

PROCESS FOR PRODUCING (3S,6R)-6-(CYANOMETHYL)- TETRAHYDRO-2H-
PYRAN-3-AMINE

CROSS-REFERENCE TO RELATED APPLICATION

[001] This international application claims priority to United States provisional patent application number 63/518,854, filed August 10, 2023, which is hereby incorporated by reference herein in its entirety.

TECHNICAL FIELD

[002] The present disclosure relates to the discovery of a dynamic process to synthesize ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine) hydrochloride, a critical drug intermediate, in high yield.

BACKGROUND

[003] The compound (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine hydrochloride, known as APA, is a chiral intermediate useful for preparing drug compounds such as the TYK2/JAK1 inhibitor BHV-8000 (previously known as TLL-041). However, existing methods to produce this chiral intermediate, or other useful salts of the compound (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, are inefficient and provide poor yield. Therefore, improved methods to produce this intermediate are necessary.

[004] It has been found that poor yield is due to an unfavorable ratio of the desired diastereomer to an undesirable diastereomer produced during a ring closing reaction step. The present disclosure provides for a dynamic synthetic process which achieves a favorable diastereomer ratio, and provides significantly improved yield at industrially-relevant scales. The dynamic process involves conversion of the undesired diastereomer back to starting material as the reaction proceeds to accumulate an excess of the desired diastereomer. The described processes also replace a harmful and costly solvent which is favorable from a green chemistry perspective. Additionally, resource-intensive steps may be avoided to produce the critical APA intermediate more efficiently.

SUMMARY

[005] Accordingly, the present disclosure relates to an improved process to synthesize ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine) hydrochloride, or other useful salts of ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine). The following embodiments are illustrative, and further embodiments described herein are contemplated.

[006] In an embodiment, provided for is a process comprising:

reacting (2S)-6-cyano-5-hexen-1-ol-2-amine, having a protecting group on the amine, with a base in an alcohol solvent to produce (via a ring-closing reaction) a reaction mixture containing a diastereomeric mixture of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine.

[007] In an embodiment, a conjugate acid of the base has a pKa from about 16 to about 20.

[008] In an embodiment, the base is a salt of an alkoxide ion.

[009] In an embodiment, the alkoxide ion is *tert*-butoxide or isopropoxide.

[0010] In an embodiment, the salt is potassium *tert*-butoxide, sodium *tert*-butoxide, or lithium *tert*-butoxide.

[0011] In an embodiment, the salt is potassium *tert*-butoxide.

[0012] In an embodiment, the alcohol solvent comprises one or more of methanol, ethanol, *n*-propanol, isopropanol, butanol, 1,2 butanediol, 1,3 butanediol, 1,4 butanediol, 2,3 butanediol, isoamyl alcohol, and *tert*-amyl alcohol.

[0013] In an embodiment, the alcohol solvent comprises isopropanol. In an embodiment, the alcohol solvent is isopropanol.

[0014] In an embodiment, the protecting group on the amine is selected from the group consisting of benzyl carbamate (Cbz), acetamide (Ac), trifluoroacetamide (TFAc), phthalimide, triphenylmethylamine (Tr), benzyldieneamine, and *p*-toluenesulfonamide (Ts), and *tert*-butyloxy carbonyl.

[0015] In an embodiment, the protecting group on the amine is *tert*-butyloxy carbonyl.

[0016] In an embodiment, the ring-closing reaction is conducted at a temperature ranging from about 10 – 50 °C, optionally at 20 – 30 °C.

[0017] In an embodiment, the ring-closing reaction is performed for about 24 hours, or until the amount of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is no longer increasing.

[0018] In an embodiment, the process further comprises quenching the reaction mixture with an acidic solution to neutralize the base after completion of the ring closing reaction.

[0019] In an embodiment, a solid phase comprising (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, precipitates from the alcohol solvent.

[0020] In an embodiment, the solid phase comprises a diastereomeric ratio of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, to (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, of at least about 75:25. In an embodiment, the diastereomeric ratio is about 90:10.

[0021] In an embodiment, the process further comprises filtering the solid phase from the reaction mixture.

[0022] In an embodiment, the process further comprises purifying (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, from the solid phase.

[0023] In an embodiment, (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is purified from the diastereomeric mixture at a diastereomeric ratio of about 99:1.

[0024] In an embodiment, the purification comprises contacting the diastereomeric mixture with a purification solvent in which (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is insoluble and precipitates from solution and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is soluble and remains in solution, and filtering a resultant, purified precipitate containing (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine.

[0025] In an embodiment, the purification solvent comprises methyl *tert*-butyl ether. In an embodiment, the purification solvent is methyl *tert*-butyl ether.

[0026] In an embodiment, the process further comprises reacting the purified (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, with hydrochloric acid to deprotect the amine and to form ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl) hydrochloride.

[0027] In an embodiment, the process further comprises isolating the ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl) hydrochloride.

[0028] In further embodiments, provided for is a process comprising:

reacting (2S)-6-cyano-5-hexen-1-ol-2-amine, having a protecting group on the amine, with a base in a solvent to produce a reaction mixture containing a solid phase, wherein:
the solid phase comprises a diastereomeric mixture of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine;
wherein the (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is insoluble in the solvent; and
wherein the (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is at least partially soluble in the solvent.

[0029] In an embodiment, the solvent is miscible with water.

[0030] In an embodiment, the solvent is a weak acid.

[0031] In an embodiment, the solvent has a pKa which is different from the pKa of a conjugate acid of the base by about 25% or less.

[0032] In an embodiment, the solvent has a pKa from about 16 to about 20.

[0033] In an embodiment, the solid phase contains a diastereomeric ratio of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, to (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, of at least about 75:25, preferably about 90:10

[0034] In further embodiments, provided for is a process comprising:

reacting (2S)-6-cyano-5-hexen-1-ol-2-amine, having a protecting group on the amine, with an alkoxide base in an alcohol solvent to produce a reaction mixture containing a solid phase, wherein:

the solid phase comprises a diastereomeric mixture of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine; and
wherein the solid phase has a diastereomeric ratio of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, to (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, of at least about 75:25.

[0035] In an embodiment, the reaction is conducted until at least about 80% of APA-7 is converted to APA-8.

[0036] In an embodiment, the reaction is conducted at a temperature from about 10 – 50 °C, optionally at 20 – 30 °C.

[0037] In an embodiment, the reaction mixture is stirred or agitated while the ring-closing reaction is conducted.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Aspects and advantages of the present disclosure will become apparent from the following exemplary embodiments taken in conjunction with the accompanying drawings, of which:

[0039] FIG. 1 depicts a reference process to produce APA-8;

[0040] FIG. 2 depicts an exemplary process to produce APA-8;

[0041] FIG. 3 depicts crystallization-induced dynamic resolution which can accumulate a diastereomeric excess of the desired APA-8 product;

[0042] FIG. 4 depicts an HPLC chromatogram for produced and purified APA-8;

[0043] FIG. 5 depicts LC-MS data for produced and purified APA-8;

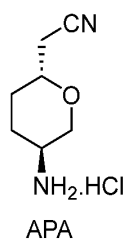
[0044] FIG. 6 depicts a ^1H NMR spectrum for produced and purified APA-8;

[0045] FIG. 7 depicts a ^{13}C NMR spectrum for produced and purified APA-8; and

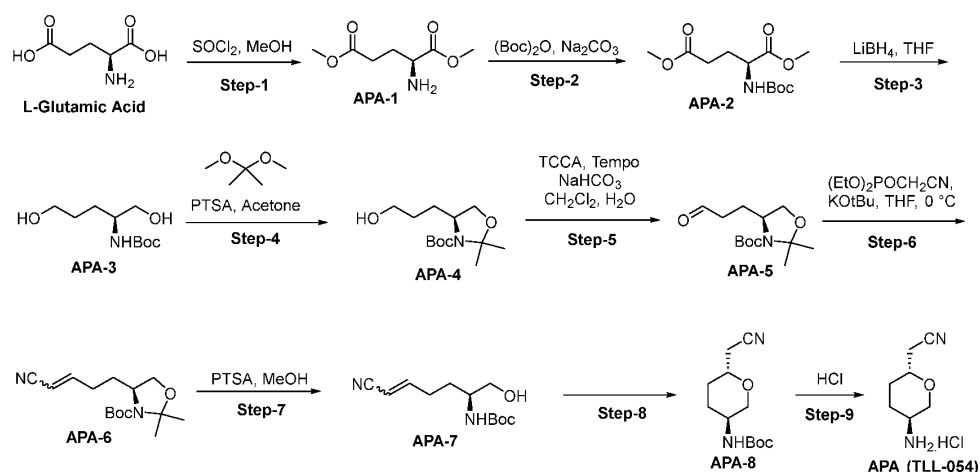
[0046] FIG. 8 depicts an IR spectrum for produced and purified APA-8.

DETAILED DESCRIPTION

[0047] The compound ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine) hydrochloride (APA) is a critical intermediate for the synthesis of drug compounds such as BHV-8000. The structure of APA, in a hydrochloride salt form, is shown below.

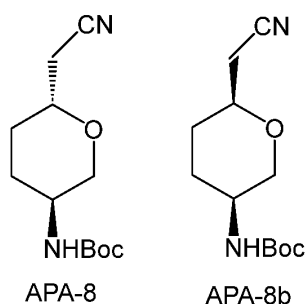


[0048] APA may be synthesized according to a synthetic scheme as shown below in Scheme 1, starting from readily-available L-glutamic acid starting material. Alternative synthetic schemes to produce APA-7 are also contemplated.



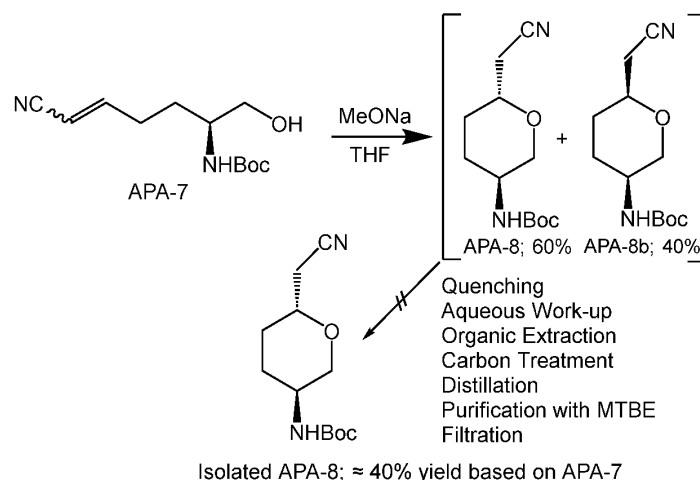
Scheme 1: Synthesis of chiral intermediate APA

[0049] At step 8 of the process, APA-7, a linear alkene ((2*S*)-6-cyano-5-hexen-1-ol-2-amine) having a protecting group on the amine, is subjected to ring-closing conditions to produce APA-8, which may be deprotected to form APA. APA-8 (i.e., tert-butyl ((3*S*,6*R*)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl)carbamate), shown above, is the *trans* diastereomer needed for the chiral intermediate APA. The ring closing reaction of APA-7 also tends to produce an undesired *cis* diastereomer, termed APA-8b (i.e., tert-butyl ((3*S*,6*S*)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl)carbamate). While “APA-8” and “APA-8b” refer to specific structures containing a Boc protecting group, it should be appreciated that recitations of these terms can encompass the same compounds having other suitable protecting groups as described herein. APA-8 and APA-8b are shown below.



[0050] The present disclosure provides for an improved synthetic procedure to produce the required diastereomer APA-8, among other related improvements. Known methods to produce APA-8 provide poor yield and unfavorable stereoisomerism of APA-8 (the desirable stereoisomer) compared to APA-8b (the undesirable stereoisomer). A related, previous process was generally described in Congxin et al., International Application Number PCT/CN2022/129966, filed December 19, 2022 corresponding to WO 2023/125102,

published July 6, 2023, which is incorporated by reference herein. An example based on this previous process is shown below.



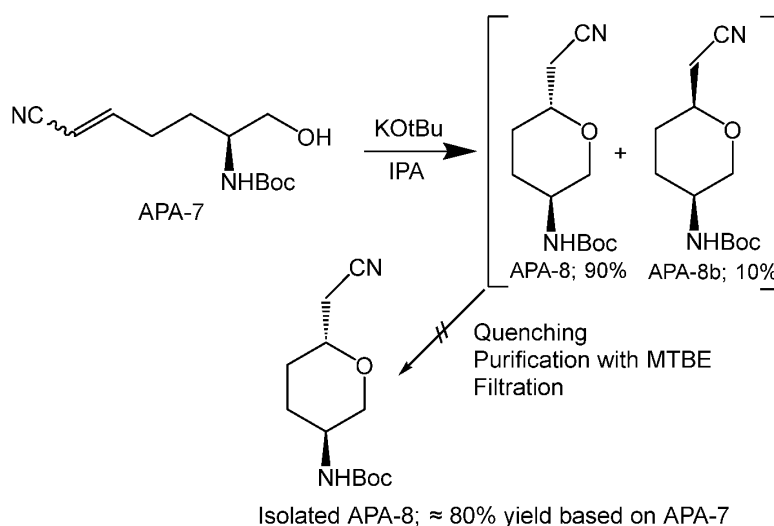
Scheme 2: Exemplary reference process to produce APA-8 from APA-7.

[0051] APA-8 corresponds to compound 2-2 of Congxin et al., and the reference reports 42.2% yield of this compound at a scale of 43.2 kg isolated. Congxin et al. do not discuss the ratios of diastereomers produced by the reaction. However, the diastereomers depicted in Scheme 2 generally result from the ring-closing reaction. To obtain APA-8 from the diastereomeric product mixture of APA-8 and APA-8b, aqueous work-up, organic extraction, carbon (charcoal) treatment, and distillation steps are utilized. As discussed herein, a version of the Congxin et al. process was performed herein with comparable yield due in part to poor diastereomeric selectivity for APA-8.

[0052] FIG. 1 depicts a flow chart of an adapted Congxin et al. process (hereinafter the “reference process”) performed as a comparison to the dynamic process described herein. Following the reference process, APA-7 was reacted with sodium methoxide (NaOMe) in tetrahydrofuran (THF) solvent. From the reaction mixture (RM), the ratio of diastereomers APA-8 to APA-8b was determined to be 60:40, meaning that 40% of the material produced is immediate waste by the reference process. Following workup, extraction, and purification (carbon treatment, distillation, and recrystallization from MTBE), APA-8 was obtained at an isolated yield of approximately 40% based on the amount of APA-7 utilized, with purity $>98\%$. The workup, extraction, carbon treatment, and distillation steps are required because the reference process is performed in a THF solvent, which is immiscible in water and which must be removed from the product. This compared well with the 42.2% yield and 96% purity reported by Congxin et al.

[0053] At industry scale, the diastereomeric ratio of 60:40 under the reference process is unacceptable for efficiency and economic reasons. Additionally, from a green chemistry perspective, it would be advantageous to replace THF with a more economical and environmentally-friendly solvent, and to avoid resource-intensive steps such as aqueous work-up, organic extraction, carbon treatment, and distillation.

[0054] As such, the present invention provides for a solution to these issues by way of an alternative, dynamic synthetic procedure which produces APA-8 from APA-7 with a reaction mixture ratio of diastereomers APA-8 to APA-8b of about 90:10, and an approximately doubled isolated yield of APA-8 of about 80% based on the amount of APA-7 utilized, at industrially-relevant scales. The process herein also avoids the use of THF, instead using a greener solvent, such as an alcohol (e.g., isopropyl alcohol (IPA) or others). Even further, resource-intensive aqueous work-up, organic extraction, carbon treatment, and distillation steps may be avoided under this dynamic process to produce the isolated product in high yield. This dynamic process is depicted below in Scheme 3.



Scheme 3: Exemplary dynamic process to produce APA-8 from APA-7.

[0055] FIG. 2 depicts an exemplary dynamic process according to the present disclosure. This process reacts APA-7 with potassium tert-butoxide (KOtBu) in isopropyl alcohol (IPA) to produce a favorable diastereomeric ratio of APA-8 (90%) compared to byproduct APA-8b (10%) as a precipitated, solid product. As a direct result of this improvement, the yield of isolated APA-8 product under the dynamic process ($\approx$ 80%) is approximately double the 40%

yield of the reference process. As will be described further herein, the dynamic process generated such high yield on multi-kilogram scales, demonstrating industrial applicability. [0056] It has been discovered that this advantageous diastereomeric ratio and resultant high yield is due to, in part, the use of a solvent in which APA-8 is insoluble and APA-8b is relatively soluble. This phenomenon is depicted in FIG. 3, and is known as crystallization-induced dynamic resolution. The term crystallization in this context does not necessarily imply any particular ordered or crystalline structure, but means that the desired material precipitates out from the reaction mixture. Because APA-8b is more soluble in the reaction mixture, it will undergo the reverse ring-opening reaction to form a linear APA-7 product, which will then undergo the ring-closing reaction again. Thus, the statistical amount of APA-8 formed from each ring closing reaction precipitates or crystallizes from the solvent where it does not readily undergo the reverse reaction, and a diastereomeric excess of the APA-8 product is formed over time. In view of their similar properties to isopropyl alcohol, alcohol solvents having from 1 to 5 carbon atoms (i.e., from methanol to pentanols having one or more hydroxyl groups) would have an advantageous effect on the diastereomer distribution compared to the reference process solvent THF. Additionally, the present disclosure contemplates other protic organic solvents in which APA-8 has poorer solubility compared to APA-8b.

[0057] The dynamic process provides several additional improvements to obtain APA-8 in high chiral purity while eliminating several disadvantageous steps utilized in the reference process, including aqueous work-up, extraction, carbon treatment, and distillation. In an aspect, these steps are avoided by use of a water-miscible solvent rather than immiscible THF. On an industrial scale, eliminating these steps can be highly significant.

[0058] In an embodiment, APA-7 is reacted with a strong or relatively strong base in a solvent to produce a favorable diastereomeric distribution of APA-8 and APA-8b. In an embodiment, the solvent is a protic organic solvent. In an embodiment, the solvent is a weak acid (in this context, meaning that it has a pK_a of about 10 or higher, or whose conjugate base is capable of deprotonating APA-7 to initiate the cyclization reaction). In an embodiment, the solvent has a pK_a ranging from about 16 to about 20. In an embodiment, the solvent has a pK_a which is different from the pK_a of a conjugate acid of the base by about 25% or less, including solvents which have the same pK_a as the pK_a of the conjugate acid of the base (for example, an isopropyl alcohol solvent and isopropoxide base). In an embodiment, the solvent is an organic solvent comprising an alcohol. In an embodiment, the solvent is an alcohol. In an embodiment, the alcohol contains from 1 to 5 carbon atoms. In an

embodiment, the alcohol is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, butanol (including 1-butanol, 2-butanol, *tert*-butanol, and isobutanol), and various isomers of butanediols and pentanols (including isoamyl alcohol and *tert*-amyl alcohol). Other alcohol solvents can include ethylene glycol, propylene glycol, etc. In an embodiment, the alcohol is isopropanol. The amount of solvent in a particular reaction may be adjusted as necessary, however in some embodiments approximately 6 mL of solvent per gram of APA-7 is utilized. In further embodiments, about 1 mL of solvent per gram of APA-7 to about 100 mL of solvent per gram of APA-7 may be utilized.

[0059] The term “APA-7” as used herein generally means the compound (2S)-6-cyano-5-hexen-1-ol-2-amine having a protecting group on the amine. While Boc (*tert*-butyl carbamate) is a suitable protecting group, other protecting groups may be utilized. As a non-limiting list of protecting groups, benzyl carbamate (Cbz), acetamide (Ac), trifluoroacetamide (TFAc), phthalimide, triphenylmethylamine (Tr), benzylideneamine, and *p*-toluenesulfonamide (Ts), among others, may be utilized in alternative embodiments. Likewise, reference to the compound (2S)-6-cyano-5-hexen-1-ol-2-amine having a protected amine, using this or similar phrasing, is intended to encompass any protected version of the compound. As should be understood, a protected amine will have one or more of its hydrogen atoms replaced by a bond to the protecting group. In general, where a compound (APA-7, APA-8, or APA-8b) is described as being “protected”, it should be understood that a protecting group is bonded to the amine group.

[0060] In an embodiment, a base having suitable basicity is utilized. In an embodiment, the base is a strong base or relatively strong base (for example, a base stronger than hydroxide but not as strong as butyllithiums and related bases). In an embodiment, the base strength may be defined by the negative log of the acid dissociation constant (pK_a) of its conjugate acid, where a higher pK_a indicates poorer acidity of the conjugate acid and thus higher basicity of the base. In an embodiment, the base has a pK_a of its conjugate acid ranging from about 16 to about 20. One example of a suitable base is an alkoxide, although other bases capable of catalyzing the ring closing reaction are contemplated. In an embodiment, the base is an alkoxide base. An alkoxide base is generally introduced as a salt of an alkoxide ion. For example, an ionic complex including a cation such as potassium, sodium, or lithium and an alkoxide anion may be utilized. In various embodiments, the cation may be an alkali cation such as potassium (K^+), sodium (Na^+), or lithium (Li^+). In alternative embodiments, other cations may be present. For example, alkaline dications such as Mg^{2+} or Ca^{2+} or monocations such as $(MgCl)^+$ may be utilized. In general, any ionic complex including a useful alkoxide

base are contemplated. The salt will generally be soluble in the reaction mixture, meaning that the ionic complex disassociates to provide some amount of accessible base.

[0061] Alkoxides may be linear (such as methoxide, ethoxide, and *n*-propoxide, etc.) or branched (such as isopropoxide, *tert*-butoxide, 2-butanolate, etc.). The amount of base used may vary depending upon reaction conditions and can alter the overall reaction time to completion. In some embodiments, the amount of strong base is about 0.1 molar equivalents of APA-7, however the amount of strong base may vary. For example, in other embodiments, the amount of strong base may be about 0.01 molar equivalents of APA-7, 0.1 molar equivalents of APA-7, 1 molar equivalent of APA-7, or higher. Because the base is catalytic, it may be generally present at lower concentration compared to APA-7.

[0062] In an embodiment, APA-8 is produced from APA-7 in a diastereomeric ratio (defined by APA-8:APA-8b) of at least 70:30, or at least 75:25, or at least 80:20, or at least 85:15, or at least 90:10 (where “at least” encompasses APA-8 proportions higher than the recited first number in the ratio and APA-8b proportions lower than the recited number in the ratio).

[0063] In an embodiment, APA-7 is reacted with the base in the solvent for a sufficient time to complete the conversion to APA-8 (and minor product APA-8b) at the given reaction temperature. For example, the reaction may be performed at $25 \pm 5^{\circ}\text{C}$ for approximately 24 hours. In alternative embodiments, the reaction may be performed at lower temperatures which are above the freezing point of the solvent, which make the reaction kinetically feasible, and which do not make the undesired APA-8b product insoluble. The reaction temperature should also not be high enough to render the desired APA-8 product soluble or to prevent its precipitation. For example, in alternative embodiments, the temperature may be from about 10°C to about 50°C . A person of skill in the art will generally be able to monitor the reaction products to determine appropriate temperature and time conditions for a given ring closing reaction of APA-7.

[0064] Following the ring-closing reaction of APA-7, the heterogeneous reaction mixture (RM) contains major product APA-8 as a precipitated or crystallized product as well as solubilized minor product APA-8b, residual APA-7, solvent, base, and trace byproducts. The precipitated APA-8 product may also contain a small amount of APA-8b, and other minor impurities, which are removed in a later purification step. The RM may then be quenched, for example, by addition of a sufficient amount of water. An excess of water may be used, such as for example 20 mL of water per gram of APA-7. Preferably, the water may contain an acid at the same or similar molar equivalent to the base. For example, in an embodiment, the water used to quench the reaction may contain ammonium chloride or another acid. The acid may

be first added in a smaller aliquot of water (such as about 0.25 mL per g of APA-7) and stirred for several minutes (e.g., 10 – 15 minutes) followed by addition of excess water. The RM may be cooled before, during, or after quenching to maintain or reduce temperature of the RM as a result of quenching exotherms. For example, the RM may be cooled and maintained at a temperature from about 0°C to about 10°C, or as necessary to avoid loss of product. The RM may be cooled for a period of time, such as for about 1 hour, to ensure quenching is complete. Once quenched, the wet product containing APA-8 may be collected by gravity filtration, vacuum filtration, or other means of removing the liquid phase. The wet product may be washed with water during filtration.

[0065] The wet product obtained from filtration may then be purified. In an alternative embodiment, the wet product may be first dried, and then re-wetted with water, although it is generally more efficient to purify the wet product obtained from the reaction. Various purification methods are contemplated, including but not limited to chemical purification, chromatographic purification (column or high-throughput), and any other method. A non-limiting example of a chemical purification is described below.

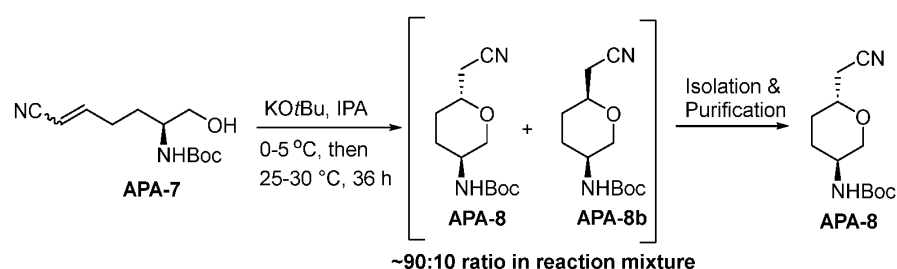
[0066] In an embodiment, a recrystallization from methyl tert-butyl ether (MTBE) is utilized to purify the product. In an embodiment, the wet material (containing APA-8) is mixed with about 3 mL of methyl tert-butyl ether (MTBE) per gram of APA-7 utilized. More or less MTBE may be utilized as would be appreciated by a person of ordinary skill in the art. The MTBE suspension may be stirred for at least about 1 hour at about 25 – 30 °C, which dissolves at least some of the wet material containing APA-8. Then, the mixture is cooled to about 0 - 5°C (where APA-8 forms solid crystals) and mixed for an additional time of at least about 1 hour. The liquid may then be removed by vacuum filtration and the solid may be washed with cooled MTBE. The solid obtained may then be dried to obtain the purified APA-8 product. While MTBE is generally preferred, any solvent in which APA-8 is relatively insoluble compared to APA-8b may be utilized for purification and crystallization of the APA-8 product.

[0067] As an optional or additional step, prior to or after the MTBE wash, the wet material may be mixed with about 5 mL of n-heptane per gram of APA-7 utilized. The n-heptane suspension may be stirred for at least about 30 minutes at 25 – 30 °C, followed by vacuum filtration and rinsing with n-heptane. The n-heptane wash may assist in removing additional solvent or other impurities from the wet material prior to recrystallization. Other volatile solvents such as hexanes may be utilized.

[0068] While the described process can advantageously avoid aqueous work-up, organic extraction, carbon treatment, and distillation, these or other processes may be employed in various alternative embodiments. Other alternative embodiments processes should be appreciated by a person of ordinary skill in the art and such alternative embodiments are contemplated herein.

EXAMPLES

[0069] **Example 1:** Synthesis of tert-butyl ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl)carbamate (APA-8):



Scheme 4: Exemplary process to produce APA-8

[0070] To a stirred solution of *tert*-butyl (S)-(6-cyano-1-hydroxyhex-5-en-2-yl)carbamate, APA7 (50.0 g, 208 mmol.) in isopropyl alcohol (300 mL) was added potassium *tert*-butoxide (2.33 g, 20.8 mmol) at 0-5 °C. The reaction mixture was allowed to 25-30 °C and stirred for 36 h at the same temperature (25-30 °C) (*Observation: The reaction mass becomes heterogeneous nature during the maintenance*). After reaction completion (chemical conversion and desired/undesired isomers ratio was monitored by HPLC), the reaction mixture was quenched with 20% ammonium chloride solution (25 mL) at below 30 °C and stirred the mass for 30 minutes at 25-30 °C. Water (1000 mL) was added to the mass at 25-30 °C over a period of 20 minutes and stirred the mass for 30 minutes. The mass was cooled to 0-10 °C and stirred for 1 h. The resultant solids were filtered and washed with water (250 mL) and vacuum dried for 30 minutes. The wet material was collected and subjected to the below purification process.

[0071] Purification of wet material: Charged MTBE (150 mL) and APA8 wet material into a round bottom flask and stirred for 1 h at 25-30 °C. The mass was cooled to 0-5 °C and stirred for 1 h at 0-5 °C. The solids were filtered and washed with MTBE (100 mL) and vacuum dried for 30 minutes. The solid was dried under vacuum for 8 h at below 45 °C. APA8 Wt.: 43.0 g, Yield: 86%.

[0072] In summary, APA-8 was successfully obtained through a process involving reaction, quenching, purification, and drying. The obtained product was characterized by various analytical techniques, including HPLC, LC-MS, ^1H NMR, ^{13}C NMR, and FT-IR.

[0073] HPLC was performed using a Dura shell C18 (250 x 4.6) mm x 5.0 μm or equivalent (Lot number: 110805) column and UV/PDA detection. The chromatographic conditions are shown in Table 1 below.

Table 1: HPLC chromatographic conditions

No.	Test Parameter Name	Method conditions
1	Instrument Model	Waters 2695 Separation Module with 2996 PDA
2	Analytical column	Union
3	Reagents	Ammonium acetate
		Acetonitrile
		Methanol
		HPLC Water
4		
5	Mobile phase A	10mM Ammonium Acetate in 1000 ml of Water.
6	Mobile phase B	100% ACN
7	Diluent	Methanol
8	Blank	Methanol
9	Pump mode	Gradient
	Flow rate	0.6 ml/min
	Detector	UV/PDA
	Injection volume	2 μL
	Column temperature	30°C
	Sample cooler temp	25°C
	Run time	2
	Needle wash	ACN: Water (1:1)
	Seal wash	ACN: Water (80:20)
10	Test sample preparation	Weigh about 5 mg of APA8 sample in to 10 mL volumetric flask dissolved and diluted up to mark with diluent.

[0074] Under these conditions, it was found that APA-7, APA-8, and APA-8b (listed by elution order) had differing retention times which could be resolved. These retention times, as shown in the exemplary chromatogram of FIG. 4, corresponded to 19.9, 24.7, and 25.7 minutes, respectively.

[0075] Mass spectrometry (MS) was performed on the APA-8 product resolved by HPLC. The instrumental conditions for MS are shown in Table 2 below, and exemplary LC-MS data is shown in FIG. 5.

Table 2: LC-MS conditions

Test Parameter Name	Condition
Instrument Model	Waters Micro mass ZQ ESCi
Ion source	ESI +
SOURCE PARAMETERS:	
Capillary (kv)	4
Cone(v)	30
Extractor(v)	3
Rf lens (v)	0.5
TEMPERARURES	
Source temperature	100°C
Desolvationtemperature	300°C
GAS FLOW:	
Desolation (l/hr.)	900 L/Hr.
Cone (l/hr.)	40 L/Hr.

[0076] NMR spectroscopy (^1H and ^{13}C) was used to characterize and verify the APA-8 structure obtained. One dimensional NMR spectra were acquired on a 300 MHz Bruker NMR spectrometer. Samples were prepared by dissolving a mass (5 mg for ^1H NMR, 20 mg for ^{13}C NMR) of APA-8 sample in 0.7mL of DMSO-d₆ solvent, then transferring the solution into an NMR tube. Exemplary ^1H and ^{13}C NMR spectra are shown in FIGs. 6 and 7, respectively.

[0077] Fourier-Transform Infrared Spectroscopy (FTIR) spectra were collected in a Shimadzu spectrometer using potassium bromide (KBr) pellet preparation. About 3 to 4 mg of sample was mixed with about 300 to 400 mg of KBr in an agate mortar. The mixed powder was pressed into

a pellet using a hydraulic press. The measurement was conducted over a scan range of 4000 to 400 cm^{-1} with a resolution of 4 cm^{-1} . An exemplary IR spectrum is shown in FIG. 8.

Summary of Analytical Data

[0078] Chemical purity by HPLC: 98.96%.

[0079] Desired & undesired isomers ratio in purified product: 99.31:0.68.

[0080] IR (KBr): 3361, 2978, 2868, 2252, 1681, 1525, 1313, 1244, 1180, 1089, 1060, 873, 607 cm^{-1} .

[0081] ^1H -NMR (300 MHz, DMSO-d_6): δ 6.804-6.778 (1H, d, $J = 7.8$ Hz), 3.821-3.777 (1H, dd, $J = 10.5, 2.4$ Hz), 3.461-3.419 (1H, m), 3.350-3.324 (1H, m), 3.021-2.950 (1H, t, $J = 10.5$ Hz), 2.787-2.600 (2H, m), 1.880-1.810 (1H, m), 1.721-1.682 (1H, m), 1.391-1.307 (2H, m), 1.350 (9H, s) ppm.

[0082] ^{13}C -NMR (75 MHz, DMSO-d_6): δ 154.97, 118.39, 77.79, 71.99, 70.29, 45.83, 29.67, 28.76, 28.18, 23.34 ppm.

[0083] Mass (ES+): $m/z = 241.2234$ ($M+1$); Melting range: 166.3 $^{\circ}\text{C}$ to 169.5 $^{\circ}\text{C}$

[0084] **Example 2:** Reference process

[0085] A reference process based upon the methodology depicted in FIG. 1 was performed as a comparison. To a stirred solution of *tert*-butyl (S)-(6-cyano-1-hydroxyhex-5-en-2-yl)carbamate, APA7 (34.0 g, 141.4 mmol.) in THF (340 mL) stirred for 10 min cooled the reaction 0-5 $^{\circ}\text{C}$, added 25% sodium methoxide in methanol (7.64 g, 35.37 mmol) and stirred the reaction mass at 0-5 $^{\circ}\text{C}$ for 1.0 h reaction mass quenched with ammonium chloride solution (85 mL) separated both the layers and aq. layer extracted with MTBE (170 mL) combined both the organic layers and wash with brine solution (100 mL). Added charcoal (3.4 g) to organic layer at 25-30 $^{\circ}\text{C}$ and raised the temperature to 45-50 $^{\circ}\text{C}$, maintained for 30 min filtered the layer on celite bed and wash with MTBE (17 mL). Filtrate was distilled under vacuum at 40 $^{\circ}\text{C}$, added MTBE (100 mL) heated to 50-55 $^{\circ}\text{C}$ and stirred for 1.0 h. Mass allowed to 20-30 $^{\circ}\text{C}$ and maintained for 1.0 h. The mass cooled to 0-10 $^{\circ}\text{C}$ and maintained for 1.0 h filtered the solid and washed with pre-cooled MTBE (34 mL). The solid was dried under vacuum for 8 h at below 45 $^{\circ}\text{C}$. APA8 Wt.: 12.9 g, Yield: 38%. Chemical purity by HPLC: 99.09%; Desired & undesired isomers ratio: 99.09:0.91.

[0086] **Example 3:** Repeat Batches and Scale-Up

[0087] Repeat batches of APA-8 under the dynamic process were performed at scales ranging from 50 grams to 62 kilograms to test reproducibility at varying reaction conditions and to scale-up to industrially-relevant scales. As seen below in Table 3, excellent diastereomeric ratios are obtained for the desired isomer (isomer 1 in the table, where isomer 2 is the undesirable APA-8b product), with high yield based on the amount of starting material (APA-7) and with high purity in the purified product for the dynamic process (Ex. No. 2 – 6). Ex. No. 1 is shown as a comparison under the reference process.

Table 3: Repeat and Scale-Up Batches

Ex. No.	Batch Size	IPC Results (Desired/Undesired ratio)	Out put	Yield	Isolated Purity by HPLC	Comments
1	50.0 g (71% assay)	Isomer-1: 58.5% Isomer-2: 41.5%	15.3 g	43.0%	Isomer-1: 97.88% Isomer-2: 1.02%	Reference process
2	50.0 g (71% assay)	Isomer-1: 91.3% Isomer-2: 8.7%	29.0 g	80.0%	Isomer-1: 98.98% Isomer-2: 0.90%	Dynamic process
3	700.0 g (71% assay)	Isomer-1: 92.3% Isomer-2: 8.7%	404.0 g	80.0%	Isomer-1: 96.05% Isomer-2: 0.60%	Dynamic process
4	62.0 kg (71% assay)	Isomer-1: 94.8% Isomer-2: 5.2%	33.6 kg	76.0%	Isomer-1: 96.64% Isomer-2: 0.40%	Dynamic process
5	3.35 kg (78.9% assay)	Isomer-1: 92.3% Isomer-2: 7.7%	2.25 kg	85.0%	Isomer-1: 98.53% Isomer-2: 0.88%	Dynamic process
6	3.0 kg (78.9% assay)	Isomer-1: 90.8% Isomer-2: 9.2%	2.05 kg	86.0%	Isomer-1: 98.96% Isomer-2: 0.84%	Dynamic process

Incorporation by Reference

[0088] The entire disclosure of each of the patent documents, including certificates of correction, patent application documents, scientific articles, governmental reports, websites, and other references referred to herein is incorporated by reference herein in its entirety for all purposes. In case of a conflict in terminology, the present specification controls.

Equivalents

[0089] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are to be considered in all respects illustrative rather than limiting on the invention described herein. In the various embodiments of the compositions and methods of the present invention, where the term comprises is used with respect to the recited components of the compositions or steps of the

methods, it is also contemplated that the compositions and methods consist essentially of, or consist of, the recited steps or components. Furthermore, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0090] In the specification, the singular forms also include the plural forms, unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present specification will control.

[0091] Furthermore, it should be recognized that in certain instances a composition can be described as being composed of the components prior to mixing, because upon mixing certain components can further react or be transformed into additional materials.

[0092] All percentages and ratios used herein, unless otherwise indicated, are by weight.

CLAIMS

What is claimed is:

1. A process comprising:
reacting (2S)-6-cyano-5-hexen-1-ol-2-amine, having a protecting group on the amine, with a base in an alcohol solvent to produce a reaction mixture containing a diastereomeric mixture of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine.
2. The process of claim 1, wherein a conjugate acid of the base has a pKa from about 16 to about 20.
3. The process of claim 1, wherein the base is a salt of an alkoxide ion.
4. The process of claim 3, wherein the alkoxide ion is *tert*-butoxide or isopropoxide.
5. The process of claim 3, wherein the salt is potassium *tert*-butoxide, sodium *tert*-butoxide, or lithium *tert*-butoxide.
6. The process of claim 5, wherein the salt is potassium *tert*-butoxide.
7. The process of claim 1, wherein the alcohol solvent comprises one or more of methanol, ethanol, *n*-propanol, isopropanol, butanol, 1,2 butanediol, 1,3 butanediol, 1,4 butanediol, 2,3 butanediol, isoamyl alcohol, and *tert*-amyl alcohol.
8. The process of claim 7, wherein the alcohol solvent comprises isopropanol.
9. The process of claim 1, wherein the alcohol solvent is isopropanol.
10. The process of claim 1, wherein the protecting group on the amine is selected from the group consisting of benzyl carbamate (Cbz), acetamide (Ac), trifluoroacetamide (TFAc), phthalimide, triphenylmethylaniline (Tr), benzylideneamine, and *p*-toluenesulfonamide (Ts), and *tert*-butyloxy carbonyl.

11. The process of claim 10, wherein the protecting group on the amine is *tert*-butoxy carbonyl.
12. The process of claim 1, conducted at a temperature ranging from about 10 – 50 °C, optionally at 20 – 30 °C.
13. The process of claim 12, performed for about 24 hours, or until the amount of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is no longer increasing.
14. The process of claim 1, further comprising quenching the reaction mixture with an acidic solution to neutralize the base.
15. The process of claim 1, wherein a solid phase comprising (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, precipitates from the alcohol solvent.
16. The process of claim 15, wherein the solid phase comprises a diastereomeric ratio of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, to (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, of at least about 75:25.
17. The process of claim 16, wherein the diastereomeric ratio is about 90:10.
18. The process of any one of claims 15 to 17, further comprising filtering the solid phase from the reaction mixture.
19. The process of any one of claims 1 to 18, further comprising purifying (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, from the solid phase.

20. The process of claim 19, wherein (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is purified from the diastereomeric mixture at a diastereomeric ratio of about 99:1.
21. The process of claim 19 or claim 20, wherein the purification comprises contacting the diastereomeric mixture with a purification solvent in which (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is insoluble and precipitates from solution and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is soluble and remains in solution, and filtering a resultant, purified precipitate containing (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine.
22. The process of claim 21, wherein the purification solvent comprises methyl *tert*-butyl ether.
23. The process of claim 21, wherein the purification solvent is methyl *tert*-butyl ether.
24. The process of any one of claims 19 to 23, further comprising reacting the purified (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, with hydrochloric acid to deprotect the amine and to form ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl) hydrochloride.
25. The process of claim 24, further comprising isolating the ((3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-yl) hydrochloride.
26. A process comprising:
 reacting (2S)-6-cyano-5-hexen-1-ol-2-amine, having a protecting group on the amine, with a base in a solvent to produce a reaction mixture containing a solid phase, wherein:
 the solid phase comprises a diastereomeric mixture of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine;

wherein the (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is insoluble in the solvent; and

wherein the (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, is at least partially soluble in the solvent.

27. The process of claim 26, wherein the solvent is miscible with water.
28. The process of claim 27, wherein the solvent is a weak acid.
29. The process of claim 26, wherein the solvent has a pKa which is different from the pKa of a conjugate acid of the base by about 25% or less.
30. The process of claim 26, wherein the solvent has a pKa from about 16 to about 20.
31. The process of claim 26, wherein the solid phase contains a diastereomeric ratio of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, to (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, of at least about 75:25, preferably about 90:10
32. A process comprising:
- reacting (2S)-6-cyano-5-hexen-1-ol-2-amine, having a protecting group on the amine, with an alkoxide base in an alcohol solvent to produce a reaction mixture containing a solid phase, wherein:
 - the solid phase comprises a diastereomeric mixture of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, and (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine; and
 - wherein the solid phase has a diastereomeric ratio of (3S,6R)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, to (3S,6S)-6-(cyanomethyl)- tetrahydro-2H-pyran-3-amine, having said protecting group on the amine, of at least about 75:25.
33. The process of claim 32, wherein the reaction is conducted until at least about 80% of APA-7 is converted to APA-8.

34. The process of claim 32, wherein the reaction is conducted at a temperature from about 10 – 50 °C, optionally at 20 – 30 °C.
35. The process of claim 32, wherein the reaction mixture is stirred or agitated while the reaction is conducted.