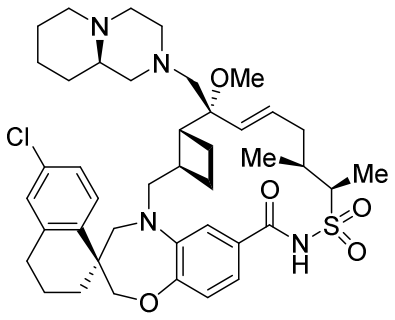


(A2).

[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.

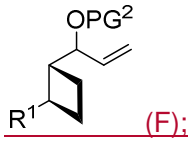
[0006] Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering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

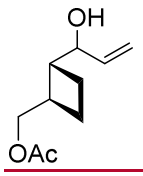
[0008a] In one aspect, provided herein is a process for synthesizing compound F or a salt thereof:

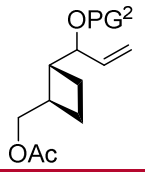


(F);

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

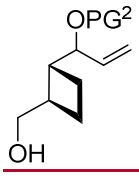
(a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



(B) and 

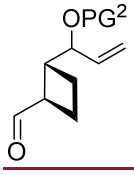
(C);

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



(D);

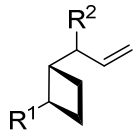
(c) oxidizing the primary alcohol of compound D, or salt thereof, to form an aldehyde of compound E, or a salt thereof:



(E); and

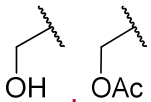
(d) protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof.

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



(I),

wherein

R^1 is 

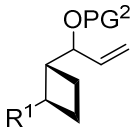
, or a protected aldehyde;

R^2 is OH or OPG^2; and

OPG^2 is a secondary alcohol protecting group,

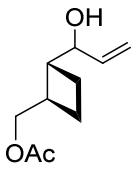
with the proviso that if R^2 is OH, then R^1 is 

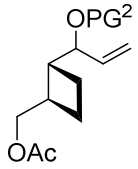
[0009] Provided herein are processes for synthesizing compound F or a salt thereof:



(F);

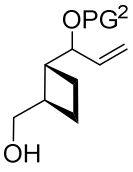
wherein OPG^2 is a secondary alcohol protecting group and R^1 is a protected aldehyde; comprising (a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



(B) and 

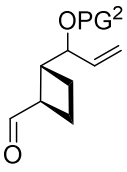
(C);

(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

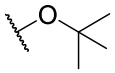
(d) protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof.

[0010] In various ~~embodiments~~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.

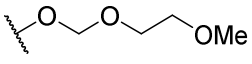
[0011] In various ~~embodiment~~examples, the alcohol protecting group reagent of step (a) is an acyl chloride or an acyl anhydride.

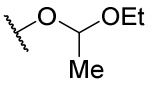
[0012] In various ~~embodiment~~examples, compound B and the alcohol protecting group reagent are present in a molar ratio of 1:1 to 1:2. In some cases, the molar ratio of compound B to alcohol protecting group reagent is 1:1.3.

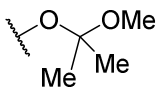
[0013] In various ~~embodiment~~examples, OPG^2 is selected from the group consisting of 

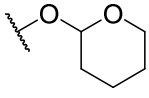
(methoxy), 

(tert-butyl ether), 

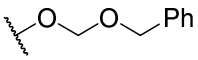
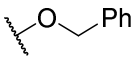
(methoxymethyl acetal, MOM), 

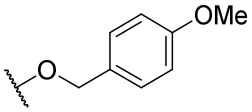
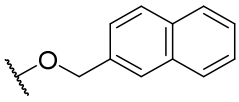
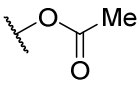
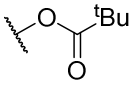
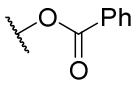
(2-methoxyethoxymethyl ether, MEM), 

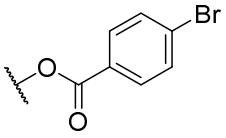
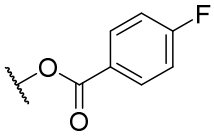
(ethoxyethyl acetal, EE), 

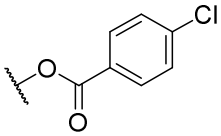
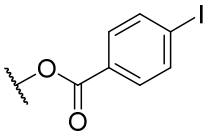
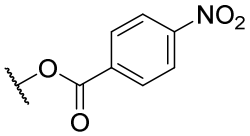
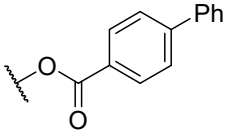
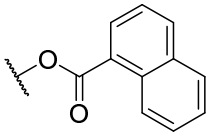
(methoxypropyl acetal, MOP), 

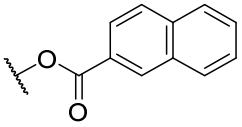
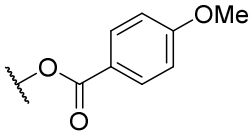
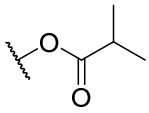
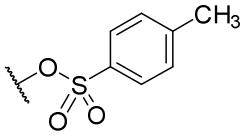
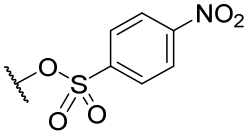
(tetrahydropyranyl acetal, THP),


(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 ~~embodiment~~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), $OSiMe_2tBu$ (*tert*-butyldimethylsilyl ether, TBS), and $OSiPh_2{}^tBu$ (*tert*-butyldiphenylsilyl ether TBDPS).

[0014] In various ~~embodiment~~examples, step (a) comprises admixing compound B, or salt thereof, the alcohol protecting group reagent, and a nucleophilic catalyst. In various ~~embodiment~~examples, the nucleophilic catalyst comprises pyridine, 4-dimethylaminopyridine, or a combination thereof. In various ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, removing the acetyl protecting group in step (b) comprises admixing compound C, or salt thereof, with a deprotecting agent.

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

[0019] In various ~~embodiment~~examples, the deprotecting agent comprises acetyl chloride and an alcohol. In various ~~embodiment~~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 ~~embodiment~~examples, the deprotecting agent is magnesium methoxide. In various ~~embodiment~~examples, the deprotecting agent is an enzyme selected from the group consisting of an ester hydrolase, a lipase, and a combination thereof. In various ~~embodiment~~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 ~~embodiment~~examples, the deprotecting agent is zirconium hydride.

[0020] In various ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the oxidizing further comprises admixing compound D and the oxidizing reagent with an oxidation catalyst. In various ~~embodiment~~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.

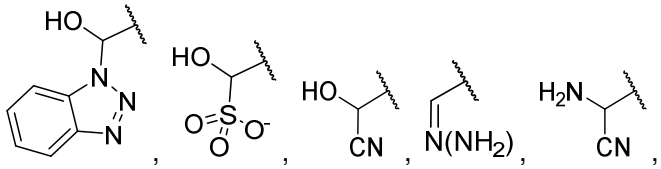
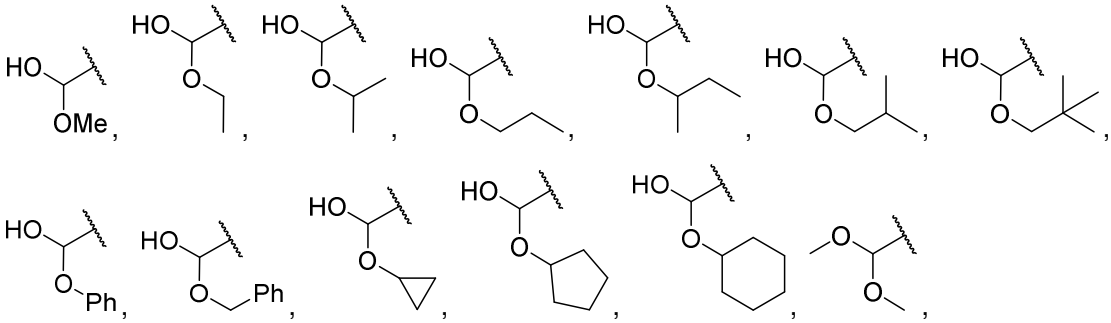
[0026] In various ~~embodiment~~examples, compound D and the oxidation catalyst are present in a molar ratio of 1:0.01 to 1:1. In some cases, the molar ratio of compound D to the oxidation catalyst is 1:0.04.

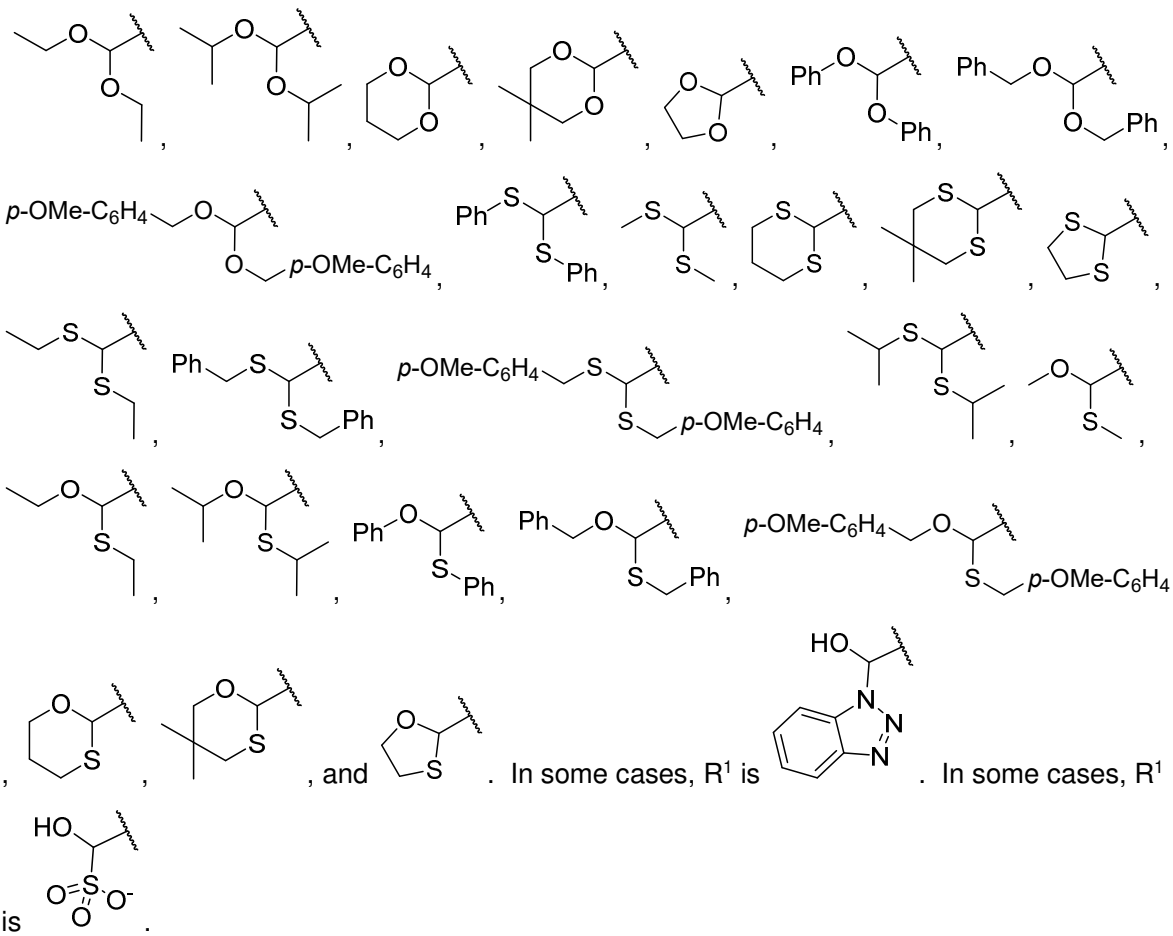
[0027] In various ~~embodiment~~examples, wherein the organic solvent (of step (c)) is selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate, ethyl acetate, and a combination thereof. 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 ~~embodiment~~examples, step (c) occurs in the presence of water. In various ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, R^1 is selected from the group consisting of , 



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

[0032] In various ~~embodiment~~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.

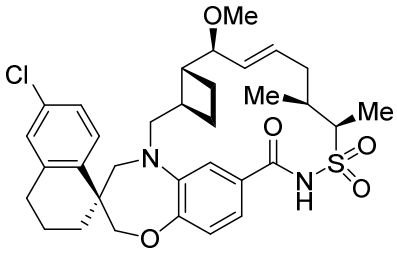
[0033] In various ~~embodiment~~examples, the solvent is selected from the group consisting of toluene, heptane, acetonitrile, water, methyl tert-butyl ether (MTBE), and a combination thereof. In various ~~embodiment~~examples, the solvent of step (d) is selected from the group consisting of toluene/heptane, 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 ~~embodiment~~examples, step (d) occurs at a temperature of 20 °C to 50 °C.

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

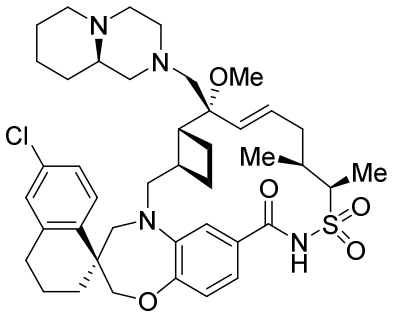
[0036] In various ~~embodiment~~examples, crystallizing comprises admixing compound F with a crystallizing solvent to form crystalline compound F. In various ~~embodiment~~examples, the crystallizing solvent comprises heptane, toluene, methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME),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

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



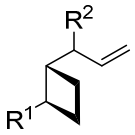
(A1).

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



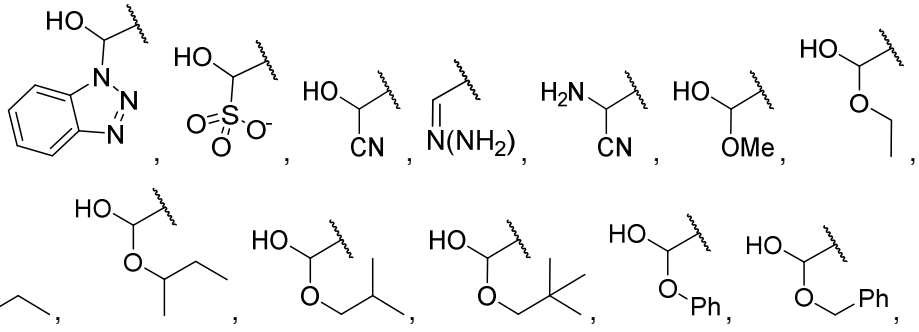
(A2).

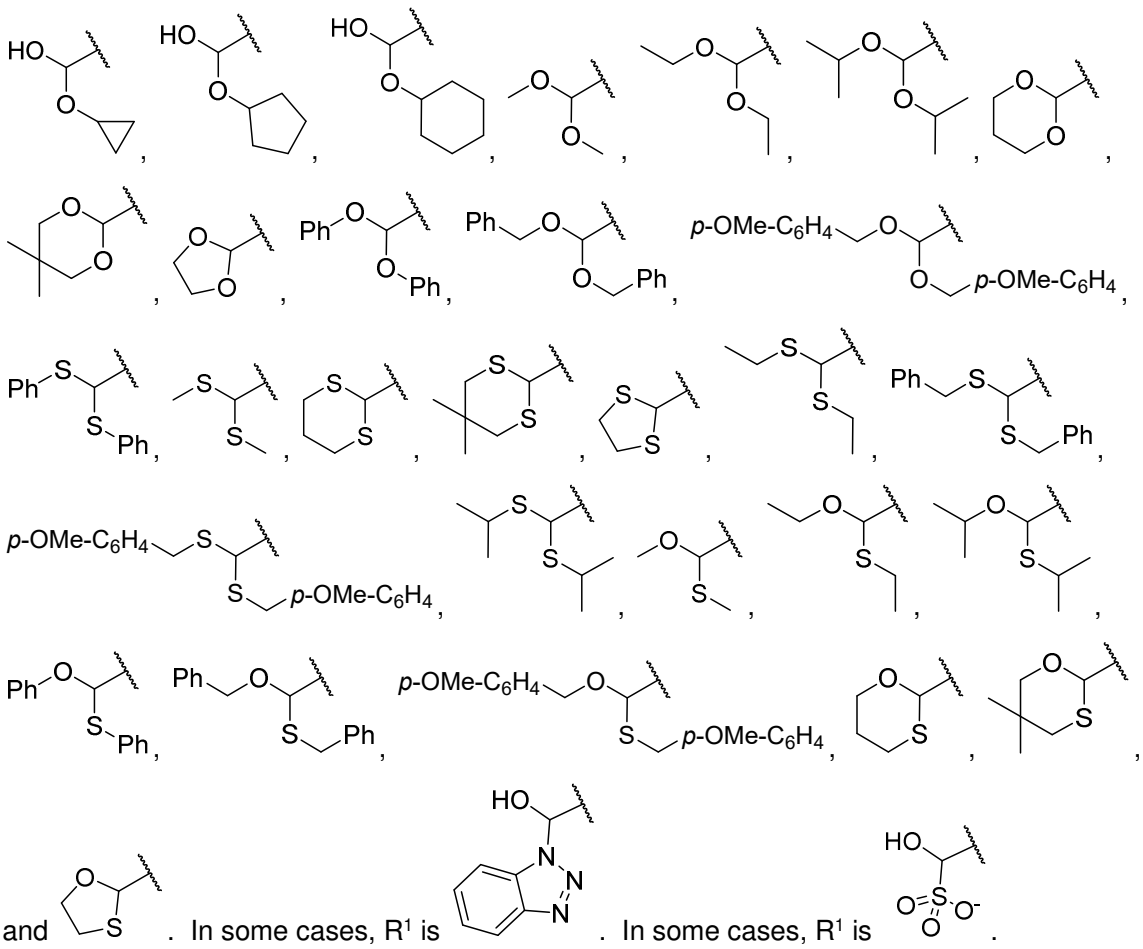
[0039] Further provided herein are compounds having the structure of Formula (I):



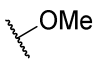
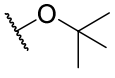
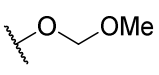
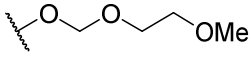
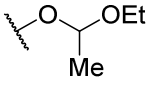
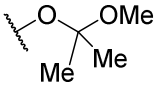
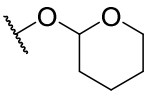
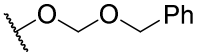
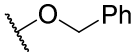
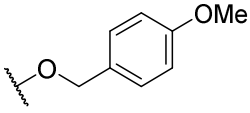
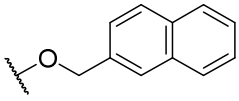
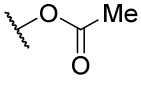
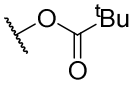
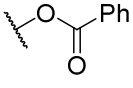
(I),

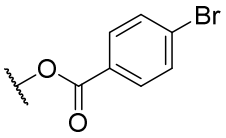
wherein R^1 is  ,  , or a protected aldehyde; R^2 is OH or OPG^2; and OPG^2 is a secondary alcohol protecting group, with the proviso that if R^2 is OH, then R^1 is  .

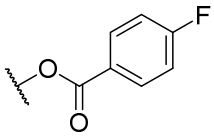
[0040] In various ~~embodiment~~examples, R^1 is  . In various ~~embodiment~~examples, R^1 is  . In various ~~embodiment~~examples, R^1 is a protected aldehyde. In some cases, R^1 is selected from the group consisting of 

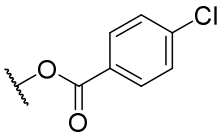


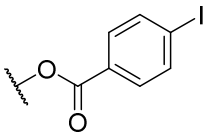
and . In some cases, R^1 is . In some cases, R^1 is .

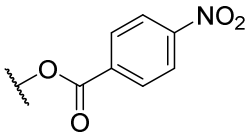
[0041] In various ~~embodiment~~examples, R^2 is OH. In various ~~embodiment~~examples, R^2 is OPG^2. In various ~~embodiment~~examples, OPG^2 selected from the group consisting of an ether, an acetal or ketal, an acyl, a sulfonyl, and a silyl ether. In some cases, OPG^2 is selected from the group consisting 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),

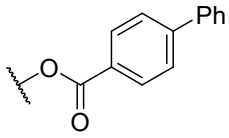


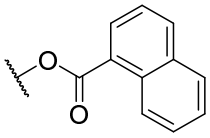
(4-bromobenzoyl, Br-Bz), 

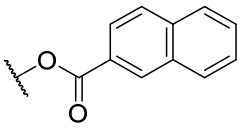
(4-fluorobenzoyl), 

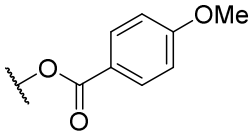
(4-chlorobenzoyl), 

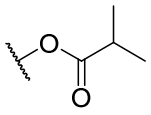
(4-iodobenzoyl), 

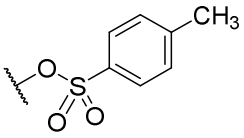
(4-nitrobenzoyl), 

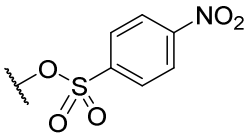
(4-phenylbenzoyl), 

(1-naphthoyl ester), 

(2-naphthoyl ester), 

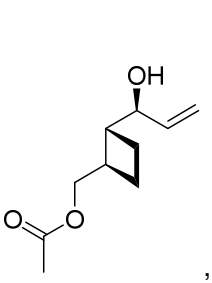
(4-methoxybenzoyl), 

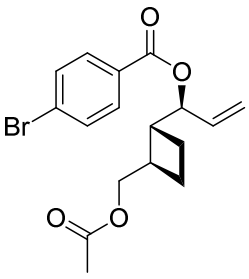
(isobutyryl), $OSiEt_3$ (triethylsilyl ether, TES), $OSi(^iPr)_3$ (triisopropylsilyl ether, TIPS), $OSiMe_3$ (trimethylsilyl ether, TMS), $OSiMe_2{}^tBu$ (*tert*-butyldimethylsilyl ether, TBS), $OSiPh_2{}^tBu$ (*tert*-butyldiphenylsilyl ether TBDPS), OSO_2Me (mesyl), 

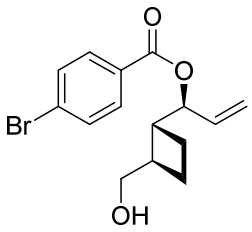
(4-toluenesulfonyl, tosyl), 

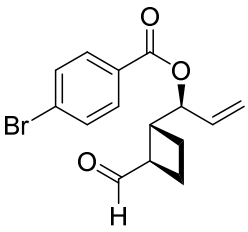
(4-nitrobenzenesulfonyl, nosyl), and OSO_2CF_3 (triflyl). In some cases, OPG^2 is 4-bromobenzoyl.

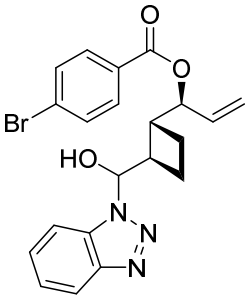
[0042] In various ~~embodiment~~examples, the compound is selected from the group consisting of:

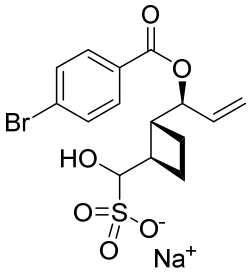


, 

, 

, 

, 

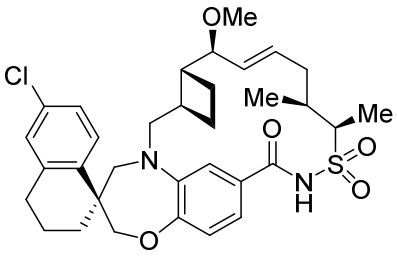
, and 

.

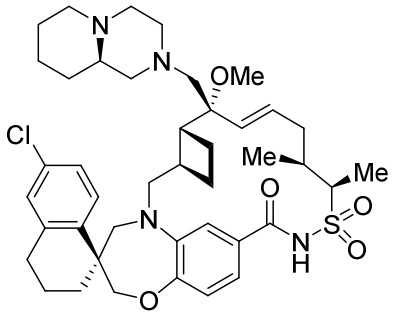
[0043] Further ~~aspects~~ examples and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific ~~embodiment~~examples with the understanding that the disclosure is illustrative, and is not intended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

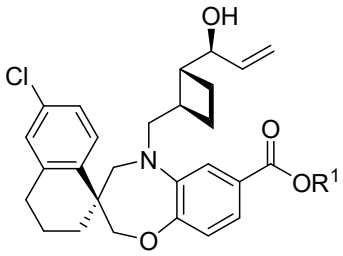


(A1) and



(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.

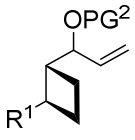


vinylic alcohol intermediate of '061 patent

[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:

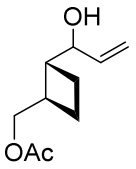
1. A process for synthesizing compound F or a salt thereof:

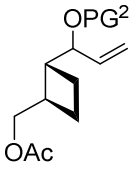


(F);

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

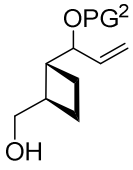
(a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



(B) and


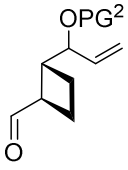
(C);

(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.

~~3. The process of claim 2,~~ 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.

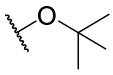
~~4. The process of claim 3,~~ optionally wherein the acyl protecting group is 4-bromobenzoyl.

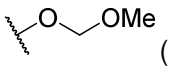
~~5.~~3. The process of ~~any one of claims 2-4~~ claim 2, wherein the alcohol protecting group reagent of step (a) is an acyl chloride or an acyl anhydride.

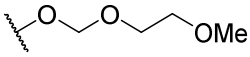
~~6.~~4. The process of any one of claims 1-~~5~~3, wherein compound B and the alcohol protecting group reagent are present in a molar ratio of 1:1 to 1:2~~.~~

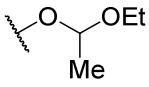
~~7. The process of claim 6~~, or wherein the molar ratio of compound B to alcohol protecting group reagent is 1:1.3.

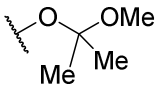
~~8.~~5. The process of claim 2, wherein OPG^2 is selected from the group consisting of 

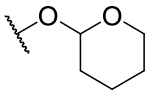
(methoxy), 

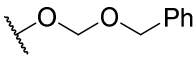
(tert-butyl ether), 

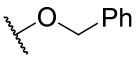
(methoxymethyl acetal, MOM), 

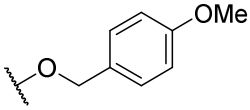
(2-methoxyethoxymethyl ether, MEM), 

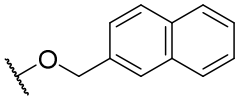
(ethoxyethyl acetal, "EE), 

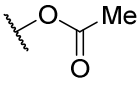
(methoxypropyl acetal, MOP), 

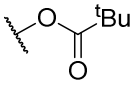
(tetrahydropyranyl acetal, "THP), 

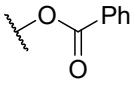
(benzyloxymethyl acetal, BOM), 

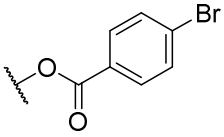
(benzyl ether, Bn), 

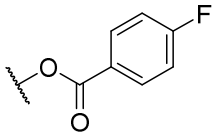
(4-methoxybenzyl ether, PMB), 

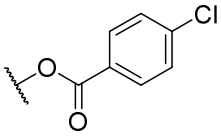
(2-naphthylmethyl ether, Nap), 

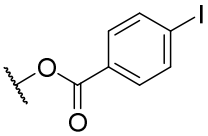
(acetyl, Ac), 

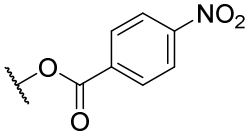
pivaloyl (Piv), 

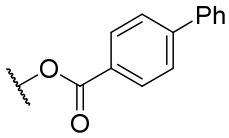
(benzoyl, Bz), 

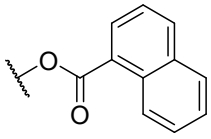
(4-bromobenzoyl, Br-Bz), 

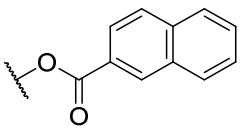
(4-fluorobenzoyl), 

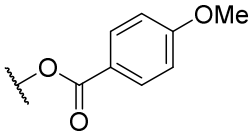
(4-chlorobenzoyl), 

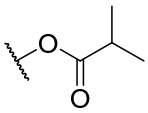
(4-iodobenzoyl), 

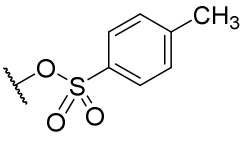
(4-nitrobenzoyl), 

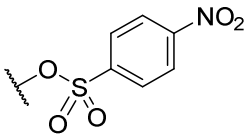
(4-phenylbenzoyl), 

(1-naphthoyl ester), 

(2-naphthoyl ester), 

(4-methoxybenzoyl), 

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

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

~~9.~~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).

~~10.~~7. The process of any one of claims 2-~~9~~6, wherein step (a) comprises admixing compound B, or salt thereof, the alcohol protecting group reagent, and a nucleophilic catalyst; optionally.

~~11. The process of claim 10,~~ wherein the nucleophilic catalyst comprises pyridine, 4-dimethylaminopyridine, or a combination thereof.

~~12.~~8. The process of claim ~~10 or 11~~7, wherein compound B and the nucleophilic catalyst are present in a molar ratio of 1:1 to 1:5.

~~13. The process of claim 12~~, or wherein the molar ratio of compound B to the nucleophilic catalyst is 1:2.

~~14.~~9. The process of any one of claims 1-~~13~~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.

~~15. The process of claim 14,~~ 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.

~~16. The process of claim 15,~~; optionally wherein the organic solvent is toluene, THF, DCM, or a combination thereof.

~~17.~~10. The process of any one of claims 1-~~16~~9, wherein step (a) occurs at a temperature of 20 °C to 100 °C.

~~18. The process of claim 17,~~; optionally wherein step (a) occurs at a temperature of 60 °C.

~~19.~~11. The process of any one of claims 1-~~18~~10, wherein removing the acetyl protecting group in step (b) comprises admixing compound C, or salt thereof, with a deprotecting agent.

20.12. The process of claim 1911, wherein the deprotecting agent comprises acetyl chloride, an enzyme, an acid, a base, a metal hydride, or a combination thereof.

21. The process of claim 20; optionally , wherein the deprotecting agent comprises acetyl chloride and an alcohol.; optionally

22. The process of claim 21, wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, and a combination thereof.

23. The process of claim 22; optionally , wherein the alcohol is methanol.

24.13. The process of claim 2012, wherein the deprotecting agent is magnesium methoxide.

25. The process of claim 20, or wherein the deprotecting agent is an enzyme selected from the group consisting of an ester hydrolase, a lipase, and a combination thereof.

26. The process of claim 20, or wherein the deprotecting agent is an acid selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and a combination thereof.

27. The process of claim 20, or wherein the deprotecting agent is zirconium hydride.

28.14. The process of any one of claims 1911-2713, wherein compound C and the deprotecting agent are present in a molar ratio of 1:0.2 to 1:2.

29. The process of claim 28, or wherein the molar ratio of compound C to the deprotecting agent is 1:0.5.

30.15. The process of any one of claims 1-2914, wherein step (b) occurs at a temperature of -15 °C to 25 °C.

31. The process of claim 30; optionally , wherein step (b) occurs at a temperature of 10 °C.

32.16. The process of any one of claims 1-3115, 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

33. The process of claim 32, wherein the oxidizing agent is selected from the group consisting of oxalyl chloride/DMSO, bleach, SO_3/pyridine, iodobenzenediacetate, and any combination thereof.

34. The process of claim 33; optionally , wherein the oxidizing agent is iodobenzenediacetate.

35.17. The process of any one of claims 32-34claim 16, wherein compound D and the oxidizing agent are present in a molar ratio of 1:1.1 to 1:2.

36. The process of claim 35, or wherein the molar ratio of compound D to the oxidizing agent is 1:1.1.

37.18. The process of any one of claims 3216-3617, further comprising admixing compound D and the oxidizing reagent with an oxidation catalyst; optionally.

38. The process of claim 37, 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.

39. The process of claim 3 8, ; optionally wherein the oxidation catalyst is TEMPO.

40.19. The process of any one of claims 37-39claim 18, wherein compound D and the oxidation catalyst are present in a molar ratio of 1:0.01 to 1:1.

41. The process of claim 40, or wherein the molar ratio of compound D to the oxidation catalyst is 1:0.04.

42.20. The process of any one of claims 32-4116-19, 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

43. The process of claim 42, 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.

44. The process of claim 43, ; optionally wherein the organic solvent is toluene.

45.21. The process of any one of claims 3216-4420, wherein step (c) occurs in the presence of water.

46.22. The process of claim 4521, wherein compound D and water are present in a molar ratio of 1:1 to 1:2.

47. The process of claim 46, or wherein the molar ratio of compound D to water is 1:1.1.

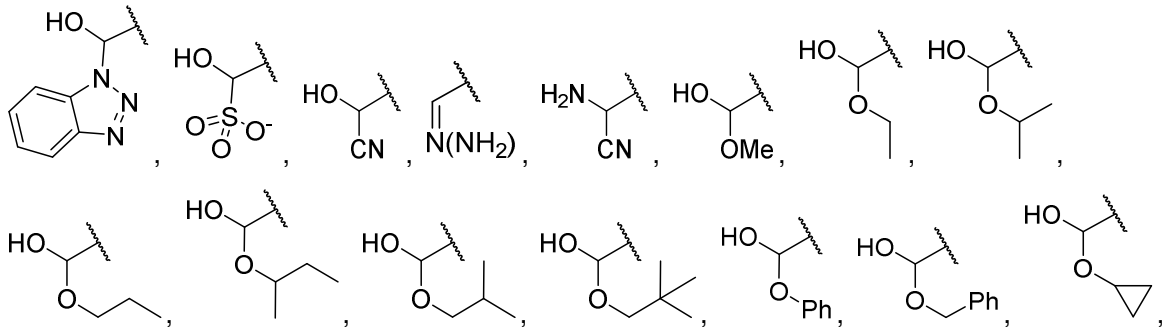
48.23. The process of any one of claims 1-4722, wherein step (c) occurs at a temperature of 5 °C to 45 °C.

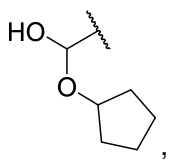
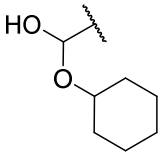
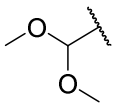
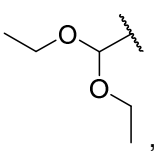
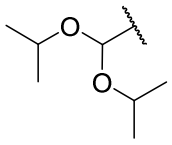
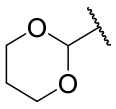
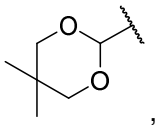
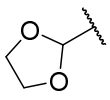
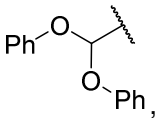
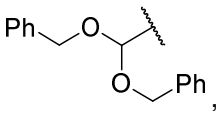
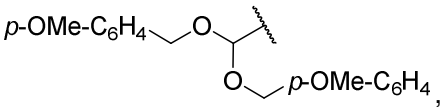
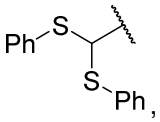
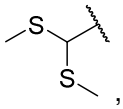
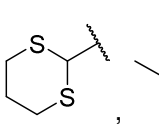
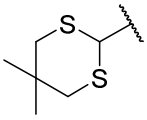
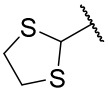
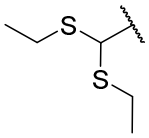
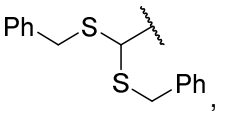
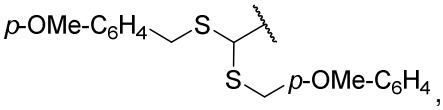
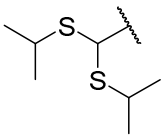
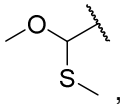
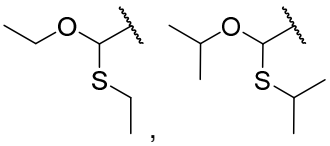
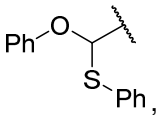
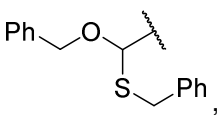
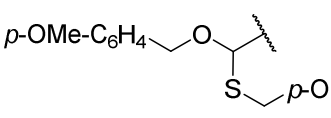
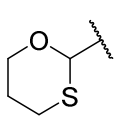
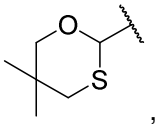
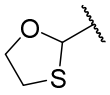
49. The process of claim 48, ; optionally wherein step (c) occurs at a temperature of 20 °C.

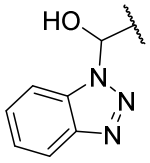
50.24. The process of any one of claims 1-4923, wherein protecting the aldehyde of compound E, or salt thereof, in step (d) comprises admixing compound E, or salt thereof, and an aldehyde protecting group reagent with a solvent.; optionally

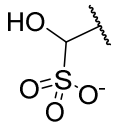
51. The process of claim 50, wherein the aldehyde protecting group reagent is selected from the group consisting of benzotriazole, a bisulfite salt, a cyanide salt, hydrogen cyanide, a thiol or dithiol, an alcohol or diol, hydrazine, ammonia, and a combination thereof.

52.25. The process of claim 5024, wherein R^1 is selected from the group consisting of



, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

53. The process of claim 52, ; optionally wherein R^1 is .

54. The process of claim 52, , or wherein R^1 is .

55.26. The process of any one of claims 5024-5425, wherein compound E and the aldehyde protecting group reagent are present in a molar ratio of 1:1 to 1:1.5.

56. The process of claim 55, or wherein the molar ratio of compound E to the aldehyde protecting group reagent is 1:1.

57.27. The process of any one of claims 5024-5626, wherein the solvent is selected from the group consisting of toluene, heptane, acetonitrile, water, methyl tert-butyl ether (MTBE), and a combination thereof.

58. The process of claim 57, ; optionally wherein the solvent is selected from the group consisting of toluene/heptane, acetonitrile/water, and methyl tert-butyl ether (MTBE).

59. The process of claim 58, ; optionally wherein the solvent is toluene/heptane.; optionally

60. The process of claim 59, wherein toluene and heptane are present in the solvent as a volume ratio of 4:7.

~~61.~~28. The process of any one of claims 1-~~60~~27, wherein step (d) occurs at a temperature of 20 °C to 50 °C.

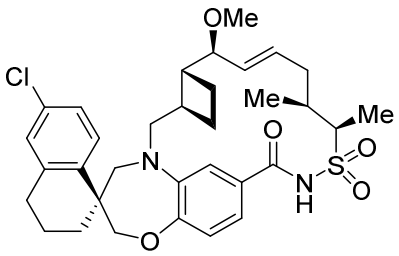
~~62.~~29. The process of any one of claims 1-~~61~~28, further comprising:

(e) crystallizing compound F~~.~~; optionally

~~63. The process of claim 62,~~ wherein crystallizing comprises admixing compound F with a crystallizing solvent to form crystalline compound F~~.~~; optionally

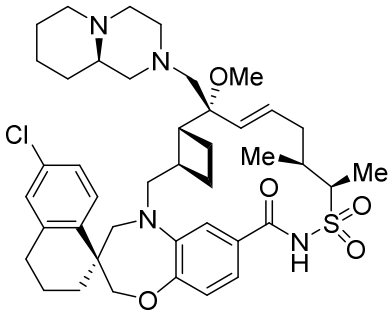
~~64. The process of claim 63,~~ wherein the crystallizing solvent comprises heptane, toluene, methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), methyl isobutyl ketone (MIBK), acetonitrile, isopropyl alcohol, isopropyl acetate, water, or a combination thereof.

~~65.~~30. The process of any one of claims 1-~~64~~29, further comprising synthesizing compound A1, or a salt or solvate thereof, using compound F:



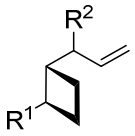
(A1)~~.~~

~~66. The process of any one of claims 1-64~~, or further comprising synthesizing compound A2, or a salt of solvate thereof, using compound F:



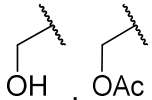
(A2).

~~67.~~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,

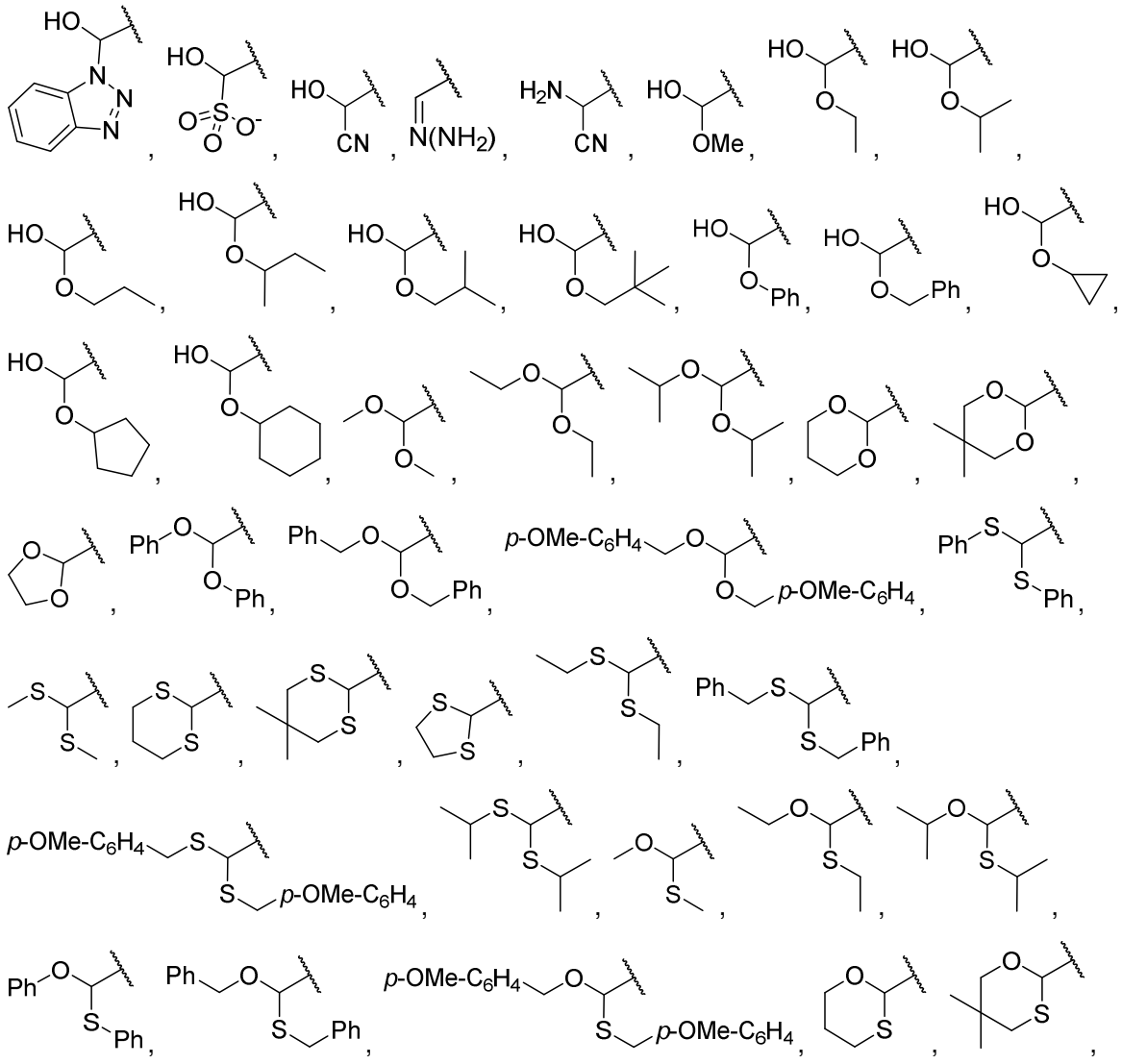
with the proviso that if R^2 is OH, then R^1 is  .

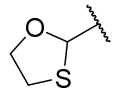
~~68.~~32. The compound of claim ~~67~~31, wherein R^1 is  ~~.~~

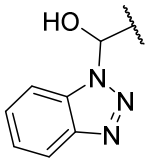
~~69.~~ ~~The compound of claim 67~~, or wherein R^1 is  ~~.~~; or

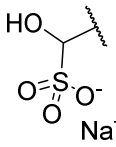
~~70.~~ ~~The compound of claim 67,~~ wherein R^1 is a protected aldehyde~~.~~; optionally

~~71.~~ ~~The compound of claim 70,~~ wherein R^1 is selected from the group consisting of



and  ~~.~~

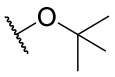
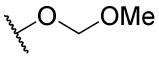
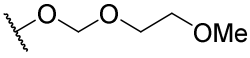
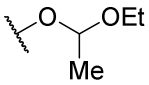
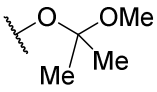
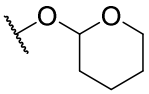
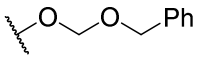
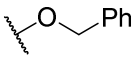
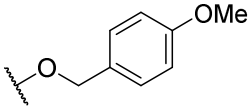
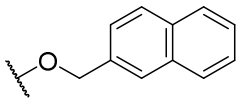
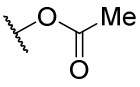
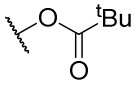
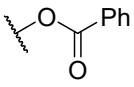
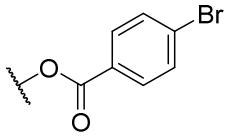
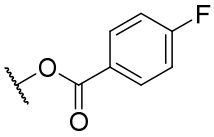
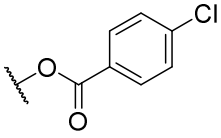
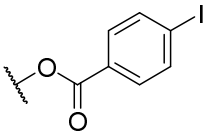
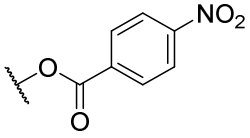
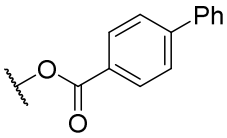
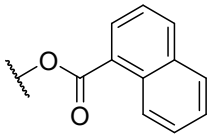
~~72. The compound of claim 70 or 71,~~ ; optionally wherein R^1 is .

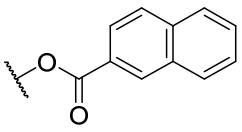
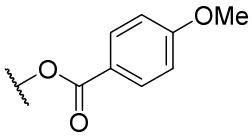
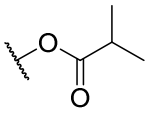
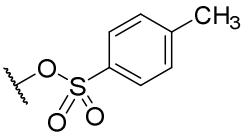
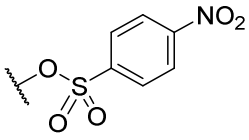
~~73. The compound of claim 70 or 71~~, or wherein R^1 is .

~~74.~~33. The compound of claim ~~67~~ 31 or ~~68~~32, wherein R^2 is OH~~.~~

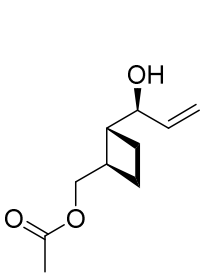
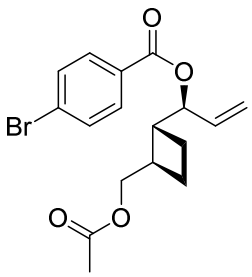
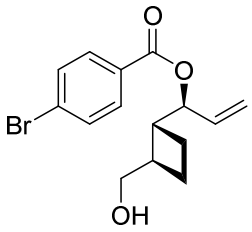
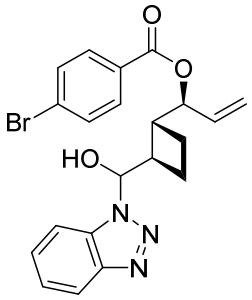
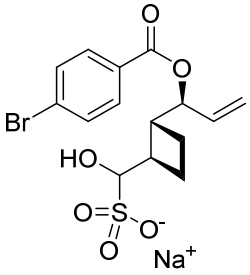
~~75. The compound of any one of claims 67-73~~, or wherein R^2 is OPG^2~~.~~; optionally

~~76. The compound of claim 75,~~ wherein OPG^2 selected from the group consisting of an ether, an acetal or ketal, an acyl, a sulfonyl, and a silyl ether~~.~~

~~77. The compound of claim 76,~~ ; 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).

~~78.~~ ~~The compound of claim 77, ;~~ optionally wherein OPG^2 is 4-bromobenzoyl.

~~79.~~34. The compound of claim ~~67~~31, wherein the compound is selected from the group consisting of: , , , , and .