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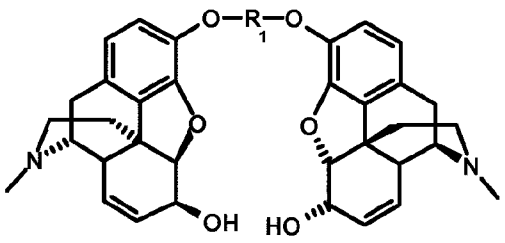
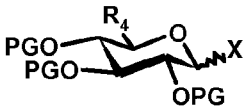
[Suite sur la page suivante]

(54) Title : SYNTHESIS OF MORPHINE-6-GLUCURONIDE OR ONE OF THE DERIVATIVES THEREOF

(54) Titre : SYNTHESE DE MORPHINE-6-GLUCURONIDE OU DE L'UN DE SES DERIVES



(I)



(II)

(57) Abstract : The invention relates to a method for preparing morphine-6-glucuronide or one of the derivatives thereof, comprising the following steps: (i) reacting a compound having formula (I), wherein R_1 represents a carbonyl group, COR_5CO or $SO_2R_6SO_2$ with a glucuronic acid derivative having formula (II) wherein PG represents an acetyl, isobutyryl, benzoyl or pivaloyl group, X represents a trihalogenoacetamidate group and R_4 represents a $(C_1$-$C_4)$alkylcarboxylate group, in the presence of an aromatic solvent and trifluoromethanesulfonyl of trimethylsilane; (ii) reacting the product obtained in step (i) with a strong basic agent; and, subsequently, (iii) recovering the product obtained in step (ii).

(57) Abrégé :

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La présente invention un procédé de préparation de morphine-6-glucuronide ou l'un de ses dérivés comprenant les étapes consistant : (ii) à faire réagir un composé répondant à la formule (I) suivante : dans laquelle : R_1 représente un groupement carbonyle, COR_5CO ou $SO_2R_6SO_2$ avec un dérivé d'acide glucuronique répondant à la formule (II) suivante : dans laquelle : PG représente un groupe acétyle, isobutyryle, benzoyle ou pivaloyle, X représente un groupe trihalogénoacétamidate, et R_4 représente un groupe (C_1-C_4)alkylcarboxylate, en présence d'un solvant aromatique et de trifluorométhanesulfonyle de triméthylsilane (ii) à faire réagir le produit obtenu à l'étape (i) avec un agent basique fort, puis (iii) à récupérer le produit obtenu à l'étape (ii).

SYNTHESIS OF MORPHINE-6-GLUCURONIDE OR ONE OF THE DERIVATIVES THEREOF

FIELD OF THE INVENTION

The present invention relates to a process for preparing morphine-6-glucuronide (M6G) or a derivative thereof.

DESCRIPTION OF THE CONTEXT OF THE INVENTION

Morphine is currently the analgesic the most widely used in the treatment of pain of moderate to strong intensity. This opioid is used in about 80% of cases of post-operative acute pain. Despite its high efficacy, the use of morphine is accompanied by many undesirable side effects, characteristic of opioids, such as respiratory depression, nausea, vomiting, inhibition of intestinal transit, dependence and tolerance (Minoru Nariata et al., *Pharmacol. Et Ther.* **2001**, 89, 1-15).

It is known that morphine undergoes substantial metabolism leading especially to the formation of morphine-6-glucuronide (M6G). This metabolite penetrates poorly into the brain on account of its hydrophilic nature. It has stronger analgesic activity than that presented by morphine via central administration, with a decrease in respiratory depression, nausea and vomiting (Paul et al., *J. Pharmacol. Exp. The* **1989**, *251*, 477-483; Frances et al., *J. Pharmacol. Exp. The* **1992**, *262*, 25-31). Patent application WO 95/05831 describes the use of M6G in oral form for treating pain.

M6G was synthesized in 1968 by Yoshimurai et al. (Yoshimura, H.; Oguri, K.; Tsukamoto, H. *Chem. Pharm. Bull.* **1968**, *16*, 2114-2119). At the industrial scale, this process, which is based on the Koenigs-Knorr principle, is of poor yield. Furthermore, the heavy metals present in trace amount in the final product are difficult to remove. Finally, the silver salts must be recycled. A process for synthesizing M6G via the synthesis of a glycosyl donor in ortho ester form in the presence of lutidinium perchlorate was moreover proposed in patent application WO 99/64430. However, this method only gives a poor glycosylation yield, of about 30%. Moreover, these methods, which involve a glycosylation in

heterogeneous medium with stirring, are difficult to implement at the industrial scale.

Other methods for performing the O-glycosylation have been envisioned, especially via activation in the form of an imidate or a thioaryl. These procedures, which require implementation under particular conditions, namely strictly anhydrous conditions, i.e. a water content of less than 100 ppm, and low temperature, impose major constraints at the industrial level. Furthermore, activation via a thioaryl intermediate generally uses thiophenol, which gives off a nauseating odor that is a problem in the context of implementation at the industrial scale.

There is thus still a need for a process for producing such derivatives at the industrial scale, not only in a high yield but also with a minimum of technical constraints.

The aim of the present invention is to propose a process for preparing M6G or a derivative thereof in a yield of at least 60%, the glycosylation step of which is performed in homogeneous medium, which is tolerant to moisture, i.e. which supports a water content ranging up to 3000 ppm, and which can be performed at a temperature of about 20°C; and/or to propose a process which at least provides the public with a useful choice.

This aim is achieved via the process according to the invention, which comprises the combined use of a glycosyl derivative with trihaloacetimidate as donor of glycosylated derivatives and dimorphine derivatives as acceptor of glycosylated derivatives, making it possible to obtain very good stereoselectivity.

A process with a satisfactory yield that has a minimum of industrial constraints has now been found.

Thus, according to a first aspect, the present invention is directed toward a process for preparing morphine-6-glucuronide or a derivative thereof, comprising the steps of:

reacting a compound corresponding to formula (I) below:

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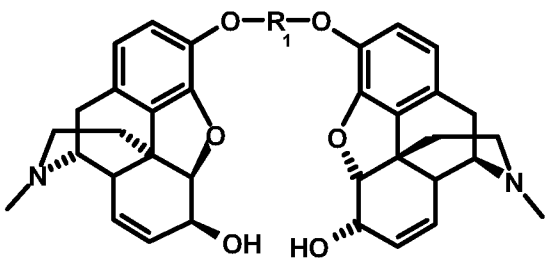
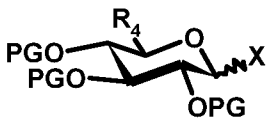


I

in which:

R_1 represents a carbonyl group, COR_5CO in which R_5 represents a group $(C_1\text{-}C_4)$alkane-diyl, $(C_2\text{-}C_4)$alkene-diyl, $(C_2\text{-}C_4)$alkyne-diyl, hetero$(C_1\text{-}C_4)$alkane-diyl, heterocyclo$(C_3\text{-}C_6)$alkane-diyl, $(C_5\text{-}C_{14})$arene-diyl, hetero$(C_4\text{-}C_{10})$arene-diyl, bi$(C_{10}\text{-}C_{16})$arene-oxide-diyl, or bi$(C_{10}\text{-}C_{16})$arene-diyl, $SO_2R_6SO_2$ in which R_6 represents a group $(C_1\text{-}C_4)$alkane-diyl, $(C_2\text{-}C_4)$alkene-diyl, $(C_2\text{-}C_4)$alkyne-diyl, hetero$(C_1\text{-}C_4)$alkane-diyl, heterocyclo$(C_3\text{-}C_6)$alkane-diyl, $(C_5\text{-}C_{14})$arene-diyl, hetero$(C_4\text{-}C_{10})$arene-diyl, bi$(C_{10}\text{-}C_{16})$arene-oxide-diyl or bi$(C_{10}\text{-}C_{16})$arene-diyl,

with a glucuronic acid derivative corresponding to formula (II) below:



(II)

in which:

PG represents an acetyl, isobutyryl, benzoyl or pivaloyl group,

X represents a trihaloacetimidate group, and

R_4 represents a group $(C_1\text{-}C_4)$alkylcarboxylate,

in the presence:

- of an aromatic solvent that is unsubstituted or substituted with one or more substituents chosen from the group formed by a halogen atom, a group $(C_1\text{-}C_4)$alkyl and a group $(C_1\text{-}C_4)$alkyloxy, said solvent having a melting point of less than or equal to - 20°C, and

- of trimethylsilyl trifluoromethanesulfonate

(ii) reacting the product obtained in step (i) with a strong basic agent, and then

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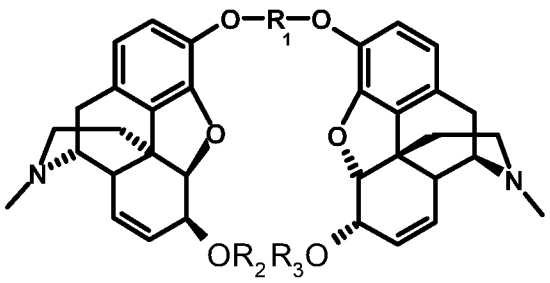
(iii) recovering the product obtained in step (ii).

A subject of the present invention is also the compounds corresponding to formula (III) below

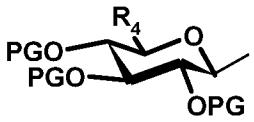


(III)

in which:

R_1 is as defined previously,

R_2 and R_3 independently represent a group PG as defined previously or a group corresponding to formula (IV) below:



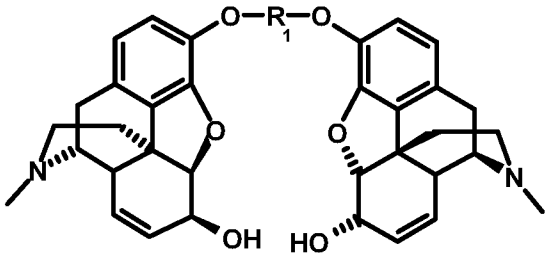
(IV)

in which:

R_4 and PG are as defined previously,

with the proviso that at least one from among R_2 and R_3 represents a group of formula (IV).

Described are compounds corresponding to formula (I) below:



I

in which:

R_1 is as defined previously.

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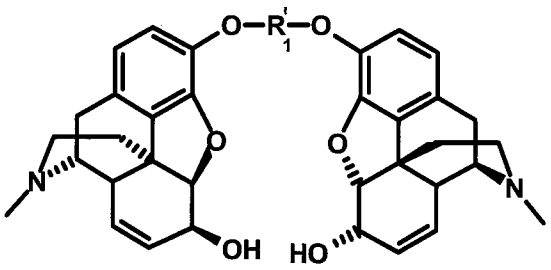
A subject of the present invention is also compounds corresponding to formula (I') below:



(I')

in which:

R'$_1$ represents a carbonyl group, COR'$_5$CO in which R'$_5$ represents a group (C_2-C_4)alkene-diyl, (C_2-C_4)alkyne-diyl, hetero(C_1-C_4)alkane-diyl, heterocyclo(C_3-C_6)alkane-diyl, (C_5-C_{14})arene-diyl, bi(C_{10}-C_{16})arene-oxide-diyl, bi(C_{10}-C_{16})arene-diyl, or hetero(C_4-C_{10})arene-diyl, $SO_2R_6SO_2$ in which R_6 represents a group (C_1-C_4)alkane-diyl, (C_2-C_4)alkene-diyl, (C_2-C_4)alkyne-diyl, hetero(C_1-C_4)alkane-diyl, heterocyclo(C_3-C_6)alkane-diyl, (C_5-C_{14})arene-diyl, hetero(C_4-C_{10})arene-diyl, bi(C_{10}-C_{16})arene-oxide-diyl or bi(C_{10}-C_{16})arene-diyl.

The present invention also provides a morphine-6-glucuronide or a derivative thereof when prepared by a process of the invention.

In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

In the description in this specification reference may be made to subject matter that is not within the scope of the claims of the current application. That subject matter should be readily identifiable by a person skilled in the art and may assist in putting into practice the invention as defined in the claims of this application.

DEFINITIONS

In the context of the present invention, the following definitions apply:

- a group PG: a protecting group that makes it possible, firstly, to protect a reactive function such as a hydroxyl or an amine during a synthesis, and, secondly, to regenerate the intact reactive function at the end of the synthesis; examples of protecting groups and of protection and deprotection methods are given in "Protective Groups in Organic Synthesis", Greene et al., 2nd Edition (John Wiley & Sons, Inc., New York), 1991; mention will be made in particular of acetyl, isobutyryl, benzoyl and pivaloyl groups;
- a halogen atom: a fluorine atom, a chlorine atom, a bromine atom or an iodine atom;
- a group (C_1-C_4)alkyl: a substituted or unsubstituted, linear or branched saturated aliphatic group containing from 1 to 4 carbon atoms; examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, etc. groups;
- a hydroxyl group: a group –OH;
- a group (C_1-C_4)alkyloxy: a group -O-(C_1-C_4)alkyl in which the group (C_1-C_4)alkyl is as defined previously;
- a carbonyl group, a group C=O;
- a group (C_1-C_4)alkane-diyl, a substituted or unsubstituted, linear, branched or cyclic divalent saturated aliphatic group, containing from 1 to 4 carbon atoms; examples that may be mentioned include methane-diyl (-CH_2-), ethane-diyl (-CH_2-CH_2-), propane-2,3-diyl (-$CH(CH_3)CH_2$-), propane-1,3-diyl (-CH_2-CH_2-CH_2-); etc. groups;

- a group (C_2-C_4)alkene-diyl, a linear or branched, monounsaturated or polyunsaturated divalent aliphatic group, containing from 2 to 4 carbon atoms, comprising, for example, one or two ethylenic unsaturations; examples that may be mentioned include ethene-diyl (-CH=CH-), 1-propene-1,3-diyl (-CH_2-CH=CH-), etc. groups;

- a group (C_2-C_4)alkyne-diyl, a linear or branched, monounsaturated or

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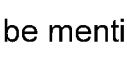
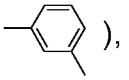
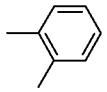
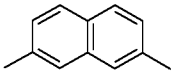
polyunsaturated divalent aliphatic group, containing from 2 to 4 carbon atoms, comprising, for example, one or two acetylenic unsaturations; examples that may be mentioned include ethyne-diyl (-C≡C-) and 1-propyne-1,3-diyl (-C≡C-CH2-) groups;

- a group (C_5-C_{14})arene-diyl, a substituted or unsubstituted divalent cyclic aromatic group preferably containing between 5 and 14 carbon atoms;

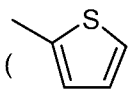
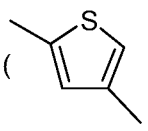
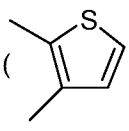
examples that may be mentioned include the groups (), (),

(), ()

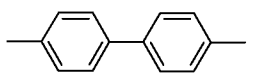
- a group hetero(C_1-C_4)alkane-diyl, a substituted or unsubstituted alkane-diyl group, as defined above, preferably containing between 1 and 4 carbon atoms, comprising one or more heteroatoms, such as nitrogen, oxygen or sulfur; an example that may be mentioned is the ether oxide-diyl group;

- a group heterocyclo(C_3-C_6)alkane-diyl, a substituted or unsubstituted group cyclo(C_3-C_6)alkane-diyl, as defined above, preferably containing between 3 and 6 carbon atoms, comprising one or more heteroatoms, such as nitrogen, oxygen or sulfur; examples that may be mentioned include oxirane-diyl, aziridine-diyl, thirane-diyl and pyran-diyl groups;

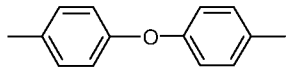
- a group hetero(C_4-C_{10})arene-diyl, a divalent cyclic aromatic group preferably containing between 4 and 10 carbon atoms and comprising one or more heteroatoms, such as nitrogen, oxygen and sulfur; examples that may be mentioned include the groups

() , () , ();

- a group bi(C_{10}-C_{16})arene-diyl, a divalent group comprising two aromatic rings, each possibly being independently substituted or unsubstituted, preferably containing from 10 to 16 carbon atoms; mention may be made of the group

(),

a group bi(C_{10}-C_{16})arene-oxide-diyl, a divalent group comprising two aromatic rings, each independently substituted or unsubstituted, containing from

10 to 16 carbon atoms; an example that may be mentioned is the group (), and

- a group -(C_1-C_4)alkylcarboxylate, a group -CO-O-(C_1-C_4)alkyl, the group (C_1-C_4)alkyl being as defined above.

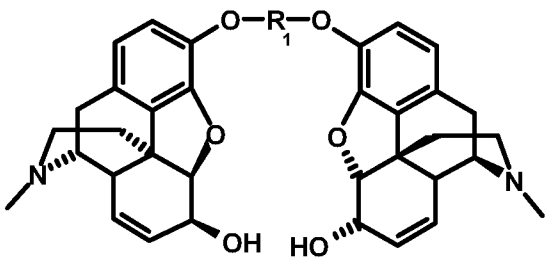
The expression "strong basic agent" denotes, in a manner known to those skilled in the art, any basic agent that fully dissociates in neutral aqueous solution or that has at least a high degree of dissociation in neutral aqueous solution. The expression "strong basic agent" in particular denotes sodium hydroxide, potassium hydroxide, lithium hydroxide and ammonium hydroxide.

- The term "room temperature" means a temperature ranging from 20 to 25°C.

- The term "comprising" as used in this specification means "consisting at least in part of". When interpreting each statement in this specification that includes the term "comprising", features other than that or those prefaced by the term may also be present. Related terms such as "comprise" and "comprises" are to be interpreted in the same manner.

DETAILED DESCRIPTION OF THE INVENTION

Compound of formula (I)



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in which:

R_1 represents a carbonyl group, COR_5CO in which R_5 represents a group (C_1-C_4)alkane-diyl, (C_2-C_4)alkene-diyl, (C_2-C_4)alkyne-diyl, hetero(C_{x1}-C_{y1})alkane-diyl, heterocyclo(C_3-C_6)alkane-diyl, (C_5-C_{14})arene-diyl, hetero(C_4-C_{10})arene-diyl

bi(C_{10}-C_{16})arene-oxide-diyl or bi(C_{10}-C_{16})arene-diyl, $SO_2R_6SO_2$ in which R_6 represents a group (C_1-C_4)alkane-diyl, (C_2-C_4)alkene-diyl, (C_2-C_4)alkyne-diyl, hetero(C_1-C_4)alkane-diyl, heterocyclo(C_3-C_6)alkane-diyl, (C_5-C_{14})arene-diyl, hetero(C_4-C_{10})arene-diyl, bi(C_{10}-C_{16})arene-oxide-diyl or bi(C_{10}-C_{16})arene-diyl.

Among the compounds of formula (I), mention may be made in particular of:

- dimorphin-3-yl terephthalate,
- dimorphin-3-yl isophthalate,

- dimorphin-3-yl phthalate,
- dimorphin-3-yl fumarate,
- dimorphin-3-yl benzene-1,2-disulfonate,
- dimorphin-3-yl benzene-1,3-disulfonate,
- dimorphin-3-yl thiophene-2,5-dicarboxylate,
- dimorphin-3-yl naphthalene-2,7-dicarboxylate,
- dimorphin-3-yl 4,4'-oxybenzoate,
- dimorphin-3-yl biphenyl-4,4'-dicarboxylate, and
- dimorphin-3-yl carbonate.

The compound of formula (I) as defined previously may be prepared according to various processes, especially by esterification of the phenol group of morphine with a dicarboxylic acid and removal of the water by azeotropic distillation.

It may also be prepared according to the process described below.

According to one particular embodiment of the process of the present invention, it comprises, prior to step (i), the steps consisting in reacting a compound of formula R_1Cl_2 in which R_1 is as defined previously, with morphine in a two-phase medium comprising at least water, a strong basic agent and an aromatic solvent that is unsubstituted or substituted with one or more substituents chosen from the group formed by a halogen atom, a group $(C_1$-$C_4)$alkyl and a group $(C_1$-$C_4)$alkyloxy, said solvent having a melting point of less than or equal to -20°C.

In this procedure for preparing a compound of formula (I), the morphine is preferably introduced in excess relative to the compound of formula R_1Cl_2, for example in a mole ratio of 2.2 mol of morphine per 1 mol of compound R_1Cl_2.

The strong basic agent used may be sodium hydroxide.

Among the solvents that may be used in the process as defined above mention may be made in particular of chlorobenzene, toluene, 1,2-dichlorobenzene, 1,3,5-trifluorobenzene and mesitylene. Chlorobenzene is advantageously used, as it offers the best solubilization of the reagents.

Advantageously, the mixture of morphine and water is first prepared, and the strong basic agent is added thereto in an amount making it possible to obtain a pH greater than or equal to 10. The mixture is stirred until a homogeneous solution

is obtained. The solvent and the compound of formula R_1Cl_2 are added to this uniform solution, preferably slowly and with vigorous stirring so as to enable the phase transfer.

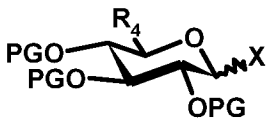
A subject of the present invention is also the compounds corresponding to formula (I'), in which

R'_1 represents a carbonyl group, COR'_5CO in which R'_5 represents a group $(C_2\text{-}C_4)$alkene-diyl, $(C_2\text{-}C_4)$alkyne-diyl, hetero$(C_1\text{-}C_4)$alkane-diyl, heterocyclo$(C_3\text{-}C_6)$alkane-diyl, $(C_5\text{-}C_{14})$arene-diyl, bi$(C_{10}\text{-}C_{16})$arene-oxide-diyl, bi$(C_{10}\text{-}C_{16})$arene-diyl, or hetero$(C_4\text{-}C_{10})$arene-diyl, $SO_2R_6SO_2$ in which R_6 represents a group $(C_1\text{-}C_4)$alkane-diyl, $(C_2\text{-}C_4)$alkene-diyl, $(C_2\text{-}C_4)$alkyne-diyl, hetero$(C_1\text{-}C_4)$alkane-diyl, heterocyclo$(C_3\text{-}C_6)$alkane-diyl, $(C_5\text{-}C_{14})$arene-diyl, hetero$(C_4\text{-}C_{10})$arene-diyl, bi$(C_{10}\text{-}C_{16})$arene-oxide-diyl or bi$(C_{10}\text{-}C_{16})$arene-diyl.

These compounds are useful as intermediates for synthesizing M6G or derivatives thereof.

Compound of formula (II)

Glucuronic acid derivative corresponding to formula (II) below:



(II)

in which:

PG represents an acetyl, isobutyryl, benzoyl or pivaloyl group,

X represents a trihaloacetimidate group, and

R_4 represents a group $(C_{x1}\text{-}C_{y1})$alkylcarboxylate.

Among the glucuronic acid derivatives of formula (II), mention may be made in particular of those having one or more of the following characteristics:

- PG represents an acetyl group,
- X represents a group $-OCNHCl_3$ or a group $-OCNPhCF_3$, and
- R_4 represents a methylcarboxylate group.

According to one particular embodiment of the process according to the invention, the glucuronic acid derivative of formula (II) is methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate.

The compound of formula (II) may be prepared according to various processes that are well known to those skilled in the art.

For example, methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate may be synthesized according to the process described in Scheme 1 below:

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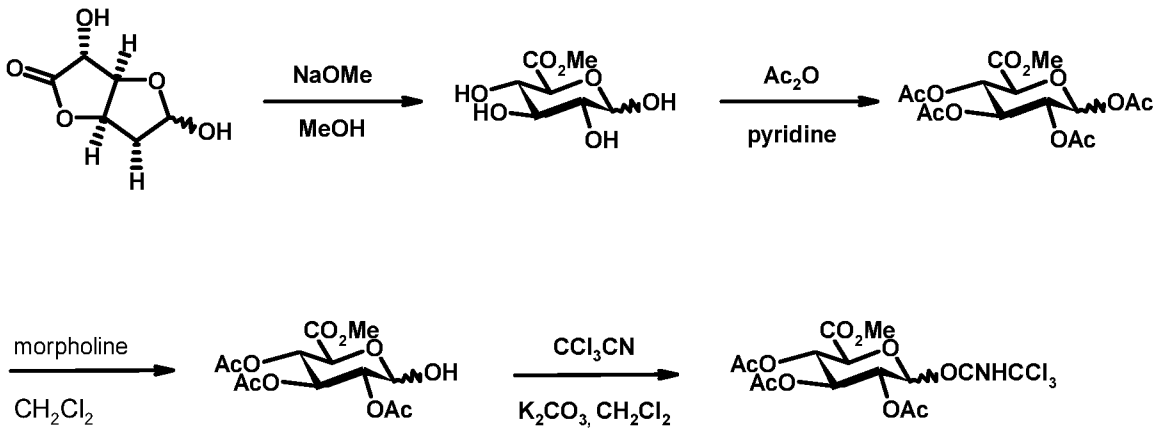
Scheme 1



Such synthetic processes are described especially in Chem. Pharm. Bull. 53 (6) 684-687 (2005) for 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate, in J. Chem. Soc. Perkin Trans. 1 1995 for the tri-O pivaloyl derivative, and in Liebigs Ann. Chem. 1983, 570-574 for the tri-O-benzoate derivative.

Parameters of step (i)

As indicated previously, in the process of the invention, in step (i), a compound of formula (I) is reacted with a glucuronic acid derivative of formula (II) in the presence of an aromatic solvent and trimethylsilyl trifluoromethanesulfonate.

Among the aromatic solvents as defined previously that may be used, mention may be made in particular of chlorobenzene, toluene, 1,2-dichlorobenzene, 1,3,5-trifluorobenzene and mesitylene. Chlorobenzene is in particular advantageously used during step (i) and during the preparation of the compound of formula (I) as indicated previously.

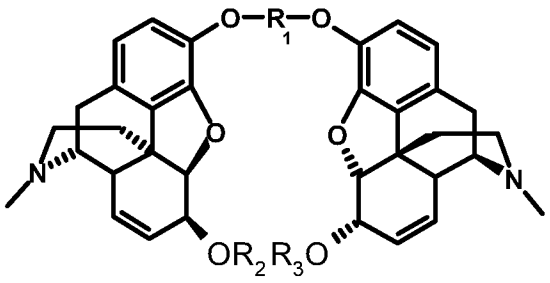
According to one particular embodiment, the mole ratio of said derivative of formula (II) to said compound of formula (I) is between 2 and 5 and is in particular 4.

The reaction is performed in the presence of a weak Lewis acid, trimethylsilyl trifluoromethanesulfonate (TMSOTf).

The mole ratio of the TMSOTf to the compound of formula (I) is between 2.2 and 20 and is in particular 3.1.

According to one particular embodiment, the TMSOTf is introduced in two stages: a first portion is introduced into the solution of the product of formula (I) in the aromatic solvent prior to the addition of the glucuronic acid derivative, in order to salify the two nitrogens of the compound of formula (I), and the remaining portion is then introduced after the addition of the glucuronic acid derivative in order to perform the O-glycosylation.

Performing step (i) leads to the formation of the compound corresponding to formula (III) below:

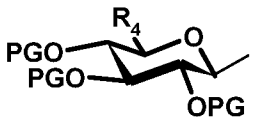


(III)

in which:

R_1 is as defined previously,

R_2 and R_3 independently represent a group PG as defined previously or a group corresponding to formula (IV) below:



(IV)

in which:

R_4 and PG are as defined previously,

with the proviso that at least one from among R_2 and R_3 represents a group of formula (IV).

A subject of the present invention is also the compounds corresponding to formula (III) as defined previously. These compounds are useful as intermediates for the synthesis of M6G or derivatives thereof.

Preferably, R_2 and R_3 both represent a group of formula (IV).

Among the compounds of formula (III) that are subjects of the invention, a first group of compounds has one or more of the following characteristics:

- R_1 represents a terephthaloyl group,

- at least one from among R_2 and R_3 represents a group of formula (IV) in which R_4 is a methyl 2,3,4-tri-O-acetyl-β-D-glucuropryranosyluronate group and PG is an acetyl group.

Among these compounds, mention may be made in particular of:

- 6-*O*-acetylmorphin-3-yl 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-gluco-pyranosyluronate)morphin-3-yl terephthalate, and

- bis[6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphin-3-yl] terephthalate.

Parameters of step (ii)

As indicated previously, the product obtained in step (i), i.e. the compound of formula (III), is reacted with a strong basic agent.

According to one particular embodiment, prior to the addition of the strong basic agent, the aromatic solvent is removed, according to methods known to those skilled in the art, for example by extracting the organic phase, optionally ending with evaporation under reduced pressure.

Generally, the compound of formula (III) is then dissolved in an aqueous-alcoholic mixture, for example in a methanol/water mixture, in a ratio ranging from 20/80 to 80/20, with stirring, until a uniform mixture is obtained.

This mixture is generally cooled to a temperature of less than or equal to 5°C.

The strong basic agent is then introduced into the mixture generally in an amount allowing a pH of greater than or equal to 10 and in particular greater than or equal to 12.5 to be obtained, preferably while maintaining the temperature at not more than 5°C.

According to one particular embodiment, the strong basic agent is sodium hydroxide.

The mixture obtained may then be heated, for example to 20°C, for a time that is sufficient to complete the reaction, for example for one hour.

When it is desired to obtain M6G or a derivative thereof in base form, the mixture, cooled beforehand, for example to a temperature of less than or equal to 5°C, is acidified so that it has a pH less than the pK_a of the product to be

synthesized, for example to pH 5.6. This acidification may be performed in particular by adding hydrochloric acid.

The mixture obtained may then be heated, for example to 20°C, for a time that is sufficient to complete the reaction, for example for 30 minutes.

Parameters of step (iii)

The product obtained after step (ii) may be recovered in the form as obtained, i.e. in crude form, for example by filtration and then concentration of the filtrate under vacuum.

Advantageously, it may be recovered in purified form, which may be performed according to any purification method known to those skilled in the art, in particular by desalting, where appropriate followed by one or more steps of adsorption and desorption on ion-exchange resins and then optionally one or more dissolution/evaporation/crystallization cycles.

In order to reduce the salt content for the purpose especially of removing the residual sodium acetate and sodium terephthalate, the filtrate may, for example, be resuspended in alcohol, in particular in methanol, under conditions allowing the dissolution of the M6G or derivatives thereof, for example at 50°C for 3 hours, and the mixture obtained may then be filtered to remove the solid particles and the residue obtained may be dried, for example by evaporation under reduced pressure.

The purification may be continued using ion-exchange resins. According to one particular embodiment, the residue obtained previously is resuspended in demineralized water, and the suspension is then acidified to a pH of between 2 and 4 and in particular greater than or equal to 3, for example by adding sulfuric acid, and is filtered, and the filtrate is placed in contact with a cationic resin under conditions allowing the adsorption of the M6G or derivative thereof, for example with stirring at 20°C for 30 minutes, and is then filtered. These operations are repeated until the filtrate is depleted of M6G or the derivative thereof. The resins are then desorbed with a basic solution, for example with aqueous ammonia. The basic solution obtained is acidified to a pH of between 5 and 7 and in particular 6, and is then dried, for example by evaporation under reduced pressure.

Finally, this residue is resuspended in an aqueous-alcoholic mixture, for example in a methanol/water mixture, in a ratio ranging from 20/80 to 80/20, heated under conditions allowing its total dissolution, for example at reflux for 30 minutes, and the homogeneous mixture is then cooled slowly, for example to 0°C over 2 hours, the first crystals appearing at 35°C.

The crystals are isolated, for example on a sinter funnel, washed, for example with methanol, and finally dried, for example by heating and evaporating under vacuum.

The invention is illustrated in a nonlimiting manner by the examples below.

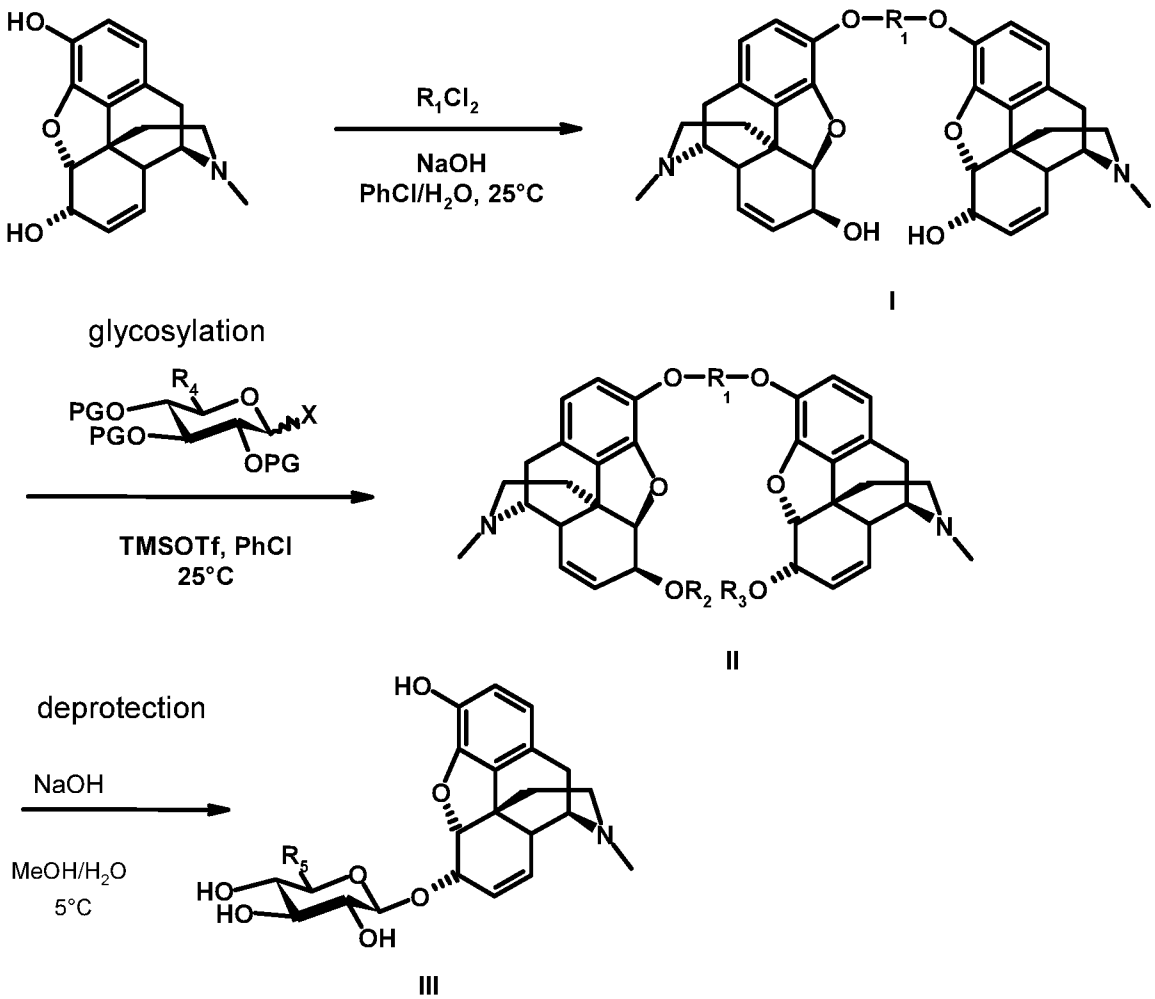
EXAMPLES

Synthesis

Scheme 2 describes the synthesis of the intermediate compounds of formulae (I) and (III) and also of M6G and derivatives thereof.

In Scheme 2, the starting compounds and the reagents, when their mode of preparation is not described, are commercially available or described in the literature, or else may be prepared according to methods that are described therein or that are known to those skilled in the art.

Scheme 2



The examples that follow describe the preparation of certain compounds in accordance with the invention. These examples are not limiting, and serve merely to illustrate the present invention.

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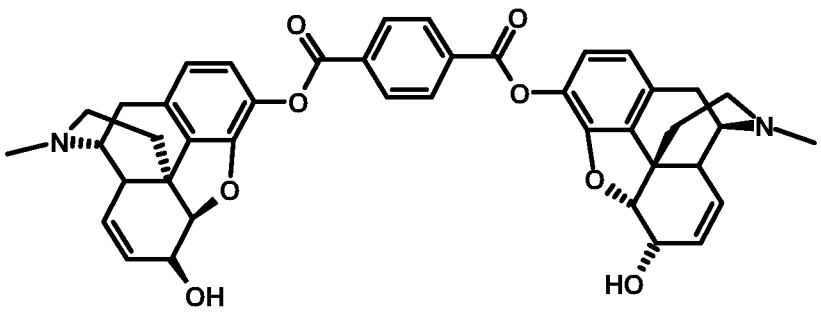
Preparation of compounds of formula (I)

Example 1- Dimorphin-3-yl terephthalate



Terephthaloyl chloride (12.0 g, 0.0594 mol) is added portionwise over 2.5 hours to a solution of morphine monohydrate (40.0 g, 0.132 mol) in 0.66N sodium hydroxide (300 mL, 0.198 mol) and chlorobenzene (300 mL), at room temperature. The reaction medium is stirred for 15 minutes after the end of the addition.

The precipitate formed is filtered off and reslurried in a chlorobenzene/0.66 N sodium hydroxide mixture (300 mL/300 mL) and then washed with water (3 × 250 mL) to obtain the dimorphin-3-yl terephthalate in the form of white crystals (38.2 g, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 4H, *CH-terephtalate*), 6.87 (d, 2H, *J* 8.0 Hz, H-1), 6.67 (d, 2H, *J* 8.0 Hz, H-2), 5.83 (m, 2H, H-8), 5.32 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.0 Hz, H-5), 4.20 (m, 2H, H-6), 3.40 (m, 2H, H-9), 3.10 (m, 2H, H-10a), 2.74 (m, 2H, H-14), 2.67-2.61 (m, 2H, H-16a), 2.47 (s, 6H, N*CH$_3$*), 2.42-2.31 (m, 4H, H-10b, H-16b), 2.13-2.05 (m, 2H, H-15a), 1.96-1.92 (m, 2H, H-15b).

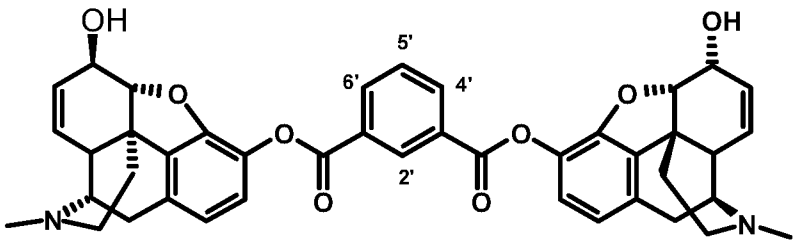
^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C=O), 148.8 (C-*ipso*), 134.3 (C-8), 130.5 (CH-*terephtalate*), 129.7, 128.6 (C-*ipso*), 127.8 (C-7), 126.4 (C-*ipso*), 121.1 (C-1), 120.0 (C-2), 92.5 (C-5), 65.9 (C-6), 58.9 (C-9), 46.4 (C-16), 43.1 (N*CH$_3$*), 42.7 (C-13), 40.5 (C-14) 35.3 (C-15), 20.9 (C-10).

High Resolution Mass (ES)

- Calculated for $C_{42}H_{42}N_2O_8$ $[M+H_2]^{2+}$: m/z = 351.1471
- Found: m/z = 351.1467

The compounds of Examples 2 to 11 below were prepared in the same manner.

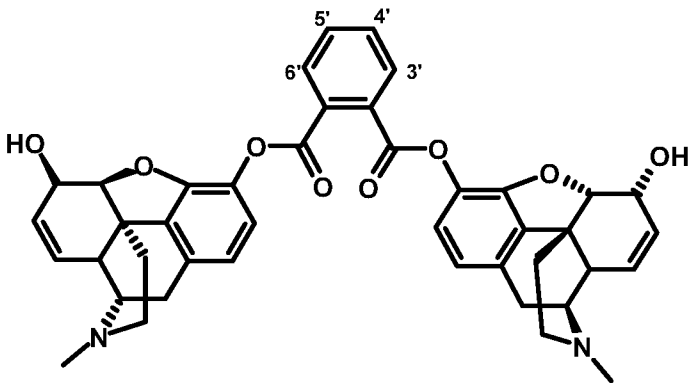
Example 2- Dimorphin-3-yl isophthalate



^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (t, 1H, *J* 1.5 Hz, H-2'), 8.44 (dd, *J* 1.5 Hz, *J* 8.0 Hz, H-4', H-6'), 7.66 (t, 1H, *J* 8.0 Hz, H-5'), 6.87 (d, 2H, *J* 8.0 Hz, H-1), 6.67 (d, 2H, *J* 8.0 Hz, H-2), 5.83 (m, 2H, H-8), 5.32 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.0 Hz, H-5), 4.20 (m, 2H, H-6), 3.40 (m, 2H, H-9), 3.09 (m, 2H, H-10a), 2.72 (m, 2H, H-14), 2.66-2.60 (m, 2H, H-16a), 2.47 (s, 6H, N*CH*$_3$), 2.43-2.30 (m, 4H, H-10b, H-16b), 2.15-2.04 (m, 2H, H-15a), 1.95-1.91 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$=701.6

Example 3- Dimorphin-3-yl phthalate

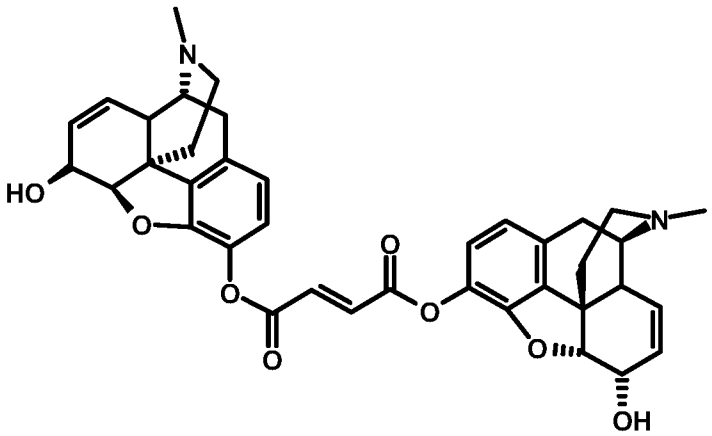


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 2H, *J* 3.5Hz, *J* 6.0 Hz, H-3', H-6'), 7.67 (dd, *J* 3.5 Hz, *J* 6.0 Hz, H-4', H-5'), 6.87 (d, 2H, *J* 8.0 Hz, H-1), 6.59 (d, 2H, *J*

8.0 Hz, H-2), 5.74 (m, 2H, H-8), 5.29 (m, 2H, H-7), 4.81 (d, 2H, *J* 6.5 Hz, H-5), 4.15 (m, 2H, H-6), 3.37 (m, 2H, H-9), 3.06 (m, 2H, H-10a), 2.70 (m, 2H, H-14), 2.61-2.56 (m, 2H, H-16a), 2.44 (s, 6H, N*CH*$_3$), 2.42-2.27 (m, 4H, H-10b, H-16b), 2.08-2.05 (m, 2H, H-15a), 1.80 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 701.6

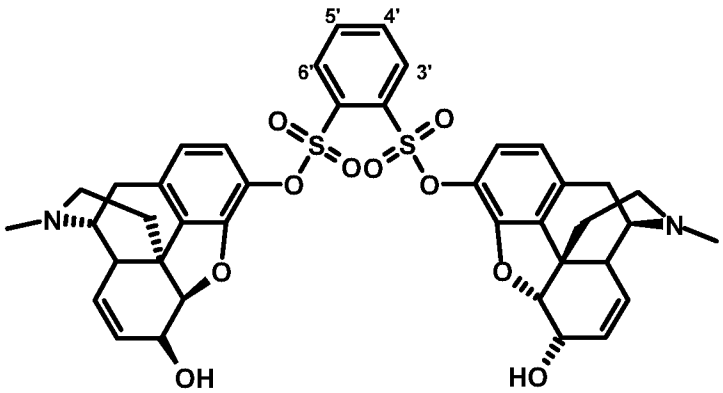
Example 4- Dimorphin-3-yl fumarate



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 2H, *CH*COO), 6.81 (d, 2H, *J* 8.0 Hz, H-1), 6.64 (d, 2H, *J* 8.0 Hz, H-2), 5.78 (m, 2H, H-8), 5.30 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.0 Hz, H-5), 4.19 (m, 2H, H-6), 3.42 (m, 2H, H-9), 3.08 (m, 2H, H-10a), 2.74 (m, 2H, H-14), 2.69-2.63 (m, 2H, H-16a), 2.47 (s, 6H, N*CH*$_3$), 2.42-2.30 (m, 4H, H-10b, H-16b), 2.16-2.06 (m, 2H, H-15a), 1.92 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 651.6

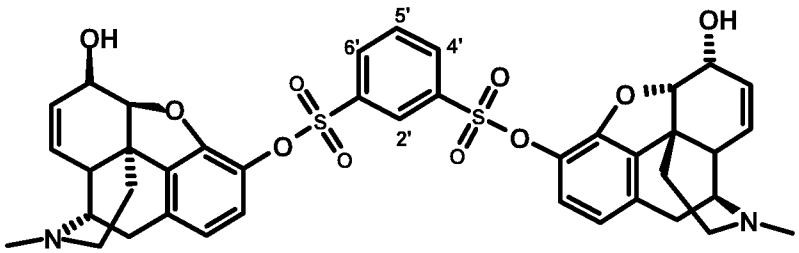
Example 5- Dimorphin-3-yl benzene-1,2-disulfonate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (dd, 2H, *J* 3.5 Hz, *J* 6.0 Hz, H-3', H-6'), 7.77 (dd, *J* 3.5 Hz, *J* 6.0 Hz, H-4', H-5'), 6.79 (d, 2H, *J* 8.5 Hz, H-1), 6.51 (d, 2H, *J* 8.5 Hz, H-2), 5.69 (m, 2H, H-8), 5.22 (m, 2H, H-7), 4.81 (d, 2H, *J* 6.5 Hz, H-5), 4.15 (m, 2H, H-6), 3.35 (m, 2H, H-9), 3.02 (m, 2H, H-10a), 2.65 (m, 2H, H-14), 2.60-2.54 (m, 2H, H-16a), 2.41 (s, 6H, N*CH*$_3$), 2.40-2.22 (m, 4H, H-10b, H-16b), 2.05-2.00 (m, 2H, H-15a), 1.77-1.72 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 773.6

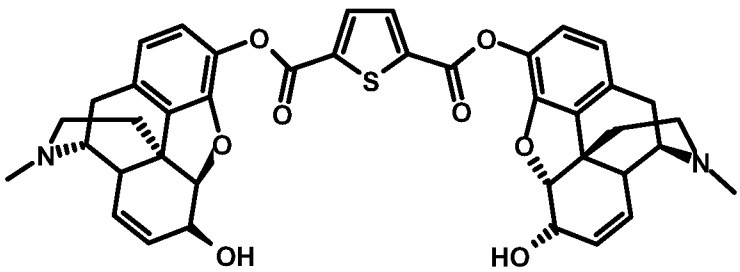
Example 6- Dimorphin-3-yl benzene-1,3-disulfonate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (m, 3H, H-2', H-4', H-6'), 7.78 (t, 1H, *J* 8.5 Hz, H-5'), 6.51 (m, 4H, H-1, H-2), 5.66 (m, 2H, H-8), 5.27 (m, 2H, H-7), 4.85 (d, 2H, *J* 6.5 Hz, H-5), 4.15 (m, 2H, H-6), 3.34 (m, 2H, H-9), 3.03 (m, 2H, H-10a), 2.65 (m, 2H, H-14), 2.61-2.55 (m, 2H, H-16a), 2.42 (s, 6H, N*CH*$_3$), 2.35-2.24 (m, 4H, H-10b, H-16b), 2.09-1.99 (m, 2H, H-15a), 1.79-1.75 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$=773.6

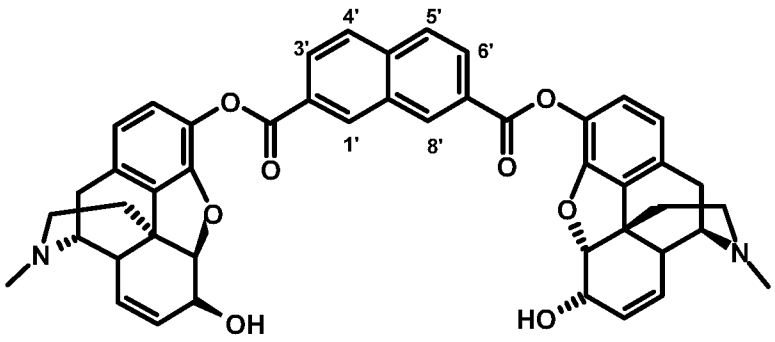
Example 7- Dimorphin-3-yl thiophene-2,5-dicarboxylate



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 2H, *CH-thiophene*), 6.86 (d, 1H, *J* 8.0 Hz, H-1), 6.66 (d, 2H, *J* 8.0 Hz, H-2), 5.79 (m, 2H, H-8), 5.30 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.5 Hz, H-5), 4.18 (m, 2H, H-6), 3.40 (m, 2H, H-9), 3.09 (m, 2H, H-10a), 2.75 (m, 2H, H-14), 2.68-2.62 (m, 2H, H-16a), 2.41 (s, 6H, N*CH$_3$*), 2.40-2.30 (m, 4H, H-10b, H-16b), 2.14-2.05 (m, 2H, H-15a), 1.95-1.90 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 708.6

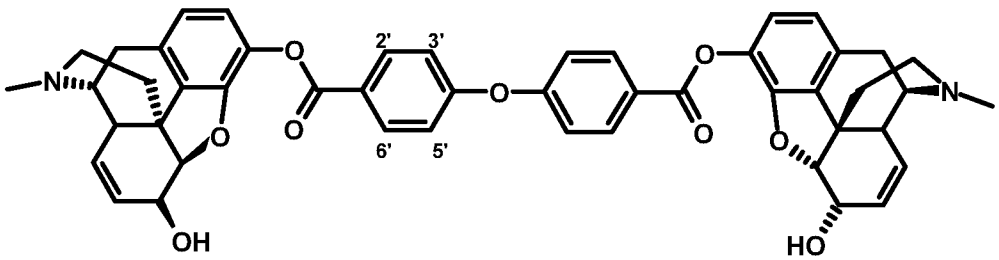
Example 8- Dimorphin-3-yl naphthalene-2,7-dicarboxylate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 2H, H-1', H-8'), 8.27 (dd, *J* 1.5 Hz, *J* 8.5 Hz, 2H, H-3', H-6'), 8.08 (d, 2H, *J* 8.5 Hz, H-4', H-5'), 6.92 (d, 1H, *J* 8.0 Hz, H-1), 6.69 (d, 2H, *J* 8.0 Hz, H-2), 5.84 (m, 2H, H-8), 5.34 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.5 Hz, H-5), 4.20 (m, 2H, H-6), 3.40 (m, 2H, H-9), 3.11 (m, 2H, H-10a), 2.74 (m, 2H, H-14), 2.68-2.61 (m, 2H, H-16a), 2.47 (s, 6H, N*CH$_3$*), 2.44-2.32 (m, 4H, H-10b, H-16b), 2.14-2.05 (m, 2H, H-15a), 1.96-1.90 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$=751.6

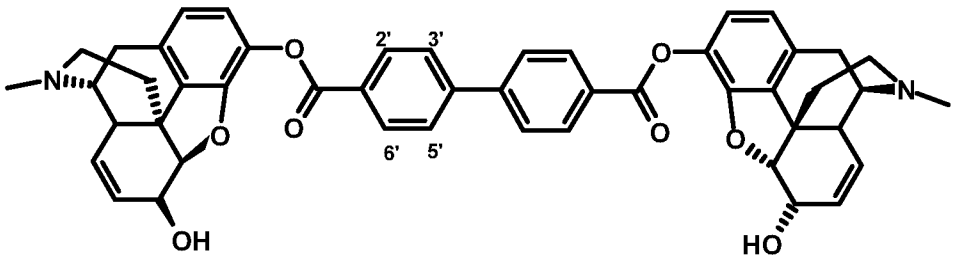
Example 9 - Dimorphin-3-yl 4,4'-oxybenzoate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 4H, *J* 8.5 Hz, H-2', H-6'), 7.14 (d, 4H, *J* 8.5 Hz, H-3', H-5'), 6.87 (d, 2H, *J* 8.5 Hz, H-1), 6.67 (d, 2H, *J* 8.5 Hz, H-2), 5.82 (m, 2H, H-8), 5.31 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.5 Hz, H-5), 4.20 (m, 2H, H-6), 3.40 (m, 2H, H-9), 3.10 (m, 2H, H-10a), 2.73 (m, 2H, H-14), 2.66-2.61 (m, 2H, H-16a), 2.42 (s, 6H, N*CH*$_3$), 2.40-2.30 (m, 4H, H-10b, H-16b), 2.18-2.10 (m, 2H, H-15a), 1.95-1.90 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 793.5

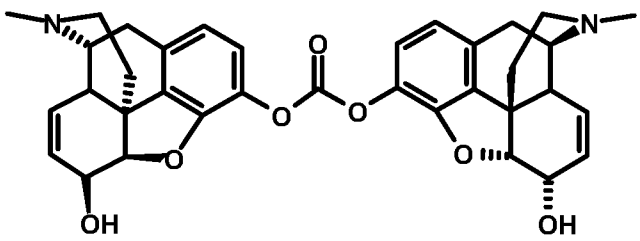
Example 10- Dimorphin-3-yl biphenyl-4,4'-dicarboxylate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, 4H, *J* 8.0 Hz, H-2', H-6'), 7.79 (d, 4H, *J* 8.0 Hz, H-3', H-5'), 6.90 (d, 2H, *J* 8.0 Hz, H-1), 6.68 (d, 2H, *J* 8.0 Hz, H-2), 5.84 (m, 2H, H-8), 5.32 (m, 2H, H-7), 4.95 (d, 2H, *J* 6.5 Hz, H-5), 4.22 (m, 2H, H-6), 3.41 (m, 2H, H-9), 3.11 (m, 2H, H-10a), 2.74 (m, 2H, H-14), 2.68-2.63 (m, 2H, H-16a), 2.43 (s, 6H, N*CH*$_3$), 2.42-2.32 (m, 4H, H-10b, H-16b), 2.17-2.11 (m, 2H, H-15a), 1.95-1.90 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 777.5

Example 11- Dimorphin-3-yl carbonate



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, 2H, J 8.0 Hz, H-1), 6.59 (d, 2H, J 8.0 Hz, H-2), 5.70 (m, 2H,H-8), 5.23 (m, 2H, H-7), 4.97 (d, 2H, J 6.5 Hz, H-5), 4.15 (m, 2H, H-6), 3.36 (m, 2H, H-9), 3.11 (m, 2H, H-10a), 2.69 (m, 2H, H-14), 2.68-2.60 (m, 2H, H-16a), 2.43 (s, 6H, NCH_3), 2.40-2.27 (m, 4H, H-10b, H-16b), 2.10-2.04 (m, 2H, H-15a), 1.94-1.90 (m, 2H, H-15b).

Mass (chemical ionization): $[M+H]^+$= 597.5

Glycosylation

TMSOTf (27 µL, 0.15 mmol) is added to a solution of dimorphin-3-yl terephthalate (50 mg, 0.071 mmol) in chlorobenzene (4 mL) at room temperature. The reaction mixture is stirred for 3 minutes, followed by addition of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate (171 mg, 0.36 mmol) and then TMSOTf (13 µL, 0.071 mmol).

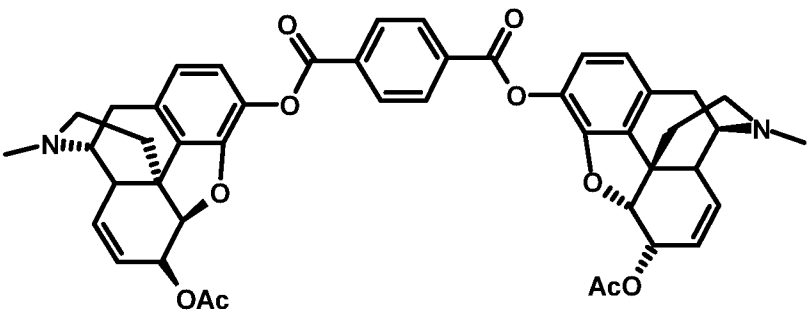
The reaction medium is stirred for 30 minutes at room temperature.

$NaHCO_3$ (100 mg) is added, followed by CH_2Cl_2 (5 mL) and water (5 mL). The organic phase is separated out and dried over Na_2SO_4.

The solvent is removed under reduced pressure. A mixture of three products: bis[6-*O*-acetylmorphin-3-yl] terephthalate, 6-*O*-acetylmorphin-3-yl 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphin-3-yl terephthalate and bis[6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphin-3-yl] terephthalate in 7/30/63 proportions is obtained.

Purification by reverse-phase preparative chromatography (95/5 to 20/80 (H_2O+0.1%TFA)/CH_3CN gradient) allows the three species to be isolated.

Example 12- Bis[6-*O*-acetylmorphin-3-yl] terephthalate



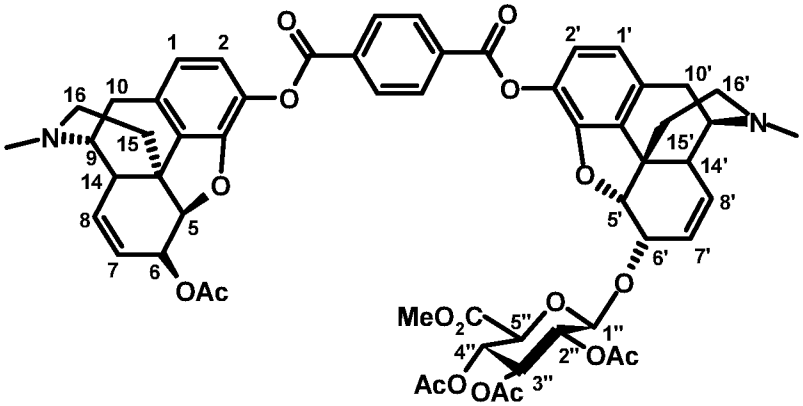
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 4H, *CH-terephtalate*), 6.91 (d, 2H, *J* 8.0 Hz, H-1), 6.66 (d, 2H, *J* 8.0 Hz, H-2), 5.67 (m, 2H, H-8), 5.46 (m, 2H, H-7), 5.15 (m, 4H, H-5, H-6), 3.43 (m, 2H, H-9), 3.10 (m, 2H, H-10a), 2.81 (m, 2H, H-14), 2.67 (m, 2H, H-16a), 2.47 (s, 6H, N*CH*$_3$), 2.43-2.34 (m, 4H, H-10b, H-16b), 2.14-1.91 (m, 10H, *CH*$_3$CO, H-15).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 163.2 (C=O), 149.5, 133.6, 132.5, 131.8, 131.6 (C-*ipso*), 130.3 (*CH-terephtalate*), 129.2 (C-7), 128.7 (C-8), 121.9 (C-1), 119.5 (C-2), 88.7 (C-5), 68.0 (C-6), 58.9 (C-9), 46.5 (C-16), 42.8 (N*CH*$_3$), 42.7 (C-13), 40.3 (C-14) 35.0 (C-15), 20.8 (C-10), 20.6 (*CH*$_3$CO).

High Resolution Mass (ES)

- Calculated for $C_{46}H_{46}N_2O_{10}$ $[M+H_2]^{2+}$: m/z = 393.1576
- Found: m/z = 393.1560

Example 13- 6-*O*-Acetylmorphin-3-yl 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphin-3-yl terephthalate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (m, 4H, *CH-terephtalate*), 6.89 (m, 2H, H-1, H-1'), 6.65 (m, 2H, H-2, H-2'), 5.77 (m, 1H, H-8'), 5.68 (m, 1H, H-8), 5.46 (m, 1H, H-7), 5.33 (m, 1H, H-7'), 5.19 (m, 2H, H-3'', H-4''), 5.15 (m, 1H, H-6), 4.96 (m, 3H, H-2'', H-5, H-5'), 4.86 (d, 1H, *J* 7.5 Hz, H-1''), 4.31 (m, 1H, H-6'), 4.05 (m, 1H, H-5''), 3.72 (s, 3H, O*CH*$_3$), 3.48 (m, 2H, H-9, H-9'), 3.11 (m, 2H, H-10a, H-10a'), 2.85-2.65 (m, 4H, H-14, H-14', H-16a, H-16a'), 2.52-2.37 (m, 10H, N*CH*$_3$, H-10b,

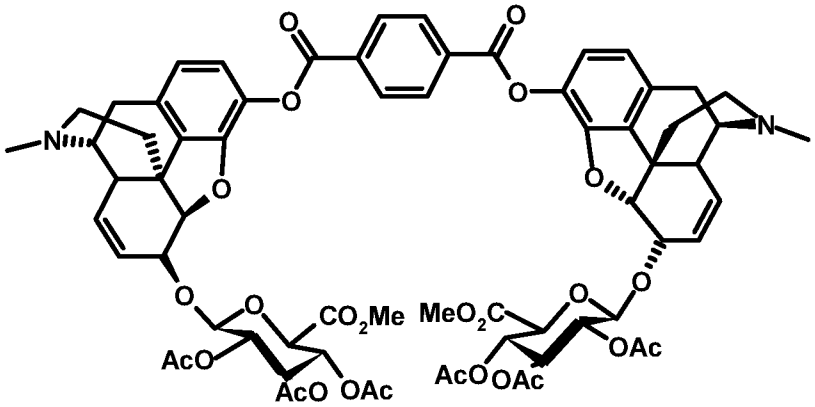
H-10b', H-16b, H-16b'), 2.15-1.85 (m, 13H, H-15, H-15', CH_3CO), 1.73 (s, 3H, CH_3CO).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 169.4, 169.0, 167.3, 163.6, 163.3 (C=O), 150.4, 149.5, 133.7, 133.6 (C-*ipso*), 132.0, 131.6, 130.8, 130.6, 130.3 129.0, 128.9 (*CH-terephtalate,* C-8, C-8', C-7, C-7', C-*ipso*), 122.2, 122.0 (C-1, C-1'), 119.6, 119.3 (C-2, C-2'), 99.3 (C-1''), 89.8, 88.7 (C-5, C-5'), 73.7 (C-6'), 72.7 (C-5''), 71.8 (C-3'' or C-4''), 71.0 (C-2''), 69.4 (C-3'' or C-4''), 67.9 (C-6), 59.0, 58.8 (C-9, C-9'), 46.6, 46.3 (C-16, C-16'), 42.8 (NCH_3), 40.6, 40.2 (C-14, C-14') 35.2, 34.9 (C-15, C-15'), 21.2, 21.0, 20.7, 20.6, 20.5, 20.4 (C-10, C-10' CH_3CO).

High Resolution Mass (ES)

- Calculated for $C_{57}H_{60}N_2O_{18}$ $[M+H_2]^{2+}$: m/z = 530.1921
- Found: m/z = 530.1918

Example 14- Bis[6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl-uronate)morphin-3-yl] terephthalate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 4H, *CH-terephtalate*), 6.90 (d, 2H, *J* 8.0 Hz, H-1), 6.63 (d, 2H, *J* 8.0 Hz, H-2), 5.77 (m, 2H, H-8), 5.34 (m, 2H, H-7), 5.23 (m, 4H, H-3', H-4'), 5.02-4.94 (m, 4H, H-2', H-5), 4.86 (d, 2H, *J* 7.5 Hz, H-1'), 4.32 (m, 2H, H-6), 4.06 (d, 2H, *J* 9.5 Hz, H-5'), 3.72 (s, 6H, OCH_3), 3.48 (m, 2H, H-9), 3.11 (m, 2H, H-10a), 2.75-2.60 (m, 4H, H-14, H-16a), 2.51-2.25 (m, 10H, NCH_3, H-10b, H-16b), 2.16-1.90 (m, 16H, H-15, CH_3CO), 1.75 (s, 6H, CH_3CO).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.4, 169.3, 167.4, 163.9 (C=O), 150.4, 133.7, 132.5, 131.7, 131.4 (C-*ipso*), 130.6 (*CH-terephtalate*, C-8), 128.9 (C-7), 122.0 (C-1), 119.3 (C-2), 99.2 (C-1'), 88.7 (C-5), 73.6 (C-6), 72.9 (C-5'), 71.7 (C-3' or C-4'), 70.9 (C-2'), 69.4 (C-3' or C-4'), 58.8 (C-9), 52.9 (OCH_3), 46.2 (C-16), 43.1 (NCH_3), 41.1 (C-14), 35.7 (C-15), 21.0 (C-10), 20.6, 20.5, 20.4 (CH_3CO).

High Resolution Mass (ES)

- Calculated for $C_{68}H_{74}N_2O_{26}$ $[M+H_2]^{2+}$: m/z = 667.2265
- Found: m/z = 667.2253

Saponification of the intermediates obtained from the O-glycoside coupling

After treatment and extraction of the organic phase (chlorobenzene) obtained from the coupling, the chlorobenzene is evaporated off under reduced pressure (15 mbar) to obtain a brownish oil (m = 47.4 g). To this oil is added a mixture of methanol (140 ml) and demineralized water (35 ml) at 30°C, with stirring, until a homogeneous mixture is obtained. The mixture is then cooled to -5°C.

62.5 ml of concentrated sodium hydroxide solution (30% m/m) are added to this mixture, taking care not to exceed a temperature of 5°C in the reactor. This mixture (pH = 12.72) is then heated at 20°C for 1 hour under nitrogen, and then cooled to -3°C.

37 ml of hydrochloric acid solution (37% HCl) are added to the mixture thus obtained (pH = 5.6). The mixture is heated at 20°C and maintained at this temperature for 30 minutes (pH stable at 5.6). The mixture is then filtered and the filtrate obtained is concentrated under vacuum (15 mbar) to obtain 67.0 g of dry extract.

Purification of the residue obtained from the saponification and acidification

This residue is suspended in 500 ml of methanol at 50°C for 3 hours (desalting) to obtain, after filtration and evaporation under reduced pressure (15 mbar), a residue of 30.8 g comprising a mixture of morphine analyzed by HPLC (of about 30%) and of M6G (of about 70%).

The residue obtained previously is suspended in 100 ml of demineralized water and the suspension obtained is acidified to pH 3.58 with 98% H_2SO_4 (2 ml) and then filtered.

6 g of the resin sold under the name "IRP 69" by the company Rohm & Haas are added to the filtrate (in a weight ratio of 3 relative to the weight of M6G contained according to the estimation obtained by HPLC). The heterogeneous mixture thus obtained is stirred at 20°C for 30 minutes and then filtered.

The operation is repeated until the M6G contained has been depleted.

The resins obtained are desorbed with dilute aqueous ammonia (3% NH_4OH) and the basic solution obtained (pH = 10.9) is neutralized to a pH of about 5 to 6 with dilute HCl.

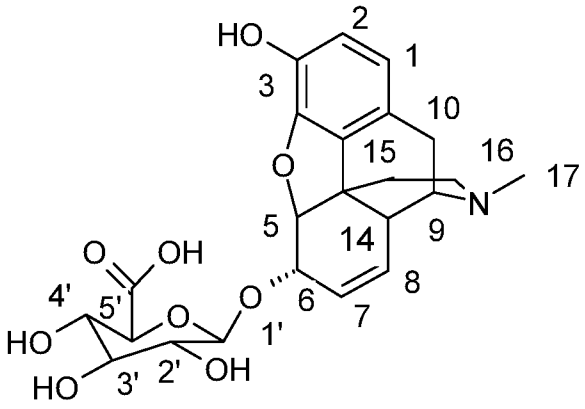
The acidic aqueous solution obtained is evaporated under reduced pressure (15 mbar) to obtain 5.6 g of dry residue.

It is identified by HPLC (M6G content of about 80%).

Recrystallization of the M6G

The preceding dry residue (5.55 g) is suspended in a mixture of water (166.5 ml) and methanol (277.5 ml). The mixture is refluxed (90°C) for 30 minutes and then cooled to 0°C over 2 hours. The first crystals form at 35°C.

The crystals are isolated on a sinter funnel and then washed with 5 ml of methanol. After drying at 80°C under 15 mbar, 2.6 g of pure M6G (organic purity > 99%) are isolated.



HPLC (M6G content) = 98.6%

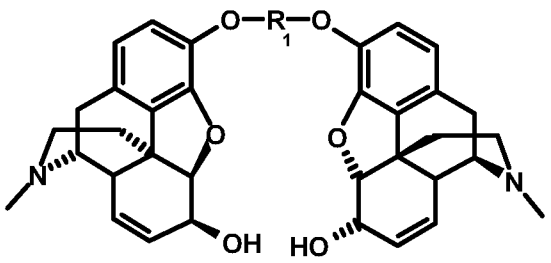
Mass (chemical ionization) = [M+ H] += 462.2

^{13}C NMR (75 MHz, $CDCl_3$) (D_2O/exchange NaOD) δ (ppm ± 0.01 ppm): 129.71, 127.42 (C1, C2); 155, 73 , 149.25 (C3, C4); 98.19 (C5); 111.12 (C1'); 85.82 , 85.17, 82.94, 82.77, 81.40 (C6, C2', C3', C4', C5'); 68.66 (C9); 55.76 (C16); 52.07 (C13); 50.79 (C17); 48.34 (C14); 42.80 (C15); 30.70 (C10); 185.30 (CO_2H)

WHAT WE CLAIM IS:

1. A process for preparing morphine-6-glucuronide or a derivative thereof, comprising the steps of:

(i) reacting a compound corresponding to formula (I) below:

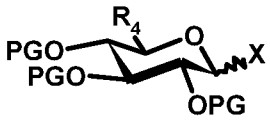


I

in which:

R_1 represents a carbonyl group, COR_5CO in which R_5 represents a group $(C_1\text{-}C_4)$alkane-diyl, $(C_2\text{-}C_4)$alkene-diyl, $(C_2\text{-}C_4)$alkyne-diyl, hetero$(C_1\text{-}C_4)$alkane-diyl, heterocyclo$(C_3\text{-}C_6)$alkane-diyl, $(C_5\text{-}C_{14})$arene-diyl, bi$(C_{10}\text{-}C_{16})$arene-oxide-diyl, bi$(C_{10}\text{-}C_{16})$arene-diyl, or hetero$(C_4\text{-}C_{10})$arene-diyl, $SO_2R_6SO_2$ in which R_6 represents a group $(C_1\text{-}C_4)$alkane-diyl, $(C_2\text{-}C_4)$alkene-diyl, $(C_2\text{-}C_4)$alkyne-diyl, hetero$(C_1\text{-}C_4)$alkane-diyl, heterocyclo$(C_3\text{-}C_6)$alkane-diyl, $(C_5\text{-}C_{14})$arene-diyl, hetero$(C_4\text{-}C_{10})$arene-diyl, bi$(C_{10}\text{-}C_{16})$arene-oxide-diyl or bi$(C_{10}\text{-}C_{16})$arene-diyl,

with a glucuronic acid derivative corresponding to formula (II) below:



(II)

in which:

PG represents an acetyl, isobutyryl, benzoyl or pivaloyl group,

X represents a trihaloacetimidate group, and

R_4 represents a group $(C_1\text{-}C_4)$alkylcarboxylate,

in the presence:

- of an aromatic solvent that is unsubstituted or substituted with one or more substituents chosen from the group formed by a halogen atom, a

group (C_1-C_4)alkyl and a group (C_1-C_4)alkyloxy, said solvent having a melting point of less than or equal to - 20°C, and

- of trimethylsilyl trifluoromethanesulfonate

(ii) reacting the product obtained in step (i) with a strong basic agent, and then

(iii) recovering the product obtained in step (ii).

2. The preparation process as claimed in claim 1, in which, prior to step (i), a compound of formula R_1Cl_2 in which R_1 is as defined in claim 1 is reacted with morphine in a two-phase medium comprising at least water, a strong basic agent and an aromatic solvent that is unsubstituted or substituted with one or more solvents chosen from the group formed by a halogen atom, a group (C_1-C_4)alkyl and a group (C_1-C_4)alkyloxy, said solvent having a melting point of less than or equal to -20°C.

3. The process as claimed in claim 1 or 2, wherein said compound of formula (I) is chosen from the group formed by:

- dimorphin-3-yl terephthalate,
- dimorphin-3-yl isophthalate,
- dimorphin-3-yl phthalate,
- dimorphin-3-yl fumarate,
- dimorphin-3-yl benzene-1,2-disulfonate,
- dimorphin-3-yl benzene-1,3-disulfonate,
- dimorphin-3-yl thiophene-2,5-dicarboxylate,
- dimorphin-3-yl naphthalene-2,7-dicarboxylate,
- dimorphin-3-yl 4,4'-oxybenzoate,
- dimorphin-3-yl biphenyl-4,4'-dicarboxylate, and
- dimorphin-3-yl carbonate.

4. The process as claimed in any one of the preceding claims, wherein said compound of formula (II) has one or more of the following characteristics:

- PG represents an acetyl group,
- X represents a group -OCNHCCl$_3$ or a group -OCNPhCF$_3$, and

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- R_4 represents a methylcarboxylate group.

5. The process as claimed in any one of the preceding claims, wherein said compound of formula (II) is methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate trichloroacetimidate.

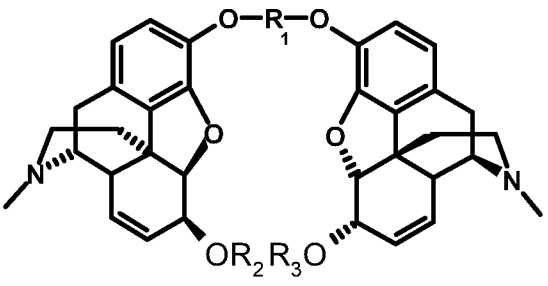
6. The process as claimed in any one of the preceding claims wherein said aromatic solvent is chosen from chlorobenzene, toluene, 1,2-dichlorobenzene, 1,3,5-trifluorobenzene and mesitylene.

7. The process as claimed in any one of the preceding claims, wherein said strong basic agent is sodium hydroxide.

8. The process as claimed in any one of the preceding claims, wherein the mole ratio of said glucuronic acid derivative of formula (II) to said compound of formula (I) is between 2 and 5.

9. The process as claimed in any one of the preceding claims, wherein the mole ratio of the trimethylsilyl trifluoromethanesulfonate to said compound of formula (I) is between 2.2 and 20.

10. A compound of formula



(III)

in which:

R_1 is as defined in claim 1,

R_2 and R_3 independently represent a group PG as defined in claim 1 or a group of formula (IV) below:

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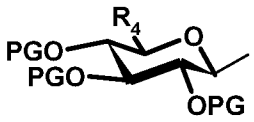


(IV)

in which:

R_4 and PG are as defined in claim 1,

with the proviso that at least one from among R_2 and R_3 represents a group of formula (IV).

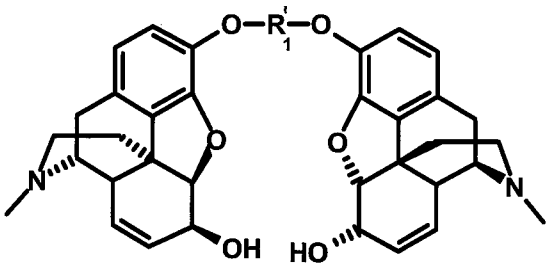
11. The compound as claimed in claim 10, wherein it has one or more of the following characteristics:

- R_1 represents a terephthaloyl group,
- at least one from among R_2 and R_3 represents a group of formula (IV) which is a methyl 2,3,4-tri-O-acetyl-β-D-glucuropryranosyluronate group and PG is an acetyl group.

12. The compound as claimed in claim 10 or 11, wherein it is chosen from the group formed by:

- 6-*O*-acetylmorphin-3-yl 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphin-3-yl terephthalate, and
- bis[6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphin-3-yl] terephthalate.

13. A compound of formula



(I')

in which:

R'$_1$ represents a carbonyl group, COR'$_5$CO in which R'$_5$ represents a group (C_2-C_4)alkene-diyl, (C_2-C_4)alkyne-diyl, hetero(C_1-C_4)alkane-diyl, heterocyclo(C_3-C_6)alkane-diyl, (C_5-C_{14})arene-diyl, bi(C_{10}-C_{16})arene-oxide-diyl, bi(C_{10}-C_{16})arene-diyl, or hetero(C_4-C_{10})arene-diyl, $SO_2R_6SO_2$ in which R_6 represents a group (C_1-C_4)alkane-diyl, (C_2-C_4)alkene-diyl, (C_2-C_4)alkyne-diyl, hetero(C_1-C_4)alkane-diyl, heterocyclo(C_3-C_6)alkane-diyl, (C_5-C_{14})arene-diyl, hetero(C_4-C_{10})arene-diyl, bi(C_{10}-C_{16})arene-oxide-diyl or bi(C_{10}-C_{16})arene-diyl.

14. The compound as claimed in claim 13, chosen from the group formed by:

- dimorphin-3-yl terephtalate,
- dimorphin-3-yl isophthalate,
- dimorphin-3-yl phthalate,
- dimorphin-3-yl fumarate,
- dimorphin-3-yl benzene-1,2-disulfonate,
- dimorphin-3-yl benzene-1,3-disulfonate,
- dimorphin-3-yl thiophene-2,5-dicarboxylate,
- dimorphin-3-yl naphthalene-2,7-dicarboxylate,
- dimorphin-3-yl 4,4'-oxybenzoate,
- dimorphin-3-yl biphenyl-4,4'-dicarboxylate, and
- dimorphin-3-yl carbonate.

15. A morphine-6-glucuronide or a derivative thereof when prepared by a process as claimed in any one of claims 1 to 9.