METHODS USEFUL IN THE SYNTHESIS OF HALICHONDRIN B ANALOGS

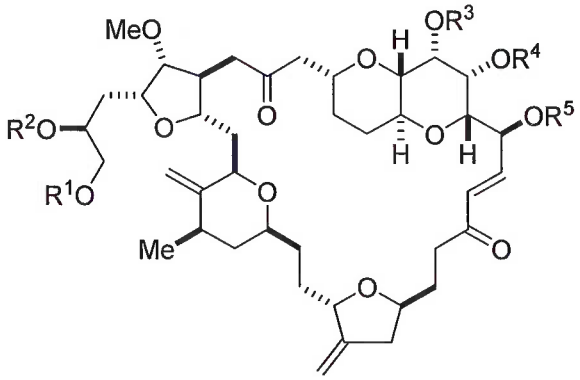
The invention relates to methods useful in the synthesis of analogs of halichondrin B, in particular ER-086526, referred to under its generic name eribulin throughout the following specification.

BACKGROUND OF THE INVENTION

Eribulin (marketed under the trade name HALAVEN® as eribulin mesylate), a nontaxane microtubule dynamics inhibitor, is a structurally simplified, synthetic analog of the marine natural product halichondrin B. Methods for the synthesis of eribulin and other halichondrin B analogs are described in U.S. Patent Nos. 6,214,865, 6,365,759, 6,469,182, 7,982,060, and 8,148,554, the syntheses of which are incorporated herein by reference. New methods for the synthesis of halichondrin B analogs, in particular eribulin and eribulin mesylate, are desirable.

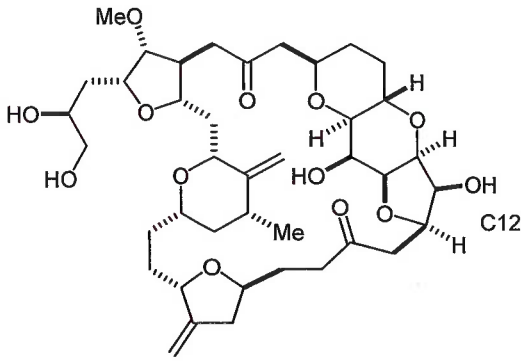
SUMMARY

In one aspect, the present invention refers to a method of preparing an intermediate in the synthesis of eribulin, said method comprising reacting a compound having formula (I):



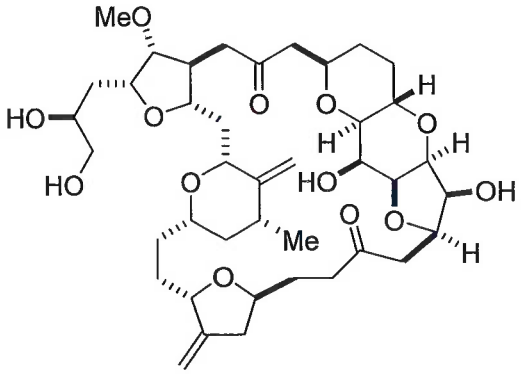
(I)

wherein each of R^1, R^2, R^3, R^4, and R^5 is independently a silyl group, with a fluoride source in a solvent comprising an amide to produce the intermediate ER-811475:



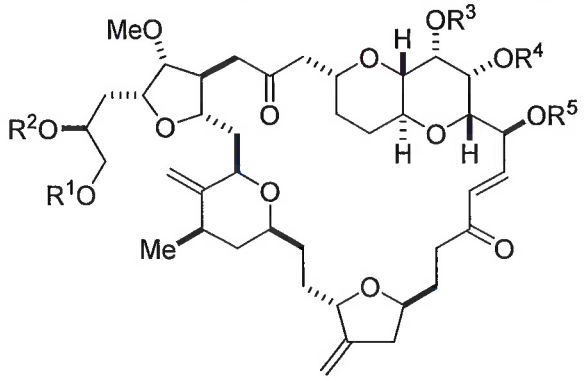
ER-811475

wherein the amide is an N,N C1-C6 dialkyl C1-C6 alkyl amide or N C1-C6 alkyl C2-C6 lactam. In another aspect, the present invention refers to a method of producing eribulin, said method comprising the steps of a) producing an intermediate ER-811475:



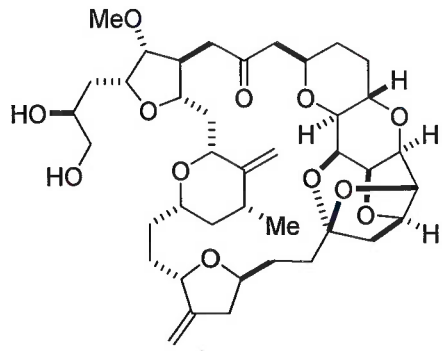
ER-811475

by reacting a compound having formula (I):



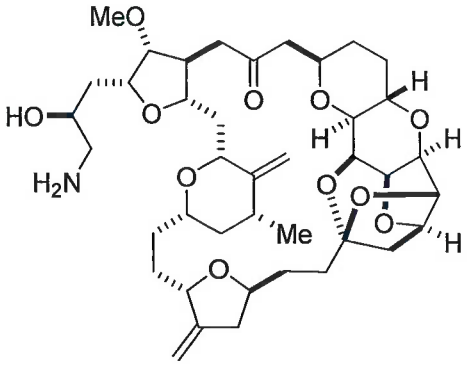
(I)

wherein each of R^1, R^2, R^3, R^4, and R^5 is independently a silyl group, with a fluoride source in a solvent comprising an amide wherein the amide is an N,N C1-C6 dialkyl C1-C6 alkyl amide or N C1-C6 alkyl C2-C6 lactam; b) ketalizing intermediate ER-811475 to produce the intermediate ER-076349:



ER-076349

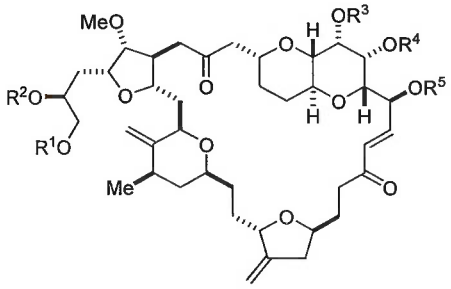
c) aminating ER-076349 to produce eribulin:



eribulin

Also described herein are methods useful for the synthesis of analogs of halichondrin B, such as eribulin and pharmaceutically acceptable salts thereof (e.g., eribulin mesylate).

In one example, disclosed herein is a method of preparing an intermediate in the synthesis of eribulin including reacting a compound having formula (I):

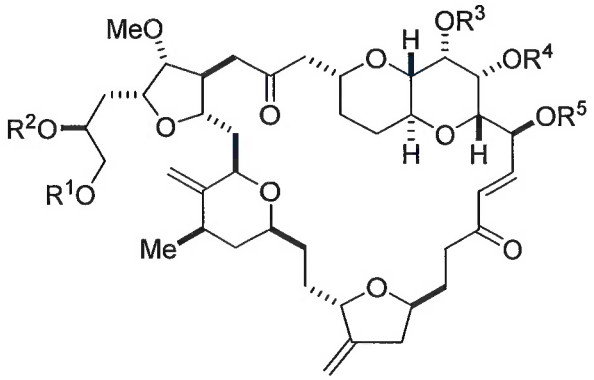


(I)

wherein each of R^1, R^2, R^3, R^4, and R^5 is independently a silyl group (e.g., trimethylsilyl (TMS), triethylsilyl (TES), *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl (TBDPS), triisopropylsilyl (TIPS), or triphenylsilyl (TPS)), with a fluoride source (e.g., tetrabutylammonium fluoride) in a solvent including an amide, e.g., a *N,N* C1-C6 dialkyl C1-C6 alkyl amide or *N* C1-C6 alkyl C2-C6 lactam, such as *N,N*-dimethylacetamide (e.g., as a mixture of tetrahydrofuran and *N,N*-dimethylacetamide), *N,N*-dimethylformamide, *N*-methyl 2-pyrrolidone, *N,N*-diethylacetamide, or *N,N*-dimethylpropionamide, to produce the intermediate ER-811475:

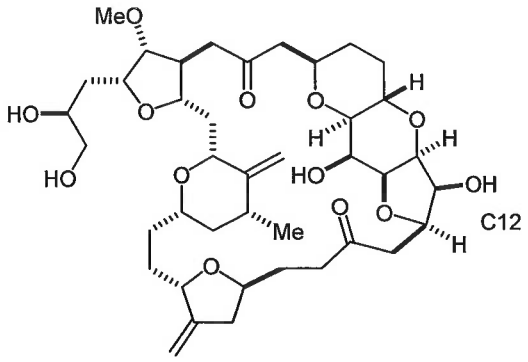
CLAIMS

1. A method of preparing an intermediate in the synthesis of eribulin, said method comprising reacting a compound having formula (I):



(I)

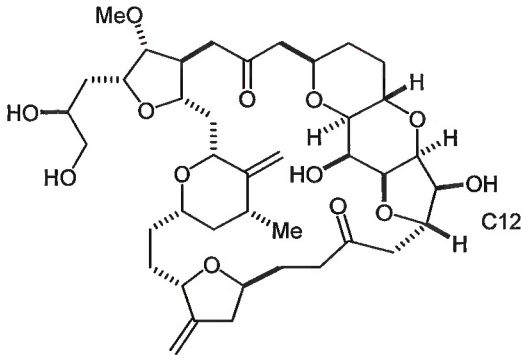
wherein each of R^1, R^2, R^3, R^4, and R^5 is independently a silyl group, with a fluoride source in a solvent comprising an amide to produce the intermediate ER-811475:



ER-811475

wherein the amide is an N,N C1-C6 dialkyl C1-C6 alkyl amide or N C1-C6 alkyl C2-C6 lactam.

2. The method of claim 1, wherein the intermediate ER-811475 is produced in a mixture with an intermediate ER-811474:



ER-811474.

3. The method of claim 2, further comprising adding a mixture of acetonitrile and water.

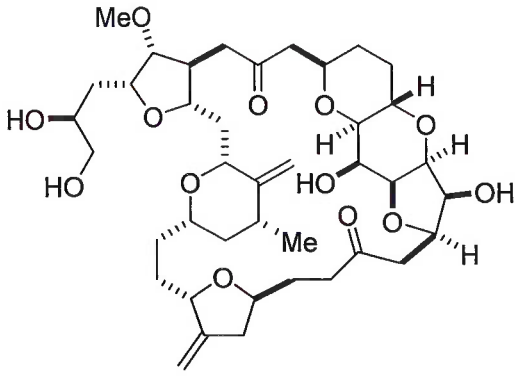
4. The method of claim 1, wherein each of R^1, R^2, R^3, R^4, and R^5 is t-butyldimethylsilyl.

5. The method of claim 1, wherein the fluoride source is tetrabutylammonium fluoride.

6. The method of claim 1, wherein the solvent further comprises tetrahydrofuran.

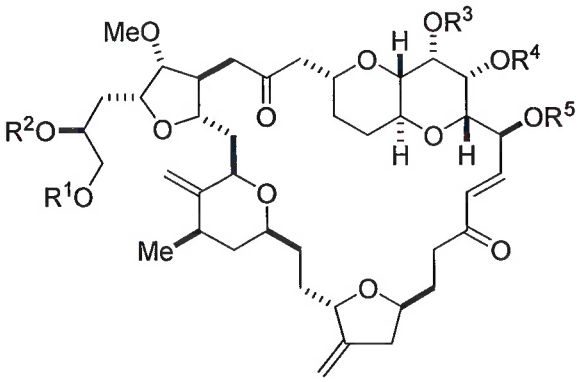
7. The method of claim 1, wherein the amide is N,N-dimethylacetamide, N,N-dimethylformamide, N-methyl 2-pyrrolidone, N,N-diethylacetamide, or N,N-dimethylpropionamide.

8. A method of producing eribulin, said method comprising the steps of:
a) producing an intermediate ER-811475:



ER-811475

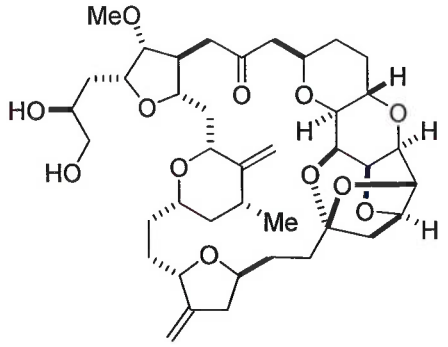
by reacting a compound having formula (I):



(I)

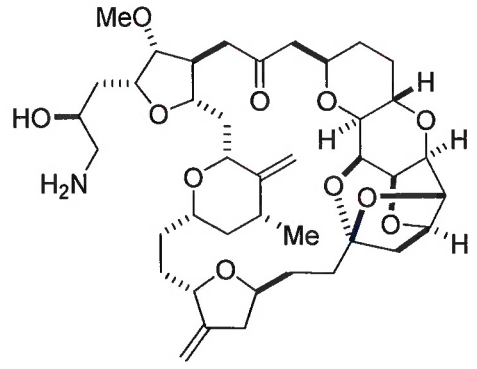
wherein each of R^1, R^2, R^3, R^4, and R^5 is independently a silyl group, with a fluoride source in a solvent comprising an amide wherein the amide is an N,N C1-C6 dialkyl C1-C6 alkyl amide or N C1-C6 alkyl C2-C6 lactam;

b) ketalizing intermediate ER-811475 to produce the intermediate ER-076349:



ER-076349

c) aminating ER-076349 to produce eribulin:



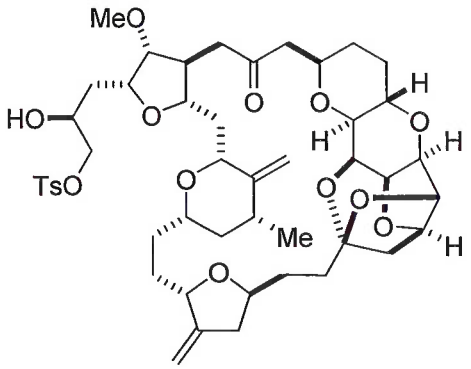
eribulin

9. The method of claim 8, further comprising salifying eribulin to produce a pharmaceutically acceptable salt of eribulin.

10. The method of claim 9, wherein said salt is the mesylate salt.

11. The method of claim 8, wherein ER-076349 is produced by reacting ER-811475 with a conjugate acid of imidazole.

12. The method of claim 8, wherein step c) comprises converting ER-076349 to ER-082892:



ER-082892

by reacting ER-076349 with a sulfonylating reagent in the presence of a metal catalyst.