US010385010B1

(12) **United States Patent**
Xu et al.

(10) **Patent No.: US 10,385,010 B1**
(45) **Date of Patent: Aug. 20, 2019**

(54) **EXPEDIENT SYNTHESIS OF OSELTAMIVIR AND RELATED COMPOUNDS VIA DIRECT OLEFIN DIAZIDATION-DIAMIDATION REACTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/970,478**

(22) Filed: **May 3, 2018**

Related U.S. Application Data

(63) Continuation-in-part of application No. 15/938,204, filed on Mar. 28, 2018.

(51) **Int. Cl.**

C07C 231/10	(2006.01)
C07C 247/14	(2006.01)
C07C 201/12	(2006.01)
C12P 13/00	(2006.01)
C07C 269/04	(2006.01)

(52) **U.S. Cl.**
CPC ***C07C 231/10*** (2013.01); ***C07C 201/12*** (2013.01); ***C07C 247/14*** (2013.01); ***C07C 269/04*** (2013.01); ***C12P 13/008*** (2013.01); *C07C 2601/16* (2017.05)

(58) **Field of Classification Search**
CPC ... C07C 231/12; C07C 201/06; C07C 247/14; C07C 2601/16; C07C 231/10; C07C 201/12; C07C 269/04; C12P 13/008
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed herein are improved methods for the preparation of oseltamivir, and intermediates useful thereto.

22 Claims, 1 Drawing Sheet

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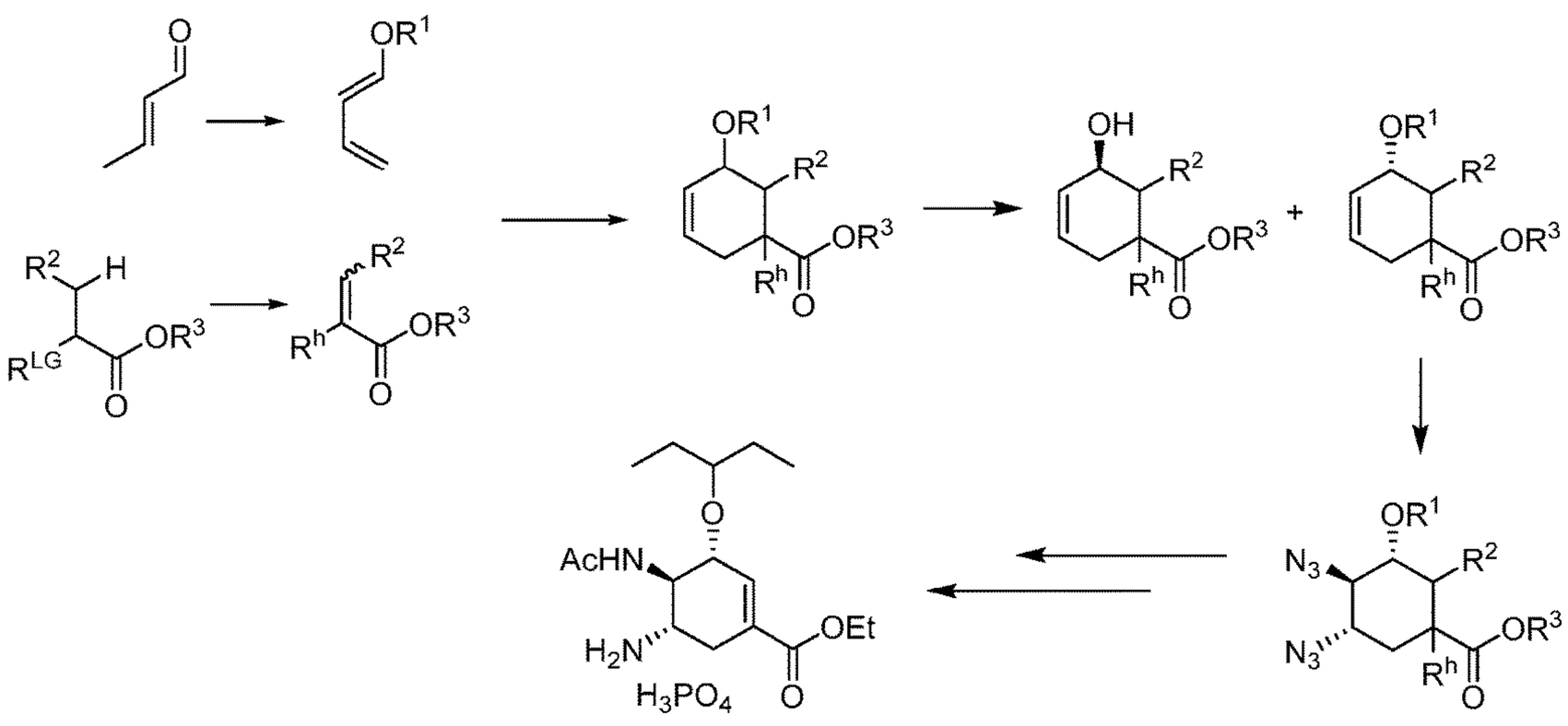
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EXPEDIENT SYNTHESIS OF OSELTAMIVIR AND RELATED COMPOUNDS VIA DIRECT OLEFIN DIAZIDATION-DIAMIDATION REACTION

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. application Ser. No. 15/938,204, filed on Mar. 28, 2018, the contents of which are hereby incorporated in its entirety.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under Grant No. GM110382 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

The invention is directed to improved new methods for obtaining oseltamivir from readily available commodity chemicals via a late-stage direct olefin diazidation-diamination reaction.

BACKGROUND

Oseltamivir phosphate, marketed by Roche under the brand name Tamiflu®, is an antiviral medication that is used to treat and prevent influenza A and influenza B (flu). It is recommended for people who have complications or are at high risk of complications within 48 hours of first symptoms of infection. Given the severe flu pandemics in 2009-2010 and in 2017-2018, there is a high demand for the development of even more robust and economical production routes of Tamiflu®.

Many current production routes rely on expensive shikimic acid (current cost is approximately $109/gram) as the starting material. The reported overall yield in one disclosed 12-step synthetic route is about 16.5%. Among these steps, at least four steps involve either cryogenic cooling (−34° C.) or heating (>60° C.). Since the development of Roche's Tamiflu® synthesis, a range of syntheses of Tamiflu® have been developed in academic labs; however, it is not believed that any of them have been commercialized in the US.

There remains a need for oseltamivir production routes that neither involve the usage of expensive starting materials like shikimic acid nor involve tedious synthetic steps, especially those are related the installation of two nitrogen-based groups.

SUMMARY

Disclosed herein are a range of new synthetic routes for oseltamivir and useful intermediates thereto. A key transformation of these improved new processes is the direct catalytic and stereoselective olefin diazidation of a highly functionalized synthetic intermediate to afford the trans-vicinal diamino moiety present in oseltamivir. The details of one or more embodiments are set forth in the descriptions below. Other features, objects, and advantages will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE FIGURE

The FIGURE depicts an embodiment of an inventive synthetic sequence, wherein R^1, R^2, R^3, R^h, and R^{LG} are as defined herein.

DETAILED DESCRIPTION

Before the present methods and systems are disclosed and described, it is to be understood that the methods and systems are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps. "Exemplary" means "an example of" and is not intended to convey an indication of a preferred or ideal embodiment. "Such as" is not used in a restrictive sense, but for explanatory purposes.

Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein, for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesirable toxicological effects. Examples of such salts are acid addition salts formed with inorganic acids, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids and the like; salts formed with organic acids such as acetic, oxalic, tartaric, succinic, maleic, fumaric, gluconic, citric, malic, methanesulfonic, p-toluenesulfonic, napthalenesulfonic, and polygalacturonic acids, and the like; salts formed from elemental anions such as chloride, bromide, and iodide; salts formed from metal hydroxides, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, and magnesium hydroxide; salts formed from metal carbonates, for example, sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate; salts formed from metal bicarbonates, for example, sodium bicarbonate and potassium bicarbonate; salts formed from metal sulfates, for example, sodium sulfate and potassium sulfate; and salts

formed from metal nitrates, for example, sodium nitrate and potassium nitrate. Pharmaceutically acceptable and non-pharmaceutically acceptable salts may be prepared using procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid comprising a physiologically acceptable anion. Alkali metal (for example, sodium, potassium, or lithium) or alkaline earth metal (for example, calcium) salts of carboxylic acids can also be made.

The term "alkyl" as used herein is a branched or unbranched hydrocarbon group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, and the like. The alkyl group can also be substituted or unsubstituted. Unless stated otherwise, the term "alkyl" contemplates both substituted and unsubstituted alkyl groups. The alkyl group can be substituted with one or more groups including, but not limited to, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, or thiol. An alkyl group which contains no double or triple carbon-carbon bonds is designated a saturated alkyl group, whereas an alkyl group having one or more such bonds is designated an unsaturated alkyl group. Unsaturated alkyl groups having a double bond can be designated alkenyl groups, and unsaturated alkyl groups having a triple bond can be designated alkynyl groups. Unless specified to the contrary, the term alkyl embraces both saturated and unsaturated groups.

The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. The term "heterocycloalkyl" is a cycloalkyl group as defined above where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, selenium or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. Unless stated otherwise, the terms "cycloalkyl" and "heterocycloalkyl" contemplate both substituted and unsubstituted cyloalkyl and heterocycloalkyl groups. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, or thiol. A cycloalkyl group which contains no double or triple carbon-carbon bonds is designated a saturated cycloalkyl group, whereas an cycloalkyl group having one or more such bonds (yet is still not aromatic) is designated an unsaturated cycloalkyl group. Unless specified to the contrary, the term cycloalkyl embraces both saturated and unsaturated, non-aromatic, ring systems.

Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer, diastereomer, and meso compound, and a mixture of isomers, such as a racemic or scalemic mixture. A compound depicted with wedges and dashed lines for bonds contemplates both the specifically depicted stereoisomer, as well the racemic mixture. The term "enantioenriched" means that the depicted enantiomer is present in a greater amount than the non-depicted enantiomer.

The term "aryl" as used herein is an aromatic ring composed of carbon atoms. Examples of aryl groups include, but are not limited to, phenyl and naphthyl, etc. The term "heteroaryl" is an aryl group as defined above where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, selenium or phosphorus. The aryl group and heteroaryl group can be substituted or unsubstituted. Unless stated otherwise, the terms "aryl" and "heteroaryl" contemplate both substituted and unsubstituted aryl and heteroaryl groups. The aryl group and heteroaryl group can be substituted with one or more groups including, but not limited to, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, or thiol.

Exemplary heteroaryl and heterocyclyl rings include: benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH carbazolyl, carbolinyl, chromanyl, chromenyL cirrnolinyl, decahydroquinolinyl, 2H,6H~1,5,2-dithiazinyl, dihydrofuro[2,3 b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, and xanthenyl.

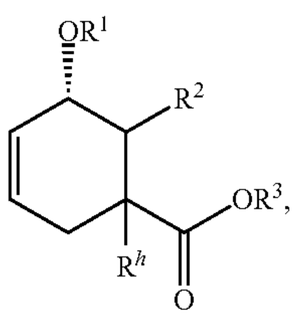
The terms "alkoxy," "cycloalkoxy," "heterocycloalkoxy," "cycloalkoxy," "aryloxy," and "heteroaryloxy" have the aforementioned meanings for alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, further providing said group is connected via an oxygen atom.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. Unless specifically stated, a substituent that is said to be "substituted" is meant

that the substituent can be substituted with one or more of the following: alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, or thiol.

Disclosed herein are methods of preparing oseltamivir by stereoselective direct diazidation of a compound of Formula (I):

[Formula (I)]



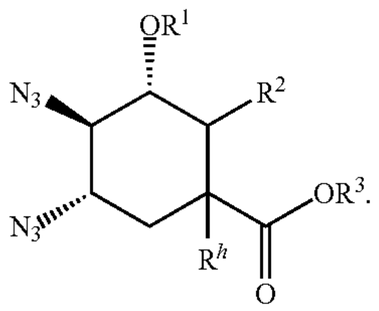
wherein R^1 is selected from R^{1a}, $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)N(R^{1a})_2$, $Si(R^{1a})_3$, wherein R^{1a} is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl;

wherein R^h is hydrogen and R^2 can be a leaving group like F, Cl, Br, I, NO_2, CN, OTs, or OMs;

R^3 can be hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl,

which includes the step of contacting the compound of Formula (I) with an iron compound, an azide source, an activator, and a ligand, to give a compound of Formula (II):

[Formula (II)]



wherein R^1, R^2, R^3 and R^h have the meanings given above, or R^h and R^2 together form a double bond.

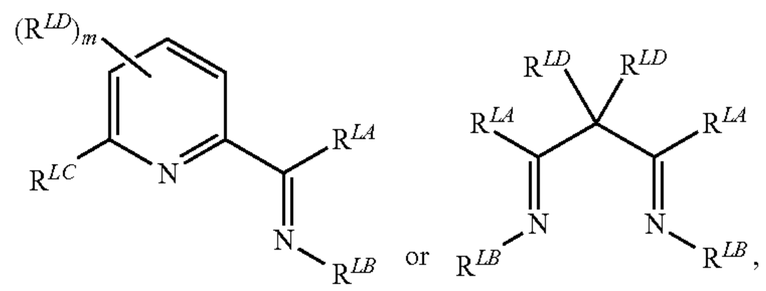
Suitable iron compounds include iron (II) salts such as $Fe(OTf)_2$, $Fe(NTf_2)_2$, $Fe(BF_4)_2$, FeF_2, $FeCl_2$, $Fe(OAc)_2$, FeI_2, $FeBr_2$, $Fe(ClO_4)_2$, $FeSO_4$, iron (II) oxalate, as well as iron (III) salts like $FeCl_3$, $FeBr_3$, FeF_3, $Fe_2(SO_4)_3$, $Fe(NO_3)_3$, $FePO_4$, iron (III) oxalate, iron citrate, and combinations thereof. The iron compound is generally included in a substoichiometric amount relative to the compound of Formula (I). For instance, the iron compound can be included in an amount from 0.1-20 mol %, from 0.5-10 mol %, from 1-10 mol %, from 1-7.5 mol %, from 2.5-7.5 mol %, or from 4-6 mol %.

Azide sources include compounds like $R_3Si—N_3$, in which R is independently selected from C_{1-8}alkyl or aryl. Preferred azide sources include TMS-N_3, TES-N_3, and TBDMS-N_3. In certain embodiments, at least a two-fold excess of azide source, relative to the compound of Formula (I) can be used, and it is preferable that at least 2.5 equivalents, at least 3 equivalents, at least 3.5 equivalents, at least 4 equivalents, at least 5 equivalents, at least 7.5 equivalents, or at least 10 equivalents of the azide source is employed relative the compound of Formula (I). In some embodiments, from 2-8 equivalents, from 2-6 equivalents, from 2-4 equivalents, or from 4-6 equivalents of the azide source is used.

The activator can be a hypervalent iodine compound or a peroxy compound. In some cases, the hypervalent iodine is an iodine (III) compound, of which iodobenzene dichloride, bisactetoxyiodo benzene (PIDA or BAIB), and benziodoxole are exemplary species. Suitable peroxo compounds including peroxyacids, especially perbenzoic acids like 2-chloroperoxybenzoic acid, 2-iodoperoxybenzoic acid, as well as peroxyacetic acid (which may also be designated peracetic acid), trifluoroperacetic acid, chloroperacetic acid, and esters thereof. Preferred esters include C_{1-8} esters, e.g., methyl, ethyl, propyl, butyl and the like. A preferred ester is tert-butyl, e.g., tert-butyl-peroxoacetate, tert-butyl-2-iodobenzoperoxoate or tert-butyl-2-chlorobenzoperoxoate.

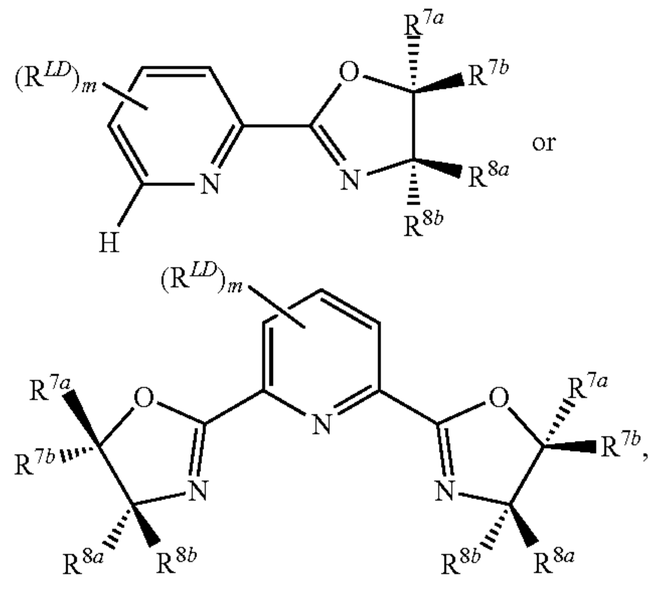
Suitable ligands include bidentate and polydentate ligands. As used herein, a bidentate ligand bears two Lewis basic atoms (nitrogen, oxygen, sulfur, phosphorous, etc. . . .) which are capable of interaction with the same Lewis acid. Likewise, a tridentate ligand bears three Lewis basic atoms capable of interaction with the same Lewis acid. Suitable ligands include substituted heterocyclic and heteroaryl rings, including bispyridines, bisoxazole, and pyridine bisoxazoles.

In some cases, the ligand can have the formula:



wherein m is selected from 0, 1, 2, or 3, and in each case R^{LA}, R^{LB}, R^{LC}, and R^{LD} are independently selected from R, OR, $N(R)_2$, PR_3, SiR_3, SR, SO_2R, $SO_2N(R)_2$, C(O)R; C(O)OR, OCOR; $C(O)N(R)_2$, $OC(O)N(R)_2$, $N(R)C(O)N(R)_2$, F, Cl, Br, I, cyano, and nitro, wherein R is in each case independently selected from hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{1-8}heteroaryl, C_{3-8}cycloalkyl, or C_{1-8}heterocyclyl; and any two or more of R^{LA}, R^{LB}, R^{LC}, R^{LD}, and R may together form a ring.

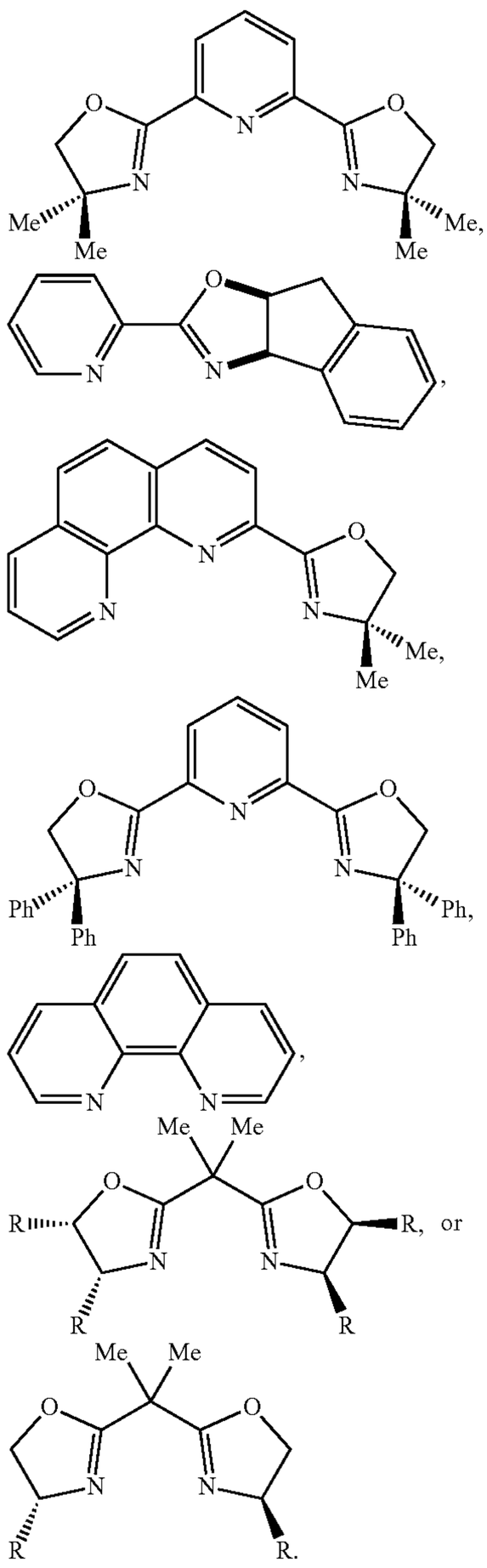
In certain preferred embodiments, the ligand can the formula:



wherein m is selected from 0, 1, 2, or 3, and each of R^{7a}, R^{7b}, R^{8a}, and R^{8b} are independently selected from R, OR, $N(R)_2$,

PR_3, SiR_3, SR, SO_2R, $SO_2N(R)_2$, C(O)R C(O)OR, OCOR; $C(O)N(R)_2$, $OC(O)N(R)_2$, $N(R)C(O)N(R)_2$, F, Cl, Br, I, cyano, and nitro, wherein R is in each case independently selected from hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{1-8}heteroaryl, C_{3-8}cycloalkyl, or C_{1-8}heterocyclyl; and any two or more of R^{7a}, R^{7b}, R^{8a}, R^{8b}, R^{LD}, and R may together form a ring.

In some embodiments, the ligand can be one of the following bidentate or tridentate compounds:



The skilled person will appreciate certain ligands can exist in enantioenriched form. Unless specified explicitly to the contrary, the ligands depicted above can be used either as the racemic mixture of in enantioenriched form. The ligand is generally included in the reaction mixture in a stoichiometric equivalent amount to the iron compound, i.e., the stoichiometric ratio of the ligand to iron compound is approximately 1:1.

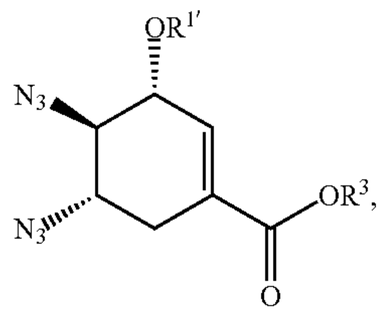
The diazidation reaction can be carried out in a suitable solvent, for instance a polar, aprotic solvent. Exemplary solvents include acetone, ethyl acetate, methylene chloride, acetonitrile, diethyl ether, 1,2-dichloroethane, dimethylformamide, dimethylsulfoxide, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, nitromethane, methyl-t-butyl ether, N-methyl-2-pyrrolidinone, tetrahydrofuran, and combinations thereof. In some embodiments, a relatively non-polar solvent can also be added, for instance, hexane, toluene, or petroleum ethers. In some instances, a small amount of an alcohol may be included as well. For instance, methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol, or ethylene glycol may be added, generally in a sub-stoichiometric amount relative to the compound of Formula (I), e.g., less than 1 equivalent, less than 0.75 equivalents, less than 0.5 equivalents, or less than 0.25 equivalents. In some embodiments, from 0.1-1, from 0.1-0.75, from 0.1-0.5, or from 0.1-0.25 equivalents of the alcohol, relative to the compound of Formula (I) can be added.

In some embodiments, R^1 is hydrogen or $C(O)R^{1a}$, and it is preferable that R^{1a} is C_{1-8}alkyl, e.g. methyl, ethyl or 2-propyl. NO_2 is a preferred R^2 group, and ethyl, as it occurs in oseltamivir, is the preferred R^3 group. The diazidation reaction can provide the compound of Formula (II) in the desired (and depicted) stereochemical configuration in an amount that is at least 85%, at least 90%, at least 92.5%, at least 95%, at least 97.5%, or at least 99%, relative to the total amount of the reaction product.

In some embodiments, the diazidation reaction can be conducted using the compound of Formula (I) in racemic form. In such embodiments, the ligand may be achiral or racemic, and the resulting racemic mixture of the compound of Formula (II) may be converted to enantioenriched form using conventional methods. In other embodiments, the compound of Formula (I) is in racemic form, and the ligand is enantioenriched. In such cases, when only a single equivalent of azide source is used (relative to the olefin in Formula (I), only the desired enantiomer will be undergo diazidation, and the enantioenriched diazide can be separated from the unreacted, opposite enantiomer. In some embodiments, the diazidation reaction can be conducted using the compound of Formula (I) in enantioenriched form. Preferably, the enantiomeric excess of the enantioenriched compound of Formula (I) is at least 85%, at least 90%, at least 92.5%, at least 95%, at least 97.5%, or at least 99%. In such embodiments, the ligand may be achiral or racemic. In other cases, the ligand may be enantioenriched itself, and the matching of the ligand and substrate will further enhance the enantiomeric excess of the product. In certain embodiments, the ligand is provided in racemic form, and the compound of Formula (I) is provided in enantioenriched form, as defined above.

In some embodiments, the compound of Formula (II) may be converted to the compound of Formula (III):

[Formula (III)]

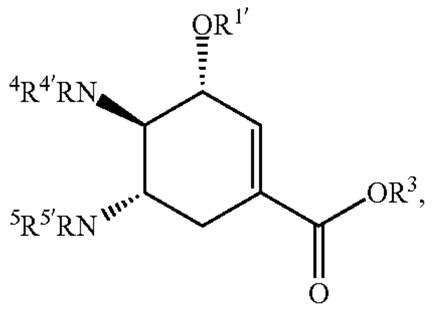


by elimination of H—R^2. R^3 has the same meanings given above, and $R^{1'}$ can be $R^{1a'}$, $C(O)R^{1a'}$, $C(O)OR^{1a'}$, C(O)N

$(R^{1a'})_2$, $Si(R^{1a'})_3$, wherein $R^{1a'}$ is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl. This process may be carried taking advantage of the acidity of the R^h proton, using either acid or base mediated chemistries. In some instances, an R^1 protecting group will be removed under these conditions as well, leading to compounds in which $R^{1'}$ is hydrogen. In such instances, the alkoxy group found in oseltamivir may be directly installed, e.g., $R^{1'}$ is 3-pentyl. Such compounds may be prepared by reaction with a compound of formula $X—CH(CH_2CH_3)_2$, in which X is Cl, Br, I, OMs, OTs, or $OC(NH)CCl_3$.

The compound of Formula (III) can be converted to the compound of Formula (IV):

[Formula (IV)]

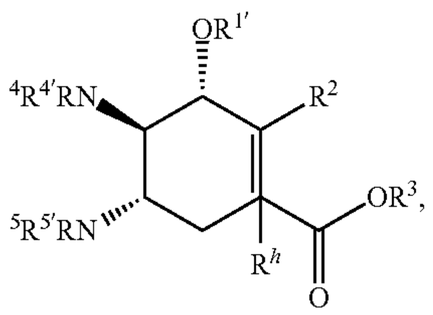


by reduction of the azide groups, in which R^4, $R^{4'}$, R^5, and $R^{5'}$ are independently selected from R^z, $C(O)R^z$, $C(O)OR^z$, $C(O)N(R^z)_2$, $Si(R^z)_3$, wherein R^z is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl. Preferred reductive condition include the use of an trialkyl and triaryl phosphines like Ph_3P, in a mixed aqueous/organic solvent. Solid-supported alkyl- and arylphosphines can also be used. In some embodiments, catalytic hydrogenation can be employed, for instance using ruthenium, rhodium, iridium, palladium, platinum, or nickel catalysts. Preferred $R^{1'}$ groups for the reduction reaction include hydrogen, $C(=O)CH_3$, and 3-pentyl.

The vicinal di-primary amine compound (i.e., R^4, $R^{4'}$, R^5, and $R^{5'}$ are each hydrogen) may be selectively protected at the 5 position to give a compound in which R^4, $R^{4'}$, and $R^{5'}$ are each hydrogen, and R^5 is $C(O)OR^z$ or $Si(R^z)_3$, followed by acylation at the 4-position, e.g, $R^{4'}$ is hydrogen and R^4 is $C(O)CH_3$, and finally conversion of R^5 to hydrogen. This process can be advantageously carried out when $R^{1'}$ is 3-pentyl. At any stage of this process, the compound of Formula (IV) may be reacted with a chiral acid and selectively crystallized to increase the enantiomeric excess of the compound. Suitable chiral acids include tartaric acid (and diester derivative thereof like dibenzoyl tartaric acid, camphorsulfonic acid, bromo-camphorsulfonic acid, and mandelic acid.

In some embodiments, the compound of Formula (I) may be converted to a compound of Formula (IV-a):

[Formula (IV-a)]

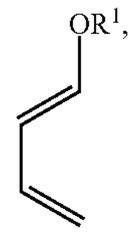


in which $R^{1'}$, R^3, R^4, $R^{4'}$, R^5, and $R^{5'}$ are as defined above, R^h is a hydrogen atom, and R^2 is selected from F, Cl, Br, I, NO_2, CN, OTs, and OMs. R^4, $R^{4'}$, R^5, and $R^{5'}$ can be converted to the groups found in oseltamivir as described above for the compound of Formula (IV), and the elimination of H—R^2 may be conducted at any advantageous point in the route.

The compound of Formula (IV) or (IV-a), when $R^{4'}$, R^5, and $R^{5'}$ are each hydrogen and R^4 is $C(O)CH_3$ may be converted to the phosphate salt to give the active ingredient found in Tamiflu. In instances in which $R^{5'}$ is protected with an acid labile group during the installation of R^4, the compound may be deprotected with phosphoric acid to give the active ingredient found in Tamiflu.

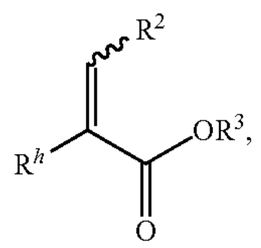
The compound of Formula (I) may be obtained from a cycloaddition reaction between compound of formula (VI):

[Formula (VI)]



and a compound of formula (VII):

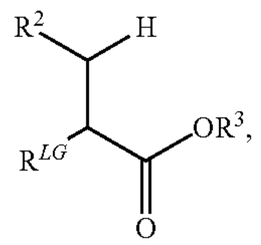
[Formula (VII)]



to give the compound of formula (I), wherein R^1, R^2, R^3 and R^h are as defined above. Preferred R^1 moieties include acyl such as acetyl, benzoyl, and then like. The compound of Formula (VI) can easily be prepared from crotonaldehyde using conventional conditions.

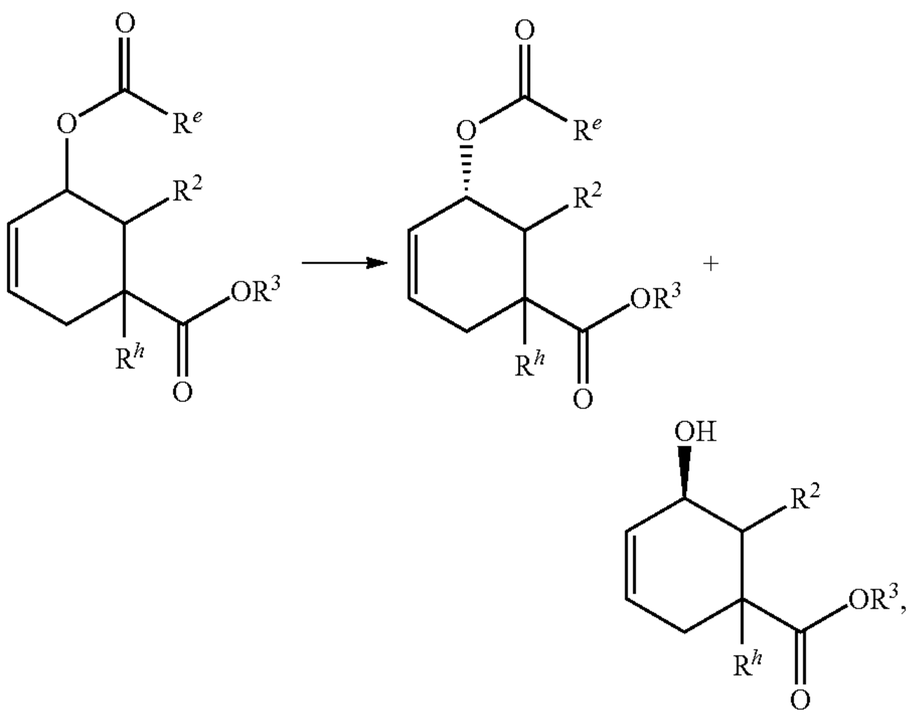
The compound of Formula (VII) may prepared in situ from a compound of Formula (VIII):

[Formula VIII]

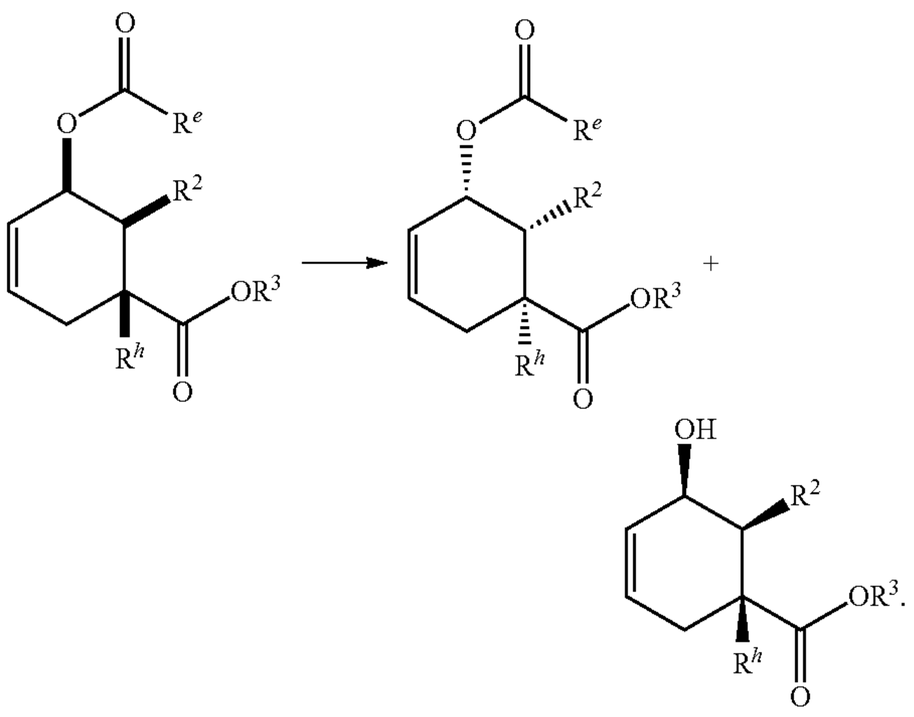


wherein R^{LG} represents a leaving group like Cl, Br, I, OTs, or OMs, and R^2 is sufficient to increase the acidity of the depicted hydrogen atom. In such cases, it is preferred that R^2 is nitro. In such embodiments, the compound of Formula (VIII) may be combined with the compound of Formula (VI) in the presence of a mild base.

The cycloaddition reaction may be conducted in the presence of a chiral catalyst or auxiliary to afford the compound of Formula (I) in enantioenriched form. In other embodiments, the compound of Formula (I) may be produced as the racemic mixture, and then enantioenriched. A preferred method of enantioenriching the compound of Formula (I) when R^1 is acyl is an enzymatic kinetic resolution:



wherein R^2, R^3, R^h are as defined above, and R^e is an alkyl or aryl group. In some embodiments, the compound of Formula (I) will have the following relative configuration:



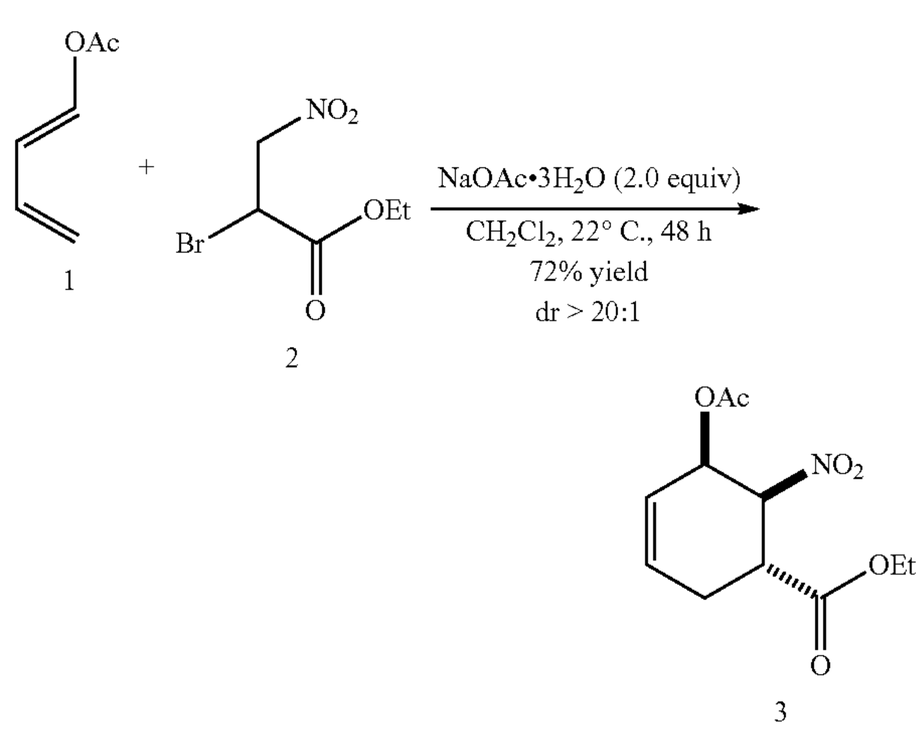
The enzymatic resolution may be conducted using a suitable lipase in an aqueous alcoholic solvent. Suitable lipases include lipase from porcine pancreas, lipase from *Rhizopus oryzae*, lipase from wheat germ, lipase from human pancreas, lipase from *Candida rugosa*, lipase from *Aspergillus niger*, lipase from *Thermomyces lanuginosus*, lipase from *Rhizomucor miehei*, lipase from *Pseudomonas cepacian*, lipase from *Aspergillus oryzae*, lipase from *Pseudomonas* sp., lipase from *Pseudomonas fluorescens*, lipase from *Rhizopus niveus*, lipase from *Mucor miehei*, lipase from *Mucor javanicus*, lipase from *Burkholderia* sp., lipase from *Candida Antarctica*, lipase from *Candida lipolytica*, Amano lipase PS, from *Burkholderia cepacian*, lipase B *Candida antarctica*, recombinant from *Aspergillus oryzae*, lipase, *Chromobacterium viscosum*, lipase A *Candida antarctica*, recombinant from *Aspergillus oryzae*, lipase from *Candida antarctica*, CLEA, lipase from *Candida rugosa*, CLEA, lipase from *Thermomyces lanuginosa*, CLEA, lipase produced by *Aspergillus oryzae*, pancreatin lipase, Amano lipase PS, Amano lipase A from *Aspergillus niger*, Amano Lipase from *Pseudomonas fluorescens*, lipoprotein lipase from *Burkholderia* sp., lipoprotein lipase from bovine milk, Amano lipase M from *Mucor javanicus*, lipoprotein lipase from *Pseudomonas* sp., Amano lipase G from *Penicillium camemberti*. Amano lipases, for instance Amano Lipase from *Pseudomonas fluorescens*, are especially preferred for the enzymatic step. The enantiomeric excess of the unreacted isomer can be at least 85%, at least 90%, at least 92.5%, at least 95%, at least 97.5%, or at least 99%. Likewise, the enantiomeric excess of the deacylated isomer can be at least 85%, at least 90%, at least 92.5%, at least 95%, at least 97.5%, or at least 99%.

The unreacted enantiomer may be separated from the hydrolyzed product using conventional techniques. If desired, the stereochemistry of the hydroxy group-bearing carbon on the undesired enantiomer can be inverted using Mitsunobu and related chemistries.

EXAMPLES

The following examples are for the purpose of illustration of the invention only and are not intended to limit the scope of the present invention in any manner whatsoever.

Example 1: Synthesis of Cyclohexene Substrate

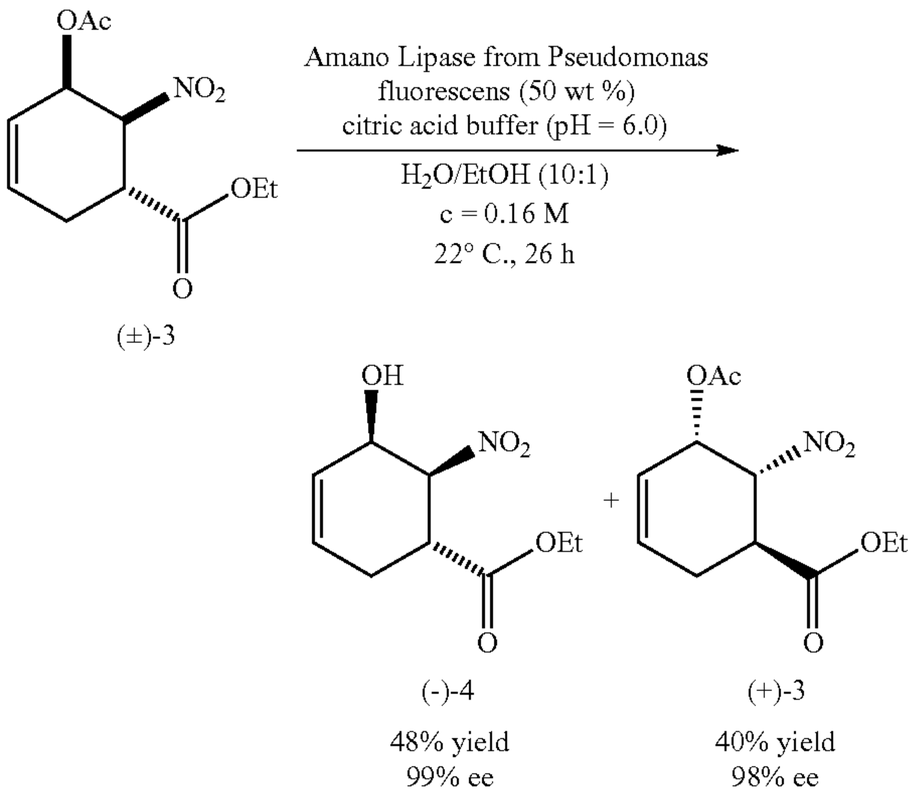


To an oven-dried 500 mL round bottom flask equipped with a stir bar was added finely ground $NaOAc.3H_2O$ (43.1 g, 316.8 mmol, 2.0 equiv). The flask was evacuated and backfilled with N_2. Subsequently, anhydrous CH_2Cl_2 (320 mL), (E)-buta-1,3-dien-1-yl acetate 1 (35.5 g, 316.8 mmol, 2.0 equiv) and ethyl 2-bromo-3-nitropropanoate 2 (35.8 g, 158.4 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 48 h until 2 was fully consumed (monitored by TLC). The reaction mixture was filtered and the solid was washed with CH_2Cl_2 (100 mL). The combined CH_2Cl_2 filtrate was washed with brine (100 mL) and dried over Na_2SO_4. After concentration in vacuo, the crude product was recrystallized from ethanol (100 mL) to furnish the desired product (±)-3 (29.3 g, 72%, dr>20:1, m.p. 75-76° C.).

(±)-Ethyl-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate ((±)-3)

IR ν_{max} (neat)/cm^{-1}: 2979 (w), 1737 (s), 1559 (s), 1373 (m), 1226 (s), 1186 (s), 1027 (m), 924 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 6.10-5.90 (m, 2H), 5.84-5.68 (m, 1H), 4.93 (dd, J=12.1, 4.2 Hz, 1H), 4.32-4.12 (m, 2H), 3.45 (td, J=11.8, 6.2 Hz, 1H), 2.74 (ddd, J=22.3, 11.2, 7.7 Hz, 1H),

2.33-2.19 (m, 1H), 1.99 (s, 3H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.4, 131.2, 122.6, 83.3, 65.8, 61.6, 38.0, 28.9, 20.6, 14.1; LRMS (ESI, m/z): calcd for $C_{11}H_{15}NNaO_6^+$, [M+Na$^+$], 280.1, found 280.1.



To a 100 mL round bottom flask were added Amano Lipase from *Pseudomonas fluorescens* (1.0 g, 50 wt %), (±)-ethyl-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate (±)-3 (2.0 g, 7.78 mmol, 1.0 equiv), aqueous citric acid—Na_2HPO_4 buffer (44.2 mL, pH=6.0, c=0.037 M) and ethanol (4.4 mL). The mixture was stirred at room temperature for 26 h. EtOAc (30 mL) was added to dilute the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×4). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the hydrolyzed product (−)-4 as colorless oil (805 mg, 48% yield, 99% ee) along with the enantio-enriched starting material (+)-3 (800 mg, 40% yield, 98% ee).

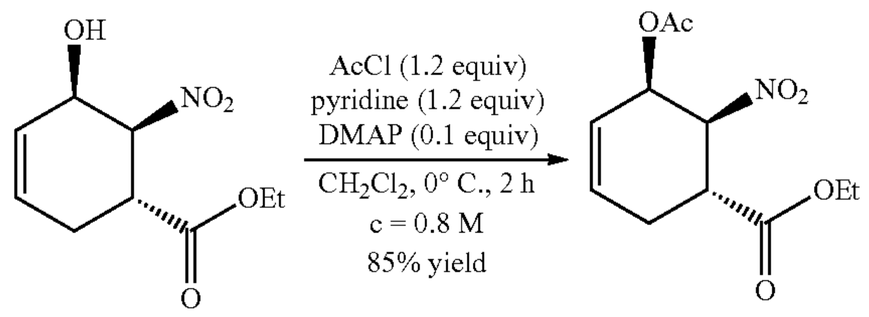
(−)-Ethyl (1R,5R,6S)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate ((−)-4)

$[\alpha]_D^{20}$=−294.5° (c 1.025, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3442 (br), 2983 (w), 2930 (w), 1726 (s), 1551 (s), 1379 (m), 961 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07-5.89 (m, 2H), 4.87 (dd, J=11.6, 4.0 Hz, 1H), 4.83-4.82 (m, 1H), 4.37-4.07 (m, 2H), 3.42 (td, J=11.5, 6.0 Hz, 1H), 2.72 (ddd, J=18.4, 6.0, 3.9 Hz, 1H), 2.30-2.20 (m, 1H), 2.11 (d, J=6.6 Hz, 1H), 1.30 (t, J=7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 129.5, 125.6, 86.1, 64.4, 61.5, 37.4, 29.0, 14.0; LRMS (ESI, m/z): calcd for $C_9H_{13}NNaO_5^+$, [M+Na$^+$], 238.1, found 238.1.

(+)-Ethyl (1S,5S,6R)-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate ((+)-3)

$[\alpha]_D^{20}$=+363.1° (c 1.175, $CHCl_3$). IR, NMR and LRMS are the same as (±)-3.

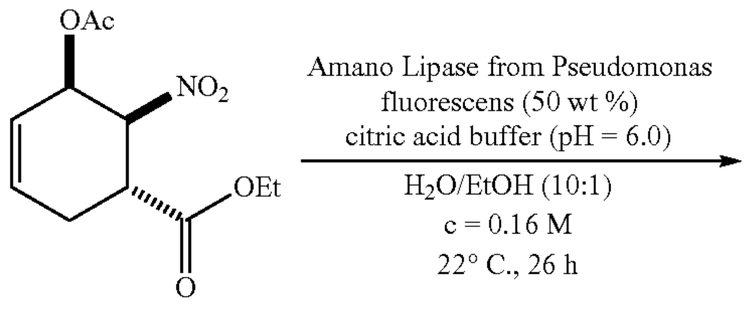
Note: the enantiomeric (−)-3 can be readily recovered from (−)-4.

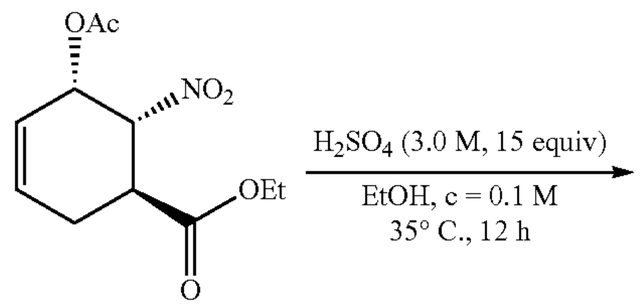


To a flame-dried 50 mL round bottom flask were added ethyl (1R,5R,6S)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate (−)-4 (860 mg, 4.0 mmol, 1.0 equiv) and DMAP (49 mg, 0.4 mmol, 0.1 equiv). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (5.0 mL) was added via a syringe and the mixture was cooled down to 0° C. Subsequently, acetyl chloride (0.34 mL, 4.8 mmol, 1.2 equiv) was added to the flask followed by pyridine (0.39 mL, 4.8 mmol, 1.2 equiv). The reaction mixture was stirred at 0° C. for 2 h until (−)-4 was fully consumed (monitored by TLC). Saturated aqueous NH_4Cl solution (5 mL) was added to quench the reaction. The organic phase was separated from aqueous phase and the aqueous phase was further extracted with CH_2Cl_2 (20 mL×3). The combined organic phase was washed with brine (30 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 4:1) to afford the desired product (−)-3 as a white solid (875 mg, 85% yield).

Ethyl (1R,5R,6S)-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate ((−)-3)

$[\alpha]_D^{20}$=−360.20 (c 1.251, $CHCl_3$). IR, NMR and LRMS are the same as (±)-3.





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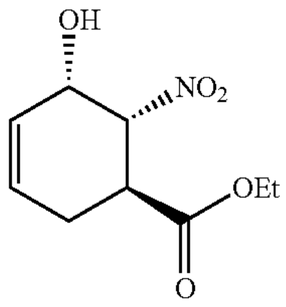


(+)-4

93% yield

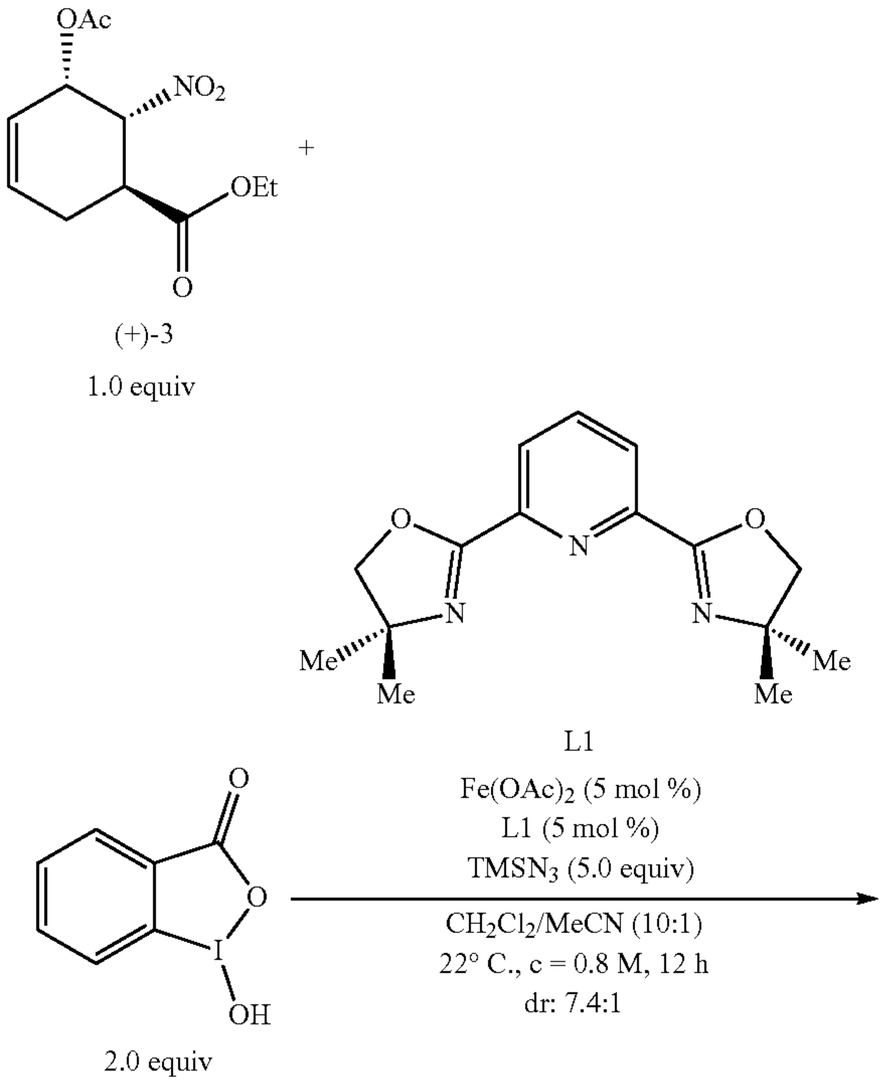
98% ee

To a 100 mL round bottom flask were added ethyl-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate (+)-3 (2.0 g, 7.78 mmol, 1.0 equiv), EtOH (39 mL) and H_2SO_4 (39 mL, 3.0 M, 116.7 mmol, 15.0 equiv). The mixture was stirred at 35° C. for 12 h. EtOAc (50 mL) was added to dilute the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×3). The combined organic phase was washed with brine (80 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the hydrolyzed product (+)-4 as colorless oil (1.56 g, 93% yield).

(+)-Ethyl (1R,5R,6S)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate ((+)-4)

$[\alpha]_D^{20}$=+294.5° (c 1.025, $CHCl_3$). IR, NMR and LRMS are the same as (−)-4.

Example 2: Stereoselective Diazidation



(+)-3

1.0 equiv

+

2.0 equiv

L1

$Fe(OAc)_2$ (5 mol %)

L1 (5 mol %)

$TMSN_3$ (5.0 equiv)

CH_2Cl_2/MeCN (10:1)

22° C., c = 0.8 M, 12 h

dr: 7.4:1

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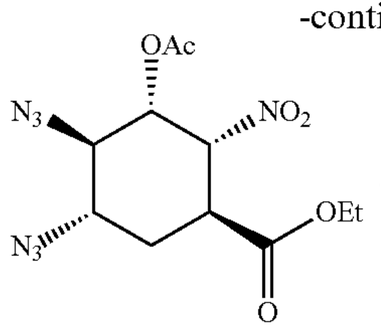


5a

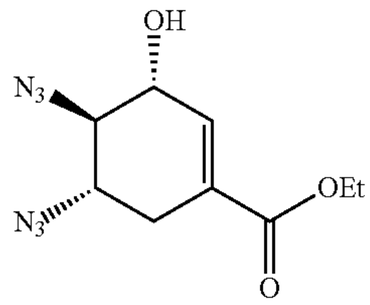
72%

$[\alpha]D^{20}$ = -6.4° (c 1.1, $CHCl_3$).

1) MsOH (3.0 equiv)
EtOH, c = 0.6 M
40° C., 7 h

2) $LiOH•H_2O$ (4.5 equiv)
EtOH, c = 0.1 M
0° C., 30 min

61% yield over 3 steps



To a flame-dried 250 mL round bottom flask equipped with a stir bar were added $Fe(OAc)_2$ (169 mg, 0.97 mmol, 5 mol %), achiral ligand L1 (265 mg, 0.97 mmol, 5 mol %), ethyl (1S,5S,6R)-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate (+)-3 (5.0 g, 19.44 mmol, 1.0 equiv) and benziodoxole (10.3 g, 38.9 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (20 mL) and MeCN (2.0 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (12.8 mL, 97.2 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until (+)-3 was fully consumed (monitored by TLC). Et_2O (150 mL) was added to dilute the reaction and the resulting suspension was stirred for 10 min. The mixture was filtered and the solid was washed with Et_2O (20 mL×2). The combined filtrate was washed with saturated $NaHCO_3$ solution (160 mL), brine (100 mL) and dried over Na_2SO_4. The mixture was filtered through a silica gel pad (ca. 6 cm long×6 cm diameter) and the pad was washed with ether (100 mL×3). After concentration in vacuo, the crude diazidation product 5 was obtained as a yellow solid, which was used in the next step directly without further purification. The crude yield and dr value were obtained by quantitative ^1H NMR experiment using an internal standard (85% NMR yield, dr: 7.4:1). For characterization purposes, it was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired pure product 5a as a white solid (4.78 g, 72% yield).

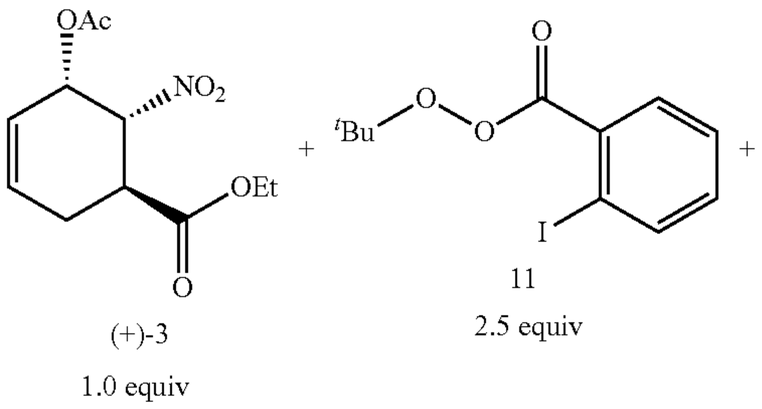
Ethyl (1S,2R,3S,4R,5S)-3-acetoxy-4,5-diazido-2-nitrocyclohexane-1-carboxylate (5a)

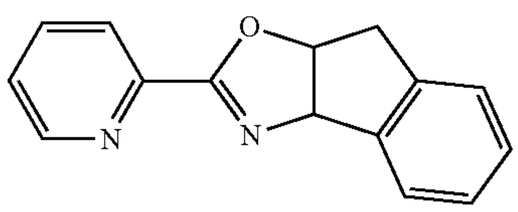
$[\alpha]_D^{20}$=−6.4° (c 1.13, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 2966 (w), 2098 (s), 1748 (s), 1727 (s), 1557 (s), 1383 (m), 1232 (s), 1189 (s), 1042 (m), 1024 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (dd, J=6.8, 4.3 Hz, 1H), 5.23 (dd, J=6.7, 4.3 Hz, 1H), 4.32-4.16 (m, 3H), 3.68 (q, J=6.1 Hz, 1H), 3.46 (q, J=6.4 Hz, 1H), 2.21 (t, J=6.1 Hz, 2H), 2.12 (s, 3H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.4, 81.7, 69.6, 62.4, 60.9, 57.8, 34.0, 27.4, 20.6, 14.1; LRMS (ESI, m/z): calcd for $C_{11}H_{15}N_7NaO_6^+$, [M+Na^+], 364.1, found 364.1.

To an oven-dried 250 mL round bottom flask were added the crude diazidation product ethyl (1S,2R,3S,4R,5S)-3-acetoxy-4,5-diazido-2-nitrocyclohexane-1-carboxylate 5a obtained in last step (14.6 mmol, 1.0 equiv). After the flask was evacuated and backfilled with N_2 twice, EtOH (24 mL) and methanesulfonic acid (2.84 mL, 43.7 mmol, 3.0 equiv) were added via syringes. The mixture was warmed up to 55° C. and stirred at this temperature for 7 h until the starting material was fully consumed (monitored by TLC). The reaction mixture was moved to ice-bath and diluted with EtOH (122 mL). Subsequently, $LiOH.H_2O$ (2.76 g, 65.7 mmol, 4.5 equiv) was added portion-wise and the mixture was stirred at 0° C. for additional 30 min until the intermediate was consumed (monitored by NMR). AcOH (0.83 mL, 1.5 equiv) was added to quench the reaction. EtOH was removed in vacuo, and the residue was diluted with EtOAc (50 mL) and water. The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (50 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product 6 as yellow oil (2.98 g, 61% yield over three steps).

Ethyl (3R,4R,5S)-4,5-diazido-3-hydroxycyclohex-1-ene-1-carboxylate (6)

$[\alpha]_D^{20}$=−102° (c 0.75, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3435 (br), 2981 (w), 2103 (s), 1704 (m), 1656 (w), 1250 (s), 1089 (m), 1043 (m), 981 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.33-4.28 (m, 1H), 4.25 (q, J=7.1 Hz, 2H), 3.63 (td, J=10.2, 5.9 Hz, 1H), 3.52-3.40 (m, 1H), 2.95 (dd, J=18.1, 5.8 Hz, 1H), 2.59-2.57 (m, 1H), 2.44-2.29 (m, 1H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 137.8, 128.5, 70.8, 68.2, 61.4, 59.6, 30.1, 14.1; LRMS (ESI, m/z): calcd for $C_9H_{12}N_6NaO_3^+$, [M+Na^+], 275.1, found 275.1.





L2

$Fe(NTf_2)_2$ (10 mol %)
L2 (10 mol %)
^{i}PrOH (0.2 equiv)
$TMSN_3$ — CH_2Cl_2/MeCN (4:1)
3.5 equiv — 0-22° C.
c = 0.5 M, 15 h
dr: 4.8:1

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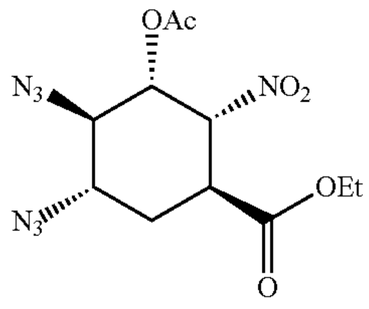
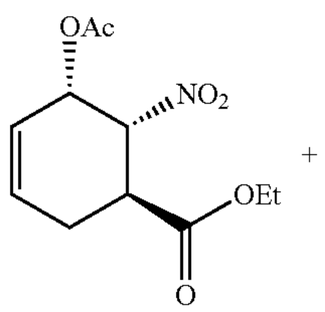


5a

71%

$[\alpha]D^{20}$ = -6.4° (c 1.1, $CHCl_3$)

To a flame-dried sealable 2-dram vial (vial A) equipped with a stir bar were added $Fe(NTf_2)_2$ (62 mg, 0.1 mmol, 10 mol %) and the ligand L2 (24 mg, 0.1 mmol, 10 mol %). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (0.6 mL) and MeCN (0.2 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. To a second flame-dried sealable 2-dram vial (vial B) equipped with a stir bar was added ethyl (1S,5S,6R)-5-acetoxy-6-nitrocyclohex-3-ene-1-carboxylate (+)-3 (257 mg, 1.0 mmol, 1.0 equiv) and tert-butyl 2-iodobenzoperoxoate 11 (800 mg, 2.5 mmol, 2.5 equiv). After this vial was evacuated and backfilled with N_2 twice, the catalyst solution in vial A, isopropanol (15 μL, 0.2 mmol, 0.2 equiv) and freshly distilled $TMSN_3$ (133 μL, 1.0 mmol, 1.0 equiv) were added to vial B at 0° C. Subsequently, additional $TMSN_3$ (332 μL, 2.5 mmol, 2.5 equiv) was added to vial B at 0° C. using a syringe pump within 4 h. The reaction mixture was warmed up to 22° C. and kept stirring for 11 h. CH_2Cl_2 (4 mL) and saturated $NaHCO_3$ solution (0.5 mL) were added to quench the reaction and to remove any residual hydrazoic acid. The organic phase was separated from the aqueous phase, and it was washed with saturated Na_2CO_3 solution (2 mL), brine (2 mL), and dried over Na_2SO_4. After concentration in vacuo, the dr was obtained by quantitative ^1H NMR experiment using an internal standard (86% NMR yield, dr: 4.8:1). The crude product was purified through column chromatography (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired pure product 5a as a white solid (243 mg, 71% yield).



(+)-4

1.0 equiv

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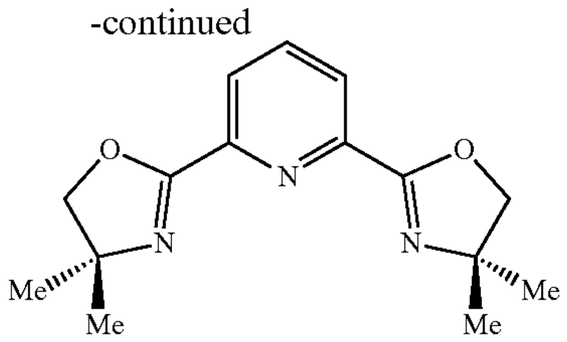
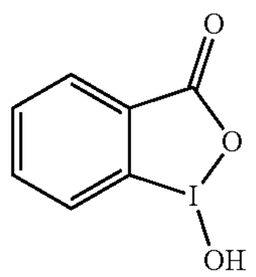


L1



2.0 equiv

OTMS

$Fe(OAc)_2$ (5 mol %)

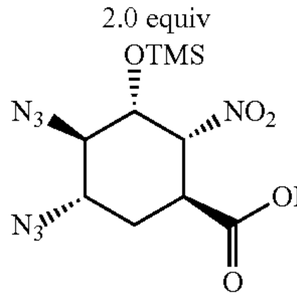
L1 (5 mol %)

$TMSN_3$ (5.0 equiv)

CH_2Cl_2/MeCN (10:1)

22° C., c = 0.8 M, 12 h

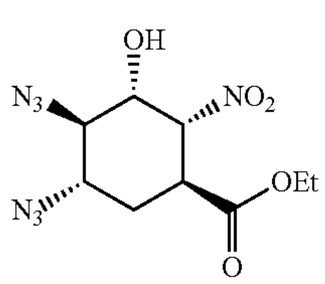
OH



5b

6% yield

+



5c

70% yield

$LiOH \cdot H_2O$

(3 equiv)

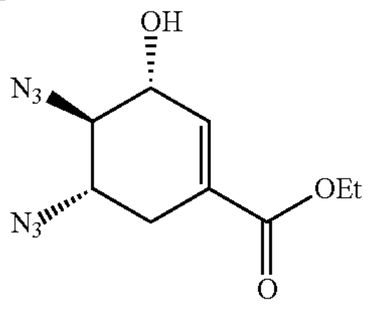
EtOH,

c = 0.1 M

0° C., 30 min

91% yield

1 M aq. H_2SO_4



6

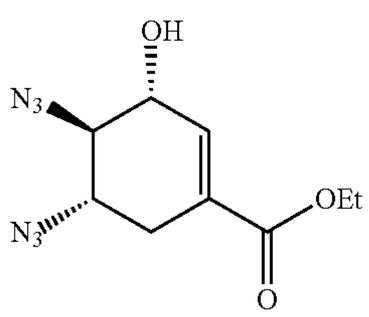
To a flame-dried 100 mL round bottom flask equipped with a stir bar were added $Fe(OAc)_2$ (61 mg, 0.35 mmol, 5 mol %), achiral ligand L1 (95 mg, 0.35 mmol, 5 mol %), ethyl (1S,5S,6R)-5-hydroxy-6-nitrocyclohex-3-ene-1-carboxylate (+)-4 (1.5 g, 6.97 mmol, 1.0 equiv) and benziodoxole (3.68 g, 13.94 mmol, 2.0 equiv). After the flask was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (8 mL) and MeCN (0.8 mL) were added via syringes and the mixture was stirred at room temperature for 10 min. Subsequently, freshly opened $TMSN_3$ (4.58 mL, 34.85 mmol, 5.0 equiv) was added to the flask at room temperature within 8 h using a syringe pump. The reaction mixture was stirred for additional 2 h until (+)-4 was fully consumed (monitored by TLC). Et_2O (50 mL) was added to dilute the reaction and the resulting suspension was stirred for 10 min. The mixture was filtered and the solid was washed with Et_2O (20 mL×2). The combined filtrate was first washed with aq. H_2SO_4 (1 M) and then saturated $NaHCO_3$ solution (100 mL), brine (50 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the desired product 5c as colorless oil (1.58 g, 76% yield).

Ethyl (1S,2R,3S,4R,5S)-4,5-diazido-3-hydroxy-2-nitrocyclohexane-1-carboxylate (5c)

IR ν_{max} (neat)/cm^{-1}: 3462 (w), 2920 (w), 2110 (s), 1729 (s), 1558 (s), 1377 (m), 1258 (s), 1200 (m), 1095 (m), 1021 (m), 955 (w), 874 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, J=8.4, 3.9 Hz, 1H), 4.40-4.36 (m, 1H), 4.27-4.18 (m, 2H), 4.06 (t, J=5.4 Hz, 1H), 3.78 (dd, J=9.6, 5.2 Hz, 1H), 3.48 (td, J=8.7, 5.2 Hz, 1H), 3.24 (d, J=7.0 Hz, 1H), 2.26-2.07 (m, 2H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 83.7, 70.0, 62.7, 62.2, 58.3, 37.4, 27.4, 14.0; LRMS (ESI, m/z): calcd for $C_9H_{13}N_7O_5Na^+$, [M+Na^+], 322.1, found 322.1.

To a 100 mL round bottom flask were added the diazidation product 5c (1.46 g, 4.88 mmol, 1.0 equiv) and EtOH (49 mL). After the flask was moved to ice-bath, $LiOH.H_2O$ (0.61 g, 14.64 mmol, 3.0 equiv) was added portion-wise and the mixture was stirred at 0° C. for 30 min until the starting material was fully consumed (monitored by TLC). AcOH (0.56 mL, 9.76 mmol, 2 equiv) was added to quench the reaction. EtOH was removed in vacuo, and the residue was diluted with EtOAc (30 mL) and water (20 mL). The organic phase was separated from aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×2). The combined organic phase was dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 3:1) to afford the desired product 6 as yellow oil (1.12 g, 91% yield).

Example 3: Synthesis of Oseltamivir



6

1) Ph_3P (2.3 equiv)

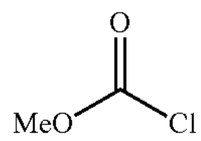
H_2O (10 equiv)

THF, 22° C., 8 h

the TsOH (2.5 equiv), 1 h

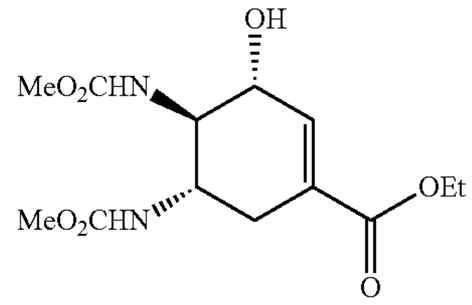
2) $NaHCO_3$, H_2O,

22° C., 2 h



(2.6 equiv)

80% overall yield



7

To a 100 mL round bottom flask with a stir bar was added ethyl (3R,4R,5S)-4,5-diazido-3-hydroxycyclohex-1-ene-1-carboxylate 6 (2.92 g, 11.6 mmol, 1.0 equiv). After the flask was evacuated and backfilled with N_2 twice, THF (50 mL) and H_2O (2.1 mL, 115.9 mmol, 10 equiv) were added via syringes. Subsequently, Ph_3P (6.9 g, 26.7 mmol, 2.3 equiv) in THF (20 mL) was added drop-wise to the reaction at 0° C. The reaction mixture was warmed up to room temperature and stirred for 8 h (monitored by IR until the absorption of azido groups disappeared). The reaction mixture will be used directly in the next step without workup and purification.

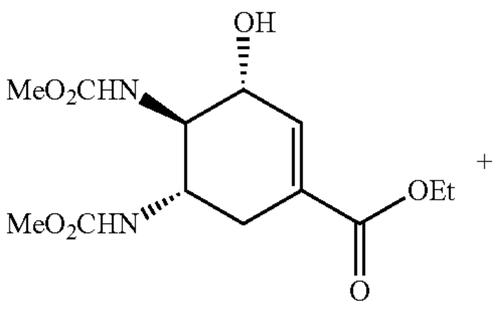
The reaction mixture from last step was added drop-wise to another 250 mL round bottom flask charged with a stir bar, $TsOH.H_2O$ (5.5 g, 28.9 mmol, 2.5 equiv), Et_2O (80 mL) and THF (10 mL). The reaction mixture was stirred at room

temperature for 1 h with the formation of white precipitates. The reaction mixture was filtered. The precipitate was dissolved in water (30 mL) and then washed with EtOAc (30 mL×2) to remove residue Ph_3PO. The filtrate was concentrated in vacuo and re-dissolved in EtOAc (10 mL). The organic phase was extracted with water (30 mL) and the combined aqueous phase will be used directly in the next step.

The aqueous solution from last step was cooled to 0° C. and $NaHCO_3$ (9.3 g, 110.6 mmol, 10 equiv) was carefully added portion-wise. The resulting solution was stirred at 0° C. for 5 min and methyl chloroformate (2.33 mL, 30.1 mmol, 2.6 equiv) was added. The mixture was warmed up to room temperature and stirred for additional 2 h. EtOAc was added to the reaction mixture. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with EtOAc (30 mL×3). The combined organic phase was dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 50:1 to 2:1) to afford the desired product 7 as a white solid (2.93 g, 80% yield, m.p. 58-59° C.).

Ethyl (3R,4R,5S)-4,5-bis((ethoxycarbonyl)amino)-3-hydroxycyclohex-1-ene-1-carboxylate (7)

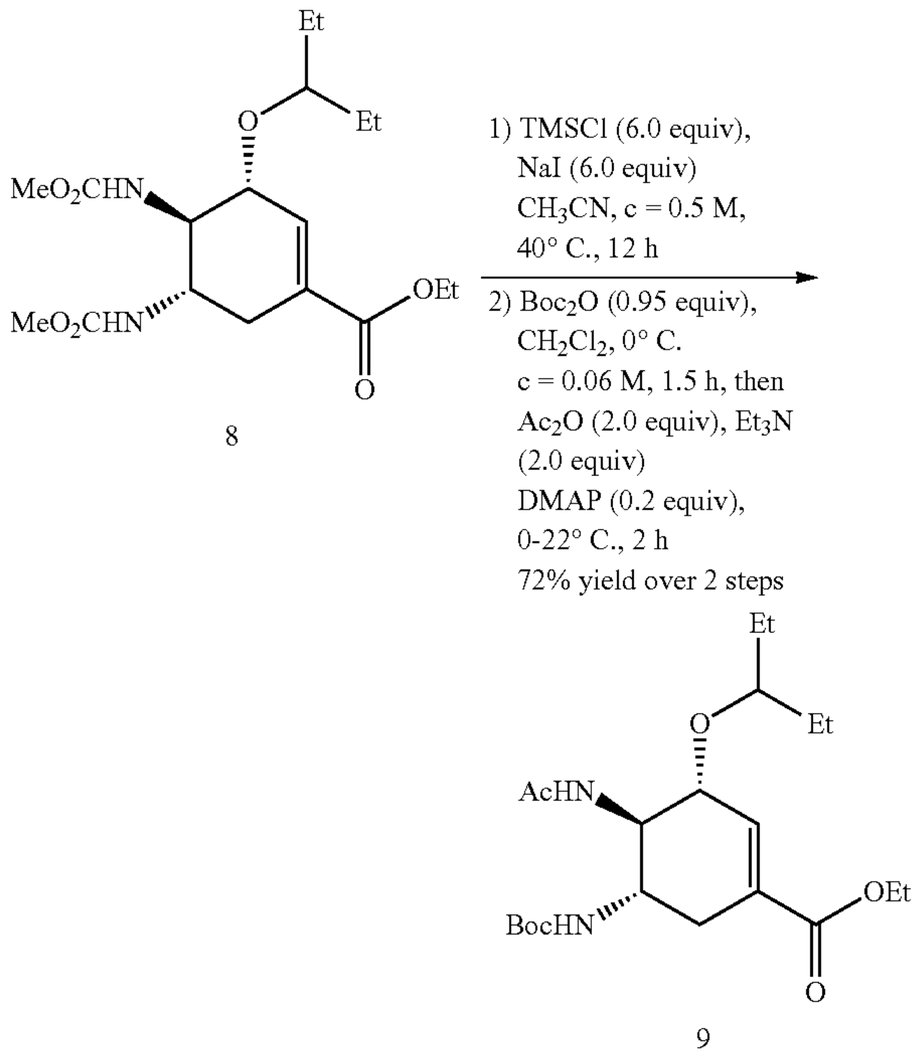
$[\alpha]_D^{20}$=−26.7° (c 0.325, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3319 (m), 2981 (w), 1692 (s), 1533 (s), 1447 (w), 1372 (w), 1239 (s), 1039 (s), 986 (m), 861 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 5.94 (d, J=8.6 Hz, 1H), 5.72 (d, J=8.9 Hz, 1H), 4.31-4.30 (m, 1H), 4.27-4.22 (m, 1H), 4.18 (q, J=7.1 Hz, 2H), 3.88-3.71 (m, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 2.82 (dd, J=17.5, 5.1 Hz, 1H), 2.34-2.18 (m, 1H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.9, 157.7, 139.1, 128.7, 71.4, 61.0, 58.8, 52.5, 52.4, 49.8, 31.3, 14.1; LRMS (ESI, m/z): calcd for $C_{13}H_{21}N_2O_7^+$, [M+H$^+$], 317.1, found 317.1.



To an oven-dried 50 mL round bottom flask equipped with a stir bar were added ethyl (3R,4R,5S)-4,5-bis((ethoxycarbonyl)amino)-3-hydroxycyclohex-1-ene-1-carboxylate 7 (1.38 g, 4.4 mmol, 1.0 equiv) and 5 Å molecular sieves powder (1.5 g). After the flask was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (9.0 mL) and freshly distilled pentan-3-yl 2,2,2-trichloroacetimidate (17 mL, 95.8 mmol, 22 equiv) were added. The reaction was cooled to 0° C. and TfOH (154 μL, 1.74 mmol, 0.4 equiv) was added. After the addition of TfOH, the reaction mixture was warmed up to 28° C. and stirred at this temperature for 22 h until 7 was fully consumed (monitored by TLC). The mixture was cooled to 0° C., and Et_3N (0.6 mL, 4.4 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added to quench the reaction. The mixture was filtered and the solid was washed with CH_2Cl_2 (10 mL×4). The filtrate was concentrated in vacuo and the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 2:1) to afford the desired product 8 as a white solid (1.21 g, 72% yield, m.p. 95-96° C.).

Ethyl (3R,4R,5S)-4,5-bis((methoxycarbonyl)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (8)

$[\alpha]_D^{20}$=−54.6° (c 0.85, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3313 (m), 2921 (s), 1697 (s), 1544 (m), 1286 (m), 1231 (m), 1058 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 5.52 (s, 1H), 4.76 (s, 1H), 4.20 (q, J=6.7 Hz, 2H), 4.06-3.74 (m, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.39 (s, 1H), 2.73 (d, J=17.1 Hz, 1H), 2.37 (d, J=11.5 Hz, 1H), 1.53-1.51 (m, 4H), 1.37-1.21 (m, 3H), 0.89-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.5, 157.1, 136.9, 129.3, 82.5, 77.3, 75.2, 60.9, 55.3, 52.3, 52.2, 49.6, 30.4, 26.2, 25.8, 14.2, 9.4, 9.3; LRMS (ESI, m/z): calcd for $C_{18}H_{31}N_2O_7^+$, [M+H$^+$], 387.2, found 387.2.



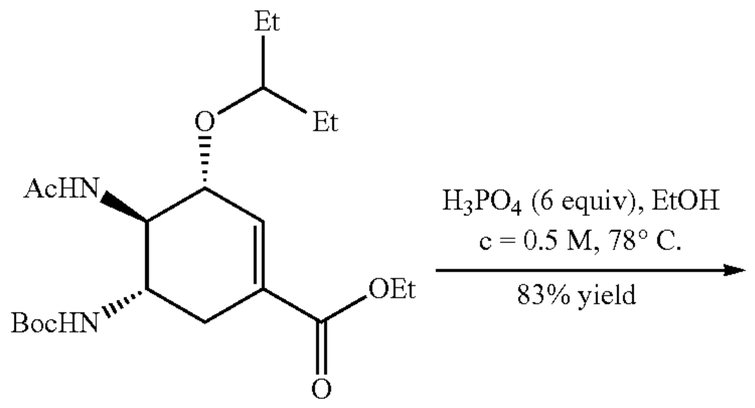
To a flame-dried 50 mL round bottom flask equipped with a stir bar were added methyl (3R,4R,5S)-4,5-bis((methoxycarbonyl)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate 8 (1.0 g, 2.6 mmol, 1.0 equiv) and anhydrous NaI (2.34 g, 15.6 mmol, 6.0 equiv). After this flask was evacu-

ated and backfilled with N_2 twice, anhydrous MeCN (5.2 mL) was added followed by drop-wise addition of freshly distilled TMSCl (1.98 mL, 15.6 mmol, 6.0 equiv) via a syringe. The mixture was warmed up to 40° C. and stirred at this temperature for 12 h in dark. The reaction was cooled down to 0° C. and diluted with CH_2Cl_2 (30 mL). Saturated Na_2CO_3 solution (10 mL), H_2O (5 mL) and saturated $Na_2S_2O_3$ solution (2 mL) were added and the mixture was stirred for additional 5 min. The organic phase was separated from the aqueous phase and the aqueous phase was further extracted with CH_2Cl_2 (80 mL×3). The combined organic phase was washed with water (10 mL×2), brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the crude diamine product will be used directly in the next step without further purification.

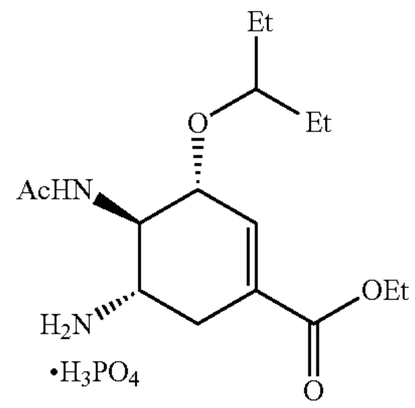
To an oven-dried 100 mL round bottom flask equipped with a stir bar was added the crude diamine product obtained in last step. The flask was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (40 mL) was added. Subsequently, a solution of Boc_2O (546 mg, 2.5 mmol, 0.95 equiv) in CH_2Cl_2 (2 mL) was added to the flask at 0° C. within 40 min using a syringe pump. The mixture was warmed up to room temperature and stirred for additional 1 h (monitored by TLC until the diamine starting material was consumed). Et_3N (0.72 mL, 5.2 mmol, 2.0 equiv), Ac_2O (0.49 mL, 5.2 mmol, 2.0 equiv) and a solution of DMAP (25 mg, 0.5 mmol, 0.2 equiv) in CH_2Cl_2 (0.5 mL) were added to the above mixture at 0° C. The reaction mixture was warmed up to room temperature and kept stirring for additional 2 h until the intermediate was consumed (monitored by TLC). Saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The organic phase was separated from the aqueous phase and the aqueous phase was extracted with CH_2Cl_2 (30 mL×2). The combined organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified through column chromatography (hexanes/EtOAc: from 30:1 to 2:1) to afford the desired product 9 as a white solid (772 mg, 72% yield over 2 steps, m.p. 141-142° C.).

Ethyl (3R,4R,5S)-4-acetamido-5-((tert-butoxycarbonyl)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (9)

$[\alpha]_D^{20}$=−77° (c 1.06, $CHCl_3$). IR ν_{max} (neat)/cm^{-1}: 3313 (m), 2971 (m), 2932 (m), 1681 (s), 1654 (s), 1544 (m), 1297 (m), 1242 (s), 1051 (m), 1013 (m), 943 (m), 733 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 5.89 (d, J=9.0 Hz, 1H), 5.17 (d, J=9.1 Hz, 1H), 4.25-4.15 (m, 2H), 4.06 (dd, J=18.5, 9.0 Hz, 1H), 3.97-3.95 (m, 1H), 3.78 (qd, J=9.7, 5.4 Hz, 1H), 3.36 (p, J=5.6 Hz, 1H), 2.73 (dd, J=17.8, 5.0 Hz, 1H), 2.43-2.20 (m, 1H), 1.97 (s, 3H), 1.62-1.45 (m, 4H), 1.41 (s, 9H), 1.28 (t, J=7.1 Hz, 3H), 0.88 (q, J=7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 165.9, 156.3, 137.6, 129.3, 82.2, 79.6, 75.8, 60.6, 54.4, 49.0, 30.9, 28.3, 26.1, 25.7, 23.4, 14.2, 9.5, 9.2; LRMS (ESI, m/z): calcd for $C_{21}H_{37}N_2O_6^+$, [M+H^+], 413.3, found 413.3.



9



10 (Tamiflu)

To an oven-dried 10 mL round bottom flask equipped with a stir bar was added ethyl (3R,4R,5S)-4-acetamido-5-((tert-butoxycarbonyl)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate 9 (1.21 g, 2.9 mmol). The flask was evacuated and backfilled with N_2 twice and then EtOH (4 mL) was added. Subsequently, H_3PO_4 (1.08 mL, 17.6 mmol, 6.0 equiv) in EtOH (1.8 mL) was added to the flask at room temperature using a syringe. The mixture was warmed up to 78° C. and stirred for additional 12 h (monitored by TLC until the starting material was consumed). The mixture was then cooled to 0° C. and stirred for 3 h with precipitates generated. The reaction mixture was filtered and the solid was washed with cold acetone (2.0 mL×3). The solid was collected and dried in vacuo to afford the desired product 10 (Tamiflu) as a white solid (1.0 g, 83% yield, m.p. 188-190° C.).

Ethyl (3R,4R,5S)-4-acetamido-5-amino-3-(pentan-3-yloxy) cyclohex-1-ene-1-carboxylate (oseltamivir phosphate, 10)

$[\alpha]_D^{20}$=−30° (c 1.01, H_2O). IR ν_{max} (neat)/cm^{-1}: 3347 (m), 3169 (br), 2966 (w), 2937 (w), 2874 (w), 1716 (s), 1656 (s), 1549 (s), 1243 (s), 1120 (s), 952 (s), 850 (m); ^1H NMR (400 MHz, D_2O) δ 6.75 (s, 1H), 4.23 (d, J=9.0 Hz, 1H), 4.15 (dt, J=7.2, 5.3 Hz, 2H), 3.95 (dd, J=11.6, 9.0 Hz, 1H), 3.55-3.39 (m, 2H), 2.86 (dd, J=17.0, 5.6 Hz, 1H), 2.50-2.35 (m, 1H), 1.98 (s, 3H), 1.41 (ddt, J=41.6, 14.2, 7.2 Hz, 4H), 1.18 (t, J=7.1 Hz, 3H), 0.76 (dt, J=17.7, 7.4 Hz, 6H); ^{13}C NMR (100 MHz, D_2O) δ 175.2, 167.3, 137.9, 127.5, 84.2, 75.0, 62.3, 52.6, 49.0, 28.1, 25.4, 25.0, 22.3, 13.2, 8.5, 8.4; LRMS (ESI, m/z): calcd for $C_{16}H_{29}N_2O_4^+$, [M−H_3PO_4+H^+], 313.2, found 313.2.

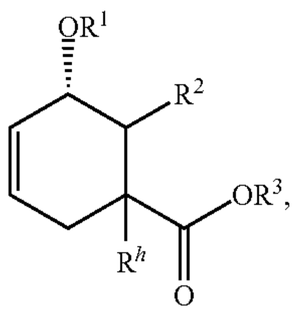
The compositions and methods of the appended claims are not limited in scope by the specific compositions and methods described herein, which are intended as illustrations of a few aspects of the claims and any compositions and methods that are functionally equivalent are intended to fall within the scope of the claims. Various modifications of the compositions and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Further, while only certain represen-

tative compositions and method steps disclosed herein are specifically described, other combinations of the compositions and method steps also are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps, elements, components, or constituents may be explicitly mentioned herein or less, however, other combinations of steps, elements, components, and constituents are included, even though not explicitly stated. The term "comprising" and variations thereof as used herein is used synonymously with the term "including" and variations thereof and are open, non-limiting terms. Although the terms "comprising" and "including" have been used herein to describe various embodiments, the terms "consisting essentially of" and "consisting of" can be used in place of "comprising" and "including" to provide for more specific embodiments of the invention and are also disclosed. Other than in the examples, or where otherwise noted, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood at the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, to be construed in light of the number of significant digits and ordinary rounding approaches.

What is claimed is:

1. A method of stereoselectively diazidating a cyclohexene compound of Formula (I):

[Formula (I)]



wherein R^1 comprises R^{1a}, $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)N(R^{1a})_2$, or $Si(R^{1a})_3$, wherein R^{1a} is in each case independently selected from the group consisting of hydrogen, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, aryl, heteroaryl, and $C_{3\text{-}8}$cycloalkyl;

wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs;

R^3 is selected from hydrogen, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, aryl, heteroaryl, and $C_{3\text{-}8}$cycloalkyl,

comprising contacting the compound of Formula (I) with:

a) an iron compound;

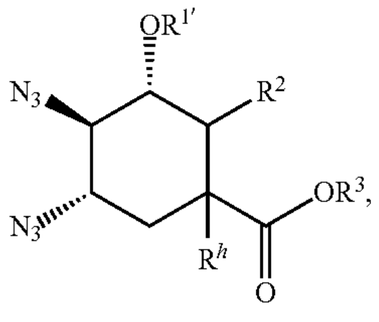
b) an azide source;

c) an activator, wherein the activator is selected from an iodine (III) compound or a peroxy compound;

d) a polydentate ligand;

to give a diazido compound of Formula (II):

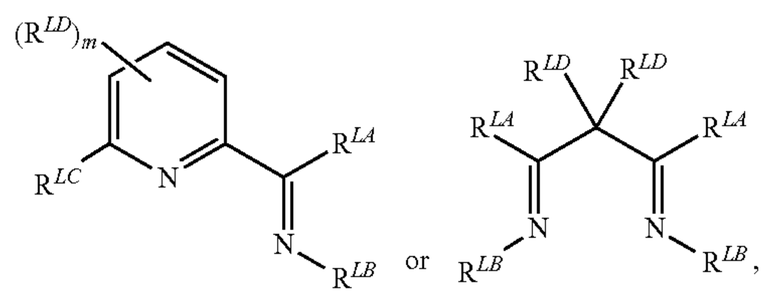
[Formula (II)]



wherein $R^{1'}$ is selected from R^{1a}, $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)N(R^{1a})_2$, $Si(R^{1a})_3$, wherein R^{1a} is in each case independently selected from the group consisting of hydrogen, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, aryl, heteroaryl, and $C_{3\text{-}8}$cycloalkyl;

wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs, or R^h and R^2 together form a double bond.

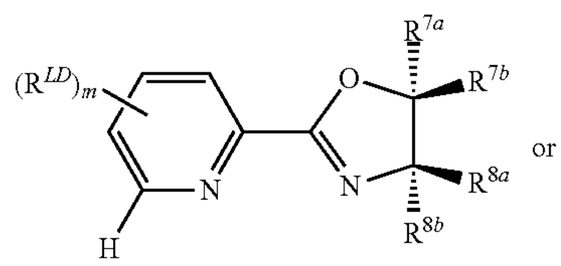
2. The method according to claim **1**, wherein the polydentate ligand has the formula:



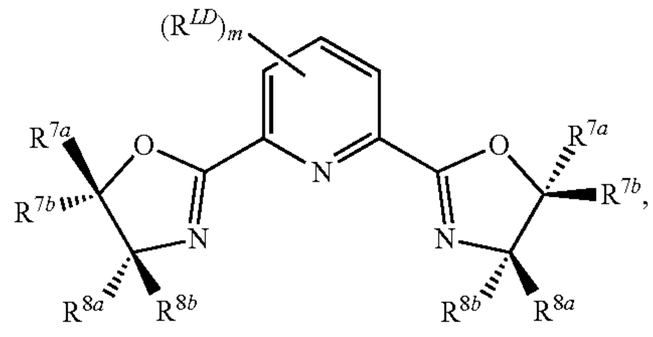
or

wherein m is selected from the group consisting of 0, 1, 2, and 3, and in each case R^{LA}, R^{LB}, R^{LC}, and R^{LD} are independently selected from the group consisting of R, OR, $N(R)_2$, PR_3, SiR_3, SR, SO_2R, $SO_2N(R)_2$, C(O)R; C(O)OR, OCOR; $C(O)N(R)_2$, $OC(O)N(R)_2$, $N(R)C(O)N(R)_2$, F, Cl, Br, I, cyano, and nitro, wherein R is in each case independently selected from the group consisting of hydrogen, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, aryl, $C_{1\text{-}8}$heteroaryl, $C_{3\text{-}8}$cycloalkyl, and $C_{1\text{-}8}$heterocyclyl; wherein any two or more of R^{LA}, R^{LB}, R^{LC}, R^{LD}, and R may together form a ring.

3. The method according to claim **2**, wherein the polydentate ligand has the formula:

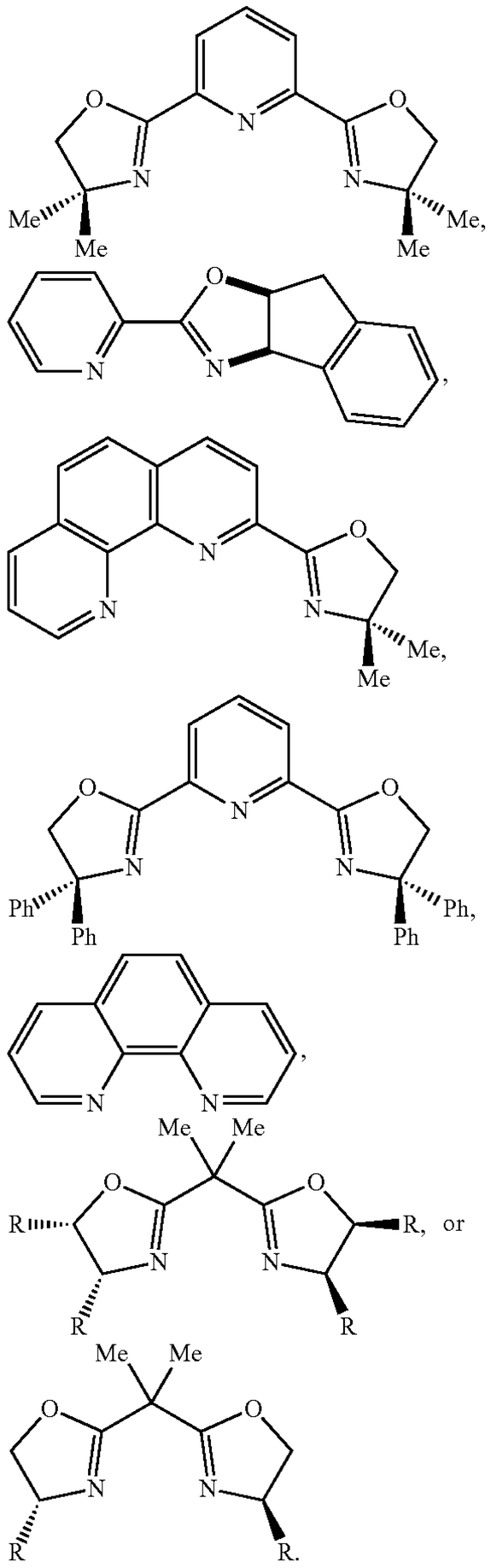


or



wherein each of R^{7a}, R^{7b}, R^{8a}, and R^{8b} are independently selected from the group consisting of R, OR, $N(R)_2$, PR_3, SiR_3, SR, SO_2R, $SO_2N(R)_2$, C(O)R; C(O)OR, OCOR; $C(O)N(R)_2$, $OC(O)N(R)_2$, $N(R)C(O)N(R)_2$, F, Cl, Br, I, cyano, and nitro, wherein R is in each case independently selected from the group consisting of hydrogen, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$-alkynyl, aryl, $C_{1\text{-}8}$heteroaryl, $C_{3\text{-}8}$cycloalkyl, and $C_{1\text{-}8}$heterocyclyl; wherein any two or more of R^{7a}, R^{7b}, R^{8a}, R^{8b}, R^{LD}, and R may together form a ring.

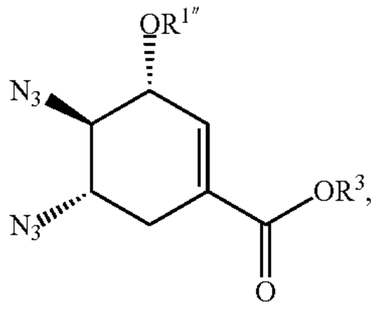
4. The method according to claim 2, wherein the polydentate ligand has the formula:



5. The method of claim 1, further comprising converting the compound of Formula (II) to oseltamivir or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, further comprising converting the compound of Formula (II) to a compound of Formula (III):

[Formula (III)]

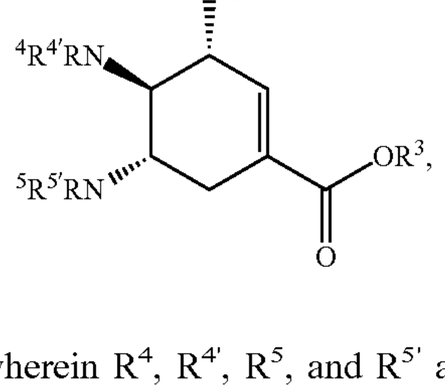


wherein $R^{1''}$ is selected from $R^{1a''}$, $C(O)R^{1a''}$, $C(O)OR^{1a''}$, $C(O)N(R^{1a''})_2$, $Si(R^{1a''})_3$, wherein $R^{1a''}$ is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, and heteroaryl, C_{3-8}cycloalkyl.

7. The method of claim 6, further comprising converting the compound of Formula (III) into oseltamivir or a pharmaceutically acceptable salt thereof.

8. The method of claim 6, further comprising converting the compound of Formula (III) to a compound of Formula (IV):

[Formula (IV)]



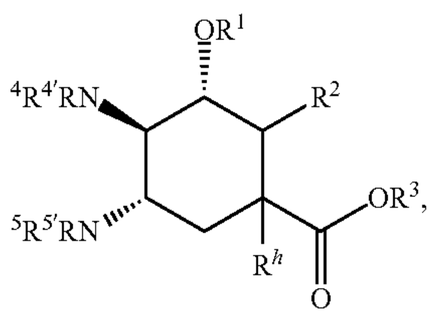
wherein R^4, $R^{4'}$, R^5, and $R^{5'}$ are independently selected from R^z, $C(O)R^z$, $C(O)OR^z$, $C(O)N(R^z)_2$, $Si(R^z)_3$, wherein R^z is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl;

$R^{1'''}$ is selected from $R^{1a'''}$, $C(O)R^{1a'''}$, $C(O)OR^{1a'''}$, $C(O)N(R^{1a'''})_2$, $Si(R^{1a'''})_3$, wherein $R^{1a'''}$ is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl.

9. The method of claim 8, further comprising converting the compound of Formula (IV) into oseltamivir, or a pharmaceutically acceptable salt thereof.

10. The method of claim 1, further comprising reducing the compound of Formula (II) into the compound of Formula (V):

[Formula (V)]

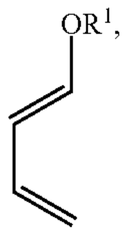


wherein R^4, $R^{4'}$, R^5, and $R^{5'}$ are independently selected from R^z, $C(O)R^z$, $C(O)OR^z$, $C(O)N(R^z)_2$, $Si(R^z)_3$, wherein R^z is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl.

11. The method of claim 10, comprising further converting the compound of Formula (V) into oseltamivir, or a pharmaceutically acceptable salt thereof.

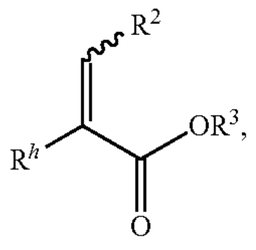
12. The method of claim 1, comprising preparing the compound of Formula (I) by cycloaddition between a compound of Formula (VI):

[Formula (VI)]



and a compound of Formula (VII):

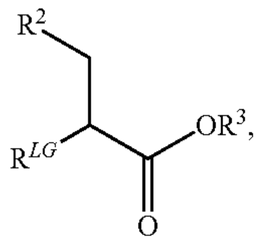
[Formula (VII)]



to give the compound of Formula (I).

13. The method of claim **10**, wherein the compound of Formula (VII) is prepared from a compound of Formula (VIII):

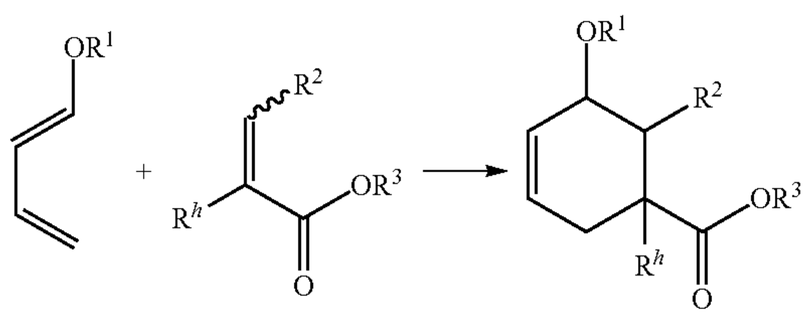
[Formula VIII]



wherein R^{LG} represents a leaving group.

14. A method comprising

a) conducting a cycloaddition reaction to give a cycloaddition product:



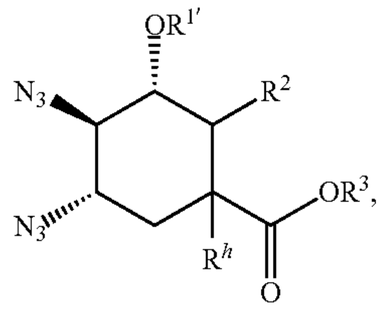
wherein R^1 comprises R^{1a}, $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)N(R^{1a})_2$, or $Si(R^{1a})_3$, wherein R^{1a} is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl;

wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs;

R^3 is selected from hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl; and

b) diazidating the cycloaddition product to give a compound of Formula (II):

[Formula (II)]



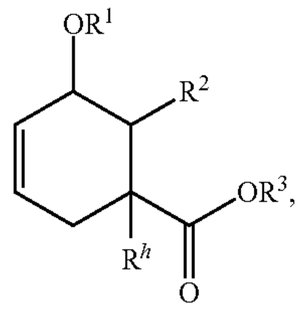
wherein $R^{1'}$ is selected from $R^{1a'}$, $C(O)R^{1a'}$, $C(O)OR^{1a'}$, $C(O)N(R^{1a'})_2$, $Si(R^{1a'})_3$, wherein $R^{1a'}$ is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl;

wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs, or R^h and R^2 together form a double bond.

15. The method according to claim **14**, comprising further converting the compound of Formula (II) to oseltamivir, or a pharmaceutically acceptable salt thereof.

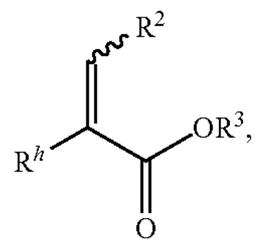
16. A method for preparing a compound of Formula (VIII):

[Formula (VIII)]

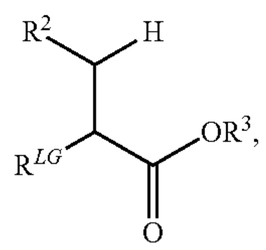


comprising generating in situ the compound of Formula (VII):

[Formula (VII)]

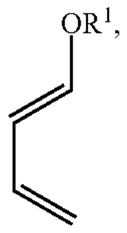


from a compound having the formula:



in the presence of a compound of Formula (VI):

[Formula (VI)]



wherein R^{LG} is a leaving group;

wherein R^1 comprises R^{1a}, $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)N(R^{1a})_2$, or $Si(R^{1a})_3$, wherein R^{1a} is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}-alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl;

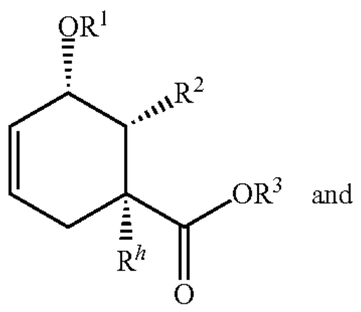
wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs; and

R^3 is selected from hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl.

17. The method according to claim **16**, further comprising converting the compound of Formula (VIII) into oseltamivir, or a pharmaceutically acceptable salt thereof.

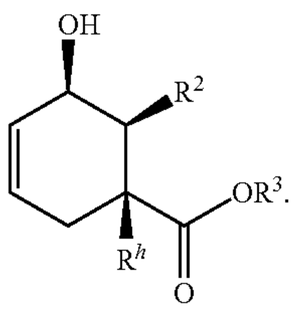
18. The method according to claim **17**, wherein the compound of Formula (VIII) is racemic and further comprising enzymatically resolving the compound of Formula (VIII) to obtain an enantioenriched compound of Formula (VIII-a) and an enantioenriched compound of Formula (IX):

[Formula (VIII-a)]



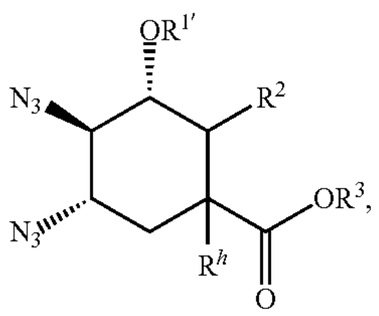
and

[Formula (IX)]



19. The method according to claim **18**, comprising further converting the compound of Formula (VIII-a) into oseltamivir, or a pharmaceutically acceptable salt thereof.

20. A compound having the formula:



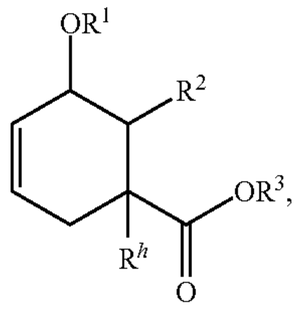
wherein $R^{1'}$ is selected from $R^{1a'}$, $C(O)R^{1a'}$, $C(O)OR^{1a'}$, $C(O)N(R^{1a'})_2$, or $Si(R^{1a'})_3$, wherein $R^{1a'}$ is in each case independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl;

wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs, or R^h and R^2 together form a double bond; and

R^3 is selected from hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl.

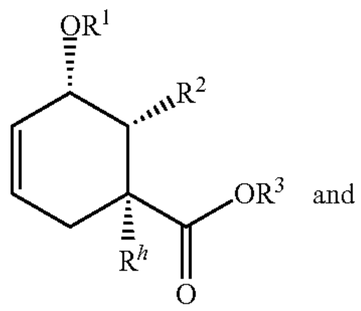
21. A method, comprising enantioselectively deacylating a racemic compound of Formula (VIII):

[Formula (VIII)]



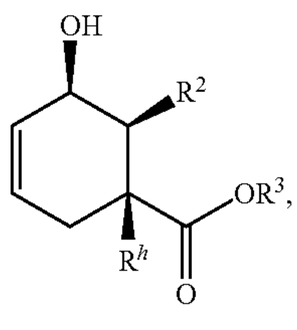
in the presence of a lipase enzyme and aqueous solvent, to obtain an enantioenriched compound of Formula (VIII-a) and an enantioenriched compound of Formula (IX):

[Formula (VIII-a)]



and

[Formula (IX)]



wherein R^1 comprises $C(O)R^{1a}$ wherein R^{1a} is selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, and C_{3-8}cycloalkyl;

wherein R^h is hydrogen and R^2 comprises F, Cl, Br, I, NO_2, CN, OTs, or OMs; and

R^3 is selected from hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heteroaryl, C_{3-8}cycloalkyl, and C_{1-8}heteroaryl.

22. The method according to claim **21**, comprising further converting the compound of Formula (VIII-a) into oseltamivir, or a pharmaceutically acceptable salt thereof.

* * * * *