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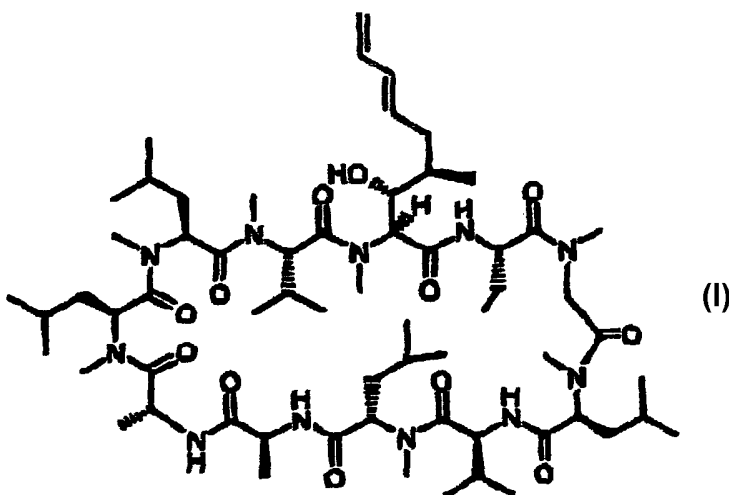
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARATION OF CYCLOSPORIN "A" ANALOGUES HAVING A TERMINAL DIENE GROUP



(57) Abstract: The invention is concerned with a new process for the preparation of a cyclosporin A analog of formula I comprising, a) allylating a protected cyclosporin A aldehyde with an allylmetal reagent and, b) converting the compound obtained in step a) to the cyclosporin A analog of formula I. In particular, the allyl reagent is a trimethylsilyl-allyl borate ester or a trimethylsilyl-allyl organometallic compound containing aluminium or titanium.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 C07K 004 C07F5/02		
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)		
IPC 7 C07K C07F		
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 practical, search terms used)		
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03/033527 A (FOSTER ROBERT T ; ISOTECHNIKA INC (CA); NAICKER SELVARAJ (CA); YATSCOF) 24 April 2003 (2003-04-24) page 21, line 30 to page 26, line 23; page 40, line 23 to page 41, line 4; figures 2A,5,6 and 12	1-22
P, X	WO 03/033526 A (JAYARAMAN SEETHARAMAN ; ABEL MARK (CA); FOSTER ROBERT T (CA); ISOTECHN) 24 April 2003 (2003-04-24) page 31, second paragraph; page 52, third paragraph; figures 2A,5,6 and 12	1-22
Y	WO 99/18120 A (FOSTER ROBERT T ; ISOTECHNIKA INC (CA); NAICKER S SELVARAJ (CA); YATSC) 15 April 1999 (1999-04-15) cited in the application figure 4; examples 5,7	1-22
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in 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 document 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		Date of mailing of the international search report
15 September 2004		15. 10. 04
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Fausti, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>TSAI D J S ET AL: "A STEREO CONTROLLED SYNTHESIS OF Z AND E TERMINAL DIENES FROM PINACOL E-1 TRI METHYLSILYL-1 PROPENE-3-BORONATE" TETRAHEDRON LETTERS, vol. 22, no. 29, 1981, pages 2751-2752, XP002288404 ISSN: 0040-4039 cited in the application abstract; reaction scheme on page 2751</p>	1-27
Y	<p>WO 98/48791 A (YANG GE ; MYLES DAVID C (US); HARRIED SCOTT S (US); UNIV CALIFORNIA (U) 5 November 1998 (1998-11-05) page 11, line 28 - page 12, line 34; figure 5</p>	1-28
Y	<p>YAMAMOTO, YOSHINORI ET AL: "Regioreversed reactions of the trimethylsilyl or phenylselenyl allylic carbanion with carbonyl compounds via allylic aluminum "ate" complexes" TETRAHEDRON LETTERS , 23(44), 4597-600 CODEN: TELEAY; ISSN: 0040-4039, 1982, XP002288405 reaction equation 2 on page 4598 and equation 3 on page 4599</p>	1-22
Y	<p>MANFRED T REETZ ET AL: "Stereoselective addition of organotitanium reagents to carbonyl compounds" CHEMISCHE BERICHTE, VERLAG CHEMIE GMBH. WEINHEIM, DE, vol. 118, no. 4, 1985, pages 1441-1454, XP002117771 ISSN: 0009-2940 paragraph joining pages 1449 and 1450</p>	1-22
A	<p>EP 0 296 122 A (SANDOZ AG ; SANDOZ AG (CH); SANDOZ AG (DE)) 21-December 1988 (1988-12-21) page 8, line 50; examples E,F; compounds 1.24,6.3</p>	
Y	<p>EP 1 291 347 A (CLARIANT GMBH) 12 March 2003 (2003-03-12) page 3, the last reaction scheme; page 4, lines 52-54</p>	23-25,27
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PCT/EP2004/003504

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	<p>THADANI AVINASH N ET AL: "A mild protocol for allylation and highly diastereoselective syn or anti crotylation of aldehydes in biphasic and aqueous media utilizing potassium allyl- and crotyltrifluoroborates." ORGANIC LETTERS. 31 OCT 2002, vol. 4, no. 22, 31 October 2002 (2002-10-31), pages 3827-3830, XP002296391 ISSN: 1523-7060 tables 2 and 3</p>	26
Y	<p>MARRON T G ET AL: "Diastereoselective Synthesis of N-Benzoyl Mycalamine, the Fully Elaborated Trioxadecalin Nucleus of Mycalamide A. Control of the Key N-Acyl Amino Stereocenter via Carbamate Acylation" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 36, no. 10, 6 March 1995 (1995-03-06), pages 1581-1584, XP004028537 ISSN: 0040-4039 cited in the application page 1583, the compounds 15-17 and the corresponding reaction scheme</p>	28
Y	<p>RATHEKE, M. R.; CHAO, E.; WU, G.: "The preparation and reactions of esters of dichloromethaneboronic acid" JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 122, no. 2, 1976, pages 145-149, XP002296392 page 146, third paragraph</p>	25

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Box 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 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 fee, this Authority did not invite payment of any additional fee.
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.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

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: 1-22

Methods for the preparation of (E)-ISA 247 by means of the addition reaction between a cyclosporin-aldehyde derivative and a 1-(trimethylsilyl)-propen-3-yl organometallic compound, followed by Peterson elimination.

2. claims: 23-25 and 27

Diethanolamine 1-(trimethylsilyl)-propene-3-boronate ester, its preparation and conversion to other 1-(trimethylsilyl)-propene-3-boron compounds.

3. claim: 26

Potassium 1-(trimethylsilyl)-propene-3-boron-trifluoride.

4. claim: 28

dimethyltartrate 1-(trimethylsilyl)-propene-3-boronate ester.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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