METHODS OF MAKING BEMPEDOIC ACID AND COMPOSITIONS OF THE SAME

CROSS-REFERENCE

This application claims the benefit of and priority to U.S. Patent Application No. 62/864,873, filed on June 21, 2019, the entire contents of which are incorporated by reference herein.

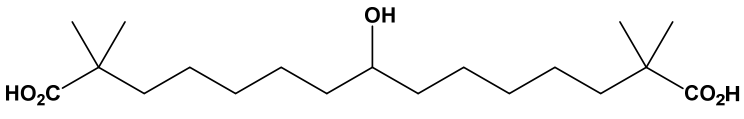
BACKGROUND

The development of robust, cost-effective and efficient manufacturing methods for the production of pharmaceutically active compounds with desired yield and purity remains a significant challenge. Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is a compound under development for the treatment of a wide variety of diseases including liver disorders and cardiovascular disease. Accordingly, a process for synthesizing bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is desired, whereby the product has purity and impurity profiles required by regulatory agencies for the production of a commercializable drug product.

SUMMARY

The inventors have discovered an efficient process for producing high purity bempedoic acid, as well as highly pure, stable forms of bempedoic acid suitable for use as an active pharmaceutical ingredient.

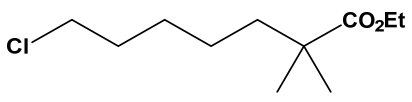
In one aspect of the present disclosure, there is provided a method of preparing a compound of formula (V):



(V),

the method comprising:

(a) contacting ethyl isobutyrate with a substituted 5-chloropentane in the presence of a first base to form a compound of formula (I):

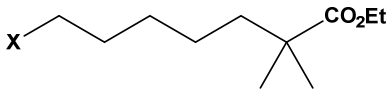


(I)

wherein the substituted 5-chloropentane is selected from the group consisting of 1-bromo-5-chloropentane and 1-iodo-5-chloropentane;

(b) contacting the compound of formula (I) with a salt of formula $[M]^+[X]^-$

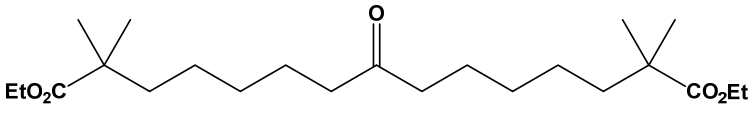
to form a compound of formula (II):



(II)

wherein $[M]^+$ is selected from the group consisting of Li^+, Na^+ and K^+, and $[X]^-$ is selected from the group consisting of Br^- and I^-;

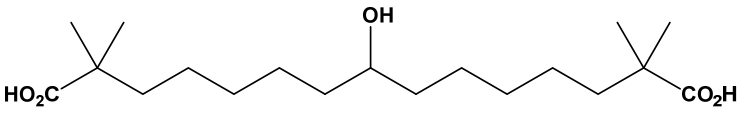
(c) contacting the compound of formula (II) with toluenesulfonylmethyl isocyanide in the presence of a second base to form a first intermediate, and contacting the first intermediate with an acid to form a compound of formula (IV):



(IV); and

(d) contacting the compound of formula (IV) with a reducing agent to form a second intermediate, and contacting the second intermediate with a hydrolyzing base to form a compound of formula (V).

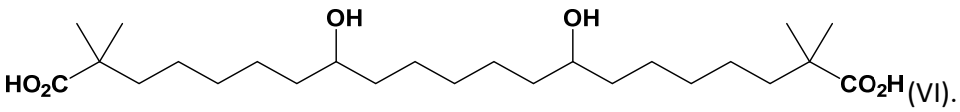
In another aspect of the present disclosure, there is provided a pharmaceutical material comprising a crystalline form of the compound of formula (V):



(V),

or a pharmaceutically acceptable salt thereof;

wherein the pharmaceutical material comprises the compound of formula (V), or a pharmaceutically acceptable salt thereof, in an amount greater than about 85% by weight based on the total weight of the pharmaceutical material and the pharmaceutical material comprises about 0.0001% to less than or equal to 0.15% of a compound of formula (VI):



(VI).

In a further aspect of the present disclosure, there is provided a pharmaceutical formulation comprising:

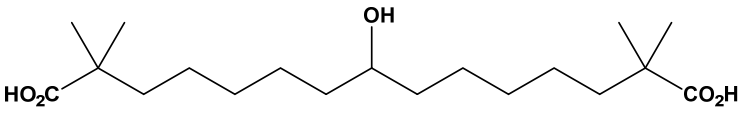
the pharmaceutical material disclosed herein; and

a pharmaceutically acceptable excipient.

In another aspect of the present disclosure, there is provided a use of the pharmaceutical material disclosed herein, or of the pharmaceutical formulation disclosed herein, in the manufacture of a medicament for treating a disease or a condition as described herein.

In a further aspect of the present disclosure, there is provided the pharmaceutical material disclosed herein, or of the pharmaceutical formulation disclosed herein, for use in therapy.

In one example, the present disclosure provides methods of preparing a compound of formula (V):



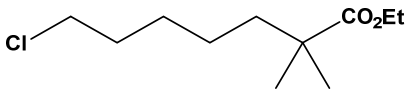
(V),

or a pharmaceutically acceptable salt thereof. The compound of formula (V), or a pharmaceutically acceptable salt thereof, can be of high purity. Accordingly, in certain examples, the present disclosure provides methods of preparing a pharmaceutical material comprising a compound of formula (V), or a pharmaceutically acceptable salt thereof, where the pharmaceutical material includes the compound of formula (V), or a pharmaceutically acceptable salt thereof, in an amount greater than 99.0% by weight based on the total weight of the pharmaceutical material.

In various examples of the present disclosure, the method generally comprises:

(a) contacting ethyl isobutyrate with a substituted 5-chloropentane in the presence of a

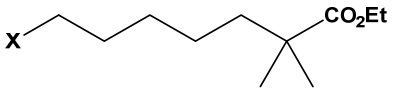
first base to form a compound of formula (I):



(I)

wherein the substituted 5-chloropentane is selected from the group consisting of 1-bromo-5-chloropentane and 1-iodo-5-chloropentane;

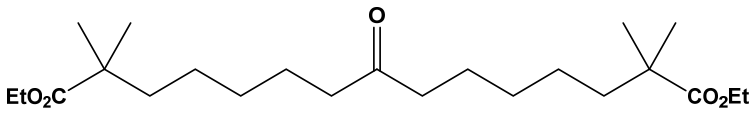
(b) contacting the compound of formula (I) with a salt of formula $[M]^+[X]^-$ to form a compound of formula (II):



(II)

wherein $[M]^+$ is selected from the group consisting of Li^+, Na^+ and K^+, wherein $[X]^-$ is selected from the group consisting of Br^- and I^-;

(c) contacting the compound of formula (II) with toluenesulfonylmethyl isocyanide in the presence of a second base to form a first intermediate, and contacting the first intermediate with an acid to form a compound of formula (IV):

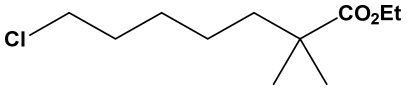


(IV); and

(d) contacting the compound of formula (IV) with a reducing agent to form a second intermediate, and contacting the second intermediate with a hydrolyzing base to form a compound of formula (V), or a pharmaceutically acceptable salt thereof.

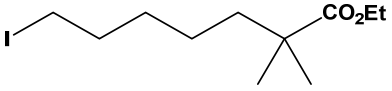
In certain examples of the present disclosure, the method comprises:

(a) contacting 1-bromo-5-chloropentane with about 1 to about 1.21 molar equivalents of ethyl isobutyrate in the presence of lithium diisopropylamide at a temperature in the range of about -20 °C to about 0 °C to form a compound of formula (I):



(I);

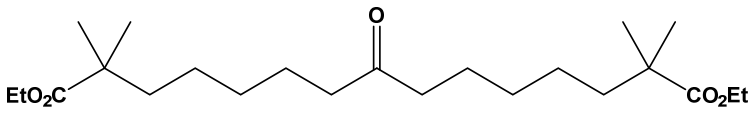
(b) contacting the compound of formula (I) with about 1.1 molar equivalents of sodium iodide in 2-butanone at a temperature in the range of about 78 °C to about 82 °C to form a compound of formula (IIa):



(IIa);

(c) contacting the compound of formula (IIa) with toluenesulfonylmethyl isocyanide in the presence of sodium tert-pentoxide in dimethylacetamide at a temperature in the range of

about -20 ºC to about 10 ºC to form an intermediate, and contacting the intermediate with an acid at a temperature in the range of about -10 ºC to about 35 ºC to form a compound of formula (IV):



(IV); and

(d) contacting the compound of formula (IV) with about 0.35 molar equivalents of sodium borohydride to form a second intermediate, and contacting the second intermediate with sodium hydroxide in a solution to form a compound of formula (V).

In certain examples of the present disclosure, the method further comprises:

(e) purifying the compound of formula (V) to provide a pharmaceutical material comprising a purified amount of the compound of formula (V).

In certain examples of the present disclosure, purifying the compound of formula (V) comprises:

(f) adjusting the pH of the solution comprising the compound of formula (V) to about 6;

(g) extracting the compound of formula (V) from the solution using methyl tert-butyl ether to provide a methyl tert-butyl ether solution comprising the compound of formula (V);

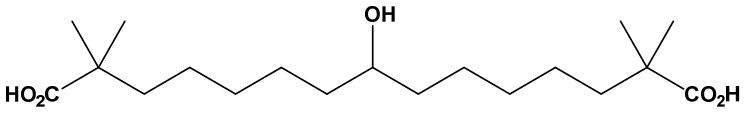
(h) exchanging the methyl tert-butyl ether of the methyl tert-butyl ether solution with ethyl acetate to provide an ethyl acetate solution comprising the compound of formula (V);

(i) filtering the ethyl acetate solution comprising the compound of formula (V) through silica gel;

(j) crystallizing the compound of formula (V) using ethyl acetate and water to provide a crystalline form of the compound of formula (V); and

(k) recrystallizing the crystalline form of the compound of formula (V) using ethyl acetate and water to provide a pharmaceutical material comprising a purified amount of the compound of formula (V).

In another example, the present disclosure provides high purity or purified bempedoic acid, or a pharmaceutically acceptable salt thereof. For example, described herein are pharmaceutical materials comprising a compound of formula (V):



(V),

or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical material comprises

the compound of formula (V), or a pharmaceutically acceptable salt thereof, in an amount greater than 99.0% by weight based on the total weight of the pharmaceutical material.

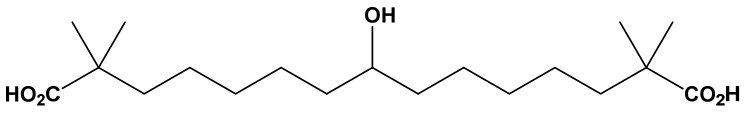
In various examples, the pharmaceutical material comprises a crystalline form of the compound of formula (V), or a pharmaceutically acceptable salt thereof. In some examples, the pharmaceutical material comprises the compound of formula (V) in an amount greater than 99.0% by weight based on the total weight of the pharmaceutical material.

In another example, the present disclosure provides pharmaceutical compositions or formulations including high purity bempedoic acid, or a pharmaceutically acceptable salt thereof, such as the pharmaceutical materials described herein. For example, a pharmaceutical composition can include a pharmaceutical material of the present disclosure (e.g., a pharmaceutical material comprising the compound of formula (V), or a pharmaceutically acceptable salt thereof, in an amount greater than 99.0% by weight based on the total weight of the pharmaceutical material); and a pharmaceutically acceptable excipient. In some examples, a pharmaceutical composition can include a therapeutically effective amount of a pharmaceutical material of the present disclosure; and a pharmaceutically acceptable excipient. In certain examples, the pharmaceutical composition comprises a crystalline form of the compound of formula (V), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

Purified bempedoic acid, or a pharmaceutically acceptable salt thereof; a crystalline form of bempedoic acid, or a pharmaceutically acceptable salt thereof; a pharmaceutical material of the present disclosure (e.g., a pharmaceutical material comprising the compound of formula (V), or a pharmaceutically acceptable salt thereof, in an amount greater than 99.0% by weight based on the total weight of the pharmaceutical material); or a pharmaceutical composition of the present disclosure can be used in treating the various conditions and diseases described herein. For example, the methods of treatment can include inhibiting adenosine triphosphate citrate lyase (ACL), inhibiting cholesterol synthesis, and/or suppressing fatty acid biosynthesis. In some examples, the condition or disease can be hyperlipidemia such as primary hyperlipidemia and the methods include treating hyperlipidemia such as primary hyperlipidemia. In some examples, the disease can be cardiovascular disease and the methods include treating cardiovascular disease. In various examples, the methods of treatment can include improving or lowering low density lipid cholesterol (LDL-C), non-high density lipid cholesterol (non-HDL-C), total serum cholesterol (TC), apolipoprotein B (apoB), and/or high sensitivity C-reactive protein (hsCRP).

CLAIMS

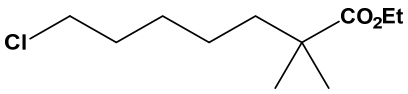
1. A method of preparing a compound of formula (V):



(V),

the method comprising:

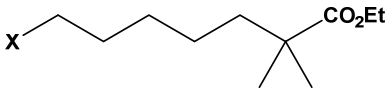
(a) contacting ethyl isobutyrate with a substituted 5-chloropentane in the presence of a first base to form a compound of formula (I):



(I)

wherein the substituted 5-chloropentane is selected from the group consisting of 1-bromo-5-chloropentane and 1-iodo-5-chloropentane;

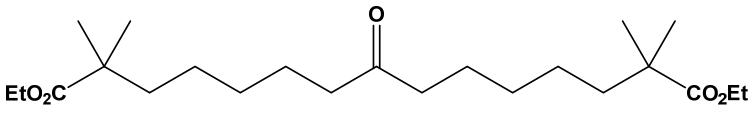
(b) contacting the compound of formula (I) with a salt of formula $[M]^+[X]^-$ to form a compound of formula (II):



(II)

wherein $[M]^+$ is selected from the group consisting of Li^+, Na^+ and K^+, and $[X]^-$ is selected from the group consisting of Br^- and I^-;

(c) contacting the compound of formula (II) with toluenesulfonylmethyl isocyanide in the presence of a second base to form a first intermediate, and contacting the first intermediate with an acid to form a compound of formula (IV):



(IV); and

(d) contacting the compound of formula (IV) with a reducing agent to form a second intermediate, and contacting the second intermediate with a hydrolyzing base to form a compound of formula (V).

2. The method of claim 1, wherein in step (a), the first base is selected from the group consisting of lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium hydride, sodium amide, lithium amide, and lithium tetramethylpiperidide.

3. The method of claim 1 or 2, wherein in step (a), contacting ethyl isobutyrate with the substituted 5-chloropentane is conducted at a temperature in the range of about -20 ºC to about 0 ºC.

4. The method of any one of claims 1-3, wherein in step (a), less than about 1% by weight of the substituted 5-chloropentane remains after forming the compound of formula (I).

5. The method of any one of claims 1-4, wherein in step (a), the molar ratio of ethyl isobutyrate to the substituted 5-chloropentane is from about 1.1:1 to about 1.21:1.

6. The method of any one of claims 1-5, wherein in step (b), contacting the compound of formula (I) with the salt of formula $[M]^+[X]^-$ is conducted in a solvent comprising one or more of acetone, 2-butanone, methyl isobutyl ketone, and tetrahydrofuran, wherein M is selected from the group consisting of Li, Na and K, and X is selected from the group consisting of Br and I.

7. The method of claim 6, wherein in step (b), the solvent comprises less than about 3% by weight water.

8. The method of any one of claims 1-7, wherein in step (b), contacting the compound of formula (I) with the salt of formula $[M]^+[X]^-$ is conducted at a temperature in the range of about 78 ºC to about 82 ºC, wherein M is selected from the group consisting of Li, Na and K, and X is selected from the group consisting of Br and I.

9. The method of any one of claims 1-8, wherein in step (b), contacting the compound of formula (I) with the salt of formula $[M]^+[X]^-$ comprises contacting the compound of formula (I) with about 1.1 molar equivalents of the salt of formula $[M]^+[X]^-$ based on the molar amount of the compound of formula (I), wherein M is selected from the group consisting of Li, Na and K, and X is selected from the group consisting of Br and I.

10. The method of any one of claims 1-9, wherein in step (b), the salt of formula $[M]^+[X]^-$ is sodium iodide.

11. The method of any one of claims 1-10, wherein in step (c), the second base is selected from sodium hydride, potassium tert-butoxide, and sodium tert-pentoxide.

12. The method of any one of claims 1-11, wherein in step (c), contacting the compound of formula (II) with toluenesulfonylmethyl isocyanide in the presence of a second base to form the

first intermediate is conducted at a temperature in a range of about -20 ºC to about 10 ºC.

13. The method of any one of claims 1-12, wherein in step (c), the molar ratio of the compound of formula (II) to toluenesulfonylmethyl isocyanide is about 1.9:1.

14. The method of any one of claims 1-13, wherein in step (c), contacting the compound of formula (II) with toluenesulfonylmethyl isocyanide is conducted in dimethylacetamide.

15. The method of any one of claims 1-14, wherein in step (c), contacting the first intermediate with an acid is conducted at a temperature in a range of about -10 ºC to about 35 ºC.

16. The method of any one of claims 1-15, wherein in step (c), the acid is hydrochloric acid.

17. The method of any one of claims 1-16, wherein in step (d), the reducing agent is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, cerium borohydride, zinc borohydride and diisobutylaluminum hydride.

18. The method of any one of claims 1-17, wherein in step (d), contacting the compound of formula (IV) with a reducing agent comprises contacting the compound of formula (IV) with about 0.2 to about 0.7 molar equivalents of the reducing agent based on the molar amount of the compound of formula (IV).

19. The method of any one of claims 1-18, wherein in step (d), the hydrolyzing base is sodium hydroxide.

20. The method of any one of claims 1-19, wherein in step (d), contacting the second intermediate with a hydrolyzing base to form a compound of formula (V) is conducted in a solution; and the method further comprises adjusting the pH of the solution comprising the compound of formula (V) to between about 3 to about 7.

21. The method of any one of claims 1-20, wherein in step (d), contacting the compound of formula (IV) with a reducing agent to form a second intermediate, and contacting the second intermediate with a hydrolyzing base to form a compound of formula (V) is conducted in a single reaction vessel.

22. The method of any one of claims 1-21, further comprising:

(e) purifying the compound of formula (V) to provide a pharmaceutical material

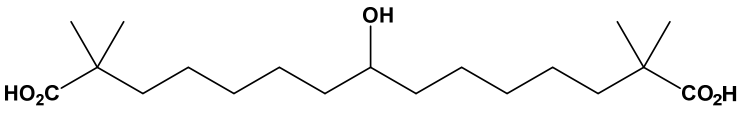
comprising a purified amount of the compound of formula (V).

23. The method of claim 22, wherein in step (e), purifying the compound of formula (V) comprises crystallizing the compound of formula (V).

24. The method of claim 22 or 23, wherein in step (e), purifying the compound of formula (V) comprises crystallizing the compound of formula (V) from a mixture of solvents, wherein the mixture of solvents comprises ethyl acetate and water.

25. The method of any one of claims 1-24, wherein the compound of formula (V) has a melting point onset temperature as determined by differential scanning calorimetry in a range between about 90 ºC to about 94 ºC.

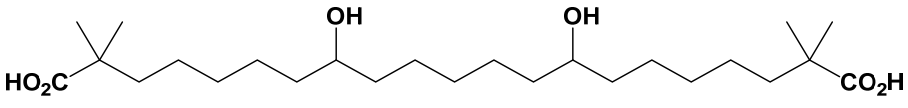
26. A pharmaceutical material comprising a crystalline form of the compound of formula (V):



(V),

or a pharmaceutically acceptable salt thereof;

wherein the pharmaceutical material comprises the compound of formula (V), or a pharmaceutically acceptable salt thereof, in an amount greater than about 85% by weight based on the total weight of the pharmaceutical material and the pharmaceutical material comprises about 0.0001% to less than or equal to 0.15% of a compound of formula (VI):



(VI).

27. The pharmaceutical material of claim 26, wherein the crystalline form of the compound of formula (V) exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):10.3±0.2, 10.4±0.2, 17.9±0.2, 18.8±0.2, 19.5±0.2, and 20.7±0.2.

28. The pharmaceutical material of claim 26 or 27, wherein the crystalline form of the compound of formula (V) is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 4.

29. The pharmaceutical material of any one of claims 26-28, wherein the crystalline form of the compound of formula (V) has a melting point onset as determined by differential scanning calorimetry in the range of from about 90 °C to about 94 °C.

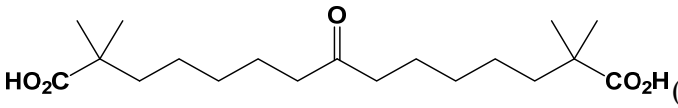
30. The pharmaceutical material of any one of claims 26-29, wherein the pharmaceutical material comprises the compound of formula (V) in an amount greater than 99.0% by weight based on the total weight of the pharmaceutical material.

31. The pharmaceutical material of any one of claims 26-29, wherein the pharmaceutical material comprises the compound of formula (V) in an amount greater than 99.5% by weight based on the total weight of the pharmaceutical material.

32. The pharmaceutical material of any one of claims 26-31, wherein the pharmaceutical material comprises the compound of formula (V) in an amount of from about 98% to about 102% by weight based on the total weight of the pharmaceutical material, as determined by a high performance liquid chromatography (HPLC) assay.

33. The pharmaceutical material of claim 32, wherein the HPLC assay uses a Waters XBridge BEH C18 column (4.6 mm i.d. x 150 mm, 2.5 μm) at a temperature of about 40 °C, with isocratic elution of a mobile phase comprising about 0.05% phosphoric acid in water/acetonitrile (about 50:50) at a flow rate of about 1.2 mL/minute, and detection at 215 nm, wherein the retention time of the compound of formula (V) is about 4.6 minutes.

34. The pharmaceutical material of any one of claims 26-33, further comprising a compound of formula (VII):



(VII),

or a pharmaceutically acceptable salt thereof.

35. The pharmaceutical material of any one of claims 26-34, further comprising less than or equal to 0.2% by weight of unknown impurities.

36. A pharmaceutical formulation comprising:
the pharmaceutical material of any one of claims 26-35; and
a pharmaceutically acceptable excipient.

37. Use of the pharmaceutical material of any one of claims 26-35, or of the pharmaceutical formulation of claim 36, in the manufacture of a medicament for treating a disease or a condition as described herein.

38. The pharmaceutical material of any one of claims 26-35, or of the pharmaceutical formulation of claim 36, for use in therapy.