:3), the title compound was obtained as a white solid (71 mg).

Melting point: 116-117°C.

IR (ATR) ν: 2942, 2875, 1590, 1469, 1394, 1317, 1295, 1270, 1241, 1201, 1145, 1083, 1012, 964, 875, 840, 798, 769, 752, 705, 686, 634, 592, 541, 530, 512, 491, 464 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 1.34-1.52(2H,m), 1.78-1.99(2H,m), 2.09-2.22(1H,m), 2.41-2.56(1H,m), 2.81-3.03(2H,m), 2.88(3H,s), 4.01(1H,dd,J=11.2,3.9Hz), 6.83(1H,d,J=7.6Hz), 6.90(1H,d,J=9.3Hz), 7.03(1H,td,J=8.1,2.2Hz), 7.23(1H,td,J=7.9,6.0Hz), 7.32-7.50(4H,m).

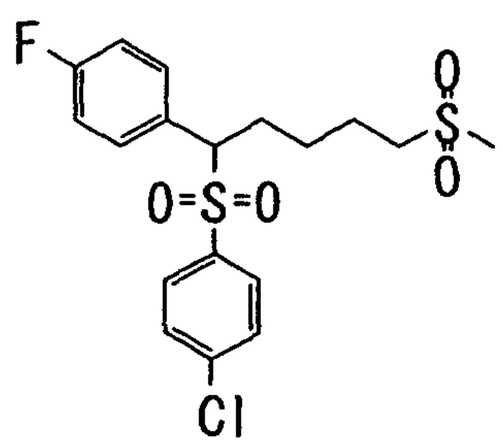
MS (m/z): 419 (M^++H).

Elemental Analysis for $C_{18}H_{20}ClFO_4S_2$

Calculated: C 51.61%; H 4.81%; Cl 8.31%; F 4.53%; S 15.31%.

Found: C 51.68%; H 4.72%; Cl 8.31%; F 4.52%; S 15.30%.

Example 55: 1-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]-4-fluorobenzene



Sodium 4-chlorobenzenesulfinate (183 mg, 0.921 mmol) and 4-fluorobenzyl bromide (112 μL, 0.921 mmol) were added to n-butanol (5 ml). The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. To the

residue was added ethyl acetate, and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether to yield a white powder (150 mg).

Then, a toluene (10 ml) solution of the resulting white powder (57 mg), the 4-(methylsulfonyl)-1-butanol (62 mg, 0.407 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (97 mg, 0.400 mmol) was heated under reflux for 17 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=2:3), the title compound was obtained as a white solid (58 mg).

Melting point: 141-142.5°C.

IR (ATR) ν: 2937, 2865, 1606, 1577, 1508, 1467, 1394, 1317, 1292, 1270, 1236, 1147, 1126, 1085, 1014, 962, 838, 825, 755, 721, 626, 574, 553, 514, 482, 455 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.50(2H,m), 1.80-1.97(2H,m), 2.09-2.21(1H,m), 2.43-2.56(1H,m), 2.88(3H,s), 2.90-3.00(2H,m), 4.01(1H,dd,J=11.2,3.9Hz), 6.97(2H,t,J=8.5Hz), 7.03-7.11(2H,m), 7.36-7.48(4H,m).

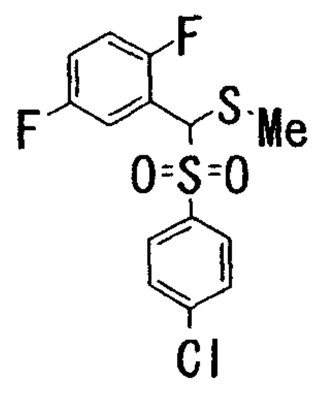
MS (m/z): 419 (M^++H).

Elemental Analysis for $C_{18}H_{20}ClFO_4S_2$

Calculated: C 51.61%; H 4.74%; Cl 8.46%; F 4.53%; S 15.31%.

Found: C 51.74%; H 4.74%; Cl 8.28%; F 4.53%; S 15.36%.

Example 56: 2-[1-[(4-Chlorophenyl)sulfonyl]-1-methylthio]methyl-1,4-difluorobenzene



Under a nitrogen atmosphere, the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (82.8 mg, 0.27 mmol) obtained in Example 5 was added to a N,N-dimethylformamide suspension (2.0 ml) of sodium hydride (12 mg, 0.30 mmol) at room temperature. The resulting mixture was stirred for 10 minutes. To the reaction mixture was added methyl methanethiosulfonate (28.1 mg, 0.27 mmol) and the mixture was stirred for another 30 minutes. The reaction mixture was added with a saturated aqueous sodium bicarbonate solution (10 ml), followed by extraction with diethyl ether. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. After filtration, the residue obtained by concentrating the filtrate under reduced pressure was purified by silica gel chromatography (hexane:diethyl ether=4:1), whereby the

title compound (36 mg, 38%) was obtained as a white solid.

Melting point: 128-129°C.

IR (ATR) ν: 1489, 1315, 1234, 1147, 1078, 829 cm^{-1}.

^{1}H-NMR (400MHz,$CDCl_3$) δ: 2.47(3H,s), 5.22(1H,s), 6.88(1H,m), 6.97(1H,m), 7.13(1H,m), 7.41(2H,m), 7.60(2H,m).

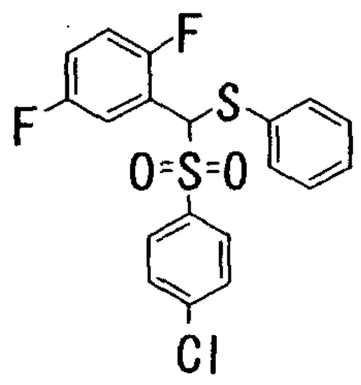
MS (m/z): 173 (M^+-SO_2Ar).

Elemental Analysis for $C_{14}H_{11}ClF_2O_2S_2$

Calculated: C 48.21%; H 3.18%; S 18.39%; Cl 10.16%; F 10.89%.

Found: C 48.41%; H 3.28%; S 17.88%; Cl 10.41%; F 10.57%.

Example 57: 2-[1-[(4-Chlorophenyl)sulfonyl]-1-phenylthio]methyl-1,4-difluorobenzene



In a similar manner to that employed in Example 56 except for the use of phenyl phenylthiosulfonate, the title compound was synthesized.

Melting point: 84-85°C.

IR (ATR) ν: 1492, 1319, 1149, 1086, 825 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 5.53(1H,s), 6.91(1H,m), 7.01(1H,m), 7.23-7.31(4H,m), 7.35-7.40(4H,m), 7.65(2H,m), 7.65(2H,m), 7.40-7.35(4H,m), 7.31-7.23(4H,m), 7.01(1H,m), 6.91(1H,m), 5.53(1H,s).

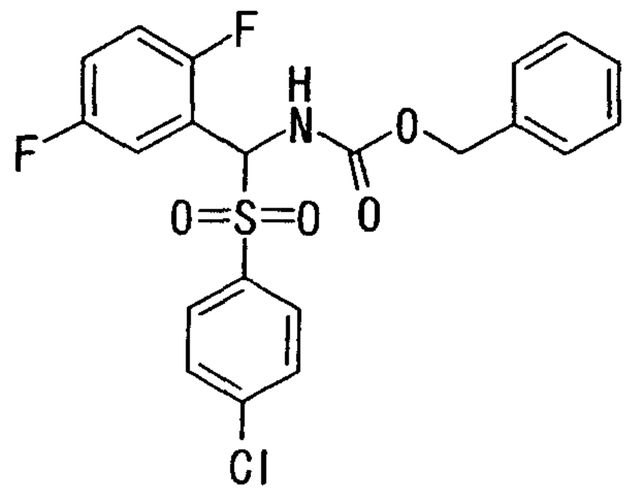
MS (m/z): 235 (M^+-SO_2Ar).

Elemental Analysis for $C_{19}H_{13}ClF_2O_2S_2$

Calculated: C 55.54%; H 3.19%; S 15.61%; Cl 8.63%; F 9.25%.

Found: C 55.50%; H 3.18%; S 15.51%; Cl 8.40%; F 9.03%.

Example 58: Benzyl [(4-chlorophenyl)sulfonyl-(2,5-difluorophenyl)methyl]carbamate



To a tetrahydrofuran solution (0.4 ml) of benzyl carbamate (151 mg, 1.0 mmol) were added water (1.0 ml), sodium chlorobenzenesulfinate (199 mg, 1.0 mmol), 2,5-difluorobenzaldehyde (142 mg, 1.0 mmol) and formic acid (0.24 ml). The resulting mixture was stirred for 19 hours at room temperature. To the reaction mixture having a white precipitate formed therein were added diethyl ether and water. The precipitate was collected by filtration and washed sufficiently with diethyl ether, whereby the title compound (251 mg, 51%) was obtained.

Melting point: 183-184°C.

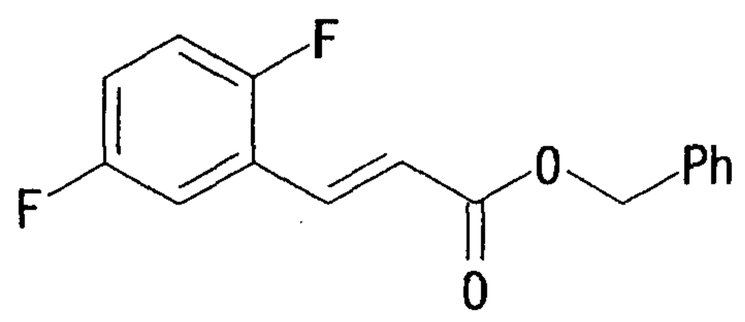
IR (ATR) ν: 1726, 1518, 1495, 1319, 1230, 1147, 831 cm^{-1}.

^1H-NMR (400MHz, DMSO-d_6) δ: 4.91(1H, d, J=12.4Hz),

4.97(1H,d,J=12.4Hz), 6.25(1H,d,J=10.4Hz), 7.2-7.45(7H,m), 7.70(2H,d,J=8.4Hz), 7.71(1H,m), 7.78(2H,d,J=8.4Hz), 9.33(1H,d,J=10.4Hz).

MS (m/z): 275 (M^+-SO_2Ar).

Referential Example 5: Benzyl 2,5-difluorophenylacrylate



Under a nitrogen atmosphere, dicyclohexyl carbodiimide (206 mg, 1.0 mmol) was added to a methylene chloride solution (10 ml) of 2,5-difluorophenylacrylic acid (184 mg, 1 mmol), benzyl alcohol (104 ml, 1 mmol), and N,N-dimethylaminopyridine (36 mg, 0.3 mmol) at room temperature and the resulting mixture was stirred for 17 hours. After concentration of the reaction mixture under reduced pressure, 10 ml of hexane-diethyl ether (4:1) was added to the residue. The precipitate thus formed was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=5:1), whereby the title compound (242 mg, 88%) was obtained.

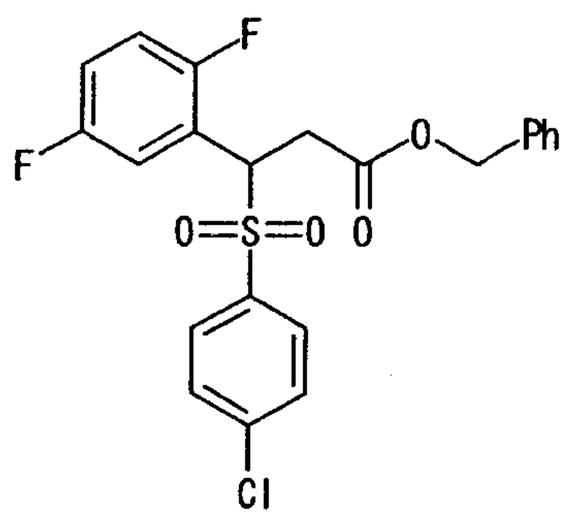
Melting point: 45-46°C.

IR (ATR) ν: 1712, 1641, 1305, 1167, 692 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 5.24(S,2H), 6.54(d,1H,J=16.4Hz),

7.03(m,2H), 7.18(m,1H), 7.37(m,5H), 7.77(d,1H,J=16.4Hz).

Example 59: Benzyl 3-(4-chlorophenylsulfonyl)-3-(2,5-difluorophenyl)propionate



Under a nitrogen atmosphere, a hexane solution (1.57M, 0.05 ml) of n-butyl lithium was added to a tetrahydrofuran (10 ml) solution of benzyl 2,5-difluorophenylacrylate (108 mg, 0.39 mmol) and 4-chlorobenzenethiol (57 mg, 0.39 mmol) at room temperature. The resulting mixture was stirred for 1 hour. After concentrating the reaction mixture under reduced pressure, the residue was subjected to silica gel chromatography. The fraction eluted with hexane:diethyl ether (=10:1) was concentrated under reduced pressure.

Then, the residue was dissolved in methanol (10 ml). To the resulting solution were added water (1.0 ml), hexaammonium heptamolybdate tetrahydrate (5.0 mg), and 30% aqueous hydrogen peroxide (2 ml) at room temperature, followed by stirring for 48 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and then, washed sufficiently with water and brine. The organic layer was dried over anhydrous magnesium sulfate and distilled under

reduced pressure to remove the solvent. The residue thus obtained was purified by silica gel chromatography (hexane:ethyl acetate=8:1), whereby the title compound (33 mg, 19%) was obtained.

Melting point: 127-128°C.

IR (ATR) ν: 1734, 1498, 1317, 1211, 1170, 1149, 748 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.12(dd,1H,J=10.4,16.8Hz), 3.48(dd,1H,J=4.4,16.8Hz), 4.98(d,1H,J=12.0Hz), 5.02(m,1H), 5.03(d,1H,J=12.0Hz), 6.79(m,1H), 6.81(m,1H), 7.1-7.2(m,3H), 7.23(m,3H), 7.38(d,2H,J=8.4Hz), 7.52(d,2H,J=8.4Hz).

Elemental Analysis for $C_{22}H_{17}ClF_2O_4S \cdot 0.5H_2O$

Calculated: C 57.46%; H 3.91% ;S 6.97%; Cl 7.70%; F 8.26%.

Found C 57.60%; H 3.89%; S 7.02%; Cl 7.83%; F 8.31%.

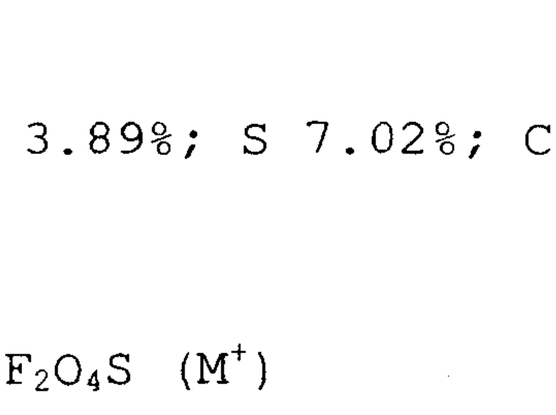
MS (m/z): 450 (M^+).

HRMS (EI): as $C_{22}H_{17}ClF_2O_4S$ (M^+)

Calculated: 450.0504

Found: 450.0496

Example 60: 2-[1-[(4-Chlorophenyl)sulfonyl]-2-pentylcyclopropyl]-1,4-difluorobenzene



Under a nitrogen atmosphere, triethylamine (36.4 µl, 0.262 mmol) and methanesulfonyl chloride (18.6 µl, 0.240 mmol) were added to a methylene chloride (4 ml) solution of the isomer mixture (91.0 mg, 0.218 mmol) of the 1-[(4-chlorophenyl)sulfonyl]-1-(2,5-difluorophenyl)-3-octanol obtained in Example 22 at 0°C. The resulting mixture was stirred at 0°C for 2 hours. The reaction mixture was diluted with methylene chloride, washed with water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was subjected to chromatography on a short silica gel column. The fraction eluted with hexane:ethyl acetate(=3:1) was concentrated under reduced pressure to yield a colorless oil.

The resulting colorless oil was dissolved in tetrahydrofuran (4 ml). In an argon gas stream and at -78°C, n-butyl lithium (a 1.57M hexane solution, 0.127 ml, 0.200 mmol) was added to the resulting solution, followed by stirring at -78°C for 3 hours. The reaction mixture was added with a saturated aqueous ammonium chloride solution, followed by extraction with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then concentrated. The residue thus obtained was purified by medium-pressure chromatography on a silica gel column (8% ethyl acetate-hexane), whereby the title compound (48.1 mg, 66%) was obtained as a colorless

oil.

IR (ATR) ν: 2929, 2925, 2858, 1585, 1496, 1317, 1250, 1176, 1146, 1090, 1014, 889, 827, 796, 760, 715, 602, 565, 478 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.43-0.62(1H,m), 0.83-0.95(3H,m), 1.13-1.70(7.66H,m), 1.82-1.93(0.33H,m), 1.99(0.33H,dd,J=9.8,5.4Hz), 2.07(0.66H,dd,J=9.8,5.9Hz), 2.26-2.40(1H,m), 6.74-6.84(1H,m), 6.91(0.33H,td,J=9.0,4.4Hz), 6.98-7.05(1H,m), 7.13(0.66H,ddd,J=8.6,5.6,3.2Hz), 7.35-7.50(4H,m).

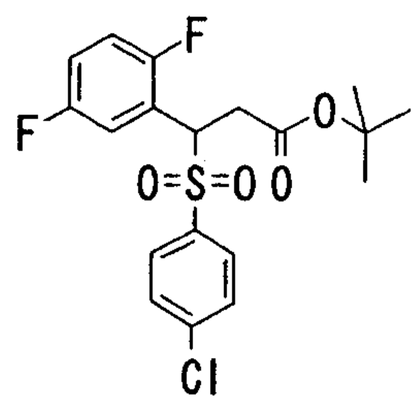
MS (m/z) 399 (M^++H).

HRMS (FAB) for $C_{20}H_{22}ClF_2O_2S$ (M^++H)

Calculated: 399.0997

Found: 399.1006

Example 61: t-Butyl 3-[(4-chlorophenyl)sulfonyl]-3-(2,5-difluorophenyl)propionate



Under an argon atmosphere and at -78°C, n-butyl lithium (a 1.57M hexane solution, 7.01 ml) was added dropwise to a dimethoxyethane solution (50 ml) of the 2-[(4-chlorophenyl)sulfonylmethyl]-1,4-difluorobenzene (3.03 g, 10.0 mmol) obtained in Example 5. The temperature of

the reaction mixture was raised to room temperature. Then, the reaction mixture was cooled to -78°C. After the addition of t-butyl bromoacetate (1.48 ml, 10.0 mmol), the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was added with a saturated aqueous ammonium chloride solution, followed by extraction with diethyl ether. The extracts were combined, washed successively with water and brine, dried over $MgSO_4$, and then distilled to remove the solvent. The residue thus obtained was subjected to chromatography on a short silica gel column (hexane-ethyl acetate 3:1). The solid thus obtained was recrystallized from hexane, whereby the title compound (3.30 g, 79%) was obtained as a colorless solid.

Melting point: 140.5-142.0°C.

IR (ATR) ν: 3074, 2983, 1722, 1585, 1496, 1427, 1396, 1369, 1275, 1257, 1215, 1142, 1086, 955, 835, 781, 750, 712, 665, 606, 559, 467 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.28(9H,s), 3.00(1H,dd,J=16.4,10.7Hz), 3.37(1H,dd,J=16.4,4.4Hz), 5.00(1H,dd,J=10.7,4.4Hz), 6.85(1H,td,J=9.0,4.6Hz), 6.96-7.03(1H,m), 7.19(1H,ddd,J=8.8,5.6,3.2Hz), 7.41(2H,d,J=8.3Hz), 7.50(2H,d,J=8.3Hz).

MS (m/z): 417 (M^++H).

HRMS (FAB) for $C_{19}H_{19}ClF_2O_4S$ (M^++H)

Calculated: 416.0661

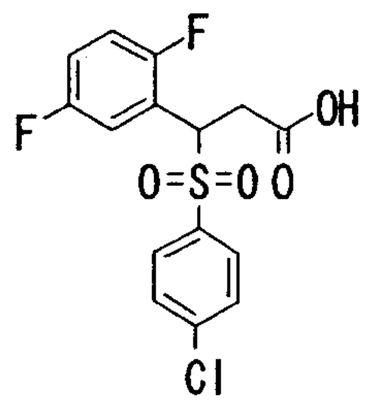
Found: 416.0690

Elemental Analysis for $C_{19}H_{19}ClF_2O_4S$

Calculated: C 54.74%; H 4.59%; Cl 8.50%; F 9.11%; S 7.69%.

Found: C 54.67%; H 4.55%; Cl 8.54%; F 9.17%; S 7.80%.

Example 62: 3-[(4-Chlorophenyl)sulfonyl]-3-(2,5-difluorophenyl)propionic acid



At 0°C, trifluoroacetic acid (10 ml) was added to a methylene chloride (30 ml) solution of t-butyl 3-[(4-chlorophenyl)sulfonyl]-3-(2,5-difluorophenyl)propionate (3.10 g, 7.43 mmol). The resulting mixture was stirred at room temperature for 2 hours. To the residue obtained by concentrating the reaction mixture was added toluene and the resulting mixture was concentrated. The residue thus obtained was recrystallized from ethyl acetate-hexane, whereby the title compound (2.29 g, 85%) was obtained as colorless needle crystals.

Melting point: 152.0-153.0°C.

IR (ATR) ν: 2956, 1707, 1576, 1496, 1427, 1396, 1321, 1255, 1217, 1115, 1086, 1012, 914, 893, 829, 795, 756, 708, 619, 536, 459 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.13(1H,dd,J=17.1,10.4Hz), 3.53(1H,dd,J=17.1,4.6Hz), 5.02(1H,dd,J=10.4,4.6Hz), 6.85(1H,td,J=9.0,4.6Hz), 6.96-7.03(1H,m), 7.18(1H,ddd,J=8.5,5.4,3.2Hz), 7.41(2H,d,J=8.8Hz), 7.55(2H,d,J=8.8Hz).

MS (m/z): 360 (M^+).

HRMS (EI): as $C_{15}H_{11}ClF_2O_4S$ (M^+)

Calculated: 360.0035

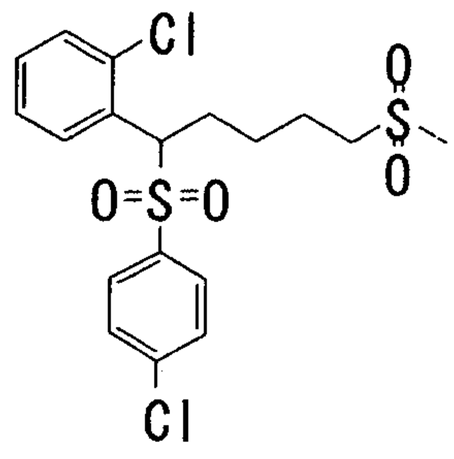
Found: 360.0026

Elemental Analysis for $C_{15}H_{11}ClF_2O_4S$

Calculated: C 49.94%; H 3.07%; Cl 9.83%; F 10.53%; S 8.89%.

Found: C 49.74%; H 2.99%; Cl 9.88%; F 10.63%; S 8.98%.

Example 63: 1-Chloro-2-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzene



Sodium 4-chlorobenzenesulfinate (205 mg, 1.03 mmol) and 2-chlorobenzyl bromide (134 μl, 1.03 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced

pressure. To the residue was added ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was washed with hexane to yield a white powder (231 mg).

A toluene (10 ml) solution of the resulting white powder (92 mg), the 4-(methylsulfonyl)-1-butanol (96 mg, 0.631 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (148 mg, 0.614 mmol) was heated under reflux for 20 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate (=1:1), the title compound (74 mg) was obtained as a colorless oil.

IR (ATR) ν: 2931, 2873, 1573, 1475, 1442, 1394, 1313, 1276, 1133, 1083, 1033, 1012, 962, 908, 829, 794, 748, 713, 684, 626, 568, 518, 464 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.33-1.52(2H,m), 1.79-1.98(2H,m), 2.15-2.30(1H,m), 2.50-2.60(1H,m), 2.86(3H,s), 2.94(2H,t,J=7.9Hz), 4.86(1H,dd,J=11.0,3.9Hz), 7.17-7.29(3H,m), 7.29-7.38(2H,m), 7.41-7.50(2H,m), 7.67(1H,d,J=7.8Hz).

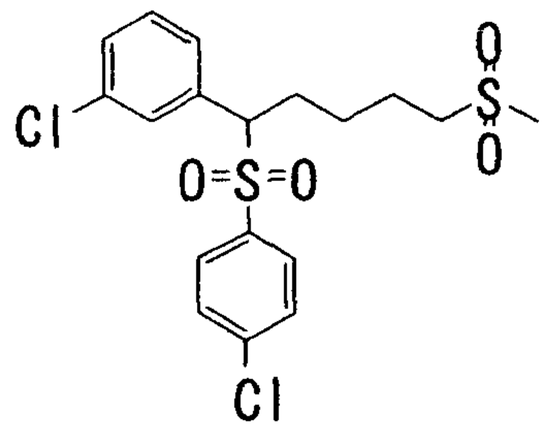
MS (m/z): 435(M^++H).

HRMS (FAB) for $C_{18}H_{21}O_4Cl_2S_2$ (M^++H)

Calculated: 435.0258

Found: 435.0264

Example 64: 1-Chloro-3-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzene



Sodium 4-chlorobenzenesulfinate (219 mg, 1.10 mmol) and 3-chlorobenzyl bromide (142 µl, 1.03 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was washed with hexane to yield a white powder (304 mg).

A toluene (10 ml) solution of the resulting white powder (92 mg), the 4-(methylsulfonyl)-1-butanol (96 mg, 0.631 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (148 mg, 0.614 mmol) was heated under reflux for 20 hours under an argon atmosphere. After cooling to room temperature, the

reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=2:3), the title compound (51 mg) was obtained as a colorless oil.

IR (ATR) ν: 3089, 3023, 1573, 1475, 1394, 1278, 1195, 1139, 1081, 1012, 962, 885, 829, 804, 750, 694, 626, 578, 530, 462 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.32-1.50(2H,m), 1.79-1.97(2H,m), 2.09-2.22(1H,m), 2.40-2.52(1H,m), 2.88(3H,s), 2.90-3.00(2H,m), 3.98(1H,dd,J=11.2,3.9Hz), 6.96(1H,d,J=7.6Hz), 7.10(1H,s), 7.20(1H,t,J=7.6Hz), 7.28-7.32(1H,m), 7.35-7.47(4H,m).

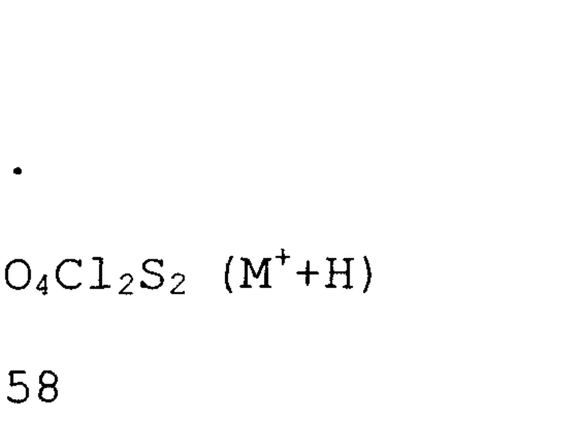
MS (m/z): 435 (M^++H).

HRMS (FAB): as $C_{18}H_{21}O_4Cl_2S_2$ (M^++H)

Calculated: 435.0258

Found: 435.0240

Example 65: <u>1-Chloro-4-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzene</u>



Sodium 4-chlorobenzenesulfinate (211 mg, 1.06 mmol)

and 4-chlorobenzyl bromide (218 mg, 1.06 mmol) were added to dimethoxyethane (5 ml), followed by stirring at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was washed with hexane to yield a white powder (274 mg).

Then, a toluene (10 ml) solution of the resulting white powder (61 mg), the 4-(methylsulfonyl)-1-butanol (63 mg, 0.414 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (97 mg, 0.403 mmol) was heated under reflux for 20 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=2:3), the title compound (37 mg) was obtained as a colorless oil.

IR (ATR) ν: 2931, 2871, 1581, 1492, 1475, 1411, 1394, 1276, 1139, 1085, 1012, 962, 908, 827, 752, 713, 661, 620, 566, 518, 470 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.51(2H,m), 1.75-1.98(2H,m), 2.05-2.25(1H,m), 2.42-2.55(1H,m), 2.84-3.10(2H,m),

2.87(3H,s), 3.99(1H,dd,J=11.0,3.9Hz), 6.99-7.10(2H,m), 7.20-7.35(2H,m), 7.35-7.55(4H,m).

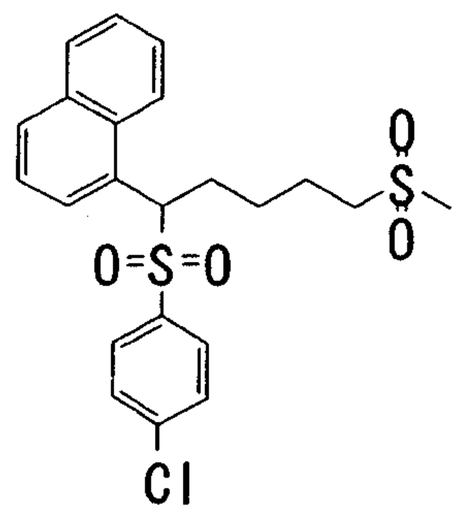
MS (m/z): 435(M^++H).

HRMS (FAB) for $C_{18}H_{21}O_4Cl_2S_2$ (M^++H)

Calculated: 435.0258

Found: 435.0240

Example 66: 1-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]naphthalene



Sodium 4-chlorobenzenesulfinate (183 mg, 0.921 mmol) and 1-bromomethylnaphthalene (204 mg, 0.921 mmol) were added to dimethoxyethane (10 ml). The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting solution, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was washed with hexane to yield a white powder (175 mg).

Then, a toluene (10 ml) solution of the resulting white powder (93 mg), the 4-(methylsulfonyl)-1-butanol (92

mg, 0.604 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (142 mg, 0.589 mmol) was heated under reflux for 18 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=1:1), the title compound was obtained as a white solid (80 mg).

IR (ATR) ν: 2929, 2869, 1577, 1511, 1475, 1394, 1301, 1276, 1137, 1083, 1012, 962, 906, 863, 808, 763, 709, 640, 622, 574, 532, 457 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.55(2H,m), 1.77-1.95(2H,m), 2.29-2.46(1H,m), 2.62-2.77(1H,m), 2.80(3H,s), 2.83-3.00(2H,m), 5.07(1H,dd,J=10.9,4.0Hz), 7.10(2H,d,J=8.3Hz), 7.22-7.48(4H,m), 7.51(1H,t,J=7.7Hz), 7.59(1H,d,J=8.6Hz), 7.67(1H,d,J=7.3Hz), 7.78(1H,d,J=8.1Hz), 7.83(1H,d,J=8.3Hz).

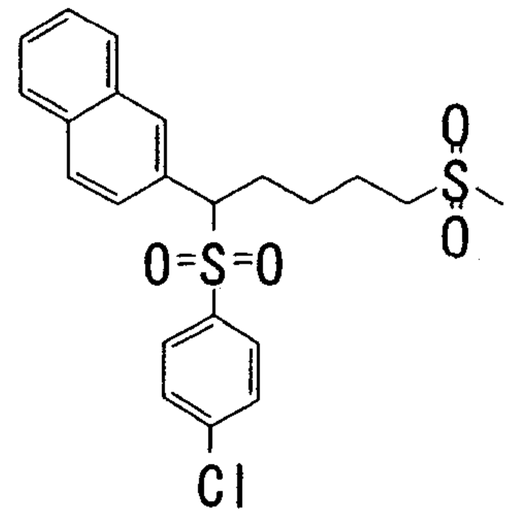
MS (m/z): 451(M^++H).

HRMS (FAB) for $C_{22}H_{24}O_4ClS_2$ (M^++H)

Calculated: 451.0805

Found: 451.0816

Example 67: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]naphthalene



Sodium 4-chlorobenzenesulfinate (211 mg, 1.06 mmol) and 2-bromomethylnaphthalene (235 mg, 1.06 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was washed with hexane to yield a white powder (90 mg).

Then, a toluene (10 ml) solution of the resulting white powder (60 mg), the 4-(methylsulfonyl)-1-butanol (59 mg, 0.388 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (91 mg, 0.379 mmol) was heated under reflux for 21 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=2:3), the title compound was

obtained as a white solid (62 mg).

Melting point: 146.0-147.0°C.

IR (ATR) ν: 2931, 2861, 1581, 1508, 1473, 1457, 1392, 1359, 1309, 1274, 1191, 1147, 1126, 1081, 1010, 968, 902, 869, 819, 752, 734, 703, 646, 624, 566, 522, 472, 453 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.34-1.51(2H,m), 1.78-1.99(2H,m), 2.25-2.40(1H,m), 2.50-2.62(1H,m), 2.84(3H,s), 2.89-3.03(2H,m), 4.19(1H,dd,J=11.2,3.9Hz), 7.18-7.36(4H,m), 7.39-7.61(4H,m), 7.69-7.90(3H,m).

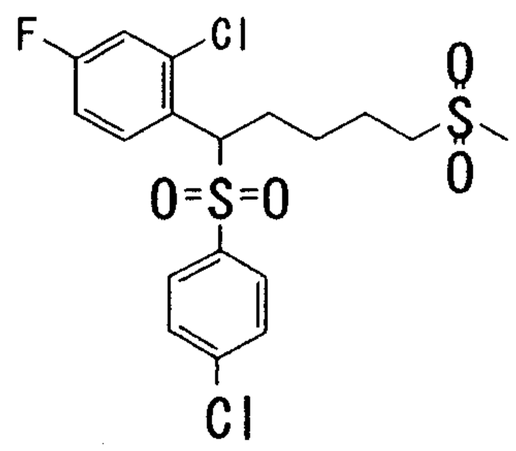
MS (m/z): 451 (M^++H).

Elemental Analysis for $C_{22}H_{23}ClO_4S_2$

Calculated: C 58.59%; H 5.14%; Cl 7.86%; S 14.22%.

Found: C 58.46%; H 5.03%; Cl 7.94%; S 14.33%.

Example 68: 2-Chloro-1-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]-4-fluorobenzene



Sodium 4-chlorobenzenesulfinate (197 mg, 0.992 mmol) and 2-chloro-4-fluorobenzyl bromide (222 mg, 0.992 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate

and from the resulting mixture, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was washed with hexane to yield a white powder (225 mg).

Then, a toluene (10 ml) solution of the resulting white powder (61 mg), 4-(methylsulfonyl)-1-butanol (59 mg, 0.394 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (93 mg, 0.384 mmol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate(=1:1), the title compound was obtained as a white solid (38 mg).

Melting point: 124.0-125.0°C.

IR (ATR) ν: 2969, 2933, 1604, 1575, 1492, 1475, 1461, 1396, 1315, 1276, 1230, 1130, 1085, 1049, 1014, 973, 902, 850, 823, 782, 748, 659, 630, 588, 549, 501, 457 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.50(2H,m), 1.79-1.98(2H,m), 2.10-2.25(1H,m), 2.48-2.60(1H,m), 2.87(3H,s), 2.95(2H,t,J=7.7Hz), 4.79(1H,dd,J=11.1,4.0Hz), 6.98(1H,dd,J=8.3,2.7Hz), 7.05-7.15(1H,m), 7.38(2H,d,J=8.3Hz), 7.48(2H,d,J=8.5Hz), 7.60-7.70(1H,m).

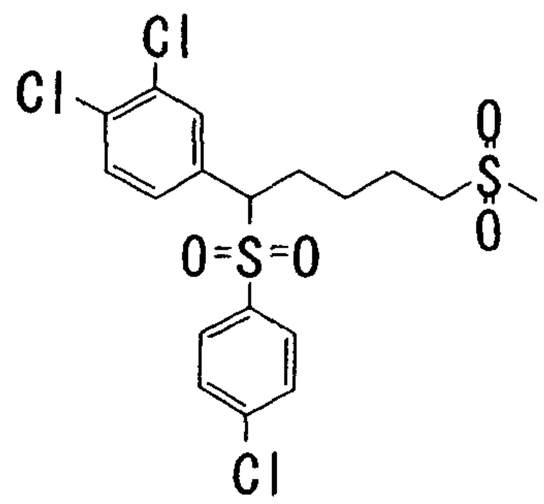
MS (m/z): 453 (M^++H).

Elemental Analysis for $C_{18}H_{19}Cl_2FO_4S_2$

Calculated: C 47.69%; H 4.22%; Cl 15.64%; F 4.19%; S 14.55%.

Found: C 47.44%; H 4.20%; Cl 15.37%; F 4.07%; S 14.33%.

Example 69: 1,2-Dichloro-4-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzene



Sodium 4-chlorobenzenesulfinate (208 mg, 1.05 mmol) and 3,4-dichlorobenzyl bromide (251 mg, 1.05 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was washed with hexane to yield a white powder (270 mg).

Then, a toluene (10 ml) solution of the resulting white powder (66 mg), the 4-(methylsulfonyl)-1-butanol (62 mg, 0.407 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (96 mg, 0.397 mmol)

was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the fraction eluted with hexane:ethyl acetate(=2:3), the title compound was obtained as a white solid (70 mg).

Melting point: 143.0-144.0°C.

IR (ATR) ν: 2929, 2865, 1573, 1459, 1392, 1365, 1317, 1299, 1276, 1186, 1145, 1079, 1031, 1010, 975, 900, 823, 748, 709, 655, 626, 588, 563, 518, 474, 439 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.32-1.49(2H,m), 1.79-1.96(2H,m), 2.05-2.19(1H,m), 2.39-2.50(1H,m), 2.88(3H,s), 2.90-3.00(2H,m), 3.97(1H,dd,J=11.2,3.9Hz), 6.94(1H,dd,J=8.3,2.2Hz), 7.21(1H,d,J=2.0Hz), 7.36(1H,d,J=8.3Hz), 7.43(2H,d,J=8.3Hz), 7.49(2H,d,J=8.6Hz).

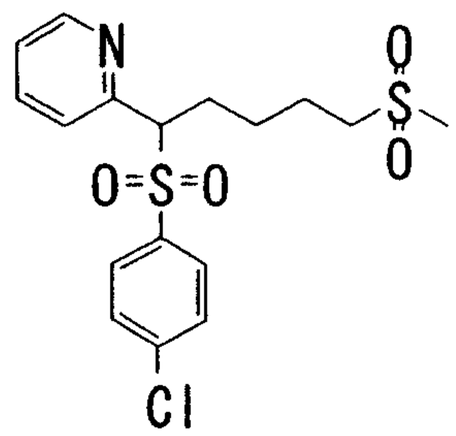
MS (m/z): 469 (M^++H).

Elemental Analysis for $C_{18}H_{19}Cl_3O_4S_2$

Calculated: C 46.02%; H 4.08%; Cl 22.64%; S 13.65%.

Found: C 45.92%; H 4.06%; Cl 22.35%; S 13.59%.

Example 70: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]pyridine



Sodium 4-chlorobenzenesulfinate (200 mg, 1.01 mmol), 2-chloromethylpyridine hydrochloride (166 mg, 1.01 mmol) and potassium acetate (198 mg, 2.02 mmol) were added to n-butanol (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. From the fraction eluted with hexane:ethyl acetate(=3:1), a white solid (123 mg) was obtained.

Then, a toluene (10 ml) solution of the resulting solid (49 mg), the 4-(methylsulfonyl)-1-butanol (57 mg, 0.374 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (88 mg, 0.366 mmol) was heated under reflux for 2 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the fraction eluted with

methanol:methylene chloride (=1:50), the title compound was obtained as a white solid (40 mg).

Melting point: 140.0-141.0°C.

IR (ATR) ν: 3012, 2948, 1587, 1471, 1436, 1392, 1321, 1290, 1263, 1197, 1149, 1089, 1006, 960, 825, 750, 703, 624, 565, 528, 499, 474, 410 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.52(2H,m), 1.79-1.99(2H,m), 2.29-2.49(2H,m), 2.86(3H,s), 2.93(2H,t,J=6.8Hz), 4.33(1H,dd,J=11.0,4.2Hz), 7.20-7.30(1H,m), 7.32-7.52(5H,m), 7.67-7.78(1H,m), 8.40(1H,d,J=4.9Hz).

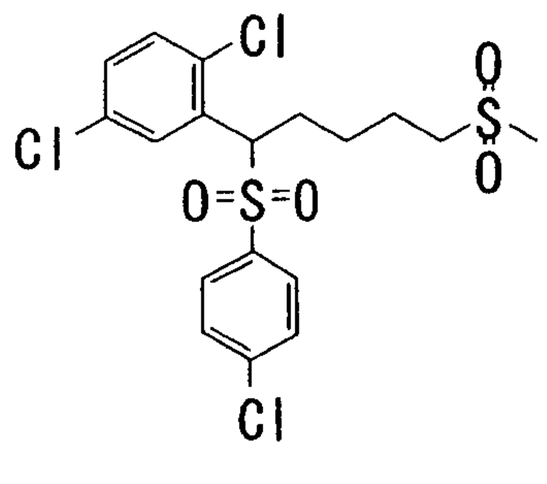
MS (m/z): 402 (M^++H).

Elemental Analysis for $C_{17}H_{20}NClO_4S_2$

Calculated: C 50.80%; H 5.02%; N 3.48%; Cl 8.82%; S 15.96%.

Found: C 50.67%; H 4.94%; N 3.53%; Cl 8.72%; S 15.90%.

Example 71: 1,4-Dichloro-2-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzene



Sodium 4-chlorobenzenesulfinate (38 mg, 0.192 mmol) and 2,5-dichlorobenzyl bromide (46 mg, 0.192 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was

stirred at 70°C for 24 hours. After cooling to room temperature, the reaction mixture was subjected to a short column (silica gel) and the fraction eluted with diethyl ether was concentrated under reduced pressure. The residue thus obtained was dissolved in toluene (5 ml). To the resulting solution were added the 4-(methylsulfonyl)-1-butanol (58 mg, 0.381 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (89 mg, 0.370 mmol), followed by heating under reflux for 23 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the fraction eluted with hexane:ethyl acetate (=1:1), the title compound (32 mg, 35%) was obtained as a colorless oil.

IR (ATR) ν: 2933, 2869, 1581, 1465, 1394, 1313, 1278, 1191, 1133, 1083, 1039, 1012, 962, 887, 821, 752, 713, 630, 588, 532, 464 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.33-1.50(2H,m), 1.80-1.96(2H,m), 2.09-2.21(1H,m), 2.48-2.59(1H,m), 2.88(3H,s), 2.90-2.99(2H,t,J=11.0,4.2Hz), 4.79(1H,dd,J=11.0,4.2 Hz), 7.15(1H,d,J=8.6Hz), 7.20-7.29(1H,m), 7.34-7.40(2H,m), 7.46-7.52(2H,m), 7.63(1H,d,J=2.5Hz).

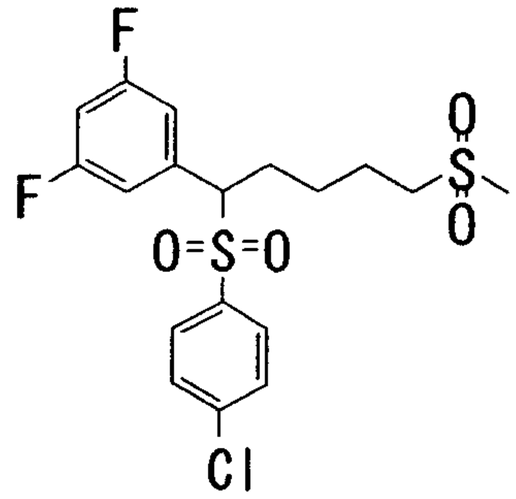
MS (m/z): 469, 471 (M^++H).

HRMS (FAB) for $C_{18}H_{20}O_4Cl_3S_2$ (M^++H)

Calculated: 468.9869

Found: 468.9907

Example 72: 1-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]-3,5-difluorobenzene



Sodium 4-chlorobenzenesulfinate (49 mg, 0.247 mmol) and 3,5-difluorobenzyl bromide (32 µl, 0.247 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 24 hours. After cooling to room temperature, the reaction mixture was subjected to a short column (silica gel) and the fraction eluted with diethyl ether was concentrated under reduced pressure. The residue thus obtained was dissolved in toluene (5 ml). To the resulting solution were added the 4-(methylsulfonyl)-1-butanol (58 mg, 0.381 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (89 mg, 0.370 mmol). The mixture was heated under reflux for 23 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the

fraction eluted with hexane:ethyl acetate (=1:1), the title compound was obtained as a white solid (39 mg, 36%).

Melting point: 126.0-127.0°C.

IR (ATR) ν: 2940, 1623, 1596, 1463, 1392, 1344, 1319, 1270, 1243, 1203, 1145, 1118, 1081, 1010, 987, 952, 863, 823, 752, 707, 680, 624, 539, 501, 478, 449 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.62(2H,m), 1.78-1.99(2H,m), 2.05-2.19(1H,m), 2.39-2.51(1H,m), 2.88(3H,s), 2.90-3.05(2H,m), 3.98(1H,dd,J=10.9,4.0Hz), 6.62-6.75(2H,m), 6.75-6.85(1H,m), 7.38-7.58(4H,m).

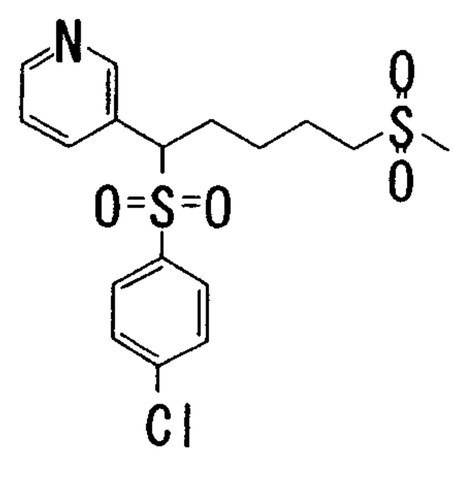
MS (m/z): 436 (M^++H).

Elemental Analysis for $C_{18}H_{19}F_2O_4S_2$

Calculated: C 49.48%; H 4.38%; Cl 8.11%; F 8.70%; S 14.68%.

Found: C 49.45%; H 4.33%; Cl 8.10%; F 8.88%; S 14.69%.

Example 73: 3-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]pyridine



Sodium 4-chlorobenzenesulfinate (207 mg, 1.04 mmol), 3-chloromethylpyridine hydrochloride (171 mg, 1.04 mmol) and potassium acetate (204 mg, 2.08 mmol) were added to n-

butanol (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. The residue was added with ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and from the fraction eluted with hexane:ethyl acetate(=2:3), a white solid (98 mg) was obtained.

Then, a toluene (10 ml) solution of the resulting solid (29 mg), the 4-(methylsulfonyl)-1-butanol (102 mg, 0.670 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (156 mg, 0.650 mmol) was heated under reflux for 2 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. To the residue was added 1N hydrochloric acid/ethanol and the mixture was concentrated under reduced pressure. The residue was washed with diethyl ether. The residue was added with a saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. After the organic layer was dried over anhydrous sodium sulfate, the solvent was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column. From the fraction

eluted with methanol:methylene chloride (=1:50), the title compound (38 mg) was obtained as a pale yellow oil.

IR (ATR) ν: 2929, 2873, 1575, 1477, 1425, 1394, 1276, 1178, 1132, 1083, 1012, 964, 908, 823, 757, 711, 651, 622, 563, 518, 458 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.52(2H,m), 1.80-1.99(2H,m), 2.13-2.26(1H,m), 2.49-2.59(1H,m), 2.88(3H,s), 2.90-2.99(2H,m), 4.05(1H,dd,J=11.1,4.0Hz), 7.30(1H,dd,J=7.8,4.9Hz), 7.38-7.48(4H,m), 7.64(1H,dt,J=8.1,2.0Hz), 8.16(1H,d,J=2.0Hz), 8.57(1H,dd,J=4.8,1.6Hz).

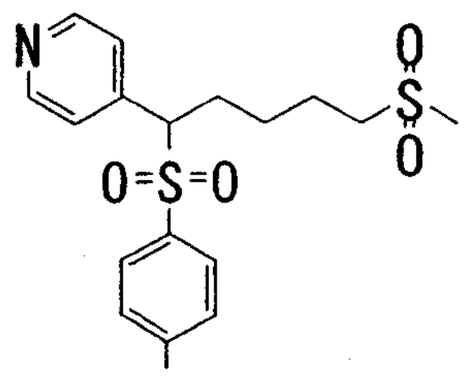
MS (m/z): 402 (M^++H).

HRMS (FAB) for $C_{17}H_{21}O_4NClS_2$ (M^++H)

Calculated: 402.0601

Found: 402.0596

Example 74: 4-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]pyridine



Sodium 4-chlorobenzenesulfinate (207 mg, 1.04 mmol), 3-chloromethylpyridine hydrochloride (171 mg, 1.04 mmol) and potassium acetate (204 mg, 2.08 mmol) were added to n-

butanol (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. To the residue was added ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the from the fraction eluted with hexane:ethyl acetate (=2:3), a white solid (117 mg) was obtained.

Then, a toluene (10 ml) solution of the resulting solid (52 mg), the 4-(methylsulfonyl)-1-butanol (90 mg, 0.592 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (140 mg, 0.582 mmol) was heated under reflux for 2 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. To the residue was added 1N hydrochloric acid/ethanol. After concentration under reduced pressure, the residue was washed with diethyl ether. To the residue was added a saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column and from the fraction eluted with methanol:methylene

chloride (=1:50), the title compound was obtained as a white solid (62 mg).

Melting point: 181.0-182.0°C.

IR (ATR) ν: 2942, 2863, 1590, 1467, 1415, 1311, 1272, 1241, 1201, 1147, 1085, 1002, 960, 908, 831, 755, 703, 632, 568, 530, 476, 453 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.53(2H,m), 1.76-1.99(2H,m), 2.10-2.25(1H,m), 2.40-2.57(1H,m), 2.88(3H,s), 2.90-3.02(2H,m), 4.00(1H,dd,J=11.1,4.0Hz), 6.95-7.09(2H,m), 7.32-7.55(4H,m), 8.43-8.60(2H,m).

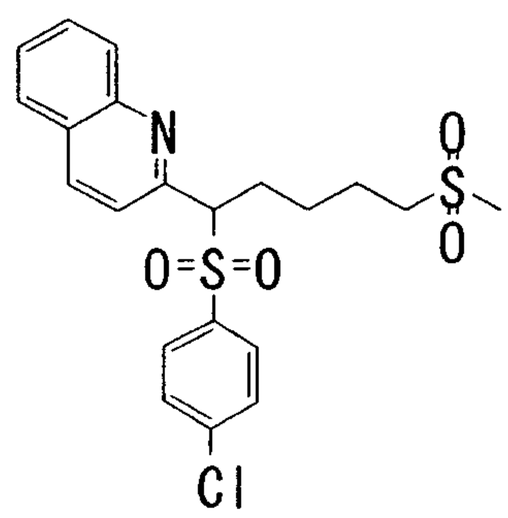
MS (m/z): 402 (M^++H).

Elemental Analysis for $C_{17}H_{20}NClO_4S_2$

Calculated: C 50.80%; H 5.02%; N 3.48%; Cl 8.82%; S 15.96%.

Found: C 50.70%; H 4.93%; N 3.55%; Cl 8.10%; S 15.83%.

Example 75: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]quinoline



Sodium 4-chlorobenzenesulfinate (196 mg, 0.987 mmol), 2-chloromethylquinoline hydrochloride (211 mg, 0.987 mmol) and potassium acetate (194 mg, 1.97 mmol) were added to n-

butanol (5 ml). The resulting mixture was stirred at 70°C for 5 hours. After cooling to room temperature, the solvent was concentrated under reduced pressure. To the residue was added ethyl acetate and from the resulting mixture, the insoluble matter was filtered off. The residue obtained by concentrating the filtrate under reduced pressure was subjected to chromatography on a silica gel column, whereby from the fraction eluted with hexane:ethyl acetate (=1:1), a white solid (97 mg) was obtained.

Then, a toluene (10 ml) solution of the resulting solid (42 mg), the 4-(methylsulfonyl)-1-butanol (104 mg, 0.684 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (160 mg, 0.666 mmol) was heated under reflux for 2 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to medium-pressure chromatography on a silica gel column and from the fraction eluted with hexane:ethyl acetate (=1:3), the title compound (49 mg) was obtained as a colorless oil.

IR (ATR) ν: 2931, 2869, 1596, 1581, 1504, 1463, 1428, 1394, 1297, 1278, 1133, 1083, 1012, 960, 875, 829, 755, 705, 663, 624, 568, 516, 457 cm^{-1}.

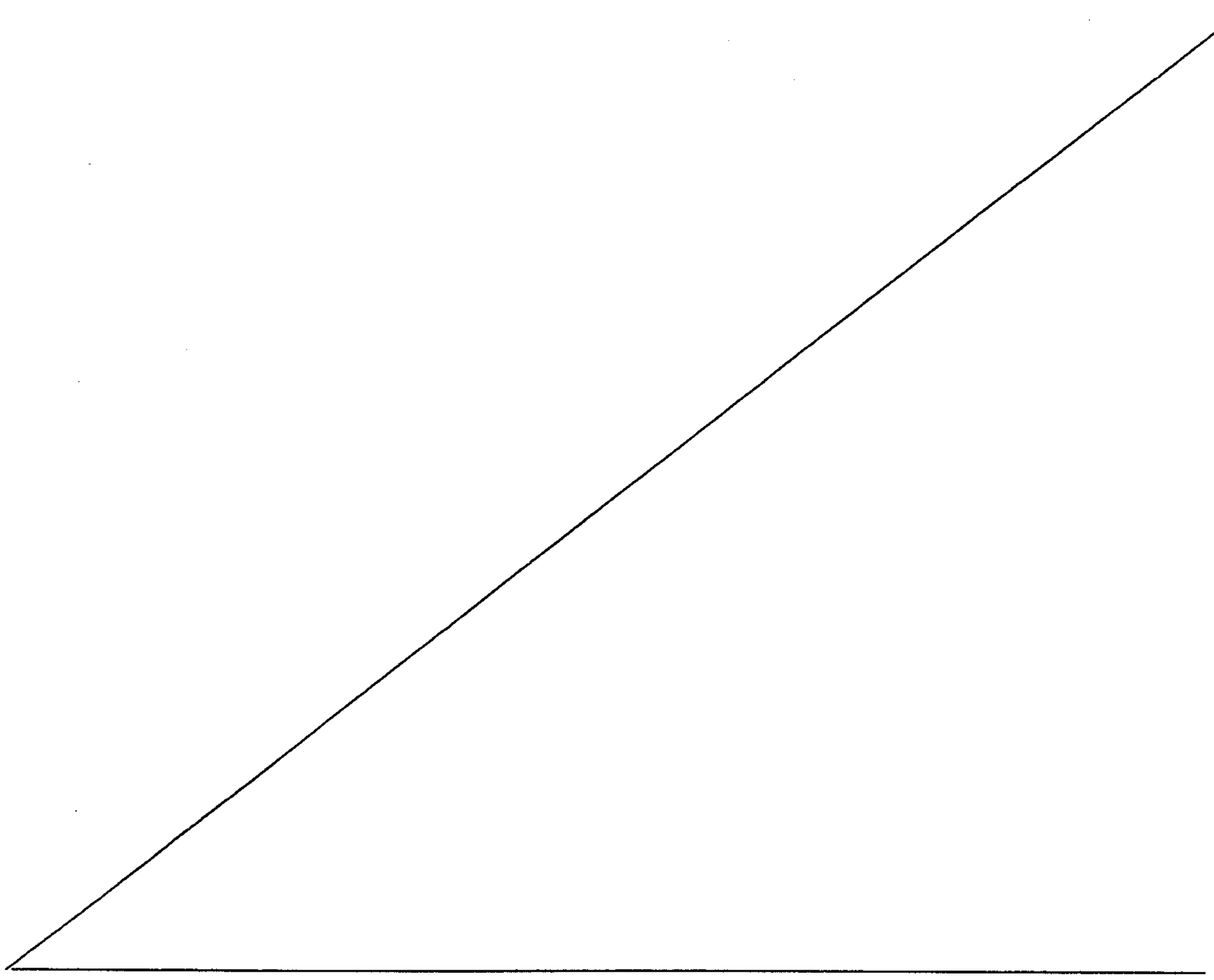
^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.60(2H,m), 1.79-1.95(2H,m), 2.40-2.50(2H,m), 2.83(3H,s), 2.91(2H,t,J=7.2Hz), 4.52(1H,dd,J=9.9,5.3Hz), 7.28-7.32(2H,m), 7.39-7.46(2H,m), 7.55-7.61(2H,m), 7.67-7.73(1H,m), 7.77-7.87(2H,m), 8.19(1H,d,J=8.6Hz).

MS (m/z): 452 (M^++H).

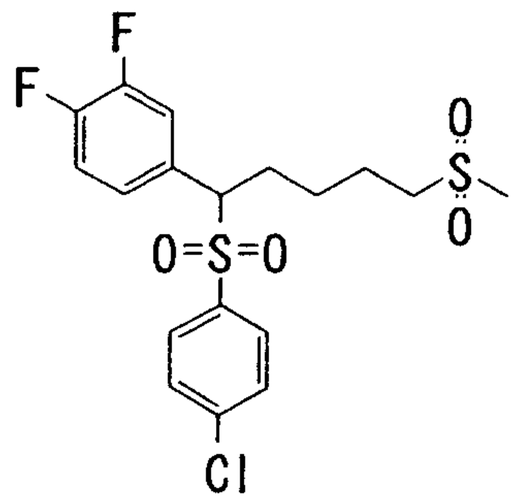
HRMS (FAB) for $C_{21}H_{23}O_4NClS_2$ (M^++H)

Calculated: 452.0757

Found: 452.0744



Example 76: 4-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-1,2-difluorobenzene



Sodium 4-chlorobenzenesulfinate (45 mg, 0.227 mmol) and 3,4-difluorobenzyl bromide (29 µl, 0.227 mmol) were added to dimethoxyethane (5 ml). The resulting mixture was stirred at 70°C for 24 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue and from the mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to chromatography on a silica gel column and the fraction obtained from the ether eluate was concentrated under reduced pressure. A toluene (5 ml) solution of the residue, the 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454 mmol) was heated under reflux for 16 hours under an argon atmosphere. After cooling to room temperature, the 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) obtained in Referential Example

3 and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454 mmol) were added, followed by heating under reflux for 22 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate (=2:3) eluate was concentrated under reduced pressure, whereby the title compound (12 mg, 12%) was obtained as a white solid. The solid was washed with hexane-ether and collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 122-124°C.

IR (ATR) ν: 2940, 2873, 1610, 1575, 1519, 1467, 1434, 1394, 1317, 1280, 1268, 1205, 1145, 1126, 1083, 1012, 962, 877, 819, 765, 754, 707, 632, 592, 549, 526, 514, 507, 484, 451, 404 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.32-1.50(2H,m), 1.79-1.97(2H,m), 2.03-2.18(1H,m), 2.40-2.50(1H,m), 2.88(3H,s), 2.90-3.00(2H,m), 3.98(1H,dd,J=11.0,3.9Hz), 6.77-6.81(1H,m), 6.99-7.10(2H,m), 7.38-7.53(4H,m).

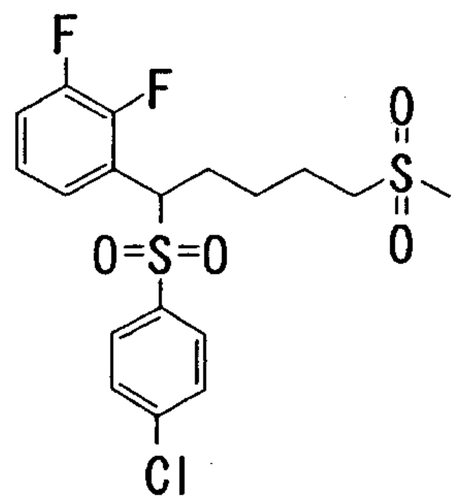
MS (m/z): 437 (M^++H).

HRMS (FAB) for $C_{18}H_{20}O_4ClF_2S_2$ (M^++H)

Calculated: 437.0460

Found: 437.0494

Example 77: 1-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-2,3-difluorobenzene



To dimethoxyethane (5 ml) were added sodium 4-chlorobenzenesulfinate (45 mg, 0.227 mmol) and 2,3-difluorobenzyl bromide (29 µl, 0.227 mmol). The resulting mixture was stirred at 70°C for 24 hours. After cooling at room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue and from the mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. The fraction obtained from the ether eluate was concentrated under reduced pressure. A toluene (10 ml) solution of the residue, the 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454 mmol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a

silica gel column. The fraction obtained from the 55% ethyl acetate/hexane eluate was concentrated under reduced pressure to give the title compound (37 mg, 37%) as a white solid. The solid was washed with hexane-ether and filtered, whereby the title compound was obtained as a white powder.

Melting point: 141-143°C.

IR (ATR) ν: 2948, 2867, 1625, 1575, 1484, 1396, 1317, 1272, 1230, 1199, 1149, 1124, 1085, 1012, 966, 935, 894, 808, 761, 717, 659, 628, 584, 547, 518, 472, 443 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.37-1.60(2H,m), 1.81-1.96(2H,m), 2.11-2.25(1H,m), 2.45-2.57(1H,m), 2.88(3H,s), 2.96(2H,t,J=7.9Hz), 4.53(1H,dd,J=11.1,4.0Hz), 7.10-7.19(2H,m), 7.22-7.33(1H,m), 7.39-7.44(2H,m), 7.49-7.54(2H,m).

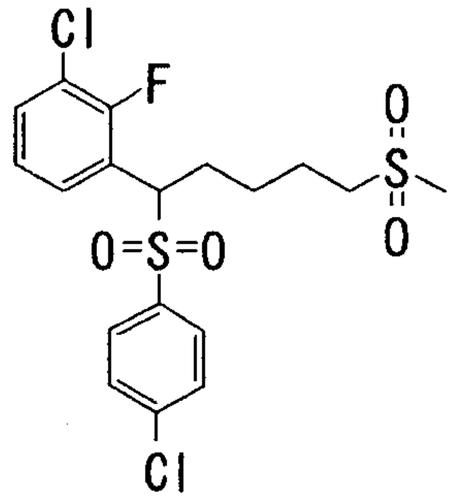
MS (m/z): 437(M^++H).

Element Analysis for $C_{18}H_{19}ClF_2O_4S_2$

Calculated: C 49.48%; H 4.38%; Cl 8.11%; F 8.70%; S 14.68%.

Found: C 49.38%; H 4.34%; Cl 8.13%; F 8.60%; S 14.56%.

Example 78: <u>1-Chloro-3-[1-(4-chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-2-fluorobenzene</u>



Cl

To dimethoxyethane (5 ml) were added sodium 4-chlorobenzenesulfinate (45 mg, 0.227 mmol) and 3-chloro-2-fluorobenzyl bromide (51 mg, 0.227 mmol). The resulting mixture was stirred at 70°C for 24 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the ether eluate was concentrated under reduced pressure. A toluene (5 ml) solution of the resulting residue, the 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454 mmol) was heated under reflux for 5 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was added with the 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454

mmol), followed by heating under reflux for 12.5 hours under an argon atmosphere. The reaction mixture was cooled to room temperature and then, concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure to give the title compound (42 mg, 41%) as a white solid. The resulting solid was washed with hexane-ether and collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 131-132°C.

IR (ATR) ν: 3038, 2938, 1579, 1459, 1392, 1313, 1286, 1234, 1151, 1120, 1085, 1010, 966, 914, 811, 750, 719, 671, 620, 584, 522, 458 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.33-1.60(2H,m), 1.80-1.98(2H,m), 2.11-2.25(1H,m), 2.42-2.56(1H,m), 2.88(3H,s), 2.96(2H,t,J=7.9Hz), 4.53(1H,dd,J=11.1,4.3Hz), 7.11-7.20(1H,m), 7.33-7.46(4H,m), 7.46-7.56(2H,m).

MS (m/z): 453 (M^++H).

Elemental Analysis for $C_{18}H_{19}Cl_2FO_4S_2$

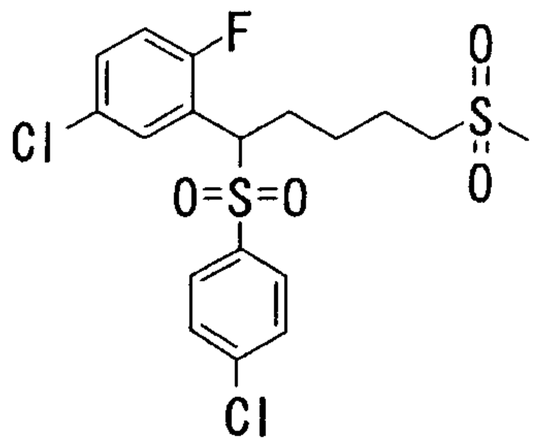
Calculated: C 47.69%; H 4.22%; Cl 15.64%; F 4.19%; S 14.15%.

Found: C 47.40%; H 4.18%; Cl 15.42%; F 4.16%; S 14.08%.

Example 79: 4-Chloro-2-[1-(4-chlorophenylsulfonyl)-5-

(

(methylsulfonyl)pentyl]-1-fluorobenzene



To dimethoxyethane (5 ml) were added sodium 4-chlorobenzenesulfinate (45 mg, 0.227 mmol) and 2-bromomethyl-4-chloro-1-fluorobenzene (51 mg, 0.227 mmol). The resulting mixture was stirred at 70°C for 24 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the ether eluate was concentrated under reduced pressure. A toluene (5 ml) solution of the residue thus obtained, the 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454 mmol) was heated under reflux for 16 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was added with 4-(methylsulfonyl)-1-butanol (71 mg, 0.454 mmol) and cyanomethylenetri-n-butylphosphorane (110 mg, 0.454 mmol),

followed by heating under reflux for 22 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate eluate (=1:1) was concentrated under reduced pressure to give the title compound (53 mg, 51%) as a white solid. The resulting solid was washed with hexane-ether and then collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 116-117°C.

IR (ATR) ν: 3097, 2946, 1577, 1490, 1407, 1317, 1278, 1240, 1174, 1147, 1083, 1047, 1012, 956, 916, 881, 823, 754, 711, 649, 626, 566, 538, 474, 433 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.38-1.52(2H,m), 1.81-1.99(2H,m), 2.09-2.21(1H,m), 2.45-2.57(1H,m), 2.89(3H,s), 2.91-3.02(2H,m), 4.48-4.53(1H,m), 6.83(1H,t,J=8.9Hz), 7.23-7.30(1H,m), 7.38-7.45(2H,m), 7.46-7.59(3H,m).

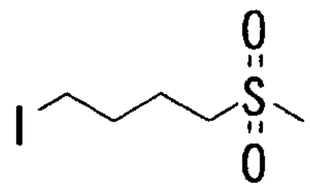
MS (m/z): 453(M^++H).

Elemental Analysis for $C_{18}H_{19}Cl_2FO_4S_2$

Calculated: C 47.69%; H 4.22%; Cl 15.64%; F 4.19%; S 14.15%.

Found: C 47.52%; H 4.19%; Cl 15.47%; F 4.24%; S 14.08%.

Referential Example 7: 1-Iodo-4-(methylsulfonyl)butane

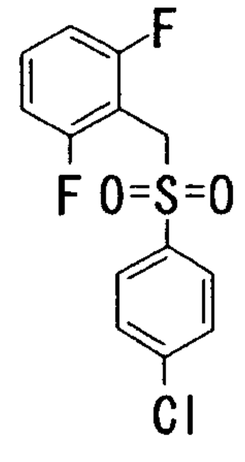


Iodine (1.87 g, 7.35 mmol) was added to a methylene chloride (30 ml) solution of the 4-(methylsulfonyl)-1-butanol (746 mg, 4.90 mmol) obtained in Referential Example 3, imidazole (500 mg, 7.35 mmol) and triphenylphosphine (1.93 g, 7.35 mmol) and the resulting mixture was stirred for 3 hours at room temperature. The reaction mixture was added with a saturated aqueous solution of sodium thiosulfate. The resulting mixture was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. The fraction obtained from the methanol:methylene chloride (=1:100) eluate was concentrated under reduced pressure, whereby the title compound (1.18 g, 92%) was obtained as a pale yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.92-2.08(4H,m), 2.93(3H,s), 3.00-3.10(2H,m), 3.18-3.28(2H,m).

MS (m/z): 263 (M^++H).

Example 80: 2-(4-Chlorophenylsulfonylmethyl)-1, 3-difluorobenzene



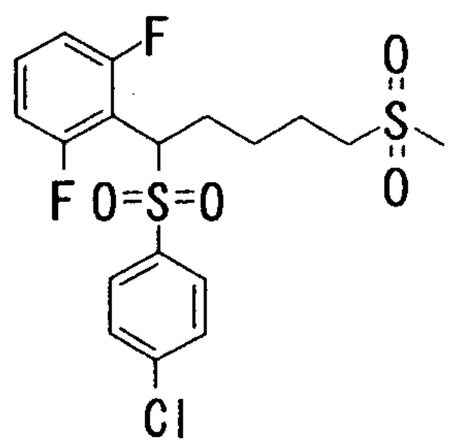
To dimethoxyethane (10 ml) were added sodium 4-chlorobenzenesulfinate (205 mg, 1.03 mmol) and 2,6-difluorobenzyl bromide (214 mg, 1.03 mmol). The resulting mixture was stirred at 70°C for 18 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue and from the resulting mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the ether eluate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=10:1) eluate was concentrated under reduced pressure, whereby the title compound (289 mg, 93%) was obtained as a white solid.

IR (ATR) ν: 3097, 2989, 1625, 1575, 1509, 1473, 1407, 1392, 1319, 1272, 1245, 1197, 1182, 1132, 1083, 998, 889, 854, 831, 802, 777, 742, 719, 686, 626, 566, 512, 478, 449, 418 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.48(2H,s), 6.88(2H,t,J=7.9Hz), 7.29-7.39(1H,m), 7.47(2H,d,J=8.6Hz), 7.68(2H,d,J=8.6Hz).

MS (m/z): 303 (M^++H).

Example 81: 2-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-1,3-difluorobenzene



At -78°C, butyl lithium (a 1.57M hexane solution; 0.55 ml, 0.864 mmol) was added dropwise to a dimethoxyethane (10 ml) solution of 2-(4-chlorophenylsulfonylmethyl)-1,3-difluorobenzene (218 mg, 0.720 mmol). After stirring at -78°C for 30 minutes, a dimethoxyethane (5 ml) solution of the 1-iodo-4-(methylsulfonyl)butane (226 mg, 0.864 mmol) obtained in Referential Example 7 was added dropwise. The temperature of the reaction mixture was elevated gradually to room temperature and at room temperature, the mixture was stirred for 15 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column and the fraction obtained from the 55% ethyl

acetate/hexane eluate was concentrated under reduced pressure to give the title compound (53 mg, 17%) as a white solid. The resulting solid was washed with hexane and collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 118-119°C.

IR (ATR) ν: 2946, 1621, 1585, 1471, 1459, 1396, 1355, 1322, 1301, 1274, 1226, 1151, 1132, 1087, 1012, 989, 958, 925, 829, 773, 761, 752, 717, 624, 572, 522, 485, 458, 406 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.55(2H,m), 1.81-1.95(2H,m), 2.48-2.58(2H,m), 2.88(3H,s), 2.91-3.10(2H,m), 2.97(1H,dd,J=15.8,6.7Hz), 6.75-7.00(2H,m), 7.25-7.35(1H,m), 7.42(2H,d,J=8.6Hz), 8.30(2H,d,J=8.3Hz).

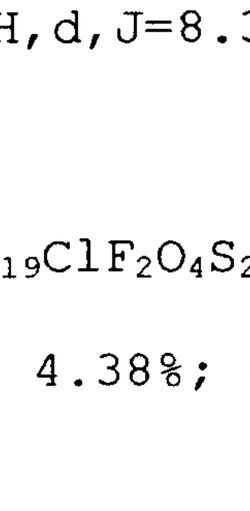
MS (m/z): 437 (M^++H).

Elemental Analysis for $C_{18}H_{19}ClF_2O_4S_2$

Calculated: C 49.48%; H 4.38%; Cl 8.11%; F 8.70%; S 14.68%.

Found: C 49.25%; H 4.32%; Cl 8.02%; F 8.50%; S 14.70%.

Example 82: 1-(4-Chlorophenylsulfonylmethyl)-3-methoxybenzene



A dimethoxyethane (10 ml) suspension of sodium 4-chlorobenzenesulfinate (210 mg, 1.06 mmol) and 3-methoxybenzyl chloride (154 µl, 1.06 mmol) was stirred at 70°C for 16 hours. After cooling to room temperature, butanol (2 ml) and tetrabutylammonium bromide (45 mg) were added and the resulting mixture was stirred further at 70°C for 16 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with water and brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=5:1) eluate was concentrated under reduced pressure, whereby the title compound (216 mg, 69%) was obtained as a white solid.

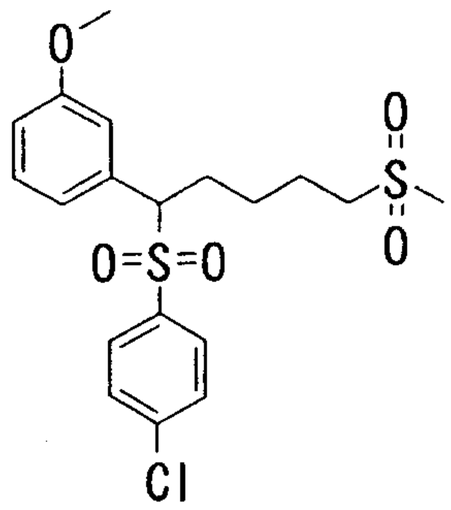
IR (ATR) ν: 3064, 2979, 2842, 1598, 1488, 1469, 1434, 1392, 1313, 1268, 1176, 1130, 1085, 1033, 1012, 941, 879, 823, 792, 765, 742, 692, 620, 574, 528, 455 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.74(3H,s), 4.27(2H,s), 6.59-6.68(2H,m), 6.82-6.90(1H,m), 7.17(1H,t,J=7.8Hz), 7.42(2H,d,J=8.6Hz), 7.56(2H,d,J=8.6Hz).

MS (m/z): 297 (M^++H).

Example 83: 1-[1-(4-Chlorophenylsulfonyl)-5-

(methylsulfonyl)pentyl]-3-methoxybenzene



A toluene (10 ml) solution of 1-(4-chlorophenylsulfonylmethyl)-3-methoxybenzene (80 mg, 0.269 mmol), the 4-(methylsulfonyl)-1-butanol (62 mg, 0.404 mmol) obtained in Referential Example 3, and cyanomethylenetri-n-butylphosphorane (98 mg, 0.404 mmol) was heated under reflux for 3 days under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure to give the title compound (61 mg, 52%) as a white solid. The white solid was washed with hexane, and collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 91-93°C.

IR (ATR) ν: 2967, 2929, 1594, 1494, 1469, 1455, 1394, 1315, 1272, 1255, 1222, 1189, 1145, 1132, 1085, 1037, 1012, 970, 879, 850, 804, 759, 705, 688, 632, 603, 532, 493, 464 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.37-1.50(2H,m), 1.79-1.93(2H,m), 2.10-2.23(1H,m), 2.40-2.52(1H,m), 2.86(3H,s), 2.89-2.98(2H,m), 3.73(3H,s), 3.97(1H,dd,J=11.1,3.8Hz), 6.59-6.67(2H,m), 6.80-6.89(1H,m), 7.15(1H,d,J=8.0Hz), 7.35(2H,d,J=8.6Hz), 7.44(2H,d,J=8.6Hz).

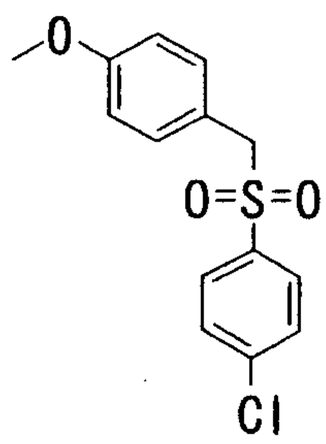
MS (m/z): 431 (M^++H).

Elemental Analysis for $C_{19}H_{23}ClO_5S_2$

Calculated: C 52.95%; H 5.38%; Cl 8.23%; S 14.88%.

Found: C 52.89%; H 5.25%; Cl 8.33%; S 14.87%.

Example 84: 1-(4-Chlorophenylsulfonylmethyl)-4-methoxybenzene



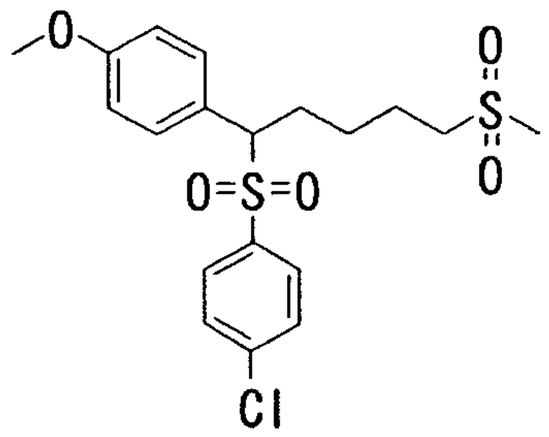
A butanol (5 ml) suspension of sodium 4-chlorobenzenesulfinate (264 mg, 1.33 mmol), 4-methoxybenzyl chloride (181 µl, 1.33 mmol) and tetrabutylammonium bromide (24 mg) was stirred at 70°C for 3 days. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue and the mixture was washed successively with water and brine, and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was

subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=5:1) eluate was concentrated under reduced pressure, whereby the title compound (90 mg, 23%) was obtained as a white solid.

IR (ATR) ν: 3072, 2996, 2942, 2836, 1608, 1583, 1509, 1467, 1396, 1309, 1292, 1240, 1176, 1147, 1089, 1031, 1016, 977, 956, 887, 829, 767, 715, 630, 532, 474, 431 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.80(3H,s), 4.25(2H,s), 6.80(2H,d,J=8.8Hz), 7.00(2H,d,J=8.6Hz), 7.42(2H,d,J=8.3Hz), 7.54(2H,d,J=8.6Hz).

Example 85: 1-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-4-methoxybenzene



A toluene (10 ml) solution of 1-(4-chlorophenylsulfonylmethyl)-4-methoxybenzene (72 mg, 0.243 mmol), the 4-(methylsulfonyl)-1-butanol (70 mg, 0.460 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (111 mg, 0.460 mmol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was added with the 4-(methylsulfonyl)-1-butanol (70 mg, 0.460 mmol)

obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (111 mg, 0.460 mmol) and the mixture was heated under reflux for 22 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane: ethyl acetate (=1:1) eluate was concentrated under reduced pressure to give the title compound (33 mg, 32%) as a white solid. The resulting white solid was washed with hexane and then collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 136-138°C.

IR (ATR) ν: 3012, 2937, 1608, 1583, 1511, 1471, 1392, 1319, 1292, 1268, 1253, 1178, 1145, 1130, 1085, 1029, 1012, 964, 833, 823, 771, 754, 723, 628, 574, 551, 530, 497, 472, 439 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.37-1.50(2H,m), 1.79-1.93(2H,m), 2.10-2.23(1H,m), 2.40-2.52(1H,m), 2.86(3H,s), 2.89-2.98(2H,m), 3.73(3H,s), 3.97(1H,dd,J=11.1,3.8Hz), 6.59-6.67(2H,m), 6.80-6.89(1H,m), 7.15(1H,d,J=8.0Hz), 7.35(2H,d,J=8.6Hz), 7.44(2H,d,J=8.6Hz).

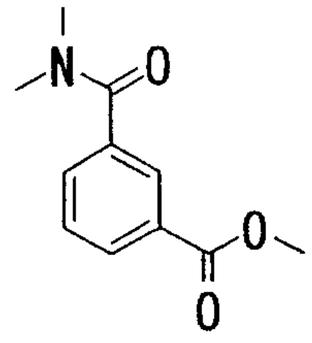
MS (m/z): 431 (M^++H).

Elemental Analysis for $C_{19}H_{23}ClO_5S_2$

Calculated: C 52.95%; H 5.38%; Cl 8.23%; S 14.88%.

Found: C 52.99%; H 5.29%; Cl 8.29%; S 14.82%.

Referential Example 8: Methyl 3-(*N*,*N*-dimethylcarbamoyl)benzoate



To a methylene chloride (20 ml) solution of monomethyl isophthalate (317 mg, 1.76 mmol) were added dimethylamine hydrochloride (172 mg, 2.11 mmol), 1-hydroxybenzotriazole (287 mg, 1.76 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (404 mg, 2.11 mmol) and *N*-methylmorpholine (0.23 ml, 2.11 mmol) and the resulting mixture was stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed successively with 1N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, and brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the methanol:methylene chloride (=1:50) eluate was concentrated under reduced pressure, whereby the title compound (290 mg, 80%) was obtained as a colorless

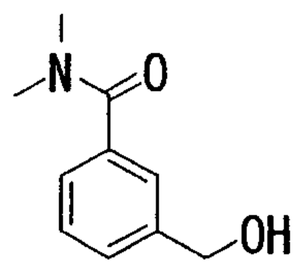
oil.

IR (ATR) ν: 1720, 1633, 1583, 1500, 1436, 1392, 1286, 1255, 1205, 1112, 1076, 979, 933, 823, 773, 730, 696, 669, 638, 580, 489, 439 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.99(3H,s), 3.13(3H,s), 3.93(3H,s), 7.49(1H,t,J=8.2Hz), 7.63(1H,t,J=7.6Hz), 8.05-8.15(2H,m).

MS (m/z): 208 (M^++H).

Referential Example 9: 3-Hydroxymethyl-*N,N*-dimethylbenzamide



Under ice cooling, sodium borohydride (264 mg, 6.97 mmol) was added to an ethanol (15 ml) solution of methyl 3-(*N,N*-dimethylcarbamoyl)benzoate (289 mg, 1.39 mmol). The temperature of the resulting mixture was allowed to rise back to room temperature and then, stirring was conducted at 50°C for 14 hours. After the reaction mixture was cooled back to room temperature, it was ice cooled. Sodium borohydride (264 mg, 6.97 mmol) was added and the mixture was stirred at 50°C for 6 hours. The reaction mixture was ice cooled, and then added with water, followed by concentration under reduced pressure. The residue thus obtained was added with water, followed by extraction with

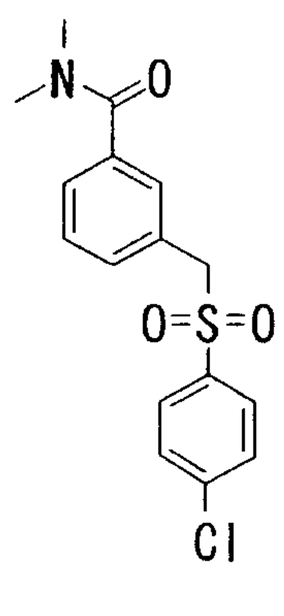
methylene chloride. The extract was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the methanol:methylene chloride (=1:30) eluate was concentrated under reduced pressure, whereby the title compound (196 mg, 79%) was obtained as a colorless oil.

IR (ATR) ν: 3367, 2929, 2869, 1600, 1583, 1508, 1479, 1452, 1394, 1267, 1236, 1170, 1097, 1079, 1049, 898, 800, 746, 719, 694, 642, 431 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.46(1H,br s), 2.97(3H,s), 3.11(3H,s), 4.67(2H,br d,J=2.9Hz), 7.23-7.48(4H,m).

MS (m/z): 180 (M^++H).

Example 86: 3-(4-Chlorophenylsulfonylmethyl)-*N*,*N*-dimethylbenzamide



To a methylene chloride (15 ml) solution of 3-hydroxymethyl-*N*,*N*-dimethylbenzamide (184 mg, 1.03 mmol) were added carbon tetrabromide (511 mg, 1.59 mmol) and

triphenylphosphine (404 mg, 1.54 mmol). The resulting mixture was stirred at room temperature for 4.5 hours. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure to give a colorless oil (239 mg).

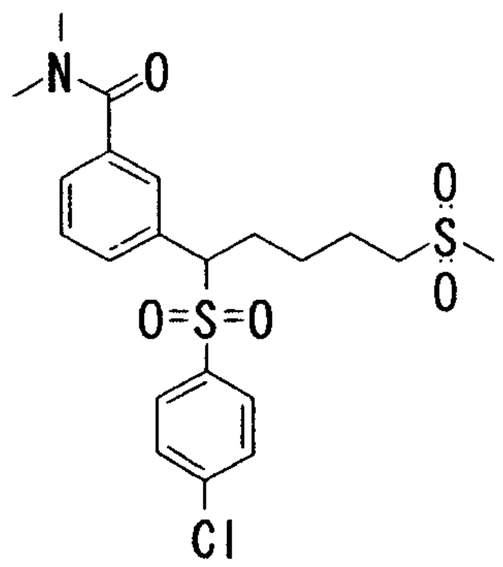
A dimethoxyethane (15 ml) suspension of the resulting colorless oil (239 mg, 0.987 mmol) and sodium 4-chlorobenzenesulfinate (234 mg, 1.18 mmol) was stirred at 70°C for 3 days. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue, followed by successive washing with water and brine and drying over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and the fraction obtained from the 70% ethyl acetate/hexane eluate was concentrated under reduced pressure, whereby the title compound (125 mg, 37%) was obtained as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.89(3H,s), 3.09(3H,s), 4.32(2H,s), 7.10-7.50(6H,m), 7.59(2H,d,J=8.6Hz).

MS (m/z): 338 (M^++H).

Example 87: 3-[1-(4-Chlorophenylsulfonyl)-5-

(methylsulfonyl)pentyl]-*N*,*N*-dimethylbenzamide



A toluene (10 ml) solution of 3-(4-chlorophenylsulfonylmethyl)-*N*,*N*-dimethylbenzamide (69 mg, 0.204 mmol), the 4-(methylsulfonyl)-1-butanol (62 mg, 0.409 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (99 mg, 0.409 mol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the 4-(methylsulfonyl)-1-butanol (62 mg, 0.504 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (99 mg, 0.504 mmol) were added. The reaction mixture was heated under reflux for 23 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the methanol:methylene chloride (=1:50) eluate was concentrated under reduced pressure, whereby the title compound (37 mg, 38%) was obtained as an amorphous

substance.

IR (ATR) ν: 2927, 1625, 1581, 1504, 1475, 1394, 1276, 1172, 1141, 1083, 1012, 964, 908, 819, 754, 705, 626, 551, 516, 468 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.32-1.49(2H,m), 1.78-1.92(2H,m), 2.12-2.28(1H,m), 2.40-2.50(1H,m), 2.83(3H,br s), 2.87(3H,s), 2.90-2.98(2H,m), 3.08(3H,br s), 4.05(1H,dd,J=11.1,3.8Hz), 7.12(1H,br s), 7.19-7.25(1H,m), 7.32-7.40(4H,m), 7.48(2H,d,J=8.6Hz).

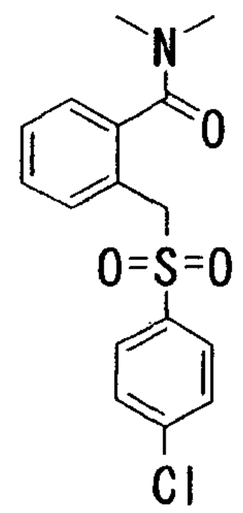
MS (m/z): 472 (M^++H).

HRMS (FAB) for $C_{21}H_{27}O_5NClS_2$ (M^++H)

Calculated: 472.1019

Found: 472.1010

Example 88: 2-(4-Chlorophenylsulfonylmethyl)-*N,N*-dimethylbenzamide



To a methanol (5 ml) solution of phthalide (639 mg, 4.76 mmol) was added a 50% aqueous solution (2 ml) of dimethylamine and the mixture was stirred at 70°C for 14 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. To the

residue was added methylene chloride. The mixture was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the methanol:methylene chloride (=1:40) eluate was concentrated under reduced pressure to yield a colorless oil (248 mg, 29%). To a methylene chloride (10 ml) solution of the colorless oil (238 mg, 1.33 mmol) were added triphenylphosphine (522 mg, 1.99 mmol) and carbon tetrabromide (660 mg, 1.99 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate (=3:2) eluate was concentrated under reduced pressure. The residue was dissolved in butanol (10 ml), followed by the addition thereto sodium 4-chlorobenzenesulfinate (264 mg, 1.33 mmol). The mixture was stirred at 70°C for 2 days. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, followed by successive washing with water and brine and drying over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The

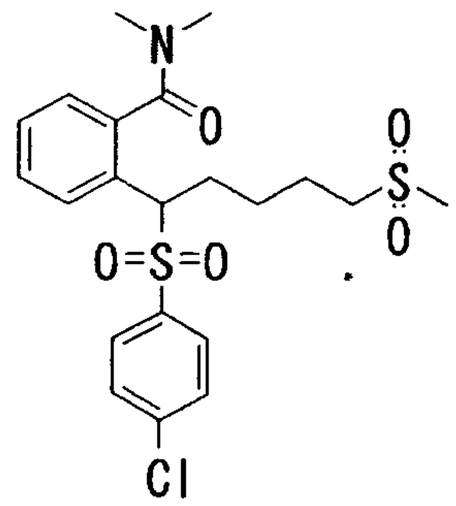
residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=3:2) eluate was concentrated under reduced pressure, whereby the title compound (216 mg, 48%) was obtained as an amorphous substance.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.97(3H,s), 3.13(3H,s), 7.50(2H,d,J=8.8Hz), 7.73(2H,d,J=8.6Hz).

IR (ATR) ν: 2931, 1621, 1598, 1581, 1504, 1475, 1444, 1392, 1317, 1278, 1191, 1151, 1083, 1068, 1012, 879, 827, 777, 757, 740, 705, 636, 607, 566, 536, 466, 447 cm^{-1}.

MS (m/z): 338 (M^++H).

Example 89: <u>2-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-*N*,*N*-dimethylbenzamide</u>



A toluene (5 ml) solution of 2-(4-chlorophenylsulfonylmethyl)-*N*,*N*-dimethylbenzamide (161 mg, 0.477 mmol), the 4-(methylsulfonyl)butanol (100 mg, 0.657 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (159 mg, 0.657 mmol) was heated under reflux for 17 hours under an argon atmosphere. After cooling to room temperature, the

reaction mixture was added with the 4-(methylsulfonyl)butanol (100 mg, 0.657 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (159 mg, 0.657 mmol). The mixture was stirred under an argon atmosphere for 24 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the 80% ethyl acetate/hexane eluate was concentrated under reduced pressure, whereby the title compound (79 mg, 35%) was obtained as an amorphous substance.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.25-1.49(2H,m), 1.63-1.80(1H,m), 1.80-1.93(1H,m), 2.00-2.20(2H,m), 2.76-2.95(2H,m), 2.82(3H,s), 2.84(3H,s), 3.11(3H,s), 4.70-4.82(1H,m), 7.22(1H,d,J=7.3Hz), 7.32-7.46(3H,m), 7.49(2H,d,J=8.6Hz), 7.63(2H,d,J=8.6Hz).

IR (ATR) ν: 2931, 2873, 1621, 1581, 1506, 1475, 1448, 1394, 1278, 1222, 1182, 1137, 1083, 1012, 962, 823, 755, 707, 630, 561, 518, 460 cm^{-1}.

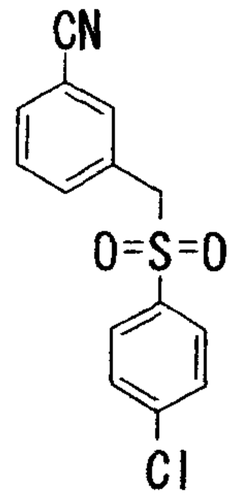
MS: 472 (M^++H).

HRMS (FAB) for $C_{21}H_{27}O_5NClS_2$ (M^++H)

Calculated: 472.1019

Found: 472.1023

Example 90: 3-(4-Chlorophenylsulfonylmethyl)benzonitrile



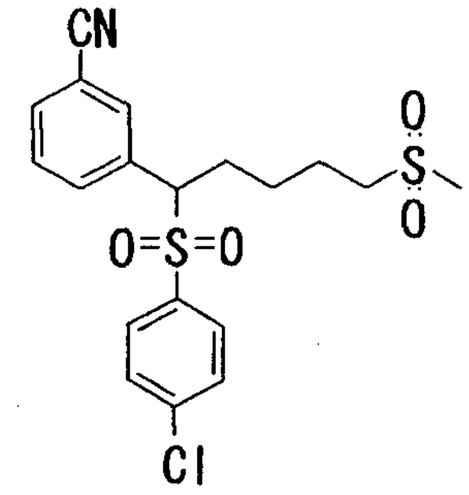
A dimethoxyethane (15 ml) suspension of sodium 4-chlorobenzenesulfinate (270 mg, 1.36 mmol) and 3-bromomethylbenzonitrile (222 mg, 1.13 mmol) was stirred at 70°C for 3 days. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with water and brine and then, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate (=3:1) eluate was concentrated under reduced pressure, whereby the title compound (318 mg, 96%) was obtained as a white solid.

IR (ATR) ν: 3087, 2985, 2229, 1581, 1581, 1475, 1432, 1394, 1317, 1282, 1265, 1228, 1145, 1081, 1012, 929, 904, 885, 844, 811, 798, 763, 723, 686, 651, 626, 578, 545, 522, 484, 462 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 4.32(2H,s), 7.38-7.52(5H,m), 7.60(2H,d,J=8.8Hz), 7.66(1H,d,J=7.6Hz).

MS (m/z): 292 (M^++H).

Example 91: 3-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzonitrile



A toluene (10 ml) solution of 3-(4-chlorophenylsulfonylmethyl)benzonitrile (60 mg, 0.204 mmol), the 4-(methylsulfonyl)-1-butanol (62 mg, 0.409 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (99 mg, 0.409 mmol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was added with the 4-(methylsulfonyl)-1-butanol (62 mg, 0.504 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (99 mg, 0.504 mmol), followed by heating under reflux for 23 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:2) eluate was concentrated under reduced pressure, whereby the title compound (69 mg, 79%) was obtained as an

amorphous substance.

IR (ATR) ν: 2931, 2229, 1579, 1475, 1432, 1394, 1278, 1137, 1083, 1051, 1012, 964, 914, 813, 752, 688, 649, 613, 549, 516, 466 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.50(2H,m), 1.79-1.97(2H,m), 2.10-2.22(1H,m), 2.40-2.51(1H,m), 2.89(3H,s), 2.90-3.00(2H,m), 4.06(1H,dd,J=11.1,4.0Hz), 7.35-7.50(7H,m), 7.64(1H,d,J=7.3Hz).

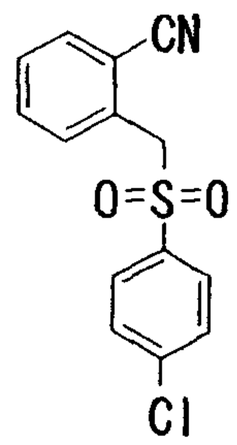
MS (m/z): 426 (M^++H).

Elemental Analysis for $C_{19}H_{20}ClNO_4S_2 \cdot 0.25H_2O$

Calculated: C 53.02%; H 4.80%; Cl 8.24%; N 3.25%; S 14.90%.

Found: C 52.94%; H 4.85%; Cl 8.54%; N 3.25%; S 14.93%.

Example 92: 2-(4-Chlorophenylsulfonylmethyl)benzonitrile



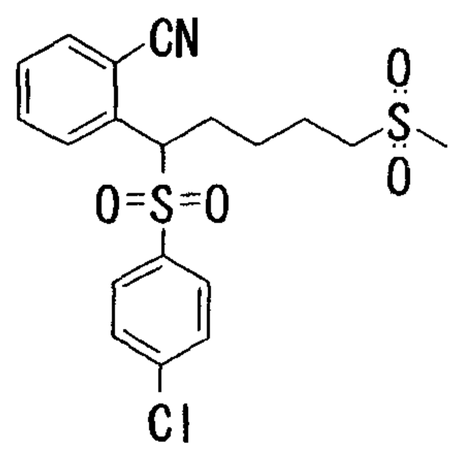
A dimethoxyethane (5 ml) suspension of sodium 4-chlorobenzenesulfinate (218 mg, 1.10 mmol) and 2-bromomethylbenzonitrile (215 mg, 1.10 mmol) was stirred at 70°C for 17 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. The residue thus obtained was subjected to chromatography on a short silica gel column and the

fraction obtained from the ether eluate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate (=3:1) eluate was concentrated under reduced pressure to give a white solid. The resulting white solid was washed with ether, and collected by filtration, whereby the title compound (226 mg, 70%) was obtained as a white powder.

IR (ATR) ν: 3079, 2979, 2227, 1573, 1488, 1473, 1450, 1425, 1392, 1321, 1299, 1280, 1253, 1209, 1174, 1143, 1081, 1010, 946, 904, 879, 829, 781, 759, 711, 682, 632, 593, 532, 480, 451 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.58(2H,s), 7.43-7.51(3H,m), 7.56-7.68(5H,m).

Example 93: 2-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]benzonitrile



A toluene (5 ml) solution of 2-(4-chlorophenylsulfonylmethyl)benzonitrile (96 mg, 0.329 mmol), the 4-(methylsulfonyl)-1-butanol (100 mg, 0.657 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (159 mg, 0.657mol) was heated under reflux

for 22 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the 60% ethyl acetate/hexane eluate was concentrated under reduced pressure, whereby the title compound (139 mg, 99%) was obtained as an amorphous substance.

IR (ATR) ν: 3089, 2931, 2225, 1575, 1475, 1448, 1394, 1315, 1295, 1278, 1214, 1176, 1139, 1124, 1083, 1012, 962, 908, 827, 794, 754, 711, 628, 553, 516, 470 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.54(2H,m), 1.81-1.98(2H,m), 2.20-2.31(1H,m), 2.47-2.59(1H,m), 2.88(3H,s), 2.90-3.00(2H,m), 4.63(1H,dd,J=11.0,4.2Hz), 7.38-7.60(6H,m), 7.67-7.73(1H,m), 7.79(1H,d,J=8.1Hz).

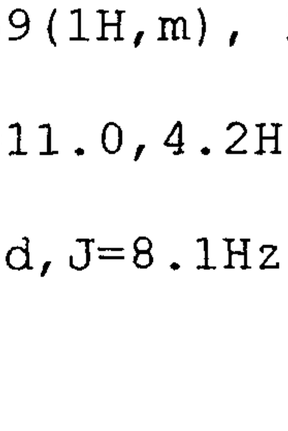
MS (m/z): 426 (M^++H).

HRMS (FAB) for $C_{19}H_{21}O_4NClS_2$ (M^++H)

Calculated: 426.0601

Found: 426.0636

Example 94: <u>1-Chloro-4-(cyclohexylmethylsulfonyl)benzene</u>



To an acetonitrile (10 ml) solution of 4-

chlorobenzenethiol (230 mg, 1.59 mmol and cyclohexylmethyl bromide (222 µl, 1.59 mmol) was added potassium carbonate (329 mg, 2.38 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. To the residue was added hexane and the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue thus obtained was dissolved in methylene chloride (20 ml), followed by the addition of 3-chloroperbenzoic acid (576 mg, 3.34 mmol). The mixture was stirred at room temperature for 17.5 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added and the mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in methylene chloride. To the resulting solution was added a 1N aqueous solution of sodium hydroxide to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the hexane: ethyl acetate (=15:1) eluate was concentrated under reduced pressure, whereby the title

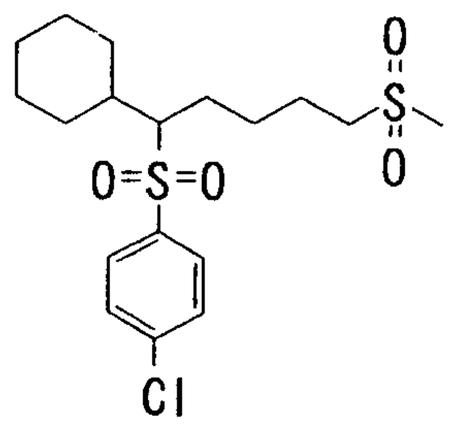
compound (301 mg, 69%) was obtained as a white solid.

IR (ATR) ν: 2921, 2850, 1583, 1475, 1446, 1394, 1305, 1274, 1172, 1143, 1083, 1014, 964, 892, 846, 831, 782, 761, 744, 703, 669, 632, 559, 528, 478, 426 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.00-1.35(5H,m), 1.60-1.76(3H,m), 1.80-2.08(3H,m), 2.97(2H,d,J=6.1Hz), 7.54(2H,d,J=8.6Hz), 7.85(2H,d,J=8.6Hz).

MS (m/z): 273 (M^++H).

Example 95: 1-Chloro-4-[1-cyclohexyl-5-(methylsulfonyl)pentylsulfonyl]benzene



At -78°C, butyl lithium (a 1.57M hexane solution; 0.60 ml, 0.937 mmol) was added dropwise to a dimethoxyethane (3 ml) solution of 1-chloro-4-(cyclohexylmethylsulfonyl)benzene (213 mg, 0.781 mmol). After stirring at -78°C for 40 minutes, a dimethoxyethane (5 ml) solution of the 1-iodo-4-(methylsulfonyl) butane (246 mg, 0.937 mmol) obtained in Referential Example 7 was added dropwise. The temperature of the reaction mixture was raised gradually to room temperature, at which stirring was conducted for 3 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was

washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure. The residue was purified by high performance liquid chromatography (using a mixed solvent of water/acetonitrile/formic acid) to give the title compound (54 mg, 17%) as a white solid. The resulting solid was washed with hexane and collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 104-106°C.

IR (ATR) ν: 2925, 2854, 1583, 1475, 1444, 1423, 1392, 1309, 1288, 1268, 1209, 1176, 1145, 1133, 1128, 1083, 1012, 960, 892, 825, 763, 727, 636, 609, 561, 528, 495, 478, 453, 430 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.02-1.32(5H,m), 1.44-2.00(12H,m), 2.76-2.83(1H,m), 2.89(3H,s), 2.97(2H,t,J=7.0Hz), 7.56(2H,d,J=8.3Hz), 7.82(2H,d,J=8.3Hz).

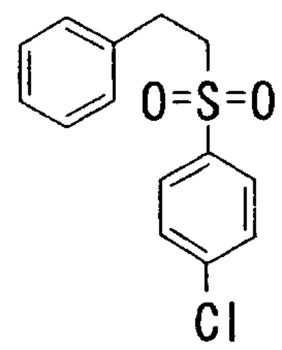
MS (m/z): 407 (M^++H).

Elemental Analysis for $C_{18}H_{27}ClO_4S_2$

Calculated: C 53.12%; H 6.69%; Cl 8.71%; S 15.76%.

Found: C 53.11%; H 6.49%; Cl 8.83%; S 15.73%.

Example 96: 1-Chloro-4-(2-phenylethylsulfonyl)benzene



To an acetonitrile (10 ml) solution of 4-chlorobenzenethiol (347 mg, 2.40 mmol) and (2-bromoethyl)benzene (329 µl, 2.40 mmol) was added potassium carbonate (498 mg, 3.60 mmol). The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure. To the residue was added hexane and the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure. The residue thus obtained was dissolved in methylene chloride (20 ml). To the resulting solution was added 3-chloroperbenzoic acid (870 mg, 5.04 mmol) and the mixture was stirred at room temperature for 19 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added. The mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in methylene chloride, followed by the addition of a 1N aqueous solution of sodium hydroxide to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. After filtration,

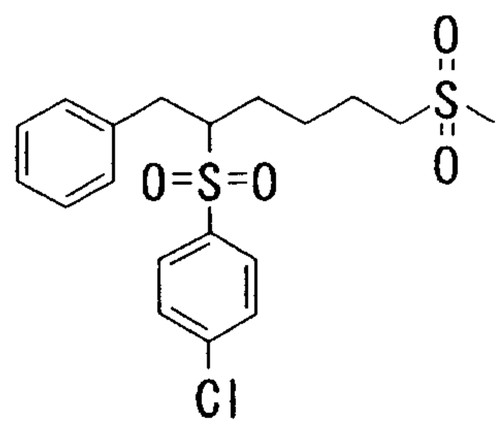
the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate (=10:1) eluate was concentrated under reduced pressure, whereby the title compound (599 mg, 89%) was obtained as a white solid.

IR (ATR) ν: 3023, 2923, 1600, 1581, 1496, 1473, 1454, 1394, 1299, 1276, 1240, 1145, 1083, 1012, 971, 908, 823, 777, 755, 732, 694, 636, 593, 570, 526, 455 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.98-3.10(2H,m), 3.29-3.42(2H,m), 7.02-7.32(5H,m), 7.55(2H,d,J=8.6Hz), 7.86(2H,d,J=8.5Hz).

MS (m/z): 281 (M^++H).

Example 97: 4-[1-Benzyl-5-(methylsulfonyl)pentylsulfonyl]-1-chlorobenzene



At -78°C, butyl lithium (a 1.57M hexane solution; 0.57 ml, 0.902 mmol) was added dropwise to a dimethoxyethane (3 ml) solution of 1-chloro-4-(2-phenylethylsulfonyl)benzene (211 mg, 0.752 mmol). After stirring at -78°C for 1 hour, a dimethoxyethane (6 ml) solution of the 1-iodo-4-(methylsulfonyl)butane (236 mg, 0.902 mmol) obtained in Referential Example 7 was added dropwise. The temperature

of the reaction mixture was gradually elevated to room temperature, at which stirring was conducted for 3 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure. The residue was purified by high performance liquid chromatography (using a mixed solvent of water/acetonitrile/formic acid) to give the title compound (72 mg, 23%) as a white solid. The resulting solid was washed with hexane and collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 68-70°C.

IR (ATR) ν: 3029, 2937, 2867, 1581, 1496, 1421, 1394, 1303, 1280, 1253, 1187, 1133, 1083, 1041, 1012, 964, 848, 825, 759, 690, 649, 588, 553, 522, 493, 455 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 1.40-1.77(5H,m), 1.82-1.96(1H,m), 2.60-2.70(1H,m), 2.75-2.91(2H,m), 2.83(3H,s), 3.18-3.29(2H,m), 7.04(2H,d,J=8.3Hz), 7.19-7.31(3H,m), 7.56(2H,d,J=8.6Hz), 7.84(2H,d,J=8.6Hz).

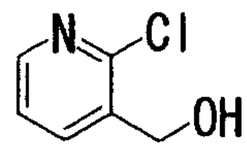
MS (m/z): 415 (M^++H).

Elemental Analysis for $C_{19}H_{23}ClO_4S_2$

Calculated: C 54.99%; H 5.59%; Cl 8.54%; S 15.45%.

Found: C 55.10%; H 5.62%; Cl 8.50%; S 15.56%.

Referential Example 10: (2-Chloropyridin-3-yl)methanol



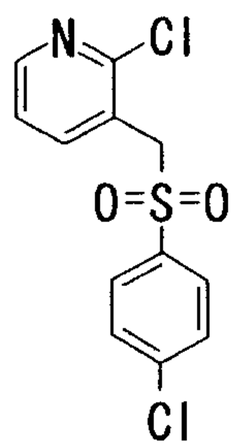
At -78°C, diisobutylaluminum hydride (a 1.0M toluene solution; 4.68 ml) was added dropwise to a methylene chloride (10 ml) solution of ethyl 2-chloronicotinate (347 mg, 1.87 mmol). Thirty minutes later, the reaction mixture was ice cooled, followed by stirring for 15 minutes. After the completion of the reaction was confirmed, brine was added to the reaction mixture and the temperature of the resulting mixture was allowed to rise back to room temperature. The reaction mixture was filtered through Celite. The filtrate was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure, whereby the title compound (211 mg, 79%) was obtained as a white solid.

IR (ATR) ν: 3245, 2827, 1587, 1571, 1452, 1407, 1324, 1251, 1193, 1118, 1087, 1041, 796, 732, 713, 655, 593, 511, 466, 414 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.21(1H,t,J=5.6Hz), 4.80(2H,d,J=5.1Hz), 7.25-7.36(1H,m), 7.85-7.98(1H,m), 8.32(1H,dd,J=4.6,1.5Hz).

MS (m/z): 144 (M^++H).

Example 98: 2-Chloro-3-(4-chlorophenylsulfonylmethyl)pyridine



A chloroform (10 ml) solution of (2-chloropyridin-3-yl)methanol (204 mg, 1.42 mmol) and thionyl chloride (0.31 ml, 4.26 mmol) was stirred at 50°C for 8.5 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in butanol (15 ml), followed by the addition of sodium 4-chlorobenzenesulfinate (423 mg, 2.13 mmol) and potassium acetate (418 mg, 4.26 mmol). The mixture was stirred at 70 to 80°C for 15 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, and the mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The

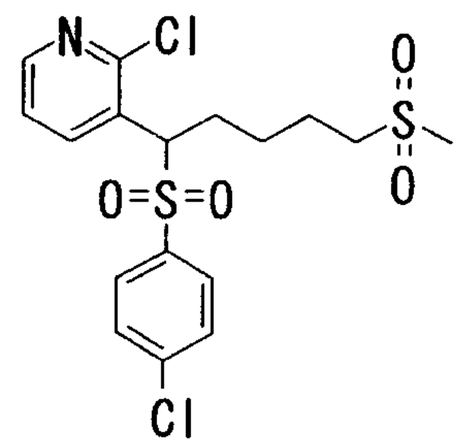
residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=2:1) eluate was concentrated under reduced pressure, whereby the title compound (252 mg, 59%) was obtained as a white solid.

IR (ATR) ν: 3093, 2992, 2931, 1579, 1562, 1473, 1450, 1407, 1321, 1278, 1249, 1195, 1153, 1133, 1116, 1083, 1060, 1010, 962, 887, 840, 813, 759, 719, 686, 636, 566, 541, 501, 466, 441 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.54(2H,s), 7.33(1H,dd,J=8.8,4.8Hz), 7.46(2H,d,J=8.6Hz), 7.58(2H,d,J=8.3Hz), 7.92(1H,dd,J=7.7,1.8Hz), 8.39(1H,dd,J=4.8,1.8Hz).

MS (m/z): 302 (M^++H).

Example 99: 2-Chloro-3-[1-(4-chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]pyridine



A toluene (10 ml) solution of 2-chloro-3-(4-chlorophenylsulfonylmethyl)pyridine (56 mg, 0.184 mmol), the 4-(methylsulfonyl)-1-butanol (56 mg, 0.368 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (89 mg, 0.368 mmol) was heated under

reflux for 19 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was added with 4-(methylsulfonyl)-1-butanol (56 mg, 0.368 mmol) and cyanomethylenetri-n-butylphosphorane (89 mg, 0.368 mmol), followed by heating under reflux for 5 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:2) eluate was concentrated under reduced pressure, whereby the title compound (76 mg, 95%) was obtained as an amorphous substance.

IR (ATR) ν: 3085, 2931, 1579, 1562, 1475, 1407, 1278, 1184, 1139, 1083, 1012, 962, 908, 821, 752, 732, 690, 626, 574, 520, 466 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.32-1.55(2H,m), 1.80-1.99(2H,m), 2.10-2.25(1H,m), 2.40-2.63(1H,m), 2.88(3H,s), 2.96(2H,t,J=7.8Hz), 4.79(1H,dd,J=11.0,4.2Hz), 7.32-7.42(3H,m), 7.48(2H,d,J=8.3Hz), 8.04(1H,dd,J=7.8,1.7Hz), 8.36(1H,dd,J=4.8,1.8Hz).

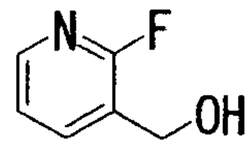
MS (m/z): 436 (M^++H).

HRMS (FAB) for $C_{17}H_{20}O_4NCl_2S_2$ (M^++H)

Calculated: 436.0211

Found: 436.0195

Referential Example 11: (2-Fluoropyridin-3-yl)methanol



Under ice cooling, trimethylsilyldiazomethane (0.72 ml) was added to a solution of 2-fluoronicotinic acid (210 mg, 1.49 mmol) in tetrahydrofuran (15 ml) and methanol (1 ml), and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=4:1) eluate was concentrated under reduced pressure.

At -78°C, diisobutylaluminum hydride (a 1.0M toluene solution; 1.60 ml) was added dropwise to a methylene chloride (10 ml) solution of the residue (95 mg, 0.612 mmol). Fifteen minutes later, the reaction mixture was ice cooled and stirred for 15 minutes. After completion of the reaction was confirmed, brine was added and the temperature of the reaction mixture was allowed to rise back gradually to room temperature. The reaction mixture was filtered through Celite. The filtrate was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=2:1) eluate was concentrated under reduced pressure, whereby the

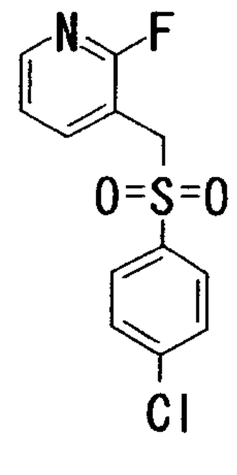
title compound (55 mg, 71%) was obtained as a white solid.

IR (ATR) ν: 3338, 2873, 1650, 1608, 1430, 1365, 1241, 1176, 1108, 1045, 1020, 858, 800, 775, 744, 619, 572, 539, 520 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.78(2H,s), 7.18-7.25(1H,m), 7.85-7.97(1H,m), 8.14(1H,d,J=4.9Hz).

MS (m/z): 128 (M^++H).

Example 100: 3-(4-Chlorophenylsulfonylmethyl)-2-fluoropyridine



A chloroform (10 ml) solution of (2-fluoropyridin-3-yl)methanol (49 mg, 0.385 mmol) and thionyl chloride (0.14 ml, 1.93 mmol) was stirred at 50°C for 3.5 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was dissolved in butanol (5 ml), followed by the addition of sodium 4-chlorobenzenesulfinate (92 mg, 0.462 mmol) and potassium acetate (76 mg, 0.770 mmol). The mixture was stirred at 70 to 80°C for 12 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, and the mixture was washed

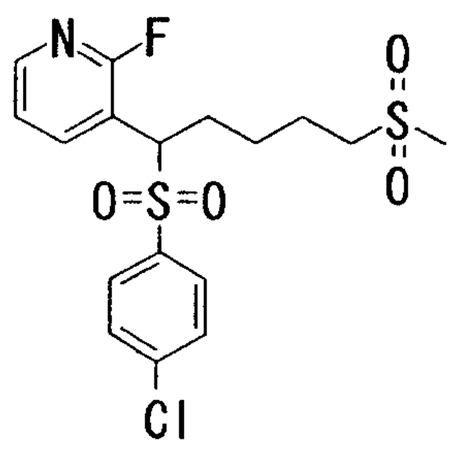
successively with a saturated aqueous solution of sodium bicarbonate and brine, and then, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=2:1) eluate was concentrated under reduced pressure, whereby the title compound (59 mg, 54%) was obtained as a white solid.

IR (ATR) ν: 3097, 2989, 2933, 1643, 1606, 1573, 1469, 1434, 1409, 1392, 1321, 1276, 1240, 1184, 1170, 1149, 1083, 1010, 956, 902, 842, 813, 779, 763, 725, 696, 640, 582, 541, 522, 480, 445 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.38(2H,s), 7.21-7.30(1H,m), 7.47(2H,d,J=8.8Hz), 7.61(2H,d,J=8.8Hz), 7.87-7.94(1H,m), 8.19-8.25(1H,m).

MS (m/z): 286 (M^++H).

Example 101: 3-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]-2-fluoropyridine



A toluene (10 ml) solution of 3-(4-chlorophenylsulfonylmethyl)-2-fluoropyridine (53 mg, 0.185 mmol), the 4-(methylsulfonyl)-1-butanol (56 mg, 0.370 mmol)

obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (89 mg, 0.370 mmol) was heated under reflux for 22 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=1:2) eluate was concentrated under reduced pressure, whereby the title compound (42 mg, 54%) was obtained as an amorphous substance.

IR (ATR) ν: 3089, 2950, 2865, 1604, 1573, 1467, 1434, 1394, 1313, 1290, 1270, 1249, 1199, 1147, 1126, 1083, 1012, 960, 906, 854, 815, 757, 738, 703, 628, 576, 536, 464, 437 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.38-1.55(2H,m), 1.85-1.99(2H,m), 2.14-2.28(1H,m), 2.45-2.60(1H,m), 2.88(3H,s), 2.96(2H,t,J=7.8Hz), 4.46(1H,dd,J=11.2,4.2Hz), 7.25-7.32(1H,m), 7.41(2H,d,J=8.6Hz), 7.50(2H,d,J=8.3Hz), 7.98-8.04(1H,m), 8.20(1H,d,J=4.9Hz).

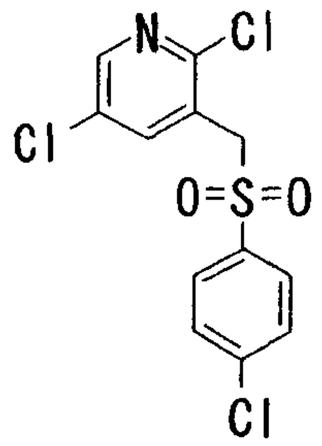
MS (m/z): 420 (M^++H).

HRMS (FAB) for $C_{17}H_{20}O_4NClFS_2$ (M^++H)

Calculated: 420.0506

Found: 420.0509

Example 102: 2,5-Dichloro-3-(4-chlorophenylsulfonylmethyl) pyridine



At -78°C, diisobutylaluminum hydride (a 1M hexane solution; 1.92 ml) was added dropwise to a methylene chloride (10 ml) solution of methyl 2,5-dichloronicotinate (188 mg, 0.912 mmol). The resulting mixture was stirred at 0°C for 30 minutes. The reaction mixture was added with brine, and the mixture was filtered through Celite. The filtrate was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=3:1) eluate was concentrated under reduced pressure. To a chloroform (10 ml) solution of the residue (128 mg) was added thionyl chloride (0.26 ml, 3.60 mmol), followed by stirring at 50°C for 6.5 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in butanol(10 ml). To the resulting solution were added sodium 4-chlorobenzenesulfinate (171 mg, 0.863 mmol) and potassium acetate (212 mg, 2.16 mmol) and the mixture was stirred at 70°C for 19 hours. After cooling to room temperature, the reaction mixture was concentrated

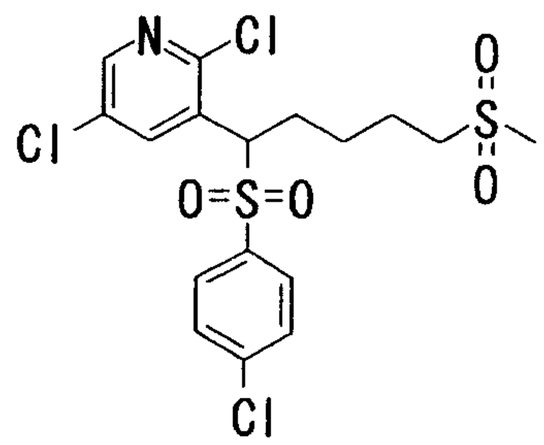
under reduced pressure. Ethyl acetate was added to the residue, followed by successive washing with water and brine and drying over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting solid was washed with hexane-diisopropyl ether, and collected by filtration, whereby the title compound (108 mg, 35%) was obtained as a white powder.

IR (ATR) ν: 3091, 3064, 2998, 2933, 1581, 1550, 1473, 1419, 1392, 1317, 1280, 1255, 1234, 1170, 1135, 1085, 1068, 1010, 910, 833, 821, 767, 727, 709, 646, 582, 539, 507, 464, 430 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.49(2H,s), 7.49(2H,d,J=8.6Hz), 7.62(2H,d,J=8.8Hz), 7.90(1H,d,J=2.5Hz), 8.35(1H,d,J=2.5Hz).

MS (m/z): 336 (M^++H).

Example 103: 2,5-Dichloro-3-[1-(4-chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]pyridine



A toluene (10 ml) solution of 2,5-dichloro-3-(4-chlorophenylsulfonylmethyl)pyridine (70 mg, 0.208 mmol), the 4-(methylsulfonyl)-1-butanol (95 mg, 0.624 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (151 mg, 0.624 mol) was heated under

reflux for 3 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure, whereby the title compound (74 mg, 76%) was obtained as an amorphous substance.

IR (ATR) ν: 3091, 3060, 2931, 1581, 1546, 1475, 1413, 1313, 1278, 1209, 1124, 1083, 1049, 1012, 964, 906, 871, 831, 754, 705, 628, 588, 532, 468 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.38-1.52(2H,m), 1.83-1.98(2H,m), 2.08-2.20(1H,m), 2.49-2.60(1H,m), 2.88(3H,s), 2.97(2H,t,J=7.8Hz), 4.72(1H,dd,J=10.9,4.0Hz), 7.43(2H, d.J=8.6Hz), 7.53(2H,d,J=8.6Hz), 8.00(1H,d,J=2.5Hz), 8.31(1H,d,J=2.5Hz).

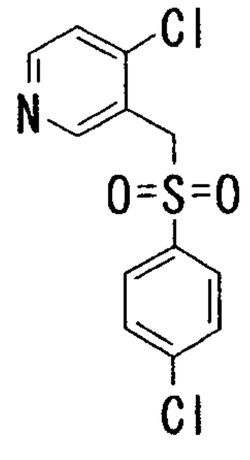
MS (m/z): 470 (M^++H).

Elemental Analysis for $C_{17}H_{18}Cl_3NO_4S_2 \cdot 0.25H_2O$

Calculated: C 42.96%; H 3.92%; Cl 22.38%; N 2.95%; S 13.49%.

Found: C 43.02%; H 3.81%; Cl 22.54%; N 3.01%; S 13.50%.

Example 104: 4-Chloro-3-(4-chlorophenylsulfonylmethyl) pyridine



A carbon tetrachloride (15 ml) suspension of 4-chloro-3-methylpyridine hydrochloride (402 mg, 2.45 mmol), *N*-chlorosuccinic acid imide (327 mg, 2.45 mmol) and 2,2'-azobis(2-methylpropionitrile) (30 mg, 0.183 mmol) was heated under reflux for 13 hours under a nitrogen atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in butanol (10 ml), followed by the addition of sodium 4-chlorophenylsulfinate (487 mg, 2.45 mmol) and potassium acetate (481 mg, 4.90 mmol). The mixture was stirred at 70°C for 24 hours. The reaction mixture was cooled to room temperature, followed by concentration under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and brine and then, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=2:1) eluate was concentrated under reduced pressure, whereby the title compound (130 mg, 18%)

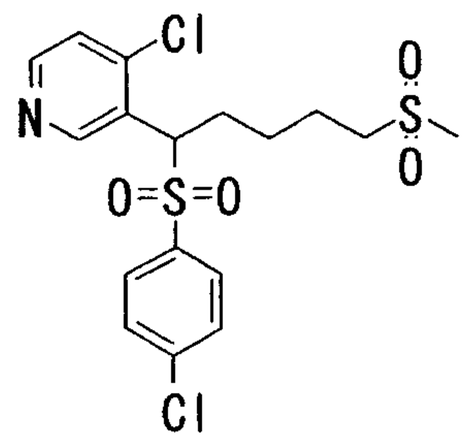
was obtained as a white solid.

IR (ATR) ν: 3060, 2917, 1708, 1573, 1556, 1475, 1413, 1403, 1311, 1280, 1232, 1189, 1155, 1120, 1079, 1012, 933, 890, 854, 833, 817, 777, 744, 721, 694, 632, 574, 557, 514, 460 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.56(2H,s), 7.28(1H,d,J=5.4Hz), 7.48(2H,d,J=8.3Hz), 7.63(2H,d,J=8.5Hz), 8.49(1H,d,J=5.4Hz), 8.54(1H,s).

MS (m/z): 302 (M^++H).

Example 105: 4-Chloro-3-[1-[(4-chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]pyridine



A toluene (10 ml) solution of 4-chloro-3-(4-chlorophenylsulfonylmethyl)pyridine (80 mg, 0.265 mmol), the 4-(methylsulfonyl)-1-butanol (81 mg, 0.529 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (128 mg, 0.529 mol) was heated under reflux under an argon atmosphere for 3 days. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:5) eluate was

concentrated under reduced pressure to give the title compound (74 mg, 64%) as a white solid. The resulting solid was washed with ether and then, collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 156-157°C.

IR (ATR) ν: 3087, 3064, 3018, 2933, 1571, 1473, 1409, 1311, 1270, 1207, 1149, 1076, 1014, 968, 906, 831, 794, 752, 700, 617, 576, 536, 497, 466 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.60(2H,m), 1.80-1.99(2H,m), 2.20-2.33(1H,m), 2.51-2.65(1H,m), 2.88(3H,s), 2.90-3.00(2H,m), 4.80(1H,dd,J=10.9,3.8Hz), 7.20(1H,d,J=5.4Hz), 7.40(2H,d,J=8.5Hz), 7.52(2H,d,J=8.6Hz), 8.46(1H,d,J=5.4Hz), 8.80(1H,s).

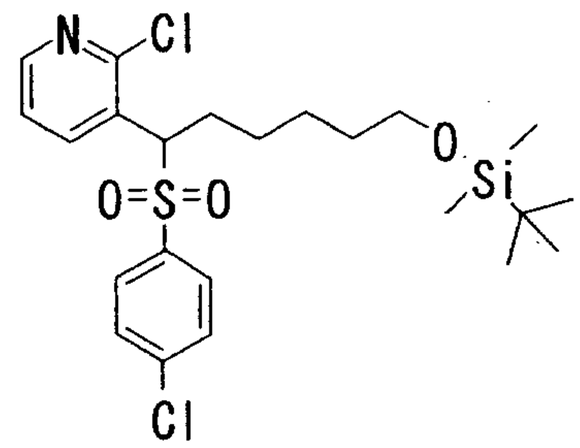
MS (m/z): 436 (M^++H).

Elemental Analysis for $C_{17}H_{19}Cl_2NO_4S_2$

Calculated: C 46.79%; H 4.39%; Cl 16.25%; N 3.21%; S 14.70%.

Found: C 46.88%; H 4.40%; Cl 16.14%; N 3.30%; S 14.52%.

Example 106: 3-[6-(tert-Butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]hexyl]-2-chloropyridine



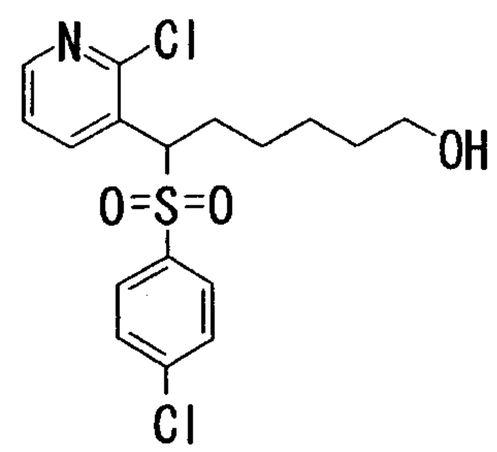
A toluene (5 ml) solution of the 2-chloro-3-(4-chlorophenylsulfonylmethyl)pyridine (200 mg, 0.662 mmol) obtained in Example 98, 5-(tert-butyldimethylsilyloxy)pentanol (288 mg, 1.32 mmol) and cyanomethylenetri-n-butylphosphorane (318 mg, 1.32 mmol) was heated under reflux for 22 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the 15% ethyl acetate/hexane eluate was concentrated under reduced pressure, whereby the title compound(307 mg, 92%) was obtained as a colorless oil.

IR (ATR) ν: 2929, 2856, 1581, 1562, 1473, 1409, 1394, 1359, 1321, 1278, 1253, 1184, 1149, 1083, 1058, 1012, 985, 921, 833, 775, 752, 734, 690, 626, 570, 534, 466 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 0.01(6H,s), 0.86(9H,s), 1.12-1.50(6H,m), 2.07-2.20(1H,m), 2.45-2.57(1H,m), 3.53(2H,t,J=6.1Hz), 4.78(1H,dd,J=11.4,3.8Hz), 7.31-7.40(3H,m), 8.79(2H,d,J=7.5Hz), 8.03(1H,dd,J=7.8,2.0Hz), 8.34(1H,dd,J=4.6,2.0Hz).

MS (m/z): 502 (M^++H).

Example 107: 6-(4-Chlorophenylsulfonyl)-6-(2-chloropyridin-3-yl)-1-hexanol



Under ice cooling, tetrabutylammonium fluoride (a 1 mol/l tetrahydrofuran solution; 0.70 ml) was added to a tetrahydrofuran (10 ml) solution of 3-[6-(tert-butyldimethylsilyloxy)-1-[(4-chlorophenyl)sulfonyl]hexyl]-2-chloropyridine (294 mg, 0.585 mmol). The resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, and the mixture was washed successively with water and brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure, whereby the title compound (212 mg, 93%) was obtained as a colorless oil.

IR (ATR) ν: 3400, 2933, 2859, 1579, 1562, 1475, 1407, 1394, 1315, 1278, 1184, 1145, 1083, 1058, 1012, 821, 752, 734,

690, 626, 605, 570, 534, 466, 412 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 1.15-1.65(8H,m), 2.07-2.20(1H,m), 2.47-2.58(1H,m), 3.59(2H,t,J=6.4Hz), 4.79(1H,dd,J=11.4,3.8Hz), 7.30-7.42(3H,m), 7.48(2H,d,J=8.8Hz), 8.03(1H,dd,J=7.8,2.0Hz), 8.34(1H,dd,J=4.1,1.7Hz).

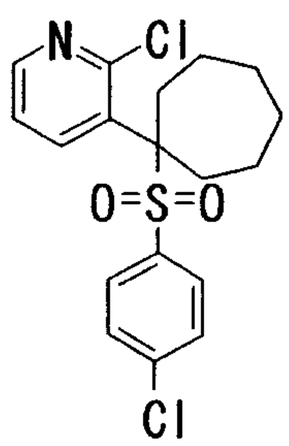
MS (m/z): 388 (M^++H).

HRMS (FAB) for $C_{17}H_{20}O_3NCl_2S$ (M^++H)

Calculated: 388.0541

Found: 388.0561

Example 108: 2-Chloro-3-[1-(4-chlorophenylsulfonyl) cycloheptyl]pyridine



At -78°C, butyl lithium (a 1.57M hexane solution; 0.62 ml, 0.966 mmol) was added dropwise to a dimethoxyethane (5 ml) solution of the 2-chloro-3-(4-chlorophenylsulfonylmethyl)pyridine (146 mg, 0.483 mmol) obtained in Example 98. At -78°C, the resulting mixture was stirred for 20 minutes, followed by the addition of 1,6-diiodohexane (0.095 ml, 0.580 mmol). The temperature of the reaction mixture was gradually raised to room temperature, at which stirring was performed for 4 hours.

Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the 15% ethyl acetate/hexane eluate was concentrated under reduced pressure. The residue thus obtained was purified by high performance liquid chromatography (using a mixed solvent of water/acetonitrile/formic acid) to yield the title compound (60 mg, 32%) as a white solid. The resulting solid was washed with hexane-ether and then collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 168-169°C.

IR (ATR) ν: 2929, 2861, 1573, 1558, 1473, 1454, 1394, 1303, 1276, 1139, 1083, 1066, 1008, 840, 800, 748, 711, 646, 613, 574, 522, 470, 412 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.30-1.50(4H,m), 1.50-1.66(2H,m), 1.85-1.98(2H,m), 2.33-2.48(2H,m), 2.94-3.10(2H,m), 7.28-7.37(3H,m), 7.40(2H,d,J=8.8Hz), 7.93(1H,dd,J=8.1,1.7Hz), 8.38(1H,dd,J=4.5,1.8Hz).

MS (m/z): 384 (M^++H).

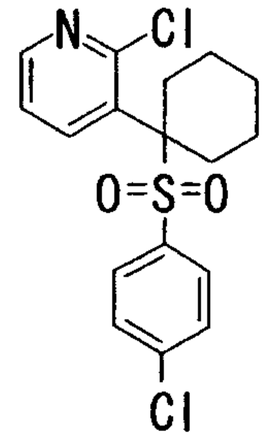
Elemental Analysis for $C_{18}H_{19}Cl_2NO_2S$

Calculated: C 56.25%; H 4.98%; Cl 18.45%; N 3.64%; S

8.34%.

Found: C 56.20%; H 4.85%; Cl 18.50%; N 3.73%; S 8.46%.

Example 109: 2-Chloro-3-[1-(4-chlorophenylsulfonyl) cyclohexyl]pyridine



At -78°C, butyl lithium (a 1.57M hexane solution; 0.66 ml, 1.03 mmol) was added dropwise to a dimethoxyethane (5 ml) solution of the 2-chloro-3-(4-chlorophenylsulfonylmethyl)pyridine (156 mg, 0.516 mmol) obtained in Example 98. At -78°C, the resulting mixture was stirred for 20 minutes, followed by the addition of 1,5-diiodopentane (0.092 ml, 0.619 mmol). The temperature of the reaction mixture was gradually elevated to room temperature, at which stirring was performed for 15 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the 15% ethyl acetate/hexane eluate was concentrated under reduced pressure. The residue thus

obtained was purified by high performance liquid chromatography (using a mixed solvent of water/acetonitrile/formic acid) to give the title compound (72 mg, 38%) as a white solid. The resulting solid was washed with hexane-ether and then collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 129-131°C.

IR (ATR) ν: 2929, 2861, 1575, 1558, 1475, 1446, 1392, 1303, 1278, 1143, 1130, 1083, 1054, 1010, 910, 875, 833, 809, 754, 742, 742, 732, 703, 646, 617, 580, 495, 458 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.05-1.30(2H,m), 1.33-1.50(1H,m), 1.52-1.70(1H,m), 1.75-1.90(2H,m), 2.02-2.30(2H,m), 2.65-3.60(2H,m), 7.29-7.39(3H,m), 7.41(2H,d,J=8.8Hz), 8.05(1H,dd,J=8.1,1.7Hz), 8.39(1H,dd,J=4.5,1.8Hz).

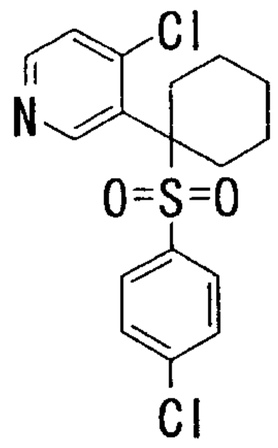
MS (m/z): 370 (M^++H).

Elemental Analysis for $C_{17}H_{17}Cl_2NO_2S$

Calculated: C 55.14%; H 4.63%; Cl 19.15%; N 3.78%; S 8.66%.

Found: C 55.06%; H 4.55%; Cl 19.15%; N 3.87%; S 8.76%.

Example 110: 4-Chloro-3-[1-(4-chlorophenylsulfonyl) cyclohexyl]pyridine



At -78°C, butyl lithium (a 1.57M hexane solution; 0.58 ml, 0.913 mmol) was added dropwise to a dimethoxyethane (5 ml) solution of the 4-chloro-3-(4-chlorophenylsulfonylmethyl)pyridine (138 mg, 0.457 mmol) obtained in Example 104. At -78°C, the resulting mixture was stirred for 20 minutes and then 1,5-diiodopentane (0.068 ml, 0.457 mmol) was added thereto. The temperature of the reaction mixture was gradually raised to room temperature, at which stirring was performed for 17 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=2:1) eluate was concentrated under reduced pressure. The residue thus obtained was purified by high performance liquid chromatography (using a mixed solvent of water/acetonitrile/formic acid) to give the title compound (30 mg, 18%) as a white solid. The resulting solid was

washed with ether and then collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 145-147°C.

IR (ATR) ν: 2929, 2863, 1579, 1469, 1452, 1392, 1346, 1305, 1280, 1270, 1211, 1143, 1081, 1012, 975, 937, 910, 871, 823, 794, 754, 725, 680, 617, 582, 563, 547, 507, 468 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.10-1.30(2H,m), 1.32-1.50(1H,m), 1.60-1.69(1H,m), 1.78-1.89(2H,m), 2.01-2.22(2H,m), 2.70-3.00(1H,m), 3.30-3.70(1H,m), 7.23(1H,d,J=5.4Hz), 7.35(2H,d,J=8.8Hz), 7.40(2H,d,J=8.8Hz), 8.41(1H,d,J=5.1Hz), 8.57(1H,s).

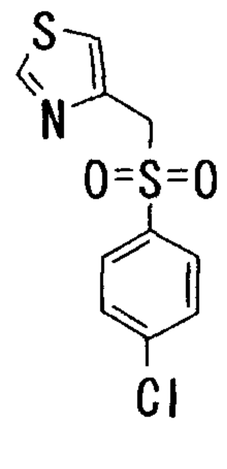
MS (m/z): 370 (M^++H).

Elemental Analysis for $C_{17}H_{17}Cl_2NO_2S$

Calculated: C 55.14%; H 4.63%; Cl 19.15%; N 3.78%; S 8.66%.

Found: C 54.99%; H 4.61%; Cl 19.06%; N 3.89%; S 8.72%.

Example 111: 4-(4-Chlorophenylsulfonylmethyl)thiazole



To 1-propanol (10 ml) were added sodium 4-chlorobenzenesulfinate (359 mg, 1.81 mmol), 4-(chloromethyl)thiazole hydrochloride (307 mg, 1.81 mmol) and potassium acetate (354 mg, 3.61 mmol) and the mixture

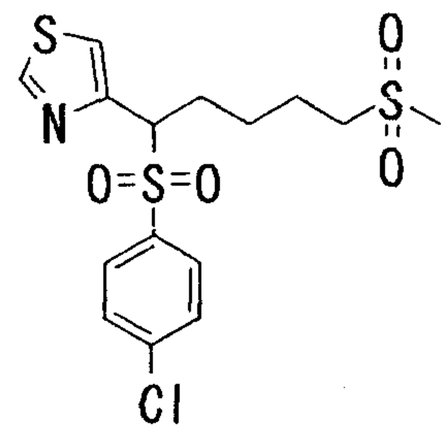
was stirred at 70°C for 21 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with water and brine and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate eluate (=3:2) was concentrated under reduced pressure. The resulting solid was washed with hexane-ether and then collected by filtration, whereby the title compound (154 mg, 31%) was obtained as a white powder.

IR (ATR) ν: 3102, 2969, 2917, 1575, 1504, 1473, 1413, 1396, 1334, 1309, 1257, 1220, 1159, 1122, 1081, 1012, 948, 898, 875, 831, 821, 784, 723, 657, 593, 561, 541, 478, 451, 418 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.64(2H,s), 7.40-7.50(3H,m), 7.62(2H,d,J=8.8Hz), 8.66(1H,s).

MS (m/z): 274 (M^++H).

Example 112: 4-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]thiazole



To butanol (5 ml) were added sodium 4-chlorobenzenesulfinate (113 mg, 0.569 mmol), 4-(chloromethyl)thiazole hydrochloride (97 mg, 0.569 mmol) and potassium acetate (112 mg, 1.14 mmol) and the resulting mixture was stirred at 70°C for 11 hours. After cooling the reaction mixture to room temperature, the solvent was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate and then, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. A toluene (10 ml) solution of the resulting residue, the 4-(methylsulfonyl)-1-butanol (130 mg, 0.853 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (206 mg, 0.853 mmol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:3) eluate was concentrated under

reduced pressure to give the title compound (111 mg, 48%) as a white solid. The white solid was washed with hexane-ether and then collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 123-125°C.

IR (ATR) ν: 3102, 2937, 1581, 1508, 1475, 1421, 1392, 1311, 1295, 1274, 1234, 1197, 1145, 1130, 1085, 1014, 964, 931, 877, 850, 821, 767, 750, 709, 665, 557, 530, 487, 455, 420 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.35-1.55(2H,m), 1.80-1.98(2H,m), 2.24-2.39(1H,m), 2.39-2.50(1H,m), 2.87(3H,s), 2.91-3.01(2H,m), 4.48(1H,dd,J=11.2,3.9Hz), 7.38-7.45(3H,m), 7.47(2H,d,J=8.6Hz), 8.65(1H,s).

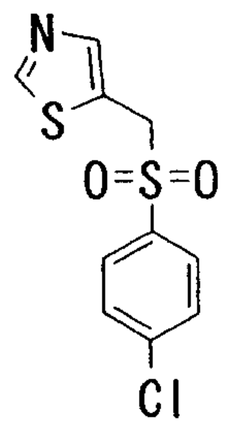
MS (m/z): 408 (M^++H).

Elemental Analysis for $C_{15}H_{18}ClNO_4S_3$

Calculated: C 44.16%; H 4.45%; Cl 8.69%; N 3.43%; S 23.58%.

Found: C 44.25%; H 4.34%; Cl 8.58%; N 3.54%; S 23.82%.

Example 113: 5-(4-Chlorophenylsulfonylmethyl)thiazole



A carbon tetrachloride (15 ml) suspension of 5-methylthiazole (380 mg, 3.83 mmol), *N*-chlorosuccinic imide

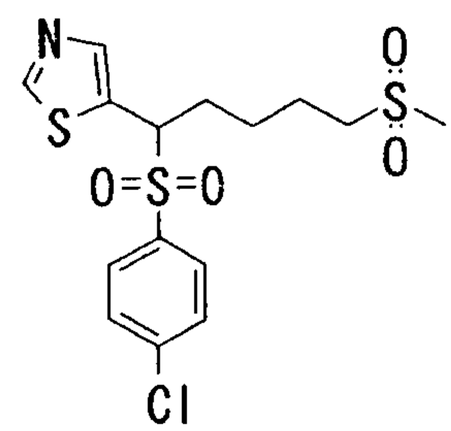
(511 mg, 3.83 mmol), 2,2'-azobis(2-methylpropionitrile) (62 mg, 0.380 mmol) and acetic acid (0.22 ml, 3.83 mmol) was heated under reflux for 18 hours under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and then, concentrated under reduced pressure. The resulting residue was dissolved in butanol (10 ml). To the resulting solution were added sodium 4-chlorophenylsulfinate (761 mg, 3.83 mmol) and potassium acetate (376 mg, 3.83 mmol), followed by stirring at 70°C for 23 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with water and brine and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure, whereby the title compound (76 mg, 7.2%) was obtained as a pale yellow solid.

IR (ATR) ν: 3085, 2975, 2915, 1671, 1577, 1521, 1473, 1392, 1313, 1253, 1193, 1143, 1081, 1012, 968, 894, 873, 836, 773, 728, 705, 651, 620, 605, 565, 543, 476, 443 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.57(2H,s), 7.49(2H,d,J=8.8Hz), 7.57(1H,s), 7.65(2H,d,J=8.6Hz), 8.81(1H,s).

MS (m/z): 274 (M^++H).

Example 114: 5-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]thiazole



A toluene (10 ml) solution of 5-(4-chlorophenylsulfonylmethyl)thiazole (51 mg, 0.186 mmol), the 4-(methylsulfonyl)-1-butanol (57 mg, 0.372 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (90 mg, 0.372mol) was heated under reflux for 21 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column. The fraction obtained from the methylene chloride:ethyl acetate (=1:2) eluate was concentrated under reduced pressure to give the title compound (53 mg, 70%) as a white solid. The resulting white solid was washed with hexane-ether, and then filtered, whereby the title compound was obtained as a white powder.

Melting point: 95-96°C.

IR (ATR) ν: 3099, 3021, 2942, 1575, 1513, 1473, 1392, 1351, 1299, 1272, 1240, 1201, 1174, 1137, 1085, 1012, 966, 914,

873, 827, 777, 746, 703, 634, 613, 566, 528, 470 cm^{-1}.

^1H-NMR (400MHz, $CDCl_3$) δ: 1.445-1.60(2H,m), 1.81-1.99(2H,m), 2.00-2.12(1H,m), 2.50-2.61(1H,m), 2.89(3H,s), 2.92-3.01(2H,m), 4.41(1H,dd,J=11.1,3.5Hz), 7.43(2H,d,J=8.5Hz), 7.47(1H,s), 7.52(2H,d,J=8.5Hz), 8.82(1H,s).

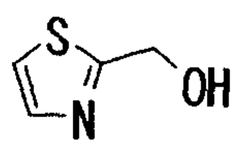
MS (m/z): 408 (M^++H).

Elemental Analysis for $C_{15}H_{18}ClNO_4S_3$

Calculated: C 44.16%; H 4.45%; Cl 8.69%; N 3.43%; S 23.58%.

Found: C 44.44%; H 4.38%; Cl 8.75%; N 3.53%; S 23.41%.

Referential Example 12: Thiazole-2-methanol



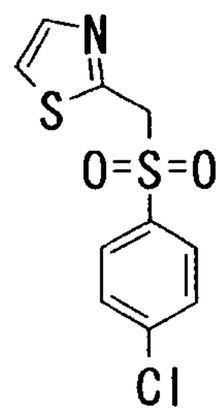
While stirring under ice cooling, sodium borohydride (242 mg, 6.40 mmol) was added to a methanol (10 ml) solution of 2-formylthiazole (483 mg, 4.27 mmol). After completion of the reaction was confirmed, water was added to the reaction mixture. The resulting mixture was concentrated under reduced pressure. Water and ethyl acetate were added to the residue to separate the organic layer. The organic layer was washed with brine and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=1:1)

eluate was concentrated under reduced pressure, whereby the title compound (324 mg, 66%) was obtained as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.30-3.70(1H,m), 5.14(2H,s), 7.32(1H,d,J=3.4Hz), 7.74(1H,d,J=3.2Hz).

MS (m/z): 116 (M^++H).

Example 115: 2-(4-Chlorophenylsulfonylmethyl)thiazole



To a chloroform (15 ml) solution of thiazole-2-methanol (171 mg, 1.49 mmol) was added thionyl chloride (0.33 ml, 4.47 mmol) and the resulting mixture was stirred at 50°C for 11 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in butanol (10 ml). To the resulting solution were added sodium 4-chlorobenzenesulfinate (296 mg, 1.49 mmol) and potassium acetate (292 mg, 2.98 mmol). The mixture was stirred at 70°C for 24 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with water and brine and then, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The

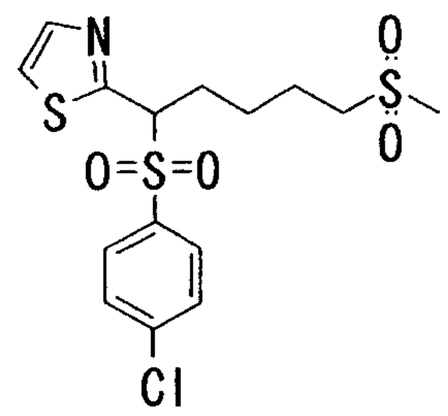
residue was subjected to chromatography on a silica gel column. The fraction obtained from the hexane:ethyl acetate (=1:1) eluate was concentrated under reduced pressure, whereby the title compound (169 mg, 41%) was obtained as a pale yellow solid.

IR (ATR) ν: 2967, 2913, 1573, 1498, 1475, 1394, 1317, 1280, 1218, 1184, 1147, 1081, 1062, 1012, 966, 887, 825, 775, 763, 730, 700, 630, 599, 563, 549, 478, 447 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.79(2H,s), 7.42(1H,d,J=3.2Hz), 7.47(2H,d,J=8.6Hz), 7.64(2H,d,J=8.8Hz), 7.72(1H,d,J=3.4Hz).

MS (m/z): 274 (M^++H).

Example 116: 2-[1-[(4-Chlorophenyl)sulfonyl]-5-(methylsulfonyl)pentyl]thiazole



A toluene (10 ml) solution of 2-(4-chlorophenylsulfonylmethyl)thiazole (75 mg, 0.274 mmol), the 4-(methylsulfonyl)-1-butanol (83 mg, 0.548 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (132 mg, 0.548 mol) was heated under reflux for 20 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was

subjected to flash chromatography on a silica gel column. The fraction obtained from the methylene chloride:ethyl acetate (=1:2) eluate was concentrated under reduced pressure to give the title compound (87 mg, 78%) as a white solid. The resulting solid was washed with ether and then, collected by filtration, whereby the title compound was obtained as a white powder.

Melting point: 118-119°C.

IR (ATR) ν: 3137, 3006, 2913, 1583, 1496, 1471, 1388, 1357, 1315, 1284, 1238, 1203, 1135, 1083, 1043, 1010, 975, 877, 842, 804, 765, 736, 705, 642, 601, 572, 526, 468, 439 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.40-1.62(2H,m), 1.80-1.99(2H,m), 2.22-2.35(1H,m), 2.48-2.58(1H,m), 2.88(3H,s), 2.92-3.00(2H,m), 4.61(1H,dd,J=11.2,3.7Hz), 7.39-7.47(3H,m), 7.51(2H,d,J=8.5Hz), 7.68(1H,d,J=3.4Hz).

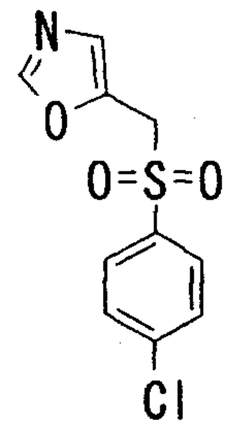
MS (m/z): 408 (M^++H).

Elemental Analysis for $C_{15}H_{18}ClNO_4S_3$

Calculated: C 44.16%; H 4.45%; Cl 8.69%; N 3.43%; S 23.58%.

Found: C 44.32%; H 4.40%; Cl 8.74%; N 3.54%; S 24.04%.

Example 117: 5-(4-Chlorophenylsulfonylmethyl)oxazole



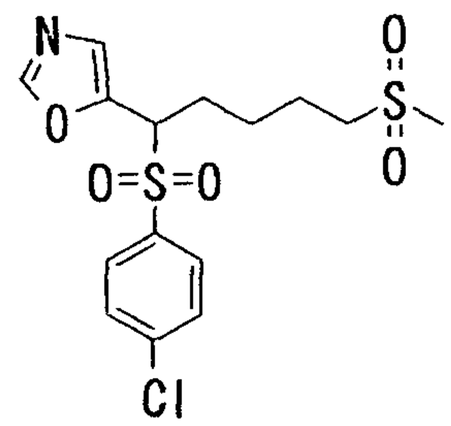
Thionyl chloride (188 µl, 2.57 mmol) was added to a chloroform (10 ml) solution of oxazol-5-ylmethanol (85 mg, 0.858 mmol). The resulting mixture was stirred at 50°C for 1.5 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was dissolved in butanol (10 ml). To the resulting solution were added sodium 4-chlorobenzenesulfinate (170 mg, 0.858 mmol), potassium acetate (252 mg, 2.57 mmol) and tetrabutylammonium iodide (15 mg), followed by stirring at 70°C for 3 days. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The mixture was washed successively with water and brine and then, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography on a silica gel column, and the fraction obtained from the hexane:ethyl acetate (=1:1) fraction was concentrated under reduced pressure, whereby the title compound (81 mg, 37%) was obtained as a white solid.

IR (ATR) ν: 3141, 3085, 2983, 2921, 1475, 1506, 1490, 1475, 1396, 1319, 1284, 1263, 1213, 1178, 1151, 1110, 968, 923, 869, 823, 769, 746, 700, 644, 559, 541, 482, 455, 422 cm^{-1}.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 4.47(2H,s), 7.02(1H,s), 7.52(2H,d,J=8.8Hz), 7.70(2H,d,J=8.8Hz), 7.82(1H,s).

MS (m/z): 258 (M^++H).

Example 118: 5-[1-(4-Chlorophenylsulfonyl)-5-(methylsulfonyl)pentyl]oxazole



A toluene (10 ml) solution of 5-(4-chlorophenylsulfonylmethyl)oxazole (65 mg, 0.252 mmol), the 4-(methylsulfonyl)-1-butanol (77 mg, 0.504 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (122 mg, 0.504 mmol) was heated under reflux for 15 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was added with the 4-(methylsulfonyl)-1-butanol (77 mg, 0.504 mmol) obtained in Referential Example 3 and cyanomethylenetri-n-butylphosphorane (122 mg, 0.504 mmol), followed by heating under reflux for 25 hours under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

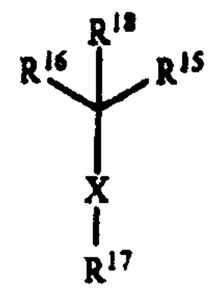
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS

1. A compound represented by the formula (3):



(3)

wherein

R^{15} represents a pyridyl group substituted with at least one group represented by the formula $-Q^{201}-Q^{202}-Q^{203}-Q^{204}-Q^{205}-Q^{206}-Q^{207}$, wherein

Q^{201} represents a single bond, an alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms or a heterocyclic group;

Q^{202} represents a single bond, —O—, —NH—, —CH=—N—, —C(alkyl)=N—, —N(alkyl)— or —S—;

Q^{203} represents a single bond, —CO—, —CS—, —SO—, —SO_2— or —CONH—;

Q^{204} represents a single bond, an alkyl group from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, a cycloalkyl group, a cycloalkenyl group, an aromatic hydrocarbon group or a heterocyclic group;

Q^{205} represents a single bond, —NH— or —N(alkyl)—;

Q^{206} represents a single bond, —O—, —CO—, —CS—, —SO_2—, —SO— or —S—; and

Q^{207} represents a hydrogen atom, a halogen atom, a hydroxy group, an oxo group, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-8} cycloalkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group, an azide group, a cyano group, an amino group, a C_{1-6} alkylamino group, a di(C_{1-6} alkyl)amino group, a C_{2-6} alkanoylamino group, a di(C_{2-6} alkanoy)amino group, a carboxyamino group, a C_{1-6} alkoxycarbonylamino group, a di(C_{1-6} alkoxy)carbonylamino group, a heterocyclic group, an aromatic hydrocarbon group, a cycloalkenyl group, a heterocyclic oxy group, or an aromatic hydrocarbon-oxy group,

wherein, the alkyl group having from 1 to 6 carbon atoms, alkenyl group having from 2 to 6 carbon atoms, cycloalkyl group, cycloalkenyl group, heterocyclic group, heterocyclic-oxy group, aromatic hydrocarbon group or aromatic hydrocarbon-oxy group are optionally substituted with 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{2-6} alkenyl groups, carboxyamino C_{1-6} alkyl groups, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl groups, formyl group, C_{2-6} alkanoyl groups, oxo group, nitro group, cyano

group, azide group, amidino group, C_{2-6} alkenyloxy groups, hydroxy group, carboxyl group, C_{7-16} aralkyl groups, thioxo group, C_{2-7} alkanoyl groups, C_{2-7} thioalkanoyl groups, thioformyl group, amino group, C_{1-6} alkylamino groups, di(C_{1-6} alkyl)amino groups, C_{1-6} alkoxycarbonyl groups, carbamoyl group, C_{1-6} alkylcarbamoyl groups, di(C_{1-6} alkyl)carbamoyl groups, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl groups, di(C_{1-6} alkyl)thiocarbamoyl groups, C_{1-6} alkoxycarbamoylamino groups, C_{1-6} alkoxycarbamoyl(C_{1-6} alkyl) amino groups, C_{2-7} alkanoylamino groups, C_{2-7} alkanoyl (C_{1-6} alkyl)amino groups, thio C_{2-7} alkanoylamino groups, thio C_{2-7} alkanoyl (C_{1-6} alkyl)amino groups, formylamino group, formyl(C_{1-6} alkyl)amino groups, thioformylamino group, thioformyl(C_{1-6} alkyl) amino groups, C_{2-7} alkanoyloxy groups, formyloxy group, C_{1-6} alkoxycarbonyloxy groups, carbamoyloxy group, C_{1-6} alkylcarbamoyloxy groups, di(C_{1-6} alkyl) carbamoyloxy groups, aminocarbonylamino group, (C_{1-6} alkyl)aminocarbonylamino groups, di(C_{1-6} alkyl) aminocarbonylamino groups, aminocarbonyl(C_{1-6} alkyl)amino groups, C_{1-6} alkyl)aminocarbonyl(C_{1-6} alkyl) amino groups, di(C_{1-6} alkyl)aminocarbonyl(C_{1-6} alkyl) amino groups, mercapto group, C_{1-6} alkylthio groups, C_{1-6} alkylsulfinyl groups, C_{1-6} alkylsulfonyl groups, aminosulfonyl group, C_{1-6} alkylaminosulfonyl groups, di(C_{1-6} alkyl)aminosulfonyl groups, C_{1-6} alkylsulfonylamino groups, C_{1-6} alkylsulfonyl(C_{1-6} alkyl)amino groups, aminosulfonylamino group, C_{1-6} alkylaminosulfonylamino groups, di(C_{1-6} alkyl)aminosulfonylamino groups, aminosulfonyl(C_{1-6} alkyl)amino groups, C_{1-6} alkylaminosulfonyl(C_{1-6} alkyl)amino groups, and di(C_{1-6} alkyl)aminosulfonyl(C_{1-6} alkyl)amino groups,

wherein said heterocyclic group is selected from the group consisting of piperazine, morpholine, piperidine, thiophene and 1,3-dioxilane;

R^{16} represents an unsubstituted phenyl group or a phenyl group substituted with at least one substituent represented by the formula $-Q^{201}-Q^{202}-Q^{203}-Q^{204}-Q^{205}-Q^{206}-Q^{207}$, wherein

Q^{201} represents a single bond, an alkyl group having from 1 to 6 carbon atoms or an alkenyl group having from 2 to 6 carbon atoms,

Q^{202} represents a single bond, —O—, —NH—, —CH=—N—, —C(alkyl)=N—, —N(alkyl)— or —S—;

Q^{203} represents a single bond, —CO—, —CS—, —SO—, —SO_2— or —CONH—;

Q^{204} represents a single bond, an alkyl group from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, a cycloalkyl group, a cycloalkenyl group or an aromatic hydrocarbon group;

Q^{205} represents a single bond, —NH— or —N(alkyl)—;

Q^{206} represents a single bond, —O—, —CO—, —CS—, —SO_2—, —SO— or —S—; and

Q^{207} represents a hydrogen atom, a halogen atom, a hydroxy group, an oxo group, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-8} cycloalkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group, an azide group, a cyano group, an amino group, a C_{1-6} alkylamino group, a di(C_{1-6} alkyl)amino group, a C_{2-6} alkanoylamino group, a di(C_{2-6} alkanoy)amino group, a carboxyamino group, a C_{1-6} alkoxycarbonylamino group, a di(C_{1-6} alkoxy)carbonylamino group, an aromatic hydrocarbon group, a cycloalkenyl group, or an aromatic hydrocarbon-oxy group,

wherein, the alkyl group having from 1 to 6 carbon atoms, alkenyl group having from 2 to 6 carbon atoms, cycloalkyl group, cycloalkenyl group, aromatic hydrocarbon group or aromatic hydrocarbon-oxy group are optionally substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{2-6} alkenyl groups, carboxyamino C_{1-6} alkyl groups, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl groups, formyl group, C_{2-6} alkanoyl groups, oxo group, nitro group, cyano group, azide group, amidino group, C_{2-6} alkenyloxy groups, hydroxy group, carboxyl group, C_{7-16} aralkyl groups, thioxo group, C_{2-7} alkanoyl groups, C_{2-7} thioalkanoyl groups, thioformyl group, amino group, C_{1-6} alkylamino groups, di(C_{1-6} alkyl) amino groups, C_{1-6} alkoxycarbonyl groups, carbamoyl group, C_{1-6} alkylcarbamoyl groups, di(C_{1-6} alkyl)carbamoyl groups, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl groups, di(C_{1-6} alkyl)thiocarbamoyl groups, C_{1-6} alkoxycarbamoylamino groups, C_{1-6} alkoxycarbamoyl(C_{1-6} alkyl)amino groups, C_{2-7} alkanoylamino groups, C_{2-7} alkanoyl (C_{1-6} alkyl)amino groups, thio C_{2-7} alkanoylamino groups, thio C_{2-7} alkanoyl (C_{1-6} alkyl)amino groups, formylamino group, formyl(C_{1-6} alkyl) amino groups, thioformylamino group, thioformyl(C_{1-6} alkyl)amino groups, C_{2-7} alkanoyloxy groups, formyloxy group, C_{1-6} alkoxycarbonyloxy groups, carbamoyloxy group, C_{1-6} alkylcarbamoyloxy groups, di(C_{1-6} alkyl)carbamoyloxy groups, aminocarbonylamino group, (C_{1-6} alkyl)aminocarbonylamino groups, di(C_{1-6} alkyl)aminocarbonylamino groups, aminocarbonyl (C_{1-6} alkyl)amino groups, C_{1-6} alkyl)aminocarbonyl (C_{1-6} alkyl)amino groups, di(C_{1-6} alkyl)aminocarbonyl (C_{1-6} alkyl)amino groups, mercapto group, C_{1-6} alkylthio groups, C_{1-6} alkylsulfinyl groups, C_{1-6} alkylsulfonyl groups, aminosulfonyl group, C_{1-6} alkylaminosulfonyl groups, di(C_{1-6} alkyl)aminosulfonyl groups, C_{1-6} alkylsulfonylamino groups, C_{1-6} alkylsulfonyl(C_{1-6} alkyl)amino groups, aminosulfonylamino group, C_{1-6} alkylaminosulfonylamino groups, di(C_{1-6} alkyl)aminosulfonylamino groups, aminosulfonyl(C_{1-6} alkyl)amino groups, C_{1-6} alkylaminosulfonyl(C_{1-6} alkyl)amino groups, and di(C_{1-6} alkyl)aminosulfonyl(C_{1-6} alkyl) amino groups;

R^{17} represents an unsubstituted phenyl group or a phenyl group substituted with at least one substituent represented by the formula $-Q^{201}-Q^{202}-Q^{203}-Q^{204}-Q^{205}-Q^{206}-Q^{207}$, wherein

Q^{201} represents a single bond, an alkyl group having from 1 to 6 carbon atoms or an alkenyl group having from 2 to 6 carbon atoms,

Q^{202} represents a single bond, —O—, —NH—, —CH=—N—, —C(alkyl)=N—, —N(alkyl)— or —S—;

Q^{203} represents a single bond, —CO—, —CS—, —SO—, —SO_2— or —CONH—;

Q^{204} represents a single bond, an alkyl group from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, a cycloalkyl group, a cycloalkenyl group or an aromatic hydrocarbon group;

Q^{205} represents a single bond, —NH— or —N(alkyl)—;

Q^{206} represents a single bond, —O—, —CO—, —CS—, —SO_2—, —SO— or —S—; and

Q^{207} represents a hydrogen atom, a halogen atom, a hydroxy group, an oxo group, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-8} cycloalkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group, an azide group, a cyano group, an amino group, a C_{1-6} alkylamino group, a di(C_{1-6} alkyl)amino group, a C_{2-6} alkanoylamino group, a di(C_{2-6} alkanoy)amino group, a carboxyamino group, a C_{1-6} alkoxycarbonylamino group, a di(C_{1-6} alkoxy)carbonylamino group, an aromatic hydrocarbon group, a cycloalkenyl group, or an aromatic hydrocarbon-oxy group,

wherein, the alkyl group having from 1 to 6 carbon atoms, alkenyl group having from 2 to 6 carbon atoms, cycloalkyl group, cycloalkenyl group, aromatic hydrocarbon group or aromatic hydrocarbon-oxy group are optionally substituted with 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, C_{2-6} alkenyl groups, carboxyamino C_{1-6} alkyl groups, C_{1-6} alkoxycarbonylamino C_{1-6} alkyl groups, formyl group, C_{2-6} alkanoyl groups, oxo group, nitro group, cyano group, azide group, amidino group, C_{2-6} alkenyloxy groups, hydroxy group, carboxyl group, C_{7-16} aralkyl groups, thioxo group, C_{2-7} alkanoyl groups, C_{2-7} thioalkanoyl groups, thioformyl group, amino group, C_{1-6} alkylamino groups, di(C_{1-6} alkyl) amino groups, C_{1-6} alkoxycarbonyl groups, carbamoyl group, C_{1-6} alkylcarbamoyl groups, di(C_{1-6} alkyl)carbamoyl groups, thiocarbamoyl group, C_{1-6} alkylthiocarbamoyl groups, di(C_{1-6} alkyl)thiocarbamoyl groups, C_{1-6} alkoxycarbamoylamino groups, C_{1-6} alkoxycarbamoyl(C_{1-6} alkyl)amino groups, C_{2-7} alkanoylamino groups, C_{2-7} alkanoyl (C_{1-6} alkyl)amino groups, thio C_{2-7} alkanoylamino groups, thio C_{2-7} alkanoyl (C_{1-6} alkyl)amino groups, formylamino group, formyl(C_{1-6} alkyl) amino groups, thioformylamino group, thioformyl(C_{1-6} alkyl)amino groups, C_{2-7} alkanoyloxy groups, formyloxy group, C_{1-6} alkoxycarbonyloxy groups, carbamoyloxy group, C_{1-6} alkylcarbamoyloxy groups, di(C_{1-6} alkyl)carbamoyloxy groups, aminocarbonylamino group, (C_{1-6} alkyl)aminocarbonylamino groups, di(C_{1-6} alkyl)aminocarbonylamino groups, aminocarbonyl (C_{1-6} alkyl)amino groups, (C_{1-6} alkyl)aminocarbonyl (C_{1-6} alkyl)amino groups, di(C_{1-6} alkyl)aminocarbonyl (C_{1-6} alkyl)amino groups, mercapto group, C_{1-6} alkylthio groups, C_{1-6} alkylsulfinyl groups, C_{1-6} alkylsulfonyl groups, aminosulfonyl group, C_{1-6} alkylaminosulfonyl groups, di(C_{1-6} alkyl)aminosulfonyl groups, C_{1-6} alkylsulfonylamino groups, C_{1-6} alkylsulfonyl(C_{1-6} alkyl)amino groups, aminosulfonylamino group, C_{1-6}

alkylaminosulfonylamino groups, di(C_{1-6} alkyl)aminosulfonylamino groups, aminosulfonyl(C_{1-6} alkyl)amino groups, C_{1-6} alkylaminosulfonyl(C_{1-6} alkyl)amino groups, and di(C_{1-6} alkyl)aminosulfonyl(C_{1-6} alkyl) amino groups;

R^{18} represents a hydrogen atom or a C_{1-6} alkyl group; and

X represents —S—, —SO— or —SO_2—;

or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

2. The compound according to claim 1, wherein R^{18} represents a hydrogen atom.

3. The compound according to claim 1, wherein X represents —SO_2—.

4. The compound according to claim 1, wherein Q^{201}, Q^{202}, Q^{203}, Q^{204}, Q^{205} and Q^{206} in the definition of R^{15} each represent a single bond.

5. The compound according to claim 1, wherein Q^{201}, Q^{202}, Q^{205} and Q^{206} in the definition of R^{15} each represent a single bond.

6. The compound according to claim 1, wherein Q^{203} in definition of R^{15} represents —CONH—.

7. The compound according to claim 1, wherein Q^{201}, Q^{202}, Q_{203}, Q_{204}, Q^{205} and Q^{206} in the definition of R^{16} each represent a single bond.

8. The compound according to claim 1, wherein Q^{201}, Q^{202}, Q_{203}, Q^{204}, Q^{205} and Q^{206} in the definition of R^{17} each represent a single bond.

9. The compound of claim 1, wherein R^{16} represents an unsubstituted phenyl group;

or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

10. The compound of claim 1, wherein R^{16} represents said substituted phenyl group;

or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

11. The compound of claim 1, wherein R^{17} represents an unsubstituted phenyl group;

or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

12. The compound of claim 1, wherein R^{17} represents said substituted phenyl group;

or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

13. The compound of claim 1, wherein R^{18} represents a C_{1-4} alkyl group;

or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

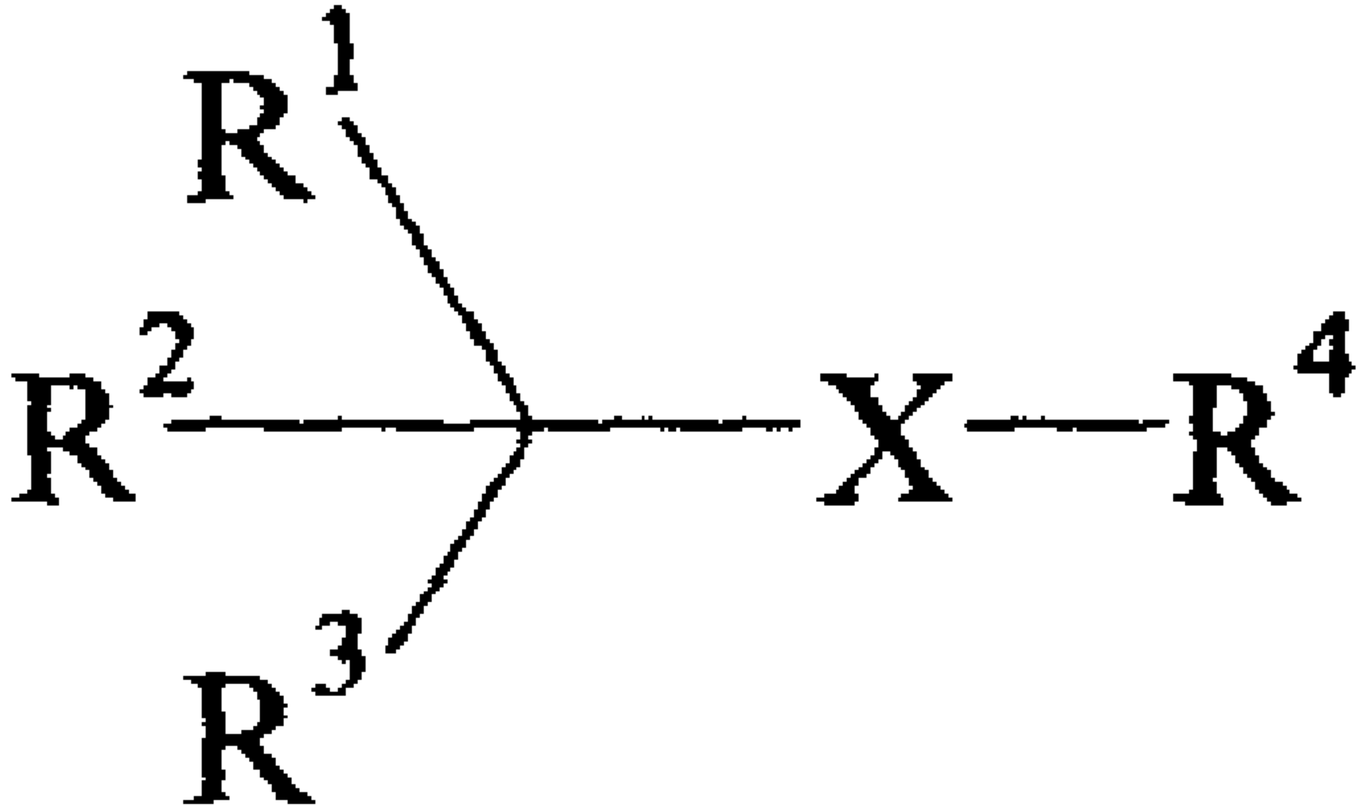
14. The compound of claim 1, wherein X represents —S—; or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

15. The compound of claim 1, wherein X represents —SO—; or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof.

16. Use of a compound of claim 1 for treating Alzheimer's disease in a subject in need thereof.

17. A pharmaceutical composition, comprising the compound of claim 1, or N-oxide or S-oxide of the compound, salt thereof, or solvate thereof and a pharmaceutically acceptable carrier.

18. A method of preparing a medicament, comprising adding the compound of claim 1, or an N-oxide or S-oxide of thereof; a salt thereof; or a solvate thereof, to a pharmaceutically acceptable carrier.



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