INTERMEDIATES IN THE SYNTHESIS OF ERIBULIN AND RELATED METHODS OF SYNTHESIS

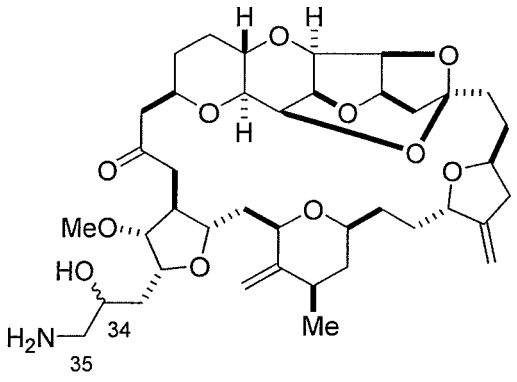
Background of the invention

Halichondrin B is a structurally complex, macrocyclic compound that was originally isolated from the marine sponge *Halichondria okadai*, and subsequently was found in *Axinella* sp., *Phakellia carteri*, and *Lissodendoryx* sp. Eribulin is a synthetic analog of halichondrin B. The mesylate salt of eribulin (eribulin mesylate, which is marketed under the trade name HALAVEN®) is approved for the treatment of patients with breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease that included an anthracycline and a taxane in either the adjuvant or metastatic setting.

Summary of the invention

The invention provides eribulin and diastereomers thereof containing carbon-11, as well as methods of synthesizing eribulin by a two-step process including a nitro aldol reaction and a reduction.

In one example, the disclosure provides a compound according to formula (**I**),



(**I**)

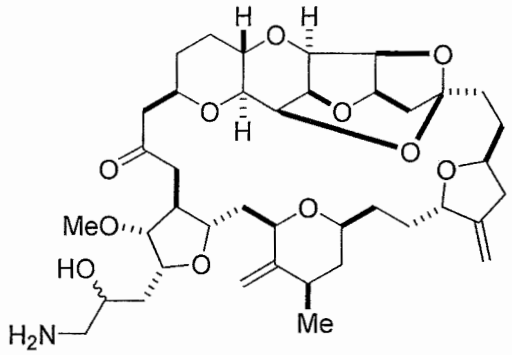
or a pharmaceutically acceptable salt thereof, wherein the compound contains carbon-11.

In some examples, the stereochemical configuration at position 34 of the compound is (*S*). In some examples, the stereochemical configuration at position 34 of the compound is (*R*). In some examples, the carbon-11 is located at position 35 of the compound of formula (**I**).

In some examples, the compound is the mesylate salt of formula (**I**).

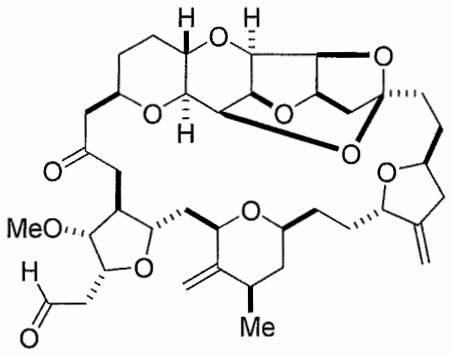
The compound of formula (**I**) may also be in the form of an isotopically enriched composition, i.e., in carbon 11. The term "isotopically enriched," as used herein, refers to a composition including an isotope, e.g., ^{11}C, at a position in the compound in an abundance greater than other isopotes, e.g., ^{12}C, at that same position. Typically and depending on the isotope, compositions enriched in a particular isotope may have an isotopic enrichment factor of at least 5, at least 10, at least 50, at least 500, at least 2000, at least 3000, at least 6000, or at least 6600, e.g., relative to ^{12}C.

In one aspect, the present invention provides a method of synthesizing a compound according to formula (I):



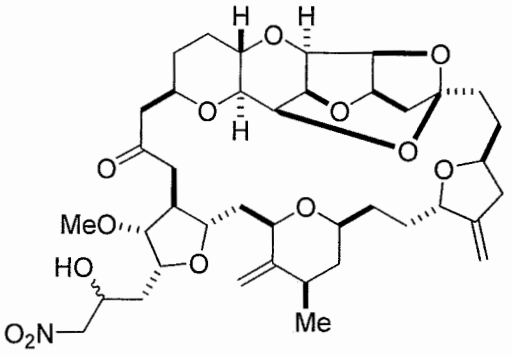
(I),

or a pharmaceutically acceptable salt thereof, the method comprising reacting an aldehyde according to formula (II):



(II)

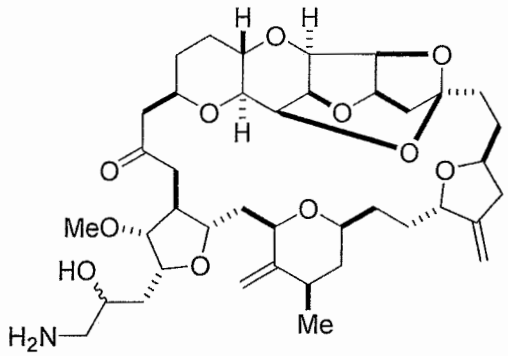
with nitromethane under Henry reaction conditions to form a compound according to formula (III):



(III);

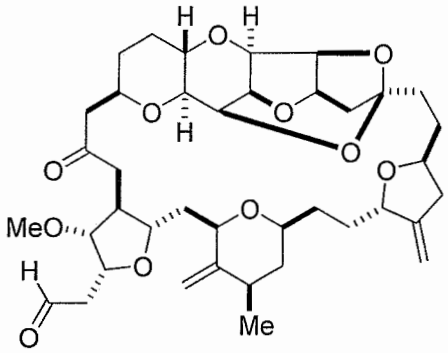
and reducing the compound according to formula (III) with a reducing agent to form the compound according to formula (I).

In another aspect, the present invention provides a method of synthesizing a compound according to formula (I):



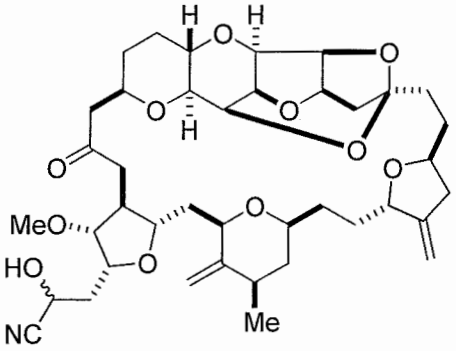
(I),

or a pharmaceutically acceptable salt thereof, the method comprising reacting an aldehyde according to formula (II):



(II)

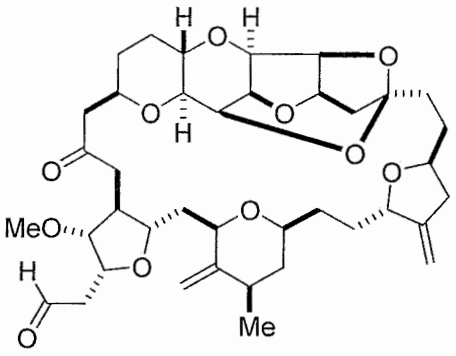
with a cyanide salt under conditions to form a cyanohydrin according to formula (IV):



(IV);

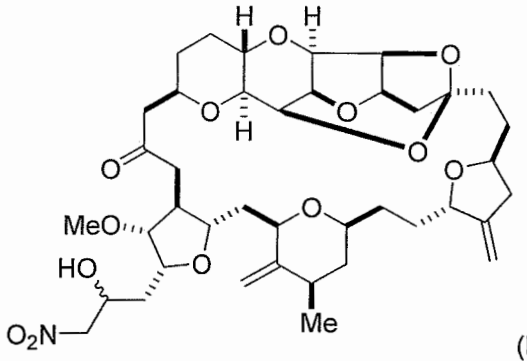
and reducing the cyanohydrin according to formula (IV) with a reducing agent to form the compound according to formula (I)

In an additional example, the disclosure relates to a method of synthesizing a compound according to formula (**I**), by reacting an aldehyde according to formula (**II**):



(II)

with nitromethane, e.g., containing carbon-11, under Henry reaction conditions to form a compound according to formula (**III**):



(III)

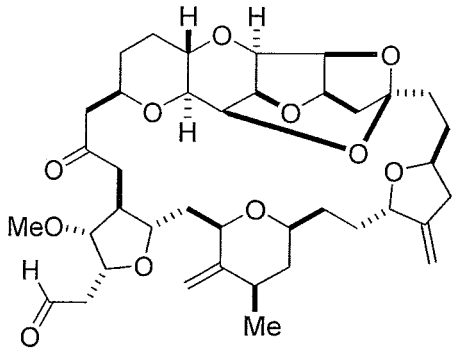
and reducing the compound according to formula (**III**) with a reducing agent to form the compound according to formula (**I**).

In some examples, the method includes dissolving the aldehyde in an alcohol, e.g., methanol, to form a solution. In some examples, the solution has a concentration of from 0.01 M to 0.5 M, e.g., about 0.1 M. In some examples, the method includes adding from 1 to 10,000 molar equivalents of the nitromethane to the aldehyde, e.g., about 1000 molar equivalents of the nitromethane to the aldehyde.

In some examples, the method includes adding a base, e.g., sodium hydroxide, to a mixture containing the aldehyde and the nitromethane.

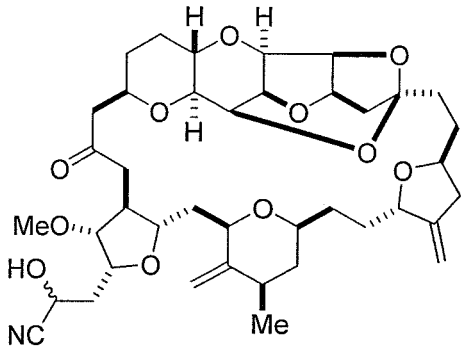
In some examples, the compound according to formula (**III**) is reduced by a lanthanide salt, such as samarium (II) iodide. In some examples, the method includes dissolving the compound according to formula (**III**) in an alcohol, e.g., methanol, to form a solution. In some examples, the solution has a concentration of compound according to formula (**III**) from 0.01 mM to 1 mM, e.g., about 0.7 mM. In some examples, the reducing agent is present in a solution at a concentration of from 0.01 M to 1 M, e.g., about 0.1 M. In some examples, the method includes mixing from 2 molar equivalents to 1000 molar equivalents of the reducing agent with the compound according to formula (**III**).

In another example, the disclosure provides a method of synthesizing a compound according to formula (**I**), by reacting an aldehyde according to formula (**II**):



(II)

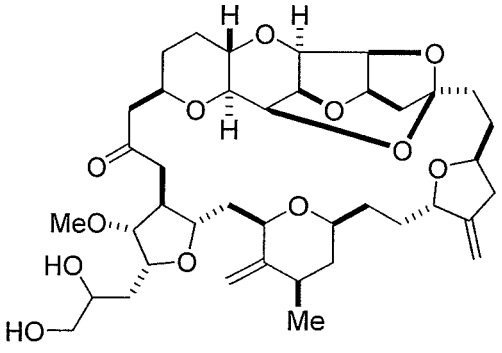
with a cyanide salt, e.g., potassium cyanide, under conditions to form a cyanohydrin according to formula (**IV**):



(IV)

and reducing the cyanohydrin according to formula (**IV**) with a reducing agent to form the compound according to formula (**I**). In some examples, the reducing agent is a silane, such as triethylsilane, used, for example, in combination with a Lewis acid, such as tris(perfluorophenyl)borane. In some examples, the cyanide salt contains carbon-11 (e.g., $K^{11}CN$).

In some examples, the aldehyde is synthesized by reacting a diol according to formula (**V**):

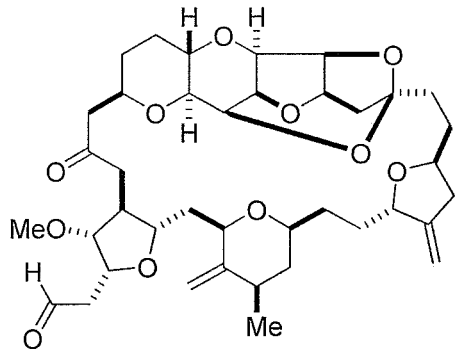


(V)

with an oxidizing agent, e.g., sodium periodate.

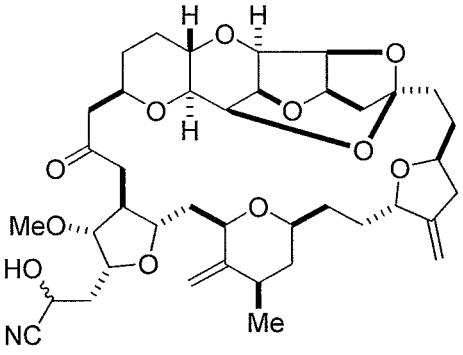
In some examples, any of the methods may further include salifying the compound of formula (**I**) to produce a pharmaceutically acceptable salt thereof, e.g., the mesylate salt. The methods may also include separating the diastereomers of the compound of formula (**I**) to isolate eribulin, or a pharmaceutically acceptable salt thereof, e.g., the mesylate salt.

In another aspect, the invention features a compound according to formula (**II**):



(II).

In another aspect, the invention features a compound according to formula (**IV**):



(IV).

The disclosure further provides a pharmaceutical composition comprising an effective amount of a carbon-11 containing compound of formula (**I**) or an isotopically enriched composition of a compound of formula (**I**) and a pharmaceutically acceptable carrier.

In an additional example, the disclosure provides a method of using a carbon-11 containing compound of formula (**I**) to image a subject, e.g., a human subject. In some examples, the method includes administering the compound to the subject and detecting the presence of the compound. In some examples, the detecting includes analyzing the subject by positron emission tomography.

Brief Description of the Figures

Figure 1 shows a series of chromatograms tracing the conversion of compound (**II**) to compound (**III**) as described in Example 1. From top to bottom, the chromatograms correspond to the reaction mixture sampled at about 5 minutes, about 30 minutes, about 1 hour and 50 minutes, and about 3 hours from the beginning of the addition of nitromethane and sodium hydroxide to compound (**II**) as outlined in Example 1.

Figure 2 shows a series of chromatograms tracing the conversion of compound (**III**) to compound (**I**) as described in Example 2. From bottom to top, the chromatograms correspond to the reaction mixture sampled at the start of the reaction, about 17 minutes following the addition of SmI_2 to the nitro adduct (**III**), and following the addition of Rochelle salt solution to the reaction mixture.

Figure 3A is a chromatogram obtained from analysis of the reaction mixture following the inverse addition of nitro adduct to reducing agent as described in Example 3.

Figure 3B is a chromatogram obtained from analysis of the reaction mixture following the addition of reducing agent to nitro adduct as described in Example 2.