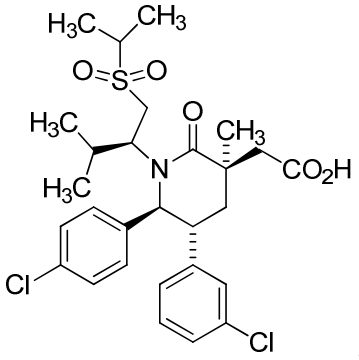
and blocking the p53 transcriptional activation domain; and 3) exporting p53 from the nucleus to the cytoplasm. All three of these mechanisms would be blocked by neutralizing the MDM2-p53 interaction. In particular, this therapeutic strategy could be applied to tumors that are $p53^{WT}$, and studies with small molecule MDM2 inhibitors have yielded promising reductions in tumor growth both in vitro and in vivo. Further, in patients with p53-inactivated tumors, stabilization of wildtype p53 in normal tissues by MDM2 inhibition might allow selective protection of normal tissues from mitotic poisons.

The present invention relates to a compound capable of inhibiting the interaction between p53 and MDM2 and activating p53 downstream effector genes. As such, the compound of the present invention would be useful in the treatment of cancers, bacterial infections, viral infections, ulcers and inflammation. In particular, the compound of the present invention is useful to treat solid tumors such as: breast, colon, lung and prostate tumors; and liquid tumors such as lymphomas and leukemias. As used herein, MDM2 means a human MDM2 protein and p53 means a human p53 protein. It is noted that human MDM2 can also be referred to as HDM2 or hMDM2.

The compound, 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, having the chemical structure below

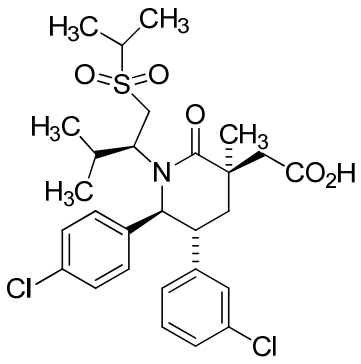


,

is disclosed in published PCT Application No. WO 2011/153,509 (Example No. 362) This compound, a MDM2 inhibitor, is being investigated in human clinical trials for the treatment of various cancers. The present invention provides processes for making the compound as well as intermediates and processes for making the intermediates. Also provided are crystalline forms of the compound and intermediates.

SUMMARY ~~OF THE INVENTION~~

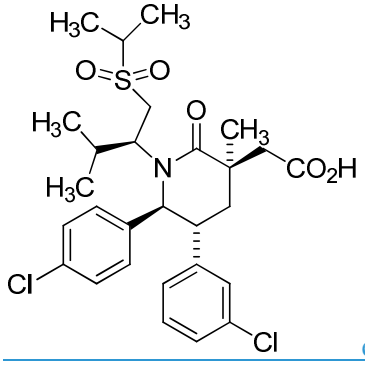
In one aspect, the present disclosure refers to a compound, wherein the compound is crystalline anhydrous



characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6.

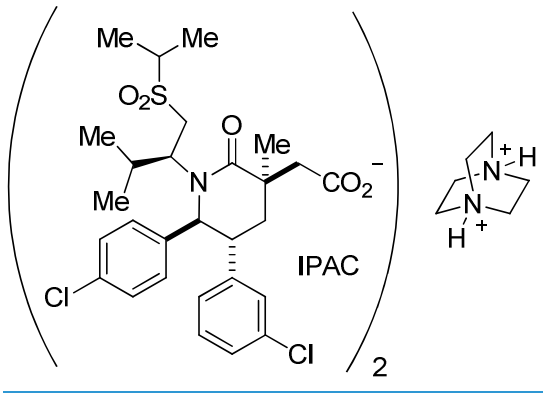
In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to a compound, wherein the compound is crystalline



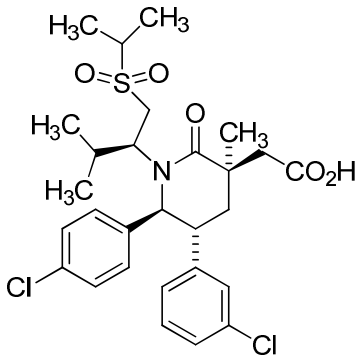
ethanolate characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 10.5, 18.2, 20.3, 21, 21.9 and 24.2.

In another aspect, the present disclosure refers to a compound, wherein the compound is crystalline



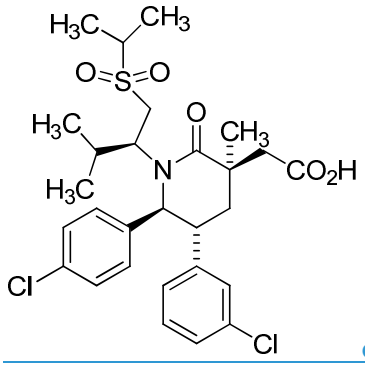
characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.5, 14.3, 15.8, 17.7, 19.5 and 20.7.

In another aspect, the present disclosure refers to a compound, wherein the compound is crystalline



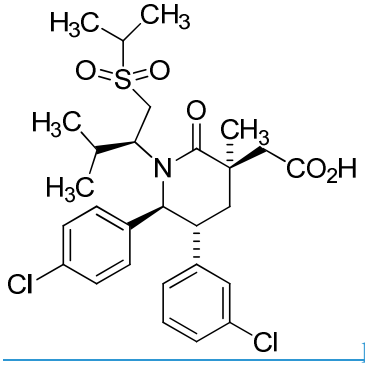
of Form 1 characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 10.7, 11.2, 19.0, 21.5 and 23.0.

In another aspect, the present disclosure refers to a compound, wherein the compound is crystalline



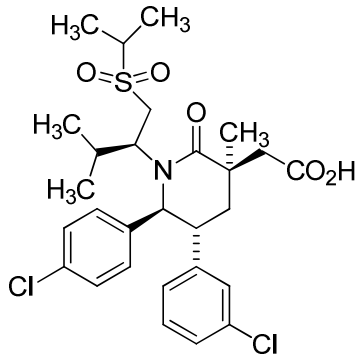
of Form 2 characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 12.9, 20.2 and 28.7.

In yet another aspect, the present disclosure refers to a compound, wherein the compound is crystalline



propanol solvate characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 9.0, 10.3, 12.7, 15.7, 17.9, 20.1 and 20.8.

In ~~embodiment~~example 1, the present ~~invention~~disclosure provides crystalline



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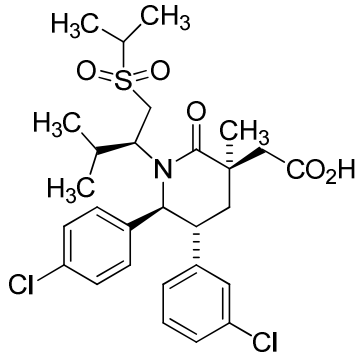
In ~~embodiment~~example 2, the present ~~invention~~disclosure provides crystalline anhydrous



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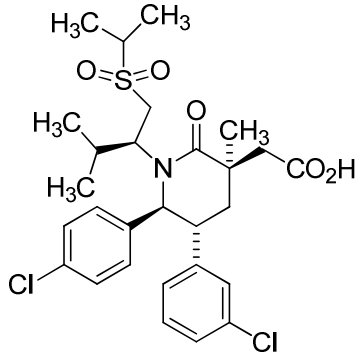
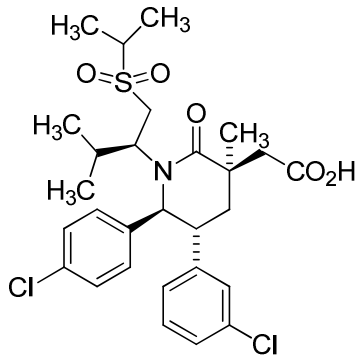
In ~~embodiment~~example 3, the present ~~invention~~disclosure provides crystalline anhydrous



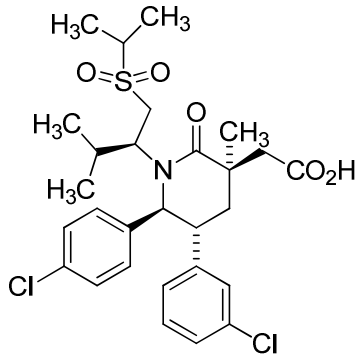
characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6.

In ~~embodiment~~example 4, the present ~~invention~~disclosure provides crystalline anhydrous



in accordance with claim 3 having the X-ray diffraction pattern substantially shown in Figure 1.

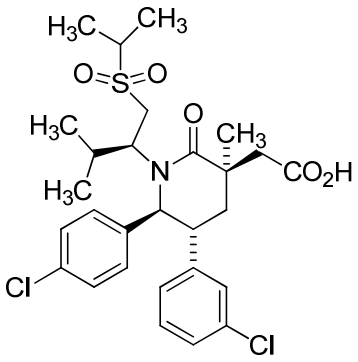
In ~~embodiment~~example 5, the present ~~invention~~disclosure provides pharmaceutical compositions comprising: crystalline



in accordance with any one of ~~embodiment~~examples 1 to 4; and a pharmaceutically acceptable excipient.

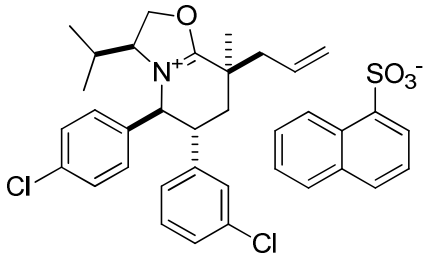
In ~~embodiment~~example 6, the present ~~invention~~disclosure provides methods of treating bladder cancer, breast cancer, colon cancer, rectal cancer, kidney cancer, liver cancer, small cell lung cancer, non-small-cell lung cancer, esophagus cancer, gall-bladder cancer, ovarian cancer , pancreatic cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer, squamous cell carcinoma, melanoma, acute lymphocytic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, acute myelogenous leukemia, chronic myelogenous leukemia, endometrial cancer, head and neck cancer, glioblastoma, osteosarcoma, or rhabdomyosarcoma, the methods comprising administering to

a patient in need thereof, a therapeutically acceptable amount of a pharmaceutical composition comprising crystalline



in accordance with any one of ~~embodiment~~examples 1 to 4.

In ~~embodiment~~example 7, the present ~~invention~~disclosure provides the compound



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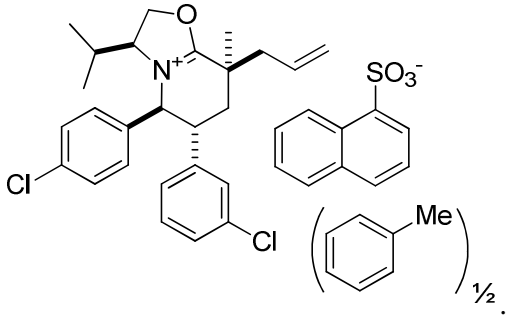
In ~~embodiment~~example 8, the present ~~invention~~disclosure provides the compound



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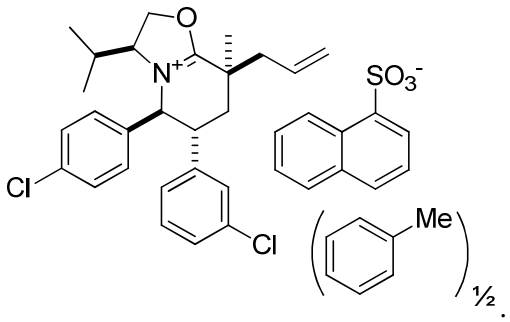
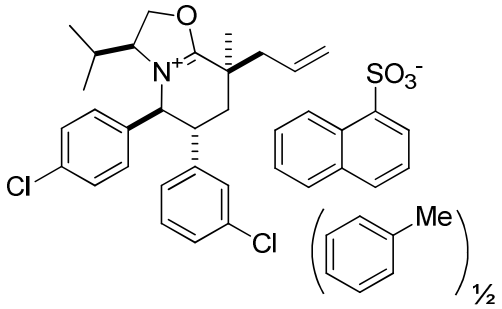
In ~~embodiment~~example 9, the present ~~invention~~disclosure provides crystalline

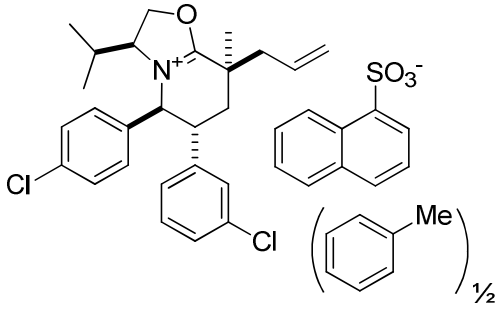


In ~~embodiment~~example 10, the present ~~invention~~disclosure provides crystalline



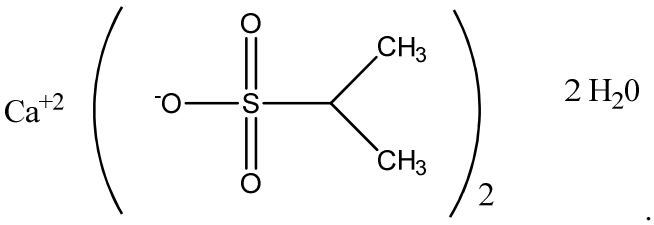
characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 8.7, 18.5, 22.6 and 26.6.

In ~~embodiment~~example 11, the present ~~invention~~disclosure provides crystalline



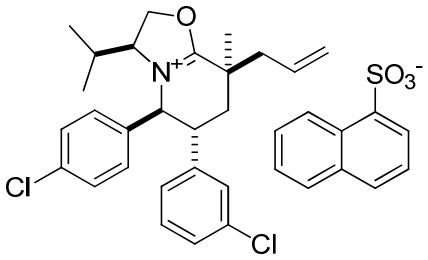
in accordance with claim 10 having the X-ray diffraction pattern substantially shown in Figure 3.

In ~~embodiment~~example 12, the present ~~invention~~disclosure provides the compound



2 H_20 .

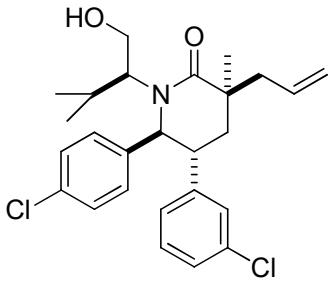
In ~~embodiment~~example 13, the present ~~invention~~disclosure provides a process for making

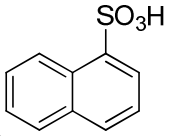


,

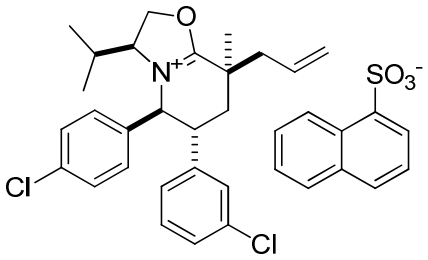
the process comprising:

reacting



under dehydrating conditions with 

to form



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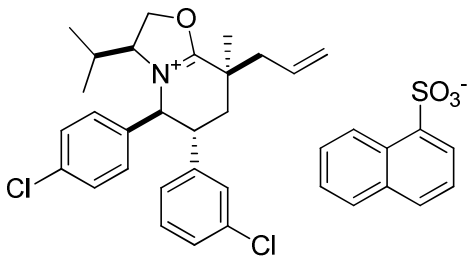
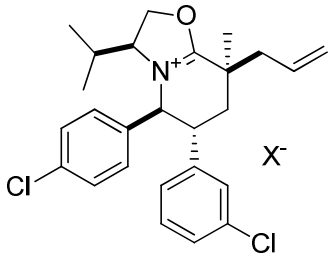
In ~~embodiment~~example 14, the present ~~invention~~disclosure provides the process of ~~embodiment~~example 13 wherein the dehydrating conditions are azeotropic distillation with toluene.

In ~~embodiment~~example 15, the present ~~invention~~disclosure provides a process of making

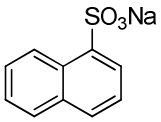


, the process comprising:

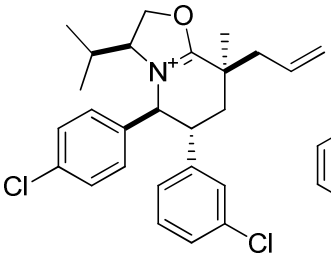
reacting



with

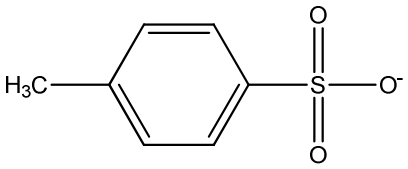


to form



,

wherein X is $CF_3SO_3^-$ or



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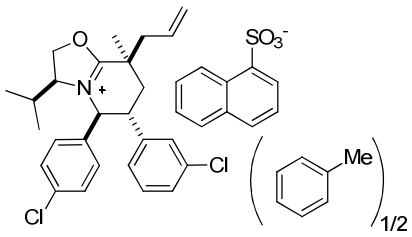
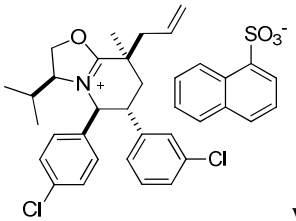
In ~~embodiment~~example 16, the present ~~invention~~disclosure provides a process of making

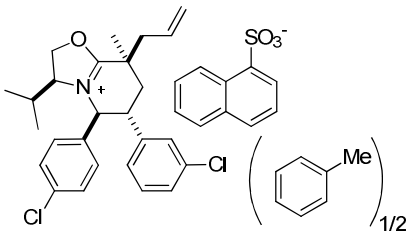


, the process comprising:

reacting



with toluene to form



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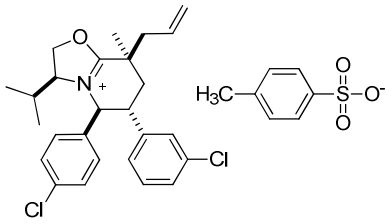
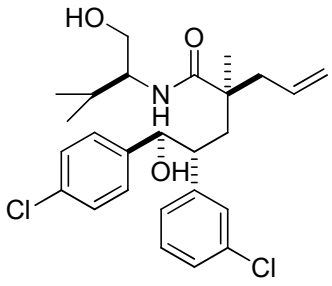
In ~~embodiment~~example 17, the present ~~invention~~disclosure provides a process of making

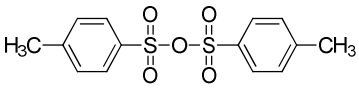


, the process comprising:

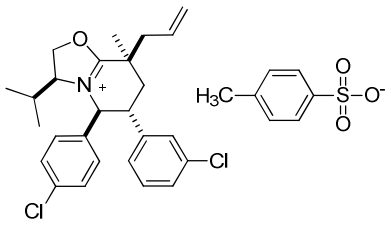
reacting



with lutidine and



to form



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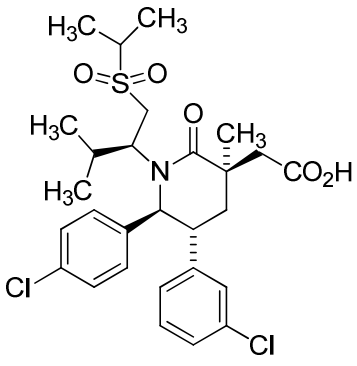
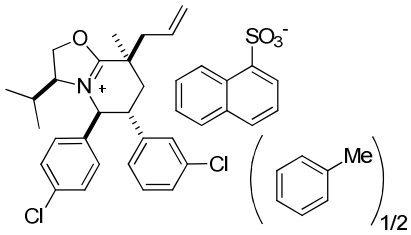
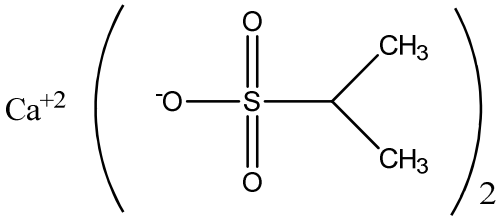
In ~~embodiment~~example 18, the present ~~invention~~disclosure provides a process of making



, the process comprising reacting

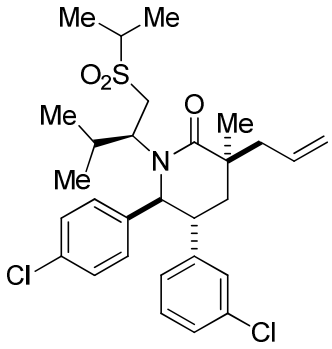


with

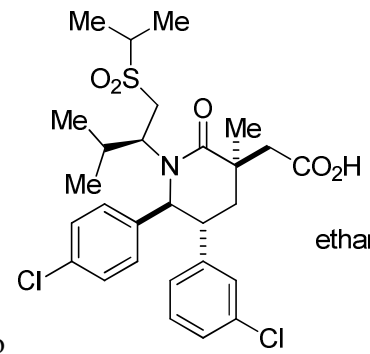


$2\ H_20$

to form

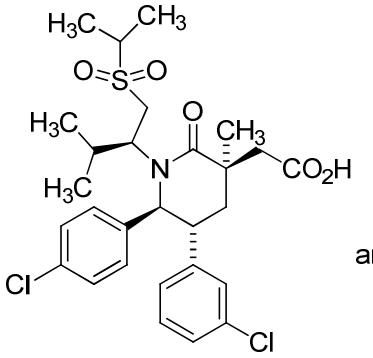


, which is oxidized to



ethanolate

, which is further converted to



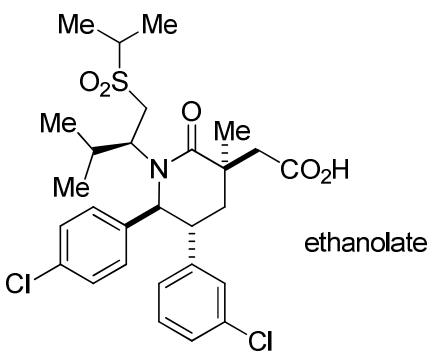
anhydrous

.

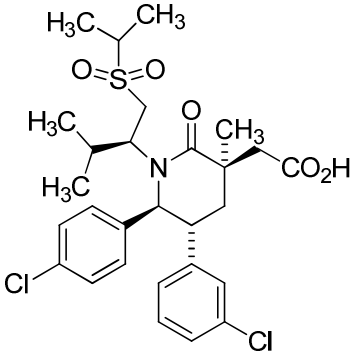
In ~~embodiment~~example 19, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 18 wherein the oxidation is accomplished using ozone.

In ~~embodiment~~example 20, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 18 wherein the oxidation is accomplished using ozone followed by Pinnick oxidation.

In ~~embodiment~~example 21 , the present ~~invention~~disclosure provides a process of ~~embodiment~~example 18 wherein the conversion of

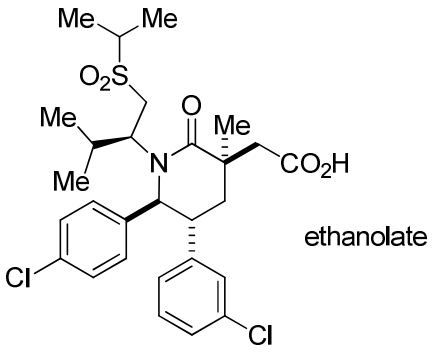


ethanolate to

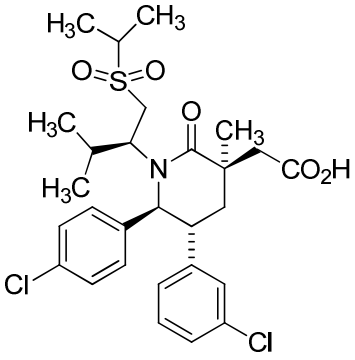


anhydrous is accomplished using methanol and water.

In ~~embodiment~~example 22, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 18 wherein the oxidation is accomplished using ozone followed by Pinnick oxidation, and the conversion of

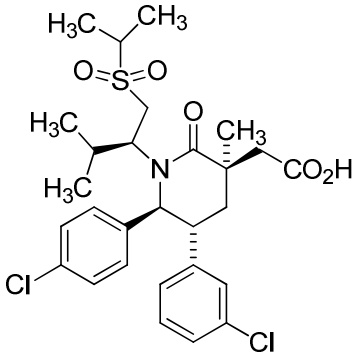


ethanolate to

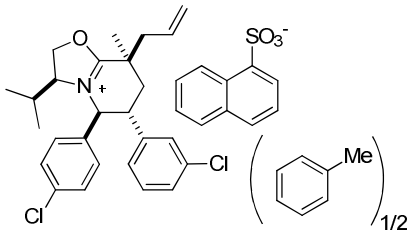


anhydrous is accomplished using methanol and water.

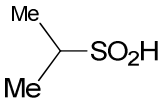
In ~~embodiment~~example 23, the present ~~invention~~disclosure provides a process of making



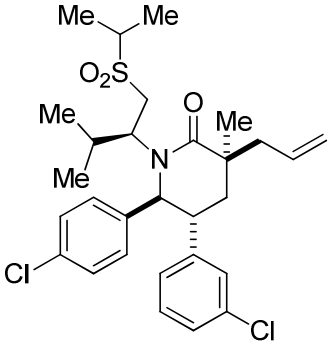
, the process comprising reacting



with

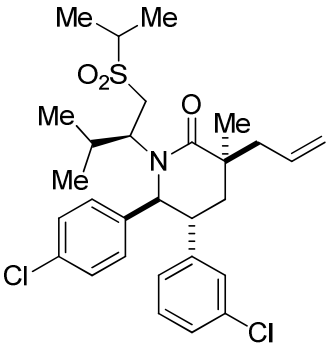


to form

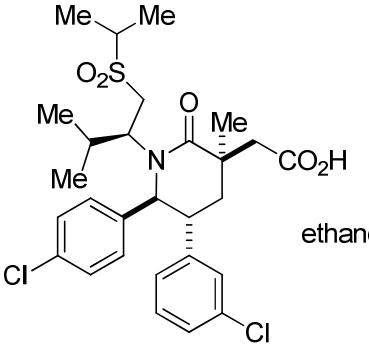


,

oxidizing

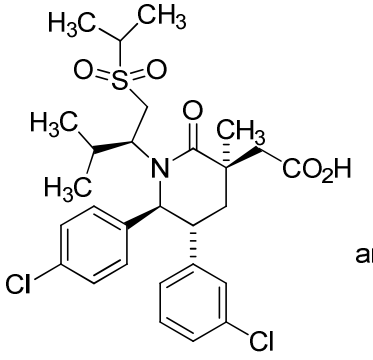


to form



ethanolate

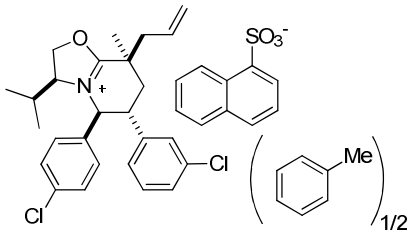
which is further converted to

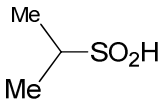


anhydrous

5 .

In ~~embodiment~~example 24, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 23 wherein the



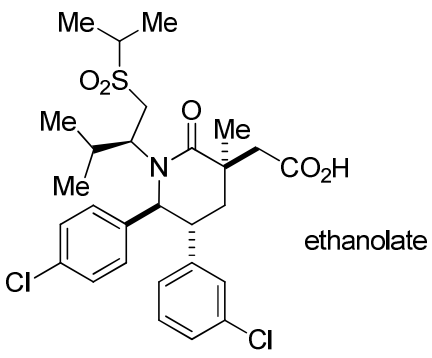
and 

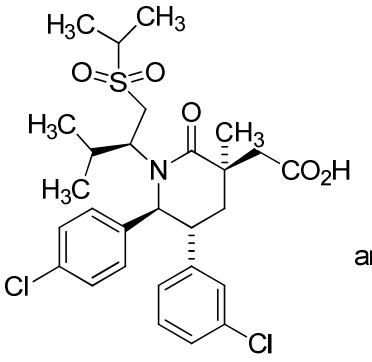
are reacted in the presence of a base.

In ~~embodiment~~example 25, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 24 wherein the base is sodium tert-butoxide.

In ~~embodiment~~example 26, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 23 wherein the oxidation is accomplished using $RuCl_3$ and $NaIO_4$.

In ~~embodiment~~example 27, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 23 wherein the conversion of

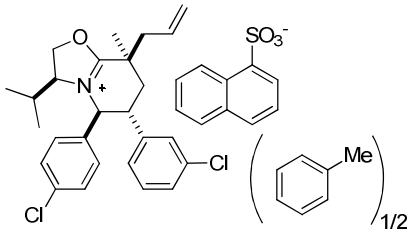
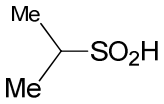


ethanolate to 

anhydrous is

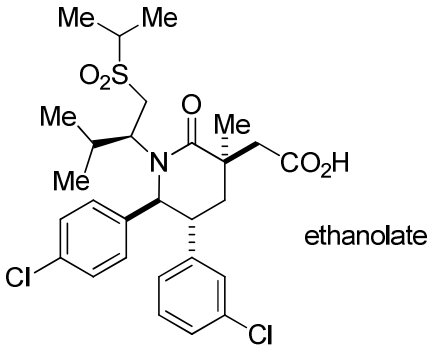
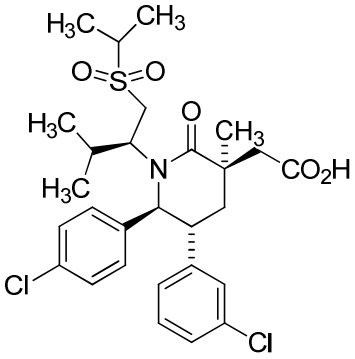
accomplished using methanol and water.

In ~~embodiment~~example 28, the present ~~invention~~disclosure provides a process of ~~embodiment~~example 23 wherein the

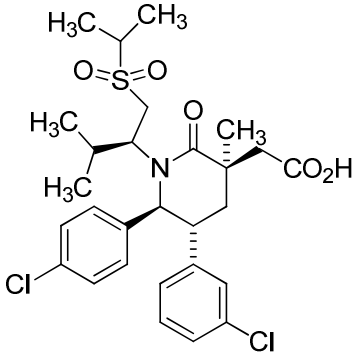
 and  are reacted in the presence of a base;

the oxidation is accomplished using $RuCl_3$ and $NaIO_4$; and

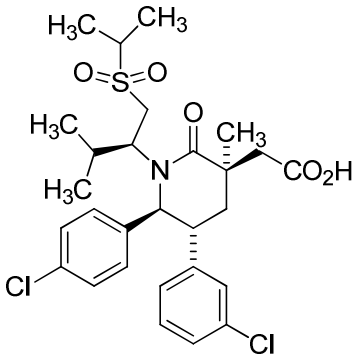
the conversion of

 ethanolate to  anhydrous is accomplished using methanol and water.

In ~~embodiment~~example 29, the present ~~invention~~disclosure provides the compound

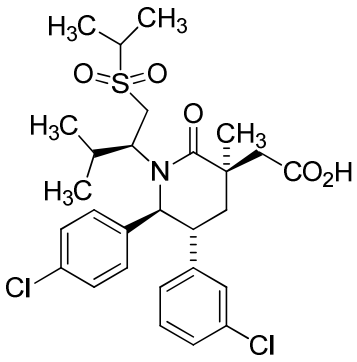
 ethanolate.

In ~~embodiment~~example 30, the present ~~invention~~disclosure provides crystalline



ethanolate.

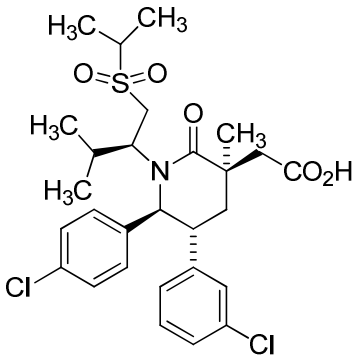
In ~~embodiment~~example 31, the present ~~invention~~disclosure provides crystalline



ethanolate

characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 10.5, 18.2, 20.3, 21, 21.9 and 24.2.

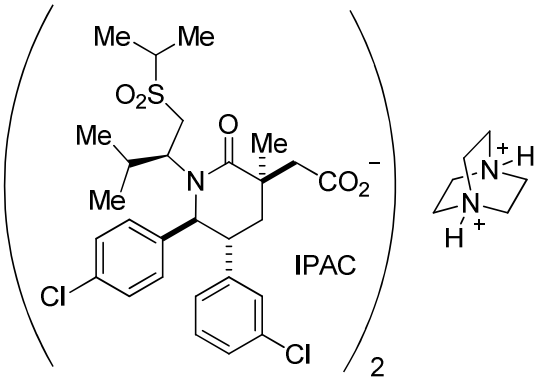
In ~~embodiment~~example 32, the present ~~invention~~disclosure provides crystalline



ethanolate

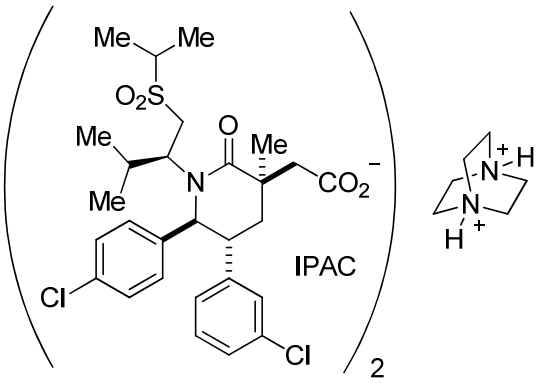
in accordance with ~~embodiment~~example 31 having the X-ray diffraction pattern substantially shown in Figure 6.

In ~~embodiment~~example 33, the present ~~invention~~disclosure provides the compound



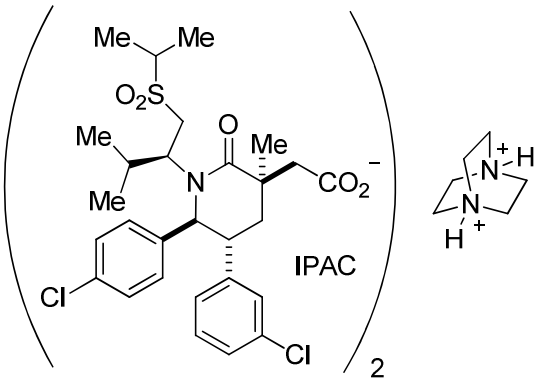
.

In ~~embodiment~~example 34, the present ~~invention~~disclosure provides crystalline



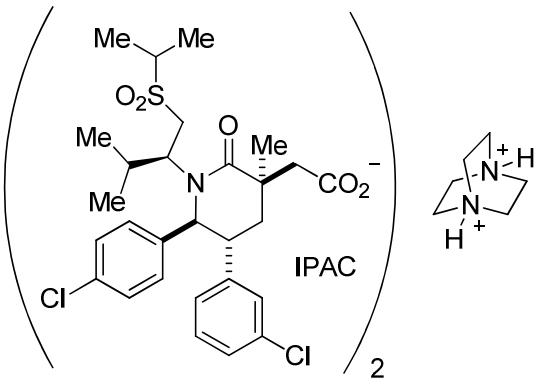
.

In ~~embodiment~~example 35, the present ~~invention~~disclosure provides crystalline



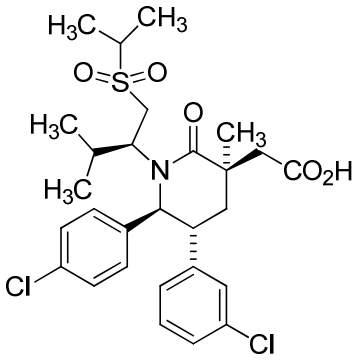
characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.5, 14.3, 15.8, 17.7, 19.5 and 20.7.

In ~~embodiment~~example 36, the present ~~invention~~disclosure provides crystalline

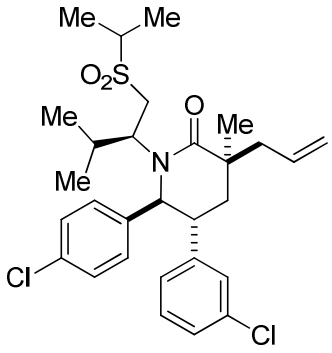


in accordance with ~~embodiment~~example 35 having the X-ray diffraction pattern substantially shown in Figure 12.

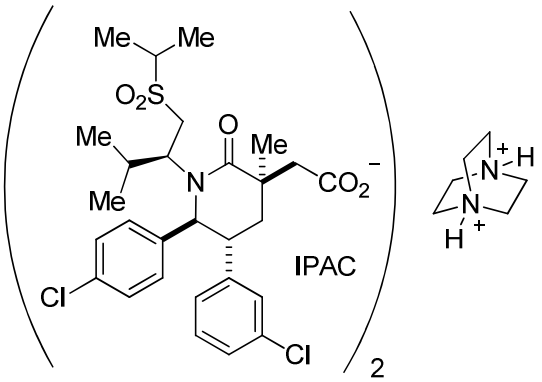
In ~~embodiment~~example 37, the present ~~invention~~disclosure provides a process of making



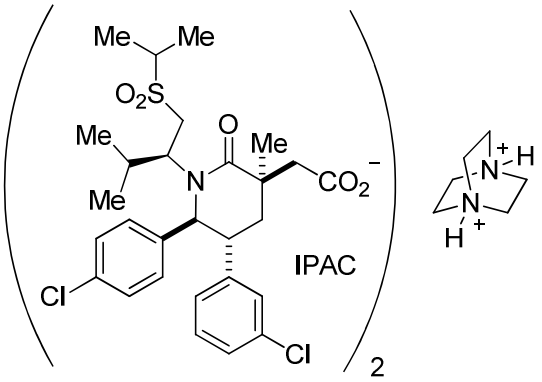
, the process comprising reacting



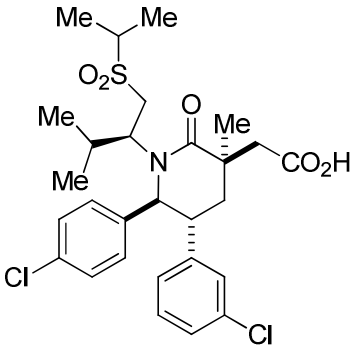
with an oxidizing agent and DABCO to form



and reacting



with an acid to form



.

In ~~embodiment~~example 38, the present ~~invention~~disclosure provides the process of ~~embodiment~~example 37 wherein the oxidizing agent is ozone and the acid is hydrochloric acid.

BRIEF DESCRIPTION OF THE FIGURES

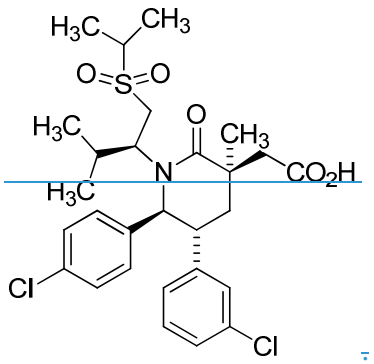
Figure 1. XRPD Pattern of Compound A Crystalline Anhydrous

Figure 2. XRPD Pattern of Compound A Amorphous

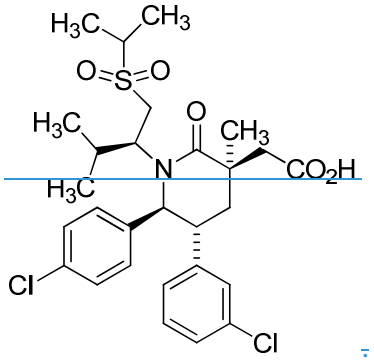
CLAIMS

What is claimed is:

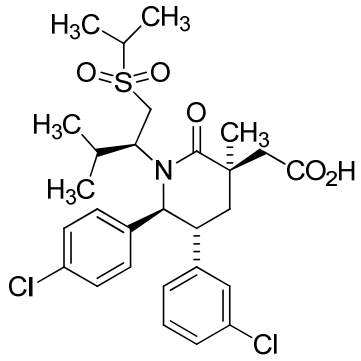
~~1. Crystalline~~



~~2. Crystalline anhydrous~~

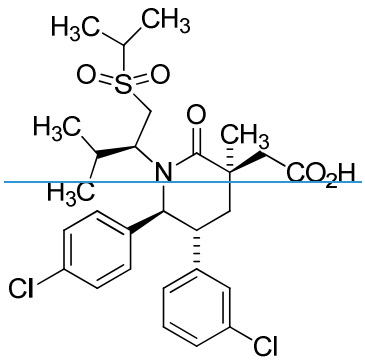


~~3~~1. A compound, wherein the compound is ~~C~~crystalline anhydrous



characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6.

~~4~~2. The compound of claim 1,~~Crystalline anhydrous~~



~~in accordance with claim 3~~ wherein the compound is characterized by ~~having~~ the representative X-ray diffraction pattern ~~substantially~~ shown in Figure 1.

3. The compound of claim 1, wherein the compound is characterized by the X-ray diffraction pattern shown in Figure 1.

4. The compound of claim 1, wherein the X-ray diffraction pattern is obtained using CuKα radiation.

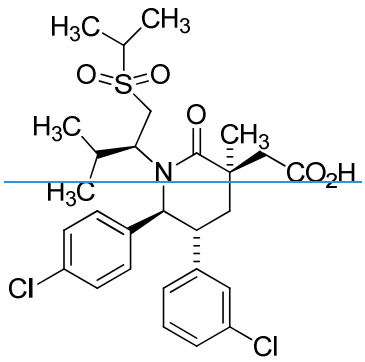
5. The compound of claim 4, wherein the X-ray diffraction pattern is obtained at room temperature.

6. The compound of claims 1, wherein the compound is characterized by having a melting point of approximately 161ºC.

7. The compound of claim 1, wherein the compound is characterized by the representative differential scanning calorimetry curve shown in Figure 8.

8. The compound of claim 1, wherein the compound is characterized by the differential scanning calorimetry curve shown in Figure 8.

~~5~~9. A pharmaceutical composition comprising~~: crystalline~~



~~in accordance with~~ the compound of any one of claims 1 ~~to 4~~-8; and a pharmaceutically acceptable excipient.

10. The pharmaceutical composition of claim 9, wherein the pharmaceutical composition is a solid dosage form.

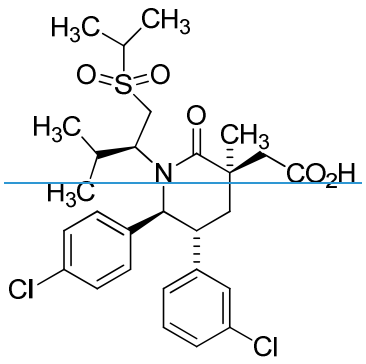
11. The pharmaceutical composition of claim 10 wherein the solid dosage form is a capsule, tablet, powder, or granule.

12. The pharmaceutical composition of claim 11, wherein the solid dosage form is a tablet.

13. The pharmaceutical composition of any one of claims 10-12, wherein the solid dosage form is for oral administration.

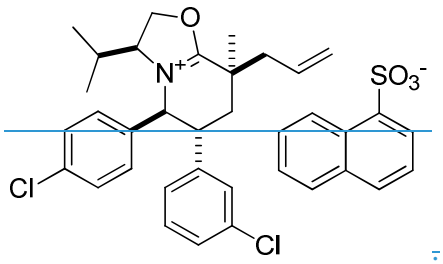
~~6. A method of treating bladder cancer, breast cancer, colon cancer, rectal cancer, kidney cancer, liver cancer, small cell lung cancer, non-small cell lung cancer, esophagus cancer, gall-bladder cancer, ovarian cancer , pancreatic cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer, squamous cell carcinoma, melanoma, acute lymphocytic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, acute myelogenous leukemia,~~

~~chronic myelogenous leukemia, endometrial cancer, head and neck cancer, glioblastoma, osteosarcoma, or rhabdomyosarcoma, the method comprising administering to a patient in need thereof, a therapeutically acceptable amount of a pharmaceutical composition comprising crystalline~~

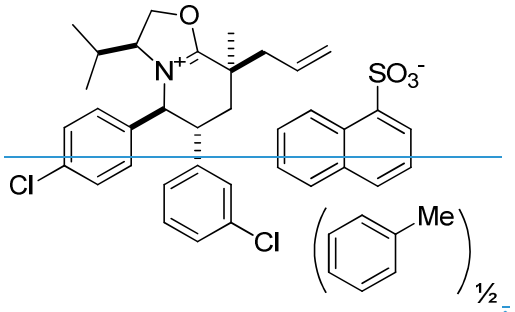


~~in accordance with any one of claims 1 to 4.~~

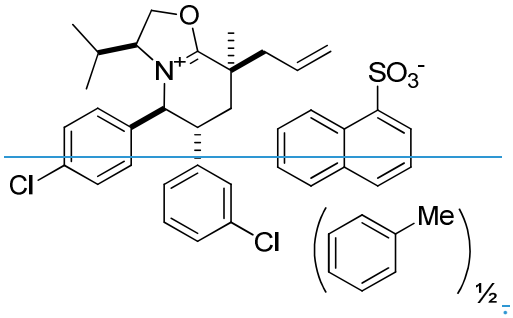
~~7. The compound~~



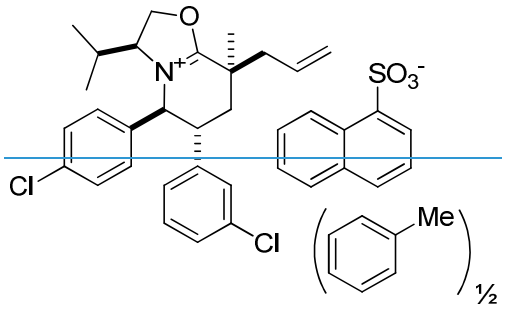
~~8. The compound~~



~~9. Crystalline~~

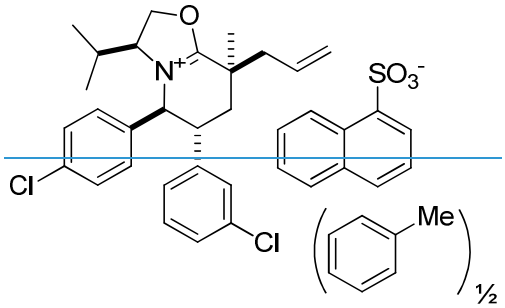


~~10. Crystalline~~



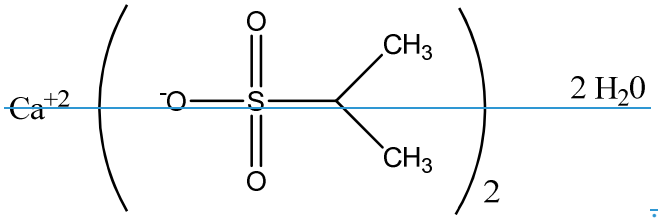
~~characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 8.7, 18.5, 22.6 and 26.6.~~

~~11. Crystalline~~

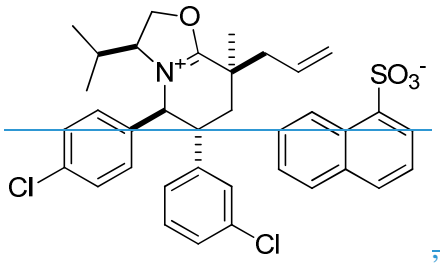


~~in accordance with claim 10 having the X-ray diffraction pattern substantially shown in Figure 3.~~

12. The compound

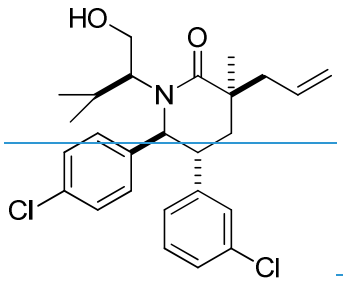


13. A process for making

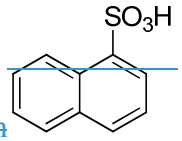


the process comprising:

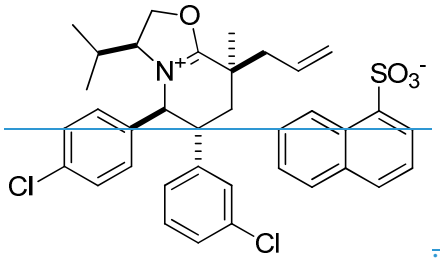
reacting



under dehydrating conditions with

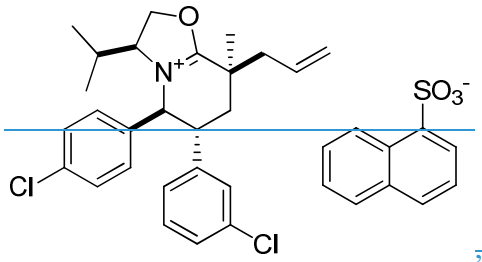


to form



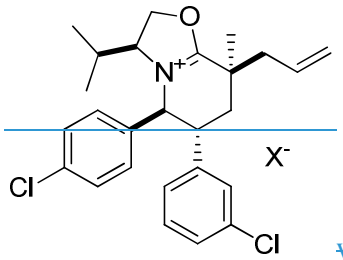
~~14. The process of claim 13 wherein the dehydrating conditions are azeotropic distillation with toluene.~~

~~15. A process of making~~

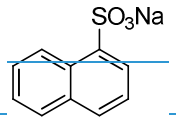


~~, the process comprising:~~

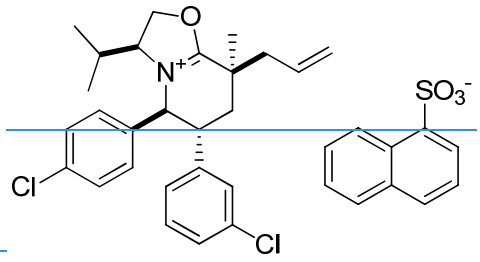
~~reacting~~



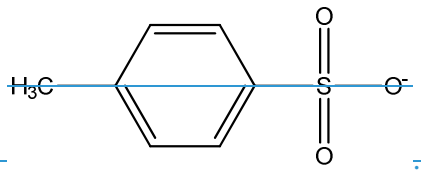
~~with~~



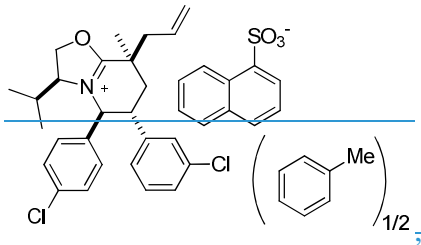
~~to form~~



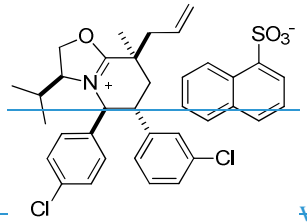
~~wherein X is $CF_3SO_3^-$ or~~

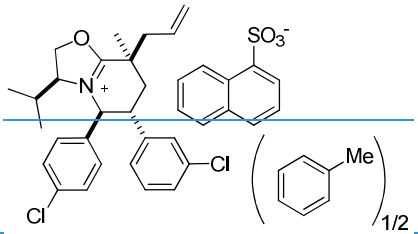


~~16. A process of making~~

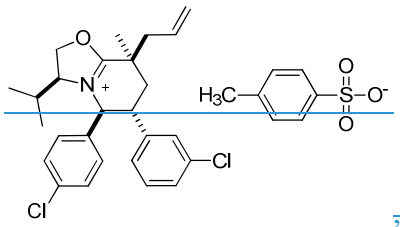


~~, the process comprising:~~



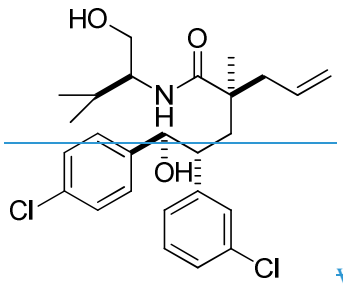
~~reacting~~ ~~with toluene to form~~  .

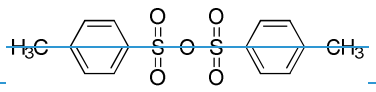
~~17. A process of making~~

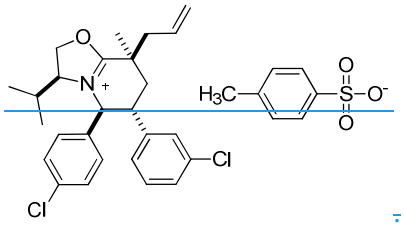


~~, the process comprising:~~

~~reacting~~

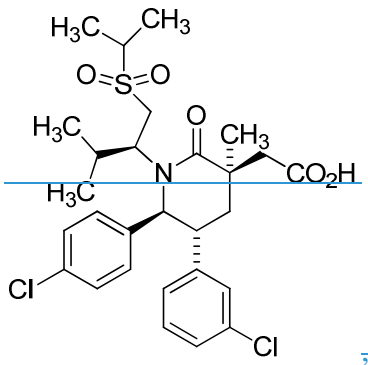


~~with lutidine and~~  ~~to form~~

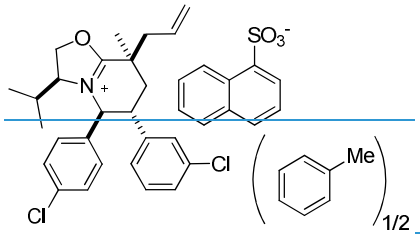


.

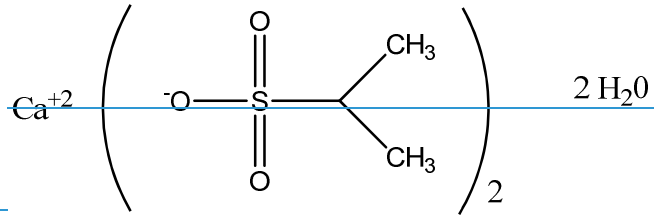
18. A process of making



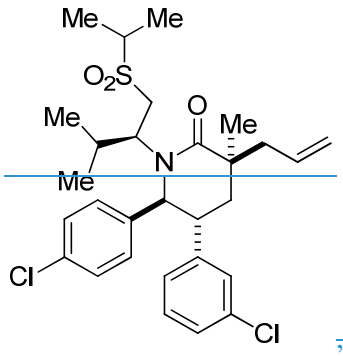
, the process comprising reacting



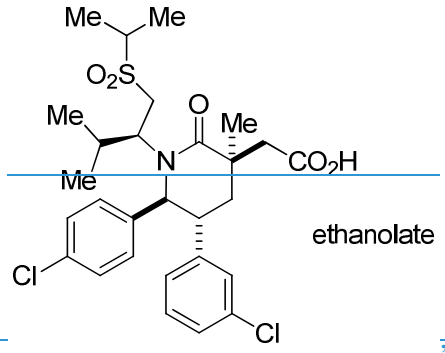
with



to form

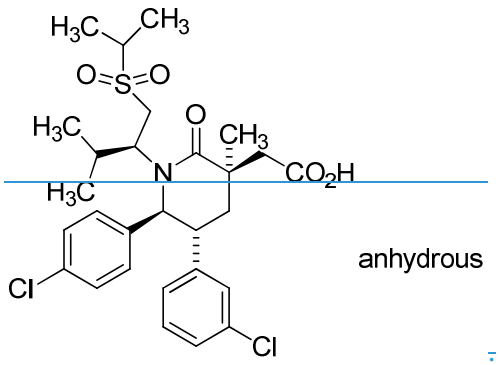


, which is oxidized to



, which

~~is further converted to~~



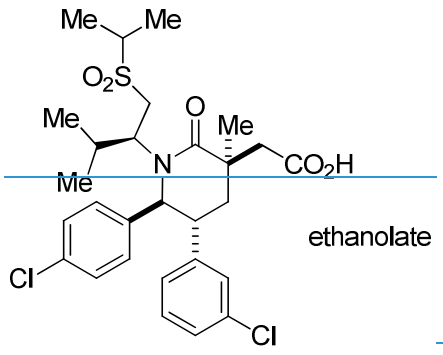
anhydrous

~~.~~

~~19. The process of claim 18 wherein the oxidation is accomplished using ozone.~~

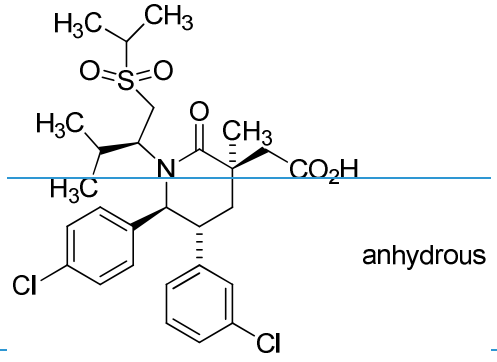
~~20. The process of claim 18 wherein the oxidation is accomplished using ozone followed by Pinnick oxidation.~~

~~21. The process of claim 18 wherein the conversion of~~



ethanolate

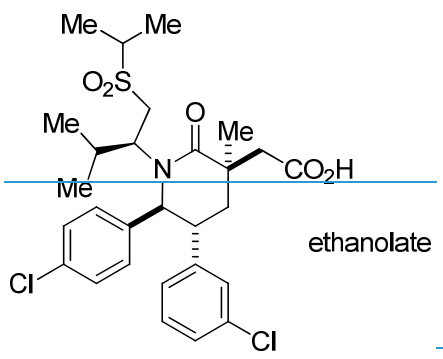
~~to~~



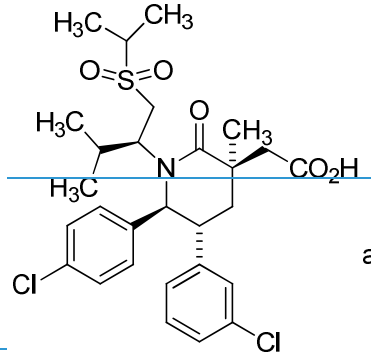
anhydrous

~~is accomplished using methanol and water.~~

~~22. The process of claim 18 wherein the oxidation is accomplished using ozone followed by Pinnick oxidation, and the conversion of~~

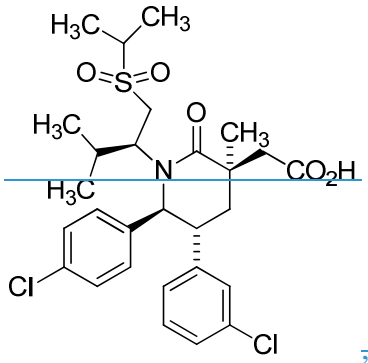


ethanolate ~~to~~

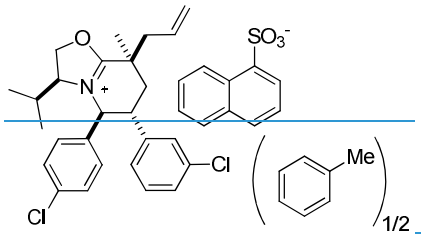


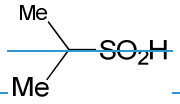
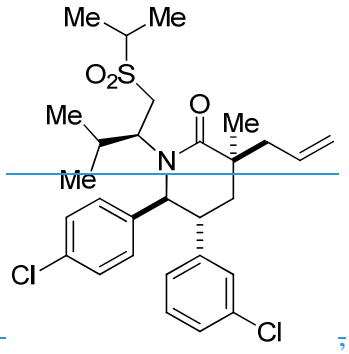
anhydrous ~~is accomplished using methanol and water.~~

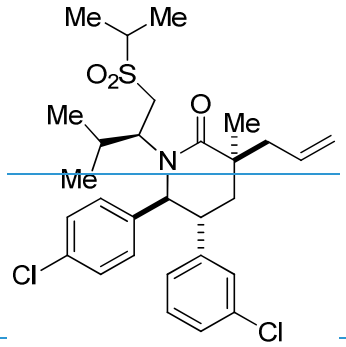
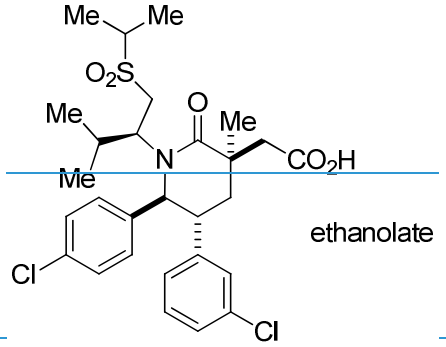
~~23. A process of making~~



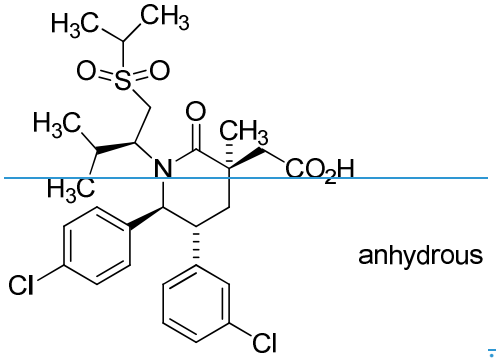
~~, the process comprising reacting~~



~~with~~  ~~to form~~  ~~,~~

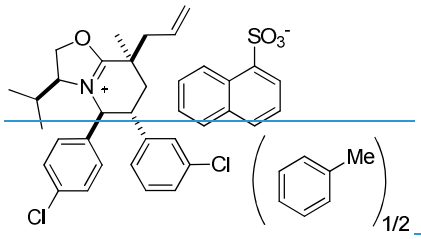
 ~~oxidizing~~ ~~to form~~  ~~which is~~

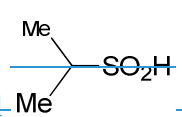
~~further converted to~~



~~.~~

~~24. The process of claim 23 wherein the~~

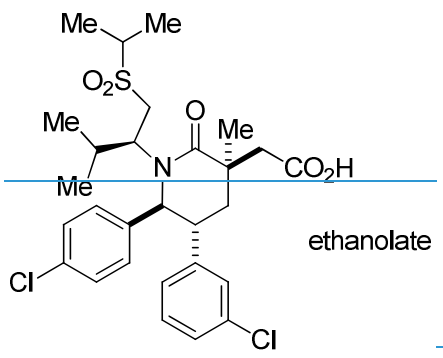


~~and~~  ~~are reacted in the presence of a base.~~

25. The process of claim 24 wherein the base is sodium tert-butoxide.

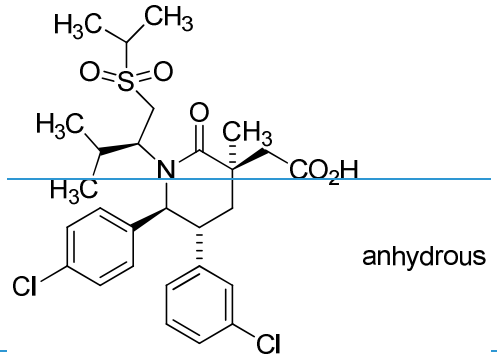
26. The process of claim 23 wherein the oxidation is accomplished using $RuCl_3$ and $NaIO_4$.

27. The process of claim 23 wherein the conversion of



ethanolate

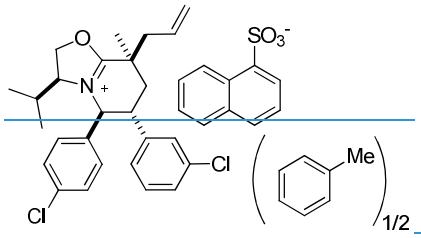
to



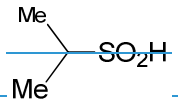
anhydrous

is accomplished using methanol and water.

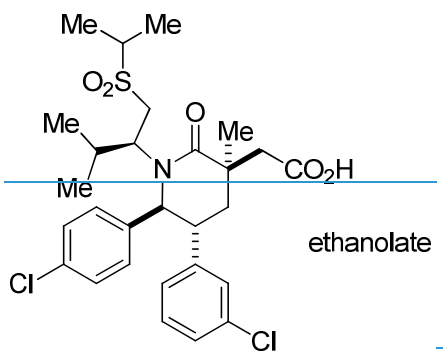
28. The process of claim 23 wherein the



and

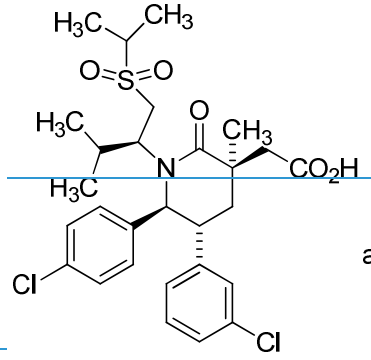


are reacted in the presence of a base; the oxidation is accomplished using $RuCl_3$ and $NaIO_4$; and the conversion of



ethanolate

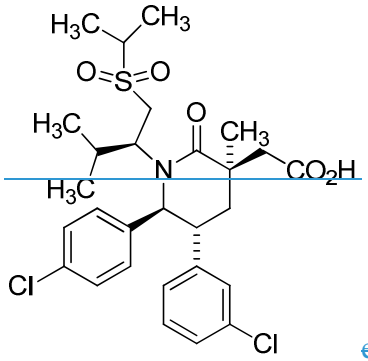
~~to~~



anhydrous

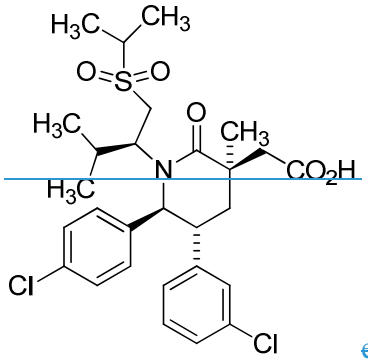
~~is accomplished using methanol and water.~~

~~29. The compound~~



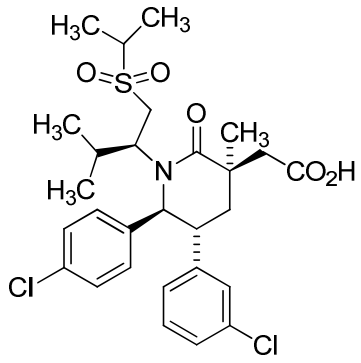
~~ethanolate.~~

~~30. Crystalline~~



~~ethanolate.~~

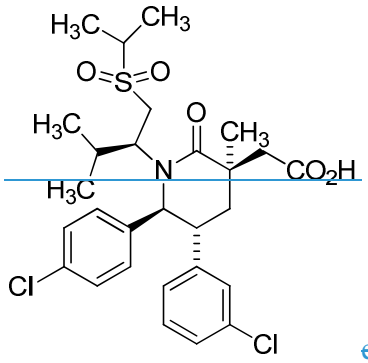
~~31~~14. A compound, wherein the compound is c~~C~~rystalline



ethanolate

characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 10.5, 18.2, 20.3, 21, 21.9 and 24.2.

~~32~~15. The compound of ~~Crystalline~~



~~ethanolate~~

~~in accordance with~~ claim ~~31~~ 14, wherein the compound is characterized by the representative ~~having the~~ X-ray diffraction pattern ~~substantially~~ shown in Figure 6.

16. The compound of claim 14, wherein the compound is characterized by the X-ray diffraction pattern shown in Figure 6.

17. The compound of claim 14, wherein the X-ray diffraction pattern is obtained using CuKα radiation.

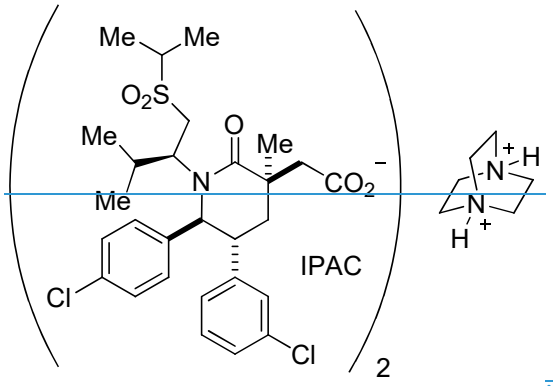
18. The compound of claim 17, wherein the X-ray diffraction pattern is obtained at room temperature.

19. The compound of claim 14, wherein the compound is characterized by having a melting point of approximately 90ºC.

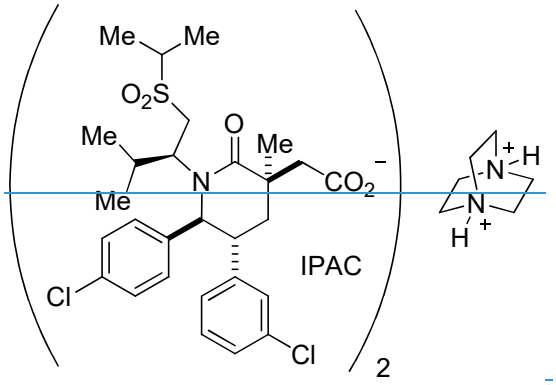
20. The compound of claim 14, wherein the compound is characterized by the representative differential scanning calorimetry curve shown in Figure 11.

21. The compound of claim 14, wherein the compound is characterized by the differential scanning calorimetry curve shown in Figure 11.

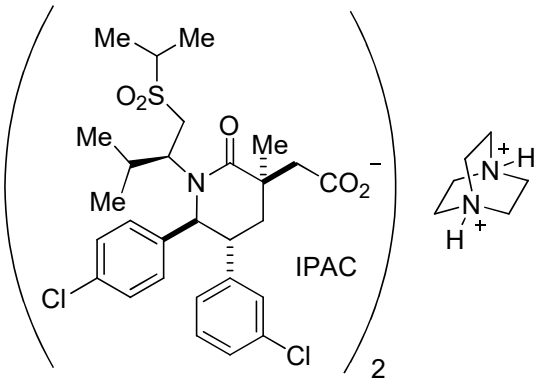
~~33. The compound~~



~~34. Crystalline~~

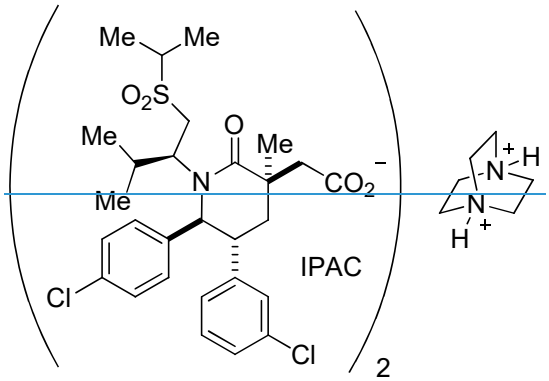


~~35~~22. A compound, wherein the compound is c~~C~~rystalline



characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.5, 14.3, 15.8, 17.7, 19.5 and 20.7.

~~36~~23. The compound of claim 22, wherein the compound is characterized by the representative ~~Crystalline~~



~~in accordance with claim 35 having the~~ X-ray diffraction pattern ~~substantially~~ shown in Figure 12.

24. The compound of claim 22, wherein the compound is characterized by the X-ray diffraction pattern shown in Figure 12.

25. The compound of claim 22, wherein the X-ray diffraction pattern is obtained using CuKα radiation.

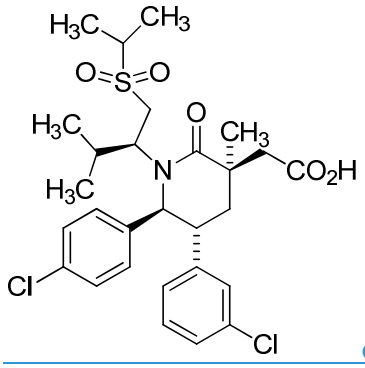
26. The compound of claim 25, wherein the X-ray diffraction pattern is obtained at room temperature.

27. The compound of claim 22, wherein the compound is characterized by having a melting point of approximately 96ºC.

28. The compound of claim 22, wherein the compound is characterized by the representative differential scanning calorimetry curve shown in Figure 13.

29. The compound of claim 22, wherein the compound is characterized by the differential scanning calorimetry curve shown in Figure 13.

30. A compound, wherein the compound is crystalline



of Form 1 characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 10.7, 11.2, 19.0, 21.5 and 23.0.

31. The compound of claim 30, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least four peaks at diffraction angle 2 theta degrees selected from the group.

32. The compound of claim 30, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 10.7, 11.2, 19.0, 21.5 and 23.0.

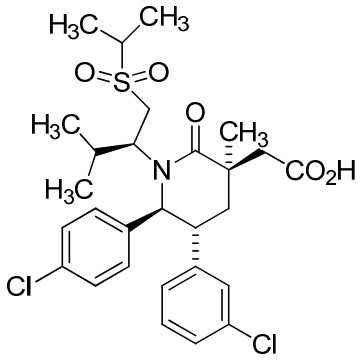
33. The compound of claim 30, wherein the compound is characterized by the representative X-ray diffraction pattern shown in Figure 4.

34. The compound of claim 30, wherein the compound is characterized by the X-ray diffraction pattern shown in Figure 4.

35. The compound of claim 30, wherein the X-ray diffraction pattern is obtained using CuKα radiation.

36. The compound of claim 35, wherein the X-ray diffraction pattern is obtained at room temperature.

37. A compound, wherein the compound is crystalline



of Form 2 characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 12.9, 20.2 and 28.7.

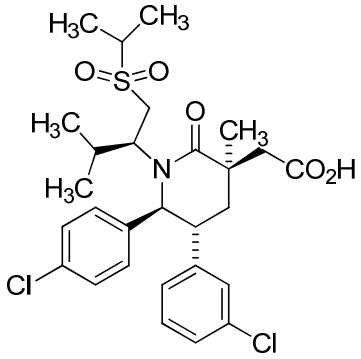
38. The compound of claim 37, wherein the compound is characterized by the representative X-ray diffraction pattern shown in Figure 5.

39. The compound of claim 37, wherein the compound is characterized by the X-ray diffraction pattern shown in Figure 5.

40. The compound of claim 37, wherein the X-ray diffraction pattern is obtained using CuKα radiation.

41. The compound of claim 40, wherein the X-ray diffraction pattern is obtained at room temperature.

42. A compound, wherein the compound is crystalline



propanol solvate characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 9.0, 10.3, 12.7, 15.7, 17.9, 20.1 and 20.8.

43. The compound of claim 42, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least five peaks at diffraction angle 2 theta degrees selected from the group.

44. The compound of claim 42, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 9.0, 10.3, 12.7, 15.7, 17.9, 20.1 and 20.8.

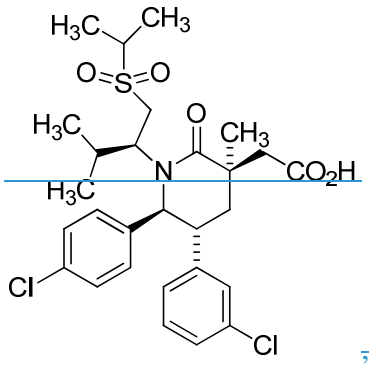
45. The compound of claim 42, wherein the compound is characterized by the representative X-ray diffraction pattern shown in Figure 7.

46. The compound of claim 42, wherein the compound is characterized by the X-ray diffraction pattern shown in Figure 7.

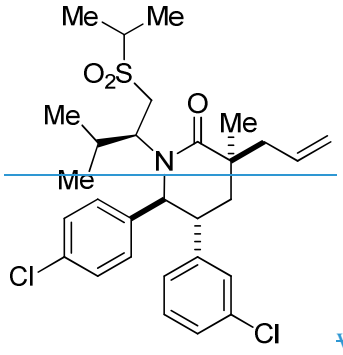
47. The compound of claim 42, wherein the X-ray diffraction pattern is obtained using CuKα radiation.

48. The compound of claim 47, wherein the X-ray diffraction pattern is obtained at room temperature.

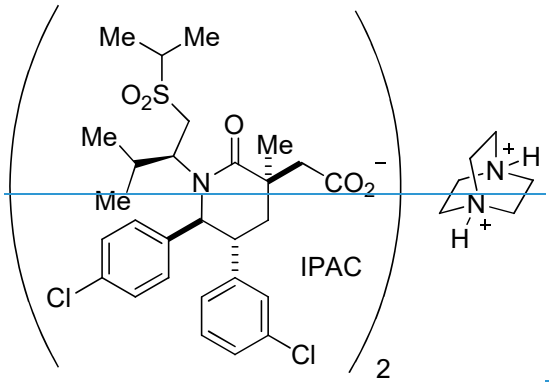
~~37. A process of making~~



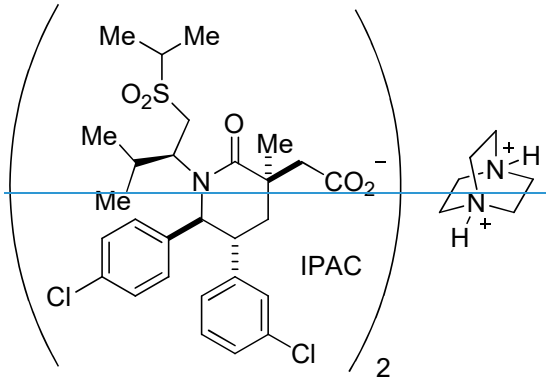
~~, the process comprising reacting~~



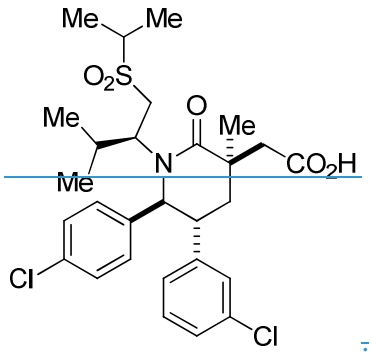
~~with an oxidizing agent and DABCO to form~~



~~and reacting~~



~~with an acid to form~~



~~38. The process of claim 37 wherein the oxidizing agent is ozone and the acid is hydrochloric acid.~~