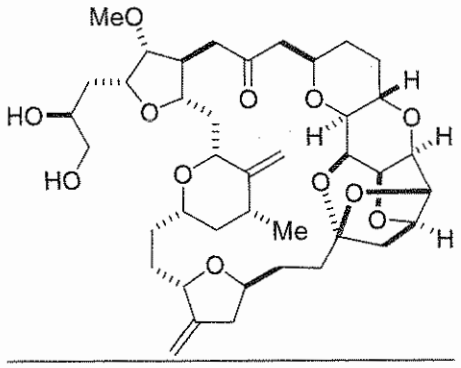
described in U.S. patents 6,214,865; 6,365,759; 6,469,182; and 6,653,341; in U.S. published patent applications 2004/0198806 and 2006/0104984; and in PCT published application WO 2005/118565, all of which are herein incorporated by reference in their entirety.

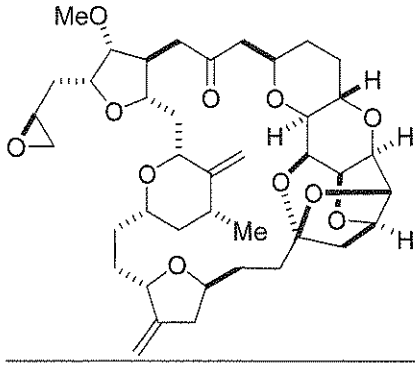
Summary of the Invention

[0005] This invention relates to halichondrin B analogs having pharmaceutical activity. The analogs have a crystalline form and/or have a further utility as a synthetic intermediate in the synthesis of the halichondrin B analog E7389, a compound having potent anticancer properties. Accordingly, the invention relates to a crystalline form of ER-076349 monohydrate; a crystalline form of ER-809681; the compound ER-820057 or a crystalline form of ER-820057; the compound ER-818906 or a crystalline form of ER-818906; the compound ER-819531 or a crystalline form of ER-819531; and the compound ER-111197 or a crystalline form of ER-111197. The invention also relates to pharmaceutical compositions containing these compounds, and methods of treating cancer by administering the compounds.

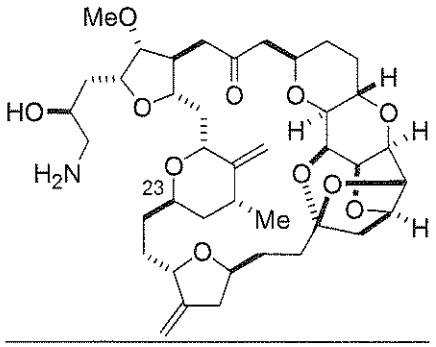
In one aspect, the present invention refers to a crystalline monohydrate of the compound:



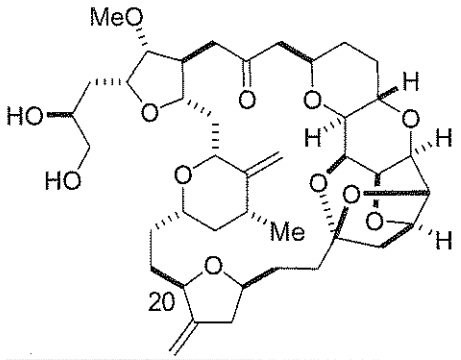
characterized by a powder x-ray diffraction pattern having peaks at 9.3 °2Θ ± 0.2 °2Θ, 10.4 °2Θ ± 0.2 °2Θ, and 13.0 °2Θ ± 0.2 °2Θ. In another aspect, the present invention refers to a crystalline form of the compound:



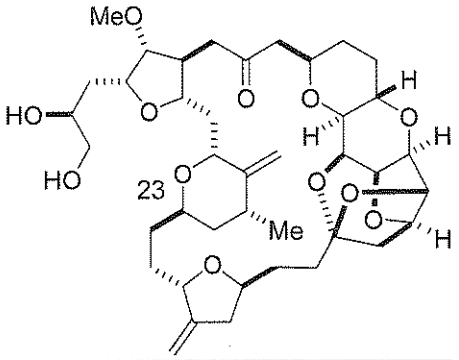
characterized by a powder x-ray diffraction pattern having peaks at 6.5 °2Θ ± 0.2 °2Θ, 9.3 °2Θ ± 0.2 °2Θ, and 17.1 °2Θ ± 0.2 °2Θ. In still another aspect, the present invention refers to a crystalline form of the compound:



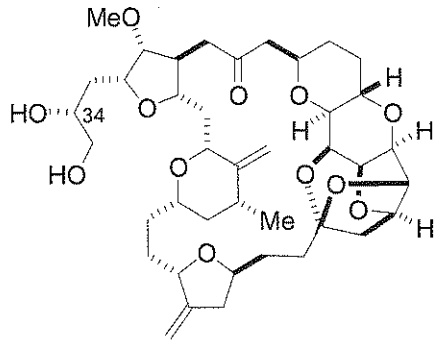
characterized by a powder x-ray diffraction pattern having peaks at 13.0 °2Θ ± 0.2 °2Θ, 15.0 °2Θ ± 0.2 °2Θ, and 15.9 °2Θ ± 0.2 °2Θ. In another aspect, the present invention refers to a crystalline mono-acetonitrile solvate of the compound:



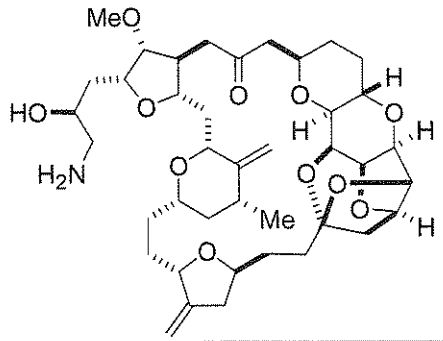
characterized by a powder x-ray diffraction pattern having peaks at 7.9 °2Θ ± 0.2 °2Θ, 23.7 °2Θ ± 0.2 °2Θ, 32.8 °2Θ ± 0.2 °2Θ, and 40.0 °2Θ ± 0.2 °2Θ. In still another aspect, the present invention refers to a crystalline monohydrate of the compound:



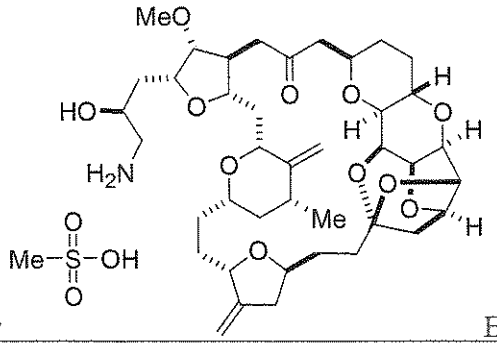
characterized by a powder x-ray diffraction pattern having peaks at 8.1 °2Θ ± 0.2 °2Θ, 13.1 °2Θ ± 0.2 °2Θ, and 14.3 °2Θ ± 0.2 °2Θ. In a further aspect, the present invention refers to a crystalline monohydrate of the compound:



characterized by a powder x-ray diffraction pattern having peaks at 8.3 °2Θ ± 0.2 °2Θ, 15.8 °2Θ ± 0.2 °2Θ, and 16.6 °2Θ ± 0.2 °2Θ. In another aspect, the present invention refers to a method of synthesizing:

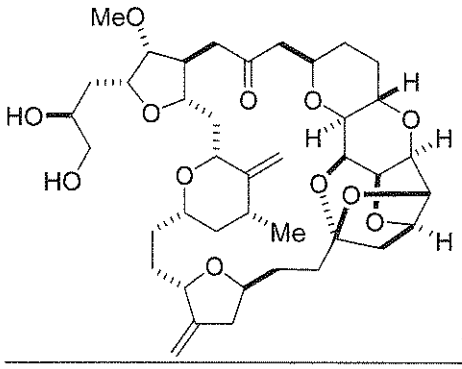


ER-086526 or



E-7389,

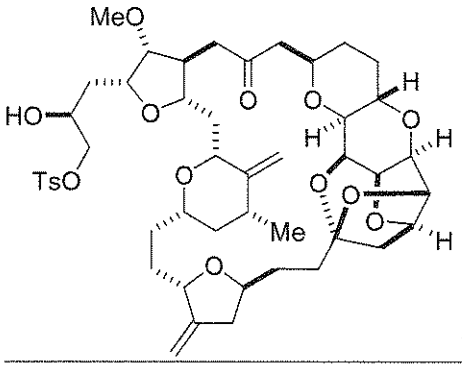
said method comprising forming a crystalline monohydrate of the compound:



ER-076349

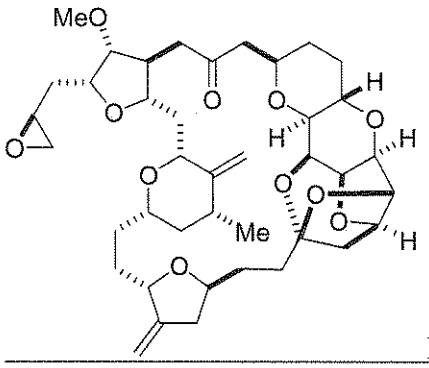
according to the present invention;

producing from said crystalline monohydrate of ER-076349 a compound having the formula:



ER-082892;

producing from ER-082892 a compound having the formula:



ER-809681;

and producing ER-086526 or E-7389 from ER-809681.

Brief Description of Figures

[0006] Fig. 1-A is an ORTEP drawing of the single crystal structure of ER-076349-00 monohydrate.

[0007] Fig. 1-B is the crystal packing diagram of ER-076349 monohydrate along the b-axis.

[0008] Fig. 1-C is the X-ray Powder Diffraction (XRPD) pattern of ER-076349 monohydrate crystallized from isopropyl alcohol.

[0009] Fig. 1-D is a plot of XRPD patterns of ER-076349 monohydrate from various solvents.

[0010] Fig. 1-E is a plot of the DSC of ER-076349 monohydrate crystallized from ethanol.

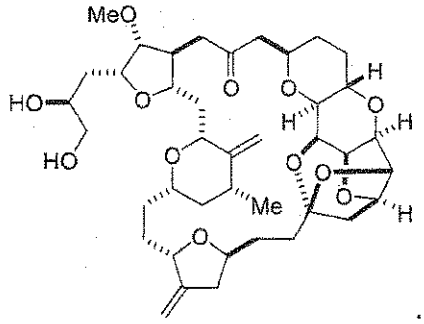
[0011] Fig. 1-F is a plot of the DSC of ER-076349 monohydrate crystallized from isopropanol.

[0012] Fig. 1-G is a plot of the DSC of ER-076349 monohydrate crystallized from propionitrile.

[0013] Fig. 2-A is an ORTEP drawing of the single crystal structure of ER-818906 mono-acetonitrile solvate.

The claimed invention is:

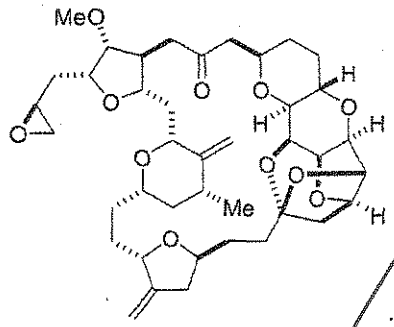
1. A crystalline monohydrate of the compound:



2. The crystalline monohydrate of claim 1, characterized by a powder x-ray diffraction pattern having peaks at 9.3 °2Θ ± 0.2 °2Θ, 10.4 °2Θ ± 0.2 °2Θ, and 13.0 °2Θ ± 0.2 °2Θ.

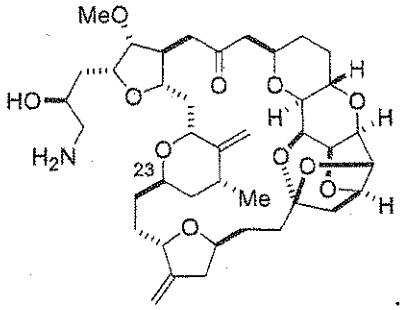
3. The crystalline monohydrate of claim 2, further characterized by a differential scanning calorimetry thermogram having an onset temperature ranging from about 157 to about 161 °C.

4. A crystalline form of the compound:



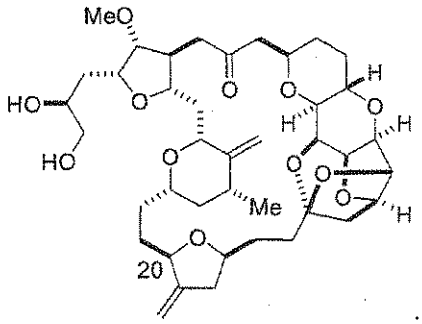
5. The crystalline form of the compound of claim 4, characterized by a powder x-ray diffraction pattern having peaks at 6.5 °2Θ ± 0.2 °2Θ, 9.3 °2Θ ± 0.2 °2Θ, and 17.1 °2Θ ± 0.2 °2Θ.

6. A crystalline form of the compound:



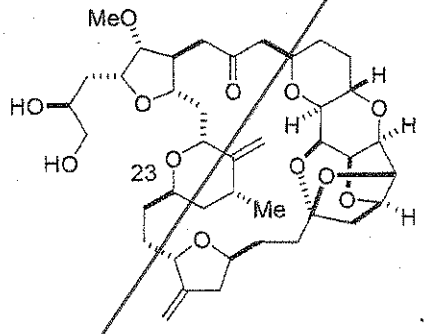
7. The crystalline form of the compound claim 6, characterized by a powder x-ray diffraction pattern having peaks at 13.0 °2Θ ± 0.2 °2Θ, 15.0 °2Θ ± 0.2 °2Θ, and 15.9 °2Θ ± 0.2 °2Θ.

8. The crystalline mono-acetonitrile solvate of the compound:



9. The crystalline solvate of claim 8, characterized by a powder x-ray diffraction pattern having peaks at 7.9 °2Θ ± 0.2 °2Θ, 23.7 °2Θ ± 0.2 °2Θ, 32.8 °2Θ ± 0.2 °2Θ, and 40.0 °2Θ ± 0.2 °2Θ.

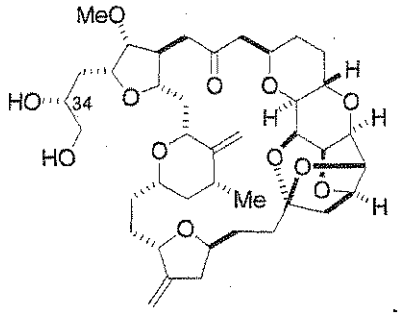
10. The crystalline monohydrate of the compound:



11. The crystalline monohydrate of claim 10, wherein the crystalline monohydrate is in a racemic form.

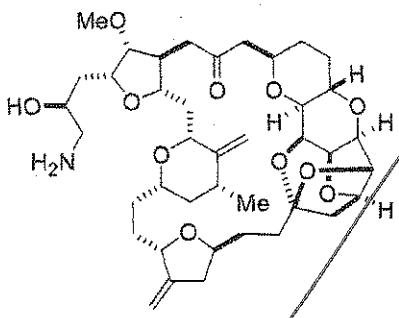
12. The crystalline monohydrate of claim 10, characterized by a powder x-ray diffraction pattern having peaks at 8.1 °2Θ ± 0.2 °2Θ, 13.1 °2Θ ± 0.2 °2Θ, and 14.3 °2Θ ± 0.2 °2Θ.

13. The crystalline monohydrate of the compound:

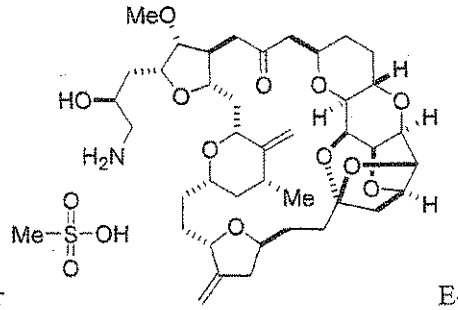


14. The crystalline monohydrate of claim 13, characterized by a powder x-ray diffraction pattern having peaks at 8.3 °2Θ ± 0.2 °2Θ, 15.8 °2Θ ± 0.2 °2Θ, and 16.6 °2Θ ± 0.2 °2Θ.

15. A method of synthesizing:

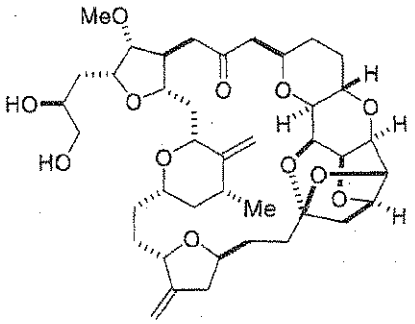


ER-086526 or



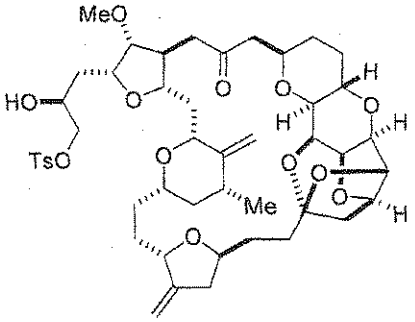
E-7389,

said method comprising forming a crystalline monohydrate of the compound:



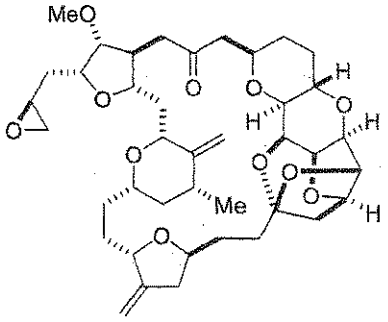
ER-076349;

producing from said crystalline monohydrate of ER-076349 a compound having the formula:



ER-082892;

producing from ER-082892 the compound:

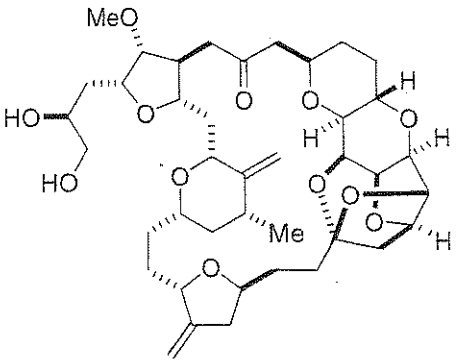


ER-809681;

and producing ER-086526 or E-7389 from ER-809681.

CLAIMS

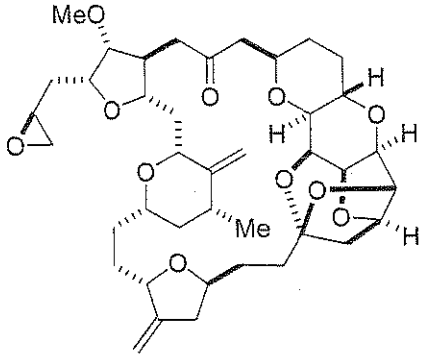
1. A crystalline monohydrate of the compound:



characterized by a powder x-ray diffraction pattern having peaks at 9.3 °2Θ ± 0.2 °2Θ, 10.4 °2Θ ± 0.2 °2Θ, and 13.0 °2Θ ± 0.2 °2Θ.

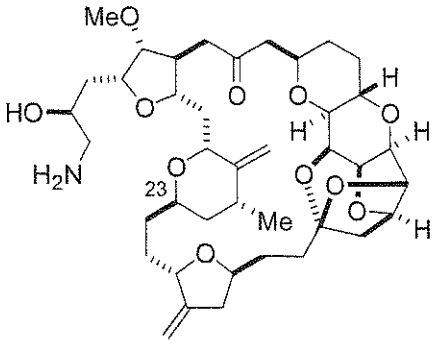
2. The crystalline monohydrate of claim 1, further characterized by a differential scanning calorimetry thermogram having an onset temperature ranging from about 157 to about 161 °C.

3. A crystalline form of the compound:



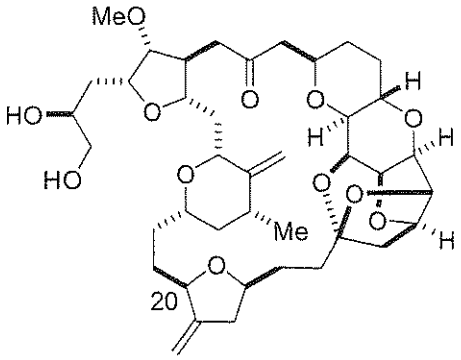
characterized by a powder x-ray diffraction pattern having peaks at 6.5 °2Θ ± 0.2 °2Θ, 9.3 °2Θ ± 0.2 °2Θ, and 17.1 °2Θ ± 0.2 °2Θ.

4. A crystalline form of the compound:



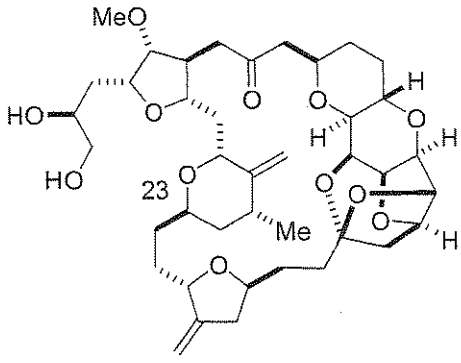
characterized by a powder x-ray diffraction pattern having peaks at 13.0 °2Θ ± 0.2 °2Θ, 15.0 °2Θ ± 0.2 °2Θ, and 15.9 °2Θ ± 0.2 °2Θ.

5. A crystalline mono-acetonitrile solvate of the compound:



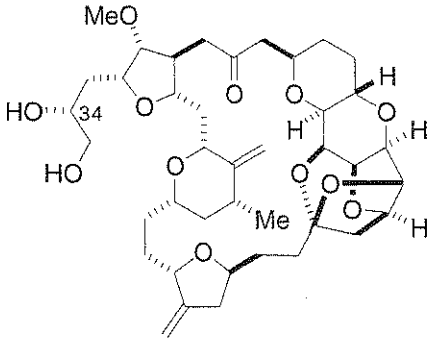
characterized by a powder x-ray diffraction pattern having peaks at 7.9 °2Θ ± 0.2 °2Θ, 23.7 °2Θ ± 0.2 °2Θ, 32.8 °2Θ ± 0.2 °2Θ, and 40.0 °2Θ ± 0.2 °2Θ.

6. A crystalline monohydrate of the compound:



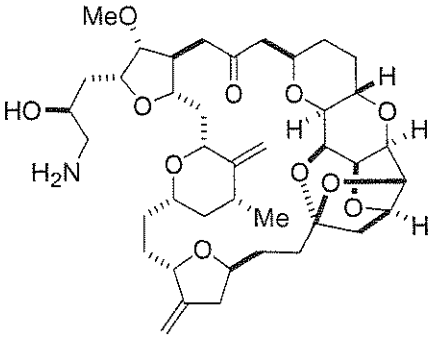
characterized by a powder x-ray diffraction pattern having peaks at 8.1 °2Θ ± 0.2 °2Θ, 13.1 °2Θ ± 0.2 °2Θ, and 14.3 °2Θ ± 0.2 °2Θ.

7. A crystalline monohydrate of the compound:

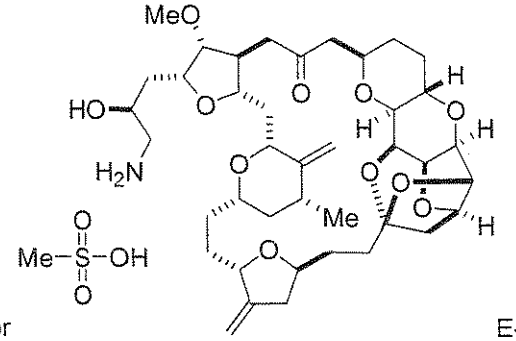


characterized by a powder x-ray diffraction pattern having peaks at 8.3 °2Θ ± 0.2 °2Θ, 15.8 °2Θ ± 0.2 °2Θ, and 16.6 °2Θ ± 0.2 °2Θ.

8. A method of synthesizing:

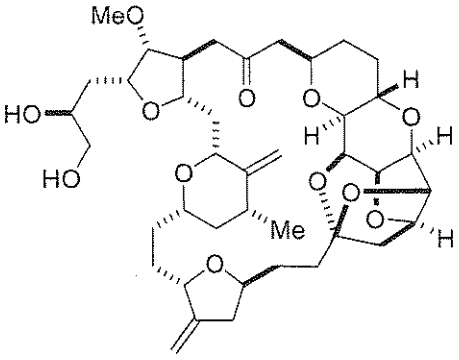


ER-086526 or



E-7389,

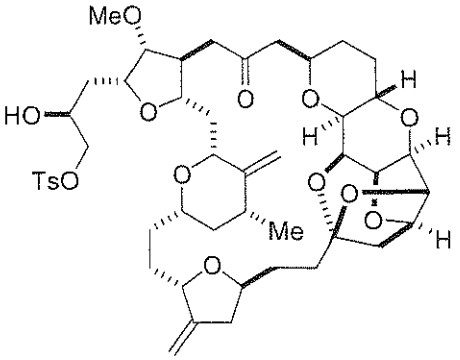
said method comprising forming a crystalline monohydrate of the compound:



ER-076349

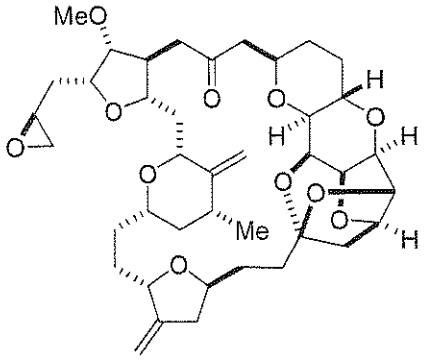
according to claim 1;

producing from said crystalline monohydrate of ER-076349 a compound having the formula:



ER-082892;

producing from ER-082892 a compound having the formula:



ER-809681;

and producing ER-086526 or E-7389 from ER-809681.