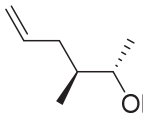
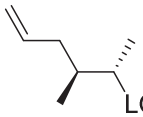
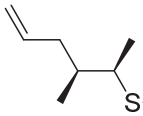
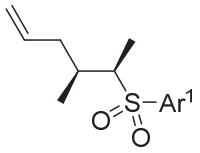
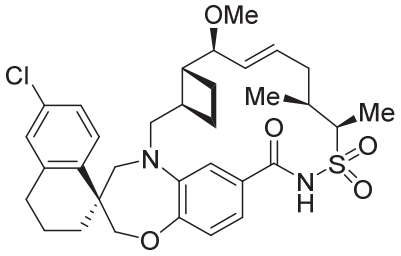
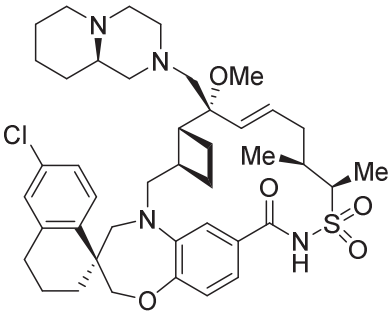
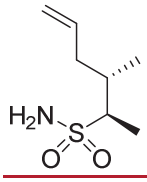
compound K  (K); (d) admixing compound K, a leaving group reagent, and an amine base to form compound L  (L), wherein LG is a leaving group;(e) admixing compound L, a non-nucleophilic base, and Ar^1-SH to form compound M  (M), wherein Ar^1 is a 5-12 membered heteroaryl comprising from 1 to 3 ring heteroatoms selected from O, N, and S; (f) oxidizing compound M to form compound N  (N); and (g) admixing compound N, a base and hydroxylamine-*O*-sulfonic acid to form compound Z.

[0010] Also provided herein are processes comprising using compound Z to synthesize compound A1 or a salt or solvate thereof, or compound A2 or a salt or solvate thereof:

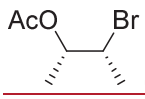
 (A1) or  (A2).

[0010a] In one aspect, provided herein is a process for synthesizing compound Z, or a salt thereof:

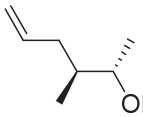
 (Z);

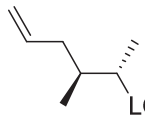
comprising:

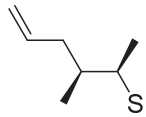
(a) admixing (2S,3S)-butane-2,3-diol, a bromide source, and acetic acid to form compound I

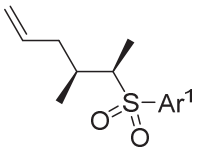
 (I);

(b) admixing compound I and a non-nucleophilic base to form compound J  (J);

(c) admixing compound J and an allyl nucleophile to form compound K  (K);

(d) admixing compound K, a leaving group reagent, and an amine base to form compound L  (L), wherein LG is a leaving group;

(e) admixing compound L, a non-nucleophilic base, and Ar^1-SH to form compound M  (M), wherein Ar^1 is a 5-12 membered heteroaryl comprising from 1 to 3 ring heteroatoms selected from O, N, and S;

(f) oxidizing compound M to form compound N  (N); and

(g) admixing compound N, a base and hydroxylamine-*O*-sulfonic acid to form compound Z.

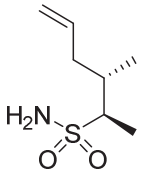
[0011] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

Detailed Description

[0012] Provided herein are processes for synthesizing Mcl-1 inhibitors and corresponding sulfonamide Mcl-1 inhibitor intermediates. In particular, the sulfonamide intermediates can be used in 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 in processes 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-

What is Claimed is:

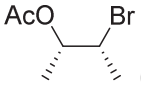
1. A process for synthesizing compound Z, or a salt thereof:



(Z);

comprising:

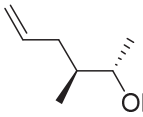
(a) admixing (2S,3S)-butane-2,3-diol, a bromide source, and acetic acid to form compound I



(I);

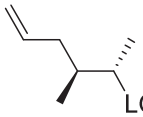
(b) admixing compound I and a non-nucleophilic base to form compound J 

(J);

(c) admixing compound J and an allyl nucleophile to form compound K 

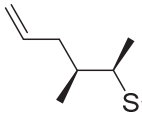
(K);

(d) admixing compound K, a leaving group reagent, and an amine base to form compound L

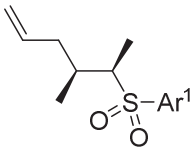


(L), wherein LG is a leaving group;

(e) admixing compound L, a non-nucleophilic base, and Ar^1-SH to form compound M



(M), wherein Ar^1 is a 5-12 membered heteroaryl comprising from 1 to 3 ring heteroatoms selected from O, N, and S;

(f) oxidizing compound M to form compound N 

(N); and

(g) admixing compound N, a base and hydroxylamine-*O*-sulfonic acid to form compound Z.

2. The process of claim 1, wherein the bromide source comprises HBr, PBr_3, or a combination thereof; optionally.

~~3. The process of claim 2~~, wherein HBr is present in acetic acid in an amount of 20 w/w% to 50 w/w%, or.

~~4. The process of claim 3,~~ wherein HBr is present as a 33% w/w solution in acetic acid.

~~5~~3. The process of any one of claims 1-~~4~~2, wherein the admixing of step (a) occurs at a temperature of -20°C to 10°C.

~~6~~4. The process of any one of claims 1-~~5~~3, wherein the admixing of step (a) occurs for 1 hour to 24 hours, or~~.~~

~~7. The process of claim 6,~~ wherein the admixing of step (a) occurs for 15 hours to 20 hours.

~~8~~5. The process of any one of claims 1-~~7~~4, wherein step (b) further comprises monoethylene glycol; optionally~~.~~

~~9. The process of claim 8~~, wherein, for step (b), the non-nucleophilic base and monoethylene glycol are stirred together prior to admixing with compound I; optionally~~.~~

~~10. The process of claim 9~~, wherein the non-nucleophile base and monoethylene glycol are stirred together at a temperature of 25°C to 40°C.

~~11~~6. The process of any one of claims 1-~~10~~5, wherein the non-nucleophilic base comprises lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, sodium tert-amylate, potassium amylate, or a combination thereof; or~~.~~

~~12. The process of claim 11~~, wherein the non-nucleophilic base comprises potassium *tert*-butoxide.

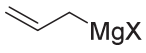
~~13~~7. The process of any one of claims 1-~~12~~6, wherein the admixing of step (b) occurs in an organic solvent comprising tert-butyl methyl ether, 2-methyltetrahydrofuran, cyclopentyl methyl ether, dimethoxyethane, or a combination thereof; or~~.~~

~~14. The process of claim 13~~, wherein the organic solvent comprises tert-butyl methyl ether.

~~15~~8. The process of any one of claims 1-~~14~~7, wherein the admixing of step (b) occurs for 10 minutes to 2 hours; or~~.~~

~~16. The process of claim 15~~, wherein the admixing of step (b) occurs for 30 minutes; optionally~~.~~

~~17. The process of any one of claims 1-16~~, wherein the admixing of step (b) occurs at a temperature of 70°C to 120°C.

~~18~~9. The process of any one of claims 1-~~17~~8, wherein the allyl nucleophile is  and X is a halide; or~~.~~

~~19. The process of claim 18~~, wherein X is Cl.

~~20~~10. The process of any one of claims 1-~~1~~9, wherein the admixing of step (c) occurs in an organic solvent comprising tetrahydrofuran, 2-methyltetrahydrofuran, tert-butyl methyl ether (MTBE), cyclopentyl methyl ether, dimethoxyethane, or a combination thereof; or~~.~~

~~21. The process of claim 20~~, wherein the organic solvent comprises tetrahydrofuran and MTBE.

~~22~~11. The process of any one of claims 1-~~21~~10, wherein compound J is added to the allyl nucleophile dropwise over 1 hour to 5 hours.

~~23~~12. The process of any one of claims 1-~~22~~11, wherein the admixing of step (c) occurs for 1 hour to 6 hours; or~~.~~

~~24. The process of claim 23~~, wherein the admixing of step (c) occurs for 3 hours.

~~25.~~13 The process of any one of claims 1-~~24~~12, wherein the admixing of step (c) occurs at a temperature of -20°C to 10°C.

~~26~~14. The process of any one of claims 1-~~25~~13, wherein compound J and the allyl nucleophile are present in a molar ratio of 1:1.05 to 1:3.

~~27~~15. The process of any one of claims 1-~~26~~14, wherein leaving group comprises F, Cl, Br, I, mesyl, tosyl, nosyl, or triflyl; or~~.~~

~~28. The process of claim 27~~, wherein the leaving group is mesyl.

~~29~~16. The process of claim 15~~27 or 28~~, wherein the leaving group reagent comprises mesyl chloride, tosyl chloride, nosyl chloride, methanesulfonic anhydride, *para*-toluenesulfonic anhydride, or a combination thereof, or~~.~~

~~30. The process of claim 29~~, wherein the leaving group reagent is mesyl chloride.

~~31~~17. The process of any one of claims 1-~~30~~16, wherein the admixing of step (d) occurs in an organic solvent comprising dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, tert-butyl methyl ether, or a combination thereof, or~~.~~

~~32. The process of claim 31~~, wherein the organic solvent comprises tetrahydrofuran.

~~33~~18. The process of claim ~~31 or 32~~17, wherein the organic solvent does not comprise dichloromethane.

~~34~~19. The process of any one of claims 1-~~33~~18, wherein the leaving group reagent is added to a solution comprising compound K and the amine base; optionally~~.~~

~~35. The process of claim 34~~, wherein the leaving group reagent is added to the solution over 2 hours to 3 hours then stirred for 10 minutes to 1 hour.

~~36~~20. The process of any one of claims 1-~~35~~19, wherein the amine base of step (d) comprises trimethylamine, pyridine, triethylamine, aniline, diisopropylethylamine, 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU), 1,4-diazabicyclo [2.2.2] octane (DABCO), 2,6-lutidine, or a combination thereof, or~~.~~

~~37. The process of claim 36~~, wherein the amine base comprises triethylamine.

~~38~~21. The process of any one of claims 1-~~37~~20, wherein the admixing of step (d) occurs at a temperature of -10°C to 10°C.

~~39~~22. The process of any one of claims 1-~~38~~21, wherein the leaving group is present at 1.2 to 2 molar equivalents, based upon compound K, or~~.~~

~~40. The process of any one of claims 1-39~~, wherein the amine base is present at 1.8 to 3.3 molar equivalents, based upon compound K.

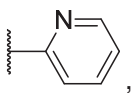
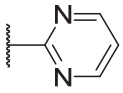
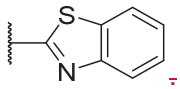
~~41~~23. The process of any one of claims 1-~~40~~22, wherein, for step (e), compound L is added to a mixture comprising Ar^1-SH and the non-nucleophilic base; optionally~~.~~

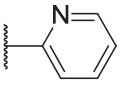
~~42. The process of claim 41~~, wherein compound L is added dropwise over 3 to 6 hours.

~~43~~24. The process of any one of claims 1-~~42~~23, wherein the non-nucleophilic base of step (e) comprises lithium hexamethyldisilazide (“HMDS”), sodium HMDS, potassium HMDS, lithium diisopropylamide, sodium diisopropylamide, potassium diisopropylamide, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, lithium *tert*-amylate, sodium *tert*-amylate, potassium *tert*-amylate, or a combination thereof, or~~.~~

~~44. The process of claim 43~~, wherein the non-nucleophilic base comprises sodium *tert*-butoxide, potassium *tert*-butoxide, or sodium *tert*-amylate.

~~45~~25. The process of any one of claims 1-~~44~~24, wherein compound L and the non-nucleophilic base of step (e) are present in a molar ratio of 1:1.1 to 1:4.

~~46~~26. The process of any one of claims 1-~~45~~25, wherein Ar^1 is selected from the group consisting of , , and .

~~47. The process of claim 46~~, or wherein Ar^1 is .

~~48~~27. The process of any one of claims 1-~~47~~26, where compound L and Ar^1-SH are present in a molar ratio of 1:1.05 to 1:2.5.

~~49~~28. The process of any one of claims 1-~~48~~27, wherein the admixing of step (e) of compound L, Ar^1-SH, and the non-nucleophilic base occurs for 3 hours to 5 hours~~.~~

~~50. The process of any one of claims 1-49,~~; optionally wherein the admixing of step (e) occurs at a temperature of 60°C to 80°C.

~~51~~29. The process of any one of claims 1-~~50~~28, wherein compound M is washed three to five times with aqueous sodium hydroxide prior to the oxidizing of step (f)~~.~~

~~52. The process of any one of claims 1-51,~~; optionally wherein the oxidizing of step (f) comprises admixing compound M with a oxidation catalyst and hydrogen peroxide~~.~~

~~53. The process of claim 52,~~; optionally wherein the oxidation catalyst is sodium tungstate dehydrate, 3-chloroperbenzoic acid, or a combination thereof~~.~~

~~54. The process of claim 53,~~; or wherein the oxidation catalyst is sodium tungstate dehydrate.

~~55~~30. The process of ~~any one of claims 52-54~~claim 29, wherein compound M and the oxidation catalyst are present in a molar ratio of 1:0.05 to 1:0.5.

~~56~~31. The process of any one of claims ~~52-55~~29 to 30, wherein the oxidizing further comprises admixing acetic acid.

~~57~~32. The process of any one of claims ~~52-56~~29 to 31, wherein compound M and hydrogen peroxide are present in a molar ratio of 1:1.3 to 1:5.

~~58~~33. The process of claim any one of claims ~~1-57~~29 to 32, wherein the oxidizing of step (f) occurs in a solvent~~.~~

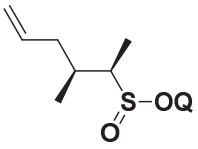
~~59. The process of claim 58,~~ optionally wherein the solvent comprises methanol or ethanol.

~~60~~34. The process of any one of claims ~~52-59~~29 to 33, wherein compound M, the oxidation catalyst, and acetic acid are admixed prior to addition of hydrogen peroxide~~.~~

~~61. The process of claim 60,~~; optionally wherein hydrogen peroxide is added over 3 hours to 5 hours.

~~62~~35. The process of any one of claims 1-~~61~~34, wherein the oxidizing of step (f) occurs at a temperature of 20°C to 25°C.

~~63~~36. The process of any one of claims 1-~~62~~35, wherein, for step (g), compound N and the



base are admixed together in a solvent to form an intermediate compound O (O) prior to admixing with hydroxylamino-*O*–sulfonic acid, wherein Q is an alkali metal cation.

~~64~~37. The process of claim ~~63~~36, wherein the admixing of compound N and the base occurs in a solvent comprising tert-butyl methyl ether, methanol, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof~~.~~

~~65. The process of claim 64,~~, or wherein the solvent comprises tert-butyl methyl ether and methanol.

~~66~~38. The process of any one of claims ~~63-65~~36 to 37, wherein the admixing of compound N and the base occurs at a temperature of 25°C to 50°C.

~~67~~39. The process of any one of claims ~~63-66~~36 to 38, wherein the base comprises sodium thiomethoxide, sodium methoxide, methanol and potassium carbonate, or a combination thereof~~.~~

~~68. The process of claim 67~~, or wherein the base is sodium thiomethoxide.

6940. The process of any one of claims 63-6836 to 39, wherein hydroxylamine-*O*-sulfonic acid is added with sodium acetate, potassium acetate, sodium formate, potassium formate, or a combination thereof, to the intermediate compound O.

70. The process of claim 69, optionally wherein hydroxylamine-*O*-sulfonic acid is added with sodium acetate trihydrate to the intermediate compound O.

7141. The process of claim 67040, wherein the admixing of the intermediate compound O, hydroxylamine-*O*-sulfonic acid, and sodium acetate occurs in a solvent comprising tert-butyl methyl ether, methanol, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof.

72. The process of any one of claims 63-71,; optionally wherein the admixing of the intermediate compound O, hydroxylamine-*O*-sulfonic acid, and sodium acetate occurs for 30 minutes to 4 hours.

73. The process of claim 72,; or wherein the admixing of the intermediate compound O, hydroxylamine-*O*-sulfonic acid and sodium acetate occurs for 2 hours.

74. The process of any one of claims 1-73,; optionally wherein the admixing of the intermediate compound O, hydroxylamine-*O*-sulfonic acid and sodium acetate occurs at a temperature of 25°C to 50°C.

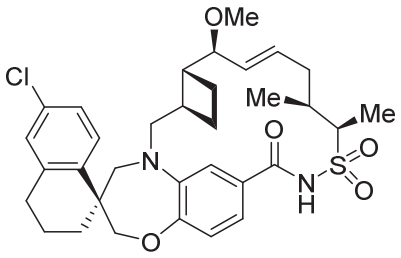
7542. The process of any one of claims 1-7441, further comprising crystallizing compound Z.

7643. The process of claim 7542, wherein the crystallizing comprises heating a solution of compound Z to 40°C to 45°C, then cooling the solution to 10°C to 15°C and adding a crystallizing solvent to the cooled solution to form crystals of compound Z.

77. The process of claim 76,; optionally wherein the solution of compound Z comprises tert-butyl methyl ether and the crystallizing solvent comprises heptane.

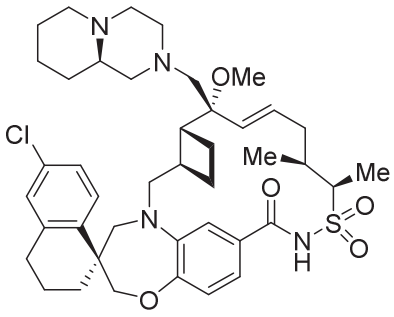
78. The process of claim 76, or wherein the solution of compound Z comprises methanol and the crystallizing solvent comprises water.

7944. The process of any one of claims 1 to 7843, wherein the process further comprises using compound Z to synthesize compound A1 or a salt or solvate thereof



(A1).

~~80. The process of any one of claims 1 to 79,~~ , or wherein the process further comprises using compound Z to synthesize compound A2 or a salt or solvate thereof



(A2)