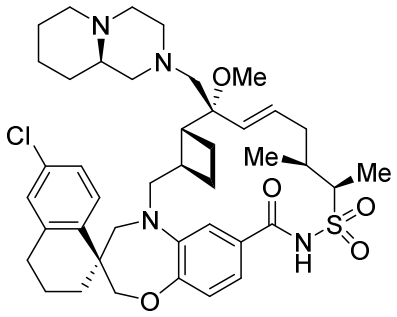


(A2).

[0005] One common characteristic of human cancer is overexpression of Mcl-1. Mcl-1 overexpression prevents cancer cells from undergoing programmed cell death (apoptosis), allowing the cells to survive despite widespread genetic damage.

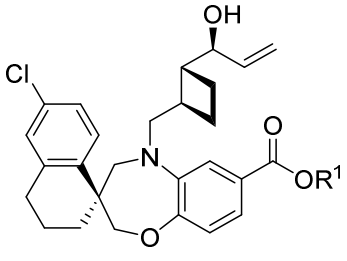
[0006] Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering apoptosis. Antiapoptotic members of the Bcl-2 family (such as Bcl-2, Bcl-XL, and Mcl-1) block the activity of BAX and BAK. Other proteins (such as BID, BIM, BIK, and BAD) exhibit additional regulatory functions. Research has shown that Mcl-1 inhibitors can be useful for the treatment of cancers. Mcl-1 is overexpressed in numerous cancers.

[0007] U.S. Patent No. 9,562,061, which is incorporated herein by reference in its entirety, discloses compound A1 as an Mcl-1 inhibitor and provides a method for preparing it. However, improved synthetic methods that result in greater yield and purity of compound A1 are desired, particularly for the commercial production of compound A1.

[0008] U.S. Patent No. 10,300,075, which is incorporated herein by reference in its entirety, discloses compound A2 as an Mcl-1 inhibitor and provides a method for preparing it. However, improved synthetic methods that result in greater yield and purity of compound A2 are desired, particularly for the commercial production of compound A2.

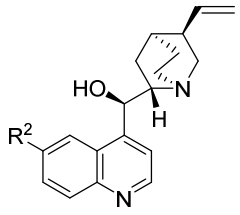
SUMMARY

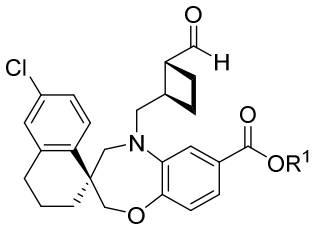
[0008a] In one aspect, provided herein is a process for synthesizing compound E, or a salt or solvate thereof:



(E);

comprising admixing compound C, compound D, , and $Zn(X^3)_2$ in an organic solvent to form compound E:



(C) and


(D);

wherein

R^1 is $C_{1\text{-}6}$alkyl;

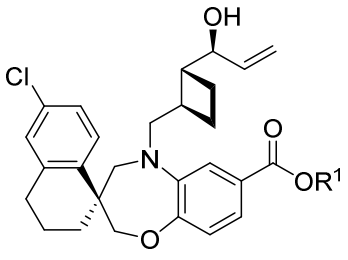
R^2 is H or $C_{1\text{-}3}$alkoxy;

X^1 is MgCl, MgBr, MgI, Li, CuLi, ZnX^2, In(I), $In(X^2)_2$;

each X^2 independently is Cl, Br, or I; and

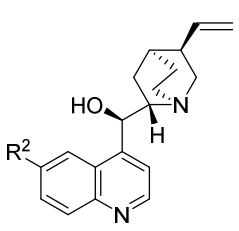
each X^3 independently is Cl, Br, I, OTf, OTs, OAc, or acac.

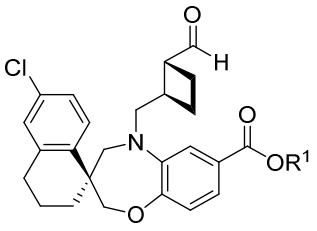
[0009] Provided herein are processes for synthesizing compound E, or a salt or solvate thereof:



(E);

comprising admixing compound C, compound D, , and $Zn(X^3)_2$ in an organic solvent to form compound E:



(C) and


(D);

wherein R^1 is C_{1-6}alkyl; R^2 is H or C_{1-3}alkoxy; X^1 is MgCl, MgBr, MgI, Li, CuLi, ZnX^2, In(I), or $In(X^2)_2$; each X^2 independently is Cl, Br, or I; and each X^3 independently is Cl, Br, I, OTf, OTs, OAc, or acac.In various examples, R^1 is methyl, ethyl, propyl, *n*-butyl, or *tert*-butyl.

[0010] In some cases, R^1 is methyl, ethyl, or *tert*-butyl.

[0011] In various examples, R^2 is H. In various examples, R^2 is C_{1-3}alkoxy. In some cases, R^2 is methoxy.

[0012] In various examples, X^1 is MgCl. In various examples, X^1 is MgBr or MgI. In various examples, X^1 is Li. In various examples, X^1 is CuLi. In various examples, X^1 is In(I) or $In(X^2)_2$. In various examples, X^1 is ZnCl or ZnBr.

[0013] In various examples, $Zn(X^3)_2$ is $ZnCl_2$. In various examples, $Zn(X^3)_2$ is $ZnBr_2$. In various examples, $Zn(X^3)_2$ is ZnI_2. In various examples, $Zn(X^3)_2$ is $Zn(OTf)_2$ or $Zn(OTs)_2$. In various examples, $Zn(X^3)_2$ is $Zn(OAc)_2$ or $Zn(acac)_2$.

[0014] In various examples, the organic solvent is degassed prior to the admixing. In various examples, the organic solvent comprises an ether solvent or acetonitrile. In some cases, the organic solvent is selected from the group consisting of tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), diethyl ether, acetonitrile, 1,2-dimethoxyethane (1,2-DME), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and a combination thereof. In some cases, the organic solvent is acetonitrile.

[0015] In various examples, the admixing is performed at a temperature of 10 °C to 35 °C.

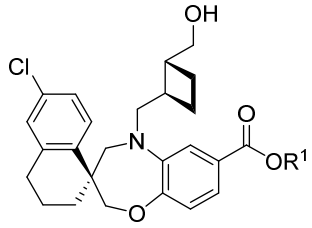
[0016] In various examples, the admixing comprises (a) admixing compound C and $Zn(X^3)_2$ in the organic solvent to form a suspension; (b) adding  to the suspension to form a solution; and (c) adding compound D to the solution to form compound E. In some cases, the suspension of step (a) is cooled to a temperature of -15 °C to -5 °C prior to adding . In some cases,  is added to the suspension as a solution in an ether solvent. In some cases, the ether solvent is THF. In some cases,  is added to the suspension at a temperature of -10 °C to 0 °C. In some cases, the solution of step (b) is brought to a temperature of 10 °C to 35 °C prior to adding compound D. In some cases, compound D is added as a solution in an organic solvent selected from the group consisting of THF, 2-MeTHF, diethyl ether, acetonitrile, 1,2-DME, MTBE, CPME, and a combination thereof. In some cases the organic solvent comprises acetonitrile.

[0017] In various examples, compound D and  are present in a molar ratio of 1:2.5 to 1:4.5. In some cases, the molar ratio of compound D to  is 1:3.2.

[0018] In various examples, compound D and $Zn(X^3)_2$ are present in a molar ratio of 1:2.5 to 1:4.0. In various cases, the molar ratio of compound D to $Zn(X^3)_2$ is 1:3.1.

[0019] In various examples, compound D and compound C are present in a molar ratio of 1:1 to 1:2. In some cases, the molar ratio of compound D to compound C is 1:1.4.

[0020] In various examples, compound D is prepared by oxidizing compound B:



(B) in the presence of an oxidizing agent and an organic solvent. In some cases, the oxidizing occurs under an inert atmosphere.

[0021] In various examples, compound B is provided as a solution in an organic solvent selected from the group consisting of dimethyl sulfoxide (DMSO), dichloromethane (DCM), dimethylformamide (DMF), THF, 2-MeTHF, acetonitrile toluene, 1,2-DME, MTBE, 1,2-dichloroethane (DCE), chloroform, and a combination thereof. In some cases, the organic solvent is DCM.

[0022] In various examples, the oxidizing agent is selected from the group consisting of oxalyl chloride, bleach, SO_3/pyridine, iodobenzenediacetate, trifluoroacetic anhydride, N-chlorosuccinimide (NCS), 2-iodooxybenzoic acid (IBX), N-methylmorpholine N-oxide (NMO), ceric ammonium nitrate (CAN), Dess-Martin periodinane, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), tetrapropylammonium perruthenate (TPAP)/NMO, NCS/dimethylsulfide, NCS/dodecyl sulfide, and a combination thereof. In some cases, the oxidizing agent is oxalyl chloride.

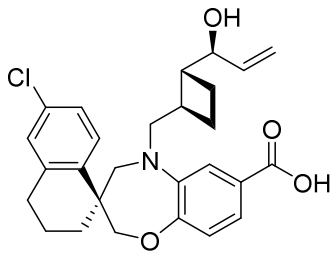
[0023] In various examples, the oxidizing is performed in the presence of a base selected from the group consisting of triethylamine, diisopropylethanolamine, *N*-methylpyrrolidine, *N*-ethylpiperidine, pyridine, 2,2,6,6-tetramethylpiperidine (TMP), pempidine, 2,6-lutidine, and a combination thereof. In some cases, the base is triethylamine.

[0024] In various examples, compound B and the oxidizing agent are present in a molar ratio of 1:1 to 1:3. In some cases, the molar ratio of compound B to the oxidizing agent is 1:1.5.

[0025] In various examples, compound B and the base are present in a molar ratio of 1:3 to 1:10. In some cases, the molar ratio of compound B to the base is 1:5.

[0026] In various examples, the oxidizing occurs in an organic solvent selected from the group consisting of dimethyl sulfoxide (DMSO), dichloromethane (DCM), dimethylformamide (DMF), THF, 2-MeTHF, acetonitrile, MTBE, 1,2-DME, toluene, DCE, CPME, and a combination thereof. In some cases, the organic solvent is DMSO.

[0027] In various examples, the oxidizing occurs at a temperature of -80 °C to -20 °C. In some cases, the oxidizing occurs at a temperature of -40 °C.

[0028] In various examples, the processes further comprise hydrolyzing compound E to form compound F:  (F), or a salt thereof.

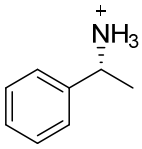
[0029] In various examples, the hydrolyzing comprises admixing a solution of compound E in an organic solvent and a hydroxide base in water to form compound F.

[0030] In various examples, the hydroxide base is selected from the group consisting of NaOH, KOH, LiOH, potassium trimethylsilanolate (TMSOK), and a combination thereof.

[0031] In various examples, compound E and the hydroxide base are present in a molar ratio of 1:1 to 1:100. In some cases, the molar ratio of compound E to the hydroxide base is 1:3.

[0032] In various examples, the organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, THF, diethyl ether, acetone, acetonitrile, 2-MeTHF, sec-butanol, and a combination thereof. In some cases, the organic solvent is ethanol.

[0033] In various examples, the hydrolyzing occurs at a temperature of 20 °C to 60 °F.

[0034] In various examples, compound F is in salt form. In some cases, the salt of compound F comprises an ammonium cation or an alkali metal cation. In some cases, the ammonium cation is selected from the group consisting of benzylammonium, methylbenzylammonium, trimethylammonium, triethylammonium, morpholinium, pyridinium, piperidinium, picolinium, dicyclohexylammonium, protonated N,N'-dibenzylethylenediamine, 2-hydroxyethylammonium, bis-(2-hydroxyethyl)ammonium, tri-(2-hydroxyethyl)ammonium, protonated procaine, dibenzylpiperidium, dehydroabietylammonium, *N*,*N*'-bisdehydroabietylammonium, protonated glucamine, protonated N-methylglucamine, protonated collidine, protonated quinine, protonated quinoline, protonated lysine, protonated arginine, protonated 1,4-diazabicyclo[2.2.2]octane (DABCO), N,N-diisopropylethylammonium, and a combination thereof. In some cases, the ammonium cation is . In some cases, the alkali metal cation is selected from the group consisting of lithium, sodium, potassium, and a combination thereof.

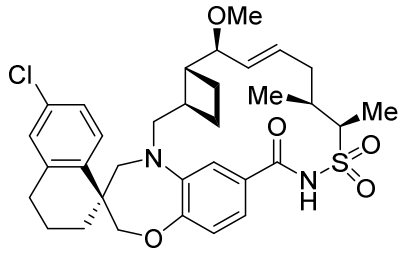
[0035] In various examples, the salt of compound F is prepared by admixing compound F, as its free acid form (compound F free acid), with an amine base or an alkali metal base in a nonpolar organic solvent to form the salt of compound F.

[0036] In various examples, compound F free acid and amine base or alkali metal base are present in a molar ratio of 1:1 to 1:2. In some cases, the molar ratio of compound F free acid to amine base or alkali metal base is 1:1.2.

[0037] In various examples, the nonpolar organic solvent is selected from the group consisting of ethyl acetate, toluene, isopropyl acetate, MTBE, and a combination thereof. In some cases, the nonpolar organic solvent is ethyl acetate.

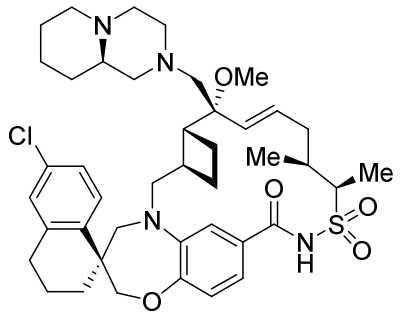
[0038] In various examples, the admixing (of compound F free acid and the amine base or alkali metal base) occurs at a temperature of 50 °C to 60 °C. In some cases, the admixing occurs in an inert atmosphere.

[0039] In various examples, the processes further comprise synthesizing compound A1 or a salt or solvate thereof using compound E:



(A1).

[0040] In various examples, the processes further comprise synthesizing compound A2 or a salt or solvate thereof using compound E:



(A2).

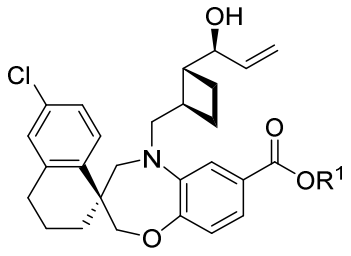
[0041] Further examples and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific examples with the understanding that the disclosure is illustrative, and is not intended to limit the disclosure to the specific examples described herein.

DETAILED DESCRIPTION

[0042] Provided herein are processes for synthesizing Mcl-1 inhibitors and corresponding vinylic alcohol intermediates. In particular, processes for synthesizing (1S,3′R,6′R,7′S,8′E,11′S,12′R)-6-chloro-7′-methoxy-11′,12′-dimethyl-3,4-dihydro-2H,15′H-spiro[naphthalene-1,22′[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.$0^{3,6}$.$0^{19,24}$]pentacosa[8,16,18,24]tetraen]-15′-one 13′,13′-dioxide (compound A1), or a salt or solvate thereof, and for synthesizing (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dinethyl-7'-((9aR)-octahydro-2H-

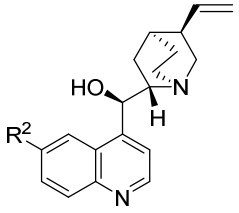
What is Claimed is:

1. A process for synthesizing compound E, or a salt or solvate thereof:

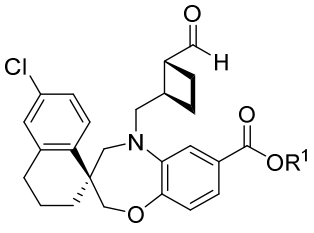


(E);

comprising admixing compound C, compound D, , and $Zn(X^3)_2$ in an organic solvent to form compound E:



(C) and



(D);

wherein

R^1 is $C_{1\text{-}6}$alkyl;

R^2 is H or $C_{1\text{-}3}$alkoxy;

X^1 is MgCl, MgBr, MgI, Li, CuLi, ZnX^2, In(I), $In(X^2)_2$;

each X^2 independently is Cl, Br, or I; and

each X^3 independently is Cl, Br, I, OTf, OTs, OAc, or acac.

2. The process of claim 1, wherein R^1 is methyl, ethyl, propyl, *n*-butyl, or *tert*-butyl; optionally

wherein R^1 is methyl, ethyl, or *tert*-butyl.

3. The process of any one of claims 1-2, wherein R^2 is H,

or wherein R^2 is $C_{1\text{-}3}$alkoxy,

or wherein R^2 is methoxy.

4. The process of any one of claims 1-3, wherein X^1 is MgCl,

or wherein X^1 is MgBr or MgI,

or wherein X^1 is Li,

or wherein X^1 is CuLi,

or wherein X^1 is In(I) or $In(X^2)_2$,

or wherein X^1 is ZnCl or ZnBr.

5. The process of any one of claims 1-4, wherein $Zn(X^3)_2$ is $ZnCl_2$,

or wherein $Zn(X^3)_2$ is $ZnBr_2$,

or wherein $Zn(X^3)_2$ is ZnI_2,

or wherein $Zn(X^3)_2$ is $Zn(OTf)_2$ or $Zn(OTs)_2$,

or wherein $Zn(X^3)_2$ is $Zn(OAc)_2$ or $Zn(acac)_2$.

6. The process of any one of claims 1-5, wherein the organic solvent is degassed prior to the admixing.

7. The process of any one of claims 1-6, wherein the organic solvent comprises an ether solvent or acetonitrile; optionally

wherein the organic solvent is selected from the group consisting of tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), diethyl ether, acetonitrile, 1,2-dimethoxyethane (1,2-DME), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and a combination thereof; optionally

wherein the organic solvent is acetonitrile.

8. The process of any one of claims 1-7, wherein the admixing is performed at a temperature of 10 °C to 35 °C.

9. The process of any one of claims 1-8, wherein the admixing comprises

(a) admixing compound C and $Zn(X^3)_2$ in the organic solvent to form a suspension;

(b) adding  to the suspension to form a solution; and

(c) adding compound D to the solution to form compound E.

10. The process of claim 9, wherein the suspension of step (a) is cooled to a temperature of -15 °C to -5 °C prior to adding ; optionally

wherein  is added to the suspension as a solution in an ether solvent; optionally

wherein the ether solvent is THF; optionally

wherein  is added to the suspension at a temperature of -10 °C to 0 °C.

11. The process of any one of claims 9-10, wherein the solution of step (b) is brought to a temperature of 10 °C to 35 °C prior to adding compound D; optionally

wherein compound D is added as a solution in an organic solvent selected from the group consisting of THF, 2-MeTHF, diethyl ether, acetonitrile, 1,2-DME, MTBE, CPME, and a combination thereof; optionally

wherein the organic solvent comprises acetonitrile.

12. The process of any one of claims 1-11, wherein compound D and  are present in a molar ratio of 1:2.5 to 1:4.5,

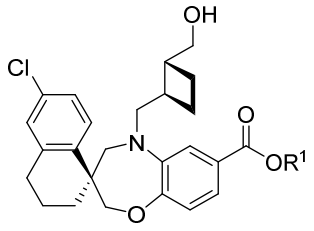
or wherein the molar ratio of compound D to  is 1:3.2.

13. The process of any one of claims 1-12, wherein compound D and $Zn(X^3)_2$ are present in a molar ratio of 1:2.5 to 1:4.0,

or wherein the molar ratio of compound D to $Zn(X^3)_2$ is 1:3.1.

14. The process of any one of claims 1-13, wherein compound D and compound C are present in a molar ratio of 1:1 to 1:2,

or wherein the molar ratio of compound D to compound C is 1:1.4.

15. The process of any one of claims 1-14, wherein compound D is prepared by oxidizing compound B:  (B) in the presence of an oxidizing agent and an organic solvent.

16. The process of claim 15, wherein the oxidizing occurs under an inert atmosphere; optionally

wherein compound B is provided as a solution in an organic solvent selected from the group consisting of dimethyl sulfoxide (DMSO), dichloromethane (DCM), dimethylformamide (DMF), THF, 2-MeTHF, acetonitrile toluene, 1,2-DME, MTBE, 1,2-dichloroethane (DCE), chloroform, and a combination thereof; optionally

wherein the organic solvent is DCM.

17. The process of any one of claims 15-16, wherein the oxidizing agent is selected from the group consisting of oxalyl chloride, bleach, SO_3/pyridine, iodobenzenediacetate, trifluoroacetic anhydride, N-chlorosuccinimide (NCS), 2-iodooxybenzoic acid (IBX), N-methylmorpholine N-oxide (NMO), ceric ammonium nitrate (CAN), Dess-Martin periodinane, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), tetrapropylammonium perruthenate (TPAP)/NMO, NCS/dimethylsulfide, NCS/dodecyl sulfide, and a combination thereof; optionally wherein the oxidizing agent is oxalyl chloride.

18. The process of any one of claims 15-17, wherein the oxidizing is performed in the presence of a base selected from the group consisting of triethylamine, diisopropylethanolamine, *N*-methylpyrrolidine, *N*-ethylpiperidine, pyridine, 2,2,6,6-tetramethylpiperidine (TMP), pempidine, 2,6-lutidine, and a combination thereof; optionally wherein the base is triethylamine.

19. The process of any one of claims 15-18, wherein compound B and the oxidizing agent are present in a molar ratio of 1:1 to 1:3,

or wherein the molar ratio of compound B to the oxidizing agent is 1:1.5.

20. The process of any one of claims 18-19, wherein compound B and the base are present in a molar ratio of 1:3 to 1:10,

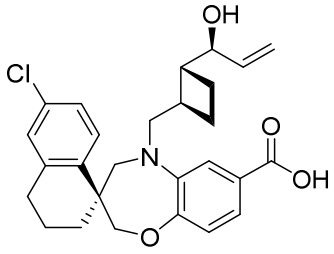
or wherein the molar ratio of compound B to the base is 1:5.

21. The process of any one of claims 15-20, wherein the oxidizing occurs in an organic solvent selected from the group consisting of dimethyl sulfoxide (DMSO), dichloromethane (DCM), dimethylformamide (DMF), THF, 2-MeTHF, acetonitrile, MTBE, 1,2-DME, toluene, DCE, CPME, and a combination thereof; optionally

wherein the organic solvent is DMSO.

22. The process of any one of claims 15-21, wherein the oxidizing occurs at a temperature of -80 °C to -20 °C; optionally

wherein the oxidizing occurs at a temperature of -40 °C.

23. The process of any one of claims 1-22, further comprising hydrolyzing compound E to form compound F:  (F), or a salt thereof.

24. The process of claim 23, wherein the hydrolyzing comprises:

admixing a solution of compound E in an organic solvent and a hydroxide base in water to form compound F; optionally

wherein the hydroxide base is selected from the group consisting of NaOH, KOH, LiOH, potassium trimethylsilanolate (TMSOK), and a combination thereof; optionally

wherein compound E and the hydroxide base are present in a molar ratio of 1:1 to 1:100, or wherein the molar ratio of compound E to the hydroxide base is 1:3.

25. The process of claim 24, wherein the organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, THF, diethyl ether, acetone, acetonitrile, 2-MeTHF, sec-butanol, and a combination thereof; optionally

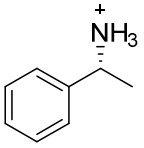
wherein the organic solvent is ethanol.

26. The process of any one of claims 24-25, wherein the hydrolyzing occurs at a temperature of 20 °C to 60 °F.

27. The process of any one of claims 23-26, wherein compound F is in salt form.

28. The process of claim 27, wherein the salt of compound F comprises an ammonium cation or an alkali metal cation; optionally

wherein the ammonium cation is selected from the group consisting of benzylammonium, methylbenzylammonium, trimethylammonium, triethylammonium, morpholinium, pyridinium, piperidinium, picolinium, dicyclohexylammonium, protonated N,N'-dibenzylethylenediamine, 2-hydroxyethylammonium, bis-(2-hydroxyethyl)ammonium, tri-(2-hydroxyethyl)ammonium, protonated procaine, dibenzylpiperidium, dehydroabietylammonium, *N,N'*-bisdehydroabietylammonium, protonated glucamine, protonated N-methylglucamine, protonated collidine, protonated quinine, protonated quinoline, protonated lysine, protonated arginine, protonated 1,4-diazabicyclo[2.2.2]octane (DABCO), N,N-diisopropylethylammonium, and a combination thereof,

or wherein the ammonium cation is .

29. The process of claim 28, wherein the alkali metal cation is selected from the group consisting of lithium, sodium, potassium, and a combination thereof.

30. The process of any one of claims 28-30, wherein the salt of compound F is prepared by admixing compound F, as its free acid form (compound F free acid), with an amine base or an alkali metal base in a nonpolar organic solvent to form the salt of compound F; optionally wherein compound F free acid and amine base or alkali metal base are present in a molar ratio of 1:1 to 1:2,

or wherein the molar ratio of compound F free acid to amine base or alkali metal base is 1:1.2.

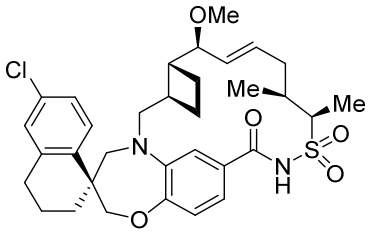
31. The process of claim 31, wherein the nonpolar organic solvent is selected from the group consisting of ethyl acetate, toluene, isopropyl acetate, MTBE, and a combination thereof; optionally

wherein the nonpolar organic solvent is ethyl acetate.

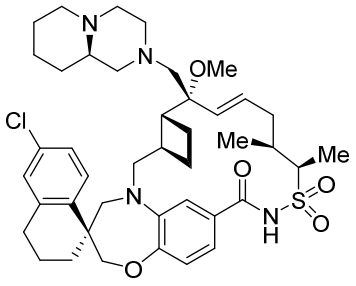
32. The process of any one of claims 31-32, wherein the admixing occurs at a temperature of 50 °C to 60 °C.

33. The process of any one of claims 27-33, wherein the admixing occurs in an inert atmosphere.

34. The process of any one of claims 1-24, further comprising synthesizing compound A1 or a salt or solvate thereof using compound E:


(A1),

or further comprising synthesizing compound A2 or a salt or solvate thereof using compound E:


(A2).