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.

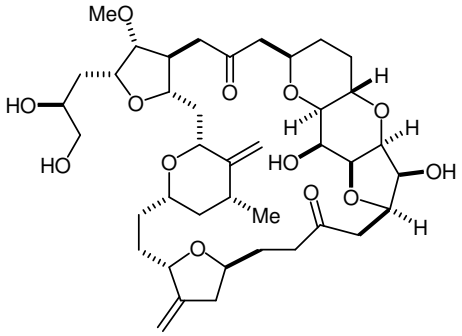
BACKGROUND OF THE INVENTION

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 ~~OF THE INVENTION~~

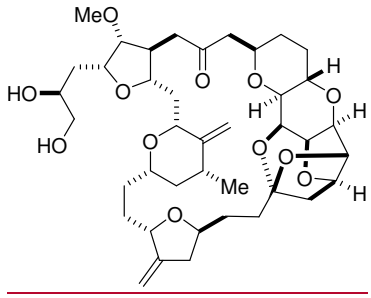
In general, the present ~~invention~~ disclosure features improved methods useful for the synthesis of analogs of halichondrin B, such as eribulin and pharmaceutically acceptable salts thereof (e.g., eribulin mesylate).

In one aspect, the disclosure provides a method of preparing an intermediate in the synthesis of eribulin, said method comprising reacting ER-811475:



ER-811475

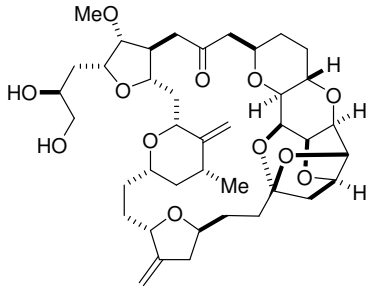
with a conjugate acid of imidazole to produce the intermediate ER-076349:



ER-076349.

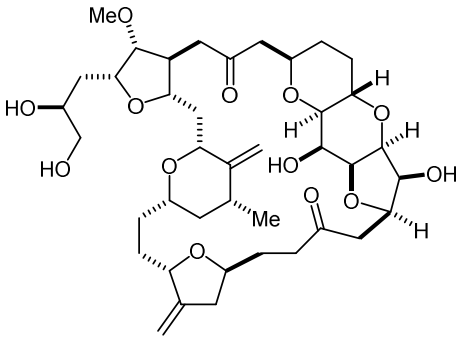
In one aspect, the disclosure provides a method of producing eribulin, said method comprising the steps of:

a) producing the intermediate ER-076349:



ER-076349

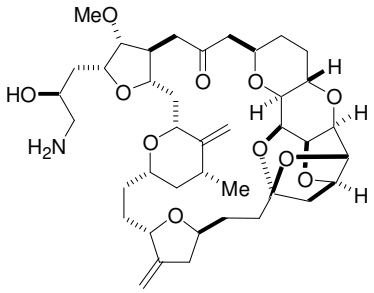
by reacting ER-811475



ER-811475

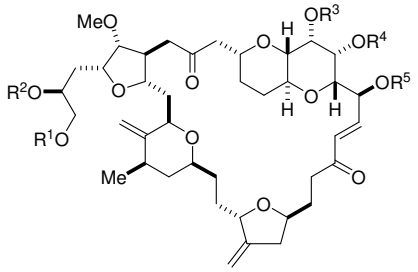
with a conjugate acid of imidazole to produce the intermediate ER-076349; and

b) aminating ER-076349 to produce eribulin:



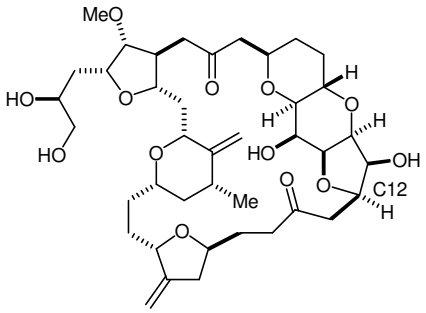
eribulin.

In one ~~aspect~~example, the ~~invention~~disclosure features a method of preparing an intermediate in the synthesis of eribulin including reacting a compound having formula (I):



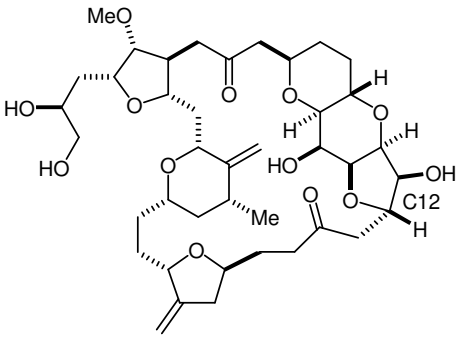
(I)

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:



ER-811475.

ER-811475 may be produced in a mixture with its C12 stereoisomer, ER-811474:

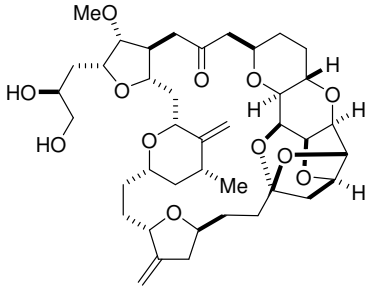


ER-811474.

The method may further include adding a mixture of acetonitrile and water to increase the yield of ER-811475.

In some ~~embodiments~~examples, each of R^1, R^2, R^3, R^4, and R^5 is *t*-butyldimethylsilyl (TBS).

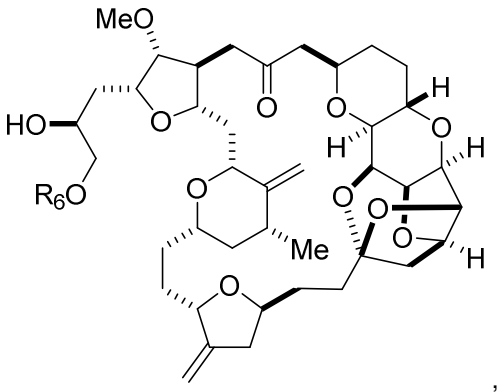
The ~~invention~~disclosure further features a method of preparing an intermediate in the synthesis of eribulin including reacting (e.g., in ethanol) ER-811475 with a conjugate acid of imidazole (e.g., imidazole hydrochloride) to produce the intermediate ER-076349:



ER-076349.

ER-811475 can be produced by any of the methods provided herein.

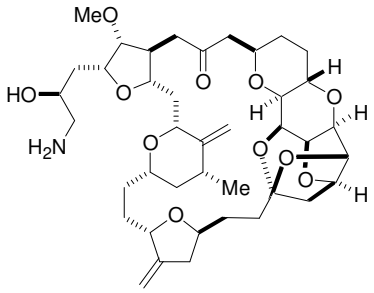
In another ~~aspect~~example, the ~~invention~~disclosure features a method of preparing an intermediate in the synthesis of eribulin. This method includes reacting (e.g., in acetonitrile) ER-076349 with a sulfonylating reagent, e.g., tosyl chloride, in the presence of a metal catalyst (e.g., dibutyltin oxide) to produce the intermediate:



,

wherein R_6 is sulfonyl, e.g.,**ER-082892**. The reacting may occur above 0°C. ER-076349 can be produced by any of the methods provided herein. The methods may also include addition of a base, e.g., a C1-6 trialkylamine, such as triethylamine or *N*,*N*-diisopropylethylamine.

The ~~invention~~disclosure also features a method of producing eribulin. This method includes producing intermediate ER-811475 by any one of the foregoing methods, ketalizing ER-811475 to produce the intermediate ER-076349, and aminating ER-076349 to produce eribulin (ER-086526):



eribulin.

The step of ketalizing ER-811475 may include converting ER-811475 to ER-076349 according to any of the methods provided herein. The step of aminating ER-076349 to produce eribulin may include converting ER-076349 to ER-082892 according to any of the methods provided herein.

The ~~invention~~disclosure further features an alternative method of producing eribulin. This method includes producing intermediate ER-076349 by any one of the foregoing methods and aminating ER-076349 to produce eribulin. The step of aminating ER-076349 to produce eribulin may include converting ER-076349 to ER-082892 according to any of the methods provided herein.

In a further ~~aspect~~example, the ~~invention~~disclosure features yet another method of producing eribulin. This method includes producing intermediate ER-082892 by any of the methods provided herein and aminating ER-082892 to produce eribulin.

Any method of producing eribulin may further include salifying eribulin to produce a pharmaceutically acceptable salt of eribulin (e.g., eribulin mesylate).

The ~~invention~~disclosure further features a method of manufacturing a pharmaceutical product including eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate). This method includes producing or directing the production of eribulin or a pharmaceutically acceptable salt thereof by any one of the foregoing methods and processing or directing the processing of eribulin or a pharmaceutically acceptable salt thereof into a pharmaceutical product including eribulin or a pharmaceutically acceptable

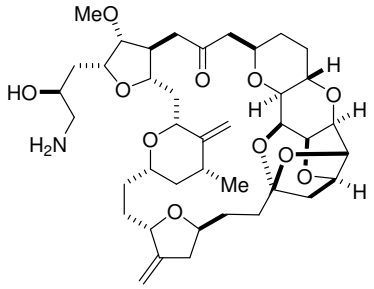
in the art, e.g., as described in *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience, 4th Edition, 2006. Specific examples of silyl groups include trimethylsilyl (TMS), triethylsilyl (TES), *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl (TBDPS), triisopropylsilyl (TIPS), and triphenylsilyl (TPS) ethers. Silyl groups may be substituted as is known in the art; for example, aryl and arylalkyl groups, such as phenyl, benzyl, naphthyl, or pyridinyl, can be substituted with C1-C6 alkyl, C1-C6 alkoxy, nitro, cyano, carboxyl, or halogen. Alkyl groups, such as methyl, ethyl, isopropyl, *n*-propyl, *t*-butyl, *n*-butyl, and *sec*-butyl, and alkenyl groups, such as vinyl and allyl, can also be substituted with oxo, arylsulfonyl, halogen, and trialkylsilyl groups.

By "sulfonyl" is meant $-S(O)_2R$, wherein R is alkyl, alkenyl, aryl, arylalkyl, or silyl. In exemplary sulfonyl groups, R is C1-C12 alkyl (e.g., C1-C8, C1-C6, C1-C4, C2-C7, C3-C12, and C3-C6 alkyl), C2-C12 alkenyl (e.g., C2-C8, C2-C6, C2-C4, C3-C12, and C3-C6 alkenyl), carbocyclic C6-C20 aryl (e.g., C6-C15, C6-C10, C8-C20, and C8-C15 aryl), monocyclic C1-C6 heteroaryl (e.g., C1-C4 and C2-C6 heteroaryl), C4-C19 heteroaryl (e.g., C4-C10 heteroaryl), (C6-C15)aryl(C1-C6)alkyl, (C4-C19)heteroaryl(C1-C6)alkyl, or (C1-C6)heteroaryl(C1-C6)alkyl. As defined herein, any heteroaryl group present in a sulfonyl group has from 1 to 4 heteroatoms selected independently from O, N, and S. Exemplary sulfonyl groups include tosyl, triflyl, and mesyl.

Other features and advantages of the ~~invention~~disclosure will be apparent from the following description and the claims.

DETAILED DESCRIPTION OF THE INVENTION

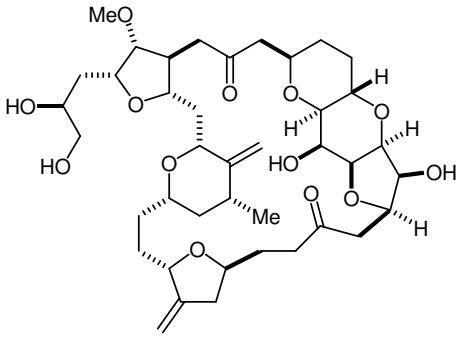
The present invention provides methods for the synthesis of halichondrin B analogs. In particular, the methods are useful for the synthesis of eribulin and pharmaceutically acceptable salts thereof:



eribulin.

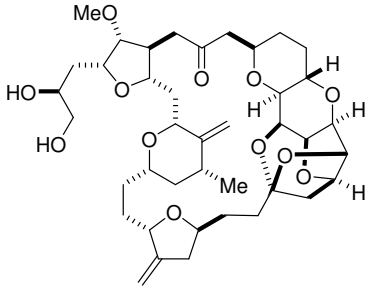
CLAIMS

1. A method of preparing an intermediate in the synthesis of eribulin, said method comprising reacting ER-811475:



ER-811475

with a conjugate acid of imidazole to produce the intermediate ER-076349:

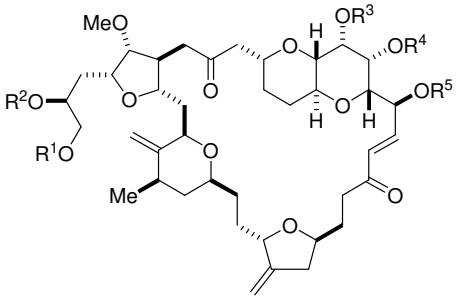


ER-076349.

2. The method of claim 1, wherein the reacting occurs in ethanol.

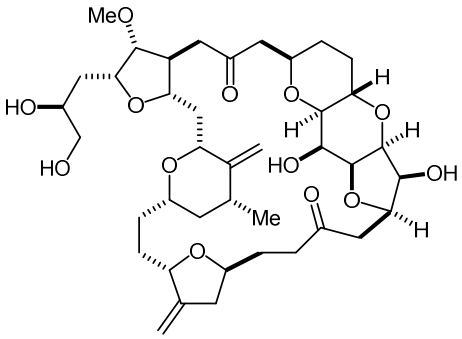
3. The method of claim 1, wherein the conjugate acid is imidazole hydrochloride.

4. The method of claim 1, wherein ER-811475 is produced by reacting a compound having formula (I):



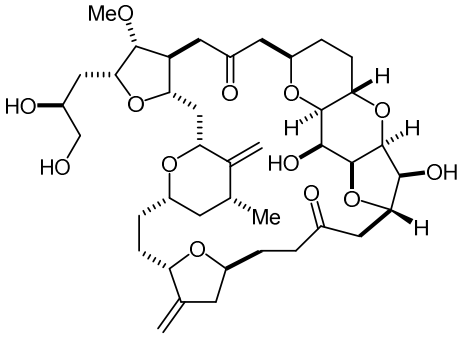
(I),

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 to produce the intermediate ER-811475:



ER-811475.

5. The method of claim 4, wherein ER-811475 is produced in a mixture with an intermediate ER811474:



ER-811474.

6. The method of claim 5, further comprising adding a mixture of acetonitrile and water.

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

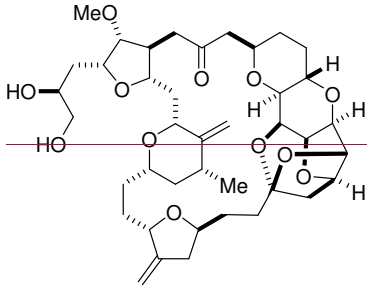
8. The method of claim 4, wherein the fluoride source is tetrabutylammonium fluoride.

9. The method of claim 4, wherein the solvent further comprises tetrahydrofuran.

10. The method of claim 4, wherein the amide is an N,N C1-C6 dialkyl C1-C6 alkyl amide or N C1-C6 alkyl C2-C6 lactam.

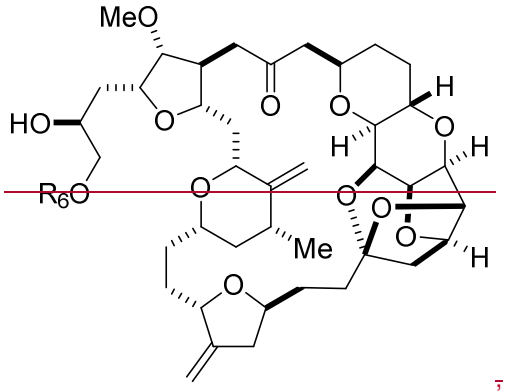
11. The method of claim 4, wherein the amide is N,N-dimethylacetamide, N,N-dimethylformamide, N-methyl-2-pyrrolidone, N, N-diethylacetamide, or N,N-dimethylpropionamide.

~~12. A method of preparing an intermediate in the synthesis of eribulin, said method comprising reacting ER-076349:~~



~~ER-076349~~

~~with a sulfonylating reagent in the presence of a metal catalyst to produce the intermediate:~~



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~~wherein R_6 is sulfonyl, wherein sulfonyl is —$S(O)_2R$, wherein R is alkyl, alkenyl, aryl, arylalkyl, or silyl.~~

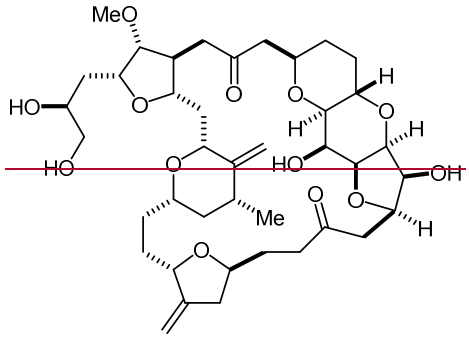
~~13. The method of claim 12, wherein the sulfonylating reagent is tosyl chloride.~~

~~14. The method of claim 12, wherein the reacting occurs in acetonitrile.~~

~~15. The method of claim 12, wherein said metal catalyst is dibutyltin oxide.~~

~~16. The method of claim 12, wherein the reacting occurs above 0 °C.~~

~~17. The method of claim 12, wherein ER-076349 is produced by reacting ER-811475:~~

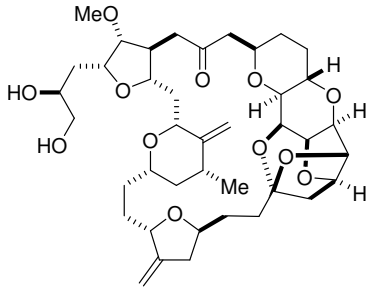


~~ER-811475~~

~~with a conjugate acid of imidazole.~~

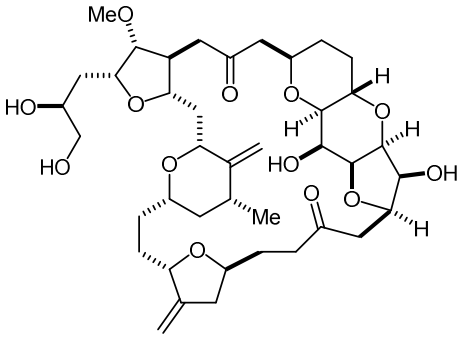
~~18~~12. A method of producing eribulin, said method comprising the steps of:

a) producing the intermediate ER-076349:



ER-076349

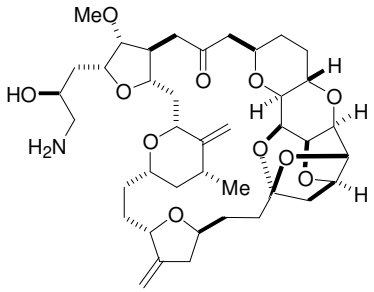
by reacting ER-811475



ER-811475

with a conjugate acid of imidazole to produce the intermediate ER-076349; and

b) aminating ER-076349 to produce eribulin:

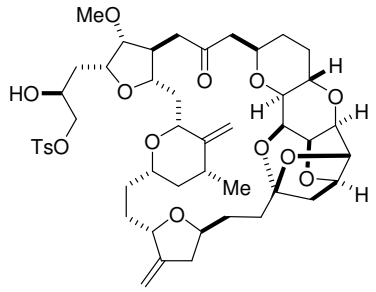


eribulin.

~~19~~13. The method of claim ~~18~~12, further comprising salifying eribulin to produce a pharmaceutically acceptable salt of eribulin.

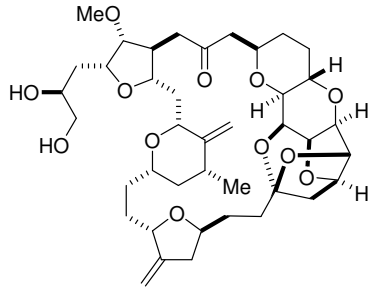
~~20~~14. The method of claim ~~19~~13, wherein said salt is the mesylate salt.

~~21~~15. The method of claim ~~18~~12, wherein step b) comprises converting the intermediate ER-076349 to ER-082892:



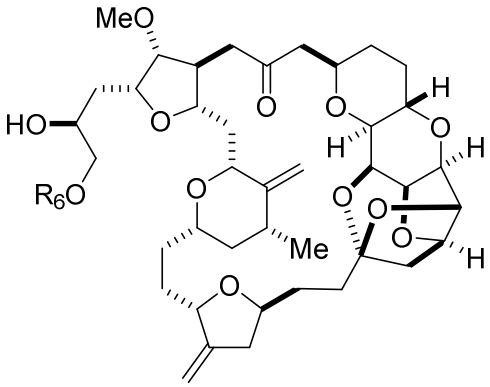
ER-082892

according to a method comprising reacting the intermediate ER-076349:



ER-076349

with a sulfonylating reagent in the presence of a metal catalyst to produce the intermediate:



,

wherein R_6 is sulfonyl, wherein sulfonyl is —$S(O)_2R$, wherein R is alkyl, alkenyl, aryl, arylalkyl, or silyl.

~~22~~16. The method of claim ~~21~~15, wherein the sulfonylating agent is tosyl chloride.

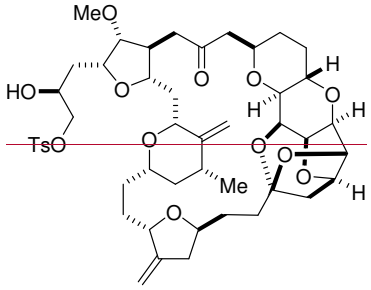
~~23~~17. The method of claim ~~21~~15, wherein the reacting occurs in acetonitrile.

~~24~~18. The method of claim ~~21~~15, wherein the metal catalyst is dibutyltin oxide.

~~25~~19. The method of claim ~~21~~15, wherein the reacting occurs above 0 °C.

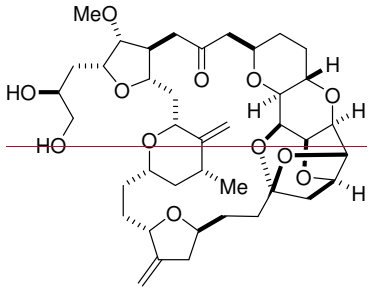
~~26. A method of producing eribulin, said method comprising the steps of:~~

~~a) producing the intermediate ER-082892:~~



~~ER-082892~~

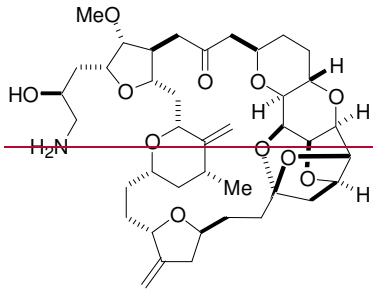
~~by reacting ER-076349~~



~~ER-076349~~

~~with a sulfonylating reagent in the presence of a metal catalyst; and~~

~~b) aminating ER-082892 to produce eribulin:~~



~~eribulin~~.

~~27. The method of claim 26, further comprising salifying eribulin to produce a pharmaceutically acceptable salt of eribulin.~~

~~28. The method of claim 27, wherein said salt is the mesylate salt.~~

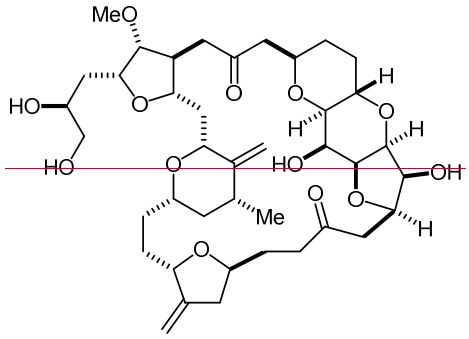
~~29. The method of claim 26, wherein the sulfonylating agent is tosyl chloride.~~

~~30. The method of claim 26, wherein the reacting occurs in acetonitrile.~~

~~31. The method of claim 26, wherein said metal catalyst is dibutyltin oxide.~~

~~32. The method of claim 26, wherein the reacting occurs above 0 °C.~~

~~33. The method of claim 26, wherein ER-076349 is produced by reacting ER-811475:~~



~~**ER-811475**~~

~~with a conjugate acid of imidazole.~~