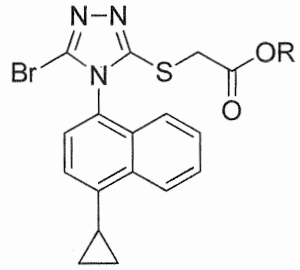
CLAIMS

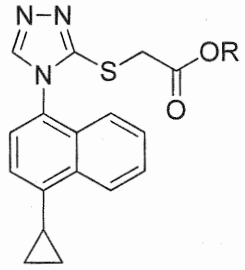
What is claimed is:

1. A process for preparing a compound of formula (III):



Formula (III);

comprising contacting a compound of Formula (II):



Formula (II);

wherein R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl;

with N-bromosuccinimide (NBS) and a solvent.

2. The process of claim 1, wherein R is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, isoamyl, pentyl, hexyl, heptyl, octyl, nonyl, terpenyl, bornyl, allyl, linalyl or geranyl.

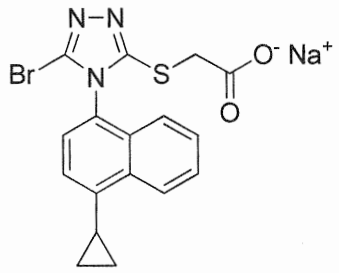
3. The process of claim 1, wherein R is methyl or ethyl.

4. The process of any one of claims 1-3, wherein the compound of Formula (II), the NBS and the solvent are stirred:

for at least 12 hours; and

at a temperature of between about room temperature and about 32°C.

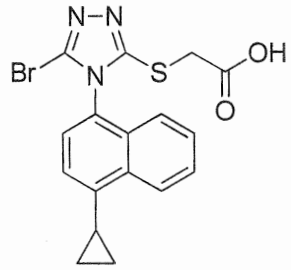
5. The process of any one of claims 1-4, further comprising contacting the compound of Formula (III) with a sodium hydroxide solution to provide Compound 4:



(Compound 4).

6. The process of claim 5, comprising crystallizing Compound 4 from the aqueous sodium hydroxide solution.

7. The process of claim 5, further comprising contacting Compound 4 with an acid to provide Compound 1:

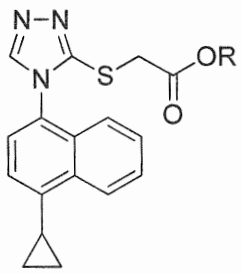


(Compound 1).

8. The process of claim 7, wherein the acid is hydrobromic acid.

9. The process of claim 5, further comprising
   (a) dissolving Compound 4 in water and adding ethyl acetate to the mixture; and
   (b) contacting the biphasic mixture of step (a) with an acid and separating the organic phase to provide Compound 1.

10. A reaction mixture comprising a compound of Formula (II):



Formula (II);

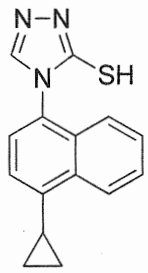
wherein R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl;

a brominating agent; and

a solvent.

11. The reaction mixture of claim 10, wherein the brominating agent is N-bromosuccinimide (NBS).

12. The process of claim 1, wherein a compound of Formula (II) is prepared by a process comprising contacting compound 5:



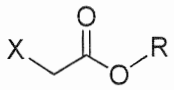
(Compound 5);

with:

a base;

a solvent; and

a compound of Formula (IV):



Formula (IV);

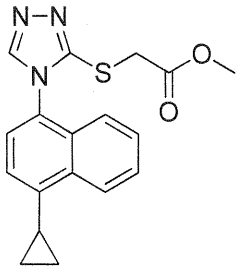
wherein X is halo, tosylate, mesylate, triflate, or besylate; and

R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl.

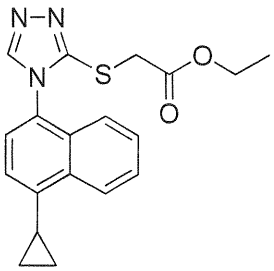
13. The process of claim 12, wherein the compound of Formula (IV) is selected from methyl bromoacetate, ethyl bromoacetate, methyl chloroacetate, and ethyl chloroacetate.

14. The process of claim 12, wherein a crude reaction product comprising a compound of Formula (II) is washed with a cooled mixture of ethyl acetate and isopropanol.

15. Compound 2 or Compound 2-A:

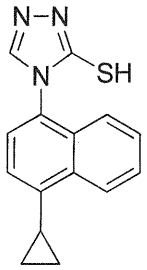


(Compound 2)



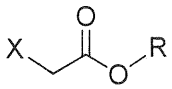
(Compound 2-A).

16. A reaction mixture comprising Compound 5:



(Compound 5);

a compound of Formula (IV):



Formula (IV);

wherein:

X is a leaving group; and

R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl or -C_3-C_{10} cycloalkenyl;

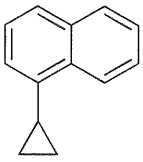
a base; and

a solvent.

17. The reaction mixture of claim 16, wherein the compound of Formula (IV) is methyl bromoacetate, ethyl bromoacetate, methyl chloroacetate, or ethyl chloroacetate.

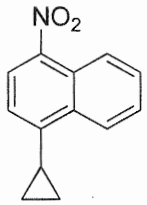
18. The process of claim 12, wherein Compound 5 is prepared by a process comprising:

(5-i) contacting Compound 6:



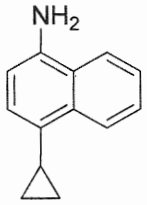
(Compound 6);

with nitric acid, water and a solvent to provide compound 7:



(Compound 7);

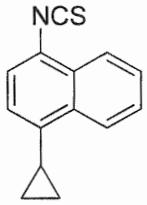
(5-ii) contacting Compound 7 with hydrogen, palladium on charcoal, and one or more solvents to provide Compound 8:



(Compound 8);

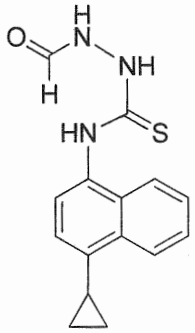
(5-iii) contacting Compound 8 with an acid to provide a salt of Compound 8;

(5-iv) contacting the salt of Compound 8 of step (5-iii) with a base, thiophosgene and a solvent to provide Compound 9:



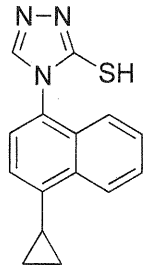
(Compound 9);

(5-v) contacting Compound 9 with formyl hydrazine and a solvent to provide Compound 10:



(Compound 10); and

(5-vi) contacting Compound 10 with a base, water and a solvent to provide Compound 5:

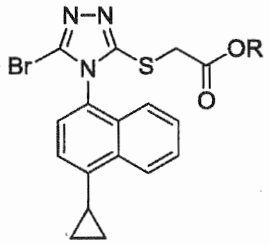


(Compound 5).

CLAIMS

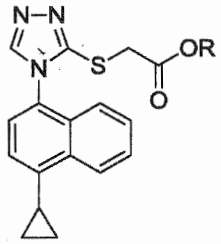
What is claimed is:

1. A process for preparing a compound of formula (III):



Formula (III);

comprising contacting a compound of Formula (II):



Formula (II);

wherein R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl;

with N-bromosuccinimide (NBS) and a solvent.

2. The process of claim **1**, wherein R is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, isoamyl, pentyl, hexyl, heptyl, octyl, nonyl, terpenyl, bornyl, allyl, linalyl or geranyl.

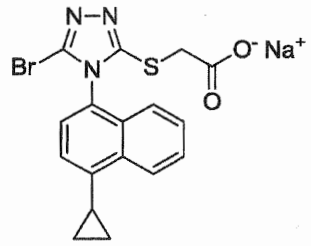
3. The process of claim **1**, wherein R is methyl or ethyl.

4. The process of any one of claims **1-3**, wherein the compound of Formula (II), the NBS and the solvent are stirred:

for at least 12 hours; and

at a temperature of between about room temperature and about 32°C.

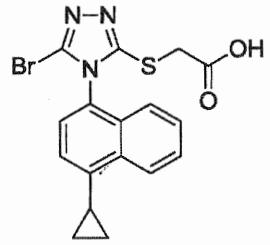
5. The process of any one of claims **1-4**, further comprising contacting the compound of Formula (III) with a sodium hydroxide solution to provide Compound 4:



(Compound 4).

6. The process of claim **5**, comprising crystallizing Compound 4 from the aqueous sodium hydroxide solution.

7. The process of claim **5**, further comprising contacting Compound 4 with an acid to provide Compound 1:



(Compound 1).

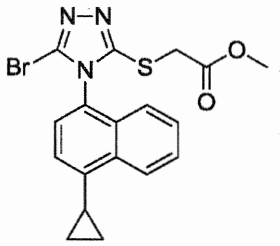
8. The process of claim **7**, wherein the acid is hydrobromic acid.

9. The process of claim **5**, further comprising

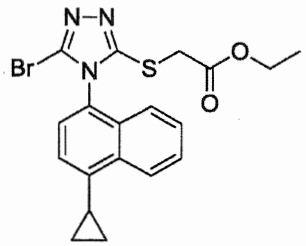
(a) dissolving Compound 4 in water and adding ethyl acetate to the mixture; and

(b) contacting the biphasic mixture of step (a) with an acid and separating the organic phase to provide Compound 1.

10. Compound 3 or Compound 3-A:



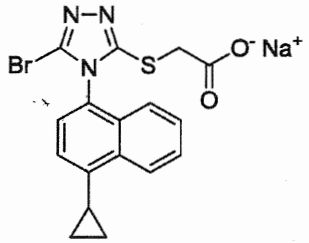
(Compound 3)



(Compound 3-A)

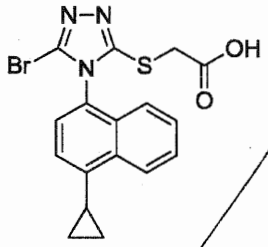
obtained by the process of claim **1**.

11. Compound 4:



obtained by the process of claim **5**.

12. Compound 1:

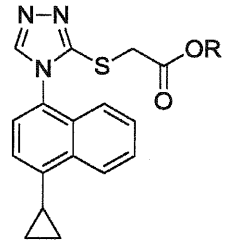


obtained by the process of claim **7**.

13. Compound 1 of claim **12**, which is a crystalline polymorph characterized by peaks at 10.46, 18.76, and 19.83°2θ±0.1°2θ.

14. Compound 1 of claim **12**, which is the crystalline polymorph form 2.

15. A reaction mixture comprising a compound of Formula (II):



Formula (II);

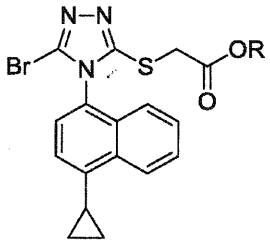
wherein R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl;

a brominating agent; and

a solvent.

16. The reaction mixture of claim **15**, wherein the brominating agent is N-bromosuccinimide (NBS).

17. A reaction mixture comprising a compound of formula (III)



Formula (III);

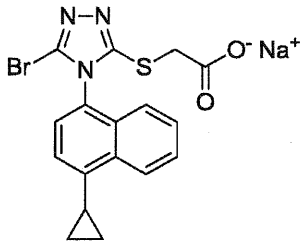
wherein R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl;

a base; and

a solvent.

18. The reaction mixture of claim **17**, wherein the base is sodium hydroxide.

19. A reaction mixture comprising Compound 4:



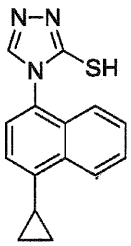
(Compound 4);

an acid; and

a solvent.

20. The reaction mixture of claim **19**, wherein the acid is hydrobromic acid.

21. The process of claim **1**, wherein a compound of Formula (II) is prepared by a process comprising contacting compound 5:



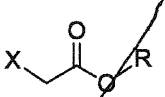
(Compound 5);

with:

a base;

a solvent; and

a compound of Formula (IV):



Formula (IV);

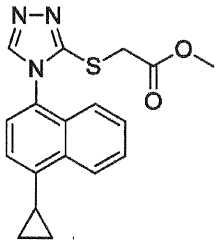
wherein X is halo, tosylate, mesylate, triflate, or besylate; and

R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl, or -C_3-C_{10} cycloalkenyl.

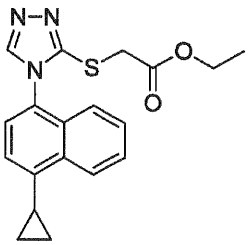
22. The process of claim **21**, wherein the compound of Formula (IV) is selected from methyl bromoacetate, ethyl bromoacetate, methyl chloroacetate, and ethyl chloroacetate.

23. The process of claim **21**, wherein a crude reaction product comprising a compound of Formula (II) is washed with a cooled mixture of ethyl acetate and isopropanol.

24. Compound 2 or Compound 2-A:



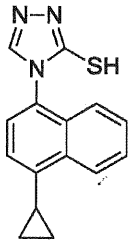
(Compound 2)



(Compound 2-A).

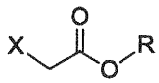
25. Compound 2 or Compound 2-A, obtained by the process of claim **21**.

26. A reaction mixture comprising Compound 5:



(Compound 5);

a compound of Formula (IV):



Formula (IV);

wherein:

X is a leaving group; and

R is -C_1-C_{20} alkyl, -C_1-C_{20} alkenyl, -C_3-C_{10} cycloalkyl or -C_3-C_{10} cycloalkenyl;

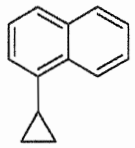
a base; and

a solvent.

27. The reaction mixture of claim **26**, wherein the compound of Formula (IV) is methyl bromoacetate, ethyl bromoacetate, methyl chloroacetate, or ethyl chloroacetate.

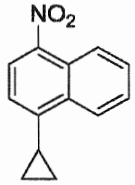
28. The process of claim **21**, wherein Compound 5 is prepared by a process comprising:

(5-i) contacting Compound 6:



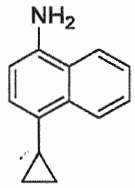
(Compound 6);

with nitric acid, water and a solvent to provide compound 7:



(Compound 7);

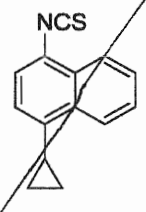
(5-ii) contacting Compound 7 with hydrogen, palladium on charcoal, and one or more solvents to provide Compound 8:



(Compound 8);

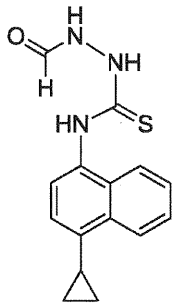
(5-iii) contacting Compound 8 with an acid to provide a salt of Compound 8;

(5-iv) contacting the salt of Compound 8 of step (5-iii) with a base, thiophosgene and a solvent to provide Compound 9:



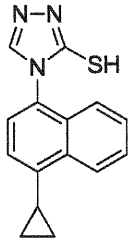
(Compound 9);

(5-v) contacting Compound 9 with formyl hydrazine and a solvent to provide Compound 10:



(Compound 10); and

(5-vi) contacting Compound 10 with a base, water and a solvent to provide Compound 5:



(Compound 5).