(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 September 2014 (18.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/145507 A1

(51) International Patent Classification:
C07K 5/078 (2006.01) *A61P 31/14* (2006.01)
A61K 38/05 (2006.01)

(21) International Application Number:
PCT/US2014/030293

(22) International Filing Date:
17 March 2014 (17.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/789,340 15 March 2013 (15.03.2013) US

(71) Applicant: **ACHILLION PHARMACEUTICALS, INC.** [US/US]; 300 George Street, New Haven, CT 06511 (US).

(72) Inventors: **PHADKE, Avinash**; 51 Gilbert Lane, Branford, CT 06405 (US). **HASHIMOTO, Akihiro**; 47 Laurel Street, Branford, CT 06405 (US).

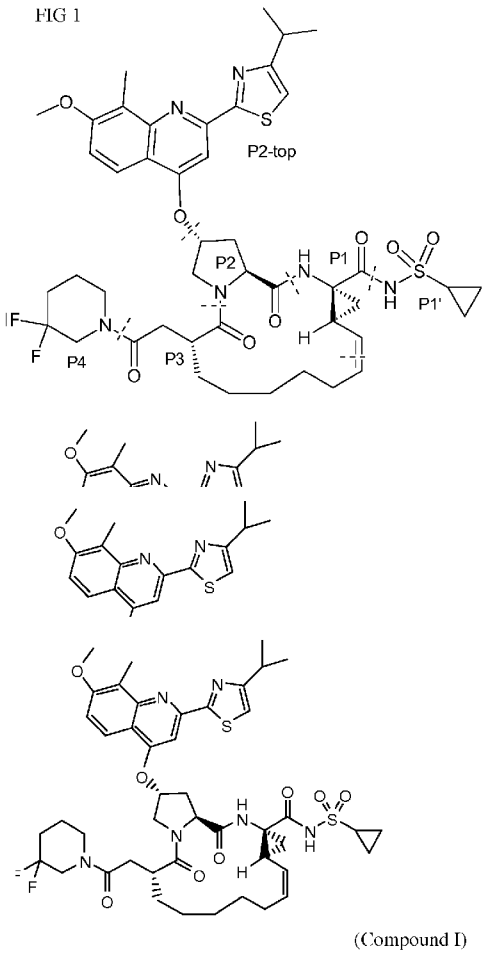
(74) Agent: **MAXWELL, Leslie-Anne**; Cantor Colburn Llp, 20 Church Street, 22nd floor, Hartford, CT 06103 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,

[Continued on next page]

(54) Title: A PROCESS FOR MAKING A 4-AMINO-4-OXOBUTANOYL PEPTIDE CYCLIC ANALOGUE, AN INHIBITOR OF VIRAL REPLICATION, AND INTERMEDIATES THEREOF

FIG 1



(Compound I)

(57) Abstract: The invention provides a process of preparing 4-amino-4-oxobutanoyl peptides and cyclic analogues thereof of Compound (I) and pharmaceutically acceptable salts thereof.

WO 2014/145507 A1

TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

A PROCESS FOR MAKING A 4-AMINO-4-OXOBUTANOYL PEPTIDE CYCLIC ANALOGUE, AN INHIBITOR OF VIRAL REPLICATION, AND INTERMEDIATES THEREOF

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Application No. 61/789,340, filed March 15, 2013, which is hereby incorporated by reference in its entirety.

FIELD OF THEDISCLOSURE

[0002] The present invention is directed to a process of preparing a 4-amino-4-oxobutanoyl peptide cyclic compound useful as an antiviral agent. The compound is a potent and / or selective inhibitor of viral replication, particularly Hepatitis C viral replication.

BACKGROUND

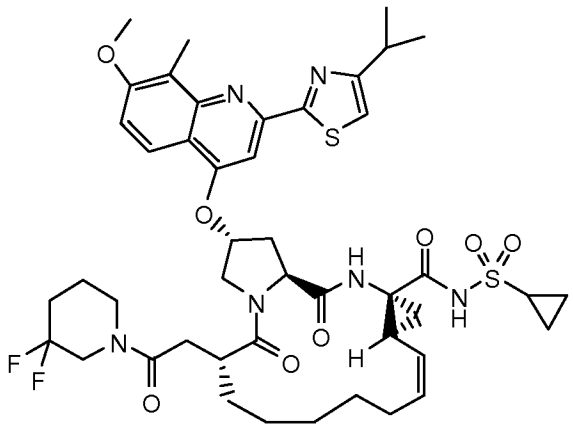
[0002] An estimated 3% of the world's population is infected with the hepatitis C virus (HCV). Of those exposed to HCV, 80% to 85% become chronically infected, at least 30 % develop cirrhosis of the liver and 1-4% develop hepatocellular carcinoma. Hepatitis C Virus (HCV) is one of the most prevalent causes of chronic liver disease in the United States, reportedly accounting for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. Chronic HCV infection is the most common cause of liver transplantation in the U.S., Australia, and most of Europe. Hepatitis C causes an estimated 10,000 to 12,000 deaths annually in the United States. While the acute phase of HCV infection is usually associated with mild symptoms, some evidence suggests that only about 15% to 20% of infected people will spontaneously clear HCV.

[0003] WO 2010/068761 A2 by Phadke et al. discloses 4-amino-4-oxobutanoyl peptide cyclic analogues, inhibitors of viral replication, which compounds are potent and/ or selective inhibitors of Hepatitis C virus replication. Phadke et al. also provides pharmaceutical compositions containing one or more of such compounds, including a salt, solvate, or acylated prodrug of such compounds, and one or more pharmaceutically acceptable carriers.

[0004] The present invention provides a novel and improved process for the preparation of Compound 128 disclosed in WO 2010/068761 A2. This process provides certain advantages which are described herein.

SUMMARY

[0005] The invention provides a process of preparing a Compound **I** or its pharmaceutically acceptable salt, represented by the following structure.

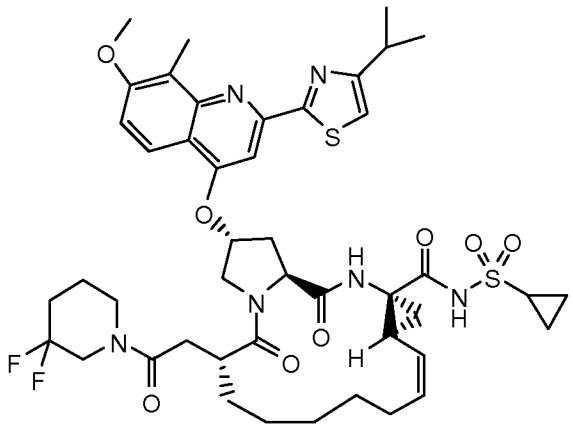


(I)

[0006] This compound and its pharmaceutically acceptable salt forms, identified as 2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, will be referred to herein as Compound I herein and its sodium salt form is referred to as Compound **IA**. This Compound **I** and its salt forms possess antiviral activity, as disclosed in US2010-0152103.

[0007] The invention further comprises novel intermediate compounds useful in making Compound I, and methods of preparing such intermediate compounds.

[0008] Thus in a first aspect the invention includes a method of preparing Compound I (or its pharmaceutically acceptable salt) having the following structure:



(I)

[0009] Within Compound **I**, the hydrogen in the NH group of the sulfonamide group can be replaced by a sodium ion or other pharmaceutically acceptable cationic species.

BRIEF DESCRIPTION OF THE DRAWING

[0010] FIG. 1. Amino acids residues P1', P1, P2, P2 Top, P3, and P4 as present in ACH-0142864.

DETAILED DESCRIPTION OF THE INVENTION

CHEMICAL DESCRIPTION AND TERMINOLOGY

[0011] Prior to setting forth the invention in detail, it may be helpful to provide definitions of certain terms to be used herein. Compounds of the present invention are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Unless clearly contraindicated by the context each compound name includes the free acid or free base form of the compound as well as hydrates of the compound and all pharmaceutically acceptable salts of the compound.

[0012] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced items. The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to"). Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0013] Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g., asymmetric carbon atoms, so that the

compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. All forms are contemplated herein regardless consistent with the methods used to obtain them.

[0014] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -$(CH_2)C_3$-C_8cycloalkyl is attached through carbon of the methylene (CH_2) group.

[0015] A bond represented by a combination of a solid and dashed line, i.e. =====, may be either a single or double bond.

[0016] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds in which the parent compound is modified by making inorganic and organic, non-toxic, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0017] Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional

non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

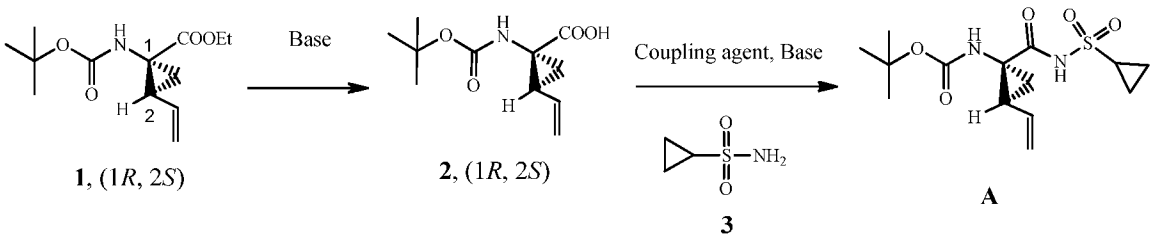
CHEMICAL DESCRIPTION

[0018] The following applications are incorporated by reference for their teachings regarding synthesis of 4-Amino-4-oxobutanoyl macrocyclic peptide analogues: US Provisional Application No. 61/121,378 filed December 10, 2008, US Provisional Application No. 61/226,323 filed July 17, 2009, and US Application No. 12/635049 filed December 10, 2009. In a number of steps peptide coupling agents are used. A particular peptide coupling agent, such as TBTU may be given as effective for a step in which a peptide coupling agent is used. However in steps in which a peptide coupling agent is used the peptide coupling agent may be N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU), [Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), N,N'-Dicyclohexylcarbodiimide (DCC), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), or a pyridinium coupling agent such as 2-Chloro-1-methylpyridinium iodide (Mukaiyama's reagent) or any other peptide coupling agent recognized in the art.

[0019] In certain embodiments it is preferred that the peptide coupling agent is N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU).

[0020] The Compound **I** and salts thereof can be made by reacting Intermediate Compounds A, B and C, as described below, in a suitable reaction scheme.

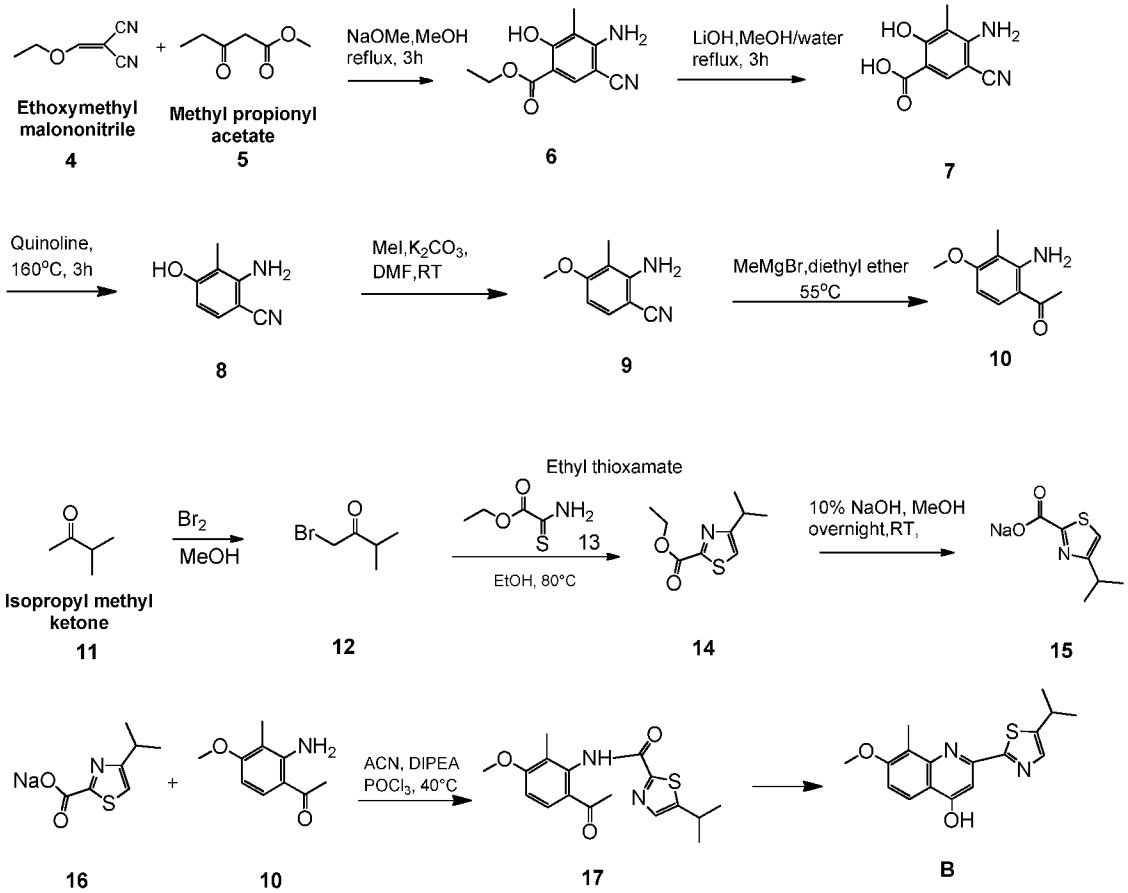
[0021] Intermediate Compound A can be made according to the following Reaction Scheme A.



Reaction Scheme A

[0022] Reaction Scheme A is reported in WO2006122188 A2 on page 33, Scheme III, in which the details of the procedure are disclosed on pages 76-78, Steps 1 to 3.

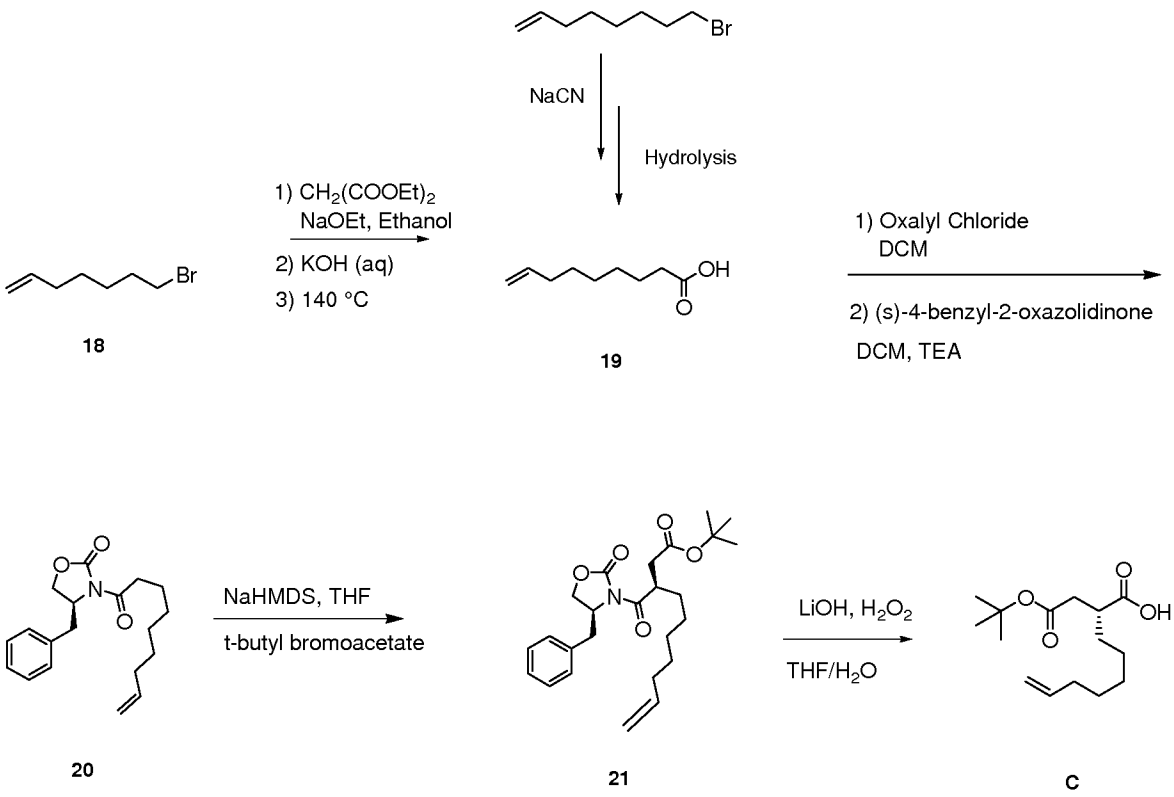
[0023] The Intermediate Compound B can be made according to the following Reaction Scheme B:



Reaction Scheme B

[0024] A method of making Intermediate Compound **B** is disclosed in US 7,659,245, which is hereby incorporated by reference for their teaching regarding the synthesis of intermediate compounds.

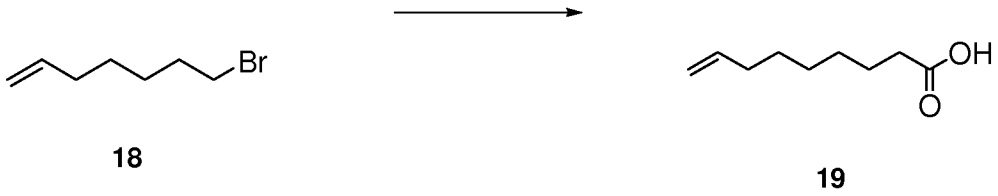
[0025] Intermediate Compound **C** can be prepared by a novel route in which nonenoic acid (Compound **19**) is obtained while avoiding the use of sodium cyanide. Compound **19** can be used to prepare Intermediate Compound **C** according the following Reaction Scheme C.



Reaction Scheme C

[0026] This reaction scheme is particularly advantageous because it avoids the need for reacting sodium cyanide with 1-bromooct-7-ene followed by hydrolysis following, as disclosed by Chan, T. H. and Stossel, D. Journal of Organic Chemistry, 51(13), 2423-8; 1986). In contrast, in the present process an ethoxide salt (sodium ethoxide) is added to a solution of diethylmalonate in solvent such as ethanol. Alternatively this can be performed by adding a strong base such as sodium hydride to a solution of diethylmalonate or other malonate diesters in a polar aprotic solvent such as THF or DMF. To this solution can be added 1-bromo-hept-6-ene. The reaction mixture can be concentrated and then treated with

aqueous potassium hydroxide, then acidified and subsequently heated at an elevated temperature, for example, 140°C to ensure decarboxylation and thereby obtain nonenoic acid. This reaction can generally be represented by the following:

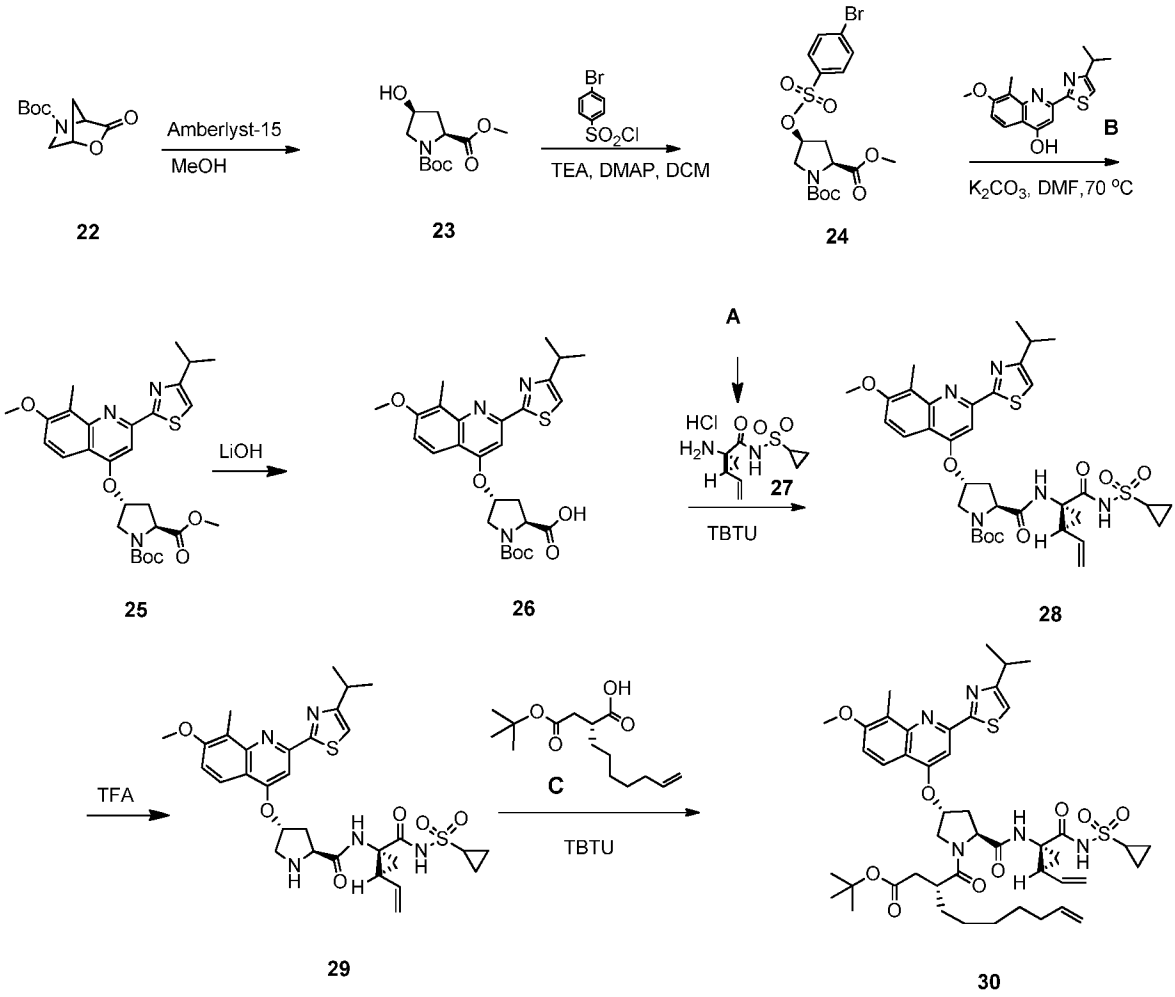


18 **19**

Reaction Scheme C-1

[0027] The procedure of converting nonenoic acid to Compound **C** is based on the procedures described in Evans et. al. *J. Org. Chem.* **1999,** *64,* 6411-6417 (Compound 5b). Thus, Compound 19 can be subsequently reacted with oxalyl chloride or thionyl chloride and then the chiral auxiliary (s)-4-benzyl-2-oxazolidinone to provide Compound 20. Compound 20 can be treated with a strong base such as NaHMDS, LDA, or n-BuLi and then reacted with t-butyl bromoacetate to obtain Compound 21. Compound 21 can be reacted with lithium hydroxide and hydrogen peroxide to remove the 4-benzyl-oxazolidinone and provide Compound **C**.

[0028] After obtaining Intermediate Compounds A, B, and C as described above, novel Compound 30 can be obtained as shown below according to Reaction Scheme D.



Reaction Scheme D

[0029] In particular, a lactone Compound **22** can be reacted in the presence of an acid catalyst such as Amberlyst-15 in methanol for a suitable time and temperature to obtain cis-hydroxy proline methyl ester (Compound **23**) in high yield and then worked up to high purity.

[0030] A solution of the cis-hydroxyproline methyl ester (Compound **23**) can then be reacted with triethylamine and catalytic dimethylaminopyridine in solvent and then reacted with Bromobenzene sulfonyl chloride (methanesulfonyl chloride can also be used) to obtain the brosylate (Compound **24**) , which can be used for the next step.

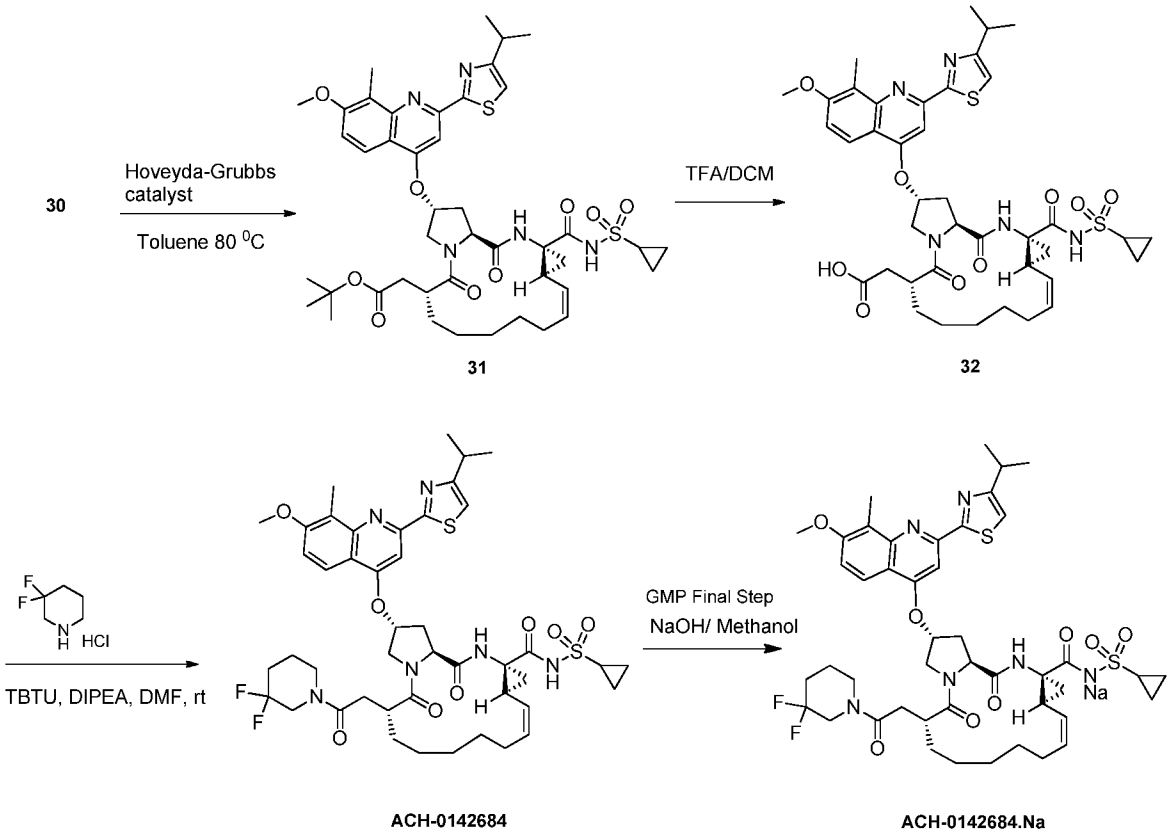
[0031] A solution of the brosylate (Compound **24**) and Intermediate Compound **B** can be reacted with potassium carbonate or the like to obtain Compound **25.**

[0032] Compound **25** can be reacted with aqueous lithium hydroxide or the like to obtain Compound **26**.

[0033] Compound **27** can be obtained by treating Intermediate Compound A with acid to remove the Boc protecting group. Then Compound **27** can be reacted with Compound **26** in presence of TBTU (N,N,N′,N′-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate) or other coupling agents to obtain Compound **28**. Other possible coupling agents may include benzotriazoles such as 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) or benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), carbodiimides such as N,N'-Dicyclohexylcarbodiimide (DCC) or 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), or pyridinium salts such as 2-Chloro-1-methylpyridinium iodide (Mukaiyama's reagent).

[0034] A solution of Compound **28** in solvent can be reacted with trifluoroacetic acid (TFA) or other strong acids such as HCl to remove the Boc protecting group and obtain Compound **29**. Compound **29** can be reacted with Intermediate Compound **C** in presence of TBTU or other coupling agents, including those mentioned for the synthesis of Compound **28**. The reaction produces Compound **30**.

[0035] Compound **30** can be used to prepare the product ACH-0142684·Na according to the following Reaction Scheme E.



Reaction Scheme E

[0036] Compound **31** can be obtained from Compound **30** using a cyclization catalyst such as the Hoveyda-Grubbs catalyst in toluene at 80 – 110 °C. Alternatively Grubbs I catalyst, Grubbs II catalyst, or related analogs could be used. Heating can be continued until completion of the reaction.

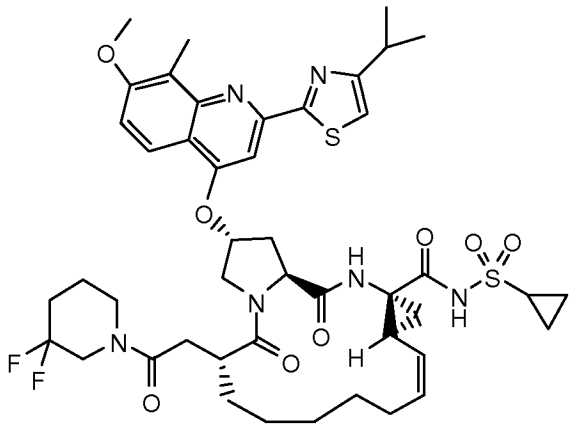
[0037] Compound **31** can be treated with trifluoroacetic acid or other strong acid as in the synthesis of Compound 29 followed by diisopropylethylamine and 3,3-difluoropiperidine hydrochloride in a presence of a peptide coupling agent such as TBTU and a base such as diisopropyl ethylamine to give ACH-0142684. ACH-0142684 can be obtained in purified form by crystallization in suitable solvent such as isopropyl alcohol. Treatment with aqueous sodium hydroxide can provide the sodium salt (ACH-0142684·Na) thereof which can be obtained in crystalline form by crystallizing in a suitable solvent such as isopropyl alcohol, purification, and collection, as will be appreciated by one of ordinary skill in the art.

[0038] ACH-0142864 is a peptidomimetic compound comprised of amino acid like residues P1', P1, P2, P2-Top, P3, and P4. The presence of these residues in ACH-0142864 is shown in FIG. 1. The sequence of steps utilized to attach the amino acid residues can vary.

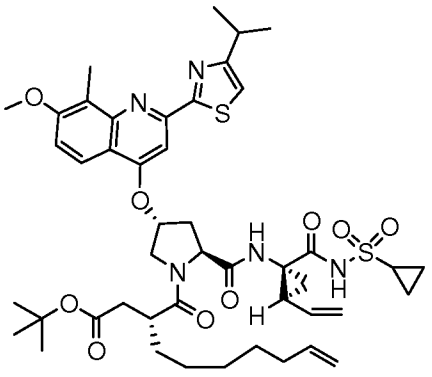
The reaction schemes and Examples provide several reaction sequences by which amino acid residues P1', P1, P2, P2-Top, P3, and P4 can be attached to form ACH-0142864. However other sequences for attaching the amino acid residues to form ACH-0142864 are possible and will be readily apparent to those of skill in the art.

[0039] The disclosure includes the following embodiments.

[0040] The disclosure includes a process of preparing ACH-0142684, represented by the structure:



or its pharmaceutically acceptable salt from the intermediate compound represented by the structure:

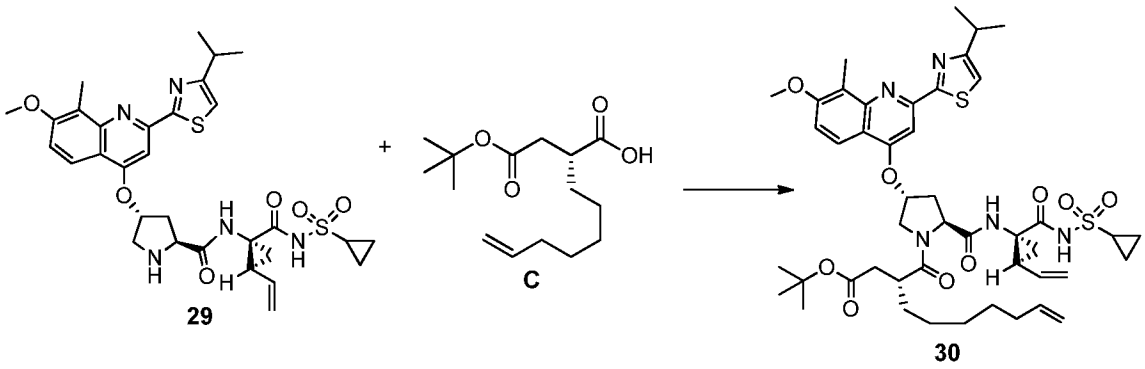


(**30**)

wherein the intermediate compound is reacted in the presence of a catalyst to join and merge the vinyl groups with the expulsion of ethylene, the butyl ester group is converted to a carboxylic acid group, and the carboxylic acid group is then reacted with 3,3-difluoropiperidine hydrochloride to provide ACH-0142684.

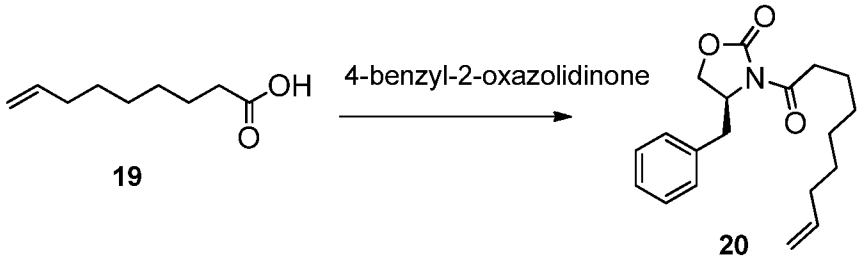
[0041] The catalyst used to join the ethylene groups may be a Grubbs I catalyst, a Grubbs II catalyst, or a Hoveyda-Grubbs catalyst or a combination of any of the foregoing.

[0042] The disclosure also includes a process of making a product intermediate compound (**30**),

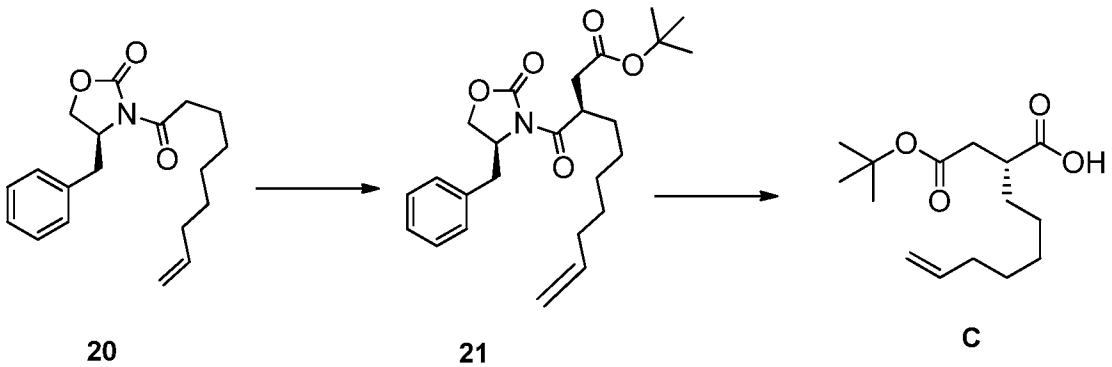


wherein an antecedent first intermediate compound (**29**) is reacted with an antecedent second intermediate Compound **C** to obtain the product intermediate compound (**30**).

[0043] The process for making the product intermediate (**30**) may additionally comprise obtaining the antecedent second intermediate Compound **C** by reacting nonenoic acid (**19**) with 4-benzyl-2-oxazolidinone to obtain an antecedent third intermediate compound (**20**)



wherein the antecedent third intermediate compound (**20**) is then reacted with a strong base and t-butyl haloacetate to obtain an antecedent fourth intermediate compound (**21**), followed by reacting the antecedent fourth intermediate compound (**21**) with hydroxide peroxide in the presence of a base such as LiOH to provide Compound **C**.



thereby obtaining the antecedent second intermediate compound **C**.

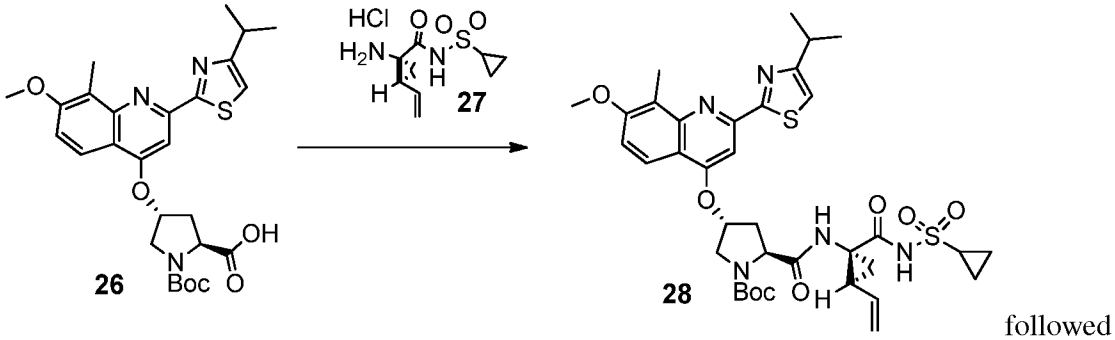
[0044] The strong base reacted with compound (**20**) and t-butyl haloacetate to obtain the antecedent fourth intermediate compound (**21**) may be sodium hexamethyldisilazide,

potassium hexamethyldisilazide, lithium hexamethyldisilazide, lithium diisopropylamide, n-butyllithium, or a combination of any of the foregoing.

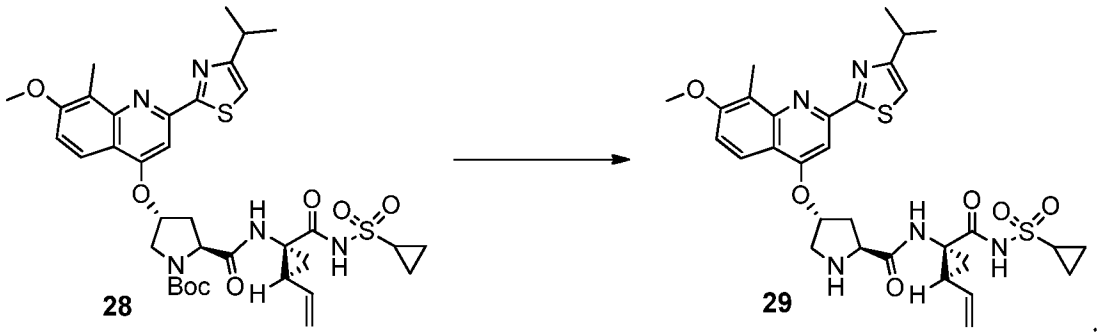
[0045] In certain embodiments the strong base is sodium hexamethyldisilazide.

[0046] The disclosure also includes a process for making the product intermediate (**30**) in which the nonenoic acid (**19**) is formed by reacting 1-bromo-hept-6-ene with an ethoxide salt and a dialkyl malonate in solvent.

[0047] The disclosure also includes a process for making the product intermediate (**30**) comprises reacting a compound (**26**), with (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (**27**) in the presence of a peptide coupling agent to obtain a protected intermediate (**28**)



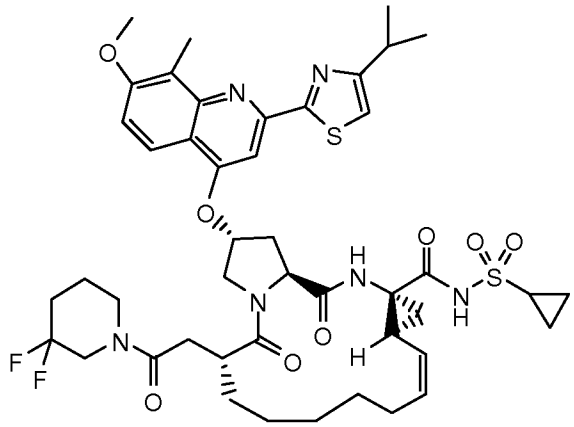
followed by deprotecting the protected intermediate (**28**) to obtain the first antecedent intermediate (**29**)



[0048] In this process the peptide coupling agent may be TBTU.

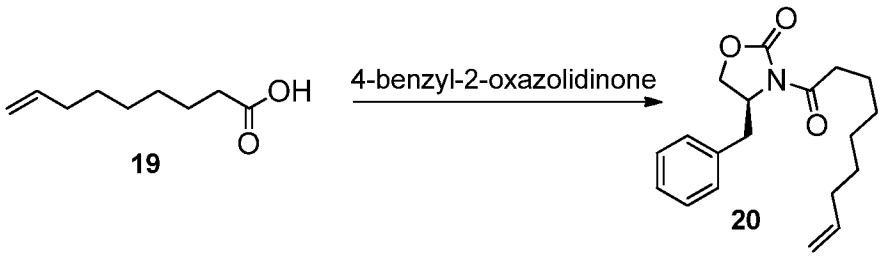
[0049] In this process the protected intermediate may be deprotected by reaction with a strong acid.

[0050] The disclosure includes a process of preparing a compound ACH-0142684 represented by the structure:

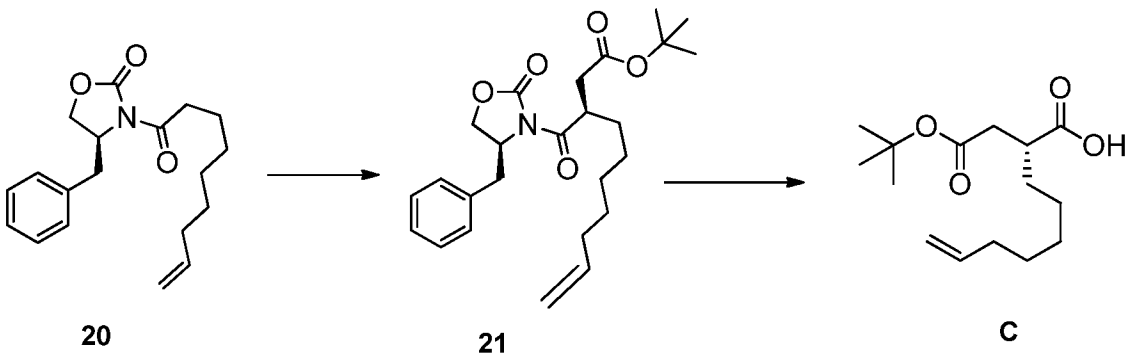


or its pharmaceutically acceptable salt, comprising

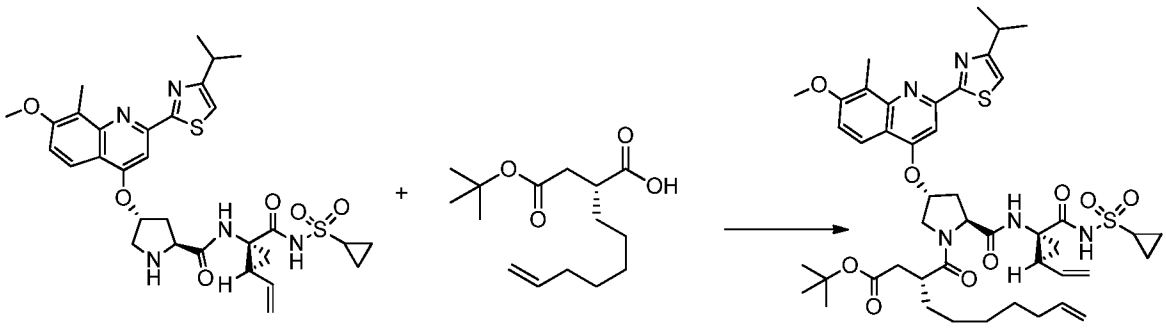
reacting nonenoic acid (**19**) with 4-benzyl-2-oxazolidinone to obtain a compound (**20**);



wherein the compound (**20**) is then reacted a strong base and t-butyl haloacetate to obtain a compound (**21**); followed by reacting the compound (**21**) with hydroxide peroxide in the presence of a base such as LiOH to provide Compound **C**;



and reacting a compound (**29**) with the Compound **C** to obtain a compound (**30**);



29 C 30

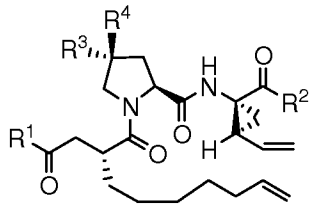
wherein the compound (**30**) is reacted in the presence of a catalyst to join and merge the vinyl groups with the expulsion of ethylene,

the butyl ester group is converted to a carboxylic acid group; and

the carboxylic acid group is reacted with a salt of 3,3-difluoropiperidine;

thereby forming the compound ACH-0142684.

[0051] The disclosure includes an intermediate compound of the formula:



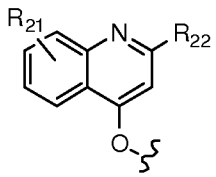
wherein

R^1 is hydroxyl, C_1-C_6 alkoxy, aryloxy, benzyloxy, 4-methoxybenzyloxy, C_1-C_6 acyloxy, halogen, or N-linked 3,3-difluoropiperidinyl;

R^2 is hydroxyl, N-linked cyclopropylsulfonamide, or N-linked benzenesulfonamide in which the benzene ring is further substituted with 0-2 nitro groups; and

R^3 is hydrogen and R^4 is halogen, hydroxyl, an O-linked mesylate group, or an O-linked benzenesulfonate group in which the benzene ring is further substituted with 0-1 groups independently chosen from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and nitro.

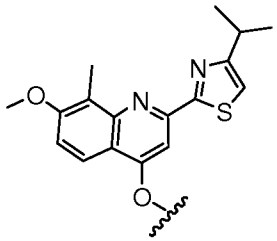
[0052] Or, R4 is hydrogen and R3 is hydroxyl or the heterocyclic group



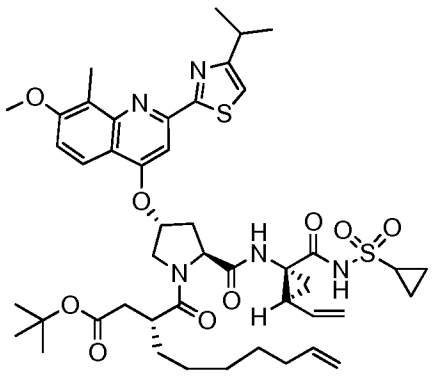
R_{21}, in this group, is 1 to 3 substituents independently chosen from halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

R_{22} is phenyl, pyridyl, or thiazolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, -COOH, $-CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy.

[0053] In certain embodiments the heterocyclic group is

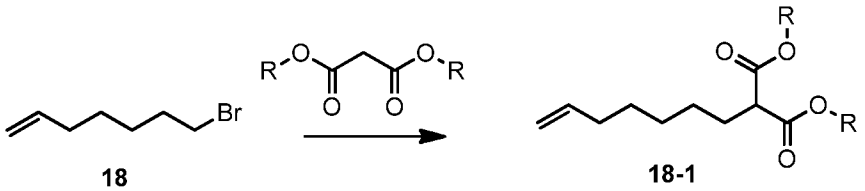


[0054] The disclosure includes an intermediate compound (**30**), having the following structure:



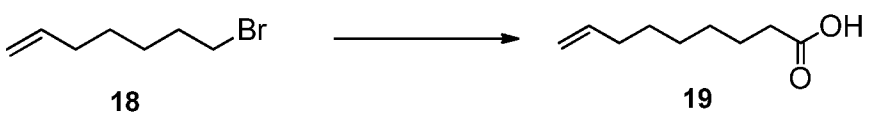
30

[0055] The disclosure includes a process for producing nonenoic acid, comprising Adding 1-bromo-hep-6-ene (**18**) to a malonate diester in a solvent to form a Compound (**18-1**)



18 **18-1**

where each R is a C_1-C_4alkyl group; and eecarboxylation of the Compound (**18-1**) to provide nonenoic acid (**19**)



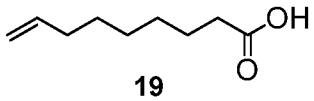
18 **19**

[0056] In an embodiment the malonate diester used to convert (**18**) to (**18-1**) is diethyl malonate (R is ethyl), ethoxide salt is added to the malonate diester, and the solvent is ethanol. In another embodiment R is ethyl, a strong base is added to the malonate diester is diethyl malonate (R is ethyl) and the solvent is an aprotic solvent, such as THF or DMF.

EXAMPLES

[0057] This invention is further illustrated by the following examples that should not be construed as limiting.

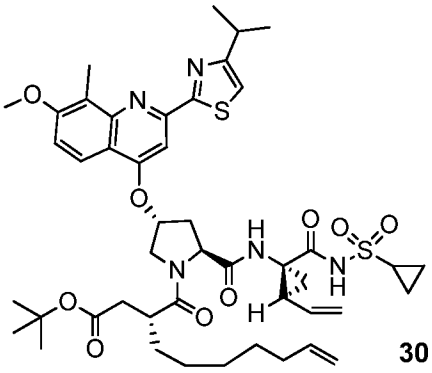
EXAMPLE 1: SYNTHESIS OF NONENOIC ACID (COMPOUND **19**)



19

[0058] Sodium ethoxide was added to a solution of diethylmalonate in ethanol. To this solution was added 1-bromo-hept-6-ene. The reaction mixture was concentrated and then treated with aqueous potassium hydroxide. The reaction mixture was acidified and then heated at 140°C to ensure decarboxylation and give nonenoic acid (**19**).

EXAMPLE 2: SYNTHESIS OF COMPOUND **30**



30

[0059] In accordance with Reaction Scheme D described above, the lactone (Compound **22**, 1 equivalent) was stirred in methanol in the presence of Amberlyst-15® cation exchange resin (30% w/w) () at room temperature for 18 hours. The resin was filtered and the filtrate evaporated to dryness to obtain cis-hydroxy proline methyl ester (Compound **23**) having a purity of greater than 97%.

[0060] A solution of cis-hydroxyproline methyl ester (Compound **23**, 1 equivalent), triethylamine and catalytic dimethylaminopyridine in dichloromethane was cooled to about 5°C. Methane sulfonyl chloride (1.5 equivalents), was added and stirred for 4h. The solution

was washed with 1M citric acid, water and brine. The organic layer was concentrated to obtain the brosylate (Compound **24**) and used for the next step without any purification.

[0061] To a solution of the brosylate compound (Compound **24**, 1 equivalent) and hydroxyquinoline (Intermediate Compound **B**, 0.95 equivalents) in DMF (dimethyl formamide) solvent is added potassium carbonate (1.3 equivalents) at room temperature. The reaction was stirred at 70°C until the reaction was complete (about18 hours) and added to 1M citric acid with vigorous stirring. The solid was isolated by filtration and dissolved in dichloromethane containing 5% methanol and filtered. The filtrate was concentrated and purified by chromatography over silica gel to give Compound **25** (purity >98%).

[0062] Compound **25** (1 equivalent) was dissolved in tetrahydrofuran and a solution of aqueous lithium hydroxide (1.5 equivalents) added at about 5°C. The reaction was stirred at room temperature until complete, about 3 h. The reaction mixture was concentrated and the residue slowly added to 1M citric acid with vigorous stirring. The solid precipitated was filtered and dried. The residue obtained was heated in heptane, cooled and filtered to obtain the acid (Compound **26**, purity >97%). This solid was used in the next step without further purification.

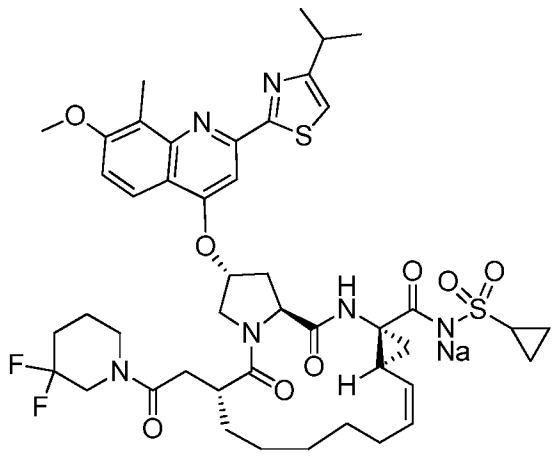
[0063] To a cold (about 5°C) solution of 4.5 N HCl in 1,4-dioxane was added Intermediate Compound **A** (1.5 equivalents relative to compound **26**) and then stirred at room temperature until reaction was complete (about 3 hours). The reaction mixture was concentrated and the residue, Compound **27**, was dissolved in dimethylformamide. To this solution was added the acid (Compound **26**, 1 equivalent) and diisopropylethyl amine (1.5 equivalent) followed by TBTU (1.3 equivalents) at 5°C. The reaction mixture was stirred at room temperature until completion (about 18 hours). The reaction mixture was then added to a solution of 1M citric acid with vigorous stirring. The solid precipitated was isolated by filtration, dissolved in dichloromethane/5%-methanol, dried and concentrated. The residue obtained was heated in heptane, cooled and filtered to give Compound **28** (purity >96%).

[0064] A solution of compound **28** (1 equivalent) in dichloromethane was cooled to 5°C and trifluoroacetic acid (TFA, 2.0 w/v) was added slowly. The reaction mixture was stirred at room temperature until complete, about 4 hours. All the volatiles were evaporated, residue dissolved in dichloromethane and evaporated again and the residue was dissolved in dimethylformamide. This solution was cooled to 5°C, diisopropypethyl amine (10 equivalents) and Compound **C** (1.4 equivalent) were added followed by TBTU (1.3 equivalents). The reaction mixture was stirred at room temperature until completion, about 18 hours. The reaction mixture was added to 1M citric acid and the solid isolate by filtration.

The solid was dissolved in dichloromethane/5%-methanol washed with brine, dried and evaporated to dryness. The residue purified over silica gel and then crystallized from isopropyl alcohol to give Compound **30** (purity >98%).

EXAMPLE 3: SYNTHESIS OF SODIUM SALT OF ACH-0142684

[0065] The synthesis of Sodium Salt of 2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide:



ACH-0142684 Sodium Salt

[0066] In accordance with Reaction Scheme E described above, Compound **30** (1 equivalent) was dissolved in toluene (1: 56 w/v) and the solution degassed by bubbling nitrogen for 15 minutes. The reaction temperature was raised to 80 -110 °C and Hoveyda-Grubbs catalyst (1-2 mol %) as a solution in toluene was added. Heating was continued until completion of the reaction and cooled to room temperature. Toluene was evaporated and the residue was purified by chromatography over silica gel. Solvent was evaporated from pooled fractions and the residue stirred with heptane and the solid filtered to obtain compound **31** (purity > 98%).

[0067] Compound **31** (1 equivalent) was dissolved in dichloromethane, cooled to 5 °C and trifluoroacetic acid (2-3 w/v) was added and stirred at room temperature for 4h. The reaction mixture was concentrated and the residue dissolved in dimethylfomamide and cooled to 5 °C before addition of diisopropylethyl amine (10 equivalents). TBTU (1.8 equivalents) was added followed by 3,3-difluoropiperidine hydrochloride (1.2 equivalents). The reaction

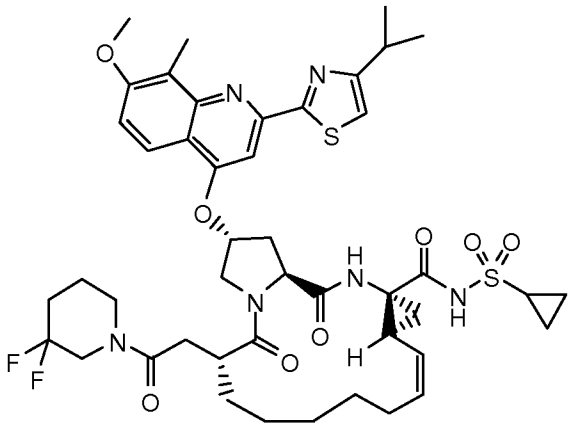
was stirred until completion and added to 1M citric acid and solid collected by filtration. The solid was crystallized from ethylacetate/heptane to give ACH-0142684 (1purity >98%). ACH-0142684 was suspended in methanol and aqueous sodium hydroxide (1.05 equivalents) was added at about 5°C to give a clear solution. The reaction mixture was concentrated to dryness and the residue crystallized from IPA to give crystalline ACH-0142684·Na. The crystalline ACH-0142684·Na was dissolved in a mixture of methanol/ethyl acetate and the solution was added to pentane. The solid was collected by filtration and dried to give ACH-0142684·Na in the amorphous form (purity >98%).

[0068] Starting materials are generally readily available from commercial sources, such as Sigma-Aldrich Corp. (St. Louis, MO). It will be apparent that the final product and any intermediate(s) shown in the following schemes may be extracted, dried, filtered and/or concentrated, and may be further purified (*e.g.,* by chromatography). Reaction Schemes, refers to any group consistent with the description of the compounds provided herein. An individual skilled in the art may find modifications of one or several of the synthetic steps described herein without diverting significantly from the overall synthetic scheme.

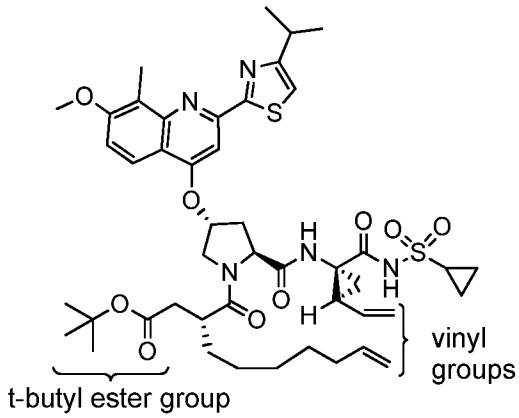
CLAIMS

What is claimed is:

1. A process of preparing a compound represented by the structure:



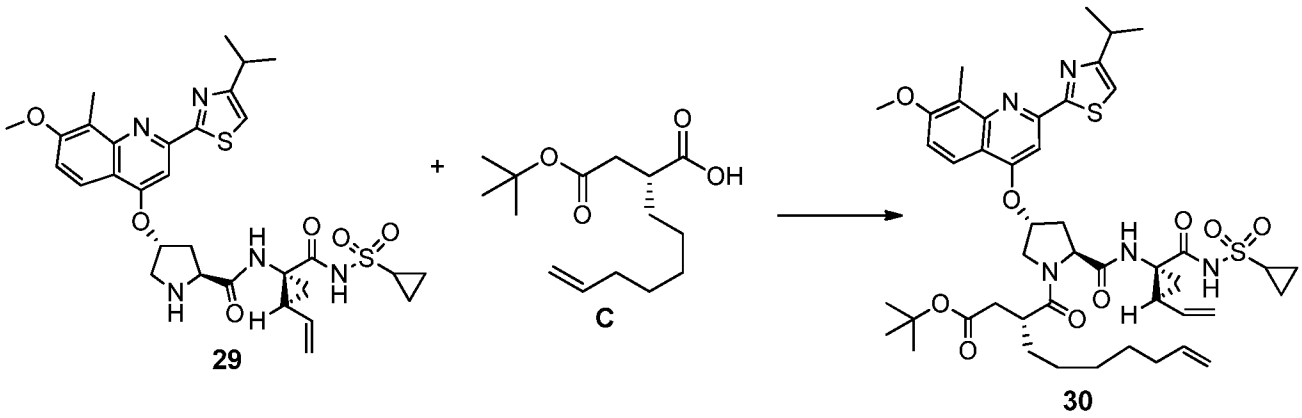
or its pharmaceutically acceptable salt from the intermediate compound represented by the structure:



wherein the intermediate compound is reacted in the presence of a catalyst to join and merge the vinyl groups with the expulsion of ethylene, the t-butyl ester group is converted to a carboxylic acid group, and the carboxylic acid group is then reacted with 3,3-difluoropiperidine to provide ACH-0142684.

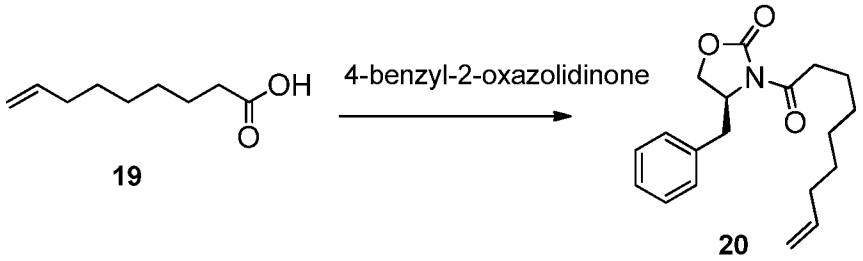
2. The process of Claim 1 wherein the catalyst to join the ethylene groups is a Grubbs I catalyst, a Grubbs II catalyst, or a Hoveyda-Grubbs catalyst or a combination of any of the foregoing.

3. A process of making a product intermediate compound (**30**),

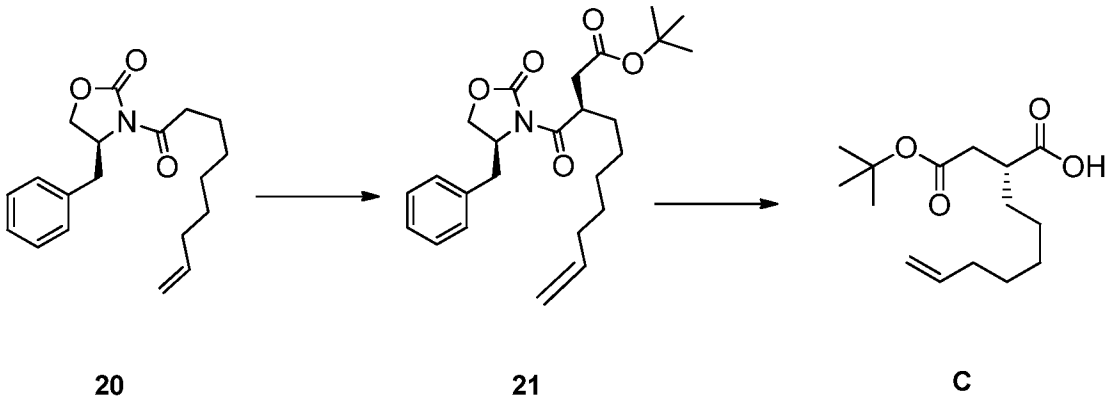


wherein an antecedent first intermediate compound (**29**)
is reacted with an antecedent second intermediate Compound **C**
to obtain the product intermediate compound (**30**).

4. The process of claim 3 additionally comprising obtaining the antecedent second intermediate Compound **C** by reacting nonenoic acid (**19**) with 4-benzyl-2-oxazolidinone to obtain an antecedent third intermediate compound (**20**)



wherein the antecedent third intermediate compound (**20**) is then reacted with a strong base and t-butyl haloacetate to obtain an antecedent fourth intermediate compound (**21**); followed by reacting the antecedent fourth intermediate compound (**21**) with hydroxide peroxide in the presence of a base such as LiOH to provide Compound **C**,



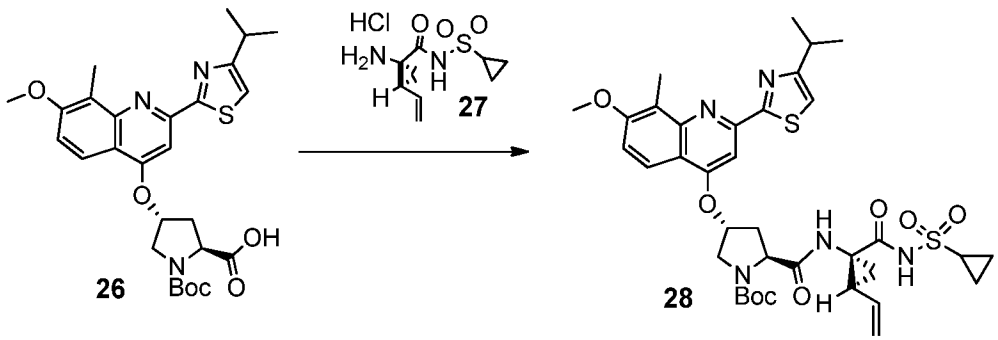
thereby obtaining the antecedent second intermediate Compound **C**.

5. The process of claim 4, wherein the strong base is sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, lithium diisopropylamide, n-butyllithium, or a combination of any of the foregoing.

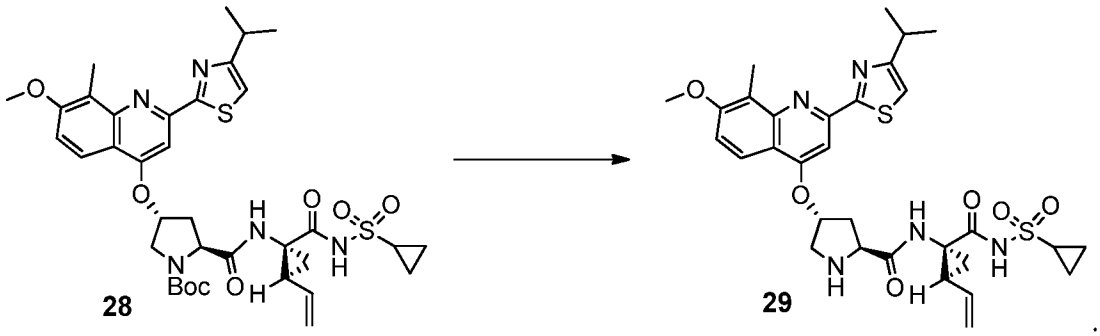
6. The process of claim 5, wherein the strong base is sodium hexamethyldisilazide.

7. The process of claim 4, wherein the nonenoic acid (**19**) is formed by reacting 1-bromo-hept-6-ene with an ethoxide salt and a dialkyl malonate in solvent.

8. The process of claim 3, where the process further comprises reacting a compound (**26**),
with (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (**27**) in the presence of a peptide coupling agent to obtain a protected intermediate (**28**)



followed by deprotecting the protected intermediate (**28**) to obtain the first antecedent intermediate (**29**)



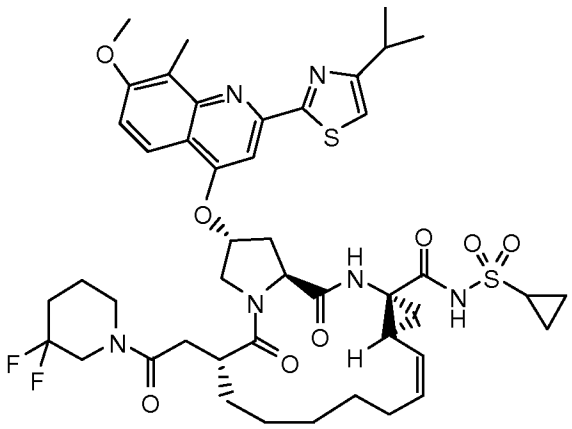
9. The process of claim 8, wherein the peptide coupling agent is N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU),

[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), N,N'-Dicyclohexylcarbodiimide (DCC), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 2-Chloro-1-methylpyridinium iodide (Mukaiyama's reagent), or a combination of any of the foregoing.

10. The process of claim 9, wherein the peptide coupling agent is N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU).

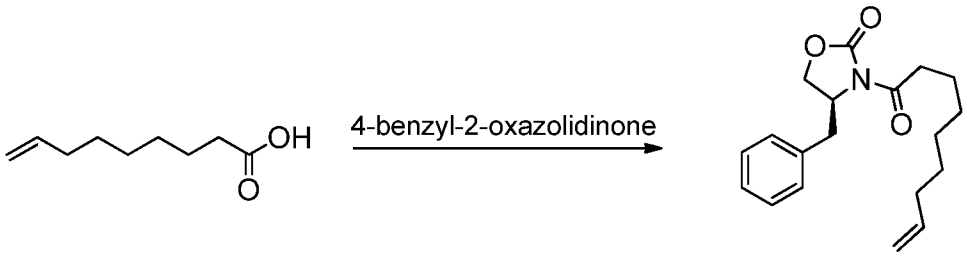
11. The process of claim 10, wherein the protected intermediate is deprotected by reaction with a strong acid.

12. A process of preparing a compoundACH-0142684 represented by the structure:



or its pharmaceutically acceptable salt, comprising

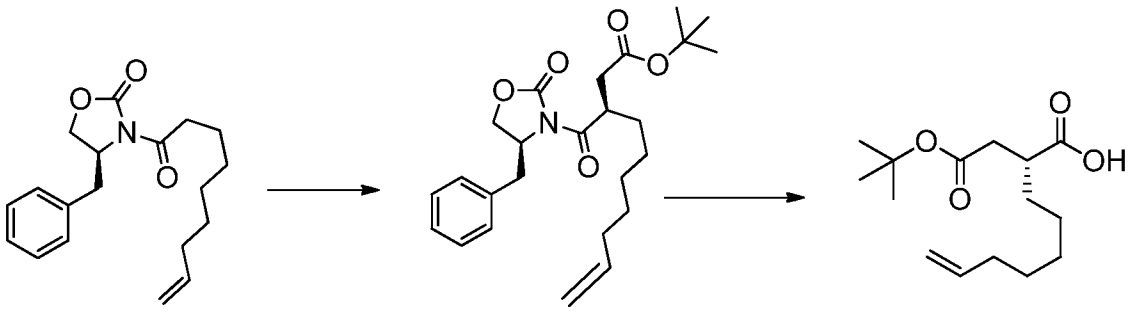
reacting nonenoic acid (**19**) with 4-benzyl-2-oxazolidinone to obtain a compound (**20**);



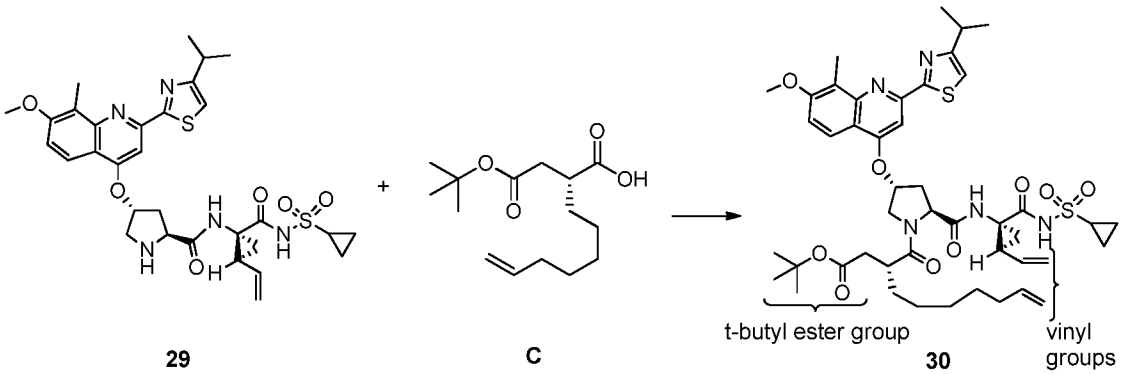
19 **20**

wherein the compound (**20**) is then reacted a strong base and t-butyl haloacetate to obtain a compound (**21**);

followed by reacting the compound (**21**) with hydrogen peroxide in the presence of a base such as LiOH to provide Compound **C**;



reacting a compound (**29**) with the Compound **C** to obtain a compound (**30**)



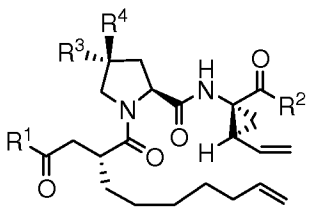
wherein the Compound **C** is reacted in the presence of a catalyst to join and merge the vinyl groups with the expulsion of ethylene,

the t-butyl ester group is converted to a carboxylic acid group; and

the carboxylic acid group is reacted with 3,3-difluoropiperidine;

thereby forming the compound ACH-0142684.

13. An intermediate compound of the formula:



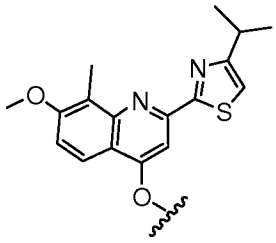
wherein

R^1 is hydroxyl, C_1-C_6 alkoxy, aryloxy, benzyloxy, 4-methoxybenzyloxy, C_1-C_6 acyloxy, halogen, or N-linked 3,3-difluoropiperidinyl;

R^2 is hydroxyl, N-linked cyclopropylsulfonamide, or N-linked benzenesulfonamide in which the benzene ring is further substituted with 0-2 nitro groups; and

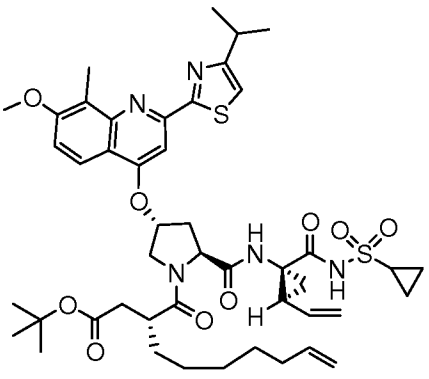
R^3 is hydrogen and R^4 is halogen, hydroxyl, an O-linked mesylate group, or an O-linked benzenesulfonate group in which the benzene ring is further substituted with 0-1 groups independently chosen from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and nitro; or

R^4 is hydrogen and R^3 is hydroxyl or the heterocyclic group



.

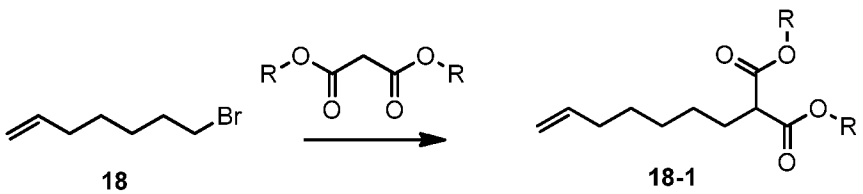
14. An intermediate compound of claim 13, having the following structure:



(**30**).

15. A process for producing nonenoic acid, comprising

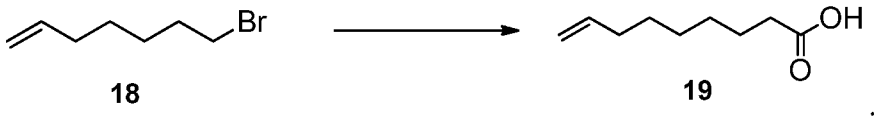
Adding 1-bromo-hept-6-ene (**18**) to a malonate diester in a solvent to form a Compound (**18-1**)



18 **18-1**

where each R is a C_1-C_4alkyl group;

Hydrolysis and decarboxylation of the Compound (**18-1**) to provide nonenoic acid (**19**)

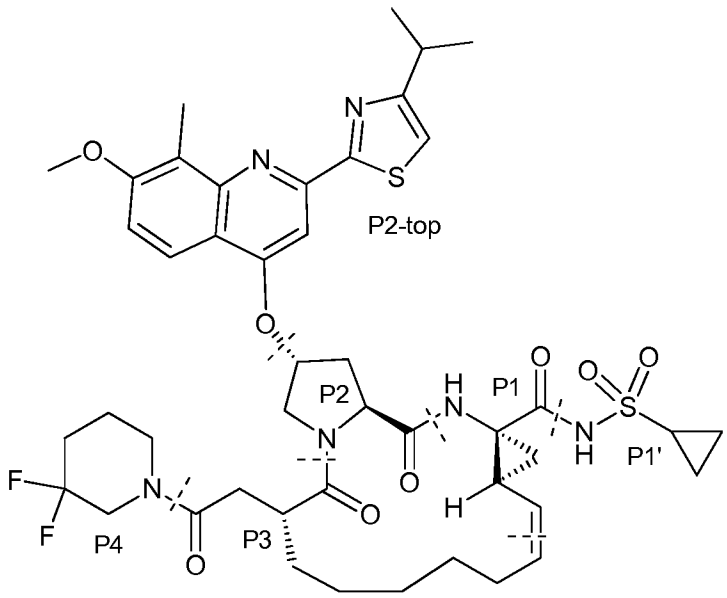


18 19

16. The process of Claim 15, wherein R is ethyl, ethoxide salt is added to the malonate diester, and the solvent is ethanol.

17. The process of Claim 15, wherein R is ethyl, a strong base is added to the malonate diester, and the solvent is an aprotic solvent.

FIG 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/030293

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/078 A61K38/05 A61P31/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/068761 A2 (ACHILLION PHARMACEUTICALS INC [US]; PHADKE AVINASH [US]; WANG XIANGZHU) 17 June 2010 (2010-06-17) cited in the application	1-6,8,9, 11-14
Y	Scheme 1, Scheme 2; compound 128	7,10

X	US 2011/306771 A1 (THOMPSON MICHAEL [CA] ET AL) 15 December 2011 (2011-12-15)	15-17
Y	Scheme 3;; figure 4	7

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2014	16/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Jetter, Sonya

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHAN W C ET AL: "Basic Procedures", 1 March 2000 (2000-03-01), FMOC-SOLID PHASE PEPTIDE SYNTHESIS-A PRACTICAL APPROACH, OXFORD UNIVERSITY PRESS, GB, PAGE(S) 40 - 76, XP007919887, ISBN: 978-0-19-963724-9 page 52 - page 53	10
A	GOUDREAU N ET AL: "Potent inhibitors of the hepatitis C virus NS3 protease: design and synthesis of macrocyclic substrate-based beta-strand mimics", THE JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 69, no. 19, 17 September 2004 (2004-09-17), pages 6185-6201, XP002313531, ISSN: 0022-3263, DOI: 10.1021/JO049288R Scheme 3	15-17
A	T. H. CHAN ET AL: "Chemistry of 1,3,5-tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene, a .beta.-tricarbonyl trianion equivalent", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 51, no. 13, 1 June 1986 (1986-06-01), pages 2423-2428, XP55116462, ISSN: 0022-3263, DOI: 10.1021/jo00363a004 cited in the application Scheme I	15-17
A	WO 2008/008502 A1 (ACHILLION PHARMACEUTICALS INC [US]; PHADKE AVINASH [US]; WANG XIANGZHU) 17 January 2008 (2008-01-17) Schemes 1 and 2	1-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/030293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010068761 A2	17-06-2010	AU 2009324644 A1	17-06-2010
		CA 2746265 A1	17-06-2010
		CN 102245598 A	16-11-2011
		EA 201100927 A1	30-12-2011
		EP 2364310 A2	14-09-2011
		JP 2012511588 A	24-05-2012
		KR 20110096557 A	30-08-2011
		NZ 592705 A	22-02-2013
		US 2010152103 A1	17-06-2010
		WO 2010068761 A2	17-06-2010
US 2011306771 A1	15-12-2011	CA 2742093 A1	10-12-2011
		US 2011306771 A1	15-12-2011
WO 2008008502 A1	17-01-2008	AU 2007272839 A1	17-01-2008
		BR PI0714343 A2	19-03-2013
		CA 2657618 A1	17-01-2008
		DK 2041156 T3	24-02-2014
		EA 200900184 A1	30-06-2009
		EP 2041156 A1	01-04-2009
		EP 2374812 A2	12-10-2011
		ES 2448494 T3	14-03-2014
		HK 1130809 A1	14-03-2014
		HK 1132754 A1	07-03-2014
		IL 196256 A	27-02-2014
		JP 2009543784 A	10-12-2009
		KR 20090029836 A	23-03-2009
		NZ 574605 A	25-11-2011
		PT 2041156 E	21-02-2014
		US 2009048297 A1	19-02-2009
		US 2011070168 A1	24-03-2011
		WO 2008008502 A1	17-01-2008