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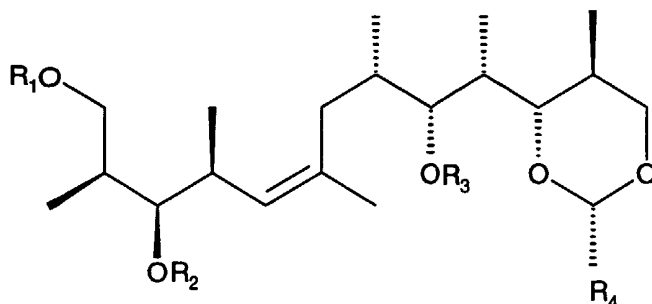
— with international search report

(88) Date of publication of the international search report:

10 October 2002

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 PREPARING INTERMEDIATES FOR THE MANUFACTURE OF DISCODERMOLIDE AND DISCODERMOLIDE ANALOGUES



(I)

(57) Abstract: The invention relates to a process for the preparation of a substituted alkene of formula (I) wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are independently of each other a protecting group for a hydroxy group or hydrogen and R<sub>4</sub> is phenyl which is unsubstituted or mono- or disubstituted by alkoxy, which alkene constitutes an intermediate for the preparation of discodermolide and discodermolide analogues.



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/00570

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D319/12 C07D263/26 C07D309/10

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 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, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BURKE ET AL.: "An alternative route to the C(7)-C(13) subunit of erythronolide B via a hydropyran template" TETRAHEDRON LETT., vol. 28, no. 36, 1987, pages 4147-4148, XP001062534 reaction of compound 12 to compound 13, step (p)	1,4-7, 10,16
Y	reaction of compound 12 to compound 13, step (n)	2,4-7, 10,16
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 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.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

5 July 2002

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2002.07.02

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/00570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAGASAWA K ET AL: "Total Synthesis of Preswinholide A. 2. Completion of the Synthesis" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 38, 16 September 1996 (1996-09-16), pages 6885-6888, XP004030775 ISSN: 0040-4039 scheme, reaction step g page 6886	2,4-7, 10,16
A	A. B. SMITH III ET AL.: "Evolution of a Gram-Scale Synthesis of (+)-Discodermolide" J. AM. CHEM. SOC., vol. 122, - 26 August 2000 (2000-08-26) pages 8654-8664, XP002194754 cf. scheme 9	3,8,9,11
A	FILLA S A ET AL: "Synthesis of C1-C8 and C9-C24 fragments of (-)-discodermolide: use of asymmetric alkylation and stereoselective aldol reactions" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 40, no. 30, July 1999 (1999-07), pages 5449-5453, XP004171484 ISSN: 0040-4039 cf. scheme 4 (reaction of 9b to 11)	3,8,9,11
A	SMITH A B ET AL: "TOTAL SYNTHESIS OF (-)-DISCODERMOLIDE" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 117, 1995, pages 12011-12012, XP001018841 ISSN: 0002-7863 cf. scheme 6	3,8,9,11
A	WO 98 48791 A (YANG GE ;MYLES DAVID C (US); HARRIED SCOTT S (US); UNIV CALIFORNIA) 5 November 1998 (1998-11-05) Figure 3, compound 15, abstract the whole document	1-14,16, 17
A	US 5 789 605 A (KOBAYASHI KAORU ET AL) 4 August 1998 (1998-08-04) Figure 3, compound (+)-10 abstract	12-14,17

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/00570

## 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.: 15  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
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

Continuation of Box I.2

Claims Nos.: 15

The following stated with regard to the second invention, i.e. claims 12-15, 17:

In the case of claim 15 the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of this claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Consequently, the search has been restricted to claims 12-14 and 17.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. Claims: 1-11,16

Process for the preparation of (I), intermediates/precursors taking part in this process and the usage of the intermediates therein

2. Claims: 12-15,17

Intermediates in the process for the preparation of discodermolide and analogues thereof, an process for the preparation of these intermediates and intermediates of these intermediates.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/00570

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9848791	A	05-11-1998	AU	7267298 A	24-11-1998
			WO	9848791 A1	05-11-1998
US 5789605	A	04-08-1998	EP	0969829 A1	12-01-2000
			JP	2001515466 T	18-09-2001
			US	6031133 A	29-02-2000
			WO	9824429 A1	11-06-1998
			US	6096904 A	01-08-2000
			US	6242616 B1	05-06-2001