

SYNTHESIS OF VINYL CYCLOBUTYL INTERMEDIATES

BACKGROUND**Cross References to Related Applications**

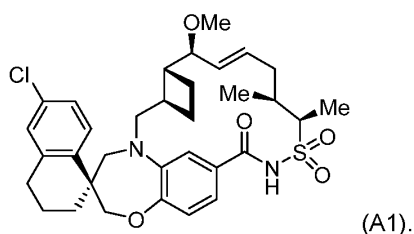
[0001] This application claims the benefit of U.S. Provisional Application No. 63/020,877, filed on May 6, 2020, which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

Technical Field

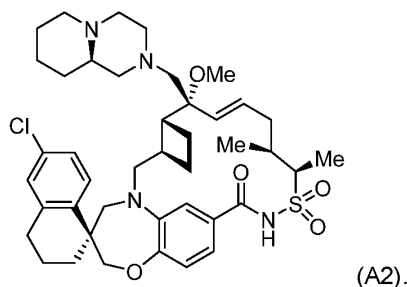
[0002] The present disclosure relates to intermediates and processes for synthesizing intermediates used in synthesizing (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0^{3,6}.0^{19,24}]pentacosa[8,16,18,24]tetraen]-15'-one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

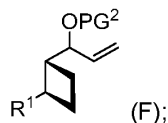
[0006] Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering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

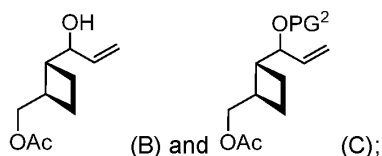
[0008] U.S. Patent No. 10,300,075, which is incorporated herein by reference in its entirety, discloses compound A2 as an Mcl-1 inhibitor and provides a method for preparing it. However, improved synthetic methods that result in greater yield and purity of compound A2 are desired, particularly for the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

SUMMARY

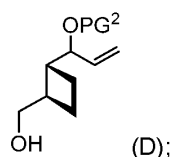
[0009] Provided herein are processes for synthesizing compound F or a salt thereof:



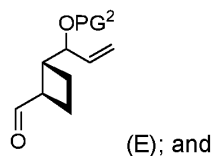
wherein OPG² is a secondary alcohol protecting group and R¹ is a protected aldehyde; comprising (a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



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



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



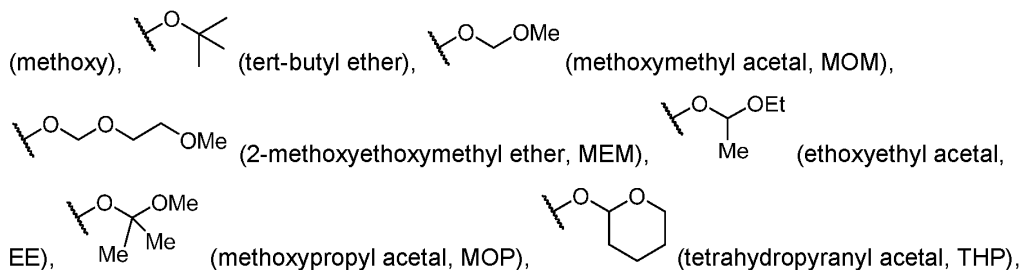
(d) protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof.

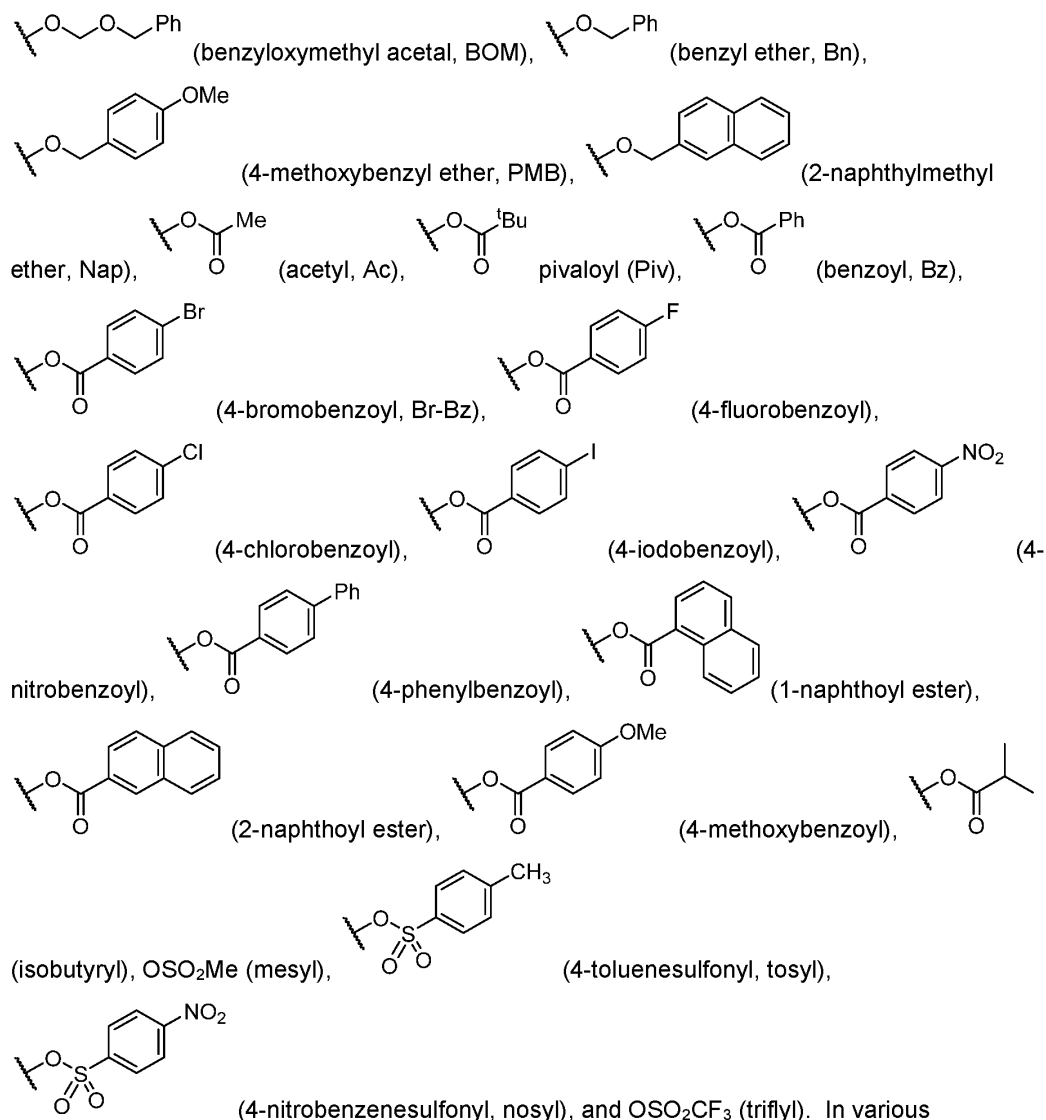
[0010] In various embodiments, OPG² comprises an acyl protecting group, an ether protecting group, acetal or ketal protecting group, a sulfonyl protecting group, and a silyl ether protecting group. In some cases, the acyl protecting group is selected from the group consisting of acetyl, pivaloyl, benzoyl, 4-bromobenzoyl, 4-chlorobenzoyl, 4-iodobenzoyl, 4-fluorobenzoyl, 4-nitrobenzoyl, 4-phenylbenzoyl, 1-naphthoyl, 2-naphthoyl, 4-methoxybenzoyl, and isobutyryl. In some cases, the acyl protecting group is 4-bromobenzoyl.

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

[0012] In various embodiments, 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 embodiments, OPG² is selected from the group consisting of





In various embodiments, the silyl ether protecting group is selected from the group consisting of OSiEt₃ (triethylsilyl ether, TES), OSi(*i*Pr)₃ (triisopropylsilyl ether, TIPS), OSiMe₃ (trimethylsilyl ether, TMS), OSiMe₂*t*Bu (*tert*-butyldimethylsilyl ether, TBS), and OSiPh₂*t*Bu (*tert*-butyldiphenylsilyl ether TBDPS).

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

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

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

[0020] In various embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the oxidizing agent is selected from the group consisting of oxalyl chloride/DMSO, bleach, SO₃/pyridine, iodobenzenediacetate, and any combination thereof. In some cases, the oxidizing agent is iodobenzenediacetate.

[0024] In various embodiments, 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 embodiments, the oxidizing further comprises admixing compound D and the oxidizing reagent with an oxidation catalyst. In various embodiments, 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 embodiments, 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.

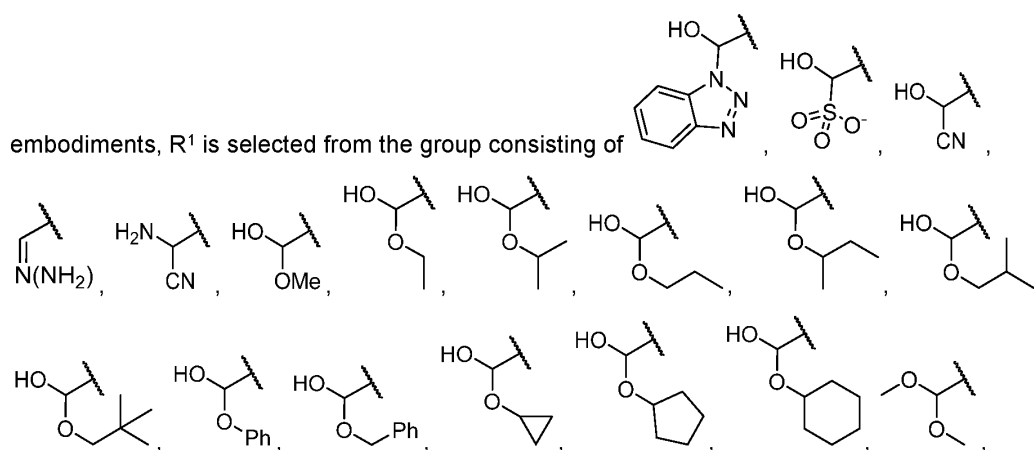
[0027] In various embodiments, wherein the organic solvent (of step (c)) is selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate, ethyl acetate, and a combination thereof. In some 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-dioxane, 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.

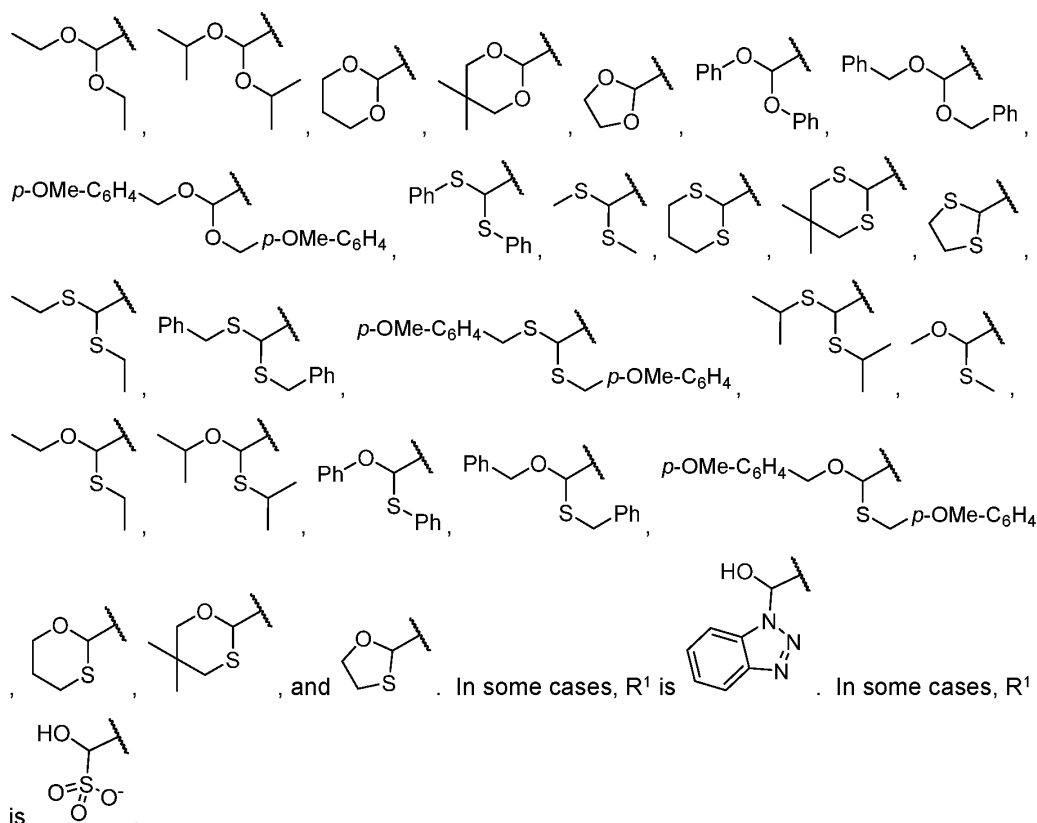
[0028] In various embodiments, step (c) occurs in the presence of water. In various embodiments, compound D and water are present in a molar ratio of 1:1 to 1:2. In some cases, the molar ratio of compound D to water is 1:1.1.

[0029] In various embodiments, 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 embodiments, 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 embodiments, 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





[0032] In various embodiments, 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.

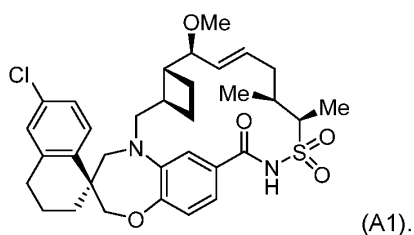
[0033] In various embodiments, the solvent is selected from the group consisting of toluene, heptane, acetonitrile, water, methyl tert-butyl ether (MTBE), and a combination thereof. In various embodiments, the solvent of step (d) is selected from the group consisting of toluene/heptane, acetonitrile/water,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

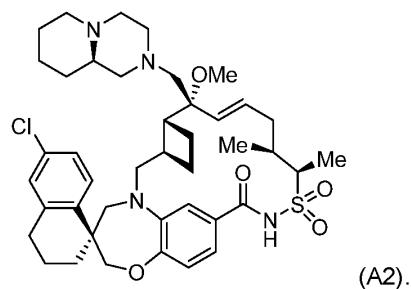
[0035] In various embodiments, the processes further comprise (e) crystallizing compound F.

[0036] In various embodiments, crystallizing comprises admixing compound F with a crystallizing solvent to form crystalline compound F. In various embodiments, 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.

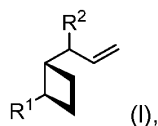
[0037] In various embodiments, the processes further comprise synthesizing compound A1, or a salt or solvate thereof, using compound F:



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

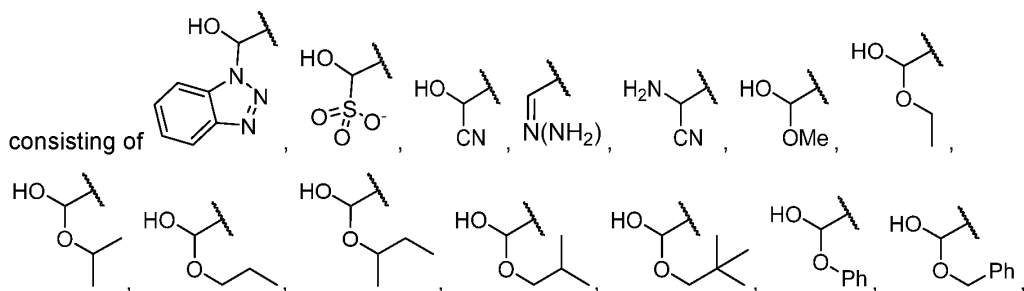


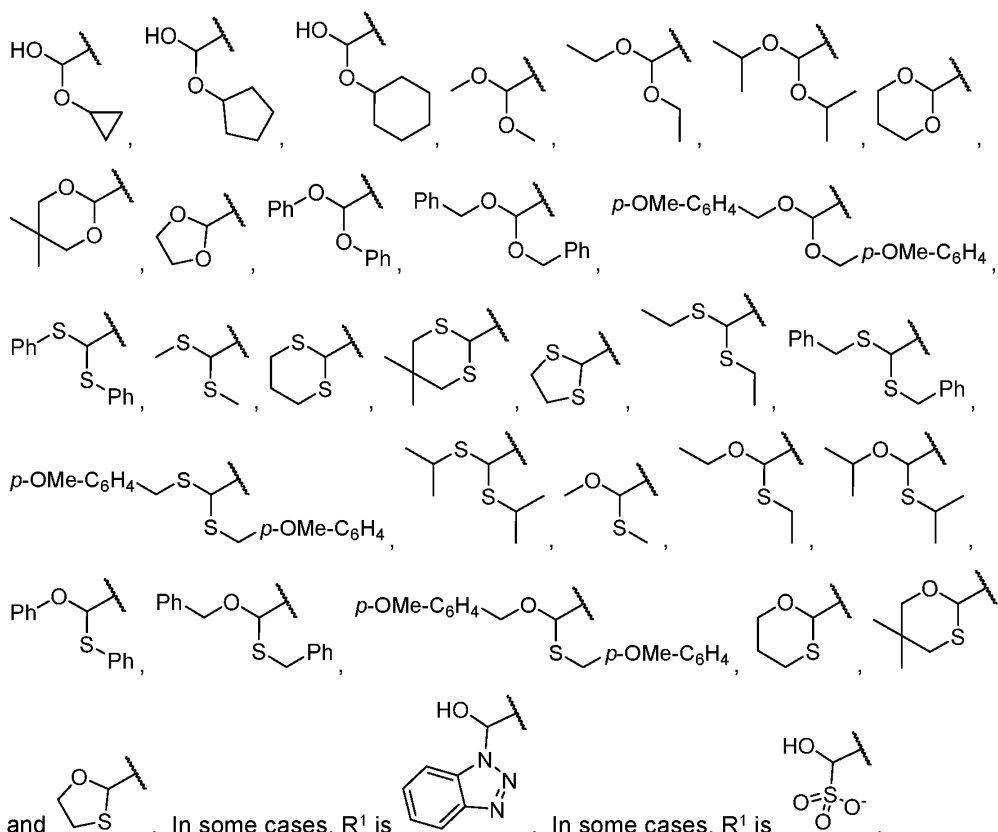
[0039] Further provided herein are compounds having the structure of Formula (I):



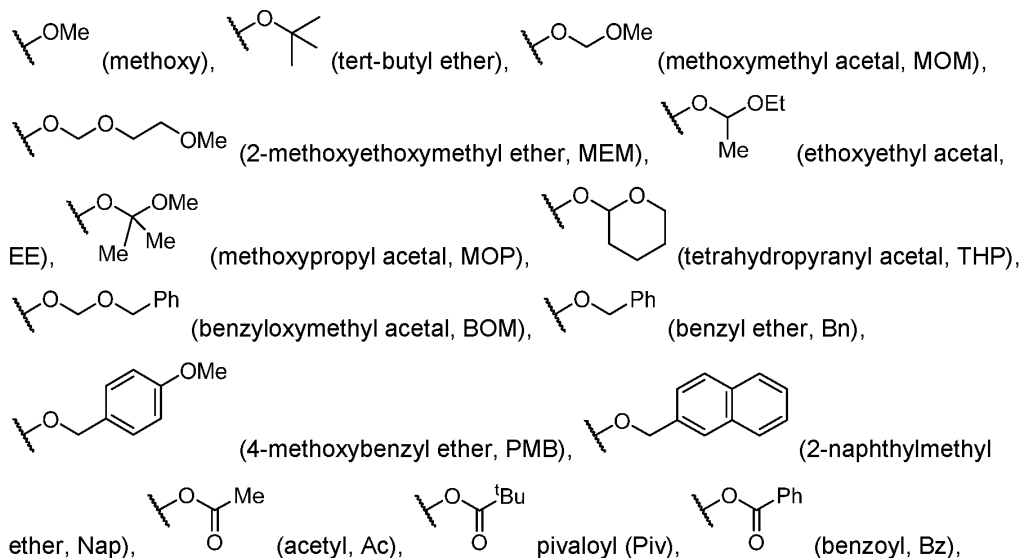
wherein R^1 is OH , OAc , or a protected aldehyde; R^2 is OH or OPG^2 ; and OPG^2 is a secondary alcohol protecting group, with the proviso that if R^2 is OH , then R^1 is OAc .

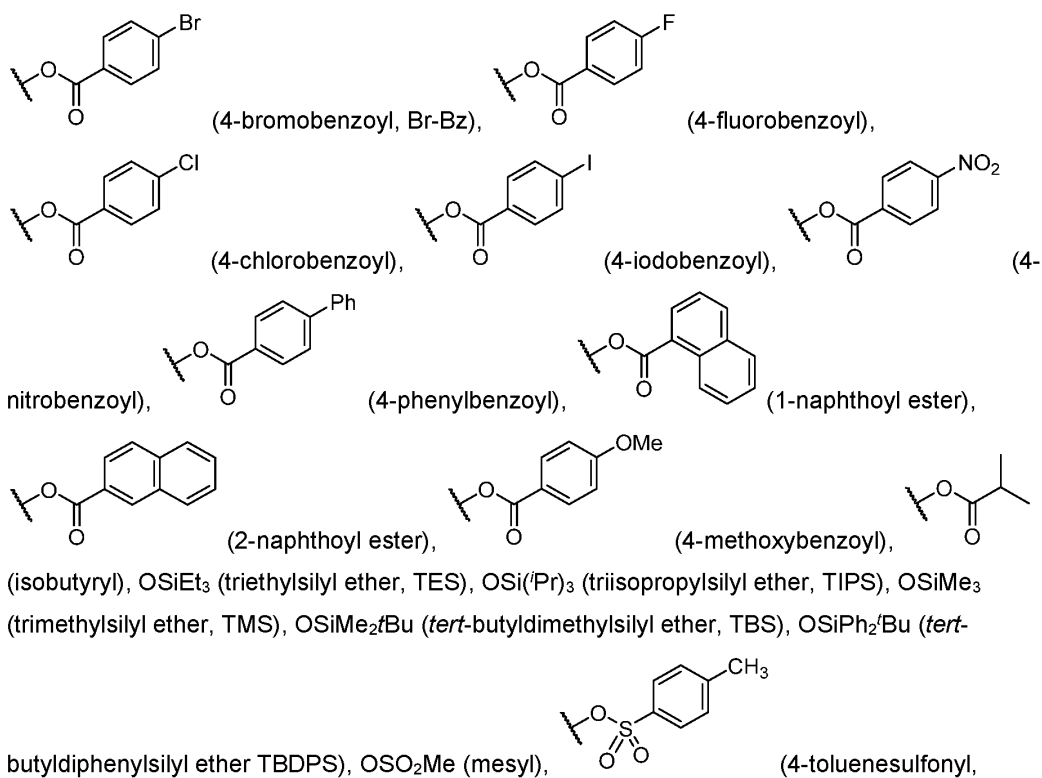
[0040] In various embodiments, R^1 is OAc . In various embodiments, R^1 is OH . In various embodiments, R^1 is a protected aldehyde. In some cases, R^1 is selected from the group





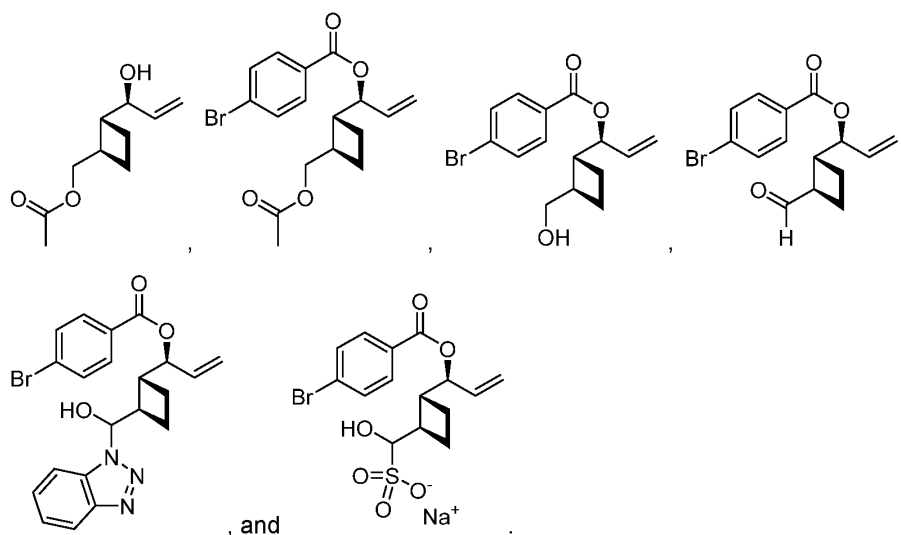
[0041] In various embodiments, R² is OH. In various embodiments, R² is OPG². In various embodiments, OPG² selected from the group consisting of an ether, an acetal or ketal, an acyl, a sulfonyl, and a silyl ether. In some cases, OPG² is selected from the group consisting of





(4-nitrobenzenesulfonyl, nosyl), and OSO₂CF₃ (triflyl). In some cases, OPG² is 4-bromobenzoyl.

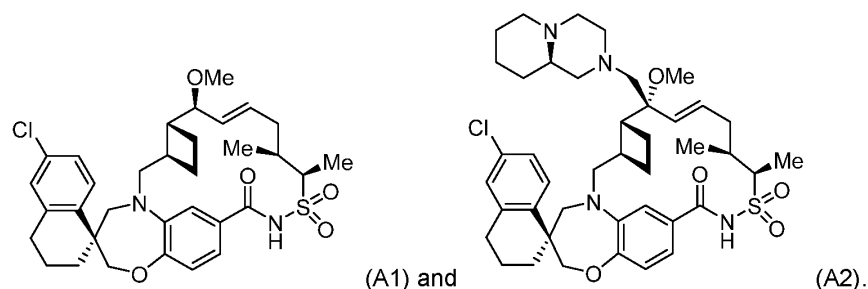
[0042] In various embodiments, the compound is selected from the group consisting of:



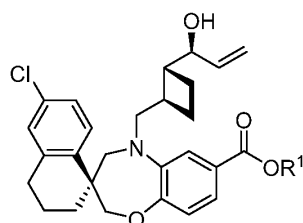
[0043] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention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

DETAILED DESCRIPTION

[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 or solvate thereof are provided:



[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.

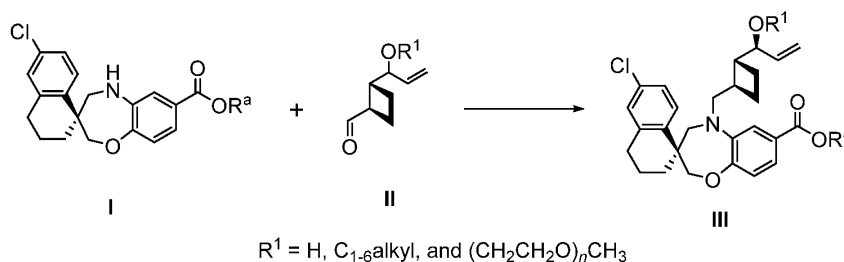


[0046] U.S. Patent No. 10,300,075, which is incorporated herein by reference in its entirety, discloses compound A2, or a salt or solvate thereof, as an Mcl-1 inhibitor and provides a

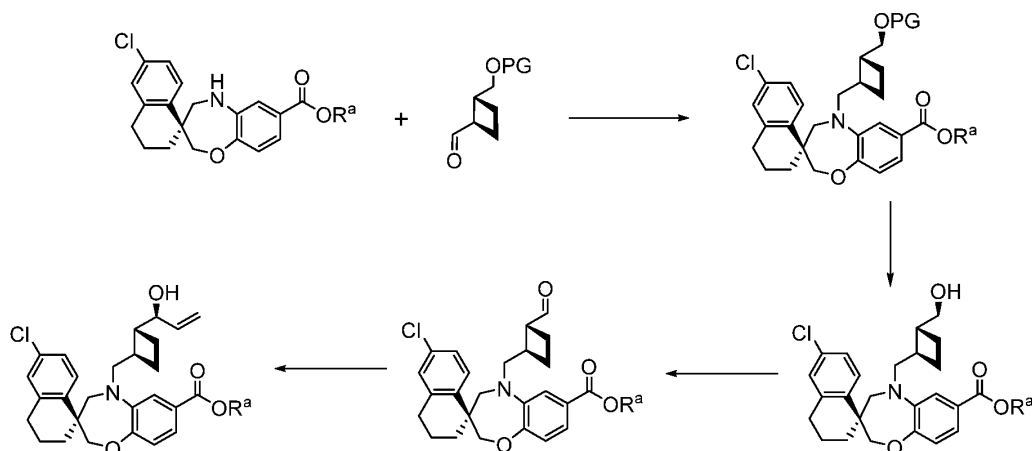
process for preparing it. The disclosure of compound A2 salts and solvates from U.S. Patent No. 10,300,075 is incorporated by reference in its entirety.

[0047] The '061 patent generally describes a procedure for making a vinylic alcohol intermediate as shown in Scheme 1, below, which is adapted from the disclosure at col. 49 of the '061 patent. The '061 patent describes that the cyclobutane carbaldehyde (intermediate II) is combined with the oxazepine (intermediate I) in a solvent at a temperature below room temperature preferably 0 °C. Sodium cyanoborohydride is added, and the mixture is added to a sodium hydroxide solution, thereby providing intermediate III. Advantageously, the processes described herein provide an improved synthetic route as compared to General Procedure 1 of the '061 patent. The processes described herein can be performed at ambient conditions (e.g., room temperature) and with milder reagents. Moreover, the processes can provide a crystalline vinyl cyclobutyl intermediate which allows for improved isolation, storage, and purity compared to the vinyl cyclobutyl intermediate of the '061 patent.

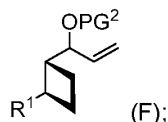
Scheme 1 – General Procedure 1 of the '061 Patent



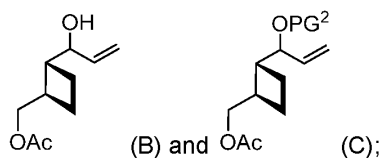
[0048] The '061 patent further describes a process for synthesizing a vinylic alcohol intermediate compound using a cyclobutyl intermediate in which the vinyl group is added to the compound after the fragment including the cyclobutyl intermediate is already joined with the benzoxazepine moiety. For example, Scheme 2, as shown below and adapted from the disclosure at cols. 66-71 of the '061 patent, represents the general process of synthesizing the vinylic alcohol as described in the '061 patent, using a cyclobutyl intermediate that does not include a vinylic group. The '061 patent describes the isolation of each of the intermediate compounds prior to use in the next step of the synthesis. Advantageously, use of the vinyl cyclobutyl intermediates and processes of making the same described herein leads to fewer steps when preparing the vinylic alcohol intermediate, and does not require isolation of any intermediates. Moreover, the vinyl cyclobutyl intermediates and processes of making the same described herein allow for a convergent fragment assembly of compounds A1 and A2, provide a superior purity profile, provide for highly crystalline intermediates, thereby improving stability, and have an overall higher yield, as compared to the '061 patent.

Scheme 2 –Synthesis of Vinylic Alcohol Intermediate of the '061 Patent**PROCESSES FOR SYNTHESIZING VINYL CYCLOBUTYL INTERMEDIATES**

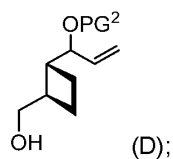
[0049] The disclosure provides processes for synthesizing compound F or a salt thereof:



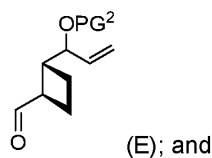
wherein OPG^2 is a secondary alcohol protecting group and R^1 is a protected aldehyde, the method including: (a) protecting a secondary alcohol of compound B, or a salt thereof, by reacting compound B, or salt thereof, with an alcohol protecting group reagent to form compound C, or a salt thereof:



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



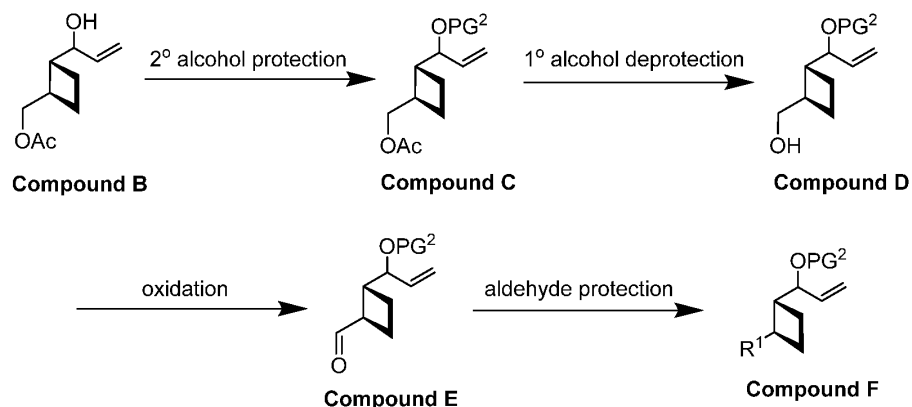
(c) oxidizing the primary alcohol of compound D, or salt thereof, to form an aldehyde of compound E, or a salt thereof:



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

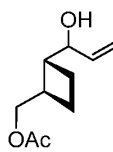
[0050] A general reaction scheme for the processes described herein is provided in Scheme 3, below:

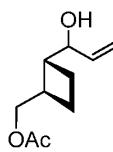
Scheme 3 – General Process for Synthesis of Cyclobutyl Intermediates



[0051] Protection of Secondary Alcohol

[0052] The processes of the disclosure include protecting a secondary alcohol of compound B, or a salt thereof. In particular, compound B, or salt thereof, is reacted with an alcohol protecting group reagent to form compound C, or a salt thereof.



[0053] As provided herein, compound B has a structure of  (B). In some embodiments, compound B is a salt. A salt of compound B, or any other compound described herein, can be prepared, for example, by reacting the compound in its free base form with a suitable organic or inorganic acid, and optionally isolating the salt thus formed. Nonlimiting examples of suitable salts for any one or more of the compounds described herein include hydrobromide, hydrochloride, sulfate, bisulfate, sulfonate, camphorsulfonate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like.

[0054] Compound B is reacted with an alcohol protecting group reagent, which thereby protects the secondary alcohol of compound B. Alcohol protecting groups are groups that mask a hydroxyl functional group, and are well known in the art. Preparation of compounds can involve the protection and deprotection of various hydroxyl groups. The need for protection and deprotection, and the selection of appropriate protecting groups, and protecting group reagents, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis*, 4d. Ed., Wiley &

Sons, 2007, which is incorporated herein by reference in its entirety. Adjustments to the alcohol protecting groups and formation and cleavage methods described herein may be adjusted as necessary in light of the various substituents. Nonlimiting examples of suitable alcohol protecting group reagents include acyl halides (e.g., acetyl chloride, pivaloyl chloride, 4-bromobenzoyl chloride, etc.), acyl anhydrides (e.g., acetic anhydride, maleic anhydride, etc.), silyl halides (e.g., trimethylsilyl chloride, chlorotriethylsilane, triisopropylsilyl chloride, etc.), and sulfonyl halides (e.g., methanesulfonyl chloride, etc.). Other alcohol protecting group reagents that can be used to provide the alcohol protecting group, OPG², as described herein, are also contemplated.

[0055] In some embodiments, the alcohol protecting group reagent is an acyl chloride or an acyl anhydride. For example, in some cases, the alcohol protecting group reagent is an acyl chloride, such as 4-bromobenzoyl chloride. In some cases, the alcohol protecting group reagent is an acyl anhydride, such as acetic anhydride.

[0056] Compound B and the alcohol protecting group reagent can be present in a molar ratio of 1:1 to 1:2, for example, at least 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, or 1:1.6, and/or up to 1:2, 1:1.9, 1:1.8, 1:1.7, 1:1.6, 1:1.5, or 1:1.4, such as 1:1 to 1:1.8, 1:1 to 1:1.5, 1:1 to 1:1.4, or 1:1.2 to 1:1.4. In some embodiments, the molar ratio of compound B to the alcohol protecting group reagent is 1:1.3.

[0057] In some embodiments, step (a) can include admixing compound B, or salt thereof, the alcohol protecting group reagent, and a nucleophilic catalyst. Nonlimiting examples of nucleophilic catalysts include pyridine, dimethylaminopyridine (DMAP), and N-methylimidazole. In some embodiments, the nucleophilic catalyst includes pyridine, 4-dimethylaminopyridine, or a combination thereof. In some embodiments, the nucleophilic catalyst is pyridine. In some embodiments, the nucleophilic catalyst is DMAP.

[0058] When the nucleophilic catalyst is present, compound B and the nucleophilic catalyst can be present in a molar ratio of 1:1 to 1:5, for example at least 1:1, 1:1.5, 1:2, 1:2.5, 1:3, or 1:3.5 and/or up to 1:5, 1:4.5, 1:4, 1:3.5, or 1:3, such as 1:1 to 1:4, 1:2 to 1:5, 1:1.5 to 1:3.5, or 1:1 to 1:3. In some embodiments, the molar ratio of compound B to the nucleophilic catalyst is 1:2.

[0059] The protection of the secondary alcohol can occur in an organic solvent. The organic solvent of step (a) can be 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. Nonlimiting examples of nonpolar aromatic solvents include toluene, benzene, xylene, chlorobenzene, fluorobenzene, naphthalene, and benzotrifluoride. Nonlimiting examples of ether solvents include tetrahydrofuran (THF), tetrahydropyran, tetrahydrofurfuryl alcohol, diethyl ether, dibutyl ether, diisopropyl ether, methyl tert-butyl ether (MTBE), 1,2-dimethoxyethane, 1,4-dioxane, 2-methyl-THF, and cyclopentylmethyl ether. Nonlimiting examples of chlorinated solvents include 1,2-dichloroethane, chloroform, carbon tetrachloride, and dichloromethane.

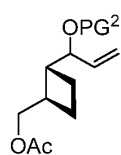
Nonlimiting examples of alcohol solvents include methanol, ethanol, propanol, 2-propanol, and tert-butanol.

[0060] In some embodiments, 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-dioxane, 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 embodiments, the organic solvent is toluene, THF, DCM, or a combination thereof.

[0061] The organic solvent can be included in an amount of 5 L/kg of compound B to 25 L/kg of compound B, for example, at least about 5, 10, 15, or 20 L/kg of compound B and/or up to about 25, 20, 25, or 10 L/kg of compound B, such as, 5 L/kg to 20 L/kg, 5 L/kg to 15 L/kg, or 5 L/kg to 10 L/kg. In some embodiments, the solvent is present in an amount of 10 L/kg of compound B.

[0062] Step (a) can occur at a temperature of 20 °C to 100 °C, for example, at least 20, 25, 30, 35, 40, 45, 50, or 55 °C and/or up to 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, or 50 °C, such as 20 °C to 80 °C, 25 °C to 75 °C, 30 °C to 70 °C, 40 °C to 70 °C, 45 °C to 65 °C or 50 °C to 60 °C. In some embodiments, step (a) occurs at a temperature of 60 °C.

[0063] The reaction of compound B with the alcohol protecting group reagent, and optionally the nucleophilic catalyst, forms compound C. As provided herein, compound C has a structure of



(C), or a salt thereof, wherein OPG² is a secondary alcohol protecting group. Salts of compound C can be similar to those as described herein for compound B.

[0064] As described above, alcohol protecting groups are groups that mask a hydroxyl functional group, and are well known in the art. In some cases, the alcohol protecting group, OPG², is selected from the group consisting of an ether, an acetal or ketal, an acyl, and a silyl ether.

[0065] In some embodiments, OPG² is an ether. Ether protecting groups comprise an alkyl moiety, either substituted or unsubstituted, attached to the oxygen from the hydroxyl group being protected (e.g., masked as an ether). Examples of suitable ethers include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, tert-butoxy, methoxymethyl acetal (MOM), 2-methoxyethoxymethyl ester (MEM), ethoxyethyl acetal (EE), and methoxypropyl ether (MOP). Other examples of contemplated ethers include, but are not limited to, benzyloxymethyl acetal (BOM), benzyl ether (Bn), 4-methoxybenzyl ether (PMB), and 2-naphthylmethyl ether (Nap).

[0066] In some embodiments, OPG² is an acetal or ketal. Acetals as a protecting group have a

general structure of , and can be as acetals (as OR' option, where R' is, e.g., an

alkyl group) or as hemiacetals (as OH option), where R-O is derived from the hydroxyl group being protected and PG' is the rest of the (hemi)acetal protecting group. Ketals as a protecting

group have a general structure of $\begin{array}{c} \text{OH/OR}' \\ | \\ \text{R}-\text{O}-\text{C}-\text{PG}' \\ | \\ \text{PG}' \end{array}$, where R-O is derived from the hydroxyl group being protected and can be as ketals (as OR' option, where R' is, e.g., an alkyl group) or as hemiketals (as OH option), and each PG' is derived from the rest of the (hemi)ketal protecting group) mask the hydroxyl group (i.e., R-OH) and can be substituted or unsubstituted. An example of a suitable acetal includes, but is not limited to, tetrahydropyranyl acetal (THP).

[0067] In some embodiments, OPG² is an acyl. As used herein, the term "acyl" refers to an alcohol protecting group in which the oxygen atom of the alcohol is bound to an acyl group -

$\begin{array}{c} \text{PG}' \\ | \\ \text{R}-\text{O}-\text{C} \\ || \\ \text{O} \end{array}$, where R-O is derived from the hydroxyl group being protected and PG' is derived from the rest of the acyl protecting group. In some embodiments, 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-naphthoyl, 4-methoxybenzoyl, and isobutyryl.

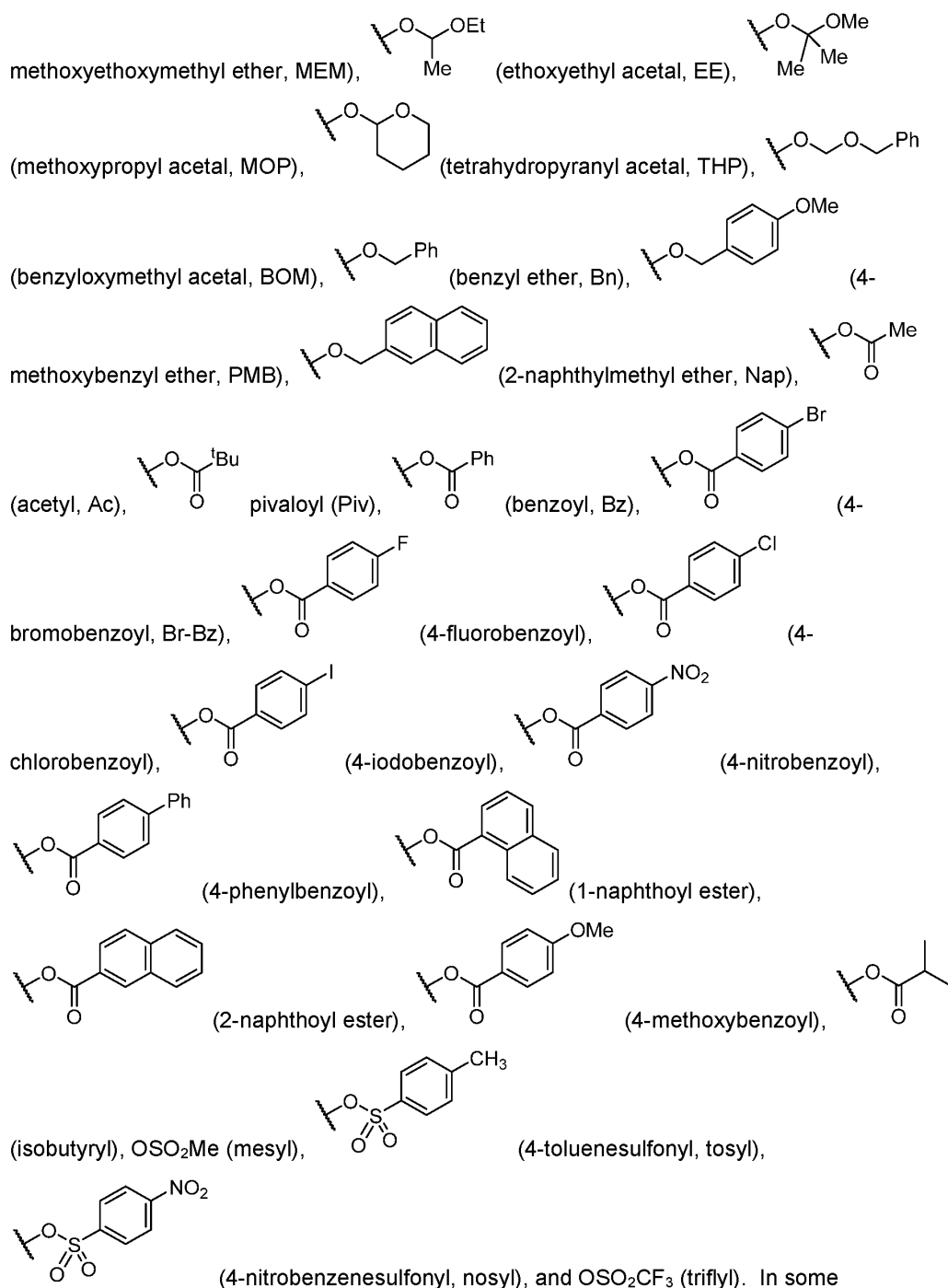
[0068] In some embodiments, OPG² is a silyl ether. As used herein, the term "silyl ether" refers to an alcohol protecting group in which the oxygen atom of the alcohol is bound to a silyl ether

group - $\begin{array}{c} \text{PG}' \\ | \\ \text{R}-\text{O}-\text{Si} \\ | \quad | \\ \text{PG}' \quad \text{PG}' \end{array}$, where R-O is derived from the hydroxyl group being protected and each PG' is derived from the rest of the silyl ether protecting group. In some embodiments, the silyl ether protecting group is selected from the group consisting of OSiEt₃ (triethylsilyl ether, TES), OSi(Pr)₃ (triisopropylsilyl ether, TIPS), OSiMe₃ (trimethylsilyl ether, TMS), OSiMe₂tBu (*tert*-butyldimethylsilyl ether, TBS), and OSiPh₂tBu (*tert*-butyldiphenylsilyl ether, TBDPS).

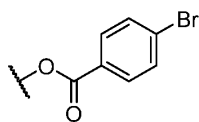
[0069] In some embodiments, OPG² is a sulfonyl protecting group. As used herein, the term "sulfonyl protecting group" refers to an alcohol protecting group in which the oxygen atom of the

alcohol is bound to a sulfonyl group - $\begin{array}{c} \text{O} \\ || \\ \text{R}-\text{O}-\text{S} \\ || \\ \text{O} \end{array}$ PG', where R-O is derived from the hydroxyl group being protected and PG' is derived from the rest of the sulfonyl protecting group. In some embodiments, the sulfonyl protecting group is selected from the group consisting of mesyl, tosyl, nosyl, and triflyl.

[0070] In some embodiments, OPG² is selected from the group consisting of $\text{CH}_3\text{O}-$ (methoxy), $\text{CH}_3\text{O}-\text{C}(\text{CH}_3)_3$ (tert-butyl ether), $\text{CH}_3\text{O}-\text{CH}_2-$ (methoxymethyl acetal, MOM), $\text{CH}_3\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$ (2-



embodiments, OPG² is selected from the group consisting of OSiEt₃ (triethylsilyl ether, TES), OSi(*i*Pr)₃ (triisopropylsilyl ether, TIPS), OSiMe₃ (trimethylsilyl ether, TMS), OSiMe₂*t*Bu (*tert*-butyldimethylsilyl ether, TBS), OSiPh₂*t*Bu (*tert*-butyldiphenylsilyl ether, TBDPS). In some



embodiments, OPG² is

[0071] Deprotection of the Primary Alcohol

[0072] The processes of the disclosure include removing the acetyl protecting group by admixing compound C, or salt thereof, with a deprotecting agent. The deprotecting agent can be selected to selectively deprotect the primary alcohol while retaining the secondary alcohol protecting group, OPG². The selection of appropriate protecting groups can be readily determined by one skilled in the art. In some embodiments, the deprotecting agent includes acetyl chloride, an enzyme, an acid, a base, a metal hydride, or a combination thereof.

[0073] In some embodiments, the deprotecting agent includes acetyl chloride and an alcohol. As described herein, nonlimiting examples of alcohol solvents include methanol, ethanol, propanol, 2-propanol, and tert-butanol. In some embodiments, the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, and a combination thereof. In some embodiments, the alcohol is methanol.

[0074] The alcohol can be included in an amount of 3 L/kg of compound C to 15 L/kg of compound C, for example, at least about 3, 5, 7, 10, or 12 L/kg of compound C and/or up to about 15, 12, 10, 7, or 5 L/kg of compound C, such as, 5 L/kg to 15 L/kg, 5 L/kg to 10 L/kg, or 5 L/kg to 7 L/kg. In some embodiments, the solvent is present in an amount of 5.5 L/kg of compound C.

[0075] In some embodiments, the deprotecting agent includes a base. Nonlimiting examples of bases include magnesium methoxide, magnesium ethoxide, and aluminum isopropoxide. In some embodiments, the deprotecting agent is magnesium methoxide. In some embodiments, the base is magnesium ethoxide. In some embodiments, the base is aluminum isopropoxide.

[0076] In some embodiments, the deprotecting agent includes an enzyme. Nonlimiting examples of suitable enzymes include ester hydrolases (e.g., NOVOZYM® 40086) and lipases (e.g., amano lipase PS). In some embodiments, the enzyme is selected from the group consisting of an ester hydrolase, a lipase, and a combination thereof. In some embodiments, the enzyme is an ester hydrolase. In some embodiments, the enzyme is a lipase.

[0077] In some embodiments, the deprotecting agent includes an acid or metal triflate. Nonlimiting examples of suitable acids include hydrochloric acid, sulfuric acid, phosphoric acid, trifluoroacetic acid (TFA), hydrobromic acid, and acetic acid. Nonlimiting examples of suitable metal triflates include ytterbium triflate and dysprosium triflate. In some embodiments, the deprotecting agent is an acid. In some embodiments, the acid is selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and a combination thereof. In some embodiments, the acid is hydrochloric acid. In some embodiments, the acid is sulfuric acid. In some embodiments, the acid is phosphoric acid. In some embodiments, the deprotecting agent is a metal triflate. In some embodiments, the metal triflate is ytterbium

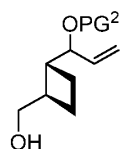
triflate. In some embodiments, the metal triflate is dysprosium triflate.

[0078] In some embodiments, the deprotecting agent includes a metal hydride or a borohydride. A nonlimiting example of a metal hydride is zirconium hydride. A nonlimiting example of a borohydride is lithium triethylborohydride. In some embodiments, the deprotecting agent is zirconium hydride. In some embodiments, the deprotecting agent is lithium triethylborohydride.

[0079] Compound C and the deprotecting agent can be present in a molar ratio of 1:0.2 to 1:2, for example, at least about 1:0.2, 1:0.5, 1:0.7, 1:1, or 1:2 and/or up to 1:2, 1:1.7, 1:1.5, 1:1.2, 1:1, or 1:0.7, such as 1:0.2 to 1:1.5, 1:0.1 to 1:1, 1:0.2 to 1:0.7 or 1:0.3 to 1:0.6. In some embodiments, the molar ratio of compound C to the deprotecting agent is 1:0.5.

[0080] Step (b) can occur at a temperature of -15 °C to 25 °C, for example, at least -15, -10, -5, -2, 0, 2, 5, or 10 °C and/or up to 25, 20, 15, 10, 5, 2, or 0 °C, such as -15 °C to 20 °C, -10 °C to 15 °C, -5 °C to 15 °C, or 5 °C to 15 °C. In some embodiments, step (b) occurs at a temperature of 10 °C.

[0081] The removal of the acetyl protecting group of compound C forms compound D:



(D), or a salt thereof, wherein OPG² is as described herein. Salts of compound D can be similar to those as described herein for compound B.

[0082] Oxidation of Primary Alcohol

[0083] The processes described herein include oxidizing the primary alcohol of compound D, or salt thereof, to form an aldehyde of compound E. The oxidizing includes admixing compound D, or salt thereof, and an oxidizing agent, with an organic solvent, and optionally water.

[0084] 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 selected from the group consisting of oxalyl chloride/DMSO, bleach, SO₃/pyridine, iodobenzenediacetate, and any combination thereof. In some embodiments, the oxidizing agent is iodobenzenediacetate.

[0085] Compound D and the oxidizing agent can be present in a molar ratio of 1:1.1 to 1:2, for example at least 1:1.1, 1:1.2, 1:1.3, 1:1.4, or 1:1.5 and/or up to 1:2, 1:1.9, 1:1.8, 1:1.7, 1:1.6, or 1:1.5, such as 1:1.1 to 1:1.7, 1:1.1 to 1:1.5, 1:1.1 to 1:1.4, or 1:1.1 to 1:1.3. In some embodiments, the molar ratio of compound D to the oxidizing agent is 1:1.1.

[0086] The oxidation of the primary alcohol can further include admixing compound D 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, and 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate. In some embodiments, 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 embodiments, the oxidation catalyst is TEMPO.

[0087] When the oxidation catalyst is present, compound D and the oxidation catalyst can be present in a molar ratio of 1:0.01 to 1:1, for example, at least 1:0.01, 1:0.04, 1:0.05, 1:0.1, 1:0.2, 1:0.3, or 1:0.5 and/or up to 1:1, 1:0.9, 1:0.7, 1:0.5, 1:0.2, or 1:0.1, such as 1:0.01 to 1:0.8, 1:0.01 to 1:0.5, 1:0.01 to 1:0.1, or 1:0.02 to 1:0.05. In some embodiments, the molar ratio of compound D to the oxidation catalyst is 1:0.04.

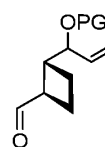
[0088] The oxidation of the primary alcohol can occur in an organic solvent. Suitable organic solvents include those generally described herein. In some embodiments, the organic solvent is selected from the group consisting of a nonpolar aromatic solvent, an ether solvent, a chlorinated solvent, methyl isobutyl ketone (MIBK), 2-butanone, acetone, isopropyl acetate, ethyl acetate, and a combination thereof. In some embodiments, 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-dioxane, 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 embodiments, the organic solvent is toluene.

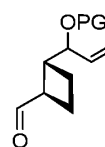
[0089] The organic solvent can be included in an amount of 3 L/kg of compound D to 15 L/kg of compound D, for example, at least about 3, 5, 7, 10, or 12 L/kg of compound D and/or up to about 15, 12, 10, 7, or 5 L/kg of compound D, such as, 5 L/kg to 15 L/kg, 5 L/kg to 10 L/kg, or 5 L/kg to 7 L/kg. In some embodiments, the solvent is present in an amount of 6 L/kg of compound D.

[0090] The oxidation of the primary alcohol can occur in the presence of water. When present, compound D and water can be present in a molar ratio of 1:1 to 1:2, for example at least 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, or 1:1.6 and/or up to 1:2, 1:1.9, 1:1.8, 1:1.7, 1:1.6, or 1:1.5, such as 1:1 to 1:1.7, 1:1 to 1:5, 1:1.1 to 1:1.5, or 1:1 to 1:1.3. In some embodiments, the molar ratio

of compound D to water is 1:1.1.

[0091] Step (c) can occur at a temperature of 5 °C to 45 °C, for example at least 5, 10, 15, 20, 25, or 30 °C and/or up to 45, 40, 35, 30, 25, or 20 °C, such as 5 °C to 30 °C, 10 °C to 35 °C, 15 °C to 30 °C, or 15 °C to 25 °C. In some embodiments, step (c) occurs at a temperature of 20 °C.

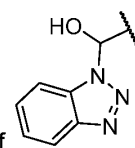


[0092] The oxidation of compound D, or salt thereof, in step (c) forms compound E:  (E), or a salt thereof, wherein OPG² is as described herein. Salts of compound E can be similar to those as described herein for compound B.

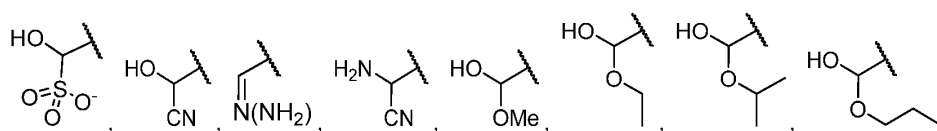
[0093] Protection of Aldehyde

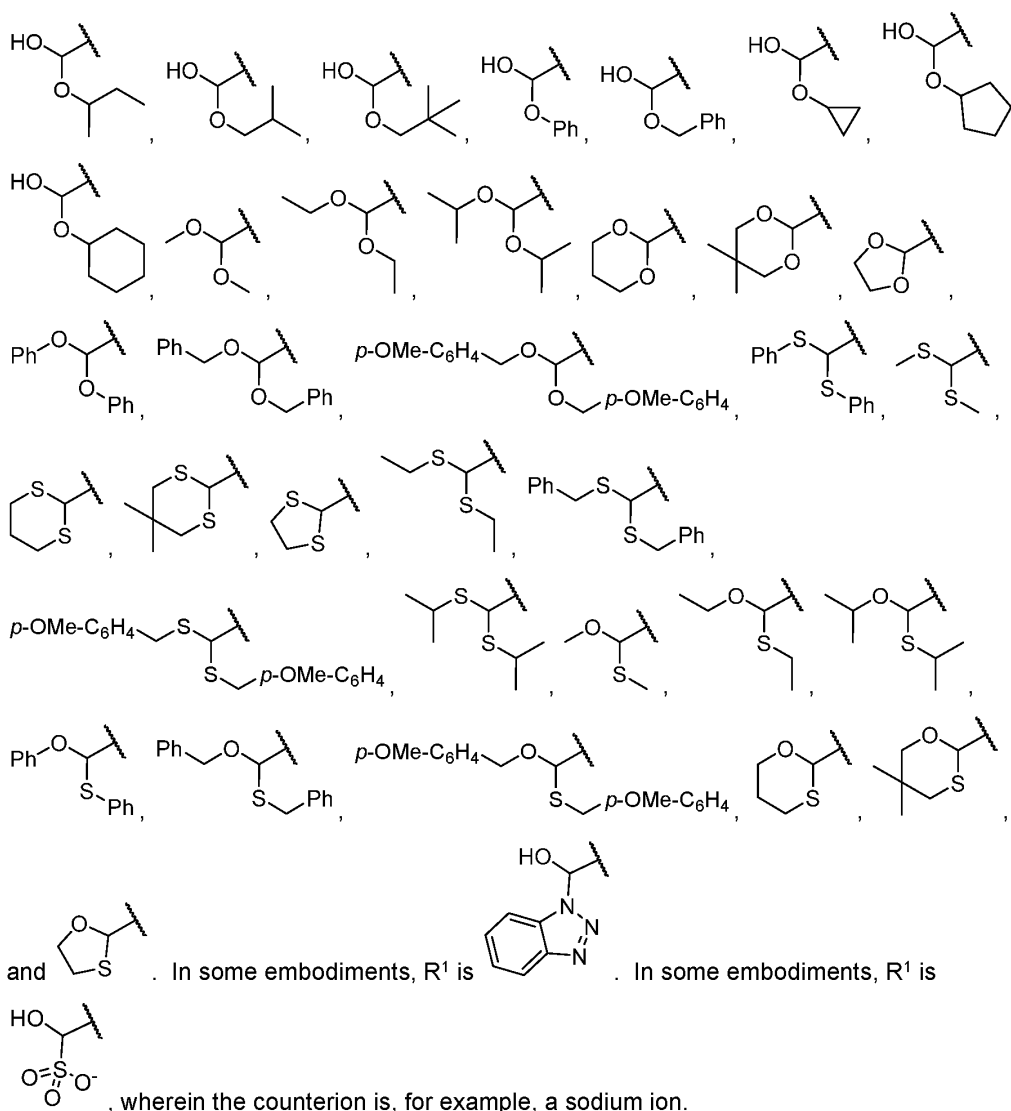
[0094] The processes of the disclosure include protecting the aldehyde of compound E, or salt thereof, to form a protected aldehyde of compound F, or a salt thereof. The protection of the aldehyde can include admixing compound E, or salt thereof, and an aldehyde protecting group reagent with a solvent.

[0095] The term "protected aldehyde" or "aldehyde protecting group" refers to any protecting group used to mask the aldehyde functionality. Aldehyde protecting groups include acetals and hemiacetals. The acetals and hemiacetals can be prepared from C₁₋₈ alcohols or C₂₋₈ diols. In some cases, the protected aldehyde is a five or six membered cyclic acetal formed from condensation of the aldehyde with ethylene or propylene glycol. In some cases, the protected aldehyde is an imine or hydroxyimine. In some cases, the protected aldehyde comprises a bisulfite or a benzotriazole. In some embodiments, the aldehyde protecting group reagent is selected from the group consisting of benzotriazole, a bisulfite salt (e.g., sodium bisulfite, calcium bisulfite, lithium bisulfite, potassium bisulfite, etc.), a cyanide salt (e.g., sodium cyanide, potassium cyanide, lithium cyanide), hydrogen cyanide, a thiol or dithiol, an alcohol or diol, hydrazine (or alkyl hydrazines), ammonia, and a combination thereof. Other aldehyde protecting group reagents that provide the aldehyde protecting group, R¹, described herein are contemplated.



[0096] In some embodiments, R¹ is selected from the group consisting of





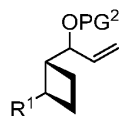
[0097] Compound E and the aldehyde protecting group reagent can be present in a molar ratio of 1:1 to 1:1.5, for example at least 1:1, 1:1.1, 1:1.2, or 1:1.3 and/or up to 1:1.5, 1:1.4, 1:1.3, or 1:1.2, such as 1:1 to 1:1.4, 1:1 to 1:1.3, or 1:1.1 to 1:1.3. In some embodiments, the molar ratio of compound E to the aldehyde protecting group reagent is 1:1.

[0098] The protection of the aldehyde can include a solvent, which can be selected from the organic solvents generally described herein. In some embodiments, the solvent is selected from the group consisting of toluene, heptane, acetonitrile, water, methyl tert-butyl ether (MTBE), and a combination thereof. In some embodiments, the solvent is selected from the group consisting of toluene/heptane, acetonitrile/water, and methyl tert-butyl ether (MTBE). In some embodiments, the solvent is toluene/heptane. The toluene and heptane can be present in a volume ratio of 1:10 to 10:1, for example 1:8 to 8:1 or 1:2 to 1:2. In some embodiments, the

volume ratio of toluene and heptane is 4:7.

[0099] Step (d) can occur at a temperature of 20 °C to 50 °C, for example at least 20, 25, 30, 35, or 40 °C and/or up to 50, 45, 40, 35, or 30 °C, such as 20 °C to 45 °C, 25 °C to 45 °C, 30 °C to 50 °C, 35 °C to 45 °C, or 30 °C to 40 °C.

[0100] The protection of the aldehyde of compound E, or salt thereof, provides compound F:



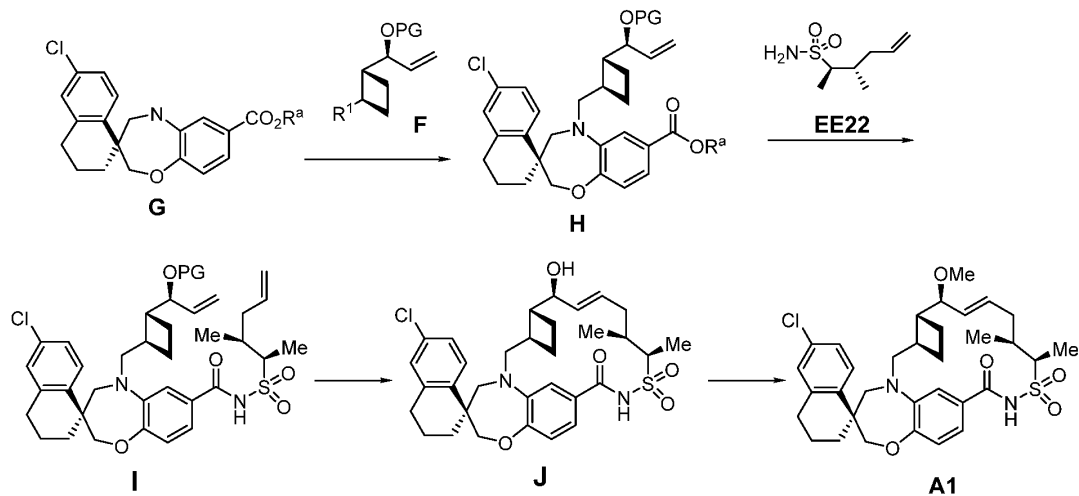
(F), wherein each of R¹ and OPG² are as described herein. Salts of compound F can be similar to those as described herein for compound B.

[0101] Crystallization

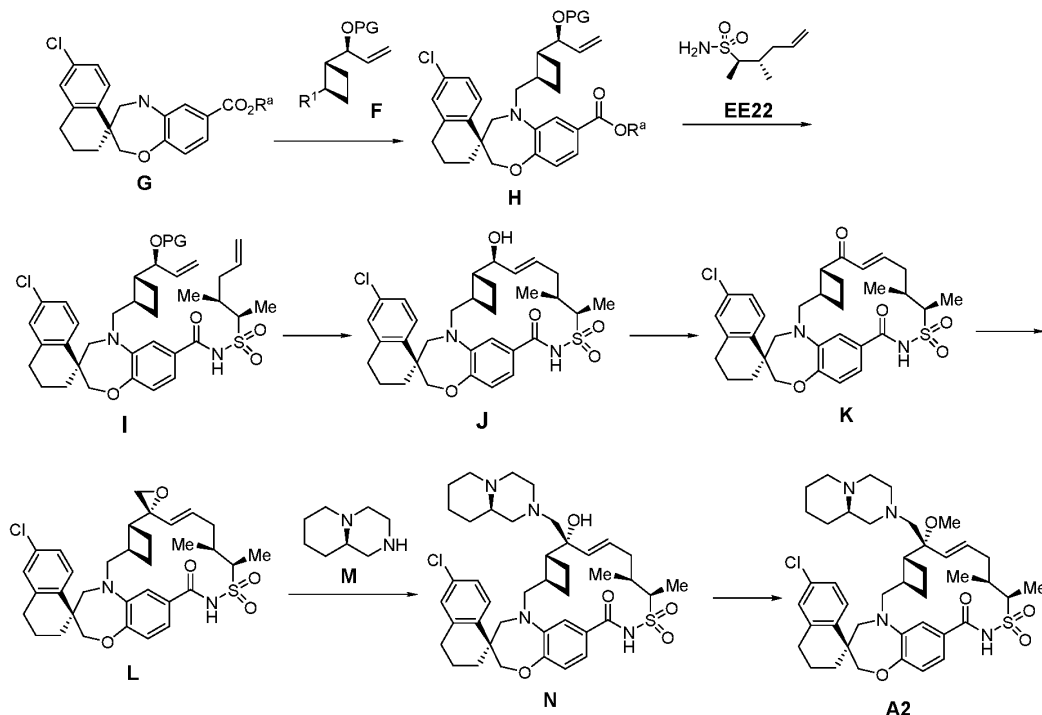
[0102] The processes of the disclosure can further include crystallizing compound F, or a salt thereof. Crystallization can include admixing compound F or salt thereof with a crystallizing solvent to form crystalline compound F or salt thereof. Suitable crystallization solvents are generally known in the art and can include, for example, water, methanol, ethanol, propanol, isopropanol, butanol, diethyl ether, isopropyl ether, methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), methyl isobutyl ketone (MIBK), pentane, hexane, cyclohexane, heptane, acetone, acetonitrile, tetrahydrofuran, 2-methyl tetrahydrofuran, ethyl acetate, isopropyl acetate, n-butyl acetate, dichloromethane, chloroform, 1,4-dioxane, and mixtures thereof.

[0103] In some embodiments, the crystallizing solvent includes 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.

[0104] The processes for synthesizing compound F or salt thereof, as described herein, can be used to synthesize compounds A1 and A2. As shown in Scheme 4, below, compound F can be used to synthesize compound A1, or salts or solvates thereof. As shown in Scheme 5, below, compound F can be used to synthesize compound A2, or salts or solvates thereof.

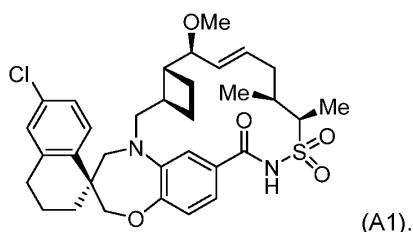
Scheme 4 – Conversion of Compound F to Compound A1

[0105] As shown in Scheme 4, compound F can be used to synthesize compound A1 and salts and solvates thereof. The synthesis of compound G and sulfonamide EE22 are disclosed in U.S. Patent No. 9,562,061. Compounds F and G can be reacted to form the protected vinylic alcohol intermediate, compound H. Compounds EE22 and H can be reacted to form compound I. Cyclization and deprotection of compound I provides compound J which can then be methylated to provide compound A1 as described in U.S. Patent No. 9,562,061.

Scheme 5 – Conversion of Compound F to Compound A2

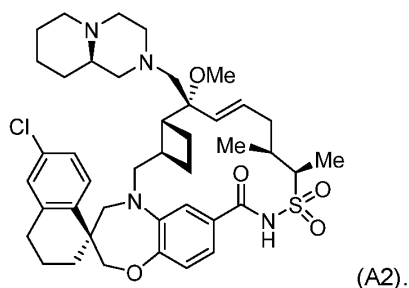
[0106] As shown in Scheme 5, compound F can be used to synthesize compound A2 and salts and solvates thereof. As described above with respect to Scheme 4, the synthesis of compound G and sulfonamide EE22 is disclosed in U.S. Patent No. 9,562,061. Compounds G and F can be reacted to form the protected vinylic alcohol intermediate, compound H. Compounds EE22 and H can be reacted to form compound I which can be cyclized to provide compound J. Compound J can then be oxidized to provide compound K, as disclosed in U.S. Patent No. 10,300,075. Alternatively, compound I can be oxidized to provide the uncyclized version of compound J, which can then cyclized to provide compound K. Compound K can then be epoxidized to compound L using the procedures disclosed in U.S. Patent No. 10,300,075. Compound L can then be reacted with bicyclic compound M to provide compound N. Finally, methylation of compound N provides compound A2 as disclosed in U.S. Patent No. 10,300,075.

[0107] In some embodiments, the process further includes synthesizing compound A1 or a salt or solvate thereof using compound F:



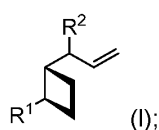
[0108] In some embodiments, the process further includes synthesizing compound A2 or a salt

or solvate thereof using compound F:



CYCLOBUTYL INTERMEDIATE COMPOUNDS

[0109] The disclosure also provides compounds having a structure of Formula (I), or a salt thereof:



wherein R¹ is CHO, OH, OAc, or a protected aldehyde; R² is OH or OPG²; and OPG² is a

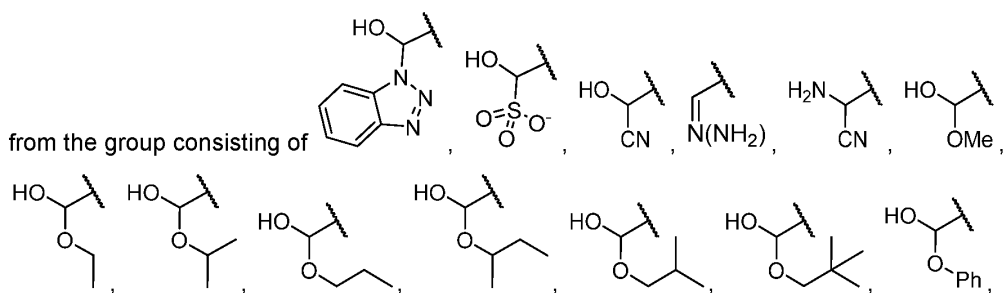
secondary alcohol protecting group, with the proviso that if R² is OH, then R¹ is OAc.

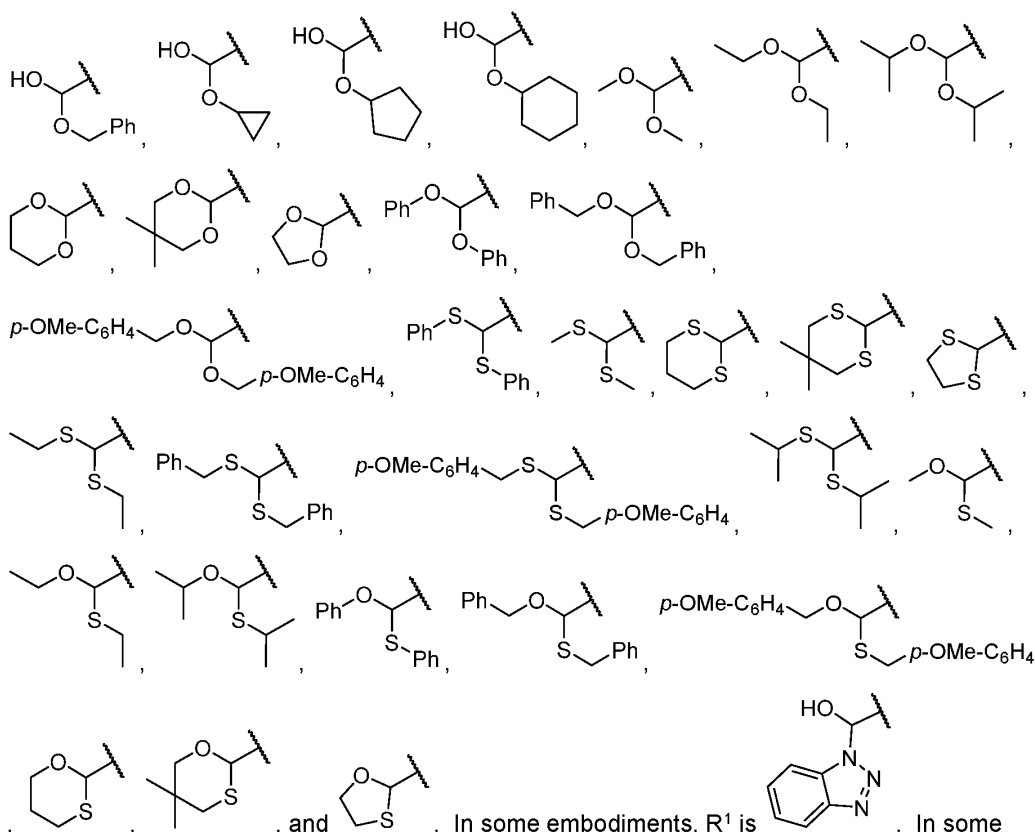
[0110] As provided herein, R¹ is CHO, OH, OAc, or a protected aldehyde. In some

embodiments, R¹ is OAc (i.e., an acetyl protected primary alcohol). In some embodiments, R¹

is OH (i.e., a primary alcohol). In some embodiments, R¹ is CHO (i.e., an aldehyde).

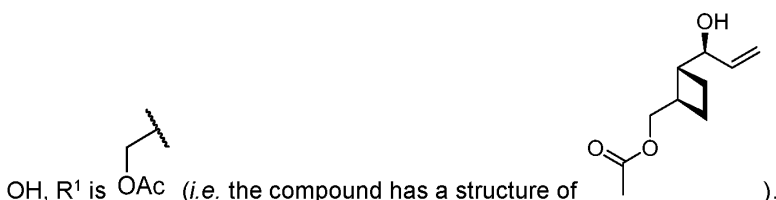
[0111] In some embodiments, R¹ is a protected aldehyde. In some embodiments, R¹ is selected





embodiments, R¹ is , wherein the counterion is, for example, a sodium ion.

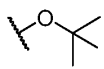
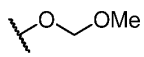
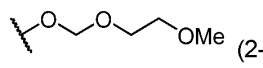
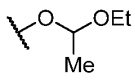
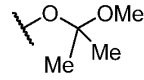
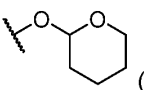
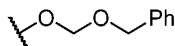
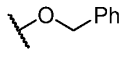
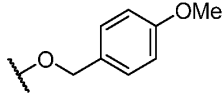
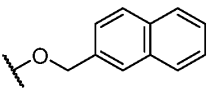
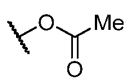
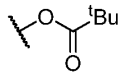
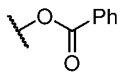
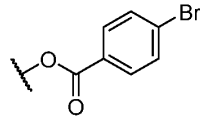
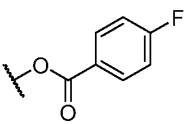
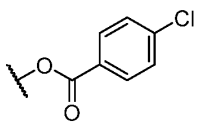
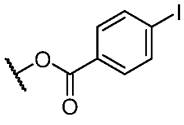
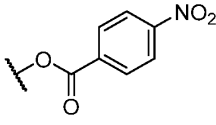
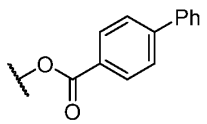
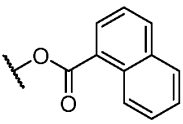
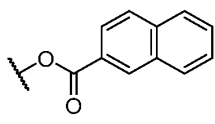
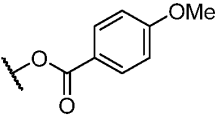
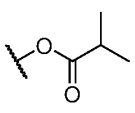
[0112] As provided herein, R² is OH or OPG². In some embodiments, R² is OH. When R² is



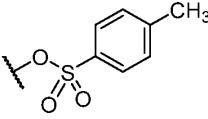
[0113] In some embodiments, R² is OPG². As described herein, OPG² is a secondary alcohol protecting group. Suitable secondary alcohol protecting groups include those described herein. For example, in some embodiments, OPG² is selected from the group consisting of an ether, an acetal or ketal, an acyl, a silyl ether, and a sulfonyl.

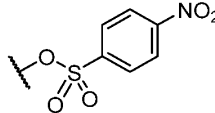
[0114] In some embodiments, OPG² is an ether (e.g., methoxy, ethoxy, propoxy, butoxy, tert-butoxy, methoxymethyl acetal (MOM), 2-methoxyethoxymethyl ester (MEM), ethoxyethyl acetal (EE), and methoxypropyl ether (MOP), benzyloxymethyl acetal (BOM), benzyl ether (Bn), 4-methoxybenzyl ether (PMB), and 2-naphthylmethyl ether (Nap)). In some embodiments, OPG² is an acetal or ketal (e.g., tetrahydropyranyl acetal (THP)). In some embodiments, OPG² is an

acyl (e.g., acetyl, pivaloyl, benzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, 4-phenylbenzoyl, 1-naphthoyl, 2-naphthoyl, 4-methoxybenzoyl, isobutyryl). In some embodiments, OPG² is a silyl ether (e.g., OSiEt₃ (triethylsilyl ether, TES), OSi(ⁱPr)₃ (triisopropylsilyl ether, TIPS), OSiMe₃ (trimethylsilyl ether, TMS), OSiMe₂^tBu (*tert*-butyldimethylsilyl ether, TBS), OSiPh₂Bu (*tert*-butyldiphenylsilyl ether TBDPS)). In some embodiments, OPG² is a sulfonyl (e.g., mesyl, tosyl, nosyl, triflyl).

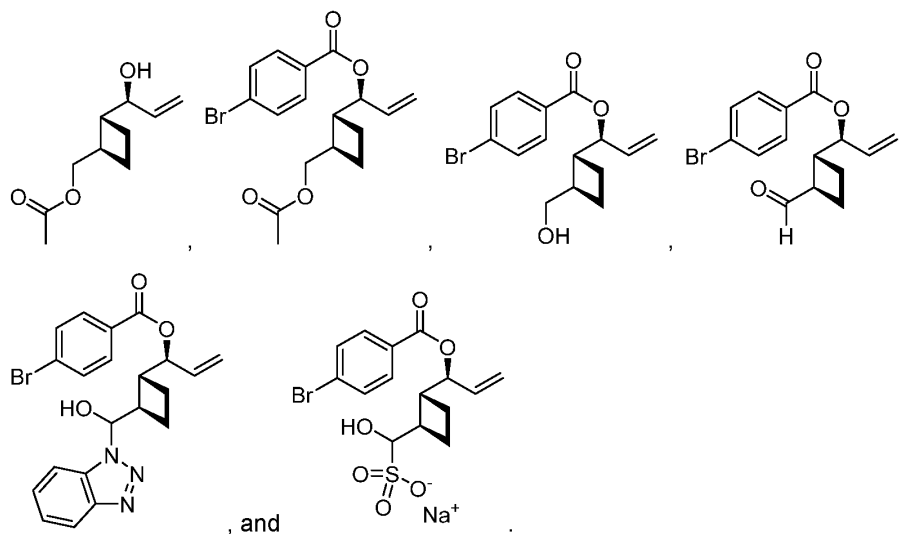
[0115] In some embodiments, OPG² is selected from the group consisting of  (methoxy),  (tert-butyl ether),  (methoxymethyl acetal, MOM),  (2-methoxyethoxymethyl ether, MEM),  (ethoxyethyl acetal, EE),  (methoxypropyl acetal, MOP),  (tetrahydropyranyl acetal, THP),  (benzyloxymethyl acetal, BOM),  (benzyl 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), OSiEt₃ (triethylsilyl ether, TES), OSi(ⁱPr)₃ (triisopropylsilyl ether, TIPS), OSiMe₃

(trimethylsilyl ether, TMS), OSiMe₂tBu (*tert*-butyldimethylsilyl ether, TBS), OSiPh₂tBu (*tert*-

butyldiphenylsilyl ether TBDPS), OSO₂Me (mesyl),  (4-toluenesulfonyl,

tosyl),  (4-nitrobenzenesulfonyl, nosyl), and OSO₂CF₃ (triflyl). In some embodiments, OPG² is 4-bromobenzoyl.

[0116] In some embodiments, the compound is selected from the group consisting of:



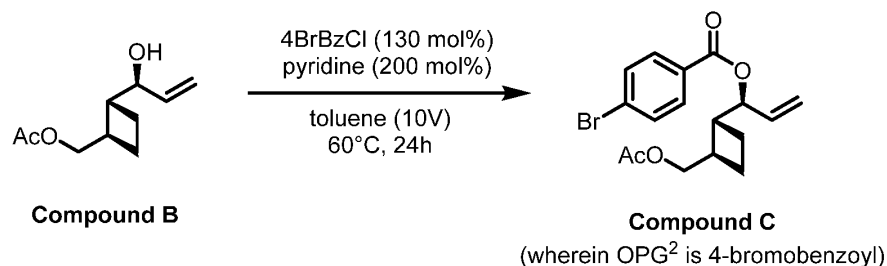
[0117] It is to be understood that while the disclosure is read in conjunction with the detailed description thereof, the foregoing description and following example are intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

EXAMPLES

[0118] The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1: Protection of Secondary Alcohol

[0119] (*S*)-1-(((1*R*,2*R*)-2-(acetoxymethyl)cyclobutyl)allyl) 4-bromobenzoate was prepared according to the following reaction scheme:

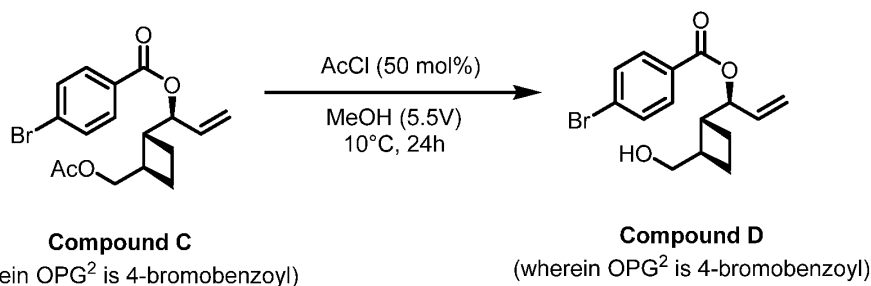


[0120] A 3100 L glass-lined reactor was flushed with nitrogen and charged with Compound B (363.5 kg, 25.3 w/w% in toluene, 1.00 equiv.), pyridine (81 L, 2.0 equiv.), and toluene (287 L, 3.1 L/kg). The mixture was stirred at 20 °C until homogenous. A solution of 4-bromobenzoyl chloride (143 kg, 1.30 equiv.) in toluene (380 L, 4.1 L/kg) was then charged to the reaction mixture. The reaction mixture was heated to 60 °C and held 4 hours or until the reaction was adjudged complete by HPLC analysis. The reaction was cooled to 5 °C and quenched with 1M HCl (367 L, 4 L/kg). The reaction mixture was filtered through a 20µm filter into a clean 14300 L glass-lined reactor forward rinsing with toluene (184 L, 2 L/kg). The biphasic mixture was warmed to 20 °C and the phases were split. The toluene solution was sequentially washed with sodium bicarbonate solution (5 w/w%, 368 L, 4 L/kg) and water (368 L, 4 L/kg). The toluene solution was then concentrated to a volume of ~184 L, maintaining the internal temperature < 40 °C. n-Heptane (460 L, 5 L/kg) was charged into the reactor and the resulting solution was cooled to 5°C. After stirring for 1 hour at 5 °C, the reaction mixture was filtered through a 0.5 µm sparkler filter into a clean 6700 L glass-lined reactor forward rinsing with n-heptane (110 L, 1.2 L/kg). The mixture was concentrated to a volume of ~262 L, maintaining the internal temperature < 40°C. The resulting solution of Compound C was cooled to 20°C and telescoped directly into the next step.

[0121] ¹H NMR (600 MHz, DMSO) δ 7.92 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 5.85 (ddd, J = 17.1, 10.6, 6.1 Hz, 1H), 5.42 (ddt, J = 8.0, 6.1, 1.4 Hz, 1H), 5.27 (dt, J = 17.1, 1.4 Hz, 1H), 5.20 (dt, J = 10.6, 1.4 Hz, 1H), 3.97 (dd, J = 11.4, 6.0 Hz, 1H), 3.95 (dd, J = 11.4, 6.0 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.47 (qui, J = 8.0 Hz, 1H), 1.94 – 1.87 (m, 2H), 1.87 (s, 3H), 1.72 (dq, J = 10.7, 9.1 Hz, 1H), 1.64 (dq, J = 11.3, 9.1 Hz, 1H). ¹³C NMR (151 MHz, DMSO) δ 170.3, 164.3, 134.5, 131.9, 131.1, 128.9, 127.5, 117.1, 77.6, 66.6, 40.5, 36.4, 20.5, 20.5, 19.9. LRMS (ESI): Calculated for C₁₇H₁₉BrO₄+H: 367, found: 367.

Example 2: Deprotection of Primary Alcohol

[0122] (S)-1-((1R,2R)-2-(hydroxymethyl)cyclobutyl)allyl 4-bromobenzoate was prepared according to the following reaction scheme:

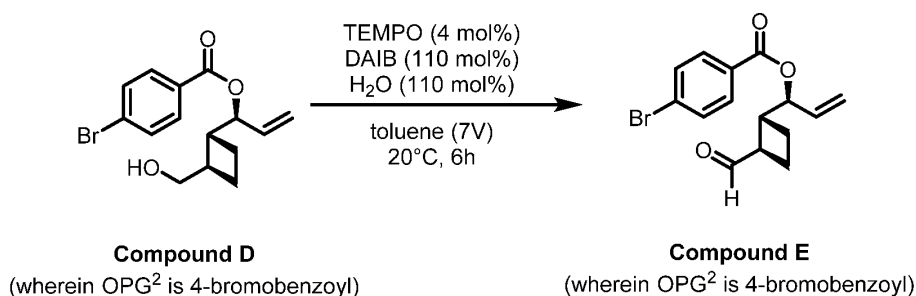


[0123] A 6700 L glass-lined reactor containing a ~262 L solution of Compound C was charged with methanol (938 L, 5.5 L/kg) and cooled to 1 °C. Acetyl chloride (16 L, 0.5 equiv.) was charged at a rate to maintain the internal temperature <5 °C. The reaction mixture was stirred at 10°C for 10 hours or until judged complete by HPLC analysis. The reaction mixture was diluted with toluene (1750 L, 10 L/kg) before being quenched with sodium bicarbonate solution (5 w/w%, 852 L, 5 L/kg) and sodium chloride solution (5 w/w%, 170 L, 1 L/kg). The biphasic mixture was warmed to 20°C and the phases were separated. The toluene layer was washed with water (852 L, 5 L/kg). The mixture was concentrated to a volume of ~186 L, maintaining the internal temperature < 40°C. Compound C (317.5 kg, 48.8 w/w% in toluene) was obtained by HPLC assay and telescoped directly into the next step.

[0124] ¹H NMR (600 MHz, DMSO) δ 7.91 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 5.86 (ddd, *J* = 17.2, 10.7, 5.7 Hz, 1H), 5.40 (ddt, *J* = 8.0, 5.7, 1.4 Hz, 1H), 5.26 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.19 (dt, *J* = 10.7, 1.4 Hz, 1H), 4.43 (t, *J* = 5.7 Hz, 1H), 3.36 (dt, *J* = 10.3, 5.7 Hz, 1H), 3.31 (dt, *J* = 10.3, 5.7 Hz, 1H), 2.42 (qui, *J* = 8.0 Hz, 1H), 2.30 (quid, *J* = 8.0, 4.2 Hz, 1H), 1.90 – 1.77 (m, 2H), 1.73 – 1.60 (m, 2H). ¹³C NMR (151 MHz, DMSO) δ 164.4, 134.8, 131.9, 131.1, 129.1, 127.4, 116.9, 78.1, 64.0, 40.0, 39.6, 20.4, 19.9. LRMS (ESI): Calculated for C₁₅H₁₇BrO₃+H: 325, found: 325.

Example 3: Oxidation of Primary Alcohol

[0125] (S)-1-((1*R*,2*R*)-2-formylcyclobutyl)allyl 4-bromobenzoate was prepared according to the following reaction scheme:



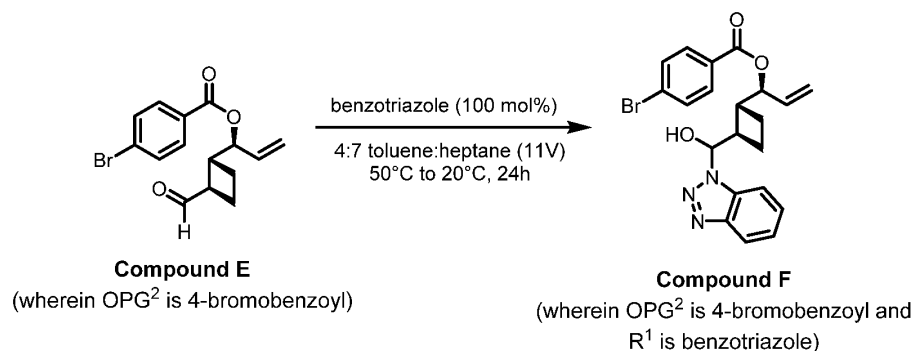
[0126] A 3600 L stainless steel reactor was flushed with nitrogen and charged with Compound D (317.5 kg, 48.8 w/w% in toluene, 1.00 equiv.) and toluene (930 L, 6 L/kg). The mixture was stirred at 20 °C until homogenous. Water (9.5 L, 1.10 equiv.) and (diacetoxyiodo)benzene (169

kg, 1.10 equiv.) were charged into the reactor. The heterogeneous mixture was cooled to 15 °C. A solution of TEMPO (2.9 kg, 0.04 equiv.) in toluene (155 L, 1 L/kg) was charged at a rate to maintain the internal temperature < 20 °C. The reaction mixture was warmed to 20 °C and held 12 hours or until the reaction was adjudged complete by HPLC analysis. The reaction was quenched with sodium thiosulfate solution (5 w/w%, 775 L, 5.0 L/kg) and the phases were separated. The toluene layer was sequentially washed with sodium carbonate solution (5 w/w%, 775 L, 5.0 L/kg) and twice with water (775 L, 5.0 L/kg). The mixture was concentrated to a volume of ~465 L, maintaining the internal temperature < 40 °C. The resulting solution of Compound E was cooled to 20 °C and telescoped directly into the next step.

[0127] ¹H NMR (600 MHz, DMSO) δ 9.61 (d, 1.9 Hz, 1H), 7.90 (d, 8.2 Hz, 2H), 7.75 (d, 8.2 Hz, 2H), 5.85 (dddd, 17.3, 10.6, 6.0, 0.6 Hz, 1H), 5.44 (ddt, 7.4, 6.0, 1.4 Hz, 1H), 5.30 (dtd, 17.3, 1.4, 0.6 Hz, 1H), 5.22 (dq, 10.6, 1.4, 0.6 Hz, 1H), 3.23 – 3.15 (m, 1H), 2.93 – 2.85 (m, 1H), 2.11 – 2.02 (m, 1H), 2.00 – 1.94 (m, 1H), 1.89 – 1.82 (m, 2H); ¹³C NMR (151 MHz, DMSO) δ 202.2, 164.3, 134.1, 131.9, 131.1, 128.8, 127.5, 117.6, 77.2, 47.3, 38.4, 19.9, 18.0. LRMS (ESI): Calculated for C₁₅H₁₅BrO₃+H: 323, found: 323.

[0128] **Example 4: Protection of Aldehyde**

[0129] (1S)-1-((1R,2R)-2-((1H-Benzo[d][1,2,3]triazol-1-yl)(hydroxy)methyl)cyclobutyl)allyl 4-bromobenzoate was prepared according to the following reaction scheme:



[0130] A 3600 L stainless steel reactor containing a ~465 L solution of Compound E was charged with benzotriazole (56.5 kg, 1.00 equiv.). The mixture was stirred at 20 °C until homogeneous. The resulting solution was filtered through a 0.5 μm polyester filter into a clean 3600 L stainless steel reactor forward rinsing with toluene (155 L, 1 L/kg.). The reaction mixture was heated to 50 °C. n-Heptane (310 L, 2 L/kg.) was then charged at a rate to maintain the internal temperature >45 °C. Milled Compound F seed (3.2 kg, 2.0 w/w%) was charged into the reactor and the suspension was held at 50 °C for 1 hour. n-Heptane (622.5 L, 4 L/kg) was dosed into the reactor over 10 hours maintaining the internal temperature at 50 °C before starting a cooling ramp to 20 °C over 4 hours. n-Heptane (310 L, 2 L/kg) was dosed into the reactor over 2 hours maintaining the internal temperature at 20 °C before initiating a 4 hours hold. The heterogeneous mixture was transferred into a 1260 L Hastelloy agitated filter dryer and

deliquored. The cake was sequentially washed with a 1:1 mixture of toluene:n-heptane (310 L, 2 L/kg) and n-heptane (310 L, 2 L/kg). The cake was dried under vacuum maintaining the internal temperature < 50 °C. Compound F (170 kg) was isolated by HPLC assay in an 80% molar yield.

[0131] **¹H NMR (600 MHz, DMSO)** δ 8.01 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.88 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.53 (ddd, *J* = 8.3, 6.9, 1.0 Hz, 1H), 7.39 (ddd, *J* = 8.3, 6.9, 1.0 Hz, 1H), 7.22 (d, *J* = 5.8 Hz, 1H), 6.29 (dd, *J* = 8.7, 5.8 Hz, 1H), 5.96 (ddd, *J* = 17.3, 10.6, 6.4 Hz, 1H), 5.57 (tt, *J* = 6.4, 1.2 Hz, 1H), 5.33 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.25 (dt, *J* = 10.6, 1.4 Hz, 1H), 3.20 (qui, *J* = 8.7 Hz, 1H), 2.78 (qui, *J* = 8.7 Hz, 1H), 1.93 (dtd, *J* = 11.6, 8.7, 3.8 Hz, 1H), 1.75 (dq, *J* = 11.6, 8.7 Hz, 1H), 1.62 (ddd, *J* = 11.9, 8.7, 3.8 Hz, 1H), 1.56 (dt, *J* = 11.9, 8.7 Hz, 1H); **¹³C NMR (150 MHz, DMSO)** δ 164.6, 145.5, 134.3, 131.7, 131.7, 131.2, 129.4, 127.1, 127.0, 123.9, 119.1, 117.7, 111.6, 85.9, 77.4, 41.7, 40.6, 19.4, 19.0. **LRMS (ESI):** Calculated for C₂₁H₂₀BrN₃O₃+H: 442, found: 442.