PHENYL CARBAMATE COMPOUNDS FOR USE IN PREVENTING OR TREATING PEDIATRIC EPILEPSY AND EPILEPSY-RELATED SYNDROMES

Publication Classification

Int. Cl.
C07C 271/12 (2006.01)
C07C 271/24 (2006.01)

CPC
C07C 271/12 (2013.01); C07C 271/24 (2013.01)

USPC
514/487; 514/476; 514/489; 514/484

ABSTRACT

The present invention provides a pharmaceutical composition for preventing and/or treating a pediatric epilepsy or epilepsy-related syndrome comprising the phenyl carbamate compound as an active ingredient, and a use of the phenyl carbamate compound for preventing and/or treating pediatric epilepsy or pediatric epilepsy-related syndromes.
FIG. 1

SIS (Multiple-hit model)

Data were represented as mean ±SEM. Statistical analysis were performed by Multivariate analysis and followed by Tukey HSD (Control vs. #1 treatment group) as a post hoc analysis using SPSS

***: p<0.001, **: p<0.01, *: p<0.05
PHENYL CARBAMATE COMPOUNDS FOR USE IN PREVENTING OR TREATING PEDIATRIC EPILEPSY AND EPILEPSY-RELATED SYNDROMES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 61/776,926, filed in the United States Patent and Trademark Office on Mar. 12, 2013, the entire contents of which are incorporated herein by reference.

[0002] The present invention provides a pharmaceutical composition for preventing and/or treating a pediatric epilepsy or epilepsy-related syndrome comprising the phenyl carbamate compound as an active ingredient, and use of the phenyl carbamate compound for preventing and/or treating pediatric epilepsy or pediatric epilepsy-related syndromes.

[0003] Epilepsy and its related syndromes may be classified according to whether the associated seizures are partial or generalized, and whether the etiology is idiopathic or symptomatic/cryptogenic. Several important pediatric syndromes can be further grouped according to age of onset and prognosis. Epilepsy is one of the most common and disabling neurologic disorders in childhood. These may be divided into the epileptic encephalopathies of infancy and early childhood, febrile convulsions, and benign partial and generalized syndromes of later childhood and adolescence.

[0004] At present, the International League Against Epilepsy classification of epilepsy syndromes according to presumed localization (partial, generalized, undetermined) and etiology (idiopathic, cryptogenic, symptomatic). In clinical practice, it is often useful to conceptualize epilepsy syndromes according to their usual age at presentation, which greatly facilitates syndrome identification in new patients and recognizes the age-related expression of many childhood epilepsies. Definitional problems exist for many pediatric epilepsy syndromes, particularly the epileptic encephalopathies of early infancy, the benign epilepsies of infancy and childhood, the myoclonic epilepsies of infancy and early childhood, and the idiopathic generalized epilepsies of childhood and adolescence. (Epilepsia. 1996; 37 Suppl 1:S26-40).

<table>
<thead>
<tr>
<th>Period</th>
<th>Epilepsy syndromes according to usual age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal period</td>
<td>Benign neonatal convulsions</td>
</tr>
<tr>
<td></td>
<td>Benign neonatal familial convulsions</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous neonatal seizures</td>
</tr>
<tr>
<td>Infancy</td>
<td>Febrile seizures</td>
</tr>
<tr>
<td></td>
<td>Early infantile epileptic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Early myoclonic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Infantile spasm</td>
</tr>
<tr>
<td></td>
<td>West syndromes</td>
</tr>
<tr>
<td></td>
<td>Severe myoclonic epilepsy of infancy</td>
</tr>
<tr>
<td></td>
<td>Benign myoclonic epilepsy of infancy</td>
</tr>
<tr>
<td></td>
<td>Benign partial epilepsy of infancy</td>
</tr>
<tr>
<td></td>
<td>Benign infantile familial convolution</td>
</tr>
<tr>
<td></td>
<td>Symptomatic/cryptogenic partial epilepsies</td>
</tr>
<tr>
<td>Early childhood</td>
<td>Epilepsy with myoclonic absences</td>
</tr>
<tr>
<td>(toddler and</td>
<td>Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>preschool age)</td>
<td>Epilepsy with myoclonic-astatic seizures (Doose syndrome)</td>
</tr>
<tr>
<td></td>
<td>Acquired epileptic aphasia (Landau-Kleffner syndrome)</td>
</tr>
</tbody>
</table>

TABLE 1-continued

<table>
<thead>
<tr>
<th>Period</th>
<th>Epilepsy classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood (School age), adolescence and young adulthood</td>
<td>Childhood absence epilepsy</td>
</tr>
</tbody>
</table>

[0005] Some childhood-onset epilepsy syndromes are well defined and easily recognizable. These include benign rolandic, various syndromes with absence, the Landau-Kleffner syndrome (LKS), and continuous spike-wave in slow sleep. Others have somewhat vague characteristics including the Lennox-Gastaut syndrome. Some are still very difficult to define including benign occipital epilepsy and myoclonic-astatic epilepsy.

[0006] The term benign epilepsy is used to refer to a group of pediatric epileptic disorders in which remission and lack of significant neurologic sequelae are expected in the vast majority of patients. These disorders are idiopathic, occur in otherwise healthy children, and have (with rare exceptions) a strong genetic component. They include generalized epilepsies and partial epilepsies. These epilepsies are presented according to the age of onset, starting from the neonatal period. Although the prognosis of neonatal convulsions remains poor, benign neonatal convulsions are differentiated by their generally good prognosis. Two syndromes in which no metabolic, hypoxic-ischemic, or structural etiology is apparent are benign familial neonatal convulsions and benign idiopathic neonatal convulsions. (Regarding the former syndrome, some authors prefer to identify it by the term familial neonatal convulsions, dispensing with the adjective benign.) These include generalized, as well as partial, epilepsies. The generalized epilepsies discussed are limited to childhood absence epilepsy, which is also called pyknolepsy, and juvenile absence epilepsy, also known as epilepsy with nonmyoklonic absences or epilepsy with spastioleptic absences. The benign partial epilepsies include benign partial epilepsy of childhood with centrotemporal spikes, benign occipital epilepsy, and benign epilepsy with affective symptoms.

[0007] In addition, presentation of variability of features as well as recent genetic findings and correlations have lead to an expansion of the syndrome to include Benign Myoclonic Epilepsy (BME), Severe Myoclonic Epilepsy of Infancy Borderland (SMEB), Severe Infantile Multifocal Epilepsy (SIMFE), and Intractable Childhood Epilepsy with Generalized Tonic Clonic Seizures (IGE-GTC). Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare and catastrophic form of intractable epilepsy that begins in infancy. Initial seizures are most often prolonged events and in the second year of life other seizure types begin to emerge. Development remains on track initially, with plateaus and a progressive decline typically beginning in the second year of life. Individuals with Dravet syndrome face a higher incidence of SUDEP (sudden unexplained death in epilepsy) and have associated conditions, which also need to be properly treated and managed. SIMFE presents in infancy
but the neuro-developmental regression occurs between ages 3 and 6 years instead of between ages 2 and 4 years in the Dravet syndrome.

[0008] Lennox-Gastaut Syndrome (LGS) also known as Lennox syndrome, is a difficult-to-treat form of childhood-onset epilepsy that most often appears between the second and sixth year of life, and is characterized by frequent seizures and different seizure types; it is often accompanied by developmental delay and psychological and behavioral problems. As a general rule, the age of seizure onset in LGS patients is between the ages of two and six; however, this does not exclude the possibility that seizures can begin before age two, or after age six. The syndrome shows clear parallels to West syndrome, enough to suggest a connection. West syndrome or West’s Syndrome is an uncommon to rare epileptic disorder in infants. Other names for it are Generalized Flexion Epilepsy, Infantile Epileptic Encephalopathy, Infantile Myoclonic Encephalopathy, Jackknife convulsions, Massive Myoclonia and Salaam spasms. The term infantile spasms can be used to describe the specific seizure manifestation in the syndrome, but is also used as a synonym for the syndrome itself. West syndrome in modern usage is the triad of infantile spasms, a pathognomonic EEG pattern (called hypsarrhythmia), and developmental regression. Compared with other forms of epilepsy, Pediatric epilepsy is difficult to treat. It is very important that the condition is diagnosed as early as possible and that treatment begins straight away. However, there is no guarantee that therapy will work even in this case. There is to clarify a need for improved medication.

**SUMMARY OF THE INVENTION**

[0009] An embodiment provides a pharmaceutical composition for the prevention and the treatment of a pediatric epilepsy or epilepsy-related symptom, comprising a phenyl carbamate compound of the following Chemical Formula 1, an enantiomer or a diastereomer thereof, or a mixture of enantiomers or diastereomers; or a pharmaceutically acceptable salt thereof.

[0010] Another embodiment is to provide a method of preventing and/or treating an epilepsy or an epilepsy-related symptom in pediatric subject comprising administering a pharmaceutically effective amount of a phenyl carbamate compound represented by Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof, to the pediatric subject in need.

[0011] Still other embodiment is to provide a phenyl carbamate compound represented by Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof, for use in the prevention and/or treatment of epilepsy or the manufacture of a pharmaceutical composition for preventing and/or treating a pediatric epilepsy or an epilepsy-related symptom.

**DETAILED DESCRIPTION OF THE EMBODIMENTS**

[0012] Continuing its research work in the field of epilepsy, the present inventors, as results of studies on the development of the drugs useful for prevention and/or treatment of a pediatric epilepsy or an epilepsy-related symptom, found that a substituted phenyl carbamate compounds of the following Chemical Formula 1 exhibits remarkably excellent anti-epilepsy activity in various emulation models and simultaneously has very low toxicity, and completed the invention. [0013] Therefore, an embodiment provides a pharmaceutical composition for the prevention and the treatment of a pediatric epilepsy or epilepsy-related symptom, comprising an organic compound, i.e., phenyl carbamate derivatives, more particularly, a phenyl carbamate compound represented by following Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof.

![Chemical Formula 1](image)

[0014] wherein,

[0015] X is a halogen, for example, chlorine, fluorine, iodine, or bromine,

[0016] n, that means the number of substituent X, is an integer from 1 to 5, for example, 1 or 2,

[0017] R1 is a linear or branched alkyl group of C1-C4, for example, methyl group, ethyl group, isopropyl group, or butyl group,

[0018] A is hydrogen or a carbamoyl derivative represented by

![image]

[0019] B is hydrogen, a carbamoyl derivative represented by

![image]

trialkyl silyl groups (e.g., a trimethyl silyl (TMS) group, a triethyl silyl (TES) group, a triisopropyl silyl (TIPS) group, t-butyl dimethyl silyl (TBDMS) group, and the like), trialkylyl silyl groups (wherein the total number of alkyl and aryl groups is three; e.g., a t-butyl diphenyl silyl (TBDPS) group and the like), or a trialkylyl silyl ether group, wherein each alkyl group may be independently selected from the group consisting of linear, branched, or cyclic C1-C4 alkyl groups, and each aryl group may be independently selected from the group consisting of C5-C8 aryl groups, preferably a phenyl group.

[0020] A and B are not carbamoyl derivatives at same time, and

[0021] R2 and R3 may be the same as or different from each other, and independently selected from the group consisting of hydrogen, a linear or branched alkyl group of C1-C4, for
example C1-C3, a cycloalkyl group of C3-C8, for example C3-C7, and benzyl group, and more specifically, R2 and R3 may be the same as or different from each other, and independently selected from the group consisting of hydrogen, methyl group, propyl group, isopropyl group, cyclopropyl group, cyclohexyl group, bicycloheptane group, and benzyl group.

[0022] Preferably, in Chemical Formula 1, A is hydrogen and B is carbamoyl group, or A is a carbamoyl group and B is hydrogen.

[0023] In the embodiment, in Chemical Formula 1,

[0024] if X is F or Br, A and B are not hydrogen at the same time,

[0025] if X is chlorine and n is 1 and A and B are hydrogen at the same time, R1 is a C2-C4 linear or branched alkyl group,

[0026] if X is chlorine and n is 1, R1 is methyl, isopropyl or butyl, and

[0027] if X is bromine located at 4-position of the aromatic ring and n is 1, R1 is methyl, propyl, isopropyl or butyl, and

[0028] if A is the carbamoyl represented by, B is hydrogen, R1 is ethyl, and n is 2 at the same time, two X are located at 2 and 3 positions, 2 and 4 positions, 2 and 5 positions, or 3 and 5 positions of the aromatic ring.

[0029] In a concrete embodiment, the phenyl carbamate compound may be selected from the group consisting of:

[0030] 1-(2-chlorophenyl)-1-hydroxypropyl-2-carbamate,
[0031] 1-(2-chlorophenyl)-1-hydroxybutyl-2-carbamate,
[0032] 1-(2-chlorophenyl)-1-hydroxy-3-methylbutyl-2-carbamate,
[0033] 1-(2-chlorophenyl)-1-hydroxyethyl-2-carbamate,
[0034] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-methylcarbamate,
[0035] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-propylcarbamate,
[0036] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-isopropylcarbamate,
[0037] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclohexylcarbamate,
[0038] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclopentylcarbamate,
[0039] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-benzylcarbamate,
[0040] 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-bicyclo[2,2,1]heptane carbamate,
[0041] 1-(2,4-dichlorophenyl)-1-hydroxypropyl-2-carbamate,
[0042] 1-(2,6-dichlorophenyl)-1-hydroxypropyl-2-carbamate,
[0043] 1-(2,4-dichlorophenyl)-1-hydroxybutyl-2-carbamate,
[0044] 1-(2,6-dichlorophenyl)-1-hydroxybutyl-2-carbamate,
[0045] 1-(2,4-dichlorophenyl)-1-hydroxy-3-methylbutyl-2-carbamate,
[0046] 1-(2,6-dichlorophenyl)-1-hydroxy-3-methylbutyl-2-carbamate,
[0047] 1-(2,4-dichlorophenyl)-1-hydroxyhexyl-2-carbamate,
[0048] 1-(2,6-dichlorophenyl)-1-hydroxyhexyl-2-carbamate,
[0049] 1-(2-chlorophenyl)-2-hydroxypropyl-1-carbamate,
[0050] 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-methylcarbamate,
[0051] 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-propylcarbamate,
[0052] 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-isopropylcarbamate,
[0053] 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclopropylcarbamate,
[0054] 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclohexylcarbamate,
[0055] 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-benzylcarbamate,
[0056] 1-(2,4-dichlorophenyl)-2-hydroxypropyl-1-carbamate,
[0057] 1-(2,6-dichlorophenyl)-2-hydroxypropyl-1-carbamate,
[0058] 1-(2,4-dichlorophenyl)-2-hydroxybutyl-1-carbamate,
[0059] 1-(2,6-dichlorophenyl)-2-hydroxybutyl-1-carbamate,
[0060] 1-(2,4-dichlorophenyl)-2-hydroxy-3-methylbutyl-1-carbamate,
[0061] 1-(2,6-dichlorophenyl)-2-hydroxy-3-methylbutyl-1-carbamate,
[0062] 1-(2,4-dichlorophenyl)-2-hydroxyhexyl-1-carbamate,
[0063] 1-(2,6-dichlorophenyl)-2-hydroxyhexyl-1-carbamate,
[0064] 1-(2-fluorophenyl)-1-hydroxypropyl-2-carbamate,
[0065] 1-(2-iodophenyl)-1-hydroxypropyl-2-carbamate,
[0066] 1-(2-iodophenyl)-1-hydroxybutyl-2-carbamate,
[0067] 1-(2,3-dichlorophenyl)-1-hydroxypropyl-2-carbamate, and
[0068] 1-(2,3-dichlorophenyl)-2-hydroxypropyl-1-carbamate.

[0069] In another concrete embodiment, the compound may not include 1-(2-chlorophenyl)-1,2-propanediol, 1-(2-chlorophenyl)-1-hydroxybutyl-2-carbamate, and 1-(2,6-dichlorophenyl)-1-hydroxybutyl-2-carbamate.

[0070] In this compound, 2 chiral carbons exist at positions 1 and 2 from phenyl group substituted with X; thus, the compound may exist in the form of an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers, as well as a racemate.

[0071] In an embodiment, the phenyl carbamate compound is selected from the group consisting of:

[0072] 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate,
[0073] 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate, racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
[0074] 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(S)-2-carbamate,
[0075] 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate, racemate of 1-(2-chlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxybutyl-(R)-2-carbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxy-3-methyl-buty1-(S)-2-carbamate, and 1-(2-chlorophenyl)-(R)-1-hydroxy-3-methyl-buty1-(R)-2-carbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-methylcarbamate,

1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-propylcarbamate,

1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-isopropylcarbamate,

1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-cyclopropylcarbamate,

1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-cyclohexyl carbamate,

1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-methylcarbamate,

1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclohexyl carbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-methylcarbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-methylcarbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-propylcarbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-propylcarbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-isopropylcarbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-isopropylcarbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-cyclopropylcarbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclopropylcarbamate,

racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-cyclohexylcarbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclohexylcarbamate,

1-(2-fluorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate,

1-(2-fluorophenyl)-(R)-1-hydroxypropyl-(S)-2-carbamate,

1-(2-iodophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate,

1-(2-iodophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate, and

1-(2-iodophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate.

Alternatively, the compound may be in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt may include an additional salt of acid or base, and its stereocchemical isomer. For example, the compound may be in the form of an additional salt of an organic or inorganic acid. The salt may not be specially limited, and include any salts that maintain the activities of their parent compounds, with no undesirable effects, in the subject, when they are administered to the subject. Such salts may include inorganic and organic salts, such as salts of acetic acid, nitric acid, aspartic acid, sulfonic acid, sulfuric acid, maleic acid, glutamic acid, formic acid, succinic acid, phosphoric acid, phthalic acid, tannic acid, tartaric acid, hydrobromic acid, propionic acid, benzene sulfonic acid, benzoic acid, stearic acid, lauric acid, boric acid, bisulfuric acid, bitartric acid, oxalic acid, butyric acid, calcium edetate, carbonic acid, chlorobezoic acid, citric acid, edetic acid, toluienesulfonic acid, fumaric acid, glucetonic acid, estolic acid, pamoic acid, gluconic acid, methyl nitric acid, malonic acid, hydrochloric acid, hydriodic, hydroxynaphtholic acid, isethionic acid, lactobionic acid, mandelic acid, mucus acid, naphthyl acid, mucic acid, p-nitromethanesulfonic acid, hexamic acid, pantethenic acid, monohydrogen phosphoric acid, dihydrogen phosphoric acid, salicylic acid, sulfamic acid, sulfuric acid, and the like. The additional salts of base may include salts of alkali metal or alkaline earth metal, such as salts of ammonium, lithium, sodium, potassium, magnesium, calcium, and the like; salts having an organic base, such as benzathine, N-methyl-D-glucamine, hydramine, and the like; and salts having an amino acid such as arginine, lysine, and the like. In addition, these salts may be converted to a released form by treating with a proper base or acid.

As demonstrated in the following experimental examples, the compound of Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or pharmaceutically acceptable salt thereof exhibits an excellent effect on preventing, improving and/or treating epilepsy. Therefore, another embodiment provides a pharmaceutical composition for preventing and/or treating epilepsy containing a phenyl carbamate compound represented by Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof, as an active ingredient.

[0010] A diol compound used in the synthesis of the carbamate compound may be synthesized by dihydroxylation of a trans-olefin compound. A diol compound having optical activity may be synthesized using a sharpless asymmetric dihydroxylation catalyst.
As indicated in the Reaction Formula II, the optically active substance of diol may also be synthesized using an reduction reagent after synthesizing a hydroxy-ketone compound using Halor-2 Mandelic acid. In the Reaction Formula II, PG may be Trialkyl Silyl group (TMS, TES, TIPS, TBDMS, TBDPS), Ether group [MOM (Methoxyethylmethyl ether), MEM (2-Methoxyethoxymethyl ether), BOM (Benziloxymethyl ether), MTM (Methyleneimethyl ether), SEM (2-(Trimethylsilyl) ethoxyethyl ether), PMBM (p-Methoxybenzy1 ether), THP (Tetrahydropyranyl ether), Ally ether, Trityl ether, Ester group [Ac (aceticate), Bz (Benzaote), Pv (Pivalate), Cbz (Benzy1 carbonate), BOC (t-Butyl carbonate), Fmoc (9-Fluorenylethylcarboxylate), Alloc (Ally1 Carboxylate), Troc (Trichloroethyl carbonate), or p-Methoxybenzoate, Methyl carbonate, and so on.

A diol compound used in the synthesis of the carbamate compound may be synthesized by dihydroxylation of a trans-olefin compound. A diol compound having optical activity may be synthesized using a sharpless asymmetric dihydroxylation catalyst.
As indicated in the Reaction Formula II, the optically active substance of diol may also be synthesized using a reduction reagent after synthesizing a hydroxy-ketone compound using Haloo-Mandelic acid. In the Reaction Formula II, PG(protecting group) may be selected from the group consisting of trialkyl silyl group (e.g., a trimethyl silyl (TMS) group, a triethyl silyl (TES) group, a trisopropyl silyl (TIPS) group, t-butyl dimethyl silyl (TBDMS) group, and the like) trialkylarylsilyl groups (wherein the total number of alkyl and aryl groups is three; e.g., a t-butyl diphenyl silyl (TBDPS) group and the like), ester group [Ac(acetate), Bz(benzoate), Piv(pivalate), Cbz(benzyl carbonate), BOC(t-buty carbonate), FMoc(9-fluorenylmethyl)carbamate, Alloc(allallyl Carbonate), Trc(trichloromethyl carbonate), p-methoxybenzoate, methyl carbonate, and so on] and the like wherein each alkyl group may be independently selected from the group consisting of linear, branched, or cyclic C1-C4 alkyl groups, and each aryl group may be independently selected from the group consisting of C5-C8 aryl groups, preferably a phenyl group.

[0103] As a highly selectivity form of regioisomer of single carbamate of diol having halogen substituent at phenyl ring (Example 1-14 and 36-67 are synthesized by reaction formula III)

[0104] Two substances in the form of regioisomers of a single carbamate of diol having halogen substituent at phenyl ring may be separated by flash column chromatography to obtain two kinds of single carbamate compounds. (Example 15-35 and 68-115 are synthesized by reaction formula IV)

[0105] In the Reaction Formula V, PG(protecting group) may be selected from the group consisting of trialkyl silyl group (e.g., a trimethyl silyl (TMS) group, a triethyl silyl (TES) group, a trisopropyl silyl (TIPS) group, t-butyl dimethyl silyl (TBDMS) group, and the like), trialkylarylsilyl groups (wherein the total number of alkyl and aryl groups is three; e.g., a t-butyl diphenyl silyl (TBDPS) group and the
like), ester group (Ac: acetate, Bz: benzoate, Pv: pivaloate, Cbz: benzyl carbonate, BOC: t-butyl carbonate, Fmoc: 9-fluorenylmethylcarbonyl, Alloc: allyl carbonate, Troc: trichloroethyl carbonate, P- methoxybenzoate, methyl carbonate, and so on) and the like, wherein each alkyl group may be independently selected from the group consisting of linear, branched, or cyclic C1-C4 alkyl groups, and each aryl group may be independently selected from the group consisting of C5-C8 aryl groups, preferably a phenyl group.

[0106] In the Reaction Formulas IV and V, R4 and R5 may be the same as or different from each other, and independently selected from the group consisting of hydrogen, a linear or branched alkyl group of C1-C4, for example C1-C3, a cycloalkyl group of C3-C8, for example C3-C7, and benzyl group, and more specifically, R4 and R5 may be the same as or different from each other, and independently selected from the group consisting of hydrogen, methyl group, propyl group, isopropyl group, cyclopropyl group, cyclohexyl group, bicycloheptane group, and benzyl group.

[0107] Two substances in the form of regioisomers of a single carbamate of diol having halogen substituent at phenyl ring may be separated by flash column chromatography to obtain two kinds of single carbamate compounds.

[0108] Another embodiment provides a method of preventing and/or treating a pediatric epilepsy and a pediatric epilepsy-related symptoms comprising administering a pharmacologically effective amount of a phenyl carbamate compound represented by Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof, to a subject in need of preventing and/or treating a pediatric epilepsy and a pediatric epilepsy-related symptoms. The method may be applied for preventing and/or treating an epilepsy and an epilepsy-related symptoms in pediatrics.

[0109] The method may further comprise a step of identifying the subject in need of preventing and/or treating a pediatric epilepsy and a pediatric epilepsy-related symptoms prior to the step of administering. Another embodiment provides a phenyl carbamate compound represented by Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof, for use in the prevention and/or treatment of a pediatric epilepsy and a pediatric epilepsy-related symptoms.

[0110] Another embodiment provides a use of a phenyl carbamate compound represented by Chemical Formula 1; a racemate, an enantiomer, a diastereomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for preventing and/or treating pediatric epilepsy and pediatric epilepsy-related symptom.

[0111] Clinically, an epileptic seizure results from a sudden and abnormal electrical discharge originating from a collection of interconnected neurons in the brain or elsewhere in the nervous system. Depending on the type of epilepsy involved, the resulting nerve cell activity may be manifested by a wide variety of clinical symptoms such as uncontrollable motor movements, changes in the patient’s level of consciousness and the like. Epilepsy and epileptic seizures and syndromes may be classified in a variety of ways (See, The Treatment of Epilepsy, Principles & Practice, Third Edition, Elaine Wyllie, M.D. Editor, Lippincott Williams & Wilkins, 2001). However, as used herein the terms; “epilepsy”, “epileptic seizures” and “epileptic syndromes” are meant to include all known types of epileptic seizures and syndromes including; partial seizures, including simple, complex and partial seizures evolving to generalized tonic-clonic convulsions and generalized seizures, both convulsive and nonconvulsive and unclassified epileptic seizures.

[0112] As used herein, the term “a subject in need of treatment” would include an individual who does not have epilepsy or analogous seizure-related disorder but who may be in a high-risk group for the development of seizures or a seizure-related disorder. The terms “subject” or “patient” are used herein interchangeably and as used herein, refer to a human being, who has been the object of treatment, observation or experiment. Herein after, the term “pediatric subject” means human subject in neonatal period, infancy, toddler, Childhood (School age), adolescence and young adulthood. The terms “subject” or “patient” are used herein interchangeably and as used herein, refer to a human being, who has been the object of treatment, observation or experiment.

[0113] In an embodiment, the term “pediatric epilepsy-related syndrome” refers to onset of epilepsy syndromes in the periods of developmental period, infant, the childhood which means usually the birth to age 12, and adolescence. These may be divided into the epileptic encephalopathies of infancy and early childhood, febrile convulsions, and benign partial and generalized syndromes of later childhood and adolescence.

[0114] The examples of the pediatric epilepsy and the pediatric epilepsy-related syndromes are listed as Epilepsy syndromes according to usual age at onset in Epilepsia. 1996; 37 Suppl 1:S26-40. Particularly, the examples of the pediatric epilepsy and the pediatric epilepsy-related syndromes include benign myoclonic epilepsy of infancy, benign partial epilepsy of infancy with complex partial seizure, benign partial epilepsy with secondarily generalized seizures in infancy, benign infantile familial convulsions, infantile spasm, Lennox-Gastaut syndrome, Childhood absence epilepsy, West’s syndrome, Rolandic epilepsy, benign focal epilepsy of childhood, childhood occipitolepental lobe epilepsy of childhood, Juvenile absence epilepsy, and Juvenile myoclonic epilepsy.

[0115] In an embodiment, the pediatric epilepsy or a pediatric epilepsy-related syndrome is selected from the group consisting of Benign Myoclonic Epilepsy(BME), Severe Myoclonic Epilepsy of Infancy Borderland(SMEB), Severe Infantile Multifocal Epilepsies(SIME), and Intractable Childhood Epilepsy with Generalized Tonic Clonic Seizures(ICEGTC), Dravet syndrome(Ds), Severe Myoclonic Epilepsy of Infancy (SMEI), Benign neonatal convulsions, Benign neonatal familial convulsions, Miscellaneous neonatal seizures, Febrile seizures, Early infantile epileptic encephalopathy, Early myoclonic encephalopathy, Infantile spasms, West syndrome, Severe myoclonic epilepsy of infancy, Benign myoclonic epilepsy of infancy, Benign partial epilepsy of infancy, Benign infantile familial convulsion, Symptomatic/cryptogenic partial epilepsies, Epilepsy with myoclonic absence, Lennox-Gastaut syndrome, Epilepsy with myoclonic-astatic seizures (Doose syndrome), Acquired epileptic aphasia (Landau-Kleffner syndrome), Epilepsy with continuous spike-wave during slow-wave sleep, Epilepsy with gastric seizures and hypothalamic hamartoma, Symptomatic/cryptogenic partial epilepsies, and Childhood absence epilepsy.
Lithium-pilocarpine induced Status epilepticus (SE) is a frequent neurologic emergency. SE is common in infants and toddlers, with more than 50% of cases of SE occurring under the age of 2 years. SE is associated with an increased risk of developing epilepsy. 30% of children presenting with SE were found to develop epilepsy subsequently. More recently, 41% of patients with acute symptomatic SE (one-third were children) developed epilepsy within the next 10 years. (Treatment of Experimental Status Epilepticus in Immature Rats; Dissociation Between Anticonvulsant and Antiepileptogenic Effects (2006), PEDIATRIC RESEARCH, SUCHOMELOVA et al.).

Picotroxin is thought to induce generalised convulsive seizures (Picotroxin-induced generalized convulsive seizure in rats: changes in regional distribution and frequency of the power of electroencephalogram rhythms (2002), Clin Neurophysiol. April; 113(4):586-96, MacKenzie L et al.)

PTZ test is thought to be predictive of anticonvulsant drug activity against nonconvulsive (absence or myoclonic) seizures (Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs (2011), Seizure 20, 359-368, Wolfgang Loscher). 61Hz test is Minimal Cronic Seizure. Multiple-hit rat model of IS is thought to be predictive of ACTH (Adrenocorticotropic hormone)-refractory infantile spasms, may be Lennox-Gastaut syndrome and West syndrome because Children with infantile spasms present typically between 4 and 18 months of age (U.S. Pat. No. 7,863,499).

Lennox-Gastaut syndrome has an onset between 3 and 5 years of age and is characterized by intractable mixed seizures with a combination of tonic, myoclonic, atonic, and absence seizures. Children between 3 and 13 years of age who suffer from benign rolandic epilepsy experience nighttime seizures during sleep. Juvenile myoclonic epilepsy of Jezus is inherited as an autosomal dominant trait that manifests in early adolescence (onset 12-18 years of age). Patients experience myoclonic jerks typically on awakening but may also have tonic-clonic (80%) or absence (25%) seizures. Children with infantile spasms or West’s syndrome present typically between 4 and 18 months of age.

West syndrome is an epileptic syndrome characterized by the triad of infantile spasm (generalized seizures), hypsarrhythmia (chaotic, abnormal EEG pattern), and arrest of psychomotor development at seizure onset (Wong & Trevathan, 2001). It occurs in approximately 0.7/100,000 people and accounts for 28-30% of infants with epilepsy. The age of onset is usually around 3 to 12 months with peak at 4-7 months (Dulac, 2001). Males tend to be at a greater risk of acquiring West syndrome than females. A family history of infantile spasms is reported in 3-6% of cases. Prenatal causes of West syndrome include tuberous sclerosis, intraterine infections, brain malformations, and inborn errors of metabolism. Postnatal causes include cerebral hypoxic events, head trauma, and infections. Cognitive impairment is found in approximately 60-70% of patients at onset of infantile spasms. The seizure characteristics found in West syndrome include a sudden onset of a tonic seizure that is bilateral and symmetrical. The spasms may vary from massive contractions of large muscle groups to contractions of only neck and abdominal muscles. A patient may have more than one type of spasm and they tend to occur in clusters of 5-10 individual spasms. An aura or warning signal such as a cry may precede the seizure. Approximately 30% of symptomatic West syndrome patients progress to Lennox Gastaut syndrome. Treatment for West syndrome includes hormonal therapy with adrenocorticotropic hormone (ACTH) or prednisone (Snead, 1996).

Infantile spasm syndrome, or infantile spasms (IS), represents an age-related epileptic syndrome characterized by brief spasms, specific EEG patterns [hypsarrhythmia (interictal) and electrodermal response (ictally)], with frequent subsequent cognitive deterioration. The incidence of IS is 2.5 per 10,000 live births (Bobo et al., 1994; Hrachovy and Frost, 2003) with a slight (60%) male predominance (Webb et al., 1996). The causes of IS are diverse and can be multifactorial, often a combination of genetic predisposition (Mizukawa et al., 1992; Bingham et al., 1996; Dulac et al., 1993a) and environmental insults (Watanabe, 1998). IS can be classified into symptomatic, cryptogenic and idiopathic groups.

The ILAE classification, 8 typical form of DS (Dravet syndrome), is defined by a refractory and mixed seizure disorder (most commonly myoclonus, atypical absence, and partial seizures) which starts after different types of febrile and afebrile seizures in an otherwise, healthy infant. In the second year of life, the child develops cognitive and behavioral difficulties (Dravet syndrome, what is new? (2013), Neurosciences, Raidah S. Al-Baradie).

The pharmaceutical composition may be formulated in various forms for oral or parenteral administration. For example, the pharmaceutical composition may be formulated in the oral administration form, such as a tablet, pill, soft or hard capsule, liquid, suspension, emulsion, syrup, granules, elixirs, and the like. In addition to the active ingredient, the oral administration form may further include pharmaceutically acceptable and conventional components, for example, a diluent such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerine, and the like; a lubricant such as silica, talc, stearic acid, magnesium or calcium salt thereof, polyethylene glycol, and the like. In the case that the oral administration form is a tablet, it may further include a binder such as magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone, and the like; and optionally include one or more additives selected from the group consisting of a disintegrant such as starch, agar, arabinose or sodium salt thereof, an absorbent, a colorant, a flavoring, a sweetener, and the like. Alternatively, the pharmaceutical composition may also be formulated in a parenteral administration form, which can be administered by subcutaneous injection, intravenous injection, intramuscular injection, injection into thoracic cavity, and the like. In order to formulate the parenteral administration form, the pharmaceutical composition may be prepared as a solution or suspension wherein the active ingredient is dissolved in water together with a stabilizer and/or a buffering agent, and such solution or suspension formulation may be prepared as a dosage form in ampule or vial.

The pharmaceutical composition may be sterilized, and/or include further additives such as a preservative, a stabilizer, a hydrating agent, an emulsification accelerator, a salt and/or buffering agent for osmoregulation, and the like, and/or further therapeutically effective ingredients. The pharmaceutical composition may be formulated by any conventional method for mixing, granulating, coating, and the like.
The pharmaceutical composition may be administered to a mammal including human, in the pharmaceutically effective amount of 0.01 to 750 mg/kg (body weight), preferably 0.1 to 500 mg/kg (body weight) per one day, based on the active ingredient. The pharmaceutically effective amount may refer to an amount capable of exhibiting a desired effect, i.e., an effect of treating and/or preventing epilepsy. The pharmaceutically effective amount may be administered through oral or parenteral pathway (e.g., an intravenous injection, an intramuscular injection, etc.). one or two or more times per one day. The pharmaceutically effective amount and the administration pathway of the present pharmaceutical composition may be properly adjusted by a person skilled in the relevant field considering the conditions of the subject (patient), desired effects, and the like. The subject may be a mammal including human or cells and/or tissues obtained therefrom.

**BRIEF DESCRIPTION OF DRAWINGS**

**EXAMPLE**

The present invention is further explained in more detail with reference to the following examples. These examples, however, should not be interpreted as limiting the scope of the present invention in any manner.

**Preparation Example 1**

Synthesis of 1-(2-chlorophenyl)-trans-1-propene

48 ml of 2-chlorobenzaldehyde (0.42 mol) and 49.7 ml of 3-pentanone (0.47 mol) were dissolved in 600 mL of hexane in flask, and then stirred with raising the temperature. 53.6 ml of Boron trifluoride ethere (BF₃·Et₂O, 0.42 mol) was added to the resultant under reflux conditions. When the reaction was completed, water was added thereto. After layer separation, the obtained organic layer was washed twice with 1M sodium hydroxide solution (1M NaOH), and then the separated organic layer was washed with water. The separated organic layer was dehydrated with anhydrous magnesium sulfate (MgSO₄) and concentrated. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (38 g, yield 58%). $^1$H NMR (400 MHz, CDCl₃) δ 7.96 (d, J=4.8 Hz, 3H), 6.24 (m, 1H), 6.78 (d, J=14 Hz, 3H), 7.11–7.51 (m, 4H)

**Preparation Example 2**

Synthesis of 1-(2-chlorophenyl)-trans-1-butene

The substantially same method as described in Preparation Example 1 was conducted, except that 3-heptanone was used instead of 3-pentanone, to obtain the title compound (2.9 g, yield 83%). $^1$H NMR (400 MHz, CDCl₃) δ 7.14 (d, J=7.6 Hz, 3H), 2.29–2.33 (m, 2H), 6.28 (dt, J=16 Hz, 6.4 Hz, 1H), 6.78 (d, J=15.6 Hz, 1H), 7.13–7.54 (m, 4H)

**Preparation Example 3**

Synthesis of 1-(2-chlorophenyl)-3-methyl-trans-1-butene

The substantially same method as described in Preparation Example 1 was conducted, except that 2,6-dimethyl-3-heptanone was used instead of 3-pentanone, to obtain the title compound (8.0 g, yield 50–90%). $^1$H NMR (400 MHz, CDCl₃) δ 7.14 (d, J=6.8 Hz, 6H), 2.25–2.57 (m, 2H), 6.20 (dd, J=16 Hz, 7.2 Hz, 1H), 7.64 (d, J=16 Hz, 1H), 7.12–7.54 (m, 4H)

**Preparation Example 4**

Synthesis of 1-(2-chlorophenyl)-trans-1-hexene

The substantially same method as described in Preparation Example 1 was conducted, except that 6-undecanone was used instead of 3-pentanone, to obtain the title compound (10 g, yield 85%). $^1$H NMR (400 MHz, CDCl₃) δ 80.96 (t, J=7.2 Hz, 3H), 1.33–1.56 (m, 4H), 2.26–2.32 (m, 4H), 6.24 (dt, J=15.6 Hz, 7 Hz, 1H), 6.78 (d, J=16 Hz, 1H), 7.13–7.54 (m, 4H)
Preparation Example 5
Synthesis of 1-(2,4-dichlorophenyl)-trans-1-propene

The substantially same method as described in Preparation Example 1 was conducted, except that 2,4-dichlorobenzaldehyde was used instead of 2-chlorobenzaldehyde, to obtain the title compound (2.4 g, yield 57%).

1H NMR (400 MHz, CDCl₃) δ 8.95 (dd, J=6.8 Hz, 1.6 Hz, 3H), 6.24 (d, J=15.6 Hz, 1H), 7.18–7.44 (m, 3H)

Preparation Example 6
Synthesis of 1-(2,4-dichlorophenyl)-trans-1-butene

The substantially same method as described in Preparation Example 5 was conducted, except that 3-heptanone was used instead of 3-pentanone, to obtain the title compound (2.1 g, yield 90%).

1H NMR (400 MHz, CDCl₃) δ 1.14 (d, J=7.6 Hz, 3H), 2.20–2.33 (m, 2H), 6.26 (dt, J=16 Hz, 6.8 Hz, 1H), 6.70 (d, J=15.6 Hz, 1H), 7.18–7.46 (m, 3H)

Preparation Example 7
Synthesis of 1-(2,4-dichlorophenyl)-3-methyl-trans-1-butene

The substantially same method as described in Preparation Example 5 was conducted, except that 2,6-dimethylheptan-4-one was used instead of 3-pentanone, to obtain the title compound (0.23 g, yield 10–40%).

1H NMR (400 MHz, CDCl₃) δ 1.15 (d, J=6.8 Hz, 6H), 2.53–2.58 (m, 1H), 6.19 (dd, J=16.4 Hz, 6.8 Hz, 1H), 6.31 (d, J=16.4 Hz, 1H), 7.18–7.46 (m, 3H)

Preparation Example 8
Synthesis of 1-(2,4-dichlorophenyl)-trans-1-hexene

The substantially same method as described in Preparation Example 5 was conducted, except that 6-undecanone was used instead of 3-pentanone, to obtain the title compound (3.2 g, yield 40–80%).

1H NMR (400 MHz, CDCl₃) δ 8.96 (t, J=7.2 Hz, 3H), 1.38–1.52 (m, 4H), 2.25–2.31 (m, 2H), 6.22 (dt, J=15.6 Hz, 6.8 Hz, 1H), 6.70 (d, J=15.6 Hz, 1H), 7.18–7.46 (m, 3H)

Preparation Example 9
Synthesis of 1-(2,6-dichlorophenyl)-trans-1-propene

The substantially same method as described in Preparation Example 1 was conducted, except that 2,6-dichlorobenzaldehyde was used instead of 2-chlorobenzaldehyde, to obtain the title compound (0.4 g, yield 10–40%).

1H NMR (400 MHz, CDCl₃) δ 1.98 (d, J=8 Hz, 3H), 6.23–6.31 (m, 1H), 6.40 (d, J=16 Hz, 1H), 7.05–7.32 (m, 3H)

Preparation Example 10
Synthesis of 1-(2,6-dichlorophenyl)-3-methyl-trans-1-butene

The substantially same method as described in Preparation Example 9 was conducted, except that 3-heptanone was used instead of 3-pentanone, to obtain the title compound (1.2 g, yield 10–40%).

1H NMR (400 MHz, CDCl₃) δ 1.17 (t, J=7.6 Hz, 3H), 2.30–2.37 (m, 2H), 6.29 (dt, J=16.4 Hz, 6 Hz, 1H), 6.57 (d, J=16.4 Hz, 1H), 7.05–7.32 (m, 3H)
Preparation Example 11

Synthesis of 1-(2,6-dichlorophenyl)-3-methyl-trans-1-butene

The substantially same method as described in Preparation Example 9 was conducted, except that 2,6-dimethyl-heptan-4-one was used instead of 3-pentanone, to obtain the title compound (0.23 g, yield 10–40%).

\[ \text{H NMR (400 MHz, CDCl}_3\):} 8 1.15 (d, J=6.8 Hz, 6H), 2.53–2.58 (m, 1H), 6.19 (dd, J=16.4 Hz, 6.8 Hz, 1H), 6.31 (d, J=16.4 Hz, 1H), 7.05–7.32 (m, 3H)

Preparation Example 12

Synthesis of 1-(2,6-dichlorophenyl)-trans-1-hexene

The substantially same method as described in Preparation Example 9 was conducted, except that 6-undecanone was used instead of 3-pentanone, to obtain the title compound (0.2 g, yield 10–40%).

\[ \text{H NMR (400 MHz, CDCl}_3\):} 8 0.99 (t, J=7.2 Hz, 3H), 1.14–1.59 (m, 4H), 2.30–2.36 (m, 2H), 6.24 (dt, J=16 Hz, 6.6 Hz, 1H), 6.38 (d, J=16.4 Hz, 1H), 7.05–7.33 (m, 3H)

Preparation Example 13

Synthesis of 1-(2,3-dichlorophenyl)-trans-1-propene

The substantially same method as described in Preparation Example 1 was conducted, except that 2,3-dichlorobenzaldehyde was used instead of 2-chlorobenzaldehyde, to obtain the title compound (0.2 g, yield 10–40%).

\[ \text{H NMR (400 MHz, CDCl}_3\):} 8 1.94 (d, J=4.8 Hz, 3H), 6.24 (m, 1H), 6.78 (d, J=14 Hz, 1H), 7.11–7.51 (m, 3H)

Preparation Example 14

Synthesis of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol

1-(2-chlorophenyl)-trans-1-propene (1.5 g, Preparation Example 1) was dissolved in 30 mL of the mixture of t-BuOH/H$_2$O (1:1 V/V). At 0°C, AD-mix-ε (Aldrich, U.S. A.) (13.7 g) and methane sulfonamide (CH$_3$SO$_2$NH$_2$, 0.76 g, 0.0080 mol) were added thereto and stirred for overnight. When the reaction was completed, the obtained product was washed with an aqueous solution of sodium sulfite (Na$_2$SO$_3$) and ethylacetate (EA). Then, the organic layer was dehydrated with anhydrous magnesium sulfate (MgSO$_4$), filtrated, and concentrated under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (1.65 g, yield 90%).

\[ \text{H NMR (400 MHz, CDCl}_3\):} 8 1.15 (t, J=4.0 Hz, 1H), 2.92 (d, J=4.4 Hz, 1H), 3.93–3.97 (m, 1H), 4.97 (t, J=4.8 Hz, 1H), 7.12–7.51 (m, 4H)

Preparation Example 15

Synthesis of 1-(2-chlorophenyl)-(R,R)-1,2-propanediol

1-(2-chlorophenyl)-trans-1-propene (2.5 g, Preparation Example 1) was dissolved in 50 mL of the mixture of t-BuOH/H$_2$O (1:1 V/V). At 0°C, AD-mix-ε (Aldrich, U.S. A.) (23.5 g) and methane sulfonamide (CH$_3$SO$_2$NH$_2$, 1.27 g, 0.013 mol) were added thereto and stirred for overnight. When the reaction was completed, the obtained product was washed with an aqueous solution of sodium sulfite (Na$_2$SO$_3$) and ethylacetate (EA). Then, the organic layer was dehydrated with anhydrous magnesium sulfate (MgSO$_4$), filtrated, and concentrated under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (2.96 g, yield 90%).

\[ \text{H NMR (400 MHz, CDCl}_3\):} 8 1.15 (t, J=4.0 Hz, 1H), 2.92 (d, J=4.4 Hz, 1H), 3.93–3.97 (m, 1H), 4.97 (t, J=4.8 Hz, 1H), 7.12–7.51 (m, 4H)
Preparation Example 16

Synthesis of the mixture of 1-(2-chlorophenyl)-(S, S)-1,2-propanediol and 1-(2-chlorophenyl)-(R,R)-1,2-propanediol

1-(2-chlorophenyl)-trans-1-propene (6.53 g, Preparation Example 1) was dissolved in 45 mL of the mixture of acetone/8-BuOH/H$_2$O (5:1:1 V/V). At the room temperature, N-methylmorpholine-N-oxide (7.51 g) and OsO$_4$ (0.54 g) were added thereto and stirred for 2-3 hours. When the reaction was completed, the obtained product was washed with water and methylenechloride (MC). Then, the organic layer was dehydrated with anhydrous magnesium sulfate (MgSO$_4$), filtrated, and concenred under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (6.42 g, yield 80%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.20 (d, J=6.4 Hz, 3H), 2.48 (d, J=4.0 Hz, 1H), 2.92 (d, J=4.4 Hz, 1H), 3.93–3.97 (m, 1H), 4.97 (t, J=4.8 Hz, 1H), 7.22–7.51 (m, 4H)

Preparation Example 17

Synthesis of 1-(2-chlorophenyl)-(S,S)-1,2-butanediol

The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2-chlorophenyl)-trans-1-butene (Preparation Example 2) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (5.1 g, yield 60–90%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.01 (t, J=7.4 Hz, 3H), 1.52–1.65 (m, 2H), 2.01 (d, J=4.4 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.69–3.75 (m, 1H), 5.05 (t, J=5.0 Hz, 1H), 7.23–7.54 (m, 4H)

Preparation Example 18

Synthesis of 1-(2-chlorophenyl)-(R,R)-1,2-butanediol

The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2-chlorophenyl)-trans-1-butene (Preparation Example 2) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.84 g, yield 60–95%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.01 (t, J=7.4 Hz, 3H), 1.52–1.65 (m, 2H), 2.01 (d, J=4.4 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.69–3.75 (m, 1H), 5.05 (t, J=5.0 Hz, 1H), 7.23–7.54 (m, 4H)

Preparation Example 19

Synthesis of the mixture of 1-(2-chlorophenyl)-(S, S)-1,2-butanediol and 1-(2-chlorophenyl)-(R,R)-1,2-butanediol

The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2-chlorophenyl)-trans-1-butene (Preparation Example 2) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.36 g, yield 95%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.01 (t, J=7.4 Hz, 3H), 1.52–1.65 (m, 2H), 2.01 (d, J=4.4 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.69–3.75 (m, 1H), 5.05 (t, J=5.0 Hz, 1H), 7.23–7.54 (m, 4H)

Preparation Example 20

Synthesis of 1-(2-chlorophenyl)-3-methyl-(S,S)-1,2-butanediol

The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2-chlorophenyl)-trans-1-butene (Preparation Example 2) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.84 g, yield 60–95%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.01 (t, J=7.4 Hz, 3H), 1.52–1.65 (m, 2H), 2.01 (d, J=4.4 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.69–3.75 (m, 1H), 5.05 (t, J=5.0 Hz, 1H), 7.23–7.54 (m, 4H)
[0187] The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2-chlorophenyl)-3-methyl-trans-1-butene (Preparation Example 3) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.96 g, yield 60–90%).

[0188] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 1.07 (t, J=7.2 Hz, 6H), 1.83–1.89 (m, 1H), 1.92 (d, J=5.6 Hz, 1H), 2.69 (d, J=6.4 Hz, 1H), 3.53–3.56 (m, 1H), 5.22–5.25 (m, 1H), 7.23–7.55 (m, 4H)

Preparation Example 21

Synthesis of 1-(2-chlorophenyl)-3-methyl-(R,R)-1,2-butanediol

[0189]

[0190] The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2-chlorophenyl)-3-methyl-trans-1-butene (Preparation Example 3) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (4.2 g, yield 60–90%).

[0191] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 1.07 (t, J=7.2 Hz, 6H), 1.82–1.90 (m, 1H), 1.93 (d, J=5.6 Hz, 1H), 2.79 (d, J=6 Hz, 1H), 3.53–3.57 (m, 1H), 5.23–5.25 (m, 1H), 7.23–7.54 (m, 4H)

Preparation Example 22

Synthesis of the mixture of 1-(2-chlorophenyl)-3-methyl-(S,S)-1,2-butanediol and 1-(2-chlorophenyl)-3-methyl-(R,R)-1,2-butanediol

[0192]

[0193] The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2-chlorophenyl)-3-methyl-trans-1-butene (Preparation Example 3) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.8 g, yield 60–90%).

[0194] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 1.07 (t, J=7.2 Hz, 6H), 1.83–1.90 (m, 1H), 1.92 (d, J=5.6 Hz, 1H), 2.69 (d, J=6.4 Hz, 1H), 3.53–3.56 (m, 1H), 5.22–5.25 (m, 1H), 7.23–7.55 (m, 4H)

Preparation Example 23

Synthesis of 1-(2-chlorophenyl)-(S,S)-1,2-hexanediol

[0195]

[0196] The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2-chlorophenyl)-trans-1-hexene (Preparation Example 4) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 4), to obtain the title compound (0.37 g, yield 90%).

[0197] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 90.90 (t, J=7.2 Hz, 3H), 1.35–1.65 (m, 6H), 2.08 (d, J=4.4 Hz, 1H), 2.71 (d, J=5.2 Hz, 1H), 3.78–3.83 (m, 1H), 5.04 (t, J=5.0 Hz, 1H), 7.23–7.53 (m, 4H)

Preparation Example 24

Synthesis of 1-(2-chlorophenyl)-(R,R)-1,2-hexanediol

[0198]

[0199] The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2-chlorophenyl)-trans-1-hexene (Preparation Example 4) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 4), to obtain the title compound (4.2 g, yield 60–90%).

[0200] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 90.91 (t, J=6.6 Hz, 3H), 1.35–1.65 (m, 6H), 2.08 (d, J=4.8 Hz, 1H), 2.70 (d, J=5.2 Hz, 1H), 3.80–3.83 (m, 1H), 5.05 (t, J=5.0 Hz, 1H), 7.24–7.56 (m, 4H)

Preparation Example 25

Synthesis of the mixture of 1-(2-chlorophenyl)-(S,S)-1,2-hexanediol and 1-(2-chlorophenyl)-(R,R)-1,2-hexanediol

[0201]

[0202] The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2-chlorophenyl)-trans-1-hexene (Preparation Example 4) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 4), to obtain the title compound (0.8 g, yield 60–90%).

[0203] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \delta 1.07 (t, J=7.2 Hz, 6H), 1.83–1.90 (m, 1H), 1.92 (d, J=5.6 Hz, 1H), 2.69 (d, J=6.4 Hz, 1H), 3.53–3.56 (m, 1H), 5.22–5.25 (m, 1H), 7.23–7.55 (m, 4H)
[0202] The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2-chlorophenyl)-trans-1-hexene (Preparation Example 4) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (7.9 g, yield 60–90%).

[0203] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.22 (d, J=6.4 Hz, 3H), 2.10 (d, J=4.4 Hz, 1H), 2.71 (d, J=4.8 Hz, 1H), 3.90–3.95 (m, 1H), 4.94 (t, J=5.0 Hz, 1H), 7.31–7.49 (m, 3H).

Preparation Example 26

Synthesis of 1-(2,4-dichlorophenyl)-(S,S)-1,2-propanediol

[0204]

[0205] The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,4-dichlorophenyl)-trans-1-propene (Preparation Example 5) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.33 g, yield 60–95%).

[0206] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.22 (d, J=6.4 Hz, 3H), 2.10 (d, J=4.4 Hz, 1H), 2.71 (d, J=4.8 Hz, 1H), 3.90–3.95 (m, 1H), 4.94 (t, J=5.0 Hz, 1H), 7.31 (dd, J=2.0 Hz, J=8.0 Hz, 1H), 7.40 (d, J=2.0 Hz, 1H), 7.49 (d, J=8.4 Hz, 1H).

Preparation Example 27

Synthesis of 1-(2,4-dichlorophenyl)-(R,R)-1,2-propanediol

[0207]

[0208] The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2,4-dichlorophenyl)-trans-1-butene (Preparation Example 6) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.32 g, yield 90%).

[0211] The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2,4-dichlorophenyl)-trans-1-propene (Preparation Example 5) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.45 g, yield 60–95%).

[0212] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.22 (d, J=6.4 Hz, 3H), 2.10 (d, J=4.4 Hz, 1H), 2.71 (d, J=4.8 Hz, 1H), 3.90–3.95 (m, 1H), 4.94 (t, J=5.0 Hz, 1H), 7.31–7.49 (m, 3H).

Preparation Example 29

Synthesis of 1-(2,4-dichlorophenyl)-(S,S)-1,2-butanediol

[0213]

[0214] The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,4-dichlorophenyl)-trans-1-butene (Preparation Example 6) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.32 g, yield 90%).

[0215] \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.02 (t, J=7.4 Hz, 3H), 1.54–1.61 (m, 2H), 2.07 (d, J=4.8 Hz, 1H), 2.74 (d, J=4.8 Hz, 1H), 3.65–3.68 (m, 1H), 5.01 (t, J=5.0 Hz, 1H), 7.31–7.49 (m, 3H).
Preparation Example 30
Synthesis of 1-(2,4-dichlorophenyl)-(R,R)-1,2-butanediol

The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2,4-dichlorophenyl)-trans-1-butene (Preparation Example 6) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.43 g, yield 60–90%).

Preparation Example 31
Synthesis of the mixture of 1-(2,4-dichlorophenyl)-(S,S)-1,2-butanediol and 1-(2,4-dichlorophenyl)-(R,R)-1,2-butanediol

The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2,4-dichlorophenyl)-trans-1-butene (Preparation Example 6) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.33 g, yield 60–90%).

Preparation Example 32
Synthesis of 1-(2,4-dichlorophenyl)-3-methyl-(S,S)-1,2-butanediol

1H NMR (400 MHz, CDCl₃) δ 1.02 (t, J=7.4 Hz, 3H), 1.54–1.61 (m, 2H), 2.07 (d, J=4.8 Hz, 1H), 2.74 (d, J=4.8 Hz, 1H), 3.65–3.68 (m, 1H), 5.01 (t, J=5.0 Hz, 1H), 7.31–7.49 (m, 3H)

Preparation Example 33
Synthesis of 1-(2,4-dichlorophenyl)-3-methyl-(R,R)-1,2-butanediol

1H NMR (400 MHz, CDCl₃) δ 1.00 (t, J=6.8 Hz, 3H), 1.60–1.65 (m, 1H), 2.35 (d, J=4.0 Hz, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.13–4.18 (m, 1H), 5.36 (t, J=7.6 Hz, 1H), 7.17–7.35 (m, 3H)
Preparation Example 34

Synthesis of the mixture of 1-(2,4-dichlorophenyl)-3-methyl-(S,S)-1,2-butanediol and 1-(2,4-dichlorophenyl)-3-methyl-(R,R)-1,2-butanediol

1H NMR (400 MHz, CDCl₃) δ 81.00 (d, J=6.8 Hz, 6H), 1.60–1.65 (m, m, 1H), 2.35 (d, J=4.0 Hz, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.13–4.18 (m, 1H), 5.36 (t, J=7.6 Hz, 1H), 7.17–7.35 (m, 3H)

Preparation Example 35

Synthesis of 1-(2,4-dichlorophenyl)-(S,S)-1,2-hexanediol

1H NMR (400 MHz, CDCl₃) δ 80.89–0.93 (m, 3H), 1.30–1.39 (m, 2H), 1.49–1.52 (m, 2H), 1.56–1.62 (m, 2H), 2.05 (d, J=5.2 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.72–3.77 (m, 1H), 4.98 (t, J=4.8 Hz, 1H), 7.28–7.50 (m, 3H)

Preparation Example 36

Synthesis of 1-(2,4-dichlorophenyl)-(R,R)-1,2-hexanediol

1H NMR (400 MHz, CDCl₃) δ 80.89–0.93 (m, 3H), 1.30–1.39 (m, 2H), 1.49–1.52 (m, 2H), 1.56–1.62 (m, 2H), 2.05 (d, J=5.2 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.72–3.77 (m, 1H), 4.98 (t, J=4.8 Hz, 1H), 7.28–7.50 (m, 3H)

Preparation Example 37

Synthesis of the mixture of 1-(2,4-dichlorophenyl)-(S,S)-1,2-hexanediol and 1-(2,4-dichlorophenyl)-(R,R)-1,2-hexanediol

1H NMR (400 MHz, CDCl₃) δ 80.89–0.93 (m, 3H), 1.30–1.39 (m, 2H), 1.49–1.52 (m, 2H), 1.56–1.62 (m, 2H), 2.05 (d, J=5.2 Hz, 1H), 2.74 (d, J=5.2 Hz, 1H), 3.72–3.77 (m, 1H), 4.98 (t, J=4.8 Hz, 1H), 7.28–7.50 (m, 3H)
Preparation Example 38

Synthesis of 1-(2,6-dichlorophenyl)-(S,S)-1,2-propanediol

The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,6-dichlorophenyl)-trans-1-propene (Preparation Example 9) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.91 g, yield 60–90%).

1H NMR (400 MHz, CDCl₃) δ 1.10 (d, J=6.4 Hz, 3H), 2.72 (d, J=2.4 Hz, 1H), 3.10 (d, J=8.4 Hz, IH), 4.47–4.54 (m, 1H), 5.24 (t, J=8.8 Hz, 1H), 7.18–7.36 (m, 3H)

Preparation Example 39

Synthesis of 1-(2,6-dichlorophenyl)-(R,R)-1,2-propanediol

The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2,6-dichlorophenyl)-trans-1-propene (Preparation Example 9) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.84 g, yield 60–90%).

1H NMR (400 MHz, CDCl₃) δ 1.10 (d, J=6.4 Hz, 3H), 2.72 (d, J=2.4 Hz, 1H), 3.10 (d, J=8.4 Hz, IH), 4.47–4.54 (m, 1H), 5.24 (t, J=8.8 Hz, 1H), 7.18–7.36 (m, 3H)

Preparation Example 40

Synthesis of the mixture of 1-(2,6-dichlorophenyl)-(S,S)-1,2-propanediol and 1-(2,6-dichlorophenyl)-(R,R)-1,2-propanediol

The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,6-dichlorophenyl)-trans-1-propene (Preparation Example 9) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.96 g, yield 60–95%).

1H NMR (400 MHz, CDCl₃) δ 0.97 (t, J=7.6 Hz, 3H), 1.26–1.53 (m, 2H), 2.64 (dd, J=6.8 Hz, J=4.0 Hz, 1H), 3.14 (d, J=8.4 Hz, 1H), 4.22–4.26 (m, 1H), 5.26 (t, J=8.4 Hz, 1H), 7.17–7.35 (m, 3H)
Preparation Example 43

Synthesis of the mixture of 1-(2,6-dichlorophenyl)-(S,S)-1,2-butanediol and 1-(2,6-dichlorophenyl)-(R,R)-1,2-butanediol

[0254] $^1$H NMR (400 MHz, CDCl$_3$) δ 0.97 (t, J=7.6 Hz, 3H), 1.26–1.53 (m, 2H), 2.64 (dd, J=0.8 Hz, J=4.0 Hz, 1H), 3.14 (d, J=8.4 Hz, 1H), 4.22–4.26 (m, 1H), 5.26 (t, J=8.4 Hz, 1H), 7.17–7.35 (m, 3H)

Preparation Example 44

Synthesis of 1-(2,6-dichlorophenyl)-3-methyl-(S,S)-1,2-butanediol

[0255] $^1$H NMR (400 MHz, CDCl$_3$) δ 0.97 (t, J=7.6 Hz, 3H), 1.26–1.53 (m, 2H), 2.64 (dd, J=0.8 Hz, J=4.0 Hz, 1H), 3.14 (d, J=8.4 Hz, 1H), 4.22–4.26 (m, 1H), 5.26 (t, J=8.4 Hz, 1H), 7.17–7.35 (m, 3H)

Preparation Example 45

Synthesis of 1-(2,6-dichlorophenyl)-3-methyl-(R,R)-1,2-butanediol

[0261]

Preparation Example 46

Synthesis of the mixture of 1-(2,6-dichlorophenyl)-(S,S)-1,2-butanediol and 1-(2,6-dichlorophenyl)-3-methyl-(R,R)-1,2-butanediol

[0262] The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-trans-1-butene (Preparation Example 11) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.37 g, yield 60–95%).

[0263] $^1$H NMR (400 MHz, CDCl$_3$) δ 1.00 (d, J=6.8 Hz, 6H), 1.60–1.65 (m, 1H), 2.35 (d, J=4.0 Hz, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.13–4.18 (m, 1H), 5.36 (t, J=7.6 Hz, 1H), 7.17–7.35 (m, 3H)

Preparation Example 47

Synthesis of 1-(2,6-dichlorophenyl)-(S,S)-1,2-hexanediol

[0264] The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-trans-1-butene (Preparation Example 11) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.47 g, yield 60–95%).

[0265] $^1$H NMR (400 MHz, CDCl$_3$) δ 1.00 (d, J=6.8 Hz, 6H), 1.60–1.65 (m, 1H), 2.35 (d, J=4.0 Hz, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.13–4.18 (m, 1H), 5.36 (t, J=7.6 Hz, 1H), 7.17–7.35 (m, 3H)

Preparation Example 48

Synthesis of 1-(2,6-dichlorophenyl)-(S,S)-1,2-hexanediol

[0267] The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-trans-1-butene (Preparation Example 11) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.25 g, yield 60–95%).

[0266] $^1$H NMR (400 MHz, CDCl$_3$) δ 1.00 (d, J=6.8 Hz, 6H), 1.60–1.65 (m, 1H), 2.35 (d, J=4.0 Hz, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.13–4.18 (m, 1H), 5.36 (t, J=7.6 Hz, 1H), 7.17–7.35 (m, 3H)
The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,6-dichlorophenyl)-trans-1-hexene (Preparation Example 12) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.36 g, yield 60–90%).

1H NMR (400 MHz, CDCl3) δ 8.05 (t, J=6.8 Hz, 3H), 1.20–1.31 (m, 4H), 1.45–1.53 (m, 2H), 2.61–2.62 (m, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.28–4.33 (m, 1H), 5.25 (t, J=8.4 Hz, 1H), 7.18–7.35 (m, 3H)

Preparation Example 48

Synthesis of 1-(2,6-dichlorophenyl)-(R,R)-1,2-hexanediol

The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2,6-dichlorophenyl)-trans-1-hexene (Preparation Example 12) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.58 g, yield 60–90%).

1H NMR (400 MHz, CDCl3) δ 8.05 (t, J=6.8 Hz, 3H), 1.20–1.31 (m, 4H), 1.45–1.53 (m, 2H), 2.61–2.62 (m, 1H), 3.12 (d, J=8.4 Hz, 1H), 4.28–4.33 (m, 1H), 5.25 (t, J=8.4 Hz, 1H), 7.18–7.35 (m, 3H)

Preparation Example 49

Synthesis of the mixture of 1-(2,6-dichlorophenyl)-(S,S)-1,2-hexanediol and 1-(2,6-dichlorophenyl)-(R,R)-1,2-hexanediol

15 g of (R)-2-chloromandelic acid was mixed with methanol (CH3OH, 150 ml) and phosphorus chloride oxide (POCl3, 0.76 ml) in a flask by stirring using a magnetic stirrer at room temperature for 6 hours. When the reaction was completed, the obtained product was washed with an aqueous solution of sodium sulfite (Na2SO3) and ethyl acetate (EA). Then, the organic layer was dehydrated with anhydrous magnesium sulfate (MgSO4), filtered, and concentrated under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (15.64 g, yield 95%).

1H NMR (400 MHz, CDCl3) δ 3.59 (d, J=5.2, 1H), 3.79 (t, J=6.0, 3H), 5.59 (d, J=5.2, 1H), 7.28–7.43 (m, 4H)

Preparation Example 50

Synthesis of methyl 2-(2-chlorophenyl)-(R)-2-hydroxyacetate

N,O-dimethylhydroxylamine hydrochloride (N,O-dimethylhydroxylamine.HCl, 15.2 g) was dissolved in dichloromethane (DCM, 150 ml), and cooled to 0°C, using an ice-bath. Then, 77.7 ml of 2.0M trimethylaluminium in hexane was slowly added thereto in drop-wise manner for 30 minutes. Thereafter, the ice-bath was removed, and the obtained product was stirred at the room temperature for 2 hours. Methyl-2-(2-chlorophenyl)-(R)-2-hydroxyacetate (15.64 g) dissolved in dichloromethane (DCM, 150 ml) was added in drop-wise manner thereto at the room temperature for 30 minutes, and subjected to reflux for 12 hours. When the reaction was completed, the obtained product was cooled to 0°C, and washed by a slow drop-wise addition of hydrochloric acid (HCl, 200 ml) The obtained organic layer was washed with distilled water and brine, dehydrated with anhydrous magnesium sulfate (MgSO4), filtered, and concentrated
under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (14.68 g, yield 82%).

Preparation Example 52
Synthesis of 2-(2-chlorophenyl)-N-methoxy-(R)-2-(t-butyldimethysiloxy)-N-methylacetamide

2-(2-chlorophenyl)-(R)-2-hydroxy-N-methoxy-N-methylacetamide (0.81 g, 3.52 mmol) obtained in Preparation Example 51 was dissolved in dichloromethane (DCM), and cooled to 0°C. Imidazole (0.36 g, 5.28 mmol) was slowly added, and stirred. TBDMS-Cl (t-butyldimethylsilyl chloride, 0.79 g, 5.28 mmol) was slowly added. When the reaction was completed, the reaction mixture was quenched with H₂O. The organic layer was separated and collected. The aqueous layer was extracted with CH₂Cl₂ (300 mL), dried over MgSO₄. Concentration under vacuum provided a title compound (0.97 g, 80-95%).

Preparation Example 53
Synthesis of 1-(2-chlorophenyl)-(R)-1-(t-butyldimethyl-siloxy)propane-2-on

1-(2-chlorophenyl)-(R)-1-(t-butyldimethyl-siloxy)propane-2-on (0.14 g) obtained in Preparation Example 53 was dissolved in ether, and cooled to −78°C. 8M hydrochloric acid (HCl, 56.2 ml) was slowly added to the obtained product was stirred. When the reaction was completed, the obtained product was washed with H₂O, dehydrated with anhydrous magnesium sulfate (MgSO₄), filtered, and concentrated under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (0.04 g, yield 25-33%, cis:trans ~ 2:1).

Preparation Example 54
Synthesis of 1-(2-chlorophenyl)-(R,S)-1,2-propanediol

1-(2-chlorophenyl)-(R)-1-(t-butyldimethyl-siloxy)-(S)-2-propanol (10.38 g) obtained in Preparation Example 54 was dissolved in methanol (CH₃OH, 100 ml), and then, cooled to 0°C. 8M hydrochloric acid (HCl, 56.2 ml) was slowly added in drop-wise manner to the obtained prod-
uct, and then, the obtained product was warmed to the room temperature, and stirred for 15 hours. When the reaction was completed, the obtained product was cooled to 0°C. 5N sodium hydroxide (NaOH, 30 mL) was slowly added thereto, and the obtained product was subjected to vacuum concentration. The obtained product was diluted with ethylacetate. The obtained organic layer was washed with distilled water, dehydrated with anhydrous magnesium sulfate (MgSO₄), filtered, and concencted under reduced pressure. The concentrated residue was purified by a silica gel column chromatography to produce the title compound (7.05 g, yield 60–90%).

Preparation Example 56
Synthesis of 1-(2-chlorophenyl)-(S,R)-1,2-propanediol

The substantially same method as described in Preparation Example 50–55 was conducted, except that (S)-2-chloromandelic acid was used instead of (R)-2-chloromandelic acid, to obtain the title compound (5.04 g, yield 84%).

Preparation Example 57
Synthesis of 1-(2,3-dichlorophenyl)-(S,S)-1,2-propanediol

The substantially same method as described in Preparation Example 14 was conducted, except that 1-(2,3-dichlorophenyl)-trans-1-propene (Preparation Example 13) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.91 g, yield 60–90%).

Preparation Example 58
Synthesis of 1-(2,3-dichlorophenyl)-(R,R)-1,2-propanediol

The substantially same method as described in Preparation Example 15 was conducted, except that 1-(2,3-dichlorophenyl)-trans-1-propene (Preparation Example 13) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.84 g, yield 60–90%).

Preparation Example 59
Synthesis of the mixture of 1-(2,3-dichlorophenyl)-(S,S)-1,2-propanediol and 1-(2,3-dichlorophenyl)-(R,R)-1,2-propanediol

The substantially same method as described in Preparation Example 16 was conducted, except that 1-(2,3-dichlorophenyl)-trans-1-propene (Preparation Example 13) was used instead of 1-(2-chlorophenyl)-trans-1-propene (Preparation Example 1), to obtain the title compound (0.91 g, yield 60–90%).

Preparation Example 60
Synthesis of 1-(2-fluorophenyl)-trans-1-propene

The substantially same method as described in Preparation Example 1 was conducted, except that 2-fluoro-
robenzenaldehyde was used instead of 2-chlorobenzenaldehyde, to obtain the title compound (6.67 g, yield 61%).

**Preparation Example 61**

**Synthesis of 1-(2-fluorophenyl)-(S,S)-1,2-propanediol**

1 H NMR (400 MHz, CDCl₃) δ 1.94 (d, J=6.8 Hz, 3H), 6.30–6.38 (m, 1H), 6.57 (d, J=16 Hz, 1H), 7.00–7.41 (m, 4H)

**Preparation Example 62**

**Synthesis of 1-(2-fluorophenyl)-(R,R)-1,2-propanediol**

1 H NMR (400 MHz, CDCl₃) δ 1.15 (d, J=6.4 Hz, 3H), 2.43 (d, J=3.6 Hz, 1H), 2.69 (d, J=4.8 Hz, 1H), 3.90–3.98 (m, 1H), 7.04–7.50 (m, 4H)

**Preparation Example 63**

**Synthesis of 2-iodobenzenealdehyde**

In a flask, 2-iodobenzyl alcohol (4 g, 17.09 mmol) was dissolved in dichloromethane (MC, 85 ml), and then, manganese oxide (MnO₂, 14.86 g, 170.92 mmol) was added thereto. The obtained reaction product was stirred under the reflux condition. When the reaction was completed, the obtained reaction product was cooled to the room temperature, and then, sitted and concentrated using celfite, to obtain the title compound (3.6 g, yield 91%).

1 H NMR (400 MHz, CDCl₃) δ 7.30–7.99 (m, 4H)

**Preparation Example 64**

**Synthesis of 1-(2-iodophenyl)-trans-1-propene**

The substantially same method as described in Preparation Example 1 was conducted, except that 2-iodobenzenealdehyde was used instead of 2-chlorobenzenealdehyde, to obtain the title compound (3.4 g, yield 65%).

1 H NMR (400 MHz, CDCl₃) δ 1.95 (dd, J=6.8 Hz, 1.6 Hz, 3H), 6.00–6.18 (m, 1H), 6.60 (dd, J=15.66 Hz, 1.8 Hz, 1H), 6.89–7.84 (m, 4H)

**Preparation Example 65**

**Synthesis of 1-(2-iodophenyl)-trans-1-butene**

The substantially same method as described in Preparation Example 1 was conducted, except that 3-heptanone was used instead of 3-pentanone, to obtain the title compound (8.5 g, yield 75%).
**Preparation Example 66**

Synthesis of 1-(2-iodophenyl)-(S,S)-1,2-propanediol

\[\text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 1.46 \text{ (t, } J=7.6 \text{ Hz, 3H), 2.26-2.34 (m, 2H), 6.17 (dt, } J=15.6 \text{ Hz, 6.6 Hz 1H), 6.57 (d, } J=15.6 \text{ Hz, 1H), 6.89-7.85 (m, 4H)}\]

**Preparation Example 67**

Synthesis of 1-(2-iodophenyl)-(R,R)-1,2-propanediol

\[\text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 1.27 \text{ (d, } J=6.4 \text{ Hz, 3H), 2.26 (brs, 1H), 2.74 (br s, 1H), 3.99 (t, } J=6.0 \text{ Hz, 1H), 4.81 (d, } J=4.0 \text{ Hz, 1H), 7.01-7.87 (m, 4H)}\]

**Preparation Example 68**

Synthesis of 1-(2-iodophenyl)-(S,S)-1,2-butanediol

\[\text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 1.04 \text{ (t, } J=7.6 \text{ Hz, 3H), 1.60-1.71 (m, 2H), 2.07 (br s, 1H), 2.74 (br s, 1H), 3.71-3.76 (m, 1H), 4.87 (d, } J=4.8 \text{ Hz, 1H), 7.01-7.87 (m, 4H)}\]

**Preparation Example 69**

Preparation of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy) propane

\[\text{To a stirred solution of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14, 67 g, 0.35 mol) in CH}_2\text{Cl}_2 (670 ml) was added Et}_3\text{N (200 ml, 1.43 mol) and TMSCl (113.9 ml, 0.89 mol) at 0}^\circ \text{C. Under N}_2. \text{The reaction mixture was allowed to stir at 0}^\circ \text{C for 3 hr.}\]

**Preparation Example 70**

Preparation of 1-(2-chlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy) propane

\[\text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 0.053 \text{ (s, 9H), 0.044 (s, 9H), 1.15 (d, } J=5.6 \text{ Hz, 3H), 3.977-3.918 (m, 1H), 4.973 (d, } J=6.4 \text{ Hz, 1H), 7.207-7.165 (m, 1H), 7.321-7.245 (m, 2H), 7.566-7.543 (m, 1H)}\]
Preparation Example 71
Preparation of 1-(2-chlorophenyl)-1,2-(Bis-trimethylsilyloxy) propane

[0340]

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)propane-1,2-diol (Preparation example 16) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (5.2 g, yield 90–120%).

[0341] ¹H NMR (400 MHz, CDCl₃) δ -0.053 (s, 9H), 0.044 (s, 9H), 1.15 (d, J = 5.6 Hz, 3H), 3.977–3.918 (m, 1H), 4.973 (d, J = 6.4 Hz, 1H), 7.21–7.54 (m, 4H)

Preparation Example 72
Preparation of 1-(2-chlorophenyl)-(S,R)-1,2-(Bis-trimethylsilyloxy) propane

[0343]

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-(S,R)-1,2-propanediol (Preparation example 56) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.4 g, yield 90–120%).

[0344] ¹H NMR (400 MHz, CDCl₃) δ -0.053 (s, 9H), 0.044 (s, 9H), 1.15 (d, J = 5.6 Hz, 3H), 3.977–3.918 (m, 1H), 4.973 (d, J = 6.4 Hz, 1H), 7.21–7.54 (m, 4H)

Preparation Example 73
Preparation of 1-(2-chlorophenyl)-(R,S)-1,2-(Bis-trimethylsilyloxy) propane

[0346]

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-(R,S)-1,2-propanediol (Preparation example 55) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.2 g, yield 90–120%).

[0347] ¹H NMR (400 MHz, CDCl₃) δ -0.053 (s, 9H), 0.044 (s, 9H), 1.15 (d, J = 5.6 Hz, 3H), 3.977–3.918 (m, 1H), 4.973 (d, J = 6.4 Hz, 1H), 7.21–7.54 (m, 4H)

Preparation Example 74
Preparation of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy) butane

[0349]

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-(S,S)-1,2-butane-1,2-diol (Preparation example 17) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.6 g, yield 90–120%).

[0350] ¹H NMR (400 MHz, CDCl₃) δ -0.053 (s, 9H), 0.044 (s, 9H), 1.01 (t, J = 7.4 Hz, 3H), 1.52–1.65 (m, 2H), 3.69–3.75 (m, 1H), 5.05 (t, J = 5.0 Hz, 1H), 7.23–7.54 (m, 4H)

Preparation Example 75
Preparation of 1-(2-chlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy) butane

[0352]

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-(R,R)-1,2-butane-1,2-diol (Preparation example 18) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.5 g, yield 90–120%).

[0353] ¹H NMR (400 MHz, CDCl₃) δ -0.053 (s, 9H), 0.044 (s, 9H), 1.01 (t, J = 7.4 Hz, 3H), 1.52–1.65 (m, 2H), 3.69–3.75 (m, 1H), 5.05 (t, J = 5.0 Hz, 1H), 7.23–7.54 (m, 4H)
Preparation Example 76
Preparation of 1-(2-chlorophenyl)-1,2-(Bis-trimethylsilanyloxy) butane

![Chemical Structure](image)

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-1,2-butandiol (Preparation example 19) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.0 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ –0.053 (s, 9H), 0.044 (s, 9H), 1.07 (t, J=7.2 Hz, 6H), 1.83–1.89 (m, 1H), 3.53–3.56 (m, 1H), 5.22–5.25 (m, 1H), 7.23–7.55 (m, 4H)

Preparation Example 77
Preparation of 1-(2-chlorophenyl)-3-methyl-(S,S)-1,2-(Bis-trimethylsilanyloxy)-butane

![Chemical Structure](image)

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-3-methyl-1,2-butandiol (Preparation example 20) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.7 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ –0.053 (s, 9H), 0.044 (s, 9H), 1.07 (t, J=7.2 Hz, 6H), 1.83–1.89 (m, 1H), 3.53–3.56 (m, 1H), 5.22–5.25 (m, 1H), 7.23–7.55 (m, 4H)

Preparation Example 78
Preparation of 1-(2-chlorophenyl)-3-methyl-(R,R)-1,2-(Bis-trimethylsilanyloxy)-butane

![Chemical Structure](image)

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-3-methyl-(R,R)-1,2-hexanediol (Preparation example 23) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.1 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ –0.053 (s, 9H), 0.044 (s, 9H), 0.90 (t, J=7.2 Hz, 3H), 1.35–1.65 (m, 6H), 3.78–3.83 (m, 1H), 5.04 (t, J=5.0 Hz, 1H), 7.23–7.53 (m, 4H)
Preparation Example 81
Preparation of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy)-hexane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-(R,R)-1,2-hexanediol (Preparation example 24) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.3 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ = 0.053 (s, 9H), 0.044 (s, 9H), 0.90 (t, J = 7.2 Hz, 3H), 1.35–1.65 (m, 6H), 3.78–3.83 (m, 1H), 5.04 (t, J = 5.0 Hz, 1H), 7.23–7.53 (m, 4H)

Preparation Example 82
Preparation of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy)-hexane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-chlorophenyl)-1,2-hexanediol (Preparation example 25) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.2 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ = 0.053 (s, 9H), 0.044 (s, 9H), 0.90 (t, J = 7.2 Hz, 3H), 1.35–1.65 (m, 6H), 3.78–3.83 (m, 1H), 5.04 (t, J = 5.0 Hz, 1H), 7.23–7.53 (m, 4H)

Preparation Example 83
Preparation of 1-(2,4-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,4-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 26) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.4 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ = 0.053 (s, 9H), 0.044 (s, 9H), 1.10 (t, J = 6.4 Hz, 3H), 4.47–4.54 (m, 1H), 5.24 (t, J = 8.8 Hz, 1H), 7.18–7.22 (m, 3H)

Preparation Example 84
Preparation of 1-(2,6-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,6-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 38) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.4 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ = 0.053 (s, 9H), 0.044 (s, 9H), 1.10 (d, J = 6.4 Hz, 3H), 4.47–4.54 (m, 1H), 5.24 (t, J = 8.8 Hz, 1H), 7.13–7.36 (m, 3H)

Preparation Example 85
Preparation of 1-(2,3-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,3-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 57) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.2 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ = 0.053 (s, 9H), 0.044 (s, 9H), 1.10 (d, J = 6.4 Hz, 3H), 4.47–4.54 (m, 1H), 5.24 (t, J = 8.8 Hz, 1H), 7.18–7.22 (m, 3H)
Preparation Example 86
Preparation of 1-(2,4-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyl)oxy)-butane

Preparation Example 87
Preparation of 1 -(2,6-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyl)oxy)-butane

Preparation Example 88
Preparation of 1-(2,6-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyl oxy)-butane

Preparation Example 89
Preparation of 1-(2,4-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyl)oxy)-hexane

Preparation Example 90
Preparation of 1-(2,4-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyl)oxy)-hexane
Preparation Example 91
Preparation of 1-(2,6-dichlorophenyl)-(S,S)-1,2-(Bis-trimethylsilyloxy)-hexane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,6-dichlorophenyl)-(S,S)-1,2-hexanediol (Preparation example 47) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.8 g, yield 90–120%).

\[ \text{H NMR (400 MHz, CDCl}_3) \delta -0.053 (s, 9H), 0.044 (s, 9H), 0.85 (t, J=6.7 Hz, 3H), 1.20-1.31 (m, 4H), 1.45-1.53 (m, 2H), 4.28-4.33 (m, 1H), 5.25 (t, J=8.4 Hz, 1H), 7.18-7.35 (m, 3H) \]

Preparation Example 92
Preparation of 1-(2,4-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-propanediol (Preparation example 27) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.2 g, yield 90–120%).

\[ \text{H NMR (400 MHz, CDCl}_3) \delta -0.053 (s, 9H), 0.044 (s, 9H), 1.22 (d, J=6.4 Hz, 3H), 3.90-3.95 (m, 1H), 4.94 (t, J=5.0 Hz, 1H), 7.31-7.49 (m, 3H) \]

Preparation Example 93
Preparation of 1-(2,6-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy)-propane

Preparation Example 94
Preparation of 1-(2,3-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy)-propane

Preparation Example 95
Preparation of 1-(2,4-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy)-butane

Preparation Example 96
Preparation of 1-(2,4-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilyloxy)-hexane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-butane (Preparation example 30) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.6 g, yield 90–120%).

\[ \text{H NMR (400 MHz, CDCl}_3) \delta -0.053 (s, 9H), 0.044 (s, 9H), 1.02 (t, J=7.4 Hz, 3H), 1.54-1.61 (m, 2H), 3.65-3.68 (m, 1H), 5.01 (t, J=5.0 Hz, 1H), 7.31-7.49 (m, 3H) \]
Preparation Example 96
Preparation of 1-(2,6-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilanyloxy)-butane

[0415]

Preparation Example 97
Preparation of 1-(2,4-dichlorophenyl)-3-methyl-(R,R)-1,2-(Bis-trimethylsilanyloxy)-butane

[0418]

Preparation Example 98
Preparation of 1-(2,6-dichlorophenyl)-3-methyl-(R,R)-1,2-(Bis-trimethylsilanyloxy)-hexane

[0421]

Preparation Example 99
Preparation of 1-(2,4-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilanyloxy)-hexane

[0424]

Preparation Example 100
Preparation of 1-(2,6-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilanyloxy)-hexane

[0427]

Preparation Example 101
Preparation of 1-(2,4-dichlorophenyl)-(R,R)-1,2-(Bis-trimethylsilanyloxy)-hexane

[0430]
Preparation Example 101
Preparation of 1-(2,4-dichlorophenyl)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,4-dichlorophenyl)-1,2-propanediol (Preparation example 28) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.7 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ 80.053 (s, 9H), 0.044 (s, 9H), 4.94 (t, J=5.0 Hz, 1H), 7.31–7.49 (m, 3H)

Preparation Example 102
Preparation of 1-(2,6-dichlorophenyl)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,6-dichlorophenyl)-1,2-propanediol (Preparation example 40) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.1 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ 80.053 (s, 9H), 0.044 (s, 9H), 1.10 (d, J=6.4 Hz, 3H), 4.47–4.54 (m, 1H), 7.18–7.36 (m, 3H)

Preparation Example 103
Preparation of 1-(2,3-dichlorophenyl)-1,2-(Bis-trimethylsilyloxy)-propane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,3-dichlorophenyl)-1,2-propanediol (Preparation example 43) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.1 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ 80.053 (s, 9H), 0.044 (s, 9H), 0.97 (t, J=7.6 Hz, 3H), 1.26–1.53 (m, 2H), 4.22–4.26 (m, 1H), 5.26 (t, J=8.4 Hz, 1H), 7.17–7.35 (m, 3H)

Preparation Example 104
Preparation of 1-(2,4-dichlorophenyl)-1,2-(Bis-trimethylsilyloxy)-butane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,4-dichlorophenyl)-1,2-butandiol (Preparation example 31) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.9 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ 80.053 (s, 9H), 0.044 (s, 9H), 1.02 (t, J=7.4 Hz, 3H), 1.54–1.61 (m, 2H), 3.65–3.68 (m, 1H), 5.01 (t, J=5.0 Hz, 1H), 7.31–7.49 (m, 3H)

Preparation Example 105
Preparation of 1-(2,6-dichlorophenyl)-1,2-(Bis-trimethylsilyloxy)-butane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,6-dichlorophenyl)-1,2-butandiol (Preparation example 34) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.1 g, yield 90–120%).

1H NMR (400 MHz, CDCl₃) δ 80.053 (s, 9H), 0.044 (s, 9H), 0.97 (t, J=7.6 Hz, 3H), 1.26–1.53 (m, 2H), 4.22–4.26 (m, 1H), 5.26 (t, J=8.4 Hz, 1H), 7.17–7.35 (m, 3H)
Preparation Example 106
Preparation of 1-(2,4-dichlorophenyl)-3-methyl-1,2-(bis-trimethylsilyl oxy)-butane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,4-dichlorophenyl)-3-methyl-1,2-butanediol (Preparation example 34) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.7 g, yield 90–120%).

Preparation Example 107
Preparation of 1-(2,6-dichlorophenyl)-3-methyl-1,2-(bis-trimethylsilyl oxy)-butane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-1,2-butanediol (Preparation example 46) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.6 g, yield 90–120%).

Preparation Example 108
Preparation of 1-(2,4-dichlorophenyl)-1,2-(bis-trimethylsilyl oxy)-hexane

The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-fluoroophenyl)-(S,S)-1,2-propanediol (Preparation example 61) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.8 g, yield 90–120%).
Preparation Example 111
Preparation of 1-(2-fluorophenyl)-(R,R)-1,2-(Bis-trimethylsilanyloxy)-propane

[0460]

F OTMS

OTMS

[0461] The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-fluorophenyl)-(R,R)-1,2-propanediol (Preparation example 62) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (2.5 g, yield 90–120%).

Preparation Example 112
Preparation of 1-(2-iodophenyl)-(S,S)-1,2-(Bis-trimethylsilanyloxy)-propane

[0463]

[0462] \(^1^H\text{NMR (400 MHz, CDCl}_3\) 8 = 0.053 (s, 9H), 0.044 (s, 9H), 1.15 (d, J=6.4 Hz, 3H), 3.90–3.98 (m, 1H), 4.78 (dd, J=4.4, 7.2 Hz, 1H), 7.04–7.50 (m, 4H)

Preparation Example 113
Preparation of 1-(2-iodophenyl)-(R,R)-1,2-(Bis-trimethylsilanyloxy)-propane

[0466]

[0464] The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-iodophenyl)-(S,S)-1,2-propanediol (Preparation example 66) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.1 g, yield 90–120%).

Preparation Example 114
Preparation of 1-(2-iodophenyl)-(S,S)-1,2-(Bis-trimethylsilanyloxy)-butane

[0469]

[0470] The substantially same method as described in Preparation Example 69 was conducted, except that 1-(2-iodophenyl)-(S,S)-1,2-butanediol (Preparation example 68) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (3.3 g, yield 90–120%).

Example 1
Preparation of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate(1)

[0472]

[0473] To a stirred solution of crude 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilanyloxy) propane (preparation example 69, 104 g, 0.31 mol) in toluene (670 mL) was added

Chlorosulfonyl isocyanate (62.5 mL, 0.71 mol) at 0° C. The reaction mixture was stirred for 2 hr.

After separation of organic layer, the aqueous was washed with NaHCO\textsubscript{3} (400 mL) and extracted with EtOAc (300 mL x 3). The EtOAc layer was washed with water, NaHCO\textsubscript{3} (500 mL) and H\textsubscript{2}O (500 mL). The organic phase was treated with charcoal for 1.5 hr. The organic phase was filtered with Celite, dried over MgSO\textsubscript{4}. Filtration and concentration under vacuum provided the title compound of white
solid (yield 85% (71.1 g), ee=99.9%, MP=83–84°C, [α]D =+57.8 (c=0.25, MeOH))

**Example 2**

Preparation of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate(2)

\[
\text{Cl} \quad \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O}
\]

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-1,2-(bis-trimethylsilylanlyoxy) propane (Preparation example 70) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilylanlyoxy) propane (Preparation example 69) to obtain the title compound (3.8 g, yield 60–90%).

**Example 3**

Preparation of 1-(2-chlorophenyl)-1-hydroxypropyl-2-carbamate(3)

\[
\text{Cl} \quad \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O}
\]

**Example 4**

Preparation of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-carbamate(4)

\[
\text{Cl} \quad \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O}
\]

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-(S,R)-1,2-(bis-trimethylsilylanlyoxy) propane (Preparation example 72) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilylanlyoxy) propane (Preparation example 69) to obtain the title compound (2.4 g, yield 60–90%).

\[
\text{Cl} \quad \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O}
\]

**Example 5**

Preparation of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(S)-2-carbamate(5)

\[
\text{Cl} \quad \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O}
\]

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-(R,S)-1,2-(bis-trimethylsilylanlyoxy) propane (Preparation example 73) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilylanlyoxy) propane (Preparation example 69) to obtain the title compound (2.3 g, yield 60–90%).

\[
\text{Cl} \quad \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O}
\]
Example 6
Preparation of 1-(2-chlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate(6)

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-(S)-1,2-(Bis-trimethylsilylanyloxy)butane (Preparation example 74) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (2.6 g, yield 60-90%).

Example 7
Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxybutyl-(R)-2-carbamate(7)

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-1,2-(Bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (1.9 g, yield 60-90%).

Example 8
Synthesis of 1-(2-chlorophenyl)-1-hydroxybutyl-2-carbamate(8)

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-1,2-(Bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (1.7 g, yield 60-90%).

Example 9
Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxy-3-methyl-butyl-(S)-2-carbamate(9)

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-3-methyl-(S,S)-1,2-(Bis-trimethylsilylanyloxy)butane (Preparation Example 77) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (1.9 g, yield 60-90%).

Example 10
Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxy-3-methyl-butyl-(S)-2-carbamate(10)

The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-3-methyl-(S,S)-1,2-(Bis-trimethylsilylanyloxy)butane (Preparation Example 77) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(Bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (1.7 g, yield 60-90%).
Example 10

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxy-3-methyl-butyl-(R)-2-carbamate(10)

Example 11

Synthesis of 1-(2-chlorophenyl)-1-hydroxy-3-methyl-butyl-2-carbamate(11)

Example 12

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxy-hexyl-(S)-2-carbamate(12)

Example 13

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxy-hexyl-(R)-2-carbamate(13)
Example 14

Synthesis of 1-(2-chlorophenyl)-1-hydroxyhexyl-2-carbamate(14)

[0514]

Example 15

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-methylcarbamate(15)

[0515] The substantially same method as described in Example 1 was conducted, except that 1-(2-chlorophenyl)-1,2-(bis-trimethylsilyl)oxy)hexane (Preparation Example 82) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy) propane (Preparation example 69) to obtain the title compound (2.1 g, yield 60–90%).

[0516] 1H NMR (400 MHz, CDCl3) δ 0.88 (dd, J=5 Hz, 3H), 1.31–1.43 (m, 4H), 1.63–1.70 (m, 1H), 1.52–1.60 (m, 1H), 3.06 (d, J=6 Hz, 1H), 4.75 (brs, 2H), 5.00–5.05 (m, 1H), 5.21 (t, J=6 Hz, 1H), 7.22–7.55 (m, 4H)

Example 16

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-propylcarbamate(16)

[0520] The substantially same method as described in Example 15 was conducted, except that propylamine was used instead of methylamine solution (CH3NH2 in EtOH), to obtain the title compound (0.79 g, yield 25%).

[0521] 1H NMR (400 MHz, CDCl3) δ 0.90 (t, J=6.8 Hz, 3H), 1.20 (d, J=5.96 Hz, 3H), 1.49 (dd, J=14.2 Hz, 2H), 3.11 (d, J=6.28 Hz, 2H), 3.34 (s, 1H), 4.84 (brs, 1H), 5.05 (t, J=5.88 Hz, 1H), 5.14 (s, 1H), 7.22–7.53 (m, 4H)

Example 17

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-isopropylcarbamate(17)

[0523] The substantially same method as described in Example 15 was conducted, except that isopropylamine was used instead of methylamine solution (CH3NH2 in EtOH), to obtain the title compound (1.5 g, yield 41%).

[0524] 1H NMR (400 MHz, CDCl3) δ 1.14 (dd, J=6.5 Hz, 6H), 1.19 (d, J=6.4 Hz, 3H), 3.21 (s, 1H), 3.73–3.82 (m, 1H), 4.59 (brs, 1H), 5.01–5.07 (m, 1H), 5.14 (t, J=5.8 Hz, 1H), 7.20–7.53 (m, 4H)

Example 18

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-cyclopropylcarbamate(18)

[0526] The substantially same method as described in Example 15 was conducted, except that cyclopropylamine

[0527] 1H NMR (400 MHz, CDCl3) δ 1.03–1.25 (m, 3H), 2.76 (s, 3H), 3.34 (s, 1H), 4.80 (br s 1H), 5.04 (t, J=12.5 Hz, 1H), 5.14 (s, 1H), 7.20–7.53 (m, 4H)
was used instead of methylanine solution (CH,NH) in EOH), to obtain the title compound (2.2 g, yield 43%).

Example 19

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-cyclohexyl carbamate(19)

![Chemical structure of Example 19](image)

**Example 19**

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-cyclohexyl carbamate(19)

**Example 20**

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-benzyl carbamate(20)

![Chemical structure of Example 20](image)

**Example 20**

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-benzyl carbamate(20)

**Example 21**

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-bicyclo[2.2.1]heptanescarbamate(21)

![Chemical structure of Example 21](image)

**Example 21**

Synthesis of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-bicyclo[2.2.1]heptanescarbamate(21)

**Example 22**

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-methyl carbamate(22)

![Chemical structure of Example 22](image)

**Example 22**

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-methyl carbamate(22)
Example 23

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-propylcarbamate (23)

The substantially same method as described in Example 22 was conducted, except that propylamine was used instead of methyamine solution (CH₃NH₂ in EtOH), to obtain the title compound (3.1 g, yield 53%).

[0542] 

$^1$H NMR (400 MHz, CDCl₃) 80.92 (t, J=7.6 Hz, 3H), 1.21 (d, J=6.4 Hz, 3H), 1.51 (m, 2H), 3.09-3.14 (m, 2H), 3.28 (d, J=4.4 Hz, 3H), 4.82 (br s, 1H), 5.03-5.09 (m, 1H), 5.14-5.17 (m, 1H), 7.22-7.55 (m, 4H)

Example 24

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-isopropylcarbamate (24)

[0544] 

$^1$H NMR (400 MHz, CDCl₃) 80.49-0.54 (m, 2H), 0.74 (d, J=7.2 Hz, 2H), 1.22 (s, 3H), 2.55-2.60 (m, 1H), 3.16 (s, 1H), 5.00 (s, 1H), 5.04-5.11 (m, 1H), 5.16 (s, 1H), 7.23-7.54 (m, 4H)

Example 25

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclopropylcarbamate (25)

[0547] 

The substantially same method as described in Example 22 was conducted, except that cyclopropylamine was used instead of methyamine solution (CH₃NH₂ in EtOH), to obtain the title compound (3.7 g, yield 69%).

[0548] 

$^1$H NMR (400 MHz, CDCl₃) 80.92 (t, J=5.8 Hz, 3H), 1.21 (d, J=4.9 Hz, 3H), 5.13 (d, J=5.2 Hz, 1H), 7.20-7.54 (m, 4H)

Example 26

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclohexyl carbamate (26)

[0550] 

The substantially same method as described in Example 22 was conducted, except that cyclohexylamine was used instead of methyamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.9 g, yield 28%).

[0551] 

$^1$H NMR (400 MHz, CDCl₃) 81.05-1.38 (m, 8H), 1.58-1.70 (m, 3H), 1.85-1.95 (m, 2H), 3.39-3.47 (m, 1H), 3.56 (s, 1H), 4.79 (br s, 1H), 5.01-5.07 (m, 1H), 5.14 (t, J=5.2 Hz, 1H), 7.20-7.54 (m, 4H)
Example 27

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-benzylcarbamate (27)

[0553]

The substantially same method as described in Example 22 was conducted, except that benzylamine was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (0.52 g, yield 19%).

[0554] ¹H NMR (400 MHz, CDCl₃) δ 8.25 (t, J=6 Hz, 1H), 1.64 (s, 1H), 3.13 (d, J=4 Hz, 1H), 4.37 (d, J=5.6 Hz, 2H), 5.12–5.19 (m, 2H), 7.23–7.55 (m, 9H)

Example 28

Synthesis of 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-bicyclo[2.2.1]heptanecarbamate (28)

[0556]

[0557] The substantially same method as described in Example 22 was conducted, except that 2-aminonorbornane was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.7 g, yield 20–50%).

[0558] ¹H NMR (400 MHz, CDCl₃) 81.08–1.35 (m, 9H), 1.65 (br s, 1H), 1.75–1.71 (m, 1H), 2.14–2.24 (m, 1H), 2.27–2.30 (m, 1H), 3.23–3.29 (m, 1H), 3.47–3.52 (m, 1H), 4.67 (br s, 1H), 5.01–5.09 (m, 1H), 5.12–5.18 (m, 1H), 7.22–7.55 (m, 4H)

Example 29

Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-methylcarbamate (29)

[0559]

[0560] The substantially same method as described in Example 15 was conducted, except that 1-(2-chlorophenyl)-1,2-propanediol (Preparation example 16) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (2.6 g, yield 45%).

[0561] ¹H NMR (400 MHz, CDCl₃) δ 1.21 (d, J=6 Hz, 3H), 2.81 (d, J=5 Hz, 3H), 3.14 (d, J=4 Hz, 1H), 4.72 (br s, 1H), 5.07 (dd, J=6 Hz, 1H), 5.16 (t, J=6 Hz, 1H), 7.22–7.56 (m, 4H)

Example 30

Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-propylcarbamate (30)

[0562]

[0563] The substantially same method as described in Example 29 was conducted, except that propylamine was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.0 g, yield 17%).

[0564] ¹H NMR (400 MHz, CDCl₃) δ 0.92 (t, J=7 Hz, 3H), 1.21 (d, J=6 Hz, 3H), 1.53 (dd, J=7 Hz, 2H), 3.13 (dd, J=7 Hz, 2H), 3.28 (d, 1H), 4.82 (s, 1H), 5.06 (dd, J=7 Hz, 1H), 5.16 (t, J=7 Hz, 1H), 7.21–7.56 (m, 4H)
Example 31
Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-isopropylcarbamate(31)

The substantially same method as described in Example 29 was conducted, except that isopropylamine was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (0.54 g, yield 16%).

[0565] ¹H NMR (400 MHz, CDCl₃) δ 1.16 (dd, J=6 Hz, 6H), 1.21 (d, J=6 Hz, 3H), 3.23 (d, J=6 Hz, 1H), 3.75–3.84 (m, 1H), 4.61 (br s, 1H), 5.06 (t, J=6 Hz, 1H), 5.16 (t, J=6 Hz, 1H), 7.22–7.56 (m, 4H)

Example 32
Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclopropylcarbamate(32)

The substantially same method as described in Example 29 was conducted, except that cyclopropylamine was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.3 g, yield 19%).

[0566] ¹H NMR (400 MHz, CDCl₃) δ 0.50 (t, J=6 Hz, 2H), 0.77 (t, J=3 Hz, 2H), 1.12 (d, J=7 Hz, 3H), 2.53–2.59 (m, 1H), 3.22 (d, J=4 Hz, 1H), 5.08 (dd, J=6 Hz, 1H), 5.15 (s, 1H), 7.22–7.55 (m, 4H)

Example 33
Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclohexylcarbamate(33)

The substantially same method as described in Example 29 was conducted, except that cyclohexylamine was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (2.2 g, yield 33%).

[0567] ¹H NMR (400 MHz, CDCl₃) δ 0.68–1.35 (m, 9H), 1.65 (br s, 1H), 1.75–1.71 (m, 1H), 2.14–2.24 (m, 1H), 2.27–2.30 (m, 1H), 3.23–3.29 (m, 1H), 3.47–3.52 (m, 1H), 4.67 (br s, 1H), 5.01–5.09 (m, 1H), 5.12–5.18 (m, 1H), 7.22–7.55 (m, 4H)

Example 34
Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-benzylcarbamate(34)

The substantially same method as described in Example 29 was conducted, except that benzylamine was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.7 g, yield 20–50%).

[0568] ¹H NMR (400 MHz, CDCl₃) δ 1.07–1.17 (m, 3H), 1.21 (d, J=6 Hz, 3H), 1.29–1.42 (m, 3H), 1.72 (dd, J=6 Hz, 2H), 1.92 (dd, J=6 Hz, 2H), 3.26 (d, J=4 Hz, 1H), 3.46 (t, J=4 Hz, 1H), 4.68 (d, J=6 Hz, 1H), 5.07 (dd, J=6 Hz, 1H), 5.16 (t, J=6 Hz, 1H), 7.22–7.55 (m, 4H)

Example 35
Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-bicyclo[2.2.1]heptanecarbamate(35)

The substantially same method as described in Example 29 was conducted, except that 2-aminonorbornane was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.3 g, yield 19%).

[0569] ¹H NMR (400 MHz, CDCl₃) δ 1.25 (d, J=6 Hz, 3H), 3.16 (d, J=4 Hz, 1H), 4.36 (d, J=6 Hz, 2H), 5.14 (dd, J=6 Hz, 3H), 7.39–7.28 (m, 9H), yield: 19% (1.3 g)

Example 36
Synthesis of 1-(2-chlorophenyl)-1-hydroxypropyl-2-N-bicyclo[2.2.1]heptanecarbamate(36)

The substantially same method as described in Example 29 was conducted, except that 2-aminonorbornane was used instead of methylamine solution (CH₃NH₂ in EtOH), to obtain the title compound (1.7 g, yield 20–50%).

[0570] ¹H NMR (400 MHz, CDCl₃) δ 1.08–1.35 (m, 9H), 1.65 (br s, 1H), 1.75–1.71 (m, 1H), 2.14–2.24 (m, 1H), 2.27–2.30 (m, 1H), 3.23–3.29 (m, 1H), 3.47–3.52 (m, 1H), 4.67 (br s, 1H), 5.01–5.09 (m, 1H), 5.12–5.18 (m, 1H), 7.22–7.55 (m, 4H)
Example 36
Synthesis of 1-(2,4-dichlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate (36)

Example 37
Synthesis of 1-(2,6-dichlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate (37)

Example 38
Synthesis of 1-(2,3-dichlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate (38)

Example 39
Synthesis of 1-(2,4-dichlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate (39)

Example 40
Synthesis of 1-(2,6-dichlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate (40)
Example 41

Synthesis of 1-(2,4-dichlorophenyl)-(S)-1-hydroxy-3-methyl-butyl-(S)-2-carbamate(41)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-3-methyl-(S,S)-1,2-(bis-trimethylsilanyloxy)butane (Preparation Example 88) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilanyloxy) propane (Preparation example 69) to obtain the title compound (1.9 g, yield 60–90%).

Example 42

Synthesis of 1-(2,6-dichlorophenyl)-(S)-1-hydroxy-3-methyl-butyl-(S)-2-carbamate(42)

The substantially same method as described in Example 1 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-(S,S)-1,2-(bis-trimethylsilanyloxy)butane (Preparation Example 89) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilanyloxy) propane (Preparation example 69) to obtain the title compound (2.1 g, yield 60–90%).

Example 43

Synthesis of 1-(2,4-dichlorophenyl)-(S)-1-hydroxy-hexyl-(S)-2-carbamate(43)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-3-hexyl-(S,S)-1,2-(bis-trimethylsilanyloxy)propane (Preparation Example 90) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilanyloxy) propane (Preparation example 69) to obtain the title compound (2.2 g, yield 60–90%).

Example 44

Synthesis of 1-(2,6-dichlorophenyl)-(S)-1-hydroxy-hexyl-(S)-2-carbamate(44)

Example 45

Synthesis of 1-(2,4-dichlorophenyl)-(R)-1-hydroxy-propyl-(R)-2-carbamate(45)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-(bis-trimethylsilanyloxy)propene (Preparation Example 92) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilanyloxy) propane (Preparation example 69) to obtain the title compound (1.2 g, yield 60–90%).

Example 46

Synthesis of 1-(2,4-dichlorophenyl)-(R)-1-hydroxy-propyl-(R)-2-carbamate(46)
Example 46
Synthesis of 1-(2,6-dichlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate (46)

The substantially same method as described in Example 1 was conducted, except that 1-(2,6-dichlorophenyl)-(R,R)-1,2-(diaminomethyl)propane (Preparation Example 43) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(diaminomethyl)propane (Preparation example 69) to obtain the title compound (1.7 g, yield 60-90%).

Example 47
Synthesis of 1-(2,3-dichlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate (47)

The substantially same method as described in Example 1 was conducted, except that 1-(2,3-dichlorophenyl)-(R,R)-1,2-(diaminomethyl)propane (Preparation Example 44) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(diaminomethyl)propane (Preparation example 69) to obtain the title compound (2.5 g, yield 60-90%).

Example 48
Synthesis of 1-(2,4-dichlorophenyl)-(R)-1-hydroxybutyl-(R)-2-carbamate (48)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-(diaminomethyl)propane (Preparation Example 45) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(diaminomethyl)propane (Preparation example 69) to obtain the title compound (2.8 g, yield 60-90%).
Example 51
Synthesis of 1-(2,6-dichlorophenyl)-(R)-1-hydroxy-3-methyl-butyl-(R)-2-carbamate(51)

The substantially same method as described in Example 1 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-(R,R)-1,2-(bis-trimethylsilyl)oxy)butane (Preparation Example 98) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 69) to obtain the title compound (2.6 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.00 (t, J=7.2 Hz, 6H), 1.73–1.79 (m, 1H), 3.67–3.69 (m, 1H), 4.85 (br s, 2H), 5.40–5.43 (m, 1H), 5.49–5.54 (m, 1H), 7.16–7.33 (m, 3H) \]

Example 52
Synthesis of 1-(2,4-dichlorophenyl)-(R)-1-hydroxy-hexyl-(R)-2-carbamate(52)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-(bis-trimethylsilyl)oxy)hexane (Preparation Example 99) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 69) to obtain the title compound (2.5 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.22 (d, J=6.4 Hz, 3H), 1.56–1.61 (m, 1H), 1.64–1.71 (m, 1H), 2.98 (d, J=5.6 Hz, 1H), 4.67 (br s, 2H), 4.96–5.00 (m, 1H), 5.17 (t, J=5.6 Hz, 1H), 7.30–7.49 (m, 3H) \]

Example 53
Synthesis of 1-(2,6-dichlorophenyl)-(R)-1-hydroxy-hexyl-(R)-2-carbamate(53)

The substantially same method as described in Example 1 was conducted, except that 1-(2,6-dichlorophenyl)-(R,R)-1,2-(bis-trimethylsilyl)oxy)hexane (Preparation Example 100) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 69) to obtain the title compound (2.4 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.20–1.35 (m, 4H), 1.36–1.41 (m, 1H), 1.59–1.63 (m, 1H), 2.71 (d, J=10.0 Hz, 1H), 4.74 (br s, 2H), 5.40–5.44 (m, 1H), 5.52–5.57 (m, 1H), 7.17–7.35 (m, 3H) \]

Example 54
Synthesis of 1-(2,4-dichlorophenyl)-1-hydroxypropyl-2-carbamate(54)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 101) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 69) to obtain the title compound (1.7 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.16 (d, J=6.4 Hz, 3H), 1.46 (br t, 1H), 4.96 (br t, 3H), 5.07 (t, J=4.8 Hz, 1H), 7.23–7.52 (m, 3H) \]
Example 55
Synthesis of 1-(2,6-dichlorophenyl)-1-hydroxypropyl-2-carbamate (55)

Example 56
Synthesis of 1-(2,3-dichlorophenyl)-1-hydroxypropyl-2-carbamate (56)

Example 57
Synthesis of 1-(2,4-dichlorophenyl)-1-hydroxybutyl-2-carbamate (57)

Example 58
Synthesis of 1-(2,6-dichlorophenyl)-1-hydroxybutyl-2-carbamate (58)
Example 59

Synthesis of 1-(2,4-dichlorophenyl)-1-hydroxy-3-methyl-butyl-2-carbamate (59)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-3-methyl-1,2-(bis-trimethylsilylanyloxy)butane (Preparation Example 108) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (1.9 g, yield 60–90%).

1H NMR (400 MHz, CDCl₃) δ 7.00 (t, J=7.2 Hz, 6H), 7.33–7.39 (m, 1H), 3.67–3.69 (m, 1H), 4.85 (br s, 2H), 5.45–5.54 (m, 1H), 5.74–5.75 (m, 3H)

Example 60

Synthesis of 1-(2,6-dichlorophenyl)-1-hydroxy-3-methyl-butyl-2-carbamate (60)

The substantially same method as described in Example 1 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-1,2-(bis-trimethylsilylanyloxy)butane (Preparation Example 108) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (2.6 g, yield 60–90%).

1H NMR (400 MHz, CDCl₃) δ 8.09 (t, J=3.6 Hz, 3H), 1.28–1.42 (m, 4H), 1.52–1.59 (m, 1H), 1.64–1.71 (m, 1H), 2.98 (d, J=5.6 Hz, 1H), 4.67 (br s, 2H), 4.96–5.00 (m, 1H), 5.17 (t, J=5.6 Hz, 1H), 7.30–7.49 (m, 3H)

Example 61

Synthesis of 1-(2,4-dichlorophenyl)-1-hydroxyhexyl-2-carbamate (61)

The substantially same method as described in Example 1 was conducted, except that 1-(2,4-dichlorophenyl)-1,2-(bis-trimethylsilylanyloxy)hexane (Preparation Example 109) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilylanyloxy) propane (Preparation example 69) to obtain the title compound (2.5 g, yield 60–90%).

1H NMR (400 MHz, CDCl₃) δ 8.84 (t, J=7.0 Hz, 3H), 1.20–1.35 (m, 4H), 1.36–1.41 (m, 1H), 1.59–1.63 (m, 1H), 3.71 (d, J=10.0 Hz, 1H), 4.74 (br s, 2H), 5.40–5.44 (m, 1H), 5.52–5.57 (m, 3H), 7.17–7.35 (m, 3H)
Example 63

Synthesis of 1-(2-fluorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate (63)

The substantially same method as described in Example 1 was conducted, except that 1-(2-fluorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 110) was used instead of 1-(2-chlorophenyl) (S,S)-1,2-(bis-trimethylsilyl)oxy) propane (Preparation example 69) to obtain the title compound (1.8 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.19 (d, J=5.2 Hz, 3H), 2.93 (d, J=4.4 Hz, 1H), 4.71 (brs, 2H), 4.99–5.06 (m, 2H), 7.04–7.48 (m, 4H) \]

Example 64

Synthesis of 1-(2-fluorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate (64)

The substantially same method as described in Example 1 was conducted, except that 1-(2-fluorophenyl)(R,R)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 111) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy) propane (Preparation example 69) to obtain the title compound (1.6 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.19 (d, J=5.2 Hz, 3H), 2.93 (d, J=4.4 Hz, 1H), 4.71 (brs, 2H), 4.99–5.06 (m, 2H), 7.04–7.48 (m, 4H) \]

Example 65

Synthesis of 1-(2-iodophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate (65)

The substantially same method as described in Example 1 was conducted, except that 1-(2-iodophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 112) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy) propane (Preparation example 69) to obtain the title compound (2.2 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.27 (d, J=6.4 Hz, 3H), 3.09 (br s, 1H), 4.83 (br s, 2H), 5.00–5.10 (m, 2H), 7.00–7.76 (m, 4H) \]

Example 66

Synthesis of 1-(2-iodophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate (66)

The substantially same method as described in Example 1 was conducted, except that 1-(2-iodophenyl)-(R,R)-1,2-(bis-trimethylsilyl)oxy)propane (Preparation Example 113) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy) propane (Preparation example 69) to obtain the title compound (1.7 g, yield 60–90%).

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta 1.27 (d, J=6.4 Hz, 3H), 2.95 (d, J=3.6 Hz, 1H), 4.73 (br s, 2H), 5.01–5.11 (m, 2H), 7.01–7.86 (m, 4H) \]
Example 67

Synthesis of 1-(2-iodophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate (67)

The substantially same method as described in Example 1 was conducted, except that 1-(2-iodophenyl)-(S, S)-1,2-(bis-trimethylsilyl)oxy)butane (Preparation Example 114) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-(bis-trimethylsilyl)oxy) propane (Preparation example 69) to obtain the title compound (2.1 g, yield 60–90%).

Example 68

Synthesis of 1-(2-chlorophenyl)-(S)-2-hydroxypropyl-(S)-1-carbamate (68)

1-(2-chlorophenyl)-(S,S)-1,2-propanediol (2.33 g, Preparation example 14) obtained in Preparation Example 14, tetrahydrofuran (THF, 12 ml), and carbonyldimidazole (CDI, 3.04 g) were put into a flask and stirred at the room temperature. After approximately 3 hours, ammonia solution (NH₄OH, 4 ml) was added thereto. When the reaction was completed, the obtained product was washed with 1M HCl solution and ethylacetate (EA). The separated organic layer was dehydrated with anhydrous magnesium sulfate (MgSO₄), filtrated, and concentrated under reduced pressure. The concentrated residue was purified by a silica gel column chromatography, to obtain the title compound (0.28 g, yield 10–30%).

Example 69

Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-carbamate (69)

The substantially same method as described in Example 68 was conducted, except that 1-(2-chlorophenyl)-(R,R)-1,2-propanediol (Preparation Example 15) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14) to obtain the title compound (0.77 g, yield 10%).

Example 70

Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-carbamate (70)

1-(2-chlorophenyl)-(S,S)-1,2-propanediol (2.33 g, Preparation example 14) obtained in Preparation Example 14, tetrahydrofuran (THF, 12 ml), and carbonyldimidazole (CDI, 3.04 g) were put into a flask and stirred at the room temperature. After approximately 3 hours, ammonia solution (NH₄OH, 4 ml) was added thereto. When the reaction was completed, the obtained product was washed with 1M HCl solution and ethylacetate (EA). The separated organic layer was dehydrated with anhydrous magnesium sulfate (MgSO₄), filtrated, and concentrated under reduced pressure. The concentrated residue was purified by a silica gel column chromatography, to obtain the title compound (0.28 g, yield 10–30%).
Example 71

Synthesis of 1-(2-chlorophenyl)-(S)-2-hydroxypropyl-(S)-1-N-methylcarbamate(71)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 15, to obtain the title compound (0.73 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 1.22 (d, J=6 Hz, 3H), 2.15 (d, J=4 Hz, 1H), 2.81 (d, J=5 Hz, 3H), 4.12 (dd, J=6 Hz, 1H), 4.83 (br s, 1H), 6.00 (d, J=6 Hz, 1H), 7.23–7.41 (m, 4H)

Example 72

Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-N-methylcarbamate(72)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 16, to obtain the title compound (0.15 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 0.91 (t, J=7 Hz, 3H), 1.22 (d, J=6 Hz, 3H), 1.52 (dd, J=7 Hz, 2H), 2.23 (d, J=4 Hz, 1H), 3.09–3.21 (m, 2H), 4.09–4.17 (m, 1H), 4.93 (s, 1H), 5.99 (d, J=6 Hz, 1H), 7.23–7.47 (m, 4H)

Example 73

Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-methylcarbamate(73)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 22, to obtain the title compound (0.69 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 0.21 (d, J=6.4 Hz, 3H), 2.80 (d, J=4.8 Hz, 3H), 3.12 (s, 1H), 4.09–4.16 (m, 1H), 4.86 (br s, 1H), 5.99 (d, J=6.0 Hz, 1H), 7.23–7.40 (m, 4H)

Example 74

Synthesis of 1-(2-chlorophenyl)-(S)-2-hydroxypropyl-(S)-1-N-propylcarbamate(74)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 29, to obtain the title compound (0.73 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 1.22 (d, J=6 Hz, 3H), 2.15 (d, J=4 Hz, 1H), 2.81 (d, J=5 Hz, 3H), 4.12 (dd, J=6 Hz, 1H), 4.83 (br s, 1H), 6.00 (d, J=6 Hz, 1H), 7.23–7.41 (m, 4H)

Example 75

Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-N-propylcarbamate(75)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 29, to obtain the title compound (0.73 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 0.91 (t, J=7 Hz, 3H), 1.22 (d, J=6 Hz, 3H), 1.52 (dd, J=7 Hz, 2H), 2.23 (d, J=4 Hz, 1H), 3.09–3.21 (m, 2H), 4.09–4.17 (m, 1H), 4.93 (s, 1H), 5.99 (d, J=6 Hz, 1H), 7.23–7.47 (m, 4H)

Example 76

Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-propylcarbamate(76)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 23, to obtain the title compound (0.04 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 0.91 (t, J=7 Hz, 3H), 1.22 (d, J=6 Hz, 3H), 1.52 (dd, J=7 Hz, 2H), 2.23 (d, J=4 Hz, 1H), 3.09–3.21 (m, 2H), 4.09–4.17 (m, 1H), 4.93 (s, 1H), 5.99 (d, J=6 Hz, 1H), 7.23–7.47 (m, 4H)
Example 76
Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-propylcarbamate(76)

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 24, to obtain the title compound (0.5 g, yield 10–30%).

Example 77
Synthesis of 1-(2-chlorophenyl)-(S)-2-hydroxypropyl-(S)-1-N-isopropylcarbamate(77)

Example 78
Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-N-isopropylcarbamate(78)

Example 79
Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-isopropylcarbamate(79)

Example 80
Synthesis of 1-(2-chlorophenyl)-(S)-2-hydroxypropyl-(S)-1-N-cyclopropylcarbamate(80)
Example 81

Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-N-cyclopropylcarbamate (81)

[0714]

[0715] A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 19, to obtain the title compound (0.24 g, yield 10–30%).

[0722] $^1$H NMR (400 MHz, CDCl₃) δ 1.10–1.39 (m, 7H), 1.61 (s, 3H), 1.71–1.74 (m, 2H), 1.87 (d, J=11.2 Hz, 1H), 2.48 (d, J=10.8 Hz, 1H), 3.46 (t, J=4 Hz, 1H), 4.10–4.11 (m, 1H), 4.80 (br s 1H), 5.97 (d, J=5.6 Hz, 1H), 7.23–7.41 (m, 4H)

Example 84

Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-N-cyclohexylcarbamate (84)

[0723]

[0724] A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 26, to obtain the title compound (0.35 g, yield 10%).

[0725] $^1$H NMR (400 MHz, CDCl₃) δ 1.10–1.39 (m, 7H), 1.61 (s, 3H), 1.71–1.74 (m, 2H), 1.87 (d, J=11.2 Hz, 1H), 2.48 (d, J=10.8 Hz, 1H), 3.46 (t, J=4 Hz, 1H), 4.10–4.11 (m, 1H), 4.80 (br s 1H), 5.97 (d, J=5.6 Hz, 1H), 7.23–7.41 (m, 4H)

Example 85

Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclohexylcarbamate (85)

[0726]

[0727] A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 33, to obtain the title compound (0.26 g, yield 10%).

[0728] $^1$H NMR (400 MHz, CDCl₃) δ 1.12–1.19 (m, 3H), 1.22 (d, J=6 Hz, 3H), 1.27–1.37 (m, 1H), 1.71 (t, J=6 Hz, 2H), 1.86–1.88 (m, 1H), 3.47 (s, 1H), 4.12 (t, J=6 Hz, 1H), 4.78 (s, 1H), 5.97 (d, J=6 Hz, 1H), 7.23–7.40 (m, 4H)
Example 86
Synthesis of 1-(2-chlorophenyl)-(S)-2-hydroxypropyl-(S)-1-N-benzylcarbamate(86)

[0729]

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 20, to obtain the title compound (0.19 g, yield 10~30%).

[0730] 1H NMR (400 MHz, CDCl₃) δ 1.23 (d, J=6 Hz, 3H), 2.16 (d, J=4 Hz, 1H), 4.12 (t, J=6 Hz, 1H), 4.31-4.44 (m, 2H), 5.22 (br s, 1H), 6.06 (d, J=6 Hz, 1H), 7.27~7.42 (m, 9H)

Example 87
Synthesis of 1-(2-chlorophenyl)-(R)-2-hydroxypropyl-(R)-1-N-benzylcarbamate(87)

[0732]

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 27, to obtain the title compound (0.07 g, yield 10~30%).

[0733] 1H NMR (400 MHz, CDCl₃) δ 1.23 (d, J=6 Hz, 3H), 2.16 (d, J=4 Hz, 1H), 4.12 (t, J=6 Hz, 1H), 4.31-4.44 (m, 2H), 5.22 (br s, 1H), 6.04 (d, J=6 Hz, 1H), 7.27~7.42 (m, 9H)

Example 88
Synthesis of 1-(2-chlorophenyl)-2-hydroxypropyl-1-N-benzylcarbamate(88)

[0735]

A regioisomer of monocarbamate was separated and purified by conducting the silica gel column chromatography as described in Example 34, to obtain the title compound (0.21 g, yield 14%).

[0736] 1H NMR (400 MHz, CDCl₃) δ 1.23 (d, J=6 Hz, 3H), 2.16 (d, J=4 Hz, 1H), 4.12 (t, J=6 Hz, 1H), 4.31-4.44 (m, 2H), 5.22 (br s, 1H), 6.04 (d, J=6 Hz, 1H), 7.27~7.42 (m, 9H)

Example 89
Synthesis of 1-(2,4-dichlorophenyl)-(S)-2-hydroxypropyl-(S)-1-carbamate(89)

[0738]

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 26) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.05 g, yield 10~30%).

[0739] 1H NMR (400 MHz, CDCl₃) δ 1.13 (d, J=6.8 Hz, 3H), 2.49 (d, J=4.0 Hz, 1H), 4.66~4.74 (m, 1H), 4.76 (br s, 2H), 6.20 (d, J=8.8 Hz, 1H), 7.39 (d, J=2.0 Hz, 2H), 7.50 (dd, J=8.4 Hz, 2.0 Hz, 1H)

Example 90
Synthesis of 1-(2,6-dichlorophenyl)-(S)-2-hydroxypropyl-(S)-1-carbamate(90)

[0741]

The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 38) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.07 g, yield 24%).

[0742] 1H NMR (400 MHz, CDCl₃) δ 1.13 (d, J=6.8 Hz, 3H), 2.49 (d, J=4.0 Hz, 1H), 4.66~4.74 (m, 1H), 4.76 (br s, 2H), 6.20 (d, J=8.8 Hz, 1H), 7.25~7.40 (m, 3H)
Example 91: Synthesis of 1-(2,3-dichlorophenyl)-(S)-2-hydroxypropyl-(S)-1-carbamate (91)

The substantially same method as described in Example 68 was conducted, except that 1-(2,3-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 57) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.08 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ1.15 (d, J=6.4 Hz, 3H), 3.66 (d, J=9.2 Hz, 1H), 4.73 (br s, 2H), 5.43 (t, J=9.0 Hz, 1H), 5.62–5.69 (m, 1H), 7.18–7.22 (m, 3H).

Example 92: Synthesis of 1-(2,4-dichlorophenyl)-(S)-2-hydroxyethyl-(S)-1-carbamate (92)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-(S,S)-1,2-butadienol (Preparation example 41) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.11 g, yield 29%).

1H NMR (400 MHz, CDCl₃) δ0.77 (t, J=7.4 Hz, 3H), 0.92–1.01 (m, 1H), 1.18–1.28 (m, 1H), 4.06–4.13 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.4 (br s, 2H), 7.25–7.40 (m, 3H).

Example 93: Synthesis of 1-(2,6-dichlorophenyl)-(S)-2-hydroxybutyl-(S)-1-carbamate (93)

The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-(S,S)-1,2-propanediol (Preparation example 29) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.07 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ1.73–1.79 (m, 1H), 3.67–3.69 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.42 (br s, 2H), 7.30–7.50 (m, 3H).

Example 94: Synthesis of 1-(2,4-dichlorophenyl)-(S)-2-hydroxy-3-methylbutyl-(S)-1-carbamate (94)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-(S,S)-3-methyl-1,2-butanediol (Preparation example 32) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.01 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ1.00 (t, J=7.2 Hz, 6H), 1.73–1.79 (m, 1H), 3.67–3.69 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.42 (br s, 2H), 7.30–7.50 (m, 3H).
Example 95

Synthesis of 1-(2,6-dichlorophenyl)-(S)-2-hydroxy-3-methyl-butyl-(S)-1-carbamate(95)

Example 96

Synthesis of 1-(2,4-dichlorophenyl)-(S)-2-hydroxy-hexyl-(S)-1-carbamate(96)

Example 97

Synthesis of 1-(2,6-dichlorophenyl)-(S)-2-hydroxy-hexyl-(S)-1-carbamate(97)

Example 98

Synthesis of 1-(2,4-dichlorophenyl)-(R)-2-hydroxy-propyl-(R)-1-carbamate(98)
Example 99

Synthesis of 1-(2,6-dichlorophenyl)-(R)-2-hydroxypropyl-(R)-1-carbamate(99)

The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-(R,R)-1,2-propanediol (Preparation example 39) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.09 g, yield 10–30%).

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} \delta 1.15 \text{ (d, } J=6.8 \text{ Hz, 3H}), \ 2.49 \text{ (d, } J=4.0 \text{ Hz, 1H}), \ 4.66-4.74 \text{ (m, 1H), } 4.76 \text{ (br s, 2H), } 6.20 \text{ (d, } J=8.8 \text{ Hz, 1H), } 7.25-7.40 \text{ (m, 3H)}\]

Example 100

Synthesis of 1-(2,3-dichlorophenyl)-(R)-2-hydroxypropyl-(R)-1-carbamate(100)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-butanediol (Preparation example 30) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.08 g, yield 10–30%).

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} \delta 0.77 \text{ (t, } J=7.4 \text{ Hz, 3H), } 0.92-1.01 \text{ (m, 1H), } 1.18-1.28 \text{ (m, 1H), } 4.06-4.13 \text{ (m, 1H), } 4.96 \text{ (d, } J=6.0 \text{ Hz, 1H), } 5.91 \text{ (d, } J=8.8 \text{ Hz, 1H), } 6.4 \text{ (br s, 2H), } 7.30-7.50 \text{ (m, 3H)}\]

Example 101

Synthesis of 1-(2,4-dichlorophenyl)-(R)-2-hydroxybutyl-(R)-1-carbamate(101)

The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-(R,R)-1,2-butanediol (Preparation example 30) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.08 g, yield 10–30%).

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} \delta 1.18-1.28 \text{ (m, 1H), } 4.06-4.13 \text{ (m, } J=6.0 \text{ Hz, 1H), } 5.91 \text{ (d, } J=8.8 \text{ Hz, 1H), } 6.4 \text{ (br s, 2H), } 7.25-7.40 \text{ (m, 3H)}\]
Example 103

Synthesis of 1-(2,4-dichlorophenyl)-(R)-2-hydroxy-3-methyl-butyl-(R)-1-carbamate (103)

[0779] The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-3-methyl-[(R,R)-1,2-propanediol (Preparation example 33)] was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 36), to obtain the title compound (0.01 g, yield 10–30%).

[0781] "H NMR (400 MHz, CDCl₃) δ 1.00 (t, J=7.2 Hz, 6H), 1.73–1.79 (m, 1H), 3.67–3.69 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.42 (br s, 2H), 7.30–7.50 (m, 3H)

Example 104

Synthesis of 1-(2,6-dichlorophenyl)-(R)-2-hydroxy-3-methyl-butyl-(R)-1-carbamate (104)

[0782] The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-3-methyl-[(R,R)-1,2-propanediol (Preparation example 45)] was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.01 g, yield 10–30%).

[0784] "H NMR (400 MHz, CDCl₃) δ 1.00 (t, J=7.2 Hz, 6H), 1.73–1.79 (m, 1H), 3.67–3.69 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.42 (br s, 2H), 7.25–7.40 (m, 3H)

Example 105

Synthesis of 1-(2,4-dichlorophenyl)-(R)-2-hydroxy-hexyl-(R)-1-carbamate (105)

[0785] The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-(R,R)-1,2-hexanediol (Preparation example 36) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.21 g, yield 10–50%).

[0787] "H NMR (400 MHz, CDCl₃) δ 0.85 (t, J=7.2 Hz, 3H), 1.18–1.33 (m, 4H), 1.48–1.55 (m, 2H), 2.35 (d, J=4.4 Hz, 1H), 4.45–4.50 (m, 1H), 4.76 (br s, 2H), 6.21 (d, J=8.4 Hz, 1H), 7.30–7.50 (m, 3H)

Example 106

Synthesis of 1-(2,6-dichlorophenyl)-(R)-2-hydroxy-hexyl-(R)-1-carbamate (106)

[0788] The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-(R,R)-1,2-hexanediol (Preparation example 48) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.12 g, yield 10–30%).

[0789] "H NMR (400 MHz, CDCl₃) δ 0.85 (t, J=7.2 Hz, 3H), 1.18–1.33 (m, 4H), 1.48–1.55 (m, 2H), 2.35 (d, J=4.4 Hz, 1H), 4.45–4.50 (m, 1H), 4.76 (br s, 2H), 6.21 (d, J=8.4 Hz, 1H), 7.16–7.34 (m, 3H)
Example 107

Synthesis of 1-(2,4-dichlorophenyl)-2-hydroxypropyl-1-carbamate(107)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-1,2-propanediol (Preparation example 28) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.05 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 1.13 (d, J=6.8 Hz, 3H), 2.49 (d, J=4.0 Hz, 1H), 4.66–4.74 (m, 1H), 4.76 (br s, 2H), 6.20 (d, J=8.8 Hz, 1H), 7.30–7.50 (m, 3H)

Example 108

Synthesis of 1-(2,6-dichlorophenyl)-2-hydroxypropyl-1-carbamate(108)

The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-1,2-propanediol (Preparation example 28) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.06 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 1.15 (d, J=6.4 Hz, 3H), 2.49 (d, J=9.2 Hz, 1H), 4.73 (br s, 2H), 5.43 (t, J=9.0 Hz, 1H), 5.62–5.69 (m, 1H), 7.18–7.22 (m, 3H).

Example 109

Synthesis of 1-(2,3-dichlorophenyl)-(R)-2-hydroxypropyl-(R)-1-carbamate(109)

The substantially same method as described in Example 68 was conducted, except that 1-(2,3-dichlorophenyl)-1,2-propanediol (Preparation example 28) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.06 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 1.18–1.28 (m, 1H), 4.06–4.13 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.4 (br s, 2H), 7.30–7.50 (m, 3H).

Example 110

Synthesis of 1-(2,4-dichlorophenyl)-2-hydroxybutyl-1-carbamate(110)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-1,2-butanediol (Preparation example 31) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.07 g, yield 10–30%).

1H NMR (400 MHz, CDCl₃) δ 0.92–1.01 (m, 1H), 1.18–1.28 (m, 1H), 4.06–4.13 (m, 1H), 4.96 (d, J=6.0 Hz, 1H), 5.91 (d, J=8.8 Hz, 1H), 6.4 (br s, 2H), 7.30–7.50 (m, 3H).
Example 111

Synthesis of 1-(2,6-dichlorophenyl)-2-hydroxybutyl-1-carbamate (111)

The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-1,2-butanediol (Preparation example 43) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.10 g, yield 10–30%).

Example 112

Synthesis of 1-(2,4-dichlorophenyl)-2-hydroxy-3-methyl-butyl-1-carbamate (112)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-3-methyl-1,2-propanediol (Preparation example 46) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.01 g, yield 10–30%).

Example 113

Synthesis of 1-(2,6-dichlorophenyl)-2-hydroxy-3-methyl-butyl-1-carbamate (113)

Example 114

Synthesis of 1-(2,4-dichlorophenyl)-2-hydroxyhexyl-1-carbamate (114)

The substantially same method as described in Example 68 was conducted, except that 1-(2,4-dichlorophenyl)-1,2-hexanediol (Preparation example 37) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.21 g, yield 10–30%).
Example 115
Synthesis of 1-(2,6-dichlorophenyl)-2-hydroxyhexyl-1-carbamate (115)

[0815]

[0816] The substantially same method as described in Example 68 was conducted, except that 1-(2,6-dichlorophenyl)-1,2-hexanediol (Preparation example 49) was used instead of 1-(2-chlorophenyl)-(S,S)-1,2-propanediol (Preparation example 14), to obtain the title compound (0.12 g, yield 10–30%).

[0817] 1H NMR (400 MHz, CDCl3) δ 0.85 (t, J=7.2 Hz, 3H), 1.18–1.33 (m, 4H), 1.48–1.55 (m, 2H), 2.35 (d, J=4.4 Hz, 1H), 4.45–4.50 (m, 1H), 4.76 (br s, 2H), 6.21 (d, J=8.4 Hz, 1H), 7.16–7.34 (m, 3H)

[0818] Compounds 1 to 115 produced in Examples 1 to 115 were summarized in following Tables 2 and 3.

<table>
<thead>
<tr>
<th>No.</th>
<th>X (position)</th>
<th>1st Chiral</th>
<th>2nd Chiral</th>
<th>R1</th>
<th>A = carbamoyl derivative</th>
<th>B = H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>4</td>
<td>CI</td>
<td>S</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5</td>
<td>CI</td>
<td>R</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>6</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>8</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>9</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>10</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>11</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>12</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>13</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>14</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>15</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>16</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Propyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>17</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>18</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Cyclohexyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>19</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>20</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>Benzyl</td>
<td>H</td>
</tr>
<tr>
<td>21</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>Bicycle [2.2.1]heptane</td>
<td>H</td>
</tr>
<tr>
<td>22</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>23</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Propyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>24</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>25</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Cyclopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>26</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Cyclohexyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>27</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Benzyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>28</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Bicycle [2.2.1]heptane</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>30</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Propyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>31</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>32</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Cyclopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>33</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Cyclohexyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>34</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Benzyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>35</td>
<td>CI</td>
<td>Rac</td>
<td>Rac</td>
<td>Bicycle [2.2.1]heptane</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>37</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>38</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>39</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>40</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>41</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>42</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>43</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>44</td>
<td>CI</td>
<td>S</td>
<td>S</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>45</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>46</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>47</td>
<td>CI</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
### TABLE 2-continued

Compounds 1 to 67 having the structure of Chemical Formula 1 where ‘A’ is a carbamoyl derivative and ‘B’ is H

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>(position)</th>
<th>1st Chiral</th>
<th>2nd Chiral</th>
<th>R1</th>
<th>A = carbamoyl derivative</th>
<th>R2</th>
<th>B = H</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>49</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>50</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>51</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>52</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>53</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>54</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>55</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>56</td>
<td>Cl</td>
<td>1(2,3-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>57</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>R</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>58</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>R</td>
<td>Et</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>59</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>Cl</td>
<td>1(2,4-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>Cl</td>
<td>1(2,6-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>65</td>
<td>I</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>66</td>
<td>I</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>67</td>
<td>I</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

### TABLE 3

Compounds 68 to 115 having the structure of Chemical Formula 1 where ‘X’ is H and ‘B’ is a carbamoyl derivative

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>(position)</th>
<th>1st Chiral</th>
<th>2nd Chiral</th>
<th>R1</th>
<th>A = H</th>
<th>R2</th>
<th>B = carbamoyl derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>69</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>70</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>71</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>72</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>73</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>74</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Propyl</td>
<td>H</td>
</tr>
<tr>
<td>75</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>Propyl</td>
<td>H</td>
</tr>
<tr>
<td>76</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>Propyl</td>
<td>H</td>
</tr>
<tr>
<td>77</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>78</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>79</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>80</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Cyclopropyl</td>
<td>H</td>
</tr>
<tr>
<td>81</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>Cyclopropyl</td>
<td>H</td>
</tr>
<tr>
<td>82</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>Cyclopropyl</td>
<td>H</td>
</tr>
<tr>
<td>83</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Cyclohexyl</td>
<td>H</td>
</tr>
<tr>
<td>84</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>Cyclohexyl</td>
<td>H</td>
</tr>
<tr>
<td>85</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>Cyclohexyl</td>
<td>H</td>
</tr>
<tr>
<td>86</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Benzyl</td>
<td>H</td>
</tr>
<tr>
<td>87</td>
<td>Cl</td>
<td>1(2-)</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>Benzyl</td>
<td>H</td>
</tr>
<tr>
<td>88</td>
<td>Cl</td>
<td>1(2-)</td>
<td>Rac.</td>
<td>Rac.</td>
<td>Me</td>
<td>H</td>
<td>Benzyl</td>
<td>H</td>
</tr>
<tr>
<td>89</td>
<td>Cl</td>
<td>1(2-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>Benzyl</td>
<td>H</td>
</tr>
<tr>
<td>90</td>
<td>Cl</td>
<td>2(2,6-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>91</td>
<td>Cl</td>
<td>2(2,3-)</td>
<td>S</td>
<td>S</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>92</td>
<td>Cl</td>
<td>2(2,4-)</td>
<td>S</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>93</td>
<td>Cl</td>
<td>2(2,6-)</td>
<td>S</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>94</td>
<td>Cl</td>
<td>2(2,4-)</td>
<td>S</td>
<td>S</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>Cl</td>
<td>2(2,6-)</td>
<td>S</td>
<td>S</td>
<td>Isopropyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>Cl</td>
<td>2(2,4-)</td>
<td>S</td>
<td>S</td>
<td>Butyl</td>
<td>H</td>
<td>H</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 3-continued

Compounds 68 to 115 having the structure of Chemical Formula 1 where ‘A’ is H and ‘B’ is a carbamoyl derivative

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>Chiral</th>
<th>Chiral</th>
<th>A = H</th>
<th>B = carbamoyl derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>95</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Et</td>
<td>H</td>
</tr>
<tr>
<td>96</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>97</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>98</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Butyl</td>
<td>H</td>
</tr>
<tr>
<td>99</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>100</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>101</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Et</td>
<td>H</td>
</tr>
<tr>
<td>102</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Et</td>
<td>H</td>
</tr>
<tr>
<td>103</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>104</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>105</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Butyl</td>
<td>H</td>
</tr>
<tr>
<td>106</td>
<td>Cl</td>
<td>R</td>
<td>R</td>
<td>Butyl</td>
<td>H</td>
</tr>
<tr>
<td>107</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>108</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>109</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>110</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Et</td>
<td>H</td>
</tr>
<tr>
<td>111</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Et</td>
<td>H</td>
</tr>
<tr>
<td>112</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>113</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Isopropyl</td>
<td>H</td>
</tr>
<tr>
<td>114</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Butyl</td>
<td>H</td>
</tr>
<tr>
<td>115</td>
<td>Cl</td>
<td>Rac</td>
<td>Rac</td>
<td>Butyl</td>
<td>H</td>
</tr>
</tbody>
</table>

### Example 116

The Chemical Induced Seizure Model

Picrotoxin (PIC) were used to induce the behavioral seizures in the experiments. Male Sprague-Dawley rats or ICR mice (purchased from Orient Bio Inc. Korea) of body weight 100-130 g (rats) or 19–26 g (mice) were used for these studies. The test materials were administered intraperitoneal (ip) route in a volume of 4 ul/g (rats) or 10 ul/g (mice) weight in rats or mice, respectively. Pharmacological effects of the test materials were evaluated to compared test groups (n=6) with a control group (n=6). Control group was administrated vehicle, only. The peak time was determined by administration of test material's random dose for 0.5, 1, 2 and 4 hour. The time that the most protect was defined as a peak time and ED50 was determined by other dose administration at the peak time. Chemical (PIC) was dissolved in 0.9% saline and administered subcutaneously (s.c.) at its CD97 (convulsive dose 97%), the dose of Chemical (PIC) that produced clonic seizures in 97% into a loose fold of skin in the midline of the neck in a volume of 2 ul/g (rats) or 10 ul/g (mice) body weight. The animals were then transferred to observation cages and observed continuously for 45 min (PIC). Clonic seizure was elicited in approximately 97% of control group. Protection was defined as a complete absence of clonic seizure over the 30-min or 45-min observation period. The effective dose of compound necessary to protect against generalized convulsive seizures to 50% of controls (i.e. ED50) was determined by log probit analysis using SPSS software program (SPSS Inc.). The obtained results are shown in following Table 1. (Reference; White H. S., J. H. Woodhead, K. S. Wilcox, J. P. Stables, H. J. Kupferberg, and H. H. Wolf. General Principles; Discovery and Preclinical Development of Antiepileptic Drugs. In: R. H. Levy, R. H. Mattsson, B. S. Meldrum, and E. Perucca, eds. Antiepileptic Drugs, 5th Ed. Lippincott Williams & Wilkins, Philadelphia 2002: pp. 36–48.)

### TABLE 4

Measurement results of anti-generalized convulsive seizure activity of compounds in the test animals (Mice)

<table>
<thead>
<tr>
<th>Compound</th>
<th>ED50 (mg/kg)</th>
<th>Peak Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>50* (16%)</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>10* (50%)</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>30* (100%)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>50* (65.7%)</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>50* (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>50* (50%)</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>50* (50%)</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>50* (50%)</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>19</td>
<td>50* (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>21</td>
<td>50* (50%)</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>23</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>24</td>
<td>50* (50%)</td>
<td>—</td>
</tr>
<tr>
<td>25</td>
<td>50* (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>26</td>
<td>50* (50%)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Injection amount (mg/kg),

n = the percentage of activity compared to the vehicle only, respectively.

### Example 117

Multiple-Hit Rat Model of IS (Infantile Spasms)

This study was used male offspring of timed pregnant Sprague-Dawley rats (Nara biotech, Seoul, Korea). Ani-
Mal preparation and surgical procedures were as described before (Scantlebury et al., 2010). At postnatal day 3 (PN3), doxurubicin (right intracerebroventricular) and lipopolysaccharide (right intraparietal) were infused stereotactically, under isoflurane anesthesia. At PN4, rats were separated for video monitoring as described (Scantlebury et al., 2010). The monitoring session consisted of 1 hour before injection and 5 hours after injection. The test materials were administered subcutaneously in a volume of 10 μl/g weight. Behavioral spasms were considered as sudden and synchronous high-amplitude movements of all limbs and body to a flexion or extension posture. Flexion or extension events that had asynchronous limb movements or appeared as an attempt of the pup to reposition were excluded to minimize false-positive events (Reference: Scantlebury M.H., Galanopoulou A.G., Chadomelova I., Raffo E., Betancourth D. and Moshe S.L. (2010). A model of symptomatic infantile spasm syndrome. Neurobiol. Dis. 37: 604-612) On PN3, pups were subjected to a minimal clonic seizure (6 Hz) test. The test result was shown in FIG. 1 and Table 5.

**Example 116 Lithium-Pilocarpine Induced Status Epilepticus Model**

**[0823]** Test compound is pre-administered to mice via i.p. injection. At varying times, individual mice (four per time point) are challenged with sufficient current delivered through corneal electrodes to elicit a psychomotor seizure in 97% of animals (32 mA or 44 mA for 3 s) (Toman et al., 1952). Untreated mice will display seizures characterized by a minimal clonic phase followed by stereotyped, automatisms behaviors described originally as being similar to the aura of human patients with partial seizures. Animals not displaying this behavior are considered protected. The test may be evaluated quantitatively by measuring the response at varying dose at a determined time of peak effect (TPE).

**TABLE 6**

| Measurement results of 6 Hz-induced seizure of 1-(2-chlorophenyl)-1-hydroxypropyl-(8)-2-carboxlate (Compound 1) in the test (Mice) |
|---|---|---|---|
| Assay | 32 mA | 44 mA | Peak Time (h) |
| ED50 (mg/kg) | 14.6 | 13.66 | 0.25 |

Example 116

Lithium-Pilocarpine Induced Status Epilepticus Model

**[0825]** Prevention Study

**[0826]** Male Sprague-Dawley rats (purchased from Orient Bio Inc. Korea) of body weight 200-230 g were used for these studies and housed 4-5 rats per cage for 4-5 days. On the day prior to status epilepticus (SE), rats received 127 mg/kg lithium chloride (Sigma, St. Louis, Mo., U.S.A.) intraperitoneally (i.p.). Approximately 18-20 h following this treatment, the rats were given 43 mg/kg pilocarpine (Sigma) intraperitoneally. An i.p. injection of 2 mg/kg methyl-scopolamine (Sigma) was administered 30 min prior to pilocarpine to block the effects of the muscarinic agonist on peripheral cholinergic receptors. The test drug was administered intraperitoneally (i.p.) in a volume of 2 μl/g body weight. Pharmacological effects of all the test materials were evaluated to compare the test groups (n=6) with a control group (n=6). Control group was administered vehicle only. The peak time was determined by administration test material’s random dose for 0.5, 1, 2, 4 hour. The time that the most protect was defined peak time and ED50 was determined by other dose administration at peak time. The animals were then transferred to observation cages and observed continuously for 90 min. The seizure activity was elicited in approximately 95% of control group. Protection was defined as a complete absence of seizure grade 4-5 based on Racine scale (Racine, 1972) over the 90-min observation period. The effective dose

---

**TABLE 5**

<table>
<thead>
<tr>
<th>Compound (Example) No.</th>
<th>ACTH-refractory IS (ip)</th>
<th>ED50 (mg/kg)</th>
<th>Peak Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.8</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>60% (65.5%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>60% (34%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>4</td>
<td>60% (24.3%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>60% (76.2%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>15</td>
<td>60% (67.44%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>36</td>
<td>60% (37.5%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>37</td>
<td>60% (83.8%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>46</td>
<td>60% (78%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>47</td>
<td>60% (91%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>65</td>
<td>60% (92.1%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>67</td>
<td>60% (81.1%)</td>
<td>14.6</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Injection amount (mg/kg), % = the percentage of activity compared to the vehicle only, respectively.*
of compound necessary to protect against seizures to 50% of controls (i.e. ED50) was determined by log probit analysis using SPSS software program (SPSS Inc.). The obtained results are shown in following Table 6.

**[0827] Intervention Study**

**[0828]** Male Sprague-Dawley rats (purchased from Orient Bio Inc. Korea) of body weight 200-230 g were used for these studies and housed 4-5 rats per a cage for 4-5 days. On the day prior to SE, rats received 127 mg/kg lithium chloride (Sigma, St. Louis, Mo., U.S.A.) intraperitoneally (i.p.). Approximately 18-20 h following this treatment, the rats were given 43 mg/kg pilocarpine (Sigma) intraperitoneally. An i.p. injection of 2 mg/kg methyl-scopolamine (Sigma) was administered 30 min prior to pilocarpine to block the effects of the muscarinic agonist on peripheral cholinergic receptors. The effects of compounds dissolved in 30% Poly Ethylene Glycol 400 (Acros Organics, Geel, Belgium) 20% Tween80 were studied at various times or 30 min after the occurrence of the first motor seizure or SE onset. The drug was administered intraperitoneally in a volume of 2 ul/g body weight. Pharmacological effects was evaluated to compare the test groups with a control group (n=8). Control group was administrated vehicle, only. The obtained results are shown in following Table 8 (Reference; Racine R. J. (1972). Modification of seizure activity by electrical stimulation: II Motor seizure. Electroenceph. Clin. Neurophysiol. 32: 281-294.)

**TABLE 7** Measurement results of Lithium-pilocarpine induced status epilepticus of compounds in the prevention test (Rats)

<table>
<thead>
<tr>
<th>(Example) No.</th>
<th>Therapeutic effect</th>
<th>Protection%</th>
<th>ED50 (mg/kg)</th>
<th>Peak Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>71.9</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31.7</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60% (50%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>60% (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60% (83.3%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>60% (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>60% (83.3%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>60% (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>60% (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>73.6 (50%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>60% (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>73.6 (100%)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 8** Measurement results of Lithium-pilocarpine induced status epilepticus of compounds in the intervention test (Rats)

<table>
<thead>
<tr>
<th>Compound (Example) No.</th>
<th>Intervention (rat, iv)</th>
<th>ED50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46% (50%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46% (83.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>46% (66.7%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>46% (50%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46% (66.7%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>46% (100%)</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>46% (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*Injection amount (mg/kg).
Protection % = the percentage of prevention activity compared to the vehicle only, respectively.

**[0829] PTZ/Pentyleneetrazol Test**

**[0830]** The obtained results are shown in following Tables 8 and 9. In this experiment, administered intraperitoneally or orally to test animals (Mouse; IC, and Rat; SD); Experimental animal, male SD rats, were purchased from OrientBio or Narabiotech, Korea, and housed 4-5 mice per a cage for 4-5 days. The range of mice body weight was used between 19 and 26 grams and range of rats body weight was used between 100 and 130 grams. After Peak Time (0.5, 1, 2 and 4 hr) from the administration, from the administration, PTZ (Pentyleneetrazol) was administered subcutaneously in the concentration capable of inducing 97% intermittent convulsions (mice & rats: 90–110 mg/kg-bw, 2 μl/g). If clonic seizure was not observed for at least 3 seconds in the PTZ administered animal, it can be considered that the test compound has anti-nonconvulsive seizure activity. The median effective dose (ED50) is determined using 6 animals per a concentration (total three different concentrations), and calculated by Litchfield and Wilcoxon log-probit method which is a dose-response relationship. The obtained results are shown in following Tables 9 and 10.

**TABLE 9** Measurement results of anti-nonconvulsive seizure activity of compounds in the test animals (Mice)

<table>
<thead>
<tr>
<th>Compound (Example) No.</th>
<th>PTZ test (ip) in Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.8</td>
</tr>
<tr>
<td>2</td>
<td>38.8</td>
</tr>
</tbody>
</table>
What is claimed is:

1. A pharmaceutical composition for preventing or treating a pediatric epilepsy or a pediatric epilepsy-related syndrome comprising a phenyl carbamate compound represented by Chemical Formula I or a pharmaceutically acceptable salt thereof, as an active ingredient:

```
    X o-     O
   /     /  \\
  B-     B-  A
   \     \  / \\
    \     \ \   \\
     \     \  \\
      \     \ \\
       \     O
```

wherein,

X is a halogen,

n, that means the number of substituent X, is an integer from 1 to 5,

R¹ is a linear or branched alkyl group of C₁⁻C₄,

A is hydrogen or a carbamoyl group represented by

```
    N-C
```

B is hydrogen, a carbamoyl group represented by

```
    N-C
```

triaxyl silyl groups, trialkaryl silyl groups (wherein the total number of alkyl and aryl groups is three), or a trialkyl silyl ether group, wherein each alkyl group is independently selected from the group consisting of linear, branched, or cyclic C₁⁻C₄ alkyl groups, and each aryl group is independently selected from the group consisting of C₅⁻C₁₀ aryl groups,

A and B are not carbamoyl derivatives at the same time, and R² and R³ may be the same as or different from each other, and independently selected from the group consisting of hydrogen, a linear or branched alkyl group of C₁⁻C₄, a cycloalkyl group of C₅⁻C₁₀ and benzy group.

2. The pharmaceutical composition according to claim 1, wherein A is hydrogen and B is carbamoyl group, or A is a carbamoyl group and B is hydrogen.

3. The pharmaceutical composition according to claim 1, wherein the phenyl carbamate compound is in the form of racemate, enantiomer, diastereomer, a mixture of enantiomer, or a mixture of diastereomer.

4. The pharmaceutical composition according to claim 1, wherein X is chlorine, fluorine, iodine, or bromine; n is 1 or 2; and R² and R³ are the same as or different from each other, and independently selected from the group consisting of hydrogen, methyl group, propyl group, isopropyl group, cyclopropyl group, cyclohexyl group, bicycloheptane group, and benzyl group.

5. The pharmaceutical composition according to claim 1, wherein the phenyl carbamate compound is selected from the group consisting of:

1-(2-chlorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2-chlorophenyl)-1-hydroxy-3-methyl-butyl-2-carbamate,
1-(2-chlorophenyl)-1-hydroxyhexyl-2-carbamate,

```
    O     O
   /     /  \\
  B-     B-  A
   \     \  / \\
    \     \ \   \\
     \     \  \\
      \     O
```

TABLE 9-continued

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>ED₅₀ (mg/kg)</th>
<th>Peak Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>15.3</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>26.7</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>15.0</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>17.9</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>20.4 (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>23</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>25</td>
<td>20.4 (66.7%)</td>
<td>—</td>
</tr>
<tr>
<td>29</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>31</td>
<td>20.4 (83.3%)</td>
<td>—</td>
</tr>
<tr>
<td>32</td>
<td>20.4 (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>36</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>37</td>
<td>25.7</td>
<td>0.25</td>
</tr>
<tr>
<td>38</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>39</td>
<td>24.3</td>
<td>0.5</td>
</tr>
<tr>
<td>40</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>42</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>44</td>
<td>20.4 (33.3%)</td>
<td>—</td>
</tr>
<tr>
<td>45</td>
<td>20.4 (16.7%)</td>
<td>—</td>
</tr>
<tr>
<td>46</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>43</td>
<td>20.4 (50%)</td>
<td>—</td>
</tr>
<tr>
<td>45</td>
<td>20.4 (100%)</td>
<td>—</td>
</tr>
<tr>
<td>67</td>
<td>25.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Injection amount (mg/kg).
Protection % (Mice)
*Peak Time (h)

TABLE 10

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>PTZ test (ip) in Rats ED₅₀ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>51.9 (2)</td>
</tr>
<tr>
<td>3</td>
<td>18.9 (0.5)</td>
</tr>
<tr>
<td>4</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>6</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>15</td>
<td>25 (33.3%)</td>
</tr>
<tr>
<td>16</td>
<td>30 (50%)</td>
</tr>
<tr>
<td>18</td>
<td>25 (33.3%)</td>
</tr>
<tr>
<td>37</td>
<td>30 (50%)</td>
</tr>
<tr>
<td>43</td>
<td>25 (33.3%)</td>
</tr>
<tr>
<td>45</td>
<td>30 (16.7%)</td>
</tr>
<tr>
<td>67</td>
<td>30 (33.3%)</td>
</tr>
</tbody>
</table>

*Injection amount (mg/kg).
Protection % (Rats)
*Peak Time (h)
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-methylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-propylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-isopropylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclopropylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclohexylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-benzylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-bicyclo [2,2.1] heptane-carbamate,
1-(2,4-dichlorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2,6-dichlorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2,4-dichlorophenyl)-1-hydroxybutyl-2-carbamate, 
1-(2,4-dichlorophenyl)-1-hydroxy-3-methyl-butyl-2-carbamate,
1-(2,6-dichlorophenyl)-1-hydroxy-3-methyl-butyl-2-carbamate,
1-(2,4-dichlorophenyl)-1-hydroxyhexyl-2-carbamate,
1-(2,6-dichlorophenyl)-1-hydroxyhexyl-2-carbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-propylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-isopropylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclopropylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclohexylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-benzylcarbamate,
1-(2,4-dichlorophenyl)-2-hydroxypropyl-1-carbamate,
1-(2,6-dichlorophenyl)-2-hydroxypropyl-1-carbamate,
1-(2-chlorophenyl)-2-hydroxybutyl-1-carbamate,
1-(2,4-dichlorophenyl)-2-hydroxy-3-methyl-butyl-1-carbamate,
1-(2,6-dichlorophenyl)-2-hydroxy-3-methyl-butyl-1-carbamate,
1-(2,4-dichlorophenyl)-2-hydroxyhexyl-1-carbamate,
1-(2,6-dichlorophenyl)-2-hydroxyhexyl-1-carbamate,
1-(2-fluorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2-isodophenyl)-1-hydroxypropyl-2-carbamate,
1-(2-isodophenyl)-1-hydroxybutyl-2-carbamate,
1-(2,3-dichlorophenyl)-1-hydroxypropyl-2-carbamate, 
and 
1-(2,3-dichlorophenyl)-2-hydroxypropyl-1-carbamate.

6. The pharmaceutical composition according to claim 1, wherein the phenyl carbamate compound is selected from the group consisting of:
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate, 
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
Early infantile epileptic encephalopathy, Early myoclonic encephalopathy, Infantile spasm, West syndromes, Severe myoclonic epilepsy of infancy, Benign myoclonic epilepsy of infancy, Benign partial epilepsy of infancy, Benign infantile familial convulsion, Symptomatic/cryptogenic partial epilepsies, Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epilepsy with myoclonic-astatic seizures (Doose syndrome), Acquired epileptic aphasia (Landau-Kleffner syndrome), Epilepsy with continuous spike-wave during slow sleep, Epilepsy with gastric seizures and hypothalamic hamartoma, Symptomatic/cryptogenic partial epilepsies, and Childhood absence epilepsy.

8. A method of preventing or treating epilepsy or epilepsy-related syndrome in a pediatric subject, comprising administering a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, to a pediatric subject in need of treatment:

wherein, X is a halogen, n, that means the number of substituent X, is an integer from 1 to 5, R is a linear or branched alkyl group of C-C, A is hydrogen or a carbamoyl group represented by

B is hydrogen, a carbamoyl group represented by

trialkyl silyl groups, trialkylaryl silyl groups (wherein the total number of alkyl and aryl groups is three), or a trialkyl silyl ether group, wherein each alkyl group is independently selected from the group consisting of linear, branched, or cyclic C-C alkyl groups, and each aryl group is independently selected from the group consisting of C-C aryl groups,

A and B are not carbamoyl derivatives at same time, and R and R may be the same as or different from each other, and independently selected from the group consisting of hydrogen, a linear or branched alkyl group of C-C, a cycloalkyl group of C-C, and benzyl group.

9. The method according to claim 8, wherein A is hydrogen and B is carbamoyl group, or A is a carbamoyl group and B is hydrogen.

10. The method according to claim 8, wherein the phenyl carbamate compound is in the form of racemate, enantiomer, diastereomer, a mixture of enantiomer, or a mixture of diastereomer.

11. The method according to claim 8, wherein X is chlorine, fluorine, iodine, or bromine; n is 1 or 2; and R and R are the same as or different from each other, and independently selected from the group consisting of hydrogen, methyl group, propyl group, isopropyl group, cyclopropyl group, cyclohexyl group, bicycloheptane group, and benzyl group.

12. The method according to claim 8, wherein the phenyl carbamate compound is selected from the group consisting of:

1-(2-chlorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2-chlorophenyl)-1-hydroxy-3-methyl-butyryl-2-carbamate,
1-(2-chlorophenyl)-1-hydroxyhexyl-2-carbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-methylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-propylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-isopropylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclopropylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-cyclohexylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-benzylcarbamate,
1-(2-chlorophenyl)-1-hydroxypropyl-2-N-bicyclo[2.2.1]heptane carbamate,
1-(2,4-dichlorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2,6-dichlorophenyl)-1-hydroxypropyl-2-carbamate,
1-(2,4-dichlorophenyl)-1-hydroxybutyl-2-carbamate,
1-(2,4-dichlorophenyl)-1-hydroxy-3-methyl-butyryl-2-carbamate,
1-(2,6-dichlorophenyl)-1-hydroxy-3-methyl-butyryl-2-carbamate,
1-(2,4-dichlorophenyl)-1-hydroxyhexyl-2-carbamate,
1-(2,6-dichlorophenyl)-1-hydroxyhexyl-2-carbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-methylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-propylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-isopropylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclopropylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-cyclohexylcarbamate,
1-(2-chlorophenyl)-2-hydroxypropyl-1-N-benzylcarbamate,
1-(2,4-dichlorophenyl)-2-hydroxypropyl-1-carbamate,
1-(2,6-dichlorophenyl)-2-hydroxypropyl-1-carbamate,
1-(2,4-dichlorophenyl)-2-hydroxybutyl-1-carbamate,
1-(2,6-dichlorophenyl)-2-hydroxybutyl-1-carbamate,
1-(2,4-dichlorophenyl)-2-hydroxy-3-methyl-butyryl-1-carbamate,
1-(2,6-dichlorophenyl)-2-hydroxy-3-methyl-butyryl-1-carbamate,
1-(2-iodophenyl)-1-hydroxypropyl-2-carbamate,
1-(2-iodophenyl)-1-hydroxybutyl-2-carbamate,
1-(2,3-dichlorophenyl)-1-hydroxypropyl-2-carbamate, and
1-(2,3-dichlorophenyl)-2-hydroxypropyl-1-carbamate.
13. The method according to claim 8, wherein the phenyl carbamate compound is selected from the group consisting of:
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(S)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate, racemate of 1-(2-chlorophenyl)-(S)-1-hydroxybutyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxybutyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxy-3-methyl-butyl-(S)-2-carbamate,
racemate of 1-(2-chlorophenyl)-(S)-1-hydroxy-3-methyl-butyl-(S)-2-carbamate and 1-(2-chlorophenyl)-(R)-1-hydroxy-3-methyl-butyl-(R)-2-carbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-methylcarbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(S)-2-N-propylcarbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-isopropylcarbamate,
1-(2-chlorophenyl)-(S)-1-hydroxypropyl-(R)-2-N-cyclopropylcarbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-isopropylcarbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclopropylcarbamate,
1-(2-chlorophenyl)-(R)-1-hydroxypropyl-(R)-2-N-cyclohexylcarbamate.
14. The method according to claim 8, wherein the pediatric epilepsy or a pediatric epilepsy-related syndrome is selected from the group consisting of Benign Myoclonic Epilepsy (BME), Severe Myoclonic Epilepsy of Infancy Borderland (SMEB), Severe Infantile Multifocal Epilepsy (SIMFE), and Intractable Childhood Epilepsy with Generalized Tonic Clonic Seizures (ICE-GTC), Dravet syndrome (DS), Severe Myoclonic Epilepsy of Infancy (SMEI), Benign neonatal convulsions, Benign neonatal familial convulsions, Miscellaneous neonatal seizures, Febrile seizures, Early infantile epileptic encephalopathy, Early myoclonic encephalopathy, Infantile spasms, West syndromes, Severe myoclonic epilepsy of infancy, Benign myoclonic epilepsy of infancy, Benign partial epilepsy of infancy, Benign infantile familial convulsions, Symptomatic/cryptogenic partial epilepsies, Epilepsies with myoclonic absences, Lennox-Gastaut syndrome, Epilepsy with myoclonic-astatic seizures (Doose syndrome), Acquired epileptic aphasia (Landau-Kleffner syndrome), Epilepsy with continuous spike-wave during low-wave sleep, Epilepsy with gastric seizures and hypothalamic hamartoma, Symptomatic/cryptogenic partial epilepsies, and Childhood absence epilepsy.