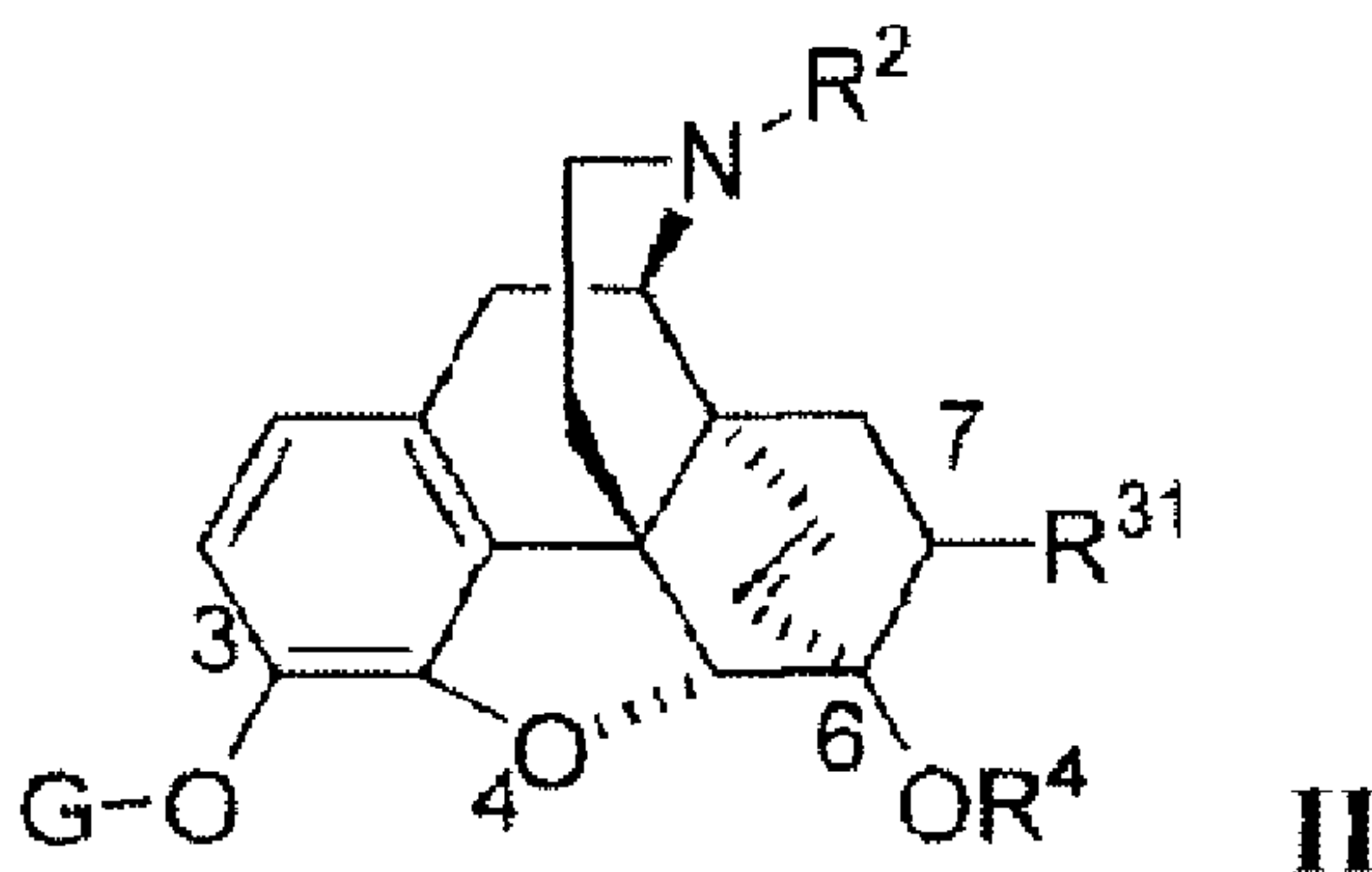




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(54) Title: PROCESS FOR PREPARING 7 β -SUBSTITUTED 6 α ,14 α -ETHENOMORPHINANS AND 7 β -SUBSTITUTED
6 α ,14 α -ETHANOMORPHINANS



(57) **Abrégé/Abstract:**

The application is directed to a process for increasing the proportion of 7 β -epimer in an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan, and specifically of compounds of Formula (I), wherein G, R²-R⁴, and are defined as set forth in the specification. The application is also directed to a process for purifying the 7 β -epimer from an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α , 14 α -ethanomorphinan. The application is also directed to a process for preparing 7 β -substituted compounds of Formula V^b wherein G and R²-R⁵ are defined as set forth in the specification.

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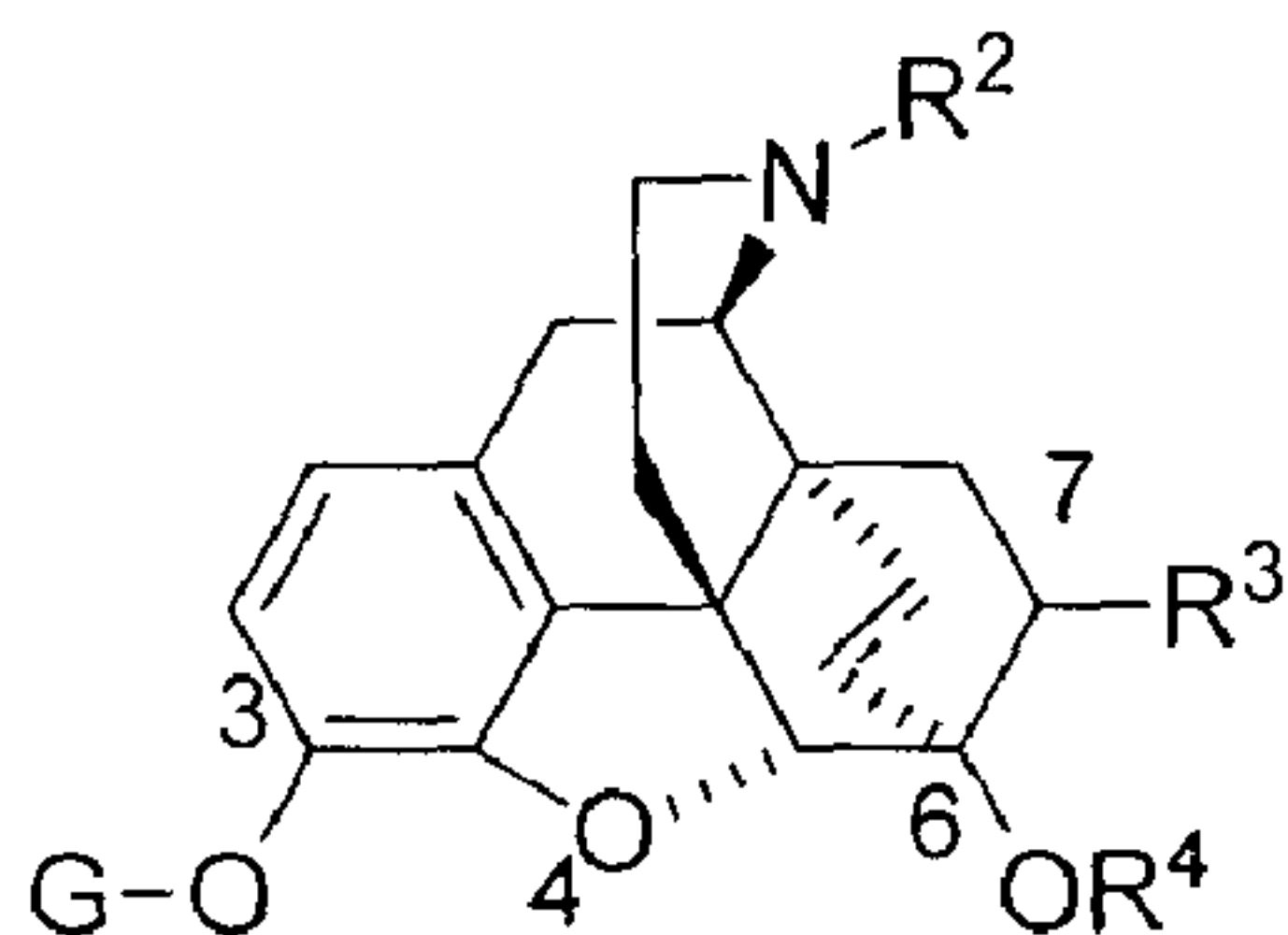
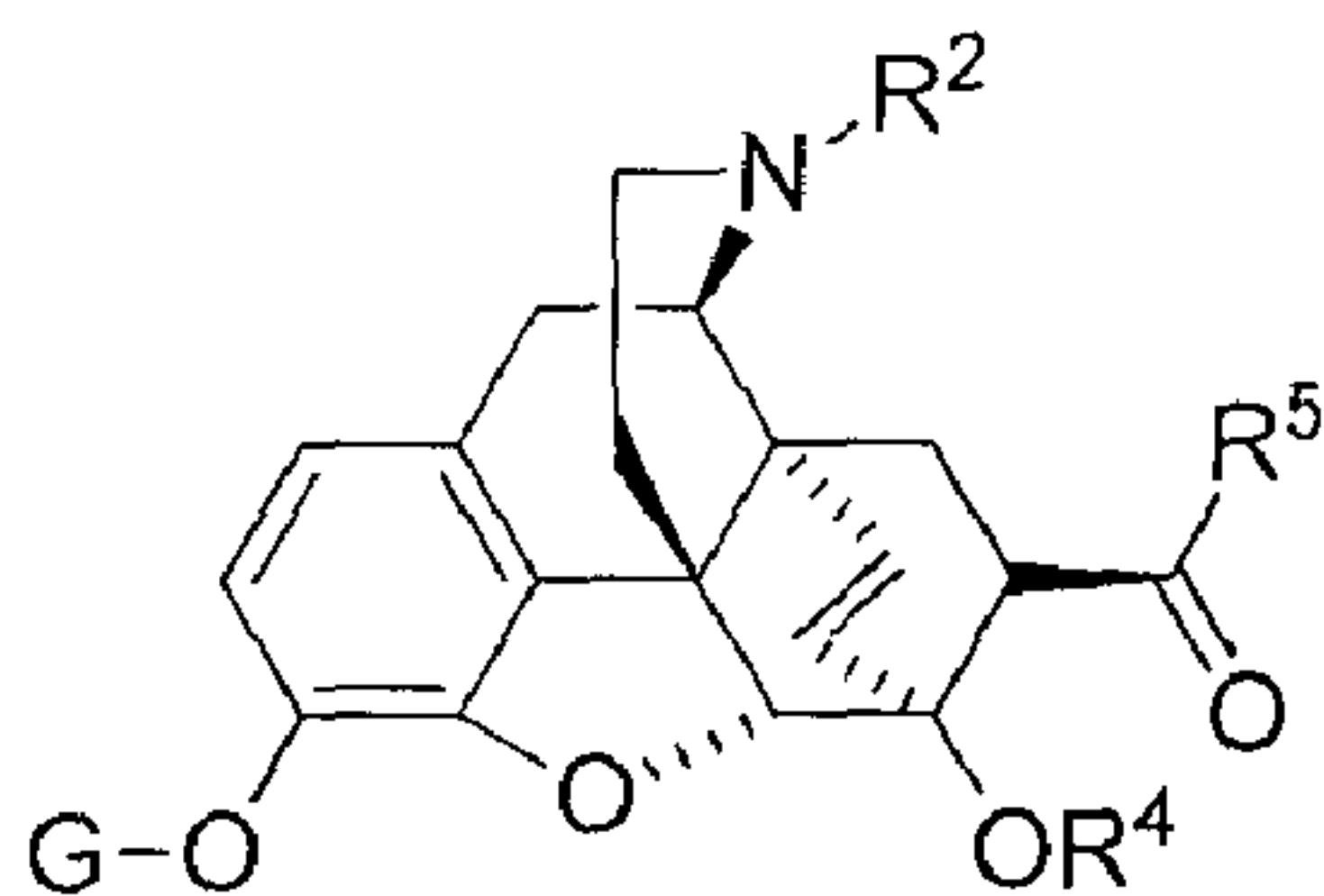
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(54) Title: PROCESS FOR PREPARING 7 β -SUBSTITUTED 6 α ,14 α -ETHENOMORPHINANS AND 7 β -SUBSTITUTED 6 α ,14 α -ETHANOMORPHINANS**I**(57) Abstract: The application is directed to a process for increasing the proportion of 7 β -epimer in an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan, and specifically of compounds of Formula (I), wherein G, R²-R⁴, and are defined as set forth in the specification. The application is also directed to a process for purifying the 7 β -epimer from an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α , 14 α -ethanomorphinan. The application is also directed to a process for preparing 7 β -substituted compounds of Formula V^b wherein G and R² -R⁵ are defined as set forth in the specification.**V^b**

Process for Preparing 7 β -Substituted 6 α ,14 α -Ethenomorphinans and 7 β -Substituted 6 α ,14 α -Ethanomorphinans

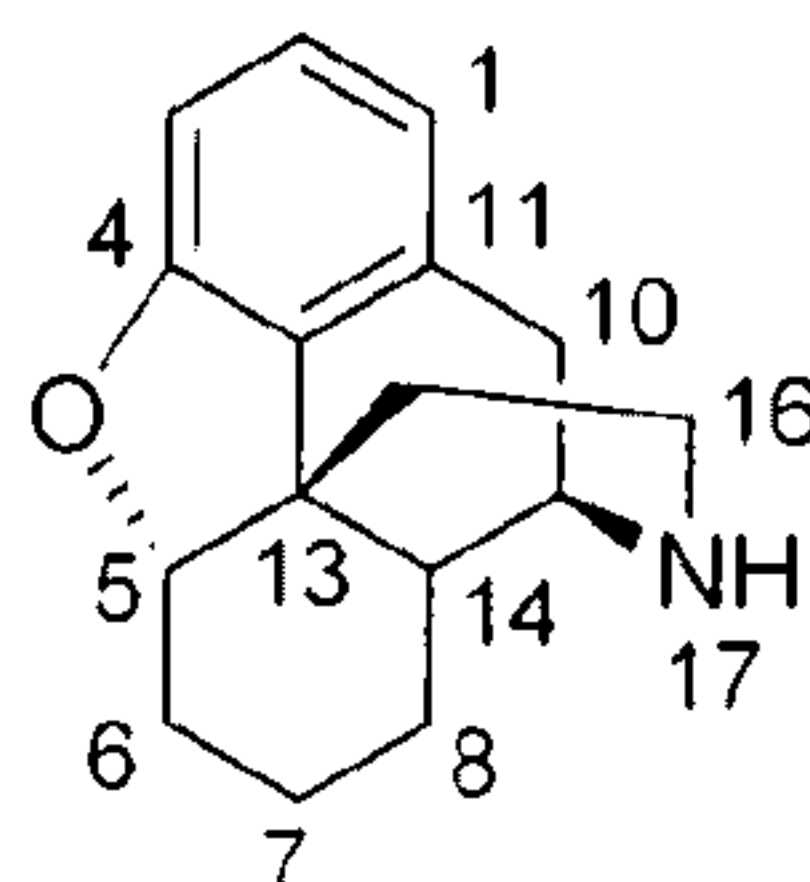
BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This application is in the field of medicinal chemistry. The application relates to a novel process for preparing 7 β -substituted 6 α ,14 α -ethenomorphinans and 7 β -substituted 6 α ,14 α -ethanomorphinans, and the pharmaceutically acceptable salts thereof. Particularly, the application relates to the selective precipitation of 7 β -substituted 6 α ,14 α -ethenomorphinans or 7 β -substituted 6 α ,14 α -ethanomorphinans from a mixture containing corresponding 7 α -epimers by treating with an acid. Contrary to optical diastereomeric resolution of enantiomers (e.g., chiral bases) which requires chiral acids to resolve single enantiomers, the separation of the above-mentioned 7 α /7 β -epimers can be achieved even with achiral acids. The application also relates to the novel, isolated compounds and salts thereof.

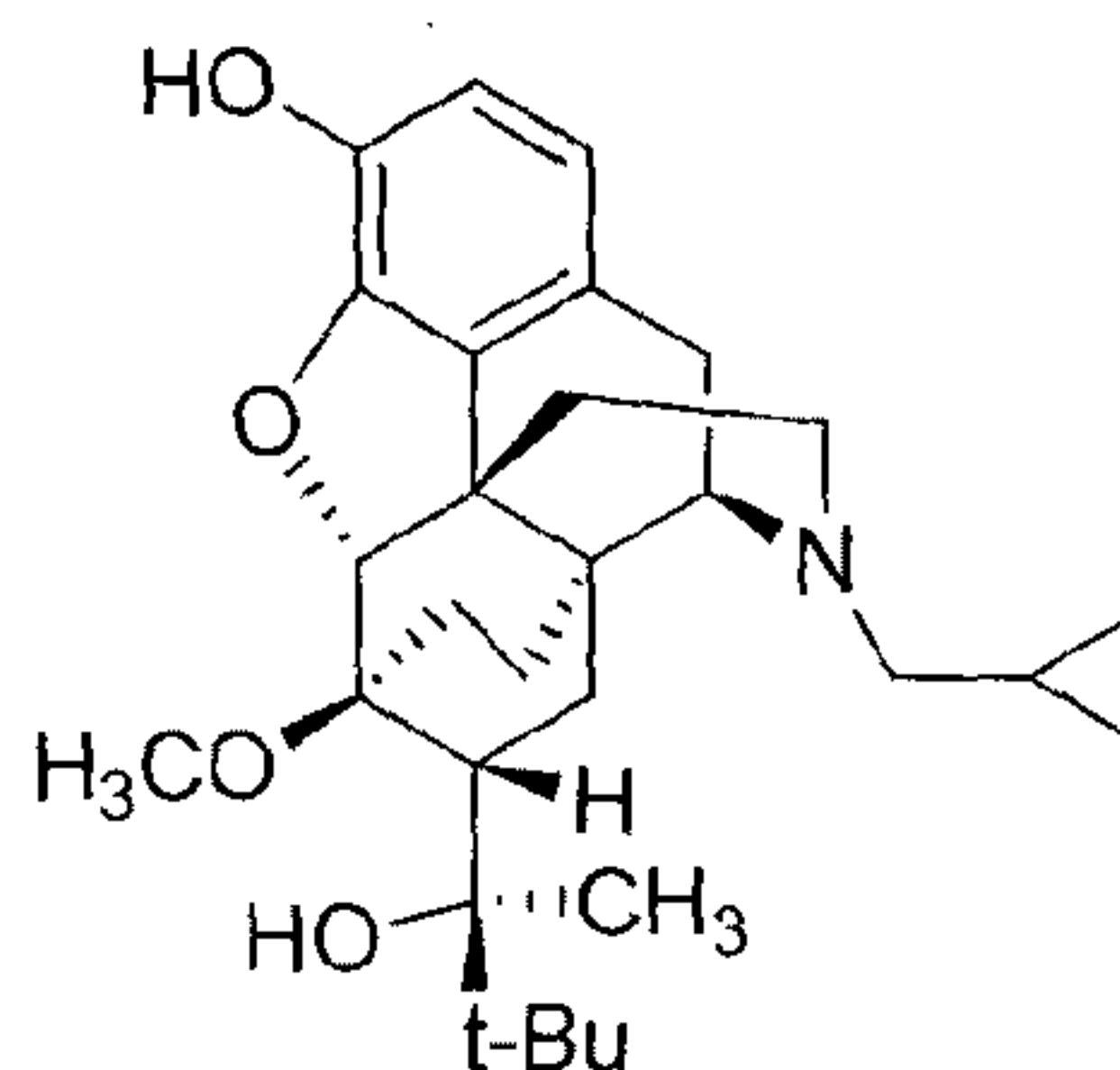
Description of the Related Art

[0002] 6 α ,14 α -Ethenomorphinans and 6 α ,14 α -ethanomorphinans are semi-synthetic oripavine or thebaine derivatives. The central structural element of this class of molecules is a morphinan ring system with an etheno or ethano bridge between the C-6 and C-14 carbons of the morphinan scaffold. Based on the nature of the carbon-carbon bond between C-18 and C-19, these compounds are classified as 6 α ,14 α -ethenomorphinans (carbon-carbon-double bond) or 6 α ,14 α -ethanomorphinans (saturated carbon-carbon bond). The morphinan scaffold has the following structure:



[0003] 6 α ,14 α -Ethenomorphinan derivatives with a substituent in the 7-position have been extensively studied over the last 60 years. During this time, drugs like Buprenorphine (Temgesic[®], Subutex[®], Suboxone[®]), Diprenorphine (Revivon[®]) and Etorphine (Immobilon[®]) were discovered. Buprenorphine is commercially the most important representative of this class of compounds and has been on the market since 1978 as a powerful analgesic and for the management of opioid dependence.

[0004] Buprenorphine, (2*S*)-2-[17-cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14 α -ethanomorphinan-7 α -yl]-3,3-dimethylbutan-2-ol, a semi-synthetic opioid having the structure:



is used to treat opioid addiction, to control moderate acute pain in non-opioid tolerant individuals, and to control moderate chronic pain. Buprenorphine can be derived from either oripavine or thebaine. K.W. Bentley discovered buprenorphine using thebaine as the initial backbone structure. Thebaine is one of the main alkaloids in the Iranian poppy (*Papaver bracteatum*). Thebaine can also be isolated from *Papaver somniferum* which is also a source for oripavine (U.S. Pat. No. 6,723,894).

[0005] Buprenorphine has an extremely high binding affinity at the μ - and κ -opioid receptors. It has partial agonist activity at the μ -opioid receptor, partial or full agonist activity at the ORL-1/nociception and δ -opioid receptors, and competitive antagonist activity at the κ -opioid receptor. Buprenorphine exhibits an analgesic effect approximately 25 to 40 times more potent than morphine (by weight of equivalent low doses). Buprenorphine is marketed as oral formulations (tablets, sublingual tablets, and sublingual films), parenteral preparations, and transdermal patches.

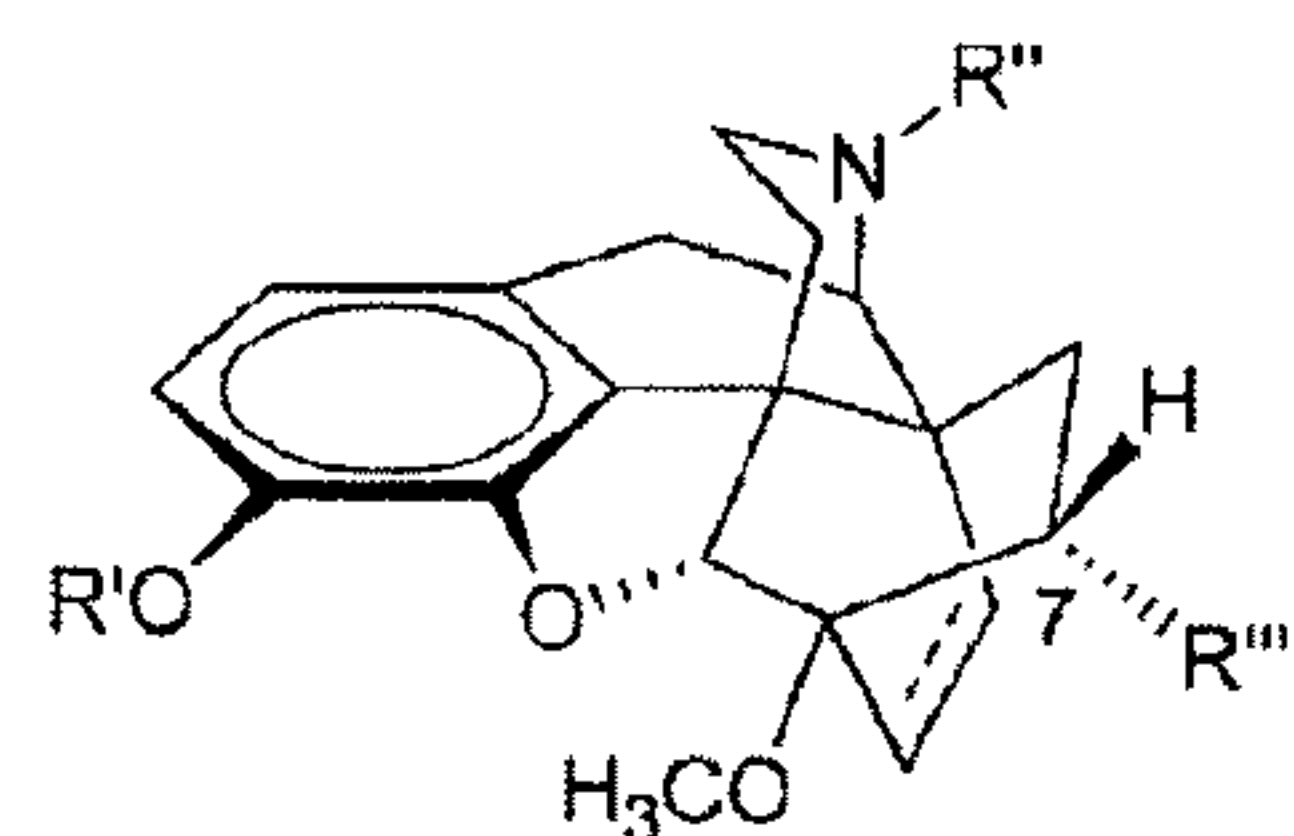
[0006] All the above-mentioned drugs within this class of compounds contain an alkyl substituent attached to the nitrogen and a hydroxyl group attached to a lipophilic substituent in 7 α -position of the C-ring. Through comparison of a large number of derivatives, it has become clear that the region above and away from C-7 has a significant impact on the μ -opioid receptor profile of these orvinols and related compounds

(Hutchins *et al.*, *J. Med. Chem.* 27:521-527 (1984); Coop *et al.*, *J. Med. Chem.* 43:1852-1857 (2000).

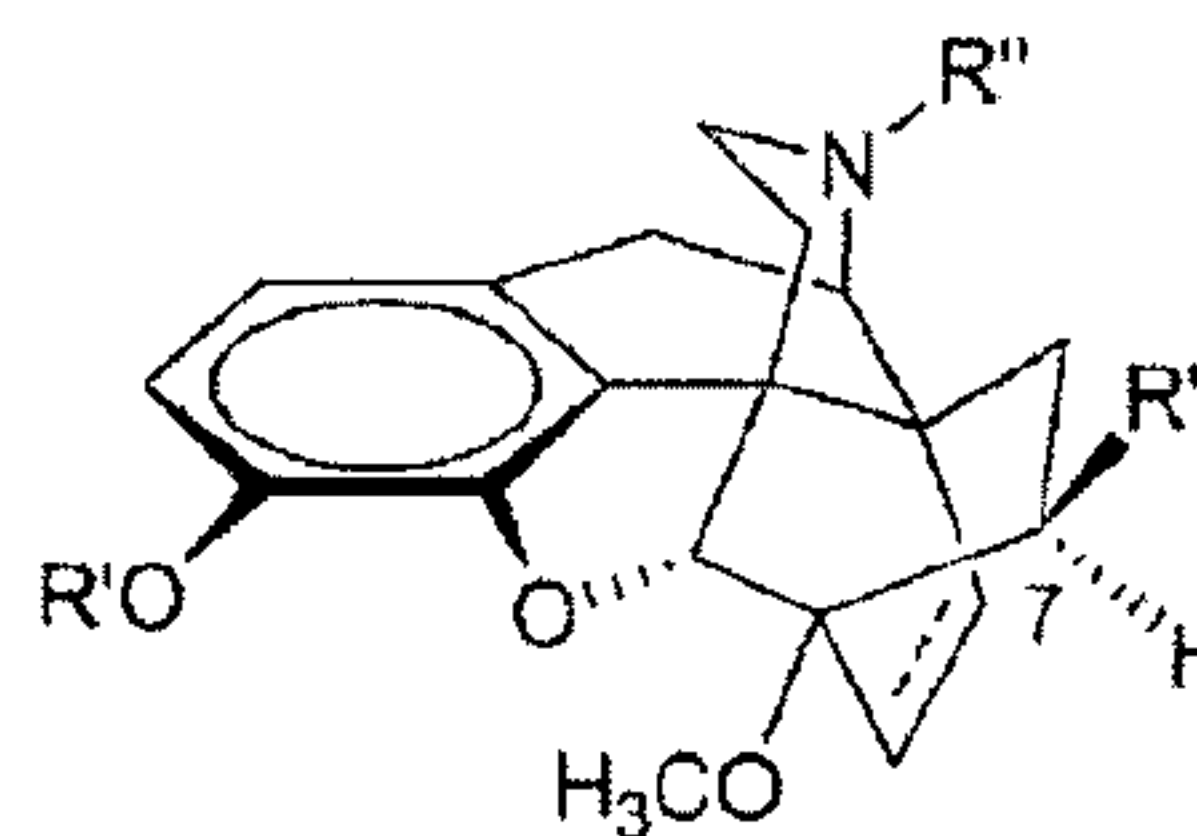
[0007] This 7 α -configuration (*e.g.* 7 α -substituted 6 α ,14 α -ethenomorphinan), found in all commercial drugs of this class of compounds, is however not a structural requirement for opioid receptor affinity, but rather a result of limited accessibility of the 7 β -substituted derivatives (*e.g.* 7 β -substituted 6 α ,14 α -ethenomorphinan). The structures of 7 α -6 α ,14 α -ethenomorphinans/ethanomorphinans and 7 β -6 α ,14 α -ethenomorphinans/ethanomorphinans are shown in Scheme 0 below:

SCHEME 0

Structure of 7 α -substituted 6 α ,14 α -ethenomorphinan/ethanomorphinan and 7 β -substituted 6 α ,14 α -ethenomorphinan/ethanomorphinan



**7 α -substituted
6 α ,14 α -ethenomorphinan/
ethanomorphinan**



**7 β -substituted
6 α ,14 α -ethenomorphinan/
ethanomorphinan**

[0008] In Scheme 0, $\diagup$ can be single bond or a double bond. Biochemical characterization of β -etorphine and β -dihydroetorphine derivatives indicate that the 7 β -substituted derivatives have a comparable high affinity for opioid binding sites as their corresponding 7 α -substituted analogs (Biyashev *et al.*, *European Journal of Pharmacology* 442:23-27 (2002)). Although extensive SAR studies have not been reported for 7 β -substituted 6 α ,14 α -ethenomorphinans, the limited data available for the β -substituted derivative of etorphine indicates that moving the substituent from position 7 α to 7 β decreased the affinity for the κ and δ receptor while the affinity for the μ receptor remained constant (Maat *et al.*, *Bioorganic & Medicinal Chemistry* 7:529-541 (1999)).

[0009] Although the 7 β -substituted derivatives of buprenorphine (Uff *et al.*, *Magnetic Resonance in Chemistry* 23:6 (1985)) as well as the corresponding 7 β -substituted derivatives of etorphine (Marton *et al.*, *Tetrahedron* 54:9143-9152 (1998)),

dihydroetorphine (Marton *et al.*, *supra*) and diprenorphine (Marton *et al.*, *Synth. Commun.* 25:829-848 (1995)), alongside the corresponding 7 β -substituted process intermediates, were synthesized and characterized, little is generally known about the chemical or biological properties of 7 β -substituted 6 α ,14 α -ethenomorphinans or 7 β -substituted 6 α ,14 α -ethanomorphinans. In contrast, the 7 α -substituted 6 α ,14 α -ethenomorphinans and 7 α -substituted 6 α ,14 α -ethenomorphinans have been extensively studied and characterized.

[0010] 7 β -Substituted 6 α ,14 α -ethenomorphinans and 7 β -substituted 6 α ,14 α -ethanomorphinans may be attractive chemotypes with potentially new pharmacological properties. However, the isolation processes of 7 β -6 α ,14 α -ethenomorphinans and 7 β -6 α ,14 α -ethanomorphinans described in the art require multiple process steps and afford the product only in a very low yield.

[0011] Accordingly, there is a need for an improved process for isolating 7 β -substituted 6 α ,14 α -ethenomorphinans and 7 β -substituted 6 α ,14 α -ethanomorphinans.

BRIEF SUMMARY OF THE INVENTION

[0012] The present disclosure provides a process for increasing the proportion of the 7 β -epimer in an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan. Said process comprises contacting a solution of the 7 α /7 β -epimer mixture with an acid to provide a precipitate, and isolating the precipitate to provide an isolated precipitate and a mother liquor. In one embodiment, the acid is an achiral acid. In another embodiment, the acid is a chiral acid.

[0013] In one embodiment, the present disclosure provides a process for increasing the proportion of the 7 β -epimer in an 7 α /7 β -epimer mixture of compounds represented by Formula I, below. In one embodiment, the 7 β -epimer is of Formula V^b, below.

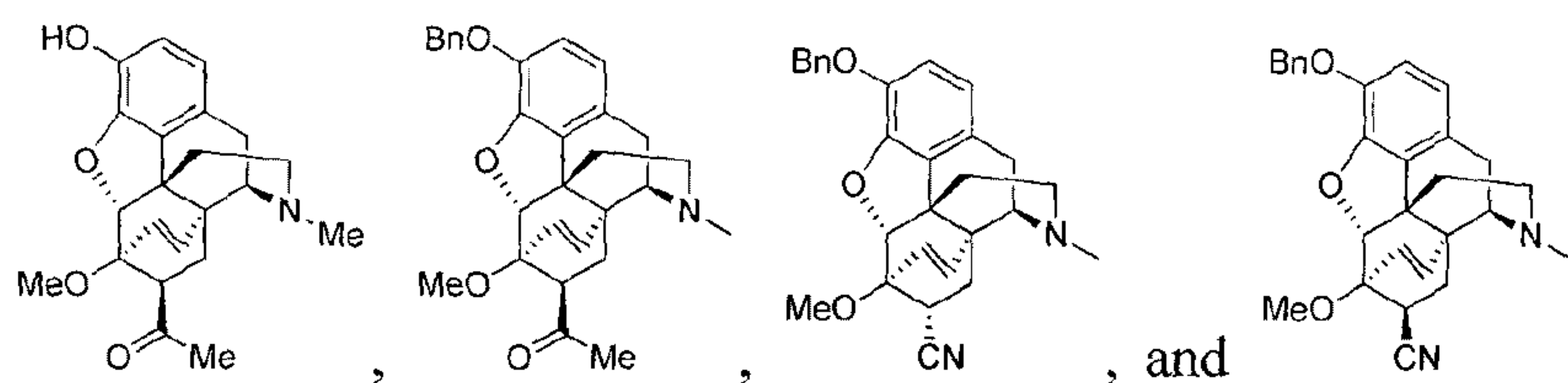
[0014] In another embodiment, the present disclosure provides a process for purifying the 7 β -epimer from a 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan. The process comprises contacting a solution of the 7 α /7 β -epimer mixture with an acid under conditions conducive to precipitation of the 7 β -epimer, and then isolating the precipitate. The isolation of the precipitate leaves behind a residual mother liquor. In one embodiment, the acid is an achiral acid. In another embodiment, the acid is a chiral acid.

[0015] In another embodiment, the present disclosure provides a process for purifying the 7 β -epimer from a 7 α /7 β -epimer mixture of compounds represented by Formula I, below. In one embodiment, the 7 β -epimer is of Formula V^b, below.

[0016] The present disclosure also provides a process for preparing 7 β -substituted compounds of Formula I, and the pharmaceutically acceptable salts thereof. The process comprises, conducting a Diels-Alder reaction to form a 7 α /7 β -epimer mixture; forming a first precipitate of the 7 α /7 β -epimer mixture; isolating the first precipitate from the reaction mixture to obtain a first mother liquor; optionally reducing the volume of the first mother liquor, and contacting the first mother liquor with an acid to provide a second precipitate; isolating the second precipitate to obtain the 7 β -substituted compound as a salt and a second mother liquor; and optionally converting the salt into its free base. The second mother liquor is optionally epimerized and contacted with the acid to obtain the 7 β -substituted compound as a salt.

[0017] The present disclosure also provides novel isolated compounds of Formula I and salts thereof, and specifically compounds of Formula V^b and salts thereof.

[0018] The present disclosure also provides Compounds



, and , or a salt thereof. In

another aspect of the present disclosure the use of these compounds or a salt thereof as a medicament is provided. In yet another aspect, the compounds or a salt thereof are used in treatment or prevention of pain, such as acute pain, chronic pain, or surgical pain. In yet another aspect, the present disclosure provides use of these Compounds of the Invention or a salt thereof in the manufacture of a medicament for treating or preventing pain, such as acute pain, chronic pain, or surgical pain. The present disclosure further provides methods of treating or preventing pain, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of the Invention. In certain embodiments, the pain includes acute pain, chronic pain, and surgical pain. In another aspect, the disclosure provides a pharmaceutical composition, comprising a therapeutically effective amount of any one of the above compounds or a

pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

[0019] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

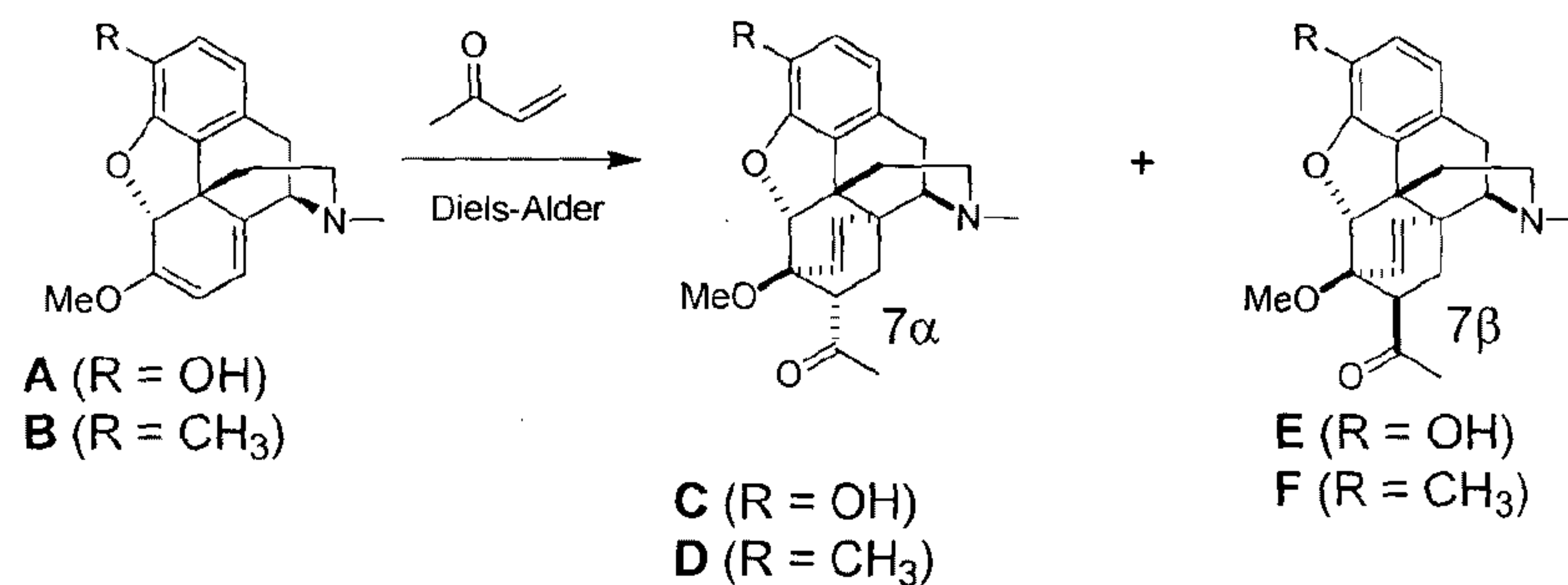
[0020] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

DETAILED DESCRIPTION OF THE INVENTION

[0021] $6\alpha,14\alpha$ -Ethenomorphinans are synthesized in the literature using a synthetic pathway comprising of a Diels-Alder reaction between a morphinan-6,8-diene and a dienophile as shown below in Scheme 1. When thebaine (**B**) or oripavine (**A**) is the diene, the 6-methoxy group determines the stereo- and regioselectivity of the Diels-Alder reaction by polarizing the diene system, and the major product of the cycloaddition reaction is the 7α -substituted $6\alpha,14\alpha$ -ethenomorphinan along with a minor amount (~1-5%) of the 7β -substituted isomer (except for compounds where CN is in the position for R^3 , wherein the product of the cycloaddition reaction forms an about 1:1 mixture of 7α - and 7β - epimers). Due to a high regio-selectivity of the reaction, 8-substituted isomers are usually not observed at all (Bentley *et al.*, *J. Am. Chem. Soc.* 89:3267-3273 (1967); Ghosh *et al.*, *J. Org. Chem.* 48:4137-4139 (1983)).

Scheme 1

Diels-Alder Reaction of Morphinan-6,8-dienes with methyl vinyl ketone



[0022] The 7 α -substituted 6 α ,14 α -ethenomorphinan is a precipitate that is isolated by a simple filtration and usually obtained in high purity without the need for an additional purification process. Since the 7 α -substituted derivative is accessible by such a simple isolation process, it is usually used as scaffold for further derivatization.

[0023] Since the Diels-Alder reaction between a morphinan-6,8-diene and a dienophile affords almost exclusively the 7 α -adduct, the isolation of the 7 β -epimer (e.g. **E** or **F**) requires, compared to the isolation of the 7 α -isomer (e.g. **C** or **D**), a much more elaborated purification process and affords the 7 β -epimer only in a very low yield. For example, Diels-Alder reaction of methyl vinyl ketone with thebaine (**B**) afforded 7 α -isomer **D** in 98% yield by simple filtration. From the filtrate, the 7 β -isomer **F** was isolated by fractional crystallization in a total yield of 0.49% (Bentley *et al.*, *supra*).

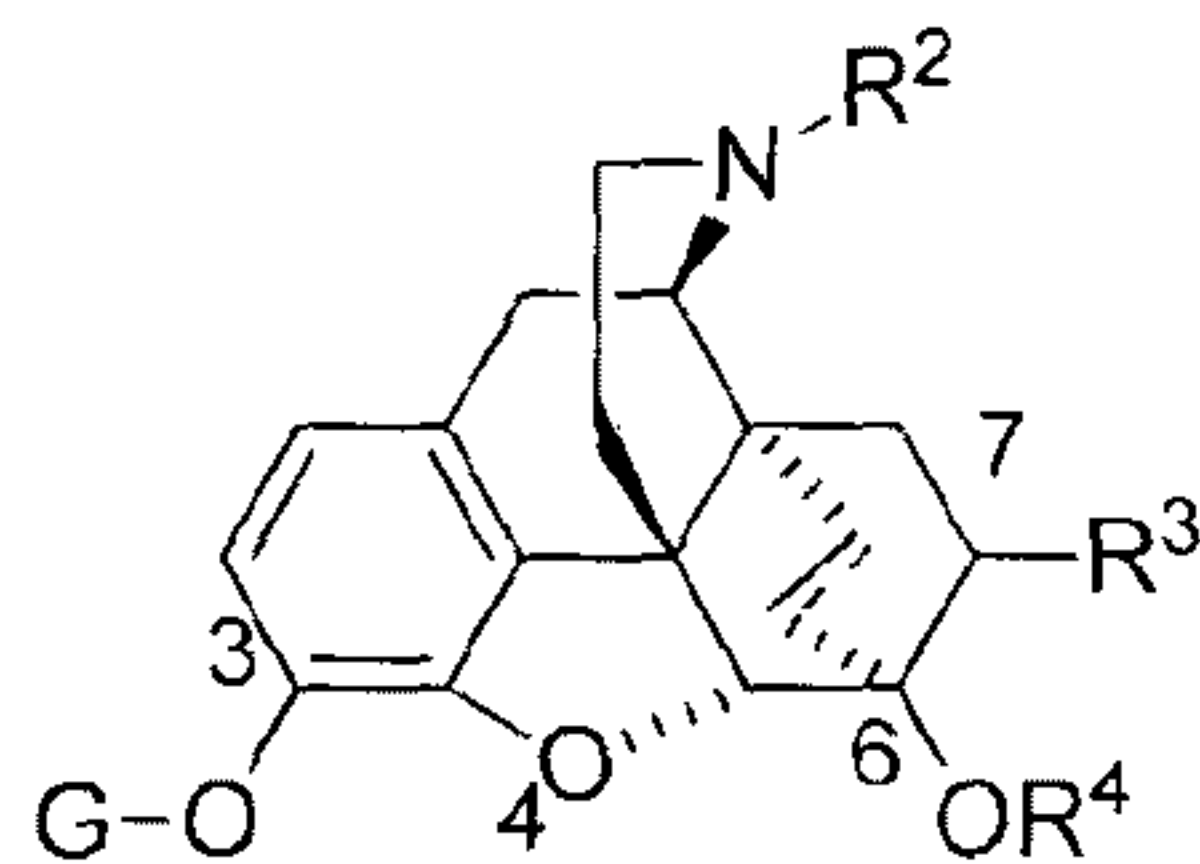
[0024] Also, Marton *et al.* (*Synth. Commun.* 25:829-848 (1995)) describe another example of the cumbersome purification process which describes the currently best-known protocol for the isolation of a β -isomer. In this process, starting from thebaine, the separation of the β -dihydrothevinone is reported in an overall yield of 0.92%.

[0025] It has now been discovered that 7 β -substituted 6 α ,14 α -ethenomorphinans and 7 β -substituted 6 α ,14 α -ethanomorphinans can easily be separated from an epimer mixture with the corresponding 7 α -epimers in a simple process affording the 7 β -epimers in about 98-100% purity and high recovery (from about 40% to over 80%).

[0026] Accordingly, the present disclosure provides a process for increasing the proportion of the 7 β -epimer in an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan, said process comprising:

contacting a solution of the 7 α /7 β -epimer mixture with an acid to provide a precipitate, and isolating the precipitate to provide an isolated precipitate and a mother liquor.

[0027] In one embodiment, the process of the present invention increases the proportion of the 7 β -epimer in an 7 α /7 β -epimer mixture of a compound of Formula I:



I, wherein:

[0028] G is R¹ or a hydroxyl protecting group PG;

[0029] R¹ is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

[0030] R² is

- (a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or
- (b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

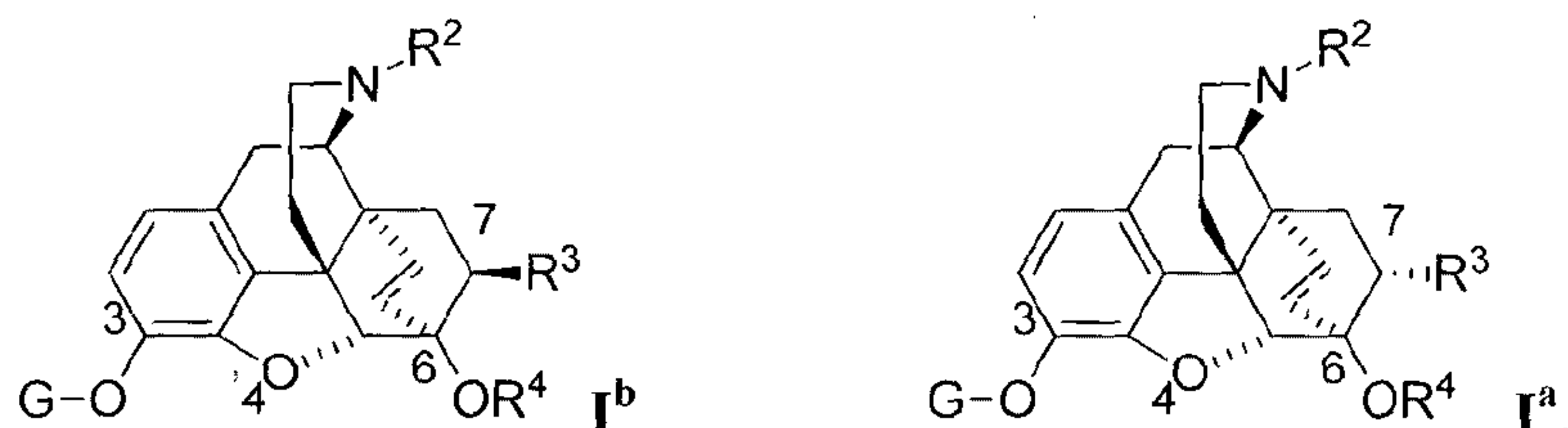
[0031] R³ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, alkylcarbonyl, (arylalkyl)carbonyl, formyl and cyano, wherein any of which, when other than formyl or cyano, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

[0032] R⁴ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl,

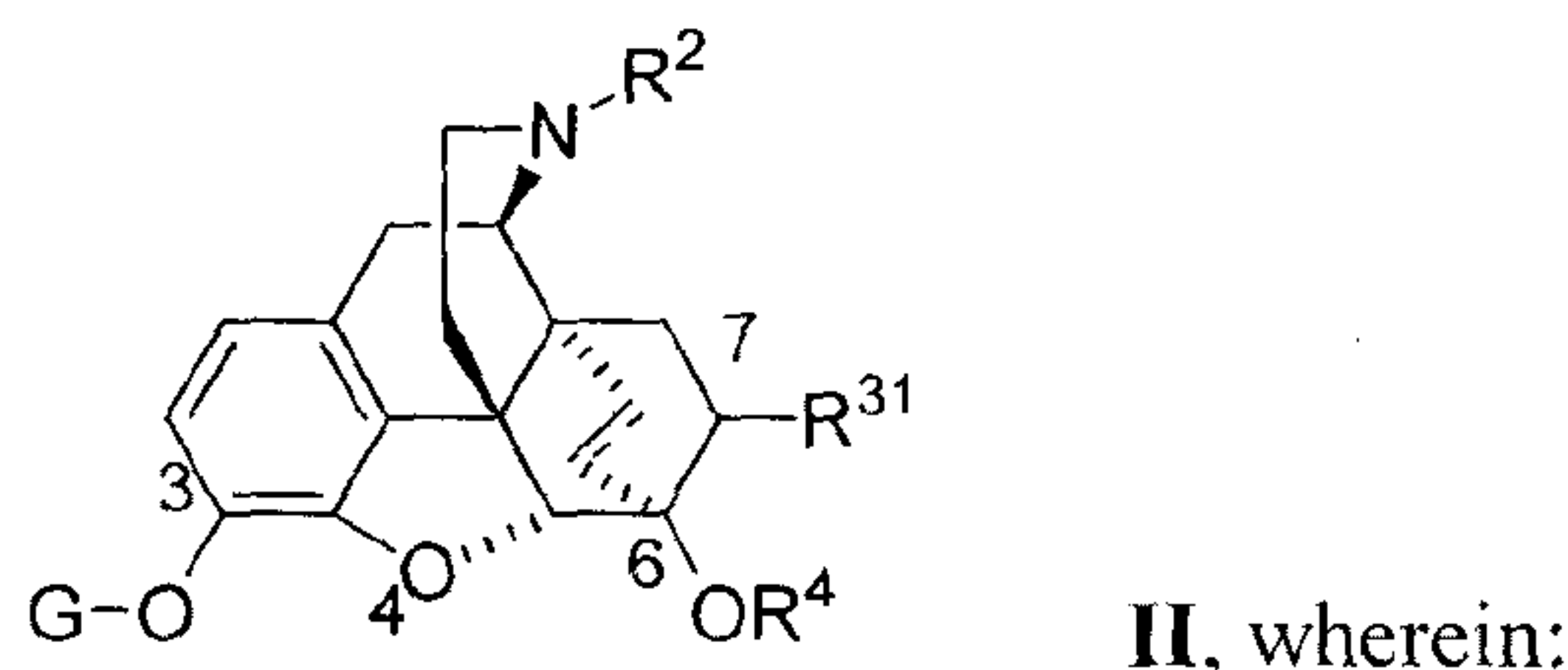
(cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and

[0033] $\diagup$ is a single bond or a double bond.

[0034] The 7 β -epimer and the 7 α -epimer of compounds of Formula I can be represented as Formulae I^b and I^a, respectively:



[0035] In another embodiment, the process of the present invention increases the proportion of the 7 β -epimer in an 7 α /7 β -epimer mixture of a compound of Formula II:



[0036] G is R¹ or a hydroxyl protecting group PG;

[0037] R¹ is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

[0038] R² is

(a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or

(b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the

group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl;

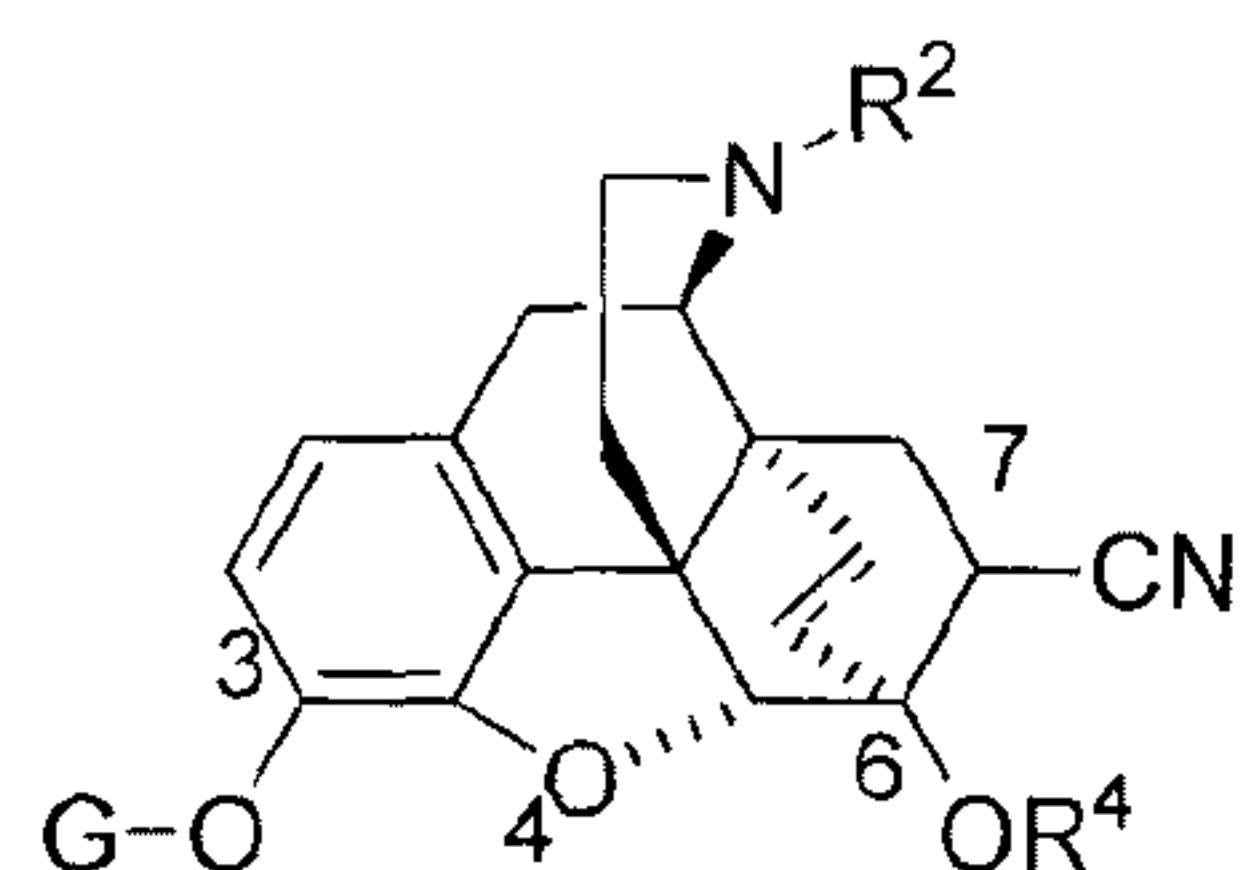
[0039] R^{31} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, alkylcarbonyl, (arylalkyl)carbonyl, and formyl, wherein any of which, when other than formyl, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl;

[0040] R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl; and

[0041] $\diagup$ is a single bond or a double bond.

[0042] In this aspect of the present invention, the isolated precipitate contains an increased proportion of the 7β -epimer as a salt relative to the $7\alpha/7\beta$ -epimer mixture of a compound of Formula II. In one embodiment, the proportion of the 7β -epimer in the isolated precipitate is at least about 60%, at least about 70%, at least about 80%, or at least about 90%.

[0043] In another embodiment, the process of the present invention increases the proportion of the 7β -epimer in an $7\alpha/7\beta$ -epimer mixture of a compound of Formula III:



III, wherein:

[0044] G is R^1 or a hydroxyl protecting group PG;

[0045] R^1 is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl

portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

[0046] R^2 is

(a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or

(b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

[0047] R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and

[0048] --- is a single bond or a double bond.

[0049] In this aspect of the present invention, an increased proportion of the 7 β -epimer salt, relative to the 7 α /7 β -epimer mixture of a compound of Formula **III**, can be found in the isolated precipitate or in the mother liquor depending on the conditions (i.e., the acid and/or the solvent) of the precipitation. In one embodiment, the isolated precipitate contains an increased proportion of the 7 β -epimer as a salt relative to the 7 α /7 β -epimer mixture of a compound of Formula **III**. In this embodiment, the proportion of the 7 β -epimer in the isolated precipitate is at least about 60%, at least about 70%, at least about 80%, or at least about 90%. In another embodiment, the mother liquor contains an increased proportion of the 7 β -epimer as a salt relative to the 7 α /7 β -epimer mixture of a compound of Formula **III**. In this embodiment, the proportion of the 7 β -epimer in the mother liquor is at least about 60%, at least about 70%, at least about 80%, or at least about 90%.

[0050] In another aspect, the present disclosure provides a process for purifying the 7 β -epimer from an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan. Said process comprises contacting a solution of the 7 α /7 β -epimer mixture with an acid under conditions conducive to precipitation of the 7 β -epimer, and isolating the precipitate. In one embodiment, the proportion of the 7 β -epimer as a salt in the isolated precipitate relative to the 7 α /7 β -epimer mixture is at least about 60%, at least about 70%, at least about 80%, or at least about 90%.

[0051] In one embodiment, the process comprises purifying the 7 β -epimer from an 7 α /7 β -epimer mixture of a compound of Formula I.

[0052] In another embodiment, the process comprises purifying the 7 β -epimer from an 7 α /7 β -epimer mixture of a compound of Formula II.

[0053] In another embodiment, the process comprises purifying the 7 β -epimer from an 7 α /7 β -epimer mixture of a compound of Formula III.

[0054] The 7 α /7 β -epimer mixture used in the processes of the present invention can be, for example, the reaction mixture after the Diels-Alder reaction (e.g., the mother liquor obtained after the first precipitate is filtered off), the reaction mixture after further functionalization of the ketone group (e.g., after the reaction with a Grignard reagent), or the reaction mixture after the hydrogenation of the double bond. In one embodiment, the 7 α /7 β -epimer mixture used in the processes of the present invention is the product of the epimerization of the first precipitate or the mother liquor obtained after the salt formation. In one embodiment, prior to contacting with the acid, the reaction mixture is typically concentrated, and then any precipitation is dissolved by optionally adding a solvent and by heating to obtain a solution.

[0055] In another embodiment, the mother liquor is concentrated to dryness and the residue is redissolved in a solvent at an elevated temperature to obtain a solution before adding the acid.

[0056] In certain embodiments, the 7 α /7 β -epimer mixture can be an isolated precipitate that is further purified with respect to the 7 β -epimer by the processes of the present invention. In this aspect of the invention, the 7 α /7 β -epimer mixture is first dissolved in a solvent at an elevated temperature to obtain a solution of the 7 α /7 β -epimer mixture before adding the acid.

[0057] In one embodiment, the solution of the 7 α /7 β -epimer mixture is contacted with the acid at about room temperature. In another embodiment, the solution of the 7 α /7 β -epimer

mixture is contacted with the acid at about 50 °C to about the boiling point of the solution. Preferably, the temperature of the solution is from about 55 °C to the reflux temperature of the solvent, and more preferably the temperature of the solution is from about 60 °C to the reflux temperature of the solvent. In another embodiment, the temperature of the solution of the 7 α /7 β -epimer mixture is from about 55 °C to about 80 °C, and more preferably the temperature is from about 60 °C to about 80 °C.

[0058] Suitable solvents to be used in the process of the present invention include, for example, aliphatic alcohols, aromatic solvents, ethers (such as aliphatic ethers or THF), and acetonitrile, or combinations thereof. Typically, the solvent is an aliphatic alcohol, an aromatic solvent, and aliphatic ether, or combinations thereof.

[0059] In one embodiment, the solvent is an aliphatic alcohol or mixtures thereof. Suitable aliphatic alcohols include C₁₋₆ alcohols, such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, n-pentanol, and n-hexanol, and preferably methanol, ethanol, n-propanol, and iso-propanol, and preferably iso-propanol.

[0060] In another embodiment, the solvent is an aromatic solvent. Suitable aromatic solvents include, for example, toluene, xylene and benzene, and preferably toluene.

[0061] In another embodiment, the solvent is an aliphatic ether. Suitable aliphatic ethers include, for example, C₅₋₆ cycloalkyl(C₁₋₆)alkyl ethers, such as cyclopentyl methyl ether.

[0062] Typically, the solvent in the processes of the present invention is selected from the group consisting of methanol, ethanol, n-propanol, iso-propanol, toluene, and cyclopropyl methyl ether, or the solvent can be a combination (i.e., a mixture) of these solvents.

[0063] The solution of the 7 α /7 β -epimer mixture is contacted with the acid either at the elevated temperature or after cooling it, for example, to room temperature. Typically, the solution of the 7 α /7 β -epimer mixture is contacted with the acid at an elevated temperature and then the mixture is cooled to form a precipitate. The solution of the 7 α /7 β -epimer mixture is contacted with the acid, for example, by simply adding, preferably portion wise (or dropwise when dissolved in a suitable solvent), a sufficient amount of the acid to the solution and mixing. The sufficient amount of the acid is an amount that is necessary for converting the 7 β -epimer of the 7 α /7 β -epimer mixture into its salt. In one embodiment, the amount of the acid is from about 0.5 to about 1.5 equivalents based on the amount of the 7 β -epimer. In another embodiment, the amount of the acid is from about 0.8 to about 1.3 equivalents, preferably from about 0.9 to about 1.2 equivalents, and more preferably about 1.0 or about 1.1 equivalents based on the amount of the 7 β -epimer. The amount of

the 7 β -epimer of the 7-substituted 6 α ,14 α -ethenomorphinan or the 7-substituted 6 α ,14 α -ethanomorphinan can be determined by conventional methods described in the art, such as, for example by ^1H NMR: interaction of the H-5 protons, as described in Uff *et al.*, *Magnetic Resonance in Chemistry* 23:6 (1985); Marton, J., *et al.*, *Acta Chemica Scandinavica* 52:1234-1238 (1998); and Derrick, I., *et al.*, *Tetrahedron Letters* 41:7571-7576 (2000), and by HPLC as described in the examples.

[0064] In one embodiment, the proportion of the 7 β -epimer in the 7 α /7 β -epimer mixture is at least about 20%. In another embodiment, the proportion of the 7 β -epimer in the 7 α /7 β -epimer mixture is at least about 50%.

[0065] In one embodiment the acid is an achiral acid. In another embodiment, the acid is a chiral acid.

[0066] In one embodiment, the acid is selected from the group consisting of an aliphatic monocarboxylic acid and an aliphatic dicarboxylic acid, or a combination thereof, any of which is optionally substituted. In another embodiment, the acid is an optionally substituted, saturated or unsaturated aliphatic monocarboxylic acid, and preferably a saturated or unsaturated C₁₋₆ aliphatic monocarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy. Typically, in this aspect of the invention, the acid is a saturated, unsubstituted C₁₋₄ aliphatic monocarboxylic acid, or a saturated C₁₋₄ aliphatic monocarboxylic acid substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of fluoro, chloro, bromo, iodo, and hydroxy. Advantageously, the monocarboxylic acid is selected from the group consisting of acetic acid, trifluoroacetic acid (TFA), trichloroacetic acid, and tribromoacetic acid, and preferably TFA.

[0067] In another embodiment, the acid is an optionally substituted, saturated or unsaturated aliphatic dicarboxylic acid, and preferably a saturated C₂₋₆ aliphatic dicarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy. Typically, in this aspect of the invention, the acid is an unsaturated C₂₋₆ aliphatic dicarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy, and preferably an unsaturated, unsubstituted C₂₋₆ aliphatic dicarboxylic acid. Advantageously, the dicarboxylic acid is fumaric acid or maleic acid.

- [0068] The precipitate can be isolated by any conventional separation process. Suitable separation processes for isolating the precipitate include, for example, filtration, such as vacuum filtration, and centrifugal separations. Preferably, the precipitate is isolated by filtration, and the filter cake is optionally washed to remove any residual mother liquor.
- [0069] In another embodiment, G in compounds of any of Formulae I-III is R¹.
- [0070] In another embodiment, R¹ is hydrogen.
- [0071] In another embodiment, R¹ is alkyl, alkenyl, or alkynyl, and specifically C₁₋₄ alkyl, C₂₋₄ alkenyl, or C₂₋₄ alkynyl. In another embodiment, R¹ is methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, iso-butyl, or sec-butyl, and advantageously R¹ is methyl. In another embodiment, R¹ is ethenyl, propenyl, isopropenyl, butenyl, or sec-butenyl. In another embodiment, R¹ is ethynyl, propynyl, butynyl, or 2-butynyl.
- [0072] In another embodiment, R¹ is (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, or heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl.
- [0073] Suitable (cycloalkyl)alkyl groups for R¹ include C₃₋₇ cycloalkyl(C₁₋₄)alkyl groups, and specifically C₃₋₆ cycloalkyl(C₁₋₄)alkyl groups, wherein the cycloalkyl portion is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl. In another embodiment, R¹ is cyclopropyl(C₁₋₄)alkyl, cyclobutyl(C₁₋₄)alkyl, cyclopentyl(C₁₋₄)alkyl, or cyclohexyl(C₁₋₄)alkyl, optionally substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, carboxy, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxycarbonyl. In another embodiment, R¹ is unsubstituted (cyclopropyl)methyl, 2-(cyclopropyl)ethyl or 3-(cyclopropyl)propyl.
- [0074] Suitable (heterocyclo)alkyl groups for R¹ include 5- or 6-membered heterocyclo(C₁₋₄)alkyl, wherein the heterocyclo portion is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and typically optionally substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, carboxy, C₁₋₄ alkoxy, C₁₋₄

alkylcarbonyl, and C₁₋₄ alkoxy carbonyl. In another embodiment, R¹ is unsubstituted 5- or 6-membered heterocyclo(C₁₋₄)alkyl, such as tetrahydrofuranyl(C₁₋₄)alkyl.

[0075] Suitable arylalkyl groups for R¹ include aryl(C₁₋₄)alkyl groups wherein the aryl portion is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxy carbonyl; and typically optionally substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, carboxy, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxy carbonyl. In another embodiment, R¹ is C₆₋₁₀ aryl(C₁₋₄)alkyl substituted with one or two substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, carboxy, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxy carbonyl. In another embodiment, R¹ is benzyl, phenethyl, or naphthylmethyl substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, methyl, ethyl, fluorine, bromine, iodine, chlorine, trifluoromethyl, carboxy, methoxy, ethoxy, methylcarbonyl, ethylcarbonyl, methoxycarbonyl, and ethoxycarbonyl. In another embodiment, R¹ is unsubstituted C₆₋₁₀ aryl(C₁₋₄)alkyl, such as benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, naphthylmethyl, 2-naphthylethyl, 3-naphthylpropyl, and 4-naphthylbutyl; typically benzyl and phenethyl, and especially benzyl.

[0076] Suitable heteroarylalkyl groups for R¹ include heteroaryl(C₁₋₄)alkyl groups wherein the heteroaryl portion is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxy carbonyl; and typically optionally substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, carboxy, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxy carbonyl. In another embodiment, R¹ is 5- or 6-membered heteroaryl(C₁₋₄)alkyl, such as furanyl(C₁₋₄)alkyl, substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, carboxy, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxy carbonyl; and typically each independently selected from the group consisting of hydroxy, halo, halo(C₁₋₂)alkyl, carboxy, C₁₋₂ alkoxy, C₁₋₂ alkylcarbonyl, and C₁₋₂ alkoxy carbonyl.

[0077] In another embodiment, R² in compounds of any of Formulae I-III is hydrogen, cyano, alkylcarbonyl, alkoxy carbonyl, or carboxamido. In this aspect of the invention,

typically R^2 is hydrogen, cyano, C_{1-4} alkylcarbonyl, C_{1-4} alkoxy carbonyl, $-\text{CONH}_2$, $-\text{CON}(\text{H})C_{1-4}$ alkyl, $-\text{CON}(C_{1-4} \text{ alkyl})_2$, or $-\text{CON}(\text{H})\text{Ph}$.

[0078] In another embodiment, R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl. Useful compounds include those where R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, 5- or 6-membered heterocyclo, aryl, 5- or 6-membered heteroaryl, C_{3-7} cycloalkyl(C_{1-4})alkyl, C_{3-7} cycloalkenyl(C_{1-4})alkyl, 5- or 6-membered heterocyclo(C_{1-4})alkyl, aryl(C_{1-4})alkyl, 5- or 6-membered heteroaryl(C_{1-4})alkyl, aryl(C_{1-4})alkoxy carbonyl, or 5- or 6-membered heteroaryl(C_{1-4})alkoxy carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl. In another embodiment, R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, 5- or 6-membered heterocyclo, C_{6-10} aryl, 5- or 6-membered heteroaryl, C_{3-7} (cycloalkyl)(C_{1-4})alkyl, C_{3-7} (cycloalkenyl)(C_{1-4})alkyl, 5- or 6-membered heterocyclo(C_{1-4})alkyl, C_{6-10} aryl(C_{1-4})alkyl, 5- or 6-membered heteroaryl(C_{1-4})alkyl, C_{6-10} aryl(C_{1-4})alkoxy carbonyl, or 5- or 6-membered heteroaryl(C_{1-4})alkoxy carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C_{1-4} alkyl, halo, halo(C_{1-4})alkyl, C_{1-4} alkoxy, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxy carbonyl, and especially optionally substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, methyl, ethyl, halo, trifluoromethyl, methoxy, ethoxy, methylcarbonyl, ethylcarbonyl, methoxycarbonyl, and ethoxycarbonyl. In another embodiment, R^2 is C_{3-7} (cycloalkyl)(C_{1-4})alkyl or C_{3-7} (cycloalkenyl)(C_{1-4})alkyl, and especially C_{3-7} (cycloalkyl)(C_{1-4})alkyl, such as cyclopropyl(C_{1-4})alkyl, cyclobutyl(C_{1-4})alkyl, cyclopentyl(C_{1-4})alkyl, or cyclohexyl(C_{1-4})alkyl, optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C_{1-4} alkyl, halo, halo(C_{1-4})alkyl, C_{1-4} alkoxy, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxy carbonyl, and especially optionally substituted with 1 or 2 substituents, each independently selected from the group consisting of hydroxy, methyl, ethyl, halo, trifluoromethyl, methoxy, ethoxy, methylcarbonyl, ethylcarbonyl, methoxycarbonyl, and ethoxycarbonyl. In

another embodiment, R^2 is unsubstituted (cyclopropyl)methyl, 2-(cyclopropyl)ethyl or 3-(cyclopropyl)propyl.

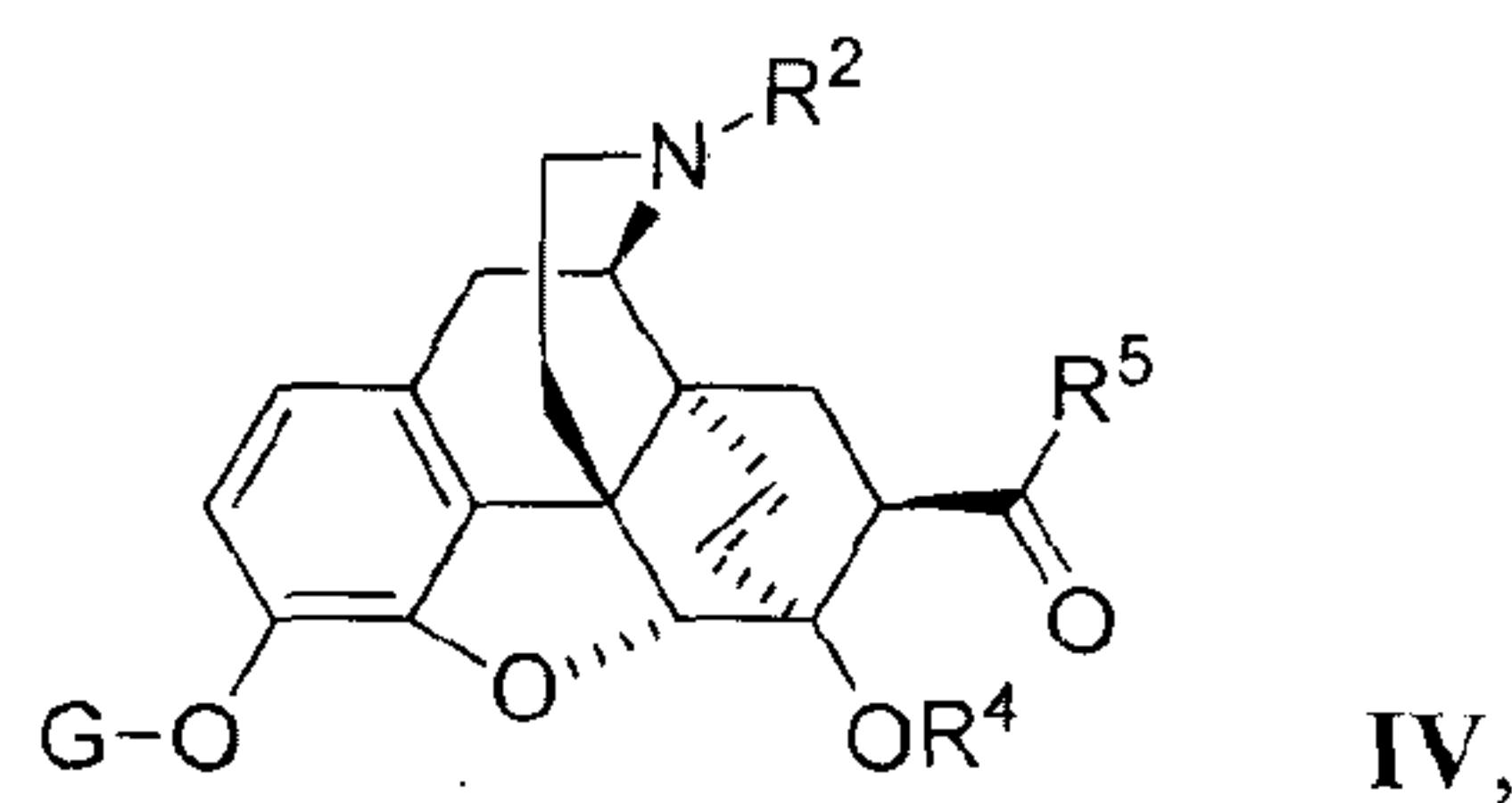
[0079] In another embodiment, R^3 in compounds of Formula I or R^{31} in compounds of Formula II is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, 5- to 6-membered heterocyclo, C_{6-12} aryl, 5- to 10-membered heteroaryl, C_{3-7} cycloalkyl(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{2-6})alkenyl, C_{3-7} cycloalkenyl(C_{1-6})alkyl, C_{3-7} cycloalkenyl(C_{2-6})alkenyl, 5- to 6-membered heterocyclo(C_{1-4})alkyl, 5- to 6-membered heterocyclo(C_{2-4})alkenyl, C_{6-12} aryl(C_{1-6})alkyl, C_{6-12} aryl(C_{2-6})alkenyl, 5- to 10-membered heteroaryl(C_{1-4})alkyl, 5- to 10-membered heteroaryl(C_{2-6})alkenyl, C_{1-6} alkylcarbonyl, (C_{6-12} aryl(C_{1-4})alkyl)carbonyl, and formyl, wherein any of which, when other than formyl, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, hydroxy(C_{1-6})alkyl, halo, halo(C_{1-5})alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, and C_{1-6} alkoxycarbonyl. In another embodiment, R^3 is C_{1-6} alkylcarbonyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, hydroxy(C_{1-6})alkyl, halo, halo(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, and C_{1-6} alkoxycarbonyl.

[0080] In another embodiment, R^4 in compounds of any of Formulae I-III is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, 5- to 6-membered heterocyclo, C_{6-12} aryl, 5- to 10-membered heteroaryl, C_{3-7} cycloalkyl(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{2-6})alkenyl, C_{3-7} cycloalkenyl(C_{1-6})alkyl, C_{3-7} cycloalkenyl(C_{2-6})alkenyl, 5- to 6-membered heterocyclo(C_{1-6})alkyl, 5- to 6-membered heterocyclo(C_{2-6})alkenyl, C_{6-12} aryl(C_{1-6})alkyl, C_{6-12} aryl(C_{2-6})alkenyl, 5- to 10-membered heteroaryl(C_{1-6})alkyl, and 5- to 10-membered heteroaryl(C_{1-6})alkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, halo, halo(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, and C_{1-6} alkoxycarbonyl. Typically, R^4 is hydrogen or unsubstituted C_{1-6} alkyl.

[0081] In another embodiment, $\diagup$ is a single bond in compounds of any of Formulae I-III.

[0082] In another embodiment, $\diagup$ is a double bond in compounds of any of Formulae I-III.

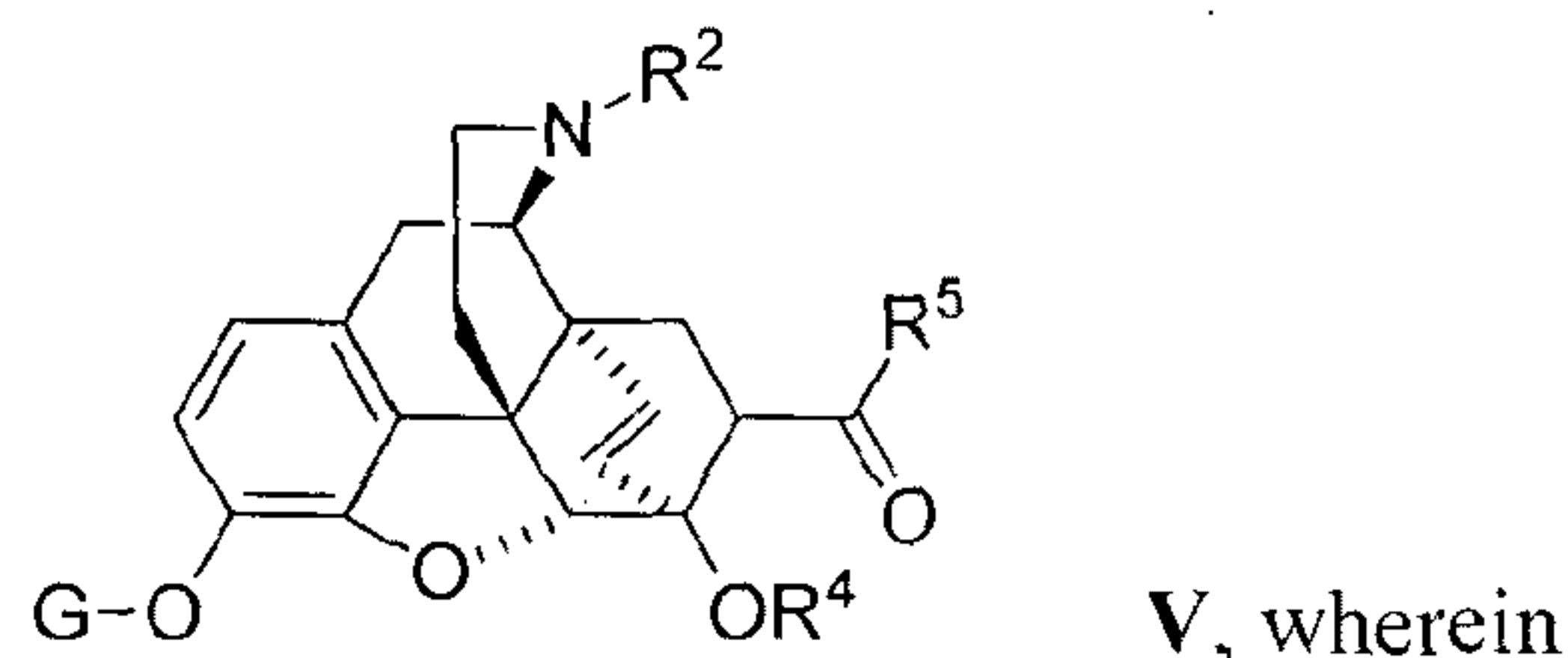
[0083] In another embodiment, the 7 β -epimer of compounds of any of Formulae I-II is represented by Formula IV:



wherein

R¹, R², R⁴, G, and $\diagup$ are as defined above for Formula I, and R⁵ is H or C₁₋₆ alkyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, hydroxy(C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylcarbonyl, and C₁₋₆ alkoxycarbonyl.

[0084] In another embodiment, the 7 α /7 β -epimer mixture of a compound of Formula I is represented by Formula V:



R¹, R², R⁴, and G are as defined above for Formula I, and R⁵ is C₁₋₆ alkyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, hydroxy(C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxycarbonyl.

[0085] In another embodiment, in compounds of any of Formulae I-V, R¹ is hydrogen, C₁₋₆ alkyl, or benzyl; R² is C₂₋₆ alkenyl, cyclopropyl(C₁₋₄)alkyl, cyclobutyl(C₁₋₄)alkyl, cyclopentyl(C₁₋₄)alkyl, or cyclohexyl(C₁₋₄)alkyl, optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxycarbonyl; and R⁴ is hydrogen or C₁₋₆ alkyl. In another embodiment, R² is unsubstituted C₂₋₆ alkenyl or unsubstituted cyclopropyl(C₁₋₄)alkyl. In another embodiment, R² is (cyclopropyl)methyl. In another embodiment, R¹ is hydrogen, C₁₋₆ alkyl, or benzyl. In another embodiment, R² is (cyclopropyl)methyl.

[0086] In another embodiment, G in compounds of any of Formulae I-V is a hydroxyl protecting group PG.

[0087] Suitable hydroxyl protecting groups for PG are well known and include, for example, any suitable hydroxyl protecting group disclosed in Wuts, P. G. M. & Greene, T. W., *Greene's Protective Groups in Organic Synthesis*, 4rd Ed., pp. 16-430 (J. Wiley & Sons, 2007).

The term "hydroxyl protecting group" as used herein refers to group that blocks (i.e., protects) the hydroxy functionality while reactions are carried out on other functional groups or parts of the molecule. Those skilled in the art will be familiar with the selection, attachment, and cleavage of protecting groups and will appreciate that many different protective groups are known in the art, the suitability of one protective group or another being dependent on the particular the synthetic scheme planned. Suitable hydroxyl protecting groups are generally able to be selectively introduced and removed using mild reaction conditions that do not interfere with other portions of the subject compounds. These protecting groups can be introduced or removed at a convenient stage using methods known in the art. The chemical properties of such groups, methods for their introduction and removal are known in the art and can be found, for example, in Greene, T.W. and Wuts, P.G.M., above. Additional hydroxy protecting groups can be found, for example, in U.S. Patent No. 5,952,495, U.S. Patent Appl. Pub. No. 2008/0312411, WO 2006/035195, and WO 98/02033.

Suitable hydroxyl protecting groups include the methoxymethyl, tetrahydropyranyl, tert-butyl, allyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, acetyl, pivaloyl, benzoyl, benzyl (Bn), and p-methoxybenzyl group.

[0088] It is apparent to a person of ordinary skill in the art that certain groups included in the definitions of R^1 and PG are overlapping, such as tert-butyl, benzyl, etc., and, thus, certain compounds of Formulae I-V having R^1 groups that act as hydroxyl protecting groups can be pharmaceutically active.

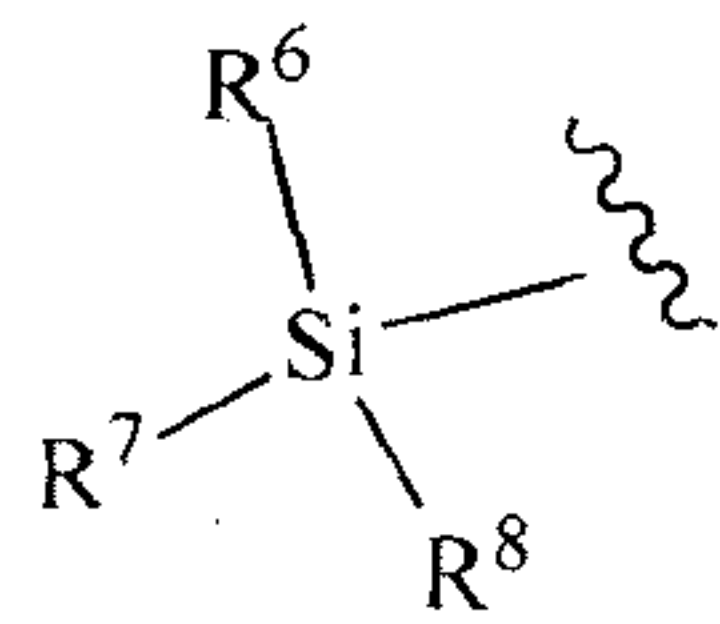
[0089] In one embodiment, the hydroxyl protecting group PG is selected from the group consisting of alkyl, arylalkyl, heterocyclo, (heterocyclo)alkyl, acyl, silyl, and carbonate, any of which are optionally substituted.

[0090] In another embodiment, the hydroxyl protecting group is an alkyl group, typically an optionally substituted C_{1-6} alkyl group, and suitably unsubstituted methyl or tert-butyl.

[0091] In another embodiment, the hydroxyl protecting group PG is an arylalkyl group. Suitable arylalkyl groups include, for example, an unsubstituted benzyl group, substituted benzyl groups, such as p-methoxybenzyl, and naphthylmethyl.

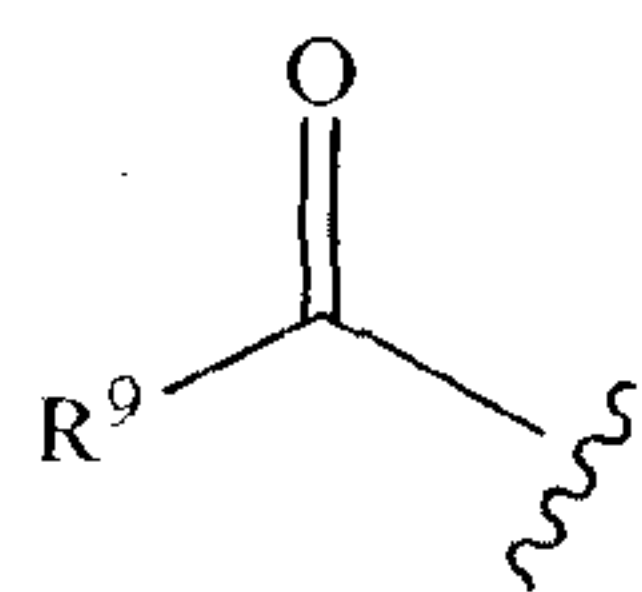
[0092] In another embodiment, the hydroxyl protecting group PG is a heterocyclo group, such as unsubstituted tetrahydropyranyl or optionally substituted tetrahydropyranyl.

[0093] In another embodiment, the hydroxyl protecting group PG is a silyl group. The term "silyl" as employed herein refers to the following group having the structure:



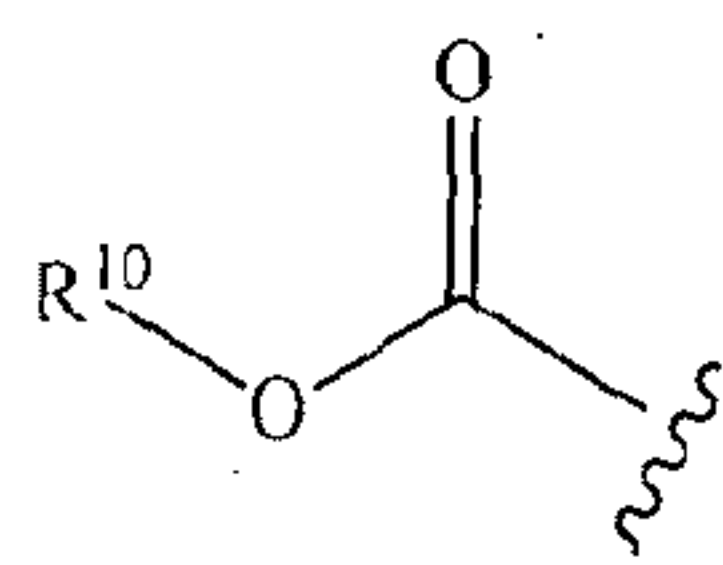
, wherein R^6 , R^7 , and R^8 are each independently selected from the group consisting of alkyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. In one embodiment, the silyl group is trimethyl silyl, tert-butyldimethyl silyl, tert-butyldiphenyl silyl, or tri-isopropyl silyl.

[0094] In another embodiment, the hydroxyl protecting group PG is an acyl group. The term "acyl" as employed herein refers to the following structure:



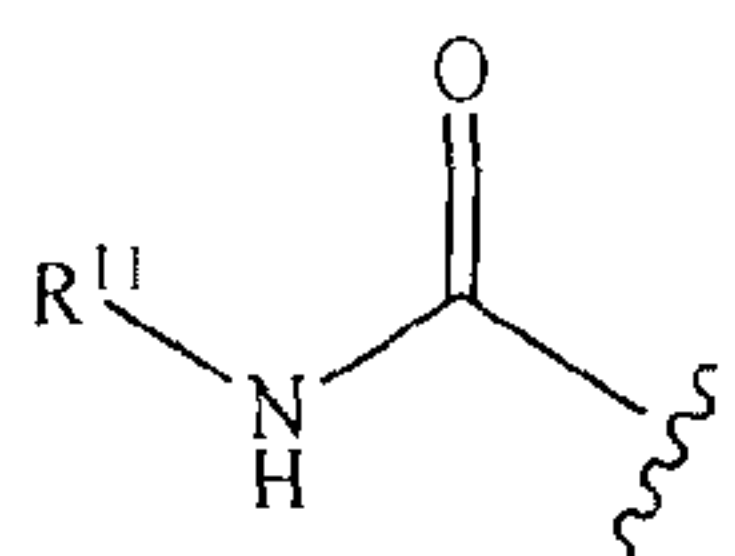
, wherein R^9 is alkyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. The acyl group can be, for example, C_{1-4} alkylcarbonyl (such as, for example, acetyl), arylcarbonyl (such as, for example, benzoyl), levulinoyl, or pivaloyl. In another embodiment, the acyl group is benzoyl.

[0095] In another embodiment, the hydroxyl protecting group is a carbonate group. The term "carbonate" as employed herein refers to the following structure:



, wherein R^{10} is alkyl, alkenyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. Typically, R^{10} is C_{1-10} alkyl (e.g., 2,4-dimethylpent-3-yl), C_{2-6} alkenyl (e.g., ethenyl or prop-2-enyl, i.e., allyl), C_{3-12} cycloalkyl (e.g., adamantyl), phenyl, or benzyl.

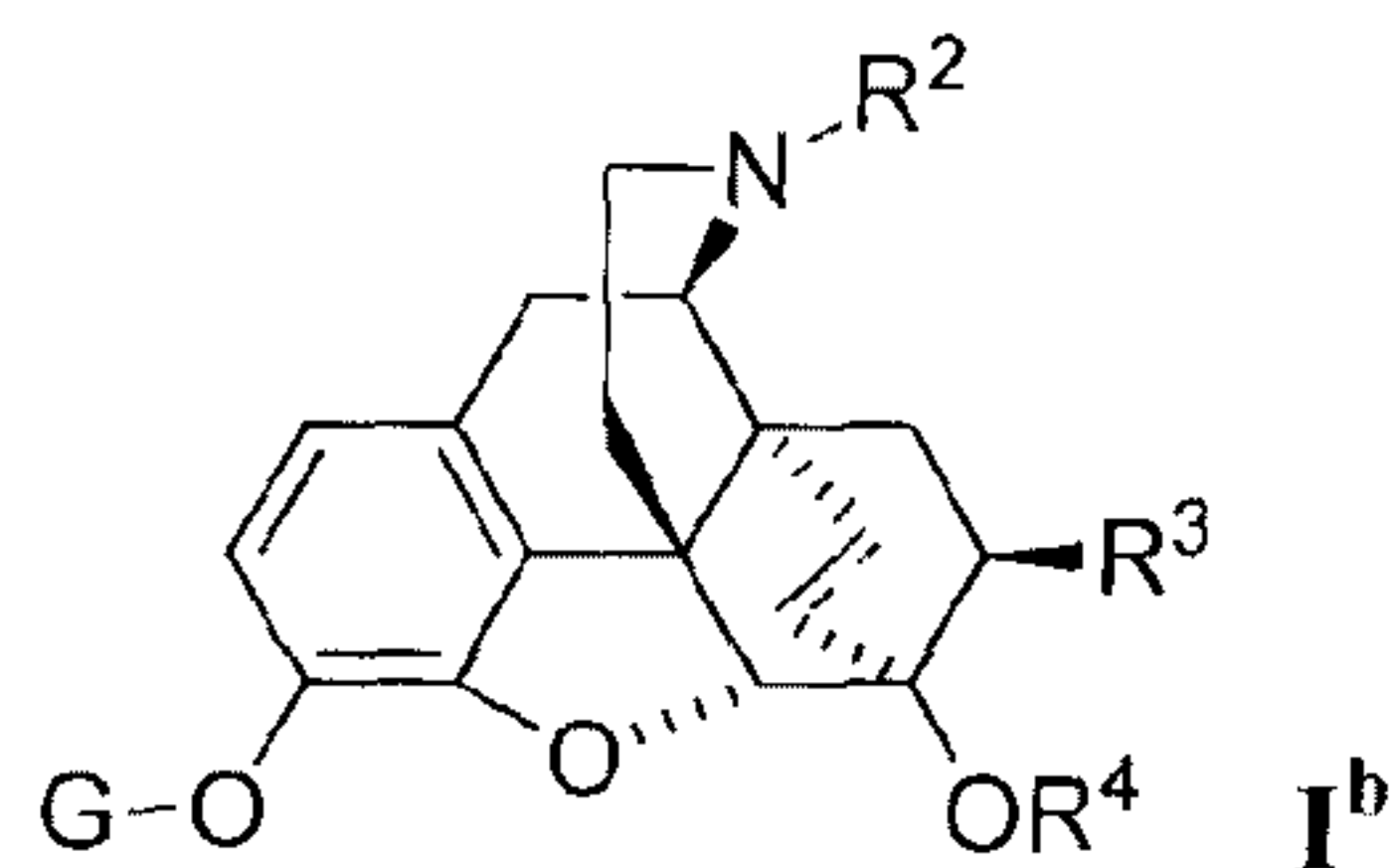
[0096] In another embodiment, the hydroxyl protecting group is a carbamate group. The term "carbamate" as employed herein refers to the following structure:



, wherein R^{11} is alkyl, alkenyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. Typically, R^{11} is C_{1-10} alkyl (e.g., tert-

butyl, 2,4-dimethylpent-3-yl), C₂₋₆ alkenyl (e.g., ethenyl or prop-2-enyl, i.e., allyl), C₃₋₁₂ cycloalkyl (e.g., adamantyl), phenyl, or benzyl.

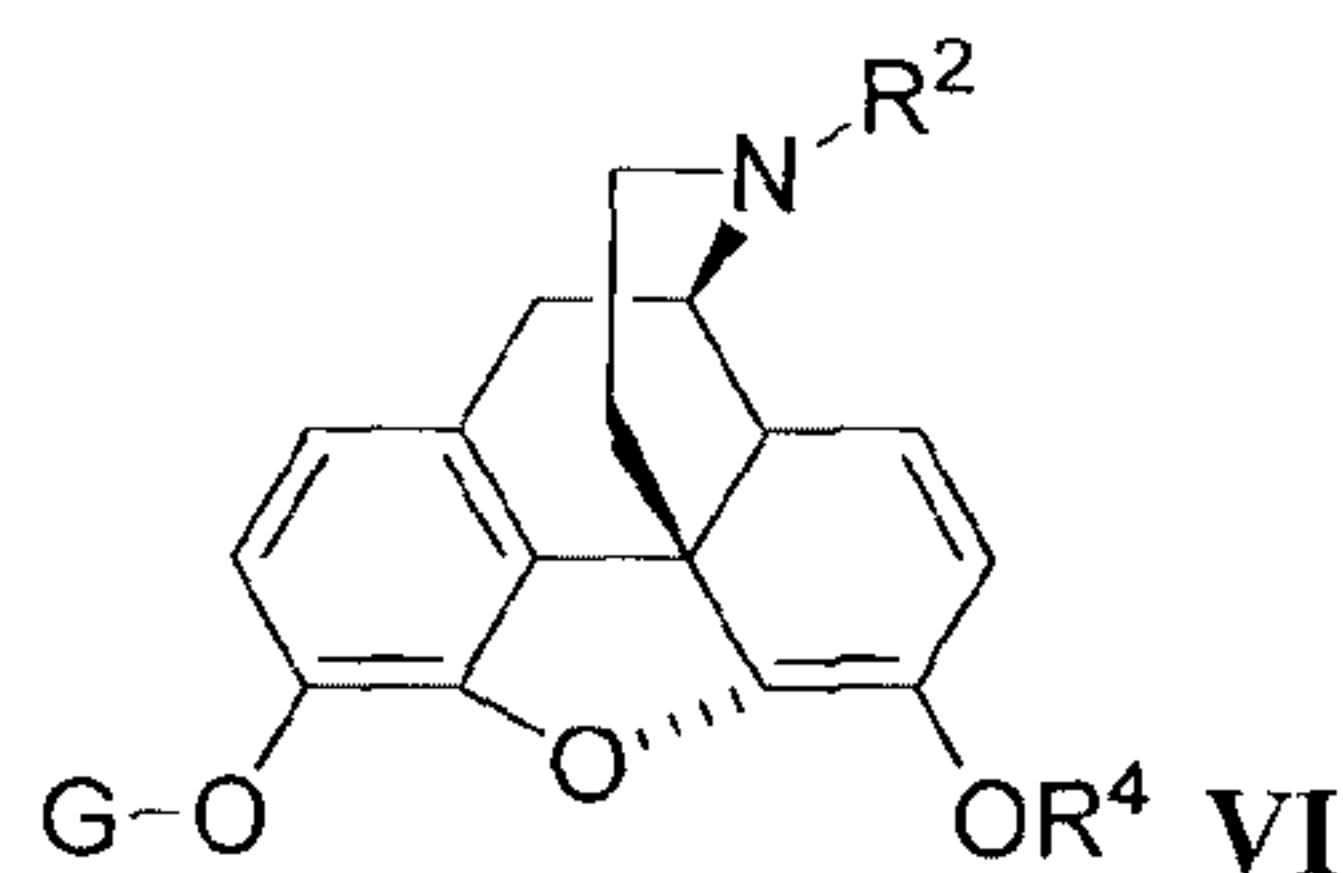
[0097] The present invention also pertains to the preparation of 7 β -substituted compounds of Formula I^b:



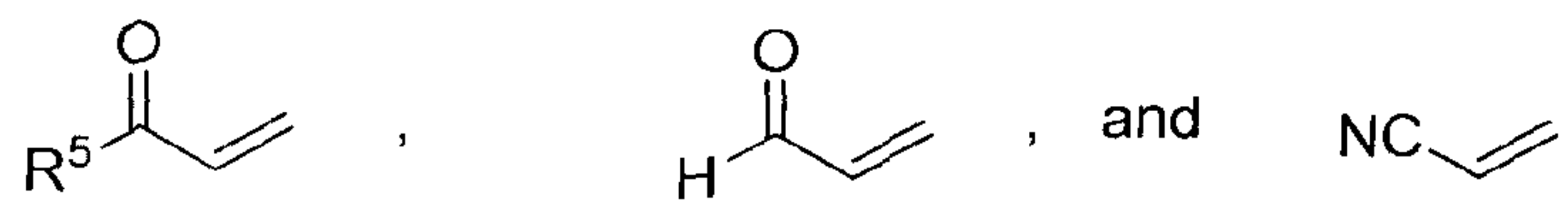
and the salts thereof, wherein

[0098] G and R²-R⁴ are as defined above for Formula I, comprising:

[0099] a) conducting a Diels-Alder reaction between a compound of Formula VI:



wherein G and R² are as defined above for Formula I, and a compound selected from the group consisting of:



wherein R⁵ is as defined above for Formula IV, to form a 7 α /7 β -epimer mixture of the compound of Formula I, where = is a double bond;

[00100] b) forming a first precipitate of the 7 α /7 β -epimer mixture;

[0100] c) isolating the first precipitate from the reaction mixture to obtain a first mother liquor;

[0101] d) optionally reducing the volume of the first mother liquor, and contacting the first mother liquor with an acid to provide a second precipitate;

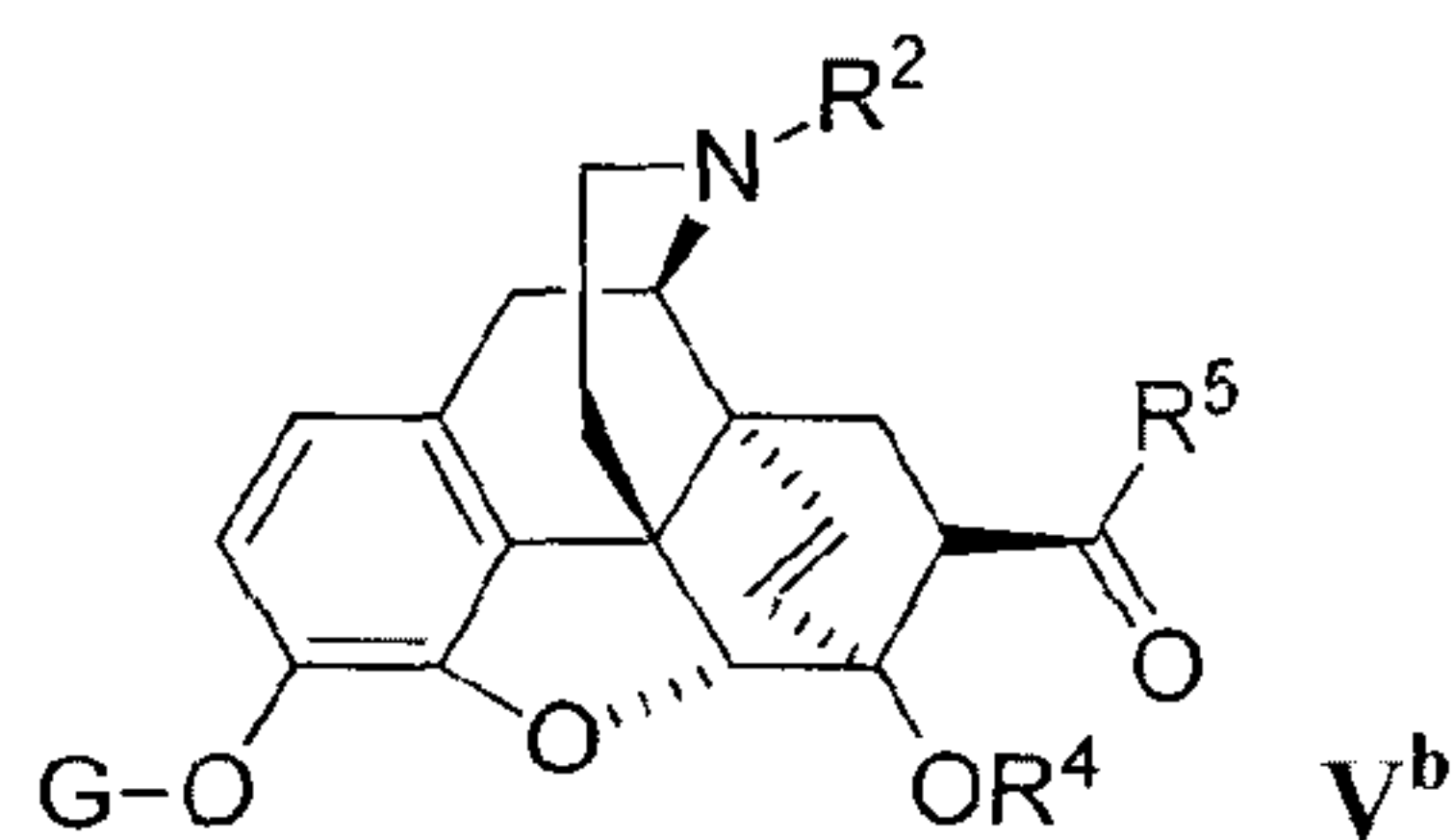
[0102] e) isolating the second precipitate to obtain the compound of Formula I^b as a salt, wherein = is a double bond, and a second mother liquor;

[0103] f) optionally converting the salt into its free base; and

[0104] g) optionally hydrogenating the double bond to obtain a compound of Formula I^b, wherein = is a single bond.

[0105] The second mother liquor and/or the first precipitate are optionally epimerized and processed according to step d) above.

[0106] The present invention also pertains to the preparation of 7 β -substituted compounds of Formula V^b:



and the salts thereof, wherein

[0107] G is R¹ or a hydroxyl protecting group PG;

[0108] R¹ is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

[0109] R² is

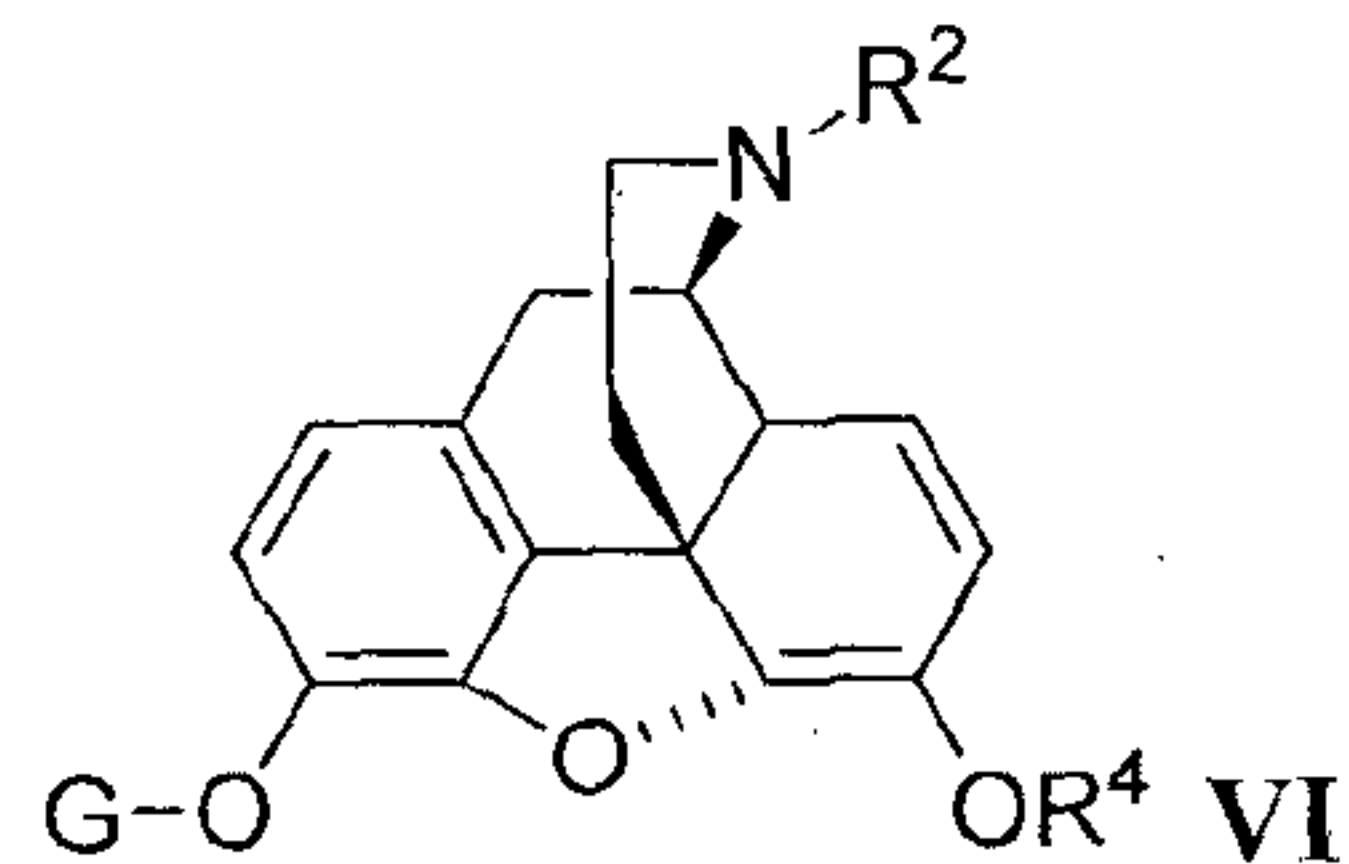
(a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or

(b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

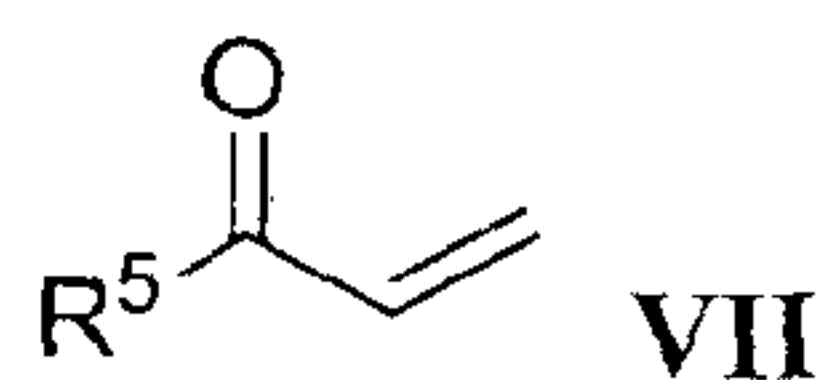
[0110] R⁴ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and

[0111] R^5 is C_{1-6} alkyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, hydroxy(C_{1-4})alkyl, halo, halo(C_{1-4})alkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxy carbonyl, comprising:

[0112] a) conducting a Diels-Alder reaction between a compound of Formula VI:



wherein G, R^2 , and R^4 are as defined above, and a compound of Formula VII:



wherein R^5 is as defined above, to form a $7\alpha/7\beta$ -epimer mixture of the compound of Formula V;

[0113] b) forming a first precipitate of the $7\alpha/7\beta$ -epimer mixture;

[0114] c) isolating the first precipitate from the reaction mixture to obtain a first mother liquor;

[0115] d) optionally reducing the volume of the first mother liquor, and contacting the first mother liquor with an acid to provide a second precipitate;

[0116] e) isolating the second precipitate to obtain the compound of Formula V^b as a salt, and a second mother liquor; and

[0117] f) optionally converting the salt into its free base.

[0118] In one embodiment, the proportion of the 7β -epimer in the first mother liquor obtained from the Diels-Alder reaction is at least about 10%, at least about 15%, at least about 20%, or at least about 25%.

[0119] The first precipitate typically forms upon cooling the Diels-Alder reaction mixture and contains the 7α -epimer as the major product. The first precipitate can be isolated by, e.g., filtration, such as vacuum filtration, or centrifugal separators. Typically, the first mother liquor is partially concentrated, e.g., by evaporation, after the isolation of the first precipitate of the $7\alpha/7\beta$ -epimer mixture. Then preferably, the first mother liquor is heated to dissolve any precipitate of the $7\alpha/7\beta$ -epimer mixture and to obtain a solution containing the $7\alpha/7\beta$ -epimer mixture. Optionally one or more additional solvents can be added to the first mother liquor. In another embodiment, the first mother liquor is

concentrated to dryness and the residue is redissolved in a solvent to obtain a solution. Useful solvents are those described above in connection with Formula I, and are typically selected from the group consisting of aliphatic alcohols, aromatic solvents, aliphatic ethers, and combinations thereof. Preferably, the solvent is iso-propanol (IPA). Typically, the partially concentrated first mother liquor including the optional additional solvent, or the solution obtained from the residue, are heated to a temperature of about 50 °C to about the boiling point of the solution. Preferably, the temperature is from about 55 °C to the reflux temperature of the solvent, and more preferably the temperature is from about 60 °C to the reflux temperature of the solvent. In another embodiment, the temperature is from about 55 °C to about 80 °C, and more preferably the temperature is from about 60 °C to about 80 °C. The term “solvent” herein, includes mixtures/combinations of one or more solvents.

[0120] The heated first mother liquor is then contacted with an acid to obtain a second precipitate. In another embodiment, the heated mother liquor is first cooled down, for example to room temperature, and then contacted with the acid to obtain the second precipitate. Suitable and preferable acids are those described above in connection with the processes for increasing the proportion of the 7 β -epimer and purifying the 7 β -epimer. In one embodiment, the acid is TFA. In another embodiment, the amount of the acid used is from about 0.5 to about 1.5 equivalents based on the amount of the 7 β -epimer. In another embodiment, the acid is used in an amount of from about 0.8 to about 1.3 equivalents, preferably from about 0.9 to about 1.2 equivalents, and more preferably about 1.0 or about 1.1 equivalents based on the amount of the 7 β -epimer.

[0121] The second precipitate can be isolated by, e.g., vacuum filtration or centrifugal separators. In one embodiment, the proportion of the 7 β -epimer in the second precipitate is at least about 60%, at least about 70%, at least about 80%, or at least about 90%.

[0122] The salts formed in the processes of the present invention can be converted to their free bases by methods known in the art and by the methods described in the examples.

[0123] The mother liquor obtained after isolating the second precipitate (the second mother liquor) is enriched with the 7 α -epimer, which can be epimerized, for example, by reacting with potassium carbonate (K₂CO₃) or diazabicycloundec-7-ene (DBU), and then repeating the process as described above to obtain a further second precipitate of the 7 β -epimer. The epimerization can be conducted, for example, as described by Marton, J., *et*

al., *Acta Chemica Scandinavia* 52:1234-1238 (1998), and Derrick, I., *et al.*, *Tetrahedron Letters* 41:7571-7576 (2000).

- [0124] The first precipitate is also enriched with the 7 α -epimer. This can be epimerized as described above by reacting with, for example, potassium carbonate (K₂CO₃) or diazabicycloundec-7-ene (DBU), and then repeating the process as described above to obtain a further second precipitate of the 7 β -epimer.
- [0125] Optional substituents attached to aryl, phenyl and heteroaryl rings each take the place of a hydrogen atom that would otherwise be present in any position on the aryl, phenyl or heteroaryl rings.
- [0126] Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.
- [0127] Useful alkyl groups are selected from straight-chain and branched-chain C₁₋₁₀ alkyl groups. Typical C₁₋₁₀ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, pentyl, 3-pentyl, hexyl, heptyl, octyl, nonyl and decyl, among others. In one embodiment, useful alkyl groups are selected from straight chain C₁₋₆ alkyl groups and branched chain C₃₋₆ alkyl groups. Typical C₁₋₆ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, pentyl, 3-pentyl, hexyl, among others. In one embodiment, useful alkyl groups are selected from straight chain C₂₋₆ alkyl groups and branched chain C₃₋₆ alkyl groups. Typical C₂₋₆ alkyl groups include ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, pentyl, 3-pentyl, hexyl among others. In one embodiment, useful alkyl groups are selected from straight chain C₁₋₄ alkyl groups and branched chain C₃₋₄ alkyl groups. Typical C₁₋₄ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl.
- [0128] Useful cycloalkyl groups are selected from saturated cyclic hydrocarbon groups containing one to three rings having from three to twelve carbon atoms (*i.e.*, C₃-C₁₂ cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl has one or two rings. In another embodiment, the cycloalkyl is a C₃-C₈ cycloalkyl. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl and the like.
- [0129] Useful cycloalkenyl groups are selected from partially unsaturated (containing one or two double bonds) cyclic hydrocarbon groups containing one to three rings having from four to twelve carbon atoms (*i.e.*, C₄-C₁₂ cycloalkenyl) or the number of carbons designated. In one embodiment, the cycloalkenyl has one or two rings. In another embodiment, the cycloalkenyl is a C₃-C₈ cycloalkyl. In one embodiment, the

cycloalkenyl group contains one double bond. Exemplary cycloalkenyl groups containing one double bond include cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl, among others. In another embodiment, the cycloalkenyl group contains two double bonds. Preferably, the cycloalkenyl groups containing two double bonds have from five to twelve carbon atoms (*i.e.*, C₅-C₁₂ cycloalkadienyl). Exemplary cycloalkenyl groups having two double bonds include cyclopentadienyl, cyclohexadienyl, cycloheptadienyl, cyclooctadienyl, cyclononadienyl, cyclodecadienyl, among others.

[0130] Useful alkenyl groups are selected from straight-chain and branched-chain C₂₋₆ alkenyl groups, preferably C₂₋₄ alkenyl. Typical C₂₋₆ alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl. Typical C₂₋₄ alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec*-butenyl.

[0131] Useful alkynyl groups are selected from straight-chain and branched-chain C₂₋₆ alkynyl groups, preferably C₂₋₄ alkynyl. Typical C₂₋₆ alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups. Typical C₂₋₄ alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

[0132] Useful haloalkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms (*e.g.*, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups).

[0133] Useful hydroxyalkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted by one or more hydroxy groups, such as monohydroxyalkyl and dihydroxyalkyl groups (*e.g.*, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxypentyl groups, and especially 2-hydroxy-3,3-dimethylbut-2-yl, 2-hydroxypent-2-yl, 2-hydroxyprop-2-yl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl).

[0134] Useful alkoxy groups include oxygen substituted by one of the C₁₋₁₀ alkyl groups mentioned above (*e.g.*, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, tert-butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy).

[0135] Useful alkoxyalkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted with any of the above-mentioned alkoxy groups (*e.g.*, methoxymethyl,

methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, 2-ethoxyethyl, 3-ethoxypropyl, 4-ethoxybutyl, propoxymethyl, iso-propoxymethyl, 2-propoxyethyl, 3-propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl).

[0136] Useful haloalkoxy groups include oxygen substituted by one of the C₁₋₁₀ haloalkyl groups mentioned above (e.g., fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy).

[0137] Useful (cycloalkyl)alkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted with any of the above-mentioned cycloalkyl groups (e.g., (cyclopropyl)methyl, 2-(cyclopropyl)ethyl, (cyclopropyl)propyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclohexyl)methyl, and the like).

[0138] Useful (cycloalkyl)alkenyl groups include any of the above-mentioned C₂₋₆ alkenyl groups substituted with any of the above-mentioned cycloalkyl groups.

[0139] Useful (cycloalkenyl)alkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted with any of the above-mentioned cycloalkenyl groups (e.g., (cyclobutenyl)methyl, 2-(cyclobutenyl)ethyl, (cyclobutenyl)propyl, (cyclopentenyl)methyl, (cyclohexenyl)methyl, (cyclopentadienyl)methyl, and the like).

[0140] Useful (cycloalkenyl)alkenyl groups include any of the above-mentioned C₂₋₆ alkenyl groups substituted with any of the above-mentioned cycloalkenyl groups.

[0141] Useful aryl groups are C₆₋₁₄ aryl, preferably C₆₋₁₂ aryl, and especially C₆₋₁₀ aryl. Typical C₆₋₁₄ aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups, more preferably phenyl, naphthyl, and biphenyl groups.

[0142] Useful aryloxy groups include oxygen substituted by one of the aryl groups mentioned above (e.g., phenoxy).

[0143] Useful arylalkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted by any of the above-mentioned aryl groups (e.g., benzyl, phenethyl, and the like).

[0144] Useful (arylalkyl)carbonyl groups include a carbonyl group substituted by any of the above-mentioned arylalkyl groups.

[0145] Useful aralkyloxy or arylalkoxy groups include oxygen substituted by one of the above-mentioned arylalkyl groups (e.g., benzyloxy).

- [0146] Useful (arylalkoxy)carbonyl groups include a carbonyl group substituted by any of the above-mentioned arylalkoxy groups (e.g., (benzyloxy)carbonyl).
- [0147] The term "heteroaryl" or "heteroaromatic" as employed herein refers to groups having 5 to 14 ring atoms, with 6, 10 or 14 π electrons shared in a cyclic array, and containing carbon atoms and 1, 2, or 3 oxygen, nitrogen or sulfur heteroatoms, or 4 nitrogen atoms. Examples of heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranal, isobenzofuranyl, benzooxazolyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolyl, quinazolinyl, pteridinyl, 4*aH*-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. Typical heteroaryl groups include thienyl (e.g., thien-2-yl and thien-3-yl), furyl (e.g., 2-furyl and 3-furyl), pyrrolyl (e.g., pyrrol-1-yl, 1*H*-pyrrol-2-yl and 1*H*-pyrrol-3-yl), imidazolyl (e.g., imidazol-1-yl, 1*H*-imidazol-2-yl and 1*H*-imidazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl and tetrazol-5-yl), pyrazolyl (e.g., 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, and 1*H*-pyrazol-5-yl), pyridyl (e.g., pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (e.g., pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, and pyrimidin-5-yl), thiazolyl (e.g., thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (e.g., isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (e.g., oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl).
- [0148] Useful heteroarylalkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted by any of the above-mentioned heteroaryl groups (e.g., (thien-2-yl)methyl, 2-furylmethyl, (pyrrol-1-yl)methyl, 2-(1*H*-pyrrol-2-yl)ethyl and the like).
- [0149] Useful heteroarylalkenyl groups include any of the above-mentioned C₂₋₆ alkenyl groups substituted by any of the above-mentioned heteroaryl groups.
- [0150] Useful heteroarylalkoxy groups include oxygen substituted by one of the above-mentioned heteroaryl groups.
- [0151] Useful (heteroarylalkoxy)carbonyl groups include a carbonyl group substituted by any of the above-mentioned heteroarylalkoxy groups.
- [0152] The terms "heterocyclic" and "heterocyclo" are used herein to mean saturated or partially unsaturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system,

which consist of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on a carbon atom or on a nitrogen atom if the resulting compound is stable. In one embodiment, the 3- to 7-membered monocyclic heterocyclic ring is either a saturated, or unsaturated non-aromatic ring. A 3-membered heterocycle can contain up to 1 heteroatom, a 4-membered heterocycle can contain up to 2 heteroatoms, a 5-membered heterocycle can contain up to 4 heteroatoms, a 6-membered heterocycle can contain up to 4 heteroatoms, and a 7-membered heterocycle can contain up to 5 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The 3- to 7-membered heterocycle can be attached via a nitrogen or carbon atom. A 7- to 10-membered bicyclic heterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The 7- to 10-membered bicyclic heterocycle can be attached via a nitrogen or carbon atom. Examples of the heterocyclic rings include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, imidazolyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, 2-oxooxazolidinyl, tetrahydrothienyl, imidazolidinyl, hexahydropyrimidinyl, benzodiazepines, and the like.

[0153] Useful (heterocyclo)alkyl groups include any of the above-mentioned C₁₋₁₀ alkyl groups substituted by any of the above-mentioned heterocyclic groups (e.g., (pyrrolidin-2-yl)methyl, (pyrrolidin-1-yl)methyl, (piperidin-1-yl)methyl, (morpholin-1-yl)methyl, (2-oxooxazolidin-4-yl)methyl, 2-(2-oxooxazolidin-4-yl)ethyl, (2-oxo-imidazolidin-1-yl)methyl, (2-oxo-imidazolidin-1-yl)ethyl, (2-oxo-imidazolidin-1-yl)propyl, and the like).

[0154] Useful (heterocyclo)alkenyl groups include any of the above-mentioned C₂₋₆ alkenyl groups substituted by any of the above-mentioned heterocyclic groups.

[0155] As used herein, the term "aminocarbonyl" refers to -C(=O)NH₂.

[0156] Useful alkylcarbonyl groups include a carbonyl group, i.e., -C(=O)-, substituted by any of the above-mentioned C₁₋₁₀ alkyl groups.

[0157] Useful alkoxy carbonyl groups include a carbonyl group substituted by any of the above-mentioned alkoxy groups (i.e., -C(=O)O-alkyl) (e.g., methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, iso-butoxycarbonyl, sec-butoxycarbonyl, and pentyloxycarbonyl).

[0158] Useful arylcarbonyl groups include a carbonyl group substituted by any of the above-mentioned aryl groups (e.g., benzoyl).

[0159] Useful alkylcarbonyloxy or acyloxy groups include oxygen substituted by one of the above-mentioned alkylcarbonyl groups.

[0160] Useful alkylcarbonylamino or acylamino groups include any of the above-mentioned alkylcarbonyl groups attached to an amino nitrogen, such as methylcarbonylamino.

[0161] As used herein, the term "carboxamido" refers to a radical of formula $-C(=O)NR^{11}R^{12}$, wherein R^{11} and R^{12} are each independently hydrogen, optionally substituted C_{1-10} alkyl, or optionally substituted aryl. Exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $-CON(CH_3)_2$, and $-CON(H)Ph$ and the like

[0162] Useful alkylaminocarbonyl and dialkylaminocarbonyl groups are any of the above-mentioned carboxamido groups, where R^{11} is H and R^{12} is C_{1-10} alkyl or where R^{13} and R^{14} are each independently selected from a C_{1-10} alkyl group, respectively.

[0163] As used herein, the term "sulfonamido" refers to a radical of formula $-SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are each independently hydrogen, optionally substituted C_{1-10} alkyl, or optionally substituted aryl. Exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, $-SO_2N(H)Ph$ and the like.

[0164] Useful mercaptoalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by a $-SH$ group.

[0165] As used herein, the term "carboxy" refers to $-COOH$.

[0166] Useful carboxyalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by $-COOH$.

[0167] As used herein, the terms "hydroxyl" or "hydroxy" refer to $-OH$.

[0168] As used herein, the term "cyano" refers to $-CN$.

[0169] As used herein, the term "formyl" refers to $-C(=O)H$.

[0170] As used herein, the term "ureido" refers to $-NH-C(=O)-NH_2$.

[0171] As used herein, the term "azido" refers to $-N_3$.

[0172] The term "mother liquor" as used herein means the part of a solution that is left over after crystallization.

- [0173] The term "ambient temperature" as used herein means the temperature of the surroundings. The ambient temperature indoors is the same as room temperature, which is from about 20 °C to about 25 °C.
- [0174] The term "about," as used herein in connection with a measured quantity, refers to the normal variations in that measured quantity, as expected by the skilled artisan making the measurement and exercising a level of care commensurate with the objective of measurement and the precision of the measuring equipment.
- [0175] As used herein, the term "optionally substituted" refers to a group that may be unsubstituted or substituted.
- [0176] Optional substituents on optionally substituted groups, when not otherwise indicated, include one or more groups, typically 1, 2, or 3 groups, independently selected from the group consisting of halo, halo(C₁₋₆)alkyl, aryl, heterocycle, cycloalkyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, cycloalkyl(C₁₋₆)alkyl, heterocyclo(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, carboxy(C₁₋₆)alkyl, alkoxy(C₁₋₆)alkyl, nitro, ureido, cyano, alkylcarbonylamino, hydroxy, thiol, alkylcarbonyloxy, aryloxy, ar(C₁₋₆)alkyloxy, carboxamido, sulfonamido, azido, C₁₋₆ alkoxy, halo(C₁₋₆)alkoxy, carboxy, aminocarbonyl, (=O), and mercapto(C₁₋₆)alkyl groups mentioned above. Preferred optional substituents include halo, halo(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, hydroxy, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, and halo(C₁₋₆)alkoxy.
- [0177] Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, such as epimers. The present invention is meant to encompass the uses of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers may be separated according to methods known to those of ordinary skill in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.
- [0178] As used herein, the term "under conditions conducive to precipitation" refers to conditions which are suitable to induce or facilitate precipitation of the desired compound.
- [0179] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes

enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0180] The term "chiral center" or "chiral" refers to a carbon atom to which four different groups are attached.

[0181] The term "chiral" in the context of the present invention also refers to a compound of group, exhibiting a "chiral center", such as a chiral acid. Exemplary chiral acids are lactic acid, tartaric acid, and the like.

[0182] The term "achiral" in the context of the present invention refers to a compound of group, wherein no "chiral center" is present. An example for achiral compounds are achiral acids, such as acetic acid, trifluoroacetic acid, tribromoacetic acid, trichloroacetic acid, fumaric acid, maleic acid, and the like.

[0183] The term "epimer" refers to diastereomers that have opposite configuration at only one of two or more tetrahedral stereogenic centres present in the respective molecular entities.

[0184] The term "stereogenic center" is an atom, bearing groups such that an interchanging of any two groups leads to a stereoisomer.

[0185] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

[0186] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

[0187] The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

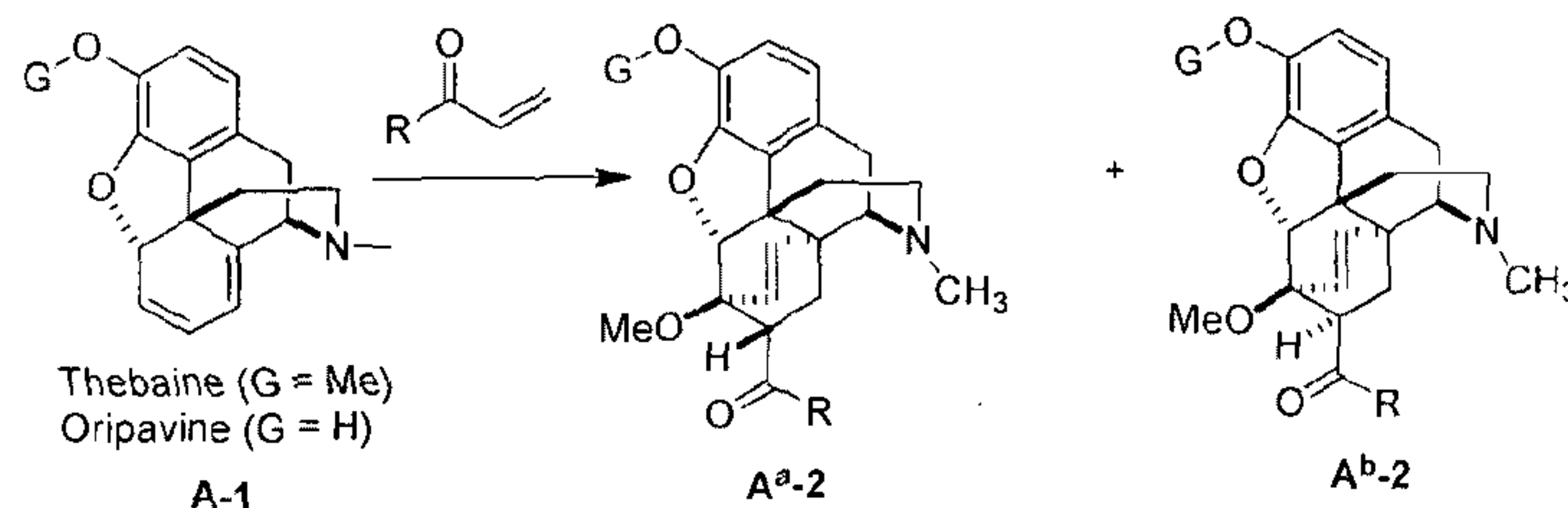
[0188] The terms "a" and "an" refer to one or more.

[0189] Open terms such as "include," "including," "contain," "containing" and the like mean "comprising."

Synthesis of Compounds

[0190] Compounds of Formula I can be prepared as shown in the schemes below. The synthesis of the compounds usually starts with a Diels-Alder reaction of thebaine or oripavine with dienophile, for example, a vinyl ketone under formation of the $7\alpha/7\beta$ -epimer mixture A-2 (7α -epimer A^a-2 and 7β -epimer A^b-2) (Scheme 2).

Scheme 2

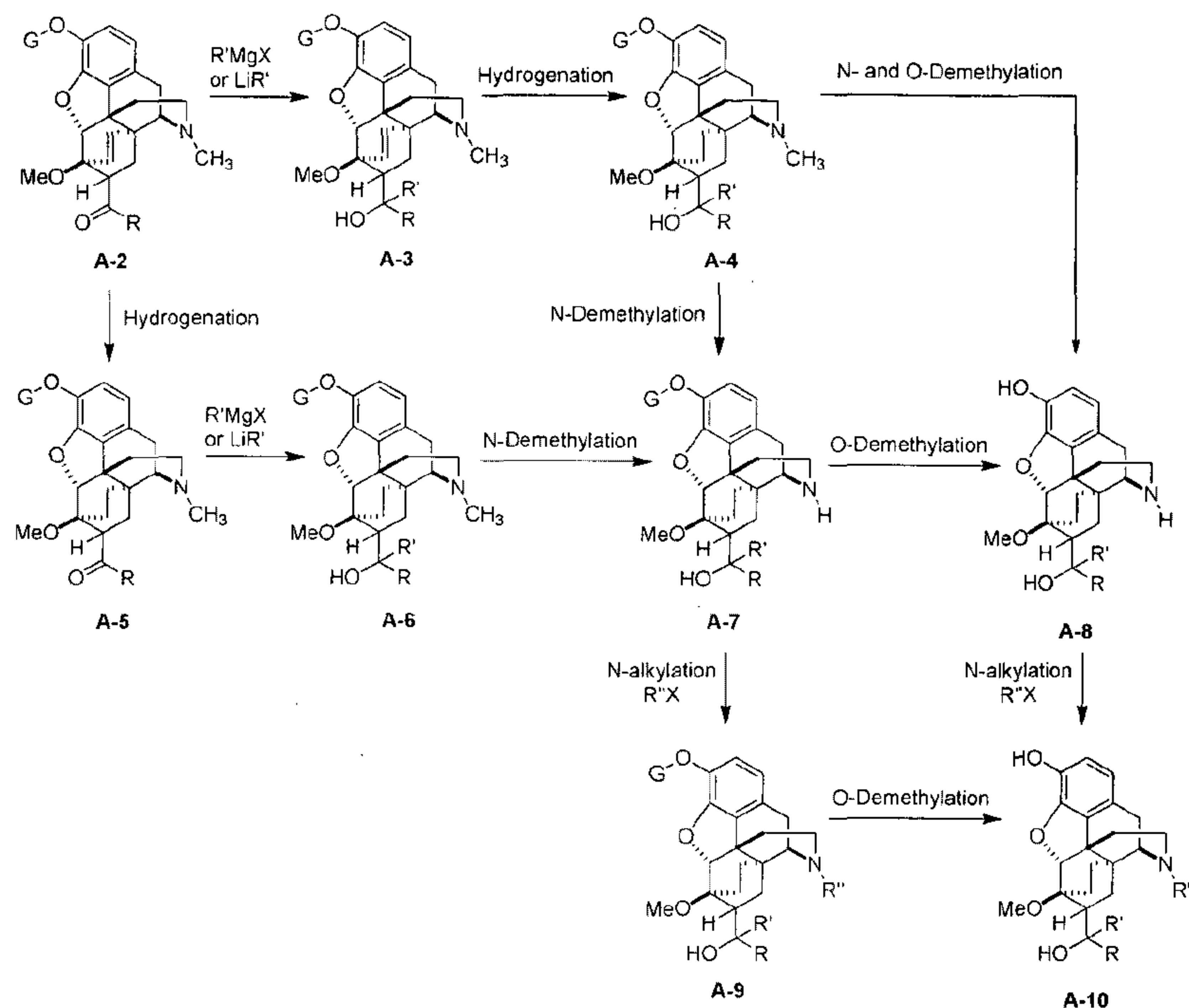
Synthesis of 7 α /7 β -epimer mixture of compounds of Formula I

In Scheme 2, G is R¹ or a hydroxyl protecting group as defined above for Formula I and R is alkyl, optionally substituted with 1, 2, or 3, substituents each independently selected from the group consisting of hydroxy, hydroxyalkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl, respectively, or a functional group that can be converted to these groups.

[0191] The 7 α /7 β -epimer mixture of compounds of Formula I, i.e., the mixture of epimers A^a-2 and A^b-2, can be synthesized by methods described in the art, for example, in Marton J., *et al.*, *Synthetic Communications* 25(6):829-848 (1995) and Bentley, K. W., *Journal of American Chemical Society* 89(13):3267-3273 (1967). Usually, the alpha (α) epimer A^a-2 is formed as the major component. The the 7 α /7 β -epimer mixture of the ketone A-2 can then be converted further through a series of transformations, which may include hydrogenation, N- and/or O-demethylation, Grignard or lithium alkyl addition as shown in Scheme 3 below as described, for example, in Bentley, K.W., *et al.*, *Journal of American Chemical Society* 89(13):3273-3280 (1967); Bentley, K. W., and Hardy, D. G., *Journal of American Chemical Society* 89(13):3281-3292 (1967); Marton, J., *et al.*, *Monatshefte für Chemie* 125:1229-1239 (1994).

Scheme 3

General scheme for the synthesis of 7 α /7 β -epimer mixtures of compounds of Formula I



In Scheme 3, G is R¹ or a hydroxyl protecting group PG as defined above for Formula I, R and R' are each independently alkyl, optionally substituted with 1, 2, or 3, substituents each independently selected from the group consisting of hydroxy, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl, respectively, or are functional groups that can be converted to these groups. R'' is as defined above for R² or a group that can be converted to R². X is halogen or tosylate.

[0192] The following examples are illustrative, but not limiting, of the compounds, compositions and methods of the present invention. Suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art in view of this disclosure are within the spirit and scope of the invention.

EXAMPLES

[0193] The following HPLC methods 1 and 2 were used:

HPLC METHOD 1

Column: Phenomenex Synergy Polar-RP, 50 × 3.0 mm, 2.5 μm
 Detection: UV 240 nm
 Injection Volume: 2.0 μL
 Flow Rate: 0.8 mL/min
 Column Temperature: Ambient
 Run Time: 15 min
 Mobile Phase A: 0.025% TFA in water
 Mobile Phase B: 0.025% TFA in acetonitrile
 Gradient Profile:

	Time	Flow	%A	%B
1	0.00	0.8	90	10
2	5.00	0.8	89	11
3	12.00	0.8	45	55
4	12.01	0.8	90	10
5	15.00	0.8	90	10

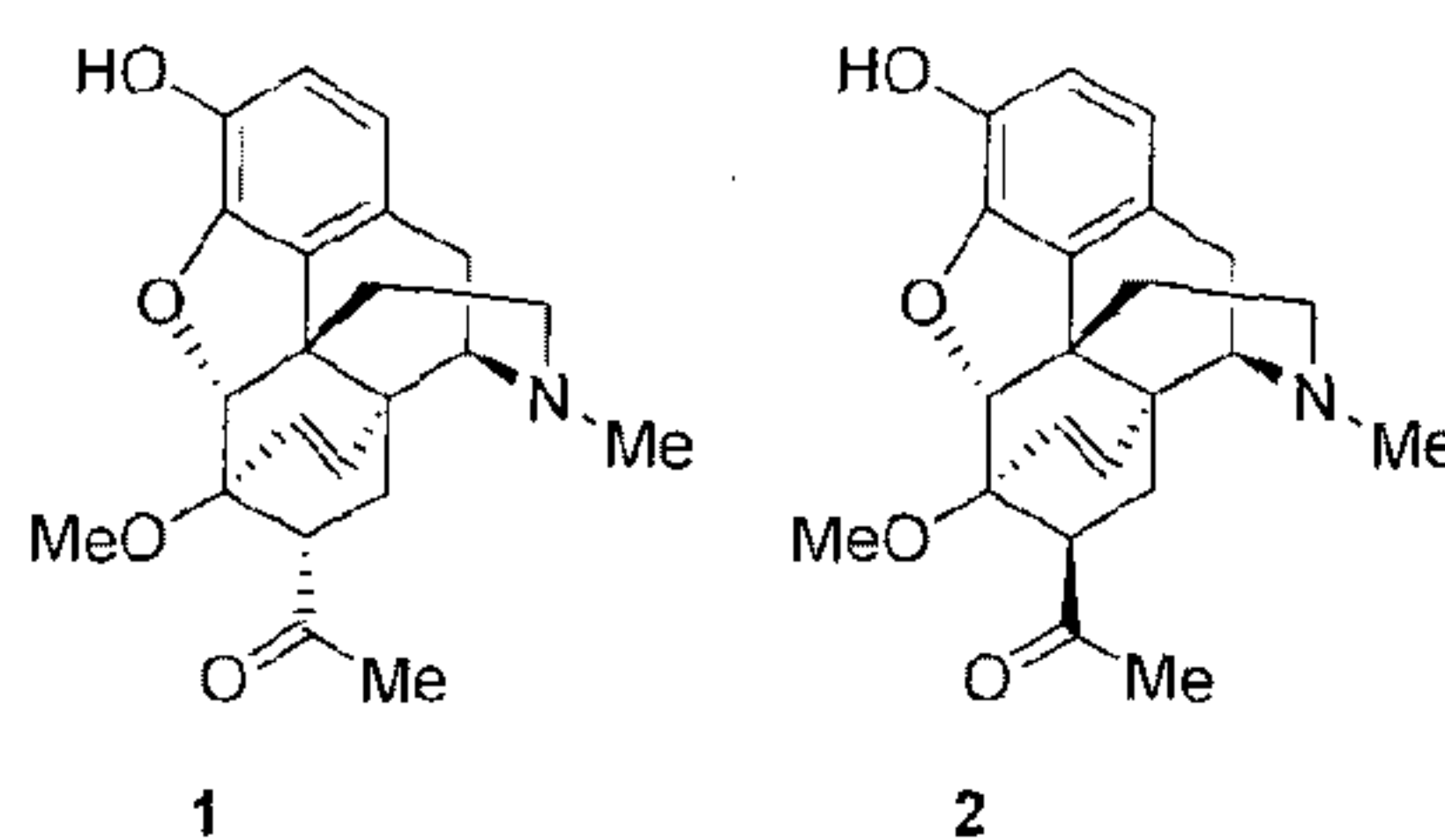
HPLC METHOD 2

Column: Phenomenex Synergy Polar-RP, 50 × 3.0 mm, 2.5 μm
 Detection: UV 240 nm
 Injection Volume: 5.0 μL
 Flow Rate: 1.5 mL/min
 Column Temperature: Ambient
 Run Time: 25 min
 Mobile Phase A: 0.025% TFA in water
 Mobile Phase B: 0.025% TFA in acetonitrile
 Gradient Profile:

	Time	Flow	%A	%B	%C	%D	Curve
1	0.00	1.50	95.0	5.0	0.0	0.0	6
2	20	1.50	35.0	65.0	0.0	0.0	6
3	21	1.50	95.0	5.0	0.0	0.0	6
4	25	1.50	95.0	5.0	0.0	0.0	6

EXAMPLE 1

Separation of a mixture containing 1-[(5 α ,7 α)-4,5-epoxy-3-hydroxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-yl]ethanone (1) and 1-[(5 α ,7 β)-4,5-epoxy-3-hydroxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-yl]ethanone (2)



[0194] *General procedure:* Compounds 1 and 2 were mixed in the corresponding solvent in a 1:1 ratio and 0.6 or 1.2 equivalents (based on total 6 α ,14 α -ethenomorphinan content) of the corresponding acid was added. In case of a precipitation, the precipitate was isolated and analyzed by HPLC analysis (HPLC method 1). From the HPLC analysis of the precipitate and the mother liquor, the amount of compound 1 and compound 2 in each fraction was calculated and the recovery of compound 2 in the isolated precipitate was determined.

[0195] To a vial was added compound 1 (0.1 g), compound 2 (0.1 g), and solvent (6 mL). The mixture was heated at 60 °C until most or all solid dissolved. To the vial was added 1.1 or 0.6 equivalents (based on the total amine content) of the acid. The mixture was allowed to cool to ambient temperature and was stirred overnight. The precipitated product was filtered, and both the solid as well as the mother liquor were analyzed by HPLC, and the yield and recovery were calculated. Tables 1 and 2 show the results of the tested solvent and acid combinations in the presence of 0.6 eq. acid and 1.1 eq. acid, respectively.

TABLE 1

Purity and recovery of isolated salts of compound 2 with 0.6 eq. acid

	Solvent	Acid	Precipitate				Mother liquor	
			Ratio ¹ α:β (%)	Yield ² (mg)	Recovery ² (%)	Purify (%)	Ratio ¹ α : β (%)	Yield ² (mg)
1	MeOH	AcOH	1.7:98.3	57	56.3	98.3	69.2:30.6	143
2	EtOH	TFA	24.4:75.6	118	89.2	75.6	86.5:13.2	82
3	n-PrOH	TFA	29.8:70.2	135	95.2	70.2	92.0:7.4	65
4	IPA	TFA	34.1:65.8	147	97.3	65.8	94.3:5.1	53
5	EtOH	Maleic	25.6:74.4	118	87.6	74.4	85.0:15.0	82
6	n-PrOH	Maleic	33.0:67.0	142	95.2	67.0	90.7:8.2	58
7	toluene	Maleic	35.2:64.8	148	95.7	64.8	91.2:8.2	52
8	EtOH	Fumaric	No precip.	NA	NA	NA	50:50	NA
9	n-PrOH	Fumaric	No precip.	NA	NA	NA	50:50	NA
10	toluene	Fumaric	8.0:92.0	35	32.4	91.9	57.9:41	165

¹ by HPLC analysis (HPLC method 1);² based on free base; calculated from the epimer ratios in the precipitate and the mother liquor

TABLE 2

Purity and recovery of isolated salts of compound 2 with 1.1 eq. acid

	Solvent	Acid	Precipitate				Mother liquor	
			Ratio ¹ α:β (%)	Yield ² (mg)	Recovery ² (%)	Purify (%)	Ratio ¹ α : β (%)	Yield ² (mg)
1	MeOH	AcOH	1.3:98.7	45	44.4	98.7	64.3:35.7	155
2	EtOH	TFA	46.2:53.8	177	95.2	53.8	78.7:21.2	23
3	n-PrOH	TFA	4.1:96.9	97	94.0	96.9	94.6:5.4	103
4	IPA	TFA	4.8:95.2	100	95.2	95.2	96.0:4.0	100
5	EtOH	Maleic	4.3:95.7	93	89.0	95.7	89.7:10.3	107
6	n-PrOH	Maleic	8.7:91.3	100	91.3	91.3	91.3:8.7	100
7	toluene	Maleic	None		NA	NA		
8	n-PrOH	Fumaric	49.8:50.2	187	93.9	50.2	52.9:47.1	13
9	toluene	Fumaric	49.5:50.5	186	93.9	50.5	55.3:43.3	14
10	CPME	Fumaric	49.5:50.5	197	99.5	50.5	83.0:16.5	3

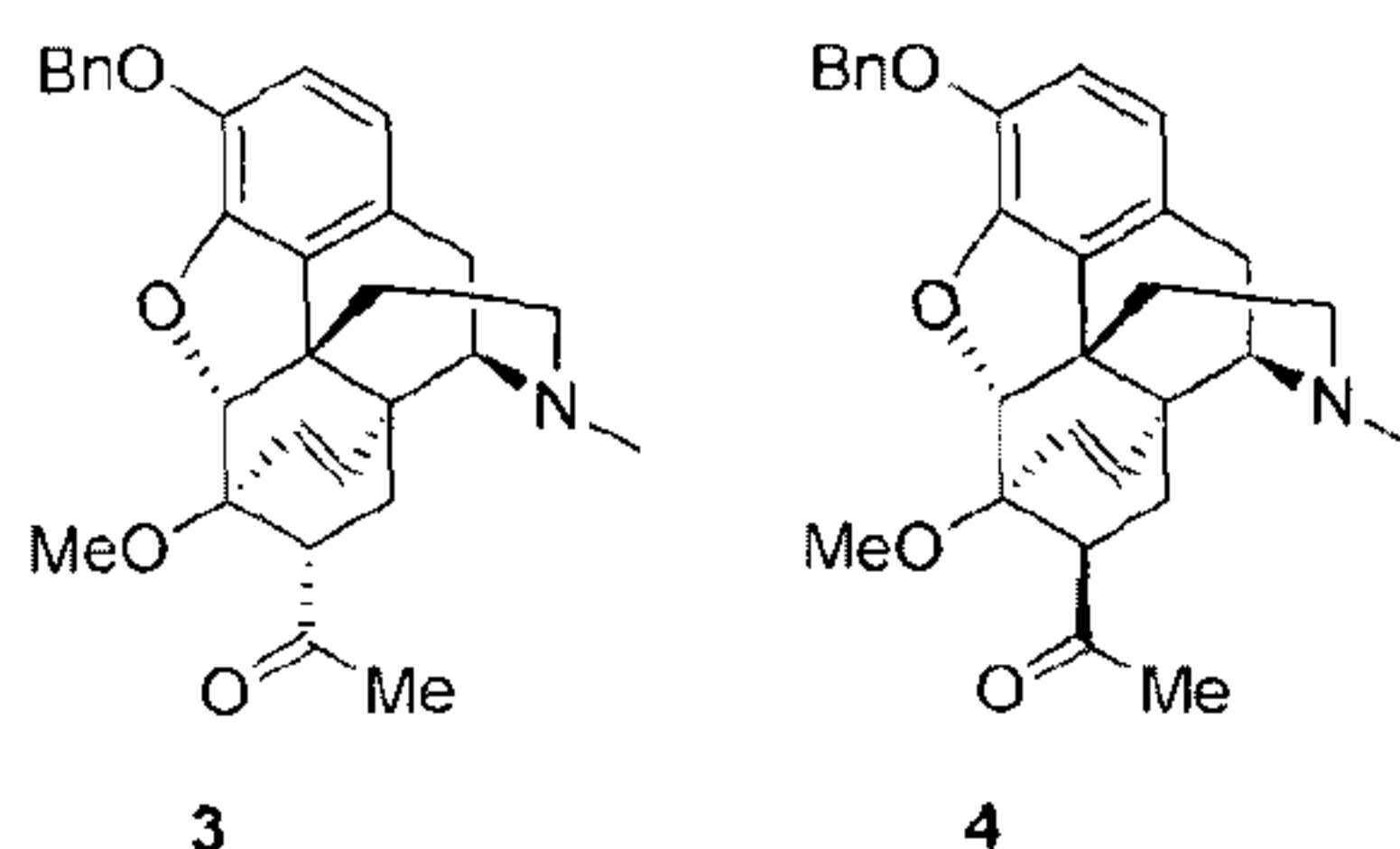
¹ by HPLC analysis (HPLC method 1);² based on free base; calculated from epimer ratios in the precipitate and the mother liquor

[0196] The results of Table 2 show that when 1.1 equivalents of acid (especially trifluoro acetic acid (TFA) or maleic acid) is used in n-propanol, isopropanol (IPA), or ethanol, high recovery and high purity of the 7β-epimer are achieved. A moderate recovery, but high purity, is achieved in the mixture of methanol and 1.1 equivalents of acetic acid.

[0197] The results of Table 1 show that 0.6 equivalents of TFA or maleic acid in alcohol provides similar recoveries than those in Table 2, but a somewhat lower purity of the 7 β -epimer. Using 0.6 equivalents of acid, a moderate recovery, but high purity, was achieved in methanol and acetic acid as well as toluene and fumaric acid.

EXAMPLE 2

Separation of a mixture containing 1-[(5 α ,7 α)-3-benzyloxy-4,5-epoxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-yl]ethanone (3) and 1-[(5 α ,7 β)-3-benzyloxy-4,5-epoxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-yl]ethanone (4)



[0198] The separation of compounds 3 and 4 was conducted using the procedure as described in Example 1. The results are described in Table 3 (0.6 eq acid) and Table 4 (1.1 eq. acid).

TABLE 3

Purity and recovery of isolated salts of compound 4 with 0.6 eq. acid

	Solvent	Acid	Precipitate				Mother liquor	
			Ratio ¹ α : β (%)	Yield ² (mg)	Recovery ² (%)	Purify (%)	Ratio ¹ α : β (%)	Yield ³ (mg)
1	MeOH	AcOH	0.7:99.3	56	55.6	99.3	68.3:30.7	144
2	EtOH	AcOH	1.4:98.6	77	75.9	98.6	79.8:19.2	123
3	n-PrOH	AcOH	1.4:98.6	72	70.1	98.6	76.4:22.6	128
4	IPA	AcOH	3.4:96.6	87	84.4	96.6	85.5:14.5	113
5	Toluene	Maleic	No precip.	NA	NA	NA	50:50	NA
6	CPME	Maleic	No precip.	NA	NA	NA	50:50	NA
7	EtOH	Fumaric	1.6:98.4	36	35.4	98.4	59.9:39.1	164
8	n-PrOH	Fumaric	1.3:98.7	28	27.6	98.7	57.6:42.4	172
9	IPA	Fumaric	5.3:94.7	74	70.1	94.7	75.56:24.4	126

¹ by HPLC analysis (HPLC method 1);

² based on free base; calculated from epimer ratios in precipitate and mother liquor

TABLE 4

Purity and recovery of isolated salts of compound **4** with 1.1 eq. acid

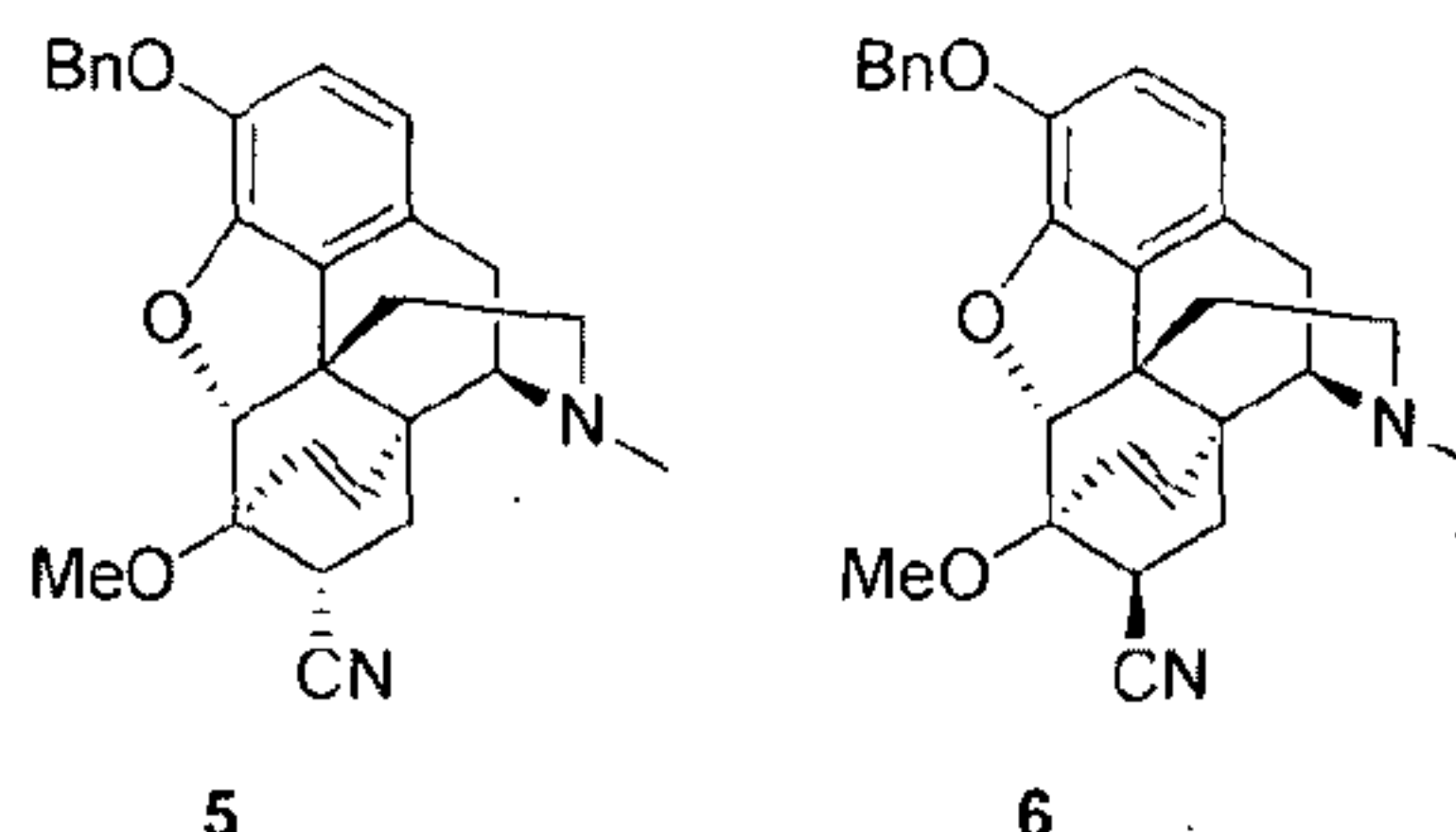
	Solvent	Acid	Precipitate				Mother liquor	
			Ratio ¹ α : β (%)	Yield ² (mg)	Recovery ² (%)	Purify (%)	Ratio ¹ α : β (%)	Yield ³ (mg)
1	MeOH	AcOH	1.4:98.6	45	44.4	98.6	63.5:36.5	155
2	EtOH	AcOH	0.4:99.6	67	66.7	99.6	74.3:24.7	133
3	n-PrOH	AcOH	0.6:99.4	63	62.6	99.4	71.7:27.3	137
4	IPA	AcOH	1.7:98.3	83	81.4	98.1	83.5:15.5	117
5	Toluene	Maleic	No precip.	NA	NA	NA	50:50	NA
6	CPME	Maleic	No precip.	NA	NA	NA	50:50	NA
7	EtOH	Fumaric	No precip.	NA	NA	NA	50:50	NA
8	n-PrOH	Fumaric	No precip.	NA	NA	NA	50:50	NA
9	IPA	Fumaric	15.2:84.8	85	72.0	84.8	74.6:24.4	115

¹ by HPLC analysis (HPLC method 1);² based on free base; calculated from epimer ratios in the precipitate and the mother liquor;

[0199] Tables 3 and 4 show that high recovery and high purity of the 7 β -epimer was achieved with 0.6 and 1.1 equivalents of acetic acid in alcohols. Recovery seemed to increase with decreasing polarity. High purity and a somewhat lower recovery of the 7 β -epimer was achieved with 0.6 equivalents of fumaric acid. Fumaric acid and IPA afforded a somewhat lower purity in 1.1 eq. of acid.

EXAMPLE 3

Separation of a mixture containing (5 α ,7 α)-4,5-epoxy-3-hydroxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-carbonitrile (**5**) and (5 α ,7 β)-4,5-epoxy-3-hydroxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-carbonitrile (**6**)



[0200] The separation of compounds **5** and **6** was conducted as described in Example 1 using HPLC method 2 instead of HPLC method 1. The results are described in Table 5 (0.6 eq acid) and Table 6 (1.1 eq. acid) below.

TABLE 5

Purity and recovery of isolated salts of compounds **5** and **6** with 0.6 eq. acid

	Solvent	Acid	Precipitate				Mother liquor	
			Ratio ¹ α : β (%)	Yield ² (mg)	Recovery ² (%)	Purify (%)	Ratio ¹ α : β (%)	Yield ³ (mg)
1	EtOH	AcOH	No precip.	NA	0	NA	50:50	
2	n-PrOH	AcOH	3.9:96.1	59	56.7	96.1	69.2:30.8	141
3	IPA	AcOH	4.9:95.1	61	58.0	95.1	69.3:30.4	139
4	EtOH	Maleic	93.8:6.2 ³	103	96.6	93.8	3.7:96.3	97
5	MeOH	Fumaric	51.4:48.6	136	69.9	51.4	47.0:53.0	63
6	EtOH	Fumaric	51.4:48.6	139	71.4	51.4	46.8:53.2	61
7	n-PrOH	Fumaric	51.7:48.3	74	38.2	51.7	49.0:51.0	126

¹ by HPLC analysis (HPLC method 2);² based on free base; calculated from epimer ratios in precipitate and mother liquor;³ 7 α -epimer is isolated

TABLE 6

Purity and recovery of isolated salts of compound **6** with 1.1 eq. acid

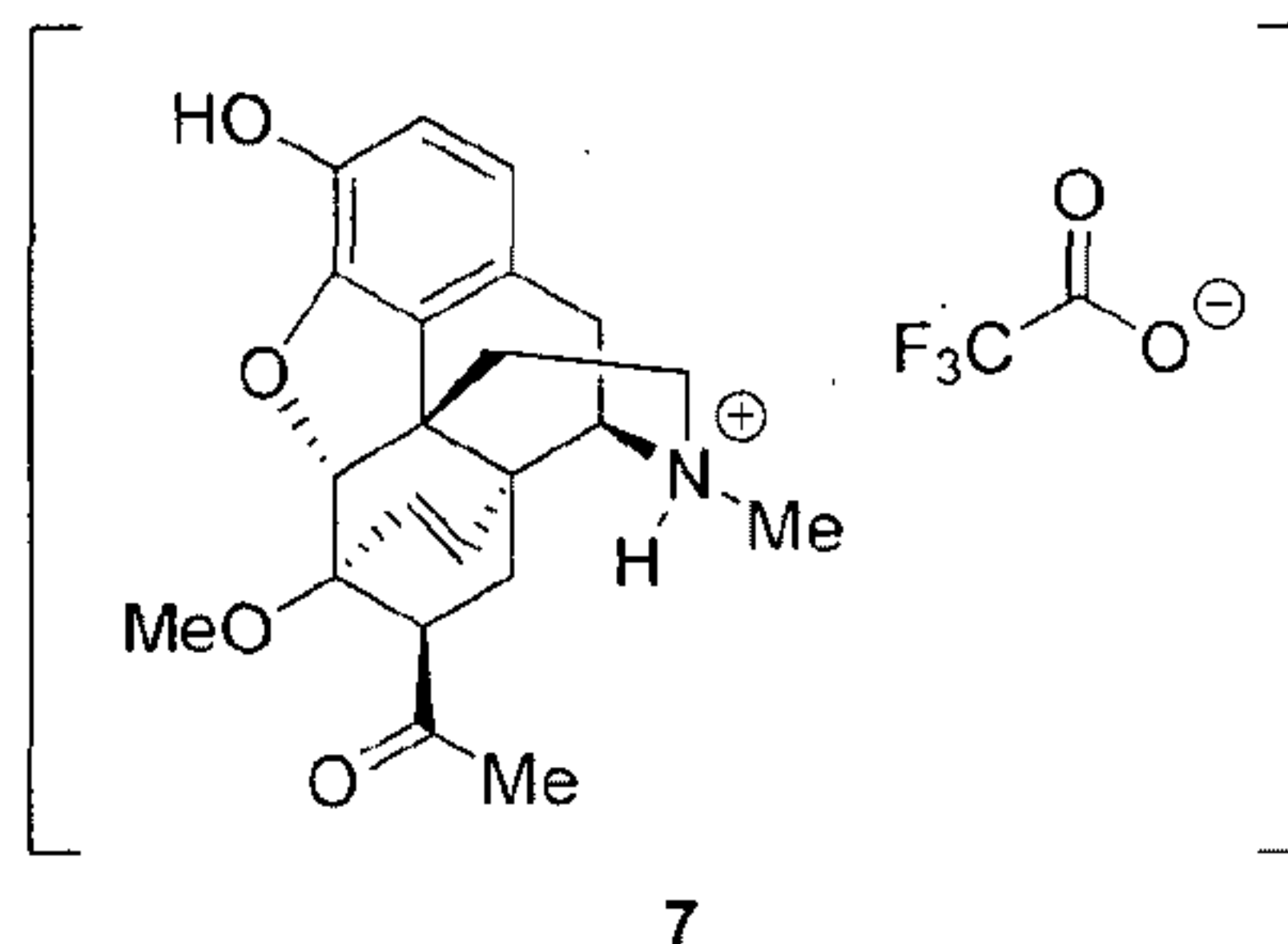
	Solvent	Acid	Precipitate				Mother liquor	
			Ratio ¹ α : β (%)	Yield ² (mg)	Recovery ² (%)	Purify (%)	Ratio ¹ α : β (%)	Yield ³ (mg)
1	EtOH	AcOH	No precip.	0	0	NA	50:50	200
2	n-PrOH	AcOH	3.8:96.2 ³	63	60	96.2	71.2:28.8	137
3	IPA	AcOH	4.5:95.5 ³	55	53	95.5	67.4:32.6	145
4	EtOH	Maleic	54.4:45.6	170	92	54.4	24.8:75.2	30
5	MeOH	Fumaric	52.5:47.5	91	48	52.5	47.9:52.1	109
6	EtOH	Fumaric	52.3:47.7	179	93	52.3	50.3:49.7	21
7	n-PrOH	Fumaric	53.1:46.9	29	15	53.1	46.7: 53.3	171

¹ by HPLC analysis (HPLC method 2);² based on free base; calculated from epimer ratios in precipitate and mother liquor;³ 7 β -epimer is isolated

[0201] High recovery and high purity of the 7 α -epimer was achieved with 0.6 eq. of maleic acid in ethanol, and the proportion of the 7 β -increased in the mother liquor. n-PrOH and IPA with acetic acid gave high purity and moderate recovery of the 7 β -epimer. No significant difference between 0.6 and 1.1 eq of acid was detected.

EXAMPLE 4**Isolation of compound 2 from a mixture of compound 2/compound 1 in a 26:74 ratio**

[0202] 21 g of a mixture containing compound 2 and compound 1 in a 26:74 ratio was suspended in IPA (350 mL) and heated to 70 °C. After all solids were dissolved, the mixture was cooled to room temperature and trifluoroacetic acid (TFA) (1.7 g, 1.0 eq based on compound 2) was added dropwise. The mixture was stirred at ambient temperature overnight. The precipitate was filtered, washed with IPA (3 × 10 mL) and dried to give an off-white solid containing compound 2 and compound 1 in a 96.3:3.7 ratio. The crude product was suspended in IPA (10 mL) and heated at 80 °C and stirred for 1 h. After cooling to room temperature, the product was filtered and dried to give 3.5 g (49% recovery, 97.6% purity) of compound 7:



[0203] Compound 7 can be converted to its free base, compound 2, following the procedure described in Example 8 below.

EXAMPLE 5**Isolation of compound 2 from a mixture of compound 2/compound 1 in a 45:55 ratio**

[0204] 70 g of a mixture containing compound 2 and compound 1 in a 45:55 ratio was dissolved in hot IPA (1.2 L). After the solution was cooled to room temperature, TFA (6.4 mL, 1.0 eq. based on compound 2) was added dropwise. The mixture was kept at room temperature overnight and the precipitate was filtered and dried to afford 38.0 g of compound 2 TFA-salt with 88% purity. The crude product was then suspended in IPA (300 mL) and heated to reflux and stirred for 1h. After cooling to room temperature, the product was filtered and dried to give 32.0 g (77% recovery, 97.8% purity) of compound 7.

EXAMPLE 6

Isolation of compound 2 from a mixture of compound 2/compound 1 in a 46:54 ratio

[0205] 14.2 g of a mixture containing compound 2 and compound 1 in a 46:54 ratio was dissolved in hot IPA (140 mL). To the hot solution, TFA (1.3 mL, 1.0 eq. based on compound 2) was added dropwise. The mixture was cooled to room temperature and stirred overnight. The precipitate was filtered. The filter cake was washed with cold IPA (2×10 mL) and the product was dried to afford 8.0 g (93% recovery, 93.6% purity) of compound 7, which can be converted to compound 2 as described in Example 8.

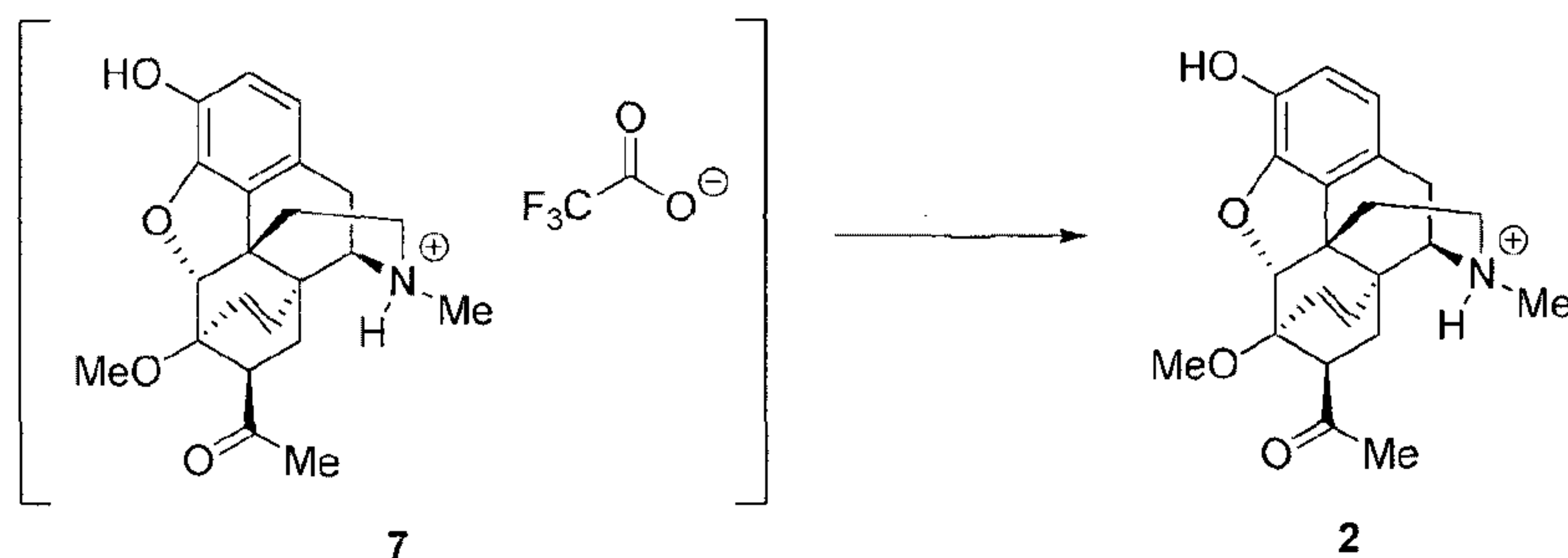
EXAMPLE 7

Isolation of compound 2 from a mixture of compound 2/compound 1 in a 60:40 ratio

[0206] 95 g of a mother liquor obtained after Diels-Alder reaction of oripavine and methyl vinyl ketone (MVK), containing in a 92% purity a mixture of compound 2 and compound 1 in a 60:40 ratio, was heated under reflux in IPA (500 mL). The mixture was cooled to ambient temperature and allowed to stir overnight. After filtering off an additional 6 g of compound 1, TFA (9.9 mL, 0.9 eq. based on compound 2) was added dropwise. The mixture was kept at room temperature overnight and the precipitate was filtered off. The crude product was then suspended in IPA (800 mL) and heated to 75 °C and stirred for 2 h. After cooling to room temperature, the product was filtered and dried to give 52.0 g (77% recovery, 97.3% purity) of compound 7, which can be converted to compound 2 as described in Example 8.

EXAMPLE 8

Conversion of compound 7 (TFA-salt of compound 2) to compound 2



[0207] **Method A:** To a mixture of 52 g of compound 7, in ethyl acetate (1000 mL) and water (300 mL) was added 28% NH₄OH and the pH of the mixture was adjusted to pH 9. The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to dryness. The crude product was triturated in methanol (MeOH) (400 mL) and stirred for 30 minutes under reflux. After cooling to ambient temperature, the product was filtered off and dried to afford 38.6 g (97% recovery, 100% purity) of compound 2:

[0208] ¹H NMR δ (400 MHz, CDCl₃): 6.59 (d, *J* = 8 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.02 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 4.88 (d, *J* = 10 Hz, 1H), 5.02 (d, *J* = 1.6 Hz, 1H), 3.59 (s, 3H), 3.22 (d, *J* = 18 Hz, 1H), 3.16 (d, *J* = 6.4 Hz, 1H), 3.02 (dd, *J* = 11.2 Hz, 4.8 Hz, 1H), 2.88 (dd, *J* = 12.8 Hz, 4.4 Hz, 1H), 2.76 (dt, *J* = 12.8 Hz, 5.6 Hz, 1H), 2.55 (dd, *J* = 11.6 Hz, 5.2 Hz, 1H), 2.44–2.38 (m, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 1.66–1.61 (m, 1H), 1.42 (dd, *J* = 12.8 Hz, 11.2 Hz, 1H). LC/MS (ESI): *m/z* = 368.1 [M + H]⁺ (Calc: 367.4).

[0209] **Alternative Method B:** Compound 7 (17.0 g) was suspended in H₂O (350 mL) and the pH of the mixture was adjusted to 9 by dropwise addition of NH₄OH. The mixture was then stirred at room temperature for 1 h. The solids were filtered off and the filter cake was washed with H₂O (2 × 100 mL) and then dried to afford 12.5 g (96.3%) of compound 2 was obtained as an off-white solid.

EXAMPLE 9

Isolation of compound 2 from a mixture of compound 2/compound 1 in a 68:32 ratio and salt breaking

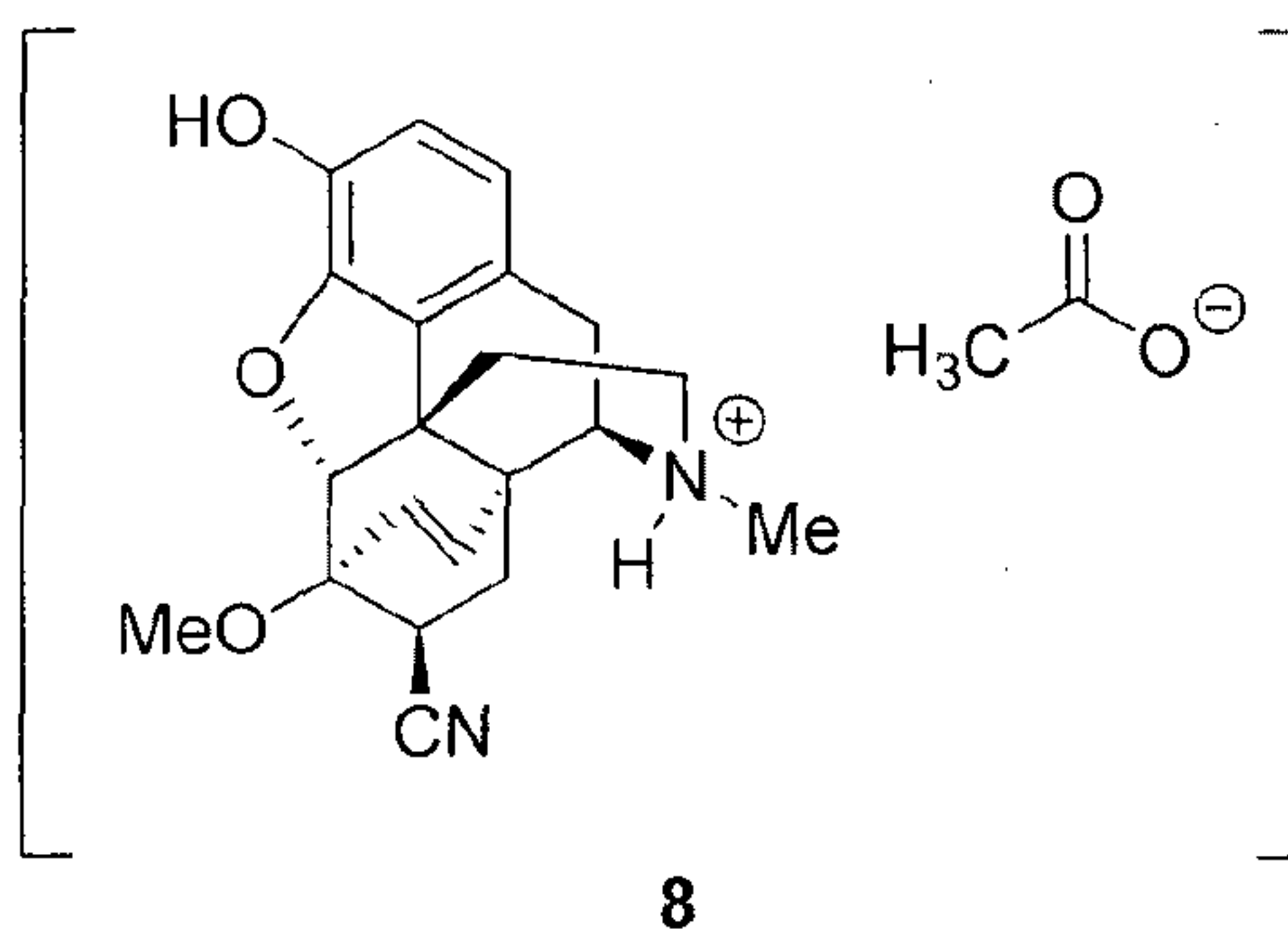
[0210] 119 g of a mother liquor obtained after Diels-Alder reaction of oripavine and MVK, containing in a 97% purity a mixture of compound 2 and compound 1 in a 68:32 ratio, was heated under reflux in IPA (600 mL). Once a solution was formed, TFA (15.5 g, 1.0 eq. based on compound 2) was added dropwise. The mixture was cooled to room temperature and compound 7 was filtered off. The crude compound 7 (103 g) was added to a mixture of EtOAc (1.5 L) and water (400 mL). Ammonium hydroxide was added (~15 mL) and the pH was adjusted to pH 9. The layers were separated and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The crude product was triturated in

MeOH (400 mL) and stirred for 30 minutes under reflux. After cooling to ambient temperature, the product was filtered off and dried to afford 44.6 g (60% recovery, 99% purity) of compound **2** as an off-white crystalline solid.

EXAMPLE 10

Isolation of compound **6** from a mixture of compound **5**/compound **6** in a 50:50 ratio

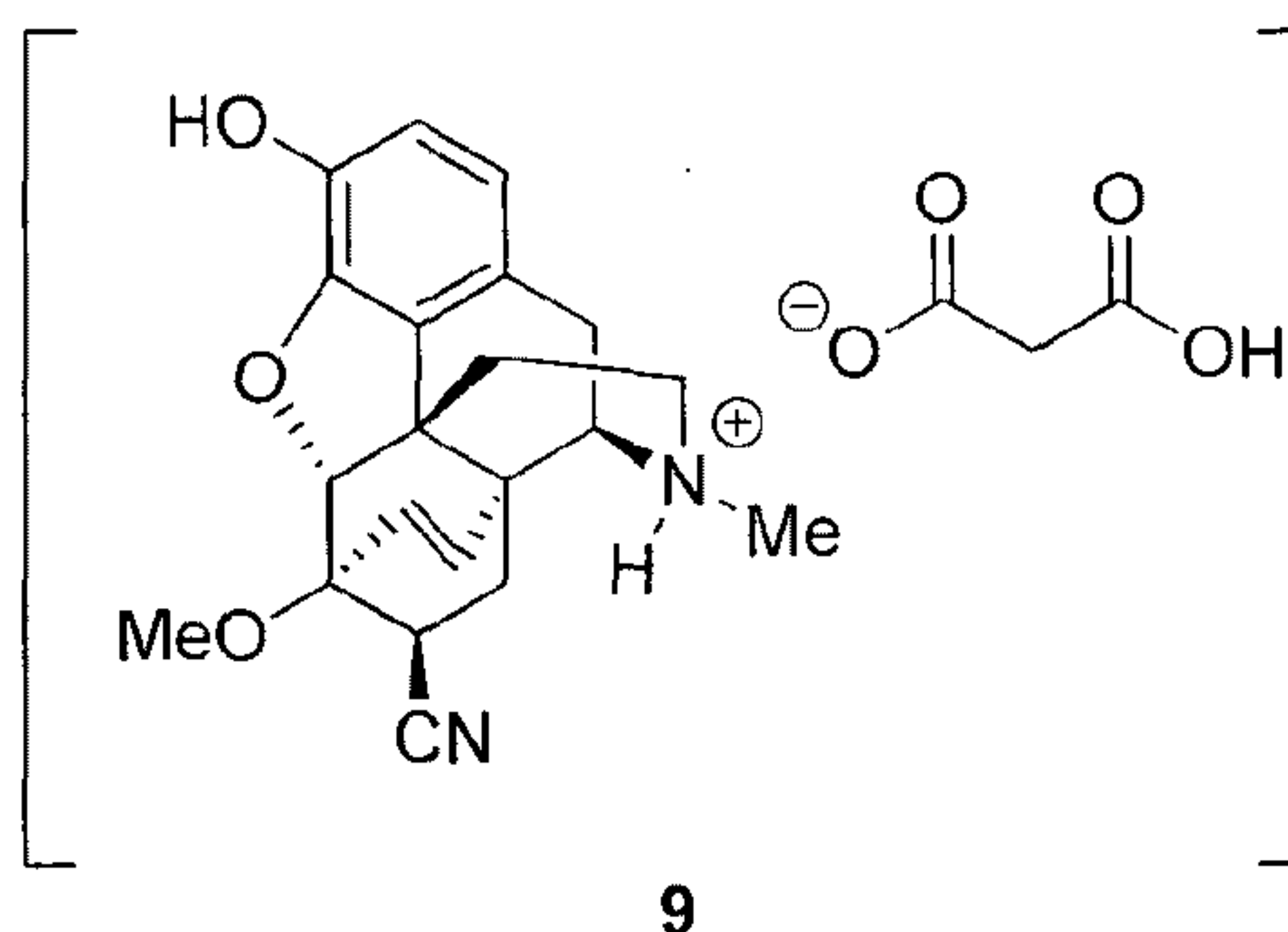
[0211] A mixture of compound **5** (5.0 g) and compound **6** (5.0 g) in IPA (300 mL) was heated to 60 °C. After a clear solution was formed acetic acid (1.03 g, 0.6 equiv to total base) was added. The mixture was cooled to ambient temperature and stirred overnight. The product was filtered off and the cake was washed with IPA (50 mL). After drying, 1.8 g (88% recovery, 98.1% purity) of compound **6** (the 7 β -epimer) acetate salt (compound **8**) was obtained:



EXAMPLE 11

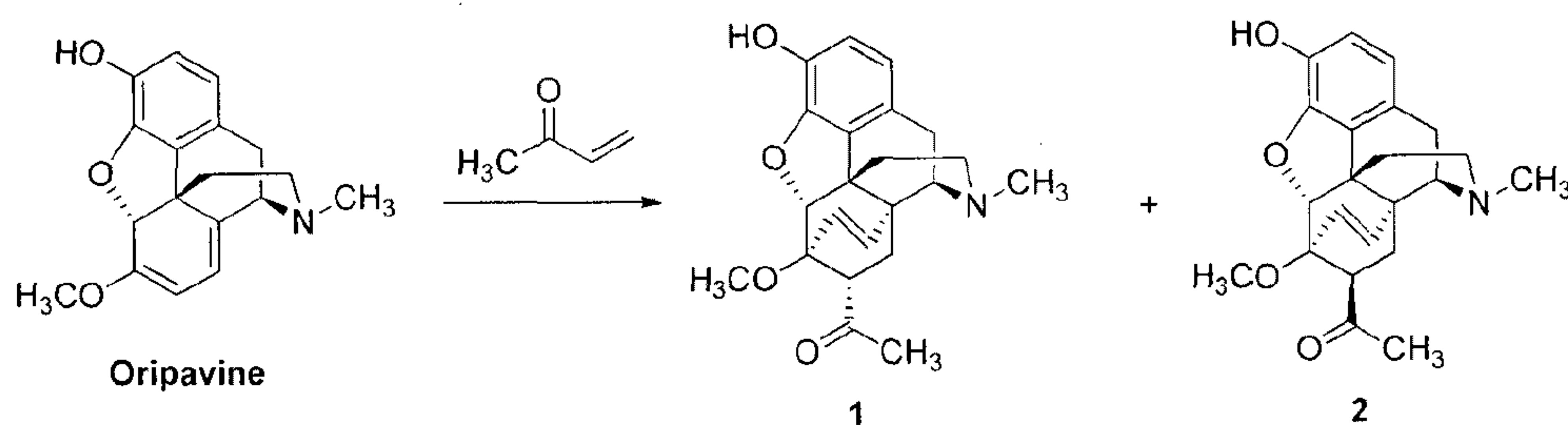
Isolation of compound **5** from a mixture of compound **5**/compound **6** in a 50:50 ratio

[0212] A mixture of compound **5** (5.0 g) and compound **6** (5.0 g) in ethanol (EtOH) (300 mL) was heated to 60 °C. After a clear solution was formed maleic acid (1.99 g, 0.6 equiv to total base) was added. The mixture was cooled to 20 °C and stirred overnight. The product was filtered off and the cake was washed with ethanol (1000 mL). After drying, 5.9 g (31% recovery, 91.2% purity) of compound **5** (the 7 α -epimer) maleate salt was obtained, while compound **6** maleate salt remained in the mother liquor (compound **9**):



EXAMPLE 12

Preparation of compound 2



[0213] (a) A mixture of 1300 g of oripavine and methyl vinyl ketone (1.5 equiv) in isopropanol (3.25 L) was heated under reflux for 2 days. The mixture was cooled to 0 °C and then filtered. The filter cake was washed twice with iso-propanol (2 × 1 L) and then dried to afford 1444 g (89 % yield, >99% purity) of compound 1:

[0214] ¹H NMR δ (400 MHz, CDCl₃): 6.60 (d, *J* = 8 Hz, 1H), 5.03 (d, *J* = 7.6 Hz, 1H), 6.49 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 5.56 (d, *J* = 9.2 Hz, 1H), 4.70 (bs, 1H), 4.59 (d, *J* = 1.2 Hz, 1H), 3.57 (s, 3H), 3.22–3.19 (m, 2H), 2.96–2.90 (m, 2H), 2.53–2.50 (m, 1H), 2.44–2.37 (m, 2H), 2.36 (s, 3H), 2.13 (s, 3H), 2.01–1.95 (m, 1H), 1.87–1.83 (m, 1H), 1.38–1.32 (m, 1H).

[0215] LC/MS (ESI): *m/z* 368.1 = [M + H]⁺ (Calc: 367.4).

[0216] (b) The mother liquor from step (a), containing about 119.5 g of compound 1 and compound 2 in a 71:29 ratio was concentrated to about 3 L. The mixture was then heated to about 60 °C and TFA (1.1 equiv based on compound 2) was added. The mixture was seeded with compound 7 and cooled to 25 °C and stirred for 3 days. The mixture was filtered and the filter cake was washed with isopropanol (1 L) then dried to

afford 28.8 g (64% yield) of compound 7, which can be converted to compound 2 as described in Example 8.

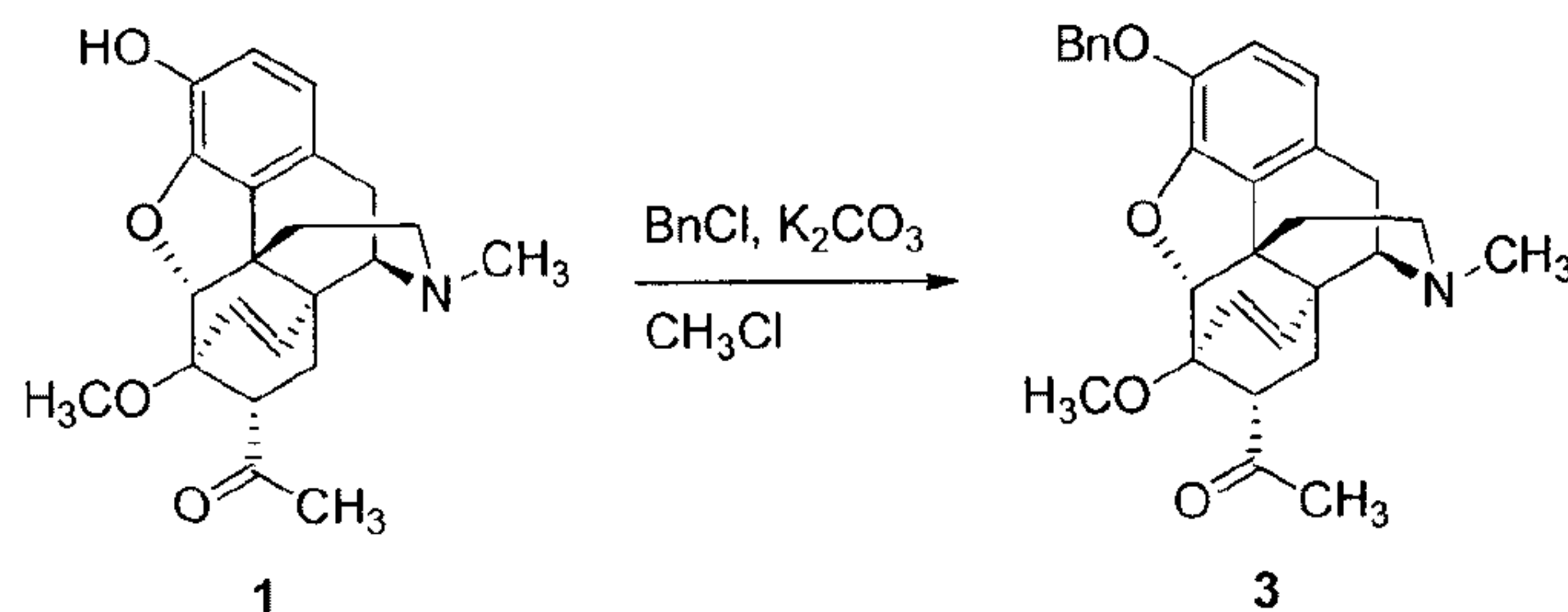
EXAMPLE 13

Epimerization of compound 1 with K_2CO_3

[0217] A mixture of compound 1 (32.5 g), K_2CO_3 (24.4, 2 equiv) in cyclopentyl methyl ether (CPME) (155 mL) and water (~3 mL) was heated to 75 °C for 48 h at which point HPLC analysis indicated 23% epimerization. The mixture was cooled to ambient temperature. Dichloromethane and water were added and the pH was adjusted to 7–8. The layers were separated and the organic layer was concentrated to dryness. The residue was triturated with ethyl acetate to afford 17.4 g of compound 1. The mother liquor, containing compounds 1 and 2 in a ratio of about 1:1, was concentrated to dryness. The residue was dissolved in IPA and treated with TFA as described in the examples above to afford 5.6 g (17.5%) of compound 2 after salt breaking.

EXAMPLE 14

Synthesis of compound 3



[0218] Compound 1 (15 g) was benzylated in chloroform with benzyl bromide (1.2 equiv) and potassium carbonate (1.2 eq). After heating the mixture under reflux for 6 hours, HPLC analysis indicated complete consumption of compound 1. The solids were filtered off and the filtrate was concentrated to afford a mixture of compound 2 and residual benzyl bromide. The residue was purified by column chromatography on silica eluting with dichloromethane to afford 20 g (100%) of compound 3 as a light yellow oil.

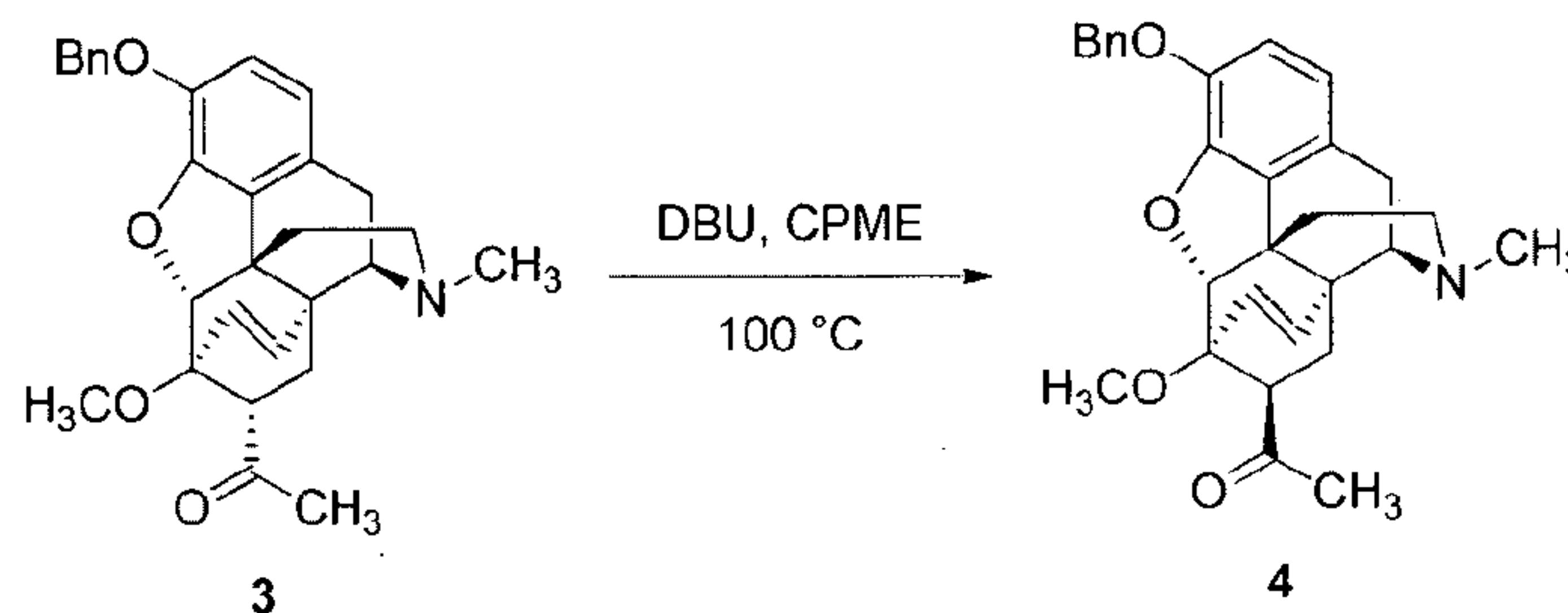
[0219] ^1H NMR δ (300 MHz, CDCl_3): 7.41–7.26 (m, 5H), 6.65 (d, 1H), 6.48 (d, 1H), 5.90 (d, 1H), 5.57 (d, 1H), 5.16–5.06 (m, 2H), 4.57 (d, 1H), 3.60 (s, 3H), 3.22 (d, 1H),

3.18 (s, 1H), 2.95–2.86 (m, 2H), 2.57–2.47 (m, 1H), 2.44–2.35 (m, 5H), 2.14 (s, 3H), 2.02–1.92 (m, 1H), 1.86–1.78 (m, 1H), 1.41–1.33 (m, 1H).

[0220] LC/MS (ESI), $m/z = 458.3$ $[M + H]^+$ (Calc: 457.6)

EXAMPLE 15

Synthesis of compound 4 after epimerization of compound 3



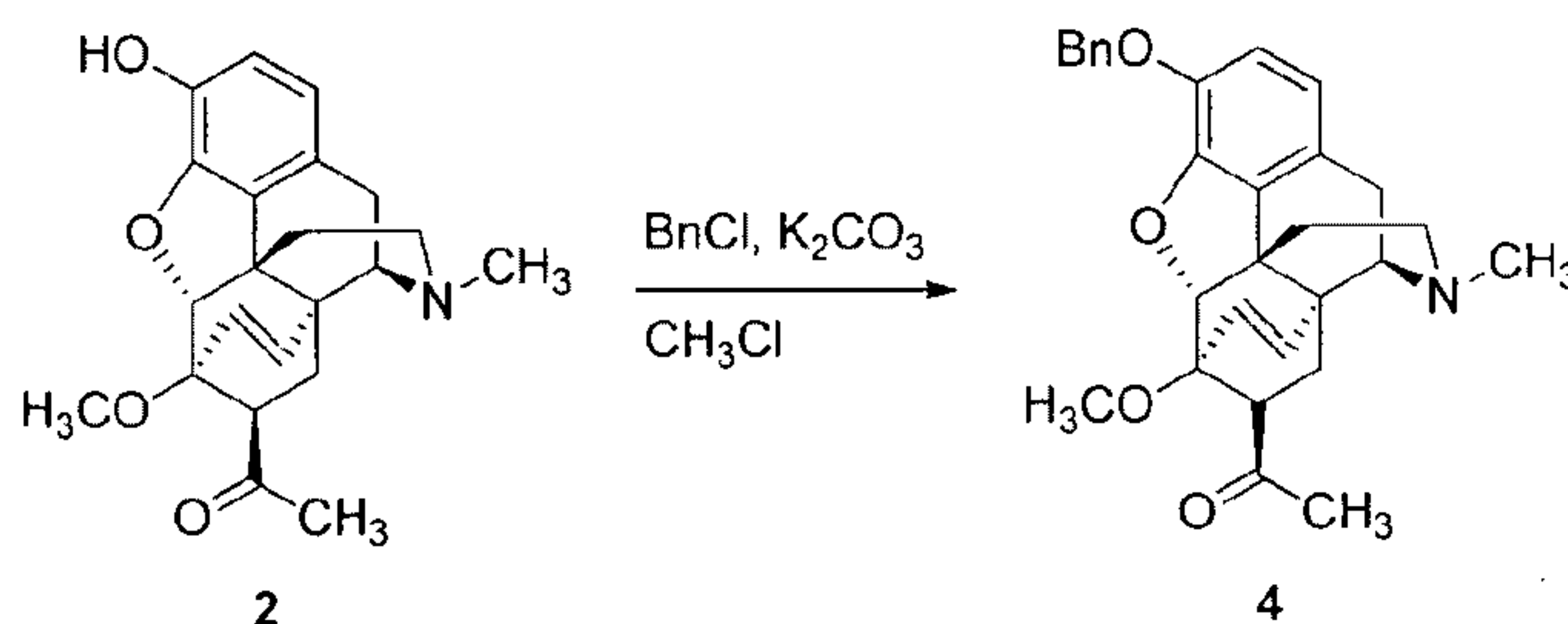
[0221] Compound 3 (20 g) was treated with 1.1 molar equivalents of DBU in cyclopentyl methyl ether (CPME) (200 mL) at 100 °C. The progress of the reaction was monitored by HPLC. After about 3 days, conversion from compound 3 to compound 4 was about 22% based on HPLC. After work-up and column purification, 4.2 g of compound 4 (21% yield, 99.6A% pure) was isolated.

[0222] ^1H NMR δ (300 MHz, CDCl_3): 7.41–7.26 (m, 5H), 6.64 (d, $J = 8.4$ Hz, 1H), 6.45 (d, $J = 8.1$ Hz, 1H), 6.03 (dd, $J = 9.3$ Hz, 1.8 Hz, 1H), 5.47 (d, $J = 9.0$ Hz, 1H), 5.17–5.06 (m, 2H), 5.00 (d, $J = 1.8$ Hz, 1H), 3.61 (s, 3H), 3.21 (d, $J = 18.9$ Hz, 1H), 3.15 (d, $J = 6.6$ Hz, 1H), 2.99–2.79 (m, 3H), 2.62–2.52 (m, 1H), 2.42–2.33 (m, 5H), 2.30 (s, 3H), 1.66–1.61 (m, 1H), 1.40 (dd, $J = 12.2$ Hz, 11.1 Hz, 1H).

[0223] LC/MS (ESI), $m/z = 458.4$ $[M + H]^+$ (Calc: 457.6)

EXAMPLE 16

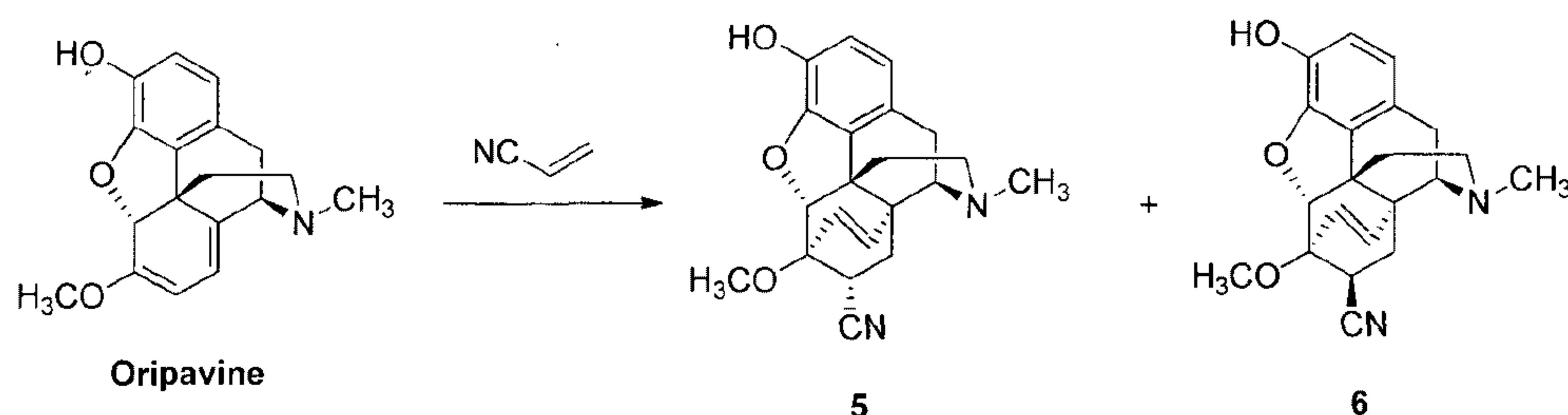
Synthesis of compound 4



[0224] Compound 4 can also be synthesized analogous to the procedure described in Example 14 using compound 2 instead of Compound 1.

EXAMPLE 17

Synthesis and isolation of compounds 5 and 6



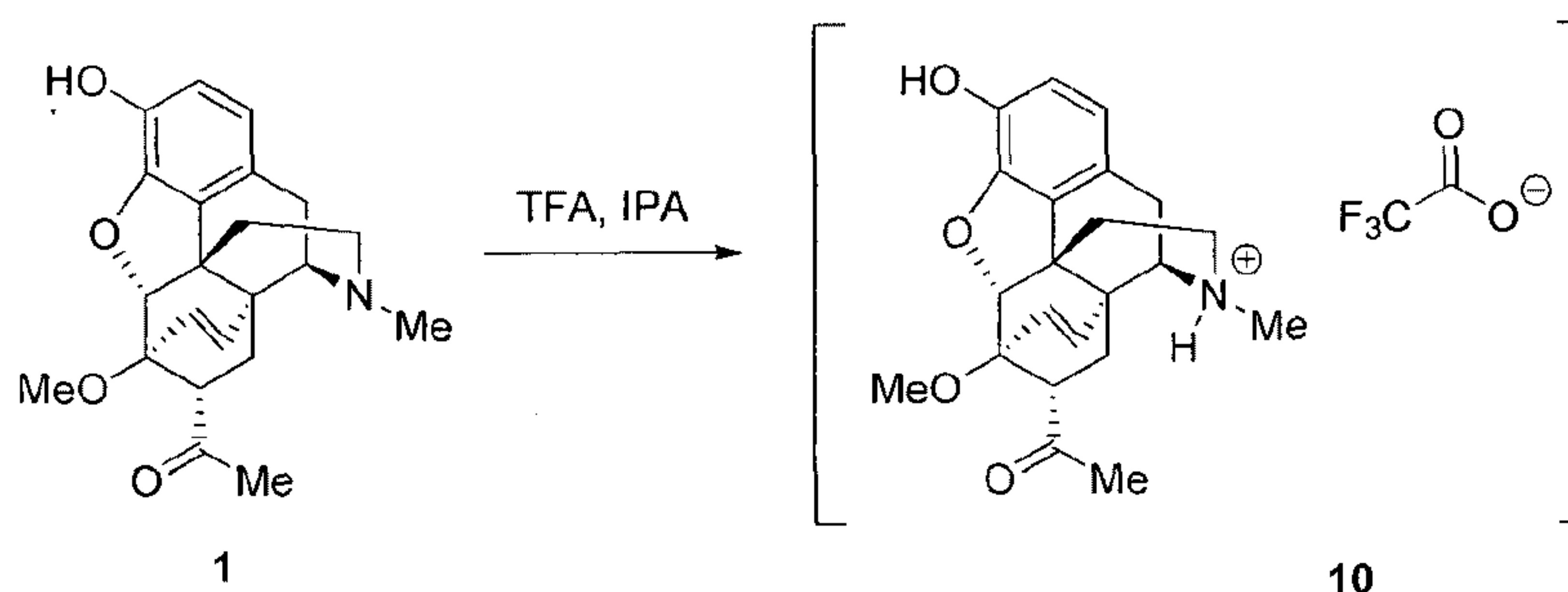
[0225] A mixture of oripavine (100 g) and acrylonitrile (1.1 equiv) in isopropanol (260 mL) was heated under in a 2-L pressure bottle at 100 °C overnight. The reaction mixture was allowed to cool to ambient temperature and sampled. HPLC analysis indicated consumption of oripavine and formation of two new products formed in about 1:1 ratio. The mixture was concentrated to dryness. The residue was redissolved in a minimal amount of dichloromethane (~400 mL) and purified by silica gel chromatography eluting with ethyl acetate/hexanes (1:1) to afford 16 g (14 %) of compound 6 as the faster eluting epimer and 22 g (19 %) of compound 5 as the slower eluting epimer. Both compounds were isolated as off-white solids. Compound 5 can also be crystallized from methanol, while compound 6 is more soluble in this solvent. Trituration of the crude ~1:1 mixture in methanol provided clean compound 6 after filtration. The mother liquor from the trituration contained compound 6 and compound 5 in about a 1:3 ratio.

[0226] Compound 6: ^1H NMR δ (300 MHz, CDCl_3): 6.62 (d, $J = 8.1$ Hz, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 5.92 (dd, $J = 8.7$ Hz, 1.8 Hz, 1H), 5.57 (d, $J = 9.6$ Hz, 1H), 5.01 (d, $J = 1.2$ Hz, 1H), 3.59 (s, 3H), 3.26–3.17 (m, 2H), 3.11 (dd, $J = 12.9$ Hz, 3.3 Hz, 1H), 2.87 (dd, $J = 11.7$ Hz, 3.6 Hz, 1H), 2.62–2.55 (m, 1H), 2.48–2.26 (s, 6H), 1.92–1.84 (m, 1H), 1.78–1.69 (m, 1H). LC/MS (ESI), $m/z = 351.0$ $[\text{M} + \text{H}]^+$ (Calc: 350.4).

[0227] Compound 5: ^1H NMR δ (300 MHz, CDCl_3): 6.62 (d, $J = 8.1$ Hz, 1H), 6.51 (d, $J = 8.4$ Hz, 1H), 5.93 (dd, $J = 8.7$ Hz, 1.8 Hz, 1H), 5.64 (d, $J = 9$ Hz, 1H), 4.53 (d, $J = 1.8$ Hz, 1H), 3.65 (s, 3H), 3.29–2.18 (m, 3H), 2.93–2.87 (m, 1H), 2.58–2.39 (m, 3H), 2.36 (s, 3H), 1.98–1.82 (m, 2H), 1.56 (dd, $J = 12.9$ Hz, 5.4 Hz, 1H). LC/MS (ESI), $m/z = 351.0$ $[\text{M} + \text{H}]^+$ (Calc: 350.4).

EXAMPLE 18

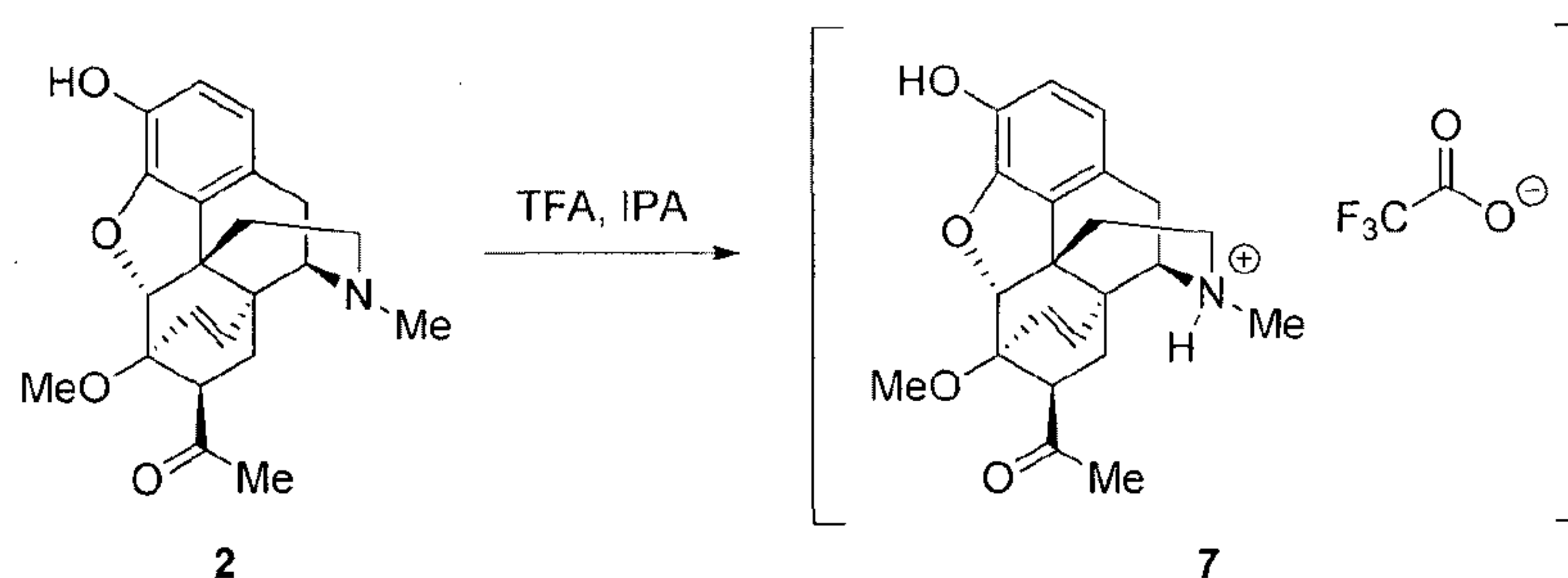
Synthesis and isolation of compound 10



[0228] Compound **1** (20.9 g) was dissolved in IPA (350 mL) at 80 °C. The solution was then cooled to 60 °C and TFA (5.2 mL, 1.2 eq.) was added dropwise. The mixture was cooled to ambient temperature and stirred overnight. The product was filtered off. The filter cake was washed with IPA (1 × 30 mL) and dried to afford 25.8 g of compound **10** (94.2 %) as an off-white solid.

EXAMPLE 19

Synthesis of Compound 7



[0229] Compound **7** can be synthesized analogous to procedure described in Example 18 using compound **2** instead of compound **1**.

[0230] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof.

[0231] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is

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intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[0232]

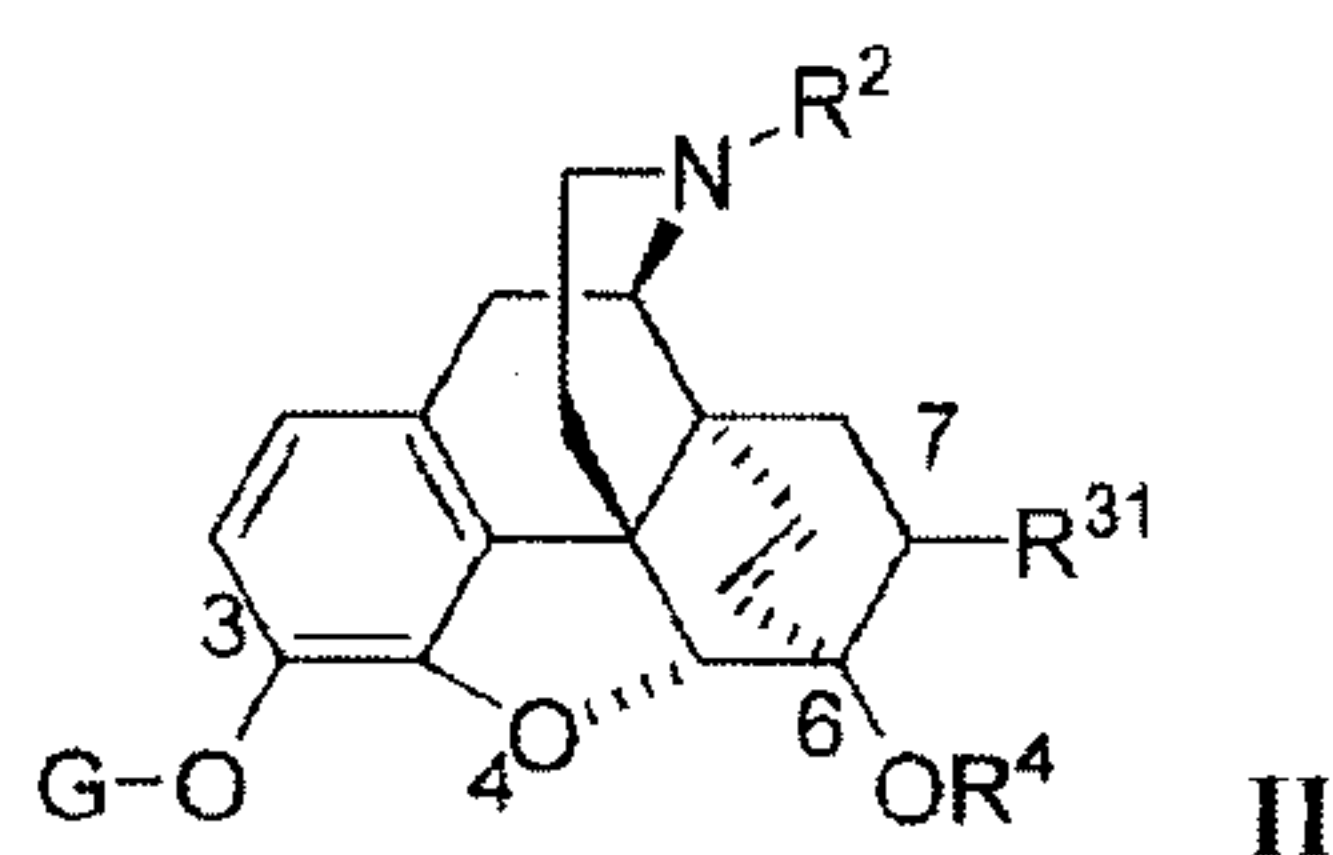
What is claimed is:

1. A process for increasing the proportion of the 7 β -epimer in an 7 α /7 β -epimer mixture of a 7-substituted 6 α ,14 α -ethenomorphinan or a 7-substituted 6 α ,14 α -ethanomorphinan, said process comprising:

contacting a solution of the 7 α /7 β -epimer mixture with an acid to provide a precipitate, and isolating the precipitate to provide an isolated precipitate and a mother liquor,

wherein the acid is an achiral acid.

2. The process of claim 1, wherein the 7-substituted 6 α ,14 α -ethenomorphinan or the 7-substituted 6 α ,14 α -ethanomorphinan is a compound of Formula II:



wherein:

G is R¹ or a hydroxyl protecting group PG;

R¹ is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R² is

(a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or

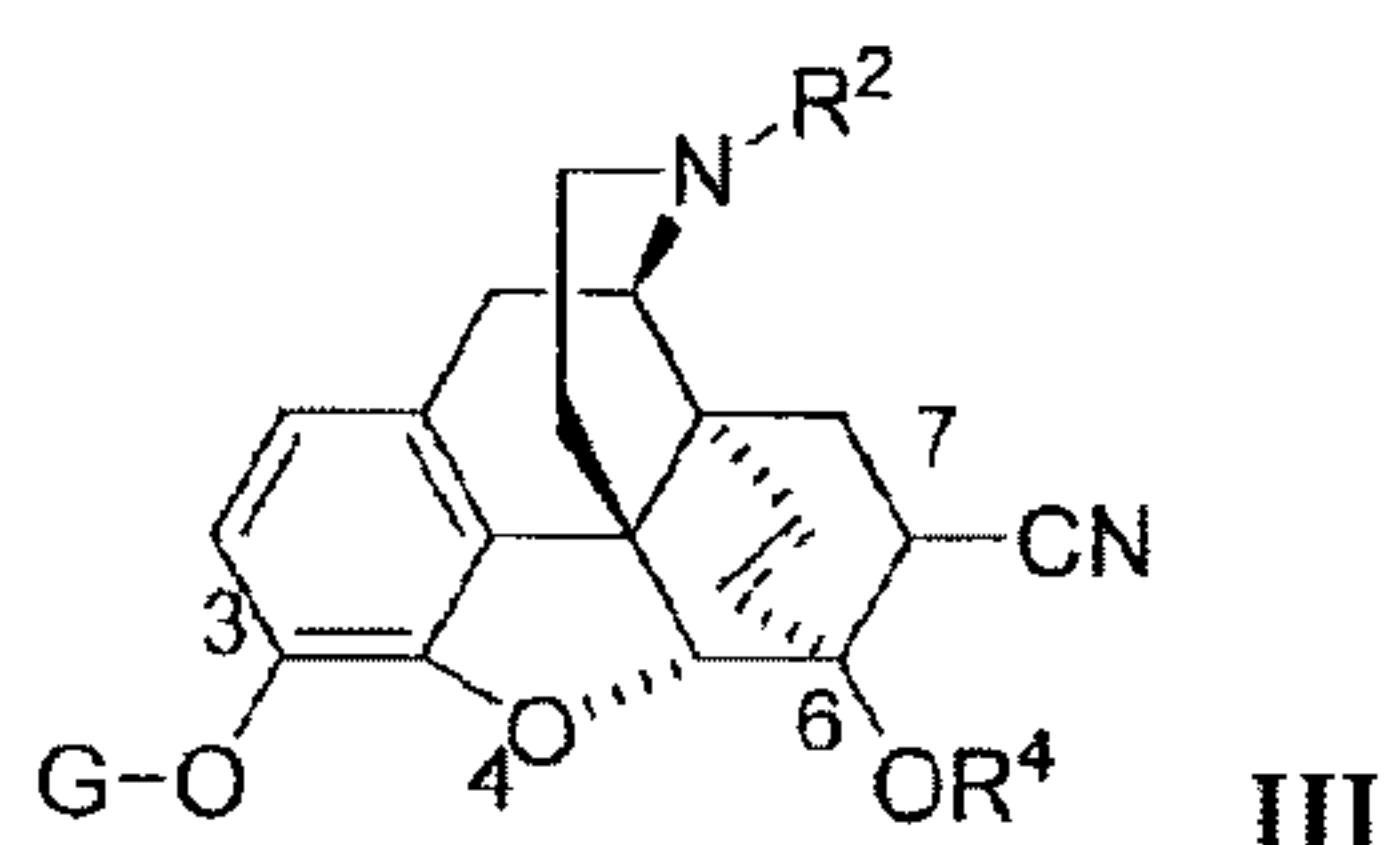
(b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R^{31} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, alkylcarbonyl, (arylalkyl)carbonyl, and formyl, wherein any of which, when other than formyl, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl; and

$\diagup$ is a single bond or a double bond.

3. The process of claim 1 or claim 2, wherein the precipitate is isolated by filtration.
4. The process of any one of claims 1-3, wherein the precipitate contains an increased proportion of the 7β -epimer as a salt relative to the $7\alpha/7\beta$ -epimer mixture.
5. The process of claim 1, wherein the 7-substituted $6\alpha,14\alpha$ -ethenomorphinan or the 7-substituted $6\alpha,14\alpha$ -ethanomorphinan is a compound of Formula III:



wherein:

G is R^1 or a hydroxyl protecting group PG;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl

portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R^2 is

- (a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or
- (b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and

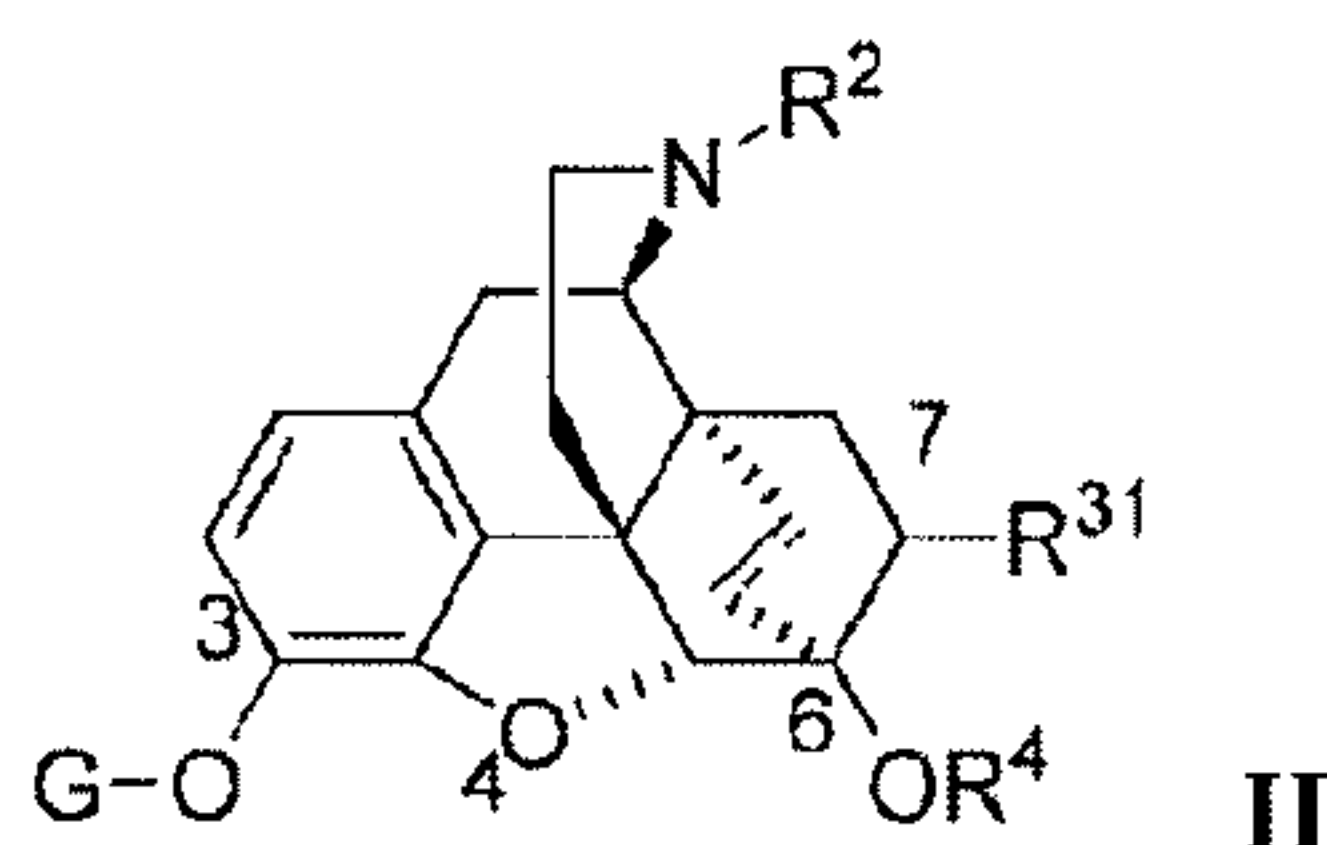
$\diagup$ is a single bond or a double bond.

- 6. The process of claim 5, wherein the precipitate is isolated by filtration.
- 7. The process of claim 5 or 6, wherein the mother liquor contains an increased proportion of either the 7β -epimer or the 7α -epimer as a salt relative to the $7\alpha/7\beta$ -epimer mixture.
- 8. The process of claim 5 or 6, wherein the precipitate contains an increased proportion of either the 7β -epimer or the 7α -epimer as a salt relative to the $7\alpha/7\beta$ -epimer mixture.
- 9. A process for purifying the 7β -epimer from an $7\alpha/7\beta$ -epimer mixture of a 7-substituted $6\alpha,14\alpha$ -ethenomorphinan or a 7-substituted $6\alpha,14\alpha$ -ethanomorphinan, said process comprising:

- contacting a solution of the 7 α /7 β -epimer mixture with an acid under conditions conducive to precipitation of the 7 β -epimer, and
- isolating the precipitate to provide an isolated precipitate and a mother liquor,

wherein the acid is an achiral acid.

10. The process of claim 9, wherein the 7-substituted 6 α ,14 α -ethenomorphinan or the 7-substituted 6 α ,14 α -ethanomorphinan is a compound of Formula II:



wherein:

G is R¹ or a hydroxyl protecting group PG;

R¹ is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R² is

- (a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or
- (b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

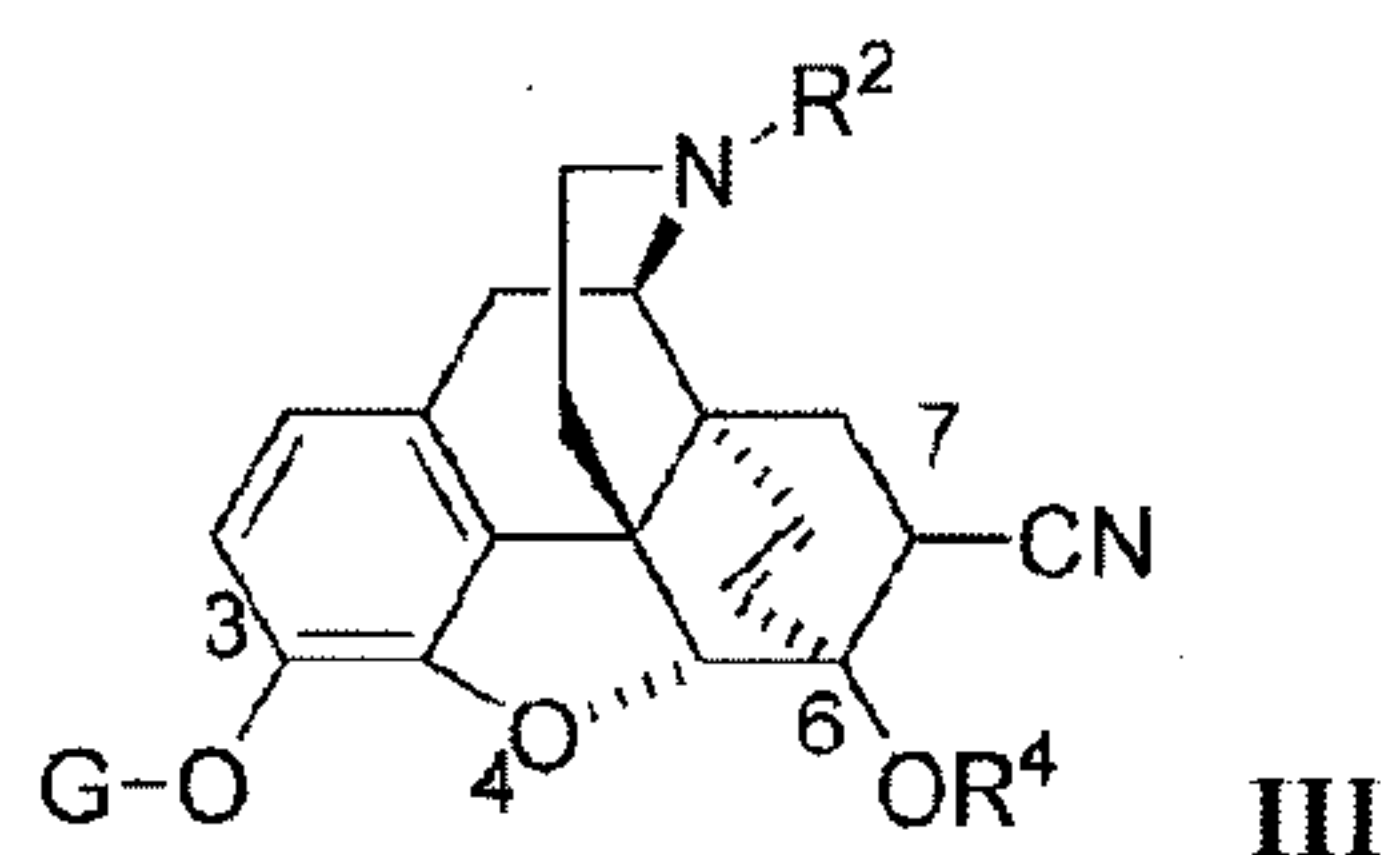
R³¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, alkylcarbonyl,

(arylalkyl)carbonyl, and formyl, wherein any of which, when other than formyl, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl:

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and

$\diagup$ is a single bond or a double bond.

11. The process of claim 9, wherein the 7-substituted 6 α ,14 α -ethenomorphinan or the 7-substituted 6 α ,14 α -ethanomorphinan is a compound of Formula III:



wherein:

G is R^1 or a hydroxyl protecting group PG;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R^2 is

- (a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido; or
- (b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is

optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl; and

$\diagup$ is a single bond or a double bond.

12. The process of any one of claims 1-11, wherein the acid is selected from the group consisting of an aliphatic monocarboxylic acid and an aliphatic dicarboxylic acid, or a combination thereof, any of which is optionally substituted.

13. The process of any one of claims 1-12, wherein the acid is an optionally substituted, saturated or unsaturated aliphatic monocarboxylic acid.

14. The process of any one of claims 1-13, wherein the acid is a saturated or unsaturated C_{1-6} aliphatic monocarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy.

15. The process of any one of claims 1-14, wherein the acid is a saturated, unsubstituted C_{1-4} aliphatic monocarboxylic acid, or a saturated C_{1-4} aliphatic monocarboxylic acid substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of fluoro, chloro, bromo, iodo, and hydroxy.

16. The process of any one of claims 1-15, wherein the acid is selected from the group consisting of acetic acid, trifluoroacetic acid, trichloroacetic acid, and tribromoacetic acid.

17. The process of any one of claims 1-12, wherein the acid is an optionally substituted, saturated or unsaturated aliphatic dicarboxylic acid.
18. The process of any one of claims 1-12, and 17, wherein the acid is a saturated C₂₋₆ aliphatic dicarboxylic acid optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of halogen and hydroxy.
19. The process of any one of claims 1-12 and 17, wherein the acid is an unsaturated C₂₋₆ aliphatic dicarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy.
20. The process of any one of claims 1-12, 17 and 19, wherein the acid is unsaturated, unsubstituted C₂₋₆ aliphatic dicarboxylic acid.
21. The process of any one of claims 1-12, 17, and 19-20, wherein the acid is fumaric acid or maleic acid.
22. The process of any one of claims 1-21, wherein the acid is used from about 0.5 to about 1.5 equivalents based on the amount of the 7 β -epimer.
23. The process of any one of claims 1-22, wherein the solution of the 7 α /7 β -epimer mixture comprises a solvent.
24. The process of claim 23, wherein the solvent is an aliphatic alcohol, an aromatic solvent, or an aliphatic ether, or a combination thereof.
25. The process of claim 24, wherein the solvent is methanol, ethanol, n-propanol, iso-propanol, toluene, or cyclopentyl methyl ether, or a combination thereof.
26. The process of any one of claims 1-25, wherein the solution is contacted with the achiral acid at a temperature of about 50 °C to about the boiling point of the solution.
27. The process of claim 26, wherein the temperature is from about 55 °C to about the reflux temperature of the solvent.

28. The process of claim 26 or 27, wherein the temperature is from about 60 °C to about the reflux temperature of the solvent.
29. The process of any one of claims 2 and 10, wherein G is R¹.
30. The process of any one of claims 2, 10 and 29, wherein R¹ is hydrogen.
31. The process of any one of claims 2, 10 and 29, wherein R¹ is alkyl, alkenyl or alkynyl.
32. The process of any one of claims 2, 10 and 29, wherein R¹ is (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl or heteroaryl portions are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl.
33. The process of any one of claims 2 and 10, wherein G is PG.
34. The process of any one of claims 2, 10 and 33, wherein PG is selected from the group consisting of alkyl, arylalkyl, heterocyclo, (heterocyclo)alkyl, acyl, silyl, and carbonate, any of which is optionally substituted.
35. The process of any one of claims 2, 10, 33 and 34, wherein PG is selected from the group consisting of alkyl, arylalkyl, heterocyclo, (heterocyclo)alkyl, benzoyl, (benzyloxy)carbonyl, alkoxycarbonyl, alkylcarbonyl, and silyl, any of which is optionally substituted.
36. The process of any one of claims 2, 10, and 33-35, wherein PG is selected from the group consisting of methyl, tert-butyl, optionally substituted benzyl, optionally substituted benzoyl, acetyl, trimethyl silyl, tert-butyldimethyl silyl, tert-butyldiphenyl silyl, and tri-isopropyl silyl.
37. The process of any one of claims 2, 10 and 29-36, wherein R² is hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido.

38. The process of any one of claims 2, 10 and 29-36, wherein R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxy carbonyl.

39. The process of any one of claims 2, 10, 29-36 and 38, wherein R^2 is C_{3-7} (cycloalkyl)(C_{1-4})alkyl or C_{3-7} (cycloalkenyl)(C_{1-4})alkyl, optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C_{1-4} alkyl, halo, halo(C_{1-4})alkyl, C_{1-4} alkoxy, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxy carbonyl.

40. The process of any one of claims 2, 10, 29-36, 38 and 39, wherein R^2 is cyclopropyl(C_{1-4})alkyl, cyclobutyl(C_{1-4})alkyl, cyclopentyl(C_{1-4})alkyl, or cyclohexyl(C_{1-4})alkyl, optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C_{1-4} alkyl, halo, halo(C_{1-4})alkyl, C_{1-4} alkoxy, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxy carbonyl.

41. The process of any one of claims 2, 10 and 29-41, wherein R^{31} is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, 5- to 6-membered heterocyclo, C_{6-12} aryl, 5- to 10-membered heteroaryl, (C_{3-7} cycloalkyl)(C_{1-6})alkyl, (C_{3-7} cycloalkyl)(C_{2-6})alkenyl, (C_{3-7} cycloalkenyl)(C_{1-6})alkyl, (C_{3-7} cycloalkenyl)(C_{2-6})alkenyl, (5- to 6-membered heterocyclo)(C_{1-6})alkyl, (5- to 6-membered heterocyclo)(C_{2-6})alkenyl, C_{6-12} aryl(C_{1-6})alkyl, C_{6-12} aryl(C_{2-6})alkenyl, 5- to 10-membered heteroaryl(C_{1-6})alkyl, 5- to 10-membered heteroaryl(C_{2-6})alkenyl, C_{1-6} alkylcarbonyl, (C_{6-12} aryl(C_{1-6})alkyl)carbonyl, and formyl, wherein any of which, when other than formyl, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C_{1-6} alkyl, hydroxy(C_{1-4})alkyl, halo, halo(C_{1-4})alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, and C_{1-6} alkoxy carbonyl.

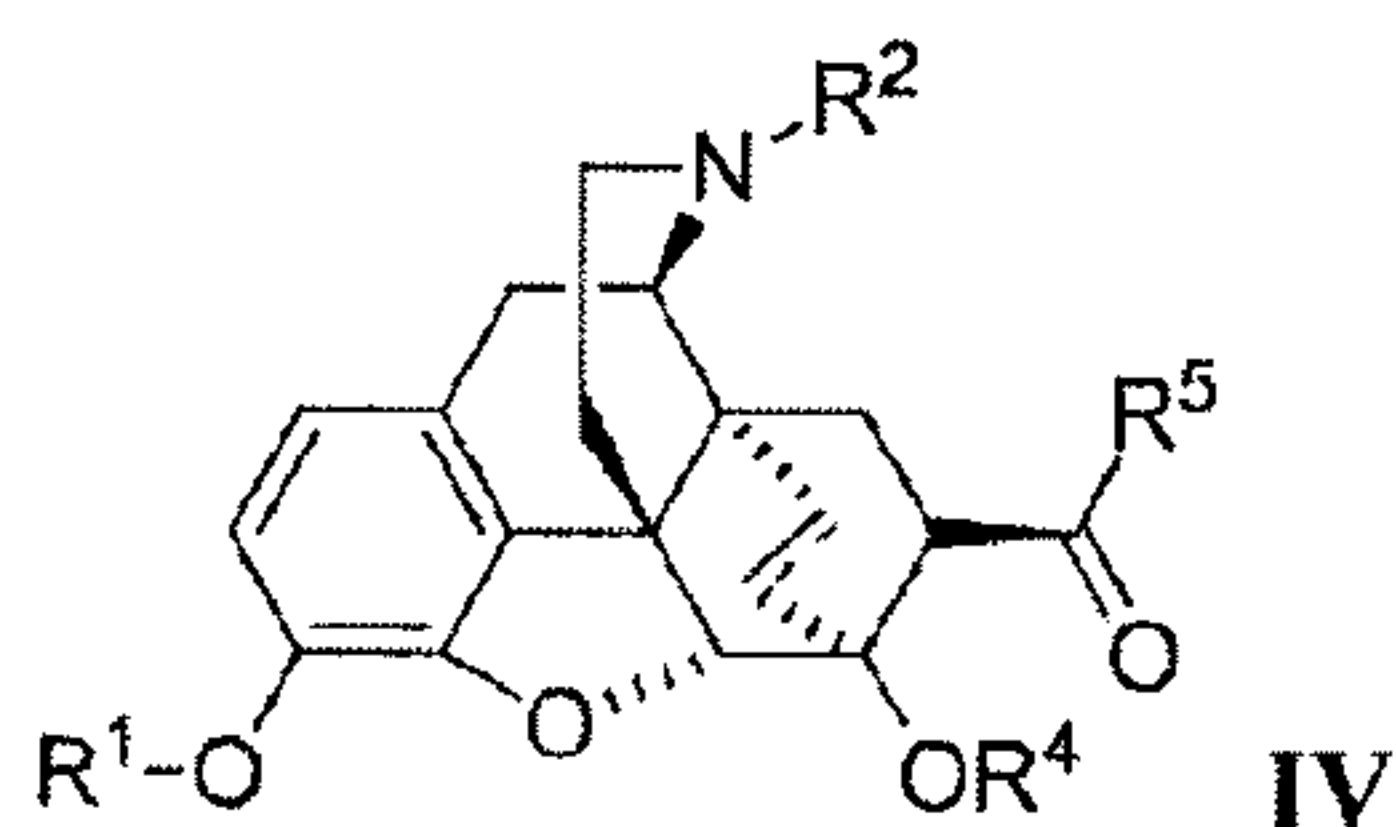
42. The process of any one of claims 2, 10 and 29-41, wherein R^{31} is C_{1-6} alkylcarbonyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each

independently selected from the group consisting of hydroxy, halo, halo(C₁₋₄)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylcarbonyl, and C₁₋₆ alkoxycarbonyl.

43. The process of any one of claims 2, 10 and 29-42, wherein R⁴ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkenyl, 5- to 6-membered heterocyclo, C₆₋₁₂ aryl, 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)(C₁₋₆)alkyl, (C₃₋₇ cycloalkyl)(C₂₋₆)alkenyl, (C₃₋₇ cycloalkenyl)(C₁₋₆)alkyl, (C₃₋₇ cycloalkenyl)(C₂₋₆)alkenyl, (5- to 10-membered heterocyclo)(C₁₋₆)alkyl, (5- to 6-membered heterocyclo)(C₂₋₆)alkenyl, C₆₋₁₂ aryl(C₁₋₆)alkyl, C₆₋₁₂ aryl(C₂₋₆)alkenyl, 5- to 10-membered heteroaryl(C₁₋₆)alkyl, and 5- to 10-membered heteroaryl(C₂₋₆)alkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, C₁₋₄ alkyl, halo, halo(C₁₋₄)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylcarbonyl, and C₁₋₆ alkoxycarbonyl.

44. The process of any one of claims 2, 10 and 29-43, wherein R⁴ is hydrogen or unsubstituted C₁₋₆ alkyl.

45. The process of any one of claims 1-4, 9, 10, and 12-44, wherein the 7β-epimer is of the Formula IV:



or a salt thereof, wherein R⁵ is H or C₁₋₆ alkyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, hydroxy(C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylcarbonyl, and C₁₋₆ alkoxycarbonyl.

46. The process of claim 45 when depending on any one of claims 1-4, 9, 10, 12-29, 33-38, and 41-44, wherein

R¹ is hydrogen, C₁₋₆ alkyl, or benzyl;

R^2 is C_{2-6} alkenyl, cyclopropyl(C_{1-4})alkyl, cyclopentyl(C_{1-4})alkyl, or cyclohexyl(C_{1-4})alkyl, optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, halo, halo(C_{1-4})alkyl, C_{1-4} alkylcarbonyl, and C_{1-4} alkoxy carbonyl; and

R^4 is hydrogen or C_{1-6} alkyl.

47. The process of any one of claims 2-8, 10-36, 38, and 41-46, wherein R^2 is unsubstituted C_{2-6} alkenyl or unsubstituted cyclopropyl(C_{1-4})alkyl.

48. The process of any one of claims 2-8, 10-36, and 38-47, wherein R^2 is cyclopropylmethyl.

49. The process of any one of claims 2-8 and 10-48, wherein $\diagup$ is a double bond.

50. The process of any one of claims 2-8 and 10-48, wherein $\diagup$ is a single bond.

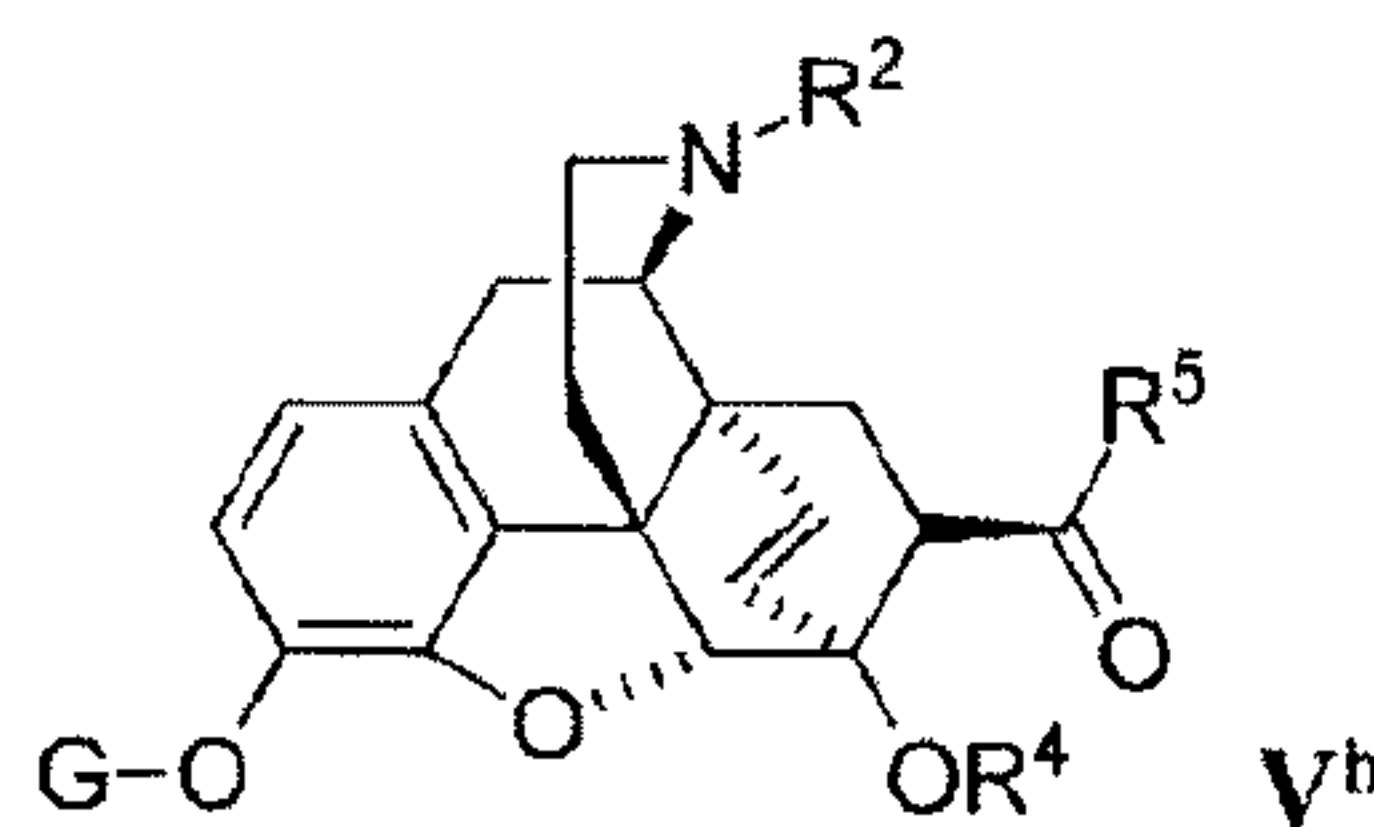
51. The process of any one of claims 1-50, wherein the proportion of the 7β -epimer in the $7\alpha/7\beta$ -epimer mixture is at least 20%.

52. The process of claim 51, wherein the proportion of the 7β -epimer in the $7\alpha/7\beta$ -epimer mixture is at least 50%.

53. The process of any one of claims 1-6 and 8-52, wherein the proportion of the 7β -epimer in the precipitate is at least 60%, at least 70%, at least 80%, or at least 90%.

54. The process of claim 7, wherein the proportion of the 7β -epimer in the mother liquor is at least about 60%, at least 70%, at least 80%, or at least 90%.

55. A process for preparing a 7β -substituted compound of Formula V^b :



or a salt thereof, wherein

G is R¹ or a hydroxyl protecting group PG;

R¹ is hydrogen, alkyl, alkenyl, alkynyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, arylalkyl, or heteroarylalkyl, wherein the cycloalkyl, heterocyclo, aryl, and heteroaryl portions thereof are optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, carboxy, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R² is

(a) hydrogen, cyano, alkylcarbonyl, alkoxycarbonyl, or carboxamido;

or

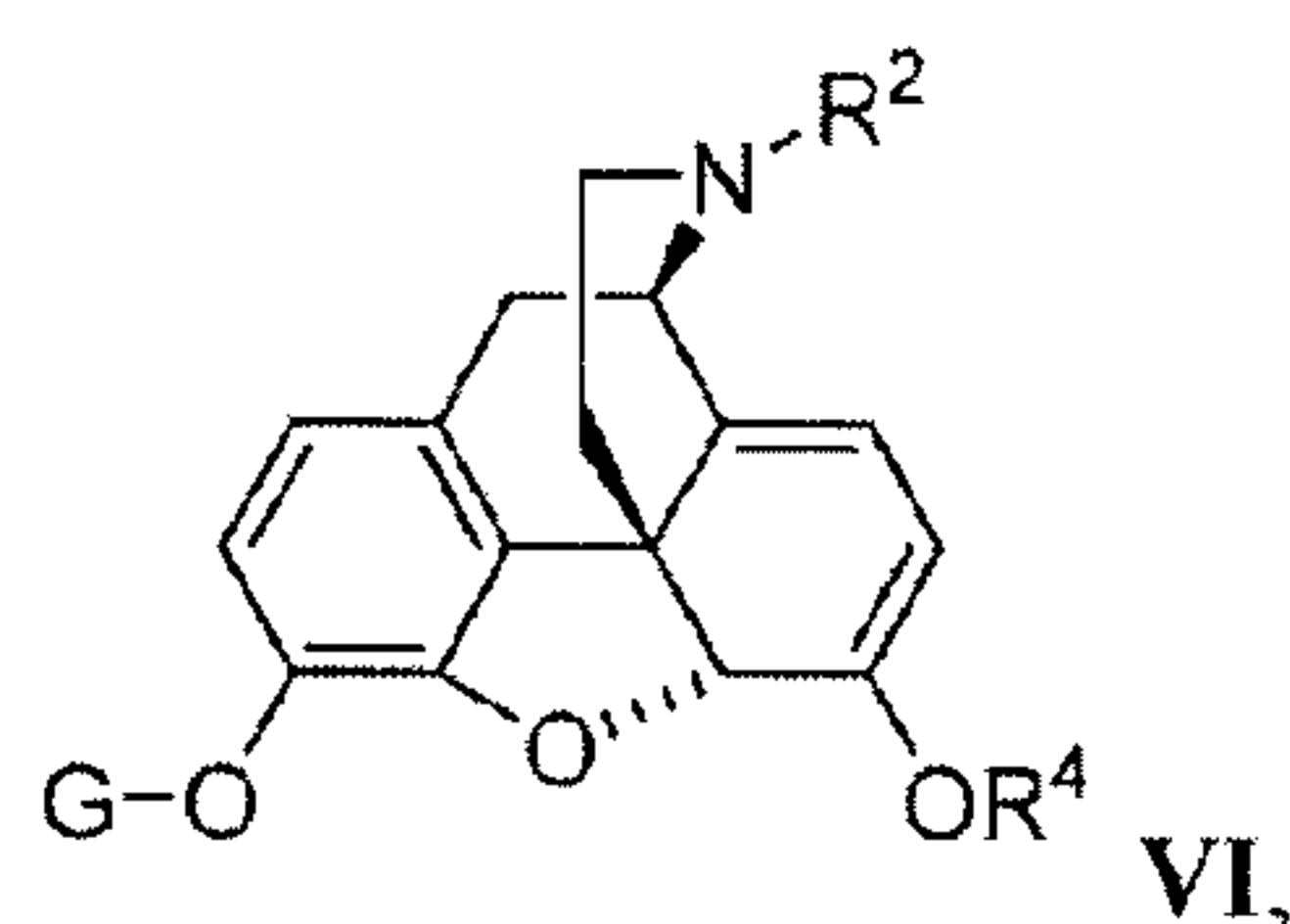
(b) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (heterocyclo)alkyl, arylalkyl, heteroarylalkyl, (arylalkoxy)carbonyl, or (heteroarylalkoxy)carbonyl, any of which is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, alkyl, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

R⁴ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkenyl)alkyl, (cycloalkenyl)alkenyl, (heterocyclo)alkyl, (heterocyclo)alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein any of which, when other than hydrogen, is optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, halo, haloalkyl, alkoxy, alkylcarbonyl, and alkoxycarbonyl;

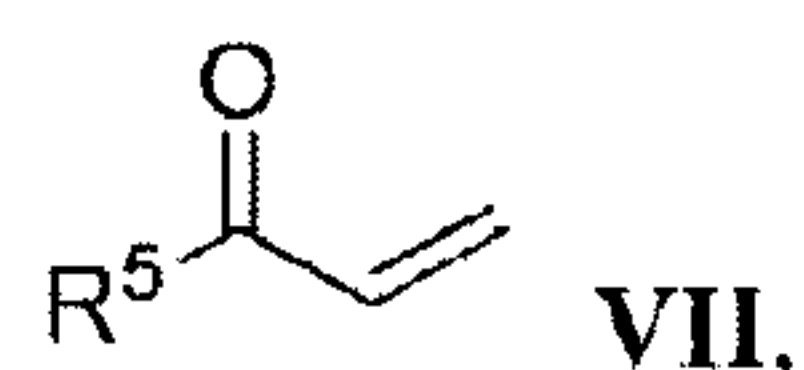
R⁵ is C₁₋₆ alkyl, which is unsubstituted or substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxy, hydroxy(C₁₋₄)alkyl, halo, halo(C₁₋₄)alkyl, C₁₋₄ alkylcarbonyl, and C₁₋₄ alkoxycarbonyl;

said process comprising:

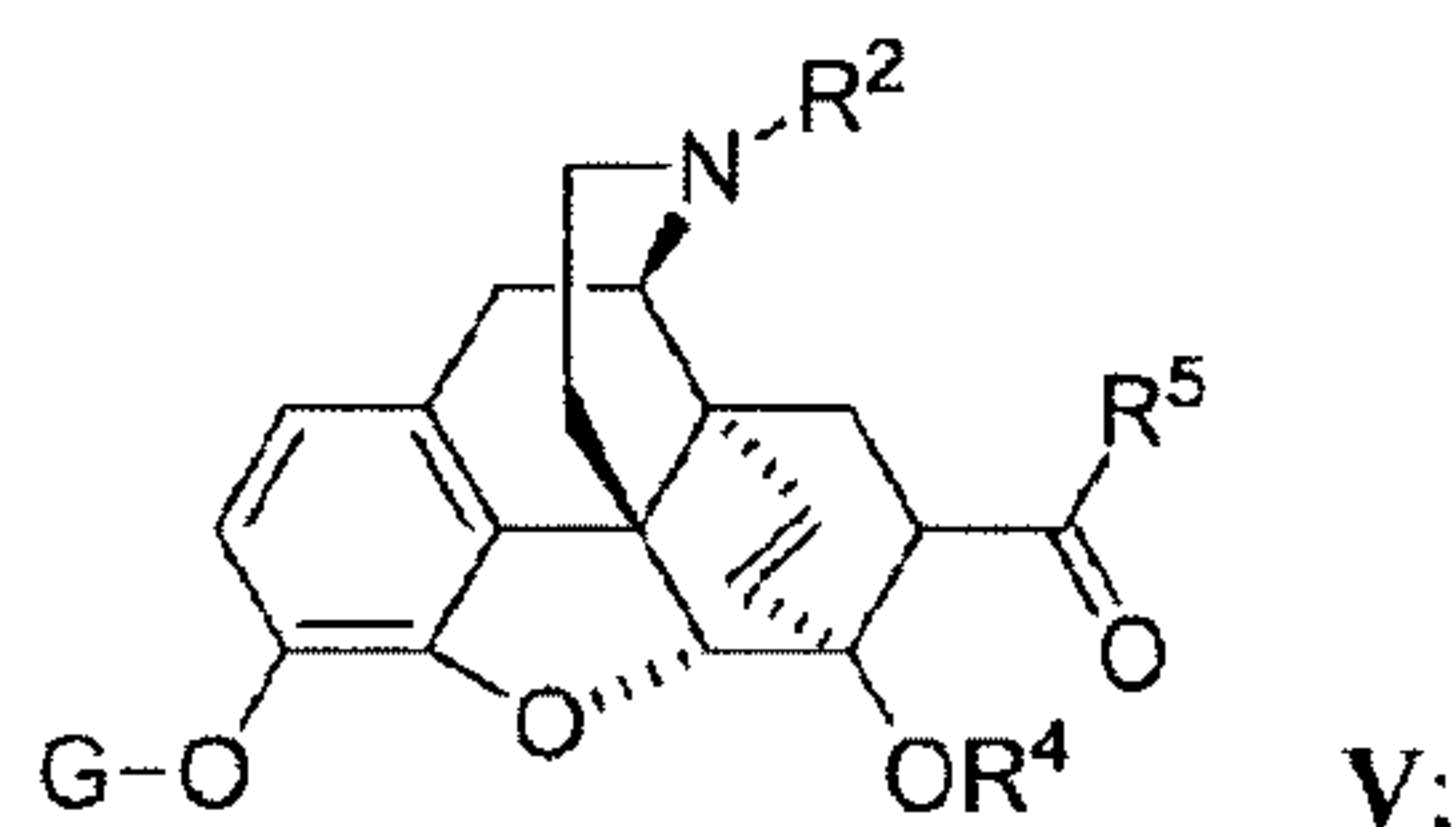
conducting a Diels-Alder reaction between a compound of Formula **VI**:



wherein G and R² are as defined above, and a compound of Formula **VII**:



wherein R⁵ is as defined above, to form a 7 α /7 β -epimer mixture of the compound of Formula **V**



forming a first precipitate of the 7 α /7 β -epimer mixture;

isolating the first precipitate from the reaction mixture to obtain a first mother liquor;

optionally reducing the volume of the first mother liquor, and contacting the first mother liquor with an acid to provide a second precipitate;

isolating the second precipitate to obtain the compound of Formula **V^b** as a salt, and a second mother liquor; and

optionally converting the acid salt into its free base,

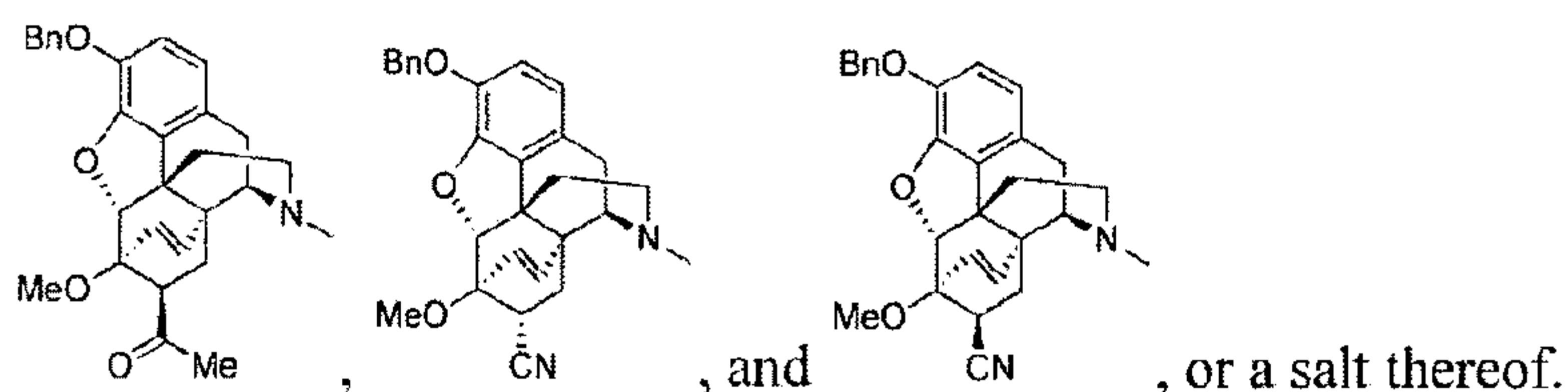
wherein the acid is an achiral acid.

56. The process of claim 55, wherein the first mother liquor is partially concentrated prior to contacting with the acid.

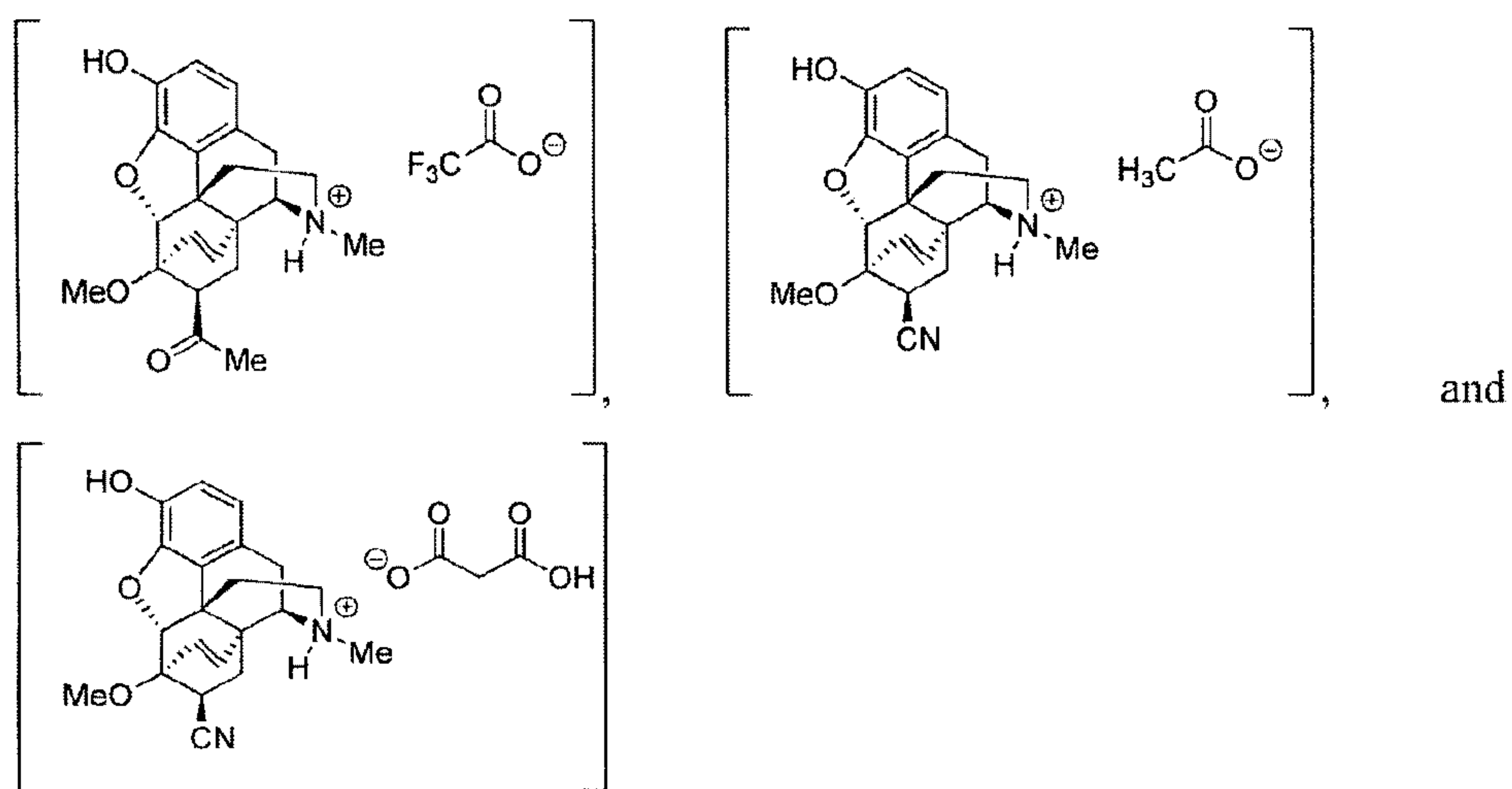
57. The process of claim 56, wherein the partially concentrated first mother liquor is heated, and optionally a solvent is added to the mother liquor, to dissolve any precipitate formed during the concentration to obtain a solution.

58. The process of claim 57, wherein the solvent is an aliphatic alcohol, an aromatic solvent, or an aliphatic ether, or a combination thereof.
59. The process of claim 57 or 58, wherein the solvent is methanol, ethanol, n-propanol, iso-propanol, toluene, or cyclopentyl methyl ether, or a combination thereof.
60. The process of any one of claims 57-59, wherein the solvent is iso-propanol.
61. The process of any one of claims 57-60, wherein the solution is contacted with the acid at a temperature of about 50 °C to about the boiling point of the solution.
62. The process of any one of claims 57-61, wherein the temperature is from about 55 °C to about the reflux temperature.
63. The process of any one of claims 57-62, wherein the temperature is from about 60 °C to about the reflux temperature.
64. The process of any one of claims 55-63, wherein the acid is selected from the group consisting of an aliphatic monocarboxylic acid and an aliphatic dicarboxylic acid, or a combination thereof, any of which is optionally substituted.
65. The process of any one of claims 55-64, wherein the acid is a an optionally substituted, saturated or unsaturated aliphatic monocarboxylic acid.
66. The process of any one of claims 55-65, wherein the acid is a saturated or unsaturated C₁₋₆ aliphatic monocarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy.
67. The process of any one of claims 55-66, wherein the acid is a saturated, unsubstituted C₁₋₄ aliphatic monocarboxylic, or is a saturated C₁₋₄ aliphatic monocarboxylic acid substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of fluoro, chloro, bromo, iodo, and hydroxy.

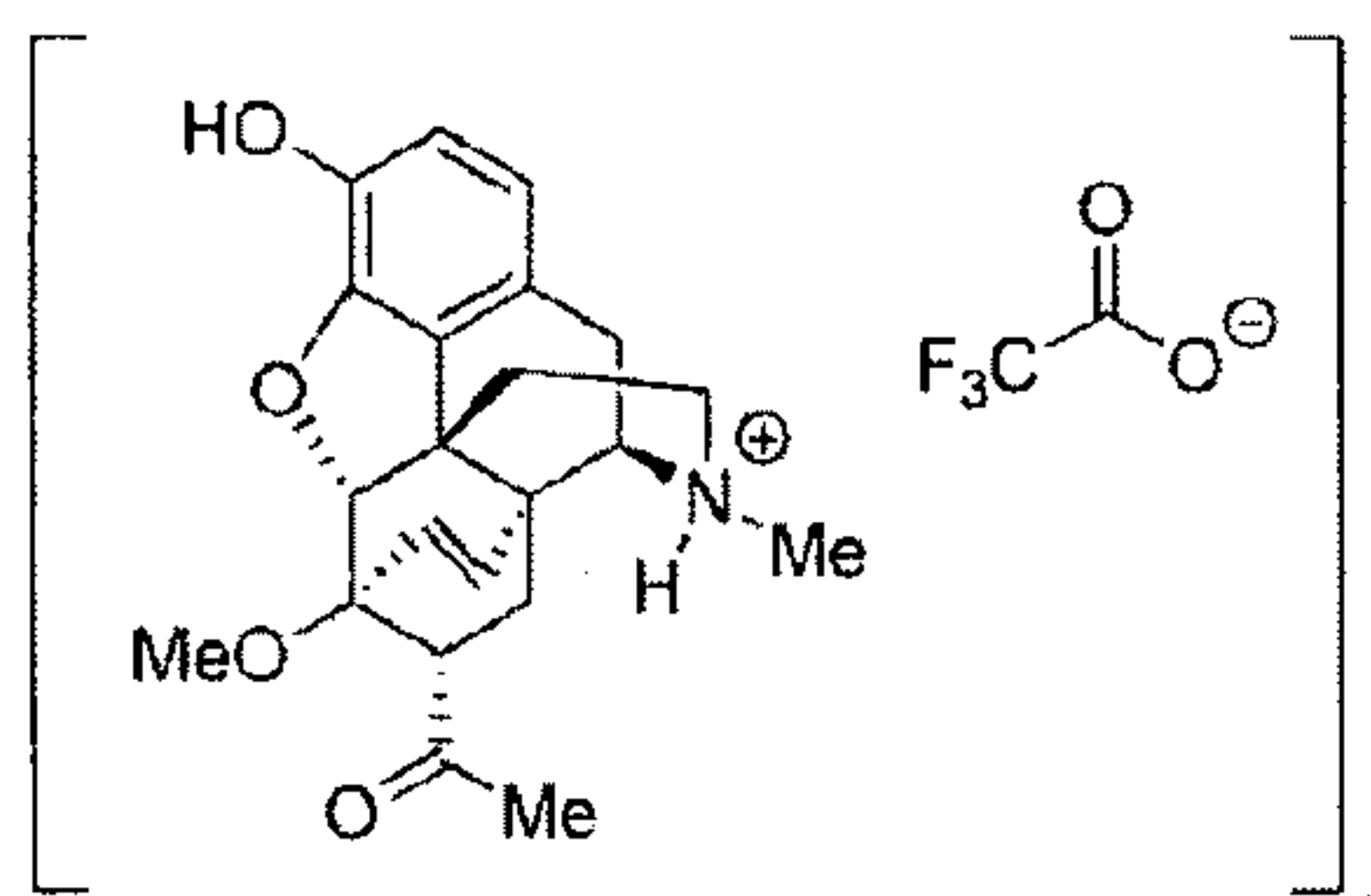
68. The process of any one of claims 55-67, wherein the acid is selected from the group consisting of acetic acid, trifluoroacetic acid, trichloroacetic acid, and tribromoacetic acid.
69. The process of claim 64, wherein the acid is an optionally substituted, saturated or unsaturated aliphatic dicarboxylic acid.
70. The process of claim 64 or 69, wherein the acid is a saturated C₂₋₆ aliphatic dicarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy.
71. The process of any one of claims 64, and 69, wherein the acid is an unsaturated C₂₋₆ aliphatic dicarboxylic acid optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of halogen and hydroxy.
72. The process of any one of claims 64, 69, and 71, wherein the acid is unsaturated, unsubstituted C₂₋₆ aliphatic dicarboxylic acid.
73. The process of any one of claims 64, 69, and 71-72, wherein the acid is fumaric acid or maleic acid.
74. The process of any one of claims 55-73, wherein the acid is used from about 0.5 to about 1.5 equivalents based on the amount of the 7 β -epimer.
75. The process of any one of claims 55-74, wherein the proportion of the 7 β -epimer in the second precipitate is at least 60%, at least 70%, at least 80%, or at least 90%.
76. A compound selected from the group consisting of

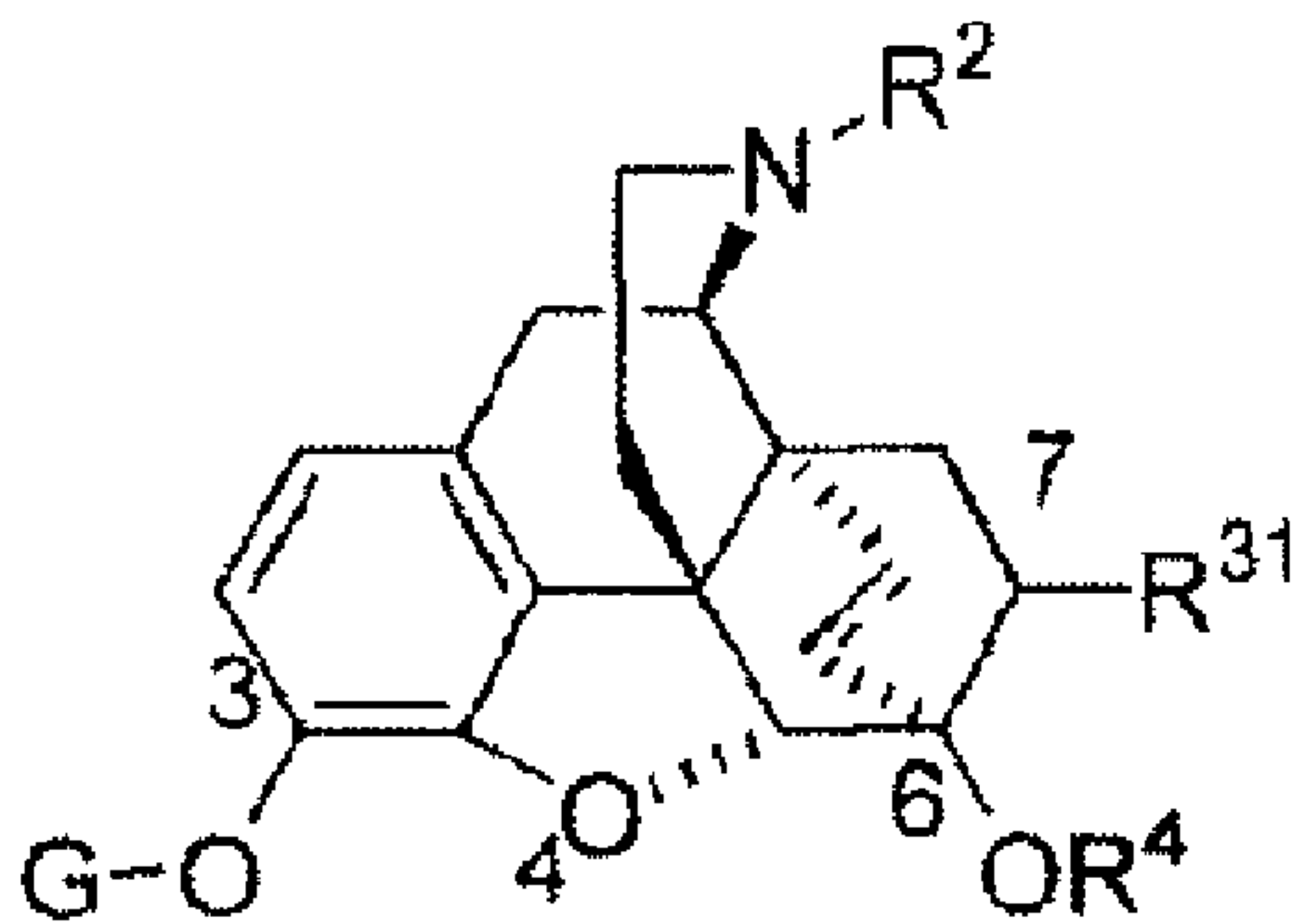


77. A compound selected from the group consisting of



78. A compound of formula:





II