

SYNTHESIS OF SULFONAMIDE INTERMEDIATES

BACKGROUND**Cross References to Related Applications**

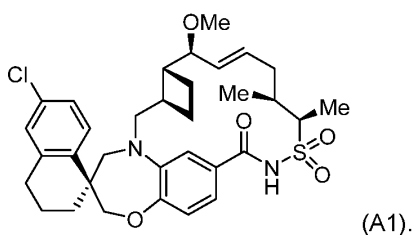
[0001] This application claims the benefit of U.S. Provisional Application No. 63/020,951, filed on May 6, 2020, which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

Technical Field

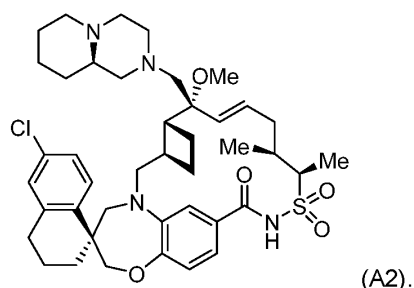
[0002] The present disclosure relates to processes for synthesizing intermediates useful in preparing (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0^{3,6}.0^{19,24}]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (compound A1; AMG 176), a salt, or solvate thereof and in preparing (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; AMG 397), a salt, or solvate thereof. These compounds are inhibitors of myeloid cell leukemia 1 protein (Mcl-1).

Description of Related Technology

[0003] The compound, (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), is useful as an inhibitor of myeloid cell leukemia 1 (Mcl-1):



[0004] The compound, (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), is useful as an inhibitor of myeloid cell leukemia 1 (Mcl-1):



[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.

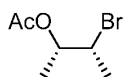
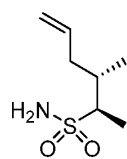
[0006] Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering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

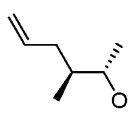
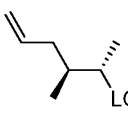
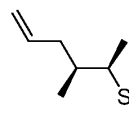
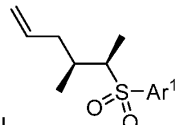
[0008] U.S. Patent No. 10,300,075, which is incorporated herein by reference in its entirety, discloses compound A2 as an Mcl-1 inhibitor and provides a method for preparing it. However, improved synthetic methods that result in greater yield and purity of compound A2 are desired, particularly for the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

Summary

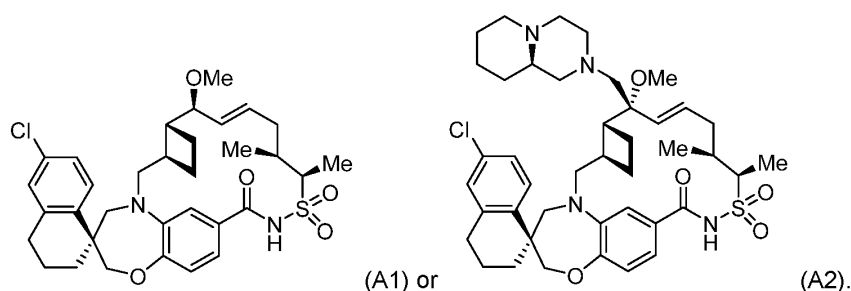
[0009] Provided herein are processes for synthesizing compound Z, or a salt thereof:



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

compound K  OH (K); (d) admixing compound K, a leaving group reagent, and an amine base to form compound L  LG (L), wherein LG is a leaving group; (e) admixing compound L, a non-nucleophilic base, and Ar¹-SH to form compound M  S-Ar¹ (M), wherein Ar¹ 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:

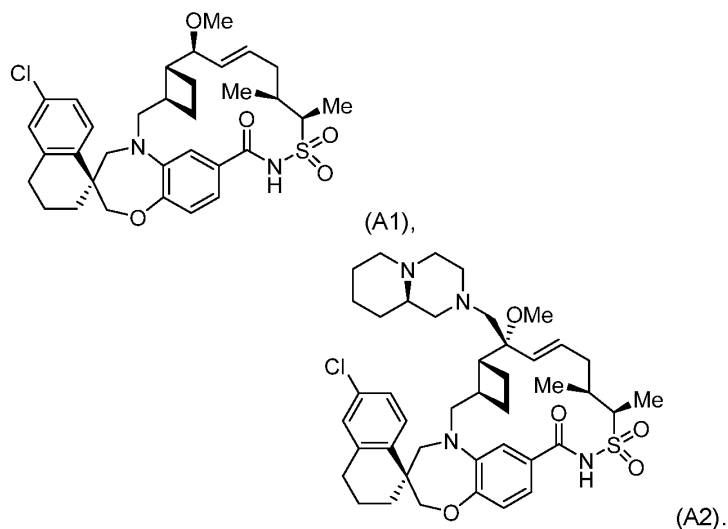


[0011] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention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

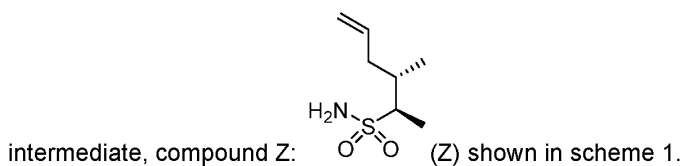
1,22'-[20]oxa[13]thia[1,14]diazatetracyclo [14.7.2.0^{3,6}.0^{19,24}]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (compound A2), or a salt or solvate thereof:



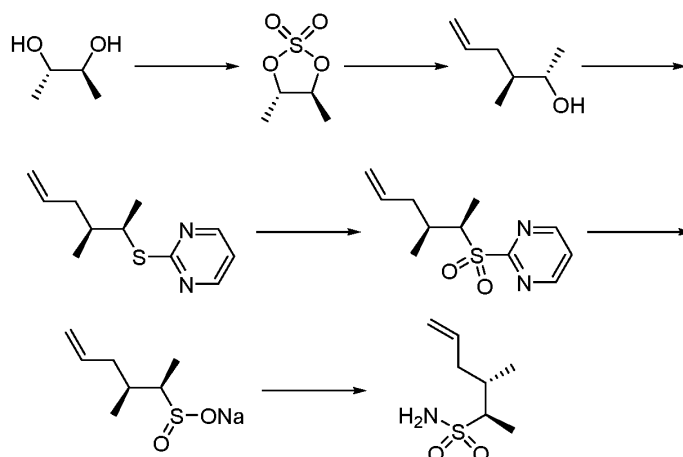
[0013] U.S. Patent No. 9,562,061, which is incorporated herein by reference in its entirety, discloses compound A1, or a salt or solvate thereof, as an Mcl-1 inhibitor and provides a process for preparing it. U.S. Patent No. 9,562,061 also discloses a process of synthesizing sulfonamide Mcl-1 inhibitor intermediates used in the synthesis of compound A1.

[0014] 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 process for preparing it. U.S. Patent No. 10,300,075 also discloses a process of synthesizing sulfonamide Mcl-1 inhibitor intermediates used in the synthesis of compound A2.

[0015] In particular, the '061 patent describes a process for synthesizing a sulfonamide

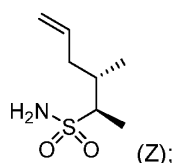


Scheme 1 –Synthesis of Sulfonamide Mcl-1 Inhibitor Intermediate from '061 Patent

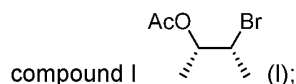


[0016] The '061 patent describes the isolation of each of the intermediate compounds prior to use in the next step of the synthesis. Further, the '061 patent disclosed the step from (4S,5S)-4,5-dimethyl-1,3,2-dioxathiolan 2,2-dioxide to (2S,3S)-3-methylhex-5-en-2-ol has synthetic results with variable chemical and chiral purities levels that can lead to laborious work-up steps, such as chromatography, that result in substantially lower yields.. Advantageously, use of the different synthetic strategy from the starting butane diol described herein leads to higher yield, better efficiency, and produces highly pure products through isolation of crystalline intermediate (e.g., compound N, Ar¹ = pyridyl or pyrimidinyl) and crystalline target compound (Z). The processes described herein avoid the formation of dimeric sulfur-based impurities that are challenging to remove, provides improved chiral and chemical purity, improved safety, and provides flexibility to produce at both small scale (e.g., < 1 gram) and large scale (e.g., multi-kg).

[0017] Provided herein are processes for synthesizing compound Z, or a salt thereof:

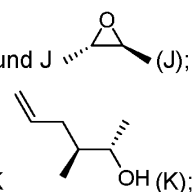


comprising: (a) admixing (2S,3S)-butane-2,3-diol, a bromide source, and acetic acid to form



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

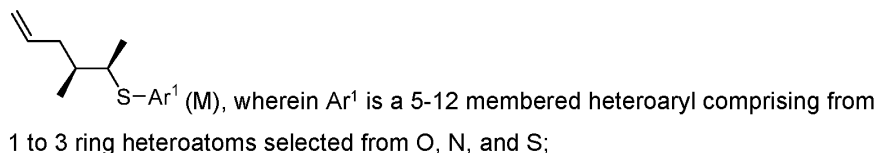
(c) admixing compound J and an allyl nucleophile to form compound K



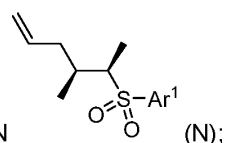
(d) admixing compound K, a leaving group reagent, and an amine base to form compound L



(e) admixing compound L, a non-nucleophilic base, and Ar¹-SH to form compound M



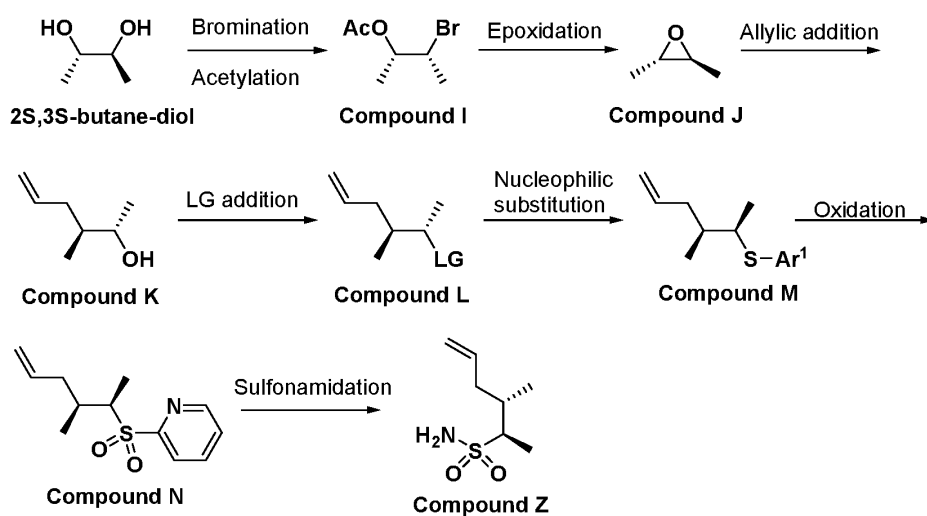
(f) oxidizing compound M to form compound N



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

[0018] A general reaction scheme for the processes described herein is provided in Scheme 2, below:

Scheme 2: General Process for Synthesis of Sulfonamide Mcl-1 Inhibitor Intermediates



[0019] Bromination and Acetylation of 2S,3S-butane-diol to Form Compound I (Step (a))

[0020] The processes of the disclosure include bromination and acetylation of 2S,3S-butane-diol to provide compound I, which comprises admixing 2S,3S-butane-diol, a bromide source, and acetic acid.

[0021] The term “bromide source” as used herein refers to a bromide source used to replace a hydroxyl group on the butane-diol. In some embodiments, the bromide source herein comprises HBr, PBr₃, or a combination thereof. In some embodiments, the bromide source herein comprises HBr.

[0022] In some embodiments, the bromide source is provided in a solution of acetic acid. In some embodiments, the bromide source can be present in acetic acid in an amount of 20 w/w% to 50 w/w%. For example, the bromide source can be present in acetic acid in an amount of 25 w/w% to 40 w/w%, 25 w/w% to 35 w/w%, or 30 w/w% to 35 w/w%, such as 20 w/w%, 25 w/w%, 30 w/w%, 32 w/w%, 33 w/w%, 34 w/w%, 35 w/w%, 40 w/w%, 45 w/w%, or 50 w/w%. In some embodiments, HBr can be present in acetic acid. In some embodiments, HBr can be present as a 33 w/w% solution in acetic acid.

[0023] 2S,3S-Butane-diol and the bromide source can be present in a molar ratio of 1:1 to 1:6, for example, at least a molar ratio of 1:1, 1.05, 1:1.2, 1:1.5, 1:1.75, 1:2, 1:2.25, 1:2.5, 1:3, 1:4 and/or up to 1:6, 1:5, 1:4, 1:3, 1:2.75, 1:2.5, 1:2.25, 1:2, or 1:1.5, such as 1:1 to 1:3.5, 1:2 to 1:4, 1:2 to 1:5, or 1:1.5 to 1:3.5. In some embodiments, the molar ratio of compound I to the non-nucleophilic base is 1:3.5.

[0024] The bromination of butane diol can occur at a temperature of -20 °C to 10 °C, for example at least -20, -15, -10, -5, 0, 5, or 10 and/or up to 10, 5, 0, or -10, such as -15 °C to 10 °C, -10 °C to 10°C, -5 °C to 10°C, or 0 °C to 10 °C. In some embodiments, the bromination occurs at a temperature of 10 °C.

[0025] In some embodiments, the admixing of step (a) can occur for 1 hour to 24 hours. In some embodiments, the admixing of step (a) can occur for 15 hours to 20 hours, or 10 hours to 24 hours, or 12 hours to 24 hours, or 14 hours to 21 hours. For example, the admixing of step (a) can be for 1 hour, 5 hours, 10 hours, 12 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, or 24 hours.

[0026] The bromination/acetylation of the butane diol provides compound I which can be through-processed directly into the next step without the need for substantial purification. As used herein, the term “substantial purification” refers to any purification methods other than washing with solvent and/or distillation, such as, chromatography (e.g., column chromatography), crystallization, filtration, or a combination thereof. In embodiments, neutralization of any remaining acid (e.g., acetic acid and/or HBr) in the formation of compound I can be achieved by admixing with a base, such as potassium carbonate in water, and

compound I can be extracted with an organic solvent such as *tert*-butyl methyl ether (MTBE). In embodiments, extracted compound I can be used in step (b) discussed below, or used after removal of the solvent used for extraction (e.g., “neat”).

[0027] In some embodiments where compound I is through-processed directly into the next step, compound I can be provided in a solution comprising an organic solvent. Organic solvents are generally known in the art. Nonlimiting examples of organic solvents contemplated include acetonitrile, toluene, benzene, xylene, chlorobenzene, fluorobenzene, naphthalene, benzonitrile, tetrahydrofuran (THF), tetrahydropyran, dimethylformamide (DMF), tetrahydrofurfuryl alcohol, diethyl ether, dibutyl ether, diisopropyl ether, methyl *tert*-butyl ether (MTBE), 2-methyltetrahydrofuran (2-MeTHF), dimethyl sulfoxide (DMSO), 1,2-dimethoxyethane (1,2-DME), 1,2-dichloroethane (1,2-DCE), 1,4-dioxane, cyclopentylmethyl ether (CPME), chloroform, carbon tetrachloride, dichloromethane (DCM), methanol, ethanol, propanol, and 2-propanol. In some embodiments, the organic solvent comprises MTBE. The organic solvent can be present in an amount of 0.1 L/kg of 2S,3S-butane-diol to 10 L/kg of 2S,3S-butane-diol, for example, at least 0.5, 1, 1.5, 2, 3, 5, 7.5 or 10 L/kg of 2S,3S-butane-diol and/or up to 10, 7.5, 5, 3.5, 1.5, or 0.5 L/kg of 2S,3S-butane-diol, such as 1 to 4 L/kg of 2S,3S-butane-diol, 1.5 to 10 L/kg of 2S,3S-butane-diol, or 5 L/kg to 10 L/kg of 2S,3S-butane-diol.

[0028] Epoxidation of Compound I to Form Compound J (Step (b))

[0029] The processes of the disclosure can include the epoxidation of compound I to provide compound J. The processes herein can comprise synthesizing compound J by admixing compound I, and a non-nucleophilic base to form compound J. As provided herein, compound J

has a structure of  (J).

[0030] The non-nucleophilic base as used herein can be any suitable non-nucleophilic base known to one of ordinary skill in the art. Contemplated non-nucleophilic bases include, for example, 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, 2,2,6,6-Tetramethylpiperidine (TMP), LiTMP, 1,1,3,3-tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene, and any combination thereof. In some embodiments, the non-nucleophilic base comprises lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, or a combination thereof. In some embodiments, the non-nucleophilic base is potassium *tert*-butoxide. In some embodiments, the non-nucleophilic base is sodium *tert*-butoxide. In some embodiments, the non-nucleophilic base is sodium *tert*-amylate. In some embodiments, the non-nucleophilic base is potassium *tert*-amylate.

[0031] Compound I and the non-nucleophilic base can be present in a molar ratio of 1:1 to 1:5,

for example, at least a molar ratio of 1:1, 1:0.5, 1:1.2, 1:1.5, 1:1.75, 1:2, 1:2.25, 1:2.5, 1:3, 1:4 and/or up to 1:5, 1:4, 1:3, 1:2.75, 1:2.5, 1:2.25, 1:2, or 1:1.5, such as 1:1 to 1:2.5, 1:1 to 1:3, 1:1 to 1:4, 1:1.25 to 1:3, or 1:1.1 to 1:2.5. In some embodiments, the molar ratio of compound I to the non-nucleophilic base is 1:2.5.

[0032] In some embodiments, step (b) further comprises monoethylene glycol. In some embodiments, step (b) comprises monoethylene glycol and potassium *tert*-butoxide. In some embodiments, step (b) comprises monoethylene glycol and sodium *tert*-butoxide.

[0033] Monoethylene glycol can be present in an amount of 2 L/kg of compound I to 5 L/kg of compound I, for example, at least 2, 2.5, 3, 5 L/kg of compound I and/or up to 5, 3.5, or 3 L/kg of compound I, such as 2 to 4 L/kg of compound I, 2.5 to 5 L/kg of compound I, or 3 L/kg to 4 L/kg of compound I.

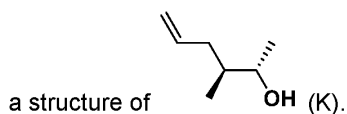
[0034] In some embodiments, the admixing of step (b) can occur in an organic solvent. In some embodiments, the organic solvent comprises *tert*-butyl methyl ether, 2-methyltetrahydrofuran, cyclopentyl methyl ether, dimethoxyethane, or a combination thereof. In some embodiments, the organic solvent comprises *tert*-butyl methyl ether.

[0035] In some embodiments, monoethylene glycol and the non-nucleophilic base are admixed together prior to admixing with compound I. This admixture of monoethylene glycol and the non-nucleophilic base can occur such that the non-nucleophilic base is added to the monoethylene glycol in a manner that maintains the temperature of the resulting admixture to 20°C to 40°C. In some embodiments, the non-nucleophilic base is added to the monoethylene glycol over 3 to 7 hours, or for 4 to 6 hours. After all the non-nucleophilic base is added to the monoethylene glycol, the admixture can be subjected to a temperature of 70 to 120°C, under reduced pressure (e.g., a pressure of 400 mm Hg), to remove resulting byproduct of the protonated non-nucleophilic base (e.g., if non-nucleophilic base is a *t*-butoxide, the resulting *t*-butanol) and leaving behind the deprotonated monoethylene glycol. Compound I can then be added to the deprotonated monoethylene glycol at a temperature of 20°C-40°C (e.g., 30°C), and admixed for 15 minutes to 120 minutes (e.g., 15 minutes to 60 minutes, or for 30 minutes). In some embodiments, the resulting epoxide, compound J, can be distilled from the reaction mixture to isolate.

[0036] The epoxidation of compound I provides compound J which can be through-processed directly into the next step without the need for separation.

[0037] *Allylic Addition to Compound J to Form Compound K (Step (C))*

[0038] The processes of the disclosure include the allylic addition to compound J to provide compound K. The processes herein can comprise synthesizing compound K by admixing compound J and an allyl nucleophile to form compound K. As provided herein, compound K has



[0039] The allylic nucleophile had a structure of  X^1 , wherein X^1 is MgCl, MgBr, Mgl, Li, CuLi, ZnX^3 , In(I), or $In(X^2)_2$; each X^2 independently is Cl, Br, or I, and X^3 is Cl, Br, I, OTf, OTs, OAc, or acac. In some embodiments, X^1 is MgCl, MgBr, or Mgl. In some embodiments, X^1 is MgCl. In some embodiments, X^1 is MgBr or Mgl.

[0040] In some embodiments, X^1 is Li. In some embodiments, X^1 is CuLi.

[0041] In embodiments, X^1 is ZnX^3 , wherein X^3 is Cl, Br, I, OTf, OTs, OAc, or acac. In some embodiments, X^1 is ZnCl or ZnBr. In some embodiments, X^1 is ZnCl. In some embodiments, X^1 is ZnBr. In some embodiments, X^1 is ZnOTf or ZnOTs. In some embodiments, X^1 is ZnOAc or Zn(acac). In some embodiments, X^1 is In(I) or InCl or InBr or InI.

[0042] Compound J and the allyl nucleophile can be present in a molar ratio of 1:1.05 to 1:3, for example, at least a molar ratio of 1:1, 1.05, 1:1.2, 1:1.5, 1:1.75, 1:2, 1:2.25, 1:2.5, and/or up to 1:3, 1:2.75, 1:2.5, 1:2.25, 1:2, or 1:1.5, such as 1:1 to 1:2.5, 1:1 to 1:2, 1:1 to 1:3, 1:1.25 to 1:2, or 1:1.1 to 1:3. In some embodiments, the molar ratio of compound J to the allyl nucleophile is 1:1.2.

[0043] In some embodiments, the admixing of step (c), the allylic addition, can occur in an organic solvent. In some embodiments, the organic solvent comprises tetrahydrofuran (THF), 2-methyltetrahydrofuran, tert-butyl methyl ether (MTBE), cyclopentyl methyl ether, dimethoxyethane, or a combination thereof. In some embodiments, the organic solvent comprises tert-butyl methyl ether. In some embodiments, the organic solvent comprises THF. In some embodiments, the organic solvent comprises THF and MTBE.

[0044] In some embodiments, compound J can be added to the allyl nucleophile dropwise. In some embodiments, compound J is added to the allyl nucleophile dropwise over 1 hour to about 5 hours, such as, over 1 hour, 2 hours, 3 hours, 4 hours or 5 hours. In some embodiments, compound J is added to the allyl nucleophile dropwise over 3 hours.

[0045] In some embodiments, after compound J and the allyl nucleophile are combined, the two are admixed for 1 hour to 6 hours, such as 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 5 hours, or 6 hours. In some embodiments, the admixing of step (c) occurs for 3 hours.

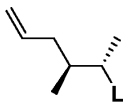
[0046] The admixing of step (c) can occur at a temperature of $-20\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$, for example at least -20 , -15 , -10 , -5 , 0 , 5 , or 10 and/or up to 10 , 7 , 5 , 0 , or -10 , such as $-15\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$, $-10\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$, $-5\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$, $0\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$, or $7\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$. In some embodiments, the admixing occurs at a temperature of $7\text{ }^{\circ}\text{C}$ to $10\text{ }^{\circ}\text{C}$.

[0047] In some embodiments, the reaction of compound J and the allyl nucleophile can be quenched by adding to a solution of citric acid in water.

[0048] The allylic addition provides compound K which can be through-processed directly into the next step without the need for substantial purification.

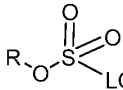
[0049] Leaving Group Addition to Compound K to Form Compound L (Step (d))

[0050] The processes of the disclosure includes the leaving group (LG) addition to compound K to provide compound L. The processes herein can comprise synthesizing compound L by admixing compound K, a leaving group reagent, and an amine base to form compound L. As

provided herein, compound L has a structure of  (L), wherein LG is a leaving group.

[0051] Compound K is reacted with a leaving group reagent and an amine base, which converts the hydroxyl group of compound K into a leaving group to form compound L. The leaving group as used herein refers to any suitable atom or functional group that can be displaced by a nucleophile upon nucleophilic substitution. Leaving group reagents that can convert a hydroxyl group to a leaving group to make nucleophilic substitution favorable are well known in the art. Nonlimiting examples of suitable leaving groups include halides, such as F, Cl, Br, or I, or sulfonyls.

[0052] In some embodiments, LG is a sulfonyl leaving group. As used herein, the term “sulfonyl leaving group” refers to a leaving group in which the oxygen atom of a hydroxyl group is bound

to a sulfonyl group - , where R-O is derived from the hydroxyl group being converted to a leaving group and LG' is derived from the rest of the sulfonyl leaving group. In some embodiments, the sulfonyl leaving group is selected from the group consisting of mesyl, tosyl, nosyl, and triflyl. In some embodiments, the sulfonyl leaving group comprises mesyl.

[0053] In general, the leaving group reagent can be any suitable leaving group reagent known to one of ordinary skill in the art as is used to convert a hydroxyl group to a leaving group. In some embodiments, the leaving group reagent can comprise mesyl chloride.

[0054] Compound K and the leaving group reagent can be present in a molar ratio of 1:1.2 to 1:2, for example, at least a molar ratio of 1:1.2, 1:1.5, 1:1.6 and/or up to 1:2, 1:1.75, 1:1.5, such as 1:1.2 to 1:1.9, 1:1.2 to 1:7, or 1:1.2 to 1:1.5. In some embodiments, the molar ratio of compound K and the leaving group reagent is 1:1.4.

[0055] The admixing of step (d) can include an amine base (e.g., mono-, di-, or trialkylamines, substituted or unsubstituted piperidines, substituted or unsubstituted pyridines). In some

embodiments, the amine base comprises pyridine, trimethylamine, 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. In some embodiments, the amine base is triethylamine.

[0056] Compound K and the amine base can be present in a molar ratio of 1:1.8 to 1:3.3, for example, at least a molar ratio of 1:1.8, 1:2, 1:2.5 and/or up to 1:3.3, 1:3, 1:2.5, such as 1:1.8 to 1:3, 1:2 to 1:3, or 1:2 to 1:2.5. In some embodiments, the molar ratio of compound K and the leaving group reagent is 1:2.3.

[0057] In some embodiments, the admixing of step (d), the leaving group addition, can occur in an organic solvent comprising dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, tert-butyl methyl ether, or a combination thereof. In some embodiments, the organic solvent comprises tert-butyl methyl ether. In some embodiments, the organic solvent comprises THF. In some embodiments, the organic solvent does not comprise dichloromethane.

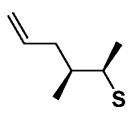
[0058] In some embodiments, the leaving group reagent can be added slowly to a solution of compound K and the amine base. In some embodiments, the leaving group reagent is added to the solution of compound K and the amine base over 2 hours to 3 hours, such as, over 2 hours, 2.5 hours, or 3 hours. In some embodiments, the leaving group reagent is added to the solution of compound K and the amine base over 2 hours to 3 hours and then stirred for 10 minutes to an hour. In some embodiments, the leaving group reagent is added to the solution of compound K and the amine base over 2.5 hours. In some embodiments, the leaving group reagent is added to the solution of compound K and the amine base over 2.5 hours and then stirred for 30 minutes.

[0059] The admixing of step (d) can occur at a temperature of -10 °C to 10 °C, for example at least -10, -5, 0, or 5 and/or up to 10, 7, 5, 0, or -10, such as -10 °C to 5 °C, -10 °C to 0°C, -5 °C to 10°C, 0 °C to 10 °C. In some embodiments, the admixing occurs at a temperature of 5°C.

[0060] The leaving group addition provides compound L which can be through-processed directly into the next step without the need for substantial purification.

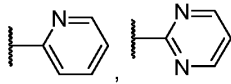
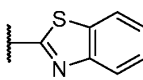
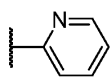
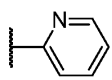
[0061] Nucleophilic Substitution of Compound L to Form Compound M (Step (e))

[0062] The processes of the disclosure include the nucleophilic substitution of compound L to provide compound M. The processes herein comprise synthesizing compound M by admixing compound L, a non-nucleophilic base, and Ar¹-SH to form compound M. As provided herein,

compound M has a structure of  S-Ar¹ (M), wherein Ar¹ is a 5-12 membered heteroaryl comprising from 1 to 3 ring heteroatoms selected from O, N, and S.

[0063] As used herein, the term "heteroaryl" refers to a cyclic aromatic ring having five to twelve

total ring atoms (e.g., a monocyclic aromatic ring with 5-6 total ring atoms), and containing one to three heteroatoms selected from nitrogen, oxygen, and sulfur in the aromatic ring. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one or more, and in particular one to four, substituents selected from, for example, halo, alkyl, alkenyl, OCF_3 , NO_2 , CN, NC, OH, alkoxy, amino, CO_2H , CO_2alkyl , aryl, and heteroaryl. In some cases, the heteroaryl group is substituted with one or more of alkyl and alkoxy groups. Heteroaryl groups can be isolated (e.g., pyridyl) or fused to another heteroaryl group (e.g., purinyl), a cycloalkyl group (e.g., tetrahydroquinoliny), a heterocycloalkyl group (e.g., dihydronaphthyridinyl), and/or an aryl group (e.g., benzothiazolyl and quinolyl). Examples of heteroaryl groups include, but are not limited to, thienyl, furyl, pyridyl, pyrrolyl, oxazolyl, quinolyl, thiophenyl, isoquinolyl, indolyl, triazinyl, triazolyl, isothiazolyl, isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl. When a heteroaryl group is fused to another heteroaryl group, then each ring can contain five or six total ring atoms and one to three heteroatoms in its aromatic ring.

[0064] In some embodiment, Ar^1 is selected from the group consisting of , , and . In some embodiments, Ar^1 is .

[0065] Compound L and $\text{Ar}^1\text{-SH}$ can be present in a molar ratio of 1:1.05 to 1:2.5, for example, at least a molar ratio of 1:1.05, 1:1.25, 1:1.5, 1:1.6 and/or up to 1:2.5, 1:2, 1:1.75, 1:1.5, such as 1:1.05 to 1:2.25, 1:1.1 to 1:2, or 1:1.05 to 1:1.2. In some embodiments, the molar ratio of compound L and $\text{Ar}^1\text{-SH}$ is 1:1.08.

[0066] The non-nucleophilic base as used herein can be any suitable non-nucleophilic base known to one of ordinary skill in the art. Suitable non-nucleophilic bases can include, for example, 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, 2,2,6,6-Tetramethylpiperidine (TMP), LiTMP, 1,1,3,3-tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene, and any combination thereof. In some embodiments, the non-nucleophilic base 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. In some embodiments, the non-nucleophilic base comprises sodium *tert*-butoxide, potassium *tert*-butoxide, or sodium *tert*-amylate.

[0067] Compound L and the non-nucleophilic base can be present in a molar ratio of 1:1.1 to 1:4, for example, at least a molar ratio of 1:1.1, 1:1.2, 1:1.5, 1:2, 1:2.5 and/or up to 1:4, 1:3.5, 1:3, 1:2.5, such as 1:1.1 to 1:3, 1:1.1 to 1:2, or 1:1.1 to 1:1.3. In some embodiments, the molar ratio of compound L and the non-nucleophilic base is 1:1.2.

[0068] In some embodiments, the admixing of step (e), can occur in an organic solvent comprising tetrahydrofuran, 2-methyltetrahydrofuran, tert-butyl methyl ether, toluene, or a combination thereof. In some embodiments, the organic solvent comprises THF.

[0069] The organic solvent can be present in an amount of 10 L/kg of compound L to 25 L/kg of compound L, for example, at least 10, 15, 20 L/kg of compound L and/or up to 25, 20, or 15 L/kg of compound L, such as 10 to 20 L/kg of compound L, 10 to 15 L/kg of compound L, or 15 L/kg to 22 L/kg of compound L.

[0070] In some embodiments, compound L can be added slowly to a mixture comprising Ar¹-SH and the non-nucleophilic base. In some embodiments, compound L is added dropwise to a mixture comprising Ar¹-SH and the non-nucleophilic base over 3 hours to 6 hours, such as, over 3 hours, 3.5 hours, 4 hours, 5 hours, 5.5 hours, or 6 hours. In some embodiments, compound L is added dropwise to a mixture comprising Ar¹-SH and the non-nucleophilic base over 5 hours.

[0071] In some embodiments, the admixing of step (e) occurs for 3 hour to 5 hours, such as 3 hour, 3.5 hours, 4 hours, 4.5 hours, or 5 hours. In some embodiments, the admixing of step (e) occurs for 4 hours.

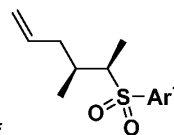
[0072] The admixing of step (e) can occur at a temperature of 60 °C to 80 °C, for example at least 60 or 65°C and/or up to 80, 75, 70, or 68, such as 60 °C to 75 °C, 65 °C to 75°C, or 65 °C to 80°C,. In some embodiments, the admixing occurs at a temperature of 68°C.

[0073] Formation of compound M in step (e) can be through-processed directly into the next step without the need for substantial purification. In some embodiments, compound M is washed three to five times with aqueous sodium hydroxide prior to the oxidizing of step (f).

Advantageously, washing compound M three to five times (e.g., five times) removes residual Ar¹-SH, resulting in improved purity profile and yield, as well as avoiding further purification (e.g., chromatographic purification).

[0074] Oxidation of Compound M to Form Compound N (Step (f))

[0075] The processes of the disclosure include the oxidation of compound M to provide compound N. The oxidizing includes admixing compound M and an oxidizing agent to form



compound N. As provided herein, compound N has a structure of (N), wherein Ar¹ is as defined above.

[0076] Suitable oxidizing agents are generally known in the art. Nonlimiting examples of oxidizing agents include peracids such as m-chloroperbenzoic acid (mCPBA), hydrogen peroxide, tert-butyl hydroperoxide and the like; perchlorates such as tetrabutylammonium perchlorate and the like; chlorates such as sodium chlorate and the like; chlorites such as sodium chlorite and the like; hypochlorites such as bleach and the like, periodates such as sodium periodate and the like; a high-valent iodine reagent such as iodosylbenzene, iodobenzenediacetate, and the like; a reagent having manganese, such as manganese dioxide, potassium permanganate and the like; leads such as lead tetraacetate and the like; a reagent having chromium, such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Jones reagents and the like; halogen compounds such as N-bromosuccinimide (NBS) and the like; oxygen; ozone; a sulfur trioxide-pyridine complex; osmium tetroxide; selenium dioxide; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In some embodiments, the oxidizing agent is hydrogen peroxide.

[0077] Compound M and the oxidizing agent can be present in a molar ratio of 1:1.3 to 1:5, for example at least 1:1.3, 1:1.5, 1:2, or 1:3 and/or up to 1:3, 1:2, 1:1.8, or 1:1.5, such as 1:1.3 to 1:4, 1:1.3 to 1:3, 1:1.3 to 1:2, or 1:1.3 to 1:1.8. In some embodiments, the molar ratio of compound M to the oxidizing agent is 1:1.5.

[0078] The oxidation of compound M can further include admixing compound M and the oxidizing reagent with an oxidation catalyst. Nonlimiting examples of oxidation catalysts include 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), tetrapropylammonium perruthenate (TPAP), 9-azabicyclo[3.3.1]nonane N-oxyl (ABNO), metal catalysts (e.g., copper, iron, etc.), 2-azaadamantane-N-oxyl, 1-methyl-2-azaadamantane-N-oxyl, 1,3-dimethyl-2-azaadamantane-N-oxyl, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, sodium tungstate dehydrate, and 3-chloroperbenzoic acid. In some embodiments, the oxidation catalyst is sodium tungstate dehydrate, 3-chloroperbenzoic acid, or a combination thereof. In some embodiments, the oxidation catalyst, is sodium tungstate dehydrate. In some embodiments, the admixing of step (f) can comprise hydrogen peroxide and sodium tungstate dehydrate.

[0079] When the oxidation catalyst is present, compound M and the oxidation catalyst can be present in a molar ratio of 1:0.05 to 1:0.5, for example, at least 1:0.05, 0.04, 1:0.1, 1:0.2, 1:0.3, or 1:0.5 and/or up to 1:0.5, 1:0.4, 1:0.3, 1:0.2, or 1:0.1, such as 1:0.05 to 1:0.4, 1:0.05 to 1:0.3, or 1:0.05 to 1:0.2. In some embodiments, the molar ratio of compound M to the oxidation catalyst is 1:0.1.

[0080] In some embodiments, the oxidizing of step (f) further comprises acetic acid. Advantageously, when acetic acid is admixed in the oxidation step, the acetic acid can enhance safety by allowing lower amounts of hydrogen peroxide to be used, improve the purity profile of compound N, and increases conversion to product because the acetic acid stabilizes the hydrogen peroxide reagent.

[0081] In some embodiments, the oxidizing of step (f), the oxidation reaction, can occur in a solvent, such as, an alcohol solvent (e.g., methanol, ethanol, isopropanol). In some embodiments, the solvent is methanol.

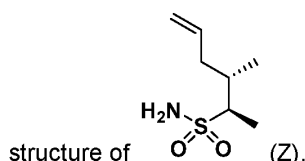
[0082] In some embodiments, the oxidizing of step (f) occurs for 12 hours to 48 hours, such as 12 hour, 15 hours, 20 hours, 24 hours, 30 hours, 35 hours, 40 hours, or 48 hours. In some embodiments, the admixing of step (f) occurs for 24 hours.

[0083] In some embodiments, the oxidizing of step (f) can occur at a temperature that is maintained at $25\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$. In some embodiments, the oxidizing of step (f) occurs at a temperature of $20\text{ }^{\circ}\text{C}$ to $25\text{ }^{\circ}\text{C}$.

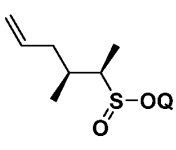
[0084] In some embodiments, compound N can be crystallized from oxidizing of step (f). In some embodiments, crystallization of compound N can occur by adding water to the oxidizing of step (f). Advantageously, crystallization of compound N occurs by addition of water to the oxidizing of step (f), wherein the direct crystallization prior to extraction of compound N improves throughput and yield, as well as improving the purity profile of the reaction mixture.

[0085] Sulfonamidation of Compound N to Form Compound Z

[0086] The processes of the disclosure include the sulfonamidation of compound N to provide compound Z, step (g). The sulfonamidation includes admixing compound N, a base, and hydroxylamine-O-sulfonic acid to form compound Z. As provided herein, compound Z has a



[0087] In some embodiments, compound N and a base are admixed together in a solvent to form an intermediate compound O prior to admixing with hydroxylamino-O-sulfonic acid. As

provided herein, compound O has a structure of  (O), wherein Q is an alkali metal cation. In some embodiments, Q is lithium, sodium potassium, or a combination thereof. In some embodiments, Q is sodium. In some embodiments, the admixing of compound N and a base occurs in a solvent. In some embodiments, the solvent comprises tert-butyl methyl ether, methanol, tetrahydrofuran, 2-methyltetrahydrofuran, or a combination thereof. In some embodiments, the solvent comprises tert-butyl methyl ether and methanol.

[0088] In some embodiments, the base comprises sodium thiomethoxide, sodium methoxide, potassium carbonate and methanol, or a combination thereof. In some embodiments, the base comprises sodium thiomethoxide.

[0089] In some embodiments, the admixing of compound N and the base occurs for 6 hours to 18 hours, such as 6 hours, 8 hours, 10 hours, 12 hour, 14 hours, 15 hours, or 18 hours. In some embodiments, the admixing of compound N and the base occurs for 12 hours.

[0090] In some embodiments, the admixing of compound N and the base can occur at a temperature of 25 °C to 50 °C, for example at least 25, 30, 35, 40°C and/or up to 50, 45, 40, or 35°C, such as 25 °C to 45 °C, 30 °C to 45°C, or 30 °C to 40°C. In some embodiments, the admixing of compound N and the base occurs at a temperature of 35°C.

[0091] In some embodiments, the admixing of compound N and the base provides the intermediate compound O which can be through-processed directly in to the addition of hydroxylamine-O-sulfonic acid without the need for substantial purification. In some embodiments, hydroxylamine-O-sulfonic acid is added with sodium acetate, potassium acetate, sodium formate, potassium formate, or a combination thereof, to the intermediate compound O. In some embodiments, hydroxylamine-O-sulfonic acid is added with sodium acetate to the intermediate compound O. In some embodiments, hydroxylamine-O-sulfonic acid is added with sodium acetate trihydrate to the intermediate compound O.

[0092] In some embodiments, the admixing of the intermediate compound O, hydroxylamine-O-sulfonic acid, and sodium acetate occurs in a solvent. In some embodiments, the solvent comprises tert-butyl methyl ether, methanol, 2-methyltetrahydrofuran, or a combination thereof. In some embodiments, the solvent comprises tert-butyl methyl ether and methanol. In some embodiments, the solvent can be a biphasic mixture. In some embodiments, the biphasic mixture comprises water and an organic solvent, such as tert-butyl methyl ether.

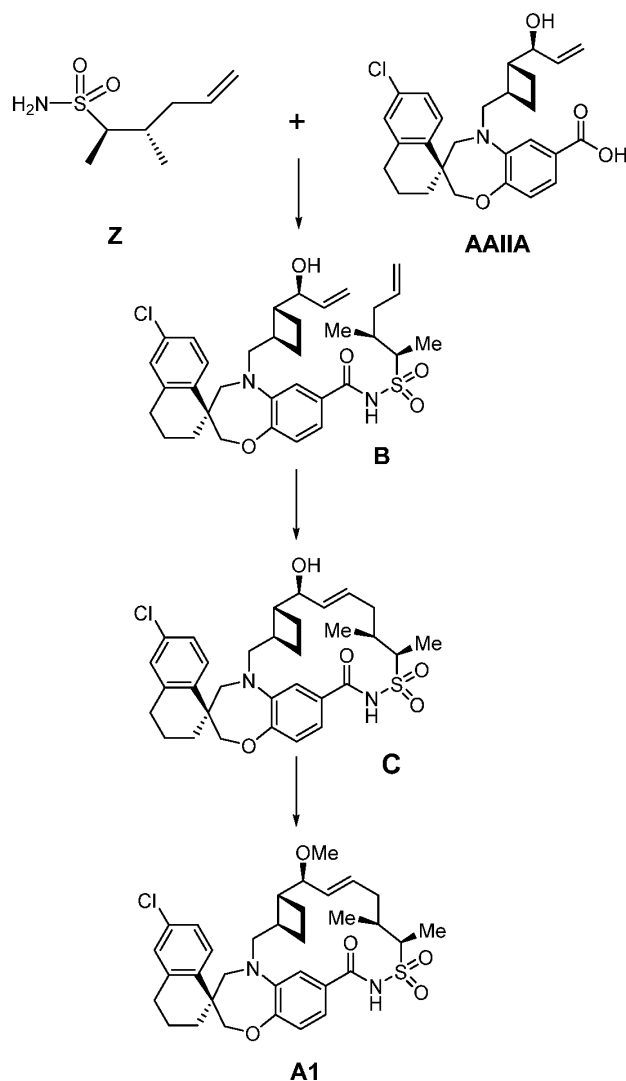
[0093] In some embodiments, the admixing of the intermediate compound O, hydroxylamine-O-sulfonic acid, and sodium acetate occurs for 30 minutes to 4 hours, such as 30 minutes, 1 hours, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours or 4 hours. In some embodiments, the admixing of the intermediate compound O, hydroxylamine-O-sulfonic acid, and sodium acetate occurs for 2 hours.

[0094] In some embodiments, the admixing of the intermediate compound O, hydroxylamine-O-sulfonic acid, and sodium acetate can occur at a temperature of 25 °C to 50 °C, for example at least 25, 30, 35, 40°C and/or up to 50, 45, 40, or 35°C, such as 25 °C to 45 °C, 30 °C to 45°C, or 30 °C to 40°C. In some embodiments, the admixing of the intermediate compound O, hydroxylamine-O-sulfonic acid, and sodium acetate occurs at a temperature of 35°C.

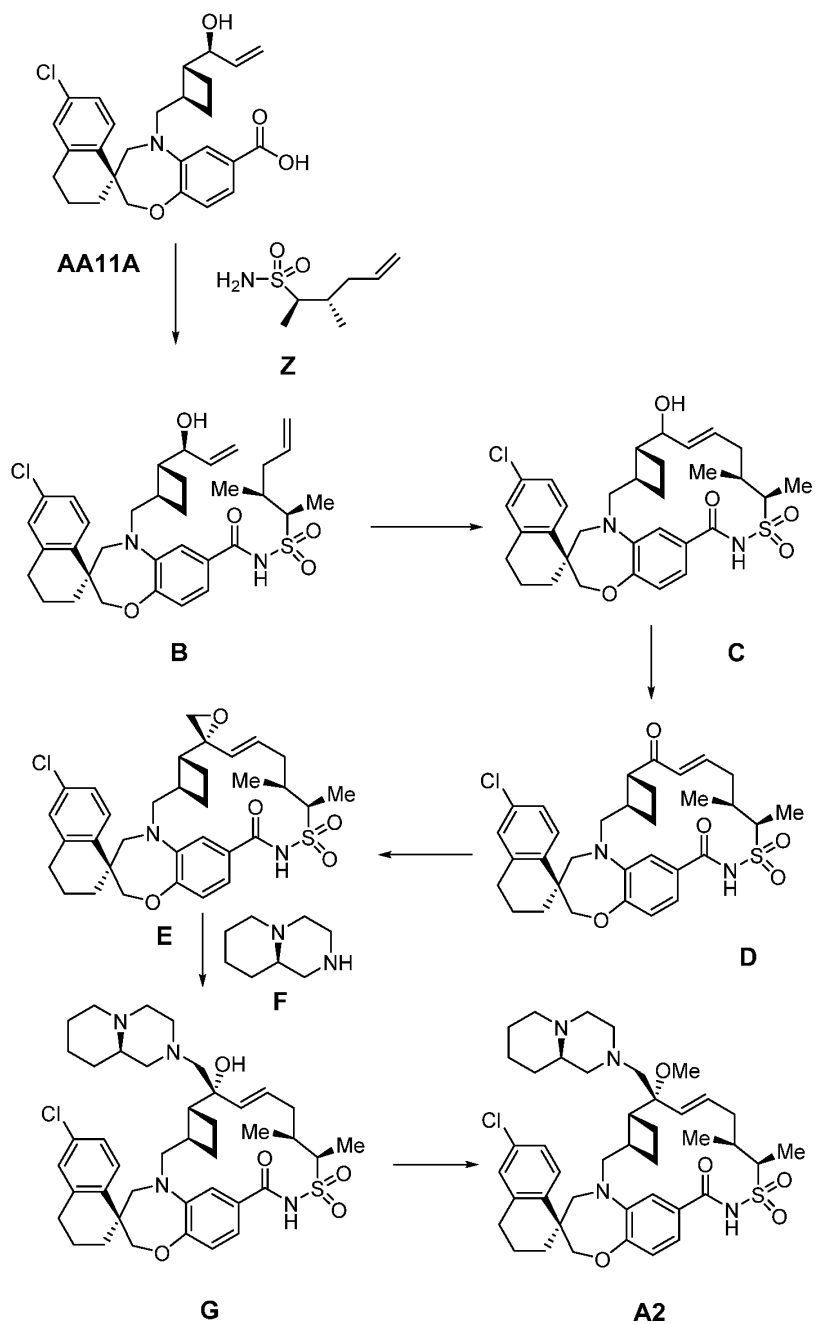
[0095] In some embodiments, compound Z can be crystallized from the sulfonamidation of step (g). In some embodiments, crystallization of compound Z comprises heating a solution of compound Z, then cooling the solution and adding a crystallizing solvent to the cooled solution to form crystals of compound Z. In some embodiments, 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. In some embodiments, the solution of compound Z comprises tert-butyl methyl ether and the crystallizing solvent comprises heptane. In some embodiments, the solution of compound Z comprises methanol and the crystallizing solvent comprises water. Advantageously, crystallization of compound Z comprises heating a solution of compound Z to 40°C to 45°C, which prevents compound Z from melting, provides a controlled crystallization, increases the yield, and improves the impurity profile. Further, the crystallization of compound Z comprises heating a solution of compound Z to 40°C to 45°C which increases purity of the product, removes chiral impurities, and rejects the crystallization of alternative chiral impurities. The crystallization of compound Z advantageously purifies the product without chromatography and its associated yield loss.

[0096] Compound Z, prepared by the processes disclosed herein, can be used to synthesize compounds A1 and A2. As shown in Scheme 3, compound Z may be used to synthesize compound A1 and salts and solvates thereof and as shown in Scheme 4, compound Z may also be used to synthesize compound A2 and salts and solvates thereof.

Scheme 3 – Conversion of Compound Z to Compound A1

[0097] As shown in Scheme 3 and described in U.S. Patent No. 9,562,061 compound Z may be used to synthesize compound A1 and salts and solvates thereof. The synthesis of AA11A is disclosed in U.S. Patent No. 9,562,061. As set forth in U.S. Patent No. 9,562,061, compounds Z and AA11A can be reacted to form compound B. Cyclization of compound B provides hydroxy compound C which can then be methylated to provide compound A1 as described in U.S. Patent No. 9,562,061.



[0098] As shown in Scheme 4 and described in U.S. Patent No. 10,300,075, compound Z may be used to synthesize compound A2 and salts and solvates thereof. As described above with respect to Scheme 3, the synthesis of AA11A is disclosed in U.S. Patent No. 9,562,061. As described above and set forth in U.S. Patent No. 9,562,061 sulfonamide Z and AA11A can be reacted to form compound B which can be cyclized to product hydroxy compound C.

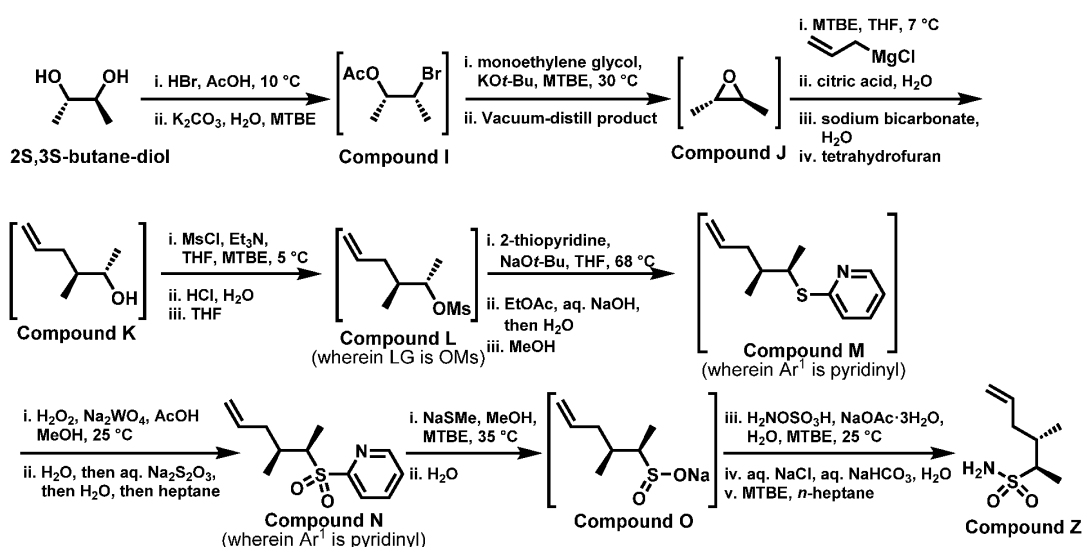
Compound C can then be oxidized to provide cyclic enone D as disclosed in U.S. Patent No. 10,300,075. Alternatively, compound B can be oxidized to provide the uncyclized enone version of compound C and then cyclized to provide cyclic enone D. Enone D can then be converted to epoxide E using the procedures disclosed in U.S. Patent No. 10,300,075. Epoxide E can then be reacted with bicyclic compound F to provide hydroxy compound G. Finally, methylation of compound G provides compound A2 as disclosed in U.S. Patent No. 10,300,075.

[0099] It is to be understood that while the disclosure is read in conjunction with the detailed description thereof, the foregoing description and following example are intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

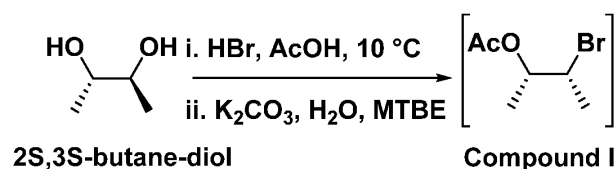
EXAMPLES

[0100] The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1: Formation of Compound Z



[0101] Synthesis of Compound I

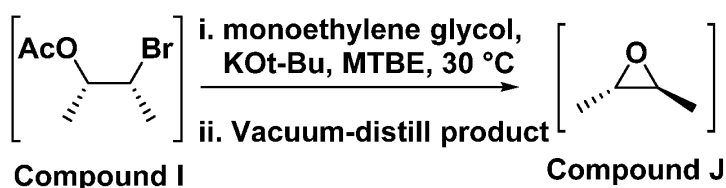


[0102] (2S,3R)-3-bromobutan-2-yl acetate (Compound I): To a 20 L glass lined, jacketed reactor was charged hydrogen bromide (33% w/w solution in acetic acid; 3.5 kg, 14.3 mol, 3.5 equiv.). The solution was cooled to +10 °C, and (2S,3S)-butane-2,3-diol (368 g, 4.08 mol, 1.0

equiv.) was added slowly while maintaining temperature no more than +10 °C (NMT +10 °C). The mixture was stirred at +10 °C for 15-20 h. The reaction mixture was then added slowly to a pre-cooled stirring solution of potassium carbonate (1.84 kg, 3.26 equiv.) in water (3.68 L, 10.0 L/kg) over 8 hours, maintaining the temperature less than +10 °C. The mixture was diluted with *tert*-butyl methyl ether (1.84 L, 5.00 L/kg), warmed to +20 to +25 °C, and stirred at least 30 min. The phases were separated and the resulting aqueous layer was washed with *tert*-butyl methyl ether (1.10 L, 3.00 L/kg). The combined organic layers were washed with a solution of potassium carbonate (644 g, 1.14 equiv.) in water (2.4 L, 6.5 L/kg). The organic layer was washed with water (740 mL, 2.0 L/kg) and distilled under reduced pressure at +45 °C. At the end of distillation, the solution was sampled to confirm low water content, and diluted with *tert*-butyl methyl ether to ~1.10 L total volume (3 L/kg). Potency-adjusted assay yield was 95-97%, typical GC-purity was > 95.0 Area%. The resulting solution of compound I in *tert*-methyl methyl ether was suitable for use directly in the next step of the process.

[0103] A sample of compound I was concentrated *in vacuo* for characterization by NMR. ¹H NMR (300 MHz, CDCl₃) □□4.84 - 4.78 (m, 1H), 4.16 - 4.04 (m, 1H), 1.96 (s, 3H), 1.55 (d, J = 7.1 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H); LRMS (ESI): Calcd. for C₆H₁₁BrO₂+Na: 217.0, found: 217.0.

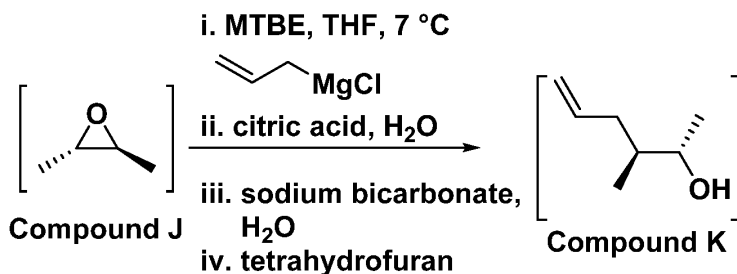
[0104] Synthesis of Compound J



[0105] **(2S,3S)-2,3-dimethyloxirane** (Compound J): To a 20 L glass lined, jacketed reactor was charged monoethylene glycol (1.22 L, 2.88 L/kg). Solid potassium *tert*-butoxide (612 g, 5.45 mol, 2.50 equiv.) was added portion-wise over ~5 h, maintaining the temperature below +40 °C. The resulting mixture was distilled under reduced pressure at +90 – 120 °C, removing approximately 500 mL of *tert*-butanol. Solvent *tert*-butyl methyl ether (2.13 L, 5.0 L/kg) was added, and the mixture was distilled under reduced pressure until the *tert*-butanol content was measured below 0.4% wt/wt by GC. After cooling to +30 °C, a solution of compound I (425 g, 2.18 mol, 1.0 equiv.) in *tert*-butyl methyl ether (425 mL, 1.00 L/kg) was added over 30 min, followed with washing the line with *tert*-butyl methyl ether (425 mL, 1.00 L/kg). The resulting mixture was stirred for 30 min at +30 °C. The reaction mixture was distilled directly under reduced pressure (condenser setting -15 °C). The product compound J was obtained in 75-80% potency-adjusted yield, with typical GC-purity > 98.0 Area%. The resulting solution of SS-DMO, containing residual *tert*-butyl methyl ether, was suitable for use directly in the next step of the process.

[0106] ^1H NMR (300 MHz, CDCl_3) δ 2.64 – 2.58 (m, 2H), 1.19 – 1.15 (m, 6H).

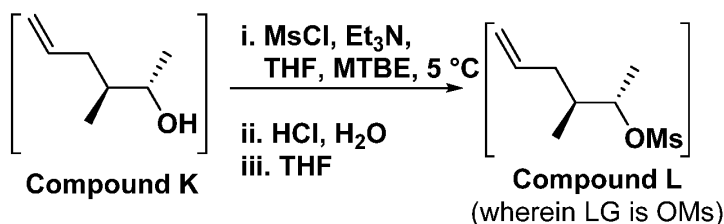
[0107] Synthesis of Compound K



[0108] **(2S,3S)-3-methylhex-5-en-2-ol** (Compound K): To a 20 L glass lined, jacketed reactor was charged allylmagnesium chloride solution in tetrahydrofuran (18% w/w solution, 7.28 mol, 1.20 equiv.) and cooled to +7 to +10 °C. A solution of compound J (438 g, 6.07 mol, 1.00 equiv.) in *tert*-butyl methyl ether (657 mL, 1.5 L/kg) was added dropwise over 3 h, maintaining the temperature below +7 °C. The reaction was stirred at +7 to +10 °C for another 3 h. The reaction mixture was added dropwise over 2 to 3 h to a pre-cooled stirred solution of citric acid monohydrate (1.68 kg, 7.89 mol, 1.3 equiv.) in water (3.50 L, 8.00 L/kg), maintaining the temperature at +5 to +10 °C. The resulting mixture was warmed to +25 °C and stirred for 30 min. The phases were separated, and the aqueous layer was washed two times with *tert*-butyl methyl ether (2x 876 mL, 2x 2.00 L/kg). The organic layers were combined, washed two times with aqueous sodium bicarbonate solution (0.8 mol/L solution; 2x 2.63L, 2x 6.0 L/kg), and then washed two times with aqueous sodium chloride solution (5.3 mol/L solution; 2x 876 mL, 2x 2.0 L/kg). The organic layer was distilled under reduced pressure at +30 °C to a total volume of 1.3 L (3.0 L/kg). Three times, solvent tetrahydrofuran (3x 1.3 L, 3x 3.0 L/kg) was added, and the mixture was distilled under reduced pressure at +30 °C to a final volume of 1.3 L (3.0 L/kg). Potency-adjusted assay yield was 90-95%, typical GC-purity was > 88.0 Area%. The resulting solution of compound K in tetrahydrofuran was suitable for use directly in the next step of the process.

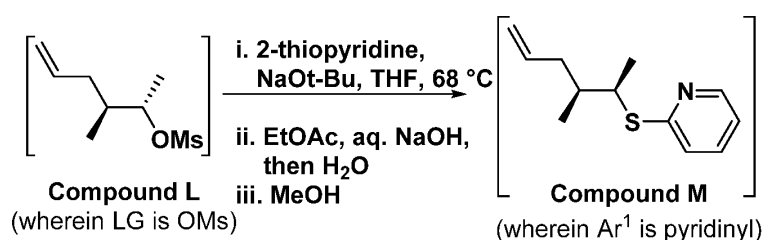
[0109] A sample of compound K was concentrated *in vacuo* for characterization by NMR. ^1H NMR (300 MHz, CDCl_3) δ 5.81 – 5.67 (m, 1H), 5.02 – 4.89 (m, 2H), 3.70 – 3.63 (m, 1H), 2.22 – 2.10 (m, 1H), 1.90 – 1.75 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H). LRMS (ESI): Calcd. for $\text{C}_7\text{H}_{14}\text{O}_1+\text{Na}$: 137.1, found: 137.1.

[0110] Synthesis of Compound L (wherein LG is OMs)



[0111] **(2S,3S)-3-methylhex-5-en-2-yl methanesulfonate** (Compound L, wherein LG was OMs): To a 20 L glass lined, jacketed reactor were charged a solution of compound K (717 g, 4.97 mol, 1.00 equiv.) in tetrahydrofuran (700 mL, 1.0 L/kg) and solvent *tert*-butyl methyl ether (5.7 L, 8.0 L/kg). The mixture was cooled to 0 °C and triethylamine (2.01 L, 11.4 mol, 2.30 equiv.) was charged, followed by *tert*-butyl methyl ether (700 mL, 1 L/kg). At 0 to +5 °C, methanesulfonyl chloride (680 mL, 6.96 mol, 1.40 equiv.) was added slowly over 2.5 h. The reaction was stirred at +5 °C for 30 min. Aqueous hydrochloric acid (1 mol/L solution; 5.0 L, 7.0 L/kg, 1.0 equiv.) was then added over 30 min, at < 15 °C. The biphasic mixture was warmed to +25 °C and stirred to 6 h and then the phases were separated. The aqueous phase was extracted with *tert*-butyl methyl ether (2.9 L, 4.0 L/kg). The combined organic phases were washed with aqueous hydrochloric acid (1 mol/L solution; 2.9 L, 4.0 L/kg, 0.6 equiv.), washed twice with aqueous sodium chloride (5.7 mol/L solution; 2x 1.4 L, 2x 3.0 L/kg), and washed with water (1.4 L, 2.0 L/kg). The organic phase was distilled under reduced pressure to 2.9 L (4.0 L/kg) total volume. Tetrahydrofuran (2.9 L, 4.0 L/kg) was added, and the mixture was distilled again under reduced pressure to 2.9 L (4.0 L/kg) total volume. Potency-adjusted assay yield was 93-97%, typical GC-purity was > 98.0 Area%. The resulting solution of compound L (wherein LG is OMs) in tetrahydrofuran was suitable for use directly in the next step of the process.

[0112] Synthesis of Compound M (wherein Ar¹ is pyridinyl)

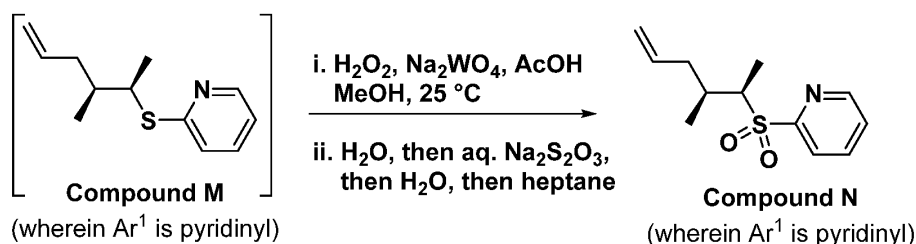


[0113] **2-(((2R,3S)-3-methylhex-5-en-2-yl)thio)pyridine** (Compound M, wherein Ar¹ is pyridinyl): To a 20 L glass lined, jacketed reactor were charged 2-thiopyridine (637 g, 5.73 mol, 1.08 equiv.) and tetrahydrofuran (10.0 L, 9.0 L/kg), and the resulting mixture was stirred for 30 min at 15 °C. Sodium *tert*-butoxide (612 g, 6.37 mol, 1.20 equiv.) was added in portions over 1 h, maintaining the temperature NMT +30 °C. After the addition, the reaction mixture was heated to gently reflux at +68 °C over 1 h. At this temperature, a solution of compound L (wherein LG is

OMs) (1,020 g, 5.31 mol, 1.00 equiv.) in tetrahydrofuran (1.0 L, 1.0 L/kg) was added dropwise over 5 h. The reaction was stirred for another 4 h. The reaction mixture was distilled at atmospheric pressure at +65 to +75 °C to remove approximately 6L of solvent. The mixture was cooled to +20 °C and water (3.0 L, 3.0 L/kg) and ethyl acetate (5.0 L, 5.0 L/kg) were added. The mixture was stirred for 30 min at +25 °C until all solids dissolve. The layers are separated and the aqueous layer was extracted with ethyl acetate (3.0 L, 3.0 L/kg). The combined organic phases were washed five times with aqueous sodium hydroxide (1 mol/L solution; 5x 2.2 L, 5x 2.2 L/kg), then one time with water (4.0 L, 4.0 L/kg). The organic layer was vacuum distilled to 3 L total volume. Twice, methanol (2x 5.0 L, 2x 5.0 L/kg) was added, and the mixture was distilled to 3L total volume. Potency-adjusted assay yield was 68-75%, typical LC-purity was > 95.0 Area%. The resulting solution of compound M (wherein Ar¹ is pyridinyl) in methanol was suitable for use directly in the next step of the process.

[0114] A sample of compound M (wherein Ar¹ is pyridinyl) was concentrated *in vacuo* for characterization by NMR. ¹H NMR (300 MHz, CDCl₃) □□ 8.30 (dd, J = 1.2, 5.1 Hz, 1H), 7.36 (ddd, J = 1.2, 7.9, 8.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 6.85 (dd, J = 5.1, 8.2 Hz, 1H). LRMS (ESI): Calcd. for C₁₂H₁₇N₁S₁+Na: 230.1, found: 230.1.

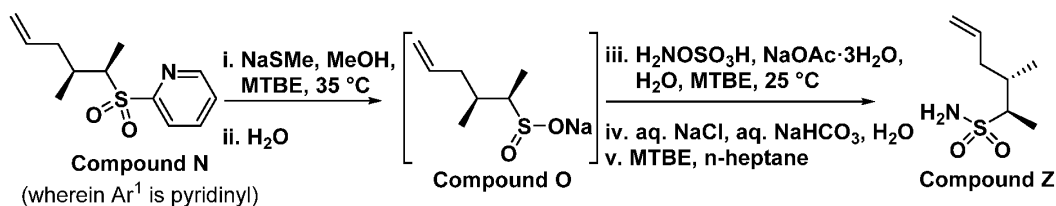
[0115] Synthesis of Compound N (wherein Ar¹ is pyridinyl)



[0116] **2-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)pyridine** (Compound N, wherein Ar¹ is pyridinyl): To a 10 L glass lined, jacketed reactor was charged compound M (wherein Ar¹ is pyridinyl) (468 g, 2.26 mol, 1.00 equiv.) and the mixture was diluted with methanol (1.4 L, 3.0 L/kg). Acetic acid (136 g, 2.26 mol, 1.00 equiv.) was added and then sodium tungstate dehydrate (75 g, 0.23 mol, 0.10 equiv.) was added. The mixture was stirred at +25 °C, and hydrogen peroxide (276 g, 2.94 mol, 1.3 equiv.) was added over 4.5 h, maintaining the temperature NMT + 25 °C. After the addition was complete, the reaction was stirred for 24 h. Water (2.34 L, 5.0 L/kg) was added over 1 h to induce crystallization. The crystallization mixture was cooled to 0 °C and stirred for 2 h. The product was then filtered at 0 °C and then the wet cake was washed under agitation with aqueous sodium thiosulfate (1.2 mol/L solution; 1.87 L, 4.0 L/kg, 2.26 mol, 1.00 equiv.) at +25 °C. The wet cake was washed under agitation with water (1.87 L, 4.0 L/kg) and was then washed with heptane (1.87 L, 4.0 L/kg). The product was dried under vacuum at +30 °C to yield 530 g compound N (wherein Ar¹ is pyridinyl) as a white crystalline solid (98% yield, 98.6 LC-Area% purity, 99.8% w/w assay).

[0117] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.81 (dd, $J = 1.2, 5.1$ Hz, 1H), 8.18 (ddd, $J = 1.2, 7.9, 8.2$ Hz, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 7.77 (dd, $J = 5.1, 8.2$ Hz, 1H), 5.68 (m, 1H), 5.05 (m, 2H), 3.70 (m, 1H), 2.26 (m, 1H), 2.05 (m, 2H), 1.09 (d, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 7.2$ Hz, 3H). LRMS (ESI): Calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_1\text{S}_1+\text{H}$: 208.3, found: 208.3. IR (neat) ν_{max} 3086, 2980, 2966, 2934, 1450, 1428, 1304, 1108, 794, 593, 541.

[0118] Synthesis of Compound Z



[0119] **(2R,3S)-3-methylhex-5-ene-2-sulfonamide** (Compound Z): To a 10 L glass lined, jacketed reactor are charged compound N (wherein Ar^1 is pyridinyl) (300 g, 1.25 mol, 1.00 equiv.) and sodium thiomethoxide (105 g, 1.50 mol, 1.20 equiv.). Degassed solvents *tert*-butyl methyl ether (3.30 L, 11.0 L/kg) and methanol (3.00 L, 1.00 L/kg) are added, and the resulting mixture was stirred at +35 $^\circ\text{C}$ for 12 h, until complete formation of compound O as measured by HPLC. The reaction was cooled to +25 $^\circ\text{C}$ and water (3.0 L, 10 L/kg) was added. The phases were separated, and the aqueous phase was washed twice with *tert*-butyl methyl ether (2x 1.5 L, 2x 5.0 L/kg). The organic phase was discarded. Air was bubbled into the product-rich aqueous layer for 4 h at +25 $^\circ\text{C}$ to consume residual sodium thiomethoxide. The aqueous layer was diluted with *tert*-butyl methyl ether (1.5 L, 5.0 L/kg). To the biphasic mixture was added sodium acetate trihydrate (200 g, 1.5 mol, 1.2 equiv.) and hydroxylamine-O-sulfonic acid (170 g, 1.5 mol, 1.2 equiv.). The biphasic mixture was stirred at +25 $^\circ\text{C}$ for 2 h until complete conversion of sulfinate to product compound Z, as measured by LC. Aqueous sodium chloride (5.5 mol/L solution, 1.35 L, 4.5 L/kg) was added and the mixture stirred for 30 min. The phases were separated, and the aqueous layer was extracted twice with *tert*-butyl methyl ether (2x 1.35 L, 2x 4.50 L/kg). The combined organic phases were washed sequentially with aqueous sodium bicarbonate (1 mol/L solution; 900 mL, 3.0 L/kg), with aqueous sodium chloride (5.5 mol/L solution, 600 mL, 2.0 L/kg), and water (600 mL, 2.0 L/kg). The organic phase was distilled under reduced vacuum at +40 to +45 $^\circ\text{C}$ to 600 mL total volume. Solvent *tert*-butyl methyl ether (1.35 L, 4.50 L/kg) was added, and the mixture was distilled under reduced vacuum +40 to +45 $^\circ\text{C}$ to 600 mL total volume. The solution was cooled to +15 $^\circ\text{C}$, and *n*-heptane (1.5 L, 5.0 L/kg) was added slowly over 2 h to promote crystallization. The slurry was cooled to 0 $^\circ\text{C}$ and stirred for 3 h. The product was filtered and the wet cake was washed with *n*-heptane (600 mL, 2.0 L/kg). The product was dried under vacuum at +30 $^\circ\text{C}$ to yield 168 g compound Z as a white crystalline solid (76% yield, 99.8 LC-Area% purity, 99.5% GC-purity, 100.0% w/w assay, 99.8% chiral-GC).

[0120] ^1H NMR (500 MHz, DMSO- d_6) δ 6.69 (s, 2H), 5.75 (m, 1H), 5.06 (m, 2H), 2.92 (m, 1H), 2.31 (m, 1H), 2.03 (m, 2H), 1.17 (d, $J = 7.2$ Hz, 3H), 0.92 (d, $J = 7.2$ Hz, 3H). LRMS (ESI): Calcd. for $\text{C}_7\text{H}_{15}\text{N}_1\text{O}_2\text{S}_1 + \text{Na}$: 200.1, found: 200.1. IR (neat) ν_{max} 3323, 3255, 2980, 2962, 1556, 1452, 1312, 1165, 11137, 900, 593, 548, 511.