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(71) Applicant: **PONCE DE LEON HEALTH DESIGNATED ACTIVITY COMPANY** [IE/IE]; 9 Hibury, Rathmullan Road, Drogheda, County Louth (IE).

(72) Inventors; and

(71) Applicants: **PEREIRA, David Eugene** [US/US]; 103 Lansbrooke Lane, Apex, NC 27502 (US). **DEO, Keshav** [IN/IN]; Villa No. 110, Gummada Prestige Park, Gundla Pochampally, Kompally, Hyderabad, Telangana 500014 (IN).

(74) Agent: **MCLAREN, Kevin;** Brannon Sowers & Cracraft PC, 47 South Meridian Street, Suite 400, Indianapolis, Indiana 46204 (US).

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(54) **Title:** PROCESS OF MAKING CALCIUM ALPHA-KETOGLUTARATE

(57) **Abstract:** Methods and processes for preparing calcium salts of alpha-ketoglutarate are described herein.

PROCESS FOR MAKING CALCIUM ALPHA-KETOGLUTARATE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application Serial Number 62/736,320, filed September 25, 2018, the disclosure of which is incorporated herein by reference in its entirety.

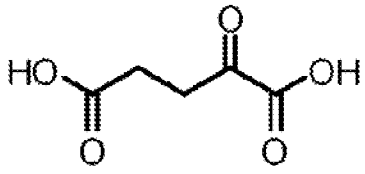
TECHNICAL FIELD

The invention described herein pertains to methods and processes for preparing calcium salts of alpha-ketoglutarate.

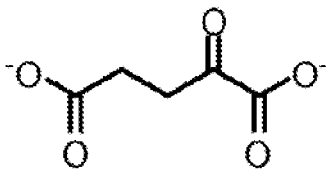
BACKGROUND

Alpha-ketoglutaric acid is an important biological molecule, which is a key intermediate in the Krebs cycle, a nitrogen transporter, and a co-substance in molecular oxidation. Alpha-ketoglutaric acid anion plays a key role in metabolism, mainly in aerobic organisms. A calcium salt of alpha-ketoglutarate (Ca-AKG) is an important source of alpha-ketoglutaric acid anion.

Alpha-Ketoglutarate anion (Formula 2, also known via the name of its acid 2-oxopentanedioic acid, 2-ketoglutaric acid, 2-oxoglutaric acid, or oxoglutaric acid depicted as Formula 1) is an intermediate in the Krebs cycle of eukaryotic organisms and is biosynthesized from isocitrate (in the Krebs cycle process) or L-glutamate (via alanine transaminase) in such organisms. Both alpha-ketoglutarate and its corresponding acid are commercially available, either via preparation from fermentation cultures (for example see US 2,776,926) or chemical synthesis from closely related compounds.



Formula 1



Formula 2

Consistent with its role in energy generation via the Krebs cycle, alpha-ketoglutarate is an important regulator of bioenergetics in cells and is implicated as an inhibitor of ATP synthase subunit β and an indirect inhibitor of the kinase mTOR, a consequence of partial inhibition of the mitochondrial electron transport chain.

Known methods for the synthesis of Ca-AKG from alpha-ketoglutaric acid require substantial purification of the final product which leads to the increased time and cost of the overall process. Accordingly, there is a need for discovery of novel methods for the synthesis of Ca-AKG

from alpha-ketoglutaric acid with reduced formation of impurities.

SUMMARY OF THE INVENTION

Disclosed herein, in certain embodiments, are methods for making calcium alpha-ketoglutarate, the methods comprise a) contacting alpha-ketoglutaric acid with an alkali metal salt and water, thereby forming the corresponding bis salt of alpha-ketoglutarate; and b) contacting the bis salt of alpha-ketoglutarate with a calcium salt, thereby forming calcium alpha-ketoglutarate. Illustratively, the alkali metal salt is an alkali metal salt of an acid, where the conjugate acid of the alkali metal salt has at least one pKa from about 4 to about 12. Illustratively, the mixture of the alkali metal salt and water has a pH in the range from about 5.0 to about 11.9.

DETAILED DESCRIPTION

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention described herein, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without unacceptable toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, “alpha-ketoglutarate” or “AKG” comprises derivatives of alpha-ketoglutaratic acid (e.g., the derivatives set forth in MacKenzie, et al. (2007) Mol Cell Biol 27(9):3282- 3289)), analogues of alpha-ketoglutarate (e.g., phosphonate analogues (e.g., those recited in Bunik, et al. (2005) Biochemistry 44(31): 10552-61), esters of alpha-ketoglutarate (e.g., dimethyl alpha-ketoglutarate and octyl alpha-ketoglutarate), and various species specific analogues, e.g., human alpha-ketoglutarate, porcine alpha-ketoglutarate, murine alpha-ketoglutarate, bovine alpha-ketoglutarate, and the like.

Alpha-Ketoglutarate (AKG)

Described herein are processes of making calcium alpha-ketoglutarate.

In certain aspects, the disclosure provides compositions that comprise compounds (e.g. alpha-ketoglutarate salts) that are available for human consumption without FDA approval or

generally recognized as safe (GRAS). Such compounds may be so classified because they are: a) present in the FDA SCOGS database and are generally recognized as safe by the U.S. Food and Drug Administration; or b) are derived from plants (for e.g. fruits, vegetables, herbs) present in traditional diets and so are recognized by the scientific community as safe for consumption. In some embodiments GRAS compounds are those compounds which are available for human consumption without FDA approval.

In some embodiments, alpha-ketoglutarate is provided as a monolithium salt, a dilithium salt, a monosodium salt, a disodium salt, a monopotassium salt, a dipotassium salt, or a mixed salt of lithium, sodium, or potassium, a calcium salt, or a zinc salt. In some embodiments, alpha-ketoglutarate is provided as a calcium salt. In further embodiments, the calcium salt of alpha-ketoglutarate is provided as anhydrous salt, monohydrate, or dihydrate. In yet further embodiments, alpha-ketoglutarate is provided as a mono- or di-valent salt with other cations described in the U.S. FDA *Orange Book.* Such cations include calcium, diolamine, lithium, lysine, magnesium, meglumine, olamine, tromethamine, and zinc.

Processes for Preparing Calcium Alpha-Ketoglutarate (Ca-AKG)

In one illustrative embodiment of the invention, described herein is a method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with an alkali metal salt of an acid and water, thereby forming a bis salt of alpha-ketoglutarate; and

b) contacting the bis salt of alpha-ketoglutarate with a calcium salt and water, thereby forming calcium alpha-ketoglutarate;

wherein the conjugate acid of the alkali metal salt of has a pKa from about 4 to about 12.

In another embodiment, described herein is a method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with an alkali metal salt of an acid and water to form a solution having a pH in the range from about 5 to about 11.9, thereby forming a bis salt of alpha-ketoglutarate; and

b) contacting the bis salt of alpha-ketoglutarate with a calcium salt and water, thereby forming calcium alpha-ketoglutarate.

Several illustrative embodiments of the invention are described by the following enumerated clauses:

1. A method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with an alkali metal salt of an acid, where the

conjugate acid of the alkali metal salt has at least one pKa from about 4 to about 12, thereby forming a bis salt of alpha-ketoglutarate; and

b) contacting the bis salt of alpha-ketoglutarate with a calcium salt, thereby forming calcium alpha-ketoglutarate.

2. The method of clause 1 wherein the conjugate of the acid has at least one pKa from about 5 to about 12

3. The method of clause 1 wherein the conjugate of the acid has at least one pKa from about 5.5 to about 12.

4. The method of clause 1 wherein the conjugate of the acid has at least one pKa from about 5.5 to about 11.5.

5. The method of clause 1 wherein the conjugate of the acid has at least one pKa from about 6 to about 11.5.

6. The method of clause 1 wherein the conjugate of the acid has at least one pKa from about 6 to about 11.

7. A method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with an alkali metal salt of an acid and water to form a solution having a pH in the range from about 5 to about 11.9, thereby forming a bis salt of alpha-ketoglutarate; and

b) contacting the bis salt of alpha-ketoglutarate with a calcium salt and water, thereby forming calcium alpha-ketoglutarate.

8. The method of clause 7 wherein the pH is in the range from about 5.3 to about 11.6.

9. The method of any one of the preceding clauses wherein the alpha-ketoglutaric acid is mixed with water.

10. The method of any one of the preceding clauses wherein the alpha-ketoglutaric acid and water mixture is prepared from or contains from about 0.05 to about 0.5 weight equivalents of alpha-ketoglutaric acid per one weight equivalent of water.

11. The method of any one of the preceding clauses wherein the alkali metal salt is mixed with water.

12. The method of clause 11 wherein the alkali metal salt and water mixture has a pH in the range from about 5 to about 11.9.

13. The method of clause 11 wherein the alkali metal salt and water mixture has a pH in the range from about 5.2 to about 11.6.

14. The method of clause 11 wherein the alkali metal salt and water mixture has a pH in

the range from about 5.3 to about 11.5.

15. The method of clause 11 wherein the alkali metal salt and water mixture has a pH in the range from about 5.3 to about 8.4.

16. The method of any one of the preceding clauses wherein the alkali metal salt and water mixture is prepared from or contains from about 0.1 to about 0.35 weight equivalents of alkali metal salt per one weight equivalent of water.

17. The method of any one of the preceding clauses wherein the alkali metal salt is selected from the group consisting of lithium, sodium, and potassium salts of bicarbonate and carbonate, and combinations thereof.

18. The method of any one of the preceding clauses wherein the alkali metal salt includes sodium bicarbonate, sodium carbonate, or a mixture thereof.

19. The method of any one of the preceding clauses wherein the alkali metal salt includes sodium bicarbonate.

20. The method of any one of the preceding clauses wherein the sodium bicarbonate and water mixture contains from about 0.2 to about 0.3 weight equivalents of sodium bicarbonate per one weight equivalent of water.

21. The method of clause 20 wherein the sodium bicarbonate and water mixture contains from about 0.23 to about 0.28 weight equivalents of sodium bicarbonate per one weight equivalent of water.

22. The method of any one of the preceding clauses wherein the alkali metal salt includes sodium carbonate.

23. The method of clause 22 wherein the sodium carbonate and water mixture contains from about 0.05 to about 0.2 weight equivalents of sodium carbonate per one weight equivalent of water.

24. The method of clause 22 wherein the sodium carbonate and water mixture contains from about 0.1 to about 0.2 weight equivalents of sodium carbonate per one weight equivalent of water.

25. The method of any one of the preceding clauses wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH of at least about 6.5, optionally after a predetermined period of time.

26. The method of clause 25 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH of at least about 7.0, optionally after a predetermined period of time.

27. The method of clause 25 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH of at least about 7.5, optionally after a predetermined period of time.

28. The method of clause 25 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH of at least about 8, optionally after a predetermined period of time.

29. The method of clause 25 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH of at least about 8.5, optionally after a predetermined period of time.

30. The method of clause 25 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH from about 6.5 to about 9, optionally after a predetermined period of time.

31. The method of clause 25 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH from about 6.5 to about 8.5, optionally after a predetermined period of time.

32. The method of any one of the preceding clauses wherein the alpha-ketoglutaric acid is from about 0.5 to about 3 weight equivalents per one weight equivalent of alkali metal salt.

33. The method of clause 32 wherein the alpha-ketoglutaric acid is from about 0.7 to about 0.9 weight equivalents per one weight equivalent of sodium bicarbonate.

34. The method of clause 32 wherein the alpha-ketoglutaric acid is from about 0.74 to about 0.88 weight equivalents per one weight equivalent of sodium bicarbonate.

35. The method of any one of the preceding clauses wherein the alpha-ketoglutaric acid is from about 1.0 to about 2.8 weight equivalents per one weight equivalent of sodium carbonate.

36. The method of clause 35 wherein the alpha-ketoglutaric acid is from about 1.1 to about 2.8 weight equivalents per one weight equivalent of sodium carbonate.

37. The method of clause 35 wherein the alpha-ketoglutaric acid is from about 1.1 to about 2.5 weight equivalents per one weight equivalent of sodium carbonate.

38. The method of clause 35 wherein the alpha-ketoglutaric acid is from about 1.1 to about 1.2 weight equivalents per one weight equivalent of sodium carbonate.

39. The method of any one of the preceding clauses wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 50 °C or less.

40. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 40 °C or less.

41. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 35 °C or less.

42. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 30 °C or less.

43. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 25 °C or less.

44. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 50 °C.

45. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 40 °C.

46. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 35 °C.

47. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 30 °C.

48. The method of clause 39 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 25 °C.

49. The method of any one of the preceding clauses wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 30 minutes.

50. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 1 hour.

51. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 2 hours.

52. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 3 hours.

53. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 4 hours.

54. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for about 30 minutes to about 6 hours or less.

55. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for about 1 hour to about 6 hours or less.

56. The method of clause 49 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for about 2 hour to about 6 hours or less.

57. The method of any one of the preceding clauses wherein the calcium salt is selected

from the group consisting of calcium formate, calcium acetate, and calcium chloride.

58. The method of clause 57 wherein the calcium salt is calcium chloride.

59. The method of any one of the preceding clauses wherein the calcium salt is mixed with water.

60. The method of clause 59 wherein the calcium salt and water mixture is prepared from or contains from about 0.1 to about 1 weight equivalents of the calcium salt per one weight equivalent of water.

61. The method of clause 59 wherein the calcium chloride and water mixture contains from about 0.1 to about 0.6 weight equivalents of the calcium chloride per one weight equivalent of water.

62. The method of clause 59 wherein the calcium chloride and water mixture contains from about 0.2 to about 0.5 weight equivalents of the calcium chloride per one weight equivalent of water.

63. The method of clause 59 wherein the calcium chloride and water mixture contains from about 0.23 to about 0.4 weight equivalents of the calcium chloride per one weight equivalent of water.

64. The method of clause 59 wherein the calcium chloride and water mixture contains from about 0.2 to about 0.5 weight equivalents of the calcium chloride per one weight equivalent of water.

65. The method of any one of the preceding clauses wherein the calcium salt is from 0.5 to 2 weight equivalents per one weight equivalent of alpha-ketoglutaric acid.

66. The method of clause 64 wherein the calcium salt is from 0.75 to 2 weight equivalents per one weight equivalent of alpha-ketoglutaric acid.

67. The method of clause 64 wherein the calcium chloride is from about 0.75 to about 1.35 weight equivalents per one weight equivalent of alpha-ketoglutaric acid.

68. The method of clause 64 wherein the calcium chloride is from about 0.9 to about 1.1 weight equivalents per one weight equivalent of alpha-ketoglutaric acid.

69. The method of any one of the preceding clauses wherein the bis salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate is contacted with the calcium salt and water mixture at about 40 °C to about 90 °C.

70. The method of clause 69 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at about 65 °C to about 75 °C.

71. The method of any one of the preceding clauses wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for at least about 30 min.

72. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for at least about 1 hour.

73. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for at least about 2 hours.

74. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for at least about 4 hours.

75. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for at least about 5 hours.

76. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for about 30 minutes to about 5 hours or less.

77. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for about 1 hour to about 5 hours or less.

78. The method of clause 71 wherein the bis alkali metal salt of alpha-ketoglutarate, such as the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for about 2 hours to about 5 hours or less.

79. The method of any one of the preceding clauses further comprising drying the calcium alpha-ketoglutarate.

80. The method of any one of the preceding clauses further comprising drying the calcium alpha-ketoglutarate to a moisture content of about 20% to about 5%.

81. The method of clause 80 comprising drying the calcium alpha-ketoglutarate to a moisture content of about 15% to about 5%.

82. The method of clause 80 comprising drying the calcium alpha-ketoglutarate to a moisture content of about 15% to about 8%.

83. The method of clause 80 comprising drying the calcium alpha-ketoglutarate to a

moisture content of about 12% to about 8%.

84. The method of clause 80 comprising drying the calcium alpha-ketoglutarate to a moisture content of about 10% to about 8%.

85. The method of any one of the preceding clauses further comprising drying the calcium alpha-ketoglutarate, where the dried calcium alpha-ketoglutarate is less than 50% calcium alpha-ketoglutarate dihydrate.

86. The method of any one of the preceding clauses further comprising drying the calcium alpha-ketoglutarate, where the dried calcium alpha-ketoglutarate is at least 50% calcium alpha-ketoglutarate monohydrate.

87. A method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with a solution of sodium bicarbonate and water, thereby forming disodium alpha-ketoglutarate; and

b) contacting the disodium alpha-ketoglutarate with a solution of calcium chloride and water, thereby forming calcium alpha-ketoglutarate;

wherein the solution of sodium bicarbonate is prepared from about 0.27 weight equivalents of sodium bicarbonate per one weight equivalent of water;

wherein the alpha-ketoglutaric acid is about 0.74 weight equivalents per one weight equivalent of sodium bicarbonate;

wherein the alpha-ketoglutaric acid is contacted with the solution of sodium bicarbonate and water at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the alpha-ketoglutaric acid and the solution of sodium bicarbonate and water is stirred for about 2 hours at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the solution of calcium chloride is prepared from about 0.2 to about 0.5 weight equivalents of the calcium chloride per one weight equivalent of water;

wherein the calcium chloride is about 0.95 weight equivalents per one weight equivalent of alpha-ketoglutaric acid;

wherein the disodium alpha-ketoglutarate and the solution of calcium chloride is stirred for about 4 hours at 65 °C to 70 °C.

88. A method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with a solution of sodium carbonate and water, thereby forming disodium alpha-ketoglutarate; and

b) contacting the disodium alpha-ketoglutarate with a solution of calcium chloride and water, thereby forming calcium alpha-ketoglutarate;

wherein the solution of sodium carbonate is prepared from about 0.18 weight equivalents of sodium carbonate per one weight equivalent of water;

wherein the alpha-ketoglutaric acid is about 1.14 weight equivalents per one weight equivalent of sodium carbonate;

wherein the alpha-ketoglutaric acid is contacted with the solution of sodium carbonate and water at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the alpha-ketoglutaric acid and the solution of sodium carbonate and water is stirred for 2 hours at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the solution of calcium chloride is prepared from about 0.2 to about 0.5 weight equivalents of the calcium chloride per one weight equivalent of water;

wherein the calcium chloride is about 0.95 weight equivalent per one weight equivalent of alpha-ketoglutaric acid;

wherein the disodium alpha-ketoglutarate and the solution of calcium salt and water is stirred for about 4 hours at 65 °C to 70 °C.

It is to be understood that all weight equivalents of components, reactants, reagents, solvents, and the like, described herein are a description of the corresponding mole equivalents, each of which is obtained from the molecular weight of such components, reactants, reagents, solvents, and the like. In addition, it is to be understood that certain weight equivalents, such as weight equivalents of specific alkali metal salts to water can be converted to the corresponding weight equivalents of alternative alkali metal salts to water by accounting for the different molecular weights of the specific alkali metal salts and the alternative alkali metal salts. It is also to be understood that the same conversion between specific weight equivalents of alpha-ketoglutaric acid to water, or weight equivalents of alpha-ketoglutaric acid to alkali metal salts, or weight equivalents of calcium salts to water, or weight equivalents of calcium salts to alpha-ketoglutaric acid to alternatives, respectively, by accounting for the different molecular weights in each case.

For example, it is to be understood that all weight equivalents of alkali metal salts of acids described herein may also be represented as mole equivalents, such as in a mole ratio or a molar concentration. Illustratively, where the water mixture contains from about 0.1 to about 0.35 weight equivalents of sodium bicarbonate per one weight equivalent of water corresponds to about 1.2 to about 4.2 mmole equivalents of sodium bicarbonate, or sodium ion, per mL of water, or a sodium ion concentration range of about 1.2 to about 4.2 mmolar. It is to be further understood that the same range of mmole equivalents, or mmolar concentrations can be used with other alkali metal

salts of acids or mixtures thereof, such as lithium bicarbonate, lithium carbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, and the like described herein. It is to be further understood that the same range of mmole equivalents, or mmolar concentration used with other alkali metal salts of acids, such as lithium bicarbonate, lithium carbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, and the like described herein, may be expressed as the corresponding weight equivalents.

Illustratively, the methods described herein include contacting alpha-ketoglutaric acid with a water mixture of potassium bicarbonate, where the water mixture contains from about 1.2 to about 4.2 mmole equivalents of potassium bicarbonate, or potassium ion, per mL of water, or a potassium ion concentration range of about 1.2 to about 4.2 mmolar. Expressed in weight equivalents, the methods described herein include contacting alpha-ketoglutaric acid with a water mixture of potassium bicarbonate, where the water mixture contains from about 0.12 to about 0.42 weight equivalents of potassium bicarbonate per one weight equivalent of water.

Illustratively, the methods described herein include contacting alpha-ketoglutaric acid with a water mixture of sodium carbonate or potassium carbonate, where the water mixture contains from about 1.2 to about 4.2 mmole equivalents of sodium or potassium ions per mL of water, or a sodium or potassium ion concentration range of about 1.2 to about 4.2 mmolar. It is to be understood that sodium carbonate includes two sodium ions, and therefore, expressed in weight equivalents, the methods described herein include contacting alpha-ketoglutaric acid with a water mixture of sodium carbonate, where the water mixture contains from about 0.06 to about 0.22 weight equivalents of sodium carbonate per one weight equivalent of water. It is also to be understood that potassium carbonate includes two potassium ions, and therefore, expressed in weight equivalents, the methods described herein include contacting alpha-ketoglutaric acid with a water mixture of potassium carbonate, where the water mixture contains from about 0.08 to about 0.29 weight equivalents of potassium carbonate per one weight equivalent of water.

Alkali metal salts

In some embodiments, the alkali metal salt is selected from lithium bicarbonate, lithium carbonate, sodium bicarbonate sodium carbonate, potassium bicarbonate, and potassium carbonate, and combinations thereof. In some embodiments, the alkali metal salt comprises sodium bicarbonate. In some embodiments, the alkali metal salt comprises sodium carbonate. In some embodiments, the alkali metal salt is sodium bicarbonate. In some embodiments, the alkali metal salt is sodium carbonate.

Ratio of alkali metal salts to water

In some embodiments, the alkali metal salt and water are added as a mixture. In some embodiments, the alkali metal salt and water mixture contains from 0.1 to 0.35 weight equivalents of alkali metal salt per one weight equivalent of water.

In some embodiments, the sodium bicarbonate and water are added as a mixture. In some embodiments, the sodium bicarbonate and water mixture contains from 0.1 to 0.3 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains from 0.1 to 0.25 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains from 0.15 to 0.3 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains from 0.15 to 0.25 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains from 0.2 to 0.3 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains from 0.2 to 0.25 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.15 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.16 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.17 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.18 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.19 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.2 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.21 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.22 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.23 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.24 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.25 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium

bicarbonate and water mixture contains 0.26 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.27 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.28 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.29 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.3 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.31 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.32 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.33 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.34 weight equivalents of sodium bicarbonate per one weight equivalent of water. In some embodiments, the sodium bicarbonate and water mixture contains 0.35 weight equivalents of sodium bicarbonate per one weight equivalent of water.

In some embodiments, the sodium carbonate and water are added as a mixture. In some embodiments, the sodium carbonate and water mixture contains from about 0.05 to about 0.35 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from about 0.05 to about 0.2 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.1 to 0.35 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.1 to 0.3 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.1 to 0.25 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.15 to 0.3 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.15 to 0.25 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.2 to 0.3 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains from 0.2 to 0.25 weight equivalents of sodium

carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.15 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.16 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.17 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.18 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.19 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.2 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.21 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.22 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.23 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.24 weight equivalents of sodium carbonate per one weight equivalent of water. In some embodiments, the sodium carbonate and water mixture contains 0.25 weight equivalents of sodium carbonate per one weight equivalent of water.

Ratio of alpha-ketoglutaric acid to alkali metal salts

In some embodiments, the alpha-ketoglutaric acid is from about 0.5 to about 3 weight equivalents per one weight equivalent of alkali metal salt. In some embodiments, the alpha-ketoglutaric acid is from 0.5 to 0.9 weight equivalents per one weight equivalent of alkali metal salt.

In some embodiments, the alpha-ketoglutaric acid is from 0.5 to 0.9 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.6 to 0.9 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha- ketoglutaric acid is from 0.7 to 0.9 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.5 to 0.8 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.6 to 0.8 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.7 to 0.8 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.7 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments,

the alpha-ketoglutaric acid is 0.71 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.72 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.73 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.74 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.75 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.76 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.77 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.78 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.79 weight equivalents per one weight equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.8 weight equivalents per one weight equivalent of sodium bicarbonate.

In some embodiments, the alpha-ketoglutaric acid is from 0.33 to 0.5 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.33 to 0.45 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.35 to 0.45 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.36 to 0.45 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.37 to 0.45 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.38 to 0.45 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha- ketoglutaric acid is from 0.39 to 0.45 mole equivalents per one mol equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.4 to 0.45 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.35 to 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.36 to 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.37 to 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.38 to 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.39 to 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha- ketoglutaric acid is from 0.4 to 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the

alpha-ketoglutaric acid is from 0.35 to 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.36 to 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.37 to 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.38 to 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.39 to 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.4 to 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.35 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.36 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.37 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.38 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.39 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.4 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.41 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha- ketoglutaric acid is 0.42 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.43 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.44 mole equivalents per one mole equivalent of sodium bicarbonate. In some embodiments, the alpha-ketoglutaric acid is 0.45 mole equivalents per one mole equivalent of sodium bicarbonate.

In some embodiments, the alpha-ketoglutaric acid is from 1 to 2.8 weight equivalents per one weight equivalent of alkali metal salt. In some embodiments, the alpha-ketoglutaric acid is from 1 to 2.8 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.9 to 1.4 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from one to 1.4 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 1.1 to 1.4 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.9 to 1.3 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from one to 1.3 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 1.1 to 1.3 weight equivalents per one weight equivalent of sodium

carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.9 to 1.2 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from one to 1.2 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 1.1 to 1.2 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha- ketoglutaric acid is 1.05 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.06 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.07 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.08 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.09 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha- ketoglutaric acid is 1.1 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.1 1 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.12 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.13 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.14 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha- ketoglutaric acid is 1.15 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.16 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.17 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.18 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 1.19 weight equivalents per one weight equivalent of sodium carbonate. In some embodiments, the alpha- ketoglutaric acid is 1.20 weight equivalents per one weight equivalent of sodium carbonate.

In some embodiments, the alpha-ketoglutaric acid is from 0.5 to one mole equivalents per one mol equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.6 to one mole equivalents per one mol equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.7 to one mole equivalents per one mol equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.8 to one mole equivalents per one mol equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.5 to 0.9 mole equivalents per one mol equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.6 to 0.9 mole equivalents per one mol equivalent of sodium

carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.7 to 0.9 mole equivalents per one mol equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is from 0.8 to 0.9 mole equivalents per one mol equivalent of sodium carbonate.

In some embodiments, the alpha-ketoglutaric acid is 0.75 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.76 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.77 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.78 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.79 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha- ketoglutaric acid is 0.8 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.81 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.82 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.83 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.84 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.85 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.86 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha- ketoglutaric acid is 0.87 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.88 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.89 mole equivalents per one mole equivalent of sodium carbonate. In some embodiments, the alpha-ketoglutaric acid is 0.9 mole equivalents per one mole equivalent of sodium carbonate.

Contacting temperature of alkali metal salts and alpha-ketoglutaric acid

In some embodiments, the alpha-ketoglutaric acid is contacted with the alkali metal salt at about 50 °C or less, about 40 °C or less, about 35 °C or less, about 30 °C or less, or about 25 °C or less. In some embodiments, the alpha-ketoglutaric acid is contacted with the alkali metal salt in the range from about 10 °C to about 50 °C, from about 10 °C to about 40 °C, from about 10 °C to about 35 °C, from about 10 °C to about 30 °C, from about 10 °C to about 25 °C.

In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 40 °C. In some embodiments, the alpha-

ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 15 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 15 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 15 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 40 °C. In some embodiments, the alpha- ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 40 °C. In some embodiments, the alpha- ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 21 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 22 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 23 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 24 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 26 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 27 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 28 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 29 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium

bicarbonate and water mixture at 30 °C.

In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 15 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 15 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 15 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C. In some embodiments, the alpha- ketoglutaric acid is contacted with the sodium carbonate and water mixture at 21 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 22 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 23 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 24 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 26 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 27 °C. In some embodiments, the alpha-

ketoglutaric acid is contacted with the sodium carbonate and water mixture at 28 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 29 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 30 °C.

Contacting time of alpha-ketoglutaric acid with alkali metal salts

In some embodiments, the alpha-ketoglutaric acid and the alkali metal salt and water mixture is stirred for at least 30 min, at least about 1 hour, at least about 2 hours, at least about 3 hours, or at least about 4 hours.

In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 30 min. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 1 hour. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 2 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 3 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 4 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 6 hours. In some embodiments, the alpha- ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 8 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 10 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for 12 hours.

In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 30 min. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 1 hour. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 2 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 3 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 4 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 6 hours. In some embodiments, the alpha- ketoglutaric acid and the sodium carbonate and water mixture is stirred for 8 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 10 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred for 12 hours.

Stirring temperature of alpha-ketoglutaric acid with alkali metal salts

In some embodiments, the alpha-ketoglutaric acid is stirred with the alkali metal salt at about 50 °C or less, about 40 °C or less, about 35 °C or less, about 30 °C or less, or about 25 °C or less.

In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 10 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 10 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 10 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 15 °C to 50 °C. In some embodiments, the alpha- ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 15 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 15 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 35 °C. In some embodiments, the alpha- ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 20 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 35 °C. In some embodiments, the alpha- ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at 25 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 20 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 21 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 22 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 23 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 24 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 25 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 26 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 27 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at

28 °C. In some embodiments, the alpha- ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 29 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred at 30 °C.

In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 10 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 10 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 10 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 15 °C to 50 °C. In some embodiments, the alpha- ketoglutaric acid and the sodium carbonate and water mixture is stirred at 15 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 15 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 20 °C to 25 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 50 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 40 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium carbonate and water mixture at 25 °C to 30 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 20 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 21 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 22 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 23 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 24 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 25 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water

mixture is stirred at 26 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 27 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 28 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 29 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred at 30 °C.

pH

In some embodiments, the alpha-ketoglutaric acid and alkali metal salt and water mixture is stirred until a reaction pH is at least about 6, at least about 6.5, at least about 7, at least about 7.5, at least about 8, at least about 8.5, at least about 9, or in the range from about 6.5 to about 9.

In some embodiments, the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred until a reaction pH is from 6 to 10. In some embodiments, a pH is from 7 to 9. In some embodiments, a pH is from 7 to 8. In some embodiments, a pH is 7.4 ± 0.4. In some embodiments, a pH is 7.1. In some embodiments, a pH is 7.2. In some embodiments, a pH is 7.3. In some embodiments, a pH is 7.4. In some embodiments, a pH is 7.5. In some embodiments, a pH is 7.6. In some embodiments, a pH is 7.7. In some embodiments, a pH is 7.8. In some embodiments, a pH is 7.9. In some embodiments, a pH is 8.

In some embodiments, the alpha-ketoglutaric acid and the sodium carbonate and water mixture is stirred until a reaction pH is from 6 to 10. In some embodiments, a pH is from 7 to 9. In some embodiments, a pH is from 7 to 8. In some embodiments, a pH is 7.4 ± 0.4. In some embodiments, a pH is 7.1. In some embodiments, a pH is 7.2. In some embodiments, a pH is 7.3. In some embodiments, a pH is 7.4. In some embodiments, a pH is 7.5. In some embodiments, a pH is 7.6. In some embodiments, a pH is 7.7. In some embodiments, a pH is 7.8. In some embodiments, a pH is 7.9. In some embodiments, a pH is 8.

Calcium salts

In some embodiments, the calcium salt is selected from commercially available calcium salts, including but not limited to calcium format, calcium acetate, calcium chloride, and the like, and mixtures thereof. In some embodiments, the calcium salt is selected from the group consisting of calcium acetate and calcium chloride. In some embodiments, the calcium salt is calcium acetate. In some embodiments, the calcium salt is calcium chloride.

Ratio of calcium salts to water

In some embodiment, the calcium salt and water are added as a mixture. In some embodiments, the calcium salt and water mixture contains from 0.1 to 1 weight equivalents of the

calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.1 to 0.8 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.1 to 0.6 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.1 to 0.5 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.3 to 1 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.3 to 0.8 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.3 to 0.6 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains from 0.3 to 0.5 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.3 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.32 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.34 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.36 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.38 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.4 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.42 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.44 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.46 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.48 weight equivalents of the calcium salt per one weight equivalent of water. In some embodiments, the calcium salt and water mixture contains 0.5 weight equivalents of the calcium salt per one weight equivalent of water.

Ratio of calcium salt to alpha-ketoglutaric acid

In some embodiments, the calcium salt is from 0.5 to 2 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 0.6 to 1.7 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the

calcium salt is from 0.7 to 1.4 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 0.8 to 1.2 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 0.9 to 1.1 weight equivalents per one weight equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 0.8 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.85 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.86 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.87 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.88 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.89 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.9 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.91 weight equivalents per one weight equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 0.92 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.93 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.94 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.95 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.96 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.97 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.98 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 0.99 weight equivalents per one weight equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 1 weight equivalent per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.01 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.02 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.03 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.04 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.05 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.06 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.07 weight

equivalents per one weight equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 1.08 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.09 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.1 weight equivalents per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.2 weight equivalents per one weight equivalent of alpha-ketoglutaric acid.

In some embodiments, the calcium salt is from 1 to 3 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1 to 2 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1 to 1.75 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1 to 1.5 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1.1 to 1.75 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1.1 to 1.5 mole equivalents per one mole equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is from 1.1 to 1.3 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1.2 to 1.75 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1.2 to 1.5 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is from 1.2 to 1.3 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is one mole equivalent per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.1 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.15 mole equivalents per one mole equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 1.16 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.17 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.18 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.19 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.2 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.21 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.22 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.23 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.24 mole equivalents per one mole

equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.25 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.26 mole equivalents per one mole equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 1.27 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.28 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.29 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.3 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.31 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.32 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.33 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.34 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.35 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.36 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.37 mole equivalents per one mole equivalent of alpha- ketoglutaric acid. In some embodiments, the calcium salt is 1.38 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.39 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.4 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.41 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.42 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.43 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.44 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.45 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.5 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.6 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.7 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.8 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 1.9 mole equivalents per one mole equivalent of alpha-ketoglutaric acid. In some embodiments, the calcium salt is 2 mole

equivalents per one mole equivalent of alpha-ketoglutaric acid.

Contacting temperature of bis salt of AKG with calcium salts

In some embodiments, the alpha-ketoglutaric acid is contacted with the calcium salt at about 40 °C or more, about 90 °C or less, or in the range from about 40 °C to about 90 °C, or about 65 °C to about 75 °C.

In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 40 °C to 90 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 50 °C to 80 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 60 °C to 75 °C. In some embodiments, the disodium alpha- ketoglutarate and the calcium salt and water mixture is stirred at 65 °C to 70 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 60 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 61 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 62 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 63 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 64 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 65 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 66 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 67 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 68 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 69 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 70 °C. In some embodiments, the disodium alpha- ketoglutarate and the calcium salt and water mixture is stirred at 71 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 72 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 73 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 74 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 75 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 76 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 78 °C. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 80 °C.

Contacting time of disodium AKG with Ca salt

In some embodiments, the bis alkali metal salt of alpha-ketoglutaric acid and the calcium salt and water mixture is stirred for at least 30 min, at least about 1 hour, at least about 2 hours, at least about 3 hours, or at least about 4 hours.

In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred from 30 min to 24 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred from 1 hour to 12 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred from 4 hours to 9 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred from 5 hours to 6 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 4 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 5 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 6 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 8 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 10 hours. In some embodiments, the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 12 hours.

Additional steps of filtering, washing, and drying

In some embodiments, the process further comprises separating the calcium alpha-ketoglutarate. In some embodiments, the separated calcium alpha-ketoglutarate is washed with water. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to a vacuum source. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to a heat source. In some embodiments, the heat source comprises a stream of hot air, an oven, or an IR lamp.

Drying temperature

In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 30 °C to at least 150 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 50 °C to at least 150 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 60 °C to at least 100 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 70 °C to at least 90 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 80 °C to at least 85 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 50 °C to at least 60 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 50 °C. In some

embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 60 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 70 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 80 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 90 °C. In some embodiments, the separated calcium alpha-ketoglutarate is heated to a temperature of at least 100 °C.

Drying time

In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source from 1 to 18 hours. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source from 2 to 15 hours. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source from 3 to 15 hours. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source from 4 to 12 hours. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source from 5 to 10 hours. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source from 6 to 8 hours. In some embodiments, the separated calcium alpha- ketoglutarate is exposed to the heat source for 2 hours. In some embodiments, the separated calcium alpha- ketoglutarate is exposed to the heat source for 4 hours. In some embodiments, the separated calcium alpha- ketoglutarate is exposed to the heat source for 6 hours. In some embodiments, the separated calcium alpha-ketoglutarate is exposed to the heat source for 8 hours. In some embodiments, the separated calcium alpha- ketoglutarate is exposed to the heat source for 10 hours. In some embodiments, the separated calcium alpha- ketoglutarate is exposed to the heat source for 12 hours.

In another aspect, described herein is a method of making calcium alpha-ketoglutarate, the method comprising the steps of:

a) contacting alpha-ketoglutaric acid with a sodium bicarbonate and water mixture, thereby forming disodium alpha-ketoglutarate; and

b) contacting a calcium salt and water mixture with the disodium alpha-ketoglutarate, thereby forming calcium alpha-ketoglutarate;

wherein the sodium bicarbonate and water mixture contains 0.27 weight equivalents of sodium bicarbonate per one weight equivalent of water;

wherein the alpha-ketoglutaric acid is 0.74 weight equivalents per one weight equivalent of sodium bicarbonate;

wherein the alpha-ketoglutaric acid is contacted with the solution of sodium bicarbonate and water at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the alpha-ketoglutaric acid and the solution of sodium bicarbonate and water is stirred for about 2 hours at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the calcium salt is calcium chloride;

wherein the calcium salt and water mixture contains from 0.2 to about 0.5 weight equivalents of the calcium salt per one weight equivalent of water;

wherein the calcium salt is 0.95 weight equivalent per one weight equivalent of alpha-ketoglutaric acid;

wherein the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 65 °C to 70 °C; and

wherein the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred for 4 hours.

In another aspect, described herein is a method of making calcium alpha-ketoglutarate, the method comprising the steps of:

a) contacting alpha-ketoglutaric acid with a sodium carbonate and water mixture, thereby forming disodium alpha-ketoglutarate; and

b) contacting a calcium salt and water mixture with the disodium alpha-ketoglutarate, thereby forming calcium alpha-ketoglutarate;

wherein the sodium carbonate and water mixture contains 0.18 weight equivalents of sodium carbonate per one weight equivalent of water;

wherein the alpha-ketoglutaric acid is 1.14 weight equivalents per one weight equivalent of sodium carbonate;

wherein the alpha-ketoglutaric acid is contacted with the solution of sodium carbonate and water at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the alpha-ketoglutaric acid and the solution of sodium carbonate and water is stirred for 2 hours at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the calcium salt is calcium chloride;

wherein the calcium salt and water mixture contains from 0.2 to about 0.5 weight equivalents of the calcium salt per one weight equivalent of water;

wherein the calcium salt is 0.95 weight equivalent per one weight equivalent of alpha-ketoglutaric acid;

wherein the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred at 65 °C to 70 °C; and

wherein the disodium alpha-ketoglutarate and the calcium salt and water mixture is stirred

for 4 hours.

In some embodiments, the methods described herein reduce formation of impurities formed during the process of making Ca-AKG using sodium hydroxide. In some embodiments, the impurity is calcium oxalate and calcium succinate. In some embodiments, the impurity is calcium oxalate. In some embodiments, the impurity is calcium succinate. In some embodiments, the impurity is an unidentified impurity. In some embodiments, the impurity is an unknown impurity.

In another aspect, described herein is a method of making dilithium alpha-ketoglutarate, the method comprising: contacting alpha-ketoglutaric acid and methanol mixture with lithium hydroxide, thereby forming dilithium alpha-ketoglutarate.

In some embodiments, the alpha-ketoglutaric acid and methanol mixture contains from 0.25 to 0.35 weight equivalents of the alpha-ketoglutaric acid per one weight equivalent of methanol. In some embodiments, the alpha-ketoglutaric acid and methanol mixture contains 0.32 weight equivalents of the alpha-ketoglutaric acid per one weight equivalent of methanol. In some embodiments, the alpha-ketoglutaric acid is from 1.6 to 1.7 weight equivalents per one weight equivalent of lithium hydroxide. In some embodiments, the alpha-ketoglutaric acid is 1.66 weight equivalents per one weight equivalent of lithium hydroxide. In some embodiments, the alpha-ketoglutaric acid and methanol mixture and the lithium hydroxide is stirred for 2 to 3 hours. In some embodiments, the alpha-ketoglutaric acid and methanol mixture and the lithium hydroxide is stirred at 50 °C to 55 °C.

In another aspect, described herein is a method of making dipotassium alpha-ketoglutarate, the method comprising: contacting alpha-ketoglutaric acid and methanol mixture with potassium hydroxide, thereby forming dipotassium alpha-ketoglutarate.

In some embodiments, the alpha-ketoglutaric acid and methanol mixture contains from 0.25 to 0.35 weight equivalents of the alpha-ketoglutaric acid per one weight equivalent of methanol. In some embodiments, the alpha-ketoglutaric acid and methanol mixture contains 0.32 weight equivalents of the alpha-ketoglutaric acid per one weight equivalent of methanol. In some embodiments, the alpha-ketoglutaric acid is from 1.3 to 1.4 weight equivalents per one weight equivalent of potassium hydroxide. In some embodiments, the alpha-ketoglutaric acid is 1.33 weight equivalents per one weight equivalent of potassium hydroxide. In some embodiments, the alpha-ketoglutaric acid and methanol mixture and the potassium hydroxide is stirred for 2 to 3 hours. In some embodiments, the alpha-ketoglutaric acid and methanol mixture and the potassium hydroxide is stirred at 25 °C to 35 °C.

In another aspect, described herein is a method of making zinc alpha-ketoglutarate, the

method comprising the steps of:

a) contacting alpha-ketoglutaric acid and water mixture with a base, thereby forming disodium alpha- ketoglutarate; and

b) contacting the disodium alpha-ketoglutarate with a zinc salt and water mixture, thereby forming zinc alpha-ketoglutarate.

In some embodiments, the base is sodium hydroxide. In some embodiments, the base is sodium bicarbonate. In some embodiments, the base is sodium carbonate.

In some embodiments, the alpha-ketoglutaric acid and water mixture contains from 0.45 to 0.55 weight equivalents of the alpha-ketoglutaric acid per one weight equivalent of water. In some embodiments, the alpha-ketoglutaric acid and water mixture contains 0.5 weight equivalents of the alpha-ketoglutaric acid per one weight equivalent of water. In some embodiments, the alpha-ketoglutaric acid is from 1.6 to 1.7 weight equivalents per one weight equivalent of sodium hydroxide. In some embodiments, the alpha- ketoglutaric acid is 1.67 weight equivalents per one weight equivalent of sodium hydroxide. In some embodiments, the alpha-ketoglutaric acid is contacted with the sodium hydroxide at 25 °C to 35 °C. In some embodiments, the alpha-ketoglutaric acid and the sodium hydroxide is stirred for 2 to 3 hours. In some embodiments, the alpha-ketoglutaric acid and the sodium hydroxide is stirred at 25 °C to 35 °C. In some embodiments, the zinc salt is zinc chloride. In some embodiments, the zinc salt and water mixture contains from 0.25 to 0.35 weight equivalents of the zinc salt per one weight equivalent of water. In some embodiments, the zinc salt and water mixture contains 0.3 weight equivalents of the zinc salt per one weight equivalent of water. In some embodiments, the zinc salt is 1.2 weight equivalent per one weight equivalent of alpha-ketoglutaric acid. In some embodiments, the disodium alpha-ketoglutarate and the zinc salt and water mixture is stirred at 80 °C to 85 °C. In some embodiments, the disodium alpha-ketoglutarate and the zinc salt and water mixture is stirred for 4 to 5 hours.

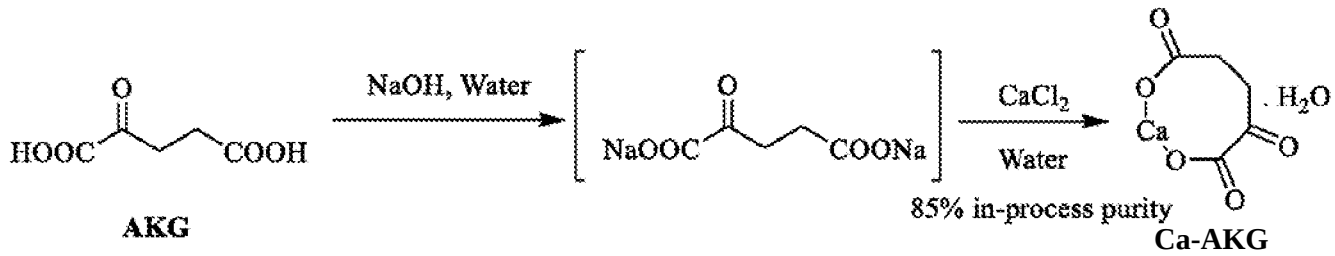
INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

EXAMPLES

The following examples are provided for illustrative purposes only, and are intended to be purely exemplary of the disclosure and are not intended to limit the scope of the claims provided herein.

Conversion of alpha-ketoglutaric acid to the calcium salt has been previously reported. However, in that process, alpha-ketoglutaric acid is first converted to alpha-ketoglutarate disodium salt using sodium hydroxide, as shown in Scheme 1.



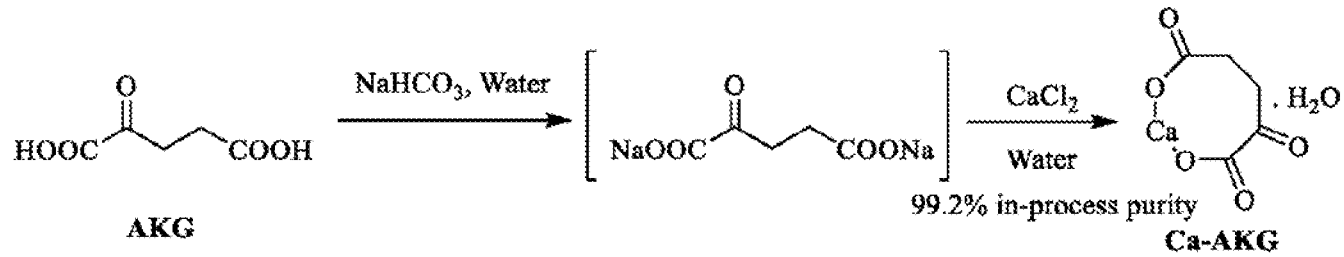
Scheme 1

It has been discovered herein that preparation of Ca-AKG under those conditions leads to the formation of impurities. The in-process material can be purified, but only to about 90.3-97.4% (See Examples 1-7). Moreover, the conversion yield only ranged from 55-83 wt/wt%.

It has been discovered that treatment of the Ca-AKG or its hydrates with a solution of 2% HC1 can further reduce the impurities and raise the purity to 99.22%. However, a concomitant decrease in yield is also observed.

It has been discovered herein that the impurities were formed during the conversion of alpha-ketoglutaric acid to alpha-ketoglutarate disodium salt. For example, the in-process HPLC sample of Example 7 showed that Ca-AKG was approximately 85% pure.

It was surprisingly found herein that treatment of alpha-ketoglutaric acid with an alkali metal salt not only provided the bis salt of alpha-ketoglutaric acid, but more importantly greatly reduced the formation of impurities found in the isolated Ca-AKG. See Example 8, and Scheme 2. The in-process HPLC sample when using an alkali metal salt such as sodium bicarbonate had a purity of more than 99% indicating, and showing negligible impurity formation. ETpon isolation and drying, the Ca-AKG (Example 11) had a purity of 99.3% and the Single Largest ETnknown Impurity (SET) was measured at only 0.46%.



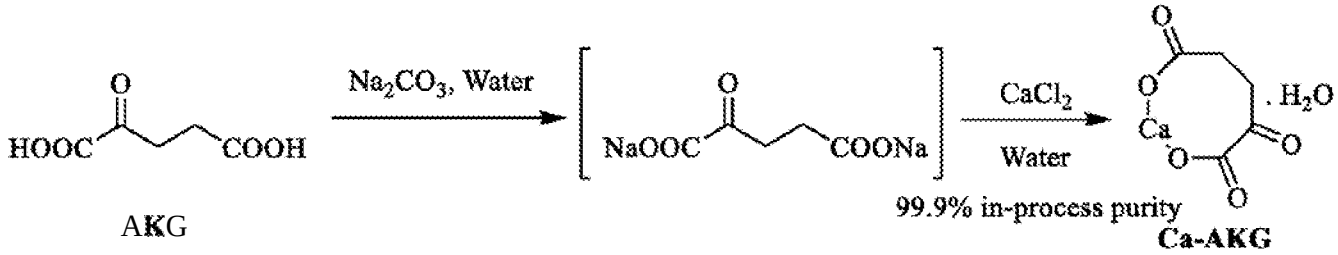
Scheme 2

Importantly, it was discovered that the process was fully scalable, and was illustratively

repeated on a 50 kg batch (Example 9). The analytical results of Example 8 and Example 9 are similar indicating that scaling the reaction does not lead to an increase in impurities.

Additionally, it was surprisingly found that the yield obtained with the 50 kg batch was actually increased compared to the 500 g batch (from 81.2 to 94.2 %). Methods and processes described herein lead to improved isolation without additional purification, resulting in a decrease in plant unit operations thus avoiding product loss (a decrease in yield) and additional cost.

Comparable results are observed for alternative alkali metal salts, such as sodium carbonate. It was found that treatment of alpha-ketoglutaric acid with sodium carbonate also greatly reduced the formation of impurities (See Example 10) found in the isolated Ca-AKG. See Scheme 3.



Scheme 3

Example 1. Synthesis of Ca-AKG using NaOH (250 g scale). Sodium hydroxide (150 g, 3.76 mol) was dissolved in 1000 mL water. alpha-Ketoglutaric acid (250.0 g, 1.71 mol) was added at 25-35°C. The solution was stirred for 2-3 hour at 25-35°C. Calcium chloride (569 g, 5.13 mol, 3.0 eq) dissolved into 1000 mL of water was added to the reaction mass at 25-35°C. The reaction mass was stirred at 65-70°C for 4-5 hours. The resultant precipitate was collected and washed with 500 mL of water. The solid was dried at 80-90°C for 6 hours to give 265 g (77% yield).

Example 2. Synthesis of Ca-AKG using NaOH (50 g scale). Sodium hydroxide (30 g, 0.75 mol, 2.2 eq) was dissolved in 200 mL water. alpha-Ketoglutaric acid (50.0 g, 0.342 mol) was added at 25-35°C. The solution was stirred for 2-3 hour at 25-35°C. Calcium chloride (113 g, 1.026 mol, 3.0 eq) dissolved into 200 mL of water was added to the reaction mass at 60-70°C. The reaction mass was stirred at 60-70°C for 4-5 hours. The resultant precipitate was collected and washed with 100 mL of water. The solid was dried at 70-80°C for 6-8 hours to give 53.8 g (78% yield).

Example 3. Synthesis of Ca-AKG using NaOH (50 g scale) with reverse addition of $CaCl_2$ (1 equiv). Sodium hydroxide (30 g, 0.75 mol, 2.2 eq) was dissolved in 200 mL water. alpha-Ketoglutaric acid (50.0 g, 0.342 mol) was added at 25-35°C. The solution was stirred for 2-3 hour at 25-35°C. The reaction mass was added to a solution of calcium chloride (38 g, 0.342 mol, 1.0 eq) dissolved into 200 mL of water at 25-35°C. The reaction mass was stirred at 65-70°C for 4-5 hours.

The resultant precipitate was collected and washed with 100 mL of water. The solid was dried at 70-80°C for 6-8 hours to give 37.9 g (55% yield).

Example 4. Synthesis of Ca-AKG using NaOH (50 g scale) with reverse addition of CaCb (2 equiv). Sodium hydroxide (30 g, 0.75 mol 2.2 eq) was dissolved in 200 mL water. alpha-Ketoglutaric acid (50.0 g, 0.342 mol) was added at 25-35°C. The solution was stirred for 2-3 hour at 25-35°C. The reaction mass was added to a solution of calcium chloride (76 g, 0.684 mmol, 2.0 eq) dissolved into 200 mL of water at 25-35°C. The reaction mass was stirred at 65-70°C for 4-5 hours. The resultant precipitate was collected and washed with 100 mL of water. The solid was dried at 70-80°C for 6-8 hours to give 55.89 g (81% yield).

Example 5. Synthesis of Ca-AKG using NaOH (100 g scale) with reverse addition of CaCb (1.3 equiv). Sodium hydroxide (60 g, 1.5 mol, 2.2 eq was dissolved in 200 mL water. alpha-Ketoglutaric acid (100.0 g, 0.684 mol) was added at 25-35°C. The solution was stirred for 2-3 hour at 25-35°C. The reaction mass was added to a solution of calcium chloride (100 g, 0.903 mol, 1.32 eq) dissolved into 200 mL of water at 25-35°C. The reaction mass was stirred at 65-70°C for 4-5 hours. The resultant precipitate was collected and washed with 100 mL of water. The solid was dried at 70-80°C for 6-8 hours to give 103.5 g (75% yield).

Example 6. Synthesis of Ca-AKG using NaOH (500 g scale) with reverse addition of CaCb (1.3 equiv). Sodium hydroxide (300, g, 7.53 mol) was dissolved in 1000 mL water. alpha-Ketoglutaric acid (500.0 g, 3.4 mmol) was added at l5-20°C. The solution was stirred for 2-3 hour at l5-20°C. The reaction mass was added to a solution of calcium chloride (500 g, 4.5 mol, 1.32 eq) dissolved into 1000 mL of water at room temperature. The reaction mass was stirred at 80-85°C for 4-5 hours. The resultant precipitate was collected and washed with 500 mL of water. The solid was dried at 80 -85°C for 6-8 hours to give 579.5 g (84% yield).

Example 7. Synthesis of Ca-AKG using NaOH (100 g scale) with HC1 wash. Sodium hydroxide (60 g, 1.50 mol) was dissolved in 200 mL water. alpha-Ketoglutaric acid (100.0 g, 0.684 mol) was added at l5-20°C. The solution was stirred for 2-3 hours at l5-20°C. The reaction mass was added to a solution of calcium chloride (100 g, 0.903 mol, 1.32 eq) dissolved into 200 mL of water at room temperature. The reaction mass was stirred at 80-85°C for 4-5 hours. The resultant precipitate was collected and washed with 100 mL of water. Wet slurry charge into 2 % HC1 solution (200 mL), the reaction mass was stirred at 80-85°C for 1-2 hours. The resultant precipitate was collected and washed with 100 mL of water. The solid was dried at 80-85°C for 6-8 hours to give 103.5 g (75% yield).

Example 8. Synthesis of Ca-AKG using NaHC03 (500 g scale). Sodium bicarbonate (690 g,

8.21 . mol) was suspended in 3000 mL water. alpha-Ketoglutaric acid (500.0 g, 3.4 mol) was added at l5-20°C. The solution was stirred for 2 hours at l5-20°C. The reaction mass was added to a solution of calcium chloride (500 g, 4.5 mol, 1.32 eq) dissolved into 1000 mL of water at room temperature. The reaction mass was stirred at 65-70°C for 4-5 hours. The resultant precipitate was collected and washed with 500 mL of water. The solid was dried at 80-85°C for 6-8 hours to give 558.9 g (8l%yield).

Example 9. Synthesis of Ca-AKG using NaHCCh (50 kg scale). alpha-Ketoglutaric acid (50 kg) was charged to 250 L of water at 25 - 35°C. Sodium bicarbonate (69 kg) was slowly added to the reaction mass at 25 - 35°C. The reaction mass was stirred until the reaction pH was (7.4 ± 0.4). The reaction mass was added to a solution of calcium chloride (50 kg) in 125 L water at 25 - 35°C. The reaction mass as heated at 65 - 70 °C for 4 hours and then cooled to 45 - 50 °C. The precipitate was collected by filtration and the resultant filter cake was washed with 50 L of water. The cake was combined with 150 L of water and the reaction mass was heated at 65 - 70 °C for 1 hour then cooled to 45 - 50 °C. The solid was collected by filtration and the filter cake washed with 50 L of water. The cake was dried at 50 - 60°C under vacuum until the moisture content was 8.5-10.0% to provide 65 kg of calcium alpha- ketoglutaric acid.

Example 10. Synthesis of Ca-AKG using Na_2CO_3 (25 g scale). Sodium carbonate (22.0 g, 0.205 mol.) was suspended in 125 mL water. alpha-Ketoglutaric acid (25.0 g, 0.171 mol.) was added at 25-30 °C. The solution was stirred for 2 hours at 25-35 °C. The reaction mass was added to a solution of calcium chloride (23.7 g, 0.213 mol), dissolved into 100 mL of water at room temperature. The reaction mass was stirred at 65-70 °C for 4-5 hours. The resultant precipitate was collected and washed with 25 mL of water. The wet slurry was charged into 100 mL water, the reaction mass was stirred at 65-70 °C for 1-2 hours. The resultant precipitate was collected and washed with 25 mL of water. The wet slurry was charged into 2 % HC1 solution (100 mL) and the reaction mass was stirred at 65-70 °C for 1-2 hours. The resultant precipitate was collected and washed with 25 mL of water. The solid was added to 100 mL water and the reaction mass was stirred at 65-70 °C for 1-2 hours. The resultant precipitate was collected and washed with 25 mL of water. The solid was dried at 50-60°C for 5-6 hours to give 28.0 g (Yield = 81.1 %).

Example 11. Synthesis of Ca-AKG using NaHCCh (500 kg scale). alpha-Ketoglutaric acid (499.8 kg, 3421 mol) was dissolved in 2500 L of water at 25-35°C. Sodium bicarbonate (675 kg, 8035 mol) was added the reaction mass over 2-4 hours at 25-35°C. The solution was stirred for 2 hours at 25-35°C. The reaction mass was added to a solution of calcium chloride (475 kg, 4280 mol) dissolved into 1500 mL of water at 25-35°C. The reaction mass was stirred at 65-70°C for 4 hours.

The reaction mass was cooled to 45-55°C then the participate was collected in an Agitated Nutsche Filter Dryer. The precipitate was stirred in 2500 L of water for 2 hours at 45-55°C then filtered. The solid was washed with 1000 L of water. The solid is dried at 50-60°C to provide 651.78 kg of calcium alpha-ketoglutarate monohydrate.

Example 12. Comparison of Impurity Data. Comparison of impurity data for Examples 7, 8, 10, and 11 is given in the following Table 1.

Table 1.

HPLCRRT	Example 4	Example 5	Example 7		Example 11
	Isolated (2% HC1 wash not used)	Isolated (2% HCl wash not used)	Pre 2% HCl wash	Post 2% HCl wash	Isolated (2% HCl wash not used)
	Area%	Area%	Area%	Area%	Area%
0.55	0.08	0.11	0.20	ND	ND
0.57 (Ca Oxalate)	0.40	0.06	0.13	0.05	ND
1.00 (AKG)	93.87	94.83	91.05	96.22	99.30
1.37	ND	ND	ND	ND	0.08
1.41	ND	0.10	ND	ND	ND
1.49 (Ca Succinate)	0.27	0.22	0.67	0.08	ND
1.74	2.21	2.42	2.42	1.85	0.46
1.93	ND	ND	0.32	0.29	ND
2.07	0.53	1.16	0.76	0.65	0.07
2.15	2.44	0.96	1.88	0.26	0.06
2.83	ND	ND	0.06	0.05	ND
3.13	ND	ND	ND	0.07	ND
3.26	ND	ND	0.07	0.05	ND
3.43	ND	ND	0.36	0.25	ND
3.47	ND	ND	ND	0.06	ND
3.55	0.07	ND	0.14	0.08	ND
3.79	ND	0.06	ND	ND	ND
4.13	0.05	ND	ND	ND	ND

4.93	ND	ND	1.83	ND	ND

a. Only impurities above ≥ 0.05% are listed

Related Compounds by HPLC:

Preparation of Buffer: Weigh and transfer about 2.72 g of potassium dihydrogen phosphate in 1000 mL water and dissolve and mix. Add 2.0 mL of orthophosphoric acid to the buffer solution and mix. Filter through 0.45 u or finer porosity membrane filter.

Mobile Phase A : Use buffer and methanol (95:05) v/v.

Mobile Phase B : Use buffer and methanol (50:50) v/v.

Preparation of dilute Hydrochloric acid: Transfer 0.8 mL of Hydrochloric acid to 100 mL volumetric flask containing about 50 mL of cooled water dilute to volume with water and mix.

Preparation of Blank Solution: Accurately transfer 5 mL of dil. HCI in 20 mL volumetric flask and make up with diluent up to the mark.

Preparation of Ca-Succinate stock solution: Accurately weigh and transfer about 5.0 mg of Ca- Succinate in 25 mL volumetric flask, add 10 mL of water and sonicate and mix, add 5 mL of dil. HCI and sonicate to dissolve. Make up the volume with diluent up to the mark and mix.

Preparation of Ca-Oxalate stock solution: Accurately weigh and transfer about 5.0 mg of Ca-Oxalate in 25 mL volumetric flask, add 10 mL of water and sonicate and mix, add 5 mL of dil. HCI and sonicate to dissolve. Make up the volume with diluent up to the mark and mix.

Preparation of COF stock solution: Accurately weigh and transfer about 5.0 mg of COF in 25 mL volumetric flask, add 10 mL of water and sonicate and mix, add 5 mL of dil. HCI and sonicate to dissolve. Make up the volume with diluent up to the mark and mix.

Preparation of System suitability solution: Accurately transfer each 5 mL of Ca-Succinate, Ca-Oxalate and COF stock solutions into 20 mL volumetric flask and make up with diluent and mix.

Preparation of Standard solution: Accurately transfer each 2.5 mL of Ca-Succinate, Ca-Oxalate and COF stock solutions into 20 mL volumetric flask and make up with diluent and mix.

Preparation of sample solution: Accurately weigh and transfer about 100.0 mg of test sample in 20 mL volumetric flask add 10 mL of water and sonicate and mix, add 5 mL of dil. HCI and sonicate to dissolve. Make up the volume with diluent up to the mark and mix.

Procedure: Inject Blank solution (Duplicate) in to the chromatograph and record the chromatogram. Disregard the average blank peak area from known impurities (if any).

Order of injections is as follows:

Injection Sequence	No of Injection
Blank	2
System Suitability solution	6
Standard solution	2
Sample solution	1
Standard (Bracketing)	1

Evaluation of system suitability: Inject system suitability solution six times in to the chromatograph and record the chromatogram.

Inject standard solution (Duplicate), sample solution in to the chromatograph and record the chromatogram. Disregard blank peaks from the sample chromatogram and calculate the results.

Calculation: Use COF standard Average area and concentration for unknown and Total impurity calculation

$$\textbf{Result (\%w/w)} = \frac{R_u}{R_s} X \frac{C_s}{C_u} X P$$

Ru = Peak response of each impurity peak (Known/ Individual Unknown/ Sum of Total except COF peak) from the sample solution.

Rs= Average area peak response of the corresponding standards from standard solution.

Cu = Concentration of sample solution.

Cs= Concentration of the corresponding standards in the standard solution.

P = Potency corresponding standards

Assay by HPLC: *(%* w/w. as such)

Buffer and dilute hydrochloric acid were prepared as above.

Mobile Phase: Use buffer and methanol (95:05) v/v.

Preparation of Blank solution: take 1 mL of dil. HCI in 10 mL volumetric flask and make up with diluent up to the mark and mix.

Preparation of Standard solution: Accurately weigh and transfer about 100.0 mg of standard in 100 mL volumetric flask add 30 mL of diluent and sonicate and mix, add 10 mL of dil. HCI and sonicate to dissolve. Make up the volume with diluent up to the mark and mix.

Preparation of Sample solution: Accurately weigh and transfer about 100.0 mg of test sample in 100 mL volumetric flask add 30 mL of diluent and sonicate and mix, add 10 mL of dil. HCI and sonicate to dissolve. Make up the volume with diluent up to the mark and mix.

Evaluation of Blank: Inject Blank solution in to the chromatograph and record the chromatogram. No peak should be observed at the retention time of analyte.

Evaluation of system suitability: Inject standard solution five times in to the chromatograph and record the chromatogram.

Procedure: Inject sample solution duplicate into the chromatograph and record the chromatograms.

Order of injections is as follows:

Order	No of injection
Blank	1
Standard solution	5
Sample solution	2
Standard Bracketing	1

$$\text{Assay (\%w/w)} = \frac{AT}{AS} \times \frac{CS}{CT} \times P$$

AT= Average Area of COF peaks in sample solution

AS =Average Area of COF peaks in standard solution

CS = Concentration of standard solution

CT = Concentration of sample solution

P = Potency of COF standard

Calcium alpha-ketoglutarate monohydrate reference standard was prepared as described in Example 12. The analytical results are presented in Table 2, Table 3, Table 4, and Table 5.

Example 13. Synthesis of Calcium alpha-Ketoglutarate Monohydrate Reference Standard

Sodium bicarbonate (552 g, 6.57 mol) was dissolved in 2000 mL water. alpha-Ketoglutaric acid (400 g, 2.73 mol) was added at 15-20 °C. The solution was stirred for 2 hours at 15-20 °C. The reaction mass was added to a solution of calcium chloride (400 g, 3.61 mol) dissolved into 800 mL of water at room temperature. The reaction mass was stirred at 65-70°C for 4-5 hours. The resultant precipitate was collected and washed with 400 mL of water. The wet slurry was charged into 1200 mL water and heated at 65-70 °C for 1 hour. The reaction mixture was cooled to 40-45°C. Reaction mixture was filtered and wash with 400 mL water. The solid was dried at 50-60 °C for 10 hours to give 501 g (yield: 1.25 w/w).

Table 2. Calcium alpha-ketoglutarate Monohydrate Reference Standard

Test		Results
^{1}H NMR		Consistent with structure: See Table 3
^{13}C NMR		Consistent with structure: See Table 4
Mass Spectromentry		m/z_{obs} = 145.0
FT-IR		Consistent with structure: See Table 5
Purity by HPLC (%w/w)		99.22
	Calcium oxalate	0.01
	Calcium succinate	Not detected
	Any unknown individual impurity	0.35
	Total impurities	0.78
Calcium content(%)		21.3
Moisture content (%w/w)		8.55
Chlorides and sulfates		< 0.2

Table 3. 'H-NMR Data for Calcium alpha-ketoglutarate Monohydrate Reference Standard

Sr. No.	Chemical Shift (ppm)	Relative integral	Multiplicity	Coupling Constant	Assignment
1	2.515	2H	t	6.4Hz	C(7) H_2
2	3085	2H	t	6.8hz	C(6) H_2

Table 4. ^{13}C-NMR Data for Calcium alpha-ketoglutarate Monohydrate Reference Standard

Sr. No.	Chemical Shift (ppm)	Type of Carbon	Assignment
1	30.73	CH_2	C(6)
2.	35.61	CH2	C(7)
3	169 .53	C=O	C(4), C(8)
4	181.73	C=O	C(5)

5

Table 5. FT-IR Data for Calcium alpha-ketoglutarate Monohydrate Reference Standard

Absorbance Band (cm^{-1})	Assignment
3501.4	OH
1703.9	C=O
1651.3	C=O
1562.8	C=O

Example 15. Synthesis of Dilithium Salt of AKG (Lb-AKG). alpha-Ketoglutaric acid (10.0 g, 0.068 mol) was dissolved in 40 mL methanol. Lithium hydroxide (6.0 g, 0.142 mol) was added to the solution. The solution was stirred for 2.0 - 3.0 hours at 50-55°C. The resulted precipitate was isolated, and the cake was washed with 10 mL methanol. The solid was dried at 75- 80°C for 5-6 hours to give 7.56 g (70% yield).

Example 16. Synthesis of Dipotassium Salt of AKG (K2-AKG). alpha-Ketoglutaric acid (10.0 g, 0.068 mol) was dissolved in 40 mL methanol, and stirred at ambient temperature to a clear solution. Potassium hydroxide (7.54 g, 0.134 mol) was added to the solution. The solution was stirred for 2.0 - 3.0 hours at 25-35°C. The resulted precipitate was isolated, and the cake was washed with 10 mL methanol. The solid was dried at 75 - 85°C for 5-6 hours to give 7.8 g (52 % yield).

Example 17. Synthesis of Zinc Salt of AKG (Zn-AKG). alpha-Ketoglutaric acid (10.0 g, 0.068 mol) was dissolved in 20 mL water. Sodium hydroxide (6.0 g, 0.149 mol) was charged into alpha-ketoglutaric acid solution. The solution was stirred for 2.5-3.0 hours at 25- 35°C. Charge zinc chloride solution (12.0 g, 0.088 mol, 1.32 eq. was dissolved into 40 mL water) into reaction mass. After complete addition of zinc chloride solution reaction mass were stirred at 80-85°C for 4-5 hours. The resultant precipitate was collected and washed with 10 mL of water. The solid was dried at 80- 85°C for 6-8 hours to give 10.2 g (73 % yield).

While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

WHAT IS CLAIMED IS:

1. A method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with an alkali metal salt of an acid, where the conjugate acid of the alkali metal salt has at least one pKa from about 4 to about 12, thereby forming a bis salt of alpha-ketoglutarate; and

b) contacting the bis salt of alpha-ketoglutarate with a calcium salt, thereby forming calcium alpha-ketoglutarate.

2. A method for making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with an alkali metal salt of an acid and water to form a solution having a pH in the range from about 5.0 to about 11.9, thereby forming a bis salt of alpha-ketoglutarate; and

b) contacting the bis salt of alpha-ketoglutarate with a calcium salt and water, thereby forming calcium alpha-ketoglutarate.

3. The method of claim 1 wherein the alpha-ketoglutaric acid is mixed with water.

4. The method of claim 3 wherein the alpha-ketoglutaric acid and water mixture is prepared from or contains from about 0.05 to about 0.5 weight equivalents of alpha-ketoglutaric acid per one weight equivalent of water.

5. The method of claim 1 wherein the alkali metal salt is mixed with water.

6. The method of claim 5 wherein alkali metal salt and water mixture is prepared from or contains from about 0.1 to about 0.35 weight equivalents of alkali metal salt per one weight equivalent of water.

7. The method of any one of claims 1 to 6 wherein the alkali metal salt is selected from the group consisting of lithium, sodium, and potassium salts of bicarbonate and carbonate, and combinations thereof.

8. The method of any one of claims 1 to 6 wherein the alkali metal salt is sodium bicarbonate, sodium carbonate, or a mixture thereof.

9. The method of any one of claims 1 to 6 wherein the alkali metal salt is sodium bicarbonate.

10. The method of claim 9 wherein the sodium bicarbonate and water mixture contains from about 0.2 to about 0.3 weight equivalents of sodium bicarbonate per one weight equivalent of water.

11. The method of any one of claims 1 to 6 wherein the alkali metal salt is sodium carbonate.

12. The method of claim 11 wherein the sodium carbonate and water mixture contains from about 0.05 to about 0.2 weight equivalents of sodium carbonate per one weight equivalent of water.

13. The method of any one of claims 1 to 6 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH of at least about 6.5, optionally after a predetermined period of time.

14. The method of any one of claims 1 to 6 wherein the alkali metal salt is added to the alpha-ketoglutaric acid to form a mixture having a pH from about 6.5 to about 9, optionally after a predetermined period of time.

15. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid is from about 0.5 to about 3 weight equivalents per one weight equivalent of alkali metal salt.

16. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid is from about 0.7 to about 0.9 weight equivalents per one weight equivalent of sodium bicarbonate.

17. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid is from about 1.0 to about 2.8 weight equivalents per one weight equivalent of sodium carbonate.

18. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 50 °C or less.

19. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 50 °C.

20. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid is contacted with the sodium bicarbonate and water mixture at about 10 °C to about 35 °C.

21. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 30 minutes.

22. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 1 hour.

23. The method of any one of claims 1 to 6 wherein the alpha-ketoglutaric acid and the sodium bicarbonate and water mixture is stirred for at least about 2 hours.

24. The method of any one of claims 1 to 6 wherein the calcium salt is selected from the group consisting of calcium formate, calcium acetate, and calcium chloride.

25. The method of claim 24 wherein the calcium salt is calcium chloride.

26. The method of any one of claims 1 to 6 wherein the calcium salt is mixed with water.

27. The method of claim 26 wherein the calcium salt and water mixture is prepared from or contains from about 0.1 to about 1 weight equivalents of the calcium salt per one weight

equivalent of water.

28. The method of any one of claims 1 to 6 wherein the calcium salt is from 0.5 to 2 weight equivalents per one weight equivalent of alpha-ketoglutaric acid.

29. The method of any one of claims 1 to 6 wherein the bis alkali metal salt of the alpha-ketoglutarate is contacted with the calcium salt and water mixture at about 40 °C to about 90 °C.

30. The method of any one of claims 1 to 6 wherein the bis alkali metal salt of the alpha-ketoglutarate and the calcium salt and water mixture is stirred for at least about 30 min.

31. The method of any one of claims 1 to 6 further comprising drying the calcium alpha-ketoglutarate.

32. The method of any one of claims 1 to 6 further comprising drying the calcium alpha-ketoglutarate to a moisture content of about 20% to about 5%.

33. The method of any one of claims 1 to 6 further comprising drying the calcium alpha-ketoglutarate, where the dried calcium alpha-ketoglutarate is less than 50% calcium alpha-ketoglutarate dihydrate.

34. The method of any one of claims 1 to 6 further comprising drying the calcium alpha-ketoglutarate, where the dried calcium alpha-ketoglutarate is at least 50% calcium alpha-ketoglutarate monohydrate.

35. A method of making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with a solution of sodium bicarbonate and water, thereby forming disodium alpha-ketoglutarate; and

b) contacting the disodium alpha-ketoglutarate with a solution of calcium chloride and water, thereby forming calcium alpha-ketoglutarate;

wherein the solution of sodium bicarbonate is prepared from about 0.27 weight equivalents of sodium bicarbonate per one weight equivalent of water;

wherein the alpha-ketoglutaric acid is about 0.74 weight equivalents per one weight equivalent of sodium bicarbonate;

wherein the alpha-ketoglutaric acid is contacted with the solution of sodium bicarbonate and water at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the alpha-ketoglutaric acid and the solution of sodium bicarbonate and water is stirred for about 2 hours at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the solution of calcium chloride is prepared from about 0.2 to about 0.5 weight equivalents of the calcium chloride per one weight equivalent of water;

wherein the calcium chloride is about 0.95 weight equivalents per one weight equivalent of

alpha-ketoglutaric acid;

wherein the disodium alpha-ketoglutarate and the solution of calcium chloride is stirred for about 4 hours at 65 °C to 70 °C.

36. A method of making calcium alpha-ketoglutarate, the method comprising:

a) contacting alpha-ketoglutaric acid with a solution of sodium carbonate and water, thereby forming disodium alpha-ketoglutarate; and

b) contacting the disodium alpha-ketoglutarate with a solution of calcium chloride and water, thereby forming calcium alpha-ketoglutarate;

wherein the solution of sodium carbonate is prepared from about 0.18 weight equivalents of sodium carbonate per one weight equivalent of water;

wherein the alpha-ketoglutaric acid is about 1.14 weight equivalents per one weight equivalent of sodium carbonate;

wherein the alpha-ketoglutaric acid is contacted with the solution of sodium carbonate and water at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the alpha-ketoglutaric acid and the solution of sodium carbonate and water is stirred for 2 hours at about 10 °C to about 35 °C, or at about 10 °C to about 25 °C;

wherein the solution of calcium chloride is prepared from about 0.2 to about 0.5 weight equivalents of the calcium chloride per one weight equivalent of water;

wherein the calcium chloride is about 0.95 weight equivalent per one weight equivalent of alpha-ketoglutaric acid;

wherein the disodium alpha-ketoglutarate and the solution of calcium salt and water is stirred for about 4 hours at 65 °C to 70 °C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/52498

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/194; C07C 51/41

CPC - A61K 31/194; C07C 51/41

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,183,409 B2 (CHRISTGAU et al.) 22 May 2012 (22.05.2012) Col 1, ln 61 to Col 2, ln 28; Col 2, ln 65-67; Col 3, ln 3-5; Col 4, ln 17-22; Col 8, ln 6-11;Col 16, ln 6-13; Col 20, Table 3 ;Col 23, ln 16-23;Col 24, ln 24-37; (Col 25, ln 57-60; Col 29, ln 58-67 ; Col 30, ln 5-13	1-36
Y	US 4,632,921 A (BAUER) 30 December 1986 (30.12.1986) Col 2, ln 10-16; Col 2, ln 31-34; Col 2, ln 42-48; Col 4, ln 8-13; Claim 11 and Claim 12	1-36
A	CN 102976927 (TIANJIN TIANCHENG PHARMACEUTICAL CO LTD) 20 March 2013 (20.03.2013) ENTIRE DOCUMENT	1-36
A	US 2,917,528 A (RAMSEY et al.) 15 December 1959 (15.12.1959) ENTIRE DOCUMENT	1-36
A	US 2008/0027139 A1 (PIERZYNOWSKI et.al.) 31 January 2008 (31.01.2008) ENTIRE DOCUMENT	1-36

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed
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"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
09 NOVEMBER 2019	18 DEC 2019
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