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

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US 2012/0283470 A1 Nov. 8, 2012

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

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

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,306,075 A 12/1981 Aristoff
4,424,376 A 1/1984 Moniot et al.
4,463,183 A 7/1984 Haslanger
4,486,598 A 12/1984 Aristoff
4,544,764 A 10/1985 Aristoff
4,668,814 A 5/1987 Aristoff
4,683,330 A 7/1987 Aristoff
5,039,814 A 8/1991 Shuman et al.
5,153,222 A 10/1992 Tadepalli et al.
6,054,486 A 4/2000 Crow et al.
6,441,245 B1 8/2002 Moriarty et al.
6,521,212 B1 2/2003 Cloutier et al.
6,528,688 B2 3/2003 Moriarty et al.
6,700,025 B2 3/2004 Moriarty et al.
6,756,033 B2 6/2004 Cloutier et al.
6,765,117 B2 7/2004 Moriarty et al.
6,803,386 B2 10/2004 Shorr et al.
6,809,223 B2 10/2004 Moriarty et al.
6,933,385 B2 8/2005 Westermann et al.
7,199,157 B2 4/2007 Wade et al.
7,384,978 B2 6/2008 Phares et al.
7,417,070 B2 8/2008 Phares et al.

2004/0176645 A1 9/2004 Moriarty et al.
2005/0085540 A1 4/2005 Phares et al.
2005/0101608 A1 5/2005 Santel
2005/0165111 A1 7/2005 Wade et al.
2005/0282901 A1 12/2005 Phares et al.
2005/0282903 A1 12/2005 Wade et al.
2007/0078095 A1 4/2007 Phares et al.
2007/0078182 A1 4/2007 Phares et al.
2008/0200449 A1 8/2008 Olschewski et al.
2008/0249167 A1 10/2008 Phares et al.
2008/0280986 A1 11/2008 Wade et al.
2009/0036465 A1 2/2009 Roscigno et al.
2009/0124697 A1 5/2009 Cloutier et al.
2009/0163738 A1 6/2009 Batra et al.
2009/0281189 A1 11/2009 Walsh
2010/0076083 A1 3/2010 Olschewski
2010/0282622 A1 11/2010 Phares
2011/0092599 A1 4/2011 Wade et al.
2011/0118213 A1 5/2011 Phares et al.
2011/0144204 A1 6/2011 Jeffs et al.
2011/0224236 A1 9/2011 Rothblatt et al.
2011/0319641 A1 12/2011 Batra et al.
2012/0004307 A1 1/2012 Wade et al.
2012/0010159 A1 1/2012 Rothblatt et al.

FOREIGN PATENT DOCUMENTS

CA 2 710 726 A1 1/2012
CN 101891596 A 11/2010
CN 101891715 A 11/2010
EP 0 004 335 A2 10/1979
EP 0 087 237 B1 5/1986
EP 0 175 450 B1 3/1989
EP 0 159 784 B1 6/1989
EP 0 496 548 A1 7/1992
WO WO 98/39337 A1 9/1998
WO WO 99/21830 A1 5/1999
WO WO 03/070163 A2 8/2003
WO WO 2005/007081 A2 1/2005
WO WO 2007/134292 A2 11/2007
WO WO 2008/100977 A2 8/2008
WO WO 2009/117095 A1 9/2009
WO WO 2012/009816 A1 1/2012

OTHER PUBLICATIONS

Alexander et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.

Aristoff et al., "Synthesis and Structure-Activity Relationship of Novel Stable Prostacyclin Analogs," Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Samuelsson et al., Eds., 1983, 11:267-274.

Aristoff et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.

Aristoff et al., "Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emons-Wittig Reaction," J. Am. Chem. Soc., 1985, 107:7967-7974.

Batra et al., "Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding," Organic Process Research & Development, 2009, 13:242-249.

(Continued)

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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.

OTHER PUBLICATIONS

- Belch et al., "Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of AS-013, a Prostaglandin E1 Prodrug, in Patients with Intermittent Claudication," *Circulation*, May 6, 1997, 95(9):2298-2302.
- Chemburkar et al., "Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development," *Organic Process Research & Development*, 2000, 4:413-417.
- Chung et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," *Organometallics*, 1993, 12:220-223.
- Clark et al., "High-Performance Liquid Chromatographic Method for Determining the Enantiomeric Purity of a Benzindene Prostaglandin by a Diastereomeric Separation," *Journal of Chromatography*, 1987, 408:275-283.
- Hardinger et al., "Triply-Convergent Syntheses of Two Homochiral Arene-Fused Prostacyclin Analogs Related to U68,215," *Bioorganic & Medicinal Chemistry Letters*, 1991, 1(1):79-82.
- Hicks et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," *J. Org. Chem.*, 1996, 61:2713-2718.
- Jeong et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," *J. Am. Chem. Soc.*, 1994, 116:3159-3160.
- Khand et al., "Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyl-dicobalt Complexes, $(R^1C_2R^2)Co_2(CO)_6$, with Norbornene and its Derivatives," *J. Chem. Soc., J.C.S. Perkin I.*, 1973, 977-981.
- Mathre et al., "A Practical Enantioselective Synthesis of α,α -Diaryl-2-pyrrolidinemethanol. Preparation and Chemistry of the Corresponding Oxazaborolidines," *J. Org. Chem.*, 1991, 56:751-762.
- Moriarty et al., "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Trepstinil)," *J. Org. Chem.* 2004, 69, 1890-1902.
- Mulzer et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," *Liebigs Ann. Chem.*, 1988, 891-897.
- Nelson, Norman A., "Prostaglandin Nomenclature," *J. Med. Chem.*, Sep. 1974, 17(9):911-918.
- Pagenkopf et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2 +2+2+1] Cycloadditions," *J. Am. Chem. Soc.*, 1996, 118:2285-2286.
- Pagenkopf, Brian L., "Substrate and Reagent Control of Diastereoselectivity in Transition Metal-Mediated Process: Development of a Catalytic Photo Promoted Pauson-Khand Reaction," *Diss. Abstr. Int.*, 57(12):7535, 1977, Abstract.
- Paulson, Peter L., "The Khand Reaction," *Tetrahedron*, 1985, 41(24):5855-5860.
- Schore, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," *Chem. Rev.*, 1988, 88:1081-1119.
- Shambayati et al., "N-Oxide Promoted Pauson-Khand Cyclizations at Room Temperature," *Tetrahedron Letters*, 1990, 31(37):5289-5292.
- Snell et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," *Crystal Growth & Design*, 2001, 1(2):151-158.
- Sorbera et al., "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.
- Takano et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," *Chemistry Letters*, 1987, 2017-2020.
- Viedma, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" *Crystal Growth & Design*, 2007, 7(3):553-556.
- Zhang et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," *J. Org. Chem.*, 1996, 61:4498-4499.
- U.S. Appl. No. 13/409,685, filed Mar. 1, 2012, Sharma, Vijay.
- Comins et al., "Ortho Metalation Directed by α -Amino Alkoxides," *J. Org. Chem.*, 1984, 49:1078-1083.
- Comins et al., "Ortho Substitution of M-Anisaldehyde via α -Amino Alkoxide Directed Lithiation," *J. Org. Chem.*, 1989, 54:3730-3732.
- Corey et al. "Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones," *Tetrahedron Letters*, 1995, 36(50):9153-9156.
- Greene et al., "Protecting Groups," *Protective Groups in Organic Synthesis*, 2d. Ed., 1991, p. 1-11.
- Pansegrau et al., "The Oxazoline-Benzene Route to 1,2,3-Trisubstituted Benzenes. Tandem Addition of Organolithiums, Organocuprates, and α -Lithionitriles to Benzynes," *J. Am. Chem. Soc.*, 1988, 110:7178-7184.
- Rowley et al., "Application of the Pauson-Khand reaction to the synthesis of pentalenic acid," *Journal of Organometallic Chemistry*, 1991, 413:C5-C9.

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.

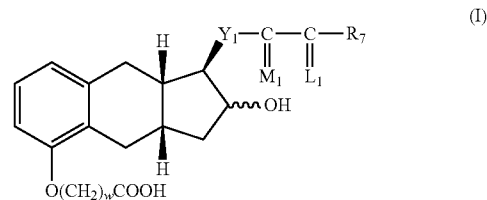
U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe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

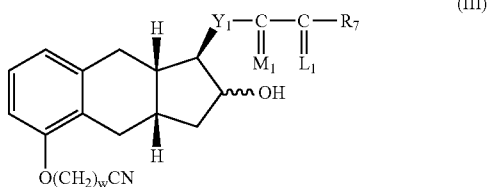
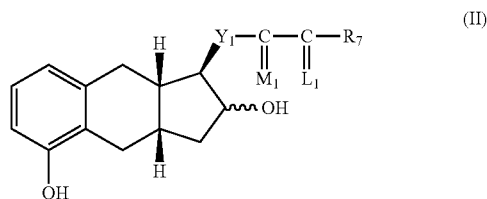
SUMMARY

The present invention provides in one embodiment a pro-

2



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;

Y₁ is trans-CH=CH—, cis-CH=CH—, —CH₂(CH₂)_m—, or —C≡C—; m is 1, 2, or 3;

R₇ is

(1) —C_pH_{2p}—CH₃, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C₁-C₃) alkyl, or (C₁-C₃)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R₇ is phenoxy or substituted phenoxy, only when R₃ and R₄ 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, (C₁-C₃)alkyl, or (C₁-C₃)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH—CH₂—CH₃,

(5) —(CH₂)₂—CH(OH)—CH₃, or

(6) —(CH₂)₃—CH=C(CH₃)₂;

wherein —C(L₁)—R₇ taken together is

(1) (C₄-C₇)cycloalkyl optionally substituted by 1 to 3 (C₁-C₅)alkyl;

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

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

(4) 3-thienyloxymethyl;

M₁ is α-OH:β-R₅ or α-R₅:β-OH or α-OR₁:β-R₅ or α-R₅:β-OR₂, wherein R₅ is hydrogen or methyl, R₂ is an alcohol protecting group, and

L₁ is α-R₃:β-R₄, α-R₄:β-R₃, or a mixture of α-R₃:β-R₄

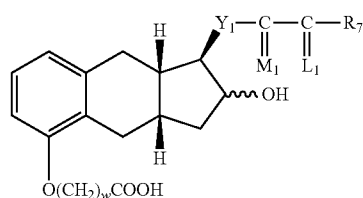
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include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulinate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoate, tosylate, triethiodide, and valerate salts.

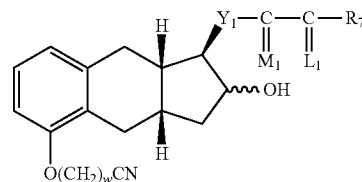
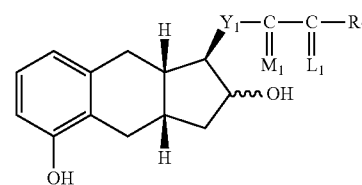
The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



The process comprises the following steps:

6



wherein

w=1, 2, or 3;

Y₁ is trans-CH=CH—, cis-CH=CH—, —CH₂(CH₂)_m—, or —C≡C—; m is 1, 2, or 3;

R₇ is

(1) —C_pH_{2p}—CH₃, wherein p is an integer from 1 to 5, inclusive,

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

(4) 3-thienyloxymethyl;

M₁ is α-OH:β-R₅ or α-R₅:β-OH or α-OR₁:β-R₅ or α-R₅:β-OR₂, wherein R₅ is hydrogen or methyl, R₂ is an alcohol protecting group, and

L₁ is α-R₃:β-R₄, α-R₄:β-R₃, or a mixture of α-R₃:β-R₄ and α-R₄:β-R₃, wherein R₃ and R₄ are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R₃ and R₄ is fluoro only when the other is hydrogen or fluoro.

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

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