Improved Process for the Preparation of Treprostinil and Derivatives Thereof

FIELD OF THE INVENTION

The present invention relates to a shortened and more convenient process for producing treprostinil as well as novel intermediates useful in the process. Key features of the described process include a regioselective Claisen rearrangement of an allyloxy benzaldehyde precursor; *tert*-butyl-dimethylsilyl (TBDMS) protection of the alcohol moiety in the alkyne-bearing side chain during the non-stereoselective, intramolecular Pauson-Khand cyclization; and enzymatic kinetic resolution and subsequent chromatographic separation of two diastereomeric late-stage intermediates. The process of this application furnishes the benzindene prostacyclin treprostinil with more than 99% diastereomeric purity.

BACKGROUND OF THE INVENTION

Treprostinil is a synthetic analog of prostacyclin (PGI2), indicated for the treatment of pulmonary arterial hypertension (PAH). The major pharmacologic mechanisms of action of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

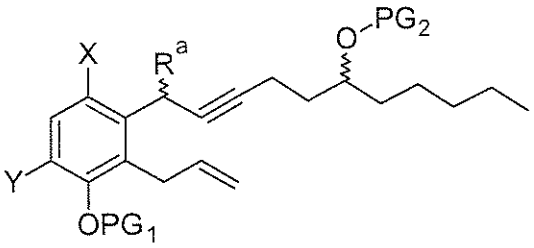
US6700025 discloses a process for the stereoselective synthesis of prostacyclin derivatives, in particular for treprostinil. However, this process and other known processes involve a large number of synthesis steps and chromatographic purifications. The objective of the present invention is the discovery of a process of increased utility that involves fewer steps and chromatographic purifications as well as a highly diastereoselective resolution of a key intermediate by enzymatic means that makes the process more suitable for scale-up.

SUMMARY ~~OF THE INVENTION~~

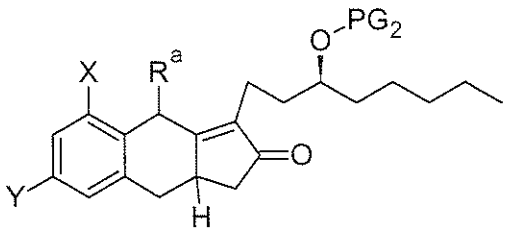
The present ~~invention~~ disclosure relates to a process for preparing treprostinil and its derivatives and intermediates by a process that involves a kinetic enzymatic resolution step using a suitable lipase and a suitable acylating agent. The ~~invention~~ disclosure also relates to the novel synthesis of intermediates prepared during the synthesis of treprostinil (such as compounds of formula 4a, 5, 8, 9, 10, 11', 12', 13a, 14a, 15a, 16a, 16 and 17). Furthermore, the ~~invention~~ disclosure relates to the preparation of an allyl benzaldehyde intermediate via Claisen rearrangement of an allyloxy benzaldehyde precursor (compound of formula V) with increased regioselectivity due to the introduction of a halogen atom in the para position to the allyoxy group. Moreover, the ~~invention~~ disclosure relates

to using a silyl protective group for the non-benzylic alcohol moiety of the C-11 side-chain.

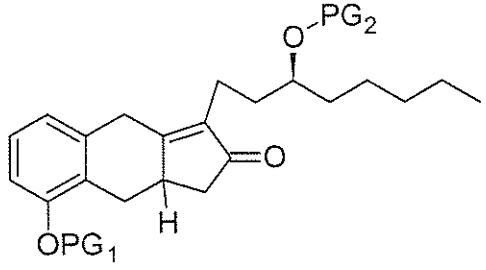
In one aspect, there is provided a compound of formula I, formula II, formula IIb, formula IIIb, or formula IVb



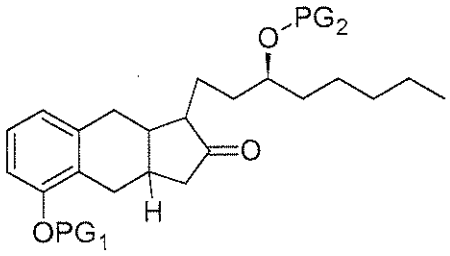
I



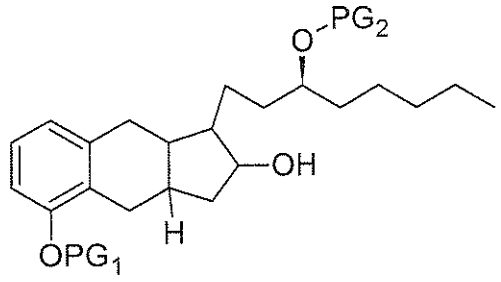
II



IIb



IIIb



IVb

wherein

X and **Y** are independently of one another selected from the group consisting of H, F, Cl, Br, I, and benzyl; and

PG_1 is selected from the group consisting of methyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, benzyl, 4-methoxybenzyl, 2,6-dichlorobenzyl, 3,4-dichloro-benzyl; $-CH_2COOH$, $-CH_2COOR_x$, and $-CH_2CH_2OPG_2$; and

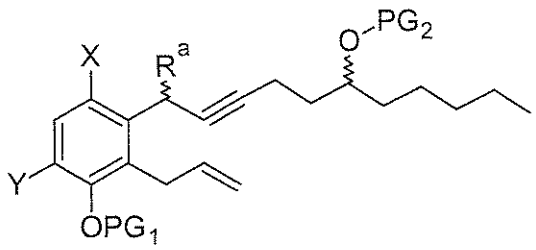
PG_2 is TBDMS; and

R^a is hydrogen, hydroxy $-OR_x$, $-OCOOR_x$, $-OSO_2R_x$, Cl, Br F, I, $-SR_x$, or $-SO_2R_x$;

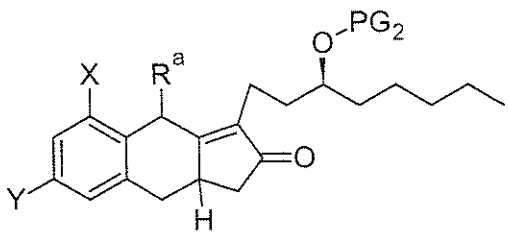
R_x is C_{1-4}alkyl or aryl; and

wherein at least one of X or Y is not H.

In another aspect, there is provided a compound of formula I, or formula II,



I



II

wherein

X and **Y** are independently of one another selected from the group consisting of H, F, Cl, Br, I, and benzyl; and

PG_1 is selected from the group consisting of methyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, benzyl, 4-methoxybenzyl, 2,6-dichlorobenzyl, 3,4-dichloro-benzyl; $-CH_2COOH$, $-CH_2COOR_x$, and $-CH_2CH_2OPG_2$; and

PG_2 is THP, $SiR_1R_2R_3$; or $-CH_2OR_x$; and

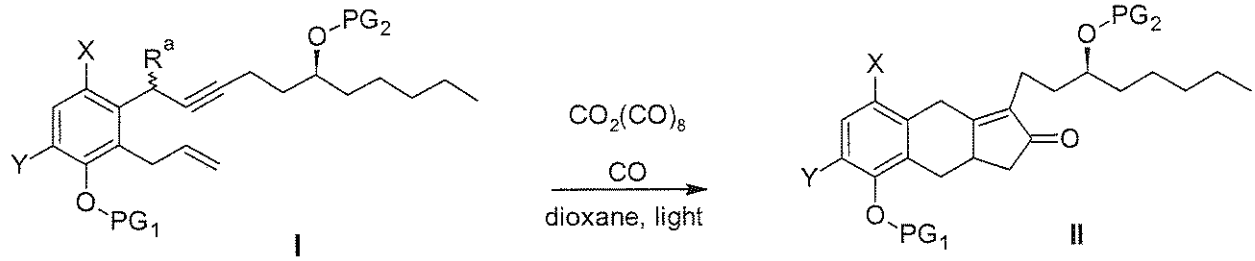
R_1, R_2, and R_3 are independently from one another selected from the group consisting of methyl, isopropyl, *t*-butyl, and phenyl

R^a is hydrogen, hydroxy $-OR_x$, $-OCOOR_x$, $-OSO_2R_x$, Cl, Br F, I, $-SR_x$, or $-SO_2R_x$;

R_x is C_{1-4}alkyl or aryl; and

wherein at least one of X or Y is not H.

In another aspect, there is provided a process for making a compound of formula (II), comprising the following step:



I II

wherein

X, **Y**, R^a, PG_1 and PG_2 are as defined above.

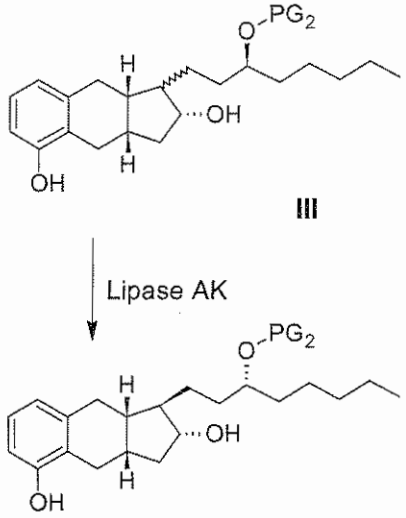
In another aspect, there is provided a process for making a compound of formula IV, comprising the steps of

a) hydrogenating and reducing a compound of formula II to obtain racemic compound

of formula III;

b) contacting racemic compound of formula III with Lipase AK in the presence of a solvent; and

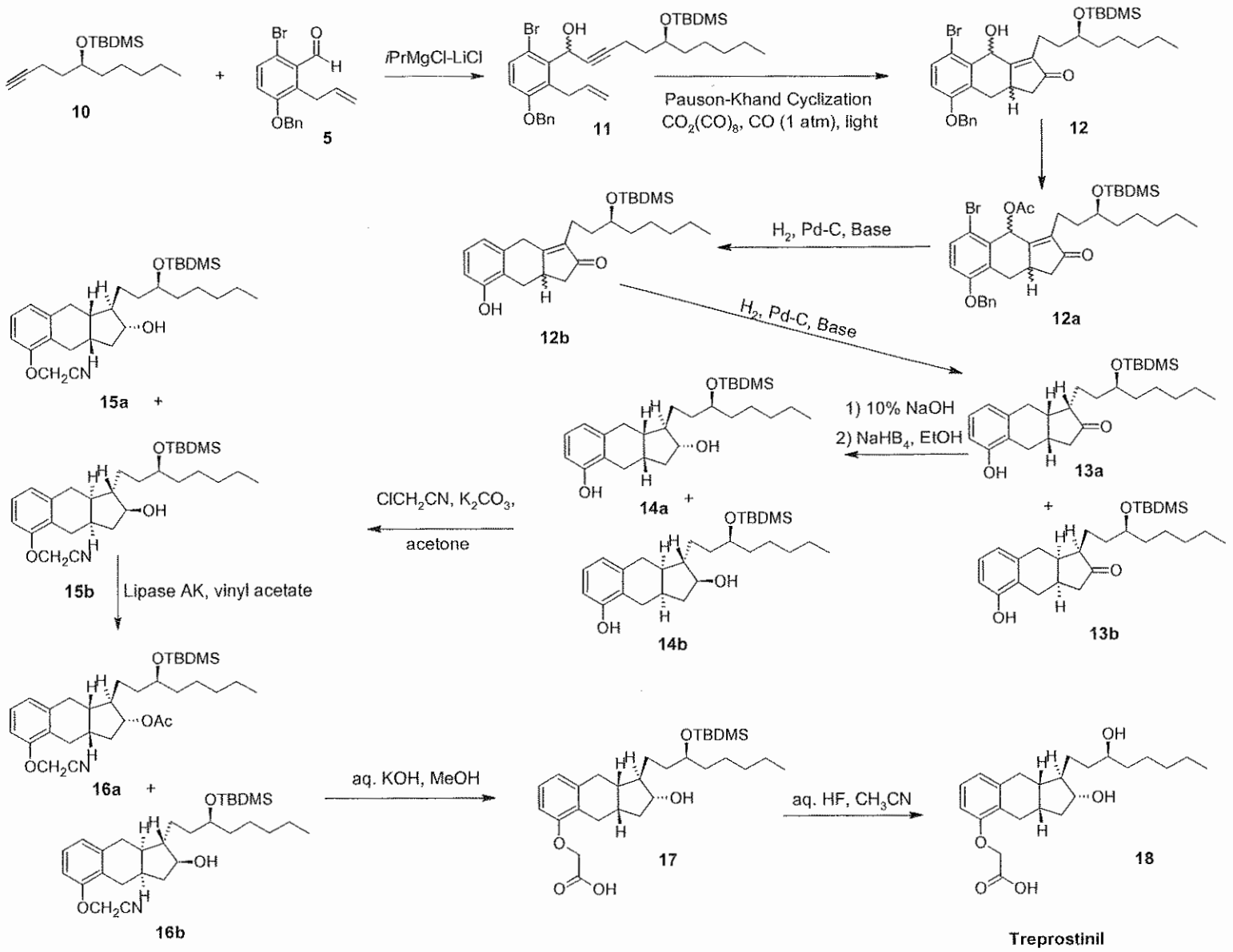
c) obtaining an optically pure compound IV;



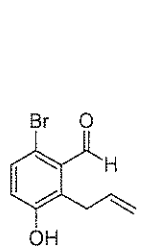
wherein

PG_2 is THP or TBDMS.

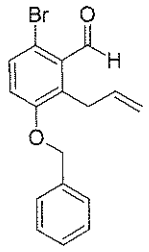
In another aspect, there is provided a process for making treprostinil (**18**) comprising the following steps:


OTBDMS
10
Br
O
H
OBn
5
iPrMgCl-LiCl
Br
OH
OTBDMS
OBn
11
Pauson-Khand Cyclization
$CO_2(CO)_8$, CO (1 atm), light
12
OAc
H_2, Pd-C, Base
12a
12b
H_2, Pd-C, Base
1) 10% NaOH
2) $NaHB_4$, EtOH
13a
13b
14a
14b
$ClCH_2CN$, K_2CO_3,
acetone
15a
15b
Lipase AK, vinyl acetate
16a
16b
aq. KOH, MeOH
17
aq. HF, CH_3CN
18
Treprostinil

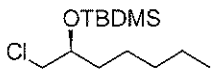
In another aspect, there is provided a new intermediate compound selected from the group consisting of



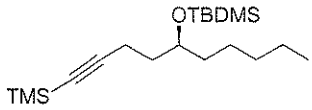
4a



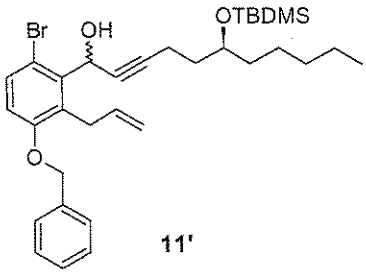
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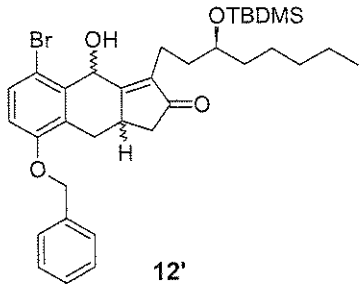
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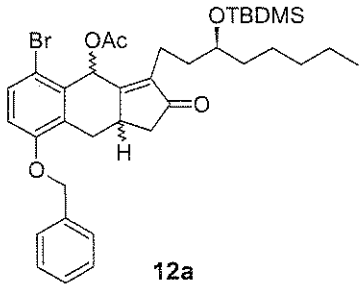
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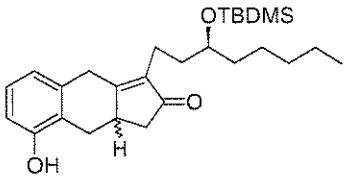
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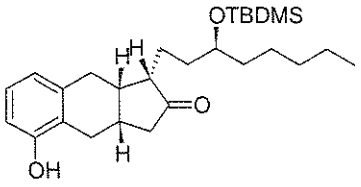
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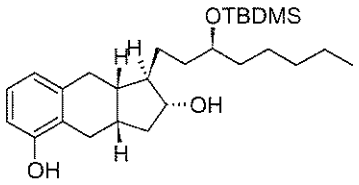
12a



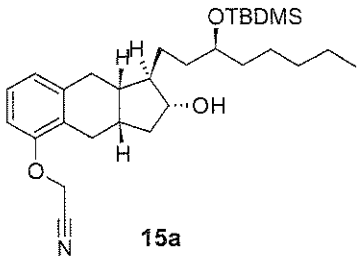
12b



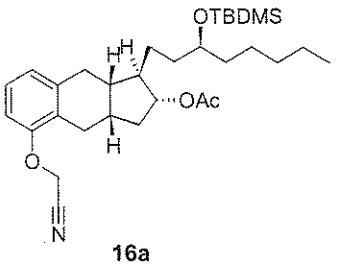
13a



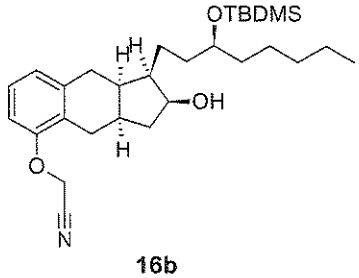
14a



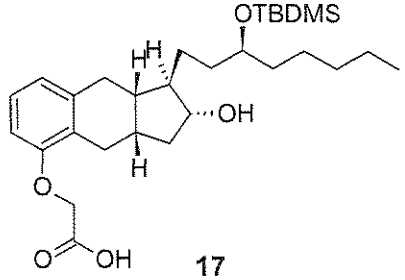
15a



16a



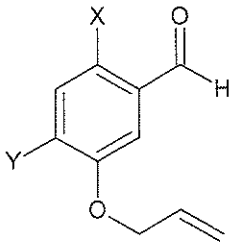
16b



17

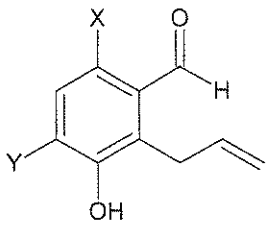
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention relates to converting, via a Claisen rearrangement, a compound of the formula V



V

into a compound of the following formula VI

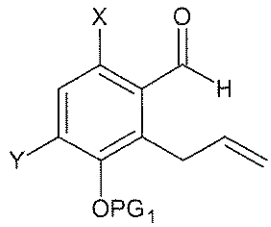


VI

wherein X and Y are independently from one another either: Br, I, Cl, F, or H; preferably, X is Br and Y is H.

Due to the regioselective Claisen rearrangement no separation of regioisomers by chromatography or distillation is necessary. The required regioisomer can be obtained by recrystallization

In another embodiment of the invention, a compound of the formula VII is obtained as an intermediate



VII

wherein X and Y are as defined above; and wherein PG_1 is a protective group for the phenol moiety such as methyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, benzyl, 4-methoxybenzyl, 2,6-dichlorobenzyl, 3,4-dichloro-benzyl; $-CH_2C(O)-OR_x$, or $-CH_2CH_2OR_x$. Preferably PG_1 is benzyl. R_x is C_{1-4} alkyl, or optionally substituted benzyl.