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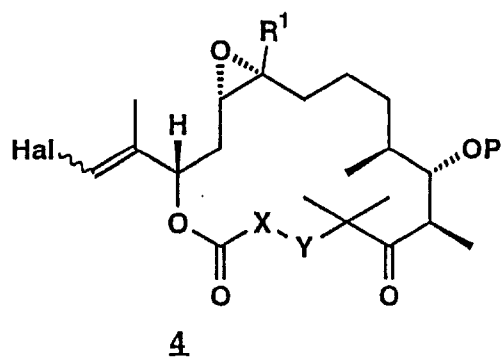
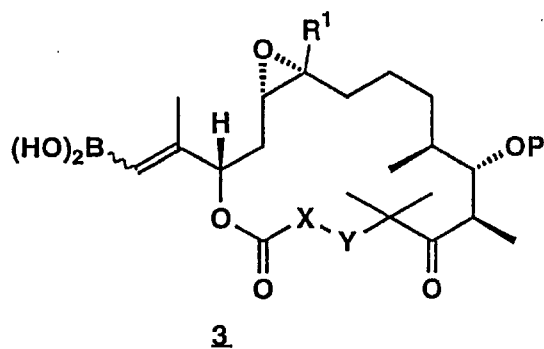
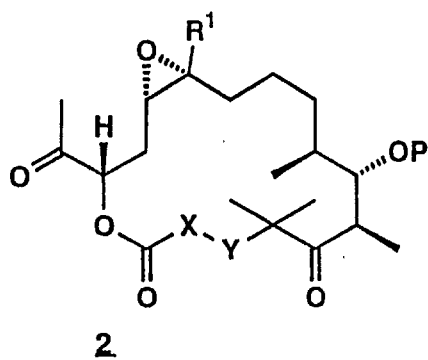


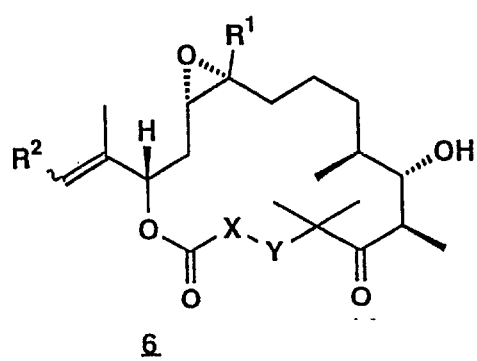
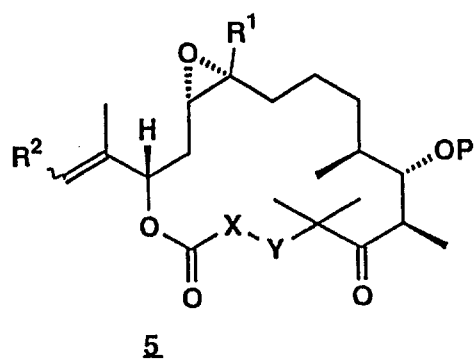
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**EPOTHILONE DERIVATIVES, A METHOD FOR THE PRODUCTION THEREOF,
AND THEIR USE**

The present invention relates generally to epothilon derivatives, to processes for their production and to their use in the manufacture of medicaments and plant protection agents. The invention relates especially to epothilon derivatives of the general formulae 2 to 6 shown below and to their use as medicaments and plant protection agents.

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In the above formulae:

R^1 = a H atom or a C_1 - to C_8 -alkyl group, preferably a C_1 - to C_6 -alkyl group, especially preferably a C_1 - to C_4 -alkyl group, especially a methyl, ethyl, propyl or butyl group,

R^2 = a monocyclic aromatic group, such as a 5- or 6-membered aromatic group (such as a phenyl ring) or a vinyl group, each of which may be substituted in the ortho- and/or meta- and/or para-position(s) by one, two, three, four or five, especially one or two, halogen atoms and/or OR^4 and/or NR^5R^6 groups and/or alkyl and/or alkenyl and/or alkynyl groups, wherein R^4 , R^5 and R^6 each independently of the others have the same meanings as R^1 , but are independent of R^1 , or

R^2 = a monocyclic 5- or 6-membered heteroaromatic group which may have one or more, especially one or two, O and/or N and/or S atoms in the ring and/or may have OR^4 and/or NR^5R^6 groups and/or alkyl and/or alkenyl and/or alkynyl groups as substituents, wherein R^4 , R^5 and R^6 are as defined above. In the definition of R^2 there are especially preferred C_1 - C_6 -alkyl or C_2 - C_6 -alkenyl and -alkynyl groups, especially C_1 - C_4 -alkyl or C_2 - C_4 -alkenyl and -alkynyl groups. As alkyl groups there are especially preferred methyl, ethyl, propyl and butyl groups and as heteroaromatic groups 6-membered heteroaromatic groups,

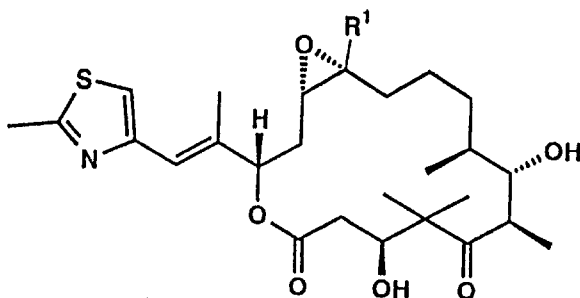
Hal = a halogen atom, such as Br or I,

X-Y = a group of the formula $-CH_2CH-OP$ or $-CH=CH-$, and

P = a protecting group, such as TMS.

The compounds according to the invention may be produced as follows:

Compounds of the formula (2) may be produced by reacting compounds of the formula (1)



as described in DE 195 42 986, the radicals being as defined above. In that reaction, especially the following conditions (i), (iii) and optionally (after (i)) also (ii) may be used:

- (i) (a) O_3 in a solvent, such as CH_2Cl_2 , and
(b) reductive working-up, for example with Me_2S ;
- (ii) (a) $(CH_3CO)_2O$, HCO_2H , NEt_3 , DMAP;
(b) DBU; and
(c) $MeOH$, NH_3 ; and
- (iii) Me_3SiCl , NEt_3 .

Compounds of the formula (3) are obtainable by reacting a compound of the formula (2) with a compound of the formula $HC[B(OR)_2]_3$, such as tris(ethylenedioxyboryl)methane; R may be an alkyl or alkenyl group as defined above.

In the reaction there is optionally used a strong base, such as a C_1 - C_4 -alkyl-Li compound (such as butyllithium) or a di- C_1 - C_4 -alkylamine-Li compound (such as a dimethylamine-lithium compound). The reaction is generally carried out at low temperatures, such as, for example, at temperatures of

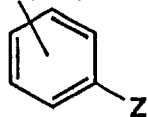
less than -30°C , preferably at temperatures of less than -50°C , especially preferably at temperatures of at least -78°C . Further reaction conditions may be found in D. Schummer, G. Höfle in *Tetrahedron* 1995, 51, 11219.

For example, a compound of the formula (2) is reacted with tris(ethylenedioxyboryl)methane and butyllithium at -78°C to form a compound of the formula (3).

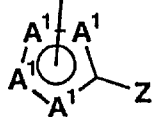
A compound of the formula (4) may be produced from a compound of the formula (3) by reaction with N-iodo- or N-bromo-succinimide, optionally in a polar solvent, such as acetonitrile. Further reaction conditions may be found in the following literature reference: N.A. Petasis, I.A. Zavialor, *Tetrahedron Lett.* 1996, 37, 567.

For the production of a compound of the formula (5), a compound of the formula (3) may be reacted within the framework of a Suzuki coupling with a compound of the formula $\text{R}^2\text{-Z}$, wherein R^2 has the meanings given above and Z may be a halogen atom or a group of the formula $-\text{OSO}_2\text{CF}_3$, $-\text{CH}=\text{CHI}$, $-\text{CH}=\text{CHOSO}_2\text{CF}_3$. The group $\text{R}^2\text{-Z}$ may especially have the following structures:

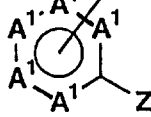
O-, N-, C-Subst.



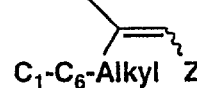
H-, O-, N-, C-Subst.



H-, O-, N-, C-Subst.



H-, O-, N-, C-Subst.

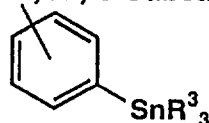


wherein A^1 represents O, S, N or C atoms and the substituents O-, N- and C- correspond to the above-described groups OR^4 , NR^5R^6 and alkyl, alkenyl and/or alkynyl groups.

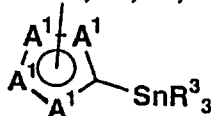
Especially preferred as substituents "C" are C_1 - C_6 -alkyl or C_2 - C_6 -alkenyl and/or -alkynyl groups, especially C_1 - C_4 -alkyl or C_2 - C_4 -alkenyl and/or -alkynyl groups. As alkyl groups there are especially preferred methyl, ethyl, propyl and butyl groups.

Alternatively, a compound of the formula (5) may be produced by reacting a compound of the formula (4) by means of a Stille coupling with R^2 - SnR^3_3 , wherein R^2 is as defined above and R^3 is a C_1 - to C_6 -alkyl group, preferably a C_1 - to C_4 -alkyl group and especially preferably a methyl, ethyl, propyl or butyl group. In addition, the compound R^2 - SnR^3_3 may have one of the following structures:

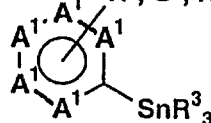
O-, N-, C-Subst.



H-, O-, N-, C-Subst.



H-, O-, N-, C-Subst.



wherein the radicals and substituents are as defined above.

Furthermore, according to the invention, a compound of the formula (6) may be produced by removing the protecting group from the compound of the formula (5), for example with a weak acid, such as citric acid, or compounds such as TBAF, pyridine x HF. Optionally an alcohol, such as methanol, may be used as solvent, the temperature preferably being adjusted to values of, for example, from 40 to 60°C, preferably about 50°C.

In summary, the compound of the formula (6) may be produced by the above-described steps (epothilon A or B $\rightarrow$ (2) $\rightarrow$ (3) $\rightarrow$ (4) $\rightarrow$ (5) $\rightarrow$ (6) or epothilon A or B $\rightarrow$ (2) $\rightarrow$ (3) $\rightarrow$ (5) $\rightarrow$ (6)).

According to the invention there are also disclosed medicaments that contain at least one of the compounds (2), (3), (4), (5) or (6) and optionally customary carriers, diluents and adjuvants.

Such compounds may especially be used also as cytostatic agents and for plant protection in agriculture and/or forestry and/or in horticulture, the compounds optionally being used together with one or more customary carriers, adjuvants and/or diluents.

Examples

Synthesis of the ketone derivatives 2

For a detailed description see DE 195 42 986 A1.

Synthesis of the alkenylboronic acid derivatives 3

(see also D. Schummer, G. Höfle, *Tetrahedron* 1995, 51, 11219)

Typical Example ($R^1 = H$, X-Y = $CH_2CHOTMS$):

A solution of tris(ethylenedioxyboryl)methane (0.30 g, 1.5 mmol) in CH_2Cl_2 /THF (1:1; 4 ml) was prepared and cooled under inert gas to $-78^\circ C$. At that temperature, butyllithium (1.6M solution in hexane; 0.73 ml, 1.2 mmol) was added drop-

wise in the course of 10 minutes. After 2 hours, ketone 2 (81 mg, 0.15 mmol) in $\text{CH}_2\text{Cl}_2/\text{THF}$ (1:1, 2 ml) was added, heated to room temperature and stirred for 17 hours. After the addition of MeOH (2 ml), the clear reaction solution was purified by means of preparative HPLC (Lichroprep RP-18, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 75 : 25). 57 mg (65 %) of alkenylboronic acid 3 were obtained in the form of an E/Z-isomeric mixture (6 : 4).

Selected typical data: LC-MS (ESI-MS): 585 ($\text{M}^+ + \text{H}$); ^1H -NMR: (300 MHz, CD_3OD): E-isomer: 1.91 (s, 3H), 5.16 (d, 1H, 10 Hz), 5.49 (s, 1H), Z-isomer; 1.85 (d, 3H, 1.1 Hz), 4.93 (s, 1H), 5.26 (d, 1H, 9.6 Hz).

Synthesis of the iodovinyl derivatives 4

(see also N.A. Petasis, I.A. Zavialor, *Tetrahedron Lett.* 1996, 37, 567)

Typical Example ($\text{R}^1 = \text{H}$, X-Y = CH_2CHOTMS):

At room temperature, N-iodosuccinimide (6.0 mg, 27 μmol) was added under inert gas and with the exclusion of light to a solution of alkenylboronic acid 3 (12 mg, 21 μmol ; E/Z 9:1) in CH_3CN (150 μl) and stirred for 3 hours. After concentration, the residue was purified by means of preparative thin-layer chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95 : 5). 9 mg (66 %) of the iodovinyl derivative 4 were isolated in the form of an E/Z-isomeric mixture (9:1).

Selected typical data: LC-MS (ESI-MS): 667 ($\text{M}^+ + \text{H}$); ^1H -NMR: (300 MHz, CDCl_3): E-isomer: 1.82 (d, 3H, 1.1 Hz), 5.36 (d, 1H, 11 Hz), 6.43 (s, 1H), Z-isomer: 1.84 (d, 3H, 1.1 Hz), 5.54 (d, 1H, 10.5 Hz), 6.09 (s, 1H).

Suzuki coupling of the alkenylboronic acid 3

(see also A. Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178; A. Torrado, S. Lopez, R. Alvarez, A.R. De Lera *Synthesis*, **1995**, 285)

Typical Example ($R^1 = H$, $X-Y = CH_2CHOTMS$, $R^2 = Ph$):

A solution of alkenylboronic acid 3 (12 mg, 21 μ mol; E/Z 2 : 8) and thallium ethanolate (2M solution in EtOH; 12 μ l, 24 μ mol) in THF (150 μ l) was stirred at room temperature for 15 minutes, then a solution of phenyl iodide (4.0 μ l, 6.0 mg, 29 μ mol) and tetrakis(triphenylphosphino)-palladium (7.1 mg, 6.2 μ mol) in THF (150 μ l) was added dropwise in 30 minutes and again stirred for 30 minutes. After purification by means of preparative thin-layer chromatography (SiO_2 , CH_2Cl_2/Et_2O 95 : 5) the phenyl-analogous epothilon 5 (10 mg, 79 %, E/Z 2 : 8) was obtained in the form of a colourless solid.

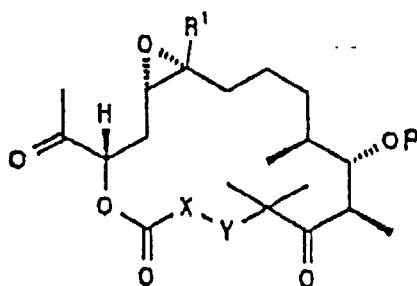
Selected typical data: LC-MS (ESI-MS): 617 ($M^+ + H$); 1H -NMR: (300 MHz, $CDCl_3$): E-isomer: 1.87 (d, 3H, 1.4 Hz), 5.35 (d, 1H, 10.7 Hz), 6.54 (s, 1H), Z-isomer: 1.80 (d, 3H, 1.5 Hz), 5.61 (d, 1H, 10.2 Hz), 6.41 (s, 1H).

Stille coupling of the iodovinyl derivatives 4

(see also K.C. Nicolaou, Y. He, F. Roschangar, N.P. King, D. Vourloumis, T. Li *Angew. Chem.* **1998**, *110*, (1/2), 89)

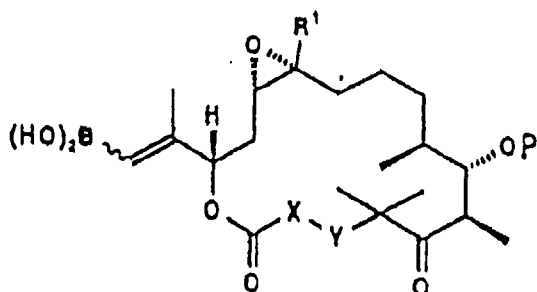
Patent Claims

1. Epothilone derivative of formula (2)



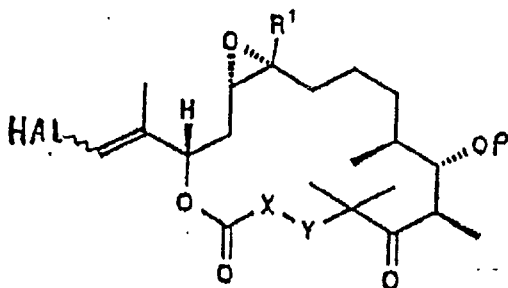
wherein R^1 is a hydrogen atom or a C_{1-8} -alkyl group, X-Y is a group of formula $-CH_2CH-OP$ or $-CH=CH-$, and P is a protective group, wherein X-Y is excluded as group of formula $-CH_2CH-OP$ if R^1 means a hydrogen atom or a C_{1-4} -alkyl group.

2. Epothilone derivative of formula (3)



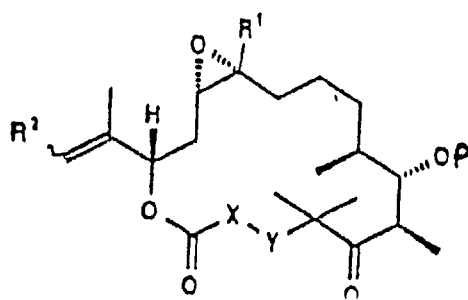
wherein the residues are as defined in claim 1.

3. Epothilone derivative of formula (4)



wherein the residues R^1 , X-Y and P are defined as in claim 1, and Hal is a halogen atom such as Br or I.

4. Epothilone derivative of formula (5)

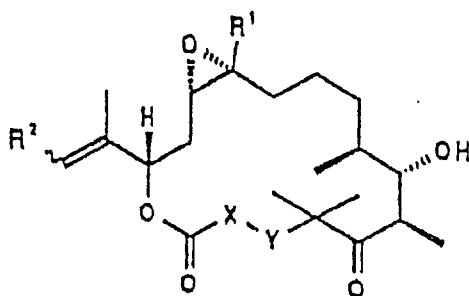


wherein the residues R^1 , X-Y and P are defined as in claim 1, and R^2 is a monocyclic aromatic which can be substituted by a halogen atoms and/or OR^4 - and/or NR^5R^6 - and/or alkyl, alkenyl and/or alkynyl groups in ortho- and/or meta- and/or para-position, or a monocyclic 5- or 6-membered hetero aromatic, which can be provided with one or several O- and/or N- and/or S-atoms in the ring and/or which can be provided with OR^4 - and/or NR^5R^6 - and/or alkyl, alkenyl and/or alkynyl groups as substituents, wherein the residues R^4 , R^5 and R^6 independently are defined as R^1 in claim 1, but are independent of R^1 , wherein

(i) XY is excluded as group of formula $-CH=CH-$ if R^1 is a hydrogen atom or a C_{1-4} -alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1 -alkyl substituent and

(ii) X-Y is excluded as group of formula $-CH_2-CH-OP$ if R^1 is a hydrogen atom or a C_{1-4} -alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1 -alkyl substituent.

5. Epothilone derivative of formula (6)



wherein the residues are defined as in claim 4 and, if X-Y means a group of formula $-\text{CH}_2\text{CH}-\text{OP}$, the protective group P has been removed, wherein

(i) XY is excluded as group of formula $-\text{CH}=\text{CH}-$ if R^1 is a hydrogen atom or a C_{1-4} -alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1 -alkyl substituent and

(ii) X-Y is excluded as group of formula $-\text{CH}_2-\text{CH}-\text{OP}$ if R^1 is a hydrogen atom or a C_{1-4} -alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1 -alkyl substituent.

6. Epothilone derivative according to any of the preceding claims, **characterized** in that R^1 , R^4 , R^5 and R^6 are a hydrogen atom or a C_{1-6} -alkyl group, especially a C_{1-6} -alkyl group.

7. Epothilone derivative according to any of claims 4 to 6, **characterized** in that the substituents of the monocyclic aromatic and/or hetero aromatic are C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkinyl groups, respectively, especially C_{1-4} -alkyl, C_{2-4} -alkenyl and C_{2-4} -alkinyl groups, respectively and the halogen atoms fluoro, chloro, bromo or iodo atoms.

8. Epothilone derivatives according to any of claims 4 to 7, **characterized** in that the aromatic and hetero aromatic, respectively, is provided with 1, 2 or 3 substituents and the hetero aromatic is provided with 1, 2 or more and especially 1, 2, 3, or 4 hetero atoms.

9. Process for the production of a compound of formula (3),

characterized in that a compound of formula (2) is reacted with the compound of formula $\text{HC}[\text{B}(\text{OR})_2]_3$ if wanted in the presence of a base, wherein the residues are defined as in any of the preceding claims and R is defined as R^1 , but is independent of R^1 .

10. Process for the production of a compound of formula (4), characterized in that a compound of formula (3) is reacted with N-iodo- or N-bromo succinimide and that the residues are defined as in any of the preceding claims.

11. Process for the production of a compound of formula (5), characterized in that a compound of formula (3) is reacted by a Suzuki coupling with a compound of formula $\text{R}^2\text{-Z}$, wherein R^2 is defined as in any of the preceding claims and Z can be a halogen atom or a group of formula $-\text{OSO}_2\text{CF}_3$, $-\text{CH}=\text{CHI}$, $-\text{CH}=\text{CHOSO}_2\text{CF}_3$.

12. Process for the production of a compound of formula (5), characterized in that a compound of formula (4) is reacted by a silent coupling (stille Kupplung) with $\text{R}^2\text{-SNR}^3$, wherein R^2 is defined as in any of the preceding claims and R^3 is a C_{1-6} -alkyl group, especially a C_{1-4} -alkyl group, preferably a methyl, ethyl, propyl or butyl group.

13. Process for the production of a compound of formula (6), characterized in that the protective group is removed from a compound of formula (5).

14. Process for the production of a compound of formula (6), characterized in that it comprises the process steps as disclosed in claims 9, 10, 11 or 12 and 13, wherein the residues are defined as in the preceding claims.

15. Therapeutical agent, containing at least one of the compounds described in claims 1 to 8 and optionally usual carriers, diluents and/or auxiliary agents.

16. Therapeutical agent according to claim 15, **characterized** in that it is a cytostaticum.

17. Plant protecting agent in agriculture and/or forest culture and/or horticulture, containing at least one compound described in claims 1 to 8 and optionally usual carriers, diluents and/or auxiliary agents.