IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

U.S. Patent No. 8,497,393 Case No. IPR 2016-00006

SteadyMed Ltd.

Petitioner

v.

United Therapeutics Corporation

Patent Owner

November 29, 2016

SteadyMed THERAPEUTICS

Topics

1. Legal Concepts
2. Key Scientific Concepts
3. Overview
4. Anticipation
5. Obviousness
   - Phares and Moriarty
   - Kawakami and Moriarty
   - Dependent Claims 6, 10, 21 & 22
6. Claim Construction

1 Legal Concepts

Legal Concepts

We have clearly stated that "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." ... "That is because of the ... longstanding rule that an old product is not patentable even if it is made by a new process."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted)

Legal Concepts

"If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985)

Legal Concepts

"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14–hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Legal Concepts

"[T]he fact that the 14–hydroxy is derived from 8α imparts no structural or functional differences in the low-ABUK [impurity] hydrocodone API as compared to the prior art products. Thus, the court did not err in disregarding the process limitation in its obviousness determination."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016)

Legal Concepts

"Cases involving the "**purification**" of a natural substance employ similar analysis. Our predecessor court recognized that merely purifying a naturally occurring substance does not render the substance patentable **unless it results in a marked change in functionality**. *In re Merz*, 25 CCPA 1314, 97 F.2d 599, 601 (1938) (holding that there was no right to a patent on a purer version of ultramarine, but recognizing that if a claimed article is "of such purity that it differs not only in degree but in kind it may be patentable") ...."

Ass'n for Molecular Pathology v. USPTO, 689 F. 3d 1303, 1353-54 (Fed. Cir. 2012) (emphases added).

Legal Concepts

"[I]f the process by which a product is made imparts 'structural **and** functional differences' distinguishing the claimed product from the prior art, then those differences 'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'"

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted) (emphasis added)

2 Key Scientific Concepts

Key Scientific Concepts

Recrystallization

Q: How long has crystallization been around as a method of purification?

A: I don't know how long it's been around.

Q: Before 2007?

A: Oh, yes.

Q: Did you learn about it when you were in college at the university?

A: Yes, I did. [...]

Q: And when did you go to college?

A: In 1968 I started. In 1968.

* * *

Q: ... But how far back does doing that process you just described, how far back does that go?

The Witness: Decades.

(Ex. 2058, 175:19-176:22, 179:11-17)

Ex. 2058 ("Ruffolo Deposition Transcript) at 45-46

Key Scientific Concepts

Melting Point

The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_o^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where *Ts,* is the sample temperature, T_0 is the melting point of the pure compound, *R* is the gas constant, X_i, is the mole fraction of the impurity, *F* is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus 1/*F* should give a straight line whose slope is proportional to X_i (Brittain *et al.,* 1991).

Stephen R. Byrn *et al., Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

Key Scientific Concepts

Melting Point

Figure 18

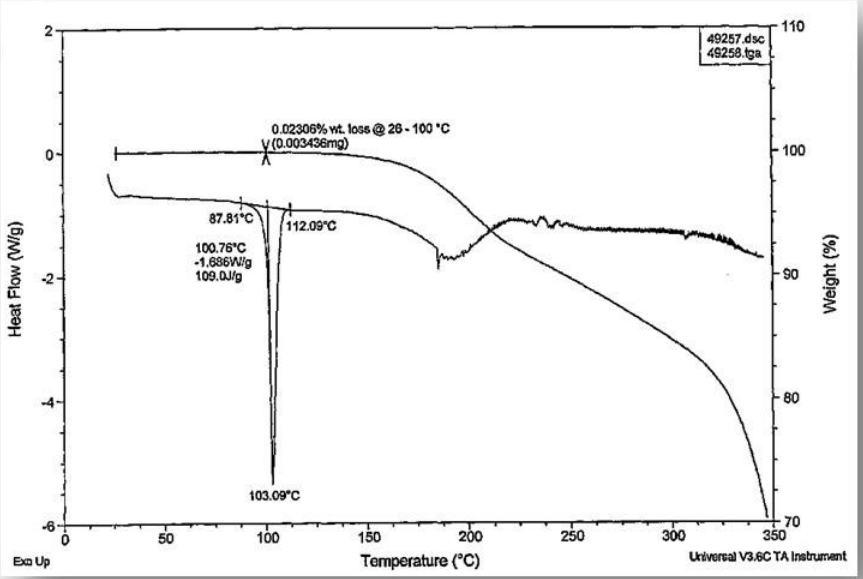
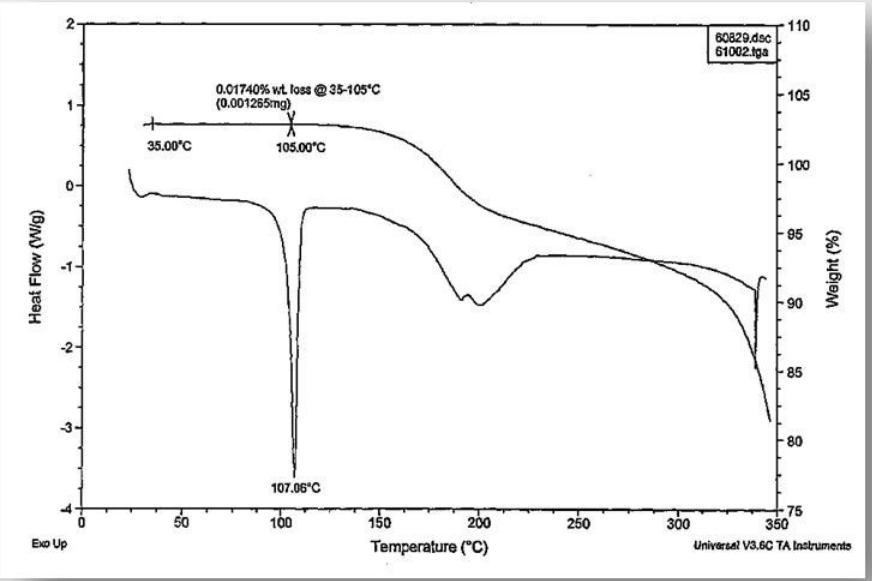


Figure 21



Ex. 1005 *("Phares")*, Figures 18 and 21.

Ex. 1005 ("Phares") at 118, 121

Key Scientific Concepts

Melting Point

The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

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Stephen R. Byrn *et al., Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

Key Scientific Concepts

HLPC and Purity

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

Ex. 1001, '393 Patent col.13, ll.50-65

Ex. 1001 ("'393 Patent") at 9

Key Scientific Concepts

HLPC and Purity

During the initial analytical method validation for the treprostinil assay, the results indicated that there is about 2% variability in the assay. Our specifications of 97.0-101.0% were centered at 99% purity for the API. When the process for the manufacture of treprostinil was instituted in Silver Spring, it was observed that the purity of the treprostinil improved to close to 100%. From a statistical stand-point, an analytical variability of 2% in the assay may result in an OOS on the high side (considering a two sigma range) when the upper limit of the specification is 101.0%. Scientifically, an API cannot have a purity of greater than 100%. If an API is 100% pure, 2% variability in the assay may result in an OOS at specifications of 97.0-101.0%. During development in Silver Spring, it was observed that there were

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UT Ex. 2006
SteadyMed v. United Therapeutics
IPR2016-00006

Ex. 2006 at 3

3 Overview

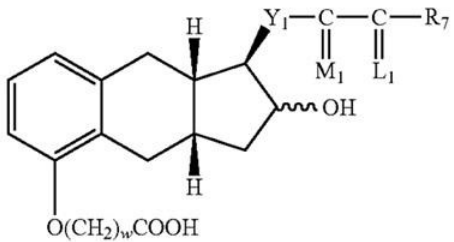
Independent Claims

Claim 1

What is claimed is:

1. A product comprising a compound of formula I

(I)



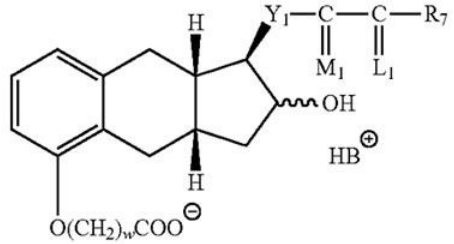
or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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

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

(c) contacting the product of step (h) 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.

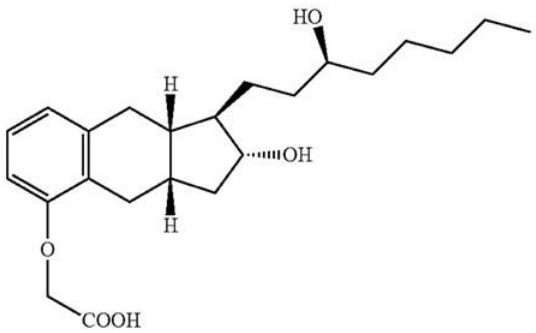
Ex. 1001 ("'393 Patent") at 11-12

Independent Claims

Claim 9

9. A product comprising a compound having formula IV

(IV)



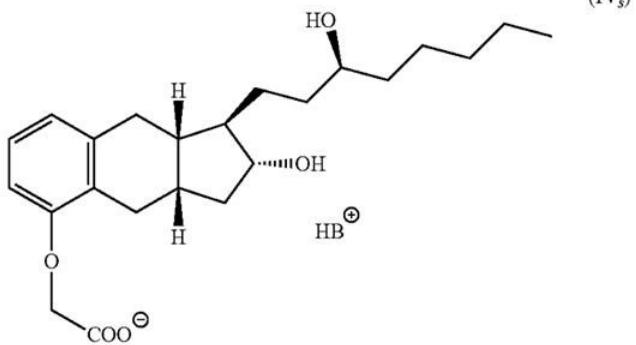
or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

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

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

(c) contacting the product of step (h) 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.

Overview

Prior Art: Moriarty

JOC*Article*

The Intramolecular Asymmetric Pauson−Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

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Received June 5, 2003

A general and novel solution to the synthesis of biologically important stable analogues of prostacyclin PGI_2, namely benzindene prostacyclins, has been achieved via the stereoselective intramolecular Pauson−Khand cyclization (PKC). This work illustrates for the first time the synthetic utility and reliability of the asymmetric PKC route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale. The synthetic route surmounts issues of individual step stereoselectivity and scalability. The key step in the synthesis involves efficient stereoselection effected in the PKC of a benzoenyne under the agency of the benzylic OTBDMS group, which serves as a temporary stereodirecting group that is conveniently removed via benzylic hydrogenolysis concomitantly with the catalytic hydrogenation of the enone PKC product. Thus the benzylic chiral center dictates the subsequent stereochemistry of the stereogenic centers at three carbon atoms (C_{3a}, C_{9a}, and C_3).

Prostacyclin (PGI_2) (**1**) is an important physiological prostanoid and occurs as a major metabolic product from arachidonic acid throughout the vasculature and is produced in the endothelium and in smooth muscles.[1a−c] PGI_2 is the most potent endogenous vasodilator in both systemic and pulmonary circulation. It exerts effects on vascular smooth muscle cells and inhibits both platelet aggregation and adhesion.[2a−f] These biological activities are relevant to a broad range of cardiovascular diseases including congestive heart failure, peripheral vascular disease, myocardial ischemia, and pulmonary hypertension.[3a−f] Use of PGI_2 as a drug for coronary disease has not been fruitful because of the fleeting half-life of this compound (~10 min at pH 7.6 at 25 °C).[4] The ability to inhibit platelet aggregation in plasma samples is lost within 5 min.[5] Application of PGI_2 to disease therapy presents a typical drug delivery challenge that is dealt with either mechanically by an appropriate pharmaceutical device or chemically by synthesizing a hydrolytically stable analogue that retains the biological activity. The first option currently is used for the treatment of pulmonary hypertension in which an aqueous solution of PGI_2 sodium salt (chemical name, epoprostenol; trade name Flolan) is pumped continuously and intravenously through a catheter permanently placed in the patient's chest via a portable external pump. PGI_2 is light sensitive and must be stored between 15 and 25 °C, and the formulation in a buffer solution must be prepared by the patient on a daily basis.[6] The PGI_2 is thereby introduced directly

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Naval Research Laboratory.

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663−665. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S. *Prostaglandins* **1976**, *12*, 915−928. (c) Vane, J. R.; Bergstrom, S., Eds. *Prostacyclin*; Raven Press: New York, 1979. (d) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293−331. (e) Bunting, S.; Gryglewski, R.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 897−913. (f) Moncada, S.; Herman, A. G.; Higgs, E. A.; Vane, J. R. *Thromb. Res.* **1977**, *11*, 323−344. (g) Marcus, A. J.; Weksler, B. B.; Jaffe, E. A. *Biol. Chem.* **1978**, *253*, 7138−7141. (h) Weksler, B. B.; Marcus, A. J.; Jaffe, E. A. *Proc. Natl. Acad Sci. U.S.A.* **1977**, *74*, 3922−3926. (i) MacIntyre, D. E.; Pearson, J. D.; Gordon, J. L. *Nature* **1978**, *271*, 549−551. (j) Nakagawa, O.; Tanaka, I.; Usui, T.; Harada, M.; Sasaki, Y.; Itoh, H.; Yoshimasa, T.; Nambu, T.; Narumiya, S.; Nakao, K. *Circulation* **1994**, *90*, 1643−1647. Syntheses of PGI_2: (k) Corey, E. J.; Kwok, G. E.; Sankely, L. *J. Am. Chem. Soc.* **1977**, *99*, 2006−2008. (l) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 4182−4184. (m) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem Soc.* **1978**, *100*, 7690−7705. (n) Corey, E. J.; Pearce, H. L.; Szekely, I.; Ishiguro, M. *Tetrahedron Lett.* **1978**, *18*, 1623−1626. (o) Tomoskozi, I.; Gulambos, G.; Simonsitse, V.; Kovacs, G. *Tetrahedron Lett.* **1977**, *18*, 2627−2628. (p) Tomoskozi, I.; Gulambos, G.; Kovacs, G.; Gruber, L. *Tetrahedron Lett.* **1978**, *20*, 1927−1930. (q) Nicolaou, K. C.; Barnette, W. F.; Gasic, G. P.; Magolda, R. L.; Spio, W. *J. J. Chem. Soc., Chem. Commun.* **1977**, 630−631. (r) Fried, J.; Barton, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2199−2203.

(2) (a) Tateson, J. E.; Moncada, S.; Vane, J. R. *Prostaglandins* **1977**, *13*, 389−397. (b) Hugh, E. A.; Moncada, S.; Vane, J. R.; Caen, J. P.; Michel, H.; Tobelem, G. *Prostaglandins* **1978**, *16*, 17−22. (c) Flower, R. J.; Cardinal, D. C.; Prostacyclin; Vane, J. R.; Bergstrom, S., Eds. Raven Press: New York, 1979; pp 211−216. (d) Gorman, R. R.; Bunting, S.; Miller, O. V. *Prostaglandins* **1977**, *13*, 377−388. (e) Ubatuba, F. B.; Moncada, S.; Vane, J. R. *Thromb. Haemostasis* **1979**, *41*, 425−434. (f) Cooper, B.; Schulte, A. I.; Puchalsky, D.; Handin, R. I. *Prostaglandins* **1979**, *17*, 561−571.

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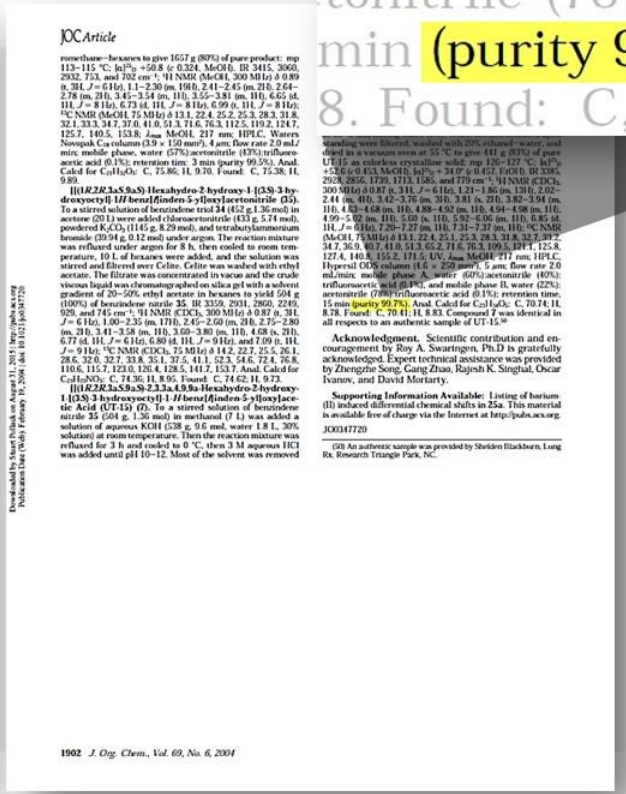


JOC*Article*

romethane−hexanes to give 1657 g (80%) of pure product: mp 113−115 °C; $[\alpha]^{25}_D$ +50.8 (*c* 0.324, MeOH). IR 3415, 3060, 2932, 753, and 702 cm^{-1}; ^1H NMR (MeOH, 300 MHz) δ 0.89 (t, 3H, J = 6 Hz), 1.1−2.30 (m, 19H), 2.41−2.45 (m, 2H), 2.64−2.78 (m, 2H), 3.45−3.54 (m, 1H), 3.55−3.81 (m, 1H), 6.65 (d, 1H, J = 8 Hz), 6.73 (d, 1H, J = 8 Hz), 6.99 (s, 1H, J = 8 Hz); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.2, 25.3, 28.3, 31.8, 32.1, 33.3, 34.7, 37.0, 41.0, 51.3, 71.6, 76.3, 112.5, 119.2, 124.7, 125.7, 140.5, 153.8; λ_{max} MeOH, 217 nm; HPLC, Waters Novapak C_{18} column (3.9 × 150 mm²), 4 μm; flow rate 2.0 mL/min; mobile phase, water (57%):acetonitrile (43%):trifluoroacetic acid (0.1%); retention time: 3 min (purity 99.5%). Anal. Calcd for $C_{23}H_{32}O_5$: C, 75.86; H, 9.70. Found: C, 75.38; H, 9.89.

[(1*R*,2*R*,3a*S*,9a*S*)-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxyacetonitrile (35). To a stirred solution of benzindene triol **34** (452 g, 1.36 mol) in acetone (20 L) were added chloroacetonitrile (433 g, 5.74 mol), powdered K_2CO_3 (1145 g, 8.29 mol), and tetrabutylammonium bromide (39.94 g, 0.12 mol) under argon. The reaction mixture was refluxed under argon for 8 h, then cooled to room temperature, 10 L of hexanes were added, and the solution was stirred and filtered over Celite. Celite was washed with ethyl acetate. The filtrate was concentrated in vacuo and the crude viscous liquid was chromatographed on silica gel with a solvent gradient of 20−50% ethyl acetate in hexanes to yield 504 g (100%) of benzindene nitrile **35**. IR 3359, 2931, 2860, 2249, 929, and 745 cm^{-1}; ^1H NMR (CDCl₃, 300 MHz) δ 0.87 (t, 3H, J = 6 Hz), 1.00−2.35 (m, 17H), 2.45−2.60 (m, 2H), 2.75−2.80 (m, 2H), 3.41−3.58 (m, 1H), 3.60−3.80 (m, 1H), 4.68 (s, 2H), 6.77 (d, 1H, J = 6 Hz), 6.80 (d, 1H, J = 9 Hz), and 7.09 (t, 1H, J = 9 Hz); ^{13}C NMR (CDCl₃, 75 MHz) δ 14.2, 22.7, 25.5, 26.1, 28.6, 32.0, 32.7, 33.8, 35.1, 37.5, 41.1, 52.3, 54.6, 72.4, 76.8, 110.6, 115.7, 123.0, 126.4, 128.5, 141.7, 153.7. Anal. Calcd for $C_{25}H_{35}NO_5$: C, 74.36; H, 8.95. Found: C, 74.62; H, 9.73.

[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxyacetic Acid (UT-15) (7). To a stirred solution of benzindene nitrile **35** (504 g, 1.36 mol) in methanol (7 L) was added a solution of aqueous KOH (538 g, 9.6 mol, water 1.8 L, 30% solution) at room temperature. Then the reaction mixture was refluxed for 3 h and cooled to 0 °C, then 3 M aqueous HCl was added until pH 10−12. Most of the solvent was removed

Acknowledgment. Scientific contribution and encouragement by Roy A. Swaringen, Ph.D is gratefully acknowledged. Expert technical assistance was provided by Zhengzhe Song, Gang Zhao, Rajesh K. Singhal, Oscar Ivanov, and David Moriarty.

Supporting Information Available: Listing of barium (II) induced differential chemical shifts in **25a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034720

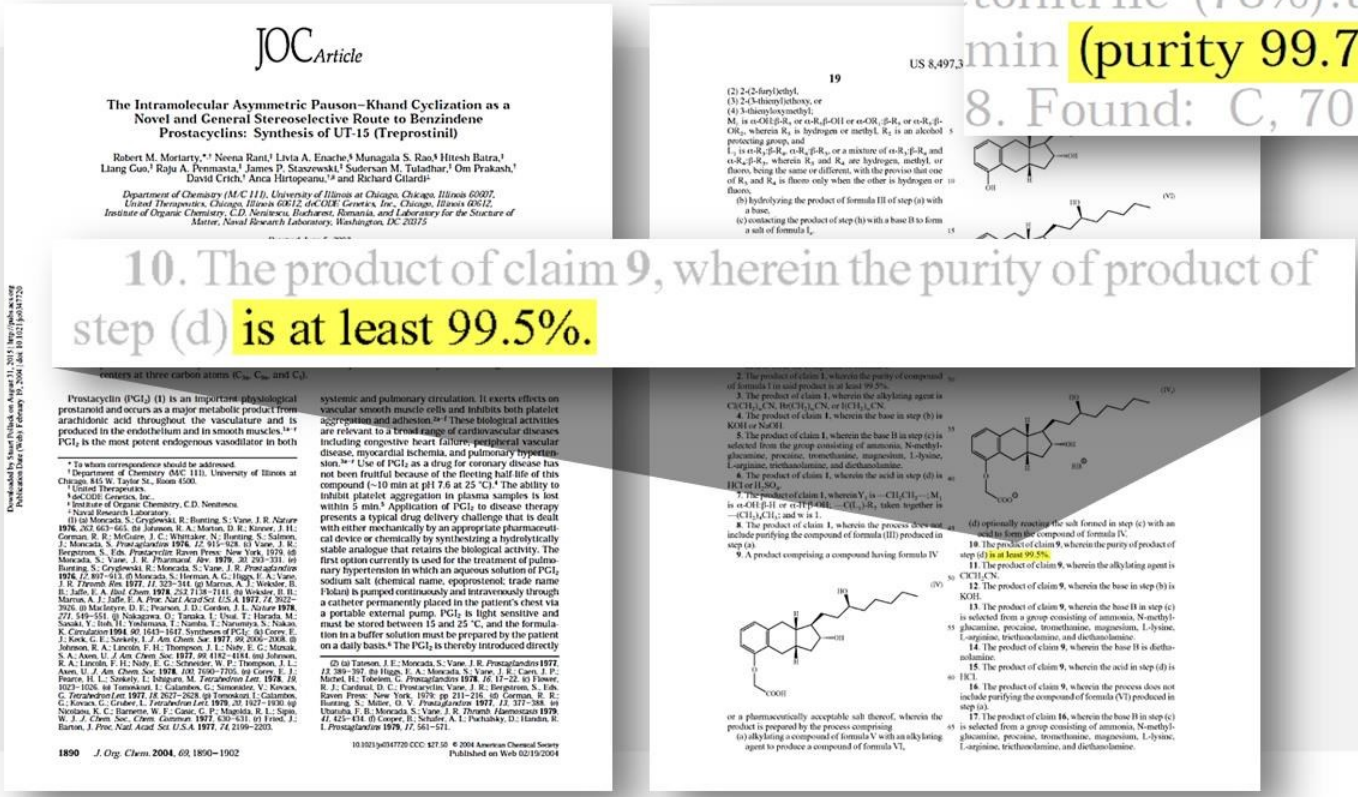
(58) An authentic sample was provided by Sheiden Blackburn, Lung Rx. Research Triangle Park, NC.

tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

Ex. 1004 ("Moriarty") at 13

Overview

Prior Art: Moriarty



JOC*Article*

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

Robert M. Moriarty,*,† Neena Rani,† Livia A. Enache,§ Munagala S. Rao,§ Hitesh Batra,† Liang Guo,† Raju A. Penmasta,† James P. Staszewski,† Sudersan M. Tuladhar,† Om Prakash,† David Crich,† Anca Hirtopeanu,†,# and Richard Gilardi‖

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Prostacyclin (PGI_2) (1) is an important physiological prostanoid and occurs as a major metabolite product from arachidonic acid throughout the vasculature and is produced in the endothelium and in smooth muscles.[1a-c] PGI_2 is the most potent endogenous vasodilator in both systemic and pulmonary circulation. It exerts effects on vascular smooth muscle cells and inhibits both platelet aggregation and adhesion.[2a-f] These biological activities are relevant to a broad range of cardiovascular diseases including congestive heart failure, peripheral vascular disease, myocardial ischemia, and pulmonary hypertension.[3a-f] Use of PGI_2 as a drug for coronary disease has not been fruitful because of the fleeting half-life of this compound (~10 min at pH 7.6 at 25 °C).[4] The ability to inhibit platelet aggregation in plasma samples is lost within 5 min.[5] Application of PGI_2 to disease therapy presents a typical drug delivery challenge that is dealt with either mechanically by an appropriate pharmaceutical device or chemically by synthesizing a hydrolytically stable analogue that retains the biological activity. The first option currently is used for the treatment of pulmonary hypertension in which an aqueous solution of PGI_2 sodium salt (chemical name, epoprostenol; trade name Flolan) is pumped continuously and intravenously through a catheter permanently placed in the patient's chest via a portable external pump. PGI_2 is light sensitive and must be stored between 15 and 25 °C, and the formulation in a buffer solution must be prepared by the patient on a daily basis.[6] The PGI_2 is thereby introduced directly

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# Institute of Organic Chemistry, C.D. Nenitzescu.
‖ Naval Research Laboratory.

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663–665. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S. *Prostaglandins* **1976**, *12*, 915–928. (c) Vane, J. R.; Bergstrom, S., Eds. *Prostacyclin* Raven Press: New York, 1979. (d) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293–331. (e) Bunting, S.; Gryglewski, R.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 897–913. (f) Moncada, S.; Herman, A. G.; Higgs, E. A.; Vane, J. R. *Thromb. Res.* **1977**, *11*, 323–344. (g) Marcus, A. J.; Weksler, B. B.; Jaffe, E. A. *Biol. Chem.* **1978**, *253*, 7138–7141. (h) Weksler, B. B.; Marcus, A. J.; Jaffe, E. A. *Proc. Natl. Acad Sci. U.S.A.* **1977**, *74*, 3922–3926. (i) MacIntyre, D. E.; Pearson, J. D.; Gordon, J. L. *Nature* **1978**, *271*, 549–551. (j) Nakagawa, O.; Tanaka, I.; Usui, T.; Harada, M.; Sasaki, Y.; Itoh, H.; Yoshimasa, T.; Nambu, T.; Narumiya, S.; Nakao, K. *Circulation* **1994**, *90*, 1643–1647. Syntheses of PGI_2: (k) Corey, E. J.; Kwok, G. E.; Sarkely, L. *J. Am. Chem. Soc.* **1977**, *99*, 2006–2008. (l) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 8182–8184. (m) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem Soc.* **1978**, *100*, 7690–7705. (n) Corey, E. J.; Pearce, H. L.; Szekely, I.; Ishiguro, M. *Tetrahedron Lett.* **1978**, *18*, 1023–1026. (o) Tomoskozi, I.; Galambos, G.; Simonsitse, V.; Kovacs, G. *Tetrahedron Lett.* **1977**, *18*, 2627–2628. (p) Tomoskozi, I.; Galambos, G.; Kovacs, G.; Gruber, L. *Tetrahedron Lett.* **1978**, *20*, 1927–1930. (q) Nicolaou, K. C.; Barnette, W. F.; Gasic, G. P.; Magolda, R. L.; Spain, W. J. *J. Chem. Soc., Chem. Commun.* **1977**, 630–631. (r) Fried, J.; Barton, J. *Proc. Natl. Acad Sci. U.S.A.* **1977**, *74*, 2199–2203.

(2) (a) Tateson, J. E.; Moncada, S.; Vane, J. R. *Prostaglandins* **1977**, *13*, 389–397. (b) Hugh, E. A.; Moncada, S.; Vane, J. R.; Caen, J. P.; Michel, H.; Tobelem, G. *Prostaglandins* **1978**, *16*, 17–22. (c) Flower, R. J.; Cardinal, D. C.; Prostacyclin; Vane, J. R.; Bergstrom, S., Eds. Raven Press: New York, 1979; pp 211–216. (d) Gorman, R. R.; Bunting, S.; Miller, O. V. *Prostaglandins* **1977**, *13*, 377–388. (e) Ubatuba, F. B.; Moncada, S.; Vane, J. R. *Thromb. Haemostasis* **1979**, *41*, 425–434. (f) Cooper, B.; Schafer, A. I.; Puchalsky, D.; Handin, R. I. *Prostaglandins* **1979**, *17*, 561–571.

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19

(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienyloxymethyl;
M, is α-OH,β-R_4 or α-R_4,β-OH or α-OR_1,β-R_4 or α-R_4,β-OR_1, wherein R_4 is hydrogen or methyl. R_2 is an alcohol protecting group, and
I_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 (h) with a base B to form a salt of formula I_a

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

3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_1CN$, $Br(CH_2)_1CN$, or $I(CH_2)_1CN$.

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, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

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 $—CH_2CH_2—M_1$ in α-OH,β-H or α-H,β-OH, $—CH_2—)_2R_4$ taken together is $—(CH_2)_4CH_2$; and w is 1.

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

9. A product comprising a compound having formula 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,

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

10. The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.

11. The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.

12. The product of claim 9, wherein the base in step (b) is KOH.

13. The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

14. The product of claim 9, wherein the base B is diethanolamine.

15. The product of claim 9, wherein the acid in step (d) is HCl.

16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).

17. The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

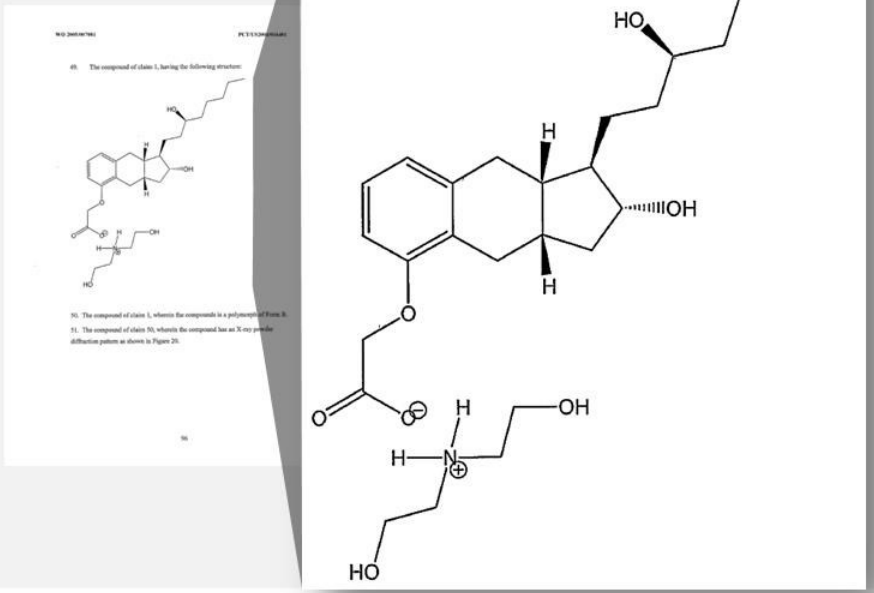
tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

10. The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.

Overview

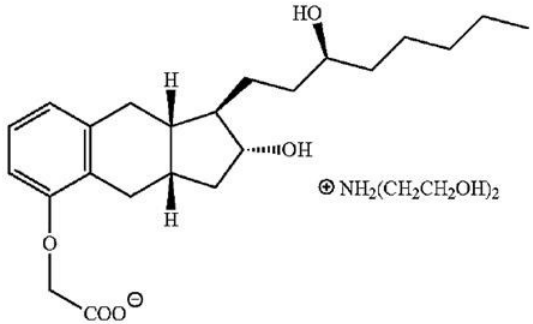
Prior Art: Phares

Ex. 1005



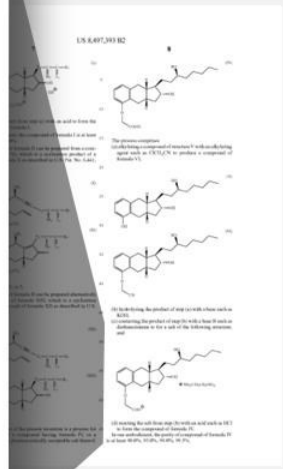
Ex. 1001

(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.

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



Ex. 1005 ("Phares") at 99 (Claim 49); Ex. 1001 at 6 ('393 Patent) col.8. ll. 47-68.

Phares and Melting Point

The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_o^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

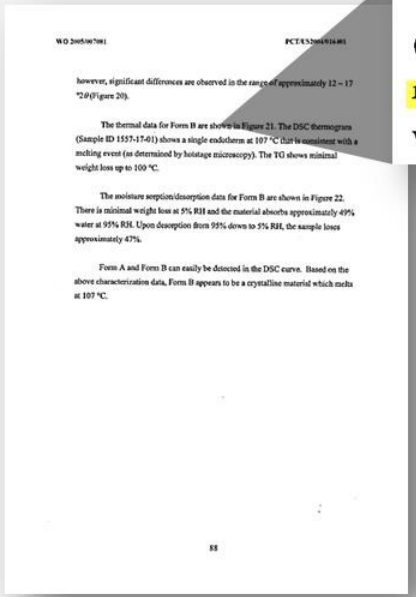
where *Ts,* is the sample temperature, T_0 is the melting point of the pure compound, *R* is the gas constant, X_i, is the mole fraction of the impurity, *F* is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus 1/*F* should give a straight line whose slope is proportional to X_i (Brittain *et al.,* 1991).

Stephen R. Byrn *et al., Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

Overview

Prior Art: Phares

Ex. 1005



WO 2005/007081 PCT/US2004/016401

however, significant differences are observed in the range of approximately 12 – 17 °2θ (Figure 20).

The thermal data for Form B are shown in Figure 21. The DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107 °C that is consistent with a melting event (as determined by hotstage microscopy). The TG shows minimal weight loss up to 100 °C.

The moisture sorption/desorption data for Form B are shown in Figure 22. There is minimal weight loss at 5% RH and the material absorbs approximately 49% water at 95% RH. Upon desorption from 95% down to 5% RH, the sample loses approximately 47%.

Form A and Form B can easily be detected in the DSC curve. Based on the above characterization data, Form B appears to be a crystalline material which melts at 107 °C.

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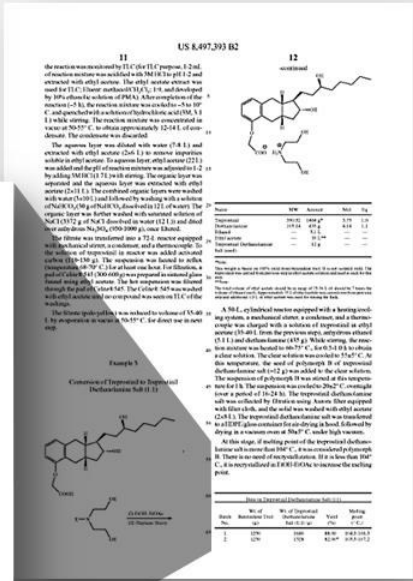
The thermal data for Form B are shown in Figure 21. The DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107 °C that is consistent with a melting event (as determined by hotstage microscopy). The TG shows minimal weight loss up to 100 °C.

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

Ex. 1001



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11 12

Example 5

Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)

Ex. 1005 ("Phares") at 91; Ex. 1001 at 8 ('393 Patent) col.12. ll. 43-68.

4 Anticipation

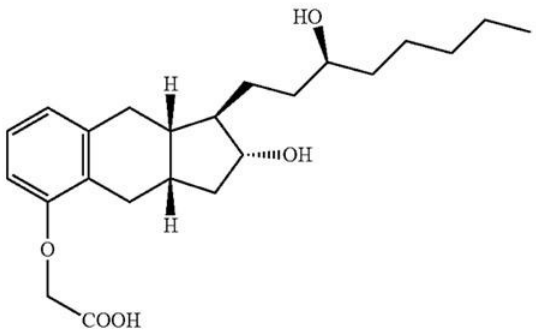
Anticipation

Independent Claims

Claim 9

9. A product comprising a compound having formula IV

(IV)



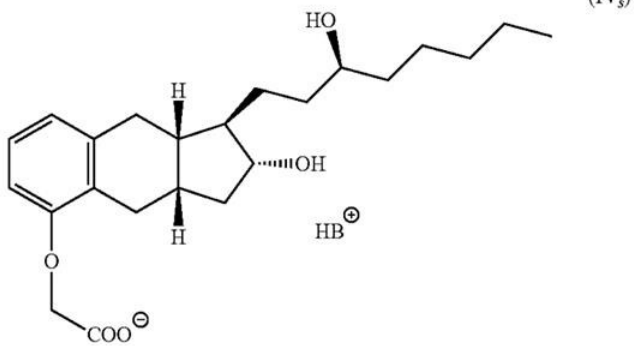
or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

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

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

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

(IV_s)

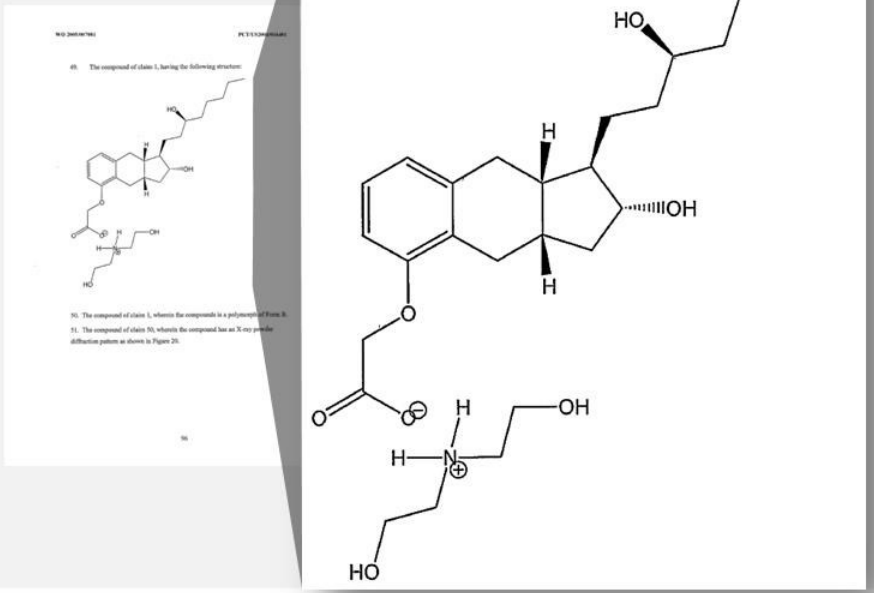


(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

Anticipation

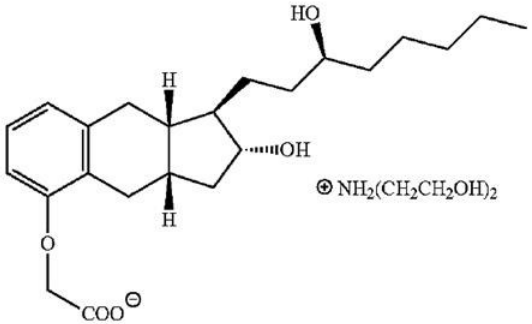
Prior Art: Phares

Ex. 1005



Ex. 1001

(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.

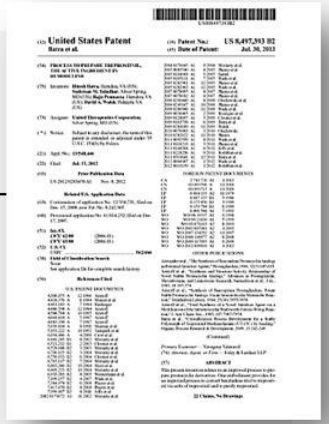
In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

Ex. 1005 ("Phares") at 99 (Claim 49); Ex. 1001 at 6 ('393 Patent) col.8. ll. 47-68.

Anticipation

'393 Patent/Phares Melting Points

Ex. 1001: '393 Patent



Example 3

Batch 1: 104.3-106.3 ^{0}C

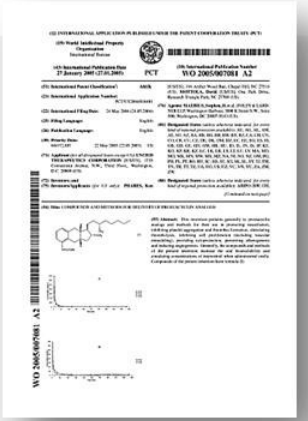
Batch 3: 104.7-106.6 ^{0}C

Example 4

Batch 1: 105.0-106.5 ^{0}C

Batch 2: 104.5-105.5 ^{0}C

Ex. 1005: Phares



"The DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107 °C that is consistent with a melting event (as determined by hotstage microscopy)."

Ex. 1005 at 91

Figure 21: "107.06 ^{0}C"

Ex. 1005 at 121

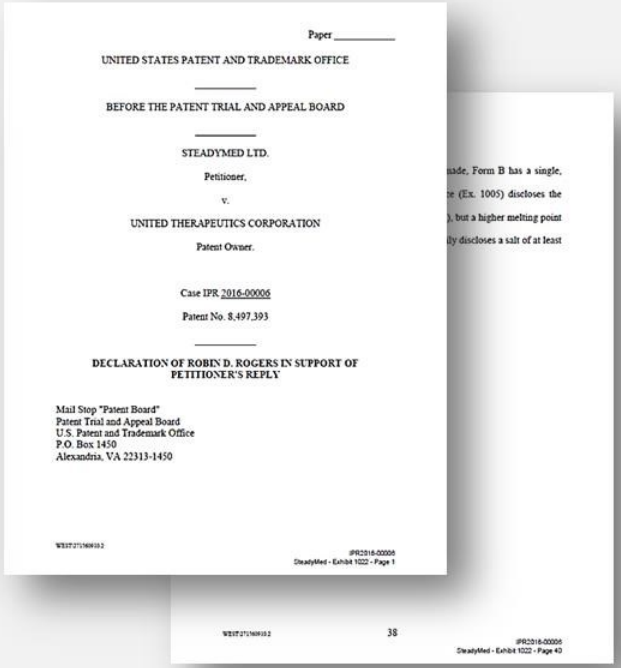
Ex. 1001 at 8-9 ('393 Patent) col.12-13; Ex. 1005 ("Phares") at 91, 121

Anticipation

Prior Art: Phares

IX. CONCLUSION

88. In summary, no matter how Form B is made, Form B has a single, defined melting point, and since the Phares Reference (Ex. 1005) discloses the same Form B crystal form as the '393 Patent (Ex. 1001), but a higher melting point than most of the '393 Patent examples, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent, if not higher.



Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393

DECLARATION OF ROBIN D. ROGERS IN SUPPORT OF PETITIONER'S REPLY

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Alexandria, VA 22313-1450

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IPR2016-00006
SteadyMed - Exhibit 1022 - Page 40

Ex. 1022 ("Rogers Declaration") at 40

Anticipation

Prior Art: Phares

Dr. Williams declared identical polymorphs might have different melting points, depending on how they were made.

THE WITNESS: Yeah. So I'm not a polymorph expert.

Ex. 2059 (Williams Dep.) 158:17-18

Q. Do you consider yourself an expert on crystal forms of organic molecules?

A. No.

Ex. 2059 (Williams Dep.) 156:25-157:2

Ex. 2059 ("Williams Deposition Transcript") at 156-58

Anticipation

Prior Art: Phares

Dr. Williams relied on "Adhiyaman reference" (Ex. 2030), which he initially believed showed different melting points for same crystal form.

Q. Okay. So each of these is really a different crystal form of the same drug; is that fair?

A. I think that's fair."

Ex. 2059 (Williams Dep.) 180:17-20.

Ex. 2059 ("Williams Deposition Transcript") at 180

Anticipation

Process can be Different

"If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985)

Anticipation

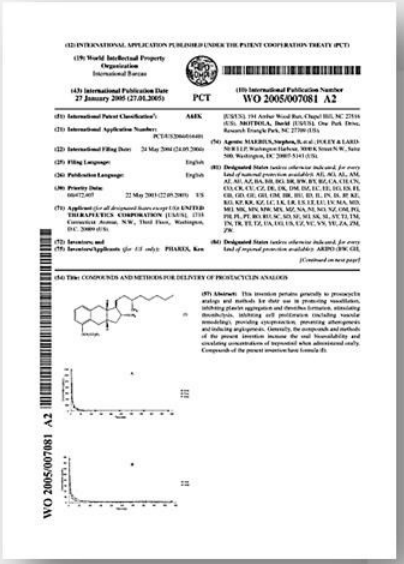
Starting Material Irrelevant

"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14–hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Anticipation

Prior Art: Phares



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

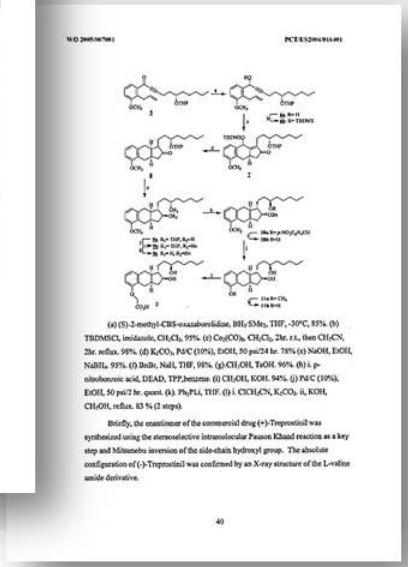
(19) World Intellectual Property Organization International Bureau

(43) International Publication Date 27 January 2005 (27.01.2005) PCT (10) International Publication Number WO 2005/007081 A2

(54) Title: COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS

(57) Abstract: This invention pertains generally to prostacyclin analogs and methods for their use in promoting vasodilation, inhibiting platelet aggregation and thrombus formation, stimulating thrombolysis, inhibiting cell proliferation including vascular remodeling, providing cytoprotection, preventing atherogenesis and inducing angiogenesis. Generally, the compounds and methods of the present invention increase the oral bioavailability and circulating concentrations of treprostinil when administered orally. Compounds of the present invention have formula (I).

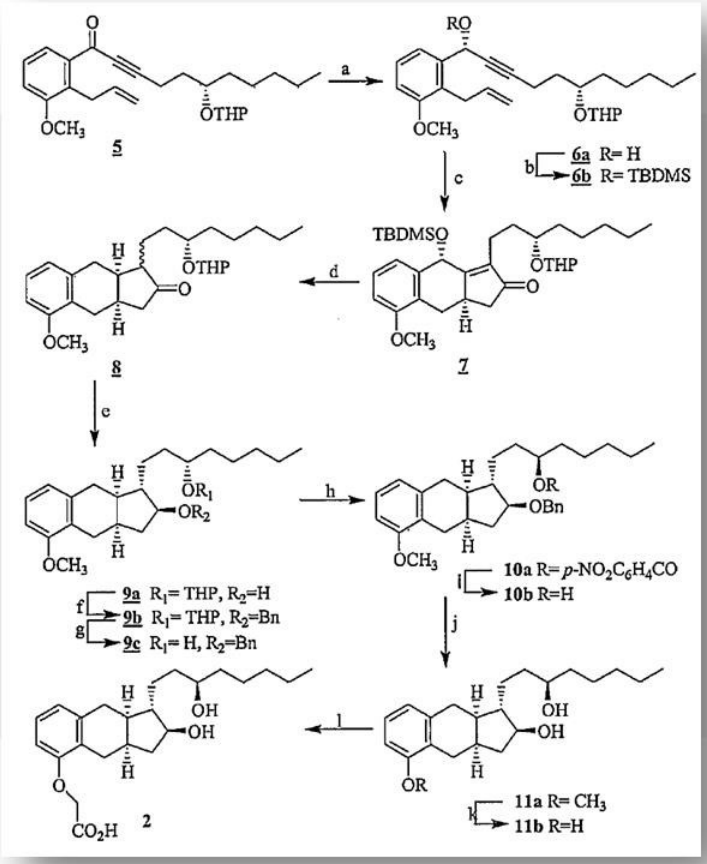
WO 2005/007081 A2



(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3·SMe_2, THF, -10°C, 85%. (b) TBDMSCl, imidazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2hr. r.t., then CH_3CN, 2hr. reflux. 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$, 95%. (f) BnBr, NaH, THF, 98%. (g) CH_3OH, TsOH. 96% (h) i. p-nitrobenzoic acid, DEAD, TPP,benzene. (i) CH_3OH, KOH. 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k). $Ph_3P.I_4$, THF. (l) i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps).

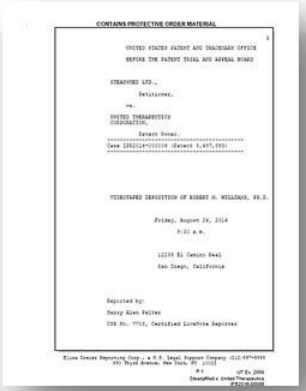
Briefly, the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group. The absolute configuration of (-)-Treprostinil was confirmed by an X-ray structure of the L-valine amide derivative.

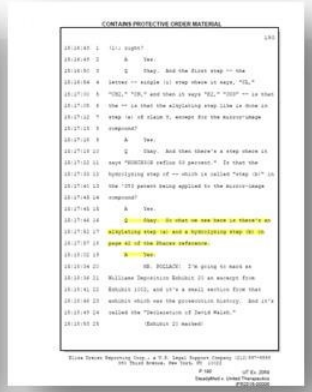
40



Anticipation

Prior Art: Phares

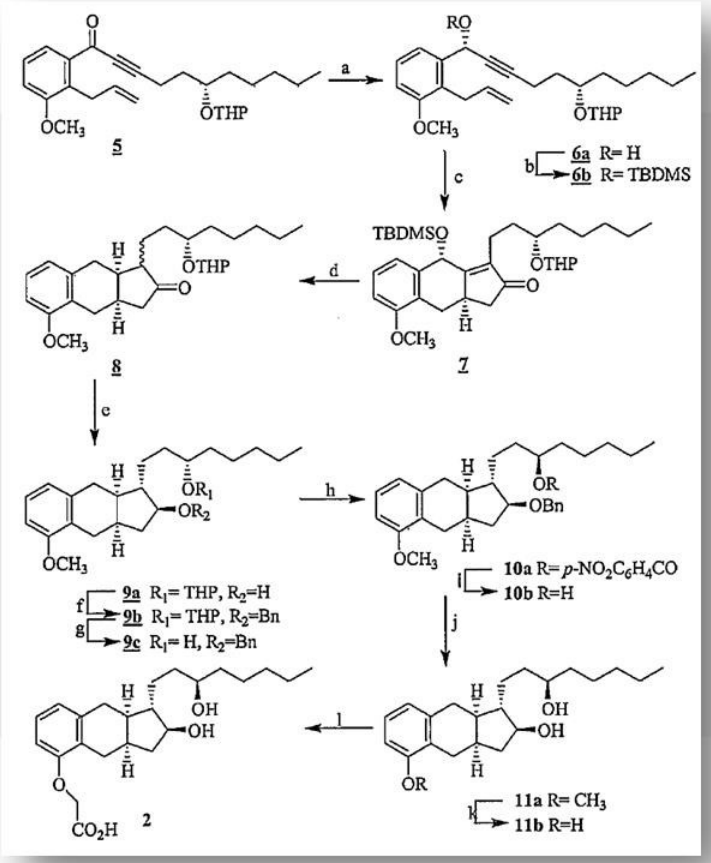




Q. Okay. So what we see here is there's an alkylating step (a) and hydrolyzing step (b) on page 42 of the Phares reference.

A. Yes.

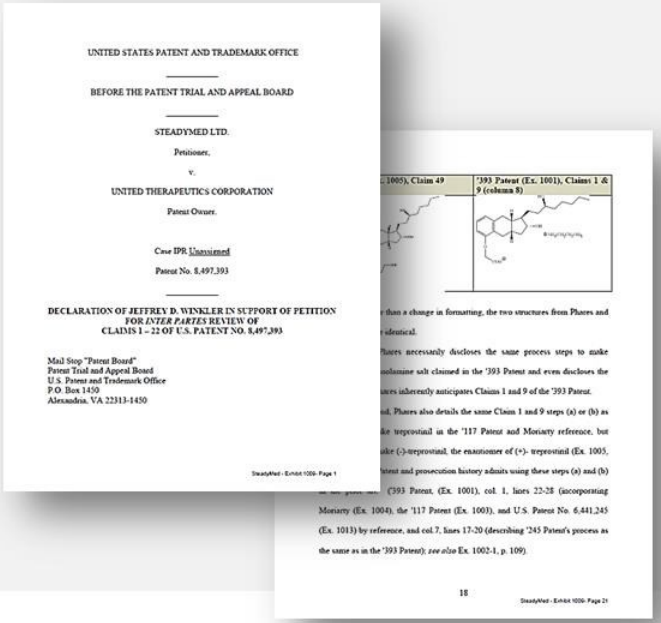
Ex. 2059 (Williams Dep.) 190: 16-19



Ex. 1005 ("Phares") at 42; Ex. 2059 (Williams Deposition Transcript) at 190.

Anticipation

Prior Art: Phares



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR Unassigned

Patent No. 8,497,393

DECLARATION OF JEFFREY D. WINKLER IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1 – 22 OF U.S. PATENT NO. 8,497,393

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Patent Trial and Appeal Board
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SteadyMed - Exhibit 1009- Page 1

	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
, 1005), Claim 49	

than a change in formatting, the two structures from Phares and identical.

Phares necessarily discloses the same process steps to make sodosamine salt claimed in the '393 Patent and even discloses the ures inherently anticipates Claims 1 and 9 of the '393 Patent.

nd. Phares also details the same Claim 1 and 9 steps (a) or (b) as ke treprostinil in the '117 Patent and Moriarty reference, but ake (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, atent and prosecution history admits using these steps (a) and (b) ('393 Patent, (Ex. 1001), col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in the '393 Patent); *see also* Ex. 1002-1, p. 109).

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SteadyMed - Exhibit 1009- Page 21

55. Second, Phares also details the same Claim 1 and 9 steps (a) or (b) as were used to make treprostinil in the '117 Patent and Moriarty reference, but applies them to make (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, p. 42). The '393 Patent and prosecution history admits using these steps (a) and (b) in the prior art. ('393 Patent, (Ex. 1001), col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in the '393 Patent); *see also* Ex. 1002-1, p. 109).

Ex. 1009 (Winkler Decl.) ¶ 55 at 21

Ex. 1009 ("Winkler Decl.") at 21.

Anticipation

Starting Material Irrelevant

"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14–hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Anticipation

Impurity Profile Irrelevant

"[T]he fact that the 14–hydroxy is derived from 8α imparts no structural or functional differences in the low-ABUK [impurity] hydrocodone API as compared to the prior art products. Thus, the court did not err in disregarding the process limitation in its obviousness determination."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016)

Anticipation

Impurity Profiles Not Different

Ex. 1004: Moriarty

TEST/REFERENCE	SPECIFICATIONS	RESULTS[1]
Chromatographic Purity (HPLC) NB 1, LDR 68 - 72		
1AU90	Not more than 0.5%	ND
2AU90	Not more than 0.5%	ND
97W86 (Benzindene Triol)	Not more than 0.2%	ND
3AU90	Not more than 1.0%	0.2%
Treprostinil Methyl Ester	Not more than 0.2%	<0.05%
Treprostinil Ethyl Ester	Not more than 0.6%	0.2%
750W93	Not more than 1.5%	0.07%
751W93	Not more than 1.3%	<0.05%
Unidentified	Not more than 0.1% AUC each	ND

Ex. 2036 at 5
(Prior Art 12/23/2003)

Ex. 1001: '393 Patent

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 %

Ex. 1002 at 249
(Walsh Declaration)

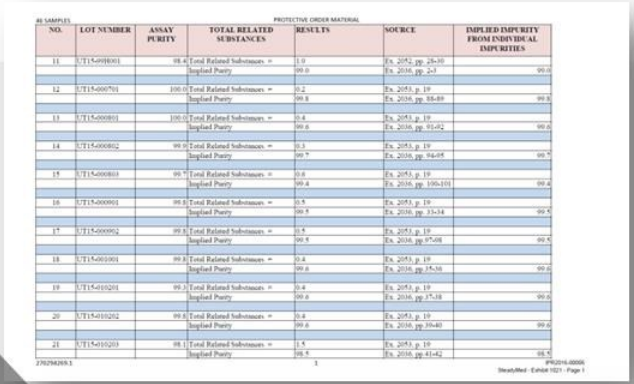
Ex. 2036 ("Phares") at 5; Ex. 1002 at 249 ('393 Patent Prosecution)

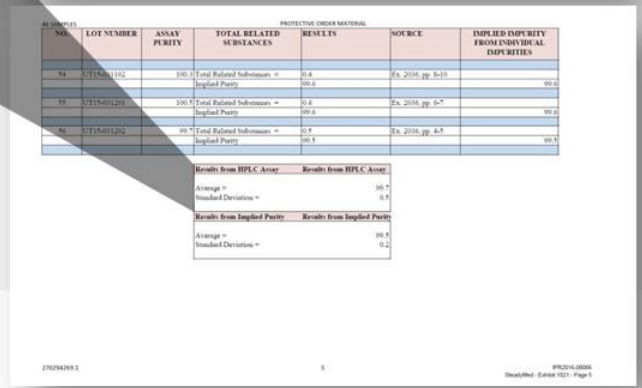
Anticipation

Impurity Profiles Meaningless

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5

99.7 ± 0.5 %





Ex. 1021 at 5 (Moriarty, average of 46 samples)

Key Scientific Concepts: HPLC and Purity

During the initial analytical method validation for the treprostinil assay, the results indicated that there is about 2% variability in the assay. Our specifications of 97.0-101.0% were centered at 99% purity for the API. When the process for the manufacture of treprostinil was instituted in Silver Spring, it was observed that the purity of the treprostinil improved to close to 100%. From a statistical stand-point, an analytical variability of 2% in the assay may result in an OOS on the high side (considering a two sigma range) when the upper limit of the specification is 101.0%. Scientifically, an API cannot have a purity of greater than 100%. If an API is 100% pure, 2% variability in the assay may result in an OOS at specifications of 97.0-101.0%. During development in Silver Spring, it was observed that there were

3

UT Ex. 2006
SteadyMed v. United Therapeutics
IPR2016-00006

Ex. 2006 at 3

Anticipation

No Functional Differences

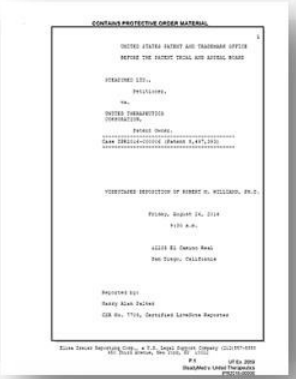
"[I]f the process by which a product is made imparts '**structural and functional differences**' distinguishing the claimed product from the prior art, then those differences 'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'"

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016)
(cites and internal quotations omitted) (emphasis added)

Anticipation

No Functional Differences

ROBERT M. WILLIAMS, PH.D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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

Friday, August 19, 2016

9:00 a.m.

Reported by:

CSR No. 7716, Certified LiveNote Reporter

Q. Do any of the -- as far as you know, any of these particular impurities have deleterious biological consequences?

THE WITNESS: I'm not a clinician, so I don't know.

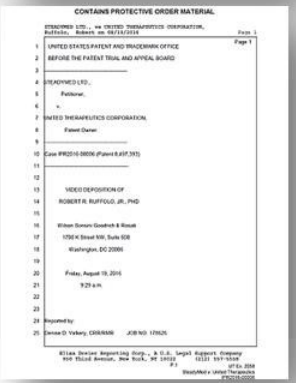
BY MR. POLLACK:

Q. You don't know?

A. I don't know.

Ex. 2059 (Williams Dep.) 47: 4-13

ROBERT R. RUFFOLO, PH.D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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

VIDEO DEPOSITION OF

ROBERT R. RUFFOLO, JR., PHD

Friday, August 19, 2016

9:29 a.m.

Reported by:

Q. Do you know if any of these listed chromatographic impurities have any adverse effects in humans?

BY MR. POLLACK:

Q. And if so, what are they?

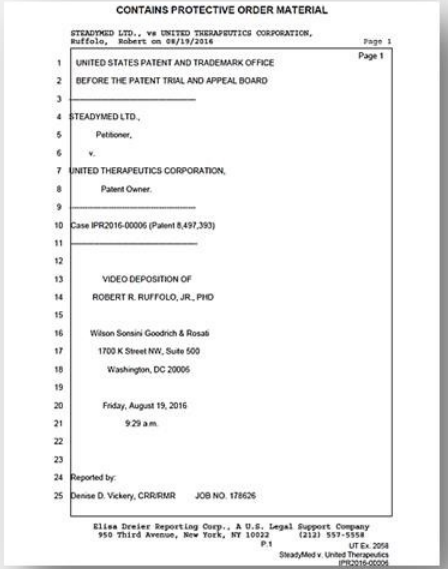
THE WITNESS: I don't know. What I can tell you is that if you review the FDA label, there are a host of adverse effects produced or observed in patients who are taking treprostinil.

Ex. 2058 (Ruffolo Dep.) 257:22-258:9

Ex. 2059 (Williams Dep. at 47; Ex. 2058 (Ruffolo Dep.) at 66

Anticipation

No Functional Differences



CONTAINS PROTECTIVE ORDER MATERIAL

STEADYMED LTD., vs UNITED THERAPEUTICS CORPORATION,
Ruffolo, Robert on 08/19/2016 Page 1

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,
v.
UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006 (Patent 8,497,393)

VIDEO DEPOSITION OF
ROBERT R. RUFFOLO, JR., PHD

Wilson Sonsini Goodrich & Rosati
1700 K Street NW, Suite 500
Washington, DC 20006

Friday, August 19, 2016
9:29 a.m.

Reported by:
Denise D. Vickery, CRR/RMR JOB NO. 178626

Elisa Dreier Reporting Corp., A U.S. Legal Support Company
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P.1

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

ROBERT R. RUFFOLO, PH.D

Q. Okay. And I make another batch of treprostinil API and I measure its HPLC analysis and it's 98.5 percent. Could that batch move on in the process?

THE WITNESS: Yes, with that current level spec, that could move on.

Ex. 2058 (Ruffolo Dep.) 160: 17-24

Q. Is there a difference between the approved Moriarty treprostinil product that was shown clinically that's different from the '393 product?

THE WITNESS: Not -- not to my knowledge.

Ex. 2058 (Ruffolo Dep.) 315:5-23

Ex. 2058 (Ruffolo Dep.) at 41, 80

Conclusions

1. No structural differences
2. No functional differences
3. No separate argument for dependent claims
4. Claims 1-5, 7-9, 11-14, 16-20 anticipated

5 Obviousness

Phares and Moriarty

Kawakami and Moriarty

Dependent claims 6, 10, 15, 21, and 22

5 Obviousness

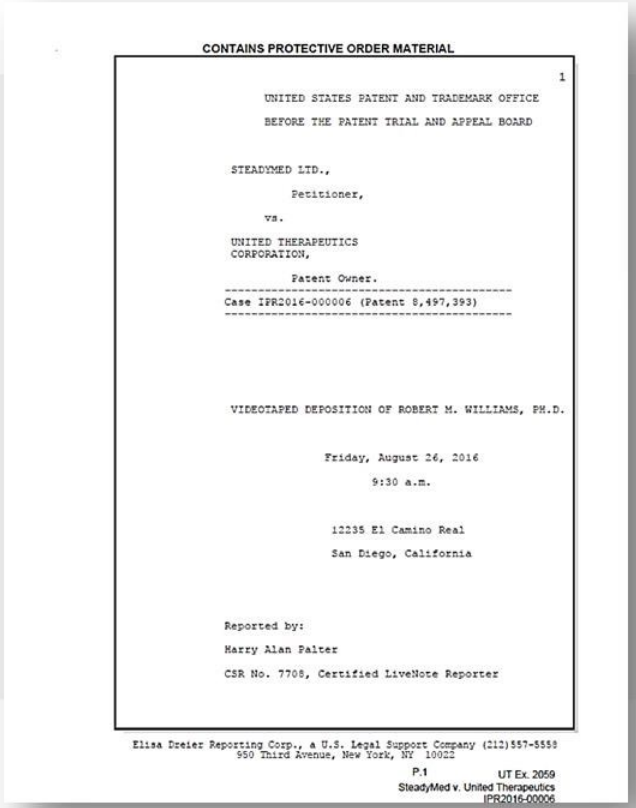
Phares and Moriarty

Kawakami and Moriarty

Dependent claims 6, 10, 15, 21, and 22

Obviousness: Phares & Moriarty

Motivation to Combine



CONTAINS PROTECTIVE ORDER MATERIAL

1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-000006 (Patent 8,497,393)

VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

Friday, August 26, 2016

9:30 a.m.

12235 El Camino Real

San Diego, California

Reported by:

Harry Alan Palter

CSR No. 7708, Certified LiveNote Reporter

Elisa Dreier Reporting Corp., a U.S. Legal Support Company (212)557-5558
950 Third Avenue, New York, NY 10022

P.1

UT Ex. 2059
SteadyMed v. United Therapeutics
IPR2016-00006

Q Okay. So a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know the best way to make treprostinil is the Moriarty method, Exhibit 12; right? Is that fair?

A I think that's fair.

Ex. 2059 (Williams Dep.) 240:2-7

Q But, you know, on average, a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005?

MS. HASPER: Objection.

THE WITNESS: It was in the literature. It wasn't buried in some obscure journal. So, sure, it was available.

BY MR. POLLACK:

Q That was a "yes" to my question, I think?

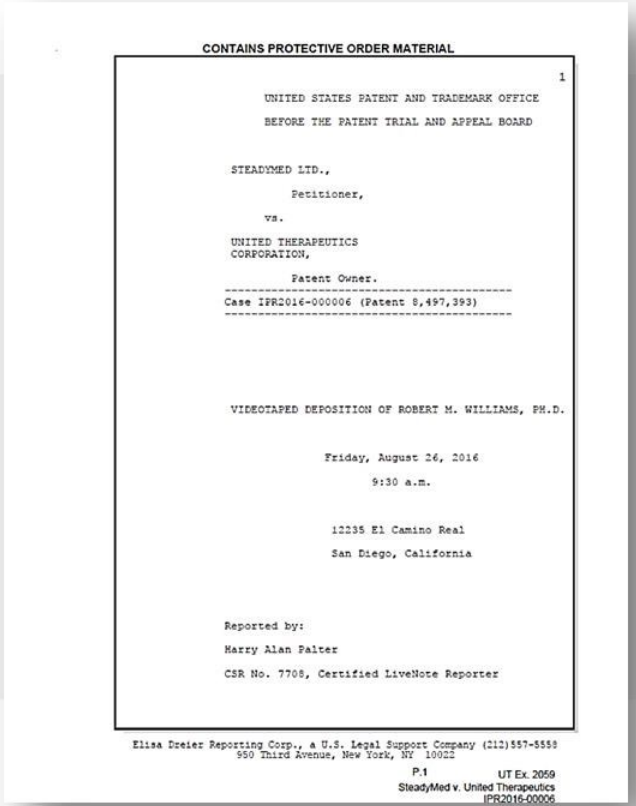
A Yes.

Ex. 2059 (Williams Dep.) 244:10-21.

Ex. 2059 (Williams Dep.) at 240, 244

Obviousness: Phares & Moriarty

Reasonable Expectation of Success



CONTAINS PROTECTIVE ORDER MATERIAL

1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

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P.1

UT Ex. 2059
SteadyMed v. United Therapeutics
IPR2016-00006

Q Sure. I understand. I'm not disagreeing with you on that. I'm just saying, you told the Patent Office that these two differed. And one of the ways they differed was one was 99.0 and the other was 99.7. Now we see that both are 99.7. How does that jive with acceptable scientific conduct?

A Well, the -- again, the '393 batches were produced without chromatography. So you could repurify and purify anything you want --

Q Of course.

A -- by chromatography to 99.99999 percent if you wanted to --

Ex. 2059 (Williams Dep.) 94:1-12.

Ex. 2059 (Williams Dep.) at 94

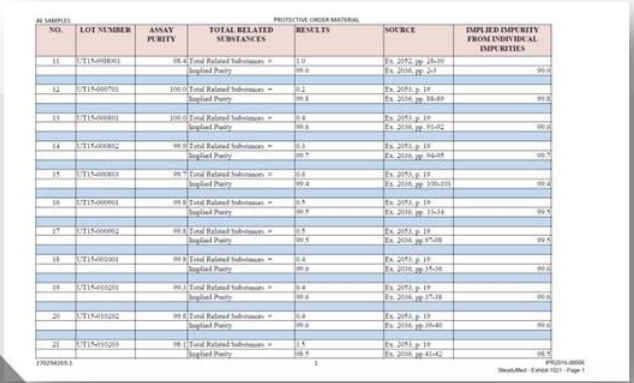
Obviousness: Phares & Moriarty

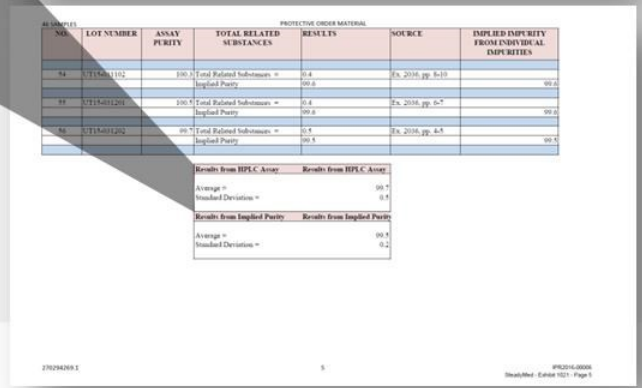
Reasonable Expectation of Success

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5

99.7 ± 0.5 %

Ex. 1021 at 5 (Moriarty, average of 46 samples)





Obviousness: Phares & Moriarty

Reasonable Expectation of Success

JOC*Article*

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

Robert M. Moriarty,*,† Neena Rani,† Livia A. Enache,‡ Munagala S. Rao,§ Hitesh Batra,† Liang Guo,† Raju A. Penmasta,† James P. Staszewski,† Sudersan M. Tuladhar,† Om Prakash,† David Crich,† Anca Hirtopeanu,†,# and Richard Gilardi⊥

Department of Chemistry (M/C 111), University of Illinois at Chicago, Chicago, Illinois 60607, United Therapeutics, Chicago, Illinois 60612, deCODE Genetics, Inc., Chicago, Illinois 60612, Institute of Organic Chemistry, C.D. Nenitzescu, Bucharest, Romania, and Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375

Received June 5, 2003

A general and novel solution to the synthesis of biologically important stable analogues of prostacyclin PGI_2, namely benzindene prostacyclins, has been achieved via the stereoselective intramolecular Pauson–Khand cyclization (PKC). This work illustrates for the first time the synthetic utility and reliability of the asymmetric PKC route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale. The synthetic route surmounts issues of individual step stereoselectivity and scalability. The key step in the synthesis involves efficient stereoselection effected in the PKC of a benzoenyne under the agency of the benzylic OTBDMS group, which serves as a temporary stereodirecting group that is conveniently removed via benzylic hydrogenolysis concomitantly with the catalytic hydrogenation of the enyne PKC product. Thus the benzylic chiral center dictates the subsequent stereochemistry of the stereogenic centers at three carbon atoms (C_{3a}, C_{9a}, and C_3).

Prostacyclin (PGI_2) (**1**) is an important physiological prostanoid and occurs as a major metabolite product from arachidonic acid throughout the vasculature and is produced in the endothelium and in smooth muscles.[1a−c] PGI_2 is the most potent endogenous vasodilator in both systemic and pulmonary circulation. It exerts effects on vascular smooth muscle cells and inhibits both platelet aggregation and adhesion.[2a−f] These biological activities are relevant to a broad range of cardiovascular diseases including congestive heart failure, peripheral vascular disease, myocardial ischemia, and pulmonary hypertension.[3a−f] Use of PGI_2 as a drug for coronary disease has not been fruitful because of the fleeting half-life of this compound (~10 min at pH 7.6 at 25 °C).[4] The ability to inhibit platelet aggregation in plasma samples is lost within 5 min.[5] Application of PGI_2 to disease therapy presents a typical drug delivery challenge that is dealt with either mechanically by an appropriate pharmaceutical device or chemically by synthesizing a hydrolytically stable analogue that retains the biological activity. The first option currently is used for the treatment of pulmonary hypertension in which an aqueous solution of PGI_2 sodium salt (chemical name, epoprostenol; trade name Flolan) is pumped continuously and intravenously through a catheter permanently placed in the patient's chest via a portable external pump. PGI_2 is light sensitive and must be stored between 15 and 25 °C, and the formulation in a buffer solution must be prepared by the patient on a daily basis.[6] The PGI_2 is thereby introduced directly

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‡ United Therapeutics.
§ deCODE Genetics, Inc.
⊥ Institute of Organic Chemistry, C.D. Nenitzescu.
Naval Research Laboratory.

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663–665. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S. *Prostaglandins* **1976**, *12*, 915–928. (c) Vane, J. R.; Bergstrom, S., Eds. *Prostacyclin*; Raven Press: New York, 1979. (d) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293–331. (e) Bunting, S.; Gryglewski, R.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 897–913. (f) Moncada, S.; Herman, A. G.; Higgs, E. A.; Vane, J. R. *Thromb. Res.* **1977**, *11*, 323–344. (g) Marcus, A. J.; Weksler, B. B.; Jaffe, E. A. *Biol. Chem.* **1978**, *253*, 7138–7141. (h) Weksler, B. B.; Marcus, A. J.; Jaffe, E. A. *Proc. Natl. Acad Sci. U.S.A.* **1977**, *74*, 3922–3926. (i) MacIntyre, D. E.; Pearson, J. D.; Gordon, J. L. *Nature* **1978**, *271*, 549–551. (j) Nakagawa, O.; Tanaka, I.; Usui, T.; Harada, M.; Sasaki, Y.; Itoh, H.; Yoshimasa, T.; Nambu, T.; Narumiya, S.; Nakao, K. *Circulation* **1994**, *90*, 1643–1647. Syntheses of PGI_2: (k) Corey, E. J.; Keck, G. E.; Szekely, I. *J. Am. Chem. Soc.* **1977**, *99*, 2006–2008. (l) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 4182–4184. (m) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem Soc.* **1978**, *100*, 7690–7705. (n) Corey, E. J.; Pearce, H. L.; Szekely, I.; Ishiguro, M. *Tetrahedron Lett.* **1978**, *18*, 1623–1626. (o) Tomoskozi, I.; Galambos, G.; Simonsitse, V.; Kovacs, G. *Tetrahedron Lett.* **1977**, *18*, 2627–2628. (p) Tomoskozi, I.; Galambos, G.; Kovacs, G.; Gruber, L. *Tetrahedron Lett.* **1978**, *20*, 1927–1930. (q) Nicolaou, K. C.; Barnette, W. F.; Gasic, G. P.; Magolda, R. L.; Spain, W. J. *J. Chem. Soc., Chem. Commun.* **1977**, 630–631. (r) Fried, J.; Barton, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2199–2203.

(2) (a) Tateson, J. E.; Moncada, S.; Vane, J. R. *Prostaglandins* **1977**, *13*, 389–397. (b) Hugo, F. A.; Moncada, S.; Vane, J. R.; Caen, J. P.; Michel, H.; Tobelem, G. *Prostaglandins* **1978**, *16*, 17–22. (c) Flower, R. J.; Cardinal, D. C.; Prostacyclin; Vane, J. R.; Bergstrom, S., Eds. Raven Press: New York, 1979; pp 211–216. (d) Gorman, R. R.; Bunting, S.; Miller, O. V. *Prostaglandins* **1977**, *13*, 377–388. (e) Ubatuba, F. B.; Moncada, S.; Vane, J. R. *Thromb. Haemostasis* **1979**, *41*, 425–434. (f) Cooper, B.; Schafer, A. I.; Puchalsky, D.; Handin, R. I. *Prostaglandins* **1979**, *17*, 561–571.

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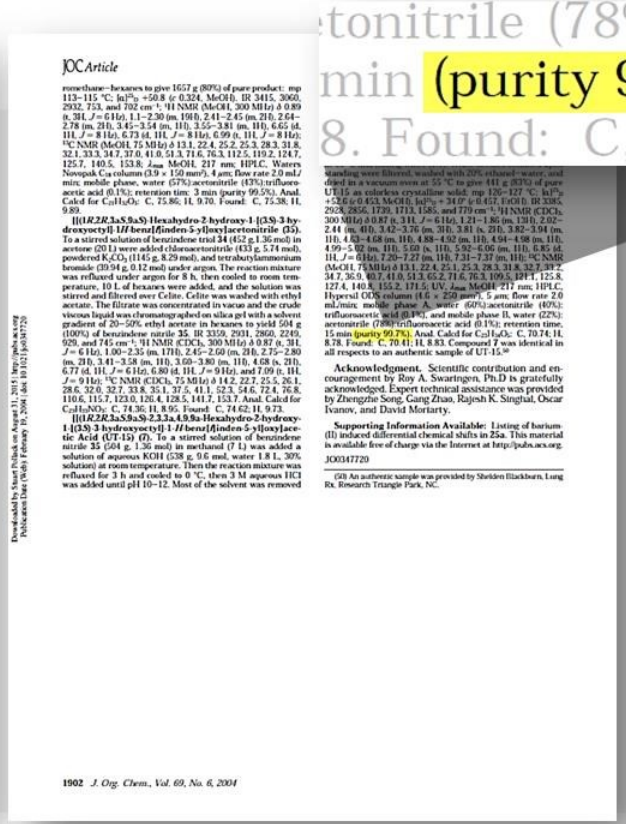


JOC*Article*

romethane–hexanes to give 1657 g (80%) of pure product: mp 113–115 °C; $[\alpha]^{25}_D$ +50.8 (*c* 0.324, MeOH). IR 3415, 3060, 2932, 753, and 702 cm^{-1}; ^1H NMR (MeOH, 300 MHz) δ 0.89 (t, 3H, J = 6 Hz), 1.1–2.30 (m, 19H), 2.41–2.45 (m, 2H), 2.64–2.78 (m, 2H), 3.45–3.54 (m, 1H), 3.55–3.81 (m, 1H), 6.65 (d, 1H, J = 8 Hz), 6.73 (d, 1H, J = 8 Hz), 6.99 (s, 1H, J = 8 Hz); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.2, 25.3, 28.3, 31.8, 32.1, 33.3, 34.7, 37.0, 41.0, 51.3, 71.6, 76.3, 112.5, 119.2, 124.7, 125.7, 140.5, 153.8; λ_{max} MeOH, 217 nm; HPLC, Waters Novapak C_{18} column (3.9 × 150 mm²), 4 μm; flow rate 2.0 mL/min; mobile phase, water (57%):acetonitrile (43%):trifluoroacetic acid (0.1%); retention time: 3 min (purity 99.5%). Anal. Calcd for $C_{23}H_{32}O_5$: C, 75.86; H, 9.70. Found: C, 75.38; H, 9.89.

[(1*R*,2*R*,3a*S*,9a*S*)-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxyacetonitrile (35). To a stirred solution of benzindene triol **34** (452 g, 1.36 mol) in acetone (20 L) were added chloroacetonitrile (433 g, 5.74 mol), powdered K_2CO_3 (1145 g, 8.29 mol), and tetrabutylammonium bromide (39.94 g, 0.12 mol) under argon. The reaction mixture was refluxed under argon for 8 h, then cooled to room temperature, 10 L of hexanes were added, and the solution was stirred and filtered over Celite. Celite was washed with ethyl acetate. The filtrate was concentrated in vacuo and the crude viscous liquid was chromatographed on silica gel with a solvent gradient of 20–50% ethyl acetate in hexanes to yield 504 g (100%) of benzindene nitrile **35**. IR 3359, 2931, 2860, 2249, 929, and 745 cm^{-1}; ^1H NMR (CDCl₃, 300 MHz) δ 0.87 (t, 3H, J = 6 Hz), 1.00–2.35 (m, 17H), 2.45–2.60 (m, 2H), 2.75–2.80 (m, 2H), 3.41–3.58 (m, 1H), 3.60–3.80 (m, 1H), 4.68 (s, 2H), 6.77 (d, 1H, J = 6 Hz), 6.80 (d, 1H, J = 9 Hz), and 7.09 (t, 1H, J = 9 Hz); ^{13}C NMR (CDCl₃, 75 MHz) δ 14.2, 22.7, 25.5, 26.1, 28.6, 32.0, 32.7, 33.8, 35.1, 37.5, 41.1, 52.3, 54.6, 72.4, 76.8, 110.6, 115.7, 123.0, 126.4, 128.5, 141.7, 153.7. Anal. Calcd for $C_{25}H_{35}NO_5$: C, 74.36; H, 8.95. Found: C, 74.62; H, 9.73.

[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxyacetic Acid (UT-15) (7). To a stirred solution of benzindene nitrile **35** (504 g, 1.36 mol) in methanol (7 L) was added a solution of aqueous KOH (538 g, 9.6 mol, water 1.8 L, 30% solution) at room temperature. Then the reaction mixture was refluxed for 3 h and cooled to 0 °C, then 3 M aqueous HCl was added until pH 10–12. Most of the solvent was removed

tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

standing were filtered, washed with 25% ethanol–water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid; mp 126–127 °C; $[\alpha]^{25}_D$ +52.6 (*c* 0.453, MeOH); $[\alpha]^{25}_{365}$ +34.0° (*c* 0.457, EtOH). IR 3385, 2928, 2856, 1739, 1713, 1585, and 779 cm^{-1}; ^1H NMR (CDCl₃, 300 MHz) δ 0.87 (t, 3 H, J = 6 Hz), 1.21–1.86 (m, 13H), 2.02–2.44 (m, 4H), 3.42–3.76 (m, 3H), 3.81 (s, 2H), 3.82–3.94 (m, 1H), 4.63–4.68 (m, 1H), 4.88–4.92 (m, 1H), 4.94–4.98 (m, 1H), 4.99–5.02 (m, 1H), 5.60 (s, 1H), 5.92–6.06 (m, 1H), 6.85 (d, 1H, J = 6 Hz), 7.20–7.27 (m, 1H), 7.31–7.37 (m, 1H); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.1, 25.3, 28.3, 31.8, 32.7, 33.7, 34.7, 36.9, 40.7, 41.0, 51.3, 65.2, 71.6, 76.3, 109.5, 121.1, 125.8, 127.4, 140.8, 155.2, 171.5; UV, λ_{max} MeOH, 217 nm; HPLC, Hypersil ODS column (4.6 × 250 mm², 5 μm; flow rate 2.0 mL/min; mobile phase A, water (60%):acetonitrile (40%); trifluoroacetic acid (0.1%), and mobile phase B, water (22%): acetonitrile (78%):trifluoroacetic acid (0.1%); retention time, 15 min (purity 99.7%). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.41; H, 8.83. Compound **7** was identical in all respects to an authentic sample of UT-15.[30]

Acknowledgment. Scientific contribution and encouragement by Roy A. Swaringen, Ph.D is gratefully acknowledged. Expert technical assistance was provided by Zhengzhe Song, Gang Zhao, Rajesh K. Singhal, Oscar Ivanov, and David Moriarty.

Supporting Information Available: Listing of barium (II) induced differential chemical shifts in **25a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034720

(30) An authentic sample was provided by Sheiden Blackburn, Lung Rx. Research Triangle Park, NC.

5 Obviousness

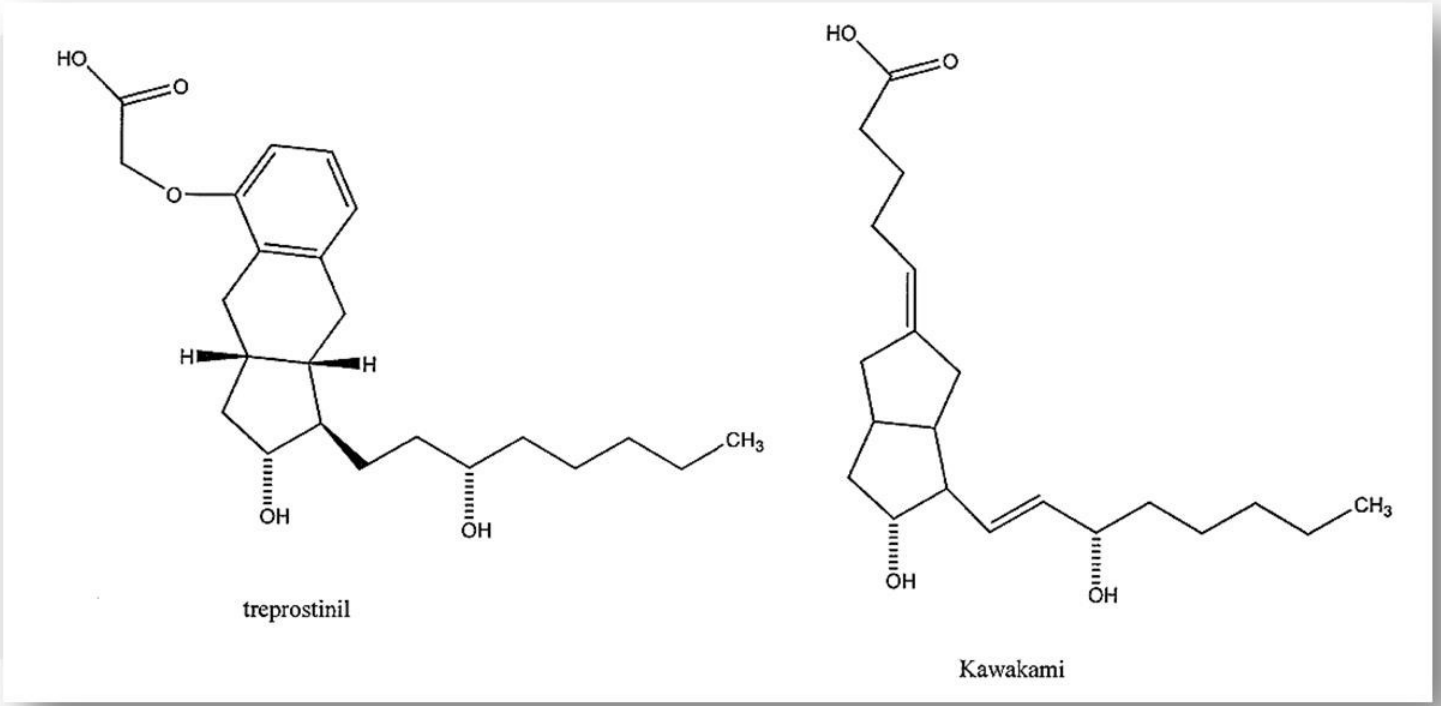
Phares and Moriarty

Kawakami and Moriarty

Dependent claims 6, 10, 15, 21, and 22

Obviousness: Kawakami & Moriarty

Motivation to Combine

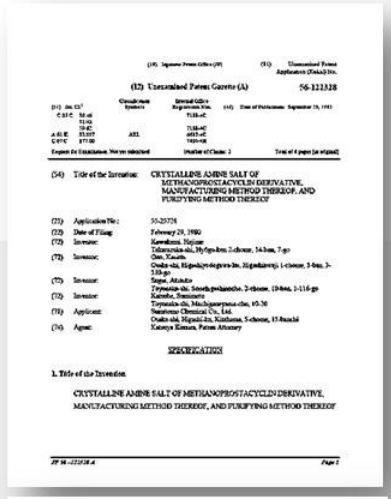


Obviousness: Kawakami & Moriarty

Motivation to Combine

Thus, establishment of an efficient and industrially viable method of separating isomers of methanoprostacyclin derivatives is essential in the development of these derivatives as pharmaceutical products.

In view of the above, the inventors conducted an examination of various separation and purification methods after achieving success in the synthesis of methanoprostacyclin, and finally succeeded in inventing an extremely simple and industrially viable purification method. The present invention relates to this novel purifying method and to a novel dicyclohexylamine salt of a methanoprostacyclin derivative [I] obtained thereby.



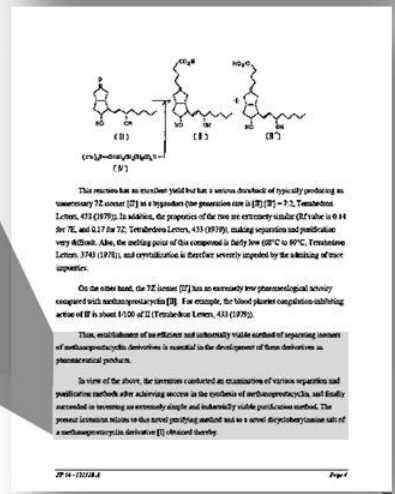
(12) Unexamined Patent Gazette (A) 56-122328

(54) Title of the Invention: CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

SPECIFICATION

1. Title of the Invention

CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF



Thus, establishment of an efficient and industrially viable method of separating isomers of methanoprostacyclin derivatives is essential in the development of these derivatives as pharmaceutical products.

In view of the above, the inventors conducted an examination of various separation and purification methods after achieving success in the synthesis of methanoprostacyclin, and finally succeeded in inventing an extremely simple and industrially viable purification method. The present invention relates to this novel purifying method and to a novel dicyclohexylamine salt of a methanoprostacyclin derivative [I] obtained thereby.

Ex. 1007 ("Kawakami") at 4

Obviousness: Kawakami & Moriarty

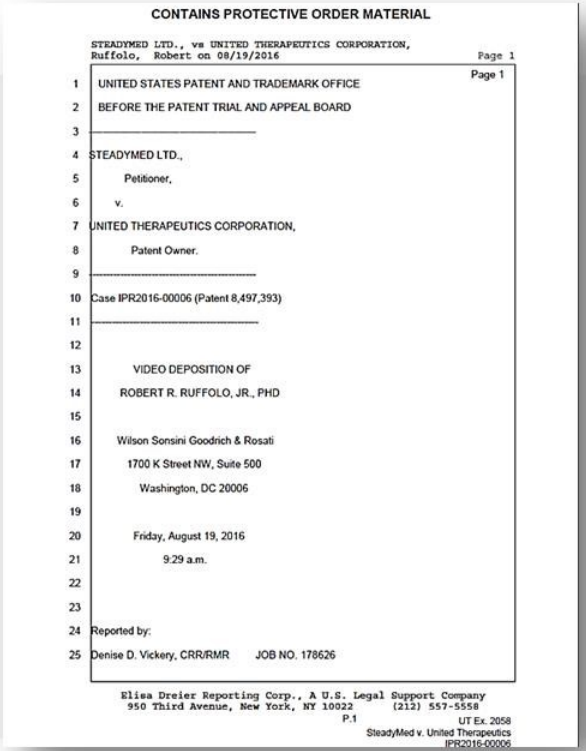
Motivation to Combine

"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007).

Obviousness: Kawakami & Moriarty

Reasonable Expectation of Success



CONTAINS PROTECTIVE ORDER MATERIAL

STEADYMED LTD., vs UNITED THERAPEUTICS CORPORATION,
Ruffolo, Robert on 08/19/2016 Page 1

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,
v.
UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006 (Patent 8,497,393)

VIDEO DEPOSITION OF
ROBERT R. RUFFOLO, JR., PHD

Wilson Sonsini Goodrich & Rosati
1700 K Street NW, Suite 500
Washington, DC 20006

Friday, August 19, 2016
9:29 a.m.

Reported by:
Denise D. Vickery, CRR/RMR JOB NO. 178626

Elisa Dreier Reporting Corp., A U.S. Legal Support Company
950 Third Avenue, New York, NY 10022 (212) 557-5558
P.1

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

Q. How long has crystallization been around as a method of purification?

THE WITNESS: I don't know how long it's been around.

Q. Before 2007?

A. Oh, yes.

THE WITNESS: Yes.

Q. Did you learn about it when you were in college at the university?

THE WITNESS: Yes, I did.

Q. What course did you -- in what course did you learn about that?

THE WITNESS: The inorganic chemistry, organic chemistry, physical chemistry, medicinal chemistry, pharmaceutical chemistry, analytical chemistry. Maybe some others.

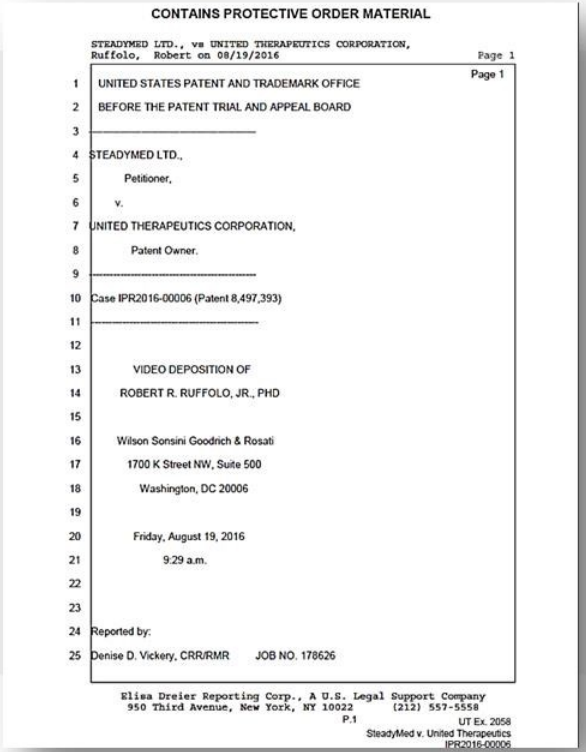
Q. And when did you go to college?

A. In 1968 I started. In 1968.

Ex. 2058 (Ruffolo Dep.) 175:19-176:22

Obviousness: Kawakami & Moriarty

Reasonable Expectation of Success



CONTAINS PROTECTIVE ORDER MATERIAL

STEADYMED LTD., vs UNITED THERAPEUTICS CORPORATION,
Ruffolo, Robert on 08/19/2016 Page 1

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE
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STEADYMED LTD.,
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Case IPR2016-00006 (Patent 8,497,393)

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Denise D. Vickery, CRR/RMR JOB NO. 178626

Elisa Dreier Reporting Corp., A U.S. Legal Support Company
950 Third Avenue, New York, NY 10022 (212) 557-5558
P.1
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

Q. Okay. Was -- was there any kind of list of what impurities were in the treprostinil made in the '393 patent?

BY MR. POLLACK:

Q. In the patent itself?

A. Without reading the whole thing, I see primarily purities of the parent compound, which is what I believe the invention is related to. And -- and so I see comparisons between the old process and new process with purities, but -- but I don't see, unless I've missed it, I don't see the impurities.

Ex. 2058 (Ruffolo Dep.) 234:25-235:12

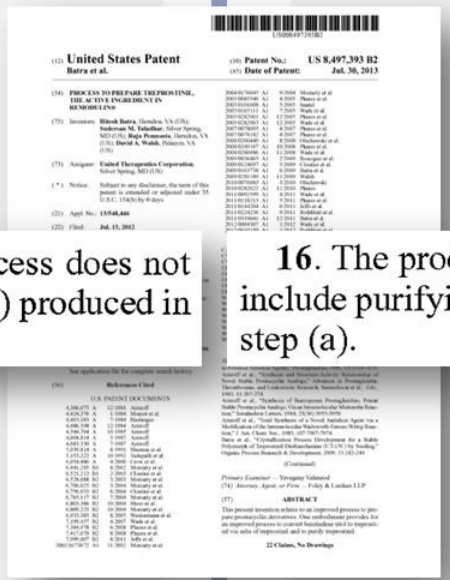
Ex. 2058 (Ruffolo Dep.) at 60

Obviousness: Kawakami & Moriarty

Dependent Claims 8 & 16

Claim 8

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



(12) **United States Patent**
Batra et al.

(10) **Patent No.: US 8,497,393 B2**
(45) **Date of Patent: Jul. 30, 2013**

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

(75) Inventors: **Hitesh Batra**, Herndon, VA (US); **Sudersan M. Taladhar**, Silver Spring, MD (US); **Raju Penmasta**, Herndon, VA (US); **David A. Walsh**, Potomac, VA (US)

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

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

(21) Appl. No.: **13/548,446**

(22) Filed: **Jul. 13, 2012**

(56) **References Cited**

U.S. PATENT DOCUMENTS

(57) **ABSTRACT**

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert beraprost tert-butyl to imperatil via salts of imperatil and to purify imperatil.

22 Claims, No Drawings

Claim 16

16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).

Obviousness: Kawakami & Moriarty

Dependent Claims 8 & 16

We have clearly stated that "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." ... "That is because of the ... longstanding rule that an old product is not patentable even if it is made by a new process."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted)

5 Obviousness

Phares and Moriarty

Kawakami and Moriarty

Dependent Claims 6, 10, 15, 21, and 22

Conclusions

1. Motivation to combine conceded by Dr. Williams
2. Reasonable expectation of success since prior-art purity already higher than patent
3. No structural differences
4. No functional differences
5. Processes well-known in the art
6. No separate argument for most dependent claims
7. Claims 8 and 16 do not generate a different product
8. Claims 1-5, 7-9, 11-14, 16-20 obvious

5 Obviousness

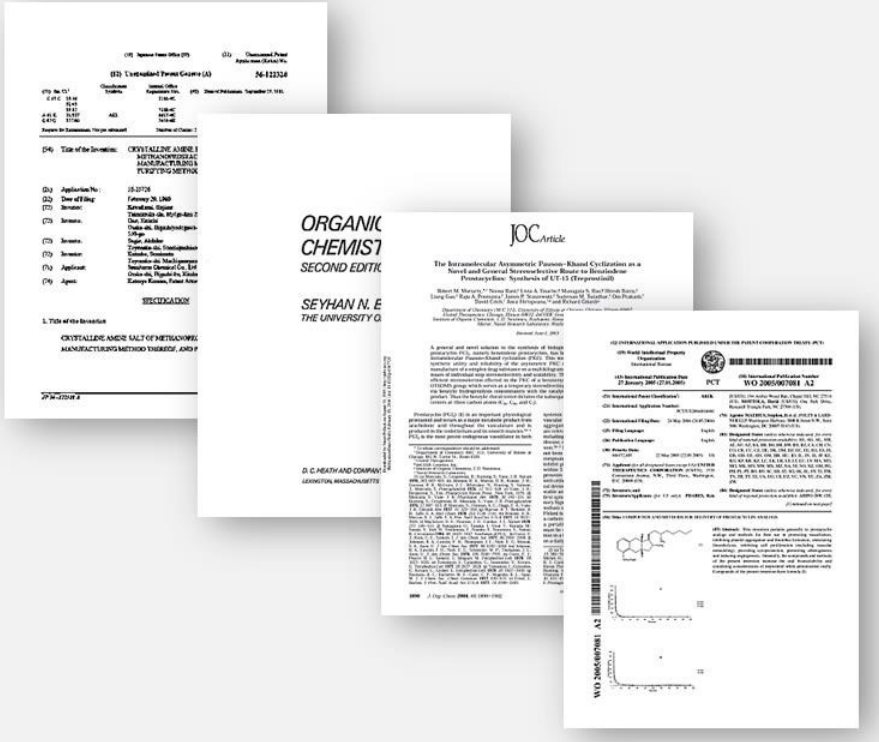
Phares and Moriarty

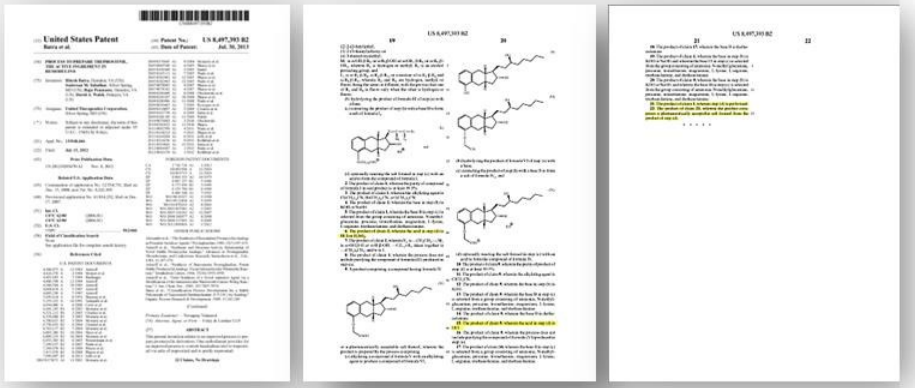
Kawakami and Moriarty

Dependent Claims 6, 10, 15, 21, and 22

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with **Moriarty, Phares** and **Eğe**





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

15. The product of claim **9**, wherein the acid in step (d) is HCl.

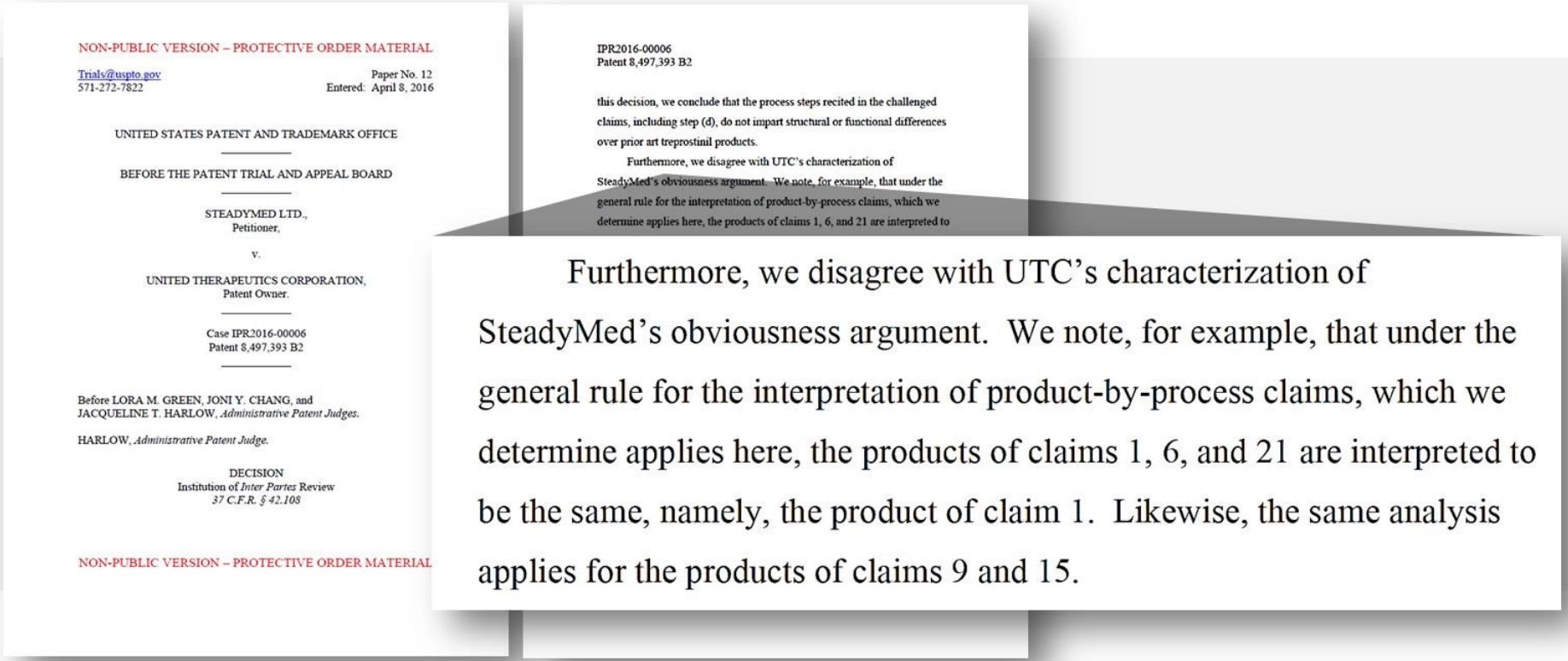
21. The product of claim **1**, wherein step (d) is performed.

22. The product of claim **21**, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

Ex. 1007 (Kawakami), Ex. 1004; Ex. 1008 (Eğe), Ex. 1005 (Phares), Ex. 1001

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with **Moriarty, Phares** and **Eğe**



NON-PUBLIC VERSION – PROTECTIVE ORDER MATERIAL

Trials@uspto.gov
571-272-7822

Paper No. 12
Entered: April 8, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006
Patent 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

NON-PUBLIC VERSION – PROTECTIVE ORDER MATERIAL

IPR2016-00006
Patent 8,497,393 B2

this decision, we conclude that the process steps recited in the challenged claims, including step (d), do not impart structural or functional differences over prior art treprostinil products.

Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to

Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, the product of claim 1. Likewise, the same analysis applies for the products of claims 9 and 15.

Institution Decision, Paper No. 12 at 47.

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Process Step Irrelevant

"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step...."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

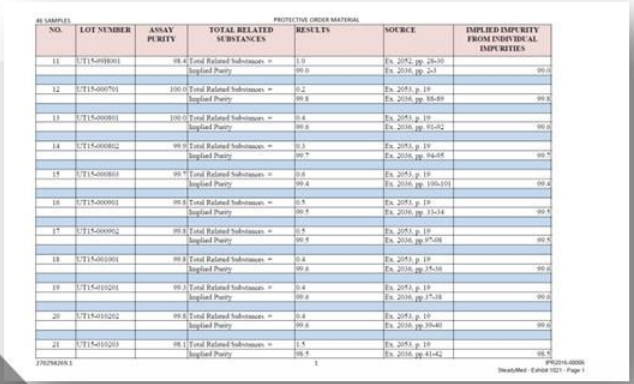
Obviousness: Dependent Claims 6, 10, 15, 21 & 22

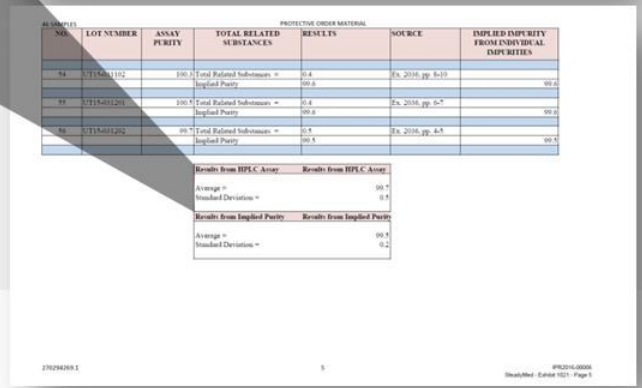
Prior Art Made Same Product

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5

99.7 ± 0.5 %

Ex. 1021 at 5 (Moriarty, average of 46 samples)



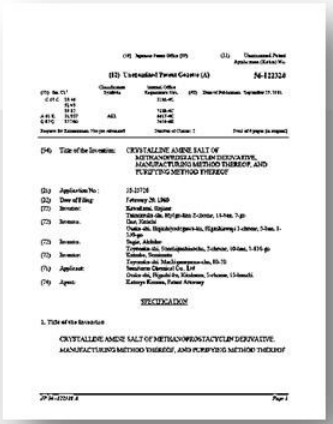


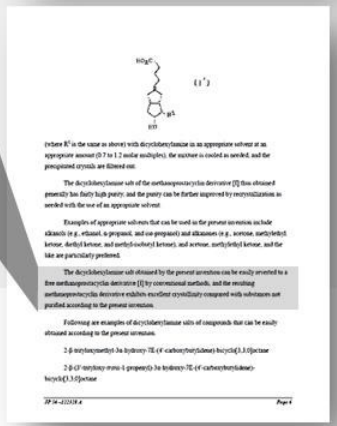
Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5
Results from Implied Purity	**Results from Implied Purity**
Average =	99.5
Standard Deviation =	0.2

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Used Same Process

The dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention.



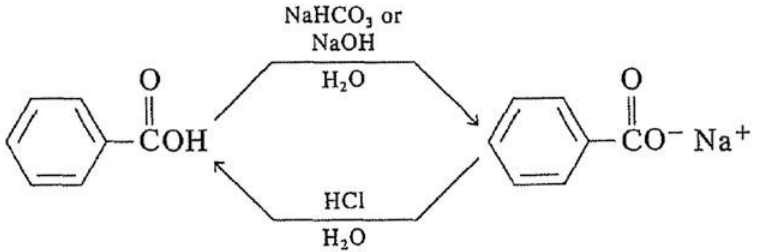


Ex. 1007 ("Kawakami") at 6

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

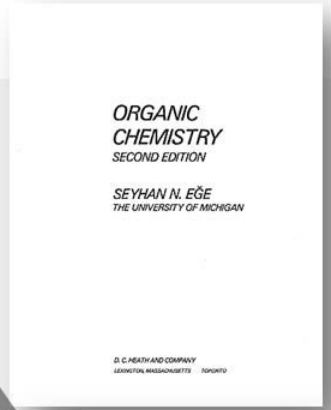
Prior Art Used Same Process

Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base (p. 95). Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.



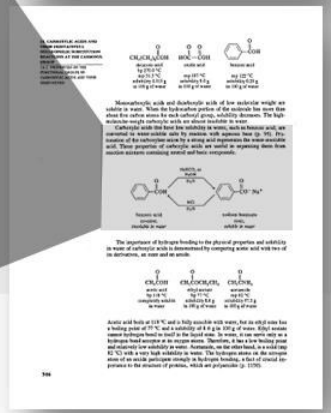
benzoic acid
covalent,
insoluble in water

sodium benzoate
ionic,
soluble in water


ORGANIC CHEMISTRY
SECOND EDITION

SEYHAN N. EĞE
THE UNIVERSITY OF MICHIGAN

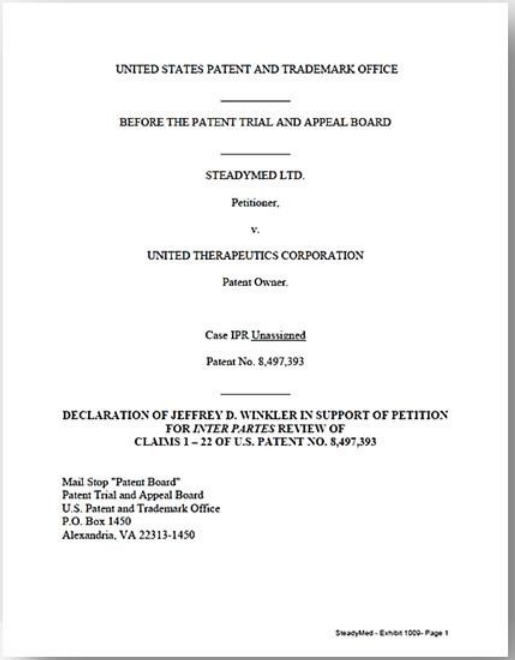
D. C. HEATH AND COMPANY
LEXINGTON, MASSACHUSETTS TORONTO



Ex. 1008 ("Eğe") at 8

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Used Same Process



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR Unassigned

Patent No. 8,497,393

DECLARATION OF JEFFREY D. WINKLER IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1 – 22 OF U.S. PATENT NO. 8,497,393

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

SteadyMed - Exhibit 1009- Page 1

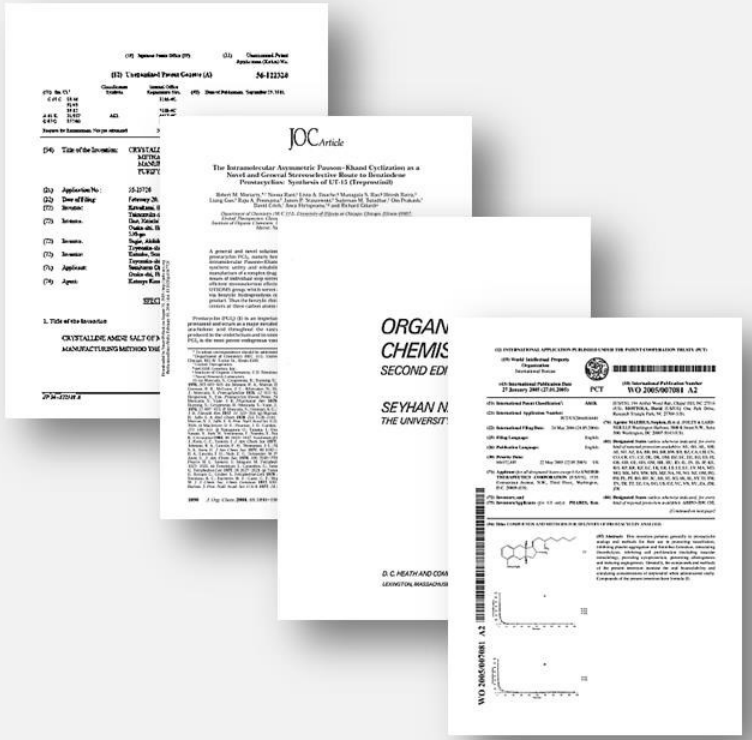
40. A person of ordinary skill in the art would recognize that the formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), is standard chemistry purification – *i.e.*, organic chemistry 101.

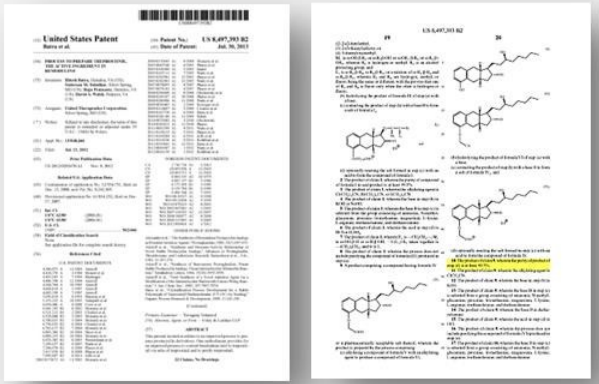
Ex. 1009 (Winkler Decl. at 12) ¶ 40

Ex. 1009 ("Winkler Declaration") at 15

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with Moriarty, Phares, and Eğe





10. The product of claim **9**, wherein the purity of product of step (d) is at least 99.5%.

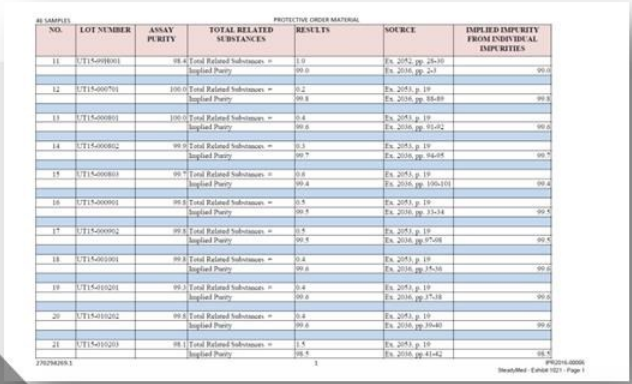
Ex. 1007 (Kawakami), Ex. 1004, Ex. 1008 (Eğe), Ex. 1005 (Phares); Ex. 1001

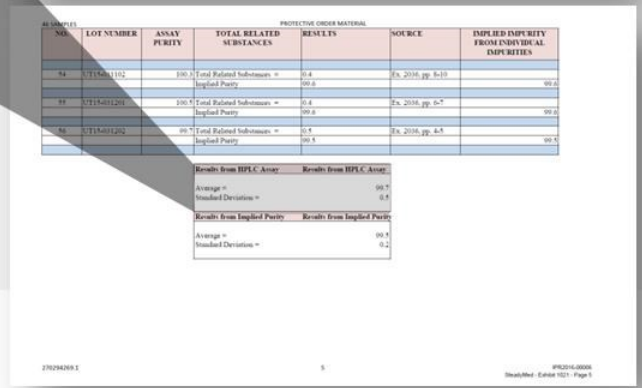
Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Made Same Product

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5

99.7 ± 0.5 %





Ex. 1021 at 5 (Moriarty, average of 46 samples)

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Made Same Product

JOC Article

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

Robert M. Moriarty,*,† Neena Rani,† Livia A. Enache,‡ Munagala S. Rao,§ Hitesh Batra,† Liang Guo,† Raju A. Penmasta,† James P. Staszewski,† Sudersan M. Tuladhar,† Om Prakash,† David Crich,† Anca Hirtopeanu,†,# and Richard Gilardi⊥

Department of Chemistry (M/C 111), University of Illinois at Chicago, Chicago, Illinois 60607, United Therapeutics, Chicago, Illinois 60612, deCODE Genetics, Inc., Chicago, Illinois 60612, Institute of Organic Chemistry, C.D. Nenitzescu, Bucharest, Romania, and Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375

Received June 5, 2003

A general and novel solution to the synthesis of biologically important stable analogues of prostacyclin PGI_2, namely benzindene prostacyclins, has been achieved via the stereoselective intramolecular Pauson–Khand cyclization (PKC). This work illustrates for the first time the synthetic utility and reliability of the asymmetric PKC route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale. The synthetic route surmounts issues of individual step stereoselectivity and scalability. The key step in the synthesis involves efficient stereoselection effected in the PKC of a benzoenyne under the agency of the benzylic OTBDMS group, which serves as a temporary stereodirecting group that is conveniently removed via benzylic hydrogenolysis concomitantly with the catalytic hydrogenation of the enyne PKC product. Thus the benzylic chiral center dictates the subsequent stereochemistry of the stereogenic centers at three carbon atoms (C_{3a}, C_{9a}, and C_3).

Prostacyclin (PGI_2) (**1**) is an important physiological prostanoid and occurs as a major metabolite product from arachidonic acid throughout the vasculature and is produced in the endothelium and in smooth muscles.[1a−c] PGI_2 is the most potent endogenous vasodilator in both systemic and pulmonary circulation. It exerts effects on vascular smooth muscle cells and inhibits both platelet aggregation and adhesion.[2a−f] These biological activities are relevant to a broad range of cardiovascular diseases including congestive heart failure, peripheral vascular disease, myocardial ischemia, and pulmonary hypertension.[3a−f] Use of PGI_2 as a drug for coronary disease has not been fruitful because of the fleeting half-life of this compound (~10 min at pH 7.6 at 25 °C).[4] The ability to inhibit platelet aggregation in plasma samples is lost within 5 min.[5] Application of PGI_2 to disease therapy presents a typical drug delivery challenge that is dealt with either mechanically by an appropriate pharmaceutical device or chemically by synthesizing a hydrolytically stable analogue that retains the biological activity. The first option currently is used for the treatment of pulmonary hypertension in which an aqueous solution of PGI_2 sodium salt (chemical name, epoprostenol; trade name Flolan) is pumped continuously and intravenously through a catheter permanently placed in the patient's chest via a portable external pump. PGI_2 is light sensitive and must be stored between 15 and 25 °C, and the formulation in a buffer solution must be prepared by the patient on a daily basis.[6] The PGI_2 is thereby introduced directly

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Naval Research Laboratory.

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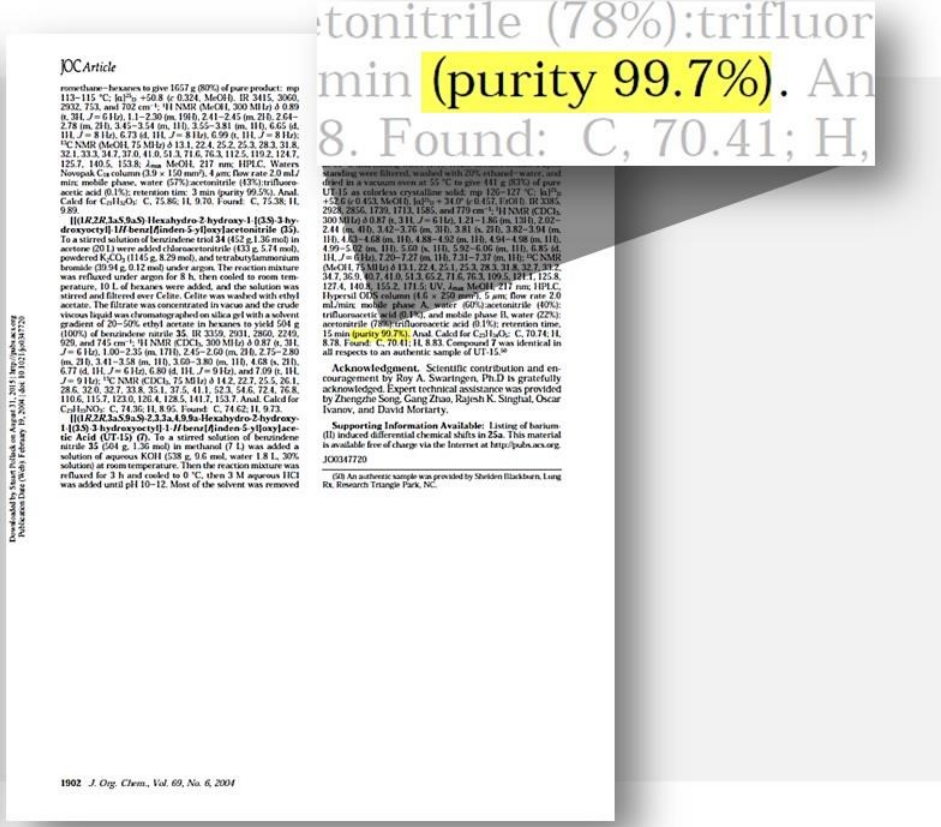


tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

JOC Article

romethane–hexanes to give 1657 g (80%) of pure product: mp 113–115 °C; $[\alpha]^{25}_D$ +50.8 (*c* 0.324, MeOH). IR 3415, 3060, 2932, 753, and 702 cm^{-1}; ^1H NMR (MeOH, 300 MHz) δ 0.89 (t, 3H, *J* = 6 Hz), 1.1–2.30 (m, 19H), 2.41–2.45 (m, 2H), 2.64–2.78 (m, 2H), 3.45–3.54 (m, 1H), 3.55–3.81 (m, 1H), 6.65 (d, 1H, *J* = 8 Hz), 6.73 (d, 1H, *J* = 8 Hz), 6.99 (t, 1H, *J* = 8 Hz); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.2, 25.3, 28.3, 31.8, 32.1, 33.3, 34.7, 37.0, 41.0, 51.3, 71.6, 76.3, 112.5, 119.2, 124.7, 125.7, 140.5, 153.8; λ_{max} MeOH, 217 nm; HPLC, Waters Novapak C_{18} column (3.9 × 150 mm²), 4 μm; flow rate 2.0 mL/min; mobile phase, water (57%):acetonitrile (43%):trifluoroacetic acid (0.1%); retention time: 3 min (purity 99.5%). Anal. Calcd for $C_{23}H_{32}O_5$: C, 75.86; H, 9.70. Found: C, 75.38; H, 9.89.

[(1*R*,2*R*,3a*S*,9a*S*)-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxyacetonitrile (35). To a stirred solution of benzindene triol **34** (452 g, 1.36 mol) in acetone (20 L) were added chloroacetonitrile (433 g, 5.74 mol), powdered K_2CO_3 (1145 g, 8.29 mol), and tetrabutylammonium bromide (39.94 g, 0.12 mol) under argon. The reaction mixture was refluxed under argon for 8 h, then cooled to room temperature, 10 L of hexanes were added, and the solution was stirred and filtered over Celite. Celite was washed with ethyl acetate. The filtrate was concentrated in vacuo and the crude viscous liquid was chromatographed on silica gel with a solvent gradient of 20–50% ethyl acetate in hexanes to yield 504 g (100%) of benzindene nitrile **35**. IR 3359, 2931, 2860, 2249, 929, and 745 cm^{-1}; ^1H NMR (CDCl₃, 300 MHz) δ 0.87 (t, 3H, *J* = 6 Hz), 1.00–2.35 (m, 17H), 2.45–2.60 (m, 2H), 2.75–2.80 (m, 2H), 3.41–3.58 (m, 1H), 3.60–3.80 (m, 1H), 4.68 (s, 2H), 6.77 (d, 1H, *J* = 6 Hz), 6.80 (d, 1H, *J* = 9 Hz), and 7.09 (t, 1H, *J* = 9 Hz); ^{13}C NMR (CDCl₃, 75 MHz) δ 14.2, 22.7, 25.5, 26.1, 28.6, 32.0, 32.7, 33.8, 35.1, 37.5, 41.1, 52.3, 54.6, 72.4, 76.8, 110.6, 115.7, 123.0, 126.4, 128.5, 141.7, 153.7. Anal. Calcd for $C_{25}H_{35}NO_3$: C, 74.36; H, 8.95. Found: C, 74.62; H, 9.73.

[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxyacetic Acid (UT-15) (7). To a stirred solution of benzindene nitrile **35** (504 g, 1.36 mol) in methanol (7 L) was added a solution of aqueous KOH (538 g, 9.6 mol, water 1.8 L, 30% solution) at room temperature. Then the reaction mixture was refluxed for 3 h and cooled to 0 °C, then 3 M aqueous HCl was added until pH 10–12. Most of the solvent was removed

standing were filtered, washed with 25% ethanol–water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid; mp 126–127 °C; $[\alpha]^{25}_D$ +52.6 (*c* 0.453, MeOH); $[\alpha]^{25}_{365}$ +34.0° (*c* 0.457, EtOH). IR 3385, 2928, 2856, 1739, 1713, 1585, and 779 cm^{-1}; ^1H NMR (CDCl₃, 300 MHz) δ 0.87 (t, 3 H, *J* = 6 Hz), 1.21–1.86 (m, 13H), 2.02–2.44 (m, 4H), 3.42–3.76 (m, 3H), 3.81 (s, 2H), 3.82–3.94 (m, 1H), 4.63–4.68 (m, 1H), 4.88–4.92 (m, 1H), 4.94–4.98 (m, 1H), 4.99–5.02 (m, 1H), 5.60 (s, 1H), 5.92–6.06 (m, 1H), 6.85 (d, 1H, *J* = 6 Hz), 7.20–7.27 (m, 1H), 7.31–7.37 (m, 1H); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.1, 25.3, 28.3, 31.8, 32.7, 33.2, 34.7, 36.9, 40.7, 41.0, 51.3, 65.2, 71.6, 76.3, 109.5, 121.1, 125.8, 127.4, 140.8, 155.2, 171.5; UV, λ_{max} MeOH: 217 nm; HPLC, Hypersil ODS column (4.6 × 250 mm²), 5 μm; flow rate 2.0 mL/min; mobile phase A, water (60%):acetonitrile (40%); trifluoroacetic acid (0.1%), and mobile phase B, water (22%): acetonitrile (78%):trifluoroacetic acid (0.1%); retention time, 15 min (purity 99.7%). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.41; H, 8.83. Compound **7** was identical in all respects to an authentic sample of UT-15.[10]

Acknowledgment. Scientific contribution and encouragement by Roy A. Swaringen, Ph.D is gratefully acknowledged. Expert technical assistance was provided by Zhengzhe Song, Gang Zhao, Rajesh K. Singhal, Oscar Ivanov, and David Moriarty.

Supporting Information Available: Listing of barium (II) induced differential chemical shifts in **25a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034720

(10) An authentic sample was provided by Sheiden Blackburn, Lung Rx. Research Triangle Park, NC.

Ex. 1004 ("Moriarty") at 13

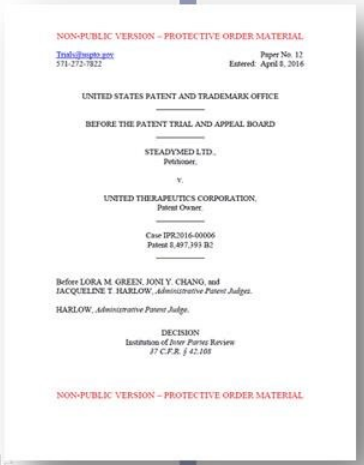
Conclusions

1. No structural differences
2. No functional differences
3. Process of adding acid is "organic chemistry 101"
4. Additional process step makes same product as independent claims
5. Prior art purity > 99.5%
6. Claims 6, 10, 15, 21, & 22 obvious

6 Claim Construction

Claim Construction

Board's Construction



NON-PUBLIC VERSION – PROTECTIVE ORDER MATERIAL

Trials@uspto.gov
571-272-7822

Paper No. 12
Entered: April 8, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006
Patent 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

HARLOW, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

NON-PUBLIC VERSION – PROTECTIVE ORDER MATERIAL

"Comprising"

Regarding the larger claim phrase "[a] product comprising a compound [of having] formula [I IV] . . . or a pharmaceutically acceptable salt thereof," as explained above, we determine that the embedded claim term "comprising" means "including, but not limited to." *See Genentech*, 112 F.3d [illegible] "including, but not limited to." [illegible] UTC's proposal that claims 1 and 9 be read to require a product "*constituted primarily of* formula I IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21 (emphasis added).

Institution Decision, Paper No. 12, at 13

"Product"

The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by

The claim term "product," as it is used in the '393 patent, **does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims.** This is evidenced by

added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001,

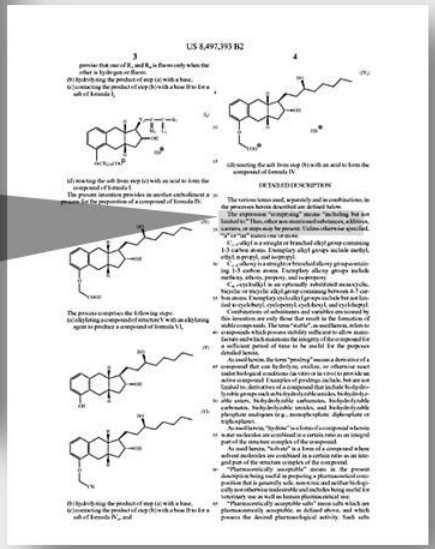
Institution Decision, Paper No. 12, at 12

Claim Construction

"Comprising"

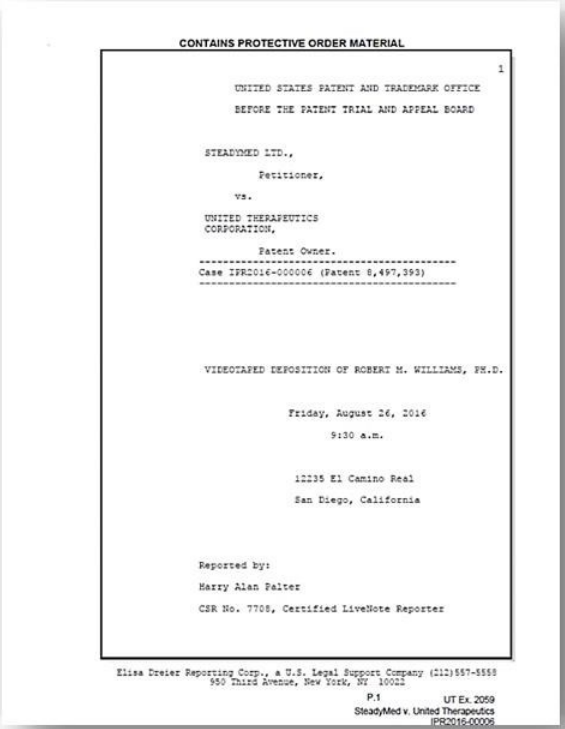
The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

Ex. 1001 ('393 Patent) col.4 ll.23-26



Claim Construction

"Product"



CONTAINS PROTECTIVE ORDER MATERIAL

1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-000006 (Patent 8,497,393)

VIDEOTAPED DEPOSITION OF ROBERT M. WILLIAMS, PH.D.

Friday, August 26, 2016

9:30 a.m.

12235 El Camino Real

San Diego, California

Reported by:

Harry Alan Falter

CSR No. 7708, Certified LiveNote Reporter

Elisa Dreier Reporting Corp., a U.S. Legal Support Company (212)557-5558
950 Third Avenue, New York, NY 10022

P.1

UT Ex. 2059
SteadyMed v. United Therapeutics
IPR2016-00006

Q. Why not?

A. Because chemists use the word "product" in two different contexts, routinely.

Q. Okay.

A. There's a molecular structural context; okay? So if I said to one of my students, "Show me the product of this reaction on my blackboard." And they'd write a structure like Ecteinascidin-743; okay?

Q. Okay.

A. And if I said, "Bring me a sample of the product that you just made in the lab," they would bring me a bottle, a flask, a vial of a real-world substance that, hopefully, contains mostly what we were trying to make, and it would also have its characteristic impurities. So there's the molecular structural context, and then there's the real-world substance context of the word "product." And chemists know what you're talking about when you use the word "product" in those two different contexts.

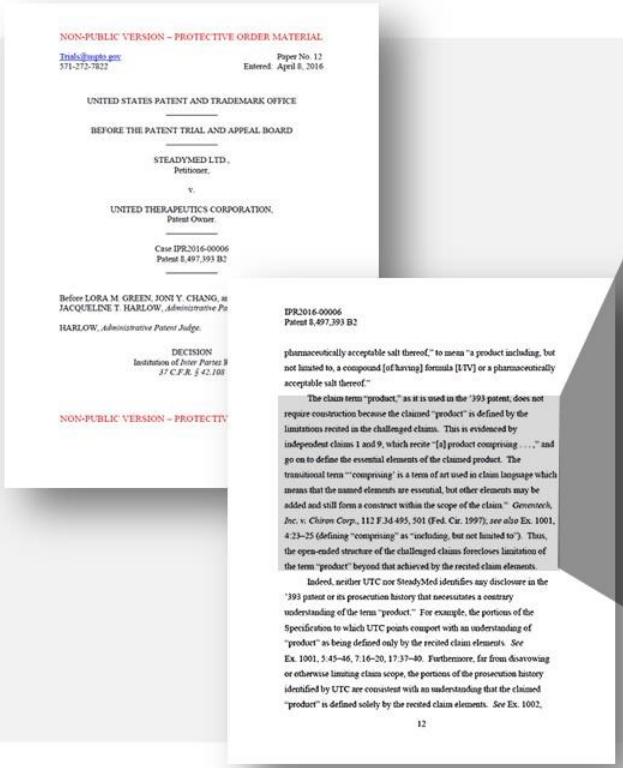
Q. Okay. Let me ask you: In the '393 patent, do you see any place where the '393 patent says: I'm going to define the word "product" for this patent? Do you see that anywhere in there?

A. I don't recall it being defined, other than its plain, ordinary meaning as it's understood, as I just explained.

Ex. 2059 at 248:4-249:6

Claim Construction

"Product"



NON-PUBLIC VERSION – PROTECTIVE ORDER MATERIAL

Trials@uspto.gov
571-272-7822

Paper No. 12
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UNITED STATES PATENT AND TRADEMARK OFFICE

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Before LORA M. GREEN, JONI Y. CHANG, and
JACQUELINE T. HARLOW, *Administrative Patent Judges*.

HARLOW, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

NON-PUBLIC VERSION – PROTECTIV

IPR2016-00006
Patent 8,497,393 B2

pharmaceutically acceptable salt thereof," to mean "a product including, but not limited to, a compound [of having] formula [I/IV] or a pharmaceutically acceptable salt thereof."

The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite "[a] product comprising . . . ," and go on to define the essential elements of the claimed product. The transitional term "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining "comprising" as "including, but not limited to"). Thus, the open-ended structure of the challenged claims forecloses limitation of the term "product" beyond that achieved by the recited claim elements.

Indeed, neither UTC nor SteadyMed identifies any disclosure in the '393 patent or its prosecution history that necessitates a contrary understanding of the term "product." For example, the portions of the Specification to which UTC points comport with an understanding of "product" as being defined only by the recited claim elements. *See* Ex. 1001, 5:45–46, 7:16–20, 17:37–40. Furthermore, far from disavowing or otherwise limiting claim scope, the portions of the prosecution history identified by UTC are consistent with an understanding that the claimed "product" is defined solely by the recited claim elements. *See* Ex. 1002,

12

The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite "[a] product comprising . . . ," and go on to define the essential elements of the claimed product. The transitional term "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining "comprising" as "including, but not limited to"). Thus, the open-ended structure of the challenged claims forecloses limitation of the term "product" beyond that achieved by the recited claim elements.

Institution Decision, Paper No. 12 at 12

Conclusions

Anticipation and Obviousness

Claims 1-5, 7-9, 11-14, 16-20

Conclusions

1. No structural differences
2. No functional differences
3. No separate argument for dependent claims
4. Phares anticipates
5. Moriarty and Phares or Kawakami make obvious

Conclusions

1. No structural differences
2. No functional differences
3. Process of adding acid is "organic chemistry 101"
4. Additional process step makes same product as independent claims
5. Prior art purity > 99.5%
6. Kawakami, Moriarty, Phares, Eğe make obvious

END