CRYSTALLINE EDG-2 RECEPTOR ANTAGONIST AND METHODS OF MAKING

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/072,848 filed on August 31, 2020 and U.S. Provisional Patent Application No. 63/227,279 filed on July 29, 2021; each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are crystalline forms of an endothelial differentiation gene 2 (EDG-2) antagonist compound, as well as pharmaceutical compositions thereof, and methods of use thereof in the treatment of diseases or conditions that would benefit with treatment with an EDG-2 antagonist compound.

BACKGROUND OF THE INVENTION

[0003] EDG-2 (also known as lysophosphatidic acid receptor 1, LPA_1 receptor, LPAR1) is a member of the G protein-coupled receptor family of integral membrane proteins that are important for lipid signaling. The LPA_1 receptor is a member of the G protein-coupled receptor family of integral membrane proteins that are important for lipid signaling. LPA_1 receptor antagonists are useful in the treatment of diseases or conditions for which abnormal LPA signaling plays a role, such as atherosclerosis, myocardial infarction, and heart failure.

SUMMARY

[0004] The present disclosure relates to various solid state forms of the LPA_1 receptor antagonist 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid and methods of making the same. Such forms of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid are useful for modulating the activity of LPA_1 receptors in mammals that would benefit from such activity.

[0004a] In an aspect of the present disclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having:

an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**, as measured using Cu (Kα) radiation; or

an X-ray powder diffraction (XRPD) pattern with peaks at 5.2 ±0.2° 2-Theta, 9.0 ±0.2° 2-Theta, 14.4 ±0.2° 2-Theta, and 17.7 ±0.2° 2-Theta, as measured using Cu (Kα) radiation; or

a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1739.6 cm^{-1}; or

unit cell parameters substantially equal to the following at 293 K:

Crystal System	triclinic
Space Group	P-1; Z=2
a (Å)	6.521(6)
b (Å)	10.548(9)
c (Å)	17.453(15)
α (°)	104.080(16)
β (°)	92.430(16)
γ (°)	101.081(17)
V (Å^3)	1137.6(17)
Calculated Density (Mg / m^3)	1.301
Unique Reflections	4753

a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 4**; or

a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 23.35, 124.43, 126.78, 127.42, and 136.47 ppm; or

combinations thereof.

[0004b] In another aspect of the present disclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) having an X-ray powder diffraction (XRPD) pattern with peaks at 5.2 ±0.2° 2-Theta, 9.0 ±0.2° 2-Theta, 14.4 ±0.2° 2-Theta, and 17.7 ±0.2° 2-Theta, as measured using Cu (Kα) radiation.

[0004c] In a further aspect of the present disclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**, as measured using Cu (Kα) radiation.

[0004d] In another aspect of the present disiclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) having unit cell parameters substantially equal to the following at 293 K:

Crystal System	triclinic
Space Group	P-1; Z=2
a (Å)	6.521(6)
b (Å)	10.548(9)
c (Å)	17.453(15)
α (°)	104.080(16)
β (°)	92.430(16)
γ (°)	101.081(17)
V (Å^3)	1137.6(17)
Calculated Density (Mg / m^3)	1.301
Unique Reflections	4753

[0004e] In a further aspect of the present disclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) having a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 4**.

[0004f] In another aspect of the present disclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) having a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at about 23.35 ppm, about 124.43 ppm, about 126.78 ppm, about 127.42 ppm, and about 136.47 ppm.

[0004g] In a further aspect of the present disclosure, there is provided a crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) having a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1739.6 cm^{-1}.

[0004h] In another aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having:

an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 6**, as measured using Cu (Kα) radiation; or

an X-ray powder diffraction (XRPD) pattern with peaks at 5.6 ±0.2° 2-Theta, 7.6 ±0.2° 2-Theta, 9.4 ±0.2° 2-Theta, 15.5 ±0.2° 2-Theta, and 16.3 ±0.2° 2-Theta, as measured using Cu (Kα) radiation; or

a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1731.7 cm^{-1}; or

unit cell parameters substantially equal to the following at 293 K:

Crystal System	orthorhombic
Space Group	Pbca; Z=8
a (Å)	6.2823(10)
b (Å)	23.285(4)
c (Å)	31.614(6)
α (°)	90.00°
β (°)	90.00°
γ (°)	90.00°
V (Å^3)	4624.5(14)
Calculated Density (Mg / m^3)	1.280
Unique Reflections	4163

a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 8**; or

a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 20.59, 126.39, 128.34, and 137.69 ppm; or

combinations thereof.

[0004i] In a further aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 6**, as measured using Cu (Kα) radiation.

[0004j] In another aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having an X-ray powder diffraction (XRPD) pattern with peaks at 5.6 ±0.2° 2-Theta, 7.6 ±0.2° 2-Theta, 9.4 ±0.2° 2-Theta, 15.5 ±0.2° 2-Theta, and 16.3 ±0.2° 2-Theta, as measured using Cu (Kα) radiation.

[0004k] In a further aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having unit cell parameters substantially equal to the following at 293 K:

Crystal System	orthorhombic
Space Group	Pbca; Z=8
a (Å)	6.2823(10)
b (Å)	23.285(4)
c (Å)	31.614(6)
α (°)	90.00°
β (°)	90.00°
γ (°)	90.00°
V ($Å^3$)	4624.5(14)
Calculated Density (Mg / m^3)	1.280
Unique Reflections	4163

[0004l] In another aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 8**.

[0004m] In a further aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 20.59, 126.39, 128.34, and 137.69 ppm.

[0004n] In another aspect of the present disclosure, there is provided a crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1731.7 cm^{-1}.

[0004o] In a further aspect of the present disclosure, there is provided a crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having:

an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 10**, as measured using Cu (Kα) radiation; or

an X-ray powder diffraction (XRPD) pattern with peaks at 4.2 ±0.2° 2-Theta, 6.8 ±0.2° 2-Theta, 15.1 ±0.2° 2-Theta, 25.0 ±0.2° 2-Theta, 25.5 ±0.2° 2-Theta, and 26.4 ±0.2° 2-Theta, as measured using Cu (Kα) radiation; or

a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1722.0 cm^{-1}; or

a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 12**; or

a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 64.56, 67.67, 122.99, and 126.71 ppm; or

combinations thereof.

[0004p] In another aspect of the present disclosure, there is provided a crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 10**, as measured using Cu (Kα) radiation.

[0004q] In a further aspect of the present disclosure, there is provided a crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having an X-ray powder diffraction (XRPD) pattern with peaks at 4.2 ±0.2° 2-Theta, 6.8 ±0.2° 2-Theta, 15.1 ±0.2° 2-Theta, 25.0 ±0.2° 2-Theta, 25.5 ±0.2° 2-Theta, and 26.4 ±0.2° 2-Theta, as measured using Cu (Kα) radiation.

[0004r] In another aspect of the present disclosure, there is provided a crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1722.0 cm^{-1}.

[0004s] In a further aspect of the present disclosure, there is provided a crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 12**.

[0004t] In another aspect of the present disclosure, there is provided a crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I), characterized as having a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 64.56, 67.67, 122.99, and 126.71 ppm.

[0004u] In a further aspect of the present disclosure, there is provided a crystalline Form 4 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) characterized as having:

an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 13**, as measured using Cu (Kα) radiation; or

a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1743.9 cm^{-1}; or combinations thereof.

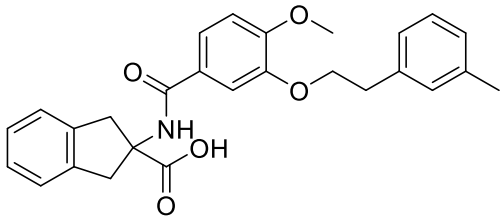
[0004v] In another aspect of the present disclosure, there is provided a crystalline Form 4 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) characterized as having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 13**, as measured using Cu (Kα) radiation.

[0004w] In a further aspect of the present disclosure, there is provided an amorphous phase of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) characterized as having: an XRPD pattern showing a lack of crystallinity, and/or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 16**.

[0004x] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the crystalline Form 1 disclosed herein and at least one pharmaceutically acceptable excipient.

[0004y] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the crystalline form disclosed herein or the amorphous phase disclosed herein and at least one pharmaceutically acceptable excipient.

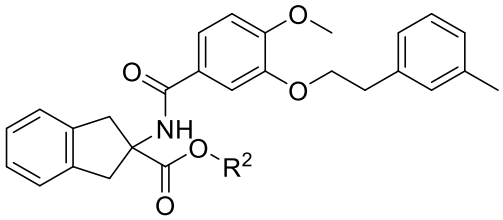
[0004z] In another aspect of the present disclosure, there is provided a process for the preparation of a compound with the structure of Compound I:



Compound I

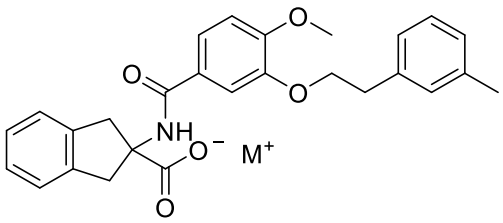
comprising:

(1) contacting the compound of Formula 6:



Formula 6

wherein R^2 is C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_3-C_{10} cycloalkyl, or C_3-C_{10} cycloalkenyl;
with a hydroxide reagent having the formula M-OH in a suitable solvent to provide a compound of Formula 7:



Formula 7

wherein M^+ is Na^+, K^+, or Li^+, and M-OH is NaOH, KOH, or LiOH, respectively;
and
(2) contacting the compound of Formula 7 with a suitable organic acid in a suitable solvent to provide Compound I.

[0005] Described herein, in some examples, is Crystalline Form 1 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I). In some examples, crystalline Form 1 of Compound I is characterized as having: an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**, as measured using Cu (Kα) radiation; or an X-ray powder diffraction (XRPD) pattern derived using Cu (Kα) radiation with peaks at 5.2 ±0.2° 2-Theta, 9.0 ±0.2° 2-Theta, 14.4 ±0.2° 2-Theta, and 17.7 ±0.2° 2-Theta, as measured using Cu (Kα) radiation; or a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1739.6 cm^{-1}; or unit cell parameters substantially equal to the following at 293 K:

Crystal System	triclinic
Space Group	P-1; Z=2
a (Å)	6.521(6)
b (Å)	10.548(9)
c (Å)	17.453(15)
α (°)	104.080(16)
β (°)	92.430(16)
γ (°)	101.081(17)
V ($Å^3$)	1137.6(17)
Calculated Density (Mg / m^3)	1.301
Unique Reflections	4753

or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 4**; or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 23.35, 124.43, 126.78, 127.42, and 136.47 ppm; or combinations thereof.

[0006] Also described herein, in some examples, is Crystalline Form 2 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I). In some examples, crystalline Form 2 of Compound I is characterized as having: an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 6**, as measured using Cu (Kα) radiation; or an X-ray powder diffraction (XRPD) pattern with peaks at 5.6 ±0.2° 2-Theta, 7.6 ±0.2° 2-Theta, 9.4 ±0.2° 2-Theta, 15.5 ±0.2° 2-Theta, and 16.3 ±0.2° 2-Theta, as measured using Cu (Kα) radiation; or a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1731.7 cm^{-1}; or unit cell parameters substantially equal to the following at 293 K:

Crystal System	orthorhombic
Space Group	Pbca; Z=8
a (Å)	6.2823(10)
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c (Å)	31.614(6)
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V ($Å^3$)	4624.5(14)
Calculated Density (Mg / m^3)	1.280
Unique Reflections	4163

or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 8**; or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 20.59, 126.39, 128.34, and 137.69 ppm; or combinations thereof.

[0007] Also described herein, in some examples, is Crystalline Form 3 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I). In some examples, crystalline Form 3 of Compound I is characterized as having: an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 10**, as measured using Cu (Kα) radiation; or an X-ray powder diffraction (XRPD) pattern with peaks at 4.2 ±0.2° 2-Theta, 6.8 ±0.2° 2-Theta, 15.1 ±0.2° 2-Theta, 25.0 ±0.2° 2-Theta, 25.5 ±0.2° 2-Theta, and 26.4 ±0.2° 2-Theta, as measured using Cu (Kα) radiation; or a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1722.0 cm^{-1}; or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 12**; or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum characterized by resonances (δc) at 64.56, 67.67, 122.99, and 126.71 ppm; or combinations thereof.

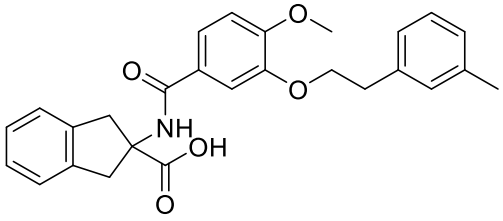
[0008] Also described herein, in some examples, is Crystalline Form 4 of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I). In some examples, crystalline Form 4 of Compound I is characterized as having: an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 13**, as measured using Cu (Kα) radiation; or a Fourier Transform IR Spectroscopy (FTIR) pattern with a peak at about 1743.9 cm^{-1}; or combinations thereof.

[0009] Also described herein, in some examples, is the amorphous phase of 2-(4-methoxy-3-(3-methylphenethoxy)benzamido)-2,3-dihydro-1H-indene-2-carboxylic acid (Compound I) characterized as having: an XRPD pattern showing a lack of crystallinity, and/or a Solid State ^{13}Carbon Nuclear Magnetic Resonance (ssNMR) spectrum substantially the same as shown in **Figure 16**.

[0010] Also described herein, in some examples, is a pharmaceutical composition comprising a crystalline form Compound I and at least one pharmaceutically acceptable excipient. For example, in some examples, described herein is a pharmaceutical composition comprising Crystalline Form 1 and at least one pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration in the form of a tablet, a pill, a capsule, a suspension, or a solution. In some examples, the pharmaceutical composition is in the form of a solid form pharmaceutical composition. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule. In some examples, the pharmaceutical composition is substantially free of Compound I impurities. In some examples, the pharmaceutical composition comprises less than about 1% w/w of Compound I impurities. In some examples, the Compound I impurities comprise one or more degradants

of Compound I, one or more intermediates used in the synthesis of Compound I, or combinations thereof. In some examples, the Compound I impurities comprise one or more intermediates used in the synthesis of Compound I.

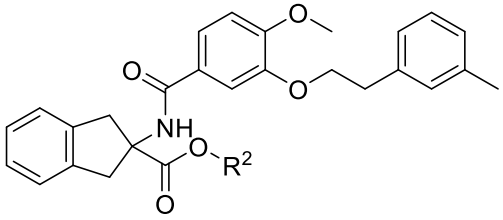
[0011] In some examples, described herein is a process for the preparation of the Compound I:



Compound I

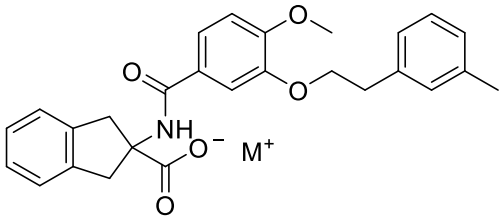
comprising the steps of:

(1) contacting the compound of Formula 6:



Formula 6

wherein R^2 is C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_3-C_{10} cycloalkyl, or C_3-C_{10} cycloalkenyl; with a hydroxide reagent having the formula M-OH in a suitable solvent to provide a compound of Formula 7:



Formula 7

wherein M^+ is Na^+, K^+, or Li^+, and M-OH is NaOH, KOH, or LiOH, respectively; and

(2) contacting the compound of Formula 7 with a suitable organic acid in a suitable solvent to provide Compound I.

[0012] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.