Abstract:

A novel prodrug of (+)-3-hydroxymorphinan (81) and its use for treating Parkinson's disease.

Inventors:


Fig. 1

Concentration of the compound of Example 2 (L.V. & P.O.)

<table>
<thead>
<tr>
<th>Concentration (μg/ml)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>1.0</td>
<td>50</td>
</tr>
<tr>
<td>0.8</td>
<td>150</td>
</tr>
<tr>
<td>0.6</td>
<td>250</td>
</tr>
<tr>
<td>0.4</td>
<td>350</td>
</tr>
<tr>
<td>0.2</td>
<td>450</td>
</tr>
<tr>
<td>0.0</td>
<td>550</td>
</tr>
</tbody>
</table>

Abstract:
The present invention is directed to a novel prodrug of (+)-3-hydroxymorphinan compound of formula (I) or a pharmaceutically acceptable salt thereof, a method for preparing the same, and its use for preventing or treating Parkinson's disease.
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ORALLY BIOAVAILABLE PRODRUGS OF (+)-3-HYDROXYMORPHINAN FOR PARKINSON'S DISEASE PREVENTION OR TREATMENT

FIELD OF THE INVENTION

The present invention relates to an orally bioavailable, novel prodrug of (+)-3-hydroxymorphinan which is effective as a neuroprotective agent for Parkinson's disease.

BACKGROUND OF THE INVENTION

There are approximately 100 million people in the world and 800,000 people in the United States alone with Parkinson's disease (PD).

Parkinson's disease is a result of chronic progressive degeneration of neurons, the cause of which has not yet completely been clarified. While the primary cause of Parkinson disease is not known, it is characterized by degeneration of dopaminergic neurons of the substantia nigra (SN). The substantia nigra is a portion of the lower brain, or brain stem that helps control voluntary movements. The shortage of dopamine in the brain caused by the loss of these neurons is believed to cause the observable disease symptoms. Clinically, it manifests in the form of the cardinal symptoms resting tremors, rigor, bradykinesia, and postural instability.

Levodopa, dopamine agonists such as rotigotine, pramipexol, bromocriptine, ropinirol, cabergoline, pergolide, apomorphine and lisuride, anticholinergics, NMDA antagonists, β-blocker as well as the MAO-B inhibitor selegiline and the COMT inhibitor entacapone are used as medicines for relief from the motor symptoms. Most of these agents intervene in the dopamine and/or choline signal cascade and thereby symptomatically influence the Parkinson-typical movement disorders.

In the present therapy for the Parkinson's disease, treatment is initiated after the appearance of the cardinal symptoms. In general, Parkinson's disease is said to be clinically evident if at least two of the four cardinal symptoms (bradykinesia, resting tremors, rigor, and postural instability) are detected and respond to L-dopa (Hughes, J Neurol Neurosurg Psychiatry 55, 1992, 181). Unfortunately, the motor function disorders in Parkinson patients become apparent only after about 70-80% of the dopaminergic neurons in the substantia nigra (SN) are irreparably damaged (Becker et
al, J Neurol 249, 2002, Suppl 3:111, 40; Hornykiewicz, Encyclopaedia of Life Science 2001, 1). Chances of a therapy with lasting effects are very bleak at that point. Hence, it is desirable to initiate the therapy as early as possible.

Current clinical observations as well as anatomical and genetic research show that diagnosis of Parkinson patients at an early stage and identification of high risk patients is possible. With that an opportunity arises for influencing the disease process at a point of time when more neurons are still there, rather than at the time of appearance of several cardinal motor symptoms of the Parkinson's disease, and thereby for protecting a quantitatively greater number of neurons. One can expect that the administration of an effective neuroprotective agent at an early stage will significantly delay the process of the development of the disease: The sooner the therapy is initiated, the higher are the chances of a long lasting prevention of the onset of symptoms, which degrade the quality of life.

Hence, such remedies are needed that not only influence the dopaminergic transmission and alleviate the symptoms of the Parkinson's disease in advanced stages, but also reverse, prevent, or at least significantly delay the dopaminergic neuron extinction in the early, to a great extent motor-asymptomatic, Parkinson stages (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

(+)-3-Hydroxymorphinan ((+)-3-HM) and its derivatives have shown the neuroprotective property in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models for Parkinson's disease. In this animal model, daily injections with (+)-3-HM or its analogs showed that dopamine (DA) neurons in substantia nigra pars compacta have been protected and DA levels in striatum has been restored (US Patent Publication No. 2005-0256147 Al; International Patent Publication No. WO2005/1 10412; Zhang et al, FASEB J. 2006 Dec. 20(14):2496-2511; Zhang et al, FASEB J. 2005 Mar, 19(3):395-397; and Kim et al. Life Science 72(2003) 1883-1895). However, (+)-3-HM and its derivatives are efficacious only if they are administered intraperitoneally or intravenously.

The present invention relates to provide novel prodrugs of (+)-3-hydroxymorphinan which are effective as a neuroprotective agent for Parkinson's disease, when they are delivered orally.

**SUMMARY OF THE INVENTION**

It is a primary object of the present invention to provide a novel prodrug of
(+)-3-hydroxymorphinan compound of formula (I) or a pharmaceutically acceptable salt thereof, which is effective as a neuroprotective agent for Parkinson's disease.

It is another object of the present invention to provide a method for preparing the inventive compound.

It is another object of the present invention to provide a pharmaceutical composition for treating or preventing Parkinson's disease, comprising the inventive compound as an active ingredient.

BRIEF DESCRIPTION OF DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the following accompanying drawings, which respectively show:

Fig. 1 illustrates pharmacokinetic profile of a compound of Example 2 in mice;

and

Fig. 2 illustrates the effects of (+)-3-HM intraperitoneal injected and the compound of Example 2 orally administered on MPTP-induced Parkinson's disease animal model.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with one aspect of the present invention, there are provided a compound of formula (I) or a pharmaceutically acceptable salt thereof and a method for preparing same:

wherein,

A is a direct bond or oxygen;

R₁ is selected from the group consisting of hydrogen, -C(O)OC₁₋₁₀ alkyl, substituted -C(O)OCL₁₀ alkyl, -C(O)OC₁₋₄ alkyl-Ar and substituted -C(O)OC₁₋₄ alkyl-Ar, Ar being selected from the group consisting of phenyl, naphthyl, furyl,
pyridyl, thienyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, benzofuranyl, indolyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiaadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, and pyrimidinyl, all of which are optionally substituted by one or more Z groups, Z being independently selected from the group consisting of C₁-₄ alkyl, C₁-₄ alkoxy, -(CH₂)ₘC(O)OR₃, C(O)NR₃R₄, -CN, -(CH₂)ₙOH, -NO₂, F, Cl, Br, I, -NR₃R₄ and NHC(O)R₃, wherein m is 0 to 4, n is 0 to 4, R₃ is hydrogen, C₁-₆ alkyl or substituted C₁-₆ alkyl, and R₄ is selected from the group consisting of C₁-₆ alkyl, substituted C₁-₆ alkyl, -CH₂Ar and Ar, Ar being as defined above; and R₂ is selected from the group consisting of C₁-₁₀ alkyl, substituted C₁-₁₀ alkyl, C₃-₁₀ carbocycle, substituted C₃-₁₀ carbocycle, (CH₂)ₙ-phenyl and substituted (CH₂)ₙ-phenyl, wherein n is 0 to 4.

One embodiment of the present invention is to provide a compound of formula (Ia) or a pharmaceutically acceptable salt thereof:

![Diagram](image)

wherein R₁ and R₂ have the same meanings as defined above.

Another embodiment of the present invention is to provide a compound of formula (Ib) or a pharmaceutically acceptable salt thereof:

![Diagram](image)

wherein R₁ and R₂ have the same meanings as defined above.
The preferred compounds of formula (I) are those compounds wherein \( R_1 \) is hydrogen, \(-\text{C}(\text{O})\text{OC}_{1-4} \) alkyl-Ar or substituted \(-\text{C}(\text{O})\text{OC}_{1-4} \) alkyl-Ar, Ar being phenyl or naphthyl, both of which are optionally substituted by one or more Z groups, Z being independently selected from the group consisting of \( \text{C}_{1-4} \) alkyl, \( \text{C}_{1-4} \) alkoxy, \(-\text{C}(\text{CH}_2)_m\text{C}(\text{O})\text{OR}_3 \), \(-\text{C}(\text{O})\text{NR}_3\text{R}_4 \), \(-\text{CN} \), \(-\text{OH} \), \(-\text{NO}_2 \), \( \text{F} \), \( \text{Cl} \), \( \text{Br} \), \( \text{I} \), \(-\text{NR}_3\text{R}_4 \) and \( \text{NHC}(\text{O})\text{R}_3 \), wherein \( m \) is \( 0 \) to 4, \( n \) is \( 0 \) to 4, \( R_3 \) is hydrogen, \( \text{C}_{1-6} \) alkyl or substituted \( \text{C}_{1-6} \) alkyl, and \( R_4 \) is selected from the group consisting of \( \text{C}_{1-6} \) alkyl, substituted \( \text{C}_{1-6} \) alkyl, \(-\text{CH}_2\text{Ar} \) and \( \text{Ar} \), \( \text{Ar} \) being as defined above; and \( R_2 \) is selected from the group consisting of \( \text{C}_{1-10} \) alkyl, substituted \( \text{C}_{1-10} \) alkyl, \( \text{C}_{3-10} \) carbocycle, substituted \( \text{C}_{3-10} \) carbocycle, \((\text{CH}_2)_n\)-phenyl and substituted \((\text{CH}_2)_n\)-phenyl, wherein \( n \) is \( 0 \) to 4.

As used herein, the term "alkyl" refers to a straight or branched chain saturated hydrocarbon radical. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl and hexyl.

As used herein, the term "substituted alkyl" refers to a straight or branched chain saturated hydrocarbon radical, which is optionally substituted by one or more substituents selected from the group consisting of \( \text{C}_{1-3} \) alkyl optionally having one to three fluorine substituents, \( \text{C}_{2-3} \) alkenyl, \( \text{C}_{2-3} \) alkynyl, \( \text{C}_{1-2} \) alkoxy optionally having one to three fluorine substituents.

As used herein, the term "carbocycle" refers to a non-aromatic cyclic hydrocarbon radical composed of three to seven carbon atoms or fused bicyclic hydrocarbon radical in which each cycle refers to a non-aromatic cyclic hydrocarbon radical composed of three to seven carbon atoms. Five-to seven-membered rings may contain a double bond in the ring structure. Exemplary "carbocycle" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, and cycloheptyl. Exemplary "fused bicycle" groups include, but are not limited to, decahyronaphthyl.

As used herein, the term "substituted carbocycle" refers to a non-aromatic cyclic hydrocarbon radical composed by three to seven carbon atoms, which is optionally substituted with one or more substituents selected from the group consisting of \( \text{C}_{1-3} \) alkyl optionally having one to three fluorine substituents, \( \text{C}_{2-3} \) alkenyl, \( \text{C}_{2-3} \) alkynyl, \( \text{C}_{1-2} \) alkoxy optionally having one to three fluorine substituents, aryl, and aryloxy.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or refers to a ring system which may result by fusing one or more optional substituents.
Exemplary optional substituents include substituted C\textsubscript{i-3} alkyl, substituted C\textsubscript{2-3} alkenyl, substituted C\textsubscript{2-3} alkynyl, heteroaryl, heterocyclic, aryl, alkoxy optionally having one to three fluorine substituents, aralkoxy, acyl, aroyl, heteroaryl, acyloxy, and aroyloxy. Such a ring or ring system may be optionally fused to aryl rings (including benzene rings) optionally having one or more substituents, carbocycle rings or heterocyclic rings. Examples of "aryl" groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, biphenyl, indanyl, anthracyl and phenanthryl, as well as substituted derivatives thereof.

As used herein, the term "alkoxy" refers to the group -OR\textsubscript{3}, where R\textsubscript{3} is alkyl as defined above. Exemplary alkoxy groups useful in the present invention include, but are not limited to, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy, isoproxy, n-butoxy and t-butoxy.

As used herein the term "aralkoxy" refers to the group -OR\textsubscript{3}R\textsubscript{b}, wherein R\textsubscript{3} is alkyl and R\textsubscript{b} is aryl as defined above.

As used herein the term "aryloxy" refers to the group -OR\textsubscript{b}, wherein R\textsubscript{b} is aryl as defined above.

It is to be understood that the present invention also includes a pharmaceutically acceptable salt and an acid addition salt of the inventive compound, such as a hydrochloride, trifluoroacetic acid, formic acid, citric acid, fumaric acid, fumarate mono-sodium, p-toluenesulfonic acid, stearic acid, citrate di-sodium, tartaric acid, malic acid, lactic acid, succinic acid, or salicylic acid addition salt. The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are incorporated within the scope of the present invention.

Compounds especially useful in the present invention are selected from the group consisting of:

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate;
(+)-(Morphinan-3-yloxy)methyl propyl carbonate;
(+)-Cyclopropylmethyl (morphinan-3-yloxy)methyl carbonate;
(+)-Cyclopentyl (morphinan-3-yloxy)methyl carbonate;
(+)-Cyclohexyl (morphinan-3-yloxy)methyl carbonate;
(+)-Cyclohexylmethyl (morphinan-3-yloxy)methyl carbonate;
(+)-Heptan-4-yl (morphinan-3-yloxy)methyl carbonate;
(+)-Decahydronaphthalen-2-yl (morphinan-3-yloxy)methyl carbonate;
(+)-Decahydronaphthalen-1-yl (morphinan-3-yloxy)methyl carbonate;
(+)-Cyclopentylmethyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Cyclobutylmethyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-2-Ethylhexyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Butyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Isobutyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-sec-Butyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Cycloheptyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-(Morphinan-3-yloxy)methyl phenethyl carbonate TFA;
(+)-(Morphinan-3-yloxy)methyl 1-phenylpropan-2-yl carbonate TFA;
(+)-Ethyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Methyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Cyclobutyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Hexyl (morphinan-3-yloxy)methyl carbonate TFA
(+)-(Morphinan-3-yloxy)methyl pentan-2-yl carbonate TFA
(+)-Decyl (morphinan-3-yloxy)methyl carbonate TFA
(+)-(Morphinan-3-yloxy)methyl isobutyrate;
(+)-(Morphinan-3-yloxy)methyl pivalate;
(+)-(Morphinan-3-yloxy)methyl pivalate TFA;
(+)-(Morphinan-3-yloxy)methyl 3,3-dimethylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl hexanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 2-propylpentanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 2-ethylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl cyclohexanoate TFA;
(+)-(Morphinan-3-yloxy)methyl cyclopentanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 2-ethylhexanoate TFA;
(+)-(Morphinan-3-yloxy)methyl butanoate TFA;
(+)-(Morphinan-3-yloxy)methyl pentanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 2-methylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl cyclopropanecarboxylate TFA;
(+)-(Morphinan-3-yloxy)methyl 3-methylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 2-phenylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 1-adamantancarboxylate TFA;
(+)-(Morphinan-3-yloxy)methyl acetate TFA;
(+)-(Morphinan-3-yloxy)methyl 3-cyclohexylpropanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 3,5,5-trimethylhexanoate TFA;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate L-(+)-tartaric acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate HCl;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate formic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate citric acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate fumaric acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate fumaric acid mono-Na;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate 4-methylbenzenesulfonic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate stearic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate succinic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate salicylic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate succinic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate HCl;
(+)-(Morphinan-3-yloxy)methyl pivalate formic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate citric acid;
(+)-(Morphinan-3-yloxy)methyl pivalate fumaric acid;
(+)-(Morphinan-3-yloxy)methyl pivalate fumaric acid mono-Na;
(+)-(Morphinan-3-yloxy)methyl pivalate 4-methylbenzenesulfonic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate stearic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate citric acid di-Na;
(+)-(Morphinan-3-yloxy)methyl pivalate L-(+)-tartaric acid;
(+)-(Morphinan-3-yloxy)methyl pivalate L-(−)-malic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate L-(+)-lactic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate salicylic acid;
(+)-(Benzyloxycarbonylmorphinan-3-yloxy)methyl isopropyl carbonate;
(+)-(Benzyloxycarbonylmorphinan-3-yloxy)methyl cyclopentyl carbonate;
(+)-(Benzyloxycarbonylmorphinan-3-yloxy)methyl cyclohexyl carbonate;
(+)-(Benzyloxycarbonylmorphinan-3-yloxy)methyl decahydronaphthalen-1-yl carbonate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclopentylmethyl carbonate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclobutylmethyl carbonate;

(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-ethylhexyl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl butyl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl isobutyl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl sec-butyl carbonate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cycloheptyl carbonate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl phenethyl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 1-phenylpropan-2-yl carbonate;

(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl ethyl carbonate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl methyl carbonate;

(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclobutyl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl heptyl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl pentan-2-yl carbonate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl isobutyrate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl pivalate;

(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl hexanoate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-propylpentanoate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-ethylbutanoate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclohexanoate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclopentanoate;

(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-ethylhexanoate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl butanoate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl pentanoate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-methylbutanoate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclopropanecarboxylate;
(+)-[N-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 3-methylbutanoate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-phenylbutanoate;
(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 1-adamantanecarboxylate; and

(+)-iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl
GENERAL SYNTHESIS OF THE COMPOUNDS OF FORMULA (I)

The compound of formula (Ia) may be prepared by, for example, (i) reacting a (+)-3-hydroxymorphinan ((+)-3-HM) hydrobromide (1) with CbzCl in aqueous NaOH to provide (+)-N-17-Cbz-3-hydroxymorphinan of formula (2), and (ii) alkylating the resulting product with iodomethyl alkyl carbonate (3) in the presence of an appropriate base such as cesium carbonate, or sodium hydride, or DBU to yield alkyl phenoxy methyl carbonate of formula (4), and finally (iii) deprotecting N-17-Cbz group of the resulting product to obtain a compound of formula (Ia), as shown in Reaction Scheme 1.

Reaction Scheme 1

in 3,5,5-trimethylhexanoate.

wherein R_2 has the same meanings as defined above.

The iodomethyl alkyl carbonate derivative (3) used as a starting material in preparing the compound of formula (Ia) may be prepared by a conventional method, e.g., by treating an chloroformic acid chloromethyl ester (5) with an alcohol in anhydrous ether with an organic base such as pyridine or DMAP to produce a corresponding chloromethyl alkyl carbonate (6), reacting the resulting product with sodium iodide in
an appropriate solvent such as acetone or acetonitrile to provide a corresponding iodomethyl alkyl carbonate (3)(see Rigel Pharmaceuticals, Inc., US2006/247287 Al), as shown in Reaction Scheme 2.

\[ \begin{align*}
\text{Reaction Scheme 2} \\
\text{Cl} \quad \text{O} \quad \text{Cl} \\
(5) \\
\text{X} + \text{R}_2\text{OH}_{\text{ether}} \quad \text{pyridine} \\
\text{Cl} \quad \text{O} \quad \text{R}_2 \quad \text{O} \\
(6) \\
\text{Nal acetone} \\
\text{Cl} \quad \text{O} \quad \text{R}_2 \\
(3)
\end{align*} \]

wherein \( \text{R}_2 \) has the same meanings as defined above.

The compound of formula (Ib) may be prepared by (i) reacting a (+)-3-hydroxymorphinan hydrobromide (1) with CbzCl in aqueous NaOH to provide (+)-N-17-Cbz-3-hydroxymorphinan of formula (2), and (ii) alkylating the resulting product with iodomethyl ester (7) in the presence of an appropriate base such as cesium carbonate, or sodium hydride, or DBU to yield phenoxymethyl ester of formula (8), and finally (iii) deprotecting N-17-Cbz group of the resulting product to obtain the compound of formula (Ib), as shown in Reaction Scheme 3.

\[ \begin{align*}
\text{Reaction Scheme 3} \\
\text{OH} \\
(1) \\
\text{CbzCl, aq. NaOH} \\
1,4-\text{dioxane} \\
\text{O} \\
(2) \\
\text{I} \quad \text{O} \quad \text{C} \quad \text{R}_2 \\
(7) \\
\text{Base} \\
\text{O} \\
(8) \\
\text{Pd/C} \\
\text{H}_2 \\
\text{O} \\
(\text{lb})
\end{align*} \]
Reaction Scheme 4

\[
\text{Cl} \quad \text{O} \quad R_2 \quad \xrightarrow{\text{Nal acetone}} \quad \text{I} \quad \text{O} \quad R_2
\]

wherein \( R_2 \) has the same meanings as defined above.

The iodomethyl ester derivative (7) used as a starting material in preparing the compound of formula (Ib) may be prepared by treating an chloromethyl ester (9) with sodium iodide in an appropriate solvent such as acetone or acetonitrile to provide a corresponding iodomethyl ester (7) as shown in Reaction Scheme 4 (see Bristol-Myers Squibb Company, US5470845 Al).

Alternatively, the preparation of compounds of the formula (Ib) is illustrated in Reaction Scheme 5 wherein, \( R_2 \) has the same meanings as defined above. The compound of formula (2) is deprotonated with a base such as sodium hydride in an appropriate solvent such as HMPA and then alkylated with chloromethyl methyl sulfide to provide the thiomethyl methyl ether (9). Treatment of the compound of formula (9) with a chlorinating agent such as sulfuryl chloride provides the chloromethyl ether of formula (10) which is then treated with a carboxylic acid in the presence of a suitable base such as cesium carbonate to provide the phenoxymethyl ester of formula (8). Finally, deprotecting N-17-Cbz group of the resulting product using Pd on charcoal under hydrogen atmosphere yields the compound of formula (Ib).
Formation of a salt form of these compounds may be obtained as illustrated in Reaction Scheme 6. Thus, Cbz-protected compound of structure (4) may be subjected to hydrogenation on Pd/C in IPA. The reaction mixture may be filtered through a Celite. To the IPA solution may be added a particular acid, for example, L-(+)-tartaric acid (11). After thorough mixing these ingredients (for example, by stirring at 40 °C for 30 min), IPA may be switched to EtOAc in order to give better solid state characteristics. The solid may then be filtered and washed with EtOAc to give the drug substance such as (Ia’) with minimal impurities.

Compounds according to Formula (I) may contain a basic functional group and are therefore capable of forming pharmaceutically-acceptable acid addition salts by
treatment with a suitable acid. Suitable acids include pharmaceutically-acceptable inorganic acids and pharmaceutically-acceptable organic acids. Representative pharmaceutically-acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methyl nitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenylacetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, p-aminosalicylate, glycolate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, o- acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), p-aminobenzenesulfonate, p-toluenesulfonate (tosylate), and naphthalene-2- sulfonate.

The compounds of the invention may exist in solid or liquid form. In the solid state, the compounds of the invention may exist in crystalline or noncrystalline form, or as a mixture thereof. For compounds of the invention that are in crystalline form, the skilled artisan will appreciate that pharmaceutically-acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve nonaqueous solvents such as acetone, ethanol, n-propanol, isopropanol, n- butanol, t-butanol, DMSO, acetic acid, ethanolamine, and ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of the invention that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder
diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

The compound of formula (I) is subjected to the hydrolysis in vivo and, then, converted into its parent compound, i.e., (+)-3-HM which is effective as a neuroprotective agent for Parkinson's disease. Accordingly, the compound of formula (I) is useful in treating or preventing Parkinson's disease.

The pharmaceutical composition may be administered orally, intramuscularly or subcutaneously. The formulation for oral administration may take various forms such as a syrup, tablet, capsule, cream and lozenge. A syrup formulation will generally contain a suspension or solution of the compound or its salt in a liquid carrier, e.g., ethanol, peanut oil, olive oil, glycerine or water, optionally with a flavoring or coloring agent. When the composition is in the form of a tablet, any one of pharmaceutical carriers routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. When the composition is in the form of a capsule, any of the routine encapsulation procedures may be employed, e.g., using the aforementioned carriers in a hard gelatin capsule shell. When the composition is formulated in the form of a soft gelatin shell capsule, any of the pharmaceutical carrier routinely used for preparing dispersions or suspensions may be prepared using an aqueous gum, cellulose, silicate or oil. The formulation for intramuscular or subcutaneous administration may take a liquid form such as a solution, suspension and emulsion which includes aqueous solvents such as water, physiological saline and Ringer's solution; or lipophilic solvents such as fatty oil, sesame oil, corn oil and synthetic fatty acid ester.

Preferably the composition is formulated in a specific dosage form for a particular patient.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/kg, and preferably from 1 mg to 100 mg/kg of the compound of Formula (I) or its pharmaceutically acceptable salt.
The suitable daily dosage for oral administration is about 0.1 mg/kg to 3 g/kg of the compound of Formula (I) or its pharmaceutically acceptable salt, may be administered 1 to 3 times a day or every two days, depending on the patient's condition.

The present invention is further described and illustrated in Examples provided below, which are, however, not intended to limit the scope of the present invention.

Example

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

As used herein, the symbols and conventions used describing the processes, schemes and examples of the present invention are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. The following abbreviations are used in the Examples:

- Hz (Hertz)
- TLC (thin layer chromatography)
- $T_r$ (retention time)
- RP (reverse phase)
- MeOH (methanol)
- $/-PrOH$ (isopropanol)
- TFA (trifluoroacetic acid)
- TEA (triethylamine)
- EtOH (ethanol)
- THF (tetrahydrofuran)
- DMSO (dimethylsulfoxide)
- EtOAc (ethyl acetate)
- DCM (dichlromethane)
- HOAc (acetic acid)
- DMF ($\alpha',\alpha$-dimethylformamide)
- Ac (acetyl)
- CDI (1,1-carbonyldiimidazole)
- Bn (benzyl)
HOSu (N-hydroxysuccinimide)
HOBT (1-hydroxybenzotriazole)
Boc (tert-butyloxycarbonyl)
mCPBA (meta-chloroperbenzoic acid)
FMOC (9-fluorenylmethoxycarbonyl)
DCC (dicyclohexylcarbodiimide)
Cbz (benzyloxycarbonyl)
NMM (N-methyl morpholine)
HOAt (1-hydroxy-7-azabenzotriazole)
TBAF (tetrabutylammonium fluoride)
THP (tetrahydro-2H-pyran-2-yl)
DMAP (4-dimethylaminopyridine)
HPLC (high pressure liquid chromatography)
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
EDCI (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride)
HBTU(O-Benzotriazole-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate)
DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)
IPA (2-propanol)

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are of the highest available purity unless otherwise indicated.

Microwave reaction was conducted with a Biotage microwave reactor.

1H NMR spectra were recorded on either a Jeol ECX-400, or a Jeol JNM-LA300 spectrometer. Chemical shifts were expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d(doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

Mass spectra were obtained with either a Micromass, Quattro LC Triple Quadrupole Tandem Mass Spectrometer, ESI or Agilent, 6110 Quadrupole LC/MS, ESI.

For preparative HPLC, ca 100 mg of a product was injected in 1 mL of DMSO.
onto a SunFire™ Prep C18 OBD 5 um 19x100mm Column with a 10 min gradient from 10% CH$_3$CN to 90% CH$_3$CN in H$_2$O. Flash chromatography was carried using Merck silica gel 60 (230-400 mesh). Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light using a 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution.

**Experiment 1.** Permeability measurement by performing a drug transport assay with MDCK monolayers

(+)-3-HM was dissolved in DMSO at 10 mM and stored at 4 °C. MDCK cells were obtained from the ATCC (American Type Culture Collection, CCL-34). MDCK cells were maintained in DMEM (Dulbecco's MEM with high glucose) containing 1X NEAA (Non-essential amino acids), 10 mM HEPES, 100 units penicillin, 0.1 mg/ml streptomycin and 8% FBS. The cells were cultivated in T-75 flasks in a cell culture incubator at 37 °C. MDCK cells were passaged twice per week. When the cells were 90% confluence, the cells were plated at 1 X $10^5$ cells/well in transwell. The cells were fed with fresh medium every other day. The Cells were grown to confluence on the transwell for 5 days. When the cells have reached confluence and are differentiated, they are ready to be used for transport studies. The TEER (Transepithelial electrical resistance) of each well was measured by Millicell-ERS system ohm meter. The electrode was immersed in 70% ethanol and PBS for 15 minutes. Then, system was adjusted with a screwdriver at the voltage potentiometer until the meter shows a voltage reading of 0.0 and the electrical resistance for each well was recorded. MDCK monolayers with TEER values >400 Ω were used. After the each well was washed by using sterile HBSS (hank's buffered solution) and (+)-3-HM was diluted 100-fold in HBSS, the apical wells were filled with 200 ul of the test compounds. The basolateral wells were filled with 1 ml of HBSS buffer. Only 0.1 % DMSO treated wells prepared to adjust for analysis. The cells were incubated at 37 °C for 1 hour. At the end of the transport period, the result samples were removed from the apical (150 ul) and basolateral (900 ul) wells. The representative compounds of Examples were conducted in same conditions.
**Experiment 2.** The HPLC analysis and the calculation of $P_{app}$

HPLC analyses were performed using a WATERS HPLC system. A ZORBAX Eclipse XDB-Cl 8 (4.6 x 250 mm, 5 µm particle size) was used. The optimal operating conditions are as follows: Mobile phase A is composed of distilled water-acetonitrile (ACN) (9:1, v/v) with 0.1% trifluoroacetic acid (TFA), and mobile phase B is 90% acetonitrile with 0.1% TFA. All buffers were used after the 0.45 µm filtration.

The UV detection was performed at 280 nm or the fluorescence detection was performed at Excitation in 228 nm and Emission in 330 nm.

The concentration of A and B buffer was performed by the gradient method and the total analysis time was 38 min. The optimal operating conditions: elution gradient 0-10 min (10-50%), 10-20 min (50-90%), 20-25 min (90%), 25-27 min (90-10%), 27-38 min (10%). After the analysis of HPLC, the percentage of area of (+)-3-HM and the compound of Example 2 were calculated by remained concentration ($µg/ml$).

The apparent permeability coefficients ($P_{app}$), expressed in nm/sec, were calculated by the following equation:

$$Permeability \ (P_{app}) = \frac{\text{Receiver Volume} \times \text{Receiver Conc.}}{\text{Filter surface area} \times \text{Reaction Time} \times \text{donor Conc.}} \times 10^7.$$  

When MDCK $P_{app}$ values were plotted against percent human absorption, an approximately sigmoidal relationship was observed (JENNIFER D. IRVINE et al., *Journal of Pharmaceutical Sciences, Vol. 88, No. 1, January 1999*).

Well-absorbed prodrug compounds showed generally high $P_{app}$ values, and poorly absorbed compounds showed generally low $P_{app}$ values.

Permeability values for known drugs such as, acetaminophen, dexamethasone, and ketoprofen are 350, 200, and 200 nm/s, respectively, and clearly their human absorption values are pretty much high for the good oral bio-availability at 94, 98, and 100%, respectively.

The results are shown in Table 1. Table 1 demonstrates that permeability values of all the tested compounds are improved by 2-fold or more as compared with the parent molecule, (+)-3-HM. As permeability values of all the tested compounds are higher than 100 nm/s except for the compounds of Examples 56 and 58, they are expected to have excellent oral bio-availabilities.
Table 1. The apparent permeability coefficients ($P_{app}$) of (+)-3-HM and the compounds of the present invention.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>$P_{app}$ (nm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM</td>
<td>33.3</td>
</tr>
<tr>
<td>80</td>
<td>185.7</td>
</tr>
<tr>
<td>105</td>
<td>202.9</td>
</tr>
<tr>
<td>15</td>
<td>337.0</td>
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<tr>
<td>54</td>
<td>288.7</td>
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<tr>
<td>58</td>
<td>60.5</td>
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<tr>
<td>17</td>
<td>227.3</td>
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<tr>
<td>60</td>
<td>202.3</td>
</tr>
<tr>
<td>56</td>
<td>94.3</td>
</tr>
<tr>
<td>66</td>
<td>162.5</td>
</tr>
<tr>
<td>70</td>
<td>166.1</td>
</tr>
<tr>
<td>72</td>
<td>131.3</td>
</tr>
<tr>
<td>23</td>
<td>203.4</td>
</tr>
<tr>
<td>25</td>
<td>203.1</td>
</tr>
<tr>
<td>27</td>
<td>234.3</td>
</tr>
<tr>
<td>68</td>
<td>101.2</td>
</tr>
<tr>
<td>31</td>
<td>223.1</td>
</tr>
<tr>
<td>37</td>
<td>135.5</td>
</tr>
<tr>
<td>41</td>
<td>230.6</td>
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<tr>
<td>2</td>
<td>262</td>
</tr>
<tr>
<td>44</td>
<td>212</td>
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<td>6</td>
<td>206</td>
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<td>4</td>
<td>153</td>
</tr>
<tr>
<td>9</td>
<td>487</td>
</tr>
<tr>
<td>3</td>
<td>219</td>
</tr>
<tr>
<td>8</td>
<td>197</td>
</tr>
</tbody>
</table>

5 Experiment 3. Pharmacokinetics study

Male Sprague-Dawley rats (200-230g) were purchased from Charles River
Laboratory. Animals were housed under standard conditions of temperature, humidity and light. Food and water were provided *ad libitum*. The day before administration, a jugular vein cannula was implanted under anesthesia with 1mL/kg solution of ketamine:xylazine (90:10, v/v) by intraperitoneal injection for blood collection. Oral administration at a dose of 60mg/10ml/kg by oral gavages and/or intravenous administration at a dose of 10mg/1ml/kg were delivered. Blood (~0.3ml/sample) were collected into heparinized tubes at various time intervals after oral and/or intravenous administration of present invented compounds, and were centrifuged. Each plasma samples (~0.2ml) were immediately frozen at until analysis. The concentrations of parent molecule (+)-3-HM in plasma after the administration of (+)-3-HM or the compound of Example 2 were determined by HPLC (Waters 2487). The results are summarized in Tables 2.1 and 2.2. The maximum plasma concentration (C_{max}), the time to reach peak plasma concentration (T_{max}), terminal half-time (t_{y2}) and the area under the plasma concentration-time curve from zero to time infinity (AUC_{0-∞}) are the primary parameters. Overall, oral bioavailability of the compound of Example 2 (92.4%) is significantly higher than HM (17.85%) at the same dose. These results indicate that the compound of Example 2 has a favorable pharmacokinetic profile as a prodrug. Such pharmacokinetic profiles show that oral availability of the compound of Example 2 has been improved by 4-fold or more (Table 2.2).

Table 2.1. Pharmacokinetic parameters of HM and the compound of Example 2 with i.v. injection experiments. Plasma concentration of (+)-3-HM were measured after (+)-3-HM or the compound of Example 2 is intravenously administered in rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HM (10mg/kg, i.v.)</th>
<th>The compound of Example 2 (10mg/kg, i.v.) (+)-3-HM</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{1/2} (hr)</td>
<td>2.55</td>
<td>1.57</td>
</tr>
<tr>
<td>CL (ml/hr/kg)</td>
<td>1.02</td>
<td>3.34</td>
</tr>
<tr>
<td>AUC last (hr×μg/ml)</td>
<td>3.15</td>
<td>2.70</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>3.33</td>
<td>1.73</td>
</tr>
</tbody>
</table>

CL: Clearance (with units of flow per weights; mL/hr/kg) is the volume of blood or plasma that must be cleared of drug in unit time per unit weight of individual.
MRT: Mean Residence time is the arithmetic mean of the duration that each drug molecule resides in the body (MRT = AUMC/AUC).
Table 2.2. Pharmacokinetic parameters of HM and the compound of Example 2 with oral administration experiments. Plasma concentration of HM were measured after (+)-3-HM and the compound of Example 2 are delivered orally in rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HM (60mg/kg, p.o.)</th>
<th>The compound of Example 2 (60mg/kg, p.o.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>0.33</td>
<td>2.00</td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu$ g / kg)</td>
<td>0.59</td>
<td>2.38</td>
</tr>
<tr>
<td>AUC last (hr× $\mu$ g / ml)</td>
<td>3.38</td>
<td>14.89</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>3.14</td>
<td>5.41</td>
</tr>
</tbody>
</table>

**Experiment 4.** *In vivo* efficacy measurement of (+)-3-HM and the compound of Example 2.

To examine the effect of (+)-3-HM and the compound of Example 2 on MPTP-induced Parkinson's animal model, C57BL6/J received daily MPTP injection for 7 days. (+)-3-HM (25mg/kg, i.p.) and the compound of Example 2 (25mg/kg, p.o.) administered 30 min before MPTP injection for the last 3 days and animals were sacrificed 3 days after the last MPTP injection. Brains were cut on a microtome and SNpc TH-immunoreactivity was performed by ABC methods. These results shown in Fig. 2 as TH-immunoreactive neurons throughout SNpc demonstrate that oral administration of the compound of Example 2 has more protection against MPTP-induced loss of dopamine neuron than intraperitoneal injection of HM at same dose.

**Example 1**

(+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy] methyl isopropyl carbonate

**Step 1:** (+)-3-Hydroxy-$\mathcal{N}$-(benzyloxycarbonyl)morphinan

To (+)-3-hydroxymorphinan (HM) hydrobromide (50.0 g, 154.2 mmol), sodium hydroxide (12.3 g, 308.4 mmol) in a mixture of 1,4-dioxane (200 mL) and water (200 mL) was added Cbz-Cl (24.2 mL, 169.6 mmol) dropwise at room
temperature. The reaction mixture was stirred vigorously at room temperature overnight. After the reaction was completed, water (200 mL) was added. The mixture was extracted with diethyl ether (500 mL x 2). The combined organics were dried over MgSO₄, filtered, and evaporated under vacuum. Standing under high vacuum provided the title compound (57.7 g, 99%) as a light yellow solid. The compound was used for the next step without further purification.

MH+ 378.

Step 2: (+)-[iV-(Benzyloxy carbonyl)morphinan-3-yl oxy]methyl isopropyl carbonate

To (+)-3-hydroxy-N-(benzyloxy carbonyl)morphinan (33.0 g, 87.4 mmol) and cesium carbonate (28.5 g, 87.4 mmol) in acetone (450 mL) was added iodomethyl isopropyl carbonate (21.3 g, 87.4 mmol) (see Rigel Pharmaceuticals, Inc. US2006/247287 A1, Appl; US2006-381215 (2006/05/02)) at room temperature. The reaction mixture was stirred vigorously at room temperature overnight. The acetone was then removed by rotary evaporation under vacuum. To the residue was added saturated NaHCO₃ solution. The mixture was extracted with EtOAc (300 mL x 2). The combined organics were washed with iiv HCl solution (300 mL), dried over MgSO₄, filtered, and evaporated under vacuum to provide the title compound (42.0 g, 97%) as a yellow gum.

[α]D²⁷ +112.0° (c=1.0, MeOH); IR (KBr) νmax 2931, 1754, 1695, 1496, 1422, 1270, 1234, 1218, 1185, 1044 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.31 (m, 5H), 6.70-6.91 (m, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.65-6.61 (m, 1H), 5.21-5.09 (m, 2H), 4.93 (m, 1H), 4.37 (br d, J = 43.2 Hz, 1H),
3.96-3.84 (m, IH), 3.17-3.05 (m, IH), 2.76-2.56 (m, 2H), 2.34 (d, J = 10.8 Hz, IH) 5
1.72-1.43 (m, 6H), 1.43-1.26 (m, 9H), 1.08-0.99 (m, IH); 13C NMR (400 MHz, CDCl3) δ 155.8, 155.4, 153.7, 140.8, 136.9, 130.9, 130.7, 129.3, 129.2, 128.4, 127.9, 127.8, 114.0, 113.4, 88.6, 72.9, 66.9, 49.8, 43.7, 41.5, 38.3, 37.6, 36.4, 31.3, 26.4, 26.3, 22.3, 22.0, 21.7.

MH+ 494.

**Example 2**

(+) -Isopropyl (morphinan-3-yloxy)methyl carbonate

![Structural formula](image)

(+) -Isopropyl [N-(benzyloxy carbonyl) morphinan-3 -yloxy]methyl carbonate (42.0 g, 84.1 mmol) from Example 1 was subjected to hydrogenation (balloon) on 10 % Pd/C (6.3 g) in EtOH (250 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with EtOH (400 mL). The combined EtOH solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC to provide the title compound (5.82 g, 19 %) as a yellow solid.

[α]D27° +27.9° (c=1.0, MeOH); IR (KBr) νmax 2980, 2929, 2856, 1753, 1610, 1496, 1271, 1218, 1112, 1045 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.06 (d, J = 8.4 Hz, IH), 6.94 (d, J = 2.6 Hz, IH), 6.87 (dd, J = 8.4, 2.6 Hz, IH), 5.77 and 5.71 (AB q, J = 6.4 Hz, 2H), 4.93 (m, IH), 3.16-3.05 (m, 2H), 2.94-2.54 (m, 4H), 2.29 (d, J = 11.9 Hz, IH), 1.78-1.74 (m, IH), 1.66-1.50 (m, 3H), 1.41-1.20 (m, 10H), 1.07-0.99 (m, IH); 13C NMR (400 MHz, CDCl3) δ 155.6, 153.7, 141.8, 132.2, 128.8, 113.9, 113.1, 88.7, 72.6, 65.9, 50.9, 46.8, 42.2, 38.9, 38.2, 36.8, 33.1, 26.7, 26.6, 22.0, 21.7.

MH+ 360.

The following compounds of Examples 3 to 42 were obtained by repeating the procedure of Example 1 and Example 2.
Example 3
(+)-(Morphinan-3-yloxy)methyl propyl carbonate

\[
\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{O}
\end{array}
\]

\[ \delta 7.05 (d, J = 8.4 \text{ Hz}, \text{IH}), 6.94 (d, J = 2.0 \text{ Hz}, \text{IH}), 6.88 (dd, J = 8.4, 2.4 \text{ Hz}, \text{IH}), 5.77 \text{ and } 5.72 (\text{AB q, J} = 6.4 \text{ Hz}, \text{2H}), 4.14 (t, 6.6 \text{ Hz}, \text{2H}), 3.14-3.04 (m, \text{2H}), 2.84-2.57 (m, \text{4H}), 2.36-2.22 (m, \text{2H}), 1.82-1.61 (m, \text{5H}), 1.51-1.49 (m, \text{2H}), 1.40-1.30 (m, \text{2H}), 1.05-0.90 (m, \text{4H}).
\]

$\text{MH}^+ 360.$

Example 4
(+)-Cyclopropylmethyl (morphinan-3-yloxy)methyl carbonate

\[
\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{O}
\end{array}
\]

\[ \delta 7.05 (d, J = 8.4 \text{ Hz}, \text{IH}), 6.94 (d, J = 2.4 \text{ Hz}, \text{IH}), 6.83 (dd, J = 8.4, 2.4 \text{ Hz}, \text{IH}), 5.78 \text{ and } 5.73 (\text{AB q, J} = 6.4 \text{ Hz}, \text{2H}), 4.01(d, J = 9.2 \text{ Hz, 2H}), 3.16-3.08 (m, \text{2H}), 2.80-2.54 (m, \text{4H}), 2.28 (d, J = 13.2 \text{ Hz, 2H}), 1.81-1.76 (m, \text{IH}), 1.66-1.50 (m, \text{3H}), 1.42-1.26 (m, \text{4H}), 1.20-1.10 (m, \text{IH}), 1.09-1.00 (m, \text{IH}), 0.60 (m, \text{2H}), 0.32 (m, \text{2H}).
\]

$\text{MH}^+ 372.$

Example 5
(+)-[\Lambda-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl cyclopentyl carbonate

\[
\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{O}
\end{array}
\]

\[ \delta 7.05 (d, J = 8.4 \text{ Hz}, \text{IH}), 6.94 (d, J = 2.4 \text{ Hz}, \text{IH}), 6.83 (dd, J = 8.4, 2.4 \text{ Hz}, \text{IH}), 5.78 \text{ and } 5.73 (\text{AB q, J} = 6.4 \text{ Hz}, \text{2H}), 4.01(d, J = 9.2 \text{ Hz, 2H}), 3.16-3.08 (m, \text{2H}), 2.80-2.54 (m, \text{4H}), 2.28 (d, J = 13.2 \text{ Hz, 2H}), 1.81-1.76 (m, \text{IH}), 1.66-1.50 (m, \text{3H}), 1.42-1.26 (m, \text{4H}), 1.20-1.10 (m, \text{IH}), 1.09-1.00 (m, \text{IH}), 0.60 (m, \text{2H}), 0.32 (m, \text{2H}).
\]

$\text{MH}^+ 372.$
**Example 6**

(+)-Cyclopentyl (morphinan-3-yloxy)methyl carbonate

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl} _3\text{) } \delta 7.39-7.32 \text{ (m, 5H)}, 7.03 \text{ (t, J = 8.4 Hz, IH)}, 6.96 \text{ (s, IH)}, 6.88 \text{ (dd, J = 8.4, 2.4 Hz, IH)}, 5.75 \text{ and 5.70 (AB q, J = 6.4 Hz, 2H)}, 5.16-5.05 \text{ (m, 3H)}, 4.37 \text{ (br d, J = 43.2 Hz, IH)}, 3.96-3.84 \text{ (m, IH)}, 3.17-3.05 \text{ (m, IH)}, 2.76-2.56 \text{ (m, 2H)}, 2.32 \text{ (d, J = 10.8 Hz, IH)}, 1.98-1.51 \text{ (m, 13H)}, 1.50-1.25 \text{ (m, 4H)}, 1.08-0.99 \text{ (m, IH)}. \]

MH+ 520.

**Example 7**

(+)-[\Lambda-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl cyclohexyl carbonate

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl} _3\text{) } \delta 7.05 \text{ (d, J = 8.4 Hz, IH)}, 6.94 \text{ (d, J = 2.4 Hz, IH)}, 6.83 \text{ (dd, J = 8.4, 2.4 Hz, IH)}, 5.76 \text{ and 5.71 (AB q, J = 6.4 Hz, 2H)}, 5.15-5.09 \text{ (m, IH)}, 3.14-3.09 \text{ (in, 2H)}, 2.81-2.60 \text{ (m, 4H)}, 2.30-2.27 \text{ (m, IH)}, 1.89-1.49 \text{ (m, HH)}, 1.49-1.26 \text{ (m, 5H)}, 1.09-1.01 \text{ (m, IH)}. \]

MH+ 386.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.32 (m, 5H), 7.03 (t, J = 8.4 Hz, IH), 6.96 (s, IH), 6.88 (dd, J = 8.4, 2.4 Hz, IH), 5.77 and 5.72 (AB q, J = 6.4 Hz, 2H), 5.18-5.13 (m, 2H), 4.70-4.63 (m, IH), 4.37 (br d, J = 43.2 Hz, IH), 3.96-3.84 (m, IH), 3.15-3.05 (m, IH), 2.76-2.56 (m, 2H), 2.34 (d, J = 10.8 Hz, IH), 1.94-1.91 (m, 2H), 1.77-1.37 (m, 10H), 1.35-1.20 (m, 7H), 1.09-0.99 (m, IH).

MH$^+$ 534.

**Example 8**

(+)-Cyclohexyl (morphinan-3-yloxy)methyl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.05 (d, J = 8.4 Hz, IH), 6.94 (d, J = 2.4 Hz, IH), 6.83 (dd, J = 8.4, 2.4 Hz, IH), 5.77 and 5.72 (AB q, J = 6.4 Hz, 2H), 4.70-4.64 (m, IH), 3.16-3.10 (m, 2H), 2.81-2.58 (m, 4H), 2.30-2.28 (m, IH), 1.92-1.24 (m, 18H), 1.09-1.01 (m, IH).

MH$^+$ 400.

**Example 9**

(+)-Cyclohexylmethyl (morphinan-3-yloxy)methyl carbonate
\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] δ 7.05 (d, J = 8.4 Hz, IH), 6.94 (d, J = 2.4 Hz, IH), 6.83 (dd, J = 8.4, 2.4 Hz, IH), 5.76 and 5.72 (AB q, J = 6.4 Hz, 2H), 3.99 (d, J = 6.4 Hz), 3.16-3.08 (m, 2H), 2.80-2.54 (m, 4H), 2.30 (d, J = 12.8 Hz, IH), 1.75-1.64 (m, 8H), 1.51-1.13 (m, 9H), 1.11-0.93 (m, 3H).

MH+ 414.

Example 10

(+)-Heptan-4-yl (morphinan-3-yloxy)methyl carbonate

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] δ 7.05 (d, J = 8.4 Hz, IH), 6.94 (d, J = 2.8 Hz, IH), 6.86 (dd, J = 8.4, 2.8 Hz, IH), 5.75 and 5.72 (AB q, J = 7.6 Hz, 2H), 4.80-4.76 (m, IH), 3.16-3.04 (m, 2H), 2.78-2.52 (m, 4H), 2.28 (d, J = 12.0 Hz, IH), 1.82-1.72 (m, IH), 1.70-1.46 (m, 8H), 1.44-1.24 (m, 7H), 1.12-0.98 (m, 2H), 0.91 (t, J = 7.2 Hz, 6H).

MH+ 416.

Example 11

(+)-Decahydonaphthalen-2-yl (morphinan-3-yloxy)methyl carbonate
\( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.04 (d, \( J = 8.4 \) Hz, 5H), 6.93 (s, IH), 6.86 (d, \( J = 8.4 \) Hz, 5H), 5.76-5.69 (m, 2H), 4.65-4.61 (m, IH), 3.19-3.07 (m, 2H), 2.76-2.65 (m, 4H), 2.28 (d, \( J = 12.9 \) Hz, 1H), 1.75-1.64 (m, 8H), 1.51-1.13 (m, 15H), 1.1 (m, 2H).

\( \text{MH}^{+} \) 454.

**Example 12**

\[ (+)-[7\text{V}-(\text{Benzyloxycarbonyl})\text{morphman-3-yloxy}]\text{methyl decahydonaphthalen-1-yl carbonate} \]

\( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.36-7.32 (m, 5H), 7.07-6.98 (m, IH), 6.95 (s, IH), 6.87 (dd, \( J = 8.3 \) Hz, 2.4 Hz, 5H), 5.73-5.71 (m, 2H), 5.15-5.12 (m, 2H), 4.71 (m, IH), 4.40-4.30 (d, \( J = 29.4 \) Hz, 5H), 3.92-3.82 (m, IH), 3.11-3.03 (m, IH), 2.72-2.56 (m, 2H), 2.31-2.28 (m, IH), 2.18-2.01 (m, IH), 1.98-1.26 (m, 24H), 1.11-1.00 (m, IH).

\( \text{MH}^{+} \) 588.

**Example 13**

\[ (+)-\text{Decahydonaphthalen-1-yl (morphinan-3-yloxy)methyl carbonate} \]
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.05 (d, $J = 8.4$ Hz, IH), 6.93 (d, $J = 2.7$ Hz, IH), 6.87 (dd, $J = 8.4$, 2.7 Hz, IH), 5.77-5.70 (m, 2H), 4.71-4.68 (m, IH), 3.09-3.08 (m, 2H), 2.77-2.59 (m, 4H), 2.01-2.17 (m, IH), 1.82-1.64 (m, 8H), 1.64-1.18 (m, 15H), 1.11-0.93 (m, 2H).

MH+ 454.

Example 14

(+)-[iV-(Benzyloxy carbonyl)morphinan-3-yloxy] methyl cyclopentylmethyl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.30 (m, 5H), 7.03-6.99 (m, IH), 6.96 (d, $J = 2.4$ Hz, IH), 6.87 (dd, $J = 8.4$, 2.4 Hz, IH), 5.73 (m, 2H), 5.16-5.11 (m, 2H), 4.41-4.31 (m, IH), 4.06 (d, $J = 7.2$ Hz, 2H), 3.98-3.82 (m, IH), 3.16-3.03 (m, IH), 2.71-2.58 (m, 2H), 2.38-2.31 (m, IH), 2.27-2.20 (m, IH), 1.80-1.42 (m, HH), 1.38-1.21 (m, 6H), 1.05-0.98 (m, IH).

MH+ 534.

Example 15

(+)-Cyclopentylmethyl (morphinan-3-yloxy)methyl carbonate TFA
**Example 16**

(+)-[JV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl cyclobutylmethyl carbonate

**Example 17**

(+)-Cyclobutylmethyl (morphinan-3-yloxy)methyl carbonate TFA
\[ ^1H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 9.00 \text{ (br s, IH)}, \ 7.12 \text{ (d, J = 8.0 Hz, IH)}, \ 6.95-6.92 \text{ (m, 2H)}, \ 5.76 \text{ and 5.71 (AB q, J = 6.8 Hz, 2H)}, \ 4.15 \text{ (d, J = 6.8 Hz, 2H)}, \ 3.70 \text{ (m, IH)}, \ 3.23-3.09 \text{ (m, 3H)}, \ 2.82-2.61 \text{ (m, 2H)}, \ 2.37-2.32 \text{ (m, IH)}, \ 2.12-2.02 \text{ (m, 3H)}, \ 1.97-1.76 \text{ (m, 5H)}, \ 1.68-1.62 \text{ (m, IH)}, \ 1.57-1.34 \text{ (m, 5H)}, \ 1.31-1.20 \text{ (m, IH)}, \ 1.09-1.01 \text{ (m, IH)}. \]

\[ \text{MH}^+ \ 386. \]

Example 18

(+)-[\text{IV-(Benzyloxy-carboiy]inorphinaii-3-yloxy}] \text{ methyl 2-ethylhexyl carbonate}

\[ ^1H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 7.40-7.29 \text{ (m, 5H)}, \ 7.02 \text{ (d, J = 8.0 Hz, IH)}, \ 6.95 \text{ (d, J = 2.0 Hz, IH)}, \ 6.87 \text{ (dd, J = 8.4, 2.4 Hz, IH)}, \ 5.75 \text{ and 5.71 (AB q, J = 6.4 Hz, 2H)}, \ 5.18-5.07 \text{ (m, 2H)}, \ 4.44-4.28 \text{ (m, IH)}, \ 4.13-4.05 \text{ (m, 2H)}, \ 3.98-84 \text{ (m, IH)}, \ 3.14-3.03 \text{ (m, IH)}, \ 2.74-2.56 \text{ (m, 2H)}, \ 2.35-2.31 \text{ (m, IH)}, \ 1.71-1.41 \text{ (m, 7H)}, \ 1.39-1.21 \text{ (m, HH)}, \ 1.07-0.98 \text{ (m, IH)}, \ 0.89-0.85 \text{ (m, 6H)}. \]

\[ \text{MH}^+ \ 564. \]

Example 19

(+)-2-\text{Ethylhexyl} \ (\text{morphinan-3-yloxy})\text{methyl carbonate} \text{ TFA}
$^1$H NMR (400 MHz, CDCl$_3$) δ 9.03 (br s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.99-6.92 (m, 2H), 5.76 and 5.71 (AB q, J = 6.8 Hz, 2H), 4.13-4.05 (m, 2H), 3.71 (m, 1H), 3.24-3.11 (m, 3H), 2.76 (m, 1H), 2.35 (d, J = 14.0 Hz, 1H), 2.08 (d, J = 12.4 Hz, 1H), 2.00-1.92 (m, 1H), 1.68-1.26 (m, 16H), 1.09-1.00 (m, 1H), 0.89-0.84 (m, 6H). MH+ 430.

**Example 20**

(+)-(N-Butyloxycarbonyl)morphinan-3-yloxy] methyl butyl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40-7.28 (m, 5H), 7.04-6.98 (m, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.87 (dd, J = 8.4, 2.4 Hz, 1H), 5.75 and 5.71 (AB q, J = 6.4 Hz, 2H), 5.18-5.08 (m, 2H), 4.41-4.28 (m, 1H), 4.17 (t, J = 6.4 Hz, 2H), 3.96-3.76 (m, 1H), 3.15-3.03 (m, 1H), 2.72-2.55 (m, 2H), 2.35-2.30 (m, 1H), 1.72-1.44 (m, 7H), 1.41-1.19 (m, 6H), 1.08-0.96 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H). MH+ 508.

**Example 21**

(+)-Butyl (morphinan-3-yloxy)methyl carbonate TFA

33
**Example 22**

(+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl isobutyl carbonate

\[ ^{1}H\text{NMR (400 MHz, CDCl}_{3}\text{)} \delta 7.39-7.29 (m, 5H), 7.08-6.98 (m, IH), 6.96 (s, IH), 6.87 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.72 (AB q, J = 6.4 Hz, 2H), 5.16-5.11 (m, 2H), 4.41-4.31 (m, IH), 3.95 (d, J = 6.4 Hz, 2H), 3.86-3.77 (m, IH), 3.13-3.03 (m, IH), 2.75-2.55 (m, 2H), 2.36-2.30 (m, IH), 2.04-1.92 (m, IH), 1.72-1.45 (m, 5H), 1.39-1.21 (m, 4H), 1.10-0.99 (m, IH), 0.93 (d, J = 6.8 Hz, 6H). MH+ 508.

**Example 23**

(+)-Isobutyl (morphinan-3-yloxy)methyl carbonate TFA

\[ ^{1}H\text{NMR (400 MHz, CDCl}_{3}\text{)} \delta 8.84 (br s, IH), 7.12 (d, J = 8.4 Hz, IH), 6.99-6.93 (m, 2H), 5.76 and 5.71 (AB q, J = 6.4 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 3.76 (m, IH), 3.24-3.08 (m, 3H), 2.77 (m, IH), 2.35 (d, J = 13.6 Hz, IH), 2.06 (d, J = 12.0 Hz, IH), 1.96-1.90 (m, IH), 1.69-1.51 (m, 3H), 1.49-1.34 (m, 7H), 1.26-1.20 (m, IH), 1.10-1.00 (m, IH), 0.92 (t, J = 7.2 Hz, 3H). MH+ 374.

\[ ^{1}H\text{NMR (400 MHz, CDCl}_{3}\text{)} \delta 7.39-7.29 (m, 5H), 7.08-6.98 (m, IH), 6.96 (s, IH), 6.87 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.72 (AB q, J = 6.4 Hz, 2H), 5.16-5.11 (m, 2H), 4.41-4.31 (m, IH), 3.95 (d, J = 6.4 Hz, 2H), 3.86-3.77 (m, IH), 3.13-3.03 (m, IH), 2.75-2.55 (m, 2H), 2.36-2.30 (m, IH), 2.04-1.92 (m, IH), 1.72-1.45 (m, 5H), 1.39-1.21 (m, 4H), 1.10-0.99 (m, IH), 0.93 (d, J = 6.8 Hz, 6H). MH+ 508.

\[ ^{1}H\text{NMR (400 MHz, CDCl}_{3}\text{)} \delta 8.84 (br s, IH), 7.12 (d, J = 8.4 Hz, IH), 6.99-6.93 (m, 2H), 5.76 and 5.71 (AB q, J = 6.4 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 3.76 (m, IH), 3.24-3.08 (m, 3H), 2.77 (m, IH), 2.35 (d, J = 13.6 Hz, IH), 2.06 (d, J = 12.0 Hz, IH), 1.96-1.90 (m, IH), 1.69-1.51 (m, 3H), 1.49-1.34 (m, 7H), 1.26-1.20 (m, IH), 1.10-1.00 (m, IH), 0.92 (t, J = 7.2 Hz, 3H). MH+ 374.

\[ ^{1}H\text{NMR (400 MHz, CDCl}_{3}\text{)} \delta 7.39-7.29 (m, 5H), 7.08-6.98 (m, IH), 6.96 (s, IH), 6.87 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.72 (AB q, J = 6.4 Hz, 2H), 5.16-5.11 (m, 2H), 4.41-4.31 (m, IH), 3.95 (d, J = 6.4 Hz, 2H), 3.86-3.77 (m, IH), 3.13-3.03 (m, IH), 2.75-2.55 (m, 2H), 2.36-2.30 (m, IH), 2.04-1.92 (m, IH), 1.72-1.45 (m, 5H), 1.39-1.21 (m, 4H), 1.10-0.99 (m, IH), 0.93 (d, J = 6.8 Hz, 6H). MH+ 508.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.03 (br s, IH), 7.12 (d, $J = 8.4$ Hz, IH), 6.99-6.93 (m, 2H), 5.76 and 5.72 (AB q, $J = 6.8$ Hz, 2H), 3.96 (d, $J = 6.4$ Hz, 2H), 3.71 (m, IH), 3.24-3.10 (m, 3H), 2.76 (m, IH), 2.35 (d, $J = 13.6$ Hz, IH), 2.08 (d, $J = 13.2$ Hz, IH), 2.04-1.90 (m, IH), 1.68-1.65 (m, IH), 1.58-1.36 (m, 6H), 1.29-1.23 (m, IH), 1.09-1.03 (m, IH), 0.93 (d, $J = 7.2$ Hz, 6H).

MH$^+$ 374.

Example 24

(+)-(IV-(Benzyloxy carbonyl)morphinan-3-yl oxy)methyl sec-butyl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.27 (m, 5H), 7.02 (t, $J = 8.4$ Hz, IH), 6.95 (s, IH), 6.87 (dd, $J = 8.4$, 2.4 Hz, IH), 5.75 and 5.71 (AB q, $J = 6.8$ Hz, 2H), 5.14-5.08 (m, IH), 4.79-4.71 (m, IH), 4.41-4.30 (m, IH), 3.93-3.72 (m, IH), 3.14-3.04 (m, IH), 2.72-2.55 (m, 2H), 2.36-2.30 (m, IH), 1.74-1.44 (m, 8H), 1.40-1.28 (m, 4H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.08-0.95 (m, IH), 0.91 (t, $J = 7.6$ Hz, 3H).

MH$^+$ 508.

Example 25

(+)-sec-Butyl (morphinan-3-yloxy)methyl carbonate TFA
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.83 (br s, IH), 7.12 (d, $J = 8.0$ Hz, IH), 6.99-6.93 (m, 2H), 5.76 and 5.71 (AB q, $J = 6.4$ Hz, 2H), 4.75 (m, IH), 3.71 (m, IH), 3.24-3.08 (m, 3H), 2.78 (m, IH), 2.35 (d, $J = 14.0$ Hz, IH), 2.06 (d, $J = 12.0$ Hz, IH), 1.96-1.90 (m, IH), 1.70-1.33 (m, 8H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.25-1.23 (m, IH), 1.10-0.96 (m, IH), 0.91 (t, $J = 7.2$ Hz, 3H).

MH$^+$ 374.

Example 26

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.28 (m, 5H), 7.02 (t, $J = 8.8$ Hz, IH), 6.95 (s, IH), 6.87 (dd, $J = 8.4$, 2.4 Hz, IH), 5.74 and 5.70 (AB q, $J = 6.8$ Hz, 2H), 5.20-5.1 1 (m, 2H), 4.86-4.80 (m, IH), 4.41-4.30 (m, IH), 3.95-3.82 (m, IH), 3.13-3.03 (m, IH), 2.71-2.58 (m, 2H), 2.35-2.31 (m, IH), 2.00-1.92 (m, 2H), 1.76-1.60 (m, 6H), 1.57-1.34 (m, 9H), 1.32-1.21 (m, 4H), 1.07-1.01 (m, IH).

MH$^+$ 548.

Example 27

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.83 (br s, IH), 7.12 (d, $J = 8.0$ Hz, IH), 6.99-6.93 (m, 2H), 5.76 and 5.71 (AB q, $J = 6.4$ Hz, 2H), 4.75 (m, IH), 3.71 (m, IH), 3.24-3.08 (m, 3H), 2.78 (m, IH), 2.35 (d, $J = 14.0$ Hz, IH), 2.06 (d, $J = 12.0$ Hz, IH), 1.96-1.90 (m, IH), 1.70-1.33 (m, 8H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.25-1.23 (m, IH), 1.10-0.96 (m, IH), 0.91 (t, $J = 7.2$ Hz, 3H).

MH$^+$ 374.

Example 27

(+)-[7V-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl cycloheptyl carbonate TFA
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.30 (br s, IH), 7.12 (d, \( J = 8.4 \) Hz, IH), 6.96-6.93 (m, 2H), 5.76 and 5.71 (AB q, \( J = 6.8 \) Hz, 2H), 4.88-4.81 (m, IH), 3.62 (m, IH), 3.17-3.06 (m, 3H), 2.85-2.72 (m, 2H), 2.35 (d, \( J = 13.6 \) Hz, IH), 2.08 (d, \( J = 12.0 \) Hz, IH), 2.01-1.88 (m, 3H), 1.77-1.65 (m, 5H), 1.58-1.36 (m, 10H), 1.35-1.21 (m, IH), 1.07-1.03 (m, IH).

Example 28

 (+)-(\textit{N}-(Benzyl)oxycarbonyl)morphinan-3-yloxy)methyl phenethyl carbonate

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.38-7.19 (m, 10H), 7.09-7.00 (m, IH), 6.94 (s, IH), 6.86 (dd, \( J = 8.4, 2.4 \) Hz, IH), 5.75 and 5.71 (AB q, \( J = 6.8 \) Hz, 2H), 5.17-5.12 (m, 2H), 4.46-4.31 (m, 3H), 3.92-3.84 (m, IH), 3.29-3.05 (m, IH), 2.99 (t, \( J = 7.2 \) Hz, 2H), 2.74-2.60 (m, 2H), 2.35-2.29 (m, IH), 1.74-1.43 (m, 5H), 1.40-1.22 (m, 4H), 1.10-0.98 (m, IH).

MH+ 556.

Example 29

 (+)-(Morphinan-3-yloxy)methyl phenethyl carbonate TFA
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.11 (br s, IH), 7.36-7.18 (m, 5H), 7.13 (d, $J$ = 8.4 Hz, IH), 6.98-6.92 (m, 2H), 5.76 and 5.71 (AB q, $J$ = 6.8 Hz, 2H), 4.39 (t, $J$ = 7.2 Hz, 2H), 3.65 (m, IH), 3.29-3.05 (m, 3H), 2.99 (t, $J$ = 7.2 Hz, 2H), 2.84-2.73 (m, IH), 2.35 (d, $J$ = 13.2 Hz, IH), 2.03 (d, $J$ = 13.2 Hz, IH), 1.95-1.87 (m, IH), 1.69-1.36 (m, 6H), 1.30-1.21 (hi, IH), 1.10-1.01 (m, IH).

MH+ 422.

Example 30

(+)-(iV-(Benzyloxycarbonyl)morphinan-3-yloxy)methyl l-phenylpropan-2-yl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.33 (m, 6H), 7.25-7.17 (m, 4H), 7.03 (t, $J$ = 8.8 Hz, IH), 6.95 (d, $J$ = 2.4 Hz, IH), 6.86 (dd, $J$ = 8.4, 2.4 Hz, IH), 5.72 and 5.68 (AB q, $J$ = 6.8 Hz, 2H), 5.16-5.11 (m, 2H), 5.04-4.97 (m, IH), 4.43-4.31 (m, IH), 3.96-3.84 (m, IH), 3.15-2.98 (m, 2H), 2.81-2.76 (m, IH), 2.73-2.56 (m, 2H), 2.35-2.32 (m, IH), 1.73-1.45 (m, 4H), 1.40-1.30 (m, 5H), 1.28 (d, $J$ = 6.4 Hz, 3H), 1.09-1.01 (m, IH).

MH+ 570.

Example 31

(+)-(Morphinan-3-yloxy)methyl l-phenylpropan-2-yl carbonate TFA
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.33 (br s, 1H), 7.28-7.16 (m, 5H), 7.12 (d, $J = 8.2$ Hz, 1H), 7.08-7.01 (m, 1H), 6.96-6.90 (m, 2H), 5.73 and 5.68 (AB q, $J = 6.4$ Hz, 2H), 5.08-4.98 (m, 1H), 3.63 (m, 1H), 3.20-2.98 (m, 4H), 2.82-2.73 (m, 1H), 2.34 (d, $J = 13.6$ Hz, 1H), 2.09 (d, $J = 12.8$ Hz, 1H), 1.95-1.88 (m, 1H), 1.69-1.36 (m, 7H), 1.29 (d, $J = 5.6$ Hz, 3H), 1.28-1.22 (m, 1H), 1.10-1.01 (m, 1H).

MH$^+$ 436.

Example 32

(+)-[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl ethyl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.32 (m, 5H), 7.05-7.01 (m, 1H), 6.96 (s, 1H), 6.88 (dd, $J = 8.4$, 2.4 Hz, 1H), 5.77 and 5.72 (AB q, $J = 6.4$ Hz, 2H), 5.17-5.12 (m, 2H), 4.44-4.32 (m, 1H), 4.24 (q, $J = 6.8$ Hz, 2H), 3.96-3.83 (m, 1H), 3.16-3.04 (m, 1H), 2.76-2.56 (m, 3H), 2.38-2.31 (m, 1H), 1.73-1.49 (m, 5H), 1.44-1.33 (m, 3H), 1.32 (t, $J = 6.8$ Hz, 3H), 1.29-1.23 (m, 1H), 1.09-1.00 (m, 1H).

MH$^+$ 480.

Example 33

(+)-Ethyl (morphinan-3-yloxy)methyl carbonate TFA
\textbf{Example 34}

(+)\-[JV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl methyl carbonate

\textbf{Example 35}

(+)\-Methyl (morphinan-3-yloxy)methyl carbonate TFA
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.92 (br s, IH), 7.13 (d, $J = 8.4$ Hz, IH), 6.97-6.94 (m, 2H), 5.78 and 5.73 (AB q, $J = 6.8$ Hz, 2H), 3.83 (s, 3H), 3.67 (m, IH), 3.24-3.06 (m, 3H), 2.78 (m, IH), 2.36 (d, $J = 13.2$ Hz, IH), 2.04 (d, $J = 12.0$ Hz, IH), 1.95-1.86 (m, IH), 1.70-1.36 (m, 6H), 1.32-1.20 (m, IH), 1.11-1.00 (m, IH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.0 (s, C5), 133.4 (s, C3), 128.4 (d, $J = 16.4$ Hz, CH$_{2}$), 127.7 (s, C7), 126.0 (s, C6), 115.0 (d, $J = 21.2$ Hz, C9), 106.6 (s, C10), 64.2 (s, CH$_2$), 55.1 (s, OCH$_3$), 54.9 (d, $J = 3.0$ Hz, C11), 40.2 (s, C12), 39.6 (s, C13), 32.4 (s, C14), 21.0 (s, C15).

MH+ 332.

**Example 36**

(+)-[\(\alpha\)-(Benzyloxycarbonyl)morphinan-3-yl]oxy)methyl cyclobutyl carbonate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.29 (m, 5H), 7.05-7.00 (m, IH), 6.96 (s, IH), 6.87 (dd, $J = 8.4$, 2.8 Hz, IH), 5.75 and 5.70 (AB q, $J = 6.4$ Hz, 2H), 5.17-5.12 (m, 2H), 5.00-4.92 (m, IH), 4.42-4.31 (m, IH), 3.96-3.82 (m, IH), 3.16-3.03 (m, IH), 2.76-2.56 (m, 2H), 2.45-2.31 (m, 3H), 2.25-2.08 (m, 2H), 1.88-1.76 (m, IH), 1.73-1.45 (m, 6H), 1.42-1.22 (m, 4H), 1.08-1.00 (m, IH).

MH+ 506.

**Example 37**

(+)-Cyclobutyl (morphinan-3-yl)oxy)methyl carbonate TFA
\[ ^1H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 9.38 \text{ (br s, } \text{IH}), \ 7.12 \text{ (d, } J = 8.2 \text{ Hz, } \text{IH}), \ 6.97-6.93 \text{ (m, } 2\text{H}), \ 5.76 \text{ and } 5.71 \text{ (AB } q, J = 6.4 \text{ Hz, } 2\text{H}), \ 5.00-4.92 \text{ (m, } \text{IH}), \ 3.62 \text{ (m, } \text{IH}), \ 3.21-3.04 \text{ (m, } 3\text{H}), \ 2.74 \text{ (m, } \text{IH}), \ 2.46-2.31 \text{ (m, } 4\text{H}), \ 2.25-2.07 \text{ (m, } 4\text{H}), \ 1.99-1.77 \text{ (m, } 2\text{H}), \ 1.71-1.35 \text{ (m, } 5\text{H}), \ 1.32-1.21 \text{ (m, } \text{IH}), \ 1.10-1.00 \text{ (m, } \text{IH}). \]

MH+ 372.

Example 38

(+)-[iV-(Beizyloxycarboiiyl)morphinan-3-yloxy] methyl hexyl carbonate

\[ ^1H \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 7.39-7.28 \text{ (m, } 5\text{H}), \ 7.03 \text{ (t, } J = 8.8 \text{ Hz, } \text{IH}), \ 6.96 \text{ (s, } \text{IH}), \ 6.88 \text{ (dd, } J = 8.4, 2.4 \text{ Hz, } \text{IH}), \ 5.77 \text{ and } 5.72 \text{ (AB } q, J = 6.8 \text{ Hz, } 2\text{H}), \ 5.21-5.12 \text{ (m, } \text{IH}), \ 4.42-4.31 \text{ (m, } \text{IH}), \ 4.17 \text{ (t, } J = 7.2 \text{ Hz, } 2\text{H}), \ 3.96-3.84 \text{ (m, } \text{IH}), \ 3.14-3.05 \text{ (m, } \text{IH}), \ 2.72-2.57 \text{ (m, } 2\text{H}), \ 2.36-2.32 \text{ (m, } \text{IH}), \ 1.72-1.43 \text{ (m, } 7\text{H}), \ 1.43-1.23 \text{ (m, } \text{HH}), \ 1.05-0.96 \text{ (m, } \text{IH}), \ 0.88 \text{ (t, } J = 6.8 \text{ Hz, } 3\text{H}). \]

MH+ 536.

Example 39

(+)-Hexyl (morphinan-3-yloxy)methyl carbonate TFA
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.28 (br s, IH), 7.12 (d, \(J = 8.4\) Hz, IH), 7.00-6.93 (m, 2H), 5.78 and 5.74 (AB q, \(J = 6.8\) Hz, 2H), 4.20 (t, \(J = 6.4\) Hz, 2H), 3.65 (m, IH), 3.25-2.70 (m, 5H), 2.36 (d, \(J = 13.6\) Hz, IH), 2.11 (d, \(J = 12.0\) Hz, IH), 1.98-1.88 (m, IH), 1.78-1.22 (m, 14H), 1.16-1.01 (m, IH), 0.88 (t, \(J = 7.2\) Hz, 3H).

**MH+ 402.**

**Example 40**

(+)-(N-(Benzyloxy carbonyl)morphinan-3-yloxy)methyl pentan-2-yl carbonate

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39-7.31 (m, 5H), 7.03 (t, \(J = 8.4\) Hz, IH), 6.96 (s, IH), 6.88 (dd, \(J = 8.4, 2.4\) Hz, IH), 5.76 and 5.72 (AB q, \(J = 6.4\) Hz, 2H), 5.17-5.12 (m, 2H), 4.86-4.78 (m, IH), 4.43-4.31 (m, IH), 3.95-3.82 (m, IH), 3.14-3.04 (m, IH), 2.72-2.56 (m, 2H), 2.38-2.32 (m, IH), 2.20-2.06 (m, 3H), 1.73-1.59 (m, 3H), 1.56-1.43 (m, 3H), 1.42-1.30 (m, 4H), 1.26 (d, \(J = 6.4\) Hz, 3H), 1.08-1.01 (m, IH), 0.91 (t, \(J = 7.2\) Hz, 3H).

**MH+ 522.**

**Example 41**

(+)-(Morphinan-3-yloxy)methyl pentan-2-yl carbonate TFA
**Example 42**

(+)-Decyl (morphinan-3-yloxy)methyl carbonate TFA

\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 9.33 \text{ (br s, IH), 7.12 (d, J = 8.0 Hz, IH), 6.89-6.89 (m, 2H), 5.77 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.86-4.78 (m, IH), 3.61 (m, IH), 3.22-3.02 (m, 3H), 2.75 (m, IH), 2.35 (d, J = 14.0 Hz, IH), 2.20-2.06 (m, 3H), 1.98-1.87 (m, IH), 1.70-1.33 (m, 8H), 1.27 (d, J = 6.4 Hz, 3H), 1.25-1.23 (m, IH), 1.11-0.95 (m, IH), 0.91 (t, J = 7.2 Hz, 3H).} \]

MH+ 388.

**Example 43**

(+)-[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl isobutyrate

Step 1: (+)-[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl methyl sulfide

To Sodium hydride (763 mg of 60% dispersion in mineral oil, 19.1 mmol) in HMPA (15 mL) was added a solution of
(+)-3-hydroxy-N-(benzyloxycarbonyl)morphinan (6.00 g, 15.9 mmol) from Example 1 in HMPA (50 mL) at room temperature. The reaction mixture was stirred for 30 min and then chloromethyl methyl sulfide (1.60 mL, 19.1 mmol) was added dropwise. The reaction mixture was stirred vigorously at room temperature overnight. The product was extracted with EtOAc (500 mL). The EtOAc layer was washed with saturated NaHCO₃ solution and dried over MgSO₄, filtered and evaporated under vacuum to provide the crude product, which was further purified by prep reverse-phase HPLC to afford the title compound (1.78 g, 26%) as a yellow gum. MH+ 438.

Step 2: (+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl isobutyrate

To (+)-[N-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl methyl sulfide (1.78 g, 4.07 mmol) in DCM (40 mL) was added sulfuryl chloride (6.1 mL, 6.11 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. After removal of excess reagent and DCM by rotary evaporation, the product was dried under vacuum to afford (+)-[N-(benzyloxycarbonyl)morphinan-3-yloxy]methyl chloride as a yellow gum. Then, it was added to a stirred suspension of cesium carbonate (1.59 g, 4.88 mmol) and isobutyric acid (0.45 mL, 4.88 mmol) in acetone (20 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. After the reaction was completed, the reaction mixture was filtered and evaporated under vacuum to provide the crude product, which was further purified by prep reverse-phase HPLC to afford the title compound (0.844 g, 43%) as a yellow solid.

1H NMR (400 MHz, CDCl₃) δ 7.38-7.33 (m, 5H), 7.02-6.93 (m, 3H), 5.75 (s, 2H), 5.17-5.12 (m, 2H), 4.36 (d, J = 43.6 Hz, IH), 3.94-3.84 (m, IH), 3.14-3.04 (m, IH), 2.72-2.56 (m, 3H), 2.33 (d, J = 12.0 Hz, IH), 1.73-1.42 (m, 6H), 1.39-1.25 (m, 3H), 1.20 (d, J = 7.2 Hz, 6H), 1.11-1.00 (m, IH).
Example 44
(+)-(Morphinan-3-yloxy)methyl isobutyrate

(+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl isobutyrate (4.12 g, 8.63 mmol) from Example 44 was subjected to hydrogenation (balloon) on 10 % Pd/C (600 mg) in EtOH (100 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with EtOH (300 mL). The combined EtOH solution was evaporated under vacuum. The residue was further purified by reverse-phase prep HPLC to provide the title compound (1.11 g, 37 %) as a light yellow gum.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.05 (d, $J = 8.4$ Hz, IH), 6.93 (d, $J = 2.8$ Hz, IH), 6.83 (dd, $J = 8.4$, 2.8 Hz, IH), 5.76 and 5.74 (AB q, $J = 6.8$ Hz, 2H), 3.15-3.06 (m, 2H), 2.77-2.67 (m, 2H), 2.63-2.55 (m, 2H), 2.28 (d, $J = 13.2$ Hz, IH), 1.79-1.74 (m, IH), 1.66-1.50 (m, 3H), 1.39-1.26 (m, 5H), 1.18 (d, $J = 6.8$ Hz, 6H), 1.05-1.01 (m, IH).

MH+ 344.

Example 45
(+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy] methyl pivalate

Step 1: (+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl pivalate
To (+)-3-hydroxy-N-(benzyloxycarbonyl)morphman (12.0 g, 31.8 mmol) from Example 1 and cesium carbonate (11.4 g, 35.0 mmol) in acetone (150 mL) was added iodomethyl pivalate (8.46 g, 35.0 mmol) (Bristol-Myers Squibb Company, US5470845 A1 (1995/11/28), Appl.; US1994-266843 (1994/07/05)) at room temperature. The reaction mixture was stirred vigorously at room temperature overnight. The acetone was then removed by rotary evaporation under vacuum. To the residue was added saturated NaHCO₃ solution. The mixture was extracted with EtOAc (150 mL x 2). The combined organics were washed with 1N HCl solution (100 mL), dried over MgSO₄, filtered, and evaporated under vacuum to provide the crude product, which was further purified by prep reverse-phase HPLC to afford the title compound (13.2 g, 84%) as a yellow gum.

^1H NMR (400 MHz, CDCl₃) δ 7.39-7.32 (m, 5H), 7.02 (t, J = 8.8 Hz, IH), 6.97 (s, IH), 6.84 (dd, J = 8.4, 2.4 Hz, IH), 5.76 and 5.72 (AB q, J = 6.4 Hz, 2H), 5.20-5.09 (m, 2H), 4.37 (br d, J = 43.6 Hz, IH), 3.95-3.84 (m, IH), 3.15-3.05 (m, IH), 2.72-2.59 (m, 2H), 2.34 (d, J = 12.0 Hz, IH), 1.73-1.42 (m, 6H), 1.39-1.25 (m, 3H), 1.21 (s, 9H), 1.11-1.00 (m, IH).

MH+ 492.

Example 46

(+)-(Morphinan-3-yloxy)methyl pivalate

(+)[N-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl pivalate (13.2 g, 26.8
mmol) from Example 46 was subjected to hydrogenation (balloon) on 10 % Pd/C (2.0 g) in EtOH (100 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with EtOH (300 mL). The combined EtOH solution was evaporated under vacuum. The residue was further purified by reverse-phase prep HPLC to provide the title compound (4.31 g, 45 %) as a light yellow gum.

\[ {^1}H \text{ NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.05 (d, J = 8.4 Hz, IH), 6.94 (d, J = 2.7 Hz, IH), 6.83 (dd, J = 8.4, 2.7 Hz, IH), 5.76 and 5.71 (AB q, J = 6.4 Hz, 2H), 3.16-3.08 (m, 2H), 2.80-2.54 (m, 4H), 2.28 (d, J = 13.2 Hz, IH), 1.81-1.76 (m, IH), 1.66-1.50 (m, 3H), 1.42-1.26 (m, 4H), 1.21 (s, 9H), 1.09-1.00 (m, IH).

\[ \text{MH}^+ 358. \]

\section*{Example 47}

(-)-(Morphinan-3-yloxy)methyl pivalate TFA

(+)-(Morphinan-3-yloxy)methyl pivalate (4.66 g, 9.48 mmol) from Example 45 was subjected to hydrogenation (balloon) on 10 % Pd/C (470 mg) in IPA (40 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with IPA (20 mL). The combined IPA solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC with 0.1 % TFA to provide the title compound (3.79 g, 85 %) as a colorless gum.

\[ {^1}H \text{ NMR (400 MHz, CD}_3\text{OD} \] \( \delta \) 7.18 (d, J = 8.4 Hz, IH), 7.06 (d, J = 2.8 Hz, IH), 6.95 (dd, J = 8.4, 2.8 Hz, IH), 5.79 and 5.73 (AB q, J = 6.8 Hz, 2H), 3.70-3.26 (m, IH), 2.74-2.67 (m, IH), 2.46 (d, J = 14.0 Hz, IH), 1.94 (d, J = 12.0 Hz, IH), 1.87-1.78 (m, IH), 1.71 (d, J = 12.8 Hz, IH), 1.60-1.40 (m, 5H), 1.34-1.25 (m, IH), 1.17 (s, 9H), 1.15-1.07 (m, IH).

\[ \text{MH}^+ 358. \]
The following compounds of Examples 48 to 78 were obtained by repeating the procedure of Example 45 and Example 47.

5 **Example 48**

(+)-(Morphinan-3-yloxy)methyl 3,3-dimethylbutanoate **TFA**

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3 \text{) } \delta 9.45 \text{ (br, 2H), } 7.11 \text{ (d, } J = 8.4 \text{ Hz, IH), } 6.94 \text{ (d, } J = 2.8 \text{ Hz, IH), } 6.90 \text{ (dd, } J = 8.4, 2.8 \text{ Hz, IH), } 5.75 \text{ (s, 2H), } 3.15-3.06 \text{ (m, 2H), } 2.77-2.67 \text{ (m, 2H), } 2.63-2.55 \text{ (m, 2H), } 2.24 \text{ (d, } J = 4.0 \text{ Hz, 2H), } 1.79-1.74 \text{ (m, IH), } 1.66-1.50 \text{ (m, 3H), } 1.39-1.26 \text{ (m, 5H), } 1.28-1.24 \text{ (m, IH), } 1.05 \text{ (s, 9H).}
\]

MH+ 372.

10 **Example 49**

(+HiV-(Benzyloxy carbonyl)morphinan-3-yloxy)methyl **hexanoate**

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3 \text{) } \delta 7.34 \text{ (br, 5H), } 7.01 \text{ (d, } J = 8.4 \text{ Hz, IH), } 6.94 \text{ (d, } J = 2.4 \text{ Hz, IH), } 6.83 \text{ (dd, } J = 8.4, 2.4 \text{ Hz, IH), } 5.75 \text{ and } 5.73 \text{ (AB q, } J = 6.4 \text{ Hz, 2H), } 5.13 \text{ (br, 2H), } 4.40 \text{ (br, IH), } 3.89 \text{ (br, IH), } 3.09 \text{ (d, } J = 8.8 \text{ Hz, IH), } 2.70-2.62 \text{ (m, 2H), } 2.34 \text{ (t, } J = 7.6 \text{ Hz, 2H), } 1.75-1.40 \text{ (m, 6H), } 1.39-1.23 \text{ (m, 9H), } 1.06-0.90 \text{ (m, 2H), } 0.85 \text{ (t, } J = 7.2 \text{ Hz, 3H).}
\]

MH+ 506.
Example 50
(+)-(Morphinan-3-yloxy)methyl hexanoate TFA

\[ \text{H NMR (400 MHz, CDCl}_3\text{) } \delta 9.20 \text{ (br, 2H), 7.10 (d, } J = 8.4 \text{ Hz, IH)} \text{, 6.93 (d, } J = 2.0 \text{ Hz, IH), 6.90 (dd, } J = 8.4, 2.4 \text{ Hz, IH), 5.75 and 5.73 (AB q, } J = 6.8 \text{ Hz, 2H), 3.63 (br, 2H), 3.17-3.07 (m, 5H), 2.75 (br, 2H), 2.34 (d, } J = 7.6 \text{ Hz, 2H), 2.06 (d, } J = 12.4 \text{ Hz, 2H), 1.97-1.88 (m, 2H), 1.68-1.23 (m, 7H), 1.09-0.92 (m, 2H), 0.86 (t, } J = 6.8 \text{ Hz, 3H). MH} + 372. \]

Example 51
(+)-[JV-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl 2-propylpentaioate

\[ \text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.34 \text{ (br, 5H), 7.01 (d, } J = 8.4 \text{ Hz, IH), 6.95 (d, } J = 2.4 \text{ Hz, IH), 6.83 (dd, } J = 8.4, 2.4 \text{ Hz, IH), 5.76 and 5.74 (AB q, } J = 6.8 \text{ Hz, 2H), 5.12 (br, 2H), 4.39 (br, IH), 3.88 (br, IH), 3.12-3.06 (m, IH), 2.70-2.62 (m, 2H), 2.43-2.31 (m, 2H), 1.70-1.18 (m, 17H), 1.09-0.97 (m, IH), 0.81 (t, } J = 7.2 \text{ Hz, 6H). MH} + 534. \]

Example 52
(+)-(Morphinan-3-yloxy)methyl 2-propylpentanoate TFA
Example 53

(+)-(4-V-(Benzyloxy carbonyl)morphinan-3-yloxy)methyl 2-ethylbutanoate

\[ \text{MH}^+ 400. \]

Example 54

(+)-(Morphinan-3-yloxy)methyl 2-ethylbutanoate TFA

\[ \text{MH}^+ 506. \]
Example 55
(+)-[iv-(Benzyloxycarbonyl)morphinaii-3-loyloxy]inethyl cyclohexanoate

\[
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) \delta 8.67 (\textit{jar}, \text{IH}), 7.80 (\textit{br}, \text{IH}), 7.11 (d, J = 8.4 \text{ Hz}, \text{IH}), 6.96 (d, J = 2.4 \text{ Hz}, \text{IH}), 6.91 (dd, J = 8.4, 2.8 \text{ Hz}, \text{IH}), 5.78 \text{ and } 5.74 (\text{AB q, J = 6.8 Hz, 2H}), 3.70 (\textit{br}, \text{IH}), 3.24-3.13 (m, 2H), 3.07 (\textit{br d, J = 19.2 Hz}, \text{IH}), 2.77-2.75 (m, \text{IH}), 2.35 (d, J = 14.0 \text{ Hz}, \text{IH}), 2.28-2.21 (m, \text{IH}), 2.03 (d, J = 12.4 \text{ Hz}, \text{IH}), 1.94-1.86 (m, \text{IH}), 1.69-1.35 (m, 10H), 1.29-1.23 (m, \text{IH}), 1.11-1.01 (m, \text{IH}), 0.84 (t, J = 7.6 \text{ Hz}, 6H).
\]
\text{MH}^+ 372.

Example 56
(+)-(Morphinan-3-loyloxy)methyl cyclohexanoate TFA

\[
\text{\textsuperscript{1}HNMR (400 MHz, CDCl}_3) \delta 7.36-7.32 (m, 5H), 7.09-6.99 (m, \text{IH}), 6.94 (s, \text{IH}), 6.86-6.81 (m, \text{IH}), 5.74 \text{ and } 5.72 (\text{AB q, J = 6.4 Hz, 2H}), 5.16-5.12 (m, \text{2H}), 4.36 (\textit{br d, J = 42.0 Hz, 2H}), 3.94-3.84 (m, \text{2H}), 3.12-3.09 (m, \text{2H}), 2.67-2.49 (m, \text{3H}), 2.37-2.30 (m, \text{2H}), 2.05 (d, J = 13.6 \text{ Hz}, \text{2H}), 1.89 (d, J = 11.2 \text{ Hz}, \text{IH}), 1.88-1.79 (m, \text{IH}), 1.70-1.17 (m, \text{HH}), 1.09-1.00 (m, \text{IH}).
\]
\text{MH}^+ 518.
$^1$H NMR (400 MHz, CDCl$_3$) δ 11.06 (br, IH), 8.73 (br, IH) 7.13 (dd, J = 25.2, 8.4 Hz, IH), 6.96-6.88 (m, 2H), 5.75 and 5.71 (AB q, J = 6.8 Hz, 2H), 3.68 (br, IH), 3.23-3.02 (m, 2H), 2.76 (br, IH), 2.57-2.50 (m, IH), 2.36-2.31 (m, 2H), 2.06-2.03 (m, 2H), 1.90-1.13 (m, 17H), 1.09-1.01 (m, IH).

MH+ 384.

Example 57

(+)-(JV-(Benzyloxycarbonyl)morphinan-3-yloxy)methyl cyclopentanoate

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.37-7.30 (m, 5H), 7.01 (t, J = 9.2 Hz, IH), 6.95 (s, IH), 6.83 (dd, J = 8.4, 2.4 Hz, IH), 5.74 (s, 2H), 5.16-5.12 (m, 2H), 4.36 (br d, J = 42.0 Hz, 2H), 3.96-3.83 (m, 2H), 3.12-3.04 (m, 2H), 2.79-2.57 (m, 3H), 2.33 (d, J = 12.4 Hz, 2H), 1.90-1.23 (m, 12H), 1.06-1.03 (m, IH), 0.88-0.85 (m, IH).

MH+ 504.

Example 58

(+)-(Morphinan-3-yloxy)methyl cyclopentanoate TFA
\[ \text{Example 59} \]

\[ (+)-(\text{Benzyloxycarbonyl})\text{morphman-3-yloxy}]\text{methyl 2-ethylhexanoate} \]

\[ \text{\textsuperscript{1}HNMR (400 MHz, CDCl}_3 \text{) } \delta 8.79 \text{ (br, IH), 8.42 (br, IH), 7.11 (d, J = 8.4 Hz, IH), 6.95 (d, J = 2.4 Hz, IH), 6.91 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.73 (AB q, J = 6.8 Hz, 2H), 3.69 (br, IH), 3.23-3.12 (m, 3H), 2.81-2.73 (m, 2H), 2.34 (d, J = 13.6 Hz, IH), 2.04 (d, J = 12.4 Hz, IH), 1.98-1.35 (m, 15H), 1.30-1.20 (m, IH), 1.11-1.01 (m, IH).} \]

\[ \text{MH}^+ 370. \]

\[ \text{Example 60} \]

\[ (+)-(\text{Morphinan-3-yloxy})\text{methyl 2-ethylhexanoate TFA} \]

\[ \text{\textsuperscript{1}HNMR (400 MHz, CDCl}_3 \text{) } \delta 7.36-7.32 \text{ (m, 5H), 7.02-6.99 (m, IH), 6.95 (s, IH), 6.83 (dd, J = 8.4, 2.4 Hz, IH), 5.77 and 5.74 (AB q, J = 6.8 Hz, 2H), 5.12 (br, 2H), 4.36 (br d, J = 41.6 Hz, IH), 3.93-3.84 (m, IH), 3.12-3.07 (m, IH), 2.71-2.64 (m, 2H), 2.35-2.26 (m, 2H), 1.67-1.15 (m, 16H), 1.08-0.99 (m, IH), 0.86-0.78 (m, 6H).} \]

\[ \text{MH}^+ 534. \]
\[^1\text{H} \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 8.76 \ (\text{br}, \text{IH}), \ 7.11 \ (d, \ J = 8.4 \text{ Hz}, \ \text{IH}), \ 6.95 \ (d, \ J = 2.0 \text{ Hz}, \ \text{IH}), \ 6.92 \ (dd, \ J = 8.4, 2.0 \text{ Hz}, \ \text{IH}), \ 5.81 \ (br, \ \text{IH}), \ 5.78 \ \text{and} \ 5.75 \ (\text{AB} \ q, \ J = 6.8 \text{ Hz}, \ 2\text{H}), \ 3.73 \ (\text{br}, \ \text{IH}), \ 3.25-3.08 \ (m, \ 2\text{H}), \ 2.81-2.73 \ (m, \ \text{IH}), \ 2.36-2.27 \ (m, \ 2\text{H}), \ 2.06 \ (d, \ J = 12.0 \text{ Hz}, \ \text{-IH}), \ 1.96-1.91 \ (m, \ \text{IH}), \ 1.69-0.99 \ (m, \ 17\text{H}), \ 0.86-0.77 \ (m, \ 6\text{H}).
\]
\[\text{MH}^+ \ 400.\]

Example 61

(+-)[7V-(Benzyloxycarbonyl)morphinan-3-yloxy] methyl butanoate

\[^1\text{H} \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 7.34 \ (\text{br}, \ 5\text{H}), \ 7.02 \ (d, \ J = 8.0 \text{ Hz}, \ \text{IH}), \ 6.94 \ (d, \ J = 2.4 \text{ Hz}, \ \text{IH}), \ 6.84 \ (dd, \ J = 8.4, 2.4 \text{ Hz}, \ \text{IH}), \ 5.76 \ \text{and} \ 5.73 \ (\text{AB} \ q, \ J = 6.4 \text{ Hz}, \ 2\text{H}), \ 5.13 \ (br, \ 2\text{H}), \ 4.41 \ (br, \ \text{IH}), \ 3.88 \ (br, \ \text{IH}), \ 3.09 \ (d, \ J = 14.8 \text{ Hz}, \ \text{IH}), \ 2.70-2.66 \ (m, \ 2\text{H}), \ 2.33 \ (t, \ J = 7.6 \text{ Hz}, \ 2\text{H}), \ 1.71-1.22 \ (m, \ 12\text{H}), \ 1.08-0.99 \ (m, \ \text{IH}), \ 0.92 \ (t, \ J = 7.6 \text{ Hz}, \ 3\text{H}).
\]
\[\text{MH}^+ \ 478.\]

Example 62

(+-)(Morphinan-3-yloxy)methyl butanoate TFA
Example 63

(+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy] methyl pentanoate

Example 64

(+)-(Morphinan-3-yloxy)methyl pentanoate TFA
\[ ^1 \text{HNMR} \ (400 \text{ MHz, } \text{CDCl}_3) \delta 9.65 \ (\text{br, IH}), \ 8.40 \ (\text{br, IH}), \ 7.12 \ (d, J = 8.4 \text{ Hz, IH}), \ 6.95 \ (d, J = 2.4 \text{ Hz, IH}), \ 6.92 \ (dd, J = 8.4, 2.4 \text{ Hz, IH}), \ 5.76 \text{ and } 5.74 \ (\text{AB q, J = 6.8 Hz, 2H}), \ 3.74 \ (\text{br, IH}), \ 3.29-3.17 \ (m, 2H), \ 3.05 \ (\text{br d, J = 19.2 Hz, IH}), \ 2.81-2.79 \ (m, \text{ IH}), \ 2.38-2.34 \ (m, 3H), \ 2.03-2.01 \ (m, \text{ IH}), \ 1.94-1.86 \ (m, \text{ IH}), \ 1.71-1.21 \ (m, \text{ HH}), \ 1.11-1.02 \ (m, \text{ IH}), \ 0.88 \ (t, J = 7.6 \text{ Hz, 3H}). \]

Example 65

\ (+)-(\text{[I-V-(Benzyloxy]carbonyl)morphinan-3-yloxy]methyl 2-methylbutanoate})

\[ ^1 \text{H NMR} \ (400 \text{ MHz, } \text{CDCl}_3) \delta 7.34 \ (\text{br, 5H}), \ 7.01 \ (d, J = 8.4 \text{ Hz, IH}), \ 6.95 \ (d, J = 2.4 \text{ Hz, IH}), \ 6.83 \ (dd, J = 8.4, 2.4 \text{ Hz, IH}), \ 5.76 \text{ and } 5.73 \ (\text{AB q, J = 6.8 Hz, 2H}), \ 5.13 \ (\text{br, 2H}), \ 4.40 \ (\text{br, IH}), \ 3.88 \ (\text{br, IH}), \ 3.09 \ (dd, J = 18.0, 2.8 \text{ Hz, IH}), \ 2.70-2.59 \ (m, 2H), \ 2.43-2.38 \ (m, \text{ IH}), \ 2.33 \ (d, J = 12.8 \text{ Hz, IH}), \ 1.72-1.22 \ (m, \text{ HH}), \ 1.14 \ (d, J = 6.8 \text{ Hz, 3H}), \ 1.08-0.99 \ (m, \text{ IH}), \ 0.86 \ (t, J = 7.6 \text{ Hz, 3H}). \]

MH+ 492.

Example 66

\ (+)-(\text{Morphinan-3-yloxy)methyl 2-methylbutanoate TFA})
\(^1\)H NMR (400 MHz, CDCl\(_3\)) 8.53 (br, IH), 7.95 (t, IH), 7.12 (d, J = 8.4 Hz, IH), 6.96 (d, J = 2.4 Hz, IH), 6.92 (dd, J = 8.4, 2.4 Hz, IH), 5.77 and 5.74 (AB q, J = 6.8 Hz, 2H), 3.74 (br, IH), 3.26-3.17 (m, 2H), 3.08 (br d, J = 19.2 Hz, IH), 2.79 (br, IH), 2.45-2.34 (m, 2H), 2.06-2.01 (m, IH), 1.95-1.89 (m, IH), 1.71-1.39 (m, 8H), 1.29-1.23 (m, IH), 1.14 (d, J = 6.8 Hz, 3H), 1.08-1.01 (m, IH), 0.86 (t, J = 7.6 Hz, 3H).

MH+ 358.

Example 67

(+)-(iV-(Benzyloxycarboiiyl)morphman-3-yloxy)methyl cyclopropanecarboxylate

\(^1\)HNMR (400 MHz, CDCl\(_3\)) 8.53 (br, IH), 7.95 (t, IH), 7.12 (d, J = 8.4 Hz, IH), 6.96 (d, J = 2.4 Hz, IH), 6.92 (dd, J = 8.4, 2.4 Hz, IH), 5.77 and 5.74 (AB q, J = 6.8 Hz, 2H), 4.37 (br d, J = 42.0 Hz, IH), 3.94-3.84 (m, IH), 3.14-3.06 (m, IH), 2.78-2.54 (m, 2H), 2.33 (d, J = 12.4 Hz, IH), 1.67-1.23 (m, 10H), 1.07-1.03 (m, 3H), 0.91-0.87 (m, 2H).

MH+ 476.

Example 68

(+)-(Morphman-3-yloxy)methyl cyclopropanecarboxylate TFA
\textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 10.35 (br, 1H), 8.32 (br, 1H), 7.12 (d, \( J = 8.4 \) Hz, 1H), 6.94-6.91 (m, 2H), 5.75 and 5.73 (AB q, \( J = 6.8 \) Hz, 2H), 3.73 (br, 1H), 3.25-3.19 (m, 2H), 3.04 (br d, \( J = 19.2 \) Hz, 1H), 2.81-2.75 (m, 1H), 2.35 (d, \( J = 13.6 \) Hz, 1H), 2.01-1.99 (m, 1H), 1.91-1.85 (m, 1H), 1.70-1.24 (m, 8H), 1.10-1.01 (m, 3H), 0.95-0.90 (m, 2H).

MH+ 342.

Example 69

(+)-(\textit{iV}-(Benzyloxycarbonyl)morphinan-3-yloxy)methyl 3-methylbutanoate

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.34 (br, 5H), 7.01 (d, \( J = 8.4 \) Hz, 1H), 6.94 (d, \( J = 2.4 \) Hz, 1H), 6.83 (dd, \( J = 8.4, 2.8 \) Hz, 1H), 5.75 and 5.73 (AB q, \( J = 6.4 \) Hz, 2H), 5.13 (br, 2H), 4.40 (br, 1H), 3.88 (br, 1H), 3.09 (br d, \( J = 15.6 \) Hz, 1H), 2.70-2.59 (m, 2H), 2.33 (d, \( J = 12.4 \) Hz, 1H), 2.23 (d, \( J = 7.2 \) Hz, 2H), 2.13-2.06 (m, 1H), 1.71-1.22 (m, 9H), 1.09-1.02 (m, 1H), 0.92 (d, \( J = 6.8 \) Hz, 6H).

MH+ 492.

Example 70

(+)-(Morphinan-3-yloxy)methyl 3-methylbutanoate TFA
$^1$HNMR (400 MHz, CDCl$_3$) δ 12.86 (br, IH), 8.48 (br, IH), 7.10 (d, J = 8.8 Hz, IH), 6.94 (d, J = 2.4 Hz, IH), 6.91 (dd, J = 8.4, 2.4 Hz, IH), 5.74 (s, 2H), 3.71 (br, IH), 3.23-3.14 (m, 2H), 3.04 (br d, J = 19.2 Hz, IH), 2.78-2.76 (m, IH), 2.34 (d, J = 14.0 Hz, IH), 2.23 (d, J = 7.2 Hz, 2H), 2.13-2.05 (m, IH), 2.01-2.00 (m, IH), 1.92-1.85 (m, IH), 1.69-1.34 (m, 6H), 1.29-1.23 (m, IH), 1.10-0.97 (m, IH), 0.92 (d, J = 6.8 Hz, 6H).

MH+ 358.

Example 7

(+)-(Benzyloxycarbonyl)morphinaii-3-yloxy)methyl 2-phenylbutanoate

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.42-7.20 (m, 10H), 6.94 (d, J = 8.0 Hz, IH), 6.87 (dd, J = 6.8, 2.4 Hz, IH), 6.71-6.68 (m, IH), 5.74 and 5.67 (AB q, J = 6.8 Hz, 2H), 5.13 (br, 2H), 4.41 (br, IH), 3.86 (br, IH), 3.48 (t, J = 7.6 Hz, IH), 3.07 (br d, J = 14.4 Hz, IH), 2.68-2.64 (m, 2H), 2.28-2.22 (m, IH), 2.15-2.04 (m, IH), 1.84-1.77 (m, IH), 1.69-1.20 (m, 8H), 1.00-0.97 (m, IH), 0.91-0.84 (m, 4H).

MH+ 554.

Example 7

(+)-(Morphinan-3-yloxy)methyl 2-phenylbutanoate TFA

(+)-(Morphinan-3-yloxy)methyl 2-phenylbutanoate TFA
\( ^{1}H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.54 (br, IH), 7.52 (br, IH), 7.27-7.24 (m, 5H), 7.03 (dd, \( J = 8.4, 2.4 \) Hz, IH), 6.85 (dd, \( J = 9.2, 2.4 \) Hz, IH), 6.78-6.74 (m, IH), 5.74-5.68 (m, 2H), 3.71 (br, IH), 3.48 (t, \( J = 7.6 \) Hz, IH), 3.21-3.13 (m, 2H), 3.03 (d, \( J = 19.2 \) Hz, IH), 2.74 (br, IH), 2.28-2.23 (m, IH), 2.16-1.99 (m, 2H), 1.92-1.75 (m, 2H), 1.67 (d, \( J = 11.2 \) Hz, IH), 1.54-1.35 (m, 4H), 1.27-1.16 (m, IH), 1.04-0.96 (m, 2H), 0.88-0.74 (m, 3H).

**Example 73**

(+)-[\( \text{IV-(Benzyloxy carbonyl)morphinan-3-yl oxy}\)]methyl 1-adamantanecarboxylate

\( ^{1}H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.30 (br, 5H), 6.99 (d, \( J = 6.0 \) Hz, IH), 6.96 (d, \( J = 2.4 \) Hz, IH), 6.82 (dd, \( J = 8.4, 2.4 \) Hz, IH), 5.76 and 5.68 (Ab q, \( J = 6.4 \) Hz, 2H), 5.12 (br, 2H), 4.41 (br, IH), 3.86 (br, IH), 3.09 (br, IH), 2.70-2.65 (m, 2H), 2.34 (d, \( J = 13.2 \) Hz, IH), 1.99 (br, IH), 1.88 (d, \( J = 2.4 \) Hz, 6H), 1.73-1.64 (m, 8H), 1.58-1.50 (m, 5H), 1.35-1.23 (m, 4H), 1.09-1.03 (m, IH).

**Example 74**

(+)-(Morphinan-3-yl oxy)methyl 1-adamantanecarboxylate TFA
\[ ^1H \text{NMR (400 MHz, CDCl}_3\] \delta 9.93 \text{ (br, IH)}, 8.50 \text{ (br, IH)}, 7.11 \text{ (d, J = 8.4 Hz, IH)}, 6.96 \text{ (d, J = 2.4 Hz, IH)}, 6.90 \text{ (dd, J = 8.4, 2.4 Hz, IH)}, 5.76 \text{ and 5.67 (AB q, J = 6.4 Hz, 2H)}, 3.71 \text{ (br, IH)}, 3.24-3.14 \text{ (m, 2H)}, 3.04 \text{ (br d, J = 19.2 Hz, IH)}, 2.78-2.76 \text{ (m, IH)}, 2.35 \text{ (d, J = 14.0 Hz, IH)}, 2.00 \text{ (br, IH)}, 1.95-1.87 \text{ (m, 8H)}, 1.73-1.64 \text{ (m, 8H)}, 1.57-1.25 \text{ (m, 7H)}, 1.11-1.02 \text{ (m, IH)}.

MH+ 436.

Example 75

\[ (+)-(\text{Morphinan-3-yloxy})\text{methyl acetate TFA} \]

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] \delta 9.00 \text{ (br, IH)}, 7.13 \text{ (d, J = 8.4 Hz, IH)}, 6.95 \text{ (d, J = 2.8 Hz, IH)}, 6.92 \text{ (dd, J = 8.4, 2.8 Hz, IH)}, 5.77 \text{ and 5.73 (AB q, J = 6.4 Hz, 2H)}, 4.00 \text{ (br, IH)}, 3.67 \text{ (br, IH)}, 3.24-3.07 \text{ (m, 3H)}, 2.85-2.76 \text{ (m, IH)}, 2.36 \text{ (d, J = 13.2 Hz, 2H)}, 2.13 \text{ (s, 3H)}, 2.09-2.04 \text{ (m, IH)}, 1.96-1.88 \text{ (m, IH)}, 1.68 \text{ (d, J = 12.4 Hz, IH)}, 1.60-1.37 \text{ (m, 4H)}, 1.31-1.25 \text{ (m, IH)}, 1.12-1.03 \text{ (m, IH)}.

MH+ 316.

Example 76

\[ (+)-(\text{Morphinan-3-yloxy})\text{methyl 3-cyclohexylpropioate TFA} \]
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.06 (br, IH), 7.12 (d, $J$ = 8.4 Hz, IH), 6.95 (d, $J$ = 2.4 Hz, IH), 6.92 (dd, $J$ = 8.4, 2.4 Hz, IH), 5.77 and 5.74 (AB $q$, $J$ = 6.4 Hz, 2H) $\delta$ 5.39 (br, IH), 3.66 (br, IH), 3.23-3.07 (m, 3H), 2.78-2.75 (m, IH), 2.39-2.34 (m, 3H), 2.05 (d, $J$ = 12.4 Hz, IH), 1.95-1.87 (m, IH), 1.77-1.37 (m, 13H), 1.31-1.04 (m, 7H), 0.90-0.82 (m, IH).

MH+ 412.

Example 77

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.28 (m, 5H), 7.02 (t, $J$ = 8.8 Hz, IH), 6.95 (s, IH), 6.85 (dd, $J$ = 8.4, 2.0 Hz, IH) $\delta$ 5.79-5.71 (m, 2H), 5.20-5.09 (m, 2H), 4.37 (br d, $J$ = 42.8 Hz, IH), 3.96-3.83 (m, IH) $\delta$ 3.14-3.05 (m, IH), 2.73-2.57 (m, 2H) $\delta$ 2.38-2.33 (m, 2H) $\delta$ 2.20-2.15 (m, IH), 2.08-2.00 (m, IH), 1.72-1.20 (m, 10H), 1.12-1.02 (m, 2H) $\delta$ 0.95 (d, $J$ = 6.4 Hz, 3H), 0.86 (s, 9H).

MH+ 548.

Example 78

(+)-(Morphinan-3-yloxy)methyl 3,5,5-trimethylhexanoate

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.06 (br, IH), 7.12 (d, $J$ = 8.4 Hz, IH), 6.95 (d, $J$ = 2.4 Hz, IH), 6.92 (dd, $J$ = 8.4, 2.4 Hz, IH), 5.77 and 5.74 (AB $q$, $J$ = 6.4 Hz, 2H) $\delta$ 5.39 (br, IH), 3.66 (br, IH), 3.23-3.07 (m, 3H), 2.78-2.75 (m, IH), 2.39-2.34 (m, 3H), 2.05 (d, $J$ = 12.4 Hz, IH), 1.95-1.87 (m, IH), 1.77-1.37 (m, 13H), 1.31-1.04 (m, 7H), 0.90-0.82 (m, IH).

MH+ 412.

Example 78

(+)-(Morphinan-3-yloxy)methyl 3,5,5-trimethylhexanoate TFA

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.28 (m, 5H), 7.02 (t, $J$ = 8.8 Hz, IH), 6.95 (s, IH), 6.85 (dd, $J$ = 8.4, 2.0 Hz, IH) $\delta$ 5.79-5.71 (m, 2H), 5.20-5.09 (m, 2H), 4.37 (br d, $J$ = 42.8 Hz, IH), 3.96-3.83 (m, IH) $\delta$ 3.14-3.05 (m, IH), 2.73-2.57 (m, 2H) $\delta$ 2.38-2.33 (m, 2H) $\delta$ 2.20-2.15 (m, IH), 2.08-2.00 (m, IH), 1.72-1.20 (m, 10H), 1.12-1.02 (m, 2H) $\delta$ 0.95 (d, $J$ = 6.4 Hz, 3H), 0.86 (s, 9H).

MH+ 548.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.63 (br, IH), 8.84 (br, IH), 7.12 (d, $J$ = 8.4 Hz, IH), 6.96 (d, $J$ = 2.4 Hz, IH), 6.93 (dd, $J$ = 8.4, 2.4 Hz, IH), 5.79-5.72 (m, 2H), 3.68 (br, IH), 3.24-3.05 (m, 3H), 2.82-2.73 (m, 1H), 2.38-2.34 (m, 2H), 2.22-2.16 (m, IH), 2.05-2.02 (m, IH), 1.92-1.86 (m, IH), 1.60-1.21 (m, 8H), 1.13-1.01 (m, 2H), 0.96 (d, $J$ = 6.4 Hz, 3H), 0.87 (s, 9H).

MH+ 414.

**Example 79**

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate TFA

(+)Isopropyl [(benzyloxycarbonyl)morphinan-3-yloxy]methyl carbonate (16.9 g, 34.2 mmol) from Example 1 was subjected to hydrogenation (balloon) on 10% Pd/C (1.7 g) in 1,4-dioxane (100 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with 1,4-dioxane (50 mL). The combined 1,4-dioxane solution was evaporated under vacuum. The residue was further purified by prep reverse-phase HPLC with 0.1% TFA to provide the title compound (8.86 g, 55%) as a colorless gum.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.11 (br, 2H), 7.12 (d, $J$ = 8.4 Hz, IH), 6.95-6.93 (m, 2H), 5.76 and 5.70 (AB, $J$ = 6.4 Hz, 2H), 4.95-4.89 (m, IH), 3.68 (br, IH), 3.23-3.11 (m, 3H), 2.75 (br, IH), 2.35 (d, $J$ = 13.6 Hz, IH), 2.08 (d, $J$ = 12.0 Hz, IH), 1.98-1.90 (m, IH), 1.66 (d, $J$ = 12.8 Hz, IH), 1.58-1.37 (m, 5H), 1.30 (d, $J$ = 6.0 Hz, 6H), 1.27-1.24 (m, IH), 1.07-1.03 (m, IH).

MH+ 360.
Example 80
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate L-(+)-tartaric acid

Method 1: (+)-Isopropyl (morphinan-3-yloxy)methyl carbonate (300 mg, 0.634 mmol) from Example 79 was dissolved in EtOAc (20 mL) and washed with saturated NaHCO₃ solution (20 mL x 2). To the EtOAc layer was added L-(+)-tartaric acid (95.2 mg, 0.634 mmol). The mixture was stirred at 40 °C for 10 min. and cooled to room temperature. The precipitated solution was filtered and washed with EtOAc (10 mL) to provide the title compound (268 mg, 83%) as a white solid.

Method 2: (+)-Isopropyl [iV-(benzyloxy carbonyl) morphinan-3-yloxy]methyl carbonate (1.72 g, 3.48 mmol) from Example 1 was subjected to hydrogenation (balloon) on 10% Pd/C (170 mg) in IPA (25 mL) at room temperature. After the reaction was completed, the reaction mixture was filtered through a Celite, and washed with IPA (20 mL). To the combined IPA solution was added L-(+)-tartaric acid (522 mg, 3.48 mmol). The mixture was stirred at 40°C for 30 min. The mixture was evaporated under vacuum. To the residue was added EtOAc (20 mL). The solution was filtered and washed with EtOAc (10 mL) to provide the title compound (1.61 g, 91%) as a white solid.

[α]D<sup>27</sup> +24.0° (G=LO, MeOH); mp 159 °C; IR (KBr) ν<sub>max</sub> 3525, 3179, 2933, 2456, 1760, 1455, 1431, 1271, 1219, 1043 cm<sup>-1</sup>; ¹H NMR (400 MHz, CD₃OD) δ 7.18 (d, J = 8.4 Hz, IH), 7.03 (d, J = 2.4 Hz, IH), 6.95 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.89-4.82 (m, IH), 4.39 (s, 2H), 3.70-3.68 (m, IH), 3.25 (d, J = 6.0 Hz, IH), 3.11 (dd, J = 13.6, 4.0 Hz, IH), 2.99 (br d, J = 18.8 Hz, IH), 2.74-2.66 (m, IH), 2.45 (d, J = 14.4 Hz, IH), 1.96 (d, J = 11.6 Hz, IH), 1.88-1.80 (m, IH), 1.70 (d, J = 12.8 Hz, IH), 1.59-1.42 (m, 5H), 1.34-1.28 (m, IH), 1.26 (d, J = 6.4 Hz, 6H), 1.14-1.04 (m, IH); ¹³C NMR (400 MHz, CD₃OD) δ 176.1, 156.5, 153.9, 139.5, 129.4, 128.9, 114.8, 113.5, 88.4, 73.1, 72.5, 51.3, 41.2, 38.4, 37.6, 36.6, 35.5, 27.7, 25.9, 25.6,
21.7, 20.7; HR-FAB-MS m/z: 360.2173 [M+H]+ (Calcd for C21H30N4O4: 360.2175).
MH+ 360.

The following compounds of Examples 81 to 92 were obtained by repeating the procedure of Example 80.

**Example 81**
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate HCl

![Chemical Structure](image)

1H NMR (400 MHz, CDCl3) δ 9.62 (br, 2H), 7.12 (d, J = 8.4 Hz, IH), 6.95-6.92 (m, 2H), 5.76 and 5.70 (ABq, J = 6.4 Hz, 2H), 4.95-4.89 (m, IH), 3.72 (br, IH), 3.26-3.14 (m, 3H), 2.73 (br, IH), 2.33 (d, J = 12.4 Hz, IH), 2.16 (d, J = 12.0 Hz, IH), 2.03-1.98 (m, IH), 1.65 (d, J = 10.8 Hz, IH), 1.57-1.36 (m, 5H), 1.30 (d, J = 6.4 Hz, 6H), 1.26-1.22 (m, IH), 1.06-1.03 (m, IH).

MH+ 360.

**Example 82**
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate formic acid

![Chemical Structure](image)

1H NMR (400 MHz, CD3OD) δ 8.51 (s, IH), 7.18 (d, J = 8.4 Hz, IH), 7.03 (d, J = 2.4 Hz, IH), 6.96 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.72 (ABq, J = 6.4 Hz, 2H), 4.93-4.82 (m, IH), 3.69-3.67 (m, IH), 3.32-3.25 (m, IH), 3.12-3.07 (m, IH), 2.97 (br d, J = 19.2 Hz, IH), 2.75-2.67 (m, IH), 2.46 (br d, J = 17.2 Hz, IH), 1.96-1.92 (m, IH),
1.86-1.78 (m, IH), 1.71 (d, J = 14.4 Hz, 5H), 1.61-1.38 (m, 5H), 1.33-1.29 (m, IH), 1.26 (d, J = 6.0 Hz, 6H), 1.14-1.04 (m, IH).

MH+ 360.

**Example 83**
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate citric acid

\[ \text{\includegraphics[width=0.5\textwidth]{example83.png}} \]

\[^1\text{H NMR (400 MHz, CD}_3\text{OD) } \delta 7.18 \text{ (d, J = 8.4 Hz, IH), 7.03 (d, J = 2.4 Hz, IH), 6.96 (dd, J = 8.4, 2.4 Hz, IH), 5.75 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.88-4.83 (m, IH), 3.71-3.68 (m, IH), 3.25 (d, J = 6.8 Hz, IH), 3.13-3.09 (m, IH), 2.98 (br d, J = 19.2 Hz, IH), 2.86-2.68 (m, 7H), 2.45 (d, J = 13.6 Hz, IH), 1.97-1.94 (m, IH), 1.87-1.79 (m, IH), 1.71 (d, J = 13.6 Hz, 3H), 1.60-1.40 (m, 5H), 1.34-1.28 (m, IH) 1.26 (d, J = 6.4 Hz, 6H), 1.14-1.04 (m, IH).} \]

MH+ 360.

**Example 84**
(+)-Isopropyl (morphman-3-yloxy)methyl carbonate fumaric acid

\[ \text{\includegraphics[width=0.5\textwidth]{example84.png}} \]

\[^1\text{H NMR (400 MHz, CD}_3\text{OD) } \delta 7.18 \text{ (d, J = 8.4 Hz, IH), 7.03 (s, IH), 6.96 (d, J = 8.4 Hz, 3H), 6.66 (s, IH), 5.75 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.89-4.86 (m, IH), 3.69-3.67 (m, IH), 3.12-3.08 (m, IH), 3.00-2.95 (m, IH), 2.74-2.68 (m, IH), 2.45 (d, J = 13.6 Hz, 3H), 1.97-1.93 (m, IH), 1.84-1.80 (m, IH), 1.75-1.66 (m, IH), 1.60-1.32 (m, 6H), 1.26 (d, J = 6.0 Hz, 6H) 1.18-1.05 (m, 2H).} \]
MH+ 360.

Example 85
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate fumaric acid mono-Na

\[
\text{H NMR (400 MHz, CD}_3\text{OD)} \delta 7.26 (d, J = 8.4 \text{ Hz, IH}), 7.03 (s, IH), 6.96 (d, J = 8.4 \text{ Hz, IH}), 6.66 (s, 2H), 5.75 and 5.72 (AB q, J = 6.8 \text{ Hz, 2H}), 4.93-4.86 (m, IH), 3.69-3.67 (m, IH), 3.32-3.08 (m, IH), 2.99-2.94 (m, IH), 2.75-2.67 (m, IH), 2.45 (d, J = 14.4 \text{ Hz, IH}), 1.96-1.93 (m, IH), 1.86-1.78 (m, IH), 1.75-1.67 (m, IH), 1.61-1.30 (m, 6H), 1.26 (d, J = 6.0 \text{ Hz, 6H}), 1.18-1.10 (m, 2H).
\]

MH+ 360.

Example 86
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate 4-methylbenzenesulfonic acid

\[
\text{H NMR (400 MHz, CD}_3\text{OD)} \delta 7.70 (d, J = 8.4 \text{ Hz, 2H}), 7.02 (d, J = 2.4 \text{ Hz, IH}), 6.95 (dd, J = 8.4, 2.8 \text{ Hz, IH}), 5.76 and 5.72 (AB q, J = 6.8 \text{ Hz, 2H}), 4.89-4.83 (m, IH), 3.68-3.66 (m, IH), 3.24 (d, J = 6.4 \text{ Hz, IH}), 3.11-3.07 (m, IH), 2.95 (br d, J = 19.2 \text{ Hz, IH}), 2.75-2.67 (m, IH), 2.44 (d, J = 13.6 \text{ Hz, IH}), 1.94-1.90 (m, IH), 1.85-1.77 (m, IH), 1.69 (d, J = 14.0 \text{ Hz, IH}), 1.59-1.28 (m, 6H), 1.24 (d, J = 8.0 \text{ Hz, 6H}), 1.08-1.04 (m, IH).
\]

MH+ 360.
Example 87

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate stearic acid

\[
\text{\textit{H NMR (400 MHz, CD} \textsubscript{3} \text{OD)} \delta 7.18 (d, J = 8.8 Hz, IH), 7.03 (d, J = 2.4 Hz, IH), 6.96 (dd, J = 8.4, 2.4 Hz, IH), 5.76 and 5.73 (AB q, J = 7.2 Hz, 2H), 4.88-4.83 (m, IH), 3.68-3.66 (m, IH), 3.26 (d, J = 6.4 Hz, IH), 3.09 (dd, J = 13.6, 3.6 Hz, IH), 2.96 (br d, J = 19.2 Hz, IH), 2.74-2.67 (m, IH), 2.46 (d, J = 14.0 Hz, IH), 2.18 (t, J = 7.6 Hz, 2H), 1.95-1.91 (m, IH), 1.86-1.78 (m, IH), 1.71 (d, J = 13.2 Hz, IH), 1.60-1.39 (m, 6H), 1.33-1.22 (m, 36H), 1.14-1.07 (m, IH), 0.89 (t, J = 6.8 Hz, 3H).
\]

MH+ 360.

Example 88

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate citric acid di-Na

\[
\text{\textit{H NMR (400 MHz, D} \textsubscript{2} \text{O)} \delta 7.21 (d, J = 8.4 Hz, IH), 7.00 (s, IH), 6.95 (d, J = 8.4 Hz, IH), 5.76 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.92-4.81 (m, IH), 3.71 (m, IH), 3.30 (s, 4H), 3.24-3.23 (m, IH), 3.16-3.12 (m, IH), 3.04-2.99 (m, IH), 2.71-2.64 (m, IH), 2.40 (d, J = 13.6 Hz, IH), 2.01-1.97 (m, IH), 1.91-1.83 (m, IH), 1.68-1.65 (m, IH), 1.58-1.38 (m, 5H), 1.26 (d, J = 6.4 Hz, 6H), 1.19-0.97 (m, 2H).
\]

MH+ 360.

Example 89

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate L-(-)-malic acid
\( ^1H \) NMR (400 MHz, CD\(_3\)OD) \( \delta 7.18 \) (d, \( J = 8.4 \) Hz, IH), 7.03 (d, \( J = 2.8 \) Hz, IH), 6.96 (dd, \( J = 8.4, 2.8 \) Hz, IH), 5.76 and 5.73 (AB q, \( J = 6.8 \) Hz, 2H), 4.89-4.83 (m, IH), 4.31 (dd, \( J = 10.0, 5.2 \) Hz, IH), 3.70-3.68 (m, IH), 3.26 (d, \( J = 6.0 \) Hz, IH), 3.10 (dd, \( J = 12.8, 4.0 \) Hz, IH), 2.97 (br d, \( J = 19.2 \) Hz, IH), 2.81-2.67 (m, 2H), 2.55-2.51 (m, IH), 2.45 (d, \( J = 14.0 \) Hz, IH), 1.95 (d, \( J = 12.4 \) Hz, IH), 1.87-1.78 (m, IH), 1.71 (d, \( J = 12.8 \) Hz, IH), 1.60-1.39 (m, 5H), 1.34-1.28 (m, IH), 1.26 (d, \( J = 6.0 \) Hz, 6H), 1.15-1.06 (m, IH).

MH\(^+\) 360.

**Example 90**

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate L-(+)-lactic acid

\( ^1H \) NMR (400 MHz, CD\(_3\)OD) \( \delta 7.18 \) (d, \( J = 8.4 \) Hz, IH), 7.04 (d, \( J = 2.4 \) Hz, IH), 6.96 (dd, \( J = 8.4, 2.4 \) Hz, IH), 5.76 and 5.73 (AB q, \( J = 6.8 \) Hz, 2H), 4.88-4.84 (m, IH), 4.05 (q, \( J = 6.8 \) Hz, IH), 3.69-3.67 (m, IH), 3.32-3.26 (m, IH), 3.10 (dd, \( J = 13.2, 3.2 \) Hz, IH), 2.96 (br d, \( J = 19.2 \) Hz, IH), 2.75-2.67 (m, IH), 2.46 (d, \( J = 14.0 \) Hz, IH), 1.93 (d, \( J = 12.4 \) Hz, IH), 1.86-1.78 (m, IH), 1.71 (d, \( J = 12.8 \) Hz, IH), 1.60-1.39 (m, 5H), 1.34-1.28 (m, 4H), 1.26 (d, \( J = 6.0 \) Hz, 6H), 1.15-1.07 (m, IH).

MH\(^+\) 360.

**Example 91**

(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate succinic acid
1H NMR (400 MHz CD3OD) δ 7.18 (d, J = 8.4 Hz, IH), 7.03 (d, J = 2.4 Hz, IH), 6.96 (dd, J = 8.4, 2.4 Hz, IH), 5.76 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.90-4.82 (m, IH), 3.66 (br, IH), 3.32-3.29 (m, IH), 3.08 (dd, J = 12.8, 3.6 Hz, IH), 2.95 (br d, J = 19.2 Hz, IH), 2.75-2.68 (m, IH), 2.50 (s, 4H), 2.49-2.44 (m, IH), 1.92 (d, J = 11.2 Hz, IH), 1.84-1.78 (m, IH), 1.71 (d, J = 13.6 Hz, IH), 1.60-1.39 (m, 5H), 1.34-1.29 (m, IH), 1.26 (d, J = 6.0 Hz, 6H) 1.14-1.05 (m, IH).
MH+ 360.

Example 92
(+)-Isopropyl (morphinan-3-yloxy)methy carbonate salicylic acid

1U NMR (400 MHz CD3OD) δ 7.82 (dd, J = 8.0, 2.4 Hz, IH), 7.03 (d, J = 2.8 Hz, IH), 6.95 (dd, J = 8.4, 2.8 Hz, IH), 5.75 and 5.72 (AB q, J = 6.8 Hz, 2H), 4.89-4.83 (m, IH), 3.70-3.68 (m, IH), 3.26 (d, J = 6.0 Hz, IH), 3.10 (dd, J = 12.8, 3.6 Hz, IH), 2.96 (br d, J = 19.2 Hz, IH), 2.74-2.68 (m, IH), 2.45 (d, J = 13.6 Hz, IH), 1.95-1.91 (m, IH), 1.85-1.77 (m, IH), 1.69 (d, J = 10.8 Hz, IH), 1.59-1.28 (m, 6H), 1.26 (d, J = 6.4 Hz, 6H) 1.13-1.06 (m, IH).
MH+ 360.

Example 93
(+)-(Morphinan-3-yloxy)methyl pivalate succinic acid

71
(+)-(Morphinan-3-yloxy)methyl pivalate trifluoroacetic acid salt (240 mg, 0.509 mmol) from Example 62 was dissolved in EtOAc (20 mL) and washed with saturated NaHCO₃ solution (20 mL x 2). To the EtOAc layer was added succinic acid (60.1 mg, 0.509 mmol). The mixture was stirred at 40 °C for 10 min. and cooled to room temperature. The precipitated solution was filtered and washed with EtOAc (10 mL) to provide the title compound (243 mg, 100%) as a white solid.

1H NMR (400 MHz, CD₃OD) δ 7.18 (d, J = 8.4 Hz, IH), 7.05 (d, J = 2.0 Hz, IH), 6.94 (dd, J = 8.4, 2.4 Hz, IH), 5.79 and 5.73 (AB q, J = 6.8 Hz, 2H), 3.69-3.67 (m, IH), 3.25 (d, J = 6.4 Hz, IH), 3.10 (dd, J = 13.2, 3.6 Hz, IH), 2.97 (br d, J = 19.2 Hz, IH), 2.72-2.65 (m, IH), 2.50 (s, 4H) 2.45 (d, J = 13.6 Hz, IH), 1.95 (d, J = 12.4 Hz, IH), 1.87-1.79 (m, IH), 1.70 (d, J = 12.4 Hz, IH), 1.58-1.38 (m, 4H), 1.34-1.21 (m, 2H), 1.17 (s, 9H), 1.10-1.04 (m, IH).

MH+ 358.

The following compounds of Examples 94 to 105 were obtained by repeating the procedure of Example 93.

**Example 94**

(+)-(Morphinan-3-yloxy)methyl pivalate HCl

1H NMR (400 MHz, CD₃OD) δ 7.19 (d, J = 8.4 Hz, IH), 7.04 (br, IH), 6.93 (d, J = 7.2 Hz, IH), 5.79 and 5.73 (AB q, J = 6.4 Hz, 2H), 3.72 (br, IH), 3.30-3.25 (m, IH), 3.13
(d, J = 9.6 Hz, IH), 3.06 (br d, J = 19.2 Hz, IH), 2.73-2.66 (m, IH), 2.44 (d, J = 14.0 Hz, IH), 2.04 (d, J = 12.8 Hz, IH), 1.95-1.87 (m, IH), 1.68 (d, J = 11.2 Hz, IH), 1.58-1.38 (m, 5H), 1.32-1.21 (m, IH), 1.16 (s, 9H), 1.12-1.05 (m, IH).

MH+ 358.

Example 95
(+)-(Morphinan-3-yloxy)methyl pivalate formic acid

\[
\text{Example 96}
\]
(+)-(Morphinan-3-yloxy)methyl pivalate citric acid

\[\text{\(^1H\) NMR (400 MHz, CD\textsubscript{3}OD) } \delta 8.30 \text{ (s, IH)}, 7.18 \text{ (d, J = 8.4 Hz, IH)}, 7.05 \text{ (d, J = 2.4 Hz, IH)}, 6.95 \text{ (dd, J = 8.4, 2.4 Hz, IH)}, 5.79 \text{ and } 5.73 \text{ (AB q, J = 6.8 Hz, 2H)}, 3.70-3.67 \text{ (m, IH)}, 3.32-3.25 \text{ (m, IH)}, 3.10 \text{ (dd, J = 13.2, 3.2 Hz, IH)}, 2.96 \text{ (br d, J = 19.2 Hz, IH)}, 2.73-2.66 \text{ (m, IH)}, 2.46 \text{ (d, J = 14.0 Hz, IH)}, 1.94 \text{ (d, J = 12.4 Hz, IH)}, 1.87-1.78 \text{ (m, IH)}, 1.68 \text{ (d, J = 11.2 Hz, IH)}, 1.60-1.40 \text{ (m, 5H)}, 1.29-1.21 \text{ (m, IH)}, 1.17 \text{ (s, 9H)}, 1.12-1.06 \text{ (m, IH)}.\]
2.82–2.65 \text{(m, 7H)}, 2.45 \text{(d, J = 14.0 Hz, 5H)}, 1.96 \text{(d, J = 12.0 Hz, 1H)}, 1.88–1.80 \text{(m, 4H)}, 1.70 \text{(d, J = 12.8 Hz, 1H)}, 1.58–1.40 \text{(m, 4H)}, 1.32–1.21 \text{(m, 2H)}, 1.17 \text{(s, 9H)}, 1.11–1.06 \text{(m, 1H)}.

\text{MH}^+ 358.

\textbf{Example 97}

\text{(+)-(Morphinan-3-yloxy)methyl pivalate fumaric acid}

\begin{center}
\begin{tikzpicture}
\node (A) {\textbf{2x}};
\end{tikzpicture}
\end{center}

$^1\text{H NMR (400 MHz, CD}_2\text{OD)} \delta 7.18 \text{(d, J = 8.4 Hz, 1H)}, 7.05 \text{(d, J = 2.4 Hz, 1H)}, 6.95 \text{(dd, J = 8.4, 2.4 Hz, 1H)}, 6.67 \text{(s, 1H)}, 5.79 \text{and 5.73 (AB q, J = 6.8 Hz, 2H)}, 3.70-3.67 \text{(m, 1H)}, 3.32-3.26 \text{(m, 1H)}, 3.10 \text{(dd, J = 13.6, 3.6 Hz, 1H)}, 2.96 \text{(br d, J = 19.2 Hz, 1H)}, 2.73-2.66 \text{(m, 1H)}, 2.46 \text{(d, J = 13.6 Hz, 1H)}, 1.94 \text{(d, J = 12.4 Hz, 1H)}, 1.87-1.79 \text{(m, 1H)}, 1.71 \text{(d, J = 13.6 Hz, 1H)}, 1.60-1.41 \text{(m, 5H)}, 1.32-1.26 \text{(m, 1H)}, 1.17 \text{(s, 9H)}, 1.14-1.07 \text{(m, 1H)}.$

\text{MH}^+ 358.

\textbf{Example 98}

\text{(+)-(Morphinan-3-yloxy)methyl pivalate fumaric acid mono-Na}

$^1\text{H NMR (400 MHz, CD}_2\text{OD)} \delta 7.16 \text{(d, J = 8.4 Hz, 1H)}, 7.04 \text{(d, J = 2.4 Hz, 1H)}, 6.92 \text{(dd, J = 8.8, 2.4 Hz, 1H)}, 6.65 \text{(s, 2H)}, 5.79 \text{and 5.73 (AB q, J = 6.8 Hz, 2H)}, 3.56-3.55 \text{(m, 1H)}, 3.29-3.22 \text{(m, 1H)}, 3.01 \text{(dd, J = 13.6, 3.2 Hz, 1H)}, 2.92 \text{(br d, J = 18.8 Hz, 1H)}, 2.69-2.62 \text{(m, 1H)}, 2.43 \text{(d, J = 13.6 Hz, 1H)}, 1.91 \text{(d, J = 12.4 Hz, 1H)}, 1.83-1.75 \text{(m, 1H)}, 1.70 \text{(d, J = 10.8 Hz, 1H)}, 1.58-1.39 \text{(m, 4H)}, 1.32-1.21 \text{(m, 2H)}, 1.17 \text{(s, 9H)}, ...$
1.10-1.04 (m, IH).
MH+ 358.

**Example 99**

(+)-(Morphinan-3-yloxy)methyl pivalate 4-methylbenzenesulfonic acid

\[
\text{\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=0.5\textwidth]{example99.png}};
\end{tikzpicture}
\end{center}
\]

\[\begin{align*}
\text{H NMR} & \quad (400 \text{ MHz, CD}_3\text{OD}) & \delta & \begin{align*}
7.72 & (d, J = 8.0 \text{ Hz}, 2\text{H}),
7.22 & (d, J = 8.0 \text{ Hz}, 2\text{H}),
7.10 & (d, J = 8.4 \text{ Hz}, 1\text{H}),
6.99 & (d, J = 2.4 \text{ Hz}, 1\text{H}),
6.87 & (dd, J = 8.4, 2.4 \text{ Hz}, 1\text{H}),
5.77 & \text{ and } 5.71 \quad (\text{AB q, } J = 6.4 \text{ Hz, 2H}),
3.38-3.36 & (m, 1\text{H}),
3.14 & (dd, J = 18.8, 6.4 \text{ Hz}, 1\text{H}),
2.91-2.85 & (m, 2\text{H}),
2.61-2.53 & (m, 1\text{H}),
2.37-2.34 & (m, 4\text{H}),
1.87-1.84 & (m, 1\text{H}),
1.76-1.69 & (m, 38\text{H}),
1.62 & (d, J = 11.6 \text{ Hz}, 1\text{H}),
1.51 & (d, J = 12.0 \text{ Hz}, 1\text{H}),
1.40-1.32 & (m, 4\text{H}),
1.28-1.19 & (m, 1\text{H}),
1.16 & (s, 9\text{H}),
1.02-0.98 & (m, 1\text{H}).
\end{align*}
\end{align*}
\]

MH+ 358.

**Example 100**

(+)-(Morphinan-3-yloxy)methyl stearic acid

\[
\text{\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=0.5\textwidth]{example100.png}};
\end{tikzpicture}
\end{center}
\]

\[\begin{align*}
\text{H NMR} & \quad (400 \text{ MHz, CD}_3\text{OD}) & \delta & \begin{align*}
7.13 & (d, J = 8.4 \text{ Hz}, 1\text{H}),
7.01 & (d, J = 8.0 \text{ Hz}, 2\text{H}),
6.89 & (dd, J = 8.4, 2.4 \text{ Hz}, 1\text{H}),
5.78 & \text{ and } 5.72 \quad (\text{AB q, } J = 6.8 \text{ Hz, 2H}),
3.37-3.36 & (m, 1\text{H}),
3.23-3.17 & (m, 1\text{H}),
2.89-2.85 & (m, 2\text{H}),
2.64-2.56 & (m, 1\text{H}),
2.40 & (d, J = 13.6 \text{ Hz}, 1\text{H}),
2.14 & (t, J = 7.6 \text{ Hz}, 2\text{H}),
1.88-1.84 & (m, 1\text{H}),
1.77-1.21 & (m, 38\text{H}),
1.17 & (s, 9\text{H}),
1.12-1.04 & (m, 1\text{H}),
0.89 & (t, J = 7.2 \text{ Hz, 3H}).
\end{align*}
\end{align*}
\]

MH+ 358.
Example 101

(+)-(Morphinan-3-yloxy)methyl pivalate citric acid di-Na

1H NMR (400 MHz, CD3OD) δ 7.13 (d, J = 8.4 Hz, IH), 7.01 (d, J = 2.4 Hz, IH), 6.98 (dd, J = 8.4, 2.4 Hz, IH), 5.78 and 5.72 (ABq, J = 6.8 Hz, 2H), 3.41-3.39 (m, IH), 3.30 (s, 4H), 3.20 (dd, J = 18.8, 6.0 Hz, IH), 2.92-2.86 (m, 2H), 2.64-2.57 (m, IH), 2.40 (d, J = 13.6 Hz, IH), 1.88-1.85 (m, IH), 1.77-1.67 (m, 2H), 1.57-1.21 (m, 6H), 1.17 (s, 9H), 1.12-1.04 (m, IH).

MH+ 358.

Example 102

(+)-(Morphinan-3-yloxy)methyl pivalate L-(-)-tartaric acid

1H NMR (400 MHz, CD3OD) δ 7.18 (d, J = 8.0 Hz, IH), 7.04 (d, J = 2.0 Hz, IH), 6.93 (dd, J = 8.4, 2.4 Hz, IH), 5.79 and 5.73 (ABq, J = 6.8 Hz, 2H), 4.32 (s, 2H), 3.68 (br, IH), 3.29-3.22 (m, IH), 3.12-3.08 (m, IH), 2.99 (br d, J = 19.2 Hz, IH), 2.70-2.63 (m, IH), 2.44 (d, J = 13.6 Hz, IH), 2.00-1.96 (m, IH), 1.89-1.81 (m, IH), 1.70 (d, J = 13.6 Hz, IH), 1.59-1.40 (m, 4H), 1.32-1.21 (m, 2H), 1.17 (s, 9H), 1.13-1.06 (m, IH).

MH+ 358.

Example 103

(+)-(Morphinan-3-yloxy)methyl pivalate L-(-)-malic acid

76
1H NMR (400 MHz, CD$_3$OD) $\delta$ 7.12 (d, $J = 8.8$ Hz, IH), 7.00 (d, $J = 2.4$ Hz, IH), 6.85 (dd, $J = 8.4$, 2.8 Hz, IH), 5.77 and 5.71 (AB q, $J = 6.8$ Hz, 2H), 4.01 (q, $J = 6.8$ Hz, 5H) 5.34-3.38 (m, IH), 5.30-3.29 (m, IH), 3.18 (dd, $J = 18.8$, 6.4 Hz, IH), 2.93-2.86 (m, 2H), 2.63-2.56 (m, 3H), 2.39 (dd, $J = 13.6$ Hz, 3H), 1.90 (d, $J = 12.4$ Hz, IH), 1.79-1.71 (m, IH), 1.66 (d, $J = 10.4$ Hz, IH), 1.55-1.35 (m, 4H), 1.32 (d, $J = 6.8$ Hz, 6H), 1.28-1.20 (m, 2H), 1.16 (s, 9H), 1.13-1.03 (m, IH). MH+ 358.

Example 104

(+)-(Morphinan-3-yloxy)methyl pivalate L-(+)-lactic acid

Example 105

(+)-(Morphinan-3-yloxy)methyl pivalate salicylic acid
$^1$HNMR (400 MHz, CD$_3$OD) δ 7.81 (dd, J = 8.0, 2.0 Hz, IH), 7.27-7.23 (m, IH), 7.17 (d, J = 8.4 Hz, IH), 7.05 (d, J = 2.4 Hz, IH), 6.94 (dd, J = 8.4, 2.4 Hz, IH), 6.77-6.72 (m, 2H), 5.79 and 5.73 (AB q, J = 6.4 Hz, 2H), 3.65 (br, IH), 3.25 (d, J = 6.0 Hz, IH), 3.08 (dd, J = 13.2, 3.6 Hz, IH), 2.95 (br d, J = 19.2 Hz, IH), 2.72-2.65 (m, IH), 2.45 (d, J = 14.0 Hz, IH), 1.93 (d, J = 12.4 Hz, IH), 1.85-1.77 (m, IH), 1.68 (d, J = 12.4 Hz, IH), 1.58-1.39 (m, 4H), 1.34-1.21 (m, 2H), 1.17 (s, 9H) 3 1.10-1.06 (m, IH).

MH+ 358.
What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:

\[
\begin{align*}
\text{(I)}
\end{align*}
\]

wherein,
A is a direct bond or oxygen;
R_1 is selected from the group consisting of hydrogen, -C(O)OC_1-10 alkyl, substituted -C(O)OC_1-4 alkyl, -C(O)OC_1-4 alkyl-Ar and substituted -C(O)OC_1-4 alkyl-Ar, Ar being selected from the group consisting of phenyl, naphthyl, furyl, pyridyl, thiophenyl, furazoyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, benzofuranyl, indolyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thia-Imidazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, and pyrimidinyl, all of which are optionally substituted by one or more Z groups, Z being independently selected from the group consisting of C_1-4 alkyl, C_1-4 alkoxy, -(CH_2)_m C(O)OR_3, C(O)NR_3R_4, -CN, -(CH_2)_n OH, -NO_2, F, Cl, Br, I, -NR_3R_4 and NHC(O)R_3, wherein m is O to 4, n is O to 4, R_3 is hydrogen, C_1-6 alkyl or substituted C_1-6 alkyl, and R_4 is selected from the group consisting of C_1-6 alkyl, substituted C_1-6 alkyl, -CH_2 Ar and Ar, Ar being as defined above; and
R_2 is selected from the group consisting of C_1-10 alkyl, substituted C_1-10 alkyl, C_3-10 carbocycle, substituted C_3-10 carbocycle, (CH_2)_n-phenyl and substituted (CH_2)_n-phenyl, wherein n is O to 4.

2. The compound according to claim 1, wherein the compound has formula (Ia):
wherein, $R_1$ and $R_2$ are as defined in claim 1.

3. The compound according to claim 1, wherein the compound has formula (Ib):

wherein, $R_1$ and $R_2$ are as defined in claim 1.

4. The compound according to claim 1, wherein $R_1$ is hydrogen, $-C(O)OC_{1-4}$ alkyl-$Ar$ or substituted $-C(O)OC_{1-4}$ alkyl-$Ar$, $Ar$ being phenyl or naphthyl, both of which are optionally substituted by one or more $Z$ groups, $Z$ being independently selected from the group consisting of $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $-(CH_2)_mC(O)OR_3$, $C(O)NR_3R_4$, $-CN_3-(CH_2)_nOH$, $-NO_2$, $F$, $Cl$, $Br$, I, $-NR_3R_4$ and $NHC(O)R_3$, wherein $m$ is 0 to 4, $n$ is 0 to 4, $R_3$ is hydrogen, $C_{1-6}$ alkyl or substituted $C_{1-6}$ alkyl, and $R_4$ is selected from the group consisting of $C_{1-6}$ alkyl, substituted $C_{1-6}$ alkyl, $-CH_2Ar$ and $Ar$, $Ar$ being as defined above; and $R_2$ is selected from the group consisting of $C_{1-10}$ alkyl, substituted $C_{1-10}$ alkyl, $C_{3-10}$ carbocycle, substituted $C_{3-10}$ carbocycle, $(CH_2)_n$-phenyl and substituted $(CH_2)_n$-phenyl, wherein $n$ is 0 to 4.

5. The compound according to claim 1, which is selected from the group consisting of:

- (+)-Isopropyl (morphinan-3-yloxy)methyl carbonate;
- (+)-(Morphinan-3-yloxy)methyl propyl carbonate;
- (+)-Cyclopropylmethyl (morphinan-3-yloxy)methyl carbonate;
- (+)-Cyclopentyl (morphinan-3-yloxy)methyl carbonate;
(+)-Cyclohexyl (morphinan-3-yloxy)methyl carbonate; 
(+)-Cyclohexylmethyl (morphinan-3-yloxy)methyl carbonate; 
(+)-Heptan-4-yl (morphinan-3-yloxy)methyl carbonate; 
(+)-Decahydropaphthalen-2-yl (morphinan-3-yloxy)methyl carbonate; 
(+)-Decahydropaphthalen-1-yl (morphinan-3-yloxy)methyl carbonate; 
(+)-Cyclopentylmethyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Cyclobutylmethyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-2-Ethylhexyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Butyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Isobutyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-sec-Butyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Cycloheptyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-(Morphinan-3-yloxy)methyl phenethyl carbonate TFA; 
(+)-(Morphinan-3-yloxy)methyl 1-phenylpropan-2-yl carbonate TFA; 
(+)-Ethyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Methyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Cyclobutyl (morphinan-3-yloxy)methyl carbonate TFA; 
(+)-Hexyl (morphinan-3-yloxy)methyl carbonate TFA 
(+)-(Morphinan-3-yloxy)methyl pentan-2-yl carbonate TFA 
(+)-Decyl (morphinan-3-yloxy)methyl carbonate TFA 
(+)-(Morphinan-3-yloxy)methyl isobutyrate; 
(+)-(Morphinan-3-yloxy)methyl pivalate; 
(+)-(Morphinan-3-yloxy)methyl pivalate TFA; 
(+)-(Morphinan-3-yloxy)methyl 3,3-dimethylbutanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl hexanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl 2-propylpentanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl 2-ethylbutanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl cyclohexanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl cyclopentanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl 2-ethylhexanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl butanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl pentanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl 2-methylbutanoate TFA; 
(+)-(Morphinan-3-yloxy)methyl cyclopropanecarboxylate TFA; 
(+)-(Morphinan-3-yloxy)methyl 3-methylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 2-phenylbutanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 1-adamantanecarboxylate TFA;
(+)-(Morphinan-3-yloxy)methyl acetate TFA;
(+)-(Morphinan-3-yloxy)methyl 3-cyclohexylpropanoate TFA;
(+)-(Morphinan-3-yloxy)methyl 3,5,5-trimethylhexanoate TFA;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate TFA;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate L-(+)-tartaric acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate HCl;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate formic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate citric acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate fumaric acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate fumaric acid mono-Na;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate 4-methylbenzenesulfonic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate stearic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate citric acid di-Na;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate L-(+)-lactic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate succinic acid;
(+)-Isopropyl (morphinan-3-yloxy)methyl carbonate salicylic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate succinic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate HCl;
(+)-(Morphinan-3-yloxy)methyl pivalate formic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate citric acid;
(+)-(Morphinan-3-yloxy)methyl pivalate fumaric acid;
(+)-(Morphinan-3-yloxy)methyl pivalate fumaric acid mono-Na;
(+)-(Morphinan-3-yloxy)methyl pivalate 4-methylbenzenesulfonic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate stearic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate citric acid di-Na;
(+)-(Morphinan-3-yloxy)methyl pivalate L-(+)-tartaric acid;
(+)-(Morphinan-3-yloxy)methyl pivalate L-(+)-malic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate L-(+)-lactic acid;
(+)-(Morphinan-3-yloxy)methyl pivalate salicylic acid;
(+)-[N-(Benzyloxy carbonyl) morphinan-3-yloxy] methyl isopropyl carbonate;
(+)-[N-(Benzyloxy carbonyl) morphinan-3-yloxy] methyl cyclopentyl carbonate;
(+-)[7V-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclohexyl carbonate;
(+)-[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl decahydropnaphthalen-1-yl carbonate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclopentylmethyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclobutylmethyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-ethylhexyl carbonate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl butyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl isobutyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl sec-butyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cycloheptyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl phenethyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 1-phenylpropan-2-yl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl ethyl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclohexylmethyl carbonate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl hexyl carbonate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl pentan-2-yl carbonate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl isobutyrate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl pivalate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl hexanoate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-propylpentanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-ethylbutanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclohexanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclopentanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-ethylhexanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl butanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl pentanoate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-methylbutanoate;
(+-)[η-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl cyclopropanecarboxylate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 3-methylbutanoate;
(+-)[iV-(Benzyloxy carbonyl)morphinan-3-yloxy]methyl 2-phenylbutanoate;
(+)-[7V-(Benzyloxycarbonyl)morphinan-3-yloxy]methyl 1-adamantanecarboxylate; and
(+)-[iV-(Benzyloxycarbonyl)morphinan-3-yloxy]niethyl 3,5,5-trimethylhexanoate.

6. A pharmaceutical composition comprising the compound according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method for treating or preventing Parkinson's disease, comprising administering to a patient in need of treatment thereof the compound according to claim 1 or a pharmaceutically acceptable salt thereof.
Fig. 1
Concentration of the compound of Example 2 (I.V. & P.O.)
Fig. 2

Sal+Sal

Sal+MPTP

HM 25 (i.p.)+MPTP

Example 2, 25 (p.o.)+MPTP
A. CLASSIFICATION OF SUBJECT MATTER

C07D 221/28(2006.01)i, A61K 31/485(2006.01)i, A61P 25/16(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IP 8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
eKIPASS, STN(REGISTRY, CA), Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tbody>
<tr>
<td>A</td>
<td>US 4673679 A (Aungst, B J et al ) 16 June 1987 See the whole document</td>
<td>1-7</td>
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<tr>
<td>A</td>
<td>US 4668685 A (Shami, E G et al ) 26 May 1987 See the whole document</td>
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<td>A</td>
<td>Kim, H-C et al &quot;New morphinan derivatives with negligible psychotropic effects attenuate convulsions induced by maximal electroshock in mice &quot; Life Science 2003, 72 1883-1895, ISSN 0024-3205 See the whole document</td>
<td>1-7</td>
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<td>A</td>
<td>WO 2005/1 10412 A1 (Green Cross Corp ) 24 November 2005 See the whole document</td>
<td>1-7</td>
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<td>A</td>
<td>Zhang, W et al &quot;3-hydroxymorphinan, a metabolite of dextromethorphan, protects nigrostatal pathway against MPTP-elicited damage both in vivo and in vitro &quot; The FASEB Journal 2006, 20 2496-2511, ISSN 0892-6638 See the whole document</td>
<td>1-7</td>
</tr>
</tbody>
</table>

* Special categories of cited documents
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search
17 JUNE 2008 (17 06 2008)

Date of mailing of the international search report
17 JUNE 2008 (17.06.2008)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seonsa-ro, Seogu, Daejeon 302-701, Republic of Korea
Facsimile No 82-42-472-7140

Authorized officer
LEE, MIN JUNG
Telephone No 82-42-481-5603

Form PCT/ISA/210 (second sheet) (April 2007)
### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

<table>
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<tr>
<th>Number</th>
<th>Claim Nos</th>
<th>Reason</th>
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<td>1</td>
<td>R7</td>
<td>because they relate to subject matter not required to be searched by this Authority, namely</td>
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Although claim 7 is directed to a method for the treatment of a human or animal body, the search has been carried out based on the alleged effects of the pharmaceutical composition containing a compound of formula (I) as an active ingredient.

<table>
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<th>Number</th>
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<th>Reason</th>
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<td>2</td>
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<td>because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically</td>
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<td>3</td>
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<td>because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)</td>
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### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

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<td>As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims</td>
</tr>
<tr>
<td>2</td>
<td>As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee</td>
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<tr>
<td>3</td>
<td>As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos</td>
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<td>No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos</td>
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**Remark on Protest**

- [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee
- [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation
- [ ] No protest accompanied the payment of additional search fees
<table>
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<tr>
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<th>Publication date</th>
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<tr>
<td></td>
<td></td>
<td>EP 0250796 A2</td>
<td>07.01.1988</td>
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<tr>
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<td></td>
<td>JP 62277324 A2</td>
<td>02.12.1987</td>
</tr>
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<td></td>
<td>CA 1301150 A1</td>
<td>19.05.1992</td>
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<td></td>
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<td>05.02.1986</td>
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