EXHIBIT 11

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March 25, 2015

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *13/548,446*
FILING DATE: *July 13, 2012*
PATENT NUMBER: *8,497,393*
ISSUE DATE: *July 30, 2013*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

M. TARVER
Certifying Officer

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Prior Appl. No.: 12/334,731

Prior Appl. Filing Date: 12/15/2008

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

[**X**] Continuation [ ] Division [ ] Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

[ ] Applicant claims small entity status under 37 CFR 1.27.

Enclosed are:

[**X**] Description, Claims, and Abstract (27 pages).

[**X**] Copy of Executed Declaration and Power of Attorney from prior application (4 pages).

[**X**] Information Disclosure Statement, Form PTO-SB08.

[**X**] Application Data Sheet (37 CFR 1.76).

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		**EFS-Web Adjustment**	**Number of Sheets for EFS-Web**
27	x	75%	21

The filing fee is calculated below:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$380.00	=	$380.00
Search Fee							$620.00		$620.00
Examination Fee							$250.00		$250.00
Size Fee	21	-	100	= 0		x	$310.00		$0.00
Total Claims:	21	-	20	= 1		x	$60.00	=	$60.00
Independent:	2	-	3	= 0		x	$250.00	=	$0.00
If any Multiple Dependent Claim(s) present:						+	$450.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration or late payment of filing fee						+	$130.00	=	$0.00
							SUBTOTAL:	=	$1310.00
[ ]					Small Entity Fees Apply (subtract ½ of above):			=	0
					Basic Filing Fee Reduction for Filing via EFS-Web				$0.00
					Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)				$0.00
					Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)				$0.00
							TOTAL FILING FEE:	=	$1310.00
Assignment Recordation Fee:						+	$40.00	=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$130.00	=	$0.00
Publication Fee									$0.00
TOTAL FEE								=	$1310.00

The above-identified fees of $1310.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date JUL 13 2012

By _____

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AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. Application No. 12/334,731, filed December 15, 2008, which claims priority from U.S. Provisional Patent Application 61/014,232, filed December 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

[0003] Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

[0004] Treprostinil, the active ingredient in Remodulin®, was first described in US patent 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.

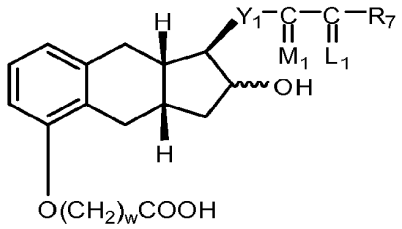
[0005] U.S. Patent No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. patents Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. patent 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. patent 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 No. 12/028,471 filed February 8, 2008,

discloses treprostinil treatment of pulmonary fibrosis. U.S. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application 11/873,645 filed October 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 No. 12/028,471 filed February 8, 2008 discloses treatment of asthma with treprostinil. U.S. 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.

[0006] 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

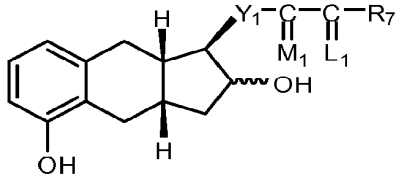
[0007] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0008] The process comprises the following steps:

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



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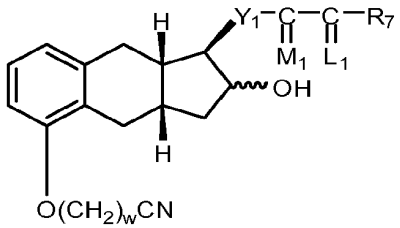


(III)

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

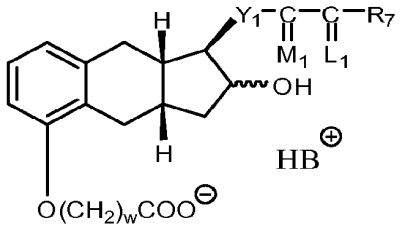
(4) 3-thienyloxymethyl;

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,

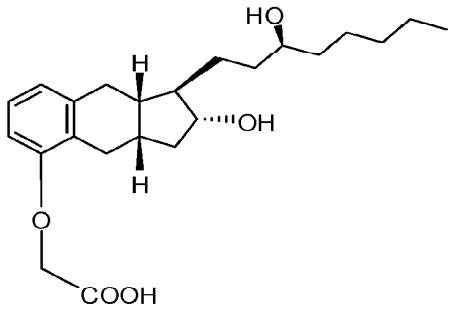
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

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

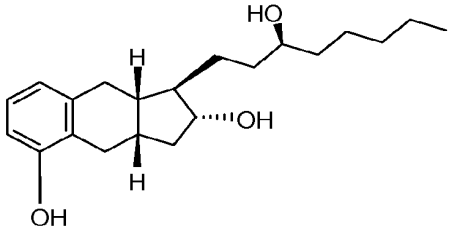
[0009] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



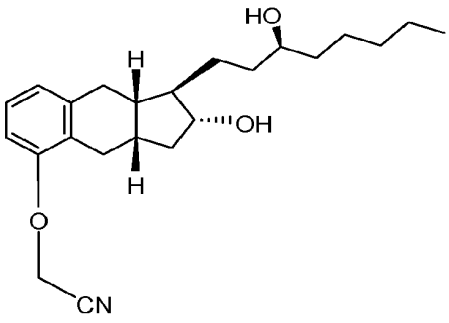
(IV)

[0010] The process comprises the following steps:

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



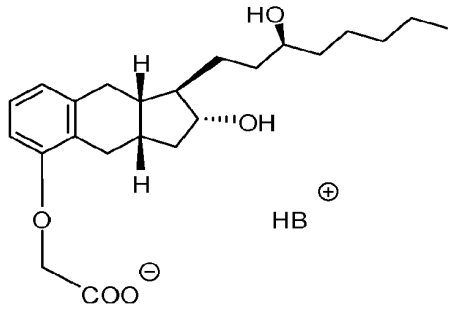
(V)



(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

[0011] The various terms used, separately and in combinations, in the processes herein described are defined below.

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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).

[0018] 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.

[0019] 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.

[0020] "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.

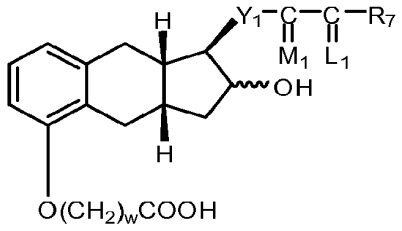
[0021] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen 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.

[0022] 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.

[0023] 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.

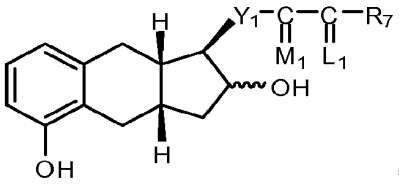
[0024] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0025] The process comprises the following steps:

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



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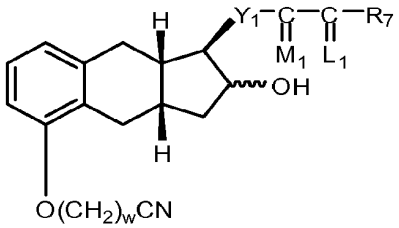


(III)

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

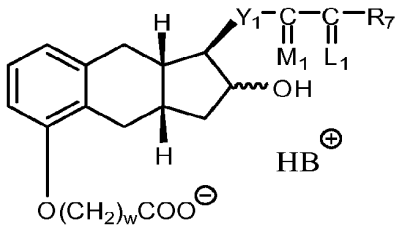
(4) 3-thienyloxymethyl;

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,

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

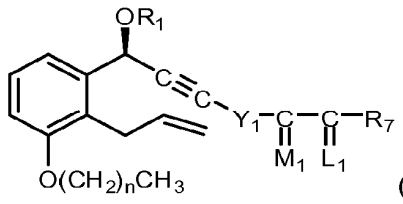


(I_s)

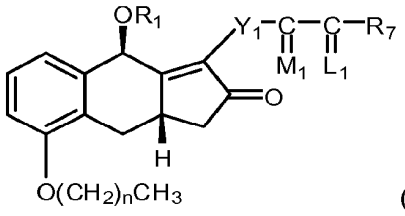
(d) reacting the salt from step (c) with an acid to form the compound of formula I.

[0026] In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

[0027] The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.



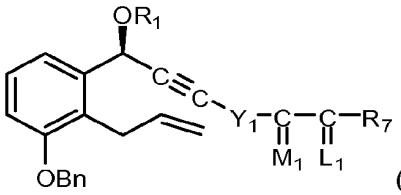
(X)



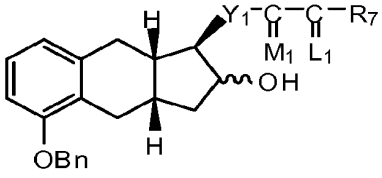
(XI)

Wherein n is 0, 1, 2, or 3.

[0028] The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

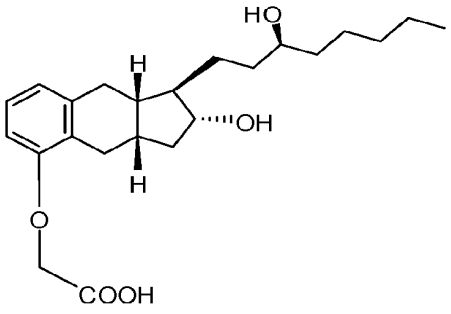


(XII)



(XIII)

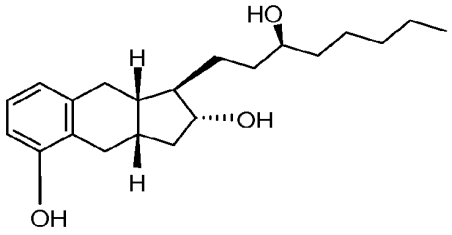
[0029] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



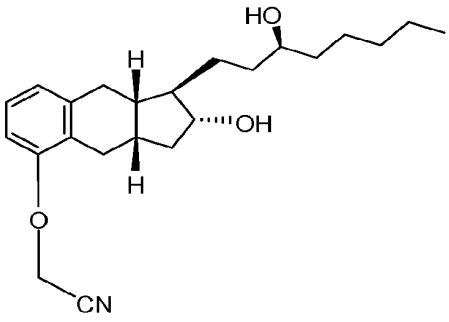
(IV)

[0030] The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,



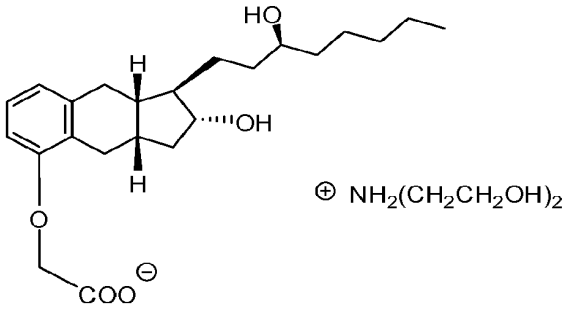
(V)



(VI)

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

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



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

[0031] In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

[0032] In one embodiment, the process further comprises a step of isolating the salt of formula IV_s.

[0033] In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

[0034] The following abbreviations are used in the description and/or appended claims, and they have the following meanings:

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

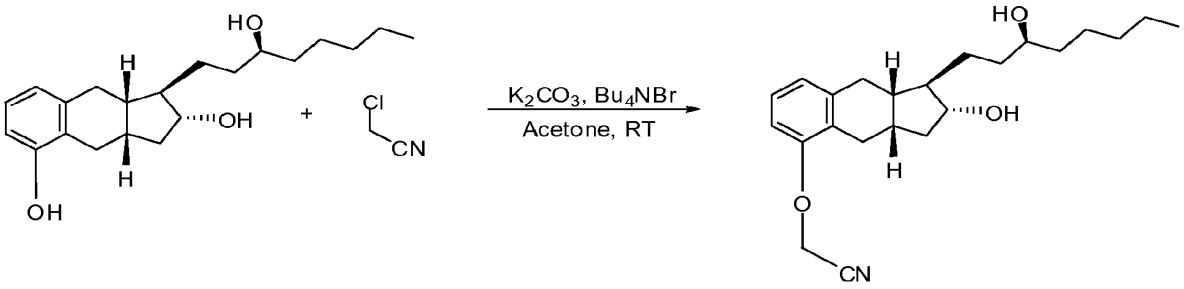
"AUC" means area under curve.

[0035] In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

[0036] The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

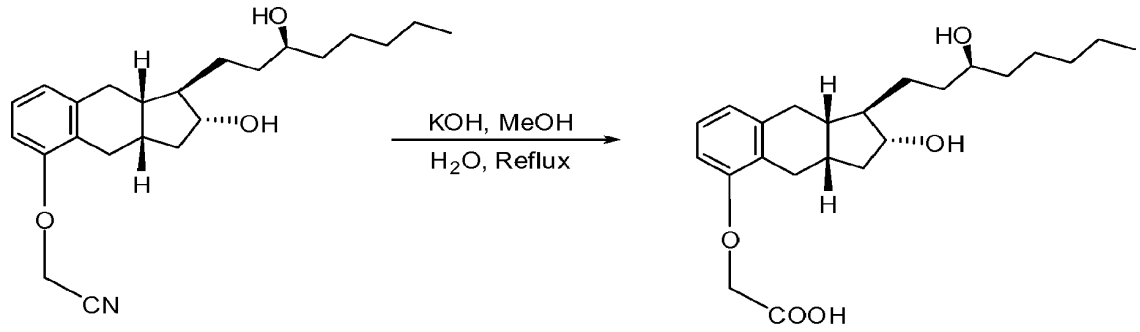
Example 1. Alkylation of Benzindene Triol



Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	--	29 L	--	--
Celite®545	--	115 g	--	--

[0037] A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2°C) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10L). The filtrate was concentrated *in vacuo* at 50-55°C to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2. Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	--	12 L	--	--
Water	--	4.25 L	--	--

*Note: This weight is based on 100% yield from the previous step. This is not isolated yield.

[0038] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2°C). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to -5 to 10°C and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated *in vacuo* at 50-55°C to obtain approximately 12-14 L of condensate. The condensate was discarded.

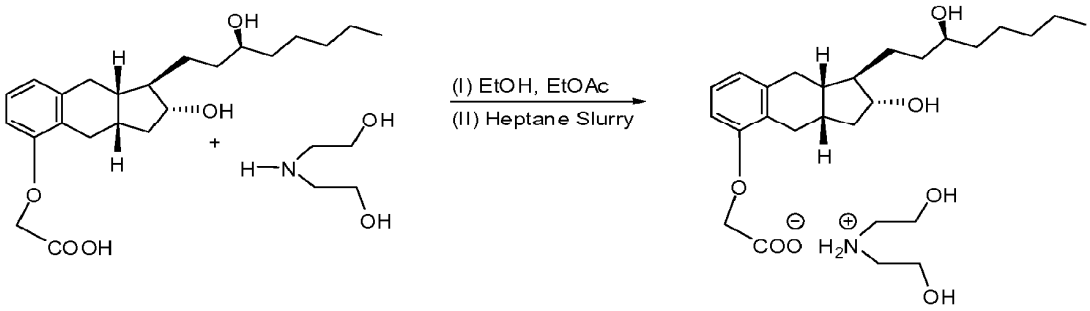
[0039] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HC1 (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 11 L). The combined organic layers were washed with water (3 × 10 L) and followed by washing with a solution of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

[0040] The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70°C) for at least one hour. For filtration, a pad of Celite®545 (300-600 g) was prepared in sintered glass

funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite®545. The Celite®545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

[0041] The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation *in vacuo* at 50-55°C for direct use in next step.

Example 3. Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	--	5.1 L	--	--
Ethyl acetate	--	35L**	--	--
Treprostinil Diethanolamine Salt (seed)	--	12 g	--	--

*Note: This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.

**Note: The total volume of ethyl acetate should be in range of 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

[0042] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75°C, for 0.5-1.0 h to obtain a clear solution. The clear solution was cooled to 55±5°C. At this temperature, the seed of

polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2°C overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2 × 8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5°C under high vacuum.

[0043] At this stage, if melting point of the treprostinil diethanolamine salt is more than 104°C, it was considered polymorph B. There is no need of recrystallization. If it is less than 104°C, it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (°C)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

**Note*: In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.

***Note*: This batch was recrystallized, for this reason yield was lower.

Example 4. Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	--	37.5 L	12

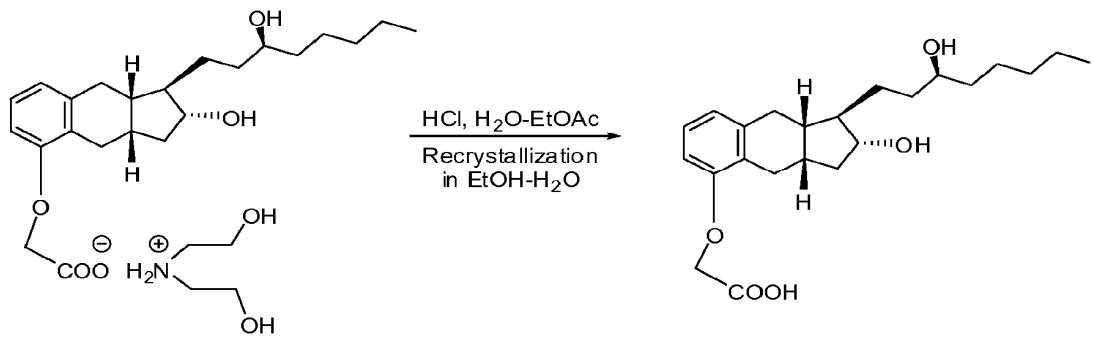
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[0044] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to 70-80°C for 16-24 h. The suspension was cooled to 22±2°C over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55°C.

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5°C	104.5-105.5°C
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
• Ethanol	• Not detected	• Not detected
• Ethyl acetate	• Not detected	• <0.05% w/w
• Heptane	• <0.05% w/w	• <0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5. Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



[0045] A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HC1 (3.2 mL) was added slowly until pH ~1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers was washed with water (2 × 100 mL), brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50°C to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50°C under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0 %	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6. Comparison of the former process and a working example of the process according to the present invention

Step No.	Steps	Former Process (Batch size: 500g)	Working example of the Process according to the present invention (Batch size: 5 kg)
		Nitrile	
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammonium bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50- gallon
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane:0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112 %	Not checked
		Treprostinil (intermediate)	
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)
17	Water	2.2 L	17 L

18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3 M)	12 L (3 M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90+45+45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75°C) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
Treprostinil Diethanolamine Salt			
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75°C.
32	Cooling	N/A	To 20°C over weekend; add 40 L ethyl acetate; cooled to 10°C
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)			
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L

38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge -0°C 24 h	50°C to 0°C ramp, 0°C overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55°C	6-15 hours, 55°C
50	Vacuum	<-0.095 mPA	< 5 Torr
51	UT-15 yield weight	~ 535 g	~ 1,100 g
52	% yield from triol)	~ 91%	~ 89%
53	Purity	~ 99.0%	99.9%

[0046] The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

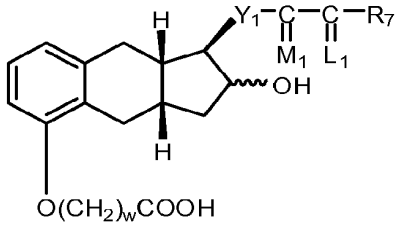
[0047] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill

in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

[0048] All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

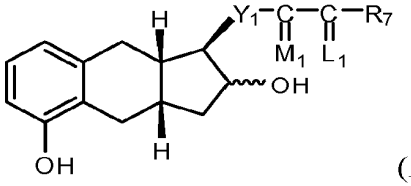
WHAT IS CLAIMED IS:

1. A product comprising a compound of formula I

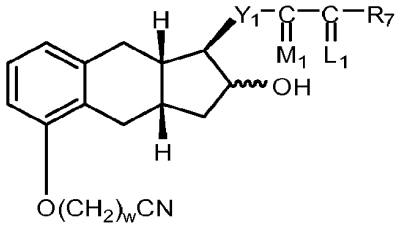


(I), wherein said product is prepared by a process comprising

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



(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) $-(CH_2)_3-CH=C(CH_3)_2$;

$-C(L_1)-R_7$ 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

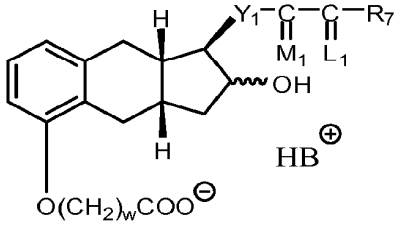
(4) 3-thienyloxymethyl;

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 formula III of step (a) with a base,

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



(I_s) and

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

2. The product of claim 1, wherein the purity of compound of formula I in said product isat least 99.5%.

3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

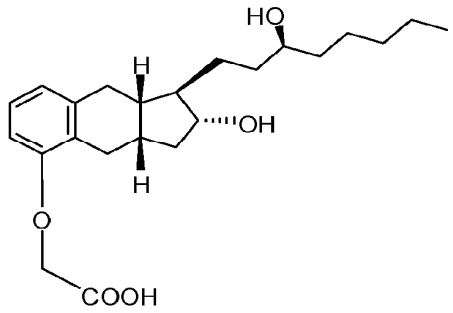
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysinc, L-argininc, tricthanolaminc, and dicthanolaminc.

6. The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. The product of claim 1, wherein Y_1 is $–CH_2CH_2–$; M_1 is α-OH:β-H or α-H:β-OH; -$C(L_1)$-R_7 taken together is $–(CH_2)_4CH_3$; and w is 1.

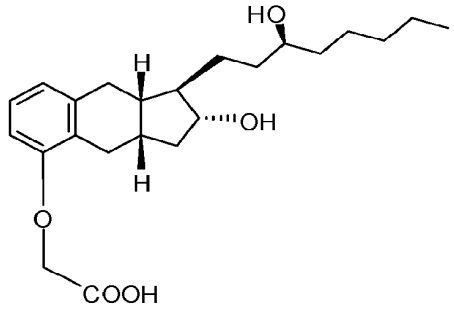
8. The product of claim 1, wherein the compound of formula I is a compound of formula IV.



(IV).

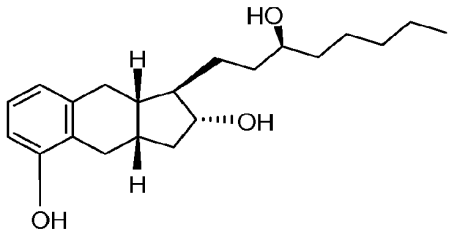
9. The product of claim 1, which the process does not include purifying the compound of formula (III) produced in step (a).

10. A product comprising a compound having formula IV

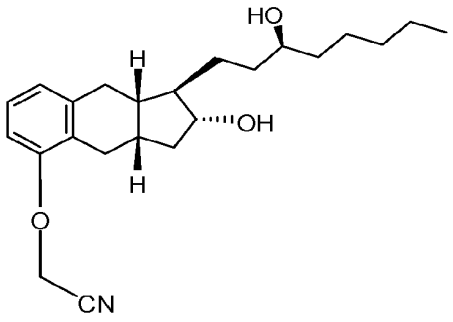


(IV), wherein the product is prepared by the process comprising

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



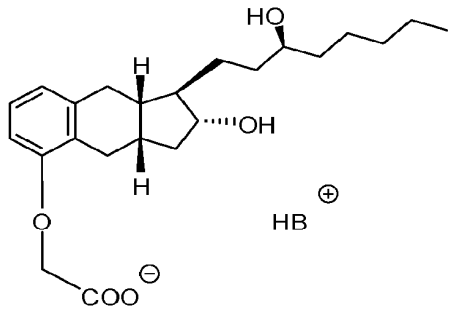
(V)



(VI)

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

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



(IV_s)

(d) reacting the salt formed in step (c) with an acid to form the compound of formula IV.

11. The process of claim 10, wherein the product of step (d) has the purity of the compound of formula IV of at least 99.5%.

12. The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. The product of claim 10, wherein the base in step (b) is KOH.

14. The product of claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

15. The product of claim 10, wherein the base B is diethanolamine.

16. The product of claim 10, wherein the acid in step (d) is HCl.

17. The product of claim 10, which the process does not include purifying the compound of formula (VI) produced in step (a).

18. The product of claim 17, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

19. The product of claim 18, wherein the base B is diethanolamine.

20. The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

21. The product of claim 10, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

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.

Atty. Dkt. No. 080618-0629

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

(Attorney Docket No. 080618-0629)

the specification of which (check one)

___ is attached hereto.

_X_ was filed on _December 15, 2008_ as United States Application Number or PCT International Application Number _12/334,731_ and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date
61/014,232	12/17/2007

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of

Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the registered attorneys and agents at Customer Number

22428

to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

I request that all correspondence be directed to:

Stephen B. Maebius
FOLEY & LARDNER LLP
Customer Number: 22428

Telephone: (202) 672-5569
Facsimile: (202) 672-5399

I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Atty. Dkt. No. 080618-0629

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Inventor's signature	David A. Walsh
Date	Jan. 13, 2009

Application Data Sheet

Application Information	
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	None
Computer Readable Form (CRF)?::	No
Title::	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Attorney Docket Number::	080618-1162
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

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Correspondence Information

Correspondence Customer Number::	22428
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Representative Information

Representative Customer Number::	22428	

Domestic Priority Information

Application::	**Continuity Type::**	**Parent Application::**	**Parent Filing Date::**
This Application	Continuation of	12/334,731	12/15/2008

12/334,731	An application claiming the benefit under 35 USC 119(e)	61/014,232	12/17/2007

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::

Assignee Information

Assignee Name:: United Therapeutics Corporation

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: Unassigned (CON of 12/334,731)

Filing Date: Herewith

Examiner: Unassigned

Art Unit: Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including application no. 12/334,731, filed 12/15/2008, for copies of references of record therein that are not being provided here; although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive

any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date JUL 13 2012

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
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Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
Date Submitted: JUL 13 2012				**Filing Date**	Herewith
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	1	of	4	Attorney Docket Number	080618-1162

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A11	2008/0249167 A1	10/09/2008	Phares et al.	
	A12	2008/0280986 A1	11/13/2008	Wade et al.	
	A13	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A14	2009/0163738 A1	06/25/2009	Batra et al.	
	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A16	4,424,376 A	01/03/1984	Moniot et al.	
	A17	4,463,183 A	07/31/1984	Haslanger, Martin F.	
	A18	4,486,598 A	12/04/1984	Aristoff, Paul A.	
	A19	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	A20	4,668,814 A	05/26/1987	Aristoff, Paul A.	
	A21	4,683,330 A	07/28/1987	Aristoff, Paul A.	
	A22	5,153,222 A	10/06/1992	Tadepalli et al.	
	A23	6,054,486 A	04/25/2000	Crow et al.	
	A24	6,441,245 B1	08/27/2002	Moriarty et al.	
	A25	6,521,212 B1	02/18/2003	Cloutier et al.	
	A26	6,528,688 B2	03/04/2003	Moriarty et al.	
	A27	6,700,025 B2	03/02/2004	Moriarty et al.	
	A28	6,756,033 B2	06/29/2004	Cloutier et al.	
	A29	6,765,117 B2	07/20/2004	Moriarty et al.	
	A30	6,803,386 B2	10/12/2004	Shorr et al.	
	A31	6,809,223 B2	10/26/2004	Moriarty et al.	
	A32	7,199,157 B2	04/03/2007	Wade et al.	
	A33	7,384,978 B2	06/10/2008	Phares et al.	
	A34	7,417,070 B2	08/26/2008	Phares et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		

Examiner Signature		Date Considered	

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: JUL 13 2012

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A37	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A38	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	A39	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	A40	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	A41	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	A42	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	A43	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	A44	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	A45	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	A46	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	A47	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		
	A48	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	A49	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, Inc.		
	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A51	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	
	A52	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	
	A53	ARISTOFF et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.	
	A54	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.	
	A55	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.	

Examiner Signature		Date Considered	

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: JUL 13 2012

(use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A56	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.	
	A57	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.	
	A58	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	A59	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.	
	A60	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.	
	A61	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	A62	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	A63	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.	
	A64	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.	
	A65	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.	
	A66	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	A67	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	A68	PAGENKOPF et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2 + 2 + 1] Cycloadditions," J. Am. Chem. Soc., 1996, 118:2285-2286.	
	A69	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.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** Date Submitted: JUL 13 2012 *(use as many sheets as necessary)* Sheet 4 of 4	***Complete if Known***	
	Application Number	Unassigned
	Filing Date	Herewith
	First Named Inventor	Hitesh BATRA
	Art Unit	Unassigned
	Examiner Name	Unassigned
	Attorney Docket Number	080618-1162

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A70	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	A71	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	A72	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	A73	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	A74	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	
	A75	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	A76	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	A77	ZHANG et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," J. Org. Chem., 1996, 61:4498-4499.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1162

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Claims in excess of 20	1202	1	60	60
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1310**

Electronic Acknowledgement Receipt

EFS ID:	13244906
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Walker
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1162
Receipt Date:	13-JUL-2012
Filing Date:	
Time Stamp:	13:00:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1310
RAM confirmation Number	10480
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File Listing:

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1	Transmittal of New Application	Transmittal.pdf	98402 0d15a8ba4dc8e253cf5c161fcb6acd703d9903b8	no	3
Warnings:					
Information:					
2		Specification.pdf	233495 78ce548ef2e882aa2afaaa098e019bef1a437bce	yes	27

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	21
	Claims	22	26
	Abstract	27	27

Warnings:					
Information:					
3	Oath or Declaration filed	Declfromprior.pdf	172162 6d5b09fdfd00144bfacb55c61acc8d6cc16d84c9	no	4
Warnings:					
Information:					
4	Application Data Sheet	ADS.pdf	63825 e6b6eaa0a08c8d18d7598119f522e77dcf999e84	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
5		IDS.pdf	555417 b297b7bd7d5776a029f5d2ceb5d22b123e568140	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	6

Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	36853 9a2b705f4401f43366f35b420a420f7e05ed11e3	no	2

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/548,446

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	21 minus 20 =	* 1			OR	x 60 =	60
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 250 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1310

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/548,446	07/13/2012	1629	1310	080618-1162	21	2

CONFIRMATION NO. 2092

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FILING RECEIPT

OC000000055586767

Date Mailed: 07/30/2012

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Applicant(s)

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Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

Assignment For Published Patent Application

United Therapeutics Corporation

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Priority data as claimed by applicant

This application is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/548,446**

Projected Publication Date: 11/08/2012

Non-Publication Request: No

Early Publication Request: No

Title

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Preliminary Class

514

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/548,446	07/13/2012	Hitesh Batra	080618-1162

CONFIRMATION NO. 2092

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

PUBLICATION NOTICE

OC000000057514237

Title:PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN?

Publication No.US-2012-0283470-A1
Publication Date:11/08/2012

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PROTECTING GROUPS

T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd edition) J. Wiley & Sons, 1991.
P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994

1. Hydroxyl groups
2. Ketones and aldehydes
3. Amines
4. Carboxylic Acids

ALCOHOLS

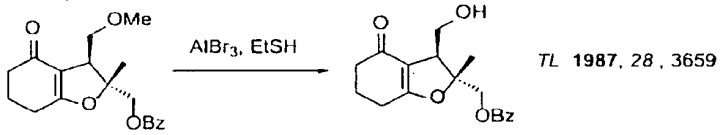
Ethers

- *Methyl ethers*

R-OH → R-OMe difficult to remove except for on phenols

Formation: - CH_2N_2, silica or HBF_4
- NaH, MeI, THF

Cleavage: - $AlBr_3$, EtSH
- PhSe⁻
- Ph_2P^-
- Me_3SiI



TL **1987**, *28*, 3659

- *Methoxymethyl ether* MOM

R-OH → R-OCH_2OMe stable to base and mild acid

Formation: - $MeOCH_2Cl$, NaH, THF
- $MeOCH_2Cl$, CH_2Cl_2, iPr_2EtN

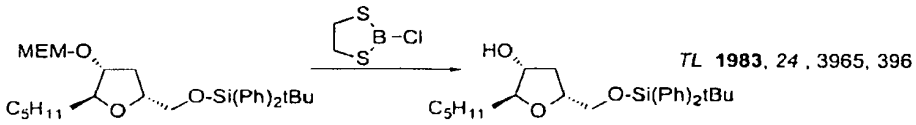
Cleavage - Me_2BBr_2 *TL* **1983**, *24*, 3969

- *Methoxyethoxymethyl ethers* (MEM)

R-OH → R-$OCH_2OCH_2CH_2OMe$ stable to base and mild acid

Formation: - $MeOCH_2CH_2OCH_2Cl$, NaH, THF
- $MeOCH_2CH_2OCH_2Cl$, CH_2Cl_2, iPr_2EtN *TL* **1976**, 809

Cleavage: - Lewis acids such as $ZnBr_2$, $TiCl_4$, Me_2BBr_2



TL **1983**, *24*, 3965, 396

- can also be cleaved in the presence of THP ethers

- *Methyl Thiomethyl Ethers* (MTM)

R-OH → R-OCH$_2$SMe Stable to base and mild acid

Formation: - MeSCH$_2$Cl, NaH, THF

Cleavage: - $HgCl_2$, CH_3CN/H_2O
- $AgNO_3$, THF, H_2O, base

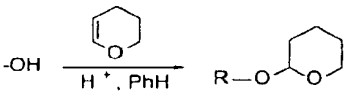
- *Benzyloxymethyl Ethers* (BOM)

R-OH → R-OCH$_2$OCH$_2$Ph Stable to acid and base

Formation: - PhOCH$_2$CH$_2$Cl, CH_2Cl_2, iPr_2EtN

Cleavage: - H_2/ PtO_2
- Na/ NH_3, EtOH

- *Tetrahydropyranyl Ether* (THP)



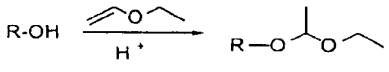
Stable to base, acid labile

Formation: - DHP (dihydropyran), pTSA, PhH

Cleavage: - AcOH, THF, H_2O
- Amberlyst H-15, MeOH

- *Ethoxyethyl ethers* (EE) *JACS* **1979**, *101*, 7104; *JACS* **1974**, *96*, 4745.

Formation: -



(R-OEE) base stable, acid labile

Cleavage: - AcOH, THF, H_2O
- Amberlyst H-15, MeOH

• *Benzyl Ethers* (R-OBn)

R-OH → R-OCH$_2$Ph stable to acid and base

Formation: - KH, THF, PhCH$_2$OCH$_2$Cl
- PhCH$_2$OC(=NH)CCl$_3$, F$_3$CSO$_3$H *JCS P1* **1985**, 2247

Cleavage: - H$_2$ / PtO$_2$
- Li / NH$_3$

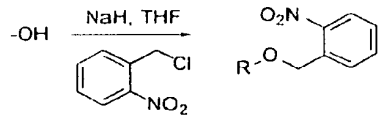
• *p- Methoxybenzyl Ethers* (PMB)

Formation: - KH, THF, p-MeOPhCH$_2$Cl
- p-MeOPhCH$_2$OC(=NH)CCl$_3$, F$_3$CSO$_3$H *TL* **1988**, *29*, 4139

Cleavage: - H$_2$ / PtO$_2$
- Li / NH$_3$
- DDQ
- Ce(NH$_4$)$_2$(NO$_3$)$_6$ (CAN)
- e$^-$

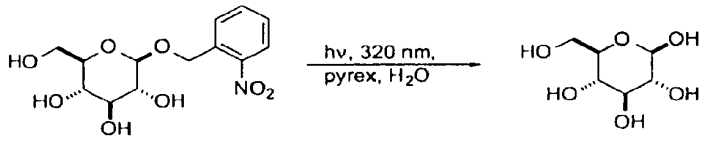
• *o-Nitrobenzyl ethers*

Review: *Synthesis* **1980**, 1; Organic Photochemistry, **1987**, *9*, 225



Formation: - as per benzyl ether

Cleavage: - photolysis at 320 nm



JOC **1972**, *37*, 2281, 2282.

Silyl Ethers *Synthesis* **1985**, 817 *Synthesis* **1993**, 11.

R-OH → R-O-SiR$_3$

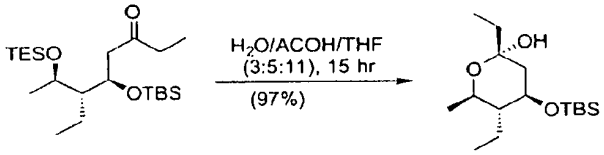
Formation: - R$_3$Si-Cl, pyridine, DMAP
- R$_3$Si-Cl, CH$_2$Cl$_2$ (DMF, CH$_3$CN), imidazole, DMAP
- R$_3$Si-OTf, iPr$_2$EtN, CH$_2$Cl$_2$

Cleavage: - acid (lability depends on specific silyl ether)
- fluoride

- Fluoride sources:
  - nBu_4NF (basic reagent)
  - $HF / H_2O / CH_3CN$ — *TL* **1979**, 3981.
  - $HF \cdot pyridine$ — *Synthesis* **1986**, 453
  - SiF_4, CH_2Cl_2 — *TL* **1992**, *33*, 2289

- *Trimethylsilyl ethers* Me_3Si-OR TMS-OR
  - very acid and water labile
  - useful for transiant protection

- *Triethylsilyl ethers* Et_3Si-OR TES-OR
  - considerably more stable that TMS
  - can be selectively removed in the presence of more robust silyl ethers with with F- mild acid



Liebigs Ann. Chem. **1986**, 1281

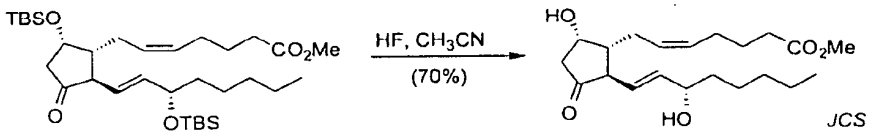
- *Triisopropylsilyl ethers* iPr_3Si-OR TIPS-OR
  - more stabile to hydrolysis than TMS

- *t-Butyldimethylsilyl Ether* $tBuMe_2Si$-OR TBS-OR TBDMS-OR

  JACS **1972**, *94*, 6190
  - Stable to base and mild acid
  - under controlled condition is selective for 1° alcohols

  t-butyldimethylsilyl triflate $tBuMe_2Si$-OTf *TL* **1981**, *22*, 3455
  - very reactive silylating reagent, will silylate 2° alcohols

  Cleavage:
  - acid
  - F^- (HF, nBu_4NF, CsF, KF)



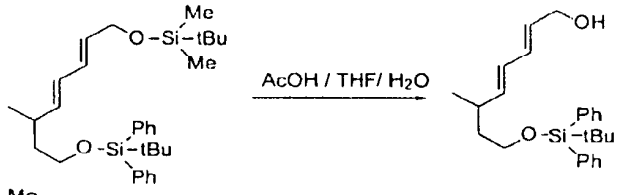
JCS Perkin Trans. 1 **1981**, 205

- *t-Butyldiphenylsilyl Ether* $tBuPh_2Si$-OR BPS-OR TBDPS-OR Σ-OR
  - stable to acid and base
  - selective for 1° alcohols

  Cleavage:
  - F^-

- Me_3Si- and iPr_3Si groups can be selectively removed in the presence of TBS or TBDP groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.

TL **1989**, *30*, 19



JOC **1981**, *46*, 1506
TL **1989**, *30*, 19.

JACS **1984**, *106*, 3748

Esters

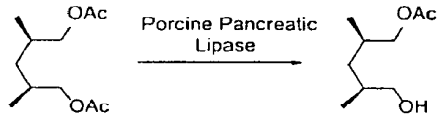
• *Acetates* R-OAc

R-OH → $R\text{-}O_2CCH_3$

- stable to acid and mild base
- not compatable with strong base or strong nucleophiles such as organometallic reagent

Formation: - Ac_2O, pyridine
- AcCl, pyridine

Cleavage: - K_2CO_3, MeOH, reflux
- KCN, EtOH, reflux
- NH_3, MeOH
- LiOH, THF, H_2O
- enzymatic hydrolysis (Lipase) *Org. Rxns.* **1989**, *37*, 1.

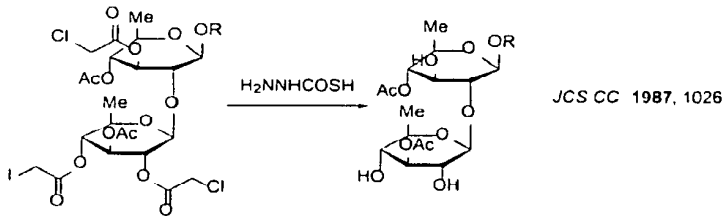


TL **1988**, *30*, 6189

(96% ee)

• *Chloroacetates*

Formation:



JCS CC **1987**, 1026

Cleavage: - can be selectively cleaved with Zn dust or thiourea.

• *Trifluoroacetates* R-OAc'

R-OH → R-O_2CCF_3

Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride in pyridine

Cleavage: - K_2CO_3, MeOH

• *Pivaloate* (t-butyl ester) R-OPiv

R-OH → R-$O_2C(CH_3)_3$

- Fairly selective for primary alcohols

Formation: - tbutylacetyl chloride or t-butylacetic anhydride

Cleavage: - removed with mild base

• *Benzoate* R-OBz

R-OH → R-O_2CPh

- more stable to hydrolysis than acetates.

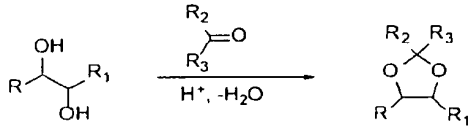
Formation: - benzoyl chloride or benzoyl anhydride in pyridine

Cleavage: - mild base
- KCN, MeOH, reflux

1,2 and 1,3- DIOLS

Synthesis **1981**, 501 *Chem. Rev.* **1974**, *74*, 581

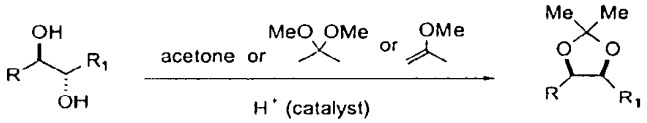
Acetals & Ketals



• *Isopropylidenes* (acetonides)

- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored

Formation:

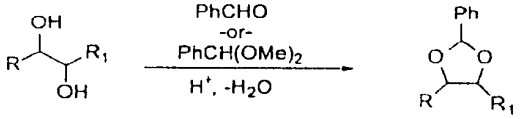


Cleavage: - cleaved with mild aqueous acid

- *Benzylidene Acetals*

  - in competition between 1,2- and 1,3-diols, 1,3-benzylidene formation for is usual favored.

  Formation:



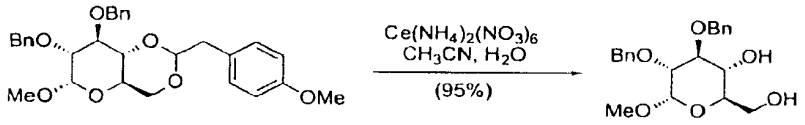
  Cleavage: - benzylidenes can be removed by acid hydrolysis or hydrogenolysis (H_2, Pd/C)

  - benzylidene are usually hydrogenolyzed more slowly than benzyl ethers or olefins.

- *p-Methoxybenzylidenes*

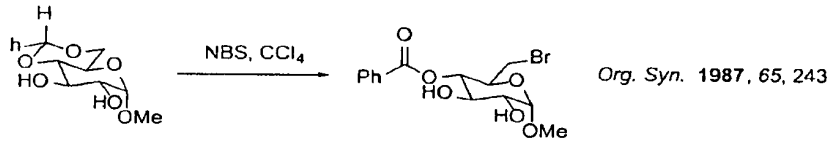
  Formation: - as per benzylidene acetals

  Cleavage:
  - hydrolyzed with acid about 10X faster than regular benzylidenes
  - H_2, Pd/C
  - Can be oxidatively removed with $Ce(NH_4)_2(NO_3)_6$ (CAN)



  Other Reactions of Benzylidenes

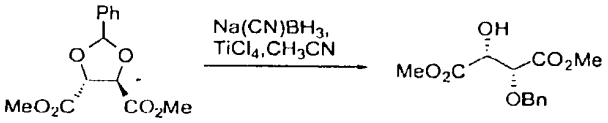
  - Reaction with NBS (Hanessian Reaction)



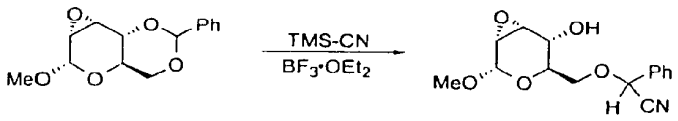
Org. Syn. **1987**, *65*, 243

  - if benzylidene of a 1° alcohol, then 1° bromide

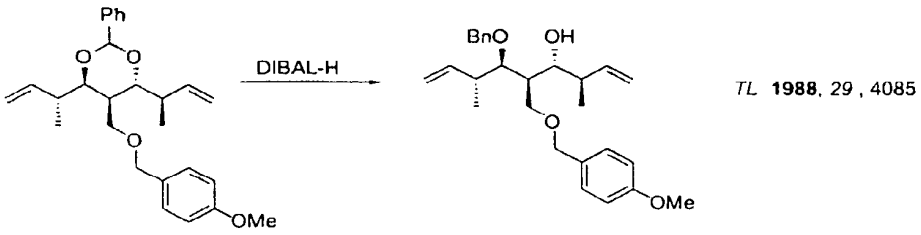
  - Other Reactions



Synthesis **1988**, 373



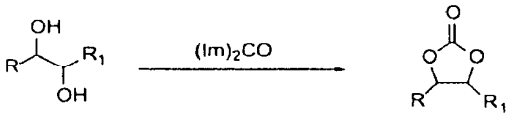
Tetrahedron **1985**, *41*, *3867*



TL **1988**, *29* , 4085

• *Carbonates*

Formation:

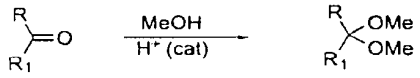


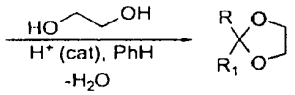
Cleavage: - stable to acid; removed with base
- more difficult to hydrolyze than esters

ALDEHYDES & KETONES

• *Acetals & Ketals*

Formation:

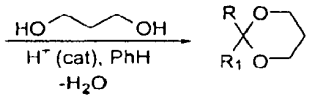




1,3-dioxolanes

-or-
$(CH_2OSiMe_3)_2$,
TMS-OTf, CH_2Cl_2

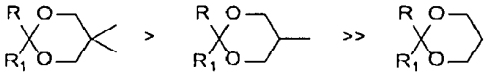
TL **1980**, *21* , 1357



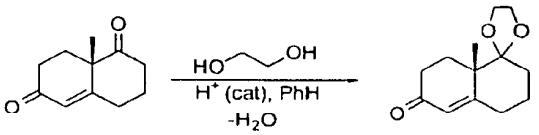
1,3-dioxanes

Cleavage: - Stable to base; removed with H_3O^+

- Cleavage rate of substituted 1,3-dioxanes: *Chem. Rev.* **1967**, *67* , 427.

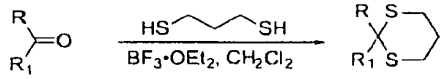


- Ketal formation of α,β-unsaturated carbonyls are usually slower than for the saturat case.



- *Thioacetals & Thioketals*

Formation:



Cleavage: - $Hg(ClO_4)_2$, MeOH or other Hg^{2+} salts
- Stable to mild acid & base

CARBOXYLIC ACIDS

Tetrahedron **1980**, *36*, 2409. *Tetrahedron* **1993**, *49*, 3691

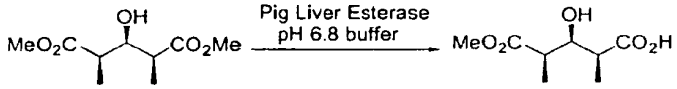
Nucelophilic Ester Cleavage:. *Organic Reactions* **1976**, *24*, 187.

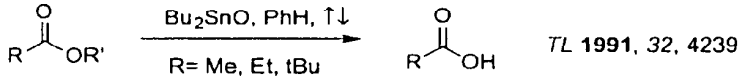
Esters

- *Alkyl Esters*

Formation:
- Fisher esterification (RCOOH +R'OH + H^+)
- Acid Chloride + R-OH, pyridine
- t-butyl esters: isobutylene and acid
- methyl esters: diazomethane (CH_2N_2)

Cleavage:
- LiOH, THF, H_2O
- t-butyl esters are cleaved with aqueous acid
- enzymatic hydrolysis *Org. Rxns.* **1989**, *37*, 1.

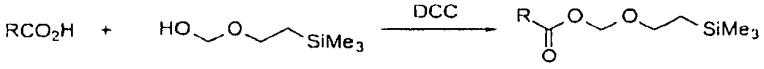




TL **1991**, *32*, 4239

- *2-Trimethylsilyl)ethoxymethyl Ester* (SEM) *HCA* **1977**, *60*, 2711.

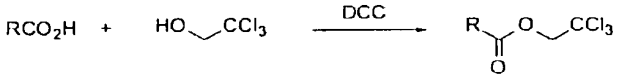
Formation:



Cleavage: - Cleaved with Bu_4NF in DMF

- *Haloesters*

Formation:



Cleavage: - Zn(0) dust
- electrochemically

- *Benzyl Esters*

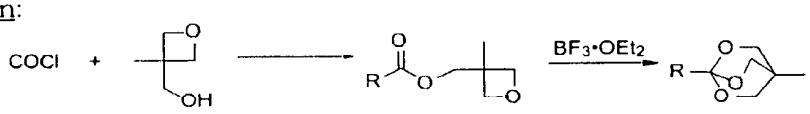
$RCO_2H + PhCH_2OH \rightarrow RCO_2Bn$

Formation: - DCC and benzyl alcohol
- Acid chloride of acid, benzyl alcohol, Et_3N

Cleavage: - H_2, Pd/C
- Na, NH_3

- *Orthoesters* *Synthesis* **1974**, 153 *Chem. Soc. Rev.* **1987**, 75 *TL* **1983**, *24*, 5571

Formation:



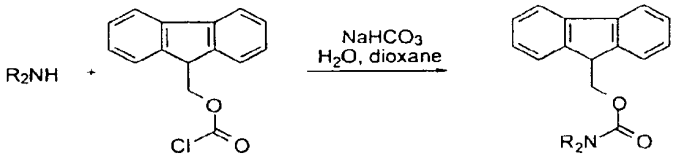
Cleavage: - Stable to base; cleaved with mild acid

AMINES

Carbamates

- *9-Fluorenylmethyl Carbamate* (Fmoc) *Acc. Chem. Res.* **1987**, *20*, 401

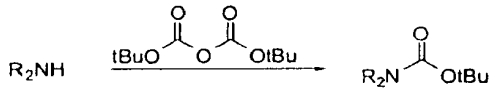
Formation:



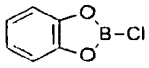
Cleavage: - Cleaved with mild base such as piperidine, morpholine or dicyclohexylamin

- *t-Butyl Carbamate* (BOC)

Formation:



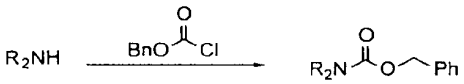
Cleavage: - with strong protic acid (3M HCl, CF_3COOH)
- TMS-I



TL **1985**, *26*, 1411

• *Benzyl Carbanate* (Cbz)

Formation:

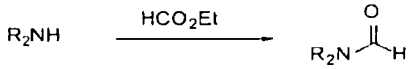


Cleavage:
- H_2, Pd/C
- $PdCl_2$, Et_3SiH
- TMS-I
- BBr_3
- hv (254 nm)
- Na/ NH_3

Amides

• *Formamides*

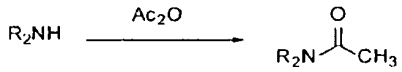
Formation:



Cleavage: - removed with strong acid

• *Acetamides*

Formation:



Cleavage: - removed with strong acid

Journal of Organometallic Chemistry, 413 (1991) C5–C9
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JOM 21873PC

Preliminary communication

Application of the Pauson–Khand reaction to the synthesis of pentalenic acid *

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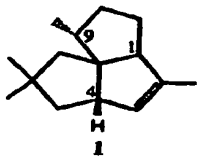
Department of Chemistry, University of California, Davis, Davis, CA 95616 (USA)

(Received November 13th, 1990; in revised form January 18th, 1991)

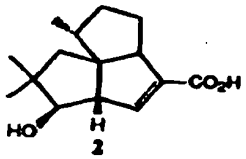
Abstract

A substituted pentynylcyclopentene precursor for the synthesis of pentalenic acid by intramolecular Pauson–Khand cycloaddition reaction has been prepared in high yield. Reaction with $Co_2(CO)_8$ produces triquinane enones in an overall yield of 33%. Three of the four possible stereoisomeric products are formed, with two of them, making up ca. 80% of the product mixture, possessing the necessary *exo*-methyl stereochemistry at C-9 for further elaboration into pentalenic acid. A formal synthesis of the latter was completed by reduction of one of the enone isomers into a ketone which had previously been carried on to the natural product.

Several years ago we demonstrated the use of the Pauson–Khand cycloaddition reaction in the preparation of the angularly fused triquinane ring system [1]. Our initial efforts at directing this methodology towards triquinane natural products led to a synthesis of (±)-pentalenene (1) [2]. In order to assess the applicability of this approach to more highly oxidized members of this class of natural products we recently turned our attention to pentalenic acid (2) [3,4]. This communication describes our results in this area.



1



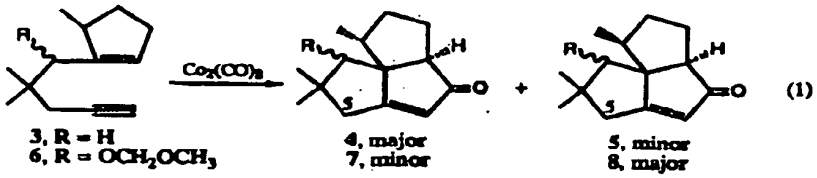
2

In a Pauson–Khand-based synthesis of 2 the critical issues are the effects of the oxygen functionality at C-5 on the yield of the cycloaddition reaction and on the stereochemical outcome at C-9. In the synthesis of 1 stereocontrol at C-9 in the crucial cycloaddition step was high (4 : 5 = ca. 8 : 1) and in the desired direction due to steric interference between the methylene at C-5 and the C-9 methyl in the

* Dedicated with the utmost respect and admiration to Professor Peter L. Pauson on the occasion of his retirement.

0022-328X/91/$03.50

transition state leading to the undesired isomer (eq. 1). In contrast, the presence of a protected alcohol at C-7 totally reversed this preference due to new steric interactions introduced in the intermediates leading to diastereomers **7** relative to diastereomers **8**.

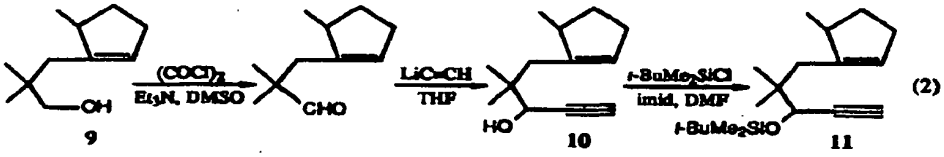


3, R = H
6, R = OCH_2OCH_3

4, major
7, minor

5, minor
8, major

The necessary cyclization precursor for the synthesis of pentalenic acid was prepared as shown in eq. 2. Oxidation of **9** [2] and treatment of the resulting aldehyde with lithium acetylide gave **10** as a ca. 55 : 45 mixture of diastereomers in 77% overall yield [5*]. Although only one of these has the correct alcohol configuration relative to that of the methyl group, it is known that the stereochemistry at C-5 may be corrected after formation of the tricyclic by oxidation followed by selective reduction [4b,d,e].



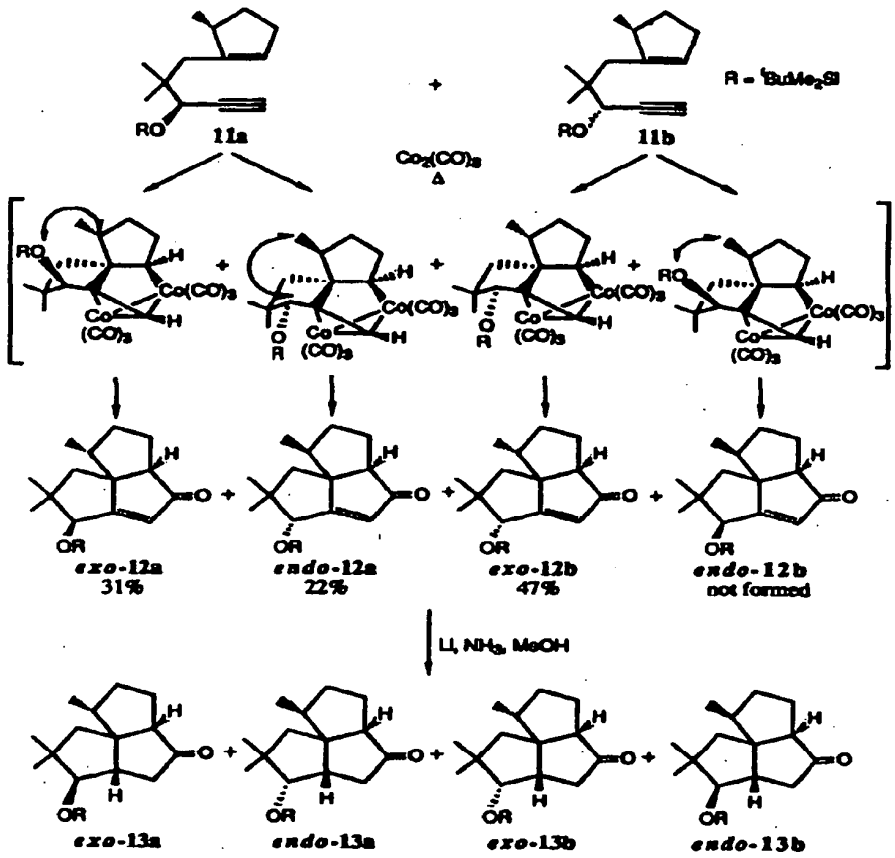
9 **10** **11**

Unprotected propargyl alcohols have generally not performed well as Pauson–Khand cycloaddition substrates [6], and alcohol **10** showed no indication of cyclization to an enone upon treatment with $Co_2(CO)_8$ and heating. The corresponding tert-butyldimethylsilyl ethers typically are much better substrates [7], and treatment of siloxy enyne **11** [8*] with dicobalt octacarbonyl under the same conditions used for cycloaddition of **3** (heptane, sealed tube, 115 °C, 19 h) gave a 33% yield of a mixture of enones. The ^1H NMR spectrum of the product of this reaction showed three different vinyl signals, indicating that three of the four possible diastereomeric products had formed.

Using the analysis developed for the cycloaddition of **3**, one would expect the stereochemistry of cycloaddition of **11** to be directed in the following manner. Enyne diastereomer **11b** should give a more favorable ratio of enone products with respect to methyl stereochemistry at C-9 than the 88 : 12 ratio observed for **3**. When the alkene inserts into the cobalt complex so that the methyl group is on the *endo* face of the macrocycle, it will experience a severe steric interaction with the siloxy group at C-5, and thus this pathway should be extremely disfavored (Scheme 1). In contrast, the cycloaddition of **11a** should be less selective because a steric interaction will develop no matter which way the alkene inserts (i.e., either C-9 methyl ↔ C-5 H or C-9 H ↔ C-5 siloxy).

Table 1 presents partial ^1H NMR data for the three separated (by MPLC) isomers of **12** [9*]. Stereochemistry at C-5 was assigned on two bases: protons on the *endo* face of a bicyclo[3.3.0]octane fragment are shielded relative to protons on

* Reference number with asterisk indicates a note in the list of references.



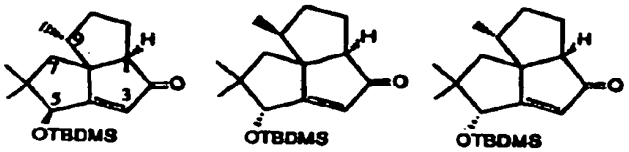
Scheme 1.

the *exo* face [10] and the coupling constant $J(H_3-H_5)$ is approximately 2 Hz when H-5 is *exo* and 0 Hz when it is *endo* [11]. The configuration of the methyl group was assigned by comparing the chemical shifts for the vinylic protons with those in enone **3** and its stereoisomer: **3**, with the *exo*-methyl, displays a vinyl signal 0.15 ppm upfield of its *endo*-methyl isomer. The assignments indicate that, as expected, enyne diastereomer **11b** cyclizes virtually exclusively to a single enone, *exo*-**12b**, while **11a** shows much lower selectivity (ca. 3 : 2). Overall, enones possessing the same *exo*-methyl configuration at C-9 as pentalenic acid make up nearly 80% of the product mixture.

Reduction of the enone mixture with lithium in liquid ammonia and methanol gave tricyclic ketones **13** [12*,13*] which were easily separated by MPLC, permitting two-dimensional NMR experiments that supported the structural assignments of the three isomers. The identity of *exo*-**13a** with an intermediate in Hudlicky's pentalenic acid synthesis [4c] confirmed these assignments. The preparation of *exo*-**13a** thus represents a formal synthesis of the natural product. Note that *exo*-**13b**, the major isomer in this mixture, is also in principle a viable pentalic acid

Table 1

NMR data for enones 12



Proton assignment	*exo*-12a	*endo*-12a	*exo*-12b
H-3	5.83, s	6.03, d, J = 1.7 Hz	5.85, d, J = 1.7 Hz
H-5	4.04, s	4.50, d, J = 1.7 Hz	4.49, d, J = 1.7 Hz
H-1	2.41, m	2.44, m	2.43, m
H-7	2.07, d, J = 13.8 Hz	1.88, d, J = 13.8 Hz	2.02, d, J = 13.8 Hz
H-7	1.22, d, J = 13.8 Hz	1.63, d, J = 13.8 Hz	1.44, d, J = 13.8 Hz
Me-6	1.11, s	1.14, s	1.17, s
Me-9	0.97, d, J = 7.2 Hz	0.93, d, J = 6.9 Hz	0.97, d, J = 7.2 Hz
Me-6	0.87, s	0.69, s	0.80, s
^{t}Bu-Si	0.86, s	0.91, s	0.90 s
Me-Si	0.07, s	0.07, s	0.07, s
Me-Si	0.01, s	0.06, s	0.05, s

precursor via alcohol inversion (*vide supra*). Hudlicky also prepared ketone *endo*-13b, and the NMR spectrum of this isomer does not match the spectra of any product of our cycloaddition–reduction sequence. These results therefore confirm that the interaction of the *endo* substituent at C-9 and the *exo* substituent at C-5 control the stereochemistry of the Pauson–Khand reaction.

Although the stereoselectivity of this cycloaddition was acceptable for our purposes, the yield was only about 2/3 that of the corresponding reaction in the pentalenene synthesis. As a result, following the procedure of Smit and Caple [14] the $Co_2(CO)_6$ complex of 11 was adsorbed onto silica and the resulting red powder heated at 80–90°C until the red color disappeared. Analysis showed that the reaction did not go to completion: enones 12 were obtained in only 16% yield while varying amounts of unreacted complexed and uncomplexed 11 were isolated together with an unidentified aromatic side product. This modification was not further pursued.

Nonetheless, the feasibility of application of the Pauson–Khand reaction to the synthesis of more highly functionalized triquinanes has been established, and dramatic confirmation of our previously suggested guidelines for stereocontrol has been provided as well. We are currently exploring the natural culmination of these studies, syntheses of the highly biologically active pentalenolactones using routes based on selective Pauson–Khand reaction. The results of these studies will be reported in due course.

Acknowledgement. We thank the National Institutes of Health (Grant GM26294) and the Chevron Research Corporation for financial support of this research. This material is based upon work supported under a National Science Foundation Graduate Fellowship to E.G.R. We also express our appreciation to Professor T. Hudlicky for supplying copies of spectra, and to Professors R. Caple and W. Smit for providing results prior to publication.

References and notes

1 (a) M.J. Knudsen and N.E. Schore, J. Org. Chem., 49 (1984) 5025; (b) N.E. Schore and M.J. Knudsen, J. Org. Chem., 52 (1987) 569. Reviews: (c) P.L. Pauson and I.U. Khand, Ann. N.Y. Acad. Sci., 295 (1977) 2; (d) P.L. Pauson, Tetrahedron, 41 (1985) 5855; (e) P.L. Pauson, in A. de Meijere and H. tom Dieck (Eds.), Organometallics in Organic Synthesis. Aspects of a Modern Interdisciplinary Field, Springer, Berlin, 1988, p. 233; (f) N.E. Schore, Chem. Rev., 88 (1988) 1081.

2 N.E. Schore and E.G. Rowley, J. Am. Chem. Soc., 110 (1988) 5224.

3 Isolation: H. Seto, H. Sasaki, J. Uzawa, S. Takeuchi and H. Yonehara, Tetrahedron Lett., (1978) 4411.

4 Syntheses: (a) K. Sakai, T. Ohtsuka, S. Misumi, H. Shirahama and T. Matsumoto, Chem. Lett., (1981) 355; (b) M.T. Crimmins and J.A. DeLoach, J. Am. Chem. Soc., 108 (1986) 800; (c) T. Hudlicky, G. Sinai-Zingde, M.G. Natchus, B.C. Ranu and P. Papadopolous, Tetrahedron, 43 (1987) 5685; (d) M. Ihara, M. Katogi, K. Fukumoto and T. Kametani, J. Chem. Soc., Chem. Commun., (1987) 721; (e) M. Ihara, M. Katogi and K. Fukumoto, J. Chem. Soc., Perkin Trans. I, (1988) 2963.

5 For 10: partial ^{1}H NMR (300 MHz, $CDCl_3$) δ4.06 and 4.09 (two d, $J = 2.1$ Hz, total 1H), 5.40 and 5.43 (two s, total 1H).

6 N.E. Schore, Pauson–Khand reaction, in B.M. Trost (Ed.), Comprehensive Organic Synthesis, Pergamon Press, Oxford, 1991.

7 E.J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94 (1972) 6190.

8 For 11: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.06 and 0.07 (two s, total 3H), 0.12 and 0.13 (two s, total 3H), 0.88 (s, 9H), 0.91 (s, 3H), 0.92 (s, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 1.2–2.3 (series of m, 6H), 2.35 (app t, $J = 2.0$ Hz, 1H), 4.01 (br s, 1H), 5.35 and 5.38 (two s, total 1H); high resolution MS, calculated for $C_{19}H_{34}OSi$–$(CH_3)_3C$: 249.1675; found: 249.1672.

9 For 12: IR (neat film) 1709 cm^{-1}; high resolution MS, calculated for $C_{20}H_{34}O_2Si$–$(CH_3)_3C$: 277.1623; found: 277.1620.

10 N.E. Schore and M.J. Knudsen, J. Org. Chem., 52 (1987) 569.

11 A.L. Veretenov, A.S. Gybin, W.A. Smith, A.S. Shashkov, V.A. Chertkov, R. Caple and K. Wiitala, personal communication.

12 Typical yield of 13 is ca. 60%. Enone 3 is a side product of this reduction (ca. 20% yield). For 13 (mixture of isomers): IR (neat film) 1736 cm^{-1}, analysis: found: C 71.41, H 10.84; $C_{20}H_{36}O_2Si$ calc.: C 71.37, H 10.78%.

13 (a) For *exo*-13a: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 0.92 (s, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.99 (s, 3H), 1.24 (d, $J = 14.1$ Hz, 1H), 1.52 (m, 1H), 1.85 (d, $J = 14.1$ Hz, 1H), 1.95 (m, 1H), 2.28 (m, 1H), 2.33 (m, 1H), 2.48 (dd, $J = 8.7$, 20.7 Hz, 1H), 3.37 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 86.9, 62.7, 48.3, 43.6, 42.8, 41.6, 34.0, 28.7, 26.2, 25.9, 22.4, 14.5, −3.8, −4.2.

(b) For *endo*-13a: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.01 (s, 3H), 0.03 (s, 3H), 0.82 (s, 3H), 0.87 (s, 9H), 0.94 (d, $J = 6.3$ Hz, 3H), 0.96 (s, 3H), 1.52 (d, $J = 13.2$ Hz, 1H), 1.66 (d, $J = 13.2$ Hz, 1H), 1.73 (m, 1H), 2.05 (dd, $J = 11.4$, 20.7 Hz, 1H), 2.47 (m, 1H), 2.55 (m, 1H), 2.72 (m, 1H), 3.62 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 192.2, 82.5, 63.6, 52.0 46.7, 43.0, 41.2, 34.5, 30.8, 29.3, 26.5, 23.0, 13.9, −3.8, −4.2.

(c) For *exo*-13b: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.02 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 0.94 (s, 3H), 0.94 (d, J = ca. 6 Hz, 3H), 0.96 (s, 3H), 1.42 (d, $J = 13.5$ Hz, 1H), 1.50 (m, 1H), 1.68 (d, $J = 13.5$ Hz, 1H), 1.97 (m, 1H), 2.23 (dd, $J = 10.6$, 20.2 Hz, 1H), 2.50 (m, 1H), 2.55 (m, 1H), 3.64 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ82.5, 63.0, 47.0, 44.2, 43.7, 38.4, 34.2, 28.5, 26.0, 24.4, 14.5, −4.1.

14 (a) W.A. Smit, S.O. Simonyan, V.A. Tarasov, G.S. Mikaelian, A.S. Gybin, I.I. Ibragimov, R. Caple, D. Froen and A. Kregger, Synthesis, (1989) 472; (b) V.A. Smit, A.S. Gybin, S.O. Veretenov and A.S. Shashkov, Izv. Akad. Nauk SSSR, Ser. Khim., (1987) 232.

The Oxazoline–Benzyne Route to 1,2,3-Trisubstituted Benzenes. Tandem Addition of Organolithiums, Organocuprates, and α-Lithionitriles to Benzynes

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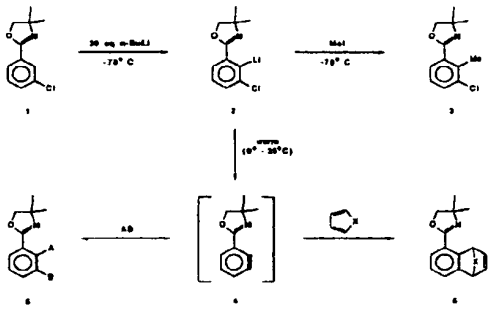
Abstract: The generation of a benzyne intermediate **4** via ortho lithiation of readily available (*m*-chlorophenyl)oxazoline **1** gives rise to a variety of polysubstituted benzene derivatives. The key property of **4** is its ability to form benzyne at temperatures between −10 and 0 °C, which allows a variety of nucleophiles to be placed in solution. As the ortho lithio intermediate loses lithium chloride to form the benzyne, mostly clean regiospecific additions occur in situ. Removal of the oxazoline produces a variety of benzoic acids with substituents derived from nucleophilic and electrophilic entry onto the benzyne intermediate. Kinetic and thermodynamic control has been successfully achieved depending upon the nature of the nucleophile present during benzyne formation. In this fashion, isomeric benzenes with little or no isomeric mixtures were formed. Cycloadditions (4 + 2) using furans, pyrroles, and thiophenes were also performed on the benzynyloxazoline.

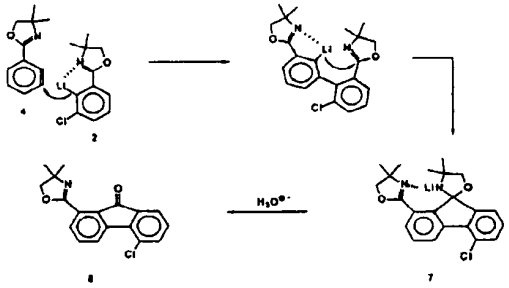
Aromatic substitution has occupied a central role in organic chemistry for over 100 years and still continues to be an area of considerable activity.[1] From the earliest studies on electrophilic substitution,[2] the Friedel–Crafts,[3] nucleophilic aromatic substitution,[4] and free-radical substitution,[5] the stream of publications on every aspect of these important processes continues to appear in periodicals. Among the most notable achievements in aromatic chemistry was the advent of a benzyne[6] intermediate in certain nucleophilic substitutions. The chemistry of benzyne has since been well incorporated into the arsenal of synthetic chemistry and today is accepted as a valuable addition to synthetic design.[7] We now describe in detail our own efforts in adding further to the synthetic utility of benzynes by demonstrating a series of regioselective reactions derived from phenyloxazoline **1**.[8-10] The (*m*-chlorophenyl)oxazoline **1**, shown in Scheme I, is readily prepared in good yields from *m*-chlorobenzoic acid. Upon metalation with *n*-butyllithium at −78 °C in THF, the ortho-lithiated derivative is formed[11] and can be alkylated smoothly with methyl iodide. However, it was our intention to coerce **2** into eliminating LiCl generating the benzyne **4**. This plan was based upon literature precedent[12] for generating benzyne from *o*-lithiochlorobenzene, which eliminates LiCl at ~−100 °C. Thus, the formation of the (2-methyl-3-chlorophenyl)oxazoline **3** was surprising.

Scheme I



However, it was soon discovered that allowing the lithio derivative to warm in THF solution in the presence of excess *n*-BuLi, other nucleophiles, or other reactive species (e.g., a diene), gave the expected benzyne adducts **5** and **6**, respectively. Thus, the sequence shown in Scheme I will form the subject of this report.

Reaction of Benzyne 4 with Organolithiums. When the lithiated phenyloxazoline **2** was allowed to warm in its THF solution, and no nucleophile or electrophile was added, the reaction produced the fluorenone **8** in 68% isolated yield. This interesting process

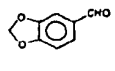
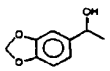


was presumed to involve addition of the ortho-lithiated oxazoline **2** to the benzyne as the temperature rose. The regioselective addition gave only **8**, which was presumed to be thermodynamically controlled and in agreement with other additions to benzynes containing an electron-withdrawing group.[7c] Furthermore, it was felt that the ortho lithio derivative would be stabilized by chelation in **2**. Addition into the C=N link of the oxazoline would be

(1) For delightful and informative reading on aromatic compounds, their structure and reactions in the early 20th century, see: *Essays on the History of Organic Chemistry in the United States, 1875–1955*; Tarbell, D. S., Tarbell, A. T., Eds.; Folio: Nashville, TN, 1986; pp 139–151.
(2) von Euler, H. J. *Justus Liebigs Ann. Chem.* **1903**, *330*, 280.
(3) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392.
(4) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968.
(5) Bachmann, W. E.; Hoffman, R. A. *Org. React. (N.Y.)* **1944**, *2*, 224.
(6) Roberts, J. D.; Simons, H. E.; Carlsmith, L. A.; Vaughn, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290.
(7) For reviews, see: (a) Fields, E. K. *Org. Chem. (N.Y.)* **1973**, *26*, 449. (b) Barton, D. H. R.; Ollis, W. D. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 1, p 477. (c) Hoffmann, R. W. *Dehydrobenzene and Cycloalkenes*; Academic: New York, 1967. (d) For a recent innovative method to generate benzynes via fluoride-induced elimination of *o*-silyl triflates, see: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. Shankaran, K.; Snieckus, V. *Tetrahedron Lett.* **1984**, *27*, 2827.
(8) Some of the studies reported here have appeared in preliminary form: (a) Meyers, A. I.; Rieker, W. F. *Tetrahedron Lett.* **1982**, *23*, 2091. (b) Meyers, A. I.; Pansegrau, P. D. *Ibid.* **1983**, *24*, 4935. (c) Meyers, A. I.; Pansegrau, P. D. *Ibid.* **1984**, *25*, 2941. (d) Meyers, A. I.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690.
(9) For a review on aromatic oxazolines in electrophilic and nucleophilic substitution, see: Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 105.
(10) For a review on asymmetric synthesis involving oxazolines, see: Lutomski, K. A.; Meyers, A. I. In *Asymmetric Syntheses* Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 3, p 213.
(11) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158. Geschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008.
(12) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217.

0002-7863/88/1510-7178$01.50/0

Table I. Addition of BuLi-Electrophile to **1** and Formation of 2,3-Disubstituted Benzoic Esters[a]

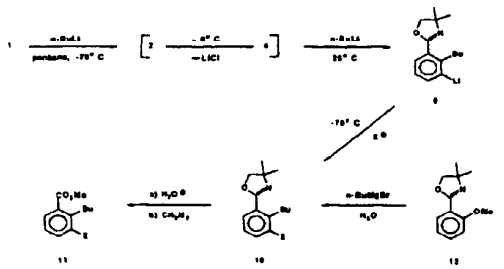
entry	electrophile	E	**10**,[b] %	**11**,[b] %
a	MeI[c]	Me	68	77
b	CH_2O	CH_2OH	58	59
c	$HCONMe_2$	CHO	55	92
d	PhCHO	CH(OH)Ph	58	
e			63	
f	PhCOCl		63	62
g	PhNCO		67	76
h	CO_2	CO_2Me	45	
i	EtOH	H	65	88

[a] Reactions performed in pentane. [b] Represent pure, homogeneous isolated products. [c] HMPA (3.0 equiv) added prior to methyl iodide.

expected to furnish **7**, and aqueous workup provided **8**. In order to confirm the regiochemistry, an X-ray structure of **8** was obtained. This result prompted a study of other organolithium reagents in the hope of preparing a variety of regioselectively 1,2,3-trisubstituted benzenes.

Since it was now established that the benzyne **4** does not form until temperatures of the solution of **2** reached ~0 °C, it would be possible to introduce a variety of nucleophiles and allow benzyne formation to take place in situ and be trapped by the nucleophile present in the solution.

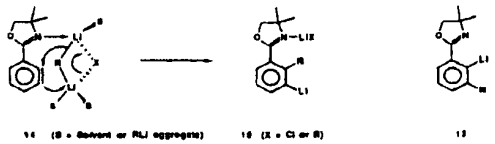
Addition of *n*-butyllithium (3.0 equiv) in pentane to **1** at −78 °C, followed by warming the solution to room temperature to allow butyllithium addition to the benzyne and recooling to −78 °C prior to electrophilic quench, gave the adducts **10**. The results with a variety of electrophiles are summarized in Table I. Hydrolysis (4.5 N HCl) of the oxazoline and esterification with diazomethane gave the benzoic esters **11**, also described in Table I.



The use of pentane or hexane as a solvent rather than THF, ether, or DME was the result of optimization experiments. It was found that nonpolar solvents, with 3.0 equiv of alkyllithiums as the base and nucleophile, gave the highest yields.

The formation of the regioisomer **10** was confirmed by an alternate unambiguous synthesis. From previous work in this laboratory,[13] we were able to form **10** (E = H) by merely treating known (2-methoxyphenyl)oxazoline **12** with *n*-butylmagnesium bromide. The products were identical in all respects. Furthermore, **11** (E = H) was degraded to phthalic acid for additional confirmation.

The formation of **9** rather than the meta addition product **13** was indeed surprising in light of the meta addition observed earlier to give the adduct **3**. However, on the basis of the solvent polarity study, wherein hexane or pentane proved to be superior to THF, we conclude that the regiochemistry observed is due to a kinetic complex-induced proximity effect (CIPE).[14] Thus, the organolithium approaches the benzyne, by chelation with the highly electron-rich π-system present in the oxazoline **14**, and this



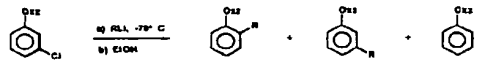
complex forces the alkyl group into the ortho position of the benzyne bond leading to **15** (or **9**) and ultimately the products described in Table I. That this chelation phenomenon (CIPE) should be totally exclusive caused us some concern, and indeed, upon examination of the crude adduct **10** (E = H) by gas chromatography we could, in fact, observe 10–12% of the *m*-butyl isomer derived from proton quench of **13**. It was now of interest to assess the steric or electronic effects that were responsible for this regiochemistry and to try to explain the difference between major ortho addition with *n*-BuLi and major meta addition with (*o*-lithiophenyl)oxazoline **2**.

Table II. Addition of Organolithiums (3.0 equiv) to **1** and Ratio of Meta to Ortho Addition

RLi	**16**,[a,d] %	**17**,[a,d] %	RLi	**16**,[a,d] %	**17**,[a,d] %
n-BuLi	70	11[e]		38[b]	31[b]
s-BuLi	46	12[e]			
PhLi	48	24		46	33
			2	0	68[f]

[a] Ratios determined by gas chromatography unless otherwise stated. [b] Ratio determined by HPLC. [c] Isolated yield. [d] Remainder of material was **1** and/or **18**. [e] Contains 12–15% **18**. [f] Ether–pentane (1:1) used to solubilize the lithium reagents at −78 °C.

A series of organolithium reagents (Table II) were added to **1** in pentane or in 1:1 pentane–ether at −78 °C and allowed to metalate the ortho position of **1**. After being warmed to room

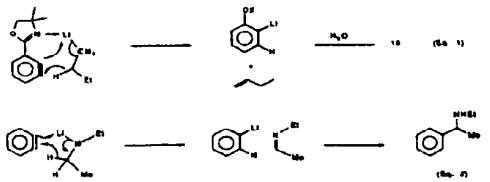


temperature, the organolithium was allowed to add to the benzyne, followed by quenching with ethanol to furnish **16**, **17**, and unexpectedly, **18**. It is seen from the ratio in Table II that there is a definite preference for ortho addition in the benzyne for *n*-butyl, *sec*-butyl, and phenyllithium. On the other hand, *o*-ethyl and *o*-methoxyphenyl lithiums are seemingly more competitive for both ortho and meta positions. This could be due to a steric crowding due to the ortho substituent or, more probably, the presence of ether in the reaction, which increases the polarity of the solvent thereby weakening the coordinating ability of the oxazoline to the organolithium reagent. In support of this, internally coordinated organolithium reagents, such as **2**, ignore the kinetic effect of coordination and simply add to the benzyne in a thermodynamically controlled process, i.e., the meta-substituted product **17** is formed exclusively. The phenyloxazoline **18** in the product mixture is presumed not to come from direct halogen–metal exchange but rather through the intermediacy of the benzyne. Since it was observed only with *n*-butyl- and *sec*-butyllithium (Table II), it can be explained by a β-hydride elimination (eq 1) analogous to the elimination reported[15] with lithium amides and benzynes (eq 2). In an attempt to further elaborate aromatic rings via the benzyne–oxazoline methodology, the *o*-methoxy derivative **19** (prepared from the benzoic acid in 79% overall yield) was subjected to *o*-methoxy displacement by Grignard reagents[9] af-

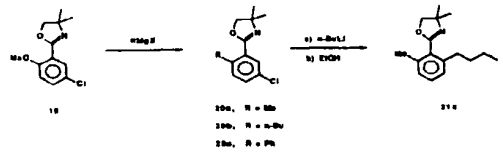
(13) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

(14) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

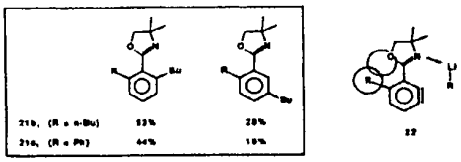
(15) Wittig, G.; Stoeber, I. *Justus Liebigs Ann. Chem.* **1972**, *758*, 84.



fording **20a–c**. It was now desirable to acertain whether treatment

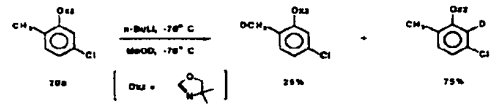


with excess *n*-butyllithium (3–3.5 equiv) in pentane would proceed with ortho metalation and subsequent loss of LiCl to furnish the benzyne or whether benzylic metalation in **20a** would compete with the desired process. Benzylic metalation in (*o*-methylphenyl)oxazolines is well-known.[5,16] As it turned out, benzyne formation, via ortho metalation, was the course followed, providing the bis-ortho-substituted system **21**, exclusively. However, for **20b** and **20c**, the addition to the benzyne intermediate was not as regioselective, giving **21b** and **21c** as mixtures of ortho and meta



addition products. This lack of selectivity of butyllithium addition to the benzynes containing ortho substituents could be due to out-of-plane twisting of the oxazoline moiety by bulky ortho substituents **22**, resulting in loss of proximity between the organolithium reagents and the ortho position of the benzyne. However, these derivatives **21a–c** were all obtained as pure homogeneous isomers after flash chromatography.

The surprising fact that ortho metalation in **20a,b**, rather than benzylic metalation, was the major deprotonation pathway prompted an experiment in competitive metalation using ether rather than pentane as the solvent. Thus, **20a** was metalated in



ether at −78 °C with 1 equiv of *n*-butyllithium and quenched immediately thereafter with methanol-*d*. The ratio of benzylic deuterium to ortho deuterium was 1:3, thus indicating even in a polar solvent such as ether, ring metalation predominates. Before leaving this section on organolithium addition to benzynes, it should be stated that the method utilized to prepare **21b**, namely, the (2,6-di-*n*-butylphenyl)oxazoline and ultimately the 2,6-disubstituted benzoic acid, is inferior to our earlier report wherein symmetrical 2,6-dialkyl derivatives are prepared.[9]

α-Lithionitrile Addition to Benzynes. The addition to the oxazoline benzyne was extended to α-lithionitriles providing an interesting, novel, and useful route to 1,2,3-trisubstituted benzenes **27**. Although nitrile anions have been previously reported[16] to add to benzynes, the process described herein (Scheme II) is

(16) Xin, H. Y.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397.

Scheme II

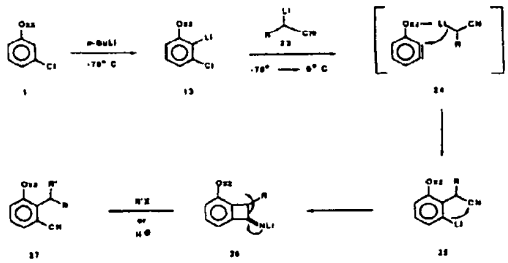


Table III. Addition of Lithionitriles to **1**[a,b] and Formation of Benzenes **27**

entry	lithionitrile **23**, R	electrophile	benzene **27** R	benzene **27** R′	yield,[c] %
a	H	EtOH	H	H	57
b	Et	EtOH	Et	H	68
cx	H	MeI	H	Me	46
d	Me	MeI	Me	Me	73
e	Et	MeI	Et	Me	73
f	H	*n*-BuBr[e]	H	*n*-Bu	45
gf	*i*-Pr	EtOH	*i*-Pr	H	42
h	*n*-hept	EtOH	*n*-hept	H	62
i	$PhCH_2$	EtOH	$PhCH_3$	H	56
j	Ph	EtOH	Ph	H	21[d]

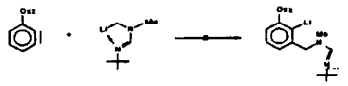
[a] All reactions performed in 1:1 ether–pentane. [b] Lithionitriles were prepared in ether with 0.5 equiv excess LDA. [c] All yields are for isolated, homogeneous material. [d] In addition, 19% of the isomeric 2-cyano-3-phenyl product was isolated. [e] HMPA added prior to addition of the halide.

considerably more interesting in that the net result is a fission of the alkyl cyanide bond which formally adds across the benzyne bonds. Specifically, treatment of **1** with 1.1 equiv of butyllithium in pentane at −78 °C gives the ortho-lithiated species **2**. At this juncture, a solution of lithiated alkyl nitriles **23** in ether was introduced such that the solvent was now 1:1 pentane–ether. Since both species **2** and **23** are nucleophiles, no interaction occurs between them other than possible chelation. As the temperature rises, LiCl is ejected forming the benzyne which, now as an electrophile, is readily attacked (**24**) by the lithiated nitrile furnishing **25**. The latter regiochemical result is again due to the complex-induced proximity effect (CIPE)[14] which influences alkyl attack on the benzyne bond at the ortho position. The 3-lithio-2-alkylnitrile **25** then undergoes intramolecular arylation to the benzocyclobutanimine **26**, which fragments to the more stable 3-cyano-2-alkylbenzene **27** (R′ = Li). Quenching lithiated **27** with a proton or an alkyl halide furnishes the final product as the nitrile **27**. A variety of lithiated nitriles were examined along with a variety of electrophilic quenches. These are tabulated in Table III.

This interesting fragmentation (**25**–**27**) has some precedent in the addition of enolates to benzynes as reported by Caubere.[17]

(17) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301. Caubere, P.; Carre, M. C.; Gregoire, B. *J. Org. Chem.* **1984**, *49*, 2050; Carre, M.; Jamart-Gregoire, B.; Geoffroy, P.; Caubere, P. *Tetrahedron* **1988**, *44*, 127.

(18) Since internally coordinated nucleophiles would be expected to be poorly complexed prior to addition to the benzene, we examined lithioformamidines[19] as potential nucleophilic agents. However, no addition to the

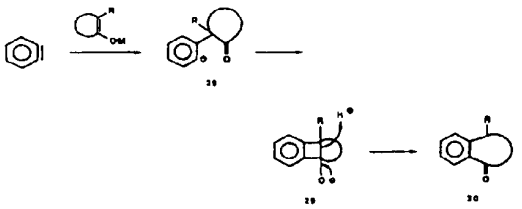


benzyne could be detected.

(19) Meyers, A. I.; ten Hoeve, W. *J. Am. Chem. Soc.* **1980**, *102*, 7125.

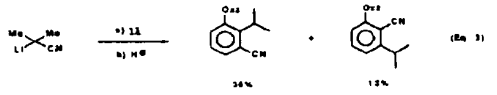
(20) Ellefson, C. R. *J. Org. Chem.* **1979**, *44*, 1533.

The attack of an enolate on benzyne furnishes **28**, which rearranges



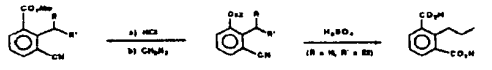
to the benzocyclobutane **29**. Because the enolates are derived from cyclic ketones, the fragmentation of **29** to **30** produces a macrocyclic benzoketone. Thus, this present process may be considered analogous to that described by Caubere.

There were some notable limitations to this tandem alkylation process. For example, tertiary lithionitriles added both poorly and nonselectively to the benzyne as shown in eq 3. Thus, steric



factors begin to play a role in the complexation step **24** allowing addition to occur under thermodynamic control. However, this is not a serious problem since highly branched ortho substitution can be introduced by alkylation of the intermediate **26**. For example, the 2-isopropyl derivative in eq 3, obtained in only 36% yield, was prepared by sequential alkylation in 73% yield (Table III, entry d). Another limitation noted was the poor addition efficiency of (lithiophenyl)acetonitrile (Table III, entry j). The "soft" nature of this anion gave poor yields of **27** and a comparable yield of the 3-phenyl isomer, analogous to the results shown in eq 3.

The cyano derivatives **27** were readily hydrolyzed in 4.5 N HCl furnishing the cyanocarboxylic acids, which were immediately esterified with diazomethane giving the methyl esters in good to

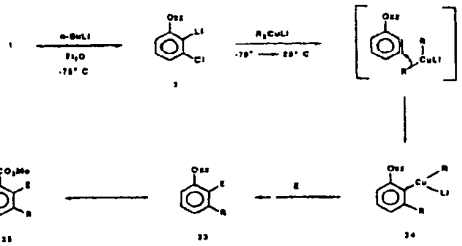


moderate yields (Table IV). If the hydrolysis was performed in refluxing 6 N sulfuric acid, both the cyano and oxazoline groups were hydrolyzed to give the isophthalic acid **32**. Furthermore, this provided additional confirmation that the regiochemical addition of the lithionitriles proceeded as mentioned above (Scheme II).

The data given in Table IV indicate that the overall process **1** → **31** was accomplished in ~50% yield, and this is considered rather satisfactory for the transformation which took place in three steps from commercially available and inexpensive *m*-chlorobenzoic acid.

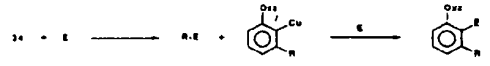
Alkyl Cuprate Additions to Benzynes. In the previous discussion on this methodology, it was shown that alkyllithiums add to the benzyne, furnishing as the major product (2-alkyl-3-E-phenyl)-oxazoline **10**. It was, for reasons outside the scope of this report, further desirable to reach the isomeric series (2-E-3-alkylphenyl)oxazolines **33** (Scheme III). Therefore, nucleophiles that may add to benzyne at the meta position were examined, and the dialkyl cuprates surfaced as the reagent of choice.

Treatment of **1** with 1.0 equiv of *n*-butyllithium in ether to generate the ortho lithio derivative **2** was followed by addition of 3.0 equiv of the appropriate cuprate in ether. The two nucleophilic reactants were, once again, inert toward each other until



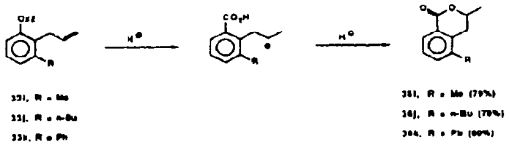
the solution was allowed to warm to room temperature. The transformation of **2** into the benzyne in the presence of the cuprate gave rise to addition product **34**. The resulting mixed cuprate **34** was then recooled and quenched with methanol, acid chloride (acetyl or benzoyl), or allyl bromide. In this fashion, a series of tri-substituted benzenes **33** was obtained (Table V) wherein the *electrophile entered exclusively at the ortho position.* No trace of the isomeric system **10** was found upon gas or high-pressure liquid chromatography. In fact, the gas chromatographic analysis of known mixtures of both isomeric series, compared to the crude reaction product derived from the cuprate addition, showed less than 0.01% (limits of detection) of **10** present in **33**. A study of various cuprates (Table V, entries b–d) showed that the extent of benzyne trapping was not affected by the nature of the cuprate (pentynyl[23] or cyano[24]), so all subsequent reactions were performed with lithium dialkylcuprates.

It was found that only the electrophiles listed in Table V were satisfactorily incorporated into the cuprate **34**, while other typical electrophiles (alkyl halides, carbonyls, epoxides) gave only starting materials or products of decomposition. This was interpreted to mean that the R group on copper in **34** is transferred instead of the aryl group, reacting with the introduced electrophile and producing the organocopper species **36**. In order to effect the



transformation to **33**, 10 equiv of electrophile were introduced into the solution of **34**. Organocopper reagents such as **36** are known to couple with allylic groups[20] and acyl groups.[21] More recently, Alexakis has shown[22] that organocopper reagents will couple with acetals in the presence of certain Lewis acids, however this failed to bring about alkylation of **34**.

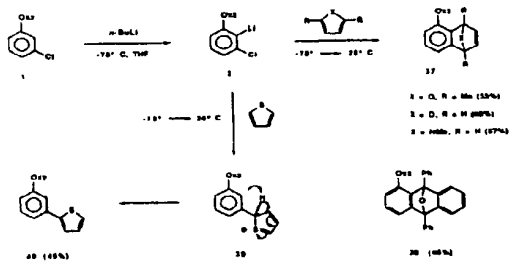
Hydrolysis of the oxazoline **33** using 4.5 N hydrochloric acid at reflux formed the carboxylic acid, which was immediately treated with diazomethane affording the methyl esters of the



benzoic acids **35**. In the case of the allyl-substituted benzenes (**33**, E = allyl), hydrolysis did not give the benzoic acids, but produced the lactones (dihydroisocoumarins) **36** in good yields. Presumably, the acidic medium generates the carbocation which is rapidly cyclized to the lactones.

Cycloaddition to Benzyne 4. The cycloaddition[7c] of several dienes to **4** was briefly examined and gave satisfactory yields of cycloadducts. Thus, a THF solution of **1** was treated with 1.1 equiv of *n*-BuLi at −78 °C, the diene (furan, pyrrole, or thiophene)

(21) Normant, J. F. *Synthesis*, **1972**, 63.
(22) Alexakis, A.; Ghiribi, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075, 3079.
(23) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(24) Levisalles, J.; Gorlier, J. P.; Hamon, S.; Wagon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 88.



was added, and the solution was allowed to warm to −10 to −15 °C, followed by stirring at room temperature overnight. Cycloadducts from the furan, pyrrole, and 2,5-diphenylisobenzofuran **37** and **38**, respectively, were obtained in moderate yields. Once again, very little cycloadduct was detected (HPLC) below −15 °C, indicating the stability of the lithiated species **2** below −15 °C. In fact, a study of time vs percent yield of cycloadduct at −12 °C showed that after 4 h only 56% cycloadduct and 40% (*m*-chlorophenyl)oxazoline **1** were present. However, at 20 °C the time–yield study showed 85% cycloadduct (~10% **1**) present after 1.75 h. This behavior of **2** going on to benzyne is consistent with all the previous results mentioned earlier in this discussion.

It is interesting to note that previous base-induced benzyne formation gave, on addition of furans, rearranged cycloadducts.[25] However, under the mild conditions employed herein, no rearranged cycloaddition products were observed, only those shown as **37–39**. The reaction of **2** with thiophene, however, did not lead to a simple, expected cycloadduct. Instead, the thiophene addition product **40** was formed. This may be explained as passing through the ylide **39** which is formed by nucleophilic thiophene addition to the benzyne.[26] Proton transfer (1,3) then leads to the product **40**. However, trans-metalation between **2** and thiophene, followed by addition of 2-lithiothiophene to the benzyne cannot be rigorously excluded.

Experimental Section[27]

2-(3-Chlorophenyl)-4,4-dimethyl-2-oxazoline (1). In a 250-mL flask were placed 100 g of 3-chlorobenzoic acid (0.639 mol; Aldrich) and 140 mL of thionyl chloride (228 g, 1.92 mol). The flask was heated in a 100 °C oil bath for 1 h and then removed from the bath. Excess thionyl chloride was then removed from the mixture via distillation. The crude acid chloride was allowed to cool to room temperature, then dissolved in 290 mL of methylene chloride, and placed in a dropping funnel over a 1-L flask containing 114 g of 2-methyl-2-aminopropanol (1.28 mol, 2 equiv) in 290 mL of methylene chloride. The flask was cooled in a 0 °C bath, and the acid chloride was added dropwise to the stirred solution of amino alcohol. After addition of the acid chloride was complete, the reaction mixture was removed from the ice bath and stirred at room temperature for 14 h. The mixture was filtered, the cake washed with methylene chloride (150 mL), and the filtrate concentrated in vacuo to leave a white solid, the crude amide alcohol (148 g, 0.649 mol, 102%). The amide alcohol was immediately carried on by dissolving in 170 mL of benzene and 500 mL of methylene chloride. The mixture was transferred to a 1-L flask fitted with a dropping funnel, condenser, and a mechanical stirrer. A total of 140 mL of thionyl chloride (228 g, 1.92 mol) was slowly added to the stirred solution. The reaction mixture was warmed to reflux and then cooled. The mixture was stirred at room temperature for 2.5 h. The excess thionyl chloride was destroyed via dropwise addition of H_2O and 40% NaOH. Addition of 40% NaOH was continued until the water layer was at pH 11. The water layer (750 mL) was extracted with diethyl ether (2 × 1.75 L). The combined ether layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave crude **1** as a yellow oil (132.2 g, 0.631 mol, 99%). Distillation in vacuo [bp 80–83 °C (0.05 mmHg)] provided **1** (93.7 g, 70%) as a colorless oil: IR (film) 2960 (C—H), 1645 (C═N), 1600 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.36 (s, 6 H), 4.08 (s, 2 H), 7.29 (t, 1 H, J = 7.85 Hz), 7.40 (ddd, 1 H, J = 1.48, 2.28, 7.58 Hz), 7.80 (dt, 1 H, J = 1.36, 7.58 Hz), 7.94 (t, 1 H, J = 1.47 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 28.19, 67.48, 78.99, 125.93, 127.91, 129.14, 129.55, 130.71, 133.93, 160.37. Anal. Calcd for $C_{11}H_{12}NOCl$: C, 63.01; H, 5.77. Found: C, 62.96; H, 5.78.

4-Chloro-8-(2-oxazolinyl)fluorenone (8). To a stirred solution of 566 mg (2.70 mol of **1** in 15 mL of THF cooled to −78 °C under nitrogen was added 1.04 mL of 2.75 M *n*-butyllithium (hexane) and the mixture stirred for 30 min. The solution was then allowed to warm to −10 °C and kept at this temperature for 2–3 h and then allowed to reach room temperature overnight. The reaction mixture was poured into saturated ammonium chloride solution and the organic layer removed by ether extraction. The ether extracts were washed successively with water, brine, and water, dried ($MgSO_4$), and concentrated to a green oil. The oil was subjected to flash chromatography (silica gel, ethyl acetate–hexane 3:7). The first fraction contained a small amount of **1**, the second fraction contained 286 mg (68%) of the fluorenone **8**: mp 136–137 °C (hexane–ethyl acetate); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.52 (s, 6 H), 4.22 (s, 2 H), 7.00–7.60 (m, 5 H), 8.20 (dd, 1 H, J = 6.0, 3.7 Hz); IR (KBr) 2995, 2800, 1715, 1660, 1590, 1110, 930, 730 cm^{-1}; MS, m/e 313 (M + 2), 311 (M^+), 298, 296 (base, 281, 240, 227, 185, 150, 78). Anal. Calcd for $C_{17}H_{14}NO_2Cl$: C, 69.35; H, 4.53. Found: C, 69.23; H, 4.57.

This analytical sample was subjected to single-crystal X-ray determination (see supplementary material).

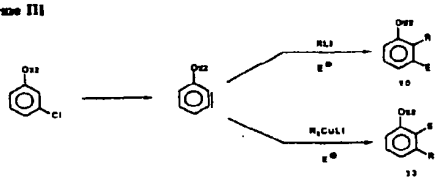
Butyllithium–Electrophile Tandem Additions to 10. Typical Procedure. 2-(2-*n*-Butyl-3-methylphenyl)-4,4-dimethyl-2-oxazoline (10a). A total of 0.398 g of **1** (1.90 mol, 1 equiv) was placed in a 50-mL flask containing an argon atmosphere, 20 mL of pentane was added, and the mixture was stirred until a homogeneous solution was obtained. The solution was then cooled in an acetone–dry ice bath, and 2.60 mL of 2.20 M *n*-butyllithium (5.72 mol, 3 equiv) was added via syringe. The reaction mixture was stirred at low temperature for 0.5 h and then at room temperature for 0.5 h. The flask was then recooled in the acetone–dry ice bath, and 1.0 mL of hexamethylphosphoramide (HMPA) (1.03 g, 5.75 mol, 3 equiv) was added via syringe. No HMPA was used in any of the subsequent procedures that follow. The reaction was stirred 3 min and then methyl iodide (0.60 mL, 1.37 g, 9.64 mol, 5 equiv) was added via syringe. The reaction mixture was allowed to slowly warm to room temperature with stirring. The mixture was stirred a total of 5–6 h following addition of methyl iodide and then concentrated in vacuo. The resulting red oil was taken up in hexane (80 mL) or ether and washed with saturated sodium chloride (2 × 40 mL). The organic layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a red oil. Medium-pressure chromatography (5% ethyl acetate–hexanes) provided 0.315 g of **10a** (1.29 mol, 68%) as a colorless oil: IR (film) cm^{-1} 2960 (C—H), 1645 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ .94 (t, 3 H, J = 6.34 Hz), 1.15–1.46 (m, 4 H), 1.38 (s, 6 H), 2.34 (s, 3 H), 2.89 (t, 2 H, J = 7.81 Hz), 4.06 (s, 2 H), 7.00–7.26 (m,

Table IV. Hydrolysis of (Cyanophenyl)oxazolines **27** to Methyl Cyanobenzoates **31**

entry	R	R′	31,[a,b] %	% overall from 1[d]
a	H	H	98	56
b	Et	H	80	54
c	H	Me	87	40
d	Me	Me	86	63
e	Me	Et	77	56
f	H	Bu	70[e]	42
g	H	*i*-Pr	79	48
h	H	*n*-hept	83[e]	50
i	H	$PhCH_2$	86	48

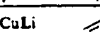
[a] All yields are for pure, homogeneous materials. [b] All hydrolyses were carried out in 4.5 N HCl, reflux, 12–15 h. [c] Hydrolyzed in 1:2 THF–H_2O solution. [d] Physical data are presented as supplementary material.

Scheme III



(25) Shepard, K. L. *Tetrahedron Lett.* **1975**, 3371. Kobrich, G. *Chem. Ber.* **1959**, *92*, 2985.
(26) A related reaction between benzyne and *N*-methylpyrrole has been reported: Keuhne, M. E.; Kitagawa, T. *J. Org. Chem.* **1964**, *29*, 1270.
(27) Microanalyses were performed by Desert Analytics, Tucson, AZ.

Table V. Addition of Cuprates to Benzyne **1** and Formation of 2,3-Disubstituted Methyl Benzoates **35**

entry	cuprate[a]	electrophile	trisubstituted benzene **33** R	E	%	ester **35**,[c] %
a	Me_2CuLi	MeOH[b]	Me	H	66	92
b	$(n\text{-Bu})_2CuLi$	MeOH[b]	*n*-Bu	H	56	95
c	*n*-BuCuCNLi	MeOH[b]	*n*-Bu	H	47	
d	*n*-Bu(pentynyl)CuLi	MeOH[b]	*n*-Bu	H	53	
e	Ph_2CuLi	MeOH[b]	Ph	H	67	99
f	Me_2CuLi	CH_3COCl	Me	MeCO	47	99
g	$(n\text{-Bu})_2CuLi$	CH_3COCl	*n*-Bu	MeCO	67	87
h	Ph_2CuLi	CH_3COCl	Ph	MeCO	28	73
i	Me_2CuLi		Me		69	*d*
j	$(n\text{-Bu})_2CuLi$		*n*-Bu		88	*d*
k	Ph_2CuLi		Ph		68	*d*
l	Me_2CuLi	PhCOCl	Me	PhCO	37	98
m	$(n\text{-Bu})_2CuLi$	PhCOCl	*n*-Bu	PhCO	70	84
n	Ph_2CuLi	PhCOCl	Ph	PhCO	66	90

[a] Three equivalents of cuprate added to lithiated **1**. [b] Degassed methanol used. [c] Yields are those of pure, homogeneous, material. [d] These products were dihydroisocoumarins **36**. [e] Physical data and experimental details are presented as supplementary material.

2 H), 7.45 (dd, 1 H, J = 1.95, 6.83 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 14.00, 19.84, 23.29, 28.42, 29.94, 32.51, 67.78, 78.75, 125.11, 127.56, 128.20, 132.12, 136.55, 140.99, 163.18. Anal. Calcd for $C_{18}H_{33}NO$: C, 78.32; H, 9.45. Found: C, 78.08; H, 9.09.

Hydrolysis of Oxazolines 10 to Methyl Esters (11). Typical Procedure. Methyl 2-*n*-Butylbenzoate (11l). In a 25-mL flask were placed 0.126 g of oxazoline **10l** (0.545 mol) and 13 mL of 4.5 N HCl. The solution was heated to reflux for 14 h and then allowed to cool to room temperature. The mixture was partitioned between diethyl ether (2 × 80 mL) and saturated sodium chloride. The combined ether layers were treated with 6 equiv of diazomethane, generated from 0.70 g of Diazald (3.27 mol, 6 equiv), stirred for 2 h, then dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Column chromatography (16 g of silica, 5% ethyl acetate–hexanes) provided 0.092 g of **11l** (88%) as a colorless oil. A portion was purified via bulb-to-bulb distillation: bp 70 °C (0.05 mmHg); IR (film) 2960 (C—H), 1720 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 3 H, J = 7.33 Hz), 1.34–1.45 (m, 2 H), 1.52–1.63 (m, 2 H), 2.94 (t, 2 H, J = 7.57 Hz), 3.87 (s, 3 H), 7.22 (d, 2 H, J = 7.64 Hz), 7.37 (d, 1 H, J = 7.47 Hz), 7.84 (d, 1 H, J = 7.80 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 13.94, 22.76, 33.97, 34.14, 51.72, 125.40, 129.31, 130.31, 130.66, 131.53, 144.44, 167.91.

2-(5-Chloro-2-methoxyphenyl)-4,4-dimethyl-2-oxazoline (19). In a 12-L flask equipped with a mechanical stirrer were placed 2.9 L of H_2O and 38 g of NaOH (0.95 mol). The mixture was stirred until a homogeneous solution was obtained. A total of 2.9 L of methylene chloride was added followed by 100 g of 5-chlorosalicylic acid (Aldrich; 0.580 mol) and 19 g of tetra-*n*-butylammonium bromide (0.590 mol). The mixture was stirred vigorously, and 165 mL of dimethyl sulfate (220 g, 1.75 mol) was slowly added to the mixture. The reaction mixture was stirred at room temperature for 4 h, during which the organic layer was separated and the water layer washed with methylene chloride (2 L). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a yellow oil. A portion was purified via bulb-to-bulb distillation: bp 57 °C (0.02 mmHg); IR (film) 2950 (C—H), 1735 (C=O), 1600 (C=C), 1235 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 3.88 (s, 6 H), 6.90 (d, 1 H, J = 9.03 Hz), 7.41 (dd, 1 H, J = 2.69, 9.03 Hz), 7.75 (d, 1 H, J = 2.69 Hz). The material was carried on to 2-methoxy-5-chlorobenzoic acid below.

The ester was placed in a 3-L flask with 1 L of 10% sodium hydroxide. The mixture was stirred at room temperature for 16 h, during which the mixture turned to a white solid. The mass was dissolved in water, by portions, and each portion acidified with concentrated hydrochloric acid to precipitate the acid. Each portion was extracted with diethyl ether, combined with the previous ether extracts, and finally dried over anhydrous magnesium sulfate. Filtration, followed by concentration in vacuo provided the crude acid (104.6 g, 97%), which was immediately carried on to the oxazoline **19**.

The crude acid (104.6 g, 0.558 mol) was placed in a 1-L flask with 121 mL of thionyl chloride (197 g, 1.66 mol). The mixture was stirred at room temperature for 0.5 h and then heated at reflux for 0.5 h. Excess thionyl chloride was removed via distillation. The resulting acid chloride was allowed to cool to room temperature, whereupon it solidified. The solid was dissolved in 300 mL of methylene chloride and placed in a dropping funnel over a 1-L flask containing 100 g of 2-amino-2-methyl-1-propanol (1.12 mol) in 255 mL of methylene chloride. The flask was cooled in an ice bath, and the acid chloride was added dropwise to the stirred solution. After addition of the acid chloride was complete, the mixture was stirred at room temperature for 20 h. The mixture was then filtered and the cake washed with 0.5 L of methylene chloride and concentrated in vacuo to leave 145 g of amide alcohol as a brown solid. The amide alcohol was dissolved in 1 L of methylene chloride and placed in a 2-L flask. To the stirred solution was slowly added 121 mL of thionyl chloride (197 g, 1.66 mol). After addition of the thionyl chloride was complete, the reaction was stirred at room temperature for 1.5 h. Excess thionyl chloride was destroyed by dropwise addition of H_2O and 40% NaOH. Addition of 40% NaOH was maintained until the water layer was pH 11. The mixture was diluted with 1 L of saturated NaCl, and the layers were separated. The water layer was washed with 1.5 L of diethyl ether, and the organic layers were combined and dried over anhydrous potassium carbonate. Filtration and concentration in vacuo gave crude **19** which was purified via bulb-to-bulb distillation to provide 110.0 g (79%) as a white solid: mp 48–50 °C; IR (film) 2970 (C—H), 1650 (C=N), 1600 (C=C), 1280 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.39 (s, 6 H), 3.87 (s, 3 H), 4.09 (s, 2 H), 6.88 (d, 1 H, J = 8.88 Hz), 7.31 (dd, 1 H, J = 2.55, 8.82 Hz), 7.73 (d, 1 H, J = 2.65 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 36.40, 59.84, 69.15, 78.66, 107.07, 112.09, 117.21, 121.98, 122.47, 143.57, 146.16. The material (**19**) was carried on to the compounds described below.

2-(2-Methyl-5-chlorophenyl)-4,4-dimethyl-2-oxazoline (20a). In a 250-mL flask containing an argon atmosphere were placed 2.56 g (10.7b mol) of **19**, 100 mL of diethyl ether, and 50 mL of THF. To the resulting solution was added 11 mL of 2.9 M methylmagnesium bromide (31.9 mol, 3 equiv) at room temperature with stirring. The reaction was stirred at room temperature for 48 h, then poured into saturated sodium chloride (200 mL), and shaken with diethyl ether (2 × 250 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Flash chromatography (70 g of silica gel, 7.5% ethyl acetate–hexanes) provided **20a**, which was further purified via bulb-to-bulb distillation [mp 60 °C (0.02 mmHg)] to provide 1.71 g (7.64 mol, 71%) as a colorless oil: IR (film) 2970 (C—H), 1650 (C=N), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.37 (s, 6 H), 2.52 (s, 3 h), 4.05 (s, 2 H), 7.12 (d, 1 H, J = 8.17 Hz), 7.25 (dd, 1 H, J = 2.31, 8.21 Hz), 7.76 (d, 1 H, J = 2.29 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 20.95, 28.42, 67.95, 78.52, 128.90, 129.37, 129.96, 130.95, 132.12, 136.73, 161.13. Anal. Calcd for $C_{12}H_{14}NOCl$: C, 64.43; H, 6.31. Found: C, 64.30; H, 6.32.

2-(2-*n*-Butyl-6-methylphenyl)-4,4-dimethyl-2-oxazoline (21a). In a 50-mL flask containing an argon atmosphere were placed 0.224 g of **20a** (1.00 mol, 1 equiv) and 30 mL of pentane. The resulting solution was cooled in an acetone–dry ice bath, and a total of 1.25 mL of 2.34 M *n*-butyllithium (3.04 mol, 3 equiv) was added via syringe. The reaction was stirred at low temperature for 0.5 h, then removed from the low-temperature bath, and stirred at room temperature for 40 min. The reaction was then quenched with absolute ethyl alcohol and partitioned between diethyl ether (120 mL) and saturated sodium chloride (30 mL). The ether layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Flash chromatography (12 g of silica gel, 5% ethyl acetate–hexanes) provided a total of 0.102 g of **21a** (0.415 mol, 42%) as a colorless oil. A portion was further purified via bulb-to-bulb distillation [mp 63 °C (0.05 mmHg)] to provide a sample for combustion analysis: IR (film) 2960 (C—H), 1665 (C=N), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (t, 3 H, J = 7.17 Hz), 1.31–1.52 (m, 2 H), 1.41 (s, 6 H), 1.52–1.64 (m, 2 H), 2.32 (s, 3 H), 2.63 (t, 2 H, J = 7.77 Hz), 4.08 (s, 2 H), 7.00–7.04 (m, 2 H), 7.18 (t, 1 H, J = 7.65 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 13.94, 19.49, 22.76, 28.42, 33.44, 33.74, 67.83, 78.69, 126.28, 127.04, 128.50, 128.96, 136.55, 141.51, 161.89. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.06; H, 9.53.

2-(2,6-Di-*n*-butylphenyl)-4,4-dimethyl-2-oxazoline (21b). In a manner similar to **21a**, the butyl oxazoline **20b** was treated with 3.3 equiv of *n*-butyllithium in pentane. Workup and flash chromatography gave 0.154 g (52%) of **21b** as a colorless oil. A portion was further purified via bulb-to-bulb distillation [mp 70 °C 0.05 mmHg)] to provide a sample for combustion analysis: IR (film) 2960 (C—H), 1670 (C=N), 1030

(C—O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.91 (t, 3 H, J = 7.28 Hz), 1.28–1.41 (m, 2 H), 1.41 (s, 6 H), 1.53–1.64 (m, 2 H), 2.62 (t, 2 H, J = 7.77 Hz), 4.07 (s, 2 H), 7.03 (d, 2 H, J = 7.58 Hz), 7.19 (d, 1 H, J = 7.66 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 13.89, 22.76, 28.31, 33.44, 33.68, 67.78, 78.63, 126.22, 128.09, 128.90, 141.40, 161.83. Anal. Calcd for $C_{18}H_{29}NO$: C, 79.39; H, 10.17. Found: C, 78.74; H, 10.16.

2-(2-Ethyl-3-cyanophenyl)-4,4-dimethyl-2-oxazoline (27c). Typical Procedure. To a stirred solution of **1** (0.285 g, 136 mol) in 20 mL of pentane under an argon atmosphere cooled in an acetone–dry ice bath was added 0.76 mL of 2.39 M *n*-butyllithium (1.33 equiv, 1.82 mol). The reaction was stirred at low temperature (acetone–dry ice) for 0.5 h and then the anion of acetonitrile was added via cannula in 20 mL of diethyl ether. The anion was generated from 4.5 equiv of LDA and 0.30 mL of acetonitrile (4 equiv) in 20 mL of diethyl ether cooled in an acetone–dry ice bath for 0.5 h under an argon atmosphere.

The flask containing both ortho-lithiated **1** and the nitrile anion was then removed from the low-temperature bath and stirred at room temperature for 45 min. During this period the reaction changed from light yellow to dark blue. The reaction was then recooled in an acetone–dry ice bath and 1.0 mL of methyl iodide (or alkyl halide, or ethanol) (16.4 mol, 12 equiv) was added to the flask. The reaction was allowed to slowly warm to room temperature with stirring for 2 h. The reaction was partitioned between anhydrous ether (60 mL) and aqueous NaCl solution. The combined ether layers were dried with anhydrous potassium carbonate. The ether solution was then filtered, and the volatile organics were removed in vacuo to leave a dark red oil. Purification was achieved via flash chromatography on 12 g of silica gel using 7.5% ethylk acetate–hexanes as eluent. In this manner 0.144 g (0.63 mol, 46%) was obtained as a colorless oil following removal of solvents in vacuo. A portion was further purified via bulb-to-bulb distillation [mp 65 °C (0.05 mmHg)] to provide **27c** as a white crystalline solid: mp 50–51 °C; IR (film) 2960 (C—H), 2220 (CN), 1645 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.28 (t, 3 H, J = 7.50 Hz), 1.41 (s, 6 H), 3.24 (q, 2 H, J = 7.50 Hz), 4.12 (s, 2 H), 7.33 (t, 1 H, J = 7.80 Hz), 7.70 (dd, 1 H, J = 1.40, 7.80 Hz), 7.94 (dd, 1 H, J = 1.40, 7.80 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 15.40, 26.09, 28.36, 68.24, 79.04, 113.84, 117.64, 126.10, 128.90, 134.28, 134.74, 148.41, 160.78. Anal. Calcd for $C_{14}H_{16}N_2$: C, 73.66; H, 7.06. Found: C, 73.44; H, 7.20.

Additions of Cuprates of Benzyne 4. Typical Procedure. 2-(2-Acetyl-3-methylphenyl)-4,4-dimethyl-2-oxazoline (33f). A total of 0.157 g (0.750 mol) of **1** was placed in a 25-mL flask with 10 mL of diethyl ether. The solution was then cooled in a acetone–dry ice bath, and 0.35 mL (0.781 mol) of 2.23 M *n*-butyllithium was added via syringe. The mixture was stirred at low temperature for 0.5 h and then 3 equiv of lithium dimethylcuprate was added via cannula in diethyl ether. The cuprate was generated from 0.420 g (2.20 mol) of CuI and 4.2 mL (4.83 mol) of 1.15 M methyllithium in 10 mL of diethyl ether at −10 °C for 0.5 h.

The main reaction flask was then removed from the low-temperature bath and stirred at room temperature for 40 min. Following this period of time, the flask was recooled in the acetone–dry ice bath and 0.53 mL (7.75 mol) of acetyl chloride was added via syringe. The reaction was allowed to slowly warm to room temperature with stirring. The reaction was stirred for a total of 16 h following addition of the acetyl chloride. If methanol is used as the quench, the reaction may be worked up immediately. The mixture was then poured into a separatory funnel (250 mL) and shaken with diethyl ether (100 mL) and 5.66% ammonium hydroxide (2 × 150 mL). The ether layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Flash chromatography of the yellow oil on 12 g of silica gel using 7.5% ethyl acetate–hexanes as eluent provided 0.079 g (0.341 mol, 45%) of **47e** as a colorless oil following combination of appropriate fractions and removal of solvent in vacuo. A portion was subjected to bulb-to-bulb distillation [mp 93 °C (0.10 mmHg)] to provide a sample for combustion analysis: IR (film) 2960 (C—H), 1705 (C=O), 1650 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.34 (s, 6 H), 2.27 (s, 3 H), 2.48 (s, 3 H), 4.05 (s, 2 H), 7.28–7.32 (m, 2 H), 7.70–7.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 19.02, 28.13, 32.04, 68.01, 79.16, 123.77, 126.45, 128.09, 132.99, 142.28, 160.32, 205.22. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.60; H, 7.49.

Hydrolysis of Allylbenzenes (33l–k) to 5-Substituted 3-Methyl-3,4-dihydroisocoumarins (36). Typical Procedure. 3,5-Dimethyl-3,4-dihydroisocoumarin (**36l**). In a 25-mL flask were placed 0.123 g (0.537 mol) of **33l**, 12.5 mL of 4.5 N HCl, and a magnetic stir bar. A condenser was added, and the mixture was heated at reflux for 12–13 h. The mixture was then allowed to cool to room temperature and was partitioned between diethyl ether (2 × 100 mL) and aqueous sodium chloride solution (40 mL). The ether layers were combined and dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow-white solid. Column chromatography on 16 g of column grade silica gel using 5% ethyl acetate–hexanes as eluent provided 0.075 g (0.424 mol, 79%) of **36l** as a white crystalline material following combination of appropriate fractions and removal on solvents in vacuo. A portion was recrystallized from ethyl acetate–hexanes to provide white needles: mp 98–100 °C; IR (film) 2960 (C—H), 1715 (C—O), 1580 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.55 (d, 3 H, J = 6.29 Hz), 2.32 (s, 3 H), 2.77 (dd, 1 H, J = 11.27, 16.27 Hz), 2.95 (dd, 1 H, J = 3.33, 16.64 Hz), 4.65 (m, 1 H), 7.28 (t, 1 H, J = 7.73 Hz), 7.40 (d, 1 H, J = 7.80 Hz), 7.98 (d, 1 H, J = 7.64 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 18.79, 21.01, 31.93, 74.20, 124.70, 126.74, 127.80, 134.80, 137.49, 165.63. Anal. Calcd for $C_{12}H_{14}O_2$: C, 74.98; H, 6.86. Found: C, 74.99; H, 6.88.

Cycloadditions to Benzyne 4. General Procedure. Benzyne–2,5-Dimethylfuran Adduct 37 (X = O, R = Me). To a stirred solution of 586 mg (2.80 mol) of **1** in 15 mL of THF, cooled to −78 °C, was added 1.08 mL of 2.75 M *n*-butyllithium solution (hexane), and the mixture was allowed to stir for 30 min. Freshly distilled 2,5-dimethylfuran (2.70 g) was added and the solution warmed to −15 °C and stirred at this temperature for 5 h. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into saturated ammonium chloride and the organic material taken up in ether, washed with water, dried ($MgSO_4$), and concentrated. The resulting oil was flash chromatographed (silica gel, 20% EtOAc–hexanes) to give 38 mg of **1** and 442 mg (55%) of the desired adduct: mp 110–111 °C (hexane–ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 6 H), 1.82 (s, 3 H), 1.98 (s, 3 H), 4.02 (s, 2 H), 6.68 (d, J = 5.0 Hz, 1 H), 6.87 (d, J = 5.0 Hz, 1 H), 7.00–7.39 (m, 3 H). Anal. Calcd for $C_{17}H_{16}NO_2$: C, 75.81; H, 7.11. Found: C, 75.46, H, 7.09.

Benzyne–2,5-Diphenylisobenzofuran Adduct 38 (X = O, R = Ph). Following the procedure above, 206 mg of **1** and 203 mg of 1,3-diphenylisobenzofuran gave, after chromatography, 145.4 mg (44%) of the desired product: mp 173.5–174.0 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 107 (s, 3 H), 1.18 (s, 3 H), 2.71 (s, 1 H), 3.68 (s, 1 H), 6.88–7.96 (m, 17 H). Anal. Calcd for $C_{31}H_{22}NO_2$: C, 83.95; H, 5.68. Found: C, 83.79; H, 5.68.

Benzyne–Furan Adduct 37 (X = O, R = H). Following the procedure above, 503 mg of **1** and 2.5 mL of freshly distilled furan gave, after flash chromatography, 363 mg (6%) of the desired product as an oil: ^{1}H NMR ($CDCl_3$ δ 1.36 (s, 6 H), 4.03 (s, 2 H), 5.67 (br s, 1 H), 6.28 (br s, 1 H), 6.78–7.68 (m, 5 H). Anal. Calcd $C_{13}H_{13}NO_2$: C, 74.68; H, 6.22. Found: C, 74.39; H, 6.18.

Benzyne–*N*-Methylpyrrole Adduct 37 (X = NMe, R = H). Following the procedure above, 506 mg of **1** and 1.96 g of freshly distilled *N*-methylpyrrole gave, after chromatography (silica gel, 1% Et_3N, 5% MeOH, 94% $CHCl_3$), 350 mg (57%) of the desired adduct, as an unstable oil: MS, m/e 254 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 6 H), 2.10 (br s, 3 H), 4.00 (s, 2 H), 4.45 (br s, 1 H), 5.18 (br s, 1 H). The compound, due to instability toward air and light, did not give a satisfactory combustion analysis.

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Supplementary Material Available: Physical data for **10**, **11**, **20**, **21**, **27**, **31**, **33**, **35**, and **36**, except for those presented herein, and tables of atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for the fluorenone **8** (25 pages). Ordering information is given on any current masthead page.

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Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones

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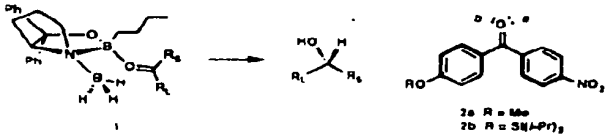
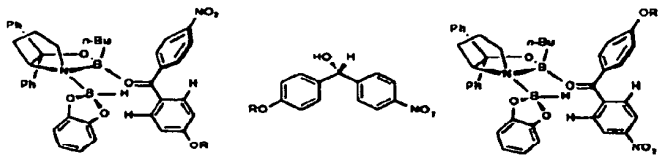
Summary: *A new class of highly enantioselective oxazaborolidine-catalyzed reductions of achiral ketones is reported which depends on stereoelectronic effects involving p-substituted non-planar aromatic ketones, or π-coordinated transition-metal containing ketones, or strained ring ketones, as exemplified in Table 1. The discovery of these reactions was guided by the transition-state model 1, for which they provide experimental support. Because high enantioselectivities (> 30 : 1) are achievable, these reductions define an excellent method for the synthesis of, for example, chiral benzhydrols, chiral propargylic, or chiral allylic alcohols. Lower enantioselectivities observed with CH_2Cl_2 as solvent, relative to toluene as solvent, are consistent with the transition-state model 1 and indicate that CH_2Cl_2 hydrogen bonds to the donor groups in the π-electron-rich carbonyl substituent (R_L in 1) thereby diminishing electron supply.*

The catalytic enantioselective reduction of ketones mediated by chiral oxazaborolidines[1] (CBS reduction[1a]) is an intriguing synthetic reaction not only because of the very broad range of practical applications,[2] but also because of the clear insights into fine mechanistic detail which have emerged from its investigation.[1,3] The enantioface-selective reduction of a large number of achiral ketones with an *S*-proline derived oxazaborolidine can be understood in terms of the transition state representation **1**, in which R_L and R_S refer to the effective steric size of these groups with respect to their effect on the equilibrium (and rate) of coordination of the syn carbonyl lone pair with the catalytic oxazaborolidine–borane complex. The hydride transfer occurs as an irreversible, rate-limiting step after a generally fast and reversible formation of the ketone-borane-oxazaborolidine complex. However, in the case of unusually electrophilic ketones, such as $RCOCF_3$, the transition state for hydride transfer (within the three-component complex) is very early and the hydride transfer may occur at a rate which is comparable to the association/dissociation of ketone with the oxazaborolidine–borane complex.[1c,3] In this paper we present a number of remarkable new findings regarding electronic effects on the effective size of the groups R_L and R_S and on the enantioselectivity of CBS reductions.

The general idea which forms the basis of this study may be illustrated by the specific case of *p*-methoxy-*p'*-nitrobenzophenone **2a**. This substrate may combine with the catalytic boron center (BX_3) at either lone pair *a* or *b*. It can be argued that coordination of BX_3, a rather bulky Lewis acid, will occur more strongly (and more rapidly) at lone pair *a*, since the resulting complex, for example **3** with the (*S*)-catalyst and catechol borane (CB), allows maximum π-electron donation from *p*-methoxyphenyl to the electron deficient carbonyl carbon with simultaneous orthogonality between the planes of the *p*-methoxyphenyl and *p'*-nitrophenyl groups to minimize steric repulsion with the bulky BX_3 moiety, as is depicted in ternary complex **3**. This mode of reduction, which leads to the *R*-carbinol **4**, ought to be considerably more favorable than reduction of **2** via **5** (coordination to lone pair *b*), assuming correctness of the mechanistic model, because **5** does not allow conjugation of the *p*-methoxyphenyl group with the electron deficient carbonyl carbon. The same arguments apply to the reduction of *p*-triisopropylsilyloxy *p'*-nitrobenzophenone **2b**, which because of its ready solubility in organic solvents allows reduction at lower temperatures than does the *p*-methoxy analog **2a**. The predictions based on these



2a R = Me
2b R = Si(*i*-Pr)$_3$



considerations were strikingly confirmed by experiments performed with unsymmetrical benzophenones and a variety of other ketonic substrates with the results summarized in Table 1.

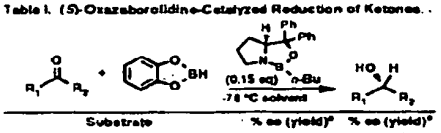
The reduction of *p*-triisopropylsilyloxy-*p'*-nitrobenzophenone (**2b**) in toluene at -78 °C was remarkably selective and afforded the predicted major enantiomer **4b** with 97.5 : 2.5 (39/1) selectivity. Reduction of **2b** under the same conditions except for CH_2Cl_2 as solvent also afforded mainly **4b**, but was considerably less selective (9/1). The reduction of *p*-methoxy-*p'*-nitrobenzophenone (**2a**) could not be carried out at -78 °C due to poor solubility of the substrate. Nonetheless, even at 0 °C the reduction proceeded enantioselectively (10 : 1 in toluene, 7 : 1 in CH_2Cl_2) to give the predicted major enantiomer **4a**.[4] In contrast to the major substituent effects observed in the reductions of **2a** and **2b**, the (*S*)-oxazaborolidine catalyzed reductions of 6-methoxy- and 6-nitro-1-tetralone proceeded to give the (*R*)-alcohol with excellent enantioselectivity in each case (Table 1, entries 3 and 4) with no appreciable substituent effects. These data support the proposition that the enantioselectivity of the reduction of **2a** or **2b** is due to preferential coordination to lone pair *a* as shown in **3** so as to allow maximum π-electron donation to the complexed carbonyl group, and that substituent effects do not operate in coplanar aryl ketones such as the 1-tetralones.

Another way of enhancing the π-electron donor properties of an aromatic ring is by complexation with the chromium tricarbonyl moiety.[5] As shown in Table 1, entry 5, such complexation with one ring of a benzophenone allows the realization of highly enantioselective reduction (32 : 1 in toluene) leading to the *R*-enantiomer, as expected for reduction via coordination of BX_3 to the lone pair anti to the $Cr(CO)_3$-complexed aromatic ring. In the BX_3-complexed ketone, the *d*-electrons of chromium can flow into the electron deficient carbonyl group if the interconnecting aromatic ring is coplanar. The synthesis of π-chromium-tricarbonyl-*p'*-chlorobenzophenone was effected as shown in Scheme 1. The absolute configuration of the reduction product was established by X-ray diffraction analysis.[6]

A different case of this type of stereoelectronic effect of remote aromatic substituents is revealed by entries 6, 7 and 8 of Table 1. The superior π-conjugating/electron-donating properties of the *E*-styryl and *E*-*p*-methoxystyryl groups account for the excellent enantiomeric ratios for the reductions summarized in entries 6 and 7 (*ca.* 50 : 1) as contrasted with the diminished selectivity for the reduction *E*-*p*-nitrostyryl methyl ketone, entry 8 (*ca.* 6 : 1).[7] In each of these cases the effective size of the *E*-styryl group is greater than methyl for the stereoelectronic reasons detailed above, which also account for the adverse effect of a *p*-nitro substituent on enantioselectivity. The previously observed enantioselective reduction of a number of *E*-β-substituted vinyl *n*-alkyl ketones to *R*-vinyl carbinols using the (*S*)-proline-derived oxazaborolidine as catalyst[1b,1e] is now readily understandable in the context of the present study.

The reduction of α,β-acetylenic ketones in the oxazaborolidine system proceeds with only mediocre enantioselectivity. For example, under the conditions outlined in Table 1, the reduction of 4-phenoxy-but-1-yne-3-one affords the corresponding propargylic alcohol in only 74% ee.[8] However, the π-adducts of α,β-ynones with the dicobalt hexacarbonyl moiety undergo the CBS reduction with superb enantioselectivity. As shown in Table 1, entry 9, the $Co_2(CO)_6$ adduct of non-3-yn-2-one is reduced to the corresponding *R* alcohol in toluene with 97% ee, 65 : 1 enantiomeric ratio. Coordination of the $Co_2(CO)_6$ unit with the C–C triple bond greatly enhances the electron-donating power relative to uncomplexed C≡C,[9] while also increasing effective steric size. Both effects contribute to enantioselection by favoring coordination of BX_3 to the lone pair anti to the $Co_2(CO)_6$-complexed triple bond. This CBS reduction of $Co_2(CO)_6$-complexed α,β-acetylenic ketones provides a very

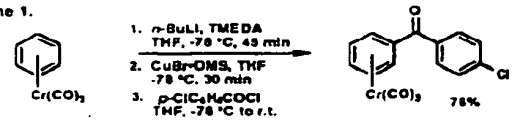
Table I. (S)-Oxazaborolidine-Catalyzed Reduction of Ketones.



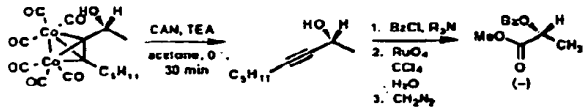
Substrate R_1	Substrate R_2	% ee (yield)[a] Toluene	% ee (yield)[a] CH_2Cl_2
1. TIPSO	(2b)	95 (88)	80 (81)
2. MeO	(2a)	81 (88)[b]	75 (72)[b]
3.		–	99 (98)
4.		–	98 (86)
5.		94 (90)	92 (87)
6.	$-CH_3$	97 (90)	87 (78)
7. MeO	$-CH_3$	95 (88)	88 (88)
8.	$-CH_3$	72 (88)	48 (88)
9.	$-CH_3$	97 (89)[c]	93 (89)[c]

[a] Ee's determined by HPLC analysis with Chiralcel columns except for entries 6 and 9 which involved ^1H NMR analysis of the Mosher ester. [b] Reaction temperature was 0 °C due to limited substrate solubility. [c] The catalyst used had the $MeB(OH)_2$ substituent on boron instead of *n*-butyl (which afforded product of ca. 87%ee).

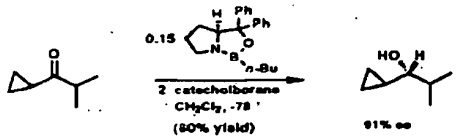
Scheme 1.



Scheme 2.



Scheme 3.



effective and useful new synthetic route to a broad range of propargylic alcohols, since the removal of cobalt is readily accomplished as shown in Scheme 2 which also depicts the method used for determination of the absolute configuration of the reduction product, correlation with levorotatory (*R*) methyl benzoyllactate.[10,11]

Cyclopropyl isopropyl ketone[12] represents an interesting test of the stereoelectronic proposal discussed above. Since the cyclopropyl group is much more electron-donating[13] than the isopropyl group, it was predicted that the CBS reduction with the (*S*)-proline-derived oxazaborolidine should produce predominantly the *R* carbinol. Indeed, this is the case, as is indicated in Scheme 3. Thus, despite the somewhat smaller steric size of cyclopropyl relative to isopropyl, the cyclopropyl group effectively functions as the bulkier group for stereoelectronic reasons[13,14] and directs BX_3 coordination to the anti lone pair in the CBS reduction. The absolute configuration of the carbinol was established by esterification with *N*-(*t*-butoxycarbonyl)-(*S*)-alanine (DCC, DMAP (cat), CH_2Cl_2, 23 °C), recrystallization of the product and X-ray analysis.[6b,15]

The reactions reported herein represent a new class of highly enantioselective carbonyl reduction, dependent on stereoelectronic effects involving special groups or remote substituents. The discovery of these reactions was guided by the transition-state model **1**, for which they provide strong support. The greater magnitude of the stereoelectronic effects in toluene vs CH_2Cl_2 as solvent (see Table I) is of great interest and may be due to a hydrogen bonding effect of CH_2Cl_2 which effectively reduces the electron-donating power of the π-rich carbonyl substituent (R_L in **1**). Finally, these results are valuable because they open the way for numerous extensions and practical synthetic applications.[16]

References and Notes

1. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey,

E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Corey, E. J. in *Proceedings 31st National Organic Chemistry Symposium of the American Chemical Society*; 1989; p 1. (e) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (f) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209. (g) Corey, E. J.; Azimioara, M; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429. (h) Singh, V. K. *Synthesis* **1992**, 605 (review).

2. (a) Corey, E. J.; Chen, C. P.; Parry, M. J. *Tetrahedron Lett.* **1988**, *29*, 2899 (PAF antagonists). (b) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201 (ginkgolides A and B). (c) Corey, E. J.; Su, W.-g. *Tetrahedron Lett.* **1988**, *29*, 3423; Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111 (bilobalide). (d) Corey, E. J.; Da Silva Jardine, P. *Tetrahedron Lett.* **1989**, *30*, 7297 (forskolin). (e) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207 (fluoxetine). (f) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275 (α-deutero alcohols). (g) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601 (isoprenoranol). (h) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442 (denopamine). (i) Corey, E. J.; Chen, C. P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547 (chiral oxazaborolidines). (j) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906 (α-amino acids). (k) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025 (antheridic acid). (l) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431 (α-hydroxy acids). (m) Corey, E. J.; Yi, K. Y.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, *33*, 2319 (2,3-oxidosqualene). (o) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1993**, *34*, 5227 (terminal epoxides). (p) Corey, E. J.; Cimprich, K. A. *Tetrahedron Lett.* **1992**, *33*, 4099 (chiral thiols). (q) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835 (chiral controllers).

3. Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107.

4. The absolute configuration of **4a** was established by the sequence: (1) acetylation, (2) oxidation of the *p*-methoxyphenyl group to carboxyl (cat. $RuCl_3$–$NaIO_4$), (3) reduction of COOH to CH_2OH with BH_3–THF, and (4) deacetylation to form *levorotatory* (2*R*)-2-hydroxy-2-*p*-nitrophenylethanol; see Westkaemper, R. B.; Hanzlik, R. P. *Arch. Biochem. Biophys.* **1981**, *208*, 195. Alcohol **4b** was correlated with **4a** by sequential desilylation and phenol methylation.

5. (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; Chapter 10. (b) Uemura, M.; Minami, T.; Hayashi, Y. *J. Organomet. Chem.* **1986**, *299*, 119. (c) Davies, S. G.; Donohoe, T. J.; Williams, J. M. J. *Pure Appl. Chem.* **1992**, *64*, 379.

6. (a) The yellow crystals of the chromium tricarbonyl complexed benzhydrol, from $CHCl_3$–pentane bilayer at 4 °C, mp 90-91 °C, $[\alpha]_D^{22}$ +29.4° (c=0.034, $CHCl_3$), were found to contain 4 molecules per unit cell: empirical formula $C_{16}H_{11}ClCrO_4$ (354.70); crystal size 1.00 x 0.90 x 0.50 mm^3; space group $P2_1$; a = 10.040(2) Å, b = 12.758(2) Å, c = 11.6750(10) Å, β = 96.450(10)°; V = 1486.0(4) $Å^3$; d = 1.585 g/cm^3; (Mo-K_α radiation, -100°C); all reflections (8772) were used in the refinement; $R_w(F^2)$ = 0.0971 with R_w (F:conventional) = 0.0378; GOF = 1.124. The crystal was shown to correspond to the major enantiomer via HPLC analysis (Chiralcel OD). (b) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

7. For absolute configuration of the product, see ref. 1e.

8. Results of Dr. Raman K. Bakshi in these laboratories (1989).

9. Nicolas, K. M. *Acc. Chem. Res.* **1987**, *20*, 208.

10. Aasen, A. J.; Kimland, B.; Enzell, C. R. *Acta Chem. Scand.* **1973**, *27*, 2107.

11. For a different enantioselective route to propargylic alcohols using chiral oxazaborolidines as catalysts see Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

12. Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.

13. Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179.

14. The most stable conformer of the cyclopropyl ketone (or the corresponding complex with BX_3) is that in which the cyclopropyl α–CH bond is coplanar with the carbonyl σ-plane, a geometry which maximizes the effective bulk of the cyclopropyl moiety. See (a) Volltrauer, H. N.; Schwendman, R. H. *J. Chem. Phys.* **1971**, *54*, 260. (b) Pelissier, M.; Serafini, A.; Devanneaux, J.; Labarre, J-F.; Tocanne, J-F. *Tetrahedron* **1971**, *27*, 3271.

15. The colorless crystals of the ester of the major cyclopropylisopropyl carbinol with *N*-(*t*-butoxycarbonyl)-L-alanine, grown from hexane at r.t., mp 86-90 °C, $[\alpha]_D^{22}$ -4.96° (c=2.40, $CHCl_3$), were found to contain 4 molecules per unit cell: empirical formula $C_{15}H_{27}NO_4$ (285.38); crystal size 1.00 x 0.35 x 0.20 mm^3; space group $P2_12_12$; a = 18.959(2) Å, b = 8.941(2) Å, c = 10.1400(10) Å; V = 1718.9(5) $Å^3$; d = 1.103 g/cm^3; (Mo-K_α radiation, 20 °C); all reflections (4132) were used in the refinement; $R_w(F^2)$ = 0.1091 with R_w (F:conventional) = 0.0431; GOF = 0.852.

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= 6 Hz, 4 H), 2.43 (t, J = 6 Hz, 4 H). The other isomer showed the following ^{1}H NMR signals: ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz), 1.26 (m), 1.57 (m).

Acknowledgment. We thank David N. Whittern for conducting the INADEQUATE and the 2D NMR analyses on a Varian XL-200 spectrometer (NSF Grant CHE-8004246). We also thank the Purdue University Biochemical Magnetic Resonance Laboratory for the use of NT-470 NMR spectrometer (NIH Grant RR-01077). The financial assistance from the National Institutes of Health (GM-10937-20) and the National Science Foundation (Grant CHE 79-18881) is gratefully acknowledged.

Registry No. 1, 280-64-8; 6, 5626-20-0; 7, 4480-56-2; 8, 60579-50-2; 9, 60579-58-0; 10, 94-65-5; 11, 1126-18-7; 12, 32362-97-3; 13, 3313-59-5; 14, 16556-72-2; BMS, 13292-87-0; 1,7-heptanediol, 629-30-1; 1,5-heptanediol, 60096-09-5; cyclooctanone, 502-49-8; 2-ethylcyclohexanone, 4423-94-3; 1,8-octanediol, 629-41-4; 1,6-octanediol, 4066-76-6; 1,9-nonanediol, 3937-56-2; 1,5-nonanediol, 13686-96-9; 1,10-decanediol, 112-47-0; 1,5-decanediol, 4203-48-9; 1,14-tetradecanediol, 19812-64-7; cyclopentadecanone, 502-72-7; *B*-methoxy-2-propylborinane, 60579-70-6; *B*-methoxy-2-butylborinane, 88703-65-5; *B*-methoxy-2-pentylborinane, 88703-66-6; *B*-methoxy-2-heptylborinane, 88729-57-1; *B*-methoxy-2-nonylborinane, 88703-67-7; 1,3-butadiene, 106-99-0; 1,5-hexadiene, 592-42-7; 1,6-heptadiene, 3070-53-9; 1,7-octadiene, 3710-30-3; 1,8-nonadiene, 4900-30-5; 1,9-decadiene, 1647-16-1; 1,11-dodecadiene, 5876-87-9; 1,13-tetradecadiene, 21964-49-8; 1,4-butanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 88703-68-8; 1,5-pentanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 81547-70-8; 1,6-hexanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 88703-69-9; 1,7-heptanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 88703-70-2; BH_3, 13283-31-3.

Ortho Metalation Directed by α-Amino Alkoxides

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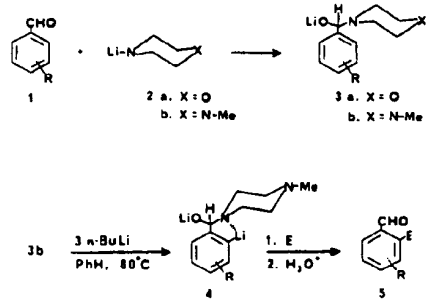
Received August 2, 1983

The addition of aromatic aldehydes to certain lithium dialkylamides in benzene or tetrahydrofuran gave α-amino alkoxides which were ortho lithiated with excess *n*-butyllithium. Subsequent alkylation and hydrolysis provided ortho-substituted aromatic aldehydes via a one-pot reaction. The ortho metalation of α-amino alkoxides derived from 1- and 2-naphthaldehyde and various substituted benzaldehydes was examined. When *N*,*N*,*N*′-trimethylethylenediamine was used as the amine component of the α-amino alkoxide, metalation could be carried out at lower temperatures. This rate increase is due to an intramolecular TMEDA-like assisted metalation. The synthetic utility of this ortho metalation, including how varying the amine component of the α-amino alkoxide affects the regiochemistry and metalation rate, is discussed.

In recent years there has been considerable interest in the area of ortho metalation.[1] A variety of ortho-directing groups have been utilized on various aromatic rings to direct regiospecific metalation in the ortho position. Carbonyl-derived directing groups include $CONR_2$,[2] CONHR,[3] oxazolines,[4] α-amino alkoxides[5] (prepared from tertiary amides and RLi), $CH(OR)_2$,[6] imidazolidines,[7] cyclohexylimines,[8] and α-amino alkoxides[9] (prepared from aromatic aldehydes and lithium *N*-methylpiperazide). We recently reported an in situ protection of aromatic and aliphatic aldehydes in high yield via the formation of α-amino alkoxides.[10] The α-amino alkoxides **3** are prepared



by the addition of an aromatic aldehyde (1) to certain

(1) For reviews, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360. Omae, I. *Chem. Rev.* **1979**, *79*, 287–321. $CONEt_2$: Snieckus, V. *Heterocycles* **1980**, *14*, 1649. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312.

(2) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823–1824. de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099–5102. de Silva, S. O.; Snieckus, V. *Ibid.* **1978**, 5103–5106. de Silva, S. O.; Ahmad, I.; Snieckus, V. *Ibid.* **1978**, 5107–5110. Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463–4464. de Silva, S. O.; Watanabe, M.; Snieckus, V. *Ibid.* **1979**, *44*, 4802–4808. de Silva, S. O.; Ahmad, I.; Snieckus, V. *Can. J. Chem.* **1979**, *57*, 1598–1605. Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457–1460. Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34–46. Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531–5533. Harvey, R. G.; Cortez, C.; Jacobs, S. A. *J. Org. Chem.* **1982**, *47*, 2120–2125. Mills, R. J.; Snieckus, V. *Ibid.* **1983**, *48*, 1565–1568. Beak, P.; Chen, C-W. *Tetrahedron Lett.* **1983**, *24*, 2945–2948. Reed, J. N.; Snieckus, V. *Ibid.* **1983**, *24*, 3795–3798. Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Ibid.* **1983**, *24*, 4515–4518.

(3) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853–856. Slocum, D. W.; Jennings, C. A. *Ibid.* **1976**, *41*, 3653–3664. Katritzky, A. R.; Rahimi-Rastgoo, S.; Ponkshe, N. K. *Synthesis* **1981**, 127–129.

(4) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158–3159. Gschwend, H. W.; Hamdan, A. *Ibid.* **1975**, *40*, 2008–2009. Meyers, A. I.; Lutomski, K. *Ibid.* **1979**, *44*, 4464–4466. Meyers, A. I.; Avila, W. B. *Ibid.* **1981**, *46*, 3881–3886. Meyers, A. I.; Rieker, W. *Tetrahedron Lett.* **1982**, *23*, 2091–2094. Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Wizenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015–4018. Edgar, K. J.; Bradsher, C. K. *J. Org. Chem.* **1982**, *47*, 1585–1587. Newman, M. S.; Hussain, N. S. *Ibid.* **1982**, *47*, 2837–2840.

(5) Michael, U.; Gronowitz, S. *Acta Chem. Scand.* **1968**, 1353. Gronowitz, S. *Ark. Kemi.* **1970**, *32*, 283. Brasky, L.; Gschwend, H. W.; McKenna, J.; Rodriquez, H. R. *J. Org. Chem.* **1976**, *41*, 3651–3652.

(6) (a) Plaumann, H. P.; Key, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921–4924. (b) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101–2108. (c) Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *Ibid.* **1983**, *48*, 3653–3657.

(7) Harris, T. D.; Roth, G. P. *J. Org. Chem.* **1979**, *44*, 2004–2007.

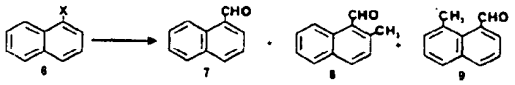
(8) (a) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564–1566. (b) Murahashi, S-I, Tamba, Y.; Yamamura, M.; Yoshimura, N. *Ibid.* **1978**, *43*, 4099–4106.

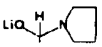
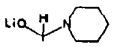
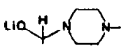
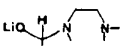
(9) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979–3982.

(10) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213–4216.

0022-3263/84/1949-1078$01.50/0

Table I



entry	x	metalation conditions	yield (GC) 7	8	9
a		3 *n*-BuLi, 3 TMEDA, ether, room temp, 7 h	15.1	5.7	12.4
b		1 *t*-BuLi, ether, −78 → 0 °C	38.5	12.5	26.5
c		1.1 *n*-BuLi, THF, −78 °C, 15 min	0	0	0
d		3 *n*-BuLi, benzene, reflux, 10 h	32	32.6	1.6
e		3 *n*-BuLi, benzene, reflux, 10 h	5	30	2.8
f		3 *n*-BuLi, benzene, reflux, 10 h	55.7	19.4	1
g		3 *n*-BuLi, benzene, reflux, 10 h	9.3	42.7	1.6
h		3 *n*-BuLi, THF, −20 °C, 24 h	27.9	51.3	4.9

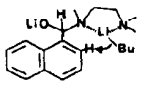
amide bases such as lithium morpholide (**2a**) or lithium *N*-methylpiperazide (**2b**). The in situ formed α-amino alkoxide protects the formyl group toward organometallic reagents. For example, the α-amino alkoxide **3b** can be treated with 3 equiv of *n*-BuLi in relfuxing benzene for several hours with only minor decomposition resulting. In fact, under these conditions the α-amino alkoxide functions not only as a protecting group, but also as an ortho-directing group for ortho metalation. Ortho lithiation of α-amino alkoxides **3b** gives dianions **4** which can be alkylated with various electrophiles. Quenching the reactions with water or aqueous acid provides ortho-substituted aromatic aldehydes (**5**) via a one-pot reaction.[9]

The convenience and synthetic potential of this reaction have prompted us to investigate its scope. This paper is a report on our continuing studies of ortho metalation directed by α-amino alkoxides.[11]

Results and Discussion

Ortho Metalation of 1- and 2-Naphthaldehyde. We have investigated the ortho alkylation of 1- and 2-naphthaldehyde by using α-amino alkoxides and other aldehyde derivatives as ortho-directing groups. The amine component of the α-amino alkoxide was varied to determine its effect on the regioselectivity of the metalation step. The results of this study using 1-naphthaldehyde are given in Table I.

The metalated 1-naphthaldehyde derivatives were alkylated with methyl iodide and hydrolyzed with dilute hydrochloric acid. The crude product was analyzed (GC) for 1-naphthaldehyde, 2-methyl-1-naphthaldehyde, and 8-methyl-1-naphthaldehyde. When an imidazolidine was used as the ortho-directing group (entry a), a low yield of methylated products was obtained with the 8-methyl-1-naphthaldehyde predominating. The analogous reaction with the dimethyl acetal derivative (entry b) gave a similar result. Reaction of the cyclohexylimine of 1-naphthaldehyde with *n*-butyllithium (entry c) gave only addition of the lithium reagent to the aromatic ring and no products derived from ortho metalation were detected. The α-amino alkoxides direct ortho lithiation mainly to the 2 position of the 1-naphthaldehyde ring. The yields of methylated products ranged from 20–57% depending on the structure of the amine component. Although varying the amine component of the α-amino alkoxide did affect the yield of methylated products, it had little effect on the regioselectivity of the metalation step. The α-amino alkoxides derived from diethylamine, pyrrolidine, piperidine, and *N*-methylpiperizine (entries d–g) were metalated with 3 equiv of *n*-butyllithium in refluxing benzene (10 h). These conditions were necessary to effect metalation in high yield. The α-amino alkoxide derived from *N,N,N'*-trimethylethylenediamine completely decomposed under these conditions. It was subsequently discovered, however, that metalation of this α-amino alkoxide could be effected at room temperature in benzene or at −20 °C in tetrahydrofuran (entry h). It is well-known that tetramethylethylenediamine (TMEDA) accelerates metalation reactions.[12] The rate enhancement discussed above is undoubtedly due to an *intramolecular* TMEDA-like assisted metalation as shown below.

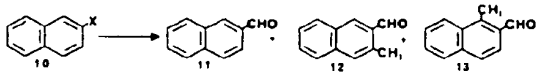


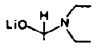
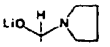
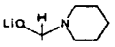
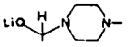
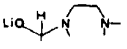
In contrast, the analogous reaction using *N*-methyl-

(11) Comins, D. L.; Brown, J. D.; Mantlo, N. B. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, Washington, March 20–25, 1983; American Chemical Society: Washington, D.C.; Abstr. ORGN 117. Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465–5468.

(12) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974.

Table II

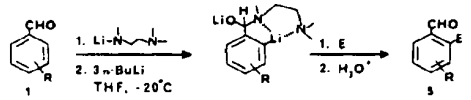


entry	x	metalation conditions	yield (GC) 11	12	13
a		3 *n*-BuLi, 3 TMEDA, ether, room temp, 7 h	25.6	31.2	8.2
b		1 *t*-BuLi, ether, −78 → 0 °C	21	13.5	9.8
c		1.1 *n*-BuLi, THF, −78 °C, 15 min	0	0	0
d		3 *n*-BuLi, benzene, reflux, 10 h	2.1	51.4	6.2
e		3 *n*-BuLi, benzene, reflux, 10 h	3.4	33.7	5.9
f		3 *n*-BuLi, benzene, reflux, 10 h	1	41	4.7
g		3 *n*-BuLi, benzene, reflux, 10 h	4.9	49.6	7.6
h		3 *n*-BuLi, benzene, room temp, 3 h	10.8	51	15.4

piperazine as the amine component gave less than 5% metalation (THF, −20 °C, 3 *n*-BuLi, 24 h).

A similar study was performed with 2-naphthaldehyde and the results are given in Table II. The crude product mixtures were analyzed for 3-methyl-2-naphthaldehyde, 1-methyl-2-naphthaldehyde, and 2-naphthaldehyde. In all examples studied, 3-methyl-2-naphthaldehyde was the major product. In general, α-amino alkoxides (entries d–h) gave better yields and product ratios than the corresponding imidazolidine and dimethyl acetal derivatives (entries a–b). Attempted metalation–alkylation of the cyclohexylimine of 2-naphthaldehyde gave mainly decomposition (entry c). The α-amino alkoxide derived from 2-naphthaldehyde and *N,N,N'*-trimethylethylenediamine again showed a rate enhancement during the metalation step. This allowed the metalation to occur at room temperature in benzene (3 h). Subsequent methylation provided a 66% yield of ortho-substituted products (entry h), the highest yield of all examples studied.

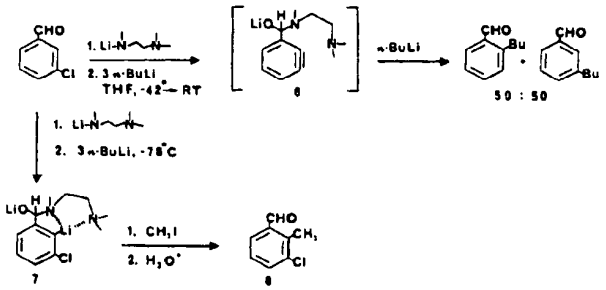
Low-Temperature Ortho Lithiation of α-Amino Alkoxides Derived from *N,N,N'*-Trimethylethylenediamine and Aryl Aldehydes. The discovery that α-amino alkoxides derived from 1- or 2-naphthaldehyde and the lithium salt of *N,N,N'*-trimethylethylenediamine could be metalated at low temperature (−20 °C) prompted us to reinvestigate our earlier work.[9] We felt that the milder



metalation conditions, for metalation of aryl α-amino alkoxides derived from *N,N,N'*-trimethylethylenediamine, would allow for higher overall yields than we obtained originally for the one-pot ortho alkylation reaction. In addition, the milder metalation conditions should allow for more functional groups to be present on the aromatic ring during this substitution reaction. The results of this study are given in Table III.

The yields of the first three examples, utilizing benzaldehyde as starting material, are 8–21% higher than the yields from our earlier work using *N*-methylpiperazine as the amine component of the α-amino alkoxides. The higher yields are indicative of less decomposition during the metalation step. A chlorine substituent activates the aromatic ring toward metalation.[1] The α-amino alkoxide from *o*- or *p*-chlorobenzaldehyde was ortho lithiated in only 3 h at −20 °C. The analogous reaction with *m*-chlorobenzaldehyde gave benzyne formation at −42 °C. Since the benzyne **6** forms in the presence of excess *n*-butyllithium and the diamine of the α-amino alkoxide, we anticipated addition of the lithium reagent to the benzyne **6** with some regioselectivity.[28] However, regioselectivity

(13) Yagupol'kii, L. M.; Matyushecheva, G. I. *Zh. Obshch. Khim.* **1966**, *36*, 1181; *Chem. Abstr.* **1967**, *66*, 55126p.
(14) Noelting, E. *Chem. Ber.* **1904**, *37*, 1015–1028.
(15) Kenner, J.; Witham, E. *J. Chem. Soc.* **1921**, *119*, 1452–1461.
(16) Harding, K. E.; Leopold, E. J..; Hudrlik, A. M.; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 2540–2549.
(17) Cresp, T. M.; Giles, R. G. F.; Sargent, M. V.; Brown, C.; Smith, D. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2435–2447.
(18) Barnes, R. A.; Gerber, N. N. *J. Org. Chem.* **1961**, *26*, 4540–4543.
(19) Aldous, F. A. B.; Barrass, B. C.; Brewster, K.; Buxton, D. A.; Green, D. M.; Pinder, R. M.; Rich, P.; Skeels, M.; Tutt, K. J. *J. Med. Chem.* **1974**, *17*, 1100–1111.
(20) Cannon, J. G.; Koble, D. L.; Long, J. P.; Verimer, T. *J. Med. Chem.* **1980**, *23*, 750–754.
(21) Tymann, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1639–1647.
(22) Tanaka, A. K.; Kobayashi, A.; Yamashita, K. *Agr. Biol. Chem.* **1973**, *37*, 669–674.
(23) Lovie, J. C.; Tomson, R. H. *J. Chem. Soc.* **1961**, 485–487.
(24) Braude, E. A.; Sondheimer, F. *J. Chem. Soc.* **1955**, 3754–3766.
(25) An aryllithium has been chlorinated with carbon tetrachloride: Carlson, J., Sterling-Winthrop Research Institute, Rensselaer, New York, unpublished results. For the reaction of carbon tetrachloride with ester enolate anions, see: Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687–3689.
(26) Alper, H.; Root, W. G. *J. Am. Chem. Soc.* **1975**, *97*, 4251–4257.
(27) Mao, C. L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 475–482.

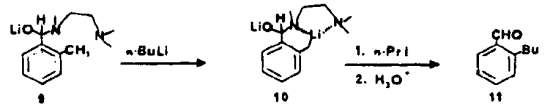


did not occur and a 50:50 mixture of 2- and 3-butylbenzaldehyde resulted. Metalation of *m*-chlorobenzaldehyde was carried out at −78 °C without benzyne formation, and the resulting dianion 7 was alkylated with methyl iodide to give 3-chloro-2-methylbenzaldehyde (8) in good yield.

We next investigated the ortho alkylation of methoxybenzaldehydes. *p*-Methoxybenzaldehyde gave only ortho metalation–alkylation at the position ortho to the aldehyde function. This result demonstrated that the α-amino alkoxide, derived from *N,N,N′*-trimethylethylenediamine, is a better ortho director than the methoxy group. However, when the amine component of the α-amino alkoxide is changed from *N,N,N′*-trimethylethylenediamine to *N*-methylpiperazine, the regioselectivity is reversed and metalation ortho to the methoxy group occurs. This useful regiochemical control is discussed in detail in the next section.

The α-amino alkoxides of *m*-methoxybenzladehyde, 3,4,5-trimethoxybenzaldehyde, and piperonal are doubly activated toward ortho metalation, so clean alkylation at the 2-position was anticipated. The ortho alkylation of *o*-methoxybenzaldehyde failed as only decomposition occurred; however, the α-amino alkoxide formed from *o*-methoxybenzaldehyde and lithium *N*-methylpiperazide is more stable and can be metalated ortho to the methoxy group with *n*-BuLi/TMEDA (see Table IV).

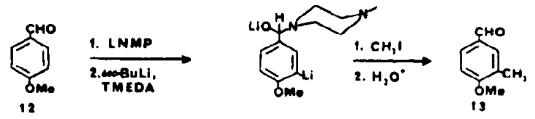
An electron-donating methyl group on the aromatic ring should decrease the metalation rate. This proved to be true; however, *m*- and *p*-tolualdehyde were ortho lithiated in high yield by using longer metalation time (48 h) at −20 °C. The ortho alkylation of *m*-tolualdehyde was highly regioselective for the less hindered 6 position. The α-amino alkoxide 9 prepared from *o*-tolualdehyde underwent lateral



metalation at the methyl group, rather than ortho metalation, to give the dianion 10 in high yield. This is not unusual, for ortho methyl aryl oxazolines, *N,N*-diethyl amides, and imidazolidines all metalate in this manner.[1,7] Alkylation of 10 with *n*-propyl iodide gave 11 in 85% yield.

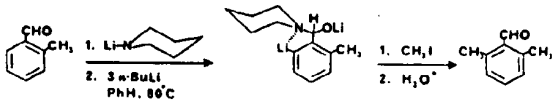
Regioselective Metalation Controlled by Varying the Amine Component of the α-Amino Alkoxide. Since the directing power of an α-amino alkoxide could be altered by simply varying the amine component, it appeared that regioselective control during the metalation of a diactivated benzene ring was feasible. We examined the ortho metalation-methylation of various methoxybenzaldehydes and the results are shown in Table IV.

p-Anisaldehyde (12) was treated with lithium *N*-



methylpiperazide (LNMP) followed by 2 equiv of *sec*-BuLi/TMEDA in THF (−20 °C) for 24 h. After methylation and workup, 4-methoxy-3-methylbenzaldehyde (13) was isolated *as the sole product* in 73% yield. This is in sharp constrast to the analogous reaction using *N,N,N′*-trimethylethylenediamine as the amine component, where 4-methoxy-2-methylbenzaldehyde was produced in 90% yield (Table III). When the same strategy was utilized, *m*-anisaldehyde was methylated in the 4-position in moderate yield; only a trace of 2-substituted product was detected. The 3,5- and 2,4-dimethoxybenzaldehydes were alkylated between the methoxy groups in excellent yield as indicated in the table; when *N,N,N′*-trimethylethylenediamine was used as the amine component for these examples, a mixture of products resulted.

In light of the above results, metalation of the α-amino alkoxide derived from *o*-tolualdehyde was reexamined. As



mentioned earlier, when *N,N,N′*-trimethylethylenediamine was used as the amine, lateral metalation occurred in high yield (see Table III). However, use of lithium piperidide to form the α-amino alkoxide effected ortho metalation–alkylation at the 6-position to provide 2,6-dimethylbenzaldehyde (50%).

Conclusion

This work significantly extends the scope of ortho metalation. The method is convenient and allows for the one-pot ortho alkylation of aromatic aldehydes. Remarkable regioselective control can be obtained by simply changing the amine component of the α-amino alkoxide, a novel versatility which should be useful in synthesis.

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. Benzene, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), *N,N,N′*-trimethylethylenediamine, *N*-methylpiperazine, piperidine, diethylamine, and pyrrolidine were distilled from calcium hydride and stored over 4-Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer and IR spectra were recorded on a Perkin-Elmer 710B spectrometer. Gas-liquid chromatography (GC) was performed with a Hewlett-Packard Model 5880 A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-17.

1,3-Dimethyl-2-(1-naphthyl)imidazolidine. Using the procedure for the preparation of 1,3-dimethyl-2-phenylimidazolidine,[7] 4.3 mL (32 mmol) of 1-naphthaldehyde and 4.1 mL (38 mmol) of *sym*-dimethylethylenediamine gave, after Kugelrohr distillation (bp 130–140 °C (0.75 mm)), 6.97 g (96%) of a clear oil: ^{1}H NMR (CCl_4) δ 9.2–8.8 (m, 1 H), 8.0–7.3 (m, 6 H), 3.9 (s, 1 H), 3.45 (m, 2 H), 2.55 (m, 2 H), 2.1 (s, 6 H); IR (neat) 2775, 1450, 1240 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.73; H, 8.03; N, 12.40.

(28) Regioselective addition of organolithium reagents to the benzyne formed from 2-(*m*-chlorophenyl)-2-oxazoline has been reported. Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935–4938. Meyers, A. I.; Rieker, W. F. *Ibid.* **1982**, *23*, 2091–2094.

Table III. Low-Temperature Ortho Lithiation of Aryl α-Amino Alkoxides

aryl aldehyde 1	metalation[a] conditions	E	product[b] 5	yield[c]	mp, °C[f] (Lit. mp, °C)
benzaldehyde	−20 °C, 24 h	Me_3SiCl	2-trimethylsilylbenzaldehyde	82	g
		MeI	*o*-tolualdehyde	75[d]	g
		n-BuI	2-butylbenzaldehyde	68	g
		CCl_4[25]	2-chlorobenzaldehyde	68	g
		PhCHO	1,3-dihydro-3-phenyl-1-isobenzofuranol	85	lactone 102–104 (103–104.5)[26]
		PhC(=O)Ph	1,3-dihydro-3,3-diphenyl-1-isobenzofuranol		lactone 115.5–117 (116–117)[27]
4-chlorobenzaldehyde	−20 °C, 3 h	MeI	4-chloro-2-methylbenzaldehyde	80	acid 166–167 (167–169)[13]
3-chlorobenzaldehyde	−78 °C, 7 h	MeI	3-chloro-2-methylbenzaldehyde	62	acid 155–157 (158)[14]
2-chlorobenzaldehyde	−20 °C, 3 h	MeI	2-chloro-6-methylbenzaldehyde	70	acid 98–100 (102)[15]
4-methoxybenzaldehyde	−20 °C, 24 h	MeI	4-methoxy-2-methylbenzaldehyde	90	acid 175–177 (176–177.5)[16]
3-methoxybenzaldehyde	−20 °C, 10 h	MeI	3-methoxy-2-methylbenzaldehyde	80	acid 145–147 (148–149)[17]
3,4,5-trimethoxybenzaldehyde	−20 °C, 3 h	MeI	2-methyl-3,4,5-trimethoxybenzaldehyde	90	DNP 189–190[6a]
piperonal	−20 °C, 3 h	MeI	2-methylpiperonal	90	72–74 (73–74.5)[6a]
p-tolualdehyde	−20 °C, 48 h	MeI	2,4-dimethylbenzaldehyde	80	g
m-tolualdehyde	−20 °C, 48 h	MeI	2,5-dimethylbenzaldehyde	60[d,e]	g
o-tolualdehyde	−20 °C, 1.5 h	*n*-PrI	2-butylbenzaldehyde	85	g

[a] The reactions were performed on a 3 mmol scale using *N,N,N'*-trimethylethylenediamine as the amine component. The metalation was carried out in THF using 3 equiv of *n*-BuLi. [b] All products gave the expected IR and ^1H NMR spectra. [c] Yield of purified product obtained from preparative layer chromatography (silica gel, acetone–hexanes). [d] Yield determined by GC. [e] 2,3-Dimethylbenzaldehyde (10%) was present in the crude product (by GC). [f] The lactones and carboxylic acids were prepared by Jones oxidation. DNP = 2,4-dinitrophenylhydrazone. [g] The product was identical with an authentic sample.

Table IV. Regioselective Alkylation of Methoxybenzaldehydes

aryl aldehyde	metalation[a] conditions	product[b]	yield[c]	mp, °C[d] (Lit. mp, °C)
4-methoxybenzaldehyde	2-*sec*-BuLi, 2 TMEDA, −20 °C, 24 h	4-methoxy-3-methylbenzaldehyde	73	DNP 234–236 (235–237)[18]
3-methoxybenzaldehyde	3 *sec*-BuLi, 3 TMEDA, −20 °C, 12 h	3-methoxy-4-methylbenzaldehyde	66	DNP 238–240 (241)[19]
2-methoxybenzaldehyde	3 *n*-BuLi, 3 TMEDA, −20 °C, 48 h	2-methoxy-3-methylbenzaldehyde	63	45–46 (44–46)[20]
3,5-dimethoxybenzaldehyde	3 *n*-BuLi, −20 °C, 24 h	3,5-dimethoxy-4-methylbenzaldehyde	95	90–91 (89–90)[21]
2,4-dimethoxybenzaldehyde	3 *n*-BuLi, −20 °C, 24 h	2,4-dimethoxy-3-methylbenzaldehyde	95	52–54 (54)[22]
2,3-dimethoxybenzaldehyde	3 *n*-BuLi, 3 TMEDA, −20 °C, 48 h	2,3-dimethoxy-4-methylbenzaldehyde	62	acid[e] 124–125 (125)[23]

[a] The reactions were performed on a 3 mmol scale using *N*-methylpiperazine as the amine component. The metalation was carried out in THF. [b] All products gave the expected IR and ^1H NMR spectra. [c] Yield of purified product obtained from preparative layer chromatography (silica gel, acetone–hexanes). [d] DNP = 2,4-dinitrophenylhydrazone. [e] Prepared by Jones oxidation.

1,3-Dimethyl-2-(2-naphthyl)imidazolidine. Following the above procedure, 2-naphthaldehyde and *sym*-dimethylethylenediamine gave the product as a clear oil (91%) after Kugelrohr distillation (bp 125–140 °C (0.75 mm)): ^1H NMR (CCl_4) δ 8.2–7.3 (m, 7 H), 3.4 (m, 3 H), 2.5 (m, 2 H), 2.15 (s, 6 H); IR (neat) 2840, 2770, 1450, 1240 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.49; H, 8.16; N, 12.41.

1-Naphthaldehyde Cyclohexylimine. The imine was prepared from 1-naphthaldehyde (1.0 equiv), cyclohexylamine (1.2 equiv, distilled), and a catalytic amount of *p*-toluenesulfonic acid in benzene solution by azeotropic removal of water. The crude product was purified by Kugelrohr distillation (bp 130–140 °C (0.3 mm)) to give a clear oil (89%): ^1H NMR (CCl_4) δ 9.2 (m, 1 H), 8.85 (s, 1 H), 8.0–7.3 (br m, 6 H), 3.2 (br s, 1 H), 2.2–1.1 (br m, 10 H); IR (neat) 2920, 2840, 1635, 1440 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.13; H, 8.07; N, 5.95.

2-Naphthaldehyde Cyclohexylimine. Following the above procedure, 2-naphthaldehyde and cyclohexylamine gave the imine as a white solid (65%) after recrystallization from methanol: mp 86.5–87 °C; ^1H NMR (CCl_4) δ 8.4 (s, 1 H), 8.3–7.3 (m, 7 H), 3.2 (br s, 1 H), 2.2–1.1 (br m, 10 H); IR (KBr) 2919, 2840, 1635, 1450 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.32; H, 8.27; N, 5.95.

Ortho Lithiation–Methylation of the Imidazolidines, Dimethyl Acetals, and Cyclohexylimines of 1- and 2-Naphthaldehyde. The lithiation–alkylation of these naphthaldehyde derivatives was carried out according to published procedures for the analogous reaction with 1,3-dimethyl-2-phenylimidazolidine,[7] the dimethyl acetal of benzaldehyde,[6] and piperonal cyclohexylimine.[8] After hydrolysis with dilute hydrochloric acid, the crude product was isolated and subjected to GC analysis using 2,3-dimethylnaphthalene as an internal standard. See Tables I and II.

Ortho Methylation of 1- and 2-Naphthaldehyde via α-Amino Alkoxide Intermediates. General Procedure (See Tables I and II, Entries d–g). To a stirred solution of the secondary amine (3.3 mmol) in 8 mL of dry benzene under nitrogen was added *n*-butyllithium (3.3 mmol, in hexane solution). After 15 min, the naphthaldehyde (3 mmol) was added slowly

dropwise, and the mixture was stirred at room temperature for 15 min. A hexane solution of *n*-butyllithium (9 mmol) was added slowly dropwise and the resulting mixture was heated at reflux for 10 h. THF (10 mL) was added and the mixture was cooled to −42 °C (CH_3CN–dry ice) followed by the addition of methyl iodide (18 mmol). After stirring for 30 min at −42 °C, the cooling bath was removed and stirring was continued at room temperature (30 min). The mixture was poured into cold stirred 10% hydrochloric acid (50 mL) and extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The crude oil obtained on concentration was subjected to GC analysis using 2,3-dimethylnaphthalene as an internal standard.

Low-Temperature Ortho Lithiation–Alkylation of α-Amino Alkoxides Derived from *N,N,N'*-Trimethylethylenediamine and Aryl Aldehydes. General Procedure. To a solution of 0.41 mL (3.2 mmol) of *N,N,N'*-trimethylethylenediamine in 8 mL of THF at −20 °C was added 3.1 mmol of *n*-BuLi dropwise. After 15 min, the aryl aldehyde (3.0 mmol) was added, the mixture was stirred for 15 min, and *n*-BuLi (9 mmol) was added via syringe. After the reaction mixture was stirred (or placed in a refrigerator) for the designated time (−20 °C), the electrophile (18 mmol) was added (−42 °C). The mixture was stirred for the designated time, poured into cold stirred 10% hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product. Purification by preparative layer chromatography (SiO_2, acetone–hexanes) gave the desired known aldehydes, or lactols, which were characterized as described in the tables.

Regioselective Metalation Controlled by Varying the Amine Component of the α-Amino Alkoxide. General Procedure. To a solution of 0.35 mL (3.2 mmol) of *N*-methylpiperazine in 8 mL of THF at −20 °C was added 3.1 mmol of *n*-BuLi dropwise. After 15 min, the aryl aldehyde (3.0 mmol) was added, the mixture was stirred for 15 min, TMEDA (6–9 mmol) and *n*-BuLi or *sec*-BuLi (6–9 mmol) were added, and the mixture was placed in a freezer (−20 °C) for the designated time (12–24 h). Methyl iodide (1.1 mL, 18 mmol) was added at −78 °C and the mixture was allowed to come to room temperature (30 min). The workup and purification were as described above. All products were known compounds which were characterized as described in Table IV.

***o*-Butylbenzaldehyde from *o*-Tolualdehyde.** The α-amino alkoxide was prepared in THF from *o*-tolualdehyde (3 mmol) and the lithium amide of *N,N,N'*-trimethylethylenediamine as described above. A hexane solution of *n*-BuLi (9 mmol) was added at −20 °C, and the mixture was stirred (−20 °C) for 1.5 h. After cooling to −78 °C, *n*-propyl iodide (1.7 mL, 18 mmol) was added, the cooling bath was removed, and the mixture was stirred at room temperature for 30 min. The workup and purification were as described above. This compound was identical with an authentic sample prepared from *o*-bromobenzaldehyde, lithium morpholide, and *n*-butyliodide via lithium–halogen exchange.[10]

2,6-Dimethylbenzaldehyde from *o*-Tolualdehyde. The α-amino alkoxide was prepared in benzene (room temperature) from *o*-tolualdehyde (3 mmol) and lithium piperidide (3.1 mmol). A hexane solution of *n*-butyllithium (9 mmol) was added slowly dropwise, and the resulting mixture was heated at reflux for 15 h. Methylation and workup were the same as described above. Purification by preparative layer chromatography (silica gel, acetone–hexanes) gave 200 mg (50%) of 2,6-dimethylbenzaldehyde as a clear oil: mp (2,4-DNP) 248–250 °C (lit.[24] mp 250–252 °C); ^1H NMR (CCl_4) δ 10.6 (s, 1 H), 7.5–6.9 (m, 3 H), 2.53 (s, 6 H); IR (neat) 2975, 1700, 1200 cm^{-1}.

Acknowledgment. Financial support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No. 1,3-Dimethyl-2-(1-naphthyl)imidazolidine, 88802-84-0; 1-(dimethoxymethyl)naphthalene, 33250-32-7; 1-naphthaldehyde cyclohexylimine, 4323-24-4; lithium α-(diethylamino)-1-naphthylmethoxide, 88802-85-1; lithium α-pyrrolidino-1-naphthylmethoxide, 88802-86-2; lithium α-piperidino-1-naphthylmethoxide, 88802-87-3; lithium α-(4-methylpiperazino)-1-naphthylmethoxide, 88802-88-4; lithium α-(trimethylethylenediamino)-1-naphthylmethoxide, 88802-89-5; 1-naphthaldehyde, 66-77-3; 2-methyl-1-naphthaldehyde, 35699-44-6; 8-methyl-1-naphthaldehyde, 6549-57-1; 1,3-dimethyl-2-(2-naphthyl)imidazolidine, 88802-90-8; 2-(dimethoxymethyl)-naphthalene, 77196-31-7; 2-naphthaldehyde cyclohexylimine, 3525-72-2; lithium α-(diethylamino)-2-naphthylmethoxide, 88802-91-9; lithium α-pyrrolidino-2-naphthylmethoxide, 88802-92-0; lithium α-piperidino-2-naphthylmethoxide, 88802-93-1; lithium α-(4-methylpiperazino)-2-naphthylmethoxide, 88802-94-2; lithium α-(trimethylethylenediamino)-2-naphthylmethoxide, 88802-95-3; 2-naphthaldehyde, 66-99-9; 3-methyl-2-naphthaldehyde, 17893-94-6; 1-methyl-2-naphthaldehyde, 35699-45-7; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 3-chlorobenzaldehyde, 587-04-2; 2-chlorobenzaldehyde, 89-98-5; 4-methoxybenzaldehyde, 123-11-5; 3-methoxybenzaldehyde, 591-31-1; 3,4,5-trimethoxybenzaldehyde, 86-81-7; piperonal, 120-57-0; *p*-tolualdehyde, 104-87-0; *m*-tolualdehyde, 620-23-5; *o*-tolualdehyde, 529-20-4; 2-methoxybenzaldehyde, 135-02-4; 3,5-dimethoxybenzaldehyde, 7311-34-4; 2,4-dimethoxybenzaldehyde, 613-45-6; 2,3-dimethoxybenzaldehyde, 86-51-1; 2-(trimethylsilyl)benzaldehyde, 17887-55-7; 2-butylbenzaldehyde, 59059-42-6; 1,3-dihydro-3-phenyl-1-isobenzofuranol, 65184-67-0; 1,3-dihydro-3-phenyl-1-isobenzofuranone, 5398-11-8; 1,3-dihydro-3,3-diphenyl-1-isobenzofuranol, 69621-97-2; 1,3-dihydro-3,3-diphenyl-1-isobenzofuranone, 596-29-2; 4-chloro-2-methylbenzaldehyde, 40137-29-9; 4-chloro-2-methylbenzoic acid, 7499-07-2; 3-chloro-2-methylbenzaldehyde, 874-27-1; 3-chloro-2-methylbenzoic acid, 7499-08-3; 2-chloro-6-methylbenzaldehyde, 1194-64-5; 2-chloro-6-methylbenzoic acid, 21327-86-6; 4-methoxy-2-methylbenzaldehyde, 52289-54-0; 4-methoxy-2-methylbenzoic acid, 6245-57-4; 3-methoxy-2-methylbenzaldehyde, 56724-03-9; 3-methoxy-2-methylbenzoic acid, 55289-06-0; 2-methyl-3,4,5-trimethoxybenzaldehyde, 74327-91-6; 2-methyl-3,4,5-trimethoxybenaldehyde DNP, 88802-96-4; 2-methylpiperonal, 58343-46-7; 2,4-dimethylbenzaldehyde, 15764-16-6; 2,5-dimethylbenzaldehyde, 5779-94-2; 4-methoxy-3-methylbenzaldehyde, 32723-67-4; 4-methoxy-3-methylbenzaldehyde DNP, 32723-68-5; 3-methoxy-4-methylbenzaldehyde, 24973-22-6; 3-methoxy-4-methylbenzaldehyde DNP, 53581-85-4; 2-methoxy-3-methylbenzaldehyde, 67639-61-6; 3,5-dimethoxy-4-methylbenzaldehyde, 1011-27-4; 2,4-dimethoxy-3-methylbenzaldehyde, 7149-92-0; 2,3-dimethoxy-4-methylbenzaldehyde, 75889-47-3; 2,3-dimethoxy-4-methylbenzoic acid, 77869-39-7; *sym*-dimethylethylenediamine, 110-70-3; *N,N,N'*-trimethylethylenediamine, 142-25-6; *N*-methylpiperazine, 109-01-3.

C(1) + C(3), 31.5, 29.0, 28.7 (2×), 22.5, 13.9 C(4)–C(9).

1-Phenylundeca-1,2-diene (11): bp 120 °C (0.4 mmHg); n^{20}_D 1.5320; IR 1951 cm^{-1}; mass, *m/e* 228, M$^{+\cdot}$; ^{1}H NMR (CCl_4) see 9, with δ 1.15–1.60 (m, 12 H); ^{13}C NMR –.

4-Methyl-1-phenylpenta-1,2-diene (12): bp 102 °C (15 mmHg); n^{20}_D 1.5395; IR 1945 cm^{-1}; mass, *m/e* 158, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 7.18 (br m, 5 H), 6.09 (dd, H_A), 5.51 (dd, H_B), 2.42 (ddsept, H_X), 1.08 (br d, 6 H, $J \simeq 7$ Hz), simulated ABX system (90 MHz) $^3J_{BX}$ = 5.75, $^4J_{AB}$ = –6.35, $^5J_{AX}$ = 3.07 Hz; ^{13}C NMR ($CDCl_3$) δ 203.5 C(2), 135.1, 128.4, 126.5, 126.3 (arom C ipso, m, p, o), 102.3 C(3), 95.6 C(1), 28.3 C(4), 22.4 C(5).

4-Methyl-1-phenylhexa-1,2-diene (13): bp 112 °C (15 mmHg), 72 °C (0.5 mmHg); n^{20}_D 1.5465; IR 1949 cm^{-1}; mass, *m/e* 172, M$^{+\cdot}$; 200-MHz ^{1}H NMR ($CDCl_3$), 2 diastereomer pairs (I) δ 7.07–7.31 (br m, 5 H), 6.15 (dd, H_A), 5.53 (dd, H_B), 2.19 (appar septet, H_M), 1.30–1.55 (m, H_X), 1.07 (d, H_Y), 0.95 (t, H_Z), $^4J_{AB}$ = –6.38, $^5J_{BM}$ = 6.39, $^6J_{AM}$ = 2.75, $^5J_{MY}$ = 6.75, $^3J_{XZ}$ = 7.30 Hz; (II) δ 7.07–7.31 (br m, 5 H), 6.14 (dd, H_A), 5.52 (dd, H_B), 2.18 (appar septet, H_M), 1.30–1.55 (m, H_X), 1.06 (d, H_Y), 0.94 (t, H_Z), $^4J_{AB}$ = 6.40, $^5J_{BM}$ = 6.55, $^6J_{AM}$ = 2.49, $^5J_{MY}$ = 6.75, $^3J_{XZ}$ = 7.30 Hz; ^{13}C NMR ($CDCl_3$) δ 204.0 C(2), 135.1, 128.4, 126.4 (arom C ipso, m, p + o), 100.7 C(3), 95.2 C(1), 35.3/35.2, 29.9/29.7, 19.9/19.8, 11.6/11.6 diaster C(4)–C(7).

4,4-Dimethyl-1-phenylpenta-1,2-diene (14): bp 102 °C (15 mmHg); n^{20}_D 1.5395; IR 1950 cm^{-1}; mass, *m/e* 172, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 7.18 (br m, 5 H), 6.09 (d, H_A), 5.48 (d, H_B), 1.10 (s, 9 H), $^4J_{AB}$ = –6.45 Hz; ^{13}C NMR ($CDCl_3$) δ 202.4 C(2), 135.2, 128.5, 126.5, 126.3 (arom C ipso, m, p, o), 106.7 C(3), 96.2 C(1), 32.6 C(4), 30.2 C(5).

2,2-Dimethylhepta-3,4-diene (16): bp 32 °C (15 mmHg); n^{20}_D 1.4370; IR 1954 cm^{-1}; mass, *m/e* 124 M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.95–5.25 (m, 2 H), 1.95 (m, 2 H), 1.01 (s, 9 H), 0.97 (br t, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.6 C(4), 103.6 C(3), 94.3 C(5), 31.5 C(2), 30.1 C(1), 22.0 C(6), 13.2 C(7).

2,2-Dimethylocta-3,4-diene (17): bp 48 °C (15 mmHg); n^{20}_D 1.4390; IR 1958 cm^{-1}; mass, *m/e* 138, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.95–5.25 (m, 2 H), 1.95 (m, 2 H), 1.42 (m, 2 H), 1.01 (s, 9 H), 0.95 (br t, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.1 C(4), 102.8 C(3), 92.5 C(5), 31.6 C(2), 30.2 C(1), 31.3, 22.4, 13.7 C(6)–C(8).

2,2-Dimethylnona-3,4-diene (18): bp 62 °C (15 mmHg); n^{20}_D 1.4402; IR 1958 cm^{-1}; mass, *m/e* 152, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.90–5.20 (m, 2 H), 1.93 (m, 2 H), 1.10–1.50 (m, 4 H), 1.01 (s, 9 H), 0.88 (unresolved t, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.0 C(4), 102.9 C(3), 92.6 C(5), 31.5 C(2), 30.1 C(1), 31.4, 28.8, 22.2, 13.8 C(6)–C(9).

2,2-Dimethyldeca-3,4-diene (19): bp 76 °C (15 mmHg); n^{20}_D 1.4417; IR 1958 cm^{-1}; mass, *m/e* 166, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.90–5.20 (m, 2 H), 1.93 (m, 2 H), 1.10–1.50 (m, 6 H), 1.01 (s, 9 H), 0.87 (unresolved t, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.0 C(4), 102.9 C(3), 92.7 C(5), 31.5 C(2), 30.1 C(1), 31.4, 29.1, 28.9, 22.4, 13.9 C(6)–C(10).

2,2,6-Trimethylhepta-3,4-diene (20): bp 39 °C (15 mmHg); n^{20}_D 1.4356; IR 1957 cm^{-1}; mass, *m/e* 138, M$^{+\cdot}$; ^{1}H NMR ($CDCl_3$) simulated $ABMX_3X'_3$ (200 MHz) δ 5.17 (dd, H_A), 5.12 (dd, H_B), 2.26 (ddsept, H_M), 1.02 (s, 9 H), 0.99 (d, 3 H_X), 0.98 (d, 3 $H_{X'}$) diaster Me, $^3J_{XM}$ = $^3J_{X'M}$ = 6.76, $^3J_{BM}$ = 5.31, $^4J_{AB}$ = –6.22, $^5J_{AM}$ = 3.36 Hz; ^{13}C NMR ($CDCl_3$) δ 199.4 C(4), 104.1 C(3), 100.1 C(5), 31.5 C(2), 30.1 C(1), 27.9 C(6), 22.5, 22.3 diaster C(7).

2,2,6,6-Tetramethylhepta-3,4-diene (21): bp 52 °C (15 mmHg); n^{20}_D 1.4375; IR 1958 cm^{-1}; mass, *m/e* 152, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 5.09 (s, 2 H), 1.00 (s, 18 H); ^{13}C NMR ($CDCl_3$) δ 198.1 C(4), 104.6 C(3) + C(5), 31.5 C(2) + C(6), 30.1 C(1) + C(7).

Trideca-3,4-diene (22): bp 98 °C (18 mmHg); n^{20}_D 1.4545; IR 1959 cm^{-1}; mass, *m/e* 180, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.85–4.20 (m, 2 H), 1.75–2.20 (m, 4 H), 1.10–1.70 (m, 12 H), 0.98 (br t, 3 H), 0.87 (unresolved t, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.4 C(4), 92.5, 91.5 C(3) + C(5), 31.8, 29.3, 29.2 (2×), 29.0 (2×), 22.6, 14.0 C(6)–C(13), 22.0 C(2), 13.4 C(1).

Tetradeca-4,5-diene (23): bp 110 °C (18 mmHg); n^{20}_D 1.4558; IR 1960 cm^{-1}; mass, *m/e* 194, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.85–5.15 (m, 2 H), 1.75–2.15 (m, 4 H), 1.10–1.65 (m, 14 H), 0.90 (br t, 3 H), 0.87 (unresolved t, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.9 C(5), 90.8, 90.6 C(4) + C(6), 31.8, 31.1, 29.3, 29.2 (2×), 29.0, 28.9, 22.6, 22.4, 14.0, 13.5 C(1)–C(3) + C(7)–C(14).

Pentadeca-5,6-diene (24): bp 125 °C (18 mmHg); n^{20}_D 1.4563; IR 1960 cm^{-1}; mass, *m/e* 208, M$^{+\cdot}$; ^{1}H NMR (CCl_4) as **23**, but δ 1.10–1.65 (m, 16 H), 0.88, 0.87 (2 unresolved t, 6 H); ^{13}C NMR ($CDCl_3$) δ 203.8 C(6), 90.8 C(5) + C(7), 31.8, 31.3, 29.4, 29.2 (2×), 29.0 (2×), 28.6, 22.6, 22.1, 14.0, 13.8 C(1)–C(4) + C(8)–C(15).

2,2-Dimethyltrideca-3,4-diene (25): bp 120 °C (18 mmHg); n^{20}_D 1.4512; IR 1958 cm^{-1}; mass, *m/e* 208, M$^{+\cdot}$; ^{1}H NMR (CCl_4) δ 4.93–5.20 (m, 2 H), 1.70–2.15 (m, 2 H), 1.10–1.60 (m, 10 H), 1.01 (s, 9 H), 0.87 (unresolved t, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.0 C(4), 102.9 C(3), 92.7 C(5), 31.5 C(2), 30.1 C(1), 31.8, 29.4, 29.2 (3×), 28.8, 22.6, 14.0 C(6)–C(13).

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Notes

Ortho Substitution of *m*-Anisaldehyde via α-Amino Alkoxide Directed Lithiation

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The addition of aromatic aldehydes to certain lithium dialkylamides gives α-amino alkoxides that can be ring-lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides ortho-substituted aryl aldehydes via a one-pot reaction.[2] This methodology works well for the one-pot substitution of heterocyclic aromatic aldehydes[3] as well as for benzaldehyde derivatives.[2] Several research groups have used this methodology with success;[4] however, two laboratories[5] have informed us that the substitution

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(2) (a) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (b) Comins, D. L.; Brown, J. D. *Ibid.* **1982**, *24*, 5485. (3) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

(3) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.

(4) Liu, J.; Young, J.; Li, Y.; Sha, C. *J. Org. Chem.* **1986**, *51*, 1120. Uemura, M.; Kobayashi, T.; Isobe, K.; Minami, T.; Hayashi, Y. *Ibid.* **1986**, *51*, 2859. Thompson, A.; Lever, J. R.; Canella, K. A.; Miura, K.; Posner, G. H.; Seliger, H. H. *J. Am. Chem. Soc.* **1986**, *108*, 4498. Uemura, M.; Kobayashi, T.; Minami, T.; Hayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 2479. Post, N. P.; McCarthy, J. R.; Sunder, S.; McCowan, *J. Synth. Commun.* **1986**, *16*, 1551. McCarthy, J. R.; McCowan, J.; Zimmerman, M. B.; Wenger, M. A.; Emmert, L. W. *J. Med. Chem.* **1986**, *29*, 1586. Harvey, R. G.; Cortez, C.; Ananthanarayan, T. P.; Schmolka, S. *J. Org. Chem.* **1988**, *53*, 3936. Miller, R. B.; Tsang, T. *Tetrahedron Lett.* **1988**, *29*, 6715.

(5) See acknowledgment.

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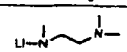
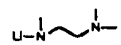
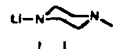
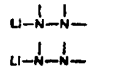
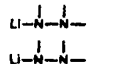
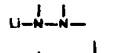
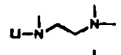
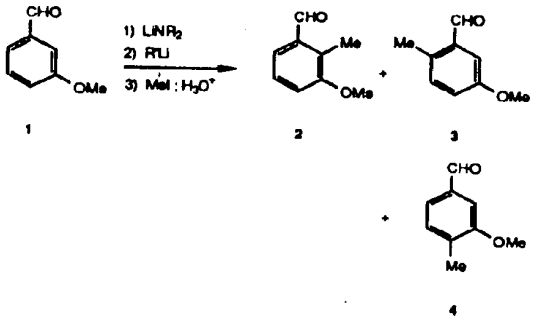
Table I. Ortho Methylation of *m*-Anisaldehyde

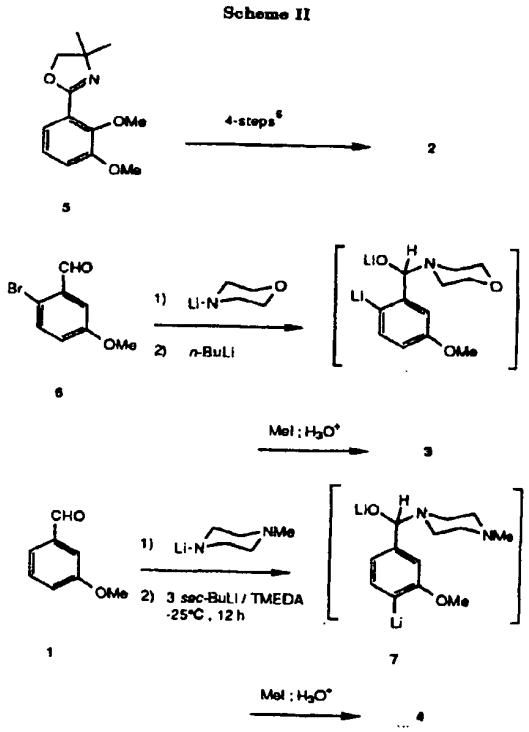
entry[a]	$LiNR_2$	conditions[b]	yield[c] of 1, 2, 3 and 4, %	ratio[d] 2:3:4:1
a		3 *n*-BuLi, THF, −20 °C, 10 h	85	90:5:3:2
b		3 *n*-BuLi, benzene, rt, 8 h	90	88:1:10:1
c		3 *n*-BuLi, benzene, rt, 8 h	94	77:0:1:22
d		3 *n*-BuLi, benzene, rt, 2 h, reflux, 1 h	95	82:0:1:17
e		3 *n*-BuLi, THF, −20 °C, 10 h	75	16:0:14:70
f		3 *n*-BuLi, benzene, rt, 2 h	91	85:2:7:6
g		3 PhLi,[e] benzene, rt, 8 h	89	97.2:0.5:0.3:2
h		3 PhLi, toluene, rt, 4 h	86	98:0:0.1:1.9
i		3 PhLi, toluene, rt, 8 h	83	99:0:0:1
j		3 PhLi, benzene, rt, 8 h	91	96:0:0:4

[a] The reactions were performed on a 3-mmol scale in 8 mL of the indicated solvent. [b] After the indicated time, the mixture was cooled to −78 °C while 8 mL of THF was added. Methyl iodide (1.1 mL) was added slowly at −78 °C, and then the mixture was allowed to come to room temperature (rt) (30 min) and poured into cold, vigorously stirred 10% HCl. Extraction with ether provided the crude products. [c] Yield of isolated aldehydes 2, 3, 4, and 1 obtained as a mixture from radial preparative-layer chromatography. [d] The product ratios were determined by GC. [e] See ref 9.

Scheme I



Scheme II



of *m*-anisaldehyde is not as regioselective for the 2-position as we reported.[2c] Because of the popularity of this methodology and the fact that substituted anisaldehydes are useful starting materials for the synthesis of natural products, we decided to investigate the "*m*-anisaldehyde problem" in detail.

The lithiation–methylation of α-amino alkoxides derived from 1 can lead to three possible ortho-methylated anisaldehydes 2, 3, and 4 (Scheme I). Authentic samples of these methylated anisaldehydes were prepared as shown in Scheme II. A sample of 2 was prepared from 2-(2,3-dimethoxphenyl)-4,4-dimethyl-2-oxazoline (5).[6] Anisaldehyde derivative 3 was synthesized from 2-bromo-5-methoxybenzaldehyde (6) by in situ protection[7] followed by lithium–halogen exchange and methylation. Anisaldehyde derivative 4 was prepared by our published procedure.[2c] The α-amino alkoxide formed from *m*-anisaldehyde (1) and lithium *N*-methylpiperazide (LNMP) in THF was treated with *sec*-butyllithium/TMEDA. Subsequent methylation of the dianion 7 and workup with 10% HCl provided 4 in 60% yield. We performed several lithiation–methylation reactions of α-amino alkoxides derived from *m*-anisaldehyde and analyzed (GC) the

(6) Lead, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098.
(7) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213.

products for starting material (1) and methylated derivatives 2, 3, and 4. The results are given in Table I. When the reaction was run with *N*-lithio-*N*,*N*′,*N*′-trimethylethylenediamine (LTMDA) by using our standard conditions,[2c] an oil was isolated in 85% yield, which contained 90% of the desired aldehyde 2, 8% of isomers 3 and 4, and 2% starting material (1). A similar reaction using benzene as the solvent (entry b) also failed to give the desired degree (>95%) of substitution at the 2-position. The use of lithium *N*-methylpiperazide (LNMP) as the amine component allowed for better regioselectivity, but incomplete metalation occurred (entries c and d).

In an attempt to find an α-amino alkoxide with the desired ortho-directing power, we examined the reaction with *N*-lithio-*N*,*N*′,*N*′-trimethylhydrazine[8] (LTMH) as the amine component. Interestingly, LTMH did form an effective ortho-directing α-amino alkoxide of intermediate strength (entries e and f). When LTMH was the amine component, benzene the solvent, and phenyllithium[9] the base, a highly regioselective lithiation–methylation occurred in high yield (entry g). Phenyllithium also proved to be an effective base for metalations of LTMDA derived α-amino alkoxides. In toluene or benzene, a highly regioselective methylation occurred to give the desired 2-methyl-3-methoxybenzaldehyde (2) in high yield (entries h–j).

Apparently, the lower basicity of phenyllithium, as compared to *n*-butyllithium, is responsible for the increased regioselectivity. The use of phenyllithium as a base allowed us to solve the "*m*-anisaldehyde problem". It is likely that phenyllithium would be effective in other directed lithiation reactions, and its potential as a base should not be overlooked.[10]

Experimental Section

Reactions were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. Benzene, toluene, *N*,*N*′,*N*′-trimethylethylenediamine, *N*-methylpiperazine, and *N*,*N*′,*N*′-trimethylhydrazine[8] were distilled from calcium hydride and stored over 3-Å molecular sieves under N_2.

Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5890A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-101. Radial preparative-layer chromatography (radial PLC) was carried out by using a Chromatotron (Harrison Assoc., Palo Alto, CA).

Preparation of 2-Methyl-3-methoxybenzaldehyde from *m*-Anisaldehyde. General Procedure for the α-Amino Alkoxide Directed Lithiation Reactions. To a solution of 0.41 mL (3.2 mmol) of *N*,*N*′,*N*′-trimethylethylenediamine in 8 mL of benzene was added 3.1 mmol of *n*-BuLi (2.3 M in hexane) dropwise with cooling (ice bath). After 15 min at room temperature, *m*-anisaldehyde (0.37 mL, 3.0 mmol) was added (0–5 °C) and the mixture was stirred at room temperature for 15 min. A solution of phenyllithium (4.5 mL, 9 mmol) in cyclohexane/ether[9] was added with cooling (ice bath). After the mixture was stirred at room temperature for 8 h, 8 mL of THF was added while the mixture was being cooled to −78 °C. Methyl iodide (1.1 mL, 18 mmol) was added slowly at −78 °C, the cooling bath was removed, and the mixture was allowed to come to room temperature (30 min). The mixture was poured into cold, vigorously stirred 10% HCl and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 510 mg of a dark oil. Purification by radial PLC (SiO_2, 5–20% EtOAc/hexanes) gave 410 mg (91%) of a light yellow oil. This oil consisted of 96% 3-methoxy-2-methylbenzaldehyde and 4% *m*-anisaldehyde as indicated by GC analysis.

Acknowledgment. We thank Larry Overman and Victor Snieckus for bringing the "*m*-anisaldehyde problem" to our attention.

(8) Trimethylhydrazine was prepared by a literature procedure, see: Class, J. B.; Aston, J. G.; Oakwood, T. S. *J. Am. Chem. Soc.* **1953**, *75*, 2937.

(9) Phenyllithium was purchased from Aldrich Chemical Co. as a 2.0 M solution in cyclohexane–ether.

(10) Phenyllithium is an effective base for the regioselective α-lithiation of certain 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines. Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *53*, 4437.

Dye-Sensitized Photooxygenation of the C=N Bond[1]

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Department of Chemistry and Biochemistry, San Francisco State University, 1600 Holloway Avenue, San Francisco, California 94132

Received November 7, 1988

Since the early 1970s, photooxygenations of a variety of compounds containing the C=N bond have been reported.[2-12] In some cases these reactions appear to use or-

(1) A preliminary account of this work was reported at the Pacific Conference on Chemistry and Spectroscopy, San Francisco, Oct 27, 1988.

(2) For a review of reactions of $^1O_2$ with nitrogen-containing heterocycles, see: George, M. V.; Bhat, V. *Chem. Rev.* **1979**, *79*, 447–478. Also useful is the review by Boyer: Boyer, J. H. *Chem. Rev.* **1968**, *80*, 495–561.

(3) (a) Imines undergo photooxygenation and photooxidative cleavage via reaction of the triplet state with triplet oxygen: Toshima, N.; Hirai, H. *Tetrahedron Lett.* **1970**, 433–436. (b) Schiff bases undergo cleavage of the C_α—C= single bond subsequent to photooxidative C_α—H cleavage by triplet oxygen: McCapra, F.; Burford, A. *J. Chem. Soc., Chem. Commun.* **1976**, 607–608. (c) N–H hydrazones react with oxygen in an ene reaction giving *C*-hydroperoxyazo adducts, thence fragmentation products; singlet oxygen is not required: Yao, H. C.; Resnick, P. *J. Org. Chem.* **1965**, *30*, 2832–2834. Lewis, G. E.; Spencer, G. I. *Aust. J. Chem.* **1975**, *28*, 1733–1739.

(4) (a) Benzophenone oxime, its methyl ether, and its conjugate base are all cleaved to benzophenone by $^1O_2$: Warner, C. C.; Herring, J. W. *J. Org. Chem.* **1976**, *41*, 1476–1477. (b) Oximes and oxime ethers are, in general, inert or almost so to $^1O_2$. Acetone oxime shows marginal reactivity.[4a] Valerophenone oxime *O*-methyl ether does not react: Ito, Y.; Konishi, M.; Matsuura, T. *Photochem. Photobiol.* **1979**, *30*, 53–57. Cyclohexanone oxime, its methyl ether, and acetophenone oxime react very sluggishly with $^1O_2$: Chawla, H. M.; Hassaner, A. *Tetrahedron Lett.* **1986**, *27*, 4619–4622. Chawla and Hassaner also showed that oxime carbamates react with $^1O_2$ preferentially at the C—N center rather than the C—N center. The relative inertness of oximes to singlet oxygen is confirmed in the present study. *C*-Nitroso compounds (formally tautomeric with oximes and oxime ethers) have been shown to quench $^1O_2$, "...probably by an energy transfer mechanism": Singh, P.; Ullman, E. F. *J. Am. Chem. Soc.* **1976**, *98*, 3018–3019.

(5) Imidazoles give a variety of products depending on the substitution pattern. These reactions appear to begin by electrophilic addition (resembling the reaction of $^1O_2$ with enamines[6]) and/or by 1,4-cycloaddition: Wasserman, H. H.; Stiller, K.; Floyd, M. B. *Tetrahedron Lett.* **1968**, 3277–3280.

(6) (a) Foote, C. S.; Lin, J. W.-P. *Tetrahedron Lett.* **1968**, 3267–3270. Foote, C. S.; Dzakpasu, A. A.; Lin, J. W.-P. *Tetrahedron Lett.* **1975**, 1247–1250. (b) For a review, see: Schaap, A. P.; Zaklika, K. A. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, 1979; p 180.

(7) (a) Sydnones are proposed to react with $^1O_2$ by 1,3-cycloaddition with subsequent fragmentation: Bhat, V.; Dixit, V. M.; Ugarkar, B. G.; Trozzolo, A. M.; George, M. V. *J. Org. Chem.* **1979**, *44*, 2957–2961. (b) An azomethine imine was shown by the same workers to be cleaved by $^1O_2$ to the parent ketone. This reaction too might begin with 1,3-cycloaddition. (c) Aziridines, via their azomethine ylide forms, afford products with $^1O_2$ which can be rationalized by 1,3-cycloaddition followed by fragmentations: Bhat, V.; George, M. V. *J. Org. Chem.* **1979**, *44*, 3288–3292. Bhat, V.; George, M. V. *Tetrahedron Lett.* **1977**, 4133–4136. (d) Diazoalkanes are cleaved by $^1O_2$ to carbonyl compounds; in the presence of aldehydes, ozonides are also formed. The initial stage is probably 1,3-cycloaddition and/or electrophilic addition: Higley, D. P.; Murray, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 3330–3332. Bethell, D.; McKeiver, R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 327–333.

0022-3263/89/1954-3732$01.50/0

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: 13/548,446

Filing Date: 7/13/2012

Examiner: Yevgeny Valenrod

Art Unit: 1621

Conf. No.: 2092

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

Atty. Dkt. No. 080618-1162

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date DEC 20 2012

By _____

FOLEY & LARDNER LLP
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Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

PTO/SB/08 (09-06)
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Date Submitted: DEC 20 2012

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Sheet 1 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B1	5,039,814 A	08/13/1991	Shuman et al.	
	B2	6,933,385 B2	08/23/2005	Westermann et al.	
	B3	7,999,007 B2	08/16/2011	Jeffs et al.	
	B4	2009/0124697 A1	05/14/2009	Cloutier et al.	
	B5	2009/0281189 A1	11/12/2009	Walsh, David A.	
	B6	2010/0076083 A1	03/25/2010	Olschewski	
	B7	2010/0282622 A1	11/11/2010	Phares, Kenneth R.	
	B8	2011/0092599 A1	04/21/2011	Wade et al.	
	B9	2011/0118213 A1	05/19/2011	Phares et al.	
	B10	2011/0144204 A1	06/16/2011	Jeffs et al.	
	B11	2011/0224236 A1	09/15/2011	Rothblatt et al.	
	B12	2011/0319641 A1	12/29/2011	Batra et al.	
	B13	2012/0004307 A1	01/05/2012	Wade et al.	
	B14	2012/0010159 A1	01/12/2012	Rothblatt et al.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B15	13/409,685	03/01/2012	Sharma, Vijay	

FOREIGN PATENT DOCUMENTS

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Sheet 2 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B16	COMINS et al., "Ortho Metalation Directed by α-Amino Alkoxides," J. Org. Chem., 1984, 49:1078-1083.	
	B17	COMINS et al., "Ortho Substitution of M-Anisaldehyde via α-Amino Alkoxide Directed Lithiation," J. Org. Chem., 1989, 54:3730-3732.	
	B18	COREY et al. "Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones," Tetrahedron Letters, 1995, 36(50):9153-9156.	
	B19	GREENE et al., "Protecting Groups," Protective Groups in Organic Synthesis, 2d. Ed., 1991, p. 1-11.	
	B20	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.	
	B21	ROWLEY et al., "Application of the Pauson-Khand reaction to the synthesis of pentalenic acid," Journal of Organometallic Chemistry," 1991, 413:C5-C9.	

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CONFIRMATION NO. 2092

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/548,446	07/13/2012	~~502~~ 562/466	1621	080618-1162

APPLICANTS

Hitesh Batra, Herndon, VA;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

**** CONTINUING DATA ***************************

This application is a CON of 12/334,731 12/15/2008 PAT 8,242,305
which claims benefit of 61/014,232 12/17/2007

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

07/25/2012

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☑ Yes ☐ No	/Y. Valenrod / Examiner's Signature	☐ Initials	VA	0	21	2

ADDRESS

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UNITED STATES

TITLE

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 01/03/2013

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EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
01/03/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	13/548,446	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-21* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-21* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/12*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriarty et al. (*J. Org. Chem.* **2004**, *69(6)*, 1890-1902).

On Page 1892, column 1 Moriarty discloses compound 7 which has the same structure as the instantly claimed product. On page1902, paragraph bridging column 1 and 2, Moriarty disclose a method of preparing compound 7. In the second column 99.7% pure compound 7 is disclosed thereby meeting the purity limitations of claims 2 and 11. The instant claims are product by process. Since the product disclosed in the art is the same as the instantly claimed product, the patentability of the product is does not depend on the method of its production.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from the product of the prior art, the claim is unpatentable even though the prior art product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (MPEP § 2113).

Conclusion

Claims 1-21 are pending

Claims 1-21 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L2	7	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L3	19	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L4	196	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L5	4	"6765117"	USPAT	OR	OFF	2012/12/28 12:33
L6	0	"20020173672"	USPAT	OR	OFF	2012/12/28 12:33
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L8	1	("2002/0173672").URPN.	USPAT	OR	OFF	2012/12/28 12:33
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L15	53	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/12/28 12:33
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2012/12/28 12:33

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2012/12/28 12:33
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2012/12/28 12:33
L19	2	("4486598").URPN.	USPAT	OR	OFF	2012/12/28 12:33
L20	63	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/12/28 12:33
L21	10	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/12/28 12:33
L22	195	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2012/12/28 12:33
L23	7	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2012/12/28 12:33
L24	807	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L25	1	L24 and treprostinil	USPAT	OR	OFF	2012/12/28 12:33
L26	10	L24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2012/12/28 12:33

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2012/12/28 12:33
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2012/12/28 12:33
L29	2	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33
L30	1	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33
L31	12	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33
L32	127	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST	12/28/2012	YV
Inventor	12/28/2012	YV

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/28/2012								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
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	20	✓								
	21	✓								

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: JUL 13 2012

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A11	2008/0249167 A1	10/09/2008	Phares et al.	
	A12	2008/0280986 A1	11/13/2008	Wade et al.	
	A13	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A14	2009/0163738 A1	06/25/2009	Batra et al.	
	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A16	4,424,376 A	01/03/1984	Moniot et al.	
	A17	4,463,183 A	07/31/1984	Haslanger, Martin F.	
	A18	4,486,598 A	12/04/1984	Aristoff, Paul A.	
	A19	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	A20	4,668,814 A	05/26/1987	Aristoff, Paul A.	
	A21	4,683,330 A	07/28/1987	Aristoff, Paul A.	
	A22	5,153,222 A	10/06/1992	Tadepalli et al.	
	A23	6,054,486 A	04/25/2000	Crow et al.	
	A24	6,441,245 B1	08/27/2002	Moriarty et al.	
	A25	6,521,212 B1	02/18/2003	Cloutier et al.	
	A26	6,528,688 B2	03/04/2003	Moriarty et al.	
	A27	6,700,025 B2	03/02/2004	Moriarty et al.	
	A28	6,756,033 B2	06/29/2004	Cloutier et al.	
	A29	6,765,117 B2	07/20/2004	Moriarty et al.	
	A30	6,803,386 B2	10/12/2004	Shorr et al.	
	A31	6,809,223 B2	10/26/2004	Moriarty et al.	
	A32	7,199,157 B2	04/03/2007	Wade et al.	
	A33	7,384,978 B2	06/10/2008	Phares et al.	
	A34	7,417,070 B2	08/26/2008	Phares et al.	

FOREIGN PATENT DOCUMENTS

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	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		

Examiner Signature		Date Considered	

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Sheet 2 of 4

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Art Unit	Unassigned
Examiner Name	Unassigned
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	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A37	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A38	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	A39	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	A40	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	A41	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	A42	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	A43	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	A44	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	A45	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	A46	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	A47	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		
	A48	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	A49	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, Inc.		
	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A51	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	
	A52	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	
	A53	ARISTOFF et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.	
	A54	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.	
	A55	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.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 4

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Art Unit	Unassigned
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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A56	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.	
	A57	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.	
	A58	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	A59	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.	
	A60	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.	
	A61	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	A62	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	A63	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.	
	A64	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.	
	A65	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.	
	A66	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	A67	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	A68	PAGENKOPF et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2 + 2 + 1] Cycloadditions," J. Am. Chem. Soc., 1996, 118:2285-2286.	
	A69	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.	

Examiner Signature		Date Considered	

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First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A70	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	A71	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	A72	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	A73	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	A74	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	
	A75	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	A76	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	A77	ZHANG et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," J. Org. Chem., 1996, 61:4498-4499.	

Examiner Signature	/Yevgeny Valenrod/	Date Considered	12/28/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Diana Meinecke
Attorney Docket Number:	080618-1162

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1202	10	62	620
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**620**

Atty. Dkt. No. 080618-1162
Appl. No. 13/548,446

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

AMENDMENT & REQUEST FOR RECONSIDERATION UNDER 37 CFR § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the Non-Final Office Action dated January 3, 2013.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

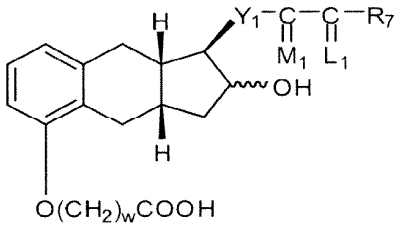
Remarks begin on page 9 of this document.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

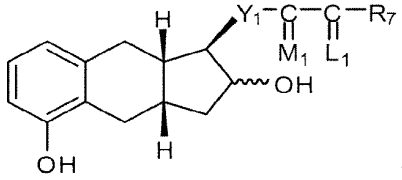
Listing of Claims:

1. (Currently Amended) A product comprising a compound of formula I

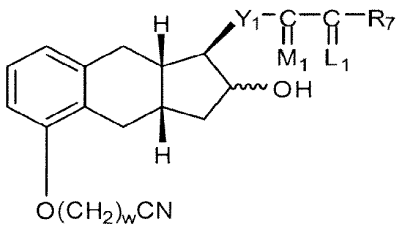


(I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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



(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=$C(CH_3)_2$;

-$C(L_1)$-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

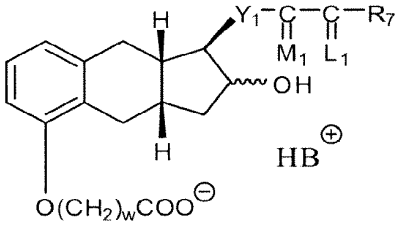
(4) 3-thienyloxymethyl;

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 formula III of step (a) with a base,

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



(I_s) and

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

2. (Currently Amended) The product of claim 1, wherein the purity of compound of formula I in said product ~~isat~~ is at least 99.5%.

3. (Original) The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

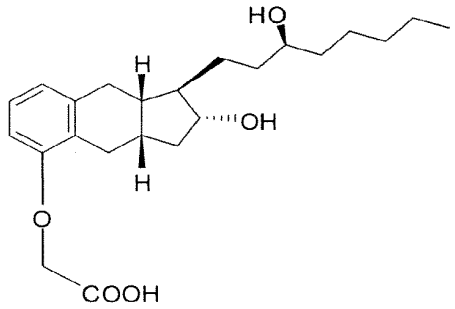
4. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. (Original) The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

6. (Original) The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. (Original) The product of claim 1, wherein Y_1 is $-CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $-(CH_2)_4CH_3$; and w is 1.

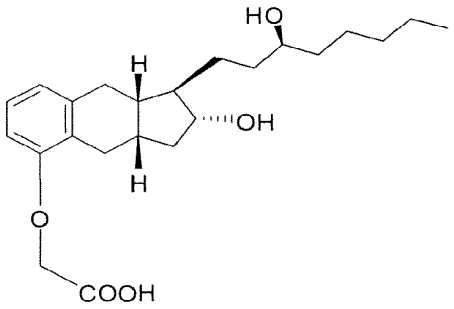
8. (Original) The product of claim 1, wherein the compound of formula I is a compound of formula IV.



(IV).

9. (Original) The product of claim 1, which the process does not include purifying the compound of formula (III) produced in step (a).

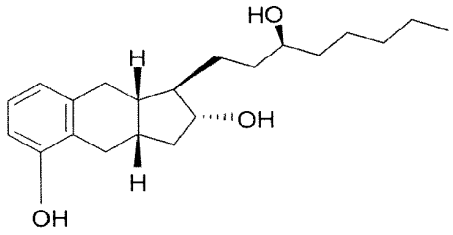
10. (Currently Amended) A product comprising a compound having formula IV



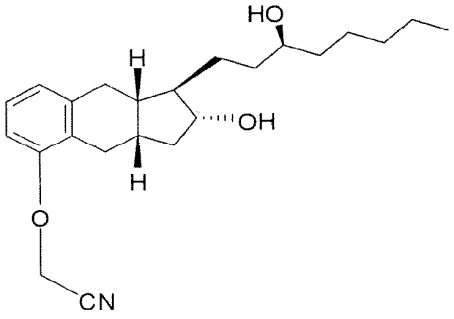
(IV) or a pharmaceutically acceptable salt thereof,

wherein the product is prepared by the process comprising

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



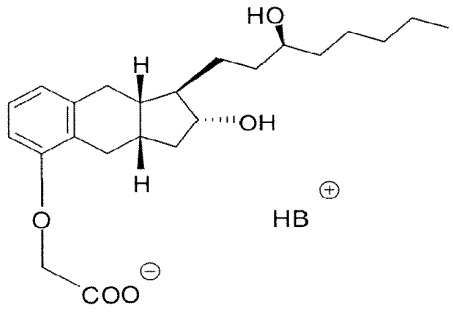
(V)



(VI)

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

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



(IV_s)

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

11. (Currently Amended) The process of claim 10, wherein the purity of product of step (d) ~~has the purity of the compound of formula IV of~~ is at least 99.5%.

12. (Original) The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. (Original) The product of claim 10, wherein the base in step (b) is KOH.

14. (Original) The product of claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

15. (Original) The product of claim 10, wherein the base B is diethanolamine.

16. (Original) The product of claim 10, wherein the acid in step (d) is HCl.

17. (Original) The product of claim 10, which the process does not include purifying the compound of formula (VI) produced in step (a).

18. (Original) The product of claim 17, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

19. (Original) The product of claim 18, wherein the base B is diethanolamine.

20. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

21. (Original) The product of claim 10, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

22. (New) The product of claim 1, wherein step (d) is performed.

23. (New) The product of claim 22, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

24. (New) A process of making a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, said process comprising contacting a solution of treprostinil with a base to form a pharmaceutically acceptable salt of treprostinil, wherein the treprostinil in the solution has not been previously isolated.

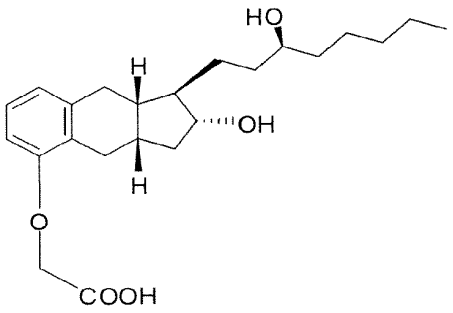
25. (New) The process of claim 24, further comprising isolating the pharmaceutically acceptable salt of treprostinil and adding a pharmaceutically acceptable carrier to form a pharmaceutical product.

26. (New) The process of claim 25, wherein the base is an inorganic base.

27. (New) The process of claim 26, wherein the salt formed by the inorganic base is a sodium salt of treprostinil.

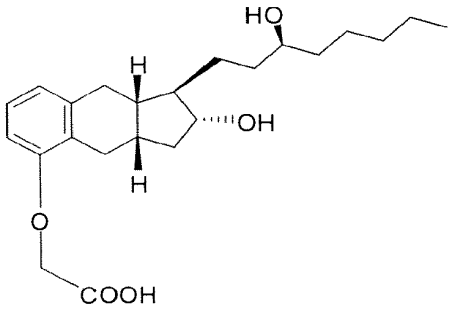
28. (New) The process of claim 26, wherein the salt formed by the inorganic base is a potassium salt of treprostinil.

29. (New) The process of claim 24, further comprising isolating the salt product followed by reacting the salt product with an acid to form a compound of the formula:



30. (New) The process of claim 29, wherein the salt product is a diethanolamine salt of treprostinil.

31. (New) The process of claim 30, further comprising adding a pharmaceutically acceptable carrier to the compound of the formula:



to form a pharmaceutical product.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIM STATUS

Applicants have amended claims 1, 2, 10, and 11 without prejudice or disclaimer, to present the claimed subject matter in a clearer manner. Support for the amended claims may be found throughout the specification as filed. Additionally, claims 22-31 have been added, support for which can be found in paragraphs 46 ("the treprostinil salts can be synthesized from the solution of treprostinil without isolation"), 20 ("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"), 21 ("[b]ase addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like," and "[i]ncluded in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein"), as well as the working examples. No new matter has been added.

After the amendment, claims 1-31 are pending. Claims 1, 10, and 24 are independent.

CLAIM REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-21 stand rejected under 35 U.S.C. 102(b) over Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902). Applicants request reconsideration.

The product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed *in situ* with treprostinil that has not been previously isolated. Specifically, when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil). By contrast, not one of these four impurities was detectable in either a batch of treprostinil salt or a batch of treprostinil acid produced

according to claims 1 and 10. This physical difference in the product results directly from the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil. Since Moriarty does not teach a product of present claims 1 and 10, withdrawal of the rejection is requested.

Concerning new claims 24-31, the same argument above applies to these claims. When a salt is formed with treprostinil *in situ* without previously isolating the treprostinil as required by the steps of these claims, the impurities mentioned in the preceding paragraph resulting from the Moriarty 2004 steps are not detected. Thus, both the steps of the process for making pharmaceutical products recited in claims 24-31 and the products resulting from those steps are different than the process and product of Moriarty 2004 cited in the Office Action. Moriarty 2004 neither teaches nor suggests the advantages resulting from this difference, including the avoidance of the 4 impurities listed above in the product.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Feb. 8, 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Agent for Applicants
Registration No. 55,264

Electronic Acknowledgement Receipt

EFS ID:	14916956
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Diana Meinecke
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1162
Receipt Date:	08-FEB-2013
Filing Date:	13-JUL-2012
Time Stamp:	16:30:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$620
RAM confirmation Number	3297
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Miscellaneous Incoming Letter	transmittal2-8-13.pdf	45393 334f796fcb79a1d176e6984cf300ec95850876ce	no	3
Warnings:					
Information:					
2		AmendRequest2-8-13.pdf	124837 8aff44c573671b9cb595066eaa7fe543438bcc11	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	8
	Applicant Arguments/Remarks Made in an Amendment	9	11

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30804 3306cdc80404039510595 3c1d8fb8c5c4fd5f081	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	201034		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: 13/548,446

Filing Date: 07/13/2012

Examiner: Yevgeny Valenrod

Art Unit: 1621

Confirmation Number: 2092

AMENDMENT TRANSMITTAL

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Transmitted herewith is an amendment in the above-identified application.

[ ] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a previous assertion of Small Entity status.

[ ] Assertion of Small Entity status is enclosed.

[**X**] The fee required for additional claims is calculated below:

	Claims As Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	31	-	21	=	10	x	$62.00	=	$620.00

Atty. Dkt. No. 080618-1162

Independent Claims:	3	-	3	=	0	x	$250.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$460.00	=	$0.00
CLAIMS FEE TOTAL								=	$620.00

[ ] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ] Extension for response filed within the first month:	$150.00	$0.00
[ ] Extension for response filed within the second month:	$570.00	$0.00
[ ] Extension for response filed within the third month:	$1,290.00	$0.00
[ ] Extension for response filed within the fourth month:	$2,010.00	$0.00
[ ] Extension for response filed within the fifth month:	$2,730.00	$0.00
EXTENSION FEE TOTAL:		$0.00
[ ] Statutory Disclaimer Fee under 37 C.F.R. 1.20(d):	$160.00	$0.00
CLAIMS, EXTENSION AND DISCLAIMER FEE TOTAL:		$620.00
[ ] Small Entity Fees Apply (subtract ½ of above):		$0.00
Extension Fees Previously Paid:		$0.00
TOTAL FEE:		$620.00

The above-identified fees of $620.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Atty. Dkt. No. 080618-1162

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date Feb. 8, 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
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Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/548,446	07/13/2012	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 02/08/2013

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)		OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 31	Minus	** 21	= 10	X $ =		OR	X $62=	620
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $250=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	620

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/SANDRA GARNETT/

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

CPC- SEARCHED		
Symbol	**Date**	**Examiner**

CPC COMBINATION SETS - SEARCHED		
Symbol	**Date**	**Examiner**

US CLASSIFICATION SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST	5/6/2013	YV
Inventor	5/6/2013	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/28/2012	05/06/2013							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							
	15	✓	✓							
	16	✓	✓							
	17	✓	✓							
	18	✓	✓							
	19	✓	✓							
	20	✓	✓							
	21	✓	✓							
	22		✓							
	23		✓							
	24		N							
	25		N							
	26		N							
	27		N							
	28		N							
	29		N							
	30		N							
	31		N							

13548446 - GAU: 1621

Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: DEC 20 2012

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B1	5,039,814 A	08/13/1991	Shuman et al.	
	B2	6,933,385 B2	08/23/2005	Westermann et al.	
	B3	7,999,007 B2	08/16/2011	Jeffs et al.	
	B4	2009/0124697 A1	05/14/2009	Cloutier et al.	
	B5	2009/0281189 A1	11/12/2009	Walsh, David A.	
	B6	2010/0076083 A1	03/25/2010	Olschewski	
	B7	2010/0282622 A1	11/11/2010	Phares, Kenneth R.	
	B8	2011/0092599 A1	04/21/2011	Wade et al.	
	B9	2011/0118213 A1	05/19/2011	Phares et al.	
	B10	2011/0144204 A1	06/16/2011	Jeffs et al.	
	B11	2011/0224236 A1	09/15/2011	Rothblatt et al.	
	B12	2011/0319641 A1	12/29/2011	Batra et al.	
	B13	2012/0004307 A1	01/05/2012	Wade et al.	
	B14	2012/0010159 A1	01/12/2012	Rothblatt et al.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B15	13/409,685	03/01/2012	Sharma, Vijay	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

4811-8493-2114.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

13548446 (Modified) 621

Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/548,446
Date Submitted: DEC 2 0 2012				**Filing Date**	7/13/2012
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1621
				Examiner Name	Yevgeny Valenrod
Sheet	2	of	2	Attorney Docket Number	080618-1162

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	B16	COMINS et al., "Ortho Metalation Directed by α-Amino Alkoxides," J. Org. Chem., 1984, 49:1078-1083.	
	B17	COMINS et al., "Ortho Substitution of M-Anisaldehyde via α-Amino Alkoxide Directed Lithiation," J. Org. Chem., 1989, 54:3730-3732.	
	B18	COREY et al. "Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones," Tetrahedron Letters, 1995, 36(50):9153-9156.	
	B19	GREENE et al., "Protecting Groups," Protective Groups in Organic Synthesis, 2d. Ed., 1991, p. 1-11.	
	B20	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.	
	B21	ROWLEY et al., "Application of the Pauson-Khand reaction to the synthesis of pentalenic acid," Journal of Organometallic Chemistry," 1991, 413:C5-C9.	

Examiner Signature	/Yevgeny Valenrod/	Date Considered	05/06/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

4811-8493-2114.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 05/15/2013

FOLEY AND LARDNER LLP
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3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
05/15/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/548,446	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8 February 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-31* is/are pending in the application.

5a) Of the above claim(s) *24-31* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/20/12*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Newly submitted claims 24-31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 24-31 are directed to a process for making a pharmaceutical product while examined claims are directed to a product.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 24-31 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Maintained Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriarty et al. (*J. Org. Chem.* **2004**, *69(6)*, 1890-1902).

On Page 1892, column 1 Moriarty discloses compound 7 which has the same structure as the instantly claimed product. On page1902, paragraph bridging column 1 and 2, Moriarty disclose a method of preparing compound 7. In the second column

99.7% pure compound 7 is disclosed thereby meeting the purity limitations of claims 2 and 11. The instant claims are product by process. Since the product disclosed in the art is the same as the instantly claimed product, the patentability of the product is does not depend on the method of its production.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from the product of the prior art, the claim is unpatentable even though the prior art product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (MPEP § 2113).

Reply to applicants' remarks

Applicants have traversed the above rejection on the grounds that the process by which the instantly claimed product is prepared results in a product that is different from the product of Moriarty. Specifically, applicants allege that treprostinil prepared by the process of Moriarty contains 4 different impurities (benzindene triol, treprostinil methyl ester and 2 different stereoisomers of treaprostinil), while the process in the instant claims results in a product where such impurities are not present. Upon a closer investigation of the Moriarty reference, Examiner has been unable to locate the description of the above mentioned impurities being present. Likewise, no comparative data demonstrating the difference between the two products has been found upon a closer review of the specification. As such, the evidence presented by the applicant

cannot be considered unless it is presented in a form of a declaration. Without such evidence, the product of Moriarty meets the limitations of the instant claims and the rejection of record is maintained.

Conclusion

Claims 1-31 are pending

Claims 1-23 are rejected

Claims 24-31 are withdrawn

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L2	7	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L3	19	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L4	198	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L5	7	"6765117"	USPAT	OR	OFF	2013/05/06 15:29
L6	0	"20020173672"	USPAT	OR	OFF	2013/05/06 15:29
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L8	1	("2002/0173672").URPN.	USPAT	OR	OFF	2013/05/06 15:29
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L15	58	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/05/06 15:29
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2013/05/06 15:29

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2013/05/06 15:29
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2013/05/06 15:29
L19	2	("4486598").URPN.	USPAT	OR	OFF	2013/05/06 15:29
L20	68	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/05/06 15:29
L21	10	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/05/06 15:29
L22	197	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2013/05/06 15:29
L23	8	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/05/06 15:29
L24	811	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L25	2	L24 and treprostinil	USPAT	OR	OFF	2013/05/06 15:29
L26	12	L24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/05/06 15:29

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2013/05/06 15:29
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2013/05/06 15:29
L29	2	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29
L30	1	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29
L31	12	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29
L32	128	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29

Electronic Acknowledgement Receipt

EFS ID:	15957665
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Diana Meinecke
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1162
Receipt Date:	05-JUN-2013
Filing Date:	13-JUL-2012
Time Stamp:	15:34:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		116Reply.pdf	391887 37da8f5eb11ff49010ea1b16cae4d9a112177dba	yes	9

Multipart Description/PDF files in .zip description					
	Document Description		**Start**		**End**
	Amendment After Final		1		1
	Claims		2		6
	Applicant Arguments/Remarks Made in an Amendment		7		9
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	DAWsigneddeclaration.pdf	147931 730f850fe95f504bd6b9ab1d587cd6e498023cd5	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	539818		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIM STATUS

Applicants have amended claims 11 and 17 to correct inadvertent typographical errors. No new matter has been added.

Applicants have canceled claims 24-31, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing application directed to the subject matter of the canceled claims.

After the amendment, claims 1-23 are pending. Claims 1 and 10 are independent.

CLAIM REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-21 stand rejected under 35 U.S.C. 102(b) over Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902). Applicants request reconsideration.

In the response filed February 8, 2013, Applicants submitted that the product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed *in situ* with treprostinil that has not been previously isolated. Specifically, Applicants noted that when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil). By contrast, not one of these four impurities was detectable in either a batch of treprostinil salt or a batch of treprostinil acid produced according to claims 1 and 10. In their February 8th response, Applicants explained that this physical difference in the product resulted directly from the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil.

In the Office Action, the PTO informed Applicants that "the evidence presented by the applicant cannot be considered unless it is presented in a form of a declaration," see sentence

bridging pages 3-4. The PTO decided to maintain the rejection because in the PTO's opinion, "[w]ithout such evidence, the product of Moriarty meets the limitations of the instant claims," see page 4.

To address the issue raised by the PTO, Applicants submit with the present response a declaration under 37 C.F.R. § 1.132 by Dr. David Walsh. In section 7 of his declaration, Dr. Walsh provides data from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process corresponding to "Moriarty", treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application, and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application. Based on the results provided, Dr. Walsh concludes "that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claimd 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty" at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty."

Since Dr. Walsh's declaration provides evidence that the product of present claims is physically difference than treprostinil produced according to the process of Moriarty, Moriarty cannot anticipate the present claims. Accordingly, Applicants request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a

check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 5, 2013

By [signature] for Alexey Saprigin Reg No 35,264
Agent for Applicants
Registration No. 56,439

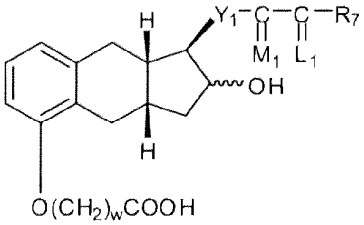
FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

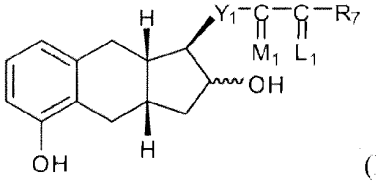
Listing of Claims:

1. (Previously Presented) A product comprising a compound of formula I

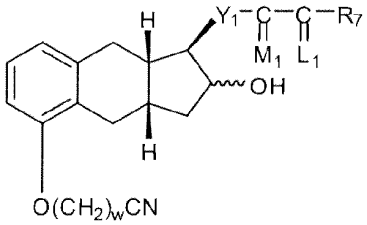


(I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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



(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=$C(CH_3)_2$;

-$C(L_1)$-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

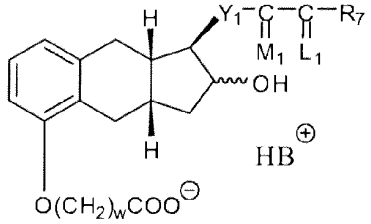
(4) 3-thienyloxymethyl;

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 formula III of step (a) with a base,

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



(I_s) and

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

2. (Previously Presented) The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.

3. (Original) The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

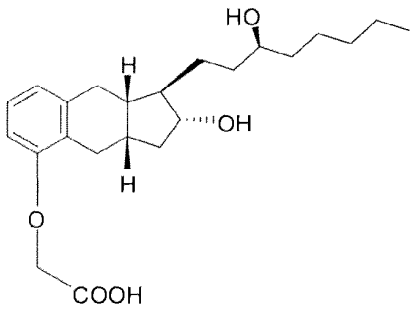
4. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. (Original) The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

6. (Original) The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. (Original) The product of claim 1, wherein Y_1 is $-CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $-(CH_2)_4CH_3$; and w is 1.

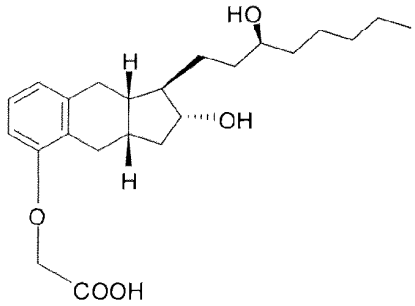
8. (Original) The product of claim 1, wherein the compound of formula I is a compound of formula IV.



(IV).

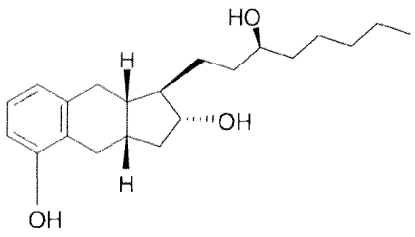
9. (Original) The product of claim 1, which the process does not include purifying the compound of formula (III) produced in step (a).

10. (Previously Presented) A product comprising a compound having formula IV

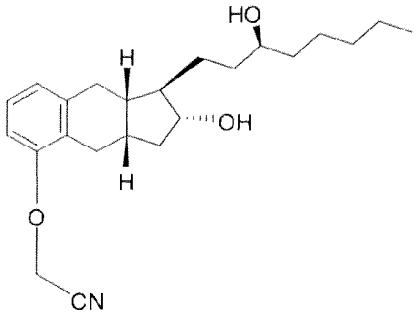


(IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

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



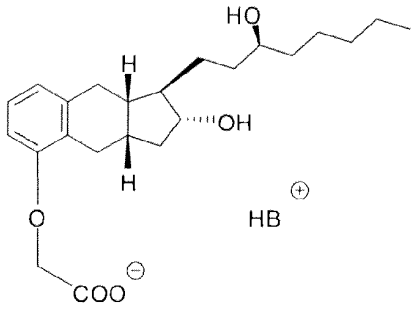
(V)



(VI)

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

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



(IV_s)

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

11. (Currently Amended) The ~~process~~ product of claim 10, wherein the purity of product of step (d) is at least 99.5%.

12. (Original) The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. (Original) The product of claim 10, wherein the base in step (b) is KOH.

14. (Original) The product of claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

15. (Original) The product of claim 10, wherein the base B is diethanolamine.

16. (Original) The product of claim 10, wherein the acid in step (d) is HCl.

17. (Currently Amended) The product of claim 10, ~~which~~ wherein the process does not include purifying the compound of formula (VI) produced in step (a).

18. (Original) The product of claim 17, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

19. (Original) The product of claim 18, wherein the base B is diethanolamine.

20. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

21. (Original) The product of claim 10, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

22. (Previously Presented) The product of claim 1, wherein step (d) is performed.

23. (Previously Presented) The product of claim 22, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

24-31. (Canceled)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

REPLY UNDER 37 CFR § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the outstanding Final Office Action dated May 15, 2013.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

Remarks begin on page 7 of this document.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
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Art Unit:	1621
Confirmation Number:	2092

DECLARATION OF DAVID WALSH UNDER 37 C.F.R. 1.132

I, David A. Walsh, do hereby declare:

1. I am the Executive Vice President of Chemical Research and Development at the United Therapeutics Corporation.

2. I have extensive experience in the field of Pharmaceutical Chemistry as evidenced by my Ph.D. degree received in organic chemistry from the University of New Hampshire and over 39 years of professional experience. My Curriculum Vitae attached as Appendix A provides additional details on my qualifications and experience.

3. My employer, United Therapeutics Corporation, is the owner of the above identified application.

4. I am not receiving additional compensation for providing this Declaration beyond my normal compensation from my employer.

BAW 6/4/13

5. I am familiar with the Office Action dated May 15, 2013, as well as with Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902, "Moriarty") cited therein.

6. In my opinion, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty." In particular, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 differ from treprostinil prepared according to the process of "Moriarty" in their respective impurity profiles. In support, I provide the following data obtained from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process of "Moriarty", treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application, and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application, respectively.

Treprostinil free acid prepared according to "Moriarty"

Chromatographic Purity (HPLC) NB 1, PDR 16	1AU90:	Not more than 0.4%	ND
	2AU90:	Not more than 0.1%	< 0.05%
	97W86 (Benzindene Trial):	Not more than 0.2%	0.07%
	3AU90:	Not more than 1.0%	0.3%
	Treprostinil Methyl Ester:	Not more than 0.2%	< 0.05%
	Treprostinil Ethyl Ester:	Not more than 0.5%	0.1%
	750W93:	Not more than 0.5%	0.1%
	751W93:	Not more than 0.3%	0.07%
	Unidentified at:	Not more than 0.1% AUC each	ND
Total Related Substances NB 1, PDR 16	Not more than 3.0%		0.6%

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Treprostinil diethanolamine prepared according to claims 1 or 10

	Com pound	Specifications	
Impurities (HPLC) [Known Impurities] (UTW-11-0327)	1AU90	Not more than 0.4 %	ND
	2AU90	Not more than 0.1 %	ND
	97W86	Not more than 0.2 %	ND
	3ALI9D	Not more than 0.5 %	< 0.05 % w/w
	Treprostinil Methyl Ester	Not more than 0.2 %	ND
	Treprostinil Ethyl Ester	Not more than 0.5 %	ND
	750W93	Not more than 0.5 %	ND
	751W93	Not more than 0.3 %	ND
Impurities (HPLC) [Unidentified Impurities] (UTW-11-0327)	Not more than 0.2 % AUC each		0.07 % AUC (RRT 0.26)
Impurities (HPLC) [Total Related Substances] (UTW-11-0327)	Not more than 1.5 %		0.1 % w/w

Treprostinil as the free acid prepared according to claims 1 or 10

	Compound	Specifications	
Impurities (HPLC)	1AU90	Not more than 0.40%	ND
	2AU90	Not more than 0.10%	ND
	3AU90	Not more than 1.00%	ND
	750W93	Not more than 0.50%	0.06 % w/w
	751W93	Not more than 0.30%	< 0.05 % w/w
	97W86 (Benzindene Triol)	Not more than 0.20%	ND
	Treprostinil Ethyl Ester	Not more than 0.50%	0.13 % w/w
	Treprostinil Methyl Ester	Not more than 0.20%	ND
Impurities (HPLC) [Unidentified Impurities]	Not more than 0.10% AUC each		ND
Impurities (HPLC) [Total Related Substances]	Not more than 3.00%		0.2 %

In each case, in the above tables, "ND" means not detected. The far right column represents the testing results for that product batch.

7. The impurity profiles shown above examine the following eight impurities: 1AU90, 2AU90 and 3AU90, each of which is a stereoisomer of treprostinil; triol; methyl ester of treprostinil and ethyl ester of treprostinil; 750W93 and 751W93, each of which is a dimer of treprostinil, in which the acid group of one treprostinil molecule esterifies with an alcohol group on another treprostinil molecule. According to the first profile above, treprostinil produced according to the process of "Moriarty" has 7 out of 8 impurities in detectable amounts. According to the second profile above, treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application has only one impurity, treprostinil stereoisomer 3A90, in a detectable amount. According to the third profile above, treprostinil as

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the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities, treprostinil ethyl ester, treprostinil dimers 750W93 and 751W93.

8. Based on the results shown above, I conclude that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty" at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty".

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States.

6/4/13

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 4th day of JUNE, 2013.

David A. Walsh

David A. Walsh

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/548,446	Filing Date 07/13/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**380**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**380**

APPLICATION AS AMENDED – PART II

AMENDMENT	06/05/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 23	Minus	** 31	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/GLORIA TRAMMELL/

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION									
CLASS	**SUBCLASS**	**CLAIMED**					**NON-CLAIMED**				
562	466	C	0	7	C	62 / 00 (2006.01.01)					
CROSS REFERENCE(S)		C	0	7	C	65 / 00 (2006.01.01)					
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**										

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621 (Primary Examiner)	06/10/2013 (Date)	O.G. Print Claim(s) 1
		O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No. 20130607

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621 (Primary Examiner)	06/10/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No. 20130607

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENRROD	1621

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621 (Primary Examiner)	06/10/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No. 20130607

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L2	7	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L3	19	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L4	201	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L5	7	"6765117"	USPAT	OR	OFF	2013/06/10 14:30
L6	0	"20020173672"	USPAT	OR	OFF	2013/06/10 14:30
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L8	1	("2002/0173672").URPN.	USPAT	OR	OFF	2013/06/10 14:30
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L15	59	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/06/10 14:30
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2013/06/10 14:30

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2013/06/10 14:30
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2013/06/10 14:30
L19	2	("4486598").URPN.	USPAT	OR	OFF	2013/06/10 14:30
L20	69	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/06/10 14:30
L21	10	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/06/10 14:30
L22	200	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2013/06/10 14:30
L23	8	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/06/10 14:30
L24	811	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L25	2	L24 and treprostinil	USPAT	OR	OFF	2013/06/10 14:30
L26	12	L24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/06/10 14:30

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2013/06/10 14:30
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2013/06/10 14:30
L29	2	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30
L30	1	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30
L31	12	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30
L32	129	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

CPC- SEARCHED		
Symbol	**Date**	**Examiner**

CPC COMBINATION SETS - SEARCHED		
Symbol	**Date**	**Examiner**

US CLASSIFICATION SEARCHED			
Class	**Subclass**	**Date**	**Examiner**

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST	6/10/2013	YV
Inventor	6/10/2013	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
562	466	6/10/2013	YV

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

OK TO ENTER: /YV/

Atty. Dkt. No. 080618-1162
Appl. No. 13/548,446

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

REPLY UNDER 37 CFR § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the outstanding Final Office Action dated May 15, 2013.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

Remarks begin on page 7 of this document.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/28/2012	05/06/2013	06/10/2013						
	1	✓	✓	=						
	2	✓	✓	=						
	3	✓	✓	=						
	4	✓	✓	=						
	5	✓	✓	=						
	6	✓	✓	=						
	7	✓	✓	=						
	8	✓	✓	=						
	9	✓	✓	=						
	10	✓	✓	=						
	11	✓	✓	=						
	12	✓	✓	=						
	13	✓	✓	=						
	14	✓	✓	=						
	15	✓	✓	=						
	16	✓	✓	=						
	17	✓	✓	=						
	18	✓	✓	=						
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	20	✓	✓	=						
	21	✓	✓	=						
	22		✓	=						
	23		✓	=						
	24		N							
	25		N							
	26		N							
	27		N							
	28		N							
	29		N							
	30		N							
	31		N							

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 06/12/2013
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/12/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/12/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax **(571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 06/12/2013
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/12/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1621	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 06/12/2013

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/12/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/548,446	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/5/13*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-23*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1162

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2080**

Electronic Acknowledgement Receipt

EFS ID:	16073423
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Walker
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1162
Receipt Date:	18-JUN-2013
Filing Date:	13-JUL-2012
Time Stamp:	16:11:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2080
RAM confirmation Number	3351
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	IFTM.pdf	192726 6b0078d7521bf2d086d8bd0dce5a2de1ea4721db	no	2
Warnings:					
Information:					
2		312amend.pdf	125080 b4bf56b3dcdf81718bd3d27af749e1f4e7d3cbe7	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32200 c03f4d01420cc49dbc42adbc1d8e95a2de483c18	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	350006		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

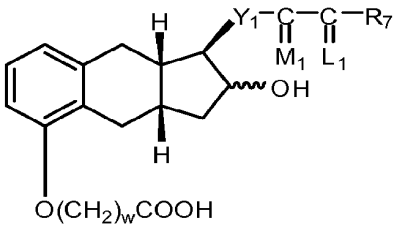
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

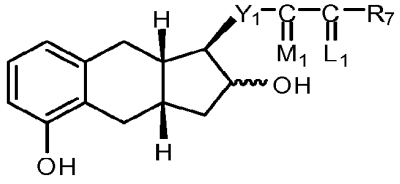
Listing of Claims:

1. (Previously Presented) A product comprising a compound of formula I

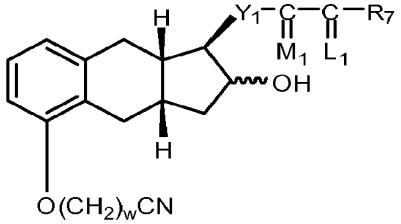


(I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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



(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=$C(CH_3)_2$;

-$C(L_1)$-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

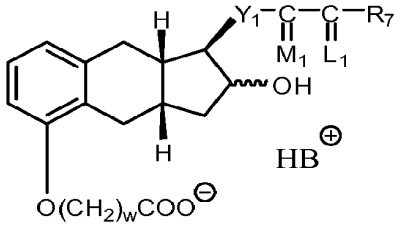
(4) 3-thienyloxymethyl;

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 formula III of step (a) with a base,

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



(I_s) and

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

2. (Previously Presented) The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.

3. (Original) The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

4. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. (Original) The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

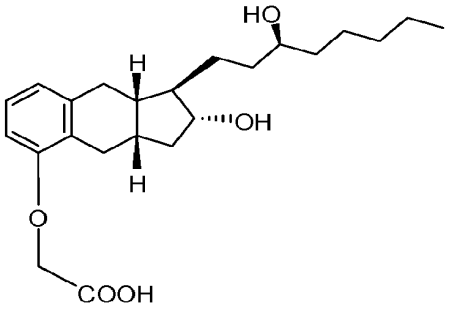
6. (Original) The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. (Original) The product of claim 1, wherein Y_1 is $-CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $-(CH_2)_4CH_3$; and w is 1.

8. (Canceled)

9. (Currently amended) The product of claim 1, ~~which~~ **wherein** the process does not include purifying the compound of formula (III) produced in step (a).

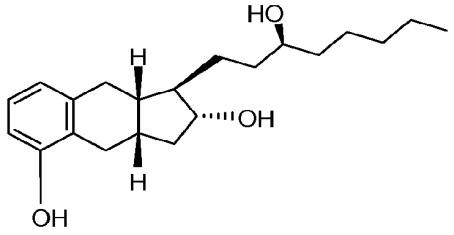
10. (Previously Presented) A product comprising a compound having formula IV



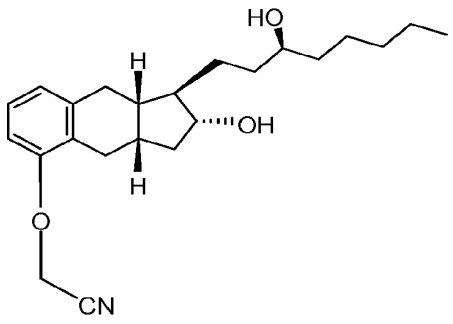
(IV) or a pharmaceutically acceptable salt thereof,

wherein the product is prepared by the process comprising

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



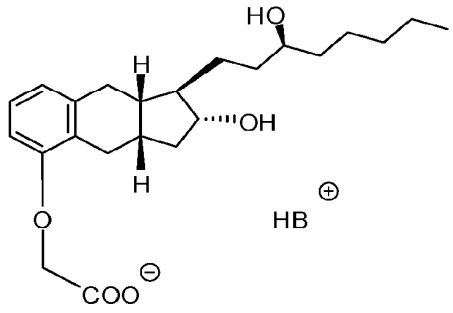
(V)



(VI)

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

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



(IV_s)

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

11. (Previously presented) The product of claim 10, wherein the purity of product of step (d) is at least 99.5%.

12. (Original) The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. (Original) The product of claim 10, wherein the base in step (b) is KOH.

14. (Original) The product of claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

15. (Original) The product of claim 10, wherein the base B is diethanolamine.

16. (Original) The product of claim 10, wherein the acid in step (d) is HCl.

17. (Previously presented) The product of claim 10, wherein the process does not include purifying the compound of formula (VI) produced in step (a).

18. (Original) The product of claim 17, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

19. (Original) The product of claim 18, wherein the base B is diethanolamine.

20. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

21. (Original) The product of claim 10, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

22. (Previously Presented) The product of claim 1, wherein step (d) is performed.

23. (Previously Presented) The product of claim 22, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

24-31. (Canceled)

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

AMENDMENT UNDER 37 CFR 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant acknowledges receipt of a Notice of Allowance in the above-captioned application. Prior to payment of the issue fee, please amend the application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

Remarks/Arguments begin on page 7 of this document.

Please amend the application as follows:

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 06/12/2013
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/12/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1621	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

United Therapeutics Corporation Silver Spring, MD

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
- ❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date JUN 1 8 2013

Typed or printed name Stephen B. Maebius Registration No. 35,264

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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PTOL-85 (Rev. 02/11) Approved for use through 08/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REMARKS

This amendment is being filed prior to or concurrently with payment of the issue fee. Entry of the foregoing amendment is respectfully requested. The amendment is made to cancel claim 8 and to correct a minor typographical error in claim 9. The amendment does not change the scope of the claims. Accordingly, entry of the amendment is requested.

A detailed listing of all claims that are, or were, in the application is presented with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-7 and 9-23 are now pending in this application.

It is believed that no fees are due in connection with this Rule 312 amendment. In the event this is not correct, the undersigned authorizes the Commissioner to charge Deposit Account No. 19-0741.

Respectfully submitted,

Date June 18, 2013

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 06/26/2013

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
06/26/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Response to Rule 312 Communication	Application No.	Applicant(s)
	13/548,446	BATRA ET AL.
	Examiner	Art Unit
	YEVGENY VALENROD	1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ The amendment filed on *18 June 2013* under 37 CFR 1.312 has been considered, and has been:

a) ☒ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

OK TO ENTER: /YV/

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

AMENDMENT UNDER 37 CFR 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant acknowledges receipt of a Notice of Allowance in the above-captioned application. Prior to payment of the issue fee, please amend the application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

Remarks/Arguments begin on page 7 of this document.

Please amend the application as follows:

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/30/2013	8497393	080618-1162	2092

22428 7590 07/10/2013

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Hitesh Batra, Herndon, VA;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

Electronic Acknowledgement Receipt

EFS ID:	17851300
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Karen Walker
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1162
Receipt Date:	08-JAN-2014
Filing Date:	13-JUL-2012
Time Stamp:	13:00:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$100
RAM confirmation Number	9398
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Request for Certificate of Correction	COC.pdf	90316 d354fa5bd08d430444455be9f704488c9a157b99	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30441 02179a308a3eb11527002940bb150e617296aeac	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	120757	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Alexey V. Saprigin/Karen Walker
Attorney Docket Number:	080618-1162

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of Correction	1811	1	100	100
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**100**

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Patent. No.:	8,497,393
Issue Date:	7/30/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 C.F.R. § 1.323

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Enclosed, in duplicate, is a Certificate of Correction, Form PTO-SB/44, for United States Patent Number 8,497,393 issued July 30, 2013.

Correction of the term"tromethanine" to "tromethamine" in five instances in the claims is requested.

Applicants submit that the noted errors do not constitute new matter, and correction thereof would not require reexamination.

Pursuant to 37 C.F.R. §1.323, Applicants request that the enclosed Certificate of Correction be approved.

Since the noted errors are not the fault of the Patent Office, payment is enclosed of the required fee of $100.00.

Atty. Dkt. No. 080618-1162

The above-identified fees are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date JAN 08 2014

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Alexey V. Saprigin
Agent for Applicants
Registration No. 56,439

4841-6757-5063.1

MODIFIED PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	8,497,393
APPLICATION NO.	:	13/548,446
DATED	:	7/30/2013
INVENTOR(S)	:	Hitesh BATRA; Sudersan M. TULADHAR; Raju PENMASTA; David A. WALSH

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Replace the term "tromethanine" with --tromethamine -- as follows:

Col. 19, claim 5, line 38;
Col. 20, claim 13, line 55;
Col. 20., claim 17, line 66;
Col. 21, claim 19, line 6; and
Col. 21, claim 20, line 11.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Foley & Lardner LLP
3000 K Street, N.W., Suite 600
Washington, D.C. 20007-5143

4845-0325-0455.1

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,497,393 B2
APPLICATION NO. : 13/548446
DATED : July 30, 2013
INVENTOR(S) : Hitesh Batra et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

Replace the term "tromethanine" with --tromethamine-- as follows:

Col. 19, claim 5, line 38;
Col. 20, claim 13, line 5;
Col. 20, claim 17, line 66;
Col. 21, claim 19, line 6; and
Col. 21, claim 20, line 11.

Signed and Sealed this
Eighteenth Day of March, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,497,393 B2
APPLICATION NO. : 13/548446
DATED : July 30, 2013
INVENTOR(S) : Hitesh Batra et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

Replace the term "tromethanine" with --tromethamine-- as follows:

Col. 19, claim 5, line 38;
Col. 20, claim 13, line 55;
Col. 20, claim 17, line 66;
Col. 21, claim 19, line 6; and
Col. 21, claim 20, line 11.

This certificate supersedes the Certificate of Correction issued March 18, 2014.

Signed and Sealed this
Twenty-seventh Day of May, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–05498–PGS–LHG	9/2/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
UNITED THERAPEUTICS CORPORATION	TEVA PHARMACEUTICALS USA, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,765,117 B2	July 20, 2004	United Therapeutic Corporation
2 US 8,497,393 B2	July 30, 2013	United Therapeutics Corporation
3 US 7,999,007 B2	August 16, 2011	United Therapeutics Corporation
4 US 8,653,137 B2	February 18, 2014	United Therapeutics Corporation
5 US 8,658,694 B2	February 25, 2014	United Therapeutics Corporation

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	9/2/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–05499–PGS–LHG	9/2/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
UNITED THERAPEUTICS CORPORATION	SANDOZ, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 8,497,393 B2	July 30, 2013	United Therapeutics Corporation
2		
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
	___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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3		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	9/2/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

Atty. Dkt. No. 080618-1162

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Patent. No.:	8,497,393
Issue Date:	7/30/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
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REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 C.F.R. § 1.323

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Enclosed is a Certificate of Correction, Form PTO-SB/44, for United States Patent Number 8,497,393 issued July 30, 2013.

Correction of the "αOR_1:β-R_5" with --αOR_2:β-R_5 -- in two instances in the specification, and in one instance in the claims, is requested.

Applicants submit that the noted errors do not constitute new matter, and correction thereof would not require reexamination.

Pursuant to 37 C.F.R. §1.323, Applicants request that the enclosed Certificate of Correction be approved.

Since the noted errors are not the fault of the Patent Office, payment is enclosed of the required fee of $100.00.