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(54) **Title**: MICROREACTOR PROCESS FOR HALICHONDRIN B ANALOG SYNTHESIS

(57) **Abstract**: The present invention provides methods for producing eribulin, intermediates useful for the synthesis of eribulin, or pharmaceutically acceptable salts thereof, e.g., eribulin mesylate using microreactors.

DESCRIPTION

TITLE OF INVENTION

MICROREACTOR PROCESS FOR HALICHONDRIN B ANALOG SYNTHESIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional application no. 61/480,098, filed April 28, 2011, which is hereby incorporated by reference.

TECHNICAL FIELD

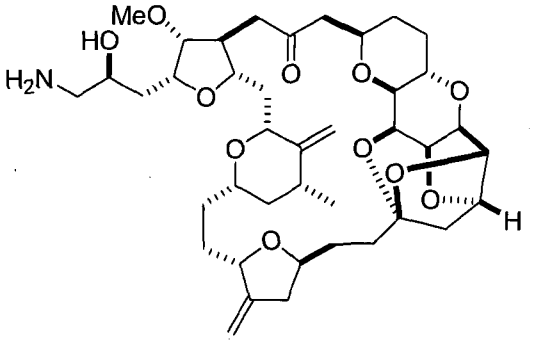
The present invention relates to methods for the preparation of compounds useful as intermediates in the synthesis of pharmaceutically active macrolide compounds.

BACKGROUND ART

Halichondrin B is a potent anticancer agent originally isolated from the marine sponge *Halichondria okadai*, and subsequently found in *Axinella* sp., *Phakellia carteri*, and *Lissodendoryx* sp. A total synthesis of halichondrin B was published in 1992 (Aicher, T. D. et al., *J. Am. Chem. Soc.* 114:3162-3164). Eribulin (also called B1939), a nontaxane microtubule dynamics inhibitor, is a structurally simplified, synthetic analog of halichondrin B. The mesylate salt of eribulin is also known as Halaven® or E7389. Methods and intermediates for the synthesis of eribulin mesylate and other halichondrin B analogs are described in International Publication Nos. WO 2005/118565, WO 2009/046308, WO 2009/064029, and WO 2009/124237 and U.S. Patent No. 6,214,865. New methods for the synthesis of halichondrin B analogs, in particular eribulin, are desirable.

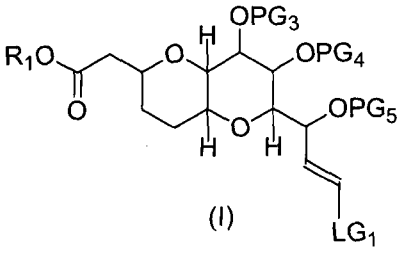
DISCLOSURE OF INVENTION

The present invention provides methods for producing eribulin, intermediates useful for the synthesis of eribulin, or pharmaceutically acceptable salts thereof, e.g., eribulin mesylate:



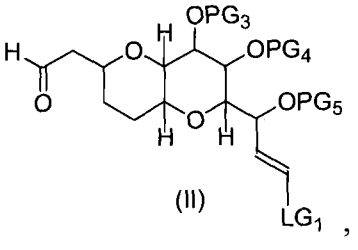
eribulin.

In one aspect, the invention features a method of producing a compound of Formula (II) from a compound of Formula (I) by contacting the compound of Formula (I):



(I)

with a reducing agent in a microreactor for a time sufficient to produce the compound of Formula (II):

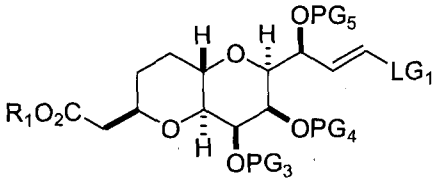


(II) ,

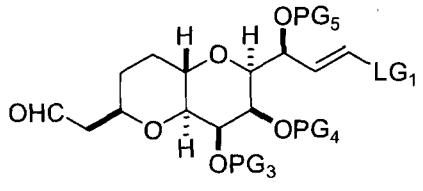
wherein each of PG_3, PG_4, and PG_5 is independently a hydroxyl protecting group; R_1 is C1 – C6 alkyl; and LG_1 is a leaving group.

In certain embodiments, one, two, or three of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II), taken with the oxygen atom(s) to which they are bound, are silyl ethers or arylalkyl ethers. For example, one, two, or three of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II) are t-butyldimethylsilyl (TBS) or benzyl, or all of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II) are t-butyldimethylsilyl (TBS). In other embodiments, LG_1 is a halogen, (C1-C6)alkylsulfonate, (C6-C10 aryl or C1-C6 heteroaryl)sulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate. Specific examples of LG_1 include iodide, mesylate, toluenesulfonate, isopropylsulfonate, phenylsulfonate, and benzylsulfonate.

The compounds of Formula (I) and Formula (II) can have the absolute stereochemistry:

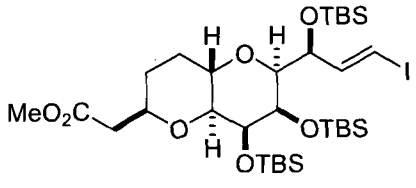


(I)-A



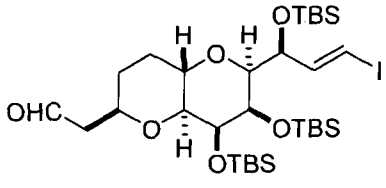
(II)-A.

A specific compound of Formula (I) for use in the present methods is



ER-803895.

A specific compound of Formula (II) for use in the present methods is



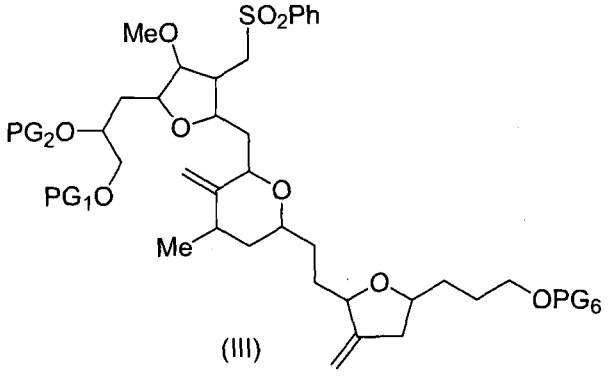
ER-803896.

Exemplary reducing agents include an aluminum hydride reagent or a borohydride reagent, e.g., lithium aluminum hydride, sodium aluminum hydride, diisobutylaluminum hydride

(DIBAL-H), sodium bis(2-methoxyethoxy)aluminum hydride (Red Al), sodium borohydride, potassium borohydride, rubidium borohydride, cesium borohydride, or sodium cyanoborohydride.

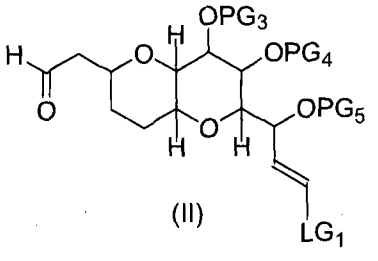
In certain embodiments, the temperature of the microreactor is between -80 and -20 °C. The residence time of the compound of Formula I in the microreactor is, e.g., 0.01 sec to 1 sec.

In another aspect, the invention features a method of producing a compound of Formula (IV) from a compound of Formula (II) and a compound of Formula (III), by contacting the compound of Formula (III):



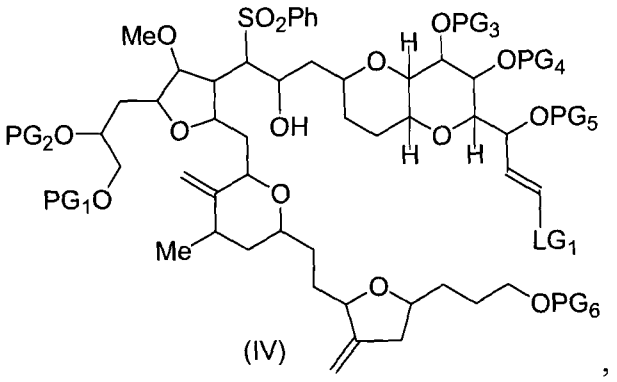
(III)

with a base in a microreactor for a time sufficient to deprotonate the compound of formula (III), wherein each of PG_1 and PG_2 is independently a hydroxyl protecting group, and PG_6 is hydrogen or a hydroxyl protecting group; and contacting the deprotonation product with a compound of Formula (II):



(II)

in a microreactor for a time sufficient to produce the compound of formula (IV):



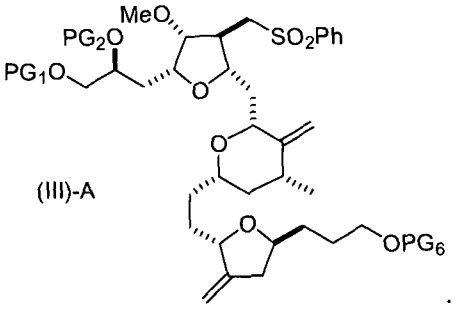
(IV)

,

wherein each of PG_3, PG_4, and PG_5 is independently a hydroxyl protecting group; and LG_1 is a leaving group.

In certain embodiments, one or both of PG_1 and PG_2 of Formula (III), taken with the oxygen atom(s) to which they are bound, are silyl ethers or arylalkyl ethers. For example, one or both of PG_1 and PG_2 are TBS or benzyl, or both PG_1 and PG_2 are TBS.

In certain embodiments, the compound of Formula (III) has the absolute stereochemistry:



(III)-A

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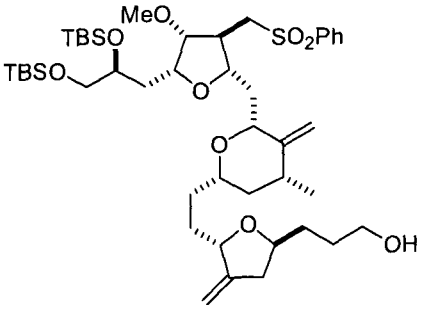
A specific compound of Formula (III) for use in the methods is ER-804028:



ER-804028

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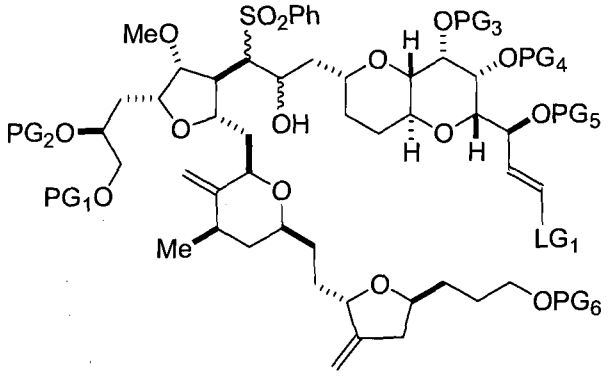
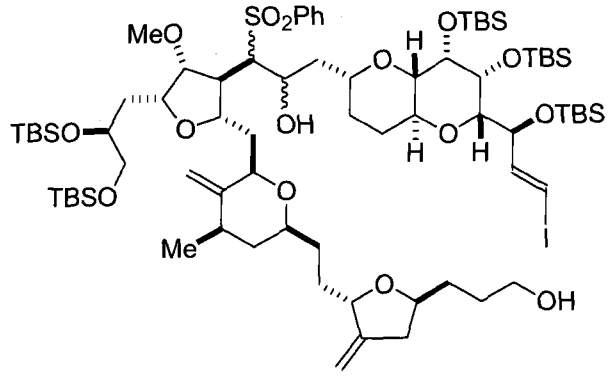
In certain embodiments, the compound of Formula(II) has the absolute stereochemistry of Formula (II)-A, or the compound is ER-803896. The method of producing the compound of Formula (IV) may further include synthesizing the compound of Formula (II) using the methods described herein.

In certain embodiments, the compound of Formula (IV) has the stereochemistry:



(IV)-A.

A specific compound of Formula IV that can be produced by the methods is ER-804029:



ER-804029.

The base can be an organometallic reagent, such as a Grignard's reagent, potassium bis(trimethylsilyl) amide, sodium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, *n*-butyl lithium, *sec*-butyl lithium, or *tert*-butyl lithium.

In other embodiments, the temperature of the microreactor in the deprotonation and/or coupling step is between -80 to 20 °C. The residence time of the compound of Formula (III) in

the deprotonation step is, e.g., 0.1 sec to 20 sec. The residence time of the compound of Formula (II) and the compound of Formula (III) in the coupling step is, e.g., 0.1 sec to 20 sec.

The invention further features a method of producing eribulin, or a pharmaceutically acceptable salt thereof, by producing a compound of Formula (II), e.g., ER-803896, as described herein and reacting the compound of Formula (II) under suitable conditions to produce eribulin, or a pharmaceutically acceptable salt thereof, e.g., eribulin mesylate. In these methods, the compound of Formula (II) can be coupled to a compound of Formula (III), e.g., ER-804028, to produce a compound of Formula (IV), e.g., ER-804029, and the compound of Formula (IV) can be reacted to produce eribulin, or the pharmaceutically acceptable salt thereof.

In another aspect, the invention features a method of producing eribulin, or a pharmaceutically acceptable salt thereof, by producing a compound of Formula (IV), e.g., ER-804029, as described herein; and reacting the compound of Formula (IV) under suitable conditions to produce eribulin, or a pharmaceutically acceptable salt thereof, e.g., eribulin mesylate.

Asymmetric or chiral centers exist in the compounds of the invention. The present invention includes the various stereoisomers of the compounds and mixtures thereof, unless otherwise specified. Individual stereoisomers of the compounds of the present invention are prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers or by preparation of mixtures of compounds followed by resolution, as is well known in the art. These methods of resolution are exemplified by direct separation of the mixture of diastereomers on chiral chromatographic columns or by chiral HPLC methods. Methods of chiral separation have been described previously (G.B. Cox (ed.) in *Preparative Enantioselective Chromatography*, 2005, Blackwell Publishing). Alternatively, chiral compounds can be prepared by an asymmetric synthesis that favors the preparation of one

diastereomer over another. Geometric isomers may also exist in the compounds of the present invention. The present invention includes the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond, such as isomers of the Z or E configuration. It is also recognized that for structures in which tautomeric forms are possible, the description of one tautomeric form is equivalent to the description of both, unless otherwise specified. In certain embodiments, a diastereomer of a compound of the invention is present in a mixture at a ratio of 10:1, 20:1, 30:1, 50:1, or greater as compared to other diastereomers.

Compounds useful in the invention may be isotopically labeled compounds. Useful isotopes include hydrogen, carbon, nitrogen, and oxygen (e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, and ^{17}O). Isotopically-labeled compounds can be prepared by synthesizing a compound using a readily available isotopically-labeled reagent in place of a non-isotopically-labeled reagent.

For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C2 alkyl group has the formula $-CH_2CH_3$. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

By "acetal" is meant -OCHRO-, wherein R is H, alkyl, alkenyl, aryl, or arylalkyl.

By "acyl" is meant –C(O)R, wherein R is H, alkyl, alkenyl, aryl, or arylalkyl. In exemplary acyl groups, R is H, 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), C6-C20 aryl (e.g., C6-C15, C6-C10, C8-C20, and C8-C15 aryl), monocyclic C1-C6 heteroaryl (e.g., monocyclic C1-C4 and C2-C6 heteroaryl), C4-C19 heteroaryl (e.g., C4-C10 heteroaryl), (C6-C15)aryl(C1-C6)alkyl, (C1-C6)heteroaryl(C1-C6)alkyl, or (C4-C19)heteroaryl(C1-C6)alkyl. As defined herein, any heteroaryl group present in an acyl group has from 1 to 4 heteroatoms selected independently from O, N, and S.

By "alkyl" is meant a straight or branched chain saturated cyclic (i.e., cycloalkyl) or acyclic hydrocarbon group of from 1 to 12 carbons, unless otherwise specified. Exemplary alkyl groups include C1-C8, C1-C6, C1-C4, C2-C7, C3-C12, and C3-C6 alkyl. Specific examples include methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl, and the like. Unless otherwise noted, alkyl groups, used in any context herein, are optionally substituted with halogen, alkoxy, aryloxy, arylalkyloxy, oxo, alkylthio, alkylenedithio, alkylamino, [alkenyl]alkylamino, [aryl]alkylamino, [arylalkyl]alkylamino, dialkylamino, silyl, sulfonyl, cyano, nitro, carboxyl, or azido.

By "alkylamino" is meant –NHR, wherein R is alkyl. By "[alkenyl]alkylamino" is meant –NRR', wherein R is alkyl, and R' is alkenyl. By "[aryl]alkylamino" is meant –NRR', wherein R is alkyl, and R' is aryl. By "[arylalkyl]alkylamino" is meant –NRR', wherein R is alkyl, and R' is arylalkyl. By "dialkylamino" is meant $-NR_2$, wherein each R is alkyl, selected independently.

By "alkylene" is meant a divalent alkyl group. Alkylene groups, used in any context herein, are optionally substituted in the same manner as alkyl groups. For example, a C1 alkylene group is $-CH_2-$.

By "alkylenedithio" is meant –S-alkylene-S-.

By "alkylthio" is meant –SR, wherein R is alkyl.

By "alkenyl" is meant a straight or branched chain cyclic or acyclic hydrocarbon group of, unless otherwise specified, from 2 to 12 carbons and containing one or more carbon-carbon double bonds. Exemplary alkenyl groups include C2-C8, C2-C7, C2-C6, C2-C4, C3-C12, and C3-C6 alkenyl. Specific examples include ethenyl (i.e., vinyl), 1-propenyl, 2-propenyl (i.e., allyl), 2-methyl-1-propenyl, 1-butenyl, 2-butenyl (i.e., crotyl), and the like. Alkenyl groups, used in any context herein, are optionally substituted in the same manner as alkyl groups. Alkenyl groups, used in any context herein, may also be substituted with an aryl group.

By "alkoxy" is meant –OR, wherein R is alkyl.

By "aryl" is meant a monocyclic or multicyclic ring system having one or more aromatic rings, wherein the ring system is carbocyclic or heterocyclic. Heterocyclic aryl groups are also referred to as heteroaryl groups. A heteroaryl group includes 1 to 4 atoms selected independently from O, N, and S. Exemplary carbocyclic aryl groups include C6-C20, C6-C15, C6-C10, C8-C20, and C8-C15 aryl. A preferred aryl group is a C6-10 aryl group. Specific examples of carbocyclic aryl groups include phenyl, indanyl, indenyl, naphthyl, phenanthryl, anthracyl, and fluorenyl. Exemplary heteroaryl groups include monocylic rings having from 1 to 4 heteroatoms selected independently from O, N, and S and from 1 to 6 carbons (e.g., C1-C6, C1-C4, and C2-C6). Monocyclic heteroaryl groups preferably include from 5 to 9 ring members. Other heteroaryl groups preferably include from 4 to 19 carbon atoms (e.g., C4-C10). Specific examples of heteroaryl groups include pyridinyl, quinolinyl, dihydroquinolinyl, isoquinolinyl, quinazolinyl, dihydroquinazolyl, and tetrahydroquinazolyl. Unless otherwise specified, aryl groups, used in any context herein, are optionally substituted with alkyl, alkenyl, aryl, arylalkyl, halogen, alkoxy, aryloxy, arylalkyloxy, oxo, alkylthio, alkylenedithio, alkylamino, [alkenyl]alkylamino, [aryl]alkylamino, [arylalkyl]alkylamino, dialkylamino, silyl, sulfonyl, cyano, nitro, carboxyl, or azido.

By "arylalkyl" is meant –R'R", wherein R' is alkylene, and R" is aryl.

By "arylalkyloxy" is meant –OR, wherein R is arylalkyl.

By "aryloxy" is meant –OR, wherein R is aryl.

By "carbamate" is meant $-OC(O)NR_2$, wherein each R is independently H, alkyl, alkenyl, aryl, or arylalkyl.

By "carbonate" is meant –OC(O)OR, wherein R is alkyl, alkenyl, aryl, or arylalkyl.

By "carboxyl" is meant –C(O)OH, in free acid, ionized, or salt form.

By "cyclic boronate" is meant –OBRO-, wherein R is alkyl, alkenyl, aryl, arylalkyl, alkoxy, or 2,6-diacetamidophenyl.

By "cyclic carbonate" is meant –OC(O)O-.

By "cyclic silylene" is meant $-OSiR_2O-$, wherein each R is independently alkyl, alkenyl, aryl, arylalkyl, or alkoxy. By "dialkylsilylene" is meant a cyclic silylene, wherein each R is alkyl.

By "ester" is meant –OC(O)R, where –C(O)R is an acyl group, as defined herein, that is bound to the oxygen atom of a protected hydroxyl, as defined below.

By "ether" is meant –OR, wherein R is alkyl, alkenyl, arylalkyl, silyl, or 2-tetrahydropyranyl.

By "halogen" is meant fluoro, chloro, bromo, or iodo.

By "ketal" is meant $-OCR_2O-$, wherein each R is independently alkyl, alkenyl, aryl, or arylalkyl, or both R groups are together alkylene.

By "oxo" or (O) is meant =O.

By "silyl" is meant $-SiR_3$, wherein each R is independently alkyl, alkenyl, aryl, or arylalkyl. Examples of silyl groups include tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, and (C6-C10 aryl or C1-

C6 heteroaryl)di(C1-C6 alkyl)silyl. It will be understood that, when a silyl group includes two or more alkyl, alkenyl, aryl, heteroaryl, or arylalkyl groups, these groups are independently selected. As defined herein, any heteroaryl group present in a silyl group has from 1 to 4 heteroatoms selected independently from O, N, and S.

By "sulfonate" is meant $-OS(O)_2R$, wherein R is alkyl, alkenyl, aryl, or arylalkyl. In exemplary sulfonates, 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 sulfonate group has from 1 to 4 heteroatoms selected independently from O, N, and S.

By "sulfonyl" is meant $-S(O)_2R$, wherein R is alkyl, alkenyl, aryl, arylalkyl, or silyl. Preferred R groups for sulfonyl are the same as those described above for sulfonates.

By "hydroxyl protecting group" is meant any group capable of protecting the oxygen atom to which it is attached from reacting or bonding. Hydroxyl protecting groups are known in the art, e.g., as described in Wuts, *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience, 4th Edition, 2006. Exemplary protecting groups (with the oxygen atom to which they are attached) are independently selected from esters, carbonates, carbamates, sulfonates, and ethers.

In exemplary ester hydroxyl protecting groups, R of the acyl group 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. Specific examples of acyl groups for use in esters include formyl, benzoylformyl, acetyl (e.g., unsubstituted or chloroacetyl, trifluoroacetyl, methoxyacetyl, triphenylmethoxyacetyl, and p-chlorophenoxyacetyl), 3-phenylpropionyl, 4-oxopentanoyl, 4,4-(ethylenedithio)pentanoyl, pivaloyl (Piv), vinylpivaloyl, crotonoyl, 4-methoxy-crotonoyl, naphthoyl (e.g., 1- or 2-naphthoyl), and benzoyl (e.g., unsubstituted or substituted, e.g., p-methoxybenzoyl, phthaloyl (including salts, such a triethylamine and potassium), p-bromobenzoyl, and 2,4,6-trimethylbenzoyl). As defined herein, any heteroaryl group present in an ester group has from 1 to 4 heteroatoms selected independently from O, N, and S.

In exemplary carbonate hydroxyl protecting 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. Specific examples include methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, t-butyl, p-nitrobenzyl, and benzyl carbonates. As defined herein, any heteroaryl group present in a carbonate group has from 1 to 4 heteroatoms selected independently from O, N, and S.

In exemplary carbamate hydroxyl protecting groups, each R is independently H, 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. Specific examples include N-phenyl and N-methyl-N-(o-nitrophenyl) carbamates. As defined herein, any heteroaryl group present in a carbamate group has from 1 to 4 heteroatoms selected independently from O, N, and S.

Exemplary ether hydroxyl protecting groups include C1-C12 alkylethers (e.g., C1-C8, C1-C6, C1-C4, C2-C7, C3-C12, and C3-C6 alkyl), C2-C12 alkenylethers (e.g., C2-C8, C2-C6, C2-C4, C3-C12, and C3-C6 alkenyl), (C6-C15)aryl(C1-C6)alkylethers, (C4-C19)heteroaryl(C1-C6)alkylethers, (C1-C6)heteroaryl(C1-C6)alkylethers, (C1-C6)alkoxy(C1-C6)alkylethers, (C1-C6)alkylthio(C1-C6)alkylethers, (C6-C10)aryl(C1-C6)alkoxy(C1-C6)alkylethers, and silylethers (e.g., tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, and (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl). Specific examples of alkylethers include methyl and t-butyl, and an example of an alkenyl ether is allyl. Examples of alkoxyalkylethers and alkylthioalkylethers include methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, and β-(trimethylsilyl)ethoxymethyl. Examples of arylalkylethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, triphenylmethyl (trityl), o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, naphthylmethyl, and 2- and 4-picolyl ethers. Specific examples of silylethers include trimethylsilyl (TMS), triethylsilyl (TES), t-butyldimethylsilyl (TBS), t-butyldiphenylsilyl (TBDPS), triisopropylsilyl (TIPS), and triphenylsilyl (TPS) ethers. An example of an arylalkyloxyalkylether is benzyloxymethyl ether. As defined herein, any heteroaryl group present in an ether group has from 1 to 4 heteroatoms selected independently from O, N, and S.

Adjacent hydroxyl groups may be protected with a diol protecting group, such as acetal (e.g., C1-C6 alkyl), ketal (e.g., C3-C6 alkyl or C3-C6 cycloalkyl), cyclic silylene, cyclic carbonate, and cyclic boronate. Examples of acetal and ketal groups include methylene,

ethylidene, benzylidene, isopropylidene, cyclohexylidene, and cyclopentylidene. An example of a cyclic silylene is di-t-butylsilylene. Another diol protecting group is 1,1,3,3-tetraisopropylsiloxanediyl. Examples of cyclic boronates include methyl, ethyl, phenyl, and 2,6-diacetamidophenyl boronates.

Protecting 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. Preferred protecting groups are TBS and Piv. Protecting groups that are orthogonal are removed under different conditions, as in known in the art.

By "leaving group" is meant a group that is displaced during a chemical reaction. Suitable leaving groups are well known in the art, e.g., see, *Advanced Organic Chemistry*, March, 4th Ed., pp. 351-357, John Wiley and Sons, N.Y. (1992). Such leaving groups include halogen, C1-C12 alkoxy (e.g., C1-C8, C1-C6, C1-C4, C2-C7, and C3-C6 alkoxy), C1-C12 alkylsulfonate (e.g., C1-C8, C1-C6, C1-C4, C2-C7, C3-C12, and C3-C6 alkylsulfonate), C2-C12 alkenylsulfonate (e.g., C2-C8, C2-C6, C2-C4, C3-C12, and C3-C6 alkenylsulfonate), carbocyclic C6-C20 arylsulfonate (e.g., C6-C15, C6-C10, C8-C20, and C8-C15 arylsulfonate), C4-C19 heteroarylsulfonate (e.g., C4-C10 heteroarylsulfonate), monocyclic C1-C6 heteroarylsulfonate (e.g., C1-C4 and C2-C6 heteroarylsulfonate), (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, (C1-C6)heteroaryl(C1-C6)alkylsulfonate, and diazonium. Alkylsulfonates, alkenylsulfonates, arylsulfonates, heteroarylsulfonates, arylalkylsulfonates, and heteroarylalkylsulfonates can be optionally substituted with halogen (e.g., chloro, iodo, bromo, or fluoro), alkoxy (e.g., C1-C6 alkoxy), aryloxy (e.g., C6-C15 aryloxy, C4-C19 heteroaryloxy,

and C1-C6 heteroaryloxy), oxo, alkylthio (e.g., C1-C6 alkylthio) , alkylenedithio (e.g., C1-C6 alkylenedithio), alkylamino (e.g., C1-C6 alkylamino), [alkenyl]alkylamino (e.g., [(C2-C6)alkenyl](C1-C6)alkylamino), [aryl]alkylamino (e.g., [(C6-C10)aryl](C1-C6)alkylamino, [(C1-C6)heteroaryl](C1-C6)alkylamino, and [(C4-C19)heteroaryl](C1-C6)alkylamino), [arylalkyl]alkylamino (e.g., [(C6-C10)aryl(C1-C6)alkyl](C1-C6)alkylamino, [(C1-C6)heteroaryl(C1-C6)alkyl](C1-C6)alkylamino, and [(C4-C19)heteroaryl(C1-C6)alkyl](C1-C6)alkylamino), dialkylamino (e.g., di(C1-C6 alkyl)amino), silyl (e.g., tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, and (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl), cyano, nitro, or azido. Alkenylsulfonates can be optionally substituted with carbocyclic aryl (e.g., C6-C15 aryl), monocyclic C1-C6 heteroaryl, or C4-C19 heteroaryl (e.g., C4-C10 heteroaryl). Arylsulfonates can be optionally substituted with alkyl (e.g., C1-C6 alkyl) or alkenyl (e.g. C2-C6 alkenyl). As defined herein, any heteroaryl group present in a leaving group has from 1 to 4 heteroatoms selected independently from O, N, and S.

Specific examples of suitable leaving groups include chloro, iodo, bromo, fluoro, methanesulfonate (mesylate), 4-toluenesulfonate (tosylate), trifluoromethanesulfonate (triflate, OTf), nitro-phenylsulfonate (nosylate), and bromo-phenylsulfonate (brosylate). Leaving groups may also be further substituted as is known in the art.

The term "microreactor" used in the present specification refers to a reaction vessel in which at least two fluids are combined and allowed to react, wherein the vessel has at least one interior dimension of 1 mm or less, e.g., the diameter of tubing or a transverse dimension of a fluidic chip.

By "pharmaceutically acceptable salt" is meant a salt within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue

toxicity, irritation, allergic response and the like and commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. A preferred salt is the mesylate salt.

By "residence time" is meant the time during which a mixture of reactants passes through the volume of a microreactor lying between the points at which two or more reactants first mix completely and the addition of a further reactant or quenching agent.

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

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a schematic depiction of a microreactor system for converting ER-803895 to ER-803896.

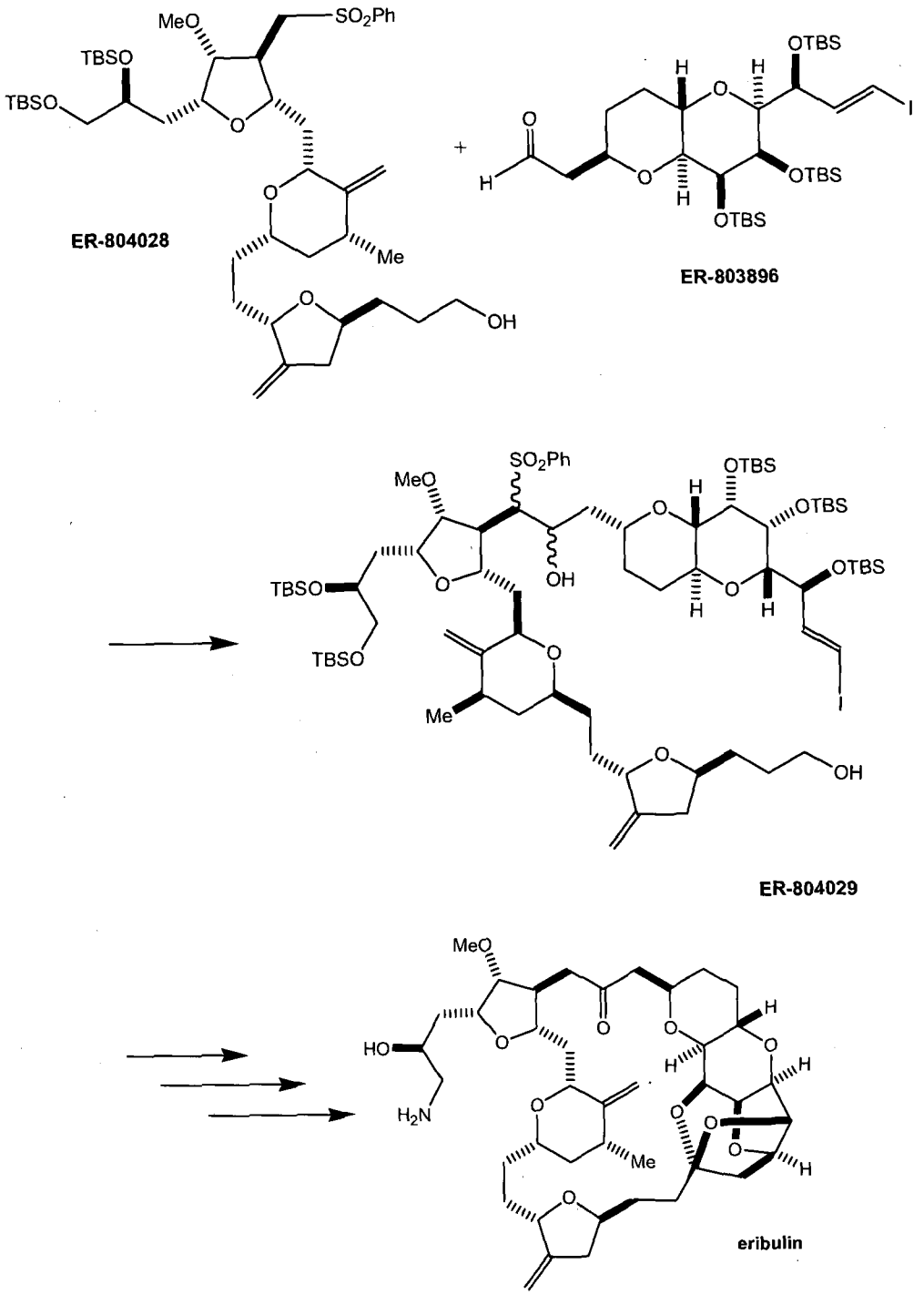
Figure 2 is a schematic depiction of a microreactor system for converting ER-803895 to ER-803896. In Figure 2, the lines from Pumps A, B and C are SUS (ϕ 0.8 mm x 2 m); the line

from Pump D is Teflon (ϕ 0.8 mm); Pump A is Shimadzu HPLC LC10AD; Pumps B and C are Shimadzu HPLC LC8A; and Pump D is EYELA VSP2200.

Figure 3 is a schematic depiction of a microreactor system for producing ER-804029 from ER-804028 and ER-803896.

BEST MODE FOR CARRYING OUT THE INVENTION

Halichondrin B analogs, e.g., eribulin or pharmaceutically acceptable salts thereof, can be synthesized by coupling the C1-C13 and C14-C35 fragments as described in U.S. Patent No. 6,214,865 and International Publication No. WO 2005/118565. A key step in this synthesis is the coupling of an anion or dianion of a C14-35 fragment with an aldehyde of a C1-13 fragment. In one example described in these references, the C14-C35 portion, e.g., ER-804028, of the molecule is coupled to the C1-C13 portion, e.g., ER-803896, to produce ER-804029, and additional reactions are carried out to produce eribulin (Scheme 1):



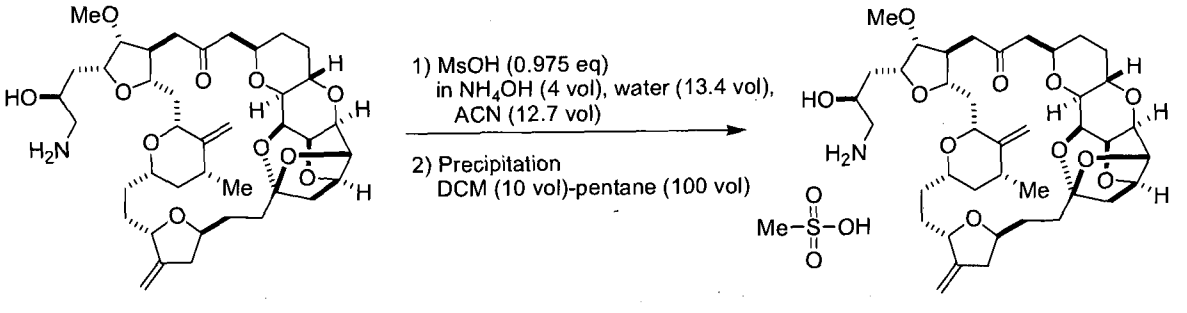
Scheme 1

Lithiation of the C14-C35 sulfone fragment followed by coupling to the C1-C13 aldehyde fragment furnishes a mixture of diastereomeric alcohols (ER-804029). Typically, these

steps occur at low temperature, e.g., -75 °C. Additional protecting group manipulation and oxidation followed by removal of the sulfonyl group and an intramolecular Nozaki-Hiyama-Kishi (NHK) reaction affords an intermediate, which, when oxidized and treated with tetrabutylammonium fluoride, undergoes intramolecular oxy-Michael ring closure. Pyridinium *p*-toluenesulfonate mediated ketal formation and conversion of the terminal alcohol to an amine furnishes eribulin.

For example, as described in WO 2005/118565 (Example 6), ER-804029 is reacted to produce ER-804030; ER-804030 is reacted to produce ER-118049; ER-118049 is reacted to produce mixture ER-118047/118048; the mixture ER-118047/118048 is reacted to produce ER-118046; ER-118046 is reacted to produce ER-811475; ER-811475 is reacted to produce ER-076349; and ER-076349 is reacted to produce eribulin.

Pharmaceutically acceptable salts of eribulin, e.g., eribulin mesylate, can be formed by methods known in the art, e.g., in situ during the final isolation and purification of the compound or separately by reacting the free base group with a suitable organic acid. In one example, eribulin is treated with a solution of MsOH and NH_4OH in water and acetonitrile. The mixture is concentrated. The residue is dissolved in DCM-pentane, and the solution is added to anhydrous pentane. The resulting precipitate is filtered and dried under high vacuum to provide eribulin mesylate, as shown in Scheme 2.



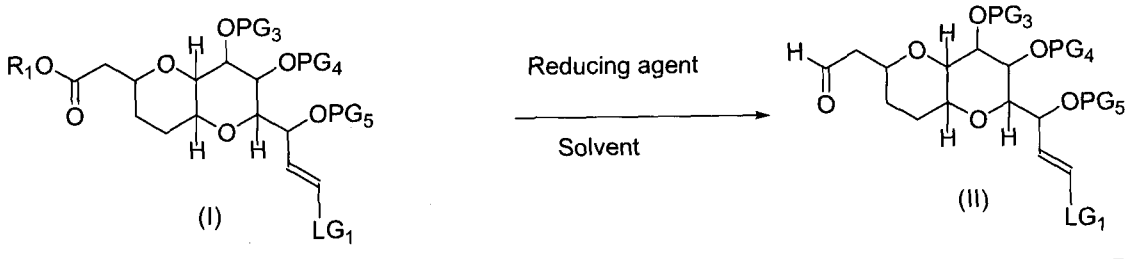
eribulin **eribulin mesylate**

Scheme 2

The present invention provides new methods for the production of a C1-13 fragment, e.g., ER-803896, and for a C1-35 fragment, e.g., ER-804029, using microreactors. Microreactors allow for accurate control of reaction temperature and/or reaction time with the benefit of using higher temperatures compared to batch processing and providing greater safety for manufacturing processes. In addition, because the microreactor reactions occur as continuous flow processes, they offer the ability to sample the process stream for monitoring the progress of the reaction and, for example, the level of byproducts generated.

Synthesis of C1-13 Fragments

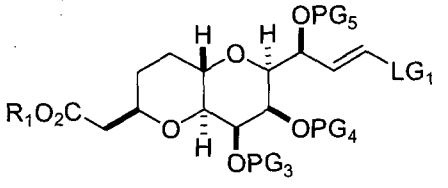
C1-13 fragments have been made by reducing a carboalkoxyester, e.g., ER-803895, to provide an aldehyde, e.g., ER-803896, as described in U.S. Patent No. 6,214,865. The invention provides a method of reducing a compound of Formula I to an aldehyde of Formula II in a microreactor:



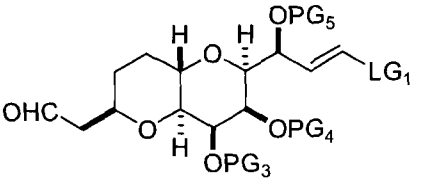
wherein each of PG_3, PG_4, and PG_5 is an independently selected hydroxyl protecting group; R_1 is C1 – C6 alkyl; and LG_1 is a leaving group. In certain embodiments, one, two, or three of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II), taken with the oxygen atom(s) to which they are bound, are silyl ethers or arylalkyl ethers. In yet other embodiments, one, two, or three of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II) are t-butyldimethylsilyl (TBS) or benzyl. In still

other embodiments, all of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II) are t-butyldimethylsilyl (TBS). PG_3 and PG_4 can also combine to form a diol protecting group. In certain embodiments, LG_1 is a halogen, such as iodide. In other embodiments, LG_1 is (C1-C6)alkylsulfonate, (C6-C10 aryl or C1-C6 heteroaryl)sulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate. Specific leaving groups include mesylate, toluenesulfonate, isopropylsulfonate, phenylsulfonate, or benzylsulfonate

In some embodiments, the compounds of Formula (I) and Formula (II) have the absolute stereochemistries depicted below:

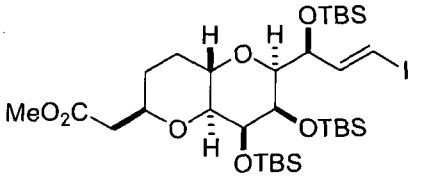


(I)-A

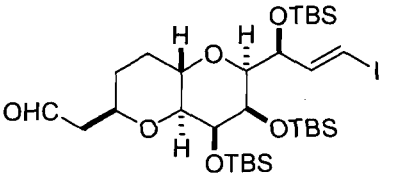


(II)-A.

In some embodiments, the compound of Formula (I) is ER-803895. In some embodiments, the compound of Formula (II) is ER-803896.



ER-803895



ER-803896.

The present invention provides methods for producing aldehydes of Formula II by the reduction of carboalkoxyesters of Formula I in a microreactor, which allows the reaction to proceed at temperatures higher than those previously disclosed for this transformation. Reducing agents useful in this transformation include an aluminum hydride reagent, a borohydride reagent, or the like. Examples of reducing agents include lithium aluminum hydride, sodium aluminum hydride, diisobutylaluminum hydride (DIBAL-H), sodium bis(2-methoxyethoxy)aluminum

hydride (Red Al), sodium borohydride, potassium borohydride, rubidium borohydride, cesium borohydride, sodium cyanoborohydride, or the like. A preferred reducing agent is DIBAL-H.

The reaction can be carried out in solvents purged with nitrogen, argon, or another such inert gas. Examples of the solvents used in this synthesis include halogen solvents such as dichloromethane, chloroform, or 1,2 dichloroethane; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, or dicyclopentyl ether; aromatic hydrocarbon solvents such as benzene or toluene; and aliphatic hydrocarbon solvents such as heptane or hexane; or mixtures thereof. A preferred solvent is toluene.

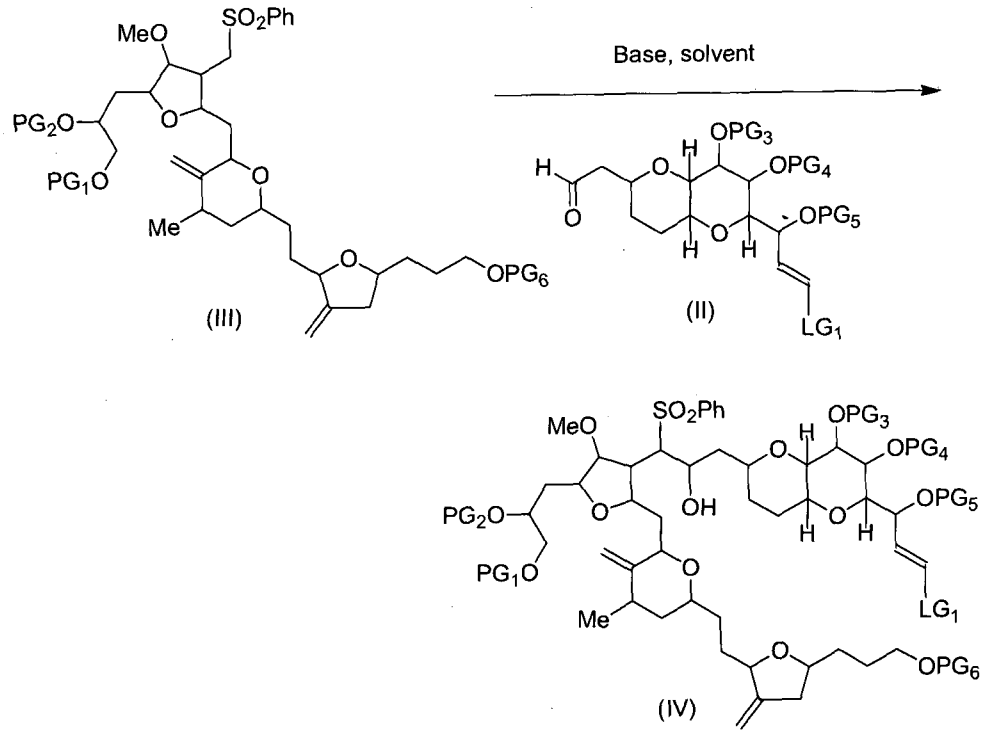
The reaction temperature is preferably between -80 and -20 °C, e.g., between -60 and -20 °C, such as approximately -50 °C. The concentration of the solution containing a compound of Formula I is preferably 0.10 g/mL to 0.30 g/mL, e.g., 0.15 g/mL to 0.25 g/mL, such as approximately 0.185 g/mL. A residence time of the compound of Formula (I) is the time sufficient to produce the compound of Formula (II), preferably 0.01 sec to 1 sec, e.g., 0.1 sec to 0.5 sec. In other embodiments, the ratio of equivalents of reducing agent, e.g., DIBAL-H, to ester is 1.0 eq to 1.5 eq, e.g., 1.215 eq to 1.485 eq, such as approximately 1.35 eq.

Compounds of Formula (I) and ER-803895 can be produced by methods known in the art, e.g., as described in U.S. Patent No. 6,214,865 and International Publication No. WO 2005/118565.

Synthesis of C1-35 Fragments

C1-35 fragments have been made by coupling a C1-13 fragment, e.g., ER-803896, to a C14-34 fragment, e.g., ER-804028, as described in U.S. Patent No. 6,214,865 and International Publication No. WO 2005/118565. The invention provides a method of coupling an anion or

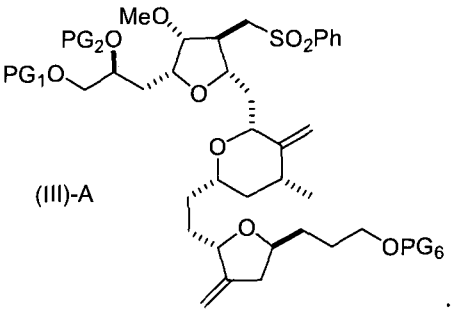
dianion of a compound of Formula III to an aldehyde of Formula I, in a microreactor, to form a compound of Formula IV:



wherein PG_3, PG_4, PG_5, and LG_1 are as defined above; each of PG_1 and PG_2 is independently hydrogen or a hydroxyl protecting group; and PG_6 is hydrogen or a hydroxyl protecting group.

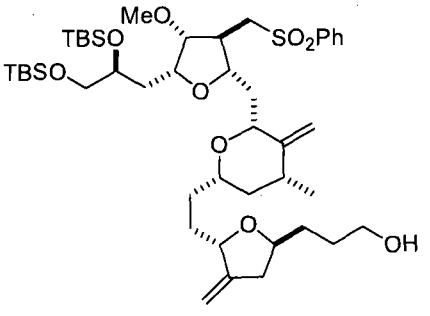
In certain embodiments, one or both of PG_1 and PG_2 of Formula (III), taken with the oxygen atom(s) to which they are bound, are silyl ethers or arylalkyl ethers. In yet other embodiments, one or both of PG_1 and PG_2 are TBS or benzyl. In still other embodiments, both PG_1 and PG_2 are TBS. In other embodiments, PG_1 and PG_2 are combined to form a diol protecting group. In some embodiments, PG_6 is hydrogen.

In some embodiments, the compound of Formula (III) has the absolute stereochemistry depicted below:



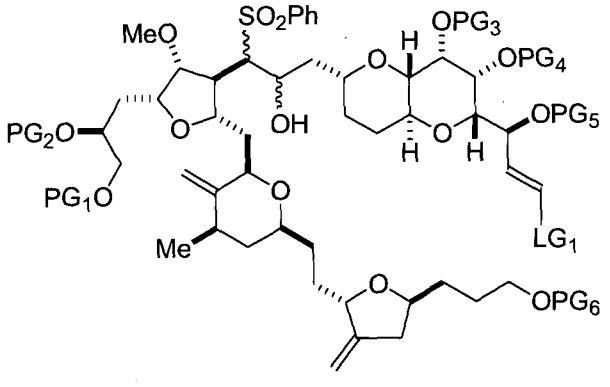
(III)-A

In some embodiments, the compound of Formula (III) is ER-804028:



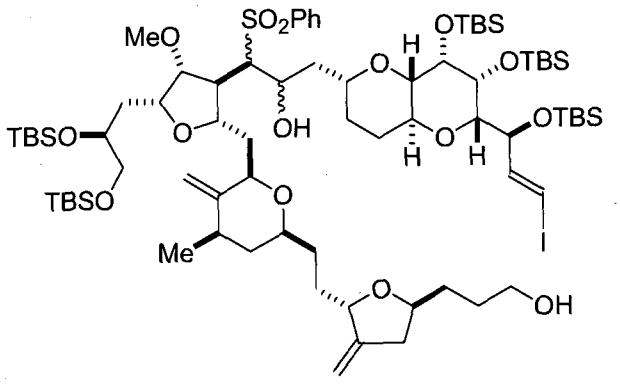
ER-804028

In some embodiments, the compound of Formula (IV) has the stereochemistry depicted below:



(IV)-A.

In some embodiments, the compound of Formula IV is ER-804029:



ER-804029.

A compound of Formula (III) is deprotonated with a base, e.g., an organometallic reagent, to produce an anion or dianion, which is reacted with a compound of Formula (II) to obtain a compound of Formula (IV). Example of organometallic reagents include a Grignard's reagent, potassium bis(trimethylsilyl) amide, sodium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, *n*-butyllithium, *sec*-butyllithium, and *tert*-butyllithium, preferably, *n*-butyllithium. The reaction can be carried out in solvents purged with nitrogen, argon, or another such inert gas. Examples of the solvent used in this synthesis include halogen solvents such as dichloromethane, chloroform, or 1,2 dichloroethane; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, or dicyclopentyl ether; aromatic hydrocarbon solvents such as benzene or toluene; and aliphatic hydrocarbon solvents such as heptane or hexane; or a mixture thereof. A preferred solvent is tetrahydrofuran or heptane. The temperature is preferably between -80 and 20 °C, e.g., between -50 to 10 °C , more preferably between -10 to 10 °C. The concentration of the solution containing the compound of Formula (II) or (III) is preferably 0.05 g/mL to 0.30 g/mL, e.g., 0.05 g/mL to 0.15 g/mL. A residence time for deprotonation of the compound of Formula (III) is the time sufficient to deprotonate the compound of formula (III), preferably 0.1 sec to 20 sec, e.g., 1 sec to 5 sec. A residence time for the coupling reaction between the compound of Formula (II) and the compound of Formula (III)

is the time sufficient to produce the compound of formula (IV), preferably 0.1 sec to 20 sec, e.g., 1 sec to 5 sec. For deprotonation, the ratio of equivalents of base, e.g., n-butyllithium, to compound of Formula (III) is preferably 2.0 eq to 2.5 eq, e.g., 2.05 eq to 2.25 eq, such as approximately 2.15 eq. The coupling of a compound of Formula III with a compound of Formula II, to produce a compound of Formula IV, in a microreactor, may proceed at temperatures higher than those previously disclosed for this transformation.

Compounds of Formula (III) and ER-804028 can be prepared using methods known in the art, e.g., as described in International Publication Nos. WO 2005/118565 and WO 2009/046308 and U.S. Patent No. 6,214,865.

Microreactors

Any suitable microreactor can be used in the present invention. Examples of microreactors include a small fluidized bed reactor and a static microreactor. A microreactor can be fabricated as a single component or be made up of separate components that are connected, e.g., by tubing. Components of a microreactor can include mixers, fluidic chips, and other devices for the combination of two or more fluids. Microreactors can be designed to mix two or more fluids and combine the resulting mixture with additional fluids. Commercially available chips can be employed. Examples of commercially available chips include COMET X-01(Techno Applications Co., Ltd.), CYTOS Series (YMC Co., Ltd), micro high Mixer (Toray engineering Co., Ltd.), LLMR(ITEC Co., Ltd.), and Micro Process Server (Hitachi Plant Technologies, Ltd.). Additional microreactors are described, for example, in Japanese Patent Laid-Open Publication No. JP 2006-241065, International Publication Nos. WO 01/70649 and WO 2009/003661, Hessel et al. Recent Patents on Chemical Engineering 2008, 1:1-16, and Tetsu

Miyazawa., Monthly Fine Chemicals 2007, 36(7):5-8, each of which is hereby incorporated by reference.

A microreactor used in the present invention can be used with any desired peripheral devices, such as heaters or coolers, temperature sensors, pressure sensors, fluid pumps, mixers, or the like. Microreactors can also be connected to analytical instrumentation, e.g., mass spectrometers or HPLC, for in-line measurement of reactants and products. Microreactors can be connected to fluid pumps or collection vessels by appropriately sized tubing. Multiple microreactors can be employed in parallel to increase rate of production of products, e.g., for use in a commercial manufacturing process.

In the invention, the flow rate of the reactants is varied according to the microreactor used in the flow reaction, and the residence time is adjusted by changing the flow rate of reactants provided to the microreactor or changing a length or internal dimension of components of the microreactor. The flow rate of the fluids provided separately to a microreactor may be the same or different.

The present invention is advantageous in that higher temperatures of reaction can be employed, compared to previous batch processing. For example, typical batch processing temperatures for the production of ER-803896 are between -60 and -80 °C, compared to -50 °C or higher, for example from -50°C to -30°C, in the present invention.

The deprotonation and coupling of ER-804028 typically occurs at between -20 and -70 °C in batch processing, compared to -10 °C or higher, for example from -10°C to 10°C, in the present invention.

Use of microreactors can also provide products that can be employed in further reactions without chromatographic purification. Furthermore, higher concentrations of the reactants can be employed in microreactors to decrease the volume of solvents used in the reaction.

Example 1

Synthesis of ER-803896

A micro flow reaction was carried out in the system of Figure 1. The reduction of ER-803895 using diisobutylaluminum hydride (DIBAL-H) was initiated in a CMPS-α01 (Hitachi Plant Technologies, Ltd., Japan) or CMPS-α02 (Hitachi Plant Technologies, Ltd.) chip. The reaction was quenched by addition of acetone to the reduction product in a CMPS-γ101H (P/N:767808-02) chip (Hitachi Plant Technologies, Ltd). Inlets of the CMPS chips were connected by PTFE tubing (internal diameter: 1.5 mm, length: 2.0 m) to a Micro Process Server MPS–α200 (Hitachi Plant Technologies, Ltd.) having injection syringes. The outlet of the CMPS-α01 or -α02 chip was connected to an inlet of the CMPS-γ101H chip by SUS316 (stainless steel) tubing (internal diameter: 0.8 mm, length: 0.1 m), and the outlet of the CMPS-γ101H chip was connected by PTFE (polytetrafluoroethylene) tubing (internal diameter: 1.0 mm, length: 0.6 m) to a collection vessel.

A 25 mL injection syringe was filled with a solution of 9.12 g (11.83 mmol) of ER-803895, 65.2 mg (0.30 mmol) of dibutylhydroxytoluene (BHT), and 49.2 mL of toluene; a 10 mL injection syringe was filled with a 1.0 M solution of DIBAL-H in toluene; and a further 25 mL injection syringe was filled with acetone (11.7 mL) in toluene (46.6 mL) as quenching reagent.

The contents of the three syringes were transferred to the CMPS chips using the MPS–α200 system as shown in Figure 1. Flow rates of ER-803895, DIBAL-H, and quenching reagent were set in various ranges, and the reactions were carried out at -30 °C to -50 °C for various residence times. The resultant reaction mixture was acidified using 1N HCl and extracted with methyl tert-butyl ether (MTBE). The purity of the organic layer was analyzed by

HPLC. ER-803896 was obtained with high selectivity under Run 9 or Run 11 compared with batch reaction conditions (Table 1). For Runs 1-11, residence times were determined based on the time required for reactants to pass through the tubing connecting the outlet of the CMPS-α01 or -α02 chip and the inlet of the CMPS-γ101H chip.

Example 2

Synthesis of ER-803896

The reduction of ER-803895 was initiated in another chip, COMET X-01 (internal diameter: 0.5mm, internal volume 29.38 μL; Techno Applications Co., Ltd., Japan) as shown in Figure 2. A solution of 330 g (428 mmol) of ER-803895, 2.36 g (10.7 mmol) of BHT, and 1780 mL of toluene was prepared in a 5 L bottle, which was placed in the line of plunger pump B. 571 mL of 1.0 M solution of DIBAL-H in toluene in a 1 L bottle was placed in the line of plunger pump A. Acetone (464 mL) in toluene (1856 mL) was prepared in a 5 L bottle and placed in the line of plunger pump C. 3300 mL of 1 N HCl in a 5 L bottle was placed in the line of plunger pump D.

The contents of the bottles were transferred to COMET chips using the plunger pump systems under the conditions of Run 9 in Table 1. The resultant reaction mixture flowed continuously for 86 min 45 sec into a workup vessel containing toluene (1687 mL) and MTBE (2310 mL). The aqueous layer was drained. The organic layer was washed sequentially with 1 N HCl (3300 mL), water (3300 mL), 5% aqueous sodium bicarbonate (3300 g), and brine (3300 g) and then concentrated under reduced pressure to afford ER-803896 without column chromatography (96.5% wt/wt assay yield, Run 12). For Run 12, the residence times was determined based on the time required for reactants to pass through the SUS316 tubing connecting the outlet of one COMET-X01-T chip and the inlet of the other COMET-X01-T chip.

Reference of batch reaction example 1 (Run 13)

Synthesis of ER-803896

ER-803895 (1.00 g, 1.30 mmol) and BHT (7.1 mg, 0.032 mmol) were dissolved in toluene (16.2 mL) and cooled to <-80°C under a nitrogen atmosphere. DIBAL-H (1.0 M in toluene, 1.54 ml, 1.55 mmol, 1.2 eq) was added at a rate to maintain the internal reaction temperature at <-80 °C. The resulting mixture was stirred for 1 hour and then quenched sequentially with anhydrous acetone (0.30 mL) in toluene (0.69 mL) and anhydrous methanol (0.17 mL) in toluene (0.69 mL), maintaining the internal reaction temperature at <-75 °C. The reaction mixture was allowed to warm to -35 °C, and then MTBE (5.0 mL) and 1 N HCl (10.0 mL) were added to the reaction mixture. The mixture was stirred for 30 minutes, and the aqueous layer was drained. The organic layer was washed sequentially with 1 N HCl (10 mL), water (10 mL), 5% aqueous $NaHCO_3$ (10 g), and brine (10 g) and then concentrated under reduced pressure to afford ER-803896 (99% wt/wt assay yield, Run 13).

Reference of batch reaction example 2 (Run 14)

Synthesis of ER-803896

ER-803895 (1.00 g, 1.30 mmol) and BHT (7.2 mg, 0.032 mmol) were dissolved in toluene (16.2 mL) and cooled to <-70 °C under a nitrogen atmosphere. DIBAL-H (1.0 M in toluene, 1.54 ml, 1.55 mmol, 1.2 eq) was added at a rate to maintain the internal reaction temperature at <-70 °C. The resulting mixture was stirred for 1 hour and then quenched sequentially with anhydrous acetone (0.31 mL) in toluene (0.70 mL) and anhydrous methanol (0.17 mL) in toluene (0.70 mL), maintaining the internal reaction temperature at <-65 °C. The reaction mixture was allowed to warm to -30 °C, and then MTBE (5.0 mL) and 1 N HCl

(10.0 mL) were added to the reaction mixture. The mixture was stirred for 30 minutes, and the aqueous layer was drained. The organic layer was washed sequentially with 1 N HCl (10 mL), water (10 mL), 5% aqueous $NaHCO_3$ (10 g), and brine (10 g) and then concentrated under reduced pressure to afford ER-803896 (96% wt/wt assay yield, Run 14).

Reference of batch reaction example 3 (Run 15)

Synthesis of ER-803896

ER-803895 (1.00 g, 1.30 mmol) and BHT (7.2 mg, 0.032 mmol) were dissolved in toluene (16.2 mL) and cooled to <-60 °C under nitrogen atmosphere. DIBAL-H (1.0 M in toluene, 1.54 ml, 1.55 mmol, 1.2 eq) was added at a rate to maintain the internal reaction temperature at <-60 °C. The resulting mixture was stirred for 1 hour and then quenched sequentially with anhydrous acetone (0.31 mL) in toluene (0.70 mL) and anhydrous methanol (0.17 mL) in toluene (0.70 mL), maintaining the internal reaction temperature at <-65 °C. The reaction mixture was allowed to warm to -30 °C, and then MTBE (5.0 mL) and 1 N HCl (10.0 mL) were added to the reaction mixture. The mixture was stirred for 30 minutes, and the aqueous layer was drained. The organic layer was washed sequentially with 1 N HCl (10 mL), water (10 mL), 5% aqueous $NaHCO_3$ (10 g), and brine (10 g) and then concentrated under reduced pressure to afford ER-803896 (91% wt/wt assay yield, Run 15).

Table 1

Run	Device		Temp	Flow Rate			Residence Time	HPLC Relative Ratio		
				ER-803895 toluene sol.	DIBAL 1M sol.	Quenching reagents		ER-803896	Alcohol	ER-803895
	for reaction	for quenching	°C	mL/min	mL/min (eq)	mL/min	sec.	%	%	%
1	CMPS-α01	CMPS-γ101H	-50	24.0	6.557 (1.35)	24.0	0.1	80.04	0.19	19.77
2	CMPS-α01	CMPS-γ101H	-50	24.0	6.557 (1.35)	24.0	0.1	86.52	0.35	13.14
3	CMPS-α01	CMPS-γ101H	-50	48.0	13.114 (1.35)	48.0	0.05	97.07	0.73	2.19
4	CMPS-α01	CMPS-γ101H	-50	72.0	19.671 (1.35)	72.0	0.03	96.71	0.87	2.41
5	CMPS-α01	CMPS-γ101H	-50	48.0	13.114 (1.35)	48.0	0.05	97.00	1.02	1.98
6	CMPS-α01	CMPS-γ101H	-40	48.0	13.114 (1.35)	48.0	0.05	95.50	2.95	1.55
7	CMPS-α01	CMPS-γ101H	-30	48.0	13.114 (1.35)	48.0	0.05	92.34	4.92	2.74
8	CMPS-α02	CMPS-γ101H	-40	24.0	6.557 (1.35)	24.0	0.1	97.73	1.56	0.71
9	CMPS-α02	CMPS-γ101H	-50	24.0	6.557 (1.35)	24.0	0.1	98.09	0.41	1.51

10	CMPS-α02	CMPS-γ101H	-50	24.0	5.828 (1.215)	24.0	0.1	96.55	0.34	3.11
11	CMPS-α02	CMPS-γ101H	-50	24.0	7.285 (1.485)	24.0	0.1	98.28	0.38	1.34
12	COMET-X01-S COMET-X01-T	COMET-X01-T	-50	24.0	6.492 (1.35)	24.0	0.1	96.72	1.57	1.71
13	Batch	Batch	-80	-	(1.20)	-	1 hr	98.6	1.4	0
14	Batch	Batch	-70	-	(1.20)	-	1 hr	96.0	4.0	0
15	Batch	Batch	-60	-	(1.20)	-	1 hr	91.1	8.9	0

Example 3
Synthesis of ER-804029

A micro flow reaction was carried out in the system of Figure 3. The coupling reaction of ER-804028 and ER-803896 using n-butyl lithium (n-BuLi) was initiated in a series of CMPS-α02 chips. Inlets of the CMPS chips were connected by PTFE tubing (internal diameter: 1.5 mm, length: 2.0 m) to a Micro Process Server MPS-α200 having injection syringes. The outlet of the first chip (A) was connected to an inlet of the second chip (B) via SUS316 tubing (internal diameter: 0.8 mm, length: 50 cm) or PTFE tubing (internal diameter: 1.0 mm, length: 32 cm or 64 cm or 96 cm). The outlet of the second chip was connected by PTFE tubing (internal diameter: 1.0 mm, length: 2.0 m or 4.0 m or 6.0 m) to a collection vessel.

A 25 mL injection syringe was filled with a solution of 8.00 g (9.397 mmol) of ER-804028 and 80 mL of anhydrous THF; a 10 mL injection syringe was filled with a 1.63 M solution of n-BuLi in hexane; and an additional 25 mL injection syringe was filled with a solution of 7.659 g (10.337 mmol) of ER-803896 and 76.6 mL of n-heptane.

The contents of the three syringes were transferred to the microreactor using the MPS-α200 system. Flow rates of ER-804028, ER-803896, and n-BuLi were set in various ranges, and the reactions were carried out at -10 °C to 10 °C for various residence times. The resultant reaction mixture was quenched with 14% aqueous ammonium chloride and extracted with MTBE. The purity of the organic layer was analyzed by HPLC. ER-804029 was obtained with high conversion under Run 12 compared with batch reaction condition (Table 2). For Table 2, residence times were determined based on the time required for reactants to pass through the tubing connecting the outlet of the first CMPS-α02 chip and the point in the second CMPS-α02 chip where ER-803896 is added.

Table 2

Run	Device		Equivalent (eq) / Flow rate (mL/min)			Temp. (°C) Deprotonation & Reaction	Residence time (sec.)		HPLC area%	
	Reactor A	Reactor B	ER-804028	n-BuLi	ER-803896		Deprotonation	Reaction	ER-804029	ER-804028
1	CMPS-α02	CMPS-α02	1 / 10.0	2.15 / 1.559	1.10 / 10.53	-10	2.3	4.3	86.8	13.2
2	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / 3.118	1.05 / 20.06	-10	1.1	2.2	93.6	6.4
3	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / 3.118	1.10 / 21.06	-10	1.1	2.1	94.9	5.1
4	CMPS-α02	CMPS-α02	1 / 30.0	2.15 / 4.677	1.10 / 31.59	-10	0.8	1.4	93.1	6.9
5	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / 3.118	1.10 / 21.06	-10	1.1	4.3	94.6	5.4
6	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / 3.118	1.10 / 21.06	-10	1.1	6.4	95.1	4.9
7	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / 3.099	1.10 / 21.06	-10	2.4	2.1	94.7	5.3
8	CMPS-α02	CMPS-α02	1 / 30.0	2.15 / 4.648	1.10 / 31.59	-10	1.6	1.4	93.9	6.1
9	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / 3.099	1.10 / 21.06	-10	1.8	2.1	94.4	5.6

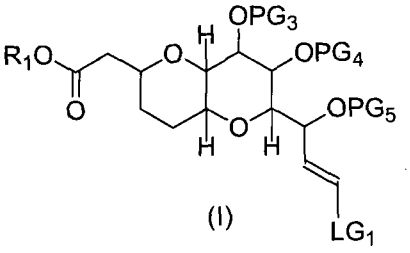
10	CMPS-α02	CMPS-α02	1 / 30.0	2.15 / / 4.648	1.10 / 31.59	-10	1.2	1.4	94.2	5.8
11	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / / 3.099	1.10 / 21.06	-10	1.1	2.1	93.6	6.5
12	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / / 3.099	1.10 / 21.06	10	2.4	2.1	96.5	3.5
13	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / / 3.099	1.10 / 21.06	0	2.4	2.1	94.4	5.6
14	CMPS-α02	CMPS-α02	1 / 20.0	2.15 / / 3.099	1.10 / 21.06	-10	2.4	2.1	93.9	6.1
15	CMPS-α02	CMPS-α02	1 / 20.0	2.05 / / 2.955	1.10 / 21.06	-10	2.5	2.1	90.3	9.7
16	CMPS-α02	CMPS-α02	1 / 20.0	2.20 / / 3.171	1.10 / 21.06	-10	2.4	2.1	90.4	9.6
17	CMPS-α02	CMPS-α02	1 / 20.0	2.25 / / 3.243	1.10 / 21.06	-10	2.4	2.1	86.5	13.5

Other Embodiments

All publications, patents, and patent application publications mentioned herein are hereby incorporated by reference. Various modifications and variations of the described compounds of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the relevant art are intended to be within the scope of the invention.

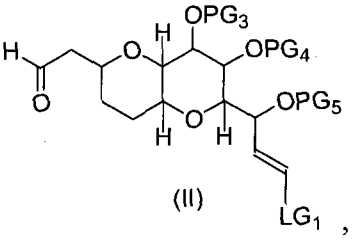
CLAIMS

1. A method of producing a compound of Formula (II) from a compound of Formula (I), said method comprising the steps of contacting the compound of Formula (I):



(I)

with a reducing agent in a microreactor for a time sufficient to produce the compound of Formula (II):



(II) ,

wherein each of PG_3, PG_4, and PG_5 is independently a hydroxyl protecting group; R_1 is C1 – C6 alkyl; and LG_1 is a leaving group.

2. The method of claim 1, wherein one, two, or three of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II), taken with the oxygen atom(s) to which they are bound, are silyl ethers or arylalkyl ethers.

3. The method of claim 1, wherein one, two, or three of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II) are t-butyldimethylsilyl (TBS) or benzyl.

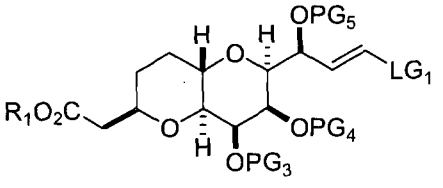
4. The method of claim 1, wherein all of PG_3, PG_4, and PG_5 of Formula (I) or Formula (II) are t-butyldimethylsilyl (TBS).

5. The method of claim 1, wherein LG_1 is a halogen, (C1-C6)alkylsulfonate, (C6-C10 aryl or C1-C6 heteroaryl)sulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

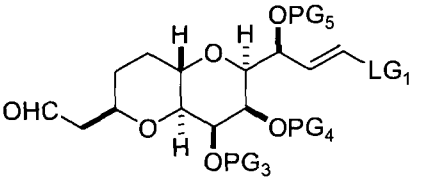
6. The method of claim 1, wherein LG_1 is mesylate, toluenesulfonate, isopropylsulfonate, phenylsulfonate, or benzylsulfonate.

7. The method of claim 1, wherein LG_1 is iodide.

8. The method of claim 1, wherein the compounds of Formula (I) and Formula (II) have the absolute stereochemistry:

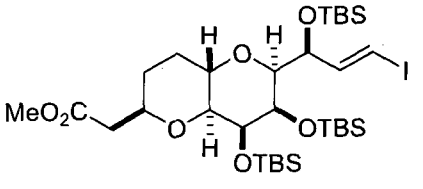


(I)-A



(II)-A.

9. The method of claim 1, wherein the compound of Formula (I) is



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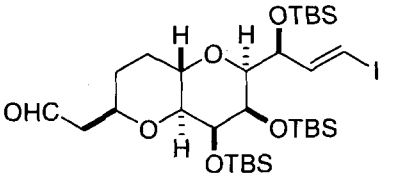
10. The method of claim 1, wherein the compound of Formula (II) is



ER-803896.

11. The method of claim 1, wherein the reducing agent is an aluminum hydride reagent or a borohydride reagent.

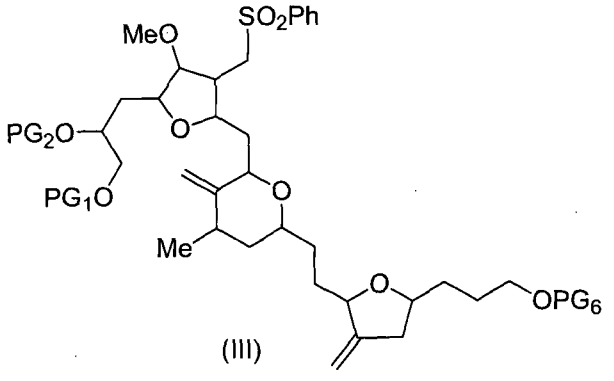
12. The method of claim 1, wherein the reducing agent is lithium aluminum hydride, sodium aluminum hydride, diisobutylaluminum hydride (DIBAL-H), sodium bis(2-methoxyethoxy)aluminum hydride (Red Al), sodium borohydride, potassium borohydride, rubidium borohydride, cesium borohydride, or sodium cyanoborohydride.

13. The method of claim 1, wherein the temperature of the microreactor is between -80 and -20 °C.

14. The method of claim 1, wherein the residence time of the compound of Formula I is 0.01 sec to 1 sec.

15. A method of producing a compound of Formula (IV) from a compound of Formula (II) and a compound of Formula (III), said method comprising the steps of

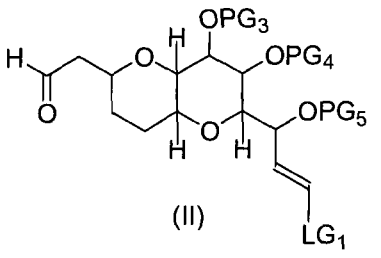
(a) contacting the compound of Formula (III):



(III)

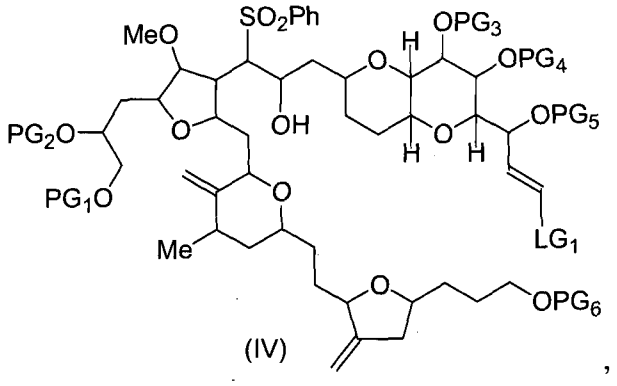
with a base in a microreactor for a time sufficient to deprotonate the compound of formula (III), wherein each of PG_1 and PG_2 is independently a hydroxyl protecting group, and PG_6 is hydrogen or a hydroxyl protecting group; and

(b) contacting the product of step (a) with a compound of Formula (II):



(II)

in a microreactor for a time sufficient to produce the compound of formula (IV):



(IV)

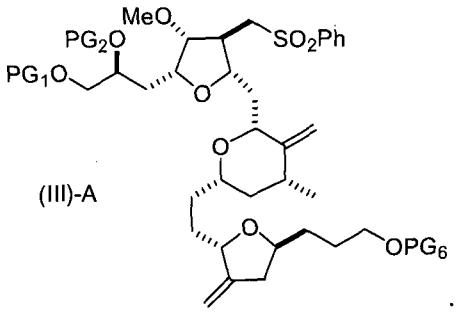
wherein each of PG_3, PG_4, and PG_5 is independently a hydroxyl protecting group; and LG_1 is a leaving group.

16. The method of claim 15, wherein one or both of PG_1 and PG_2 of Formula (III), taken with the oxygen atom(s) to which they are bound, are silyl ethers or arylalkyl ethers.

17. The method of claim 15, wherein one or both of PG_1 and PG_2 are TBS or benzyl.

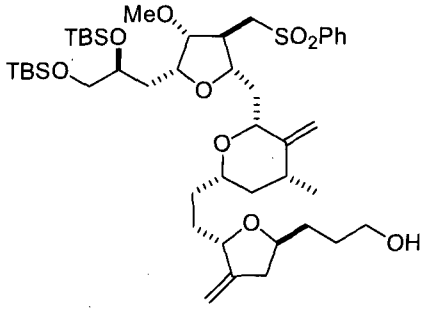
18. The method of claim 15, wherein both PG_1 and PG_2 are TBS.

19. The method of claim 15, wherein the compound of Formula (III) has the absolute stereochemistry:



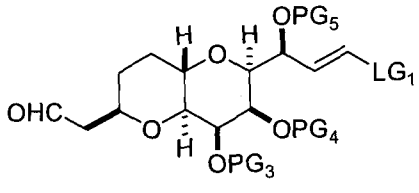
(III)-A

20. The method of claim 15, wherein the compound of Formula (III) is ER-804028:



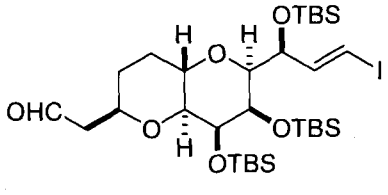
ER-804028

21. The method of claim 15, wherein the compound of Formula (I) has the absolute stereochemistry:



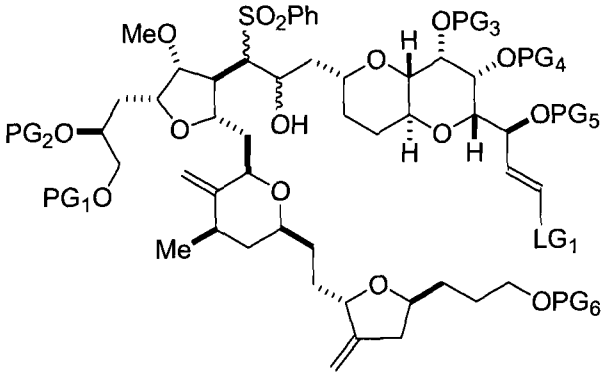
(II)-A.

22. The method of claim 15, wherein the compound of Formula (II) is



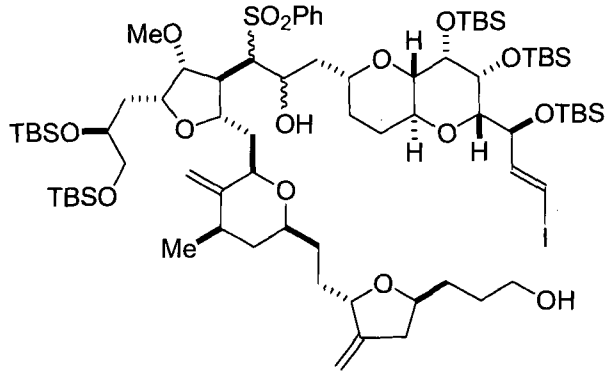
ER-803896.

23. The method of claim 15, wherein the compound of Formula (IV) has the stereochemistry:



(IV)-A.

24. The method of claim 15, wherein the compound of Formula IV is ER-804029:



ER-804029.

25. The method of claim 15, wherein the base is an organometallic reagent.

26. The method of claim 15, wherein the base is a Grignard's reagent, potassium bis(trimethylsilyl) amide, sodium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, *n*-butyl lithium, *sec*-butyl lithium, or *tert*-butyl lithium.

27. The method of claim 15, wherein the temperature of the microreactor in step (a) and/or step (b) is between -80 to 20 °C.

28. The method of claim 15, wherein the residence time of the compound of Formula (III) in step (a) is 0.1 sec to 20 sec.

29. The method of claim 15, wherein the residence time of the compound of Formula (II) and the compound of Formula (III) in step (b) is 0.1 sec to 20 sec.

30. A method of producing eribulin, or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(a) producing a compound of Formula (II) by the method of any one of claims 1-14;

(b) reacting the compound of Formula (II) under suitable conditions to produce eribulin, or the pharmaceutically acceptable salt thereof.

31. The method of claim 30, wherein in step (b) the compound of Formula (II) is coupled to a compound of Formula (III) to produce a compound of Formula (IV), and said compound of Formula (IV) is reacted to produce eribulin, or the pharmaceutically acceptable salt thereof.

32. The method of claim 30, wherein eribulin mesylate is formed in step (b).

33. A method of producing eribulin, or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(a) producing a compound of Formula (IV) by the method of any one of claims 15-29;

(b) reacting the compound of Formula (IV) under suitable conditions to produce eribulin, or the pharmaceutically acceptable salt thereof.

34. The method of claim 33, wherein eribulin mesylate is formed in step (b).

Figure 1

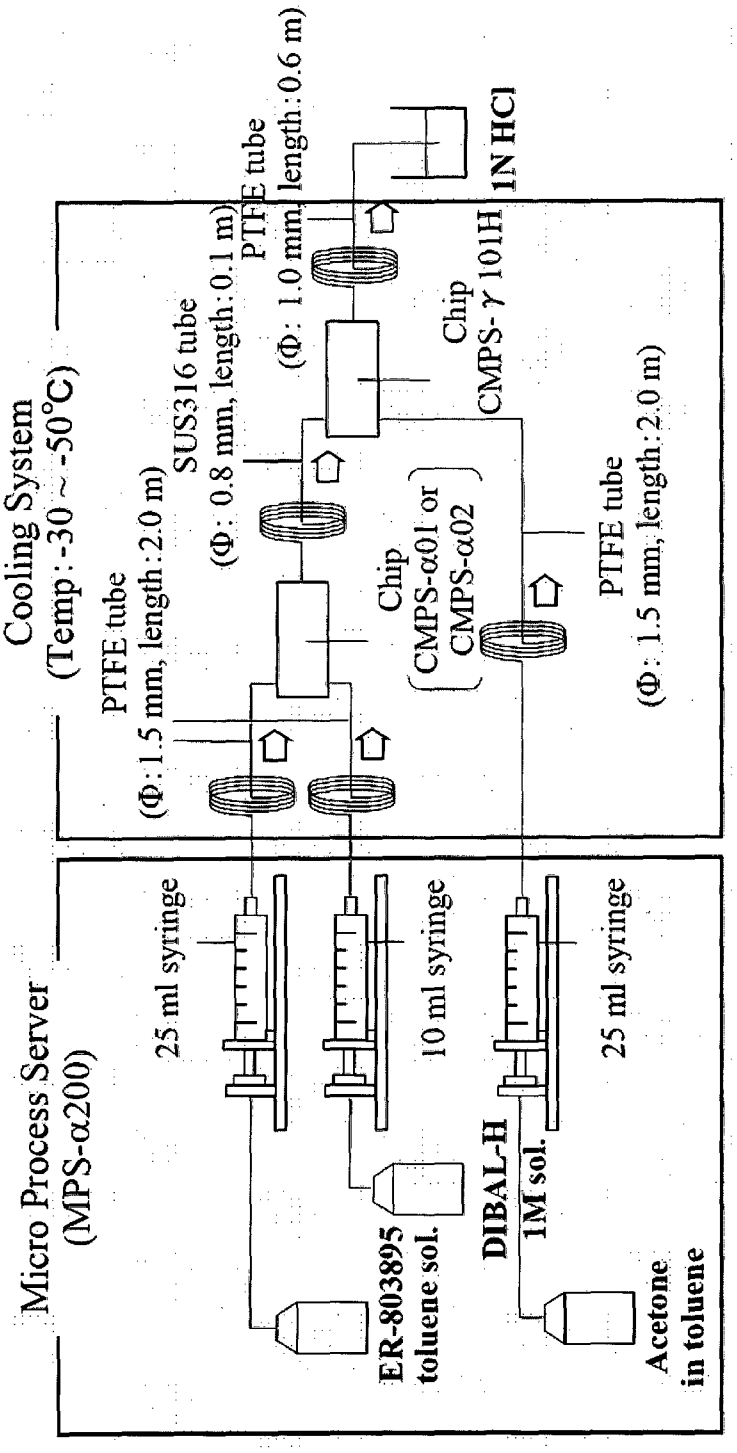

Micro Process Server
(MPS-α200)
Cooling System
(Temp: -30 ~ -50°C)
25 ml syringe
10 ml syringe
25 ml syringe
PTFE tube
(Φ: 1.5 mm, length: 2.0 m)
SUS316 tube
(Φ: 0.8 mm, length: 0.1 m)
PTFE tube
(Φ: 1.0 mm, length: 0.6 m)
Chip
CMPS-γ 101H
Chip
CMPS-α01 or
CMPS-α02
PTFE tube
(Φ: 1.5 mm, length: 2.0 m)
1N HCl
ER-803895
toluene sol.
DIBAL-H
1M sol.
Acetone
in toluene

Figure 2

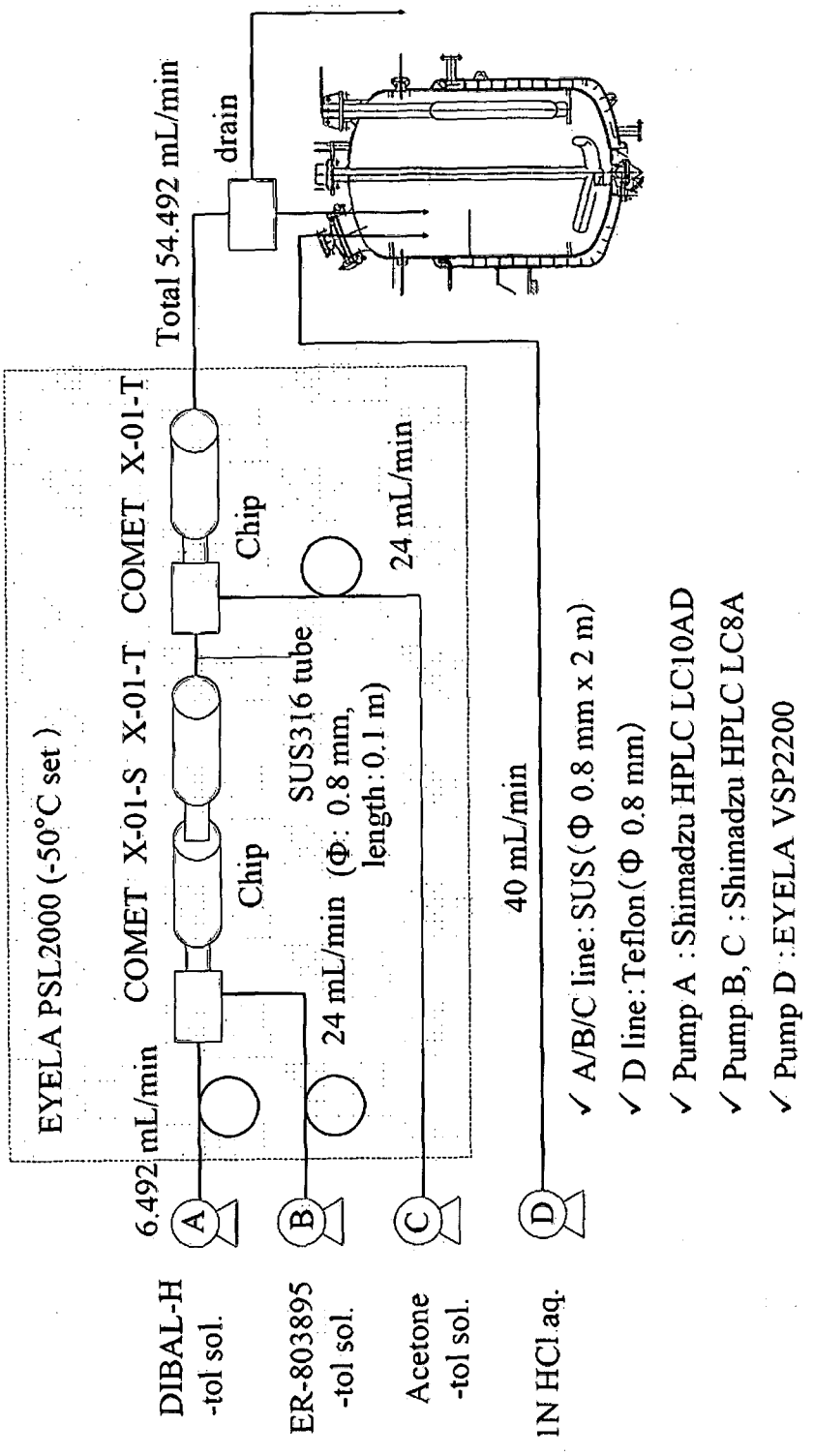
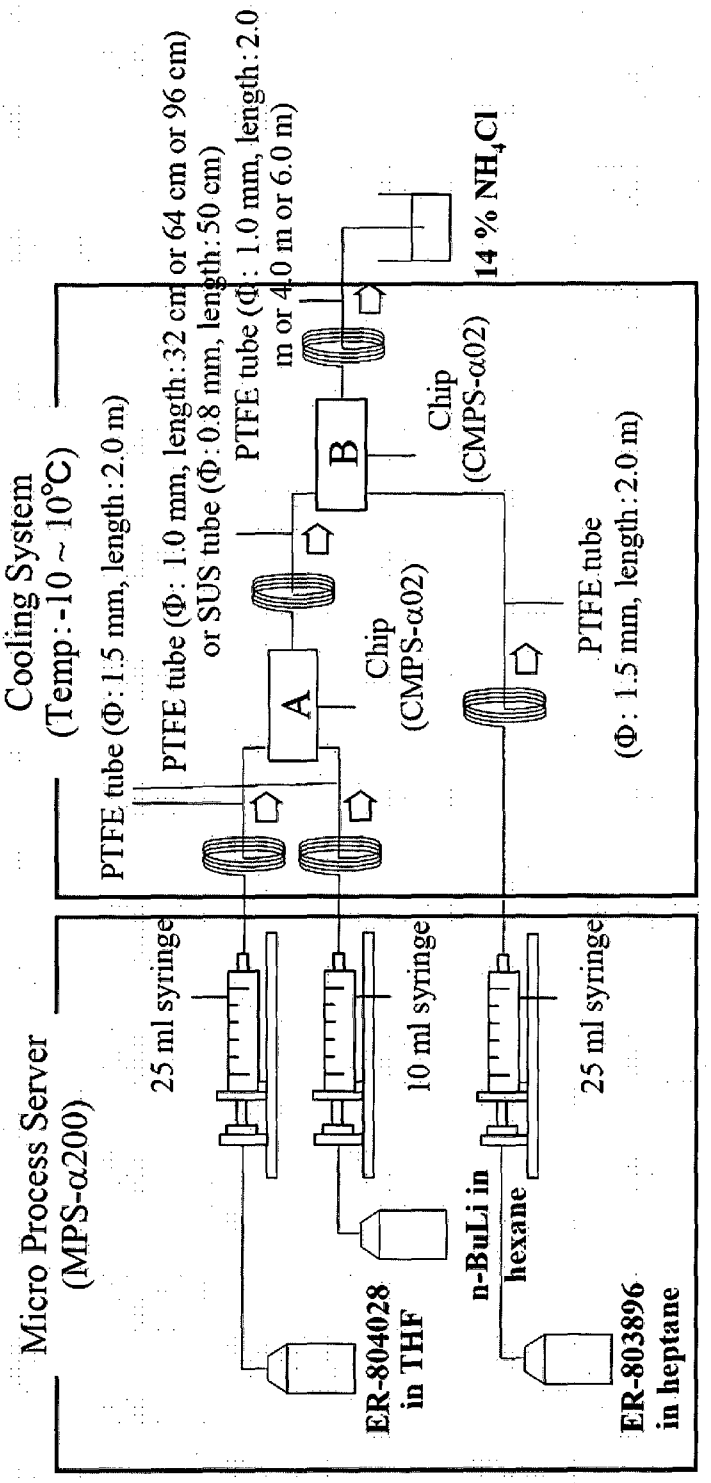

EYELA PSL2000 (-50°C set)
COMET X-01-S X-01-T COMET X-01-T
Chip
Chip
SUS316 tube
(Φ: 0.8 mm,
length: 0.1 m)
24 mL/min
24 mL/min
40 mL/min
Total 54.492 mL/min
drain
6.492 mL/min
A
B
C
D
DIBAL-H
-tol sol.
ER-803895
-tol sol.
Acetone
-tol sol.
1N HCl aq.
✓ A/B/C line: SUS (Φ 0.8 mm x 2 m)
✓ D line: Teflon (Φ 0.8 mm)
✓ Pump A : Shimadzu HPLC LC10AD
✓ Pump B, C : Shimadzu HPLC LC8A
✓ Pump D : EYELA VSP2200

Figure 3


Micro Process Server
(MPS-α200)
Cooling System
(Temp: -10 ~ 10°C)
25 ml syringe
10 ml syringe
25 ml syringe
PTFE tube (Φ: 1.5 mm, length: 2.0 m)
PTFE tube (Φ: 1.0 mm, length: 32 cm or 64 cm or 96 cm)
or SUS tube (Φ: 0.8 mm, length: 50 cm)
PTFE tube (Φ: 1.0 mm, length: 2.0
m or 4.0 m or 6.0 m)
A
B
Chip
(CMPS-α02)
Chip
(CMPS-α02)
PTFE tube
(Φ: 1.5 mm, length: 2.0 m)
14 % NH4Cl
ER-804028
in THF
n-BuLi in
hexane
ER-803896
in heptane

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2012/061307

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D493/04 C07D493/22
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/118565 A1 (EISAI CO LTD [JP]; AUSTAD BRIAN [US]; CHASE CHARLES E [US]; FANG FRANC) 15 December 2005 (2005-12-15) cited in the application page 85, paragraph 00202 - page 86, paragraph 00203	1-34
A	KAROLIN GEYER ET AL: "Microreactors as Tools for Synthetic Chemists-The Chemists' Round-Bottomed Flask of the 21st Century?", CHEMISTRY - A EUROPEAN JOURNAL, vol. 12, no. 33, 15 November 2006 (2006-11-15), pages 8434-8442, XP55031983, ISSN: 0947-6539, DOI: 10.1002/chem.200600596 the whole document	1-34

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2012	17/07/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Moriggi, J

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2012/061307

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	HIROYUKI CHIBA, KATSUYA TAGAMI: "Research and Development of HALAVEN TM (Eribulin Mesylate)", JOURNAL OF SYNTHETIC ORGANIC CHEMISTRY, JAPAN, vol. 69, no. 5, 11 July 2011 (2011-07-11), pages 600-610, XP009160915, DOI: 10.5059/yukigoseikyokaishi.69.600 figure 13; tables 1, 2 -----	1-34

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2012/061307

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005118565 A1	15-12-2005	AU 2005250487 A1	15-12-2005
		CA 2567984 A1	15-12-2005
		CN 101899026 A	01-12-2010
		EP 1771431 A1	11-04-2007
		JP 2008501715 A	24-01-2008
		KR 20070030260 A	15-03-2007
		US 2007244187 A1	18-10-2007
		US 2012029213 A1	02-02-2012
		WO 2005118565 A1	15-12-2005

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2012/061307

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 30-32

   The method of producing a compound of formula (II) as well as the method of producing eribulin through a synthetic intermediate of formula (II)

   ---

2. claims: 15-29, 33, 34

   The method of producing a compound of formula (IV) as well as the method of producing eribulin through a synthetic intermediate of formula (IV)
