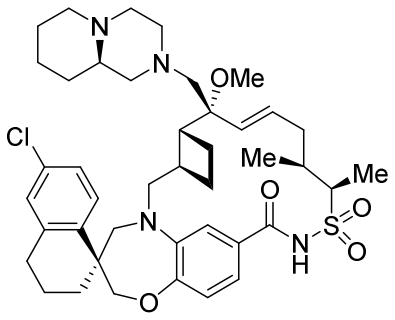


(A2).

[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.

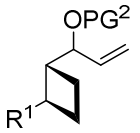
[0006] Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering 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

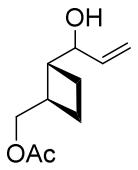
[0008a] In one aspect, provided herein is a process for synthesizing compound F or a salt thereof:

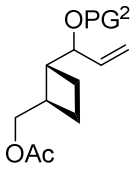


(F);

wherein OPG^2 is a secondary alcohol protecting group and R^1 is a protected aldehyde; comprising:

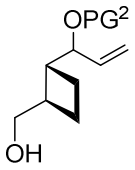
(a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



(B) and 

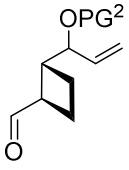
(C);

(b) removing compound C's acetyl group to form a primary alcohol of compound D, or a salt thereof:



(D);

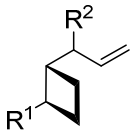
(c) oxidizing the primary alcohol of compound D, or salt thereof, to form an aldehyde of compound E, or a salt thereof:



(E); and

(d) protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof.

[0008b] In another aspect, provided herein is a compound having the structure of Formula (I):



(I),

wherein

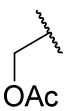
R^1 is 

, 

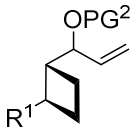
, or a protected aldehyde;

R^2 is OH or OPG^2; and

OPG^2 is a secondary alcohol protecting group,

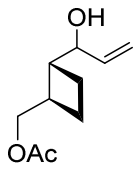
with the proviso that if R^2 is OH, then R^1 is 

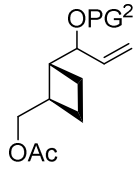
[0009] Provided herein are processes for synthesizing compound F or a salt thereof:



(F);

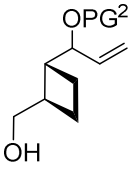
wherein OPG^2 is a secondary alcohol protecting group and R^1 is a protected aldehyde; comprising (a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



(B) and


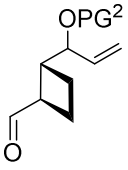
(C);

(b) removing compound C's acetyl group to form a primary alcohol of compound D, or a salt thereof:



(D);

(c) oxidizing the primary alcohol of compound D, or salt thereof, to form an aldehyde of compound E, or a salt thereof:



(E); and

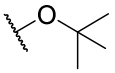
(d) protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof.

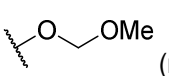
[0010] In various examples, OPG^2 comprises an acyl protecting group, an ether protecting group, acetal or ketal protecting group, a sulfonyl protecting group, and a silyl ether protecting group. In some cases, the acyl protecting group is selected from the group consisting of acetyl, pivaloyl, benzoyl, 4-bromobenzoyl, 4-chlorobenzoyl, 4-iodobenzoyl, 4-fluorobenzoyl, 4-nitrobenzoyl, 4-phenylbenzoyl, 1-naphthoyl, 2-napthoyl, 4-methoxybenzoyl, and isobutyryl. In some cases, the acyl protecting group is 4-bromobenzoyl.

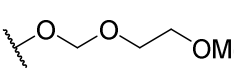
[0011] In various examples, the alcohol protecting group reagent of step (a) is an acyl chloride or an acyl anhydride.

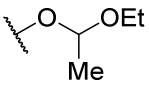
[0012] In various examples, compound B and the alcohol protecting group reagent are present in a molar ratio of 1:1 to 1:2. In some cases, the molar ratio of compound B to alcohol protecting group reagent is 1:1.3.

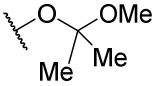
[0013] In various examples, OPG^2 is selected from the group consisting of 

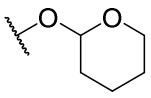
(methoxy),


(tert-butyl ether),


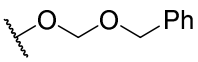
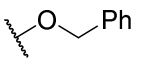
(methoxymethyl acetal, MOM),


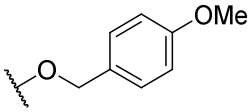
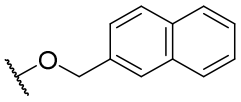
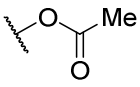
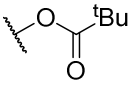
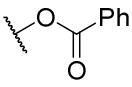
(2-methoxyethoxymethyl ether, MEM),


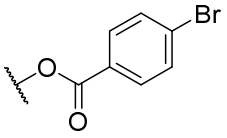
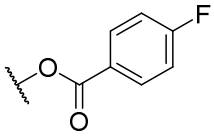
(ethoxyethyl acetal, EE),


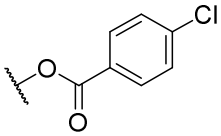
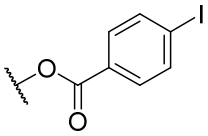
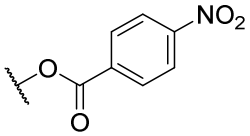
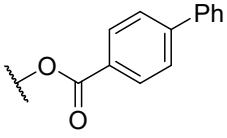
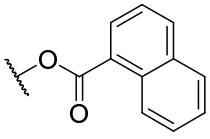
(methoxypropyl acetal, MOP),


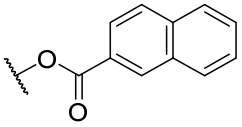
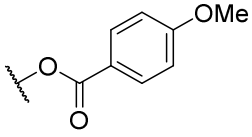
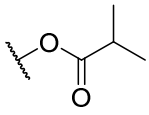
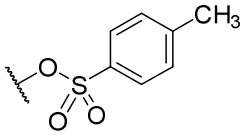
(tetrahydropyranyl acetal, THP),

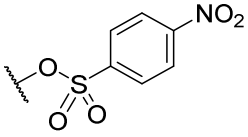
 (benzyloxymethyl acetal, BOM),  (benzyl ether, Bn),

 (4-methoxybenzyl ether, PMB),  (2-naphthylmethyl ether, Nap),  (acetyl, Ac),  pivaloyl (Piv),  (benzoyl, Bz),

 (4-bromobenzoyl, Br-Bz),  (4-fluorobenzoyl),

 (4-chlorobenzoyl),  (4-iodobenzoyl),  (4-nitrobenzoyl),  (4-phenylbenzoyl),  (1-naphthoyl ester),

 (2-naphthoyl ester),  (4-methoxybenzoyl),  (isobutyryl), OSO_2Me (mesyl),  (4-toluenesulfonyl, tosyl),

 (4-nitrobenzenesulfonyl, nosyl), and OSO_2CF_3 (triflyl). In various examples, the silyl ether protecting group is selected from the group consisting of $OSiEt_3$ (triethylsilyl ether, TES), $OSi(^iPr)_3$ (triisopropylsilyl ether, TIPS), $OSiMe_3$ (trimethylsilyl ether, TMS), $OSiMe_2{}^t$Bu (*tert*-butyldimethylsilyl ether, TBS), and $OSiPh_2{}^t$Bu (*tert*-butyldiphenylsilyl ether TBDPS).

[0014] In various examples, step (a) comprises admixing compound B, or salt thereof, the alcohol protecting group reagent, and a nucleophilic catalyst. In various examples, the nucleophilic catalyst comprises pyridine, 4-dimethylaminopyridine, or a combination thereof. In various examples, compound B and the nucleophilic catalyst are present in a molar ratio of 1:1 to 1:5. In some cases, the molar ratio of compound B to the nucleophilic catalyst is 1:2.

[0015] In various examples, step (a) occurs in an organic solvent selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, acetonitrile,

dimethylformamide (DMF), methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate (IPAc), ethyl acetate, and a combination thereof. In some cases, the organic solvent is selected from the group consisting of toluene, benzene, xylene, tetrahydrofuran (THF), tetrahydropyran, diethyl ether, dibutyl ether, diisopropyl ether, dimethoxymethane, 1,2-dimethoxyethane, 1,4-dixoane, dichloromethane (DCM), carbon tetrachloride, chloroform, 1,2-dichloroethane, 2-methyltetrahydrofuran (2-MeTHF), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and a combination thereof. In some cases, the organic solvent is toluene, THF, DCM, or a combination thereof.

[0016] In various examples, step (a) occurs at a temperature of 20 °C to 100 °C. In some cases, step (a) occurs at a temperature of 60 °C.

[0017] In various examples, removing the acetyl protecting group in step (b) comprises admixing compound C, or salt thereof, with a deprotecting agent.

[0018] In various examples, the deprotecting agent comprises acetyl chloride, an enzyme, an acid, a base, a metal hydride, or a combination thereof.

[0019] In various examples, the deprotecting agent comprises acetyl chloride and an alcohol. In various examples, the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, and a combination thereof. In some cases, the alcohol is methanol. In various examples, the deprotecting agent is magnesium methoxide. In various examples, the deprotecting agent is an enzyme selected from the group consisting of an ester hydrolase, a lipase, and a combination thereof. In various examples, the deprotecting agent is an acid selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and a combination thereof. In various examples, the deprotecting agent is zirconium hydride.

[0020] In various examples, compound C and the deprotecting agent are present in a molar ratio of 1:0.2 to 1:2. In some cases, the molar ratio of compound C to the deprotecting agent is 1:0.5.

[0021] In various examples, step (b) occurs at a temperature of -15 °C to 25 °C. In some cases, step (b) occurs at a temperature of 10 °C.

[0022] In various examples, oxidizing of step (c) comprises admixing compound D, or salt or solvate thereof, and an oxidizing agent, with an organic solvent, and optionally water.

[0023] In various examples, the oxidizing agent is selected from the group consisting of oxalyl chloride/DMSO, bleach, SO_3/pyridine, iodobenzenediacetate, and any combination thereof. In some cases, the oxidizing agent is iodobenzenediacetate.

[0024] In various examples, compound D and the oxidizing agent are present in a molar ratio of 1:1.1 to 1:2. In some cases, the molar ratio of compound D to the oxidizing agent is 1:1.1.

[0025] In various examples, the oxidizing further comprises admixing compound D and the oxidizing reagent with an oxidation catalyst. In various examples, the oxidation catalyst is

selected from the group consisting of 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), tetrapropylammonium perruthenate (TPAP)/N-methylmorpholine-N-oxide (NMO), Cu/9-azabicyclo[3.3.1]nonane N-oxyl (ABNO), Fe/ABNO, and a combination thereof. In some cases, the oxidation catalyst is TEMPO.

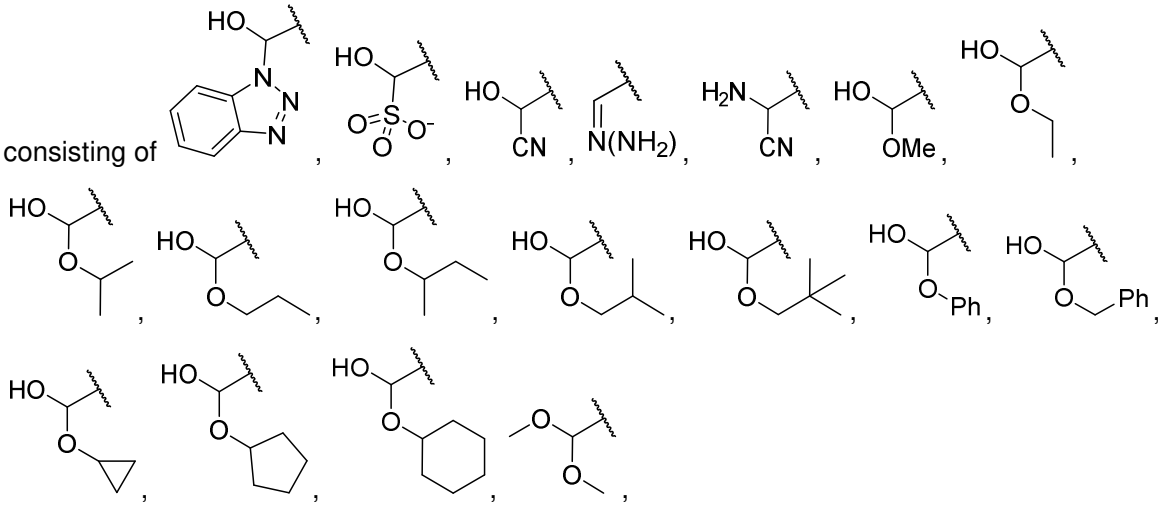
[0026] In various examples, compound D and the oxidation catalyst are present in a molar ratio of 1:0.01 to 1:1. In some cases, the molar ratio of compound D to the oxidation catalyst is 1:0.04.

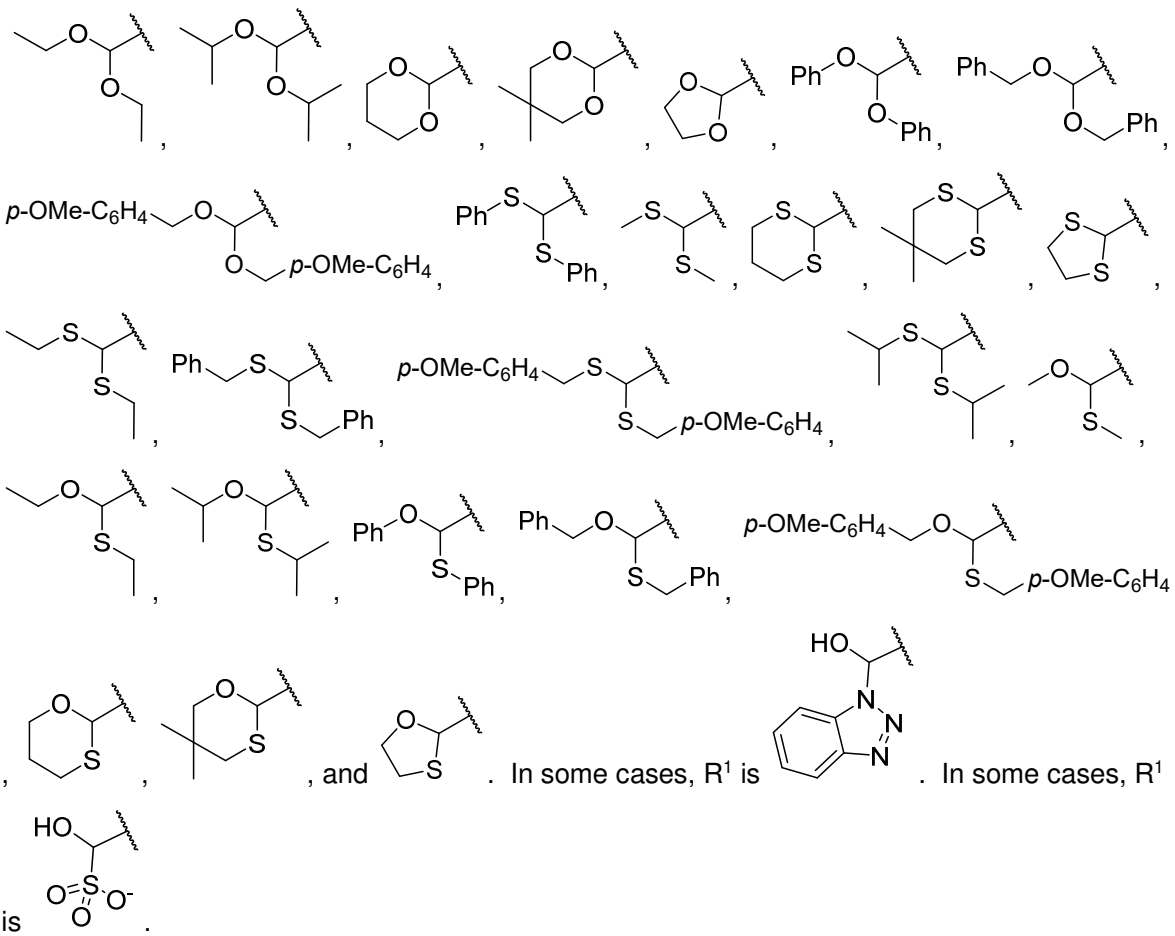
[0027] In various examples, wherein the organic solvent (of step (c)) is selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate, ethyl acetate, and a combination thereof. In some cases, the organic solvent is selected from the group consisting of toluene, benzene, xylene, tetrahydrofuran (THF), tetrahydropyran, diethyl ether, dibutyl ether, diisopropyl ether, dimethoxymethane, 1,2-dimethoxyethane, 1,4-dixoane, dichloromethane (DCM), carbon tetrachloride, chloroform, 1,2-dichloroethane, 2-methyltetrahydrofuran (2-MeTHF), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and a combination thereof. In some cases, the organic solvent is toluene.

[0028] In various examples, step (c) occurs in the presence of water. In various examples, compound D and water are present in a molar ratio of 1:1 to 1:2. In some cases, the molar ratio of compound D to water is 1:1.1.

[0029] In various examples, step (c) occurs at a temperature of 5 °C to 45 °C. In some cases, step (c) occurs at a temperature of 20 °C.

[0030] In various examples, protecting the aldehyde of compound E, or salt thereof, in step (d) comprises admixing compound E, or salt thereof, and an aldehyde protecting group reagent with a solvent.

[0031] In various examples, the aldehyde protecting group reagent is selected from the group consisting of benzotriazole, a bisulfite salt, a cyanide salt, hydrogen cyanide, a thiol or dithiol, an alcohol or diol, hydrazine, ammonia, and a combination thereof. In various examples, R^1 is selected from the group consisting of 



[0032] In various examples, compound E and the aldehyde protecting group reagent are present in a molar ratio of 1:1 to 1:1.5. In some cases, the molar ratio of compound E to the aldehyde protecting group reagent is 1:1.

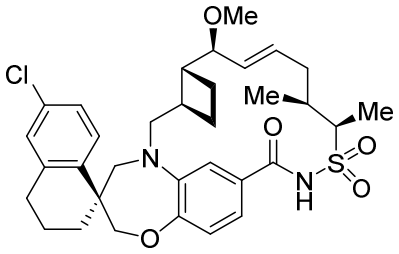
[0033] In various examples, the solvent is selected from the group consisting of toluene, heptane, acetonitrile, water, methyl tert-butyl ether (MTBE), and a combination thereof. In various examples, the solvent of step (d) is selected from the group consisting of toluene/heptane, acetonitrile/water, and methyl tert-butyl ether (MTBE). In some cases, the solvent is toluene/heptane. In some cases, toluene and heptane are present in the solvent as a volume ratio of 4:7.

[0034] In various examples, step (d) occurs at a temperature of 20 °C to 50 °C.

[0035] In various examples, the processes further comprise (e) crystallizing compound F.

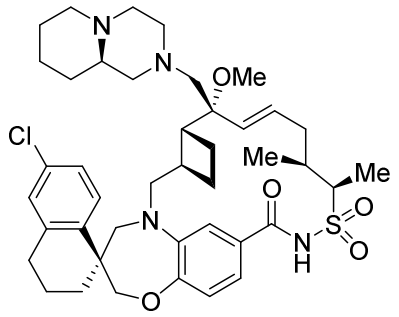
[0036] In various examples, crystallizing comprises admixing compound F with a crystallizing solvent to form crystalline compound F. In various examples, the crystallizing solvent comprises heptane, toluene, methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), methyl isobutyl ketone (MIBK), acetonitrile, isopropyl alcohol, isopropyl acetate, water, or a combination thereof.

[0037] In various examples, the processes further comprise synthesizing compound A1, or a salt or solvate thereof, using compound F:



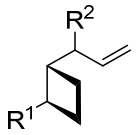
(A1).

[0038] In various examples, the processes further comprise synthesizing compound A2, or a salt of solvate thereof, using compound F:



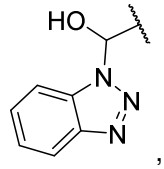
(A2).

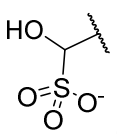
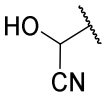
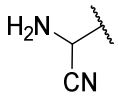
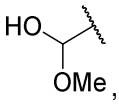
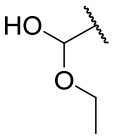
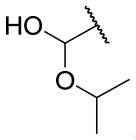
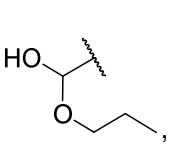
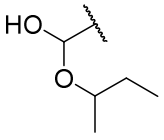
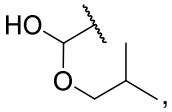
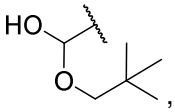
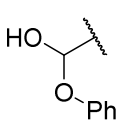
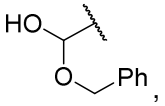
[0039] Further provided herein are compounds having the structure of Formula (I):

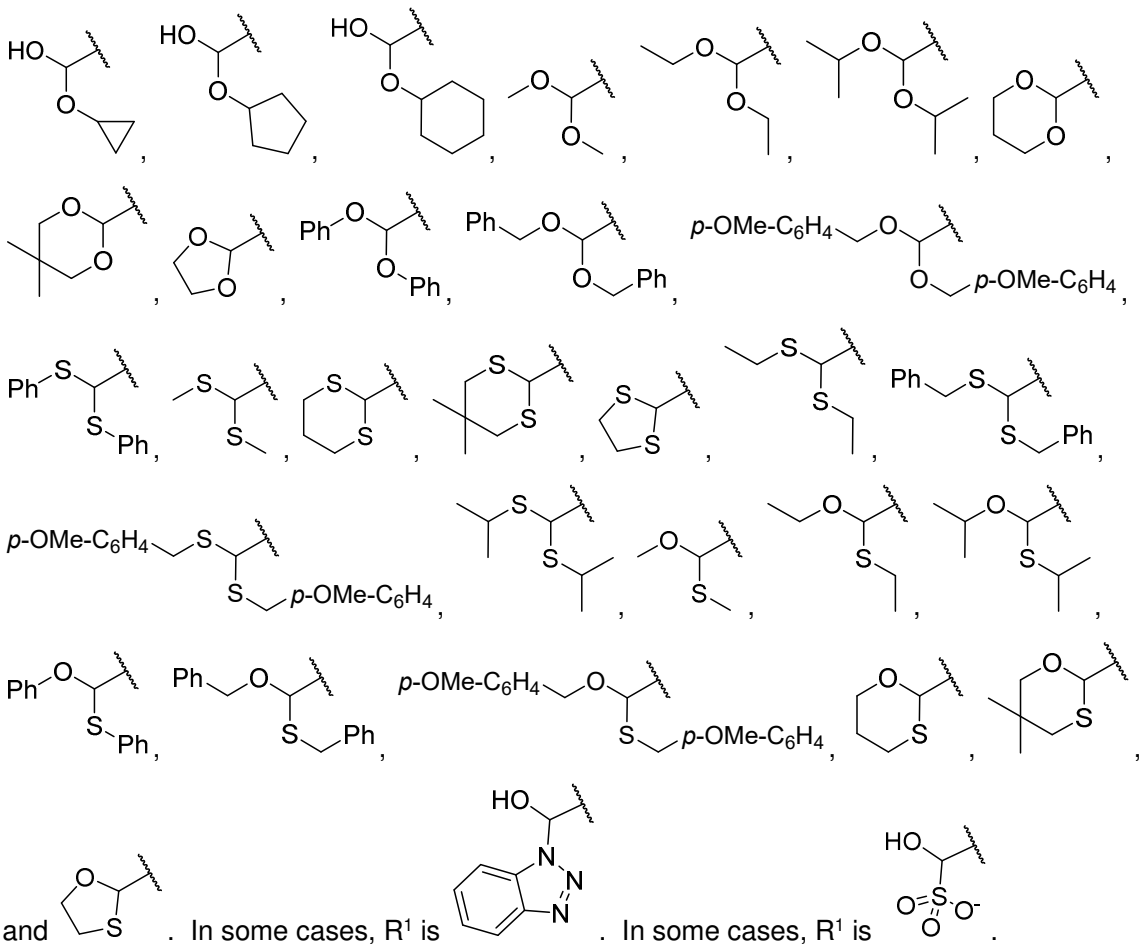


(I),

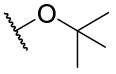
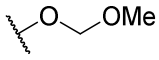
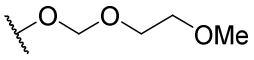
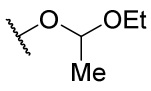
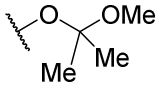
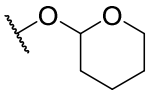
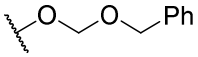
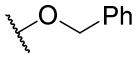
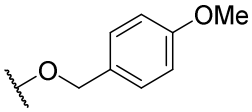
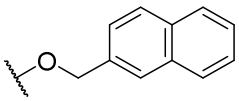
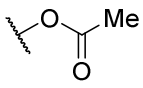
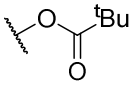
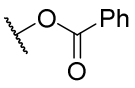
wherein R^1 is , , or a protected aldehyde; R^2 is OH or OPG^2; and OPG^2 is a secondary alcohol protecting group, with the proviso that if R^2 is OH, then R^1 is .

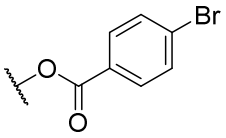
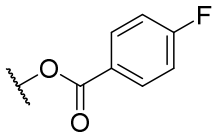
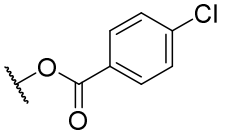
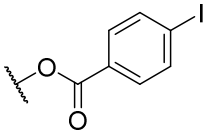
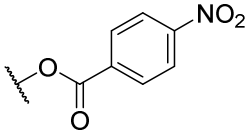
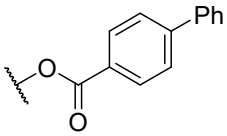
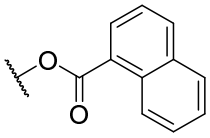
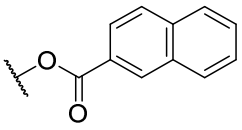
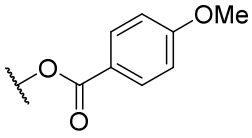
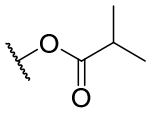
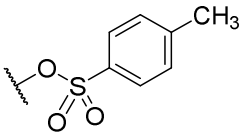
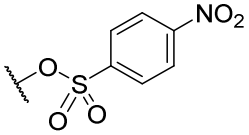
[0040] In various examples, R^1 is . In various examples, R^1 is . In various examples, R^1 is a protected aldehyde. In some cases, R^1 is selected from the group consisting of ,

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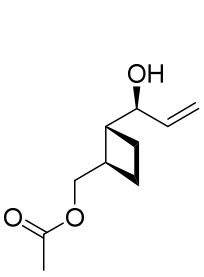
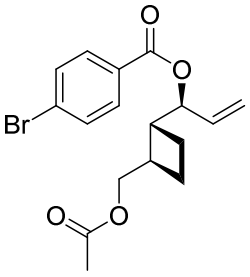
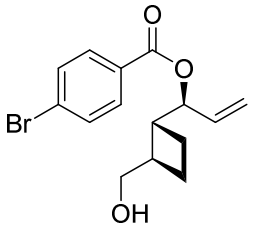
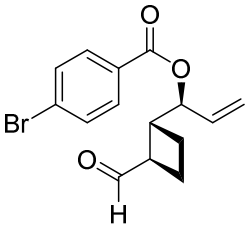
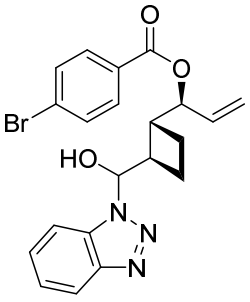
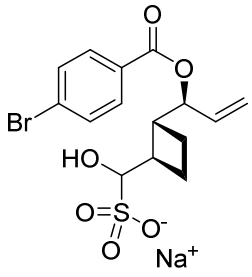


and . In some cases, R^1 is . In some cases, R^1 is .

[0041] In various examples, R^2 is OH. In various examples, R^2 is OPG^2. In various examples, OPG^2 selected from the group consisting of an ether, an acetal or ketal, an acyl, a sulfonyl, and a silyl ether. In some cases, OPG^2 is selected from the group consisting of  (methoxy),  (tert-butyl ether),  (methoxymethyl acetal, MOM),  (2-methoxyethoxymethyl ether, MEM),  (ethoxyethyl acetal, EE),  (methoxypropyl acetal, MOP),  (tetrahydropyranyl acetal, THP),  (benzyloxymethyl acetal, BOM),  (benzyl ether, Bn),  (4-methoxybenzyl ether, PMB),  (2-naphthylmethyl ether, Nap),  (acetyl, Ac),  pivaloyl (Piv),  (benzoyl, Bz),

 (4-bromobenzoyl, Br-Bz),  (4-fluorobenzoyl),  (4-chlorobenzoyl),  (4-iodobenzoyl),  (4-nitrobenzoyl),  (4-phenylbenzoyl),  (1-naphthoyl ester),  (2-naphthoyl ester),  (4-methoxybenzoyl),  (isobutyryl), $OSiEt_3$ (triethylsilyl ether, TES), $OSi(^{i}Pr)_3$ (triisopropylsilyl ether, TIPS), $OSiMe_3$ (trimethylsilyl ether, TMS), $OSiMe_2{}^{t}Bu$ (*tert*-butyldimethylsilyl ether, TBS), $OSiPh_2{}^{t}Bu$ (*tert*-butyldiphenylsilyl ether TBDPS), OSO_2Me (mesyl),  (4-toluenesulfonyl, tosyl),  (4-nitrobenzenesulfonyl, nosyl), and OSO_2CF_3 (triflyl). In some cases, OPG^2 is 4-bromobenzoyl.

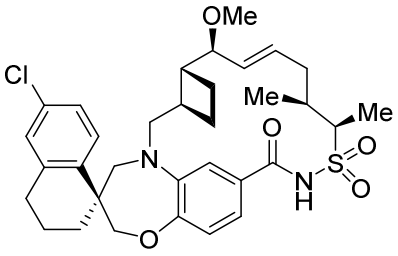
[0042] In various examples, the compound is selected from the group consisting of:

, , , , , and .

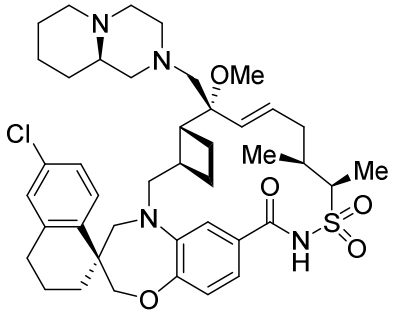
[0043] Further examples and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific examples with the understanding that the disclosure is illustrative, and is not intended to limit the disclosure to the specific examples described herein.

DETAILED DESCRIPTION

[0044] Provided herein are processes for synthesizing Mcl-1 inhibitors and corresponding vinyl cyclobutyl 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-pyrido[1,2-a]pyrazin-2-ylmethyl)-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 A2), or a salt of solvate thereof are provided:

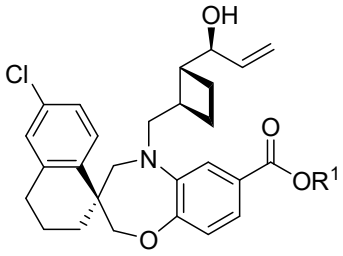


(A1) and



(A2).

[0045] U.S. Patent No. 9,562,061, which is incorporated herein by reference in its entirety, discloses compound A1, or a salt or solvate thereof, as an Mcl-1 inhibitor and provides a process for preparing it. The disclosure of compound A1 salts and solvates from U.S. Patent No. 9,562,061 is incorporated by reference in its entirety. This patent also discloses a process of synthesizing a vinylic alcohol intermediate compound shown below used in the synthesis of compound A1.

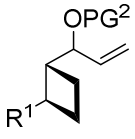


vinylic alcohol intermediate of '061 patent

[0046] U.S. Patent No. 10,300,075, which is incorporated herein by reference in its entirety, discloses compound A2, or a salt or solvate thereof, as an Mcl-1 inhibitor and provides a

What is Claimed is:

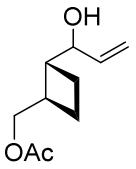
1. A process for synthesizing compound F or a salt thereof:

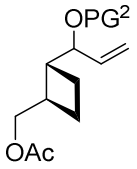


(F);

wherein OPG^2 is a secondary alcohol protecting group and R^1 is a protected aldehyde; comprising:

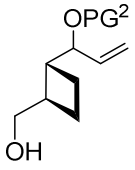
(a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



(B) and


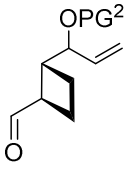
(C);

(b) removing compound C's acetyl group to form a primary alcohol of compound D, or a salt thereof:



(D);

(c) oxidizing the primary alcohol of compound D, or salt thereof, to form an aldehyde of compound E, or a salt thereof:



(E); and

(d) protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof.

2. The process of claim 1, wherein OPG^2 comprises an acyl protecting group, an ether protecting group, acetal or ketal protecting group, a sulfonyl protecting group, and a silyl ether protecting group; optionally

wherein the acyl protecting group is selected from the group consisting of acetyl, pivaloyl, benzoyl, 4-bromobenzoyl, 4-fluorobenzoyl, 4-chlorobenzoyl, 4-iodobenzoyl, 4-nitrobenzoyl, 4-phenylbenzoyl, 1-naphthoyl, 2-napthoyl, 4-methoxybenzoyl, and isobutyryl

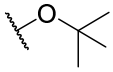
optionally wherein the acyl protecting group is 4-bromobenzoyl.

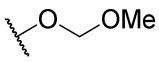
3. The process of claim 2, wherein the alcohol protecting group reagent of step (a) is an acyl chloride or an acyl anhydride.

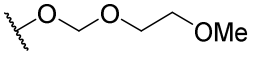
4. The process of any one of claims 1-3, wherein compound B and the alcohol protecting group reagent are present in a molar ratio of 1:1 to 1:2

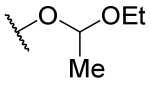
, or wherein the molar ratio of compound B to alcohol protecting group reagent is 1:1.3.

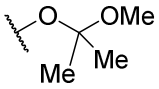
5. The process of claim 2, wherein OPG^2 is selected from the group consisting of 

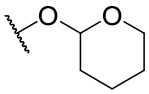
(methoxy), 

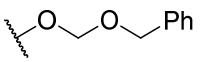
(tert-butyl ether), 

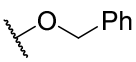
(methoxymethyl acetal, MOM), 

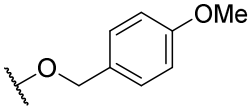
(2-methoxyethoxymethyl ether, MEM), 

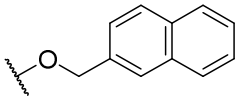
(ethoxyethyl acetal, "EE), 

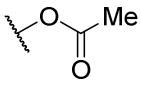
(methoxypropyl acetal, MOP), 

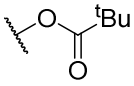
(tetrahydropyranyl acetal, "THP), 

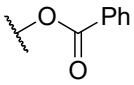
(benzyloxymethyl acetal, BOM), 

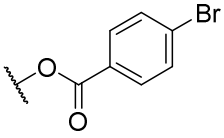
(benzyl ether, Bn), 

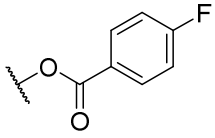
(4-methoxybenzyl ether, PMB), 

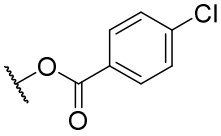
(2-naphthylmethyl ether, Nap), 

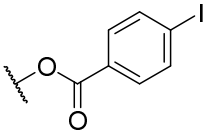
(acetyl, Ac), 

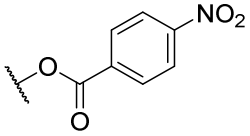
pivaloyl (Piv), 

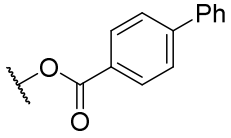
(benzoyl, Bz), 

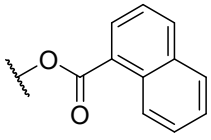
(4-bromobenzoyl, Br-Bz), 

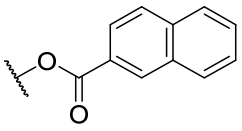
(4-fluorobenzoyl), 

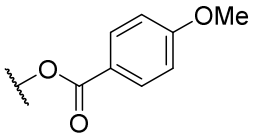
(4-chlorobenzoyl), 

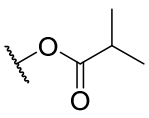
(4-iodobenzoyl), 

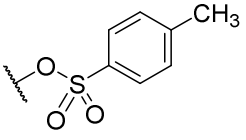
(4-nitrobenzoyl), 

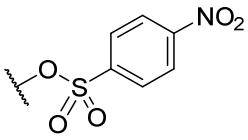
(4-phenylbenzoyl), 

(1-naphthoyl ester), 

(2-naphthoyl ester), 

(4-methoxybenzoyl), 

(isobutyryl), OSO_2Me (mesyl),  (4-toluenesulfonyl, tosyl),

 (4-nitrobenzenesulfonyl, nosyl), and OSO_2CF_3 (triflyl).

6. The process of claim 2, wherein the silyl ether protecting group is selected from the group consisting of $OSiEt_3$ (triethylsilyl ether, TES), $OSi(^iPr)_3$ (triisopropylsilyl ether, TIPS), $OSiMe_3$ (trimethylsilyl ether, TMS), $OSiMe_2tBu$ (*tert*-butyldimethylsilyl ether, TBS), and $OSiPh_2{}^tBu$ (*tert*-butyldiphenylsilyl ether TBDPS).

7. The process of any one of claims 2-6, wherein step (a) comprises admixing compound B, or salt thereof, the alcohol protecting group reagent, and a nucleophilic catalyst; optionally wherein the nucleophilic catalyst comprises pyridine, 4-dimethylaminopyridine, or a combination thereof.

8. The process of claim 7, wherein compound B and the nucleophilic catalyst are present in a molar ratio of 1:1 to 1:5,

or wherein the molar ratio of compound B to the nucleophilic catalyst is 1:2.

9. The process of any one of claims 1-8, wherein step (a) occurs in an organic solvent selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, acetonitrile, dimethylformamide (DMF), methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate (IPAc), ethyl acetate, and a combination thereof; optionally wherein the organic solvent is selected from the group consisting of toluene, benzene, xylene, tetrahydrofuran (THF), tetrahydropyran, diethyl ether, dibutyl ether, diisopropyl ether, dimethoxymethane, 1,2-dimethoxyethane, 1,4-dixoane, dichloromethane (DCM), carbon tetrachloride, chloroform, 1,2-dichloroethane, 2-methyltetrahydrofuran (2-MeTHF), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and a combination thereof;

optionally wherein the organic solvent is toluene, THF, DCM, or a combination thereof.

10. The process of any one of claims 1-9, wherein step (a) occurs at a temperature of 20 °C to 100 °C;

optionally wherein step (a) occurs at a temperature of 60 °C.

11. The process of any one of claims 1-10, wherein removing the acetyl protecting group in step (b) comprises admixing compound C, or salt thereof, with a deprotecting agent.

12. The process of claim 11, wherein the deprotecting agent comprises acetyl chloride, an enzyme, an acid, a base, a metal hydride, or a combination thereof;

optionally wherein the deprotecting agent comprises acetyl chloride and an alcohol; optionally wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, and a combination thereof;

optionally wherein the alcohol is methanol.

13. The process of claim 12, wherein the deprotecting agent is magnesium methoxide, or wherein the deprotecting agent is an enzyme selected from the group consisting of an ester hydrolase, a lipase, and a combination thereof,
or wherein the deprotecting agent is an acid selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and a combination thereof,
or wherein the deprotecting agent is zirconium hydride.

14. The process of any one of claims 11-13, wherein compound C and the deprotecting agent are present in a molar ratio of 1:0.2 to 1:2,
or wherein the molar ratio of compound C to the deprotecting agent is 1:0.5.

15. The process of any one of claims 1-14, wherein step (b) occurs at a temperature of -15 °C to 25 °C;
optionally wherein step (b) occurs at a temperature of 10 °C.

16. The process of any one of claims 1-15, wherein oxidizing of step (c) comprises admixing compound D, or salt or solvate thereof, and an oxidizing agent, with an organic solvent, and optionally water; optionally
wherein the oxidizing agent is selected from the group consisting of oxalyl chloride/DMSO, bleach, SO_3/pyridine, iodobenzenediacetate, and any combination thereof;
optionally wherein the oxidizing agent is iodobenzenediacetate.

17. The process of claim 16, wherein compound D and the oxidizing agent are present in a molar ratio of 1:1.1 to 1:2,
or wherein the molar ratio of compound D to the oxidizing agent is 1:1.1.

18. The process of any one of claims 16-17, further comprising admixing compound D and the oxidizing reagent with an oxidation catalyst; optionally
wherein the oxidation catalyst is selected from the group consisting of 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), tetrapropylammonium perruthenate (TPAP)/N-methylmorpholine-N-oxide (NMO), Cu/9-azabicyclo[3.3.1]nonane N-oxyl (ABNO), Fe/ABNO, and a combination thereof;
optionally wherein the oxidation catalyst is TEMPO.

19. The process of claim 18, wherein compound D and the oxidation catalyst are present in a molar ratio of 1:0.01 to 1:1,
or wherein the molar ratio of compound D to the oxidation catalyst is 1:0.04.

20. The process of any one of claims16-19, wherein the organic solvent is selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate, ethyl acetate, and a combination thereof; optionally
wherein the organic solvent is selected from the group consisting of toluene, benzene, xylene, tetrahydrofuran (THF), tetrahydropyran, diethyl ether, dibutyl ether, diisopropyl ether,

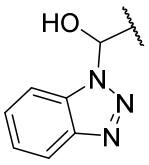
dimethoxymethane, 1,2-dimethoxyethane, 1,4-dixoane, dichloromethane (DCM), carbon tetrachloride, chloroform, 1,2-dichloroethane, 2-methyltetrahydrofuran (2-MeTHF), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and a combination thereof;
optionally wherein the organic solvent is toluene.

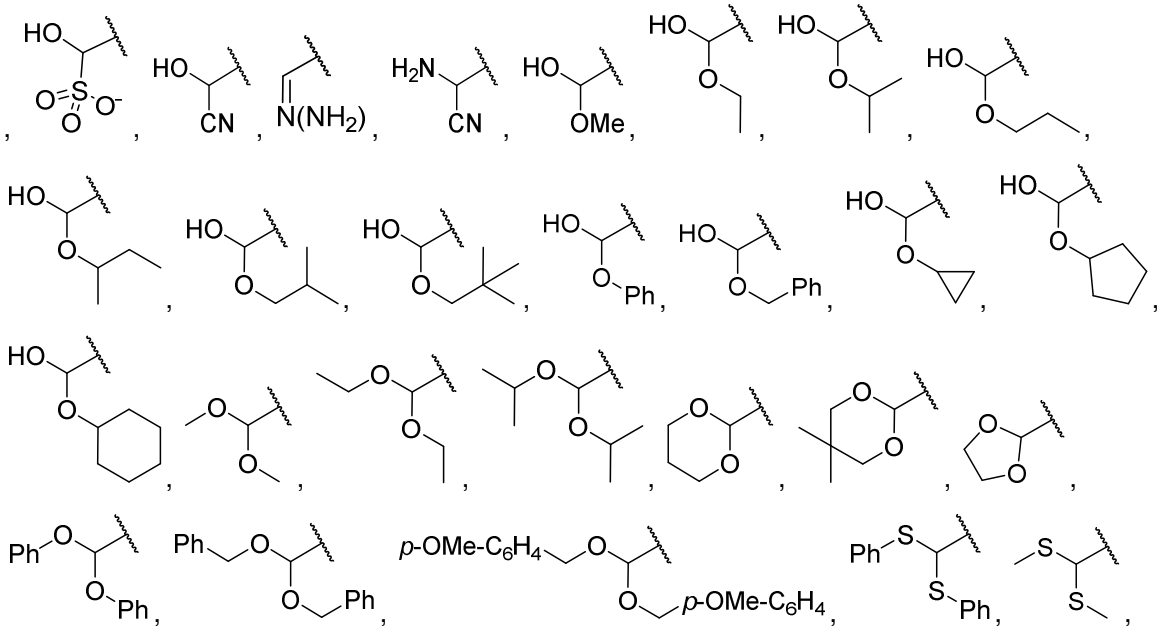
21. The process of any one of claims 16-20, wherein step (c) occurs in the presence of water.

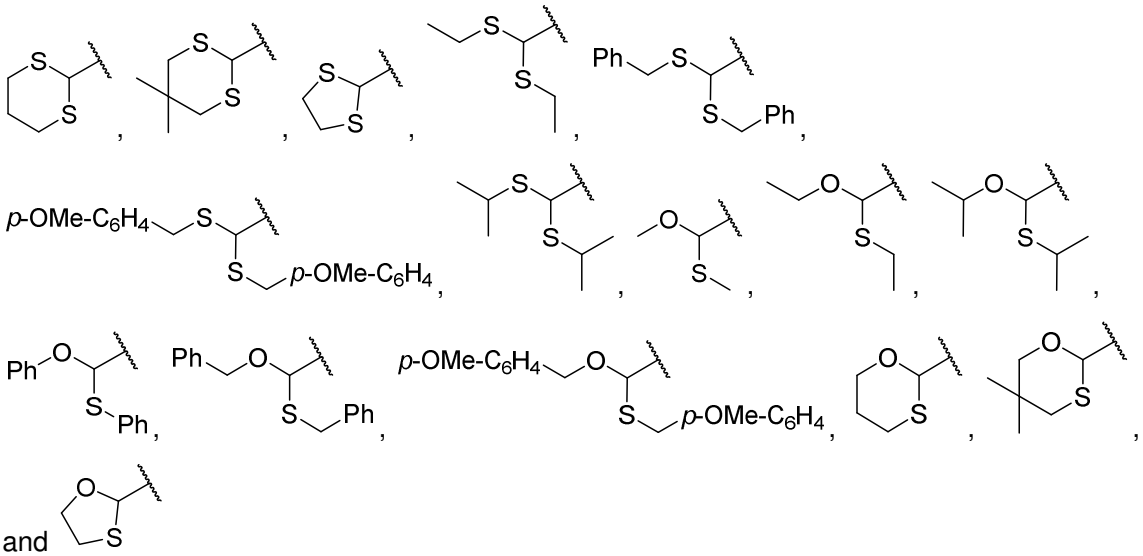
22. The process of claim 21, wherein compound D and water are present in a molar ratio of 1:1 to 1:2,
or wherein the molar ratio of compound D to water is 1:1.1.

23. The process of any one of claims 1-22, wherein step (c) occurs at a temperature of 5 °C to 45 °C;
optionally wherein step (c) occurs at a temperature of 20 °C.

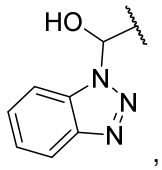
24. The process of any one of claims 1-23, wherein protecting the aldehyde of compound E, or salt thereof, in step (d) comprises admixing compound E, or salt thereof, and an aldehyde protecting group reagent with a solvent; optionally
wherein the aldehyde protecting group reagent is selected from the group consisting of benzotriazole, a bisulfite salt, a cyanide salt, hydrogen cyanide, a thiol or dithiol, an alcohol or diol, hydrazine, ammonia, and a combination thereof.

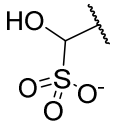
25. The process of claim 24, wherein R^1 is selected from the group consisting of 





and

; optionally wherein R^1 is ,

or wherein R^1 is .

26. The process of any one of claims 24-25, wherein compound E and the aldehyde protecting group reagent are present in a molar ratio of 1:1 to 1:1.5,

or wherein the molar ratio of compound E to the aldehyde protecting group reagent is 1:1.

27. The process of any one of claims 24-26, wherein the solvent is selected from the group consisting of toluene, heptane, acetonitrile, water, methyl tert-butyl ether (MTBE), and a combination thereof;

optionally wherein the solvent is selected from the group consisting of toluene/heptane, acetonitrile/water, and methyl tert-butyl ether (MTBE);

optionally wherein the solvent is toluene/heptane; optionally

wherein toluene and heptane are present in the solvent as a volume ratio of 4:7.

28. The process of any one of claims 1-27, wherein step (d) occurs at a temperature of 20 °C to 50 °C.

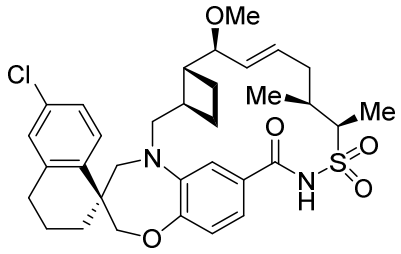
29. The process of any one of claims 1-28, further comprising:

(e) crystallizing compound F; optionally

wherein crystallizing comprises admixing compound F with a crystallizing solvent to form crystalline compound F; optionally

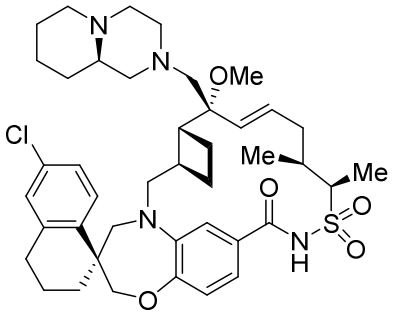
wherein the crystallizing solvent comprises heptane, toluene, methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), methyl isobutyl ketone (MIBK), acetonitrile, isopropyl alcohol, isopropyl acetate, water, or a combination thereof.

30. The process of any one of claims 1-29, further comprising synthesizing compound A1, or a salt or solvate thereof, using compound F:



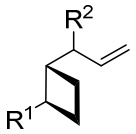
(A1),

or further comprising synthesizing compound A2, or a salt of solvate thereof, using compound F:



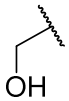
(A2).

31. A compound having the structure of Formula (I):



(I),

wherein

R^1 is 

, 

, or a protected aldehyde;

R^2 is OH or OPG^2; and

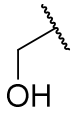
OPG^2 is a secondary alcohol protecting group,

with the proviso that if R^2 is OH, then R^1 is 

.

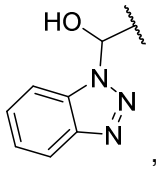
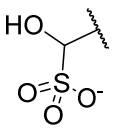
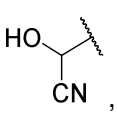
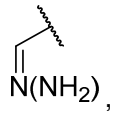
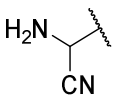
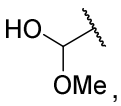
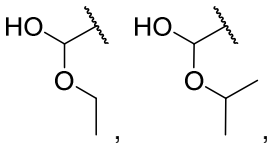
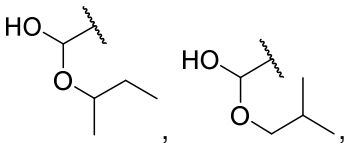
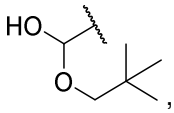
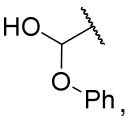
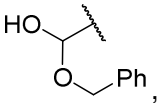
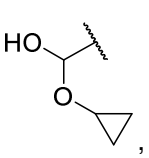
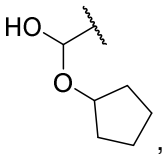
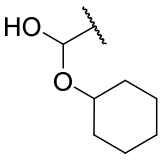
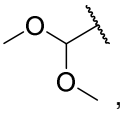
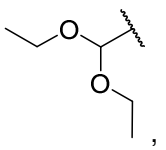
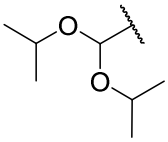
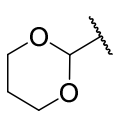
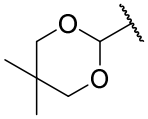
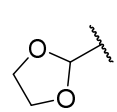
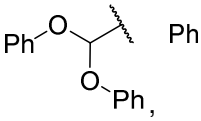
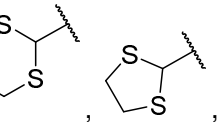
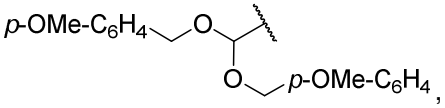
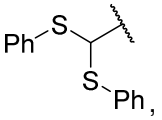
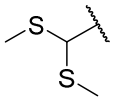
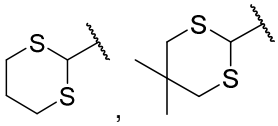
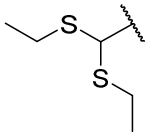
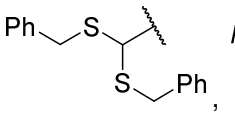
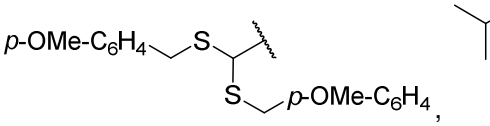
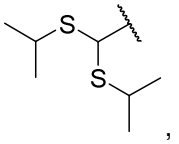
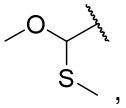
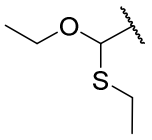
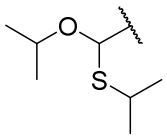
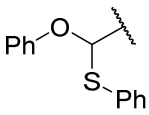
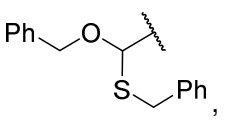
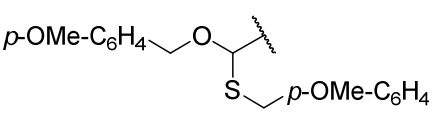
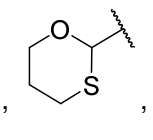
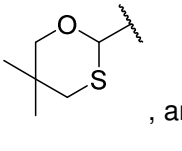
32. The compound of claim 31, wherein R^1 is 

,

or wherein R^1 is 

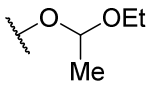
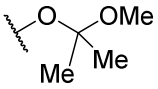
; or

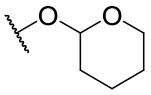
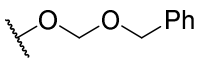
wherein R^1 is a protected aldehyde; optionally

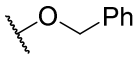
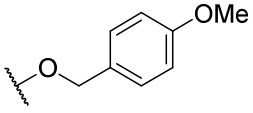
wherein R^1 is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and ; optionally wherein R^1 is , or wherein R^1 is .

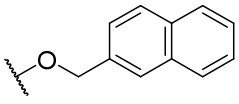
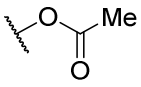
33. The compound of claim 31 or 32, wherein R^2 is OH, or wherein R^2 is OPG^2; optionally wherein OPG^2 selected from the group consisting of an ether, an acetal or ketal, an acyl, a sulfonyl, and a silyl ether;

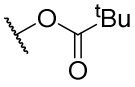
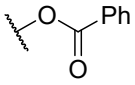
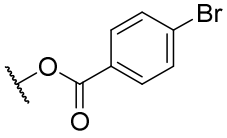
optionally wherein OPG^2 is selected from the group consisting of (methoxy), (tert-butyl ether), (methoxymethyl acetal, MOM), (2-

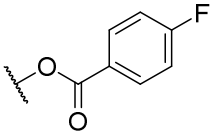
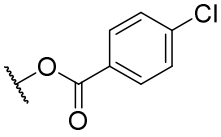
methoxyethoxymethyl ether, MEM),  (ethoxyethyl acetal, EE), 

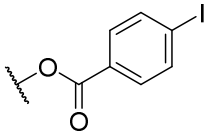
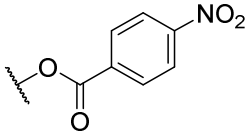
(methoxypropyl acetal, MOP),  (tetrahydropyranyl acetal, THP), 

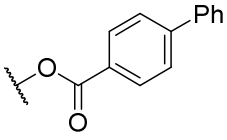
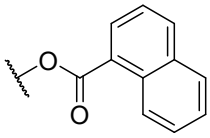
(benzyloxymethyl acetal, BOM),  (benzyl ether, Bn),  (4-

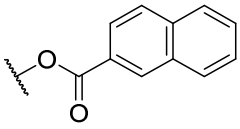
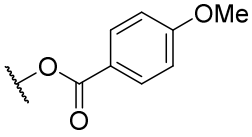
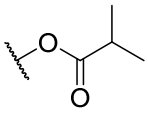
methoxybenzyl ether, PMB),  (2-naphthylmethyl ether, Nap), 

(acetyl, Ac),  pivaloyl (Piv),  (benzoyl, Bz),  (4-

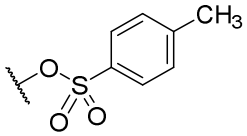
bromobenzoyl, Br-Bz),  (4-fluorobenzoyl),  (4-

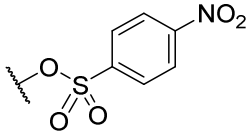
chlorobenzoyl),  (4-iodobenzoyl),  (4-nitrobenzoyl),

 (4-phenylbenzoyl),  (1-naphthoyl ester),

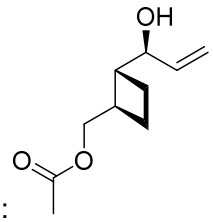
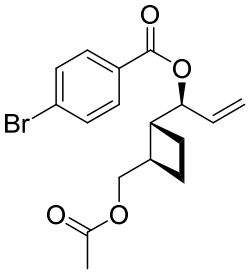
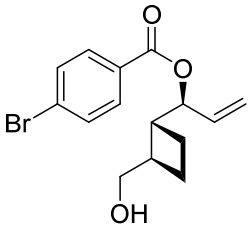
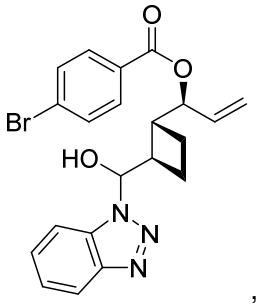
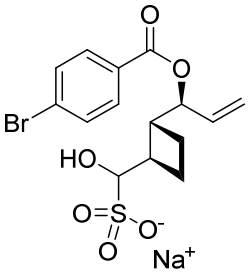
 (2-naphthoyl ester),  (4-methoxybenzoyl), 

(isobutyryl), $OSiEt_3$ (triethylsilyl ether, TES), $OSi(^iPr)_3$ (triisopropylsilyl ether, TIPS), $OSiMe_3$ (trimethylsilyl ether, TMS), $OSiMe_2tBu$ (*tert*-butyldimethylsilyl ether, TBS), $OSiPh_2{}^tBu$ (*tert*-

butyldiphenylsilyl ether TBDPS), OSO_2Me (mesyl),  (4-toluenesulfonyl,

tosyl),  (4-nitrobenzenesulfonyl, nosyl), and OSO_2CF_3 (triflyl)

; optionally wherein OPG^2 is 4-bromobenzoyl.

34. The compound of claim 31, wherein the compound is selected from the group consisting of: , , , , and .