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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: PREPARATION OF EPOTHILONE INTERMEDIATES

(57) Abstract: The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially enzymatically degrading certain epothilone compounds to form ring-open structures containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a thiphenylphosphine adduct to yield a compound containing an ester group at position 1 which is subsequently hydrolyzed to form a second intermediate.



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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12P17/14 C07D277/00

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 C12P C07D

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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 54319 A (SQUIBB BRISTOL MYERS CO) 28 October 1999 (1999-10-28) page 17, scheme 2 page 17, line 4-8 page 28, scheme 9 page 28, line 11 -page 29, line 21 page 30, scheme 10 page 31, line 20 -page 32, line 4 ---	1,3,4
Y	WO 97 19086 A (BIOTECHNOLOG FORSCHUNG GMBH ;KIFFE MICHAEL (DE); HOEFLE GERHARD (D) 29 May 1997 (1997-05-29) page 4, line 18-20 page 6, line 22-30 examples 11-14 claims 7,8 --- -/--	1,4

☒ Further documents are listed in the continuation of box C.

☒ 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

17 January 2002

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INTERNATIONAL SEARCH REPORT

International Application No

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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.
X	WO 99 07692 A (KLAR ULRICH ; SCHERING AG (DE); BUCHMANN BERND (DE); SKUBALLA WERNE) 18 February 1999 (1999-02-18)	2
Y	page 3, line 25 -page 5, line 33 page 40, line 1 -page 53, line 17 example 1 claims 9,17,27 ----	3
A	WO 99 27890 A (SQUIBB BRISTOL MYERS CO) 10 June 1999 (1999-06-10) the whole document ----	1,3,4
A	NICOLAOU K C ET AL.: "Total syntheses of epothilones A and B via a macrolactonization-based strategy." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 34, 1997, pages 7974-7991, XP002095719 ISSN: 0002-7863 cited in the application schemes 1,3,5,7,9 ----	1-4
A	NICOLAOU K C ET AL.: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833 the whole document schemes 10-13 -----	1-4

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 II Observations where unity of invention is lacking (Continuation of item 2 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. Claim : 1 (partially)

A process for preparing a compound represented by formula I comprising treating an epothilone compound of formula III with an enzyme to form a compound represented by formula VI, optionally esterifying the carboxyl group of said compound, optionally reacting the resulting esterified compound to form protecting groups on the hydroxyl groups of said compound, and reacting the resulting compound with a suitable oxidizing agent to form a compound represented by formula I.

2. Claim : 1 (partially)

A process for preparing a compound represented by formula I comprising treating an epothilone compound of formula IV with an enzyme to form a compound represented by formula VI, optionally esterifying the carboxyl group of said compound, optionally reacting the resulting esterified compound to form protecting groups on the hydroxyl groups of said compound, and reacting the resulting compound with a suitable oxidizing agent to form a compound represented by formula I.

3. Claims: 2, 3 (both completely)

A process for preparing a compound represented by formula II comprising reacting a compound represented by formula I with a compound represented by formula IX to form a compound represented by formula X, and hydrolyzing the ester group on said compound in the presence of a suitable base to form a compound represented by formula II.

A process for preparing a compound represented by formula II comprising treating an epothilone compound of formula III or IV with an enzyme to form a compound represented by formula VI, esterifying the carboxyl group of said compound, reacting the resulting esterified compound to form protecting groups on the hydroxyl groups of said compound, reacting the resulting compound with a suitable oxidizing agent to form a compound represented by formula I, reacting said compound with a compound represented by formula IX to form a compound represented by formula X, and hydrolyzing the ester group on said compound in the presence of a suitable base to form a compound represented by formula II.

4. Claim : 4 (completely)

A process for preparing a compound represented by formula I

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

comprising treating an epothilone compound represented by formula XV with an enzyme to form a compound represented by formula XVI, esterifying the carboxyl group of said compound to form an ester compound represented by formula XVII, hydrolyzing the ester compound to form a diol compound represented by XVIII, reacting the diol compound with a suitable oxidizing agent to form a compound represented by formula I.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/09620

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9954319	A	28-10-1999	AU 3382799 A	08-11-1999
			AU 3471699 A	08-11-1999
			BR 9909795 A	26-12-2000
			CN 1298398 T	06-06-2001
			EP 1073647 A1	07-02-2001
			EP 1073648 A1	07-02-2001
			TR 200003036 T2	22-01-2001
			WO 9954318 A1	28-10-1999
			WO 9954319 A1	28-10-1999
WO 9719086	A	29-05-1997	DE 19542986 A1	22-05-1997
			DE 19639456 A1	26-03-1998
			WO 9719086 A1	29-05-1997
			EP 0873341 A1	28-10-1998
			EP 0903348 A1	24-03-1999
			JP 2000500757 T	25-01-2000
			US 6288237 B1	11-09-2001
			US 2001034452 A1	25-10-2001
WO 9907692	A	18-02-1999	DE 19735574 A1	11-02-1999
			DE 19735575 A1	11-02-1999
			DE 19735578 A1	11-02-1999
			DE 19748928 A1	29-04-1999
			DE 19749717 A1	06-05-1999
			DE 19751200 A1	20-05-1999
			DE 19813821 A1	23-09-1999
			AU 9340998 A	01-03-1999
			WO 9907692 A2	18-02-1999
			EP 1005465 A2	07-06-2000
			JP 2001512723 T	28-08-2001
WO 9927890	A	10-06-1999	AU 739380 B2	11-10-2001
			AU 1613499 A	16-06-1999
			EP 1035824 A1	20-09-2000
			WO 9927890 A2	10-06-1999