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Batra et al.

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(45) **Date of Patent: *Mar. 14, 2017**

(54) **PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®**

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(73) Assignee: **United Therapeutics Corporation**, Silver Spring, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

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(51) **Int. Cl.**

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C07C 39/17	(2006.01)
C07C 59/60	(2006.01)

(52) **U.S. Cl.**

CPC ***C07C 59/72*** (2013.01); ***C07C 51/08*** (2013.01); ***C07C 51/41*** (2013.01); ***C07C 51/412*** (2013.01); ***C07C 213/08*** (2013.01); ***C07C 405/0075*** (2013.01); *A01N 37/10* (2013.01); *C07C 39/12* (2013.01); *C07C 39/17* (2013.01); *C07C 59/60* (2013.01)

(58) **Field of Classification Search**

CPC C07C 59/72; C07C 51/08; C07C 51/41; C07C 51/412; C07C 213/08; C07C 405/0075

See application file for complete search history.

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(57) **ABSTRACT**

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

10 Claims, No Drawings

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PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Divisional of U.S. application Ser. No. 13/933,623, filed Jul. 2, 2013, which is a Continuation of U.S. application Ser. No. 13/548,446, filed Jul. 13, 2012, which is a Continuation of U.S. application Ser. No. 12/334,731, filed Dec. 15, 2008, which claims priority from U.S. Provisional Patent Application 61/014,232, filed Dec. 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future,* 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

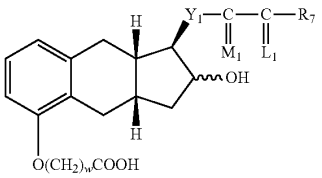
U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008, discloses treprostinil treatment of pulmonary fibrosis. U.S. Pat. No. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application Ser. No. 11/873,645 filed Oct. 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008 discloses treatment of asthma with treprostinil. U.S. Pat. Nos. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.

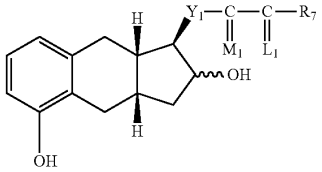
(I)



The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,

(II)



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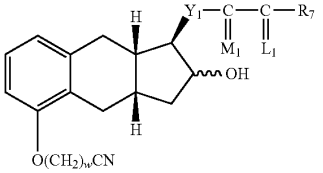


wherein

w=1, 2, or 3;

Y_1 is trans-CH═CH—, cis-CH═CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 1 S

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH═$C(CH_3)_2$;

wherein —C(L_1)-R_2 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

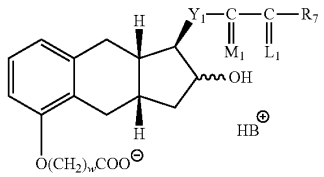
M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s

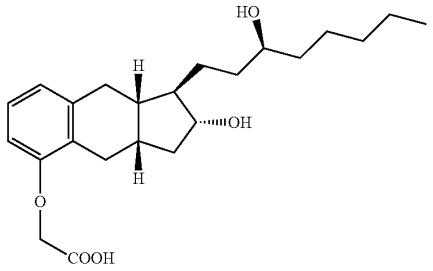
(I_s)



(d) reacting the salt from step (c) with an acid to form the compound of formula I.

The present invention provides in another embodiment a process for the preparation of a compound of formula IV.

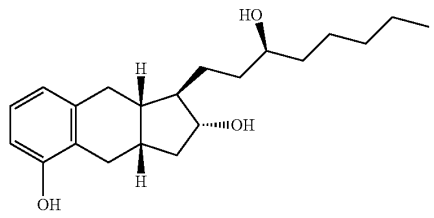
(IV)



The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,

(V)



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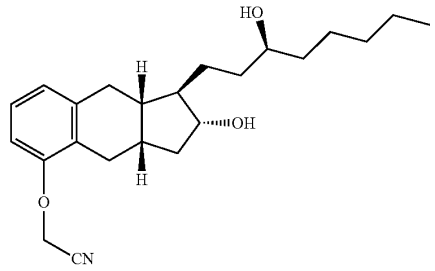
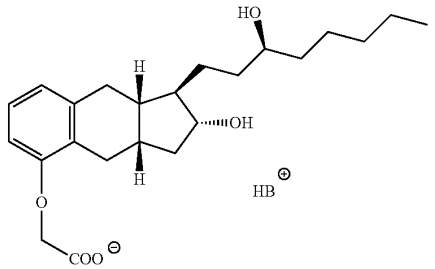
(VI)



(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and

(IV_s)



(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION

The various terms used, separately and in combinations, in the processes herein described are defined below.

The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound. Examples of prodrugs include, but are not

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