24 February 1998/pl

Our references: 9200, 9201, 9202 and 9203
Gesellschaft fuer Biotechnologische Forschung mbH (GBF)
Reichenbach et al.; Epothilones which are modified in the side chain

Epothilones which are modified in the side chain

Epothilones A and B have been disclosed; cf., for example, DE 4 138 042 and PCT/EP 96/05 080.

The invention now relates to a process for the preparation of epothilones which are modified in the 16,17-position, in which process the starting materials are 3,7-protected or unprotected epothilones A or B and

a) these are hydrogenated on the 16,17-double bond or

b) subjected to an addition reaction with halogen on the 16,17-double bond or

c) epoxidized on the 16,17-double bond and, if appropriate, the resulting epoxide is reduced to give the 16-alcohol.

The process according to the invention may be characterized in that,

- in method (a), hydrogenation is effected with diimine or hydrogen and a heterogeneous or homogeneous metal catalyst or
- in method (c), epoxidation is effected with a peracid or a dioxirane.

This Sheet Has Been Replaced



REPLACED SHEETS SG
☑ Description : paged ...1... to paged ...10...
☑ Claim(s) : paged ...11... to paged ...13...
☐ Drawing(s) : paged ...—... to paged ...—...
☐ Abstract : paged ...—... to paged ...—...

Furthermore, the invention concerns a process for the preparation of 2,3-unsaturated epothilone N-oxides in which either (i) 3,7-protected epothilones A or B are converted into an N-oxide in a manner known per se and, the 3-substituent is eliminated by a base to give the 2,3-double bond, or (ii) 7-protected or 7-unprotected epothilones A or B which have a double bond in the 2,3-position are converted into an N-oxide in a manner known per se and,

if appropriate, the resulting N-oxide is subjected to O-alkylation and an O-alkylation product is obtained.

Furthermore, the invention relates to a process for the preparation of epothilone N-oxides in which 3,7-protected or unprotected epothilones A or B are converted into an N-oxide in a manner known per se and, if appropriate, the resulting N-oxide is subjected to O-alkylation and an O-alkylation product is obtained.

This process according to the invention may be characterized in that N-oxidation is performed with peracid or a dioxirane and electrophilic alkyl, aryl or heteroaryl reagents, in particular methyl iodide or trimethyloxonium tetrafluoroborate, are used for the optional O-alkylation.

This Sheet Has Been Replaced



Furthermore, this process according to the invention may be characterized in that a resulting N-oxide is subjected to a Katada reaction, in particular as described in Houben-Weyl, Volume E7b, page 646.

Furthermore, this process according to the invention may be characterized in that the Katada reaction is performed with an activated carboxylic acid derivative, in particular carboxylic anhydride or carboxylic acid chloride.

Furthermore, this process according to the invention may be characterized in that the Katada reaction is carried out with acetic anhydride and, if appropriate, the 21-acetoxyepothilones obtained are cleaved in a manner known per se to give 21-hydroxyepothilones A or B (epothilones E and F, respectively).

Furthermore, this process according to the invention may be characterized in that the optional cleavage process is performed hydrolytically or enzymatically.

Furthermore, the invention relates to a process for the preparation of epothilones which are modified in the C19-position, in which process 3,7-protected or unprotected epothilones A or B are metalated in the C19-position and captured with electrophilic reagents in a manner known per se as alkyl-, aryl-, heteroaryl-, halogen-, oxygen- or sulphur-substituted epothilones which are modified in the C19-position.

This process according to the invention may be characterized in that metalation is performed using butyllithium.

Furthermore, the invention relates to a process for the preparation of epothilones which are modified in the C27-position, in which process the allyl group (C17, C16 and C27) is substituted in a manner known per se on the C27-methyl group by a hetero atom.

This process according to the invention may be characterized in that the C27-methyl group is substituted by a bromine atom, in particular with the aid of N-bromosuccinimide, and, if appropriate, the resulting bromide

This Sheet Has Been Replaced

This Sheet Has Been Replaced

is converted into a C27-hydroxy compound.

Finally, the invention relates to compounds prepared by the process according to the invention.

Experiment 1: **Diepoxyepothilone A. 1a)**

A solution of epothilone A (5 mg, 10 µmol) in acetone (1 ml) was treated at 0°C with dimethyldioxirane (0.4 ml, 28 µmol, 0.07 M in acetone). The solution was brought to room temperature in the course of a few hours and was stirred for 20 hours at this temperature. Since TLC confirmed that starting material was still present, more dimethyldioxirane (0.25 ml, 17 µmol) was added, and the reaction mixture was again stirred for 20 hours at room temperature. The solvent was removed and the residue was purified by means of PLC (0.25 x 200 x 200 mm, 10% MeOH:CH_2Cl_2). The following were isolated:

1. 1.4 mg (27%) of diepoxyepothilone A (3:2 epimer mixture on C16-C17). R_f 0.63 (10% MeOH:CH_2Cl_2); R_f: 6.79 (isomer 1) and 7.39 (isomer 2) min (RP 18, 250 x 4 mm, MeOH:H_2O 65:35, 1 ml/min); MS: (m/z) = 510 (M^+); ^1H NMR (400 M_3Hz, $CDCl_3$, selected signals, isomer 1): δ = 6.96 (s, 1H, H-19), 5.48 (dd, J = 12.2 and 2.5 Hz, 1H, H-15), 4.37 (dbr, J = 10.7 Hz, 1H, H-3), 4.10 (s, 1H, H-17), 3.67 (dd, J = 5.6 and 2.5 Hz, 1H, H-7), 3.14 (qd, J = 6.6 and 2.5 Hz, 1H, H-6), 3.00 (ddd, J = 9.7, 3.6 and 2.5 Hz, 1H, H-13), 2.88 (dt, J = 8.6 and 3.6 Hz, 1H, H-12), 2.71 (s, 3H, H-21), 2.53 (dd, J = 13.7 and 11.7 Hz, 1H, H-2a), 1.41 (s, 3H, H-22), 1.27 (s, 3H, H-26), 1.17 (d, J = 6.6 Hz, 3H, H-24), 1.08 (s, 3H, H-23), 0.97 (d, J = 7.1 Hz, 3H, H-25); (isomer 2) δ = 6.98 (s, 1H, H-19), 5.11 (dd, J = 11.7 and 2.5 Hz, 1H, H-15), 4.27 (dbr, J = 10.7 Hz, 1H, H-3), 4.14 (s, 1H, H-17), 3.06 (qd, J = 6.6 and 2.9 Hz, 1H, H-6), 2.96 (ddd, J = 9.7, 3.6 and 2.5 Hz, 1H, H-13), 2.31 (dt, J = 14.7 and 2.0 Hz, 1H, H-14a), 1.36 (s, 3H, H-22), 1.15 (d, J = 6.6 Hz, 3H, H-24), 1.14 (s, 3H, H-26), 1.07 (s, 3H, H-23).

2. 0.8 mg (16%) of epothilone A N-oxide. R_f 0.44 (10% MeOH:CH_2Cl_2); R_f: 4.25 min (RP 18, 250 x 4 mm, MeOH:H_2O 65:35, 1 ml/min); MS: (m/z) = 510 (M^+); ^1H NMR: see

This Sheet Has Been Replaced

method 1

Experiment 2: **Dihydroepothilone A. (1c)**

Palladium on charcoal (5 mg, 10%) was added to a solution of epothilone A (11 mg, 22 µmol) in ethanol (2 ml) and the black suspension was exposed to an H_2 atmosphere for 24 hours at room temperature. Since TLC indicated that the reaction was not yet complete, a further portion of Pd/C was added and the reaction mixture was stirred for a further 20 hours under an H_2 atmosphere. The products were separated by means of PLC (1 x 200 x 200 mm, 10% MeOH:CH_2Cl_2). The following were isolated:

1. 0.5 mg (5%) of dihydroepothilone A. R_f 0.60 (10% MeOH:CH_2Cl_2); R_f: 10.80 min (RP 18, 250 x 4 mm, MeOH:H_2O 65:35, 1 ml/min); MS: (m/z) = 496 (M^+), 478, 407, 308; ^1H NMR (400 MHz, $CDCl_3$, selected signals): δ = 7.05 (d, J = 6.6 Hz, 1H, OH), 6.77 (s, 1H, H-19), 5.23 (dd, J = 12.4 and 2.3 Hz, 1H, H-15), 4.42 (ddd, J = 11.7, 6.6 and 3.0 Hz, 1H, H-3), 3.70 (ddd, J = 5.3 and 2 Hz, 1H, H-7), 3.12 (qd, J = 6.6 and 3.0 Hz, 1H, H-6), 3.07 (d, J = 12.7 Hz, 1H, H-17a), 2.96 (ddd, J = 9.7, 3.6 and 2.0 Hz, 1H, H-13), 2.91 (ddd, J = 9.7, 3.6 and 2.6 Hz, 1H, H-12), 2.68 (s, 3H, H-21), 2.51 (dd, J = 13.7 and 11.7 Hz, 1H, H-2a), 2.24 (d, J = 12.7 Hz, 1H, H-17b), 2.19 (m, 1H, H-16), 2.13 (dd, J = 13.7 and 3.0 Hz, 1H, H-2b); 1.35 (s, 3H, H-22), 1.15 (d, J = 6.6 Hz, 3H, H-24), 1.09 (s, 3H, H-23), 0.99 (d, J = 7.1 Hz, 3H, H-25), 0.93 (d, J = 6.6 Hz, 3H, H-26).

2. 8 mg (72%) of 15-deoxydihydroepothilonic acid. R_f 0.10 (10% MeOH:CH_2Cl_2).

Experiment 3: **16-Hydroxyepothilone A. (1b)**

Palladium on charcoal (10 mg, 10%) was added to a solution of diepoxyepothilone A (7 mg, 14 µmol), 1:1 epimer mixture on C-16) in ethanol (2 ml) and the black suspension was exposed to an H_2 atmosphere for 24 hours at room temperature. Since TLC indicated that the reaction was not yet complete, a further portion of Pd/C was added and the reaction mixture was stirred for a further 80 hours

This Sheet Has Been Replaced

under an H_2 atmosphere. The products were separated by means of PLC (1 x 200 x 200 mm, 10% MeOH:CH_2Cl_2). The following were isolated:

1. 3 mg (43%) of 16-hydroxyepothilone A (isomer 1). R_f 0.38 (10% MeOH:CH_2Cl_2); R_f: 6.65 min (RP 18, 250 x 4 mm, MeOH:H_2O 65:35, 1 ml/min); ^1H NMR (400 MHz, $CDCl_3$, selected signals): δ = 6.85 (s, 1H, H-19), 5.02 (dd, J = 11.7 and 2.0 Hz, 1H, H-15), 4.38 (dbr, J = 11.2 Hz, 1H, H-3), 3.67 (dd, J = 4 and 3 Hz, 1H, H-7), 3.14 (qd, J = 6.8 and 3.0 Hz, 1H, H-6), 2.95 (d, J = 15.3 Hz, 1H, H-17a), 2.89 (d, J = 15.3 Hz, 1H, H-17b), 2.89 (ddd, J = 10.2, 3.6 and 2.0 Hz, 1H, H-13), 2.81 (ddd, J = 9.7, 3.6 and 2.5 Hz, 1H, H-12), 2.70 (s, 3H, H-21), 2.53 (dd, J = 15.8 and 11.7 Hz, 1H, H-2a), 2.14 (dd, J = 15.8 and 2.0 Hz, 1H, H-2b), 2.08 (dt, J = 14.3 and 2.0 Hz, 1H, H-14a), 1.39 (s, 3H, H-22), 1.25 (s, 3H, H-26), 1.19 (d, J = 6.6 Hz, 3H, H-24), 1.05 (s, 3H, H-23), 0.99 (d, J = 7.1 Hz, 3H, H-25).

2. 3 mg (43%) of 16-hydroxyepothilone A (isomer 2). R_f 0.31 (10% MeOH:CH_2Cl_2); R_f: 6.10 min (RP 18, 250 x 4 mm, MeOH:H_2O 65:35, 1 ml/min); ^1H NMR (300 MHz, $CDCl_3$, selected signals): δ = 6.85 (s, 1H, H-19), 5.21 (dd, J = 11.3 and 1.9 Hz, 1H, H-15), 4.42 (dbr, J = 10.5 Hz, 1H, H-3), 3.71 (sbr, 1H, H-7), 3.21 (d, J = 14.3 Hz, 1H, H-17a), 3.13 (qd, J = 6.8 and 3.0 Hz, 1H, H-6), 3.09 (dt, J = 9.8 and 3.4 Hz, 1H, H-13), 2.87 (dt, J = 9.4 and 3.0 Hz, 1H, H-12), 2.73 (d, J = 14.3 Hz, 1H, H-17b), 2.68 (s, 3H, H-21), 2.63 (dd, J = 16.6 and 11.7 Hz, 1H, H-2a), 2.27 (dt, J = 14.7 and 2.3 Hz, 1H, H-14a), 2.24 (dd, J = 16.6 and 2.6 Hz, 1H, H-2b), 1.39 (s, 3H, H-22), 1.22 (s, 3H, H-26), 1.19 (d, J = 6.8 Hz, 3H, H-24), 1.05 (s, 3H, H-23), 0.99 (d, J = 7.2 Hz, 3H, H-25).

Epothilone A N-oxide (2a): 100 mg of 70% *m*-chloroperbenzoic acid in 0.5 ml of dichloromethane were added to 100 mg of epothilone A in 1 ml of dichloromethane. After the mixture has been stirred for 6 hours at room temperature, it is diluted with dichloromethane and extracted by shaking in succession with sodium sulphite solution to

destroy excess peracid and with sodium bicarbonate solution. The solvent is evaporated in vacuo, and the residue is separated by preparative HPLC on a Nucleosil RP-18 column (250 x 20 mm, eluent methanol/water 60:40). Yield 60 mg of colourless oil.

R_f=0.60 (silica gel TLC aluminium foil, eluent dichloromethane/methanol 9:1);

ESI-MS (neg. ions) m/z 510;

UV (methanol): lamda max. 240 nm;

^{13}C NMR ($CDCl_3$): C-1 170.5, C-2 39.9, C-3 70.8, C-4 55.1, C-5 221.4, C-6 40.9, C-7 72.9, C-8 37.6, C-9 31.8, C-10 22.8, C-11 28.0, C-12 58.0, C-13 55.8, C-14 32.2, C-15 75.5, C-16 144.5, C-17 111.4, C-18 143.4, C-19 110.3, C-20 145.6, C-21 13.5, C-22 15.4, C-23 23.3, C-24 12.0, C-25 16.5, C-27 18.2 ppm;

^1H NMR ($CDCl_3$): 2a-H 2.12 dd, 2b-H 2.47 dd, 3-H 4.55 dd, 3-OH 6.48 broad, 6-H 3.25 dq, 7-H 3.72 dd, 8-H 1.81 m, 9a-H 1.34 m, 9b-H 1.56 m, 10-H_2 1.48 m, 11a-H 1.27 m, 11b-H 1.87 m, 12-H 2.92 ddd, 13-H 2.98 m, 14a-H 1.67 ddd, 14b-H 2.23 d, 15-H 5.33 d, 17-H 6.82 s, 19-H 7.09 s, 21-H_3 2.61 s, 22-H_3 1.02 s, 23-H_3 1.42 s, 24-H_3 1.18 d, 25-H_3 0.99 d, 27-H_3 2.04 s ppm.

21-Acetoxyepothilone A (= 21-acetylepothilone E) (3a): 0.05 ml of 2,6-di-tert-butylpyridine and 0.1 ml of acetic anhydride are added to 50 mg of epothilone A N-oxide (**2a**) in 0.5 ml of dichloromethane. After the mixture has been heated at 75°C for 15 minutes, solvent and reagents are evaporated in vacuo and the residue is separated by preparative HPLC on Nucleosil RP-18 (250 x 20 mm, eluent methanol/water 60:40). Yield 30 mg of colourless oil.

R_f 0.50 (silica gel TLC aluminium foil, eluent dichloromethane/methanol 95:5);

ESI-MS (neg. ions) m/z 552;

UV (methanol): lamda max. 210, 250 nm;

^1H NMR ($CDCl_3$, signals different with respect to **2a**): 15-H 5.45 dd, 17-H 6.60 s, 19-H 7.15 s, 21-H_2 5.35 s, CH_3CO 2.15 s ppm.

This Sheet Has Been Replaced



This Sheet Has Been Replaced

Epothilone E (3b): 1 drop of concentrated ammonia solution is added to 10 mg of 21-acetoxyepothilone A (**3a**) in 0.5 ml of methanol, and the mixture is heated for 1 hour at 40°C and is evaporated to dryness in vacuo. The residue is separated by preparative TLC. Yield 6 mg, identical with an authentic sample of epothilone E.

Experiment 4: **19-Methylepothilone A. (4b)**

A solution of epothilone A (15 mg, 30 μmol) in THF (1 ml) was treated at -90°C with *n*-butyllithium (100 μl, 160 μmol, 1.6 M in hexane). The solution immediately turned golden orange. After the reaction solution had been stirred for 15 minutes at -90°C, it was treated with methyl iodide (100 μl, 1.6 mmol). The resulting pale greenish-yellow solution was warmed to -30°C and quenched with buffer pH = 7.0 (2 ml). The emulsion was brought to pH 6 with 0.1 N hydrochloric acid. After the mixture had been saturated with solid NaCl, the aqueous phase was extracted with CH_2Cl_2 (2 × 5 ml) and ethyl acetate (5 ml), the combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was removed on a Rotavap. Purification was done by PLC (1 × 200 × 200 mm, 10% MeOH;CH_2Cl_2) and HPLC (RP 18, 250 × 16 mm, MeOH:H_2O 65:35). The following were isolated:

1. 2.5 mg (17%) of 19-methylepothilone A. R_f 0.50 (10% MeOH:CH_2Cl_2); R_f: 11.70 min (RP 18, 250 × 4 mm, MeOH:H_2O 65:35, 1 ml/min); MS: (m/z) = 508 (M^+), 420, 320; ^1H NMR (300 MHz, $CDCl_3$, selected signals): δ = 6.41 (s, 1H, H-17), 5.46 (dd, J = 9.0 and 2.3 Hz, 1H, H-15), 4.15 (dd, J = 10.5 and 3.0 Hz, 1H, H-3), 3.77 (dd, J = 8 and 4 Hz, 1H, H-7), 3.20 (qd, J = 6.8 and 4.5 Hz, 1H, H-6), 3.04 (dt, J = 7.5 and 3.8 Hz, 1H, H-13), 2.91 (dt, J = 7.5 and 3.8 Hz, 1H, H-12), 2.61 (s, 3H, H-21), 2.51 (dd, J = 14.4 and 10.5 Hz, 1H, H-2a), 2.38 (dd, J = 14.4 and 3.0 Hz, 1H, H-2b), 2.32 (s, 3H, H-27), 2.15 (ddd, J = 15.1, 3.8 and 3.0 Hz, 1H, H-14a), 2.01 (d, J = 1.5 Hz, 3H, H-26), 1.91 (dt, J = 15.1 and 8.8 Hz, 1H, H-14b); 1.34 (s, 3H, H-22), 1.16 (d, J = 6.8 Hz, 3H, H-24), 1.10 (s, 3H, H-23), 1.00 (d, J = 6.8 Hz, 3H,

H-25).

2. approx. 50% of epothilone A

Experiment 5: **19-Bromoepothilone A. (4a)**

A solution of epothilone A (25 mg, 50 µmol) in THF (2.5 ml) was treated at -90°C with *n*-butyllithium (160 µl, 225 µmol, 1.6 M in hexane). The solution immediately turned golden orange. After the mixture had been stirred for 15 minutes at -90°C, N-bromosuccinimide (27 mg, 150 µmol), dissolved in THF (0.5 ml), was added. The solution discoloured slowly. The reaction mixture, now a pale brownish colour, was warmed to -30°C and brought to pH 6.5 with 0.1 N hydrochloric acid (1 ml). After the mixture had been saturated with solid NaCl, the aqueous phase was extracted with CH_2Cl_2 (2 × 5 ml) and ethyl acetate (5 ml), the combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was removed on a Rotavap. Purification was done by PLC (1 × 200 × 200 mm, 10% MeOH:CH_2Cl_2) and HPLC (RP 18, 250 × 16 mm, MeOH:H_2O 65:35). The following were isolated:

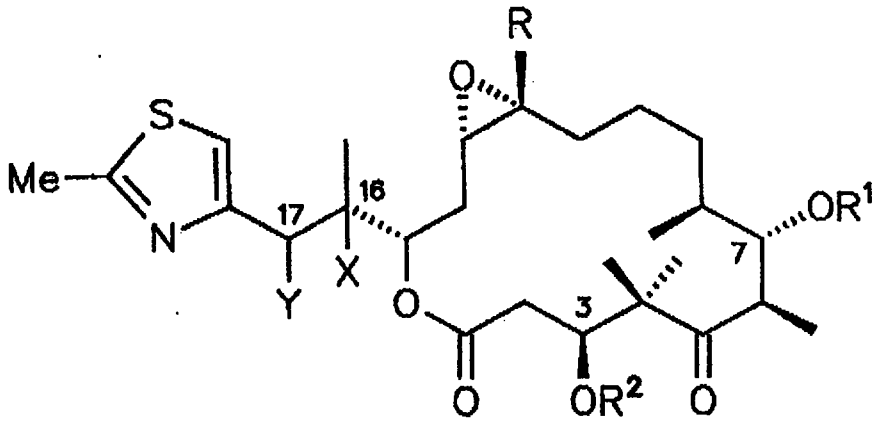
1. 2.6 mg (9%) of 19-bromoepothilone A. R_f 0.53 (10% MeOH:CH_2Cl_2); R_f: 20.78 min (RP 18, 250 × 4 mm, MeOH:H_2O 65:35, 1 ml/min); MS: (m/z) = 574 and 572 (M^+), 556, 554, 468, 466, 386, 384, 341; ^1H NMR (300 MHz, $CDCl_3$, selected signals): δ = 6.43 (s, 1H, H-17), 5.46 (dd, J = 8.7 and 2.3 Hz, 1H, H-15), 4.13 (ddd, J = 9.4, 6.0 and 3.8 Hz, 1H, H-3), 3.80 (dd, J = 8 and 4 Hz, 1H, H-7), 3.38 (d, J = 6.0 Hz, 1H, OH), 3.22 (qd, J = 6.8 and 5.3 Hz, 1H, H-6), 3.05 (dt, J = 8.3 and 4.1 Hz, 1H, H-13), 2.91 (dt, J = 7.5 and 3.7 Hz, 1H, H-12), 2.66 (s, 3H, H-21), 2.55 (dd, J = 14.7 and 9.4 Hz, 1H, H-2a), 2.47 (dd, J = 14.7 and 3.8 Hz, 1H, H-2b), 2.16 (d, J = 1.1 Hz, 3H, H-26), 2.14 (dt, J = 14.7 and 3.8 Hz, 1H, H-14a), 1.90 (dt, J = 15 and 8.3 Hz, 1H, H-14b); 1.34 (s, 3H, H-22), 1.17 (d, J = 6.8 Hz, 3H, H-24), 1.11 (s, 3H, H-23), 1.01 (d, J = 6.8 Hz, 3H, H-25).

2. approx. 60% of epothilone A

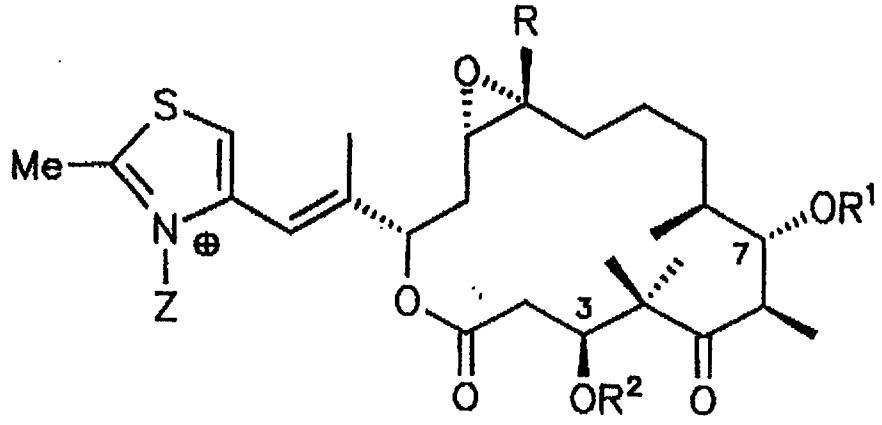
This Sheet Has Been Replaced



Synthesis Examples 1a to 5a

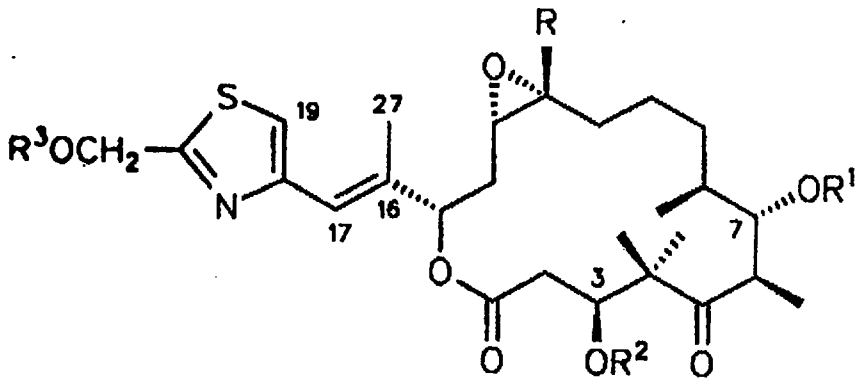


1a R^1, R^2 = H, X, Y = -O-, R = H
b R^1, R^2 H, X = OH Y = H, R = H
c R^1, R^2 = H, X = H Y = H, R = H



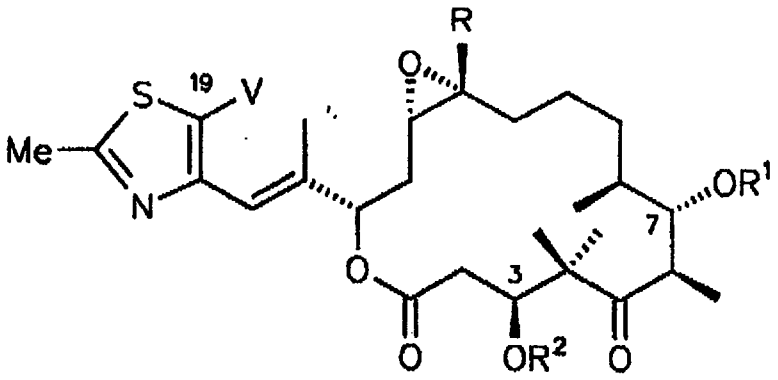
5 2a R^1, R^2 = H, Z = O^-, R = H
b R^1, R^2 = H, Z = OCH_3 BF_4^-, R = H

This Sheet Has Been Replaced



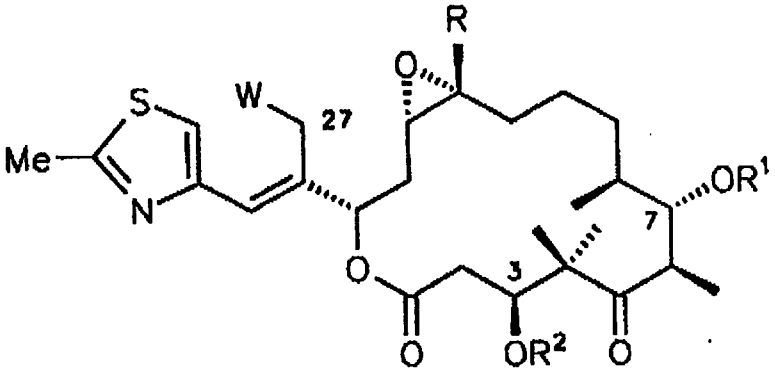
3a R^1, R^2 = H, R^3 = acetyl, R = H

b R^1, R^2, R^3 = H, R = H



4a R^1, R^2 = H, V = Br, R = H

b V = CH_3, R^1, R^2 H, R = H



5 5a R^1, R^2 = H, W = OH, R = H

This Sheet Has Been Replaced

This Sheet Has Been Replaced

24 February 1998/pl

Our references: 9200, 9201, 9202 and 9203
Gesellschaft fuer Biotechnologische Forschung mbH (GBF)
Reichenbach et al.; Epothilones which are modified in the side chain

Patent Claims

1. Process for the preparation of epothilones which are modified in the 16, 17-position, in which process the starting materials are 3,7-protected or unprotected epothilones A or B and

a) these are hydrogenated on the 16, 17-double bond or

b) subjected to an addition reaction with halogen on the 16, 17-double bond or

c) epoxidized on the 16, 17-double bond and, if appropriate, the resulting epoxide is reduced to give the 16-alcohol.

2. Process according to Claim 1, **characterized in that,**

- in method (a), hydrogenation is effected with diimine or hydrogen and a heterogeneous or homogeneous metal catalyst or
- in method (c), epoxidation is effected with a peracid or a dioxirane.

3. Process for the preparation of 2,3-unsaturated epothilone N-oxides in which either

(i) 3,7-protected epothilones A or B are converted into an N-oxide in a manner known per se and, the 3-substituent is eliminated by a base to give the 2,3-double bond, or

(ii) 7-protected or 7-unprotected epothilones A or B which have a double bond in the 2,3-position are converted into an N-oxide in a ~~known~~ manner known per se and, if appropriate, the resulting N-oxide is subjected to O-alkylation in a manner known per se and an O-alkylation product is obtained.

4. Process for the preparation of epothilone N-oxides in which 3,7-protected or unprotected epothilones A or B are converted into an N-oxide in a manner

* C L M S *

This Sheet Has Been Replaced

known per se and, if appropriate, the resulting N-oxide is subjected to O-alkylation and an O-alkylation product is obtained.

5. Process according to Claim 3 or 4, **characterized in that** N-oxidation is performed with peracid or a dioxirane and electrophilic alkyl, aryl or heteroaryl reagents, in particular methyl iodide or trimethyloxonium tetrafluoroborate, are used for the optional O-alkylation.

6. Process according to Claim 3 or 4, **characterized in that** a resulting N-oxide is subjected to a Katada reaction, in particular as described in Houben-Weyl, Volume E7b, page 646.

7. Process according to Claim 6, **characterized in that** the Katada reaction is performed with an activated carboxylic acid derivative, in particular carboxylic anhydride or carboxylic acid chloride.

8. Process according to Claim 7, **characterized in that** the Katada reaction is carried out with acetic anhydride and, if appropriate, the 21-acetoxyepothilones obtained are cleaved in a manner known per se to give 21-hydroxyepothilones A or B (epothilones E and F, respectively).

9. Process according to Claim 8, **characterized in that** the optional cleavage process is performed hydrolytically or enzymatically.

10. Process for the preparation of epothilones which are modified in the C19-position, in which process 3,7-protected or unprotected epothilones A or B are metalated in the C19-position and captured with electrophilic reagents in a manner known per se as alkyl-, aryl-, heteroaryl-, halogen-, oxygen- or sulphur-substituted epothilones which are modified in the C19-position.

11. Process according to Claim 10, **characterized in that** metalation is performed using butyllithium.

12. Process for the preparation of epothilones which are modified in the C27-position, in which process the allyl group (C17, C16 and C27) is substituted in a manner

known per se on the C27-methyl group by a hetero atom.

13. Process according to Claim 12, **characterized in that** the C27-methyl group is substituted by a bromine atom, in particular with the aid of N-bromosuccinimide, and, if appropriate, the resulting bromide is converted into a C27-hydroxy compound.

14. Compounds obtainable by a process in accordance with one of the preceding claims.

This Sheet Has Been Replaced



