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.

(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.

(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)

Primary Examiner — Yevegeny Valenrod
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(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 (Treprostinil)," *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 Promjoted 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-Benzyne 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.

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.

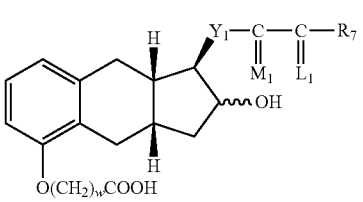
Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future,* 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 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.

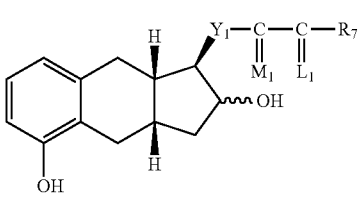
SUMMARY

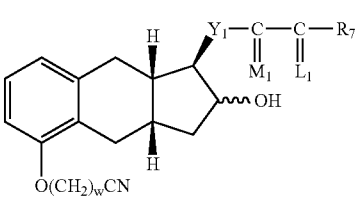
The present invention provides in one embodiment a pro-



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_1 is trans-CH═CH—, cis-CH═CH—, —CH_2 $(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_7 is

(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_7 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;

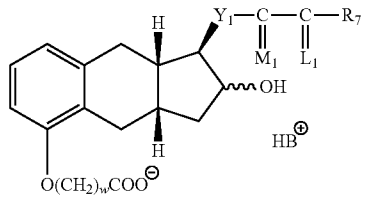
M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

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

proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

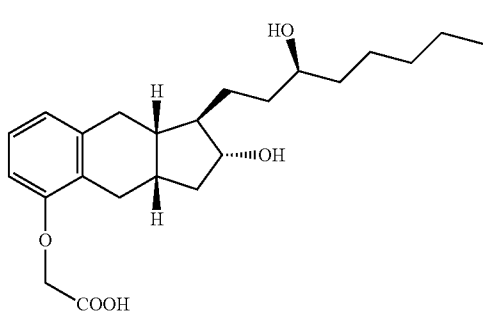
(b) hydrolyzing the product of step (a) with a base,

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



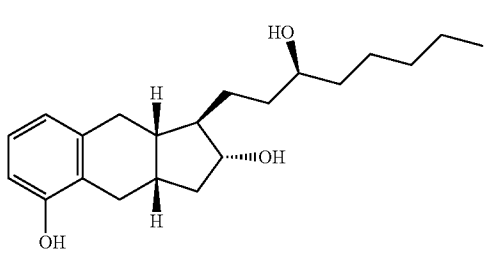
(d) reacting the salt from step (c) with an acid to form the compound of formula I.

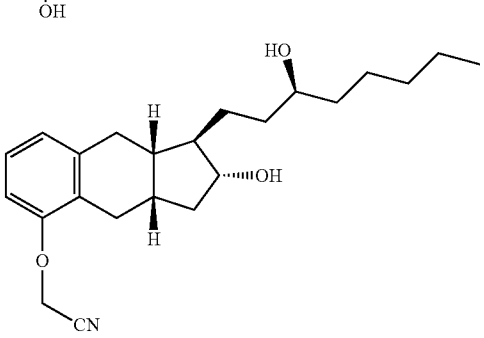
The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



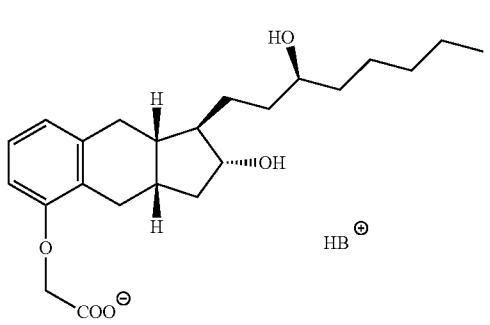
The process comprises the following steps:

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





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



(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 limited to, derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (e.g., monophosphate, diphosphate or triphosphate).

As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

"Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are

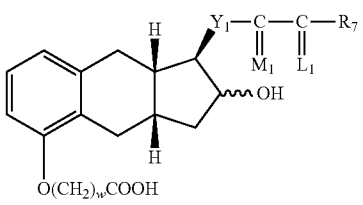
include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, 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, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, 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, teoclate, 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.

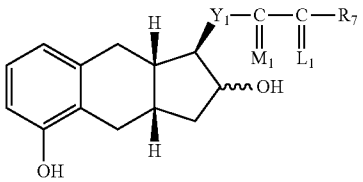
One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.

(I)

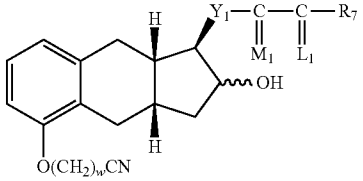


The process comprises the following steps:

(II)



(III)



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 is

(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_7 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_1: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,

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.