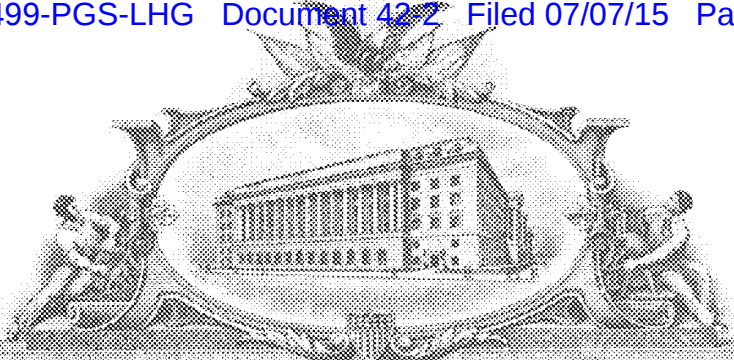


# EXHIBIT 1



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ISSUE DATE: *July 30, 2013*

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US008497393B2

**(12) United States Patent**  
**Batra et al.****(10) Patent No.: US 8,497,393 B2**  
**(45) Date of Patent: Jul. 30, 2013**

- (54) **PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®**
- (75) Inventors: **Hitesh Batra**, Herndon, VA (US); **Sudersan M. Tuladhar**, Silver Spring, MD (US); **Raju Penmasta**, Herndon, VA (US); **David A. Walsh**, Palmyra, VA (US)
- (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.

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(21) Appl. No.: **13/548,446**(22) Filed: **Jul. 13, 2012****(65) Prior Publication Data**

US 2012/0283470 A1 Nov. 8, 2012

**Related U.S. Application Data**

- (63) Continuation of application No. 12/334,731, filed on Dec. 15, 2008, now Pat. No. 8,242,305.
- (60) Provisional application No. 61/014,232, filed on Dec. 17, 2007.

- (51) **Int. Cl.**  
**C07C 62/00** (2006.01)  
**C07C 65/00** (2006.01)

- (52) **U.S. Cl.**  
USPC ..... **562/466**

- (58) **Field of Classification Search**  
None  
See application file for complete search history.

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*Primary Examiner* — Yevegeny Valenrod  
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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.

**22 Claims, No Drawings**

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**1**  
**PROCESS TO PREPARE TREPROSTINIL,**  
**THE ACTIVE INGREDIENT IN**  
**REMODULIN®**

CROSS-REFERENCE TO RELATED  
 APPLICATIONS

This application 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.

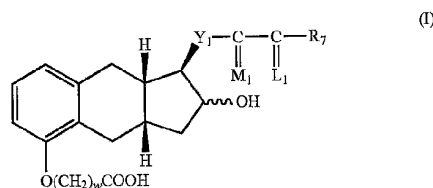
U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe 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. No. 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.

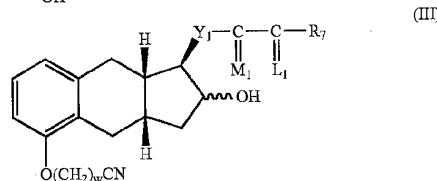
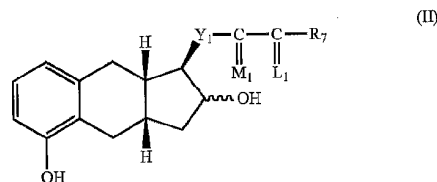
SUMMARY

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.

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The process comprises the following steps:  
 (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



wherein

w=1, 2, or 3;

Y<sub>1</sub> is trans-CH=CH-, cis-CH=CH-, -Cl, (CH<sub>2</sub>)<sub>m</sub>-, or -C=C-; m is 1, 2, or 3;

R<sub>7</sub> is

(1) -C<sub>p</sub>H<sub>2p</sub>-CH<sub>3</sub>, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C<sub>1</sub>-C<sub>3</sub>) alkyl, or (C<sub>1</sub>-C<sub>3</sub>)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R<sub>7</sub> is phenoxy or substituted phenoxy, only when R<sub>3</sub> and R<sub>4</sub> 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<sub>1</sub>-C<sub>3</sub>)alkyl, or (C<sub>1</sub>-C<sub>3</sub>)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH<sub>2</sub>-CH<sub>3</sub>,

(5) -(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-CH<sub>3</sub>, or

(6) -(CH<sub>2</sub>)<sub>3</sub>-CH=C(CH<sub>3</sub>)<sub>2</sub>;

wherein -C(L<sub>1</sub>)-R<sub>7</sub> taken together is

(1) (C<sub>4</sub>-C<sub>7</sub>)cycloalkyl optionally substituted by 1 to 3 (C<sub>1</sub>-C<sub>3</sub>)alkyl;

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

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

(4) 3-thionyloxymethyl;

M<sub>1</sub> is α-OH:β-R<sub>5</sub> or α-R<sub>5</sub>:β-OH or α-OR<sub>1</sub>:β-R<sub>5</sub> or α-R<sub>5</sub>:β-OR<sub>2</sub>, wherein R<sub>5</sub> is hydrogen or methyl, R<sub>2</sub> is an alcohol protecting group, and

L<sub>1</sub> is α-R<sub>3</sub>:β-R<sub>4</sub>, α-R<sub>4</sub>:β-R<sub>3</sub>, or a mixture of α-R<sub>3</sub>:β-R<sub>4</sub> and α-R<sub>4</sub>:β-R<sub>3</sub>, wherein R<sub>3</sub> and R<sub>4</sub> are hydrogen, methyl, or fluoro, being the same or different, with the

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