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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Published:

- with international search report (Art. 21(3))
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(88) Date of publication of the international search report:

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(54) Title: PROCESS FOR THE PREPARATION OF TREPROSTINIL AND DERIVATIVES THEREOF

(57) Abstract: A method for the preparation of treprostinil and its derivatives is described. In contrast to prior art, this method utilizes an easily scalable enzymatic resolution of a key intermediate for making these compounds. Another significant improvement of the described method over prior methods is the regioselective Claisen rearrangement of a 5-allyloxy-benzaldehyde precursor, which is facilitated by a bromo substituent in 2-position.



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/060472

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C67/29 C07C69/18 C07F7/18 C12P41/00 C07C47/565
C07C47/575 C07C51/377 C07C59/72

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07F C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/153363 A1 (UNITED THERAPEUTICS CORP [US]; BATRA HITESH [US]; PENMASTA RAJU [US];) 8 December 2011 (2011-12-08) page 36; claims 1,15; compound 6 ----- -/--	1,14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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08/05/2014

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/060472

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MORIARTY ROBERT M ET AL: "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)", JOURNAL OF ORGANIC CHEMISTRY, ACS, US, vol. 69, no. 6, 1 January 2004 (2004-01-01), pages 1890-1902, XP002523983, ISSN: 0022-3263, DOI: 10.1021/J00347720 [retrieved on 2004-02-19] Scheme 4;; page 1894; compounds 31,32 -----	10-12
X	US 6 700 025 B2 (MORIARTY ROBERT M [US] ET AL) 2 March 2004 (2004-03-02)	1-8,14
Y	columns 5,6 column 9, line 53 - line 55 -----	1-3,5-8, 14
A	WO 2012/009816 A1 (ALPHORA RES INC [CA]; MCGOWAN GRAHAM [CA]; GIUST WALTER [CA]; DI DONAT) 26 January 2012 (2012-01-26) claim 7; example 2 -----	1-14
Y	BRUCE ET AL: "Claisen rearrangement of meta-substituted allyl phenyl ethers", JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY, LETCHWORTH; GB, vol. 10, 1 January 1981 (1981-01-01), pages 2677-2679, XP002198137, ISSN: 0300-922X, DOI: 10.1039/P19810002677 table 2; compound 4 -----	1-3,5-8
A	US 2011/118213 A1 (PHARES KEN [US] ET AL) 19 May 2011 (2011-05-19) paragraph [0096]; compound 9 -----	1,14
A	US 6 242 482 B1 (SHORR ROBERT [US] ET AL) 5 June 2001 (2001-06-05) example 2 -----	13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/060472

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annexes

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4, 6-9, 13(completely); 5, 10-12, 14(partially)
compounds of formulae (I), (II), (IIb), (IIb), (IVb) with
PG2 being SiR₁R₂R₃

2. claims: 5, 10-12(all partially)
compounds of formulae (I) and (II) with PG2 being THP

3. claim: 5(partially)
compounds of formulae (I) and (II) with PG2 being -CH₂O_{Rx}

4. claim: 14(partially)
compounds 8 and 9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/060472

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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